CLINICAL RESEARCH STUDY

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# Disparities in Representation of Women, Older Adults, and Racial/Ethnic Minorities in Immune Checkpoint Inhibitor Trials

**Irbaz B. Riaz, MD, MS,[a,c,h] Mahnoor Islam, MD,[d] Ahsan Masood Khan, MD,[e] Syed Arsalan Ahmed Naqvi, MBBS,[a] Rabbia Siddiqi, MD,[d] Kaneez Zahra Rubab Khakwani, MBBS,[f] Noureen Asghar, MD,[f] Waleed Ikram, MD,[a] Syed A. Hussain, MBBS, MSc, MD,[g] Parminder Singh, MD,[a] Jeremy L. Warner, MD, MS,[b] Guru P. Sonpavde, MD,[h] Folakemi T. Odedina, PhD,[i] Kenneth L. Kehl,[h] Narjust Duma, MD,[h] Alan H. Bryce, MD[a]**

*[a]Mayo Clinic, Phoenix, Ariz; [b]Vanderbilt University Medical Center, Nashville, Tenn; [c]Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; [d]Dow University of Health Sciences, Karachi, Pakistan; [e]University of Louisville, Louisville, Kent; [f]University of Arizona, Tucson, Ariz; [g]University of Sheffield and Sheffield Teaching Hospitals, Sheffield, UK; [h]FL Dana-Farber Cancer Institute, Harvard Medical School, Boston, Mass; [i]Mayo Clinic, Jacksonville, Fla.*

## ABSTRACT

**PURPOSE:** We aim to describe reporting and representation of minority patient populations in immune checkpoint inhibitor (ICI) clinical trials and assess predictors of enrollment disparity.

**METHODS:** Trial-level data were acquired from eligible phase II and III trials. Population-based estimates were acquired from the SEER 18 and Global Burden of Disease incidence databases. Trials reporting race, age, and sex were summarized using descriptive statistics. Enrollment-incidence ratio (EIR) was used to assess representation of subgroups. Average annual percentage change (AAPC) in EIR was calculated using Joinpoint Regression Analysis. Trial-level characteristics associated with EIR were assessed using multivariable linear regression.

**RESULTS:** A total of 107 trials with 48,095 patients were identified. Participation of Black, White, Asian, Native American, Pacific Islander, and Hispanic participants was reported in 65 (61%), 77 (72%), 68 (64%), 40 (37%,) and 24 trials (22%), respectively. Subgroup analyses of clinical outcomes by race, age, and sex were reported in 17 (22%), 62 (78%), and 57 (57%) trials, respectively. Women (trial proportion [TP]: 32%; EIR: 0.90 [95% confidence interval [CI]: 0.84-0.96]), patients aged ≥65 years (TP: 42%; EIR: 0.78 [95% CI: 0.72-0.84]), Black participants (TP: 1.9%; EIR: 0.17 [95% CI: 0.13-0.22]) and Hispanics (TP: 5.9%; EIR: 0.67 [95% CI: 0.53-0.82]) were underrepresented. Representation of Black patients decreased significantly from 2009 to 2020 (AAPC: −23.13). Black participants were significantly underrepresented in phase III trials ($P < .001$).

**CONCLUSION:** The reporting of participation by racial or ethnic subgroup categories is inadequate. Women, older adults, as well as Black and Hispanic participants are significantly underrepresented in ICI clinical trials.

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**KEYWORDS:** Clinical trial enrolment; Disparities; Immune checkpoint inhibitors; Older adults; Race; Women

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Requests for reprints should be addressed to Irbaz Riaz, MD, MS, Brigham and Women's Hospital, and Dana-Farber Cancer Institute, Mayo Clinic, Phoenix, AZ, 85054.

E-mail address: riaz.dr@mayo.edu

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## INTRODUCTION

Clinical outcomes in patients with cancer treated with immune-checkpoint inhibitors (ICI) can differ across subgroups of sex, age, and race and ethnicity.[1-4] Biological differences among men and women of different ethnicities and ages are known to impact response to anticancer chemotherapeutic agents,[5] and this likely also applies to immunotherapy. Indeed, studies show that, among patients with non-small-cell lung cancer (NSCLC) treated with ICI agents, Asian patients have longer overall survival,[2] and Hispanic patients have lower response rates[3] compared with white patients. Similarly, previous reports have also identified a larger survival benefit of combination therapy (chemotherapy plus immunotherapy) but a smaller benefit from immunotherapy alone in women versus men with advanced lung cancer.[1] Aging phenomena such as immunosenescence[6] also give reason to anticipate differences in patient outcomes by age with ICI use.[7]

### CLINICAL SIGNIFICANCE

- The enrollment of Blacks, older adults, and women is low in immune checkpoint inhibitors trials relative to their share of cancer incidence.
- Black representation has been consistently declining, while the representation of older adults has improved in the last decade.
- Caution must be exercised in applying the overall results from immune checkpoint inhibitors clinical trials to the care of patients who are racial and ethnic minorities.

Disparities in clinical trial enrollment directly impact the care of minority subpopulations with cancer. Adequate representation and reporting of these subpopulations is necessary to ensure precise recommendations. Although prior studies have discussed minority representation within oncology trials in general,[8-10] systematic assessment of inclusiveness for immunotherapy trials is lacking. The latter is critical to answering the question of whether the patient demographics represented in ICI trials are diverse enough to inform ongoing clinical and translational research that aims to expand the benefit of immunotherapy beyond a small subset of patients.[11]

Thus, the aim of this study was to assess the reporting and participation of vulnerable subgroups of sex, race and ethnicity and age in ICI clinical trials while accounting for cancer incidence in these subgroups.[12] We also assessed trends in the enrollment of minority subgroups and analyzed associations between specific trial characteristics and enrollment disparity across ICI clinical trials.

## METHODS

### Search Strategy and Study Selection

A comprehensive search strategy was developed to identify randomized phase II and III immunotherapy trials in all cancer types (detailed search strategy in Supplementary Methods, available online).

### Data Extraction

We extracted data for baseline trial characteristics, reporting, and representation of predefined subgroups of race, ethnicity, age, and sex (as per the Food and Drug Administration [FDA] position statement on categories of race, ethnicity, age, and sex[13]), and subgroup analyses for primary endpoint by these subgroups. Details of the data extraction process are detailed in Supplementary Methods, available online. US population-based incidence data for racial and ethnic subgroups were acquired from the Surveillance, Epidemiology and End Results (SEER) program database (SEER 18: 2000-2017).[14] Global incidence data for sex- and age-related subgroups were acquired from the Global Burden of Disease (GBD) database (http://ghdx.healthdata.org/gbd-results-tool)[15] to account for the inclusion of global trials and compensate for differences in cancer incidence between different regions.

### Statistical Analysis and Outcome Measures

Descriptive statistics were used to summarize baseline trial characteristics and sociodemographic characteristics of enrolled participants. We measured enrollment disparity for each subgroup by computing the enrollment-incidence ratio (EIR), that is, the proportion of patients of a particular subgroup category among trial participants, divided by the estimated proportion of similar patients diagnosed with cancer among the US or global population.[8] For the analysis of racial and ethnic enrollment disparity, we included US trials and international trials recruiting patients from the United States (Figure 1). US trials were defined as the trials recruiting patients exclusively from the United States. SEER was used to acquire population estimates for racial and ethnic subgroups to calculate EIR. We also conducted a sensitivity analysis, which included US trials only, to assess disparity in the enrollment of racial and ethnic subgroups. The choice of including trials recruiting from the United States and of using SEER to acquire population estimates was made because racial and ethnic disparity in clinical trial enrollment is a US-centric issue, and most trials that report race and ethnicity subgroups do so in accordance with the FDA position statement. However, we included all available trials in the age and sex analyses and used global population estimates from Global Burden of Disease to acquire cancer incidence in sex- and age-related subgroups. Nonparametric percentile bootstrapping with 10,000 resamples was used to generate 2-sided 95% confidence intervals (CI).[12]

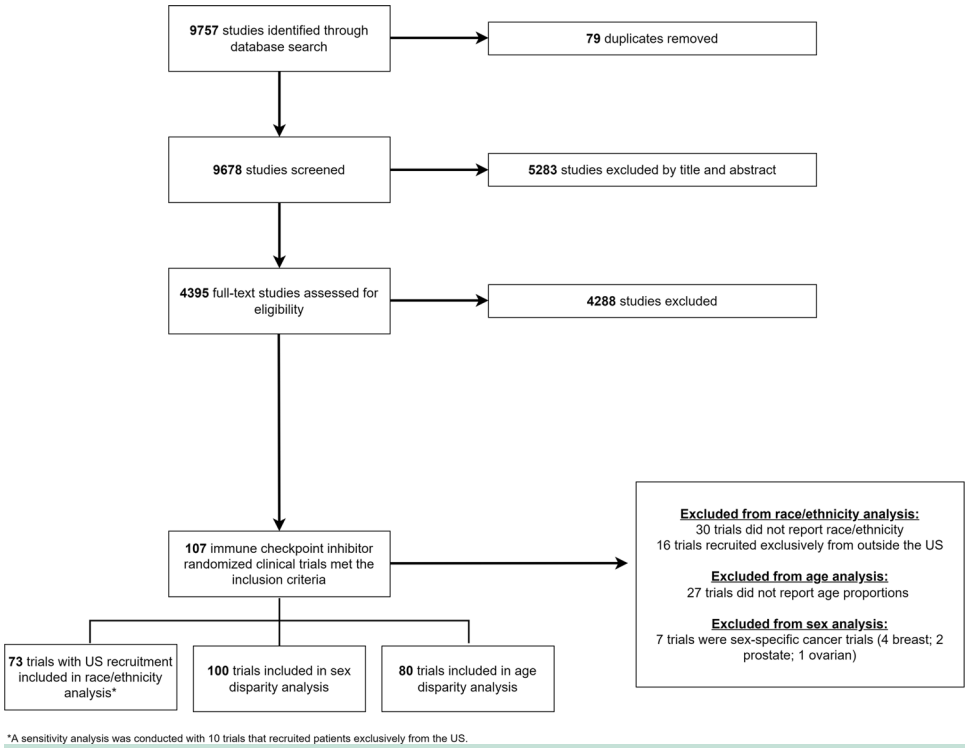


**Figure 1** A flowchart indicating the number of studies identified, included, and excluded in each disparity analysis.

Univariable linear regression was conducted to assess associations between each trial characteristic and log-transformed EIR calculated at the level of individual trials. For adjusted analysis, multivariable linear regression models were built by a backward selection process. *P* values were 2-sided and considered statistically significant when <0.05. All statistical analyses were conducted in R (v.4.0.2). Additionally, Joinpoint Regression Program[12] was used to conduct linear regression analyses to show average annual percentage change (AAPC) in logarithmic EIR from 2009 to 2020.

A post hoc analysis was conducted to explore the association between enrollment disparity and socioeconomic status in underrepresented racial and ethnic subgroups. We used the SEER database to extract the proportion of cancer patients from each racial and ethnic subgroup in the low-income bracket (defined as a median annual household income of less than $40,000[16]), and correlated these proportions with logarithmic EIRs for each respective cancer type using Pearson product-moment correlation. We also calculated the proportions of white and Black cancer patients in the low-income bracket from SEER and analyzed the difference using the $\chi^2$ test.

## RESULTS

### Trial Characteristics

We identified 107 eligible phase II and phase III ICI RCTs published between 2009 and 2020, with a total of 48,095 participants. Eighteen different cancer types are represented in our included trials (Supplementary Table 1, available online). Majority of trials had international recruitment in addition to enrolling patients from the United States (80 [74.8%]), and 11 trials (10.3%) recruited patients from within the United States only. Trial characteristics are outlined in Table 1.

### Reporting and Subgroup Analyses

Out of 107 ICI trials, we excluded 7 sex-specific cancer trials from our analysis of reporting/representation by sex. The remaining 100 trials all reported patient proportions by sex. A total of 57 trials (57%) also reported subgroup analyses of clinical outcomes by sex.

For race and ethnicity reporting, 77 trials (72.0%) reported race as a baseline characteristic. Only 40 trials (37.4%) reported all 5 racial categories (Black, white, Asian, Native American, and Pacific Islander), while 21 trials (19.6%) reported 3 racial categories of Black, white, and Asian only. For each race individually, whites were reported in 77 trials (72.0%), Asians in 68 trials (63.6%), Black patients in 65 trials (60.7%), and Native Americans and Pacific Islanders in 40 trials (37.4%). Hispanic and non-Hispanic ethnicity were reported in 24 trials (22.4%). Among trials with race and ethnicity reporting, only 17 trials (22.1%) reported outcomes by racial and ethnic subgroups.

Similarly, 80 trials (74.8%) reported proportions by specific age categories. Patient ages were most frequently

**Table 1** Summary of Trial Characteristics

| Trial characteristics | Number of trials (%) |
|---|---|
| All trials | 107 (100) |
| Trial phase | |
| 3 | 63 (58.9) |
| 2 | 44 (41.1) |
| Arms | |
| 2 | 80 (74.8) |
| ≥3 | 27 (25.2) |
| Size of trial | |
| Small (<100) | 16 (15.0) |
| Intermediate (100-500) | 46 (43.0) |
| Large (>500) | 45 (42.0) |
| Monotherapy/combination* | |
| Combination therapy | 62 (57.9) |
| Monotherapy | 61 (57.0) |
| Primary endpoint* | |
| OS | 60 (56.1) |
| PFS | 41 (38.3) |
| Other | 38 (35.5) |
| Positive trial? | |
| Yes | 61 (57.0) |
| No | 39 (36.4) |
| Funding source | |
| Industry | 102 (95.3) |
| Nonindustry | 5 (4.7) |
| Center | |
| Multicenter | 106 (99.1) |
| Single center | 1 (0.9) |
| Recruitment | |
| United States + Outside United States | 80 (74.8) |
| Outside United States only | 16 (15.0) |
| United States only | 11 (10.3) |

ICI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival.

*Total percentages for monotherapy/combination add up to >100% due to different ICI agents and regimens being evaluated in multiple treatment arms of the same trial. The primary endpoint characteristic also adds up to >100% due to some trials having >1 primary endpoint.

reported as more or less than 65 years (76 out of 80 trials; 95.0%). Among the trials reporting age categories, 62 trials also reported subgroup analyses of clinical outcomes by age (77.5%).

## Trial Proportions and EIR

Figure 2 summarizes overall trial proportions (TPs) and the proportion of patients diagnosed with cancer in the general population for each minority subgroup. Table 2 also summarizes the recruitment of minority subgroups, along with expected participation based on population estimates.

A total of 100 trials were included in the analysis to assess enrollment disparity by sex. Overall, women and men constituted 31.9% and 68.0% of the trial population, respectively. Women were underrepresented in ICI clinical trials relative to their cancer incidence in the global population (EIR: 0.90 [95% confidence interval [CI]: 0.84-0.96]). This underrepresentation was consistent across trials grouped by each cancer type (Supplementary Table 2, available online), except for multiple myeloma trials (TP: 57.3%; EIR: 1.21 [95% CI: 1.13-1.32]) and small-cell lung cancer trials (TP: 32.8%; EIR: 1.09 [95% CI: 1.02-1.16]). The greatest degree of under representation was seen in head-and-neck cancer (TP: 16.6%; EIR: 0.64 [95% CI: 0.63-0.66]).

A total of 73 trials recruiting patients from the United States were included in the analysis to assess enrollment disparity by racial and ethnic subgroups. White participants were recruited predominantly in the overall trial population (TP: 82.5%; EIR: 1.01 [95% CI: 0.97-1.05]). In contrast, Black participants constituted only 1.9% of the trial population and were largely underrepresented (EIR: 0.17 [95% CI: 0.13-0.22]). Asians, while constituting only 14.3% of the overall trial population, were overrepresented compared to population estimates (EIR: 2.38 [95% CI: 1.86-2.89]). Similarly, Native Americans constituted 0.5% of the trial population but were not significantly underrepresented (EIR: 0.98 [95% CI: 0.40-1.84]).

A total of 10 trials recruiting from the United States only were included in the sensitivity analysis, among which whites were reported in all 10, Black patients in 9, and Asians in 6. Small number of trials precluded any meaningful statistics to assess disparity for Native American and Hispanic patients. The results showed consistent underrepresentation of Black participants (TP: 5.4%; EIR: 0.50 [95% CI: 0.17-0.88]) and overrepresentation of white participants (TP: 88.5%; EIR: 1.09 [95% CI: 1.01-1.16]). Asian patients were also significantly underrepresented in U.S. trials (TP: 3.3%; EIR: 0.55 [95% CI: 0.06-0.91]).

Across specific cancers, Black patients were underrepresented, with gastric/gastroesophageal junction cancer trials accounting for the greatest degree of disparity (TP: 0.8%; EIR: 0.06 [95% CI: 0.0-0.07]) (Figure 3). Asians were underrepresented in esophageal cancer (TP: 4.3%; EIR: 0.96), mesothelioma (TP: 1.6%; EIR: 0.50), prostate cancer (TP: 1.2%; EIR: 0.25), and ovarian cancer (TP: 5.0%; EIR: 0.66) trials. Hispanic participants were also underrepresented in trials recruiting from the United States, both overall (TP: 5.9%; EIR: 0.67 [95% CI: 0.53-0.82]) and in most cancer types separately; exceptions to cancer-specific underrepresentation were melanoma (TP: 5.9%; EIR: 1.96 [95% CI: 0.82, 2.74]) and non-small-cell lung cancer (TP: 5.6%; EIR: 1.03 [95% CI: 0.20-1.90]), as shown in Supplementary Table 3, available online.

Across 80 trials that reported patient numbers by age categories, older adults constituted 41.8% of the trial population and were significantly underrepresented in view of cancer incidence in this subpopulation (EIR: 0.78 [95% CI: 0.72-0.84]). Breast cancer trials (TP: 17.4; EIR: 0.50 [95% CI: 0.03-0.70]) accounted for the greatest degree of underrepresentation among all cancer types. Hepatocellular cancer (TP: 53.8%; EIR: 1.19 [95% CI: 1.11-1.28]) was the only cancer type wherein older adults were significantly

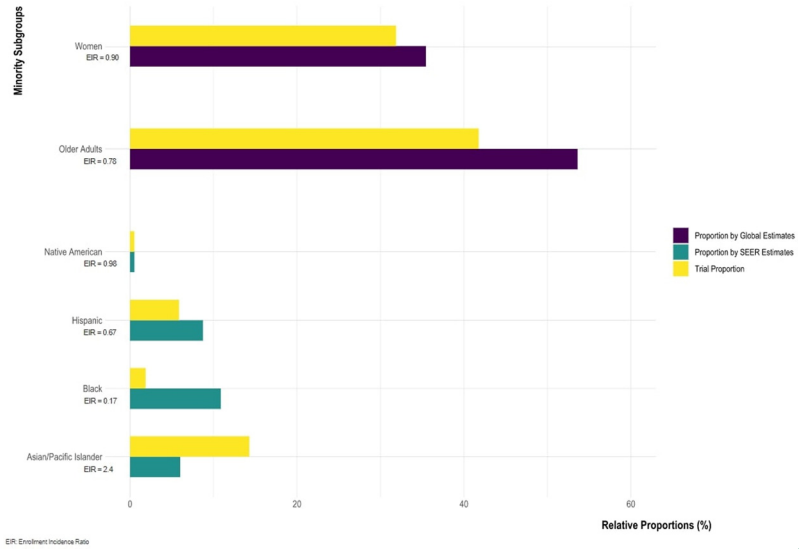


**Figure 2** Visual representation of how trial proportions compare against the proportion of patients diagnosed with cancer in the United States (for racial and ethnic subgroups) or globally (for sex- and age-related subgroups) for each minority subgroup.

**Table 2** Participation of All Subgroups in Immune Checkpoint Inhibitor Trials, Compared with U.S. or Global Population Estimates

| Subgroup | Trial participants, No. (%) | Proportion of cancer incidence in population,* % | Enrollment-incidence ratio | Observed number of participants (per 1000) | Expected number of participants (per 1000) |
|---|---|---|---|---|---|
| Race/ethnicity† | | | | | |
| White | 27724 (82.5) | 81.5 | 1.01 | 825 | 815 |
| Black | 559 (1.9) | 10.9 | 0.17 | 19 | 109 |
| Asian/Pacific Islander | 4408 (14.3) | 6.0 | 2.38 | 143 | 60 |
| Native American | 96 (0.5) | 0.5 | 0.98 | 5 | 5 |
| Hispanic | 551 (5.9) | 8.7 | 0.67 | 59 | 87 |
| Sex | | | | | |
| Men | 30485 (68.0) | 64.6 | 1.05 | 680 | 646 |
| Women | 14284 (31.9) | 35.4 | 0.90 | 319 | 354 |
| Age | | | | | |
| Younger | 23478 (58.5) | 46.4 | 1.26 | 585 | 464 |
| Older | 17194 (41.8) | 53.6 | 0.78 | 418 | 536 |

*U.S. population estimates were used for racial and ethnic subgroups; global population estimates were used for sex- and age-related subgroups.
†These numbers are reported for all trials recruiting from the United States (international plus United States-only).

overrepresented in trials instead (Supplementary Table 2, available online).

## Trends in Enrollment Disparity

Enrollment of Black participants has significantly declined over time (AAPC: −23.13; $P < .05$), and recruitment of Hispanics also appears to be decreasing (AAPC: −1.70; $P \geq .05$), though the change is not statistically significant (Figure 4, Supplementary Figure 1, available online). A significant increase was seen in the enrollment of older adults (AAPC: 2.78; $P < .05$) relative to their cancer incidence, indicating improvement in representation. Although EIR for women was observed to be increasing, the change was not statistically significant (AAPC: 2.64; $P \geq .05$).

## Associations with Trial Characteristics

Associations between EIR and trial characteristics on multivariable analysis are summarized in Supplementary Table 4, available online. Increasing size of the trial was associated with greater enrollment disparity for women. Greater

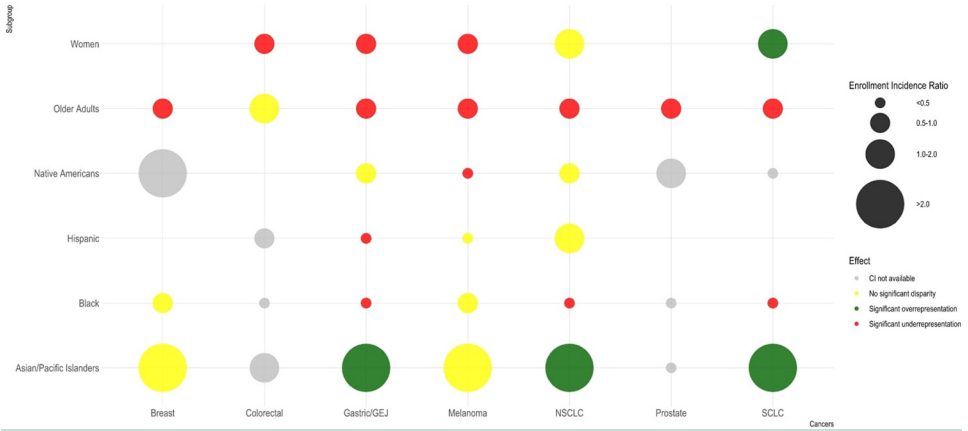


**Figure 3** An evidence map of enrollment incidence ratios for each minority subgroup within trials by cancer type. The "effect" denotes statistical significance of enrollment incidence ratios on the basis of 95% confidence intervals.

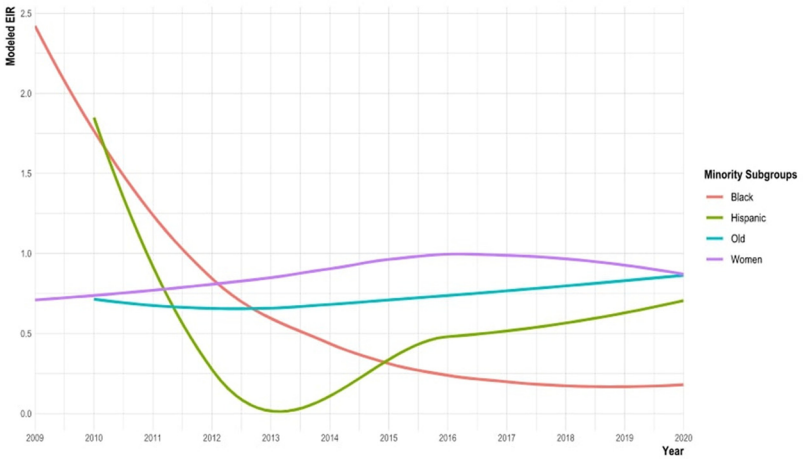


**Figure 4** Trends in the representation of patients who are Black, Hispanic, older adults, and women.

enrollment disparity for older adults was identified in trials with a nonmetastatic clinical setting, trials without overall survival as a primary endpoint, and trials investigating PD-L1 inhibitors only (compared with those investigating combination ICI therapy). Black patients were significantly underrepresented in phase III trials as compared with phase II trials.

## Correlation Between EIR and Median Household Income

The proportion of Black or Hispanic patients with a low median household income in the U.S. population (among all Black and Hispanic patients diagnosed with a particular cancer) was inversely (but nonsignificantly) correlated with cancer-specific logEIR ($r = -0.30$, $P = .30$ for Black patients; $r = -0.04$, $P = .92$ for Hispanic patients).

For every cancer type except small-cell lung cancer, the proportion of Black patients from a low-income household was significantly higher than the proportion of white patients in the low-income bracket ($P < .001$).

## DISCUSSION

We found both suboptimal reporting about participation as well as consistent underrepresentation of women, older adults, and racial and ethnic minorities (particularly Black and Hispanic participants) in ICI clinical trials from 2009 to 2020 even after adjusting for cancer incidence in these subgroups. Trends over the last decade indicate that the representation of Black and Hispanic patients in ICI trials is consistently declining. Representation of women and Black patients suffers even more in larger, phase III trials. Only about one-half of trials report clinical outcomes by sex and only one-fifth report outcomes by race and ethnicity. These findings demonstrate a clear inferential gap and have important implications on the generalizability of ICI trials and,

ultimately, on optimal recruitment strategies in future trials and therapeutic interventions for these populations in current clinical practice. This is the first study to evaluate minority representation in immunotherapy trials; the findings of this study are comparable to patterns of disparity previously identified in cancer trials with conventional drugs,[8,9,17] indicating the persistence of former barriers into the newer age of immunotherapy.

Black representation was less than 2% in ICI trials, and the 23% annual decrease in recruitment is particularly disturbing in this historically underrepresented minority in cancer trials.[8] We also show that Black participants are even less likely to be represented in large trials that are actually practice-changing. The fact that most clinical trials are conducted at large academic centers may amplify the problem, given the difficulty vulnerable populations face in accessing these centers. Lung cancer is particularly interesting in this regard. Unsatisfactory trial enrollment despite increasing incidence of lung cancer in minority populations may relate to upstream disparity in lung cancer screening and treatment on a larger scale. Black patients are less likely than white patients to receive treatment for early-stage lung cancer[18] and to fit eligibility criteria for lung cancer screening[19] because the current screening criteria disfavor Black demographics (lower average cigarette consumption per day, younger age at cancer development in Black patients). Unfortunately, there are many more prevalent reasons for this underrepresentation. Black patients, for example, are 4 times more likely to be affected by chronic kidney disease than white patients,[20] resulting in disproportionate exclusion of the former based on creatinine and estimated glomerular filtration rate criteria. Lack of awareness of clinical trials or unwillingness to enroll due to a lack of trust in the health care system also contributes to disparities.[21]

It is important to note that race by itself is not a biological entity but a social construct.[22] Racial and ethnic minorities experience poorer health outcomes due to greater social and financial barriers in accessing health care.[23] Our exploratory analysis corroborates this, indicating that Black patients diagnosed with cancer are much more likely than white patients to belong to a low-income household; the higher percentages of low-income Black and Hispanic patients with a particular cancer type can impair recruitment into the respective clinical trials. Thus, this underrepresentation by race is likely a surrogate to other socioeconomic markers of disparity, such as insurance status and educational well-being. Thus, linking socioeconomic variables with race for clinical trial participants can offer deeper insights into the likelihood of clinical trial participation.[24-26]

The representation of women (32%) and adults older than 65 years (42%) was also lower than their fair share of representation, but there is an improving trend over last 2 decades. Representation of older adults was particularly low in lung cancer and breast cancer trials; however, for breast cancer trials, this may simply reflect that most ICI trials target triple-negative breast cancer, which disproportionately affects younger women.[27,28] Physicians are often reluctant to enroll older patients with comorbidities to avoid toxicity. This concern also extends to functional status, wherein participation of older adults was found to be 22% lower in trials that excluded patients with mild-moderate functional impairment than trials without this exclusion criterion.[29,30] Certain eligibility criteria, such as an ejection fraction of ≤40% and glomerular filtration rate <30 mL/min/1.73 $m^2$, have also been suggested to favor a male pattern of disease and exclude women consistently.[31] Many of these criteria have been carried over from an age of cytotoxic chemotherapy; however, safety profiles for ICI are generally more favorable and may allow use of these agents in patients with certain comorbidities.[11,32] Revisiting and broadening the eligibility criteria for immunotherapy trials, especially with respect to comorbidities and performance status, may help to diversify participation and minimize disparities.[33]

Moreover, a recent analysis of immunotherapy trials identified significant sex differences in the risk of experiencing adverse events.[34] Given the evidence of a greater magnitude of harm in women receiving immunotherapy,[34] evaluating sex-specific outcomes in trials is clearly necessary for appropriate clinical decision-making. In fact, differences in the magnitude of treatment effect may also extend to racial, ethnic, and older-age minorities, and their under-recruitment in trials leads to uncertainty in decision-making when treating these populations.

A durable solution to health care inequities will require engagement from all stakeholders, including health care providers, patients, industry, and regulatory agencies. Grassroots-level efforts by health care providers, their employers, and patient groups must be matched by an equal commitment from industry and guidance from federal agencies such as FDA. These efforts must be balanced by the need to accelerate rather than stifle innovation because delays in discovery and evidence can be fatal for patients who are waiting for the next breakthrough. We propose that the FDA, with the support of industry, mandate a level of minority accrual to studies necessary to establish clinical validity of the overall trial results for those populations. This can be designed in such a way that accrual to subpopulations can continue beyond the accrual required for the primary analysis. In essence, we propose that a study should be designed to accrue additional patients to extend the validity of study results to subpopulations, but that initial reporting of the primary analysis not be linked to specific demographic goals. All stakeholders should invest in the infrastructure and outreach efforts necessary to address the concerns of underrepresented minority groups and bring those groups to the table for future problem-solving.

There are several strengths of our analyses. The use of an incidence-based measure (EIR) to assess disparities allows interpretation of TP in the context of cancer epidemiology. This provides a truer measure of disparity than TP alone because it directly compensates for any epidemiologic

differences in cancer incidence between subgroups at the population-level. It is important to note that the choice of baseline estimate used in the calculation of EIR can influence results. Thus, we used SEER estimates for assessment of racial disparity by restricting our analyses to trials recruiting from the United States and used global estimates for assessment of sex and age disparity, including multinational trials to account for international recruitment of the included clinical trials. We also assessed the impact of socioeconomic status as well as trial characteristics to explain enrollment disparity. Finally, this is the first analysis to report disparity trends in ICI trials over the last decade. Regarding limitations, there is a possibility of missing data because our eligibility criteria exclude any trials that may have been published as conference abstracts only, as well as subgroup data from any trials that may have been reported as separate publications. We also recognize that regional differences in incidence can impact the calculation of enrollment-incidence disparity, depending on the level of recruitment from different regions in multinational ICI trials. However, most trials do not adequately report regional recruitment percentages to allow an analysis accounting for this. The disparities identified in certain cancers may also be influenced by the type of cancer and its treatment, though the use of cancer-specific incidence in quantifying disparity helped offset this. Finally, we did not assess representation of minority subgroups specifically in ICI trials leading to FDA approval because small sample size would preclude any meaningful statistics.

## CONCLUSION

The results of our study suggest that, until we achieve adequate minority representation in immunotherapy trials, caution must be exercised in interpreting the risk-to-benefit ratio reported in these trials and using them to make management decisions for minority patients. We hope that our findings and discussion will inform the potential solutions for aiding recruitment in oncology clinical trials.

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**Authorship:** All authors had access to the data and a role in writing this manuscript.

## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.03.042.

## SUPPLEMENTARY MATERIALS

## eMethods

**Data Sources and Study Selection.** A comprehensive search of several databases from each database's inception to September 11, 2018, in any language was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for phase 2 or 3 clinical trials, systematic reviews, and meta-analyses of immune checkpoint inhibitor (ICI) drugs. Following the initial search, subsequent searches were conducted every 2-6 months thereafter to identify additional trials, up till August 4, 2020. Two independent reviewers (RS and NA) screened and selected the relevant trials based on a priori eligibility criteria. Primary reports of original phase II and III randomized controlled trials (RCTs) with an ICI in at least 1 arm, either as monotherapy or combination therapy, were included. We excluded phase I and single-arm trials; trials with unpublished results; conference abstracts; non-English language articles; follow-up reports; and exploratory, subgroup and post hoc analyses. We included both region-specific and global studies.

**Search Strategy.** *Ovid.* Database(s): Embase 1988 to 2018 Week 37, EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 5, 2018, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 10, 2018

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | pembrolizumab/ | 6811 |
| 2 | nivolumab/ | 8486 |
| 3 | atezolizumab/ | 2047 |
| 4 | durvalumab/ | 1487 |
| 5 | avelumab/ | 855 |
| 6 | Ipilimumab/ | 10815 |
| 7 | (Atezolizumab or Avelumab or Bavencio or Durvalumab or Imfinzi or Ipilimumab or Keytruda or Nivolumab or Opdivo or Pembrolizumab or Tecentriq or Yervoy).ti,ab,hw,kw. | 25301 |
| 8 | or/1-7 | 25301 |
| 9 | *monoclonal antibody/ | 57887 |
| 10 | *Antibodies, Monoclonal/ | 139215 |
| 11 | *Immunotherapy/ | 42136 |
| 12 | ("biologic response modifier therap*" or "biological response modifier therap*" or "BRM therap*" or "clonal antibod*" or "CTLA-4 inhibitor*" or "hybridoma antibod*" or "immune checkpoint inhibitor*" or "immune therap*" or "immunoglobulin therap*" or "immunological therap*" or "immunological treatment*" or "monoclonal antibod*" or "PD-1 inhibitor*" or "PD-L1 inhibitor*").ti. | 93600 |
| 13 | 9 or 10 or 11 or 12 | 209442 |
| 14 | exp *Neoplasms/dt | 769877 |
| 15 | (cancer* or neoplasm* or neoplastic or paraneoplas* or tumor* or tumor* or neoplasia* or "section 16" or leukemia* or carcinoma* or lymphoma* or Astrocytoma* or glioma* or adenoma* or carcinoid* or Sarcoma* or ostesarcoma* or histiocytoma* or craniopharyngioma* or ependymoma* or chordoma* or "Chronic Myeloproliferative Disorder*" or craniopharyngioma* or "Mycosis Fungoide*" or "Sézary Syndrome*" or Esthesioneuroblastoma* or melanoma* or retinoblastoma* or histeocytoma* or "gestational trophoblastic disease*" or histiocytos* or burkitt* or Macroglobulinemia* or Mesothelioma* or neuroblastoma* or Papillomatos* or paraganglioma* or "pheochromocytoma* multiple myeloma*" or blastoma* or Rhabdomyosarcoma* or nonmelanoma* or metasta*).ti. | 4454635 |
| 16 | 14 or 15 | 4644634 |
| 17 | 13 and 16 | 54729 |
| 18 | 8 or 17 | 76801 |
| 19 | meta analysis/ | 239443 |
| 20 | clinical trial, phase ii/ | 29640 |
| 21 | clinical trial, phase iii/ | 14138 |
| 22 | phase 2 clinical trial/ | 66661 |
| 23 | phase 3 clinical trial/ | 35242 |
| 24 | ((meta adj analys*) or metaanalys* or (systematic* adj3 review*) or (("phase 2" or "phase II" or "phase 3" or "phase III") adj5 (trial or study))).ti,ab,kw. | 698623 |

| | | |
|---|---|---|
| 25 | or/19-24 | 801767 |
| 26 | 18 and 25 | 7889 |
| 27 | (exp animals/ or exp nonhuman/) not exp humans/ | 9198737 |
| 28 | ((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw. | 7872281 |
| 29 | 26 not (27 or 28) | 7816 |
| 30 | limit 29 to yr="2017 -Current" | 2629 |
| 31 | remove duplicates from 30 | 1976 |
| 32 | 29 not 30 | 5187 |
| 33 | remove duplicates from 32 | 4209 |
| 34 | 31 or 33 | 6185 |

*Scopus.*

1. TITLE-ABS-KEY(Atezolizumab OR Avelumab OR Bavencio OR Durvalumab OR Imfinzi OR Ipilimumab OR Keytruda OR Nivolumab OR Opdivo OR Pembrolizumab OR Tecentriq OR Yervoy)
2. TITLE("biologic response modifier therap*" OR "biological response modifier therap*" OR "BRM therap*" OR "clonal antibod*" OR "CTLA-4 inhibitor*" OR "hybridoma antibod*" OR "immune checkpoint inhibitor*" OR "immune therap*" OR "immunoglobulin therap*" OR "immunological therap*" OR "immunological treatment*" OR "monoclonal antibod*" OR "PD-1 inhibitor*" OR "PD-L1 inhibitor*")
3. TITLE(cancer* or neoplasm* or neoplastic or paraneoplas* or tumor* or tumor* or neoplasia* or "section 16" or leukemia* or carcinoma* or lymphoma* or Astrocytoma* or glioma* or adenoma* or carcinoid* or Sarcoma* or ostesarcoma* or histiocytoma* or craniopharyngioma* or ependymoma* or chordoma* or "Chronic Myeloproliferative Disorder*" or craniopharyngioma* or "Mycosis Fungoide*" or "Szary Syndrome*" or Esthesioneuroblastoma* or melanoma* or retinoblastoma* or histeocytoma* or "gestational trophoblastic disease*" or histiocytos* or burkitt* or Macroglobulinemia* or Mesothelioma* or neuroblastoma* or Papillomatos* or paraganglioma* or "pheochromocytoma* multiple myeloma*" or blastoma* or Rhabdomyosarcoma* or nonmelanoma* or metasta*)
4. TITLE-ABS-KEY((meta W/1 analys*) OR metaanalys* OR (systematic* W/3 review*) OR (("phase 2" or "phase II" or "phase 3" or "phase III") W/5 (trial or study)))
5. (1 or (2 and 3)) and 4
6. TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR

llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
7. 5 and not 6
8. INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
9. 7 and not 8

**Data Extraction.** We extracted data for baseline trial characteristics that included but were not limited to: trial identification information, year of publication, sample size, ICI drug class, ICI agent regimen, control arm regimen, funding source, primary endpoint(s), and whether the primary endpoint was met (as per the statistical significance of any difference reported in the primary endpoint). In case of multiple primary endpoints, the trial was considered positive if any one of the primary endpoints was met or, in instances of coprimary endpoints, the trial was considered positive if all primary endpoints were met. The decision to consider endpoints as multiple or coprimary was based on the original authors' definitions. Furthermore, in the case of multiarm trials (more than 2 arms), primary endpoint was considered to have been reached if any 1 of the treatment arms differed significantly from the control. We also extracted information about whether each trial recruited participants from the United States, based on the study authors' explicit mention of where the trial was conducted or which region(s) patients were recruited from.

We followed the U.S. Food and Drug Administration position statement on categories of race (Caucasian/White, Black, American Indian/Alaskan native, native Hawaiian/Pacific Islander, and Asians), ethnicity (Hispanic/Latino and non-Hispanic/non-Latino), age (<65 years for younger adults and ≥65 years for older adults), and sex (male and female). Two independent reviewers (MI and AMK) extracted data from published reports of eligible trials. Supplementary contents with appendices, protocols, and clinical trial registry (ClinicalTrials.gov) were also accessed for data not available in published reports. Any discrepancies between the 2 reviewers or among the data sources were

**Supplementary Table 1** Additional Trial Characteristics

| Trial characteristics | Number of trials (%) |
|---|---|
| Cancer type | |
| Brain | 1 (0.9) |
| Breast | 4 (3.7) |
| Colorectal | 2 (1.9) |
| Esophageal | 1 (0.9) |
| Gastric/GEJ | 6 (5.6) |
| Head and neck | 5 (4.7) |
| Hepatocellular | 2 (1.9) |
| Hodgkin lymphoma | 1 (0.9) |
| Melanoma | 31 (29.0) |
| Mesothelioma | 2 (1.9) |
| Multiple myeloma | 2 (1.9) |
| Non-small cell lung cancer | 26 (24.3) |
| Ovarian | 1 (0.9) |
| Pancreatic | 3 (2.8) |
| Prostate | 2 (1.9) |
| Renal cell carcinoma | 7 (6.5) |
| Small cell lung cancer | 6 (5.6) |
| Urothelial | 5 (4.7) |
| Class of ICI* | |
| PD1 inhibitor | 51 (47.7) |
| PD-L1 inhibitor | 26 (24.3) |
| CTLA-4 inhibitor | 24 (22.4) |
| PD1 inhibitor + CTLA-4 inhibitor | 11 (10.3) |
| PD-L1 inhibitor + CTLA-4 inhibitor | 6 (5.6) |
| Name of ICI* | |
| Atezolizumab | 15 (14.0) |
| Avelumab | 3 (2.8) |
| Durvalumab | 11 (10.3) |
| Ipilimumab | 22 (20.6) |
| Nivolumab | 27 (25.2) |
| Pembrolizumab | 27 (25.2) |
| Tremelimumab | 4 (3.7) |
| Clinical setting | |
| Adjuvant | 7 (6.5) |
| Maintenance | 2 (1.9) |
| Metastatic/recurrent (unresectable) | 92 (86.0) |
| Neoadjuvant | 5 (4.7) |
| Type of combination | |
| ICI + ICI | 19 (17.8) |
| ICI + chemotherapy | 30 (28.0) |
| ICI + other | 16 (15.0) |
| Type of control | |
| Best supportive care | 3 (2.8) |
| BRAFi+MEKi | 2 (1.9) |
| Chemo | 50 (46.7) |
| Anti-EGFR | 5 (4.7) |
| Interferon | 1 (0.9) |
| ICI | 30 (28.0) |
| mTOR inhibitor | 1 (0.9) |
| Multikinase inhibitor | 2 (1.9) |
| Placebo | 10 (9.3) |
| TKI | 7 (6.5) |
| Vaccine | 1 (0.9) |
| Anti-VEGF | 1 (0.9) |

GEJ = gastroesophageal junction; ICI = immune checkpoint inhibitor; PD1 = programmed cell death-1; PD-L1 = programmed death-ligand 1.
*Total percentages in some trial characteristics (class of ICI, name of ICI) add up to >100% due to different ICI agents and regimens being evaluated in multiple treatment arms of the same trial.

resolved by consensus and input from a third reviewer (IBR).

For race and ethnicity, we determined the frequency and percentage of trials that reported the proportion of patients according to race and ethnicity. We also extracted data regarding the completeness of reporting for all categories, whether race and ethnicity were combined in reporting. For age, we calculated the frequency and percentage of trials that reported age proportion (eg, the proportion of older adults in the trial population), trials that reported age range but not proportion, and trials that excluded older adults. The age brackets into which trial participants were categorized were also noted. Similar data were extracted for male versus female patients. Sex-specific subgroup data extraction was not applicable to trials with sex-specific cancers such as prostate and ovarian cancers, and the proportion of the patients of a particular subgroup (race, ethnicity, age, and sex) was calculated after excluding trials that failed to report data on that subgroup category. In the case of trials that reported certain demographic proportions only within a subpopulation, the size of that subpopulation was considered in the calculation (rather than the total sample size) to prevent underestimation of categorical representation.

**Supplementary Table 2** Enrollment Disparity for Men and Women, and for Older Adults and Younger Adults Across Each Cancer Type

| | Women | | Men | | Older Adults | | Younger Adults | |
|---|---|---|---|---|---|---|---|---|
| Cancer | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) |
| Melanoma | 38.3 | 0.78 (0.76-0.81) | 61.3 | 1.20 (1.17-1.22) | 33.9 | 0.83 (0.72-0.95) | 66.1 | 1.12 (1.04-1.20) |
| NSCLC | 32.6 | 1.08 (0.94-1.22) | 67.4 | 0.96 (0.91-1.02) | 46.3 | 0.78 (0.74-0.82) | 53.6 | 1.31 (1.26-1.38) |
| SCLC | 32.8 | 1.09 (1.02-1.16) | 67.2 | 0.96 (0.93-0.99) | 42.1 | 0.71 (0.62-0.81) | 57.9 | 1.42 (1.28-1.55) |
| Gastric/GEJ | 29.7 | 0.85 (0.81-0.88) | 70.3 | 1.08 (1.06-1.10) | 39.6 | 0.71 (0.68-0.77) | 60.4 | 1.36 (1.28-1.40) |
| Urothelial | 24.2 | 1.04 (1.00-1.09) | 75.8 | 0.99 (0.97-1.00) | 59.6 | 0.90 (0.73-0.96) | 40.4 | 1.18 (1.08-1.51) |
| Renal | 26.1 | 0.70 (0.67-0.73) | 73.9 | 1.18 (1.16-1.20) | 37.8 | 0.78 (0.75-0.80) | 62.2 | 1.21 (1.19-1.24) |
| Hodgkin Lymphoma | 59.6 | 1.47 (NA) | 40.4 | 0.68 (NA) | — | — | — | — |
| Head and Neck | 16.6 | 0.64 (0.63-0.66) | 83.4 | 1.13 (1.12-1.13) | 31.7 | 0.85 (0.82-0.89) | 68.3 | 1.09 (1.06-1.11) |
| Colorectal | 37.8 | 0.84 (0.73-0.89) | 62.2 | 1.14 (1.09-1.23) | 64.1 | 1.06 (0.86-1.17) | 35.9 | 0.90 (0.75-1.21) |
| Hepatocellular | 17.7 | 0.60 (0.59-0.61) | 82.3 | 1.17 (1.16-1.17) | 53.8 | 1.19 (1.11-1.28) | 46.2 | 0.84 (0.77-0.91) |
| Esophageal | 13.1 | 0.44 (NA) | 86.9 | 1.24 (NA) | 53.0 | 0.97 (NA) | 47.0 | 1.03 (NA) |
| Mesothelioma | 23.3 | 0.82 (0.70-0.84) | 76.7 | 1.07 (1.06-1.12) | 58.5 | 1.00 (NA) | 41.5 | 1.00 (NA) |
| Multiple Myeloma | 57.3 | 1.21 (1.13-1.32) | 42.7 | 0.81 (0.71-0.89) | 68.2 | 1.09 (0.89-1.25) | 44.2 | 1.18 (NA) |
| Pancreatic | 45.1 | 0.96 (0.85-1.02) | 53.1 | 1.00 (0.88-1.13) | 69.5 | 1.10 (NA) | 30.5 | 0.83 (NA) |
| Brain | 36.3 | 0.80 (NA) | 63.7 | 1.16 (NA) | 19.2 | 0.58 (NA) | 80.8 | 1.20 (NA) |
| Prostate* | — | — | — | — | 55.9 | 0.75 (0.59-0.97) | 28.1 | 1.09 (NA) |
| Breast* | — | — | — | — | 17.4 | 0.50 (0.03-0.70) | 80.9 | 1.24 (1.16-1.35) |

EIR = enrollment incidence ratio; GEJ = gastroesophageal junction; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; TP = trial proportion.

Trial proportions for men or women were not calculated in sex-specific cancers (breast, prostate); no trial proportions for older/younger adults are available for Hodgkin lymphoma because there were no Hodgkin lymphoma trials that reported age proportions. The 95% confidence intervals (CI) could not be calculated for cancers with <2 trials.

*Both younger and older adults were reported to be overrepresented in 1 breast cancer trial; in 1 multiple myeloma trial and 1 prostate cancer trial, the proportion of older adults (aged 65 years or older) was underestimated and the proportion of younger adults was not recorded due to thresholds of age reporting being discordant with our own; in 1 NSCLC trial, the proportion of younger adults (aged less than 65 years) was underestimated and the proportion of older adults was not recorded due to the threshold of age reporting being discordant with our own. The 95% confidence intervals (CI) could not be calculated for cancers with <2 trials.

**Supplementary Table 3** Enrollment Disparity for Racial and Ethnic Minorities Across Each Cancer Type

| | Black | | White | | Asian/Pacific Islander | | Native American | | Hispanic | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cancer | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) | TP (%) | EIR (95% CI) |
| Melanoma | 0.38 | 0.81 (0.39-1.53) | 96.1 | 1.01 (0.99-1.03) | 1.79 | 2.90 (0.47-7.31) | 0.05 | 0.24 (0.00-0.62) | 5.92 | 1.96 (0.82-2.74) |
| NSCLC | 2.01 | 0.18 (0.14-0.21) | 78.6 | 0.96 (0.91-1.02) | 16.8 | 2.82 (1.99-3.61) | 0.36 | 0.78 (0.29-1.34) | 5.61 | 1.03 (0.20-1.89) |
| SCLC | 0.84 | 0.10 (0.09-0.11) | 79.0 | 0.90 (0.87-0.96) | 19.1 | 5.90 (4.48-6.95) | 0.25 | 0.43 (NA) | — | — |
| Gastric/GEJ | 0.78 | 0.06 (0.00-0.07) | 65.0 | 0.91 (0.77-1.07) | 34.0 | 2.50 (2.06-4.57) | 0.68 | 0.80 (0.00-1.38) | 8.09 | 0.47 (0.19-0.50) |
| Urothelial | 1.15 | 0.21 (0.10-0.88) | 76.3 | 0.85 (0.82-1.01) | 16.3 | 4.09 (0.46-5.61) | 0.74 | 2.45 (NA) | - | - |
| Renal | 1.08 | 0.09 (0.05-0.18) | 79.5 | 0.97 (0.88-1.07) | 14.7 | 3.01 (1.84-3.84) | 0.17 | 0.19 (0.00-0.37) | 5.29 | 0.41 (0.34-0.49) |
| Head and Neck | 2.94 | 0.28 (0.19-0.36) | 82.6 | 0.99 (0.97-1.02) | 10.5 | 2.17 (1.08-2.92) | 0.26 | 0.47 (0.00-0.72) | 5.28 | 0.76 (0.52-0.86) |
| Colorectal | 2.75 | 0.23 (NA) | 81.5 | 1.02 (NA) | 11.8 | 1.59 (NA) | 0 | 0 (NA) | 6.89 | 0.71 (NA) |
| Hepatocellular | 3.17 | 0.24 (0.15-0.35) | 51.8 | 0.74 (0.74-0.75) | 49.2 | 3.13 (2.56-3.61) | 1.45 | 1.12 (NA) | 8.47 | 0.45 (NA) |
| Esophageal | — | — | 95.7 | 1.15 (NA) | 4.30 | 0.96 (NA) | — | — | — | — |
| Mesothelioma | — | — | 97.2 | 1.07 (NA) | 1.58 | 0.50 (NA) | — | — | — | — |
| Myeloma | 6.55 | 0.34 (0.20-0.50) | 76.9 | 1.04 (1.01-1.06) | 15.8 | 2.99 (2.43-3.45) | 0 | 0 (NA) | 3.81 | 0.35 (0.24-0.48) |
| Pancreatic | 2.82 | 0.23 (0.00-0.43) | 76.8 | 0.96 (0.75-1.08) | 19.0 | 2.75 (0.38-5.57) | 0 | 0 (NA) | 3.08 | 0.31 (NA) |
| Breast | 7.99 | 0.75 (0.61-1.24) | 69.7 | 0.86 (0.84-0.96) | 15.5 | 2.05 (0.85-2.38) | 4.43 | 8.26 (NA) | — | — |
| Prostate | 5.15 | 0.35 (NA) | 90.7 | 1.16 (NA) | 1.16 | 0.25 (NA) | 0.50 | 1.36 (NA) | — | — |
| Ovarian | 7.00 | 0.83 (NA) | 86.0 | 1.04 (NA) | 5.00 | 0.66 (NA) | 0 | 0 (NA) | 4.00 | 0.33 (NA) |

EIR = enrollment incidence ratio; GEJ = gastroesophageal junction; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; TP = trial proportion.

No trial proportions for Black, Hispanic, and Native American patients are available for esophageal cancer and mesothelioma because there were no esophageal cancer and mesothelioma trials that reported the proportion of these racial and ethnic subgroups. The proportion of Hispanic participants was also not reported by any small-cell-lung, breast, and prostate cancer trials. The 95% confidence intervals (CI) could not be calculated for cancers with <2 trials; EIRs were not available for certain cancers due to zero trials reporting the number of participants from certain racial and ethnic subgroups.

**Supplementary Table 4** Multivariable Analysis of Enrollment-Incidence Ratio for Women, Black Patients, and Older Adults

| | Women | | Black | | Older Adults | |
|---|---|---|---|---|---|---|
| | Beta* (95% CI) | *P* value | Beta (95% CI) | *P* value | Beta (95% CI) | *P* value |
| Cancer type | | | | | | |
| Melanoma | −0.42 (−0.55 to −0.28) | <.001† | reference | | −0.03 (−0.36 to 0.30) | .850 |
| GI‡ | −0.41 (−0.59 to −0.23) | <.001† | −2.10 (−2.79 to −1.41) | <.001† | reference | |
| GU§ | −0.29 (−0.47 to −0.11) | .002† | −2.05 (−2.68 to −1.42) | <.001† | −0.21 (−0.58 to 0.15) | .254 |
| Lung | reference | | −2.16 (−2.68 to −1.65) | <.001† | −0.24 (−0.54 to 0.07) | .122 |
| Other‖ | −0.32 (−0.51 to −0.12) | .002† | −1.26 (−1.88 to −0.64) | <.001† | −0.36 (−0.72 to −0.0002) | .050† |
| Trial size | | | | | | |
| <100 | reference | | — | — | — | — |
| 100-500 | −0.11 (−0.27 to 0.05) | — | — | — | — | — |
| > 500 | −0.17 (−0.34 to −0.003) | — | — | — | — | — |
| Clinical setting | | | | | | |
| Metastatic (vs nonmetastatic) | — | — | — | — | 0.44 (0.12 to 0.75) | .008† |
| Phase | | | | | | |
| 3 (vs 2) | — | — | −0.95 (−1.35 to −0.54) | <.001† | — | — |
| Primary endpoint | | | | | | |
| OS (vs non-OS) | — | — | — | — | 0.26 (0.03 to 0.49) | .029† |
| Class of ICI | | | | | | |
| PD-1 inhibitor only | — | — | — | — | −0.07 (−0.34 to 0.19) | .573 |
| PD-L1 inhibitor only | — | — | — | — | −0.33 (−0.64 to −0.018) | .038† |
| CTLA-4 inhibitor only | — | — | — | — | −0.23 (−0.52 to 0.06) | .114 |
| PD−1/PD−L1 inhibitor + CTLA-4 inhibitor combination therapy | — | — | — | — | reference | |

EIR = enrollment-incidence ratio; GEJ = gastroesophageal junction; GI = gastrointestinal; GU = genitourinary; ICI = immune checkpoint inhibitor; OS = overall survival;

*The beta-coefficient signifies the *change* in the log of the EIR for a particular category of trials, relative to the reference category (eg, logEIR for women decreases (indicated by the negative sign) by 0.42 units in melanoma trials as compared with lung cancer trials), when trial size is kept constant (because this is a multivariable model with trial size as the only other variable). For detailed EIRs of each subgroup, please refer to Supplementary Tables 2-4, available online.

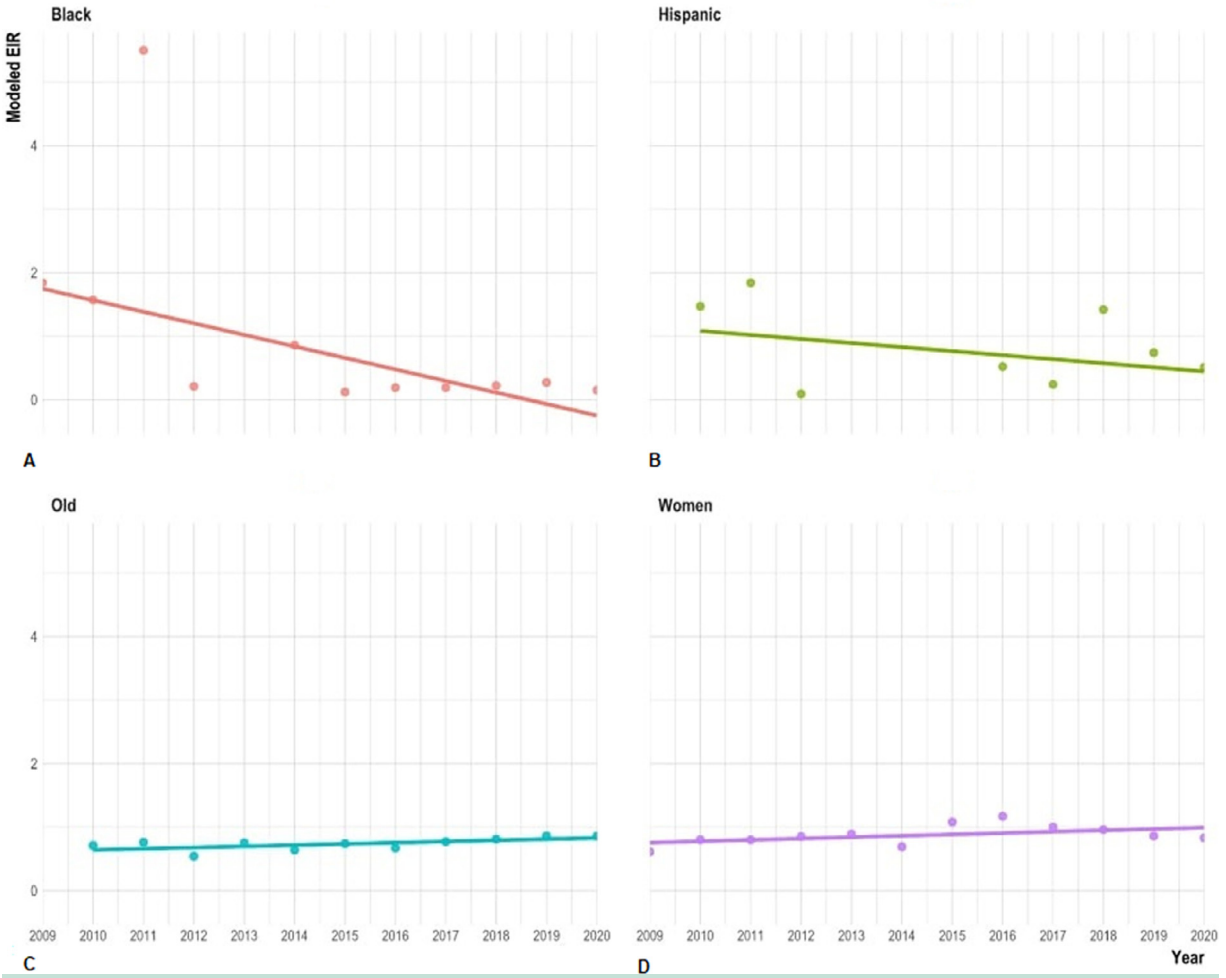
†Indicates statistical significance.

‡Includes colorectal cancer, esophageal cancer, gastric/GEJ cancer, hepatocellular carcinoma, and pancreatic cancer.

§Includes prostate cancer, renal cell carcinoma, and urothelial carcinoma.

‖Includes head-and-neck cancer, mesothelioma, multiple myeloma, breast cancer, and ovarian cancer.

Em-dashes indicate empty cells where the respective variables were not statistically significant in the final multivariable model for a particular subgroup. Reference categories for regression on cancer type (ie, lung cancer for women, melanoma for Black patients, gastrointestinal cancer for older adults) were selected according to whichever category of trials had the highest average logEIR on univariable analysis.




**Supplementary Figure** Trends in the representation of **(A)** Black patients (AAPC is significantly different from zero at the alpha = 0.05 level), **(B)** Hispanic patients (AAPC is not significantly different from zero), **(C)** older adults (AAPC is significantly different from zero at the alpha = 0.05 level), and **(D)** women (AAPC is not significantly different from zero). AAPC = average annual percentage change.