# Supplementary Information

## Supplementary Results

### Results of primary analyses

*Overall Response Rate (ORR)*

At data cut-off of August 4, 2022, patients in the dostarlimab plus chemotherapy group received a mean of 10.1 cycles of dostarlimab (standard deviation: 6.0) and 9.3 cycles of pemetrexed (standard deviation: 5.7), with 79% of patients completing all 4 cycles of platinum-based chemotherapy. Patients in the pembrolizumab plus chemotherapy group received a mean of 8.3 cycles of pembrolizumab (SD: 5.7) and 8.0 cycles of pemetrexed (SD: 5.6), with 72% of patients completing all 4 cycles of platinum-based chemotherapy. For dostarlimab plus chemotherapy, the confirmed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 based on blinded independent central review (BICR) was 46% (56/121; 95% confidence interval [CI]: 37–56%), with two complete responses (CRs) (2%) and 54 partial responses (PRs) (45%). For pembrolizumab plus chemotherapy, ORR was 37% (45/122; 95% CI: 28–46%), with three CRs (2%) and 42 PRs (34%) (9% difference [80% CI: 1.46–17.18%; 95% CI: -2.70–21.33%]) (**Supplementary Table 5**). BICR-assessed maximum percentage reduction from baseline in tumor measurement is shown in **Supplementary Figure 2**. Five patients (4%) in the dostarlimab treatment group and 13 patients (11%) in the pembrolizumab treatment group had unknown or missing responses and were classified as 'not done' (**Supplementary Table 4; Supplementary Table 5**). These results are supported by the analysis of ORR based on Investigator assessment, which was 41% (50/121; 95% CI: 32–51%) in the dostarlimab plus chemotherapy treatment group and 29% (35/122; 95% CI: 21–38%) in the pembrolizumab plus chemotherapy group.

Subgroup analyses of ORR based on BICR by PD-L1 status are shown in **Supplementary Table 5** and **Supplementary Table 6**. Differences in ORR between treatment groups by PD-L1 status are shown in **Supplementary Figure 3**. The highest ORR was observed in the tumor proportion score (TPS) ≥50% subgroups of both dostarlimab plus chemotherapy (74% [20/27; 95% CI: 54–89%]) and pembrolizumab plus chemotherapy treatment groups (48% [13/27; 95% CI: 29–

68%]). Patients in the PD-L1-positive (TPS ≥1%) subgroup treated with dostarlimab plus chemotherapy had an ORR of 59% (42/71; 95% CI: 47–71%), while those treated with pembrolizumab plus chemotherapy had an ORR of 39% (28/71; 95% CI: 28–52%). ORR for PD-L1-negative (TPS <1%) patients was 28% (14/50; 95% CI: 16–43%) in the dostarlimab plus chemotherapy subgroup and 33% (17/51; 95% CI: 21–48%) in the pembrolizumab plus chemotherapy subgroup.

*Safety*

Overall, the safety profiles of dostarlimab plus chemotherapy and pembrolizumab plus chemotherapy were similar (**Supplementary Table 10**; **Supplementary Figure 5**). The proportion of patients experiencing any treatment-emergent adverse event (TEAE) was the same for both treatment groups (97%). The most frequent TEAEs were largely balanced between the two groups, although a smaller proportion of patients in the dostarlimab plus chemotherapy group experienced neutropenia than in the pembrolizumab plus chemotherapy group (12% vs 22%, respectively) (**Supplementary Table 11**; this difference diminished over time (17% vs 22%, respectively; data cut-off July 7, 2023). The proportion of patients experiencing any treatment-related adverse event (TRAE) was similar between groups (82% for dostarlimab plus chemotherapy and 79% for pembrolizumab plus chemotherapy). The four most frequent TRAEs (related to any study treatment) in both the dostarlimab plus chemotherapy and pembrolizumab plus chemotherapy groups were anemia (37% and 38%, respectively), asthenia (18% and 22%, respectively), nausea (18% and 19%, respectively), and neutropenia (12% and 18%, respectively) (**Supplementary Table 11**). The most frequent TRAEs related to dostarlimab or pembrolizumab specifically were anemia and rash (10% each) in the dostarlimab plus chemotherapy group and asthenia (13%) in the pembrolizumab plus chemotherapy group (**Supplementary Table 11**).

While more patients experienced dostarlimab-related AEs (64%) than pembrolizumab-related AEs (53%), a numerical trend favoring dostarlimab was observed in the proportion of patients experiencing immune-related adverse events (AEs) (26% for dostarlimab plus chemotherapy and 34% for pembrolizumab plus chemotherapy), serious adverse events (SAEs) (38% and 45%,

respectively), AEs leading to treatment discontinuation (25% and 32%, respectively), and AEs leading to immunotherapy discontinuation (15% and 24%, respectively) (**Supplementary Table 10**). Fatal TRAEs were observed in 2% of patients in the dostarlimab plus chemotherapy group and 4% of patients in the pembrolizumab plus chemotherapy group; individual fatal TRAEs are also summarized in **Supplementary Table 10**.

**Supplementary Table 1. Institutions and IEC/IRB committees**

| Institution | IEC/IRB Committee |
|---|---|
| Clinica Universitaria Reina Fabiola | CIEIS Fabiola |
| Instituto de Investigaciones Metabólicas | CEIC Dr. Stamboulian |
| Fundacion Respirar | CIEFC- CIE para Ensayos en Farmacología Clínica |
| Centro Oncológico Riojano Integral | CEIC Dr. Stamboulian |
| Centro de Investigacion Pergamino* | Comité de Ética en Investigación Fundación OncoSalud |
| Clinica Viedma S.A. | Comité de Ética en Investigación Clínica (CEIC) |
| CEMER | Comite de etica en Investigacion CEMER |
| Centro Polivalente de Asistencia e Inv. Clinica CER | CEIC Dr. Stamboulian |
| Centro Oncologico de Rosario | Instituto de Oncología y Especialidades Médicas |
| Centro Platense en Investigaciones Respiratorias | Comité de Ética Instituto Médico Platense |
| Núcleo de Pesquisa Clínica da Rede São Camilo | Comitê de Ética em Pesquisa do Instituto Brasileiro de Controle do Câncer |
| Hospital Santa Rita, Centro de Pesquisa Clínica | Hospital Univ Cassiano Antônio de Moraes da Univ Federal do Espírito Santo |
| CRIO - Centro Regional Integrado de Oncologia | Comitê de Ética em Pesquisa da Universidade Federal do Caerá |
| INCA - Instituto Nacional do Cancer | Comitê de Ética em Pesquisa - CEP – INCA |
| Sociedade Beneficência e Caridade de Lajeado – Hospital Bruno Born* | Comite de Etica em Pesquisa da Universidade do Vale do Taquari – UNIVATES |
| Liga Norte RioGrandense Contra o Câncer | Com de Et em Pesq com Seres Humanos da Liga Norte Riograndense Cont o Canc |
| Fundação PIO XII - Hospital de Câncer de Barretos | Comite de Etica em Pesquisa da Fundacao Pio XII |
| Orlandi Oncologia | Comité de Ética Científico SSMO |
| Centro de Investigaciones del Cancer James Lind* | NA[†] |
| Centro de estudios Clinicos SAGA Spa* | Comité de Ética Científico SSMO |

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| CHU de Caen - Hôpital Côte de Nacre | CPP Ile-de-France II - Hôpital Necker |
| Institut de Cancérologie de l'Ouest - Site Saint Herblain | CPP Ile-de-France II - Hôpital Necker |
| Clinique Teissier – Groupe AHNAC | CPP Ile-de-France II - Hôpital Necker |
| CH Le Mans, Pneumologie – Oncologie Thoracique | CPP Ile-de-France II - Hôpital Necker |
| CHU de Bordeaux - GH Sud - Hôpital Haut-Lévêque | CPP Ile-de-France II - Hôpital Necker |
| CHU de Limoges - CHU Dupuytren 1 | CPP Ile-de-France II - Hôpital Necker |
| Krankenhaus Merheim | Ethikkommission der Aerztekammer Nordrhein |
| Krankenhaus Nordwest | Ethik-Kommission der Landesärztekammer Hessen |
| Pius Hospital | Carl von Ossietzky Univerität Oldenburg, Medizinische Ethikkommission |
| St. Vincentius-Kliniken gAG Karlsruhe* | NA[†] |
| Charite-Universitaetsmedizin Berlin | Ethikkommission des Landes Berlin |
| Fachklinik f. Lungenerkrankungen | Ethik-Kommission der Landesärztekammer Hessen |
| Studienzentrum Haematologie/Onkologie/Diabetologie* | Ethik-Kommission der Bayerischen Landesärztekammer |
| Klinikum Kassel GmbH* | Ethik-Kommission der Landesärztekammer Hessen |
| Arnas Garibaldi – P.O. Nesima | Segreteria Scientifico-Amministrativa |
| Centro Di Riferimento Oncologico – IRCCS – Sevizio Sanitario Regionale FVG | Comitato Etico Regionale Unico c/o AOU Santa Maria della Misericordia |
| Istituto Europeo di Oncologia | Com.Etico IRCCS – Ist. Europeo di Oncologia e Centro Cardiologico Monzino |
| Spedali Civili di Brescia | Comitato Etico di Brescia |
| Istituto Nazionale dei Tumori IRCCS | Comitato Etico Ind dell'Istutituto Naz per lo Studio e la Cura dei Tumori |
| Azienda Ospedaliera San Camillo Forlanini | Comitato Etico Lazio 1, Segreteria Scientifico-Amministrativa |
| A.O.R.N. Ospedali dei Colli "Monaldi-Cotugno-CTO | Comitato Etico dell'A.O.R.N. dei Colli di Napoli |
| Samsung Medical Center | Samsung Medical Center |
| Asan Medical Center | Asan Medical Center |

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| Severance Hospital | Severance Hospital |
| Chungbuk National University Hospital | Chungbuk National University Hospital |
| Inje University Haeundae Paik Hospital | Inje University Haeundae Paik Hospital |
| Centrum Medyczne Pratia* | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Samodzielny Publiczny Zespol Gruzlicy I Chorob Pluc | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Samodzielny Publiczny Szpital Kliniczny w Lublinie | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Med-Polonia Sp. z o. o. NSZOZ | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Ars Medical Sp. z o.o* | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Centrum Terapii Wspolczesnej | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| Centrum Onkologii im. prof. F. Lukaszczyka | Kom Bioet przy Okręgowej Izbie Lekarskiej Wielkopolskiej Izby Lekarskiej |
| SC Radiotherapy Center Cluj SRL | Comisia Nationala de Bioetica a medicamentelor si a Dispozitivelor Medicale |
| Spitalul de Psihiatrie Titan Dr Constantin Gorgos | National Ethics committee |
| Centrul de Oncologie "Sf. Nectarie" | Comisia Nationala de Bioetica a medicamentelor si a Dispozitivelor Medicale |
| Hospital del Mar | Hospital del Mar |
| Complejo Hospitario Nuestra | Hospital del Mar |
| Complejo Hospitalario de Jaén | Hospital del Mar |
| Hospital Universitario Virgen de la Victoria | Hospital del Mar |
| Hospital Universitario Lucus Augusti | Hospital del Mar |
| Tri-Service General Hospital | Tri-Service General Hospital |
| Changhua Christian Hospital | Changhua Christian Hospital |
| The Texas Cancer Center* | United States Oncology Incorporated Institutional Review Board |
| Rocky Mountain Cancer Centers-Sky Ridge | United States Oncology Incorporated Institutional Review Board |

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| Cancer Care Centers of Brevard, Incorporated* | United States Oncology Incorporated Institutional Review Board |
| Virginia Cancer Specialists | United States Oncology Incorporated Institutional Review Board |
| Woodlands Medical Specialists* | United States Oncology Incorporated Institutional Review Board |
| Texas Oncology - Tyler* | United States Oncology Incorporated Institutional Review Board |
| Oncology Hematology Care, Incorporated | United States Oncology Incorporated Institutional Review Board |

*No patients enrolled; [†]study site not activated.

NA, not applicable.

**Supplementary Table 2. Protocol deviations**

| **Description of change** | **Brief rationale** |
|---|---|
| Minor editorial changes as needed to align with Sponsor's protocol template | Alignment with the Sponsor's standard protocol template and ways of working |
| Included *"BRAF V600E mutations and other genomic aberrations for which an approved targeted therapy is available"* in the disease eligibility criterion | Per Health Authority feedback, these patients should not be included in the study as there are available targeted treatments for their disease |
| Removed IMP and NIMP definitions from table of study treatments administered | As definitions of IMP and NIMP of the chemotherapies administered in the protocol may vary across countries, these have been removed for clarity |
| Changed "*use*" listed for pembrolizumab in table of study treatments administered from "*background intervention"* to *"comparator"* | Pembrolizumab is being used as a comparator in this study |
| Schedule of activities amended to correct inaccurate infusion times for chemotherapy agents | Revision to correct an error in the study protocol |
| Updated efficacy and safety information for dostarlimab added to protocol introduction | Revision to incorporate updated information added at the request of Health Authority feedback |
| Reasons for required withdrawal/discontinuation was updated to more explicitly differentiate between scenarios requiring discontinuation and potential scenarios | Revision to address request of Health Authority |
| Instructions for emergency unblinding during the course of the study added | Revision to provide more comprehensive information consistent with the Blinding Plans |
| Instructions for dose modifications updated in tables of dose levels and dose adjustment | Revisions to ensure that information is consistent with the product information for the study interventions utilized in the study |

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| Clarification added that PK and immunogenicity for pembrolizumab will be assessed only if needed | Dostarlimab PK and immunogenicity samples analyzed as scheduled, but pembrolizumab samples analyzed only if the study Sponsor determines necessary. The population for immunogenicity analysis includes a broader population to enable further subset analysis, including the one currently defined. |
| Correction to timeframe for reporting AEs. Rather than all AEs being reported from the signing of informed consent, only TRSAEs will be reported from the signing of informed consent and all AEs will be reported from the start of study treatment | Alignment of the protocol language throughout with GSK guidance on AE/SAE collection |
| Correction of timing for baseline tumor assessment of the chest and abdomen from within 28 days prior to first dose to 35 days | Clarifying that the window for baseline tumor assessments should be 28 (+7 days), as opposed to 28 (+/- 7 days) |
| Text updated as below (updates in **bold**):<br>*"**The CT component of** positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines, with full radiation dose diagnostic CT and IV CT contrast, and as clinically indicated"* | Clarifying that the CT component of diagnostic quality PET/CT may be used for tumor assessment per RECIST v1.1 guidelines; prior text indicated that PET/CT could be used for diagnostic quality |
| Text updated as below (updates in **bold**):<br>*"Treatment cycles are 21 days long with **dosing scheduled** on D1 of each cycle. **All assessment should be done prior to drug administration and within 72 h prior to 1st dose of study drugs administered in that cycle, unless otherwise specified (NB: this includes C1D1 and all cycles).** Visits **starting at Cycle 2 can be performed** ±3 days **of the scheduled date"*** | Protocol updated to allow flexibility for sample collection at Day 1 |
| For archival (or fresh) tumor tissue samples, additional instruction added: | Expanding the window when the sample can be sent for biomarker analysis to allow greater flexibility in obtaining a sample |

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| ***"If PD-L1 status is known and the participant has agreed to provide archival sample via the optional consent, this sample may be provided within 28 days of the start of study treatment"*** | |
| Additional assessment "*Evaluate genomic aberration"* added to schedule of activities table | Indicated in the schedule of assessment that results of genomic aberrations are needed at screening. This was to align with the rest of the protocol |
| Additional instruction added to the schedule of activities of table for optional blood sample for genetic testing to clarify sample may be obtained after randomization during first cycle if not collected at screening | Allowing flexibility for sample collection to reduce collection burden at Day 1 |
| PRO collection timepoints updated in schedule of activities table to reflect timepoints in cycles rather than weeks | Added to align the protocol with other study documents |
| Updated schedule of activities table to reflect that PROs should be collected prior to any clinical procedures, whenever possible | Allowing flexibility for these assessments, reducing both burden to participants and the operational burden to site staff |
| Clarification added to schedule of activities table that urinalysis starts at Cycle 6, Day 1 | Clarification |
| Clarification added to schedule of activities table that urinalysis starts at Cycle 2, Day 1 | Clarification |
| Removed statement on EU approval of pembrolizumab monotherapy in NSCLC | Corrected an error as pembrolizumab is only approved for the indication described in the introduction in the US |
| Added additional detail on the potential risks of exposure to ionizing radiation due to the inclusion in the study of CT scans | Added to include risk assessment considerations related to radiographic imaging and radiation exposure |

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| Protocol revised to note the duration of contraception for female and males post-chemotherapy must be consistent with local regulations with a minimum of 180 days for males and females, consistent with dostarlimab guidance | Revision to incorporate additional flexibility as may be guided by local labelling requirements |
| Reworded inclusion criterion (updates in strikethrough and **bold**):<br><br>~~Target~~ **Measurable** lesions situated in a previously irradiated area ~~are~~ **may be** considered ~~measurable~~ **target** lesions in progression has been demonstrated in such lesions and if there are other target lesions | Clarification |
| Reworded exclusion criterion (updates in strikethrough and **bold**):<br><br>Participant has an additional malignancy or a history of prior malignancy, with the exception of adequately treated basal or squamous skin cancer, cervical carcinoma in situ, ~~or~~ **superficial** bladder ~~carcinoma in situ~~ **cancer** without evidence of disease, **other in situ cancers**, or had a malignancy treated with curative intent and with no evidence of disease recurrence for 5 years since the initiation of that therapy. | Inconsistency identified during study conduct. Previously allowed one type of superficial bladder cancer but not others of similar or lesser risk. |
| Removed the requirement for participants who test positive for the presence of hepatitis B core antibody to be excluded | Included in error and not applicable to this study |
| The protocol was amended to provide additional flexibility for local guidelines with relation to infusion times for chemotherapy agents | Revision to correct discrepancy in the study protocol introduced by way of regional differences in labelling instructions |
| Instructions for the collection of PROs updated | To correct an error in the collection method for PROs when subjects are unable to attend a clinic visit |
| Added definition of best overall response as **confirmed** CR or PR | Update to clarify that response confirmation is required for ORR analysis |

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| Added that samples may be used for additional exploratory biomarker testing and for the development of a diagnostic test | Additional language to ensure that the information is aligned with elsewhere in protocol, the exploratory biomarker objectives and potential future use for CDx development |
| "*Future Biomedical Research"* section renamed to *"Biomedical Research"* | This section contains both planned analysis for the current study and potential future investigations |
| Additional text added to describe a potential, future population PK analysis including data from this study | Population PK analysis will be performed if study sponsor determines it is necessary |
| Amended the use of X-rays for the assessment of measurable lesions to the assessment of progression due to new lesions | Clarification: CT/MRI should be used to assess measurable/target lesions; X-rays are not appropriate for target lesion assessment in this study |
| Removed the definition of a measurable lesion as ≥10 mm caliper/ruler measurement by clinical examination or medical photography | Clarification: CT/MRI should be used to assess measurable/target lesions; clinical exam and photography are not appropriate to use for target lesion assessment in this study |
| Added statement to clarify laboratory assessments for each cycle can occur up to 72 hours before treatment | Alleviating patient burden by reducing time at site on day 1 |
| Removed all references to the eCRF requirement for documenting causality review | Alignment with current protocol template guidance |
| Corrected typographical error incorrectly capturing GARNET lung cancer population as previously "*untreated"* NSCLC patients | Typographical error |
| Criteria for treatment withdrawal/stopping rules was clarified to include the text *"or other adverse event"* to the criterion of unacceptable toxicity | Additional editorial revisions to provide further clarity to the study design |

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| Text updated (shown in **bold**):<br><br>*"Tumor tissue will be evaluated for PD-L1 expression using IHC and may be correlated with ORR* ***and potentially other clinical endpoints*** *to treatment"* | To expand the potential scope of this exploratory endpoint |
| Pemetrexed should be administered according to the local label, thus guidance on infusion rate has been removed | In response to local requirements, sites are allowed to follow their local recommendations |
| Instructions for dose modifications for non-hematological chemotherapy toxicities updated. Removed the requirement for PD-1 inhibitors to be withheld in the event of all drug-related toxicities. Instructions for dose modification guidelines for PD-1 inhibitor-related AEs updated | Revisions to ensure that information is consistent with the product information for the study interventions utilized in the study |
| Removed number of participants limit per strata | Due to the standard of care treatment available to participants whose TPS score is >50%, enrolment into this stratum is relatively limited. Therefore, by removing the requirement to evenly distribute participants across three strata, it is anticipated that study enrolment rate and accessibility will benefit |
| Post-dosing timepoints for PK and biomarker sample collection is done after immunotherapy infusion | Clarified that post-dose collection timepoints refer to immunotherapy dosing and not patient treatment, including chemotherapy |
| *"Permanently discontinue"* for Grade 4 severity was removed from adrenal insufficiency, hypophysitis, hypothyroidism and hyperthyroidism | Clinical management of these endocrinopathies are amendable to hormone replacement therapies or thyroid suppressive therapy and the adequacy of supplementation monitorable symptomatically and with laboratory assessments |

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| Updates to dose modifications:<br>• Updated dose modifications for adrenal insufficiency to include endocrine consultation as follow-up<br>• Expanded dose modifications for Guillain-Barré syndrome to include several severe neurological events (myasthenic syndrome/myasthenia gravis and transverse myelitis were added), to include Grade 2, to include corticosteroid and other therapy guidelines, and to include neurology consultation as follow-up<br>• Updated dose modifications for myocarditis<br>• Added DRESS to dose modifications for rash/skin reactions<br>• Added corticosteroid and other therapy guidelines and consultation follow-up for other irARs | Clarification/correction/program updates, including mitigation of potentially serious complications of immune-related events, including severe neurological events, severe skin reactions and myocarditis |
| Removed footnote that decision to withhold or discontinue PD-1 inhibitor is at the discretion of the investigator or treating physician | Incorrect footnote removed to ensure clarity about the reason to discontinue or withhold PD-1 inhibitor. This decision should be deduced from the protocol instructions rather than based on investigator assessment. |

(N)IMP, (non-)investigational medicinal product; AE, adverse event; C, cycle; CDx, clinical diagnostics; CR, complete response; CT, computed tomography; D, day; DRESS, drug reaction with eosinophilia and systemic symptoms; eCRF, electronic case report form; h, hour; irAR, immune-related adverse reaction; IV, intravenous; MRI, magnetic resonance imaging; ORR, overall response rate; PD-(L)1, programmed death (ligand) 1; PET, positron emission tomography; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TRSAE, treatment-related serious adverse event; v, version.

**Supplementary Table 3. Full inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
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| • ≥18 years old, able to understand study procedures, and agrees to participate in the study by providing written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the study protocol<br>• Histologically- or cytologically- confirmed metastatic non-squamous NSCLC with documented absence of a sensitizing EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available; mixed tumors will be categorized by the predominant cell type; if the tumor has predominantly squamous cell histology or if small cell elements are present, participant is ineligible<br>• Measurable disease (presenting with at least 1 measurable lesion per RECIST v1.1 as determined by the local site investigator/radiology assessment); measurable lesions in previously irradiated areas may be considered target lesions if progression has been demonstrated in such lesions and if there are other target lesions (ineligible if only 1 target lesion previously irradiated)<br>• Documented PD-L1 status by the 22C3 pharmDx assay<br>• Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1<br>• Life expectancy ≥3 months | • Prior systemic therapy for the treatment of metastatic NSCLC; participants who received neoadjuvant or adjuvant chemotherapy are eligible if completed ≥12 months prior to development metastatic disease<br>• Prior therapy with a PD-(L)1/2 inhibitor, CTLA-4 inhibitor, TIM-3 inhibitor, or any other IO agent for the treatment of cancer<br>• Radiation to the lung >30 Gy within 6 months of the first dose of study treatment<br>• Completion of palliative radiotherapy within 7 days of the first dose of study treatment<br>• Any of the following hepatic characteristics present:<br>o ALT >2.5x upper limit of normal (ULN) without liver metastases/tumor infiltration<br>o ALT >5x ULN with liver metastases/tumor infiltration<br>o Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN acceptable if bilirubin is fractionated and direct bilirubin <35%)<br>o Current active liver or biliary disease (exceptions: Gilbert's syndrome, asymptomatic gallstones, liver metastases, otherwise stable chronic liver disease per Investigator assessment)<br>• QTc >450 ms (>480 ms for participants with BBB)<br>• Major surgery within 3 weeks of the first dose of study treatment or has not adequately recovered from any AEs (Grade ≤1) and/or |

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| • Adequate organ function (hematologic, hepatic, renal)<br>• Recovered to Grade ≤1 from any prior treatment-related toxicities at the time of randomization (exception: Grade 2 alopecia)<br>• Contraceptive use consistent with local regulations regarding methods of contraception for those participating in clinical studies<br>• Male participants must agree to the following for the treatment period and for ≥180 days after the last dose of study treatment:<br>  ○ Refrain from donating sperm<br>  ○ Either be abstinent from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent OR agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant or when engaging in any activity that allows for passage of ejaculate to another person<br>• Female participants must not be pregnant or breastfeeding and one of the following conditions must apply:<br>  ○ Be of non-childbearing potential<br>  ○ Be of childbearing potential but use a highly effective contraceptive method (failure rate <1% per year, preferably with low user dependency) during the treatment period and for ≥180 days after the last dose and agree not to donate eggs for the purposes of reproduction during the same period; participants of child-bearing potential should have a negative highly sensitive | complications from major surgery; surgical implantation of a port catheter is not exclusionary<br>• Additional malignancy or a history of prior malignancy (exceptions: adequately treated basal or squamous skin cancer, cervical carcinoma in situ, superficial bladder cancer without evidence of disease, other in situ cancers, malignancy treated with curative intent and with no evidence of disease recurrence for 5 years since the initiation of that therapy)<br>• Known active brain metastases and/or leptomeningeal metastases (exceptions: participants who have received prior therapy for their brain metastases and have radiographically stable central nervous system disease and are neurologically stable for at least 2 weeks before study entry and off corticosteroids within 3 days prior to the first dose of study treatment, or participants with known untreated, asymptomatic brain metastases). Exception: participants with known untreated asymptomatic brain metastases (i.e., no neurological symptoms, requirements for corticosteroids, lesions >1.5 cm, and no or minimal surrounding edema)<br>• Positive test for hep B surface antigen or positive hep C antibody test result at screening/within 3 months prior to first dose of study treatment<br>• Active infection requiring systemic therapy within 1 week prior to the anticipated first dose of study treatment<br>• Known HIV |

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| pregnancy test within 72 hours before the first dose of study treatment | • Active autoimmune disease that required systemic treatment in the past 2 years, is immunocompromised in the opinion of the investigator, or is receiving systemic immunosuppressive treatment (replacement therapy not considered a systemic treatment)<br>• Received systemic steroid therapy within 3 days prior to the first dose of study treatment or receiving any other form of immunosuppressive medication (inhaled corticosteroids, local steroid injections, or steroid eye drops is allowed)<br>• Symptomatic ascites or pleural effusion (exception: clinically stable following treatment of these conditions)<br>• Current interstitial lung disease, current pneumonitis, or a history of pneumonitis that required the use of oral or IV glucocorticoids to assist with management<br>• History or current evidence of any medical condition, therapy, or laboratory abnormality that might confound the study results, interfere with their participation for the full duration of the study treatment, or indicate it is not in the best interest of the participant to participate, in the opinion of the Investigator<br>• Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, or peritoneal carcinomatosis<br>• Pre-existing peripheral neuropathy that is Grade ≥2 by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 criteria<br>• Live vaccine within 30 days of the first dose of study treatment |

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| | • Not meeting requirements per local prescribing guidelines for receiving treatment with either pemetrexed and cisplatin or carboplatin<br>• Sensitivity to any of the study treatments, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation<br>• Unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam) |

AE, adverse event; ALT, alanine transaminase; BBB, bundle branch block; CTLA-4, cytotoxic T-lymphocyte associated protein 4; HIV, human immunodeficiency virus; IO, immunotherapy; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer; PD-(L)1/2, programmed death (ligand) 1/2; QTc, corrected QT interval; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIM-3, T-cell immunoglobulin and mucin domain 3; ULN, upper limit of normal.

**Supplementary Table 4. Reasons for unknown or missing ('not done') patient responses**

| Reasons for unknown or missing responses | Dostarlimab + CT (n=5) | Pembrolizumab + CT (n=13) |
|---|---|---|
| **No post-baseline disease assessments available due to death from a fatal AE** | 2 (40) | 8 (62) |
| **No post-baseline disease assessments available due to death from disease under study** | 3 (60) | 1 (8) |
| **No post-baseline disease assessments available due to withdrawal from study*** | 0 (0) | 2 (15) |
| **Started new anti-cancer therapy before first assessment** | 0 (0) | 1 (8) |
| **Independent BICR assessment missing** | 0 (0) | 1 (8) |

*Withdrawal reasons were withdrawal of consent (n=1) and went into hospice care (n=1). Responses are applicable to both the primary and updated analyses.

AE, adverse events; BICR, blinded independent central review; CT, chemotherapy.

**Supplementary Table 5. ORRs for patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy (ITT population as of August 4, 2022)**

| | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| **Best overall response, n (%)** | | |
| Complete response | 2 (2) | 3 (2) |
| Partial response | 54 (45) | 42 (34) |
| Stable disease | 48 (40) | 52 (43) |
| Progressive disease | 12 (10) | 11 (9) |
| Not evaluable | 0 | 1 (<1) |
| Not done* | 5 (4) | 13 (11) |
| **ORR** | | |
| Complete response + partial response, n (%) | 56 (46) | 45 (37) |
| 95% CI | 37.2–55.6 | 28.3–46.1 |
| **ORR by PD-L1 TPS subgroup, n/N (%)** | | |
| TPS <1% | 14/50 (28) | 17/51 (33) |
| 95% CI | 16–43 | 21–48 |
| TPS ≥1% | 42/71 (59) | 28/71 (39) |
| 95% CI | 47–71 | 28–52 |
| TPS 1–49% | 22/44 (50) | 15/44 (34) |
| 95% CI | 35–65 | 21–50 |
| TPS ≥50% | 20/27 (74) | 13/27 (48) |
| 95% CI | 54–89 | 29–68 |

ORR was assessed per RECIST v1.1 based on BICR.

*Patients with ORR listed as "not done" had unknown or missing responses. The reasons for unknown or missing responses in each arm are listed in **Supplementary Table 4**.

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; ORR, overall response rate; PD-L1, programmed death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

**Supplementary Table 6. Summary of best overall responses by PD-L1 TPS subgroup for the primary analyses (ITT population as of August 4, 2022)**

| | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| **TPS <1%, n (%)** | | |
| Complete response | 2 (4) | 1 (2) |
| Partial response | 12 (24) | 16 (31) |
| Stable disease | 29 (58) | 23 (45) |
| Progressive disease | 6 (12) | 5 (10) |
| Not evaluable | 0 (0) | 0 (0) |
| Not done* | 1 (2) | 6 (12) |
| **TPS ≥1%, n (%)** | | |
| Complete response | 0 (0) | 2 (3) |
| Partial response | 42 (59) | 26 (37) |
| Stable disease | 19 (27) | 29 (41) |
| Progressive disease | 6 (8) | 6 (8) |
| Not evaluable | 0 (0) | 1 (1) |
| Not done* | 4 (6) | 7 (10) |
| **TPS 1–49%, n (%)** | | |
| Complete response | 0 (0) | 0 (0) |
| Partial response | 22 (50) | 15 (34) |
| Stable disease | 15 (34) | 17 (39) |
| Progressive disease | 5 (11) | 6 (14) |
| Not evaluable | 0 (0) | 1 (2) |
| Not done* | 2 (5) | 5 (11) |
| **TPS ≥50%, n (%)** | | |
| Complete response | 0 (0) | 2 (7) |
| Partial response | 20 (74) | 11 (41) |
| Stable disease | 4 (15) | 12 (44) |
| Progressive disease | 1 (4) | 0 (0) |
| Not evaluable | 0 (0) | 0 (0) |
| Not done* | 2 (7) | 2 (7) |

ORR was assessed by BICR per RECIST v1.1. *Patients with ORR listed as “not done” had unknown or missing responses. The reasons for unknown or missing responses in each arm are listed in **Supplementary Table 2**.

BICR, blinded independent central review; ORR, overall response rate; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

**Supplementary Table 7. Median PFS by PD-L1 TPS subgroup for patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy (ITT population as of August 4, 2022)**

| | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) | HR (95% CI) |
|---|---|---|---|
| **TPS <1%** | | | |
| N analyzed | 50 | 51 | 0.77 (0.46–1.28) |
| Median PFS, months (95% CI) | 7.0 (4.9–9.7) | 6.9 (4.7–9.6) | |
| **TPS ≥1%** | | | |
| N analyzed | 70 | 71 | 0.66 (0.41–1.03) |
| Median PFS, months (95% CI) | 10.4 (6.8–13.6) | 6.1 (4.8–7.1) | |
| **TPS 1–49%** | | | |
| N analyzed | 44 | 44 | 0.67 (0.38–1.19) |
| Median PFS, months (95% CI) | 9.0 (5.3–NR) | 5.4 (3.2–11.3) | |
| **TPS ≥50%** | | | |
| N analyzed | 27 | 27 | 0.60 (0.27–1.29) |
| Median PFS, months (95% CI) | 10.4 (5.8–NR) | 6.7 (4.2–NR) | |

PFS was assessed per RECIST v1.1 based on investigator assessment.

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; PD-L1, programmed death ligand 1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

**Supplementary Table 8. Primary OS analyses for patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy (ITT population as of August 4, 2022)**

| Variable | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| Median OS follow-up time, months (IQR) | 10.9 (7.7–13.2) | 10.9 (7.5–13.3) |
| OS events observed, n | 42 | 48 |
| Median OS (95% CI), months | NR (12.6–NR) | 14.0 (10.8–17.1) |
| Estimated probability of OS, % (95% CI)<br>6 months<br>12 months | <br>77 (68–83)<br>62 (51–71) | <br>77 (69–84)<br>60 (50–69) |

CI, confidence interval; IQR, interquartile range; ITT, intention-to-treat; NR, not reached; OS, overall survival.

**Supplementary Table 9. Primary analyses of AEs by preferred term occurring in ≥10% of patients (safety population as of July 7, 2023)**

| AE (n, %) | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| **TEAEs** | 119 (98) | 119 (98) |
| Alanine aminotransferase increased | 15 (12) | 15 (12) |
| Anemia | 61 (50) | 60 (49) |
| Aspartate aminotransferase increased | 13 (11) | 8 (7) |
| Asthenia | 41 (34) | 41 (34) |
| Back pain | 8 (7) | 12 (10) |
| Blood creatinine increased | 16 (13) | 9 (7) |
| Constipation | 23 (19) | 23 (19) |
| Cough | 24 (20) | 21 (17) |
| Decreased appetite | 23 (19) | 19 (16) |
| Diarrhea | 21 (17) | 18 (15) |
| Dyspnea | 23 (19) | 19 (16) |
| Fatigue | 15 (12) | 16 (13) |
| Nausea | 30 (25) | 31 (25) |
| Neutropenia | 20 (17) | 27 (22) |
| Peripheral oedema | 13 (11) | 11 (9) |
| Respiratory tract infection | 8 (7) | 13 (11) |
| Pneumonia | 10 (8) | 19 (16) |
| Pyrexia | 14 (12) | 17 (14) |
| Rash | 15 (12) | 7 (6) |
| Pruritus | 11 (9) | 14 (11) |
| Thrombocytopenia | 14 (12) | 11 (9) |
| Vomiting | 24 (20) | 15 (12) |
| **TRAEs*** | 103 (85) | 99 (81) |
| Alanine aminotransferase increased | 9 (7) | 12 (10) |
| Anemia | 50 (41) | 48 (39) |
| Asthenia | 25 (21) | 28 (23) |
| Decreased appetite | 12 (10) | 13 (11) |
| Diarrhea | 42 (35) | 46 (38) |
| Nausea | 24 (20) | 24 (20) |
| Neutropenia | 18 (15) | 22 (18) |

| | | |
|---|---|---|
| Rash | 14 (12) | 3 (2) |
| Thrombocytopenia | 13 (11) | 9 (7) |
| Vomiting | 13 (11) | 10 (8) |
| **TRAEs related to dostarlimab/pembrolizumab** | 86 (71) | 70 (57) |
| Anemia | 15 (12) | 9 (7) |
| Asthenia | 11 (9) | 17 (14) |
| Rash | 13 (11) | 3 (2) |

*Adverse events described as treatment-related could be related to any study treatment agent.

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

**Supplementary Table 10. AE summary for patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy (safety population as of August 4, 2022)**

| AE, n (%) | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| Any TEAE | 117 (97) | 118 (97) |
| TRAEs* | 99 (82) | 96 (79) |
| SAEs | 46 (38) | 55 (45) |
| TRSAEs* | 20 (17) | 29 (24) |
| irAEs | 31 (26) | 41 (34) |
| Grade ≥3 irAEs | 11 (9) | 17 (14) |
| irSAEs | 9 (7) | 11 (9) |
| AEs leading to any treatment discontinuation | 30 (25) | 39 (32) |
| AEs leading to dostarlimab/pembrolizumab discontinuation | 18 (15) | 29 (24) |
| Fatal TRAEs* | 3 (2) | 5 (4) |
| Immune-mediated lung disease | 1 (<1) | 0 (0) |
| Myelosuppression | 0 (0) | 1 (<1) |
| Pneumonia | 0 (0) | 1 (<1) |
| Pneumonitis | 1 (<1) | 0 (0) |
| Respiratory failure | 0 (0) | 1 (<1) |
| Septic shock | 0 (0) | 1 (<1) |
| Urosepsis | 1 (<1) | 0 (0) |
| Thrombocytopenia | 0 (0) | 1 (<1) |

*AEs described as treatment-related could be related to any study treatment agent.

AE, adverse event; irAE, immune-related AE; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related SAE.

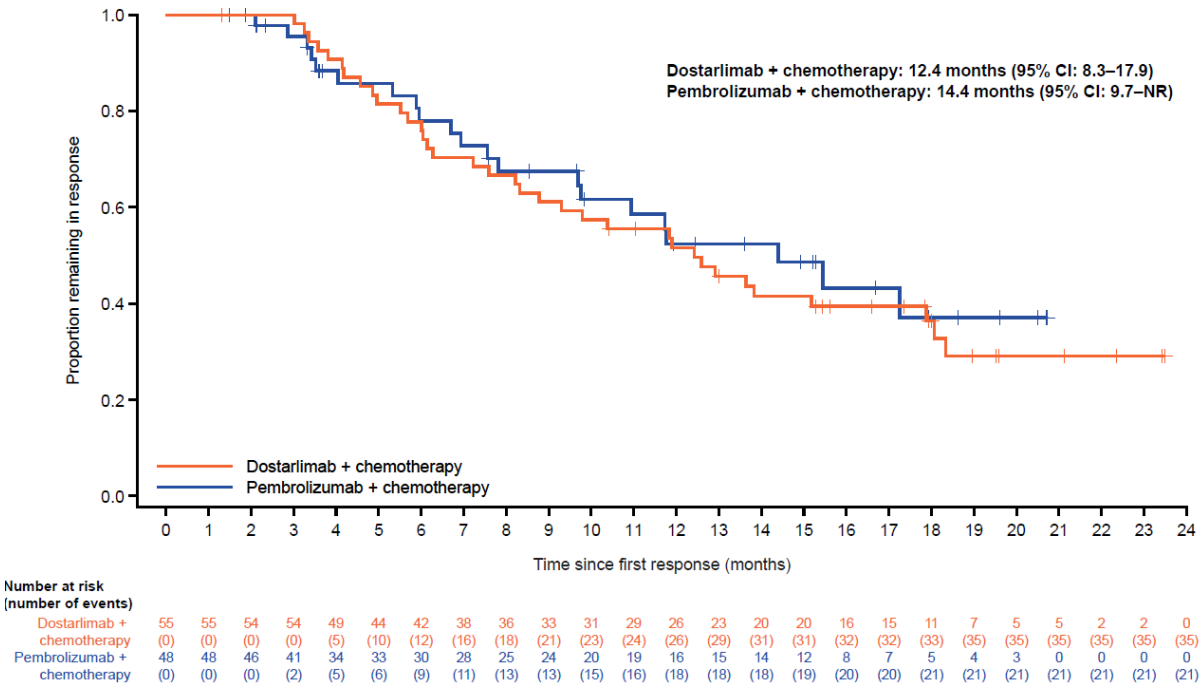
**Supplementary Table 11. Primary analyses of AEs by preferred term occurring in ≥10% of patients (safety population as of August 4, 2022)**

| AE (n, %) | Dostarlimab + chemotherapy (N=121) | Pembrolizumab + chemotherapy (N=122) |
|---|---|---|
| **TEAEs** | 117 (97) | 118 (97) |
| Alanine aminotransferase increased | 11 (9) | 14 (11) |
| Anemia | 54 (45) | 59 (48) |
| Asthenia | 39 (32) | 39 (32) |
| Back pain | 7 (6) | 12 (11) |
| Blood creatinine increased | 13 (11) | 6 (5) |
| Constipation | 23 (19) | 21 (17) |
| Cough | 22 (18) | 20 (16) |
| Decreased appetite | 18 (15) | 15 (12) |
| Diarrhea | 15 (12) | 17 (14) |
| Dyspnea | 21 (17) | 18 (15) |
| Fatigue | 14 (12) | 12 (10) |
| Nausea | 28 (23) | 29 (24) |
| Neutropenia | 15 (12) | 27 (22) |
| Pneumonia | 10 (8) | 17 (14) |
| Pyrexia | 12 (10) | 15 (12) |
| Rash | 14 (12) | 6 (5) |
| Thrombocytopenia | 13 (11) | 10 (8) |
| Vomiting | 20 (17) | 14 (11) |
| **TRAEs*** | 99 (82) | 96 (79) |
| Anemia | 45 (37) | 46 (38) |
| Asthenia | 22 (18) | 27 (22) |
| Decreased appetite | 9 (7) | 12 (10) |
| Nausea | 22 (18) | 23 (19) |
| Neutropenia | 14 (12) | 22 (18) |
| Rash | 13 (11) | 3 (2) |
| Thrombocytopenia | 12 (10) | 8 (7) |
| **TRAEs related to dostarlimab/pembrolizumab** | 78 (64) | 65 (53) |
| Anemia | 12 (10) | 8 (7) |
| Asthenia | 10 (8) | 16 (13) |
| Rash | 12 (10) | 3 (2) |

*Adverse events described as treatment-related could be related to any study treatment agent.

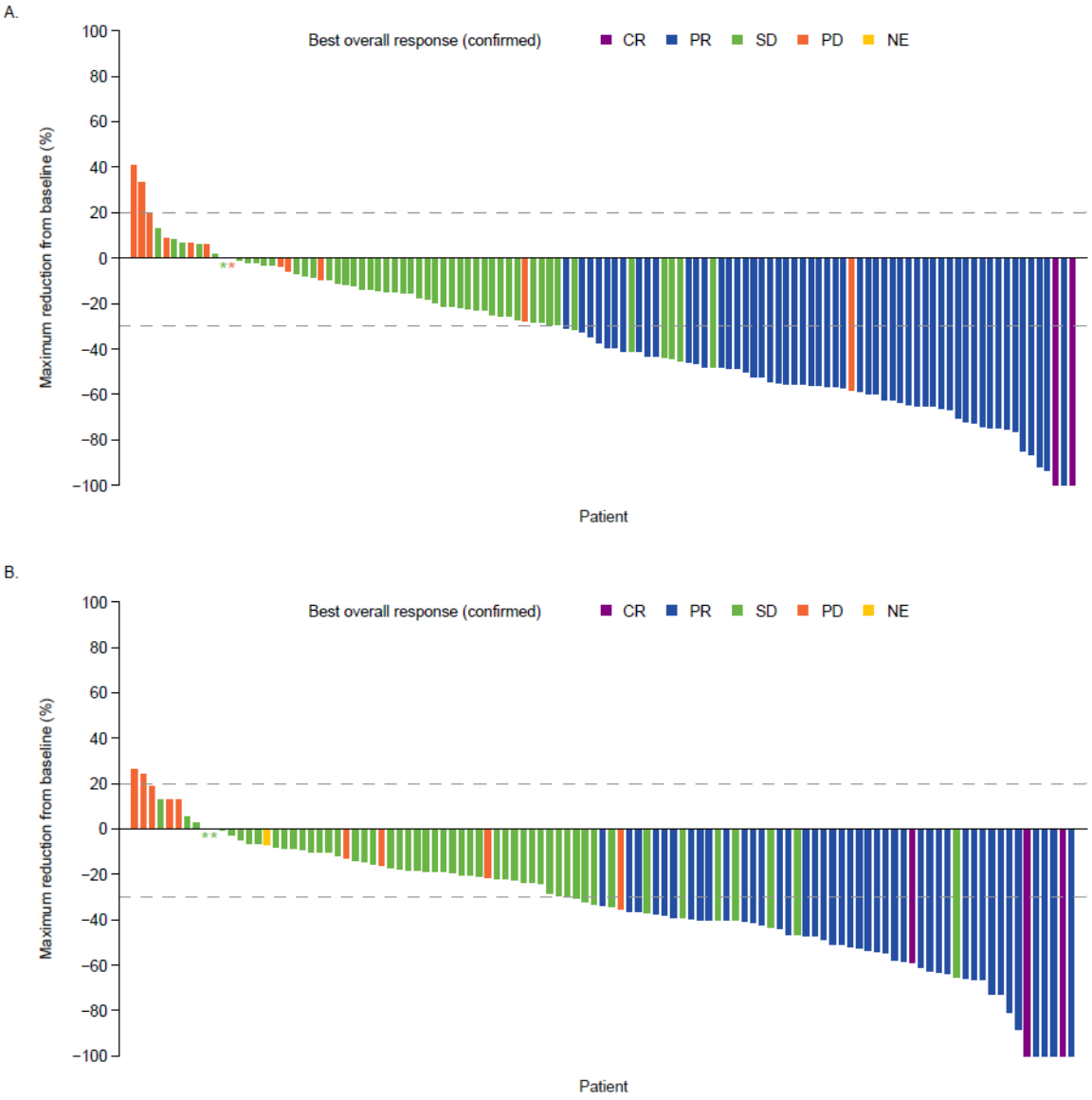
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

**Supplementary Figure 1. DOR Kaplan–Meier curves for dostarlimab plus chemotherapy and pembrolizumab plus chemotherapy (ITT population as of July 7, 2023)**




CI, confidence interval; DOR, duration of response; HR, hazard ration; ITT, intention-to-treat; NR, not reached.

**Supplementary Figure 2. BICR-assessed maximum percentage reduction from baseline in tumor measurement (ITT population as of August 4, 2022).**



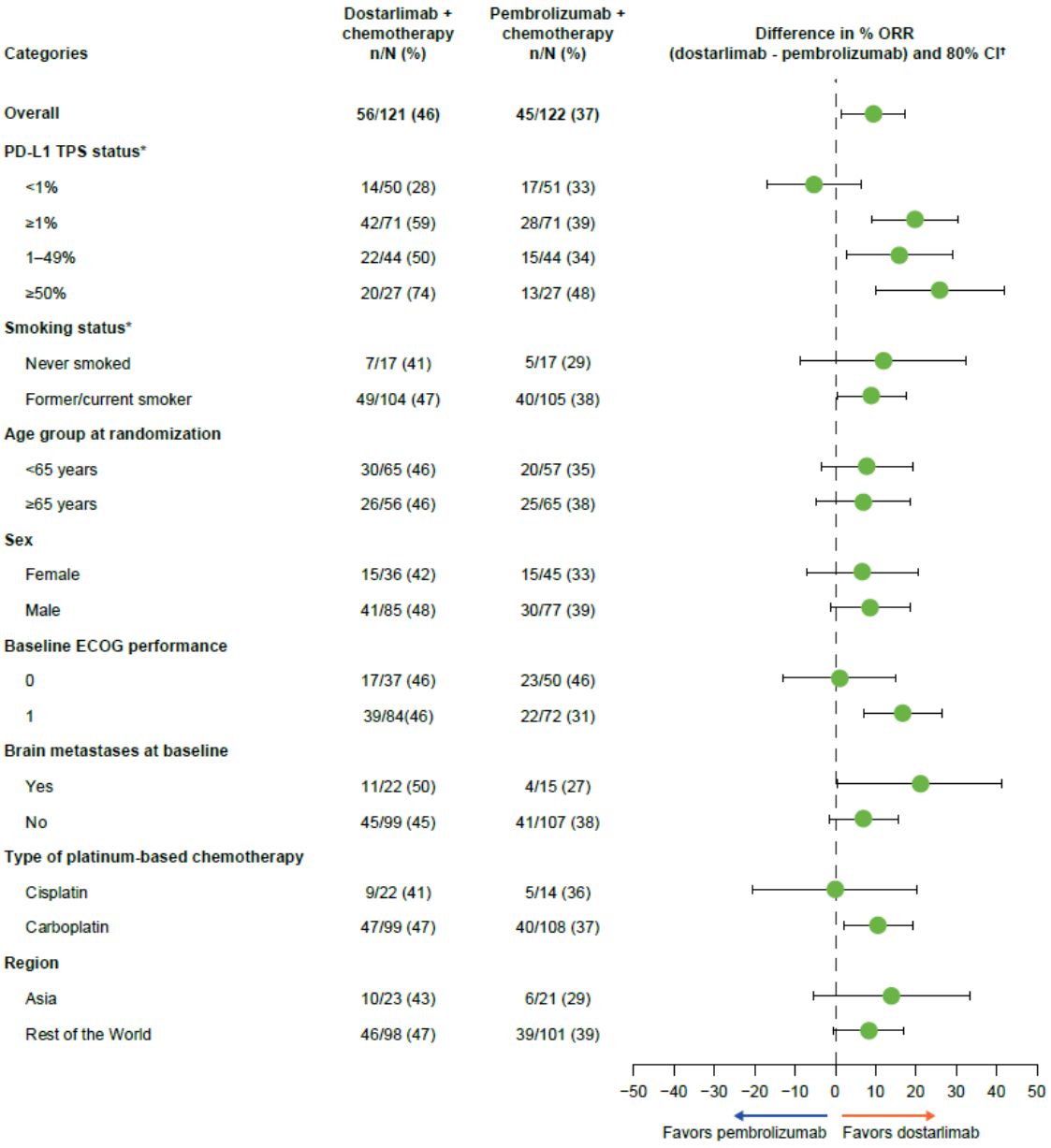

(A) dostarlimab plus chemotherapy (N=121) and (B) pembrolizumab plus chemotherapy (N=122).

*Maximum reduction from baseline of 0%.

Note: one patient with CR with less than 100% BICR-assessed maximum percent reduction from baseline had only lymph node selected by BICR to derive the best overall response as CR.

BICR, blinded independent central review; CR, complete response; ITT, intention-to-treat; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

**Supplementary Figure 3. Forest plot of differences in ORR (dostarlimab – pembrolizumab, %) for patients receiving dostarlimab + chemotherapy (N=121) and pembrolizumab + chemotherapy (N=122) and 80% CI (ITT population as of August 4, 2022)**




Note: n represents the number of patients in the subgroup with a best overall response of CR or PR and N represents the number of patients in the subgroup.

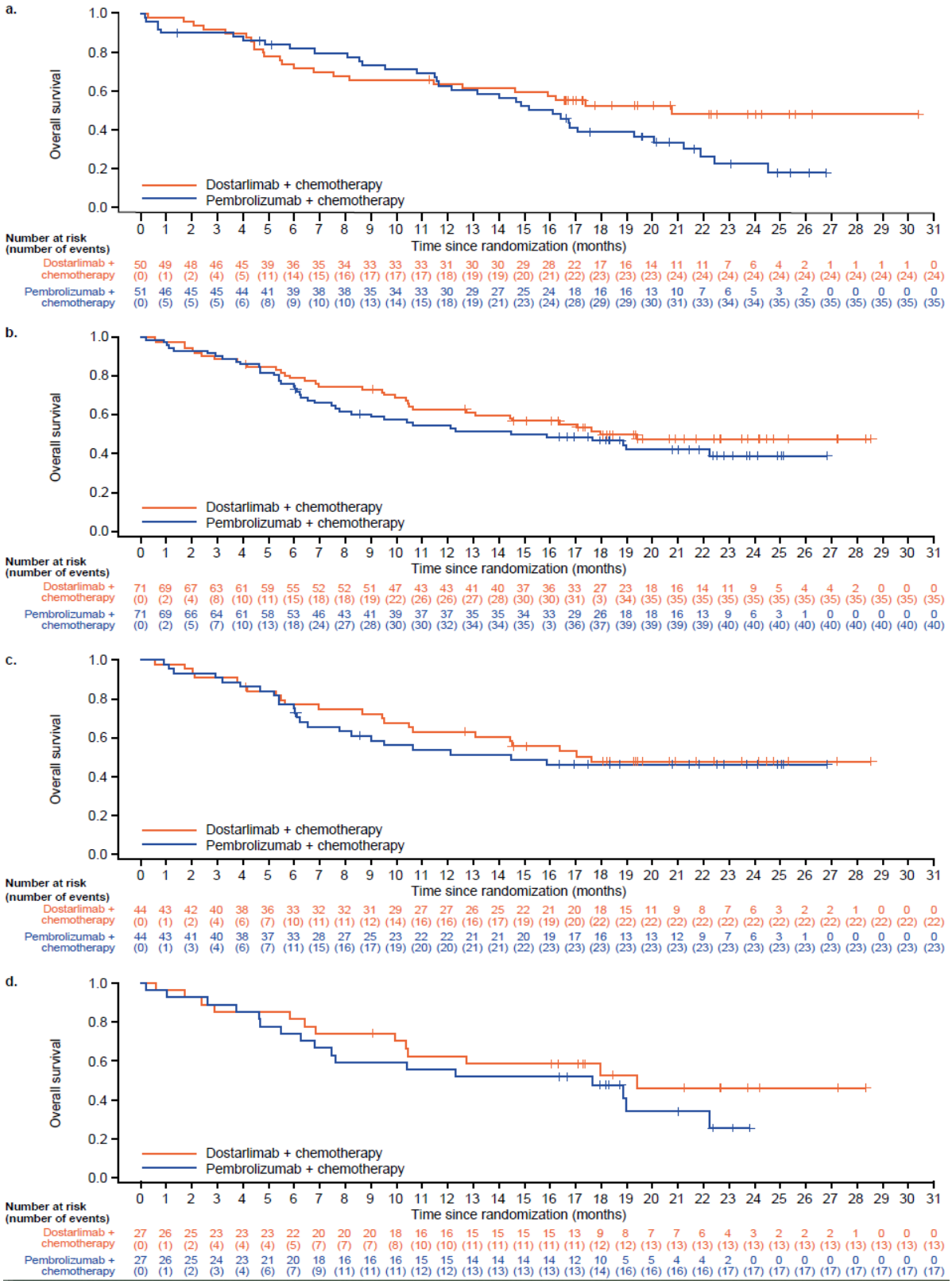
*Based on the strata collected in Interactive Response Technology at randomization.

†Mantel and Haenszel method with Sato's variance estimator stratified by PD-L1 TPS status (TPS <1% vs 1%–49% vs ≥50%) and smoking status (never vs former/current) based on strata data collected in Interactive Response Technology at randomization.

PD-L1 TPS Status is not included as a stratification factor for the PD-L1 TPS status subgroups.
Smoking status is not included as a stratification factor for the smoking status subgroups.

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PD-L1, programmed death ligand 1; PR, partial response; TPS, tumor proportion score.

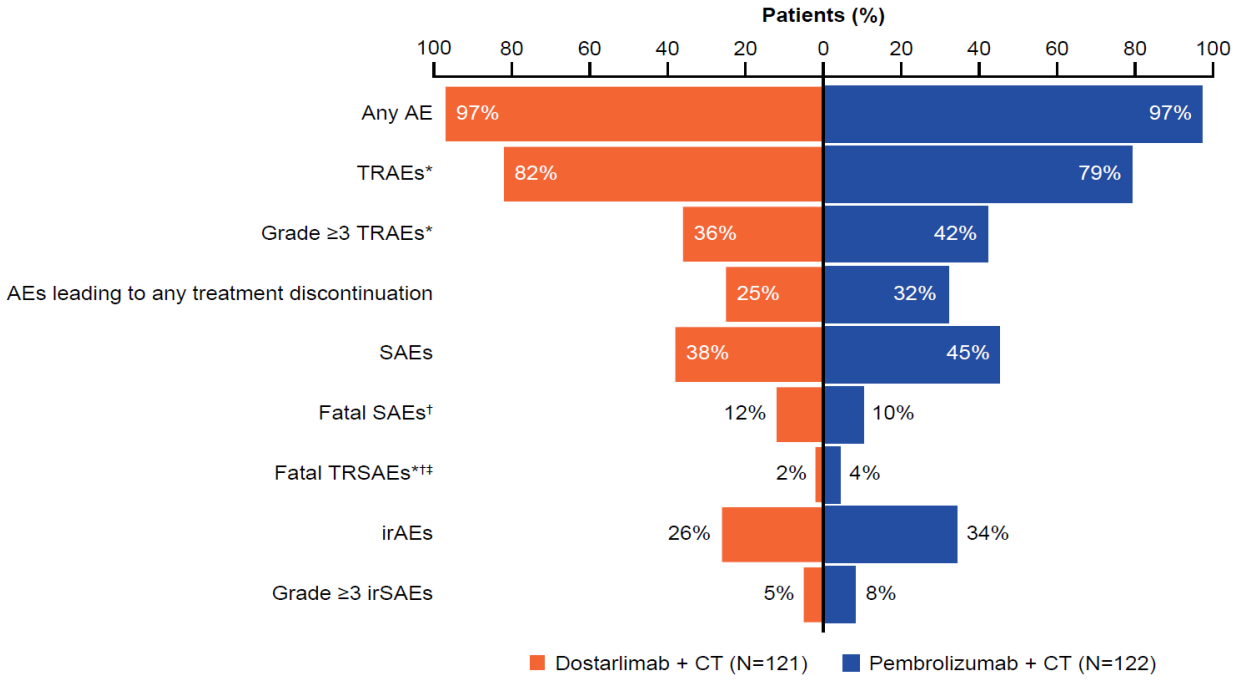
**Supplementary Figure 4. OS Kaplan–Meier curves by PD-L1 TPS status for dostarlimab plus chemotherapy and pembrolizumab plus chemotherapy (ITT population as of July 7, 2023)**



A) <1% PD-L1 TPS B) ≥1% PD-L1 TPS C) 1–49% PD-L1 TPS and D) ≥50% PD-L1 TPS (data cut-off July 7, 2023).

CI, confidence interval; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

**Supplementary Figure 5. Tornado plot showing types of AEs in patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy (safety population as of August 4, 2022)**




*Adverse events described as treatment-related could be related to any study treatment agent.

†Patients who had a fatal SAE recorded and whose death was not recorded as due unequivocally to disease under study.

‡Fatal TRSAEs for dostarlimab + CT were immune-mediated lung disease, pneumonitis, and urosepsis and for pembrolizumab + CT were myelosuppression, pneumonia, respiratory failure, septic shock, and thrombocytopenia (one patient each).

AE, adverse event; CT, chemotherapy; irAE, immune-related adverse event; irSAE, immune-related serious adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.