nature portfolio

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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	N/A
Data analysis	SAS version 9.3 or later was used for the statistical analyses

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

Anonymized individual participant data (IPD) on completed studies and applicable supporting clinical trial documents may be available upon request at https://vivli.org. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/. Additional information can be found 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	Table 1 of the manuscript reports the sex of the patients. No sex- or gender-based analyses were included in this manuscript because only 3 males were included in the study. Sex was based on self reported demographics obtained at screening per protocol.
Reporting on race, ethnicity, or other socially relevant groupings	Race is reported in Table 1 of the manuscript. There were no analyses based on race, ethnicity, or socially relevant groupings. Race was based on self reported demographics obtained at screening per protocol.
Population characteristics	Population characteristics are provided in Table 1 of the manuscript.
Recruitment	Recruitment criteria are available in the protocol and have been reported previously: Modi S et al. N Engl J Med 2022; 387:9-20.
Ethics oversight	Independent ethics committees or institutional review boards at each site reviewed and approved the protocol as described in the Trial Oversight section of the manuscript. The full list of study sites has been published previously (Modi S et al. N Engl J Med 2022; 387:9-20.). Written informed consent was provided by all patients before trial participation. Patients did not receive compensation for participating in the study.

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 data cutoff for the primary endpoint of PFS by BICR in patients with HR+, HER2-low metastatic breast cancer was planned when approximately 318 PFS events had been observed. This number of events would ensure a power of 90%, under the assumption of a hazard ratio of 0.68 and a two-sided alpha level of 0.05. Thus, a total enrollment of approximately 540 patients was planned (~480 HR+ patients [~320 T-DXd and ~160 TPC] and ~60 HR– patients [~40 T-DXd and ~20 TPC]). For more information please refer to Study Protocol and the Methods section (Statistical analysis) of the manuscript.
Data exclusions	None
Replication	N/A; this is an analysis of a randomized clinical trial so there were no replicates.
Randomization	Patients were randomly assigned in a 2:1 ratio to receive T-DXd or TPC, which included capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel. Randomization stratification factors were HER2 IHC/ISH status (IHC 1+ vs IHC 2+/ISH–), number of previous lines of chemotherapy for metastatic disease (1 vs 2), and HR status (positive vs negative). For more information please refer to Study Protocol and the Methods section (Study design) of the manuscript.
Blinding	This was an open-label study. Blind treatment allocations were not feasible because of different routes of administration, different treatment schedules, and different AE profiles between T-DXd and TPC. For more information please refer to Study Protocol and the Methods section (Study design) of the manuscript.

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

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	NCT03734029
Study protocol	Study protocol has been published as supplementary material in Modi S et al. N Engl J Med 2022; 387:9-20.
Data collection	From December 27, 2018, through December 31, 2021, a total of 713 patients with HER2-low metastatic breast cancer were screened for potential trial entry. Study sites were located in North America, Europe/Israel, and Asia. Data were analyzed and interpreted by the sponsor and authors.
Outcomes	The primary endpoint was PFS by BICR in the HR+ cohort. Key secondary endpoints were PFS by BICR in the overall cohort and OS in the HR+ cohort and overall cohort. These endpoints were predefined in the protocol, along with other secondary/exploratory endpoints. Because the statistical boundary for the primary and secondary endpoints was crossed during the primary analysis (Modi S et al. N Engl J Med 2022; 387:9-20), BICR analysis was concluded. For the updated data cutoff (1 March 2023), analyses included OS and PFS by investigator in the overall (HR+ and HR−) and HR+ cohorts.

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.*