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

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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 (mKRAS) 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 mKRAS 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 mKRAS 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 mKRAS population, STK11 and/or KEAP1 mutations were associated with inferior OS and PFS across treatments compared with STK11-WT and/or KEAP1-WT. In mKRAS patients with co-occurring mSTK11 and/or mKEAP1 (44.9%) or mTP53 (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 mKRAS and KEAP1-WT and STK11-WT population vs mKRAS and mKEAP1 and mSTK11 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 mKRAS 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 (mKRAS) 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 (mSTK11) and KEAP1 (mKEAP1) 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. 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. 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 tumorspecific immunity. 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. 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. 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.

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). 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. ABCP continued to show benefit vs BCP in an updated OS analysis with an additional ≈20 months of follow-up. ABCP also prolonged OS and PFS vs BCP in an exploratory subgroup analysis of patients with EGFR-sensitizing mutations. Although studies of immune checkpoint inhibitors alone or with chemotherapy have demonstrated survival benefit in patients with mKRAS tumors, it remains unclear how co-occurring mutations—including mSTK11, mKEAP1, and mTP53—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 mKRAS population by PD-L1 status and by co-occurring mSTK11, mKEAP1, and mTP53 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.

The coprimary endpoints were PFS and OS in the ITT-WT population, which excluded patients with EGFR or ALK genomic alterations. 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/m² paclitaxel (patients of Asian ethnicity were given 175 mg/m²). 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
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 mKRAS, mSTK11, mKEAP1, and mTP53 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 mKRAS population, 44.9% (101/225) of mKRAS patients also had co-occurring mutations in STK11 and/or KEAP1, and 49.3% (111/225) of mKRAS 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 mKRAS, mSTK11, mKEAP1, and mTP53 populations compared with the overall MEP or ITT population. Smoking history was associated with mKEAP1, mSTK11, and mKRAS. Elevated C-reactive protein levels, a poor prognostic factor, appeared highest in mKEAP1 and mSTK11 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

|                      | ITT       | MEP       | KRAS-WT*  | ACP       | ACP       | ACRP      | ACP       | ABCP      | BCP       | ACP       | ABCP      | BCP       | ACP       | ABCP      | BCP       | ACP       | ABCP      | BCP       |
|----------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| N                    | 1047      | 920       | 695       | 74        | 80        | 71        | 125       | 129       | 127       | 48        | 57        | 40        | 50        | 46        | 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 (83.3)| 109 (85.8)| 42 (91.3) | 49 (86.0) | 35 (87.5) | 46 (92.0) | 38 (82.6) | 32 (86.5) |
| Median age           | 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)| 50 (62.5) | 44 (62.0) | 81 (64.8) | 91 (70.5) | 84 (66.1) |           | 33 (71.7)| 45 (79.0) | 29 (72.9) | 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 (38.5) | 44 (35.2) | 43 (33.9) |           | 13 (28.3)| 12 (21.1) | 11 (27.9) | 19 (38.0) | 14 (30.4) | 12 (32.4) |
| ECOG PS, n (%)†      | 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 (35.9) | 16 (32.0) | 16 (34.8) | 12 (33.3) |
| 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     | 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 (%)|           |           |           |           |           |           |           |           |           |           |           |           |           |           |           |           |           |           |
| Baseline SLD, median, mm | 73.0     | 74.0      | 90.0      | 83.0      | 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; mKEAP1, mutation in kelch-like ECH associated protei 1; mKRAS, mutation in the Kirsten rat sarcoma viral oncogene homolog; mSTK11, mutations in serine/threonine kinase 11; mTP53, 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; mKRAS, mutations in KRAS; MEP, mutation-evaluable population. WT, wild-type.

Efficacy by mKRAS 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 mKRAS 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 mKRAS 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 mKRAS 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 KRASWT 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 mKRAS tumors were enriched for high PD-L1 expression (TC ≥50%) compared with the KRAS-WT population and overall MEP/SP263 BEP (figure 3A). In mKRAS 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, mKRAS 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 vs BCP (median, 9.9 months) (figure 3B). For patients with negative PD-L1 expression (TC <1%), the HR was 0.43 (95% CI 0.21 to 0.93; median OS, 12.4 months) for ABCP vs BCP (median, 9.9 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 mKRAS patients, median
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 mKRAS**

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 mKEAP1 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 mSTK11 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 mKRAS tumors are often classified and treated as a single population; however, numerous mKRAS comutations—including STK11, KEAPI, 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/KEAPI mutants, clinical efficacy and PD-L1 status in the mKRAS and comutated STK11/KEAPI or TP53 subgroups were evaluated. In patients with mKRAS and co-occurring mSTK11 and/or mKEAPI 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 mSTK11 and/or mKEAPI tumors, OS was

![Figure 4](image_url)
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 0.85 to 2.33) vs BCP (median, 12.5 months) (online supplemental figure S6).

In the BEP, which included patients with and without mKRAS, a PFS improvement was observed in patients with mKEAPI 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 KEAPI-WT and mSTK11 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 mKRAS and STK11-WT and KEAPI-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 mKRAS, STK11-WT and KEAPI-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 mKRAS and KEAPI-WT and STK11-WT population than in the mKRAS and mKEAPI and mSTK11 comutation population, suggesting both prognostic and predictive effects.

Because of the observed efficacy differences between the mKRAS subpopulations, we also examined whether differences existed between baseline PD-L1 TC expression. mKRAS tumors bearing co-occurring mSTK11 and/or mKEAPI were associated with reduced PD-L1 expression compared with the overall MEP/SP263 BEP group, whereas mKRAS patients with STK11-WT and KEAPI-WT status correlated with high PD-L1 expression (figure 4C).

OS and PFS were also examined in mKRAS patients with or without co-occurring mutations in mTP53 (figure 5). Among patients with tumors bearing mKRAS and co-occurring mTP53, 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 mKRAS 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 mKRAS tumors with co-occurring mSTK11 and/or mKEAPI, mKRAS tumors showed differential PD-L1 expression depending on TP53 status. mKRAS tumors with co-occurring mTP53 were enriched for high PD-L1 expression compared with the overall MEP/SP263 BEP population and mKRAS TP53-WT tumors. Conversely, mKRAS 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 mKRAS, mSTK11, mKEAP, and mTP53 mutation and comutation subgroups from the IMpower150 all-comer nonsquamous NSCLC patient population. Overall, patients with mKRAS 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. Both PD-L1- and PD-L1-low or negative subgroups. From previous studies, it remains unclear how underlying comutations affected outcomes after immune checkpoint blockade. In the mutation-eligible IMpower150 population, mSTK11, mKEAPI, and mTP53 were frequently comutated with mKRAS and, similar to the overall mKRAS 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 mKRAS 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 mKRAS population, which aligns with existing evidence of an association between KRAS-mutant tumors and increased PD-L1 expression. Both PD-L1-high and PD-L1-low mKRAS 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 mKRAS 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
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 mKRAS 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 mK Ras and co-occurring mTP53 tumors, whereas no apparent OS improvements were observed with ABCP among patients with mK Ras tumors in the presence of comutations associated with poor prognosis (mSTK11 and mKEAP1). Notably, mK Ras and mTP53 tumors had elevated PD-L1 expression, whereas mK Ras and co-occurring mSTK11 and mKEAP1 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 mK Ras and mTP53 comutations; this effect was attributed to an underlying increased sensitivity to PD-1 inhibition conferred by this double-mutant phenotype. Together, these results suggest that the addition of bevacizumab to atezolizumab may be the preferred treatment strategy for K Ras and TP53 comuted NSCLC.

Smoking is strongly associated with genetic heterogeneity in mK Ras tumors and confers a greater mutational burden and higher frequency of co-occurring mutations in TP53 or STK11 than never smoking. In this analysis, the mK Ras 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 mK Ras patients (median 9.86 months) than in the KRASWT population (median 18.23 months). Additionally, the enrichment of higher PD-L1 expression in mK Ras tumors (vs KRASWT 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 mK Ras 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. However, consistent evidence has been lacking on the utility of mK Ras as a sole predictive or prognostic biomarker for immune checkpoint inhibitor therapy, likely due to heterogeneity in comutations. The findings from these analyses suggest that it is plausible that consideration of mK Ras and co-occurring mutations in STK11, KEAP1, and TP53 may dictate treatment choices in the future, similar to mEGFR being a determinant of outcomes to targeted therapies with tyrosine kinase inhibitors. 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 to mK Ras 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 mK Ras was found to be slightly lower in this study than previously published. 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 K Ras, 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; 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 mK Ras and co-occurring mutations in STK11 and/or KEAP1 and TP53.

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