Lung Cancer: Targets and Therapy

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COMMENTARY

The Additional Exclusions of *ROS1* Fusions (In Addition to *EGFR* Mutation and *ALK* Fusions) in the Cemiplimab NSCLC FDA Indication (EMPOWER-Lung 1 and -Lung 3). Catching Up with Current Scientific View of Immunotherapy in Never-Smoker Predominant Actionable Driver Mutation Positive NSCLC?

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Abstract: Cemiplimab is one of seven immune checkpoint inhibitors (ICIs) approved for the first-line (1L) treatment of advanced NSCLC in the US based on EMPOWER-Lung 1 and -Lung 3 trials. In addition to exclusion of NSCLC patients harboring *EGFR* mutations and *ALK* fusion from 1L treatment with ICIs, exclusion of *ROS1* fusion is an additional unique exclusion the use of criterion for cemiplimab in the US FDA indication based on the design of the EMPOWER lung trials. We review the effectiveness of ICIs in never-smoker predominant NSCLC with driver mutations (*EGFR, ALK, ROS1, RET, HER2*) and question whether exclusion of *ROS1* fusion would put cemiplimab at a competitive disadvantage given the requirement for insurance to prove *ROS1* fusion negativity. We further discuss whether the US FDA as a regulatory authority has the right and responsibility to harmonize the use of ICIs in these actionable driver mutations to standardize community practice for the benefit of patients and to advance the development of next-generation treatment for these driver mutations.

Keywords: cemiplimab, immunotherapy, actionable driver mutation, ROS1 fusion

Introduction

As of March 2023, there are seven immune checkpoint inhibitors (ICIs) approved in the United States (US) for the first-line (1L) treatment of advanced or metastatic non-small cell lung cancer (NSCLC). These ICIs include pembrolizumab (Keynote [KN]-024, KN-042, KN-189, and KN-407),[1–4] atezolizumab (IMpower-110, −130, −150),[5–7] cemiplimab (EMPOWER-Lung-01, −03),[8,9] nivolumab + ipilimumab (without or witho chemotherapy (Checkmate [CM CM-227, CM-9LA] respectively),[10,11] and durvalumab + tremelimumab with chemotherapy (POSEIDON)[12] based on 12 positive pivotal randomized Phase 3 clinical trials (Table 1).

Some of the ICIs approvals rely on the level of PD-L1 expression while some are histology-specific. Some of the regimens are ICI monotherapy, combination ICIs, ICI in addition to chemotherapy or all (Table 1). As presented in Table 1, there is substantial overlap in the indications especially among NSCLC regardless of histology thus medical oncologists have many treatment options. Uniform among indications for all regimens is that NSCLC patients with

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Table 1 Approved ICI Regimens in the US for 1st-Line Treatment of Advanced NSCLC by Histology and PD-L1 Expression

		NSCLC			Non-Squamous NSCLC			Squamous NSCLC		
		< 1%	1–49%	≥50%	< 1%	1–49%	≥50%	< 1%	1–49%	≥50%
Pembrolizumab (± chemotherapy)										
Regimen	Keynote-024		■	■						
	Keynote-042			■						
	Keynote-189				■	■	■			
	Keynote-407							■	■	■
Atezolizumab (± chemotherapy)										
Regimen	IMpower-110			■						
	IMpower-130				■	■	■			
	IMpower-150				■	■	■			
Cemiplimab (± chemotherapy)										
Regimen	EMPOWER-Lung 1			■						
	EMPOWER-Lung 3	■	■	■						
Nivolumab + Ipilimumab (± chemotherapy)										
Regimen	Checkmate-227		■	■						
	Checkmate-9LA	■	■	■						
Durvalumab + Tremelimumab (+ chemotherapy)										
Regimen	POSEIDON	■	■	■						

Note: ■ Approved by US FDA.
Abbreviation: ICI, immune checkpoint inhibitor.

activating epidermal growth factor receptor *(EGFR)* mutations (*EGFR*+) and anaplastic lymphoma kinase *(ALK)* fusions (*ALK*+) were excluded (not indicated by US package insert). Additionally, unique to cemiplimab usage included an addition exclusion of ROS proto-oncogene 1 *(ROS1)* fusions (*ROS1*+) based on the designs of EMPOWER-Lung trials. This editorial focuses on the implication of this unique *ROS1*+ exclusion for cemiplimab and the deeper role of efficacy and use of immunotherapy in never-smoker predominant driver mutation positive NSCLC.

Primary Data of EMPOWER-Lung 1 and -Lung 3

The exclusion of *ROS1* fusions in the indication of cemiplimab is due to the design of EMPOWER-Lung-01 and −03 trial both excluding *ROS1*+ NSCLC patients in addition to standard exclusions of *EGFR*+ and *ALK*+ NSCLC patients common to all other 10 chemotherapy regimens.[13] The Food and Drug Administration (FDA) approved cemiplimab monotherapy in PD-L1 ≥ 50% on February 22, 2021 based on the EMPOWER-Lung 1 trial (NCT03088540).[8] NSCLC patients with PD-L1 expression ≥ 50% (N = 710) were randomized 1:1 to either cemiplimab 350 milligrams (mg) intravenously every 3 weeks versus platinum-based chemotherapy. Primary outcomes were progression-free survival (PFS) and overall survival (OS) assessed by blinded independent central review (BICR). Overall, cemiplimab demonstrated statistically significant improvement in median OS at 22.1 months (95% confidence interval (CI): 17.7 to not reached) for patients receiving cemiplimab compared with 14.3 months (95% CI: 11.7–19.2) in the platinum chemotherapy arm (HR = 0.68; 95% CI: 0.53–0.87, p=0.0022). Median PFS per BICR assessment was also statistically significantly improved at 6.2 months (95% CI: 4.5–8.3) verses 5.6 months (95% CI: 4.5–6.1) in the cemiplimab and

chemotherapy arms, respectively (HR = 0.59; 95% CI: 0.49, 0.72, p<0.0001). The authors found overall response rate (ORR) of 37% (95% CI: 32–42) treated with cemiplimab and 21% (95% CI: 17, 25) treated with chemotherapy.

Subsequently, FDA granted approval for chemotherapy + cemiplimab on November 22, 2022 based on EMPOWER-Lung 3 trial.[9] Four hundred sixty-six NSCLC patients were randomized in a 2:1 assignment to either cemiplimab plus platinum-based chemotherapy every 3 weeks for a total of 4 cycles followed by cemiplimab plus maintenance chemotherapy or placebo plus platinum-based chemotherapy every 3 weeks for a total of 4 cycles followed by placebo and maintenance chemotherapy. The primary outcome was OS with secondary outcomes of PFS and ORR as assessed by BICR. In the most recent update of June 14, 2022, data cut-off, the median duration of follow-up for the study was 28.4 months (interquartile range [IQR]: 26.0–31.0): 28.3 months (IQR: 25.9–31.1) in the cemiplimab plus chemotherapy arm and 28.7 months (IQR: 26.2–31.0) in the placebo plus chemotherapy arm. Median OS with the cemiplimab combination was 21.1 months (95% CI: 15.9–23.5) versus 12.9 months (95% CI: 10.6–15.7) with chemotherapy alone (HR = 0.65; 95% CI: 0.51–0.82; P=0.0003). Patients with squamous (SqCC) NSCLC (n=200) demonstrated a 2-year median OS of 22.3 months (95% CI: 15.7–27.2) with the cemiplimab plus chemotherapy versus 13.8 months (95% CI: 9.3–18.0) with chemotherapy alone (HR=0.61; 95% CI: 0.42–0.87). Importantly with longer follow-up time, the OS was significantly improved further than the outcomes observed at the initial time of data presentation. The median OS for non-SqCC histology was 19.4 months (95% CI: 14.0–23.5) with cemiplimab plus chemotherapy versus 12.4 months (95% CI: 10.1–16.1) with chemotherapy alone (HR = 0.64; 95% CI: 0.47–0.88).[14] In the cemiplimab plus chemotherapy group, median PFS was 8.2 months (95% CI: 6.4–9.0) versus 5.5 months (95% CI: 4.3–6.2) with chemotherapy alone (HR = 0.55; 95% CI: 0.44–0.68; P<0.0001). When analyzed by independent central review, the ORR was 43.6% (95% CI: 38.0–49.3) in the cemiplimab plus chemotherapy group versus 22.1% (95% CI: 15.8–29.5) in the chemotherapy alone group (P<0.0001). The most common associated with cemiplimab (≥15% of participants) adverse events include alopecia, musculoskeletal pain, nausea, fatigue, peripheral neuropathy, and decreased appetite.

Actionable Driver Mutation in NSCLC Associated with Never-Smokers

Many actionable driver mutations are associated with never-smoking status such as *EGFR* mutations (del19, L858R, exon 20 insertions, L861, S761, G719X), human epidermal growth factor receptor 2 *(HER2)* exon 20 insertions, and the three major receptor tyrosine kinase fusions (ALK, ROS1, RET [rearranged during transfection]).[15] A large-scale global retrospective analysis of ICIs in never-smoker associated actionable driver mutations indicated that ICIs have minimal activity in this setting.[16]

Discussion Point 1. Reviewing the Evidence of ICI in *EGFR*+ NSCLC, the Most Common Canonical Actionable Driver Mutation Associated with Never-Smokers

The most common never-smoker associated actionable driver mutation in NSCLC are the canonical *EGFR* mutations (deletion 19 and L858R). There is now ample evidence from small scale to randomized phase 3 trial that indicated ICI alone or with chemotherapy has minimal activity in *EGFR*+ NSCLC with no statistical improvement in PFS or OS.[17–20] While much less has been reported on the efficacy of ICI in *EGFR* exon 20 insertion *(EGFRex20ins)* mutations, patient characteristics are similar to patients with canonical *EGFR* mutation.[21,22] Thus, it is generally accepted that *EGFRex20ins* will respond minimally to ICI similar to the canonical *EGFR* mutations.[23] A series of 36 *EGFRex20ins* patients showed ORR 25% treated with ICI compared to 0% with classic mutations.[23] Similarly, PFS with ICI was 2.9 months in *EGFRex20ins* verses 1.9 months with classic *EGFR* mutations. Indeed the pivotal registration trials in the first-line setting, of the two drugs approved for treatment of *EGFRex20ins*, platinum-based chemotherapy is the standard comparison arm not combination of chemotherapy and ICI. For mobocertinib (TAK-788), the pivotal trial (EXCLAIM-2, NCT04129502) is comparing mobocertinib to platinum-based chemotherapy. For amivantamab, the pivotal trial is comparing platinum-based chemotherapy with or without amivantamab (PAPILLON, NCT04538664).

Discussion Point 2. Does Pembrolizumab, Atezolizumab, Nivolumab + Ipilimumab, and Durvalumab + Tremelimumab Work in *ROS1*+ NSCLC That By FDA Indication Cemiplimab Does Not?

While this seems like a rhetorical question, it is generally believed there is really no discernable difference in efficacy among the current PD-1 and PD-L1 inhibitors in NSCLC. Thus, we would anticipate the six other ICIs would have minimal efficacy in *ROS1*+ NSCLC. There is much less literature on the role of ICIs in *ROS1*+ NSCLC. From the 7 *ROS1*+ NSCLC patients in the immunotarget database,[16] only 1 (16.7%) out of 7 patients had responded to ICI therapy. It is generally assumed that oncologist would not prescribe ICIs for *ROS1*+ NSCLC patients. Nonetheless, the lack of specific FDA exclusion of other ICIs in *ROS1*+ NSCLC and the absence of negative efficacy data, the exclusion of cemiplimimab may paradoxically encourage a minority of oncologists to try ICIs other than cemiplimab in *ROS1*+ NSCLC.

Discussion Point 3. What is the Implication of Additional Exclusion of *ROS1* Fusion in Order to Use Cemiplimab? Good Science but Bad Business?

Insurance companies in the US are increasingly requesting negative *EGFR* mutation and *ALK* fusion results before authorizing the use of ICIs as 1L treatment for NSCLC especially if it is combined with chemotherapy or double ICIs + chemotherapy. Although next-generation sequencing or at least multiplex sequencing platforms commonly used to molecularly profile NSCLC will include *ROS1* fusion detection, the requirement to submit a *ROS1* fusion negative report can be a detriment for the use of cemiplimab in many regions of the world where only *EGFR* mutation by polymerase chain reaction (PCR), *ALK* fusion by Immunohistochemistry (IHC), and PD-L1 expression by IHC were performed. While we agree ICI regimens should not be used as 1L treatment of *ROS1*+ NSCLC, we think the additional requirement of a negative *ROS1* fusion test will dissuade oncologists to order cemiplimab in a treatment landscape where there are well-established and entrenched leaders, such as pembrolizumab. Paradoxically, this may dissuade pharmaceutical sponsors in the future to exclude additional molecular subtypes of NSCLC beyond *EGFR*+ and *ALK*+ NSCLC that clearly will not benefit from ICI and set the treatment of NSCLC backwards if FDA follow its traditional approval pathway of how the sponsor designed the trial.

Discussion Point 4. What is the Role of Immunotherapy in RET Fusion-Positive (*RET*+) NSCLC?+

NSCLC with *RET* fusion is one of the three most common receptor tyrosine kinases (RTKs). Like *ALK* and *ROS1* fusions, the majority of *RET*+ NSCLC patients are never-smokers.[24] The limited evidence of ICIs in *RET*+ NSCLC was also from the immunotarget database where the 1 out of 16 (6.3%) *RET*+ NSCLC patients responded to ICI therapy.[16] Currently, there are two pivotal randomized trials comparing the approved RET TKIs, selpercatinib (LIBRETTO-431, NCT04194944) and pralsetinib (AcceleRET-Lung, NCT04222972) to platinum-based chemotherapy with or without pembrolizumab per investigator choice. Thus, the optional inclusion of pembrolizumab into platinum-based chemotherapy indicates the existence of equipoise of the efficacy of adding ICI to chemotherapy in *RET*+ NSCLC. The results of these two trials will go a long way to address the role of ICI in *RET*+ NSCLC.

Discussion Point 5. What is the Role of ICIs in HER2 Exon 20 Insertion Positive (*HER2*+) NSCLC?

Similarly, *HER2* exon 20 insertion (*HER2ex20ins*) is another rare but actionable driver of mutation that has now FDA approved therapy with trastuzumab deruxtecan.[25] Efficacy of ICI in *HER2ex20ins* is limited.[26,27] Of the 91 patients with various *HER2* mutations, 52 (57%) were never-smokers. Response of *HER2ex20ins* were examined in the pivotal randomized trial comparing trastuzumab deruxtecan to chemotherapy + ICI based on Keynote-189, which included pembrolizumab (DESTINY-Lung-04, NCT05048797). The chemotherapy regimen did not allow opting out of pembrolizumab. Hence the results of DESTINY-Lung-04 will help us understand any additional efficacy conferred by ICI with

comparison to historic results of chemotherapy in likely actionable driver mutation positive NSCLC, but definitive will add toxicities. In this case, the sponsor took the conservative approach and the widely used the standard of care chemotherapy plus ICI regimen (Keynote-189 which only excluded *EGFR*+ and *ALK*+ NSCLC) for the comparison arm.

Discussion Point 6. What is the Role of ICI in *METex14* Splice Site Mutation Positive NSCLC, *BRAF* V600E Positive NSCLC, and *KRAS* G12C+ NSCLC?

Not all actionable driver mutation positive NSCLC are found predominantly in never-smokers. In the FDA approval summary of capmatinib and tepotinib, two specific MET TKI approved for treatment of *METex14*+ NSCLC, 40% (39/97) of the capmatinib patients reported smoking history and 50% (76/152) of the tepotinib patients were ever-smokers.[28] In the FDA approval summary of dabrafenib with or without trametinib for the treatment of *BRAF* V600E mutated NSCLC, 72.2% (143/198) of the *BRAF* V600E+ NSCLC patients were ever-smokers. In the FDA approval of sotorasib for *KRAS* G12C+ NSCLC, only 4.8% (6/126) of the sotorasib-treated *KRAS* G12C+ NSCLC were never-smokers. Similarly, only 4.3% (5/116) of the adagrasib-treated *KRAS* G12C+ NSCLC were never-smokers. Thus, a large percentage of these driver mutation positive NSCLC would likely respond to ICI monotherapy or in combination with chemotherapy.

Discussion Point 7. The Use of ICI is Not Prohibited in Resected Early or Locally Advanced NSCLC

The current US FDA indication for the use of ICI as monotherapy as adjuvant treatment for early-stage NSCLC after surgical resection based on IMpower-010[29] and Keynote-091[30] or as consolidation therapy after definitive chemoradiation based on results of the PACIFIC trial[31] did not exclude *EGFR*+ or *ALK*+ NSCLC. Subgroup analysis of all three trials did not show any disease-free survival (DFS) benefit[29–31] or OS)[32] for *ALK*+ NSCLC. Subgroup analysis also did not show any DFS benefit for *EGFR*+ NSCLC for two of the three trials[29,31] and no OS benefit for *EGFR*+ NSCLC.[32] Indeed, further subgroup analysis of PACIFIC and other regional practice further confirmed consolidation ICI (durvalumab) did not improve OS.[33,34] Thus, because FDA approval of any indication is only based on totality of that specific trial overall primary endpoint (not exclusion negative subgroup in positive or approving positive subgroup in a negative trial) result without consideration of existing scientific observations, the "non-exclusion" of ICI in the adjuvant treatment in early and maintenance treatment of locally advanced stage two most common driver mutation positive NSCLC is confusing and contradictory.

Discussion Point 8. Should the FDA Harmonize the Exclusion of ICI to a Set of Driver-Mutation Positive NSCLC Found Primarily in Never-Smokers Regardless of Stage Rather Than Let Sponsor Defined What Driver Mutation to Be Excluded and at What Stage?

At the time the EMPOWER-Lung trials initiated, the majority of data suggested ICIs are ineffective against never-smoker predominant driver mutation positive NSCLC. However, the cemiplimab *ROS1*+ NSCLC exclusion has inadvertently created a two-tier system for clinical use.

The remaining six ICI agents did not have *ROS1*+ NSCLC as an exclusion criterion for use. However, we doubt seasoned medical and thoracic oncologists will use ICI alone, ICIs in combination, chemo + IO, or chemo + ICI+ ICI in *ROS1*+ NSCLC. There exists clear evidence from published literature that ICI does not work on many of the established driver-mutation positive NSCLC (*EGFR, ALK, ROS1*). Nevertheless, without explicit FDA prohibition against the other six ICIs in *ROS1*+ NSCLC, less experienced medical professionals may consider their use in *ROS1*+ NSCLC without evidence of benefit. Furthermore, this prohibition is not extended to earlier stage NSCLC. It is hard to imagine that if ICI is generally not considered effective in stage 4, that the use of ICI is not excluded for use in earlier stage NSCLC especially the overwhelming evidence argues against any significant efficacy by subgroup analysis.

Concluding Remarks

We wrote this editorial fully understanding that FDA approval of each indication depends on the overall design of the trial based on intention to treat patient population. Given both positive EMPOWER lung trials excluded *ROS1*+ NSCLC in addition to *EGFR*+/*ALK*+ NSCLC, cemiplimab indication in the US carries the exclusion of *ROS1*+ NSCLC in addition to *EGFR*+/*ALK*+ NSCLC. However, we also question if specific exclusion of *ROS1* fusion from cemiplimab indication may paradoxically encourage some oncologists to use the other six ICIs in *ROS1*+ NSCLC because no such prohibition existed for *ROS1*+ NSCLC for these six other ICIs (pembrolizumab, nivolumab, atezolizumab, durvalumab, ipilimumab, and tremelimumab) although there is no reason to believe any of the six ICIs would have appreciable efficacy in *ROS1*+ NSCLC. From a marketing standpoint, having to provide an additional negative molecular profiling test may be a "bridge too far" for cemiplimab especially if molecular profiling is done sequentially first with *EGFR* mutation followed by *ALK* or a small multiplex approach with IHC for PD-L1 and *ALK* and RT-PCR for *EGFR* mutations. Although this exclusion may seem like a minor difference in the overall drug indication between cemiplimab and the other six ICIs, it may muddle the tremendous advances in NSCLC by creating two "classes" of ICIs in the treatment of *ROS1*+ NSCLC. Worse, it may give the impression to some oncologists that is OK to use other ICIs in *ROS1*+ NSCLC but is likely ineffective. Thus, FDA should consider standardization the indication of ICIs in never-smoker predominant driver-mutation-positive NSCLC, such as *ROS1*+ NSCLC where currently registration trials for next-generation ALK TKIs.

Disclosure

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