



Recent treatment strategy for advanced squamous cell carcinoma of the lung in Japan

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Abstract

Squamous cell carcinoma of the lung is associated with smoking in its development and comprises about 20–30% of all lung cancers. Its treatment strategy had been limited for the past decades, inevitably resulting in the poor outcome. However in the 2010s, it has dramatically changed mainly with the recent clinical introduction of immune checkpoint inhibitors. In this review, we will introduce various clinical studies involving squamous cell carcinoma of the lung.

Keywords Squamous cell carcinoma of the lung · Cytotoxic drug · Immune checkpoint inhibitor

Introduction

Squamous cell carcinoma (SCC) of the lung is associated with smoking in its development. Although the number of patients with SCC has been decreasing in recent years due to the decline in the proportion of smoking, it still comprises about 20–30% of all lung cancers [1, 2]. The evidence in the treatment for SCC has been relatively poor as compared with that of non-SCC; however, in recent years, clinical trials of immune checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC) including SCC have been extensively conducted, having brought us various pivotal results applicable to daily practices. This article hardly deals specifically with the evidence regarding large cell neuroendocrine carcinoma (LCNEC) since it is not documented whether or not LCNEC was included in each eligibility criteria in most of studies we have introduced here.

Cytotoxic chemotherapy with or without anti-angiogenic agents

In the twentieth century, there was no concept of sub-classification of non-SCC and SCC, and both were treated together as NSCLC, mainly with platinum-based chemotherapy [3–10]. In a pivotal study comparing cisplatin plus pemetrexed therapy with cisplatin plus gemcitabine therapy, non-inferiority in overall survival (OS) of the former regimen was demonstrated as compared with the latter one; interestingly in the subgroup analysis, cisplatin plus pemetrexed showed better OS in patients with non-SCC, whilst it showed worse OS in those with SCC [11]. This study was a first to lead to the new treatment strategy stratified by tumor histology in NSCLC; although pemetrexed was finally approved for advanced or recurrent NSCLC by the Japanese government, the Japanese guideline has not recommended its use for SCC. As for bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, grade 3 or worse hemorrhage occurred more frequently in SCC than in the whole NSCLC (31% vs. 9.1%, respectively) [12]. This precluded the further development of bevacizumab in SCC. As documented above, the development of novel agents combined with platinum had been stagnant in SCC of the lung.

In 2015, a new treatment option for SCC of the lung was reported from Japan. A phase 3 study of nedaplatin, third generation of platinum compound, versus the standard cisplatin in combination with docetaxel was performed for advanced SCC of the lung in the first-line setting. Nedaplatin and docetaxel therapy significantly prolonged OS time

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[median 13.6 months versus 11.6 months, respectively, OS hazard ratio (HR)=0.81 [95% confidence interval (CI) 0.65–1.02], $p=0.037$] [13]. Although nedaplatin had originally had an indication for NSCLC broadly in Japan, its positioning has become clearer in the treatment of SCC of the lung through this evidence. However, such treatment strategy only with the cytotoxic agents did not yield enough satisfactory outcome with the median OS time of approximately 1 year.

The SQUIRE trial, designed for patients with untreated metastatic SCC of the lung, showed a survival efficacy of adding necitumumab, a fully human IgG1 monoclonal antibody directed against the binding domain of epidermal growth factor receptor (EGFR), on cisplatin plus gemcitabine combination therapy [median OS 11.5 months versus 9.9 months, respectively, OS-HR = 0.84 (95% CI 0.74–0.96), $p=0.01$] [14]. Based on the result, necitumumab has been approved for metastatic SCC of the lung in the United States and Europe, but not in Japan. In Japan, a randomized phase 2 trial has been done for those with SCC in a quite similar design to the SQUIRE trial. This also showed a survival advantage of necitumumab combination therapy compared with chemotherapy alone [median OS 14.9 months versus 10.8 months, respectively, OS-HR = 0.66 (95% CI 0.47–0.93), $p=0.001$] [15]. With these evidences, necitumumab will be approved soon in Japan.

Kinase inhibitors

Discovery of driver oncogenes has made a great impact in creating the novel treatment strategy for NSCLC. Kinase inhibitors targeting each of four gene aberrations, *EGFR*, anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), have now been approved, and been widely used according to the aberrant status in clinical practices [16–24]. That is based on the numerous clinical trial results showing the efficacy of kinase inhibitors in each driver oncogene-positive tumor [25–29]. However, it should be noted that a quite limited number of SCC cases were actually accrued in trials that evaluated the efficacy of kinase inhibitors [25–28], and thus, the evidence of kinase inhibitors in SCC was substantially restricted [30]. The Japanese guideline for the treatment of lung cancer 2017 mentions that the examination for *EGFR* mutation and *ALK* translocation is not always essential for SCC patients; however, when SCC is detected pathologically in the small tumor specimens such as biopsy or cytological samples, driver oncogenes including *EGFR* mutation or *ALK* translocation is to be checked. If either of the driver oncogenes is found positive, it is suggested to administer kinase inhibitor corresponding to its driver oncogene [31]. Especially in Japan, SCC cases often have a

history of smoking that has been pointed out as one of the risk factors for the development of interstitial lung disease induced by kinase inhibitors [32–34]. Therefore, it is necessary for us to keep in mind that they would be treated with kinase inhibitors, considering the risk–benefit balance in each situation.

Immune checkpoint inhibitors

The recent years have witnessed a remarkable development of ICIs in NSCLC including SCC. Nowadays, nivolumab and pembrolizumab, anti-programmed cell death 1 (PD-1) antibodies, and atezolizumab and durvalumab, anti-programmed cell death ligand 1 (PD-L1) antibodies, have been approved in Japan. Details of durvalumab are not mentioned in this review article since it is approved only for local advanced setting.

Only pembrolizumab has gotten an indication for the first-line setting of advanced NSCLC, according to the results of KEYNOTE-024, 042, and 407 trials. In KEYNOTE-024, the study for advanced NSCLC with PD-L1 expression level of $\geq 50\%$ but without *EGFR*-mutant or *ALK*-aberrant tumors, a fixed dose of pembrolizumab (200 mg/body) showed better progression-free survival (PFS) and OS compared with platinum-based chemotherapy [PFS-HR = 0.50 (95% CI 0.37–0.68), $p < 0.001$; and OS-HR = 0.63 (95% CI 0.47–0.86), $p = 0.002$]; the subgroup analysis also showed a similar survival efficacy in SCC patients to that of the whole NSCLC patients [35–37]. In KEYNOTE-042, the study for advanced NSCLC with PD-L1 expression level of $\geq 1\%$, pembrolizumab monotherapy could prolong overall survival over platinum-based chemotherapy [OS-HR = 0.81 (95% CI 0.71–0.93), $p = 0.002$] [38]. On the basis of KEYNOTE-024 and 042 results, a single agent of pembrolizumab has now been approved for untreated advanced NSCLC with PD-L1 expression level of $\geq 1\%$, regardless of tumor histology. However, of note, pembrolizumab could not show any superiority in OS in patients with tumor PD-L1 expression level of 1–49% [OS-HR = 0.92 (95% CI 0.77–1.11)].

In addition, a remarkable result of KEYNOTE-407 was reported in 2018. This trial targeted untreated metastatic SCC of the lung, regardless of tumor PD-L1 expression levels. Adding pembrolizumab on carboplatin plus [nab-] paclitaxel prolonged successfully both PFS and OS times [OS-HR = 0.64 (95% CI 0.49–0.85), $p = 0.0008$ and PFS-HR = 0.56 (95% CI 0.45–0.70), $p < 0.0001$]. It is, however, noted that the median follow-up time is only 7.8 months [39]. Finally, this combination regimen was expandingly approved in Japan for untreated unresectable advanced or recurrent SCC of the lung, irrespective of tumor PD-L1 status, in December 2018.

Another evidence of combination therapy of cytotoxic chemotherapy and ICI has been made. The IMpower131 trial was performed to investigate the efficacy of combination of atezolizumab and platinum-based chemotherapy, targeting untreated advanced SCC of the lung. Patients who participated in this trial were allocated into three arms: carboplatin + paclitaxel + atezolizumab (arm A), carboplatin + nab-paclitaxel + atezolizumab (arm B), and the standard carboplatin + nab-paclitaxel (arm C). The arm B has had a better PFS in comparison with the arm C [median 6.3 months versus 5.6 months, respectively, PFS-HR = 0.71, (95% CI 0.60–0.85), $p = 0.0001$] [40]. However, any OS benefit has not yet been shown in the second interim analysis [OS-HR = 0.92 (95% CI 0.76–1.12), $p = 0.41$] [41].

There was a negative study for combination use of chemotherapy and ICIs. The study was performed in metastatic or recurrent SCC of the lung, evaluating the addition of anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, ipilimumab, on the standard cytotoxic chemotherapy of carboplatin and paclitaxel from its third cycle. Unfortunately, this combined therapy failed to show any OS benefit (median 13.4 months versus 12.4 months, respectively, OS-HR = 0.91 (95% CI 0.77–1.07), $p = 0.25$) [42].

In the part 1 of CheckMate 227 trial, advanced or recurrent NSCLC patients were first divided into two groups (tumor PD-L1 expression levels of $\geq 1\%$ or $< 1\%$), and then randomly allocated to three abovementioned regimens in each group: (1) nivolumab plus ipilimumab, (2) nivolumab-based regimen (nivolumab monotherapy or combination of nivolumab plus chemotherapy for tumors with PD-L1 $\geq 1\%$ or with $< 1\%$, respectively), and (3) histology-based standard chemotherapy. The study had two co-primary endpoints: (1) PFS in the nivolumab plus ipilimumab arm versus the platinum-based chemotherapy arm in patients with high tumor mutational burden (TMB) tumors (≥ 10 mutations per megabase), regardless of the tumor PD-L1 expression level; (2) OS in PD-L1-selected population. The first co-primary endpoint met the criteria showing that nivolumab plus ipilimumab prolonged PFS time compared with platinum-based chemotherapy [median 7.2 months versus 5.5 months, PFS-HR = 0.58 (95% CI 0.41–0.81), $p < 0.001$] in the high TMB tumors. Assuming that SCC patients accounted for approximately 30% of the whole NSCLC patients, this subpopulation also had a better PFS in the ICI combination therapy (PFS-HR = 0.63) [43].

As for the salvage setting, nivolumab was the first ICI approved for NSCLC. CheckMate 017, a phase 3 trial, targeted specifically SCC of the lung refractory to the first-line platinum-based chemotherapy. Nivolumab significantly prolonged OS time in comparison with docetaxel [median 9.2 months versus 6.0 months, respectively, OS-HR = 0.59 (95% CI 0.44–0.79), $p < 0.001$]. OS-HR seemed hardly

affected by the PD-L1 status; PD-L1 $\geq 1\%$ (OS-HR = 0.69) and PD-L1 $< 1\%$ (OS-HR = 0.58) [44].

The KEYNOTE-010 investigated if pembrolizumab could produce better OS in comparison with docetaxel, targeting PD-L1-positive NSCLC refractory to platinum-based chemotherapy. In this study, two doses of pembrolizumab were investigated (2 mg/kg and 10 mg/kg), both of which yielded a significant survival advantage compared with docetaxel monotherapy [2 mg/kg group, median 10.4 months, OS-HR = 0.71 (95% CI 0.58–0.88), $p = 0.0008$; 10 mg/kg group, median 12.7 months, OS-HR = 0.61 (95% CI 0.49–0.75), $p < 0.0001$; and docetaxel group, median 8.5 months]. Of special note, the currently approved dosage is 200 mg/body based on the KEYNOTE-024 trial results. Irrespective of histological subtype, the survival advantage of pembrolizumab was almost consistent, with OS-HR of 0.63 and 0.74 for adenocarcinoma and SCC, respectively [45].

In OAK study, atezolizumab, an anti-PD-L1 antibody, showed a survival advantage over docetaxel in NSCLC patients who had been previously treated with platinum-based chemotherapy [median OS time 13.8 months versus 9.6 months, respectively, OS-HR = 0.73 (95% CI 0.62–0.87), $p = 0.0003$]. This agent also showed almost same level of OS-HR in subgroup analysis restricted to the SCC patients (OS-HR = 0.73). In this study, PD-L1 expression levels in both tumor cells (TCs) and tumor-infiltrating immune cells (ICs) were assessed with the SP142 antibody, and divided into four subcategories (TC0 and IC0, TC1/2/3 or IC1/2/3, TC2/3 or IC2/3, and TC3 or IC3). In TC0 and IC0 group, regarded as the PD-L1-negative population, OS-HR was 0.75, almost as similar as that of the overall population [46]. The survival advantage of atezolizumab was also observed in PD-L1-negative population defined by the 22C3, the companion diagnostic of pembrolizumab [47].

Treatment after platinum-based chemotherapy and immune checkpoint inhibitors

In the Japanese guideline, docetaxel monotherapy, docetaxel plus ramucirumab combination therapy, and S-1 monotherapy are recommended in patients who relapsed from platinum-based chemotherapy and ICIs [31]. Although single-agent docetaxel had long been a standard therapy in patients refractory to the platinum-based chemotherapy, docetaxel plus ramucirumab showed better OS than docetaxel alone in the REVEL trial reported in 2014 [median 10.5 months versus 9.1 months, respectively, OS-HR = 0.86 (95% CI 0.75–0.98), $p = 0.023$]. In the subgroup analysis, HR for SCC patients was 0.88, almost identical to that of the overall ones [48]. Thus, we should consider any suitability of adding

ramucirumab in those with SCC who are to be treated with docetaxel therapy.

The EAST-LC trial clearly showed non-inferiority in OS of S-1 compared with docetaxel [median 12.5 months versus 12.8 months, respectively, OS-HR = 0.95 (95% CI 0.83–1.07) with the inferiority margin = 1.2, $p = 0.38$]. As for SCC patients, OS-HR was 0.88, which was almost similar score compared with that of the overall patients [49]. Finally, S-1 can also be one of the treatment options for SCC patients.

Clinical implementation and future direction

Clinical trials we have mentioned are summarized in Table 1. As above, consecutive pivotal results have recently been released, clearly changing the treatment strategy in NSCLC involving SCC in clinical practices. To summarize these

reports, PD-L1 levels should be evaluated when advanced SCC of the lung is detected. Especially when the diagnosis is done with biopsy or cytology specimen, the driver oncogene status including *EGFR* and *ALK* should also be checked. In patients with tumors expressing PD-L1 of $\geq 50\%$, pembrolizumab monotherapy or the combination of platinum-based chemotherapy and pembrolizumab is recommended in the first-line setting, according to the KEYNOTE-024 and 407 study results [35–37, 39]; if pembrolizumab monotherapy is selected, platinum-based chemotherapy in the salvage setting is recommended. In patients with tumors of PD-L1 $< 50\%$, platinum-based chemotherapy and pembrolizumab would be recommended mainly based on the KEYNOTE-407 study result [39].

Even after the release of pivotal evidences, we still have unresolved clinical questions. First, we have to know the best treatment strategy for tumors with PD-L1 $\geq 50\%$; since no direct comparison has been reported yet, it is not sure which

Table 1 Representative phase III trials evaluating the efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer

Study	Eligible patients	Regimens	PFS-HR (95% CI)	PFS-HR for SCC	OS-HR (95% CI)	OS-HR for SCC
KEYNOTE-024 [35–37]	NSCLC with PD-L1 $\geq 50\%$	Pembrolizumab Platinum-based chemotherapy	0.50 [0.37–0.68]	0.35	0.63 [0.47–0.86]	0.73
KEYNOTE-042 [38]	NSCLC with PD-L1 $\geq 1\%$	Pembrolizumab Platinum-based chemotherapy	1.07 [0.94–1.21]	Not reported	0.81 [0.71–0.93]	0.75
KEYNOTE-407 [39]	SCC	CBDCA + [nab-] PTX + pembrolizumab CBDCA + [nab-] PTX + placebo	0.56 [0.45–0.70]		0.64 [0.49–0.85]	
IMpower131 (Arm B versus Arm C) [40, 41]	SCC	CBDCA + nab-PTX + atezolizumab CBDCA + nab-PTX + placebo	0.71 [0.60–0.85]		0.92 [0.76–1.12]	
CA184-104 [42]	SCC	CBDCA + PTX + ipilimumab CBDCA + PTX + placebo	0.87 [0.75–1.01]		0.91 [0.77–1.07]	
CheckMate 227 (Part 1) [43]	NSCLC with TMB ≥ 10 per megabase	Nivolumab + ipilimumab Platinum-based chemotherapy	0.58 [0.41–0.81]	0.63	Not reported	Not reported
CheckMate 017 [44]	SCC	Nivolumab DOC	0.62 [0.47–0.81]		0.59 [0.44–0.79]	
KEYNOTE-010 [45]	NSCLC with PD-L1 $\geq 1\%$	Pembrolizumab ^a DOC	0.85 [0.73–0.98]	0.86	0.67 [0.56–0.80]	0.74
OAK [46]	NSCLC	Atezolizumab DOC	0.95 [0.82–1.10]	Not reported	0.73 [0.62–0.87]	0.73

PFS progression-free survival, SCC squamous cell carcinoma, HR hazard ratio, CI confidence interval, OS overall survival, NSCLC non-small cell lung cancer, CBDCA carboplatin, PTX paclitaxel, nab-PTX nab-paclitaxel, TMB tumor mutational burden, DOC docetaxel

^aPooled analyses of two doses: 2 mg/kg and 10 mg/kg

of the treatments is better, pembrolizumab monotherapy or its combination with platinum-based chemotherapy. Or, as another clinical question, it is not sure what subpopulation among those with high PD-L1-expressed tumors benefits most from the combination therapy. Regarding the latter issue, some biomarkers will help us make a more precise treatment decision. TMB has recently been of great concern as a potential predictive biomarker other than PD-L1. Especially, SCC was reported to be a high TMB tumor [50]. The TMB was positively correlated with the effect of ICIs, and, of note, had no correlation with the expression level of PD-L1 [51]. Recently, both concomitant use of TMB and PD-L1 for the predictive markers has also been of interests [52]. Further investigation is strongly warranted to clarify all these questions. Simply saying, adding chemotherapy on pembrolizumab can enhance toxicity, and thus at this stage, we should take its risk–benefit balance into consideration for selecting the best regimen in each patient.

Second, the significance of combination therapy of ICIs has not been fully assessed yet. As a background, the combination therapy showed a synergistic effect in preclinical model [53]. Clinically in melanoma and renal cell carcinoma, the pivotal studies have already shown its survival advantage over the existing standard treatments. As for advanced melanoma, nivolumab plus ipilimumab combination favored over the standard therapy [OS-HR = 0.54 (95% CI 0.44–0.67), $p < 0.001$] [54, 55]. In untreated, intermediate- or poor-risk, advanced renal cell carcinoma, this combination yielded a greater survival benefit compared with sunitinib [OS-HR = 0.63 (95% CI 0.44–0.89), $p < 0.001$] [56]. In NSCLC including both SCC and non-SCC, Check-Mate 227 study has now been evaluating this issue [43], but no relevant results including mature OS data have not yet been released. In addition to this study, an ongoing trial in untreated, advanced NSCLC now evaluates the efficacy of nivolumab plus ipilimumab in the combination of platinum-based chemotherapy (NCT03215706). These will clarify any clinical significance of the ICI combination therapy and its indication.

Conclusion

The therapeutic strategy for SCC of the lung has now been outlined above. Again, in recent years, there has been remarkable development in the treatment of SCC of the lung. Many other clinical trials are ongoing and physicians should keep their eyes on future relevant reports for providing the best treatment in each patient.

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Compliance with ethical standards

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