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Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in *KRAS*-mutated non-small cell lung cancer with *STK11, KEAP1,* or *TP53* comutations: subgroup results from the phase III IMpower150 trial

Howard Jack West ,[1] Mark McCleland,[2] Federico Cappuzzo,[3] Martin Reck,[4] Tony SK Mok,[5] Robert M Jotte,[6,7] Makoto Nishio,[8] Eugene Kim,[2] Stefanie Morris,[9] Wei Zou,[2] David Shames,[2] Meghna Das Thakur,[2] Geetha Shankar,[2] Mark A Socinski[10]

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For numbered affiliations see end of article.

Correspondence to
Dr Howard Jack West;
jackwestmd@gmail.com

ABSTRACT

Background The efficacy of atezolizumab (A) and/or bevacizumab (B) with carboplatin/paclitaxel (CP) chemotherapy was explored in the phase III, randomized IMpower150 study in patients with non-squamous non-small cell lung cancer (NSCLC) according to *KRAS* mutations (m*KRAS*) and co-occurring *STK11*, *KEAP1,* or *TP53* mutations.

Methods Mutation status was determined by circulating tumor DNA next-generation sequencing. Overall survival (OS) and progression-free survival (PFS) were analyzed in a mutation-evaluable intention-to-treat population (MEP; n=920) and SP263 (programmed cell death ligand 1 (PD-L1)) biomarker-evaluable population (n=774).

Results Within the m*KRAS* population (24.5% of MEP), ABCP showed numerical improvements vs BCP in median OS (19.8 vs 9.9 months; HR 0.50; 95% CI 0.34 to 0.72) and PFS (8.1 vs 5.8 months; HR 0.42; 95% CI 0.29 to 0.61)—greater than with ACP (OS: 11.7 vs 9.9 months; HR 0.63; 95% CI 0.43 to 0.91; PFS: 4.8 vs 5.8 months; HR 0.80; 95% CI 0.56 to 1.13) vs BCP. Across PD-L1 subgroups in m*KRAS* patients, OS and PFS were longer with ABCP vs BCP, but OS with ACP was similar to BCP in PD-L1-low and PD-L1-negative subgroups. Conversely, in *KRAS*-WT patients, OS was longer with ACP than with ABCP or BCP across PD-L1 subgroups. *KRAS* was frequently comutated with *STK11*, *KEAP1,* and *TP53*; these subgroups conferred different prognostic outcomes. Within the m*KRAS* population, *STK11* and/or *KEAP1* mutations were associated with inferior OS and PFS across treatments compared with *STK11*-WT and/or *KEAP1*-WT. In m*KRAS* patients with co-occurring m*STK11* and/or m*KEAP1* (44.9%) or m*TP53* (49.3%), survival was longer with ABCP than with ACP or BCP.

Conclusions These analyses support previous findings of mutation of *STK11* and/or *KEAP1* as poor prognostic indicators. While clinical efficacy favored ABCP and ACP vs BCP in these mutational subgroups, survival benefits were greater in the m*KRAS* and *KEAP1*-WT and *STK11*-WT population vs m*KRAS* and m*KEAP1* and m*STK11* population, suggesting both prognostic and predictive effects. Overall, these results suggest that atezolizumab combined with bevacizumab and chemotherapy is an efficacious first-line treatment in metastatic NSCLC subgroups with m*KRAS* and co-occurring *STK11* and/or *KEAP1* or *TP53* mutations and/or high PD-L1 expression.

BACKGROUND

Mutations in the Kirsten rat sarcoma viral oncogene homolog (m*KRAS*) oncogene are a major driver of nonsquamous non-small cell lung cancer (NSCLC) and occur in ≈25%–40% of patients (≈5%–10% in the Asian population), with the glycine 12 to cysteine (G12C) activating mutation demonstrating the highest prevalence.[1–4] *KRAS* is frequently comutated with the serine/threonine kinase 11 (*STK11*), kelch-like ECH associated protein 1 (*KEAP1*), and tumor protein 53 (*TP53*) tumor suppressor genes, but it is generally mutually exclusive with mutations in the epidermal growth factor receptor (*EGFR*) gene.[2–4] In patients with NSCLC, tumors bearing mutations in *STK11* (m*STK11*) and *KEAP1* (m*KEAP1*) were recently shown to be associated with poor prognosis and variable response to treatment, including immune checkpoint inhibitors (anti-programmed cell death ligand 1 (PD-L1)/programmed cell death 1 protein (PD-1)).[1–3 5] However, exploratory analysis of KEYNOTE-042 found that pembrolizumab monotherapy was associated with improved overall survival (OS) when compared with chemotherapy,

regardless of *STK11* and *KEAP1* mutational status; however, patient populations were small.[6] Combining treatments such as immune checkpoint inhibitors with chemotherapy and/or targeted therapy may overcome the challenges associated with treating NSCLC in difficult-to-treat patient groups, including those with *KRAS*-bearing tumors and comutations in *STK11* and/or *KEAP1*.[7]

Atezolizumab is a humanized engineered immunoglobulin G1 monoclonal antibody that blocks the immune checkpoint protein PD-L1 from binding to the PD-1 and B7.1 receptors, thereby restoring tumor-specific immunity.[8 9] In addition to its known antiangiogenic effects, bevacizumab's inhibition of vascular endothelial growth factor (VEGF) has immune modulatory effects, including normalization of tumor vasculature, reprogramming of the tumor microenvironment from immune-suppressive to immune-permissive, and promotion of dendritic cell maturation.[7 10–12] In combination with bevacizumab and chemotherapy, atezolizumab's T-cell-mediated cancer cell killing may be further enhanced through both reversal of VEGF-mediated immunosuppression and chemotherapy-induced cell death.[12 13] In clinical trials that combined anti-PD-L1 and anti-VEGF therapies, synergy has been observed that resulted in positive outcomes and benefits to patients over each therapy alone.[7 10 14]

The randomized, phase III IMpower150 study evaluated atezolizumab plus carboplatin/paclitaxel chemotherapy (ACP) or atezolizumab plus bevacizumab plus carboplatin/paclitaxel chemotherapy (ABCP) vs bevacizumab plus carboplatin/paclitaxel (BCP).[15 16] Among randomized patients with no *EGFR* or anaplastic lymphoma kinase (*ALK*) alterations (intention-to-treat wild-type (ITT-WT) population), ABCP was associated with significant improvements in progression-free survival (PFS) and OS compared with BCP.[15] ABCP continued to show benefit vs BCP in an updated OS analysis with an additional ≈20 months of follow-up.[17] ABCP also prolonged OS and PFS vs BCP in an exploratory subgroup analysis of patients with *EGFR*-sensitizing mutations.[16] Although studies of immune checkpoint inhibitors alone or with chemotherapy have demonstrated survival benefit in patients with m*KRAS* tumors,[6 18–20] it remains unclear how co-occurring mutations—including m*STK11*, m*KEAP1*, and m*TP53*—affect prognosis and predictive outcomes following immune checkpoint blockade. It is, therefore, imperative to determine whether differential responses to treatment and consequent effects on survival outcomes exist among patients with *KRAS*-mutant tumors harboring different combinations of comutations.

This retrospective analysis of the IMpower150 trial explored efficacy endpoints within the m*KRAS* population by PD-L1 status and by co-occurring m*STK11*, m*KEAP1*, and m*TP53* subgroups in patients with nonsquamous NSCLC in the first-line setting.

METHODS

Study design and patients

IMpower150 was an international, open-label, randomized, phase III trial of ACP or ABCP vs BCP in 1202 patients with NSCLC enrolled from 240 study centers across 26 countries (NCT02366143; figure 1A). Chemotherapy-naive patients with stage IV metastatic nonsquamous NSCLC and measurable disease at baseline per Response Evaluation Criteria in Solid Tumors V.1.1 were eligible for inclusion in the study if they also had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and available tumor tissue for biomarker testing. All patients provided written informed consent. Further detailed information on patient eligibility criteria and study design methodology were published elsewhere.[15 16]

The coprimary endpoints were PFS and OS in the ITT-WT population, which excluded patients with *EGFR* or *ALK* genomic alterations.[15] In this post hoc study, exploratory survival analyses were undertaken in the population of patients without *EGFR* or *ALK* genomic alterations (herein referred to as the ITT population) and mutation-evaluable population (MEP) from the third/final OS clinical cut-off date. PD-L1 expression was analyzed in the SP263 biomarker-evaluable population (SP263 BEP).

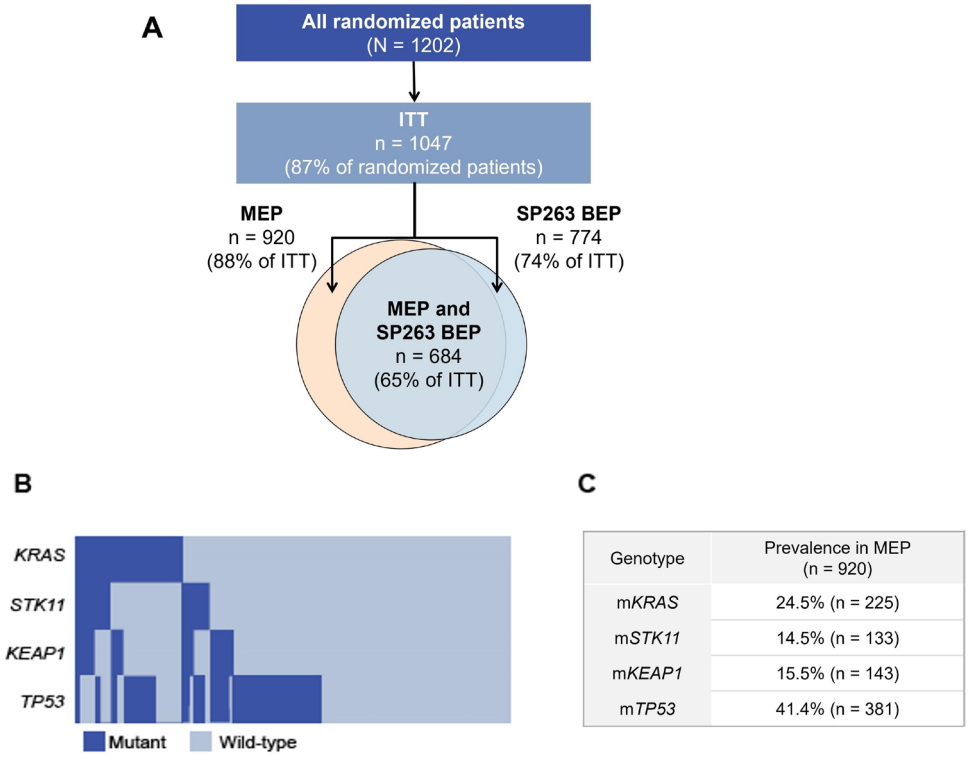
Treatment and assessments

Patients were randomized (1:1:1) to ACP, ABCP, or BCP. Induction chemotherapy was administered for four or six cycles, as determined by the investigator before randomization, every 21 days. The number of chemotherapy cycles patients actually received may have differed based on factors such as toxicities and disease progression. On day 1 of each 21-day cycle, treatments were administered intravenously as follows: 1200 mg atezolizumab; 15 mg/kg bevacizumab; area under the concentration–time curve of 6 mg/mL per minute carboplatin; and 200 mg/m^2 paclitaxel (patients of Asian ethnicity were given 175 mg/m^2). After the induction phase, patients continued bevacizumab until unmanageable toxicity or disease progression (ABCP or BCP) or atezolizumab until loss of clinical benefit (ABCP or ACP).

Key exploratory efficacy endpoints of this IMpower150 subgroup analysis were investigator-assessed PFS per Response Evaluation Criteria in Solid Tumors V.1.1 and OS. Safety was assessed in all patients who received at least 1 dose of study treatment. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0.

Investigations

The mutation status of *KRAS*, *STK11*, *KEAP1*, and *TP53* was determined by blood-based circulating tumor DNA next-generation sequencing (Foundation Medicine, Cambridge, Massachusetts, USA) from baseline plasma samples. Mutations included known, likely, and unknown



Genotype	Prevalence in MEP (n = 920)
m*KRAS*	24.5% (n = 225)
m*STK11*	14.5% (n = 133)
m*KEAP1*	15.5% (n = 143)
m*TP53*	41.4% (n = 381)

Figure 1 Overall study flow (A) and distribution (B) and prevalence (C) of mutation subpopulations in the MEP. Disposition of randomized, ITT, MEP, and SP263 BEP patient populations included in this analysis (A). Oncoplot (B) and prevalence (C) of *KRAS*, *STK11*, *KEAP1*, and *TP53* mutations in the MEP population. ITT, intention-to-treat; MEP, mutation-evaluable population; *KEAP1*, kelch-like ECH associated protein 1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; SP263 BEP, SP263 biomarker-evaluable population; *STK11*, serine/threonine kinase 11; *TP53*, tumor protein 53; WT, wild-type.

functional impact status; synonymous mutations were excluded.

For this analysis of IMpower150, PD-L1 expression in tumor cells (TC) was analyzed in archival or fresh tumor tissue by the VENTANA SP263 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA). PD-L1-positive expression was defined as staining on TC ≥1%, whereas PD-L1 high was defined as TC ≥50%.

Statistical analysis

Kaplan-Meier curves and associated medians were estimated for survival outcomes in the MEP, SP263 BEP, and mutation-defined subpopulations. For each survival comparison, HRs and corresponding 95% CIs were calculated from unstratified Cox proportional models.

RESULTS

Disposition and baseline characteristics of the ITT and MEP populations

Of the 1202 patients enrolled in IMpower150, 1047 patients were included in the ITT population (data cut-off date: September 13, 2019; figure 1A). Among the ITT population, 920 and 774 patients were included in the MEP and SP263 BEP, respectively. Of the 920 MEP patients, 684 (65% of ITT) were also deemed SP263 BEP. The median follow-up duration in the ITT population was 39.4 months.

Among MEP patients, 24.5% (n=225), 14.5% (n=133), 15.5% (n=143), and 41.4% (n=381) had m*KRAS*, m*STK11*, m*KEAP1*, and m*TP53* tumors, respectively (figure 1B,C). All mutational subgroups in the MEP are shown in online supplemental figure S1. In the MEP, G12C (9.8% of MEP), glycine 12 to aspartate (3.8%), and glycine 12 to valine (3.7%) were the most frequently occurring *KRAS* mutations. Within the m*KRAS* population, 44.9% (101/225) of m*KRAS* patients also had co-occurring mutations in *STK11* and/or *KEAP1*, and 49.3% (111/225) of m*KRAS* patients had co-occurring mutations in *TP53* (online supplemental figure S2).

Baseline characteristics were generally well balanced between treatment arms across mutation-defined patient subgroups and consistent between the MEP and ITT population (table 1). Higher ECOG PS, median baseline sum of longest diameter of target lesion, and baseline liver metastases were observed in the m*KRAS*, m*STK11*, m*KEAP1*, and m*TP53* populations compared with the overall MEP or ITT population. Smoking history was associated with m*KEAP1*, m*STK11*, and m*KRAS*. Elevated C-reactive protein levels, a poor prognostic factor, appeared highest in m*KEAP1* and m*STK11* populations compared with other mutational subgroups and overall MEP. Safety was similar between the MEP and ITT population (online supplemental table S1).

Table 1 Baseline demographics and characteristics

				m*KRAS*			m*TP53*			m*KEAP1*			m*STK11*		
	ITT	MEP	*KRAS*-WT*	ACP	ABCP	BCP	ACP	ABCP	BCP	ACP	ABCP	BCP	ACP	ABCP	BCP
N	1047	920	695	74	80	71	125	129	127	46	57	40	50	46	37
Race, n (%)															
Asian	93 (8.9)	86 (9.4)	72 (10.4)	7 (9.5)	6 (7.5)	1 (1.4)	11 (8.8)	17 (13.2)	10 (7.9)	3 (6.5)	7 (12.3)	1 (2.5)	1 (2.0)	5 (10.9)	1 (2.7)
White	894 (85.4)	780 (84.8)	584 (84.0)	64 (86.5)	68 (85.0)	64 (90.1)	105 (84.0)	107 (83.0)	109 (85.8)	42 (91.3)	49 (86.0)	35 (87.5)	46 (92.0)	38 (82.6)	32 (86.5)
Median age (range), years	63 (31–89)	63 (31–89)	63 (31–89)	63.5 (38–85)	65.5 (43–81)	62 (42–83)	62 (32–82)	63 (31–79)	63 (41–87)	65 (48–85)	62 (43–81)	62 (43–82)	65.5 (38–85)	62 (46–77)	60 (41–82)
Male, n (%)	649 (62.0)	575 (62.5)	440 (63.3)	41 (55.4)	50 (62.5)	44 (62.0)	81 (64.8)	91 (70.5)	84 (66.1)	33 (71.7)	45 (79.0)	29 (72.5)	31 (62.0)	32 (69.6)	25 (67.6)
Female, n (%)	398 (38.0)	345 (37.5)	255 (36.7)	33 (44.6)	30 (37.5)	27 (38.0)	44 (35.2)	38 (29.5)	43 (33.9)	13 (28.3)	12 (21.1)	11 (27.5)	19 (38.0)	14 (30.4)	12 (32.4)
ECOG PS, n (%)†															
0	439 (42.2)	392 (42.8)	311 (45.0)	29 (39.2)	26 (32.9)	26 (36.6)	52 (41.6)	44 (34.7)	45 (36.0)	15 (32.6)	15 (26.8)	14 (35.0)	16 (32.0)	16 (34.8)	12 (33.3)
1	602 (57.8)	523 (57.2)	380 (55.0)	45 (60.8)	53 (67.1)	45 (63.4)	73 (58.4)	83 (65.4)	80 (64.0)	31 (67.4)	41 (73.2)	26 (65.0)	34 (68.0)	30 (65.2)	24 (66.7)
Smoking history, n (%)															
Never smoker	154 (14.7)	134 (14.6)	126 (18.1)	3 (4.1)	2 (2.5)	3 (4.2)	14 (11.2)	17 (13.2)	9 (7.1)	2 (4.3)	1 (1.8)	0 (0)	2 (4.0)	2 (4.3)	0 (0)
Current/ previous smoker	893 (85.3)	786 (85.4)	569 (81.9)	71 (95.9)	78 (97.5)	68 (95.8)	111 (88.8)	112 (86.8)	118 (92.9)	44 (95.7)	56 (98.2)	40 (100)	48 (96.0)	44 (95.7)	37 (100)
Liver metastasis, n (%)	135 (12.9)	122 (13.3)	82 (11.8)	11 (14.9)	10 (12.5)	19 (26.8)	22 (17.6)	28 (21.7)	32 (25.2)	9 (19.6)	8 (14.0)	12 (30.0)	9 (18.0)	7 (15.2)	9 (24.3)
Baseline SLD, median, mm	73.0	74.0	71.0	90.0	83.0	90.0	90.0	86.4	90.0	97.8	90.0	91.5	95.8	97.0	109.0
CRP, median, mg/L	13.9	14.8	10.3	30.8	22.2	35.2	20.9	21.7	26.9	43.7	36.1	33.8	44.8	40.1	32.1

*Refers to patients with *KRAS*-WT tumors.
†N=1041; 6 ITT patients had missing ECOG values.
ABCP, atezolizumab plus bevacizumab plus carboplatin/paclitaxel; ACP, atezolizumab plus carboplatin/paclitaxel; BCP, bevacizumab plus carboplatin/paclitaxel; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; *KRAS*-WT, Kirsten rat sarcoma viral oncogene homolog wild type; MEP, mutation-evaluable population; m*KEAP1*, mutation in kelch-like ECH associated protein 1; m*KRAS*, mutation in the Kirsten rat sarcoma viral oncogene homolog; m*STK11*, mutations in serine/threonine kinase 11; m*TP53*, mutation in tumor protein 53; SLD, sum of longest diameter of target lesion; WT, wild-type.

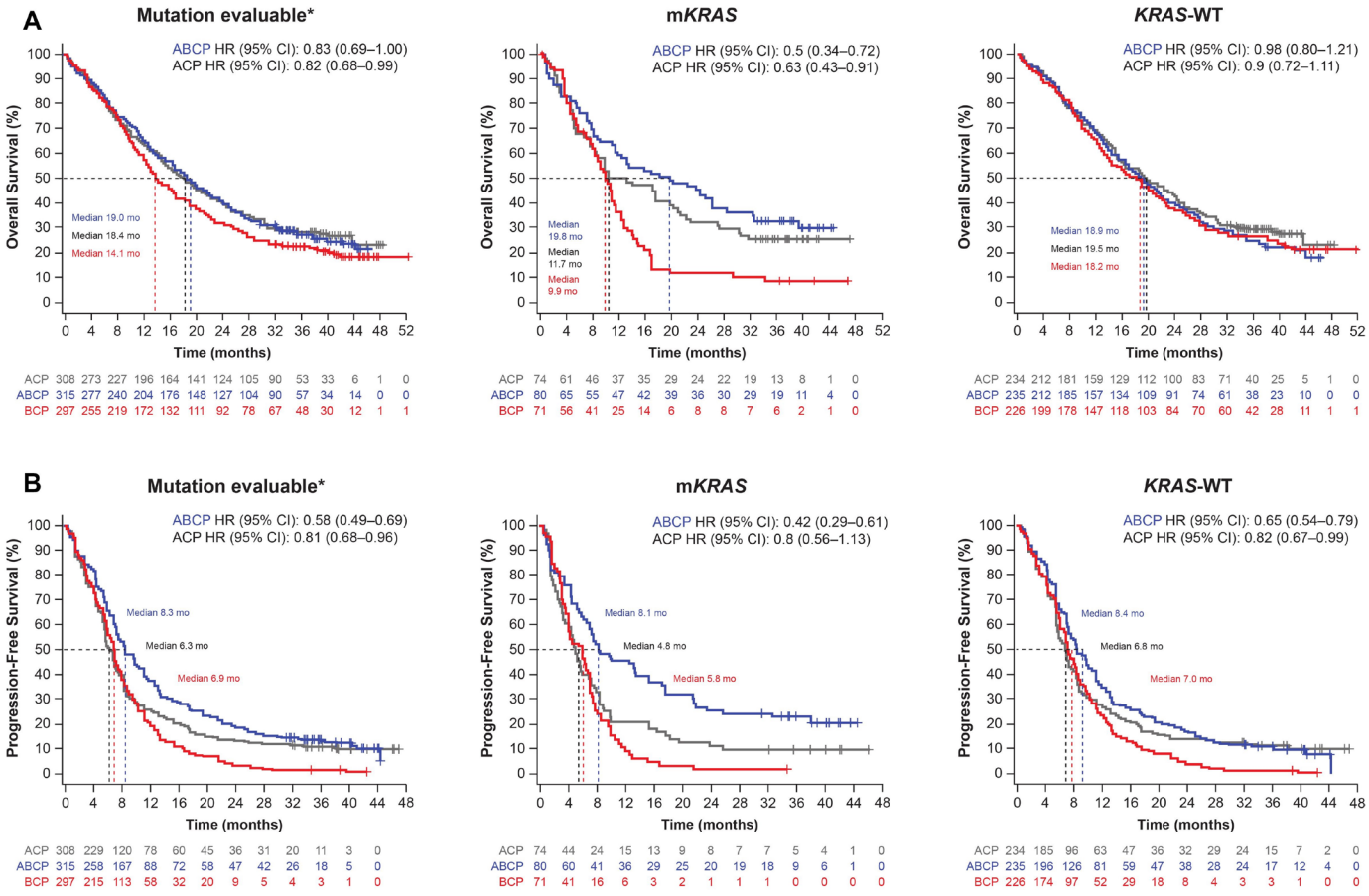


Figure 2 Survival in patients with and without *KRAS* mutations. Kaplan-Meier estimates of OS (A) and PFS (B) among the MEP and *KRAS* populations by treatment arm. All HRs are vs BCP. *Within the ITT population. ABCP, atezolizumab plus bevacizumab plus carboplatin/paclitaxel chemotherapy; ACP, atezolizumab carboplatin/paclitaxel; BCP, bevacizumab plus carboplatin/paclitaxel; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; m*KRAS*, mutations in *KRAS*; MEP, mutation-evaluable population. WT, wild-type.

Efficacy by m*KRAS* status and by PD-L1 subgroup

As shown in figure 2A,B, efficacy in the ABCP and ACP arms vs the BCP arm was observed in the m*KRAS* population. Across treatment arms, median OS of 19.8 (ABCP), 11.7 (ACP), and 9.9 (BCP) months and median PFS of 8.1 (ABCP), 4.8 (ACP), and 5.8 (BCP) months were observed. Both the ABCP and ACP arms demonstrated greater survival improvements compared with the BCP arm in this population. However, compared with BCP, the ABCP arm showed numerically greater survival than the ACP arm in m*KRAS* patients: OS (HR 0.50; 95% CI 0.34 to 0.72 vs HR 0.63; 95% CI 0.43 to 0.91) and PFS (HR 0.42; 95% CI 0.29 to 0.61 vs HR 0.80; 95% CI 0.56 to 1.13).

In *KRAS*-WT patients, median OS was 18.9 months in the ABCP arm, 19.5 months in the ACP arm, and 18.2 months in the BCP arm. In contrast to the m*KRAS* subgroups, *KRAS*-WT patients demonstrated no apparent OS improvement with ABCP (HR 0.98; 95% CI 0.80 to 1.21) or ACP (HR 0.90; 95% CI 0.72 to 1.11) vs BCP. Across treatment arms in the *KRAS*-WT population, median PFS values were 8.4 (ABCP), 6.8 (ACP), and 7.0 (BCP) months; PFS was greater in the ABCP arm (HR 0.65; 95% CI 0.54 to 0.79) than in the ACP arm (HR 0.82; 95% CI 0.67 to 0.99) relative to the BCP arm.

Consistent with previously published literature,[1] m*KRAS* tumors were enriched for high PD-L1 expression (TC ≥50%) compared with the *KRAS*-WT population and overall MEP/SP263 BEP (figure 3A). In m*KRAS* patients with high PD-L1 expression (TC ≥50%), a similar prolonged OS was observed for patients treated with both ABCP (median 23.9 months; HR 0.40; 95% CI 0.19 to 0.85) and ACP (median 19.9 months; HR 0.35; 95% CI 0.17 to 0.74) compared with BCP (median, 9.9 months) (figure 3B). In contrast, m*KRAS* patients with low or negative PD-L1 expression demonstrated greater OS in the ABCP arm than in the ACP arm. For patients with low PD-L1 expression (TC 1-<50%), the HR was 0.37 (95% CI 0.15 to 0.91; median OS, 17.5 months) for ABCP and 0.83 (95% CI 0.36 to 1.90; median OS, 4.8 months) for ACP vs BCP (median OS, 5.0 months) (figure 3B). For patients with negative PD-L1 expression (TC <1%), the HR was 0.43 (95% CI 0.21 to 0.90; median OS, 22.4 months) for ABCP and 0.95 (95% CI 0.49 to 1.83; median OS, 7.9 months) for ACP vs BCP (median OS, 8.7 months) (figure 3B). In contrast, *KRAS*-WT patients with high (TC ≥50%) and low (TC 1-<50%) PD-L1 expression demonstrated greater OS in the ACP arm than in the ABCP or BCP arm (online supplemental figure S3). In m*KRAS* patients, median

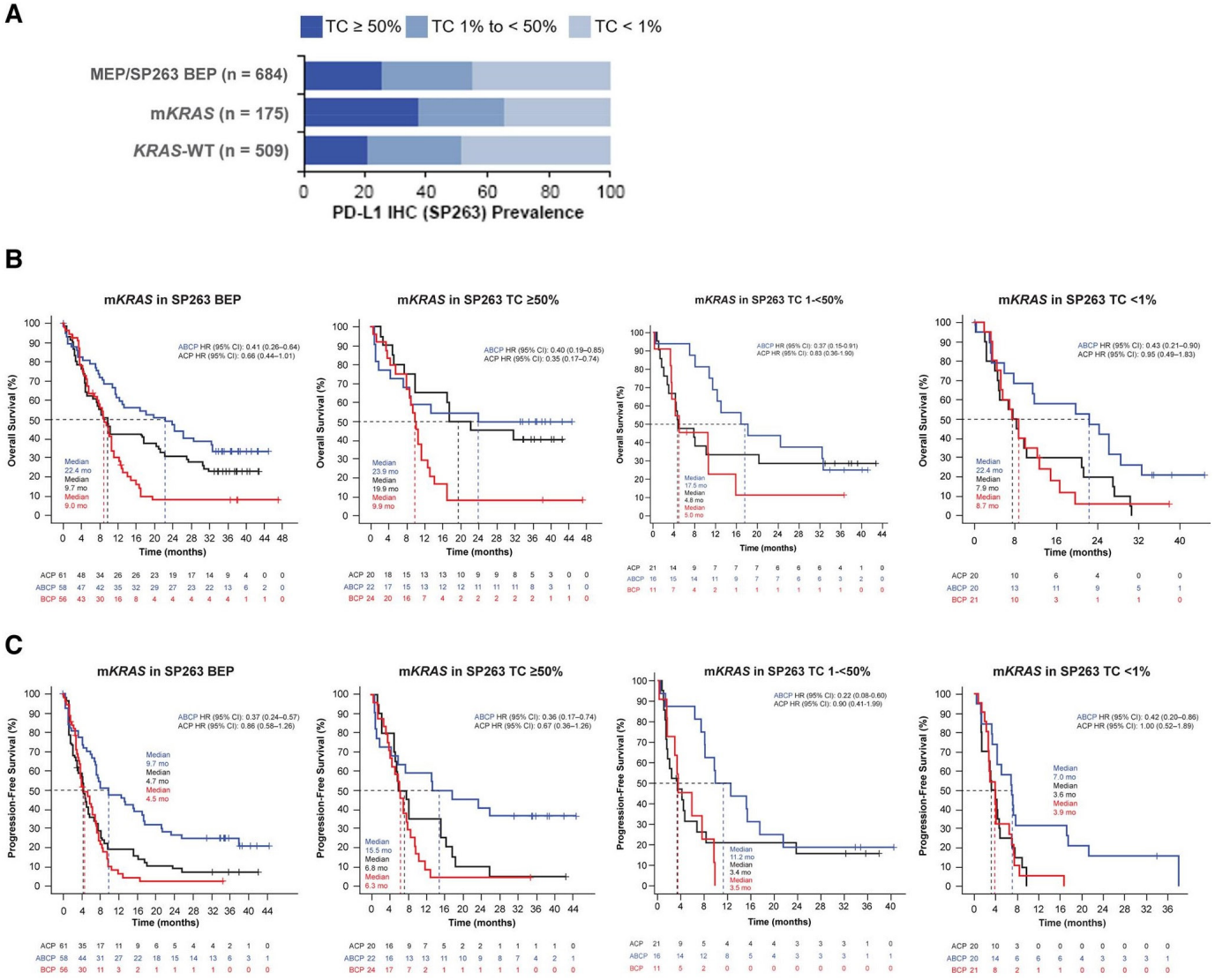


Figure 3 PD-L1 prevalence in the overall BEP and *KRAS*-defined populations and survival according to PD-L1 expression status in patients with *KRAS* mutations. PD-L1 prevalence in the MEP/SP263 BEP and *KRAS* subgroups (A), and Kaplan-Meier estimates of OS (B) and PFS (C) among the m*KRAS* population according to SP263 PD-L1 status. All HRs are vs BCP. ABCP, atezolizumab plus bevacizumab plus carboplatin/paclitaxel chemotherapy; ACP, atezolizumab carboplatin/paclitaxel; BCP, bevacizumab plus carboplatin/paclitaxel; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MEP, mutation-evaluable population; m*KRAS*, mutation in *KRAS*; PD-L1, programmed cell death ligand 1; SP263 BEP, SP263 biomarker-evaluable population; TC, tumor cells.

PFS was longer in the ABCP arm than in the ACP or BCP arms in the PD-L1-high, PD-L1-low, and PD-L1-negative subgroups (figure 3C). PFS improvements in the ABCP vs BCP arm were similar among patients with PD-L1-high (HR 0.36; 95% CI 0.17 to 0.74), PD-L1-low (HR 0.22; 95% CI 0.08 to 0.60), and PD-L1-negative (HR 0.42; 95% CI 0.20 to 0.86) expression.

Effect of comutations on clinical efficacy in patients with or without m*KRAS*

Efficacy was evaluated in patients with individual mutations in *STK11*, *KEAP1*, and *TP53*, independent of comutation status (online supplemental figure S4). Similar to previous reports, *STK11* and *KEAP1* mutations were associated with overall poorer PFS and OS prognosis; patients with *STK11/KEAP1* double mutation had the worst prognosis (online supplemental figure S5). Patients with m*KEAP1* status showed no OS improvement with ABCP (median 11.4 months; HR 0.92; 95% CI 0.59 to 1.44) and limited improvement with ACP (median 6.9 months; HR 1.51; 95% CI 0.96 to 2.37) when compared with BCP (median 11.7 months). In m*STK11* patients, longer OS was seen in the ABCP arm (median 12.1 months; HR 0.71; 95% CI 0.44 to 1.13) and similar OS in the ACP arm (median 7.7 months; HR 1.01; 95% CI 0.64 to 1.58) vs the BCP arm (median 9.9 months). In patients with *TP53*-mutated tumors, an OS improvement was observed with both ABCP (median 18.9 months; HR 0.72; 95% CI 0.54 to 0.95) and ACP (median 14.3 months; HR 0.91; 95% CI

0.69 to 1.20) vs BCP (median 11.2 months), and the patients in the ABCP arm had longer OS than those in the ACP arm. A similar trend in PFS was observed across all mutational subgroups, whereby the ABCP arm demonstrated the longest PFS; limited PFS improvement was observed in the ACP arm compared with the BCP arm.

Patients with m*KRAS* tumors are often classified and treated as a single population; however, numerous m*KRAS* comutations—including *STK11*, *KEAP1*, and *TP53*—are frequently found in NSCLC.[2 3] Considering the numerical differences in median OS and published prognostic associations of individual *TP53* and *STK11/KEAP1* mutants, clinical efficacy and PD-L1 status in the m*KRAS* and comutated *STK11/KEAP1* or *TP53* subgroups were evaluated. In patients with m*KRAS* and co-occurring m*STK11* and/or m*KEAP1* tumors (figure 4A), a longer OS was observed in the ABCP arm (median, 11.1 months; HR 0.60; 95% CI 0.34 to 1.03) than in the ACP arm (median, 7.9 months; HR 0.87; 95% CI 0.52 to 1.45) vs the BCP arm (median 8.7 months). A similar effect was also observed with PFS: ABCP (median 6.0 months; HR 0.49; 95% CI 0.28 to 0.84) and ACP (median 3.2 months; HR 0.88; 95% CI 0.54 to 1.46) vs BCP (median 3.4 months) (figure 4B). However, in *KRAS*-WT patients with m*STK11* and/or m*KEAP1* tumors, OS was

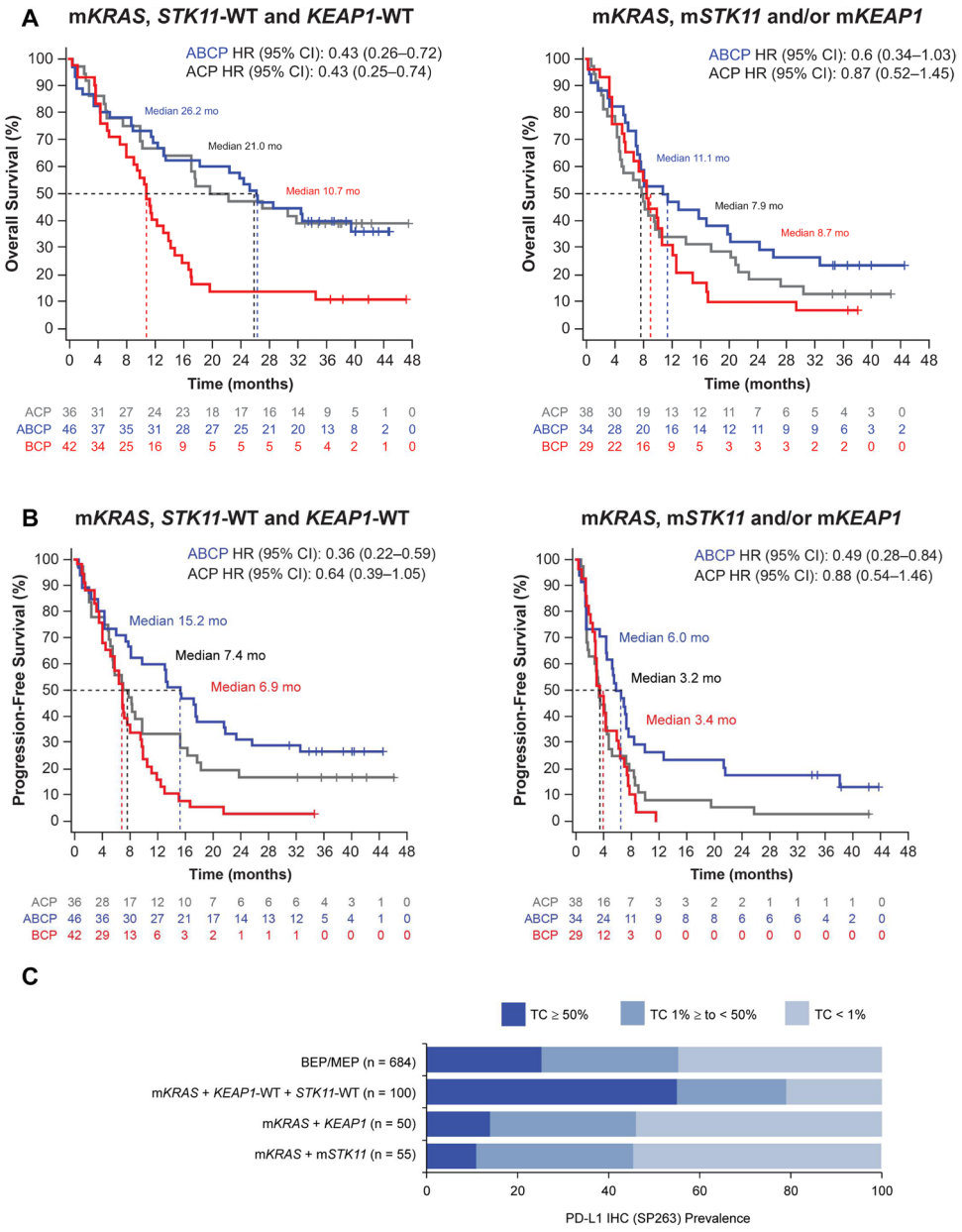


Figure 4 Survival and PD-L1 expression status in patients with *KRAS* mutations according to *STK11/KEAP1* mutational status. Kaplan-Meier estimates of OS (A), PFS (B), and PD-L1 expression status (C) in m*KRAS* patients and co-occurring *STK11/KEAP1* mutation or WT status. All HRs are vs BCP. ABCP, atezolizumab plus bevacizumab plus carboplatin/paclitaxel chemotherapy; BCP, bevacizumab plus carboplatin/paclitaxel; IHC, immunohistochemistry; *KEAP1*, kelch-like ECH associated protein 1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MEP, mutation-evaluable population; m*KRAS*, *KRAS* mutations; PD-L1, programmed cell death ligand 1; *STK11*, serine/threonine kinase 11; TC, tumor cells; WT, wild-type.

not improved with ABCP (median, 13.2 months; HR 1.04; 95% CI 0.66 to 1.64) or ACP (median, 9.0 months; HR 1.39; 95% CI 0.83 to 2.33) vs BCP (median 12.5 months) (online supplemental figure S6).

In the BEP, which included patients with and without m*KRAS*, a PFS improvement was observed in patients with m*KEAP1* and *STK11*-WT tumors with ABCP vs ACP or BCP; however, no difference in OS was observed between treatment arms (online supplemental figure S7). In patients with *KEAP1*-WT and m*STK11* tumors, PFS improvements were seen in the ACP arm and ABCP arm vs the BCP arm. This effect was not observed for OS.

Patients with m*KRAS* and *STK11*-WT and *KEAP1*-WT comutation status showed similar OS improvements between the ABCP (median 26.2 months; HR 0.43; 95% CI 0.26 to 0.72) and ACP (median 21.0 months; HR 0.43; 95% CI 0.25 to 0.74) arms vs the BCP arm (median 10.7 months) (figure 4A). In contrast, the m*KRAS*, *STK11*-WT and *KEAP1*-WT patient population had longer PFS in the ABCP arm (median 15.2 months; HR 0.36; 95% CI 0.22 to 0.59) than in the ACP arm (median, 7.4 months; HR 0.64; 95% CI 0.39 to 1.05) vs the BCP arm (median 6.9 months) (figure 4B). Although clinical efficacy favored ABCP and ACP vs BCP in these subgroups, median survival and overall clinical efficacy was greater in the m*KRAS* and *KEAP1*-WT and *STK11*-WT population than in the m*KRAS* and m*KEAP1* and m*STK11* comutation population, suggesting both prognostic and predictive effects.

Because of the observed efficacy differences between the m*KRAS* subpopulations, we also examined whether differences existed between baseline PD-L1 TC expression. m*KRAS* tumors bearing co-occurring m*STK11* and/or m*KEAP1* were associated with reduced PD-L1 expression compared with the overall MEP/SP263 BEP group, whereas m*KRAS* patients with *STK11*-WT and *KEAP1*-WT status correlated with high PD-L1 expression (figure 4C).

OS and PFS were also examined in m*KRAS* patients with or without co-occurring mutations in m*TP53* (figure 5). Among patients with tumors bearing m*KRAS* and co-occurring m*TP53*, overall OS improvements favored ABCP (median 30.6 months; HR 0.37; 95% CI 0.21 to 0.65) and ACP (median 11.7 months; HR 0.67; 95% CI 0.40 to 1.14) compared with BCP, with the greatest improvement demonstrated in the ABCP arm (figure 5A). Median PFS was also greater in the ABCP arm (14.3 months; HR 0.26; 95% CI 0.15 to 0.47) than in the ACP arm (4.6 months; HR 0.68; 95% CI 0.40 to 1.14) (figure 5B).

In patients with m*KRAS* and *TP53*-WT tumors, overall OS improvements favored ABCP (median 13.4 months; HR 0.67; 95% CI 0.40 to 1.12) and ACP (median 12.1 months; 0.61; 95% CI 0.36 to 1.04) vs BCP (median 10.7 months), with similar OS between ABCP and ACP (figure 5A). In this subgroup, median PFS was 5.2 months in the ACP arm (HR 0.95; 95% CI 0.59 to 1.54) and 7.3 months in the ABCP arm (HR 0.67; 95% CI 0.40 to 1.10) compared with 7.0 months in the BCP arm (figure 5B). As observed for m*KRAS* tumors with co-occurring m*STK11* and/or m*KEAP1*, m*KRAS* tumors showed differential PD-L1 expression depending on *TP53* status. m*KRAS* tumors with co-occurring m*TP53* were enriched for high PD-L1 expression compared with the overall MEP/SP263 BEP population and m*KRAS* *TP53*-WT tumors. Conversely, m*KRAS* tumors with *TP53*-WT status had PD-L1 prevalence rates similar to those of the overall MEP/SP263 BEP population (figure 5C).

DISCUSSION

We present survival findings from a retrospective exploratory analysis of the efficacy of ABCP in m*KRAS*, m*STK11*, m*KEAP*, and m*TP53* mutation and comutation subgroups from the IMpower150 all-comer nonsquamous NSCLC patient population. Overall, patients with m*KRAS* tumors demonstrated greater OS and PFS improvements with ABCP than with ACP or BCP, regardless of comutations. However, it should be noted that a higher proportion of patients treated with BCP (vs ABCP and in some cases ACP) had liver metastases across the mutation subgroups. These results are consistent with reported survival improvements with immune checkpoint inhibitors in *KRAS*-mutant NSCLC.[6 18–20] In contrast, similar survival improvements were not observed across treatment arms in the *KRAS*-WT population in this analysis. ACP and ABCP demonstrated no notable OS and PFS benefit vs BCP in patients with *KRAS*-WT tumors but it should be noted that the BCP arm overperformed with respect to median OS compared with historical controls for chemotherapy-treated *KRAS*-WT patients.[18 19] From previous studies, it remains unclear how underlying comutations affected outcomes after immune checkpoint blockade. In the mutation-evaluable IMpower150 population, m*STK11*, m*KEAP1*, and m*TP53* were frequently comutated with m*KRAS* and, similar to the overall m*KRAS* population, were observed to have greater survival with ABCP than with ACP or BCP.

Notably, in our analysis, it was demonstrated that relative survival improvements in the m*KRAS* population were associated with the underlying PD-L1 status and the presence and type of additional comutations. In particular, PD-L1 expression was enriched among the m*KRAS* population, which aligns with existing evidence of an association between *KRAS*-mutant tumors and increased PD-L1 expression.[1] Both PD-L1-high and PD-L1-low m*KRAS* subgroups demonstrated OS improvement with ABCP, whereas ACP was less beneficial in the PD-L1-low or negative subgroups. Median OS with ACP was shorter in the m*KRAS* PD-L1-low subgroup than the PD-L1-negative subgroup (4.8 vs 7.9 months, respectively). This discrepancy may be attributed to the small patient numbers in each treatment arm. The differences in OS improvements between the ABCP and ACP arms are likely to be driven by the contribution of bevacizumab. However, IMpower150 was designed and statistically powered to compare ABCP and ACP to BCP; therefore, caution must be exercised when comparing differences between ABCP and ACP. In addition to its established anti-angiogenic effects, bevacizumab further

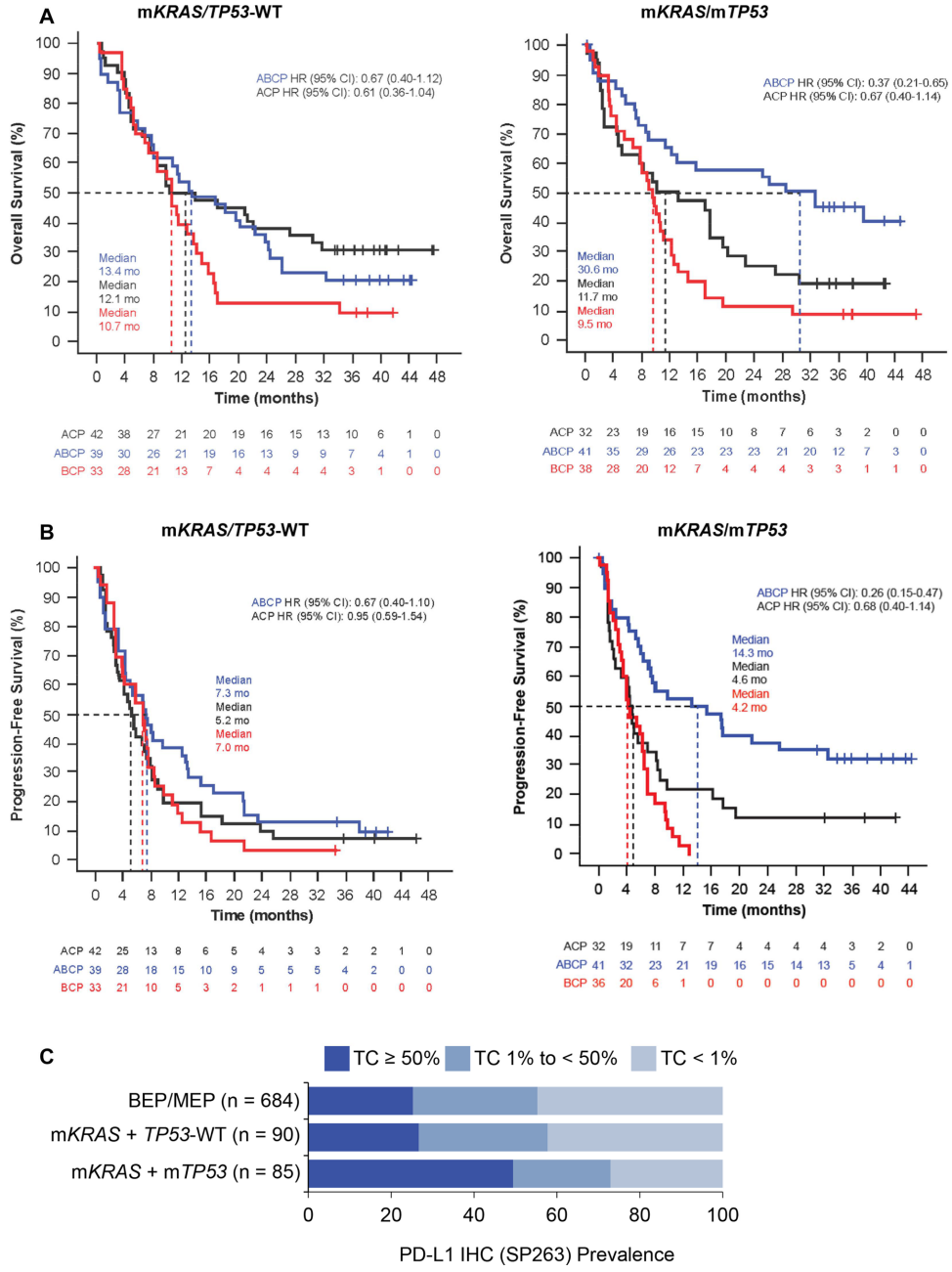


Figure 5 Survival and PD-L1 expression status in patients with *KRAS* mutations according to *TP53* mutational status. Kaplan-Meier estimates of OS (A), PFS (B), and PD-L1 expression status (C) in m*KRAS* patients and co-occurring *TP53* mutation or WT status. HRs are vs BCP. ABCP, atezolizumab plus bevacizumab plus carboplatin/paclitaxel chemotherapy; BCP, bevacizumab plus carboplatin/paclitaxel; BEP, biomarker-evaluable population; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; m*KRAS*, mutation in the Kirsten rat sarcoma viral oncogene homolog; MEP, mutation-evaluable population; PD-L1, programmed cell death ligand 1; TC, tumor cells; *TP53*, tumor protein 53; WT, wild-type.

enhances atezolizumab's T-cell-mediated killing by inhibiting VEGF-related immunosuppression, promoting T-cell tumor infiltration and creating a favorable tumor microenvironment for T-cell reinvigoration.[7 10–13] Specifically, in low or no PD-L1–expressing tumors, atezolizumab may enhance T-cell priming in the lymph node through blockade of the PD-L1/B7.1 interaction.[20–24] Furthermore, reprogramming of the tumor microenvironment from an immune suppressive to immune stimulatory state through VEGF inhibition by the addition of bevacizumab may facilitate interferon gamma–mediated induction of PD-L1 expression on TC and render the tumor further amenable to PD-L1 inhibition.[25]

Consistent with prior reports of *STK11* and *KEAP1* as poor prognostic indicators,[26] the findings from these analyses demonstrated that patients with m*KRAS* and comutations in *STK11* and/or *KEAP1* had an overall poorer prognosis than patients with *STK11*-WT and *KEAP1*-WT status, regardless of the treatment combination they received. Notably, the findings suggest a possible

correlation between biomarker and comutation status with respect to survival outcomes in the atezolizumab arms versus BCP. The adverse impact of *STK11* and/or *KEAP1* mutations was enhanced in patients treated with either ACP or ABCP, suggesting a strong negative predictive effect of *STK11* and/or *KEAP1* mutations on clinical outcomes with atezolizumab containing regimens. A marked OS improvement with ABCP was observed in patients with m*KRAS* and co-occurring m*TP53* tumors, whereas no apparent OS improvements were observed with ABCP among patients with m*KRAS* tumors in the presence of comutations associated with poor prognosis (m*STK11* and m*KEAP1*). Notably, m*KRAS* and m*TP53* tumors had elevated PD-L1 expression, whereas m*KRAS* and co-occurring m*STK11* and m*KEAP1* tumors had reduced PD-L1 expression. A previous retrospective analysis also demonstrated noteworthy clinical benefit with a checkpoint inhibitor among patients with high PD-L1-expressing tumors harboring m*KRAS* and m*TP53* comutations; this effect was attributed to an underlying increased sensitivity to PD-1 inhibition conferred by this double-mutant phenotype.[27] Together, these results suggest that the addition of bevacizumab to atezolizumab may be the preferred treatment strategy for *KRAS* and *TP53* comutated NSCLC.

Smoking is strongly associated with genetic heterogeneity in m*KRAS* tumors and confers a greater mutational burden and higher frequency of co-occurring mutations in *TP53* or *STK11* than never smoking.[28] In this analysis, the m*KRAS* population and other mutation subgroups were enriched for smokers and patients with other known poor prognostic factors (such as ECOG PS status of 1 and higher median sum of longest diameter of target lesion or C-reactive protein levels) compared with the overall MEP or ITT population. The adverse effect of these prognostic factors was evident for OS in the BCP arm, which was markedly worse in m*KRAS* patients (median 9.86 months) than in the *KRAS*-WT population (median 18.23 months). Additionally, the enrichment of higher PD-L1 expression in m*KRAS* tumors (vs *KRAS*-WT tumors) may also account for the observed differences in treatment outcomes.

The current findings from this study offer insights into the personalized treatment of patients with *KRAS*-mutated NSCLC. Certain subgroups of m*KRAS* and comutations (eg, *STK11/LKB1*, *TP53*, and *CDKN2A/B* inactivation) are postulated to generate biological diversity in NSCLC, which, in turn, warrants a personalized approach to treatment.[29] However, consistent evidence has been lacking on the utility of m*KRAS* as a sole predictive or prognostic biomarker for immune checkpoint inhibitor therapy,[1 30 31] likely due to heterogeneity in comutations. The findings from these analyses suggest that it is plausible that consideration of m*KRAS* and co-occurring mutations in *STK11*, *KEAP1*, and *TP53* may dictate treatment choices in the future, similar to m*EGFR* being a determinant of outcomes to targeted therapies with tyrosine kinase inhibitors.[3] Collectively, findings from this and previous analyses of IMpower150 have shown the consistent benefits of ABCP in specific mutant subgroups ranging from patients with *EGFR*-mutant tumors[16] to m*KRAS* populations with co-existing mutations in *STK11*, *KEAP1*, or *TP53*.

A major limitation of this retrospective exploratory analysis was that some mutation-defined subgroup sizes were small. The prevalence of m*KRAS* was found to be slightly lower in this study than previously published.[1–4] This may be attributed to the use of blood-based mutation analysis vs using a tissue-based approach, which may underestimate the prevalence and limit sensitivity. Due to limitations in obtaining tissue at baseline, tissue mutation calls were not explored in the present study. Therefore, due to the small subgroup sizes, comparisons were not adequately powered to detect treatment differences, although exploratory endpoints were prespecified. Additionally, this analysis included patients with any alterations in *KRAS*, *STK11*, *KEAP1* or *TP53* regardless of functional relevance, which may be a confounding factor. It has also been reported that *STK11/LKB1* functional loss can occur by nonmutational mechanisms[32]; however, this was not evaluated in patients in this study. Accordingly, caution should be applied in extending these findings to a clinical setting. Overall, prospective studies are essential to verify the promising findings observed in this subgroup analysis.

This exploratory analysis supports previous findings that mutation of *STK11* and/or *KEAP1* is associated with poorer prognosis. This analysis also suggests that atezolizumab combined with bevacizumab and chemotherapy is an efficacious first-line treatment option for patients with metastatic NSCLC, including difficult-to-treat NSCLC patient groups with m*KRAS* and co-occurring mutations in *STK11* and/or *KEAP1* and *TP53*.

Author affiliations
[1]Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, California, USA
[2]Genentech Inc, South San Francisco, California, USA
[3]Oncology Department, Istituto Nazionale Tumori "Regina Elena", Rome, Italy
[4]Department of Thoracic Oncology, LungenClinic Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany
[5]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China
[6]Department of Medical Oncology, Rocky Mountain Cancer Centers, Denver, Colorado, USA
[7]US Oncology, Houston, Texas, USA
[8]Thoracic Medical Oncology Department, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[9]Product Development Medical Affairs, F Hoffmann-La Roche Ltd, Basel, Switzerland
[10]Thoracic Oncology, AdventHealth Cancer Institute, Orlando, Florida, USA

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ORCID iD

Howard Jack West http://orcid.org/0000-0003-3257-0086

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