REAL-WORLD DATA IN CANCER TREATMENT

Bridging the gap between trials and clinical practice

RAWA ISMAIL

Real-world data in cancer treatment

Bridging the gap between trials and clinical practice

Rawa Kamaran Ismail

© copyright Rawa Kamaran Ismail, 2022

Printing: ProefschriftMaken || www.proefschriftmaken.nl

ISBN: 9789464238075

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the author or the copyright-owning journals for previous published chapters.

Real-world data in cancer treatment

Bridging the gap between trials and clinical practice

Praktijkgegevens bij kankerbehandeling

De kloof dichten tussen experimentele studies en de dagelijkse praktijk

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 18 mei 2022 des ochtends te 10.15 uur

door

Rawa Kamaran Ismail

geboren op 15 maart 1994
te Kirkuk, Irak

Promotoren:
Prof. dr. A. de Boer
Prof. dr. M.W.J.M. Wouters

Copromotoren:
Dr. D.L. Hilarius
Dr. M. van Dartel

Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van:
- Dutch Institute for Clinical Auditing (DICA)
- College ter Beoordeling van Geneesmiddelen (CBG)
- SOLV Advocaten

Contents

CHAPTER 1

General introduction and thesis outline

General introduction

The dynamic cancer treatment landscape

Cancer is worldwide still one of the leading causes of morbidity and mortality. In 2018, 17 million new cancer cases and 9.6 million cancer deaths worldwide occurred[1]. The treatment landscape for patients with certain types of cancer (advanced melanoma, lung cancer, and advanced breast cancer) has dramatically changed in recent years with the important breakthroughs in medical treatment[2,3]. These include immunotherapies and targeted therapies and lead to improved clinical outcomes (**figure 1**). In advanced melanoma patients, chemotherapy was the only systemic treatment option until the beginning of last decade. From 2011 onwards, ipilimumab, BRAF- and MEK-inhibitors, and anti-PD1 therapies received marketing authorization and contributed to an increased life expectancy of patients with advanced melanoma. The treatment of patients with metastasized lung cancer has also improved with novel therapies. These patients also benefitted from the introduction of the anti-PD1 inhibitors and targeted therapies. In advanced breast cancer, the treatment landscape changed from chemotherapy to more targeted therapies. One of these systemic therapies was palbociclib, a CDK-4/6 inhibitor that improves clinical outcomes in patients with locally advanced or metastasized breast cancer. Palbociclib received marketing authorization in 2016 and has been reimbursed in the Netherlands since 2017. Besides the increase in availability of new therapies, the survival of patients with cancer has also improved by improvements in prevention, early diagnosis, and (centralized) cancer care organization.

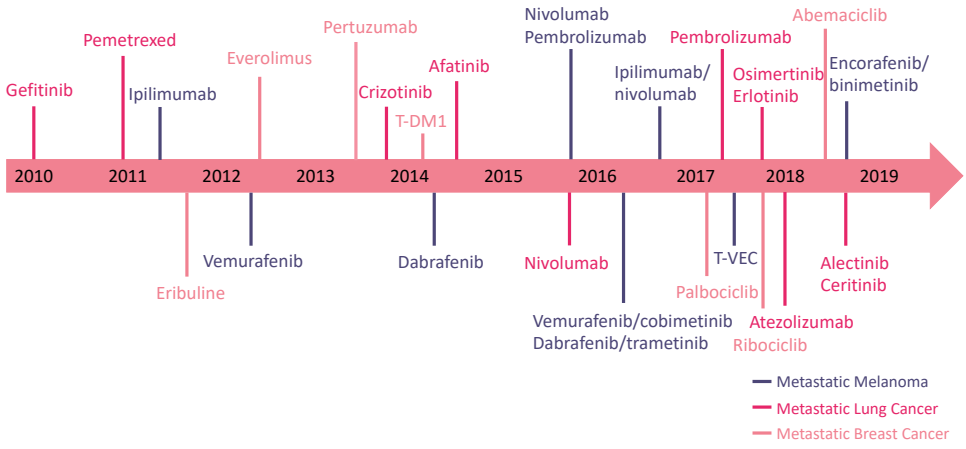


Figure 1: Timeline of novel targeted- and immunotherapies in the treatment of patients with advanced melanoma, metastatic NSCLC, or metastatic breast cancer.

The European Medicines Regulatory Network

The Medicines Evaluation Board (MEB, *College ter Beoordeling van Geneesmiddelen*) is the Dutch national competent authority (NCA). Together with the European Medicines Agency (EMA)[4], the other national competent authorities and the European Commission, the MEB operates in the European Medicines Regulatory Network (EMRN). For new anti-cancer drugs a positive opinion is issued by the Committee for Medicinal Products for Human Use (CHMP), i.e. one of the Committees of the EMA, and subsequently the European Commission approves the drug. Each of the 27 countries in the CHMP has one vote. Marketing authorization holders submit their data to the EMA secretariat and these data are then assessed within the EMRN[5]. For applications for new medicinal products always two NCA's are in the lead, those are the Rapporteur and Co-Rapporteur. There is difference in the number of Rapporteurships per member state; the Netherlands belongs to the top 3 countries in the number of Rapporteurships.

Trials versus real-world

Randomized controlled trials (RCTs) are considered the golden standard to determine the efficacy of new treatments[6,7]. The different aspects of a RCT and the processes used (randomization, blinding, and long follow-up) minimize the risk of confounding and information- and selection bias that could influence the results. This improves the internal validity of clinical trials, enabling the estimation of new treatments' valid treatment effects. The controlled setting in which RCTs are conducted cannot always be extrapolated towards the real world. A previous review of Jin *et al.* on cancer clinical trials showed that the eligibility criteria limit the study population to lower-risk patients[8]. The strict in- and exclusion criteria cause a significant difference between patients enrolled in RCTs and the heterogeneous patient population treated in routine clinical practice, which lowers the external validity of RCTs[9,10]. Real-world patients differ from the clinical trial patients in terms of patient- and tumor characteristics. An example is the Eastern Cooperative Oncology Group Performance Score (ECOG PS) in patients with advanced melanoma. Only patients with an ECOG PS of ≤1 were included in the clinical trials researching the efficacy of the novel therapies[11–14]. This results in a relatively healthy study population, while the real-world population also contains fewer fit patients also including patients with an ECOG PS of ≥2. Patients with brain metastases were also excluded from the phase IIII clinical trials but treated in clinical practice since there was no limitation in the indication at marketing authorization. In scientific literature, these differences between trial- and real-world patients are described and often show poorer clinical outcomes in real-world patients compared to trial patients[15–17]. A second con for RCTs is that specific types of cancer can be rare, making it difficult to include sufficient numbers of patients in pivotal phase III RCTs. In addition, single-arm trials have been used in oncology in the case of well-defined patient populations with a high unmet medical need[18]. Furthermore, RCTs can be expensive to

perform for specific research questions and take many years to complete. For these reasons, RCTs are not always feasible, and there is a need for a different type of valuable data[19].

Another issue in the field of cancer is the rising health care costs[20]. Novel treatments are often expensive[21]. Reimbursement of systemic therapies is usually based on trial data collected for market approval. Since a broader population in clinical practice will be treated with these therapies, information on real-world effectiveness of treatments is necessary for daily clinical practice, health technology assessment bodies (HTA's), and insurers.

Real-world data

In recent years, real-world data (RWD) has gained the interest of different stakeholders in cancer care. A consensus on the definition of RWD has not yet been established, with some stakeholders defining all data collected in study designs other than RCTs as RWD and others having less precise definitions of RWD as data collected in the real world or as part of routine clinical practice[22]. Makady *et al.* defined three categories of RWD definitions, with the first category being closest to the highly controlled RCT setting and the third category is closer to the non-controlled setting of routine clinical practice (**figure 2**)[22]:

1. Data collected in a non-RCT setting (e.g., non-controlled single-arm studies, historically controlled trials).

2. Data collected in a non-controlled and non-interventional setting, but is still conducted with an experimental intention (e.g., health surveys, post-authorisation efficacy studies (PAESs)).

3. Data collected in a non-experimental setting (e.g., electronic health records (eHRs), claims databases, registries, patient charts, post-authorisation safety studies (PASSs)).

RWD has gained major interest in daily clinical practice, in the regulatory process, and in reducing health care costs. Real-world evidence (RWE), defined as evidence derived from RWD, could be used in patient care by using data on the effective use of medicines or to generate data that can inform patients on expected clinical outcomes or safety issues. Effective use of medicines can eventually also lead to cost reduction. After marketing authorization of new medicines, sometimes additional data are needed. An example is the marketing authorization of BRAF-MEK inhibitors in patients with advanced melanoma. Regulators requested additional information on the effectiveness of this therapy in patients with brain metastases since these patients were excluded from the clinical trials[23]. For post-approval data on drugs, often expensive, time-consuming clinical trials are conducted. RWD might be helpful in post-approval data collection as well, which could help regulatory agencies in the life-time follow-up of drugs.

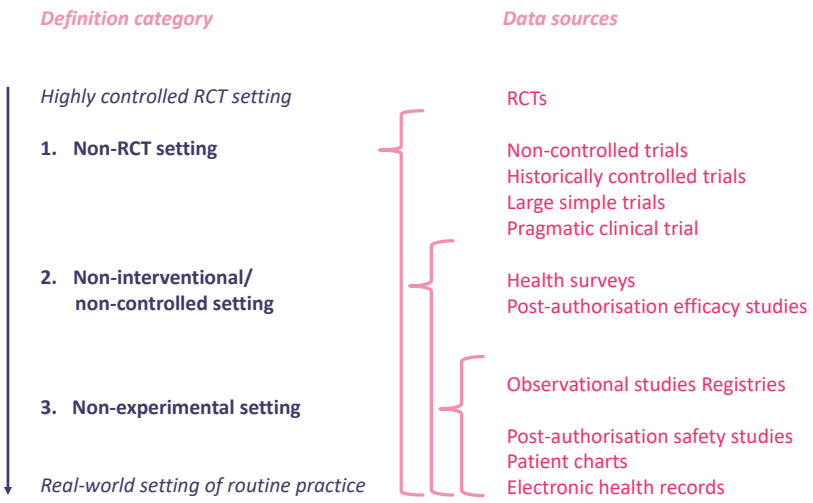


Figure 2. Data sources in relation to real-world data definition categories. Figure adapted from Makady et al[22].

The clinical outcomes of systemic therapies in phase III trials (efficacy) and the real-world outcomes in daily clinical practice (effectiveness) can differ due to the different patient populations. To treat patients in daily clinical practice effectively and to be able to give patients realistic treatment expectations, it is necessary to estimate the real-world effectiveness of therapies based on the patients' characteristics. The efficacy-effectiveness gap, the difference in clinical outcomes of treatment between patients treated in clinical trials and real-world practices, can be compared with different methods, such as multivariate Cox models and propensity score matching when sufficient patient-level data are available. When these data are not available, the results from the scientific papers can be digitized with software, such as DigitizeIt, to allow comparison between trial and real-world patients[24,25]. An improved understanding of the real-world effectiveness of systemic therapies is also important in the reimbursement of new therapies since health care costs are rising due to the increase in newly approved cancer drugs. One solution for reducing costs is value-based pricing, pricing based on drug outcomes, which has gained more interest in recent years.

Quality registries and real-world data

Observational data are needed to understand the use and clinical outcomes of systemic therapies in the real-world population. In the Netherlands, multiple organizations have developed disease-specific quality registries in which real-world, observational data are registered. These registries aim to improve health care through benchmarking or scientific research and are also needed for data collection for reimbursement of therapies. One of these organizations is the Dutch Institute for Clinical Auditing (DICA), founded in 2009 by

the professional societies of medical specialists in the Netherlands[26]. The DICA manages 22 disease-specific, nationwide quality registries, mainly focusing on oncology indications. Clinical auditing proved to be a valuable process for the improvement of medical care and patient outcomes. The use of quality registries or clinical audits has been effective in the last decade in evaluating and improving medical care by minimizing undesired practice variation and improving patient outcomes[27]. The DICA uses quality indicators, giving insight in hospital performances, and in addition the collected data are used for scientific research to improve the quality of cancer care. Quality indicators include structure-, process-, and outcome indicators that provide hospitals with insights into their performance compared to all other hospitals (the benchmark). Examples of quality indicators are complications after surgery, the performance of an MRI of the brains at diagnosis, or the 1-year survival of patients with cancer. The results from these quality indicators are discussed with peers, leading to sharing best practices and eventually improving care[27]. An example is the relatively high use of neoadjuvant radiotherapy in patients with rectal cancer in the Netherlands. This insight led to guideline adjustment, decreasing radiotherapy use from 84.2 to 64.4% in two years, without compromising oncologic outcomes[28]. Another example is the decrease in hospital variation in patients undergoing lung cancer surgery[27] and the improvements in postoperative mortality in patients with colon- and rectal cancer[29]. Clinical auditing provides insights in quality of care in several domains of Dutch health care and has led to impressive improvements on a national level[27,30]. Though, clinical auditing for systemic treatments, for example for the systemic treatment of patients with advanced melanoma or lung cancer is relatively new and the impact of data registration remains unknown.

Dutch Melanoma Treatment Registry

One of the quality registries managed by DICA is the Dutch Melanoma Treatment Registry (DMTR), in which all patients with advanced (irresectable stage III and stage IV) melanoma are registered[31]. The DMTR was set up in 2013 to collect data on the real-world use of expensive drugs that just received marketing authorization to provide insights into the quality of the treatment and stimulate improvements by the melanoma centers[31]. DICA analyzes the data from the DMTR, and the melanoma centers receive their data, including a comparison with the benchmark. The National Health Care Institute (*Zorginstituut Nederland)* obliged the introduction of a quality registry to collect RWD on ipilimumab use in advanced melanoma patients. Ipilimumab was authorized and reimbursed in 2011, and since this treatment is costly, the authorities requested additional data on the effectiveness in daily clinical practice. These data were collected in the DMTR, and the costs of real-world use of ipilimumab treatment were published in 2018[32]. Furthermore, advanced melanoma treatment was centralized in 14 melanoma centers in the Netherlands to assure the quality of care.

Data registration

Even though quality registries can cause improvements in cancer care, they also come with a registration burden. Manual registration can be very time-consuming and can lead to registration mistakes or incomplete data. With the upcoming new systemic therapies, data registration becomes more detailed and complex, and the databases become more complicated and extensive. There is a need for automatic data collection from existing data sources to reduce the registration burden. High-quality (validated and complete) registries are needed to monitor the use of expensive drugs in real-world practice. This RWE can help improve treatment decisions and shared decision-making[33]. The federation of medical specialists (*Federatie Medisch Specialisten*) published a vision document on the rising healthcare costs, the expensive drugs, and the need for RWE to stimulate RWD use without causing an extra registration burden[34].

Thesis outline

The rapid changes in treatment options for patients with cancer and the rising healthcare costs cause a need for RWE. This thesis aims to investigate how the real-world population of patients with cancer differs from the trial population and how RWD can be used in daily clinical practice to improve cancer care. We researched patients with advanced melanoma (chapters 4, 6, 7, and 8), lung cancer (chapters 3, 5, and 10), and advanced breast cancer (chapter 9). This thesis is divided into four parts. In part I, we focus on quality registries and new methods to collect RWD from existing data sources without causing an additional registration burden. In part II, we describe different approaches to compare real-world and clinical trial outcomes. We then describe in part III various research focusing on the differences in outcomes between real-world and clinical trial patients. We conclude this thesis with part IV, in which we describe the value of real-world data in clinical practice.

Part I: The use of quality registries to generate real-world data

Previous research has already described how quality registries can improve care[27]. Originally, the DICA quality registries were mainly focused on the primary, often surgical treatment of cancer. With the increase in systemic treatment options and the increased focus on multidisciplinary treatment, detailed registration of systemic treatment becomes more and more important. The need for RWE on systemic treatment and their clinical outcomes led to the initiation of the DICA Medicines Program in 2018[35]. In **chapter 2**, the initiation of this program and the first results are described. Insights that were provided by using existing data sources linked to each other are presented.

Another recently initiated quality registry was the Dutch Lung Cancer Audit for Lung Oncology (DLCA-L). The surgical and radiotherapeutic treatments of lung cancer patients

in the Netherlands have already been registered in the DLCA-surgery (DLCA-S)[36] and DLCA-radiotherapy (DLCA-R)[37] since 2012 and 2013, respectively. In 2016, the sub-registration DLCA-L started, focusing on the diagnoses and systemic treatments of all lung cancer patients in the Netherlands. Quality indicators were developed while the data quality improved over the years. **Chapter 3** describes the initiation of the DLCA-L and focuses on the first results of three years of clinical auditing.

Part II: Methods to compare real-world and clinical trial outcomes

Appropriate methods to investigate the differences between real-world and clinical trial patients are necessary.

Chapter 4 investigates whether data from a quality registry could provide comparable data as post-approval clinical trials. For advanced melanoma patients, no direct comparisons between real-world and trial patients existed. We, therefore, conducted a study on advanced melanoma patients with brain metastases that were treated with BRAF-MEK therapy. We used data from the DMTR for the real-world population and data from four post-approval clinical trials derived from the MEB. Two methods were used to compare the two groups: a Cox hazard regression model and propensity score matching.

Another important aspect of comparing real-world and clinical trial outcomes is the availability of patient-level data. Many studies have compared real-world clinical outcomes of immunotherapy in patients with metastatic non-small cell lung cancer (NSCLC) with reported outcomes from pivotal trials. However, any differences observed could be only limitedly explored further for causation because of the unavailability of patient-level data from trial participants[38]. The study described in **chapter 5** aimed to explore the additional benefit of a comparison from pivotal trial data with patient-level data, focusing on nivolumab treatment in stage IV NSCLC patients.

Part III: Differences in outcomes between real-world and trial patients with melanoma.

It is important to quantify and understand the differences in real-world population outcomes and the outcomes presented in phase III clinical trials to improve clinical decisions based on RWD. As mentioned before, the phase III clinical trials investigating new anti-cancer treatments for advanced melanoma patients used strict in-and exclusion criteria. However, after marketing authorization, almost all advanced melanoma patients were treated with these therapies in daily clinical practice.

Chapter 6 describes the real-world population of advanced melanoma patients and the proportion of patients treated in clinical practice that would not have been considered eligible for phase III trial participation based on their patient- and tumor characteristics. In this study, the focus was on ineligible advanced melanoma patients and their real-world

outcomes. Since these patients are generally excluded from the phase III trials, this real-world information is significant for clinical practice.

Adjuvant treatment with anti-PD1 and BRAF-MEK therapy in stage III melanoma patients has recently been investigated in pivotal trials[39,40]. At the time the DMTR was initiated, only advanced melanoma patients were registered into the quality registry. The changing treatment landscape leads to changes in data collection in quality registries; therefore, the DMTR was expanded in 2018 to include melanoma patients treated with adjuvant therapy. **Chapter 7** reports the real-world outcomes of adjuvant-treated melanoma patients. This study shows treatment patterns, relapse, and toxicity rates beyond the clinical trial setting.

Recently, 5-year survival outcomes of advanced melanoma patients treated with BRAF-MEK therapies in RCTs were published[41–43]. These results are auspicious, but the real-world results remain unknown. Since all advanced melanoma patients in the Netherlands have been registered in the DMTR since 2013, sufficient data are collected to describe long-term survival. In **chapter 8,** we investigated the real-world survival of these patients and identified characteristics of long-term survivors with advanced melanoma.

Part IV: The value of real-world data in clinical practice

In part IV, different studies are described in which RWD were used to create valuable evidence that can be used in clinical practice.

Chapter 9 focuses on a different patient population, patients with advanced breast cancer treated with palbociclib. Medical oncologists have been treating patients since 2018 with palbociclib, but data on dose reductions and the effect of these dose reductions on patient outcomes are lacking. A need for RWE on older patients treated with palbociclib is necessary to reduce uncertainties in clinical practice. Using data from the DICA Medicines program, these relevant clinical questions on the real-world treatment of palbociclib and dose reductions were explored. This study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with advanced breast cancer.

Another value of quality registries is the availability of RWD in extraordinary settings. To investigate the effects of the SARS-COV-2 pandemic on regular lung cancer care in the Netherlands, we studied in **chapter 10** the impact on patients with lung cancer registered in the Dutch Lung Cancer Audit (DLCA), which includes detailed information on patient, tumor, and treatment characteristics and follow up.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. Front Pharmacol 2018;9.

[3] Pasquali S, Hadjinicolaou A V., Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2018;2018.

[4] Medicines Evaluation Board. Cooperation in Europe. https://english.cbg-meb.nl/topics/about-meb-cooperation-in-europe.

[5] European Medicines Agency. From laboratory to patient: the journey of a centrally authorised medicine. EMA 2019.

[6] Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet 2015;385:1502–3.

[7] Akobeng AK. Understanding randomised controlled trials. Arch Dis Child 2005;90:840–4.

[8] Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: Analysis of investigational new drug applications in 2015. J Clin Oncol 2017;35:3745–52.

[9] Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet 2005;365:82–95.

[10] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16:1–14.

[11] Hodi FS, O'Day SJ, McDermott DF, Weber, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 2010;363:711–23.

[12] Long G V., Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386:444–51.

[13] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated Melanoma. N Engl J Med 2015;373:23–34.

[14] Robert C, Schachter J, Long G V., Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521–32.

[15] Lakdawalla DN, Shafrin J, Hou N, Peneva D, Vine S, Park J, et al. Predicting Real-World Effectiveness of Cancer Therapies Using Overall Survival and Progression-Free Survival from Clinical Trials: Empirical Evidence for the ASCO Value Framework. Value Heal 2017;20:866–75.

[16] Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, de Wit R, van den Bergh ACM, Coenen JLLM, et al. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry. Eur Urol Focus 2018;4:694–701.

[17] Khozin S, Carson KR, Zhi J, Tucker M, Lee SE, Light DE, et al. Real-World Outcomes of Patients with Metastatic Non-Small Cell Lung Cancer Treated with Programmed Cell Death Protein 1 Inhibitors in the Year Following U.S. Regulatory Approval. Oncologist 2019;24:648–56.

[18] ESMO. Single-arm trials improve early access ro rare cancer drugs. https://www.esmo.org/meetings/past-meetings/esmo-2016-congress/Press-Media/Single-Arm-Trials-Improve-Early-Access-to-Rare-Cancer-Drugs (accessed January 1, 2019).

[19] Frieden TR. Evidence for Health Decision Making — Beyond Randomized, Controlled Trials. N Engl J Med 2017;377:465–75.

[20] Zorgvisie. Healthcare costs rise to 174 billion in 2040. https://www.zorgvisie.nl/rivm-zorgkosten-stijgen-naar-174-miljard-in-2040/ (accessed March 1, 2019).

[21] Leeneman B, Uyl-de Groot CA, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, van den Eertwegh AJM, et al. Healthcare Costs of Metastatic Cutaneous Melanoma in the Era of Immunotherapeutic and Targeted Drugs. Cancers (Basel) 2020;12:1003.

[22] Makady A, de Boer A, Hillege H, Klungel O, Goettsch W. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. Value Heal 2017;20:858–65.

[23] European Medicines Agency (EMA). EPAR Zelboraf 2012. https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf.

[24] Phillips CM, Parmar A, Guo H, Schwartz D, Isaranuwatchai W, Beca J, et al. Assessing the efficacy-effectiveness gap for cancer therapies: A comparison of overall survival and toxicity between clinical trial and population-based, real-world data for contemporary parenteral cancer therapeutics. Cancer 2020;126:1717–26.

[25] DigitizeIt. https://www.digitizeit.xyz/ (accessed August 25, 2021).

[26] Dutch Institute for Clinical Auditing (DICA). https://dica.nl/ (accessed August 25, 2021).

[27] Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, Ten Berge MG, et al. The dutch surgical colorectal audit. Eur J Surg Oncol 2013;39:1063–70.

[28] Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. Ann Surg 2020;271:627–31.

[29] Gietelink L, van Groningen J, Tollenaar RAEM, Wouters MWJM, Marijnen CAM, Wouters MWJM, et al. Changes in nationwide use of preoperative radiotherapy for rectal cancer after revision of the national colorectal cancer guideline. Eur J Surg Oncol 2017;43:1297–303.

[30] Gietelink L, Wouters MWJM, Bemelman WA, Dekker JW, Tollenaar RAEM, Tanis PJ. Reduced 30-day mortality after laparoscopic colorectal cancer surgery. Ann Surg 2016;264:135–40.

[31] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156–65.

[32] Franken MG, Leeneman B, Jochems A, Schouwenburg MG, Aarts MJB, Van Akkooi ACJ, et al. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands. Anticancer Drugs 2018;29:579–88.

[33] Sheldon Greenfield. Making Real-World Evidence More Useful for Decision Making. Value Heal 2017;20:1023–4.

[34] Federatie Medisch Specialisten. Visiedocument Dure Geneesmiddelen 2016:1–40.

[35] DICA. DICA Medicines Program. https://dica.nl/dicageneesmiddelen.

[36] ten Berge M, Beck N, Heineman DJ, Damhuis R, Steup WH, van Huijstee PJ, et al. Dutch Lung Surgery Audit: A National Audit Comprising Lung and Thoracic Surgery Patients. Ann Thorac Surg 2018;106:390–7.

[37] Belderbos J, van der Woude L, van Bockel LW, DeJaeger K, Koppe F, Pomp J, et al. The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R): Real-World Data on Elderly Stage III Non-Small Cell Lung Cancer Treated with Definitive Chemoradiation. Int J Radiat Oncol 2019;105:S45–6.

[38] Cramer-Van Der Welle CM, Peters BJM, Schramel FMNH, Klungel OH, Groen HJM, Van De Garde EMW. Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer. Eur Respir J 2018;52.

[39] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824–35.

[40] Eggermont AMM, Blank CU, Mandala M, Long G V., Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018;378:1789–801.

[41] Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019;381:626–36.

[42] Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248–60.

[43] Ribas A, Daud A, Pavlick AC, Gonzalez R, Lewis KD, Hamid O, et al. Extended 5-Year Follow-up Results of a Phase Ib Study (BRIM7) of Vemurafenib and Cobimetinib in BRAF -Mutant Melanoma 2019:1–9.

PART I

THE USE OF QUALITY REGISTRIES TO GENERATE REAL-WORLD DATA

CHAPTER 2

The DICA Medicines Program: insights in medication use and clinical outcomes.

Submitted.

R.K. Ismail[*], J. van Breeschoten[*], S. van der Flier, C.T. van Loosen, A.M.G Pasmooij, M. van Dartel, A.J.M. van den Eertwegh, A. de Boer, M.W.J.M. Wouters, D.L. Hilarius.
*These authors contributed equally to this manuscript.

Abstract

Background: The DICA Medicines program was set up in September 2018 to evaluate expensive medicine use in daily practice in terms of real-world effectiveness only using existing data sources. Our study aims to describe the possibilities of the addition of declaration data to quality registries to provide participating centers with benchmark information about use and outcomes of medicines.

Methods: Four national population-based registries, were linked to financial data from the hospital pharmacy, the Dutch *DBC information system* including in-hospital activities, and survival data from health care insurers. The first results of real-world data (RWD) linkage are presented using descriptive statistics to assess patient, tumor, and treatment characteristics. Time-to-next-treatment (TTNT) and overall survival (OS) were estimated with the Kaplan-Meier method.

Results: A total of 21 Dutch hospitals participated in the DICA Medicines program, which included 7412 colorectal cancer patients, 1981 metastasized colon cancer patients, 3860 lung cancer patients, 1253 metastasized breast cancer patients, and 7.564 patients with rheumatic disease. The data were used for hospital benchmarking to receive insights into medication use in specific patient populations, treatment information, clinical outcomes, and costs. Detailed treatment information (duration and treatment steps) led to insights into differences between hospitals in daily clinical practices. Furthermore, exploratory analyses on clinical outcomes (TTNT and OS) were possible.

Conclusions: The DICA Medicines program shows that it is possible to gather and link RWD about medicines to four disease-specific population-based registries. Since these RWD became available with minimal registration burden and effort for hospitals, this method can be explored in other population-based registries to evaluate real world efficacy.

Introduction

Regulatory authorities approve the majority (76%) of new cancer drugs based on evidence provided by randomised controlled trials (RCTs) [1]. These RCTs hold great internal validity and are widely considered the gold standard for establishing the efficacy of new drugs [2]. Many new cancer drugs are recently approved based on highly selected patient groups, surrogate outcomes, lower patient numbers, and are increasingly approved in accelerated tracks [3,4]. The selected patients' groups and the well-controlled setting of these RCTs results in criticism of their external validity [5]. In addition, recent research has shown that almost half of the RCTs that applied for marketing authorisation of new cancer drugs in Europe were at high risk of bias. This increased risk of bias was caused by their design, conducted analyses, and conduct deficits [1]. Further, as a result of the increase in newly approved cancer and rheumatic disease drugs, healthcare costs rise. Total expenditures of hospitals on expensive medicines in the Netherlands reached 2.1 billion euros in 2019 [8].

Following market entry, new cancer drugs are prescribed to a broader group of patients with different characteristics. This leads to a gap in clinical outcomes evidence between RCTs and the real world [6,7]. During routine clinical practice, real-world data (RWD) are generated and registered in validated population-based cancer registries. Clinical quality registries are an important tool for quality assessment and improvement in hospitals, consequently leading to demonstrable improvements in patient outcomes [10]. Benchmarking hospitals results in insights in differences in outcomes, which can lead to improvement of care [10,11]. Furthermore, data from quality registries are used for outcome research and to study practice variation between centers using quality indicators[16]. Besides clinical quality registries, specifically on the use of (expensive) drug treatments detailed administrative and declaration data are available. The combination of these data in clinical quality registries, hospital administrative data and declaration data of drugs used in these indications could be valuable to bridge the efficacy-effectiveness gap.

Previous initiatives linked various databases on drugs to clinical data. This linkage made it feasible to study drug utilization, health resources utilization, costs, effectiveness, and safety of medicines [9]. However, a gap remains for recently approved expensive cancer drugs.

To better understand the effectiveness of expensive cancer medicines in a real-world population, the Dutch Institute for Clinical Auditing (DICA) initiated a Medicines program in 2018. The program aims to (i) identify variation in use and clinical outcomes of expensive medicines, (ii) provide post-marketing authorization data, (iii) provide a tool for clinicians to benchmark their practice on expensive medicines use, (iv) stimulate interactions between clinicians to share best practices. In this program existing data sources were used. Our study aims to describe the possibilities of the addition of declaration data to quality registries

to provide participating centers with benchmark information about use and outcomes of medicines.

Methods

Data sources

Different existing data sources were used in the DICA Medicines program that were linked. The first data sources were national population-based registries, that are managed by the DICA. DICA is a non-profit organization that facilitates 23 population-based registries on different disciplines and diseases. These registries include information on clinical characteristics but include limited data on the use of medicines. The DICA Medicines program uses the Dutch ColoRectal Audit (DCRA)[11], the Dutch Lung Cancer Audit (DLCA) [12], and the NABON Breast Cancer Audit (NBCA)[13]. These quality registries include information on patient-, tumor-, and treatment characteristics and are used to benchmark hospitals on structure-, process- and clinical outcomes [14,15]. A previous study has shown that the data entered in the DICA registries are accurate and complete [17].

The second data source was financial, administrative data, including declarations for health insurers of expensive medicines from hospital pharmacies. These expensive medicines are listed as expensive (>€1000 per patient per year) by the Dutch Healthcare Authority (NZa) [18]. This data source includes precise and valid information about the diagnosis, date of prescription, and the dose and quantity of the prescribed drug. Administrative data of hospitals include declarations for reimbursement of expensive medicines. Only expensive medicines that were relevant and related to the diagnosis were linked to the clinical data.

The third data source includes the Dutch diagnosis treatment combinations (DBC) information system, which contains information on in-hospital activities, such as CT scans, infusions, hospital admissions, day treatment, radiology treatment, and treatment of toxicities. The DBC information system is used for the registration and reimbursement of hospital and medical specialist care. This system was introduced in the Netherlands to increase transparency of care. Furthermore, DBC's were initiated to realise a supply-led system, increase efficiency and facilitate competition between health care providers [19]. Because the DCRA and NBCA quality registries only include patients undergoing surgery, metastasized patients without surgery are missing. To include metastasized colorectal and metastasized breast cancer patients the DBC data were used and were linked to the fourth data source.

The fourth data source was survival data from the national claims database (VEKTIS) from health insurers [20]. VEKTIS is the national insurance database which contains administrative

data from the Dutch national healthcare insurers, covering approximately 17 million individuals. By adding this data source, we could assess overall survival (OS) from diagnosis and the start of systemic therapy. Data were retrospectively collected from patients treated from 2017 to 2020. Although the DICA Medicines Program was set up in 2018, the data from 2017 were available in the hospitals and linked.

Data linkage and privacy

The first step in data linkage was identifying patients diagnosed with colorectal cancer, lung cancer, breast cancer, and rheumatic disease using the DBC information system. The DBC information system is used for the registration and reimbursement of health care in the Netherlands. The second step was to identify whether these patients used relevant expensive drugs, and the third step was to determine whether these patients are registered in the national quality registry. Information on date of death from the VEKTIS database was added for deceased patients (**figure 1**). Data were linked based on hospital patients' ID. A third party pseudonymized this ID. Results were visualized in dynamic web-based dashboards, in which (systemic) treatment was linked to clinical parameters. Filters on patient- and tumor characteristics, clinical outcomes, and therapy varied for the different diagnoses, depending on relevance. Furthermore, participating hospitals were benchmarked, and practice variation was visualized and discussed to share knowledge on medical treatment differences.

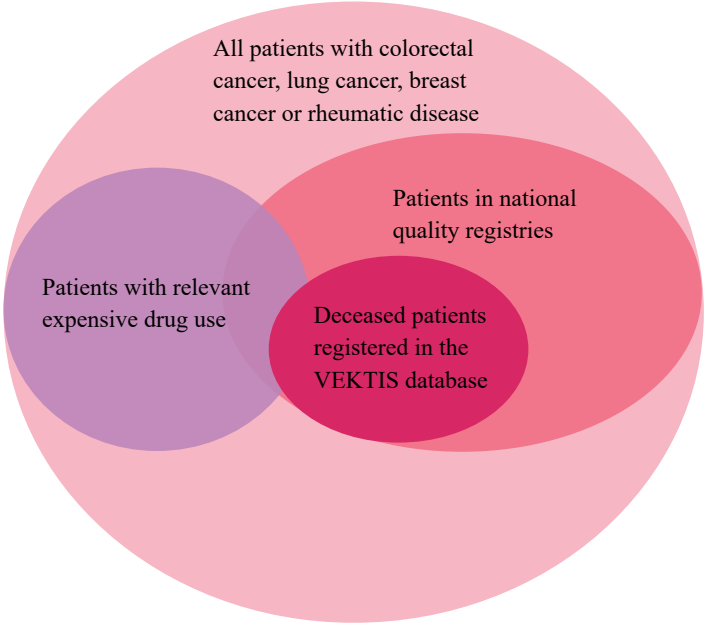


Figure 1: Visualisation of the patients included in our study and the different data sources used.

Statistical analysis

The analyses in this manuscript are exploratory. Descriptive statistics were used to assess patient, tumor, and treatment characteristics. Time-to-next-treatment (TTNT) and OS were estimated with the Kaplan-Meier method. Survival times were calculated from the start of a systemic therapy until subsequent treatment (TTNT) or until death from any cause (OS). Patients alive or lost to follow-up were right-censored at the time of last registered expensive medicine use. All the statistical data were analyzed using RStudio software program (version 3.5.2; packages tidyverse [21], TableOne[22], Survminer[23]).

Results

Database

A total of 21 Dutch hospitals participated in the DICA Medicines program and were included in this study. Of these hospitals, nine were top-clinical, eleven were peripheral hospitals, and one was academic. The geographic location of these hospitals is shown in **figure 2** and is spread all over the country. The DICA Medicines database included a total of 7412 colorectal cancer patients, 1981 metastasized colon cancer patients, 3860 lung cancer patients, 1253 metastasized breast cancer patients, and 7564 patients with rheumatic disease.

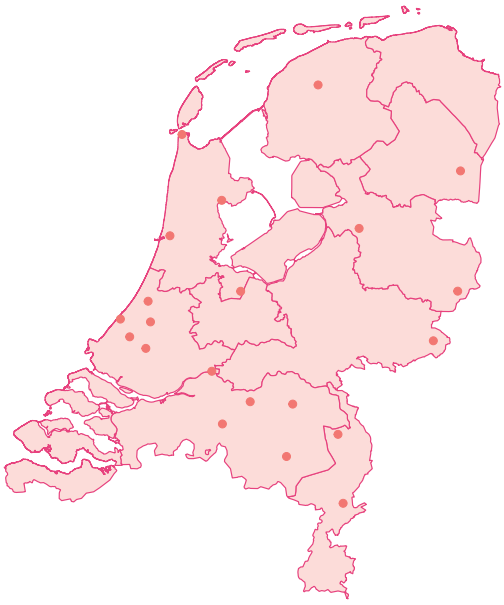


Figure 2. Map of the Netherlands including the geographic location of the DICA Medicines program participating hospitals (orange dots).

Benchmarking

One of the possibilities with the DICA Medicines program is to benchmark results between hospitals to improve the quality of care. Hospitals were provided with web-based dynamic dashboards, continuously comparing their data to the benchmark. The benchmark consisted of all other participating hospitals. An example of benchmarking is the use of systemic therapies at the end of life in metastatic colorectal cancer patients. This varied between hospitals from 4.2% to 27.8%, with a median of 13.4% (**figure 3**). The dashboards also provide information on the type of systemic therapy used at the end of life (**figure 4**). A signaling function is included in the dashboard if hospitals deviate from the benchmark. Deviation from the benchmark was defined as a ranked average with (percentage of own hospital – percentage of the benchmark)2 + number of patients in the benchmark).

Use of medicines and patient characteristics

The linkage of different data sources led to new insights into hospitals' use of medicines and patient populations. The patient-, and tumor characteristics are listed per medicine in the dashboard as a table that hospitals can compile themselves with available variables. One of the participating hospitals discovered a deviation from the benchmark in pemetrexed

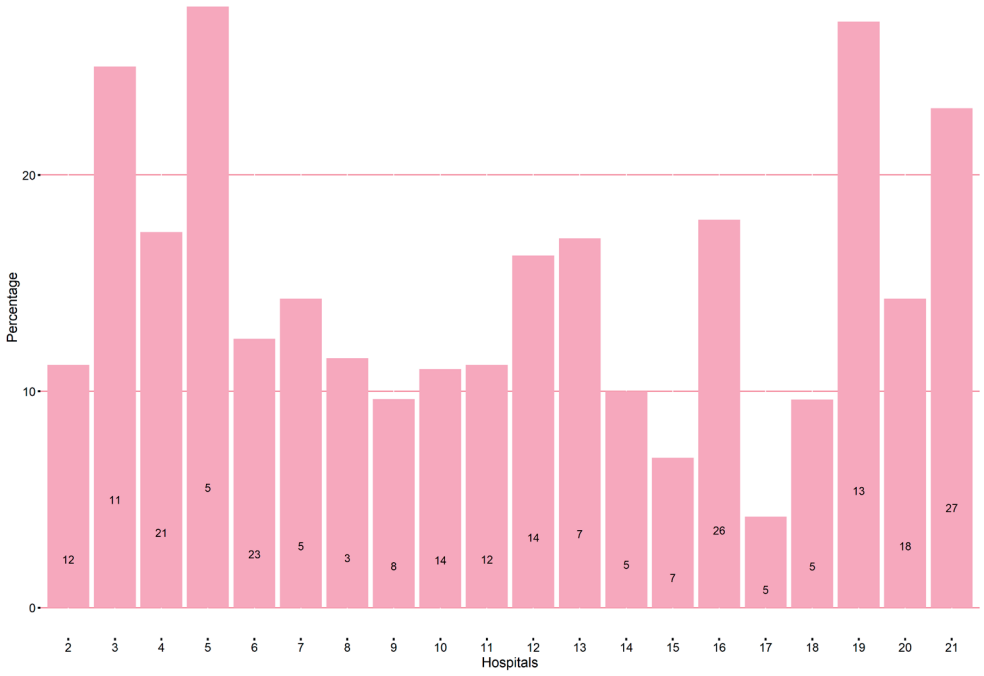


Figure 3. Percentage of patients with colorectal cancer that received a new systemic therapy within 6 weeks before death per hospital. *The percentage is calculated based on the total number of patients that died. The numbers in the bars represent the absolute number of patients per hospital. Data from hospital 1 is not shown as date of death is missing.*

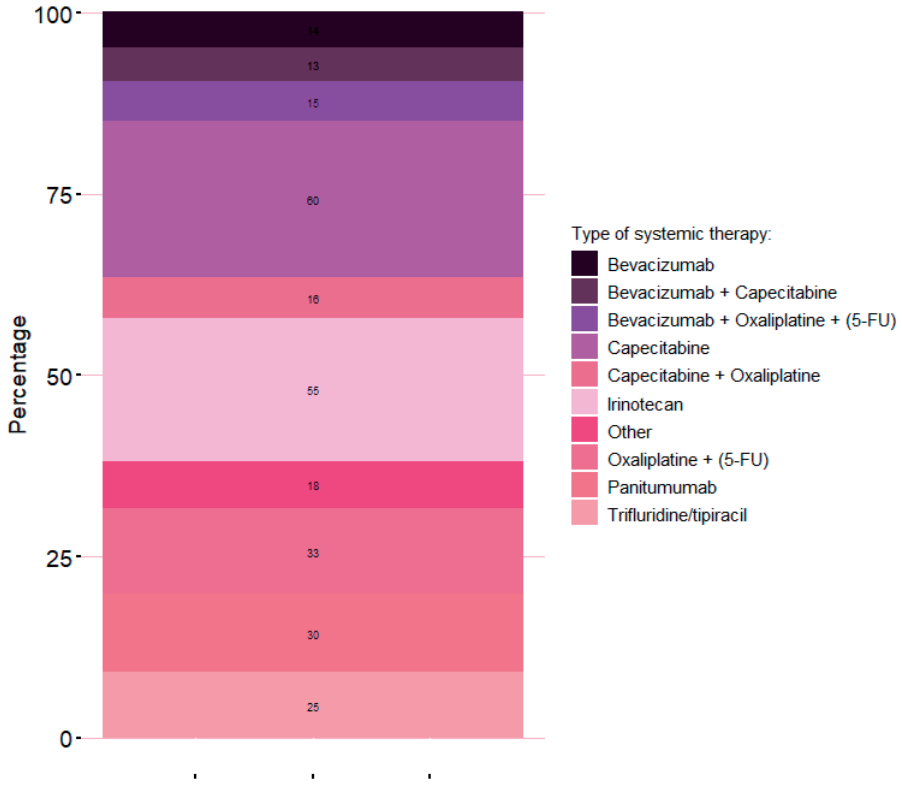


Figure 4. The type of systemic therapies started within six weeks before death of patients with colon cancer. *Percentage is the % type of systemic therapy among all therapies started within six weeks before death. 5-FU is depicted in brackets as these data are not available.*

use between 2017 and 2020. This was 33% for the specific hospital, compared to only 18% in the benchmark. They were able to explain this difference in pemetrexed use by using the dashboard, in which the use of medication was linked to the patient characteristics. This showed a higher percentage of mesothelioma patients (36%) compared to the benchmark (15%) (data not shown).

Treatment information

Linking clinical data to systemic treatment information also led to detailed information per medicine, such as treatment duration in months and the number sof cycles per patient. An example is the number of courses of capecitabine + oxaliplatine for the adjuvant treatment of colorectal cancer (**figure 5**). Furthermore, administrative data were used to visualize treatment steps in Sankey diagrams in the dashboard, which can be adjusted for specific filters on patient-, tumor-, and treatment characteristics. **Figure 6** shows the Sankey diagram of metastasized colon cancer patients that were treated between 2017 and 2020. The dashboards also contain detailed information on diagnostic imaging (CT

Figure 5. Number of courses of capecitabine + oxaliplatine for the adjuvant treatment of colorectal cancer patients per hospital.

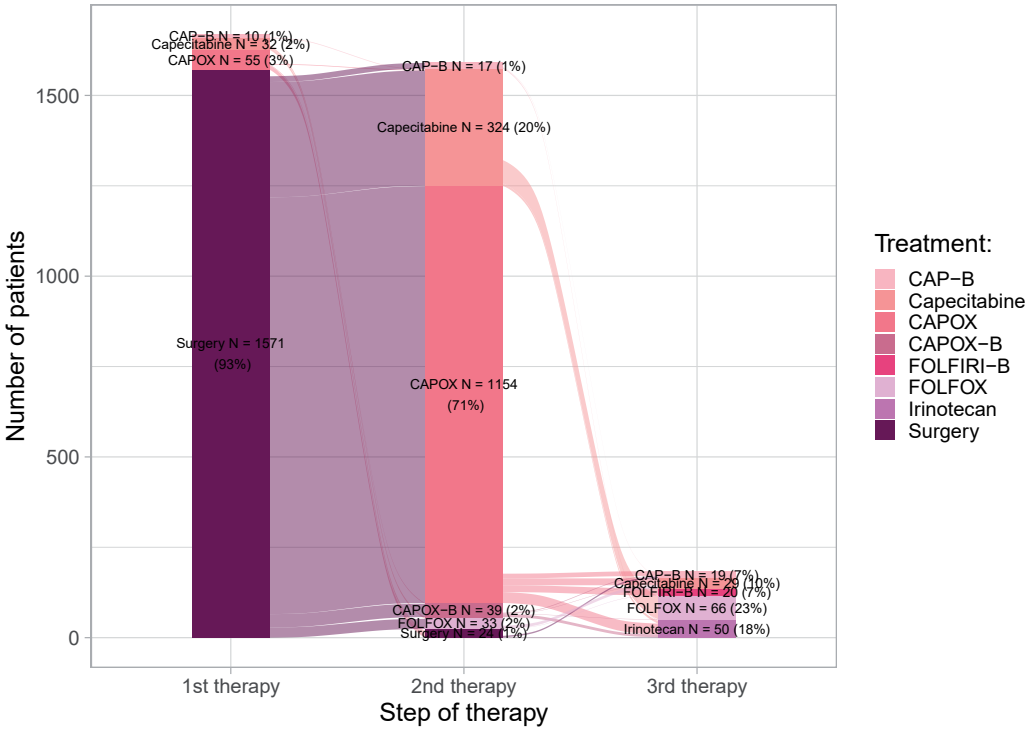


Figure 6. Treatment patterns in patients with stage III colon cancer treated between 2017 and 2020. *The Sankey diagram shows the flow of patients from 1st treatment step to 2nd treatment step and from 2nd treatment step to 3rd treatment step. The width of the lines corresponds with the number of patients. Systemic therapies with less than 5 patients are not displayed in this graph.*

scans, MRI's), the number of (tele-)consults, clinical admissions, and ER visits pre-and post-treatment per medicine.

Clinical outcomes

The DICA Medicines program also provides hospitals data on clinical outcomes, such as TTNT and OS. **Figure 7a** shows the TTNT of metastasized lung cancer patients treated with first-line pembrolizumab or pembrolizumab and pemetrexed combination therapy. The median TTNT was 22.5 months (95%CI: 17.0-NR) and 14.9 months (95%CI: 12.4-21.6) for respectively pembrolizumab monotherapy and pembrolizumab + pemetrexed. The OS of these treatments is presented in **figure 7b**. Hospitals receive their outcomes compared to the benchmark. It is also possible to compare clinical outcomes between treatments in exploratory head-to-head comparisons for hospitals specifically or the benchmark in specific patient populations.

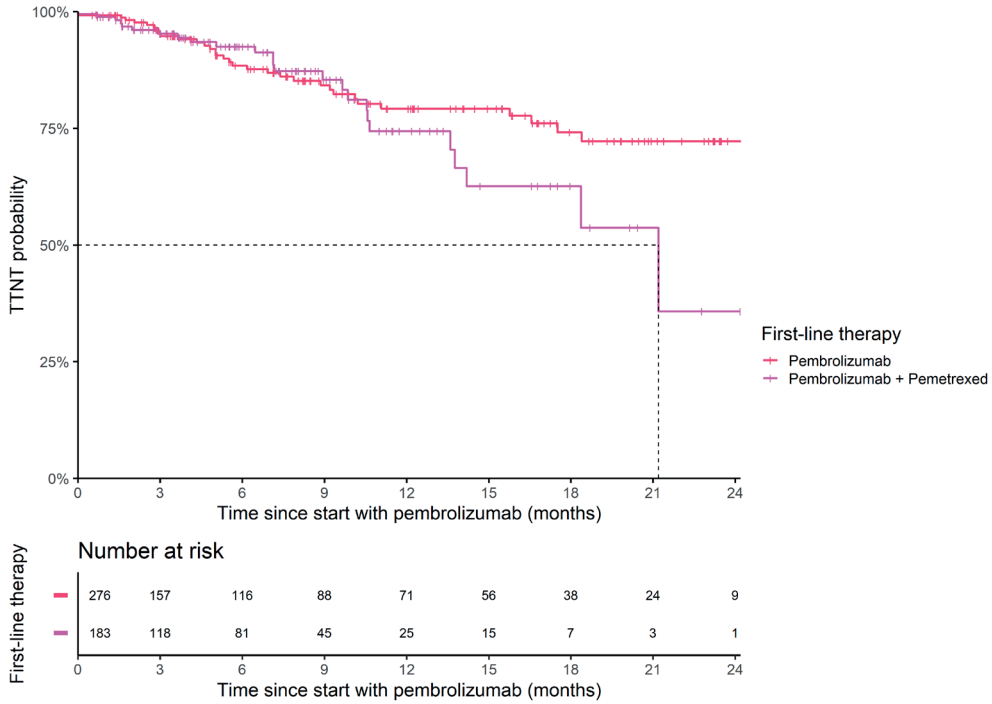


Figure 7a. Time-to-next-treatment (TTNT) of lung cancer patients treated with first-line pembrolizumab or pembrolizumab + pemetrexed between 2017 and 2020.

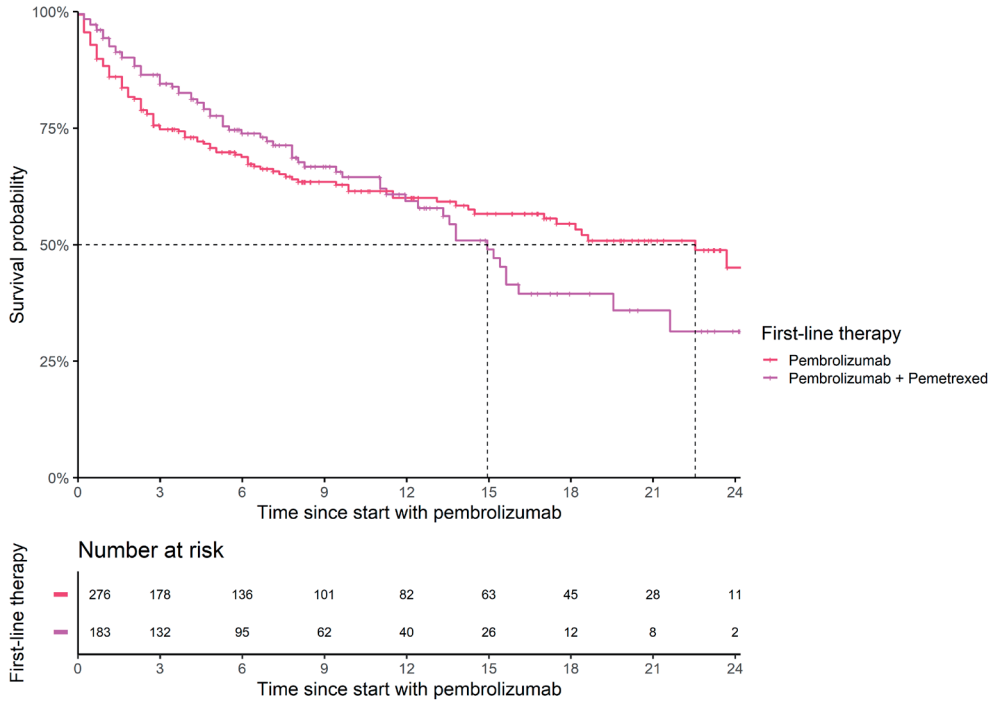


Figure 7b. Overall survival (OS) of lung cancer patients treated with first-line pembrolizumab or pembrolizumab + pemetrexed between 2017 and 2020.

Costs

Use of the financial, administrative database from hospital pharmacies led to detailed information on costs of systemic therapies (total costs per treatment and costs per patient) in certain subgroups. Hospitals can upload their paid prices into the dashboard, which is then connected to the medicines- and patient information. Prices paid by other hospitals are not shown due to confidential agreements between pharmaceutical companies and hospitals.

Discussion

This article reports on the first results on possibilities of the DICA Medicines program in which RWD is generated by linking four data sources, including data from quality registries, financial pharmacy data, in-hospital activities systems, and reimbursement data of 21 Dutch hospitals. In this article we reported on the possibilities of this program in terms of benchmarking, treatment information, clinical outcomes and costs. To be able to use the data as benchmark information, the data were visualized in web-based dashboards available for clinicians, insurers, and researchers and led to insights in medication use, benchmarking clinical outcomes, and costs without any additional registration burden for hospitals. Benchmarking hospital performance is relatively uncommon in the field of medical oncology in contrast to surgical oncology, where many quality registries exist that monitor the quality of care in every hospital [11]. Benchmarking information can support hospital pharmacists, oncologists, and other medical professions involved in the systemic treatment of patients to reach a certain level of care. Real-world data on the use and efficacy of systemic therapies is needed in daily clinical practice. As the real-world setting differs from the randomized clinical trial setting, these data are needed after marketing authorization. With a growing interest in real-world evidence, this project provides information from the real-world, that can turn into real-world evidence. We should be cautious with definitive conclusions based on observational data. Minor observed differences could be the result of unknown confounding factors [23]. Other initiatives on the linkage of administrative data are similar and, in addition, also link patient-centered health data such as patient-reported outcome measures (PROMS) and clinical laboratory measurements but involve small patient groups [24] or limited patient- and tumor characteristics [9].

Strengths

First, data are validated at the time of delivery from the hospitals with the clinicians. A lot of effort is put in validation of the algorithms that are used in the dashboards, for example in building Sankey diagrams for treatment sequences in specific patient populations. The second strength of the DICA Medicines program includes the use of existing data sources, thereby minimizing the extra registration burden for medical specialists. This

could also be used by others to minimize registration burden and to maximize the value of available RWD sources. Thirdly, the program consists of many participating hospitals with a widespread geographic location, resulting in many patients and a representation of the Dutch population. Another strength is the linkage of survival data to the other data sources. The database from the national health insurers is a valid source as healthcare insurance stops when a patient dies. The last strength is that the data are up-to-date and representative of the current situation. This is especially valuable in situations such as the COVID-19 pandemic, where systemic treatment of some patients with cancer was adjusted. Since the data are quarterly updated, it was possible to monitor the impact of COVID-19 in certain subgroups of patients in the dashboard. The DICA Medicines program led to various insights into medication use. Questions related to the effective use of (expensive) medicines can easily be answered using the dashboards in which users can select patient populations or treatments of interest.

Limitations and future perspectives

In the clinical registrations used for this study not all clinical data were available for all indications. The Dutch ColoRectal Audit only includes patients undergoing surgery, which leads to incomplete clinical data in metastasized patients with colorectal cancers. This was also the case for metastasized breast cancer patients. In this subpopulation of breast cancer patients, essential tumor information such as receptor status is lacking. In addition, we are unable to extract information about weight, response status, date of progression or toxicities from the declaration data. These are mostly data registered in unstructured text in the electronical medical records. However, our intention is to complement the clinical data of these patient groups with other techniques that do not lead to more registration burden such as text mining. Secondly, due to privacy regulations in the Netherlands [26], it is not allowed to follow-up patients when they are referred to other hospitals for treatment. The same unique patient may have gone for a second opinion to another hospital. This may have led to incomplete treatment information and double-included patients. Especially in university hospitals, where many patients are referred to, it is necessary to have the complete treatment information. Previous analyses on the entire lung cancer population showed this was the case in <5% of all patients in the Netherlands. In this study, there may be an overestimate in the number of patients, but not the number of prescriptions, as these are validated declarations made by the hospitals. Thirdly, more information on patient- and tumor characteristics are needed to allow for head-to-head comparisons of medicines. Registries should therefore include information on response status and detailed treatment-related toxicity within each line of treatment. At this moment, emergency room (ER) visits and hospital admissions are linked to the use of medication and presented in the dashboards. However, these are only surrogate outcomes and do not give insight in the exact response or toxicity. Adding more outcomes of systemic therapies to the quality registries will also be an opportunity for surgical quality registries to become

multidisciplinary where both surgeon and medical oncologist register specific patients' characteristics and outcomes. We are currently exploring text-mining opportunities to add toxicities and response status to the quality registries.

At this moment, hospitals use dashboards to benchmark their results to other hospitals and gain insights into the use of medication and patient population, as we showed in this study. The dashboards can in the future also be used for multiple other purposes and by different stakeholders. First, dashboards and RWD can serve as a communication tool between physicians and their patients. Based on specific patient- and tumor characteristics, clinical outcomes can help patients better understand their disease course and improve shared-decision making. Secondly, registration authorities can also benefit from data as presented in this study. Data on newly approved medicines used in clinical practice are available in financial pharmacy data and can be linked to population-based registries. Especially for post-approval measurements, this information is valuable in monitoring medicines' safety and effectiveness [27]. This can, in certain cases, eventually lead to the replacement of post-approval clinical studies, which will save time and costs. The European Medicines Agency and the Food and Drug Agency are increasingly interested in RWD for medicines evaluation [28,29]. Furthermore, health care insurers are interested in these data for reimbursement and effective use of expensive medication in the real-world setting [30].

In the future, accurate data from DBC's and financial information could automatically prefill quality registry items. The DICA quality registry items are now entered manually, which is time-consuming and prone to registration errors. Reusing these data sources will lower the registration burden, reduce missing data, and validate data. These data can be used to complete registries and reduce hospital differences. Furthermore, RWD can also be used in HTA decisions. This will be explored in the near future within EU programs [31]. However, other data sources, such as pathology databases, need to be linked to enrich the data. This additional data on histopathology and mutation status is essential as certain medication targets a specific mutation and can influence outcomes. To improve shared decision-making, data sources, including patient-reported outcome measurements, need to be linked to the existing data sources.

Conclusion

The DICA Medicines program has shown that it is possible to gather and link RWD sources about medicines. In addition, these data became available with minimal registration burden and effort for hospitals. This method of providing RWD can be used in other population-based registries. The DICA Medicines program provided participating centers

with benchmark information and provided tools to evaluate the effectiveness of expensive medicine in real world setting.

References

[1] Naci H, Davis C, Savović J, Higgins J, Sterne J, Gyawali B, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting European Medicines Agency approvals of cancer drugs, 2014-2016: cross-sectional analysis. Bmj. 2019;

[2] Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet. 2015;385(9977):1502-3.

[3] Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals without a randomised controlled study: Analysis of EMA and FDA approvals 1999-2014. BMJ Open. 2016;6(6).

[4] Booth CM, Eisenhauer EA. Progression-free survival: Meaningful or simply measurable? J Clin Oncol. 2012;30(10):1030–3.

[5] Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet. 2005;365:82–95.

[6] Cramer-Van Der Welle CM, Peters BJM, Schramel FMNH, Klungel OH, Groen HJM, Van De Garde EMW. Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer. Eur Respir J. 2018;52(6).

[7] van Zeijl MCT, Ismail RK, de Wreede LC, van den Eertwegh AJM, de Boer A, van Dartel M, et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. Int J Cancer. 2020;(February):1–10.

[8] Dutch Healthcare Authority (Dutch). Uitgaven aan dure geneesmiddelen stijgen naar 2,1 miljard. 2019. Available from: https://www.pw.nl/nieuws/2019/uitgave-dure-medicatie-stijgt-naar-20ac-2-1-miljard.

[9] van Herk-Sukel MPP, van de Poll-Franse L V., Lemmens VEPP, Vreugdenhil G, Pruijt JFM, Coebergh JWW, et al. New opportunities for drug outcomes research in cancer patients: The linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395–404.

[10] Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. Ann Surg. 2020;271(4):627–31.

[11] Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, Ten Berge MG, et al. The dutch surgical colorectal audit. Eur J Surg Oncol. 2013;39(10):1063–70.

[12] Ismail RK, Schramel FMNH, van Dartel M, Hilarius DL, de Boer A, Wouters MWJM, et al. The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients. Lung Cancer. 2020;149(July):68–77.

[13] van Bommel ACM, Spronk PER, Vrancken Peeters MJTFD, Jager A, Lobbes M, Maduro JH, et al. Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: The national NABON Breast Cancer Audit. J Surg Oncol. 2017;115(3):243–9.

[14] Spiegelhalter DJ. Funnel plots for comparing institutional performance. Stat Med. 2005;24(8):1185–202.

[15] Rakow T, Wright RJ, Spiegelhalter DJ, Bull C. The pros and cons of funnel plots as an aid to risk communication and patient decision making. Br J Psychol. 2015;106(2):327–48.
[16] Hoeijmakers F, Beck N, Wouters MWJM, Prins HA, Steup WH. National quality registries: how to improve the quality of data? J Thorac Dis. 2018;10(Suppl 29):S3490–9.
[17] van der Werf LR, Voeten SC, van Loe CMM, Karthaus EG, Wouters MWJM, Prins HA. Data verification of nationwide clinical quality registries. BJS Open. 2019;857–64.
[18] Dutch Healthcare Authority (NZa). NZA. Available from: https://www.nza.nl/english.
[19] Oostenbrink JB, Rutten FFH. Cost assessment and price setting of inpatient care in the Netherlands. The DBC case-mix system. Health Care Manag Sci. 2006;9(3):287–94.
[20] Vektis database (Dutch). 2021 [cited 2022 Mar 23]. Available from: https://www.vektis.nl/
[21] Wickham H, Averick M, Bryan J, Chang W, McGowan LD, Francois R, et al. Welcome to the {tidyverse}. J Open Source Softw. 2019;4(43):1686.
[22] Yoshida K, Bartel A. Tableone: Create "Table 1" to Describe Baseline Characteristics with or without Propensity Score Weights [Internet]. 2020. Available from: https://cran.r-project.org/package=tableone
[23] Kassambra, Alboukadel, Kosinski, Marcin, Biecek P. survminer: Drawing Survival Curves using "ggplot2" [Internet]. 2020. Available from: https://cran.r-project.org/package=survminer
[24] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence — What Is It and What Can It Tell Us? N Engl J Med. 2016;375(23):2293–7.
[25] Dhruva SS, Ross JS, Akar JG, Caldwell B, Childers K, Chow W, et al. Aggregating multiple real-world data sources using a patient-centered health-data-sharing platform. NPJ Digit Med. 2020;3(1):60.
[26] Justice DG, Working party 136: Directorate C (Civil Justice Rights and Citizenship) of the European Commission Directorate General Justice, Article 29 Working Party, WP29. ARTICLE 29 DATA PROTECTION WORKING PARTY Opinion 4/2007 on the concept of personal data. Office. 2007;(Lx):1–19.
[27] Ismail RK, Sikkes NO, Wouters MWJM, Hilarius DL, Pasmooij AMG, van den Eertwegh AJM, et al. Postapproval trials versus patient registries: Comparability of advanced melanoma patients with brain metastases. Melanoma Res. 2021;31(1):58-66.
[28] European Medicines Agency (EMA). Initiative for patient registries. 2015;44(September).
[29] U.S. Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. FDA Guid. 2017;1–24.
[30] Roberts MH, Ferguson GT. Real-World Evidence: Bridging Gaps in Evidence to Guide Payer Decisions. PharmacoEconomics–Open. 2021;5(1):3–11.
[31] European Commission. New methods for the effective use of real-world data and/or synthetic data in regulatory decision-making and/or in health technology assessment. Available from: https://www.ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2022-tool-11-02.

Contribution of R.K. Ismail: substantial contributions to the acquisition of the hospitals to participate in the program. Substantial contribution to conceptualization of the work, methodology, interpretation, writing and revising of the manuscript.

CHAPTER 3

The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients.

Lung Cancer. 2020 Nov 01;149:68-77.

R.K. Ismail, F.M.N.H. Schramel, M. van Dartel, D.L. Hilarius, A. de Boer, M.W.J. M. Wouters, H.J.M. Smit, *on behalf of the Dutch Lung Cancer Audit Scientific Committee.*

Abstract

Background: This study describes the initiation of the Dutch Lung Cancer Audit for Lung Oncology (DLCA-L) and reports the first results of three years of clinical auditing.

Methods: The initiation, dataset, and data quality of the DLCA-L are described. For the analyses, all patients registered from 2017 to 2019 were included. Descriptive statistics were used to assess the first outcomes of the DLCA-L, including results from quality indicators, patient- and tumor characteristics, and the real-world use of immunotherapy.

Results: The DLCA-L was initiated after the surgery and radiotherapy audit for lung cancer. In total, 33.788 NSCLC patients and 4.293 SCLC patients were registered in the DLCA-L from 2017 to 2019. Seventy-three (97%) Dutch hospitals participated in the DLCA-L in 2019. The registry became nation-wide in 2020. The data quality improved over the years, with complete cases in 90% of the NSCLC patients. In total, 15 quality indicators were established based on DLCA-L data to improve processes and clinical outcomes. An example of these quality indicators was brain imaging at diagnosis of stage III NSCLC patients, which increased from 80% in 2017 to 90% in 2019 and hospital variation was reduced. The DLCA-L provided data on immunotherapy use in stage IV NSCLC (n=4.415) patients. These patients had a median age of 67 years and 11% of the patients had an ECOG PS ≥2. The number of patients treated with immunotherapy in different hospitals varied between two to 163 patients per hospital.

Conclusion: The DLCA-L has become a valuable and complete data source with national coverage in 2020. A high number of registered patients and limited missing data resulted in better insights into hospital processes and outcomes of lung cancer care. Quality indicators were, with success, used to establish improvements and minimize hospital variation. The DLCA-L also provides hospitals real-world information on the use of (systemic) therapies.

Introduction

Clinical auditing proved to be a valuable process for the improvement of medical care and patient outcomes [1]. The use of quality registries or clinical audits has been effective in the last decade in evaluating and improving medical care by minimizing undesired practice variation and improving patient outcomes. National audits for lung cancer patients included mostly surgical treatment of lung cancer [2–4].

Nationwide lung cancer registries, such as the National Lung Cancer Audit (NLCA), showed in 2017 practice variation in the number of stage III and IV non-small cell lung cancer (NSCLC) patients treated with anti-cancer systemic therapy and a difference in 1-year survival across organizations [5]. Registries provide data on hospital variation and improvements of care but are also valuable in generating real-world data, leading to a better understanding of daily clinical practice [6].

Registries are also valuable in the evaluation of medicines after marketing authorization by measuring real-world effectiveness and long-term safety. Immunotherapy treatment, for example, gained interest in stage III and stage IV NSCLC patients when trials showed significant improvements in progression-free survival (PFS) and overall survival (OS) [7–10]. Real-world data research in immunotherapy treated NSCLC patients showed an efficacy-effectiveness gap of 25 %, resulting in poorer outcomes for real-world treated patients [11]. Registries can provide real-world effectiveness data on these medicines on a nation-wide level. Immunotherapy treatment results from a real-world setting were provided by the National Immunotherapy Registry, including lung cancer patients from 2015 to 2017 in the Netherlands [12].

In 2012, the Dutch Lung Cancer Audit for Surgical treatment (DLCA-S) was initiated, which became a mandatory registry in 2015, leading to a nationwide population-based registry in the Netherlands [13]. The DLCA-S does not include radiotherapy and systemic treatment of lung cancer patients.

The Dutch Lung Cancer Audit for Lung Oncology (DLCA-L) was set up in 2015 to provide insights into the quality of care of lung cancer patients treated with systemic therapy by focusing on diagnostics, monitoring of in-hospital times and outcomes of systemic therapy. The professional association of chest physicians (NVALT) made participation in the DLCA-L mandatory. The DLCA-L provides feedback information to hospitals to stimulate the improvement of clinical care for lung cancer patients. Registered data of the hospitals are analyzed, and benchmarked indicator results on the quality of their care processes and patient outcomes are fed back in secured web-based dashboards to the hospitals [14].

This study describes the initiation of the DLCA-L and reports the first results of three years of clinical auditing.

Methods

Organizational structure

In 2015, the DLCA-L was initiated by the professional association of chest physicians (NVALT). The registry is facilitated by the Dutch Institute for Clinical Auditing (DICA), a non-profit organization, which is structurally funded by the umbrella organization of healthcare insurers in the Netherlands (ZN) [15]. DICA facilitates 22 nation-wide quality registries [16]. The DLCA-L is part of the multidisciplinary Dutch Lung Cancer Audit (DLCA), which consists of three clinical audits: DLCA-Surgery (DLCA-S), DLCA-Radiotherapy (DLCA-R), and the sub-registry for the diagnosis and systemic treatment of lung cancer (DLCA-L). A clinical audit board, consisting of medical specialists mandated by their professional association, leads the DLCA. Every sub-registry has a scientific committee with experts from the field. The scientific committee of the DLCA-L, consisting of pulmonologists, gathers four times a year to discuss results from the DLCA-L, develop new quality indicators, and improve the dataset. The three sub-registries of the DLCA are not merged yet due to privacy legislation. The separate data sources will be linked in the future to improve data on the total treatment of lung cancer patients. The sub-registries work together in projects, developing quality indicators and improving the registries.

Database

Data collection in the DLCA-L started in January 2015, including all patients diagnosed with (clinically suspected) primary lung carcinoma. In the registry, the suspected indication is further specified with data on pathological confirmation when present. Carcinoma in situ and invasive tumors are included. Premalignant disorders are excluded. Patients under 18 are not registered in the DLCA-L. The database consists of patient identifiers, the episode, and the follow-up. In the episode, detailed clinical information on baseline patient- and tumor characteristics, diagnostics, and first-line treatment are registered. Toxicity is scored using the CTCAE criteria. The options for toxicity after treatment (different modules for chemotherapy, immunotherapy and targeted therapy) are: "No toxicity or toxicity with grade <3'' or "Toxicity with grade ≥3. Another important variable in the episode section is the treatment intention of lung cancer patients. Curative treatment intention is defined as the treatment of patients with the intent to cure them instead of reducing symptoms. Every non-curative treatment defines palliative treatment intention. The mandatory 1-year follow-up section consists of information on treatment response, follow-up treatments, and the date and cause of death. These data can be used to calculate 1-year PFS and OS. The database contains 153 variables, of which 44% is mandatory and should be registered

by all hospitals to analyze the data for quality indicators (**supplement 1**). The total list of variables used in the DLCA-L is freely accessible at the DICA website [17].

In 2020, the DLCA-L dataset was expanded with variables from the NVALT "National Immunotherapy Registry" [12]. This registry was initially a separate nation-wide registry focusing on immunotherapy treatment, including PD-L1 expression and the different lines of therapy patients received. Registration also included information on safety and hospital admission rate and duration [12]. The NVALT registry was merged with the DLCA-L to reduce the registration burden as a result of multiple lung cancer registries. A summary of the DLCA-L dataset is shown in **supplement 1**.

In compliance with Dutch regulations, no patient informed consent or approval of the medical ethical committee was necessary for registration in the DLCA-L. Data from the hospitals is processed by Medical Research Data Management (MRDM). Privacy issues and informed consent of patients is established in the contracts between the hospitals and MRDM. For the initiation of the DLCA-L, no other privacy issues were necessary other than already consisting contracts between DICA and MRDM involving the processes with anonymized data.

Data quality and validation

The data quality of the DLCA-L is assured by using precise definitions for the variables in the registry, described in a manual for data managers. Data managers are often quality employees in hospitals and commonly trained and qualified to register quality registry data. The web-based data-collection environment also includes technical conditions and validations for specific data entry items to minimize unreliable data. Patient records with missing data of required variables are notified on a digital signal list and the record cannot be completed if mandatory data are missing. Involved medical specialists supervise entered data. Data validation is realized by independent external reviewers comparing registered DLCA-L data records with data in the electronic patient records of the hospital.

Quality indicators

Quality indicators are established by the scientific committee and external parties, such as ZN and the Dutch Health Care Institute (ZiN). Quality indicators are based on national quality standards and evidence-based guidelines. In the Netherlands, quality is assured by using the SONCOS (the Dutch Federation of Oncologic Societies) quality standards. Specific thresholds for quality indicators are therefore not mentioned by the DLCA-L. One of the requirements mentioned in SONCOS is participation in the DLCA-L. The SONCOS requirements are used in the DLCA-L to set up the registry and to develop new quality indicators, i.e., brain imaging in stage III NSCLC patients. Since 2015, DLCA-L data led to the development of 15 quality indicators. Quality indicator results lead to information on the

quality of care of individual hospitals, which are analyzed and discussed by the professional association. Hospitals receive their data compared to the benchmark, visualized in funnel plots, to improve processes in hospitals. Hospital specific results of a selected set of indicators are shared with stakeholders and are publicly available.

Statistical analysis

The first outcomes of the DLCA-L were assessed using descriptive statistics. Outcomes included patient-, tumor-, and treatment characteristics of NSCLC and small-cell lung cancer (SCLC) patients, diagnosed and registered from 2017 to 2019. Descriptive statistics were also used to analyze complete cases and the use of immunotherapy in a real-world setting. Complete cases were defined as no missing data in all of the following essential variables in the registry: date of birth, gender, subgroup disease, date of the first hospital visit, Eastern Cooperative Oncology Group Performance Score (ECOG PS) and molecular diagnosis.

The results of the 15 quality indicators are presented for 2017 until 2019, including the variation (minimum and maximum outcomes) between hospitals. Quality indicator results are presented to the hospitals in funnel plots using 95% and 99% CI limits [18]. In a funnel plot, the observed rate of a specific indicator is plotted against the volume of the hospital. The 95% and 99% CI limits change in relation to the number of patients per hospital [18,19]. Variation in brain imaging among individual hospitals was visualized in a funnel plot as an example.

Data handling and statistical analyses were performed using the R software system for statistical computing (version 3.6.1.; packages tidyr, lubridate, tableone, ggplot2, ggthemes, dplyr, ggpubr, RColorBrewer).

Results

Patient population

The total number of diagnosed lung cancer patients in three years [2017–2019] registered in the DLCA-L consisted of 33.788 NSCLC patients and 4.293 SCLC patients. The number of hospitals that participated in the DLCA-L has changed over the years, from 39 [2015], 73 [2016], 74 [2017], 75 [2018] to 73 hospitals in 2019. Of all Dutch hospitals treating lung cancer, 97% participated in the DLCA-L in 2019. The number of diagnosed lung cancer patients per hospital varied between three and 496 patients, with an average of 181 patients per hospital (**supplement 2**). All Dutch hospitals are participating in the DLCA-L in 2020.

The total number of NSCLC patients registered in the DLCA-L has increased from 10.061 patients in 2017, 11.904 patients in 2018, to 11.823 patients in 2019. The number of

registered SCLC patients stayed constant over time. The Netherlands Cancer Registry has reported an incidence of over 13.000 lung cancer patients a year since 2017 [20]. In **supplement 3**, the proportions of patients in which the registration is complete (complete cases) are shown. Complete cases for NSCLC patients were 88% [2017], 87% [2018] and 90% [2019]. The proportion of complete cases in SCLC patients in 2019 was 89% (**supplement 3**).

Patient- and treatment characteristics of registered NSCLC and SCLC patients are shown in **table 1**. The proportion of not available or unknown information of the mandatory variables was ≤10%. In the NSCLC patient group, 56% was male and 44% female, the median age was 70 years, and 31% of the patients were older than 75 years. Of these real-world patients, 22% had an ECOG PS ≥2.

Quality indicators

The 15 quality indicators are described in **table 2**, with average outcome and variation between hospitals from 2017 to 2019. The definitions of the quality indicators can be found in **supplement 4**. The quality indicators showed improvements in registration completeness and diagnostic processes over the years. Data completeness improved from 88% [2017] to 93% [2019]. An increase of 89% [2017] to 93% [2019] in the performance of molecular diagnostics in stage IV adenocarcinoma patients was reached. Toxicity after chemotherapy treatment in stage IV NSCLC patients <70 years showed a decrease of 19% [2017] to 12% [2019]. An example of how hospitals receive their data compared to the benchmark in a funnel plot is shown in **figure 1**. This funnel plot shows the variation in brain imaging in stage III NSCLC patients among hospitals, which varied between 25-100% in 2017 (**figure 1a**). Hospital variation was reduced in 2019 (56-100%), and the overall performance of all hospitals increased from 80 % in 2017 to 90 % in 2019 (**figure 1b**).

First-line treatment choices

Figure 2 shows first-line treatment choices of all NSCLC patients treated with active tumor treatment (with curative or palliative intention) in the Netherlands between 2017 and 2019**.** Registration of patients that receive best supportive care is not further specified. The most used treatments in stage 0-II NSCLC patients were radiotherapy and surgery. This did not differ over the years 2017 to 2019. Radiotherapy treatment was used in 42% of the patients in 2017, 44% in 2018, and 43% in 2019. Of all stage 0-II NSCLC patients, 42% received surgery in 2017, 43% in 2018, and 46% in 2019. In stage III NSCLC patients, 39% received chemo-radiotherapy in 2019. In stage IV patients, the increase in immunotherapy led to a decrease in chemotherapy treatment. The number of unknown treatments has drastically decreased to 0% between 2017 and 2019.

Table 1: Patient- and tumor characteristics of all NSCLC and SCLC patients registered in the DLCA-L from 2017 to 2019.

		NSCLC	SCLC
n		33.788	4.293
Year of first hospital visit; n(%)	2017	10.061 (30)	1.401 (33)
	2018	11.904 (35)	1.472 (34)
	2019	11.823 (35)	1.420 (33)
Age; median (range)		70 (18, 101)	69 (24, 117)
Age; n(%)	<65	10.439 (31)	1.419 (33)
	65-75	12.839 (38)	1.771 (41)
	>75	10.510 (31)	1.103 (26)
Gender; n(%)	Male	18.741 (56)	2.124 (50)
	Female	15.018 (44)	2.165 (50)
	Unknown	29 (0)	4 (0)
Stage; n(%)	0	306 (1)	17 (0)
	I	6793 (20)	102 (2)
	II	2801 (8)	119 (3)
	III	6.524 (19)	989 (23)
	IV	15.156 (45)	2.850 (66)
	Unknown	2.208 (7)	216 (5)
ECOG PS; n(%)	≤1	23.024 (68)	2.741 (64)
	≥2	7.516 (22)	1.143 (27)
	Unknown	3.248 (10)	409 (10)
Diagnosis; n(%)	Cytology	6.670 (20)	1.210 (28)
	Histology	14.591 (43)	2.133 (50)
	Only imaging	4.550 (14)	91 (2)
	Resection- histology	994 (3)	15 (0)
	Unknown	6.983 (21)	844 (20)
Treatment intention*; n(%)	Curative	14.861 (44)	1.045 (25)
	Palliative	17.321 (51)	3.100 (72)
	Unknown	1.606 (5)	148 (3)

ECOG PS = Eastern Cooperative Oncology Group Performance Score
NSCLC = Non-small-cell lung cancer
SCLC = Small-cell lung cancer
*Curative treatment intention refers to the treatment of patients with the intent to cure them instead of reducing symptoms. Every non-curative treatment defines palliative treatment intention.

Table 2: Structure-, process, and outcome quality indicators of the DLCA-L

Indicator type and number	Description	2017	2018	2019
Structure				
1.	Complete registration of registered lung cancer patients in the DLCA-L; %	88 (0-100)	90 (29-100)	93 (60-100)
2.	Newly diagnosed primary lung cancer patients registered in the DLCA-L; n	10.545	12.504	12.562
3.	Hospitals treating more than 50 lung cancer patients per year; %	93	93	97
Process				
4.	Stage III NSCLC patients undergoing brain imaging before the start of systemic therapy with curative intention; %	82 (25-100)	83 (25-100)	90 (56-100)
5.	Stage IV adenocarcinoma lung cancer patients undergoing molecular diagnostics before the start of systemic therapy with curative intention; %	89 (50-100)	92 (59-100)	93 (71-100)
6.	Patients discussed in multidisciplinary consultation before treatment; %			
	a. Stage I-III curative treatment	98 (82-100)	99 (67-100)	99 (80-100)
	b. Palliative treatment	98 (73-100)	98 (62-100)	98 (66-100)
7.	Duration of diagnostic trajectory; %			
	a. <21 days without invasive mediastinal diagnostics	62 (30-100)	60 (0-100)	62 (0-100)
	b. <21 with EUS/EBUS, but without mediastinoscopy	44 (0-100)	44 (0-80)	46 (0-100)
	c. <35 days with mediastinoscopy	54 (0-100)	53 (0-100)	59 (0-100)
8.	Diagnostics of stage III NSCLC patients with EUS/EBUS; %	59 (7-100)	56 (0-100)	61 (0-100)
9.	Stage III NSCLC patients treated with adjuvant chemotherapy; %	12 (0-67)	15 (0-100)	15 (0-100)
10.	First-line systemic treatment of stage IV NSCLC patients without curative intention; %			
	a. Chemotherapy	31 (0-85)	25 (0-47)	30 (0-60)
	b. Immunotherapy	8 (0-46)	18 (0-61)	33 (0-67)
	c. Targeted therapy	6 (0-39)	8 (0-32)	10 (0-100)
11.	First-line systemic treatment of stage IV SCLC patients without curative intention; %			
	a. Chemotherapy	65 (0-100)	64 (0-100)	68 (0-100)
	b. Immunotherapy	0 (0-13)	2 (0-29)	5 (0-74)

Table 2 continued

Indicator type and number	Description	2017	2018	2019
12.	Use of immunotherapy in elderly patients with stage IV NSCLC disease with no curative intention; %			
	a. <70 years	8 (0-43)	18 (0-59)	35 (0-73)
	b. >70 years	5 (0-49)	14 (0-62)	23 (0-59)
13.	Use of chemo-immunotherapy in elderly patients with stage IV NSCLC disease with no curative intention; %			
	a. <70 years	1 (0-10)	4 (0-27)	23 (0-64)
	b. >70 years	0 (0-11)	2 (0-15)	13 (0-40)
Outcome				
14.	Toxicity after treatment with systemic therapy in stage IV NSCLC young (<70 years) patients; %			
	a. Chemotherapy	19 (0-100)	13 (0-60)	12 (0-100)
	b. Immunotherapy	7 (0-50)	5 (0-50)	7 (0-73)
	c. Targeted therapy	7 (0-100)	8 (0-100)	8 (0-100)
	d. Chemo radiotherapy	14 (0-100)	13 (0-100)	5 (0-100)
15.	Toxicity after treatment with systemic therapy in stage IV NSCLC elderly (>70 years) patients; %			
	a. Chemotherapy	19 (0-56)	18 (0-100)	11 (0-55)
	b. Immunotherapy	6 (0-100)	7 (0-100)	6 (0-56)
	c. Targeted therapy	11 (0-100)	12 (0-100)	10 (0-100)
	d. Chemo radiotherapy	27 (0-100)	8 (0-100)	2 (0-33)

The outcomes of the quality indicators are presented on a nation-wide level with an average of the outcomes of all hospitals and the minimum and maximum outcome of all hospitals from 2017-2019. More information on the definitions of the quality indicators can be found in supplement 4.

Increase in immunotherapy use

Since 2016, multiple immunotherapies became available in the Netherlands (nivolumab in March 2016, pembrolizumab in July 2017, durvalumab in June 2018, and atezolizumab in September 2019) after receiving marketing authorization by the European Medicines Agency (EMA) for treatment of locally advanced and metastatic NSCLC. The percentage of stage III and stage IV NSCLC patients treated with immunotherapy or immune-chemotherapy increased over the years. Immunotherapy treatment consisted of 15% of all treatments in 2017, followed by 33% in 2018 and 57% in 2019. Stage III NSCLC patients received relatively less immunotherapy treatment, 3.5% in 2017, 13% in 2018, and 25% in 2019. Durvalumab has been indicated for stage III NSCLC patients who have been treated with previous concurrent chemoradiotherapy.

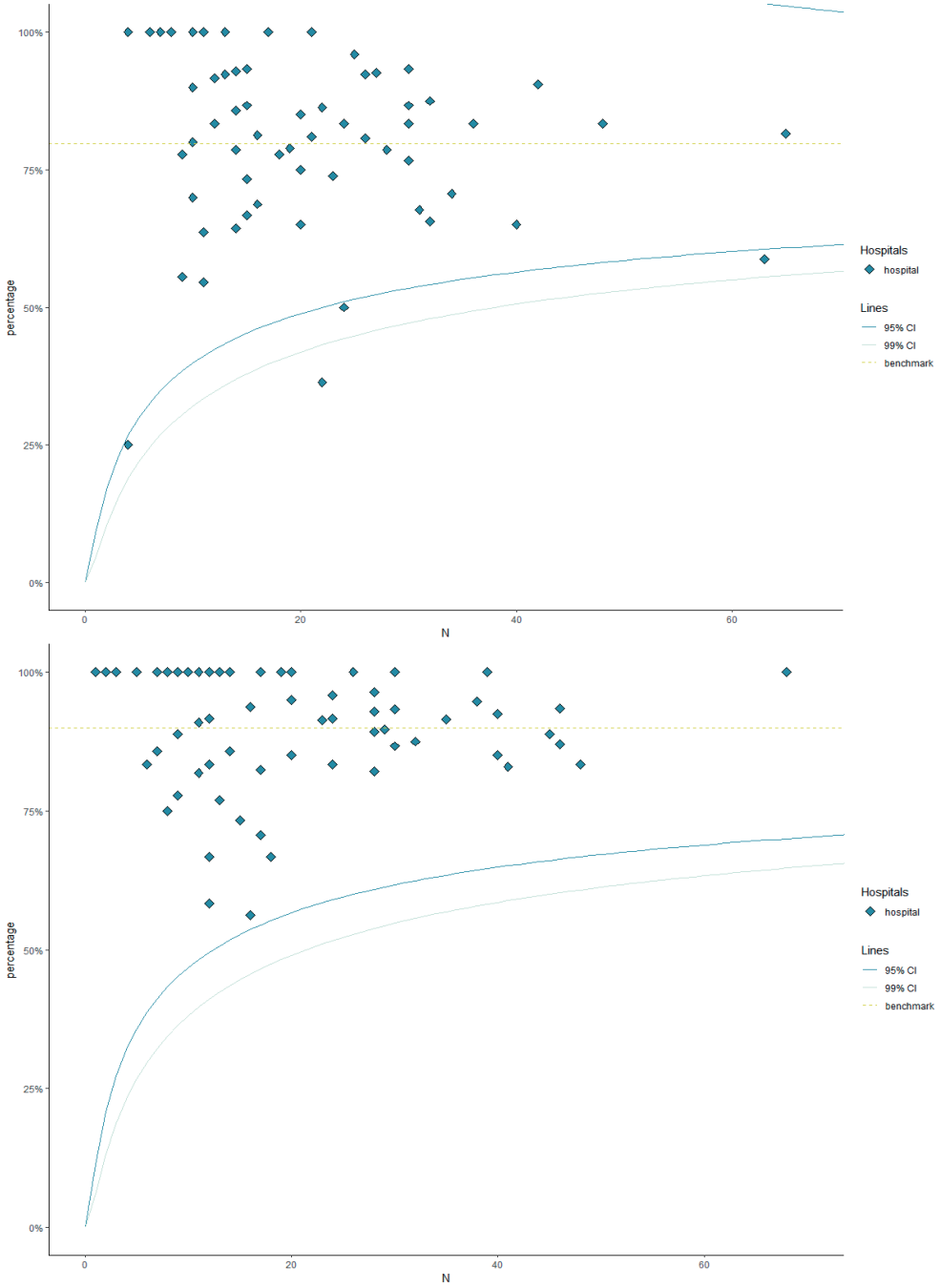


Figure 1: Percentage of patients with stage III NSCLC registered in the DLCA-L undergoing brain imaging with PET or CT before the start of therapy with curative intention in 2017 (upper graph, 1a) and 2019 (lower graph, 1b). Every symbol is a hospital in the Netherlands. The x-axis shows the number of patients with stage III NSCLC receiving therapy per hospital.

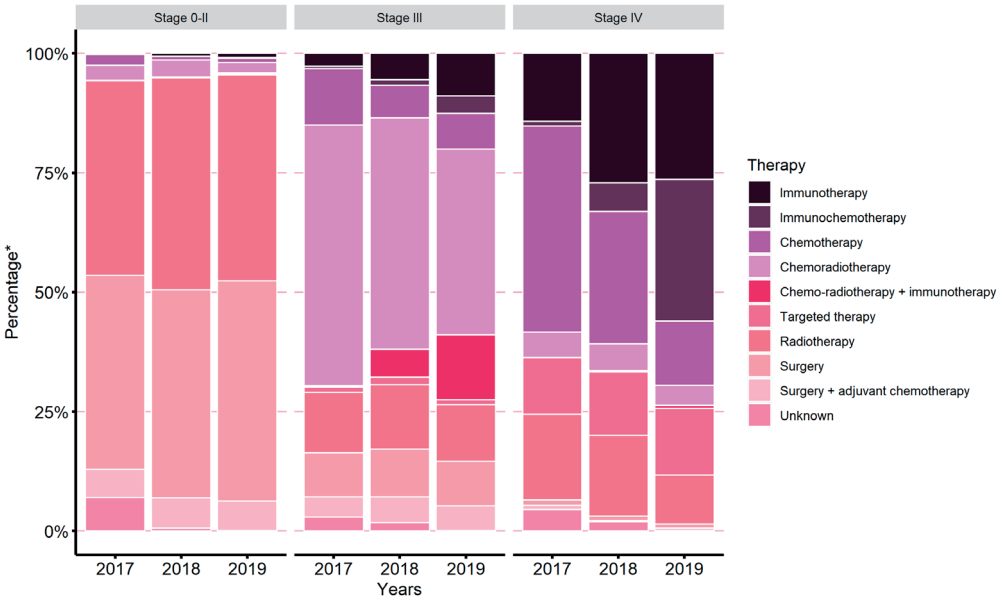


Figure 2: First-line treatment (combinations) of patients with NSCLC treated with active tumor treatment (surgery and radiotherapy with curative intention or/and (palliative) chemotherapy, immunotherapy, or targeted therapy) from 2017 to 2019.

Patient- and tumor characteristics of immunotherapy treated patients (n=4,415) from 2017 to 2019 are shown in **table 3.** Although phase-III trials included relatively young and fit patients, in real-world practice, the median age was 67 years, 17% was older than 75 years, and 11% of the patients had an ECOG PS of ≥2. In 2019, 75% of the patients underwent molecular diagnostics, including PD-L1 expression and mutation analyses (KRAS/EGFR/ALK/EML-4-ALK) (**table 3**).

Immunotherapy use in elderly (75-80 years) was 36% and similar to the use in patients of 70-75 years, which was 38%. Thirty percent of the patients older than 80 years (n=689) were treated with immunotherapy. Of all patients >80 years, 23% had an ECOG PS ≥2, compared to 17% in patients aged 70-75 years. The percentage of ECOG PS ≥2 increased with increasing age. The use of immunotherapy among stage IV NSCLC patients with different age categories is shown in **supplement 5**.

Immunotherapy treatment was not immediately available in all hospitals in the Netherlands. In the early years, patients were referred to specialized hospitals to receive immunotherapy treatment. In 2017, 60 hospitals treated patients with immunotherapy, but this number of hospitals increased over the years to 72 hospitals in 2019. In 2017, only 5 of 60 hospitals

Table 3: Patient- and tumor characteristics of first-line immunotherapy treated patients

		2017	2018	2019
Patients; n		486	1.375	2.554
Age; median (range)		67 (31, 88)	66 (24, 117)	67 (24, 90)
Age; n(%)	<65	205 (42)	607 (44)	1.080 (42)
	65-75	202 (42)	526 (38)	1.034 (41)
	>75	79 (16)	242 (18)	440 (17)
Gender; n (%)	Male	257 (53)	725 (53)	1.429 (56)
	Female	227 (47)	650 (47)	1.123 (44)
	Unknown	2 (0)	0	2 (0)
Subgroup; n(%)	NSCLC	479 (99)	1.352 (98)	2.490 (98)
	SCLC	7 (1)	23 (2)	64 (2)
Stage; n(%)	0-II	7 (1)	22 (2)	40 (2)
	III	54 (11)	228 (17)	459 (18)
	IV	362 (75)	1.065 (78)	1.962 (77)
	Unknown	63 (13)	60 (4)	93 (4)
ECOG PS; n(%)	<2	388 (80)	1.125 (82)	2.149 (84)
	≥2	67 (14)	147 (11)	276 (11)
	Unknown	31 (6)	103 (8)	129 (5)
Molecular diagnostics; n(%)	No	91 (19)	256 (19)	543 (21)
	Yes	362 (74)	1.051 (76)	1.925 (75)
	Yes, but not successful	5 (1)	9 (1)	26 (1)
	Unknown	28 (6)	59 (4)	60 (2)
Treatment intention; n(%)	Curative intention	94 (19)	242 (18)	463 (18)
	Palliative	326 (67)	1.071 (78)	2.061 (81)
	Unknown	66 (14)	62 (5)	30 (1)

ECOG PS = Eastern Cooperative Oncology Group Performance Score
NSCLC = Non-small-cell lung cancer
SCLC = Small-cell lung cancer

treated more than 20 patients with immunotherapy. In 2019 the number of patients treated with immunotherapy varied between hospitals from 2 patients to 163 patients (**figure 3**).

In total, three dynamic web-based dashboards have been developed for the DLCA-L. The quality indicators are presented in counts and funnel plots in Codman Indicators. The patient population and the outcomes and trends are presented in Codman Exploration, in which filters can be used to select specific patient-, tumor- and treatment characteristics. Outcomes and trends can be compared to the benchmark. The third dashboard is Codman

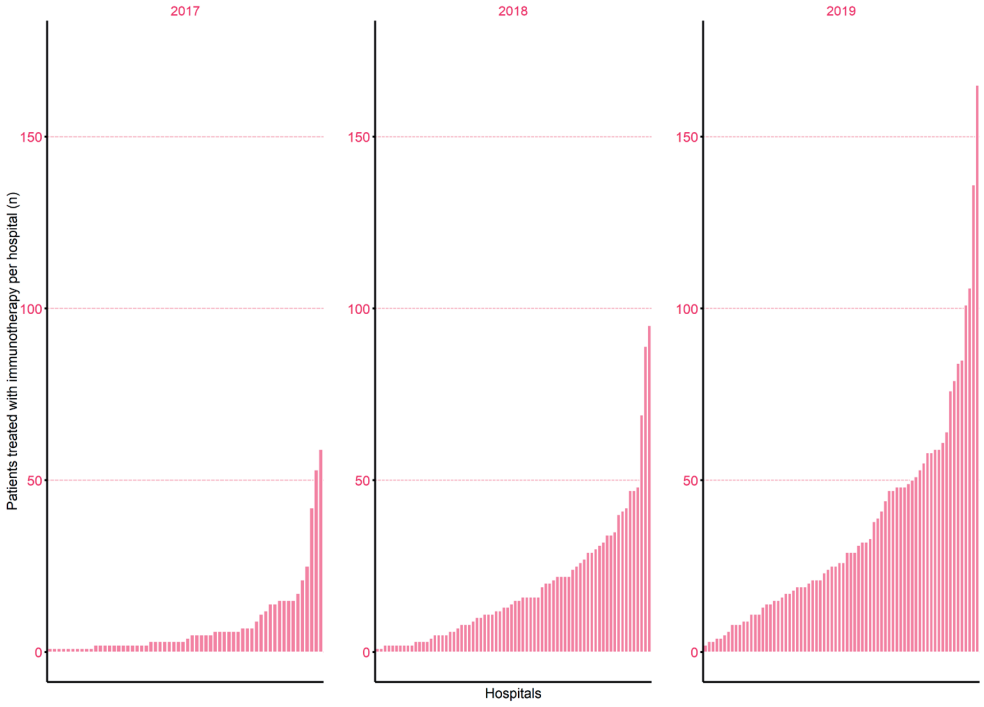


Figure 3: Number of patients with lung cancer treated with immunotherapy per hospital from 2017 to 2019 in the Netherlands.

Descriptives, which includes basic information on the patients registered in the own hospital compared to the benchmark.

Discussion

Within three years, the DLCA-L has become a valuable registry for clinical auditing of systemically treated lung cancer patients in the Netherlands. By improving data completeness, nationwide hospital participation, and the development of valuable quality indicators, the DLCA-L gave insight into the real-world treatment landscape of lung cancer patients and the variation in processes between hospitals.

Comparison with other audits

The completeness of the DLCA-L dataset improved over the years and is considered a reliable data source since 2017 since the number of registered lung cancer patients equals the lung cancer incidence of the Netherlands Cancer Registry (NCR) [20]. Compared to the NCR, the DLCA-L data consisted of 82 % [2017], 97 % [2018], and 96 % [2019] of the NCR published incidence. A small number of patients has not been registered in the DLCA-L

when treatment consisted only of surgery. However, these patients are registered in the surgical audit, DLCA-S. The relatively high numbers of registered patients are considered as a reliable, population-based representation of all lung cancer patients in the Netherlands. The number of hospitals participating in the DLCA-L decreased from 2018 to 2019, which can be explained by the fact that hospitals merged over time.

The Danish Lung Cancer Registry (DLCR) was established in 2000, and data completeness was considered sufficient from 2003 [21]. The DLCR also created quality indicators to improve lung cancer care, mainly focusing on the surgical treatment of lung cancer patients. A study from 2013 reported outcomes of the quality indicators from the DLCR, including a structural quality indicator measuring the waiting time after referral (<42 days). This quality indicator cannot be compared to the quality indicator of the DLCA-L, since the time from the first visit in the hospital to the first oncological treatment is measured in the Netherlands instead of the first referral [21]. The incidence of lung cancer in Denmark is significantly lower than in the Netherlands. The DLCR reported almost 39.000 registered patients from 2003 to 2012, while the DLCA-L includes over 43.000 records registered from 2017 to 2019. The population of Denmark is 5.7 million [2019] compared to 17.3 million [2019] in the Netherlands [22,23].

The incidence of lung cancer registered in the Swedish National Quality Registry for Lung Cancer (NLCR) is around 3000 patients a year, compared to 13.000 patients newly diagnosed lung cancer patients in the Netherlands. Patient coverage in the NLCR was 94 % in 2014, which is comparable with the DLCA-L [24]. As to our knowledge, outcomes of lung cancer quality indicators from the NLCR are not reported.

Compared to the NLCA of the UK, the DLCA-L is a starting audit. This results in different outcome measurements between the two audits. While data from the NLCA is sufficient to measure survival outcomes, the DLCA-L has been primarily focusing on data quality, data completeness and intern processes [25]. The NLCA reported 83% of advanced adenocarcinoma patients underwent molecular testing in 2017. The DLCA-L reported a score of 89%, but differences in definitions of these quality indicators made it impossible to compare outcomes. While the NLCA specifies molecular testing as testing of three biomarkers (EGFR, ALK and PD-L1), the definition of the DLCA-L quality indicator does not include the type of molecular testing [26]. Linkage of the DLCA-L to insurers data on date of death will lead to the establishment of survival data. The NLCA reported over 39.000 diagnosed patients in 2017, which is three times the lung cancer incidence numbers in the Netherlands. In examining the total amount of newly diagnosed Lung cancer patients it is important not only to include pathologically confirmed cases, but also unconfirmed cases to get a complete overview.

Outcomes

An important purpose of continuous feedback to medical specialists on the DLCA-L quality indicators is the improvement of in-hospital processes and guideline adherence. Quality indicators may show hospital variation, and therefore improvements in care can be made, resulting in fewer hospital outliers and more similar outcomes. Information on hospital outliers is notified to the professional association, which is in the lead to discuss these quality issues with their colleagues in the underperforming hospital to improve on certain processes or outcomes. In the DLCA-L, hospitals have been anonymized until recently, since it was a starting registration. Though professional associations of other quality registries facilitated by DICA, such as the Dutch Colorectal Audit (DCRA), receive hospital-specific data from the registry and discuss these with the participating hospitals to improve care on a local level. The Association of Surgeons in the Netherlands, for example, made participation in the DCRA mandatory and also agreed with their members in their General Assembly that hospital-specific data are available for the board and can be used in visitations to hospitals. Data are also used to evaluate the adherence to the quality standards established by the same societies. The scientific committee of the DLCA-L evaluates the improvements in quality indicators and adjust and improve these when needed.

A first example of outcomes from the DLCA-L showed that brain imaging at diagnosis in stage III NSCLC patients, who are candidates for combined modality treatment, was not standard care in specific hospitals, despite the recommendations in national and international guidelines [27,28]. The quality indicator presented in funnel plots was used to assess the variation between hospitals, taking into account random variability. In 2017, four hospitals were considered outliers. With the benchmark information, these hospitals got insights into their procedures, leading to an improvement in adherence to guidelines. The average percentage of patients undergoing brain imaging increased and the variation between hospitals decreased from 2017 to 2019. However, the outcomes of other quality indicators show that there is still room for improvement. The duration of the diagnostic trajectory, for example, is still not within the range agreed on in quality standards for each patient. The improvement in data completeness of the DLCA-L over the years results in more trustworthy outcomes for the quality indicators. Differences in the more recently established quality indicators [10-15] can also be partly explained by improvements in the registration of variables necessary for these indicators. Stimulating improvement is in line with the primary purpose of the DLCA-L: quality assurance of the diagnostics of lung cancer patients, the in-hospital processes, and the treatment with systemic therapies. Continuous feedback and the possibility to explore the data to individual patient level in the Codman dashboards, called after the founder of clinical auditing, made improvement cycles less time-consuming [16].

Outcomes from the DLCA-L can also be used to receive insights in real-world clinical practice. Treatment with immunotherapies gained significant interest in past years, and significantly higher use of immunotherapy was seen. Real-world NSCLC patient characteristics treated with immunotherapy differed from patients included in clinical studies. These trials excluded patients with ECOG PS ≥2, while 11% of the real-world patients had this performance score. The phase III trials researching immunotherapies (KEYNOTE-024, CheckMate-057, OAK, and PACIFIC) included in general more male patients, while this is almost equal for real-world treated patients [7–10]. Treated real-world patients were older than included trial patients. These differences between trial and real-world patients also occur in advanced melanoma patients. Clinical outcomes (OS, PFS) of treated real-world patients could, therefore, be poorer than in trials. The accurate and complete registration of survival in the DLCA-L has been one of the main goals for improvement and will be available in the near future.

The NVALT registration showed that the use of nivolumab in the Netherlands was according to the trial inclusion criteria and that real-world outcomes were similar to the studies [12]. In the years after, a broader patient population was treated with nivolumab. These data from the DLCA-L will be used to investigate differences in real-world and study patients and the impact on clinical outcomes. This evidence will be important for the efficient use of expensive treatments.

Real-world data outcomes from registries can also be used by regulators and health technology assessment organizations. Post-approval registry data could be used to gain information on real-world (long-term) safety and effectiveness. Furthermore, detailed information on molecular analyses, mutational burden, and outcomes of specific patient populations, excluded from phase-III trials can lead to improved insights in real-world effectiveness of medicines. These data are presently collected in the DLCA-L.

Limitations

A limitation of the present study and the first outcomes of the DLCA-L is that patients are registered as new patients when they are referred to other hospitals. Due to privacy regulations, the unique citizen service number of each individual cannot be shared with external parties other than the hospital. Therefore, the number of lung cancer patients can be overestimated. However, this does not affect the quality indicators since data of individual hospitals are shown for a specific part of the therapy or diagnosis. Double registration of patients affects the total number of patients, but it does not affect the number of patients treated with immunotherapy. Additional analyses of double registered patients showed <5% of the patients are registered more than once in the DLCA-L. This number is relatively low since all hospitals in the Netherlands, including peripheral hospitals, treat patients with lung cancer. Patients are referred in case of second opinions, second primary tumors, or for immunotherapy (trial) treatments in specialized centers.

A second limitation of quality registries, in general, is the administrative registration burden associated with (manual) data collection. The database of the DLCA-L is extensive and very detailed since multiple aspects of lung cancer care are involved. Detailed information is necessary to correct (hospital) outcomes for case-mix. Future registration burden will be minimalized by automatic data retrieval and source linkage.

The third limitation of the DLCA-L might be the accuracy of the data. Real-world data are used, including patients treated in an uncontrolled setting. Examples of possible registration bias are reported ECOG PS or progression, which may be subjective in real-world practice. In clinical trials, more standardized and uniform criteria may have been used. Data registered in the DLCA-L derives from electronic patient files, which could include missing data or registered data, could incorrectly be interpreted and registered. Therefore, multiple measures are taken to improve the data quality, such as the internal (by medical specialists) and external (by independent reviewers) data verification, the use of mandatory variables, and the use of validations and errors in the web-based registry. Data managers have been trained over the years. Interpretation mistakes are reduced with the use of manuals and direct contact with the clinical audit managers. The percentage of complete cases is over 95% with limited missing data in key variables in the dataset.

Future perspectives

Automated data retrieval from other data sources into the registry will be accomplished, leading to a reduced registration burden. The linkage of multiple existing data sources, such as administrative data of hospital pharmacies on expensive medicines, mortality information from national insurances, and filled electronic patient records in hospitals, will lead to more extensive and accurate information. National insurance information on the date of death of patients will also reduce the need for long follow-up times of patients and, therefore, reduce the registration burden. The linkage of the sub-registries of the DLCA will also be valuable in the future, to gain insights on the complete lung cancer care of patients.

With increased treatment options and improved survival of stage IV NSCLC patients, quality of life becomes more important. Data collection on patient-reported outcomes measures (PROMs) can improve well-informed patient choices and shared decision making. Other DICA registries already have linked information of PROMs to the clinical data of the registry. Patients are requested to fill in the PROMs in a web-based environment at multiple time points in the treatment. This linkage could also be possible for the DLCA-L, using the questionnaires chosen by the International Consortium for Healthcare Outcomes Measurement (ICHOM) [29]. Individual participating hospitals are already using PROMs in daily clinical care, but these data are not yet linked to the clinical data from the DLCA-L. Other lung cancer registries, such as the Danish and Swedish registries, have included PROMs to measure the quality of life [3,24].

The measures taken to improve data quality stimulate the initiation of outcome quality indicators. The current indicators are mainly process- and structure indicators, but with the improving data quality, outcome indicators such as 1-year survival will be established. Outcome information is displayed in dynamic dashboards with filter options on patient-, tumor-, and treatment characteristics. Hospitals can get insights into specific patient populations and the treatments used in the hospital versus the benchmark (all other hospitals in the Netherlands). These dashboards also provide information on outcome trends, which makes it possible to visualize improvements over time.

Since the initiation of the DLCA-L in 2015, the registry has become a valuable and complete data source with national coverage in 2020. A high number of registered patients and limited missing data resulted in better insights into hospital processes and outcomes of lung cancer care. Quality indicators were, with success, used to establish improvements and minimize hospital variation. The DLCA-L also provides hospitals real-world information on the use of (systemic) therapies. These data will eventually lead to improved insights into real-world practice and outcomes to further improve lung cancer care in the Netherlands.

References

[1] N.J. Van Leersum, H.S. Snijders, D. Henneman, N.E. Kolfschoten, G.A. Gooiker, M.G. Ten Berge, E.H. Eddes, M.W.J.M. Wouters, R.A.E.M. Tollenaar, The dutch surgical colorectal audit, Eur. J. Surg. Oncol. 39 (2013) 1063–1070. https://doi.org/10.1016/j.ejso.2013.05.008.

[2] A.L. Rich, L.J. Tata, R.A. Stanley, C.M. Free, M.D. Peake, D.R. Baldwin, R.B. Hubbard, Lung cancer in England: Information from the National Lung Cancer Audit (LUCADA), Lung Cancer. 72 (2011) 16–22. https://doi.org/10.1016/j.lungcan.2010.07.002.

[3] E. Jakobsen, T.R. Rasmussen, The Danish lung cancer registry, Clin. Epidemiol. 8 (2016) 537–541. https://doi.org/10.2147/CLEP.S99458.

[4] P.E. Falcoz, A. Brunelli, The European general thoracic surgery database project, J. Thorac. Dis. 6 (2014). https://doi.org/10.3978/j.issn.2072-1439.2014.04.20.

[5] The Royal College of Physicians, Improving care for lung cancer patients : a collaborative approach Improvement stories from lung cancer teams Improving care for lung cancer patients : a collaborative approach, (2012).

[6] M.C.T. van Zeijl, R.K. Ismail, L.C. de Wreede, A.J.M. van den Eertwegh, A. de Boer, M. van Dartel, D.L. Hilarius, M.J.B. Aarts, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, G.A.P. Hospers, E. Kapiteijn, D. Piersma, R.S. van Rijn, K.P.M. Suijkerbuijk, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, J.B.A.G. Haanen, M.W.J.M. Wouters, Real-world outcomes of advanced melanoma patients not represented in phase III trials, Int. J. Cancer. (2020) 1–10. https://doi.org/10.1002/ijc.33162.

[7] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crina, G.R. Blumenschein, S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, J.R. Brahmer, Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, N. Engl. J. Med. 373 (2015) 1627–1639. https://doi.org/10.1056/NEJMoa1507643.

[8] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, R. Hui, T. Csöszi, A. Fülöp, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, M.A. Leiby, G.M. Lubiniecki, Y. Shentu, R. Rangwala, J.R. Brahmer, Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer, N. Engl. J. Med. 375 (2016) 1823–1833. https://doi.org/10.1056/NEJMoa1606774.

[9] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. De Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. De Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, M. Özgüroğlu, Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer, N. Engl. J. Med. 377 (2017) 1919–1929. https://doi.org/10.1056/NEJMoa1709937.

[10] A. Rittmeyer, F. Barlesi, D. Waterkamp, K. Park, F. Ciardiello, J. von Pawel, S.M. Gadgeel, T. Hida, D.M. Kowalski, M.C. Dols, D.L. Cortinovis, J. Leach, J. Polikoff, C. Barrios, F. Kabbinavar, O.A. Frontera, F. De Marinis, H. Turna, J.S. Lee, M. Ballinger, M. Kowanetz, P. He, D.S. Chen, A. Sandler, D.R.

Gandara, Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial, Lancet. 389 (2017) 255–265. https://doi.org/10.1016/S0140-6736(16)32517-X.

[11] C.M. Cramer-Van Der Welle, B.J.M. Peters, F.M.N.H. Schramel, O.H. Klungel, H.J.M. Groen, E.M.W. Van De Garde, Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer, Eur. Respir. J. 52 (2018). https://doi.org/10.1183/13993003.01100-2018.

[12] H.J.M. Smit, J. Aerts, M. van den Heuvel, T.J.N. Hiltermann, I. Bahce, E.F. Smit, A.M.C. Dingemans, L.E. Hendriks, J.A. Stigt, F.M.N.H. Schramel, H. van Tinteren, H.J.M. Groen, Effects of checkpoint inhibitors in advanced non-small cell lung cancer at population level from the National Immunotherapy Registry, Lung Cancer. 140 (2020) 107–112. https://doi.org/10.1016/j.lungcan.2019.12.011.

[13] M. ten Berge, N. Beck, D.J. Heineman, R. Damhuis, W.H. Steup, P.J. van Huijstee, J.P. Eerenberg, E. Veen, A. Maat, M. Versteegh, T. van Brakel, W.H. Schreurs, M.W. Wouters, Dutch Lung Surgery Audit: A National Audit Comprising Lung and Thoracic Surgery Patients, Ann. Thorac. Surg. 106 (2018) 390–397. https://doi.org/10.1016/j.athoracsur.2018.03.049.

[14] N. Beck, F. Hoeijmakers, E.M. Wiegman, H.J.M. Smit, F.M. Schramel, W.H. Steup, A.F.T.M. Verhagen, W.H. Schreurs, M.W.J.M. Wouters, Lessons learned from the Dutch Institute for Clinical Auditing: The Dutch model for quality assurance in lung cancer treatment, J. Thorac. Dis. 10 (2018) S3472–S3485. https://doi.org/10.21037/jtd.2018.04.56.

[15] Zorgverzekeraars Nederland–About ZN, (n.d.). https://www.zn.nl/about-zn (accessed August 11, 2020).

[16] N. Beck, A.C. van Bommel, E.H. Eddes, N.J. van Leersum, R.A. Tollenaar, M.W. Wouters, The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis, Ann. Surg. 271 (2020) 627–631. https://doi.org/10.1097/SLA.0000000000003665.

[17] Onderzoek–DICA, (n.d.). https://dica.nl/dlca/onderzoek (accessed August 13, 2020).

[18] D.J. Spiegelhalter, Funnel plots for comparing institutional performance, Stat. Med. 24 (2005) 1185–1202. https://doi.org/10.1002/sim.1970.

[19] T. Rakow, R.J. Wright, D.J. Spiegelhalter, C. Bull, The pros and cons of funnel plots as an aid to risk communication and patient decision making, Br. J. Psychol. 106 (2015) 327–348. https://doi.org/10.1111/bjop.12081.

[20] NKR Cijfers–IKNL, (n.d.). https://www.iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=6&fs%7Ctumor_id=434%2C257%2C259&fs%7Cregio_id=155&fs%7Cperiode_id=78%2C79%2C80%2C81%2C82%2C83%2C84%2C85%2C86%2C87%2C88%2C89%2C90%2C91%2C92%2C93%2C94%2C95%2C96%2C97%2C98%2C99%2C100%2C101%2C102%2C103%2C104%2C105%2C106%2C108%2C110&fs%7Cgeslacht_id=15&fs%7Cleeftijdsgroep_id=67%2C36%2C37%2C38%2C39%2C40%2C41&fs%7Cjaren_na_diagnose_id=16&fs%7Ceenheid_id=2&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=leeftijdsgroep_id&cfs%7Ctumor_id=434&ts%7CrowDimensions=periode_

id&ts%7CcolumnDimensions=tumor_id%2Cleeftijdsgroep_id&lang%7Clanguage=en (accessed August 11, 2020).

[21] E. Jakobsen, A. Green, K. Oesterlind, T.R. Rasmussen, M. Iachina, T. Palshof, Nationwide quality improvement in lung cancer care: The role of the Danish Lung Cancer Group and Registry, J. Thorac. Oncol. 8 (2013) 1238–1247. https://doi.org/10.1097/JTO.0b013e3182a4070f.

[22] Denmark Population (2020)–Worldometer, (n.d.). https://www.worldometers.info/world-population/denmark-population/ (accessed August 13, 2020).

[23] Netherlands Population (2020)–Worldometer, (n.d.). https://www.worldometers.info/world-population/netherlands-population/ (accessed August 13, 2020).

[24] M. Fredriksson, C. Halford, A.C. Eldh, T. Dahlström, S. Vengberg, L. Wallin, U. Winblad, Are data from national quality registries used in quality improvement at Swedish hospital clinics?, Int. J. Qual. Heal. Care. 29 (2017) 909–915. https://doi.org/10.1093/intqhc/mzx132.

[25] A. Khakwani, A.L. Rich, H.A. Powell, L.J. Tata, R.A. Stanley, D.R. Baldwin, J.P. Duffy, R.B. Hubbard, Lung cancer survival in England: Trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit, Br. J. Cancer. 109 (2013) 2058–2065. https://doi.org/10.1038/bjc.2013.572.

[26] The Royal College of Physicians, Policy on Molecular Testing in Lung Cancer, (2020) 49–55. https://www.rcplondon.ac.uk/projects/outputs/spotlight-audit-molecular-testing-advanced-lung-cancer-2019-diagnoses-2017.

[27] D. Goedkeuring, L.W. Longtumoren, Niet-kleincellig-longcarcinoom-22-mei-2011.pdf, (2011).

[28] P.E. Van Schil, M.D. Hellmann, S. Peters, E. Guidelines, ESMO Clinical Practice Guidelines for mNSCLC, Ann Oncol. 29 (2019) iv192–iv237. https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer.

[29] ICHOM, ICHOM Reference Guide. Lung Cancer, (2017) 44. https://ichom.org/files/medical-conditions/lung-cancer/lung-cancer-reference-guide.pdf.

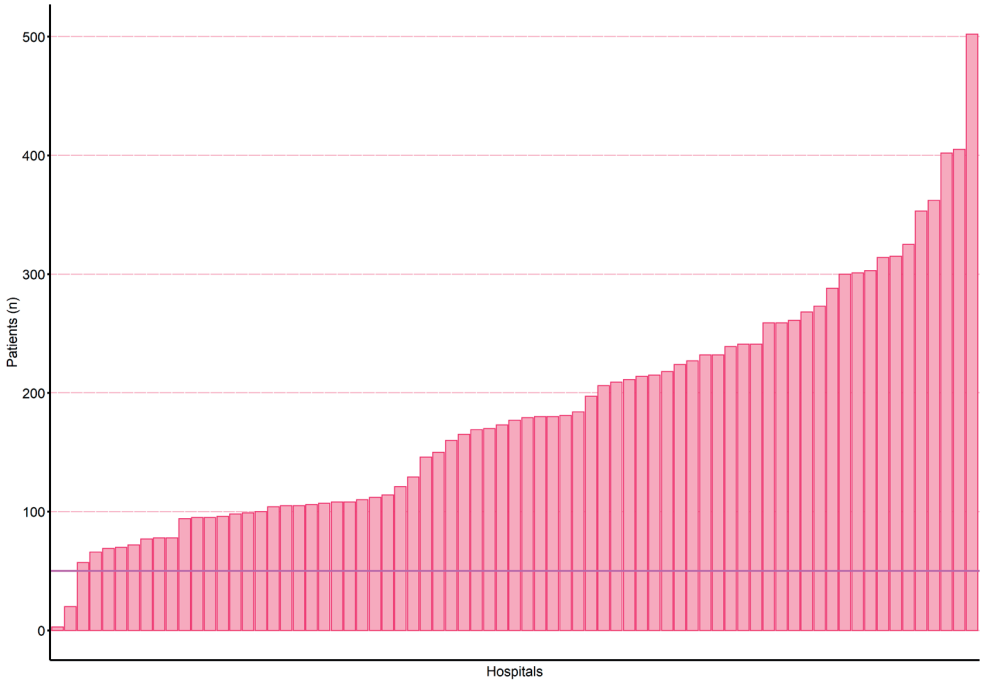
Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

Supplements

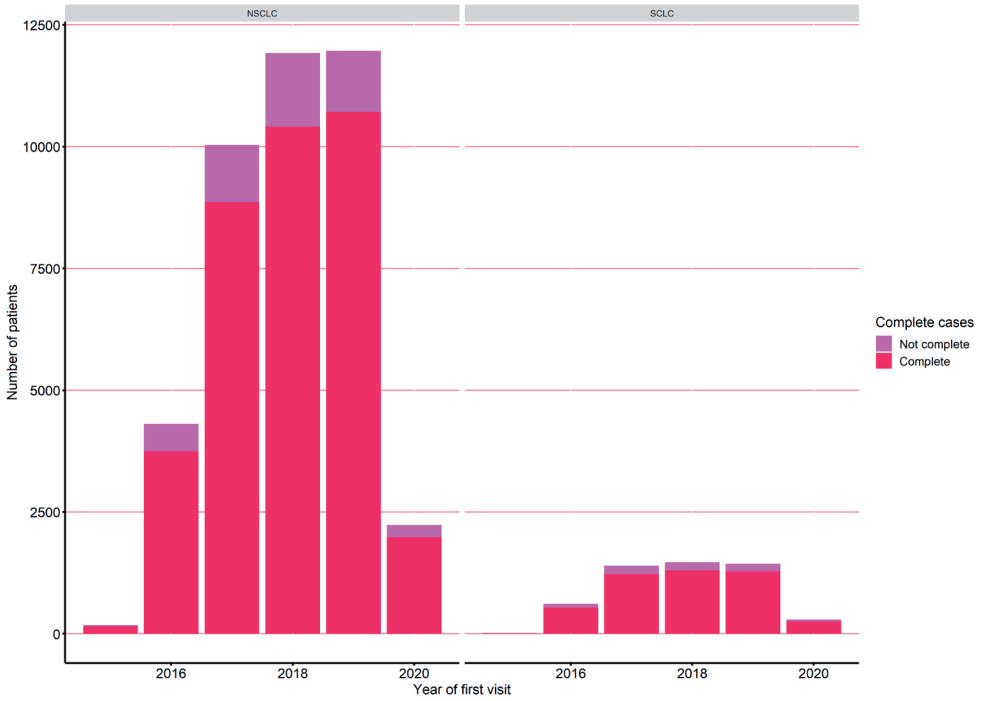
Supplement 1: A summary of the different aspects and variables of the DLCA-L registry dataset.

Section of the data set	Components of the section
Patient section	
Patient information	Name, security number, gender, date of birth, address, date of death
Hospital ID	Name of hospital admitted
Episode section	
General information	Subgroup lung cancer, date of first admission hospital, previous therapy, outcome first hospital visit, a second opinion
Patient characteristics	ECOG PS, smoking status
Diagnostics	EUS/EBUS, mediastinoscopy, transthoracic puncture biopsy, FEV1, DLCO, VO2
Tumor characteristics	Pathology information, multiple primary tumors, histopathology, molecular diagnostics, PD-L1 expression, mutation status, TNM-stage, location of metastases
Multidisciplinary team meeting (MDT)	The patient discussed at (MDT), date of MDT
Executed treatment plan	Treatment goal, brain imaging, trial participation, active tumor treatment
Treatment modules	Detailed information on treatment; start- and end date treatment, specific treatment, toxicity
Follow-up section	
Disease state	Date follow-up, ECOG PS, disease state and date (progression/ recidive)
Follow-up treatment	Second-, third-, fourth-line of treatment
Death	Date of death, cause of death, systemic treatment <6 weeks before death

ID: Identifier
ECOG PS: Eastern Cooperative Oncology Group Performance Status
EUS/EBUS: endoscopic (esophageal) ultrasound/ endobronchial ultrasound with real-time guided transbronchial needle aspiration
FEV1: Forced Expiratory Volume 1 second
DLCO: Diffusing capacity of the lungs for carbon monoxide test
VO2: Peak oxygen consumption (Volume O_2)
PD-L1: Programmed Death Ligand 1



Supplement 2: The total number of patients with lung cancer per hospital, registered in the DLCA-L in 2019. The horizontal line represents the minimum standard of 50 patients.



Supplement 3: Total number of patients with primary lung cancer (NSCLC left and SCLC right) registered in the DLCA-L from 2016 to 2019, including the proportion of complete registration cases per subgroup.

Supplement 4: definitions of quality indicators used by the DLCA-L.

#QI	Name QI	Numerator definition	Denumerator definition
1	Complete registration of registered lung cancer patients in the DLCA-L; %	The number of patients of whom the information in the registration is complete[1].	The number of patients with lung cancer (NSCLC and SCLC) that are seen and treated by the pulmonologist and registered in the DLCA-L.
2	Newly diagnosed primary lung cancer patients registered per hospital in the DLCA-L; n	The number of new patients with a primary lung carcinoma that are registered in the DLCA-L.	None
3	Hospitals treating more than 50 lung cancer patients per year; %[2]	The number of hospitals that have been treating more than 50 patients per year.	The total number of hospitals that are participating in the DLCA-L registry.
4	Stage III NSCLC patients undergoing brain imaging before the start of systemic therapy with curative[3] intention; %	The number of patients in which a CT or MRI of the brains has been performed before the start of systemic therapy.	The number of patients with a clinical stage III NSCLC and a curative treatment.
5	Stage IV adenocarcinoma lung cancer patients undergoing molecular diagnostics before the start of systemic therapy with curative intention; %	The number of patients in which molecular diagnostics have been performed.	The number of patients with stage IV pathologically proven adenocarcinoma who are not treated curatively.
6	Patients discussed in multidisciplinary consultation before treatment.		
	a. Stage[4] I-III curative treatment	The number of patients that have been discussed in multidisciplinary consultation before the start of treatment[5].	The number of patients with stage I-III NSCLC or SCLC, with curative treatment.
	b. Palliative treatment	The number of patients that have been discussed in multidisciplinary consultation before the start of treatment.	The number of patients with stage I-III NSCLC or SCLC, with palliative treatment.
7	Duration of the diagnostic trajectory of NSCLC patients		
	a. 21 days without invasive mediastinal diagnostics	The number of patients with a lead time of ≤ 21 days if no invasive mediastinal diagnostics has performed.	The number of NSCLC patients with stage I-IV disease, who did not receive a second opinion, and that have been discussed in a multidisciplinary consultation before treatment and who did not receive invasive mediastinal diagnostics.
	b.<21 with EUS/EBUS, but without mediastinoscopy	The number of patients with a lead time of ≤ 21 days if mediastinal diagnostics have been performed by EUS/EBUS, but without mediastinoscopy.	The number of NSCLC patients with stage I-IV disease, who did not receive a second opinion, that have been discussed in a multidisciplinary consultation before treatment and who did receive invasive mediastinal diagnostics by EUS/EBUS, but without mediastinoscopy.
	c. <35 days with mediastinoscopy	The number of patients with a lead time of ≤35 days if mediastinal diagnostics have been performed by mediastinoscopy.	The number of NSCLC patients with stage I-IV disease, who did not receive a second opinion, that have been discussed in a multidisciplinary consultation before treatment and who did receive invasive mediastinal diagnostics by mediastinoscopy.
8	Diagnostics of stage III NSCLC patients with EUS/EBUS	The number of stage III NSCLC patients in whom an EUS and/or EBUS has been performed.	The number of stage III NSCLC patients.

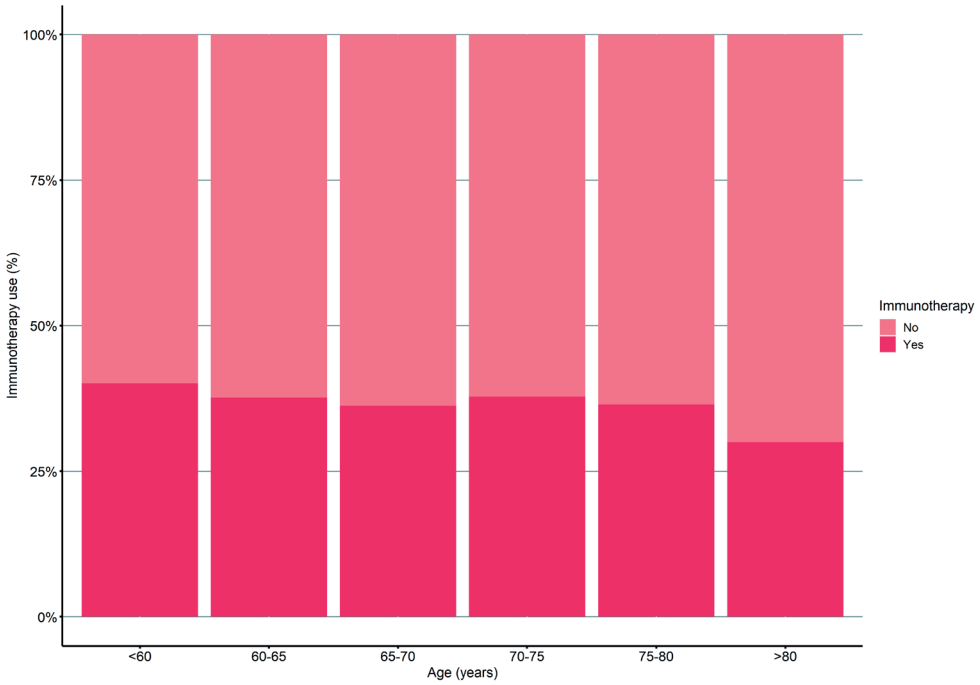
Supplement 4 continued

#QI	Name QI	Numerator definition	Denumerator definition
9	Stage III NSCLC patients treated with adjuvant chemotherapy	The number of patients who were treated with neoadjuvant chemotherapy[6].	The number of clinical stage II NSCLC patients.
10	First-line systemic treatment of stage IV NSCLC patients without curative intention.		
	a. Chemotherapy	The number of stage IV NSCLC patients who are not eligible for curative treatment, treated with first-line chemotherapy.	The number of stage IV NSCLC patients who are not eligible for curative treatment and received first-line systemic therapy.
	b. Immunotherapy	The number of stage IV NSCLC patients who are not eligible for curative treatment, treated with first-line immunotherapy.	Similar to QI 10a.
	c. Targeted therapy	The number of stage IV NSCLC patients who are not eligible for curative treatment, treated with first-line targeted therapy.	Similar to QI 10a.
11	First-line systemic treatment of stage IV SCLC patients without curative intention.		
	a. Chemotherapy	The number of stage IV SCLC patients who are not eligible for curative treatment, treated with first-line chemotherapy.	The number of stage IV SCLC patients who are not eligible for curative treatment and received first-line systemic therapy.
	b. Immunotherapy	The number of stage IV SCLC patients who are not eligible for curative treatment, treated with first-line immunotherapy.	Similar to QI 11a.
12	Use of immunotherapy in elderly patients with stage IV NSCLC disease with no curative intention.		
	a. <70 years	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line immunotherapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line systemic therapy.
	b. ≥70 years	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line immunotherapy.	Similar to QI 12a.
13	Use of chemo-immunotherapy in elderly patients with stage IV NSCLC disease with no curative intention.		
	a. <70 years	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line chemo-immunotherapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line systemic therapy.
	b. ≥70 years	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line chemo-immunotherapy.	Similar to QI 13a.

Supplement 4 continued

#QI	Name QI	Numerator definition	Denumerator definition
14	Toxicity[7] after treatment with systemic therapy in stage IV NSCLC young (<70 years) patients.		
	a. Chemotherapy	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line chemotherapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line chemotherapy.
	b. Immunotherapy	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line immunotherapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line immunotherapy.
	c. Targeted therapy	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line targeted therapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line targeted therapy.
	d. Chemoradiotherapy	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line chemo-radiotherapy.	The number of stage IV NSCLC patients aged <70 years, which are not eligible for curative treatment, and received first-line chemo-radiotherapy.
15	Toxicity after treatment with systemic therapy in stage IV NSCLC elderly (≥70 years) patients.		
	a. Chemotherapy	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line chemotherapy.	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line chemotherapy.
	b. Immunotherapy	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line immunotherapy.	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line immunotherapy.
	c. Targeted therapy	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line targeted therapy.	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line targeted therapy.
	d. Chemoradiotherapy	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and developed toxicity as a result of first-line chemo-radiotherapy.	The number of stage IV NSCLC patients aged ≥70 years, which are not eligible for curative treatment, and received first-line chemo-radiotherapy.

[1]Complete= patients of whom all items are registered that are needed to calculate the quality indicators that are made public.
[2]The minimum number of patients that should be treated per hospital is 50, which is decided by the SONCOS norms.
[3]Curative intention is defined as the goal of the treatment during the last multidisciplinary consultation before the start of the first treatment. It refers to the treatment of patients with the intent to cure them instead of reducing symptoms.
[4]The stage of disease is calculated by the TNM8 classification.
[5]The last multidisciplinary consultation before the start of treatment is meant, which should be performed by the guidelines and include all necessary disciplines.
[6]The combination of chemoradiotherapy is excluded.
[7]Toxicity is scored using the CTC AE criteria. The options for toxicity after treatment (different modules for chemotherapy, immunotherapy and targeted therapy) are: "No toxicity or toxicity with grade <3" or "Toxicity with grade ≥3". Only patients with toxicity grade ≥3 are counted in the quality indicators.



Supplement 5: Use of immunotherapy in patients with stage IV NSCLC treated with active tumor treatment in different age categories.

PART II

METHODS TO COMPARE REAL-WORLD AND CLINICAL TRIALS OUTCOMES

CHAPTER 4

Postapproval trials versus patient registries: comparability of advanced melanoma patients with brain metastases.

Melanoma Res. 2021 Feb 01;31(1):58-66.

R.K. Ismail, N.O. Sikkes, M.W.J.M. Wouters, D.L. Hilarius, A.M.G. Pasmooij, A.J.M. van den Eertwegh, M.J.B. Aarts, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, K.P.M. Suijkerbuijk, B. ten Tije, A.A.M. van der Veldt, A. Vreugdenhil, M. van Dartel, A. de Boer.

Abstract

Background: Postapproval trials and patient registries have their pros and cons in the generation of postapproval data. No direct comparison between clinical outcomes of these data sources currently exists for advanced melanoma patients. We aimed to investigate whether a patient registry can complement or even replace postapproval trials.

Methods: Postapproval single-arm clinical trial data from the Medicines Evaluation Board and real-world data from the Dutch Melanoma Treatment Registry were used. The study population consisted of advanced melanoma patients with brain metastases treated with targeted therapies (BRAF- or BRAF-MEK inhibitors) in the first line. A Cox hazard regression model and a propensity score matching (PSM) model were used to compare the two patient populations.

Results: Compared to patients treated in postapproval trials (n=467), real-world patients (n=602) had significantly higher age, higher ECOG performance status, more often ≥3 organ involvement and more symptomatic brain metastases. Lactate dehydrogenase levels were similar between both groups. The unadjusted median overall survival (mOS) in postapproval clinical trial patients was 8.7 (95%CI, 8.1–10.4) months compared to 7.2 (95%CI, 6.5–7.7) months (P<0.01) in real-world patients. With the Cox hazard regression model, survival was adjusted for prognostic factors, which led to a statistically insignificant difference in mOS for trial and real-world patients of 8.7 (95%CI, 7.9–10.4) months compared to 7.3 (95%CI, 6.3–7.9) months, respectively. The PSM model resulted in 310 matched patients with similar survival (P=0.9). Clinical outcomes of both data sources were similar.

Conclusion: Registries could be a complementary data source to postapproval clinical trials to establish information on clinical outcomes in specific subpopulations.

Introduction

For certain subgroups of patients, long-term benefits, safety, and efficacy of novel drugs or drug combinations may not be proven at the time of market access. To obtain additional evidence, specific patient populations are investigated in post-approval clinical trials. These trials use strict inclusion and exclusion criteria, creating efficacy and safety data in a relatively homogenous patient population [1]. A new method to collect post-approval clinical data, incorporating patients in a "real-world" setting, is the use of drug-, patient- or disease-specific registries. To guide the use of these registries in the medicine evaluation by regulators, the European Medicines Agency (EMA) launched a "Patient Registries Initiative" in 2015 [2]. Several programs and projects were also initiated by the US Food and Drug Administration (FDA) to use real-world evidence (RWE) in regulatory decision making [3].

Post-approval clinical trials and registries have their pros and cons. Trials can be time-consuming and expensive and are not always representative of the real-world population. Trials include a homogeneous study cohort consisting of patients with similar characteristics and treatments, resulting in high internal validity and more readily interpretable results. Assessment of safety and disease progression in trial patients are structured and similar for all patients. On the other hand, real-world patients have heterogeneous patient and disease characteristics and are not always treated identically. Hence, efficacy and safety results are not obtained, assessed, and reported in the same way. Data on patients in registries can be an advantage in answering questions related to long-term outcomes and the safety of medicines, which cannot be investigated in post-approval clinical trials with a short follow-up. Furthermore, large registries covering all patients with a specific disease or disease stage, provide information on higher numbers of specific patient populations, compared to oftentimes limited numbers of patients in post-approval clinical trials. These advantages of registries may be valuable to assess the benefit of cancer therapies. The need for post-approval effectiveness data is becoming increasingly more important since benefit-risk assessments of new medicines have been based on smaller, single-arm trials. Post-approval data can be used for additional insights of these medicines, and to confirm expected benefits.

Multiple targeted therapies and immunotherapies received marketing authorization, leading to increased treatment options for stage III and stage IV (advanced) melanoma patients [4]. Phase III trials including these drugs, showed significant improvements in the survival of these patients [5–9]. The approved indication of drugs is sometimes broader than the strictly selected patient population investigated in trials. For example, during the time of approval of the BRAF-inhibitors, regulators requested more data of the applicant on the efficacy of the BRAF-inhibitors in advanced melanoma patients with brain metastases (BM). Patients with BM, whether asymptomatic or symptomatic, were excluded from pivotal

trials, but the approved indication included these patients [10–12]. Such patients are a subgroup of significant interest since melanoma is the third most common cancer with metastases to the brain [13]. Post-approval trials in advanced melanoma patients with BM were conducted to answer questions from regulators on the efficacy of targeted therapies in this particular subgroup.

Data on advanced melanoma patients has also been collected in the nationwide Dutch Melanoma Treatment Registry (DMTR). This disease-specific registry was established in 2012 to assure the safety and quality of advanced melanoma care in the Netherlands by providing insight into the outcomes of daily clinical practice [14]. The DMTR includes all advanced melanoma patients and provides information about patient, tumor, and treatment characteristics as well as outcomes. The DMTR is thus a potential source for post-approval data collection.

Earlier research has shown that patient registries are a less used resource for regulatory authorities in the assessments of drugs [15]. This may be because, while post-approval clinical trials and patient registries can both be used for post-approval data collection, no direct comparison of patient characteristics and survival in these two post-approval data sources yet exists. This study uses advanced melanoma patient data to compare these two data sources for post-approval data collection and to explore whether the DMTR can complement post-approval clinical trials.

Methods

Patients

The study population consisted of advanced melanoma patients (≥18 years) with symptomatic or asymptomatic BM treated with first-line targeted therapy, including BRAF-MEK combination and BRAF monotherapy. We constructed two treatment groups: patients treated in post-approval clinical trials (trial patients) and patients treated in daily clinical practice (real-world patients). Real-world patients were treated in the 14 designated melanoma centers in the Netherlands between 2012 and 2019.

Data sources

The database of the Medicines Evaluation Board (MEB) was used, including post-approval clinical trials. These data were supplied by applicants to the EMA after market authorization. The second data source, the DMTR, is a nationwide prospective patient registry, including all advanced melanoma patients diagnosed since 2012 [14].

Pooling of trials

To find potential differences between the trials, patient- and tumor baseline characteristics of patients treated in single-arm post-approval trials were analyzed with a Chi-square test. Analyzed baseline characteristics were age, gender, Eastern Cooperative Oncology Group Performance score (ECOG PS), serum lactate dehydrogenase (LDH), prior brain radiation, previous brain surgery, number of organ sites with metastases, symptomatic or asymptomatic BM, type of targeted therapy and year of treatment. These baseline characteristics have been previously described as predictive factors for clinical outcomes of advanced melanoma patients [16]. Overall survival (OS) of the trials was adjusted for prognostic factors by a Cox proportional hazard regression model. After adjustment for baseline characteristics, the hazard ratios for survival did not differ between the trials. The trials could, therefore, be aggregated as one population. The total number of trial patients were compared to real-world patients.

Primary outcome

The primary outcome in the post-approval clinical trials was the (intracranial) response rate. The secondary outcome was OS meeting the requested effectiveness of advanced melanoma patients with BM. Since the intracranial response rate is not registered in the DMTR, we used the Kaplan Meier method to analyze median overall survival (mOS) as the primary outcome with corresponding 95% confidence intervals.

Statistical analysis

Patient characteristics of trial and real-world patients were analyzed using descriptive statistics. OS was calculated from the date of start systemic therapy until the date of death from any cause or date of the last contact. Patients who did not reach the endpoint were censored at last contact. Median follow-up time was calculated using the reverse Kaplan-Meier method [17].

Two statistical models were used to compare trial patients with real-world patients. The first was a multivariable Cox hazard regression model. The proportionality assumption of the variables in the Cox model was investigated using scaled Schoenfeld residuals. Overall survival was adjusted for baseline characteristics using the Cox model. The Kaplan-Meiers of the two patient populations were compared with a log-rank test. The second model used to compare the two data sources was propensity score matching (PSM). This model gives a propensity score to each individual based on baseline patient, tumor and treatment characteristics. The propensity scores of patients from the trial group are matched to individuals from the real-world data group. This model only focuses on matched patients, meaning these patients were equal to each other in terms of patient, tumor and treatment characteristics. Matching was performed on age, gender, ECOG PS LDH, number of organ sites, type of therapy, year of treatment and symptomatic or asymptomatic BM. Since

matched groups are not independent in this model, the two groups were compared with the stratified log-rank test.

Data handling and statistical analyses were performed using the R software system for statistical computing (version 3.6.1.; packages tidyverse, lubridate, car, survival, survminer).

Results

Baseline characteristics

Four single-arm post-approval clinical trials in patients with advanced melanoma and BM were pooled, resulting in 467 patients. All these trial patients were treated with first-line BRAF-MEK combination or BRAF monotherapy. Between 2012 and 2019, 1199 patients with advanced melanoma and BM were registered in the DMTR (**figure 1)**, with 602 (50%) patients treated with first-line targeted therapy. The main differences in patient- and tumor characteristics between trial and real-world patients treated with first-line targeted therapy are shown in **table 1.** Real-world patients had significantly poorer characteristics: higher age, higher ECOG PS, more organ site involvement, and more often symptomatic BM. The unadjusted median overall survival (mOS) of real-world patients was 7.2 (95%CI;

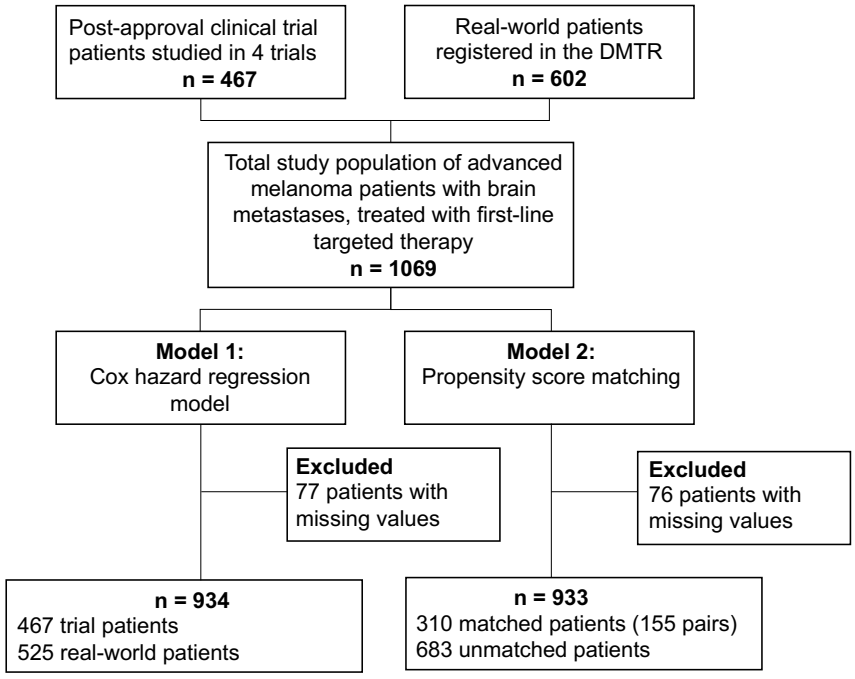


Figure 1: flowchart of patient population and the two statistical models used.

Table 1. Baseline characteristics of targeted therapy treated advanced melanoma patients with brain metastases in clinical trials and in real-world

Baseline	Clinical trials	Real-world	p-value
Patients; n	467	602	
Gender; n (%)			0.069
Male	295 (63.2)	346 (57.5)	
Female	172 (36.8)	256 (42.5)	
Age (median [range])	53 [19-87]	58 [18-92]	<0.001
ECOG PS; n (%)			<0.001
≤1	459 (98.3)	401 (66.6)	
≥2	8 (1.7)	129 (21.4)	
Unknown	0	72 (12.0)	
LDH; n (%)			<0.001
Not determined	0	21 (3.5)	
Normal	212 (45.4)	293 (48.8)	
1-2xULN	148 (31.7)	174 (29.0)	
>2xULN	107 (22.9)	112 (18.7)	
Distant metastases; n (%)			<0.001
<3 organ sites	196 (42.0)	172 (28.6)	
≥3 organ sites	271 (58.0)	430 (71.4)	
Type of therapy; n (%)			<0.001
BRAFi mono	342 (73.2)	262 (43.5)	
BRAFi/MEKi combi	125 (26.8)	340 (56.5)	
Brain metastases; n (%)			<0.001
Asymptomatic	426 (91.2)	189 (31.5)	
Symptomatic	41 (8.8)	411 (68.5)	
Brain surgery; n (%)			<0.001
No	364 (77.9)	560 (93.0)	
Yes	103 (22.1)	42 (7.0)	
Brain radiation; n (%)			<0.001
No	318 (68.1)	336 (55.8)	
Yes	149 (31.9)	265 (44)	
Unknown	0	1 (0.2)	
Start target therapy year; n (%)			<0.001
2010-2011	219 (46.9)	0	
2012-2013-2014	188 (40.3)	185 (30.7)	
2015-2016	60 (12.8)	168 (27.9)	
2017-2018-2019	0	249 (41.4)	

ECOG PS - Eastern Cooperative Oncology Group Performance Score, Distant metastases - number of organ sites with metastases, LDH - lactate dehydrogenase

6.5-7.7) months and significantly lower (p<0.01) than the mOS of post-approval clinical trial patients, which was 8.7 (95%CI; 8.1-10.4) months (**figure 2**). After having adjusted for baseline characteristics, median survival times in the two groups were similar.

Cox hazard regression model

A multivariable Cox regression hazard model, comparing real-world patients to those treated in the post-approval clinical trials, showed a hazard ratio (HR) on survival of 1.19 (95%CI; 0.93-1.51, p=0.165) for real-world patients. This HR is adjusted for the prognostic factors shown in **figure 3.** In this Cox model, age >70 years, ECOG PS ≥2, symptomatic BM, metastases in ≥3 organ sites, and elevated LDH were significantly negatively associated with survival. As compared to BRAF monotherapy, combination therapy with BRAF-MEK was significantly positively associated with survival (HR 0.67, 95%CI;0.54-0.84, p<0.001). Another factor that improved survival was prior brain surgery, compared to patients who did not receive brain surgery, with an HR of 0.68 (95%CI; 0.53-0.87, p=0.002). Survival was also influenced by the start year of targeted therapy, with patients treated in more recent years having an improved survival (**figure 3**). The OS of the two subgroups was adjusted for prognostic factors, which led to a statistically insignificant difference in mOS

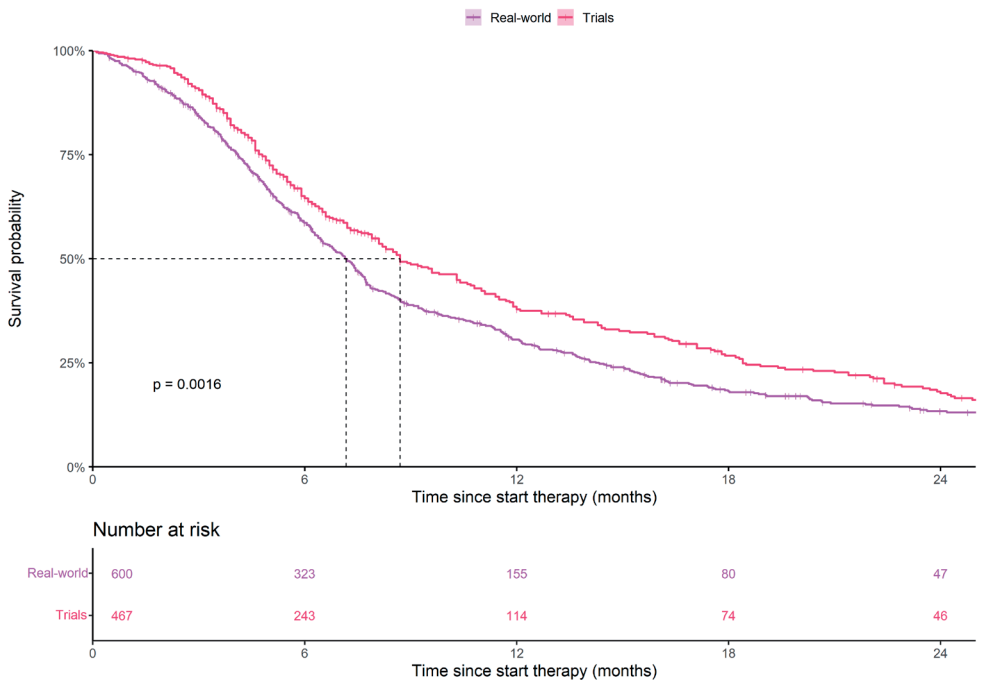


Figure 2: Log-rank test comparison of unadjusted overall survival of patients treated in post-approval clinical trials with patients treated in the real-world.
mo=months, CI=Confidence interval

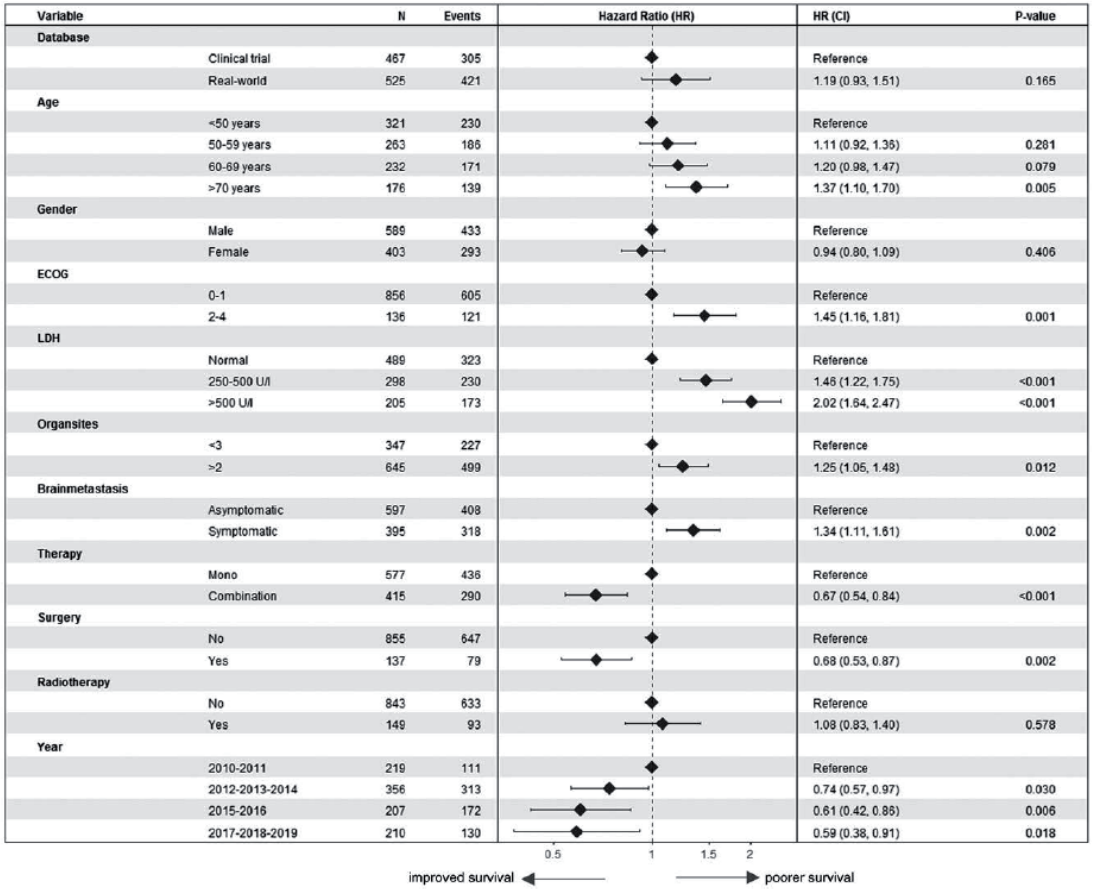


Figure 3: Hazard ratios of a multivariable Cox proportional hazard model of advanced melanoma patients with brain metastases treated in post-approval clinical trials and the real world. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase

of respectively 8.7 (95%CI; 7.9-10.4) compared to 7.3 (95%CI; 6.3-7.9) months for trial and real-world patients.

Propensity score matching model

The total patient population consisted of 602 real-world patients and 467 trial patients. To perform PSM, 76 real-world patients with missing values were excluded from the model before matching. In total 993 patients remained for matching and 310 (30.6%) patients were matched, resulting in 155 pairs of patients from the real-world and trial population. After matching, none of the prognostic factors differed between the two data sources. The stratified log-rank test resulted in similar survival (p=0.9) of real-world and trial patients. The other 683 patients could not be matched with an individual from the other data source, because of differences in ECOG PS and the presence of symptomatic versus asymptomatic BM. Only a limited number of patients with symptomatic BM and ECOG PS≥2 were included in the trials (**table 1**).

Discussion

Comparison of the outcomes of the data sources

In this study, we compared outcomes of post-approval clinical trials with data from a disease-specific registry to explore whether a registry can complement post-approval clinical trials after market authorization of medicines. The absolute difference in the unadjusted median OS of the two groups was minimal (1.5 months), which can be explained by the fact that these patients with BM are included in post-approval clinical trials, but would have been excluded from the phase-III trials. Therefore these patients included in the post-approval clinical trials are more similar to real-world patients than advanced melanoma patients included in phase-III trials. However, post-approval trial patients did not completely represent the real-world population. There were still major differences in patient- and tumor characteristics between the two groups. Real-world patients had more often symptomatic BM (69%) compared to trial patients (9%). Differences were also found in age, ECOG PS, organ site involvement and whether prior brain surgery was performed. Patients receiving brain surgery have relatively more favorable characteristics. These differences resulted in seemingly better survival among clinical trial patients, which is in general, the case for other conditions as well. After correction for baseline characteristics, the clinical outcomes of the two patient populations did not differ. We can, therefore, argue that no other prognostic factors (i.e., stricter treatment schedules and controls) contribute to the differences in survival between these patients treated in post-approval trials and real-world patients registered in the DMTR. The survival of real-world patients who were matched to trial patients was similar.

Other outcomes for measurement

The primary outcome in the post-approval trials was intracranial response. This outcome has not been registered in the DMTR and therefore the OS of the two patient groups was compared. Survival is an objective outcome that is well documented in both sources.

Safety or quality-of-life of advanced melanoma patients with BM were not investigated and compared in this study since registration of adverse events in post-approval trials and the DMTR are different. Individual data on the grade of toxicity in the post-approval trials were lacking and since only grade 3 and 4 toxicities are registered in the DMTR, we could not compare safety. Furthermore, the patient-reported outcome measurements (PROMs) questionnaires are filled out by a relatively low number of patients in the DMTR and were not used in these post-approval trials. In the future, safety and quality-of-life could also be measured in registries using similar methods as in trials, including grade 1 and 2 toxicities and more specific data on the date of toxicity and the consequences of toxicity (discontinuation, hospitalization). Registries can then be used for safety concerns or measurements in post-approval data collection.

Requirements of the data sources

Post-approval clinical trials and registries are both used by regulators in the medicine's evaluation. However, earlier research showed registry data are more often used by regulators for (long-term) safety of medicines and less used for effectiveness [18]. In only seven of the 73 (9.6%) registries, that were used in the Risk Management Plan of medicines, the primary goal was real-world safety and effectiveness [18]. Real-world information on medicines is also used by other stakeholders, such as Health Technology Assessment (HTA) organizations, payers and manufacturers [19].

Both data sources need to meet several requirements to lead to valuable and trustworthy data for regulatory assessments. In both data sources, patient numbers and the length of follow-up should be of sufficient duration to measure clinical outcomes. The proportion of excluded patients in post-approval trials should be minimalized to be representative of actual clinical care [1]. The post-approval trials used in this study were single-arm trials and therefore lacked a comparator. The inclusion and exclusion criteria used, except for the presence of BM, were similar to those used in the pivotal clinical trials, leading to an underrepresentation of the real-world population.

To reduce bias, registries need to be validated, complete, and consistent. This requires consistency in the registration of variables by hospitals and the measurement of clinical outcomes. Important factors supporting the consistency, allowing the use of registries in medicine evaluation by regulators, would include, for example, the use of common datasets and coding terminologies, complete data collection, and quality assurance and

consistent governance [15,20]. The registry used in this study, the DMTR, is a validated, nationwide patient registry with limited missing patients and data. DMTR data quality control is performed by medical oncologists and independent reviewers. Data managers are trained to register data accurately. They follow patients until death, and electronic patient records are checked every three months. DMTR data are also accessible and shared with multiple stakeholders [14]. At the same time, since an adequate (untreated) comparator is lacking, registry data are not sufficient to determine the benefit/risk balance of novel drugs. Furthermore, registry data reflects the less tightly controlled and registered dosing schedules and medication adherence of real-world practice, possibly leading to variation in clinical outcomes.

Deciding which data source to use

The comparison of data sources leads to the question of which data source regulators should request and allow when the gathering of post-approval data is needed. This choice highly depends on three main aspects. First, the choice depends on the questions that regulators have when they are deciding on marketing approval. When researching clinical benefit or treatment strategies of novel drugs, trials are preferred. Registries can be of major value to indicate outcomes of specific populations, such as mucosal or uveal melanoma patients and ineligible patients. Data from registries can also be used to measure outcomes of practical treatment schedules and strategies, such as treatment steps and treatment duration. These results from registries can then be confirmed by randomized controlled trials. An example of supporting evidence from DMTR data on advanced melanoma patients treated with first-line targeted therapy with high LDH showed subsequent immunotherapy could lead to long-term survival if normalization of LDH was reached [21]. This information is easily obtained with the use of a registry including real-world practices.

Secondly, the choice for a data source depends on the availability of a high-quality registry and available data, or the resources to initiate post-approval clinical trials. In the case of the treatment with targeted therapies in patients with BM, the intracranial response was used as a surrogate endpoint to assess effectiveness in these patients. An intracranial response in these patients, regulators argued, would lead to a clinical benefit, meaning treatment of these patients would be justified. Since the intracranial response is not registered in the DMTR, the core data set should have been expanded to match regulatory needs. The addition of such a data key point in a registry would in general require less effort than conducting new post-approval studies.

Thirdly, the choice depends on the patient population in question. Registries are a better data source when the remaining questions concern patients rarely included in phase III trials, such as the elderly or children. Registries can include rare patient populations over a longer period of time, leading to more data. This was the case when the Pediatric

Committee (PDCO) of the EMA requested additional safety information in pediatric patients treated with ipilimumab [22]. The DMTR was chosen as a data source for these data because the number of children with advanced melanoma is limited. For this patient population, conducting a post-approval trial would be very challenging.

Broader perspective

Setting up or expanding disease-specific registries for post-approval evidence requires criteria sets. Registries come with a registration burden for caregivers and therefore the data set should be minimalized, including only the data points most important for the multiple stakeholders (not only regulators but also caregivers, patients, HTAs, insurers and pharmaceutical companies). Such concision would reduce the registration burden. To use registry data to evaluate medicines, it also needs to be systemically collected, using criteria similar to those used in trials. This means data should also be noted concisely in electronic patient records, or that key data points should be automatically filled. Using registries in this way to gather post-approval data on medicines will eventually be more effective than setting up and conducting (multiple) trials, which may have a longer lead-time. In a study including 600 non-required post-approval trials, the median duration of these trials was 37 [22-57] months [23]. The median duration of trials on cancer or hematology (n=437) was 43 [29-66] months. Of 204 completed or terminated post-approval trials, the duration from completion to reporting was 16 [13-25] months. This research [23] also showed 32% of the post-approval trials did not report results within 35 months after trial completion. The speed of data collection and gathering depends on the research question and the availability of information in a registry. Delays affect patient care but can be addressed by registries from which outcomes could eventually be generated and reported more quickly if the data are already available.

Conclusion

High-quality population-based registries could be a complementary data source to post-approval clinical trials to establish information on clinical outcomes in specific subpopulations with advanced melanoma after market authorization. Disease registries are more representative for the real-world population than patients treated in post-approval clinical trials, leading to improved understanding of the effectiveness of medicines in the real world. Post-approval data from registries can support regulatory decisions for remaining questions on new medicines instead of post-approval studies.

References

[1] Kim ES, Bruinooge SS, Roberts S, Ison G, Lin NU, Gore L, Uldrick TS, Lichtman SM, Roach N, Beaver JA, Sridhara R, Hesketh PJ, et al. Broadening eligibility criteria to make clinical trials more representative: American society of clinical oncology and friends of cancer research joint research statement. *J Clin Oncol* 2017;35:3737–44.

[2] Medicines Agency E. Initiative for patient registries Strategy and pilot phase. 2015;44. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195576.pdf

[3] FDA. Framework for FDA's Real-World Evidence Program. *FDA Framew [Internet]* 2018;Available from: www.fda.gov

[4] Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, Larkin J, Long G V., Lorigan P, McArthur GA, Ribas A, Robert C, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. *Eur J Cancer* 2017;83:247–57.

[5] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Chiarion-Sileni V, Dutriaux C, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol [Internet]* 2018;19:603–15. Available from: http://dx.doi.org/10.1016/S1470-2045(18)30142-6

[6] Long G V., Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion-Sileni V, Lebbe C, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015;386:444–51.

[7] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, et al. Combined nivolumab and ipilimumab or monotherapy in untreated Melanoma. *N Engl J Med* 2015;373:23–34.

[8] Robert C, Long G V., Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.

[9] Schachter J, Ribas A, Long G V., Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet [Internet]* 2017;390:1853–62. Available from: http://dx.doi.org/10.1016/S0140-6736(17)31601-X

[10] European Medicines Agency. EPAR Zelboraf [Internet]. 2012. Available from: https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf

[11] European Medicines Agency. EPAR Tafinlar [Internet]. 2013. Available from: https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf

[12] European Medicines Agency. EPAR Bravtofi [Internet]. 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf

[13] Bafaloukos D, Gogas H. The treatment of brain metastases in melanoma patients. *Cancer Treat Rev* 2004;30:515–20.

[14] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, Gelderblom H, Uyl-de Groot CA, Aarts MJB, van den Berkmortel FWPJ, Blokx WAM, Cardous-Ubbink MC, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. *Eur J Cancer [Internet]* 2017;72:156–65. Available from: http://dx.doi.org/10.1016/j.ejca.2016.11.021

[15] McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, Kurz X, Mol PGM. Patient Registries: An Underused Resource for Medicines Evaluation: Operational proposals for increasing the use of patient registries in regulatory assessments. *Drug Saf [Internet]* 2019;42:1343–51. Available from: https://doi.org/10.1007/s40264-019-00848-9

[16] Long G V., Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, Lane SR, Mak C, Legenne P, Flaherty KT, Davies MA. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. *Lancet Oncol [Internet]* 2016;17:1743–54. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30578-2

[17] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;17:343–6.

[18] Jonker CJ, van den Berg HM, Kwa MSG, Hoes AW, Mol PGM. Registries supporting new drug applications. *Pharmacoepidemiol Drug Saf* 2017;26:1451–7.

[19] Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang S V., Watkins J, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Heal* 2017;20:1003–8.

[20] Franklin JM, Glynn RJ, Suissa S, Schneeweiss S. Emulation Differences vs. Biases When Calibrating Real-World Evidence Findings Against Randomized Controlled Trials. *Clin Pharmacol Ther* 2020;0:2019–21.

[21] Schouwenburg MG, Suijkerbuijk KPM, Koornstra RHT, Jochems A, Van Zeijl MCT, Van Den Eertwegh AJM, Haanen JBAG, Aarts MJ, Van Akkooi ACJ, Van Den Berkmortel FWPJ, De Groot JWB, Hospers GAP, et al. Switching to immune checkpoint inhibitors upon response to targeted therapy; the road to long- term survival in advanced melanoma patients with highly elevated serum LDH? *Cancers (Basel)* 2019;11.

[22] EMA. Summary of risk management plan for YERVOY. 2018;Available from: https://www.ema.europa.eu/en/documents/rmp-summary/nerlynx-epar-risk-management-plan-summary_en.pdf.

[23] Skydel JJ, Luxkaranayagam AT, Dhruva SS, Ross JS, Wallach JD. Analysis of Postapproval Clinical Trials of Therapeutics Approved by the US Food and Drug Administration Without Clinical Postmarketing Requirements or Commitments. *JAMA Netw open* 2019;2:e193410.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

CHAPTER 5

Patient-level data to enhance causation study in efficacy-effectiveness gap research.

Submitted.

R.K. Ismail, F.M.N.H. Schramel, M. van Dartel, A.M.G. Pasmooij, C.M. Cramer-van der Welle, D.L. Hilarius, A. de Boer, M.W.J.M. Wouters, E.M.W. van de Garde.

Abstract

Background: Many studies have compared real-world clinical outcomes of immunotherapy in patients with metastatic non-small cell lung cancer (NSCLC) with reported outcomes data from pivotal trials. However, any differences observed could be only limitedly explored further for causation because of the unavailability of patient-level data (PLD) from trial participants. The present study aims to explore the additional benefit of comparison with PLD.

Methods: This study compares progression free survival (PFS) and overall survival (OS) of metastatic NSCLC patients treated with second line nivolumab in real-world clinical practice (n=141) with PLD from participants in the Checkmate-057 clinical trial (n=292). Univariate and multivariate Cox proportional hazards models were used to construct HRs for real-world practice versus clinical trial.

Results: Real-world patients were older (64 vs. 61 years), had more often ECOG PS≥2 (5 vs. 0%) and were less often treated with subsequent anti-cancer treatment (28.4 vs. 42.5%) compared to trial patients. The median PFS in real-world patients was longer (3.84 (95%CI: 3.19-5.49) vs 2.30 [2.20-3.50] months) and the OS shorter than in trial participants (8.25 [6.93-13.2] vs. 12.2 [9.90-15.1] months). Adjustment with available patient characteristics, led to a shift in the hazard ratio (HR) for OS, but not for PFS (HRs from 1.13 [0.88-1.44] to 1.03 [0.79-1.33], and from 0.82 [0.66-1.03] to 0.79 [0.63-1.00], respectively).

Conclusion: This study showed that analyzing PLD from both real-world and trial patients together can lead to better insight in potential factors responsible for a gap in outcomes between these two settings. This emphasizes the relevance of making PLD from clinical trials available to the international research community.

Introduction

The treatment landscape of metastatic lung cancer patients has changed over recent years[1]. Chemotherapy used to be the cornerstone therapy for metastatic non-small cell lung cancer (NSCLC) patients, but the introduction of immunotherapy has positively changed the clinical outcomes of these patients[2–4]. Immunotherapy is increasingly more prescribed in the Netherlands. The Dutch Lung Cancer Audit showed that immunotherapy-based treatments consisted of 15% of all treatments in 2015 and increased to 57% in 2019[5].

The phase-III marketing authorization trials researching immunotherapy in NSCLC patients used strict in- and exclusion criteria[4,6,7]. Patients treated in real-world practice can differ from these trial patients, leading to different clinical outcomes, also known as the efficacy-effectiveness (EE) gap[8]. Because of the unavailability of patient-level data (PLD) from clinical trials, the standard approach for comparing trial and real-world patients is using Kaplan-Meier curves from scientific publications. These are digitized with software, such as DigitizeIt, to allow comparison between trial and real-world patients and to measure the hazard ratio (HR) between the curves[8,9]. Previous Dutch research on immunotherapy treatment (nivolumab and pembrolizumab) also used this approach and showed differences in clinical outcomes between real-world metastatic NSCLC and trial patients[10]. However, further search for causation, for example, through multivariable regression modeling, was not put forward because of unavailable patient-level data from the respective trials.

Recently, for one of the pivotal trials involved in the Dutch EE gap study, the PLD have come available. The aim of the present study is to explore the additional benefit of comparison with PLD, available from the Checkmate-057 clinical trial studying nivolumab in patients with progressive disease after platinum-containing chemotherapy.

Methods

Data sources

This study is an in-depth study of the study of Cramer-van der Welle *et al*[10]. The data from that study were re-used. The trial data from the Checkmate-057 trial were collected from the internal ICI database of the Medicines Evaluation Board database.

Patients and outcomes

The population under study consisted of metastatic nonsquamous NSCLC patients treated with second line nivolumab after prior platinum-containing chemotherapy. Real-world patients were treated with nivolumab in the years 2015 to 2018. Participants in the

Checkmate-057 clinical trial were treated before marketing authorization[4]. The outcomes in this study were progression-free survival (PFS) and overall survival (OS).

Statistical Analyses

Patient- and tumor characteristics of the study population were analyzed using descriptive statistics. These included age, gender, stage, Eastern Cooperative Oncology Group Performance Score (ECOG PS), the presence of brain metastases at diagnosis, tumor histology, programmed death-ligand 1 (PD-L1) expression, and use of subsequent anti-cancer systemic treatment.

The Kaplan-Meier method with log-rank test was used to compare the PFS and OS between real-world and trial patients. Survival times were calculated from the start of nivolumab treatment (real-world patients) or randomization date (trial patients). Patients not reaching the endpoint at data cut-off were censored at the last known alive date. Median follow-up duration was calculated for the study population using the reverse Kaplan-Meier method[11].

Univariate and multivariate Cox proportional hazards models were used to construct HRs for real-world practice versus clinical trial patients for both outcomes. All patient- and tumor characteristics (see above) were assessed as potential prognostic factors, except for the variable "use of subsequent treatment," which was analyzed only for OS. Age was categorized in <70 and ≥70 years, since NSCLC has a median onset at age 70 years[12]. Theoretically, variables that result in adjustment of the HR towards 1.00 were considered as potential causative for the EE-gap. Since this study does not compare two different treatments but two groups treated similarly, we argue that the influence of long-term survivors on the proportionality of the Cox model is limited. Statistical analyses were stated significant if the p-value was <0.05.

Data handling and statistical analyses were performed using the R software system for statistical computing[13] (version 4.1.0.; packages tidyverse, lubridate, tableone, ggplot2, survival, survminer, gtsummary, forestmodel).

Ethical statement

The Santeon Institutional Review Board approved the study, all clinical information was provided in a de-identified fashion, and the need for informed consent was waived (SDB219-008).

Results

Patient characteristics

A total of 292 metastatic NSCLC patients were treated with nivolumab in the Checkmate-057 trial and 141 patients in real-world clinical practice. The median follow-up duration of the total population (n= 433) was 20.0 (95%CI: 18.5-21.3) months. Real-world patients were older (64 [44-80] years vs 61 [37-84], p=0.003) compared to trial patients. Five percent (n=7) of the real-world patients had an ECOG PS of 2, compared to 0% in trial patients. The trial patients were more often treated with subsequent anti-cancer treatment compared to real-world patients (42.5% vs. 28.4%, p=0.006). These characteristics are presented in **table 1**.

Progression-free survival

The median PFS of real-world patients was 3.84 (95%CI: 3.19-5.49) months compared to 2.30 (95%CI: 2.20-3.50) months in trial patients (p=0.104) **(figure 1)**. The unadjusted HR for real-world versus trial was 0.82 (95%CI: 0.66-1.03). Patient characteristics associated with PFS were ECOG PS 1 (p=0.018) and PD-L1 expression >50% (p<0.001) **(table 2)**. The

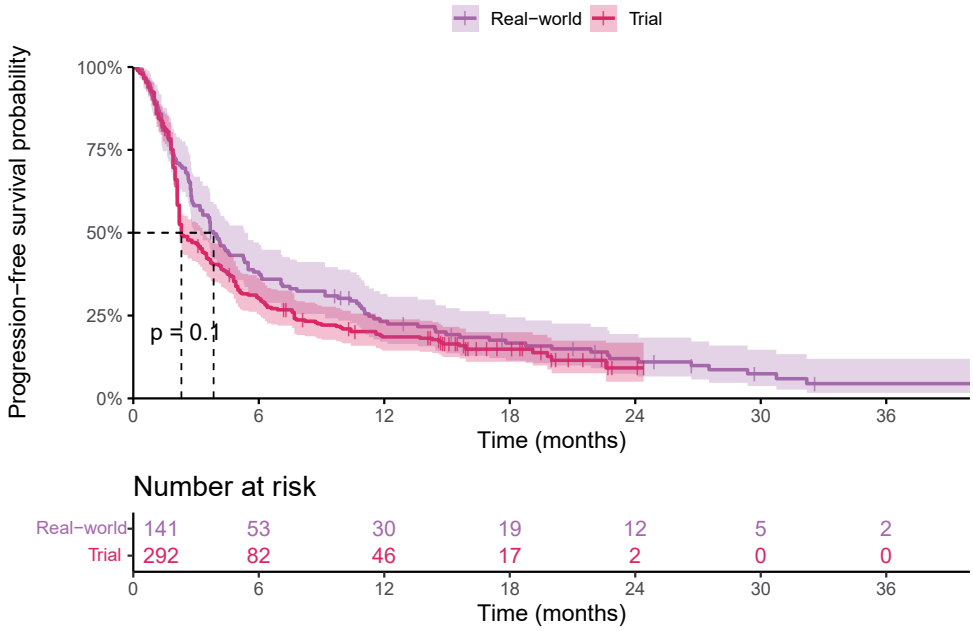


Figure 1: Kaplan-Meier estimate of the progression-free survival (PFS) of metastatic NSCLC patients treated with nivolumab in the clinical trial versus real-world.
The progression-free survival time was calculated from randomization date to first progression in clinical trial patients and from start of nivolumab treatment to first progression in real-world patients.

Table 1: Patient characteristics of metastatic non-small cell lung cancer (NSCLC) patients treated with nivolumab in the randomized controlled trial (RCT) and real-world.

	Trial patients	Real-world patients	P-value
n	292	141	
Age at diagnosis in years; median (range)	61 (37-84)	64 (44-80)	0.003
Age in categories; n (%)			0.182
<70 years	241 (82.5)	108 (76.6)	
≥70 years	51 (71.5)	33 (23.4)	
Gender; n (%)			0.962
Male	151 (51.7)	74 (52.5)	
Female	141 (48.3)	67 (47.5)	
Stage; n (%)			0.003
IIIB	20 (6.8)	0	
IV	272 (93.2)	141 (100)	
ECOG PS; n (%)			<0.001
0	84 (28.8)	44 (31.2)	
1	208 (71.2)	90 (63.8)	
2	0	7 (5.0)	
Presence of brain metastases; n (%)			0.114
Yes	34 (11.6)	25 (17.7)	
No	258 (88.4)	116 (82.3)	
Histology tumor; n (%)			0.006
Adenocarcinoma	270 (92.5)	130 (92.2)	
Large cell carcinoma	7 (2.4)	8 (5.7)	
Adenosquamous	3 (1.0)	0	
Other	11 (3.8)	0	
Not otherwise specified (NOS)	0	3 (2.1)	
PD-L1 expression; n (%)			<0.001
<1%	108 (37.0)	33 (23.4)	
1-49%	57 (19.5)	29 (20.6)	
>50%	66 (22.6)	10 (7.1)	
Unknown	61 (20.9)	69 (48.9)	
Subsequent systemic therapy; n (%)			0.006
Yes	124 (42.5)	40 (28.4)	
No	168 (57.5)	101 (71.6)	

ECOG PS = Eastern Cooperative Oncology Group Performance Score, PD-L1 = Programmed death-ligand 1, RCT = randomized controlled trial

Table 2: Univariate analysis (PFS)

Variable	n	HR (95%CI)	P-value
Population			
Trial patients	292	1.00	
Real-world patients	141	0.82 (0.66-1.03)	0.088
Age (years)			
<70	349	1.00	
≥70	84	1.21 (0.94-1.56)	0.146
Gender			
Male	225	1.00	
Female	208	1.02 (0.83-1.25)	0.852
Stage			
IV	413	1.00	
IIIB	20	0.72 (0.42-1.22)	0.221
ECOG PS			
0	128	1.00	
1	298	1.32 (1.05-1.66)	0.018
2	7	1.68 (0.78-3.62)	0.182
Presence of brain metastases			
No	374	1.00	
Yes	59	0.95 (0.7-1.29)	0.749
Histology tumor			
Adenocarcinoma	400	1.00	
Large cell carcinoma	15	1.18 (0.68-2.06)	0.558
Adenosquamous	3	1.15 (0.37-3.59)	0.808
Other	11	0.97 (0.48-1.97)	0.943
Not otherwise specified (NOS)	3	1.74 (0.56-5.44)	0.339
PD-L1 expression			
<1%	141	1.00	
1-49%	86	0.85 (0.63-1.14)	0.272
>50%	76	0.53 (0.39-0.74)	<0.001
Unknown	130	0.93 (0.72-1.21)	0.601

ECOG PS = Eastern Cooperative Oncology Group Performance Score, PD-L1 = Programmed death-ligand 1, HR = Hazard Ratio

multivariate Cox model, including all patient characteristics, yielded an adjusted HR for real-world versus trials of 0.79 [0.63-1.00] **(figure 2)**.

Overall survival

The median OS was 8.25 (95%CI: 6.93-13.2) months for real-world patients and 12.2 (95%CI: 9.90-15.1) months for trial patients (p=0.33) **(figure 3)**. ECOG PS 1 (p<0.001) and ECOG PS 2 (p=0.001), PD-L1 expression >50% (p=0.001), and subsequent anti-cancer treatment (p=0.001) were significantly associated with OS **(table 3)**. The unadjusted and fully adjusted HR for real-world versus trials were 1.13 (95%CI: 0.88-1.44) and 1.03 (95%CI: 0.79-1.33), respectively **(figure 4)**.

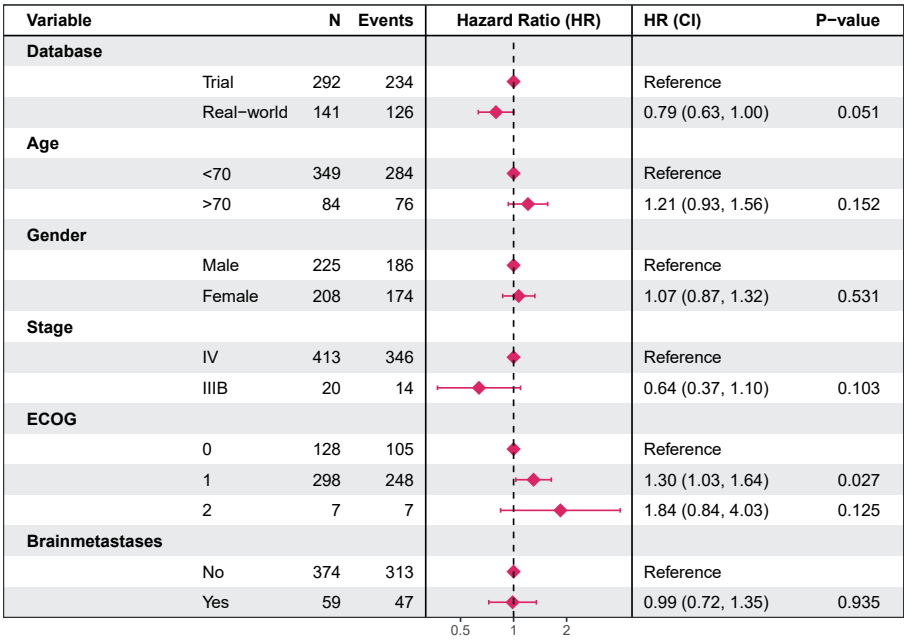


Figure 2: Forest plot visualizing multivariate proportional hazard cox regression model of factors associated with the progression-free survival (PFS) of metastatic NSCLC patients.

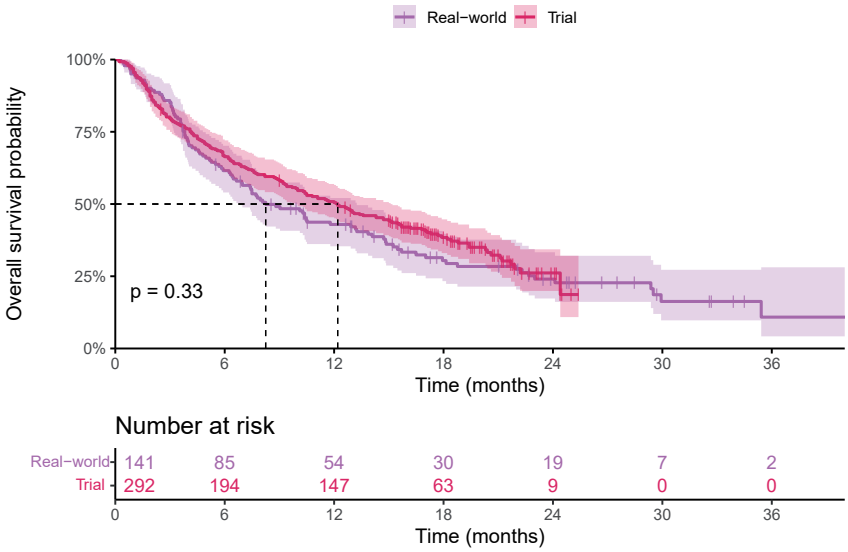


Figure 3: Kaplan-Meier estimate of the overall survival (OS) of metastatic NSCLC patients treated with nivolumab in the clinical trial versus real-world.
The overall survival time was calculated from randomization date to death in clinical trial patients and from start of nivolumab treatment to death in real-world patients.

Variable		N	Events	Hazard Ratio (HR)	HR (CI)	P−value
Database						
	Trial	292	190		Reference	
	Real−world	141	104		1.03 (0.79, 1.33)	0.8442
Age						
	<70	349	232		Reference	
	>70	84	62		1.26 (0.95, 1.67)	0.1155
Gender						
	Male	225	155		Reference	
	Female	208	139		0.99 (0.78, 1.25)	0.9329
Stage						
	IV	413	282		Reference	
	IIIB	20	12		0.85 (0.47, 1.53)	0.5914
ECOG						
	0	128	70		Reference	
	1	298	217		1.92 (1.46, 2.53)	<0.001
	2	7	7		3.80 (1.70, 8.47)	0.0011
Brainmetastases						
	No	374	247		Reference	
	Yes	59	47		1.42 (1.03, 1.95)	0.0327
Subsequent						
	No	269	185		Reference	
	Yes	164	109		0.72 (0.57, 0.92)	0.0095

Figure 4: Forest plot visualizing multivariate proportional hazard cox regression model of factors associated with overall survival (OS) of metastatic NSCLC patients.

Table 3: Univariate analysis (OS)

Variable	n	HR (95%CI)	P-value
Population			
Trial patients	292	1.00	
Real-world patients	141	1.13 (0.88-1.44)	0.34
Age (years)			
<70	349	1.00	
≥70	84	1.25 (0.94-1.66)	0.118
Gender			
Male	225	1.00	
Female	208	0.92 (0.73-1.15)	0.454
Stage			
IV	413	1.00	
IIIB	20	0.85 (0.48-1.22)	0.584
ECOG PS			
0	128	1.00	
1	298	1.95 (1.48-2.55)	<0.001
2	7	3.82 (1.75-8.33)	0.001
Presence of brain metastases			
No	374	1.00	
Yes	59	1.35 (0.99-1.85)	0.059
Histology tumor			
Adenocarcinoma	400	1.00	
Large cell carcinoma	15	1.24 (0.68-2.26)	0.488
Adenosquamous	3	0.94 (0.23-3.79)	0.932
Other	11	0.59 (0.24-1.43)	0.246
Not otherwise specified (NOS)	3	2.45 (0.78-7.65)	0.123
PD-L1 expression			
<1%	141	1.00	
1-49%	86	0.92 (0.66-1.28)	0.606
>50%	76	0.53 (0.36-0.77)	0.001
Unknown	130	1.24 (0.94-1.63)	0.13
Subsequent systemic therapy			
No	269	1.00	
Yes	164	0.68 (0.53-0.86)	0.001

ECOG PS = Eastern Cooperative Oncology Group Performance Score, PD-L1 = Programmed death-ligand 1, HR = Hazard Ratio

Discussion

This EE study with PLD from both real-world patients and trial participants showed that through the arisen possibility of multivariable modeling potential causative factors for an EE gap can be identified. For OS, the HR for real-world versus trials moved to 1.03 after adjustment, suggesting that differences in the available characteristics between both settings can largely explain the altered OS in real-world practice. The latter phenomenon was not observed for PFS, suggesting that for that outcome other unmeasured factors are involved.

The median PFS of real-world patients was longer compared to trial patients, resulting in an HR for PFS below 1.00. Although ECOG PS was statistically significant in the multivariate Cox analyses, the adjusted HR between real-world and trial patients did not change. The etiology for this gap in PFS is believed to be multifactorial, with contributing factors including differences in patient populations, healthcare delivery, and variability in the experience of treating health care providers. Multiple factors which could explain differences in patient populations were measured but did not lead to a difference in HR. Unmeasured factors involving PFS could be smoking status, comorbidities, and frailty. Previous research also showed that use of corticosteroids and the number of organs with metastases are associated with PFS[14]. Healthcare delivery was different in terms of response measurement. According to the original Checkmate-057 trial study protocol, response was evaluated in week 9 after nivolumab initiation and every six weeks thereafter [15]. In real-world practice, response was assessed every eight weeks. This led to visible drops in the Kaplan-Meier for PFS of trial patients, while these are less obvious in the real-world PFS **(supplement 1).** Furthermore, measuring progressive disease using the Response Evaluation Criteria in Solid Tumors (RECIST)- criteria can be less structured and strict in real-world than in trial patients[16]. In clinical practice, the immune responses assigned using RECIST (iRECIST) criteria are used, which include unconfirmed progression[17]. Consequently, conclusions about progressive disease might be delayed in clinical practice what could result in considering possibilities for subsequent systemic treatment later as well. Hypothetically, real-world patients remain treated with nivolumab while with progressive disease, in turn leading to further clinical deterioration reducing the tolerability of subsequent docetaxel, eventually leading to the inverse of the HR for overall survival.

In contrast to PFS, the non-significant difference in OS between real-world and trial almost completely disappeared after adjustment for the available characteristics in the data (aHR of 1.03 (95%CI: 0.79-1.33)). This suggests that differences in ECOG PS, presence of brain metastases, and use of subsequent anti-cancer treatment can almost entirely explain the observed shorter OS in real-world practice. This observation can be considered as a potential for analyzing real-world data.

Unfortunately, no data about ECOG PS at time of deciding for subsequent systemic treatment was available so we could not assess whether applying subsequent treatment or not would be modifiable in clinical practice.

Apart from the advantages of multivariable adjustment, this study also confirms the results using the standard approach of trial and real-world comparison using software applications. The unadjusted calculated HRs for PFS and OS in the study of Cramer-van der Welle *et al* are identical to the findings of this study using PLD.

Strengths and limitations

To our knowledge, this study is the first to use PLD to compare trial and real-world NSCLC patients. The real-world data quality was high since the data were prospectively collected from electronic healthcare records and had very few missing data. An exception is the PD-L1 expression status which was often missing in real-world (48.9%), since it is not mandatory to measure this before nivolumab treatment in second line. We therefore could not use this factor in the multivariate analyses.

A possible limitation was that the trial data only included PFS and OS calculated from the date of randomization and not from the start of nivolumab treatment as in real-world practice. However, as stated in the RCT protocol, nivolumab treatment should be initiated within three business days after randomization[15]. This very short period is unlikely to affect the outcomes of this study and will not introduce bias in the comparison with the Cramer et al paper because that study calculated survival times similarly.

In the present study we assessed the value of PLD with second line nivolumab, while Cramer-van der Welle *et al.* also reported a significant impaired OS in real-world with first line pembrolizumab. Unfortunately, due to unavailability of trial PLD on pembrolizumab, we could not assess what the added value of adjustment with PLD would be for that regimen. The European Medicines Agency (EMA) started an initiative to publish clinical trial data submitted to EMA as part of marketing authorization applications[18]. At the moment, trial data on COVID-19 medicines do become publicly available[19]. Hopefully, initiatives from the EMA and others like ClinicalStudyDataRequest.com will help to improve the availability of much more privacy-proof clinical trial data to allow better identification of factors associated with an efficacy-effectiveness gap (if any), in turn facilitating individualized prognoses and treatment planning [20–22].

Conclusion

This study showed that analyzing PLD from both real-world and trial patients together can lead to better insight in potential factors responsible for a gap in outcomes between these two settings. This emphasizes the relevance of making PLD from clinical trials available to the international research community.

References

[1] Yuan M, Huang L, Chen J, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non- small-cell lung cancer. Signal Transduct Target Ther 2019. doi:10.1038/s41392-019-0099-9.

[2] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csöszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33. doi:10.1056/NEJMoa1606774.

[3] Gettinger SN, Redman MW, Bazhenova L, Hirsch FR, Mack PC, Schwartz LH, et al. Nivolumab Plus Ipilimumab vs Nivolumab for Previously Treated Patients With Stage IV Squamous Cell Lung Cancer The Lung-MAP S1400I Phase 3 Randomized Clinical Trial 2021;06520. doi:10.1001/jamaoncol.2021.2209.

[4] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39. doi:10.1056/NEJMoa1507643.

[5] Ismail RK, Schramel FMNH, Dartel M Van, Hilarius DL, Boer A De, Wouters M, et al. Lung Cancer The Dutch Lung Cancer Audit : Nationwide quality of care evaluation of lung cancer patients 2020;149:68–77. doi:10.1016/j.lungcan.2020.08.011.

[6] Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540–50. doi:10.1016/S0140-6736(15)01281-7.

[7] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65. doi:10.1016/S0140-6736(16)32517-X.

[8] Phillips CM, Parmar A, Guo H, Schwartz D, Isaranuwatchai W, Beca J, et al. Assessing the efficacy-effectiveness gap for cancer therapies: A comparison of overall survival and toxicity between clinical trial and population-based, real-world data for contemporary parenteral cancer therapeutics. Cancer 2020;126:1717–26. doi:10.1002/cncr.32697.

[9] DigitizeIt. DigitizeIt n.d. https://www.digitizeit.xyz/ (accessed August 25, 2021).

[10] Cramer-Van Der Welle CM, Peters BJM, Schramel FMNH, Klungel OH, Groen HJM, Van De Garde EMW. Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer. Eur Respir J 2018;52. doi:10.1183/13993003.01100-2018.

[11] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6. doi:10.1016/0197-2456(96)00075-X.

[12] Vora N, Reckamp KL. Non-Small Cell Lung Cancer in the Elderly: Defining Treatment Options. Semin Oncol 2008;35:590–6. doi:10.1053/j.seminoncol.2008.08.009.

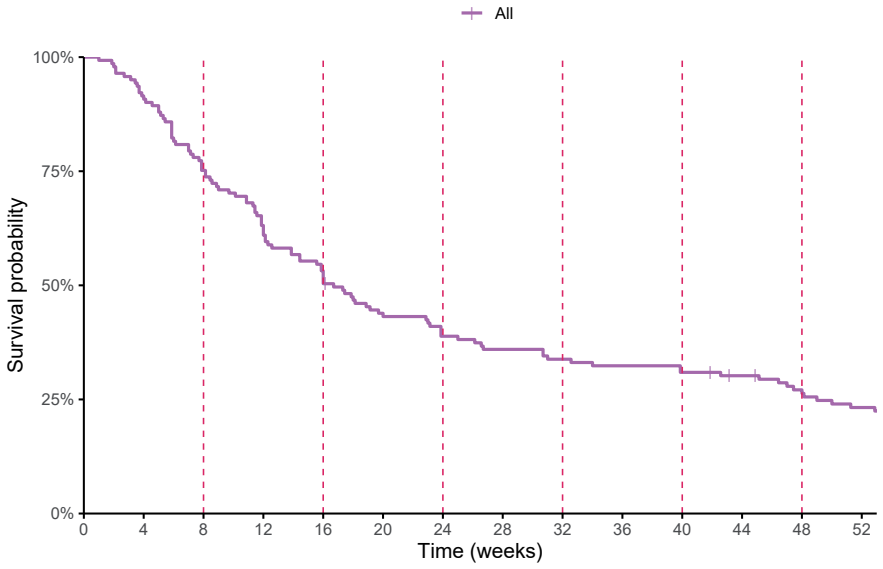
[13] RStudio Team. RStudio: Integrated Development for R n.d.

[14] Hendriks LEL, Henon C, Auclin E, Mezquita L, Ferrara R, Audigier-valette C. Outcome of Patients with Non – Small Cell Lung Cancer and Brain Metastases Treated with Checkpoint Inhibitors. J Thorac Oncol 2019;14:1244–54. doi:10.1016/j.jtho.2019.02.009.

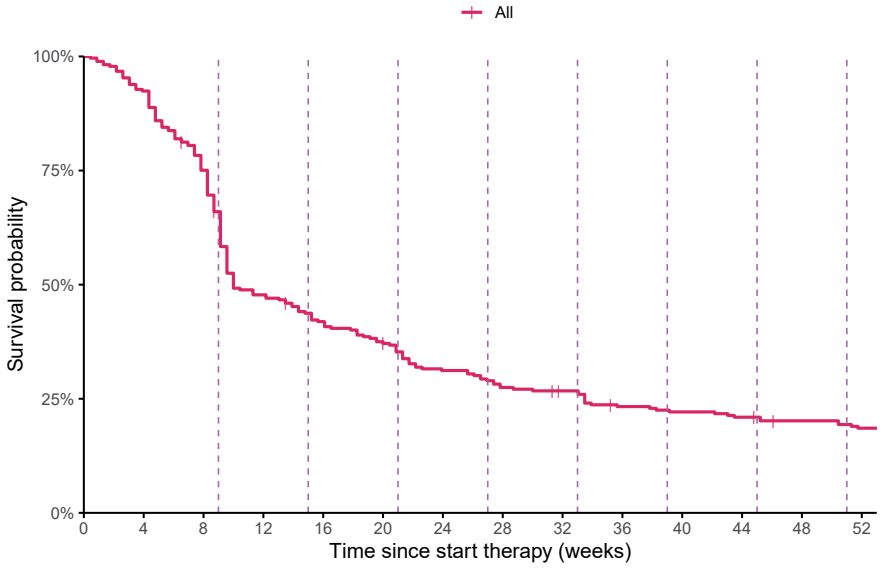
[15] BMS. Clinical Protocol CA209057. 2012. doi:10.1056/NEJMoa1507643.
[16] Feinberg BA, Zettler ME, Klink AJ, Lee CH, Gajra A, Kish JK, et al. Comparison of Solid Tumor Treatment Response Observed in Clinical Practice with Response Reported in Clinical Trials. JAMA Netw Open 2021;4:2–11. doi:10.1001/jamanetworkopen.2020.36741.
[17] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52. doi:10.1016/S1470-2045(17)30074-8.
[18] European Medicines Agency (EMA). Clinical data publication n.d. https://ema.europe.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication (accessed September 7, 2021).
[19] European Medicines Agency (EMA). Online access to clinical data for medicinal products for human use n.d. https://clinicaldata.ema.europa.eu/web/cdp (accessed September 7, 2021).
[20] ClinicalStudyDataRequest.com n.d. https://www.clinicalstudydatarequest.com/ (accessed August 17, 2021).
[21] Kuntz RE, Antman EM, Califf RM, Ingelfinger JR, Krumholz HM, Ommaya A, et al. Individual Patient-Level Data Sharing for Continuous Learning: A Strategy for Trial Data Sharing. NAM Perspect 2019. doi:10.31478/201906b.
[22] Tucker K, Branson J, Dilleen M, Hollis S, Loughlin P, Nixon MJ, et al. Protecting patient privacy when sharing patient-level data from clinical trials. BMC Med Res Methodol 2016;16. doi:10.1186/s12874-016-0169-4.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

Supplement



A



B

Supplement 1: Kaplan-Meier estimate of the PFS of real-world (a) and trial (b) metastatic NSCLC patients treated with nivolumab.
A. Real-world patients in which response is evaluated every eight weeks in the first year of nivolumab treatment.
B. Trial patients in which response was evaluated in week 9 after nivolumab initiation and then every six weeks from week 9, in the first year of nivolumab treatment.

PART III

DIFFERENCES IN OUTCOMES BETWEEN REAL-WORLD AND TRIAL PATIENTS WITH MELANOMA

CHAPTER 6

Real-world outcomes of advanced melanoma patients not represented in phase III trials.

Int J Cancer. 2020 Dec 15;147(12):3461-3470.

M.C.T. van Zeijl*, **R.K. Ismail***, L.C. de Wreede, A.J.M. van den Eertwegh, A. de Boer, M. van Dartel, D.L. Hilarius, M.J.B. Aarts, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, K.P.M. Suijkerbuijk, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, J.B.A.G. Haanen, M.W.J.M Wouters.

*These authors contributed equally to this manuscript

Abstract

Background: The aim was to provide evidence on systemically treated patients with advanced melanoma not represented in phase III trials to support clinical decision-making.

Methods: Analysis were performed on advanced melanoma patients diagnosed between 2014 and 2017 in the Netherlands, treated with immune- or targeted therapy, who met ≥1 trial exclusion criteria. These criteria were derived from the KEYNOTE-006 and CHECKMATE-067/-066 phase III trials. Prognostic importance of factors associated with overall survival (OS) was assessed with the Kaplan Meier method, Cox models, predicted OS probabilities of prognostic subgroups and a conditional inference survival tree (CIST). A nationwide population-based registry was used as data source.

Results: Of 2.536 systemically treated patients with advanced melanoma, 1.004 (40%) patients were ineligible for phase IIII trials. Ineligible patients had a poorer median OS (mOS) compared to eligible patients (8.8 versus 23 months). Eligibility criteria strongly associated with OS in systemically treated ineligible patients were Eastern Cooperative Oncology Group Performance Score (ECOG PS) ≥2, brain metastases (BM) and lactate dehydrogenase (LDH) of >500 U/L. Patients with ECOG PS of ≥2 with or without symptomatic BM had a predicted mOS of 6.5 and 11.3 months and a 3-year survival probability of 9.3% and 23.6%, respectively. The CIST showed the strongest prognostic covariate for survival was LDH, followed by ECOG PS. The prognosis of patients with LDH of >500 U/L is poor, but long-term survival is possible.

Conclusion: The prognosis of ineligible patients with advanced melanoma in real-world was very heterogeneous and highly dependent on LDH value, ECOG PS and symptomatic BM.

Introduction

In recent years, treatment options for advanced melanoma have increased as immune- and targeted therapies became available. The randomized controlled trials (RCTs) used for marketing approval for these treatments showed major improvements in overall response rate, progression-free survival and overall survival (OS) compared to standard treatments[1].

RCTs are considered the gold standard to determine efficacy of new treatments. Strict in- and exclusion criteria are applied to create a homogenous patient population. This improves the internal validity of clinical trials which enables estimation of valid treatment effects of new treatments. A large proportion of real-world patients with advanced melanoma are not represented in clinical trials[2]. Real-world patients not fulfilling the RCT inclusion criteria (ineligible patients) are being treated without evidence of the efficacy and safety in daily clinical practice. Donia et al[3]. concluded that also ineligible patients might have benefited from the introduction of new treatments.

However, the ineligible patient population is heterogeneous. Additional information is needed to determine which subgroups of ineligible patients do not benefit from these new treatments. More efficient use of systemic treatment can spare patients severe adverse events [4,5] and perhaps reduce the financial burden for society[6].

In our study, the nationwide prospective population-based Dutch Melanoma Treatment Registry (DMTR) was used to report clinical outcomes of ineligible patients[7]. Our study aimed to identify prognostic factors for survival for systemically treated ineligible patients, to predict survival for prognostic subgroups of ineligible patients and to order the impact of prognostic factors with a decision tree to help guide clinical decision-making.

Methods

Study design and patients

Patients of 18 years and older, diagnosed with unresectable stage IIIC or stage IV melanoma between 1 January 2014 and 31 December 2017, were included. Criteria to distinguish ineligible from eligible patients were derived from the KEYNOTE-006 and CHECKMATE-067/-066 phase III trials[8–10]. Patients were considered ineligible for potential trial participation if they met one or multiple of the following exclusion criteria:

- Brain metastasis or leptomeningeal metastasis
  - In the DMTR data no distinction could be made between active or not active brain metastasis

- Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2
- Active autoimmune disease(s)
  - Rheumatoid disease, systemic lupus erythematosus, vasculitis, inflammable bowel disease (Crohn's or colitis ulcerosa)
- Immune-modulating medication
  - Azathioprine or interferon
- Known history of Human Immunodeficiency Virus or AIDS
- Liver disease or failure or kidney failure
- Serious psychiatric disorder
  - Schizophrenia, severe depression or psychosis

Dataset cutoff date was 1 June 2019. The medical ethics committee judged that informed consent was not necessary for the DMTR and all patients were offered an opt-out possibility.

Statistical analysis

Baseline patient- and tumor characteristics of systemically treated ineligible and eligible patients were analyzed with descriptive statistics. OS estimates of these groups were estimated with the Kaplan Meier method. Survival times were calculated from the start of systemic therapy until death or last follow-up. Median follow-up time was estimated with the reverse Kaplan-Meier method[11]. Within the systemically treated ineligible patient population, univariable and multivariable Cox proportional hazards regression models were used to estimate the association of exclusion criteria and other clinically relevant prognostic factors with OS[12]. Variables assessed were lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group Performance Score (ECOG PS), age, gender, metastases in ≥3 organ sites, brain metastases, liver metastases, year of diagnosis, autoimmune disease, psychiatric disorder and BRAF mutation. The analyses of complete cases are not shown. The proportionality assumption in the Cox models was investigated by means of scaled Schoenfeld residuals.

For further analyses, we created prognostic subgroups of patients based on the most important factors from the multivariable Cox model. We used the full multivariable Cox model to predict the patient-specific probability of OS. For all subgroups the median OS (mOS) and 3-year OS probability were calculated based on these individual predicted probabilities.

To assess the potential benefit of systemic therapy in the absence of a historical cohort, we created a control group by selecting systemically treated and untreated ineligible patients diagnosed with advanced melanoma in 2013. We compared casemix-adjusted survival curves of this 2013 cohort with our study population. In the 2013 cohort of ineligible patients, 29% received no systemic treatment, 14% received chemotherapy, 37%

ipilimumab or BRAF inhibitor monotherapy as first-line treatment and 21% of the patients received another systemic therapy (patients treated in named-patient or compassionate use programs or in trials).

We constructed a decision tree model using the recursive binary partitioning approach. The method of Hothorn et al. [13] was used to create a conditional interference survival tree (CIST). The variables used in the model were gender, age, LDH, ECOG PS, number of organs with distant metastases, brain- and liver metastases, year of diagnosis and BRAF-mutation. First, the model determines which variable is most strongly associated with OS. Secondly, a cut-off value in this variable is calculated that optimally splits the data creating two most prognostically different subpopulations. The model then repeats these two steps taking the two new nodes as the basis. The model stops if no variable significantly associated with OS is left and no prognostic difference is seen when partitioning the subpopulation further[13].

Data handling and statistical analyses were performed using the R software system for statistical computing (version 3.6.1.; packages tidyverse, lubridate, car, survival, survminer, partykit).

Results

From 2014 to 2017, 3,460 patients were diagnosed with unresectable stage IIIC and stage IV (advanced) melanoma prospectively registered in the DMTR. Patients diagnosed with uveal melanoma, age of <18 years and patients with missing values to determine eligibility or missing survival data were excluded from further analyses. Of the remaining 3,009 patients, 1,004 (40%) systemically treated patients with advanced melanoma were considered ineligible.

Eligible versus ineligible patients

The main differences in characteristics between ineligible patients and eligible patients were related to the exclusion criteria, such as the presence of brain metastases (*n*=682, 67.9%), ECOG PS of ≥2 (*n*=281, 28.0%) and the presence of active autoimmune diseases (*n*=141, 14.0%) in ineligible patients (**table 1**). Besides these differences in exclusion criteria, other baseline characteristics were significantly more common in ineligible patients compared to eligible patients, such as elevated LDH level of ≥250 U/L, stage IVM1c disease, liver metastasis, metastasis in ≥3 organ sites and the presence of BRAF mutation (**table 1**).

The mOS of systemically treated ineligible patients was shorter compared to systemically treated eligible patients (8.8 months (95%CI: 7.9-11.0) versus 23 months (95%CI: 21-27)). The 3-year OS probability was 22% (95%CI: 19-25) for ineligible patients and 41% (95%CI:

Table 1 Patient- and tumor characteristics of systemically treated for phase III trials ineligible and eligible patients[a]

	Ineligible (n = 1004)	Eligible (n = 1532)	P-value
Median age, year (range)	62 [19, 94]	64 [19, 94]	0.080
Age categories			0.035
<50yr	176 (17.5)	273 (17.8)	
50-59yr	259 (25.8)	320 (20.9)	
60-69yr	274 (27.3)	452 (29.5)	
>70yr	295 (29.4)	487 (31.8)	
Female	422 (42.0)	607 (39.6)	0.238
ECOG PS			
0	357 (38.3)	1028 (67.1)	
1	295 (31.6)	504 (32.9)	
2	204 (21.9)	-	
≥3	77 (8.3)	-	
Unknown	71	-	
LDH level			<0.001
Normal	528 (54.0)	1052 (69.8)	
250-500 U/L	283 (28.9)	332 (22.0)	
>500 U/L	167 (17.1)	124 (8.2)	
Unknown	26	24	
Stage			<0.001
IIIc	17 (1.7)	150 (9.8)	
IV-M1a	22 (2.2)	172 (11.2)	
IV-M1b	29 (2.9)	246 (16.1)	
IV-M1c	934 (93.2)	962 (62.9)	
Metastases in ≥3 organ sites	620 (61.9)	549 (35.8)	<0.001
Brain metastasis			
No	308 (31.1)	1532 (100.0)	
Yes, asymptomatic	237 (23.9)	-	
Yes, symptomatic	445 (44.9)	-	
Unknown	14	-	
Liver metastasis	311 (31.7)	387 (25.4)	0.001
Auto-immune disease*	141 (14.0)	-	
IM medication**	4 (0.4)	-	
HIV or AIDS	1 (0.1)	-	
Psychiatric disorder***	51 (5.1)	-	
BRAF mutant	671 (66.8)	833 (54.3)	<0.001

* Rheumatoid disease, systemic lupus erythematosus, vasculitis, inflammable bowel disease (Crohn's or colitis ulcerosa).** Azathioprine, interferon.***Schizophrenia, major depression, psychosis and other psychiatric disorders. ECOG PS - Eastern Cooperative Oncology Group performance status, LDH – lactate dehydrogenase, IM- immune modulating.

[a]Values are n (%) unless otherwise indicated.

38-43) for eligible patients (**figure 1**). The median follow-up of systemically treated ineligible patients was 38 months.

Treatment and clinical outcomes of ineligible patients

A total of 862 (85.9% of the ineligible patients) patients would have been excluded from trial participation, because of either brain metastases or ECOG PS ≥2, or both. The first- and second-line treatments of ineligible patients are shown in **figure 2**.

In the multivariable Cox model, ECOG PS ≥2, elevated LDH ≥500 U/L and the presence of symptomatic brain metastases and liver metastases were negatively associated with OS. BRAF mutational status was not associated with OS (**table 2**).

Comparison of the casemix-adjusted survivalcurves of the 2013 cohort with our study cohort of 2014 to 2017 indicated that OS for ineligible patients has increased when more systemic therapies were available (mOS of 5.7 months versus 8.8 months, respectively). The 3-year OS probability of the 2013 cohort was 7.5% versus 22% of our study cohort (data not

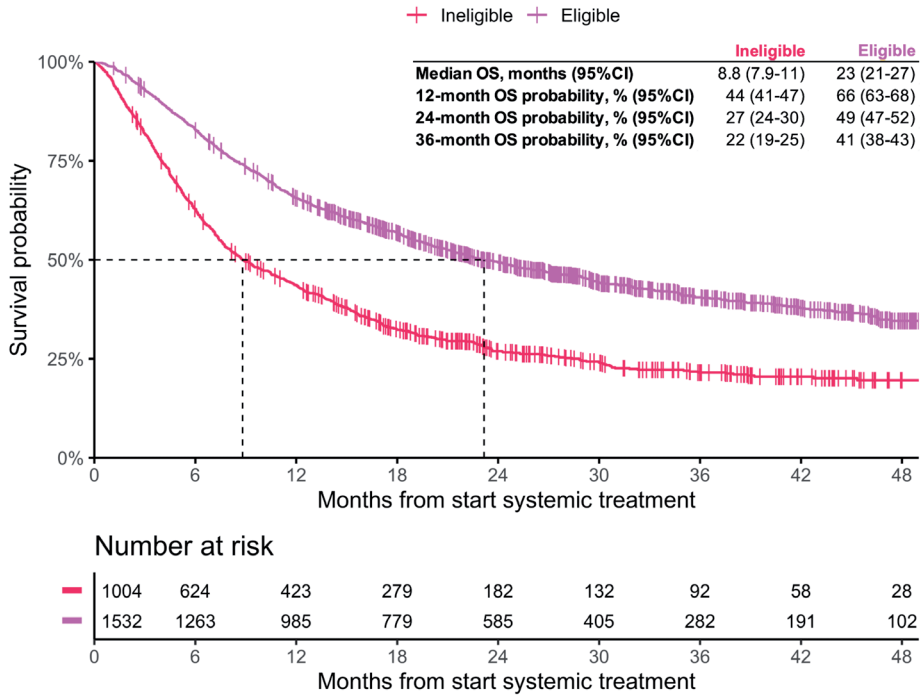


Figure 1: Overall survival of systemically treated ineligible and eligible advanced melanoma patients estimated with the Kaplan-Meier method.

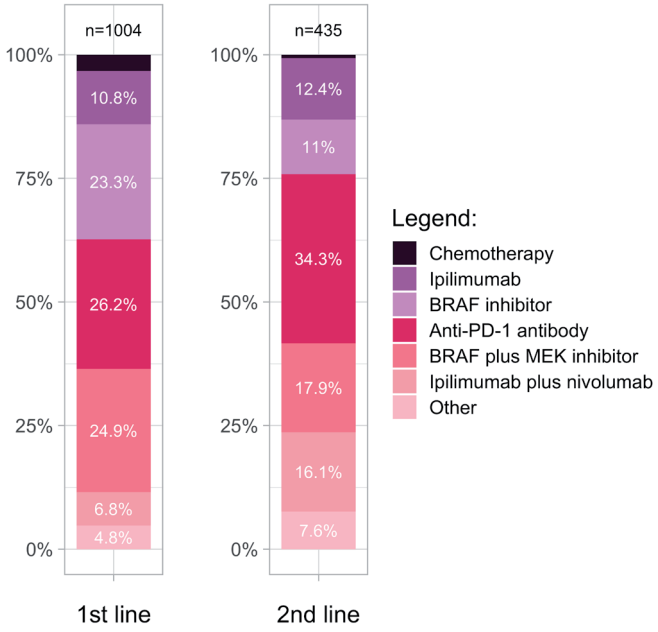


Figure 2: First- and second-line systemic treatments for systemically treated ineligible advanced melanoma patients in 2014-2017.

Table 2 Cox model of systemically treated ineligible patients for the association of prognostic factors with overall survival.

	Univariable				Multivariable			
	n	**HR**	**95% CI**	**P-value**	**n**	**HR**	**95% CI**	**P-value**
Year of diagnosis								
2014	203	1			173	1		
2015	262	0.91	(0.75-1.12)	0.383	226	0.84	(0.67-1.05)	0.129
2016	244	0.76	(0.61-0.93)	0.009	219	0.70	(0.56-0.87)	0.002
2017	295	0.73	(0.59-0.91)	0.004	264	0.61	(0.48-0.77)	<0.001
Age								
≤50	176	0.70	(0.56-0.87)	0.002	148	0.65	(0.51-0.84)	0.001
50-59	259	0.84	(0.69-1.02)	0.08	228	0.79	(0.64-0.98)	0.032
60-69	274	1			245	1		
≥70	295	0.98	(0.81-1.18)	0.792	261	1.02	(0.83-1.24)	0.885
Gender								
Male	582	1			511	1		
Female	422	0.90	(0.78-1.04)	0.149	371	0.91	(0.78-1.07)	0.245
ECOG PS								
0	357	1			342	1		
1	295	1.46	(1.21-1.75)	<0.001	278	1.35	(1.11-1.65)	0.003
≥2	281	2.09	(1.75-2.51)	<0.001	262	1.95	(1.52-2.5)	<0.001

Table 2 continued

	Univariable				Multivariable			
	n	**HR**	**95% CI**	**P-value**	**n**	**HR**	**95% CI**	**P-value**
LDH								
Normal	528	1			475	1		
250-500 U/L	283	1.44	(1.21-1.7)	<0.001	259	1.23	(1.02-1.49)	0.03
>500 U/L	167	2.64	(2.17-3.2)	<0.001	148	1.89	(1.49-2.41)	<0.001
Metastases in ≥3 organ sites								
No	382	1			339	1		
Yes	620	1.57	(1.35-1.83)	<0.001	543	1.25	(1.03-1.51)	0.021
Brain metastasis								
Absent	308	1			295	1		
Asymptomatic	237	0.95	(0.78-1.16)	0.614	208	1.31	(0.98-1.75)	0.069
Symptomatic	445	1.25	(1.06-1.48)	0.01	379	1.71	(1.34-2.18)	<0.001
Liver metastasis								
No	671	1			602	1		
Yes	311	1.64	(1.4-1.9)	<0.001	280	1.22	(1-1.48)	0.049
Auto-immune disease								
No	863	1			754	1		
Yes	141	0.71	(0.57-0.89)	0.003	128	1.02	(0.77-1.35)	0.892
Psychiatric disorder								
No	953	1			835	1		
Yes	51	0.69	(0.49-0.99)	0.044	47	0.93	(0.62-1.4)	0.721
BRAF-mutant								
No	333	1			302	1		
Yes	671	1.06	(0.91-1.24)	0.47	580	0.94	(0.79-1.12)	0.474

ECOG PS – Eastern Cooperative Oncology Group performance status, LDH – lactate dehydrogenase, HR – hazard ratio, CI – confidence interval

shown). The mOS of systemically untreated ineligible patients diagnosed with advanced melanoma from 2014 to 2017 (*n*=327) was 2.4 (95%CI: 2.1-2.8) months (data not shown).

We created 18 subgroups of systemically treated ineligible patients by combining the most important exclusion criteria from the multivariable Cox model, ECOG PS, and brain metastases with LDH level, as LDH level is an important prognostic factor for survival [12,14]. Each subgroup was assessed for the predicted mOS and 3-year survival probability (**table 3**). The predicted survival curves of individual patients in the subgroups showed substantial prognostic variation in survival between patients in a subgroup (data not shown). The covariates BRAF mutational status, LDH, ECOG PS and brain metastases violated the proportionality assumption. To keep interpretation easy and avoid overfitting, time-dependent effects of these risk factors were not modeled explicitly. The HRs have to be interpreted as averages over the follow-up time. The predicted probability curves also

represent these averaged effects. The non-proportionality of BRAF mutation was further investigated in a Cox model in which this variable was entered as a stratification factor.

The conditional inference survival tree resulted in six subgroups (**figure 3**). The covariate with the strongest association with survival was LDH. For patients with an LDH level of >500 U/L, other covariates did not significantly influence the OS. The most prognostic covariate in the subgroup of patients with a normal or LDH level of 250-500U/L was ECOG PS followed by symptomatic brain metastases.

BRAF mutational status

We performed an additional analysis of BRAF-mutant versus BRAF wild-type melanoma because BRAF mutational status was not associated with OS in the multivariable Cox model

Table 3 Subgroups of ineligible patients with predicted median overall survival and median of predicted 3-year survival probability based on the multivariable Cox model.

ECOG PS	Brain metastasis	LDH level	n	Predicted mOS (months)	3-year Survival (%)
0-1	Absent	normal	82	22.7	44.5
0-1	Absent	250-500U/L	32	15.4	33.1
0-1	Absent	>500U/L	14	7.9	15.3
0-1	Asymptomatic	normal	119	16.4	35.1
0-1	Asymptomatic	250-500U/L	63	9.9	21.0
0-1	Asymptomatic	>500U/L	16	6.0	7.2
0-1	Symptomatic	normal	191	11.9	25.0
0-1	Symptomatic	250-500U/L	94	7.2	12.4
0-1	Symptomatic	>500U/L	21	5.0	3.7
≥2	Absent	normal	53	11.3	23.6
≥2	Absent	250-500U/L	50	7.6	14.1
≥2	Absent	>500U/L	65	4.8	3.2
≥2	Asymptomatic	normal	3	11.0	22.7
≥2	Asymptomatic	250-500U/L	6	6.2	8.1
≥2	Asymptomatic	>500U/L	10	4.8	3.1
≥2	Symptomatic	normal	37	6.5	9.3
≥2	Symptomatic	250-500U/L	18	4.7	3.1
≥2	Symptomatic	>500U/L	24	3.4	0.3

mOS - median overall survival, ECOG PS – Eastern Cooperative Oncology Group performance status, LDH – lactate dehydrogenase, ULN – upper limit of normal

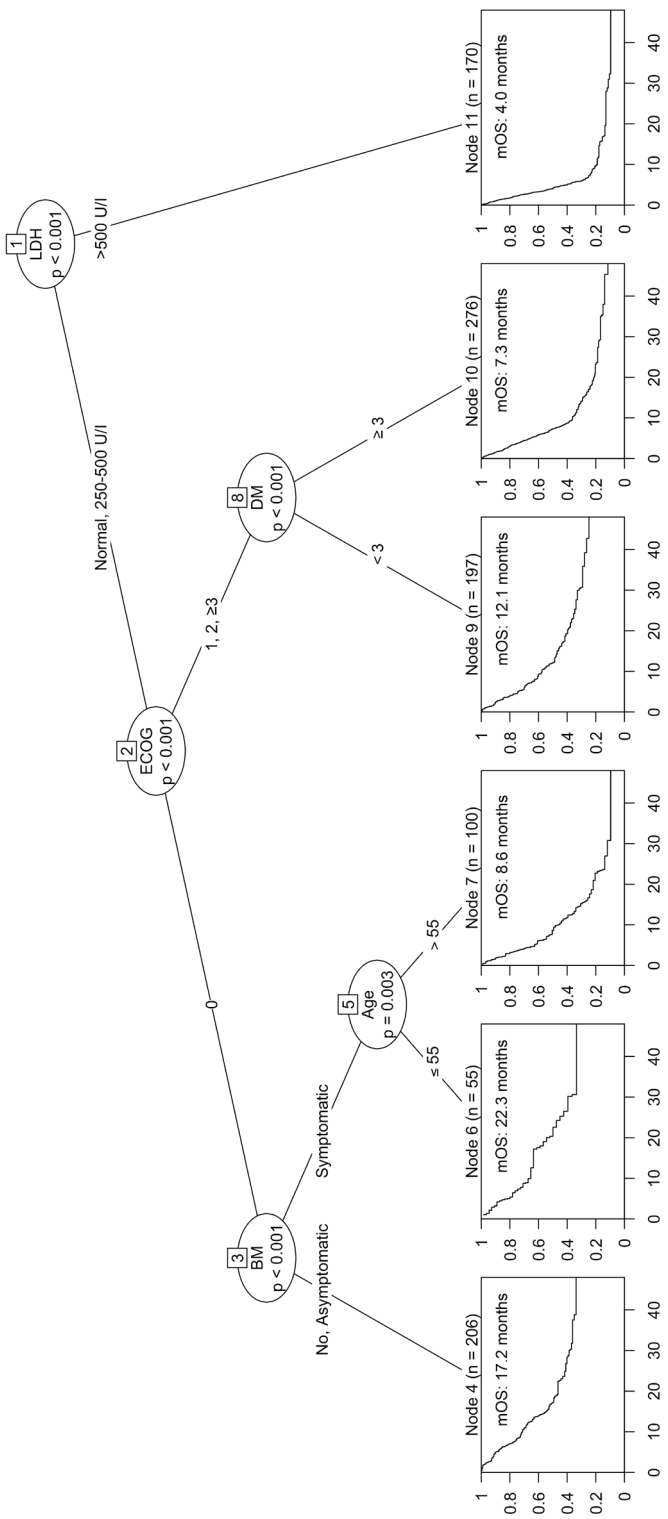


Figure 3: Conditional inference survival tree incorporating disease and patient variables into prognostic models for survival, based on year of diagnosis, age, gender, ECOG PS, LDH level, distant metastases, brain- and liver metastases and BRAF mutational status. P-values are from log-rank statistics.

(**table 2**). The casemix-adjusted OS curves showed that the small survival benefit in favor of the BRAF mutated melanoma established in the first 6 months, disappeared after 10 months (data not shown).

Discussion

Our study focused on clinical outcomes of ineligible advanced melanoma patients treated with systemic therapy in real-world. There is no RCT evidence to justify treatment in these patients, but our study fills this knowledge gap and provides guidance in shared decision-making. Forty percent of the systemically treated patients were considered ineligible following the exclusion criteria of phase III trials[8–10]. Although OS of systemically treated ineligible patients was significantly lower than the OS of systemically treated eligible patients, the 3-year OS probability of ineligible patients was still 22%. There was a high variation in (predicted) OS within the ineligible patient population, except for most subgroups with an LDH level of >500 U/L. The decision tree (CIST) [13] technique identified clinically interesting prognostic subgroups that can be used to prognostically stratify and inform ineligible patients in daily practice.

In-depth post-approval research cannot replace RCTs, but it is necessary to try to substantiate the effectiveness of using new systemic treatments in real-world patients. The distinction in eligibility for trial participation is factitious. Eligibility depends on having one or multiple exclusion criteria that were once defined for phase III trials, but not all exclusion criteria are equally important with regard to the prognosis and/or effect of treatment (i.e. psychiatric disorder and immune-modulating medication). The ineligible patient population is heterogeneous in itself and with different statistical approaches, we attempted to provide in-depth evidence on what effect exclusion criteria have on survival in the real-world.

In our study, 86% of systemically treated ineligible patients had brain metastasis, ECOG PS of ≥2 or both. Brain metastases and ECOG PS were combined with LDH level, a non-exclusion criterion that is generally known for its prognostic and predictive importance, to create subgroups[12,14]. For subgroups of patients with (a)symptomatic brain metastases, the prognosis was relatively good, provided that ECOG PS was ≤1 and LDH level was normal. The decision tree (CIST) model also showed that ineligible patients with an LDH level of >500 U/L were a prognostic subgroup with poor survival. We previously showed the dismal prognosis in this group of patients and proposed switching to ICI upon response to BRAF(/MEK-)-inhibition with LDH normalization as a potential strategy to obtain long-term survival in these patients[15]. This information supports well-informed use of systemic therapy in this patient group.

Clinical benefit

It is important to estimate the clinical benefit of systemic treatment in ineligible patients to decide whether possible treatment benefit is worth the risk of side-effects for individual patients and the financial burden for society. Donia et al. [2,3] found that the (unadjusted) survival of ineligible patients improved over time and suggested that these patients might have benefited from systemic treatment. In the Netherlands, there are no guidelines for patients with advanced melanoma recommending systemic treatment for specific subgroups. Results from RCTs have to be extrapolated to the real-world population. For specific subgroups of patients, the choice to offer systemic therapy is, in most cases, based on the expertise of the medical team. In general, the interpretation of observational data for the effectiveness of treatment is complicated by the lack of a comparator. Moreover, a clear definition of significant clinical benefit is lacking. The American Society of Clinical Oncology (ASCO) Value Framework [16] and the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) [17,18] were developed to assess the clinical benefit of new cancer therapies in clinical trials. However, lack of real-world comparison prohibits translation of these scales into daily practice.

We attempted to estimate the magnitude of the benefit from systemic treatment by comparing our study cohort to a surrogate control group from the DMTR. This surrogate control group was comprised of patients comprised of both systemically treated and untreated ineligible patients diagnosed in 2013 when only chemotherapy, ipilimumab and BRAF-inhibitors (dabrafenib and vemurafenib) monotherapy were available as standard treatments outside a trial setting. We observed a mOS benefit of 3.1 months and a 3-year survival probability increase of 14% to 22% of our study cohort (**figure 3**). This suggest that ineligible patients have benefitted from systemic treatments. We are aware of the statistical limitations of the comparison with the artificially created 'control group'. However, HRs of year of diagnosis 2016 and 2017 from the Cox also indicate that with the availability of more effective immune- and targeted therapies, OS has improved for systemically treated trial-ineligible patients with advanced melanoma in the Netherlands. Importantly, the full potential of ipilimumab plus nivolumab combination therapy may not have been achieved yet, because it only became available in the Netherlands in November 2016.

BRAF mutational status

A high proportion of systemically treated ineligible patients had a BRAF-mutated melanoma. For patients who are in poor condition, which can be partly due to advanced melanoma, or patients with brain metastases (or both), the threshold to start with targeted therapy may be low. Targeted therapy for advanced melanoma is known for its potential dramatic anti-tumor activity and short time to first response[19]. A notable finding in our Cox model was that BRAF-mutational status was not associated with OS. The initial survival advantage of patients with BRAF-mutated melanoma did not persist. Our results do not appear to

support an alleged synergy of (sequential) treatment with targeted- and immunotherapy in the ineligible patient population[20].

RCT recommendations

Currently, evidence on the effectiveness of systemic treatment in patients with melanoma brain metastases is being generated in phase II clinical trials[21,22]. In our study, 27% of all patients with advanced melanoma had (a)symptomatic brain metastases. We found that of the trial exclusion criteria, that having brain metastasis was one of the most important prognostic factors for survival. We observed, on the other hand, that some of these patients with brain metastasis could still reach long-term survival. Therefore, we advocate that patients with brain metastases should be included in RCTs. This will lead to a more representative casemix and an increase in evidence for effective systemic treatment of patients[23].

Limitations

There are limitations to our study. We used observational data of a nationwide population-based registry to analyze daily practice. Systemic treatment of ineligible patients was dependent on considerations of the medical team and patient. The mOS of untreated ineligible patients in the same period was less than 3 months (data not shown). This indicates that the selection of ineligible patients suitable for treatment was justified. However, we were not able to estimate the influence of systemic treatment, because we do not know what the outcomes would have been if untreated patients would have been treated and vice versa. The effectiveness of individual targeted- or immunotherapies could not be investigated due to confounding by indication. We did not analyze safety of systemic treatment, and data on quality of life and exact treatment costs were not available, but these topics are important to further improve clinical decisions for starting systemic therapy in ineligible patients.

Strengths

Although we used registry data, we argue the data are of high quality since trained data managers check electronic patient records every 3 months with quality control of data by medical oncologists. The DMTR has nationwide coverage and includes patients without treatment as well [7].

Results from our study can be used to inform patients on probable prognosis to make well-informed shared-decision and set realistic treatment goals. In patients with (multiple) unfavorable prognostic factors refraining from systemic treatment should be seriously considered. Our real-world clinical results can be used in the treatment of future ineligible patients. The CIST method could also be used in future research for the entire patient population of advanced melanoma patients to further improve shared-decision making.

Furthermore, if individual trial data would be publicly available, comparison of RCT data with real-world data could lead to a better understanding of clinical outcomes.

References

[1] Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247-57. doi:10.1016/j.ejca.2017.06.028.

[2] Donia M, Kimper-Karl ML, Høyer KL, Bastholt L, Schmidt H, Svane IM. The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials. Eur J Cancer 2017;74:89-95. doi:10.1016/j.ejca.2016.12.017.

[3] Donia M, Ellebaek E, Øllegaard TH, Duval L, Aaby JB, Hoejberg L, et al. The real-world impact of modern treatments on the survival of patients with metastatic melanoma. Eur J Cancer 2019;108:25-32. doi:10.1016/j.ejca.2018.12.002.

[4] Schadendorf D, Wolchok JD, Stephen Hodi F, Chiarion-Sileni V, Gonzalez R, Rutkowski P, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: A pooled analysis of randomized phase II and III trials. J Clin Oncol 2017;35:3807–14. doi:10.1200/JCO.2017.73.2289.

[5] Daud A, Tsai K. Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma. Oncologist 2017;22:823–33. doi:10.1634/theoncologist.2016-0456.

[6] Franken MG, Leeneman B, Jochems A, Schouwenburg MG, Aarts MJB, Van Akkooi ACJ, et al. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands. Anticancer Drugs 2018;29:579–88. doi:10.1097/CAD.0000000000000628.

[7] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156–65. doi:10.1016/j.ejca.2016.11.021.

[8] Schachter J, Ribas A, Long G V., Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853–62. doi:10.1016/S0140-6736(17)31601-X.

[9] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated Melanoma. N Engl J Med 2015;373:23–34. doi:10.1056/NEJMoa1504030.

[10] Robert C, Long G V., Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30. doi:10.1056/NEJMoa1412082.

[11] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6. doi:10.1016/0197-2456(96)00075-X.

[12] Long G V., Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination

treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol 2016;17:1743–54. doi:10.1016/S1470-2045(16)30578-2.

[13] Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: A conditional inference framework. J Comput Graph Stat 2006;15:651–74. doi:10.1198/106186006X133933.

[14] Diem S, Kasenda B, Spain L, Martin-Liberal J, Marconcini R, Gore M, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. Br J Cancer 2016;114:256–61. doi:10.1038/bjc.2015.467.

[15] Schouwenburg MG, Suijkerbuijk KPM, Koornstra RHT, Jochems A, Van Zeijl MCT, Van Den Eertwegh AJM, et al. Switching to immune checkpoint inhibitors upon response to targeted therapy; the road to long- term survival in advanced melanoma patients with highly elevated serum LDH? Cancers (Basel) 2019;11. doi:10.3390/cancers11121940.

[16] Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33:2563–77. doi:10.1200/JCO.2015.61.6706.

[17] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015;26:1547–73. doi:10.1093/annonc/mdv249.

[18] Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017;28:2340–66. doi:10.1093/annonc/mdx310.

[19] Kong BY, Carlino MS, Menzies AM. Biology and treatment of BRAF mutant metastatic melanoma. Melanoma Manag 2016;3:33–45. doi:10.2217/mmt.15.38.

[20] Wargo JA, Cooper ZA, Flaherty KT. Universes collide: Combining immunotherapy with targeted therapy for cancer. Cancer Discov 2014;4:1377–86. doi:10.1158/2159-8290.CD-14-0477.

[21] Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722–30. doi:10.1056/NEJMoa1805453.

[22] Long G V., Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672–81. doi:10.1016/S1470-2045(18)30139-6.

[23] Kim ES, Bruinooge SS, Roberts S, Ison G, Lin NU, Gore L, et al. Broadening eligibility criteria to make clinical trials more representative: American society of clinical oncology and friends of cancer research joint research statement. J Clin Oncol 2017;35:3737–44. doi:10.1200/JCO.2017.73.7916.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology, interpretation, writing and revising of the manuscript.

CHAPTER 7

Adjuvant treatment for melanoma in clinical practice – trial versus reality.

Eur J Cancer. 2021 Nov 01;158:234-245.

M.M. de Meza*, **R.K. Ismail***, D.Rauwerdink, O.J. van Not, J. van Breeschoten, W.A.M. Blokx, A. de Boer, M.van Dartel, D.L. Hilarius, E. Ellebaek, H.J. Bonenkamp, C.U. Blank, M.J.B. Aarts, A.C.J. van Akkooi, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, J.B.A.G Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, A.A.M. van der Veldt, A. Vreugdenhil, H.M. Westgeest, A.J.M. van den Eertwegh, K.P.M. Suijkerbuijk, M.W.J.M. Wouters.

*These authors contributed equally to this manuscript

Abstract

Background: Little is known about outcomes of adjuvant-treated melanoma patients beyond the clinical trial setting. Since 2019, adjuvant-treated melanoma patients have been registered in the DMTR, a population-based registry to monitor the quality and safety of melanoma care in the Netherlands. This study aims to describe treatment patterns, relapse, and toxicity rates of adjuvant-treated melanoma patients beyond the clinical trial setting.

Methods: Analyses were performed on adjuvant-treated melanoma patients included in the DMTR. Descriptive statistics were used to analyze patient-, and treatment characteristics. A baseline registration completeness analysis was performed, and an analysis on trial eligibility in clinical practice patients. Recurrence-free survival (RFS) at 12-months was estimated with the Kaplan-Meier method.

Results: A total of 641 patients were treated with adjuvant anti-PD-1 therapy. RFS at 12-months was 70.6% (95% CI, 66.9-74.6) with a median follow-up of 12.8 months. Sex, stage of disease and Breslow thickness were associated with a higher hazard for RFS. Eighteen percent of the anti-PD-1-treated patients developed grade ≥3 toxicity. Sixty-one percent of patients prematurely discontinued anti-PD-1 therapy.

Conclusion: Adjuvant anti-PD-1 treatment of resected stage III/IV melanoma in daily practice showed slightly higher toxicity rates and more frequent premature discontinuation but similar RFS rates compared to trials.

Introduction

Since 2011, the treatment landscape of metastatic melanoma has changed dramatically[1]. With the introduction of immunotherapy and targeted therapy, the survival of these patients has improved[2,3]. In July 2013, the Dutch Melanoma Treatment Registry (DMTR) was initiated, and advanced melanoma care in the Netherlands was centralized in 14 melanoma centers to assure the safety and quality of care for these patients[4].

The DMTR is one of the 22 national quality registries facilitated by the Dutch Institute for Clinical Auditing (DICA)[5]. The DMTR is a population-based nationwide registry, including all irresectable stage IIIC and stage IV melanoma patients in the Netherlands[4]. After the approval and reimbursement of adjuvant systemic therapy with checkpoint inhibitors in December 2018, the inclusion criteria of the DMTR were extended in 2019 also to include patients with resectable stage III and IV melanoma, who were referred to one of the melanoma centers for adjuvant systemic treatment[6,7]. All patients with a completely resected melanoma stage IIIA (≥1 mm metastasis) or higher are eligible for adjuvant systemic treatment in the Netherlands[8].

The Checkmate-238 trial and EORTC 1325/Keynote-054 trial were the clinical trials that led to the registration and approval of immune checkpoint inhibitors as adjuvant systemic treatment in resected stage III and IV melanoma. In the Checkmate-238, nivolumab demonstrated longer recurrence-free survival at 12-months compared to ipilimumab in patients with resected stage IIIB-C and stage IV melanoma. In the nivolumab group recurrence-free survival at 12-months was 70.5% (95% IC, 66.1-74.5) compared to 60.8% (95% CI, 56.0-65.2) in the ipilimumab group[9]. Nivolumab also demonstrated lower toxicity compared to ipilimumab 14.4% versus 45.9% treatment-related grade 3-4 toxicity in the nivolumab and ipilimumab group, respectively[9]. In the EORTC 1325/Keynote-054 trial, pembrolizumab was compared to placebo in high-risk resected stage III melanoma patients. At 12 months, the recurrence-free survival rate was 75.4% (95% CI, 71.3-78.9) in the pembrolizumab group, compared to 61.0% (95% CI, 56.5-65.1) in the placebo group. Treatment-related grade 3-5 toxicity was reported in 14.7% of patients in the pembrolizumab group, compared to 3.4% in the placebo group.

Little is known about the outcomes of adjuvant systemic therapy beyond the clinical trial setting. Previous studies on real-world results of adjuvant treatment of stage III melanoma patients showed that anti-CTLA-4 therapy in stage III melanoma patients improved overall survival[10]. In another study in daily practice patients, Owen et al. demonstrated the poor outcomes of patients who recur on adjuvant anti-PD-1 therapy[9]. Here, we aim to give an overview of patients receiving adjuvant systemic treatment for resected stage III/IV melanoma in daily clinical practice and describe the first adjuvant treatment results with checkpoint inhibitors in the Netherlands.

Methods

Study population and database

Data for this study were derived from the nationwide prospective DMTR[4]. Data are registered into the DMTR through an online survey by trained data managers. The coordinating oncologist then approves these data derived from the patients' electronic medical records. The DMTR database is updated annually to reflect new developments in melanoma care and changes in clinical practice. These include new treatment modalities or drugs, novel treatment regimens, or insight into new biomarkers or mutations. Fourteen data entry items were added to the DMTR to include (neo-)adjuvant treated patients. These items are listed in **supplement 1** and consist of, for example, the additional registration of stage III substage, the presence and extent of in-transit metastases, lymph node dissection procedures and their radicality, and the context of the combination of systemic therapy and surgery (adjuvant or neo-adjuvant). In **supplement 2,** the structure of the dataset is shown.

This study's patient population consisted of all resectable stage III and IV cutaneous melanoma patients diagnosed between 01-07-2018 and 31-12-2019 and treated with adjuvant systemic treatment as the first line of systemic therapy. The data cut-off date was March 1st, 2021. Adjuvant systemic therapy was defined as 'systemic therapy after complete resection of melanoma'. Per the Dutch consensus on stage III/IV resected melanoma treatment, adjuvant systemic treatment is given for 12 months and should be initiated within 12 weeks of complete surgical resection[8]. Patients who received adjuvant treatment underwent FDG-PET-CT or CT scanning within three months before the start of systemic therapy. In the inclusion period, adjuvant anti-PD-1 (nivolumab or pembrolizumab) for 12 months was the only adjuvant systemic therapy reimbursed in the Netherlands. For this reason, only a limited number of patients were treated with BRAF/MEK inhibitors. These patients were excluded from further analysis.

Statistical analysis

Study population

Descriptive statistics were used to describe patient- and tumor characteristics. A baseline patient record was considered complete if the following items were registered: age, gender, Eastern Cooperative Oncology Group performance score (ECOG PS), primary tumor location, Breslow thickness (BT), and presence of ulceration, date of surgery, starting date of systemic therapy, type of systemic therapy. Items registered as 'unknown' were considered incomplete. In melanoma with an unknown primary location, the patient record was considered complete if age, gender, ECOG PS, date of surgery, starting date of systemic therapy, and type of systemic therapy were registered. Data completeness was analyzed to give insight into the data quality of patients treated with adjuvant systemic treatment.

We performed an analysis on the eligibility for trial participation in our study population, based on the patient- and tumor characteristics used as in- and exclusion criteria for the EORTC 1325/Keynote-054 and the Checkmate-238 trial[9–11]. Patients were considered ineligible if they met one or more of the following criteria: age ≤15 years, ECOG PS≥2, uveal melanoma, presence of auto-immune disease, and presence of HIV infection.

We provide a description of the treatment characteristics of our study population and give an overview of toxicity rates and estimate the recurrence-free survival (RFS) at 12-months. The RFS at 12-months was estimated with the Kaplan-Meier method. Patients who did not meet the endpoint (recurrence or death) were censored at the date of last follow-up. The median follow-up duration was calculated with the reversed Kaplan-Meier method. Comparison between different stages of disease was performed using a log-rank test at a two-sided alpha level. Stage of disease was classified using the American Joint Committee on Cancer (AJCC) 7th and AJCC 8th edition[12, 13]. A univariate and multivariate Cox-proportional hazard model analysis was performed to identify factors (age, gender, performance score, stage of disease, Breslow thickness, ulceration, BRAF-V600-status, in-transit metastases) influencing RFS. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Only CTCAE grade ≥3 treatment-related toxicity and any grade toxicity necessitating treatment discontinuation are registered in the DMTR.

One-year follow-up group

Analyses of toxicity and early discontinuation rates were performed in patients with a minimum follow-up time of 12 months since starting adjuvant anti-PD-1 treatment or death within 12 months. We will refer to this group as the one-year follow-up group.

The treatment patterns and responses of the one-year follow-up group were described and visualized in a Swimmer plot. Early treatment discontinuation was defined as discontinuation of therapy within 12 months of starting systemic treatment. Since anti-PD-1 is administered in up to 6-weekly intervals, 46 weeks between the date of the first and last infusion was considered one full year of treatment. Treatment discontinuation because of COVID-19 was registered as "other".

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.0.2.; packages lubridate, ggthemes, plyr, stringr, readxl, survminer, EnvStats, survival, forestmodel, RColorBrewer, dplyr, car, tidyverse, magrittr, tidyr tableone, ggplot2)[14–30].

Results

Patient- and tumor characteristics

In total, 2199 patients were registered in the DMTR database between 01-07-2018 and 31-12-2019. Of these patients, 641 received adjuvant anti-PD-1 therapy **(figure 1)**.

The patient- and tumor characteristics of these patients are shown in **table 1.** Of this group, 362 patients (56.5%) were males, and the median age was 62 years (range 19-90). Eleven percent of the patients had AJCC-7 stage IIIA disease, 39.5% stage IIIB, 40.1% stage IIIC, and 6.9% stage IV. The majority of the patients (93.4%) had an ECOG PS ≤1. The primary melanoma was cutaneous in 93.3% of the cases, and 5.9% had an unknown primary. Twenty-five percent of the patients had in-transit metastases. The baseline registration completeness of these patients was 92.7%. Of these patients, 85.6% began treatment within 12 weeks of definitive surgical resection. The median duration between resected stage III/IV diagnosis and the start of anti-PD-1 therapy was 66 days (IQR 47-89). The median time between the last surgery and anti-PD-1 therapy in this group was 58 days (IQR 42-77). Fifteen patients (2.3%) were not included in these analyses due to missing data. The one-year follow-up group included 367 patients **(table 1)**.

Ineligibility for trial participation

Forty-five of the 641 patients (7.0%) treated with adjuvant anti-PD-1 therapy had one or multiple patient- or tumor characteristics registered in the DMTR, which would have made

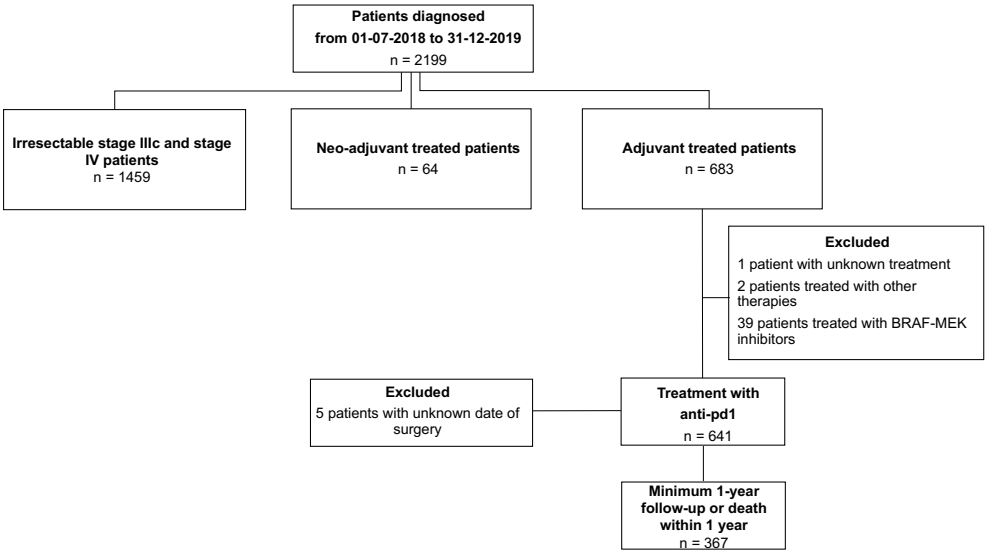


Figure 1: Flowchart of the study population

Table 1: Patient- and tumor characteristics of adjuvant treated patients (study population and patient with minimum 1-year follow-up)

		Study population	One-year follow-up group
N		641	367
Sex; n (%)	Male	362 (56.5)	206 (56.1)
	Female	279 (43.5)	161 (43.9)
Age in years; median (range)		62 (19-90)	62 (22-90)
Stage; n (%) AJCC v7	IIIA	71 (11.1)	34 (9.3)
	IIIB	253 (39.5)	137 (37.3)
	IIIC	257 (40.1)	153 (41.7)
	IV (resectable)	44 (6.9)	30 (8.2)
	Unknown	16 (2.5)	13 (3.5)
Stage; n (%) AJCC v8	IIIA	36 (5.6)	20 (5.4)
	IIIB	231 (36.0)	111 (30.2)
	IIIC	255 (39.8)	156 (42.5)
	IIID	7 (1.1)	6 (1.6)
	IV	46 (7.2)	31 (8.4)
	Unknown	66 (10.3)	43 (11.7)
ECOG PS; n (%)	0	466 (72.7)	253 (68.9)
	1	133 (20.7)	83 (22.6)
	≥2	10 (1.6)	7 (1.9)
	Unknown	32 (5.0)	24 (6.5)
Location; n (%)	Unknown primary	38 (5.9)	26 (7.1)
	Cutaneous**	598 (93.3)	336 (91.6)
	Mucosal	2 (0.3)	2 (0.5)
	Location unknown	3 (0.5)	3 (0.8)
Type melanoma; n (%)	Superficial spreading	326 (50.9)	181 (49.3)
	Nodular	161 (25.2)	92 (25.1)
	Acrolentiginous	16 (2.5)	11 (3.0)
	Lentigo maligna	7 (1.1)	2 (0.5)
	Desmoplastic	3 (0.5)	1 (0.3)
	Other	4 (0.6)	2 (0.5)
	Unknown	123 (19.2)	78 (21.3)
Breslow thickness (mm); median [range]*		2.7 [0.1-21.8]	2.8 [0.4-18.5]
	Unknown	74 (11.5)	55 (15.0)
Ulceration; n (%)*	No	322 (54.2)	165 (49.3)
	Yes	201 (33.8)	122 (36.4)
	Unknown	71 (12.0)	51 (15.0)
In transit metastases; n (%)*	No	442 (69.0)	261 (77.0)
	Yes	160 (25.0)	78 (23.0)
	Unknown	39 (6.0)	0 (0.0)

Table 1 continued

		Study population	One-year follow-up group
BRAF-V600 Mutation	Wild-type	224 (34.9)	146 (39.8)
	Mutant	271 (42.3)	143 (39.0)
	Unknown	146 (22.8)	78 (21.3)
LDH U/L; n (%)	<250	603 (94.1)	337 (91.8)
	250-500	22 (3.4)	18 (4.9)
	Not determined	10 (1.6)	7 (1.9)
	Unknown	6 (0.9)	5 (1.4)
Type of systemic therapy; n (%)	Nivolumab	534 (83.3)	317 (86.4)
	Pembrolizumab	107 (16.7)	50 (13.6)

*Patients with an unknown primary tumor (n=38 and n=26) were excluded from the analyses on Breslow thickness, ulceration, and in-transit metastases. **Including patients with acral melanoma (n=20 and n=17). AJCC = American Joint Committee on Cancer, ECOG PS = Eastern Cooperative Oncology Group performance score, LDH = lactate dehydrogenase

them ineligible for trial participation **(supplement 3)**. Ten patients had ECOG PS≥2, 32 patients had a history of auto-immune disease (other than thyroid disease), two patients had HIV, and one patient had both an auto-immune disease as well as HIV.

Recurrence-free survival

Recurrence-free survival rate at 12-months was 70.6% (95% CI, 66.9-74.6) for the entire study population **(figure 2a)**. Fourteen patients were excluded from this analysis due to missing follow-up data. The median follow-up time in this population was 12.8 months. At the time of this report, the median recurrence-free survival rate had not been reached. A total of 188 (30.0%) patients had recurred or died at the data cut-off. The recurrence-free survival rate at 12-months differed significantly (p<0.001) between disease stages according to the AJCC-7 and AJCC-8 classification **(figure 2b and supplement 4a)**.

Among patients with AJCC-7 stage IIIA disease, the recurrence-free survival rate at 12-months was 87.0% (95% CI, 78.7-96.2). In stage IIIB and IIIC, the recurrence-free survival rate at 12-months was 76.5% (95% CI, 70.9-82.5) and 60.3% (95% CI, 54.2-67.2), respectively. Among those with stage IV disease, the 12-month recurrence-free survival rate was 69.1% (95% CI, 56.4-84.6). Male sex, higher disease stage, ulceration present in primary melanoma, Breslow thickness and BRAF-V600 mutation were significantly associated with a higher hazard for RFS **(table 2)**. Male sex, disease stage and Breslow thickness were significantly associated with higher hazard for RFS rates after adjustments for covariates (**supplement 5**).

3.4 One-year follow-up group

This group consisted of 367 patients with a minimum follow-up period of 12 months or death within 12 months (n=31) **(figure 3)**. The median follow-up period in these patients was 15.6 months. A CT- or FDG-PET-scan was performed in 98.9% and an MRI-scan of the

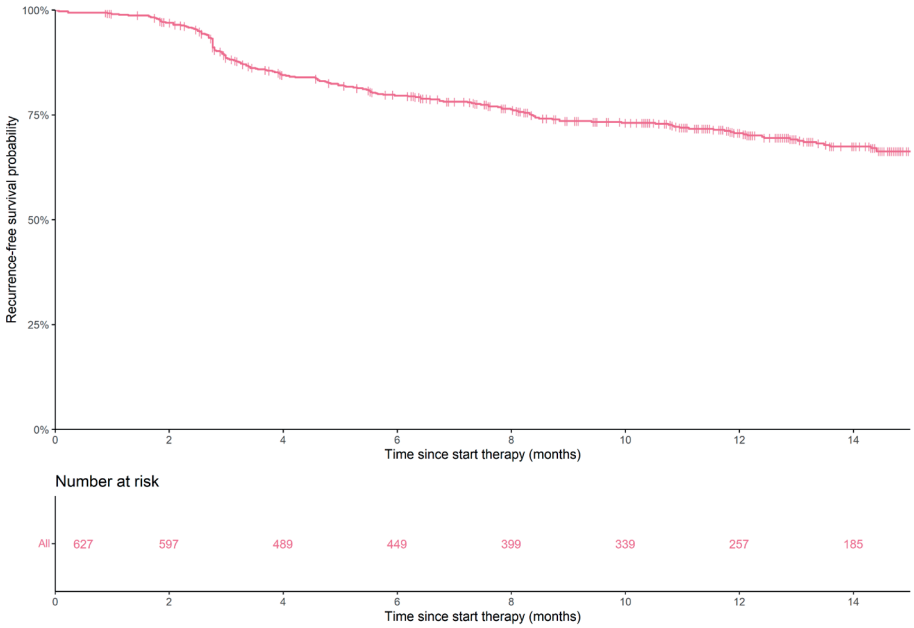


Figure 2a: Kaplan-Meier estimate of recurrence-free survival (RFS) in melanoma patients treated with adjuvant anti-PD-1 therapy. Fourteen patients were not included in this analysis due to missing data necessary for calculating RFS.

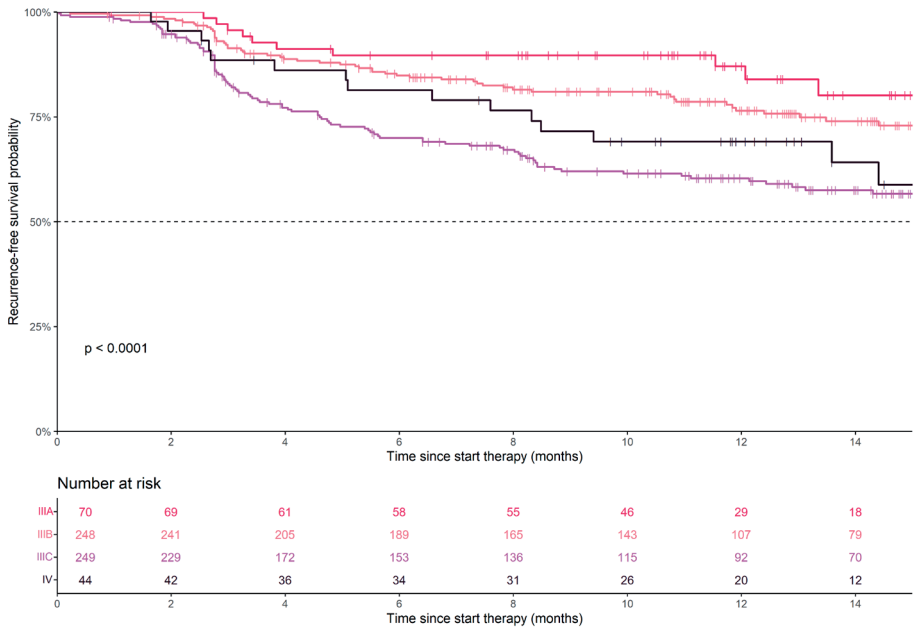


Figure 2b: Kaplan-Meier estimate of recurrence-free survival (RFS) in melanoma patients treated with adjuvant anti-PD-1 therapy, according to the AJCC 7th edition stage of disease classification. Thirty patients were not included in this analysis due to missing data (e.g. stage of disease) necessary for calculating RFS.

Table 2: Univariate Cox regression model for factors associated with recurrence-free survival, in melanoma patients treated with adjuvant anti-PD-1 therapy.

Variable	N	Events	Hazard Ratio (95% CI)	P-value
Age in years	627	188	1.00 (0.99, 1.02)	0.441
Sex				
Male	355	123	Reference	
Female	272	65	0.64 (0.48, 0.87)	0.004
ECOG PS				
0	455	129	Reference	
1	131	43	1.05 (0.74, 1.48)	0.800
2	9	2	0.65 (0.16, 2.63)	0.500
Stage AJCC 7th				
Stage IIIA	70	10	Reference	
Stage IIIB	248	57	1.66 (0.85, 3.25)	0.140
Stage IIIC	249	99	3.30 (1.72, 6.33)	<0.001
Stage IV	44	17	2.77 (1.27, 6.06)	0.010
Breslow Thickness (mm)	557	175	1.08 (1.04, 1.13)	<0.001
Ulceration				
No	315	81	Reference	
Yes	198	75	1.51 (1.10, 2.07)	0.010
ITM				
No ITM	433	125	Reference	
ITM	155	48	1.15 (0.83, 1.61)	0.400
BRAF-V600 Mutation				
Wild Type	218	75	Reference	
Mutant	263	78	0.91 (0.66, 1.25)	0.570
Missing	146	35	0.67 (0.45, 1.00)	0.050

ECOG PS = Eastern Cooperative Oncology Group performance score, AJCC = American Joint Committee on Cancer, ITM = in-transit metastases

brain was performed in 64.6% of patients before starting adjuvant systemic treatment. A total of 67 (18.3%) of patients developed grade ≥3 toxicity. The most common grade ≥3 toxicities were colitis/diarrhoea (4.6%), hepatitis (1.1%), rash/pruritus (0.5%), dyspnoea/pneumonitis (1.1%), and "other" in 6.8%. The relative proportion of grade ≥3 toxicities are displayed in **figure 4**. There were no treatment-related deaths during the study period.

Two hundred and twenty-four patients (61.0%) discontinued anti-PD-1 therapy within 12 months. Reasons for premature discontinuation were any grade toxicity (18.0%), progression (17.4%), agreed on by physician and patient (13.1%), patients' choice (0.5%), poor clinical condition (1.1%), unknown (0.5%), or other reasons (10.4%). **Figure 5** shows

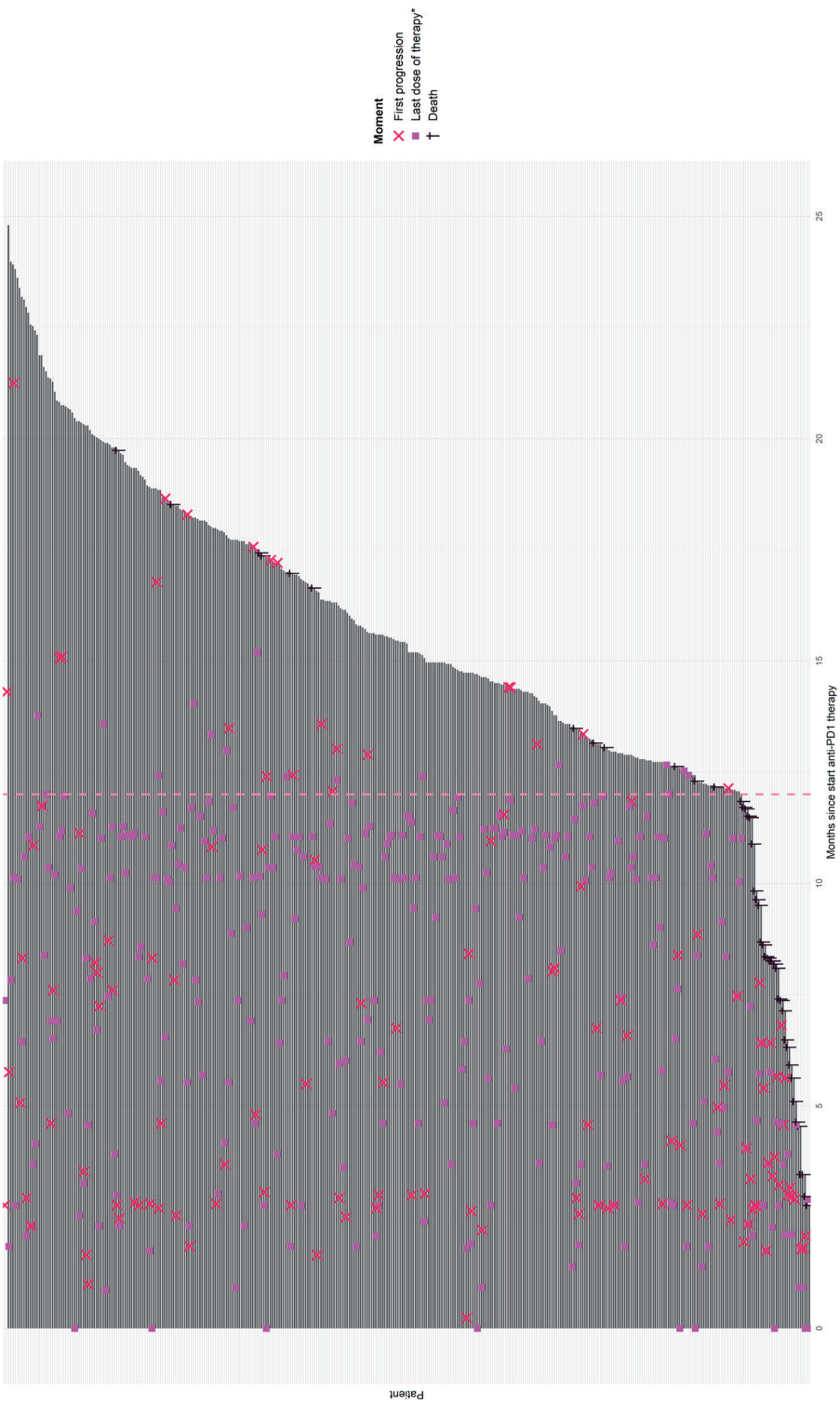


Figure 3. Swimmer plot of anti-PD-1 adjuvant treated melanoma patients in the one-year follow-up group. **This represents the date of the first dose of the last cycle (adjuvant anti-PD-1 given in 2-weekly up to 6-weekly doses).*

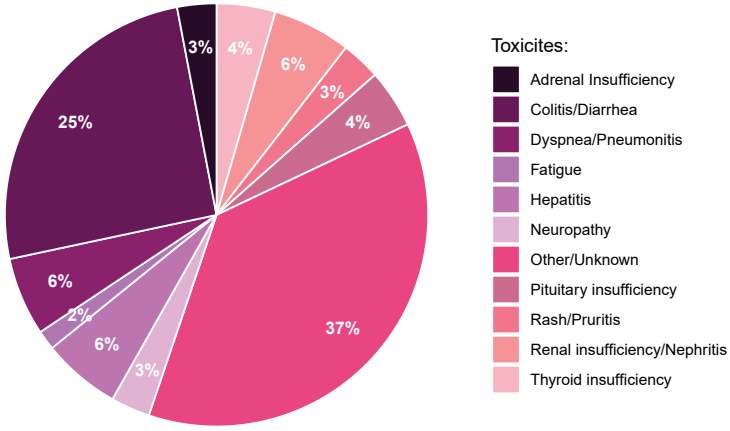


Figure 4. Type of grade 3 toxicity during or after treatment with anti-PD-1 therapy.

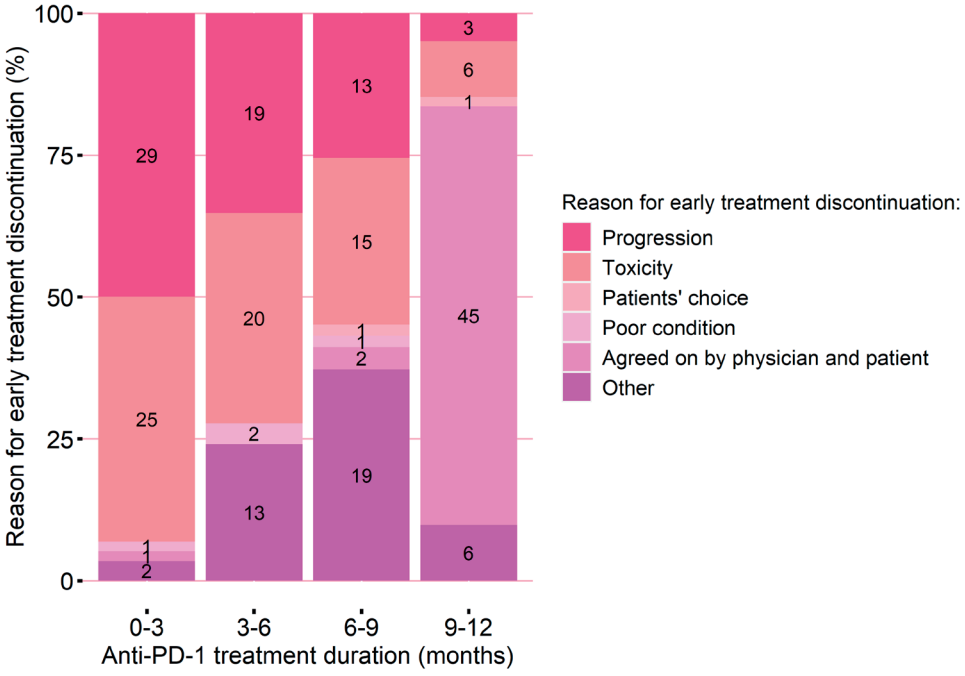


Figure 5: Reasons for early discontinuation of anti-PD-1 adjuvant treated patients.

the treatment duration of the patients who prematurely discontinued anti-PD-1 treatment and the reason and timing of discontinuation. Fifty-eight (15.8%) of the one-year follow-up patients discontinued treatment within three months, 14.7% between three and six months, 13.9% between six and nine months, and 16.6% between nine and twelve months. Since the start of the COVID-19 pandemic (starting in March 2020), more patients prematurely discontinued treatment because of "other" reasons compared to before the pandemic (38.7% vs. 7.4%). We also note an increased discontinuation rate registered as "agreed on with treating physician" in the last three months of treatment since the COVID-19 pandemic (79% vs. 64%, respectively).

The 12-months RFS rate for patients in the one year follow-up group was 69.5% (95% CI, 64.9-74.4) (**supplement 4b**). The median RFS had not been reached for this group at the time of this report. A total of 134 (36.5%) patients had recurred or died at dataset cut-off.

Discussion

The current study is, to our knowledge, the first nationwide cohort study comparing daily clinical practice outcomes in adjuvant-treated melanoma patients to the registration trials. We report a similar recurrence-free survival rate at 12-months in our study population compared to those treated in the registration trials. However, we report higher rates of treatment-related adverse events (grade ≥3) and, strikingly, higher rates of premature treatment discontinuation in patients treated with adjuvant anti-PD-1 compared to the registration trials.

Adjuvant systemic treatment in the Netherlands

Data of the first year of adjuvant patients in the DMTR demonstrates that most patients treated in the Netherlands received anti-PD-1 checkpoint inhibitors, specifically nivolumab. Until November 2020, adjuvant BRAF-MEK inhibition was only available in an expanded access program for patients with contraindications to immunotherapy. Therefore, the number of patients treated with adjuvant BRAF/MEK inhibitors in our study is limited. The majority of patients treated with adjuvant anti-PD-1 started systemic therapy within 12 weeks after definitive surgical resection, which is in accordance with the trial designs of the EORTC 1325/Keynote-054 trial and the Checkmate-238 trial[9, 10].

Real-world versus trial

We report similar recurrence-free survival rates at 12-months compared to the trials. In our study recurrence-free survival rate at 12-months was 87.0% (95% CI, 78.7-96.2) for AJCC-7 stage IIIA, compared to 93.4% (95% CI, 84.9-97.2) in the EORTC 1325/Keynote-054 trial[31]. For stage IIIB and IIIC, we report a recurrence-free survival rate at 12-months of 76.5%

(95% CI, 70.9-82.5) and 60.3% (95% CI, 54.2-67.2) compared to 75.8% (95% CI, 69.7-80.9) and 67.7% (95% CI, 60.6-73.8) in the EORTC 1325/Keynote-054 trial. Similarly, RFS rates per stage of disease according to the AJCC 8th edition were roughly comparable to those of the EORTC 1325/Keynote-054 trial **(supplement 4)** [31].

In the Checkmate-238 trial, 12 month RFS for stage IIIB/C was not reported separately but was 72.3% (95% CI, 67.4-76.7) for stages IIIB and IIIC combined[9]. For stage IV patients, we report a recurrence-free survival rate at 12-months of 69.1% (95% CI, 56.4-84.6) compared to 63.0% (95% CI, 51.6-72.5) in the Checkmate-238 trial.

Our eligibility analysis also shows similarities between daily clinical practice patients and trial patients, with only 7.0% of daily clinical practice patients not meeting eligibility criteria[9, 10]. This is in contrast to our previous research in which we showed that up to 44% of the metastatic melanoma patients in daily practice did not meet the eligibility criteria for trial participation[32]. This difference can be explained by the fact that patients treated with adjuvant therapy do not have brain metastases, which was the main factor for ineligibility in advanced melanoma patients. The eligibility analysis was based on available information in the DMTR. Since the DMTR lacks information on items such as organ function, actual numbers of ineligible patients might thus be higher than reported.

Factors associated with a higher hazard for RFS in our patient population were sex, stage IIIC disease and Breslow thickness **(supplement 5)**. Women represented 43.5% of our study population compared to 43.0% and 37.0% in the registration trials. In our study population, 34.4% of patients had ulcerated primary melanoma compared to 40.5% and 41.5% in the trials. Breslow thickness of the primary melanoma was not specified in the trial population. Interestingly, the presence of ITM, which is generally considered prognostically unfavorable[33] was not associated with higher hazard for RFS.

Toxicity rates in our study appear slightly higher than reported in previous adjuvant trials (18.2% grade ≥3 treatment-related adverse events, compared to 14.4% in Checkmate-238 and 14.7% in EORTC 1325/Keynote-054 trial). Additionally, 17.9% of premature treatment discontinuation in our population was caused by any grade treatment-related adverse events, which was higher than the 7.7% and 13.0% reported in the Checkmate-238 and EORTC 1325/Keynote-054 trial, respectively. Furthermore, the 18% of patients experiencing severe toxicity in our adjuvant populations appears higher than the 11% we previously reported for advanced anti-PD-1 treated melanoma patients in the same registry[34]. Altogether we show that although adjuvant treated patients in daily clinical practice based on eligibility criteria seem to adequately reflect the trial population, they experience more severe adverse effects and discontinue treatment more frequently than patients in the registration trials.

Furthermore, the all-cause rate of premature discontinuation of therapy was 61.0% in our follow-up population. These rates are remarkable higher than reported in the registration trials, in which 39.2% and 44.6% of patients discontinued treatment within one year[9, 10].

The higher discontinuation rates in our population do not seem to be caused by more frequent progressive disease. We report lower rates of treatment discontinuation due to progressive disease compared to trials, respectively, 17.4% compared to 21.4%[9] and 26.7%[10]. Early discontinuation of treatment in our population might, however, in part, have been due to factors related to the COVID-19 pandemic where patients who started systemic therapy after March 2019 potentially discontinued treatment before reaching the one-year mark. This is supported by our findings that during the COVID-19 pandemic more patients discontinued treatment due to "other reasons". We are currently conducting further research into the effects of the COVID-19 pandemic on adjuvant therapy for melanoma. Additionally, trial patients could be more motivated to continue treatment in spite of toxicity.

Benchmarking and comparison with other nationwide registries

The goal of the DMTR is to monitor patient safety and quality of care. The scientific committee of the DMTR consists of medical oncologists representing the 14 melanoma centers in the Netherlands, melanoma surgeons, pathologists, and delegates from a Health Technology Assessment Institute. Quarterly meetings in which quality indicators are discussed lead to the identification of potential differences in clinical practice that can be associated with variation in outcomes between melanoma centers. By discovering discrepancies and potential blind spots, melanoma centers can use this information to improve their care.

To our knowledge, the Danish Metastatic Melanoma Database (DAMMED) is the only other nationwide registry of adjuvant treated melanoma[35]. To facilitate the comparison of treatment patterns and outcomes from registries across Europe, the authors believe that there should be a consensus on data collection in European countries. Initiatives such as EuMelaReg will, in the future, possibly enable such comparisons[36].

Strengths and limitations

The high level of baseline data completeness in the DMTR illustrated the quality of data registration. Nevertheless, we are continuously improving the methods of data collection to minimize registration delays. Future addition of automatic linkage of pathology data from the pathology database in the Netherlands (PALGA) will facilitate patient inclusion, reduce registration burden, and further increase case completeness and quality of DMTR data. Additionally, this will facilitate the early detection of relapses, resulting in a more real-time follow-up of our study population.

For daily clinical practice, it is essential to indicate the effectiveness of all available adjuvant treatment options. With the recent approval and reimbursement of BRAF/MEK inhibitors for adjuvant treatment of resected stage III melanoma in the Netherlands, research into the use of these drugs in daily practice will be carried out as soon as data are available. Furthermore, analyses on overall survival will be presented once data are more mature.

Conclusion

Despite similar patient characteristics, premature discontinuation of adjuvant anti-PD-1 in daily clinical practice occurs more often than reported in clinical trials, while toxicity rates also appear slightly higher. Nevertheless, recurrence-free survival at 12-months is similar between daily clinical practice and trial patients. Future analyses into factors contributing to premature treatment cessation and its effect on overall survival are needed once follow-up data in daily clinical practice patients are more mature.

References

[1] Hepner A, Salgues A, Dos Anjos CA, Sahade M, Camargo VP, Garicochea B, et al. Treatment of advanced melanoma–A changing landscape. Rev Assoc Med Bras 2017;63:814–23. doi:10.1590/1806-9282.63.09.814.

[2] Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247–57. doi:10.1016/j.ejca.2017.06.028.

[3] van Zeijl MCT et al. Recente behandelresultaten van uitgezaaid melanoom. Ned Tijdschr Geeneeskd 2018;162:D2420.

[4] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJM, Haanen JBAG, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156–65. doi:10.1016/j.ejca.2016.11.021.

[5] Beck N, van Bommel AC, Eddes EH, van Leersum NJ, Tollenaar RA, Wouters MW. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. Ann Surg 2020;271:627–31. doi:10.1097/SLA.0000000000003665.

[6] Commissie BOM. Adjuvant nivolumab bij stadium IIIb, IIIc, of IV melanoom na volledige chirurgische resectie. Med Oncol 2018:53–6.

[7] Commissie BOM. Adjuvant dabrafenib in combinatie met trametinib bij stadium III melanoom. Med Oncol 2018:47–50.

[8] Van Den Eertwegh F. Adjuvante behandeling van het hoogrisicomelanoom. Med Oncol 2018;21:e-publicatie.

[9] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824–35. doi:10.1056/nejmoa1709030.

[10] Eggermont AMM, Blank CU, Mandala M, Long G V., Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018;378:1789–801. doi:10.1056/nejmoa1802357.

[11] Ascierto PA, Del Vecchio M, Mandalá M, Gogas H, Arance AM, Dalle S, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2020;21:1465–77. doi:10.1016/S1470-2045(20)30494-0.

[12] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206. doi:10.1200/JCO.2009.23.4799.

[13] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long G V., Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472–92. doi:10.3322/caac.21409.

[14] Garrett Grolemund HW. Dates and Times Made Easy with {lubridate} 2011.

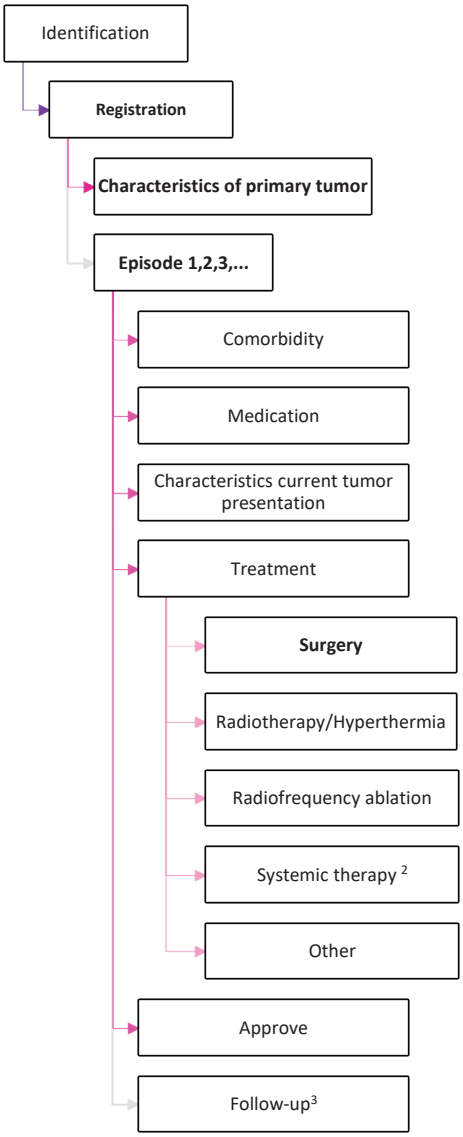
[15] Wickham H. The Split-Apply-Combine Strategy for Data Analysis 2011.
[16] Wickham H. stringr: Simple, Consistent Wrappers for Common String Operations 2019.
[17] Bryan HW and J. readxl: Read Excel Files 2019.
[18] Biecek AK and MK and P. survminer: Drawing Survival Curves using "ggplot2" 2020.
[19] Millard SP. EnvStats: An R Package for Environmental Statistics 2013.
[20] T T. A Package for Survival Analysis in R 2020.
[21] Kennedy N. forestmodel: Forest Plots from Regression Models 2020.
[22] Neuwirth E. RColorBrewer: ColorBrewer Palettes 2014.
[23] Hadley Wickham, Romain François LH and KM. dplyr: A Grammar of Data Manipulation 2021.
[24] RStudio Team. RStudio: Integrated Development Environment for R 2021.
[25] Weisberg JF and S. An {R} Companion to Applied Regression 2019.
[26] Yutani HW and MA and JB and WC and LDM and RF and GG and AH and LH and JH and MK and TLP and EM and SM. Welcome to the {tidyverse} 2019. doi:10.21105/joss.01686.
[27] Wickham SMB and H. magrittr: A Forward-Pipe Operator for R 2014.
[28] Bartel KY and A. tableone: Create "Table 1" to Describe Baseline Characteristics with or without Propensity Score Weights 2020.
[29] Wickham H. ggplot2: Elegant Graphics for Data Analysis 2016.
[30] Arnold JB. ggthemes: Extra Themes, Scales and Geoms for "ggplot2" 2021.
[31] Eggermont AMM, Blank CU, Mandala M, Long G V, Atkinson VG, Haydon A, et al. ScienceDirect Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325 / KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma 2019;116:148–57. doi:10.1016/j.ejca.2019.05.020.
[32] van Zeijl MCT, Ismail RK, de Wreede LC, van den Eertwegh AJM, de Boer A, van Dartel M, et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. Int J Cancer 2020;147:3461–70. doi:10.1002/ijc.33162.
[33] Read RL, Haydu L, Saw RPM, Quinn MJ, Shannon K, Spillane AJ, et al. In-transit Melanoma Metastases: Incidence, Prognosis, and the Role of Lymphadenectomy. Ann Surg Oncol 2015;22:475–81. doi:10.1245/s10434-014-4100-0.
[34] Verheijden RJ, May AM, Blank CU, Van Der Veldt AAM, Boers-Sonderen MJ, Aarts MJB, et al. Lower risk of severe checkpoint inhibitor toxicity in more advanced disease. ESMO Open 2020;5. doi:10.1136/esmoopen-2020-000945.
[35] Ellebaek E, Svane IM, Schmidt H, Haslund CA, Donia M, Hoejberg L, et al. The Danish metastatic melanoma database (DAMMED): A nation-wide platform for quality assurance and research in real-world data on medical therapy in Danish melanoma patients. Cancer Epidemiol 2021;73. doi:10.1016/j.canep.2021.101943.
[36] The European Melanoma Registry (EUMelaReg). https://www.eumelareg.org/. Date last accessed: 01-07-2021.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

Supplement

Supplement 1: List of new data entry items added to the DMTR to include adjuvant treated patients

Variable	Subset database	Description
Stage prior to adjuvant treatment	Characteristics of primary tumor	Unresectable stage IIIC was added to the options of this already existent variable
Adjuvant systemic treatment	Episode	New variable on whether the patient was treated adjuvant, neoadjuvant or unknown if receiving systemic therapy in combination with surgical resection.
In transit metastasis present	Surgery	Variable on if there were in transit metastasis present if the patient was treated with adjuvant therapy and the target of the resection was skin/ subcutis.
Number of in transit metastasis if present	Surgery	Number of in transit metastasis resected
Number of lymph nodes removed	Surgery	Number of lymph nodes removed during resection
Lymph node dissection procedure	Surgery	Which procedure was used if lymph nodes were resected.
Number of lymph nodes removed	Surgery	New variable added to the database.
Number of positive lymph nodes removed	Surgery	Number of lymph nodes removed during resection that were positive for tumor
Lymph node tumor burden	Surgery	Maximum diameter of largest tumor in resected lymph node
Resection margin lymph nodes	Surgery	Resection margin of removed lymph nodes
Treatment target at time of registration in DMTR	Registration	The treatment type of the patient at inclusion was either: (neo)adjuvant, systemic treatment, unknown.
Extranodal extension	Surgery	Whether there was extranodal extension

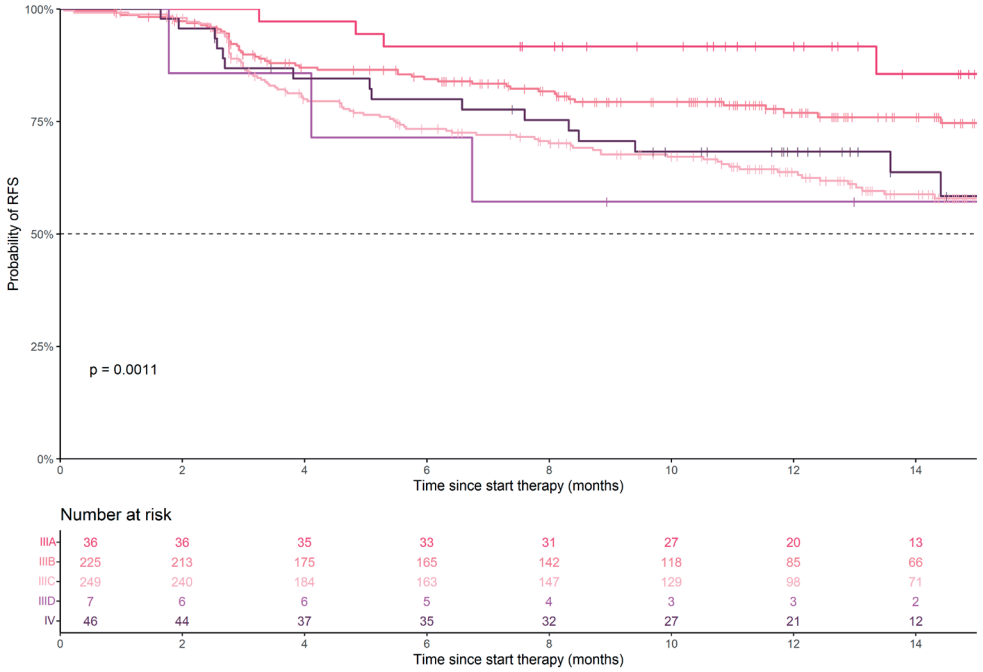


Supplement 2: The structure of the DMTR database. The subsets in which variables regarding adjuvant treatment were added are illustrated in bold.
Flowchart:
[1] (Neo-)adjuvant of unresectable at first registration in the DMTR
[2] All systemic therapies have their own module
[3] Follow-up is to be recorded every three months.

Supplement 3: Patient- and tumor characteristics in patients meeting eligibility criteria for trial participation

		Eligible	Ineligible
N		596	45
Gender	Male	337 (56.5)	25 (55.6)
	Female	259 (43.5)	20 (44.4)
Age; median (range)		62 [19, 90]	62 [27, 85]
Stage; n (%) AJCC v7	IIIA	69 (11.6)	2 (4.4)
	IIIB	235 (39.4)	18 (40.0)
	IIIC	237 (39.8)	20 (44.4)
	IV (resected)	40 (6.7)	1 (2.2)
	Unknown	15 (2.5)	4 (8.9)
ECOG PS; n (%)	0	442 (74.2)	24 (53.3)
	1	123 (20.6)	10 (22.2)
	≥2	0 (0.0)	10 (22.2)
	Unknown	31 (5.2)	1 (2.2)
Location; n (%)	Primary unknown	33 (5.5)	5 (11.1)
	Cutaneous*	558 (93.6)	40 (88.9)
	Mucosal	2 (0.3)	0 (0.0)
	Location unknown	3 (0.5)	0 (0.0)
Type melanoma; n (%)	Superficial spreading	304 (51.0)	22 (48.9)
	Nodular	151 (25.3)	10 (22.2)
	Acrolentiginous	14 (2.3)	2 (4.4)
	Lentigo maligna	6 (1.0)	1 (2.2)
	Desmoplastic	3 (0.5)	0 (0.0)
	Other	4 (0.7)	0 (0.0)
	Unknown	114 (19.1)	10 (22.2)
BRAF mutation	Wild-type	204 (34.2)	20 (44.4)
	Mutant	257 (43.1)	14 (31.1)
	Unknown	135 (22.7)	11 (24.4)
LDH; n (%)	Normal	561 (94.1)	42 (93.3)
	250-500	20 (3.4)	2 (4.4)
	Not determined	9 (1.5)	1 (2.2)
	Unknown	6 (1.0)	0 (0.0)

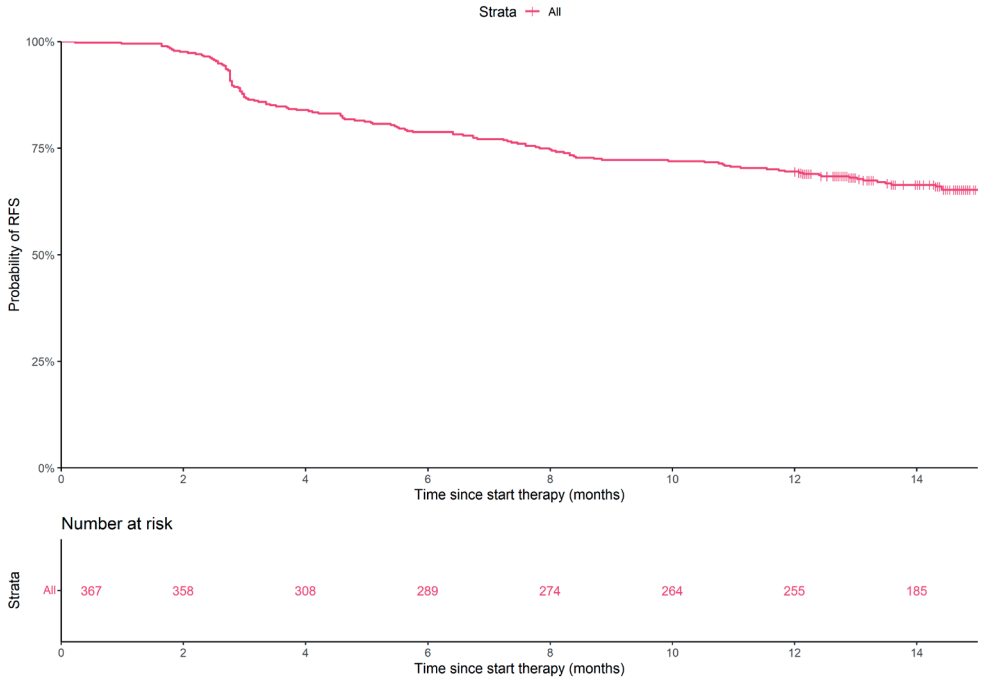
*including patients with acral melanoma (n=17 and n=3). AJCC = American Joint Committee on Cancer, ECOG PS = Eastern Cooperative Oncology Group Performance Score, LDH = lactate dehydrogenase.



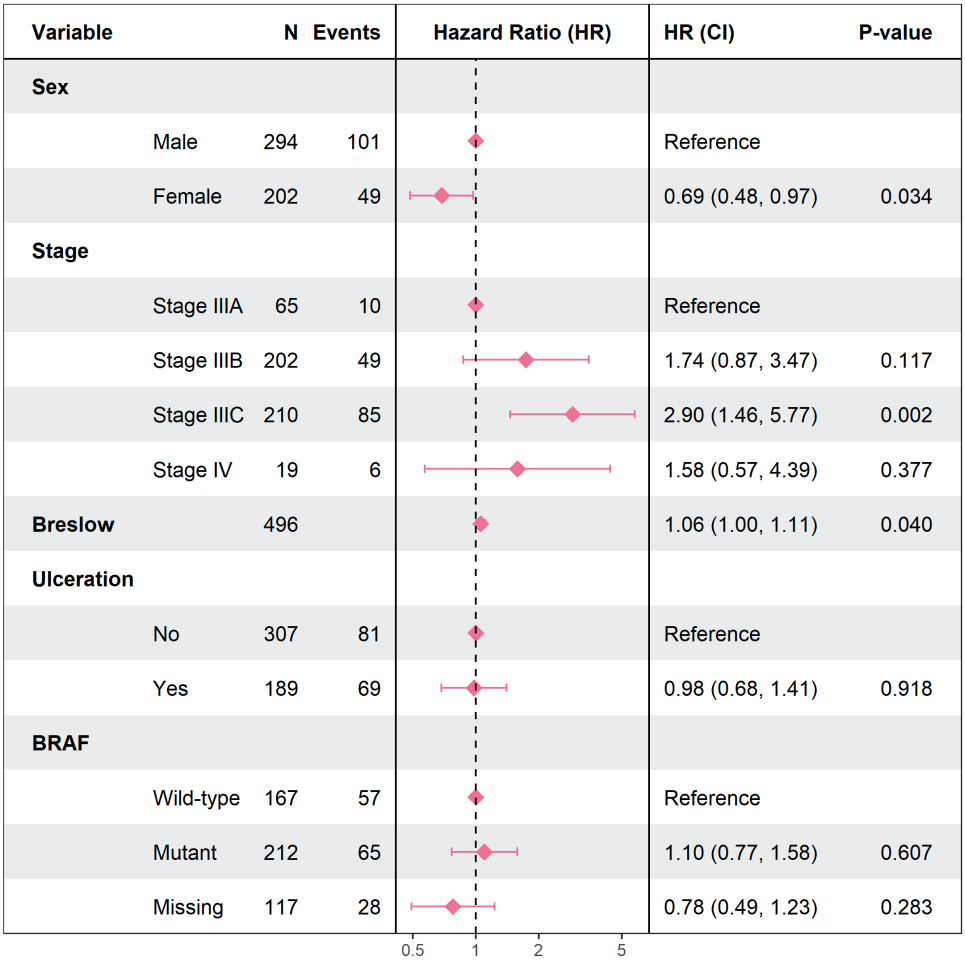
Supplement 4a: Kaplan-Meier estimate of recurrence-free survival in melanoma patients treated with adjuvant anti-PD-1 therapy in the one-year follow-up group, according to the stage of disease (AJCC 8th edition).

RFS = recurrence-free survival, FUP = Follow-up.

Fifty patients missing due to missing data (e.g. stage of disease) necessary for calculating RFS.



Supplement 4b: Kaplan-Meier estimate of recurrence-free survival in melanoma patients treated with adjuvant anti-PD-1 therapy in the one-year follow-up group.
RFS = recurrence-free survival.
Two patients were excluded from analyses due to missing data necessary for calculating RFS.



Supplement 5: Multivariate Cox regression model for factors associated with recurrence-free survival, visualized in a forest plot in melanoma patients treated with adjuvant anti-PD-1 therapy. *Breslow Thickness in mm. *Stage according to AJCC 8th edition staging system.*

CHAPTER 8

Advanced melanoma patients reaching long-term survival after treatment with targeted therapy: a population-based study.

Submitted.

R.K. Ismail, K.P.M. Suijkerbuijk, A. de Boer, M. van Dartel, D.L. Hilarius, A.M.G. Pasmooij, M.C.T. van Zeijl, M.J.B. Aarts, F.W.P.J.van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, A.A.M. van der Veldt, G. Vreugdenhil G., H. Westgeest, A.J.M. van den Eertwegh, M.W.J.M. Wouters.

Abstract

Background: Recent results of patients with advanced melanoma treated with first line BRAF-MEK inhibitors in clinical trials showed 5-year survival in one third of patients with a median overall survival (OS) of more than 2 years. This study aimed to investigate these patients' real-world survival and identify the characteristics of long-term survivors.

Methods: The study population consisted of patients with advanced cutaneous melanoma with a BRAF-V600 mutated tumor who were treated with first-line BRAF-MEK inhibitors between 2013 and 2017. Long-term survival was defined as a minimal overall survival (OS) of 2 years from start therapy.

Results: The median progression-free survival (mPFS) and median OS (mOS) of real-world patients (n=435) were respectively 8.0 (95% CI, 6.8-9.4) and 11.7 (95%CI, 10.3-13.5) months. Two-year survival was reached by 28% of the patients, 22% reached 3-year survival, and 19% reached 4-year survival. Real-world patients often had brain metastases (41%), stage IV M1c disease (87%), ECOG PS ≥2 (21%), ≥3 organ sites (62%), and elevated LDH of ≥250 U/I (49%). Trial-eligible real-world patients had a mOS of 17.3 months. Patients surviving more than 2 years (n=116) more often had an ECOG PS ≤1 (83%), normal LDH (60%), no brain metastases (60%), no liver metastases (63%) and <3 organ sites (60%).

Conclusion: Long-term survival of real-world patients treated with first-line BRAF-MEK inhibitors is significantly lower than that of trial patients, which is probably explained by poorer baseline characteristics of patients treated in daily practice. Long-term survivors generally had more favorable characteristics with regard to age, LDH level, and metastatic sites, compared to patients not reaching long-term survival.

Introduction

The systemic treatment landscape for advanced (i.e., unresectable stage IIIc or IV) melanoma patients has dramatically changed in recent years with the introduction of immunotherapies (CTLA-4 and PD-1 inhibitors) and targeted therapies (BRAF- and MEK- inhibitors)[1]. In 40-50% of the patients with advanced melanoma, *BRAF* gene mutations are present, leading to the continued activation of the mitogen-activated protein kinase (MAPK) signaling pathway and increased cell growth and proliferation[2]. Targeted therapies inhibit BRAF- and MEK-proteins in the MAPK signaling pathway. Treatment of BRAF mutated patients with these BRAF-MEK inhibitors led to major improvements in patient outcomes regarding response and survival[3].

In 2012, BRAF inhibitor (BRAFi) vemurafenib was authorized by the European Medicines Agency (EMA), followed by BRAF-inhibitors dabrafenib in 2013, and encorafenib in 2018. The addition of MEK-inhibitors (cobimetinib, trametinib, and binimetinib) to BRAF-inhibitors further improved clinical outcomes over monotherapy due to the dual blockade of proteins in the MAPK signaling pathway. These results led to the approval of combined targeted therapy with BRAF-MEK inhibitors as standard therapy in patients with advanced melanoma[3, 4].

Recently, updated results from the phase III clinical trials were published demonstrating long-term survival outcomes of patients treated with BRAF-MEK inhibitors. The COMBI-d and COMBI-v trial, including patients treated with dabrafenib/trametinib, showed a 5-year survival rate of 34% (95% CI 30-38%) and a 5-year progression-free survival rate of 19% (95% CI 15-22%)[5]. Two- and 3-year survival rates were 52% (95% CI 45-59%) and 44% (95% CI 36-51%), respectively[4]. Extended 5-year follow-up results of patients treated in the BRIM-7 trial with vemurafenib/cobimetinib showed a 5-year survival of 39% (95% CI 26-52%) in BRAF inhibitor-naïve patients[6]. Patients treated with encorafenib/binimetinib in the COLUMBUS trial had a 5-year OS rate of 35% (95% CI 28-42%)[7]. Considering the heterogenic patient population and the uncontrolled setting in daily practice[8, 9], it is of major relevance to know how these data from the clinical trials translate into benefits in real-world patients.

Information on which patients are likely to benefit long-term and which treatment strategies are best used to achieve long-term survival is essential. This information can be used in daily clinical practice to support treatment decisions and help to set realistic expectations for individual patients. This study aimed to investigate the real-world survival of patients with advanced melanoma treated with BRAF-MEK inhibitors and identify the patient, tumor, and treatment characteristics of those who derive long-term benefit.

Methods

Data source

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR). The DMTR is a prospective population-based registry with baseline patient, tumor, treatment characteristics, and clinical outcomes of all patients with advanced melanoma in the Netherlands[10]. In compliance with Dutch regulations, the DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act. The dataset cut-off date was July 15th, 2021.

Patients

All advanced cutaneous melanoma patients with a BRAF-V600 mutated tumor who received first-line BRAF-MEK inhibitors between January 1st, 2013 and December 31st, 2017, were included. Uveal and mucosal melanoma patients and patients under 18 years were excluded from this study. Patients treated with induction BRAF-MEK therapy were also excluded. This was defined as short therapy (<3 months) with BRAF-MEK inhibitors followed by treatment with checkpoint inhibitors without any signs of progression. Long-term survival was defined as a minimal OS of 2 years from start therapy.

A subanalysis on trial eligible patients was performed, using the eligibility criteria of the COMBI-D trial. Eligible patients were defined as patients with Eastern Cooperative Oncology Group Performance Score (ECOG PS) ≤1, no brain metastases, BRAF V600E or V600K mutation, and no previous surgery, treated with first-line BRAF-MEK inhibitors.

Data analysis

Descriptive statistics were used to analyze baseline patient- and disease characteristics at diagnosis. Baseline characteristics of real-world patients treated with first-line BRAF-MEK inhibitors were compared to patients treated in phase III clinical trials. The progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method with corresponding two-sided 95% confidence intervals (CI). PFS was calculated from the start of BRAF-MEK inhibitors to the date of progressive disease or death. OS was calculated from the start of BRAF-MEK inhibitors to the date of death from any cause or last follow-up. A multivariable Cox proportional hazards regression model was used to estimate the association of prognostic factors with survival. Factors included in this model were age, gender, disease stage calculated with the AJCC 7th edition, ECOG PS, lactate dehydrogenase (LDH), the number of organ sites metastasized, brain metastases, and liver metastases. Only complete cases were included in the model. Treatment characteristics of long-term survivors were analyzed with descriptive statistics and visualized by a Sankey diagram. 'Other' treatment was defined as treatment registered as other, chemotherapy, or trial

treatment in the DMTR. The treatment duration of BRAF-MEK inhibitors was calculated using the start- and stop date of the BRAF-inhibitor. If the date of discontinuation was missing, the date of the last contact was used. The median follow-up times for PFS and OS were calculated with the reverse Kaplan-Meier method[11].

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.1.0.; packages tidyr, ggplot2, tableone, ggthemes, stringr, forestmodel, car, survival, survminer, ggalluvial, easyalluvial)[12].

Results

Patient characteristics of the study population

Of the 4290 patients diagnosed with irresectable melanoma between 2013 and 2017, a total of 435 patients received BRAF-MEK-inhibitors in first-line **(figure 1)**. The differences in patient- and tumor characteristics between patients treated with BRAF-MEK inhibitors in the real-world study population and phase III trials are shown in **table 1**. Real-world

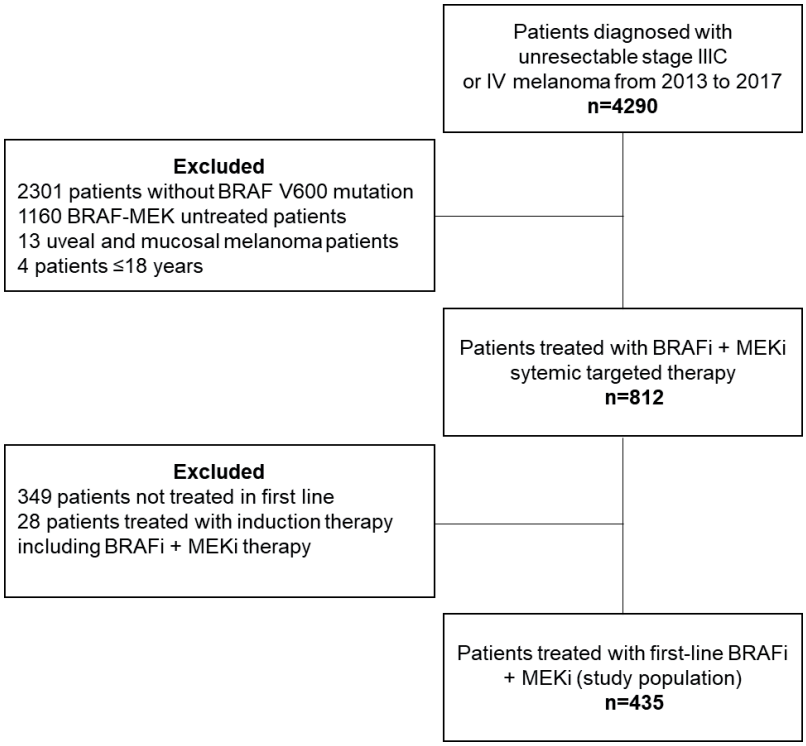


Figure 1: Flowchart of the study population included in this study.

Table 1: Patients treated in the phase-III study versus real-world patient cohort.

	Combi-v trial (dabrafenib/ trametinib)[24]	CoBRIM trial (vemurafenib/ cobimetinib)[25]	Real-world patients treated with BRAF-MEK inhibitors
Patients; n	352	247	435
Median age; years (range)	55 (18-91)	56 (23-88)	59 (19-91)
Male patients; n (%)	208 (59)	146 (59)	229 (53)
ECOG PS; n (%)			
0	248/350 (71)	184/243 (76)	151 (35)
1	102/350 (29)	58/243 (24)	151 (35)
≥2	0	1/243 (<1)	90 (21)
Unknown	0		43 (10)
Stage (AJCC 7th); n (%)			
IVM1c	221/351 (63)	146 (59)	378 (87)
IIIc, IVM1a, IVM1b	130/351 (37)	101 (41)	57 (13)
Metastasis stage; n (%)			
M0	14/351 (4)	21 (9)	31 (7)
M1a	55/351 (16)	40 (16)	14 (3)
M1b	61/351 (17)	40 (16)	12 (3)
M1c	221/351 (63)	146 (59)	378 (87)
Number of disease sites; n (%)			
<3	177/351 (50)	NA	164 (38)
≥3	174/351 (50)	NA	271 (62)
Baseline LDH; n (%)			
Above ULN	118/351 (34)	112/242 (46)	215 (49)
ULN or less	233/351 (66)	130/242 (54)	209 (48)
Unknown	-	_	11 (3)
BRAF mutation; n (%)			
V600E	312/346 (90)	170 (69)	361 (83)
V600K	34/346 (10)	24 (10)	61 (14)
Not evaluated	0	53 (21)	0
Other V600	0	0	13 (3)
Previous immunotherapy; n (%)	61 (17)	NA	0
Type of BRAF-MEK inhibitors; n (%)			
Dabrafenib + trametinib	352 (100)	0	372 (86)
Vemurafenib + cobimetinib	0	247 (100)	63 (14)
Encorafenib + binimetinib	0	0	0 (0)
Other	0	0	0 (0)

ECOG PS - Eastern Cooperative Oncology Group Performance Score, AJCC - American Joint Committee on Cancer, LDH = lactate dehydrogenase.

patients were older (median age 59 versus 55-56 years), more often had an ECOG PS of ≥2 (21% versus <1%), M1c disease (87% versus 59-63%), and metastases in ≥3 organ sites (62% versus 50%) than trial patients. Normal LDH levels were less often found in real-world patients than in trial patients (48% versus 54%-66%). A total of 243 (55%) real-world patients received subsequent anti-cancer therapy after first-line BRAF-MEK.

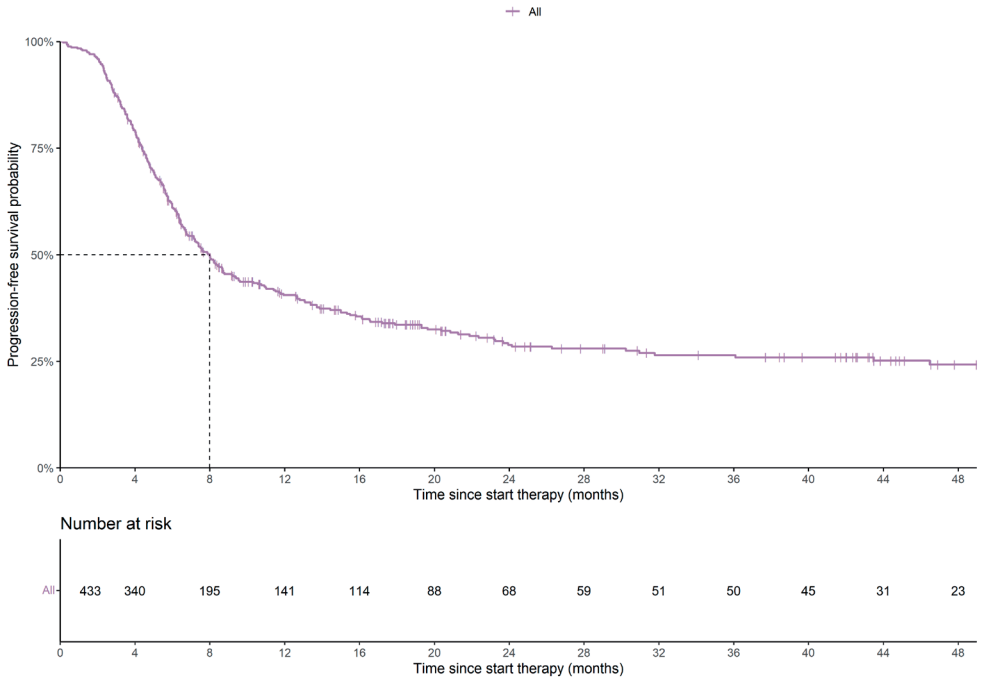


Figure 2a: Kaplan-Meier estimates of median progression-free survival of patients with advanced melanoma treated with first-line BRAF-MEK inhibitors.

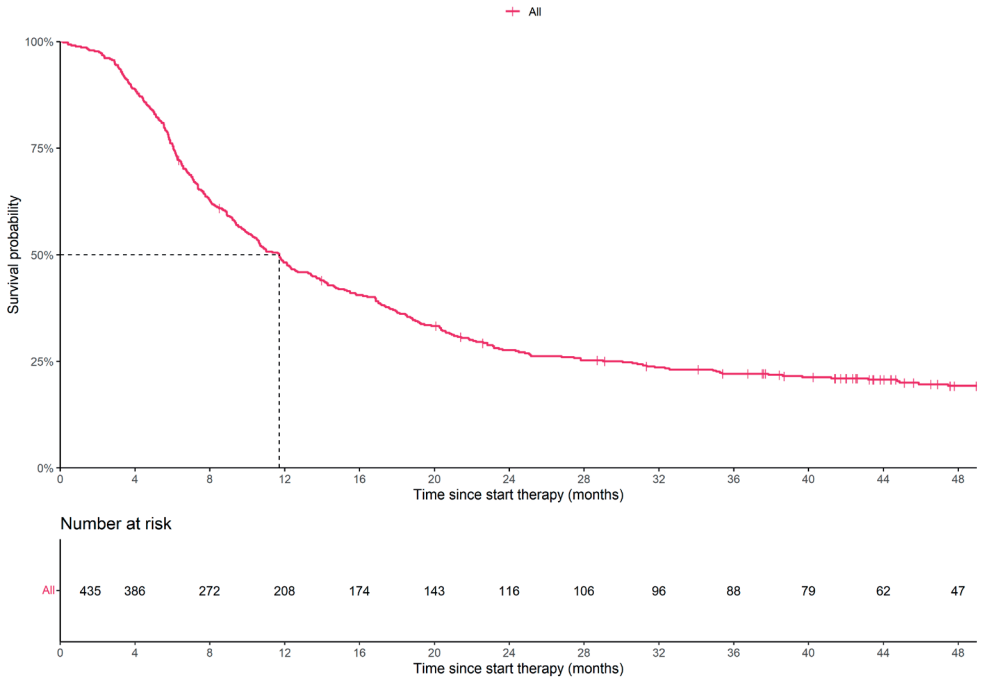


Figure 2b: Kaplan-Meier estimates of median overall survival, 2-year, 3-year, and 4-year survival probability of patients with advanced melanoma treated with first-line BRAF-MEK inhibitors.

Progression-free survival and overall survival

The median progression-free survival (mPFS), median OS (mOS), and 2-, 3-, and 4-year PFS and OS rates of patients treated with first-line BRAF-MEK inhibitors are shown in **figures 2a and 2b**. The mPFS and mOS were 8.0 (95% CI, 6.8-9.4), and 11.7 (95% CI, 10.3-13.5) months, respectively. The median follow-up time for PFS was 27.8 (95%CI, 22.8-39.7) and for OS was 51.9 (95%CI, 47.6-55.7) months.

Best overall response

Complete response (CR) occurred in 37 (9%) patients treated with first-line BRAF-MEK inhibitors. Among patients with a complete response, the 2-year and 3-year OS were 81% (95% CI, 69-95), and the 4-year OS was 75% (95%CI, 63-91%) (**figure 3)**. In patients with a CR who reached 4-year OS (n=19), 53% received no subsequent therapy, and 42% received subsequent immunotherapy. Of all patients with CR, 14 (38%) had one or more poor characteristics (brain metastases, ECOG PS ≥2, elevated LDH, or ≥3 organ sites) at baseline. Patients with a partial response had a 2-year survival rate of 26% (95% CI, 22-32%). This was 19% (95% CI, 12-31%) for stable disease **(figure 3)**. Forty-nine (11%) patients had progressive disease, with a mOS of 5.0 (95% CI, 4.1-5.9) months, and a 2-year OS of 14%

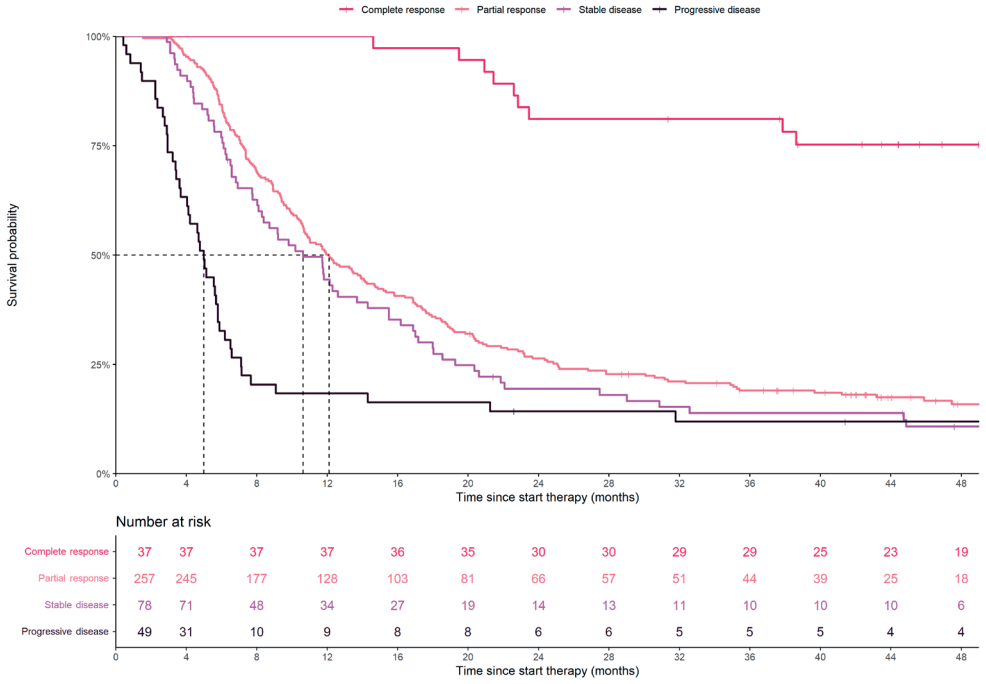


Figure 3: Kaplan-Meier estimates of median overall survival according to the best overall response rate in patients with advanced melanoma treated with first-line BRAF-MEK inhibitors. *Fourteen patients were not evaluable for response.*

(95% CI, 7-28%). Poor baseline characteristics were present in 94% of the patients with progressive disease.

Ineligibility

A total of 52% of the patients treated with first-line BRAF-MEK inhibitors was considered ineligible for phase III trial participation. In 76% of the ineligible patients, brain metastases were present (69% were symptomatic and 31% were asymptomatic), and 39% had an ECOG PS ≥2. Patients who would be considered eligible (n=208) had a mOS of 17.3 (95% CI, 13.5-21.1) months, compared to 8.9 (95% CI, 7.7-10.2) months in ineligible patients (n=227) (**figure 4**). The baseline patient- and tumor characteristics of ineligible and eligible patients are shown in **supplement 1.**

Patient- and tumor characteristics of long-term survivors

Factors associated with improved survival in the real-world population were age <70 years, LDH <500 U/l, no symptomatic brain metastases, and <3 organ sites with metastases (data not shown).

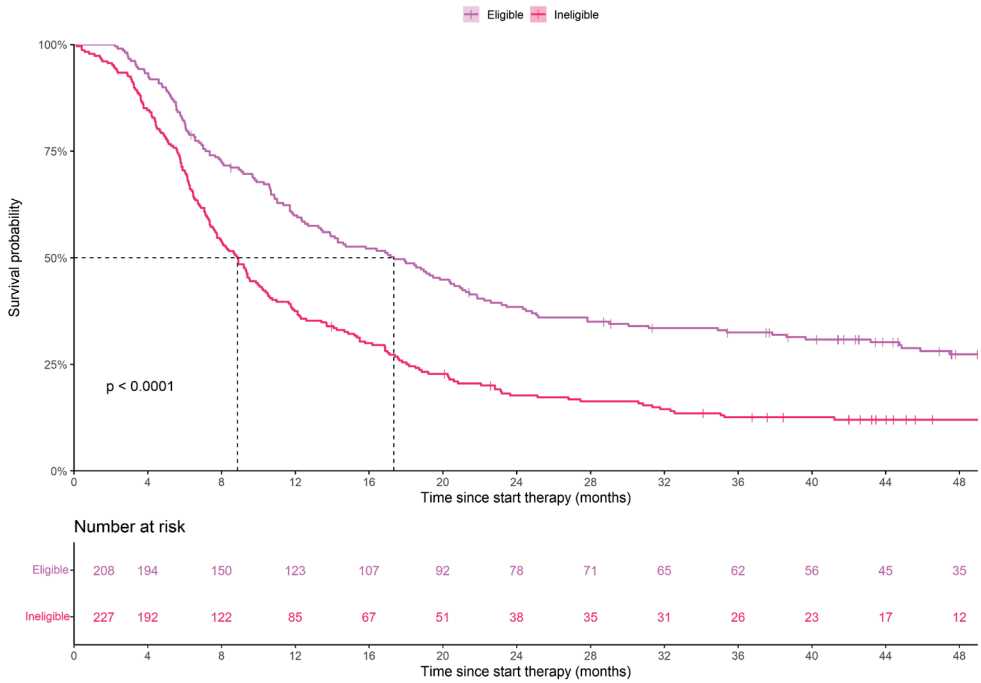


Figure 4: Kaplan-Meier estimates of median overall survival of real-world patients with advanced melanoma with characteristics according to trial eligibility criteria, treated with first-line BRAF-MEK inhibitors.

Table 2: Patient-, tumor-, and treatment characteristics of patients treated with first-line BRAF-MEK inhibitors not reaching long-term survival versus 2-,3-,4-,and 5-year survivors.

	Patients surviving <2 years	Patients surviving >2 years	Patients surviving >3 years	Patients surviving >4 years	Patients surviving >5 years
Patients; n	319	116	88	47	14
Median age, year (range)	59 (19, 88)	58 (27, 91)	58 (27-91)	57 (34-86)	51 (36-84)
Gender; n (%)					
Male	173 (54.2)	56 (48.3)	44 (50.0)	18 (38.3)	6 (42.9)
Female	146 (45.8)	60 (51.7)	44 (50.0)	29 (61.7)	8 (57.1)
ECOG PS; n (%)					
0	96 (30.1)	55 (47.4)	43 (48.9)	29 (61.7)	11 (78.6)
1	110 (34.5)	41 (35.3)	33 (37.5)	12 (25.5)	2 (14.3)
≥2	76 (23.8)	14 (12.1)	9 (10.2)	3 (6.4)	0 (0.0)
Unknown	37 (11.6)	6 (5.2)	3 (3.4)	3 (6.4)	1 (7.1)
LDH level U/l; n (%)					
Normal	140 (43.9)	69 (59.5)	54 (61.4)	30 (63.8)	10 (71.4)
250-500	98 (30.7)	39 (33.6)	29 (33.0)	14 (29.8)	3 (21.4)
>500	74 (23.2)	4 (3.4)	2 (2.3)	1 (2.1)	0 (0.0)
Not determined	7 (2.2)	4 (3.4)	3 (3.4)	2 (4.3)	1 (7.1)
Stage (AJCC 7th); n (%)					
IIIc	12 (3.8)	19 (16.4)	16 (18.2)	9 (19.1)	3 (21.4)
IV-M1a	5 (1.6)	9 (7.8)	9 (10.2)	5 (10.6)	2 (14.3)
IV-M1b	5 (1.6)	7 (6.0)	5 (5.7)	4 (8.5)	1 (7.1)
IV-M1c	297 (93.1)	81 (69.8)	58 (65.9)	29 (61.7)	8 (57.1)
Metastasis in ≥3 organ sites; n (%)	224 (70.2)	47 (40.5)	32 (36.4)	15 (31.9)	4 (28.6)
Brain metastasis; n (%)					
No	149 (46.7)	70 (60.3)	54 (61.4)	30 (63.8)	10 (71.4)
Yes, asymptomatic	44 (13.8)	10 (8.6)	6 (6.8)	4 (8.5)	1 (7.1)
Yes, symptomatic	109 (34.2)	15 (12.9)	11 (12.5)	4 (8.5)	0 (0.0)
Unknown	17 (5.3)	21 (18.1)	17 (19.3)	9 (19.1)	3 (21.4)
Liver metastasis; n (%)	139 (43.6)	24 (20.7)	16 (18.2)	7 (14.9)	2 (14.3)
Best overall response; n (%)					
Complete response	7 (2.2)	30 (25.9)	29 (33.0)	19 (40.4)	5 (35.7)
Partial response	191 (59.9)	66 (56.9)	44 (50.0)	18 (38.3)	6 (42.9)
Stable disease	64 (20.1)	14 (12.1)	10 (11.4)	6 (12.8)	3 (21.4)
Progressive disease	43 (13.5)	6 (5.2)	5 (5.7)	4 (8.5)	0 (0.0)
LTFU	14 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BRAF mutation; n (%)					
V600E	269 (84.3)	92 (79.3)	68 (77.3)	37 (78.7)	12 (85.7)
V600K	43 (13.5)	18 (15.5)	15 (17.0)	7 (14.9)	2 (14.3)
Other	7 (2.2)	6 (5.2)	5 (5.7)	3 (6.4)	0 (0.0)
Subsequent therapy after first-line BRAF-MEK; n (%)					
No	158 (49.5)	34 (29.3)	27 (30.7)	16 (34.0)	6 (42.9)
Immunotherapy	151 (47.3)	75 (64.7)	57 (64.8)	28 (59.6)	8 (57.1)
Other	9 (2.8)	7 (6.0)	4 (4.5)	3 (6.4)	0 (0.0)

ECOG PS - Eastern Cooperative Oncology Group Performance Score, AJCC - American Joint Committee on Cancer, LDH = lactate dehydrogenase.

Baseline characteristics of long-term survivors on first-line BRAF-MEK inhibitors were favorable compared to patients not reaching 2-year OS (**table 2**). These long-term survivors more often had an ECOG PS ≤1 (83% vs. 65%), normal LDH (60% vs. 44%), and less often had a highly elevated LDH of ≥500 U/L (3% vs. 23%), stage IVM1c disease (70% vs. 93%) or metastases in ≥3 organ sites (41% vs. 70%). Furthermore, long-term survivors more often did not have brain metastases (60% vs. 47%) and liver metastases (79% vs. 56%) (**table 2**). These favorable prognostic factors were even more pronounced in patients who survived more than 3 or 4 years. The proportion of patients experiencing a CR increased when comparing the cohorts of 2-year (26%), 3-year (33%), 4-year (40%), and 5-year (36%) long-term survivors. Normal LDH levels increased from 60% (2-year survival) to 71% (5-year survival), and an ECOG PS ≥2 decreased from 12% to 0% (**table 2)**. Patients with a minimal 4-year PFS (n=23) generally had favorable characteristics. Still, 4% had an ECOG PS ≥2, 1 patient (4%) had a LDH level of ≥500 U/L, and 13% had brain metastases at baseline.

Treatment characteristics of long-term survivors

In 34 (29%) long-term survivors (>2 year OS), no other subsequent therapy was used. Five (15%) of these patients were treated until the last contact date. These five patients had a median age of 49 years, ECOG PS ≤1, normal LDH-level (80%), and no brain metastases. Subsequent immunotherapy was given in 65% of the long-term survivors. This consisted of anti-PD1 therapy (47%), ipilimumab and nivolumab combination therapy (44%), and ipilimumab monotherapy (9%). A third-line treatment was given in 45% of the patients (data not shown). Rechallenge with third-line BRAF-MEK inhibitors after second-line immunotherapy treatment (n=64) occurred in 21 patients (33%). Eight patients were treated with third-line immunotherapy after second-line immunotherapy (13%). In patients reaching 4-year OS, 34% received no subsequent treatment and 60% immunotherapy.

The median treatment duration of long-term survivors treated with first-line BRAF-MEK inhibitors was 18.2 months. This was 15.0 months for 3-year and 15.8 months for 4-year survivors. The 34 patients who survived >2 years and received no subsequent therapy had a median treatment duration of 16.2 (IQR 3.7-29.9) months. Long-term survivors treated with subsequent immunotherapy (n=75) received first-line BRAF-MEK inhibitors for 18.8 (IQR 5.8-30.3) months.

Discussion

This population-based study shows that real-world patients treated with BRAF-MEK inhibitors have poorer survival than trial patients, which is likely related to poorer baseline characteristics such as higher age, poorer ECOG PS, higher LDH, more organ sites with metastases, and metastases at locations with known poorer prognosis (brains and liver).

Of all patients treated with first-line BRAF-MEK inhibitors in the real world, 28% reached 2-year, 22% 3-year, and 19% 4-year survival. Previous real-world studies did not focus only on patients treated with BRAF-MEK inhibitors or had smaller cohorts than described in this study [13, 14].

Trials vs. real-world

Based on the baseline characteristics of real-world patients treated with first-line BRAF-MEK inhibitors, 53% [204/435] would have been considered ineligible for trials due to ECOG PS≥2 and the presence of brain metastases. In previous research we showed that patients with brain metastases treated with BRAF-MEK inhibitors have similar outcomes to matched patients included in postapproval clinical trials[15]. The number of ineligible patients for phase III trials in this study is higher than reported in our previous study (40%), in which we focused on all patients with advanced melanoma, regardless of the treatment[16]. This difference can be explained by the generally poorer characteristics of patients treated with first-line BRAF-MEK inhibitors. Real-world patients with characteristics corresponding to the phase III trial inclusion criteria (eligible) had an mOS of 17.3 months and a 2-year survival rate of 38%, both lower than in the phase III trials. In pooled data from the COMBI-d and COMBI-v trial, the median OS was 25.9 months for dabrafenib/trametinib, with a 2-year survival rate of 52%[5]. In the coBRIM trial, this was 22.5 months and 49%, respectively[17].

Our real-world patients eligible for trial participation still had poor baseline characteristics, such as more often stage IV M1c disease and highly elevated LDH levels of >500 U/l (**supplement 1**). BRAF-MEK inhibitors are preferred as first-line treatment for patients with aggressive disease because of its immediate effect. Patients with LDH ≥500 U/l at diagnosis almost did not reach long-term survival (<4%). This is in line with previously reported research which showed that LDH is a strong prognostic factor for survival in patients treated with BRAF inhibitor monotherapy[18]. Long-term survival does not solely depend on patient- and tumor characteristics but also on real-world treatment strategies. Real-world treatment can be different than the tightly controlled treatment setting in trials in terms of treatment duration, early discontinuation because of toxicity, compliance, and other treatment regimes can contribute to differences in effectiveness.

Thirteen patients in the study cohort had a V600-BRAF mutation other than the V600E or V600K mutation. Analyses performed excluding these patients led to the same results (data not shown). In the real-world population, subsequent anti-cancer therapy was used in 52% of the patients, which was comparable to data from the COMBI-v and -d trial (53%) and the coBrim trial (51%)[5, 17].

Female gender and ECOG PS ≤1 were positively associated with survival in the trials but were not significantly associated with OS in our multivariate Cox model[19]. Although

patient characteristics were more favorable as survival improved, some patients reaching 3- and 4-year survival also had poor characteristics at baseline. In 62% of the 4-year survivors, the stage of disease was IVM1c, 32% LDH was elevated at baseline, and 17% had brain metastases, compared to respectively 93%, 54%, and 48% in patients not reaching long-term survival (<2-year OS). In patients with LDH >500 U/l, first-line treatment with BRAF-MEK inhibitors continued until progression rarely resulted in long-term survival. This is in line with our previously published analysis in patients with LDH >500 U/l, in which we showed that induction treatment might lead to more favorable outcomes for these patients[20].

Treatment strategies

A majority (65%) of the long-term survivors on first-line BRAF-MEK inhibitors received subsequent immunotherapy compared to 47% of the patients not reaching 2-year OS. Immunotherapy prolongs median survival, and subsequent immunotherapy is expected to contribute to long-term survival in our study population. Still, we cannot say which sequence is most valuable since comparing two groups would lead to confounding by indication as these treatment strategies are based on the characteristics of the patients and therefore a well-considered choice. We previously showed that in matched patients with BRAFV600-mutant advanced melanoma with relatively favourable characteristics, first-line anti-PD-1 monotherapy lead to an improved OS compared to first-line BRAF/MEK inhibition[21]. Recently reported prospective trial data from the randomized phase 3 Dreamseq trial comparing first-line ipilimumab/nivolumab vs dabrafenib/trametinib confirmed this[22]. Similarly, data from SECOMBIT, a three-arm randomized phase 2 trial comparing first-line encorafenib/binimetinib, first-line ipilimumab/nivolumab and encorafenib/binimetinib induction followed by ipilimumab/nivolumab, thus far seem to favour first-line ICI [23].

Limitations

The treatment landscape of patients with advanced melanoma changed over the years. This has resulted in more treatment options and improved survival. Ipilimumab/nivolumab combination therapy has been increasingly used since 2017. As a result, BRAF-MEK inhibitors have been prescribed to a lesser extent in first-line. Still, patients with a contraindication for immunotherapy can be treated with BRAF-MEK inhibitors, and these data are valuable for these patients.

We chose to investigate patients diagnosed between 2013 and 2017 to limit the time bias and to have sufficient follow-up time. However, novel treatments as subsequent therapies could still have influenced these results. Another limitation is the number of patients included in this study, resulting in a selected group of patients with mainly aggressive disease. Furthermore, our study population was not treated with encorafenib/binimetinib

since these BRAF-MEK inhibitors gained market access after 2017. Our data can therefore not be extrapolated for these drugs.

Conclusion

Survival rates of real-world patients with advanced melanoma treated with BRAF-MEK are lower than in trial patients, which is possibly related to poorer characteristics with regard to age, LDH level, and metastatic sites. Still, patients with poor characteristics treated with first-line BRAF-MEK can achieve long-term survival, especially when obtaining a complete response.

References

1. Lee CS, Thomas CM, Ng KE. An Overview of the Changing Landscape of Treatment for Advanced Melanoma. Pharmacotherapy 2017; 37(3):319–333.
2. Kong BY, Carlino MS, Menzies AM. Biology and treatment of BRAF mutant metastatic melanoma. Melanoma Manag. 2016; 3(1):33–45.
3. Silva IP, Long G V. Systemic therapy in advanced melanoma: Integrating targeted therapy and immunotherapy into clinical practice. Curr. Opin. Oncol. 2017; 29(6):484–492.
4. Long G V., Flaherty KT, Stroyakovskiy D et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/ K-mutant melanoma: Long-term survival and safety analysis of a phase 3 study. Ann. Oncol. 2017; 28(7):1631–1639.
5. Robert C, Grob JJ, Stroyakovskiy D et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N. Engl. J. Med. 2019; 381(7):626–636.
6. Ribas A, Daud A, Pavlick AC et al. Extended 5-Year Follow-up Results of a Phase Ib Study (BRIM7) of Vemurafenib and Cobimetinib in BRAF -Mutant Melanoma. 2019:1–9.
7. Dummer R, Flaherty KT, Robert C et al. 1041MO 5-year update on COLUMBUS: A randomized phase III trial of encorafenib (enco) + binimetinib (bini) versus enco or vemurafenib (vem) in patients (pts) with BRAF V600-mutant melanoma. Ann. Oncol. 2021; 32(19):S872–S873.
8. Gyawali B, Parsad S, Feinberg BA, Nabhan C. Real-World Evidence and Randomized Studies in the Precision Oncology Era: The Right Balance. JCO Precis. Oncol. 2017; (1):1–5.
9. Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: Clinical research based on electronic medical records. J. Korean Med. Sci. 2018; 33(34):1–7.
10. Jochems A, Schouwenburg MG, Leeneman B et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur. J. Cancer 2017; 72:156–165.
11. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control. Clin. Trials 1996; 17(4):343–346.
12. RStudio Team. RStudio: Integrated Development for R. .
13. Rigo R, Doherty J, Koczka K et al. Real world outcomes in patients with advanced melanoma treated in Alberta, Canada: A time-era based analysis. Curr. Oncol. 2021; 28(5):3978–3986.
14. Moser JC, Chen D, Hu-Lieskovan S et al. Real-world survival of patients with advanced BRAF V600 mutated melanoma treated with front-line BRAF/MEK inhibitors, anti-PD-1 antibodies, or nivolumab/ipilimumab. Cancer Med. 2019; 8(18):7637–7643.
15. Ismail R, Sikkes N, Wouters M et al. Post-approval trials versus patient registries: Comparability of advanced melanoma patients with brain metastases. Ann. Oncol. 2020; 31:S754.
16. van Zeijl MCT, Ismail RK, de Wreede LC et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. Int. J. Cancer 2020; 147(12):3461–3470.
17. Ascierto PA, Dréno B, Larkin J et al. 5-Year Outcomes with Cobimetinib plus Vemurafenib in BRAF V600 Mutation–Positive Advanced Melanoma: Extended Follow-up of the coBRIM Study . Clin. Cancer Res. 2021; 27(19):5225–5235.

18. Schouwenburg MG, Jochems A, Leeneman B et al. Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: Prognostic factors associated with clinical outcomes. Melanoma Res. 2018; 28(4):326–332.
19. Long G V., Grob JJ, Nathan P et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol. 2016; 17(12):1743–1754.
20. Schouwenburg MG, Suijkerbuijk KPM, Koornstra RHT et al. Switching to immune checkpoint inhibitors upon response to targeted therapy; the road to long- term survival in advanced melanoma patients with highly elevated serum LDH? Cancers (Basel). 2019. doi:10.3390/cancers11121940.
21. van Breeschoten J, Wouters MWJM, Hilarius DL et al. First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAFV600-mutant advanced melanoma patients: a propensity-matched survival analysis. Br. J. Cancer 2021; 124(7):1222–1230.
22. Atkins MB, Lee SJ, Chmielowski B et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134. ASCO Plenary Ser. Abstr. 356154. Present. Novemb. 16, 2021. .
23. P.A. Ascierto, M. Mandala, P.F. Ferrucci, P. Rutkowski, M. Guidoboni, A.M. Arance Fernandez, V. Ferraresi, E. Maiello, M. Guida, M. Del Vecchio, M.T. Fierro, P. Queirolo, C. Lebbe, H. Helgadottir, I. Melero, G. Palmieri, D. Giannarelli, A.M. Grimaldi, R. VCS. LBA40–SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study. Ann. Oncol. 2021; 32(Suppl_5):S1283–S1346.
24. Robert C, Karaszewska B, Schachter J et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N. Engl. J. Med. 2015; 372(1):30–39.
25. Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016; 17(9):1248–1260.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

Supplements

Supplement 1: Patient- and tumor characteristics of patients treated with first-line BRAF-MEK inhibitors who are considered eligible and ineligible for phase III trial participation.

	Eligible	Ineligible	P-value
Patients; n	208	227	
Median age, year (range)	60 (26-91)	59 (19-87)	0.981
Age categories; n (%)			0.583
<50yr	51 (24.5)	53 (23.3)	
50-59yr	52 (25.0)	65 (28.6)	
60-69yr	59 (28.4)	51 (22.5)	
70-79yr	33 (15.9)	44 (19.4)	
>80yr	13 (6.2)	14 (6.2)	
Gender; n (%)			0.701
Male	107 (51.4)	122 (53.7)	
Female	101 (48.6)	105 (46.3)	
ECOG PS; n (%)			
0	99 (47.6)	52 (22.9)	<0.001
1	87 (41.8)	64 (28.2)	
≥2	2 (1.0)	88 (38.8)	
Unknown	20 (9.6)	23 (10.1)	
LDH level (U/l); n (%)			0.103
Normal	102 (49.0)	107 (47.1)	
250-499	65 (31.2)	72 (31.7)	
>500	35 (16.8)	43 (19.0)	
Not determined	3 (1.4)	5 (2.2)	
Stage (AJCC 7th); n (%)			<0.001
IIIc	28 (13.5)	3 (1.3)	
IV-M1a	13 (6.2)	1 (0.4)	
IV-M1b	9 (4.3)	3 (1.3)	
IV-M1c	158 (76.0)	220 (96.9)	
Metastasis in ≥3 organ sites; n (%)			<0.001
Yes	105 (50.5)	166 (73.1)	
No	103 (49.5)	61 (26.9)	
Brain metastasis; n (%)			<0.001
No	171 (82.2)	48 (21.1)	
Yes, asymptomatic	0 (0.0)	54 (23.8)	
Yes, symptomatic	5 (2.4)	119 (52.4)	
Unknown	32 (15.4)	6 (2.6)	
Liver metastasis; n (%)	81 (38.9)	82 (36.1)	<0.001

Supplement 1 continued

	Eligible	Ineligible	P-value
Best overall response; n (%)			<0.001
Complete response	32 (15.4)	5 (2.2)	
Partial response	112 (53.8)	145 (63.9)	
Stable disease	39 (18.8)	39 (17.2)	
Progressive disease	22 (10.6)	27 (11.9)	
LTFU	3 (1.4)	11 (4.8)	
BRAF mutation; n (%)			0.002
V600E	177 (85.1)	184 (81.1)	
V600K	31 (14.9)	30 (13.2)	
Other	0	13 (5.7)	
Subsequent therapy after first-line BRAF/MEK; n (%)			0.388
No	87 (41.8)	105 (46.3)	
Immunotherapy	110 (52.9)	116 (51.1)	
Other	11 (5.3)	6 (2.6)	

ECOG PS - Eastern Cooperative Oncology Group Performance Score, AJCC - American Joint Committee on Cancer, LDH = lactate dehydrogenase.

PART IV

THE VALUE OF REAL-WORLD DATA IN CLINICAL PRACTICE

CHAPTER 9

Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer.

Breast. 2021 Dec 01;60:263-271.

R.K. Ismail, J. van Breeschoten, M.W.J.M. Wouters, M. van Dartel, S. van der Flier, A.K.L. Reyners, P. de Graeff, A.M.G. Pasmooij, A. de Boer, K.E. Broekman, D.L. Hilarius.

Abstract

Background: This study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with advanced breast cancer (BC).

Methods: Patients with advanced BC treated with palbociclib from 2017 to 2020 were included. The Kaplan-Meier method was used to calculate time to next treatment (TTNT) and overall survival (OS) for patients with or without dose reductions. These clinical outcomes were also compared in subgroup analyses for older patients (≥70 years) and younger patients (<70 years) and for patients discontinuing palbociclib early (<4 administrations)

Results: A total of 598 patients with advanced BC were included, with a median age of 64 years. Palbociclib dose reductions occurred in 33% of all patients. Early discontinuation of palbociclib without dose reductions occurred in 23% of the patients. Patients who required a palbociclib dose reduction were older (median age 67 years vs. 63 years). Patients with dose reductions had a significantly higher TTNT of 16.9 vs. 11.4 months ($p<0.001$) and median OS of 29.7 vs. 21.9 months ($p=0.003$) compared to patients without dose reductions. The TTNT in older patients was significantly longer (16.9 vs. 11.6 months, $p=0.013$) than younger patients, but OS was similar (20.7 vs. 26.7 months, $p=0.051$).

Conclusion: Palbociclib dose reductions occurred in real-world practice similarly to the PALOMA-3 trial. Patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. Older patients treated with palbociclib had more frequent dose reductions, but this did not appear to affect OS.

Introduction

The overall survival (OS) of patients with advanced breast cancer (BC) has improved over the last decades[1]. Since 1970, progression-free survival and OS have improved due to the introduction of several new systemic therapies. These therapies include chemotherapy, anti-HER2 directed therapy, aromatase inhibitors, and most recently, the cyclin-dependent kinases 4 and 6 (CDK-4/6) inhibitors[1]. Hormone-positive BC is the most common type of BC and comprises about 80% of all breast cancers[2]. The CDK-4/6 inhibitors are registered for use in hormone-positive, HER2-negative advanced BC patients[3].

The European Medicines Agency (EMA) approved the first CDK-4/6 inhibitor, palbociclib, in 2016. The PALOMA-3 trial showed a significant benefit in median PFS of palbociclib in combination with fulvestrant (9.5 months) after prior endocrine therapy compared to placebo (4.6 months, p<0,0001)[4–6]. The most recent follow-up of the PALOMA-3 trial in 2021 showed an OS benefit of 6.8 months (p=0.0221)[7]. Palbociclib is also registered as first-line treatment combined with aromatase inhibitors (letrozole, anastrozole)[4]. The combination of palbociclib/letrozole was compared to letrozole monotherapy in the PALOMA-2 trial and showed a median PFS of 24.8 months compared to 14.5 months for letrozole monotherapy (p<0.001)[8].

The use of palbociclib in older BC patients has been investigated in a pooled analysis of the PALOMA trials[9]. This study demonstrated a PFS benefit in patients treated with palbociclib regardless of age. The safety profile was comparable, but myelosuppression was more frequent in patients ≥75 years[9]. A review on the use of targeted therapies described the evidence gap in toxicities and efficacy of these therapies in older patients[10]. Real-world data (RWD) includes information of older patients which are underrepresented in phase III clinical trials and can be helpful in daily clinical practice to treat older patients effectively.

The advised initial dose for palbociclib is 125 mg once daily[4]. Reduced doses (100 mg and 75 mg) are recommended in the SmPC to manage adverse events (AE's) of CTCAE grade 3 or higher[11]. The dose is first reduced to 100 mg/day and then to 75 mg/day, and the complete blood count should be monitored[11]. Primarily, palbociclib toxicity is characterized by gastrointestinal side effects and hematologic toxicity such as neutropenia[12]. Phase III clinical trials did not specifically investigate the efficacy of reduced palbociclib dosages, even though these reductions occur in clinical practice[13]. Older patients could be prone to toxicity because of their comorbidities, comedication use, and higher frailty. This could result in a higher need for dose reductions. A previous review on palbociclib included several real-world studies investigating palbociclib dose modifications, but the real-world effectiveness of such modifications was not described[14].

Clinical outcomes can differ between the real-world population and clinical trial patients due to differences in patient-, tumor-, and treatment characteristics[13]. Furthermore, medication use (treatment patterns, dosing schedules, therapy compliance) can differ from the recommended posology in daily clinical practice. The Dutch Institute for Clinical Auditing (DICA) Medicines project was set up in 2018 to generate RWD from existing data sources to improve the effective use of medicines in daily clinical practice[15]. RWD provide insights into the use of new medicines and are important as these data provide valuable information on treatment aspects not investigated in clinical trials.

The effect of palbociclib dose reductions on clinical outcomes in advanced BC patients remains unknown. In addition, a previous study showed that older patients treated with palbociclib experience higher toxicity rates[16]. Therefore, this study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with breast cancer.

Methods

Data sources

Data were retrieved from the DICA medicines program. In this program, existing data sources are re-used and combined to provide insights into the real-world (systemic) therapy of Dutch patients with cancer and their outcomes. The DICA medicine data consist of administrative and financial files on systemic therapies from the hospital pharmacy, linked to clinical patient- and tumor data registered in DICA quality registries. Furthermore, a third data source, the Dutch *DBC information system*[17], is linked to the other data sources focusing on in-hospital activity information and information on diagnosis and treatment. Survival data are the fourth data source, derived from the Vektis database, a national database that comprises the date of deaths of Dutch citizens[18]. The database contains data starting from 1-1-2017. This study used administrative and financial data, providing detailed information on palbociclib treatment (prescription dates and doses) linked to the *DBC information system*.

Patients

The patients included in this study were treated in clinical practice in one of eight general hospitals participating in the DICA medicines program. Seventy-four hospitals in the Netherlands are treating patients with BC. All patients treated with palbociclib from 01-01-2017 to 31-12-2020 were selected. Patients with hormone receptor-positive, HER-2 negative BC without any contraindications are treated with palbociclib in clinical practice. Contraindications for palbociclib include hypersensitivity to palbociclib or any of the excipients or the use of St. John's Wort[11]. Grade 3 and 4 neutropenia and concomitant

use of CYP3A4-inhibitors or -inducers are relative contraindications, and use of palbociclib in patients with other comorbidities (i.e., interstitial lung disease, infections, hepatic and renal impairments) should be cautious[11]. Palbociclib treatment was combined with fulvestrant (after failing endocrine therapy) or aromatase inhibitors (first-line therapy).

Data analysis

The patient population was divided into two groups based on prescribed dose reductions. Dose reduction was defined as reducing the dose of palbociclib from 125 mg to 100 mg or 75 mg (≥20% dose reduction). Separate analyses were performed on patients with an initial treatment dose lower than 125 mg. Furthermore, subanalyses were performed on older patients, defined as patients ≥70 years. We chose 70 years as an acceptable cut-off point since this is a common cut-off point in geriatric oncology. The International Society of Geriatric Oncology guideline for geriatric assessment in older patients with breast cancer uses 70 years as the cut-off point for geriatric research[19]. Another subanalysis included patients who discontinued early. Early discontinuation was defined as discontinuation before the fourth administration of palbociclib without dose reduction. Response evaluation often occurs after three treatment courses in daily clinical practice. Differences in OS over the years (2017-2020) and between the two palbociclib treatment combinations (fulvestrant or aromatase inhibitors) were also analyzed.

Descriptive statistics were used to analyze the available baseline patient characteristics from the DICA medicines program database. These included age at diagnosis, gender, and the Charlson comorbidity index (CCI)[20]. The CCI was calculated based on DBC information in the year palbociclib was first prescribed and includes age and a list of different comorbidities such as diabetes, liver disease, malignancies, AIDS, kidney diseases, heart failure, and COPD. The different groups were compared with Pearson's chi-squared test. Comparisons were considered statistically significant for two-sided P-values <0.05.

To determine differences in clinical outcomes between patients with or without dose reductions and between older and younger patients, we used time-to-next treatment (TTNT) and OS. The TTNT and OS were estimated using the Kaplan-Meier method with corresponding two-sided 95% confidence intervals (CI). TTNT and survival time were calculated from the date of the first palbociclib prescription to the date of next treatment or date of death, respectively. Patients who did not receive a subsequent treatment or who were alive at the dataset cut-off date were censored on the last date of palbociclib (TTNT) and the last date of any medicine administration (OS), respectively. At this date, the patient was considered alive. The median follow-up time was calculated with the reverse Kaplan-Meier method[21].

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.1.0.; packages lubridate, tidyr, ggplot2, tableone, ggthemes, survival, survminer)[22].

Results

Real-world use of palbociclib

Between 2017 and 2020, a total of 598 BC patients were treated with palbociclib. In 2017, 103 patients were treated with palbociclib; in 2018, 176 patients; in 2019, 175 patients; and in 2020, 144 patients. The median follow-up time for OS of all patients treated with palbociclib was 12.9 months. The median age of the study population was 64 years, ranging from 25 to 92 years. Of all patients, 422 (71%) received palbociclib combined with fulvestrant and 173 (29%) combined with aromatase inhibitors. The baseline characteristics of the patient population can be found in **table 1**. Most patients (N= 565, 94.5%) started palbociclib treatment with the advised dose of 125 mg. Thirty patients (5%) received a starting dose of 100mg and 3 patients (0.5%) received a starting dose of 75mg. In patients who started palbociclib with an initial dose of 100 or 75 mg (N = 33), 64% were older than 70 years. **Figure 1** shows the dosing patterns of all patients treated with palbociclib over time. Patients who received a dose reduction did not have a dose increase over time.

Table 1: Patient- and tumor characteristics of patients treated with palbociclib from 2017-2020.

	Categories	Patients
N (total)		598
Year of initiation therapy; n (%)	2017	103 (17.2)
	2018	176 (29.4)
	2019	175 (29.3)
	2020	144 (24.1)
Gender; n (%)	Male	9 (1.5)
	Female	589 (98.5)
Age (median [range])		64 [25, 92]
Age (category); n (%)	<70 years	409 (68.4)
	≥70 years	189 (31.6)
Charlson comorbidity index; n(%)	≤2	35 (5.9)
	≥3 and <6	310 (51.8)
	≥6	195 (32.6)
	Unknown	58 (9.7)
Treatment combination; n (%)	Combination with aromatase inhibitor	173 (28.9)
	Combination with fulvestrant	422 (70.6)
	Unknown	3 (0.5)

N=absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.

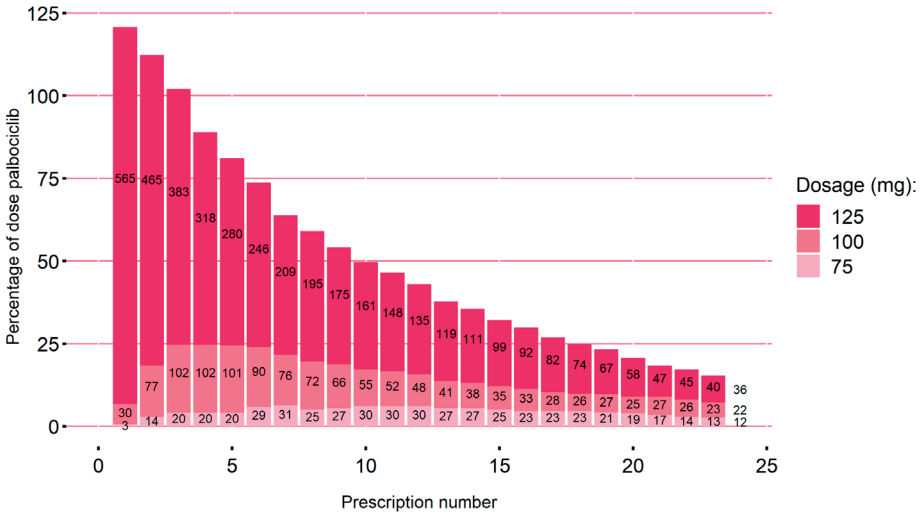


Figure 1: The dosing patterns of palbociclib over the number of prescriptions. **The numbers in the bars represent the absolute number of patients that were treated with the specific dose of palbociclib per prescription number*

Dose reductions or early discontinuation

Dose reductions occurred in 33% (N=195) of the patients. In 59% (N=116) of the patients with dose reductions, a reduction was required in the first three months after initiation of therapy (**figure 2**). The median time to dose reduction was 69 days (IQR 36-152). Patients who required a dose reduction were older compared to patients without dose reduction, median age of 67 years vs. 63 years (p=0.004), respectively (data not shown). The CCI did not differ significantly (p=0.526) between the groups (**table 2**). Patients with dose reductions had a median TTNT of 16.9 months (95%CI: 15.3-24.1) compared to 11.4 months (95%CI: 9.7-13.9) in patients without dose reductions (p<0.001) **(figure 3a).** The median OS of patients with dose reductions was significantly higher compared to patients without dose reductions (29.7 months (95%CI: 26.7-34.8) vs. 21.9 months (95%CI: 20.3-24.9), p=0.003) **(figure 3b)**.

In 136 (23%) of the patients who initially started palbociclib treatment, treatment was discontinued within four courses, without a dose reduction. Another 22 (4%) patients discontinued within four courses and had a dose reduction before discontinuation. There were no significant differences in age (p=0.348) and CCI (p=0.082) between patients who received >3 administrations of palbociclib and patients who discontinued early without dose reduction **(supplement 1)**. The median OS of patients early discontinuing palbociclib was 7.6 months (95%CI: 5.1-11.3) and 28.6 months (95%CI: 25.6-32.2) in patients treated with >3 administrations of palbociclib (p<0.001) (**supplement 2**).

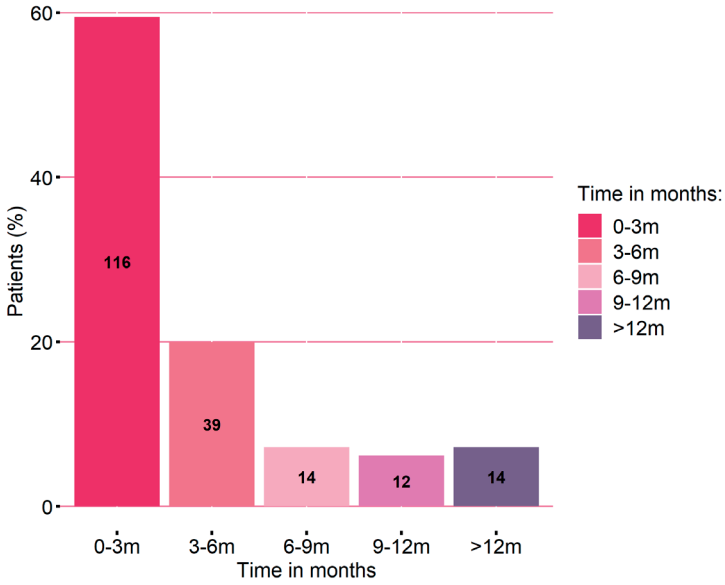
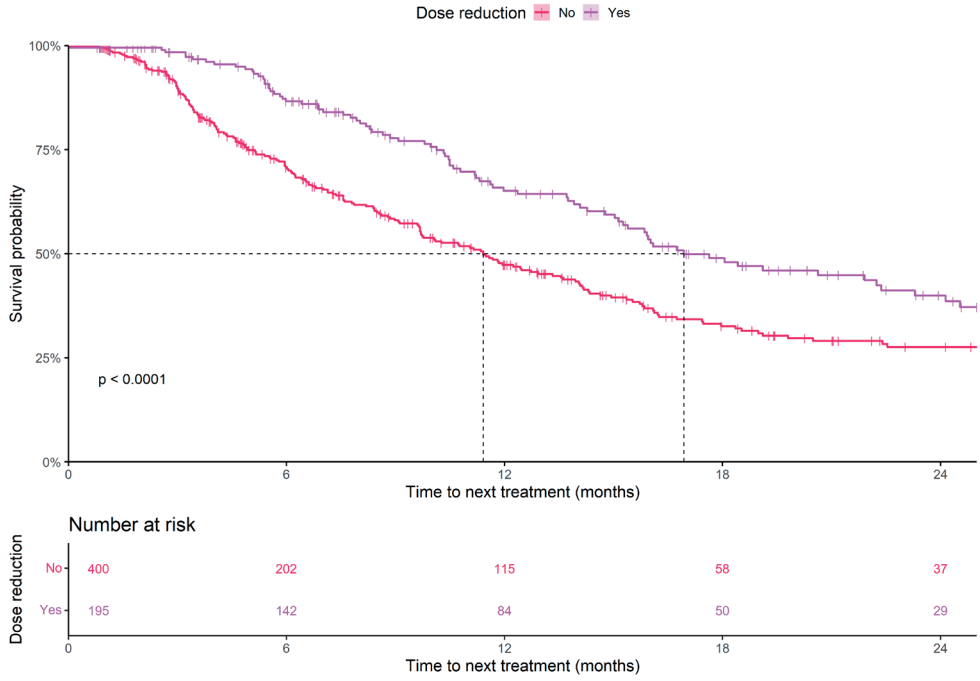


Figure 2: The time to palbociclib dose reduction from start of therapy. *The numbers in the bars represent the absolute number of patients in which a dose reduction occurred.

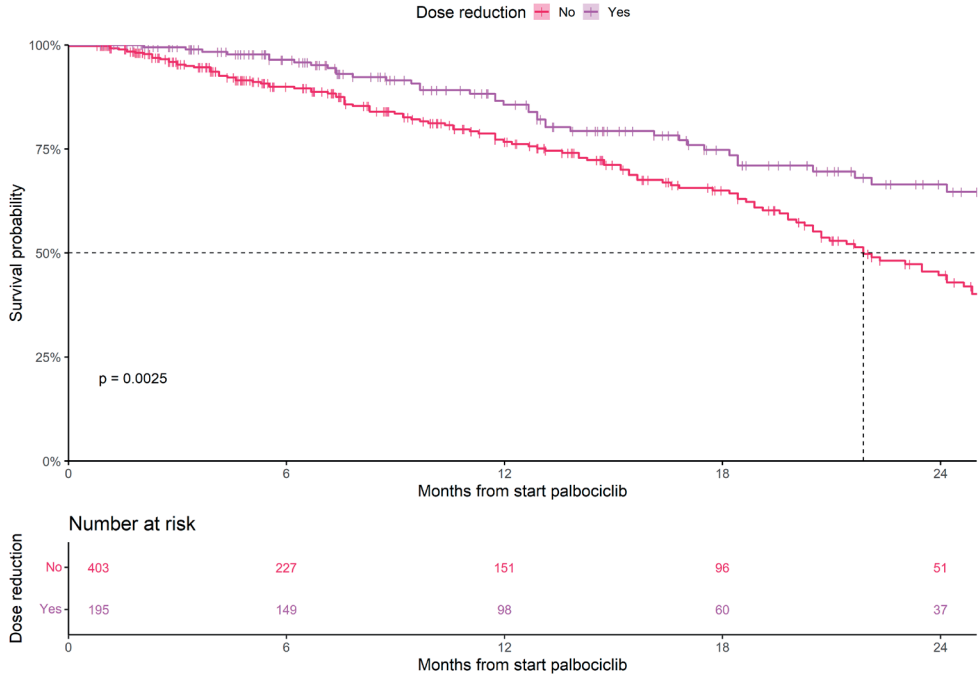
Table 2: Patient- and tumor characteristics of patients with and without a palbociclib dose reduction

	Categories	No dose reduction	Dose reduction	P-value
N (total)		403	195	
Year of initiation therapy; n (%)	2017	77 (19.1)	26 (13.3)	0.022
	2018	110 (27.3)	66 (33.8)	
	2019	109 (27.0)	66 (33.8)	
	2020	107 (26.6)	37 (19.0)	
Gender; n (%)	Male	8 (2.0)	1 (0.5)	0.304
	Female	395 (98.0)	194 (99.5)	
Age in years (median [range])		63 [25-88]	67 [36-92]	0.004
Age in years (category); n (%)	<70	287 (71.2)	122 (62.6)	0.041
	≥70	116 (28.8)	73 (37.4)	
Charlson comorbidity index; n(%)	≤2	23 (5.7)	12 (6.2)	0.526
	≥3 and <6	216 (53.6)	94 (48.2)	
	≥6	129 (32.0)	66 (33.8)	
	Unknown	35 (8.7)	23 (11.8)	
Treatment combination; n (%)	Combination with aromatase inhibitor	115 (28.5)	58 (29.7)	0.422
	Combination with fulvestrant	287 (71.2)	135 (69.2)	
	Unknown	1 (0.2)	2 (1.0)	

N=absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.



a



b

Figure 3: Kaplan-Meier estimate of time to next treatment (a) and overall survival (b) in patients treated with palbociclib; with or without dose reduction

Median OS of patients without a dose reduction, but who received >3 palbociclib administrations (N=267), was 26.7 months (95%CI: 23.5-33.2) compared to 29.7 months (95%CI: 26.7-34.8) in patients with a dose reduction (p=0.75) (**supplement 3**).

Use of palbociclib in older patients

Thirty-two percent of the patients (N=189) treated with palbociclib were ≥70 years, with a median age of 75 years (IQR: 70-92). In older patients, 39% required a dose reduction, compared to 30% (p=0.041) in the younger population of <70 years, with a median age of 58 years (IQR: 25-69) **(supplement 4)**. The median treatment duration of palbociclib was not statistically significantly different between patients <70 and ≥70 years (7.5 months (IQR: 3.8-14.4) vs. 7.0 months (IQR: 2.9-15.6), p=0.41). A significant difference (p=0.013) in TTNT was observed between older (16.9 months) and younger patients (11.6 months) **(figure 4a)**. The median OS of older patients was not significantly different from younger patients (20.7 vs. 26.7 months, p=0.051) **(figure 4b)**.

Differences between study years

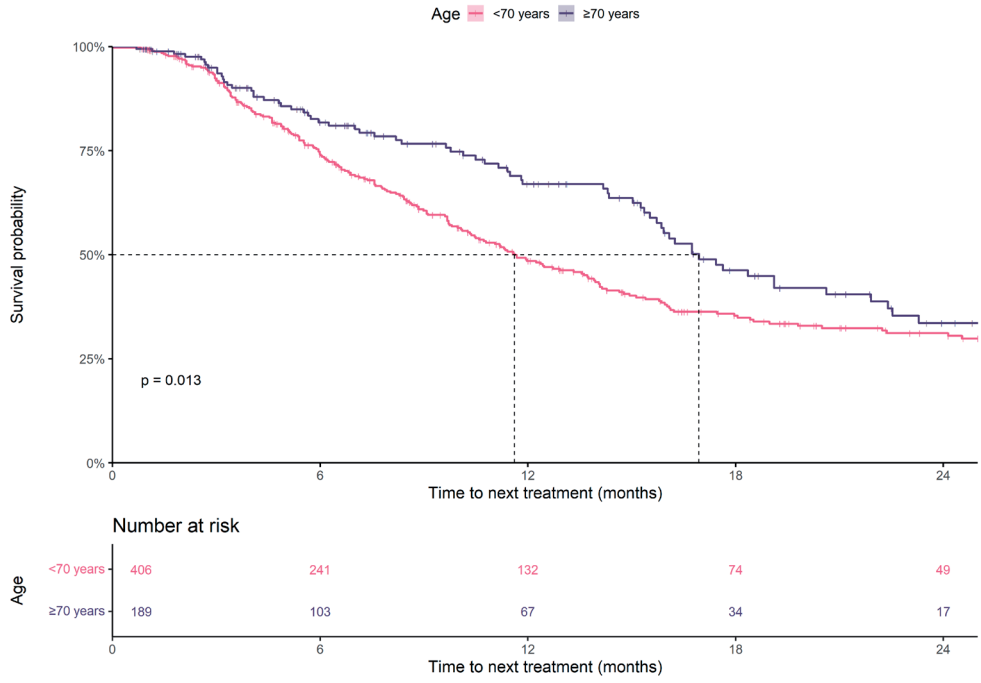
The patient and tumor characteristics of patients treated with palbociclib in 2017 were similar to those treated in the years after. The median OS did not differ between 2017 and 2020. Moreover, no difference in median OS between patients treated with fulvestrant or aromatase inhibitors was observed (data not shown).

Discussion

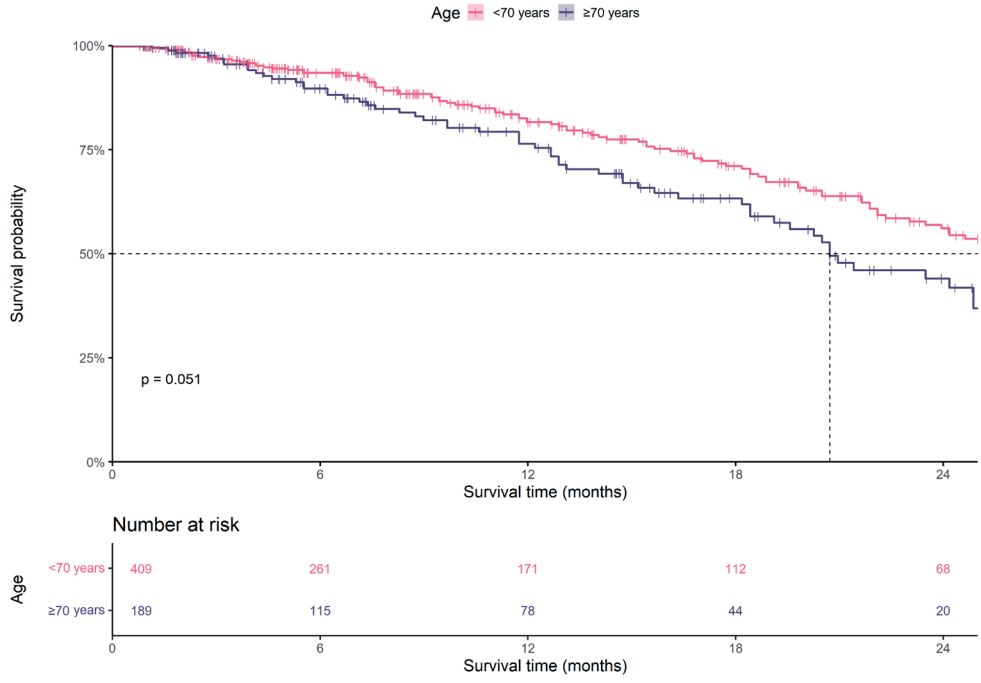
This study shows that 33% of the patients treated with palbociclib required a dose reduction. Most dose reductions were performed within three months (59%) after start of palbociclib and occurred more often in patients ≥70 years. The TTNT was significantly longer in older patients compared to patients <70 years. The OS of older patients did not differ significantly from younger patients despite the more frequent dose reductions.

Previous research

Previous research on palbociclib dose reductions by Kish et al. in the USA showed a dose reduction rate of 20%, and 12% of the patients started with a lower dose of 100 or 75 mg, respectively[14]. The median time to dose reduction was 39 days. In this current study, 33% of the patients required a dose reduction, 5.5% started with a lower dose, and the median time to dose reduction was 69 days. This previous study did not assess clinical benefit because of limited follow-up time. Our study has a longer median follow-up time, possibly resulting in a higher number of dose reductions. In addition, our results are comparable to the number of dose reductions in the registration trials. In the PALOMA-3 trial (palbociclib/fulvestrant), with a median follow-up time of 44.8 months, 34% of the patients had a dose



a



b

Figure 4: Kaplan-Meier estimate of (a) time to next treatment and (b) overall survival in older (≥70 years) BC patients treated with palbociclib versus younger patients (<70 years)

reduction[6]. In the PALOMA-2 trial (palbociclib/letrozole), 36% of the patients had a dose reduction.

Another real-world study, investigating the effectiveness of palbociclib showed there was no efficacy-effectiveness gap in BC patients treated with palbociclib[13]. This study showed fewer dose reductions (22%) but was based on 46 patients treated between 2016 and 2018. We found more dose reductions, in a larger population, with a higher OS for patients with dose reductions. Data on the moment of progressive disease are needed to estimate PFS. TTNT was used as a surrogate for PFS since subsequent treatment is presumably due to progressive disease. This resulted in patients with dose reductions having a longer TTNT than patients without dose reductions. Response to palbociclib treatment is evaluated three to six months after starting therapy. This could explain the decline in the numbers at risk in the group of patients without dose reduction in the Kaplan-Meier estimate of TTNT (**figure 3a**). Presumably, these patients progressed, palbociclib treatment was discontinued, and subsequent treatment was started, while patients with dose reductions did not progress but experienced toxicity that required lowering the treatment dose. This might have introduced a bias to the analyses, which also affected OS analyses. One-third (33.7%) of the patients without a dose reduction discontinued treatment within three palbociclib courses. We presume that these patients discontinued treatment mainly because of progressive disease. In the PALOMA-3 trial[6], only 4% of the patients discontinued treatment due to an adverse effect, and in the PALOMA-2 trial, the main reason for treatment discontinuation was progressive disease (39%)[8]. Similar OS between patients with or without dose reductions was found when we excluded these patients from the analysis (p=0.75) (**supplement 3**). This confirms our hypothesis that the outcomes of patients without a dose reduction are strongly affected by this group of patients early discontinuing therapy. Our results suggest that dose reductions do not affect survival outcomes.

Older patients

Although we observed more dose reductions in older patients, their clinical outcomes were similar to those of younger patients. Older patients are more prone to toxicity which could explain their higher number of dose reductions. The treatment duration of palbociclib in our study was similar between older and younger patients. This contrasts with the pooled analysis of the PALOMA trials, which showed longer treatment duration for older patients (>65 years).

Real-world data monitors uptake of new medicines

The DICA medicines program collects RWD which can help monitor the uptake of new medicines in clinical practice. Clinical questions on palbociclib dose reductions and treatment in older patients were the basis of this study. Monitoring palbociclib real-world usage showed that the OS of real-world patients is lower than in the PALOMA-3

trial, presumably due to more comorbidities of real-world patients. Palbociclib became available in the Netherlands in 2017, but we did not observe significant differences in patient characteristics or outcomes since its introduction.

Limitations and strengths

The use of RWD has limitations. First, RWD includes no predefined progression evaluation, standardized toxicity registration, and incomplete history of the disease and treatment. Secondly, additional information on receptor status, menopausal status, specific stage of disease, previous treatments, adverse events, response status, and the reason for dose reduction or palbociclib discontinuation were missing and would have improved the data. If the reason for dose reduction or discontinuation had been available, we could further limit the bias by distinguishing patients discontinuing early because of early unacceptable toxicity from patients with early progressive disease. In addition, frailty information, which is important in the comparison between older and younger patients, was missing. This information could have explained which selected group of older patients was treated. The CCI did not differ between the old and young patients, suggesting the older patients treated were relatively fit patients. A third limitation is that data from 2020 were incomplete in the databases, which led to lower numbers of patients. Finally, as mentioned before, comparing patients requiring a dose reduction to those who did not could be biased since patients who progress early cannot get to dose reductions. Their shorter prognosis could lower the estimated survival in the group without dose reductions. We, therefore, cannot conclude that dose reductions lead to improved survival. However, these results indicate that dose reductions can be performed safely, without affecting TTNT and OS.

Future research

High-quality data on medicine use can improve the effective use of medicines and eventually lead to changes in practice guidelines. We suggest that this study has to be repeated when more hospitals participate in the DICA medicines program, eventually leading to population-based data on palbociclib usage.

Since only 33 (6%) patients initially started with a lower dose of palbociclib in our study, we could not compare patients starting with a lower-dose palbociclib to patients who needed a dose reduction. Starting lower-dose palbociclib could benefit patients by preventing adverse events. This would hardly affect dose intensity as most dose reductions were performed within three months. Our study demonstrated that dose reductions did not affect the effectiveness of palbociclib treatment, but this should be investigated prospectively. Older or frail patients can experience more adverse events. Starting a lower dose of palbociclib can be even more critical for this group to reduce the probability of adverse events and facilitate extended treatment on palbociclib.

Conclusion

Palbociclib dose reductions occurred in real-world practice similarly to the phase-III clinical trial (PALOMA-3). Patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. Older patients treated with palbociclib had more frequent dose reductions, but this did not appear to affect OS.

References

[1] Caswell-Jin JL, Plevritis SK, Tian L, Cadham CJ, Xu C, Stout NK, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. JNCI Cancer Spectr 2018;2:1–10. doi:10.1093/jncics/pky062.

[2] WebMD Cancer Center. Types of Breast Cancer. 01-07-2020 n.d. https://www.webmd.com/breast-cancer/breast-cancer-types-er-positive-her2-positive (accessed July 26, 2021).

[3] European Medicines Agency (EMA). Ibrance: EPAR for the public 2018;44:1–2.

[4] European Medicines Agency's (EMA). Palbociclib EPAR-Committee for Medicinal Products for Human Use (CHMP) Assessment report 2016;44.

[5] Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015;373:209–19. doi:10.1056/nejmoa1505270.

[6] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phas. Lancet Oncol 2016;17:425–39. doi:10.1016/S1470-2045(15)00613-0.

[7] Massimo Cristofanilli, Hope S. Rugo, Seock-Ah Im, Dennis J. Slamon, Nadia Harbeck, Igor Bondarenko, Norikazu Masuda, Marco Colleoni, Angela DeMichele, Sherene Loi, Hiroji Iwata, Ben O'Leary, Eustratios Bananis, Yuan Liu, Xin Huang, Sindy Kim, Mariajose Le NCT. Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Updated analyses from PALOMA-3. J Clin Oncol 2021:1000. doi:10.1200/JCO.2021.39.15_suppl.1000 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 1000-1000.

[8] Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925–36. doi:10.1056/nejmoa1607303.

[9] Rugo HS, Turner NC, Finn RS, Joy AA, Verma S, Harbeck N, et al. Palbociclib plus endocrine therapy in older women with HR+/HER2– advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer 2018;101:123–33. doi:10.1016/j.ejca.2018.05.017.

[10] Battisti NML, Decoster L, Williams GR, Kanesvaran R, Wildiers H, Ring A. Targeted Therapies in Older Adults With Solid Tumors. J Clin Oncol 2021;39:2128–37. doi:10.1200/JCO.21.00132.

[11] European Medicines Agency (EMA). Summary of Product Characteristics Palbociclib 2016. doi:10.1017/s0167676800003524.

[12] Watson GA, Deac O, Aslam R, O'Dwyer R, Tierney A, Sukor S, et al. Real-World Experience of Palbociclib-Induced Adverse Events and Compliance With Complete Blood Count Monitoring in Women With Hormone Receptor–Positive/HER2-Negative Metastatic Breast Cancer. Clin Breast Cancer 2019;19:e186–94. doi:10.1016/j.clbc.2018.09.002.

[13] Bui TB V., Burgers DMT, Agterof MJ, van de Garde EMW. Real-World Effectiveness of Palbociclib Versus Clinical Trial Results in Patients With Advanced/Metastatic Breast Cancer

That Progressed on Previous Endocrine Therapy. Breast Cancer Basic Clin Res 2019;13. doi:10.1177/1178223418823238.

[14] Kish JK, Ward MA, Garofalo D, Ahmed H V., McRoy L, Laney J, et al. Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval. Breast Cancer Res 2018;20:1–8. doi:10.1186/s13058-018-0958-2.

[15] Ismail R.K., van Breeschoten J., Wouters M.W.J.M, de Boer A., van den Eertwegh A.J., van Dartel M., van Loosen C.T. HD. Use of linked data sources in dynamic dashboards to visualize hospital practice differences in medication use and outcomes 2021:1022. https://www.eahp.eu/sites/default/files/gpi_documents/psq10227.pdf (accessed April 6, 2021).

[16] Howie LJ, Singh H, Bloomquist E, Wedam S, Amiri-kordestani L. original reports abstract Outcomes of Older Women With Hormone Receptor – Positive , Human Epidermal Growth Factor Receptor – Negative Metastatic Breast Cancer Treated With a CDK4 / 6 Inhibitor and an Aromatase Inhibitor : An FDA Pooled Analysis 2019;37. doi:10.1200/JCO.18.02217.

[17] Zorgwijzer. DBC system n.d. https://www.zorgwijzer.nl/faq/dbc (accessed September 3, 2021).

[18] Vektis. Vektis database n.d. www.vektis.nl (accessed July 5, 2021).

[19] Biganzoli L, Battisti NML, Wildiers H, McCartney A, Colloca G, Kunkler IH, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol 2021;22:e327–40. doi:10.1016/S1470-2045(20)30741-5.

[20] Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: A perspective on risk adjustment in critical care research. J Crit Care 2005;20:12–9. doi:10.1016/j.jcrc.2004.09.007.

[21] Schemper M, Smith TL. A Note on Quantifying Follow-up in Studies of Failure Time 1996;346:0–3.

[22] RStudio Team. RStudio: Integrated Development for R n.d.

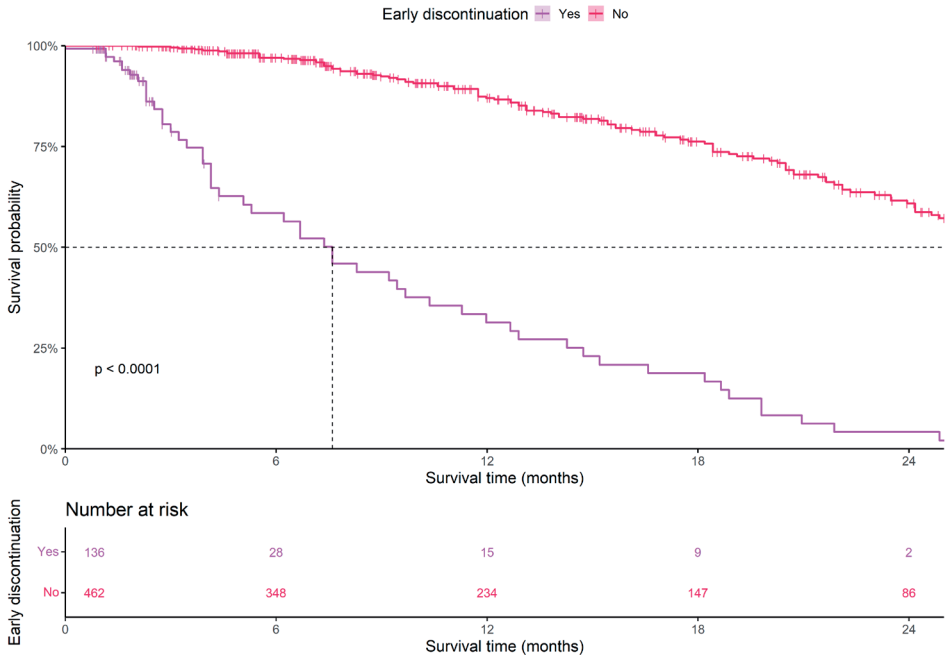
Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology and analyses, interpretation, writing and revising of the manuscript.

Supplements

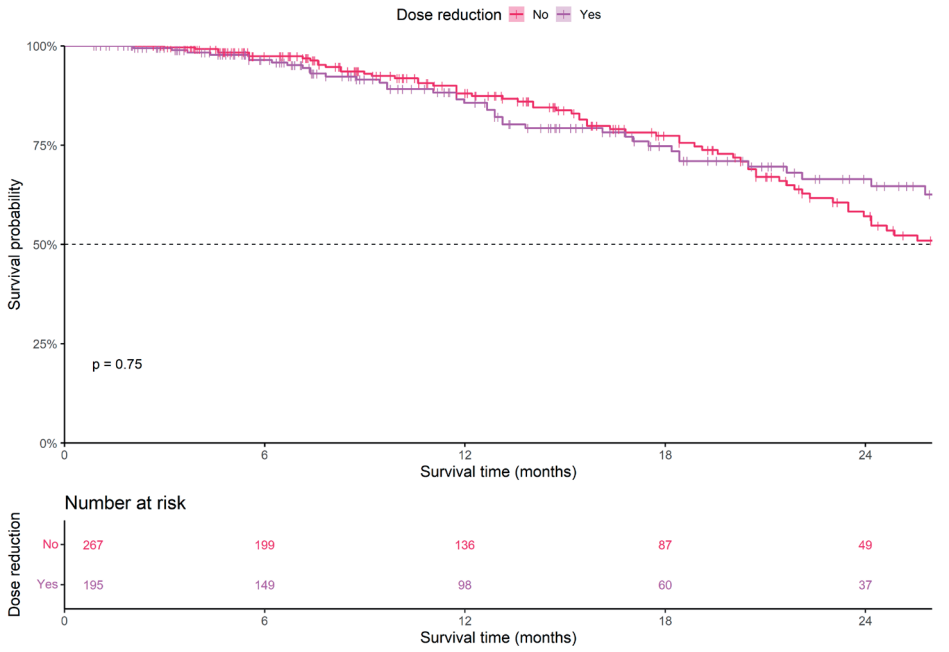
Supplement 1: Patient- and tumor characteristics of patients early (≤3 administrations) discontinuing palbociclib versus patients treated longer (>3 administrations)

	Categories	≤3 administrations palbociclib	>3 administrations palbociclib	P-value
N (total)		136	462	
Year of initiation therapy; n (%)	2017	21 (15.4)	82 (17.7)	<0.001
	2018	34 (25.0)	142 (30.7)	
	2019	30 (22.1)	145 (31.4)	
	2020	51 (37.5)	93 (20.1)	
Gender; n (%)	Male	1 (0.7)	8 (1.7)	0.661
	Female	135 (99.3)	454 (98.3)	
Age (median [range])		64 [32-88]	64.5 [25-92]	0.348
Age (category); n (%)	<70 years	90 (66.2)	319 (69.0)	0.597
	≥70 years	46 (33.8)	143 (31.0)	
Charlson comorbidity index; n(%)	≤2	5 (3.7)	30 (6.5)	0.082
	≥3 and <6	61 (44.9)	249 (53.9)	
	≥6	53 (39.0)	142 (30.7)	
	Unknown	17 (12.5)	41 (8.9)	
Treatment combination; n (%)	Combination with aromatase inhibitor	40 (29.4)	136 (29.4)	0.908
	Combination with fulvestrant	95 (69.9)	324 (70.1)	
	Unknown	1 (0.7)	2 (0.4)	

N=absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.



Supplement 2: Kaplan-Meier estimate of overall survival of BC patients early discontinuing palbociclib treatment (≤3 administrations) compared to patients with more extended treatment (>3 administrations)



Supplement 3: Kaplan-Meier estimate of overall survival of BC patients with no dose reduction and >3 palbociclib administrations compared to patients with dose reductions.

Supplement 4: Patient- and tumor characteristics of BC patients <70 years and ≥70 years

		<70 years	≥70 years	p
n		409	189	
Year of initiation therapy; n (%)	2017	74 (18.1)	29 (15.3)	0.514
	2018	113 (27.6)	63 (33.3)	
	2019	123 (30.1)	52 (27.5)	
	2020	99 (24.2)	45 (23.8)	
Gender; n (%)	Male	6 (1.5)	3 (1.6)	1.000
	Female	403 (98.5)	186 (98.4)	
Age (median [range])		58 [25, 69]	75 [70, 92]	<0.001
Charlson comorbidity index; n (%)	≤2	35 (8.6)	0 (0.0)	<0.001
	≥3 and <6	235 (57.5)	75 (39.7)	
	≥6	96 (23.5)	99 (52.4)	
	Unknown	43 (10.5)	15 (7.9)	
Dose reduction; n (%)	No	287 (70.2)	116 (61.4)	0.041
	Yes	122 (29.8)	73 (38.6)	
Treatment combination; n (%)	Combination with aromatase inhibitor	124 (30.3)	49 (25.9)	0.545
	Combination with fulvestrant	283 (69.2)	139 (73.5)	
	Unknown	2 (0.5)	1 (0.5)	

N=absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.

10

CHAPTER 10

An invisible group of COVID-19 victims; impact on Dutch lung cancer care.

Lung Cancer. 2021 Sep 01;159:177-178.

J. van Breeschoten*, **R.K. Ismail***, H.J.M. Smit, O.C.J. Schuurbiers, F.M.N.H Schramel *on behalf of the Dutch Lung Cancer Audit Scientific Committee.*
*These authors contributed equally to this manuscript.

Dear editor,

Clinical outcomes of lung cancer patients with COVID-19 have been investigated extensively [1]. Recently, a study of the effects of COVID-19 showed severe delays in detection, diagnosis, and treatment in British lung cancer patients [2]. To investigate the effects of the SARS-COV-2 pandemic on regular lung cancer care in the Netherlands, we studied every patient with lung cancer registered in the Dutch Lung Cancer Audit (DLCA), which includes detailed information on patient, tumor, and treatment characteristics and follow up [3].

We observed a major decline in the number of non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) patients diagnosed during the first wave of the COVID-19 pandemic (16-03-2020 until 24-05-2020) compared to the same period in previous years (2018 and 2019). During the first wave, 1746 patients were diagnosed with NSCLC compared to an average of 2641 patients in 2018 and 2019. The most severe decline in lung cancer diagnoses was 50%, with only 146 weekly diagnoses with NSCLC vs. 296 weekly diagnoses with NSCLC in the control period. Between the first and second wave, the number of patients diagnosed recovered to the expected numbers observed in 2018 and 2019. However, during the second wave (21-09-2020 until 27-12- 2020), we observed another 25% decline of newly diagnosed lung cancer patients. With such a major decrease, we expect a significant increase in the proportion of newly diagnosed lung cancer patients with a high stage of disease in the first months of 2021 compared to the control period.

Compared to the control period, NSCLC patients diagnosed during the first wave of the pandemic presented with significantly worse Eastern Cooperative Oncology Group Performance Score (ECOG PS) ≥2 (26% vs. 20%, p-value < 0.001), and more patients presented with metastatic disease compared to the control period in 2018 and 2019 (49% vs. 43%, p-value <0.001). No significant differences were found in gender and age. We observed comparable results for the 2nd wave regarding ECOG PS and increase of metastatic disease. The latter seems to result from a small shift of stage III to stage IV disease. A probable cause of this stage shift might be patient delay during both COVID waves if symptoms were neglected or hospital visits avoided for fear of contamination.

Time between the first hospital visit and date of diagnosis is also registered in the DLCA and showed shorter intervals during the first wave, second wave, and the period in-between, indicating timely care for patients at least after presentation. We hypothesize that due to the lower numbers of diagnosed patients and awareness of urgency for this patient group, time between the first visit and diagnosis was short.

In the coming years, outcomes such as the overall survival of patients diagnosed in 2020 will be compared to previous years. At present, the follow-up time of these patients, especially

those diagnosed during the second wave in 2020, is still limited. We fear that the impact of the COVID pandemic on lung cancer care will remain visible in upcoming years and that delayed lung cancer diagnosis may lead to a different victim group of COVID-19.

References

[1] Luo J, Rizvi H, Preeshagul IR, Egger J V., Hoyos D, Bandlamudi C, et al. COVID-19 in patients with lung cancer. Ann Oncol 2020;31:1386–96. doi:10.1016/j.annonc.2020.06.007.

[2] Gourd E. Lung cancer control in the UK hit badly by COVID-19 pandemic. Lancet Oncol 2020;21:1559. doi:10.1016/S1470-2045(20)30691-4.

[3] Ismail RK, Schramel FMNH, van Dartel M, Hilarius DL, de Boer A, Wouters MWJM, et al. The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients. Lung Cancer 2020;149:68–77. doi:10.1016/j.lungcan.2020.08.011.

Contribution of R.K. Ismail: Substantial contribution to conceptualization of the work, methodology, interpretation, writing and revising of the letter.

DISCUSSION AND CONCLUSION

11

CHAPTER 11

General discussion and future perspectives

The real-world effectiveness of anti-cancer therapies has become an increasingly important subject due to the rising health care costs and the differences between the trial and real-world population. This thesis showed how the real-world population of patients with cancer differs from the trial population and how real-world evidence can be used in daily clinical practice to improve cancer care.

Main findings

We showed the value of quality registries and other existing real-world data sources in generating real-world data (RWD) and real-world evidence (RWE) to improve cancer care. The DICA Medicines program generates RWD without causing an extra registration burden, and the Dutch Lung Cancer Audit for Lung Oncology (DLCA-L) uses quality indicators to improve cancer care (**Chapters 2 and 3).** These RWD can be used to compare real-world and trial patients for an improved understanding of real-world drug effectiveness. We showed that propensity-score matching or multivariate Cox regression analyses can be used to compare these groups and that patient-level data (PLD) can lead to better insight into potential factors responsible for the efficacy-effectiveness gap of drugs (**Chapters 4 and 5**).

Patient characteristics, treatment, and clinical outcomes differ between real-world and trial patients. In real-world advanced melanoma patients, 40% of the systemically treated patients would have been considered ineligible for phase III trials. Trial-eligibility affects clinical outcomes, with poorer overall survival in ineligible patients (**Chapter 6**). In real-world melanoma patients treated with adjuvant treatment, 61% of the patients prematurely discontinued anti-PD1 treatment. Real-world patients also experienced more toxicity than trial patients (**Chapter 7**). We also showed that the survival rates in advanced melanoma patients treated with first-line BRAF-MEK inhibitors were poorer in the real world compared to the trial results (**Chapter 8**).

Chapter 9 showed the value of RWD in clinical practice in patients with advanced breast cancer treated with palbociclib. We found that patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. We also showed that RWD are important in monitoring cancer care in extremely unexpected situations, such as the COVID-19 pandemic. The pandemic led to a decline in lung cancer diagnosis in the Netherlands. In addition, patients with diagnosed lung cancer had poorer characteristics (higher stage of disease and ECOG PS) compared to recent years (**Chapter 10**).

Relevant literature

Numerous other studies have researched RWD use in cancer care in past years. The efficacy-effectiveness gap of immunotherapies in lung cancer care was also investigated by Cramer-van der Welle *et al.*[1]. Our study using PLD of trial patients supports this previous study's results and shows the relevance of making PLD from clinical trials available to the international research community (Chapter 5). In advanced melanoma care, registry studies from Denmark showed high rates of ineligible patients treated in real-world[2]. We focused on ineligible patients systemically treated in clinical practice by modeling a survival decision tree that medical oncologists and patients can use to set realistic treatment goals in daily clinical practice. This patients-like-me principle can be helpful in expectation management (Chapter 6)[3].

A systematic literature review by Dunn *et al.* focusing on lung cancer, breast cancer, and prostate cancer showed that older age groups are underrepresented in cancer clinical trials[4]. Chapter 9 showed that older patients with advanced breast cancer treated with palbociclib had similar overall survival compared to younger patients[5]. RWD are important to increase the evidence of effective treatment in this group of patients.

Relevance of these findings

Clinical practice

We showed that the real-world outcomes of new therapies could differ in patients that are ineligible for trial participation[3,6]. Data on these patients can be useful in clinical practice. As mentioned, the survival tree can be used to set realistic treatment goals[3]. Furthermore, data on the real-world adjuvant anti-PD1 treatment and the higher numbers of premature discontinuation and slightly higher toxicity rates in melanoma patients are relevant for clinical practice. These data ensure that medical oncologists are aware of these differences in treatment in clinical practice, but this study also showed that these differences did not affect the recurrence-free survival[6]. Therefore, medical oncologists might discuss premature anti-PD1 discontinuation with patients when toxicities are experienced with more confidence.

RWD can also be used to monitor new systemic treatments in certain patient groups, such as the adjuvant treatment in melanoma patients, the systemic treatment of patients with stage IV lung cancer, or when new therapies receive marketing authorization (i.e., palbociclib). Monitoring new drugs or specific patient groups ensures quality of care[5–7]. The first results of the DICA Medicines Program and the starting DLCA-L quality registry show that a lot of information can be generated within a short period of time, which can be useful

for hospitals in daily clinical care. For example, data from quality registries include valuable information on systemically treated patient groups that were not researched in pivotal trials. In chapter 4, we focused on advanced melanoma patients with brain metastases treated with BRAF-MEK inhibitors, who are normally excluded from the phase III clinical trials[8]. These data showed a difference in clinical outcomes between trial- and real-world patients, but this difference disappeared when adjusting for prognostic factors.

Regulators and other stakeholders in cancer care

The insights described in this thesis are relevant for clinical practice, and authorities such as the Dutch health institute (ZiN), insurers (*Zorgverzekeraars Nederland*), and regulators. However, observational data always comes with limitations, and the studies described in this thesis were not set up for these purposes. For example, more evidence is needed to treat all real-world patients similarly to eligible patients.

In recent years, many initiatives were started by regulators to improve the use of RWD in the regulatory process. In 2015, the Patients' initiative was started by the EMA to facilitate harmonization of data collected in disease registries, to support the evaluations throughout the medicines authorization process, and to capitalize on networks of registry stakeholders[9]. We showed that RWD could be used in post-marketing authorization studies complementary to post-approval clinical trials[8]. The results from our study show that in specific cases, post-approval trials can be replaced by RWD from high-quality registries. Questions that arise during the regulatory assessment of new drugs and after marketing authorization might be answered in shorter periods since the data are already structurally collected. When RWD can be used under certain conditions, this will eventually reduce the costs of expensive clinical trials.

The systemic therapies used in patients with advanced melanoma are broadly used. We showed that trial-ineligible real-world patients can experience reduced effectiveness. The Data Analysis and Real World Interrogation Network (DARWIN EU) will be a coordination centre for RWE across Europe. RWD will be used by regulators throughout the lifecycle of a medicinal product, which could also involve the use of drugs in specific patient populations[10,11]. In 2024, DARWIN EU is expected to be fully operational. Furthermore, the European Medicines Agency (EMA) published recently a new guideline for registry-based studies[12]. This will benefit cancer care by supporting development of new anti-cancer drugs.

Limitations

The research described in this thesis had some limitations. The limitations of each study have been discussed in the relevant chapters. Some general limitations are mentioned here.

First, RWD are observational in nature, and low quality of these data can limit research. Most studies included registry data with missing data. Data are lacking when data managers cannot find essential data in the electronic patient dossier or when the data entry items are not mandatory in the quality registry. Furthermore, the DICA Medicines program uses information from the quality registries, which can have other purposes than the real-world effectiveness of drugs. For example, the Dutch breast cancer registry (NBCA) includes the surgical treatment and (neo)adjuvant radiotherapeutic and systemic treatments of patients with breast cancer. Therefore it does not include all data entry items necessary for research focusing on the systemic treatment of advanced breast cancer patients. Some essential information was missing in our study on palbociclib and dose reductions (Chapter 9), i.e., the reason for dose reduction or discontinuation and hormone receptor status[5].

Secondly, data on patients' quality of life related to the systemic treatment are essential for improving shared decision-making. Patient-reported outcomes (PROMs) are linked to the clinical data from the DMTR, but the number of completed questionaries is limited. Safety data are also important to make well-informed choices for treatment, but toxicities are limitedly registered in the DMTR, which focuses only on CTCAE grade ≥3 toxicities.

A third limitation of observational data is the uniformity of the data that different hospitals register in the Netherlands. These discrepancies are reduced by training data managers and including information help texts in the registries. In the DICA Medicines program, differences in the registration of DBC data were observed, which could have influenced the quality and the homogeneity of the data.

Lastly, this thesis focused on the differences between real-world and trial patients. Different methods were used to increase the reliability for a fair comparison. Even though most important prognostic factors that explain the differences between the groups were present, we argue that some unmeasured factors can have influenced the results. This could be drug adherence, interpretation of clinical outcomes, comorbidities, or frailty. For example, measuring progressive disease using the Response Evaluation Criteria in Solid Tumors (RECIST)- criteria can be less structured and strict in real-world than in trial patients. In clinical practice, the immune responses assigned using RECIST (iRECIST) criteria are used, which include unconfirmed progression.

Future perspectives

RWD can be increasingly used and more usable if the data landscape is more automatized. The DICA Medicines program is the first step in this automatization. In coming years, automatically retrieved data from sources such as the DBC Information system or the drug administrative data (add-on declarations) can replace manually registered data entry items of the quality registries. In addition, structured data from hospital electronic patient dossiers will be retrieved automatically. Furthermore, the data of the quality registries can be enrichened. At this moment, only the first-line systemic therapies are registered for lung cancer patients in the DLCA-L. With the use of the data sources of the DICA Medicines program, this information can be extended with second-, third-, and fourth-line treatments without causing an extra registration burden. This can also be applied to the DMTR. The manual registration in the DMTR costs data managers around four hours per patient, which can be considerably reduced if existing data sources are linked to the registry.

In this thesis, we showed that registry data could help monitor gaps in cancer care for hospital improvement. However, these results alone are not enough to improve care. Results need to be shared and discussed. This is incorporated in quarterly meetings within scientific committees of the quality registries or in benchmark meetings organized in the DICA Medicines program. We argue that these meetings motivate care providers to dive into their data and set up improvements within their hospitals.

Future research should be more focused on the trial-ineligible patient. These patients are now treated in real-world practice with often little evidence. Exploring the options for the indication labels for these drugs at the time of marketing authorization or post-approval should benefit the patient by reducing over-or undertreatment. Furthermore, long-term outcomes of novel drugs should be considered at marketing authorization. As described in this thesis, the 5-year survival outcomes of advanced melanoma patients treated with BRAF/MEK were high, but the real-world survival rates were significantly lower. It should be researched when the effectiveness of drugs should be critically scrutinized after marketing authorization. This is often performed for the long-term safety of drugs, but as showed in this thesis, it could also be of major significance for drugs effectiveness. In recent years, conditional approvals for marketing authorization or conditional reimbursement of drugs have been granted. We argue that conditional approval or reimbursement in the general population can only be justified if validated post-approval RWD are collected, and the conditional approval is re-evaluated. Follow-up studies should investigate the different approvals and measures applied for approval (off-label use, Annex II forms, pay for performance, post-approval data) to come with recommendations for approval in the right patient population.

This thesis showed that specific research questions could be answered more easily or only be answered using observational data from registries and other RWD sources. Future research should focus on questions that arise in daily clinical practice or with regulators, HTA's, insurers, or health institutes. This will lead to immediate changes in practice without the need for clinical trials, which can be time-consuming and expensive. Examples are real-world treatment (dose reductions, treatment durations, sequences of therapies), health care or treatment costs, or specific (rare) patient populations.

References

[1] Cramer-van der Welle CM, Verschueren M V., Tonn M, Peters BJM, Schramel FMNH, Klungel OH, et al. Real-world outcomes versus clinical trial results of immunotherapy in stage IV non-small cell lung cancer (NSCLC) in the Netherlands. Sci Rep 2021;11:1–9. doi:10.1038/s41598-021-85696-3.

[2] Donia M, Kimper-Karl ML, Høyer KL, Bastholt L, Schmidt H, Svane IM. The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials. Eur J Cancer 2017;74:89–95. doi:10.1016/j.ejca.2016.12.017.

[3] van Zeijl MCT, Ismail RK, de Wreede LC, van den Eertwegh AJM, de Boer A, van Dartel M, et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. Int J Cancer 2020:1–10. doi:10.1002/ijc.33162.

[4] Dunn C, Wilson A, Sitas F. Older cancer patients in cancer clinical trials are underrepresented. Systematic literature review of almost 5000 meta- and pooled analyses of phase III randomized trials of survival from breast, prostate and lung cancer. Cancer Epidemiol 2017;51:113–7. doi:10.1016/j.canep.2017.11.002.

[5] Ismail RK, van Breeschoten J, Wouters MWJM, van Dartel M, van der Flier S, Reyners AKL, et al. Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer. Breast 2021;60:263–71. doi:10.1016/j.breast.2021.11.013.

[6] de Meza MM, Ismail RK, Rauwerdink D, van Not OJ, van Breeschoten J, Blokx WAM, et al. Adjuvant treatment for melanoma in clinical practice – Trial versus reality. Eur J Cancer 2021;158:234–45. doi:10.1016/j.ejca.2021.08.044.

[7] Ismail RK, Schramel FMNH, van Dartel M, Hilarius DL, de Boer A, Wouters MWJM, et al. The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients. Lung Cancer 2020;149:68–77. doi:10.1016/j.lungcan.2020.08.011.

[8] Ismail RK, Sikkes NO, Wouters MWJM, Hilarius DL, Pasmooij AMG, Van Den Eertwegh AJM, et al. Postapproval trials versus patient registries: Comparability of advanced melanoma patients with brain metastases. Melanoma Res 2021:58–66. doi:10.1097/CMR.0000000000000707.

[9] European Medicines Agency (EMA). Patient Registry Initiative- Strategy and Mandate of the Cross-Committee Task Force 2017;EMA/180341:1–8.

[10] Arlett P, Kjær J, Broich K, Cooke E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Clin Pharmacol Ther 2022;111:21-3. doi:10.1002/cpt.2479.

[11] European Medicines Agency (EMA). Data Analysis and Real World Interrogation Network (DARWIN EU) n.d.

[12] European Medicines Agency (EMA). Guideline on registry-based studies 2021;31.

12

CHAPTER 12

English Summary

English Summary

The treatment landscape for patients with certain types of cancer (advanced melanoma, lung cancer, and advanced breast cancer) has dramatically changed in recent years with the important breakthrough in medical treatments[1,2]. Randomized controlled trials (RCTs) are considered the golden standard to determine the efficacy of new treatments[3,4]. The different aspects of a RCT and the processes used (randomization, blinding, and long follow-up) minimize the risk of confounding and information- and selection bias that could influence the results. This improves the internal validity of clinical trials, enabling the estimation of new treatments' valid treatment effects. The strict in- and exclusion criteria used in a RCT cause a significant difference between patients enrolled in RCTs and the heterogeneous patient population treated in routine clinical practice, which lowers the external validity of RCTs[5,6]. To treat patients in daily clinical practice effectively and to be able to give patients realistic treatment expectations, it is necessary to estimate the real-world effectiveness of therapies based on patients' characteristics.

An issue in the field of cancer is the rising health care costs[7]. Novel treatments are often expensive[8]. Reimbursement of systemic therapies is usually based on the trial data collected for market approval. Since a broader population in clinical practice will be treated with these therapies, information on the real-world effectiveness of treatments is necessary for daily clinical practice, health technology assessment bodies (HTA's), and insurers.

In recent years, real-world data (RWD) has gained the interest of different stakeholders in cancer care. The RWD used in this thesis are data collected in a non-experimental setting. The rapid changes in treatment options for patients with cancer and the rising healthcare costs cause a need for RWD. The studies in this thesis aimed to investigate how the real-world population of patients with cancer differs from the trial population and how real-world data can be used in daily clinical practice to improve cancer care.

Part I: The use of quality registries to generate real-world data

In part I, we focused on quality registries and new methods to collect RWD from existing data sources without causing an extra registration burden. In **chapter 2**, we describe the initiation of the DICA Medicines program and present the first RWD results. This program uses multiple existing real-world data sources to provide valuable insights into cancer care without causing an extra registration burden.

Chapter 3 describes the initiation and first results of the Dutch Lung Cancer Audit for Lung Oncology (DLCA-L). The DLCA-L started in 2016, collecting RWD on all lung cancer patients diagnoses and systemic treatment in the Netherlands. Quality indicators were developed, which led to improvement in in-hospital cancer care. An example of a quality indicator is

brain imaging at diagnosis of stage III NSCLC patients, which increased from 80% in 2017 to 90% in 2019, and thus hospital variation was reduced. The DLCA-L has also been very valuable in monitoring immunotherapy use in the Netherlands[9].

Part II: Methods to compare real-world and clinical trial outcomes

In part II, we discuss appropriate methods to investigate the differences between real-world and clinical trial patients. **Chapter 4** described whether data from a quality registry could provide comparable data as post-approval clinical trials. For advanced melanoma patients, no direct comparisons between real-world and trial patients existed. We, therefore, conducted a study on advanced melanoma patients with brain metastases that were treated with BRAF-MEK inhibitors. We used data from the Dutch Melanoma Treatment Registry (DMTR) for the real-world population and data from four post-approval clinical trials derived from the Medicines Evaluation Board. Two methods were used to compare the two groups: a Cox hazard regression model and propensity score matching. Both methods showed no difference between the groups when matching on or adjusting for patient- and tumor characteristics. This study showed that registries could be a complementary data source to post-approval clinical trials to establish information on clinical outcomes in specific subpopulations[10]. In **chapter 5** we aimed to explore the additional benefit of a comparison from pivotal trial data with patient-level data (PLD), focusing on nivolumab treatment in stage IV NSCLC patients. Previous studies used reported outcomes from pivotal trials, but any observed differences could only be limitedly explored further for causation because of the unavailability of patient-level data from trial participants[11]. This study showed that analyzing PLD from both real-world and trial patients together can lead to better insight in potential factors responsible for a gap in outcomes between these two settings.

Part III: Differences in outcomes between real-world and trial patients with melanoma

It is important to quantify and understand the differences in real-world population outcomes and the outcomes presented in phase III clinical trials to improve clinical decisions based on RWD. **Chapter 6** focuses on ineligible advanced melanoma patients and their real-world outcomes. Ineligible patients were defined as patients who met one or multiple exclusion criteria of the phase III clinical trials. Since ineligible patients are excluded from phase III trials, this real-world information is significant for clinical practice. A total of 40% of the systemically treated advanced melanoma patients would have been considered ineligible for phase III clinical trials. Ineligible patients had a poorer median overall survival (mOS) compared to eligible patients (8.8 versus 23 months), but the 3-year OS probability was still 22%. This study concluded that the prognosis of ineligible patients with advanced melanoma in real-world was very heterogeneous and highly dependent

on lactate dehydrogenase (LDH) value, Eastern Cooperative Oncology Group Performance Score (ECOG PS), and symptomatic brain metastases[12].

Chapter 7 reports the real-world outcomes of adjuvant-treated resected stage III/IV melanoma patients. This study shows treatment patterns, relapse, and toxicity rates beyond the clinical trial setting. The recurrence-free survival (RFS) at 12 months was 70.6% (95% CI, 66.9-74.6), similar to the trial RFS rates. However, adjuvant anti-PD-1 treatment in daily practice showed slightly higher toxicity rates (18% versus 14%) compared to trials. Sixty-one percent of patients prematurely discontinued anti-PD-1 therapy[13].

In **chapter 8,** we investigated the real-world survival of advanced melanoma patients treated with BRAF-MEK inhibitors and identified characteristics of long-term survivors with advanced melanoma. Recently, 5-year survival outcomes of advanced melanoma patients treated with BRAF-MEK therapies in RCTs were published[14–16]. These results are favourable, but the real-world results remained unknown. The median progression-free survival (mPFS) and mOS of real-world patients were respectively 8.0 (95% CI, 6.8-9.4) and 11.7 (95%CI, 10.3-13.5) months. Two-year survival was reached by 28% of the patients, 22% reached 3-year survival, and 19% reached 4-year survival. Long-term survival of real-world patients treated with first-line BRAF-MEK inhibitors is significantly lower than that of trial patients, which is probably explained by poorer baseline characteristics of patients treated in daily practice.

Part IV: The value of real-world data in clinical practice

In part IV, two studies are described in which RWD were used to create valuable evidence that can be used in clinical practice. **Chapter 9** focuses on a different patient population, patients with advanced breast cancer treated with palbociclib. This study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with advanced breast cancer. Dose reductions occurred in 33% of all patients (n=598), which is similar to the PALOMA-3 trial[17]. Patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. Older patients treated with palbociclib had more frequent dose reductions, but this did not appear to affect OS (20.7 vs. 26.7 months, p=0.051)[18].

Another value of quality registries is the availability of RWD in extraordinary settings. To investigate the effects of the SARS-COV-2 pandemic on regular lung cancer care in the Netherlands, we studied in **chapter 10** every patient with lung cancer registered in the DLCA-L. We observed a major decline in the number of non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) patients diagnosed during the first wave of the COVID-19 pandemic compared to the same period in 2018 and 2019. Furthermore, NSCLC patients diagnosed during the first wave of the pandemic presented with significantly worse ECOG

PS ≥2 (26% vs. 20%, p-value < 0.001), and more patients presented with metastatic disease compared to the control period (49% vs. 43%, p-value <0.001)[19]. We fear that the impact of the COVID pandemic on lung cancer care will remain visible in upcoming years and that delayed lung cancer diagnosis may lead to a different victim group of COVID-19.

In **chapter 11** a general discussion on the studies in this thesis is presented. The main findings, relevant literature, the relevance of our findings, limitations of the studies and future perspectives are discussed.

References

[1] Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. Front Pharmacol 2018;9. doi:10.3389/fphar.2018.01300.

[2] Pasquali S, Hadjinicolaou A V., Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2018;2018. doi:10.1002/14651858.CD011123.pub2.

[3] Jones DS, Podolsky SH. The history and fate of the gold standard. Lancet 2015;385:1502–3. doi:10.1016/S0140-6736(15)60742-5.

[4] Akobeng AK. Understanding randomised controlled trials. Arch Dis Child 2005;90:840–4. doi:10.1136/adc.2004.058222.

[5] Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet 2005;365:82–95.

[6] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16:1–14. doi:10.1186/s13063-015-1023-4.

[7] Zorgvisie. Healthcare costs rise to 174 billion in 2040 n.d. https://www.zorgvisie.nl/rivm-zorgkosten-stijgen-naar-174-miljard-in-2040/ (accessed March 1, 2019).

[8] Leeneman B, Uyl-De Groot CA, Aarts MJB, Van Akkooi ACJ, Van Den Berkmortel FWPJ, Van Den Eertwegh AJM, et al. Healthcare costs of metastatic cutaneous melanoma in the era of immunotherapeutic and targeted drugs. Cancers (Basel) 2020;12:1–11. doi:10.3390/cancers12041003.

[9] Ismail RK, Schramel FMNH, van Dartel M, Hilarius DL, de Boer A, Wouters MWJM, et al. The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients. Lung Cancer 2020;149:68–77. doi:10.1016/j.lungcan.2020.08.011.

[10] Ismail RK, Sikkes NO, Wouters MWJM, Hilarius DL, Pasmooij AMG, Van Den Eertwegh AJM, et al. Postapproval trials versus patient registries: Comparability of advanced melanoma patients with brain metastases. Melanoma Res 2021:58–66. doi:10.1097/CMR.0000000000000707.

[11] Welle CMC Van Der, Verschueren M V, Tonn M. Real - world outcomes versus clinical trial results of immunotherapy in stage IV non - small cell lung cancer (NSCLC) in the Netherlands 2021:1–9. doi:10.1038/s41598-021-85696-3.

[12] van Zeijl MCT, Ismail RK, de Wreede LC, van den Eertwegh AJM, de Boer A, van Dartel M, et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. Int J Cancer 2020:1–10. doi:10.1002/ijc.33162.

[13] de Meza MM, Ismail RK, Rauwerdink D, van Not OJ, van Breeschoten J, Blokx WAM, et al. Adjuvant treatment for melanoma in clinical practice – Trial versus reality. Eur J Cancer 2021;158:234–45. doi:10.1016/j.ejca.2021.08.044.

[14] Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med 2019;381:626–36. doi:10.1056/nejmoa1904059.

[15] Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248–60. doi:10.1016/S1470-2045(16)30122-X.

[16] Ribas A, Daud A, Pavlick AC, Gonzalez R, Lewis KD, Hamid O, et al. Extended 5-Year Follow-up Results of a Phase Ib Study (BRIM7) of Vemurafenib and Cobimetinib in BRAF -Mutant Melanoma 2019:1–9. doi:10.1158/1078-0432.CCR-18-4180.

[17] Cristofanilli M, Rugo HS, Im S-A, Slamon DJ, Harbeck N, Bondarenko I, et al. Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Updated analyses from PALOMA-3. J Clin Oncol 2021;39:1000. doi:10.1200/JCO.2021.39.15_suppl.1000.

[18] Ismail RK, van Breeschoten J, Wouters MWJM, van Dartel M, van der Flier S, Reyners AKL, et al. Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer. Breast 2021;60:263–71. doi:10.1016/j.breast.2021.11.013.

[19] van Breeschoten J, Ismail R, Smit H, Schuurbiers O, Schramel F. An invisible group of COVID-19 victims; impact on Dutch lung cancer care. Lung Cancer 2021;159:177–8. doi:10.1016/j.lungcan.2021.06.023.

APPENDICES

DUTCH SUMMARY/ NEDERLANDSE SAMENVATTING

Dutch Summary/ Nederlandse samenvatting

Het behandellandschap van patiënten met bepaalde soorten kanker (gemetastaseerd melanoom, longkanker en borstkanker) is in de afgelopen jaren zeer veranderd door de komst van nieuwe medicijnen. De gerandomiseerde, gecontroleerde klinische studies (RCT's) zijn de gouden standaard voor het bepalen van de effectiviteit en bijwerkingen van deze nieuwe behandelingen. De verschillende aspecten van een RCT en de processen die gebruikt worden (randomisatie, blinderen, en een lange follow-up) minimaliseren het risico voor confounding en informatie- en selectiebias die invloed kunnen hebben op de resultaten. Dit bevordert de interne validiteit van klinische studies, waardoor de behandeleffecten en -risico's van nieuwe behandelingen bepaald kunnen worden. In RCT's worden strikte in- en exclusiecriteria gebruikt die bepalen welke patiënten er kunnen deelnemen aan de studies. Deze criteria zorgen voor een verschil tussen de patiënten die in de studies deelnemen en de heterogene patiëntenpopulatie die buiten studies in de dagelijkse klinische praktijk wordt behandeld. Dit zorgt voor een verminderde externe validiteit van RCT's. Om patiënten in de dagelijkse praktijk effectief te behandelen met medicijnen en om deze patiënten een realistisch beeld te geven van wat er verwacht kan worden van de behandelingen, is het belangrijk om de echte-wereld effectiviteit en risico's van behandelingen te bepalen.

Een nadelig effect van deze innovatieve geneesmiddelen voor de behandeling van kanker zijn de toenemende gezondheidskosten. Nieuwe, innovatieve behandelingen zijn vaak kostbaar. De vergoeding van deze systemische behandelingen is mede gebaseerd op de data uit de klinische studies (kosten gerelateerd aan de effectiviteit), die gebruikt worden om markttoelating te krijgen. Aangezien een grotere populatie in de klinische praktijk met deze behandelingen zal worden behandeld, is het belangrijk om informatie te hebben over de echte-wereld effectiviteit van behandelingen. Deze informatie is van belang voor de klinische praktijk, gezondheidstechnologie beoordelaars en verzekeraars. In de afgelopen jaren heeft echte-wereld data (RWD) steeds meer de interesse gewekt bij verschillende belanghebbenden in de behandeling van kanker. De RWD die gebruikt zijn in dit proefschrift zijn verzameld in een niet-experimentele setting, namelijk routinematig verzamelde gegevens van patiënten die in de dagelijkse praktijk worden behandeld.

De snelle veranderingen in de behandelopties voor patiënten met kanker en de toenemende zorgkosten zorgen voor een behoefte aan RWD. De studies in dit proefschrift onderzoeken hoe de echte-wereld populatie van patiënten met kanker verschilt van de studiepopulatie en hoe RWD in de dagelijkse klinische praktijk gebruikt kunnen worden om de kankerzorg te verbeteren. **Hoofdstuk 1**, de algemene inleiding, beschrijft de achtergrond en de doelen van dit proefschrift.

Deel I: het gebruik van kwaliteitsregistraties om echte-wereld data te genereren

In het eerste deel van dit proefschrift wordt er gefocust op de kwaliteitsregistraties en nieuwe methodes om RWD uit bestaande databronnen te verzamelen, zonder dat daar een extra registratielast bij komt kijken. In **hoofdstuk 2** wordt de start van het DICA Geneesmiddelen programma en de eerste resultaten hieruit beschreven. Dit programma gebruikt verschillende bestaande echte-wereld databronnen die waardevolle inzichten kunnen geven in de behandeling van kanker, zonder dat er extra registratielast ontstaat.

Hoofdstuk 3 beschrijft de start en de eerste resultaten van de *Dutch Lung Cancer Audit for Lung Oncology* (DLCA-L), de longkanker kwaliteitsregistratie. De DLCA-L is in 2016 gestart met het verzamelen van echte-wereld data van alle patiënten met longkanker in Nederland, met een focus op de diagnose en behandeling van deze patiënten. Er zijn kwaliteitsindicatoren ontwikkeld, die leiden tot een verbetering in de kankerzorg in het ziekenhuis. Een voorbeeld hiervan is de kwaliteitsindicator die gaat over beeldvorming van de hersenen bij diagnose van patiënten met stadium III niet-kleincellig longcarcinoom (NSCLC). Dit percentage was 80% in 2017 en is toegenomen tot 90% in 2019. Daarbij is tevens de praktijkvariatie tussen Nederlandse ziekenhuizen gereduceerd. De DLCA-L is ook waardevol gebleken in het monitoren van de immunotherapiebehandeling in Nederland.

Deel II: Methodes om de echte-wereld en klinische studies resultaten te vergelijken

In deel II worden verschillende methodes bediscussieerd die de verschillen tussen de patiënten in de echte-wereld en in de klinische studies onderzoeken. **Hoofdstuk 4** beschrijft een studie waarin is onderzocht of data van een kwaliteitsregistratie dezelfde resultaten geeft als data uit klinische studies die worden gedaan na toelating op de markt (post-autorisatie klinische studies). Voor patiënten met gemetastaseerd melanoom, was er geen directe vergelijking tussen echte-wereld en trial patiënten. Derhalve is er een onderzoek verricht waarbij er gekeken is naar patiënten met gemetastaseerd melanoom die ook hersenmetastases hadden, en die behandeld werden met BRAF-MEK remmers. We hebben data uit de *Dutch Melanoma Treatment Registry (DMTR)* gebruikt voor de echte-wereld populatie. Vanuit de database van het College ter Beoordeling van Geneesmiddelen (CBG) zijn de data uit vier post-autorisatie klinische studies verkregen, over een vergelijkbare groep patiënten. Twee methodes zijn gebruikt om de twee groepen en hun uitkomsten te vergelijken: een Cox hazard regressie model en *propensity score matching*. Beide methodes toonden geen verschil aan tussen de twee groepen, wanneer patiënten uit de groepen werden gematcht of als er gecorrigeerd werd voor de patiënt- en tumorkarakteristieken. Deze studie toonde aan dat registraties een complementaire databron zijn aan post-autorisatie klinische studies om data over klinische uitkomsten van specifieke subpopulaties te verkrijgen. In **hoofdstuk 5** hebben we onderzocht wat de

toegevoegde waarde van individuele patiëntdata uit klinische studies is in het vergelijken van trial- en echte-wereldpatiënten. Hierbij werd er gefocust op de nivolumab behandeling van patiënten met stadium IV NSCLC. In eerder onderzoek werd er gebruik gemaakt van de gepubliceerde gegevens van de klinische studies, maar verschillen die geobserveerd werden konden beperkt worden onderzocht en verklaard, omdat de individuele patiëntdata van de trialpatiënten niet beschikbaar waren. Deze studie toonde aan dat het analyseren van individuele patiëntdata van de echte-wereld en trialpatiënten samen betere inzichten geeft in de potentiële factoren die verantwoordelijk zijn voor de verschillen tussen deze twee settings.

Deel III: Verschillen in uitkomsten tussen echte-wereld- en trialpatiënten met melanoom.

Het is belangrijk om de verschillen in uitkomsten tussen de echte-wereld populatie en de populatie die behandeld is in de fase III klinische studies te kwantificeren en te begrijpen, om uiteindelijk klinische keuzes op basis van echte-wereld data te verbeteren. **Hoofdstuk 6** richt zich op de klinische uitkomsten van gemetastaseerde melanoompatiënten die niet in aanmerking zouden komen voor de fase III klinische studies (*ineligible* patiënten). *Ineligible* patiënten werden gedefinieerd als patiënten die karakteristieken hadden die overeenkwamen met één of meerdere exclusiecriteria van de fase III klinische studies voor gemetastaseerd melanoom. Aangezien *ineligible* patiënten geëxcludeerd worden uit de fase III klinische studies, is informatie over uitkomsten van deze patiënten relevant voor de klinische praktijk. Veertig procent van de systemisch behandelde patiënten met gemetastaseerd melanoom zou *ineligible* zijn voor de fase III klinische studies. Deze *ineligible* patiënten hadden een slechtere mediane overleving (mOS) vergeleken met patiënten die wel in aanmerking zouden komen voor de studies (8,8 versus 23 maanden), maar de 3-jaars overleving was alsnog 22% in *ineligible* patiënten. Deze studie concludeerde dat de prognose van de *ineligible* patiënten met gemetastaseerd melanoom in de echte-wereld zeer heterogeen is en sterk afhangt van een aantal factoren. Dat zijn de lactaatdehydrogenase (LDH) waarde, de Eastern Cooperative Oncology Group Performance Score (ECOG PS), en de aanwezigheid van symptomatische hersenmetastasen.

Hoofdstuk 7 rapporteert de echte-wereld uitkomsten van patiënten met stadium III/IV melanoom die adjuvant behandeld zijn. Deze studie toont de behandelpatronen, de terugval, en toxiciteit aan die we buiten de klinische trial setting zien. De ziektevrije overleving (RFS) op 12 maanden was 70.6% (95% CI 66.9-74.6). Dit is vergelijkbaar met de RFS percentages in de klinische studie. In de dagelijkse praktijk wordt er wel enigszins meer toxiciteit gezien (18% versus 14%) vergeleken met de trials. Een ander belangrijk verschil is dat de anti-PD-1 adjuvante behandeling in 61% van de patiënten vroegtijdig werd gestopt in de klinische praktijk.

In **hoofdstuk 8** is de echte-wereld overleving van patiënten met gemetastaseerd melanoom die behandeld zijn met eerstelijns BRAF-MEK remmers onderzocht. Daarnaast werden de karakteristieken van patiënten beschreven die lang overleefden. Recent zijn de 5-jaars overlevingscijfers van deze groep patiënten, die behandeld werden in de fase III klinische studies, gepubliceerd. Dit zijn goede resultaten, maar de overleving in de dagelijkse praktijk is niet onderzocht. De mediane progressie-vrije overleving en de mediane overleving van de echte-wereld patiënten waren respectievelijk 8,0 (95% CI, 6,8-9,4) en 11,7 (95%CI, 10,3-13,5) maanden. De 2-jaars overleving was 28%, 22% overleefde 3 jaar, en 19% bereikte de 4-jaars overleving. Lange-termijn overleving van echte-wereld patiënten die behandeld werden met eerstelijns BRAF-MEK remmers is lager dan die van de trialpatiënten. Dit wordt verklaard door de slechtere baseline karakteristieken van patiënten die in de dagelijkse praktijk worden behandeld.

Deel IV: De waarde van echte-wereld data in de klinische praktijk

In deel IV van dit proefschrift worden verschillende studies beschreven waarin RWD gebruikt zijn om waardevolle informatie te creëren die gebruikt kunnen worden in de klinische praktijk. **Hoofdstuk 9** focust op een andere patiëntenpopulatie, namelijk patiënten met gemetastaseerde borstkanker die behandeld werden met palbociclib. Deze studie onderzocht het gebruik van palbociclib in de klinische praktijk, en ook de dosisreducties en de effectiviteit van deze behandeling in (oudere) patiënten met gemetastaseerd borstkanker. Dosisreducties vonden in 33% van alle patiënten (n=598) die behandeld waren met palbociclib plaats. Dit komt overeen met de PALOMA-3 trial waarin palbociclib werd onderzocht in een fase III klinische studie. Patiënten met een dosisreductie leken geen slechtere uitkomsten te hebben dan patiënten die geen dosisreductie nodig hadden. Oudere patiënten (>70 jaar) die behandeld werden met palbociclib kregen vaker een dosisreductie, maar dit leek geen effect te hebben op de overleving (20,7 vs. 26,7 maanden, p=0,051).

Een ander waardevol aspect aan kwaliteitsregistraties is de beschikbaarheid van RWD in bijzondere settings. In **hoofdstuk 10** wordt het effect van de SARS-COV-2 pandemie op de reguliere longkankerzorg in Nederland beschreven. Alle patiënten met longkanker zijn geregistreerd in de DLCA-L. Er was een significante daling in het aantal NSCLC en kleincellig longcarcinoom (SCLC) diagnoses tijdens de eerste golf van de COVID-19 pandemie, vergeleken met dezelfde periode in 2018 en 2019. Verder hadden patiënten met NSCLC die gediagnosticeerd werden in de eerste golf van de pandemie slechtere patiëntkarakteristieken, zoals een ECOG PS ≥2 (26% vs. 20%, p-waarde < 0.001), en meer patiënten presenteerden zich met gemetastaseerd ziekte in vergelijking met de controle periode (49% vs. 43%, p-waarde <0.001). De impact van de COVID pandemie zal in de komende jaren zichtbaar blijven en we verwachten dat de vertraagde longkanker diagnoses zullen leiden tot een andere slachtoffergroep van COVID-19.

In **hoofdstuk 11** wordt een algemene discussie over de studies in dit proefschrift beschreven. De belangrijkste bevindingen, relevante literatuur, de relevantie van onze bevindingen, beperkingen van de studies en toekomstige perspectieven worden bediscussieerd.

LIST OF PUBLICATIONS

Author's list of publications

Publications in this thesis

1. **Linking healthcare data: valuable insights in medication use and outcomes.**
   R.K. Ismail*, J. van Breeschoten*, S. van der Flier, C.T. van Loosen, A.M.G Pasmooij, M. van Dartel, A.J.M. van den Eertwegh, A. de Boer, M.W.J.M. Wouters, D.L. Hilarius. Submitted.
   **Contributed equally as first author.*

2. **The Dutch Lung Cancer Audit: Nationwide quality of care evaluation of lung cancer patients.**
   R.K. Ismail, F.M.N.H. Schramel, M. van Dartel, D.L. Hilarius, A. de Boer, M.W.J. M. Wouters, H.J.M. Smit, *on behalf of the Dutch Lung Cancer Audit Scientific Committee.* Lung Cancer. 2020 Nov;149:68-77.

3. **Postapproval trials versus patient registries: comparability of advanced melanoma patients with brain metastases.**
   R.K. Ismail, N.O. Sikkes, M.W.J.M. Wouters, D.L. Hilarius, A.M.G. Pasmooij, A.J.M. van den Eertwegh, M.J.B. Aarts, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, K.P.M. Suijkerbuijk, B. ten Tije, A.A.M. van der Veldt, A. Vreugdenhil, M. van Dartel, A. de Boer. Melanoma Res. 2021 Feb 1;31(1):58-66.

4. **Patient-level data to enhance causation study in efficacy-effectiveness gap research.**
   R.K. Ismail, F.M.N.H. Schramel, M. van Dartel, A.M.G. Pasmooij, C.M. Cramer-van der Welle, D.L. Hilarius, A. de Boer, M.W.J.M. Wouters, E.M.W. van de Garde. Submitted.

5. **Real-world outcomes of advanced melanoma patients not represented in phase III trials.**
   M.C.T. van Zeijl*, R.K. Ismail*, L.C. de Wreede, A.J.M. van den Eertwegh, A. de Boer, M. van Dartel, D.L. Hilarius, M.J.B. Aarts, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de Groot, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, K.P.M. Suijkerbuijk, A.J. ten Tije, A.A.M. van der Veldt, G. Vreugdenhil, J.B.A.G. Haanen, M.W.J.M Wouters. Int J Cancer. 2020 Dec 15;147(12):3461-3470. **Contributed equally as first author.*

6. **Adjuvant treatment for melanoma in clinical practice – trial versus reality.**
   M.M. de Meza*, R.K. Ismail*, D.Rauwerdink, O.J. van Not, J. van Breeschoten, W.A.M. Blokx, A. de Boer, M.van Dartel, D.L. Hilarius, E. Ellebaek, H.J. Bonenkamp, C.U. Blank, M.J.B. Aarts, A.C.J. van Akkooi, F.W.P.J. van den Berkmortel, M.J. Boers-Sonderen, J.W.B. de

Groot, J.B.A.G Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, A.A.M. van der Veldt, A. Vreugdenhil, H.M. Westgeest, A.J.M. van den Eertwegh, K.P.M. Suijkerbuijk, M.W.J.M. Wouters. Eur J Cancer. 2021 Nov;158:234-245. **Contributed equally as first author.*

7. **Advanced melanoma patients reaching long-term survival after treatment with targeted therapy: a population-based study.**
   R.K. Ismail, K.P.M. Suijkerbuijk, A. de Boer, M. van Dartel, D.L. Hilarius, A.M.G. Pasmooij, M.C.T. van Zeijl, M.J.B. Aarts, F.W.P.J.van den Berkmortel, C.U. Blank, M.J. Boers-Sonderen, J.W.B. de Groot, J.B.A.G. Haanen, G.A.P. Hospers, H.W. Kapiteijn, D. Piersma, R.S. van Rijn, A.A.M. van der Veldt, G. Vreugdenhil G., H. Westgeest, A.J.M. van den Eertwegh, M.W.J.M. Wouters. Submitted.

8. **Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer.**
   R.K. Ismail, J. van Breeschoten, M.W.J.M. Wouters, M. van Dartel, S. van der Flier, A.K.L. Reyners, P. de Graeff, A.M.G. Pasmooij, A. de Boer, K.E. Broekman, D.L. Hilarius. Breast. 2021 Dec 01;60:263-271.

9. **An invisible group of COVID-19 victims; impact on Dutch lung cancer care.**
   J. van Breeschoten*, R.K. Ismail*, H.J.M. Smit, O.C.J. Schuurbiers, F.M.N.H Schramel *on behalf of the Dutch Lung Cancer Audit Scientific Committee*. Lung Cancer. 2021 Sep;159:177-178. **Contributed equally as first author.*

Other publications

1. **The unfavorable effects of COVID-19 on Dutch advanced melanoma care.**
   O.J. van Not, J. van Breeschoten, A.J.M. van den Eertwegh, D.L Hilarius, M.M. De Meza, J.B. Haanen, C.U. Blank, M.J.B. Aarts, F.W.P.J. van den Berkmortel, J.W.B. de Groot, G.A.P. Hospers, R.K. Ismail, E. Kapiteijn, D. Piersma, R.S. van Rijn, M.A.M. Stevense-den Boer, A.A.M. van der Veldt, G. Vreugdenhil, M.J. Boers-Sonderen, W.A.M. Blokx, K.P.M. Suijkerbuijk, M.W.J.M. Wouters. Int J Cancer. 2022 Mar 1; 150(5):816-824.

2. **Response to immune checkpoint inhibitors in acral melanoma: A nationwide cohort study.**
   O.J. van Not, M.M. De Meza, A.J.M. van den Eertwegh, J.B. Haanen, C.U. Blank, M.J.B. Aarts, F.W.P.J. van den Berkmortel, J. van Breeschoten, J.W.B. de Groot, G.A.P. Hospers, R.K. Ismail, E. Kapiteijn, D. Piersma, R.S. van Rijn, M.A.M. Stevense-den Boer, A.A.M. van der

Veldt, G. Vreugdenhil, H. Bonenkamp, M.J. Boers-Sonderen, W.A.M. Blokx, M.W.J.M. Wouters, K.P.M. Suijkerbuijk. Eur J Cancer. 2022 May; 167:70-80.

3. **End-of-life use of systemic therapy in advanced melanoma patients: results from the Dutch Melanoma Treatment Registry.**
   J. van Breeschoten, R.K. Ismail, M.W.J.M. Wouters, D.L Hilarius, L.C. de Wreede, J.B. Haanen, , C.U. Blank, M.J.B. Aarts, F.W.P.J. van den Berkmortel, J.W.B. de Groot, G.A.P. Hospers, E. Kapiteijn, D. Piersma, R.S. van Rijn, M.A.M. Stevense-den Boer, A.A.M. van der Veldt, G. Vreugdenhil, M.J. Boers-Sonderen, K.P.M. Suijkerbuijk, A.J.M. van den Eertwegh. Submitted.

PHD PORTFOLIO

Ph.D. Portfolio

Name Ph.D. student: Rawa Kamaran Ismail
University of Utrecht department: Division of Pharmacoepidemiology and Clinical Pharmacology
Ph.D. period: September 2018-December 2021

COURSES		**ECTS**
2021	Balance: coping with stress and pressure	0.20
2021	Pharmacoepidemiology and Drug Safety	1.50
2020	Writing for academic publication	2.00
2020	Scientific Poster Presentations	0.50
2020	Giving Effective Presentations	0.60
2020	Survival analysis	1.50
2019	Translational Immuno-oncology: cancer & immune therapies from bench to bedside	1.50
2019	Working Consciously and Effectively	0.10
2019	R Advanced Course	0.85
2019	R Basic Course	1.10
2019	Supervising Research of MSc students at the GSLS	1.20
2019	Practical Biostatistics	1.40

CONFERENCES AND SEMINARS		**ECTS**
2021	Oral presentation European Cancer Organisation Round table Lung Cancer meeting: *"The Dutch Lung Cancer Audit: Nationwide quality of care evaluation using quality Indicators"*	0.50
2021	Win-O online symposium melanoma	0.30
2021	Oral presentation FIGON Dutch Medicines Days *"The impact and use of quality registries: can real-world data complement post-approval clinical trials?*	0.50 *"*
2021	ESMO Immuno-Oncology Congress 2021 (virtual)	0.30
2021	IMPACT congress (virtual)	0.30
2020	Drug Innovation introduction day (virtual)	0.50
2020	Poster presentation ESMO 2020 (virtual) "*Post-approval trials versus patient registries: comparability of advanced melanoma patient with brain metastases"*	0.50
2020	Poster presentation ESMO 2020 (virtual) *"Long-term survival of advanced melanoma patients treated with targeted therapy"*	0.50

2020	Poster presentation ASCO 2020 (virtual) *"Real-world outcomes of advanced melanoma patients not represented in phase III trials"*	0.50
2020	NVMO ePost-ASCO 2020 (virtual)	0.30
2020	Interview MedTalks *van eigen bodem* ASCO 2020 poster	-
2020	Interview *Hollandse bodem* Novartis ASCO 2020 poster	-
2020	Poster presentation MEB Science day 2020	0.50
2019	Nationale Longkanker Symposium	0.30
2019	Win-O symposium melanoma	0.30
2019	SONCOS Lustrumsymposium	0.30
2019	CBG *Collegedag*	0.30
2019	RSNN workshop: The future of clinical trials and evidence generation, and their use in regulatory decision making	0.30
2019	ESMO Congress	0.30
2019	DICA Congress: oral presentation DICA Medicines Program	0.50
2019	PECP PhD retreat 2019	0.30
2019	KNAW Symposium *Nieuwe geneesmiddelenontwikkeling*	0.30
2019	CBG *Wetenschapsdag*	0.30
2018	Win-O symposium melanoma	0.30
2018	FIGON Dutch Medicines Days	0.30
2018	NVZA *Ziekenhuisfarmaciedagen*: oral presentation Initiation of the DICA Medicines Program	0.50
2018	NKR Symposium: The future of cancer management, from big Data to smart data.	0.30
2018	SONCOS *Themasymposium: Innovatie in de kankerzorg*	0.30

TEACHING		**ECTS**
2019-2021	Education Journal club DICA	0.10
2019-2021	Education Promovendi- and students' meetings CBG	1.00
2019-2020	Supervision Master Thesis Nienke Sikkes, Pharmacy student	2.85
2020	Supervision Master Thesis Chaima Mouhdad, Pharmacy student	2.85
2021	Supervision Master Thesis Kasper Blom, Drug Innovation student	2.85
2021	Hospital pharmacists in training course day: presentation about the DICA Medicines Program	0.50

ACKNOWLEDGMENTS/ DANKWOORD

Dankwoord

Dit proefschrift heb ik met veel plezier geschreven en is het werk van drie jaar hard werken. Ik heb ontzettend veel geleerd en genoten van mijn tijd als onderzoeker. Ik wil iedereen bedanken die daar, op welke manier dan ook, aan heeft bijgedragen. Een aantal mensen wil ik in het bijzonder bedanken.

Allereerst kon ik mij geen beter promotieteam wensen. Door de verschillende expertises ontstonden er goede discussies in onze maandelijkse overleggen. Het tempo lag hierdoor hoog, maar door jullie grote betrokkenheid kijk ik positief terug op mijn promotietijd.

Prof. dr. de Boer, beste **Ton**, wat heb ik veel van u mogen leren. Uw kritische blik op het gebruik van real-world data zorgde ervoor dat ik altijd scherp was op mijn woordkeuzes. En hoewel u erg druk bent geweest met de COVID-19 vaccinaties, kon ik altijd op uw feedback rekenen. Het werd bijna een traditie dat u feedback gaf op alle stukken in de nacht voor het promotieteamoverleg op dinsdagochtend. Dank voor de prettige begeleiding de afgelopen jaren.

Prof. dr. Wouters, beste **Michel**, mede dankzij jou kunnen we binnen DICA mooi onderzoek doen. Jouw betrokkenheid bij met name de DMTR heeft ervoor gezorgd dat er in Nederland, maar ook internationaal aandacht is voor de registry. Ik ben er trots op dat ik één van de eerste promovendi ben die je hebt begeleid in de rol als hoogleraar aan het LUMC. Je hebt mij altijd weten te enthousiasmeren om nog meer te doen dan gepland stond. Daardoor werden de stukken altijd beter en heb ik uiteindelijk een proefschrift geschreven waar ik erg trots op ben, dank daarvoor.

Dr. Hilarius, beste **Doranne**, vanaf sollicitatie tot aan dit proefschrift heb ik onze samenwerking heel prettig ervaren. Zonder jou was er geen DICA Geneesmiddelen en de energie die je in het programma hebt gestopt is onbeschrijfelijk. In drie jaar tijd is het idee uitgewerkt tot een goed lopend programma waardoor geneesmiddelen in de praktijk doelmatiger kunnen worden ingezet. Jouw enthousiasme werkt aanstekelijk. Dank voor jouw betrokkenheid, jouw luisterend oor en natuurlijk de gezelligheid. Bij jou kon ik altijd mijzelf zijn.

Dr. van Dartel, beste **Maaike**, wat heb ik veel steun gehad van jou. Hoewel we elkaar niet meer fysiek konden zien de laatste twee jaren, vond ik onze online bijpraatsessies heel prettig. Je kan altijd goed relativeren en na elke meeting besefte ik mij dat ik goed op weg was. Ik heb bewondering voor jouw wetenschappelijke mindset en heb daar veel van kunnen leren. Dank voor jouw waardevolle bijdrage aan dit proefschrift.

Dr. ir. Pasmooij, beste **Marjon**, hoewel je op papier geen co-promotor was, heb ik dat niet zo ervaren. Kort na mijn start bij DICA hebben we samen de samenwerking tussen DICA en het CBG opgezet en sindsdien ben je altijd nauw betrokken geweest bij het promotietraject. Daardoor heb ik ook veel over het CBG kunnen leren. Dank dat ik altijd op jou kon rekenen.

Geachte leden van de promotiecommissie, **prof. dr. Koopman, prof. dr. van der Hoeven, prof. dr. Groenwold, prof. dr. Klungel, dr. Gardarsdottir, en prof. dr. Bouvy**, veel dank voor jullie bereidheid om mijn proefschrift te beoordelen en zitting te nemen in de promotiecommissie.

Voor de meeste stukken in dit proefschrift is de input vanuit de **wetenschappelijke commissies van de DMTR en DLCA-L** onmisbaar geweest, dank voor jullie altijd kritische feedback. **Fons en Karijn**, dank voor de fijne samenwerking, ik heb veel van jullie mogen leren. **Hans, Franz en Olga,** dank voor jullie inzet om de DLCA-L naar een hoger niveau te tillen. Ik voelde mij altijd welkom om vragen te stellen.

Alle andere co-auteurs die hebben bijgedragen aan dit proefschrift, dank daarvoor. In het bijzonder wil ik **Ewoudt** bedanken. Ons stuk samen heeft veel voeten in de aarde, maar de aanhouder wint.

Nienke, Chaima en Kaspar, ik had geen betere masterstudenten kunnen wensen. Ik heb jullie met heel veel plezier begeleid. Dank voor alle hulp die ik van jullie heb gekregen om mooi onderzoek op te zetten. Ik wens jullie het allerbeste in jullie toekomstige carrières.

Beste **DICA-collega's**, dank voor de fijne samenwerking. De **directie en het managementteam** wil ik bedanken voor de mogelijkheid om op een unieke plek mijn promotie te mogen doen en de kansen die jullie mij hebben geboden. Dank aan de **Informatie collega's** voor het helpen met scripting en de gezellige gesprekken. **Tante Q, Ingeborg en Elly**, jullie zorgden altijd voor een lach op mijn gezicht. Dank dat ik altijd bij jullie terecht kon voor een goed gesprek en om mijn suikerspiegel op peil te brengen. **Logex collega's**, wat hebben we veel bereikt in de afgelopen jaren. Dank voor deze fijne samenwerking en de gezellige uitjes. **CBG-collega's**, ik heb veel geleerd van jullie. **Paulien**, ik hoop dat we in de toekomst contact blijven houden en ik door jou nog meer wandelroutes in Zeist ontdek, dank voor de fijne gesprekken.

Lief cluster, jullie hebben het de afgelopen jaren leuker gemaakt. **Jesper**, vanaf dag één werkten we nauw samen en hebben we heel veel meegemaakt. Van uren in de trein naar alle uithoeken van Nederland tot aan R-frustraties, ik vond het een eer dat ik het allemaal met jou mocht meemaken. Dank voor al je hulp de afgelopen jaren en ik wens je het allerbeste toe. **Olivier**, jouw humor en stickers had ik voor geen goud willen missen. Dank

dat je altijd zo positief bent en ik bij jou terecht kon. Ik kan niet anders zeggen dan: live, love, laugh. **Melissa**, het is voor mij een eer dat ik bij jouw eerste artikel betrokken was en de blijdschap om je eerste publicatie mocht meemaken. Ik vind het ontzettend knap hoe jij alle ballen hooghoudt. Ik zal jullie gezelligheid ontzettend missen.

Michiel, godfather van de DMTR, wat heb ik veel van je geleerd. Door jou hadden we een flitsende start bij het managen van de registratie, dank! **Dominique**, bedankt voor de fijne wandelingen en goede gesprekken. Fijn dat we af en toe even lekker konden zeuren. **Nishita**, hopelijk zullen we de fijne gesprekken nog een lange tijd voortzetten als indirecte collega's. **Lisa**, ik zal nooit vergeten hoe jij mij steunde toen ik slecht nieuws kreeg. Jouw positieve energie maakt de wereld een stukje mooier! Lieve **mede-clusterhoofden**, wat hebben we toch veel discussies gehad binnen DICA, maar gelukkig vaak met succes. Alle andere **AO-ers**, dank voor jullie altijd kritische houding tijdens onderwijs en promovendi-uurtje en uiteraard de gezelligheid tijdens de AO-weekenden.

Thank you to my friends and family in and outside the Netherlands for always supporting me.

Lieve **Sawen** en **Shukriti**, ik kan mij geen betere paranimfen wensen dan jullie. De afgelopen jaren hebben we lief en leed gedeeld en stonden jullie altijd voor mij klaar. Ik ben dankbaar dat jullie mij ook hierin ondersteunen en naast me zullen staan.

Mijn lieve **schoonfamilie**, jullie weten als geen ander hoeveel er voor mij veranderd is de afgelopen jaren. Dank voor al jullie steun. Ik heb er een geweldige familie bij gekregen. **Alend**, ik kan mij geen betere schoonbroer wensen. Wat jij allemaal voor ons hebt gedaan om mijn stress-level te reduceren is onbeschrijfelijk. **Hawler, Holya en Maria**, lieve schoonzusjes, ik ben ontzettend trots op jullie!

Range en Ahmad, jullie kleine zusje zal altijd opkijken naar haar grote broers. Ook al zijn jullie niet inhoudelijk betrokken, ik heb mij altijd heel erg gesteund gevoeld door jullie. Ik zal altijd voor jullie klaarstaan en ik hoop dat we voor altijd zo hecht blijven. Lieve **Saz**, je bent het zusje dat ik altijd wilde, ik kan niet wachten om nog meer herinneringen met je te maken. Ik hou van jullie.

Lieve **mama en papa**, woorden kunnen niet beschrijven hoeveel ik van jullie houd. Door jullie onvoorwaardelijke liefde en steun sta ik nu hier. Jullie zijn altijd mijn voorbeeld geweest en door jullie weet ik dat hard werken loont. Mijn doel is altijd geweest om jullie trots te maken, omdat ik weet dat alle keuzes die jullie hebben gemaakt voor een betere toekomst voor ons waren. Dank voor alles dat jullie mij hebben geleerd en gegeven. Ik ben gelukkig wanneer jullie dat zijn.

Lieve **Blend**, mijn soulmate, steun en toeverlaat. Jij weet als geen ander hoeveel energie dit proefschrift heeft gekost. De afgelopen jaren was jij altijd de eerste bij wie ik terecht kon bij hoogte- maar ook dieptepunten. Door jouw positiviteit en nuchterheid kon je alles relativeren, mij weer aan het lachen maken en mij motiveren om door te gaan. Je brengt het beste in mij naar boven. Dank voor alle mooie momenten samen en ik kijk uit naar onze toekomst. Ik hou van je.

ABOUT THE AUTHOR

About the author

Rawa Kamaran Ismail was born on the 15th of March 1994 in Kirkuk, a city in the Kurdish region of Iraq. When she was nearly two years old, she and her parents and two brothers moved to the Netherlands. She graduated from high school in 2012 from KSG de Breul in Zeist. Afterward, she started studying Pharmacy at the University of Utrecht.

She gained plenty of experience at community pharmacy Orion in Amersfoort during her studies. Her enthusiasm for patient care led to winning the National Patient Counseling competition in 2017. She represented the Netherlands at the world competition in Mendoza, Argentina, in 2018, where she also won several competitions. She also fulfilled different student board roles related to health care innovation and her Kurdish roots. During her Pharmacy master's, she gained interest in the oncology field and felt the urge to improve cancer treatment.

After graduating from Pharmacy school in 2018, she started her Ph.D. at the University of Utrecht and the Dutch Institute for Clinical Auditing (DICA). She was supervised by her promotors, prof. dr. A. de Boer and prof. dr. M.W.J.M. Wouters, and her copromotores dr. D.L. Hilarius and dr. M. van Dartel. A collaboration with the Medicines Evaluation Board (MEB) was established, with the major help of dr. ir. A.M.G. Pasmooij. Her research focused on the differences between real-world and trial patients with cancer and their clinical outcomes.

At DICA, she was responsible for the DICA Medicines Program and the Dutch Lung Cancer Audit. In the first year of her role as a researcher-pharmacist, she co-managed the Dutch Melanoma Treatment Registry. Furthermore, she represented her fellow DICA Ph.D. colleagues within management team meetings for three years.

In January 2022, she started as a medical advisor oncology at Merck Sharp and Dohme in the Netherlands. Currently, she is responsible for prostate- and bladder cancer indications.