



KEYNOTE-042: is lowering the PD-L1 threshold for first-line pembrolizumab monotherapy a good idea?

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Background

Prior to the advent of inhibitory antibodies targeting programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1), the median overall survival (OS) for advanced/metastatic non-small cell lung cancer (NSCLC) patients receiving first-line platinum doublet chemotherapy was approximately 8–12 months and 5-year survival rates were estimated at 2% (1-3). Subsequently, randomized phase III trials comparing atezolizumab, nivolumab or pembrolizumab to docetaxel as second-line therapy were conducted in NSCLC. In each of these trials, there was an OS benefit when comparing the respective PD-1 or PD-L1 inhibitor to docetaxel (4-7). Within KEYNOTE-010, patients with PD-L1 $\geq 50\%$ on tumor cells (TCs) administered pembrolizumab had a greater magnitude of benefit compared to docetaxel than patients with PD-L1 of 1–49% (6). In each of these second-line trials patients with epidermal growth factor receptor (EGFR) activating mutations did not benefit from PD-1 axis inhibitors when compared to docetaxel, with data on any included *ALK* rearranged patients not detailed (4-7). Subsequently, KEYNOTE-024 demonstrated that for advanced/metastatic NSCLC patients with PD-L1 $\geq 50\%$ on TCs by the 22-C3 immunohistochemistry assay and lacking EGFR activating mutations/*ALK* fusions that pembrolizumab had a significantly greater objective response rate (ORR), progression-free survival (PFS) and OS when compared to platinum-based doublets as first-line therapy (8,9).

Because of KEYNOTE-024, multiple regulatory agencies and guideline panels approved pembrolizumab monotherapy for patients with newly diagnosed advanced/metastatic NSCLC, PD-L1 $\geq 50\%$ on TCs and lacking EGFR activating mutations/*ALK* fusions. Following this, both atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) and pembrolizumab plus histology dependent chemotherapy were compared to platinum-based chemotherapy in randomized phase III trials. For patients lacking EGFR activating mutations/*ALK* fusions these chemo-immunotherapy combinations improved efficacy outcomes compared to platinum-based chemotherapy (10-12). In KEYNOTE-189, pembrolizumab plus platinum/pemetrexed had better ORR (47.6% *vs.* 18.9%, $P < 0.001$), PFS [hazard ratio (HR) 0.52, $P < 0.001$] and OS (HR 0.49, $P < 0.001$) than platinum/pemetrexed across non-squamous NSCLC patients with any level PD-L1 staining (including PD-L1 negative patients) (10). In IMpower150, the regimen of ABCP also demonstrated improved ORR (63.5% *vs.* 48%), PFS (HR 0.62, $P < 0.001$) and OS (HR 0.78, $P = 0.02$) for non-squamous NSCLC patients regardless of PD-L1 staining when compared to carboplatin plus paclitaxel plus bevacizumab (12). Similarly, within KEYNOTE-407, pembrolizumab plus platinum/taxane demonstrated improved ORR (57.9% *vs.* 38.4%), PFS (HR 0.56, $P < 0.001$) and OS (HR 0.64, $P < 0.001$) for squamous NSCLC patients regardless of PD-L1 staining (11). CheckMate-026, which compared nivolumab to histology dependent platinum-

based doublets in patients without EGFR activating mutations/*ALK* fusions, failed to demonstrate improved OS for nivolumab in the overall study population with PD-L1 $\geq 5\%$ on TCs or in the subgroup with PD-L1 $\geq 50\%$ on TCs (13). Until recently, the recommended first-line therapy by most guideline panels and regulatory agencies for metastatic NSCLC patients lacking an approved targeted therapy option has been pembrolizumab monotherapy or chemo-immunotherapy (ABCP or pembrolizumab plus histology dependent chemotherapy) if PD-L1 was $\geq 50\%$ on TCs and chemo-immunotherapy if PD-L1 was $< 50\%$ on TCs.

KEYNOTE-042

KEYNOTE-042 compared pembrolizumab to histology dependent platinum-based doublets as initial treatment in locally advanced or metastatic patients with PD-L1 $\geq 1\%$ on TCs and lacking EGFR activating mutations/*ALK* fusions. The trial headline was that pembrolizumab monotherapy might be an additional effective option for this patient population (14). Subsequently, on April 11th 2019 the Food and Drug Administration (FDA) approved pembrolizumab monotherapy for NSCLC patients lacking EGFR activating mutations/*ALK* fusions expressing PD-L1 $\geq 1\%$ on TCs who are metastatic or have stage III disease not felt appropriate for surgery/chemoradiation (15). However, a detailed analysis of KEYNOTE-042 raises the possibility that pembrolizumab monotherapy may not be the best option for many patients with advanced/metastatic NSCLC who lack EGFR activating mutations/*ALK* fusions and have PD-L1 of 1–49% on TCs.

The basis for the FDA approval was that pembrolizumab demonstrated a significantly improved OS in KEYNOTE-042 when compared to platinum-based doublets for patients with PD-L1 $\geq 50\%$, $\geq 20\%$ and $\geq 1\%$ on TCs (15). However, nearly half of patients with PD-L1 $\geq 1\%$ and approximately 75% of patients with PD-L1 $\geq 20\%$ had expression $\geq 50\%$ on TCs. For patients with PD-L1 $\geq 50\%$ on TCs there was a statistically significantly improved OS compared to chemotherapy in this trial, median OS was 20 *vs.* 12.2 months, HR 0.69 (95% CI, 0.56–0.85). In contrast, for patients with PD-L1 of 1–49% on TCs there was no significant difference in OS compared to chemotherapy, median OS was 13.4 *vs.* 12.1 months, HR 0.92 (95% CI, 0.77–1.11). A closer look at the OS curves suggests that for patients who expressed PD-L1 of 1–49% on TCs that OS was actually worse with pembrolizumab when compared

to platinum-based doublets up until approximately the 12-month mark. The survival curves crossed at 12 months, suggesting an unidentified subgroup within patients who expressed PD-L1 of 1–49% on TCs who were benefiting from pembrolizumab monotherapy. Since the median follow-up was only 12.8 months on this trial, it is possible that with longer follow-up that the prolonged durations of response seen with pembrolizumab monotherapy may result in a significant OS benefit in the future for patients with PD-L1 of 1–49% on TCs (14).

The PFS was improved on KEYNOTE-042 for patients with PD-L1 $\geq 50\%$ on TCs who were treated with pembrolizumab when compared to platinum-based doublets, median 7.1 *vs.* 6.4 months, HR 0.81 (95% CI, 0.67–0.99). In contrast, there was no PFS benefit for pembrolizumab in patients with PD-L1 $\geq 20\%$ on TCs [HR 0.94 (95% CI, 0.80–1.1)] or $\geq 1\%$ on TCs [HR 1.07 (95% CI, 0.94–1.21)]. The PFS curves suggest that for over half of the patients in the $\geq 20\%$ and $\geq 1\%$ PD-L1 groups that PFS was worse with pembrolizumab when compared to chemotherapy. The PFS data for the 1–49% subgroup is not available; however, it is a reasonable conclusion based on the available evidence that the PFS was likely worse for patients treated with pembrolizumab monotherapy who expressed PD-L1 of 1–49% on TCs (14).

The ORR was greater on KEYNOTE-042 for patients with PD-L1 $\geq 50\%$ on TCs treated with pembrolizumab monotherapy when compared to chemotherapy, ORR of 39% *vs.* 32%. However, the ORR was similar in the PD-L1 $\geq 20\%$ and $\geq 1\%$ groups, 33% *vs.* 29% and 27% *vs.* 27%, respectively. Thus, while not provided, ORR was likely inferior in the patients expressing PD-L1 of 1–49% on TCs treated with pembrolizumab monotherapy when compared to platinum-based doublets (14).

How do we incorporate data from KEYNOTE-042 into our treatment practices?

It is important to look at KEYNOTE-042 in the context of the current standard of care, which is no longer first-line platinum-based doublets. The current standard of care first-line treatment for most metastatic NSCLC patients expressing PD-L1 of 1–49% on TCs, with the exception of patients with an oncogene for which there is an approved targeted therapy, is platinum-based doublets plus a PD-1 axis inhibitor. The available chemo-immunotherapy combinations include pembrolizumab plus platinum/pemetrexed and ABCP for non-squamous NSCLC,

and pembrolizumab plus platinum/taxane for squamous NSCLC (16).

Since the IMpower150 study utilized a different PD-L1 staining assay (SP-142) which does not correlate well with the 22-C3 assay and also stains immune cells, it is hard to define a patient population within this trial that is similar to patients with PD-L1 of 1–49% on TCs by the 22-C3 assay (12,17). However, for patients on KEYNOTE-189 and KEYNOTE-407, a comparison between the patients with PD-L1 of 1–49% on TCs enrolled in KEYNOTE-042 can be made. The PFS was significantly improved on both of these trials with pembrolizumab plus histology dependent chemotherapy for patients with PD-L1 of 1–49% on TCs, HR 0.55 (95% CI, 0.37–0.81) for KEYNOTE-189 and HR 0.56 (95% CI, 0.39–0.80) for KEYNOTE-407. Additionally, OS was significantly improved with pembrolizumab plus histology dependent chemotherapy for patients with PD-L1 of 1–49% on TCs treated on both KEYNOTE-189 [HR 0.55 (95% CI, 0.34–0.90)] and KEYNOTE-407 [HR 0.57 (95% CI, 0.36–0.90)]. Pembrolizumab plus histology dependent chemotherapy also improved the 1-year OS in both KEYNOTE-189 (71.5% vs. 50.9%) and KEYNOTE-407 (65.9% vs. 50.0%) for patients with PD-L1 of 1–49% on TCs (10,11). In KEYNOTE-042, pembrolizumab monotherapy likely had a worse PFS than chemotherapy for patients with PD-L1 of 1–49%. Also, in KEYNOTE-042, the 1-year OS with pembrolizumab monotherapy was nearly identical when compared to chemotherapy for this PD-L1 subgroup and there was no significant OS benefit (14).

In patients with non-squamous NSCLC who receive platinum/pemetrexed chemotherapy the utilization of continuation maintenance with pemetrexed has been associated with improved PFS and OS (18). In the KEYNOTE-189 study 90% of eligible patients received pemetrexed maintenance (10). However, in KEYNOTE-042 only 66% of eligible patients received pemetrexed maintenance (14). A low percentage of patients receiving pemetrexed maintenance if anything would bias towards improved OS with pembrolizumab monotherapy. However, for non-squamous patients across all PD-L1 groups in KEYNOTE-042 there was not a statistically significant benefit in OS for pembrolizumab (14). Greater utilization of pemetrexed maintenance in KEYNOTE-042 may have resulted in the two treatment arms being even more similar.

Additionally, never smokers had no OS benefit in KEYNOTE-042 from receipt of pembrolizumab (14).

This suggests that it may be important to test for other oncogene drivers besides EGFR activating mutations/ALK fusions prior to starting first-line treatment (e.g., *ROS-1* fusions, *NTRK* fusions, *MET* exon 14 skipping mutations, *BRAF* V600E mutations and *RET* fusions). These patient populations with the aforementioned molecular targets have available therapies either as standard of care or on trial that are likely to result in better ORR and PFS than pembrolizumab monotherapy. Patients with these molecular drivers, with the exception of the *BRAF* V600E mutation, have lower tumor mutational burden (TMB) and do not respond well to single agent PD-1 axis inhibitors (19–21).

Chemotherapy is not a good standard of care arm to compare pembrolizumab monotherapy to in the current era for patients with PD-L1 of 1–49% on TCs. The chemotherapy arm on KEYNOTE-042 was also not reflective of the recommended management in patients who receive first-line platinum-based doublets and develop progressive disease (14). If a patient receives platinum-based doublets as initial treatment and progresses, immune checkpoint inhibition with a PD-1 or PD-L1 inhibitor is recommended as the next line of treatment absent contraindications; however, on KEYNOTE-042, cross over was not allowed and only 20% of the patients on the control arm received subsequent immunotherapy (14,16). Thus, many patients on the chemotherapy arm of KEYNOTE-042 did not receive standard second-line therapy. In CheckMate-026, where the rate of crossover to receive subsequent immunotherapy in the chemotherapy arm was 60%, there was no OS difference when comparing nivolumab to platinum-based doublets (13). Thus, the lack of crossover and lack of receipt of subsequent immunotherapy in KEYNOTE-042 biased OS outcomes in favor of the pembrolizumab arm.

In the absence of a head-to-head comparison between all available options, how do we care for advanced NSCLC patients with PD-L1 of 1–49% on TCs when they are metastatic or otherwise not candidates for chemoradiation? Until more evidence is available, adopting pembrolizumab monotherapy as a recommended option may not result in optimal patient outcomes despite its FDA approval. ABCP and pembrolizumab plus histology dependent chemotherapy were superior to platinum-based doublets for such patients (10–12). Pembrolizumab monotherapy did not have an improved OS when compared to platinum-based doublets for such patients despite biases towards that arm (e.g., lack of cross-over, low rates of subsequent immunotherapy and lack of receipt of pemetrexed

maintenance in many patients). Additionally, PFS and ORR were likely worse with pembrolizumab in such patients (14). Thirty to 60 percent of patients are lost when going from first to second-line therapy due to becoming too sick for subsequent treatment and/or other factors (10-12,14). Thus, there are inherent risks and no proven benefit (or even equivalence) for pembrolizumab monotherapy when compared to chemo-immunotherapy in patients with PD-L1 of 1–49% on TCs; especially in the absence of a biomarker that reliably predicts who within this group may benefit from pembrolizumab.

Conclusions

Which patients with PD-L1 of 1–49% on TCs may be appropriate for initial treatment with pembrolizumab monotherapy? Certainly, for poor Eastern Cooperative Oncology Group (ECOG) performance status patients who cannot tolerate chemotherapy it is nice to have another option for first-line therapy; however, one has to realize that such patients were not included in KEYNOTE-042 (14). Additionally, platinum-based doublets provided survival benefit when compared to single agent chemotherapy for patients with ECOG performance status 2; however, a randomized trial has not compared pembrolizumab monotherapy to any first-line systemic regimen in a similar patient population (22). The available data, which is only from single arm studies, is mixed with regards to whether the outcomes seen with PD-1 axis inhibitors in patients with ECOG performance status 2 (not included in KEYNOTE-042) are similar to those in patients with ECOG performance status 0–1 (included in KEYNOTE-042) (23,24). In addition, pembrolizumab monotherapy may be an intriguing option for patients with high TMB and PD-L1 of 1–49% on TCs; however, data on TMB in KEYNOTE-042 is not available (14). It is also not known how best to define high TMB or what is the optimum method of assessing this biomarker. Until more data and improved biomarkers are available, chemo-immunotherapy combinations should be recommended for most patients with advanced NSCLC who lack an approved targeted therapy option, have PD-L1 of 1–49% on TCs and are not candidates for chemoradiation.

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Footnote

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