Breakthroughs in the treatment of advanced squamous-cell NSCLC: not the neglected sibling anymore?

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Abstract: During the last years, translational research has contributed in many advances in the treatment of non-small cell lung cancer (NSCLC) discovering genetic alternations or recognizing the immuno-escape and neo-angiogenesis of lung cancer. Although the majority of these advances took place in the non-squamous histological subtype, therapeutic options for patients diagnosed with advanced squamous cell lung cancer (SqCLC) have been also enriched significantly with the addition of nab-paclitaxel in the conventional chemotherapy; the introduction of necitumumab, afatinib and erlotinib in the inhibition of epidermal growth factor receptor (EGFR) axis and of ramucirumab in the inhibition of VEGF-induced angiogenesis and last with the approvals of nivolumab, pembrolizumab atezolizumab and durvalumab soon in the promising field of immunotherapies. Agents targeted various other pathways including FGFR, IGF-1, PI3K, CDK4/6, MET and PARP inhibitors are under investigation in order to open new prospects in the treatment of SqCLC. In this review, we present all published data that led to recent approvals for the treatment of advanced SqCLC and all ongoing clinical trials that keep searching for new molecular targets following a more-personalized approach.

Keywords: Non-small cell lung cancer (NSCLC); squamous cell lung cancer (SqCLC); targeted therapy; immunotherapy

Introduction

Lung cancer remains the most common cancer diagnosis and the leading cause of cancer-related deaths, with approximately 1.8 million new cases and 1.59 million deaths accounting every year worldwide (1). During 2017, only in the USA the newly diagnosed cases and the estimated deaths were 222,500 and 155,870 respectively (2). Non-small cell lung cancer (NSCLC) covers the 80% of these lung cancer cases and mainly includes two large histological subsets, adenocarcinoma (46.6%) and squamous cell lung cancer (SqCLC) (23.2%) (3). Clinicopathologically, SqCLC differs remarkably from adenocarcinoma since its lesions are usually located more centrally, arose segmentally involving lobar or main bronchi and often showing central cavitation. The distinct histological nature of SqCLC and its different molecular background determine the variable therapeutic behavior of the disease to novel agents. Targeting genomic alterations, such as epidermal growth factor receptor (*EGFR*) mutations (4-8), anaplastic lymphoma kinase (*ALK*)

gene rearrangements (9-12) and more recently *ROS1* (13), and *BRAF* (14) led to the approval of 9 novel agents and radically changed the treatment of patients with NSCLC from conventional chemotherapy to a more individualized molecularly-targeted approach. However, these gene alterations are rarely detected in patients with SqCLC and these patients are less benefited by the targeted therapies compared to patients with lung adenocarcinoma. Thus, the conventional platinum-based chemotherapy remains up to recently the main 1st-line option for patients with SqCLC, but the introduction of immune checkpoint inhibitors enriched the therapeutic armamentarium of medical oncologists and signaled the beginning of a new era in the management of lung cancer.

In this review, we will focus on the latest advances in the treatment of metastatic/advanced squamous-cell NSCLC and present all approved anti-VEGF and anti-EGFR agents as well as all recently developed immunotherapies that changed the landscape of SqCLC treatment during the last years.

Chemotherapy

The combination of cisplatin or carboplatin with a third generation cytotoxic agent such as paclitaxel, docetaxel, vinorelbine, or gemcitabine consists the backbone of frontline approach for advanced SqCLC according to ESMO guidelines (15). No clinical trials or meta-analyses recognized any superior combination among them (16,17). Comparing the two most commonly used doublets, cisplatin-gemcitabine with cisplatin-pemetrexed a phase III non-inferiority study enrolled chemotherapy-naive NSCLC patients and stratified them according to the histological type. This study reached to prolonged survival times of cisplatin-gemcitabine arm (median progression-free survival, PFS 5.5 *vs.* 4.4 months, and median overall survival, OS 10.8 *vs.* 9.4 months, P=0.05) in the SqCLC population; whereas in the subgroup of patients with non-squamous NSCLC, the regimen of cisplatin-pemetrexed was found more tolerable and effective (median PFS 5.3 *vs.* 4.7 months, and median OS 11.8 *vs.* 10.4 months, P=0.03). Based on these outcomes, the doublet of cisplatin-gemcitabine received a clear indication for 1st-line treatment of SqCLC (18).

An additional approved chemotherapeutic agent for the treatment of advanced/metastatic SqCLC is nab-paclitaxel (an albumin bound form of paclitaxel). In 1st-line setting, the doublet of carboplatin with nab-paclitaxel was compared by a phase III study with standard (solvent-based) paclitaxel plus carboplatin in 1,052 patients with advanced NSCLC (19). The regimen of carboplatin with nab-paclitaxel was found more effective achieving an overall response rate (ORR) of 41% *vs.* 24% (P<0.001) but not reaching to statistically significance for PFS and OS. The doublet of carboplatin and nab-paclitaxel presented lesser grade 3/4 toxicities compared to the conventional combination of carboplatin plus paclitaxel including mainly peripheral neuropathy, (3% *vs.* 12%) and musculoskeletal pain (13% *vs.* 25%). The same combination of carboplatin and nab-paclitaxel has been compared with the doublet of gemcitabine plus carboplatin in a phase II trial of 120 untreated patients with advanced SqCLC patients and the results are still expecting (20). The role of this nanoparticle albumin-bound taxane in second line is also under investigation by an ongoing phase III study (21).

According to studies conducted mainly in Japanese population, two additional agents, the oral fluoropyrimidine derivative S-1 and the second-generation platinum analog nedaplatin, showed efficacy in SqCLC but have not included yet into the ESMO or NCCN guidelines. A combination of the first agent with carboplatin was compared with carboplatin/paclitaxel in frontline approach by a non-inferiority trial resulting in a median OS of 15.2 and 13.3 months in the experimental and control arm respectively (P=0.002) (22). Particularly for squamous histology, median OS was 14.0 and 10.6 months in the carboplatin/S-1 and carboplatin/paclitaxel arm respectively (P=0.093) (23). The S-1 derivative was also examined in combination with cisplatin versus cisplatin-docetaxel in a mixed histology NSCLC population including similar proportions of patients with SqCLC in the experimental and control arm respectively (16.6% and 16.3%). The regimen containing S-1 was found non-inferior to the regimen of docetaxel regarding OS (median, 16.1 *vs.* 17.1 months) and PFS (median, 4.9 *vs.* 5.2 months), but showed better tolerability (significantly lower febrile neutropenia—1.0% *vs.* 7.4%, P<0.001; grade 3/4 neutropenia 22.9% *vs.* 73.4%, P<0.001; grade 3/4 infection 5.3% *vs.* 14.5%; grade 1/2 alopecia 12.3% *vs.* 59.3%, P<0.001) and improved quality of life (global health status/QoL functioning, P<0.0001) (24). In parallel, the second-generation platinum analog nedaplatin was compared with cisplatin, plus docetaxel, in Japanese cases with advanced or relapsed SqCLC presented a favorable safety profile (grade ≥3 toxicities: nausea 4.0% *vs.* 14.3%, fatigue 3.4% *vs.* 10.9%, hyponatremia 13.6% *vs.* 30.3%, hypokalemia 2.3% *vs.*

8.6%) and a higher efficacy as depicted with a significant prolongation of median OS for the experimental arm (13.6 *vs.* 11.4 months; P=0.037) (25). Nedaplatin was also examined in advanced SqCLC by a phase II trial, as a doublet with irinotecan, but the preliminary results did not justify further investigation (26). Finishing the reporting of available chemotherapeutic options, cabazitaxel is tested in a mixed NSCLC population (containing 28.3% SqCLC patients) by a phase II study in 2nd and 3rd line setting (progression after docetaxel) and found well-tolerable (95% treatment compliance, 13% dose reductions), achieving an ORR of 50%, a median PFS of 2.1 months and a median OS of 7.4 months (27).

Targeted therapies

Anti-VEGF treatment

Based on the results of a phase III trial, bevacizumab has been approved for NSCLC in combination with paclitaxel/carboplatin, offering a median OS benefit of 2 months (28). However, this pivotal trial had not included patients with SqCLC due to safety concerns about life-threatening pulmonary hemorrhage, observed in the earlier phase II trial, mainly at centrally-located SqCLC lesions (29). Radiographically, tumor cavitation was the only finding, identified as a potential risk factor for hemorrhagic events (30). Given these findings, bevacizumab is currently contraindicated in tumors of squamous histology. The risk of bleeding did not stop the further investigation of anti-angiogenic effect in SqCLC. In the randomized phase III REVEL study another compound of anti-VEGF treatment, the IgG1 monoclonal antibody (mAb) of the extracellular domain of VEGFR-2, called ramucirumab was compared with placebo, as a 2nd line doublet with docetaxel in both squamous and non-squamous stage IV NSCLC patients. The regimen of taxane plus ramucirumab was found significantly superior to taxane-placebo combination both for PFS (median, 4.5 *vs.* 3.0 months, P<0.0001) and OS (median, 10.5 *vs.* 9.1 months, P=0.023). This OS benefit was also retained for the SqCLC subgroup (median, 9.5 *vs.* 8.2 months) (31). These results led to the approval of ramucirumab for both histologies.

Keep targeting VEGF pathway, axitinib, a novel pan-VEGFR inhibitor (e.g., inhibitor of all three VEGFR-1, -2 and -3) was evaluated by a phase II trial and compared with the standard 1st-line regimen of cisplatin and gemcitabine in patients with SqCLC. Treated patients reached to a median

PFS of 6.2 months and to a median OS of 14.2 months, while the most usually presented ≥3 grade toxicities were neutropenia (13.2%) and hypertension (13.2%). Only 3 (7.9%) patients experienced hemoptysis, one of which fatal (2.6%) (32).

Anti-EGFR agents

In contrast to adenocarcinoma, SqCLC is rarely characterized by *EGFR* mutations. Although it is not often mutated, EGFR can be overexpressed or presented with gene copy alterations in 60–80% and 7–10% of squamous lung tumors, respectively (33,34). Based on these data, several anti-EGFR agents have been tested in patients with SqCLC, but unfortunately in the context of clinical trials including patients with NSCLC of all histologies. Two EGFR tyrosine kinase inhibitors (TKIs), erlotinib and afatinib and one mAb, necitumumab are the only agents targeting EGFR axis that have been approved for patients with SqCLC; the TKIs in 2nd-line and the mAb in 1st-line treatment (15). The SQUIRE study enrolled only SqCLC patients to receive the standard cisplatin-gemcitabine combination plus or not necitumumab as 1st-line approach. The combination of anti-EGFR mAb with chemotherapy presented longer OS (median, 11.5 *vs.* 9.9 months, P=0.012), longer PFS (median, 5.7 *vs.* 5.5 months, P=0.020) and increased disease control rate (82% *vs.* 77%; P=0.043) but additional toxicity of at least one grade 3 or worse AE (72.1% *vs.* 61.6%) including mainly rash and hypomagnesaemia. This unfavorable safety profile of triplet with anti-EGFR mAb was clinically translated with higher treatment discontinuations (31.2% *vs.* 24.6%) in this arm (35).

Erlotinib was approved after 1st- or 2nd-line treatment of SqCLC based on the results of BR.21 trial that showed a statistically significant prolongation of OS compared to placebo in the overall population of NSCLC (6.7 *vs.* 4.7 months, P<0.001) and in the SqCLC subgroup (median, 5.6 *vs.* 3.6 months, P=0.07) (36). Afatinib acts in *EFGR* mutated-NSCLC (6) binding to the ErbB intracellular domain and inhibiting heterodimerization of the ErbB receptor. This EGFR TKI entered into ESMO Guidelines for SqCLC, through a single phase-III trial, named Lux-Lung 8 including only patients with squamous histology. In this study afatinib was compared with erlotinib, resulting in a statistically significant difference in PFS (2.6 *vs.* 1.9 months; P=0.010), ORR (5.5% *vs.* 2.8%; P=0.055) and median OS (7.9 *vs.* 6.8 months; P=0.008) in favor of the

Table 1 Selected trials of agents targeting EGFR axis

Treatment line	Treatment	SqCLC patients/all patients	Outcome	P value	Reference
1st	Cisplatin/gemcitabine +/– erlotinib	482/1,172	OS 10.8 mos (chemo plus erlotinib) vs. 11.0 mos (chemo alone)	0.49	(38)
1st	Carboplatin/paclitaxel +/– erlotinib	185/1,059	OS 10.6 mos (erlotinib) vs. 10.5 mos (placebo)	0.95	(39)
2nd–3rd	Vandetanib vs. erlotinib	272/1,240	PFS 2.6 mos (vandetanib) vs. 2.0 mos (erlotinib)	0.721	(40)
2nd	Erlotinib + bevacizumab vs. erlotinib	28/636	OS 9.3 mos (erlotinib + bevacizumab) vs. 9.2 mos (erlotinib)	0.7583	(41)
2nd	Docetaxel/pemetrexed vs. erlotinib	154/304	OS 5.5 mos (erlotinib) vs. 5.3 mos (chemotherapy)	0.73	(42)
2nd–3rd	Sunitinib + erlotinib vs. erlotinib	270/960	OS 9.0 mos (sunitinib + erlotinib) vs. 8.5 mos (erlotinib)	0.1388	(43)
2nd	Docetaxel vs. erlotinib in EGFR wild type	54/222	8.2 mos (docetaxel) vs. 5.4 mos (erlotinib)	0.05	(44)
1st	Cisplatin/gemcitabine +/– gefitinib	327/1,093	OS 9.9 mos (gefitinib 500 mg q day) vs. 9.9 mos (gefitinib 250 mg q day) vs. 10.9 mos (placebo)	0.46	(45)
1st	Carboplatin/paclitaxel +/– gefitinib	195/1,037	OS 8.7 mos (gefitinib 500 mg q day) vs. 9.8 mos (gefitinib 250 mg q day) vs. 9.9 mos (placebo)	0.64	(46)
2nd	Gefitinib vs. placebo	586/1,692	OS 5.6 mos (gefitinib) vs. 5.1 mos (placebo)	0.09	(47)
2nd	Gefitinib vs. docetaxel	361/1,466	OS 7.6 mos (gefitinib) vs. 8.0 mos (docetaxel)	>0.05	(48)
1st	Cisplatin/vinorelbine +/– cetuximab (EGFR positive)	377/1,125	OS 11.3 mos (chemotherapy plus cetuximab) vs. 10.1 mos (chemotherapy alone)	0.04	(49)
1st	Carboplatin/taxanes +/– cetuximab	171/676	PFS 4.4 mos (chemo plus cetuximab) vs. 4.2 mos (chemo alone)	0.24	(50)

SqCLC, squamous cell lung cancer; EGFR, epidermal growth factor receptor; mos, months.

experimental arm, with no major tolerance differences, although afatinib-treated patients presented more grade 3/4 diarrhea (10%/0.5% vs. 2%/0.3%) and grade 3 stomatitis (4.1% vs. 0%) (37). Table 1 presents the most important clinical trials investigating anti-EGFR treatments (either alone or in combinations with chemotherapy or other targeted agents) in patients with mixed NSCLC histology (38-50). The small number of clinical trials including exclusively SqCLC populations and the absence of strong results could not support and upgrade the use of anti-EGFR

agents as frontline therapeutic decision for patients with SqCLC. Thus, anti-EGFR agents are classified at the lower rungs of ESMO Magnitude of Clinical Benefit Scale (51).

Other molecular examined pathways

The amplification of the FGFR pathway is recognized in about 12% of SqCLC cases (52) and found to be associated with worse prognosis (53). This finding leaded to further investigation of novel FGFR targeted molecules in patients

with NSCLC including patients with SqCLC. In this category, nintedanib is the only approved agent limited to adenocarcinoma patients as the phase III trial, LUME-Lung 1 that enrolled NSCLC patients to receive docetaxel +/− nintedanib as 2nd-line treatment, resulted in a median OS prolongation for adenocarcinoma patients and especially those progressing in less than nine months after 1st-line (10.9 *vs.* 7.9 months, P=0.0073) but not for the total study population (median 10.1 *vs.* 9.1 months, P=0·2720) (54). Dovitinib is a multiple inhibitor of FGFR axis (FGFR1–3, VEGFR1–3, PDGFRβ, c-KIT and FLT3), but its results from a phase II trial in pretreated patients with exclusively FGFR-amplified SqCLC, (ORR: 11.5%, median OS 5.0 months and median PFS 2.9 months) were not so promising (55). Other agents such as AZD4547 and BGJ398 have only phase I results (56,57) and NCT01761747 trial of ponatinib had been early terminated due to safety reasons (58). Therefore, no additional agents except of nintedanib targeting the FGFR axis are expecting to be approved soon for NSCLC treatment.

In SqCLC tumors (47%) there are some alterations in the intracellular protein compounds of the PI3K-Akt-mTOR pathway that implicated in tumor growth (52). A phase II trial enrolled 63 NSCLC patients with PI3K activation and treated them with buparlisib monotherapy but failed to demonstrate strong efficacy (59). Another PI3K inhibitor, labeled as PX-866, was tested in combination with docetaxel in 2nd-line setting, by a phase II trial of NSCLC, containing SqCLC cases but had also negative results (60). Taselisib is the last addition in the list of investigated PI3K inhibitors as 2nd-line options but the phase II trial in patients with PI3K activated SqCLC is still ongoing (58).

Increased levels of free IGF-1 have been identified in squamous lung tumors (61). However, all investigated regimens targeting IGF-1 implicated pathway were not found significantly effective either as 1st-line treatment or as later options. For instance, figitumumab combined with paclitaxel and carboplatin in not previously treated patients with non-adenocarcinoma lung cancer had shown no superior efficacy in a phase III trial (62) while the IGF-1R modulation by AXL-1717 despite the improved frequency of severe neutropenia compared to docetaxel in a phase II trial of pretreated patients with squamous histology, had similar frequencies of non-progression at week 12 (25.9% *vs.* 39%) (63).

Based on the impressive results of the approved CDK4/6

inhibitors in patients with breast cancer (64), the role of cyclin dependent kinases (CDK) including CDK4 and CDK6 in the Rb1 pathway is also evaluated in the treatment of NSCLC. Specifically in SqCLC, the CDK-Rb1 pathway is deregulated via multiple ways (65,66). The first-in-class agent, palbociclib, was investigated in a single-arm phase II trial in 19 recurrent NSCLC patients, negative for p16 expression. The median PFS was 12.5 weeks and disease was stable in 50% of patients. This response was not correlated with histological type or *EGFR* mutational status (67).

In parallel, MET alternations found to be associated with poor prognosis through resistance to EGFR TKIs in lung adenocarcinoma and are recognized in approximately 6–10% of SqCLC, (68,69). Several MET inhibitors have been evaluated in SqCLC patients with modest results to date. Onartuzumab, a mAb directed against MET has shown minimal efficacy, either in a phase II trial in combination with platinum-doublet chemotherapy as 1st-line approach of SqCLC, or in a phase III trial in combination with erlotinib in a selected pretreated population (70,71). Two other molecules that inhibited MET pathway, cabozantinib and tivantinib have been tested but their combinations with erlotinib had favorable preliminary results only limited to non-squamous *KRAS*-mutated and *EGFR* wild-type NSCLC patients, respectively (72,73).

Regarding the proteasome inhibition, the outcomes of a phase II trial after the addition of bortezomib to gemcitabine and cisplatin in chemo-naïve patients with SqCLC were also disappointing (ORR: 17%, median PFS: 2.5 months and median OS: 10.6 months) (74).

Among the other non-approved but investigated agents, veliparib, an oral PARP inhibitor, showed the most promising results of phase II testing. By disabling DNA single-strand breaks repair, PARP inhibitors presented great antitumor activity in ovarian cancer especially as maintenance after response to platinum containing chemotherapy (75,76). In general, SqCLC is considered a platinum-sensitive tumor, so PARP inhibitors may take a place in the sequence of its treatments. Veliparib was studied in combination with paclitaxel and carboplatin, in the first line approach of NSCLC patients (49% of patients enrolled were SqCLC) by a placebo-controlled phase II trial. The results of this trial were more favorable for the experimental triplet compared to the standard carboplatin/paclitaxel doublet, also in the squamous histology subgroup, presenting a median PFS of 6.1 *vs.* 4.1 months and a median

OS of 10.3 *vs.* 8.5 months (77).

Immunotherapy

After the fundamental paper of Hanahan and Weinberg in *Cell* (78), where the tumor-induced immunosuppression was recognized as an emerging hallmark of cancer, the immunotherapy was introduced as a new breakthrough anticancer treatment and exponentially administered in several tumor types and treatment lines, from melanoma (79) and lung (80) to unknown primary (81) and from metastatic to adjuvant setting (82,83) changing in total the clinical approach of oncological patients. Particularly in NSCLC, many years after the initial clinical trials of immunotherapies, it is important to notice that the use of immunotherapy not only improved the quality of life but also multiplied the overall and the disease-free survival of treated patients (84).

Nivolumab

Nivolumab was the first immunotherapy agent that received approval for the second line approach of SqCLC, based on the results of CheckMate 017 that included exclusively patients with SqCLC and compared nivolumab versus docetaxel in the 2nd-line setting after a platinum doublet as 1st-line. This phase III, randomized trial resulted in a statistically significant improvement of ORR (20% versus 9%) and a survival benefit (median OS: 9.2 months, 95% CI: 7.33–12.62 *vs.* 6.0 months, 95% CI: 5.29–7.39 and 2-year OS%: 24% *vs.* 8%) for the immunotherapy arm. In contrast with the non-squamous subset, PD-L1 expression was not associated with efficacy of nivolumab and notably, no survival or response advantage was found in different levels of PD-L1 (1%, 5% and 10%). As expected, nivolumab presented a more tolerable safety profile compared to conventional 2nd-line chemotherapy with lesser toxicities of any grade (59% *vs.* 87%) and lesser toxicities of grade 3/4 (8% *vs.* 56%) while treatment discontinuation rates were 5% and 10%, respectively (85,86).

Before the pivotal CheckMate 017 trial, nivolumab has been initially evaluated in the third-line and beyond setting, in a phase II, single-arm study CheckMate 063 that enrolled 117 SqCLC patients who had progressed after a platinum-doublet and one more systematic treatment resulting in ORR of 14.5%, median OS of 8.2 months, 12- and 18-month OS rates 39% and 27%, respectively. Regarding safety, 75% of patients experienced AEs of any grade and 17% grades 3–4 whereas immunotherapy had to be terminated due to toxicity in 17% of them (87).

Trying to improve further the depth and the duration of response, nivolumab has been tested in combinations with an anti-CTLA4 agent, ipilimumab and several other established chemotherapy doublets. However, the preliminary results of the nivolumab-ipilimumab doublet emerged some safety concerns as ipilimumab, at melanoma-established doses of 3 mg/kg every 3 weeks in combination with nivolumab was not found well-tolerated, leading to high rates of AEs (49%) and even to therapy-related deaths (88). Consequently, the "nivo-ipi" combination was re-evaluated at a different dose-schedule administration of ipilimumab at 1 mg/kg either every 6 or 12 weeks in 77 NSCLC patients (including 13 SqCLC patients) as 1st-line treatment with ORR of 38% and 47%, respectively for the 6- and 12-week schedule. Interestingly when a PD-L1 expression cut-off level of at least 1% was used ORR was found even better for both schedules (approximately 57%). Data for 1-year OS% were mature only for the 6-week cohort reaching to 69% (89). Immunotherapy-related AEs greater than grade 3 occurred in about 35% in both dose-schedules. This particular immuno-combination is now being evaluated in a phase II trial that has completed accrual and results are expecting to be published soon (90).

Nivolumab at 10 mg/kg has also been evaluated in combination with three different chemotherapy doublets (pemetrexed-cisplatin for adenocarcinoma, gemcitabine-cisplatin for SqCLC and paclitaxel-carboplatin for all NSCLC histologies) and as monotherapy at 5 mg/kg in a multi-cohort phase I trial (91) resulting in ORR of 47%, 33% and 47% for the nivo-cis-pem, nivo-cis-gem and nivo-carbo-taxol cohorts, respectively and in 43% at the half-dose of nivo monotherapy, irrespectively of PD-L1 status. The 2-year OS% for the three immuno-chemo combinations were 33% for cis-pem, 25% for cis-gem, 27% for carbo-taxol and reached to 62% for the half-dose nivolumab. All immuno-chemo combinations presented similarly impaired safety profile. For example, 45% of treated patients reported grade 3/4 toxicities and 21% had to discontinue their treatment.

Pembrolizumab

Pembrolizumab is the only checkpoint inhibitor approved in both 1st- and 2nd-line treatment of NSCLC expressed PD-L1 in more than 50% and 1% of tumor cells (TC), respectively for the two settings. These indications based on

the results of the Keynote 024 and 010 trials that in contrast to nivolumab studies, enrolled patients with both squamous and non-squamous lung cancer.

As frontline treatment, pembrolizumab at a fixed dose of 200mg was compared with a platinum-based doublet (investigator's decision, out of five different options), in 305 patients with NSCLC (56 with SqCLC histology—18% in each arm) expressing more than 50% PD-L1. Results were in favor of immunotherapy arm regarding median PFS (10.3 vs. 6.0 months, P<0.001) and 6-month OS% (80.2% vs. 72.4%, P=0.005). In the SqCLC subpopulation the risk of disease progression or death was significantly reduced in immunotherapy arm (HR =0.35, 95% CI: 0.17–0.71). Similar to other immunotherapies, pembrolizumab appeared fewer toxicities compared to chemotherapy arm (any grade 73.4% vs. 90.0% and grade 3/4 26.6% vs. 53.3%, respectively). Most immunotherapy-related AEs were early detected at grade 1 or 2 and well managed with no recorded immunotherapy-related deaths. The superior efficacy and safety results of immunotherapy compared to standard platinum-containing doublet led to the early publication of findings and supported the approval of pembrolizumab as the recommended 1st-line regimen for patients with NSCLC expressed >50% PD-L1 (92).

In 2nd-line setting, pembrolizumab was evaluated after progression in a platinum-containing doublet by Keynote 010 phase II/III trial. This trial enrolled 1,034 patients with NSCLC (222 SqCLC), expressing PD-L1 at least 1%. Patients were randomized to receive: (I) either low-dose pembrolizumab (2 mg/kg, n=345), (II) high-dose pembrolizumab (10 mg/kg, n=346), or (III) standard dose docetaxel (75 mg/m^2, n=343) every 3 weeks. Immunotherapy at both doses was found more efficient and less toxic than chemotherapy. The risk of death was significantly reduced in both immunotherapy arms (HR =0.71, 95% CI: 0.58–0.88, P=0.0008 and HR =0.61, 95% CI: 0.49–0.75, P<0.0001 for the low- and high-dose schedules, respectively) (93). Median OS was prolonged either for patients with PD-L1 expression ≥50% or ≥1% for both dosing schedules. For patients with tumors expressing PD-L1 ≥50%, the median OS of pembrolizumab at 2 mg/kg, was 14.9 vs. 8.2 months for docetaxel (HR =0.54, 95% CI: 0.38–0.77) and for patients with tumors expressing PD-L1 ≥1%, the median OS was 9.4 vs. 8.6 months for docetaxel (HR =0.79, 95% CI: 0.61–1.04). The median OS for the higher doses was 17.3 vs. 8.2 months (HR =0.50, 95% CI: 0.36–0.70) compared to docetaxel for the 1–49% PDL1 expression and 10.8 vs. 8.6 months (HR =0.71, 95% CI: 0.53–0.94) for the

≥50% PDL1 expression. The PD-L1 inhibition appeared again more tolerable than chemotherapy with less grades 3/4 AEs (13% for low-dose pembrolizumab, 16% for high-dose pembrolizumab and 35% for chemotherapy) (93).

Aiming in the improvement of efficacy, trials are evaluating pembrolizumab in different combinations with either targeted therapy, or chemotherapy or other immune-modulating agents. Keynote 021 is a multi-cohort phase 1/2 randomized trial that enrolled NSCLC patients to receive one of the following combinations: carboplatin-paclitaxel-pembrolizumab or paclitaxel-carboplatin-bevacizumab-pembrolizumab or carboplatin-pemetrexed-pembrolizumab or ipilimumab-pembrolizumab or erlotinib-pembrolizumab or gefitinib-pembrolizumab. Results are announced and led to the approval of carboplatin-pemetrexed-pembrolizumab due to a significant PFS prolongation for patients receiving the combination but will not be further analyzed as only non-SqCLC patients were enrolled at this cohort (94).

Atezolizumab

Atezolizumab is a humanized IgG1-kappa mAb that binds PD-L1 and inhibits PD-L1/PD-1 and PD-L1/B7.1 interactions. It was subsequently approved for patients with NSCLC, in 2nd-line setting. Atezolizumab was initially evaluated in a phase II randomized trial, where 277 patients (97 cases with SqCLC) were randomized to receive atezolizumab 1,200 mg or docetaxel every 3 weeks, resulting in a 3-month prolongation of overall survival in favor of immunotherapy arm (12.6 vs. 9.7 months, P=0.04). The ORR and the duration of response for the immunotherapy arm were 15.3% and 18.6 months respectively (95). Atezolizumab was further evaluated in a phase III (OAK) study that enrolled 1,225 NSCLC patients of squamous (222 cases) and non-squamous (628 cases) histology to receive atezolizumab 1,200 mg or docetaxel at standard dose after failure of platinum-based 1st-line chemotherapy. PD-L1 expression was evaluated not only in TC but also in tumor infiltrating immune cells (IC) in order to recognize a combinatorial marker that could predict response to immunotherapy. Median OS was significantly prolonged in the whole cohort and in the subgroups of PD-L1 expression. More specifically, for expression ≥1% PD-L1 (TC or IC) the OS was 15.7 vs. 10.3 months (P=0.010); for expression <1% PD-L1 (TC or IC) 12.6 vs. 8.9 months (P=0.022); for high PD-L1 (TC ≥50% or IC ≥10%) expression 20.5 vs. 8.9 months (P<0.0001); and for the whole population 13.8 vs. 9.6 months (P=0.0003). For

subpopulation of SqCLC, the anti-PDL1 agent offered a lower OS benefit compared to standard docetaxel (8.9 vs. 7.7 months, P=0.038). Similarly to the other checkpoint inhibitors and in contrast to docetaxel, atezolizumab was tolerated more well with grades 3–4 AEs, 15% vs. 43% (96).

Durvalumab

Durvalumab is under approval for use in NSCLC patients in the non-metastatic setting after the recently announced results of the PACIFIC trial in the last ESMO meeting 2017. In this trial, 713 patients with stage III NSCLC non-progressing after at least two cycles of chemo-radiation were randomized to receive consolidation treatment with the human IgG1 monoclonal anti-PD-L1 antibody at 10 mg/kg or placebo, every other week, for up to a year. The PFS curves were significantly different in favor of the experimental arm, resulting in a median PFS (16.8 vs. 5.6 months, P<0.001). The ORR was also improved in the durvalumab arm (28.4% vs. 16.0%; P<0.001 and 72.8% vs. 46.8% with ongoing response at 18 months, respectively). The median time to death or distant metastasis was also prolonged for approximately 10 months (23.2 vs. 14.6 months; P<0.001) for the immune checkpoint inhibitor arm. In the consolidation, the safety profile of durvalumab was similar to placebo regarding toxicities greater than grade 3 (29.9% vs. 26.1%, and the most commonly observed pneumonia presented in 4.4% vs. 3.8% of cases, respectively) (82).

Durvalumab was also investigated in an immunotherapy combination with tremelimumab (anti-CTLA4 fully human IgG2 isotype inhibitor) by a phase1B trial. In this trial, durvalumab tested in 102 NSCLC patients including 10 with SqCLC. The dose for both immunotherapies was established for further trials into 10 mg/kg for durvalumab and 1 mg/kg for tremelimumab and in a 4-week cycle. Unfortunately, 36% of patients (in all testing doses) experienced serious AEs and 3 treatment-related deaths were recorded possibly due to immune-related toxicities (such as myasthenia gravis, pericardial effusion, and neuromuscular disorder). In the finally selected dose combination, the ORR was 40% and 22% for PD-L1 expression of >25% and 0%, respectively (97). With some serious concerns about its safety profile this combination is under further investigation in several studies of different treatment settings [chemo-refractory/ARCTIC study (98) and initial treatment/MYSTIC study (99)].

Avelumab

Avelumab is the less investigated of anti-PD-L1 agents in NSCLC with only some preliminary (phase 1b) results announced earlier this year. This study enrolled 184 patients with NSCLC (53 with SqCLC) to receive avelumab after failure of platinum-based chemotherapy for recurrent or metastatic NSCLC. The most common AEs of any grade observed in treatment with avelumab were fatigue (25%), infusion-reactions (21%) and nausea 13%, while the most common AEs worse than grade 3 were infusion reactions (2%) and increased lipase level (2%). Bearing in mind the limitations of a phase I trial for estimating efficacy, the ORR and DCR were found 12% and 50%, respectively (100).

Ipilimumab

The last introduced agent in the field of immunotherapy for NSCLC was ipilimumab, an anti-CTLA4 antibody. Based on its established role in the treatment of melanoma (101), ipilimumab is under investigation in combination with nivolumab or pembrolizumab in NSCLC (90,91,95). A phase III study enrolled 956 patients with exclusively SqCLC to receive ipilimumab or placebo in addition to carboplatin-paclitaxel chemotherapy as 1st-line treatment but the immuno-chemo combination failed to improve OS. In more details, the median OS was 13.4 and 12.4 months for the immuno-chemo and conventional chemo arms respectively (P=0.25) whereas the two groups performed exactly the same median PFS =5.6 months (102).

Conclusions

The introduction of anti-VEGF, anti-EGFR, anti-PD-1, anti-PD-L1 and anti-CTLA4 agents has dramatically changed the treatment of SqCLC multiplying the therapeutic options for patients with SqCLC. Although that many advances happened during the last years in order to move from the limited treatments to the rising question about their optimal sequencing, further insights are still needed to identify new prognostic or predictive molecular biomarkers that will lead to a more individualized approach of SqCLC patients. Better histologically, molecularly and genetically determined subpopulations will increase the efficacy of targeted agents reducing in parallel the frequency of toxicity events, while the appropriate use of immunotherapy will extend the survival of treated patients improving in parallel their quality of life.

Acknowledgements

Footnote

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