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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Data was collected in Microsoft Excel Spreadsheets
Data analysis	Clinical analyses: SAS 9.4 for Windows Biospecimen analyses: GraphPad Prism7 Singlet immunohistochemistry: Aperio ImageScope Multiplex immunohistochemistry: Microsoft Excel Whole exome sequencing/mutational load: Illumina's Consensus Assessment of Sequence And Variation (CASAVA) tool (v1.8.2), MuTect (v1.1.4), Pindel (v0.2.4) T cell receptor sequencing: ImmunoSeq Analyzer software by Adaptive Biotechnologies

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/reviewers upon request. 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

The authors declare that the data supporting the findings of this study are available within the paper and its supplementary information files.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	A total of 20 patients in each arm were planned for enrolment. We assumed the pCR rate would be 5% for patients in Arm A and 15% for Arm B, based on extrapolation from RECIST CR rates in published studies which corresponds to the prior probability of 0.64 for at least 1 out of 20 patients experiencing the primary outcome event in Arm A and 0.96 for Arm B.
Data exclusions	No data were excluded.
Replication	The clinical trial findings cannot be replicated or reproduced. The correlative findings were assessed via multiple methodologies for confirmation.
Randomization	Randomization was 1:1
Blinding	As investigators were prescribing the immunotherapeutic medications and managing toxicities, they were not blinded to study randomization in order to ensure patient safety. There was no formal blinding of pathologists or radiologists who were performing analyses on pathologic specimens and reading radiographic imaging, respectively. Identification of the patients on the clinical trial was required to allow for triage of the pathologic and radiographic studies to the appropriate trial collaborators. There was also no blinding of laboratory investigators as knowledge of treatment assignment was essential for data grouping.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Supplemental Table 1 describes all patient characteristics for patients enrolled in this trial. 12 patients were enrolled on the neoadjuvant nivolumab arm with median age of 55 and 75% being male. All patients had ECOG performance status of 0 and most were clinical stage IIIB by the AJCC 7th Edition or stage IIIC by the 8th Edition. The majority of patients had normal LDH and the median sum of lesion diameters was 28.5mm. Most patients had superficial spreading primary melanomas. A majority of patients had PDL1 staining of at least 1% with 58% having BRAF mutations. Most patients were

treatment naive. For the ipilimumab/nivolumab treated patients, median age was 49 with 91% male. All had ECOG performance status of 0 and most were clinical stage IIIC by both the 7th and 8th edition of the AJCC. All patients had normal LDH. The primary tumor subtype was more commonly nodular and unknown primary. PDL-1 expression was at least 1% in 64% of patients. 36% of patients had BRAF mutations. 36% of patients were treatment naive and 36% had prior surgery.

Recruitment

Patients for this clinical trial were recruited from the MD Anderson Melanoma Medical Oncology and Surgical Oncology clinics. As patients had a 50% chance of being randomized to ipilimumab/nivolumab which is known to be a toxic regimen, it is possible that patients enrolled in this protocol were specifically selected to be able to withstand potential toxicity, which may limit generalizability to the melanoma population as a whole.