

Mono-Immunotherapy in Non-Small Cell Lung Cancer: Controversies and Challenges

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ABSTRACT In recent years, we have seen a rapid transformation in the standard of care for non-small-cell lung cancer. Particularly in the last decade, immunotherapy has become common at almost every stage of lung cancer. Unfortunately, immunotherapies are not effective for every patient. There are many postulations about the ineffectiveness of immunotherapies, e.g., some non-targetable and/or co-occurring mutations might cause resistance to immunotherapy, while some actionable mutations might lead to a better response to immunotherapy. Hence, in addition to traditional predictive biomarkers, it is now recommended to investigate the presence of both targetable and non-targetable mutations by detailed genomic analysis to optimize the decision on mono-immunotherapy. There is ongoing research about the biomarkers that could be strong predictors of the outcomes with first-line and subsequent mono immunotherapy. In addition, the impact of clinical negative predictive biomarkers is debatable. The present work aims to discuss these controversies and challenges.

Keywords: Mono-immunotherapy; predict; actionable mutation; microbiota; central nervous system metastasis; KRAS; co-mutation

Pembrolizumab, an anti-programmed death 1 (PD-1) monoclonal antibody, was the first approved agent for the first-line treatment of metastatic non-small-cell lung cancer (NSCLC), both as monotherapy [$\geq 50\%$ programmed death ligand 1 (PD-L1)] and combined with platinum-based chemotherapy in patients without sensitizing EGFR/ALK genomic aberrations.^{1,2} A survival benefit of combination therapy over chemotherapy has been demonstrated regardless of PD-L1 expression in both squamous and adenocarcinoma subtypes.¹⁻⁴ Mono-immunotherapy improved overall and progression-free survival (PFS) in patients with PD-L1 expression $\geq 50\%$. Additionally, it showed efficacy equivalent to that of chemotherapy in patients with pdL^{-1} level $\geq 1\%$.⁵⁻⁸ Accumulating newer data has led to a debate on how to better predict the efficacy of immunotherapies. Hence, there is ongoing research for an optimal biomarker, such as the cut-off value of PD-L1 expression and tumor mutational burden (TMB).⁹

In recent years, we have seen a rapid transformation in the standard of care of NSCLC. In addition to therapies targeting common alterations, including EGFR mutations, ALK-ROS1 gene rearrangements, BRAF mutations, and NTRK gene fusion, targeted therapies as first-line treatment have also been approved for other alterations such as RET-rearranged and MET-ex14 skipping mutated lung cancer.¹⁰ In addition, tyrosine kinase inhibitors (TKIs) targeting KRAS G12C, Exon20 insertion, and HER-2 mutations have been approved as second-line therapies, and the results of studies investigating their efficacy as first-line therapies are awaited.^{11,12} Most of these targeted agents are more effective than standard chemotherapy, sometimes also from immunotherapy. Detailed genomic analysis is very important in identifying other mutations that are not yet targetable and co-occurring mutations, which might be responsible for resistance to immunotherapy. Therefore, despite the U.S. Food and Drug Administration approval for

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the conditions mentioned above, it is recommended to investigate the presence of any actionable mutations by performing a detailed genomic analysis known as next-generation sequencing for an optimal decision on the use of first-line mono-immunotherapy. Thus, when a detailed genomic analysis is not available, initiating mono-immunotherapy for both first-line and subsequent treatment of NSCLC based only on the presence of common targetable mutations might be inappropriate.

While some non-targetable and targetable mutations were found to be negative predictive biomarkers for outcomes with immunotherapy, some others have provided a survival benefit similar to that in patients without mutations. Therefore, it might be more appropriate to use immunotherapy following disease progression despite targeted therapy in patients with an actionable mutation. The efficacy of immunotherapy alone in such cases is debatable. Moreover, this disadvantage of mono-immunotherapy in the presence of some actionable mutation does not hold true for every mutation, such as KRAS mutation with PD-L1 expression or MET amplification. Therefore, mono-immunotherapy might be the best treatment option for select patients with driver mutations.

In Phase III randomized trials assessing the efficacy of combination therapies, while patients with the an asymptomatic central nervous system (CNS) were included in the studies, patients with known active CNS metastases were excluded.¹⁻⁴ Additionally, patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1 were also excluded. The concept of “microbiota”, a rising value, is accepted as a key predictive parameter in the era of immunotherapy. Microbiota is considered important in the design of many clinical studies, and patients taking antibiotics are not included in many immunotherapy-related studies. Therefore, patients with active CNS metastasis, ECOG PS >1, and/or taking antibiotics or having poor nutrition status should be evaluated individually, even if combination therapy is used. Expecting benefits in these poor prognostic patient populations can be disappointing, especially when starting mono-immunotherapy, even with positive predictive biomarkers at first and subsequent lines. Other than immunotherapy-related

studies, when patients are selected for clinical trials, those with more favorable clinical features are included; hence, the benefit of any treatment strategy in patients with poor prognostic patient groups is reduced. However, considering the cost of immunotherapies, especially in low-middle-income countries, it is increasingly important to select the right patients for a more cost-effective approach. The present work aims to discuss these controversies and challenges.

PREDICTIVE BIOMARKERS FOR SELECTING PATIENTS WITH NSCLC FOR MONO-IMMUNOTHERAPY

When the data of pembrolizumab combined with chemotherapy were analyzed, the superiority of combination therapy over chemotherapy was seen regardless of PD-L1 expression in both squamous-cell and adenocarcinoma, while increased objective response rates (ORR) of 32.3% and 61.4% were observed in patients with PD-L1 expression <1% and $\geq 50\%$, respectively.^{13,14} In contrast, a survival benefit regardless of PD-L1 expression was not valid for mono-immunotherapy. While pembrolizumab monotherapy improved overall and PFS in patients with PD-L1 expression $\geq 50\%$, it was not superior to chemotherapy in patients with PD-L1 expression $\leq 50\%$.^{5,8} Moreover, the ORR in patients with PD-L1 expression $\geq 50\%$ was 44.8%, which was lower than that with combination therapy, although there is no head-to-head comparison. Although the survival rates with combination and monotherapy were similar in the presence of PD-L1 expression $\geq 50\%$, differences in the ORR might be clinically significant, especially in patients with high tumor burden. Therefore, monotherapy might not provide the expected benefit in such patients and should be used with caution.

CUT-OFF VALUE OF PD-L1 EXPRESSION FOR MONO-IMMUNOTHERAPY: 50% OR HIGHER?

There is limited information about the clinical relevance of a detailed investigation of PD-L1 levels in the population with PD-L1 levels >50%. A multicenter retrospective analysis evaluated the effect of

PD-L1 level on the ORR, PFS, and overall survival (OS) in 187 patients with NSCLC treated with pembrolizumab.¹⁵ The ORR was 44.4% (37.1%-51.8%), the median PFS was 6.5 months (4.5-8.5 mo), and the median OS was not reached (NR) consistent with that in the previous published Phase III trial of pembrolizumab.⁵ Patients with 90%-100% PD-L1 levels had a significantly higher ORR (60.0% vs. 32.7%, $p<0.001$), a better PFS [14.5 vs. 4.1 month, 0.50; (0.33-0.74), $p<0.01$], and OS [NR vs. 15.9 months, 0.39; (0.21-0.70), $p=0.002$] compared to that in patients with PD-L1 levels 50%-89%.¹⁵ Another study supporting these data is the Phase III study of cemiplimab monotherapy, a different anti-PD-1 monoclonal antibody. The HRs for median PFS were 0.28 (0.17-0.46), 0.55 (0.38-0.80), 0.79 (0.56-1.12) in patients with PD-L1 levels ≥ 90 , 60-90, and 50-60, respectively.⁷ In addition, median OS increased from 21.9 (13.2-NR) months (0.77; 0.49-1.23) to NR (17.3-NR) months (0.46; 0.25-0.85) as the PD-L1 levels increased. Based on this evidence, a cut-off value of ≥ 90 instead of ≥ 50 seems more confident especially in patients with high tumor burden and in the presence of other confounding factors.

IS TMB A BETTER PREDICTIVE BIOMARKER THAN PD-L1 EXPRESSION IN NSCLC?

Although higher PD-L1 expression levels are associated with higher response to immunotherapy in NSCLC, response to first-line mono-immunotherapy is seen at all PD-L1 expression levels, especially as shown after first-line therapy. Furthermore, PD-L1 expression is temporary and heterogeneous, and additional precise biomarkers are necessary. TMB was found to be a potential predictive biomarker associated with the efficacy of mono-immunotherapy in different tumor types; however, it was not found to be a robust biomarker for NSCLC in large prospective clinical trials.¹⁶⁻¹⁸ Hence, the predictive role of TMB as a biomarker in NSCLC remains elusive. In an analysis of a large database, it was found that patients with ≥ 20 TMB (in mutations/Mb) had a better median OS [16.8; (11.6-24.9) months vs. 8.5; (7.6-9.0) months; $p<0.001$], and clinical benefit (80.7% vs. 56.7%; $p<0.001$) compared to that in patients with <20 TMB.¹⁶ However, TMB was not a prognostic

biomarker in patients who were not treated with immunotherapy [TMB-H vs. TMB-L/I median OS: 9.0; (7.3-11.1) months vs. 7.9; (7.2-8.7); $p=0.11$].¹⁹ A recently published large study demonstrated that patients with ≥ 19.0 TMB (mutations per megabase) had a better ORR with PD-1/PD-L1 inhibitors (42.5% vs. 18.0%; $p<0.001$), as also improved median PFS [0.38; (0.28-0.52); $p<0.001$] and OS [0.46; (0.32-0.65); $p<0.001$] compared to patients with lower TMB independent of driver mutations.⁹ Moreover, a high TMB was found to be a predictive biomarker for ORR and survival, independent of PD-L1 expression. Additionally, the presence of higher levels of both biomarkers showed the highest survival benefit. ORR, median PFS, and OS were 57%, 18.1 months, and 47.7 months, respectively, in patients with high TMB and PD-L1 expression $\geq 50\%$ treated with mono-immunotherapy. In contrast, patients with both lower TMB and without PD-L1 expression had the poorest ORR (8.7%), PFS (2.1 months), and OS (10.4 months).⁹ In conclusion, though TMB appears to be a better predictive biomarker than PD-L1 expression, this finding needs to be confirmed by a randomized Phase III trial to be strongly incorporated into our clinical practice.

TKIs are recommended as first-line therapy in the presence of actionable mutation as they have been found to be most effective, and the efficacy of immunotherapy has decreased.^{20,21} Some mutations were shown to have an immunosuppressive microenvironment.^{22,24} In addition, patients with EGFR, ALK, RET, and ROS1 mutations were found to have lower TMB, whereas those with BRAF and KRAS mutations had the highest TMB.^{9,19} The Immunotarget registry study analyzed the efficacy of mono-immunotherapy according to mutational types.²⁵ It was seen that PFS was longer in the presence of PD-L1 expression in patients with KRAS or EGFR mutation, also positively associated with smoking status in BRAF or HER2 mutation, while OS was not associated with PD-L1 expression for any mutation. Additionally, patients with EGFR, ALK, ROS1, and RET mutation showed early progression compared to those with KRAS mutation.²⁵ Thus, each targetable mutation should be evaluated individually, as only some actionable mutations might benefit from immunotherapy.

The largest data on the efficacy of immunotherapies in the presence of a driver mutation has been obtained from studies of the EGFR mutation; however, the results were mixed.^{25,26} Compared with EGFR wild-type lung cancers, the overall response rates and OS with immunotherapy were found to be poor in the presence of exon 19 EGFR mutation but similar for EGFR^{L858R} and EGFR^{T790M} lung tumors regardless of PD-L1 expression (<1% vs. ≥1%).²⁷ In another study, it was shown that the median PFS was significantly longer in those with HER2 mutation (3.6; 1.6-NR months) or an EGFR exon 20 insertions (4.8; 1.2-8.6 months) compared to those with an EGFR-sensitizing mutation (1.7; 1.1-2.1 months) at next line treatments. In addition, the median PFS was 5.9 months (1.0-11.6), 3.7 months (0.1-5.5), and 1.8 months (0.9-2.4) in patients with PD-L1 ≥50%, 1-49%, and <1%, respectively.²⁸ Therefore, immunotherapy can be considered as a treatment option in the presence of ≥50% PD-L1 expression for some EGFR mutation groups after targeted treatments have failed. However, chemoimmunotherapy seems to be more confident according to the Phase III IMpower150 trial, especially for patients with sensitizing EGFR mutation.⁴ In the presence of HER2 mutation or exon 20 insertions, chemoimmunotherapy is recommended as the first-line treatment as TKIs have not yet been approved for first-line therapy. However, immunotherapy can be considered as a treatment option in later lines in patients with PD-L1 levels ≥50%.

A real-world database trial analyzed the efficacy of immunotherapy in patients with BRAF, HER2, MET, and RET mutations.²⁹ It was seen that median PFS [4.3 (2.1-8.5) months and 3.0 (1.2-NR) months] and OS [35.8 (9.0-35.2) months and 11.7 (4.1-NR) months] were better in patients with PD-L1 expression than in patients without PD-L1 expression. Thus, immunotherapy seems to be equally effective in patients with or without these mutations.²⁹ Similarly, a recent analysis demonstrated that ORRs with immunotherapies in the presence of BRAF (0-54%), c-MET (12-49%), and KRAS (18.7-66.7%) mutation were comparable to those in patients without these mutations, while the ORRs were lower in patients with RET and ALK fusion.³⁰ Considering this evi-

dence, mono-immunotherapy might not be an appropriate option for fusion genes, but it can be considered for patients with BRAF, HER2, and MET mutations.

The remarkable actionable mutation for which the efficacy of immunotherapy has been demonstrated is MET alterations.³¹ In the largest study, patients with MET-alteration were evaluated to assess the efficacy of immunotherapy. OS was found to be longer in patients treated with immunotherapy than in those treated with chemotherapy [19.0 (15.8-22.2) months vs. 8.0 (5.8-10.2) months; $p < 0.0001$, respectively]. Moreover, a higher OS benefit with immunotherapy was seen; this was not significant in patients with MET exon 14 skipping mutation. Although the efficacy of MET TKIs was found to be poor in patients with MET amplified tumors in Phase III clinical trials, immunotherapy seems to be a rational treatment option in this population.³¹

Taken together though first-line targeted therapies are the standard of care for NSCLC except for patients with KRAS mutation, HER2 mutation, EGFR exon 20 insertion, and MET amplification, immunotherapy can be considered in some cases that have disease progression following TKI therapy.

EFFICACY OF IMMUNOTHERAPY IN THE PRESENCE OF KRAS MUTATION

Abnormalities in tumor suppressor genes, including TP53, STK11, and KEAP1, are common mutations, but they are not yet targetable. Thus, in the presence of these mutations, patients are treated by considering general rules. KRAS is the common driver in the adenocarcinoma subtype of NSCLC, and sotorasib has been shown to have activity in patients with KRAS G12C mutation after first-line treatment in the Phase II CodeBreaK100 Trial.³² Despite promising results, no satisfactory benefit was seen compared to other targeted therapies. The results of a first-line trial of sotorasib targeting KRAS G12C mutation are still awaited, and there is no standard targeted first-line treatment of KRAS mutations. In the post-hoc analysis of Phase III KEYNOTE-042 trial, pembrolizumab showed an extremely high PFS and OS in patients harboring KRAS mutation, especially the

KRAS G12C mutation in those with $\geq 1\%$ PD-L1 levels.³³ These results need to be confirmed by Phase III trials; however, mono-immunotherapy yielded satisfying results as first-line treatment in patients with PD-L1 expression and KRAS mutation. One of the main reasons for higher survival with pembrolizumab could be that the TMB was higher in the presence of the KRAS mutation.⁹ In the clinical study analyzing the effect of sotorasib as first-line therapy, this issue was considered, and the presence of a tumor with PD-L1 expression has been accepted as one of the exclusion criteria (ClinicalTrials.gov Identifier: NCT04933695). Therefore, in the presence of PD-L1 levels $\geq 1\%$, pembrolizumab can be one of the main first-line treatment options for patients with KRAS mutants.

THE EFFICACY OF PD-1/PD-L1 INHIBITORS IN THE PRESENCE OF KRAS CO-MUTATIONS

Interestingly, the co-existence of KRAS and STK11/KEAP mutations is a predictive biomarker for poor efficacy of immunotherapy. This might be due to the high prevalence of KRAS co-mutations with STK11/KEAP1 in patients with low TMB.⁹ Moreover, a recently published study showed that the presence of this co-mutation was a poor predictive parameter for response to mono-immunotherapy despite high PDL-1 expression.³⁴ In addition, this work revealed that the presence of KRAS co-mutation led to resistance to immunotherapy and poor survival.³⁵ While the OS rates were 11-12 months with conventional therapies, the OS decreased to 4-6 months in patients with co-mutations.³⁴ This co-mutation is a prognostic rather than a predictive biomarker for response to immunotherapy, and the response to any treatment modality, including immunotherapy, is low, except for sotorasib.

CNS METASTASIS

The presence of symptomatic brain metastases is one of the exclusion criteria in chemoimmunotherapy studies. However, patients with CNS involvement were included in some studies. Among the studies on combination therapy, the KEYNOTE-189 study included patients with asymptomatic brain metastases or those with clinically stable lesions for at least 2

weeks and not taking steroids for 3 days prior to dosing with the study medication.¹ The CheckMate 9LA study included patients treated for brain metastases if the neurological symptoms were absent for 2 weeks before enrollment. However, patients were not eligible if they took >10 mg of prednisone before enrollment.³ Hazard ratios (HRs) for OS were not worse in patients with CNS metastases than in those without CNS metastases in these studies [HR 95%: 0.38; (0.24-0.60) vs. 0.75; (0.61-0.92) in patients without and with CNS metastases, respectively]. However, in studies on mono-immunotherapy, it is seen that the recruitment criteria for patients with CNS metastasis were more restricted. In the Keynote-024 study, patients were ineligible if they had received systemic glucocorticoids at any time or if they had untreated brain metastases.⁵ The inclusion criteria of the study in which atezolizumab was given as first-line monotherapy specified that patients should be treated with local treatment modalities despite having asymptomatic brain metastases and should not require corticosteroids as therapy for CNS disease.⁶ A large-scale retrospective study analyzed the efficacy of mono-immunotherapy in the presence of brain metastasis.³⁶ In all, 255 patients (24.9%) had brain metastasis at the initiation of immunotherapy. The presence of non-irradiated and/or growing brain metastases was categorized as active brain metastases and metastases treated with local modalities, and no progression was defined as stable brain metastasis. The ORR was not significantly different for patients with (n=255; 20.6%) and without (n=770; 22.7%) brain metastases. The presence of brain metastases and treatment line (>2 vs. ≤ 2) did not affect the PFS and OS, while the use of corticosteroid [HR; 95% confidence interval (CI): 1.31; (1.07-1.62) for PFS] stable brain metastases at the initiation of immunotherapy [HR; 95%: 0.62; (0.44-0.88) for PFS], and ECOG PS [>1 vs. ≤ 1 , 2.29; (1.89-2.77)] were independent predictive and prognostic parameters. Hence, initiation of immunotherapy as monotherapy or combination therapy might be more appropriate in patients treated with local modalities with no disease progression after local treatment, have showing clinical benefit, not requiring corticosteroids, and having good ECOG PS. Opting for combination therapies

might be better in such patient populations than mono immunotherapy since Phase III studies of monotherapy either did not analyze the efficacy in the subgroup with CNS metastases or few patients with CNS metastases were included.

MICROBIOTA/ANTIBIOTIC USE

In the last decade, a growing body of evidence has shown that gut microbiota might affect the response to immunotherapy and the progression of cancer through its effect on the inflammatory system and metabolism.³⁷ Although gut microbiota has been known to be associated with the toxicity of conventional chemotherapy, its influence has become more evident with the widespread use of immunotherapies.^{38,39} Data shows that the effectiveness of immunotherapies is reduced in the presence of dysbiosis in many cancer types.^{40,42} Moreover, some microorganisms have been shown to be positively associated with the efficacy of immunotherapy, while others were predictive of poor response in many types of cancers, including NSCLC.^{40,43} Therefore, many Phase I-II studies aiming to increase the effectiveness of immunotherapies by altering the intestinal microbiota have been conducted, and the results are awaited.⁴⁴ Data shows that antibiotic use until 2 months before immunotherapy is both a poor predictor and negative prognostic factor for response to immunotherapy in solid tumors.⁴⁵ Among patients with NSCLC treated with mono immunotherapy, it was seen that the proportion of those with progressive disease (50% vs. 22.5%, $p=0.006$) was high, and PFS (2 months vs. 7 months, $p<0.001$) and OS (4 months vs. 22 months, $p<0.001$) were shorter in the group that took antibiotics than in the no antibiotics group.⁴⁴ In addition, antibiotic usage, ECOG PS, stage, CNS involvement, presence of PD-L1 expression and EGFR mutation were independent predictive parameters for PFS [2.34 (1.3-4.4), $p=0.006$] and OS [3.8 (1.7-8.5), $p=0.001$].⁴⁵ In fact, many of these parameters that

have been shown to be prognostic for immunotherapy outcomes also induce dysbiotic gut microbiota and result in a reduced immune response. The latest meta-analysis presented in European Society for Medical Oncology immuno-oncology virtual meeting also showed that antibiotic use was a poor prognostic clinical biomarker for outcomes with mono-immunotherapy [HR 95% CI: 1.73; (1.38-2.17)].⁴⁶ However, antibiotic use did not have a detrimental effect on survival in the patients treated with chemoimmunotherapy.⁴⁷ Thus, the use of chemoimmunotherapy appears to be more confident in this patient population. In addition to antibiotic use, gut microbiota may be affected by lifestyle. It has been shown that patients with melanoma fed a diet with high fiber content and not using probiotics respond better to immunotherapy.⁴⁸

In conclusion, in addition to predictive biomarkers, including actionable and other non-targetable mutations, PD-L1 expression level, and TMB, corticosteroid use, dietary habits, ECOG PS, and antibiotic use should be considered in the treatment decision for mono-immunotherapy.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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