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The role of Real-World Data and evidence in oncology medicines approved in EU in 2018–2019

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ABSTRACT

Use of Real-World Data (RWD) has gained the interest of different stakeholders in cancer care. The aim of this study was to identify and describe the use of RWD/RWE during the pre-authorization phase of products authorized by the EMA in 2018 and 2019 (n = 111), with the focus on oncology medicines (n = 24). Information was extracted from the European Public Assessment Report (EPAR) summaries and recorded for 5 stages (11 categories) of the drug development lifecycle (discovery, early development, clinical development, registration/market launch, lifecycle management). Specific chapters of full EPAR were reviewed to substantiate the findings on RWD/RWE use in clinical trial design, efficacy, safety, and effectiveness evaluation. RWD/RWE is present in all stages of the oncology drug development; 100.0 % in discovery, 37.5 % early development, 58.3 % in clinical development, 62.5 % in registration decision and 100.0 % in post-authorization lifecycle management. Examples showed that trial design supported by RWD/RWE included use of open label/single arm studies; efficacy was about using either comparison of results to historical controls, supplying survey data obtained outside the clinical trial or utilizing expert panel advice; safety about including literature findings in evidence; and effectiveness on comparison of trial results of the given product to historical data or existing standard of care. The findings of this study provide specific insights into how RWD/RWE is used in development of cancer therapeutics, how it contributes to regulatory decision making and can guide further policy developments in this field.

1. Background

In 2020, 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred worldwide [1]. The number of diagnosed cases continue to increase while the number of cancer deaths is increasing at a slower pace as the treatment landscape for certain types of cancers has dramatically changed in recent years with the important breakthroughs in medical treatment [2–4]. The positive trend is driven by improved prevention, diagnosis, and treatment while increasingly the therapy selection in oncology is tailored to the individual patient and disease characteristics where for example the cell and gene-based therapies provide a potential cure [5,6]. Yet, drawing conclusions from the evidence generated in pre-approval phase of cancer medicines to regulatory decision making can be challenging. The use of overall survival (OS) as a primary endpoint is the reference standard to demonstrate patient clinical benefit, but the increasing number of effective second-line treatments has resulted in the need for a larger number of patients to be included and/or the need of a more prolonged observation period to attain sufficient data for arbitration and decision making; this requires a longer duration to obtain results and can increase the cost of clinical trials [7,8]. Earlier assessment of evidence is possible if tumor-centered clinical endpoints, such as progression-free survival, is used as they are

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designed to interfere with a genetic pathway expressed in a tumor [9]. Characterizing tumors so specifically results on the other hand in smaller target patient groups and brings more uncertainty at the point of regulatory approval with the difficulty to demonstrate efficacy with the small number of trial patients.

Use of Real-World Data (RWD) can play an important role in cancer care by providing the evidence complementing the data collected in randomized controlled trials (RCTs) with the aim to particularly increase the external validity of results in real world [10,11]. The traditional drug development paradigm, consisting of sequential phases and randomized studies, has been challenged particularly in oncology and hemato-oncology in their regulatory context and several new products have been authorized based on nonrandomized efficacy and safety data and through expedited regulatory pathways [12–14]. Both US FDA and European Medicines Agency (EMA) already recognize the value of fit-for-purpose evidence generation that embraces a complimentary role of RWD/RWE to RCTs in regulatory decision making [15,16].

Infrequently, RWD on historical clinical outcomes is drawn from chart reviews, expanded access programs, disease and product registries, and other clinical practice settings and supports clinical data from RCTs for which control arm is infeasible or unethical and where a large effect size is expected based on initial data [17–19]. Skovlund et al. outlined already in 2018, the overwhelming interest of health systems, pharmaceutical policies, and doctor-patient relationship to generate evidence on factors determining treatment effects of cancer in the real world [10]. In addition, three recent studies assessed market authorization approvals granted by US FDA (in 2019–2021) and EMA (in 2018–2019), respectively, and found that use of RWD/RWE for demonstrating safety and efficacy was the highest for oncology products [20–22]. While there is this increasing pool of evidence that RWD/RWE can support the medicines development and initial regulatory decision making, there are still knowledge gaps in how it is exactly applied to support the development of oncology products [23]. The research and regulatory community may miss out a prominent solution to improve cancer treatment options and patient outcomes unless there is an increased knowledge of situations in which RWD/RWE can contribute to.

The aim of this study was to identify and describe the use of RWD/RWE during the pre-authorization phase of oncology products, with a positive opinion received in 2018 and 2019 by the EMA. We wanted to increase the knowledge on what role RWD/RWE plays in oncology drug development from discovery, clinical research, regulatory decisions to planning the post-approval lifecycle management.

2. Methods

2.1. Cohort

For this study a cohort of medicinal products centrally authorized in Europe from January 1, 2018, until December 31, 2019 (n = 111) was assembled based on the "Download table of medicines", retrieved from EMA website [24]. Generics and biosimilars were excluded based on the expectation that evidence on medicine's efficacy and safety have been derived through cross-referencing data which is already assessed by the regulatory authority for the innovative product.

2.2. Oncology cohort and co-variables

The cohort of oncology products initially determined by their ATC code (where L refers to the antineoplastic and immunomodulating agents) (n = 30) were further refined to include only those medicines that are indicated for cancer (n = 24) [25]. Furthermore, these were grouped to carcinomas (lung or breast), hematological cancers and other cancer types including for example some histology independent tumors. In addition, we defined the products as orphan oncology products (or not) based on the categorization by EMA which was validated by the information retrieved from the European Union Register of medicinal products [24,26]. The information was collected for all medicines on medicine's name, therapeutic area per high-level ATC code (adjusted to oncology products as described), active substance, approved condition/indication, the year of authorization and approval date, whether the medicine had received a conditional approval or was assessed under accelerated assessment or exceptional circumstances (Appendix 1).

2.3. Data source and review

Data for the study was retrieved from publicly available European Public Assessment Reports (EPAR) released at initial marketing authorization approval by EMA [24]. EPAR contains scientific discussions and technical summaries that reflect the regulatory evaluation of evidence provided by the marketing authorization holder including quality, pre-clinical and clinical data submitted in the registration dossier to support the marketing authorization application. For this study all EPAR overviews (n = 111) were reviewed, while the selected chapters (2.5 Clinical Efficacy, 2.6 Clinical Safety, 2.7 Risk Management and 3. Benefit Risk Balance) of a full EPAR overview were reviewed for a subset of products (explained in the following paragraph).

2.4. Signatures of RWE use

Signatures of RWE use were extracted from the EPAR overviews as per peer reviewed methodology of Eskola et al. using the "RWE Data Matrix" [21]. "RWE signature" (scored as 1) was defined by any reference to potential use of RWE in the marketing authorization application as presented in the EPAR overview. "RWE signature with data" (scored as 2) was defined by any reference to potential use of RWE and associated with more data (e.g., explanation of specific biomarker used in early development for population identification). Absence of the RWE signature was scored as 0. To be able to substantiate the findings of "RWE signature with data", for all products that scored 2, the selected full chapters of the EPAR were reviewed and specific findings extracted from the text were mapped to the chosen categories of interest (2.5 Clinical Efficacy, 2.6 Clinical Safety, 2.7 Risk Management and 3. Benefit Risk Balance).

2.5. Data analyses

The characteristics of the cohort and use of RWD/RWE in the oncology and non-oncology drugs were evaluated with descriptive statistics. All analysis was performed using SPSS® (IBM® SPSS Statistics, version 28).

3. Results

All oncology (n = 24/24, 100.0 %) and nearly all non-oncology products (n = 85/87, 97.7 %) included RWE signatures (any) in discovery phase, whereas two third of oncology (66.7 %) in comparison to about a quarter (24.1 %) non-oncology products included RWE signatures with data in this phase (Table 1). RWE signatures supported the lifecycle management for all products, and RWE signatures with data supported 95.0 % oncology and 81.1 % non-oncology products in this phase. The considerations over the therapeutic benefit were supported by RWE signatures (any) in 62.5 % of oncology and 42.5 % of non-oncology products, but only a few with data (8.3 % oncology and 4.6 % non-oncology products, respectively). In the full development phase (RWE supporting clinical trial design, safety, and efficacy evaluation) 58.3 % of oncology and less than half (47.9 %) non-oncology products had RWE signatures (any), while RWE signatures with data were found in 16.7 % oncology and 5.7 % non-oncology products. Looking at the early development phase (comparison to current practice) the differences between oncology and non-oncology products were not noteworthy, as 37.5 % of oncology products and 33.3 % of non-oncology

Table 1
RWD signatures and RWE signatures with data of oncology and non-oncology products, respectively, across the main drug development phases in the cohort of medicinal products evaluated centrally by EMA in 2018–2019.

	Oncology products	Non-oncology products	All products
Number of All MAAs (n = 111/ percentage %)	n = 24 (21.6 %)	n = 87 (78.4 %)	n = 111 (100.0 %)
1. Discovery/Epidemiology of disease			
- RWE signature (any)	24 (100.0 %)	85 (97.7 %)	109 (98.2 %)
- RWE signature with data	16 (66.7 %)	21 (24.1 %)	37 (33.3 %)
2. Early Development/ Comparison to current (clinical) practice			
- RWE signature (any)	9 (37.5 %)	29 (33.3 %)	39 (35.1 %)
- RWE signature with data	0 (0.0 %)	1 (1.1 %)	1 (0.9 %)
3. Full Development/Clinical Development			
- RWE signature (any)	14 (58.3 %)	40 (46.0 %)	54 (48.6 %)
- RWE signature with data	4 (16.7 %)	5 (5.7 %)	9 (8.1 %)
4. Registration/Market Access/ Therapeutic Benefit			
- RWE signature (any)	15 (62.5 %)	37 (42.5 %)	52 (46.8 %)
- RWE signature with data	2 (8.3 %)	4 (4.6 %)	6 (5.4 %)
5. Lifecycle Management/Safety Profile/Clinical Guidance			
- RWE signature (any)	24 (100 %)	87 (100.0 %)	111 (100.0 %)
- RWE signature with data	23 (95.8 %)	67 (77.0 %)	90 (81.1 %)

products had RWE signatures (any) and nearly no RWE signatures with data were found for either oncology or non-oncology products (0.0 % and 1.1 %, respectively).

The more detailed analyses for the sub-categories of products treating different cancer types (lung and breast carcinomas (n = 8), hematological cancers (n = 8), other types of cancers (n = 8)) revealed further nuances about the use of RWD/RWE between the specific types of oncology products (Fig. 1 and Appendices 2 and 4). Nearly all products (n = 7) for carcinomas were supported by RWE and half of products for the other groups respectively (n = 4) in early discovery. In the full development phase, most RWE signatures with data were found in the products treating rare and hematological cancers (n = 3, respectively), while this was found only for one product treating carcinoma and none for a product for other cancer type. Same was seen for the registration phase where three products developed for hematological cancers were most supported by RWE with data but only one product for carcinoma and none for products for other type of cancers had signatures with data. RWE signatures with data were present to nearly all products (n = 23) in this cohort to manage the lifecycle of the product (e.g., safety profile, class effect and clinical guidance/active monitoring). Comparison between orphan (n = 8) and non-orphan (n = 16) oncology products could reveal some further differences (Appendix 3). For half of orphan (n = 4, 50.0 %) and a third of non-orphan oncology products (n = 5, 31.3 %) had RWE signatures (any) to make comparisons to non-existing/existing current clinical practice respectively, whereas more RWE signatures (any) were present to non-orphan (n = 11, 68.8 %) in comparison to orphan oncology products (4 =4, 50.0 %) in demonstration of the therapeutic benefit over alternative therapies existing on the market.

Finally, in this study the review of the specific full chapters of EPAR

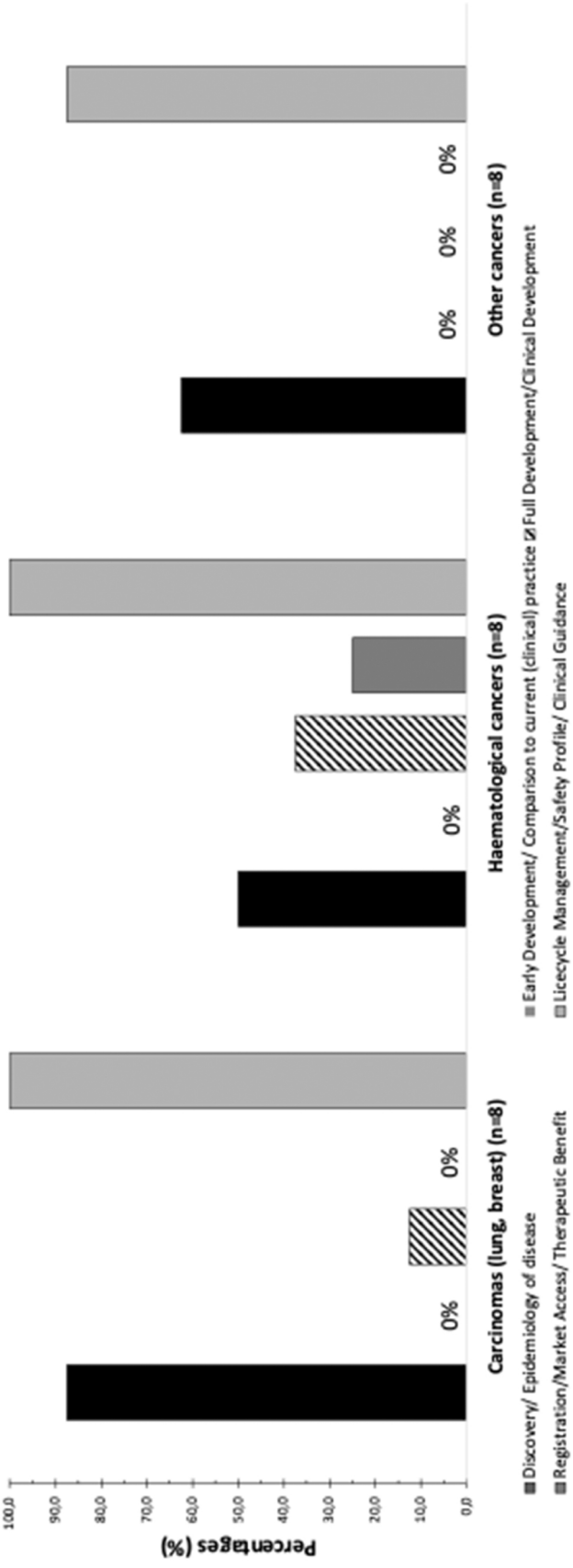


Fig. 1. Overview of *RWE signatures with data* identified in EPAR overviews of oncology products (n = 24); carcinomas (lung/breast, n = 8), hematological cancers (n = 8) and other types of cancers (n = 8).

aimed to substantiate the results on the findings (RWE signature with data, n = 12 in total, whereby n = 6 found for oncology products), on how exactly the RWD/RWE had supported the evaluation of the regulatory application in terms of its clinical trial design, efficacy, safety, and effectiveness (Fig. 2). Case examples of oncology products showed that trial design supported by RWD/RWE included the use of open-label/single arm studies; efficacy was supported by using either comparison of results to historical controls, supplying survey data obtained outside the clinical trial or utilizing expert panel advice; safety was supported by including literature findings in evidence for decision making; and effectiveness by comparison of trial results of the given product to historical data or existing standard of care in a descriptive manner.

4. Discussion

Real-World Data and Evidence play a significant role in oncology product development and the results of this study are aligned of those from earlier research findings confirming that RWD/RWE is supporting more oncology than other therapeutic areas [13,21–23]. Our findings reaffirm that RWE is present in all stages of the oncology drug development, authorization decision, and guiding the lifecycle management for the post-authorization phase. It is not surprising to find in this study that RWD/RWE is used to large extent in the discovery phase (i.e., exploring the burden of disease, disease features and population identification) and around product launch for planning the lifecycle management (safety profile, class effect and clinical guidance/active monitoring) for all cancer products in the cohort, and most for carcinomas. Defining a concise Target Product Profile at the beginning of drug development requires e.g., critical data on medical need, disease course and epidemiology of occurrence of disease [26]. Our data confirms this for high-prevalence cancers like lung and breast carcinomas (87.5 % had RWE signatures with data), where RWD collection is most feasible. In this cohort, *the case example of talazoparib* for breast carcinoma is used to treat locally advanced or metastatic HER2-negative breast cancer of cancer cells with deleterious mutations in breast cancer susceptibility genes 1 or 2 (BRCA1/2). Target patient population was identified with testing by BRACAnalyses (Myriad Genetics) [27].

While the RCTs are still regarded as a golden standard of clinical care, their validity is lowered when strict in- and exclusion criteria to clinical trials are applied and therefor provide reduced insights into anticipated routine therapeutic use [28]. It's acknowledged there is a significant difference between patients enrolled in the study and the heterogeneous patient population in oncology treated in routine clinical practice [29]. Incentives to add RWD to drug development in oncology include choosing the right comparator drug as it is critical in translating the trial results into meaningful treatment scenarios [30]. Like in the *case example of daunorubicin/cytarabine* in this cohort, single-arm studies for oncology products are more often used where a comparison is made with historical controls (either being the older RCTs and/or RWD), particularly when a randomized comparison is not feasible such as is often the case of rare diseases [10,28].

The peak seen of RWD/RWE use for rare cancers in demonstration of the efficacy, reflects the strong need for RWE in development phase. In the *case example of axicabtabene cilaleucal*, the efficacy profile was compared to the retrospective global patient-level pooled data. The demonstration of efficacy for rare cancers would be extremely difficult if it only relied on the RCTs in this context due to the small population size in the life-threatening leukemic disease. Our findings show that more innovative approaches are used in oncology and in particular in hemato-oncology, where RWD particularly contributed to the trial design.

Contribution of RWD/RWE to oncology drug development noted in this study also indicates that there might be the increased need to compare the novel cancer treatment to current clinical practice/absence of a treatment. In this study, a good *example is treosulfan*, used as conditioning treatment before a blood or bone marrow transplant, for which the trial results in pediatrics with malignant diseases were compared to the historical data available in registries and to the results obtained from studies in adults. Equally in the demonstration of safety, it might be difficult to obtain results just in RCTs for specific populations such as for children [31]. In our cohort, *another example of gemtuzumab ozogamicin*

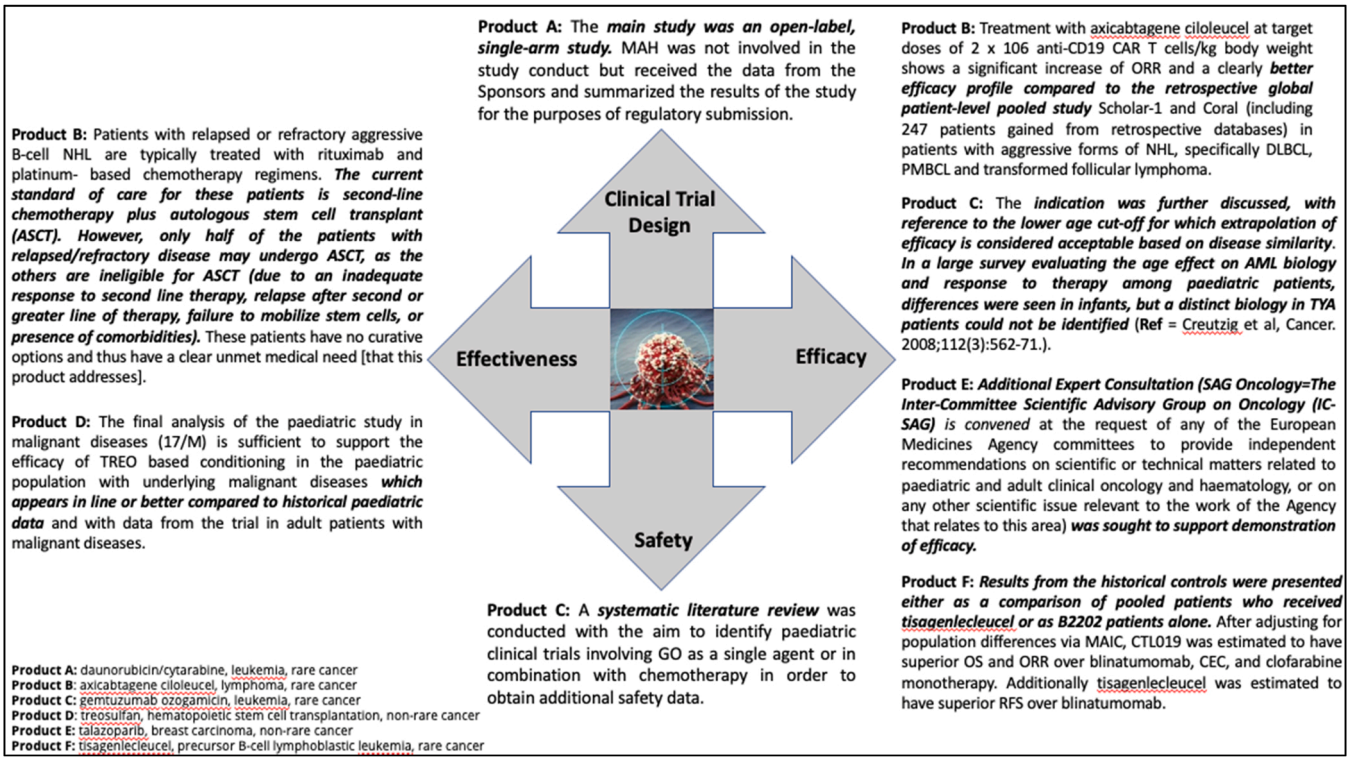


Fig. 2. Case examples of oncology products with "RWE signatures with details" that were identified as part of the review of specific chapters of full EPAR based on the review of categories: clinical trial design, efficacy, safety, and effectiveness.

indicated for leukemia, showed that additional safety data in children population was sought from the systematic literature review rather than conducting an RCT.

Nearly all oncology products had "RWE signatures with data" in lifecycle management stage, which reflects the importance of these insights to guide safe use and clinical evidence generation. This supports the findings by Mofid et al. [32] that the use of RWD for post-marketing surveillance activities of products is pronounced already at the authorization. For drug development in pre-approval phase there is also a strong need and reliance on availability of RWD from the clinical community. Many initiatives on the use of registries by the regulators, patients and industry are now further enhanced with the primary aim of European Health Data Space Regulation to allow cross-border sharing of electronic health records to make the optimal use of these [33–36].

The strength of this study is that it evaluates a full sample of all authorized innovative products from a period of two years in a consistent manner and provides detailed insights into the cohort of oncology products on what RWD/RWE constitutes across the drug development phases. Despite the limitation that these findings are based on a small number of oncology products, the novelty of the study in comparison to other published studies of our knowledge, is that it provides a good indication and concrete examples on how RWD/RWE can be utilized in oncology and what is accepted for regulatory decision making by EMA. Although the EPAR overview is a subjective judgment for inclusion of important elements in the assessment, it also has its' limitations. Potential for misguiding conclusions drawn from EPAR overview level were further mitigated by reviewing specific chapters of full EPARs which provide more detailed information.

Finally, our results can contribute to the ongoing discussions about the role and importance of RWD/RWE in medicine development and regulatory decision making in the context of the revision of the EU general pharmaceutical legislation, Paediatric and Orphan Medicinal Product legislations [37–41]. The importance of RWD/RWE particularly for cancer therapies (incl rare and pediatric diseases) should be acknowledged by the clinical community and industry and its role alongside the conduct of RCTs adequately reflected in the legislative framework. Guidelines could further describe the overarching framework of RWD/RWE (quality and discoverability, best practice for data governance, limitations etc.) [42]. However, the suitability of RWD/RWE in each application requires a case-by-case analysis considering its purpose of use, implying reflection on the data source, together with its assets and limitations, study objectives and designs, and the overall evidence package issued [13]. Furthermore, as the important policy developments keep moving forward driven by the European Regulatory Network (EMA and National Competent Authorities) [15], US FDA or PMDA in Japan, and international coalitions such as ICMRA or ICH, the findings of this study can help in setting the right perspectives on how much and in what context fit-for-purpose RWD/RWE can support medicines development and regulatory decision making, specifically in development of cancer therapeutics.

5. Conclusion

Therapeutic options to treat patients with cancer have increased impressively over the last decades. But there is still a great need for new and more targeted products. Whether these products will bring clinical benefit to patients with cancer depends very much also on how new drug development is integrated with clinical oncology practice. In our study we found that the clinical context (e.g., natural course of disease, comorbidities, standard care) relevant to a new oncology product, cemented in RWD/RWE, plays a significant role in new oncology product development and is present in virtually all stages of the product development lifecycle. In the past, such data were primarily collected after the product was launched on the market. Our study shows a shift to pre-approval drug development. This shift has been feasible thanks to the many advances in collecting relevant data from daily oncology practice, building registries and other RWD/RWE initiatives.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sini M. Eskola conducts a part-time professional PhD at Utrecht Centre for Pharmaceutical Policy and Regulation. In her daily work, she holds a position as Director Regulatory Strategy and Team Leader at European Federation of Pharmaceutical Industries and Associations (EFPIA). This research is independent and not funded by EFPIA. Andrew Bate is a full-time employee and stock and options holder in GlaxoSmithKline. The views expressed in this article represent the author's own thoughts and are independent of their employers. This research is independent and not funded by GSK. Hubertus G.M Leufkens, Marie L. De Bruin, and Helga Gardarsdottir are employed by Utrecht University conducting research under the umbrella of the Centre for Pharmaceutical Policy and Regulation. This centre receives no direct funding or donations from private parties, including those in the pharmaceutical industry. Research funding from public–private partnerships (e.g., IMI, The Escher Project (http://escher.lygature.org/), is accepted under the condition that no company-specific product or company-related study is conducted). The centre has received unrestricted research funding from public sources, for example, the World Health Organization (WHO), Netherlands Organization for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EC Horizon 2020, the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health.

Appendix 1. Characteristics of the products in the cohort with the focus on oncology and non-oncology products

	Oncology, 24 (21.6 %)	Non-Onco, 87 (78.4 %)	All, 111 (100.0 %)
Conditional approval	4 (16.7 %)	5 (5.7 %)	9 (8.1 %)
Orphan medicine	8 (33.3 %)	19 (21.8 %)	27 (24.3 %)
Exceptional circumstances	0 (0.0 %)	3 (3.4 %)	3 (2.7 %)
Accelerated assessment	0 (0.0 %)	7 (8.0 %)	7 (6.3 %)

Appendix 2. RWE signatures and RWE signatures with data across the drug development phases for different cancer product categories (n = 24). NOTE: The sum of subgroup counts (categories 1, 3 and 5) can amount to a higher number than the overall count for a developmental phase as the subgroups are not mutually exclusive

Cancer type	Carcinomas (lung, breast)	Hematological cancers	Other
n = Number of MAAs (percentage %)	**n = 8 (33.3 %)**	**n = 8 (33.3 %)**	**n = 8 (33.3 %)**
1. Early Discovery			
RWE signature (any)	8 (100.0 %)	8 100.0 %)	8 (100.0 %)
RWE signature with data	7 (87.5 %)	4 (50.0 %)	5 (62.5 %)
1.1 Epidemiology of disease			
RWE signature (any)	2 (25.5 %)	3 (37.5 %)	4 (50.0 %)
RWE signature with data	1 (12.5 %)	0 (0.0 %)	1 (12.5 %)
1.2 Disease features			
RWE signature (any)	7 (87.5 %)	3 (37.5 %)	7 (87.5 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
1.3 Population identification			
RWE signature (any)	8 (100.0 %)	8 (100.0 %)	6 (75.0 %)
RWE signature with data	7 (87.5 %)	4 (50.0 %)	4 (50.0 %)
2.1 Comparison to current clinical practice/general stratification			
RWE signature (any)	3 (37.5 %)	4 (37.5 %)	2 (25.0 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
3. Full Development/Clinical Development			
RWE signature (any)	5 (62.5 %)	5 (62.5 %)	4 (50.0 %)
RWE signature with data	1 (12.5 %)	3 (37.5 %)	0 (0.0 %)
3.1 Trial design			
RWE signature (any)	4 (50.0 %)	0 (0.0 %)	3 (37.5 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
3.2 Efficacy			
RWE signature (any)	3 (37.5 %)	5 (62.5 %)	2 (25.0 %)
RWE signature with data	1 (12.5 %)	3 (37.5 %)	0 (0.0 %)
3.3 Safety			
RWE signature (any)	2 (25.0 %)	3 (37.5 %)	3 (37.5 %)
RWE signature with data	0 (0.0 %)	1 (12.5 %)	0 (0.0 %)
4. Registration/Access/Therapeutic Benefit			
RWE signature (any)	4 (50.0 %)	5 (62.5 %)	6 (75.0 %)
RWE signature with data	0 (0.0 %)	2 (25.0 %)	0 (0.0 %)
5. Lifecycle management			
RWE signature (any)	8 (100.0 %)	8 (100.0 %)	8 (100.0 %)
RWE signature with data	8 (100.0 %)	8 (100.0 %)	7 (87.5 %)
5.1 Safety profile/pharmacovigilance			
RWE signature (any)	8 (100.0 %)	7 (87.5 %)	8 (100.0 %)
RWE signature with data	3 (37.5 %)	3 (37.5 %)	3 (37.5 %)
5.2 Safety profile/Class effect			
RWE signature (any)	2 (25.0 %)	1 (12.5 %)	2 (25.0 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
5.3 Clinical guidance/active monitoring			
RWE signature (any)	8 (100.0 %)	8 (100.0 %)	8 (100.0 %)
RWE signature with data	8 (100.0 %)	8 (100.0 %)	7 (87.5 %)

Appendix 3. RWE signatures and RWE signatures with details across the drug development phases for orphan cancer medicines developed for rare cancers (n = 8). NOTE: The sum of subgroup counts (categories 1, 3 and 5) can amount to a higher number than the overall count for a developmental phase as the subgroups are not mutually exclusive

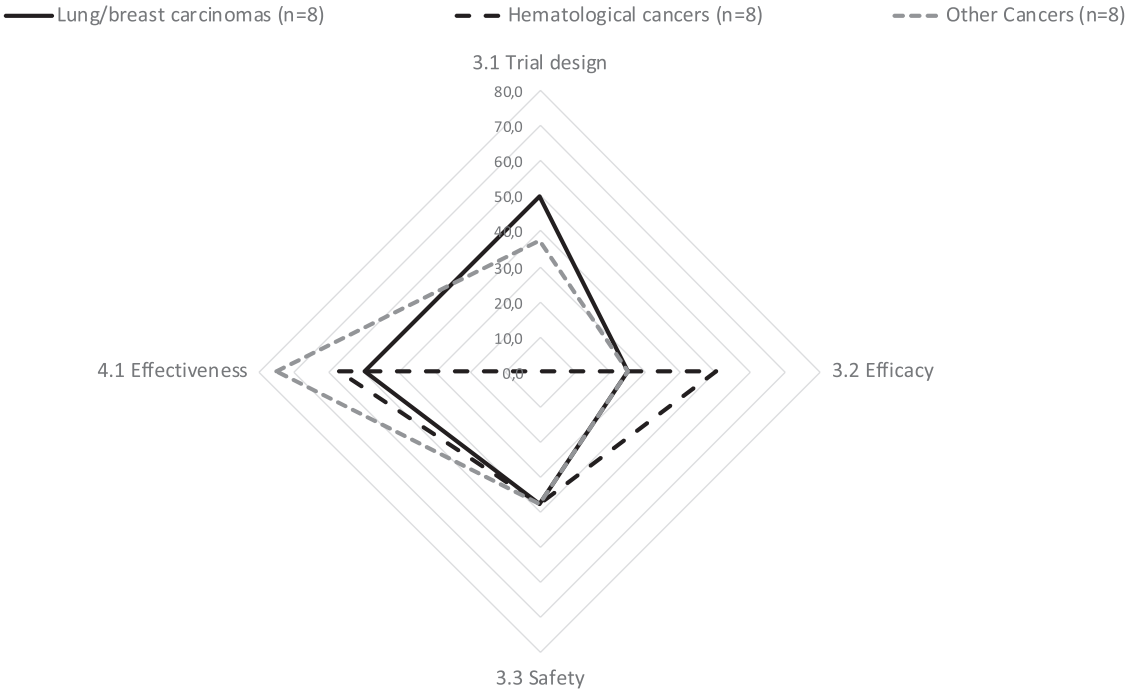
Product status	Orphan	Non-orphan
n = Number of MAAs (percentage %)	**n = 8 (33.3 %)**	**n = 16 (66.7 %)**
1. Early Discovery		
RWE signature (any)	8 (100.0 %)	16 (100.0 %)
RWE signature with data	4 (50.0 %)	12 (75.0 %)
1.1 Epidemiology of disease		
RWE signature (any)	5 (62.5 %)	4 (25.0 %)
RWE signature with data	1 (12.5 %)	1 (6.3 %)
1.2 Disease features		
RWE signature (any)	4 (50.0 %)	13 (81.3 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)
1.3 Population identification		
RWE signature (any)	6 (75.0 %)	16 (100.0 %)
RWE signature with data	3 (37.5 %)	12 (75.0 %)
2.1 Comparison to current clinical practice/general stratification		
RWE signature (any)	4 (62.5 %)	5 (31.3 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)
3. Full Development/Clinical Development		
RWE signature (any)	5 (62.5 %)	9 (56.3 %)
RWE signature with data	3 (37.5 %)	1 (6.3 %)

(*continued on next page*)

(*continued*)

Product status	Orphan	Non-orphan
3.1 Trial design		
RWE signature (any)	5 (62.5 %)	7 (43.8 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)
3.2 Efficacy		
RWE signature (any)	5 (62.5 %)	5 (31.3 %)
RWE signature with data	3 (37.5 %)	1 (6.3 %)
3.3 Safety		
RWE signature (any)	3 (37.5 %)	5 (31.3 %)
RWE signature with data	1 (12.5 %)	0 (0.0 %)
4. Registration/Access/Therapeutic Benefit		
RWE signature (any)	4 (50.0 %)	11 (68.8 %)
RWE signature with data	1 (12.5 %)	1 (6.3 %)
5. Lifecycle management		
RWE signature (any)	8 (100.0 %)	16 (100.0 %)
RWE signature with data	8 (100.0 %)	16 (100.0 %)
5.1 Safety profile/pharmacovigilance		
RWE signature	8 (100.0 %)	15 (93.4 %)
RWE signature with data	5 (62.5 %)	4 (25.0 %)
5.2 Safety profile/Class effect		
RWE signature	1 (12.5 %)	4 (25.0 %)
RWE signature with data	0 (0.0 %)	0 (0.0 %)
5.3 Clinical guidance/active monitoring		
RWE signature	8 (100.0 %)	16 (100.0 %)
RWE signature with data	8 (100.0 %)	15 (93.8 %)

Appendix 4. Patterns of 'RWE signatures' (any) found to support specific categories (trial design, efficacy, safety and effectiveness) of oncology products; carcinomas (lung/breast), hematological cancers and other types of cancers. More details found in Appendices 2 and 3



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