Checkpoint Inhibitors in Squamous Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Checkpoint inhibitors have demonstrated efficacy in squamous NSCLC with tolerable toxicity profile. They are used as a monotherapy, in combination with chemotherapy or following chemo-radiotherapy as a first line, second line or consolidation therapy. As a first line, Pembrolizumab improves outcome (PFS) as a monotherapy in patients with PD-L1 expression of ≥ 50% (HR; 0.35). When used with chemotherapy, it improves PFS (HR; 0.56) irrespective of PD-L1 expression level. Nivolumab also improves PFS (HR; 0.62), when used as a second line for those progressing with chemotherapy. Durvalumab improves PFS (HR; 0.68) when used following chemo-radiotherapy as a consolidation therapy.

Keywords: Checkpoint Inhibitors; Pembrolizumab; Nivolumab; Atezolizumab; Durvalumab; PD-L1; Squamous NSCLC; Progression Free Survival; Overall Survival

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]. Non-small cell lung cancer (NSCLC) covers the 80% of these lung cancer cases and mainly includes two large histological subsets, adenocarcinoma and squamous non-small cell lung cancer (Sq NSCLC). Clinically also Sq NSCLC differs remarkably from adenocarcinoma as it is located more centrally, and arise segmentally involving lobar or main bronchi and often having central cavitation. There is difference in molecular markers also. Based on molecular changes targeted therapies have been developed for subtypes of adenocarcinoma of lung e.g. EGFR inhibitors. Their use is associated with improved outcome with better tolerability. However, such advances have not taken place in management of Sq NSCLC and the conventional platinum-based chemotherapy remained the first line and second line option for patients with Sq NSCLC till recently. Necitumab approved for Sq NSCLC did not became popular due to its side effect profile and limited benefit [2]. Introduction and development of checkpoint inhibitors has changed the management of Sq NSCLC. Checkpoint inhibitors have been evaluated in NSCLC in whole spectrum ranging from neoadjuvant to third line settings and has been indicated as first line, second line and consolidation therapy [2,3]. In this review, information related to use of check point inhibitor in the treatment of Sq NSCLC is presented. Pembrolizumab (Keynote-407), Atezolizumab (IMpower-131) have been evaluated with chemotherapy in first line management of advanced Sq NSCLC. Nivolumab (CheckMate 017) has been evaluated in second line management of Sq NSCLC as monotherapy. Rest of studies evaluated checkpoint inhibitors in management of Sq NSCLC as a subgroup in main study. They are also included in this review.

Checkpoint Inhibitors as a Neoadjuvant Therapy

Nivolumab has been evaluated in neoadjuvant setting prior surgical resection in 21 patients [4]. All patients received two doses of 3mg/kg of nivolumab, two weeks apart. Of 6 patients included in the study, two had pathological response. This was associated with lymphocytic infiltration of tumor. There was higher frequency of T-cell clones that were shared between intratumoral and peripheral compartments and a higher clonality of the T-cell population. Many of these clones were not detected in the peripheral blood before treatment. Tumor response to nivolumab was also related to tumor mutation burden.
**Checkpoint Inhibitors as a First Line Therapy**

Checkpoint inhibitors have been evaluated as a monotherapy in patients having PD-L1 expression Tumor Proportion Score (TPS) ≥ 50% as well as in patients with high mutation burden. In all, the majority of the Task Force recommended pembrolizumab monotherapy for patients with Sq NSCLC and PD-L1 TPS ≥ 50% based on Level A evidence. For patients with squamous histology and PD-L1 TPS < 50%, the Task Force unanimously recommended combination pembrolizumab + chemotherapy pending FDA approval, based on Level A evidence.

**Monotherapy**

**Pembrolizumab**

Pembrolizumab as monotherapy has been compared against first line chemotherapy in KEYNOTE-024 and KEYNOTE-042 clinical studies. KEYNOTE-024 enrolled patients with PD-L1 expression level ≥ 50% while KEYNOTE-042 enrolled patients with PD-L1 expression level ≥ 01%.

**KEYNOTE-024 [5]**

305 patients, were randomized to receive pembrolizumab (200 mg fixed dose every 3 weeks) or investigator’s choice of platinum-based chemotherapy. Patients eligible for EGFR inhibitors or ALK inhibitors were excluded. It included 56 with Sq NSCLC histology 18% in each arm) expressing more than 50% PD-L1. Progression Free Survival (PFS) was significantly better in the Sq NSCLC subpopulation receiving immunotherapy compared to chemotherapy [Hazard Ratio (HR) =0.35, 95% Confidence Interval (CI): 0.17–0.71]. This was also better than the improvement seen with pembrolizumab in whole group [HR 0.5 for group vs 0.35 for Sq NSCLC]. 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 adverse events (AEs) were early detected at grade 1 or 2 and well managed with no recorded immunotherapy-related deaths.

**KEYNOTE-042 [6]**

1274 patients, were randomized to receive pembrolizumab (200 mg fixed dose every 3 weeks) or investigator’s choice of platinum-based chemotherapy. Patients eligible for EGFR inhibitors or ALK inhibitors were excluded. It included 492 patients with Sq NSCLC histology of which 243 received pembrolizumab. Overall Survival (OS) was significantly better in the Sq NSCLC subpopulation receiving immunotherapy compared to chemotherapy [HR = 0.75, 95% CI: 0.60–0.93]. This was also better than the improvement seen with pembrolizumab in non-squamous NSCLC [HR 0.86; 95% CI: 0.72-1.03].

**Nivolumab**

Nivolumab has been evaluated as first line therapy in checkmate 227 and checkmate 026.

**Checkmate227 [7]**

Combination of checkpoint inhibitors (Nivolumab + Iplimumab) was evaluated against chemotherapy in patients with advanced NSCLC (squamous and non-squamous) in the CheckMate227 study in first line setting. All patients had high tumor mutational burden [more than 10]. It had 100 patients with Sq NSCLC and 199 patients with non-squamous NSCLC. HR for disease progression or death for squamous NSCLC was 0.63 (95% CI, 0.39–1.04). It was lower (0.63 vs 0.55) compared to non-squamous NSCLC as well as compared to whole group [0.63 vs 0.58]. Survival data is immature.

**Checkmate026 [8]**

CheckMate026 evaluated Nivolumab as first line therapy compared chemotherapy in 541 untreated patients having advanced NSCLC with PD-L1 expression >1%. It included 130 patients with Sq NSCLC. Trial failed to demonstrate significant advantage of nivolumab in whole group analysis or any subgroup analysis. Though not significant, Nivolumab improved median PFS by 0.5 months [HR; 0.83 (95% CI, 0.54–1.26)] and median OS by 0.3 months [HR; 0.82 (95% CI 0.54-1.24)] in patients with Sq NSCLC. In non-squamous NSCLS, chemotherapy performed better (Table 1).

**Table 1:** First line therapy: Checkpoint inhibitors as monotherapy.

| Study* | Comparison | Selection | PFS HR (95% CI) | OS HR (95% CI) |
|--------|------------|-----------|----------------|----------------|
| KEYNOTE-024* (n=56) | Pembrolizumab vs. platinum doublet | PD-L1 ≥ 50% | HR=0.35, (0.17-0.71) |  |
| KEYNOTE-042* (n=243) | Pembrolizumab vs. platinum doublet | PD-L1 ≥ 1% | HR=0.75, (0.60-0.97) |  |
| CheckMate 227* (n= 100) | Nivolumab + Yervoy vs. platinum doublet | TMB-high ≥ 10 mutations/megabase | HR=0.63, (0.39-1.04) | Immature |
| CheckMate 026* (n= 130) | Nivolumab vs platinum doublet | PD-L1 ≥ 1% | HR=0.83, (0.54-1.26) | HR=0.81, (0.54-1.24) |

**Combination with Chemotherapy**

Checkpoint inhibitors have been evaluated with chemotherapy in management of squamous as well as non-squamous NSCLC.

For Sq NSCLC, Pembrolizumab as well as atezolizumab has been evaluated in combination with paclitaxel containing platinum doublet. Both are associated with improved outcome.
Pembrolizumab [9]

Pembrolizumab in combination with carboplatin + nab-paclitaxel/paclitaxel as first-line treatment was evaluated in KEYNOTE-407 clinical trial in 559 treatment naïve patients with advanced, Sq NSCLC. Combination was associated with increase in response rate by 23.4% [Objective Response Rate (ORR) 58.4% vs. 35%, p<0.01]. The duration of response was also more durable [7.7 versus 4.8 months ]. Improved response rate was also associated with improved PFS by 1.6 months [6.4 months vs 4.8 months; HR=0.56, 95% CI: 0.35–0.98]; TPS 1-49%, HR = 0.57 [95% CI: 0.36–0.90]; TPS >50%, HR = 0.64 [95% CI: 0.37–1.10]. Grade 3-5 AEs were comparable across the pembrolizumab/chemotherapy and placebo cohorts (69.8% vs. 68.2%, respectively). PD-L1 status was measured by tumor proportion score (TPS) was identical in both arms. It was 34.2% vs. 35.2% for TPS <1%, 37.1% vs. 35.2%, for TPS 1%-49%, and 26.1% vs. 26% TPS ≥50%. The HR for OS was 0.61, 0.57, and 0.64 favouring the pembrolizumab arm in the TPS <1%, <1%-49%, and ≥50% subgroups, respectively. Across the same 3 subgroups, the HR for PFS favouring the pembrolizumab arm was 0.68, 0.56, and 0.37, respectively.

Atezolizumab [10]

IMpower131 study is evaluating atezolizumab + carboplatin & nab-paclitaxel in patients with advanced Sq NSCLC. Addition of atezolizumab improved response rate by 8% (49% vs 41%). Improvement in PFS was 0.7 months (6.3 months vs 5.6 months, HR = 0.71 [95% CI: 0.60–0.85], p < 0.0001). Improvement in OS was of 9.5 months in patients with high-PD-L1, (23.6 months vs 14.1 months, HR = 0.56 [95% CI: 0.32–0.99]. No improvement in OS was seen remaining patients with low [12.4 months vs 16.6 months, HR = 1.34 [95% CI: 0.95–1.90] or no PD-L1 expression (13.8 months vs 12.5 months, HR = 0.86 [95% CI: 0.65–1.15]).

Nivolumab [11]

CheckMate227 also evaluated nivolumab + chemotherapy against chemoradiotherapy. PFS with Nivolumab + CT was found to be little better (HR=0.92) which was not significant. Patients with non-squamous NSCLC did better (HR=0.68) (Table 2).

Table 2: First line therapy: Checkpoint inhibitors with chemotherapy.

| Study            | Comparision                                      | ORR         | PFS months HR (95% CI) P | OS months HR (95% CI) P |
|------------------|--------------------------------------------------|-------------|--------------------------|-------------------------|
| KEYNOTE-407      | Carboplatin (nab-paclitaxel/paclitaxel) +/- Pembrolizumab | 58% vs. 35% | 1.6 months HR=0.56; (0.45–0.70) p<0.01 | 4.6 months HR = 0.64, (0.49–0.85) p = 0.0008 |
| IMpower131       | Carboplatin (nab-paclitaxel/paclitaxel) +/- Atezolizumab | 49% vs. 41% | 0.7 months HR = 0.71; (0.60–0.85) p < 0.0001 | 9.5 months Only in with high-PD-L1 HR = 0.56 (0.32–0.99) No improvement rest |
| CheckMate 227*   | Platinum doublet ± Nivolumab                      | -           | HR=0.92                  | immature                |

Checkpoint inhibitors as a Consolidation therapy

Checkpoint inhibitors has been evaluated as a consolidation therapy following chemo-radiotherapy.

Durvalumab [12]

In a PACIFIC study, 713 patients with stage III NSCLC non-progressing after at least two cycles of chemo-radiation were randomized to receive durvalumab (n=476) at 10 mg/kg or placebo (273), every other week, for up to a year as consolidation/maintenance therapy following chemo-radiation. It included 326 patients with Squamous NSCLC. 224 patients with squamous NSCLC received durvalumab and 102 received placebo. Durvalumab was associated improved progression free survival. The hazard ratio was 0.45 (0.33–0.59) for adenocarcinoma and 0.68 (0.50-0.92) for squamous NSCLC. Thus Durvalumab provides better outcome for adenocarcinoma compared to Squamous NSCLC. 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).
Pembrolizumab [13]

Pembrolizumab was evaluated in 92 patients without progression following chemoradiotherapy in Lun14-179 (a single arm) study. 55 (59.8%) had stage IIA and 37 (40.2%) had IIB disease. It included 40 (43.5%) patients with Sq NSCLC. All received pembrolizumab 200 mg IV q3wk for up to 1 year. Separate subgroup analysis for Sq. NSCLC is not available. For 92 patients, median time to distant metastasis or death was 22.4 months (95% CI; 17.9- NR). Median PFS was 17.0 months (95% CI; 11.9-NR).

**Table 3:** Second line therapy: Checkpoint inhibitors as monotherapy.

| Study     | Comparison   | Overall survival | Progression-free survival |
|-----------|--------------|------------------|---------------------------|
|           |              | Months           | HR (95% CI)  | P value | Months | HR (95% CI) | P value |
| CheckMate017 (n=272) | Nivolumab vs. Docetaxel | 3.2 | 0.59 (0.44-0.79) | p < 0.001 | 0.7 | 0.62 (0.47-0.81) | p < 0.001 |
| KEYNOTE-010* (n=222) | Pembrolizumab vs. Docetaxel | 1.2 | 0.74 (0.50-1.09) | -- | -- | -- | -- |
| Poplar* (n=97) | Atezolizumab vs. Docetaxel | 1.5 | 0.8 (0.49-1.30) | -- | -- | -- | -- |
| OAK* (n=222) | Atezolizumab vs. Docetaxel | 1.2 | 0.73 (0.54-0.98)** | P = 0.038 | -- | -- | -- |

Atezolizumab was initially evaluated in a phase II randomized trial [POPLAR study], where 277 patients were randomized to receive atezolizumab 1,200 mg or docetaxel every 3 weeks [19]. It included 97 patients with Sq NSCLC of which 49 received Atezolizumab. Atezolizumab improved over all survival in patients with Sq NSCLC by 1.5 months (HR 0.80; 95% CI 0.49–1.30). This was inferior to improvement seen in the non-squamous NSCLC (HR 0.69; 95% CI 0.47-1.01) [19]. OAK study evaluated atezolizumab.
200 mg or docetaxel at standard dose after failure of platinum-based first 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 (Table 3). It included 222 patients with squamous and 628 patients with non-squamous histology [18]. For subpopulation of Sq NSCLC [26%], atezolizumab failed to provide any benefit. Actually docetaxel was found to be associated with better OS (8.9 vs. 7.7 months, HR: 0.73; 95% CI: 0.54 to 0.98 p=0.038) [20]. However, as a group it provided improvement in OS with atezolizumab compared to docetaxel as a group. Improvement seen as a group was of 4.2 months (13.8 months vs. 9.6 months; HR 0.74, 95% CI: 0.63–0.87; p = 0.004) [20].

**Patients with poor performance status and PD-L1 TPS < 50% to ≥ 1%:** The may be administered pembrolizumab due to its better tolerance.

**Maintenance Therapy**

Pembrolizumab, if used as first line therapy should be used as maintenance therapy also.

**Second-Line Therapy**

With use of checkpoint inhibitors in first line therapy, their use in second line will be limited to those who have not received it as first line. Nivolumab is the only checkpoint inhibitor studied in squamous NSCLC. Pembrolizumab and atezolizumab are evaluated as a subgroup of the cohort. Atezolizumab is inferior to docetaxel in subgroup analysis and so should be avoided. Pembrolizumab needs evaluation of PD-L1 expression and benefit seems to be lower than Nivolumab (HR for OS; 0.59 vs 0.74). Nivolumab is also found useful in elderly patients.

**Conclusion**

For management of advanced Sq NSCLC, Pembrolizumab (monotherapy) is suggested as a first line therapy in place of chemotherapy in patients expressing PD-L1≥50%. It needs to be used with paclitaxel and carboplatin in remaining patients with PD-L1< 50%. Nivolumab is indicated as a second line therapy if checkpoint inhibitor is not used in first line therapy. Durvalumab is indicated for localised Sq NSCLC following chemoradiotherapy as consolidation therapy.

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