

## Immunotherapy in Nonsmall Cell Lung Cancer (Basket of Choices)

### Abstract

The advent of immunotherapy has changed the landscape of lung cancer management over the past few years. Once a uniformly fatal disease with limited therapeutic options, the physicians now have a myriad of options to choose from while offering therapy to a patient of metastatic nonsmall cell lung cancer.

**Keywords:** Atezolizumab, checkpoint inhibitors, chemotherapy, nonsmall cell lung cancer, PDL1 testing, pembrolizumab

### Courting Controversy: Right Choice of Therapy for Metastatic Non-Small Cell Lung Cancer

The index patient is a 45 year old, male, smoker, with no comorbidities except well-controlled diabetes mellitus, who presented with cough with hemoptysis. Clinical examination was nonproductive; however, chest X-ray revealed blunting of left costophrenic angle. Computed tomography (CT) scan and later positron emission tomography scan revealed an evidence of 4 cm left lower lobe mass, 4 liver metastases (largest being 3 cm in size), multiple left-sided pleural nodules, and mild pleural effusion. VATS-guided biopsy was positive for adenocarcinoma. Tumor genomic testing was negative for targetable EGFR, ALK, ROS, MET, and BRAF alterations. All blood tests were found to be within normal limits, except for mild elevation of alkaline phosphatase. PDL1 testing with PD-L1 22C3 pharmDx as well as SP142 assay, both reveal >90% positivity in tumor cells. The patient is well educated and requests to offer him the best possible treatment that can maximize his overall survival (OS) with least possible side effects and disruption of his quality of life. The patient is reimbursable and can afford all treatments.

After carefully considering his requests, you decide to offer him:

- Paclitaxel, platinum, atezolizumab, and bevacizumab
- Single-agent pembrolizumab
- Pemetrexed, platinum, pembrolizumab
- Pemetrexed, platinum, atezolizumab
- Nab-paclitaxel, platinum, atezolizumab
- Any other.

I would offer this patient a single-agent pembrolizumab keeping in mind the histology, PDL1 status, age, performance status, site of metastases, survival estimates, and expected side effects of therapy. All of the options given are effective therapies for patients of metastatic nonsmall cell lung cancer (NSCLC). This highlights the revolution brought about by immunotherapy in the management of NSCLC in the last decade. Historically, patients of metastatic NSCLC without actionable target mutations were treated with platinum-based combination chemotherapy with median progression-free survival (PFS) and OS not exceeding 9–12 months. The development of checkpoint inhibitors and companion diagnostic tests has changed the landscape of metastatic NSCLC management, and I have a big basket to choose from when offering therapy. I will try to rationalize my choice in the paragraphs below using the available data.

Approximately 23%–28% of advanced NSCLC patients have a high PDL1 expression (defined as membranous PDL1 expression on 50% or more tumor cells, regardless of intensity of expression).<sup>[1]</sup> Pembrolizumab is a highly selective humanized anti-PD1 molecule which is now an Food and Drug

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Administration-approved therapy as a single agent for advanced NSCLC with PDL1 tumor proportion score of 50% or higher.<sup>[2]</sup> Keynote-024 study showed a superior OS, PFS, and overall response rates (ORRs) of single-agent pembrolizumab over platinum-based chemotherapy as shown in Table 1.<sup>[3,4]</sup> The updated analysis for OS showed that the benefit was maintained, despite significant crossover (approximately 54% of chemotherapy arm patients received pembrolizumab at progression).<sup>[4]</sup>

Pembrolizumab has also been studied in combination with chemotherapy for the treatment of PDL1 unselected advanced nonsquamous NSCLC in Phase 3 KEYNOTE-189 study.<sup>[5]</sup> It also demonstrated superior OS and PFS of pembrolizumab plus chemotherapy versus chemotherapy alone in the entire population.<sup>[6]</sup> The median PFS, OS, and ORR were significantly higher in population subset with PDL1 >50% as shown in Table 1.<sup>[6]</sup>

There is no trial till date which has evaluated chemotherapy plus pembrolizumab versus pembrolizumab alone in high PDL1 population. The conundrum to use pembrolizumab as a monotherapy versus combination remains a controversial area for such patients. Cross-trial comparisons between KEYNOTE-024 and the PDL1-high subgroup of KEYNOTE-189 suggest comparable outcomes between pembrolizumab and chemotherapy and pembrolizumab alone [Table 1].<sup>[3,6]</sup> This is despite the fact that there was superior response rates in PDL1 high subset of patients in KEYNOTE-189 (61%) as compared to monotherapy in KEYNOTE-024 (44%).<sup>[4,6]</sup> However, this comparison is only hypothesis generating and formal conclusions can only be drawn after a head-to-head trial comparisons between the two. It is also notable that the corresponding chemotherapy control arms experienced somewhat different 12-month OS rates (55% and 48% in KEYNOTE-024 and KEYNOTE-189 [PD-L1-high subgroup], respectively).<sup>[3,5]</sup>

There was however a notable difference in rates of grade 3–4 toxicity between immunotherapy arms of the two studies, and as shown in Table 1, there was 40% more Grade 3/4 toxicity observed with chemotherapy combination.<sup>[3,5]</sup>

To answer this question, a meta-analysis of five randomized clinical trials was done in patients with

high PDL1 expression (>50% PDL1 score) comparing pembrolizumab monotherapy, pembrolizumab combined with chemotherapy, versus chemotherapy alone.<sup>[7]</sup> Both the immunotherapy arms were superior to chemotherapy-alone arm in terms of PFS and OS. Indirect comparison showed that pembrolizumab plus chemotherapy was superior to pembrolizumab alone, in terms of ORR (relative risk 1.62, 1.18–2.23) and PFS (hazard ratio [HR] 0.55, 0.32–0.97). A trend toward improved OS was also observed (HR 0.76, 0.51–1.14); however, it was not statistically significant.<sup>[7]</sup> The result of this meta-analysis can be very tempting for a physician to choose the combination over single-agent pembrolizumab alone, but indirect comparisons and potential for severe toxicities with a similar survival rates cast a doubt on the results.

In the absence of direct comparative data and keeping in mind the patient's desire for maximal survival with minimal toxicity, I have chosen pembrolizumab monotherapy for the patient, thus allowing for the option of using a platinum-based doublet in the second-line setting.

Atezolizumab in combination with nab-paclitaxel and carboplatin is also approved as a first-line therapy for patients with nonsquamous NSCLC in PDL1 unselected population. The approval for this is based on the pivotal Phase 3 Study IMPower 130.<sup>[8]</sup> The combination of atezolizumab with nab-paclitaxel and carboplatin significantly improved PFS and OS versus chemotherapy alone as shown in Table 2.<sup>[8]</sup> Nab-paclitaxel was chosen as it does not require a steroid premedication, which may affect the response to immunotherapy. Grade 3–4 adverse events noted in this study were 71.3%, making it a toxic therapy. Liver metastases were present in approximately 15% of each arm of the study. The subgroup of patients with baseline liver metastases failed to show the PFS and OS benefit.<sup>[8]</sup> The high incidence of Grade 3–4 toxicity and poorer outcomes of patients with baseline liver metastases makes the use of atezolizumab in combination with nab-paclitaxel and carboplatin, a less preferred option for our patient who has multiple liver metastases.

The presence of hemoptysis which is a contraindication to the use of bevacizumab makes atezolizumab, bevacizumab,

**Table 1: Comparison of key outcomes in KEYNOTE-024 and KEYNOTE-189 study**

<b>Trials</b>	<b>KEYNOTE-024 (pembrolizumab alone)</b>	<b>KEYNOTE-024 (chemotherapy alone)</b>	<b>KEYNOTE-189* (pembrolizumab plus chemotherapy)</b>	<b>KEYNOTE-189* (chemotherapy alone)</b>
PFS (months, HR)	10.3 (0.50)	6.0	11.1 (0.36)	4.8
OS (months, HR)	30 (0.63)	14	NR (0.59)	10.1
OS rate at 2 years (%)	51.5	34.5	51.9	39.4
Response rates (CR + PR) (%)	44.8	27.8	62.1	24.3
Grade 3/4 toxicity (%)	26.6	53.3	67.2	65.8
Treatment discontinuation rates (%)	7.1	10.7	13.8	7.9

\*PFS and OS shown are for subgroup of population with PDL1 >50%. PFS – Progression-free survival; OS – Overall survival; CR – Complete response; PR – Partial response; HR – Hazard ratio; PDL1 – Programmed death-ligand 1; NR – Not reached

**Table 2: Key outcomes in IMPower 130 and IMPower 150 studies**

	IMPOWER 130* Atezolizumab + chemotherapy	IMPOWER 130* Chemotherapy	IMPOWER 150 ABCP	IMPOWER 150 BCP
PFS (months, HR)	6.4 (0.51)	4.6	8.3 (0.62)	6.8
OS (months, HR)	17.3 (0.84)	16.9	19.2 (0.78)	14.7
PFS in baseline liver mets (months, HR)	4.2 (0.93)	4.4	8.2 (0.41)	5.4
OS in baseline liver mets (months, HR)	10.0 (1.04)	8.8	13.3 (0.52)	9.4

\*For PDL1 high subgroups. PFS – Progression-free survival; OS – Overall survival; HR – Hazard ratio; PDL1 – Programmed death-ligand 1; mets – Metastases

paclitaxel, and platinum (ABCP) an unacceptable option for our patient. ABCP had otherwise shown superiority over combination of bevacizumab, paclitaxel, and platinum (BCP) in IMPower 150 study of advanced, PDL1 unselected nonsquamous NSCLC patients.<sup>[9]</sup> An updated subgroup analysis of IMPower 150 demonstrated improved PFS and OS in patients with baseline liver metastases [Table 2], a finding which was not observed in the subset analysis of immunotherapy arm of IMPower 130.<sup>[8,10]</sup> IMPower 150 had a third arm of atezolizumab, paclitaxel, and platinum (ACP). The ACP arm failed to show superiority over BCP in patients with baseline liver metastases.<sup>[10]</sup>

The combination of atezolizumab with pemetrexed and carboplatin has been compared to pemetrexed and carboplatin in advanced nonsquamous NSCLC in IMPower 132 study which demonstrated improved PFS (7.6 months vs. 5.2 months; HR 0.60), but there was only trend toward difference in OS at the time of first analysis (18.1 vs. 13.5 months; HR 0.46).<sup>[11]</sup> In view of nonavailability of robust data for OS for this regimen at this time, it cannot be recommended as a first-line therapy for our patient.

We have seen how there are a plethora of choices while choosing therapy for metastatic NSCLC in the first-line setting. The right choice of therapy can be decided by the presence of molecular driver alterations, PDL1 expression, comorbidities, performance status, burden of disease, and most importantly financial abilities of the patient. The various trials discussed above can guide us in choosing therapy, but the final decision must always be individualized after an informed decision-making with patient and physician. For example, in a young patient with high burden of disease, a significant response will be an ideal primary goal and a combination of chemotherapy and immunotherapy will be the best option. On the other hand, for an elderly gentleman with comorbidities and borderline performance status, single-agent immunotherapy will be a preferred choice where minimal toxicity and good quality of life with maximal survival advantage are desired. Unfortunately, not much data are available regarding the efficacy of immunotherapy drugs in Indian patients, but we can always extrapolate the data available from studies from the west. Another major concern for patients in a third world country is financial status of the family. A good

fraction of patients presenting in Indian hospitals cannot afford traditional chemotherapy; immunotherapy will be out of reach of most patients which is 40–80 times costlier. It will still be long before chemotherapy can be completely done away in the management of lung cancer, particularly in an Indian healthcare system.

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### Conflicts of interest

There are no conflicts of interest.

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