Editorial

Putting the brakes on CTLA-4 inhibition in lung cancer?

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Immune checkpoint inhibitors have fundamentally changed the treatment landscape of non-small cell lung cancer (NSCLC). Indeed, within the last 3 years, single-agent programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors have become standard therapies in both the first- and second-line settings for patients with advanced disease (1-4). Despite these advancements, however, only a minority of patients experience durable responses to PD-1 pathway inhibition. As a result, recent efforts have focused on identifying alternative immune checkpoints and combination strategies to potentiate anti-cancer immune responses.

In the manuscript accompanying this commentary, Govindan and colleagues report findings from a phase 3 study evaluating the activity of ipilimumab, a cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) inhibitor, in combination with paclitaxel and carboplatin in advanced squamous NSCLC (5). Eligible patients had recurrent or treatment-naïve stage IV squamous NSCLC. Subjects were randomly assigned in a 1:1 ratio to receive paclitaxel and carboplatin plus blinded ipilimumab 10 mg/kg or placebo every 3 weeks on a phased induction schedule that was comprised of six chemotherapy cycles, with ipilimumab or placebo administered between cycles 3 to 6. Following induction, ipilimumab or placebo maintenance was administered every 12 weeks. The primary endpoint was overall survival (OS). Of note, due to a higher than anticipated discontinuation rate of subjects prior to initiation of blinded study therapy, the primary endpoint was amended to OS in the modified intention-to-treat (mITT) population (all assigned subjects who received at least 1 dose of blinded study therapy). Importantly, in the mITT population (n=749), there was no difference in OS between study arms. Furthermore, equivocal results were seen across most pre-defined sub-groups. Secondary efficacy endpoints, including progression-free survival (PFS) and overall response rate (ORR), also did not differ between arms. Notably, there were higher rates of significant toxicity in the ipilimumab combination cohort compared with the placebo arm (grade ≥3 events, 53% *vs.* 36%, respectively), with more grade 5 events (n=7 *vs.* 1, respectively) and more patients discontinuing treatment because of toxicity (28% *vs.* 7%, respectively).

Given the above findings, the study by Govindan and colleagues raises several important questions. Most notably, why did CTLA-4 inhibition fail to improve outcomes when coupled with chemotherapy in this study? The background rationale for this combination is that cytotoxic chemotherapy may induce immunogenic cancer cell death, and checkpoint inhibition may consolidate this response by inducing long-lasting, immune-mediated tumor control (6,7). Early signals of activity from such an approach came from two randomized phase II studies of ipilimumab and chemotherapy (carboplatin/paclitaxel) in patients with treatment-naïve, advanced small cell and NSCLC, both of which demonstrated improvements in immune-related PFS with phased ipilimumab (i.e., beginning with cycle 3), but not concurrent ipilimumab (i.e., beginning with cycle 1) (8,9). Despite these promising results, however, recent confirmatory phase III studies of phased ipilimumab in combination with chemotherapy in both patient populations have been negative (5,10).

One potential explanation for these negative findings is that compared to other disease settings (e.g., advanced melanoma), the dose of ipilimumab in these studies (10 mg/kg) was too high and contributed to excess treatment-related toxicity. Indeed, Govindan *et al.* postulate that the increased toxicity and treatment discontinuation rates in the ipilimumab arm, along with corresponding reductions in exposure to chemotherapy, may have contributed to the lack of efficacy.

An alternative explanation is that the study was performed without a biomarker selection strategy. Based upon the experience with other forms of immunotherapy, it's possible that only a small subset of patients with lung cancer derive benefit from the addition of CTLA-4 inhibition to chemotherapy, but such benefit may have been obscured in an unselected patient population. For example, in melanoma, only ~10–15% of patients experience objective responses to single-agent ipilimumab (11,12). In NSCLC, the activity is likely to be even lower. Indeed, in early studies, CTLA-4 inhibitors had minimal anti-tumor activity as single agents in NSCLC (13). While chemotherapy has been hypothesized to augment this activity, it is unlikely that such benefit would extend beyond a subgroup of patients. Therefore, biomarker selection would ideally be incorporated into such trials, but unfortunately, predictive biomarkers for CTLA-4 inhibition have proven elusive to date.

Beyond toxicity considerations and the lack of an effective predictive biomarker, an additional hypothesis for the limited activity of ipilimumab in NSCLC revolves around the mechanism of action of CTLA-4 inhibition. Ipilimumab is believed to stimulate early-stage T-cell activation in the lymphoid compartment; however, this may be insufficient to generate an effective antitumor response within the tumor microenvironment. To induce the latter, stimulation of effector T-cell function within the tumor microenvironment may also be necessary (14).

When taking the above factors together, we are left with a fundamental question: is there still a place for CTLA-4 inhibition in NSCLC? While the above data by Govindan and colleagues certainly dampens enthusiasm for use of CTLA-4 inhibitors with chemotherapy, CTLA-4 inhibition may still have a role in certain settings—particularly when used in combination with other immune checkpoint inhibitors. Indeed, multiple studies evaluating combinations of CTLA-4 and PD-1 pathway inhibitors are now ongoing with the rationale that blockade of CTLA-4 may enhance early immune activation in lymphoid tissue while PD-1 inhibition may enhance tumor cell kill in the periphery (15). Thus, blockade of both CTLA-4 and PD-1/PD-L1 may produce non-overlapping effects (16). Indeed, *in vivo* studies demonstrate synergy with dual checkpoint blockade compared with either single-agent alone (17).

In the clinic, combinations of PD-1/PD-L1 and CTLA-4 inhibitors were initially explored in advanced melanoma, and initial data from Checkmate-067 was suggestive that combination therapy was destined to become the new standard of care. In this phase III trial, nivolumab 3 mg/kg alone or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg was compared to single agent ipilimumab 3 mg/kg in patients with metastatic melanoma. Despite robust PFS and ORR data (18), enthusiasm for the front-line combination has been tempered in part due to concerns regarding the tolerability of combined checkpoint blockade. For example, treatment-related grade 3 or 4 toxicity exceeded 50% with combination nivolumab and ipilimumab, and 36% of patients discontinued therapy (18). Furthermore, though the study was not powered for direct comparison of combination therapy *vs.* single-agent PD-1 inhibition, the recently published 3-year OS rates (combination therapy 58%, nivolumab alone 52%) forces clinicians to weigh the risks and benefits of dual checkpoint blockade and carefully select patients for the combinatorial approach (19).

In NSCLC, PD-(L)1 plus CTLA-4 combinations have also shown initial promise (20-22). For example, in Checkmate-012, the combination of nivolumab and ipilimumab produced objective responses in 38–47% of treatment-naïve patients, including responses among PD-L1 negative patients (22). Given the experience of such combinations in melanoma, several different doses and schedules were evaluated in Checkmate-012 in an effort to improve tolerability. Ultimately, a dose-schedule of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks was selected for further evaluation, including in an ongoing randomized phase III study (Checkmate-227; NCT02477826).

Despite the initial promising results of combined CTLA-4 plus PD-1 pathway inhibition above, enthusiasm for this strategy has been somewhat stifled more recently with a preliminary report from the phase III MYSTIC trial (23). In this randomized, open-label, global study, patients with treatment-naïve, advanced NSCLC were randomized 1:1:1 to receive the PD-L1 inhibitor durvalumab, durvalumab plus tremelimumab (a CTLA-4 antagonist), or platinum-based chemotherapy. Notably, this study failed to meet its primary endpoint of improved PFS in the durvalumab/tremelimumab arm compared to

chemotherapy among patients with high PD-L1 expression (defined as PD-L1 expression on 25% or more of their cancer cells). Data pertaining to ORR, duration of response, as well as OS of durvalumab +/– tremelimumab is pending.

CTLA-4-based combination strategies are also under investigation in small-cell lung cancer (SCLC). Interestingly, despite the high mutational burden of SCLC, single agent PD-1/PD-L1 therapy has produced ORRs of only ~10%. However, the addition of ipilimumab 3 mg/kg to nivolumab 1 mg/kg was associated with a doubling of the ORR compared to nivolumab monotherapy (24). Moreover, OS rates at 1 and 2 years were also significantly higher with the combination compared to nivolumab monotherapy (25). Importantly, and in contrast to NSCLC, PD-L1 expression did not predict for response in SCLC; however, emerging data suggests that a high tumor mutational burden (TMB) may serve as a predictive biomarker for combined checkpoint blockade in this setting (26). Further prospective validation and optimization of TMB cut-off values will be required before it is incorporated in clinical practice.

While the therapeutic landscape for patients with advanced lung cancer has evolved dramatically over the last 5 years, a majority of patients still fail to respond to immune checkpoint blockade. It is hoped that combination approaches may enhance efficacy and durability of immune-based therapies while keeping toxicity at a minimum. The important work by Govindan and colleagues (5) demonstrates that combination cytotoxic chemotherapy and CTLA-4 antagonism is not the best path forward. With this knowledge, investigators can now focus on alternative strategies, including the investigation of novel immunotherapies and new combinations.

Based upon its single-agent activity and tolerability, PD-1/PD-L1 inhibition is the logical backbone of any front-line combination strategy moving forward. It remains to be seen however whether cytotoxic chemotherapy or a second immune checkpoint inhibitor (e.g., CTLA-4 inhibitor) is the most effective and tolerable partner for PD-1 blockade. Recently, data from two randomized studies, KEYNOTE 021G and IMpower 150, demonstrated improved outcomes with PD-1/PD-L1 inhibition plus chemotherapy compared to chemotherapy alone, and one regimen (carboplatin/pemetrexed/pembrolizumab) recently gained regulatory approval in the United States for the first-line treatment of nonsquamous NSCLC (27,28). As a result, data from several ongoing phase III studies evaluating PD-1 inhibition added to platinum-based chemotherapy [e.g., KEYNOTE-189 (NCT02578680), KEYNOTE-407 (NCT02775435), Checkmate 227 (NCT02477826)] are highly anticipated. In addition, a host of clinical trials are now underway exploring various co-stimulatory, co-inhibitory, and immune-metabolic agents. While studies of these combinations mature, it appears CTLA-4 inhibition will remain in the conversion, but for how long remains unclear.

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Footnote

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