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Reporting Summary

Nature Portfolio 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 Portfolio 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	The data collection software used for the clinical study is not central to this article and therefore specific details are not included here or in the manuscript. Software used for CODEX data collection is described in the relevant parts of the Methods section.
Data analysis	Clinical data analysis was completed using SAS 9.2 for Unix. Software used for CODEX data analysis is described in the Methods section.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

A data availability statement has been included in the article, saying: "Bristol Myers Squibb will honor legitimate requests for our clinical trial data from qualified researchers with a clearly defined scientific objective. We share data from phase 2–4 interventional clinical trials completed on or after 1 January 2008, which evaluate medicines and indications approved in the US, EU, and other designated markets. Data shared may include non-identifiable patient-level and study-level clinical trial data, full clinical study reports and protocols. Sharing is subject to protection of patient privacy and respect for the patient's informed consent,

publication of the primary results in peer-reviewed journals, and approval by the Independent Review Committee. For details about the data sharing criteria and process for submitting a request, please visit https://vivli.org/ourmember/bristol-myers-squibb/. To set up an account for a data request, please visit https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. CODEX data have been deposited in Zenodo (https://zenodo.org/doi/10.5281/zenodo.17652425). The TCGA dataset used in this study are available in the TCGA-PRAD, https://portal.gdc.cancer.gov database. The remaining data are available within the Article, Supplementary Information or as a Source Data file. In addition, the study protocol is provided in the Supplementary Information."

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Due to the nature of prostate cancer, only patients of biologically male sex were included in the study.
Reporting on race, ethnicity, or other socially relevant groupings	The ethics guidelines on race and ethnicity (outlined at the link above) were followed, where applicable. The race category distribution among the study participants is described in Table 1.
Population characteristics	Select baseline characteristics for the patient populations are reported in the article (see Supplemental Table 1).
Recruitment	Enrollment into the randomized portion of the CheckMate 650 study was conducted between 5 August 2019 and 8 September 2021. All relevant details on recruitment criteria are included in the Methods section of the article and/or have been described in the previous associated publication (Sharma, P. et al. Cancer Cell 2020;38:489-499 e483).
Ethics oversight	Details on the ethics approvals are provided in the article.

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

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 CheckMate 650 trial is based on an overarching hypothesis that nivolumab plus ipilimumab would have clinical activity in patients with mCRPC. However, neither the signal-seeking portion nor the randomized portion of the trial were designed to statistically compare between cohorts, and sample sizes in the randomized portion were not based on statistical power calculations. Initially, the randomized portion of the trial was planned with two parts: part 1, to assess the optimal dose(s) for the nivolumab plus ipilimumab combination and to identify potential biomarker(s) of response, and part 2, to further investigate the identified optimal dose(s) and biomarker(s) in an expanded patient population. However, based on slow enrollment and changing priorities for the study sponsor, the randomized portion was altered via a protocol amendment to focus on assessing two alternative nivolumab plus ipilimumab regimens, ipilimumab monotherapy, and cabazitaxel; again with no planned statistical analyses. Per this protocol amendment, approximately 259 patients with postchemotherapy mCRPC were planned for randomization across the four new cohorts (74, 74, 37, and 74 patients in the N3I1, N1I3, I-mono, and CABA cohorts, respectively) with the number of patients with non-measurable disease at baseline capped at 105, so the remaining 154 patients (44, 44, 22, and 44 patients in the N3I1, N1I3, I-mono, and CABA cohorts, respectively) would have measurable disease at baseline. Although the overall sample sizes were not related to any statistical power calculations, the number of enrolled patients with measurable disease was based on an expected ORR of approximately 30% in the N3I1 and/or N1I3 cohorts (i.e., 13 responders among the 44 treated patients), which would give a two-sided 95% CI of 16.8% to 45.2%, with the lower CI (16.8%) being higher than the expected ORR for the CABA cohort (estimated at approximately 15% based on the TROPIC study [de Bono, J. S. et al. Lancet 2010;376:1147-1154]).
Data exclusions	Any data exclusions are described in the Methods, as applicable.
Replication	The number of patients is provided for all described analyses. Replication of clinical analyses was not performed. In addition, since the biomarker and CODEX analysies used precious patient tissue samples, experimental replicates were not performed.
Randomization	Patients with postchemotherapy mCRPC were randomized (2:2:1:2) across the N3I1, N1I3, I-mono, and CABA cohorts. Randomization was performed using an interactive response technologies web-based system with stratification by the presence or absence of measurable disease per investigator assessment. The randomization procedures were carried out via permuted blocks within each stratum.
Blinding	This was an open-label trial, with no blinding.

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
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	PD-L1 IHC 28-8 pharmDx assay (Dako, an Agilent Technologies, Inc., Santa Clara, CA, USA)
Validation	Obtained from Dako, an Agilent Technologies, Inc. (Santa Clara, CA, USA)

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	ClinicalTrials.gov NCT02985957.
Study protocol	The study protocol is included as part of the supplemental material and is available at https://cdn.clinicaltrials.gov/large-docs/57/NCT02985957/Prot_SAP_000.pdf
Data collection	Study details for CheckMate 650 are described in full in the article and/or the previous associated publication (Sharma, P. et al. Cancer Cell 2020;38:489-499 e483). Enrollment into the randomized portion of CheckMate 650 was conducted between 5 August 2019 and 8 September 2021. Data for the study were collected at participating sites in Australia, Austria, Canada, Denmark, France, Germany, Italy, Poland, Spain, and the USA.
Outcomes	Coprimary endpoints for the clinical study were ORR (the proportion of patients with measurable disease at baseline achieving a confirmed complete or partial response using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) and rPFS (time from date of randomization to first documented progression [using RECIST v1.1 for soft tissue disease and PCWG2 criteria for bone lesions] or death in all randomized patients with no censoring for subsequent systemic anticancer therapy) as assessed per BICR. Key secondary endpoints included OS, PSA response rate (PSA-RR; the proportion of randomized patients with a baseline plus ≥1 postbaseline PSA assessment achieving a PSA decline ≥50% from baseline), and safety. All outcomes related to the preplanned exploratory endpoints and CODEX analyses are described in full in the Methods section of the article.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*