



The KEY to the end of the chemotherapy in advanced non-small cell lung cancer, or not yet?

Yiqing Huang¹, Robert J. Walsh¹, Ross A. Soo^{1,2}

¹Department of Haematology Oncology, National University Cancer Institute Singapore, Singapore, Singapore; ²Cancer Science of Institute, National University of Singapore, Singapore, Singapore

Correspondence to: Ross A. Soo. Department of Haematology-Oncology, National University Cancer Institute Singapore, National University Health System, 1E Kent Ridge Road, NUHS Tower Block Level 7, Singapore 119228, Singapore. Email: ross_soo@nuhs.edu.sg.

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Immune checkpoint inhibitors (ICIs) have altered the treatment landscape of advanced non-small cell lung cancer (NSCLC) that lack driver mutations. In 2016, Reck and colleagues first reported the superiority of pembrolizumab versus chemotherapy in advanced NSCLC with PD-L1 tumour proportion score (TPS) $\geq 50\%$ (KEYNOTE 024) (1). Patients with advanced NSCLC, high TPS of $\geq 50\%$, and ECOG performance status of 0-1 were eligible; while those with sensitizing *EGFR* mutations, *ALK* rearrangements, or untreated brain metastases, were excluded. Progression free survival (PFS) was the primary end point, while overall survival (OS), objective response rates (ORR) and safety were key secondary end points. Crossover from chemotherapy to pembrolizumab arm was allowed at the time of progression. Based on the recommendation of the data and safety monitoring committee, the study was terminated early after second interim analysis showed an OS superiority with pembrolizumab. Pembrolizumab was associated with an improvement in PFS (10.3 *vs.* 6 months, $P < 0.001$) and OS (estimated 6-month OS 80.2% *vs.* 72.4%, $P = 0.005$) when compared with chemotherapy. This is despite a high initial crossover rate of 43% from chemotherapy arm to pembrolizumab. In addition, pembrolizumab was associated with a higher ORR (44.8% *vs.* 27.8%) and less frequent grade 3 to 5 treatment related toxicities (27% *vs.* 53%) when compared with chemotherapy. Patients assigned to pembrolizumab also experienced improved quality of life and a delay to deterioration of symptoms (2).

In this update, the authors reported the updated OS and tolerability analysis. They included 3 statistical methods to adjust for potential bias introduced by crossover from chemotherapy to pembrolizumab. After a median follow-up of 25.2 months, survival doubled in the pembrolizumab arm compared to chemotherapy (30 *vs.* 14.9 months, nominal $P = 0.002$). At data cut-off, 54.3% of patients cross over from chemotherapy to receive pembrolizumab. Fifteen additional patients receive anti-PD1 treatment outside of crossover, making a crossover rate of 64.2% in the intention to treat (ITT) population (3).

Several findings are worth highlighting. Despite a high crossover rate, and analyses to adjust for potential bias with crossover, hazard ratios consistently favoured pembrolizumab arm. Overall survival benefit was maintained with the curves delineating clear separation on longer follow-up. In those who crossover from chemotherapy to receive 2nd line pembrolizumab, the ORR was 20.9%: this result is similar to that of previous studies of 2nd line anti-PD1 treatment (4-6). Safety profile continued to favour pembrolizumab, with lower grade 3 to 5 treatment related adverse events (31% *vs.* 53%) on longer follow-up.

Limitations to the current update include a relatively short median follow-up period of 25.2 months. This compares to a minimum 58.5 months follow-up reported in the updated CA209-003: a study of Nivolumab in pre-treated NSCLC (7). In KEYNOTE 024, pembrolizumab could continue to 2 years and at the point of updated analysis, 11.0% of patients had completed therapy, while

19.9% remained on treatment. A longer follow-up will inform of outcomes after per protocol treatment cessation and provide robust long-term safety and efficacy data.

The three statistical models to adjust for effect of treatment crossover suffer inherent elements of error and accepted standard remains ITT analysis. Rank-preserving structural failure time (RPSFT) adjustment assumes common treatment effect of pembrolizumab regardless of when it is received, either first line or after crossover. While both inverse probability of censoring weighting (IPCW) and the simplified two-stage approach may be at increased risk of error due to the high crossover rate, and both assume the absence of unmeasured confounding factors. Despite these technical limitations, the three methods give similar adjusted HR for OS in the pembrolizumab arm (0.49, 0.52, 0.52 for two-stage, TPSFT, IPCW respectively), suggesting a reliable result. Given the significant result in the ITT population, this adjustment analysis does not serve to alter the overall results of the study or treatment implications, but emphasises the significant benefit of pembrolizumab monotherapy in this population.

Several trials using single agent ICI in the treatment-naïve setting have been conducted (*Table 1*).

In CHECKMATE 026, a phase III study of nivolumab, no OS benefit was seen (HR 1.02) (10). Differences between KEYNOTE 024 and CHECKMATE 026 may be attributed to differences in patient population and PD-L1 assays (13). More recently, KEYNOTE 042 reported OS benefit with 1st line pembrolizumab versus platinum-based chemotherapy in treatment-naïve NSCLC patients with PD-L1 TPS $\geq 1\%$ (9). At a median follow-up of 12.8 months, OS benefit was seen across all subgroups: TPS $\geq 50\%$ (20 *vs.* 12.2 months, $P=0.0003$); $\geq 20\%$ (17.7 *vs.* 13.0 months, $P=0.002$); and $\geq 1\%$ (16.7 *vs.* 12.1 months, $P=0.0018$). Notably, patients with PD-L1 TPS $\geq 50\%$ constituted approximately half of the entire cohort—a proportion much higher than the 30% seen in the general population (14). With the benefit largely driven by the high TPS group, this study highlights the benefit of single agent pembrolizumab in those with high TPS of 50%. However, unlike KEYNOTE 024, patients with high PD-L1 TPS of $\geq 50\%$ in KEYNOTE 042 did not show superiority in PFS for pembrolizumab compared to chemotherapy. Based on the results of KEYNOTE 042, the US FDA recently approved pembrolizumab for patients with advanced NSCLC expressing PD-L1 of at least 1%.

Apart from single agent ICI, other studies evaluating ICIs with chemotherapy or with another ICI have been reported (*Table 2*).

In KEYNOTE 189, a phase III study of pembrolizumab and pemetrexed and a platinum compared with placebo and chemotherapy in non-squamous metastatic NSCLC, pembrolizumab and chemotherapy was associated with an improvement in OS (12-month OS 69.2% *vs.* 49.4%, $P<0.001$) and PFS (8.8 *vs.* 4.9 months, $P<0.001$), irrespective of PD-L1 expression. Overall response rate in the pembrolizumab-combination and control arm was 47.6% and 18.9%, respectively. In the subgroup of patients with TPS $\geq 50\%$, a high ORR of 61% was seen in the pembrolizumab-combination arm (20). In a study of patients with advanced squamous NSCLC (KEYNOTE 407), pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel was associated with an improvement in OS (15.9 *vs.* 11.3 months, $P<0.001$) and PFS (6.4 *vs.* 4.8 months, $P<0.001$) compared to placebo plus chemotherapy (15). Once again, the benefit was seen across all PD-L1 categories. Both KEYNOTE 189 and KEYNOTE 407 have established the role of pembrolizumab and chemotherapy combination in 1st line non-squamous and squamous NSCLC, respectively, regardless of PD-L1 expression.

Atezolizumab, an anti-PDL1 antibody, has also been studied with chemotherapy in advanced non-squamous and squamous NSCLC. In IMPOWER 130, the addition of atezolizumab to carboplatin plus nab-paclitaxel was associated with an improved PFS (7.0 *vs.* 5.5 months; $P<0.0001$) and OS (18.6 *vs.* 13.9 months, $P=0.033$) compared with chemotherapy alone, with benefit seen across all PD-L1 subgroups (17). A study of atezolizumab with platinum and pemetrexed in non-squamous NSCLC also showed improved PFS (7.6 *vs.* 5.2 months, $P<0.0001$) with addition of atezolizumab (18). At interim analysis, there was no difference in OS. In IMPOWER 150: a three-arm phase III study evaluating (I) atezolizumab and carboplatin and paclitaxel, (II) atezolizumab plus bevacizumab and carboplatin and paclitaxel, or (III) bevacizumab and carboplatin and paclitaxel in treatment-naïve non-squamous advanced NSCLC (19), the study included a small proportion of patients with *EGFR* mutation and *ALK* rearrangements. In the WT population, an improvement in PFS (8.3 *vs.* 6.8 months, $P<0.001$) and OS (19.2 *vs.* 14.7 months, $P=0.02$) were seen with addition of atezolizumab to bevacizumab and chemotherapy compared with bevacizumab and chemotherapy. An improvement in PFS was also seen in the ITT population, including patients with *EGFR* mutations and *ALK* rearrangements, with a PFS of 8.3 *vs.* 6.8 months ($P<0.0001$). This study brings to surface the possible benefit of chemotherapy-immunotherapy combination in patients with oncogene

Table 1 Progression free survival (PFS) and overall survival (OS) data from clinical trials evaluating immune checkpoint inhibitor monotherapy in first line treatment of non-small cell lung cancer

Therapy	Trial	Trial size	Treatment regimen	ORR (%)	Median PFS (months)	HR (95% CI) [†]	Median OS (months)	HR (95% CI)
ICI Monotherapy	KEYNOTE 001 (8)	495	Pembrolizumab	45.2 (PD-L1 ≥50%); 19.4 (overall)	6.3	-	NR	-
	KEYNOTE 024 (1)	305	Pembrolizumab vs. Platinum doublet	44.8 vs. 27.8	10.3	0.50 (0.37-0.68)	30.0 vs. 14.2	0.63 (0.47-0.86)
	KEYNOTE 042 (9)	1,274	Pembrolizumab vs. Platinum doublet (PD-L1 ≥1%)	27 vs. 27	5.4 vs. 6.5	1.07 (0.94-1.21)	16.7 vs. 12.1	0.81 (0.71-0.93)
	Checkmate 026 (10)	423	Nivolumab vs. Platinum doublet (PD-L1 ≥5%)	26 vs. 33	4.2 vs. 5.9	1.15 (0.91-1.45)	14.4 vs. 13.2	1.02 (0.80-1.30)
	BIRCH (11) (Cohort 1)	139	Atezolizumab (PD-L1 ≥5%)	25	5.4	-	23.5	-
	MYSTIC (12)	488	Durvalumab vs. Platinum doublet (PD-L1 ≥25%)	35.6 vs. 37.7	4.7 vs. 5.4	0.87 (99.5%, 0.59-1.29)	16.3 vs. 12.9	0.76 (97.5%, 0.56-1.02)

[†], confidence interval specified when not 95. NR, not reached; CI, confidence interval; ORR, objective response rate; HR, hazard ratio; PFS, progression free survival; OS, overall survival.

Table 2 PFS and OS data from clinical trials evaluating combination chemotherapy-immune checkpoint inhibitor (ICI) and combination ICI-ICI in first line treatment of non-small cell lung cancer

Therapy	Trial	Trial size	Treatment regimen	ORR (%)	Median PFS (months)	HR (95% CI) [†]	Median OS (months)	HR (95% CI)
Combination Chemo-ICI	Keynote 407 (15) (squamous)	559	Platinum doublet vs. Platinum doublet + pembrolizumab	57.9 vs. 38.4	6.4 vs. 4.8	0.56 (0.45–0.70)	15.9 vs. 11.3	0.64 (0.49–0.85)
	IMpower131 (16) (squamous)	1,021	A: carboplatin/paclitaxel/atezolizumab; B: carboplatin/nab paclitaxel/atezolizumab; C: carboplatin/nab paclitaxel	Arm B vs. C: 59.4 vs. 51.3	Arm B vs. C: 6.3 vs. 5.6	Arm B vs. C: 0.72 (0.60–0.85)	Arm B vs. C: 14.6 vs. 14.3	0.92 (0.76–1.12)
	IMpower130 (17) (non-squamous)	679	Carboplatin/nab-paclitaxel +/- atezolizumab	49.2 vs. 31.9	7.0 vs. 5.5	0.64 (0.54–0.77)	18.6 vs. 13.9	0.79 (0.64–0.98)
	IMpower132 (18) (non-squamous)	578	Atezolizumab + Platinum doublet vs. Platinum doublet	46.9 vs. 32.3	7.6 vs. 5.2	0.60 (0.49–0.72)	18.1 vs. 13.6	0.81 (0.64–1.03)
Dual ICI	IMpower150 (19) (non-squamous)	1,202	ACP: atezolizumab/carboplatin/paclitaxel; BCP: bevacizumab/carboplatin/paclitaxel; ABCP: atezolizumab/bevacizumab/carboplatin/ paclitaxel	ABCP vs. BCP: 63.5 vs. 48.0	ABCP vs. BCP: 8.3 vs. 6.8	ABCP vs. BCP: 0.62 (0.52–0.74)	ABCP vs. BCP: 19.2 vs. 14.7	0.78 (0.64–0.96)
	Keynote 189 (20) (non-squamous)	616	Platinum doublet vs. Platinum doublet + pembrolizumab	47.6 vs. 18.9	8.8 vs. 4.9	0.52 (0.43–0.64)	NR vs. 11.3	0.49 (0.38–0.64)
	KEYNOTE 021 (21) (non-squamous)	123	Carboplatin + pemetrexed +/- pembrolizumab	56.7 vs. 30.2	24.0 vs. 9.3	0.53 (0.33–0.86)	NR vs. 21.1	0.56 (0.32–0.95)
	Checkmate 227 (22)	1,739	Nivolumab + Ipilimumab vs. Platinum doublet (TMB ≥10 per MB)	45.3 vs. 26.9	7.2 vs. 5.5	0.58 (97.5%, 0.41–0.81)	–	–
Dual ICI	MYSTIC (12)	488	Durvalumab + Tremelimumab vs. Platinum doublet (PD-L1 ≥25%)	34.4 vs. 37.7	3.9 vs. 5.4	1.05 (99.5%, 0.72–1.53)	11.9 vs. 12.9	0.85 (98.8% 0.61–1.17)

[†], confidence interval specified when not 95%. ORR, objective response rate; HR, hazard ratio; PFS, progression free survival; OS, overall survival; CI, confidence interval; TMB, tumour mutational burden; MB, megabase; NR, not reached.

addicted NSCLC that have progressed on targeted therapies. Prospective large randomized controlled trials, however, are required to validate this. In IMPOWER 131 (advanced squamous NSCLC), there was an improvement in PFS for atezolizumab/carboplatin/nab-paclitaxel compared to chemotherapy (6.3 *vs.* 5.6 months, $P=0.0001$) however, there was no difference in OS at interim analysis (23).

Dual ICIs in the 1st line setting has also been reported. CHECKMATE 227 randomized patients with advanced NSCLC to platinum doublet chemotherapy, nivolumab plus ipilimumab, or either nivolumab monotherapy (in those PD-L1 $\geq 1\%$), or nivolumab and chemotherapy (in those PD-L1 $< 1\%$) (22). In patients with high tumour mutational burden (TMB), a PFS benefit was seen with nivolumab and ipilimumab, regardless of PD-L1 status (7.2 *vs.* 5.5 months, $P<0.001$). The ORR was also higher with combination immunotherapy in those with high TMB (45.3% *vs.* 26.9%). Notably, at 1 year, patients treated with nivolumab and ipilimumab versus chemotherapy exhibited ongoing responses (68% *vs.* 25%). Nonetheless, longer follow-up and OS data are required. Preliminary results from CHECKMATE 227 of nivolumab with chemotherapy versus chemotherapy in those with PD-L1 $< 1\%$ have reported an improvement in PFS compared with chemotherapy alone (24).

Despite the positive data from KEYNOTE 024 update, several questions remain in clinical practice. With the establishment of pembrolizumab and chemotherapy combination as 1st line treatment for NSCLC irrespective of PD-L1 expression (15,20), should we be using pembrolizumab alone or chemo-immunotherapy combination for patients with high TPS $\geq 50\%$? Is there still a subset of patients who will derive benefit from single agent pembrolizumab? Given the existing data, we believe single agent pembrolizumab should be considered in patients who are relatively asymptomatic. In patients who are symptomatic or have aggressive disease, a combination approach should be considered either pembrolizumab with chemotherapy, or a quadruplet regimen with atezolizumab, bevacizumab, carboplatin and paclitaxel, all of which have been approved by the US Food and Drug Administration in the 1st line setting. Other combinations atezolizumab with a platinum plus a taxane or with pemetrexed but these combination have not been approved yet (18-20).

Whether pembrolizumab improves survival compared with chemotherapy in patients with PD-L1 TPS $< 1-49\%$ remains a question of clinical interest. In KEYNOTE

042, in an exploratory analysis of patients with PD-L1 TPS 1–49%, there was no difference in OS between pembrolizumab and chemotherapy (9). A phase II PEOPLE trial evaluating 1st line pembrolizumab in advanced NSCLC with low PD-L1 ($< 50\%$) expression is currently ongoing (ClinicalTrials.gov identifier NCT03447678).

Several trials are examining combination ICIs and combinations of ICI and next generation immunotherapy. Such agents include vaccine based therapies (TG4010), LAG3 fusion protein, and tumour infiltrating lymphocytes (TILs) (ClinicalTrials.gov identifiers NCT03353675, NCT03625323, NCT03215810). The role of target lesion radiation therapy as an immune primer in combination with ICI is also under investigation (ClinicalTrials.gov identifier NCT03168464). With the ongoing expansion of the role of ICI in NSCLC, patient selection is key. Currently, PD-L1 remains the only approved biomarker in widespread clinical use. TMB appears a promising biomarker for benefit from ICI combination but is not yet in mainstream use (24). Treatment duration also requires further consideration, with significant clinical and financial toxicities associated with indefinite ICI use. CHECKMATE 153 showed improved PFS with continuous nivolumab until progression versus discontinuation at 1 year, with long term OS data awaited (25). The recruiting DICIPLÉ trial compares 6 months of combination ICI with re-challenge at progression versus continuation of combination ICI to progression (ClinicalTrials.gov identifier NCT03469960).

In conclusion, KEYNOTE 024 has established the role of single agent pembrolizumab in advanced NSCLC with high PD-L1 TPS $\geq 50\%$, with continual OS benefit and favourable toxicity profile at longer follow-up. Combination of pembrolizumab and chemotherapy has also been established, with the benefit seen across all PD-L1 expression levels. We await more data and longer follow-up on other chemotherapy-immunotherapy combinations, and dual immunotherapy combinations.

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Footnote

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