Editorial Commentary

Pembrolizumab plus ipilimumab or pegylated interferon alfa-2b for patients with melanoma or renal cell carcinoma: take new drugs but keep the old?

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Provenance: This is an invited article commissioned by the Guest Section Editor Tao Shi (Clinical Cancer Institute of Nanjing University, Nanjing, China).

Comment on: Atkins MB, Hodi FS, Thompson JA, *et al.* Pembrolizumab Plus Pegylated Interferon alfa-2b or Ipilimumab for Advanced Melanoma or Renal Cell Carcinoma: Dose-Finding Results from the Phase Ib KEYNOTE-029 Study. Clin Cancer Res 2018;24:1805-15.

Submitted Mar 26, 2019. Accepted for publication Apr 18, 2019.

doi: 10.21037/atm.2019.04.57

View this article at: http://dx.doi.org/10.21037/atm.2019.04.57

In the last decade, the arrival of immune checkpoint blockade (ICB) targeting the programmed death 1 (PD-1) pathway has dramatically altered the systemic treatment landscape of both metastatic melanoma (mM) and metastatic renal cell carcinoma (mRCC). Single agent ICB with pembrolizumab for melanoma, and nivolumab for both melanoma and RCC, has resulted in durable and clinically meaningful disease control with overall survival (OS) ranging from 43–55% at 2 years for metastatic mM and 35% at 3 years in mRCC (1-3). Additionally, combined ICB with the addition of ipilimumab targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway to PD-1 blockade has further increased overall response rates (ORR) and durable remissions in both diseases, albeit at the expense of increased toxicity (4,5). In mM patients, combination therapy increased ORR to 58%, which also happens to be the percent of patients alive at 3 years. However, treatment-related adverse events (TRAEs) of grade 3 or 4 occurred in 59% of patients (4). In the CheckMate 214 trial of patients with treatment naïve mRCC, the ORR in the intention to treat population was 39%, with 71% alive at 2 years, and grades 3–4 TRAEs reported in 46% (5,6).

It should come as no surprise that these two tumor types were some of the first to demonstrate benefit with this new class of immunotherapies. For decades, mM and mRCC were the original immune sensitive tumors—leading to apparent long-term remissions and even cures in select cases and in both mM and mRCC there are case reports of spontaneous remission (7-9). Once the role of cytokines was established in the 1960s and 1970s, followed by development of pharmaceutical grade products in the 1980s, there was great interest in attempting to leverage these new therapies to stimulate anti-tumor immunity. High dose interleukin-2 (IL-2) garnered Food and Drug Administration (FDA) approval in 1992 for treatment of mRCC based on pooled results from seven phase II studies (10). Long term follow-up demonstrated 7% of patients experienced a durable complete response (CR) (11). Similarly, the compilation of several trials for patients with mM led to the FDA approval of high dose IL-2 for mM in 1998, with a similar durable CR rate of 6% (10). Despite this promise, use of high dose IL-2 has been limited by its narrow therapeutic window, with eligible patients required to be young and healthy, and with treatment only available at high volume centers. Interferon-alfa (IFN-α) is another cytokine that found a niche in both diseases. High dose IFN-α was approved for use in patients with localized melanoma in the adjuvant setting based on demonstration of improved OS compared to observation, though other trials and pooled analyses only demonstrated a relapse-free survival benefit, with no effect on OS (12,13). For patients with mRCC, IFN-α became a commonly used standard of care though it never received official FDA-approval as a single agent. It was approved in combination with bevacizumab in 2009 based on the combination achieving a near doubling of the progression-

free survival (PFS), though with no improvement in OS (14). Owing to the undesirable constellation of side effects with IFN-α, a pegylated formulation (PEG-IFNα) was developed in an attempt to optimize dose and efficacy with an improved toxicity profile. A randomized trial of PEG-IFNα as adjuvant therapy for melanoma after surgery versus observation demonstrated a recurrence-free survival benefit without an OS benefit, but this led to US FDA approval (15). This drug is not used for mRCC. Taken together, these past modest successes of cytokine therapy for mM and mRCC suggested some anti-tumor efficacy, likely limited by toxicity and lack of complete understanding of the complicated cytokine/immune interplay. However, with evolution comes new promise, and there was great interest to combine the stimulatory effects of cytokine therapy with checkpoint inhibition, hoping to capitalize on two potentially complementary strategies to re-engineer the immune system to a more potent and durable anti-tumor response.

Merging the eras of immunotherapy for mM and mRCC, Atkins *et al.* recently published their trial entitled "Pembrolizumab Plus Pegylated Interferon alfa-2b or Ipilimumab for Advanced Melanoma or Renal Cell Carcinoma: Dose-Finding Results from the Phase Ib KEYNOTE-029 Study." (16). This phase I trial with planned expansions enrolled patients with mM and mRCC (any number of prior therapies for mM; at least 1 prior for mRCC; no prior immunotherapy exposure for either group) and randomized them to pembrolizumab 2 mg/kg every 3 weeks (Q3W) with either ipilimumab 1 mg/kg Q3W (times four doses) or escalating dose levels of PEG-IFNα administered subcutaneously weekly. The primary endpoints differed for the two cohorts. The goal in the pembrolizumab/ipilimumab (pembro/ipi) cohort was to determine the tolerability of the combination using ipilimumab at lower than standard doses. At the time of the design of this trial, optimal dosing of combination PD-1/CTLA-4 blockade had not yet been established for each disease. Notably, current approved dosing of combination therapy with nivolumab differs between the two malignancies, with ipilimumab at 3 mg/kg in mM but at 1 mg/kg for mRCC. For the pembro/PEG-IFNα arm, the primary endpoint was determination of the maximum tolerated dose (MTD) of PEG-IFNα. The safety and efficacy results of both dose exploration arms were reported.

While the trial design called for randomization between the two cohorts, some notable differences between the groups justify mentioning. The pembro/ipi arm had a relatively even split amongst mM and mRCC (55% and 45%, respectively), while the pembro/PEG-IFNα arm was split 29%/71% (mM/mRCC). Indirectly owing to this variance, 59% of patients in the pembro/ipi arm were treatment naïve, while only 35% in the pembro/PEG-IFNα arm were treatment naïve. Similarly, only 18% in the pembro/ipi arm received even two prior treatments, while 47% had received ≥2 prior therapies in the pembro/PEG-IFNα arm. While this trial was not designed to compare these two arms to each other, efficacy outcomes should be considered with these facts in mind. One potential reason for these differences may be that the pembro/ipi arm completed accrual in just over seven months, including the accrual of four additional patients to replace those that were not evaluable for dose limiting toxicities (DLTs). Yet, the pembro/PEG-IFNα arm took 16 months to complete accrual, which may be explained by study holds for DLT assessments prior to dose level changes. Though not discussed in the manuscript, this may be one factor affecting the differences in the treatment populations.

In the pembro/ipi arm, 6 of 19 DLT-evaluable patients experienced DLTs during cycle 1, which met the pre-specified threshold for acceptable tolerability. All but one DLT was grade 3 in severity (grade 4 lipase elevation in a patient who discontinued early for progression), and all resolved. Grades 3–4 adverse events (AEs) occurred in 59% of patients, with no treatment-related deaths, and treatment discontinuation of one or both drugs occurred in 46% of patients. Overall, this toxicity profile is comparable to what has been demonstrated in other PD-1/CTLA-4 combination studies, though not markedly improved from what might be expected with a higher dose of ipilimumab (4). In regards to efficacy, the ORR in 11 evaluable mM patients was 42% [1 CR, 4 partial responses (PRs)], and in 10 evaluable mRCC pts was reported as 30% (1 CR, 2 PRs). Responses were durable in both diseases, with median duration of response not reached in the five responding patients with mM, and 24 months in the mRCC responders.

Outcomes differed somewhat in the pembro/PEG-IFNα arm. This arm enrolled 17 total pts at two dose levels. The first three patients were enrolled to a cohort with PEG-IFNα administered at 1 μg/kg/wk and no DLTs were reported. Three more patients were enrolled to the next cohort where PEG-IFNα was administered at 2 μg/kg/wk, however two of these patients experienced a DLT. Subsequent enrollment continued at the first dose level (1 μg/kg/wk and deemed the MTD), which was completed with two further DLTs. While depression was

the only grade 3 AE reported in more than one patient, one of these patients also was reported to have had a grade 4 suicide attempt. Depression is a known potential side effect of type 1 IFNs and anti-depressants were not prescribed routinely as part of this protocol. 59% of patients had at least 1 grade 3 AE, and 47% of patients (8/17 across both dose levels) discontinued PEG-IFNα due to TRAEs. Grades 1–2 AEs including fatigue, chills, and pyrexia were relatively common. Turning to efficacy, the benefit did not seem to justify the toxicity. In the five mM patients, one had a PR for an ORR of 20%, and 2 of 12 mRCC pts achieved a PR (ORR 17%), not much different than what one might expect from pembrolizumab alone. Taken together, the authors concluded this combination did not warrant further development in either disease.

So what can we take away from this trial? The pembro/ipi combo in this small cohort produced comparable results from what has been demonstrated from nivolumab with ipilimumab in both mM and mRCC. The dose of ipilimumab used in this trial is lower than what is approved for mM, but the same as the combination dosing used for mRCC. Regardless, neither the toxicity nor the efficacy seemed to differ appreciably from approved regimens. The combination with PEG-IFNα offered a potential new combination partner, however it was clear the toxicity of this combination makes it unsuitable for further study, owing both to prevalence of low grade, nuisance toxicity that impairs quality of life, without a clear reduction in high grade AEs, and consequently many treatment-related discontinuations. The demonstrated efficacy was underwhelming, potentially limited by the high proportion of heavily pretreated mRCC patients, a group of patients not known to benefit from PEG-IFNα. An early report from a separate study combining pembrolizumab with PEG-IFNα in mM patients demonstrated a more favorable 43% ORR, so disease type does seem to matter (17). However, even in mM, any efficacy advantage of PEG-IFNα over high dose IFNα has been difficult to detect, and as this trial showed, the pegylated formulation does not abrogate toxicity. Yet, combination approaches with cytokines new and old still hold promise. For example, the PIVOT-2 trial evaluated the anti-PD-1 drug nivolumab in combination with NKTR-214 for patients with mM and mRCC, (in addition to other tumor types, NCT02983045). NKTR-214 is a prodrug of conjugated IL-2 that *in vivo* leads to slow release of IL-2 conjugates (18). In results presented at the 2018 American Society of Clinical Oncology Annual Meeting, the efficacy was very encouraging (ORR: 52% 1L mM; 54% 1L mRCC), with all responses on-going at the time of presentation, and only 11% TRAEs at the recommended phase two dose of NKTR-214 (19). Several trials in these diseases and others using NKTR-214 are on-going (NCT03635983, NCT03138889, NCT03435640). Formulations of other cytokines (IL-7, IL-10, IL-12, IL-15, IL-21, GM-CSF) combined with ICB, as single agents, or in other combinations, are in various stages of development (20,21). Time will tell whether a resurgence of cytokine therapy will prove effective in combination with modern immunotherapy like ICB.

Acknowledgments

None.

Footnote

Conflicts of Interest: M Zibelman, Scientific advisor: EMD Serono, Pfizer; Honoraria: Pfizer; Grants for Clinical Research: BMS, Pfizer, Horizon Pharma. ER Plimack, Scientific Advisor: BMS, Genentech, Incyte, Janssen, Merck, AstraZeneca, Pfizer; Grants for clinical research: Astellas, BMS, Genentech, Merck, Peloton, Pfizer.

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Cite this article as: Zibelman M, Plimack ER. Pembrolizumab plus ipilimumab or pegylated interferon alfa-2b for patients with melanoma of renal cell carcinoma: take new drugs but keep the old? Ann Transl Med 2019;7(Suppl 3):S95. doi: 10.21037/atm.2019.04.57

