Editorial Commentary

Extended follow-up on KEYNOTE-024 suggests significant survival benefit for pembrolizumab in patients with PD-L1 ≥50%, but unanswered questions remain

Jose M. Pacheco[1], Dexiang Gao[2], D. Ross Camidge[1]

[1]Division of Medical Oncology, Department of Internal Medicine, University of Colorado Anschutz Cancer Center, Aurora, Colorado, USA; [2]School of Medicine and Colorado School of Public Health, University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado, USA

Correspondence to: Jose M. Pacheco. University of Colorado Cancer Center, 1665 Aurora Court, Room 5309, Mail Stop F704, Aurora, Colorado 80045, USA. Email: jose.m.pacheco@ucdenver.edu.

Provenance: This is an invited article commissioned by the Section Editor Song Xu, MD, PhD (Department of Lung Cancer Surgery, Tianjin Medical University General Hospital; Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Comment on: Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019;37:537-46.

Submitted May 21, 2019. Accepted for publication May 27, 2019.
doi: 10.21037/atm.2019.05.72
View this article at: http://dx.doi.org/10.21037/atm.2019.05.72

Background

Platinum-based doublets were the recommended systemic therapy for newly diagnosed patients with stage IV non-small cell lung cancer (NSCLC) for decades. Median overall survival (OS) for patients whose first treatment was these chemotherapy regimens was 8–12 months and 5-year OS was estimated at 2% (1-3). Subsequently, tyrosine kinase inhibitors (TKIs) with activity against specific molecular alterations [e.g., anaplastic lymphoma kinase (*ALK*) gene rearrangements and epidermal growth factor receptor (EGFR) activating mutations] were developed. These TKIs altered the treatment landscape for patients with these driver alterations by improving objective response rate (ORR), progression free survival (PFS) and OS compared to starting with platinum-based doublets (4,5). However, these and several other subsequently described actionable oncogene drivers are found in a minority of NSCLC patients. For the patients lacking these targetable alterations something else was needed.

The first ray of hope for NSCLC patients lacking molecular alterations targeted by the initial TKIs came with second line trials comparing programmed death 1 (PD-1) inhibitors and programmed death ligand 1 (PD-L1) inhibitors to docetaxel. In these trials atezolizumab, nivolumab and pembrolizumab all led to significantly improved OS compared to docetaxel. Patients with EGFR activating mutations did not benefit from these PD-1 axis inhibitors when compared to docetaxel. Data on patients with other oncogene drivers and whether or not they benefited from PD-1 axis inhibitors were not provided (6-9). KEYNOTE-010 suggested that the benefit from pembrolizumab compared to docetaxel was much greater for patients with PD-L1 ≥50% on tumor cells (TCs) when compared to patients with PD-L1 of 1–49% as measured by the 22C3 immunohistochemistry assay (8).

KEYNOTE-024

This trial built upon the success of second line pembrolizumab in patients with PD-L1 ≥50% on TCs. KEYNOTE-024 enrolled newly diagnosed stage IV NSCLC patients with PD-L1 ≥50% on TCs, randomizing them in a 1:1 fashion to receive pembrolizumab or histology dependent platinum-based doublets. Patients with EGFR activating mutations or *ALK* gene rearrangements were excluded (10,11). The first presentation of the data suggested significantly improved ORR (44.8% *vs.* 27.8%), PFS (HR 0.50, 95% CI, 0.37–0.68) and OS (HR 0.60, 95% CI, 0.41–0.89) with pembrolizumab versus chemotherapy

for this patient population. The median follow-up at the time of this analysis was 11.2 months and median OS for the pembrolizumab arm was not reached (10).

Recently, the KEYNOTE-024 investigators presented an update to this trial after a median follow-up of 25.2 months. The median OS was 30 months for pembrolizumab (95% CI, 18.3–not reached) and the median OS for chemotherapy was 14.2 months (95% CI, 9.8–19.0), HR 0.63 (95% CI, 0.47–0.86). There was built in crossover on this study. Fifty-five percent of patients (n=82) on the chemotherapy arm crossed over on study to receive pembrolizumab. An additional 15 patients on the chemotherapy arm crossed over off study to receive PD-1 inhibition, for an effective crossover rate of 65% (11).

Randomized controlled trials such as this one allow crossover for ethical reasons when there is a presumed benefit of the experimental treatment even in a later line and to help facilitate accrual. When patients in the control group crossover and benefit from the experimental treatment this may dilute the true OS benefit of the experimental group compared to the control group when using the intention to treat (ITT) analysis. There are multiple OS adjustment methods, all of which have assumptions, which try to estimate a more accurate OS effect of the experimental versus the control group when crossover is allowed. The investigators used three adjustment methods to account for the effect of crossover at the time of progression on the control arm (platinum-based doublets) to subsequently receive pembrolizumab (11). Such methods may have biases beyond the assumptions that are inherent to such models if they do not adequately adjust for prognostic factors at the time of progression on the control arm patients who do or do not crossover (12).

The two-stage adjustment method is one model that was used in this study (11). This model compared the OS for patients on the control arm who crossed over to pembrolizumab at the time of progression to the OS for patients on the control arm who did not crossover at the time of progression. The treatment effect generated by this comparison was used to estimate the OS for the patients who crossed over to pembrolizumab as if they had never received pembrolizumab (i.e., counterfactual OS). The counterfactual OS for the patients who crossed over was then combined with the OS for the patients on the control arm who did not crossover at the time of progression to generate a new median OS for this cohort. This adjusted median OS was then compared to the OS on the pembrolizumab arm (11,12). The result of this analysis suggests that the true OS benefit of pembrolizumab when compared to platinum-based doublets may be better than that demonstrated in the ITT analysis (HR 0.49, 95% CI, 0.34–0.69) (11).

Two other OS adjustment methods that were used in this study were the rank preserving structural failure time (RPSFT) model and the inverse probability of censoring weights (IPCW) model (11). The RPSFT model assumes the treatment effect for patients who crossover to pembrolizumab at the time of progression is the same as in the patients who receive pembrolizumab as initial treatment (12). However, we know that this assumption is not entirely true as patients who received pembrolizumab as initial treatment on this trial had a better ORR than patients who crossed over to pembrolizumab at time of progression (44.8% *vs.* 20.7%) (11). The IPCW model censors patients at the time of crossover to pembrolizumab. Since censor time for patients who crossed over is informative (disease progressed), the censoring time needs to be modeled and adjusted for the patients who did not crossover. The IPCW method adjusts for informative censoring by weighting the patients who did not crossover using the inverse probability of censoring, where the probability of censoring is modeled assuming all confounders are observed and included in the model. The latter is a very strong assumption (11,12). However, despite some of the weaknesses of these two models, they demonstrated a similar adjusted OS benefit of pembrolizumab when compared to platinum-based doublets as that suggested by the two-stage analysis, HR 0.52 (95% CI, 0.33–0.75) for the RPSFT method and HR 0.52 (95% CI, 0.33–0.80) for the IPCW method. Additionally, the median OS for the control arm when using each of the three adjustment methods was similar to that of historical controls: median OS 8.7 months for the two-stage analysis and 11.8 months for both the RPSFT and IPCW models. Since the confidence intervals (CIs) of these OS adjustment models all overlap with the CI in the ITT analysis (HR 0.63, 95% CI, 0.47–0.86), there is a possibility that the true OS benefit of pembrolizumab is not as much as that suggested by the adjustment models used in this trial (11).

In KEYNOTE-024, the non-smokers did not benefit from pembrolizumab when compared to chemotherapy. The OS HR for non-smokers was 0.90 (95% CI, 0.11–1.62). While patients with EGFR activating mutations and ALK rearrangements were excluded from KEYNOTE-024, we do not know the incidence of non-smoking patients with other oncogene drivers that were enrolled and treated on this trial (11). Patients who are never smokers or light

smokers with other oncogene drivers (besides EGFR activating mutations or ALK rearrangements) generally do not respond well to single agent PD-1 axis inhibitors (13,14).

First line treatment for stage IV NSCLC patients with PD-L1 ≥50% on TCs

KEYNOTE-024 was important because it established pembrolizumab monotherapy as a preferred first line regimen for stage IV NSCLC patients with PD-L1 ≥50% on TCs and lacking EGFR activating mutations/ALK rearrangements (10,11). The benefit of pembrolizumab versus platinum-based doublets for this patient population was supported by the results of KEYNOTE-042, which compared pembrolizumab versus platinum-based doublets in patients with PD-L1 ≥1% who lacked EGFR activating mutations or ALK rearrangements. For the subgroup of patients with PD-L1 ≥50% on TCs enrolled on KEYNOTE-042, there was also a significant OS benefit for pembrolizumab, median 20 versus 12.2 months, HR 0.69 (95% CI, 0.56–0.85) (15). In contrast to KEYNOTE-024, on KEYNOTE-042 there was minimal PFS benefit for pembrolizumab in patients with PD-L1 ≥50% (median PFS 7.1 versus 6.4 months, HR 0.81, 95% CI, 0.67–0.99). For patients with PD-L1 ≥50% the OS benefit of pembrolizumab monotherapy on KEYNOTE-042 was not as robust as on KEYNOTE-024, despite a lower percentage of patients receiving a subsequent PD-1 inhibitor on KEYNOTE-042 (20% versus 65%) (10,11,15). This brings up the possibility that the benefit of pembrolizumab in patients with PD-L1 ≥50% who lack EGFR activating mutations/ALK rearrangements may not be as significant as suggested by the models attempting to adjust for crossover on KEYNOTE-024. Reasons for the discrepancy between the survival results of KEYNOTE-024 and KEYNOTE-042 for patients with PD-L1 ≥50% is unclear. However, the higher percentage of non-smokers on KEYNOTE-042 (21%) versus on KEYNOTE-024 (3.2%) could be a contributing factor. Data on tumor mutational burden (TMB) was not provided for either of these two trials, thus it is unknown whether there were differences in the percentage of patients with high TMB between the two studies (10,11,15). Equally, tumors with PD-L1 levels ≥50% do not represent a uniform population and balance between levels at high cut-offs, e.g., ≥70% or ≥90% is unknown.

What is the best initial therapy for patients with PD-L1 ≥50% and lacking an oncogene driver for which there is an approved targeted therapy became more debatable following the presentation of the KEYNOTE-189 and KEYNOTE-407 data (16,17). KEYNOTE-189 compared pembrolizumab plus platinum plus pemetrexed to platinum plus pemetrexed as first line treatment in stage IV non-squamous NSCLC patients (16). KEYNOTE-407 compared pembrolizumab plus platinum plus taxane to platinum plus taxane in stage IV squamous NSCLC patients (17). Both KEYNOTE-189 and KEYNOTE-407 demonstrated improved PFS and OS for pembrolizumab plus chemotherapy when compared to chemotherapy across all PD-L1 subgroups (PD-L1 negative, PD-L1 of 1–49% on TCs and PD-L1 ≥50% on TCs) (16,17).

No randomized trial has presented results comparing pembrolizumab versus pembrolizumab plus histology dependent platinum-based doublets for patients with PD-L1 ≥50% on TCs and lacking EGFR activating mutations/ALK rearrangements, however such a trial has recently commenced (NCT03793179). Thus, we are currently forced to use cross-trial comparisons to guide our treatment decision-making. For this patient population pembrolizumab plus histology dependent chemotherapy has demonstrated improved ORR (approximately 60%) when compared to pembrolizumab monotherapy (39–45%). In contrast, cross trial comparisons have yet to demonstrate significant OS differences between these therapies (10,11,16-18). Part of this could be because of much shorter follow-up on the chemo-immunotherapy trials; however, another possibility is that chemo-immunotherapy responses, which may contain responders to each element separately or to the combination, may not be as long lasting on average as pure immunotherapy responses (18).

Outside of clinical trial data-driven decision-making, some physicians may prefer to give chemo-immunotherapy to patients with more aggressive tumors and/or greater tumor burden to take advantage of the perceived higher response rate with the combination. Similarly, pembrolizumab monotherapy may be preferred in patients in order to avoid the toxicity of chemotherapy, including in those whose performance status may not be as good, who have more indolent tumor biology and/or lower tumor burden.

To help determine if chemo-immunotherapy or pembrolizumab monotherapy is best for patients with PD-L1 ≥50%, we need to improve biomarkers of response to pembrolizumab monotherapy and/or define better who within this PD-L1 subgroup may benefit most from pembrolizumab monotherapy (18,19). A single arm retrospective study of patients treated with pembrolizumab suggested that patients with PD-L1 of 90–100% on TCs

may have better PFS (median 7.4 versus 3.7 months, HR 0.53, 95% CI, 0.36–0.78) and OS (median 33.6 versus 15.2 months, HR 0.41, 95% CI, 0.24–0.70) when compared to patients with PD-L1 of 50–89% on TCs (20). This brings up the possibility that patients lacking an oncogene driver with an approved targeted therapy who have PD-L1 of 50–89% on TCs may benefit more from chemo-immunotherapy and the same patient population with PD-L1 of 90–100% on TCs may benefit just as well from pembrolizumab monotherapy when compared to chemo-immunotherapy. However, in the absence of randomized data no firm conclusions can be made in this regard. High TMB when combined with PD-L1 ≥50% on TCs better predicted for benefit of nivolumab when compared to platinum-based doublets (21). It is important to evaluate further if the combination of these two markers themselves and/or combined with other predictors may better elucidate which patients with PD-L1 ≥50% should receive pembrolizumab monotherapy versus chemo-immunotherapy.

CheckMate-026 compared nivolumab to platinum-based doublets as first line therapy in patients with PD-L1 ≥5% on TCs and lacking EGFR activating mutations/ALK rearrangements. For the overall patient population on this study and in patients with PD-L1 ≥50% on TCs there was no OS benefit of nivolumab compared to platinum-based doublets (21). Cross-trial comparisons suggest much lower PFS and OS for nivolumab when compared to results of pembrolizumab in KEYNOTE-024 and KEYNOTE-042 (10,11,15,21). Reasons for the differing survival outcomes of nivolumab and pembrolizumab between these studies is not entirely clear. It is unlikely that the different PD-L1 staining assays account for these differences since their staining of TCs is similar (22). Pembrolizumab binds to a different area on PD-1 than nivolumab and this may account for some of the observed differences between these first line trials (23,24). The percentage of patients with high TMB or PD-L1 levels of ≥70%, ≥90%, etc., on KEYNOTE-024 and KEYNOTE-042 is not available, thus whether relative differences in such biomarkers could have contributed in part to the differing results between first line pembrolizumab and nivolumab is unknown.

Conclusions

KEYNOTE-024 was a groundbreaking trial that led to widespread use of pembrolizumab monotherapy as first line treatment for patients with PD-L1 ≥50% on TCs and lacking an oncogene driver for which there is an approved targeted therapy. The updated OS results presented recently by Reck *et al.* in *Journal of Clinical Oncology* have suggested a long-term OS benefit of pembrolizumab for this patient population (11). However, who within this patient population should get pembrolizumab monotherapy or pembrolizumab plus histology dependent chemotherapy is unclear. Improved single biomarkers and/or combinations of biomarkers are needed to better answer this question (19).

Acknowledgments

None.

Footnote

Conflicts of Interest: JM Pacheco: Advisory board/consulting for AstraZeneca and Novartis. Honorarium from Genentech and Takeda. Research funding from Pfizer. DR Camidge: Consulting fees from Takeda, Arrys/Kyn, AstraZeneca, Bio-Thera, Celgene, Clovis, Daiichi Sankyo, Genoptix, G1 Therapeutics, Hansoh, Hengrui, Ignyta, Lycera, Mersana Therapeutics, Novartis, Orion, Regeneron, Revolution Medicine and Roche/Genentech. Research funding from Takeda. D Gao has no conflicts of interest to declare.

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Cite this article as: Pacheco JM, Gao D, Camidge DR. Extended follow-up on KEYNOTE-024 suggests significant survival benefit for pembrolizumab in patients with PD-L1 ≥50%, but unanswered questions remain. Ann Transl Med 2019;7(Suppl 3):S127. doi: 10.21037/atm.2019.05.72

