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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data entered manually was collected via the electronic data capture database through the use of electronic case report forms. No software was used for data collection.
Data analysis	SAS software version 9.4 was used for the data analysis and figure generation. Other softwares used were the EdgeSeq parser (version 10196100G; HTG Molecular Diagnostics, Inc.) and R Statistical Computing Platform (version 4.0.5).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Databases used for data analysis included HTG EdgeSeq Oncology Biomarker Panel, HistoGeneX NV (Antwerp, Belgium), Foundation Medicine (Cambridge, MA, USA), Illumina TruSeq RNAaccess (MedGenome), Agilent SureSelect (MedGenome), and gene set enrichment analysis (GSEA) with signatures from the molecular signatures database (MsigDB). Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/

research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)(https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm). All relevant data are available and are included with the manuscript; minor variations, which do not alter the conclusions of this work, may be present. IMbassador250 raw data analyzed in this study has been submitted to the European Genome-Phenome Archive (EGA) with accession number EGAS00001004852. Raw RNAseq data from IMmotion150 and IMvigor210 has been submitted to EGA with accession number EGAS00001004386.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The study was designed to enroll approximately 730 patients: 10 in the safety run-in phase and 720 in the randomised phase. The primary comparison of OS between treatment arms was based on a stratified log-rank test. The HR for death in the experimental arm compared with the control arm was estimated using a stratified Cox regression model, and the 95% CI was provided. An interim analysis of the primary endpoint of OS was planned to be performed when approximately 432 deaths had occurred and the final analysis when 540 deaths had occurred. Based on study assumptions, these 540 events would provide 97% power to detect a difference in the duration of OS between treatment arms.
Data exclusions	For the various biomarkers reported within this manuscript, no data was excluded, data from all evaluable patients for a given readout was included in each evaluation.
Replication	No experimental replication was attempted - N/A in a phase III randomised controlled clinical trial. The results of this trial did not support replication because of ethical and humane reasons.
Randomization	Randomisation (1:1) was stratified according to presence of liver metastasis (yes vs no), received at least two cycles of a taxane-containing regimen (yes vs no), LDH level (≤ULN vs >ULN), and pain severity (BPI-SF Question 3 score <4 vs ≥4). A stratified permuted-block randomisation was implemented to balance treatment assignment across levels of stratification factors.
Blinding	The study was a Phase 3, multicenter, randomised, open-label study in which 759 patients were enrolled and randomized to receive either atezolizumab + enzalutamide or enzalutamide alone.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Anti-human CD8 rabbit monoclonal antibody SP16 (Spring Bioscience; cat# M3160); VENTANA anti-PD-L1 rabbit monoclonal antibody (SP142) (RPA; Ventana Medical Systems Inc)
Validation	The anti-CD8 antibody has been validated in clinical samples as reported in Mariathasan et al, Nature, 2018. PMID: 29443960; VENTANA PD-L1 (SP142) assay validation can be found at https://www.accessdata.fda.govcdrh_docs/pdf16/p160002c.pdf. It is also reported in Powles et al, Nature, 2021. PMID: 34135506

Human research participants

Policy information about studies involving human research participants

Population characteristics	Eligible patients were aged ≥18 years and had metastatic castration-resistant prostate cancer (mCRPC) after failure of an androgen synthesis inhibitor (e.g. abiraterone acetate) and after failure of, ineligibility for, or refusal of a taxane regimen, but not on a hormone receptor inhibitor (e.g. enzalutamide). Key eligibility criteria included PSA or radiological disease progression in soft tissue or bone prior to enrollment and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1. Patients were excluded if they had active or a history of autoimmune disease or immune deficiency, coinfection with hepatitis B or hepatitis C virus, or prior treatment with immunotherapy, enzalutamide, or any other newer AR antagonist. A complete listing of the inclusion and exclusion criteria is available in the protocol (Appendix). Ages of patients: 40-92 years old Sexes of patients: Male Races of patients: White, Black or African American, Asian, American Indian, native Hawaiian Patients were randomized in 1:1 ratio to receive either atezolizumab along with enzalutamide or enzalutamide alone until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity (up to approximately 42 months).
Recruitment	IMbassador250 (NCT03016312) is a multicenter, randomized, open-label, phase 3 trial comparing atezolizuman + enzalutamide or enzalutamide alone. Randomisation (1:1) was stratified according to presence of liver metastasis (yes vs no), received at least two cycles of a taxane-containing regimen (yes vs no), LDH level (≤ULN vs >ULN), and pain severity (BPI-SF Question 3 score <4 vs ≥4). Patient recruitment criteria: - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 - Life expectancy greater than or equal to (>/=) 3 months - Histologically confirmed adenocarcinoma of the prostate - Known castrate-resistant disease with serum testosterone level less than or equal to (</=) 50 nanograms per deciliter (ng/dL) with prior surgical castration or ongoing androgen deprivation for the duration of the study - Progressive disease prior to screening by PSA or imaging per PCWG3 criteria during or following the direct prior line of therapy in the setting of medical or surgical castration - One prior regimen/line of a taxane-containing regimen for mCRPC or refusal or ineligibility of a taxane-containing regimen - Progression on a prior regimen/line of an androgen synthesis inhibitor for prostate cancer - Availability of a representative tumor specimen from a site not previously irradiated that is suitable for determination of programmed death-ligand 1 (PD-L1) status via central testing - Adequate hematologic and end organ function
Ethics oversight	This study was approved by local institutional review boards at all study sites and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent. Protocol approval was obtained from independent Institutional Review Boards or ethics committees at each participating center.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03016312
Study protocol	Full protocol was published with primary manuscript:
Data collection	Data was collected between June 2017 and May 2018 from 156 sites. The full list can be found in the supplemental data.
Outcomes	The primary outcome of IMbassador250 was Overall Survival, which was defined as the time from randomization to death from any cause (up to approximately 42 months). The secondary outcomes were percentage of participants who survived at month 12 and 24, and Radiographic Progression-Free Survival (rPFS) with a time frame from baseline until disease progression or death from any cause (up to approximately 42 months). rPFS is defined as the time from randomization to the earliest occurrence of one of the following: - A participant is considered to have progressed by bone scan if: The first bone scan with ≥2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline); the date of progression is the date of the first post-treatment scan, OR After the first post-treatment scan, ≥2 new lesions are observed relative to the first post-treatment scan, which is confirmed on a subsequent scan ≥6 weeks later; the date of progression is the date of the post-treatment scan when ≥2 new lesions were first documented. - Progression of soft tissue lesions - Death from any cause