1-1-2022

Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non-Small Cell Lung Cancer: Results From the Randomized OAK Trial

Shirish M. Gadgeel
Henry Ford Health, sgadgee1@hfhs.org

Fred R. Hirsch

Keith Kerr

Fabrice Barlesi

Keunchil Park

See next page for additional authors

Recommended Citation

Gadgeel S, Hirsch FR, Kerr K, Barlesi F, Park K, Rittmeyer A, Zou W, Bhatia N, Koeppen H, Paul SM, Shames D, Yi J, Matheny C, Ballinger M, McCleland M, and Gandara DR. Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non-Small Cell Lung Cancer: Results From the Randomized OAK Trial. Clin Lung Cancer 2022; 23(1):21-33.

Authors

Shirish M. Gadgeel, Fred R. Hirsch, Keith Kerr, Fabrice Barlesi, Keunchil Park, Achim Rittmeyer, Wei Zou, Namrata Bhatia, Hartmut Koeppen, Sarah M. Paul, David Shames, Jing Yi, Christina Matheny, Marcus Ballinger, Mark McCleland, and David R. Gandara

Comparison of SP142 and 22C3 Immunohistochemistry PD-L1 Assays for Clinical Efficacy of Atezolizumab in Non–Small Cell Lung Cancer: Results From the Randomized OAK Trial

Shirish Gadgeel,[1] Fred R. Hirsch,[2] Keith Kerr,[3] Fabrice Barlesi,[4] Keunchil Park,[5] Achim Rittmeyer,[6] Wei Zou,[7] Namrata Bhatia,[7] Hartmut Koeppen,[7] Sarah M. Paul,[7] David Shames,[7] Jing Yi,[7] Christina Matheny,[7] Marcus Ballinger,[7] Mark McCleland,[7] David R. Gandara[8]

Abstract

It is unclear whether PD-L1 assays differ in their ability to predict clinical outcomes with checkpoint immunotherapy. This OAK analysis indicated greater survival with atezolizumab than docetaxel regardless of the assay used to determine tumor PD-L1 status (SP142 or 22C3) in a second-/third-line metastatic NSCLC population. The SP142 and 22C3 assays similarly predict atezolizumab efficacy at validated PD-L1 thresholds.

Background: This phase III OAK trial (NCT02008227) subgroup analysis (data cutoff, January 9, 2019) evaluated the predictive value of 2 PD-L1 IHC tests (VENTANA SP142 and Dako 22C3) for benefit from atezolizumab versus docetaxel by programmed death ligand 1 (PD-L1) status in patients with previously treated metastatic non–small cell lung cancer. **Methods:** PD-L1 expression was assessed prospectively with SP142 on tumor cells (TC) and tumor-infiltrating immune cells (IC) and retrospectively with 22C3 using a tumor proportion score (TPS) based on TC membrane staining. Efficacy was assessed in the 22C3 biomarker-evaluable population (22C3-BEP) (n = 577; 47.1% of SP142-intention-to-treat population) and non–22C3-BEP (n = 648) in PD-L1 subgroups (high, low, and negative) and according to selection by 1 or both assays. **Results:** In the 22C3-BEP, overall survival benefits with atezolizumab versus docetaxel were observed across PD-L1 subgroups; benefits were greatest in SP142-defined PD-L1–high (TC3 or IC3: hazard ratio [HR], 0.39 [95% confidence interval (CI), 0.25-0.63]) and 22C3-defined PD-L1–high (TPS ≥ 50%: HR, 0.56 [95% CI, 0.38-0.82]) and low (TPS, 1% to < 50%: HR, 0.55 [95% CI, 0.37-0.82]) groups. Progression-free survival improved with increasing PD-L1 expression for both assays. SP142 and 22C3 assays identified overlapping and unique patient populations in PD-L1–high, positive, and negative subgroups. Overall survival and progression-free survival benefits

Abbreviations: CI, confidence interval; HR, hazard ratio; IC, tumor-infiltrating immune cells; IHC, immunohistochemistry; ITT, intention to treat; NSCLC, non–small cell lung cancer; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; TC, tumor cells; TPS, tumor proportion score.

[1]Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA
[2]Icahn School of Medicine, Mount Sinai, NY, USA
[3]Aberdeen Royal Infirmary, Aberdeen University Medical School, Aberdeen, Scotland
[4]Aix Marseille Universite, Assistance Publique Hôpitaux de Marseille, Marseille, France
[5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[6]Lungenfachklinik Immenhausen, Immenhausen, Germany
[7]Genentech Inc, South San Francisco, CA, USA
[8]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA

Submitted: Mar 3, 2021; Revised: May 21, 2021; Accepted: May 21, 2021; Epub: 30 May 2021

Address for correspondence: Shirish Gadgeel, MD, Henry Ford Cancer Institute/Henry Ford Health System, 2800 W Grand Blvd, Detroit, MI 48202 USA
E-mail contact: sgadgee1@hfhs.org

https://doi.org/10.1016/j.cllc.2021.05.007

favored atezolizumab over docetaxel in double PD-L1–positive and negative groups; patients with both SP142- and 22C3-positive tumors derived the greatest benefit. **Conclusions:** Despite different scoring algorithms and differing sensitivity levels, the SP142 and 22C3 assays similarly predicted atezolizumab benefit at validated PD-L1 thresholds in patients with non–small cell lung cancer.

Clinical Lung Cancer, Vol. 23, No. 1, 21–33 © 2021 The Authors. Published by Elsevier Inc.

Keywords: Programmed death ligand 1, Inter-assay concordance, Progression-free survival, Overall survival, Biomarker-evaluable population

Introduction

Docetaxel was a long-standing standard of care for the second- or third-line treatment of advanced non–small cell lung cancer (NSCLC) based on improved overall survival (OS) in controlled phase III studies.[1-3] The introduction of checkpoint inhibitors targeting the programmed death ligand 1 (PD-L1)/programmed death 1 (PD-1) pathway has dramatically altered the management of NSCLC, with shown OS benefits in patients with advanced disease, both in first and subsequent lines of therapy.[4] The immune checkpoint protein PD-L1 is expressed on tumor cells (TC) and tumor-infiltrating immune cells (IC) and can facilitate suppression of anticancer immune mechanisms by binding to the PD-1 and B7.1 receptors.[5-7] The humanized engineered IgG1 monoclonal antibody atezolizumab blocks the binding of PD-L1 to its receptors PD-1 and B7.1, thus restoring tumor-specific immunity.[6,8]

The phase III OAK trial in a population of patients receiving second- or third-line treatment for NSCLC showed improved survival with atezolizumab versus docetaxel regardless of PD-L1 expression on TC or IC, as identified using the VENTANA PD-L1 SP142 immunohistochemistry (IHC) assay.[9,10] Among patients with advanced NSCLC, atezolizumab improved median OS compared with docetaxel, both in the primary analysis based on the first 850 patients enrolled (intention-to-treat [ITT] population; data cutoff, July 7, 2016: hazard ratio [HR], 0.73 [95% confidence interval (CI), 0.62-0.87]; $P = .0003$) and in the final analysis of 1225 patients (SP142-ITT1225; data cutoff, January 9, 2019: HR, 0.78 [95% CI, 0.68-0.89]; $P < .0001$).[9-11] In the OAK study, OS favored atezolizumab over docetaxel across PD-L1–positive subgroups, with patients who had PD-L1–high tumors (TC3 or IC3) deriving the greatest OS benefit (HR, 0.41 [95% CI, 0.27-0.64]).[10] OS improvement with atezolizumab versus docetaxel was also shown in patients with PD-L1–negative tumors (TC0 and IC0) (HR, 0.75 [95% CI, 0.59-0.96]).[10] Based on these findings, atezolizumab has been approved as a second- or later-line treatment for patients with metastatic NSCLC.[12]

Multiple PD-L1 IHC assays incorporating alternative antibody clones (eg, SP263, 22C3, and 28-8) and scoring criteria different from those of the SP142 assay have been clinically validated as companion diagnostics for PD-L1/PD-1 inhibitors.[13-15] For NSCLC, the SP263, 22C3, and 28-8 assays are used to measure PD-L1 expression specifically on TC, as opposed to the SP142 assay, which measures PD-L1 expression on both TC and IC. Notably, for other tumor types, the 22C3 assay has been modified to include both TC and IC measurement in a combined positive score.[16-20] Numerous analytical comparisons of these assays have been performed in efforts to harmonize the NSCLC PD-L1 testing landscape, and results from key studies, such as the Blueprint PD-L1 IHC Assay Comparison Project, suggest that the TC-based assays generally show high analytical concordance, whereas SP142 was less sensitive for both TC and IC staining.[21-24] However, the comparative clinical sensitivity of IHC assays at validated PD-L1 cutoffs has not been extensively investigated in patients with NSCLC after treatment.

The aim of the study was to evaluate the predictive value of 2 PD-L1 IHC tests for benefit from atezolizumab therapy in patients with metastatic NSCLC treated with atezolizumab or docetaxel from the OAK trial, in particular the VENTANA SP142 and Dako 22C3 IHC assays, which have different characteristics with respect to TC and IC staining.

Materials and Methods

Patients and Treatment

OAK was a randomized, open-label, international, phase III study assessing the efficacy and safety of atezolizumab versus docetaxel in 1225 patients with metastatic NSCLC (NCT02008227). Detailed patient eligibility criteria and study methodology have been described previously for the primary and final analyses.[9-11] Briefly, eligible adult patients had squamous or nonsquamous NSCLC, measurable disease per Response Evaluation Criteria in Solid Tumors and an Eastern Cooperative Oncology Group performance status of 0 or 1.

Patients were randomly assigned (1:1) to receive either atezolizumab 1200 mg or docetaxel 75 mg/m^2 intravenously every 3 weeks until loss of clinical benefit or disease progression, as assessed by the investigator. Continuation of atezolizumab treatment beyond disease progression was permitted if the patient was judged by the investigator to be deriving clinical benefit. Crossover from docetaxel to atezolizumab was only allowed after the primary analysis revealed benefit with atezolizumab.[9,10] The primary endpoint of the study was OS in the ITT population and the PD-L1–positive subgroup (≥ 1% PD-L1 expression [TC1/2/3 or IC1/2/3]).[10]

The study protocol was reviewed and approved by the independent ethics committees of the 208 participating sites and was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by all patients.

Immunohistochemistry Assays

Archival or fresh tumor samples (blocks or formalin-fixed paraffin-embedded slides) were prospectively centrally assessed at HistoGeneX laboratories (Antwerp, Belgium, and Naperville, IL) for PD-L1 expression using the VENTANA SP142 PD-L1 IHC assay (Ventana Medical Systems Inc). In addition, 22C3 staining was performed retrospectively using the Dako pharmDx 22C3 IHC assay (Dako North America Inc) on freshly cut tissue sections or tissue sections < 6 months old that were stored under appropriate conditions.[25,26]

Published scoring criteria for the SP142 assay were used to assess TC expressing PD-L1 as a percentage of total TC and IC expressing PD-L1 as a percentage of tumor area: (1) PD-L1 positive: TC or IC ≥ 1% (TC1/2/3 or IC1/2/3); (2) PD-L1 low: TC or IC ≥ 1% and TC < 50% and IC < 10% (TC1/2 or IC1/2); (3) PD-L1 high: TC ≥ 50% or IC ≥ 10% (TC3 or IC3, respectively); and (4) PD-L1 negative: TC and IC < 1% (TC0 and IC0, respectively).[27] For the 22C3 assay, PD-L1 status was defined by tumor proportion score (TPS) cutoff values: (1) PD-L1 positive: TPS ≥ 1%; (2) PD-L1 low: TPS of 1% to < 50%; (3) PD-L1 high: TPS ≥ 50%; and (4) PD-L1 negative: TPS < 1%.[26]

Statistical Analysis

Analyses were performed in the 22C3 biomarker-evaluable population (22C3-BEP) (comprising patients with available formalin-fixed paraffin-embedded tumor tissue slides that were sectioned within the 6-month cut slide–stability staining window[26]) and non–22C3-BEP. Kaplan-Meier estimates and corresponding medians for survival outcomes were calculated for the 22C3-BEP and SP142-ITT populations and for each assay at the predefined PD-L1 cutoff values and according to selection using both assays (patients with tumors that were double positive, double negative, and uniquely positive by both assays). Efficacy was assessed by each assay independently within the 22C3-BEP and also within the overlapping and uniquely identified patient populations. Because subgroup analyses were exploratory in nature and might potentially comprise small sample populations, HRs and 95% CIs were derived from unstratified and unadjusted Cox models in comparisons of investigator-assessed progression-free survival (PFS) and OS within evaluable populations and PD-L1 subgroups. Concordance between SP142- and 22C3-defined PD-L1 subgroups was visualized and presented descriptively using Venn diagrams.

Results

Characteristics of the OAK SP142-ITT and Biomarker Populations

Overall, 1225 patients were included in the SP142-ITT population based on a data cutoff date of January 9, 2019. Of these, 577 patients (atezolizumab, 295; docetaxel, 282), or 47.1%, of the SP142-ITT population made up the 22C3-BEP according to the availability of tumor samples within the 6-month cut slide–stability window for 22C3 analysis. The remaining 648 patients made up the non–22C3-BEP (atezolizumab, 318; docetaxel, 330). Baseline clinical and demographic characteristics were generally balanced between the treatment arms in the SP142-ITT and 22C3-BEP (Table 1). The proportions of Asian patients were markedly lower in the 22C3-BEP (atezolizumab, 3.4%; docetaxel, 5.7%) than in either the non–22C3-BEP (35.9% and 33.0%, respectively) or overall SP142-ITT population (20.2% and 20.4%, respectively), but the distribution was balanced between arms. Additionally, in the non–22C3-BEP, we observed numerically higher frequencies of *EGFR* mutations in both arms and lower baseline sum of longest diameters in the docetaxel arm relative to those in the SP142-ITT and 22C3-BEP. When defined by the SP142 assay, prevalence rates for PD-L1–positive (TC1/2/3 or IC1/2/3) subgroups were similar between the SP142-ITT population (56%)[11] and 22C3-BEP (62%) (Table 2). Negative PD-L1 expression (SP142 TC0 and IC0) was observed in 43% and 37% of tumors in the SP142-ITT population and 22C3-BEP, respectively. Prevalence rates for 22C3-defined PD-L1–positive groups according to TPS ≥ 1% or ≥ 50% were 47% and 24%, respectively, whereas 53% of patients had PD-L1–negative (TPS < 1%) tumors (Table 2).

Outcomes in the SP142-ITT and 22C3-BEP

At the data cutoff (January 9, 2019), the median follow-up was 47.7 months in the SP142-ITT population.[11] Survival analyses for atezolizumab versus docetaxel in the 22C3-BEP are shown in Figure 1 and Supplemental Figure S1. In general, survival benefits with atezolizumab relative to docetaxel were similar in the SP142-ITT population[11] and the 22C3-BEP for both OS (median OS, 12.3 vs. 8.2 months; HR, 0.65 [95% CI, 0.54-0.78]) and PFS (median PFS, 2.8 vs. 3.1 months; HR, 0.80 [95% CI, 0.67-0.95]). Less favorable benefit was observed in the non–22C3-BEP for OS (median OS, 13.8 vs. 12.4 months; HR, 0.90 [95% CI, 0.76-1.07]) and PFS (median PFS, 2.7 vs. 4.2 months; HR, 1.13 [95% CI, 0.96-1.32]) than in the BEP and ITT populations.[11]

Overall response rates (ORRs) with atezolizumab and docetaxel were 16% and 9%, respectively, in the 22C3-BEP (difference in ORR between atezolizumab and docetaxel [ΔORR], 7% [Δ95% CI, 1%-12%]); 13% and 15%, respectively, in the non–22C3-BEP (ΔORR, −2% [Δ95% CI, −8% to 3%]); and 14% and 12%, respectively, in the SP142-ITT (ΔORR, 2% [Δ95% CI, −2% to 6%]) populations (Figure 3).

Outcomes by Assay-Defined PD-L1 Subgroups

There were OS benefits with atezolizumab versus docetaxel across PD-L1 subgroups (positive, high, low, and negative expression) regardless of IHC assay in the 22C3-BEP (Figures 1A and 2). OS benefits were greatest in the group with the highest PD-L1 expression defined by the SP142 assay (TC3 or IC3: HR, 0.39 [95% CI, 0.25-0.63]) and high and low PD-L1 expression defined by the 22C3 assay (TPS ≥ 50%: HR, 0.56 [95% CI, 0.38-0.82]; TPS, 1% to < 50%: HR, 0.55 [95% CI, 0.37-0.82]). The HR point estimates for OS were higher for atezolizumab versus docetaxel in the SP142-defined PD-L1–low expression group (TC1/2 or IC1/2: HR, 0.80 [95% CI, 0.60-1.05]) and all PD-L1–negative subgroups (SP142 TC0 and IC0: HR, 0.66 [95% CI, 0.49-0.89]; 22C3 TPS < 1%: HR, 0.75 [95% CI, 0.59-0.97]). Similar trends for OS were observed across PD-L1 subgroups in the SP142-ITT population.[11]

PFS in the atezolizumab and docetaxel groups according to assay-defined PD-L1 expression are shown in Figure 1B and Supplemental Figure S2. Atezolizumab was associated with increasing PFS efficacy

Table 1 Baseline Demographics and Characteristics

Characteristic	Atezolizumab			Docetaxel		
	SP142-ITT (n = 613)	22C3-BEP (n = 295)	Non–22C3-BEP (n = 318)	SP142-ITT (n = 612)	22C3-BEP (n = 282)	Non–22C3-BEP (n = 330)
Median age (range), years	63 (25-84)	63 (25-82)	63 (33-84)	63 (34-85)	64 (34-85)	63 (34-85)
Sex, n (%)						
Male	379 (61.8)	185 (62.7)	194 (61)	379 (61.9)	175 (62.1)	204 (61.8)
Female	234 (38.2)	110 (37.3)	124 (39)	233 (38.1)	107 (37.9)	126 (38.2)
Race, n (%)						
White	438 (71.5)	253 (85.8)	185 (58.2)	432 (70.6)	235 (83.3)	197 (59.7)
Asian	124 (20.2)	10 (3.4)	114 (35.9)	125 (20.4)	16 (5.7)	109 (33)
Other[a]	51 (8.3)	32 (10.9)	19 (6)	55 (9)	31 (11)	24 (7.3)
Region, n (%)						
Asia-Pacific	121 (19.7)	7 (2.4)	114 (35.9)	112 (18.3)	6 (2.1)	106 (32.1)
Central/South America	14 (2.3)	5 (1.7)	9 (2.8)	15 (2.5)	5 (1.8)	10 (3)
Europe	318 (51.9)	172 (58.3)	146 (45.9)	300 (49)	153 (54.3)	147 (44.6)
North America	160 (26.1)	111 (37.6)	49 (15.4)	185 (30.2)	118 (41.8)	67 (20.3)
ECOG PS, n (%)						
0	221 (36.1)	110 (37.3)	111 (34.9)	234 (38.2)	98 (34.8)	136 (41.2)
1	392 (64)	185 (62.7)	207 (65.1)	378 (61.8)	184 (65.3)	194 (58.8)
History of tobacco use, n (%)						
Never	112 (18.3)	51 (17.3)	61 (19.2)	96 (15.7)	33 (11.7)	63 (19.1)
Current or previous	501 (81.7)	244 (82.7)	257 (80.8)	516 (84.3)	249 (88.3)	267 (80.9)
Histology type, n (%)						
Nonsquamous	452 (73.7)	207 (70.2)	245 (77)	452 (73.9)	192 (68.1)	260 (78.8)
Squamous	161 (26.3)	88 (29.8)	73 (23)	160 (26.1)	90 (31.9)	70 (21.2)
Liver metastases						
No	487 (79.5)	230 (78)	257 (80.8)	497 (79.6)	219 (77.7)	268 (81.2)
Yes	126 (20.6)	65 (22)	61 (19.2)	125 (20.4)	63 (22.3)	62 (18.8)
Metastatic sites, mean	2.9	3	2.9	2.9	3.1	2.8
SLD, median (range), mm	70 (10-316)	69 (10-309)	71 (10-316)	66 (10-314)	72.5 (10-240)	60 (11-314)
EGFR mutation, n (%)						
Positive	60 (9.8)	20 (6.8)	40 (12.6)	53 (8.7)	19 (6.7)	34 (10.3)
Negative	455 (74.2)	218 (73.9)	237 (74.5)	464 (75.8)	207 (73.4)	257 (77.9)
Unknown	98 (16)	57 (19.3)	41 (12.9)	95 (15.5)	56 (19.9)	39 (11.8)
EML4-ALK translocation, n (%)						
Positive	4 (0.7)	2 (0.7)	2 (0.6)	1 (0.2)	0 (0)	1 (0.3)
Negative	315 (51.4)	130 (44.1)	185 (58.2)	288 (47.1)	124 (44)	164 (49.7)
Unknown	294 (48)	163 (55.3)	131 (41.2)	323 (52.8)	158 (56)	165 (50)

Abbreviations: BEP = biomarker-evaluable population; ECOG = Eastern Cooperative Oncology Group performance status; SLD = sum of longest diameters.
[a] Other includes American Indian, Alaska Native, African American, black, Hawaiian Native, other Pacific Islander, other, multiple, and unknown.

with increasing PD-L1 expression when defined by the SP142 assay within the 22C3-BEP, with the greatest improvement observed at the highest cutoff (TC1/2 or IC1/2: HR, 0.82 [95% CI, 0.64-1.06]; TC1/2/3 or IC1/2/3: HR, 0.73 [95% CI, 0.58-0.91]; TC3 or IC3: HR, 0.50 [95% CI, 0.32-0.80]). A similar trend was observed in PD-L1 subgroups within the SP142-ITT population. Increasing PFS efficacy was also observed across 22C3-defined PD-L1 subgroups, with the greatest improvement observed at the highest cutoff (TPS, 1% to < 50%: HR, 0.77 [95% CI, 0.53-1.12]; TPS ≥ 1%: HR, 0.62 [95% CI, 0.47-0.80]; TPS ≥ 50%: HR, 0.52 [95% CI, 0.36-0.76]). No PFS improvement with atezolizumab was observed in the PD-L1–negative subgroup defined by SP142 or 22C3.

In the 22C3-BEP, ORRs with atezolizumab ranged from 9% to 27% among SP142-defined PD-L1 subgroups (TC0 and IC0 to TC3 or IC3) and from 10% to 26% across 22C3-defined PD-L1 subgroups (TPS < 1% to TPS ≥ 50%) (Figure 3). Among the 22C3-BEP, ORRs with docetaxel were similar across 22C3-defined PD-L1 subgroups (9% for all groups) and showed variation in PD-L1 subgroups defined by the SP142 assay (4%-14%).

Table 2 PD-L1 Prevalence Within the 22C3-BEP

Assay-Defined PD-L1 Subgroup, n (%)	22C3-BEP (n = 577)[a]
SP142	
TC0 and IC0	215 (37.3)
TC1/2 or IC1/2	266 (46.3)
TC1/2/3 or IC1/2/3	360 (62.4)
TC3 or IC3	94 (16.3)
22C3	
TPS < 1%	306 (53)
TPS 1% to < 50%	133 (23.1)
TPS ≥ 1%	271 (47)
TPS ≥ 50%	138 (23.9)

Abbreviations: 22C3-BEP = biomarker-evaluable population; IC = tumor-infiltrating immune cells; ITT = intention to treat; PD-L1 = programmed death ligand 1; TC = tumor cells; TPS = tumor proportion score.
[a] Analysis of PD-L1 prevalence in the TC1/2 or IC1/2 subgroup was based on an evaluable population of 575 patients.

Overall, ORRs were increased with atezolizumab versus docetaxel across PD-L1–negative (TC0 and IC0: ΔORR, 3% [Δ95% CI, −4% to 11%]), PD-L1–low (TC1/2 or IC1/2: ΔORR, 3% [Δ95% CI, −6% to 13%]), and PD-L1–high (TC3 or IC3: ΔORR, 22% [Δ95% CI, 6%-38%]) groups according to the SP142 assay in the 22C3-BEP. ORRs were also greater with atezolizumab than with docetaxel in 22C3-defined PD-L1–negative (TPS < 1%: ΔORR, 1% [Δ95% CI, −6% to 8%]), PD-L1–low (TPS, 1% to < 50%: ΔORR, 8% [Δ95% CI, −5% to 21%]), and PD-L1–high (TPS ≥ 50%: ΔORR, 17% [Δ95% CI, 4%-31%]) assays in the 22C3-BEP.

Inter-assay Concordance

Analyses of inter-assay concordance identified a proportion of overlapping and uniquely positive patients between the SP142 and 22C3 assays (Figure 4 A and B and Supplemental Figure S3). Overall, 60% (215/360) of the SP142 TC1/2/3 or IC1/2/3

Figure 3 Response in Assay-Defined PD-L1 Subgroups.
ORRs in SP142-ITT and 22C3-BEP according to PD-L1 status determined by SP142 and 22C3 assays. Delta between arms and corresponding 95% CI are shown.
Abbreviations: BEP = biomarker-evaluable population; IC = tumor-infiltrating immune cells; ITT = intention to treat; ORR = objective response rate; PD-L1 = programmed death ligand 1; TC = tumor cells; TPS = tumor proportion score.

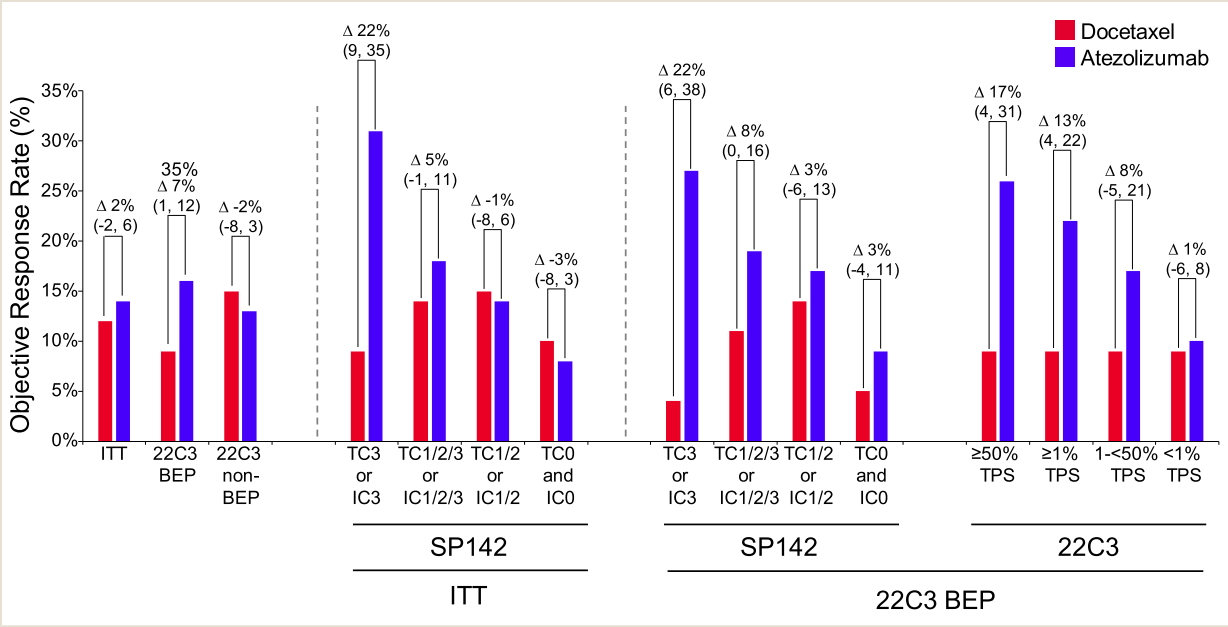
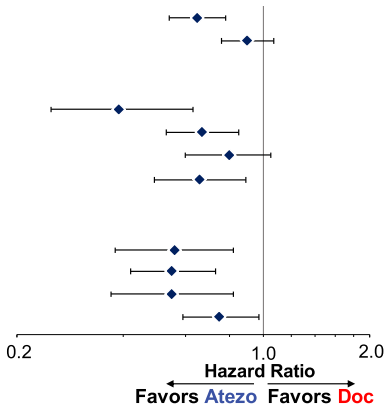


Figure 1 OS and PFS in Overall Populations and Assay-Defined PD-L1 Subgroups.
Forest plots of OS (A) and PFS (B) for atezolizumab and docetaxel in the SP142-ITT, 22C3-BEP, and non–22C3-BEP subpopulations and by SP142- and 22C3-defined PD-L1 status in the 22C3-BEP.
*OS results for atezolizumab versus docetaxel in the overall and PD-L1 subgroups in the SP142-ITT population have been previously published.[11]
Abbreviations: Atezo = atezolizumab; BEP = biomarker-evaluable population; doc = docetaxel; IC = tumor-infiltrating immune cells; ITT = intention to treat; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TC = tumor cells; TPS = tumor proportion score.

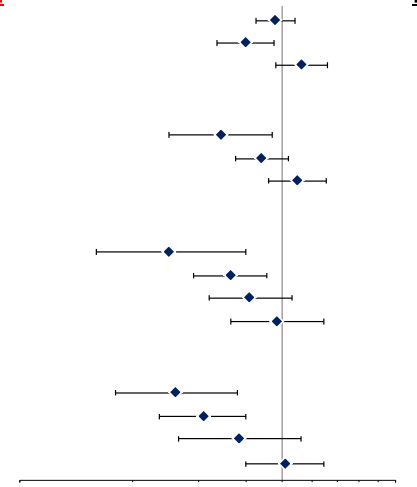
A

Subgroup*	Atezo, n	Doc, n	OS HR (95% CI)	Median OS, mo: Atezo	Median OS, mo: Doc
SP142-ITT					
22C3 BEP	295	282	0.65 (0.54-0.78)	12.3	8.2
non-22C3-BEP	318	330	0.90 (0.76-1.07)	13.8	12.4
SP142 (22C3-BEP)					
TC3 or IC3	49	45	0.39 (0.25-0.63)	20.4	8.4
TC1/2/3 or IC1/2/3	191	169	0.67 (0.53-0.85)	14.3	8.7
TC1/2 or IC1/2	142	124	0.80 (0.60-1.05)	12.3	8.8
TC0 and IC0	103	112	0.66 (0.49-0.89)	9.9	7.0
22C3 (22C3-BEP)					
TPS ≥50%	72	66	0.56 (0.38-0.82)	16.3	9.0
TPS ≥1%	141	130	0.55 (0.42-0.73)	14.9	8.4
TPS 1%–<50%	69	64	0.55 (0.37-0.82)	12.9	7.9
TPS <1%	154	152	0.75 (0.59-0.97)	10.6	7.5



B

Subgroup	Atezo, n	Doc, n	PFS HR (95% CI)	Median PFS, mo: Atezo	Median PFS, mo: Doc
SP142-ITT	613	612	0.96 (0.85-1.08)	2.7	3.8
22C3 BEP	295	282	0.80 (0.67-0.95)	2.8	3.1
non-22C3-BEP	318	330	1.13 (0.96-1.32)	2.7	4.2
SP142 (SP142-ITT)					
TC3 or IC3	89	85	0.69 (0.50-0.94)	4.2	3.4
TC1/2/3 or IC1/2/3	347	337	0.88 (0.75-1.04)	2.8	3.7
TC0 and IC0	260	271	1.10 (0.92-1.31)	2.4	4.0
SP142 (22C3-BEP)					
TC3 or IC3	49	45	0.50 (0.32-0.80)	4.14	2.8
TC1/2/3 or IC1/2/3	191	169	0.73 (0.58-0.91)	2.81	3.1
TC1/2 or IC1/2	142	124	0.82 (0.64-1.06)	2.76	3.3
TC0 and IC0	103	112	0.97 (0.73-1.29)	1.84	3.1
22C3 (22C3-BEP)					
TPS ≥50%	72	66	0.52 (0.36-0.76)	4.9	2.6
TPS ≥1%	141	130	0.62 (0.47-0.80)	3.9	2.8
TPS 1%–<50%	69	64	0.77 (0.53-1.12)	2.7	3.1
TPS <1%	154	152	1.02 (0.80-1.29)	1.7	3.3



subgroup was also considered PD-L1 positive (TPS ≥ 1%) according to the 22C3 assay. Among patients with high PD-L1–expressing tumors defined by the SP142 assay (TC3 or IC3), 64% (60/94) were also considered PD-L1 high (TPS ≥ 50%) by the 22C3 assay. In patients with tumors that had lower levels of PD-L1 expression, 31% (82/266) of the SP142 TC1/2 or IC1/2 subgroup was also considered PD-L1 low (TPS, 1% to < 50%) by the 22C3 assay.

Each assay identified a unique population of patients in the 22C3-BEP who were nonoverlapping (single positive) between the assays: 6% of the patients were defined as SP142 PD-L1 high but were not 22C3 PD-L1 high; 25% were SP142 PD-L1 positive but not 22C3 PD-L1 positive; 13% were 22C3 PD-L1 high but not SP142 PD-L1 high; and 9% were 22C3 PD-L1 positive but not SP142 PD-L1 positive (Figure 4 A and B). Of the SP142

Figure 2 **Overall Survival in Assay-Defined PD-L1 Subgroups in the 22C3-BEP.**
Kaplan-Meier plots of OS according to assay-defined PD-L1 subgroups within the 22C3-BEP: (A) PD-L1–high expression defined as SP142 TC ≥ 50% or IC ≥ 10% (TC3 or IC3) or 22C3 TPS ≥ 50%; (B) PD-L1–positive expression as SP142 TC or IC ≥ 1% (TC1/2/3 or IC1/2/3) or 22C3 TPS ≥ 1%; (C) PD-L1–low expression as SP142 TC or IC ≥ 1% and TC < 50% and IC < 10% (TC1/2 or IC1/2) or 22C3 TPS 1% to < 50%; and (D) PD-L1–negative expression as SP142 TC and IC < 1% each (TC0 and IC0) or 22C3 TPS < 1%. OS results for atezolizumab versus docetaxel in the overall and PD-L1 subgroups in the SP142-ITT population have been previously published.[11]
Abbreviations: BEP = biomarker-evaluable population; IC = tumor-infiltrating immune cells; ITT = intention to treat; OS = overall survival; PD-L1 = programmed death ligand 1; TC = tumor cells; TPS = tumor proportion score.

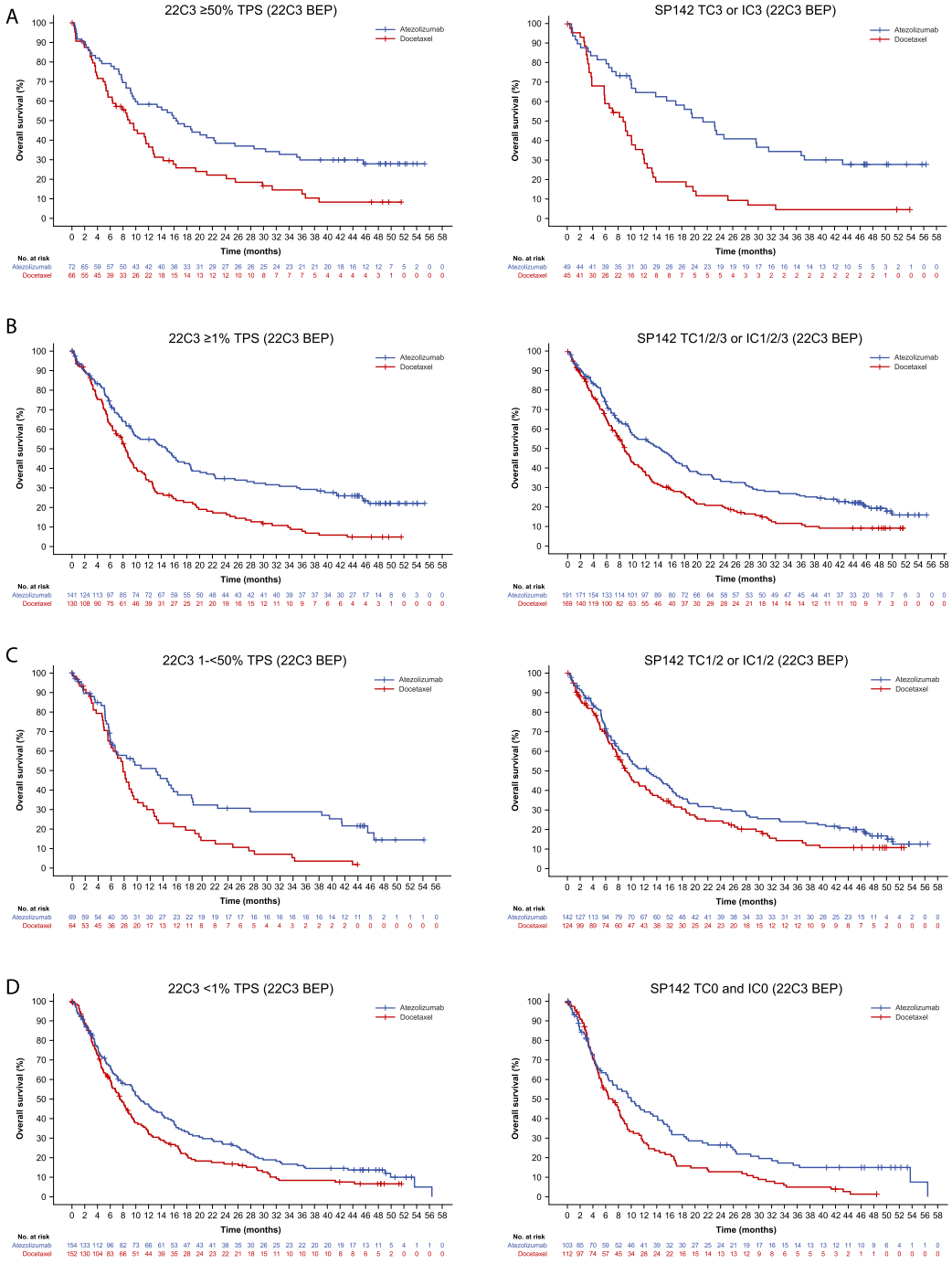
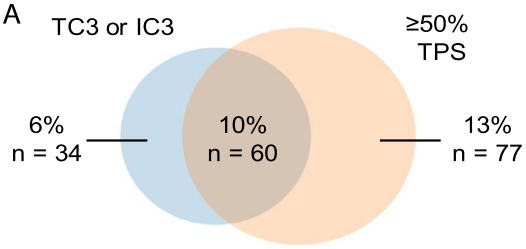


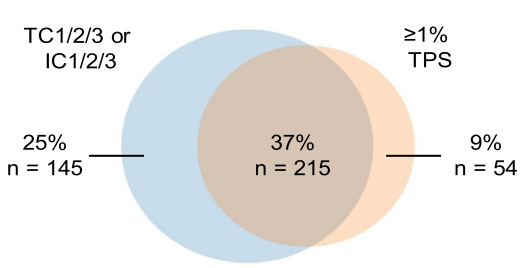
Figure 4 **Analytical Concordance Between SP142 and 22C3 Assays and Treatment Effects on Clinical Outcomes in Overlapping and Nonoverlapping PD-L1 Populations.**
Venn diagrams of the overlap between assays by PD-L1 expression status according to A) SP142 TC3 or IC3 (TC ≥ 50% or IC ≥ 10%) and 22C3 TPS ≥50% (PD-L1 high) and B) SP142 TC1/2/3 or IC1/2/3 (TC or IC ≥ 1%) and 22C3 TPS ≥ 1%; and Forest plots of OS (C) and PFS (D) in 22C3-BEP double-selected populations according to SP142 and 22C3-defined PD-L1 status.
Abbreviations: Atezo, atezolizumab; BEP = biomarker-evaluable population; CI = confidence interval; doc = docetaxel; DN = double negative; DP = double positive; HR = hazard ratio; IC = tumor-infiltrating immune cells; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed death ligand 1; SP = single positive; TC = tumor cells; TPS = tumor proportion score.

A



BEP, n = 576		22C3 TPS <50	22C3 TPS ≥50
SP142	TC0/1/2 or IC0/1/2	70% (405)	13% (77)
	TC3 or IC3	6% (34)	10% (60)

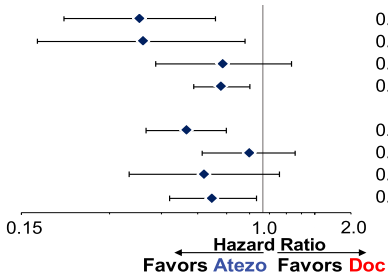
B



BEP, n = 575		22C3 TPS <1%	22C3 TPS ≥1%
SP142	TC0 and IC0	28% (161)	9% (54)
	TC1/2/3 or IC1/2/3	25% (145)	37% (215)

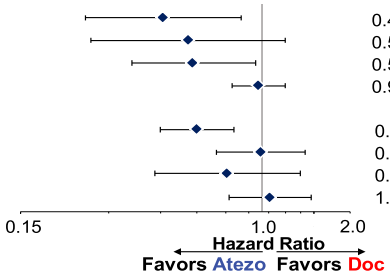
C

Subgroup	Atezo, n	Doc, n	OS HR (95% CI)	Median OS, mo Atezo	Median OS, mo Doc
22C3-BEP					
DP TC3 or IC3 AND TPS ≥50%	28	32	0.38 (0.21-0.69)	22.4	8.4
SP TC3 or IC3 AND TPS <50%	21	13	0.39 (0.17-0.87)	19.6	7.8
SP TC0/1/2 or IC0/1/2 AND TPS ≥50%	43	34	0.73 (0.43-1.25)	14.1	12.7
DN TC0/1/2 or IC0/1/2 AND TPS <50%	202	203	0.72 (0.58-0.90)	10.5	7.9
DP TC1/2/3 or IC1/2/3 AND TPS ≥1%	114	101	0.55 (0.40-0.75)	15.7	9.0
SP TC1/2/3 or IC1/2/3 AND TPS <1%	77	68	0.90 (0.62-1.29)	12.5	8.4
SP TC0 and IC0 AND TPS ≥1%	26	28	0.63 (0.35-1.14)	13.3	6.0
DN TC0 and IC0 AND TPS <1%	77	84	0.67 (0.48-0.95)	9.4	7.3



D

Subgroup	Atezo, n	Doc, n	PFS HR (95% CI)	Median PFS, mo Atezo	Median PFS, mo Doc
22C3-BEP					
DP TC3 or IC3 AND TPS ≥50%	28	32	0.46 (0.25-0.85)	4.1	2.5
SP TC3 or IC3 AND TPS <50%	21	13	0.56 (0.26-1.20)	4.1	3.0
SP TC0/1/2 or IC0/1/2 AND TPS ≥50%	43	34	0.58 (0.36-0.95)	5.1	2.7
DN TC0/1/2 or IC0/1/2 AND TPS <50%	202	203	0.97 (0.79-1.20)	2.0	3.3
DP TC1/2/3 or IC1/2/3 AND TPS ≥1%	114	101	0.60 (0.45-0.80)	4.1	2.8
SP TC1/2/3 or IC1/2/3 AND TPS <1%	77	68	0.99 (0.70-1.40)	1.7	3.1
SP TC0 and IC0 AND TPS ≥1%	26	28	0.76 (0.43-1.35)	2.1	2.1
DN TC0 and IC0 AND TPS <1%	77	84	1.06 (0.77-1.47)	1.8	3.3



uniquely identified PD-L1–high subgroup, the majority were classified as IC3 and not TC3 (Supplemental Figure S4). Likewise, most patients uniquely identified as having PD-L1–positive tumors by SP142 were classified as IC1/2/3 and not TC1/2/3 (Supplemental Figure S4). When restricting the SP142 assay scoring to TC staining only (any IC status), the 22C3 assay identified a larger proportion of patients in both the PD-L1–positive (SP142 TC1/2/3 and 22C3 TPS $\geq$ 1%) and the PD-L1–high (SP142 TC3 and 22C3 TPS $\geq$ 50%) subgroups (Supplemental Figure S5). Moreover, most SP142 TC-only defined tumors were captured within the 22C3 TPS population (Supplemental Figure S5).

Clinical Outcomes in SP142 and 22C3 Overlapping and Nonoverlapping Populations

Clinical benefit within the SP142 and 22C3 overlapping and uniquely identified subgroups were examined at the PD-L1–high and positive cutoffs (Figures 4 C and D and 5 and Supplemental Figure S6). Among PD-L1–high subgroups, there were OS benefits with atezolizumab versus docetaxel in the double-positive population with tumors defined as SP142 TC3 or IC3 and 22C3 TPS $\geq$ 50% (difference in median OS [ΔmOS], 14 months; HR, 0.38 [95% CI, 0.21-0.69]) and among SP142 uniquely positive patients with tumors identified as SP142 TC3 or IC3 and 22C3 TPS < 50% (ΔmOS, 11.8 months; HR, 0.39 [95% CI, 0.17-0.87]) (Figures 4C and 5). Reduced OS benefit with atezolizumab versus docetaxel was observed in the 22C3 uniquely positive population classified as SP142 TC0/1/2 or IC0/1/2 and 22C3 TPS $\geq$ 50% (ΔmOS, 1.4 months; HR, 0.73 [95% CI, 0.43-1.25]) and double-negative patients with tumors defined as SP142 TC0/1/2 or IC0/1/2 and 22C3 TPS < 50% (ΔmOS, 2.6 months; HR, 0.72 [95% CI, 0.58-0.90]). PFS benefits were observed with atezolizumab versus docetaxel in the SP142 TC3 or IC3/22C3 TPS $\geq$ 50% double-positive population and in SP142 uniquely positive (SP142 TC3 or IC3 and 22C3 TPS < 50%) and 22C3 uniquely positive (SP142 TC0/1/2 or IC0/1/2 and 22C3 TPS $\geq$ 50%) populations (Figure 4D and Supplemental Figure S6). No PFS differences were shown between atezolizumab and docetaxel in the double-negative PD-L1 subgroup (Figure 4D and Supplemental Figure S6).

At the PD-L1–positive cutoff, OS benefit with atezolizumab versus docetaxel was observed in the SP142 TC1/2/3 or IC1/2/3 and 22C3 TPS $\geq$ 1% double-positive population (ΔmOS, 6.6 months; HR, 0.55 [95% CI, 0.40-0.75]), 22C3 uniquely positive patients with tumors defined as SP142 TC0 and IC0 and 22C3 TPS $\geq$ 1% (ΔmOS, 7.4 months; HR, 0.63 [95% CI, 0.35-1.14]), and double-negative patients with tumors defined as SP142 TC0 and IC0 and 22C3 TPS < 1% (ΔmOS, 2.2 months; HR, 0.67 [95% CI, 0.48-0.95]) (Figures 4C and 5). Among SP142 uniquely positive patients (with tumors classified as SP142 TC1/2/3 or IC1/2/3 and 22C3 TPS < 1%), median OS was 12.5 months in the atezolizumab group and 8.4 months in the docetaxel group (ΔmOS, 4.1 months), with a HR point estimate of 0.90 (95% CI, 0.62-1.29). PFS HR point estimates for atezolizumab versus docetaxel were 0.60 (95% CI, 0.45-0.80) in the SP142 TC1/2/3 or IC1/2/3 and 22C3 TPS $\geq$ 1% double-positive population and 0.76 (95% CI, 0.43-1.35) in 22C3 uniquely positive patients (with tumors defined as SP142 TC0 and IC0 and 22C3 TPS $\geq$ 1%) (Figure 4D and Supplemental Figure S6). The double-negative and SP142 uniquely positive subgroups did not show PFS improvements with atezolizumab compared with docetaxel (Figure 4D and Supplemental Figure S6).

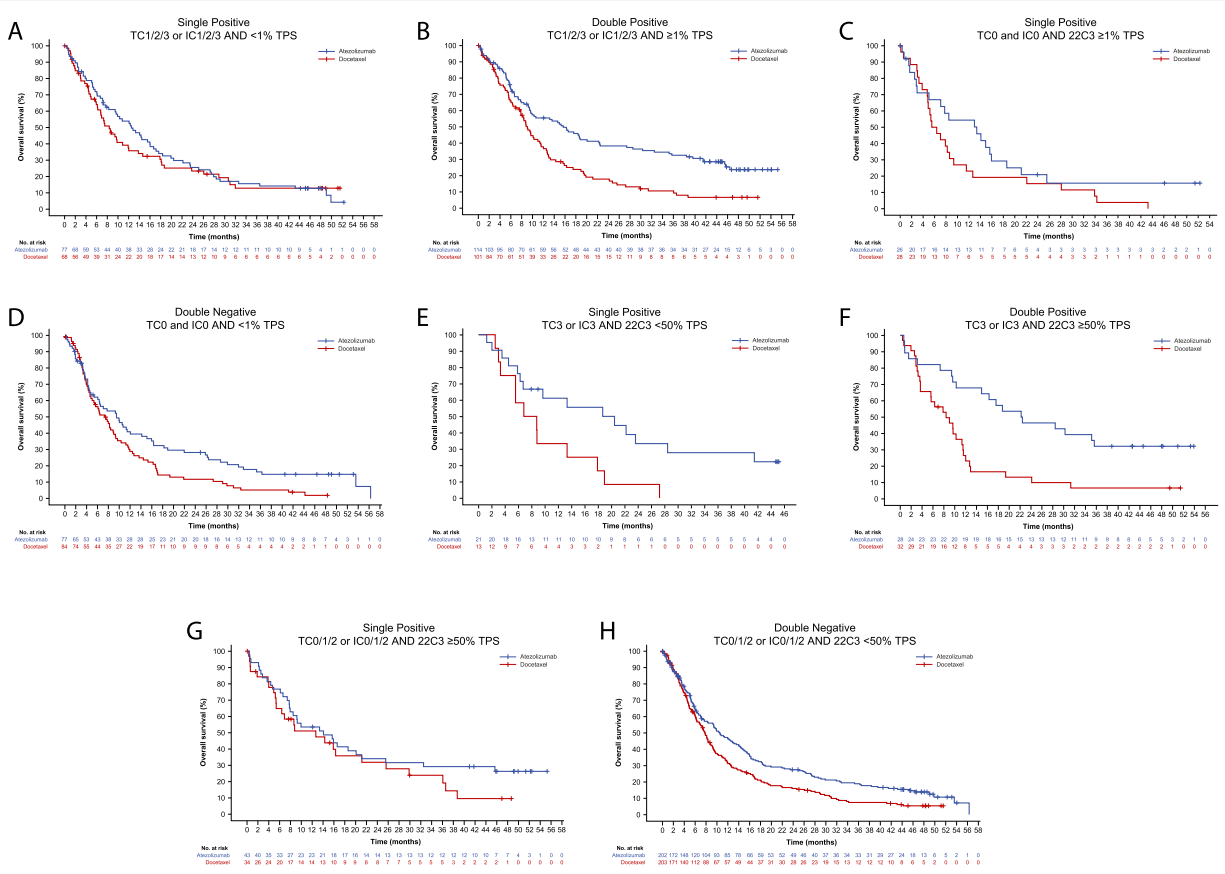
Discussion

In this retrospective exploratory analysis from the OAK trial, we compared the analytical and predictive value of the SP142 and 22C3 PD-L1 IHC assays. Despite differences in assay sensitivity and scoring algorithms, both assays were able to predict benefit from atezolizumab in the second-line setting in patients with NSCLC. Survival benefit was observed for atezolizumab over docetaxel across PD-L1 subgroups from the 22C3-BEP, including patients bearing tumors negative for PD-L1 by both assays.

Increasingly, first-line approvals of checkpoint inhibitor monotherapy and in combination chemotherapy are superseding their use in the second-line treatment setting. Atezolizumab monotherapy showed clinically meaningful OS benefit over chemotherapy in first-line NSCLC, specifically in patients with PD-L1–high tumors (TC3 or IC3) defined by the SP142 assay.[12,18,28,29,30] Likewise, pembrolizumab monotherapy showed OS benefit over chemotherapy in NSCLC populations with PD-L1–expressing tumors defined by the 22C3 assay (TPS $\geq$ 1 and TPS $\geq$ 50%).[12,18,28,29] As a result, PD-L1 testing is recommended in the first-line setting.[28,29] The finding that both the SP142 and 22C3 assays effectively predict atezolizumab benefit in these OAK subgroup analyses of a second-line NSCLC population, particularly among patients with tumors having PD-L1–high expression (TC3 or IC3 or TPS $\geq$ 50%), is relevant for informing current practice recommendations for PD-L1–based selection of checkpoint inhibitor monotherapy in the first-line setting. Indeed, while recognizing the limitations of comparing assay performance and predictive values between all-comer patients in the second-line setting and first-line PD-L1-selected populations, interim results from the NSCLC phase III IMpower110 study showed an OS benefit with first-line atezolizumab monotherapy compared with platinum-based chemotherapy among PD-L1–high patients defined by either the SP142, 22C3, or SP263 assays.[30] Such findings are supportive of the inter-assay clinical concordance presented here and highlight the clinical utility of the SP142 assay in selecting for patients deriving benefit from atezolizumab across therapy lines.

Lower sensitivity of the SP142 assay for TC and differences in staining patterns compared with 22C3 and other PD-L1 IHC assays has been previously established in the Blueprint studies, among others,[21,23,24,31] and aligns with our finding that most unique SP142-defined populations were positive for IC and not TC. Nevertheless, despite slight differences in identified patient populations between the SP142 and 22C3 assays (the SP142 assay will identify a proportion of patients who are excluded by the 22C3 assay and vice versa), the current finding of OS benefit with atezolizumab versus docetaxel in double-positive PD-L1 subgroups implies that both assays effectively select for patients who derive clinical benefit with atezolizumab. Although such studies are generally lacking, a previous report also suggests general agreement in inter-assay biomarker predictiveness for survival outcomes with immunotherapy in NSCLC. Small sample sizes within single selected subgroups preclude a definitive conclusion with respect to the predictiveness

Figure 5 **Overall Survival in 22C3-BEP Double-Selected Populations Defined by Different PD-L1 Group Combinations.**
Kaplan-Meier plots of OS in 22C3-BEP double-selected populations defined by PD-L1–positive (A-D) or high (E-H) status. PD-L1–positive expression status was defined as SP142 TC or IC ≥ 1% (TC1/2/3 or IC1/2/3) or TC ≥ 50% or IC ≥ 10% (TC3 or IC3; PD-L1 high), or as 22C3-defined TPS ≥ 1% or ≥ 50% (PD-L1 high).
Abbreviations: BEP = biomarker-evaluable population; IC = tumor-infiltrating immune cells; OS = overall survival; PD-L1 = programmed death ligand 1; TC = tumor cells; TPS = tumor proportion score.



of IC versus TC in this analysis and may prove misleading given that, by detecting PD-L1 on both TC and IC, the SP142 assay is designed to comprehensively characterize the PD-L1 status of a given tumor.[27] Indeed, analyses of NSCLC cases from atezolizumab clinical studies have shown that, although PD-L1 expression (and therefore anticancer immunity) is differentially regulated on TC and IC, PD-L1 status on both TC and IC independently predicts clinical benefit from atezolizumab.[30,32,33]

In support of the clinical utility of an assay algorithm that combines TC and IC scoring, the shown predictive value of the 22C3 combined positive score (TC/IC) has formed the basis for pembrolizumab treatment in head and neck, urothelial, gastric, esophageal, and cervical cancer as well as triple-negative breast cancer, for which PD-L1 scoring of TC alone is not adequately predictive.[16,18,20,34] Similarly, IC-driven PD-L1 selection by the SP142 assay underlies atezolizumab use in urothelial cancer and triple-negative breast cancer.[35]

Consistent with our study results, clinical trial observations support PD-L1 as a continuous biomarker for predictiveness of efficacy with immunotherapy in NSCLC, with greater benefit as PD-L1 expression levels increase.[36] This subanalysis also identified a population of patients with tumors that were PD-L1 negative by either assay who gained benefit from atezolizumab, highlighting the need to determine additional, well-characterized biomarkers to accurately select the likelihood of response to checkpoint inhibitors in the absence of detectable PD-L1 levels. Blood tumor mutational burden is a promising biomarker for selecting response to checkpoint inhibitors[37] and may be of enhanced predictive value when used in conjunction with selection for PD-L1–high expression. Notably, an analysis of the OAK and POPLAR studies reported an association between longer survival (PFS and OS) and high and low blood tumor mutational burden in PD-L1–high subgroups receiving atezolizumab.[38] Additional clinical trials, as well as utilizing novel analyses both retrospectively and prospectively, are needed to

characterize and combine new biomarkers with PD-L1 status to more accurately identify patients who would benefit from checkpoint inhibitors.

Greater survival benefits with atezolizumab versus docetaxel in 22C3-BEP relative to non–22C3-BEP is a potential limitation of the current retrospective, exploratory analysis, and results should be interpreted with caution. This appears to be the result of docetaxel overperformance in the non–22C3-BEP and may be attributed to differences in baseline prognostic factors, such as lower sum of longest diameters or demographic disparities. Only patients with available tissue blocks or slides within the 6-month cut slide–stability window were included in the 22C3-BEP; therefore, there was a significantly lower number of Asian patients. Asian countries are more likely to provide slides at enrollment instead of tissue blocks, likely resulting in time differences in cut slide stability and a lack of available tissue. Balanced proportions of Asian patients between arms and association of Asian ethnicity with a favorable disease prognosis[39] preclude a lower frequency of Asian patients as a reason for improved survival in 22C3-BEP versus non–22C3-BEP and SP142-ITT populations. It should be noted that the prevalence rates for the 22C3-defined PD-L1–positive subgroup (47%) were slightly lower than previously reported in the published literature (22C3 TPS $\geq$ 1% PD-L1 prevalence is approximately 57% of the ITT population[26,40]). This is unlikely to be explained by pre–cut slide–stability issues and epitope deterioration because samples in this study were stored and prepared in line with manufacturer instructions for the 22C3 assay.

Conclusion

This current analysis from OAK provides further support that, although each assay has a different scoring algorithm and differing levels of sensitivity, both SP142 and 22C3 assays are predictive for atezolizumab benefit at validated PD-L1 expression thresholds in patients with NSCLC. Moreover, the observed results verify the atezolizumab all-comer benefit observed in the second-line or higher NSCLC setting and inform the changing landscape of PD-L1–selected treatment in the first-line setting.

Clinical Practice Points

- The phase III OAK trial previously showed greater survival with atezolizumab than the historical standard-of-care treatment, docetaxel, in a population of patients with metastatic NSCLC receiving second- or third-line treatment regardless of tumor PD-L1 status by the VENTANA SP142 IHC assay.
- To extend knowledge on the comparative clinical sensitivities of IHC assays, this analysis of the OAK trial evaluated the SP142 and Dako 22C3 IHC assays at established PD-L1 cutoffs.
- Our results showed survival benefits with atezolizumab versus docetaxel across PD-L1–positive and negative subgroups from the 22C3-BEP.
- Overall, despite different scoring algorithms and clinical sensitivities, the SP142 and 22C3 assays similarly predict for atezolizumab efficacy at validated PD-L1 expression levels in patients with NSCLC.
- As well as confirming the all-comer benefit of atezolizumab in second-line or higher NSCLC, our findings may be of value for PD-L1–defined treatment selection in the first-line setting.

Contributors

All authors participated in the data analyses, contributed to data interpretation and the writing of the manuscript, approved the final version of the submitted manuscript, and agreed to be accountable for all aspects of the report.

S.G.: conceptualization; investigation; writing, editing and review; visualization; supervision. F.R.H.: conceptualization; writing, original draft; writing, editing and review; visualization. K.K.: conceptualization; writing, editing and review; visualization. F.B.: investigation; resources; writing, editing and review. K.P.: validation; investigation; resources; writing, editing and review; visualization; supervision. A.R.: investigation; resources; writing, editing and review. W.Z.: methodology; software; validation; formal analysis; data curation; writing, editing and review, visualization. N.B.: software; formal analysis. H.K.: formal analysis; writing, editing and review. S.M.P.: writing, editing and review. D.S.: conceptualization; writing, editing and review. J.Y.: conceptualization; methodology; investigation; writing, editing and review; supervision; funding acquisition. C.M.: data curation; writing, editing and review. M.B.: conceptualization; investigation; resources; writing, original draft; writing, editing and review; supervision; project administration; funding acquisition. M.M.: conceptualization; methodology; validation; investigation; data curation; writing, original draft; writing, editing and review; visualization; supervision. D.R.G.: conceptualization; methodology; validation; investigation; writing, editing and review; visualization; supervision; project administration.

Role of the Funding Source

This work was supported by F. Hoffmann-La Roche Ltd and Genentech Inc, a member of the Roche Group. The sponsor was involved in study design; collection, analysis and interpretation of data, and development and submission of this report. Editorial support, funded by the sponsor, was provided by an independent medical writer under the guidance of the authors.

Data Sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform at https://vivli.org/. Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, visit https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Disclosure

Dr. Gadgeel reports personal fees from Genentech/Roche, AstraZeneca, Merck, Bristol Myers Squibb, Novartis, Daichii-Sanyko, Boehringer-Ingelheim, Xcovery, Jazz Pharmaceuticals,

Pfizer, and Janssen, outside the submitted work. Dr. Hirsch reports scientific advisory board for Genentech/Roche, Merck, Bristol Myers Squibb, Novartis, AstraZeneca/Daiichi, Regeneron/Sanofi, and Amgen, outside the submitted work. Dr. Kerr reports personal fees from AbbVie, Amgen, AstraZeneca, Archer Diagnostics, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Debiopharm, Diaceutics, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, and Roche Diagnostics/Ventana, outside the submitted work. Dr. Barlesi reports personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda, outside the submitted work. Dr. Park has nothing to disclose. Dr. Rittmeyer reports grants from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Pfizer, Roche, and Novartis, outside the submitted work. Dr. Zou reports employment from Genentech, outside the submitted work. Dr. Bhatia reports employment from Genentech, outside the submitted work. Dr. Koeppen reports employment from Genentech, outside the submitted work. Dr. Paul reports employment from Genentech, outside the submitted work. David Shames reports employment from Genentech and stock ownership from Roche, outside the submitted work. Dr. Yi reports employment and spousal employment from Genentech and stock ownership from Roche, outside the submitted work. Dr. Matheny reports employment from Genentech, during the conduct of the study, and employment from Genentech, outside the submitted work. Dr. Ballinger reports employment from Genentech and stock ownership from Roche, outside the submitted work. Dr. McCleland reports employment from Genentech, outside the submitted work. Dr. Gandara reports personal fees and institutional grants from Genentech, outside the submitted work.

Acknowledgments

The authors thank the patients and the patients' families. Medical writing assistance for this manuscript was provided by Anusha Bolonna, PhD, of Health Interactions and funded by F. Hoffmann-La Roche Ltd.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2021.05.007.

References

1. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095–2103.
2. Laurie SA, Kris MG. Single-agent docetaxel (Taxotere) in the treatment of advanced non small-cell lung cancer: clinical concepts and commentary. *Clin Lung Cancer*. 2000;1(suppl 1):S5–S9.
3. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy regimens: the TAX 320 Non–Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354–2362.
4. Lim SM, Hong MH, Kim HR. Immunotherapy for non–small cell lung cancer: current landscape and future perspectives. *Immune Netw*. 2020;20:e10.
5. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol*. 2008;8:467–477.
6. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1–10.
7. Kim JM, Chen DS. Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure). *Ann Oncol*. 2016;27:1492–1504.
8. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti–PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515:563–567.
9. Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non–small cell lung cancer. *J Thorac Oncol*. 2018;13:1156–1170.
10. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non–small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255–265.
11. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab versus docetaxel in pretreated patients with NSCLC: final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials. *J Thorac Oncol*. 2021;16:140–150.
12. TECENTRIQ®. *(atezolizumab) [package insert]*. South San Francisco, CA: Genentech Inc; 2019.
13. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
14. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.
15. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non–small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830.
16. Kulangara K, Zhang N, Corigliano E, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med*. 2019;143:330–337.
17. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015–1026.
18. KEYTRUDA®. *(pembrolizumab) [package insert]*. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2020.
19. Guo H, Ding Q, Gong Y, et al. Comparison of three scoring methods using the FDA-approved 22C3 immunohistochemistry assay to evaluate PD-L1 expression in breast cancer and their association with clinicopathologic factors. *Breast Cancer Res*. 2020;22:69.
20. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo–controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396:1817–1828.
21. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. *J Thorac Oncol*. 2017;12:208–222.
22. Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non–small cell lung cancer. *JAMA Oncol*. 2017;3:1051–1058.
23. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. *J Thorac Oncol*. 2018;13:1302–1311.
24. Hendry S, Byrne DJ, Wright GM, et al. Comparison of four PD-L1 immunohistochemical assays in lung cancer. *J Thorac Oncol*. 2018;13:367–376.
25. VENTANA. *PD-L1 (SP142) assay (CE-IVD) [package insert]*. Tucson, AZ: Ventana Medical Systems Inc; 2019.
26. DAKO. *PD-L1 IHC 22C3 pharmDx assay [instructions for use]*. Carpinteria, CA: Dako North America Inc; 2018.
27. Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. *Appl Immunohistochem Mol Morphol*. 2019;27:92–100.
28. Planchard D, Popat S, Kerr K, et al. Metastatic non–small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4) iv192-237.
29. Non–small cell lung cancer. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology–v.8.2020. National Comprehensive Cancer Network [Web site].
30. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
31. Xu H, Lin G, Huang C, et al. Assessment of concordance between 22C3 and SP142 immunohistochemistry assays regarding PD-L1 expression in non–small cell lung cancer. *Sci Rep*. 2017;7:16956.
32. Kowanetz M, Zou W, Gettinger SN, et al. Differential regulation of PD-L1 expression by immune and tumor cells in NSCLC and the response to treatment with atezolizumab (anti–PD-L1). *Proc Natl Acad Sci U S A*. 2018;115:E10119–E10126.
33. Herbst RS, Kuriki H, Spigel DR. Atezolizumab for PD-L1–selected patients with NSCLC. *N Engl J Med*. 2021;384:583–585.
34. Park Y, Koh J, Na HY, et al. PD-L1 testing in gastric cancer by the combined positive score of the 22C3 PharmDx and SP263 assay with clinically relevant cut-offs. *Cancer Res Treat*. 2020;52:661–670.
35. TECENTRIQ®. *(atezolizumab) [package insert]*. South San Francisco, CA: Genentech Inc; 2020.
36. Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti–PD-1/PD-L1 immunotherapy and survival of non–small cell lung cancer patients: a meta-analysis of randomized controlled trials. *Transl Lung Cancer Res*. 2019;8:413–428.

37. Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non–small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24:1441–1448.
38. Nie W, Qian J, Xu MD, et al. A non-linear association between blood tumor mutation burden and prognosis in NSCLC patients receiving atezolizumab. *Oncoimmunology*. 2020;9.
39. Davis JS, Prophet E, Peng HL, et al. Potential influence on clinical trials of long-term survivors of stage IV non–small cell lung cancer. *JNCI Cancer Spectr*. 2019;3 pkz010.
40. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non–small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540–1550.