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IMpower150: Exploratory Analysis of Brain Metastases Development

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BACKGROUND

- The recommended first-line treatments for patients with advanced non-small cell lung cancer (NSCLC) include[1,2]:
  - Tyrosine kinase inhibitors: for patients with genomic alterations such *EGFR* mutations, ALK translocations, *ROS1* fusion events and *BRAF* mutations
  - Pembrolizumab (anti–programmed death-1 [PD-1]) monotherapy: for patients with untreated metastatic NSCLC (tumor proportion score ≥ 1%)[3]
  - Platinum-based chemotherapy alone or in combination with bevacizumab,[4] pembrolizumab[5] or atezolizumab + bevacizumab[6,7]
- In patients with advanced NSCLC, brain metastases are common, occurring in approximately 46%-57% of cases at initial presentation[8]
- Although survival rates for patients with brain metastases and NSCLC have improved compared with past decades, the prognosis can be poor[9]
  - Treatment of brain metastases in NSCLC allows for either stereotactic radiosurgery alone or surgical resection followed by stereotactic radiosurgery or whole-brain radiotherapy[2]

Combining Atezolizumab + Bevacizumab + Chemotherapy

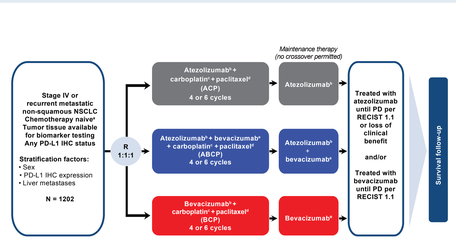
- The monoclonal antibody atezolizumab (anti–programmed death-ligand 1 [PD-L1]) restores tumor-specific immunity by inhibiting the binding of PD-L1 to its receptors PD-1 and B7.1[10,11]
- Atezolizumab has shown efficacy in patients with NSCLC as monotherapy and combined with chemotherapy[12,13]
- The recombinant humanized vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, in combination with chemotherapy, showed a significantly better outcome for overall survival (OS) than chemotherapy alone in patients with advanced NSCLC in a Phase II/III study (E4599; NCT00021060)[4]
- Furthermore, bevacizumab has been shown to delay or prevent progression of brain metastases in NSCLC[14,15]
  - The Phase III AVAiL trial, which evaluated patients with Stage IIIb/IV, non-squamous NSCLC treated with bevacizumab plus chemotherapy vs chemotherapy, demonstrated a significantly lower rate of brain metastases recurrence (2.6% vs 5.8%; $P = 0.01$) and a lower risk of the development of brain metastases (hazard ratio [HR], 0.36; $P = 0.001$) in the bevacizumab vs chemotherapy arm
- The combination of atezolizumab with bevacizumab and chemotherapy may enhance atezolizumab's T-cell–mediated cancer cell killing properties through the reversal of VEGF-mediated immunosuppression[16] and through chemotherapy-induced cell death[17]
- IMpower150, a Phase III study, demonstrated statistically significant and clinically meaningful improvements with atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) vs bevacizumab + carboplatin + paclitaxel (BCP) in progression-free survival (PFS; HR, 0.62 [95% CI: 0.52, 0.74]; $P < 0.001$) and OS (HR, 0.78 [95% CI: 0.64, 0.96]; $P = 0.02$)[6]
- The objective of this analysis was to assess the development of brain metastases in patients treated with ABCP, BCP and atezolizumab + CP (ACP) in IMpower150

METHODS

Study Design and Patient Population

- The global, randomized, open-label, international, Phase III IMpower150 study (NCT02366143) was designed to evaluate the efficacy and safety of ACP or ABCP vs BCP in chemotherapy-naive patients with metastatic non-squamous NSCLC (Figure 1)
- The intention-to-treat (ITT) population was composed of 1202 patients
- The previously reported co-primary endpoints were[6]:
  - PFS as assessed by investigator in the ITT–wild-type (WT) population, which excluded patients whose tumors had *EGFR* or *ALK* genomic alterations, and in ITT-WT patients whose tumors had high expression of a T-effector gene signature
  - OS in the ITT-WT population
- This report focuses on exploratory analyses, including rate and time to development (TTD) of new brain metastases in the ITT population, regardless of the presence of brain metastases at baseline, as well as safety in patients with and without brain metastases
  - Brain scans (computed tomographic or magnetic resonance imaging, with or without contrast) were performed as clinically indicated, and analyses were based on investigator assessments
  - For TTD, Kaplan-Meier methodology was used to estimate the median and construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology was used to construct the 95% CIs and HRs for each treatment arm
  - The incidence, nature and severity of adverse events (AEs) were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Multiple occurrences of the same AE were counted once at the maximum grade

Figure 1. IMpower150 Study Design



IHC, immunohistochemistry; IV, intravenous; PD, progressive disease; q3w, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have PD or intolerance of treatment with ≥ 1 approved targeted therapy. [b] Atezolizumab 1200 mg IV q3w. [c] Carboplatin area under the curve 6 IV q3w. [d] Paclitaxel 200 mg/m^2 IV q3w. [e] Bevacizumab 15 mg/kg IV q3w.

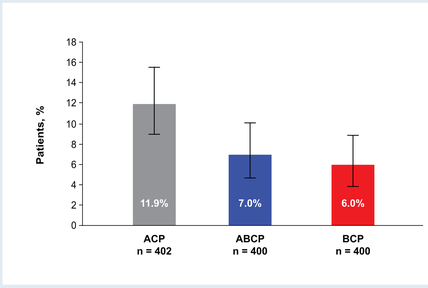
RESULTS

- At the data cutoff date of September 13, 2019, median follow-up in the ITT population was 39.3 months
- Median follow-up was 39.5 months (range, 0.0-49.8) for ABCP, 38.8 months (range, 0.4+-48.5) for ACP and 39.8 months (range, 0.0-52.2) for BCP

New Brain Lesions in the ITT population

- In the ITT population, 100 patients had developed new brain metastases, with the highest rate of new brain lesions observed in the ACP (11.9%; n = 48) vs the ABCP (7.0%; n = 28) and BCP (6.0%; n = 24) arms (Figure 2)

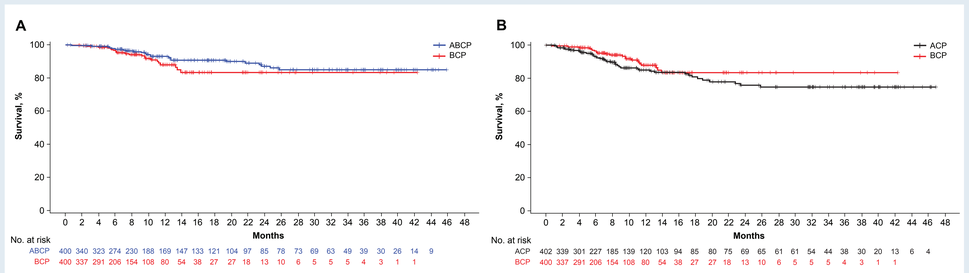
Figure 2. Rate of New Brain Lesions in the ITT Population[a]



[a] Among the 100 patients with new brain lesions, 53 were diagnosed by MRI only, 42 by CT only and 5 by both MRI and CT. Error bars represent 95% confidence intervals.

- Median TTD was not reached in any arm (Figure 3); a trend toward delayed TTD was seen in the ABCP vs BCP arm (HR, 0.68 [95% CI: 0.39, 1.19])

Figure 3. TTD of New Brain Lesions in the ITT Population



Baseline Demographics and Characteristics of Patients With New Brain Lesions

- Baseline demographics and clinical characteristics of patients with new brain metastases were generally balanced between treatment arms; similar numbers of patients had new brain metastases in the ABCP and BCP arms (Table 1)
  - Key baseline demographics and clinical characteristics displayed include those with observed numerical differences between treatment arms or patient subgroups (with vs without new brain metastases)
  - Numerical differences were observed for Eastern Cooperative Oncology Group performance status (ECOG PS) and PD-L1 status; most patients had an ECOG PS of 1, and patients in the ABCP and BCP arms were mostly PD-L1 negative (PD-L1 expression on < 1% of tumor cells [TC] and tumor-infiltrating immune cells [IC]; TC0 and IC0). Compared with the ACP and BCP arms, the ABCP arm had fewer patients with high PD-L1 expression (PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC; TC3 or IC3) and more patients with an ECOG PS of 1

Table 1. Key Baseline Demographics and Clinical Characteristics in Patients With New Brain Lesions

	ABCP (n = 28)	ACP (n = 48)	BCP (n = 24)
Male, n (%)	16 (57.1)	25 (52.1)	13 (54.2)
Median age (range), years	62.0 (47-77)	64.5 (32-79)	57.5 (43-81)
Tobacco use, n (%)			
Never	7 (25.0)	10 (20.8)	7 (29.2)
Current	6 (21.4)	9 (18.8)	5 (20.8)
Previous	15 (53.6)	29 (60.4)	12 (50.0)
ECOG PS, n (%)			
0	11 (39.3)	21 (43.8)	11 (45.8)
1	17 (60.7)	27 (56.3)	13 (54.2)
Positive *ALK* rearrangement status, n (%)	1 (3.6)	1 (2.1)	0
Positive *EGFR* mutation status, n (%)	5 (17.9)	7 (14.6)	5 (20.8)
PD-L1 status, n (%)			
TC3 or IC3	2 (7.1)	9 (18.8)	5 (20.8)
TC2/3 or IC2/3 exclude TC3 or IC3	6 (21.4)	14 (29.2)	5 (20.8)
TC1/2/3 or IC1/2/3 exclude TC2/3 or IC2/3	2 (7.1)	7 (14.6)	1 (4.2)
TC0 and IC0	18 (64.3)	18 (37.5)	13 (54.2)

IC, tumor-infiltrating immune cell; PD-L1, programmed death ligand 1; TC, tumor cell; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1; TC0 and IC0 = TC < 1% and IC < 1% PD-L1.

Patterns of PD in Patients With New Brain Lesions

- PD in patients with new brain lesions also included PD at target lesions, generally in lung, lymph nodes, liver and adrenal glands, in all treatment arms and PD at non-target lesions, primarily in liver and bone, in all treatment arms (Table 2)

Table 2. Patterns of Disease Progression in Patients With New Brain Lesions

Site of PD, n (%)	ABCP (n = 28)	ACP (n = 48)	BCP (n = 24)
Target lesion	11 (39.3)	14 (29.2)	5 (20.8)
Lung	11 (39.3)	12 (25.0)	5 (20.8)
Lymph node	6 (21.4)	5 (10.4)	2 (8.3)
Liver	3 (10.7)	2 (4.2)	1 (4.2)
Adrenal gland	2 (7.1)	2 (4.2)	1 (4.2)
Head	0	1 (2.1)	0
Mediastinum	1 (3.6)	0	0
Other	1 (3.6)	0	0
Pleura	1 (3.6)	0	0
Soft tissue	0	0	1 (4.2)
Non-target lesion	5 (17.9)	6 (12.5)	1 (4.2)
Liver	1 (3.6)	2 (4.2)	1 (4.2)
Bone	1 (3.6)	1 (2.1)	1 (4.2)
Brain	1 (3.6)	2 (4.2)	0
Lung	1 (3.6)	1 (2.1)	0
Lymph node	0	1 (2.1)	0
Pleura	1 (3.6)	0	0
Other new lesion	5 (17.9)	12 (25.0)	2 (8.3)

Safety

- ABCP was tolerable in patients with and without brain metastases (Table 3)
  - Grade 3-4 treatment-related AEs were reported in 64.3%, 35.4% and 41.7% of patients with brain metastases and 56.7%, 44.0% and 49.5% of patients without brain metastases in the ABCP, ACP and BCP arms, respectively
- Serious treatment-related AEs in patients with brain metastases are presented in Table 4
  - No serious treatment-related AEs were reported in patients with brain metastases in the BCP arm
  - In the atezolizumab-containing arm, no Grade 5 serious treatment-related AEs occurred in patients with brain metastases

Table 3. Safety Summary

	With New Brain Metastases			Without New Brain Metastases		
	ABCP (n = 28)	ACP (n = 48)	BCP (n = 24)	ABCP (n = 365)	ACP (n = 352)	BCP (n = 370)
Median treatment duration (range), months						
Atezolizumab	8.4 (1-35)	7.3 (0-43)	–	8.1 (0-45)	6.4 (0-48)	–
Bevacizumab	6.1 (1-23)	–	5.7 (1-13)	6.7 (0-45)	–	5.1 (0-44)
Patients with ≥ 1, n (%)						
Any AE	28 (100.0)	48 (100.0)	24 (100.0)	358 (98.1)	343 (97.4)	366 (98.9)
Grade 3-4	21 (75.0)	27 (56.3)	14 (58.3)	234 (64.1)	214 (60.8)	220 (59.5)
Grade 5	0	1 (2.1)	1 (4.2)	26 (7.1)	10 (2.8)	21 (5.7)
Treatment-related AE	27 (96.4)	46 (95.8)	23 (95.8)	343 (94.0)	331 (94.0)	355 (95.9)
Grade 3-4	18 (64.3)	17 (35.4)	10 (41.7)	207 (56.7)	155 (44.0)	183 (49.5)
Grade 5	0	0	0	12 (3.3)	4 (1.1)	10 (2.7)
Serious AE	15 (53.6)	20 (41.7)	4 (16.7)	172 (47.1)	149 (42.3)	138 (37.3)
Serious treatment-related AE	7 (25.0)	8 (16.7)	0	98 (26.8)	73 (20.7)	80 (21.6)
AE leading to any treatment discontinuation	12 (42.9)	5 (10.4)	8 (33.3)	150 (41.1)	53 (15.1)	96 (25.9)
AE leading to any dose modification/interruption	21 (75.0)	28 (58.3)	16 (66.7)	235 (64.4)	181 (51.4)	174 (47.0)

Table 4. Serious Treatment-Related AEs in Patients With New Brain Lesions

	ABCP (n = 28)		ACP (n = 48)	
n (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any serious treatment-related AE[a]	7 (25.0)	5 (17.9)	8 (16.7)	6 (12.5)
Febrile neutropenia	1 (3.6)	1 (3.6)	2 (4.2)	2 (4.2)
Pneumonia	1 (3.6)	1 (3.6)	0	0
Encephalitis	0	0	1 (2.1)	1 (2.1)
Lower respiratory tract infections	0	0	1 (2.1)	0
Diarrhea	0	0	2 (4.2)	0
Pulmonary embolism	1 (3.6)	1 (3.6)	0	0
Pleurisy	1 (3.6)	1 (3.6)	0	0
Peripheral sensory neuropathy	0	0	1 (2.1)	1 (2.1)
Cognitive disorder	0	0	1 (2.1)	1 (2.1)
Pyrexia	1 (3.6)	0	0	0
Renal failure	1 (3.6)	0	0	0
Erythema multiforme	0	0	1 (2.1)	1 (2.1)
Platelet count decreased	1 (3.6)	1 (3.6)	0	0
Hypothyroidism	0	0	1 (2.1)	1 (2.1)
Compartment syndrome	1 (3.6)	1 (3.6)	0	0

[a] Patients with > 1 AE are only counted once.

CONCLUSIONS

- The bevacizumab-containing arms of ABCP and BCP had comparable, lower rates of new brain lesion development on study
- A trend toward delayed development of new brain lesions was observed with ABCP
- The data suggest that the addition of atezolizumab to BCP may not reduce the rate of new brain lesion development but may delay the time to new lesion development
- No new safety signals were observed in this exploratory analysis
- ABCP remains a standard-of-care first-line treatment regimen for patients with metastatic non-squamous NSCLC

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