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Current Perspectives for External Control Arms in Oncology Clinical Trials: Analysis of EMA approvals 2016-2021

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ABSTRACT

Leveraging external control data, especially real-world data (RWD), has drawn particular attention in recent years for facilitating oncology clinical development and regulatory decision-making. Medical regulators have published guidance on accelerating the use of RWD and external controls. However, few systematic discussions have been conducted on external controls in cancer drug submissions and regulatory feedback.

This study aimed to identify European oncology drug approvals using external control data to demonstrate clinical efficacy. We included 18 eligible submissions employing 24 external controls and then discussed the use of external control, data sources, analysis methods, and regulators' feedback.

The external controls have been actively submitted to the European Medical Agency (EMA) recently. We found that 17% of the EMA-approved cancer drugs in 2016-2021 used external controls, among which 37% of the cases leveraged RWD. However, nearly one-third of the external controls were not considered supportive evidence by EMA due to limitations regarding heterogeneous patient populations, missing outcome assessment in RWD, and inappropriate statistical analysis.

This study highlighted that proper use of external controls requires a careful assessment of clinical settings, data availability, and statistical methodology. For better use of external controls in oncology clinical trials, we recommend: prospective study designs to avoid selection bias, sufficient baseline data to ensure the comparability of study populations, consistent endpoint measurements to enable outcome comparison, robust statistical methodology for comparative analysis, and collaborative efforts of sponsors and regulators to establish regulatory frameworks.

KEYWORDS

external control; historical control; oncology; clinical trial; real-world data

1. Introduction

Randomized controlled trials (RCTs) are the gold standard for evaluating the efficacy of new treatments[1]. RCTs establish causal conclusions by randomly assigning patients to either an investigational or concurrent control treatment that usually consists of a placebo or standard of care. Nevertheless, ethical or feasibility issues can hinder the randomization process in oncology clinical trials. For example, when a promising new therapy is being studied in early-stage clinical trials for cancer with high unmet needs, enrolling patients into control arms may cause ethical issues and unwillingness to participate[2]. Besides, with the advances in molecular classification and precision medicine in oncology - further dividing patient populations into smaller groups - the number of patients available for a particular clinical trial may be insufficient to produce valid evidence [3,4]. Medical regulators acknowledge these challenges and have granted conditional approvals to submissions with single-arm trials[5,6].

External controls have been introduced as a pragmatic approach to knowledge production, which can improve the interpretation of single-arm trial results and reduce the bias due to the lack of randomization[6]. Data from historical clinical trials or real-world databases expand the use of external controls to minimize patient burden and facilitate drug development[7–9].

Recent technological advances and a dynamic policy landscape have created a fertile ground for using real-world data (RWD) to improve clinical evidence generation[10]. RWD are qualified as routinely collected data relating to patient health status and the delivery of health care other than traditional RCTs such as electronic health records (EHRs), claims, registries, or patient-generated data[11,12]. Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from the analysis of RWD is then considered real-world evidence (RWE). The regulatory authorities have signaled their support for using RWD to generate clinical evidence. In 2018, the US Food and Drug Administration (FDA) published the framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements[11]. In 2019, the European Medicines Agency (EMA) published the OPTIMAL framework for RWE, consisting of operational, technical and methodological[12]. Besides, the EMA outlined the vision for establishing the value of RWE for various regulatory uses by 2025[13].

Recent evidence shows that RCT and RWE findings were not always matched despite attempts to emulate RCT design and confounder adjustment[14]. Thus, challenges remain before external controls can be an integrated part of decision-making[15]. On the other hand, researchers proposed the combination of RCTs and RWE data for clinical knowledge generation in the era of precision medicine[4]. External controls leveraging RWD are of particular interest in oncology drug development to foster patients' access to innovative therapy in the context of segmentation of tumor entities and targeted therapy [16,17]. Learning from previous external control applications can inform future studies and avoid common pitfalls. So far, however, few systematic discussions have been conducted about external controls in oncology drug development.

This study aims to systematically review the external controls in oncology clinical development and understand their impact on regulatory decision-making. Section 2 defines external control and reviews statistical considerations. Sections 3 and 4 describe the study methodology and outline the search findings. Section 5 discusses the statistical characteristics of external controls, their impact on regulatory decision-making, and recommendations for using external controls. Finally, Section 6 concludes the study.

2. External controls and Statistical considerations

In an externally controlled trial, patients receiving the investigational treatment are compared with patients external to the study. The external control can consist of patients treated earlier than the concurrent clinical trial (historical control) or during the same period on different clinical conditions[18]. External control is also known as synthetic control, implying the control data have been selected and processed before being incorporated into the analysis. "External control", "historical control", and "synthetic control" are used interchangeably in practice[7,19–22]. This study uses "external control" to refer to data derived outside the concurrent clinical trial.

In single-arm or parallel-group trials, external controls serve as the sole comparator to provide benchmarks and contextualize the new treatment[9,21]. In RCTs with unequal randomization, external controls can augment the concurrent control to form hybrid control arms composed of internal and external control data, which allows randomizing fewer patients to the control arm[3,23–25].

Clinical data for creating external controls fall into two major categories: clinical trial data and real-world data (RWD). The choice of data sources depends on the research questions. For example, for the endpoints of interest

measured in a specialized manner such as key biomarker testing, previous clinical trial data can be appropriate. On the other hand, RWD might be better suited for cancers with limited experience from clinical trials.

External controls are subject to systematic biases due to the absence of randomization. The validity of external control lies in its exchangeability with the internal patients, for which Pocock proposed six evaluation criteria in 1976: (1) the same defined standard treatment; (2) the same patient eligibility; (3) the same treatment evaluation; (4) comparable distributions of essential patient characteristics; (5) performed in the same organization; (6) no other observed confounders[22]. While these criteria are stringent in non-randomized clinical conditions, applying them to the most significant degree possible can minimize the risk of substantial biases. The FDA cited these criteria in the statistical review for drug approvals[26].

Statistical analysis methods have been developed to mitigate the biases of incorporating external controls. Frequentist approaches ensure between-group comparability of baseline characteristics by following two main steps: (1) estimate a balance score (e.g., propensity score, Mahalanobis distance) using a selection of covariates that can impact the treatment assignment and outcome, (2) employ the balance score to obtain comparable external and internal cohorts through analysis such as matching, inverse probability weighting, and covariate adjustment[27,28]. Bayesian approaches account for the outcome heterogeneity by incorporating and discounting the external control data into the new clinical trial, using power prior, commensurate prior, or meta-analytic prior[29,30].

3. Search methodology and data extraction

We searched European public assessment reports (EPARs) for human medicines (<https://www.ema.europa.eu/en/medicines>) to identify regulatory submissions referring to external control data in clinical efficacy. We included original marketing applications for cancer drugs in 2016-2021 and excluded drugs for diagnostic use only or withdrawn from the market. The search was conducted in 31 May 2022.

From January 1, 2016, to December 31, 2021, 113 cancer drugs were granted marketing authorization by EMA (Figure 1). Two drugs for diagnostic use and eight withdrawn from the market were excluded from the study. After screening the EPARs of the eligible 103 medicines, we identified 18 (17%) drug submissions using external controls. Figure 2 presents the number of screened cancer drugs and eligible external control cases.

We examined the characteristics of the drug approvals concerning: drug name, class of drug, approval year, marketing authorization holder, therapeutic area and indication. We scrutinized the clinical efficacy section in the EPAR of such approvals to extract information on pivotal studies and external controls: pivotal study design, use of external control, source of external control data, method of analysis, and EMA's decision on the external controls.

Figure 1: Selection of external control cases from cancer drug approvals

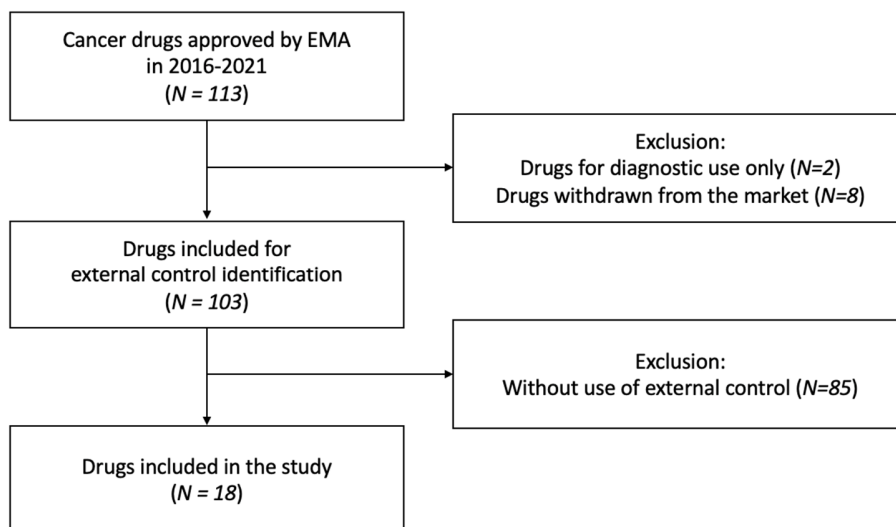
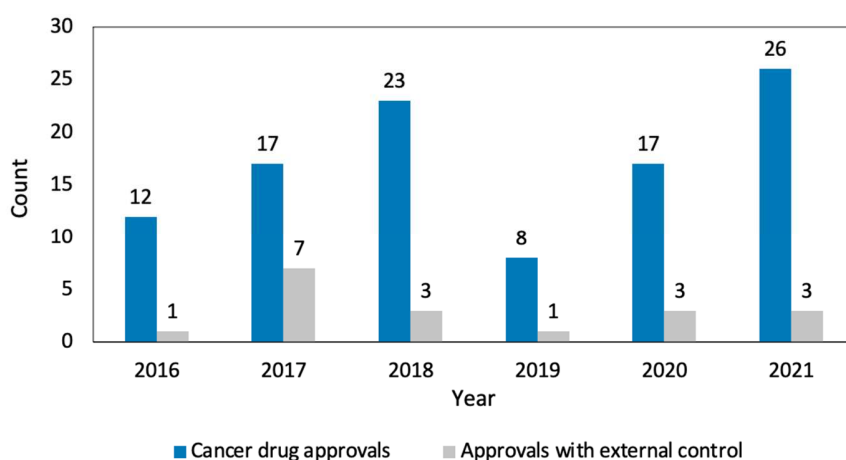


Figure 2: Summary of identification results in 2016-2021



4. Results

Table 1 lists the identified drugs and external controls. 7 (39%) of the 18 identified drugs were granted conditional approval, all of which were submitted after 2019. Note that six drug submissions have used multiple external controls for one pivotal study or have conducted pivotal studies for multiple indications; therefore, the 18 submissions leveraged 24 external controls. Though all drugs were approved by EMA, some external controls were not deemed supportive. We considered the EMA's decision "accepted" if the external controls were included as supportive evidence to demonstrate efficacy and "rejected" if the external controls were deemed inadequate for decision-making.

Table 1: Cancer drug approvals using external controls

Drug	Year	Class of drug	Therapeutic area	Conditional	Pivotal study design	Use of external control	Source of external	Method of analysis	EMA's decision
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				approval			control data		
Minjuvi (tafasitamab)	2021	Monoclonal antibody	Lymphoma	Yes	Phase 2, single-arm, open-label, multicentre	Comparative efficacy analysis	RWD	Confounding adjustment	Rejected
Abecma (idecabtagene vicleucel)	2021	Autologous cellular immunotherapy	Multiple Myeloma	Yes	Phase 2, single-arm, open-label, multicentre	Comparative efficacy analysis	RWD	Confounding adjustment	Rejected
Enhertu (trastuzumab deruxtecan) - 1	2021	Antibody-drug conjugate	Breast Neoplasms	Yes	Phase 2, single-arm, open-label, multicenter, 2-part	Comparative efficacy analysis	RWD	Confounding adjustment	Rejected
Enhertu (trastuzumab deruxtecan) - 2	2021	Antibody-drug conjugate	Breast Neoplasms	Yes	Phase 2, single-arm, open-label, multicenter, 2-part	Understanding the natural history of disease	Published observational studies	Meta-analysis	Accepted
Blenrep (belantamab mafodotin)	2020	Antibody-drug conjugate	Multiple Myeloma	Yes	Phase 2, two-arm, randomized, open-label, multicentre	Historical benchmark	Published observational studies	Descriptive	Accepted
Rozlytrek (entrectinib)	2020	Kinase inhibitor	Non-Small-Cell Lung Cancer	Yes	Phase 2, single-arm, open-label, multicenter, basket study	Comparative efficacy analysis	RWD	Confounding adjustment	Rejected
Tecartus (brexucabtagene autoleucel) - 1	2020	Autologous cellular immunotherapy	Lymphoma	Yes	Phase 2, single-arm, open-label, multicentre	Historical benchmark	Published observational studies	Descriptive	Accepted
Tecartus (brexucabtagene autoleucel) - 2	2020	Autologous cellular immunotherapy	Lymphoma	Yes	Phase 2, single-arm, open-label, multicentre	Historical benchmark	Published observational studies	Meta-analysis	Rejected
Libtayo (cemiplimab)	2019	Monoclonal antibody	Squamous Cell Carcinoma	Yes	Phase 2, single-arm, 3-group, multicenter	Comparative efficacy analysis	RWD	Descriptive	Accepted
Apealea (paclitaxel)	2018	Mitotic inhibitor	Ovarian Neoplasms	No	Phase 3, parallel-g, randomized, controlled, open-label, non-inferiority study	Defining margin of non-inferiority	Historical clinical trials	Meta-analysis	Accepted
Verzenio (abemaciclib) - 1	2018	Kinase inhibitor	Breast Neoplasms	No	Phase 2, single-arm, open-label, multicentre	Historical benchmark	Unspecified	Descriptive	Accepted
Verzenio (abemaciclib) - 2	2018	Kinase inhibitor	Breast Neoplasms	No	Phase 2, single-arm, open-label, multicentre	Comparative efficacy analysis	RWD	Confounding adjustment	Rejected
Yescarta (axicabtagene ciloleucel)	2018	Autologous cellular immunotherapy	Lymphoma	No	Phase 2, single-arm, open-label, multicentre	Comparative efficacy analysis	RWD and historical clinical trials	Meta-analysis	Accepted
Bavencio (avelumab)	2017	Monoclonal antibody	Neuroendocrine Tumors	No	Phase 2, single-arm, open-label, multicentre	Understanding the natural history of disease	RWD	Descriptive	Accepted
Qarziba (dinutuximab beta) - 1	2017	Monoclonal antibody	Neuroblastoma	No	retrospective data analysis under a compassionate use program	Comparative efficacy analysis	RWD	Descriptive	Accepted
Qarziba (dinutuximab beta) - 2	2017	Monoclonal antibody	Neuroblastoma	No	retrospective data analysis under a compassionate use program	Comparative efficacy analysis	Historical clinical trials	Descriptive	Accepted
Rydapt (midostaurin)	2017	Kinase inhibitor	Leukemia, Mastocytosis	No	Phase 2, single-arm, multicentre	Comparative efficacy analysis	Historical clinical trials	Confounding adjustment	Rejected
Tecentriq (atezolizumab) - 1	2017	Monoclonal antibody	Non-Small-Cell Lung Cancer	No	Phase 2, single-arm, multicentre	Historical benchmark	Historical clinical trials	Descriptive	Rejected
Tecentriq (atezolizumab) - 2	2017	Monoclonal antibody	Urologic Neoplasms	No	Phase 2, single-arm, multicentre, two-cohort	Historical benchmark	RWD	Confounding adjustment	Rejected
Ledaga (chlormethine)	2017	Alkylating agent	Mycosis Fungoides	No	phase 2, multicenter, randomized, comparator-controlled, third party (observer) blinded, non-inferiority study	Defining margin of non-inferiority	Unspecified	Descriptive	Accepted

Blitzima (rituximab)	2017	Monoclonal antibody	Lymphoma, Leukemia	No	Phase 1, randomized, controlled, multicentre, 2-arm, parallel-group, double-blind	Comparative efficacy analysis	Historical clinical trials	Descriptive	Accepted
Truxima (rituximab) - 1	2017	Monoclonal antibody	Lymphoma, Leukemia	No	Phase 1, randomized, controlled, multicentre, 2-arm, parallel-group, double-	Comparative efficacy analysis	Historical clinical trials	Descriptive	Accepted
Truxima (rituximab) - 2	2017	Monoclonal antibody	Lymphoma, Leukemia	No	open-label, single-arm, maintenance study	Defining margin of non-inferiority	Historical clinical trials	Descriptive	Accepted
Darzalex (daratumumab)	2016	Monoclonal antibody	Multiple Myeloma	No	Phase 2, open-label, multicentre, 2-arm	Historical benchmark	Published observational studies	Descriptive	Accepted

Table 2 summarizes the characteristics of external controls regarding use for clinical efficacy, data source, analysis method, and EMA's decision.

Table 2: Summary of external control characteristics

	n Total=24	%
Use of external control		
Comparative efficacy analysis	12	50%
Historical benchmark	7	29%
Defining margin of non-inferiority	3	13%
Understanding nature history of disease	2	8%
Source of external control data		
Real-world data (RWD)	9	37%
Historical clinical trials	7	29%
RWD and historical clinical trials	1	4%
Published observational studies	5	21%
Unspecified	2	8%
Method of analysis		
Descriptive analysis	13	54%
Comparative analysis with confounding adjustment (matching, inverse probability weighting)	7	29%
Meta-analysis	4	17%
EMA's decision on external control		
Accepted	15	63%
Rejected	9	37%

Table 3 summarizes the EMA's decision on external controls by data sources and analysis methods.

Table 3: EMA's decision on external controls

	EMA's decision on external controls		
	Accepted	Rejected	Total
Source of external control data			
Real-world data (RWD)	3 (33%)	6 (67%)	9 (100%)

Historical clinical trials	5 (71%)	2 (29%)	7 (100%)
RWD and historical clinical trials	1 (100%)	0 (0%)	1 (100%)
Published observational studies	4 (80%)	1 (20%)	5 (100%)
Unspecified	2 (100%)	0 (0%)	2 (100%)
Method of analysis			
Descriptive	12 (92%)	1 (8%)	13 (100%)
Confounding adjustment	0 (0%)	7 (100%)	7 (100%)
Meta-analysis	3 (75%)	1 (25%)	4 (100%)
Total	15 (63%)	9 (37%)	24 (100%)

Table 4 presents the limitations cited by EMA for rejecting external controls to support clinical efficacy.

Table 4: Limitations identified by EMA on external controls

Drug	Year	Source of external control data	Method of analysis	Limitations identified by EMA
Minjuvi (tafasitamab)	2021	RWD	Confounding adjustment	Heterogeneous patient populations, differences in standard of care received during treatment, suboptimal statistical methodology
Abecma (idecabtagene vicleucel)	2021	RWD	Confounding adjustment	Selection bias of the study population, missing data of prognostic factors
Enhertu (trastuzumab deruxtecan) - 1	2021	RWD	Confounding adjustment	Selection bias of the study population, missing assessment of response, differences in the measurement of endpoint, not optimal statistical methodology
Rozlytrek (entrectinib)	2020	RWD	Confounding adjustment	Limitations of the study design, limited data
Tecartus (brexucabtagene autoleucel) - 2	2020	Published observational studies	Meta-analysis	Heterogeneous patient populations, limited information on the study design
Verzenio (abemaciclib) - 2	2018	RWD	Confounding adjustment	Heterogeneous patient populations
Rydapt (midostaurin)	2017	Historical clinical trials	Confounding adjustment	Limited information on the baseline characteristics, no correction for the time of initiation of treatment
Tecentriq (atezolizumab) - 1	2017	Historical clinical trials	Descriptive	Limited information on the determination of historical response rates
Tecentriq (atezolizumab) - 2	2017	RWD	Confounding adjustment	Heterogeneous patient populations

5. Discussion

We identified that 50% of external controls were used for comparative efficacy analysis, and 29% served as historical benchmarks in the superiority study design. Moreover, 8% of external controls provided contextual information on the natural history of disease in rare indications. Besides, 13% of external controls were included in defining the margin of non-inferiority for non-inferiority hypotheses. All external controls were employed in single-arm trials.

We did not find external controls supplementing the concurrent control arm in RCTs. Though there have been discussions on combining external with internal data in RCTs[21,31], the hybrid control arm has yet to be applied for EMA submissions. Nevertheless, the hybrid design allows one to evaluate population comparability and can be considered in future external control studies[25].

We observed that the external controls used most individual RWD (38%) and historical clinical trials (29%). 21% cited published studies, including prospective or retrospective observational studies. 8% did not specify the data source. One case (4%) employed individual RWD and historical clinical trial data. The results highlighted the broad usage of RWD in external controls in recent cancer drug approvals.

We found that 54% of the external controls used descriptive analysis and naive comparison, and 17% applied meta-analysis using aggregate or patient-level data. Besides, 29% performed comparative efficacy analysis with adjustment for confounding covariates, including matching and inverse probability weighting (based on propensity score or Mahalanobis distance) with individual patient data from RWD or historical clinical trials.

The EMA accepted 63% of the external controls for demonstrating clinical efficacy. However, Table 3 shows that only 33% of external controls using RWD were considered supportive evidence. By contrast, the majority of external controls using data from historical clinical trials (71%), both RWD and historical clinical trials (100%), published studies (80%), or unknown sources (100%) were accepted. Regarding the analysis method, the EMA accepted most external controls using descriptive analysis (92%) or meta-analysis (75%). In comparison, no case applying methods of confounding adjustment (0%) was considered supportive evidence. These results indicate that the EMA primarily considered the pivotal study results in decision-making, and various data sources or analysis methods did not mitigate the concerns about the systematic bias of external controls.

The limitations of external controls cited by EMA (Table 4) primarily concerned the Pocock criteria discussed in Section 2.2. Heterogeneity in the external and internal patients was a significant issue. It was caused by differences in the standard of care or limited information from the sponsors on baseline characteristics, especially on significant prognostic factors. The regulators also pointed out that missing or different assessment of endpoints was an essential downside of using RWD in external controls. Besides, unclear study design and selection bias hindered regulators' understanding and acceptance of external controls. Unluckily, these biases were hardly compensated through statistical methodology as the regulators deemed the sponsors applied suboptimal analysis.

To improve the use of external controls in regulatory decision-making, we first suggest a priori trial planning considering external control data. Sponsors should engage with regulators early to align the acceptability of external control for the target population, the study design, and the methodology to avoid selection bias. Secondly, we recommend evaluating external data using Pocock's criteria to confirm population comparability and outcome assessment. Thirdly, we advise robust statistical analysis with adjustment for confounders to reduce potential bias. For example, use doubly robust estimation for propensity score methods because propensity score estimation is subject to model misspecification[32,33]. Besides, using individual RWD to emulate target trials can help ensure fit-for-purpose data and confounding control[34]. Fourthly, we suggest performing sensitivity analysis to validate data quality and study results. Finally, we encourage sponsors to work with regulators to develop regulatory guidance on external controls for study design, data selection, and analysis plans.

Our study was conducted in a systematic manner with in-depth extractions of external control characteristics and objective discussions on the issues of external controls. Despite this, our study was subject to several limitations. First, we limited our scope with a prespecified inclusion period of 2016-2021 under the presumption that external control using RWD is a recently emerging research interest in oncology. Second, our data extraction was limited to the EMA's public assessment reports rather than the sponsors' original submission documents. As a result, some details on external controls may have been omitted. Finally, we did not scrutinize the impact of external control on regulatory pathways, such as conditional marketing authorization. Besides, the prespecified period of 2016-2021

may limit the assessment of post-authorization changes. It can be interesting for future work to study the use of external controls for diverse regulatory pathways.

6. Conclusion

There has been growing research interest in leveraging external controls to facilitate oncology clinical trials. Medical regulatory agencies have published frameworks on accelerating the use of RWD and external controls for regulatory decision-making. However, few systematic discussions were conducted about current applications of external controls in oncology drug development and regulatory feedback. This study identified 18 EMA-approved oncology drugs leveraging 24 external controls. We discussed the use of external control, data sources, analysis methods, and regulators' decision.

We found that external controls had been actively submitted to the EMA. 17% of the EMA-approved cancer drugs in 2016-2021 used external controls, among which 37% of the cases leveraged RWD. However, nearly one-third of the external controls were not considered supportive evidence by EMA due to limitations regarding heterogeneous patient populations, missing outcome assessment in RWD, and inappropriate statistical analysis. This study highlighted that the validity of external controls requires carefully assessing data availability and determining the optimal clinical and statistical methodology.

Our findings highlighted that proper use of external controls requires a careful assessment of clinical settings, data availability, and statistical methodology. For better use of external controls in oncology clinical development, we suggest: *a priori* study designs to avoid selection bias, sufficient baseline data to ensure the comparability of study populations, consistent endpoint measurements to enable outcome comparison, robust statistical methodology for comparative analysis, and collaborative efforts of sponsors and regulators to establish frameworks on external controls.

Declaration of Interest statement

XW receives Ph.D. funding from Sanofi and Association Nationale de la Recherche et de la Technologie (ANRT).

FD, RH, and CL are employees of Sanofi.

The other authors declare no conflict of interest.

Author Contributions

XW: Writing – original draft; Writing – review & editing.

FD: Writing – review & editing.

CL: Writing – review & editing.

RH: Writing – review; Supervision.

AL: Writing – review & editing; Supervision.

RR: Writing – review & editing; Supervision.

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