The authorisation of anticancer medicinal products

Clinical benefit, precision medicine and regulatory flexibility

Jorn Mulder

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Clinical benefit, precision medicine and regulatory flexibility

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(met een samenvatting in het Nederlands)

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Contents

Chapter 1

Introduction

General introduction

Cancer is one of the leading causes of premature death in more than 100 countries [1]. Despite countless efforts to improve outcomes in patients with cancer, it remains a devastating disease. For patients with unresectable, disseminated disease, palliative treatment options may be of limited value. For example, half of the patients with pancreatic cancer are diagnosed with metastatic disease and are not candidate for potential curative therapy (e.g., surgery) [2]. In Europe, the recommended first-line therapy for metastatic pancreatic cancer is a combination of fluorouracil, leucovorin and oxaliplatin (FOLFIRINOX) or gemcitabine ± nab-paclitaxel [3]. These therapies improved overall survival [4, 5], but the prognosis of pancreatic cancer remains poor. These are conventional, cytotoxic therapies, which do not discriminate between tumour cells and other "normal" cells [6]. There is, however, an increasing interest in a more precise approach in targeting tumour cells. To illustrate, pancreatic tumours may harbour actionable molecular alterations, and there is evidence indicating that patients with these tumours can benefit from "matched" targeted therapies [7].

Advances in technology and a better understanding of tumour biology led to the development of "precision" medicine. This term is used interchangeably with "personalised", "stratified" or "individualised" medicine [8]. The definition of precision medicine may vary across stakeholders [9], but the National Institutes of Health defines it as "an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle" [10]. The relevance of precision medicine in oncology is evident by its incorporation in clinical practice guidelines [11, 12]. For example, molecular testing plays an important role in non-small-cell lung cancer, and treatment decisions are based on the presence or absence of actionable molecular alterations (e.g., anaplastic lymphoma kinase, epidermal growth factor receptor, c-ros oncogene 1) [11]. Notably, precision medicine may show promising or even dramatic antitumour activity early during clinical development, warranting expedited authorisation. An example is larotrectinib – a tropomyosin receptor kinase inhibitor; the responses observed in a set of patients enrolled in three early phase clinical trials were referred to as "dramatic" [13]. In 2019, the European Commission (EC) conditionally authorised larotrectinib for the treatment of patients with solid tumours that harbour a Neurotrophic Tyrosine Receptor Kinase gene fusion [14]. This is the first medicinal product authorised by the EC for a "histology-independent" – also called "tissue-agnostic" – indication.

Obtaining a marketing authorisation is a key prerequisite for placing a medicinal product on the market. In the European Union (EU), a regulatory network exists that is based on a partnership between the EC, the European Medicines Agency (EMA) and the regulatory authorities from 30 European Economic Area countries, i.e., 27 Member States, Iceland, Liechtenstein and Norway [15]. Authorising bodies are the EC for centralised procedures and the national authorities for mutual recognition, decentralised and national procedures [16]. The legal basis for the authorisation of human medicinal products is laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 [16]. The required particulars and documents accompanying

an application for marketing authorisation are set out in Annex 1 of Directive 2001/83/EC [17]. These include chemical, pharmaceutical and biological information (module 3) and non-clinical/clinical reports (module 4 and module 5, respectively), which must demonstrate that the risks are outweighed by the therapeutic efficacy [17]. The benefit-risk balance is an important part of the scientific evaluation of an application for marketing authorisation [18]. A medicinal product is granted marketing authorisation only if the benefit-risk balance is positive.

As by the legal framework, i.e. Regulation (EC) No 726/2004, anticancer medicinal products with a new active substance must be authorised via the centralised procedure [19]. For this procedure, the Committee for Medicinal Products for Human Use – one of the committees of the EMA – is responsible for the scientific evaluation of applications for marketing authorisation [20]. They issue an opinion on marketing authorisation that forms the basis for the EC decision [20]. To facilitate the authorisation of anticancer medicinal products, the EMA has published a guidance document on the clinical evaluation of anticancer medicinal products [21]. An overview of European Public Assessment Reports (EPARs) generated from the EMA database (access date: 5 April 2022) allows us to identify all anticancer medicinal products currently authorised by the EC. **Figure 1** shows the number of anticancer medicinal products authorised, withdrawn or refused between 1995 and 2021.

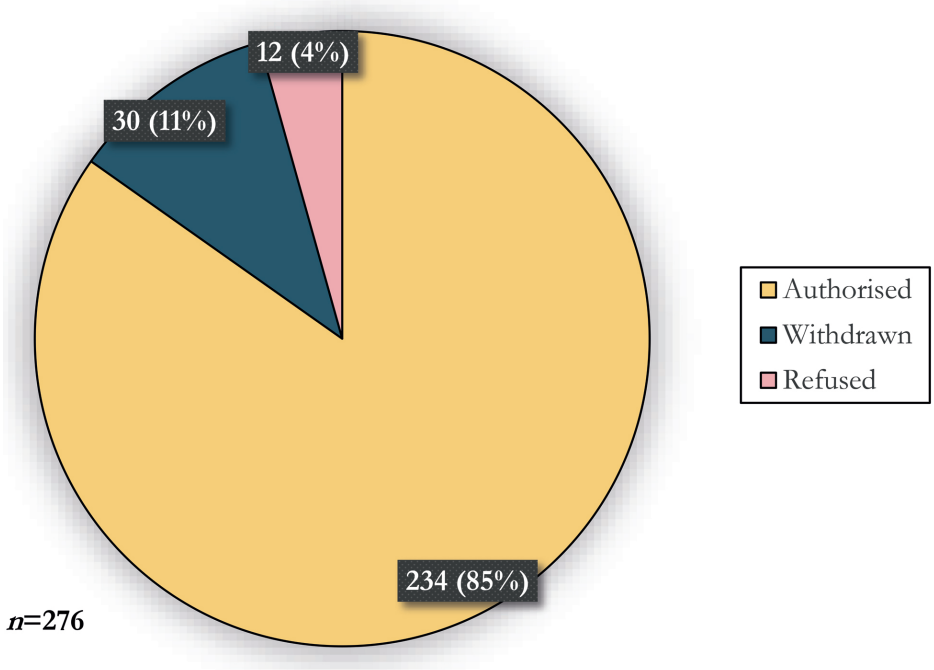

Figure 1. Anticancer medicinal products evaluated by the European Medicines Agency between 1995 and 2021.

Evidence generation may continue after a medicinal product is authorised. This can concern authorised use (e.g., dose optimisation, fulfilment of post-authorisation measures, real-world effectiveness and safety) or unauthorised use (e.g., repurposing). Evidence is generated by conducting additional clinical trials and/or real-world studies, and various stakeholders might be interested in exploring optimal or additional use of authorised medicinal products. For instance, there are several examples of clinical trials conducted by independent researchers to investigate new uses for authorised medicinal products. One of these examples is the Drug Rediscovery Protocol (DRUP). The DRUP is an adaptive clinical trial testing medicinal products outside their authorised indication(s) with the aim to identify antitumour activity in patients whose tumours harbour actionable molecular alterations [22]. Such initiatives provide unique opportunities to test medicinal products for indications that are otherwise difficult to study or for which there is a lower financial incentive.

Overall, the progress made in the development of anticancer medicinal products has resulted in promising new therapies. To address an unmet medical need, regulatory agencies have implemented programs to facilitate earlier access to beneficial medicinal products [23, 24]. While this approach is considered positive, it also requires more flexibility from regulators (and other stakeholders). A reflection on regulatory decision-making with regard to the authorisation of promising anticancer medicinal products is therefore needed.

Dissertation outline

In this dissertation, the difficulties and challenges related to the authorisation of anticancer medicinal products are discussed. Three parts are attributed to the different stages of the life cycle of a medicinal product, that is before (**part 1**), during (**part 2**) and after (**part 3**) marketing authorisation of anticancer medicinal products. The last chapter (**chapter 7**) provides a general discussion and perspectives**.**

Part 1. Before marketing authorisation: identifying promising medicinal products on the basis of preliminary data and the use of regulatory schemes
The EC provides incentives to stimulate the research and development and the placing on the market of orphan medicinal products as set out in Regulation (EC) No 141/2000 [25]. Pancreatic cancer classifies as a rare disease. Over the years, numerous applications for orphan medicinal product designation for this disease have been evaluated by the Committee for Orphan Medicinal Products. However, pancreatic cancer remains a dismal disease and only a few treatment options are available. In **chapter 2**, we will focus on the development of orphan medicinal products for pancreatic cancer with all its caveats.

One of the expedited programs of the Food and Drug Administration is the Breakthrough Therapy designation [24]. More recently, the EMA launched a scheme that has overlap with the Breakthrough Therapy designation program, which is called PRIority Medicine [26]. Prior experiences are useful in determining whether these initiatives are living up to their expectations.

In **chapter 3**, we will investigate whether Breakthrough Therapy designated anticancer medicinal products are indeed breakthroughs, based on a validated tool to measure clinical benefit.

Part 2. Marketing authorisations and variations: pivotal trials included in applications submitted to the Agency

If randomised-controlled trials are not ethical or feasible, single-arm trials may support the authorisation of new medicinal products. Even though this allows for earlier approval of potentially beneficial medicinal products, it can be challenging to determine the relevance of treatment effects in absence of a control arm. **Chapter 4** will deal with EC approvals based on single-arm trials.

Academic researchers may discover new applications of existing medicinal products. If results are promising, it may be desirable to extent the therapeutic indication of the concerned medicinal product. **Chapter 5** will describe the regulatory challenges associated with the extension of indication for authorised oncology products on the basis of results from investigator-initiated trials.

Part 3. After marketing authorisation: remaining issues to be addressed in the post-authorisation setting

To date, there is limited regulatory experience with tissue-agnostic approvals. Moreover, regulatory decision-making might be different between independent agencies. For instance, regulatory agencies can have different strategies to tackle the (remaining) issues identified during the scientific evaluation of applications for marketing authorisation. **Chapter 6** will show the approach of three independent regulatory agencies to resolve outstanding issues related to tissue-agnostic approvals.

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Part 1

Before marketing authorisation: identifying promising medicinal products on the basis of preliminary data and use of regulatory schemes

Chapter 2

Orphan medicinal products for the treatment of pancreatic cancer: lessons learned from two decades of orphan designation.

Mulder J, van Rossum T, Mariz S, Magrelli A, de Boer A, Pasmooij AMG, Stoyanova-Beninska V.
Frontiers in Oncology. 2021 Dec 20;11:809035

Abstract

Pancreatic cancer has a dismal prognosis, and only few treatment options are available. In the European Union, pancreatic cancer classifies as a rare disease, allowing drug developers to apply for orphan medicinal product (OMP) designation. The aim of this study was to provide more detail on OMPs for pancreatic cancer. All applications for OMP designation submitted to the European Medicines Agency between 2000 and 2019 were identified. For each medicinal product that received an OMP designation the mode of drug action (MoA), use of protocol assistance and current lifecycle status were determined. Fifty-two medicinal products received an OMP designation. At the time of submission, 18 OMPs were at the non-clinical and 34 OMPs were at the clinical stage of development. At least 14 kinds of MoA were explored in the condition. For 18 out of 52 OMPs protocol assistance was sought. At the time of data analysis, one OMP received marketing authorisation and 24 OMPs were ongoing in development. Many medicinal products for pancreatic cancer received an OMP designation and the majority of these products was already in the clinical stage of development. Nonetheless, the success rate of OMPs for pancreatic cancer that reach the market is low, and increasing this rate is something to aspire. Fortunately, development is still ongoing for a part of the OMPs, and few developers are planning to submit a marketing authorisation application in the near future. This, however, does not guarantee success, as pancreatic cancer remains a difficult disease to treat. Developers are advised to make optimal use of incentives such as protocol assistance, establishing (early) dialogue between regulators and drug developers and to agree on important topics (e.g., clinical trial design).

Introduction

Pancreatic cancer has a poor prognosis and is currently the seventh leading cause of cancer-related death worldwide [1]. The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma [2], and many patients are diagnosed when the cancer is already in the advanced stage of the disease [3]. A reason for late diagnosis is that patients often do not experience any symptoms in the earlier stages of the disease [4, 5].

A few treatment options exist for patients with pancreatic cancer. Curative treatment is only optional in those that have a resectable tumour at the time of diagnosis; the minority of patients. Palliative treatment can be considered for patients with advanced or metastatic disease. According to clinical practice guidelines, FOLFIRINOX (PS 0 or 1), albumin-bound paclitaxel in combination with gemcitabine (PS 0 or 1) or gemcitabine monotherapy (PS 2 and/or bilirubin higher than 1.5 x upper limit normal) is a recommended first-line treatment option depending on the performance status (PS) of the patient [6]. The only recommended second-line treatment option is liposomal irinotecan in combination with 5-fluoruracil [7]. The median overall survival for first-line therapy varies between 6 and 11 months, depending on the therapy that is administered [8]. Despite available therapies, overall survival is generally poor

as reflected by the median OS being less than one year in patients with advanced pancreatic cancer. Hence, there is a clear unmet medical need.

According to the European Union Orphan Regulation, pancreatic cancer classifies as a rare disease [9], allowing drug developers to submit an application for orphan medicinal product (OMP) designation to the European Medicines Agency (EMA). Drug developers can submit an application for OMP designation if their product meets a couple of criteria. These criteria concern the seriousness of the disease, the prevalence of the disease and the existence of a satisfactory method of diagnosis, prevention or treatment of the condition. Once an application is submitted to the EMA, the Committee for Orphan Medicinal Products (COMP) – one of the committees of the EMA – will assess the application. The final COMP opinion on OMP designation will be sent to the European Commission (EC), and the EC decides whether the OMP designation will be granted [10]. A range of incentives is offered by the EC through the Orphan Regulation. These incentives include protocol assistance (PA), fee reductions for regulatory procedures and market exclusivity [11]. Protocol assistance is a kind of scientific advice specifically for OMPs [12]. The aim of the Orphan Regulation is to stimulate research and development of medicinal products for rare diseases and ensure that effective medicinal products are authorised for diseases with a high unmet medical need.

To date, the COMP has approximately 20 years of experience with applications for OMP designation for pancreatic cancer. Through the years, many applications have been submitted to the EMA, and we are of opinion that this orphan condition deserves further attention. The aim of this study was to provide a detailed overview on OMPs for pancreatic cancer, which can be of value for various stakeholders, including regulators and drug developers. Of special interest were the use of PA incentive and the current lifecycle status.

Methods

Data sources

Internal and publicly available documents from the EMA were used in this study. Internal data was derived from EMA/COMP summary reports on applications for OMP designation, PA letters and annual reports on designated OMPs. Publicly available data was retrieved from public summaries of positive opinion for orphan designation and European Public Assessment Reports (EPARs); both available at www.ema.europa.eu.

Data collection

All applications for OMP designation for medicinal products for the treatment of pancreatic cancer submitted to the COMP between 17 April 2000 and 31 December 2019 were included in this study.

From the summary reports the following information was obtained: date of submission, final COMP opinion, mode of drug action (MoA) and stage of development at time of submission.

In addition to the summary reports, information on MoAs was also obtained from public summaries. If the MoA was not clearly described in the summary report and/or public summary, literature describing the MoA was sought via PubMed.

PA letters were used to determine how many developers made use of this incentive and if advice on clinical development was sought.

From the annual reports the (development) status and the planned submission date were subtracted.

EPARs provided insight in the number of marketing authorisation applications (MAAs) submitted to the EMA. The time from OMP designation to Committee for Medicinal Products for Human Use (CHMP) opinion or withdrawal was determined by calculating the days between the date of the OMP designation and the date of final CHMP opinion or withdrawal of the MAA. Public summaries enabled the identification of OMPs that were withdrawn from the Community Register of orphan medicinal products (access date: 12 March 2021).

Statistics

Descriptive statistics were used.

Results

Applications for OMP designation

Between 2000 and 2019, a total of 80 applications for OMP designation for pancreatic cancer were evaluated by the COMP. Of the 80 applications, 52 received a positive opinion on OMP designation, two received a negative opinion on OMP designation and 26 were withdrawn by the applicant prior to final COMP opinion. Seven applications were resubmitted to the agency after the first application was withdrawn; six applications were resubmitted once and one application was resubmitted twice. Of these, six were granted a positive opinion on OMP designation; these positive opinions were already included in the total number of positive opinions mentioned above. The other application resulted in a second withdrawal and eventually a negative opinion; this negative opinion was already included in the total number of negative opinions mentioned above. All medicinal products that received a positive opinion by the COMP were granted OMP designation by the EC (**Supplementary Table 1**).

Simplified MoA

Table 1 shows the simplified MoAs of the OMPs for pancreatic cancer. The OMPs either 'stimulated an immune response'; 'blocked signalling pathway(s)'; 'inhibited DNA synthesis'; 'infiltrated tumour cells and replicated therein'; 'improved the effectiveness of existing medicinal products'; 'induced DNA lesions'; 'countered migration of tumour cells'; 'induced cell cycle arrest'; 'depleted hyaluronan in tumour stroma'; 'depleted an essential amino acid required for cell growth'; 'delivered radiation specifically to tumour cells'; 'collapsed mitochondrial

metabolism'; 'triggered apoptosis' or 'induced oxidative stress'. The remaining OMPs had multiple MoAs. Additional information on the MoA can be found in **Supplementary Table 1**.

Table 1. Mode of drug action of orphan medicinal products for the treatment of pancreatic cancer.

Mode of drug action (simplified)	Number of OMPs
Stimulates an immune response	12
Blocks signalling pathway(s)	8
Inhibits DNA synthesis	5
Infects tumour cells and replicates therein	5
Improves the effectiveness of existing medicinal products	4
Multiple mechanisms	4
Induces DNA lesions	3
Counters migration of tumour cells	2
Induces cell cycle arrest	2
Delivers radiation specifically to tumour cells	2
Depletes hyaluronan in tumour stroma	1
Depletes an essential amino acid required for cell growth	1
Collapses mitochondrial metabolism	1
Triggers apoptosis	1
Induces oxidative stress	1

Stage of drug development at time of orphan designation

To determine which data were considered sufficient to grant OMP designation, the stage of development was identified for the 52 OMPs. At the time of submission, 18 medicinal products were at the non-clinical and 34 medicinal products were at the clinical stage of development. For the medicinal products in the non-clinical stage of development one was investigated in an in vitro study and 17 were investigated in one or more in vivo ± in vitro studies (**Figure 1A**). For the medicinal products in the clinical stage of development Phase I, II and III clinical trials were ongoing/completed for 7, 25 and 2 medicinal products, respectively (**Figure 1B**).

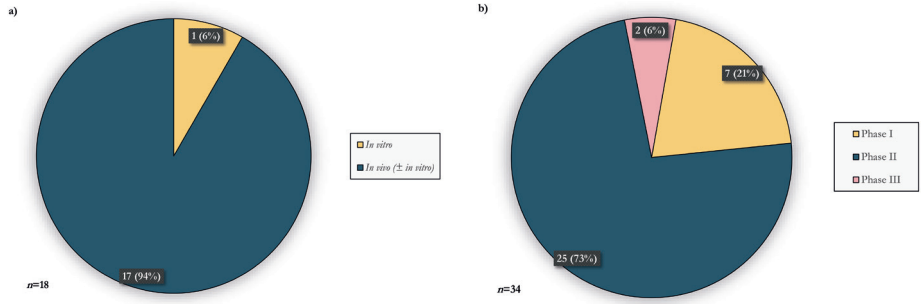

Figure 1. Stage of development at time of designation. (A) Study(ies) conducted in the non-clinical stage of development. (B) Latest study ongoing or completed in the clinical stage of development.

Use of incentives

For 18 OMPs PA on the development of the product was sought. In total, PA was requested 23 times, including two follow-up advices and three additional advices for products for which PA was already requested previously. Nineteen of the PA requests contained questions concerning the clinical development of the OMP. Of these, 12 contained questions concerning a planned Phase III trial. For four OMPs a question on a conditional marketing authorisation was included in the PA. For six OMPs a question on significant benefit was included in the PA.

Current status of the orphan medicinal products

At the time of analysis, 36 medicinal products still had an OMP designation and 16 medicinal products were withdrawn from the EC Community Register. Of the medicinal products that still had an OMP designation, one was authorised in the EU for the treatment of pancreatic cancer; that is, Onyvide (**Figure 2**). For two OMPs (i.e., Masiviera and Orathecin) a MAA was submitted to the EMA, but these applications did not result in marketing authorisation. For Onyvide, Masiviera and Orathecin the time from OMP designation to final CHMP opinion or withdrawal of the MAA was 1687, 1669 and 955 days, respectively. The development status was determined for the remaining 33 OMPs. Development was ongoing for 24 OMPs, stopped for two OMPs and not determined for seven OMPs. Development was stopped due to financial or strategic reasons. Development status was undetermined due to the absence of an annual report, while still being included in the Community Register.

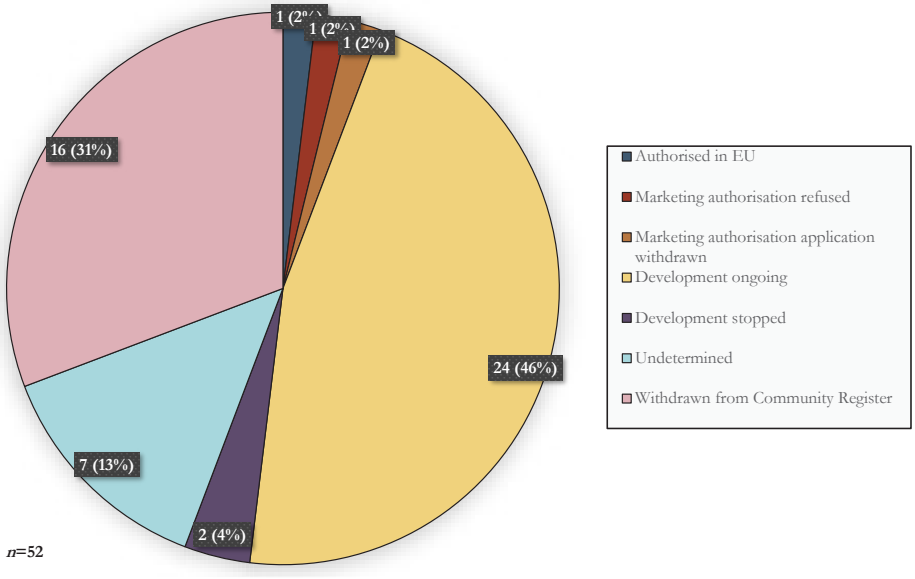

Figure 2. Lifecycle status of medicinal products that received an orphan medicinal product designation for pancreatic cancer. When a recent annual report was absent the development lifecycle status was labelled as undetermined.

Ongoing OMPs and planned submissions

A planned submission date for MAA was included in the latest annual report for 14 out of 24 OMPs that were ongoing in development. Of the 14 annual reports that included a planned submission date, six developers planned to submit a MAA before 2021 and eight developers planned to submit a MAA in 2021 or thereafter (**Figure 3**). The remaining sponsors did not specify a planned submission date.

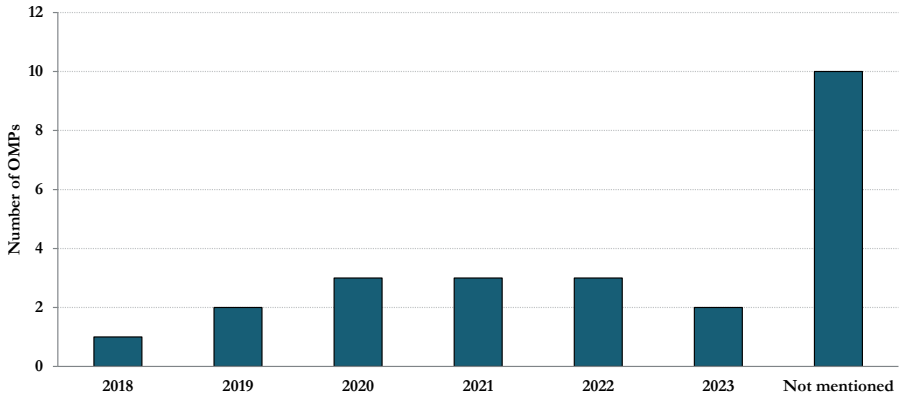

Figure 3. Planned submission date for an application for marketing authorisation for orphan medicinal products ongoing in development.

Discussion

To date, the COMP has two decades of experience with OMPs for pancreatic cancer, which prompted our interest in these products and their lifecycle status. Through the years, a total of 52 medical products for pancreatic cancer were granted OMP designation. The major findings regarding these OMPs will be discussed in detail below.

Many of the medicinal products (65%) were already in the clinical stage of development when the developers applied for an OMP designation. This finding is, however, not solely confined to OMPs for the treatment of pancreatic cancer. Pauwels and colleagues revealed that the majority of anticancer medicinal products were in the clinical stage of development at the time of submission for OMP designation [13]. Additionally, Mariz and colleagues showed that 68% of the applications for OMP designation were supported by preliminary clinical data [14]. It may appear promising that many of the OMPs are already in the clinical stage of development, but it should be noted that the later stages of clinical development are often the most challenging. Hence, success cannot be guaranteed, in spite of encouraging non-clinical and preliminary clinical data. This is particularly the case for pancreatic cancer, as it is a notoriously difficult disease to treat with a high failure rate in drug development [15].

Our results show that OMPs for pancreatic cancer have distinct MoAs. The most frequently investigated OMPs were those that stimulated an immune response, blocked signalling pathways, infected tumour cells and replicated therein and inhibited DNA synthesis. These OMPs can be classified as immunotherapy, targeted therapy, oncolytic virus therapy and chemotherapy, respectively. Chemotherapy continues to play an important role in the treatment of pancreatic cancer. However, other types of therapy have, unfortunately, not yet demonstrated definitive efficacy in pancreatic cancer, which concerns both OMPs as well as medicinal products without an OMP designation. Targeted therapy could be considered an exception, as a Phase III clinical trial showed a statistically significant improvement in overall survival for erlotinib plus gemcitabine compared to gemcitabine monotherapy [16]. However, the clinical relevance of this outcome is questioned, because the gain in median overall survival is approximately two weeks [6]. There are several reasons why pancreatic cancer is a difficult disease to treat. For instance, it is reported that a considerable part of the tumour mass is made up of a highly fibrotic stroma and this is associated with poor survival outcome [17]. Furthermore, within the stroma, macrophages and inflammatory cells construct an immunosuppressive microenvironment, preventing an antitumour immune response [18, 19]. Developing effective medicinal products remains challenging, despite the attempts to overcome these hurdles; evident by the MoAs of the OMPs included in this study. Therefore, a better understanding of the disease remains important.

To stimulate the development of medicinal products for rare diseases, incentives have been implemented in the EU Orphan Drug legislation [20]. We found that PA, one of these incentives, was sought only for the minority of OMPs (35%). Moreover, almost all of the

PAs requests included questions on the clinical development, along with questions on the design of Phase III clinical trials. Hence, it appears that developers are more likely to seek PA when their product is transitioning to the late stage of clinical development. This is not surprising, as agreement(s) between regulators and developers on the design of Phase III trials, the confirmatory trial, is of importance when considering potential future MAAs. There might be several reasons why not all of the developers have requested PA, including no advancement in development, financial limitations or lack of efficacy in previously ongoing clinical trials. Besides, developers might not be aware of the benefit of PA and, therefore, do not make use of this incentive. An analysis performed by Hofer and colleagues showed that compliance with PA was associated with a higher probability for MA. They advised that drug developers should make use of the incentive, as the development plan could be discussed and amended. This may prevent major outstanding issues during the evaluation of a MAA [21]. Therefore, it remains important that developers continue to seek PA, taking into account the benefit of this incentive.

Even though the majority of medicinal products was already in the clinical stage of development when the developers applied for OMP designation, only one OMP for pancreatic cancer received MA, namely irinotecan hydrochloride trihydrate [22]. Irrespective of orphan condition, the success rate of medical products that reach the market as OMPs is estimated to be 8% [23], which is four times higher than our finding. These data highlight that, despite the efforts of developers, not many OMPs will reach the market eventually; especially not those for pancreatic cancer. Nonetheless, the lower success rate is of course related to the difficulties in treating the condition. This is further highlighted by the fact that the CHMP was of the opinion that the benefit-risk balance was not considered positive for two OMP for pancreatic cancer considered for MA (i.e., rubitecan and masitinib) [24, 25]. These submissions resulted in a withdrawal of MA application and a refusal on MA, respectively.

A positive finding in our results is that development is still ongoing for almost half of the OMPs (46%), and a couple of developers are planning to submit an application for MA in the near future. Of all these developers, a few planned to submit a MAA in previous years but this has not been realised so far. The reasons might be delayed of failed development. For the remaining OMPs it could not be determined whether development is still ongoing, as the annual reports were absent or OMPs were withdrawn from the Community Register. It remains difficult to speculate on the reasons behind this. Yet, plausible reasons could be failure in development or financial considerations. This might, at least, be the case for the products that have received an OMP designation a while ago.

This study has a few limitations, one of which is the lack of correction for time. For example, some medicinal products have received an OMP designation recently, while others have received OMP designation years ago. Products that have been granted OMP designation recently might still face potential developmental challenges in the future. Another limitation is the incompleteness of our overview on the status of drug development, which is due to the lack of (recent) annual reports for part of the OMPs. Determining whether the OMP is still

in the drug pipeline of the developer would provide a more definitive answer on the lifecycle status than currently provided in our study.

Conclusion

The success rate of medical products for pancreatic cancer that reach the market as OMPs is lower than for OMPs in general and increasing this success rate is something to aspire. Despite pancreatic cancer is such a difficult disease to treat, a substantial number of applications has been submitted to the EMA for this condition. This indicates interest among drug developers. Development is still ongoing for a part of the OMPs, and for few of these OMPs a submission for MAA is planned in the near future. It should be reminded that an OMP designation is supported by promising non-clinical and/or preliminary clinical data, but efficacy and safety still needs to be determined in the challenging late stages of development. Therefore, an OMP designation is not a guarantee for successful MA. In this respect, developers are advised to make optimal use of incentives inherent with an OMP designation such as PA, establishing (early) dialogue between regulators and drug developers to agree on important topics (e.g., clinical trial design). In addition, developers are strongly encouraged to provide yearly updates on advancements in development. Close monitoring of the drug development through the annual reports and transparency regarding the reason(s) for stopping development are crucial for saving human and financial resources and redirecting efforts in promising concepts.

Author disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of the EMA or one of its committees, working parties, or any of the national agencies.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

Supplementary Table 1. Medicinal products for pancreatic cancer that were granted orphan medicinal product designation between 2000 and 2019.

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
(1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) diamidophosphate	17-07-2013	Pancreatic cancer, like most solid tumours, has areas with poor blood supply and therefore low levels of oxygen. The low level of oxygen in these areas is known to make tumour cells more resistant to standard chemotherapy. This medicine is expected to be converted into an active, toxic form called bromo-isophosphoramide mustard under conditions of low oxygen, allowing it to attack the tumour cells in low oxygen areas. This medicine is intended to be given with standard chemotherapy medicines and this is expected to help kill the tumour cells in low oxygen areas as well as other areas of the tumours.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3131152
[5-amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone	22-08-2014	This medicine is expected to work in patients with pancreatic cancer by blocking the action of proteins called p38 MAP kinases. In pancreatic cancer, p38 MAP kinases play an important role in regulating the way that cells of the immune system (the body's natural defences) respond to various chemical messengers from the cancer. By blocking p38 MAP kinases, the medicine is expected to improve the ability of the immune system to recognise and destroy cancer cells, thereby slowing the progression of the disease.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141323
4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl) cyclopent-2-en-1-yl] pyrimidin-2-one	12-10-2017	The medicine is activated inside cancer cells by an enzyme called UCK2. Because this enzyme is present mainly in cancer cells, the medicine is activated only in these cells. The activated form of the medicine blocks the production of the cell's genetic material, RNA and DNA, and so kills the cancer cells. This is expected to slow down the growth of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171937
4-imino-1, 3-diazobicyclo-[3.1.0]-hexan-2-one	27-07-2005	Cells contain several substances needed for their normal functioning (e.g. glutathione, cysteine, thiols). They also contain small structures (so-called mitochondria), responsible for the production of the energy necessary for the cell functioning, through a process named "cellular respiration". 4-imino-1, 3-diazobicyclo-[3.1.0] hexan-2-one might induce a certain reaction in the cancer cells leading to a shortage of the cell fundamental substances and the destruction of the surface of the mitochondria. This would then induce the destruction of the cell itself, through a process called "programmed cell death" (apoptosis).	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu305299
5,10-methylene-tetrahydrofolic acid	02-09-2004	5,10-methylene-tetrahydrofolate belongs to a group of substances that are called folates. Folates, are necessary for the human body. They are obtained from the diet or from bacteria that live normally in the gut. They help in the building of new body substances. Cancer cells need to build new genetic material in order to grow. Several proteins work in the cells in order to build the new genetic material. One of these proteins is called thymidylate synthase. It builds new genetic material using 5,10-methylene-tetrahydrofolate, which is transformed in the process. If fluorouracil is present, however, the transformation stops, and the protein is blocked. This damages the cells that are growing, because the building of new genetic material becomes impossible. Fluorouracil works best only if folates are present. As the folates from the diet may not be sufficient, it is expected that by giving additional 5,10-methylene-tetrahydrofolate, this will help fluorouracil to block the thymidylate synthase. Thus, giving 5,10-methylene-tetrahydrofolate together with fluorouracil could help to stop the growth of pancreatic cancer cells.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu304221

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
5-10-Methylene-tetrahydrofolate	11-06-2003	5,10-methylene-terahydrofolate belongs to a group of substances that are called folates. Folates, are necessary for the human body. They are obtained from the diet or from bacteria that live normally in the gut. They help in the building of new substances. Cancer cells need to build new genetic material in order to grow. Several proteins work in the cells in order to build the new genetic material. One of these proteins is called thymidylate synthase. It builds new genetic material using 5,10-methylene-terahydrofolate, which is transformed in the process. If fluorouracil is present, however, the transformation stops, and the protein is blocked. This damages the cells that are growing. Florouracil works best only if folates are present. As the folates from the diet may not be sufficient, it is expected that by giving additional 5,10-methylene-terahydrofolate, this will help fluorouracil to block the thymidylate synthase. Thus, giving 5,10-methylene-terahydrofolate together with fluorouracil could help to stop the growth of pancreatic cancer cells.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu303143
5'-O-(trans-9''-octadecenoyl)-1-beta-D-2'-deoxy-2',2'-difluorocytidine	28-10-2009	5'-O-(trans-9"-octadecenoyl)-1-beta-D-2'-deoxy-2',2'-difluorocytidine belongs to the group 'anti-metabolites'. In the body, this medicine is expected to be incorporated into the genetic material of cells (DNA and RNA) and interfere with the enzymes involved in making new DNA and RNA. As a result, it is expected to inhibit the growth of tumour cells and eventually kill them.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309680
6,8-bis(benzylthio) octanoic acid	14-12-2018	The medicine, which is taken up in large amounts by cancer cells, blocks two enzymes that are needed for mitochondria (the energy-producing components within cells) to work properly. As a result, the cells cannot produce the energy needed to survive and grow. This is expected to lead to the death of cancer cells in patients with pancreatic cancer and thereby slow down the growth of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182105
9-nitro-20 (S) camptothecin (Rubitecan)	10-06-2003	Rubitecan, belongs to a group of alkaloids called camptothecins. Alkaloids are substances that are naturally found in plants. Certain camptothecins are useful in medicine as anti-cancer agents. When cells are growing, as is the case for cancer cells, the genetic material (DNA) inside the cell may become twisted. Cells have several proteins which help to remove any twists in the DNA. This avoids that the DNA breaks, which would damage the cells. Camptothecins are able to block one of the proteins that can remove twists in the DNA. This protein is called topoisomerase I. By blocking this protein, rubitecan is expected to damage the cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu303145

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Adenoviral vector of serotype 5 modified to contain a chimeric sequence consisting of a minimal urokinase-type plasminogen activator receptor promoter preceded by three Notch-responsive elements, and coated with oligopeptide end-modified poly (beta-amino) esters	16-10-2017	This medicine is an advanced therapy that belongs to the group called 'gene therapy products'. These are medicines that work by delivering genes into the body. The medicine is made up of an 'oncolytic' virus, a virus that has been genetically modified so that it is able to target, multiply in and destroy cancer cells while sparing normal cells. The virus is coated with a substance that protects it from the immune system (the body's natural defences) and allows it to be drawn to the cancer. When inside a cancer cell, the virus is expected to take over the cell's replication apparatus and use it to make more copies of itself. This is expected to kill the cell, leaving the virus to spread to neighbouring cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171917
Anti-CEA sheep-human chimeric monoclonal antibody labeled with iodine-131	07-05-2003	Antibodies are proteins that are able to distinguish certain foreign substances called antigens. Examples of antigens are proteins found on the surface of cancer cells or bacteria. Anti-CEA sheephuman chimeric monoclonal antibody targets a substance present on the surface of pancreatic cancer cells. This substance is called carcinoembryonic antigen, or CEA. The antibody is called chimeric because it is composed of parts that were first found in different species of living things. In this case, the species are sheep, and man. It is called monoclonal because it is produced using cells that have identical genes, and produce exactly the same antibody. The antibody is also linked (labelled) with a tiny part, called iodine-131. Iodine-131 can give off radiation. Radiation can damage and kill cells, especially those that are dividing, such as cancer cells. Thus, the antibody is used to deliver the radiation to the pancreatic cancer cells and to kill them with the radiation.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu303142
Antroquinonol	12-01-2017	Antroquinonol is expected to work by blocking 'the Ras signalling pathway'. This is a mechanism within cells that helps them to grow and survive. However, in cancer cells it works abnormally, leading to the growth of the cancer. By blocking the Ras pathway, antroquinonol is expected to kill cancer cells and slow down the growth of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161812
Autologous human adipose perivascular stromal cells genetically modified to secrete soluble tumour necrosis factor-related apoptosis-inducing ligand	19-11-2018	The medicine is made of cells that have been modified to produce TRAIL, a protein in the body that triggers cancer cell death. When the medicine is injected into the patient's cancer, the cells in the medicine will produce the TRAIL protein, which will attach to receptors (targets) on the surface of cancer cells and trigger their death.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182085

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Bovine bile extract	20-06-2005	This medicinal product is a biological preparation isolated from the bile of cattle. The mechanism of action of bovine bile extract is not fully known. It is believed to activate a certain type of white blood cells, a type of cell belonging to the body's defence system (immune system), the so-called macrophages. The main role of macrophages is to take-up material (such as bacteria, cancer cells or cell fragments). Following the uptake they degrade the material and present parts of this material to the other components of the body's defence system. Activation of these cells may thus stimulate an immune response of the organism, which might cause the immune system to recognise and kill the cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu305287
Brivudine	28-01-2010	Brivudine is expected to work by blocking the activity of a protein called 'heat shock protein 27 (Hsp27), which is found in high amounts in pancreatic cancer cells. Hsp27 is known to play a key role in 'chemoresistance'. This means that it makes cancer cells not respond ('resistant') to chemotherapy, helping them to survive. When brivudine is given together with other anticancer medicines, it is expected to prevent the cancers cells from developing resistance to the medicines, helping to treat the disease.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309703
Chimeric antibody to mesothelin	17-03-2008	Mesothelin is a protein that can be found on the surface of some normal cells and it is also found on the surface of cancer cells. Mesothelin and other substances that are present outside the cells interact with other substances in the cell surroundings and are part of the mechanisms that allow cells to grow and move (migrate). This is important for the development of cancers as these mechanisms are necessary for cancer growth and spreading. Antibodies are proteins in the body that target and bind specific structures on the surface of foreign bodies, such as bacteria or cancer cells. This antibody to mesothelin is able to bind mesothelin and interfere with its function on cell growth and migration. The product is expected to be able to inhibit cancer cell growth and spreading in the body.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308536
Chimeric monoclonal antibody against claudin-18 splice variant 2	05-08-2013	Claudin-18 splice variant 2 is a protein found in the cells of the ducts of the pancreas, where it helps the cells to stick to each other. In patients with pancreatic cancer, this protein is produced in large amounts and is thought to be involved in the survival and spread of the cancer cells. The medicine is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a part of the claudin-18 splice variant 2 protein in the cancer cells. By attaching to this protein, this medicine is expected to stimulate the immune system (the body's natural defences) to kill the cancer cells, slowing down the spread of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3131177
Cisplatin (liposomal)	08-06-2007	Cisplatin (liposomal) is a new formulation of cisplatin, which has been an anti-cancer drug for a long time. The inclusion of cisplatin in liposomes (special particles coated with molecules of fat) is expected to increase the concentration of the drug in the cancer cells, compared to normal cells, and decrease the adverse effects of the drug. Cisplatin works by damaging and eventually killing cancer cells, through the formation of special compounds, called "reactive oxygen species", which are toxic for the cells	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307451

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Cysteamine bitartrate	26-03-2014	The active substance in this medicine, cysteamine bitartrate, is thought to block the action of certain enzymes called matrix metalloproteinases. Tumours such as pancreatic cancer produce high levels of these enzymes, which break down the substances that cement normal cells together in the tissues, enabling the cancer cells to spread more easily between them. By blocking the action of the enzymes, the medicine is expected to reduce the spread of cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141252
Cytochrome P450 isoform 2B1 gene transfected human embryonic kidney 293 cells encapsulated in polymeric cellulose sulphate	30-06-2003	This orphan medicinal product is made of cells whose genetic material has been modified by adding a gene. This gene allows the cells to be very efficient in activating an anti-cancer agent called ifosfamide. The active ifosfamide is then able to kill tumour cells. After having been genetically modified, the cells are packed into capsules, and the product is administered in a vessel near to the cancer. Polymeric cellulose sulphate is a material that is used so that the capsules get trapped into the small vessels of the tumour. Once the cells are in place, the agent ifosfamide is given. In this way, it is expected that the cells will be able to produce high levels of active ifosfamide near the tumour where it is most needed for killing the cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu303149
Deuterium oxide	20-10-2004	Deuterium oxide is, in very small amounts, present in normal drinking water. In high amounts deuterium oxide might influence and block several processes in cancer cells necessary for tumour growth. Therefore it might prevent cancer cells from growing when given in higher concentrations.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu304239
G17(9) gastrin-diphtheria toxoid conjugate	24-01-2003	Gastrin is a hormone that is normally produced by the body. Gastrin stimulates the stomach to produce gastric juice. Gastrin also makes certain digestive system cancers grow faster. G17(9) gastrin-diphtheria toxoid conjugate is designed to stimulate the body to make antibodies against gastrin. Antibodies are proteins which specifically recognise and block certain substances. Antibodies against gastrin are expected to specifically link to this hormone, thus blocking its activity. This would consequently slow down the growth of pancreatic cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302129
Genetically modified human adenovirus encoding human PH20 hyaluronidase	21-06-2011	This medicine is made up of an 'oncolytic' virus, a virus that has been genetically modified so that it is able to target, replicate itself in and destroy tumour cells while sparing normal cells. When inside a tumour cell, the virus is expected to take over the cell's replication apparatus and use it to make more copies of itself. This is expected to kill the cell, leaving the virus to spread to neighbouring tumour cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311880
Glufosfamide	15-04-2011	Glufosfamide is made of another anticancer medicine called isophosphoramide mustard linked to glucose (a sugar). It is a cytotoxic (cell-killing) substance that belongs to the group 'alkylating agents'. Alkylating agents kill cancer cells by attaching to their DNA while they are reproducing. As a result, cancer cells cannot reproduce and this slows down the growth of tumours. The glucose in the medicine is expected to help glufosfamide enter the tumour cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311851

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Heat-killed Mycobacterium obuense (whole cell)	16-12-2014	In the early stages of cancer, the body's immune system (its natural defences) can often combat the growth and spread of tumour cells, but over time the immune system may become less effective in controlling the cancer, allowing it to grow. This medicine contains a species of bacteria called Mycobacterium obuense (NCTC 13365) that have been killed by heating so they can no longer grow or cause infection. When the medicine is injected, the body's immune system is activated to become more effective, because the bacteria are considered a possible new threat. This activation of the immune system is expected to help the body also combat the cancer more effectively.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141385
Herpes simplex type 1 virus containing cellular B-myb gene as tumour-specific promoter	15-01-2015	This medicine consists of an 'oncolytic' virus (a virus that kills cancer cells) that contains a part of a gene (called B-myb). This is expected to allow the virus to multiply and kill only cells that have high levels of the gene B-myb (such as pancreatic cancer cells), while sparing normal cells. The virus in the medicine (a herpes virus) has been modified so that it does not cause disease in humans.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141412
Human reovirus type 3 Dearing strain	24-04-2015	This medicine is made up of an 'oncolytic' virus called reovirus that it is able to target, infect and destroy cancer cells but does not infect normal cells. When inside a cancer cell, the virus is expected to take over the cell's replication apparatus and use it to make more copies of itself. This is expected to kill the cell, leaving the virus to spread to neighbouring cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151477
Human telomerase reverse transcriptase peptide (611-626)	25-07-2006	Human telomerase reverse transcriptase peptide (611-626) is a part of the enzyme (a protein that triggers chemical reactions) telomerase reverse transcriptase, which is often present in pancreatic cancer tumour cells. Human telomerase reverse transcriptase is needed for tumour cells to be able to divide many times (proliferate) and subsequently for the tumour to grow. The medicinal product is designed to activate the body's natural defence system, the immune system against the cells containing the human telomerase reverse transcriptase. According to the sponsor the product will trigger the immune system against the pancreatic cancer tumour cells, thus destroying the tumour cells with the body's own defence system.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu306384
Humanised IgG4 monoclonal antibody to the human toll-like receptor type 2	27-02-2017	The medicine is a monoclonal antibody (a type of protein), that has been designed to attach to another protein called the human toll-like receptor type 2 (TLR2). TLR2 is part of the immune system (the body's natural defences) and may play a role in the spread of cancer. By attaching to TLR2, this medicine is expected to block its activity, thereby reducing cancer spread.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171838

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Immunoglobulin G1, anti-(human tumour-associated calcium signal transducer 2) (human-Mus musculus monoclonal hRS7 heavy chain), disulfide with human-Mus musculus monoclonal hRS7 k-chain, dimer, hexakis(thioether) with (4S)-4-[[[[4-[[(2S)-2-(4-aminobutyl)-2-[[2-[2-[[26-[4-[[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl] cyclohexyl]carbonyl] amino]methyl]-1H-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacos-1-yl] amino]-2-oxoethoxy] acetyl]amino]-1-oxoethyl] amino]phenyl]methoxy] carbonyl]oxy]-4,11-diethyl-9-hydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-b] quinoline-3,14(4H,12H)-dione	15-10-2014	This medicine contains a monoclonal antibody (a type of protein) that is able to recognise and attach to a target substance called Trop-2, which is found on the surface of pancreatic cancer cells. The antibody has been linked to the activated form of an existing cancer medicine called irinotecan. When the antibody attaches to Trop-2, the activated irinotecan is delivered into the cancer cells where it blocks the action of topoisomerase I, an enzyme needed for the cells to divide and grow, and so leads to their death. By specifically targeting the cancer cells, side effects on normal cells should be reduced.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141343

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
L-asparaginase encapsulated in erythrocytes	15-05-2009	L-asparaginase is an enzyme that breaks down the substance L-asparagine, which is required for cell growth. Certain cancer cells, such as the cancerous cells in pancreatic cancer, cannot make L-asparagine, so they need to take it up from the blood in order to grow. By reducing the levels of L-asparagine in the blood, this medicine is expected to deprive the cancerous pancreatic cells of their supply of L-asparagine, causing them to die. L-asparaginase has already been used for the treatment of acute lymphoblastic leukaemia (a cancer of the white blood cells) since the 1970s. This medicine is made up of erythrocytes (red blood cells) that have been loaded with L-asparaginase so that the L-asparaginase is 'encapsulated' (contained) within the erythrocytes. The erythrocytes reduce the exposure of L-asparaginase to the immune system (the body's natural defences). This results in the immune system producing fewer antibodies against L-asparaginase, which could otherwise cause side effects such as allergic reactions. The erythrocytes also form tiny compartments where the breakdown of L-asparagine can take place. Together, these properties are expected to increase how long L-asparaginase remains active in the body and to allow a lower dose of the enzyme to be used for the same anticancer effect as the free enzyme.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309633
Live attenuated Listeria monocytogenes delta actA/delta inlB strain expressing human mesothelin	11-01-2016	The medicine works by stimulating the patient's immune system, the body's natural defences, so that it targets and destroys the cancer cells. It is made of Listeria monocytogenes bacteria, which have been attenuated (weakened) so that they do not cause disease in humans. The bacteria have also been modified to produce mesothelin. Mesothelin is found at high levels on many types of cancer cells, including pancreatic cancer cells. When the medicine is injected into the body, the patient's immune system learns to treat mesothelin as 'foreign' and is expected to destroy pancreatic cancer cells carrying mesothelin on their surface. The medicine is given as part of a combination treatment including another medicine (called 'two allogeneic irradiated pancreatic tumour cell lines' or GVAX) which is also expected to stimulate the immune system to recognise pancreatic cancer cells as foreign and so causes the body to attack the cancer.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151603
Masitinib mesilate	28-10-2009	Masitinib mesylate is expected to work by blocking types of enzymes known as tyrosine kinases. These enzymes can be found in some receptors on the surface of cancer cells, including 'c-Kit' receptors and 'platelet-derived growth factor' (PDGF) receptors. These are receptors involved in stimulating the cells to divide uncontrollably. By blocking these receptors, masitinib mesylate is expected to help to control cell division, slowing down the rate of growth of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309684
Mixture of seven synthetic fragments consisting of p21 RAS peptides	05-08-2011	The medicine contains seven synthetic peptides (short chains of amino acids) that are also found in a protein called 'p21 RAS'. The peptides contain mutations which are normally only expressed by certain cancer cells such as pancreatic cancer cells. The medicine is expected to act as a vaccine by 'teaching' the specialised cells of the body's immune system called T cells (a type of white blood cell) to recognise the p21 RAS proteins containing the mutations. It is expected that this will lead the T cells to attack and kill the pancreatic cancer cells containing these proteins.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311885

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Mixture of two allogeneic human pancreatic cancer cell lines stably transduced with a retroviral vector encoding the murine alpha-(1,3)-galactosyltransferase gene	10-10-2012	The medicine is expected to work as a 'cancer vaccine', by activating the patient's immune system (the body's natural defences) so that it attacks and kills the cancer cells. The medicine is made of pancreatic cancer cells that have been modified to produce an enzyme called alpha-(1,3)-galactosyltransferase. This enzyme is responsible for the production of substances called alpha-Gal, which are known to trigger an immune response. When the patient is given the vaccine, the patient's immune system is expected to stimulate an immune response not only against the cancer cells in the vaccine which contain alpha-Gal, but also against the cancer cells in the patients even though they do not contain alpha-Gal.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121048
Modified adenovirus serotype 5/35 containing a CMV promoter-driven transgene cassette with the human transgenes for a membrane-bound CD40 ligand and full length 4-1BBL	28-07-2015	The medicine is made up of an 'oncolytic' virus, a virus that has been modified so that it can target, infect and destroy cancer cells, but not normal cells. When inside a cancer cell, the virus is expected to take over the cell's replication apparatus and use it to make more copies of itself. This is expected to kill the cell, leaving the virus to spread to neighbouring cancer cells. In addition, the modifications to the virus prepare the cell for self-destruction and cause infected cells to produce substances that stimulate the immune system (the body's natural defences), which will also help to destroy the cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151516
N-[(2S)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophenyl) amino]isonicotinamide hydrochloride	09-11-2009	N-[(2S)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophenyl)amino]isonicotinamide hydrochloride is expected to work by blocking an enzyme called MEK1/2, which is involved in stimulating cells to grow and divide. MEK1/2 is over-activated in cancer cells, which makes these cells divide uncontrollably. By blocking this enzyme, the medicine is expected to control cell division and slow down the rate of growth of the cancer.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309685
Nanoliposomal irinotecan	09-12-2011	Irinotecan is an anticancer medicine that belongs to the group 'topoisomerase inhibitors'. It blocks an enzyme called topoisomerase I, which is involved in the division of cell DNA. When the enzyme is blocked, the DNA strands break. This prevents the cancer cells from dividing and they eventually die. Free irinotecan is already authorised for the treatment of colorectal cancer. In this medicine, irinotecan is contained within tiny fat particles called 'nanoliposomes'. The nanoliposomes are expected to accumulate within the tumour and release the medicine slowly over time, thereby decreasing the rate at which the irinotecan is removed from the body and allowing it to act for longer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311933

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Nanoparticle albumin-bound paclitaxel	26-11-2010	Paclitaxel, the active substance in nanoparticle albumin-bound paclitaxel, belongs to the group of anticancer medicines known as the 'taxanes'. Paclitaxel blocks the ability of cancer cells to break down their internal 'skeleton' that allows them to divide and multiply. With their skeleton still in place, the cells cannot divide and they eventually die. Paclitaxel has been available as an anticancer medicine since 1993 but is not authorised for pancreatic cancer. Conventional types of paclitaxel contain substances that dissolve the paclitaxel, but which can cause hypersensitivity (allergic) reactions. Nanoparticle albumin-bound paclitaxel does not contain these substances. Instead, the paclitaxel is attached to a human protein called albumin in tiny particles known as 'nanoparticles'. This makes it easy to prepare a suspension of paclitaxel, which can be infused into a vein. The nanoparticles may also modify the way the medicine is distributed within the body, and this is expected to have a positive effect on its benefits and risks, in comparison with conventional medicines containing paclitaxel	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu310809
Nimotuzumab	03-06-2008	Nimotuzumab is an anticancer medicine that belongs to the group 'epidermal growth factor receptor (EGFR) inhibitors'. It blocks the receptors for a protein called 'epidermal growth factor', which are found on the surface of certain tumour cells. Epidermal growth factor normally stimulates cells to grow and divide. By blocking its receptor, nimotuzumab prevents the tumour cells receiving the messages they need for growth, progression and spreading.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308550
Paclitaxel (liposomal)	31-10-2006	When cells divide and grow, there are structures (tubules) inside the cells that need to assemble and disassemble in a very orderly way. Paclitaxel interferes with the assembly of these tubules and subsequently with the growth of cells. Liposomal paclitaxel is delivered to the cancer cells in the tumour in little lipid particles (liposomes) that bind specifically to the cells that line blood vessels. According to the sponsor, paclitaxel (liposomal) will, by inhibiting the growth of newly formed blood vessels, contribute to the destruction of the tumour.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu306419
Pegylated recombinant human hyaluronidase PH20	16-12-2014	The medicine contains a version of a natural enzyme, hyaluronidase, which breaks down a compound, hyaluronan. Hyaluronan is found in large amounts in many pancreatic cancers and helps the cancer to grow and to resist the effects of cancer medicines. By breaking down the excess hyaluronan, the medicine is expected to make the cancer easier to treat with other authorised therapies. In this medicine, hyaluronidase has been 'pegylated' (combined with a chemical called polyethylene glycol). This decreases the rate at which the substance is removed from the body and allows the medicine to be given less often.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141394
Pegylated recombinant human interleukin-10	12-12-2016	This medicine is a type of immunotherapy, which means that it acts on the body's immune system (the body's natural defences). It activates white blood cells known as CD8+ T cells. These cells can infiltrate pancreatic cancer tumours, where they are expected to kill cancer cells and improve survival.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161804

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Polyinosine-polycytidylic acid coupled with the polycationic polyethyleneimine	06-06-2012	The medicine is expected to act against tumour cells by activating an enzyme within the cell called helicase MDA-5, which will cause the cell to digest and kill itself. Moreover, the medicine is expected to stimulate the immune system to recognise and attack tumour cells	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121000
Recombinant human monoclonal antibody of the IgG1 kappa class against prostate stem cell antigen	24-01-2013	The medicine 'recombinant human monoclonal antibody of the IgG1 kappa class' is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a specific structure (called an antigen) that is found in the body. It is expected to attach to an antigen called 'prostate stem=cell antigen', which is found on the surfaces of normal cells as well as in high amounts on the surface of prostate, bladder and pancreatic cancer cells. The exact function of prostate stem-cell antigen is not fully understood, although it is thought to play a role in regulating cell growth through regulating the transmission of chemical signals between cells. When the medicine attaches to prostate stem-cell antigen, it is expected to alter the antigen's normal activity, including blocking the transmission of chemical signals, thereby reducing the growth and spread of the pancreatic cancer cells.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3121090
Relacorilant	21-08-2019	Relacorilant is a 'glucocorticoid receptor antagonist'. This means that it attaches to the same receptors (targets) that the hormone cortisol attaches to inside cells. When cortisol attaches to these receptors in pancreatic cancer cells it helps them to grow and resist cancer medicines. Relacorilant reduces cortisol's ability to attach to the receptors, and this is expected to slow the growth of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3192191
S-[2,3-bispalmitoyloxy-(2R)-propyl]-cysteinyl-GNNDESNISFKEK	15-05-2009	S-[2,3-bispalmitoyloxy-(2R)-propyl]-cysteinyl-GNNDESNISFKEK is a peptide (a protein fragment) that is expected to work by attaching to and activating two receptors called 'Toll-like receptor 2' and 'Toll-like receptor 6'. These receptors are part of the immune system (the body's natural defences) and their activation leads to an immune response. The medicine is injected directly into the pancreas, from where it is expected to stimulate the release of substances of the immune system that attack the cancer cells, particularly when it is combined with other cytotoxic (cell-killing) medicines.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309634
Salirasib	21-06-2011	Salirasib is expected to work by blocking 'the Ras signalling pathway'. This is a mechanism within cells that helps them to grow and survive. However, in cancer cells it works abnormally, leading to the growth of the cancer. Salirasib is expected to attach to specific proteins on the membrane of cancer cells and thus detach proteins called Ras. By detaching Ras, the medicine is expected to block the signalling pathway, thereby slowing down the growth of the cancer.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu311871

Supplementary Table 1. Continued

Active substance	Date of OMP designation	How is the medicine expected to work	Withdrawn	EMA hyperlink
Sodium 2-hydroxylinoleate	23-08-2017	This medicine is expected to work by reducing the activity of several proteins in the 'Akt/mTOR signalling pathway'. This is a mechanism within cells which is important in regulating their growth and survival. In many cancers, including pancreatic cancer, this pathway is overactive, allowing the cancer cells to grow uncontrollably. By reducing the activity of this pathway, the medicine is expected to slow down the progression of the cancer.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171911
Trabedersen	24-07-2009	Trabedersen is an 'antisense oligonucleotide', a short piece of DNA that has been designed to attach to the genetic material of cells responsible for producing a protein called TGF-β2. This blocks the production of TGF-β2. TGF-β2 is produced in large quantities in pancreatic cancer cells, and is involved in the growth, progression, and spreading of the cancer, as well as in the suppression of the body's immune system (the body's natural defences). By blocking the production of TGF-β2, trabedersen is expected to stop the cancer cells from growing and multiplying. In addition, blocking the production of TGF-β2 may stimulate the immune system to attack the cancer cells.	No	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu309660
Two allogenic irradiated pancreatic tumour cell lines	11-01-2016	The medicine works by stimulating the patient's immune system, the body's natural defences, so that it targets and destroys the cancer cells. It is made of two types of pancreatic cancer cells that have been modified to produce granulocyte-macrophage colony stimulating factor (GM-CSF) and have been treated with radiation to prevent them from growing. GM-CSF stimulates the immune system to recognise as 'foreign' certain proteins, such as mesothelin, which are found at high levels on the surface of pancreatic cancer cells. This is expected to stimulate the immune system to destroy pancreatic cancer cells. The medicine is given as part of a combination treatment including another medicine (called 'live attenuated Listeria monocytogenes delta actA/delta inlB strain expressing human mesothelin' or CRS-207) which helps the immune system to recognise mesothelin as foreign and so stimulate the body to attack the cancer.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151604
Yttrium (90Y)-DOTA-radiolabelled humanized monoclonal antibody against mucin 1	06-02-2009	Mucin 1 is a protein found on the membrane of many types of cells. However, abnormally high levels or changes in its structure have been associated with some types of cancer and mucin 1 is highly expressed in pancreatic cancer cells. This medicinal product contains an antibody that specifically binds to mucin 1 and is labelled with radioisotope Yttrium (90Y)-DOTA. Antibodies are proteins used by the immune system to identify and neutralize foreign proteins expressed by bacteria or viruses known as antigens. Antigens and antibodies have a lock-and-key relationship; an antibody can specifically recognize and bind only one antigen. As medicinal products, antibodies can be used to identify specific antigens expressed only on cells of interest. This medicinal product is expected to recognise mucin 1 on pancreatic cancer cells, bind on them and deliver the radioisotope on the tumour. Radioisotopes are used to destroy cancer cells. The antibody is expected to help identify pancreatic cancer cells expressing mucin-1, and once the product is bound, Yttrium (90Y)-DOTA is expected to destroy them.	Yes	https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308608

Chapter 3

Breakthrough therapy-designated oncology drugs: are they rightfully criticized?

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Abstract

The United States Food and Drug Administration (FDA) has four expedited programs, including the breakthrough therapy designation (BTD). Recently, this program has been criticised. In this feature, we determine whether BTD oncology drugs were truly a breakthrough based on the outcome of a validated instrument to measure clinical benefit. Our results indicate that only a few drugs were likely a breakthrough, indicating that the success rate of the BTD program is somewhat low. Despite this, we believe that programs for fast drug approval do have a place in the current regulatory practice and that the necessary efforts for their improvement should be further explored, especially considering the remaining unmet medical need for patients with cancer.

Introduction

Drug development is a lengthy process and it takes years before a drug reaches the market [1]. Fast approval of drugs can be desirable, especially when preliminary data indicate extraordinary clinical benefit and there is an unmet medical need. Nonetheless, a drug is approved only after a regulatory agency concludes that the drug has a positive benefit–risk balance, for which a certain level of evidence is required.

Regulatory agencies provide access to several programs that facilitate earlier availability of promising drugs. The FDA has four expedited programs, namely priority review, accelerated approval, fast track and breakthrough therapy designation (BTD). These programs can, for example, shorten the time necessary to review an application (priority review) or enable the approval of a drug based on the outcome of a surrogate endpoint (accelerated approval) [2]. In 2012, the FDA launched the BTD program. BTD drugs are "intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies" [3]. Features of this program include guidance on drug development and action to accelerate the review [2]. In 2016, the European Medicines Agency (EMA) launched the PRIority MEdicines (PRIME) scheme [4], which bears a resemblance to the BTD program.

Recently, the BTD program has been criticised. Darrow et al. implied that the efficacy of BTD drugs was 'modest', questioning whether this program can live up to its expectations [5]. They also showed that a considerable amount of BTD drugs were approved for the treatment of patients with cancer. In another study, the treatment effect of numerous BTD oncology drugs were investigated, and it was stated that no significant difference in treatment effect (gain in response rate/progression-free survival) was observed between BTD drugs and non-BTD oncology drugs [6].

Yet, determining the clinical benefit of a drug is not always straightforward, and a couple of aspects should be taken into account, such as treatment effect, surrogate endpoints and quality

of life. Few instruments have been developed to evaluate the clinical benefit of oncology drugs, including the European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS). The ESMO-MCBS is a validated instrument for grading the magnitude of clinical benefit for drugs indicated for the treatment of patients with solid tumours. It takes into account the benefits of a drug (e.g., improvement in survival or quality of life) as well as the risks (e.g., treatment toxicity) [7]. Comparable to the ESMO-MCBS, the American Society of Clinical Oncology (ASCO) also developed a valid, reliable and unbiased instrument to evaluate the clinical benefit of oncology drugs, namely the ASCO Value Framework. Although scores of the ESMO-MCBS and ASCO Value Framework are not completely interchangeable, a recent publication found that the correlation coefficient was 0.68, indicating at least a moderate association between the scores from both instruments [8]. Our study was performed to determine whether BTD oncology drugs were truly a breakthrough based on the outcome of the ESMO-MCBS. The outcome would enable us to determine whether the criticism towards the BTD is justified. Furthermore, experiences from the BTD program might also be of value to comparable programs of other regulatory agencies.

BTD oncology drugs and their clinical benefit

The Center for Drug Evaluation and Research Breakthrough Therapy Approvals reports published by the FDA provided an overview of all BTD drugs approved between 1 November 2013 and September 2018. At the time of data collection, there were 120 approvals, including 71 approvals for oncology drugs. As we were interested in the clinical benefit of drugs the first time they were introduced to the market and because the ESMO-MCBS is developed for solid tumours only, we focused on original approvals for BTD drugs indicated for the treatment of patients with solid tumours. After excluding supplements to new drug approvals and approvals for haemato-oncology drugs, a total of 18 original approvals remained (**Supplementary Table 1**). **Figure 1** shows the BTD drugs separated by indication. Most represented indications were skin cancer (n=4), lung cancer (n=4) and breast cancer (n=3).

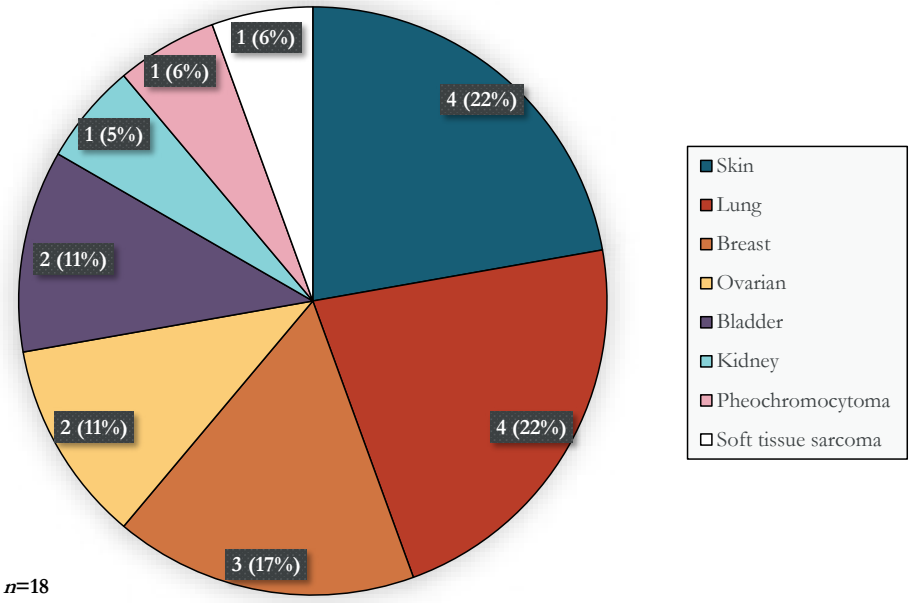

Figure 1. Breakthrough therapy designation oncology drugs separated by indication. Drugs were approved between 2013 and 2018 (original approvals only).

The clinical benefit of novel oncology drugs is mostly expressed as an improvement in survival and/or quality of life [7]. However, in reality, when the outcome of a surrogate endpoint suggests extraordinarily clinical benefit, earlier and faster approval might be warranted. This is particularly the case when the drug addresses an unmet medical need. Inherent with this demand, all applications for BTD oncology drugs were reviewed faster because of priority review (**Supplementary Table 2**). Moreover, 12 out of 18 approvals were supported by data from Phase II clinical trials, many with response rate as the primary endpoint (**Supplementary Table 3**). This carries certain risks for the predictability of the impact of novel oncology drugs in real life, such as the correlation between surrogate endpoints and clinically relevant endpoints such as overall survival. Only four approvals were supported by data from Phase III clinical trials, the gold standard for investigating the efficacy and safety of a drug.

After identifying all approved BTD oncology drugs, the next step was to assign the ESMO-MCBS scores to the clinical trials investigating these drugs. For each drug the most representative clinical trial was identified in PubMed. Confirmatory clinical trials were preferred, even if those clinical trials did not support the approval. Clinical trial results were published for all drugs except iobenguane I131. ESMO-MCBS scores were assigned to clinical trials according to ESMO instructions [9]. ESMO-MCBS scores A or B (curative therapies) and 4 or 5 (non-curative therapies) correspond to a substantial improvement in clinical benefit (i.e., high level of clinical benefit) [7]. For context, the ASCO Value Framework Net Health Benefit

(NHB) scores ≥45 correspond to ESMO-MCBS score 4 or 5 [8]. The ASCO Value Framework NHB scores that correspond to ESMO-MCBS score A or B have not yet been determined. BTD drugs are expected to show substantial improvement over existing drugs, once approved. Therefore, we assume that a drug is more likely a breakthrough when the clinical trial has been assigned a high ESMO-MCBS score [scores A or B (curative therapies) and 4 or 5 (non-curative therapies)]. The ESMO-MCBS scores could be assigned to 14 clinical trials (either by us or already assigned and published by ESMO). Unfortunately, the ESMO-MCBS scores could not be determined for the clinical trials investigating nivolumab, atezolizumab and durvalumab, because the primary endpoint was not met (nivolumab and atezolizumab) or there were insufficient data available to assign a score (durvalumab) [10, 11, 12]. According to ESMO-MCBS instructions, a Phase III clinical trial should show statistically significant improvement in the primary endpoint to be evaluated [9]. Of all evaluable clinical trials, only five were assigned a high ESMO-MCBS score, namely those investigating alectinib, ceritinib, olaratumab, osimertinib and pembrolizumab (in melanoma) (**Figure 2**, **Supplementary Tables 4** and **Supplementary Table 5**). The remaining clinical trials were assigned a low ESMO-MCBS score, indicating that many drugs did not show a substantial improvement in clinical benefit and, consequently, were less likely a breakthrough. Based on these results, it might be concluded that the success rate of the BTD is somewhat low.

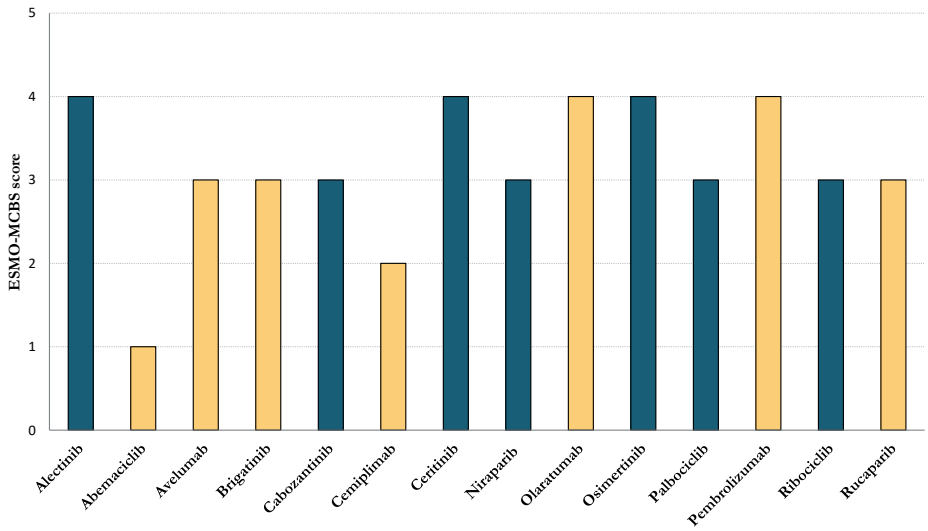

Figure 2. European Society for Medical Oncology(ESMO)-magnitude of clinical benefit scale (MCBS) scores assigned to clinical trials investigating breakthrough therapy designation oncology drugs. A score of 4 or 5 (non-curative therapies) corresponds to a substantial improvement in clinical benefit. ESMO-MCBS scores assigned to Phase II clinical trials (single-arm or randomised) are shown in yellow. ESMO-MCBS scores assigned to Phase III clinical trials are shown in dark blue. The ESMO-MCBS scores for clinical trials investigating alectinib, cabozantinib, ceritinib, niraparib, olaratumab, palbociclib, pembrolizumab, and ribociclib were published by ESMO [9,13,22]. The remaining ESMO-MCBS scores were assigned by the authors.

Hurdles in determining clinical benefit and assigning the ESMO-MCBS scores

Determining which drug is likely a breakthrough may not always straightforward due to the uncertainties related to, for example, the level of evidence available. In general, a Phase III clinical trial is considered one of the more reliable data sources to determine the clinical benefit of a drug. However, as mentioned earlier, many approvals for BTD oncology drugs were supported by data from Phase II clinical trials. There remains a chance that the clinical benefit observed in the confirmatory clinical trial does not correspond to that observed in the earlier stage clinical trials. Hwang et al. also discussed this issue, and mentioned that atezolizumab did not show an improvement in overall survival compared with chemotherapy in the confirmatory clinical trial, while showing promising antitumour activity in the earlier conducted Phase II clinical trial [6]. Atezolizumab was not the only BTD drug for which the primary endpoint of the confirmatory clinical trial was not met. The Phase II clinical trial investigating olaratumab in soft-tissue sarcoma was assigned a high ESMO-MCBS score, because treatment resulted in a compelling gain in median overall survival [13, 14]. Recently, the Marketing Authorisation Holder announced that the confirmatory clinical trial did not meet the primary endpoint [15]. The above-mentioned examples illustrate the uncertainties inherent with approvals supported by data from earlier stage clinical trials, which needs to be balanced against the unmet medical need. Several other ESMO-MCBS scores shown in **Figure 2** were based on Phase II clinical trials results, namely those of abemaciclib, avelumab, brigatinib, cemiplimab, pembrolizumab and rucaparib. One might argue that the ESMO-MCBS scores assigned to Phase II clinical trials might be less reliable compared with those assigned to Phase III clinical trials. Fortunately, for alectinib, ceritinib, osimertinib and palbociclib confirmatory clinical trials results were published and the ESMO-MCBS scores were based on these results.

Another uncertainty is related to the endpoints that were studied in the clinical trials. As described earlier, the clinical benefit of novel oncology drugs is mostly expressed as an improvement in survival and/or quality of life. The clinical benefit of BTD oncology drugs was primarily based on the outcome of a surrogate endpoint, and it is not always established whether a drug might improve overall survival and/or quality of life. For instance, overall survival was a secondary endpoint in the clinical trials investigating niraparib and ribociclib, but overall survival data were not mature at the time of analysis [16, 17]. Similarly, quality of life was a secondary endpoint in only four of the 14 clinical trials that were evaluated in this study (data not shown). Important to note is that uncertainties regarding surrogate endpoints are incorporated in the ESMO-MCBS and have an influence on the maximum ESMO-MCBS score that can be assigned [7]. Nonetheless, the availability of overall survival and/or quality of life data could have a positive influence on the ESMO-MCBS score if a significant improvement is observed, and the absence of such data might be considered a disadvantage.

Not all criticism towards the BTD program is justified

Even though our results indicate that not every BTD oncology drug is likely a breakthrough, one might question whether all criticism toward the BTD is justified. There were some BTD drugs that showed substantial benefit, according to the assigned ESMO-MCBS score; hence, clinical benefit was not negligible for all BTD drugs. Besides, a couple of drugs have changed the treatment landscape. For instance, programmed death-1 receptor inhibitors (nivolumab and pembrolizumab) are the preferred first-line treatment options for patients with metastatic melanoma [18, 19]. CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) have been mentioned 'game changers', and are recommended treatment options for patients with oestrogen receptor-positive advanced breast cancer [20, 21]. All other drugs except cemiplimab, durvalumab and iobenguane I-131 are incorporated in ESMO and/or National Comprehensive Cancer Network (NCCN) clinical practice guidelines. For example, alectinib, ceritinib and osimertinib are recommended treatment options for patients with advanced non-small cell lung cancer, depending on the presence of predictive biomarkers [22, 23]. Poly (ADP-ribose) polymerase inhibitors are recommended as maintenance therapy in patients with platinum-sensitive ovarian cancer [24]. The fact that these drugs are recommended in clinical guidelines does not necessarily mean they are breakthroughs, but these examples show their relevance in the current therapeutic landscape and might justify their earlier approval.

Room for improvement for the breakthrough therapy program

It is acknowledged that 'breakthrough therapy' is a powerful label, which can influence the expectations of physicians and patients regarding the clinical benefit of these drugs [5, 6]. Hence, drugs that are granted BTD should indeed show clinically relevant benefit, once approved. Given that not all drugs showed a substantial improvement over existing therapies, it appears that there is still some room for improvement. Several ideas to improve BTD program have already been discussed in literature. For instance, it was stated that the eligibility criteria for the BTD program are not stringent enough, and that the bar should be raised [6].

Based on Medical Reviews it appears that BTDs were often granted based on response rate (or progression-free survival) data. Unfortunately, predicting clinical benefit based on the outcome of surrogate markers remains difficult. For instance, DiMagno et al. stated that response rate might not always correlate with an improvement in survival or quality of life [25]. In a recent study, the clinical benefit of oncology drugs that received accelerated approval was assessed, and the authors stressed the importance of validated surrogate endpoints [26]. A better understanding of surrogate endpoints and biomarkers for the prediction of clinical benefit could be key in the identification of drugs that have high potential to provide a breakthrough in the treatment of certain types of cancer. Efforts to this end could increase the success rate of the FDA BTD program. This is not only important for the BTD, but could also be applicable to comparable programs initiated by other regulatory agencies, such as the PRIME scheme of the EMA. In 2018, the first two PRIME designated drugs were approved by the European Commission

[27]. Given that the PRIME scheme was launched several years later than the BTD, experience with this program is not as extensive as with the BTD, and a comparison cannot be made.

In our study, we assigned an ESMO-MCBS score after the drug was already approved. However, one might question whether instruments that evaluate the clinical benefit of oncology drugs can be helpful tools in the approval process of a drug. Hypothetically, ESMO-MCBS scores could be used to further substantiate certain regulatory decisions, and might even be useful in assessing whether a particular designation, such as the BTD, can be maintained. Nevertheless, the decision for granting marketing authorisation is based on a thorough benefit–risk assessment, in which regulators take into account several aspects, such as quality, methodology, efficacy, safety and regulatory precedents. A benefit–risk assessment can be challenging, especially for drugs that have been granted BTD or PRIME scheme. These submissions are often supported by limited data, while there is a high unmet medical need. For instance, the pivotal trial supporting a submission might not be assigned a high ESMO-MCBS score (e.g., limited data or use of surrogate endpoints), while it still could be considered promising till confirmatory clinical trials suggest otherwise. Hence, further research is necessary to determine the role of these instruments in the regulatory process.

Concluding remarks

Based on our findings, it could be concluded that the success rate of the BTD program is lower than anticipated, given the few clinical trials that were assigned a high ESMO-MCBS score. Our findings partly confirm results from earlier publications, indicating that the clinical benefit of BTD drugs might not be as compelling as the name of the designation would suggest [5, 6]. However, the determination of clinical benefit is not always straightforward. Moreover, numerous BTD drugs are recommended in treatment guidelines, showing their relevance in the current therapeutic landscape. Besides, some of the BTD drugs did show substantial benefit, and a few have even been called 'game changers'. Therefore, it can be questioned whether all criticism towards the BTD program is justified.

Considering the remaining unmet medical need for patients with cancer, we believe that programs for fast drug approval do have a place in the current regulatory practices. Programs such as the BTD can be appropriate tools to enable earlier approval of promising drugs; hence, the necessary efforts for their improvement should be further explored. A better understanding of surrogate endpoints and biomarkers for the prediction of clinical benefit could be key in the identification of drugs that have high potential to provide a breakthrough in the treatment of certain types of cancer.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of the EMA or one of its committees, working parties, or any of the national agencies.

Conflicts of interest

J.H.M.S. is patent holder on oral taxanes and shareholder and part-time employee of Modra Pharmaceuticals BV.

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Supplementary material

Supplementary Table 1. Name of the drug and therapeutic indication of oncology drugs granted breakthrough therapy designation approved by the Food and Drug Administration till September 2018.

Drug	Therapeutic indication
Abemaciclib	Treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
Alectinib	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib
Atezolizumab	Treatment of locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Avelumab	Treatment of adults and paediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC)
Brigatinib	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Cabozantinib	Treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy
Cemiplimab-rwlc	Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation
Ceritinib	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Durvalumab	Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Iobenguane I-131	Treatment of adult and paediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy
Niraparib	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
Nivolumab	Treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
Olaratumab	Treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype, in combination with doxorubicin, for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery

Supplementary Table 1. Continued

Drug	Therapeutic indication
Osimertinib	Treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small cell lung cancer (NSCLC), as detected by an FDA approved test, who have progressed on or after EGFR TKI therapy
Palbociclib	Treatment of postmenopausal women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease
Pembrolizumab	Treatment of patients with unresectable or metastatic melanoma & disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
Ribociclib	Treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine-based therapy
Rucaparib	Treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies

Supplementary Table 2. Overview of Food and Drug Administration's expedited programs. Programs facilitating earlier availability are accelerated approval, priority review, fast-track and breakthrough therapy.

Drug	Accelerated approval	Priority review	Fast-track	Breakthrough Therapy
Abemaciclib	No	Yes	Yes	Yes
Alectinib	Yes	Yes	No	Yes
Atezolizumab	Yes	Yes	No	Yes
Avelumab	Yes	Yes	Yes	Yes
Brigatinib	Yes	Yes	No	Yes
Cabozantinib	No	Yes	Yes	Yes
Cemiplimab-rwlc	No	Yes	No	Yes
Ceritinib	Yes	Yes	No	Yes
Durvalumab	Yes	Yes	No	Yes
Iobenguane I-131	No	Yes	Yes	Yes
Niraparib	No	Yes	Yes	Yes
Nivolumab	Yes	Yes	Yes	Yes
Olaratumab	Yes	Yes	Yes	Yes
Osimertinib	Yes	Yes	No	Yes
Palbociclib	Yes	Yes	No	Yes
Pembrolizumab	Yes	Yes	No	Yes
Ribociclib	No	Yes	No	Yes
Rucaparib	Yes	Yes	No	Yes

Supplementary Table 3. Pivotal trial(s) supporting the approval of breakthrough therapy designated drugs.

Drug	Name of trial	Phase of trial	Primary endpoint
Abemaciclib	I3Y-MC-JPBL (MONARCH 1)	Phase II trial (single-arm)	Objective response rate
Alectinib	NP28761, NP28673	Phase I/II trial (single-arm), Phase I/II trial (single arm)	Objective response rate, objective response rate
Atezolizumab	GO 29293 (IMVIGOR 210)	Phase II trial (single-arm)	Objective response rate
Avelumab	EMR 100070-003	Phase II trial (single-arm)	Best overall response
Brigatinib	AP26113-13-201 (ALTA)	Phase II trial (randomised, dose-comparative)	Objective response rate
Cabozantinib	XL184-308	Phase III trial (randomised, controlled)	Progression-free survival
Cemiplimab-rwlc	R2810 ONC-1540	Phase II trial (single-arm)	Overall response rate
Ceritinib	CLDK378X2101	Phase I trial (single-arm)	Overall response rate
Durvalumab	CD-ONMEDI4736-1108	Phase I/II trial (single-arm)	Objective response rate
Iobenguane I-131	MIP-IB12B	Phase II trial (single-arm)	Proportion of patients who received at least one therapeutic dose with a reduction (including discontinuation) of all antihypertensive medications by at least 50% for at least six months, beginning during the 12- month efficacy phase.
Niraparib	PR-30-5011-C (NOVA)	Phase III trial (randomised, controlled)	Progression-free survival
Nivolumab	CA209037 (CheckMate 037)	Phase III trial (randomised, controlled)	Overall response rate and overall survival
Olaratumab	15B-IE-JGDG	Phase II trial (randomised, controlled)	Progression-free survival
Osimertinib	D5160C00001 (AURA Extension), D5160C00002 (AURA2)	Phase I/II trial (single arm), Phase II trial	Objective response rate, objective response rate
Palbociclib	A5481003 (PALOMA-1)	Phase I/II trial (randomised, controlled)	Progression-free survival
Pembrolizumab	P001	Phase I trial (randomised, dose-comparative)	Overall response rate
Ribociclib	CLEE011A2301 (MONALEESA-2)	Phase III trial (randomised, controlled)	Progression-free survival
Rucaparib	CO-338-010 (Study 10) , CO-338-017 (ARIEL2)	Phase I/II trial (single-arm), Phase II trial (single-arm)	Objective response rate, progression-free survival (part 1) and objective response rate (part 2

Supplementary Table 4. The ESMO-MCBS score for oncology drugs granted breakthrough therapy designation determined by the ESMO (source: ESMO Clinical Practice Guidelines and ESMO-MCBS v1.1).

Drug	Trial	Setting	ESMO-MCBS (v1.1) score	Reference
Alectinib	ALUR	ALK+ advanced NSCLC pre-treated with platinum-based doublet chemotherapy and crizotinib	4	[1, 2]
Cabozantinib	METEOR	Advanced RCC who had progressed after VEGFR-targeted therapy.	3	[3, 4]
Ceritinib	ASCEND-5	ALK+ advanced NCSLC who had previously received platinum-based doublet chemotherapy and crizotinib	4	[1, 5]
Niraparib	NOVA	Ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histologic features who had shown sensitivity to platinum-based treatment and had received at least two such regimens.	3 (gBRCA cohort/ HRD-positive cohort/ non-gBRCA cohort)	[3, 6]
Olaratumab	I5B-IE-JGDG	Advanced STS not previously treated with an anthracycline	4	[7, 8]
Osimertinib	AURA3	T790M+ advanced NSCLC cancer who had progressed after first-line EGFR-TKI therapy	4	[3, 9]
Palbociclib	PALOMA-2	ER+, HER2- advanced breast cancer who had not received prior treatment	3	[3, 10]
Pembrolizumab	KEYNOTE-002	Advanced melanoma who had progressed after ipilimumab and, if $BRAF^{V600}$ mutant-positive, a BRAF inhibitor	4	[3, 11]
Ribociclib (in combination with letrozole)	MONALEESA-2	HR+, HER2- advanced breast cancer who had not received previous systemic therapy for advanced disease	3	[3, 12]

Abbreviations: ALK+= anaplastic lymphoma kinase-positive, EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor, ESMO-MCBS= European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, gBRCA= germline BRCA, HER2- = human epidermal growth factor receptor 2-negative, HR+= hormone receptor-positive , HRD= homologous recombination deficiency, NSCLC= non-small cell lung cancer, RCC= renal-cell carcinoma, STS = soft-tissue sarcoma, T790M= p.Thr790Met point mutation-positive, UC= urothelial carcinoma, VEGFR= vascular endothelial growth factor receptor

Supplementary Table 5. ESMO-MCBS score for oncology drugs granted breakthrough therapy designation (single-arm trials, ESMO-MCBS form 3).

Drug	Setting	Trial	Stratification	ORR	DoR	PFS	Survival	Toxicity	QoL	ESMO-MCBS (v1.1) score	Reference
Abemaciclib	HR+, HER2- metastatic breast cancer who had progressed on or after prior endocrine therapy and had 1 or 2 chemotherapy regimens in the metastatic setting	MONARCH 1		19.7% (95% CI: 13.3 - 27.5)	8.6 months (95% CI: 5.8 - 10.2)					1	[13]
Avelumab	Metastatic MCC who had progressed after at least one previous line of chemotherapy for metastatic disease.	JAVELIN Merkel 200		33% (95% CI: 23.3 - 43.8%)	NR (95% CI: 18.0 - NR)					3	[14]
Brigatinib	ALK+ advanced NSCLC who had progressed after crizotinib (180 mg with 7-day lead-in at 90 mg)	ALTA		54% (97.5% CI: 43% - 65%)	11.1 months (95% CI: 9.2 - 13.8)				Not convincingly improved.	3	[15]
Cemiplimab	Metastatic cutaneous squamous-cell carcinoma			47% (95% CI:34 - 61)	NR					2	[16]
Rucaparib	High-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma and had received at least one previous platinum therapy	ARIEL2	BRCA mutant			12.8 months (95% CI:9.0 - 14.7)				3	[17]

Abbreviations: ≥2L= second-line or greater post-platinum, ALK+= anaplastic lymphoma kinase-positive, CI= confidence interval, DoR= duration of response, HER2-= human epidermal growth factor receptor 2-negative, HR+= hormone receptor-positive, MCC= merkel cell carcinoma, NE= not evaluable, NR= not reached, NSCLC= non-small cell lung cancer, ORR= objective response rate, PFS= progression-free survival, QoL= quality of life

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Part 2

Marketing authorisations and variations: pivotal trials included in applications submitted to the Agency

Chapter 4

Single-arm trials supporting the approval of anticancer medicinal products in the European Union: contextualisation of trial results and likelihood of clinical benefit.

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Manuscript submitted

Abstract

Sometimes, single-arm trials (SATs) can be used to support marketing authorisation of anticancer medicinal products in the European Union. The level and durability of antitumour activity of the product as well as context are important aspects to determine the relevance of trial results. The aim of this study was to provide detail on the contextualisation of trial results and to evaluate the magnitude of benefit of medicinal products approved based on SATs. We focused on anticancer medicinal products for solid tumours approved on the basis of SAT results (2012 - 2021). Data was retrieved from European Public Assessment Reports and/or published literature. The benefit of these medicinal products was evaluated via the European Society for Medical Oncology (ESMO) - magnitude of clinical benefit scale (MCBS). Eighteen medicinal products were approved based on one or more SATs. For the majority of clinical trials a clinically relevant treatment effect was (pre)specified (67%) and most often an accompanying sample size calculation was provided. For nine studies, each testing a different medicinal product, a justification for the threshold for a clinically relevant treatment effect could be identified. At least 12 applicants included information to facilitate the contextualisation of trial results, including six supportive studies. Of the pivotal SATs analysed (n=21) in our analysis, three were assigned an ESMO-MCBS score of 4, which corresponds to "substantial" benefit. The clinical relevance of the treatment effects of medicinal products tested in SATs depends on the effect size and context. To facilitate regulatory decision-making, optimising these aspects will be of importance, as our results indicate that there is room for improvement. Hence, prespecifying and motivating a clinically relevant effect, and aligning the sample size to that effect is important. External controls may facilitate in the contextualisation process, but the associated limitations must be addressed.

Introduction

Randomised-controlled trials (RCTs) are referred to as the "gold standard" in testing medicinal products [1]. These trials have several advantages over clinical trials with other designs due to their design features. For example, randomisation ensures that subjects in the experimental and control group are similar at baseline. Randomisation and blinding are useful techniques to determine if there is a cause-effect relation between treatment and outcome [2, 3]. RCTs are the preferred trials to be included in applications for marketing authorisation as laid down in Directive 2001/83/EC. In this Directive, it is stated that clinical trials relevant to the indication "shall be done as 'controlled clinical trials' if possible, randomised; any other design shall be justified" [4]. Yet, it is not always possible to conduct a RCT, and consequently clinical trials with other designs need to be considered for registrational purposes [5]. The latter includes the use of single-arm trials (SATs).

Tenhunen et al. identified that, between 2010 and 2019, the European Commission (EC) approved 22 medicinal products for the treatment of solid tumours or haematological malignancies on the basis of SAT results [6]. Many of the medicinal products included in their study received "conditional marketing authorisation" (CMA) [6]. This type of approval has been introduced to address an unmet medical need, and is based on less complete data than is usually required for standard approval [7]. It should be mentioned, however, that SATs can also support standard approvals – albeit less common. Examples are the approvals of engineered autologous T-cell immunotherapies [8, 9]. Despite the regulatory precedents, demonstrating that an investigational medicinal product provides benefit can be challenging when tested in a SAT solely. Trials like these are associated with different forms of bias, including selection bias [10,11]. Besides, surrogate endpoints such as objective response rate (ORR) are commonly used in SATs, at least when focusing on cancer research [12, 13]. Objective response rate is not a direct measure of clinical benefit, but it is a measure of (antitumour) activity as spontaneous regression occurs infrequently in cancer [13].

Some guidance exists on the use of SATs for regulatory purposes. It is stated in the "guideline on the clinical evaluation of anticancer medicinal products" of the European Medicines Agency (EMA) that resorting to a non-randomised design should be justified by, among others, a large treatment effect on ORR and duration of response (DoR); that is, effects that will likely translate into clinical benefit [5]. Moreover, in the same guideline, it is stated that contextualisation of results is an important topic for SATs, particularly for less evident cases [5]. Indirect comparisons with available therapies are often made for these purposes [14, 15]. While it is not the task of regulatory agencies to ensure comparative efficacy [16], they generally need to ensure that new medicinal products are not worse – in terms of efficacy and/or safety – than standard of care. Importantly, the aspects described above (i.e. the size and durability of the treatment effect and context) will help to determine the clinical relevance of trial results.

The aim of this study was to provide detail on how the clinical benefit of anticancer medicinal products tested in SATs was determined, including the methods used to contextualise the trial results. In addition, we were interested in how many of the authorised medicinal products based on SATs showed "substantial" benefit. We started with investigating whether a threshold for the relevant treatment effect was (pre)specified in the pivotal trials, for example in a power calculation. Subsequently, we determined if applicants included additional evidence to contextualise the SAT results. Finally, by limiting this study to medicinal products for the treatment of solid tumours, we evaluated the magnitude of benefit of the medicinal products via a validated tool; the European Society for Medical Oncology (ESMO)-magnitude of clinical benefit scale (MCBS).

Methods

Medicinal products

An overview of all human medicines that were granted approval by the European Commission (EC) was retrieved from the EMA database (https://www.ema.europa.eu/en/medicines). Products were identified on the basis of their Anatomic Therapeutic Chemical codes, i.e., L01-04 for antineoplastic and immunomodulating agents. We focused on medicinal products for the treatment of solid tumours authorised between 2012 and 2021; that is, a 10 year period. The inclusion criterion for our analysis was initial approvals based on a SAT(s). Approvals based on RCTs were excluded. Approvals of generic and biosimilar products were also excluded.

Data sources

The main data source was the European Public Assessment Reports (EPARs). These reports were obtained from the EMA database. EPARs contain information on the scientific evaluation conducted by the Committee for Medicinal Products for Human Use (CHMP) – a committee of the EMA. The scientific evaluation forms the basis for the EC decision on approval. Another data source was published literature on pivotal clinical trials. Relevant publications were identified via PubMed and/or Clinicaltrials.gov.

Data collection

Data was retrieved from EPARs and/or scientific publications. We collected the following information on the main study(ies): the study design, dosing regimen, study population, planned sample size, statistical methods, primary/secondary endpoints and clinical outcomes. We also determined whether applicants made additional efforts to contextualise the results of the single-arm trial(s). This concerned analyses (e.g., within-patient analysis) and/or external evidence (e.g., publications, additional studies) that were included in the EPAR.

Determining clinical benefit

The ESMO created the ESMO-MCBS, a validated tool to evaluate the magnitude of clinical benefit [17]. The ESMO already assigned ESMO-MCBS scores to numerous clinical trials, including several SATs that supported EC approvals. We identified all SATs for which an

ESMO-MCBS score was included in scorecards and pivotal publications. We assigned an ESMO-MSCB score to the remaining SATs included in our analysis, which was done according to ESMO instructions [18]. For non-curative therapies, ESMO-MCBS scores ≥ 4 represent substantial benefit [19].

Results

Approval of medicinal products for the treatment of solid tumours

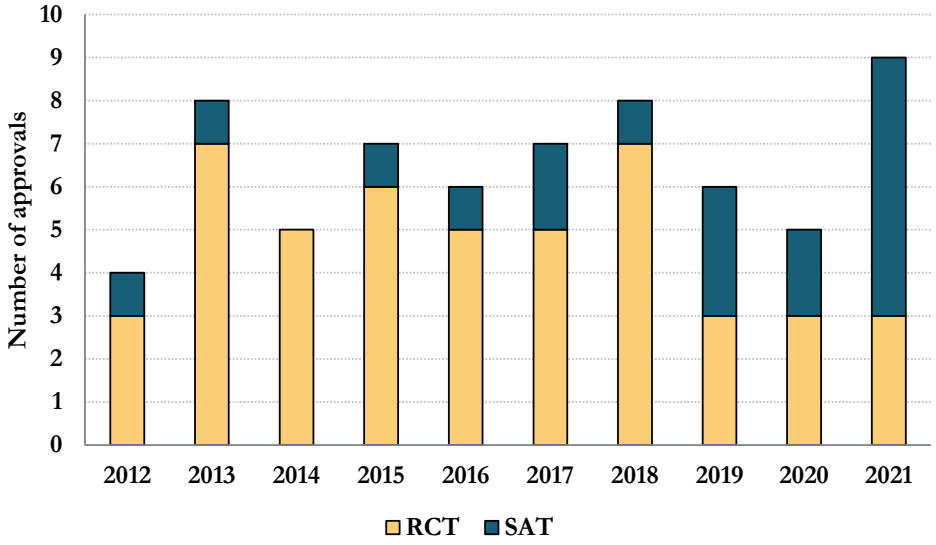

Figure 1. Number of medicinal products for the treatment for solid tumours approved by the European Commission per year. Generic and biosimilar medicinal products were excluded. In blue the number of approvals based solely on single-arm trials (SATs) and in yellow the number of approvals based on randomised-controlled trials (RCTs).

Sixty-five medicinal products for the treatment of solid tumours were granted initial approval by the EC between 2012 and 2021 – excluding generics or biosimilars. The number of approvals per year can be seen in **Figure 1**. In recent years, the proportion of approvals based on SATs increased compared to prior years. In total, 18 medicinal products were approved based on one or more SATs (**Supplementary Table 1**). The approvals of alectinib, avapritinib and crizotinib were based on SATs. However, top-line results from RCTs – albeit not always in a similar setting (e.g., different line of therapy) – were also provided during the evaluation of these products. Yet, the SATs remained the pivotal studies supporting these applications, and the three products retained in our analyses. Of the 18 medicinal products approved based on SATs, all were granted conditional marketing authorisation. Half of the approvals concerned medicinal products for the treatment of advanced non-small cell lung cancer (NCSLC). **Supplementary Table 2** shows the intended patient population for which the medicinal products were approved.

Studies and thresholds for clinically relevant treatment effect
Most approvals were supported by one pivotal trial. The approvals of entrectinib, larotrectinib, osimertinib and rucaparib were supported by two or more SATs. For the approvals of entrectinib and larotrectinib integrated analyses, created by pooling data across the trials, were used for the evaluation of efficacy. For all studies or integrated analyses the primary endpoint was ORR (**Supplementary Table 1**).

For the majority of clinical trials a clinically relevant treatment effect was (pre)specified, and most often an accompanying sample size calculation was provided (**Table 1)**. The test for a relevant effect was often defined as the lower bound of the 95% confidence interval (CI) for ORR exceeding a (predefined) value, which is equivalent to testing a null-hypothesis corresponding to that value. For the studies investigating entrectinib, larotrectinib, pemigatinib and selpercatinib a clinically relevant lower boundary of the CI for ORR was defined, but the null and alternative hypothesis was not explicitly mentioned in the EPARs/publications. For the studies testing ceritinib, crizotinib, lorlatinib, osimertinib and rucaparib no power calculations were performed. At least based on the information presented in the EPARs and/or publications. Regarding study CO-338-017, that is, one of the SATs testing rucaparib, it seems that some sample size assumptions were made for subgroup allocation (part 1 and 2) and comparison (part 1) of the study, but no calculations were made based on expected treatment effects.

For nine studies, each testing a different medicinal product, a justification for the threshold for a clinically relevant treatment effect could be extracted from EPARs/publications (**Table 1)**. Mostly, the treatment effect of available therapies was used as a benchmark (n=5). Other justifications were "consistent with the response rates seen with approved targeted therapies in genetically-defined patient populations who have progressed on prior therapies" (n=2), "limited treatment options" (n=1) and "absence of literature documenting treatment outcomes for second-line patients" (n=1).

Pralsetinib and selpercatinib were tested in studies that included patients with RET fusion-positive NCSLC who previously received platinum-based chemotherapy. The specified clinically relevant lower bound of the 95% CI for ORR was different between the two studies, namely 23% and 30%, respectively (**Table 1**). Larotrectinib and entrectinib were tested in clinical trials that included patients with NTRK gene fusion-positive tumours. The clinically relevant lower bound of the 95% CI for ORR was 30% for the integrated analysis across clinical trials supporting both approvals (**Table 1**).

Table 1. Statistical aspects of single-arm trials.

Medicinal product	Study(ies)	Therapeutic area	Available therapies in treatment setting	Sample size calculations*	Lower bound of the 95% CI for ORR considered to be clinically meaningful	Justification	Ref.
Alectinib	NP28761	Lung cancer	Chemotherapy	Yes	>35%	Not provided	[20]
	NP28673	Lung cancer	Chemotherapy	Yes	>35%	Not provided	[21]
Amivantamab	EDI1001	Lung cancer	Chemotherapy or immunotherapy	Yes	>12%	Single-agent chemotherapy as the benchmark	[22]
Avapritinib	BLU-285-1101	Sarcoma	Tyrosine kinase inhibitors	Yes	>10%	Benchmarked against available therapies	[23]
Avelumab	EMR100070-003	Skin cancer	Chemotherapy	Yes	>20%	Absence of literature documenting treatment outcomes for second-line patients	[24]
Cemiplimab	2810-ONC-1540	Skin cancer	EGFR inhibitors and/or chemotherapy	Yes	laCSCC >25%	Based on previous studies	[25]
				Yes	mCSCC >15%	Based on previous studies	[26]
Ceritinib	CLDK378X2101	Lung cancer	Chemotherapy	No	Not specified	Not applicable	[27]
Crizotinib	A8081001	Lung cancer	Chemotherapy	No	Not specified	Not applicable	[28]
Dostarlimab	4010-01-001	Endometrial cancer	Chemotherapy or bevacizumab	Yes	>20%	Expected ORR for conventional therapy	[29]

Table 1. Continued

Medicinal product	Study(ies)	Therapeutic area	Available therapies in treatment setting	Sample size calculations*	Lower bound of the 95% CI for ORR considered to be clinically meaningful	Justification	Ref.
Entrectinib	ALKA-372-001, RXDX-101-01, and RXDX-101-03	Lung cancer	Crizotinib	Yes (on precision and implicitly on power)	>50%	Observed with standard of-care ROS1 fusion-positive NSCLC treatment	[30]
		Cancer	No appropriate available therapies	Yes (on precision and implicitly on power)	>30%	Not provided	[31]
larotrectinib**	LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003	Cancer	No appropriate available therapies	Yes	>30%	Consistent with the response rates seen with approved targeted therapies in genetically-defined patient populations who have progressed on prior therapies.	[32]
Lorlatinib	B7461001	Lung cancer	(platinum-based) chemotherapy/ immunotherapy	No	Not specified	Not applicable	[33]
Osimertinib***	AURA extension	Lung cancer	(platinum-based) chemotherapy or tyrosine kinase inhibitor rechallenge	Yes (based on precision)	Not specified	Not applicable	[34]
	AURA 2		(platinum-based) chemotherapy or tyrosine kinase inhibitor rechallenge	Yes (based on precision)	Not specified	Not applicable	[35]

Table 1. Continued

Medicinal product	Study(ies)	Therapeutic area	Available therapies in treatment setting	Sample size calculations*	Lower bound of the 95% CI for ORR considered to be clinically meaningful	Justification	Ref.
Pemigatinib	INCB 54828-202	Bile duct cancer	Chemotherapy	Yes	> 15%	Proportions of patients with an objective response reported by previous studies	[36]
Pralsetinib	BLU-667-1101	Lung cancer	(platinum-based) cytotoxic chemotherapy and/or immunotherapy	Yes	>48%	Not provided	[37]
			Chemotherapy ± ramucirumab or immunotherapy	Yes	>23%	Not provided	
Rucaparib***	CO-338-010	Ovarian cancer	Chemotherapy	No	Not specified	Not applicable	[38]
	CO-338-017		Chemotherapy	No	Not specified	Not applicable	[39]
Selpercatinib	LOXO-RET-17001	Lung cancer	chemotherapy ± ramucirumab or immunotherapy	Yes	NSCLC >30%	Consistent with the response rates seen with approved targeted therapies in molecularly defined populations who failed prior therapies	[40]
		Thyroid cancer	Treatment options in these settings are limited –tyrosine kinase inhibitors rechallenge– or even lacking	Yes	MTC >20%	The limited treatment options	[41]
				No	TC Not specified	Not applicable	[41]

Table 1. Continued

Medicinal product	Study(ies)	Therapeutic area	Available therapies in treatment setting	Sample size calculations*	Lower bound of the 95% CI for ORR considered to be clinically meaningful	Justification	Ref.
Trastuzumab deruxtecan	DS8201-A-U201	Breast cancer	HER2-targeted therapy in combination with chemotherapy	Yes	20%	Not provided	[42]
Vismodegib	SHH4476g	Skin cancer	Radiation therapy or chemotherapy	Yes	mBCC >10%	Not provided	[43]
				Yes	aBCC >20%	Not provided	[43]

Abbreviations: aBCC=advanced basal cell carcinoma, CI=confidence interval, HER2= human epidermal growth factor receptor 2, laCSCC=locally advanced cutaneous squamous cell carcinoma, mBCC=metastatic basal cell carcinoma, mCSCC= metastatic cutaneous squamous cell carcinoma, MTC=medullary thyroid cancer, NSCLC=non-small-cell lung cancer, ORR=objective response rate, ROS1= c-ros oncogene 1, TC=thyroid cancer.

* Sample size calculations were based on power unless otherwise specified.

* integrated analysis were performed based on two or three studies.

** separated and integrated analysis were performed for studies AURA and AURA2.

Contextualisation

The information included for contextualisation purposes varied between applications (**Table 2** and **Table 3**). At least 12 applicants included additional information for contextualisation purposes. Six out of 18 applications included supportive studies to contextualise the SAT results (**Table 3**). One of these supportive studies concerned a bibliographic reference, namely the Dermatologic Cooperative Oncology Group (DeCOG) study. The supportive studies were of retrospective nature, and included real-world data from various sources. The objective of the supportive studies was mainly to provide detail on the treatment outcomes with available therapies. For the supportive studies included in the applications of trastuzumab deruxtecan and entrectinib, i.e., the Unicancer study and WO40977, respectively, matched populations were generated. In the latter study, a comparative analysis with a matched crizotinib arm derived from real-world data was conducted.

Table 2. information provided by applicants to contextualise single-arm trial results.

Medicinal product	Information included in the European Public Assessment Report
Avelumab	Best response on the last prior anticancer drug therapy for metastatic disease
Avapritinib	A comparison of trial versus natural history data
Crizotinib	Indirect comparison versus other treatment*
	Results to previous treatment
Dostarlimab	Best overall response from last platinum-containing prior anticancer therapy
Larotrectinib	Comparison of larotrectinib with available systemic treatment for cancer
Lorlatinib	A comparison between time to tumour progression on lorlatinib and the time to tumour progression on last treatment prior to lorlatinib
Pemigatinib	An analysis of second-line treatment
Rucaparib	Results from prospective studies in platinum-sensitive disease that included third-line treatment
Trastuzumab deruxtecan	A literature-based analysis to understand the historical context

* Data of the indirect comparison were not shown in EPAR

Table 3. Supportive study(ies) provided by applicants to further contextualise the results from the single-arm trial.

Investigation product	Study name	Design	Aim/objective	Data source	Remarks by CHMP
Amivantamab	61186372NSC100	Retrospective cohort study	To better understand the prognosis of patients with NSCLC with EGFR 20 insertion mutations and to confirm treatment utilization and outcomes with available therapies	The Advanced NSCLC Flatiron Registry electronic health record -derived deidentified database	"Comparison with submitted real-world data should be done with caution"
Avelumab	100070-Obs001	Retrospective, observational, descriptive study	Part A and B To assess objective response rate based on best overall response to the index (second line or later) chemotherapy treatment	Part A US Oncology Network outpatient medical oncology practice Part B Merkel cell carcinoma Registry	"Hence, as the data is not deemed to be robust, no clear conclusion could be drawn from the study and the data can only be considered as supportive"
Avapritinib	BLU-285-1002	A retrospective natural history study	Not specified	Three study centres	"Taking into account all the inherent limitations of indirect comparisons, the data presented is merely informative"
Cemiplimab	Dermatologic Cooperative Oncology Group (DeCOG) study	Retrospective study	Not specified	Twenty German and Austrian clinical sites	"The DeCOG analysis provides some "real world" experience in advanced CSCC in the EU, although the number of patients included in the analysis as well as information on the treatments received by patients is very limited"

Table 3. Continued

Investigation product	Study name	Design	Aim/objective	Data source	Remarks by CHMP
Entrectinib	WO40977	A retrospective non-interventional study	To bring additional evidence in support of the ROS1 NSCLC application and to compensate the lack of a direct comparative data from a randomised clinical trial	The Flatiron Health Analytic Database	"The proposed RW analysis as the only comparative evidence between entrectinib and crizotinib is not considered a robust demonstration of the superiority of entrectinib over the approved agent in ROS1 positive NSCLC ROS1 inhibitor naïve due to important limitation of the study design and real word data collection, and it is not sufficient to change the overall conclusion"
Trastuzumab deruxtecan	The Unicancer study	Not specified	To supplement the clinical data package with real-world evidence and to estimate the expected clinical benefit of other therapies with a comparable patient population	Unicancer ESME database	"So, given the identified limitations and remaining uncertainties related to the use of the Unicancer cohort, the results from this cohort cannot be considered supportive."

Abbreviations: CHMP = committee for medicinal products for human use, CSCC = cutaneous squamous cell carcinoma, DeCOG= Dermatologic Cooperative Oncology Group, EGFR= epidermal growth factor receptor, ESME = epidemiological strategy and medical economics, EU = European Union, NSCLC = non-small-cell lung cancer, RW= real-world, US = United States

Evaluating benefit

Figure 2 and **Supplementary Table 3** show the ESMO-MCBS scores for the pivotal SATs, either assigned by us or already published by ESMO. For all the SATs included in our study three SATs were assigned an ESMO-MCBS score of '4'. Fifteen SATs were assigned an ESMO-MCBS score of '3' and three SATs were assigned an ESMO-MCBS score of '2'. ESMO-MCBS scores of '4' were assigned as a result of the score upgrades for quality of life; i.e., the investigators reported improvements in quality of life.

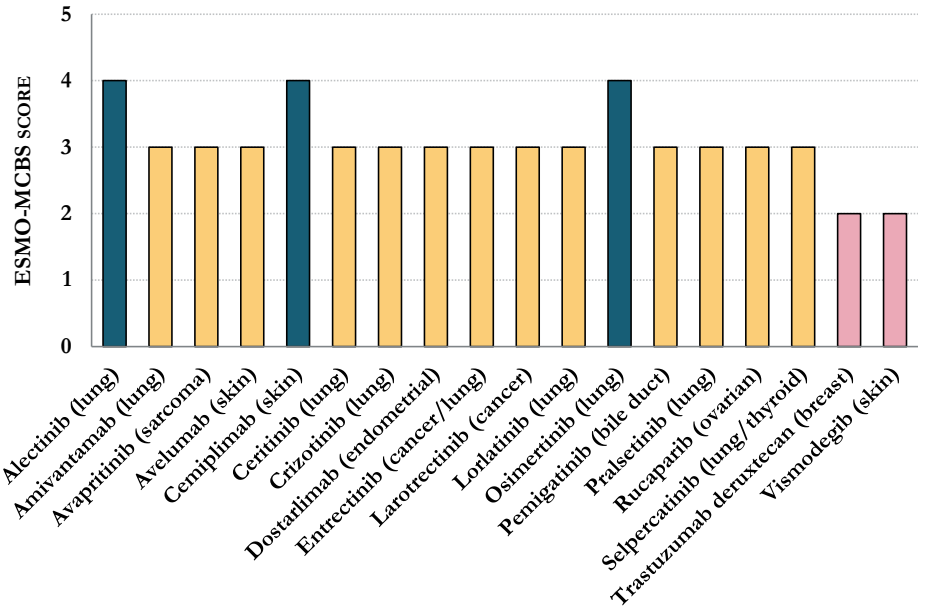

Figure 2. ESMO-MCBS scores assigned to pivotal single-arm trials. In blue the trials are depicted that were assigned a high ESMO-MCBS score. Scores were either made publicly available by the ESMO or were assigned by us. Supplementary Table 3 provides additional scoring details and reference to publications or scorecards for the scores assigned by ESMO.

Discussion

In specific situations, medicinal products may receive (expedited) regulatory approval on the basis of results from SATs. Aspects such as the antitumour activity and durability thereof as well as context are important for the evaluation of SATs, as these help to understand the trial results as meaningful. This study provides more detail on the above-mentioned aspects by analysing pivotal SAT-based applications for anticancer medicinal products in the European Union. Between 2012 and 2021, 18 medicinal products for the treatment of solid tumours received an approval based on one or more SATs. At least 12 applicants provided additional information to contextualise the results from the pivotal trials, including supportive studies, external evidence, information on response to prior therapy and a within-patient comparison.

Of all the SATs or integrated analyses supporting the 18 EC approvals, three were assigned an ESMO-MCBS score of '4'; i.e., a score indicating substantial benefit.

While SATs generally use statistical testing to determine whether the treatment effect is above a specified threshold, our results indicate that a justification for the threshold for clinical meaningful treatment effect is not always reported in the EPAR. Tenhunen et al. reported that the threshold for clinically relevant treatment effect in pivotal single-arm studies is relatively uniform (i.e., a response rate of 20%) and often not scientifically justified [6]. Our study does not confirm the observation that the relevant treatment effect is uniform, but this might also be explained by the partially different datasets. For SATs the meaningfulness of an investigational product depends on whether the null-hypothesis is rejected in favour of the alternative hypothesis, P_o and P_1, respectively[44]. The null-hypothesis can be defined based on historical data or clinical judgement, which often reflects ORR in patients treated with available treatment or standard of care[45]. Sometimes other justifications are also provided, as evident by our results. For example, the threshold for selpercatinib in NSCLC was based on consistency in treatment effects seen with approved targeted therapies in molecularly defined populations[40]. In general, it is important to select a threshold before conducting a SAT and motivate why this threshold of treatment effect constitutes a clinically relevant outcome. This is particularly relevant when other therapies are available and it is expected that this trial will be pivotal for registration.

During the process of approving a medicinal product, context may be sought via indirect comparisons with (well-)documented outcomes for clinical trials testing available therapies. We demonstrate that applicants frequently provide additional information for contextualisation purposes, including results from supportive studies. This is, for instance, carried out by using the outcomes of available therapies as benchmark. However, it seems that matched comparisons with external controls are rare, at least in our dataset. Only one comparative analysis with standard of care was performed, albeit not a 'formal' comparison. For comparisons with a (unadjusted) benchmark for standard of care, differences between study populations may lead to inappropriate comparisons [46]. There are limitations associated with cross-trial comparisons [47], which necessitate caution when interpreting these results. One approach to partly overcome these limitations is to use patient-level data to generate a matched external control [48]. Interestingly, Schröder et al. demonstrated that external controls generated from electronic health record-derived databases were successful in replicating a control arm from a RCT in metastatic colorectal cancer [49]. External controls, however, cannot be corrected for confounders that are unknown or unmeasured [49]. For instance, mechanisms by which patients are recruited in the clinical trials and in the external data source may lead to different selections. There is some regulatory guidance available to reduce potential bias with external controls [5,50]. Applicants should strive to address the limitations inherent with the use of external evidence at forehand, also considering the limitations already flagged in some EPARs for some of the medicinal products included in this study. After addressing all the limitations as much as possible, the issue remains that if there is a high likelihood for residual bias, the

outcome in a SAT has to be larger to compensate for the potential bias. Importantly, the quality of data and it being appropriate for a comparative analysis will likely determine the extent to which external controls can be used for regulatory decision-making [51].

Pignatti et al. highlighted that the definition of clinical value is different between stakeholders, which may lead to different conclusions [52]. While the CHMP concluded that the benefit of the medicinal products included in our analysis is clinically relevant, stakeholders other than regulators might appreciate benefit differently. For instance, the ESMO considers benefit as "living longer and/or living better", which resonates in the ESMO-MCBS form for SATs [17, 53]. This is evident by our results, as the benefit of the majority of products was "modest" on the basis of the ESMO-MCBS scores. Tibau et al. stated that large treatment effects in combination with an improvement in quality of life (QoL) – or data from post-marketing studies – is needed for SATs to be assigned a high ESMO-MCBS score [54]. However, QoL is not always a secondary endpoint in clinical trials [55], and one of the shortcomings of the ESMO-MCBS is that it does not take into account delayed publications or publication bias for QoL [56]. Besides, the CHMP repeatedly stated in assessment reports that no firm conclusion can be drawn from QoL data generated by SATs [57, 58, 59, 60]. Another method to evaluate the benefit of approved anticancer medicinal products is by using the PASKWIL criteria for non-randomised trials – albeit only implemented in the Netherlands [61]. A committee of the Dutch Society of Medical Oncology created the PASKWIL criteria (for non-randomised trials), for which the ESMO-MCBS was used as a basis. In comparison to the ESMO-MCBS, QoL and safety are not incorporated in the instrument, and benefit is based on predefined ORR and DoR thresholds [61]. As frameworks are created on a national level that do not completely align with the ESMO-MCBS, there might be a need to fine-tune what can be considered benefit on a European level. This will prevent potential inequality in care. Of note, there are several approaches to reduce long-term uncertainties related to the benefit-risk balance of medicinal products approved based on SATs, including some not discussed in this article; for instance, adequate post-authorisation measures.

While this study provides insights into the contextualisation process of SAT results, it is limited to SATs supporting initial approvals. While extensions of therapeutic indication(s) can be based on SATs, these approvals are not included in our analysis. For an extension of indication there is already existing knowledge on the benefits and risks of the concerned medicinal product due to the initial marketing authorisation. This might impact decision-making. It can also be considered a limitation that we restricted our research to publicly available documents. However, we assume that all information relevant to the benefit-risk assessment is incorporated in the EPARs, because it is a reflection of the core documents included in an application.

In conclusion, determining the benefit-risk balance of medicinal products tested in SATs is challenging, and benefit can be appreciated differently by various stakeholders. The clinical relevance of the treatment effects shown by medicinal products tested in SATs is dependent

on the effect size and context, especially if other therapies are available that provide benefit. Optimising these aspects will be of importance, since our results indicate that there is room for improvement. Hence, prespecifying and motivating a clinically relevant effect and aligning the sample size to that effect is of importance. External controls may facilitate in the contextualisation process, but the limitations associated with such comparisons must be (adequately) addressed. Preferably, such comparisons should be prespecified. It is of relevance that information on these aspects is presented in the EPAR as this provides transparency on regulatory decision-making towards stakeholders. Finally, it is considered of value to further discuss among stakeholders what can be considered the benefit of medicinal products investigated in SATs and when approval on the basis of lower levels of evidence is justified. This is considered of importance, as SATs will likely continue to play a role in the registration of new medicinal products.

Author disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of the EMA or one of its committees, working parties, or any of the national agencies.

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Supplementary material

Supplementary Table 1. Main study(ies) supporting the approvals.

Medicinal product	Trial	Study design	Dosage regimen	Study population	(co-) Primary endpoint	Planned sample size
Alectinib	NP28761; Phase II part of the study	A multi-centre, single arm, open-label, dose escalation, Phase I/ II study	600 mg BID, orally	Patients with ALK-rearranged Non-Small Cell Lung Cancer previously treated with crizotinib	ORR (RECIST v1.1)	85 patients
	NP28673; Phase II part of the study	An open-label, non-randomised, multicentre, Phase I/ II trial	600 mg BID, orally	Patients with Non-Small Cell Lung Cancer who have ALK mutation and who have failed crizotinib treatment.	ORR (RECIST v1.1)	130 patients
Amivantamab	EDI1001 (CHRYSALIS); Phase I, part 2 of the study	open-label, Phase I study	1050 mg (patients <80 kg), 1400 mg (patients ≥ 80 kg) Q1W (first four weeks), Q2W, intravenously	Patients with Advanced Non-Small Cell Lung Cancer	ORR (RECIST v1.1)	Total: 460 patients Cohort A: 40 patients Cohort B: 20 patients Cohort C, D, MET-1, MET-2: 100 patients per cohort
Avapritinib	BLU-285-1101 (NAVIGATOR); Phase I, part 2 of the study	An open-label, multicentre, Phase 1 study	300/400mg QD, orally	Patients with unresectable or metastatic GIST or other relapsed or refractory solid tumours.	ORR (modified RECIST v1.1)	Group 1: 100 patients Group 2: 35 patients Group 3: 50 patients
Avelumab	EMR100070-003 (JAVELIN Merkel 200)	An open-label, multicentre, Phase II study	10 mg/kg Q2W, intravenously	Patients with merkel cell carcinoma	ORR (RECIST v1.1)	84 patients
Cemiplimab	R2810-ONC-1540	A single-arm, 3-group, multicentre, Phase II study	3 mg/kg Q2W (group 1 and 2), 350 mg Q3W (group 3), intravenously	Patients with cutaneous squamous cell carcinoma	ORR (RECIST v1.1)	Group 1: 50 patients Group 2: 72 patients Group 3: 53 patients

Supplementary Table 1. Continued

Medicinal product	Trial	Study design	Dosage regimen	Study population	(co-) Primary endpoint	Planned sample size
Ceritinib	CLDK378X2101; Phase I, expansion part of the study	A multicentre, open-label, Phase I study	750 mg QD, orally	Patients with tumours characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)	ORR (RECIST v1.0)	At least 25 and up to 100 patients in each non-small cell lung cancer arm
Crizotinib	A8081001, expansion phase	An open-label, multicentre, Phase I study	250 mg	Patients with Advanced Cancer	ORR	At least 25 patients per cohort
Dostarlimab	4010-01-001(GARNET); part 2B of the study	Open-label, multi-cohort, single-arm, Phase I study	500 mg Q3W (first 4 cycles), 1,000 mg Q6W, intravenously	Patients with advanced solid tumours	ORR and DOR (RECIST v1.1)	Total: 680 patients; Cohort A1: 100 patients
Entrectinib	RXDX-101-02	Open-Label, multicentre, global, Phase II Basket Study	600 mg QD, orally	Patients with Solid Tumours that Harbour NTRK1/2/3, ROS1, OR ALK Gene Rearrangements	ORR (RECIST v1.1)	62 patients per basket (150 patients in ROS-1 basket)
Larotrectinib	LOXO-TRK-15002	A multicentre, multinational, open label Phase II "basket" study	100 mg BID, orally	Patients with Human Neurotrophic Tyrosine Kinase Receptor (NTRK) Fusion-Positive Tumours	ORR (RECIST v1.1)	226 patients
Lorlatinib	B7461001; Phase II part of the study	Multicentre, multiple-dose, dose-escalation, Phase I/II study	100 mg QD, orally	Patients With Advanced Non-Small Cell Lung Cancer Harbouring Specific Molecular Alterations	ORR (RECIST v1.1)	240 patients

Supplementary Table 1. Continued

Medicinal product	Trial	Study design	Dosage regimen	Study population	(co-) Primary endpoint	Planned sample size
	AURA; Phase II part of the study	An open-label, multicentre, Phase I/ II study	80 mg QD, orally	Patients with advanced non-small-cell lung cancer who have progressed following prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor agent	ORR (RECIST v1.1)	175 patients
Osimertinib	AURA 2	An open-label, single-arm, Phase II study	80 mg QD, orally	Patients with non-small-cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours are epidermal growth factor receptor mutation and T790M mutation positive	ORR (RECIST v1.1)	175 patients
Pemigatinib	INCB 54828-202 (FIGHT-202)	An open-Label, single-arm, multicentre Phase II study	13.5 mg QD, orally	Patients with Cholangiocarcinoma including FGFR2 translocations who failed previous therapy	ORR (RECIST v1.1)	Cohort A: 100 patients
Pralsetinib	BLU-667-1101 (ARROW); Phase II part of the study	An open-label, 2-part, Phase 1/2 study	400 mg QD, orally	Patients with thyroid cancer, NSCLC, and other advanced solid tumours	ORR (RECIST v1.1)	Group 1: 80 patients Group 2: 170 patients

Supplementary Table 1. Continued

Medicinal product	Trial	Study design	Dosage regimen	Study population	(co-) Primary endpoint	Planned sample size
Rucaparib	CO-338-010; Phase II, part 2A, of the study	An open-label, 3-part, Phase 1/2 study	600 mg BID, orally	Patients with gBRCA mutation ovarian cancer or other solid tumours	ORR (RECIST v1.1)	41 patients
	CO-338-017 (ARIEL2)	An open-label, 2-part, Phase II	600 mg BID, orally	Patients with relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer	Part 1: PFS (RECIST v1.1) Part 2: ORR (RECIST v1.1)	Part 1: 180 patients Part 2: 300 patients
Selpercatinib	LOXO-RET-17001 (LIBRETTO-001); Phase II part of the study	A multicentre, open-label, multicohort, Phase I/II study	160 mg BID, orally	Patients with solid tumours, including RET fusion-positive solid tumours, medullary thyroid cancer and other tumours with RET activation	ORR (RECIST v1.1)	Cohort 1: 55 patients Cohort 2: 59 patients Cohort 3: 83 patients Cohort 4: 55 patients
Trastuzumab deruxtecan	DS8201-A-U201 (Destiny-Breast 01)	An open-label, multicentre, 2-part, Phase II study	5.4 mg/kg Q3W, 6.4 mg/kg Q3W, 7.4 mg/kg Q3W (part 1), 5.4 mg/kg Q3W (part 2), intravenously	Patients with HER2-positive breast cancer previously treated with T-DM1	ORR (RECIST v1.1)	230 patients
vismodegib	SHH4476g	A multicentre, single-arm, two-cohort, Phase II study	150 mg QD, orally	Patients with Advanced Basal Cell Carcinoma	ORR	100 patients

Abbreviations: ALK = anaplastic lymphoma kinase, BID = twice daily, DLT= dose-limiting toxicity, DOR = duration of response, FGFR2= Fibroblast Growth Factor Receptor 2, HER2 = human epidermal growth factor receptor 2, MTD = maximum tolerated dose, NTRK = Neurotrophic Tyrosine Receptor Kinase, ORR = objective response rate , PFS=Progression-free survival ,QD= once daily, Q1W= once every week, Q2W = once every two weeks, Q3W = once every three weeks, RECIST = response evaluation criteria in solid tumours, RET = rearranged during transfection, ROS1 = Proto-oncogen tyrosine-protein kinase 1, RP2D = recommended phase 2 dose, T-DM1 = trastuzumab emtansine

Supplementary Table 2. Medicinal products and their intended use.

Medicinal product	Indication
Alectinib	Alecensa as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib
Amivantamab	Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy
Avapritinib	AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation
Avelumab	Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC
Cemiplimab	Libtayo as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation
Ceritinib	Zykadia is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib
Crizotinib	XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
Dostarlimab	Jemperli is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen
Entrectinib	Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have not received a prior NTRK inhibitor - who have no satisfactory treatment options (see sections 4.4 and 5.1) Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors
Larotrectinib	Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have no satisfactory treatment options (see sections 4.4 and 5.1)

Supplementary Table 2. Continued

Medicinal product	Indication
Lorlatinib	Lorlatinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after: - alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or - crizotinib and at least one other ALK TKI
Osimertinib	Tagrisso is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)
Pemigatinib	Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy
Pralsetinib	Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor
Rucaparib	Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy
Selpercatinib	Retsevmo as monotherapy is indicated for the treatment of adults with: - advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy - advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib
Trastuzumab deruxtecan	Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti HER2 based regimens.
vismodegib	Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma, - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

Supplementary Table 3. Single-arm studies scored using form 3.

Medicinal product	Therapeutic area	Trial name	ORR	DoR	Toxicity	QoL	ESMO-MCBS	Ref./hyperlink
Alectinib	Lung cancer	NP28761	48%	13.5 months	-	Improved	4	[1]
Alectinib	Lung cancer	NP28673	49%	11.2 months	-	-	3	[2]
Amivantamab	Lung cancer	CHRYSALIS	40%	11.1 months	-	-	3	[3]
Avapritinib	Sarcoma	NAVIGATOR	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-211-1
Avelumab	Skin cancer	JAVELIN Merkel 200	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-248-1
Cemiplimab	Skin cancer	R2810-ONC-1540	laCSCC 44.9% mCSCC 50.8%	laCSCC NR (95%CI: 18.4, NE) mCSCC NR (95%CI: 20.7, NE)	-	Improved	4	[4]
Ceritinib	Lung cancer	CLDK378X2101	-	-	-	-	3*	[5]
Crizotinib	Lung cancer	PROFILE 1001	-	-	-	-	3*	[2]
Dostarlimab	Endometrial cancer	GARNET	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-256-1
Entrectinib	Lung cancer/ cancer	Three Phase I/II trials	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-209-1; https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-210-1
Larotrectinib	Cancer	Three Phase I/II trials	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-143-1
Lorlatinib	Lung cancer	B7461001	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-142-1

Supplementary Table 3. Continued

Medicinal product	Therapeutic area	Trial name	ORR	DoR	Toxicity	QoL	ESMO-MCBS	Ref./hyperlink
Osimertinib	Lung cancer	AURA	-	-	-	-	3*	[2]
Osimertinib	Lung cancer	AURA2	70%	11.4 months	-	Improved	4	[6]
Pemigatinib	Bile duct cancer	FIGHT-202	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-231-1
Pralsetinib	Lung cancer	ARROW	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-293-1
Rucaparib	Ovarian cancer	CO-338-010	59.5%	7.8 months	Grade ≥3 impacting on daily well-being	-	2	[7]
Rucaparib	Ovarian cancer	ARIEL2	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-190-1
Selpercatinib	Lung cancer/ thyroid cancer	LIBRETTO-001	-	-	-	-	3*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-223-1; https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-226-1
Trastuzumab deruxtecan	Breast cancer	DESTINY-Breast01	-	-	-	-	2*	https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-164-1
Vismodegib	Skin cancer	Erivance BCC	laBCC 43% mBCC 30%	laBCC 7.6 months mBCC 7.6 months	-	-	2	[8]

* ESMO scores determined by others and published by the ESMO.

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Chapter 5

Extension of indication for authorised oncology products in the European Union: a joint effort of multiple stakeholders.

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Abstract

After marketing authorisation, the development of a medicinal product often continues with studies investigating new therapeutic indications. Positive results can lead to changes to the terms of marketing authorisation, such as an extension of therapeutic indication(s). These studies can be initiated and sponsored by the marketing authorisation holder (MAH) or others. When results from an investigator-initiated trial suggest that an authorised medicinal product is safe and effective for a new therapeutic indication, physicians may want to treat their patients with this medicinal product. In such a situation, it is desirable to extend the therapeutic indication(s) via the regulatory approval process, as this can facilitate patient access within the European Union. There may, however, be challenges when the MAH did not conduct the study and might not have access to the data. In this perspective, we focus on the possibilities to extend the therapeutic indication(s) of an already authorised medicinal product based on results from investigator-initiated trials. We address: (1) the advantages of an extension of indication; (2) the regulatory requirements for a variation application; (3) investigator-initiated trials as a basis for regulatory approval; (4) the role of the MAH in extending the indication. With this article, we want to emphasise the importance of a collaborative approach and dialogue between stakeholders with the aim to facilitate access to effective medicinal products.

Introduction

After marketing authorisation, the development of a medicinal product often continues with studies investigating new therapeutic indications. Positive results can potentially lead to changes to the terms of the marketing authorisation, such as an extension of therapeutic indication(s). Studies investigating new therapeutic indications can be initiated and sponsored by the marketing authorisation holder (MAH) or others, such as academic researchers. Studies initiated by academic researchers are referred to as "investigator-initiated studies" and can be conducted independently or via different forms of collaboration with the MAH. There are several examples of investigator-initiated studies in the area of oncology, including the Drug Rediscovery Protocol (DRUP).

The DRUP is an ongoing, national, prospective, multi-drug and pan-cancer trial sponsored by the Netherlands Cancer Institute (ClinicalTrials.gov Identifier: NCT02925234; EudraCT Number: 2015-004398-33) [1]. In the DRUP, 35 anticancer medicinal products, including those still on-patent, are used outside of the terms of their marketing authorisation to treat treatment-exhausted patients with metastatic cancer that harbour an actionable oncogenic driver [1]. van der Velden et al. reported the study design and first treatment results in 2019 [1]; in short, a two-stage design was used for each cohort. As per protocol, cohorts consisting of a tumour type, a molecular target and a matched treatment were considered successful if ≥5 out of 24 patients had either complete or partial response, or absence of disease progression for ≥16 weeks [1]. Recently, Hoes et al. presented the results of the first 500 patients, and showed that the cohort of patients with microsatellite instable (MSI) tumours treated with nivolumab and the cohort of patients with BRCA-positive tumours treated with olaparib were considered successful [2].

Nivolumab and olaparib are authorised in the European Union (EU), but not for the treatment of MSI tumours or for the treatment of BRCA-positive tumours, respectively, i.e., so-called tissue-agnostic indications. A third stage has been added to the DRUP that allows for partial reimbursement as well as confirmation of the results observed in the earlier stages of the trial [3]. The nivolumab cohort already expanded to this stage, and similar plans for olaparib are in an advanced phase. This performance-based, personalised reimbursement scheme is currently running as a pilot in the Netherlands [3]. Yet, in other EU member states, the unauthorised use of these medicinal products might not be reimbursed.

When results from an investigator-initiated trial indicate that an authorised medicinal product is safe and effective for new therapeutic indications, physicians may want to treat their patients with this medicinal product. In such a situation, it is desirable to apply for an extension of the therapeutic indication(s) via the regulatory approval process, as this can facilitate patient access within the EU. To initiate this process for (anticancer) medicinal products authorised via the centralised procedure, the MAH needs to submit a variation application to the European Medicines Agency (EMA). There may, however, be challenges when the MAH did not conduct the study and might not have access to the data. Here, the DRUP is used as an example of an

investigator-initiated trial, but it should be noted that the adequacy of the dataset to support an extension of indication has not been formally assessed by regulatory agencies.

On 23 June 2020, the Regulatory Science Network Netherlands (RSNN) held an expert meeting that focussed on "Label modification based on evidence deriving from investigator-initiated trials" [4]. During that meeting, the DRUP was used as an example and the need to extend the therapeutic indication(s) based on results from investigator-initiated trials, ownership of data and regulatory possibilities were discussed. In this article, we want to elaborate on the latter, as during the expert meeting it became clear that more information on this topic is warranted. Therefore, we consider it of relevance to further discuss the possibilities concerning the addition of a new therapeutic indication to an already authorised medicinal product based on results from investigator-initiated trials. This will become increasingly important, as the growing experiences with precision medicine, advancements in technology and use of innovative trial designs (e.g., basket and umbrella trials) contribute to more efficient development of medicinal products; especially in the field of oncology. We specifically focus on medicinal products that are still on-patent and approved via the centralised procedure, but many aspects discussed below also apply to off-patent medicinal products. This article is a collaborative approach from authors with different affiliations, since this topic concerns several stakeholders.

Advantages of an extension of the therapeutic indication

Reimbursement of off-label use depends on national health insurance legislation. In most EU member states, reimbursement is limited to approved therapeutic indication(s) [5]. Hence, when the benefit-risk balance could be considered positive, an extension of the therapeutic indication(s) is warranted. Importantly, an application for the addition of a new therapeutic indication triggers an independent assessment of the efficacy and safety data that are submitted. A new therapeutic indication will be approved only if the benefit-risk balance is considered positive by regulators. In addition, the benefit-risk balance is re-evaluated on a continuous basis, taking into account potential new safety findings in the post-marketing setting [6]. Besides, liability issues for prescribers can arise if a medicinal product causes adverse reactions when used off-label, which can be prevented by regulatory approval [5].

Regulatory requirements for a variation application

To extend the therapeutic indication(s) of a medicinal product approved via the centralised procedure, the MAH has to submit a type II variation application to the EMA [7]. A variation application concerning the addition of a new therapeutic indication shall comply to the same standard data requirements as for an initial marketing authorisation application (MAA) with regard to the evidence required to demonstrate safety and efficacy. Clinical standards and protocols in respect to the testing of medicinal products are described in detail in Annex I of the Directive 2001/83/EC [8]. With regulatory purposes in mind, data requirements would apply to any clinical trial, regardless of its sponsor.

The type of evidence necessary to demonstrate the efficacy and safety of a medicinal product are defined by EU law [9]. However, the amount of evidence that can be gathered will not always be similar. For instance, the rarity of a disease, or even the frequency of an actionable oncogenic driver, may impact the feasibility of conducting large randomised-controlled trials (RCTs). This has also been addressed in the EMA Committee for Medicinal Products for Human Use (CHMP) draft guideline on the clinical evaluation of anticancer medicinal products, which includes a section on specific designs for specific situations [10]. While RCTs are still considered the gold standard for the demonstration of efficacy and safety in a new therapeutic indication, there are examples where results from trials with alternative designs have supported a variation. For example, the extension of indication for crizotinib to include treatment of adult patients with ROS1-positive advanced non-small cell lung cancer (NSCLC) was supported by results from a single-arm trial, considering the high response rate observed and that ROS1-positive NSCLC represents a rare, serious and life-threatening distinct molecular subset [11]. The scientific evaluation of a variation application is done on a case-by-case basis, taking into account all relevant factors, including those mentioned above. Before submitting a variation application, the MAH could consider to request scientific advice from regulatory authorities to discuss the use of results from an investigator-initiated trial to support the extension of indication.

Investigator-initiated trials as a basis for regulatory approval

The MAH does not have to be the sponsor of the clinical trial to apply for an extension of indication as long as he has access to the data. For example, an extension of indication for rituximab for the treatment of adult patients with pemphigus vulgaris was supported by results from an investigator-initiated trial, and the sponsor of the clinical trial transferred all necessary data to the MAH before submission [12]. Alternatively, if the MAH does not have access to the data, bibliographic references can be used to support a variation application. The pharmaceutical legislation allows for mixed marketing authorisation applications dossiers where parts of modules 4 (non-clinical reports) and/or 5 (clinical study reports) are replaced by bibliographical references [9]. An example is the extension of the indication for arsenic trioxide in combination with all-trans-retinoic acid for first-line treatment of acute promyelocytic leukaemia [13]. In this variation, results were submitted in the form of bibliographic references, but it is noteworthy that the data included in these references were considered sufficiently detailed – allowing for a thorough scientific evaluation.

Stakeholders other than the MAH cannot submit a variation application concerning the addition of a new therapeutic indication, since they are not the owner of the marketing authorisation. The possibilities to evaluate data from investigator-initiated trials by European regulators without the involvement of the MAH have been discussed during several meetings of the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) and an ad hoc session with stakeholders in the context of the development of a framework for the repurposing of established medicines [14]. An opinion on a scientific matter can be drawn up by the EMA/CHMP at the request of the Executive Director of the Agency

or the Commission representative without the direct involvement of the MAH(s), namely via an Article 5(3) procedure of Regulation (EC) No 726/2004 [15]. However, this is an exceptional procedure in emergency situations or where there is a high public health interest on a focused scientific issue. In September 2020, the EMA endorsed the use of dexamethasone in hospitalised patients with COVID-19 based on the results from the investigator-initiated RECOVERY trial, following an Article 5(3) procedure triggered by the Executive Director of the EMA [16, 17]. The EMA published that the new use for dexamethasone can be added to the product licence upon request by a MAH [17]. Yet, following an Article 5(3) procedure, the MAH(s) would still need to submit a variation application before any changes to the terms of the marketing authorisation can be made but is not obligated to do so.

The role of the MAH in extending the therapeutic indication

As described by Rauh et al., the MAH remains a central player when considering an extension of indication [18]. Addressing the various reasons why the MAH may, or may not, want to apply for an extension of indication is outside the scope of this article, but a few reasons that might influence the preparedness of the MAH to apply for an extension of indication are discussed below. The MAH would need to prepare and submit an application, which costs time and resources, while the outcome of the assessment is uncertain. It should be noted that specific regulatory exclusivities exist in Europe to incentivise companies to invest in the development of new indications for authorised products [19]. However, several criteria need to be met for a product to be eligible for such incentives and previous research has shown that the available incentives may not be enough to stimulate the development of new indications [20, 21]. Also, the MAH may prioritise the development of other products included in its pipeline or might simply not be interested in extending the therapeutic indication(s), because the new indication is outside their therapeutic focus. In some EU countries, the pricing of the medicinal product will be renegotiated after a new therapeutic indication is added to the terms of the marketing authorisation [19]. There is a risk that the price of a medicinal product decreases following the extension of indication [22], which may represent a barrier for MAHs when considering the addition of a new therapeutic indication.

Discussion

When results from well-conducted investigator-initiated trials establish that an authorised medicinal product can be used outside the terms of the marketing authorisation, patients should be given the opportunity to be treated with such a medicinal product. Extending the therapeutic indication(s) would allow an independent assessment of the benefit-risk balance of a medicinal product in that specific indication and may facilitate reimbursement. In addition, extending the therapeutic indication(s) would decrease the gap between clinical practise and regulatory approval.

It is important to discuss among stakeholders the regulatory possibilities in case (robust) evidence on the use of a medicinal product outside the therapeutic indication(s) emerges from investigator-initiated trials, especially if there is an unmet medical need. The MAHs should not be reluctant to use results from investigator-initiated trials to support an extension of indication, as long as standard regulatory requirements are met. Therefore, early dialogue between regulators and the MAH to discuss the proposed indication and the use of results from investigator-initiated trials can be helpful; for instance, via scientific advice. In addition, the importance of scientific advice was highlighted by the Commission Expert group STAMP as a way to support academic researchers in designing pivotal clinical trials that meet regulatory standards and generate comprehensive data in the context of repurposing established medicines (23), which is of importance if the trial has not yet been initiated. It is essential to ensure that investigator-initiated trials meet the standard quality requirements such as good clinical practice, especially if these trials will be used for regulatory purposes. In the context of future revision of the pharmaceutical legislation, there is a need to consider a mechanism to evaluate results from investigator-initiated trials without the involvement of the MAH. This may stimulate MAHs to submit a variation application after a positive opinion has been issued at EU level.

In conclusion, it is possible to support an extension of indication by results from investigator-initiated trials, but regulatory requirements still need to be met. We want to emphasise the importance of a collaborative approach and dialogue between stakeholders with the aim to facilitate access to effective medicinal products. In the end, the data tell the story and should make the difference.

Author disclaimer

The views expressed in this comment are the personal views of the author(s) and may not be understood nor quoted as being made on behalf of, or reflecting the position of, their organisations.

Conflict of interest

EV initiated and led the DRUP as one of the principal investigators.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Part 3

After initial marketing authorisation: remaining issues to be addressed in the post-authorisation setting

Chapter 6

A comparison of post-marketing measures imposed by regulatory agencies to confirm the tissue-agnostic approach.

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Abstract

There are currently four anticancer medicinal products approved for a tissue-agnostic indication. This is an indication based on a common biological characteristic rather than the tissue of origin. To date, the regulatory experience with tissue-agnostic approvals is limited. Therefore, we compared decision-making aspects of the first tissue-agnostic approvals between the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA). Post-marketing measures (PMMs) related to the tissue-agnostic indication were of specific interest. The main data source was publicly available review documents. The following data were collected: submission date, approval date, clinical trials and datasets and PMMs. At the time of data collection, the FDA and PMDA approved pembrolizumab, larotrectinib and entrectinib for a tissue-agnostic indication, while the EMA approved larotrectinib and entrectinib for a tissue-agnostic indication. There were differences in analysis sets (i.e., integrated vs. non-integrated), submission dates and requests for data updates between agencies. All agencies had outstanding issues that needed to be addressed in the post-market setting. For pembrolizumab, larotrectinib and entrectinib, the number of imposed PMMs varied between one and eight, with the FDA requesting the most PMMs compared to the other two agencies. All agencies requested at least one PMM per approval to address the remaining uncertainties related to the tissue-agnostic indication. The FDA and EMA requested data from ongoing and proposed trials, while the PMDA requested data from use-result surveys. Confirmation of benefit in the post-marketing setting is an important aspect of tissue-agnostic approvals, regardless of agency. Nonetheless, each approach to confirm benefit has its inherent limitations. Post-marketing data will be essential for the regulatory and clinical decisions-making of medicinal products with a tissue-agnostic indication.

Introduction

On 23 May 2017, the Food and Drug Administration (FDA) approved for the first time a medicinal product for a tissue-agnostic indication; i.e., an indication based on a common biological characteristic rather than the tissue of origin [1]. This approval concerned pembrolizumab for the treatment of patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours. During the following years, the FDA approved three other medicinal products for a tissue-agnostic indication and pembrolizumab for an additional tissue-agnostic indication [2–5]. The European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA), as well as other agencies, also recommended approval for medicinal products for a tissue-agnostic indication. These recommendations resulted in approvals granted by the European Commission (EC) and the Japanese Ministry of Health, Labor and Welfare (MHLW), respectively.

Pembrolizumab was granted 'accelerated approval' for the treatment of MSI-H/dMMR solid tumours by the FDA [1]. Accelerated approval is based on an effect on a surrogate endpoint that is likely to predict clinical benefit [6]. For this type of approval the drug developer is obligated to provide additional data in the post-marketing setting to confirm clinical benefit. Hence, confirmatory data is expected for pembrolizumab for the above-mentioned indication. To accommodate similar cases, the EMA also established – years ago – an expeditated approval pathway comparable to that of the FDA called "conditional marketing authorisation." Conditional marketing authorisation is based on less comprehensive data than normally required [7]. Importantly, both expedited programs are developed to address an unmet medical need [6, 7].

As there are, currently, few tissue-agnostic approvals, regulatory experience is limited. The EMA and PMDA have issued guidance documents that include information on master protocol designs and the approval of medicinal products for tissue-agnostic indications [8, 9]. Another relevant document is the FDA guidance for industry on developing targeted therapies in low-frequency molecular subsets of a disease [10]. However, detailed information on data requirements for tissue-agnostic approvals or how to confirm the tissue-agnostic indication in the post-marketing setting is not available at this moment. Therefore, we believe that evaluation of the first tissue-agnostic approvals will allow to better define the requirements for this type of indication.

The main purpose of our study was to compare decision-making aspects of the first tissue-agnostic approvals between regulatory agencies. We were specifically interested in the post-marketing measures (PMMs) imposed to resolve outstanding issues related to the tissue-agnostic indication and whether these PMMs were different between regulatory agencies. Other aspects of interest were the datasets supporting each approval and the submission and approval dates. We limited our research to the founding regulatory members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; i.e., the FDA, EMA and PMDA.

Methods

Data sources

The primary data source was publicly available review documents. These included the Multi-Discipline Reviews from the FDA, the European Public Assessment Reports (EPARs) from the EMA and the Review Reports from the PMDA. Other documents used in this study were the Approval Letters from the FDA, Summary of Product Characteristics (SmPCs) from the EMA and the List of Approved Products from the PMDA. Review documents are available at the website of each respective agency: https://www.ema.europa.eu/en/medicines, https://www.accessdata.fda.gov/scripts/cder/daf/, and https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html.

Data collection

The following data were collected from the review documents: submission date, approval date, (pivotal) clinical trials, clinical datasets and PMMs. For procedures reviewed by the EMA and the PMDA, the approval date was the date the EC and MHLW granted approval, respectively. The clinical datasets were those initially included in the submission, i.e., without any updates. For the post-marketing activities the overarching term "post-marketing measures" was used. This includes the "postmarked requirements," "post-authorization measures" and "post-marketing investigations" as defined by the FDA, EMA and PMDA, respectively. The final date for data collections was 14 May 2021 and last check for tissue-agnostic approvals per agency was 1 October 2021.

Data analysis

The submission and approval dates, clinical data packages and the PMMs were descriptively compared between agencies. No statistics were used in this study.

Results

Approvals per regulatory agency

Both the FDA and MHLW approved pembrolizumab for the treatment of patients with MSI-H or dMMR solid tumours (**Figure 1**). The application was first submitted to the FDA, with a difference of 571 days between submissions. The FDA granted "accelerated approval" and the MHLW granted "partial change approval." Of note, in July 2021 an extension of indication was applied for at the EMA for pembrolizumab as monotherapy in the treatment of unresectable or metastatic MSI-H or dMMR colorectal, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy [11]. The review was ongoing at the final check for data availability. The FDA also approved pembrolizumab for the treatment of patients with Tumour Mutational Burden (TMB)-High solid tumours; i.e., a second tissue-agnostic indication for this medicinal product [12]. However, no review documents were available for this approval at the final check for data availability.

The FDA and EC approved larotrectinib for the treatment of solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion (**Figure 1**). The application was first submitted to the FDA, and the difference between submissions was 82 days. The FDA granted an "accelerated approval" and the EC granted a "conditional marketing authorisation." On 23 March 2021, the MHLW approved larotrectinib, but no review documents were available at the final check for data availability [13].

The FDA, EC and MHLW approved entrectinib for the treatment of solid tumours that have a NTRK gene fusion (**Figure 1**). The application was first submitted to the FDA, but the difference between the submission dates was small; i.e., 21 days or less. The FDA granted an "accelerated approval," the EC granted a "conditional marketing authorisation" and the MHLW granted a "new approval."

Finally, on 17 August 2021, the FDA granted an "accelerated approval" for dostarlimab for the treatment of patients with dMMR recurrent or advanced solid tumours. Since only the FDA approved dostarlimab for a tissue-agnostic indication, no comparison could be made between the three agencies. Therefore, dostarlimab was not included in our analysis.

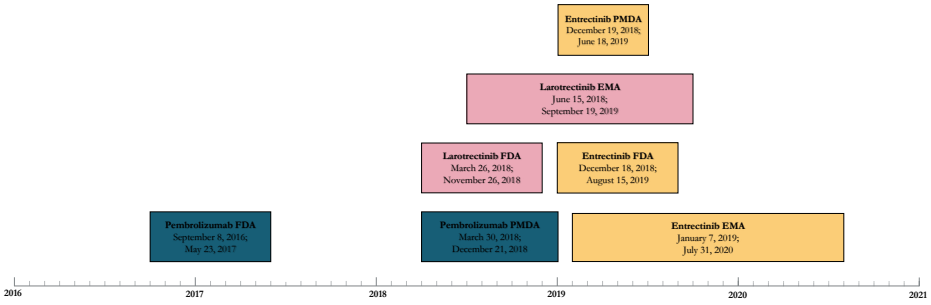

Figure 1. Review timelines for medicinal products for tissue-agnostic indications per agency (pembrolizumab in blue, larotrectinib in pink, and entrectinib in yellow). For each review, the submission date and approval data are displayed, respectively.

Clinical data supporting the submission

The FDA and PMDA approved pembrolizumab for MSI-H/dMMR solid tumours based on five and two clinical trials, respectively (**Table 1**). Data from KEYNOTE158 and KEYNOTE164 were submitted to both agencies, but different data cut-off dates were used. The most frequent tumour types included in the efficacy datasets were colorectal cancer and endometrial cancer (**Supplementary Table 1**). The application submitted to the FDA included pooled efficacy data from five clinical trials and pooled safety data from two trials (i.e., KEYNOTE016A and KEYNOTE164). The pooled efficacy population consisted of 149 patients. The primary endpoint was overall response rate (ORR). ORR was 35.6% (95% CI: 27.9, 43.8). The pooled safety population consisted of 89 patients. During the review, the FDA received updated

efficacy data from KEYNOTE158 and KEYNOTE164. The data cut-off dates for the updated efficacy data were 7 August 2016 and 23 November 2016 for KEYNOTE158 and 3 August 2016 and 23 November 2016 for KEYNOTE164. Updated safety data was also provided, but the safety review was based on the initial dataset. The application submitted to the PMDA included separately presented efficacy and safety data from KEYNOTE158 and KEYNOTE164. ORR was the primary endpoint in both studies. Response rates were 34.9% (95% CI: 24.8, 46.2) and 27.9% (95% CI: 17.1, 40.8), respectively.

The FDA and EMA approved larotrectinib for NTRK fusion-positive solid tumours on the basis of three clinical trials (**Table 2**). The most frequent tumour types included in the efficacy datasets were sarcoma and salivary gland (**Supplementary Table 1**). Both applications included pooled efficacy and safety data from the three clinical trials, but there were small differences in data cut-off dates and population sizes. The primary endpoint of the integrated analysis was ORR. The agencies focused their review on different analysis sets, which resulted in differently sized efficacy populations. The FDA focused on the primary analysis set (PAS), which consisted of the first 55 patients with NTRK fusion-positive solid tumours enrolled across the three studies. ORR was 75% (95% CI: 61, 85). The pooled safety population consisted of 144 patients from three studies. During the review, the FDA received updated efficacy and safety data. The updated clinical data cut-off date was 19 February 2018. The EMA initially focused their review on the PAS – same as the FDA – but considered the second extended PAS (ePAS2) to be the main analysis set. This analysis set consisted of 93 patients from the same clinical trials but was based on updated efficacy data. ORR in the ePAS2 was 72% (95% CI: 62, 81). The pooled safety dataset consisted of 176 patients from three studies. During the review, the EMA also received updated safety data. The updated clinical cut-off date was 30 July 2018.

Table 1. Clinical trials supporting the approval of pembrolizumab for the treatment of microsatellite instability-high/mismatch repair deficient tumours.

Name	Design	Population	Dose	Primary endpoint	FDA		PMDA	
					Number of patients	Data cut-off date	Number of patients	Data cut-off date
KEYNOTE164	Open-label, multicentre, Phase II trial	Previously treated patients with MSI-H CRC	200 mg every 3 weeks	ORR	61	3 June 2016	61	10 February 2017
KEYNOTE016A	Investigator-initiated, open label, multicentre, 2-stage, Phase II trial	Previously treated patients with MSI-H CRC	10 mg/kg every 2 weeks	ORR	28	19 February 2016	N.A.	N.A.
KEYNOTE016C	Investigator-initiated, open label, multicentre, 2-stage, Phase II trial	Previously treated patient with MSI-H non-CRC	10 mg/kg every 2 weeks	ORR	30	13 April 2016	N.A.	N.A.
KEYNOTE158	Open-label, multicentre, multi-cohort, Phase II trial	Patients with advanced solid tumours evaluated for predictive biomarkers	200 mg every 3 weeks	ORR	19	17 June 2016	94	28 April 2017
KEYNOTE012	Multicentre, multi-cohort trial	Patients with advanced solid tumours	10 mg/kg every 2 weeks	ORR	6	26 April 2016	N.A.	N.A.
KEYNOTE028	Open-label, multicentre, multi-cohort, Phase Ib trial	Patients with PD-L1 positive advanced solid tumours	10 mg/kg every 2 weeks	ORR	5	20 June 2016	N.A.	N.A.

Abbreviations: CRC=colorectal cancer, FDA= Food and Drug Administration, MSI-H=microsatellite instability-high, N.A.= not applicable, ORR=overall response rate, PD-L1=programmed cell death-1 ligand 1, PMDA = Pharmaceuticals and Medical Devices Agency

The FDA and EMA approved entrectinib for NTRK fusion-positive solid tumours on the basis of four clinical trials, while the PMDA approved entrectinib for NTRK fusion-positive solid tumours on the basis of three clinical trials (**Table 3**). The most frequent tumour types included in the efficacy datasets were sarcoma and salivary gland (**Supplementary Table 1**). The applications submitted to the FDA and EMA included pooled efficacy and safety data from these clinical trials. The primary endpoint for the integrated efficacy analysis was ORR. The FDA and EMA focused on different analysis sets, which resulted in differently sized efficacy populations. The FDA focused on the PAS, which consisted of the first 54 patients enrolled in ALKA-372-001, RXDX-101-01 and RXDX-101-02. ORR was 57.4% (95% CI: 43.2, 70.8). The pooled safety population consisted of 355 patients from four studies. Updated efficacy and safety data was submitted. The updated clinical data cut-off date was 31 October 2018. The EMA initially focused on the PAS but considered the extended PAS to be the main analysis set. This analysis set consisted of 74 patients from ALKA-372-001, RXDX-101-01 and RXDX-101-02 but was based on updated efficacy data. ORR in the extended PAS was 63.5% (95% CI: 51.5, 74.4). The pooled safety population consisted of 355 patients from four studies. During the review, the EMA also received updated safety data. The updated clinical data cut-off date was 31 October 2018. The application submitted to the PMDA included efficacy data from RXDX-101-02 and separately presented safety data from ALKA-372-001, RXDX-101-01 and RXDX-101-02. The PMDA focused on the PAS that consisted of 51 patients from study RXDX-101-02. The primary endpoint was ORR. Response rate was 56.9% (95% CI: 42.3, 70.7).

Post-marketing measures

The FDA imposed four PMMs and the PMDA imposed one PMM for pembrolizumab (**Table 4** and **Supplementary Table 2**). Both agencies imposed a PMM to address the small sample size of patients with MSI-H/dMMR solid tumours other than colorectal cancer. To resolve this issue, the FDA requested the final study reports from KEYNOTE 158 and KEYNOTE 164. In contrast, the PMDA requested a use-result survey. The FDA imposed three other PMMs, which are related to safety in paediatric patients and use of companion diagnostics. The latter was not relevant to the PMDA review, as a companion diagnostic assay was approved in Japan on 10 September 2018.

Table 2. Clinical trials supporting the approval of larotrectinib for the treatment of NTRK tumour.

Name	Design	Population	Dose	Primary endpoint	FDA		EMA	
					Number of patients	Data cut-off date	Number of patients	Data cut-off date
LOXO-TRK-14001	Open-label, multicentre, Phase I Study	Adult patients with solid tumours	50–400 mg/day QD or BID	Safety, MTD, RP2D	66	17 July 2017	70	19 February 2018
LOXO-TRK-15002	Open-label, multicentre, Phase II Basket Study	Patients 12 years of age or older with NTRK fusion advanced cancer	100 mg BID	BOR	47	17 July 2017	63	19 February 2018
LOXO-TRK-15003	Open-label, Multicentre, Phase I/II Study	Paediatric patients with advanced solid or primary central nervous system tumours	Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m2 BID (maximum of 100 mg BID)	Safety, DLT (part 1); ORR (part 2)	31	17 July 2017	43	19 February 2018

Abbreviations: BID= twice daily, BOR = best overall response, EMA = European Medicines Agency, FDA = Food and Drug Administration, MTD= maximum tolerated dose NTRK = Neurotrophic Tyrosine Receptor Kinase, ORR=overall response rate, QD= once daily, RP2D= recommended phase 2 dose.

Table 3. Clinical trials supporting the approval of entrectinib for the treatment of NTRK tumours.

Name	Design	Population	Primary endpoint	Dose	FDA	PMDA	EMA	Data cut-off date
					Number of patients			
ALKA-371-001	A dose escalation, Phase I study	Adult patients With Advanced/ Metastatic Solid Tumours	First cycle DLTs, MTD	100–1600 mg QD	57	57	57	31 May 2018
RXDX-101-01	Open-label, multicentre, Phase I study	Adult patients with Locally Advanced or Metastatic Cancer	Dose escalation part: first cycle DLTs, MTD, and a biologically effective and RP2D Dose expansion part: ORR	100-800 mg QD	76	76	76	31 May 2018
RXDX-101-02	Open-label, multicentre, global Phase II Basket Study	Patients with Locally Advanced or Metastatic Solid Tumours that Harbour NTRK1/2/3, ROS1, or ALK Gene Rearrangements	ORR	600 mg QD	206	206	206	31 May 2018
RXDX-101-03	Open-label, dose-escalation and expansion, Phase I/ Ib study	Children and Adolescents with Recurrent or Refractory Solid Tumours and Primary CNS Tumours, with or without TRK, ROS1, or ALK Fusions	MTD, RP2D	Dosing nomogram based on BSA, ranging from 250 mg/m2 to 750 mg/ m2	16	N.A.	16	31 May 2018

Abbreviations: ALK= Anaplastic Lymphoma Kinase, BSA =body surface area, EMA = European Medicines Agency, FDA = Food and Drug Administration, MTD= maximum tolerated dose N.A.= not applicable, NTRK = Neurotrophic Tyrosine Receptor Kinase, ORR=overall response rate, QD= once daily, PMDA = Pharmaceuticals and Medical Devices Agency, ROS1= Proto-oncogen tyrosine-protein kinase 1,RP2D= recommended phase 2 dose.

The FDA imposed seven PMMs and the EMA imposed three PMMs for larotrectinib. Both agencies imposed a PMM to address the small sample size of patients with NTRK fusion-positive tumours in relation to the complexity of the tissue-agnostic indication (**Table 5** and **Supplementary Table 2**). Both agencies requested a larger dataset from (ongoing) clinical trials to resolve this issue. Unique to the PMM imposed by the EMA is that it will address two additional issues; i.e., the lack of prospectively studied cohorts and secondary NTRK mutations that cause resistance to larotrectinib. In addition, both agencies imposed a PMM to address the limited safety data in paediatric patients, which resulted in comparable measures. The other PMMs were imposed by only one of the two agencies and addressed issues related to: (1) duration of response (FDA only); (2) the dose in paediatric patients (EMA only); (3) the third dosage modification (FDA only); (4) moderate CYP inhibitors/inducers (FDA only) and (5) companion diagnostics (FDA only). The underlying issues were not identified by the other agency or were not relevant for the review. The approval of a companion diagnostic was not required by the EMA, but it is indicated in the SmPC that the presence of a NTRK gene fusion in a tumour specimen should be confirmed with a validated test. The risks related to co-administration with CYP inhibitors/inducers were addressed in the SmPC of Vitrakvi. The following statement was included: "No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected."

The FDA imposed eight measures and the PMDA and EMA imposed two measures each for entrectinib (**Table 6** and **Supplementary Table 2**). All three agencies imposed a PMM to address the small sample size of patients with NTRK fusion-positive tumours in relation to the complexity of a tissue-agnostic indication. The FDA and EMA both requested an expanded dataset from ongoing clinical trials. The PMDA requested a use-result survey. The agencies also imposed, sometimes, integrated PMMs to address to the risk of fractures (FDA, EMA), growth and development issues (FDA, PMDA, and EMA), and congestive heart failure (FDA, PMDA, EMA). The other PMMs were imposed by only one of the three agencies and addressed issues related to: (1) the duration of response (FDA only); (2) off-target activity (FDA only); (3) dose in patients with hepatic impairment (FDA only); (4) companion diagnostics (FDA only) and (5) concomitant genetic mutations (EMA only). The underlying issues were not identified by the other agencies or were not relevant for the review. A companion diagnostic was already approved in Japan. The approval of a companion diagnostic was not a requirement by the EMA, but it is indicated in the SmPC that a validated assay is required for the selection of patients with NTRK gene fusion-positive solid tumours.

Table 4. Post-marketing measures for pembrolizumab for the treatment of MSI-H/dMMR tumours.

Agency	Type of measure	Short description of issue(s)	Short description of measure	Planned sample size	Due date
FDA	Accelerated approval requirements	Limited experience with treatment of patients with MSI-H/dMMR tumours other than metastatic colorectal cancer and endometrial cancer	Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of pembrolizumab in patients with MSI-H/dMMR tumours	≥124 patients (KEYNOTE164); ≥300 patients (KEYNOTE158)	March 2023
	Postmarketing requirements under 505(o)	Limited experience of pembrolizumab in children with congenital mismatch repair deficiency syndromes	Conduct a trial to determine a reasonably safe dosage regimen in children with MSI-H/dMMR primary central nervous system malignancies	Unspecified or not applicable	March 2023
	Postmarketing commitments subject to reporting requirements under section 506B	There remains uncertainty regarding the performance characteristics across all laboratories which may be performing tests for determination of MSI-H and dMMR tumour status	Commitment to support the availability of an in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with dMMR tumours	Unspecified or not applicable	June 2019
	Postmarketing commitments subject to reporting requirements under section 506B	There remains uncertainty regarding the performance characteristics across all laboratories which may be performing tests for determination of MSI-H and dMMR tumour status	Commitment to support the availability of an in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with MSI-H tumours	Unspecified or not applicable	June 2019
PMDA	Post marketing surveillance	Limited data is available as to the efficacy of pembrolizumab in the treatment of MSI-H tumours (except colorectal cancer)	A drug use-results survey to collect information on the characteristics of patients treated with pembrolizumab, to promptly collect data on the efficacy and safety of pembrolizumab, and to take necessary actions to ensure the proper use of pembrolizumab.	≥30 patients	Not specified

Abbreviations: dMMR= Mismatch repair deficient, FDA= Food and Drug Administration, MSI-H=microsatellite instability-high, PMDA = Pharmaceuticals and Medical Devices Agency

Table 5. Post-marketing measures for larotrectinib for the treatment of NTRK tumours.

Agency	Type of measure	Short description of issue(s)	Short description of measure	Planned sample size	Due date
FDA	Accelerated approval requirements	Due to the small sample size, there is an uncertainty regarding the magnitude of the treatment effect of larotrectinib in any single histologic subtype of solid tumours with an activating NTRK fusion	Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of larotrectinib	Unspecified or not applicable	August 2025
	Accelerated approval requirements	Not described/ The median DOR had not been reached as of the February 19, 2018 data cut-off date.	Submit the final report, including datasets, from the first 55 patients with NTRK fusion solid tumours to further characterize the duration of response in patients who achieved a complete or partial response to larotrectinib.	55 patients	March 2020
	Postmarketing Requirements under 505 (o)	The number of paediatric patients in the safety database was small and there are inherent limitations in interpreting longitudinal growth and development information in single arm trials	Conduct a study in paediatric patients with NTRK-fusion solid tumours to evaluate the potential serious risk of adverse long-term effects of larotrectinib on the growth and development	Unspecified or not applicable	August 2028
	Postmarketing Requirements under 505 (o)	Limited clinical experience with a third dose modification	Conduct a study in adult or paediatric patients with a body surface area of at least 1.0 m2 who experienced an adverse reaction requiring a third dosage modification of larotrectinib to better characterize the tolerability of this dosage modification	Unspecified or not applicable	August 2028
	Postmarketing Requirements under 505 (o)	The effects of moderate and weak CYP3A4 inhibitors on the PK of larotrectinib have not been studied	Conduct a physiologically-based pharmacokinetic modelling study to evaluate the effect of a moderate CYP3A4 inhibitor on the pharmacokinetics of larotrectinib	Unspecified or not applicable	September 2019
	Postmarketing commitments subject to reporting requirements under section 506B	The effects of CYP3A moderate and weak inducers on the pharmacokinetics of larotrectinib have not been studied	Conduct a physiologically-based pharmacokinetic modelling study to evaluate the effect a moderate CYP3A4 inducer on the pharmacokinetics of larotrectinib	Unspecified or not applicable	September 2019
	Postmarketing commitments subject to reporting requirements under section 506B	Several challenges remain for NTRK fusion testing	Conduct an analytical and clinical validation study that is adequate to support labelling of an in vitro diagnostic device that is essential to the safe and effective use of larotrectinib	Unspecified or not applicable	July 2021

Table 5. Continued

Agency	Type of measure	Short description of issue(s)	Short description of measure	Planned sample size	Due date
EMA	Specific Obligations	1) The small efficacy data base raises issues with regard to the representativeness in relation to the indication sought, encompassing any solid tumour type; 2) The application is lacking in prospectively studied cohorts that could provide an unbiased estimate of ORR; and 3) Secondary NTRK mutations altering the kinase domain of TRK thus appear to be a major acquired resistance mechanism to larotrectinib	In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002	200 patients (LOXO-TRK-15002 and LOXO-TRK-15003)	30 June 2024
	Specific Obligations	The long-term safety follow-up is limited and neurodevelopment in paediatric patients is a concern based on preclinical data.	In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients the MAH should submit the final report of study LOXO-TRK-15003 including 5 year follow up data	Unspecified or not applicable	31 March 2027
	Specific Obligations	There is uncertainty in the predicted exposure in the smallest children (< 6 years of age) due to few patients included in each age group	In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003	Unspecified or not applicable	30 September 2021

Abbreviations: CYP3A4= cytochrome P450 3A4, DOR= duration of response, EMA= European Medicines Agencies, FDA= Food and Drug Administration, PK= pharmacokinetics, MAH= marketing authorisation holder, NTRK= neurotrophic tyrosine receptor kinase , ORR= overall response rate

Table 6. Post-marketing measures for entrectinib for the treatment of NTRK +s.

Agency	Type of measure	Short description of issue(s)	Short description of measure	Planned sample size	Due date
FDA	Accelerated approval requirements	Not specified	Submit the final report, including datasets, from the first 54 patients with NTRK-fusion solid tumours enrolled across ALKA-372-001, RXDX-101-01, and RXDX-101-02 to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to entrectinib	54 patients	June 2021
	Accelerated approval requirements	Due to the small sample size, there is a degree of uncertainty regarding the magnitude of the treatment effect of entrectinib in any single histologic subtype of solid tumours with an activating NTRK fusion	Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of entrectinib	Unspecified or not applicable	March 2027
	Postmarketing requirments under 505(o)	Entrectinib had potential activity against other receptors that could contribute to CNS effects	Determine functional activation or inhibition of off-target receptors, transporters, and/or channels that, at concentrations of 10 μM, showed greater than 50% inhibition by entrectinib or M5 in the secondary pharmacology studies.	Unspecified or not applicable	September 2020
	Postmarketing requirments under 505(o)	Congestive heart failure events were reported in 12 (3.4%) patients, including Grade 3 (2.3%)	Submit integrated safety analyses and supporting data from patients enrolled in clinical trial(s) designed to characterize the cardiac risks and its sequelae in patients exposed to entrectinib with reasonable precision	Unspecified or not applicable	June 2022
	Postmarketing requirments under 505(o)	The small number of paediatric patients in the safety database, the limited duration of follow-up, and limitations inherent in interpreting longitudinal growth and development information in single arm trials	Conduct clinical trial(s) of entrectinib in paediatric patients 12 years of age and older with NTRK-fusion solid tumours to evaluate the potential serious risk of adverse long-term effects of entrectinib on growth and development	Unspecified or not applicable	August 2029
	Postmarketing requirments under 505(o)	Seventeen (5%) adult patients and 7 (23%) paediatric patients experienced fractures	Submit integrated safety analyses and supporting data from patients enrolled in clinical trial(s) designed to characterize the risk of fractures and its sequelae in patients exposed to entrectinib with reasonable precision	Unspecified or not applicable	March 2025

Table 6. Continued

Agency	Type of measure	Short description of issue(s)	Short description of measure	Planned sample size	Due date
EMA	Postmarketing requirments under 505(o)	There is no pharmacokinetic data to recommend entrectinib dose for patients with moderate and severe hepatic impairment.	Complete a pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function	Unspecified or not applicable	December 2021
	Postmarketing commitments subject to reporting requirements under section 506B	Several challenges remain for NTRK fusion testing	Commit to providing adequate analytical and clinical validation results from clinical trial data to support labelling of the F1CDx test to detect NTRK rearrangements for identifying patients who may benefit from entrectinib	Unspecified or not applicable	December 2019
	Specific Obligation	1) The estimates by tumour types are not robust due to the small sample sizes of individual subgroups and the limited number of tumour types; and 2) The available safety data in the paediatric setting is limited	In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from RXDX-101-02, RXDX-101-03 and any additional clinical trial conducted according to an agreed protocol	200 patients (RXDX-101-02, RXDX-101-03)	31 March 2027
	Specific Obligation	Concomitant genetic mutations occur frequently in tumours with NTRK fusion	In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue together with clinical outcomes association per tumour histology	Unspecified or not applicable	31 March 2027
PMDA	post-marketing surveillance	The safety information from patients treated with entrectinib, including Japanese patients, is limited, and the number of patients with NTRK fusion-positive, advanced/recurrent solid tumours (patients eligible for entrectinib therapy) is extremely limited	to conduct a post-marketing use-results survey covering all patients treated with entrectinib, in order to obtain information on the characteristics of patients treated with entrectinib, to promptly collect data on the safety and efficacy of entrectinib, and to take necessary measures to ensure proper use of entrectinib	200 patients	Not specified
	post-marketing surveillance	The number of paediatric patients with NTRK fusion-positive, advanced/recurrent solid tumours is extremely limited	To conduct a post-marketing use-results survey to investigate delayed growth and development in paediatric patients in clinical practice	Unspecified or not applicable	Not specified

Abbreviations: CNS= central nervous system, EMA= European Medicines Agencies, FDA= Food and Drug Administration, F1CDx= Foundation One companion diagnostic test, MAH= marketing authorisation holder, NTRK= neurotrophic tyrosine receptor kinase , PMDA= Pharmaceuticals and Medical Devices Agency

Discussion

This study was conducted to compare decision-making aspects of tissue-agnostic approvals between regulatory agencies. Specifically, we were interested in the PMMs imposed by the regulatory agencies to resolve outstanding issues related to the tissue-agnostic indication. At the time of our analysis, pembrolizumab, larotrectinib and entrectinib received regulatory approval for a tissue-agnostic indication(s) by most, or all three, regulatory agencies. Datasets supporting the approvals were generally small, especially for the two TRK inhibitors. Numerous PMMs were imposed by the agencies and these were mostly imposed to address issues related to efficacy, safety and pharmacokinetics.

There remain uncertainties concerning the treatment effect across tumour types for medicinal products for tissue-agnostic indications. Our data shows that all three agencies will receive additional data to further confirm the tissue-agnostic indication in the post-marketing setting. Larger datasets will be collected from (ongoing) clinical trials or real-world studies. These studies shall include patients with tumour types that were underrepresented in the initial datasets. However, both approaches to collect data in the post-marketing setting, meaning, clinical trials vs. real-world studies, have inherent challenges and/or limitations. For example, clinical trials may have stringent eligibility criteria, which result in limited generalisability of the study results [14]. While generalisation may be improved with real-world studies, these studies are not without challenges either, which can be of operational, technical and/or methodological nature [15]. For instance, the quality and completeness of information is critical to describe the patients characteristics and treatment effects [16]. There is currently limited guidance available on the data requirements to confirm a tissue-agnostic indication in the post-marketing setting. In the guideline of the PMDA it is recommended that high quality data, including data from cancer types not evaluated in the clinical trials, is required after marketing authorisation [9]. For future applications, a global strategy toward the generation of data in the post-marketing setting may be of interest, dependent on emerging insights from the current approaches.

As the FDA and EC granted expedited approval, i.e., "accelerated approval" and "conditional marketing authorisation," respectively, the drug developers are obligated to provide confirmatory data in the post-marketing setting. Importantly, regulatory action can be taken if new data alters the benefit-risk ratio, which might also impact tissue-agnostic indications. Randomised-controlled trials remain the gold standard to determine the efficacy and safety of a medicinal product and are often preferred as confirmatory trials. However, as addressed by the FDA reviewers, it will be challenging to conduct a randomised-controlled trial in the tissue-agnostic setting [17]. Some biomarker-tumour combinations are extremely rare [18]. The low prevalence of a biological characteristic may lead to recruitment challenges, even for basket trials [19]. In addition, shared among medicinal products approved for a tissue-agnostic indication is the "strong scientific rationale" [20]. Such a scientific/biological rationale and the demonstration of large treatment effects may bring clinical equipoise into question. This

explains why confirmatory data for the tissue-agnostic approvals will be obtained from ongoing single-arm (basket) trials or real-worlds studies. Recently, Seligson et al. reflected on tissue-agnostic approvals by the FDA and suggested that real-world data can be used as an alternative strategy to confirm benefit [20]. Miksad et al. described that the identification of real-world patients could expand the evidence base for the NTRK population [16]. Real-world data might also provide a more comprehensive understanding of long-term effects for drugs approved on the basis of earlier phase clinical trials; i.e., Phase I or Phase II trials [21]. More general, it has been published that post-marketing studies are sometimes delayed [22]. Regardless of PMM, it is important that regulators insist that the due date for these (mandatory) measures will be met, as the confirmation of benefit is an important aspect of tissue-agnostic approvals.

The first approvals set precedent for the level of evidence necessary to register medicinal products for a tissue-agnostic indication. Our results show that tissues-agnostic approvals are supported by somewhat small (efficacy) datasets – albeit sufficient for the initial assessment of the benefit-risk balance; especially considering the complexity of a tissue-agnostic indication. Furthermore, agencies have a different approach towards reviewing the submitted data, i.e., some agencies accept integrated datasets, focus on particular analysis sets and/or request updated data. Findings from literature confirm that the size of the efficacy populations supporting the tissue-agnostic approvals can be considered smaller than generally observed for approval. For example, Tenhunen et al. reported that the median number of patients in the target population was 175 for EC approvals based on results from single-arm trials [23]. This is substantially larger than the initial efficacy population supporting the approval of the TRK inhibitors. The current tissue-agnostic approvals were based on a strong biological rationale and thereby the expectation of consistency in treatment effect across tumour types [20]. The importance of a strong biological rationale to support a tissue-agnostic approach is highlighted in the EMA draft guidance document. It is specified in this guidance document that the assessment of homogeneity can be conducted only if a sufficient number of patients is included in the study, which is not always feasible [8]. The PMMs will allow re-assessment of homogeneity based on a larger dataset in the post-marketing setting, sometimes including data from at least 200 additional patients; that is, based on our findings. Regarding the integrated analysis sets, Seligson et al. reported that the FDA accepted pooled data due to the consistent anti-tumour activity across trials [20]. However, not every agency might accept this strategy. For instance, the PMDA considered RXDX-101-02 to be the sole pivotal study to support the application of entrectinib and focused its review on the NTRK fusion-positive cohort [24]. Early dialogue between developers and regulators to discuss (clinical) development plans may prevent regulatory hurdles.

Our results show that not all developers submitted an application to all agencies at the same time. The differences in submission date for pembrolizumab are the most noticeable. For instance, only recently an extension of indication for six MSI-h tumours for pembrolizumab was submitted to the EMA [11]. Remarkably, the developer did not apply for a tissue-agnostic indication in the European Union (EU) [25]; a different strategy compared to the applications submitted to FDA and PMDA. Understanding why the developer did not seeking a tissue-indication

is of interest but can only be speculated on. Likewise, while the EC approved dostarlimab for the treatment of patients with dMMR/MSI-H recurrent or advanced endometrial cancer, the applicant did not apply for a tissue-agnostic indication in the EU [26]. A delay in submission is one of the factors that may contribute to disparity in approved therapies between countries or continents. In the absence of regulatory approval, patients in Europe are often dependent of clinical trials or patients access programs [27]. Initiatives such as the personalised reimbursement scheme incorporated in the Drug Rediscovery Protocol enable access to promising medicinal products for unapproved indications, but only on a national level [28].

To our knowledge, this is the first comparison of tissue-agnostic approvals between three independent regulatory agencies. However, our study is limited to the products that received regulatory approval for a tissue-agnostic indication(s). Additional approvals might make such a study more sensitive to determine differences in regulatory decision-making between agencies. Despite this limitation, we consider that the currently available information is sufficiently abundant to compare at least some aspects related to decision-making for tissue-agnostic approvals.

Conclusion

The current approvals set precedent for the level of evidence necessary to register medicinal products for tissue-agnostic indication. A strong biological rationale and consistency in treatment effect across tumour types may allow for (expedited) approval, but confirmation of benefit in the post-marketing setting remains an important aspect of tissue-agnostic approvals. There are different approaches to further confirm the tissue-agnostic indication in the post-marketing setting, albeit these are not without inherent limitations. The approaches to collect post-marketing data could complement existing data packages, but it will be of importance that "new" data are of high quality. For future applications, a global strategy toward data generation post-marketing may be of interest, dependent on emerging insights from the current approaches. Eventually, only the post-marketing data will continue to shed light on the appropriateness of the tissue-agnostic indication.

Author disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of the EMA or one of its committees, working parties, or any of the national agencies.

Conflict of interest

EV initiated and led the DRUP as one of the principal investigators.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

Supplementary Table 1. Distribution of tumour types within the initial datasets per medicinal product and agency.

product	Cancer	FDA	PMDA	EMA
		Number of patients		
Pembrolizumab	Colorectal cancer	90	61	N.A.
	Endometrial cancer	14	24	N.A.
	Biliary cancer	11	9	N.A.
	Small intestinal cancer	8	13	N.A.
	Gastric cancer	8	13	N.A.
	Pancreatic cancer	6	10	N.A.
	Oesophageal cancer	1	-	N.A.
	GE junction cancer	1	-	N.A.
	Breast cancer	2	-	N.A.
	Prostate cancer	2	1	N.A.
	Bladder cancer	1	2	N.A.
	Sarcoma	1	1	N.A.
	Thyroid cancer	1	2	N.A.
	Retroperitoneal cancer	1	1	N.A.
	Small cell lung cancer	1	3	N.A.
	Renal cell cancer	1	-	N.A.
	Adrenocortical carcinoma	-	3	N.A.
	Mesothelioma	-	3	N.A.
	Cervical cancer	-	2	N.A.
	Neuroendocrine tumours	-	2	N.A.
	Brain tumour	-	1	N.A.
	Ovarian cancer	-	1	N.A.
	Salivary gland cancer	-	1	N.A.
	Testicular tumour	-	1	N.A.
	Tonsil cancer	-	1	N.A.

Supplementary Table 1. Continued

product	Cancer	FDA	PMDA	EMA
Larotrectinb	Soft tissue sarcoma	11	N.A.	11*
	Salivary gland	12	N.A.	12*
	Lung cancer	4	N.A.	4*
	Colorectal cancer	4	N.A.	4*
	Infantile fibrosarcoma	7	N.A.	7*
	Thyroid cancer	5	N.A.	5*
	Melanoma	4	N.A.	4*
	Breast cancer	1	N.A.	1*
	GIST	3	N.A.	3*
	Pancreatic cancer	1	N.A.	1*
	Cholangiocarcinoma	2	N.A.	2*
	Appendix cancer	1	N.A.	1*
Entrectinib	Sarcoma	13	13	13**
	Non-small cell lung cancer	10	9	10**
	Mammary analogue secretory carcinoma	7	6	7**
	Breast cancer	6	6	6**
	Thyroid cancer	5	5	5**
	Colorectal cancer	4	3	4**
	Neuroendocrine cancers	3	3	3**
	Pancreatic cancer	3	3	3**
	Gynaecological cancers	2	2	2**
	Cholangiocarcinoma	1	1	1**

*The EMA focused its review on an extended primary analysis set, i.e., the ePAS2, but the initial primary analysis set for efficacy consisted of the first 55 patients enrolled in study LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003. It is therefore likely that the distribution of tumour types was similar between the FDA and EMA submissions.

**The EMA focused its review on an extended primary analysis set, i.e., the ePAS, but the initial primary analysis set for efficacy consisted of the first 54 patients enrolled in ALKA-372-001, RXDX-101-01, and RXDX-101-02. It is therefore likely that the distribution of tumour types was similar between the FDA and EMA submissions.

Supplementary Table 2. All post-marketing measures imposed by each agency per medicinal product.

Drug	Agency	Type of measures	Description of measure
Pembrolizumab	FDA	Accelerated approval requirements	Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of pembrolizumab 200 mg intravenously every three weeks in patients with microsatellite instability high or mismatch repair deficient tumours including at least 124 patients with colorectal cancer enrolled in Merck-initiated trials; at least 300 patients with non-colorectal cancer, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer; and ovarian cancer; and 25 children. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.
		Postmarketing requirements under 505(o)	Conduct a trial that will characterize the safety of pembrolizumab administered intravenously at 2 mg/kg up to a maximum of 200 mg intravenously every three weeks or to determine a reasonably safe dosage regimen in an adequate number of children with primary central nervous system malignancies that are mismatch repair deficient or microsatellite instability high. Submit a final report and datasets for paediatric patients with primary CNS malignancies.
		Postmarketing commitments subject to reporting requirements under section 506B	Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labelling of an immunohistochemistry based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumours that are mismatch repair deficient.
			Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labelling of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumours that are microsatellite instability high.
	EMA	Not applicable	Not applicable
	PMDA	Post marketing surveillance	To conduct a use-results survey after the market launch to collect information on the characteristics of patients treated with the product, to promptly collect data on the efficacy and safety of the product, and to take necessary actions for the proper use of the product.
		Accelerated approval requirements	Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of larotrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and paediatric patients with solid tumours with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion and without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment. A sufficient number of patients will be evaluated to characterize response and durability of response for each of the following tumour types: colorectal cancer, non-small cell lung cancer, central nervous system tumours, and melanoma. A minimum of 40 patients with cancers other than colorectal cancer, non-small cell lung cancer, central nervous system tumours, melanoma, soft tissue sarcoma, thyroid cancer, infantile fibrosarcoma, and salivary cancers (e.g., breast cancer, gastrointestinal stromal tumours, cholangiocarcinoma, biliary tract cancers) will also be studied. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

Supplementary Table 2. Continued

Drug	Agency	Type of measures	Description of measure
Larotrectinib	**FDA**	Postmarketing Requirements under 505 (o)	Submit the final report, including datasets, from the first 55 patients with NTRK fusion solid tumours enrolled across Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431), to further characterize the duration of response in patients who achieved a complete or partial response to larotrectinib. All responding patients will be followed for at least 2 years from the onset of response and duration of response will be assessed by independent central review.
			Conduct a study of larotrectinib in a sufficient number of paediatric patients with NTRK-fusion solid tumours to evaluate the potential serious risk of adverse long-term effects of larotrectinib on the growth and development of paediatric patients. Patients will be evaluated for growth and developmental milestones using age appropriate screening tools and undergo neurological examination at appropriate intervals (for example, every six months) until larotrectinib is discontinued or for minimum of five years, whichever occurs first. Evaluations should include a neurologic exam, developmental milestone assessment, Karnofsky/Lansky score, growth as measured by weight and height, height velocity, height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females), and Tanner Stage.
		Postmarketing commitments subject to reporting requirements under section 506B	Conduct a study of larotrectinib 100 mg orally once daily in a sufficient number of adult or paediatric patients with a body surface area of at least 1.0 m2 who experienced an adverse reaction requiring a third dosage modification of larotrectinib to better characterize the tolerability of this approved dosage modification for larotrectinib. The following information will be provided for each patient: patient age and body surface area (if paediatric), adverse reactions leading to each prior dose reduction of larotrectinib, duration of treatment on prior dose levels, duration of treatment at the 100 mg orally once daily regimen, best overall response and duration of response. and tumour information collected while receiving the 100 mg orally once daily dosage regimen.
			Conduct a physiologically-based pharmacokinetic modelling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of larotrectinib to address the potential for excessive drug toxicity.
			Conduct a physiologically-based pharmacokinetic modelling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of larotrectinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.
			Conduct an analytical and clinical validation study, using clinical trial data, that is adequate to support labelling of an in vitro diagnostic device that is essential to the safe and effective use of larotrectinib for patients with NTRK gene fusions in solid tumour specimens.

Supplementary Table 2. Continued

Drug	Agency	Type of measures	Description of measure
			In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).
	EMA	Specific Obligations	In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.
			In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).
	PMDA	Not Applicable	Not applicable
		Accelerated approval requirements	Submit the final report, including datasets, from the first 54 patients with NTRK-fusion solid tumours enrolled across the ALKA, STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267] studies to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to entrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.
			Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and paediatric patients 12 years of age and older with solid tumours with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion and without a known acquired resistance mutation; are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment. A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for each of the following tumour types: paediatric solid tumours, colorectal cancer, central nervous system cancers, gynaecological cancers, and melanoma. A minimum of 40 patients with cancers other than paediatric solid tumours, colorectal cancer, central nervous system cancers, gynaecological cancers, melanoma, soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer will also be studied. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

Supplementary Table 2. Continued

Drug	Agency	Type of measures	Description of measure
Entrectinib	**FDA**	Postmarketing requirments under 505(o)	Determine functional activation or inhibition of off-target receptors, transporters, and/or channels that, at concentrations of 10 μM, showed greater than 50% inhibition by entrectinib or M5 in the secondary pharmacology studies submitted to NDA 212725 and 212726. As part of an integral safety assessment, include EC50 or IC50 data for target receptors, transporters, and channels that are still significantly affected at a concentration less than 1 μM, particularly those involved in suicidal intent and behaviour, as described in Muller et al., 2015.
			Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the cardiac risks and its sequelae in patients exposed to entrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to support labelling instructions for dose modification and monitoring. The design of the trial should include sufficient cardiac monitoring to achieve these objectives.
			Conduct clinical trial(s) of entrectinib in a sufficient number of paediatric patients 12 years of age and older with NTRK-fusion solid tumours to evaluate the potential serious risk of adverse long-term effects of entrectinib on growth and development, including neurological outcomes with reasonable precision. Patients will be monitored for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner Stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.
			Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the risk of fractures and its sequelae in patients exposed to entrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to support labelling recommendations to mitigate the risk of skeletal fractures. The design of the trial should include sufficient bone monitoring to achieve these objectives, including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.
			Complete a pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function in accordance with the FDA Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling," available at: https://www.fda.gov/media/71311/download.
		Postmarketing commitments subject to reporting requirements under section 506B	Commit to providing adequate analytical and clinical validation results from clinical trial data to support labelling of the F1CDx test to detect NTRK rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for the NTRK indication. The clinical validation should be supported by a clinical bridging study comparing F1CDx and the clinical trial enrolment assays.

Supplementary Table 2. Continued

Drug	Agency	Type of measures	Description of measure
	EMA	Specific Obligation	In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol. The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan. In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.
	PMDA	post-marketing surveillance	to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.
	PMDA	post-marketing surveillance	To conduct a post-marketing use-results survey to investigate delayed growth and development in paediatric patients in clinical practice.

Chapter 7

Discussion and perspectives

General discussion

Rigorous testing of investigational medicinal products is of utmost importance to prevent ineffective and/or unsafe products being placed on the market. Randomised-controlled trials (RCTs) are the "gold standard" to investigate the efficacy and safety of (anticancer) medicinal products [1]. Implementing design features such as randomisation and blinding within a trial will minimise the chance of bias and confounding [2, 3, 4]. Not surprisingly, RCTs are the preferred clinical trials to determine if there is a cause-effect relation between treatment and outcome [5]. There are, however, some limitations to RCTs. For instance, RCTs are resource intensive – i.e., with regard to time and costs – and can be infeasible for rare diseases [6]. In addition, "unprecedented" (antitumour) activity identified early during clinical development may question if there still is clinical equipoise to conduct a RCT [7]. Observing large treatment effects early during drug development will likely become more common within the field of oncology, as there is an ongoing focus on precision medicine. Consequently, early access to promising medicinal products intended to treat life-threating diseases requires regulatory flexibility. Tools are, therefore, available to stimulate development and expedite authorisation of medicinal products that address an unmet medicinal need. In this dissertation, several regulatory difficulties and challenges related to evaluation and authorisation of new anticancer medicinal products are discussed.

During the course of development, designations can be granted to investigational medicinal products that are intended to be used for life-threatening diseases. Two designations are discussed in this dissertation. **Chapter 2** concerns orphan designations granted by the European Commission (EC) and **chapter 3** concerns breakthrough therapy designations (BTDs) granted by the Food and Drug Administration (FDA). These chapters illustrate the difficulties in predicting the benefits of medicinal products solely on the basis of non-clinical and/or preliminary clinical data. This is highlighted by the fact that orphan medicinal products for the treatment of pancreatic cancer rarely reach the market and breakthrough therapies are not always perceived as "true" breakthroughs. Obviously, such designations do not guarantee successful marketing authorisation. Caution is, however, necessary when evaluating results obtained early during the development process. The later stages of clinical development can be particularly challenging. A recent report on clinical development success rates showed that the Phase II success rate in oncology was the lowest of all phases (24.6%), followed by the Phase III success rate (47.7%) [8]. Several publications addressed Phase III trials failures in oncology as well as other therapeutic areas [9, 10, 11]. Of these failures, a considerable amount is due to efficacy and/or safety issues [9, 10]. Over recent years, research and development strategies have improved, resulting in an increased end-to-end success rate; i.e., Phase I to approval [12, 13].

A RCT remains the preferred trial to support the authorisation of a new medicinal product. However, in **chapter 4** and **chapter 6** we show that single-arm trials (SATs) play a notable role in the authorisation of medicinal products for rare cancers or biomarker-defined subsets of cancers. Large treatment effects on surrogate endpoints frequently justified expedited approval

from a regulatory point of view. Furthermore, **chapter 5** illustrates the value of trials other than RCTs in repurposing authorised medicinal products. Clinical trials included in an application for marketing authorisation should clearly, or rigorously, demonstrate that the benefit-risk balance is positive. This can be challenging with SATs. For instance, SATs have inherent limitations, including the lack of a control arm [14]. Besides, objective response rate (ORR) is often the primary endpoint in SATs. Even though this is an interpretable endpoint, given that the baseline tumour measurements act as internal controls [15], it remains uncertain whether ORR is an adequate surrogate for overall survival [16, 17]. The use of SATs for regulatory purposes remains somewhat controversial. Due to the limitations associated with SATs, concerns have been raised regarding approvals supported by these trials [18]. Others, however, discussed potential situations in which approvals based on SATs may be justified [19, 20, 21]. This includes, but is not limited to, the detection of "unprecedented" tumour response [19].

Chapter 4 and **chapter 6** show that most medicinal products authorised on the basis of SAT results were granted conditional marketing authorisation; i.e., authorisation on the basis of less complete data. Conditional marketing authorisations are subject to specific obligations, which necessitates that marketing authorisation holders (MAHs) complete or initiate studies to resolve outstanding issues and confirm a positive benefit-risk balance in the post-authorisation setting [22]. However, both chapters exemplify that for some conditionally authorised medicinal products it is not feasible (anymore) to conduct RCTs; a hurdle acknowledged by the Committee for Medicinal Products for Human Use. Importantly, to which extent outstanding issues can be addressed by the imposed specific obligations depends on the possibilities with regard to the feasibility and methodology of new and/or ongoing clinical trials. Of interest is research conducted by Banzi et al., as they stated that it was unclear to which extent confirmatory trials have added to the available evidence on medicinal products that received expedited authorisation by the EC [23]. Nonetheless, creative solutions will sometimes be necessary to resolve the outstanding issues at hand, particularly if (large) RCTs are not feasible.

Overarching considerations

While we discuss the limitations related to our research separately in each chapter, some overarching considerations are described here. Firstly, we generally focused on the registration of medicinal products within the European Union. Even though other parts of the world, such as Japan and the United States of America, were also of interest, we did not investigate the approval of medicinal products worldwide. Highlighting the differences in regulatory decision-making between agencies remains a topic of interest. Secondly, we only focused on medicinal products for the treatment of solid tumours. A considerable number of anticancer medicinal products are authorised for the treatment of haematological malignancies. The decision to discriminate between solid tumours and haematological malignancies was mainly due to practical reasons. Namely, this allowed us to use validated tools to measure clinical benefit. It will be of interest to evaluate the benefit of medicinal products for haematological malignancies once the European Society for Medical Oncology (ESMO) – Magnitude of

Clinical benefit Scale (MCBS) is also validated for these products. Of note, a validated version of the ESMO-MCBS might be foreseeable in the future [24]. Thirdly, it is important to mention that the authorisation of a medicinal product is only one step towards medicinal product access and availability. Hwang et al. proposed that the evidence necessary for the authorisation of medicinal products should be aligned with that necessary for bodies that make reimbursement decisions [25]. However, it is outside the scope of this dissertation to discuss the impact of regulatory decision-making on the product life cycle and assessments conducted by heath technology assessment bodies and payers. Finally, we narrowed our research to the development and authorisation of anticancer medicinal products. To which extent our findings are relevant to disease areas other than oncology has not been investigated by us and may deserve further attention.

Perspectives and future research

This dissertation concerns aspects related to the authorisation of (new) anticancer medicinal products. In the individual chapters, we provide recommendations that we consider to be of value to regulators, developers and other stakeholders. Our research, however, is only a fraction of all that has been published on regulatory decision-making and anticancer medicinal products over the recent years. For example, others previously addressed: expedited tools/programs [26, 27, 28, 29]; clinical trial designs [30, 31, 32]; surrogate endpoints [33, 34]; clinical benefit [35, 36, 37, 38]; raising the bar [39, 40]; et cetera. Nonetheless, scientific advancements and a more profound understanding of disease biology will continue to have an influence on the medicinal product life cycle, including regulatory decision-making. This warrants further investigation.

Ellen Sigal – who founded the Friends of Cancer Research – recently reflected on the BTD. While acknowledging that the BTD is not perfect, she stated that "many BTD drugs are making differences in patient's lives" [41]. Sigal also stated that the FDA has become more selective with assigning the designation [41]. This shows that experience and reflection can be of value to the program, allowing further refinement. This is not only relevant for the BTD but also for other regulatory programs, regardless of agency. For example, the PRIority MEdcines (PRIME) scheme, which was launched by the European Medicines Agency, shares similarities with the BTD [42]. Continued reflection on regulatory programs can be of added value. It is, however, of importance to take into account the evidence that is currently available as well as the evidence still to be generated via post-authorisation measures. Besides, limiting factors like the use of surrogate endpoints can make it difficult to determine the "true" benefits of a medicinal product. Instead, focussing on why some medicinal products did not met expectations may be helpful to further refine programs like PRIME and BTD.

Precision medicine continues to play an important role in oncology, and targeted therapies have a higher chance of showing prominent effects early during drug development. Yet, authorisation based on earlier phase clinical trials is not without uncertainties regarding the benefit-risk balance. If medicinal products are granted conditional marketing authorisation, specific

obligations will likely address these uncertainties in the post-authorisation setting. However, years ago, critics already discussed that confirmatory trials may suffer from enrolment issues – either due to the unwillingness of patients to be randomised or the reluctance of the sponsor to (timely) complete clinical trials [43]. While topics such as expedited authorisation and post-authorisation measures already received considerable attention in the past, it may, however, still be relevant to conduct additional research. For instance, the use of unconventional methods and strategies to generate more rigorous evidence, before authorisation and in the post-marketing setting, can be further explored.

Evidence generation plays a vital role during the entire product life cycle. Additional studies using authorised medicinal products are generally initiated by the MAH but may also be initiated by other stakeholders. For instance, recently, the Drug Rediscovery Protocol, an investigator-initiated trial, demonstrated that targeted therapies may be beneficial in rare cancers harbouring actionable molecular alterations [44]. Nonetheless, results from investigator-initiated trials seldomly lead to amendments to the product information, except when safety issues are identified [45]. A clear example of the latter is the accumulating evidence on the association between dihydropyrimidine dehydrogenase deficiencies and fluoropyrimidine-related toxicity, which led to amendments to the product information of fluoropyrimides [46, 47]. Evidence like this is relevant to patients and healthcare professionals, regardless of source and independent of who conducted the study. Besides, with more efficient ways to gather and analyse data from various sources, the evidence pool on authorised medicinal products will only increase in the future. It might be of interest to further explore how evidence that is generated in the post-marketing setting, regardless of source and independent of who initiated the study, can be used to change the terms of a marketing authorisation; with or without initiatives of the MAH.

In conclusion, further research is needed to ensure that beneficial medicinal products are timely authorised, especially when they address an unmet medical need. The development of promising medicinal products starts with a profound understanding of disease biology and a clear pharmacological rational. Early identification of highly active medicinal products is key, as this allows for optimal use of regulatory mechanisms. Trials with designs other than RCTs play an important role in drug development. The use of these trials to support marketing authorisation requires regulatory flexibility. With that in mind, the community should strive to improve methodology for trials that have inherent biases. Moreover, evidence generation is an important aspect during the entire drug life cycle, and the continually growing evidence pool has lots of potential. This also applies to data from unsolicited clinical trials that are initiated by others than the MAH. On a more general note, reflecting on prior decision-making and exploring regulatory possibilities, from a multi-stakeholder perspective, will be necessary to continue safeguarding public health.

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Appendix

Summary

Advances in technology and a better understanding of tumour biology led to the development of "precision medicine". With this approach it has become more common that investigational medicinal products show large treatment effects early during drug development. To facilitate early availability of promising medicinal products intended to treat life-threatening diseases, regulatory flexibility is required. Regulatory tools are therefore available to stimulate development and expedite authorisation of medicinal products that address an unmet medical need. In this dissertation, the difficulties and challenges related to the approval of anticancer medicinal products are discussed.

Chapter 1 provides a general introduction, in which topics such as precision medicine, the relevant European Union legal framework, authorised anticancer medicinal products and the importance of evidence generation are discussed. This chapter emphasises the need for a reflection on regulatory decision-making in regard to the authorisation of promising anticancer medicinal products.

Part 1 reflects on two different regulatory designations that facilitate the development and approval of medicinal products. **Chapter 2** concerns experimental medicinal products that have received orphan designation by the European Commission (EC). In this chapter, an overview on orphan medicinal products (OMPs) for the treatment of pancreatic cancer is provided. Between 2000 and 2019, a total of 52 investigational medicinal products for treatment of pancreatic cancer received an OMP designation. At the time of submission, 18 medicinal products were at the non-clinical and 34 medicinal products were at the clinical stage of development. At least 14 types of mode of action were explored in the condition. Protocol assistance was sought for 18 OMPs. At the time of our analysis, one OMP had received marketing authorisation and 24 OMPs were still under development. We conclude that, in spite the considerable number of investigational products for pancreatic cancer that received OMP designation, the success rate of OMPs for pancreatic cancer that reach the market is low. Increasing this rate is important. Developers are advised to make optimal use of incentives for OMPs such as protocol assistance. In addition, developers are strongly encouraged to provide yearly updates on advancements in development of their products. Close monitoring of the drug development through annual reports and transparency regarding the reason(s) for stopping development are crucial for saving human and financial resources and redirecting efforts in promising concepts. **Chapter 3** is dedicated to the Breakthrough Therapy designation (BTD) of the Food and Drug Administration (FDA). The BTD was, recently, criticised by others. Therefore, we raised the question if investigational medicinal products that were granted BTD by the Food and Drug Administration (FDA) are truly breakthroughs. We used a validated tool to measure clinical benefit of anticancer medicinal products; that is, the European Society for Medical Oncology-magnitude of clinical benefit scale (ESMO-MCBS). A total of 18 original approvals for BTD medicinal products indicated for the treatment of patients with solid tumours were included in our study. We found that only

five pivotal/confirmatory clinical trials were assigned a high ESMO-MCBS score. Based on these findings, we conclude that the success rate of the BTD program is lower than anticipated, given the few clinical trials that were assigned a high ESMO-MCBS score. However, numerous BTD medicinal products are recommended in treatment guidelines and a few have even been called 'game changers'. Therefore, it can be questioned whether all criticism towards the BTD program is justified. We believe that programs for fast drug approval do have a place in current regulatory practices to facilitate rapid availability of promising medicinal products that address an unmet medical need.

Marketing authorisations and variations (extension of indication[s]) are the central theme in **part 2.** Over the last years, anticancer medicinal products were more frequently authorised based on single-arm trials (SATs). The lack of a control group in these studies makes it difficult to interpret time-to-event endpoints such as overall survival. Therefore, antitumour activity is investigated in SATs via surrogate endpoints such as response rate. **Chapter 4** provides detail on how clinical benefit of anticancer medicinal products tested in SATs was determined. Between 2012 and 2021, 18 out of 65 medicinal products received EC approved based on one or more SATs (21 studies in total). For the majority of clinical trials supporting the approval of these medicinal products, a clinically relevant treatment effect was (pre-)specified and in most cases an accompanying sample size calculation was provided. For nine studies, each testing a different medicinal product, a justification for the threshold for a clinically relevant treatment effect could be identified. At least 12 applicants included information to facilitate the contextualisation (i.e., indirect comparisons with available treatments) of trial results, including 6 supportive studies. Of the pivotal SATs included in our analysis (n=21), only three were assigned an ESMO-MCBS score of 4; that is, a score that corresponds to "substantial" clinical benefit. In general, aspects such as the antitumour activity and durability thereof, as well as context, are important for the evaluation of SATs, as these help to understand the clinical meaningfulness of trial results. Our research however indicates that there is some room for improvement. This includes prespecifying and motivating a clinically relevant effect size and aligning the sample size to that effect. External controls may facilitate the contextualisation process, but the limitations associated with such indirect comparisons must be addressed. We consider it of value to further discuss among stakeholders (e.g., regulators, academia and industry) when approval on the basis of lower levels of evidence is justified. In **chapter 5**, the possibilities to extend the therapeutic indication(s) of an already authorised medicinal product on the basis of results from investigator-initiated trials (IIT) are explored. When results from an IIT suggest that an authorised medicinal product is safe and effective for new therapeutic indications, it may be desirable to apply for an extension of the therapeutic indication(s) via the regulatory approval process. In this chapter we address the advantages of an extension of indication, the regulatory requirements for a variation application, the use of investigator-initiated trials data to support regulatory approval, and the role of the MAH in extending the indication. When results from a well-conducted IIT establish that an authorised medicinal product can be used outside the terms of the marketing authorisation, patients should be given the opportunity to be treated with a beneficial medicinal product. We conclude that it is

possible to support an extension of indication of an authorised medicinal product on the basis of results from IITs, but regulatory requirements still need to be met. Therefore, a collaborative approach and early dialogue between stakeholders with the aim to facilitate access to effective medicinal products is of importance for future decision-making.

Part 3 focusses on important issues related to the benefit-risk balance that need to be addressed after a medicinal product received marketing authorisation. In **chapter 6**, decision-making aspects of the first tissue-agnostic approvals are compared between the European Medicines Agency (EMA), FDA and Pharmaceuticals and Medical Devices Agency (PMDA). A tissue-agnostic indication is an indication that is based on a biomarker (e.g., neurotrophic tyrosine receptor kinas gene fusions) rather than the tissue of origin. Post-marketing measures (PMMs; imposed by agencies to complement premarketing datasets) related to the tissue-agnostic indication were of specific interest. At the time of our analysis, pembrolizumab, larotrectinib and entrectinib received regulatory approval for a tissue-agnostic indication(s) by most, or all three, regulatory agencies. Datasets supporting the approvals were generally small, especially for the two tropomyosin receptor kinase inhibitors (larotrectinib and entrectinib). For pembrolizumab, larotrectinib and entrectinib, the number of imposed PMMs varied between one and eight, with the FDA requesting the most PMMs compared to the other two agencies. All agencies requested at least one PMM per approval to address the remaining uncertainties related to the tissue-agnostic indication. The FDA and EMA requested data from ongoing and proposed trials, while the PMDA requested data from use-result surveys (i.e., real-world studies). A strong biological rationale and consistency in treatment effect across tumour types may allow for (expedited) approval, but confirmation of benefit in the post-marketing setting remains an important aspect of the tissue-agnostic approvals. Our results show that there are different approaches to further confirm the tissue-agnostic indication in the post-marketing setting, albeit these are not without inherent limitations. The approaches to collect post-marketing data could complement existing data packages, but it will be of importance that the additionally collected data are of high quality. For future applications, a global strategy toward data generation post-marketing may be of interest, dependant on emerging insights from the current approaches.

The final chapter (**chapter 7**) contains a general discussion and perspectives for follow-up research. It is concluded that further research is needed to ensure that beneficial medicinal products are timely authorised, especially when they address an unmet medical need. Early identification of highly active medicinal products is key, as this allows for optimal use of regulatory mechanisms. The use of trials with designs other than randomised-controlled trials to support marketing authorisation requires regulatory flexibility. With that in mind, the community should strive to improve methodology for trials that have inherent biases. Moreover, evidence generation is an important aspect during the entire drug life cycle, and the continuously growing evidence pool has a lot of potential. On a more general note, reflecting on prior decision-making and exploring regulatory possibilities, from a multi-stakeholder perspective, will be necessary to continue safeguarding public health.

Nederlandse samenvatting

Technologische vooruitgang en meer kennis over tumorbiologie hebben geleid tot de ontwikkeling van zogeheten 'precisiemedicijnen'. Bij deze aanpak komt het vaker voor dat experimentele geneesmiddelen al in een vroeg stadium van de ontwikkeling grote behandeleffecten laten zien. Om de beschikbaarheid van veelbelovende geneesmiddelen voor de behandeling van levensbedreigende ziekten te versnellen, is flexibiliteit in de regelgeving nodig. Daarom zijn er regulatoire instrumenten beschikbaar om de ontwikkeling van geneesmiddelen te stimuleren en de markttoelating te versnellen. In dit proefschrift worden de problemen en uitdagingen die betrekking hebben op de goedkeuring van kankergeneesmiddelen behandeld.

In **hoofdstuk 1** wordt een algemene inleiding gegeven, waarin onderwerpen zoals precisiemedicijnen, de relevante Europese Unie wetgeving, de goedkeuring van kankergeneesmiddelen en het genereren van aanvullend bewijs (na het verkrijgen van een handelsvergunning) aan bod komen. In dit hoofdstuk wordt benadrukt dat er behoefte is aan reflectie op besluitvorming ten aanzien van de markttoelating van veelbelovende kankergeneesmiddelen.

Deel 1 gaat in op twee regulatoire designations die de ontwikkeling en goedkeuring van geneesmiddelen ondersteunen. **Hoofdstuk 2** gaat over de weesgeneesmiddelen status die aan experimentele medicijnen zijn toegekend door de Europese Commissie (EC). In dit hoofdstuk wordt een overzicht gegeven van de weesgeneesmiddelen voor de behandeling van alvleesklierkanker. Tussen 2000 en 2019 kregen in totaal 52 experimentele geneesmiddelen voor de behandeling van alvleesklierkanker een status als weesgeneesmiddel. Op het moment van indiening waren 18 weesgeneesmiddelen in de preklinische fase en 34 weesgeneesmiddelen in de klinische fase van ontwikkeling. Er werden ten minste 14 verschillende werkingsmechanismen onderzocht. Voor 18 weesgeneesmiddelen werd protocol assistance gevraagd. Op het moment van onze analyse had één weesgeneesmiddel een handelsvergunning verkregen en waren 24 weesgeneesmiddelen nog in ontwikkeling. We concluderen dat, ondanks het aanzienlijke aantal geneesmiddelen met een weesgeneesmiddelenstatus, het slagingspercentage van weesgeneesmiddelen voor alvleesklierkanker dat een handelsvergunning krijgt laag is. Verhoging van dit percentage is belangrijk. We adviseren ontwikkelaars om optimaal gebruik te maken van de incentives voor weesgeneesmiddelen zoals protocol assistance. Daarnaast worden zij sterk aangemoedigd om jaarlijkse updates te geven met betrekking tot de ontwikkeling van hun product. Monitoring van geneesmiddelenontwikkeling via jaarverslagen en transparantie over de reden(en) voor het stopzetten van de ontwikkeling zijn cruciaal om middelen efficiënt te gebruiken en inspanningen te richten op veelbelovende producten. **Hoofdstuk 3** is gewijd aan de Breakthrough Therapy Designation (BTD) van de Food and Drug Administration (FDA). Recentelijk werd de BTD door anderen bekritiseerd. Om die reden onderzochten we of experimentele geneesmiddelen die een BTD hebben gekregen, ook daadwerkelijk een doorbraak zijn. We hebben een gevalideerd instrument gebruikt om het klinische voordeel van kankergeneesmiddelen te meten. Dit instrument wordt de European Society for Medical

Oncology-magnitude of clinical scale (ESMO-MCBS) genoemd. In totaal werden 18 BTD-geneesmiddelen voor de behandeling van patiënten met solide tumoren in ons onderzoek opgenomen. We ontdekten dat slechts vijf pivotale/bevestigende klinische studies een hoge ESMO-MCBS-score toegewezen hebben gekregen. Op basis hiervan concluderen we dat het slagingspercentage van het BTD-programma lager is dan verwacht. Echter, een groot aantal BTD-geneesmiddelen wordt aanbevolen in behandelrichtlijnen en een aantal van deze geneesmiddelen wordt zelfs 'game changers' genoemd. Het is dan ook de vraag of eerdere kritiek op het BTD-programma terecht is. Wij zijn van mening dat programma's voor een versnelde goedkeuring van geneesmiddelen een plaats hebben in de huidige regelgeving om, indien nodig, een snelle beschikbaarheid van veelbelovende geneesmiddelen voor patiënten mogelijk te maken.

In **deel 2** staan handelsvergunningen centraal. De laatste jaren werden kankergeneesmiddelen steeds vaker goedgekeurd op basis van single-arm trials (SATs). Deze studies hebben geen controle groep, waardoor time-to-event eindpunten zoals overall survival niet goed te interpreteren zijn. Om deze reden wordt antitumor activiteit onderzocht in SATs via surrogaat eindpunten zoals response rate. **Hoofdstuk 4** biedt inzicht in het aantonen van klinisch voordeel van kankergeneesmiddelen onderzocht in SATs. Tussen 2012 en 2021 kregen 18 van de 65 geneesmiddelen een EC-goedkeuring op basis van één of meer SATs (21 studies in totaal). Voor de meeste klinische studies die de aanvraag voor een handelsvergunning ondersteunden, werd een klinisch relevant behandelingseffect (vooraf) gespecificeerd en werd in het merendeel van de gevallen een bijbehorende berekening van de steekproefomvang verstrekt. Voor 9 van de 21 studies kon een onderbouwing voor de drempel voor een klinisch relevant behandelingseffect worden vastgesteld. Ten minste 12 aanvragers voegden informatie toe om de contextualisering (indirecte vergelijking[en] met reeds beschikbare behandelingen) van onderzoeksresultaten te faciliteren, waaronder zes ondersteunende studies. Van de pivotale SATs opgenomen in onze analyse (n=21), kregen er slechts drie een ESMO-MCBS score van 4 toegewezen; een score die overeenkomt met een 'substantieel' voordeel. In het algemeen zijn aspecten zoals antitumoractiviteit (uitgedrukt in response rate) en de duur daarvan, evenals de context, belangrijk voor de evaluatie van SATs. Deze aspecten helpen in het bepalen of de onderzoeksresultaten klinisch relevant zijn. Ons onderzoek geeft echter aan dat er ruimte is voor verbetering. Met name het vooraf specificeren en motiveren van een klinisch relevante effectgrootte en het hierop afstemmen van de steekproefgrootte. Externe controles kunnen faciliteren in het contextualiseringsproces, maar de beperkingen die gepaard gaan met indirecte vergelijkingen moeten zoveel mogelijk worden gereduceerd. We zijn van mening dat het waardevol is dat belanghebbenden (bijv. regulators, academici en de industrie) met elkaar bespreken wanneer goedkeuring op basis van een lager niveau van bewijsvoering gerechtvaardigd is. In **hoofdstuk 5** worden de mogelijkheden verkend om de therapeutische indicatie(s) van een reeds geregistreerd geneesmiddel uit te breiden op basis van resultaten van onderzoeker-geïnitieerde studies (investigator-intiated trials [IIT]). Wanneer een IIT aantoont dat een goedgekeurd geneesmiddel voldoende veilig en werkzaam is voor een nieuwe therapeutische indicatie, dan kan het wenselijk zijn om een uitbreiding van de therapeutische indicatie(s) aan te vragen via een registratieautoriteit. In dit hoofdstuk gaan we in op de

voordelen van een indicatie-uitbreiding, de regulatoire vereisten voor een wijzigingsaanvraag, het gebruik van IIT resultaten ter ondersteuning van een handelsvergunning en de rol van de vergunninghouder bij het aanvragen van een indicatie-uitbreiding. Wanneer een goed uitgevoerde IIT aantoont dat een geregistreerd geneesmiddel kan worden gebruikt buiten de voorwaarden van de handelsvergunning, patiënten de kans moeten krijgen om te worden behandeld met dit geneesmiddel. We concluderen dat het mogelijk is om een indicatie uitbreiding te ondersteunen met resultaten van IITs, zolang wordt voldaan aan de wettelijke vereisten. Daarom is een gezamenlijke aanpak en een vroegtijdige dialoog tussen belanghebbenden, met als doel de toegang tot effectieve geneesmiddelen te vergemakkelijken, van belang voor toekomstige besluitvorming.

Deel 3 richt zich op resterende onzekerheden die onderzocht worden nadat een handelsvergunning is verstrekt. In **hoofdstuk 6** worden besluitvormingsaspecten van de eerste tumor-agnostische geneesmiddelen vergeleken tussen de European Medicines Agency (EMA), FDA en Pharmaceuticals and Medical Devices Agency (PMDA). Postmarketing measures (PMMs; opgelegd door een agentschap om beschikbare datasets aan te vullen) die betrekking hebben op de tumor-agnostische indicatie, waren van specifiek belang. Bij een dergelijke indicatie is de tumorsoort niet meer van belang maar wordt de indicatie bepaald door een biomarker (bijv. neurotrofische tyrosine receptor kinase gen fusies). Ten tijde van onze analyse hadden pembrolizumab, larotrectinib en entrectinib een handelsvergunning voor een tumor-agnostische indicatie(s) gekregen. Datasets ter ondersteuning waren over het algemeen klein, vooral voor de twee tropomyosin receptor kinase-remmers (larotrectinib en entrectinib). Voor pembrolizumab, larotrectinib en entrectinib varieerde het aantal opgelegde PMMs tussen de één en acht, waarbij de FDA de meeste PMMs had opgelegd in vergelijking met de andere twee instanties. Alle instanties vroegen ten minste één PMM per goedkeuring om de resterende onzekerheden met betrekking tot de tumor-agnostische indicatie op te lossen. De FDA en EMA vroegen om data van lopende en voorgestelde klinische studies, terwijl de PMDA om data vroeg van use-result studies (real-world studies). Een sterke biologische rationale en consistentie in behandelingseffect kan voldoende zijn voor een (voorwaardelijke) goedkeuring, maar bevestiging van het klinische voordeel in de postmarketing setting blijft een belangrijk aspect van de tumor-agnostische geneesmiddelen. Onze resultaten laten zien dat er verschillende aanpakken zijn om de correctheid van een tumor-agnostische indicatie verder te bevestigen in de postmarketing setting, al zijn deze aanpakken niet zonder inherente beperkingen. Gegevens verzameld in de postmarketing setting zouden bestaande datapakketten kunnen complementeren, maar het is van belang dat deze gegevens van hoge kwaliteit zijn. Voor toekomstige aanvragen kan een wereldwijde strategie voor het genereren van data na het verstrekken van een handelsvergunning van toegevoegde waarde zijn, afhankelijk van inzichten opgedaan uit de huidige aanpak.

Het laatste hoofdstuk (**hoofdstuk 7**) bevat een algemene discussie, perspectieven voor vervolgonderzoek en een conclusie. Verder onderzoek is nodig om ervoor te zorgen dat werkzame geneesmiddelen tijdig worden toegelaten op de markt, vooral wanneer ze voorzien in

een onvervulde behandelbehoefte. Vroegtijdige identificatie van veelbelovende geneesmiddelen is essentieel, omdat er dan optimaal gebruik kan worden gemaakt van regulatoire instrumenten. Niet-gerandomiseerd onderzoek ter ondersteuning van een handelsvergunning vereist flexibiliteit in de regelgeving. Met dat in gedachten moet de wetenschappelijke gemeenschap ernaar streven de methodologie te verbeteren voor studies die inherente biases hebben. Bovendien is het genereren van bewijs een belangrijk aspect tijdens de gehele levenscyclus van een geneesmiddel, dus ook nadat het op de markt is gekomen. In zijn algemeenheid zal het nodig zijn om vanuit een multi-stakeholderperspectief eerdere besluitvorming voor de toelating van geneesmiddelen verder te evalueren en de toekomstige regulatoire mogelijkheden te onderzoeken om geneesmiddelen die in een belangrijke behoefte voorzien zo snel als mogelijk met voldoende kennis over de werkzaamheid en veiligheid voor patiënten beschikbaar te maken.

List of publications

Publications in this dissertation

1. A Comparison of Post-marketing Measures Imposed by Regulatory Agencies to Confirm the Tissue-Agnostic Approach.
   Mulder J, van Stuijvenberg OC, van Hennik PB, Voest EE, Pasmooij AMG, Stoyanova-Beninska V, de Boer A.
2. Orphan Medicinal Products for the Treatment of Pancreatic Cancer: Lessons Learned From Two Decades of Orphan Designation.
   Mulder J, van Rossum T, Mariz S, Magrelli A, de Boer A, Pasmooij AMG, Stoyanova-Beninska V.
3. Extension of Indication for Authorised Oncology Products in the European Union: A Joint Effort of Multiple Stakeholders.
   Mulder J, Verjans R, Verbaanderd C, Pean E, Weemers J, Leufkens HGM, Pignatti F, de Boer A, Voest EE, Stoyanova-Beninska VV, Pasmooij AMG.
4. Single-arm trials supporting the approval of anticancer medicinal products in the European Union: contextualisation of trial results and likelihood of clinical benefit. **Mulder J**, Teerenstra S, van Hennik PB, Pasmooij AMG, Stoyanova-Beninska V, Voest EE, de Boer A. Manuscript submitted.
5. Breakthrough therapy-designated oncology drugs: are they rightfully criticized? **Mulder J**, Pasmooij AMG, Stoyanova-Beninska VV, Schellens JHM.

Other publications

6. Combinations in the first-line treatment of patients with advanced/metastatic renal cell cancer: regulatory aspects.
   Moscetti L, Hennik P, Bolstad B, Camarero J, Josephson F, Melchiorri D, Sommerfelt Grønvold M, Sjoberg J, Botezatu M, **Mulder J**, Meulendijks D, Trullas Jimeno A, Zafiropoulos N, Bergh J, Enzmann H, Pignatti F.

Dankwoord

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Curriculum vitae

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