



Pembrolizumab plus platinum-based chemotherapy for squamous non-small cell lung cancer: the new kid on the block

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Introduction

Immune checkpoint inhibitors (ICIs) and targeted therapies have revolutionised the diagnostic and treatment paradigm of advanced non-small cell lung cancer (NSCLC). However, treatment advances in squamous cell subtype have been much slower than those occurring in adenocarcinoma, mainly due to the lack of targetable oncogenic aberrations in squamous tumours. The unprecedented durable response and favourable toxicity profile observed with ICIs in advanced squamous NSCLC, represents a true therapeutic milestone in a population previously limited to cytotoxic chemotherapy (Cht).

The inhibition of programmed cell death ligand 1 (PD-1/PD-L1) pathway has been extensively investigated in NSCLC and currently dominates the treatment landscape of advanced NSCLC. The first approval of ICIs came from several randomized trials conducted in platinum-treated advanced NSCLC patients (any histology) (1-4) where overall survival (OS) and toxicity profile favoured PD-1/PD-L1 inhibitors over docetaxel. Subsequently, KEYNOTE-024 (5) showed that, in advanced NSCLC patients (all histologies) with a PD-L1 tumour proportion score (TPS) $\geq 50\%$, first-line pembrolizumab achieved higher objective response rates (ORR) and longer progression-free survival (PFS) and OS when compared to standard platinum-based Cht. However, high

PD-L1 expression only occurs in a third of NSCLC patients and, until recently, platinum-based Cht remained the only approved option for fit patients with a PD-L1 TPS $< 50\%$.

In the phase III trial KEYNOTE-407 (6), 559 patients with treatment-naïve advanced squamous NSCLC and performance status 0-1 were randomised to receive 4 cycles of carboplatin (AUC 6, 3 weekly) with either Paclitaxel (200 mg/m², 3 weekly) or nab-paclitaxel (100 mg/m² on day 1, 8 and 15) plus Pembrolizumab (200 mg, 3 weekly) or placebo for 35 cycles. Stratification factors were PD-L1 TPS $\geq 1\%$ versus $< 1\%$ assessed by 222C3 assay, type of taxane (paclitaxel versus nab-paclitaxel) and geographic region (East Asia versus rest of the world). The co-primary endpoints were PFS and OS.

After a median follow-up of 7.8 months, the chemio-immunotherapy arm achieved longer PFS (4.8 *vs.* 6.4 months, HR 0.56; 95% CI, 0.45–0.70; $P < 0.0001$) and OS (15.9 *vs.* 11.3 months, HR 0.64; 95% CI, 0.49–0.85; $P < 0.001$). At progression, 42.8% of the patients randomized to the control arm received ICI (75 patients crossed over to Pembrolizumab and 12 more received ICI as subsequent line). The benefit in OS and PFS was consistent across all PD-L1 subgroups (TPS $< 1\%$, 1–49% and $> 50\%$). Incidence of grade ≥ 3 adverse events (AEs) (69.8% *vs.* 68.2%) and AEs leading to death (8.3% *vs.* 6.4%), was similar between the two arms. According to an exploratory analysis (7),

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the type of taxane (paclitaxel versus nab-paclitaxel) did not impact in treatment tolerance or treatment efficacy in terms of OS, PFS and ORR. Furthermore, the addition of Pembrolizumab to chemotherapy maintained or improved Health-related quality of life (HRQoL) measurements relative to baseline. There was also improved HRQoL at weeks 9 and 18 versus chemotherapy alone (8). On the basis of KEYNOTE-407, the combination of carboplatin and (nab)paclitaxel plus pembrolizumab is now approved by FDA and EMA as a first line option for advanced squamous NSCLC patients, independently on PD-L1 expression.

Putting KEYNOTE-407 into context

KEYNOTE-024 (5) compared pembrolizumab (200 mg 3 weekly for up to 35 cycles) to standard platinum-based chemotherapy in untreated NSCLC patients with PD-L1 $\geq 50\%$. Patients were ALK and EGFR negative and included squamous (n=56) and non-squamous (n=249) subtypes. The choice of platinum-based chemotherapy (4–6 cycles) was at investigators' discretion. The most common chemotherapy combination was carboplatin and pemetrexed (n=67), however other regimes included cisplatin/pemetrexed (n=36), carboplatin/gemcitabine (n=20), cisplatin/gemcitabine (n=11) and carboplatin/paclitaxel (n=17). Crossover to pembrolizumab was permitted at progression for patients treated with standard chemotherapy upon meeting eligibility criteria. In addition, maintenance therapy with pemetrexed following platinum-pemetrexed chemotherapy was permitted in non-squamous patients. Primary end point was PFS and secondary end point was OS. At the second pre-planned interim analysis (median follow-up: 11.2 months), pembrolizumab was associated with longer PFS (HR 0.50; 95% CI, 0.37–0.68; P=0.001) and OS (HR 0.60; 95% CI, 0.41–0.89; P=0.005). Median OS was not reached (NR) in either arm. An updated analysis, with a median follow-up of 25.2 months, confirmed a longer OS (30 *vs.* 14.2 months, HR 0.63; 95% CI, 0.47–0.86) in the pembrolizumab arm. Hazard ratio for disease progression or death in squamous cell carcinoma was 0.35 (95% CI, 0.17–0.71) *vs.* 0.55 (95% CI, 0.39–0.76) compared to 0.55 (95% CI, 0.39–0.76) in non-squamous histology, indicating efficacy of pembrolizumab in both groups. Given the OS and PFS benefits observed in KEYNOTE-024, pembrolizumab remains the only checkpoint inhibitor approved in the first-line setting as monotherapy for patients with PD-L1 $\geq 50\%$.

KEYNOTE-042 (9) was conducted to evaluate

the efficacy of pembrolizumab in 3 different PD-L1 expression brackets ($\geq 50\%$, $\geq 20\%$ and $\geq 1\%$). Treatment naïve advanced NSCLC patients (ALK/EGFR negative) with a PD-L1 expression of $\geq 1\%$ were randomized to receive pembrolizumab and carboplatin plus paclitaxel (squamous cell histology) or carboplatin plus pemetrexed (non-squamous histology). Pembrolizumab demonstrated a significant improvement in OS across all three PD-L1 thresholds: TPS $\geq 50\%$: 20 *vs.* 12.2 months (HR 0.69; 95% CI, 0.56–0.85, P=0.0003), TPS $\geq 20\%$: 17.7 *vs.* 13 months (HR 0.77; 95% CI, 0.64–0.92, P=0.0020), TPS $\geq 1\%$: 16.7 *vs.* 12.1 months (HR 0.81; 95% CI, 0.71–0.93, P=0.0018). An exploratory analysis for patients with a PD-L1 expression of 1–49% did not show a difference in OS between the two arms (13.4 *vs.* 12.1 months, HR 0.92; 95% CI, 0.77–1.11). Crossover from pembrolizumab to ChT was not allowed in the protocol and therefore the OS benefit is likely driven by patients with a PD-L1 expression $\geq 50\%$.

Notably, PFS was not significantly improved in the PD-L1 $\geq 50\%$ group and was therefore not tested in the other lower PDL1 expression subgroups. This was different from KEYNOTE-024 (5) which showed significant improvement in PFS in the pembrolizumab group, investigators concluded this may be due to lack of cross over to immunotherapy following progressive disease in this study and the geographical demographics of the patients [KEYNOTE-042 (9) was mainly Asia-Pacific, eastern European and South America whereas KEYNOTE-024 (5) was North American and Western Europe] which may have limited to availability of immunotherapy in the second line settings in the former groups.

IMpower-131 (10) evaluated unselected treatment naïve squamous advanced NSCLC patients who were randomised to receive either atezolizumab (1,200 mg three weekly) plus carboplatin (AUC 6)/paclitaxel (200 mg/m²) (Arm A – ACP) or atezolizumab plus carboplatin/nab-paclitaxel (100 mg/m²) (Arm B – ACnP) or carboplatin/nab-paclitaxel alone (Arm C – CnP). CnP +/- atezolizumab was the initial test setting. Pts received ChT \pm atezolizumab for 4 or 6 cycles as per investigator choice, followed by atezolizumab maintenance (Arms A and B). Co-primary endpoints were investigator-assessed PFS and OS in the intention to treat (ITT) population. PFS was longer in arm B with the addition of nab-paclitaxel (6.3 *vs.* 5.6 months, HR 0.71; CI, 0.60–0.85) but Interim analysis indicated no significant difference in OS with the addition of atezolizumab to CnP. However, in patients with high PDL-1 expression there was a longer OS

in the chemo-immunotherapy arm (23.6 *vs.* 14.1 months, HR 0.56; CI, 0.32–0.99). More than 40% of patients in the chemotherapy arm, received immunotherapy as later line. This was not dissimilar to what reported for Keynote 407 (6) and therefore unlikely to be the cause of lack of OS benefit seen in IMpower 131 (10).

CHECKMATE 227 (11,12) investigated the role of first-line nivolumab and nivolumab-based regimens in advanced NSCLC without sensitizing alterations, irrespective of tumour histology. Patients with a PD-L1 expression of $\geq 1\%$ ($n=1,189$) were enrolled in Part 1a of the study and randomized (1:1:1) to receive nivolumab plus low dose ipilimumab ($n=396$), histology based ChT ($n=397$) or nivolumab monotherapy ($n=396$). Part 1b of the study recruited patients with $<1\%$ PD-L1 expression ($n=550$) who were then randomized (1:1:1) to either receive nivolumab plus ipilimumab ($n=187$), ChT ($n=186$) or ChT plus nivolumab ($n=177$) (12). The independent co-primary endpoints were PFS in patients harboring tumors with a high tumour mutational burden (TMB) defined as ≥ 10 mutations per megabase, irrespective of PD-L1 expression level, and OS in patients with tumours expressing PD-L1 $\geq 1\%$. 94.8% of the 1,739 randomized patients' tumour samples available for TMB assessment with 44.2% having at least 10 mut/Mb. PFS was longer (7.2 *vs.* 5.4 months, HR 0.58; 95% CI, 0.41–0.81; $P=0.0002$) in the ICI-doublet compared to the ChT arm. The PFS benefit was consistent irrespective of PD-L1 expression and tumour histology. Updated results did not show a difference in OS when patients were stratified by TMB (13).

In patients with PD-L1 $\geq 1\%$, nivolumab plus ipilimumab demonstrated longer OS (17.1 *vs.* 14.9 months, HR 0.79; 97.72% CI, 0.65–0.96, $P=0.007$) over ChT (14). Sub-group analysis based on %PD-L1 expression showed OS benefit was only seen in those patients with $\geq 50\%$ PD-L1 expression. Of note, the median duration of response was 23.2 months with nivolumab plus ipilimumab *vs.* 6.2 months with ChT. A remarkable proportion (49.9%) of patients in the nivolumab-ipilimumab arm showed continued response at 2 years.

In part 2 of Checkmate 227 trial, patients with advanced NSCLC (any histology and unselected for PD-L1 expression), were randomised to receive histology-based chemotherapy with or without nivolumab (15). OS in the non-squamous population was the primary endpoint and was not met (18.8 *vs.* 15.6 months, HR 0.86; CI, 0.69–1.08, $P=0.1859$). A descriptive analysis for patients with squamous histology ($n=212$), showed a longer OS in the chemo-IO

arm (18.3 *vs.* 12 months, HR 0.69; CI, 0.50–0.97). There was no data from any biomarker analysis to suggest any potential reason for the differential effect seen in squamous patients. Notably, this analysis was underpowered and remains hypothesis generating.

Conclusions

The lack of head-to-head comparison makes it very difficult to determine which is the best immune checkpoint blockade strategy as first-line treatment of squamous NSCLC. Evidence from KEYNOTE-407 (6) suggests PFS and OS benefit with the addition of pembrolizumab to platinum-taxane chemotherapy and this was consistent across all PD-L1 subgroups (TPS $<1\%$, 1–49% and $>50\%$). In IMpower131 (10), there was no OS benefit in the ITT population but patients with high PD-L1 expression (TC3 or IC3) appeared to derive an OS benefit with the addition of atezolizumab. Notably, the study was not powered for this subgroup analysis.

Trial interpretation is also made difficult due to the maintenance phase of PD(L)-1 inhibition following initial platinum doublet. This is also confounded by switches in the control arms on progression to allow crossover to receive ICI in some of the above trials (5,6,10,11). High levels of crossover make OS data potentially prone to error and this is not standardised across trials. Geographical location of the studies may indirectly limit access to second line immunotherapy which again may skew OS data, depending on the sites of recruitment, socioeconomic backgrounds of patients and type of healthcare system.

At present, the KEYNOTE407 (6) regimen represents the only first-line chemo-immunotherapy achieving OS benefit over standard chemotherapy for squamous NSCLC patients. This combination is certainly an option for fit patients with PD-L1 expression of 1–49% but further research is needed to identify which patients with PD-L1 $\geq 50\%$ should receive chemo-immunotherapy instead of single agent pembrolizumab.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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