Editorial

Promising results from Checkmate 012: better patients or better immunotherapy?

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Platinum-based doublet chemotherapy has traditionally been the standard of care as initial therapy in patients with advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC). However, now patients with tumors that harbor genomic abnormalities in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), or have high expression of programmed cell death 1 ligand (PD-L1) initially get non-chemotherapy approaches (1-4). Immunotherapy has emerged as a promising, new approach to cancer treatment and the US FDA has approved several immune checkpoint inhibitors (ICIs) in various malignancies. While these ICIs are promising, only inhibitors of the interaction between programmed cell death 1 (PD-1) and its ligand PD-L1 are approved outside of melanoma. Combination therapies are being pursued in an effort to increase the population of patients that may benefit from ICIs. Data from one such study was recently published in *The Lancet Oncology*, "Nivolumab plus ipilimumab as first-line treatment for advanced NSCLC (Checkmate 012): results on an open-label, phase 1, multi-cohort study". This article presents data showing a favorable toxicity profile and promising efficacy when the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor ipilimumab is administered at a frequency no greater than every six weeks along with the PD-1 inhibitor nivolumab in patients with advanced NSCLC.

The combination of nivolumab and ipilimumab represents a rational approach, as CTLA-4 regulates the early T cell activation phase in lymphoid tissue while PD-1 regulates antigen experienced T cells in peripheral and tumor tissue. Nivolumab is approved in the US following phase III trials in which nivolumab monotherapy showed superior overall survival to chemotherapy in previously treated patients with advanced NSCLC (5,6). These agents are approved together for the initial treatment of patients with melanoma, albeit with a different dose and schedule.

The Checkmate 012 trial was a phase 1, multi-cohort, multi-institutional trial in which patients with stage IIIB or IV NSCLC were randomized to receive nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab, or as monotherapy. Per clincaltrials.gov, the trial had 19 cohorts, including 10 cohorts in which ipilimumab was given with nivolumab. Eligible patients had stage IIIB or stage IV NSCLC that was chemotherapy-naïve. Patients who had previously received tyrosine kinase inhibitors were also allowed if they had completed treatment at least 2 weeks prior to randomization. Patients and investigators were not blinded to treatment regimen.

The 77 patients in the cohorts that were the focus of the publication received intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 or 12 weeks. Treatment continued until disease progression, withdrawal of consent, or intolerable toxicities. PD-L1 expression was retrospectively assessed. An additional arm in which patients received nivolumab 1 mg/kg every 2 weeks plus

ipilimumab 1 mg/kg every 6 weeks was briefly mentioned, but the authors noted that this arm was not pursued further due to suboptimal efficacy.

The combination demonstrated a confirmed objective response in 47% of patients in the ipilimumab every 12 weeks cohort and 38% in the ipilimumab every 6 weeks cohort. Median progression free survival was 8.1 months in the ipilimumab every 12 weeks cohort and 3.9 months in the ipilimumab every 6 weeks cohort. Efficacy was greatest in patients with tumors having 50% or greater PD-L1 expression, with 12 out of these 13 patients having a confirmed objective response.

Any-grade treatment-related adverse events were reported in 82% of the patients in the ipilimumab every 12 weeks cohort and in 72% of the ipilimumab every 6 weeks cohort. Grade 3–4 treatment-related adverse events occurred in 37% of patients in the ipilimumab every 12 weeks cohort and in 33% of the ipilimumab every 6 weeks cohort, with 11% of patients in the ipilimumab every 12 weeks and 13% of patients in the ipilimumab every 6 weeks cohort discontinuing study due to treatment-related adverse events. Although numerically the treatment-related adverse events were greater than in the previously published, non-randomized nivolumab monotherapy cohort of this study, the rate of treatment discontinuation was similar (7). The article acknowledges that while these cohorts compared favorably numerically to nivolumab monotherapy cohorts, the comparison is limited due to the non-randomized nature of the study.

Perspective

This article presents exciting data and suggests that the combination of nivolumab plus ipilimumab may provide significant clinical benefit for patients with NSCLC. The study does raise some concerns, however, including the potential that the excellent results could be driven largely by selection of the "best" cohorts from this multi-cohort study and/or selection of the "best" patients for those cohorts. Data on most of the ipilimumab plus nivolumab cohorts has not been published. The only cohort described in which nivolumab was given at 1 mg/kg had suboptimal efficacy, which is consistent with poor results seen when this dosage of nivolumab was given as a single agent (7,8). From the publication, we know that ipilimumab was not able to salvage an ineffective nivolumab dose.

Although the authors feel that the reported cohorts performed superiorly because the optimal dosing was found, that is not the only potential explanation. In some of the cohorts of nivolumab plus ipilimumab not discussed in the paper, a similar approach was used except ipilimumab was given every 3 weeks. Data from these cohorts has only been presented in abstract form, but generally, these cohorts with more frequent ipilimumab were associated with greater toxicity and lower efficacy (9). It is possible that after investigators struggled with toxicity in the earlier cohorts, more robust patients were enrolled in the later cohorts.

Because the best two cohorts were selected out of several similar cohorts, the results do not necessarily show that the combination therapy is responsible for more favorable outcomes. Were the patients to be divided into deciles by birthdate (36.5-day deciles), there certainly would be better and worse deciles, due to chance. Although it is reasonable to imagine that cohorts with less ipilimumab would be associated with less toxicity, an inverse relationship between ipilimumab frequency and response is not typical for the efficacy to dose relationship seen with most therapeutic agents.

The data presented in this study looks promising, but may be showing an incomplete picture of the efficacy and safety of this combination therapy. Randomized clinical studies are required to determine if the combination of nivolumab plus ipilimumab could become standard frontline therapy for patients with metastatic NSCLC. We look forward to seeing data from randomized studies of this combination that will demonstrate whether the favorable results seen in Checkmate 012 are based on superiority of the combination as opposed to some of the potential biases noted.

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Footnote

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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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