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Blood tumor mutational burden and response to pembrolizumab plus chemotherapy in non–small cell lung cancer: KEYNOTE-782

Jair Bar [a,b,*], Emilio Esteban [c], Delvys Rodríguez-Abreu [d], Santiago Ponce Aix [e], Zsuzsanna Szalai [f], Enriqueta Felip [g], Maya Gottfried [h], Mariano Provencio [i], Andrew Robinson [j], Andrea Fülöp [k], Suman Bannur Rao [l], D. Ross Camidge [m], Giovanna Speranza [n], Steven M. Townson [o], Julie Kobie [o], Mark Ayers [o], E.J. Dettman [o], Nathan Hunkapiller [p,1], Robert McDaniel [p], Byoungsok Jung [p], David Burkhardt [p], Ruth Mauntz [p], Tibor Csőszi [q]

[a] Sheba Medical Center, Tel Hashomer, Derech Sheba 2, Ramat Gan 5262000, Israel
[b] Tel-Aviv University Medical School, P.O Box 39040, Ramat Aviv, Tel-Aviv 69978, Israel
[c] Central Hospital Universitario Central de Asturias, Avenida de Roma, 33011 Oviedo, Spain
[d] Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Avenida Marítima del Sur, s/n, 35016 Las Palmas De Gran Canaria, Spain
[e] Hospital Universitario 12 de Octubre, H120-CNIO Lung Cancer Clinical Research Unit, Universidad Complutense and CIBERONC, Avenida de Séneca 2, 28040 Madrid, Spain
[f] Petz Aladár Egyetemi Oktató Kórház, Győr, 9224, Vasvári Pál 2-4, Hungary
[g] Vall d'Hebron University, Vall d'Hebron Institute of Oncology (VHIO), Centro Cellex, Carrer de Natzaret, 115-117, 08035 Barcelona, Spain
[h] Meir Medical Center, 59 Tchernichovsky, Kfar-Sava 4428164, Israel
[i] Hospital Universitario Puerta de Hierro, Calle Joaquin Rodrigo 1, 28222 Madrid, Spain
[j] Queen's University, 90 University Ave, Kingston, Ontario K7L 3N9, Canada
[k] Országos Korányi Pulmonológiai Intézet, 1121 Korányi Frigyes Út 1, Budapest, Hungary
[l] Ascension Saint Agnes Hospital, 900 S Caton Ave, Baltimore, MD 21229, USA
[m] University of Colorado School of Medicine, 13001 E 17th Pl, Aurora, CO 80045, USA
[n] Centre Integré de Cancérologie de la Montérégie, Université de Sherbrooke, 3120 boulevard Taschereau, Greenfield Park, Québec J4V 2H1, Canada
[o] Merck & Co., Inc., 126 E Lincoln Ave, Rahway, NJ 07065, USA
[p] GRAIL LLC, 1525 Obrien Dr, Menlo Park, CA 94025, USA
[q] Jász-Nagykun-Szolnok County Hospital, 5000 Tószegi út 21, Szolnok, Hungary

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ABSTRACT

Background: First-line pembrolizumab plus chemotherapy has shown clinical benefit in patients with metastatic non–small cell lung cancer (NSCLC) regardless of tissue tumor mutational burden (tTMB) status. Blood tumor mutational burden (bTMB), assessed using plasma-derived circulating tumor DNA (ctDNA), may be a surrogate for tTMB. The KEYNOTE-782 study evaluated the correlation of bTMB with the efficacy of first-line pembrolizumab plus chemotherapy in NSCLC.

Methods: Previously untreated patients with stage IV nonsquamous NSCLC received pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 and investigator's choice of carboplatin area under the curve 5 mg/mL/min or cisplatin 75 mg/m^2 for 4 cycles, then pembrolizumab plus pemetrexed for ≤31 additional cycles every 3 weeks. Study objectives were to evaluate the association of baseline bTMB with objective response rate (ORR) (RECIST v1.1 by investigator assessment; primary), progression-free survival (PFS; RECIST v1.1 by investigator assessment), overall survival (OS), and adverse events (AEs; all secondary). A next-generation sequencing assay (GRAIL LLC) with a ctDNA panel that included lung cancer-associated and immune gene targets was used to measure bTMB.

Results: 117 patients were enrolled; median time from first dose to data cutoff was 19.3 months (range, 1.0–35.5). ORR was 40.2 % (95 % CI 31.2–49.6 %), median PFS was 7.2 months (95 % CI 5.6–9.8) and median OS was 18.1 months (95 % CI 13.5–25.6). Treatment-related AEs occurred in 113 patients (96.6 %; grade 3–5, $n = 56$ [47.9 %]). Of patients with evaluable bTMB ($n = 101$), the area under the receiver operating characteristics curve for

* Corresponding author at: Sheba Medical Center–Tel Hashomer, Ramat Gan, Israel.
E-mail address: bar.jair@gmail.com (J. Bar).
[1] Current affiliation: Curve Biosciences, 319 N Bernardo Ave, Mountain View, CA, USA.

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continuous bTMB to discriminate response was 0.47 (95 % CI 0.36–0.59). Baseline bTMB was not associated with PFS or OS (posterior probabilities of positive association: 16.8 % and 7.8 %, respectively).
Conclusions: AEs were consistent with the established safety profile of first-line pembrolizumab plus chemotherapy in NSCLC. Baseline bTMB did not show evidence of an association with efficacy.

1. Introduction

Somatic tumor mutational burden (TMB) may result in the formation of neoantigens that increase the likelihood of tumor cell recognition by infiltrating immune cells and has shown predictive value of response to immunotherapy agents that promote T-cell activation [1]. TMB assessed using tissue (tTMB) is predictive of response to pembrolizumab monotherapy in advanced solid tumors, including nonsquamous non–small cell lung cancer (NSCLC), with response enrichment in high tTMB (cutoff $\geq$ 175 mutations/exome using whole exome sequencing; equivalent to $\geq$ 10 mutations/megabase on the clinically validated FoundationOne® CDx) [1–3]. Blood TMB (bTMB) assessed using plasma-derived circulating tumor DNA (ctDNA) may be a more accessible surrogate for tTMB and allow for early biomarker detection and identification of patients with high TMB eligible for programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/L1) inhibitors.

In the phase 3 KEYNOTE-189 study, first-line pembrolizumab plus platinum-based chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) compared to chemotherapy with a manageable adverse event (AE) profile in metastatic NSCLC with up to 5-years follow-up [4]. In exploratory analyses of KEYNOTE-189, tTMB was not correlated with efficacy [5]. bTMB was also not consistently correlated with efficacy; however, samples for bTMB assessment were only available in 38 % of patients from the study [6].

The phase 2 KEYNOTE-782 study was designed to prospectively evaluate the correlation of bTMB with the efficacy of first-line pembrolizumab plus platinum-based chemotherapy in patients with metastatic nonsquamous NSCLC, and hence to confirm the exploratory TMB findings from KEYNOTE-189.

2. Methods

2.1. Study design and patients

KEYNOTE-782 (NCT03664024) was a multicenter, single-arm phase 2 study. Eligible patients had histologically or cytologically confirmed stage IV nonsquamous NSCLC (per the American Joint Committee on Cancer 8th edition); measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and were ineligible for epidermal growth factor receptor- (EGFR), V-raf murine sarcoma viral oncogene homolog B (BRAF)-, c-ros oncogene 1 (ROS1)- or anaplastic lymphoma kinase (ALK)-directed therapy. All patients had not received prior systemic therapy for advanced/metastatic NSCLC. Patients who received adjuvant or neoadjuvant systemic therapy that was completed $\geq$ 12 months prior to development of metastatic disease were eligible to participate in the study.

All patients received pembrolizumab 200 mg IV every 3 weeks (Q3W), pemetrexed 500 mg/m^2 Q3W and 4 cycles of the investigator's choice of carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2. Treatment with pembrolizumab and pemetrexed was continued for $\leq$ 35 cycles until unacceptable toxicity, progressive disease or withdrawal from the study. Treatment with maintenance pemetrexed could continue at the investigator's discretion. After completion of the study, patients could enroll in an extension study (NCT03486873) and could receive additional pembrolizumab as part of their maintenance regimen. Discontinuation of treatment could also be considered for patients who attained a confirmed complete response (CR) and received $\geq$ 8 cycles of pembrolizumab, including $\geq$ 2 administrations given with platinum-based chemotherapy, and $\geq$ 80 % of the planned doses (35 cycles) of pemetrexed after initial CR.

The study protocol and all amendments were approved by the institutional review board or ethics committee at each institution. The study was conducted in accordance with the protocol and its amendments, the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local and national regulations. All patients provided written informed consent.

2.2. Assessments

Baseline bTMB in ctDNA from cell-free DNA (cfDNA; extracted from plasma obtained prior to treatment initiation) was assessed retrospectively using a next-generation sequencing assay with a 1.9 megabase, 654-gene cancer panel, which included specific lung cancer–associated and immune gene targets (GRAIL LLC, Menlo Park, CA) [7]. Paired white blood cell genomic DNA sequencing was also performed to eliminate potential clonal hematopoiesis-derived somatic mutations and germline variants present in cfDNA from bTMB calculation. An analysis pipeline was implemented to enable detection of mutations at low allele fraction by suppressing noise caused by assay and alignment processes. This pipeline included a joint cfDNA/white blood cell DNA variant machine learning model that enabled accounting for clonal hematopoiesis of indeterminate potential and other artifacts. bTMB was calculated as the number of nonsynonymous mutations per megabase pair of genome sequenced [7].

Tumor response was assessed at baseline, week 6 and week 12 from treatment initiation, every 9 weeks until week 48, and every 12 weeks thereafter by computed tomography (CT) or by MRI when CT was contraindicated. AEs were reported through 30 days after treatment discontinuation (90 days for serious AEs or 30 days if new anticancer therapy was initiated). AEs were assessed according to the NCI Common Terminology Criteria for Adverse Events, v4.0.

2.3. Objectives

The primary objective was to evaluate the association of baseline bTMB (on a continuous scale) with objective response rate (ORR) per RECIST v1.1 by investigator assessment. Secondary objectives were to evaluate the association of baseline bTMB with PFS per RECIST v1.1 by investigator, OS and safety/tolerability of pembrolizumab plus platinum-based chemotherapy.

2.4. Statistical analysis

Efficacy and safety were assessed in all patients who received $\geq$ 1 dose of study treatment. Logistic regression modeling of responders (complete response or partial response) and nonresponders were used to estimate the level of association between baseline bTMB and ORR. A Bayesian logistic regression model of ORR adjusted for ECOG PS was used to estimate the posterior probability (based on 10,000 sets of model parameters) that the model coefficient for bTMB was $>$ 0. The association of bTMB with ORR was also evaluated using the area under the receiver operating characteristics curve (AUROC). Bayesian Weibull regression models of PFS and OS adjusted for ECOG PS were used to estimate the posterior probability that the model coefficients for bTMB were $<$ 0.

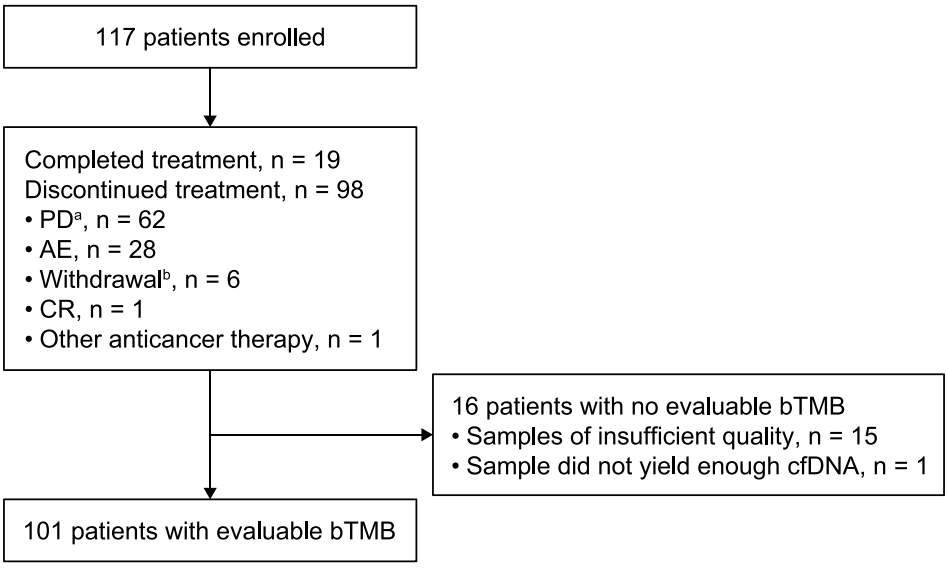

Fig. 1. Patient disposition. AE = adverse event. Abbreviations: bTMB = blood tumor mutational burden. cfDNA = cell-free DNA. CR = complete response. PD = progressive disease. [a]Either PD or clinical progression. [b]Withdrawal from the study by physician or patient decision.

3. Results

3.1. Patients

Between October 30, 2018, and November 5, 2021, 117 patients were enrolled and received ≥ 1 dose of pembrolizumab plus platinum-based chemotherapy. Median time from first dose to data cutoff was 19.3 months (range, 1.0–35.5). At the data cutoff, 19 patients (16.2 %) had completed treatment and 98 patients (83.8 %) had discontinued treatment (Fig. 1). Of the 117 patients enrolled, 101 patients (86.3 %) had evaluable bTMB data (Table 1; Fig. 1).

3.2. Efficacy and association with bTMB

The ORR was 40.2 % (95 % CI 31.2–49.6) (Table 2). Median PFS and OS were 7.2 (95 % CI 5.6–9.8) and 18.1 months (95 % CI 13.5–25.6), respectively. In the bTMB-evaluable population, the posterior probability of a positive association of baseline bTMB with ORR was 22.5 % and the AUROC for discriminating response by baseline bTMB was 0.47 (95 % CI 0.36–0.59) (Fig. 2A). The distribution of baseline bTMB was similar among responders and nonresponders (Fig. 2B). The posterior probability of a positive association of baseline bTMB with PFS and OS was 16.8 % and 7.8 %, respectively.

Table 1
Patient characteristics.

	Pembrolizumab + Chemotherapy, *N* = 117	Pembrolizumab + Chemotherapy (biomarker evaluable), *n* = 101
Male	71 (60.7)	64 (63.4)
Age, median (range), years	64.0 (37–85)	64.0 (37–85)
ECOG PS		
0	36 (30.8)	35 (34.7)
1	81 (69.2)	66 (65.3)
Smoking status[a]		
Never	12 (10.3)	10 (9.9)
Former/Current	101 (86.3)	87 (86.1)
Brain metastasis present	9 (7.7)	7 (6.9)
Platinum chemotherapy		
Cisplatin	36 (30.8)	34 (33.7)
Carboplatin	81 (69.2)	67 (66.3)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status.
All data are *n* (%) unless otherwise specified.
[a] Smoking status was unknown for 4 patients (3.4%) in the overall population.

3.3. Safety

Treatment-related AEs occurred in 113 patients (96.6 %) (Table 2). The most common (≥20 %) treatment-related AEs were anemia (53.0 %), neutropenia (25.6 %), and nausea (23.9 %) (Table S1). Grade 3–5 treatment-related AEs occurred in 56 patients (47.9 %), most commonly (≥10 %) anemia (16.2 %) and neutropenia (11.1 %) (Table S1); 8 patients (6.8 %) died due to a treatment-related AE (Table S1). Immune-

Table 2
Efficacy and adverse event summary.

	Pembrolizumab + Chemotherapy, *N* = 117
Efficacy	
ORR, % (95 % CI)[a]	40.2 (31.2–49.6)
CR, *n* (%)	6 (5.1)
PR, *n* (%)	41 (35.0)
PFS, median (95 % CI), months[a]	7.2 (5.6–9.8)
OS, median (95 % CI), months	18.1 (13.5–25.6)
Adverse events, *n* (%)	
Any	117 (100)
Grade 3–5	80 (68.4)
Serious	60 (51.3)
Led to discontinuation	45 (38.5)
Led to death	14 (12.0)
Treatment-related AE[b]	113 (96.6)
Grade 3–5	56 (47.9)
Serious	25 (21.4)
Led to discontinuation	33 (28.2)
Led to death	8 (6.8)

Abbreviations: AE = adverse event. CR = complete response. PFS = progression-free survival. PR = partial response. RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1. ORR = objective response rate. OS = overall survival.
[a] CR or PR per RECIST v1.1. by investigator assessment.
[b] Determined by the investigator to be related to study treatment.

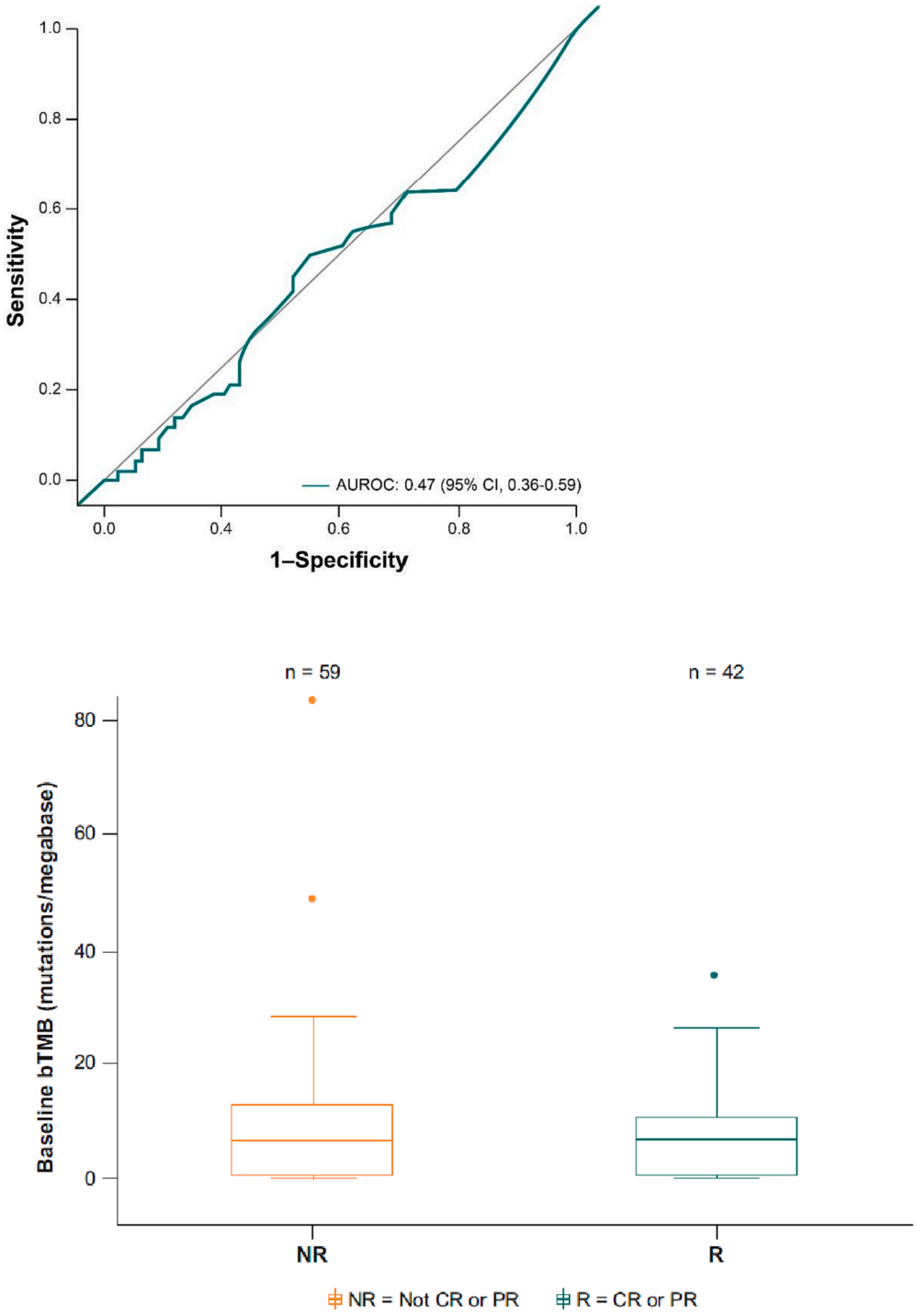

Fig. 2. (A) Baseline bTMB area under the receiver operating characteristics curve for association with objective response rate and (B) baseline bTMB by confirmed objective response. Abbreviations: bTMB = blood tumor mutational burden. NR = nonresponder. R = responder.

mediated AEs and infusion reactions occurred in 34 patients (29.1 %) (Table S2).

4. Discussion

In this single-arm study of patients with metastatic nonsquamous NSCLC treated with pembrolizumab plus platinum-based chemotherapy, efficacy and safety were similar to previous reports [4]. Baseline bTMB was successfully assessed in 86.3 % of patients; baseline bTMB was not associated with efficacy.

In previous reports, TMB was predictive of response to PD-1/L1 inhibitor monotherapy or combination immunotherapy [8,9] but not to PD-1/L1 inhibitor plus chemotherapy in NSCLC [2,3]. In a post hoc retrospective analysis of the KEYNOTE-010 and KEYNOTE-042 trials of patients with previously treated and previously untreated PD-L1–positive NSCLC, tTMB was significantly associated with ORR, PFS and OS with pembrolizumab monotherapy but not chemotherapy [2]. A trend of correlation between high bTMB and improved efficacy with PD-1/L1 inhibitor monotherapy or combination immunotherapy has been observed in previously untreated metastatic NSCLC across several studies, including the B-F1RST and B-FAST studies of atezolizumab [8–10]. In an exploratory analysis of KEYNOTE-189, bTMB was

significantly associated with PFS, but not with ORR and OS, for pembrolizumab plus platinum-based chemotherapy [5]. The KEYNOTE-782 study is not directly comparable to KEYNOTE-189 because of differences in study design and the assay used to analyze bTMB. For example, KEYNOTE-782 was a single-arm prospective study and excluded patients who had tumors with *BRAF* and *ROS-1*mutations, whereas KEYNOTE-189 was a retrospective study with an active comparator arm and allowed patients who had tumors with *BRAF* and *ROS-1* mutations [4]. Also, a lung cancer-associated and immune gene panel (GRAIL LLC) was used to assess bTMB in this study compared with the Guardant Health Omni assay used to assess bTMB in KEYNOTE-189 [6]. Generally, the results of this study are similar to those from KEYNOTE-189, suggesting limited relationships between bTMB and efficacy in metastatic nonsquamous NSCLC patients treated with first-line pembrolizumab plus chemotherapy.

This analysis was the first to prospectively evaluate the association of bTMB and clinical outcomes with pembrolizumab plus platinum-based chemotherapy. Although a tissue-based assay remains the standard, a blood-based assessment of TMB may have clinical utility as a more accessible way for identifying patients likely to respond to immunotherapy combinations. However, our results suggest that bTMB does not have predictive value for efficacy with pembrolizumab plus platinum-based chemotherapy.

Most cfDNA-based assays target a small panel of genes or hotspot mutations in key cancer genes and do not incorporate matched white blood cell sequencing to eliminate potential clonal hematopoiesis-derived somatic mutations and germline variants present in cfDNA. The cfDNA sequencing assay used in this study covered a large genomic region based on a joint analysis of cfDNA and white blood cell DNA, allowing for robust detection of somatic mutations and mitigating sequencing errors [7]. With use of this state-of-the-art assay, the results for the association between bTMB and clinical outcomes in KEYNOTE-189 were confirmed and the possibility that clonal hematopoiesis interfered with the previous bTMB analyses was ruled out. Importantly, mutations vary in their potential to direct the formation of neoantigens, and if formed, their potential to be presented by the major histocompatibility complex and to activate cytotoxic T cells. At present, these factors are not taken into consideration during bTMB evaluation.

In summary, baseline bTMB, assessed using a next-generation sequencing ctDNA panel that included lung cancer-associated and immune gene targets, was not associated with efficacy with first-line pembrolizumab plus platinum-based chemotherapy in nonsquamous NSCLC. The safety profile of pembrolizumab plus platinum-based chemotherapy was generally consistent with its established safety profile.

CRediT authorship contribution statement

Jair Bar: Investigation, Data curation, Writing – review & editing. **Emilio Esteban:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Delvys Rodríguez-Abreu:** Formal analysis, Validation, Writing – review & editing. **Santiago Ponce Aix:** Formal analysis; Writing - review & editing. **Zsuzsanna Szalai:** Writing – review & editing. **Enriqueta Felip:** Data curation, Writing – review & editing. **Maya Gottfried:** Writing – review & editing. **Mariano Provencio:** Data curation, Formal analysis, Validation, Writing – review & editing. **Andrew Robinson:** Data curation, Validation, Writing – review & editing. **Andrea Fülöp:** Writing – review & editing. **Suman Bannur Rao:** Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **D. Ross Camidge:** Formal analysis, Validation, Writing – review & editing. **Giovanna Speranza:** Validation, Writing – review & editing. **Steven M. Townson:** Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Julie Kobie:** Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Mark Ayers:** Conceptualization, Writing – review & editing. **E.J. Dettman:** Formal analysis, Validation, Writing – review & editing. **Nathan Hunkapiller:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Robert McDaniel:** Writing – review & editing. **Byoungsok Jung:** Conceptualization, Data curation, Validation, Writing – review & editing. **David Burkhardt:** Conceptualization, Formal analysis, Validation, Writing – review & editing. **Ruth Mauntz:** Writing – review & editing. **Tibor Csőszi:** Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **J. B.** reports advisory roles with AbbVie, AstraZeneca, Bayer, BMS, Causalis, Merck Serono, MSD, Novartis, Roche, and Takeda and receiving research funding from Immunai, OncoHost, MSD, and AstraZeneca. **D.R. A.** reports personal fees/honoraria for consultancy or advisory roles and lectures from Roche, Genentech, AstraZeneca, Bristol Myers Squibb, Boehringer Ingleheim, MSD, Merck Serono, Eli Lilly, Gilead, Sanofi, Regeneron, Incyte, Pfizer, Takeda, and Novartis; and travel expenses from Roche, Bristol Myers Squibb, MSD, Sanofi, Regeneron, and Novartis. **E.F.** reports personal fees or honoraria for advisory roles from Abbvie, Amgen, AstraZeneca, Bayer, Bergen Bio, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffman-La Roche, GSK, Janssen, Merck Serono, MSD, Novartis, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, and Turning Point; speaker's bureau fees from Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, F. Hoffman-La Roche, Janssen, Medical Trends, Medscape, Merck Serono, MSD, Peervoice, Pfizer, Sanofi, Takeda, and Touch Oncology; and independent board membership with Grifols. **M.P.** reports lecture fees, honoraria, or other fees from Bristol Myers Squibb, Roche, MSD, AstraZeneca, Takeda, Eli Lilly and Company, F. Hoffman-La Roche, Janssen, and Pfizer; and research funds from MSD, AstraZeneca, Roche, Boehringer Ingleheim, and Bristol Myers Squibb. **D.R.C.** reports lecture fees, honoraria or other fees from Roche and AstraZeneca. **S.M.T**, **J.K.**, and **E.J.D.** report employment with MSD. **M.A.** reports employment and stock ownership with MSD. **N.H.** reports advisory or consultancy roles and stock ownership with Curve Biosciences. **R.Mc.** and **B.J.** report employment with Grail LLC. **R.Ma** reports employment with Grail LLC and stock ownership with Illumina. **D.B.** reports employment with GRAIL LLC and stock ownership with Illumina. **E.E.**, **S.P.A.**, **M.G.**, **A.R.**, **A.F.**, **S.B.R.**, **G. S.**, **T.C.** have no conflicts of interest to disclose.

Data availability.

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated

to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Ethics Statement

Approval of the research protocol by an Institutional Reviewer Board: This study was approved by the institutional review board of each participating institution. The study was conducted in accordance with the protocol, its amendments, the ethical principles originating from the Declaration of Helsinki, and Good Clinical Practice guidelines. Written informed consent was provided by all patients before enrolment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107506.

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