

Review

Anti PD-L1 antibody: is there a histologic-oriented efficacy? Focus on atezolizumab in squamous cell non-small cell lung cancer

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1. Abstract

Squamous cell lung cancer (SqCLC) is the second most common histotype of non-small cell lung cancer (NSCLC) and is characterized by severe prognosis and lack of specific target agents. Atezolizumab is the first anti Programmed Death Ligand-1 (PDL-1) inhibitor approved for NSCLC patients of both histology in case of disease progression after first or further lines of therapy. Numerous studies are investigating the potential role of atezolizumab in different therapeutic setting, including SqCLC subtype. We searched for published clinical trials in Pubmed database, using the terms “atezolizumab”, “squamous cell lung cancer”, “NSCLC” and “non-small cell lung cancer”. We also searched for recently concluded and not yet published or ongoing trials in clinicaltrials.gov and in data from the latest international congresses. The aim of this review is to summarize current evidence on atezolizumab in SqCLC, from first line setting to novel potential indications from ongoing trials. Strengths and weaknesses of atezolizumab treatment were highlighted to speculate the role of this immune checkpoint inhibitor in novel future clinical scenarios.

2. Introduction

Squamous cell lung cancer (SqCLC) represents 20–30% of all lung cancers histotypes and is characterized by different and more severe prognosis than non-squamous counterpart [1]. Treatment for advanced SqCLC is challenging, since as of today there are no specific therapeutic agents for the major biomolecular targets [2–5]. In addition, clinical characteristics of SqCLC patients — older age, higher burden of comorbidity, history of tobacco smoke exposure and possible renal toxicity— make difficult the use of platinum-based doublets in real world clinical practice [6].

Central localization of bulky tumors and the frequent large blood vessel involvement even enhance the occurrence of clinical complications, including haemoptysis and fatal bleeding [7, 8]. Thus, higher radiotherapy doses on target volume is usually contraindicated, further reducing the possibility to clinically control the aggressive behavior of this cancer [7, 8]. For these reasons, SqCLC has remained for decades an orphan disease without curative solutions, apart from surgery and chemo-radiotherapy combination in early and locally advanced stages.

The availability of immune-check point inhibitors (ICIs) against protein death 1/ligand 1 (PD1/PDL1) represented the turning point for refractory and heavily pre-treated SqCLC, paving the way for novel clinical and therapeutic scenarios with longer clinical control. In 2015, the phase II, single arm, CHECKMATE 063 study firstly demonstrated a clinically significant overall response rate (ORR) of 14.5% achieved with nivolumab in refractory SqCLC. For the first time, a single agent showed a long-term control, as the duration of response was not reached [9]. The subsequent CHECKMATE 017 trial confirmed the results of former phase 2 study: nivolumab prolonged median overall survival (mOS) by 3.2 months compared to standard chemotherapy in pretreated SqCLC patients, improving also median progression free survival (mPFS) and ORR, independently from PD-L1 expression levels [10]. In a pooled analysis of the CHECKMATE 017, on SqCLC, and CHECKMATE 057, on non-squamous Non-Small Cell Lung Cancer (nsqNSCLC), nivolumab confirmed its superiority compared to docetaxel for efficacy and activity outcomes after more than 3 years of follow-up [11]. Furthermore, nivolumab showed a significant impact in health-related quality of life and relief of symptoms-burden compared to chemotherapy in advanced and pretreated setting [12].

Pembrolizumab, another anti PD-1 antibody (Ab), was evaluated in pretreated positive PDL1 patients, but not specifically in SqCLC [13]. The results of the KEYNOTE 010 study indicated that this drug was effective in SqCLC patients as well, without significant differences with nsqNSCLC [14].

More recently, atezolizumab, the first anti PD-L1 Ab, proved efficacy in a non histotype restricted PD-L1 population and determined a statistically significant improvement of mOS compared to docetaxel, specifically in SqCLC patients, regardless PD-L1 expression levels [15]. In October 2016, based on the results of the OAK trial, atezolizumab was approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic NSCLC whose disease progresses during or following a platinum-containing chemotherapy; the drug has been approved for this indication in many other countries. Atezolizumab is associated also to a more favourable safety profile, compared to that reported with docetaxel treatment.

In this review, we aimed to point out the role of atezolizumab in SqCLC patients in different settings from the first line to subsequent lines of treatment. We tried to highlight the differences among atezolizumab and other ICIs, considering the limitation of subgroup analysis in clinical trials non-specifically restricted to SqCLC. An insight on future development of atezolizumab in early stages of SqCLC has also been provided.

3. Atezolizumab in SqCLC: first line setting

Frequently in clinical trials the use of ICIs in first line setting is associated with greater efficacy than in second- or further lines, maybe because of a more effective immune system and a more limited disease burden. This higher efficacy is particularly evident when patient selection is based on PDL1 expression. As for other ICIs, atezolizumab was first evaluated in clinical trials in advanced and heavily pre-treated patients; then, the activity was confirmed in the naïve population.

The IMpower project is a set of trials testing atezolizumab alone or in combination with different platinum-based chemotherapies in selected PD-L1 positive tumors or all NSCLC population in first-line setting [Table 1]. In this project, the efficacy of atezolizumab and its synergism with platinum-based doubled were tested in both types of histology [16–20].

The IMpower 110 trial specifically assessed the efficacy of atezolizumab monotherapy compared with chemotherapy in SqCLC and nsqNSCLC populations [16]. Fifty hundred seventy-two patients were randomized to receive atezolizumab 1200 mg every 3 weeks or chemotherapy - (platinum/derivatives-pemetrexed for nsqNSCLC or gemcitabine for SqCLC). OS was the primary endpoint in a wild-type (wt) population tested hierarchically from strong positive PDL1 tumors (TC3 or IC3), followed by TC2/3 or IC 2/3, then TC1/2/3 or IC 1/2/3. In this trial, as in the previous OAK study [15], PD-L1 expression was assessed both in tumor cells (TC) and in tumor-infiltrating immune cells (IC) with the VENTANA SP142 IHC assay, using a peculiar score system [15]. SqCLC patients were less than one third of the whole population and 25% among strong positive PDL1 tumors. After a median follow-up of 15.7 months, atezolizumab was superior to chemotherapy in terms of median OS (mOS) (20.2 vs 13.1 months) in the PD-L1 high wt population, with 64.9% of 12-month survival rate. Among TC 3 or IC 3 SqCLC mOS was not reached in the atezolizumab arm and 15.3 months in chemotherapy arm (HR 0.56, 95% CI 0.23–1.27). This survival benefit was comparable to that observed in non-squamous counterpart (HR 0.62, 95% CI 0.40–0.96). OS data among patients with high or intermediate PD-L1 expression did not cross the prespecified alpha boundary, so, according to the hierarchically statistical design, OS was not formally tested in this population nor in patients with any PD-L1 expression and data on SqCLC subgroup are not available [16]. Based on these data, similarly to pembrolizumab, atezolizumab monotherapy might be an alternative treatment in patients with high PD-L1 expression (TC3 or IC3 with SP142 Ventana) also in SqCLC. Evidence on potential use of atezolizumab in first-line setting will derive from subgroup analyses of IMpower 110 trial since the twin study IMpower 111 [17], comparing atezolizumab to platinum-based and

Table 1. The IMpower trials: design of the studies and key end-points.

Identifier/Phase	Disease	Arms and intervention	Primary end-point	Key secondary end-points
IMpower-110, Phase III	PDL-1 positive, stage IV, squamous or non-squamous	Atezolizumab 1200 mg1q21 vs platinum- based chemotherapy: - non-SCC: cisplatin/carboplatin + pemetrexed - SCC: cisplatin/carboplatin + gemcitabine	OS in WT population	Investigator-assessed PFS per RECIST 1.1, ORR and DOR
IMpower-111, Phase III	PDL-1 positive, stage IV, squamous	Atezolizumab 1200 mg 1q21 vs cisplatin/carboplatin + Gemcitabine	Investigator-assessed PFS per RECIST 1.1	OS, ORR, DOR
IMpower-130, Phase III	Stage IV, non-squamous	Carboplatin AUC6 + Nab-paclitaxel + Atezolizumab 1200 mg 1q21 vs Carboplatin AUC 6 + Nab-paclitaxel	Investigator-assessed PFS and OS in the WT	PFS and OS in the ITT population, ORR and DOR
IMpower-131, Phase III	Stage IV, squamous	Arm A: Atezolizumab 1200 mg1q21 + Carboplatin AUC6 + Paclitaxel 200 mg/m ² Arm B: Atezolizumab 1200 mg 1q21 + Carboplatin AUC6 + Nab-Paclitaxel 100 mg/mq Arm C: Carboplatin AUC 6 + Nab-paclitaxel 100 mg/mq	Investigator-assessed PFS and OS in the ITT- population	PFS and OS in the TC or IC 2/3 and 1/2/3 population, OS in the tGE population, ORR and DOR in the ITT-population
IMpower-132, Phase III	Stage IV, non-squamous	Cisplatin 75 mg/mq/Carboplatin AUC6 + Pemetrexed 500 mg/mq ± Atezolizumab 1200 mg	Investigator-assessed PFS and OS in the ITT-population	ORR, DOR

AUC, Area Under Curve; IC, immune cells; ITT, Intention to treat; ORR, Overall Response Rate; DOR, Duration of Response; OS, Overall Survival; PFS, Progression Free Survival; TC, Tumor Cells; TC or IC 1, PDL1 1–5%; TC or IC 2, PDL1 5–49%; TC or IC 3, PDL1 >50%; ICWT, WildType.

Table 2. The IMpower trials: results by first and key secondary end-points.

Identifier, phase	Intervention	Median follow-up	mOS	mPFS	ORR% (95% CI)	DOR (range)
IMpower-110 Phase III	Atezolizumab 1200 mg1q21 vs platinum- based chemotherapy: - non-SCC: cisplatin/carboplatin + pemetrexed - SCC: cisplatin/carboplatin + gemcitabine	13.4 (0–35 months)	17.5 vs 14.1 months HR 0.83 <i>p</i> = 0.1481	5.7 vs 5.5 months HR 0.77 <i>p</i> = 0.014	29.2 (24.0, 35.0)	NE (1.8 to 29.3) vs 5.7 (2.4 to 23.9)
IMpower-111 Phase III	Atezolizumab 1200 mg 1q21 vs cisplatin/carboplatin + Gemcitabine	N/A	N/A	N/A	N/A	N/A
IMpower-130 Phase III	Carboplatin AUC6 + Nab-paclitaxel + Atezolizumab 1200 mg 1q21 vs Carboplatin AUC 6 + Nab-paclitaxel	18.5 vs 19.2 months	18.6 vs 13.9 months HR 0.79 <i>p</i> = 0.033	7.0 vs 5.5 months HR 0.64 <i>p</i> < 0.0001	49.2 vs 31.9	8.4 (6.9–11.8) vs 6.1 (5.5–7.9) months <i>p</i> = 0.0004
IMpower-131 Phase III	Arm A: Atezolizumab 1200 mg1q21 + Carboplatin AUC6 + Paclitaxel 200 mg/m ² Arm B: Atezolizumab 1200 mg 1q21 + Carboplatin AUC6 + Nab-Paclitaxel 100 mg/mq Arm C: Carboplatin AUC 6 + Nab-paclitaxel 100 mg/mq	N/A	B vs C: 14.2 vs 13.5 months HR 0.88 <i>p</i> = 0.16 In PDL-1 high: 23.4 vs 10.2 months	6.5 vs 5.6 months HR 0.75 <i>p</i> = 0.16	49.4 vs 41.3	7.5 vs 5.2 months
IMpower-132 Phase III	Cisplatin 75 mg/mq/Carboplatin AUC6 + Pemetrexed 500 mg/mq ± Atezolizumab 1200 mg	14.8 months	N/A	7.6 vs 5.2 months HR 0.60 <i>p</i> < 0.0001	47 vs 32	10.1 vs 7.2

AUC, Area Under Curve; CI, confidence interval; N/A, Not Available; ORR, Overall Response Rate; DOR, Duration of Response; OS, Overall Survival; PFS, Progression Free Survival.

gemcitabine chemotherapy in a naïve PDL1-selected population, was prematurely closed due to low accrual rate.

Parallel to IMpower 130 on nsqNSCLC [18], atezolizumab in combination with chemotherapy in SqCLC was extensively explored in phase III trial IMpower 131 [19]. The trial enrolled 1021 naïve, stage IV SqCLC patients, randomized in a 1:1:1 ratio to receive atezolizumab + carboplatin + paclitaxel (arm A) or atezolizumab + carboplatin + nab-paclitaxel (arm B) or carboplatin + nab-paclitaxel alone (arm C). Primary endpoints were mPFS per RECIST 1.1 in the ITT and mOS. Atezolizumab + carboplatin + nab-paclitaxel improved PFS of 0.7 months (6.3 vs 5.6 months) and reduced the risk of progression by 29% (HR 0.71, 95% CI 0.60–0.85, $p < 0.0001$) versus carboplatin + nab-paclitaxel. With a median follow-up of 25.5 months, mOS was not statistically different in the atezolizumab + carboplatin + nab-paclitaxel group compared to the chemotherapy group (14.2 vs 13.5 months, HR 0.88, 95% CI 0.72–1.05, $p = 0.1581$); however, a mOS improvement was observed in patients with high PD-L1 expression with atezolizumab + carboplatin + nab-paclitaxel (mOS 23.4 vs 10.2 months; HR 0.48 95% CI: 0.29, 0.81) [19]. Due to these negative results, no further analyses will be done on arm A and arm C and differences in synergistic effects with anti-microtubule agents will not be examined. Overall, the IMpower 131 is a negative trial and its final results only suggest that patients with metastatic SqCLC and high tumor PD-L1 expression may potentially benefit from combining carboplatin + nab-paclitaxel with atezolizumab. Results of the above studies are summarized in Table 2.

Opposite results are observed in the KEYNOTE 407 trial [20]. In this trial, pembrolizumab was combined with the same chemotherapeutic regimen examined in the IMpower 131 study. After a median follow-up of 7.8 months, the addition of pembrolizumab to chemotherapy prolonged both mOS (15.9 vs 11.3 months, HR for death 0.64, 95% CI, 0.49–0.85; $p < 0.001$), regardless PDL1 level of expression, and mPFS [6.4 (95% CI, 6.2 to 8.3) vs 4.8 (95% CI, 4.3 to 5.7) months, HR, 0.56; 95% CI, 0.45–0.70; $p < 0.001$] [20]. These results have been recently confirmed at the updated after a median follow-up of 14.3 months: pembrolizumab combination is clinically significantly superior to the comparator arm (17.1 vs 11.6 months; HR 0.71, 0.58–0.88) [21].

The different results obtained in the IMpower 131 and KEYNOTE 407 studies may be potentially explained by several reasons. First of all, the proportion of PD-L1 high patients was slightly higher in KEYNOTE 407 than in the IMpower 131, thus determining an imbalance between patient populations. Furthermore, the different assays and scores used to determine PD-L1 (SP142 in IMpower 131 and 22C3 in KEYNOTE 407) might have influenced PD-L1 level evaluation and data interpretation. Immune-related Adverse Events (irAEs) were similar between Pembrolizumab combinations in the KEYNOTE 407

and Atezolizumab combinations in IMpower 131, despite only indirect comparisons should be performed [19, 20]. Finally, there may be some differences in the interaction between ICIs and chemotherapy which have not been well clarified yet.

A similar situation has been previously reported for nivolumab and pembrolizumab when the results from the CHECKMATE 026 trial [22] and the KEYNOTE 189 trial [23] were compared: only pembrolizumab plus chemotherapy was superior to chemotherapy alone.

Despite they act on the same pathway axis, anti PD1 and anti PDL1 Ab may display different biological activity. They have distinct binding interfaces and compound orientations: anti PD-1 inhibits the binding between PD-1 and its ligands PD-L1 and PD-L2, while anti PD-L1 antibodies interfere with the binding of PD-L1 to PD-1 and CD-80 [24]. These differences may account for the different clinical activity observed in trials, which, however, do not translate in a different toxicity profile, except for a slightly lower frequency of pneumonitis that was observed with an anti PDL1, with respect to an Ab anti PD-1 [25]. Anyway, the lack of head-to-head trials among ICIs does not allow to reach conclusive observations.

A different histologic-oriented efficacy for PD-1 versus PD-L1 inhibitors might also be taken in account. Generally, SqCLC benefits more from anti PD-1 than nsqNSCLC, as shown in the subgroup analysis from the Keynote 024 (OS HR 0.35 in squamous vs 0.55 in non-squamous), Checkmate 026 (HR for OS 0.82 vs 1.17 for squamous and non-squamous) and the Empower- Lung 1 with the new PD-1 inhibitor cemiplimab (HR 0.48 vs 0.64) [22, 26, 27]. The OS improvement seems to be more pronounced for sqCLC even with the nivolumab-ipilimumab combinations, as reported in the Checkmate 227 and Checkmate 9LA [28, 29], while this difference was not so evident with PD-L1 inhibitors, atezolizumab (as reported above) and durvalumab [30].

ICIs immunogenicity may generate anti-drug antibodies (ADA) that interfere with their ability to trigger the immune response against tumor. ADA were detected after the first dose of atezolizumab infusion in 20–30% of cases. These neutralizing antibodies may accelerate clearance and reduce the exposure and, therefore, the activity of the drug. Data on the relationship between ADA and ICIs efficacy are, however, conflicting and not conclusive [26]. Theoretically, ICIs - chemotherapy combination has an immunosuppressive effect that can reduce the possibility to generate ADA; however, in an exploratory analysis of the IMpower 150 trial, the rate of atezolizumab ADAs was 36% and mOS was shorter in patients developing ADAs vs those not developing ADAs [31].

Finally, each chemotherapeutic agent may impact differentially on the immune system, thus potentially affecting the synergy of the combination with ICIs. As an example, *in vitro* studies demonstrated that platinum agents

had immunomodulatory activities, increasing tumoral antigens re-uptake and exposure, whereas gemcitabine inhibited B-cell proliferation reduced the activity of myeloid-derived suppressor cells [32, 33]. In the Phase 1, multi-cohort, CHECKMATE 012 study, nivolumab demonstrated good safety results and equivalent activity in combination with platinum-doublet chemotherapy, even if the combination with platinum + paclitaxel in the small population analyzed seemed to be the most promising [34].

Finally, atezolizumab alone or in combination with chemotherapy in first line setting in sqCLC seems to improve outcome, but the final results of IMpower 110 and 131 trials on OS do not completely support its use in clinical practice.

4. Atezolizumab in SqCLC: second and further lines

Prognosis of pretreated advanced SqSLC is poor with median OS ranging between 2–4 months with best supportive care and between 6–9 months with chemotherapy [35]. Docetaxel has been considered as the standard of care after a platinum-based first-line chemotherapy. However, chemotherapy and docetaxel trigger significant toxic effects that must be taken in account, considering the palliative setting and the frailty of pretreated lung cancer patients.

ICIs approval has radically changed the landscape of second and further lines for patients with advanced or metastatic squamous NSCLC. Both American and European guidelines recommend ICIs for patients with advanced sqCLC pretreated with chemotherapy [36, 37].

The first evidence of atezolizumab's efficacy in second or subsequent lines derived from two phase II single-arm trials involving SqCLC and nsqNSCLC selected for PDL-1, BIRCH and the FIR trials, which reported an overall response rate (ORR) of 19% and 21%, respectively, confirming the activity of atezolizumab in this setting in both histology type (Table 3) [38, 39].

In the phase 2, multicenter, randomized, POPLAR trial, patients with advanced NSCLC previously treated with platinum-based chemotherapy received intravenous atezolizumab (fixed dose 1200 mg) or docetaxel (75 mg/m²) once every 3 weeks. Patients were stratified by histology (non-squamous vs squamous), tumor-infiltrating immune cell PD-L1 expression and previous lines of therapy (one or two). The primary endpoint was centrally assessed OS in the ITT population and PD-L1 subgroups. Secondary endpoints were investigator-assessed ORR, PFS, duration of response (DOR), and safety. The study enrolled 287 patients, 142 received at least one dose of atezolizumab and 135 received docetaxel. Of 287 enrolled patients, 97 (34%) had squamous histology. In the overall population, at a median follow-up of 13 months, atezolizumab significantly improved OS (12.6 vs 9.7 months; HR 0.73, 95% CI 0.53–0.99; $p = 0.04$), without increasing PFS (2.7 vs 3.0 months;

HR 0.94, 95% CI 0.72–1.23). ORR was 15% in both group but responses were more durable with atezolizumab, with a mDOR of 14.3 months (95% CI 11.6–non-estimable) vs 7.2 months (95% CI 5.6–12.5) with docetaxel. Atezolizumab was confirmed to be superior to chemotherapy in both histologies. In patients with squamous disease, atezolizumab improved OS (10.1 vs 8.8 months; HR 0.80, 95% CI 0.49–1.30). Contrary to other ICIs, the OS benefit was more pronounced in non-squamous subgroup (mOS 15.5 months vs 10.9 months in 95 patients in the docetaxel group (HR 0.69; 95% CI 0.47–1.01) [40].

Based on these interesting results and due to the limited size of the POPLAR trial which makes difficult to draw conclusions about atezolizumab effects in subgroups, the phase 3 OAK study was conducted [15]. This was a randomised, international, open-label phase 3 trial that enrolled patients with squamous and non-squamous locally advanced or metastatic NSCLC pre-treated with one or two chemotherapy regimens, at least one platinum-based. Patients were stratified by histology (non-squamous vs squamous), number of previous chemotherapy regimens (one vs two) and PD-L1 expression on tumor cells or tumor-infiltrating immune cells (IC0 vs IC1 vs IC2 vs IC3 level). Coprimary endpoints were OS in the ITT and PD-L1 expression population TC1/2/3 or IC1/2/3 (PD-L1 expression on $\geq 1\%$ of tumor cells or tumor-infiltrating immune cells). Secondary endpoints were investigator-assessed PFS, ORR and safety. The study enrolled 1225 patients, while 850 were available for the ITT population analysis. Among these, 222 (26%) had squamous histology, 112 (26%) in the atezolizumab arm and 110 (26%) in the docetaxel arm. Compared with docetaxel, patients exhibited an improved mOS with atezolizumab in the ITT population (13.8 months [95% CI 11.8–15.7] vs 9.6 months [95% CI 8.6–11.2]) and in the TC1/2/3 or IC1/2/3 populations (15.7 months [95% CI 12.6–18.0] vs 10.3 months [8.8–12.0]). PFS and ORR were similar between the two arms, but the median duration of response was longer in the atezolizumab group (16.3 months; 95% CI 10.0–not evaluable) compared with the docetaxel arm (6.2 months; 95% CI 4.9–7.6). Atezolizumab improved OS regardless of PD-L1 expression. In patients with squamous histology atezolizumab confirmed OS benefit, with a median OS of 8.9 vs 7.7 months (HR 0.73; 95% CI 0.54–0.98; $p = 0.0383$), but even in this case, the OS benefit was higher in non-squamous histology, in which mOS was 15.6 months with atezolizumab versus 11.2 months with docetaxel ($p = 0.0015$) [15]. The absence of benefit in terms of PFS may be related to antitumour immune activation beyond progression that might be sustained by continued treatment.

Recently, final results of the two randomized phase II (POPLAR) and phase III trials (OAK), At a median follow-up of 4 years, most survivor patients had non-squamous histology, ECOG PS 0 and about half of them were still on response to the treatment.

Table 3. Atezolizumab second or further lines trials.

Identifier, phase	Disease	Intervention	mOS	mPFS	ORR% (95% CI)
BIRCH Phase II	PDL-1 positive, IIIB-IV or recurrent NSCLC	Atezolizumab monotherapy	2L: 15.5 (95% CI, 12.3–19.3) 3L: 13.2 (95% CI, 10.3–17.5)	2L: 2.8 (95% CI, 1.5–3.9) 3L: 2.8 (95% CI, 2.7–3.0)	2L: 19% (95% CI, 15–25) 3L: 18% (95% CI, 13–23)
FIR Phase II	PDL-1 positive, IIIB-IV or recurrent NSCLC 2C: II or more line without brain metastases 3C: II or more line with treated brain metastases	Atezolizumab monotherapy	2C: 9.3 (95% CI 5.8–17.6) 3C: 6.8 (95% CI, 3.2–19.4)	2C: 3.7 (95% CI: 0.0–45.5) 3C: 4.3 (95% CI: 1.1–16.2)	2C: 21% (95% CI: 13–30) 3C: 17% (95% CI: 12–22)
POPLAR Phase II	NSCLC progressed to prior platinum-based chemotherapy	Atezolizumab vs Docetaxel	12.6 (95% CI 9.7–16.4) vs 9.7 months (8.6–12.0) [HR] 0.73 [95% CI 0.53–0.99]; <i>p</i> = 0.04	2.7 vs 3.0 months HR 0.94, 95% CI 0.72–1.23	15 vs 15
OAK Phase III	Squamous or non-squamous NSCLC, stage IIIB–IV, progressed to platinum-based chemotherapy	Atezolizumab vs Docetaxel	13.8 (95% CI 11.8–15.6) vs 9.6 (95% CI 8.6–11.2) months HR 0.75 (95% CI 0.53–0.99; <i>p</i> = 0.0003)	2.8 (95% CI 2.6–3.0) vs 4.0 (95% CI; 3.3–4.2) months HR 0.95 (95% CI 0.82–1.10; <i>p</i> = 0.4928)	17.8 vs 16.2

C, cohort; L, lines; CI, confidence interval; HR, Hazard Ratio; N/A, Not Available; ORR, Overall Response Rate; DOR, Duration of Response; OS, Overall Survival; PFS, Progression Free Survival; resulted for the POPLAR and OAK trial refers to ITT population.

Table 4. Current trials in neoadjuvant setting.

Identifier, phase	Stage	Intervention	Primary outcomes	Status	Estimated completion date
NCT03456063 (IMpower 030) III	Resectable Stage II, IIIA, or Select IIIB NSCLC	Atez + platinum-based chemotherapy (nab paclitaxel, pemetrexed, carboplatin, cisplatin, gemcitabine) vs Placebo + Chemotherapy	MPR; IRF-Assessed Event Free Survival	Recruiting	Mar-25
NCT02927301 II	IB, II, IIIA NSCLC	Atez as neoadv and adjuvant therapy	MPR based on surgical resection	Recruiting	Jul-23
NCT02994576 (PRINCEPS) II	IB, II, IIIA (non N2) NSCLC	Atez as neoadv therapy	Rate of patients without major toxicities or morbidities	Recruiting	May-21
NCT02716038 II	Stage IB-III A NSCLC	Atez + Nab-paclitaxel and Carboplatin as neoadv	Number of subjects with MPR.	Active, not recruiting	Dec-20
NCT03102242 II	Unresectable or inoperable IIIA/B NSCLC	Atez as neoadv therapy, with CRT, and as adjuvant therapy	DCR after 12 weeks induction	Active, not recruiting	Mar-20

Atez, atezolizumab; CRT, chemoradiotherapy; MPR, major pathological response; DCR, disease control rate; IRF, independent review facility; NSCLC, non-small cell lung cancer.

In squamous patients, the 4-year OS rate in POPLAR was 7.0% (95% CI: 0.0%–14.7%) in patients receiving atezolizumab, while it was 19% (95% CI: 10.5%–26.7%) in non-squamous patients. In OAK the 4-year OS rates for patients treated with atezolizumab were respectively 9% (95% CI: 3.6%–13.5%) and 18% (95% CI: 14.0%–21.7%) [41].

From a post-hoc analysis of the OAK study, the benefit from atezolizumab is evident beyond progressive disease. Indeed, patients who experienced radiographic progressive disease showed longer median OS post-progression in the atezolizumab arm (8.6 months; 95% CI: 7.0–9.9) than patients in the docetaxel arm (6.4 months; 95% CI: 5.3–7.6). Moreover, at a follow-up of 18 months post-progression, 26% of patients in the atezolizumab group vs 18% in the docetaxel group were alive. However, the number of SqCLC patients who continued the treatment beyond progression was small 42 (24%) and no data on this specific subgroup are available for analysis [42].

One of the limitations of these studies concerns the small population size of subgroups, that hinders definitive conclusions about benefit estimation. Meta-analyses are useful tools to explore the efficacy of ICIs as second and further lines for NSCLC, especially when only data from small population are available, as in the case of the squamous histology. Furthermore, fractional polynomials network meta-analyses (NMA) can overcome the assumption of proportional hazards for the survival functions accounting for long-term effect of immunotherapy and for differences observed in survival patterns. A meta-analysis on six studies comparing ICI to standard chemotherapy included 942 SqCLC patients and 2520 non-sq NSCLC. The analysis confirmed, after a median follow-up of five years, a 29% reduction of the death risk by ICIs in patients with SqCLC (HR = 0.71 [95% CI, 0.60–0.83], $p < 0.0001$), without significant heterogeneity, and also 23% reduction in the risk for death for non-sq NSCLC (HR = 0.77 [95% CI, 0.63–0.94], $p = 0.01$) [43]. Direct comparison among different ICI remains difficult. Another recent meta-analysis tried to compare nivolumab, pembrolizumab and atezolizumab in pre-treated NSCLC, founding that all the three PD-L1/PD-1 inhibitors had comparable expected 5-year OS and all performed better than chemotherapy; however, no stratification for histology was performed in this analysis [44].

Another important point in the setting of SqCLC is the identification of predictive biomarkers. As reported above, PD-L1 expression is not the optimal biomarker: in clinical trials different IHC assays with different cut-offs for positivity are used and often a small sample biopsy may not be representative of the overall complexity of the tumor due to intra/inter-tumor heterogeneity. Recently, a pooled analysis of the OAK and POPLAR trial in pre-treated NSCLC patients reported an association between high blood Tumor Mutation Burden (TMB) (defined as >16 mut/MB) and better outcome [45]. On the other hand, in the B-FIRST

study, assessing blood TMB in chemo-naïve patients, high TMB was not associated with improved PFS, suggesting that TMB could be a prognostic rather than predictive factor [46]. Squamous histology is usually smoke-related and, for this reason, may potentially have higher antigen load, reflecting higher TMB levels. However, in these studies, histology-related differences were not assessed and further trials are needed to identify predictive biomarkers, also in the squamous histology. The clinically meaningful survival benefit over docetaxel, more durable responses and the favorable safety profile make atezolizumab a standard of care in second and further lines setting for advanced squamous NSCLC.

5. Atezolizumab in SqCLC: new indications

5.1 Neoadjuvant therapy

The use of immunotherapy in neoadjuvant setting is intriguingly and challenging since the tumor is potentially resectable for cure. Five-year survival rates range from 50% for stage IA disease to 20% for stage IIIA disease, and in the majority of patients, who underwent surgery progression of disease occurs [47]. The addition of perioperative platinum-based chemotherapy increases the survival rate only by 5.4% respect to surgery alone and is burdened by high toxicity and negative impact on quality of life [48, 49]. Nevertheless, in this setting the primary tumor can be utilized as an antigen source for expansion and activation of tumor-specific T cells and systemic surveillance of micrometastases [50].

Impressive results derived from a recently published phase II, single arm, trial investigating the efficacy of Atezolizumab in combination with carboplatin and nab-paclitaxel for four cycles before surgery in stage IB-IIIa NSCLC, stratified for histology [51]. Thirty patients were enrolled, 12 (40%) with squamous histology at diagnosis. Major pathological response (MPR), defined as $\leq 10\%$ of viable tumor tissue, and pathological complete response (pCR) rate were higher among squamous than non-squamous patients. 80% (8/10) of squamous versus 53% (8/15) of non-squamous patients achieved a MPR, while 50% (5/10) versus 33% (5/15) had a pCR. Achievement of MPR and pCR was correlated with improved disease-free survival in the ITT-population [51]. However, the small number of patients and the chemotherapy regimen combined unable to drive any conclusion. The role of single agent atezolizumab as neoadjuvant treatment is under investigation, too. A phase II single-arm trial is investigating atezolizumab monotherapy given as a neoadjuvant therapy for two cycles at the fixed dose of 1200 mg every three weeks in patients with NSCLC with stage IB to IIIA. Primary endpoint is the MPR following surgery, a part 2 is planned with adjuvant atezolizumab up to 12 months for patients who benefit from part 1, but data are still missing [52].

Table 5. Current trials with atezolizumab and radiotherapy.

Identifier, phase	Stage	Intervention	Primary outcomes	Status	Estimated completion date
NCT04214262 III	Inoperable stage I–IIA NSCLC	SBRT with or without atez	OS	Not yet recruiting	May-28
NCT04081688 I	Unresectable NSCLC (stages III to IV) progressed on prior PD-1/PD-L1 therapy	Atez and Varlilumab in combination with SBRT	To assess the safety and tolerability of atez and varlilumab in combination with SBRT	Recruiting	Jun-23
NCT02599454 I	Inoperable stage I NSCLC	Atez + SBRT	To determine the MTD of atez that can be given with SBRT	Active, not recruiting	Sep-21
NCT02400814 I	Stage IV NSCLC	Atez + SBRT	To determine which administration schedule of atez and SBRT will be used in a phase II trial based on safety and objective response rate	Active, not recruiting	Apr-21
NCT02992912 II	Patients with metastatic tumours (including NSCLC)	Atez + SBRT	PFS using RECIST 1.1	Recruiting	Oct-20

Atez, atezolizumab; SBRT, Stereotactic body radiation therapy; MTD, maximum tolerated dose; OS, Overall survival; PFS, progression free survival; NSCLC, non-small cell lung cancer.

Preliminary data of the PRINCEPS trial, a phase II study assessing efficacy of only one cycle of single agent atezolizumab before surgery, have recently been presented at the latest ESMO Meeting, showing MPR of 14.5%. However, subgroup data on squamous histology were not presented [53]. More recently, preliminary data of the phase II Lung Cancer Mutation Consortium (LCMC)3 showed 21% of MPR and 7% of pCR in stage IB–IIIB NSCLC treated with two cycles neoadjuvant atezolizumab; however, even in these cases, stratification for histology was not reported [54]. Furthermore, neoadjuvant atezolizumab in NSCLC is being investigated in different clinical studies, both as single agent and in combination with chemotherapy (Table 4). Currently, results are not available, but are eagerly awaited to clarify the role of the drug in this setting. These studies hopefully will answer to many open questions, such as the definition of the most effective duration of neoadjuvant therapy, the best predictive biomarkers of response and the possible correlation of the pathological response (resulting from neoadjuvant immunotherapy) with overall survival. Anyway, data on SqCLC in this setting will be probably derived from a subgroup analysis as studies are not specifically targeting this histology.

5.2 Radiotherapy

Radiotherapy represents one of the most important strategies in NSCLC treatment.

Its role is well defined across all NSCLC disease stages including curative or palliative purpose. Preclinical and clinical data show a synergistic influence between radiotherapy and immunotherapy in NSCLC [55]. It is important to underline that the type of immunotherapy used, as well as the irradiated volume, timing, dose, and method of irradiation are crucial factors to determine the effect of the combination [55]. Radiotherapy can boost antitumor immune responses also augmenting the upregulation of dif-

ferent stimulatory immune signals (i.e., Fas and ICAM) [55, 56] and increasing tumor-specific CD8+ T-cells infiltration [57, 58]. Furthermore, tumor microenvironment has a key role in the efficacy of treatment. Indeed, it has been showed that even single low doses of RT have effects in re-programming tumor microenvironment and enriching local immune responses [59, 60].

On this basis, atezolizumab in combination with stereotactic ablative radiotherapy (SAR) in stage I NSCLC patients who cannot be candidate to surgery is under evaluation in a phase I trial to assess the maximum tolerated dose of atezolizumab that can be concomitantly administered with radiotherapy [61]. Recently, the PACIFIC study has provided encouraging results in terms of PFS, time to distant metastases, and OS with another ICI, durvalumab which has become the gold standard in treating in stage III NSCLC after concomitant chemo-radiation, despite restricted to PD-L1 positive patients (PD-L1 $\geq 1\%$) in many european countries [30]. Similar data are lacking for atezolizumab. However, a phase II study is evaluating atezolizumab given concomitant or sequential to chemoradiation in stage III unresectable NSCLC; primary endpoint is time to toxicity, defined as any G3–G4 AE in the first 15 weeks or any irAE [59]. Table 5 summarizes the ongoing clinical trials in this setting. Results are largely awaited since the combination strategy is promising.

5.3 Novel combinations

Growing interest has emerged in associating immunotherapy with other molecules and/or chemotherapies to improve outcomes. Early clinical data focusing on such combinations demonstrated encouraging results [62]. As previously mentioned, phase III clinical trials have led to the approval of some combinations of PD1-L1 inhibitors for the treatment of metastatic non-squamous and squamous NSCLC [63–65].

Table 6. Clinical trials ongoing on sqCLC.

Identifier	Intervention	Status
NCT03735121	A Study to Investigate the Pharmacokinetics, Efficacy, and Safety of Atezolizumab Subcutaneous in Patients With Stage IV Non-Small Cell Lung Cancer (IMscin001)	Recruiting
NCT03801304	Trial to Evaluate Safety and Efficacy of Vinorelbine With Metronomic Administration in Combination With Atezolizumab as Second-line Treatment for Patients With Stage IV Non-small Cell Lung Cancer (Vin-MetAtezo)	Recruiting
NCT03600701	Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer	Recruiting
NCT03455556	Anetumab Ravnansine and Atezolizumab in Treating Participants With Advanced Non-small Cell Lung Cancer	Active, not recruiting
NCT04081688	Atezolizumab and Varlilumab in Combination With Radiation Therapy for NSCLC	Recruiting
NCT03170960	Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors	Recruiting
NCT03616691	Atezolizumab Monotherapy and Consequent Therapy With Atezolizumab Plus Bevacizumab for NSCLC	Not yet recruiting

A careful evaluation of phase III data on the efficacy and safety is necessary, as well as patient selection, cost implications, and health equity.

Many combinations with other agents, like the MEK inhibitor cobimetinib or the multi TKi cabozantinib, are being investigated in many clinical trials and in different settings for both histology types (Table 6).

Among these, the combination of anti- T cell immunoglobulin and ITIM domain (TIGIT) antibody, Tiragolumab, with Atezolizumab showed promising results also in SqCLC. TIGIT is a novel inhibitor receptor expressed on T cells and NK cells, whose binding to its ligand in tumor cells and APCs downregulates immune- response [66]. In preclinical models, the combination of anti-TIGIT and anti-PD-L1 synergistically improved tumor control and survival [67].

Recently, data of the CITYSCAPE trial have been presented at the latest ASCO. This is a randomized phase II trial of tiragolumab plus atezolizumab versus atezolizumab alone in untreated NSCLC, stratified for histology (40% sqNSCLC) and selected for PD-L1 expression [64]. Primary endpoints were ORR and PFS in the ITT population. The combination of tiragolumab + atezolizumab significantly improved ORR (37% vs 21%) and PFS (mPFS 5.42 vs 3.58, HR 0.57), independently from the histology, with a greater magnitude benefit in patients with PD-L1 >50% [68]. This could be an interesting chemo-sparing strategy; longer follow-up and phase III trial are required.

6. Conclusions

Atezolizumab is currently considered as a valid therapeutic option in NSCLC in second or further lines of therapy without histologic restriction. Some concerns regarding its use in sqCLC in first-line setting arise from the randomized IMpower 110 and 131 clinical trials, jeopardizing the role of Ab antiPDL1 over antiPD1 agents in a naïve population. While encouraging results and more robust data are expected from the ongoing neoadjuvant trials in which

atezolizumab is widely employed in different combination with chemo/radiotherapy. While, generally, sqCLC benefited more from ICIs than nsqNSCLC with PD-1 inhibitors, as reported from Keynote 024, CheckMate 026 and 017, this difference is not so evident with atezolizumab single agent or combined with chemotherapy, in first nor further line of treatment. The mere HR comparison is not sufficient to provide recommendation. However, a kind of histologic dependent different efficacy could be an hypothesis to be explored with more extensive subgroup data and ad hoc studies.

7. Author contributions

MG, SC, FC, DC wrote and revised the manuscript; MG searched for the literature and prepared tables; DC and PB had a significant role in editing revising the manuscript.

8. Ethics approval and consent to participate

Not applicable.

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11. Conflict of interest

The authors declare no conflict of interest.

12. References

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Abbreviations: SqCLC, Squamous cell lung cancer; NSCLC, non-small cell lung cancer; nsqNSCLC, non-squamous Non Small-Cell Lung Cancer; PD-L1, Programmed Death Ligand-1; ICIS, immune-check point inhibitors; ORR, overall response rate; mOS, median Overall Survival; mPFS, median Progression Free Survival; Ab, antibody; FDA, Food and Drug Administration; ADA, anti-drug antibodies; NMA, network meta-analyses; TMB, Tumor Mutation Burden.

Keywords: Immune check point inhibitors; Squamous non-small cell lung cancer; First-line therapy; Advanced setting; Neo-adjuvant setting

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