v. 3, n. 102, 2023

International Journal of Health Science

OVERVIEW OF PHASE IV CLINICAL TRIALS IN ONCOLOGY IN BRAZIL

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Abstract: Introduction: Phase IV trials are conducted as postmarketing efforts to evaluate a new drug's characteristics further, and they may be essential for understanding a drug's toxicity profile.
Objectives: This study aims to analyze phase IV trials concerning oncology in Brazil in the last five years, paralleling a recent Chinese study that examined phase IV clinical trials worldwide and identified areas that require greater attention.
Methods: This integrative review was restricted to phase IV clinical trials concerning oncology in Brazil between 2018 and 2023. A data set of 15 studies was found on the website ClinicalTrials.gov on June 30, 2023. We further identified trials whose purposes were 'Treatment'. Then, studies that included the pediatric population and hematological malignancies were excluded. Finally, six eligible phase IV trials were included in our analysis.
Results and Discussion: When comparing the selected trials, they may take years to be finalized, demanding considerable financial resources, and many of them are developed with the sponsorship of pharmaceutical industries, which may lead to bias. None of the studies include only the Brazilian population, which is another biased source.
Conclusions: Despite the importance of phase IV trials in evaluating the long-term efficacy and safety of drugs, only a few of these trials concerning oncology took place in Brazil in the last five years. In this perspective, we hope that researchers develop more phase IV studies in the following years, adapted to the national population and reality and with the contribution from different sectors of society.
Keywords: Phase IV Trials, Oncology, Brazilian Researchers.

INTRODUCTION

Due to the modest size of developmental drug programs, evaluating a drug's toxicity profile and overall understanding of its safety can only partially be determined prior to approval [1]. Phase IV trials are conducted as postmarketing efforts to evaluate further the new drug's characteristics concerning safety, efficacy, new indications for additional patient populations, and new formulations [2].

Regulatory authorities may require these trials, or they may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs or on specific population groups who are unlikely to subject themselves to trials) [3]. Therefore, Phase IV activities are at the center of cooperation of marketing, medical, drug regulatory, R&D (research and development), and legal functions. The aim is to deliver the maximum benefit to the patients and to reap the investments during development [4]. On the other hand, harmful effects discovered by them may result in a drug being withdrawn from the market or restricted to specific uses [3].

ClinicalTrials.gov is a Web-based resource that provides patients, healthcare professionals, researchers, and the public easy access to publicly and privately supported clinical studies on various diseases and conditions. Information on the website is provided and updated by the sponsor or principal investigator of the clinical studies, which are generally registered when they begin, and the information is updated throughout them. Studies listed in the database are conducted in more than 220 countries [5].

Harnessing this resource, a recent sizable Chinese study [6] examined the characteristics of registered phase IV clinical trials regarding drug safety worldwide and identified areas that

require greater attention. The objective of this study is to do a similar analysis considering phase IV trials concerning oncology, which took place in Brazil in the last five years.

MATERIALS AND METHODS

DATA SOURCE

Our analysis was restricted to phase IV clinical trials registered with ClinicalTrials.gov concerning oncology, which took place in Brazil between 2018 and 2023. A data set of 15 phase IV clinical studies registered with ClinicalTrials.gov was found on the website on June 30, 2023.

STUDY SELECTION

Two authors (MFHV and CMV) selected the eligible studies and summarized their results independently. Figure 1 shows the complete selection process. Our analysis was restricted to phase IV clinical trials registered between January 1, 2018, and June 30, 2023 (n= 15), according to the first date submitted to ClinicalTrials.gov.

Initially, we excluded the studies that started before January 1, 2018. We further identified trials whose purposes were 'Treatment,' only including specific oncological treatments.

Then, studies that included the pediatric population and hematological malignancies were excluded. Finally, six eligible phase IV trials with all these characteristics were included in our analysis.

DATA COLLECTION

Trial data were reported by the trial sponsors or investigators, as required by the ClinicalTrials.gov registry. Each record contained data elements describing the study's conditions, enrolment, study design, eligibility criteria, location, sponsor, and other protocol information.

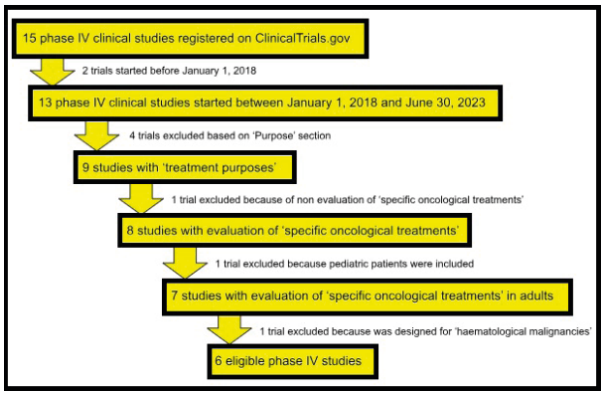

Figure 1 - Flow chart of inclusion and exclusion

RESULTS

Despite the importance of phase IV trials in evaluating the long-term efficacy and safety of drugs, only fifteen of these studies concerning oncology took place in Brazil in the last five years, according to research on ClinicalTrials.gov. After applying the inclusion and exclusion criteria of this study, only 6 of them were left. Tables 1 and 2 describe the characteristics of these trials.

These six trials have many characteristics in common. None had results available, and half were still recruiting participants by the time the research was done. Besides, half describe the role of immunotherapy, which is responsible for a considerable amount of advances in oncology in recent years and has been introduced in the treatment of many kinds of solid tumors (as we can see, some studies apply to solid tumors or cancer in a broader sense, not just referring to the origin in a specific organ or even to specific histology).

Table 1 shows three established adverse events as primary outcome measures. Table 2 shows that pharmaceutical companies sponsored all trials and were open-label. They also occur in several countries simultaneously (an average of 18 nations per study) and have a medium original estimated enrollment of approximately 512 participants.

DISCUSSION

When analyzing the primary outcome measures of the phase IV trials included in our study, we realize that the evaluation of adverse events is the leading goal, reflecting the importance of these trials in describing more types of adverse reactions in a larger population. In a recent sizeable Chinese study [6] about phase IV trials, most of the 4722 studies included were small (median enrolment: 35.5 participants). Although the median expected enrollment of the trials evaluated in our study may seem more significant (512 participants), both include a smaller population than usually found, with less than one thousand participants. Also, the actual accrual tends to be much lower than expected.

In this perspective, the small sample size is the most significant concern in phase IV trials involving the safety surveillance of an approved drug, considering that small trials might not have sufficient power to detect adverse events, especially less common ones. For trials with safety assessment as their primary purpose, the sample size should be estimated according to the probability of occurrence expected for each adverse event [6].

All trials included in our study had yet to have the results available by the time the research was done, demonstrating that phase IV trials may take years to be finalized, demanding considerable financial resources. In this context, it is essential to emphasize that many of them are developed with the sponsorship of pharmaceutical industries (this applies to all of the six trials analyzed in this study). Considering that these companies have interests in expanding the profit obtained with the commercialization of the specific drugs, this situation may lead to bias as financial interests may cloud objectivity in cancer research and influence the preclinical development of diagnostics and therapies and their translation to the clinic [7].

However, considering all financial interests as detrimental does not appreciate the benefits of industry involvement through sponsorship and public-private partnerships for scientific breakthroughs, translational development, and speedy innovation. So, it is crucial to introduce and maintain strong safeguards against potential conflicting interests and detrimental biases. With these measures, we may uphold the integrity of science while reaping the benefits of broad collaborative efforts across academia and the industry [7].

By 2060, an estimated 48 million people (47% of all deaths globally) will die from severe health-related suffering, representing an 87% increase from 26 million people in 2016. 83% of these deaths will occur in low-income and middle-income countries like Brazil. In absolute terms, it will be driven by rises in cancer deaths (16 million people, a 109% increase between 2016 and 2060). In relative terms, this increase will be most apparent in low-income countries, where the absolute burden of severe health-related suffering associated with malignant neoplasms will increase from 300,000 people in 2016 to 1.6 million people in 2060, a 5-fold increase [8].

Globalization of cancer clinical trials over the past few decades has led to some successful collaboration between researchers from low and middle-income countries and those from high-income countries, overcoming geographical and political boundaries. High-income countries and the entire global scientific community stand to gain from such cooperation in terms of cost-effectiveness and timely completion of clinical trials, which translates to faster adoption of newer and novel treatments. Low- and middle-income countries also seemingly benefit from improved infrastructure, reduced abandonment, trained human resources,

Study Title	Status	Conditions	Interventions	Primary Outcome Measures
A Study of Abemaciclib (LY2835219) in Participants With HR+, HER2- Advanced Breast Cancer	Withdrawn	Metastatic Breast Cancer	Drug: Abemaciclib Drug: Nonsteroidal Aromatase Inhibitor (NSAI)	PFS ORR
Rollover Study to Allow Continued Access to Ribociclib	Recruiting	Metastatic Breast Cancer	Drug: Ribociclib Drug: Letrozole Drug: Anastrozole Drug: Goserelin Drug: Tamoxifen Drug: Fulvestrant	Percentage of participants with AES
Durvalumab Long-Term Safety and Efficacy Study	Active, not recruiting	Solid Tumor	Drug: Durvalumab	Number of participants with adverse events as assessed by CTCAE v5.0
A Study in Patients Previously Enrolled in a Genentech and/or F. Hoffmann-La Roche Ltd Sponsored Atezolizumab Study	Recruiting	Cancer	Drug: Atezolizumab	Number of Participants With Continued Access to Atezolizumab-Based Therapy and/or Comparator Agent(s)
The FLOTILLA Study: Providing Continued Access to The Study Medicines Encorafenib and Binimetinib for Participants in Prior Clinical Trials	Recruiting	Solid Tumors	Drug: Binimetinib only treatment Drug: Encorafenib only treatment Drug: Encorafenib & Binimetinib Treatment Drug: Treatment of Encorafenib & Binimetinib & Ribociclib Drug: Treatment of Encorafenib, Binimetinib, Cetuximab	Number of participants with adverse events leading to permanent discontinuation of study intervention, Number of serious adverse events reported for all participants
A Study of Pembrolizumab (MK-3475) Plus Carboplatin and Paclitaxel as First-line Treatment of Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (MK-3475-B10/KEYNOTE B10)	Active, not recruiting	Recurrent / Metastatic Squamous Cell Carcinoma of Head and Neck	Drug: Pembrolizumab Drug: Carboplatin Drug: Paclitaxel	ORR

TABLE 1. Characteristics of the trials - Part 1.

Progression Free Survival (PFS); Objective Response Rate (ORR); Treatment-emergent adverse events (AES); Common Toxicity Criteria for Adverse Events (CTCAE).

Study Title	Location / Countries	Sponsor / Information provided by (Responsible Party):	Original Estimated Enrollment	Intervention Model / Masking
A Study of Abemaciclib (LY2835219) in Participants With HR+, HER2- Advanced Breast Cancer	Argentina, Austria, Belgium, Brazil, Germany, Italy, Puerto Rico, Taiwan, United States	Eli Lilly and Company / Eli Lilly and Company	650 participants	Single Group Assignment / None (Open Label)
Rollover Study to Allow Continued Access to Ribociclib	Brazil, Greece, Hong Kong, Italy, Japan, Korea, the Republic of Lebanon, Mexico, Poland, Portugal, Singapore, South Africa, Spain, Taiwan, Turkey, the United States, Vietnam	Eli Lilly and Company / Eli Lilly and Company	650 participants	Single Group Assignment / None (Open Label)

Durvalumab Long-Term Safety and Efficacy Study	Argentina, Australia, Belgium, Brazil, Bulgaria,Canada, Chile, CzechiaFrance, Germany,Greece, Hungary,India, Israel, Japan, Korea, Malaysia, Netherlands, Poland, Romania, Russian Federation, Serbia, Spain, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States,Vietnam	AstraZeneca / AstraZeneca	600 participants	Parallel Assignment / None (Open Label)
A Study in Patients Previously Enrolled in a Genentech and/or F. Hoffmann-La Roche Ltd Sponsored Atezolizumab Study	Australia, Belgium, Brazil, Bulgaria,Canada, Chile, Czechia, Denmark, France, Germany, Greece,Guatemala, Hong Kong, Hungary, Italy, Japan, Korea, Latvia, Mexico, Norway, Poland, Portugal, Romania, Russian Federation, Singapore, Slovakia, Spain, Switzerland, Taiwan, Thailand, Ukraine, United Kingdom, United States	Hoffmann-La Roche / Hoffmann-La Roche	1000 participants	Single Group Assignment / None (Open Label)
The FLOTILLA Study: Providing Continued Access to The Study Medicines Encorafenib and Binimetinib for Participants in Prior Clinical Trials	Brazil, Canada, France, Germany, Hungary, Israel, Italy, Japan, Korea, Netherlands, Slovakia, Spain, United States,	Pfizer/Pfizer	75 participants	Parallel Assignment / None (Open Label)
A Study of Pembrolizumab (MK-3475) Plus Carboplatin and Paclitaxel as First-line Treatment of Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (MK-3475-B10/KEYNOTE B10)	Argentina, Australia, Brazil, Canada, United States	Merck Sharp & Dohme LLC / Merck Sharp & Dohme LLC	101 participants	Single Group Assignment / None (Open Label)

TABLE 2. Characteristics of the trials - Part 2.

better follow-up, and early access to novel technologies [9].

On the other hand, as academic and economic resources heavily favor high-income countries, researchers and companies from these countries drive research agendas, including where research is done, and largely determine which questions get answered [10]. In the Chinese study [6], the most common research sites in the phase IV trials were from North America, Asia, the Pacific, and Europe, which accounted for 34.4%, 28.2%, and 26.5%, respectively. Finally, in our study, a fact related to the higher prevalence of pharmaceutical companies in developed countries is that none of the analyses of our trial include only the Brazilian population but several countries. This may be another source of bias, so it is essential to compare the demographic characteristics of each of them to the Brazilian population to diminish the chance of bias.

CONCLUSIONS

Scientists throughout the world need to conduct, together, rigorous research driven by local agendas. Incorporating diverse perspectives in medical research can help produce better science. Empowering investigators in low and middle-income countries with appropriate institutional capacity to pursue their research agendas could lead to additional discoveries and

advances in human health [10].

Despite the importance of phase IV trials in evaluating the long-term efficacy and safety of drugs, only a few of these trials concerning oncology took place in Brazil in the last five years. In this perspective, we hope that Brazilian researchers in oncology develop more phase IV studies in the following years, adapted to the national population and reality and with the contribution from different sectors of society.

DECLARATIONS

Authors have no conflict of interest to declare.

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