



Clinical Trials of Solid Tumor Drugs Approved in Europe: Evidence-Based-Medicine

Aseel Bin Sawad¹, Amin Aissaoui², Nahaj Aissaoui², Ahmed Bin Sawad³, Fatema Turkistani^{4*}

¹Clinical Pharmacy Department, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia

²Paris Dauphine University, PSL, Paris, France

³King Abdulaziz University, Jeddah, Saudi Arabia

⁴Clinical and Hospital Pharmacy Department, College of Pharmacy, Taibah University, Medina, Saudi Arabia

Abstract: The Response Evaluation Criteria in Solid Tumors (RECIST) were introduced to determine response to therapy by evaluation of change from baseline while on the treatment of the solid tumor. These criteria are used mainly in clinical trials where tumor objective response (tumor shrinkage) or disease progression is the primary endpoint. RECIST is widely used by academic institutions, cooperative groups, and industry for oncology clinical trials. Regulatory authorities use RECIST as an appropriate guideline for risk-benefit assessments of oncology drugs. This study aimed to assess the impact on pivotal clinical trial designs due to adopting the RECIST for assessing the risk-benefit ratio for oncology drugs approved in Europe for treatment of solid tumors (2000–2019). The Summary of Product Characteristics for all oncology drugs was reviewed to identify the pivotal clinical trials. Results: There were 78 pivotal clinical trials for 38 oncology drugs approved, by the European Medicines Agency (EMA), for treatment of solid tumors. Open-label randomized controlled trials (RCTs) account for 62.82% of the pivotal clinical trials compared to 37.18% blinded RCTs. A total of 6,721 patients (average=1,120) participated in 78 pivotal clinical trials. Around sixty-three percent (4,211 out of 6,721) of patients participated in blinded RCTs, and 37.34% (2,510 out of 6,721) of patients participated in open-label RCTs. Conclusion: Less restrictive rules for oncology drugs approval were applied by the regulatory agency. Over 19 years, EMA had approved oncology drugs based on open-label trials, especially when an oncology drug was compared to an active comparator, with results of few or no clinical improvement over existing therapy. The approval process of oncology drugs should be supported by clear evidence about the clinical effects of the new oncology drugs compared to the existing effective oncology therapies using clinical trial designs that are methodologically rigorous.

Keywords: EMA, Oncology, Overall Survival, Pivotal, Progression-Free Survival.

***Corresponding Author**

Fatema Turkistani , Clinical and Hospital Pharmacy Department, College of Pharmacy, Taibah University, Medina, Saudi Arabia



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I. INTRODUCTION

Clinical evaluation of oncology drugs is usually assessed by the change in tumor burden. There are two important endpoints in oncology clinical trials, which are tumor shrinkage (objective response) and time to the development of disease progression. In phase II screening trials, the objective response found to be the most accurate measurement tool that predicts the promising treatment effect. On the other hand, time to progression (or progression-free survival) is an endpoint that is highly used in advanced disease settings to determine the efficacy of oncology drugs in both phase II and phase III clinical trials. Time to progression endpoint is based on anatomical measurement of tumor size. For solid tumors, evidence suggests that oncology drugs, which produce tumor shrinkage in a proportion of patients during phase II trials, have a good chance of demonstrating an improvement in overall survival (OS) or other time to event measures in phase III randomized controlled trials (RCTs).¹⁻⁴ Solid tumors are defined as an abnormal growth of cells that form an abnormal mass of tissue free from any liquid or cysts. Solid tumors may affect numerous places in the body like organs, muscles, and bones. In 1981, the World Health Organization (WHO) published tumor response criteria, to standardize the assessment and reporting of clinical trials results based on anatomical tumor burden.⁵ The tumor response criteria evaluated oncology products of bi-dimensional lesion measurements to determine the disease response to oncology drugs. The response to oncology drugs is determined by measuring the change from baseline while patients on the treatment. Academic institutions, cooperative groups, and pharmaceutical industry had used the tumor response criteria when tumor response was the primary endpoint in clinical trials. Some agencies made modifications on tumor response criteria to accommodate new technologies, which lead to difficulty in interpretation of trial results.⁶ In 2000, new standardized and simplified response criteria were introduced to determine response to oncology therapy by evaluation of change from baseline while on the treatment of the solid tumor. These criteria are used mainly in clinical trials where tumor objective response (tumor shrinkage) or disease progression is the primary endpoint. These criteria are known as RECIST (Response Evaluation Criteria in Solid Tumors).⁷ Because RECIST are consistent and validated, they have been used in many oncology clinical research trials to evaluate the efficacy of new oncology drugs.^{6,7} In 2009, an updated version of RECIST was published to address some issues of the previous RECIST version.⁸ RECIST is widely used by academic institutions, cooperative groups, and industry for oncology clinical trials. Regulatory authorities use RECIST as an appropriate guideline for risk-benefit assessments of oncology drugs. European Medicines Agency (EMA) accepts a prolongation in time to progression as a primary endpoint for new oncology drug approval in the European Union. The objective of our study was to assess the impact of adopting the RECIST guideline, for assessing the risk-benefit ratio for oncology drugs approved in Europe for treatment of solid tumors, on pivotal clinical trial designs in the period 2000–2019.

2. MATERIALS AND METHODS

The list of all EMA-approved oncology drugs for the treatment of solid tumors in the period between January 2000 and January 2019 was identified. EMA is the regulatory

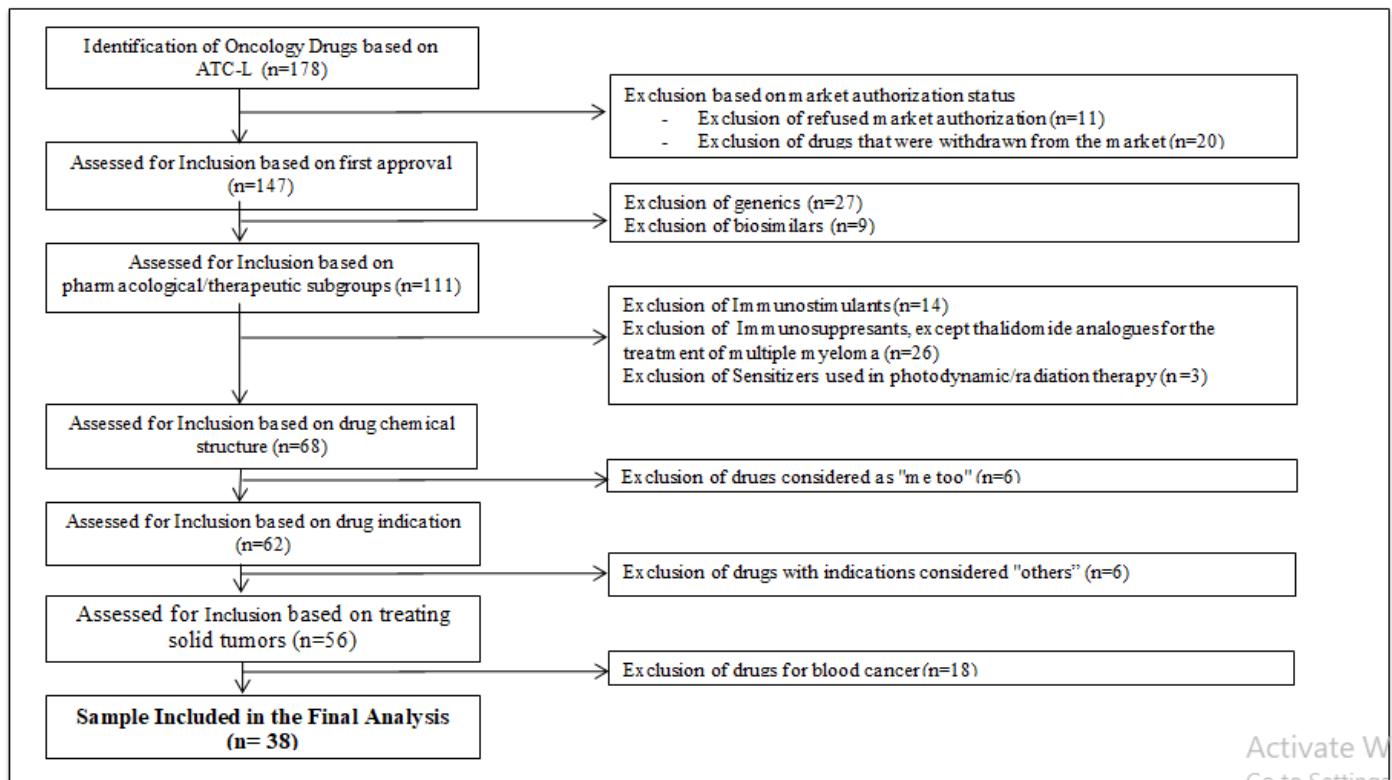
authority that is responsible for evaluating drug applications for marketing authorization in Europe.⁹ The sample selection process in this study was based on the Anatomical Therapeutic Chemical (ATC) classification system of the WHO Collaborating Centre for Drug Statistics Methodology of the Norwegian Institute of Public Health.¹⁰ ATC is a pharmaceutical coding system that classifies the active substance of drugs according to "the organ or system on which they act and their therapeutic, pharmacological and chemical properties".¹¹ Under ATC classifications, all pharmaceutical products are classified in groups at five different levels.^{10,11} Level one classified drugs into fourteen main groups. Level two divided drugs according to their pharmacological/therapeutic subgroups. Level three and level four divided drugs according to their chemical/pharmacological/therapeutic subgroups. Level five divided drugs according to their chemical substance.¹⁰ According to the ATC classification system, category L includes antineoplastic and immunomodulating agents.¹⁰ Our study sample selection process included seven steps that started with identifying all antineoplastic and immunomodulating agents classified as ATC-L from the WHO website. The second step was using EMA website, and excluded from our sample all drugs that received a market authorization refusal from EMA and all drugs that were withdrawn from the European market during the study period. Our study focuses on brand oncology drugs approved for treatment of solid tumors. Therefore, the third step was excluding all generics and biosimilars (based on the first approval). The fourth step was excluding immunostimulants, immunosuppressants, sensitizers used in photodynamic/radiation therapy (using level two of ATC classification from WHO website). Only thalidomide analogues for the treatment of multiple myeloma were included from the immunosuppressants category as an exception due to their mechanism activities that have a direct impact on the cancer cells of multiple myeloma. The fifth step was reviewing EMA website to identify and exclude me too drugs. Me too drugs were defined as any pharmaceutical products that are structurally very similar to already known ones, with only minor changes. The sixth step was using package leaflets from the EMA website to identify and exclude any drugs that were indicated to treat other than solid tumors. Finally, drugs used to treat blood cancer were identified and excluded using package leaflets from the EMA website (Figure 1). The Summary of Product Characteristics (SmPC) for all oncology drugs included in our study was reviewed to identify the pivotal clinical trials that were used by EMA to approve the oncology drugs. The SmPC is a medicinal product legal document prepared to EMA, the regulatory agency for European countries, as a part of the drug marketing authorization applications. The stakeholders for SmPC are healthcare professionals. A pivotal clinical trial is the one used to provide evidence of drug safety and efficacy and required by the regulatory authority for marketing authorization.

3. STATISTICAL ANALYSIS

All pivotal clinical trials for oncology drugs used for the treatment of solid tumors were categorized based on three levels. Level one was based on clinical trials design, whether they were blinded RCTs or open-label RCTs. Level two was based on comparators used in clinical trials, whether they used active comparator or placebo. For this level, we categorized the clinical trials into "Best Supportive Trials"

and "Placebo Trials." Best Supportive Trials were defined in our study as trials that compare the oncology drugs to the standard of care for treatment of the solid tumor. On the other hand, Placebo Trials were defined as trials that compare the oncology drugs for the treatment of the solid tumor to placebo. Finally, level three category was based on the results of clinical trials. All studies were further categorized depending on their results into patients'

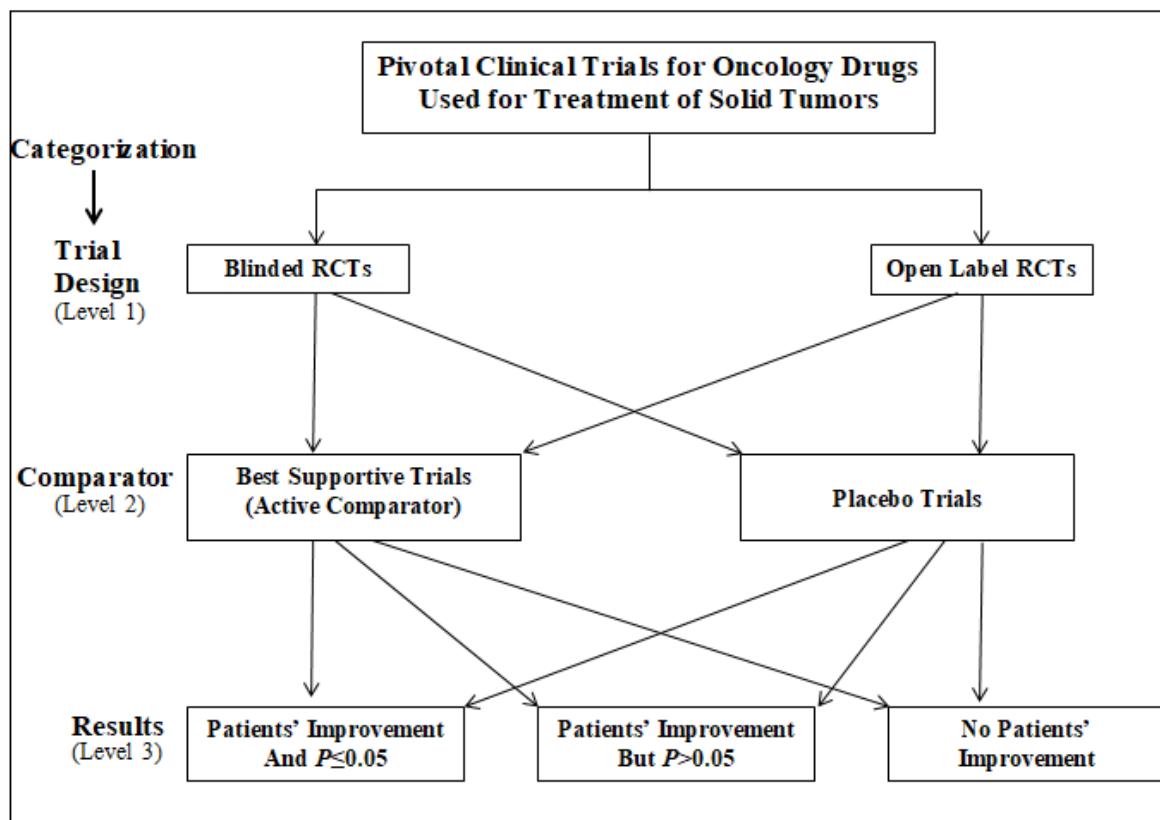
improvement with statistically significant results ($P \leq 0.05$), patients' improvement but with no statistically significant results ($P > 0.05$), and no patients' improvement (Figure 2). The patient improvement was defined in our study as a positive oncology drug effect (improvement in outcomes) that was measured by OS or progression-free survival. All Statistical Analyses were performed using Microsoft Excel 2019.



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RCTs: randomized controlled trials

Fig 1. Sample Selection Process of Oncology Drugs Approved by EMA (2000-2019) for Treatment of Solid Tumor



RCTs: randomized controlled trials

Fig 2. Categorization of Pivotal Trials for Oncology Drugs used for Treatment of Solid Tumor

4. RESULTS

A total of 38 oncology drugs were approved by EMA between 2000 and 2019 for metastatic and/or advanced and/or refractory solid tumors (figure 1). A total of eighty-two clinical trials were identified for these 38 oncology

drugs. Four clinical trials were excluded from the analysis, as they were phase II clinical trials with a single arm. Seventy-eight pivotal clinical trials for 38 oncology drugs used for the treatment of solid tumors were included in the final analysis (Table 1).

Table 1. Number of Pivotal Clinical Trials for Oncology Drugs approved in Europe for Treatment of Solid Tumors in the Period 2000–2019.

Pivotal Clinical Trials for Oncology Drugs Used for Treatment of Solid Tumors	RCTs (blinded)	RCTs (Open)	Total
Active comparator (total number of clinical trials)	7	46	53
Patients' Improvement and $P\leq0.05$	4	16	20
Patients' Improvement but $P>0.05$	1	16	17
No Patients' Improvement	2	14	16
Placebo (total number of clinical trials)	22	3	25
Patients' Improvement and $P\leq0.05$	6	0	6
Patients' Improvement but $P>0.05$	12	0	12
No Patients' Improvement	4	3	7
Total	29	49	78

4.1 Pivotal Clinical Trials

Over half of pivotal clinical trials for oncology drugs approved for treatment of solid tumors were open-label RCTs that account for 62.82% (49 out of 78 trials) of the pivotal clinical trials in the study period compared to 37.18% (29 out of 78 trials) blinded RCTs. The percentage of pivotal clinical trials that used active comparators (best supportive trials) was 67.95% (53 out of 78 trials) compared to 32.05% (25 out of 78 trials) clinical trials used placebo comparators. Among 49 open-label RCTs, 93.88% (46 out of 49 trials) used active comparators, and only 6.12% (3 out of 49 trials) used

placebo as comparators. On the other hand, 75.86% (22 out of 29 trials) of blinded RCTs used placebo while only 24.14% (7 out of 29 trials) of blinded RCTs used active comparators (Table 1).

4.2 Results of Best Supportive Trials

Thirty-seven percent (20 out of 53 trials) of pivotal clinical trials that used active comparators reached patients' improvement with a statistically significant difference ($P\leq0.05$) between the investigational drug and the active comparator. Of these trials, 80% (16 out of 20 trials) were open labeled

RCTs, and 20% (4 out of 20 trials) were blinded RCTs. Thirty-two percent (17 out of 53 trials) of RTCs that used active comparators reached patients' improvement, but there was no statistically significant difference ($P>0.05$) between the investigational drug and the active comparator. Of these trials, 94.12% (16 out of 17 trials) were open labeled RCTs while only 5.88% (1 out of 17 trials) were blinded RCTs. Finally, thirty percent (16 out of 53 trials) of RTCs that used active comparators did not reach patients' improvement. Of these trials, 87.50% (14 out of 16 trials) were open labeled RCTs, and the remaining 12.50% (2 out of 16 trials) were blinded RCTs (Table 1).

4.3 Results of Placebo Trials

Twenty-four percent (6 out of 25 trials) of pivotal clinical trials that used placebos as comparators reached patients' improvement with a statistically significant difference ($P\le0.05$) between the investigational drug and the placebo. All of those trials were blinded RCTs. Forty-eight percent (12 out of 25 trials) of RTCs that used placebos as comparators reached patients' improvement, but the results were not statistically significant ($P>0.05$) comparing the investigational drug to the placebo. All of those trials were blinded RCTs. Finally, twenty-eight percent (7 out of 25 trials) of RTCs that used placebos as comparators did not reach patients' improvement. Of these trials, 57.14% (4 out of 7 trials) were

blinded RCTs, and 42.86% (3 out of 7 trials) were open labeled RCTs (Table 1).

4.4 Patients Participated in the Pivotal Clinical Trials

A total of 6,721 patients (Average [Ave]=1,120 patients [Pts]) participated in 78 pivotal clinical trials for 38 oncology drugs approved in Europe for treatment of solid tumors (Table 2). Around sixty-three percent (4,211 out of 6,721) of patients participated in blinded RCTs, and 37.34% (2,510 out of 6,721) of patients participated in open-label RCTs. On the other hand, the total number of patients participating in pivotal clinical trials using active comparators was 4,310 (64.13%) patients while the total number of patients participating in RCTs using placebos as comparators was 2,411 (35.87%) patients. Among 4,211 patients participated in blinded RCTs, 53.05% (2,234 out of 4,211 Pts) of the patients were randomized to either investigational drug or placebo while 46.95% (1,977 out of 4,211 Pts) of the patients were randomized to either investigational drug or active comparators. On the other hand, 2,510 patients participated in open-label RCTs, 92.95% (2,333 out of 2,510 Pts) of the patients were randomized to either investigational drug or active comparators while only 7.05% (177 out of 2,510 Pts) of the patients were randomized to either investigational drug or placebo (Table 2).

Table 2. Number of Patients Treated in the Pivotal Clinical Trials for Oncology Drugs approved in Europe for Treatment of Solid Tumors in the Period 2000–2019.

Pivotal Clinical Trials for Oncology Drugs Used for Treatment of Solid Tumors	RCTs (blinded)	RCTs (Open)	Total (Average)
Active comparator, total number of patients (Average)	1,977 (659)	2,333 (778)	4,310 (1,437)
Patients' Improvement and $P\le0.05$	578	632	1,210 (605)
Patients' Improvement but $P>0.05$	736	688	1,424 (712)
No Patients' Improvement	663	1,013	1,676 (838)
Placebo, total number of patients (Average)	2,234 (745)	177 (59)	2,411 (804)
Patients' Improvement and $P\le0.05$	804	0	804 (402)
Patients' Improvement but $P>0.05$	840	0	840 (420)
No Patients' Improvement	590	177	767 (383.5)
Total number of patients (Average)	4,211 (702)	2,510 (418)	6,721 (1,120)

RCTs: randomized controlled trials.

4.5 Results of Best Supportive Trials

Twenty-eight percent (1,210 out of 4,310 Pts) of patients who participated in best supportive trials showed an improvement in their health-related outcomes with a statistically significant difference ($P\le0.05$) between the investigational drug and the active comparator. Among these participants, 52.23% (632 out of 1,210 Pts) were enrolled in open labeled RCTs, and 47.77% (578 out of 1,210 Pts) were enrolled in blinded RCTs. Thirty-three percent (1,424 out of 4,310 Pts) of patients who participated in best supportive trials showed an improvement in their health-related outcomes without a statistically significant difference ($P>0.05$) between the investigational drug and the active comparator. Of these participants, 48.31% (688 out of 1,424 Pts) were enrolled in open labeled RCTs, and 51.69% (736 out of 1,424 Pts) were enrolled in blinded RCTs. Lastly, thirty-eight (1,676 out of 4,310 Pts) of patients who participated in best supportive trials did not show any improvement in their health-related outcomes. Among these participants, 60.44%

(1,013 out of 1,676 Pts) were enrolled in open labeled RCTs, and 39.56% (663 out of 1,676 Pts) were enrolled in blinded RCTs (Table 2).

4.6 Results of Placebo Trials

Thirty-three percent (804 out of 2,411 Pts) of patients who participated in placebo trials showed an improvement in their health-related outcomes with a statistically significant difference ($P\le0.05$) between the investigational drug and the placebo. All of those participants were enrolled in blinded RCTs. Thirty-four percent (840 out of 2,411 Pts) of patients who participated in placebo trials showed an improvement in their health-related outcomes without a statistically significant difference ($P>0.05$) between the investigational drug and the placebo. All of those participants were enrolled in blinded RCTs. Lastly, 31.81% (767 out of 2,411 Pts) of patients who participated in placebo trials did not show any improvement in their health-related outcomes. Among these participants, 23.08% (177 out of 767 Pts) were enrolled in

open labeled RCTs, and 76.92% (590 out of 767 Pts) were enrolled in blinded RCTs (Table 2).

5 DISCUSSION

With an increase in the demand for reducing the time of oncology drugs approval and demonstrating clinical benefits while limiting the number of patients who may be exposed to potentially toxic drugs, EMA accepts the time to progression endpoint as a primary endpoint in pivotal clinical trials for oncology drugs approval. A pivotal clinical trial is the one used to provide evidence of a drug's safety and efficacy and required by the regulatory authority for marketing authorization. Our study explored the impact of adopting the RECIST guideline for oncology drugs approved in Europe for treatment of solid tumors on pivotal clinical trial designs in the period 2000–2019. Although the time to progression endpoint was accepted by EMA, it is suitable for blinded randomized studies. Time to progression is a subjective endpoint, which depends on the evaluation methods and schedules that were used. Using time to progress can introduce bias by knowing the therapy that was received. Our study found that over half of pivotal clinical trials for the solid tumor were open-label studies. In open-label studies, progression endpoints can introduce bias if the progression occurred closer to the last visit. Hence, this could explain our finding that among pivotal clinical trials that used active comparators and reached patients' improvement with a statistically significant difference between the investigational drug and the active comparator, 80% were open labeled RCTs. Although using placebo-trials is considered unethical when available drugs show an improvement in survival rate or reduce serious morbidity, which is the case for oncology drugs,¹² we found that more than a third of the pivotal oncology clinical trials in the study period used a placebo. Also, active comparators trials raised their ethical concerns when they fail to provide scientifically valid or clinically meaningful results.^{13,14} Our study found that among patients who participated in active comparator trials, 38.89% did not show any improvement in their health-related outcomes. We found that over half (62.82%) of pivotal clinical trials for oncology drugs approved for treatment of solid tumors were open-label RCTs. Previous studies argue the methodological weaknesses of oncology clinical trials compared to trials for other diseases.^{15–18} A previous study compared 8,942 clinical trials for oncology drugs conducted between 2007 and 2010 with trials for other diseases and found that oncology clinical trials were 1.8 times more likely not to be blinded.¹⁵ Donald and Joel¹⁶ were arguing that the previous finding did not determine the validity of the results but reflects what regulators will approve. They assumed that less valid clinical trials reflect an easy ride from regulatory agents for drugs that offer fewer significant benefits for patients.¹⁶ A previous review found that among EMA approved drugs for solid tumors; the overall new oncology drugs improved survival by a mean equal to 1.5 months and median of 1.2 months only.¹⁷ Moreover, only 42% of approved oncology drugs met criteria set by the American Society of Clinical Oncology Cancer Research Committee for meaningful results for patients.¹⁸ Our study found that 66.67% of pivotal oncology clinical trials had results that either showed patients' improvement without statistically significant results or no patients' improvement at all. Among all patients enrolled in these trials, we found that 70.03% of patients had either improved without statistically significant results or did not improve at all. In 2012, 11 out of 12 approved oncology drugs provided

only small clinical benefits to patients.^{19,20} In 2013, more than a hundred oncologists were against the high prices charged for oncology drugs, twelve of the 13 new oncology drugs approved in 2012 were priced above \$100,000 annually, and a 20% copayment makes them unaffordable.²¹ With less restrictive rules for regulatory approvals that lower the efficacy bar, 90% of new drugs that companies developed were adding few or no clinical improvement over existing ones and had risks of serious drug adverse effects.^{19,22} A few changes could greatly improve the quality of approved oncology drugs and protect the public. Overall survival results give clear evidence about the efficacy of new oncology drugs. The approval process should be supported by clear evidence about the clinical effects of the new drugs compared to the current effective therapy using designs that are methodologically rigorous.¹⁶

5.5 Study Limitations

This study has some limitations. Our study focused on pivotal RCTs of solid tumors, so our results are not generalizable to other tumor types as they have different disease characteristics. Also, by limiting our search to 19 years (study period: 2000–2019), we did not capture all pivotal RCTs before the adoption of the RECIST guideline. Further longitudinal interrupted time series design study needed to confirm our results. Our study focused on pivotal phase III clinical trials, so our study results are not generalizable to phase II pivotal clinical trials. Our study focused on the oncology pivotal clinical trial designs (i.e., blinded and open-label RCTs) and then divided the clinical trials based on their statistical significant results (patients' improvement and $P \leq 0.05$, patients' improvement but $P > 0.05$, and no patients' improvement). Perception of what considers patients' improvement is a complex process that depends on many factors and may involve other variables that were not considered in our study. More studies are needed to explore the specific types of blinded RCTs (single, double, and triple blinded RCTs) as well as associations between funding of oncology RCTs and reporting of positive results.

6 CONCLUSION

A shift has occurred over the past years in the design of pivotal clinical trials for oncology drugs used for the treatment of solid tumors. Less restrictive rules for oncology drugs approval was applied by the regulatory agency. Over 19 years, EMA had approved oncology drugs based on open-label trials, especially when an oncology drug was compared to an active comparator, with results of few or no clinical improvement over existing therapy. The approval process of oncology drugs should be supported by clear evidence about the clinical effects of the new oncology drugs compared to the existing effective oncology therapies using clinical trial designs that are methodologically rigorous.

7 AUTHORS CONTRIBUTION STATEMENT

Aseel Bin Sawad, Pharm D, MSc, MCR, MS, PhD, DBA contributed to the study design, data collection and analysis, and manuscript writing. Amin Aissaoui, MS, PhD contributed to the study design, data collection and analysis, and manuscript modification and revision. Najah Aissaoui, MS contributed to data collection and analysis, and manuscript revision. Ahmed Bin Sawad contributed to data collection and analysis, and manuscript revision.

Fatema Turkistani, Pharm. D, MSc, PhD, DBA contributed to the study design, data analysis, and manuscript writing. All the authors read and approved the final version of the manuscript.

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