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Atezolizumab in the treatment of small cell lung cancer

Authors

Kacper Ordon [KO]

Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz

https://orcid.org/0009-0000-1764-3422

kacper.ordon1c@wp.pl

Karolina Skonieczna [KS]

Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz

https://orcid.org/0009-0009-0153-7444

karolina.skonieczna05@gmail.com

Olimpia Wiciun [OW]
Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
https://orcid.org/0000-0002-1264-0481
wiciunolimpia@gmail.com

Magdalena Badziąg [MB]
University Clinical Center in Gdansk, Poland
80-952 Gdansk, Debinki 7
https://orcid.org/0009-0008-8598-1034
badziagmagdalena@gmail.com

Paulina Szulc [PS]
Dr Jan Biziel's University Hospital No. 2, Ujejskiego 75, 85-168 Bydgoszcz
https://orcid.org/0009-0007-7614-9214
paulinaszulc210@gmail.com

Laura Kurczoba [LK]
Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
https://orcid.org/0009-0004-1330-991X
laurakurczoba@vp.pl

Martyna Kłossowska [MK]
Baltic Clinic Sp. z o.o.
ul. Wielkokacka 2, 81-611 Gdynia, Poland
https://orcid.org/0009-0002-7444-1637
marklossowska@gmail.com

Olga Kądziołka [OK]
Independent Public Health Care Facility in Szamotuły, Sukiennicza 13, 64-500 Szamotuły
https://orcid.org/0009-0006-1052-4504
olgkadz9393@gmail.com

Abstract

Small cell lung cancer (SCLC) remains one of the most aggressive cancers, with a high relapse rate and limited treatment outcomes. The introduction of immunotherapy, including PD-L1 inhibitors such as atezolizumab and durvalumab, has changed the standard of care, especially in advanced-stage disease (ES-SCLC). Combining immunotherapy with chemotherapy allows for prolonged survival and disease control, as confirmed in the IMpower133 and CASPIAN studies. New strategies, such as consolidation with lurbinectedin in the IMforte study, indicate further opportunities to improve treatment outcomes. In limited-stage disease (LS-SCLC), the groundbreaking results of the ADRIATIC study established immunotherapy with durvalumab as the standard of care after chemoradiotherapy. However, later lines of treatment and resistance to therapy remain a challenge, which is driving the development of new methods such as PARP inhibitors, anti-DLL3 antibodies, and adoptive immunotherapy. Advances in the molecular classification of SCLC and the identification of biomarkers pave the way for more precise and effective therapeutic approaches that may significantly improve patient prognosis in the future.

Keywords

Small cell lung cancer (SCLC), Immunotherapy, Atezolizumab, Durvalumab, Lurbinectidine, Biomarker-driven therapies, Chemoradiotherapy, Targeted therapies

Introduction

Small cell lung cancer (SCLC) constitutes about 13–15% of all lung cancers, and in most cases (approx. 70%) is diagnosed in the advanced stage, the so-called extensive stage (ES-SCLC). It is characterized by an aggressive course and initially high chemosensitivity, but unfortunately, also a tendency to early relapses. Despite obtaining good initial responses, progression occurs in most patients within a few months of completing treatment, and the 2-year survival rate is only about 7% in ES-SCLC (1). The prognosis in the limited-stage (LS-SCLC) form is slightly better, but even with aggressive combined treatment Only 20% of patients survive for two years when treated with chemoradiotherapy and prophylactic brain irradiation. For many decades, there has been no significant improvement in the treatment outcomes of SCLC, which is why this tumor has been referred to as an "orphan" tumor in oncology (2).

The breakthrough came with immunotherapy – a treatment based on inhibiting immune checkpoints. Atezolizumab – a monoclonal antibody blocking the PD-L1 ligand – combined with chemotherapy was the first to demonstrate prolonged survival in patients with advanced SCLC. The results of the IMpower133 study published in 2018 showed that adding atezolizumab to the standard etoposide + carboplatin regimen significantly prolonged median overall survival (3). Following atezolizumab, the CASPIAN study yielded positive results – using the anti-PD-L1 antibody durvalumab with the same chemotherapy also improved median OS (4). Since 2019, immunochemotherapy has become a new standard of first-line treatment for ES-SCLC worldwide (5). This review article discusses the mechanism of action of atezolizumab and key clinical trials involving it in patients with SCLC. It presents this form of therapy's efficacy, safety, and development prospects.

Mechanism of action of atezolizumab

Atezolizumab is a recombinant IgG1 monoclonal antibody directed against programmed death receptor ligand 1 (PD-L1). Its binding to PD-L1 inhibits the interaction of this ligand with the PD-1 receptor on T lymphocytes (and with the B7.1 co-stimulator), abolishing the mechanism of immune surveillance evasion by tumor cells. In physiological conditions, the PD-1/PD-L1 pathway acts as a "brake" - binding of PD-L1 (expressed, among others, on antigen-presenting cells) to PD-1 on activated T lymphocytes induces their anergy or apoptosis,

protecting tissues from autoaggression. Cancer cells use this mechanism of immune escape: many tumors (including SCLC) show abnormally high expression of PD-L1, which leads to inhibition of the local antitumor response. Atezolizumab reverses this process – by blocking PD-L1, it releases the brake imposed on T lymphocytes, restoring their ability to recognize and destroy cancer cells (3). Unlike anti-PD-1 antibodies (e.g., nivolumab, pembrolizumab), atezolizumab neutralizes the PD-L1 ligand on both cancer cells and immune cells in the tumor microenvironment, which may be important in the context of the immunologically "cold" phenotype of SCLC. At the same time, the Fc fragment of atezolizumab has been modified to limit the induction of antibody-dependent cytotoxicity (ADCC) so that the drug does not eliminate activated T lymphocytes expressing PD-L1 but blocks the transmission of the inhibitory signal by them. It is worth emphasizing that small cell lung cancer is one of the cancers with the highest mutational burden (TMB) – it is the result of long-term exposure to tobacco smoke and reaches a median of about 8–10 mutations/Mb, exceeding the TMB of many non-small cell cancers (6). High mutation density translates into numerous neoantigens of the tumor, which in turn is a rational basis for therapy that unblocks the lymphocyte response. Paradoxically, however, SCLC shows a very low expression of PD-L1 – positive immunohistochemical staining (according to various criteria) is found in only <5–10% of cases of this tumor (7). There is, therefore, a slight correlation between the TMB value and immunogenicity measured by PD-L1 expression, which suggests that other mechanisms (e.g., immunosuppressive microenvironment with the participation of Treg cells, MDSC, etc.) may play a major role in inhibiting the immune response in SCLC. However, the combination of chemotherapy with atezolizumab seems to act synergistically: cytostatics cause the release of tumor antigens and modify the tumor's immune infiltration, and simultaneous PD-L1 blockade allows maintaining the antitumor activity of T lymphocytes against the remaining tumor cells (3). In summary, atezolizumab "unmasks" the tumor from the immune system, which, in combination with classical chemotherapy, leads to an intensified cytotoxic effect.

Clinical Trial Overview

IMpower133 (atezolizumab in first-line ES-SCLC): This landmark phase III trial demonstrated the survival benefit of immunotherapy in small cell lung cancer. The trial included 403 previously untreated patients with ES-SCLC who were randomly assigned (1:1) to receive etoposide and carboplatin-based chemotherapy plus atezolizumab (1200 mg intravenously every 3 weeks for four induction cycles, followed by maintenance monotherapy) or identical chemotherapy plus placebo. The primary endpoints were overall survival (OS) and progression-

free survival (PFS). After a median follow-up of 13,9 months, a significant prolongation of OS was observed in the atezolizumab group – median OS was 12,3 months compared to 10,3 months in the control group. After 1 year from randomization, 51,7% of patients receiving immunotherapy were alive compared to 38.2% receiving chemotherapy alone. An improvement in PFS was also noted: median PFS was 5,2 vs 4,3 months. The objective response rate (ORR) was similar in both groups (approximately 60%), indicating that the main effect of atezolizumab was the prolongation of disease control time after chemotherapy-induced remission. The safety profile of immunochemotherapy was acceptable – the frequency of severe grade 3/4 adverse events was almost identical to chemo alone (56,6% vs 56,1%)(3). No new toxicity signals were observed; typical immunological adverse events (such as hypothyroidism, rash, and diarrhea) were generally mild and managed with symptomatic treatment. IMpower133 established a new standard of care in ES-SCLC in 2018 – the etoposide + platinum + atezolizumab regimen was approved by the FDA and EMA and entered into the treatment guidelines (8).

CASPIAN (durvalumab in first-line ES-SCLC): The phase III CASPIAN study was conducted parallel to IMpower133. It provided independent confirmation of the benefit of adding a PD-L1 inhibitor to first-line chemotherapy for SCLC. The study included 805 previously untreated patients with ES-SCLC who were randomized to one of three arms: (A) etoposide + cisplatin/carboplatin + durvalumab, (B) the same regimen + durvalumab + tremelimumab (anti-CTLA-4 antibody), or (C) etoposide + platinum (control arm). Durvalumab was administered at a dose of 1500 mg every 3 weeks in combination with chemotherapy (4 cycles) and then every 4 weeks as monotherapy until progression. The primary analysis comparing arms A vs. C showed a significant improvement in OS with durvalumab: median OS was 13,0 months vs. 10,3 months with chemotherapy. At 18 months after randomization, 33,9% of patients receiving durvalumab were alive vs. 24,7% receiving chemotherapy alone. Median PFS was slightly longer in the immunotherapy arm, although PFS was not formally assessed as an endpoint of the study. It is worth noting that the CASPIAN protocol allowed up to 6 cycles of chemotherapy in the control arm and optional use of prophylactic brain irradiation (PCI) after completion of chemotherapy – despite these measures "favoring" the control group, immunotherapy still showed an advantage. Concomitant administration of durvalumab and tremelimumab (triple arm) did not improve the results over durvalumab alone – median OS in the tremelimumab arm was similar (12.9 months), and the frequency of adverse events was higher. Thus, it was confirmed that PD-L1 blockade is beneficial, while concurrent CTLA-4 inhibition does not increase efficacy in first-line SCLC. Durvalumab therapy was well tolerated – severe adverse events (G3/4) occurred in 62% of

patients in the durvalumab group vs 62% in the control group (4). CASPIAN has established the role of immunotherapy in SCLC; since 2020, durvalumab has been used interchangeably with atezolizumab in combination with first-line chemotherapy. KEYNOTE-604 (pembrolizumab in first-line ES-SCLC): The third phase III study evaluating immunotherapy in first-line SCLC involved the PD-1 inhibitor pembrolizumab. 453 previously untreated patients with ES-SCLC were randomized to receive four cycles of etoposide plus cisplatin/carboplatin + pembrolizumab 200 mg every 3 weeks (up to 35 cycles) or identical chemotherapy + placebo. The study met one of the two primary endpoints: pembrolizumab significantly prolonged PFS. The median OS was longer in the immunotherapy group, but the difference did not reach the protocol-defined statistical significance threshold. After 2 years of follow-up, 22,5% of patients in the pembrolizumab group were alive vs 11,2% in the control group, indicating a potential benefit (9).

KEYNOTE-604 (pembrolizumab in first-line ES-SCLC): The third phase III study evaluating immunotherapy in first-line SCLC evaluated the PD-1 inhibitor pembrolizumab. 453 previously untreated patients with ES-SCLC were randomized to 4 cycles of etoposide plus cisplatin/carboplatin + pembrolizumab 200 mg every 3 weeks (up to 35 cycles) or identical chemotherapy + placebo. The study met one of its two primary endpoints: pembrolizumab significantly prolonged PFS. The median OS was longer in the immunotherapy group, but the difference did not reach the threshold of statistical significance adopted in the protocol. After 2 years of follow-up, 22,5% of patients in the pembrolizumab group survived vs. 11,2% in the control group, indicating a potential long-term benefit in some patients despite the lack of significance in the entire population. The toxicity profile of immunochemotherapy with pembrolizumab was similar to that observed in IMpower133 – G3/4. Adverse events occurred in 76.7% of patients (9). The KEYNOTE-604 results confirmed the activity of pembrolizumab in SCLC (previously suggested by phase II studies, see below), although they did not formally meet the requirement for improved OS. Based on these data, pembrolizumab received accelerated (conditional) FDA approval in 2019 for the treatment of refractory SCLC (after ≥2 lines of therapy) – an indication based on a 19% response rate in the KEYNOTE-028/158 studies and was withdrawn in 2021 due to lack of evidence of improved OS (7,10).

CheckMate 032 (nivolumab and ipilimumab in relapsed SCLC): one of the first studies evaluating immunotherapy in SCLC, conducted in a population of patients after relapsed disease. The phase I/II CheckMate 032 study was a multi-cohort, open-label study – patients with advanced SCLC after platinum chemotherapy received nivolumab (N) as monotherapy or nivolumab in combination with ipilimumab (I) at various doses. In the monotherapy cohort (98

patients), nivolumab was administered at a dose of 3 mg/kg every 2 weeks; in two cohorts of combination therapy nivolumab 1 mg/kg + ipilimumab 3 mg/kg (61 patients) or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (54 patients) – in both cases every 3 weeks for a maximum of 4 cycles, followed by continuation of nivolumab. The primary objective was to determine ORR. The results were encouraging: N monotherapy gave an ORR of 10% (10/98), while the combination of N+I at doses of 1+3 mg/kg – an ORR of 23% (14/61). The median duration of response was 17,9 months (N) and 18,0 months (N+I 1+3), indicating the possibility of achieving long-term remissions in some patients. The median OS was 4,4 months (N monotherapy), 7,7 months (N+I 1+3), and 6.0 months (N+I 3+1). The N+I combination was associated with higher toxicity: G3/4 adverse events occurred in 30% of patients (vs 13% with nivolumab monotherapy), most commonly increased pancreatic enzyme activity, diarrhea, and colitis. Nevertheless, CheckMate 032 demonstrated immunotherapy activity in refractory SCLC, paving the way for FDA approval of nivolumab in 2018 in the 3rd line of treatment (after platinum and subsequent regimen) (11). Importantly, this indication was also later withdrawn (2021) due to the results of a confirmatory study (CheckMate 451), which did not show an OS benefit (10).

CheckMate 451 (nivolumab and ipilimumab as maintenance therapy): a phase III study evaluating immunotherapy in patients with ES-SCLC who had at least stable disease after first-line chemotherapy. Eight hundred thirty-four patients who had not progressed after four cycles of etoposide with cisplatin/carboplatin were randomized to 3 groups: (A) nivolumab + ipilimumab (N 1 mg/kg + I 3 mg/kg every 3 weeks for four doses, then N 240 mg every 2 weeks), (B) nivolumab (240 mg every 2 weeks), or (C) placebo, administered for up to 1 year. Unfortunately, the second interim analysis of the study found no benefit from immunotherapy – median OS was 9,2 months in the N+I arm vs 9,6 months in the placebo arm. Nivolumab monotherapy resulted in a median OS of 10,4 months. An increase in median PFS was noted (1,8 months placebo vs. 2,6 months N vs. 2,4 months N+I) – however, the improvement in PFS did not translate into a durable effect in OS. In an exploratory analysis, a trend for OS benefit was observed in the subgroup of patients with high TMB, but this was not conclusive. A significant limiting factor was toxicity – the N+I combination caused G3/4 adverse events in 52% of patients (vs. 11,5% after N alone and 8,4% after placebo). The most common immunological complications included enteritis, hepatitis, and endocrine disorders. As a result, maintenance immunotherapy after first-line therapy was not used in SCLC – the results of CheckMate 451 contributed to the withdrawal of nivolumab and pembrolizumab indications in subsequent lines, and interest was directed towards consolidation strategies after completion of

chemoradiotherapy (see ADRIATIC below) instead of concurrent immuno-chemical therapy (12).

IFCT-1603 (atezolizumab vs chemotherapy in second line): a French randomized phase II study evaluating the efficacy of atezolizumab monotherapy versus standard chemotherapy in patients with relapsed SCLC after a platinum regimen. Seventy-three patients with relapsed disease (61 platinum-sensitive, 12 resistant) were randomly assigned in a 2:1 ratio to atezolizumab (49 patients, 1200 mg every 3 weeks) or chemotherapy (24 patients, most often topotecan). The primary endpoint was the disease control rate at 6 weeks. Unfortunately, atezolizumab did not demonstrate significant activity: ORR was only 2.3% (1/43 treated; one partial response), while in the chemotherapy group, ORR reached 10%. Median PFS was also worse in immunotherapy – 1,4 vs 4,3 months. The median OS did not differ significantly, but only 20% of patients in the atezolizumab arm survived 1 year, which confirms the lack of clinical advantage. It is worth adding that in the immunohistochemical analysis of tumors, only 1 of 53 samples tested (2%) showed PD-L1 expression, which reflects the immunologically "cold" nature of advanced SCLC. Atezolizumab was well tolerated - only 4% of patients experienced G3 adverse events (fatigue, hormonal disorders), while after chemotherapy this percentage reached 75% (mainly bone marrow suppression). The IFCT-1603 study confirmed the limited efficacy of atezolizumab monotherapy in relapsed SCLC. It indicated that immunotherapy makes sense primarily in combination with other methods (chemotherapy, radiotherapy) in the early phase of the disease (13).

KEYNOTE-028 and 158 (pembrolizumab in relapsed SCLC): Finally, it is worth mentioning two single-arm studies that paved the way for immunotherapy in refractory SCLC. The multi-cohort phase Ib KEYNOTE-028 trial evaluated pembrolizumab in 24 patients with relapsed SCLC, but only in those with PD-L1 expression ≥1%, achieving an ORR of 33% (8/24) in this selected group. This was followed by the phase II KEYNOTE-158 trial, which administered pembrolizumab to 107 patients without PD-L1 matching and achieved an ORR of 18.7% (20/107). The median duration of response was 17.9 months (7). These results (pooled analysis of 131 patients with ORR 19% and median OS 9 months) were the basis for accelerated registration of pembrolizumab in the US (2019) in 3rd line SCLC – as mentioned, this indication was withdrawn after the publication of KEYNOTE-604 and CheckMate 451 results, which did not confirm OS prolongation (9,10,12). Nevertheless, the KEYNOTE-028/158 studies proved that about 1/5 of patients with relapsed SCLC can achieve objective remission after immunotherapy, sometimes lasting more than a year. Searching for predictors of this

extraordinary sensitivity (e.g., the role of PD-L1 level, TMB, and molecular subtypes is being studied) remains an important goal of further research.

S1929 study (atezolizumab + talazoparib as maintenance therapy): Immunotherapy for small cell lung cancer also develops towards targeted and personalized therapies. An example is the American phase II S1929 study (SWOG), in which the PARP inhibitor talazoparib was used in combination with atezolizumab as maintenance therapy in patients with ES-SCLC, selected for Schlafen 11 protein (SLFN11) expression. SLFN11 is a biomarker of sensitivity to PARP inhibitors; it is expressed by approximately 40% of SCLC tumors. Only SLFN11-positive patients who did not progress after completion of induction immunochemotherapy (carboplatin + etoposide + atezolizumab) were qualified for S1929. 106 such patients were randomized to continue atezolizumab alone (control arm) or atezolizumab in combination with talazoparib. The primary endpoint was time to progress. Results presented in 2023 showed that adding talazoparib significantly prolonged PFS: median PFS was 2,9 vs 2,4 months. At month 6, the percentage of patients free from progression was 34% in the combination group vs 20% in the atezolizumab group. Median OS was similar (15,3 vs 15,6 months) – no difference in overall survival has been observed so far, although the follow-up is short. Importantly, S1929 prospectively confirmed the value of biomarker-based patient selection: in SLFN11-positive patients, maintenance therapy with atezolizumab plus a PARP inhibitor prolonged disease control. This is the first such report in SCLC and may become a starting point for subsequent phase III maintenance therapy studies based on the tumor's molecular features (14).

IMforte (lurbinectidine + atezolizumab as consolidation): Recent strategies investigate adding a third agent to immunochemotherapy. An example is the phase III IMforte study, which evaluated the maintenance of remission with lurbinectidine (a transcription inhibitor, cytotoxic drug approved in 2nd-line SCLC) in combination with atezolizumab, compared with atezolizumab alone, in patients with ES-SCLC after induction with a standard regimen (platinum + etoposide + atezolizumab). In October 2024, it was announced that the combination of lurbinectidine with atezolizumab significantly improved survival compared to atezolizumab monotherapy. According to a press release (preliminary data), median OS and PFS were prolonged in the combination arm, and the safety profile was acceptable. The full results of the IMforte study have not yet been published (they are scheduled for presentation at a scientific conference). However, this combination is already seen as a potential new consolidation standard after the first line. In the future, this could lead to the approval of a four-drug regimen (chemotherapy + atezolizumab + lurbinectidine) in ES-SCLC (15).

NRG-LU005 (atezolizumab with chemoradiotherapy in LS-SCLC): Immunotherapy is also being evaluated in a limited stage. NRG-LU005 is a randomized phase II/III trial adding atezolizumab to standard concurrent chemoradiotherapy in patients with LS-SCLC. Interim analysis results were presented at the ASTRO meeting in September 2024 – unfortunately, atezolizumab given concurrently with chemoradiotherapy did not improve survival compared with chemoradiotherapy alone. The 2-year survival rate was 48% in both arms. Therapy with atezolizumab also proved more difficult to manage – in particular, concurrent chest irradiation and immunotherapy were associated with a higher risk of pneumonia. The conclusion from NRG-LU005 is that immunotherapy in LS-SCLC should be administered sequentially, after completion of chemoradiotherapy, rather than concurrently (16).

ADRIATIC (durvalumab ± tremelimumab after chemoradiotherapy for LS-SCLC): The most groundbreaking study in the limited stage was the ADRIATIC study – the first to show prolonged survival with immunotherapy in patients with LS-SCLC. In this study, after completion of radical chemoradiotherapy (4–6 cycles of platinum + etoposide + radiation), patients were randomized to receive durvalumab (1500 mg every 4 weeks for 2 years), durvalumab + tremelimumab (75 mg × 4 doses), or placebo. The results were published in 2024: durvalumab monotherapy significantly prolonged OS and PFS compared with placebo. The median OS was 55,9 vs. 33,4 months, and the median PFS was 16.6 vs. 9,2 months. After 3 years from randomization, 71% of patients receiving durvalumab were alive vs. 57% in the placebo group. The addition of tremelimumab did not further improve the results (the triple arm remains blinded, but the study already met its objective in comparing durvalumab vs. placebo). Durvalumab was relatively well tolerated – the incidence of G3/4 pneumonitis was 3,1% (vs. 2,6% in placebo). The ADRIATIC study has set a new standard in LS-SCLC: In 2023, the FDA and EMA approved durvalumab as consolidation therapy after chemoradiotherapy in patients who did not progress after induction. Analyses are currently ongoing to determine the optimal timing of immunotherapy initiation (ADRIFT – after vs. during radiotherapy) and the potential benefit of additional CTLA-4 blockade (tremelimumab arm) (17).

Efficacy and safety of therapy

Efficacy: Atezolizumab and other PD-1/PD-L1 inhibitors have revolutionized the treatment of SCLC, but their efficacy depends on the clinical setting. The most significant benefits are observed in first-line ES-SCLC in combination with chemotherapy. Immunochemotherapy (atezolizumab or durvalumab + etoposide/cisplatin or carboplatin) has

become a standard, providing an extension of median OS by about 2–3 months and an increase in the 2-year survival rate from <10% to 20–25%. Although the absolute difference in median OS seems small, the hazard ratios (0,70 for atezolizumab and 0,73 for durvalumab) confirm a reduction in the risk of death by 27–30%. It is worth noting that the benefit of adding immunotherapy is visible only after 6 months of treatment initiation – survival curves diverge after chemotherapy completion, suggesting that atezolizumab primarily prolongs the duration of remissions. In subgroup analyses in both IMpower133 and CASPIAN, improved OS was observed in all distinguished patient categories (regardless of age, sex, performance status, stage of disease, or presence of CNS metastases) (3,4). Importantly, the efficacy of immunotherapy seems to be independent of PD-L1 expression – PD-L1-negative cases predominate in SCLC, yet they derive comparable benefits from atezolizumab (3,13). Another biomarker studied was TMB: in the analysis of patients with IMpower133, high TMB had no significant effect on OS with immunotherapy, although, in CheckMate 451, a trend towards prolonged OS was observed with N+I therapy in patients with TMB ≥ 13 Mut/Mb (12,18). Further work is underway to identify markers, e.g., genetic signature based on SCLC subtypes (see below) or the level of TIGIT family receptors (inhibiting activation of NK and T cells). In subsequent lines of treatment, the efficacy of immunotherapy is lower. Monotherapy with nivolumab or pembrolizumab in refractory SCLC gives an ORR of 10–20% while standard cytotoxics (e.g., topotecan) – about 10–25%. Although the rate of immunological long-term responses is higher (stable remissions ≥1 year in ~10% of patients), nivolumab and pembrolizumab in the late line setting failed to improve median OS compared to chemotherapy (CheckMate 331 study – nivolumab vs topotecan) (7,10,11). Therefore, immunotherapy is currently not routinely used in relapsed SCLC outside of research protocols. Greater hopes are associated with targeted therapies: lurbinectidine received conditional FDA approval in 2020 (ORR 35% in a phase II study) (19). The future of refractory SCLC treatment may lie in regimens combining immunotherapy with targeted therapies, as demonstrated by the S1929 study (atezolizumab + talazoparib in SLFN11+ patients) (14). Safety: Immunotherapy for small cell lung cancer has a toxicity profile consistent with that observed in other malignancies, and the addition of atezolizumab to chemotherapy does not significantly worsen treatment tolerance. In the IMpower133 and CASPIAN studies, the incidence of grade 3–4 adverse events was 60% in both the immunochemotherapy and control groups (3,4). Chemotherapy-related toxicity predominated (myelosuppression – neutropenia 40%, anemia 30%, thrombocytopenia 10–20%), while serious immunological complications were relatively rare. The most common adverse events of atezolizumab include fatigue (all grades 39% of patients), rash (20%), thyroid

dysfunction (10%, mainly hypothyroidism), diarrhea (10%), and increased transaminases (10%). Most of them are mild or moderate and respond well to symptomatic treatment or short courses of steroid therapy. Severe immunologic adverse events (pneumonia, colitis, severe hepatitis, grade 3/4 endocrinopathies) occur in <5% of patients (3,9). No new deaths related to durvalumab were observed in the CASPIAN study (4), and lethal toxicity in IMpower133 was 1,4% vs 1,6% (3). Taken together, these data suggest that the addition of atezolizumab does not significantly increase the overall toxicity of treatment, and the risk of severe immunologic complications is limited to isolated cases. However, it is essential to closely monitor patients during immunotherapy – especially after chemotherapy, when immunological effects begin to dominate – and respond quickly to the first symptoms (fever, shortness of breath, diarrhea, hormonal disorders). Implementing algorithms for adverse immunological effects and patient education are important practice elements.

Clinical application and development prospects

Clinical application: Atezolizumab has become integral to treating metastatic small-cell lung cancer. Current guidelines (including ASCO and NCCN) recommend etoposide + platinum + PD-L1 inhibitor (atezolizumab or durvalumab) as the first-line standard in all patients with ES-SCLC without contraindications (5,15). Immunochemotherapy should include four cycles of induction therapy, followed by a continuation of atezolizumab (or durvalumab) as monotherapy every 3–4 weeks until disease progression or unacceptable toxicity (5). Currently, no factors allow for selecting which patient would benefit more from immunotherapy – PD-L1 expression is not used, and TMB testing is not required. Atezolizumab is usually well tolerated, even by older people and those in poorer general conditions, which is important because the median age of SCLC patients is over 65 years. Population analyses indicate that patients ≥70 years of age also benefit from immunochemotherapy and do not report a significant deterioration in quality of life compared to chemotherapy alone (5). Contraindications to atezolizumab include active autoimmune diseases and organ transplants – in such situations, treatment with chemotherapy alone should be considered. In limited-stage disease (LS-SCLC), immunotherapy was not standard until recently. However, the results of the ADRIATIC study have changed this – from 2023, incorporating durvalumab after completing chemoradiotherapy is becoming the new consolidation standard (5,17). It should be noted, however, that immunotherapy in LS-SCLC should be initiated after completing radiotherapy (as in ADRIATIC), and not simultaneously – this was confirmed by the negative NRG-LU005 study (16). Apart from the above indications, immunotherapy in monotherapy in later lines should be

conducted as part of clinical trials or experimental protocols (in Poland, until 2021, there was a nivolumab program in 3rd line SCLC, but it was terminated). Exceptionally, the use of a PD-1/PD-L1 inhibitor may be considered in a patient after multiple lines of treatment who is diagnosed with, for example, high TMB or persistently low tumor mass after subsequent therapies - although these are individual decisions outside the condition recommended in the guidelines.

Development prospects: Despite progress, SCLC remains a cancer with an inferior prognosis. Hence, numerous studies are being conducted to improve the results further. One direction is to intensify first-line treatment – for example, by adding another drug to immunochemotherapy (as in the IMforte study with lurbinectidine) (15). Another approach is to add drugs targeting the microenvironment to immunotherapy – an example is the anti-TIGIT antibody tiragolumab, which blocks an additional checkpoint on lymphocytes and NK cells. Unfortunately, in the phase III SKYSCRAPER-02 study, the combination of tiragolumab with atezolizumab did not improve survival over immunochemotherapy alone (20), which cooled the expectations for this combination. However, the studies are still ongoing – other antibodies (anti-LAG-3, anti-CD47) and kinase inhibitors (e.g., domanexafor – CXCR4 inhibitor) are being analyzed. A significant area of research is the identification of biomarkers. Apart from the aforementioned TMB and SLFN11, the most significant interest is the molecular classification of SCLC into four subtypes: SCLC-A (ASCL1), SCLC-N (NEUROD1), SCLC-P (POU2F3) and SCLC-I (inflamed, characterized by low expression of neuroendocrine factors and high activation of immune pathways) (16). It turns out that the SCLC-I subtype has a rich lymphocytic infiltrate and shows higher sensitivity to immunotherapy (16). Work is underway on tests distinguishing these subtypes in practice (e.g., appropriate immunohistochemical panels); potentially, in the future, patients with subtype I could be candidates for more intensive immunotherapy, and patients with "cold" subtypes - directed immediately to protocols with targeted therapies. In the second-line and subsequent treatment, new drugs are being intensively tested (16). However, in a phase III study, it did not improve OS over placebo, and drug development was discontinued.

Summary and conclusions

The introduction of atezolizumab to the treatment of small-cell lung cancer was a milestone that broke the period of therapeutic stagnation lasting over 30 years. For the first time, extending the survival of patients with advanced SCLC was possible – immunotherapy in combination with chemotherapy became the first-line standard, increasing the percentage of

long-term survival of patients. Atezolizumab works by unblocking the immune response against the tumor, which, combined with the cytotoxic effect of chemotherapy, brings a synergistic effect. Key studies (IMpower133, CASPIAN) showed a reduction in the risk of death by about 25–30% with the addition of a PD-L1 inhibitor (3,4). Subsequent clinical trials have established the role of immunotherapy – pembrolizumab and durvalumab confirmed activity in SCLC, although not all of them achieved statistical significance in OS (9,12). Immunotherapy proved particularly valuable in maintaining remission after treatment induction; it performs worse in monotherapy in recurrent disease, which encourages its combination with other methods or uses in populations selected by biomarkers (13,14). The safety profile of atezolizumab is favorable – it does not significantly increase the toxicity of chemotherapy, and serious immunological complications are rare and usually reversible with appropriate treatment (3,9). Thanks to atezolizumab, small-cell lung cancer has become the first respiratory cancer in which immunotherapy has improved treatment results – similar success was previously noted in melanoma, renal cancer, or non-small cell lung cancer. Work is currently underway to further improve the therapy: intensification of first-line treatment (e.g., adding lurbinectidine – IMforte study), the introduction of immunotherapy to the limited stage (ADRIATIC study), and overcoming resistance in subsequent lines (targeted drugs, vaccines, additional monoclonal antibodies). The results to date are encouraging – for example, the use of durvalumab after chemoradiotherapy for LS-SCLC extended the median survival to almost 5 years (17), and new anti-PD-1 antibodies (serplulimab, tislelizumab) in combination with chemotherapy achieved median OS of around 15 months in ES-SCLC (21). However, SCLC remains a challenging disease to treat and requires innovative solutions. Atezolizumab paved the way for these innovations, providing evidence that even in such an aggressive tumor, activation of the immune system can prolong the life of patients. Future progress – based on immunotherapy and targeted therapies – will allow us to hope that SCLC will become an increasingly controllable disease in the coming years.

Disclosure

Author's Contribution

Conceptualization: Kacper Ordon, Karolina Skonieczna, Olimpia Wiciun,

Formal analysis: Magdalena Badziąg, Paulina Szulc, Laura Kurczoba

Investigation: Kacper Ordon, Martyna Kłossowska, Olga Kądziołka

Writing rough preparation: Kacper Ordon, Karolina Skonieczna, Olimpia Wiciun, Magdalena Badziąg, Paulina Szulc

Writing review and editing: Kacper Ordon, Karolina Skonieczna, Olimpia Wiciun, Magdalena Badziąg, Paulina Szulc, Laura Kurczoba, Martyna Kłossowska, Olga Kądziołka

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References

1. Belluomini L, Calvetti L, Inno A, Pasello G, Roca E, Vattemi E, et al. SCLC Treatment in the Immuno-Oncology Era: Current Evidence and Unmet Needs. Front Oncol. 2022 Apr 14;12:840783. doi: 10.3389/fonc.2022.840783
2. Remon J, Aldea M, Besse B, Planchard D, Reck M, Giaccone G, et al. Small cell lung cancer: a slightly less orphan disease after immunotherapy. Ann Oncol. 2021 Jun;32(6):698–709. doi: 10.1016/j.annonc.2021.02.025
3. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec 6;379(23):2220–9. doi: 10.1056/NEJMoa1809064
4. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. The Lancet. 2019 Nov;394(10212):1929–39. doi: 10.1016/S0140-6736(19)32222-6
5. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021 Feb 20;39(6):619–30. doi: 10.1200/JCO.20.01055
6. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primer. 2021 Jan 14;7(1):3. doi: 10.1038/s41572-020-00235-0
7. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol. 2020 Apr;15(4):618–27. doi: 10.1016/j.jtho.2019.12.109
8. Khurshid H, Ismaila N, Bian J, Dabney R, Das M, Ellis P, et al. Systemic Therapy for Small-Cell Lung Cancer: ASCO-Ontario Health (Cancer Care Ontario) Guideline. J Clin Oncol. 2023 Dec 10;41(35):5448–72. doi: 10.1200/JCO.23.01435
9. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol. 2020 Jul 20;38(21):2369–79. doi: 10.1200/JCO.20.00793
10. Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, et al. Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC). J Thorac Oncol. 2018 Sep;13(9):1393–9. doi: 10.1016/j.jtho.2018.05.002

11. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883–95. doi: 10.1016/S1470-2045(16)30098-5
12. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol. 2021 Apr 20;39(12):1349–59. doi: 10.1200/JCO.20.02212
13. Pujol JL, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, et al. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. J Thorac Oncol. 2019 May;14(5):903–13. doi: 10.1016/j.jtho.2019.01.008
14. Karim NA, Miao J, Reckamp KL, Gay CM, Byers LA, Zhao YQ, et al. Phase II Randomized Study of Maintenance Atezolizumab Versus Atezolizumab Plus Talazoparib in Patients With SLFN11 Positive Extensive-Stage SCLC: S1929. J Thorac Oncol. 2025 Mar;20(3):383–94. doi: 10.1016/j.jtho.2024.10.021
15. Targeted Oncology [Internet]. 2024 [cited 2025 Apr 16]. IMforte Shows Benefits of Lurbinectedin/Atezolizumab in ES-SCLC. Available from: https://www.targetedonc.com/view/imforte-shows-benefits-of-lurbinectedin-atezolizumab-in-es-sclc
16. Peters S, Pujol JL, Dafni U, Dómine M, Popat S, Reck M, et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy – results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. Ann Oncol. 2022 Jan;33(1):67–79. doi: 10.1016/j.annonc.2021.09.011
17. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. N Engl J Med. 2024 Oct 10;391(14):1313–27. doi: 10.1056/NEJMoa2404873
18. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021 Jan;22(1):51–65. doi: 10.1016/S1470-2045(20)30539-8
19. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020 May;21(5):645–54. doi: 10.1016/S1470-2045(20)30068-1
20. Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021 Dec;19(12):1441–64. doi: 10.6004/jnccn.2021.0058
21. Gay CM, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021 Mar;39(3):346-360.e7. doi: 10.1016/j.ccell.2020.12.014