nature reviews
drug discovery

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Reprinted from *Nature Reviews Drug Discovery*, Vol. 31, pp. 870–871, December 2022

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Biobusiness briefs

https://doi.org/10.1038/d41573-022-00189-w

Population diversity in immuno-oncology trials

The rapid uptake of immunotherapies has revolutionized cancer care for over a decade. However, response to immunotherapy varies substantially between patients, highlighting the importance of testing immuno-oncology (IO) treatments in diverse populations that reflect the heterogeneity of the oncology patient spectrum.

To analyse the landscape of racial and ethnic diversity in IO clinical trials, the Cancer Research Institute (CRI) conducted a retrospective analysis of patient diversity in studies of IO therapies that led to FDA approvals during the past 12 years (henceforth referred to as 'pivotal IO trials'). We also used an IQVIA proprietary clinical trial database, the TriNetX database of real-world data, and a questionnaire targeted at clinical trialists to identify the main barriers to diversifying enrolment, as well as potential solutions.

Race and ethnicity data in pivotal IO trials

Between January 2010 and August 2022, the FDA approved 92 IO drugs and combinations across more than 20 cancer indications (Supplementary Table 1). According to the public documentation related to the 113 pivotal IO trials that led to these approvals (involving a total of 59,546 patients; Supplementary Fig. 1), 58% of the studies reported data for at least six of the seven racial categories used by the US National Institutes of Health (NIH): white, Black or African American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander (Supplementary Fig. 1a). Only 52% included ethnicity data for the two categories used by the NIH: Hispanic/Latino or not Hispanic/Latino (Supplementary Fig. 1b); and 20% did not report patient race.

We further inspected those studies with available patient demographic information on at least the three largest racial groups in the USA: white, Black or African American, and Asian (72.5% of the total number of studies). Comparing patient enrolment in these pivotal IO trials with US disease prevalence for each demographic group indicated that Black or African American patients were largely under-represented in the indications that gathered the most IO approvals, except for melanoma (Fig. 1a and Supplementary Fig. 2 (all indications)). In total, Black or African American patients represented 2% of the patients in trials from this dataset (Fig. 1b).

Notably, 96% of the registrational trials in this dataset were multi-country, with sites mostly concentrated in the USA, Canada, Central/South Europe, Australia, and Japan. Latin-American countries had only moderate involvement, whereas South-East Asian, West Asian and African countries were virtually uninvolved (Supplementary Fig. 4). Although multi-country studies involve geographies with very different demographic distributions from that of the USA, the available data indicate that Black or African American patients were largely under-represented in trials leading to IO therapy approvals in the USA, where this racial group constitutes 13.6% of the population according to the US 2021 census.

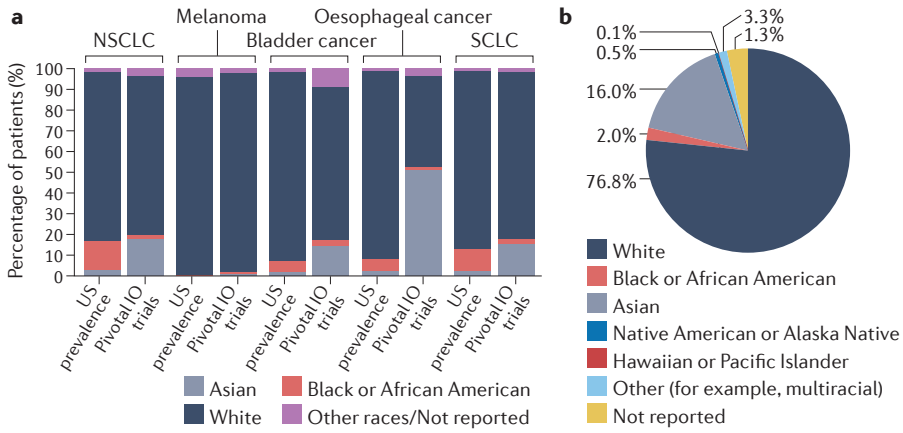

Fig. 1 | Racial distribution in the pivotal IO trials dataset and comparison to disease prevalence in the USA. a, Comparison of relative enrolment with disease prevalence, by race, in the trials for the five indications gathering the most immuno-oncology (IO) approvals in the dataset. US prevalence is according to Surveillance, Epidemiology, and End Results Program (SEER) 2019 data. 'Other races' category includes American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander. **b**, Percentage of each racial group in the pivotal IO trials dataset. See Supplementary information for details. NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

Barriers to diverse patient enrolment

Multiple factors have been linked to racial and ethnic disparities in oncology clinical trial enrolment (*J. Clin. Oncol.* **40**, 2163–2171; 2022). These include barriers related to clinicians (such as clinician bias), patients (such as lack of information or financial burden), or the trials themselves (such as eligibility criteria), as well as institutional barriers (such as trial location). We surveyed 61 oncology clinical trial professionals in IQVIA and CRI's network to gain insight into the impact of these factors.

The survey indicated that the greatest barriers to more diverse enrolment are institutional hurdles — such as distance to study sites and lack of involvement of community sites — closely followed by the financial burden of participating in clinical trials, which includes both direct costs (such as travelling to clinical sites) and indirect costs (such as missing work or finding child support) (Fig. 2a and Supplementary Fig. 5).

Potential strategies to reduce barriers

We addressed the same group of experts with a second questionnaire to understand potential strategies to reduce these barriers. In this survey, implementation of financial support systems was ranked as the most impactful strategy for increasing enrolment of patients from under-represented groups (Fig. 2b). In the USA, private insurers cover the direct costs of clinical trial participation and, since the 2020 Clinical Treatment Act, these are also covered for low-income individuals insured under Medicaid, but survey results indicate that additional measures — such as financial

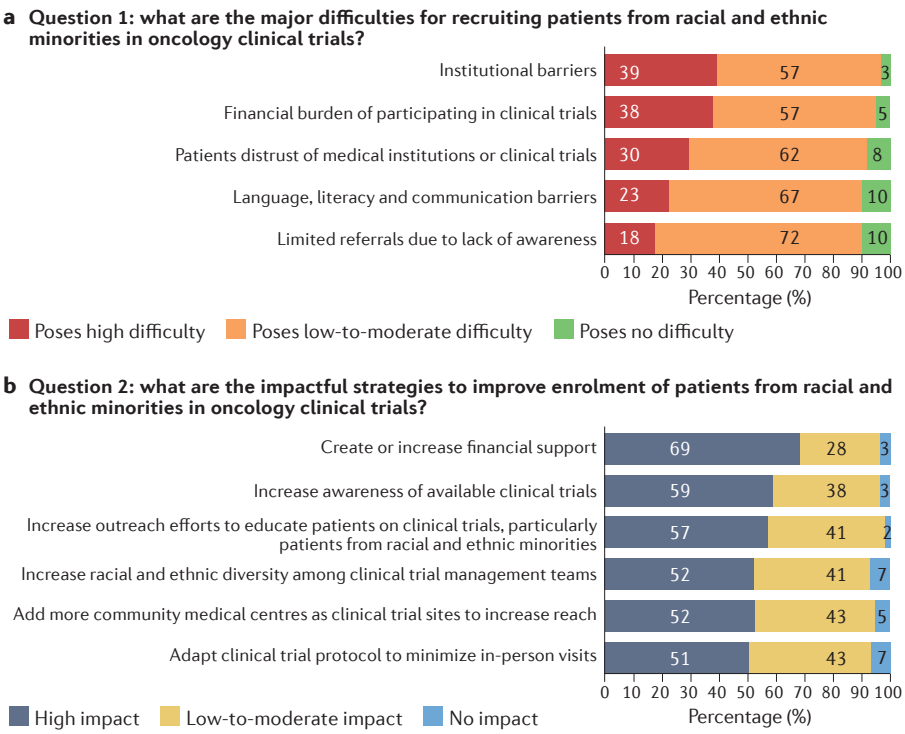

Fig. 2 | Selected responses to a survey on barriers to diverse patient enrolment in oncology clinical trials and potential solutions. a, Highest rated difficulties for diverse patient enrolment in oncology clinical trials. **b**, The top six most impactful strategies to improve patient enrolment in oncology clinical trials. Responders included 27 clinical leads, 12 medical directors/advisors, 13 clinicians involved in trial execution and other trial staff (9 members). See Supplementary information for details.

compensation for missed work days or financial aid for child support – are needed to offset indirect costs of trial participation.

The survey responses also highlight the importance of increasing awareness of ongoing trials among primary oncologists, and adding more community centres that serve minority racial and ethnic groups in future studies. Inclusion of clinical sites at locations of higher racial diversity can contribute to increased local enrolment of people from minority racial and ethnic groups. US state-level clinical trial data from IQVIA's database indicates that recruitment of Black or African American patients is highest in Mississippi, Louisiana, Alabama, Maryland and the District of Columbia (Supplementary Table 3).

Initiatives to decentralize trials, incorporate remote management and optimize protocol design to reduce hospital visits could also help reach people from minority racial and ethnic groups. The COVID-19 pandemic accelerated implementation of many strategies to minimize risk for patients, which should be embraced to promote diverse enrolment (*Nat. Rev. Drug. Disc.* **19**, 376–377; 2020).

Restrictive exclusion criteria also disproportionally affect some groups owing to higher prevalence of comorbidities (*J. Clin. Oncol.* **40**, 2193–2202; 2022). We used TriNetX real-world data from five cancer indications to analyse comorbidities that are commonly listed under exclusion criteria in IO trials. This indicated that Black or African American patients meet exclusion criteria at higher rates than other racial groups in four out of the five indications investigated: non-small-cell lung cancer, melanoma, bladder cancer and oesophageal cancer (Supplementary Fig. 6). Following the 2020 FDA guidance for enhancing diversity in clinical trials, organizations have released updated recommendations for broadening and modernizing eligibility criteria.

Importantly, these measures need to go hand-in-hand with initiatives to build trust among patients, including addressing racial and ethnic disparities among medical professionals, and building solid relationships with affected communities.

Conclusion

The safety and efficacy of IO treatments needs to be validated in patients that reflect the heterogeneity of the real-world patient population. Our analysis of pivotal trials leading to IO approvals by the FDA indicates that racial and ethnic demographic information is under-reported, and although the available data are limited, they indicate substantial disparities in the enrolment of Black or African American patients across oncology indications. Although steps are being taken in the right direction, there is a pressing need for trial sponsors to increase diverse enrolment and transparent reporting. This will allow data-driven discussions about racial and ethnic disparities, more effective identification of barriers to diverse recruitment, and solutions to deliver IO therapies to all cancer patients.

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Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/d41573-022-00189-w.