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REVIEW ARTICLE

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Immune checkpoint inhibitors in the first-line treatment of metastatic small-cell lung cancer

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ABSTRACT

Small-cell lung cancer is the most aggressive form of lung cancer. Most patients are diagnosed at a late disease stage when the prognosis is poor. The treatment algorithm for small-cell lung cancer remained unchanged for years, with chemotherapy as the first-line option. However, progress has been made with the recent development of immune checkpoint inhibitors, two of which — atezolizumab and durvalumab — have been approved in combination with chemotherapy as first-line treatment for advanced small-cell lung cancer. This review presents detailed data concerning the efficacy and safety of atezolizumab and durvalumab from both registration trials and real-world studies, as well as the results of clinical trials of other immune checkpoints inhibitors. Finally, the issue of identifying biomarkers to predict the efficacy of immunochemotherapy is discussed.

Key words: small-cell lung cancer, chemotherapy, immunotherapy, predictive markers, systemic therapy

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Introduction

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma that is diagnosed in about 15% of patients with primary lung neoplasms. It is estimated that SCLC causes 250 000 new cases and at least 200 000 deaths globally each year. In Europe, the prevalence of SCLC is about 1–5 per 10 000 people [1–3]. In Poland, 21 226 new cases of lung cancer were reported in 2018 and more than 3 000 were estimated to be SCLC [4].

When lung cancer is diagnosed, a pathological evaluation according to the current World Health Organization (WHO) classification criteria is required to determine the histological type of the tumor and relevant staging parameters [1–5]. Cells of SCLC under a microscope appear round, oval, or spindle-shaped, and have poorly defined cell borders, scant cytoplasm, high nuclear-to-cytoplasmic ratio, granular nuclear chromatin, and absent or inconspicuous nucleoli. Numerous mitoses are characteristic features of SCLC cells. In rare cases, combined SCLC can occur, which consists of typical small cells and other cells of adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, or sarcomatoid (spindle- or giant-cell) carcinoma areas, and non-small-cell lung cancer (NSCLC) [6]. Additionally, when a pathomorphological diagnosis is equivocal, immunohistochemical staining should be applied. The most sensitive marker is CD56, but it has low specificity. Thyroid transcription factor 1 (TTF1) is also a helpful marker, and Ki-67 is used to distinguish high-grade SCLC from carcinoid tumors [5, 7, 8].

Small-cell lung cancer grows rapidly, and distant metastases develop early, leading most cases to be diagnosed at an advanced stage. Staging of SCLC should be made according to the Union for International Cancer Control (UICC) Tumor, Nodes, Metastases (TNM) classification (8th edition) [9]. However, due to the

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high dynamics of disease progression, the usefulness of TNM classification in treatment planning may be limited. Therefore, to unify the different stages in relation to therapeutic options the terms limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC) are often used in clinical trials and in practice [1, 10]. Only about 30% of patients with SCLC are diagnosed with LS-SCLC, which means that it is confined to one hemithorax and regional lymph nodes. Hence, most patients have ES-SCLC at diagnosis, which corresponds to stage IV according to the TNM classification in most publications [1, 10, 11].

Treatment options for patients with SCLC are determined by stage, general condition (WHO performance status), and comorbidities. Although treatment for LS-SCLC is of curative intent and treatment for ES-SCLC is palliative, chemotherapy forms the backbone of treatment, either alone or combined with irradiation [3]. Surgery (followed by chemotherapy and radiotherapy) is performed in only the very few patients who are diagnosed at a very early disease stage. However, more typically, patients with early-stage or locally advanced disease are also treated with radiochemotherapy [1, 10].

Recently, there has been a breakthrough in the treatment of ES-SCLC with the introduction of a new class of drugs, and this will be described in this article.

Treatment of metastatic SCLC

For many years the first-line treatment for metastatic SCLC was chemotherapy with cisplatin or carboplatin and etoposide. In patients under 75 years, with good performance status (PS) after treatment, and with documented stabilization or regression of lesions, prophylactic cranial irradiation (PCI) should be considered. For patients not undergoing PCI, magnetic resonance imaging (MRI) of the brain is recommended, and serial MRIs are then advised as part of follow-up [1].

When first-line treatment is ineffective or if relapse occurs within three months, treatment with topotecan may be considered in patients with acceptable general condition and without persistent side effects of previous chemotherapy. When the response to first-line chemotherapy lasts more than three months, repetition of the first-line regimen (reinduction) may be favorable [1, 10, 12].

Although the response rate to chemotherapy is high and could reach more than 70%, most patients relapse; as a consequence, the overall prognosis in patients with SCLC is poor. The 5-year relative survival rate has improved over time but is still very low (about 6%) [3, 10, 13]. For patients with ES-SCLC, median survival is less than 12 months and long-term disease-free survival is rare [14]. These facts highlighted the urgency of developing novel treatments; however, standard therapy remained unchanged for years, as trials failed to offer any improvement.

Immune checkpoint inhibitors

It is known that SCLC, like other cancers, expresses some neoantigens on the cell surface, which are recognized by T cells. This should be followed by a multi-step antitumor immune system response and protective immunity (Fig. 1); however, this mechanism often fails. This may be due to the tumor's ability to attenuate or avoid T-cell-mediated anticancer activity at each step of the immune response. One strategy involves interaction between the programmed cell death 1 (PD-1; also known as CD279) and programmed cell death ligand 1 (PD-L1; also called CD274). Immune checkpoint protein PD-1 is an apoptosis-associated molecule expressed mainly on the surface of activated T lymphocytes. In turn, PD-L1 is the ligand for PD-1 and is expressed on the surface of antigen-presenting cells or macrophages. The binding of PD-L1 with PD-1 plays a role in the maintenance of peripheral tolerance, and the prevention of autoimmunity via several mechanisms (e.g. by affecting the production of cytokines and inhibiting activation of immune cells) [15–18].

This fact shifted researchers' interest in immune checkpoint inhibitors (ICIs) as inhibition of the PD-1/PD-L1 axis was assumed to prevent suppression of T cells and to enhance antitumor activity. Several studies of monoclonal antibodies targeting PD-L1 or PD-1 in different tumors indicated that such therapy may be effective [19, 20]. The efficacy of ICIs was investigated in various cancers and beneficial outcomes led to the registration of this class of drugs for many indications (e.g. melanoma, Hodgkin lymphoma, renal-cell cancer, and NSCLC) as monotherapy or in combination with chemotherapy [21–24]. This prompted investigators to evaluate the synergistic effects of ICIs combined with chemotherapy in patients with ES-SCLC. Finally, after many years of unsuccessful attempts, progress in the treatment of ES-SCLC has been made. In 2019 and 2020, atezolizumab and durvalumab in combination with carboplatin and etoposide were approved by the US Food and Drug Administration (FDA) for the first-line treatment of patients with ES-SCLC [25]. In the same years, the European Medicines Agency (EMA) recommended the use of these drugs in European Union countries [26, 27].

Immunochemotherapy with atezolizumab and durvalumab in ES-SCLC

Atezolizumab

Atezolizumab is a fully-humanized kappa IgG1 monoclonal antibody that can bind to PD-L1 and inhibit its interaction with PD-1, preventing the downregulation of T-cell function and allowing T cells to mediate tumor cell death [28]. Atezolizumab can also bind B7-1, which

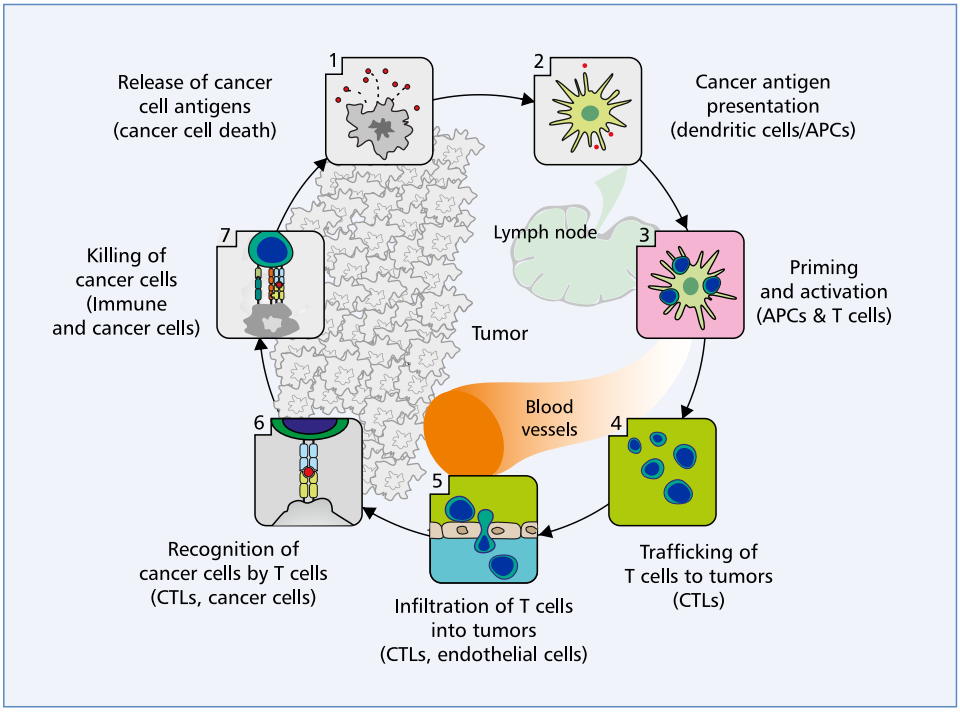

Figure 1. Cancer-immunity cycle [18]; APCs — antigen-presenting cells; CTLs — cytotoxic T lymphocytes

is found on activated antigen-presenting cells and can inhibit T-cell proliferation via binding to PD-L1 [29].

Approval of atezolizumab was based on data from the multinational, phase-3, IMpower133 trial [30], which evaluated the efficacy and safety of atezolizumab in 403 adult chemotherapy-naive patients with ES-SCLC. The induction phase involved four cycles administered every 21 days, and the maintenance phase lasted until disease progression, as assessed with Response Evaluation Criteria in Solid Tumor Version 1.1. (RECIST v1.1), or unacceptable toxicity. Patients were randomized to two arms: atezolizumab (1200 mg intravenously on day 1 of cycles 1–4 and cycle 5 onward) or placebo, both with carboplatin (AUC = 5 intravenously on day 1 of cycles 1–4) and etoposide (100 mg/m^2 intravenously on days 1–3 of cycles 1–4).

The primary outcomes were progression-free survival (PFS) assessed with RECIST v1.1, measured from baseline until disease progression or death, whichever occurred first (up to approximately 23 months), and overall survival (OS), measured from baseline until death from any cause (up to approximately 23 months). The median age of all patients was 64 years, and most were male (65%) and current or previous smokers (97%). Approximately 9% of patients in each treatment arm had brain metastases at baseline. The first evaluation was performed after a median follow-up of 13.9 months, a median of 4.7 months of atezolizumab (4.1 months for placebo) treatment, and a median of seven atezolizumab doses (six doses for placebo). The median number of chemotherapy doses was the same in both groups [31].

The addition of atezolizumab to chemotherapy significantly prolonged PFS and OS (Tab. 1). The 12-month OS rate was also higher in the atezolizumab group than in the placebo group (51.7 *vs.* 38.2%). In the atezolizumab group, 51.7% of patients died *vs.* 66.3% in the control group, and 85.1% had disease progression or died *vs.* 93.6% of patients in the control group. Adverse events (AEs) related to the regimen occurred in 94.9% of patients in the atezolizumab group *vs.* 92.3% in the placebo group. Rates of grade 3 or 4 treatment-related AEs (TRAEs) were similar between the groups (56%), with myelosuppression being the most common. Immune-related AEs (irAEs) occurred slightly more often in the atezolizumab group (39.9 *vs.* 24.5%), with rash and hypothyroidism being the most common [31].

Detailed analysis of safety data and patient-reported outcomes in the IMpower133 trial two years later revealed that the addition of atezolizumab to chemotherapy does not reduce the safety of treatment or patients' quality of life [32].

The most recent updated analysis of the IMpower133 study outcomes was performed at a median follow-up of 22.9 months [33] and showed that OS, PFS, and the rate of AEs were similar to those obtained in the interim analysis (Tab. 1). The updated data continued to demonstrate the clinical benefit of adding atezolizumab to chemotherapy [33].

Table 1. Comparison of data from registration studies of atezolizumab and durvalumab in patients with ES-SCLC

		IMpower133 NCT02763579		CASPIAN NCT03043872	
Reference		Horn et al., 2018 [31]	Liu et al., 2021 [33]	Paz-Ares et al., 2019 [38]	Goldman et al., 2021 [39]
Study type		Phase 1/3, randomized, double-blind, placebo-controlled		Phase 3, randomized, open-label	
Patients	Number	403		537/805	805
	PS score	0/1		0/1	
	Treated asymptomatic brain metastases	+ (9%)		+ (10%)	
Treatment	Arms	Atezolizumab + CP/ET *vs.* placebo + CP/ET		(I) Durvalumab + tremelimumab + P/ET *vs.* (II) durvalumab + P/ET *vs.* (III) P/ET	
				(II) and (III) assessed	(I) and (II) and (III) assessed
	Number of ICI doses [median (range)]	7 (1–30)	7 (1–39)	7 (6–11)	(I) 6 (4–10) (II) 7 (6–11)
	Months of ICI treatment [median (range)]	4.7 (0–21)	4.7 (0–29)	7.0 (5–11)	(I) 8.0 (4–10) (II) 7.0 (5–11)
	Chemotherapy cycles	Every 3 weeks		Every 3 weeks	
	Number of chemotherapy cycles	Four in both groups		Four in the ICI group, Six in the P/ET group	
	PCI	Permitted in both groups (11%)		Permitted in the P/ET group only (8%)	
Median follow-up (months)		13.9	22.9	14.2	25.1
Results	Median OS (months)	12.3 *vs.* 10.3	12.3 *vs.* 10.3	13.0 *vs.* 10.3	10.4 *vs.* 12.9 *vs.* 10.5
	12-month median OS (%)	51.7 *vs.* 38.2	51.9 *vs.* 39.0	54 *vs.* 40	43.8 *vs.* 52.8 *vs.* 39.3
	24-month median OS (%)	nd	22.0 *vs.* 16.8	nd	23.4 *vs.* 22.2 *vs.* 14.4
	Median PFS (months)	5.2 *vs.* 4.3 (*)	5.2 *vs.* 4.3	5.1 *vs.* 5.4	4.9 *vs.* 5.1 *vs.* 5.4
	ORR (%)	60.2 *vs.* 64.4	60.2 *vs.* 64.4	68 *vs.* 58	58 *vs.* 68 *vs.* 58
	Median DoR (months)	4.2 *vs.* 3.9	4.2 *vs.* 3.9	5.1 *vs.* 5.1	5.2 *vs.* 5.1 *vs.* 5.1
	Remaining responsive at 12 months (%)	14.9 *vs.* 5.4 (at data cutoff)	nd	23 *vs.* 6	24.9 *vs.* 23.2 *vs.* 7.3
	Remaining responsive at 24 months (%)	nd	nd	nd	17.2 *vs.* 13.5 *vs.* 3.9
	Any TRAEs (%)	94.9 *vs.* 92.3	94.9 *vs.* 92.3	89 *vs.* 90	90 *vs.* 89 *vs.* 90
	Grade 3 or 4 TRAEs (%)	56.6 *vs.* 56.1	57.1 *vs.* 56.1	46 *vs.* 52	55 *vs.* 46 *vs.* 52
	irAEs (%)	40 *vs.* 25	40 *vs.* 24	20 *vs.* 3	36 *vs.* 20 *vs.* 3

CP/ET — carboplatin plus etoposide; ICI — immune checkpoint inhibitor; irAEs — immune-related adverse events; DoR — median duration of treatment; nd — no data; ORR — overall response rate; OS — overall survival; PCI — prophylactic cranial irradiation; P/ET — platin (carboplatin or cisplatin) plus etoposide; PFS — progression-free survival; PS — performance status; TRAEs — treatment-related adverse events

An exploratory analysis focused on long-term survivors (i.e. patients who survived ≥18 months after randomization) in the IMpower133 study found that the percentage of long-term survivors was higher in the atezolizumab group than in the control group (34% *vs.* 20%). Although the authors concluded that patients with ES-SCLC can benefit from chemotherapy combined with atezolizumab regardless of patient and disease characteristics, some differences exist between subgroups. Patients with worse PS, higher lactate dehydrogenase activity, larger tumor load, and brain metastases at baseline were less likely to benefit from immunochemotherapy [34].

Based on the above results, atezolizumab was given first-in-class approval to be combined with chemotherapy as an option for untreated patients with ES-SCLC. Treatment of patients with ES-SCLC with atezolizumab was included in the current National Comprehensive Cancer Network (NCCN) guidelines [11]. Atezolizumab has been reimbursed in Poland for adult patients with ES-SCLC since July 2021 [35].

Durvalumab

The second immune checkpoint inhibitor that may be applied in ES-SCLC therapy is durvalumab, another human IgG1 kappa monoclonal antibody that targets PD-L1. The CASPIAN clinical trial recently evaluated the efficacy of durvalumab added to standard chemotherapy in patients with ES-SCLC [36]. In a subgroup of patients, dual ICIs treatment was applied using tremelimumab, an inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on the surface of T cells. Signaling from CTLA-4 inhibits T-cell activation, so blockade of CTLA-4 with a monoclonal antibody might be expected to enhance the antitumor response [37]. In the study, 805 adult participants with previously untreated SCLC were randomly assigned to three arms: (I) durvalumab plus tremelimumab plus platinum plus etoposide; (II) durvalumab plus platinum plus etoposide; and (III) platinum plus etoposide chemotherapy. Durvalumab was given at a dose of 1500 mg every three weeks (four cycles) followed by every four weeks in the maintenance phase. Tremelimumab was given at a dose of 75 mg every three weeks (four cycles), and an additional dose was given in week 16. Chemotherapy consisted of etoposide 80–100 mg/m^2 (administered on days 1–3 of 21-day cycles), with carboplatin (AUC = 5–6 intravenously) or cisplatin (75–80 mg/m^2 intravenously on day 1 of each cycle) and was administered for up to four cycles in the experimental arms and up to six cycles in the control arm.

The primary outcomes were OS, assessed at interim analysis, measured from baseline until death from any cause (up to approximately 23 months) for arm II and III and OS, assessed at the final analysis, measured from baseline until death from any cause (up to approximately 33 months) for arms I, II, and III.

The interim analysis performed after a median follow-up of 14.2 months presents only the results of patients from arms II and III (n = 537) [38]. Their median age was 63 years, and most were men (70%), current or former smokers (93%), with stage IV disease at diagnosis (90%); 10% of patients had brain metastases at baseline. The median duration of durvalumab treatment was 28 weeks, and patients received a median of seven doses. The median duration of chemotherapy treatment was 11.9 weeks for the immunochemotherapy group (arm II) and 18.7 weeks for the chemotherapy group (arm III). In both groups, 78% of participants received carboplatin [38]. The results of this trial showed a significant improvement in OS in patients treated with durvalumab plus platinum plus etoposide (Tab. 1). The 12-month and 18-month OS rates were also higher in the immunochemotherapy group than in the control chemotherapy group (54% *vs.* 40% 12-month OS; and 34% *vs.* 25% 18-month OS).

In the durvalumab group, 58% of patients died compared with 67% in the chemotherapy group, and 84% in the durvalumab group had disease progression or died compared with 87% in the chemotherapy group. Grade 3 or 4 TRAEs occurred with the same frequency (62%) in both groups, with neutropenia and anemia being the most common. Immune-mediated AEs were reported in 20% of patients treated with immunochemotherapy and 3% of patients treated with chemotherapy only, with most being grade 1–2 [38].

The next evaluation of CASPIAN trial results was performed after a median follow-up of 25.1 months and included all three arms of the study (805 participants) [39]. The median age of patients was 63 years, and most were male (72%), current or former smokers (94%), with stage IV disease at diagnosis (91%). The median duration of treatment with durvalumab was 23.1 weeks (median six doses) in the immunotherapy plus tremelimumab group and 28 weeks (median seven doses) in patients receiving immunotherapy. Despite a lack of OS benefit in the durvalumab and tremelimumab plus chemotherapy arm *vs.* chemotherapy alone (Tab. 1), durvalumab plus chemotherapy led to higher OS at 24 months and higher PFS at 12 and 24 months compared with chemotherapy alone. This analysis confirmed that the improvement in OS with durvalumab first demonstrated in the interim evaluation was sustained [38]. However, the survival benefit observed in patients with brain and liver metastases at baseline was negligible compared with outcomes in patients without lesions [39, 40]. The percentage of patients who died was highest in the chemotherapy group (86%) and lower in patients with immunochemotherapy (78%) or immunochemotherapy plus tremelimumab (77%). In all groups, TRAEs occurred at a similar frequency and about half were grade 3 or 4; however, immunotherapy plus tremelimumab was associated with a higher proportion of serious AEs. The most common TRAEs were neutropenia and anemia. In turn, irAEs were noted most frequently in patients treated with tremelimumab, and the most common were hypothyroid events [38]. Moreover, analysis of patient-reported outcomes revealed that the addition of durvalumab to first-line chemotherapy maintained the quality of life and delayed worsening of patient-reported symptoms, functioning, and global health status compared with chemotherapy alone [41].

Durvalumab in combination with chemotherapy was the second monoclonal antibody approved for first-line treatment of adult patients with ES-SCLC. The recommended dose of durvalumab in the induction phase is 1500 mg given before chemotherapy on the same day, every 3 weeks (21 days) for four cycles, and the maintenance phase includes 1500 mg given every 4 weeks until disease progression or unacceptable toxicity [42]. Durvalumab in combination with chemotherapy is also included in the NCCN guidelines [11]. However, in Poland, durvalumab is reimbursed only for consolidation therapy in patients with locally advanced, inoperable NSCLC after completion of concurrent chemoradiotherapy [35].

Analysis of PD-L1 expression in available tissue samples from patients included in the CASPIAN study showed expression of PD-L1 greater than 1% in 27% of samples, mainly on immunochemotherapy. No correlation between PD-L1 expression and treatment outcomes was observed, which suggests that PD-L1 is not a predictive biomarker for treatment outcomes in patients with ES-SCLC treated with durvalumab [43].

Comparison of the main results and design of the IMpower133 and CASPIAN studies

The IMpower133 and CASPIAN trials demonstrated that the addition of atezolizumab or durvalumab to chemotherapy provided benefits in the first-line treatment of patients with ES-SCLC. Moreover, a systematic review and network meta-analysis of first-line treatment options for patients with ES-SCLC revealed that the combination of durvalumab or atezolizumab with chemotherapy may be an optimal approach [44, 45]. However, data comparing the effectiveness and safety of these drugs are scant. Some insight was provided by a recent meta-analysis that demonstrated no significant difference between the drugs in improving OS and PFS. According to this analysis, durvalumab was superior to atezolizumab in terms of the overall response rate (ORR) but also had a higher risk of irAEs [46].

Conclusions concerning the efficacy of atezolizumab and durvalumab in subgroups of patients with brain or liver metastases were slightly different. The IMpower133 study found no benefit of adding atezolizumab in patients with these lesions [33]. The results of the CASPIAN trial suggested that durvalumab provides OS benefits regardless of baseline brain and liver metastases [39]. However, the observed benefit in patients with these lesions seemed to be minimal.

However, it is worth noting some differences in study designs (most are presented in Tab. 1). IMpower133 was double-blind, in contrast to the open-label design of the CASPIAN study. Furthermore, the protocol of the CASPIAN study allowed the use of either cisplatin or carboplatin, whereas only carboplatin was permitted in the IMpower133 study. The control group in the CASPIAN study also seems to be a stronger comparator than the IMpower133 control group because of the higher maximum number of chemotherapy cycles received (six *vs.* four). The number of chemotherapy cycles administered in the control group in the CASPIAN trial was also higher than that given in the durvalumab group (four cycles), whereas both the control and atezolizumab groups received the same number of cycles (four cycles) in the IMpower133 study. Another difference concerns PCI — this procedure was permitted only in the control group in the CASPIAN study but was allowed in both groups in the IMpower133 trial [31, 38].

Long-term durability of response in the IMpower133 and CASPIAN studies

The CASPIAN study results showed that the percentage of patients with a response after 12 and 24 months was more than three times higher in the durvalumab group than in the chemotherapy group [38, 39]. Moreover, this result was estimated to be sustained at a 3-year follow-up (17.6% *vs.* 5.8%) [47]. In the IMpower133 study, the percentage of patients with a response after 12 months was 14.9% for the atezolizumab group and 5.4% for the chemotherapy group. Response rates at 24 months were not provided [31].

Real-world evidence studies

Real-world evidence (RWE) studies concerning immunochemotherapy with atezolizumab or durvalumab are still limited.

The first RWE study of atezolizumab for the treatment of ES-SCLC was performed in Canada [48] and included 67 patients with ES-SCLC, 34 of whom were treated with chemotherapy plus atezolizumab and 33 of whom received chemotherapy only. Although the study aimed to include untreated patients, it was revealed during evaluation that 74% of patients in the atezolizumab group had already received at least one cycle of chemotherapy. At a median follow-up of 18 months, 18% of patients in the atezolizumab group were alive compared with 1% of patients in the chemotherapy group. Most patients in both groups developed progressive disease (91% *vs.* 97%, respectively). Median PFS and OS were better in the atezolizumab group; however, in patients with a performance status score of 2, there was no significant difference in survival between the groups. The median OS in patients without atezolizumab maintenance was half that of patients with atezolizumab maintenance. Moreover, patients who had thoracic radiation had a reduced risk of death. More patients had any AEs in the atezolizumab group. The most common AEs in both groups were hematology-related. Although the results of this study are similar to those of the Im-

power133 trial in terms of the efficacy of atezolizumab, they demonstrated a lower incidence of AEs; however, about half of AEs were severe. The studied population was rather small, and therefore outcomes should be interpreted with caution. The patient population in the RWE study was also more heterogeneous than that in the clinical trial [48].

Another RWE on ES-SCLC treatment with atezolizumab comes from Korea [49]. This study was conducted on 68 patients who were slightly older than those in the Impower133 trial, and more of them had worse PS and brain metastasis at baseline. After a median of 11.6 months of follow-up, treatment with chemotherapy plus atezolizumab led to a median OS of 12 months and median PFS of 4.6 months. The obtained ORR (75%) was higher than that in the IMpower133 study. TRAEs were noted in 89.7% of patients and half were grade 3 or 4 (mainly neutropenia, anemia, and thrombocytopenia), and irAEs were reported in 32.4% of patients [49].

Results of the third RWE study with atezolizumab were presented at the European Society for Medical Oncology (ESMO) Virtual Annual Meeting in September 2021. Although the median follow-up was half as long as in the IMpower133 study, the observed median PFS was similar [50].

At the same conference, the RWE phase-3b open-label, single-arm, multicenter trial concerning durvalumab was announced; however, the results have not yet been published [51].

Impact of brain metastases on treatment outcomes and safety

The efficacy of combining ICIs with chemotherapy in patients with ES-SCLC and brain metastases at diagnosis is controversial. The IMpower133 and CASPIAN trials included similar percentages of patients with asymptomatic or treated brain metastases at baseline, but the proportion of patients with brain involvement was small in both studies (9% *vs.* 10%). The results of the IMpower133 study showed a lack of OS benefit from the addition of atezolizumab in this subgroup [31, 33]. In the CASPIAN trial, the authors concluded that all patient subgroups benefitted; however, the observed OS and PFS benefits in patients with brain metastases were much lower than those in patients without central nervous system (CNS) lesions [39, 52]. The results may therefore be affected by the small number of patients with brain metastases included in the study (55 *vs.* 482 patients without CNS lesions) or by the worse clinical status of patients with lesions, which might reduce therapeutic benefits. Therefore, further detailed evaluation of the impact of ICIs in patients with brain metastases is necessary.

It was also observed that PCI performed in patients in the control group did not reduce the number of newly developed brain lesions. In the absence of baseline brain metastases, the safety profiles in the durvalumab and control subgroups were similar; in patients with lesions, durvalumab plus chemotherapy caused a lower number of serious AEs than chemotherapy alone [52].

The summary of product characteristics for atezolizumab and durvalumab does not discuss this issue and states only that subjects with treated metastases were involved in both trials and that those with active or untreated CNS metastases were excluded [42, 53]. Treatment with atezolizumab is not reimbursed for patients with CNS metastases in Poland [35]. Therefore, the effectiveness of immunochemotherapy in patients with EC-SCLC and brain metastases requires clarification in further studies.

Immunochemotherapy with pembrolizumab, nivolumab, and ipilimumab in ES-SCLC

The effectiveness of PD-L1 inhibitors (nivolumab and pembrolizumab) has also been assessed in patients with ES-SCLC. Early studies of pembrolizumab showed effectiveness in patients with previously treated ES-SCLC [54–56]. Pembrolizumab was approved as third-line therapy in patients with metastatic SCLC [25]. The efficacy of pembrolizumab as first-line therapy was recently assessed in patients with ES-SCLC within the KEYNOTE-604 study [57]. The addition of pembrolizumab to chemotherapy significantly improved PFS but did not provide the expected statistically significant benefits in OS (Tab. 2).

Significant improvements in both OS and PFS were observed when nivolumab was combined with chemotherapy for first-line treatment of previously untreated patients with ES-SCLC in a phase-2 study (Tab. 2) [58]. A phase-3 trial would therefore be reasonable for a more detailed assessment of the efficacy and safety of nivolumab in ES-SCLC. Based on the results of the CheckMate 032 trial, nivolumab was approved for third-line therapy in patients with metastatic SCLC [59]. In January 2021, nivolumab was withdrawn from the US market for the indication of SCLC with disease progression after platinum-based chemotherapy and at least one other line of therapy, following consultation with the FDA [60].

Ipilimumab is an ICI that can bind to CTLA-4 and impede immune system suppression. Ipilimumab given with carboplatin and paclitaxel improved immune-related PFS in untreated ES-SCLC in a phase-2 trial [61]. However, in a phase-3 study in a large group of patients with newly diagnosed ES-SCLC, the addition of

Table 2. Data from phase 2/3 studies of pembrolizumab, nivolumab, and ipilimumab in ES-SCLC

		KEYNOTE-604 NCT03066778	EA5161 NCT03382561	CA184-156 NCT01450761
Reference		Rudin et al., 2020 [57]	Leal et al., 2020 [58]	Reck et al., 2016 [62]
Study type		Phase 3, randomized, double-blind, placebo-controlled	Phase 2, randomized	Phase 3, randomized, double-blind
Patients	Number	453	160	1132
	PS score	0/1	0/1	0/1
	Treated brain metastases	+	+	+
Treatment	Arms	Pembrolizumab + P/ET *vs.* placebo + P/ET	Nivolumab + P/ET *vs.* P/ET	Ipilimumab + P/ET *vs.* placebo + P/ET
	Cisplatin option	+	+	+
	PCI	Permitted in both arms	Permitted in both arms	Permitted in both arms
Median follow-up (months)		21.6	nd	10.5 *vs.* 10.2
Results	Median OS (months)	10.8 *vs.* 9.7	11.3 *vs.* 9.3	11.0 *vs.* 10.9
	12-month median OS (%)	45.1 *vs.* 39.6	nd	40 *vs.* 40
	Median PFS (months)	4.5 *vs.* 4.3	5.5 *vs.* 4.7	4.6 *vs.* 4.4
	ORR (%)	70.6 *vs.* 61.8	52.3 *vs.* 47.7	62 *vs.* 62
	Median DoR (months)	4.2 *vs.* 3.7	nd	4.01 *vs.* 3.45
	Any TRAEs (%)	nd	nd	82 *vs.* 76
	Grade 3 or 4 TRAEs (%)	nd	77 *vs.* 62	48 *vs.* 44
	irAEs rate (%)	24.7 *vs.* 10.3	nd	57 *vs.* 28

irAEs — immune-related adverse events; DoR —duration of response; ORR — overall response rate; OS — overall survival; PCI — prophylactic cranial irradiation; P/ET — platin (carboplatin or cisplatin) plus etoposide; PFS — progression-free survival; PS — performance status; TRAEs — treatment-related adverse events

ipilimumab to chemotherapy showed no improvement in OS compared with chemotherapy alone (Tab. 2) [62].

The results of the above-mentioned clinical trials were verified in meta-analyses that have confirmed that combining anti-PD-1/PD-L1 inhibitors with chemotherapy as first-line treatment improves clinical efficacy in patients with SCLC compared with chemotherapy alone [63, 64]. Moreover, the efficacy of PD-1 or PD-L1 inhibitors added to chemotherapy is similar in terms of OS, PFS, and ORR. Safety profiles are also similar, although PD-L1 combined with chemotherapy demonstrated a lower risk of treatment discontinuation caused by AEs than PD-1 addition [65].

Predictive biomarkers

Despite the rational assumptions of combining ICIs with chemotherapy, many patients do not benefit from immunochemotherapy. Therefore, biomarkers are needed to predict the efficacy of ICIs in ES-SCLC.

The predictive role of PD-L1 expression in SCLC is controversial. The subgroup analysis of the IMpower133 study revealed that the efficacy of atezolizumab plus chemotherapy in patients with ES-SCLC was unrelated to PD-L1 expression [33]. Similar observations were made in the CASPIAN and KEYNOTE-604 studies, which suggests that PD-L1 expression has no predictive value in the first-line therapy of ES-SCLC [43, 57]. A combined positive score, which reflects the proportion of all PD-L1 positive cells to all viable tumor cells, seems to be a potential biomarker of response to pembrolizumab in advanced SCLC [55].

As SCLC is related to tobacco smoking, its genome exhibits a high tumor mutational burden (bTMB), defined as a high number of somatic non-synonymous mutations within a tumor genome. However, bTMB was not a valuable predictive biomarker of long-term survival after first-line immunochemotherapy; but, it might be useful in nivolumab monotherapy or nivolumab plus ipilimumab therapy in recurrent SCLC [33, 66].

Recently, it was demonstrated that SCLC can be divided into subtypes based on the expression of transcription factors. One of these subtypes, SCLC-I (the "inflamed subtype"), has low expression of ASCL1, NEUROD1, and POU2F3 but often shows high expression of genes related to immune cell infiltration, PD-L1, and other different immune checkpoint mole-

cules. This is a possible reason why the SCLC-I subtype benefits the most from the addition of PD-L1 inhibitors to chemotherapy compared with other subtypes [67]. The SCLC-I subtype, therefore, seems to be a strong candidate predictive biomarker; however, further research is needed.

Systematic inflammatory and nutritional indexes have also been evaluated as prognostic factors. The platelet-lymphocyte ratio (PLR) measured before therapy might serve as such a marker as patients with a high PLR obtained poorer OS and PFS than patients with a low PLR; however, further research is needed [68].

Data regarding the usefulness of clinical characteristics as predictors of OS benefit from the addition of ICIs to SCLC therapy are limited to subgroup analyses. Among various evaluated clinical factors (e.g. age, sex, ethnicity, PS, elevated lactate dehydrogenase activity, presence of CNS metastases, and previous PCI), none consistently predicts either response or OS duration in patients with SCLC receiving ICIs [69]. However, a recent meta-analysis demonstrated that specific clinical factors, including PS of 1, the use of cisplatin, and the absence of brain metastases, are associated with OS benefits in patients treated with ICIs added to chemotherapy [70].

Despite many attempts, definitive predictive biomarkers for responses to ES-SCLC treatment have not yet been identified. Research is impeded by the low quantity and quality of tissue samples and by the lack of molecular analysis of SCLC in clinical practice. The development of blood-based methods might, therefore, enable the analysis of a wide range of molecules and lead to the identification of predictive biomarkers [71].

Conclusions

The addition of immune checkpoint inhibitors to chemotherapy provides meaningful value in the treatment of patients with ES-SCLC. Observations from clinical practice are required to evaluate the efficacy of combined immunochemotherapy. The main challenge is to evaluate the efficacy of immunochemotherapy in patients with ES-SCLC and CNS metastases and to identify predictive biomarkers of response to immunotherapy to identify the patients who would benefit the most.

Contributions

MKW and DMK conceived the concept of the study and the drafts. MK supervised the drafts. All authors approved the final version.

Conflicts of interest

MKW received speaker's fees, conference support, consultancy, and Advisory Board: Roche-Genentech, BMS, MSD, Pfizer, Boehringer–Ingelheim, Astra Zeneca, TAKEDA, DMK received speaker's fees, conference support, consultancy, and Advisory Board: Roche-Genentech, BMS, MSD, Merck, Pfizer, Boehringer–Ingelheim, Astra Zeneca, TAKEDA, MK declares no conflict of interest.

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