



Keynote 42: Pembrolizumab, PD-L1, and where to draw the line

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Comment on: Mok TSK, Wu YL, Kudaba I, *et al.* Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;393:1819-30.

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Immune therapy with PD-L1 checkpoint blockade (ICB) has changed the landscape of treatment for NSCLC (1). However, only a portion of patients will receive benefit from ICB and the PD-L1 tumor proportion score (TPS) has emerged as a biomarker that predicts clinical benefit (2). In the frontline treatment setting, Keynote 24 showed the superiority of pembrolizumab over chemotherapy in a highly selected group of patients with a PD-L1 TPS score greater than or equal to 50% (3). However, questions remain regarding the benefit of immune checkpoint blockade in comparison to chemotherapy for patients whose tumors have a low or intermediate PD-L1 TPS (1–49%).

In the *Lancet*, Mok *et al.* report the second interim analysis of Keynote 42 which evaluated the use of pembrolizumab monotherapy *vs.* platinum doublet chemotherapy in patients with previously untreated metastatic or locally advanced squamous or non-squamous NSCLC and a PD-L1 TPS of $\geq 1\%$ (4). This was an open label, randomized international trial in 32 countries involving 1,274 patients. In the primary outcome, the trial showed superiority of single agent pembrolizumab over chemotherapy across all PD-L1 positive TPS subgroups. The median overall survival among patients who received pembrolizumab monotherapy for tumors with TPS $\geq 50\%$, $\geq 20\%$ and $\geq 1\%$ was 20, 17.7 and 16.7 months with hazard ratios of 0.69, 0.77 and 0.81 respectively compared to chemotherapy. Importantly, the trial did not allow cross over to pembrolizumab as part of the protocol. Only 20% of patients in the chemotherapy arm received immune checkpoint blockade at time of progression while many

patients receiving initial pembrolizumab therapy would have access to second-line chemotherapy. The toxicity profile was significantly better with pembrolizumab compared to chemotherapy, with grade 3 or higher adverse events occurring in 18% *vs.* 41% of patients respectively.

Keynote 42 is a pivotal phase III trial that established pembrolizumab monotherapy as a front-line therapeutic option for any non-small cell lung cancer with a TPS PDL-1 score $\geq 1\%$. Keynote 42 also confirms the results of Keynote 24 with superior efficacy and less toxicity for pembrolizumab compared to chemotherapy for NSCLC with TPS $\geq 50\%$. However, the results for Keynote 42 should be viewed with caution for tumors with TPS 1–49% as the superiority of pembrolizumab compared to chemotherapy for all patients with PD-L1 TPS $\geq 1\%$ was likely driven by the subset of patients with PD-L1 TPS $\geq 50\%$. An exploratory analysis showed that the overall survival in the TPS 1–49% group treated with pembrolizumab appears similar but not superior to chemotherapy (13.4 *vs.* 12.1 months), although the study was not powered for superiority or non-inferiority for the TPS 1–49% subset. However, since only 20% of patients randomized to initial chemotherapy received subsequent ICB, in some respects, this study tests whether ICB followed by chemotherapy is superior to chemotherapy alone. Given data supporting the benefit of ICB following progression on frontline chemotherapy (1,2) this does limit the relevance of the standard comparison arm in Keynote 42 (although this was not yet the standard of care when the protocol was written in 2014). Nonetheless, when considering the

toxicity profile advantage of pembrolizumab monotherapy, it is reasonable to consider pembrolizumab monotherapy as an option over chemotherapy alone in the frontline setting for any patients with a PD-L1 TPS $\geq 1\%$.

Despite overall survival benefit seen in Keynote 42, there is no statistically significant progression free survival advantage with pembrolizumab monotherapy across the PD-L1 TPS subgroups. This is in contrast to Keynote 24 where there was a progression free survival benefit with PD-L1 $\geq 50\%$. There is no clear explanation for the difference between trials, even among the subset with PD-L1 $\geq 50\%$. However, it does highlight that caution should be used with pembrolizumab monotherapy when needing an effective early response to treatment. In particular, the early crossover of the Kaplan Myer curve suggests patients receiving pembrolizumab monotherapy may be at risk for early disease progression compared to chemotherapy. Furthermore, this finding appears to be more pronounced in the PDL1 1–49% cohort. Given this finding, patients with a significant disease burden or symptoms may experience early disease progression on ICB alone and not be fit enough to receive subsequent chemotherapy, raising concern about the overall benefit of frontline ICB monotherapy in this setting. Thus, for the group of patients with PD-L1 TPS 1–49%, combination chemotherapy with ICB would be optimal when medically appropriate and available.

The results of phase III trials showing superior progression free survival and survival for chemotherapy plus ICB compared to standard chemotherapy need to be considered when choosing treatment options for patients with low or intermediate PD-L1 (1–49%). This includes the Keynote 189 and 407 trials, which examined the combination of pembrolizumab and platinum doublet chemotherapy in patients with non-squamous and squamous NSCLC respectively (5,6), and Impower 150 which tested the combination of bevacizumab, atezolizumab and platinum doublet chemotherapy to doublet chemotherapy alone in patients with non-squamous NSCLC (7). It is postulated that the inclusion of chemotherapy sensitizes tumors to immune checkpoint blockade, and the addition of chemotherapy also mitigates the risk of early progression and decompensation inherent to ICB monotherapy. Specifically, Keynote 189 and 407 show a clear overall survival, progression free survival, and response rate benefit to the combination of ICB with chemotherapy over chemotherapy alone, including in subgroups specifically examining PD-L1 TPS 1–49%. While cross-trial comparisons are limited, response rate

and overall survival at 1 year with combination therapy in Keynote 189 appear superior compared to pembrolizumab monotherapy in Keynote 42 (OS at 1-year nearly 70% *vs.* 60%) (5). Additionally, Impower 150 showed a survival advantage in adding bevacizumab and atezolizumab to doublet chemotherapy regardless of PD-L1 expression, and there was a clear progression free survival advantage to combination therapy (HR 0.56) among patients with tumor cell PD-L1 expression 1–49% (notably, using a different PD-L1 assay than in Keynote 42) (7). However, there has not yet been publication of the atezolizumab trial arm that did not include bevacizumab, limiting the interpretation of the efficacy of adding VEGF inhibition to frontline therapy. Recently, Checkmate 227 has examined the combination of nivolumab and ipilimumab, also showing superiority over chemotherapy in a population of patients with PD-L1 TPS $\geq 1\%$ (median overall survival 17.1 *vs.* 14.9 months and HR 0.79) (8). This study did include a nivolumab monotherapy arm but this comparison is limited, as it was not established as the primary outcome of the trial. Nonetheless, nivolumab and ipilimumab did have a higher response rate 35.9% *vs.* nivolumab 27.5% and importantly a longer duration of response 23.2 *vs.* 15.5 months than nivolumab monotherapy or chemotherapy alone (RR 30% and DOR 6.2 months).

Non-small cell lung cancer has proven to be responsive to immune therapy, raising the question—who can receive a chemotherapy-free regimen as initial treatment for metastatic disease? Keynote 42 shows that pembrolizumab monotherapy is superior to chemotherapy for patients whose tumors have a PD-L1 TPS $\geq 1\%$. It is reasonable to use pembrolizumab monotherapy for patients with modest cancer related symptoms and a low tumor burden. Pembrolizumab monotherapy is particularly appropriate for those patients who are not optimal candidates for chemotherapy, due to comorbidities, performance status, or patient preference. However, the high rate of early tumor progression, and lack of progression free survival benefit for pembrolizumab in patients with low and intermediate PD-L1 TPS (1–49%) must be taken into account. Therefore, combination chemotherapy plus ICB would be preferred regimens for patients symptomatic from their cancer and/or with high tumor burden and fit for chemotherapy in PD-L1 TPS 1–49% tumors. Dual checkpoint blockade with nivolumab and ipilimumab is a particularly appealing emerging treatment option given the potential for longer duration of response and tolerance of side effects even with comorbidities and lower performance status especially in tumors that are TPS $< 1\%$ (9). Future trials will help clarify

which combinations of checkpoint blockade, chemotherapy and targeted agents are most effective in different patient cohorts. Keynote 42 has established pembrolizumab monotherapy as an important new treatment option for patients with NSCLC PD-L1 TPS $\geq 1\%$, and clinicians can consider individual patient circumstances and preferences when choosing whom to offer this treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.01.65>). NR: Advisory role with Merck, BMS, AZ, Genentech, AbbVie, Celgene; JC: Speaking role with Merck, Advisory role with AstraZeneca, Guardant, Merck, Eli Lilly, Pfizer, and NGM Biopharmaceuticals. Travel compensation from Merck, AstraZeneca, Pfizer, and NGM bio. Board of Directors-Lung Cancer Initiative of North Carolina (uncompensated). Trial PI for: Bristol-Myers Squibb, Eli Lilly, Genentech, Spectrum, Adaptimmune, Medpacto, Bayer, AbbVie, Moderna, GlaxoSmithKline, Array, and AstraZeneca. JI has no conflicts of interest to declare.

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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