New & Emerging Drugs for Squamous Cell Lung Cancer

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Introduction

Lung Cancer is the leading cause of cancer-related death worldwide. Squamous cell lung cancer (SQCLC) is the second most common histology (20-30% of cases) among non-small cell lung cancers (NSCLC), yet the treatment options remain limited [1]. The current standard for first line treatment of advanced or metastatic SQCLC consists of mainly platinum based chemotherapy. Recently, necitumumab in combination with platinum based doublet therapy was approved as front-line therapy. Second line options until recently included docetaxel, gemcitabine, nab-paclitaxel and erlotinib. Now newer agents including afatinib, ramucirumab/docetaxel, nivolumab and pembrolizumab are also available with superior clinical benefits comparing to traditional treatment. On the other hand, a number of potential targets have been identified with clinical trials ongoing.

Available New Agents

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Available New Agents for treatment of SQCLC.

EGFR Targeted Therapies

Agents targeting the epidermal growth factor receptor (EGFR) have been used effectively in both squamous and non-squamous NSCLC despite a low incidence of activating EGFR mutations in SQCLC. This may in part be due to higher EGFR protein expression or increased gene copy number/amplification seen with squamous histology [3]. Previous trials with erlotinib demonstrated its modest benefit as second-line versus placebo or as maintenance therapy [4,5]. However, multiple Phase III studies including TAILOR (Tarceva Italian Lung Optimization Trial) and DELTA (Docetaxel and Erlotinib Lung Cancer) demonstrated the superiority of second line docetaxel over erlotinib in both PFS and OS in the population of EGFR-WT patients (which includes most SQCLC patients), precluding widespread adoption of second line Erlotinib for SQCLC [6,7].

Results from the Phase III LUX-Lung 8 trial of second-line afatinib vs erlotinib in patients with advanced SQCLC revealed significant improvement in PFS (HR 0.81, p=0.0003) and OS (HR 0.81, p=0.0077) with afatinib resulting in FDA acceptance of regulatory filing in August 2015 [8]. A similar study involving gefitinib as second line agent in SQCLC is ongoing (NCT01485809).
Recently, necitumumab was approved by the FDA in November 2015 as first line treatment in combination with chemotherapy for SQCLC. The Phase III Study (SQUIRE) showed significantly improved OS (HR=0.84, p=0.012) and PFS (HR=0.85, p=0.020) with the addition of necitumumab to gemcitabine/cisplatin [9].

**VEGF Targeted Therapy**

In 2014, ramucirumab, a human IgG1 antibody targeting the extracellular domain of the vascular endothelial growth factor receptor 2 (VEGFR-2) was approved for use in the second line in conjunction with docetaxel. The Phase III REVEL Trial showed a 1.4 month OS benefit (HR 0.86, p=0.023) and 1.5 month PFS benefit (HR 0.76, p<0.0001) with use of ramucirumab/docetaxel versus docetaxel alone as second line treatment in Stage IV NSCLC. The study included all histologies of NSCLC, but based on unplanned subgroup analyses squamous and non-squamous histologies showed similar benefit [10].

**Immunotherapy**

Of all the recent advances in treatment of SQCLC, the most promising have been in immunotherapy, particularly in agents targeting immune check points. Programed death 1 (PD-1) is involved in limiting the activity of T cells allowing tumor cells to evade the immune response. SQCLC shows increased expression of ligands for PD-1 known as PD-L1. Blocking either the receptor or ligand could overcome immune resistance leading to tumor regression [11]. Nivolumab is a human IgG4 PD-1 antibody which was approved for second line treatment of metastatic SQCLC in April 2015. The Phase II CheckMate 063 trial of 117 patients with advanced, refractory SQCLC showed objective response in 14.5% of patients with median duration of response not reached and stable disease in 26% of patients with median duration of 6 months [12]. Subsequently a Phase III study of nivolumab vs docetaxel as second line therapy for Stage IIIB or IV SQCLC who have failed platinum based chemotherapy also reported positive results [13]. The median OS was 9.2 months with nivolumab vs 6 months with docetaxel (HR for death 0.59, p<0.001). Response rate was 20% with nivolumab vs 9% with docetaxel (p=0.008) and reassuringly grade 3-4 adverse events were reported in only 7% of the nivolumab group versus 55% of the docetaxel patients. Interestingly, expression of PD-L1 was neither prognostic nor predictive of benefit. Trials are ongoing to evaluate the use of nivolumab in the front line for metastatic NSCLC (NCT02041533), as neoadjuvant therapy in resectable NSCLC (NCT02259621) and as frontline for Stage IIIB/IV NSCLC in combination with nab-paclitaxel (NCT 02309177).

In October 2015, pembrolizumab became the second immunotherapy agent approved in NSCLC. Pembrolizumab is a humanized IgG4 antibody approved for use in patients with advanced NSCLC with documented PD-L1 expression after progression on chemotherapy and targeted agents (if patient has a targetable mutation). The KEYNOTE-001 study of patients with locally advanced or metastatic NSCLC reported an ORR of 19.4% in all patients with median PFS of 3.7 months and median OS of 12 months. Additionally, in the subset of patients who had documented expression of PD-L1 by IHC in greater than 50% of their tumor cells, the ORR was 45.2% with PFS of 6.3 months. Overall survival was not yet reached at the time of publication [14]. Pembrolizumab is also undergoing Phase III trial as first line for Stage IIIB/IV NSCLC versus platinum based chemotherapy (NCT02142738) and Phase II/III trial as a single agent vs docetaxel in previously treated NSCLC (NCT01905657). The PEARLS trial is a phase III trial evaluating pembrolizumab vs placebo in the adjuvant setting post resection for Stage IB-IIIA NSCLC (NCT 02504372).

**Emerging Agents**

Numerous agents targeting MET, FGFR1, PI3K/AKT, BRAF, PARP-1, CTLA-4 and PD1/PD-L1 are currently in various stages of development. Unfortunately, early successes in Phase II trials with many of the molecurally targeted agents have not borne fruit in Phase III trials. Furthermore, due to the relatively low incidence of many biomarkers, it is difficult to accrue enough patients to single-target clinical trials. One innovative ongoing clinical trial arising in response to the abundance of mutations identified in SQCLC is the LUNG-MAP Study, a Phase II/III biomarker driven master protocol for second or more line therapy of squamous cell lung cancer. Patients with Stage IV NSCLC who have failed first line platinum based therapy undergo genomic testing. Based on results, if they have actionable genetic alterations in PI3K, CDK4/6 or FGFR, they are treated with a corresponding targeted investigational agent. If none of the above alterations are found, patients are treated with PD-L1 antibody MEDI4736 [15].

In addition to nivolumab and pembrolizumab, several antibodies targeting PD-1 and PD-L1 are currently in Phase III trials. Atezolizumab (MPDL-3280A) is an antibody to PD-L1 with two Phase III trials (POPLAR and BIRCH) recently reporting promising results. The POPLAR trial included 287 patients with advanced NSCLC that had progressed on first line chemotherapy and randomized them to docetaxel or atezolizumab. At a follow up of 13 months, among all patients median OS was 12.6 months with atezolizumab vs 9.6 months with docetaxel (p=0.04). Furthermore, the authors reported higher ORR with increasing PD-L1 expression by tumor cells[16]. The BIRCH trial enrolled patients with high tumor expression of PD-L1 to either first, second or third line and higher treatment with atezolizumab. Survival data are not mature, but ORR of 17% in all patients and up to 27% in high PD-L1 expression patients was noted [17]. Other trials of atezolizumab as first line versus carboplatin based chemotherapy for advanced or metastatic SQCLC (Phase III, NCT02367794) and as first line versus gemcitabine/platinum for SQCLC (Phase II, NCT02409355) are ongoing.

Another PD-L1 antibody, durvalumab (MEDI4736) is currently in phase III trials as adjuvant therapy vs placebo in resected Stage IB-IIIA NSCLC (NCT02273375) and following definitive chemoradiation for Stage IIIA NSCLC (NCT02125461). It is also being tested in a phase II trial for Stage IIIB/IV NSCLC patients who have failed at least 2 prior therapies. Durvalumab demonstrated an ORR of 21% in SQCLC patients and 14% in all NSCLC patients in Phase I trials [18].

Additional success with immunotherapy has been seen with Ipilimumab and Tremelimumab, antibodies to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Both drugs enhance the immune response by blocking down regulation of the immune system caused by CTLA-4. Recently, a Phase 1 trial of first line Nivolumab plus Ipilimumab in NSCLC reported that the combination was well tolerated with an ORR of 13-39% [19]. A Phase II trial of first line ipilimumab plus carboplatin/paclitaxel in advanced NSCLC showed improved PFS and OS with even greater gains in patients with squamous histology [20]. The results of the phase III trial of carboplatin/paclitaxel plus ipilimumab or placebo are eagerly awaited (NCT01285609). Ipilimumab is also in phase I trials in combination with targeted inhibitors erlotinib or crizotinib (NCT 01998126) and immunotherapy agents atezolizumab and pembrolizumab
Tremelimumab has not seen success as a single agent, but is currently in a phase III trial in combination with durvalumab versus durvalumab monotherapy versus standard of care platinum based therapy for front line treatment of stage IIIB/IV NSCLC (NCT02352948). Despite these promising results, immune therapy is hindered by our inability to select for patients who will respond. In the case of nivolumab, overexpression of the PD-1 receptor or ligand are not associated with response or prognosis. In some other studies testing PD-1 and PD-L1 agents, greater expression of PD-L1 seems to be associated with improved ORR although survival data is still not broadly available. Furthermore, the assays used to test for PD-L1 expression and the levels defined as significant are not standardized making it challenging to compare across studies. Further research is needed to identify and validate predictive biomarkers for selection and monitoring of therapy.

Conclusion

Recent advances in lung cancer management have largely benefitted patients with the adenosquamous histologic subtype. Despite SQCLC accounting for up to 25% of all lung cancer cases, treatment traditionally consists of classical chemotherapy with long term disease control and survival remaining elusive. Recent breakthroughs in genomic typing of SQCLC have revealed multiple actionable mutations and pathways. As effective molecular targeted agents are identified, the struggle will remain to find predictive biomarkers for these therapies. Further hope exists as SQCLC appears to be responsive to immune mediated therapies. Along with molecular targeted agents, immune based therapy will play an increasing role in management of SQCLC in the future. Better understanding of tumor biology and discovery of predictive biomarkers will further improve clinical benefits and efforts at tailored therapies.

References