Editorial Commentary

CM227/CM9-LA: evidence supporting ipilimumab-based immunotherapy in the first-line treatment of metastatic NSCLC

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Received: 23 October 2020; Accepted: 16 November 2020; Published: 30 December 2020.

doi: 10.21037/pcm-2020-02

View this article at: http://dx.doi.org/10.21037/pcm-2020-02

Lung cancer is the second most common cancer in the United States and the leading cause of cancer death, with over 135,000 people expected to succumb by the end of 2020 (1). While this remains a deadly disease, there has been a significant expansion of the number of treatment options available to patients with metastatic NSCLC (mNSCLC) over the last 10 years. Cytotoxic chemotherapy was the standard—and only—treatment for metastatic lung cancer until the mid-2000s, with numerous drugs and combinations trialed. While these regimens improved survival, they did so at the cost of toxic side effects and long-term prognosis remained poor (2). As our understanding of cancer biology expanded during the 2000s–2010s, better drugs were added to our armamentarium with the introduction of targeted therapies for oncogene-addicted NSCLC and anti-VEGF drugs added to traditional chemotherapy. But perhaps the most significant progress in the treatment of NSCLC came with the introduction of checkpoint inhibitors into the cancer treatment landscape.

Increasing understanding of the importance of the immune system in cancer pathogenesis led to the discovery of "immune checkpoints": these inhibitory pathways were shown to be upregulated in tumors and the surrounding microenvironment, suppressing the ability of the immune system to react to and destroy cancer cells (3). Drugs targeting these pathways "take the brakes" off the immune system, allowing the body's own immune system to act. Monoclonal antibodies targeting two of these pathways, PD1/PD-L1 and CTLA-4, have revolutionized the treatment of many types of cancer, including NSCLC.

Several landmark trials were published between 2015–2017 demonstrating the efficacy of drugs targeting the PD1/PD-L1 pathway in both the refractory and the first-line setting for mNSCLC (4-9). Treatment with PD1/PD-L1 inhibitors has produced significant improvements in survival for patients when compared with chemotherapy, and a subset of patients experience remarkably prolonged remissions (5). However, many patients, especially those with tumors expressing no or low PD-L1, do not respond to anti-PD1/PD-L1 drugs. Multiple strategies have been employed to increase response rates, including combination with chemotherapy as well as other immune modulatory drugs. In that context there has been ongoing interest in the combination of PD1/PD-L1 inhibitors with the other established class of checkpoint inhibitors targeting CTLA-4.

The combination of nivolumab (anti-PD1) and ipilimumab (anti-CTLA-4) has shown remarkable success in melanoma and renal cell carcinoma (10-12). In these populations, the drugs appear to act synergistically, improving the responses seen with either drug alone (11). Early trials adding ipilimumab to chemotherapy did not demonstrate a benefit in NSCLC (13), but given successes in melanoma there has been interest in this combination as a way to increase response rates and prolong survival. Although other anti-CTLA-4/PD1 combinations have been studied (14), ipilimumab and nivolumab have demonstrated the most success. To date, several trials have explored this combination in patients with mNSCLC (15-18). Positive data from two recent trials, CheckMate 227 and 9LA, have led to the FDA approval of two regimens containing the combination of ipilimumab and nivolumab for the first-line treatment of stage IV NSCLC (16,17). A review of these results, as well as data from earlier trials, support a role for this combination in the frontline treatment of NSCLC,

even as further study may help us define which patient populations will benefit the most.

The initial trial evaluating this combination in mNSCLC was CheckMate 012, a multi-arm phase I study that included ipilimumab/nivolumab (ipi/nivo) at different dosing schedules in treatment naïve patients (15). Patients were eligible with any PD-L1 expression level and were randomized to receive three different dosing regimens of ipi/nivo. Two of these initial dosing schedules proved to be quite toxic, resulting in the addition of four more cohorts using lower doses. Of the six regimens, only two were ultimately considered suitable for further clinical development based on toxicity and efficacy results: nivolumab 3 mg/kg every 2 weeks (Q2W) given with ipilimumab 1 mg/kg at every 12 weeks (Q12W) or every 6 weeks (Q6W). A combined analysis of the 77 patients in these two cohorts demonstrated an overall response rate (ORR) of 43%. Subset analysis of patients with PD-L1 ≥1% showed an ORR of 54%, which was significantly higher than historical controls for nivolumab monotherapy in this population (26% in CheckMate 026) (19). Although the numbers were small, patients with PD-L1 ≥50% demonstrated an ORR of over 90%, again higher than historical ORR of 34% seen with nivolumab monotherapy in that population. Patients with PD-L1 <1% had a less impressive ORR of 18%. Tolerability was considerably improved with these two lower dose regimens, showing rates of grade 3–4 toxicity comparable to those seen historically with nivolumab monotherapy. This study had multiple limitations, including small sample size and lack of any randomized comparator regimens. However, these results did suggest clinical activity with the combination and potential for improved response rates over chemotherapy and checkpoint monotherapy when compared with historical controls. In addition, these results demonstrated that clinical activity could be seen at lower and more tolerable dosing regimens.

CheckMate 568 was a phase 2 study assessing safety and efficacy of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W in patients with previously untreated recurrent or mNSCLC (18). Results were similar to those seen in CheckMate 012, with overall ORR of 30% (2.4% with complete responses) and a 6-month progression free survival (PFS) of 43%. Subset analysis by PD-L1 expression showed ORR of 50% in patients with PD-L1 ≥50%, 41% for patients with PD-L1 ≥1%, and 15% for PD-L1 <1%. Responses were durable, with median duration of response not reached at a median follow up of 8.8 months. Safety profile was found to be similar to that seen in CheckMate 012, with grade 3–4 adverse events (AEs) in 29% of patients.

While the results from CheckMate 012 and 568 suggest clinical efficacy and relative tolerability, neither study compared the combination immunotherapy with other treatment regimens. CheckMate 227 and 9LA were designed to compare ipi/nivo containing regimens with platinum doublet chemotherapy in the first-line setting.

CheckMate 227 was a randomized phase 3 trial which evaluated the efficacy and safety of ipi/nivo, nivolumab monotherapy and chemo-immunotherapy compared with chemotherapy alone (*Table 1*) (16). The study was powered for evaluation of a primary endpoint of overall survival (OS) for ipi/nivo versus chemotherapy in patients with PD-L1 ≥1%, however multiple descriptive analyses of other subgroups were also performed. The study enrolled 2,876 NSCLC patients (of which 1,739 were ultimately randomized) with untreated mNSCLC and no *EGFR* or *ALK* alterations. Patients were stratified by PD-L1 expression, including 550 patients with PD-L1 expression <1% and 1,189 patients ≥1% PD-L1 expression. Patients with PD-L1 ≥1% (part 1a) were randomized 1:1:1 to receive either ipilimumab (1 mg/kg Q6W) + nivolumab (3 mg/kg Q2W), nivolumab alone, or chemotherapy (selected based on tumor histology). In the PD-L1 <1% group (part 1b), patients were randomized 1:1:1 to ipi/nivo, chemotherapy alone or nivolumab + chemotherapy. At the time of reporting, minimum follow up was 29.3 months, and patients were overall well balanced between groups.

The study met its primary endpoint, demonstrating a survival benefit for PD-L1 positive patients treated with ipi/nivo compared with those receiving chemotherapy. The median OS was 17.1 months with ipi/nivo versus 13.9 months with chemotherapy (HR: 0.73, P=0.007) and the 2-year OS was 40% *vs.* 33%, respectively. Of note, ORR was only modestly improved with ipi/nivo versus chemotherapy (35% *vs.* 30%) but there was a dramatic improvement in median duration of response (23.2 *vs.* 6.2 months). Grade 3–4 treatment related events were similar between ipi/nivo and chemotherapy (35% *vs.* 36%). Sub-group analyses showed that the benefit was maintained across most groups with a few notable exceptions: never-smokers (a group known to be less responsive to immunotherapy), older patients (>65 years) and patients with liver metastases. Subgroup analysis of patients by PD-L1 expression demonstrated that the majority of the OS benefit for PD-L1 positive patients was driven by those with PD-L1

Table 1 Summary of efficacy and toxicity in CheckMate 227*

	Combined population‡		PD-L1 ≥1%			PD-L1 ≥50%§			PDL1 <1%‡		
	N + I	CT	N + I	N‡	CT	N + I	N	CT	N + I	N + CT	CT
Median OS (months)	17.1	13.9	17.1	15.7	14.9	21.2	18.1	14.0	17.2	15.2	12.2
Median PFS (months)	5.1	5.5	5.1	4.2	5.6	6.7	5.6	5.6	5.1	5.6	4.7
ORR (%)	33.1	27.8	35.9	27.5	30	44.4	36.9	35.4	27.3	37.9	23.1
Median DOR (months)	19.6	5.8	23.2	15.5	6.2	31.8	17.5	5.8	18	8.3	4.8
TRAE (%)											
All grades	76.7	81.9	77.2	65.5	83.7	–	–	–	75.7	92.4	78.1
Grade 3–4	32.8	36.0	35.5	19.4	36.4	–	–	–	27.0	55.8	35.0

*, CheckMate 227 primary endpoint: OS for nivolumab + ipilimumab vs. CT in PD-L1 ≥1%: HR: 0.79, P=0.007. ‡, Pre-specified descriptive analyses. §, Pre-planned subset analyses. N + I: nivolumab (3 mg/kg Q2W) + ipilimumab (1 mg/kg Q6W); CT: platinum doublet chemotherapy ×4 cycles; N: nivolumab 240 mg Q2W; N + CT: nivolumab 360 mg Q3W + platinum doublet chemotherapy Q3W ×4 cycles. OS, overall survival; PFS, progression free survival; ORR, overall response rate; DOR, duration of response; TRAE, treatment related adverse events.

≥50%. In this group, the median OS was 21.2 months for ipi/nivo versus 14 months for chemotherapy. Minimal OS benefit was seen in the subgroup of patients with PD-L1 1–49%, with a hazard ratio for death of 0.94 for ipi/nivo versus chemo and a confidence interval crossing 1. These subgroup analyses should be interpreted with caution as patients in the PD-L1 ≥1% cohort were not stratified by PD-L1 expression prior to randomization, potentially leading to imbalances in the subgroups. This may explain the lack of benefit for patients with PD-L1 1–49%, despite an observed benefit in patients with PD-L1 <1% (discussed below).

In a pre-specified descriptive analysis, treatment with ipi/nivo was also compared with nivolumab monotherapy in the PD-L1 ≥1% population. The combination treatment was found to have a modest OS benefit over nivolumab alone (2-year OS of 40% *vs.* 36%), as well as increased ORR (36% *vs.* 27%). An OS benefit was seen even in patients with PD-L1 ≥50% (2-year OS of 48% *vs.* 42%), in addition to a marked improvement in the median duration of response (31.8 *vs.* 17.5 months). While treatment with ipi/nivo was generally tolerable, there were a greater number of grade 3–4 AEs for dual therapy in this population as compared with nivolumab alone (35% *vs.* 19%), the most common being rash, diarrhea and fatigue.

Several other pre-specified descriptive analyses were of interest and clinical relevance. The combination of ipi/nivo was evaluated in the PD-L1 <1% population and appeared to be superior to chemotherapy with an OS of 17.2 *vs.* 12 months (HR: 0.62) and a 2-year OS of 40% *vs.* 23%, respectively. More importantly, the ipi/nivo combination was shown to have a survival benefit when compared with nivolumab + chemotherapy (2-year OS of 40% *vs.* 34.7%), and a dramatically prolonged duration of response (18 *vs.* 8.3 months). Patients getting the ipi/nivo combination in this subgroup (PD-L1 <1%) had lower rates of grade 3–4 AEs when compared with those receiving chemo-immunotherapy and chemotherapy alone (27% *vs.* 55% and 35%).

The results from the recent CheckMate 9LA trial (*Table 2*) pre-planned interim analysis were presented at the ASCO Annual Meeting in 2020 and led to FDA approval of another ipi/nivo containing regimen for frontline mNSCLC treatment (17). In this phase 3 trial, 719 treatment naive patients with mNSCLC were randomized to combination therapy with ipilimumab (1 mg/kg Q6W) + nivolumab (360 mg Q3W) + 2 cycles of chemotherapy (determined by histology) versus chemotherapy alone. Patients were eligible to enroll with any histology or PD-L1 status. The combination of ipi/nivo/chemotherapy demonstrated a survival benefit compared to chemotherapy alone with a median OS of 14.1 *vs.* 10.7 months (HR: 0.69, P=0.0006, minimum follow up 8.1 months). This benefit was increased with longer follow up of 12.7 months (median OS 15.6 *vs.* 10.9), with a 1-year OS of 63% for ipi/nivo/chemo *vs.* 47% for chemo alone. Subgroup analyses showed similar magnitude of benefit across patients regardless of PD-L1 status and histology. Two subgroups did not seem

Table 2 Summary of efficacy and toxicity in CheckMate 9LA[†]

	Combined population		PD-L1 ≥1%[§]		PD-L1 ≥50%[§]		PDL1 <1%[§]	
	N + I + CT	CT	N + I + CT	CT	N + I + CT	CT	N + I + CT	CT
Median OS (months)	15.6	10.9	15.8	10.9	18	12.6	16.8	9.8
Median PFS (months)	6.7	5.0						
ORR (%)	38	25						
Median DOR (months)	11.3	5.6						
TRAE (%)								
All grades	92	88						
Grade 3–4	47	38						

[†], CheckMate 9LA primary endpoint: OS for nivolumab + ipilimumab + CT vs. CT (at pre-planned interim analysis): HR: 0.69, P=0.006. [§], Pre-planned subset analyses. N + I + CT: nivolumab 360 Q3W + ipilimumab 1 mg/kg Q6W + platinum doublet chemotherapy Q3W ×2 cycles; CT: platinum doublet chemotherapy ×4 cycles. OS, overall survival; PFS, progression free survival; ORR, overall response rate; DOR, duration of response; TRAE, treatment related adverse events.

to benefit from the combined regimen: never smokers and patients older than 75. Grade 3–4 treatment related adverse events (TRAEs) were more common in the combination group (92% *vs.* 88%) as was discontinuation due to toxicity (19% *vs.* 7%), though it should be noted that patients were generally treated for longer duration with the ipi/nivo combination than with chemo (median of 6.1 *vs.* 2.4 months).

There is currently a wide array of regimens approved for the first-line treatment of mNSCLC (*Table 3*). The accumulation of data shows that the combination of ipilimumab and nivolumab has good clinical activity with the potential for durable response in patients with mNSCLC. Although toxicity is limiting at higher doses of ipilimumab, lower dose regimens of ipi/nivo appear to be more tolerable (though toxicity is increased compared to checkpoint monotherapy). All of the currently approved regimens for initial treatment of NSCLC have demonstrated benefit versus chemotherapy but no trial has yet demonstrated superiority of any regimen over another in a head to head comparison. Results from ongoing studies will likely provide additional insights, but for now clinicians must make nuanced decisions based on multiple patient- and disease-related factors when selecting the initial treatment for patients with mNSCLC.

Data from the previously discussed trials suggest that the combination of ipilimumab and nivolumab improves ORR and duration of response, providing a survival benefit in patients with PD-L1 expression ≥1% and <1%. The data suggest that even patients with PD-L1 ≥50% may benefit from the addition of ipilimumab in frontline regimens, though the use of single-agent checkpoint inhibitor therapy may be sufficient for this population. For a young and otherwise healthy patient in whom an aggressive approach is desired, the use of an immunotherapy combination may improve the chance of a prolonged response compared with checkpoint inhibitor monotherapy or chemo-immunotherapy. These combination regimens may have an even more important clinical role in patients with low or absent PD-L1 expression; these patients have fewer treatment options, and are less likely to see prolonged and durable responses with current checkpoint inhibitor regimens, including single-agent immunotherapy and chemo-immunotherapy combinations. While ORR was still generally low in PD-L1 negative patients across these trials, CheckMate 227 showed that patients with PD-L1 <1% had a dramatically improved duration of response compared with chemotherapy and even chemo-immunotherapy, as well as the suggestion of improved OS (though the study was not powered for this analysis). Currently the CheckMate 227 regimen is approved only for PD-L1 positive patients, but the CheckMate 9LA regimen could provide a dual immunotherapy option for PD-L1 negative patients that are able to tolerate the 4-drug regimen.

Other populations may also benefit from the addition of ipilimumab to PD1 inhibitor monotherapy or chemo-immunotherapy. The approval of ipi/nivo provides a first-line treatment option for patients with PD-L1 1–49% who may not be good candidates for chemotherapy

Table 3 FDA approved immunotherapy containing regimens for the first-line treatment of mNSCLC without alterations in *EGFR* or *ALK*

Histology	PD-L1 ≥50%	PD-L1 ≥1%	PD-L1 <1%
Non-squamous	Carboplatin/pemetrexed + pembrolizumab[1]	Carboplatin/pemetrexed + pembrolizumab[1]	Carboplatin/pemetrexed + pembrolizumab[1]
	Carboplatin/paclitaxel + bevacizumab + atezolizumab[2]	Carboplatin/paclitaxel + bevacizumab + atezolizumab[2]	Carboplatin/paclitaxel + bevacizumab + atezolizumab[2]
	Carboplatin/nab-paclitaxel + atezolizumab[3]	Carboplatin/nab-paclitaxel + atezolizumab[3]	Carboplatin/nab-paclitaxel + atezolizumab[3]
	Nivolumab/ipilimumab + platinum doublet[4]	Nivolumab/ipilimumab + platinum doublet[4]	Nivolumab/ipilimumab + platinum doublet[4]
	Pembrolizumab[5]	Pembrolizumab[6]	
	Nivolumab/ipilimumab[7]	Nivolumab/ipilimumab[7]	
	Atezolizumab[8]		
Squamous	Carboplatin + (paclitaxel or nab-paclitaxel) + pembrolizumab[9]	Carboplatin + (paclitaxel or nab-paclitaxel) + pembrolizumab[9]	Carboplatin + (paclitaxel or nab-paclitaxel) +pembrolizumab[9]
	Nivolumab/ipilimumab + platinum doublet[4]	Nivolumab/ipilimumab + platinum doublet[4]	Nivolumab/ipilimumab + platinum doublet[4]
	Pembrolizumab[5]	Pembrolizumab[6]	
	Nivolumab/ipilimumab[7]	Nivolumab/ipilimumab[7]	
	Atezolizumab[8]		

[1], KEYNOTE-189; [2], Impower150; [3], Impower130; [4], CheckMate 9LA; [5], KEYNOTE-024; [6], KEYNOTE-042; [7], CheckMate 227; [8], Impower110; [9], KEYNOTE-407. mNSCLC, metastatic NSCLC.

due to certain comorbidities or preferences. While pembrolizumab monotherapy is technically approved in these patients on the basis of Keynote 042, much of the benefit in that trial was derived from patients with higher PD-L1 expression (5). Further study may define other subgroups that are likely to specifically benefit from a combination immunotherapy option—for instance the subgroup analysis of CheckMate 9LA showed patients with CNS metastases seemed to derive particular benefit. In this age of increasingly personalized cancer therapy, the future may see additional biomarkers that will be able to predict which patients are most likely to benefit from ipi/nivo combination regimens.

Despite the numerous advances in treatment for mNSCLC, it remains a devastating disease with a poor long-term prognosis for most patients. As our knowledge of cancer biology has grown, it has become increasingly apparent that no single treatment will be appropriate for all patients. An increasing array of options at our disposal will benefit patients as we move towards more individualized cancer treatment. There is certainly space for the use of these newly approved ipilimumab containing regimens, and they will be the appropriate initial treatment for a subset of the many patients diagnosed with mNSCLC each year. Further study will hopefully help us define which patients will benefit the most.

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-2020-02). The series "Evidence and

Controversies in the treatment of metastatic NSCLC" was commissioned by the editorial office without any funding or sponsorship. SBG reports grants and personal fees from AstraZeneca, and Boehringer Ingelheim, as well as personal fees from Bristol-Myers Squibb, Eli Lilly, Genentech, Amgen, Spectrum, Blueprint Medicine, Sanofi Genzyme, and Daiichi-Sankyo, outside the submitted work. 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.

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doi: 10.21037/pcm-2020-02
Cite this article as: Collier EF, Goldberg SB. CM227/CM9-LA: evidence supporting ipilimumab-based immunotherapy in the first-line treatment of metastatic NSCLC. Precis Cancer Med 2020;3:34.