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Assessing population diversity in phase III trials of cancer drugs supporting Food and Drug Administration approval in solid tumors

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Abstract

Our study aimed to assess inequities in the clinical trial participation for the selected patient groups. We searched the Food and Drug Administration (FDA) database and extracted phase-III clinical trial data from MEDLINE for each approved drug by the FDA between January 1, 2006, and June 30, 2020. We analyzed the inclusion/exclusion criteria, participation according to gender, ethnic group, performance score, the positivity of HBV and HCV, and HIV, having comorbidities and brain metastasis. We compared the findings with that of the general population by retrieving data from the Surveillance, Epidemiology and End Results (SEER) database. We identified 142 phase III pivotal oncology trials that enrolled 105 397 patients. The proportion of female patients in trials was lower than their relative prevalence in the general population from SEER region (36% vs 49.6%, $P < .001$). The rates of black patients included were lower than their relative prevalence from SEER region (2.1% vs 9.8%, $P < .001$). 1.3% and 0.8% of patients had HBV and HCV infections, respectively. The patients' numbers with organ dysfunction were not established due to insufficient data from clinical trials. 1.6% of all patients had controlled brain metastasis. Black patients, women and patients with brain metastasis or with HBV and HCV were underrepresented. Our study underscores the importance of expanding the inclusion/exclusion criteria of pivotal oncology trials to be more representative of patients seen in clinical practice.

KEYWORDS
clinical trials, diversity, underrepresented patients

What's new?

The number of clinical trials for cancer drugs is on the rise, and it's essential to enroll trial populations that adequately represent the patient population to properly understand the generalizability of the results. Enrollment often excludes racial and ethnic minorities as well as people

Abbreviations: Anti-VEGF, vascular endothelial growth factor antagonists; ASCO, American Society of Clinical Oncology; BBB, blood-brain barrier; CKD, chronic kidney disease; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated-protein 4; DAAs, direct-acting antivirals; DDI, drug-drug interactions; DOI, digital object identifier; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; HAART, highly active antiretroviral therapy; HBV, hepatitis virus B; HCC, hepatocellular carcinoma; HCV, hepatitis virus C; HF, heart failure; HIV, human immunodeficiency virus; ICIs, immune checkpoint inhibitors; IQR, interquartile range; LFA, liver function abnormalities; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PLWH, patients living with human immunodeficiency virus; PS, performance score; SEER, Surveillance, Epidemiology and End Results; TKI, tyrosine kinase inhibitors.

with certain comorbidities. Here, the authors systematically assessed inequities in clinical trial enrollment for drugs approved between 2006-2020. They found that females, Black patients, and patients with HIV or hepatitis were underrepresented relative to their share of the general population. Inclusion criteria of pivotal oncology trials should be more representative of patients seen in clinical practice.

1 | INTRODUCTION

Clinical trials are important to bring new therapeutic options, thus instrumental to improve outcomes for patients with cancer.[1,2] In fact, 27% of all drugs approved by the Food and Drug Administration (FDA) between 2010 and 2018 were cancer drugs.[3] Although the number of clinical trials of cancer drugs, and the number of new cancer drugs approved by the FDA, has increased remarkably over the years, concerns are being raised that the participants in these clinical trials are not representative of the real-world populations and specifically exclude various minority groups. In this context, clinical trial participation has been largely limited to healthier younger patients who lack comorbidities and have access to proper psychosocial support. This issue hinders the participation of patients who are members of minorities or vulnerable groups, thereby possibly affecting the trial results' generalizability. The lack of appropriate population diversity in clinical trials involves not only the tiny participation among ethnic and gender-defined groups but is marked by some disease-specific patterns of exclusion, such as patients living with human immunodeficiency virus (HIV) (PLWH), hepatitis virus B (HBV) and hepatitis virus C (HCV) infection, selected organ dysfunctions and brain metastasis.[4-7] In the era of highly active antiretroviral therapy (HAART) in HIV care, direct-acting antivirals (DAAs) in HCV treatment, improvements in the management of organ dysfunctions and the possibility of effective control of brain metastases, there is an urgent need to tackle avoidable systematic exclusion from cancer clinical trials. Fortunately, the FDA has recently published key recommendations in this regard.[8-10] However, no study to our knowledge has comprehensively studied the extent to which clinical trials of FDA-approved cancer drugs included these patient groups.[4,11]

Clinical trials' populations may differ in solid tumors and hematologic malignancies. In a study by Loree et al, the drug number approved by the FDA for solid tumors was higher than the hematologic malignancies. Besides, the rate of reporting outcomes according to ethnic group was higher in the solid tumor trials than in the hematologic malignancy trials.[12] Furthermore, another study conducted by Nazha et al showed that the representation of minorities in the immunotherapy clinical trials was low in solid tumors.[13]

In our study, we aimed to assess the inclusion/exclusion criteria and reporting status of the various patient groups (as defined in the methods) in clinical trials, and to understand the current landscape of the population enrolled into pivotal cancer drug trials that led to FDA approval of solid tumors.

2 | METHODS

2.1 | Study cohort

Two lead authors (E.Y. and Y.U.) extracted all the cancer drugs approved by the FDA from January 1, 2006, to June 30, 2020, in the FDA database and identified the drugs with a solid tumor indication in any stage for adults.[14] Drugs approved solely for benign hematologic diseases, hematologic malignancies including lymphomas and multiple myeloma, and pediatric patients were excluded. We subsequently identified the pivotal studies that supported the FDA decisions for approvals. The search for pivotal trials was performed on the US National Library of Medicine "ClinicalTrials.gov" database. In addition, we obtained full-text articles of identified phase-III clinical trials by searching *MEDLINE*. We excluded approved drugs for which no phase-III clinical trials could be identified or published full-text articles were unavailable. The selection process of included drugs and phase-III clinical trials is shown in Figure S1.

2.2 | Data extraction

The following information for each trial was extracted in a data collection sheet: drug data (*international nonproprietary name of the drug*, *approval year*, *therapeutic indication*), manuscript publication data (*digital object identifier (DOI)*, *National Clinical Trial Registry number*, *author(s)' name(s)*, *publication year*, *journal name*), data on study sites that operated the clinical trials (*number of countries*, *number of sites*, *continents*), inclusion/exclusion criteria for subgroups (*age*, *reported ethnic group*, *gender*, *performance score [PS]*, *HIV/HBV/HCV positivity*, *and presence of organ dysfunction and brain metastasis*), patient characteristics, data for subgroup analyses and funding agency for the study. Data extraction item is shown in Table S1.

To compare the results retrieved from clinical trials with the general population, estimates of cancer epidemiology in the United States were obtained from "*Surveillance*, *Epidemiology*, *and End Results (SEER) Explorer*."[15]

2.3 | Data and statistical analysis

Data were analyzed using descriptive statistics methods. Mean ± SD or median (interquartile range [IQR]) were calculated for continuous variables according to normal or nonnormal distribution of variables,

TABLE 1 Baseline characteristics of clinical trials

Publishing journals	n	(%)
New England Journal of Medicine (*NEJM*)	73	(51.4)
Lancet/Lancet Oncology	41	(28.9)
Journal of Clinical Oncology (*JCO*)	21	(14.8)
Annals of Oncology	2	(1.4)
Journal of American Medical Association (*JAMA*)	1	(0.7)
Other journals	4	(2.8)
Median number of countries (IQR)	20	(14-25)
Median number of cites (IQR)	139	(101-199)
Continents	n	(%)
Europe	130	(91.5)
North America	120	(84.5)
Asia	114	(80.3)
Australia	98	(69)
South America	85	(59.9)
Africa	21	(14.8)
Antarctica	0	(0)
Median number of continents (IQR)	5	(4.5)
Cancer types, n (%)	n	(%)
Lung	29	(20.4)
Breast	23	(16.2)
Genitourinary	23	(16.2)
Gastrointestinal	21	(14.8)
Skin	15	(10.6)
Gynecological	10	(7)
Head and Neck	9	(6.3)
Hepatobiliary	6	(4.2)
Sarcoma	6	(4.2)
Median number of patients (IQR)	653	(417-890)
Primary outcomes	n	(%)
PFS	69	(48.6)
OS	43	(30.3)
PFS and OS	19	(13.4)
MFS	3	(2.1)
ORR	2	(1.4)
DOR	1	(0.7)
Other combinations	5	(3.5)
Funding	n	(%)
Government	8	(5.6)
Drug companies	134	(94.4)
Drug types	n	(%)
Targeted therapies	90	(63.4)
Immunotherapeutic agents	20	(14.1)
Combinations	19	(13.3)
Chemotherapeutics	13	(9.2)

Abbreviations: DOR, duration of response; IQR, interquartile range; MFS, metastasis-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

respectively. Frequencies were calculated for categorical variables. The relative prevalence of cancer according to ethnic group and gender was calculated using *SEER Explorer software*[15] The relative prevalence of cancer for ethnic subgroups was calculated by dividing the number of patients in each ethnic subgroup by the total number of patients. Likewise, the relative prevalence of cancer for gender was calculated by dividing the number of male or female patients by the total number of patients. The Chi-square test was used to compare these proportions in each subgroup. All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Mac, version 27.0, IBM Corp., New York).

3 | RESULTS

We identified 142 phase III clinical trials (Table S2). The median number of countries and sites per clinical trial was 20 (IQR: 14-25) and 139 (IQR: 101-199), respectively. The most common geographical areas where clinical trials were executed were Europe (91.5%) and North America (84.5%). Most trials were conducted across the globe (median number of continents per trial: 5). The median number of patients per clinical trial was 662 (IQR: 418-883). The majority of trials were funded by pharmaceutical companies (94.4%) (Table 1).

Approximately two-thirds of the drugs approved by the FDA through phase-III clinical trials were targeted agents, such as tyrosine kinase inhibitors (TKI) and monoclonal antibodies. Furthermore, 14% of them were immune checkpoint inhibitors (ICIs), namely programmed death-1 (PD-1), programmed death ligand-1 (PDL-1) or cytotoxic T-lymphocyte-associated-protein 4 (CTLA-4) inhibitors. Combinations, such as two ICIs, or an ICI plus targeted agents or other combinations (eg, chemotherapy plus targeted agents, chemotherapy plus ICI), comprised 14% of the trials. The remaining drugs (9%) were chemotherapeutics (Table 1). The number of cancer drugs approved by the FDA each year has been increasing over the last 15 years. A total of 70 cancer drugs were approved through a phase III trial between the years 2006 and 2015. However, the number of drugs approved by the FDA in the last 4.5 years was 72. Lung cancer was the most represented indication of the new drugs approved between 2006 and 2020.

3.1 | Inclusion and exclusion criteria of clinical trials

Almost all trials had a minimum age criterion for the inclusion of patients. All trials except one were limited to patients 18 years and older. One trial for patients with sarcoma included patients starting at 15 years of age.[16] Gender was an inclusion criterion in 33 clinical trials (23.2%), of which 20 included only female and 13 included only male patients, but this was mandatory as these gender-specific trials studied either breast, gynecologic or prostate cancer. We found no mention of possible restrictions or comments for the inclusion or exclusion of transgender persons with genital, urinary tract or breast neoplasms.

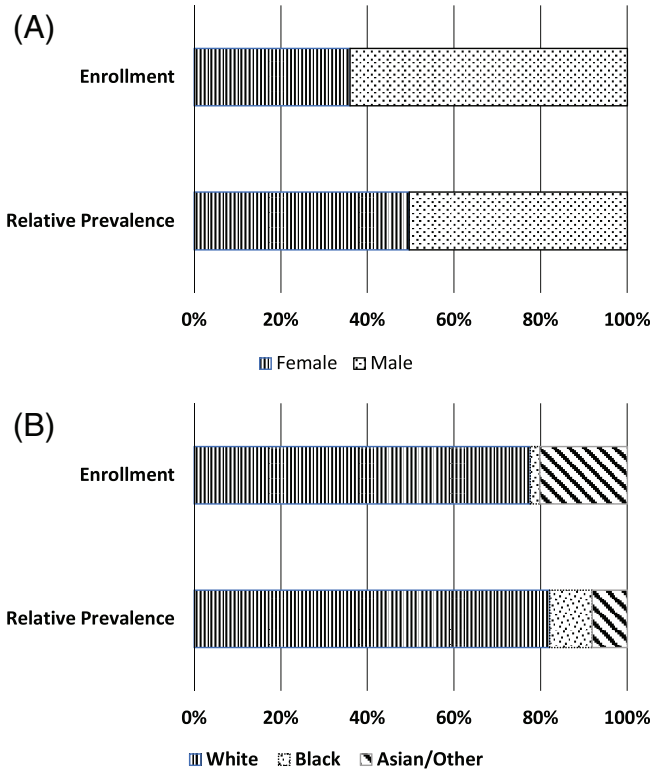

FIGURE 1 Relative prevalence of cancer and clinical trial enrollment status. A, The comparison of relative prevalence and enrollment for gender. (Relative prevalence of all cancer types was calculated using prevalence data from SEER Program.[15]) B, The comparison of relative prevalence and enrollment for ethnic subgroups. (Relative prevalence of all cancer types after the age of 15 in the last 25 years was calculated using data from SEER Program.[17]) [Color figure can be viewed at wileyonlinelibrary.com]

There was no clinical trial with restrictions for inclusion or exclusion criteria based on ethnic group. Performance score was listed as an inclusion criterion in 112 trials (78.9%) and as an exclusion criterion in 2 trials (1.4%). Most trials (83.6% of all trials reporting data for PS) included patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1 or equivalent scales (eg, Karnofsky grade >70%).

HIV infection was an exclusion criterion in 46 trials (32.4%). Furthermore, HBV and HCV positivity were exclusion criteria in 41 trials (28.9%). Organ dysfunction, such as chronic kidney disease (CKD) (eg, patients with estimated glomerular filtration rate lower than 60 mL/min/1.73 m^2), liver function abnormalities (LFA) and heart failure (HF), was an exclusion criterion in 40 trials (28.2%). Conversely, adequate organ function was an inclusion criterion in 37 trials (26.1%). Besides, brain metastasis was an exclusion criterion in 83 trials (57.7%). There was no specification for the presence of brain metastasis in 59 trials (41.6%). All inclusion and exclusion criteria of included trials are shown in Table S3.

3.2 | Patient characteristics in clinical trials

In total 105 397 patients were included in the trials; 49% of them were female. After exclusion of gynecologic, breast and prostate cancers that had gender-specific criteria for inclusion or exclusion, male patients were overrepresented in rest of the cancer types. The proportion of women in trials was lower than the relative proportion of women with cancer in the general population from SEER region (36% vs 49.6%, $P < .001$). The comparison of relative prevalence and trial enrollment rate for each gender is shown in Figure 1A.

There was information on ethnic group in 106 trials (75%). White patients were included in almost all trials and Asian patients were represented in 96 trials (91.4%). Black and ethnic minorities (eg, Native Indians, Hispanics) were included in 88 trials (83.8%) and 80 trials (76.2%), respectively. However, in terms of population size, the rates of White, Asian, black and other subgroups of patients were 74.7%, 16.8%, 2.1% and 2.6%, respectively. The rates of black persons included in clinical trials were lower than their relative prevalence in the general population from SEER region (2.1% vs 9.8%, $P < .001$). In contrast, the rates of Asian and other subgroups in trials were higher than their relative prevalence in the general population from SEER region (19.4% vs 8.1%, $P < .001$, Figure 1B).

Information on the status of HIV, HBV and HCV could be retrieved from 44 (31% of all trials) trials. No trial had included PLWH. In contrast, there were 1425 (1.3%) patients positive to HBV and 840 (0.8%) to HCV. All trials including patients with HBV or HCV were conducted for hepatocellular carcinoma (HCC) treatment.

Approximately half of the clinical trials had information for patients having organ dysfunction, such as CKD, LFA and HF. However, the number of patients having any organ dysfunction was not clear due to a lack of data.

Ninety-eight trials (69%) had information for patients with brain metastasis and 1723 patients (1.6%) with controlled brain metastasis were included in these trials. There was information for PS in 131 trials (92.3%). Eighty-two percent of all patients had ECOG PS 0-1 or equivalent in other systems. Patients' characteristics in clinical trials are shown in Table 2.

3.3 | Subgroup analyses in clinical trials

Subgroup analyses based on ethnic group, age, sex and PS were conducted in 46 trials (32.4%), 115 trials (81%), 78 trials (54.9%) and 92 trials (64.8%) respectively. Five trials (3.5%) reported subgroup analysis either for HIV, HBV or HCV status and 13 trials (9.2%) for brain metastasis. Conversely, there was no subgroup analysis for patients having organ dysfunction (Table 3).

4 | DISCUSSION

We embarked on a comprehensive study to assess underrepresented groups of patients enrolled in phase III clinical trials that had led to the approval of cancer drugs by the FDA. According to our study results, some groups appear systematically underrepresented.

Ethnical underrepresentation in clinical trials has been identified by the FDA as a significant limitation to assure external

TABLE 2 Characteristics of included patients in clinical trials

	n	%
Total number of patients	105 397	(100)
Female	52 039	(49)
Male	53 358	(51)
Number of patients after exclusion of gender specific cancers (eg, gynecological, breast and prostate cancers)	60 361	(100)
Female	21 999	(36)
Male	38 362	(64)
Presence of data for ethnic group in trials (n = 142)		
Yes	106	(75)
No	36	(25)
Representation of ethnic Subgroups in Trials (n = 106)		
White	104	(98.1)
Asian	96	(91.4)
Black	88	(83.8)
Other	80	(76.2)
Number of patients in each ethnic subgroup	77 740	(100)
White	58 077	(74.7)
Asian	13 093	(8.16)
Black	1610	(1.2)
Other	2036	(2.6)
Unknown	2924	(3.8)
Presence of data for performance score in trials (n = 142)		
Yes	131	(92.3)
No	11	(7.7)
Number of patients with ECOG performance score 0-1	88 141	(83.6)
Presence of data for cancer stage in trials (n = 142)		
Yes	142	(100)
No	0	(0)
Presence of data for HIV positive patients in trials (n = 142)		
Yes	44	(31)
No	98	(69)
Number of patients with HIV	0	(0)
Presence of data for HBV positive patients in trials (n = 142)		
Yes	44	(31)
No	98	(69)
Number of patients with HBV	1425	(1.3)
Presence of data for HCV positive patients in trials (n = 142)		
Yes	44	(31)
No	98	(69)
Number of patients with HCV	840	(0.8)
	n	%
Presence of data for patients with CKD in trials (n = 142)		
Yes	*62*	*(43.7)*
No	*80*	*(56.3)*
Number of patients with CKD	*0*	*(0)*
Presence of data for patients with abnormal liver function in trials (n = 142)		
Yes	*61*	*(43)*
No	*81*	*(57)*
Number of patients with abnormal liver function	*0*	*(0)*
Presence of data for patients with heart failure in trials (n = 142)		
Yes	*64*	*(45.1)*
No	*78*	*(54.9)*
Number of patients with heart failure	*0*	*(0)*
Presence of data for patients with COPD in trials (n = 142)		
Yes	*63*	*(44.4)*
No	*79*	*(55.6)*
Number of patients with COPD	*0*	*(0)*
Presence of data for patients with brain metastasis in trials (n = 142)		
Yes	*98*	*(69)*
No	*44*	(31)
Number of patients with brain metastasis	*1723*	*(1.6)*

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

generalizability of the study findings. For instance, in the FDA Report *Global Participation in Clinical Trials*, black participants only represented 2.74% of all patients enrolled in pivotal oncology trials.[18] Similar findings have been confirmed for Hispanic (10%) patients.[12] Curiously, Asian patients' enrollment rates are portrayed in an opposite trend, probably resulting from the rapidly growing health investments in cancer in the most populated regions of the world (ie, Western Pacific and South East Asian regions) and the expanding pharmaceutical investments in high-income and transition-economy Asian countries.[12,19,20] While no explicit exclusion of ethnic-defined groups are mandated by the clinical protocols, barriers in the participation to clinical trials are multifaceted. This should be referred to the broader landscape of disparities in the access to healthcare, driven by social health determinants and permeated by cultural factors. In fact, when

TABLE 3 Subgroup analyses in clinical trials

	n = 142	%
Subgroup analysis for ethnic group		
Yes	46	(32.4)
No	79	(55.6)
Subgroup analysis for age		
Yes	115	(81)
No	11	(7.7)
Subgroup analysis for sex		
Yes	78	(54.9)
No	48	(33.8)
Subgroup analysis for organ dysfunction		
Yes	0	(0)
No	126	(88.7)
Subgroup analysis for performance score		
Yes	92	(64.8)
No	35	(24.6)
Subgroup analysis for brain metastasis		
Yes	13	(9.2)
No	113	(79.6)
Subgroup analysis for HIV, HBV, HCV positivity		
Yes	5	(3.5)
No	120	(84.5)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

accounting for socioeconomic factors, ethnic group was not associated anymore with the likelihood of inclusion in clinical trials.[21]

A marked gender gap was delineated, consistently with previous investigations.[4] While no convincing data have been provided to understand the discrepancies, it has been suggested that the gender inequality resides possibly in the role that society assigns to women, which may be especially sensitive in some cultural groups.[22]

In contrast to ethnic and gender inclusion, disease-specific exclusion criteria have proactively persisted in limiting the access to experimental treatments. For PLWH, immunodeficiency and lymphopenia have been reported as the most common historical justifications for excluding these patients. However, in the HAART era, PLWH have the same life expectancy of HIV-negative persons, together with an increased risk of cancer, mostly non-HIV related malignancies. This suggests that the reasons for systematic exclusion may intersect a mixture of nonupdated clinical knowledge, health stigma and nonevidence informed positions. Likewise, the American Society of Clinical Oncology (ASCO) has published recommendations for clinical trial eligibility of PLWH in 2015.[23] According to these recommendations, the presence of HIV as an explicit exclusion criterion should be discouraged. Some have reported concerns for immunotherapy agents: one study, for example, showed that HIV status was an exclusion criterion in 72.9% of the analyzed trials.[24] Other concerns have also been raised regarding drug-drug interactions (DDI) between HAART agents and the study medications. However, clinical protocols well recognize and pose specific caveats for selected DDI; therefore, excluding for HIV status regardless of the treatments received is largely inappropriate and not justified solely by DDI.[25,26]

A similar pattern has been identified for patients with HBV and HCV, commonly excluded from trials. Reports from the literature have estimated an inclusion rate of HBV and/or HCV positive patients between 0.7% and 6.5%, consistently with our findings.[27,28] The FDA has recently published a guideline for patients with HBC and HCV in clinical studies.[8] According to this guideline, HBV and HCV infection should not be standard exclusion criteria from clinical trials.[8] Despite significant improvements in HCV infection treatment, and the very high rates of sustained viral responses with DAAs, a previous study showed that half of the patients excluded from clinical trials had HCV.[29] In the present study, we show that 28.9% of all clinical trials excluded patients with HBV and HCV. This discrepancy across the different studies may be associated with the inclusion of only phase III clinical trials in our study. Early phase studies have more restricted eligibility criteria. The main reasons adduced for the exclusion of patients with HBV and HCV patients were concern regarding reactivation of the HBV and HCV infections despite antiviral therapies, as well as DDI between antiviral therapies and experimental drugs.[29]

While organ dysfunction as an exclusion criterion is essential to ensure a safe patients' selection, some restrictions in the eligibility may impair the generalizability of the trial results. Abnormal cardiac, renal and hepatic functions could affect drug metabolism and some experimental compounds can even accelerate a decompensation in organ functions. The FDA has recently published a guideline to orient on the inclusion of patients with organ dysfunctions in clinical trials.[10] A restriction related to an organ dysfunction narrowing the eligible population in a clinical trial should be well documented by the sponsors, providing scientific and medical justifications beyond default safety precautions, for the specific clinical investigation; therefore, it should be a motivated decision.Similarly, patients with poorer PS have been systematically excluded from clinical trials. In the current clinical practice, poorer PS alone is not a contraindication to cancer treatment. In the context of disease-related impairments of the general conditions, cancer treatment can be performed especially for those therapies providing durable benefits in a short term with a good tolerability and no expected adjunctive toxicities.[30] The exclusion of patients with poor PS from clinical trials can affect the results' generalizability and hinders their enrollment and benefit from clinical trials. This is especially relevant for patients with PS ECOG score 2, who are largely represented in real-life settings.[31]

In our study, approximately half of the trials excluded patients with brain metastases. In most experimental drugs, the limited penetration across the blood-brain barrier (BBB) is a concern for experimental drugs' efficacy in central nervous system (CNS) tumors.[32] Furthermore, despite a lack of convincing data, intracranial hemorrhage during treatment is still regarded as a critical adverse event,

especially with the use of some vascular endothelial growth factor antagonists (anti-VEGF).[33] The FDA has recently published recommendations for the inclusion of patients with brain metastasis in trials. According to these recommendations, active brain metastasis should not be a universal exclusion criterion. Patients should be evaluated whether brain metastases require immediate treatment. If there is no need for immediate treatment, patients should be included in clinical trials without hesitation.[9]

Limitations of the present investigation must be noted. First, we obtained data for clinical trials from published manuscripts and ClinicalTrials.gov. As we could not access the original study datasets, about the subgroups of interest, some data can still be missed from the publicly available and published material. We could not classify Hispanic patients as a subgroup due to heterogeneous reporting in clinical trials. We calculated the prevalence of cancer in different ethnic groups and ages using data from the SEER database for 2017, as the most recent data source accessible to us. However, in our study, we included trials published from 2006 to 2020. Additionally, the SEER database encompasses only cancer data for the United States, and the generalization of SEER data to all populations enrolled in the studies may be debatable. However, to our knowledge, no global reference of cancer epidemiology is publicly accessible, reporting the kind of details required for our analyses. In addition, we could not access the data from clinical trials for calculation of "indirect standardization" that will help to more clarify the comparison of patient populations in clinical trials and the SEER database.In conclusion, we evaluated disadvantaged and underrepresented patient groups in clinical trial participation. In real life, we usually extrapolate data from clinical trials and treat patients otherwise not eligible in the original clinical trials. Our study is important to help clinicians cover the gap between patient population in trial and in real life. The value of enhancing diversity in clinical studies—as underlined by the FDA—should be entertained. As a result, the trial results' external validity and generalizability across the under- or nontested populations should be considered conditional for some subgroups of patients, sometimes reasonably warranting ad hoc confirmation studies.

CONFLICT OF INTEREST

Emre Yekedüz, Dario Trapani, Chris Labaki, Chadi Nabhan, Wenxin Hu, Shuchi Gulati, Güngör Utkan and Yüksel Ürün declared no conflict of interest. Bishal Gyawali received consulting fees from Vivio Health. Giuseppe Curigliano reports personal fees for advisory board from Roche, Pfizer, Novartis, Lilly, Foundation Medicine, BMS, Samsung, AstraZeneca, Daiichi Sankyo, GSK, Seagen and grants from Merck, other from Ellipsis, outside the submitted work. Toni K. Choueiri serves on the advisory board of Pfizer, Exelixis, Merck, BMS, AstraZeneca, Roche and Lilly for oncology drugs. Elisabeth G. E. de Vries has institutional financial support for advisory boards from Daiichi Sankyo, NSABP, Crescendo Biologics; for clinical trials or contracted research from Amgen, Genentech, Roche, Synthon, Bayer, Servier, Regeneron, G1 Therapeutics, all outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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