The KEY to the end of chemotherapy in non-small cell lung cancer?

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Until recently, advances in the treatment of non-small cell lung cancer (NSCLC) has been with the use of molecular targeted therapy in tumors harboring oncogenic drivers such as epidermal growth factor receptor (EGFR) mutation, *anaplastic lymphoma kinase* (*ALK*) or *ROS1* gene rearrangement (1-3). However, a majority of non-Asian NSCLC do not harbor an actionable driver oncogene (4) and a platinum doublet with or without bevacizumab is still the standard of care in the first line setting (5).

The introduction of PD-1 and PD-L1 immune checkpoint inhibitors has altered the therapeutic landscape in advanced NSCLC. In the second line setting, phase III trials have demonstrated the superiority of immune checkpoint inhibitors over docetaxel. CHECKMATE 017 and CHECKMATE 057 were phase III studies of nivolumab versus docetaxel in patients who have progressed on a platinum-based chemotherapy. CHECKMATE 017 recruited patients with squamous NSCLC whilst CHECKMATE 057 enrolled non-squamous NSCLC. In CHECKMATE 017, the overall survival (OS) was 9.2 *vs.* 6 months, (HR =0.59, P<0.001) (6) and in CHECKMATE 057, the OS was 12.2 *vs.* 9.4 months (HR =0.73, P=0.002) (7). Toxicity profile favored the nivolumab arm. In a phase II/III study (KEYNOTE 010), patients with pre-treated PDL1 +ve (defined as tumour proportion score (TPS) of at least 1%) advanced NSCLC were randomized to pembrolizumab 2 or 10 mg/kg every 3 weeks or docetaxel. In the overall population, the OS in patients treated with pembrolizumab 2 and 10 mg/kg was 10.4 (HR =0.71, P=0.00076) and 12.7 months (HR =0.61, P=0.0001), respectively compared with docetaxel with an OS of 8.5 months (8). Of note, in patients with a TPS ≥50%, the OS with pembrolizumab 2 and 10 mg/kg was 14.9 months (HR =0.54, P=0.0002) and 17.3 months (HR =0.50, P<0.0001 months), respectively versus 8.2 months with docetaxel. Recently, in a phase III study of atezolizumab versus docetaxel in pre-treated advanced NSCLC unselected for PDL-L1 expression (OAK study), the OS was 13.8 *vs.* 9.6 months (HR =0.73, P=0.0003). Atezolizumab was beneficial regardless of PD-L1 expression and histology (9). This led to the FDA approval of atezolizumab in patients with pre-treated advanced NSCLC.

Given the activity of immune checkpoint inhibitors in pre-treated patients, studies have examined the role in the 1st line setting. Preliminary activity of pembrolizumab in the 1st line setting was suggested in a phase I study (KEYNOTE 001) (10). In particular, pembrolizumab was highly active in patients with high PD-L1 expression. In patients with a TPS of ≥50%, 1–49% and <1%, the objective response rate (ORR) was 58.3%, 17.4%, and 10%, respectively, the progression free survival (PFS) was 12.5, 4.2, and 3.5 months, respectively and the OS was not reached, 19.5, and 14.7 months, respectively (11). Results from KEYNOTE 001 and KEYNOTE 010 supported PD-L1 expression as a predictive biomarker for pembrolizumab.

These promising results have led to the highly anticipated results of KEYNOTE 024, reported by Reck *et al.* (12). KEYNOTE 024 was a randomized phase

III study that compared pembrolizumab 200 mg every 3 weeks for 2 years versus platinum doublet chemotherapy in 305 treatment-naïve advanced NSCLC patients. Key eligibility criteria included advanced NSCLC, high tumor PD-L1 expression (defined as TPS of ≥50%), and ECOG 0–1. Patients with sensitising *EGFR* mutations or *ALK* rearrangement, or untreated brain metastases were excluded. The primary end point was PFS, secondary end points were OS, ORR and safety. The trial was stopped after second interim analysis on the recommendation of the data and safety monitoring committee. An improvement in PFS was seen with pembrolizumab compared with compared to chemotherapy (10.3 *vs.* 6 months, HR=0.5; 95% CI: 0.37 to 0.68; P<0.001). The benefit was seen in all subgroups. An improved OS with pembrolizumab was also seen (estimated 6months OS 80.2% *vs.* 72.4%, HR=0.6, P=0.005). The safety profile of pembrolizumab was consistent with that seen in previous studies, and lower than that with chemotherapy (grade 3/4 adverse events 27% *vs.* 53%). In addition, pembrolizumab was associated with an improvement in quality of life and a longer time to deterioration for cough, dyspnea and chest pain (13). Results from the chemotherapy arm were consistent with previous first line studies, with ORR of 30% and PFS of 6 months.

Several findings from this study should be highlighted. Firstly, a high ORR of 44.8%, impressive for single agent therapy and similar to ORR of 58% reported in KEYNOTE 001 in the TPS ≥50 % cohort. Secondly, no delay in responses was seen with pembrolizumab with a median time to response of 2.2 months, the same as that for chemotherapy. Another important feature was, despite a high cross over rate (43%) from the chemotherapy arm to pembrolizumab, OS benefit was still maintained. Finally, the optimal dose of pembrolizumab remains unclear. In KEYNOTE 024, pembrolizumab was administered at a fixed dose of 200 mg every 3 weeks whereas in KEYNOTE 010, pembrolizumab was dosed at 2 and 10 mg/kg (8). A pharmacokinetic study (14) reported pembrolizumab 200 mg provided similar exposure distribution as weight-based dosing regimen of 2 mg/kg. Given the high costs of immunotherapy, future studies are required to establish a minimum effective dose of pembrolizumab as these can potentially reduce costs in patients with low body weight.

A similarly designed phase III study of nivolumab in treatment naïve advanced NSCLC (CHECKMATE 026) was presented recently. In this study, 541 patients with tumor PD-L1 expression ≥1% were randomized to nivolumab or a platinum doublet. In patients with tumor PD-L1 ≥5%, the PFS was 4.2 *vs.* 5.9 months (HR =1.15, P=0.25), OS was 14.4 *vs.* 13.3 months (HR =1.02) and ORR was 26.1% *vs.* 33.5%. The reasons for the difference in results between KEYNOTE 024 and CHECKMATE 026 are unclear but may be due to differences in patient selection. In CHECKMATE 026, an unusually high number of patients received palliative radiotherapy prior to starting treatment. The biomarker assays were different with the 28-8 assay not validated prospectively and patients were selected based on a tumor PD-L1 expression cut-off of 1% (*Table 1*).

Despite the improvement in outcomes seen in KEYNOTE 024, several important issues remain. Firstly, only about 30% of patients have high tumor PD-L1 expression, and for the remaining 70% of patients with low or absent PD-L1 expression, chemotherapy is still the current standard. Improving treatment for this large group of patients remains crucial. This will be addressed by the ongoing KEYNOTE 042 and other studies (*Table 2*). Secondly, despite the improvement in PFS, progression still occurs (median 10.3 months). Thirdly, patients with *EGFR* mutations or *ALK* translocation were excluded. To address these issues, trials of checkpoint inhibitor in combination with chemotherapy, or targeted therapy or another checkpoint inhibitor are ongoing (*Table 2*).

Early phase studies of checkpoint inhibitors with chemotherapy in the first line setting have been reported. In a phase I study of nivolumab and platinum based doublet, safety was as expected but treatment discontinuation due to adverse events was 21%. The ORR was 33–47% and the 2-year OS was 25–62% (15). In a randomized phase II study (KEYNOTE 021) comparing pembrolizumab and platinum doublet versus platinum doublet in PD-L1 unselected non-squamous NSCLC, results were highly encouraging with a PFS of 13 *vs.* 8.9 months and an ORR of 55% *vs.* 29% (P=0.0016), respectively. In patients with TPS ≥50%, the ORR was 80% for the combination arm. Toxicities were manageable and did not lead to higher discontinuation rates (11% *vs.* 13%) (16). Phase III studies of combination immune checkpoint inhibitors and chemotherapy versus chemotherapy are ongoing in both squamous and non-squamous NSCLC (*Table 2*).

Several early phase studies of immune checkpoint inhibitors and molecular targeted therapy in the first line setting are ongoing (*Table 2*). Preliminary results of first line durvalumab and osimertinib in *EGFR* mutant NSCLC reported an ORR of 70% but grade 3/4 toxicities was

Table 1 Comparison of selected study characteristics between KEYNOTE 024 and CHECKMATE 026

Study	KEYNOTE 024		CHECKMATE 026	
Treatment	Pembrolizumab	Platinum doublet	Nivolumab	Platinum doublet
Never smokers	3.2%	12.6%	32%	45%
Non-squamous histology	81%	82%	76%	76%
Prior radiotherapy	NA	NA	37.6%	39.6%
Tumor biopsy	At time of diagnosis of metastatic disease		Obtained ≤6 months before enrollment	
Prospectively validated assay	Yes		No	
Clone	22C3		28-8	
PD-L1 IHC cutoff	50%		1% (for enrollment), 5% (for primary endpoint)	
Imaging interval	Every 9 weeks		Every 6 weeks	
Maintenance pemetrexed	–	30.4%	–	38%
Post progression immune checkpoint inhibitor treatment	NA	43.7%	1.4%	60.4%

IHC, immunohistochemistry; NA, not available; PD-L1, programmed death-ligand 1.

Table 2 Selected immune checkpoint inhibitor studies in advanced non-small cell lung cancer

Study	Key patient population	Experimental arm	Control arm	Primary endpoint	Clinical trial Identifier
Immune checkpoint inhibitor monotherapy					
CHECKMATE 026	PD-L1 positive Non-squamous NSCLC	Nivolumab	Platinum doublet	PFS	NCT02041533
KEYNOTE 024	PD-L1 positive	Pembrolizumab	Platinum doublet	PFS	NCT02142738
KEYNOTE 042	PD-L1 positive	Pembrolizumab	Platinum doublet	OS	NCT02220894
IMpower 110	PD-L1 positive Non-squamous NSCLC	Atezolizumab	Platinum/ pemetrexed	PFS	NCT02409342
IMpower 111	PD-L1 positive Squamous NSCLC	Atezolizumab	Platinum/ gemcitabine	PFS	NCT02409355
Javelin Lung 100	PD-L1 positive NSCLC	Avelumab	Platinum doublet	PFS	NCT02576574
Immune checkpoint inhibitor in combination with chemotherapy					
KEYNOTE 189	Non-squamous NSCLC	Pembrolizumab/Platinum/ Pemetrexed	Platinum/ Pemetrexed	PFS	NCT02578680
KEYNOTE 407	Squamous NSCLC	Pembrolizumab/Carboplatin and Paclitaxel or Nab-paclitaxel	Carboplatin and Paclitaxel or Nab-paclitaxel	PFS, OS	NCT02775435
IMpower 130	Non-squamous NSCLC	Atezolizumab/Carboplatin/Nab-paclitaxel	Carboplatin/Nab-paclitaxel	PFS	NCT02367781

Table 2(*continued*)

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Study	Key patient population	Experimental arm	Control arm	Primary endpoint	Clinical trial Identifier
IMpower 131	Squamous NSCLC	1. Atezolizumab/Carboplatin/ Nab-paclitaxel 2. Atezolizumab/Carboplatin/ Paclitaxel	Carboplatin/Nab-paclitaxel	PFS, OS	NCT02367794
IMpower 150	Non-squamous NSCLC	1. Atezolizumab/Carboplatin/ Paclitaxel 2. Atezolizumab/Bevacizumab/ Paclitaxel/Carboplatin	Bevacizumab/ Paclitaxel/ Carboplatin	PFS	NCT02366143
Immune checkpoint inhibitor in combination with targeted therapy					
KEYNOTE 021	Advanced NSCLC	1. Pembrolizumab/Erlotinib or Gefitinib 2. Pembrolizumab/Platinum doublet +/- Bevacizumab 3. Pembrolizumab/Ipilimumab	NA	ORR	NCT02039674
KEYNOTE 050	ALK$^+$ advanced NSCLC	Crizotinib/Pembrolizumab	NA	DLT	NCT02511184
Phase I	ALK$^+$ advanced NSCLC	Ceritinib/Nivolumab	NA	ORR, MTD	NCT02393625
Phase 1b	ALK$^+$ or EGFR$^+$ advanced NSCLC	Atezolizumab/Alectinib or Erlotinib	NA	DLT	NCT02013219
Immune checkpoint inhibitor in combination with immune checkpoint inhibitor					
CHECKMATE 227	Advanced NSCLC	1. Nivolumab 2. Nivolumab/Ipilimumab 3. Nivolumab/Platinum doublet (PD-L1 negative)	Platinum doublet	OS, PFS	NCT02477826
MYSTIC	Advanced NSCLC	1. Durvalumab 2. Durvalumab/Tremelimumab	Platinum doublet	PFS, OS	NCT02453282
NEPTUNE	Advanced NSCLC	Durvalumab/Tremelimumab	Platinum doublet	OS	NCT02542293
CHECKMATE 722	EGFR+ T790M-ve acquired resistance 1L EGFR TKI	1.Nivolumab/Platinum/ Pemetrexed 2. Nivolumab/Ipilimumab	Platinum/ Pemetrexed	PFS	NCT02864251

ALK, anaplastic lymphoma kinase; DLT, dose limiting toxicities; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NA, non-applicable; NSCLC, non small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; TKI, tyrosine kinase inhibitor; 1L, first line.

unacceptably high at 59% and any grade interstitial lung disease was 64% (17). High rates of grade 3/4 treatment related toxicity (55%) was also reported in a phase I study of durvalumab and gefitinib (18). The combination of erlotinib with atezolizumab reported an ORR of 75% and disease control rate of 95%, with 39% grade 3/4 adverse events (19).

A phase I study of ipilimumab and nivolumab as first line treatment of advanced NSCLC has recently been reported (20). Treatment discontinuation due to treatment related toxicity was 11% and the ORR was 38–47% overall and 57% in PD-L1 +ve (≥1%). Notably, an ORR was 92% in patients with high tumor PD-L1 expression (≥50%). Whilst this result should be viewed with caution given the small sample size and possible selection bias in a phase I study, it suggests the improved efficacy of combination immune checkpoint inhibitors in tumors with high PD-L1 expression.

In conclusion, KEYNOTE-024 is a landmark trial that

has established the role of first line pembrolizumab in patients with PD-L1 positive, advanced NSCLC without an oncogenic alteration. Patients with high tumor PD-L1 expression were selected using a prospectively validated PD-L1 assay. Studies addressing the efficacy of combination therapies in tumors without high PD-L1 expression are ongoing.

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Footnote

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