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Regulatory Issues: FDA

FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. FDA approval • Atezolizumab and durvalumab in small cell lung cancer

Abstract

The U.S. Food and Drug Administration (FDA) granted approval to atezolizumab and durvalumab in March of 2019 and 2020, respectively, for use in combination with chemotherapy for first-line treatment of patients with extensive stage small cell lung cancer. These approvals were based on data from two randomized controlled trials, IMpower133 (atezolizumab) and CASPIAN (durvalumab). Both trials demonstrated an improvement in overall survival (OS) with anti–programmed death ligand 1 antibodies when added to platinum-based chemotherapy as compared with chemotherapy alone. In IMpower133, patients receiving atezolizumab with etoposide and carboplatin demonstrated improved OS (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.54–0.91; p = .0069), with median OS of 12.3 months compared with 10.3 months in patients receiving etoposide and carboplatin. In CASPIAN, patients receiving durvalumab with etoposide and either cisplatin or carboplatin also demonstrated improved OS (HR, 0.73; 95% CI, 0.59–0.91; p = .0047) with median OS of 13.0 months compared with 10.3 months in patients receiving etoposide and either cisplatin or carboplatin. The safety profiles of both drugs were generally consistent with known toxicities of immune-checkpoint inhibitor therapies. This review summarizes the FDA perspective and data supporting the approval of these two agents. ***The Oncologist*** 2021;26:433–438

Implications for Practice: Effective therapeutic options for small cell lung cancer (SCLC) are limited, and there has been modest improvement in the overall survival (OS) of patients with SCLC over the past 3 decades. The approvals of atezolizumab and of durvalumab in combination with chemotherapy for first-line treatment of patients with extensive stage SCLC represent the first approved therapies with OS benefit for this patient population since the approval of etoposide in combination with other approved chemotherapeutic agents. Additionally, the efficacy results from IMpower133 and CASPIAN lay the groundwork for possible further evaluation in other treatment settings in this disease.

Introduction

Small cell lung cancer (SCLC) accounts for 10%–15% of all lung cancer diagnoses. Although SCLC accounts for a minority of lung cancer diagnoses and the incidence in the U.S. has been decreasing over the past 2 decades [1], it remains a highly aggressive and fatal disease. The prognosis of patients with SCLC remains dismal, with a 5-year overall survival (OS) rate of less than 10%, including patients with both limited stage and extensive stage disease. It is estimated that 57% of patients with SCLC present with extensive stage SCLC (ES-SCLC), which has a 5-year OS rate of 3% [1, 2]. Although SCLC is initially highly responsive to chemotherapy with significant reduction in tumor burden, this is often followed by relapse and development of chemotherapy resistance. Despite significant progress in understanding of the genetics and molecular pathways underlying SCLC, identification of efficacious therapeutics remains elusive; molecularly targeted agents such as mTOR inhibitors and vascular endothelial growth factor inhibitors have not demonstrated clinically significant antitumor activity [3, 4]. The standard of care for first-line treatment of ES-SCLC since the 1980s has

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been platinum-based doublet chemotherapy with or without prophylactic cranial irradiation (PCI). This leads to response rates close to 70% but with a progression-free survival (PFS) of only 5.5 months and a median OS of less than 10 months [5]. Unfortunately, life expectancy for patients diagnosed with SCLC has not improved over the past 3 decades [6, 7].

The advent of anti–programmed death ligand 1 (PD-L1) monoclonal antibodies has transformed the paradigm of treatment in a variety of solid tumors, including the treatment of non-small cell lung cancer (NSCLC) [8]. SCLC has biologic and clinical features that provide optimism for the potential of therapeutic benefit with immune-modulating treatments. These include a strong association with smoking and the presence of high tumor mutational burden, which is hypothesized to release tumor neoantigens capable of eliciting immune responses [9]. Because of the rapidly progressive and initial chemo-sensitive nature of SCLC, most trials have evaluated immune checkpoint inhibitors in combination with chemotherapy for first-line treatment of patients with ES-SCLC [10]. Initial results from this approach were not encouraging, as a randomized trial evaluating ipilimumab (anti–CTLA-4) in combination with chemotherapy for first-line treatment of patients with ES-SCLC did not demonstrate an improvement in OS compared with chemotherapy alone [11]. However, on March 18, 2019, the U.S. Food and Drug Administration (FDA) approved atezolizumab (TECENTRIQ; Genentech Inc.) for use in combination with carboplatin and etoposide for the first-line treatment of adult patients with ES-SCLC based on an improvement in OS (Table 1). On March 27, 2020, the FDA approved durvalumab (IMFINZI, AstraZeneca) in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with ES-SCLC based on an improvement in OS (Table 2). In this article, we summarize key review findings that supported these two approvals.

Clinical Trial Designs

IMpower133 and CASPIAN both enrolled patients with ES-SCLC who had not received first-line chemotherapy regardless of PD-L1 tumor expression; efficacy was evaluated in the intent-to-treat (ITT) population. Although IMpower133 had coprimary endpoints of OS and investigator-assessed PFS, CASPIAN had a primary endpoint of OS with investigator-assessed PFS as a key endpoint. Other efficacy endpoints in both studies included objective response rate (ORR) and duration of response (DoR).

IMpower133 is a randomized, multicenter, double-blind, placebo-controlled trial in which patients were randomized (1:1) to either atezolizumab in combination with etoposide and carboplatin (A+EC) or placebo in combination with etoposide and carboplatin. Chemotherapy in both arms consisted of etoposide 100mg/m^2 intravenously (IV) on days 1–3 and carboplatin area under the curve (AUC) 5 mg/mL per minute IV on day 1 of each 21-day cycle. Patients in the A+EC arm received atezolizumab 1,200 mg IV in combination with chemotherapy for four cycles followed by atezolizumab 1,200 mg IV every 21 days, whereas patients in the EC arm received chemotherapy alone for four cycles followed by placebo every 21 days. PCI could be administered during the maintenance phase per investigator's discretion. Patients were treated until disease progression, unacceptable toxicity, or patient or physician decision to discontinue therapy. Tumor assessments per RECIST v1.1 were performed at baseline and every 6 weeks for 48 weeks, then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks irrespective of patient time on study. The primary analysis for both primary endpoints (OS and PFS) was via a stratified log-rank test performed on the ITT population with use of the O'Brien-Fleming boundary to adjust for an interim analysis planned to be performed at approximately 240 deaths (78% information). A group sequential Holm procedure was specified to control for multiplicity arising from testing multiple endpoints.

CASPIAN is a randomized, multicenter, open-label, sponsor-blind, three-arm, comparative trial in which patients were randomized (1:1:1) to receive durvalumab 1,500 mg IV, etoposide, and cis- or carboplatin IV (D+EP); durvalumab 1500 mg IV, tremelimumab 75 mg IV, etoposide, and cis- or carboplatin (D+T+EP); or etoposide and cis- or carboplatin alone (EP). Durvalumab was administered on day 1 of each cycle, and chemotherapy consisted of etoposide 80–100 mg/m^2 IV on days 1–3 of each 21-day cycle with investigator's choice of either cisplatin 75–80 mg/m^2 IV on day 1 of each cycle or carboplatin AUC 5–6 mg/mL per minute IV on day 1 of each cycle. Patients in the immunotherapy groups received up to four cycles of therapy with either D+EP or D+T+EP followed by maintenance durvalumab 1,500 mg every 4 weeks. Patients in the EP control group received up to six cycles of EP with optional PCI after chemotherapy (per investigator's discretion). Tumor assessments per RECIST 1.1 were performed at baseline and every 6 weeks until week 12, then every 8 weeks thereafter. The primary endpoint was analyzed using a stratified log-rank test adjusting for planned platinum treatment, with hazard ratios (HRs) and 95% confidence intervals (CIs) estimated using a Cox proportional hazards model. At the time of the planned interim analysis (planned to be performed at approximately 318 OS events between D+EP and EP alone and between D+T+EP and EP alone groups; 60% maturity), the independent data monitoring committee recommended that the D+EP and EP treatments arms be unmasked to the sponsor as this comparison met the prespecified boundary for statistical significance. The D+T+EP arm had not met the statistical significance threshold at the time of interim analysis and is not included or discussed in this review.

Results

A+EC; IMpower133

Key baseline demographic characteristics of patients enrolled on IMpower133 are noted in Table 3. The data set supporting the approval of atezolizumab was based on a prespecified interim analysis, which included 238 deaths and 360 PFS events. At the time of data cutoff, 11% of patients remained on study treatment. Of patients discontinuing treatment, 72% did so for disease progression and 12% did so because of adverse events.

Efficacy

Efficacy results are shown in Table 4. Patients in the A+EC arm demonstrated a statistically significant and clinically meaningful improvement in OS compared with those in the control arm, with a median OS of 12.3 months (95% CI, 10.8–15.9) compared with 10.3 months (95% CI, 9.3–11.3).

Table 1. Atezolizumab background information

Atezolizumab	Description
Structure	Fc-engineered, humanized, nonglycosylated IgG1 kappa immunoglobulin with a calculated molecular mass of 145 kDa.
Mechanism of action	PD-L1 blocking antibody.
Pharmacokinetics	Patients' exposure to atezolizumab increases dose-proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the dose of 1,200 mg every 3 wk. Steady state is achieved after 6 to 9 wk following multiple doses.
Prior approvals	Metastatic NSCLC: first-line treatment of patients whose tumors have high PD-L1 expression (PD-L1 stained ≥50% of tumor cells [≥50%] or PD-L1 stained tumor-infiltrating IC covering ≥10% of the tumor area [IC ≥10%]) with no EGFR or ALK genomic tumor aberrations; in combination with bevacizumab, carboplatin, and paclitaxel for the first-line treatment of patients with nonsquamous NSCLC without EGFR or ALK genomic aberrations; in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations; patients with disease progression on platinum-containing chemotherapy. Advanced or metastatic urothelial carcinoma: patients who are cisplatin-ineligible and whose tumors express PD-L1 IC ≥5%; patients ineligible for any platinum therapy regardless of PD-L1 status; patients with disease progression during or following any platinum-containing chemotherapy or within 12 mo of neoadjuvant or adjuvant chemotherapy (accelerated approval). Advanced or metastatic triple-negative breast cancer: in combination with paclitaxel protein-bound for patients whose tumors express PD-L1 IC ≥1% (accelerated approval).

Source: Atezolizumab [12].
Abbreviations: EGFR, epidermal growth factor receptor; IC, immune cell; IgG, immunoglobulin G; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1.

Table 2. Durvalumab background information

Durvalumab	Description
Structure	Human IgG1 kappa monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture.
Mechanism of action	Programmed cell death ligand 1 blocking antibody.
Pharmacokinetics	PK exposure increases more than dose proportionally at doses <3 mg/kg and dose proportionally at doses ≥3mg/kg every 2 wk. Steady state is achieved at approximately 16 wk.
Prior approvals	Advanced or metastatic urothelial carcinoma: patients with disease progression on platinum-containing chemotherapy; patients with disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (accelerated approval). Unresectable, stage III non-small cell lung cancer: treatment of patients whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Source: Durvalumab [13].
Abbreviations: IgG, immunoglobulin G; PK, pharmacokinetics.

The HR for PFS as assessed by investigator favored the atezolizumab arm, with an HR of 0.77 (95% CI, 0.62–0.96; p = .0170 as compared with an allocated α of 0.05), corresponding to an estimated median PFS of 5.2 months (95% CI, 4.4–5.6) in the A+EC arm compared with median PFS of 4.3 months (95% CI, 4.–4.5) in the control arm. Overall, complete responses were seen in 2% of patients with 58% of patients experiencing a partial response. With a median duration of follow-up of 14 months, ORR and DoR were similar between the arms, with confirmed ORR of 60% (95% CI, 53–67) in the A+EC arm and 64% (95% CI, 57–71) in the control arm and estimated median DoR of 4.2 months and 3.9 months, respectively.

Safety

In IMpower133, 198 patients received at least one dose of atezolizumab. Adverse events were graded as per CTCAE v4.0. The median duration of atezolizumab for patients in the A+EC arm was 4.7 months (range, 0 to 21). Among the 198 patients receiving atezolizumab, 32% were exposed to atezolizumab for 6 months or longer, and 12% were exposed for 12 months or longer. Although the incidence of grade 3 or 4 adverse events (AEs) was similar between the two treatment arms, more patients receiving A+EC discontinued any drug in the three-drug regimen because of an AE (11%) compared with the control arm (3%). The most frequent adverse reaction requiring permanent discontinuation in more than 2% of patients was infusion-related reaction (2.5%).

The most common adverse events occurring in at least 20% of patients treated with A+EC were fatigue or asthenia (39%), nausea (38%), alopecia (37%), decreased appetite (27%), constipation (26%), and vomiting (20%). The most common grade 3–4 adverse events occurring in at least 2% of patients treated with A+EC were fatigue or asthenia (5%), febrile neutropenia (3.5%), pneumonia (3.0%), infusion-related reaction (2.0%), vomiting (2%), and diarrhea (2%). The grade 3–4 laboratory abnormalities occurring in at least 2% of patients treated with atezolizumab included neutropenia (45%), thrombocytopenia (20%), anemia (17%), hyponatremia (15%), lymphopenia (14%), hyperglycemia (10%), hypomagnesemia (5%), increased blood creatinine (4%), hypocalcemia (3%), and increased alanine aminotransferase (3%). Deaths due to AE were reported for four patients (2%) in the A+EC treatment arm. These included

Table 3. Key baseline characteristics of patients in CASPIAN and IMpower133

Characteristics	D+EP (*n* = 268)	A+EC (*n* = 201)
Age group, *n* (%), years		
<65	167 (62)	111 (55)
≥65	101 (38)	90 (45)
Gender, *n* (%)		
Male	190 (71)	129 (64)
Female	78 (29)	72 (36)
Race, *n* (%)		
White	229 (85)	163 (81)
Black or African American	2 (1)	1 (0)
Asian	36 (13)	33 (16)
Other	1 (<1)	4 (2)
Smoking/nicotine history, *n* (%)		
Current	120 (45)	74 (37)
Former	126 (47)	118 (59)
Never	22 (8)	9 (5)
WHO/ECOG performance status, *n* (%)		
(0) Normal activity	99 (37)	73 (36)
(1) Restricted activity	169 (63)	128 (64)

Abbreviations: A+EC, atezolizumab in combination with etoposide and carboplatin; D+EP, durvalumab + etoposide/platinum; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization.

pneumonia (1), respiratory failure (1), death not otherwise specified (1), and neutropenia (1).

Immune-mediated adverse events (imAEs) are known toxicities of the checkpoint inhibitor class of products and were included as adverse events of special interest in IMpower133. The most common imAEs in the A+EC arm (>10%) included colitis and diarrhea (19%) and thyroid endocrinopathies (15%). Grade 3–4 imAEs >2% included colitis and diarrhea (3%) and infusion-related reactions (2%). Overall, the incidence of the most common imAEs in the atezolizumab arm in IMpower133 is similar to (hypothyroidism, hyperthyroidism, colitis) or lower (pneumonitis, and hepatitis) than that observed in patients with NSCLC treated with atezolizumab in combination with platinum-based chemotherapy with or without bevacizumab in IMpower150. The incidence of infusion-related reactions in atezolizumab-treated patients in IMpower133 was similar to that in IMpower150. The incidence of infections was lower in atezolizumab-treated patients in IMpower133 (32%) relative to atezolizumab administered as a single agent (43%) and atezolizumab-treated patients in IMpower150 (47%). There was no increase in the incidence of grade 3–4 imAEs in atezolizumab-treated patients in IMpower133 relative to atezolizumab-treated patients in IMpower150.

D+EP; CASPIAN

Key baseline demographic characteristics of patients enrolled on CASPIAN are noted in Table 3. The data set supporting the approval of D+EP was based on the data cutoff date used for the interim analysis, which occurred after a total of 336 death events had occurred between the D+EP and EP groups (62.6% maturity). At the time of data cutoff, 43 (16%) patients randomized to D+EP remained on study treatment.

Table 4. CASPIAN and IMpower133 efficacy results

Efficacy Parameters	D+EP	A+EC
Median OS (95% CI), mo	13.0 (11.5–14.8)	12.3 (10.8–15.9)
Hazard ratio[a] (95% CI)	0.73 (0.59–0.91)	0.70 (0.54–0.91)
Median PFS (95% CI), mo	5.1 (4.7–6.2)	5.2 (4.4–5.6)
Hazard ratio[a] (95% CI)	0.78 (0.65–0.94)	0.77 (0.62–0.96)
Confirmed ORR, % (95% CI)	68 (62–73)	60 (53–67)
Median DoR (95% CI), mo	5.1 (4.9–5.3)	4.2 (4.1–4.5)

[a]Hazard ratio of treatment vs. control computed using the Cox model. For D+EP, the hazard ratios were stratified by planned platinum therapy in Cycle 1 (carboplatin or cisplatin). For A+CE, the hazard ratios were stratified by sex and ECOG performance status.
Abbreviations: A+EC, atezolizumab in combination with etoposide and carboplatin; CI, confidence interval; D+EP, durvalumab + etoposide/platinum; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

Efficacy

Efficacy results for CASPIAN with a median duration of follow-up in censored patients of 14.2 months in the D+EP arm and 13.5 months in the control arm are shown in Table 4. Patients treated with D+EP demonstrated a statistically significant and clinically meaningful improvement in OS with a hazard ratio of 0.73 (95% CI, 0.59–0.91; p = .0047); median OS was 13.0 months (95% CI, 11.5–14.8) in the durvalumab plus EP arm compared with 10.3 months (95% CI, 9.3–11.2) in the EP alone arm, with 34% (95% CI, 26.9–41.0) versus 25% (95% CI, 18.4–31.6) of patients alive at 18 months, respectively. No statistically significant difference was seen in PFS between the two treatment arms, with a median PFS of 5.1 months (95% CI, 4.7–6.2) in the D+EP arm and 5.4 months (95% CI, 4.8–6.2) in the control arm. However, an overall treatment benefit of D+EP over EP alone (HR, 0.78; 95% CI, 0.65–0.94) was observed with a delayed separation of the Kaplan-Meier curves for PFS beginning at 6 months. The confirmed ORR in the D+EP group was 68% (95% CI, 62–73) compared with 58% in the control group (odds ratio, 1.56; 95% CI, 1.10–2.22). In total, six patients in the D+EP arm achieved complete responses compared with two patients in the EP arm. Although the median DoR was 5.1 months in both groups, the proportion of patients estimated as having continued response at 12 months after the onset of response was numerically higher in the D+EP arm compared with the control arm (22.7%, vs. 6.3%, respectively). FDA also conducted analyses to estimate overall survival by type of platinum chemotherapy received at treatment cycle 1. For patients who received cisplatin, the median OS was 14.9 months in the D+EP arm and 12.8 months in the control arm, with an HR of 0.88 (95% CI, 0.55–1.41). For patients who received carboplatin, the median OS was 12.5 months in the D+EP arm and 10.1 months in the control arm, with an HR of 0.70 (95% CI, 0.55–0.89).

Table 5. FDA benefit-risk assessment

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	Lung cancer is the leading cause of cancer death in the U.S.; SCLC accounts for 13% of all lung cancer cases. Approximately 75% of patients with SCLC present with extensive stage. disease, for which median OS is 8–10 mo.	This disease is serious and life-threatening and represents a significant unmet medical need.
Current treatment options	In the US, current standard front line treatment for patients with ES-SCLC is a platinum-based (cisplatin or carboplatin) doublet chemotherapy most commonly with etoposide.	Current treatments have been the standard of care for many years and are palliative in nature with generally short response durations.
Benefit	A+EC: Improvement in mOS of 12.3 mo compared with 10.3 mo in the control arm with a HR of 0.70 (95% CI, 0.54–0.91; p = .0069). D +EP: improvement in mOS of 13.0 mo compared with 10.3 mo in the control arm with a HR of 0.73 (95% CI, 0.59–0.91; p = .0047).	Substantial evidence of effectiveness for first-line use of atezolizumab or durvalumab with platinum-based chemotherapy in this patient population with clinically meaningful improvement in OS over currently available therapy.
Risk	Tolerated in majority of patients. Important risks include endocrine disorders, hepatitis, pneumonitis, colitis, and infection.	No new safety signals were noted for either atezolizumab or durvalumab in this patient population.
Risk management	Significant clinical experience with immune checkpoint inhibitors, both as monotherapy, and in combination with chemotherapy. AESI include imAEs for which close monitoring and corticosteroid use are recommended.	The safe use of both atezolizumab and durvalumab in combination with chemotherapy can be managed through routine pharmacovigilance.

Abbreviations: A+EC, atezolizumab in combination with etoposide and carboplatin; AESI adverse events of special interest; CI, confidence interval; ES, extensive stage; HR, hazard ratio; imAE, immuno-mediated adverse event; mOS, median overall survival; OS, overall survival; SCLC, small cell lung cancer.

Safety

In CASPIAN, 265 patients received at least one dose of D +EP. Adverse events were graded per CTCAE v 4.03. The median total duration of exposure to durvalumab was 28 weeks (range, 0.3–94.3) for patients in the D+EP treatment arm. The rates of grade 3 or 4 AEs were similar between both the D+EP and control arms at 59% and 59%, respectively, as were the rates of AEs leading to dose delay or interruption of study treatment at 42% and 38%, respectively.

The most common adverse events occurring in at least 20% of patients treated with D+EP were neutropenia (42%), anemia (39%), nausea (34%), and alopecia (31%). The most common grade 3–4 AEs occurring in at least 2% of patients treated with D+EP included neutropenia (24%), anemia (9%), leukopenia (6%), neutrophil count decrease (6%), thrombocytopenia (6%), febrile neutropenia (5%), hyponatremia (4%), increased lipase (3%), hypertension (3%), and amylase increased (2%). Causally related AEs leading to death in the D+EP arm included hepatotoxicity (1), dehydration (1), sepsis (1), pancytopenia (1), and cardiac arrest (1).

Immune-mediated AEs were reported in 19.6% of patients in the D+EP arm. Grade 3 or 4 imAEs were reported in a total of 4.5% of patients, with 1.1% of patients discontinuing study treatment. Grade 3 or 4 imAEs occurring in >1% of patients included immune-mediated hepatic events (1.9%) and type 1 diabetes (1.5%). No notable difference was demonstrated in the incidence and severity of imAEs or rates of steroid use between patients on CASPIAN treated with D+EP versus a pooled safety data analysis of 1,889 patients across multiple clinical trials treated with durvalumab monotherapy.

Discussion

FDA review of IMpower133 and CASPIAN found that treatment with both atezolizumab and durvalumab in combination with platinum-doublet chemotherapy had a favorable benefit-risk profile (Table 5) in the treatment of patients with ES-SCLC. Both trials reported similar efficacy results. No new safety signals for either atezolizumab or durvalumab were identified in IMpower133 or CASPIAN, and the observed safety profiles of both A+EC and D+EP are acceptable when assessed in the context of the treatment of a life-threatening disease.

IMpower133 and CASPIAN did have some key differences in study design and patient populations. Patients in IMpower133 only received carboplatin, whereas patients in CASPIAN were allowed to receive carboplatin or cisplatin therapy, although only 25% of patients received cisplatin. Additionally, patients in the control arm in IMpower133 received four cycles of platinum-based chemotherapy, whereas in CASPIAN, up to six cycles could be administered. Despite this difference, patients receiving standard of care chemotherapy in IMpower133 and CASPIAN both had median OS of 10.3 months, supporting the adequacy of treatment in the control arm in both trials and establishing expectations for survival with traditional platinum-based chemotherapy in this patient population. IMpower133 also only enrolled patients that had treated brain metastases, whereas CASPIAN allowed patients to have asymptomatic, untreated brain metastases. Whereas PCI was permitted in IMpower133 in both the experimental and control arms during the maintenance therapy with either atezolizumab or placebo, in CASPIAN, PCI was only allowed in the control arm, following chemotherapy. Importantly, however, despite these differences, the efficacy results and overall benefit-risk profile of both

atezolizumab and durvalumab in combination with platinum-based chemotherapy is acceptable and comparable.

The parallel results in these large, randomized trials in ES-SCLC provide confidence in the combination strategy of immunotherapy and chemotherapy. Prior to these results, there have been mixed findings regarding the efficacy of anti–PD-L1 antibodies in SCLC. Both pembrolizumab (KEYNOTE-158, KEYNOTE-028) and nivolumab (CHECKMATE-032) were granted accelerated approval in the third-line treatment of patients with SCLC who had progression on platinum-based chemotherapy and at least one other prior line of therapy based on ORR and DoR. However, multiple phase III randomized controlled trials have had negative results. CHECKMATE-331, which evaluated nivolumab as second-line treatment versus chemotherapy in SCLC patients after progression on platinum-based chemotherapy and CHECKMATE-451, which evaluated nivolumab with or without ipilimumab maintenance therapy versus placebo after platinum-based chemotherapy failed to show improvement in OS. KEYNOTE-604 evaluated pembrolizumab in combination with platinum-based chemotherapy compared with chemotherapy alone as front-line treatment and demonstrated an improvement in PFS but not OS.

Although IMpower133 did demonstrate that immunochemotherapy could improve survival in first-line treatment of patients with SCLC, the negative results from the aforementioned studies led to a degree of uncertainty regarding whether immunochemotherapy was an effective therapeutic modality in the SCLC patient population. The results of CASPIAN are therefore supportive in validating the efficacy of immunochemotherapy in this patient population. The evidence for both atezolizumab and durvalumab in combination with platinum-based chemotherapy, as summarized in the benefit-risk assessment in Table 5, is considered sufficient for the respective approvals of A+EC and D+EP for the intended clinical use. These two approvals provide the first novel treatments to demonstrate an improvement in OS in the front-line treatment of advanced SCLC in over 3 decades and validate the activity of immunochemotherapy in this patient population.

Conclusion

The IMpower133 and CASPIAN studies demonstrated acceptable benefit-risk profiles to support the approvals of atezolizumab and durvalumab in combination with platinum-based chemotherapy for the first-line treatment of patients with ES-SCLC. These approvals were based on statistically significant and clinically meaningful improvements in overall survival. Although the results of IMpower133 and CASPIAN demonstrate the activity of immunochemotherapy in this patient population and have led to the first approvals in small cell lung cancer with a survival benefit since platinum-based chemotherapy, the benefits continue to be limited to a subset of patients without the identification of predictive biomarkers. Continued investigation of immune-modulative therapies in this disease is warranted.

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Disclosures

The authors indicated no financial relationships.

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