Single-Arm Clinical Trials as Pivotal Evidence for Cancer Drug Approval: a Retrospective Cohort Study of Centralised European Marketing Authorizations between 2010-2019

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Word Count: 4220, 3874 (excluding title page and abstract)

Key words: regulatory; oncology; clinical trials

CONFLICT OF INTEREST: The authors declare no competing interests for this work.

FUNDING: No funding was received for this work.

Abstract

The traditional drug development paradigm, consisting of sequential phases and randomized studies, has been challenged in oncology and hemato-oncology. In the regulatory context, a number of new products have been authorized based on non-randomized efficacy and safety data. We retrospectively analysed the European public assessment reports for anti-cancer treatments authorized between 2010 and 2019 to describe the data behind

such approvals. Twenty two (22) initial marketing authorizations, mainly conditional, were identified. Fifty (50)% of the products had an orphan indication, and 77% had received previous scientific advice. Conclusions of clinical benefit were based on tumour responses, ranging between 15.8-88%. Our data shows that single-arm clinical studies leading to positive regulatory outcomes share common methodological approaches and end points, mostly comparing the overall response rate with a fixed success threshold as the primary analysis. The clinical indications in these approvals are clustered in late-line settings, hematological malignancies and lung cancer. Our findings underline the need to reflect on the current practice, the methodological aspects and end points in single-arm studies, and develop specific regulatory guidance on non-randomized and novel study designs.

Introduction

The traditional paradigm of drug development in malignancies is a sequential evaluation of efficacy and safety, from primary safety evaluation in phase I and first-in-man studies, to be followed by dose finding and preliminary efficacy studies in phase II.[1] When successful, these exploratory findings in advanced disease patients would then lead to confirmation of clinical efficacy and safety, and benefits relative to the existing, best available standard-of-care, in a randomized phase III clinical trial (RCT). Generally, RCTs are also recommended by the EMA anti-cancer guideline and have been considered a way to obtain high-quality data for clinicans and patients to make informed treatment decisions, and to faciliate evidence-based global access to new anti-cancer products.[1,2,3]

Advances in molecular biology and immunology have refined and challenged our understanding of cancer biology and new therapeutic targets for anti-cancer products.[2] Leading to concepts of personalized cancer therapy, targeted agents and precision oncology, these findings have had multiple consequences on the evolution of clinical study designs.[4,5] Indeed, the majority of novel study designs emerged during the recent years have first been applied in oncology. These include master protocols, such as umbrella, basket and platform trials, with a common denominator to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure, potentially without a conventional control arm.[6] Non-randomized study designs without an internal control group, referred to as single-arm trials (SATs), have been traditionally applied in exploratory anti-cancer drug development to investigate drug activity. These studies have generally been conducted in small populations with various tumour types and in very advanced patients, which do not necessarily represent the group for which the product is ultimately intended. More importantly, these studies aim at investigating safety, dose and activity, and therefore apply study endpoints that reflect these aims, such as safety and pharmacokinetic endpoints, and overall response rate (ORR) and duration of response to demonstrate an anti-tumour effect and the time in which this is maintained.[7,8,9]

All novel anti-cancer agents are centrally authorized in the European Union member states, and their development is guided by common regulatory guidance documents.[3,9] The current European guidance clearly recognizes the role of study designs without an internal control group in the exploratory phase, but is less conclusive in terms of such data sets as the sole basis of benefits and risks of a novel anti-cancer product.[3,9] Even in the absence of guidance, there have been a number of such approvals during the recent years. There are few publications that characterise recent regulatory decisions in oncology by the US Food and Drug Administration, and a previous study to report high level regulatory characteristics of all approvals based on

studies without randomization during 2009-2014[10,11,12], but no scientific studies which would have systematically analysed these approvals in oncology. Scientific understanding of these approvals could thus be of fundamental importance for drug development in oncology. With these aims, we sought to systematically study the European regulatory approvals based on uncontrolled efficacy and safety data in oncology, leading to a marketing authorization in the EU, during the time period of 2010-2019. We found that these approvals and studies share common elements of efficacy and safety data generation.

Methods

All novel anti-cancer agents authorized in the EU by the European Commission have been assessed through the centralised marketing authorization procedure falling within the Article 3(1) of Annex of Regulation (EC) No 726/2004.[9] The legal basis of applications for new active substances is within the Article 8.3 of Directive 2001/83/EC, complete and independent application. As a result of assessments, EMA provides a public assessment report (EPAR), which is available in the public domain, as adopted by the Committee for Medicinal Products for Human Use (CHMP) with only information of a commercially confidential nature deleted. These EPARs provide a comprehensive summary of the quality, non-clinical, and clinical pharmacology, safety and efficacy data that have been submitted by the Applicant and used as the basis for the regulatory outcome, and include the scientific justifications for considering the benefit/risk of the product as positive.

We performed a systematic analysis of European marketing authorisations during the time period of 2010-2019 by searching the publicly available EMA database for EPARs in the relevant therapeutic are of L01-04 ATC codes. On the basis of summaries of efficacy data in the EPARs, we identified the products that were recommended for approval on the basis of non-randomized pivotal clinical studies. The analysis was based on

documents that were categorized within "initial authorization documents" in the EMA database, i.e. extensions of indications of licenced products were excluded from the analysis. This restriction was due to different regulatory framework and requirements for initial authorizations and type II marketing authorization variation applications. In addition, the analysis was excluded generic, hybrid and biosimilar applications. The search covered products for which the European Commission had granted a marketing authorization during time period from 1st of January 2010 to 31st of December 2019.

After collecting the data on the regulatory steps taken for the assessment and type of approval, we then described the key characteristics of the pivotal clinical trials, including primary and secondary efficacy end points and extent of safety data sets, and their results generating the evidence on clinical efficacy and safety that have been used in the benefit/risk assessment and as a basis of opinion in each of the identified authorizations. When there were multiple analyses, data cut offs, cohorts or indications, analyses and studies that had been considered as pivotal and included the benefit-risk analysis or efficacy summary of the EPARs were used.

The search was performed and data analysed by three independent readers (O.T., F.L. and E.P), and verified against EMA internal data base and available original publications in the scientific literature whenever needed. Difficulties or disagreements in interpretation were resolved by discussion and concensus among the lead investigators (O.T. and M.T.). Descriptive statistics were performed using Microsof Excel and SAS 9.4 softwares.

Results

Regulatory characteristics of European approvals of anti-cancer products based on SATs

Twenty two (22) initial authorizations based on SATs were identified (Table S1); of these, the first authorization was dated 19th April 2010, and the last 19th September 2019. By the cut-off date (31st January, 2020) of this analysis, one of the 22 marketing authorizations had been withdrawn.

The analysis revealed 14 chemical and 8 biological products. Ten of the 22 products were authorized in hematological malignancies, while 12 targeted solid tumours (Table S1). Among solid tumours, the most common indication was non-small cell lung cancer (NSCLC) with specific genetic alterations, with 5 products (Table S1 online). One approval was based on a basket study design and histology independent indication, and included in this analysis. In addition, two products (allogeneic T-cells and everolimus in tuberous sclerosis complex) within the ATC classification L01-02 were identified but excluded from the analysis as not being essentially indicated in an anti-cancer indication. The approval of dinutuximab beta was considered "under exceptional circumstances" and based on historical data and therefore not included in the analysis.

Among the authorizations, 16 were conditional approvals with specific obligations and 6 were full approvals; in 5 cases divergent opinions by the CHMP members were expressed, while the majority (17/22) were recommended for approval based on consensus (Fig.1). The median time from initial regulatory submission to date of issuing of marketing authorization valid throughout the European Union was 433 days (Fig.1).

In terms of pre-authorization activities, 77% (17/22) of the products had sought scientific advice (SA) or protocol assistance from EMA, with a median number of 2 advice letters (Fig.1). 50% of the products (11/22)

had an orphan designation, and two had a pediatric indication, while two were classified as advanced therapy medicinal products (ATMPs) and had a priority medicines scheme (PRIME) designation.

Clinical studies and efficacy data used as a basis for authorisations

We next analyzed the details of the key efficacy data that had formed the basis of the individual benefit/risk evaluation of the marketing authorization procedures based on the EPARs. All approvals apart from one were based on 1 or 2 efficacy studies that were considered pivotal, while the total number of clinical studies in the dossiers including dose finding, PK and other supportive studies was higher with more than 50% of the dossiers consisting of between 5 to 10 studies (median 8 studies; range from 1 to 24 individual studies; Fig.1, Table 1). One of the applications contained supportive data from a randomized phase III study, and one approval included a study in which patients had been randomized into two different dose levels. In the rest of the studies, no internal control grops was used, and data was reported from a single or multiple uncontrolled study cohorts. One product was authorized in a histology independent indication based on a multiple cohort study including data from a basket trial.

The median of total numbers of patients in the target indication, with individual study cohorts of each product pooled, reflecting the total sizes of efficacy databases, was 175 patients (Fig.1; n=22), with more thatn 50% of the products having an efficacy data base size between 100 and 200 patients. The range in patient numbers was 96-517 patients for products, and from 8 to 517 patients within individual study cohorts, respectively.

Study designs and primary efficacy endpoints

The primary efficacy endpoint was unequivocally defined in all authorizations and studies. 19 of the 22 studies reported ORR as the primary endpoint, while major cytogenetic or major hematological response was used in 2 approvals in chronic lymphocytic leukemia, and CR rate in one approval in B-precursor acute lymphoblastic leukemia (Table 1).

We next analyzed the reported ORRs and treatment effect magnitudes by collecting data from individual patient cohorts of the studies. Pooled data from individual cohorts was used in cases in which the benefit/risk evaluation summary reported a pooled ORR as key basis of the evaluation. Consequently, we found ORRs reported from 45 different cohorts, with a range from 15.8% to 88%; the median was 54.7% (Fig.2). Among the clinical indications, highest ORRs were generally observed in hematological malignancies. Defined response assessment criteria (RECIST or other relevant criteria in hematological malignancies) had been used in all studies, and the majority of studies had used an independent review committee (data not shown).

The studies analyzed generally shared a similar statistical design, hypothesis and sample size calculation, designed to demonstrate that the lower limit of the 2-sided 95% confidence interval for the point estimate of the ORR was above a pre-sepcified value. The pre-specified value was discussed in the EPARs for most of the products, being 20% in the majority of cases, but often without a clear clinical justification (data not shown).

Secondary efficacy endpoints

All data sets provided supportive efficacy data and secondary efficacy endpoints in addition to the primary outcome. 15 out of the 22 data sets provided a median duration of response in 21 separate cohorts, while in the remaining seven cases it was either not reached or not estimated at the time of MAA assessment. When reported, the medians in the cohorts ranged between 5.6 to 26.5 months, with a median of 11.1 months (Fig.3; n=21). Time-to-event (TTE) endpoints, such as PFS and OS, were also provided for the majority of the approvals. Median PFS/RFS data for at least one study cohort was reported in 19 applications, ranging from 2.1 months to 27.2 months (Fig.3). Median OS for at least one study cohort was available in 9 authorizations, while not reported or not reached in 13 authorizations.

Safety data used as a basis for authorisations

We next analysed the extent of safety data at the time of authorization, in comparison to available efficacy data using the safety data reported in the B/R evaluation section and summaries of EPARs. Exposure numbers were significantly higher than patient numbers in efficacy analyses. The median number of patients in the safety evalutions was 300 (Fig.4), together with a very broad range of individual databases between 119 to 2160 subjects. Median duration of exposure in study subjects was reported for 18/22 data sets (data not shown).

Discussion

Randomization has three key roles in clinical trials: first, to ascertain that groups of patients within the trial are balanced with respect to both known and unknown prognostic factors, and hence with respect to their risks of any type of health outcome; second, to provide an unbiased effect size estimate allowing a causal attribution to the treatment, and third, to relate observed effects to a recognized reference treatment to judge clinical relevance.[13] While these principles are widely recognized, the field of anti-cancer medicinal products has noted an emerging number of regulatory approvals based on non-randomized clinical data both in the US and Europe. Our present study is the first to systematically characterize these in the European regulatory framework.

Unmet medical need in advanced malignancies is high, and fast availability of novel innovations is emphasized by the community. As a regulatory reflection, these requirements underline the need for adaptive and faster regulatory assessment and decision making.[14] Arguments to justify regulatory approval based on non-randomized studies are lack of equipoise for randomization in setting where available therapies provide little benefit and where uncontrolled trials allow to assume efficacy in terms of important clinical endpoints and a positive balance of benefits and risks.[15] Our data indicates that conditions, in which data from non-randomized trials has been deemed acceptable for a positive benefit/risk are not necessarily rare: only half of the products had an orphan designation, and the clinical indications were rather dominated by late treatment lines of hematological malignancies and molecular subtypes of NSCLC. The observed sizes of efficacy populations may also imply that rarity of a disease or unfeasibility to recruit patients into a randomized study is not the sole underlying rationale leading to a positive regulatory outcome based on uncontrolled data, while high unmet medical need plays a major role. Notably, increased collaboration and the usage of novel study designs, for example master protocols allowing a shared control arm for different experimental therapies, could have facilitated randomized studies in these settings. Our data included only one authorization that was essentially based on a basket trial design.[16]

Another key finding of this study is that SATs leading to a positive regulatory outcome in oncology share common methodological elements. Key conclusions on clinical benefit were drawn based on response rates, either ORR, CR or molecular responses in all of the approvals. Anti-tumour response is an efficacy endpoint that can unambiguously be attributed to the drug effect, as spontaneous responses seldomly occur in malignancies, and therefore it is thought that a counterfactual is not needed for it. Our data however showed a broad range of ORRs in the approvals, raising the question how to set a uniform relevant bench mark magnitude of response rate, orto translate observed ORRs into clinical benefit.[17] While in some instances, such as in the case of inoperable squamous cell carcinoma[18], tumour shrinkage *per se* may be a direct benefit to the patient, tumour response is an inherently heteregeneous concept. In our data set, targeted therapies and hematological malignancies were generally associated with higher response rates than e.g. immune therapies; this is in line with the fact that the clinical value of ORR may ultimately be different also for different types of pharmacological agents, and should be interpreted in connection with DoR, depth of response and other supporting evidence.[17,19,20] On the other hand, against this background our finding that the success thresholds for comparison with the lower bound of the 95%-confidence interval for the ORR point estimates have been relatively uniform may indirectly imply that zero hypotheses and target ORRs in the studies have not been set based fully on scientific and clinical justifications but rather on consistency or tradition within the field of oncology. As opposed to response rates, the value of TTEs has generally been considered limited in the

absence of comparative data. Nevertheless, we noted that the majority of studies did provide TTE data as supportive evidence to the primary end point. In contrast to the provision of TTE data, the use of historical or real-world data to contextualize the observations was limited.

Our present study is limited to successful MA applications only, which constitutes a survivor bias overestimating the ability of SATs to provide sufficient evidence and the probability of success of SAT-based applications. Accordingly, the presented approvals should not be read as precendents overruling the theoretical limitation of SAT in generating evidence appropriate for decision making. On the other hand, our data may also underestimate the frequency SATs are used for regulatory purposes, as we excluded extensions of therapeutic indications from the analysis, and have studied the European regulatory framework only. These restrictions however were necessary to have a homogenous data base in terms of regulatory characteristics, as the total level of evidence is considered different in initial approvals and type II variations intended for extensions of indications. Finally, an obvious limitation of our study is the basis in original clinical study reports only to the extent the data can be shared in a public domain.

In conclusion, our present study demonstrates that SATs used as a pivotal basis for regulatory approval share common methodological approaches, primary endpoints and success thresholds, and as expected given the heterogeneity of indications, variable magnitudes of treatment effect. Equally, the licensures show consistent regulatory characteristics, as demonstrated e.g. by the conditional nature of the majority of approvals. At the same time, it supports the view that, such applications cannot generally be concluded yet to define a uniform regulatory concept of a authorization based on evidence from SATs alone. Furher scientific work is needed both from drug developers and regulatory community to further understand the role of non-randomized evidence in the decision making process and whether and how the drug effects that can be identified through non-randomized data translate into an impact on time-dependent endpoints such as PFS and OS, as well as on HRQoL.

Study Highlights

What is the current knowledge on the topic?

Previous studies have reported regulatory data on single-arm trial and conditional approvals in general, but data from the last ten years, details of data sets and data in oncology are currently lacking.

What question did this study address?

Our study addresses the question of the regulatory and scientific basis of European anti-cancer drug approvals based on single-arm trials.

What does this study add to our knowledge?

We systematically analyzed the data behind European marketing authorizations based on single-arm trials in oncology, and provide comprehensive data on study designs and end points used.

How might this change clinical pharmacology or translational science?

Current drug development is dominated by anti-cancer products. Our study highlights the need to re-align regulatory guidance and practice.

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 European Medicines Agency or one of its committees or working parties or the Finnish Medicines Agency or the Norwegian Medicines Agency.

Author Contributions: O.T., F.L., A.S., E.P., and M.T. wrote the manuscript; O.T., F.L., A.S., E.P., and M.T. designed the research; O.T., M.T., F.L., E.P., and M.T. performed the research, O.T., F.L., and E.P. analyzed the data.

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Figure legends

Figure 1. Key regulatory characteristics of initial SAT approvals in Europe. (A) Number of divergent and concensus opinions. (B) Total number of clinical studies included in benefit-risk evaluations. (C) Review times

(days from submission to authorization in the EU). (D) Numbers of pre-authorization scientific advice letters. Results are expressed as % of approvals/authorizations, quantiles and interquartile ranges, n=22.

Figure 2. Efficacy data bases and end points in benefit-risk evaluation of single arm regulatory approvals. (A) Number of patients in the efficacy evaluation/efficacy data base. Results are expressed as % of approvals/authorizations, quantiles and interquartile ranges, n=22. (B) ORRs in study cohorts with ORR as a primary end point. Results are expressed as % of approvals/authorizations, quantiles and interquartile ranges, n=45. (C) ORRs in identified individual study cohorts, n=45.

Figure 3. Supportive efficacy end points in benefit-risk evaluation of single arm regulatory approvals. (A) Durations of responses in study cohorts with ORR as primary end point, n=21. (B) Median PFS values for individual study cohorts. (C) Median OS values for individual study cohorts.

Figure 4. Sizes of safety data bases. Results are expressed as % of approvals/authorizations, quantiles and interquartile ranges, n=22.

Supplemental Files

1. Supplemental Table 1

Table 2. Key characteristics of products and studies included in the analysis.

Product	Primary end point in the pivotal study	Pooled total number of patients in the key MA efficacy evaluation set	Type of initial regulatory approval	Type of supportive data in the MA evaluation	Randomized phase III study as a post-authorization condition
Alectinib	ORR	225	Conditional	PK studies	Yes
Atezolizumab	ORR	429	Full	PK studies; interim data from a randomized study; phase I study	Yes
Avelumab	ORR	127	Conditional	Part B of the pivotal study; PK study; historical data	No
Axicabtagene ciloloucel	ORR	111	Full	Phase I efficacy/ safety/feasibility studies	No
Blinatumomab	CR/CRh rate	189	Conditional	2 supportive efficacy studies	Yes
Bosutinib	MCyR	571	Conditional	PK, PD studies	No
Brentuximab vedotin	ORR	160	Conditional	PK, dose escalation studies; efficacy data in Asian population	No
Cemiplimab	ORR	193	Conditional	Phase I dose finding study	No
Ceritinib	ORR	246	Conditional	PK, PD studies	Yes
Crizotinib	ORR	125	Conditional	Supportive phase I efficacy /safety PK studies; early phase III data	Yes
Ibrutinib	ORR	115	Conditional	PK studies; data from a phase III study in a different indication	Yes
Idelalisib	ORR	125	Full	PK, PD, efficacy studies; data from a phase III study in a different indication	Yes
Larotrectinib	ORR	102	Conditional	PK; additional data from the basket study	No
Lorlatinib	ORR	198	Conditional	Phase I part of the pivotal study; PK studies	Yes
Ofatumumab*	ORR	138	Conditional	PK, dose finding studies	Yes
Osimertinib	ORR	398	Conditional	PK; extension phase of ongoing studies	Yes
Ponatinib	MCyR/MaHR	444	Full	PK	No
Rucaparib	ORR	157	Conditional	PK, supportive efficacy	Yes
Sonidegib	ORR	210	Full	Randomization to two dose levels; PK; dose-response study	No
Tisagenlecleucel	ORR	240	Full	PK; historical data	No
Venetoclax	ORR	107	Conditional	PK, dose response, supportive	No

				safety/efficacy data	
Vismodegib	ORR	96	Conditional	Supportive phase I efficacy/safety PK/dose response data	No

*Marketing authorization withdrawn after initial authorization; ORR=overall response rate; CR=complete response; MCyR=major cytogenetic response; MaHR=major hematological response PK=pharmacokinetics; PD=pharmacodynamics;