

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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                                |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                                   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), 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 | No software was used for data collection                                                                                                                                   |
| Data analysis   | No custom code was used. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc.) and R (version 4.5.1; R Foundation for Statistical Computing) |

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](#)

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.  
Data for studies directly listed on Vivli can be requested through Vivli at [www.vivli.org](http://www.vivli.org). Data for clinical studies not listed on Vivli could be requested through Vivli at [info@vivli.org](mailto:info@vivli.org)

## 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                                        | Data on sex were collected via the Case Report Form as allowed by local regulatory guidelines and are reported in the patient baseline characteristics supplementary table. Analyses in this manuscript are not controlled for sex. No further sex-based analyses were conducted as significant differences in pathological response and safety were not expected between male and female patients.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Reporting on race, ethnicity, or other socially relevant groupings | Data on race were collected via the Case Report Form as allowed by local regulatory guidelines and are reported in the patient baseline characteristics supplementary table. Analyses were not controlled for race or ethnicity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Population characteristics                                         | Newly diagnosed patients with resectable NSCLC, without actionable genomic alterations. Median (range) age in Arms 1, 2 and 4 was 66.5 (30–79), 66.0 (48–83) and 65.0 (38–81) years, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Recruitment                                                        | Patients were recruited by participating cancer treatment centers. All patients were centrally assigned to randomized study interventions using an interactive response technology (IRT). Eligibility was determined by pre-defined inclusion and exclusion criteria. Eligibility criteria and screening procedures minimized the potential for self-selection bias. Central randomization and stratification by baseline PD-L1 expression were used to reduce potential imbalance between treatment arms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Ethics oversight                                                   | The study was performed in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice Guidelines and all applicable laws and regulations. The study included a safety review committee that conducted safety reviews of all enrolled patients throughout the study. The study protocol, protocol amendments, informed consent form, investigator brochure and other relevant documents were reviewed and approved by the Institutional Review Boards and Ethics Committees at each participating center, as follows. Belgium, UZ Leuven. Canada: McGill University Health Centre; Centre hospitalier de l'Université de Montréal; Alberta Health Services Cross Cancer Institute. France: CHU de Bordeaux Hôpital Saint André; Centre Hospitalier de Cornouaille; CHU Dupuytren; Hôpital Foch; CHU Rouen Hôpital; Hôpital d'Instruction des Armées Sainte Anne; Centre Hospitalier D'Avignon Hôpital Henri Duffaut Médecine Interne Onco-Hématolo. Hungary: Bacs-Kiskun Varmegyei Oktatókórház; Tudományintézet Torokbalint; Fejér Varmegyei Szent György Egyetemi Oktató Kórház; Szent Borbála Kórház. Ireland: University Hospital Galway; Mater Misericordiae Hospital. Italy: Regina Elena; Istituto Nazionale dei Tumori; Istituti Fisioterapici Ospitalieri (IFO); Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS); Ospedale San Gerardo – ASST di Monza, IRCCS; Istituto Clinico Humanitas Rozzano, IRCCS; Istituto Oncologico Veneto, IRCCS; Ospedale S. Maria della Misericordia; AO di Perugia S.C. Oncologia Medica; Ospedale Policlinico San Martino, IRCCS; SO di Cisanello; AOU Pisana; AOU Careggi UO Radioterapia; Ospedale Niguarda; ASST Grande Ospedale Metropolitano Niguarda; ASST Spedali Civili di Brescia. Portugal: Hospital da Luz; Centro Hospitalar e Universitário Lisboa Central Hospital Santo António dos Capuchos; Instituto Português Oncologia Francisco Gentil do Porto; Instituto Português de Oncologia de Lisboa Francisco Gentil. South Korea: Asan Medical Center; Seoul National University Hospital Department of Internal; The Catholic University of Korea; St. Vincent's Hospital Oncology; CHA Bundang Medical Center; CHA University; Inje University Haeundae Paik Hospital. Spain: Hospital Teresa Herrera (CHUAC); Hospital Universitario Puerta De Hierro De Majadahonda; H.U.M. de Terrassa; H.U. Sant Joan de Reus; Hospital Clínico San Carlos; H. Clínico de Valencia; Hospital Universitario Virgen De La Macarena; Hospital Regional Universitario de Málaga; Hospital Clinic De Barcelona; Fundación Jiménez Díaz; Hospital General Universitario De Alicante. Taiwan: National Cheng Kung University Hospital; Taipei Medical University Shuang Ho Hospital Pulmonology. Turkey: Goztepe Prof. Dr. Süleyman Yalcin Şehir Hastanesi Tıbbi Onkoloji. United States: MD Anderson Cancer Center; Cleveland Clinic Medical Oncology/Hematology; John Hopkins Medicine Hematology/oncology; US Oncology Virginia Cancer Specialists, P.C. (VCS); Cleveland Clinic Florida Martin Health. |

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](https://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 sample size is not based on type I error and power consideration. Instead, the sample size of up to 70 patients per treatment arm is to ensure the accuracy of making a Go or No-Go decision at the interim and final analyses, and to obtain a preliminary assessment of anti-tumour activity with a certain degree of precision. |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | No data were excluded.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Replication     | No replication was performed as this was a clinical trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Randomization   | A randomization method with dynamically changing allocation ratio of treatment assignment was employed to account for fluctuations in the number of enrolling treatment arms over the course of the study, and to allow an increase in enrollment to one or more treatment arms at the discretion of the Sponsor and/or recommendation by the Safety Review Committee. Where there was only a single arm enrolling, all patients were allocated to that arm. The actual treatment given to patients was determined by the randomization scheme, which was produced by a computer software program that incorporates a standard procedure for generating randomization numbers. A blocked randomization was generated, and randomization was balanced within the IRT at the central level. |
| Blinding        | This is an open label study, however, the specific study interventions were assigned using an IRT. The site contacted the IRT prior to the start of study intervention administration for each patient. The site recorded the study intervention assignment on the applicable electronic Case Report Form, if required. Potential bias was reduced by use of central randomization                                                                                                                                                                                                                                                                                                                                                                                                        |

## 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                                  |
|-------------------------------------|--------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Clinical data      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> 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 | NCT05061550                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Study protocol              | Uploaded as supplementary file                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Data collection             | Data collection occurred at 55 participating centers across 12 countries worldwide (Belgium, Canada, France, Hungary, Ireland, Italy, Portugal, South Korea, Spain, Taiwan, Turkey, and the United States), including hospitals, clinical trial sites, clinics, and infusion centers, with data documented by electronic data capture. All methods of data collection were reviewed and ensured patient privacy was upheld at all times. Data collection for Arm 1 started on May 3, 2022, for Arm 2 on August 12, 2022, and for Arm 4 on August 23, 2023. Data collection for all three arms continued until March 25, 2026.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Outcomes                    | <p>Primary endpoints:</p> <p>pCR is the proportion of patients with no residual viable tumour cells (0%) in all resected tissue after neoadjuvant treatment. Resected tissue includes both the primary lung lesion and the lymph nodes.</p> <ul style="list-style-type: none"> <li>Assessed by: a central BIPR laboratory.</li> <li>Method: IASLC 2020 (Travis et al., 2020; <a href="https://www.sciencedirect.com/science/article/pii/S1556086420300265">https://www.sciencedirect.com/science/article/pii/S1556086420300265</a>).</li> </ul> <p>Safety and tolerability</p> <ul style="list-style-type: none"> <li>Evaluated in terms of adverse events, vital signs and clinical laboratory parameters</li> </ul> <p>Key Secondary Endpoint: (EFS)</p> <p>EFS is the time from randomisation to the first of these events:</p> <ul style="list-style-type: none"> <li>Recurrence (local or distant) after surgery, per investigator RECIST 1.1.</li> <li>Death from any cause.</li> <li>Progression that prevents surgery. This covers progression judged before surgery (dated at that determination) and progression found during an attempted surgery that stops it (dated at the first attempt).</li> <li>Progression in patients without completed surgery for other reasons. This is RECIST 1.1 progression after the surgery-eligibility decision (no surgery) or after the attempted surgery (incomplete).</li> </ul> <p>Not EFS events (censored):</p> <ul style="list-style-type: none"> <li>R1/R2 margins. Patients stay in follow-up. R2 patients cannot get adjuvant therapy and go to local standard of care.</li> <li>A new primary malignancy confirmed by pathology.</li> </ul> |

## New lesions:

- Biopsy them where possible, and use pathology results when available.
- An equivocal new lesion counts only once a later visit confirms it as unequivocal. The event is then backdated to the visit where it first appeared.

## Key Secondary Endpoint: (mPR)

mPR is the proportion of patients with 10% or less residual viable tumour in the primary lung tumour at resection after neoadjuvant treatment. Unlike pCR, this measure covers only the primary tumour, not the lymph nodes.

- Assessed by: a central BIPR laboratory.
- Method: IASLC 2020 (Travis et al., 2020).
- Scoring: The lab records the estimated % of residual viable tumour. A value of 10% or less is scored Yes, and a value above 10% is scored No.
- Counted as non-mPR: patients who cannot be evaluated centrally (including those with R2 margins) and patients with no surgical specimen. Their response is recorded as "non-evaluable" or "missing."

## Key Secondary Endpoint: (Feasibility to Surgery)

Feasibility to surgery is the proportion of patients who have their planned surgical resection within 40 days of the last neoadjuvant dose.

- Not feasible: patients who do not have, or do not intend to have, surgery within that 40-day window.

## 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, mosaicism, off-target gene editing) were examined.*