



# Breakthrough 5-year survival with pembrolizumab in Keynote-001 study: horizon shifting in advanced non-small cell lung cancer with immune check point inhibition

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Lung cancer remains the leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) the most common type of lung cancer is responsible for around 85% of cases (1,2). Unfortunately, the majority of people diagnosed with NSCLC will have advanced disease at diagnosis with palliative systemic therapy the main treatment option. Since the realisation that systemic chemotherapy can improve survival over best supportive care in 1995, platinum-based chemotherapy has been the mainstay of upfront treatment (3). Since then, our understanding of the NSCLC biologic subtypes has enabled therapy selection by subgroups and a more personalised approach over empiric systemic therapy, especially with the use of receptor tyrosine kinase inhibitors (TKIs) for the small subset of patients with oncogenic driven cancers. Yet 5-year overall survival for patients with advanced/metastatic NSCLC has remained poor and <5% (2). For the remaining majority of patients with *EGFR* and *ALK* “wild-type” NSCLC treated empirically, a breakthrough has come with the discovery of immunotherapy. The Keynote-001 study, a phase Ib, multi-cohort adaptive study, was the first trial to evaluate pembrolizumab in locally advanced or metastatic NSCLC (4). First reported in 2015 and now updated with 5-year overall survival data in 2019 it has demonstrated renewed hope for longer term survival for patients with advanced NSCLC (4,5).

Empiric platinum-based chemotherapy, with or without maintenance therapy followed by second-line chemotherapy, has been the standard treatment option for most patients with advanced NSCLC in the last 15 years, however median survival expectations are modest up to 1 year (6). The discovery of sensitizing *EGFR* mutated and *ALK* gene rearranged NSCLC in 2004 and 2007 respectively and their sensitivity to targeted oral TKIs established the paradigm of targeted therapy for oncogene driven lung cancer (7-10). For the first time, overall survival for selected patients with advanced oncogene addicted NSCLC exceeded 2 years (8,10). Numerous oncogenes have now been described, including *ROS1* rearrangements amongst others, most peculiar to adenocarcinoma histology and all demonstrating high response rates to targeted TKIs (8,10,11). Long term results have demonstrated 5-year survival expectations in patients with sensitizing *EGFR* mutations greater than 14%, and 4-year survival in *ALK* and *ROS1* gene rearranged advanced NSCLC of 56.6%, and 51% respectively (10-12), thus setting the bar high for survival expectations in NSCLC oncogene selected small patient sub-groups.

For the remaining majority of patients treated empirically, it has been the discovery of modern immunotherapy with immune check point inhibitors (CPIs) that has seen the greatest revolution in therapy. A recognised hallmark of cancer, immune evasion, where the immune system does not mount an adequate antitumor response, has been the subject

of significant research investment, particularly with immune modulation using antibodies that block immune regulatory checkpoints (13,14). The T-cell programmed cell death 1 (PD-1) receptor was identified as an important immune checkpoint, that binds to its ligands PD-L1 or PD-L2 on tumour cells, to inhibit a cytotoxic T-cell response (14). Tumours can co-opt this pathway to evade T-cell-induced antitumor responses (14). Pembrolizumab was developed as a highly selective, humanized monoclonal antibody (Mab) against PD-1, to disrupt the engagement of PD-1 with its ligands and thus block inhibitory signals in T cells, leading to tumour recognition by cytotoxic T cells (14). Immune CPIs investigated in Phase III trials in lung cancer and now approved by many regulatory bodies around the world in advanced lung cancer in various clinical settings include the anti-PD-1 Mabs pembrolizumab and nivolumab, and the anti-PD-L1 Mabs atezolizumab and durvalumab.

The phase Ib, multi-cohort adaptive study, Keynote-001, was the first prospective trial to evaluate pembrolizumab in locally advanced or metastatic NSCLC (4,5). The study began with multiple cohorts to assess safety and efficacy of pembrolizumab in advanced solid organ malignancies. To date, the study remains one of the largest phase I trials to be conducted in oncology. Recruitment for Keynote-001 began in 2014, and the NSCLC cohort importantly included both treatment naïve and pre-treated patients. The study explored a then novel assay for tissue PD-L1 staining by immunohistochemistry using the novel 22C3 antibody (PharmDx, Dako), to record tumour proportion score (TPS), to explore the relationship between PD-L1 tissue expression and benefit from pembrolizumab. The study selected a fitter population, excluding patients with untreated brain metastases, ECOG >2, or autoimmune disease requiring immune suppression (4).

Following an initial positive signal with 4/7 NSCLC patients in the initial dose finding cohort (Cohort A) demonstrating stable disease with pembrolizumab, a cohort of 38 previously treated patients was included, to receive pembrolizumab 10 mg/kg every three weeks (Cohort C). Following a further positive signal, three further cohorts of NSCLC patients were added including treatment naïve (n=101) and previously treated patients (n=449), resulting in a total of 550 NSCLC patients (5). These patients were randomized to receive pembrolizumab at 2 mg/kg every three weeks, or 10 mg/kg every two or three weeks, however, after a protocol amendment, all patients went on to receive a flat dose of 200 mg every three weeks. Randomised comparisons and pooled analyses showed

no difference in efficacy or safety amongst the varying pembrolizumab doses or schedules (4,5). Patients provided contemporaneous tissue for PD-L1 TPS. The primary endpoint was overall response rate (ORR) and disease control rate, with secondary endpoints being progression free- and overall-survival (PFS and OS) and toxicity. At the final data cut off on November 2018, median follow up was 60.6 months and maturity had been reached, 82% of patients had died (5).

The investigator reported ORR was 24.8% for previously untreated patients and 18% for previously treated patients (4). The ORRs were similar regardless of pembrolizumab dose or schedule but were greater with higher PD-L1 TPS (4). Notwithstanding the selection biases inherent in single arm Phase Ib/II studies, the updated OS from the Keynote-001 study reported in June 2019 is compelling (5). Median OS for treatment naïve patients was 22.3 months, nearly double that generally observed with standard first line platinum-based chemotherapy. Median OS (mOS) in pre-treated patients was 10.5 months (5). The landmark 5-year OS was 23.2% in treatment naïve patients, and 15.5% in previously treated patients. As seen in multiple subsequent related trials, outcomes varied by PD-L1 expression, and patients with TPS >50% ('high') experienced a mOS benefit of 35.4 months (5). Five-year OS was 29.6% for treatment naïve, and 25.0% for previously treated patients in this PD-L1 'high' group (5). Of note, there was a still a significant benefit for PD-L1 'low' patients (TPS 1–49%), with a mOS of 19.5 months and 5-year OS 15.7% (5). One hundred patients (18%) were still alive at data cut-off, 78% of which had experienced an objective response, indicating response might be an important predictor for long survival. Of the 60 patients who received at least two years of therapy (14 treatment naïve and 46 previously treated), 46 (77%) were still alive at data cut-off. No clinicopathologic characteristics appeared to predict for response.

Immune-mediated adverse events (irAEs) occurred in only 17% of patients by 5 years, which was similar to the incidence reported at 3-year follow up indicating no significant late toxicity signals (4,5). This incidence of irAEs is comparable to those reported with other anti-PD1/PD-L1 therapies in related trials (15-19). Treatment related adverse events led to discontinuation in only 31 (6%) of patients, 9 of whom were alive at data cut off, seven with an ongoing response (4,5).

Since Keynote-001, multiple Phase III studies have evaluated anti-PD1/PD-L1 agents versus docetaxel

chemotherapy in the second line setting in advanced/metastatic NSCLC, either alone or combination with chemotherapy in the first line setting (20-28). In the second line setting, the Phase III Checkmate-017 and -057 evaluated nivolumab versus docetaxel chemotherapy in PD-L1 TPS unselected patients with squamous cell or non-squamous NSCLC respectively, demonstrating superior survival with nivolumab, establishing it as a second line standard option in many parts of the world (21,22). The randomised open-label phase II/III Keynote-010 study, reported in 2016, demonstrated superior ORR and OS for pembrolizumab over docetaxel chemotherapy in advanced NSCLC patients with PD-L1 TPS >1% and any histology (22). And following this the randomised phase 3 OAK study reported results of the PD-L1-targeted therapy, atezolizumab compared with docetaxel in previously treated NSCLC, demonstrating improvement in OS versus docetaxel, regardless of PD-L1 expression or histology (23). These studies collectively established a strong evidence base for the use of CPIs as standard second line therapy of advanced/metastatic NSCLC.

The next significant breakthrough occurred with a series of studies evaluating the use of CPIs in the first line setting, alone or in combination with chemotherapy (15,24-29). The randomised open-label phase III Keynote-024 study demonstrated superior survival of first line pembrolizumab over standard chemotherapy in selected patients with advanced NSCLC and PD-L1 TPS >50% (excluding *EGFR/ALK* positive patients) defining a new standard of care in this sub-group of patients (24). Of note patients in this and all phase III pembrolizumab trials therapy was ceased after two years. After a median of 11 months follow up pembrolizumab therapy was associated with superior ORR (44.8% *vs.* 27.8%), median PFS (10.3 *vs.* 6.0 months), and estimated six-month OS (80.2% *vs.* 72.4%) over chemotherapy (24). Updated OS results from this study in 2019 showed an unprecedented estimated 2-year OS of 51.5% for pembrolizumab and 34.5% for chemotherapy, despite 64.2% in the chemotherapy arm crossing over to receive pembrolizumab (29).

Subsequently, in 2019, the randomised open-label phase III Keynote-042 study showed superiority of first line pembrolizumab over standard chemotherapy in patients with PD-L1 TPS >1% (26). Interim analysis after a median of 12.8 months follow up showed longer median OS for pembrolizumab in all three TPS categories (20.0 *vs.* 12.2 months for TPS >50%, 17.7 *vs.* 13 months for TPS >20%, and 16.7 *vs.* 12.1 months for TPS >1%) (26).

A key next step in the evolution of the role of immunotherapy with CPIs in patients with advanced/metastatic NSCLC, has been their combination with chemotherapy (15,27-29). The randomised double-blind phase III Keynote-189 study confirmed superiority of first-line combination pembrolizumab/chemotherapy compared to standard chemotherapy alone in patients with non-squamous NSCLC (27) despite 30% of patients in this study having a PD-L1 TPS of <1%. Response rates and 1-year survival were 61.4% *vs.* 22.9% and 73.0% *vs.* 48.1% respectively (27).

The subsequently reported randomised double-blind phase III Keynote-407 confirmed superior survival of first line pembrolizumab in combination with chemotherapy over chemotherapy alone in patients with advanced squamous NSCLC irrespective of PD-L1 TPS and despite 35% of patients with a PD-L1 TPS <1% (15). Survival appeared to correlate with increasing PD-L1 TPS, although the same trend was not observed with ORR, with the highest ORR reported in patients having a PD-L1 TPS <1% (63.2% *vs.* 40.4%) (15).

In 2017, the Checkmate-026 study was notable for failing to show a superior PFS of first line nivolumab over standard chemotherapy in patients with advanced NSCLC and PD-L1 TPS  $\geq$ 1% (25). Several reasons have been proposed, including significant crossover of chemotherapy patients to nivolumab, imbalanced favourable characteristics of patients in the chemotherapy arm, e.g., fewer patients with liver metastases, lower burden of disease, and more women, and the use of a different and lower PD-L1 TPS cut point ( $\geq$ 5%) and antibody detection assays. Subsequent analyses demonstrated that tumour mutational burden (TMB) correlated with response (25).

The next key positive first-line Phase III trial of combined chemotherapy and CPIs was the IMPower150 study evaluating the addition of atezolizumab (A) to the standard regimen carboplatin, paclitaxel and bevacizumab (CPB), followed by maintenance AB in patients with metastatic non-squamous NSCLC (28). Patients with any PD-L1 TPS were eligible, and for the first time, patients with *EGFR* or *ALK* genomic alterations who failed or were intolerant of at least one prior TKI were included. The addition of atezolizumab to CPB significantly improved PFS and OS regardless of PD-L1 expression (28). Furthermore, PFS benefit was observed in the patients with *EGFR* or *ALK* genomic alterations and *KRAS* mutant sub-populations (28). This observation was important for demonstrating the efficacy of an immune CPI in molecularly driven cancers,

especially after early observations in *EGFR*-mutant advanced NSCLC, second-line CPIs did not improve OS over docetaxel (16). Furthermore, the predictive value of PD-L1 overexpression, in the *EGFR*-mutant subgroup, is unclear.

Keynote-001 reports the most mature advanced NSCLC dataset of patients treated with pembrolizumab, with 5-year OS exceeding 25% in patients with TPS  $\geq 50\%$  (PD-L1 high), a significant landmark achievement in advanced NSCLC (4,5). This observation is supported by the 5-year survival rate of 13% seen in patients receiving nivolumab from the recently reported pooled analysis of the Checkmate -017 and -057 studies (17). Many national regulatory agencies have now approved pembrolizumab and atezolizumab as first line CPIs in patients with advanced/metastatic NSCLC. However, many questions remain regarding the optimal treatment strategy incorporating immune CPIs in a given patient. The optimal duration of therapy is unknown nor what to do when there is progression on CPIs after prolonged initial benefit. Knowing if and when to necessarily add chemotherapy upfront to a CPI such as pembrolizumab or when to sequence therapy is not known. Furthermore, a proportion of patients still do not respond or benefit from upfront immunotherapy. Moving beyond PD-L1 and TMB, further research into the molecular basis of non-responders and exceptional responders to identify more reliably predictive biomarkers to guide patient selection is vital. A recent example of such discoveries includes the identification of *STK11/LKB1* alterations as the most prevalent genomic predictor of primary resistance to PD-1 inhibitors in *KRAS*-mutant lung adenocarcinoma (18,19).

In conclusion, the long-term survival results from Keynote-001 study provide a new landmark for long-term benefit with pembrolizumab in selected patients with NSCLC, with numerically longest survival seen in PD-L1 TPS high patients. Multiple high quality randomized controlled Phase III studies of several CPIs have since established their place in the treatment landscape of patients of advanced/metastatic NSCLC. Future research is required to address the many open questions including predictive markers to assist patient selection for the use of CPIs as monotherapy or when to use CPIs in combination with chemotherapy.

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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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