



Pembrolizumab monotherapy in the first-line treatment of EGFR/ALK wildtype, PD-L1 tumor proportion score (TPS) 1–49%, advanced non-small cell lung cancer (NSCLC): con: “It takes two to tango”

Claire Griffiths, Smitha Menon

Medical College of Wisconsin, Milwaukee, WI, USA

Correspondence to: Claire Griffiths, MD. Medical College of Wisconsin, Milwaukee, WI, USA. Email: cgriffiths@mcw.edu.

Received: 25 September 2020; Accepted: 16 November 2020; Published: 30 December 2020.

doi: 10.21037/pcm-20-54

View this article at: <http://dx.doi.org/10.21037/pcm-20-54>

Non-small cell lung cancer (NSCLC) is a common malignancy in both men and women, and advanced disease is a leading cause of death around the world (1). For those with lung cancers that do not harbor a driver mutation rendering susceptibility to targeted therapies (e.g., EGFR and ALK mutations), treatment options were limited to chemotherapy and the prognosis was particularly grim. However, in the last 5 years, the success of immunotherapy utilizing checkpoint inhibitors has expanded treatment paradigms offering hope for many of these patients. Besides histology, PD-L1 expression in tumor cells [known as PD-L1 tumor proportion score (TPS)] is a key factor in deciding first-line treatment options for metastatic NSCLC lacking a targetable EGFR/ALK/ROS1 mutation (2) with patients divided into three groups, PD-L1 $\geq 50\%$, 1–49% and $< 1\%$. For NSCLC with a PD-L1 expression of $\geq 50\%$, PD-1 inhibition with the monoclonal antibody pembrolizumab is highly effective with a median overall survival (OS) of 30.0 months compared to 14.2 months with chemotherapy. Additionally, grade 3 or higher adverse events occurred in 53.3% of the chemotherapy group compared to 31.2% of the pembrolizumab monotherapy group (3). Hence, expert guidelines recommend pembrolizumab monotherapy as the front-line choice in metastatic NSCLC except when tumor burden is high enough or disease is progressing rapidly enough to cause early decline in functional status precluding second line chemotherapy, in which case front-line chemoimmunotherapy is preferred (4–6). Patients with NSCLC with PD-L1 expression of $\geq 50\%$ represent the minority of cases with a prevalence of only 23.2%. More

than one third of NSCLC, on the other hand, has a PD-L1 expression of 1–49% (7). Pembrolizumab monotherapy offers a tempting alternative to chemoimmunotherapy but here we present compelling evidence that chemoimmunotherapy is superior to pembrolizumab monotherapy and should be the treatment of choice in eligible patients with intermediate PD-L1 status.

Biological rationale for combination chemoimmunotherapy

Traditionally, the mechanism of action of chemotherapy was presumed to be exclusively from the inhibition of rapidly proliferating cells, thus preferentially inducing cytotoxicity against malignant cells. Recently, there is increased recognition that chemotherapy can modulate the tumor immune micro environment effecting cancer cell death using immunostimulatory mechanisms (8). Cancer cell death induced by chemotherapy leads to an abnormal accumulation of cellular and genetic material prompting pattern recognition receptors (PRRs) on antigen-presenting cells (APCs) to recognize a danger signal and recruit the adaptive immune system to enact immunogenic tumor cell death. Chemotherapeutic drugs can also interact directly with the host immune system causing lymphodepletion with subsequent immune system renewal, depletion of immunosuppressive cells [including regulatory T-cells (Treg)], and activation of immune effector cells (including cytotoxic T-lymphocytes).

Pre-clinical studies of pemetrexed, a common anti-

folate chemotherapy used in NSCLC, demonstrated that it enhanced intra-tumoral T cell immune response and these effects were amplified by combination with PD-L1 antibody (9). Pemetrexed can upregulate PD-L1 expression in tumor cells (10) and thus seems a very rational choice for combination therapy with PD-1 inhibitors. A study of blood samples from patients undergoing paclitaxel-based chemotherapy demonstrated that there is reduction of immunosuppressive Treg cells compared to other T cell subsets as well as increased activation of CD4⁺ and CD8⁺ T cells (11). Thus, chemotherapy can prime cancer cells to be more susceptible to concurrent or subsequent immune checkpoint inhibition.

Clinical results

Chemotherapy combined with pembrolizumab

Based on the above preclinical rationale, various studies have explored the efficacy of combination chemotherapy and immunotherapy. In the phase 2 KEYNOTE-021 study of treatment-naïve advanced, non-squamous NSCLC, the addition of pembrolizumab to carboplatin and pemetrexed was compared to chemotherapy alone (12). Patients with all PD-L1 categories, including non-expressors, were included, with encouraging improvement in response rates from 29% to 55% with the addition of pembrolizumab to chemotherapy. Progression-free survival (PFS) was also improved with the addition of pembrolizumab from 8.9 to 13.0 months. Additionally, the incidence of severe adverse events and treatment-related deaths was similar between the two groups. In the pembrolizumab plus chemotherapy group, response rates were similar for PD-L1 $\geq 1\%$ (54%) versus non-expressors (57%). The follow-up KEYNOTE-189 double blind phase 3 trial demonstrated an OS benefit with the addition of pembrolizumab to chemotherapy versus chemotherapy alone in this same patient population (4). At 10.8 months of follow-up, the estimated 12-month OS was 69.2% in the pembrolizumab-chemotherapy arm versus 49.4% in the placebo-chemotherapy arm. This survival benefit with the addition of pembrolizumab persisted across all PD-L1 expression categories, however, hazard ratios (HRs) progressively increased with decreasing PD-L1 expression. Based on the KEYNOTE-189 study, the FDA approved use of frontline platinum-pemetrexed-pembrolizumab for the treatment of advanced adenocarcinoma of the lung.

Subsequent to KEYNOTE-189, the KEYNOTE-407

double-blind phase 3 trial assigned 559 patients with treatment-naïve, metastatic squamous NSCLC to receive 4 cycles of chemotherapy (carboplatin plus paclitaxel or nanoparticle albumin-bound paclitaxel) plus pembrolizumab (up to 35 cycles) versus chemotherapy plus placebo (5). Like KEYNOTE-189, this study demonstrated an OS advantage with the addition of pembrolizumab to chemotherapy (15.9 versus 11.3 months, $P < 0.001$). This benefit persisted for PD-L1 non-expressors [HR 0.61, 95% confidence interval (CI): 0.38–0.98] as well as PD-L1 expression of 1–49% (HR 0.57, 95% CI: 0.36–0.90), but interestingly the significance was lost with PD-L1 high expressors (HR 0.64, 95% CI: 0.37–1.10). The HRs for PFS, on the other hand, were all statistically significant and did progressively decrease with increased PD-L1 expression.

Pembrolizumab monotherapy

In the randomized, phase 3 KEYNOTE-042 study, the use of frontline pembrolizumab monotherapy was compared to frontline platinum-based chemotherapy doublet (13). Patients enrolled to this study had EGFR/ALK wildtype, advanced NSCLC, but unlike KEYNOTE-024, patients with any PD-L1 expression (e.g., $\geq 1\%$), were randomized. Initially encouraging survival data emerged from this large ($N=1,274$) study, with 47% of the study population represented by PD-L1 high expressors (much higher than the 23.2% seen in KEYNOTE-001). For “all comers” in this study, e.g., any patient with PD-L1 expression $\geq 1\%$, the median OS in the pembrolizumab monotherapy group was 16.7 versus 13.0 months in the chemotherapy doublet arm (HR 0.81, $P=0.0018$). However, in an exploratory subgroup analysis of PD-L1 1–49% “low expressors”, this survival benefit disappeared, with median OS of 13.4 months in the pembrolizumab monotherapy group and 12.1 months in the chemotherapy doublet group (HR 0.92, 95% CI: 0.77–1.11). These OS data were generated with an average of 12.8 months of follow-up, therefore, an improved PFS benefit with immunotherapy might indicate an OS benefit with longer follow-up. However, the PFS in the PD-L1 low expression group was similarly non-significant.

Non-pembrolizumab regimens

Atezolizumab is a anti-PD-L1 antibody that has been widely studied as monotherapy as well as in combination with chemotherapy. In the IMpower 150 trial, 1,202 patients with advanced nonsquamous NSCLC were randomized to

atezolizumab combined with the chemotherapy backbone of carboplatin and paclitaxel (ACP) versus atezolizumab plus bevacizumab with chemotherapy (ABCP), or bevacizumab combined with chemotherapy (BCP) with the ABCP arm showing superior PFS (8.3 versus 6.8 months, HR 0.62, 95% CI: 0.52–0.74, $P < 0.001$) over BCP as well as improved OS (19.2 versus 14.7 months; HR 0.78, 95% CI: 0.64–0.96, $P = 0.02$) and this benefit translated to all PD-L1 subgroups (14). IMpower 130 was another study of atezolizumab in nonsquamous NSCLC with carboplatin and abraxane as the chemotherapy backbone with improvement in PFS (7.0 versus 5.5 months; HR 0.64, 95% CI: 0.54–0.77, $P < 0.0001$) as well as OS (18.6 versus 13.9 months; HR 0.79, 95% CI: 0.64–0.98, $P = 0.033$) with the addition of atezolizumab (15) across all PD-L1 subgroups. Similarly, in squamous NSCLC patients, IMpower 131 showed that atezolizumab improved PFS (6.3 versus 5.6 months; HR 0.72, 95% CI: 0.60–0.85, $P = 0.0001$), but not OS (14.2 versus 13.5 months; HR 0.88, 95% CI: 0.73–1.05, $P = 0.16$) in combination with carboplatin plus nab-paclitaxel (16). Analogous to KEYNOTE-042, IMpower 110 compared single agent atezolizumab to chemotherapy with improvement in OS in the high PD-L1 (TC3/IC3) subgroup but not in the other PD-L1 subsets but with a favorable safety profile (17).

The Checkmate 9LA trial demonstrated a similar synergism between chemotherapy and immunotherapy in metastatic NSCLC. Compared to 4 cycles of chemotherapy, 2 cycles of chemotherapy plus ipilimumab and nivolumab significantly improved OS with a HR of 0.69 (95% CI: 0.55–0.87, $P = 0.0006$) (18). This survival benefit was independent of initial tumor PD-L1 expression, highlighting the importance of chemotherapy-induced tumor cell immunogenicity.

In summary, the majority of chemoimmunotherapy trials have demonstrated clear superiority over chemotherapy with improvement of OS in the PD-L1 1–49% group. In contrast, single agent immunotherapy did not provide an OS benefit over chemotherapy in the PD-L1 1–49% group. As the comparator arm in all the trials has been chemotherapy, there has been no formal comparison between chemoimmunotherapy and immunotherapy. Pathak et al performed a network meta-analysis including 10 phase 3 randomized controlled trials (RCTs) with a total of 7,218 patients and reported that there was no OS advantage for chemoimmunotherapy over immunotherapy in the PD-L1 1–49% group (19). However, they included multiple treatment regimens in the chemo-immune-

checkpoint inhibitor (ICI) group including platinum doublets with atezolizumab, which has not shown OS benefit (16). Further, prospective data are clearly needed to determine the efficacy of pembrolizumab monotherapy versus chemoimmunotherapy in treatment naïve patients with advanced, NSCLC with PD-L1 expression of 1–49% and no EGFR/ALK mutations. The National Cancer Institute is currently recruiting patients to a phase III trial (NCT03793179) to determine the optimal sequencing of pembrolizumab monotherapy and chemoimmunotherapy, although patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of ≥ 2 are notably excluded (20).

Special considerations

Hyperprogression is a unique pattern of response seen more commonly with immunotherapy where there is a paradoxical acceleration of tumor growth during and potentially in response to cancer-directed treatment. In a multicenter cohort study of 406 patients with advanced, NSCLC receiving PD-1/PD-L1 inhibitors, Ferrara *et al.* reported a 13.8% rate of hyperprogression which was associated with a significantly worse OS when compared to disease progressing at slower rates (3.4 versus 6.2 months, $P < 0.003$). The study also evaluated 59 patients with advanced NSCLC receiving single agent chemotherapy and found that only 5.1% of these patients demonstrated hyperprogression (21). Interestingly, many of the randomized trials comparing single agent immunotherapy to chemotherapy show early worsening in the immunotherapy arm with eventual crossing over suggestive of a hyperprogressive effect (22). While the molecular and clinical factors associated with hyperprogression are not clearly defined, experts have suggested that combination chemoimmunotherapy may be an effective way to abrogate hyperprogression (22).

Additionally, in metastatic NSCLC, we would strongly advocate giving the best treatment first and not to reserve therapy. In the KEYNOTE-042 trial, 49% of the patients receiving pembrolizumab and who had progressed did not receive subsequent therapy (13). In the real world, these numbers may be even smaller with potentially only one third of patients able to get second line therapy (6).

Toxicities

While the mechanism of action of chemotherapy and immunotherapy is synergistic, fortunately, they have

minimal overlapping toxicities. KEYNOTE-407 and -189 both demonstrated an increase in efficacy without a significant increase in the overall grade ≥ 3 adverse events with the addition of pembrolizumab to chemotherapy. For example, in KEYNOTE-407, 69.8% of the patients in pembrolizumab and chemotherapy combination arm had grade 3 or higher adverse events compared to 68.2% in the chemo combination arm. However, 19.4% of participants receiving chemoimmunotherapy had to discontinue some component of their treatment due to grade 3 or higher toxicity, nearly twice the rate of discontinuation of a treatment for the same grade toxicities in the chemotherapy-placebo group (10.4%). Hepatitis occurred in 1.8% of patients receiving chemoimmunotherapy, and all cases were grade 3 or higher. This is in comparison to no patients developing hepatitis in the chemotherapy- placebo group of KEYNOTE-407, and no patients developing hepatitis in the pembrolizumab monotherapy group of KEYNOTE-024.

Similarly, in KEYNOTE-189, 67.2% of patients receiving pembrolizumab and chemotherapy experienced grade 3 or higher adverse events compared to 65.8% in the placebo combination arm. However, 20.0% of participants receiving chemoimmunotherapy had to discontinue some component of their treatment due to grade 3 or higher toxicity, nearly twice the rate of discontinuation of a treatment for the same grade toxicities in the chemotherapy group (10.9%). A unique toxicity of the pembrolizumab and pemetrexed combination is nephritis. Although kidney injury caused by pemetrexed is typically an acute tubular necrosis as compared to the acute interstitial nephritis caused by immunotherapy, the combination of these two therapies increased the rates of acute kidney injury from 0.5% in the chemotherapy-placebo arm to 5.2% in the chemoimmunotherapy arm. These rates are also higher than the rate of acute kidney injury reported in the pembrolizumab monotherapy arm of KEYNOTE-24, which was 1.9% (23).

In contrast, other chemotherapy combinations, for example platinum doublet plus bevacizumab (24), have synergism that comes with a cost of a significant increase in adverse events. Thus, compared to other chemotherapy combinations, the addition of pembrolizumab to platinum-doublet has quite a favorable benefit to risk ratio and shows improved patient reported outcomes over chemotherapy with superior quality of life scores after 21 weeks of therapy (25).

Conclusions

In summary, there is strong biologic rationale that

chemotherapy can modulate the immune system increasing tumor cell immunogenicity and rendering it more susceptible to immunotherapy. Multiple clinical trials have demonstrated the robust synergy between immunotherapy and chemotherapy with increased overall response rate (ORR), PFS and OS, while pembrolizumab monotherapy has offered no clear survival advantage over chemotherapy for treatment naïve advanced NSCLC with PD-L1 expression of 1–49%. For this group of low-expressing PD-L1 NSCLC, the immune environment of the tumor cell is relatively “cold” compared to the more immunogenic PD-L1 $\geq 50\%$ group and chemotherapy is a vital step needed to prime the response to immunotherapy. Additionally, in the real world, many advanced NSCLC patients are unable to receive second line therapy and hence, access to effective combination treatment without compromising safety is essential for improving outcomes. Therefore, we conclude that combination chemoimmunotherapy should be the first-line treatment of choice in all eligible EGFR/ALK wild type advanced NSCLC patients with PD-L1 TPS of 1–49%.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor Grace K. Dy for the series “Evidence and Controversies in the treatment of metastatic NSCLC” published in *Precision Cancer Medicine*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/pcm-20-54>). The series “Evidence and Controversies in the treatment of metastatic NSCLC” was commissioned by the editorial office without any funding or sponsorship. The authors have no other 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons

Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015.
- Hanna NH, Schneider BJ, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol* 2020;38:1608-32.
- 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.
- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:2078-92.
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;379:2040-51.
- Davies J, Patel M, Gridelli C, et al. Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced non-small cell lung cancer: A systematic review of recently published studies. *PLoS One* 2017;12:e0175679.
- Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018-28.
- Galluzzi L, Humeau J, Buqué A, et al. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol* 2020;17:725-41.
- Novosiadly R, Schaer D, Amaladas N, et al. Abstract 4549: Pemetrexed enhances anti-tumor efficacy of PD1 pathway blockade by promoting intra tumor immune response via immunogenic tumor cell death and T cell intrinsic mechanisms. *Cancer Res* 2018;78:abstr 4549.
- Lin EPY, Yang CY, Lin CW, et al. Priming PD-L1 expression by chemotherapeutic agents in non-small cell lung cancers. *J Clin Oncol* 2017;35:e20087.
- Zhang L, Dermawan K, Jin M, et al. Differential impairment of regulatory T cells rather than effector T cells by paclitaxel-based chemotherapy. *Clin Immunol* 2008;129:219-29.
- Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016;17:1497-508.
- 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.
- Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018;378:2288-301.
- West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924-37.
- Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in Combination with Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. *J Thorac Oncol* 2020;15:1351-60.
- Jassem J, Herbst RS, de Marinis F, et al. IMpower110: Clinical safety in a phase III study of atezolizumab (atezo) monotherapy (mono) vs platinum-based chemotherapy (chemo) in first-line non-small cell lung cancer (NSCLC). *J Clin Oncol* 2020;38:e21623.
- Reck M, Ciuleanu TE, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. *J Clin Oncol* 2020;38:abstr 9501.
- Pathak R, Lopes G, Yu H, et al. Comparative efficacy of chemoimmunotherapy versus immunotherapy alone in the front-line treatment of advanced non-small cell lung cancer: A systematic review and network meta-analysis. *J Clin Oncol* 2020;38:abstr 9552.
- Borghaei H. Testing the Timing of Pembrolizumab Alone or With Chemotherapy as First Line Treatment and Maintenance in Non-small Cell Lung Cancer. 2020. Available online: <https://clinicaltrials.gov/ct2/show/NCT03793179>
- Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive

- Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy. *JAMA Oncol* 2018;4:1543-52.
22. Suda K. The ABCs of preventing hyperprogressive disease after immunotherapy: awareness, biomarkers, and combination. *J Thorac Dis* 2019;11:S347-51.
 23. Dumoulin DW, Visser S, Cornelissen R, et al. Renal Toxicity From Pemetrexed and Pembrolizumab in the Era of Combination Therapy in Patients With Metastatic Nonsquamous Cell NSCLC. *J Thorac Oncol* 2020;15:1472-83.
 24. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer [published correction appears in *N Engl J Med*. 2007 Jan 18;356(3):318]. *N Engl J Med* 2006;355:2542-50.
 25. Garassino MC, Gadgeel S, Esteban E, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020;21:387-97.

doi: 10.21037/pcm-20-54

Cite this article as: Griffiths C, Menon S. Pembrolizumab monotherapy in the first-line treatment of EGFR/ALK wildtype, PD-L1 tumor proportion score (TPS) 1–49%, advanced non-small cell lung cancer (NSCLC): con: “It takes two to tango”. *Precis Cancer Med* 2020;3:33.