Editorial Commentary

Long-term benefit of immunotherapy in metastatic non-small cell lung cancer: the tale of the tail

Ayse Ece Cali Daylan^, Balazs Halmos

Department of Oncology, Montefiore Medical Center, Bronx, NY, USA

Correspondence to: Balazs Halmos, MD. Department of Oncology, Montefiore Medical Center, 111 E 210th St., Bronx, NY 10467, USA. Email: bahalmos@montefiore.org.

Comment on: de Castro G Jr, Kudaba I, Wu YL, *et al*. Five-year outcomes with pembrolizumab versus chemotherapy as first-line therapy in patients with non-small-cell lung cancer and programmed death ligand-1 tumor proportion score ≥1% in the KEYNOTE-042 study. J Clin Oncol 2023;41:1986-91.

Keywords: Immunotherapy; metastatic; non-small cell lung cancer (NSCLC); pembrolizumab

Submitted Apr 10, 2023. Accepted for publication May 19, 2023. Published online May 31, 2023.
doi: 10.21037/tlcr-23-245
View this article at: https://dx.doi.org/10.21037/tlcr-23-245

The discovery of immune checkpoints established a new treatment modality for cancer patients by unleashing the anti-tumor capabilities of the immune system. Initial studies of immune checkpoints were concentrated on cytotoxic T lymphocyte associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). CTLA-4 inhibits naïve T cell activation at the priming phase of the immune system in the lymph nodes (1). PD-1 interaction with its ligand, programmed cell death ligand 1 (PD-L1), acts to decrease effector T cell activation in peripheral tissues (1). These checkpoints are cornerstones of the immune system to allow self-tolerance and diminish damage to collateral tissues. However, the tumor cells exploit these checkpoint mechanisms, for instance, by expressing PD-L1 to evade immune-mediated anti-tumor activity. Unleashing the brakes on the immune cells via checkpoint inhibitors led to outstanding results that could be considered as cure for some patients with advanced solid tumors. For example, in metastatic melanoma, the poster child for immunotherapy, the combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) achieved a complete response in 22% of patients and a median overall survival (OS) of 72 months (2,3). In a previously treated cohort of microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer, the combination of nivolumab and ipilimumab led to a complete response in 13% of patients and an OS rate of 71% at 4 years (4). These unprecedented responses in metastatic solid tumors were groundbreaking. This revolutionary discovery was awarded the 2018 Nobel prize in Physiology or Medicine. Since the initial discovery of immune checkpoint inhibitors, the percentage of patients with advanced cancer in the US who are receiving immunotherapy increased exponentially. This commentary will focus on the updated 5-year analysis of the KEYNOTE-042 trial and review select randomized metastatic non-small cell lung cancer (NSCLC) trials with recently published long term survival outcomes.

The incorporation of immunotherapy has transformed metastatic NSCLC outcomes tremendously. Platinum-based doublet chemotherapy regimens, which were the standard of care for decades in metastatic NSCLC, provide modest survival benefits with a median OS of around 12 months (5). With the advent of immunotherapy, median OS lengthened to 18–24 months when used in the first line setting (*Table 1*). Initial phase 1 studies of nivolumab achieved an 18% of response rate in heavily pretreated metastatic NSCLC patients with durable responses in a fraction of patients lasting more than a year. This study also showed a positive correlation with PD-L1 expression and response rate (6). PD-L1 tumor proportion score

^ ORCID: 0000-0003-1237-0132.

Table 1 Five-year updates from select randomized immunotherapy trials in metastatic NSCLC

Trial	Patient population	Treatment arms	PD-L1 TPS	5-year OS, HR (95% CI)	5-year OS rate (%)	Median OS (months)
KEYNOTE-042	Locally advanced and metastatic NSCLC with PD-L1 TPS ≥1%	Pembrolizumab *vs.* chemotherapy	≥50%	0.68 (0.57–0.81)	21.9 *vs.* 9.8	20.0 *vs.* 12.2
			≥20%	0.75 (0.64–0.87)	19.4 *vs.* 10.1	18.0 *vs.* 13.0
			≥1%	0.79 (0.70–0.89)	16.6 *vs.* 8.5	16.4 *vs.* 12.1
KEYNOTE-024	Metastatic NSCLC with PD-L1 TPS ≥50%	Pembrolizumab *vs.* chemotherapy	≥50%	0.62 (0.48–0.81)	31.9 *vs.* 16.3	26.3 *vs.* 13.4
KEYNOTE-407	Metastatic squamous NSCLC	Pembrolizumab or placebo plus chemotherapy	Any	0.71 (0.59–0.85)	18.4 *vs.* 9.7	17.2 *vs.* 11.6
			≥50%	0.68 (0.47–0.97)	23.3 *vs.* 8.3	19.9 *vs.* 11.5
			1–49%	0.61 (0.45–0.83)	20.6 *vs.* 7.6	18.0 *vs.* 13.1
			<1%	0.83 (0.61–1.13)	10.7 *vs.* 13.1	15.0 *vs.* 11.0
KEYNOTE-189	Metastatic nonsquamous NSCLC	Pembrolizumab or placebo plus chemotherapy	Any	0.60 (0.50–0.72)	19.4 *vs.* 11.3	22.0 *vs.* 10.6
			≥50%	0.68 (0.49–0.96)	29.6 *vs.* 21.4	27.7 *vs.* 10.1
			1–49%	0.65 (0.46–0.90)	19.8 *vs.* 7.7	21.8 *vs.* 12.1
			<1%	0.55 (0.39–0.76)	9.6 *vs.* 5.3	17.2 *vs.* 10.2
CheckMate-227	Metastatic NSCLC	PD-L1 ≥1%: nivolumab plus ipilimumab *vs.* nivolumab *vs.* chemotherapy	≥1%	0.77 (0.66–0.91)	24 *vs.* 17 *vs.* 14	17.1 *vs.* 15.7 *vs.* 14.9
		PD-L1 <1%: nivolumab plus ipilimumab *vs.* nivolumab plus chemotherapy *vs.* chemotherapy	<1%	0.65 (0.52–0.81)	19 *vs.* 10 *vs.* 7	17.4 *vs.* 15.2 *vs.* 12.2

NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; OS, overall survival; HR, hazard ratio; CI, confidence interval.

(TPS) is the most widely used predictor of PD-1/PD-L1 inhibition response due to its positive correlation in many clinical trials. KEYNOTE-001, a phase 1 study evaluating pembrolizumab in pre-treated metastatic NSCLC demonstrated a median progression-free survival (PFS) of 6.3 months and an overall response rate of 45.2% in the subgroup of patients with PD-L1 TPS ≥50% (7). A phase 2/3 study, KEYNOTE-010, further established the predictive biomarker role of PD-L1 expression by investigating the effect of pembrolizumab compared to docetaxel on survival outcomes in previously treated metastatic NSCLC patients with PD-L1 ≥1% and PD-L1 ≥50% (8). It demonstrated a clear survival advantage (OS: 17.3 *vs.* 8.2 months, P=0.0002) favoring pembrolizumab in TPS ≥50% group. These encouraging results allowed the introduction of immunotherapy into the front-line setting.

KEYNOTE-024, a phase III study, compared single-agent pembrolizumab to platinum-based chemotherapy in the first line setting for metastatic NSCLC with high PD-L1 expression. KEYNOTE-024 reported a median PFS benefit 10.3 *vs.* 6.0 months with a hazard ratio (HR) of 0.50 [95% confidence interval (CI): 0.37 to 0.68], a higher OS rate of 80.2% *vs.* 72.4% at 6 months (HR, 0.60; 95% CI: 0.41 to 0.89) favoring pembrolizumab (9). This landmark trial led to the approval of pembrolizumab in the first-line setting in metastatic NSCLC patients with PD-L1 TPS ≥50% without actionable epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) alterations. Atezolizumab and cemiplimab followed suit by improving OS and gaining Food and Drug Administration (FDA) approval in the front-line setting for patients with PD-L1 TPS ≥50% per IMpower110 and EMPOWER-Lung 1 trials, respectively (10,11).

As single-agent pembrolizumab's use became solidified in front line setting of biomarker selected metastatic NSCLC group, KEYNOTE-042, was designed to investigate the

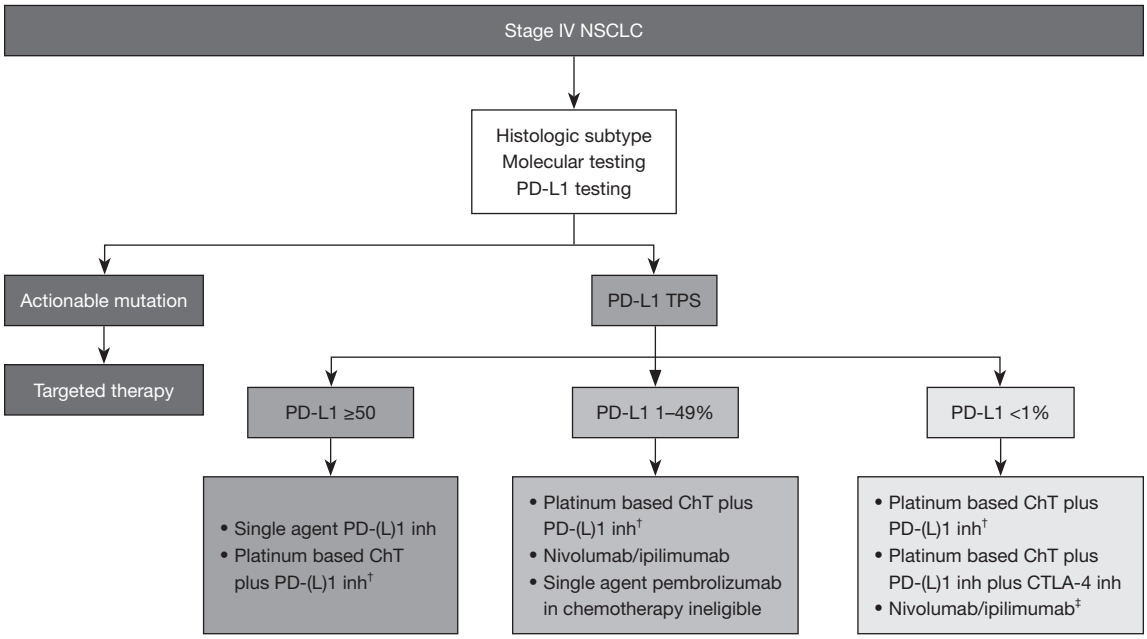

Figure 1 Suggested treatment algorithm for stage IV NSCLC. †, ± bevacizumab for nonsquamous NSCLC if IMpower150 regimen is opted for; ‡, not FDA approved. NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; PD-1, programmed cell death protein 1; ChT, chemotherapy; inh, inhibitor; CTLA-4, cytotoxic T lymphocyte associated antigen 4; FDA, Food and Drug Administration.

efficacy of single-agent pembrolizumab over platinum-based chemotherapy in a broader biomarker selected population, PD-L1 ≥1% (12). KEYNOTE-042 trial randomized 1,274 patients with locally advanced or metastatic NSCLC with PD-L1 TPS ≥1% without *EGFR/ALK* alterations 1:1 to single-agent pembrolizumab for up to 35 cycles or platinum-based chemotherapy. The initial results showed an OS benefit favoring pembrolizumab with HR of 0.81 for PD-L1 ≥1% (95% CI: 0.71 to 0.93) (12). Even though single agent immunotherapy was better tolerated than chemotherapy, it led to severe immune related adverse events in select patients. 9% of patients had to discontinue treatment while 2% of patients died on the immunotherapy arm due to treatment related adverse events. Severe immune related adverse events included pneumonitis, hepatitis, and skin rash. In addition, the survival benefit was mainly driven by the high PD-L1 subgroup. This trial led to the Food and Drug Administration (FDA) approval of single-agent pembrolizumab in the first line setting for patients with PD-L1 TPS ≥1%. However, due to concerns regarding benefit in the group with PD-L1 1–49%, EMA did not approve pembrolizumab for this biomarker subgroup.

Immunotherapy provides long-lasting survival benefits, but this remains limited to a select group of patients. In order to expand the benefits of immunotherapy to a broader population, combination therapies have been investigated. Synergistic effects of pembrolizumab with platinum-based chemotherapy regardless of PD-L1 expression in metastatic non-squamous NSCLC per KEYNOTE-189 (13) and in squamous NSCLC per KEYNOTE-407 (14) led to OS benefit and FDA approvals as the front line treatment. Today, chemoimmunotherapy remains the most commonly used regimen in patients with PD-L1 TPS <50% (*Figure 1*).

The combination of CTLA-4 and PD-(L)1 inhibition also has synergistic effects due to their complementary mechanisms. CheckMate-227, compared nivolumab/ipilimumab to platinum based chemotherapy while CheckMate-9LA investigated whether addition of a short course, two cycles of platinum based chemotherapy to nivolumab and ipilimumab would increase efficacy (15,16). Both studies met their primary endpoints of OS. Even though the nivolumab/ipilimumab combination showed longer OS in the descriptive analysis of the PD-L1 negative subgroup, CheckMate-227 was designed to assess OS in PD-L1 ≥1%. Therefore, the combination of nivolumab and ipilimumab was approved only for PD-L1 ≥1% by the US

FDA. CheckMate-9LA assessed OS regardless of PD-L1 expression, leading to the FDA approval of nivolumab and ipilimumab with a short course of chemotherapy in the overall population, including PD-L1 negative patients. The combination of durvalumab, anti-PD-L1 and tremelimumab, anti-CTLA4 antibodies with four cycles of platinum based chemotherapy is also a treatment option in front-line metastatic NSCLC regardless of PD-L1 expression based on OS benefit per POSEIDON trial (17). However, these regimens are used less commonly due to concern for increased toxicity with the addition of ipilimumab and modest survival benefit with the durvalumab/tremelimumab combination.

The durable responses with immunotherapy which were unheard of in the era of conventional chemotherapy became evident with the recent release of 5-year updates from multiple landmark immunotherapy trials. KEYNOTE-042, with a median follow-up of 61.1 months continues to demonstrate prolonged OS favoring pembrolizumab with HR of 0.68 for TPS ≥50%, 0.75 for TPS ≥20% and 0.79 for TPS ≥1% (*Table 1*) (18). The median OS for TPS ≥1% is 16.4 months in this trial. KEYNOTE-024 reported an ongoing survival benefit favoring pembrolizumab by doubling the median OS to 26 months despite a high cross-over rate of 66% which may have dampened the outcome differences (19). Adding pembrolizumab to platinum doublet chemotherapy in metastatic nonsquamous NSCLC per KEYNOTE-189 improved median OS to 22 months and in metastatic squamous NSCLC per KEYNOTE-407 to 17.2 months regardless of PD-L1 expression (20,21). CheckMate-227 also continues to show an OS benefit with nivolumab and ipilimumab with a median OS of 17.1 months in TPS ≥1% and 17.4 months in TPS <1% compared to platinum-based chemotherapy (22) (*Table 1*). Strikingly, even though most of these trials discontinued immunotherapy at the 2-year mark per protocol, a fraction of patients achieved long periods of treatment free intervals without disease progression.

KEYNOTE-042's 5-year update solidifies the durable survival benefit favoring pembrolizumab in patients with PD-L1 TPS ≥1%. However, the main contributor remains the high PD-L1 expressor group. The exploratory analysis of patients with TPS 1–49% reveals a HR of 0.88 (95% CI: 0.75 to 1.04). As the CI crosses 1, the superiority of pembrolizumab in this subgroup remains questionable. In addition, a pooled FDA analysis of patients with PD-L1 1–49% receiving chemoimmunotherapy had better OS with a median of 21.4 *vs.* 14.5 months compared to patients receiving immunotherapy alone (23). On the other hand, in patients with PD-L1 score ≥50%, median OS was not statistically different between chemoimmunotherapy and immunotherapy arms (24). In addition, the Kaplan-Meier curves of OS in KEYNOTE-042 trial cross around 6 months of treatment, implicating increased mortality with single agent pembrolizumab compared to the chemotherapy arm in the initial few months of therapy. This initial decrease in survival with single agent immunotherapy is very concerning and could be secondary due to rapidly progressive disease. Therefore, in current practice, chemoimmunotherapy is preferred for medically fit patients with PD-L1 score of 1–49%. However, this trial serves single-agent pembrolizumab as a treatment choice for patients with PD-L1 TPS ≥1% who cannot tolerate chemotherapy.

Remarkably, the group of patients who completed the preplanned 35 cycles of immunotherapy (16% of patients in the immunotherapy arm, n=102) in KEYNOTE-042 have yet to reach the median OS. This group has a 4-year OS (6 years from the randomization) rate of 61.8%, an overall response rate of 84.3%, and a median duration of response of 47.7 months. These patients who benefit the most from immunotherapy comprise the majority of the tail of the Kaplan-Meier curve and can live longer than 5 years with metastatic NSCLC which was unprecedented before the immunotherapy era. The exploration of outcomes in this cohort is important to understand the optimal duration of immunotherapy and the long-term side effects. In total, 40.2% of this cohort was alive without disease progression and subsequent therapy at the 5-year data cut-off. This points out that immunotherapy creates long lasting effects beyond the duration of therapy, and patients can achieve long periods of treatment-free intervals without disease progression. Whether a shorter course of maintenance immunotherapy would produce a similar result, or a longer course would prolong the OS remains a topic of interest. CheckMate-153, randomizing patients to observation or continuous nivolumab upon completion of 1 year of immunotherapy revealed improved survival outcomes with continuation while IFCT-1701 trial which was halted prematurely, randomizing patients to observation or continuous nivolumab and ipilimumab upon completion of 6 months did not demonstrate a survival benefit (25,26). In addition to the duration of immunotherapy, the outcomes of rechallenge with immunotherapy upon progression are of interest. Recent updates from KEYNOTE-024, KEYNOTE-189, KEYNOTE-407 reported that 12 patients, nine patients and twelve patients received a

second course of pembrolizumab upon disease progression, respectively. Even though these were small groups, one third of this group had partial response and half had stable disease per KEYNOTE-024 trial. These results suggest that rechallenge with immunotherapy may provide benefit. This strategy may limit the side effects and healthcare costs. However, whether a continuous immunotherapy course or a fixed duration with rechallenge upon progression leads to better survival outcomes needs to be investigated by prospective studies.

Interestingly, a significant proportion (45%) of patients who completed 35 cycles of immunotherapy had PD-L1 score <50% in the KEYNOTE-042 trial. Even though the most clinically relevant predictive marker for PD-1/PD-L1 inhibitor response is the PD-L1 expression, some patients with low PD-L1 expression derive significant survival benefits from immunotherapy alone, as noted above. As with the current treatment guidelines, a small group of patients with PD-L1 1–49% is getting overtreated with the addition of chemotherapy with higher toxicity. The contrary is also true since some patients with high PD-L1 progress early and there tends to be increased mortality with single agent immunotherapy in the initial months of treatment. Given the lack of head-to-head comparison for chemoimmunotherapy and immunotherapy in the high PD-L1 group, the decision relies on shared decision making between clinicians and patients. This decision may be affected by the patient's comorbidities, presence of molecular alterations, e.g., serine/threonine kinase 11 (*STK11*)/Kelch-like ECH-associated protein (*KEAP*) mutations, and disease burden. The development of more precise predictive biomarkers may eventually answer these questions. Tumor mutational burden, immune infiltration score, gene expression signatures from the tumor tissue, and blood-based assays of immune activation are under investigation as predictors (27). However, developing immunotherapy predictive markers is challenging due to the complexity of the immune resistance mechanisms, including the inherent properties of tumor cells, tumor microenvironment, and the effect of concomitant or preceding cancer-directed therapy modalities.

The current data for immunotherapy in metastatic NSCLC are impressive due to the flattening of the Kaplan-Meier curves with the use of immunotherapy which was absent in traditional chemotherapy trials. This remarkable survival benefit of immunotherapy, having around 20% of patients alive at 5-year mark in metastatic NSCLC compared to a median survival of 12 months a decade ago, is a very appealing part of today's oncology practice. However, this durable response to immunotherapy remains limited to a select group of patients for whom the unique predictors are not well defined yet. In addition, when immunotherapy is used as a single agent immunotherapy, especially in the low PD-L1 group, it leads to increased mortality in the first few months of treatment. Therefore, the treatment regimens are being refined by the addition of chemotherapy or CTLA-4 inhibitors with the guidance of the PD-L1 biomarker. Tackling immunotherapy resistance with novel drug development and combination therapies is a popular area of research leading to many clinical trials. Antibody-drug conjugates targeting human epidermal growth factor receptor 2 (HER2), trophoblast cell surface antigen 2 (TROP2), c-Met, and carcinoembryonic antigen-related cell adhesion molecule-5 (CEACAM5) in combination with PD-(L)1 inhibitors are actively being investigated in NSCLC. Another intriguing method is combinatory inhibition of PD-(L1) with novel immune checkpoints, including T cell immunoglobulin and ITIM domain (TIGIT), lymphocyte activation gene 3 (LAG3), and T-cell immunoglobulin mucin protein 3 (TIM3). Even though several phase III clinical trials investigating anti-TIGITs have been disappointing, the sheer number of novel immune checkpoints, and encouraging preclinical and early clinical trial results justify further investigations. Other novel approaches include CAR T and vaccine based therapies are other strategies to harness immune system's ability to attack cancer cells but these have been challenging so far partly due to the heterogeneity of antigens in NSCLC. Multiple inhibitory molecules modulating of tumor microenvironment to diminish immunosuppressive forces also build on this foundation to overcome immune resistance. In current practice, the optimal treatment selection for individual patients is still challenging due to the lack of head-to-head comparison trials. Given immunotherapy's unique feature of durable responses, long-term follow-up and tracking the tails of these curves are crucial to better guide informed decision making discussions (28). Ultimately, the development of more precise biomarkers guiding the addition of chemotherapy or CTLA-4 inhibitors will offer tailored therapies maximizing benefit-to-risk ratios. In addition, the optimal duration of immunotherapy needs further refinement. The selection of specific combination therapy and its duration will likely be tailored to individual patients based on better understanding of immune resistance mechanisms and the use of refined predictive biomarkers.

This commentary focuses on the 5-year updates

of KEYNOTE-042 trial which is a crucial trial in the metastatic NSCLC without actionable *EGFR* or *ALK* alterations, proving single-agent pembrolizumab as a treatment option for patients with PD-L1 TPS ≥1 with ongoing benefits at 5-year follow-up. Future advances in this arena will continue to shape treatment algorithms to offer more personalized treatment regimens and will increase the proportion of patients who fall under the promised land of the tail of the curve.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-245/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-245/coif). BH has grants or contracts from Boehringer Ingelheim, Astra Zeneca, Merck, BMS, Advaxis, Amgen, AbbVie, Daiichi, Pfizer, GSK, Beigene, Janssen, Numab and Arrivent and is on monitoring/advisory boards of Astra Zeneca, Boehringer Ingelheim, Apollomics, Janssen, Takeda, Merck, BMS, Genentech, Pfizer, Eli-Lilly, TPT and Arcus. The other author has no 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.

References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
2. Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. J Clin Oncol 2022;40:abstr 9522.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019;381:1535-46.
4. André T, Lonardi S, Wong KYM, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol 2022;33:1052-60.
5. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
6. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
7. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
8. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
9. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.
10. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med 2020;383:1328-39.
11. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 2021;397:592-604.
12. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.

13. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
14. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
15. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
16. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:198-211.
17. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol 2023;41:1213-27.
18. de Castro G Jr, Kudaba I, Wu YL, et al. Five-year outcomes with pembrolizumab versus chemotherapy as first-line therapy in patients with non-small-cell lung cancer and programmed death ligand-1 tumor proportion score ≥1% in the KEYNOTE-042 study. J Clin Oncol 2023;41:1986-91.
19. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50. J Clin Oncol 2021;39:2339-49.
20. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol 2023;41:1999-2006.
21. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol 2023;41:1992-8.
22. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer in CheckMate 227. J Clin Oncol 2023;41:1200-12.
23. Akinboro O, Vallejo JJ, Mishra-Kalyani PS, et al. Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis. J Clin Oncol 2021;39:abstr 9001.
24. Akinboro O, Vallejo JJ, Nakajima EC, et al. Outcomes of anti–PD-(L) 1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA pooled analysis. J Clin Oncol 2022;40:abstr 9000.
25. Zalcman G, Flandin ACM, Molinier O, et al. 972O Nivolumab (Nivo) plus ipilimumab (Ipi) 6-months treatment versus continuation in patients with advanced non-small cell lung cancer (aNSCLC): Results of the randomized IFCT-1701 phase III trial. Ann Oncol 2022;33:S992.
26. Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153. J Clin Oncol 2020;38:3863-73.
27. Camidge DR, Doebele RC, Kerr KM. Comparing and contrasting predictive biomarkers for immunotherapy and targeted therapy of NSCLC. Nat Rev Clin Oncol 2019;16:341-55.
28. Friedlaender A, Liu SV, Addeo A. Tracking the tail. J Immunother Cancer 2020;8:e000971.

Cite this article as: Cali Daylan AE, Halmos B. Long-term benefit of immunotherapy in metastatic non-small cell lung cancer: the tale of the tail. Transl Lung Cancer Res 2023;12(7):1636-1642. doi: 10.21037/tlcr-23-245