Editorial Commentary

Novel immune checkpoint inhibitor strategies in advanced non-small cell lung cancer: towards biomarker-driven therapies?

M. Benthe Muntinghe-Wagenaar^, T. Jeroen N. Hiltermann^

Department of Pulmonary Diseases and Tuberculosis, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
Correspondence to: T. Jeroen N. Hiltermann, MD, PhD. Department of Pulmonary Diseases and Tuberculosis, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Postbus 30.001, HPC AA11, 9700RB Groningen, the Netherlands. Email: t.j.n.hiltermann@umcg.nl.
Comment on: Besse B, Pons-Tostivint E, Park K, *et al.* Biomarker-directed targeted therapy plus durvalumab in advanced non-small-cell lung cancer: a phase 2 umbrella trial. Nat Med 2024;30:716-29.

Keywords: Immune checkpoint inhibition; biomarker; non-small cell lung cancer (NSCLC); programmed death-ligand 1 (PD-L1)

Submitted Oct 18, 2024. Accepted for publication Jan 17, 2025. Published online Feb 24, 2025.
doi: 10.21037/tlcr-24-966
View this article at: https://dx.doi.org/10.21037/tlcr-24-966

The introduction of immune checkpoint inhibitors (ICI) in the treatment of non-small cell lung cancer (NSCLC) has been an incredible advancement in the field. Particularly in patients without targetable molecular alterations, clinical outcomes in means of both progression-free survival (PFS) and overall survival (OS), have improved significantly. Nevertheless, only a small proportion of patients experience a durable response, and the majority will develop resistance to treatment and show progressive disease. To date, the only predictive biomarker clinically used is programmed death-ligand 1 (PD-L1) expression on tumor cells (1). But also, patients with a low tumor mutational burden (TMB) and STK11/KEAP1/EGFR alterations may not benefit from ICI at all (2). Nevertheless, there remains a need for biomarkers to identify patients that will benefit from different ICI treatment strategies. This editorial commentary outlines the advances with immunotherapy, will dive into the results of the HUDSON-2 trial and briefly look into the future of ICI strategies in NSCLC (3).

Less than a decade ago, ICI monotherapy was introduced into the clinical practice for NSCLC treatment following the positive results of the CheckMate 017 (squamous) and CheckMate 057 (non-squamous) trials, which were confirmed in the KEYNOTE-010 (4-6). The superiority of ICI in first-line setting was demonstrated shortly thereafter in the KEYNOTE-024 and KEYNOTE-042 trials using pembrolizumab monotherapy (7,8). An overview of trials most relevant to current standard treatment, with corresponding treatment line and PD-L1 expression is provided in *Table 1*. Best objective response rate (ORR) and OS are achieved in patients with a high (≥50%) PD-L1 tumor proportion score (TPS). Subsequently, chemo-immunotherapy trials showed encouraging results for patients with lower PD-L1 TPS (1–49% and <1%). The CheckMate 9LA investigated the combination of dual ICI (nivolumab and ipilimumab) with chemotherapy versus chemotherapy alone (9). Especially patients with a PD-L1 TPS <1% appear to benefit from this combination. Despite all these developments in the field of NSCLC, most patients will not benefit from will not benefit from, or develop resistance to or develop resistance to the ICI treatment. Resistance may either be primary (i.e., progressive disease as best response) or acquired (i.e., progression occurring >6 months) (16). The cancer-immunity cycle provides a tool to better understand how resistance occurs (17). It describes the complexity of the cancer immune response in different steps, linked in a cycle, that lead to effective killing of cancer cells. Resistance may occur within each step and can be due to various factors of the tumor itself, the tumor microenvironment (TME), patient genetics, endocrine and

^ ORCID: M. Benthe Muntinghe-Wagenaar, 0000-0003-3785-7406; T. Jeroen N. Hiltermann, 0000-0002-0665-2160.

Table 1 Overview of most relevant trials with current standard treatment

Trial	Treatment	Treatment line	N	PD-L1	ORR [95% CI], %	5-year OS rate [95% CI], %	Median OS [95% CI], months
KEYNOTE-001	Pembrolizumab	1st line	27	≥50%	50 [25–75]	30 [8–56]	35 [20–64]
			52	1–49%	19 [7–39]	16 [7–27]	20 [11–26]
			12	<1%	17 [0–65]	NE	NE
		≥2nd line	138	≥50%	43.9 [30.7–57.6]	25.0 [18.0–32.5]	15.4 [10.6–18.8]
			168	1–49%	15.6 [8.3–25.6]	12.6 [7.9–18.5]	8.5 [6.0–12.6]
			90	<1%	9.1 [1.1–29.2]	3.5 [0.7–10.0]	8.6 [5.5–10.6]
KEYNOTE-024	Pembrolizumab	1st line	154	≥50%	46.1 [38.1–54.3]	31.9 [24.5–39.5]	26.3 [18.3–40.4]
KEYNOTE-189	Pembrolizumab + chemotherapy (non-squamous)	1st line	202	≥50%	62.1 [53.3–70.4]	29.6 [22.0–37.6]	27.7 [20.4–38.2]
			186	1–49%	50.0 [41.0–59.0]	19.8 [13.4–27.1]	21.8 [17.7–25.6]
			190	<1%	33.1 [25.0–42.0]	9.6 [5.3–15.6]	17.2 [13.8–22.8]
KEYNOTE-407	Pembrolizumab + chemotherapy (squamous)	1st line	176	≥1%	59.1 [51.4–66.4]	UK	18.9 [14.0–22.2]
			95	<1%	67.4 [57.0–76.6]	UK	15.0 [13.2–19.4]
CheckMate 9LA†	Nivolumab + ipilimumab + chemotherapy	1st line	204	≥1%	43 [UK]	21 [16–27]	15.8 [13.8–22.2]
			135	<1%	31 [UK]	23 [16–30]	17.7 [13.7–20.3]
KEYNOTE-010	Pembrolizumab	2nd line	139	≥50%	30.2 [22.7–38.6]	25.0 [UK]	16.9 [12.3–21.4]
			344	≥1%	18.0 [14.1–22.5]	15.6 [UK]	11.8 [10.4–13.1]

The table includes several trials that have contributed to the clinical use of mentioned ICI (combinations) in different settings (9-15). †, OS update after 4 years. N, number of patients; PD-L1, programmed death-ligand 1; ORR, objective response rate; CI, confidence interval; OS, overall survival; NE, not evaluable; UK, unknown/not mentioned; ICI, immune checkpoint inhibitor.

metabolic cues, environmental, or other factors (17,18).

Due to advancements in tumor biology and an ever-growing understanding of various (resistance) mechanisms in oncology, new trial designs have emerged. One such design is the so-called umbrella trial, investigating different therapies within a single disease (19). Most umbrella trials are conducted in the field of oncology, particularly in patients with NSCLC (20). This leads us to the interesting phase 2 umbrella trial of Besse *et al.*, that addressed a few steps of the cancer-immune cycle and was designed to better understand resistance mechanisms to ICI clinically and develop effective treatment strategies to overcome them. They investigated different durvalumab-based combination therapies in patients with NSCLC who previously received a platinum-doublet therapy and progressed on an anti-PD-(L)1 inhibitor (3). Detrimental DDR mutations, as well as an 18-gene T-cell inflamed inflammatory signature in the TME are associated with better clinical outcomes in patients treated with PD-(L)1 inhibitors (21,22). Their hypothesis was that either targeting the TME by anti-CD73 or a STAT3 inhibitor, or targeting DNA damage response (DDR) and repair pathways by inhibition of poly(ADP-ribose) polymerase (PARP) or ataxia telangiectasia RAD-2 related (ATR) could reverse resistance to PD-L1 inhibition. After molecular profiling at screening, patients were stratified by the occurrence or absence of specific targets ("biomarkers"). A total of 268 patients were included in either a biomarker-matched, targeting TME or DDR, or in a biomarker-non-matched cohort. Of these patients, 40.7% had primary resistance and 58.2% acquired resistance on the prior immunotherapy regimen. Their primary outcome was the ORR and showed the most promising treatment module was aimed at targeting the DDR by using a combination of durvalumab with ATR inhibitor ceralasertib. This cohort was specifically aimed at targeting ATM alterations, which confer ATR dependency in NSCLC and potentially results

in higher sensitivity to ICI (23). It included patients of whom 36.7% had primary resistance and 60.8% acquired resistance to prior immunotherapy and yielded an ORR of 13.9%, compared to 2.6% in the other regimens. Furthermore, a median PFS of 5.8 [80% confidence interval (CI): 4.6–7.4] and median OS of 17.4 (80% CI: 14.1–20.3) months compared to 2.7 (80% CI: 1.8–2.8) and 9.4 (80% CI: 7.5–10.8) months, respectively, in the other regimens was observed. Although patient numbers were small and the ORR and PFS appeared somewhat promising, the clinical responses in terms of survival were mostly observed during the first 2 years whereafter no differences were observed between the biomarker-matched (ATM) and non-matched cohorts. This may be due to immaturity of data but may also indicate non-durable responses. This will be further investigated in the phase 3 LATIFY trial (NCT05450692). No clear effect was seen for the PARP inhibitor, nor for the combinations targeting the TME. On one hand, this lack of effect could be due to the fact that the study was conducted in a resistance setting. On the other hand, it may indicate that those approaches are not the way to move forward, and a different treatment strategy may be required.

There are multiple other ongoing trials in NSCLC employing immunotherapy-based combination strategies with promising results. Trials are conducted both in first-line and in further-line settings, including different PD-L1 expression cohorts and using different bispecific antibodies and antibody-drug conjugates. *Table 2* provides an overview of some of the trials that were presented at the World Conference on Lung Cancer (WCLC) 2024. Likewise, various ICI-based agents appear to be most effective in a first-line setting, with some cohorts achieving ORRs above 50% (*Table 2*). Although some of these results are very promising, it is important to consider and balance the toxicity of these new agents.

Ultimately, we strive for biomarker-driven therapies in NSCLC, however up to now no clear biomarker has been identified. Potentially, better results and insights into new treatment modalities and possible biomarkers might be obtained through studies in the neo-adjuvant setting by studying patients with resectable instead of metastatic disease. Especially research with resected tumors that appear to be refractory to treatment, those without a so-called complete pathological response, i.e., no vital tumor left. Studying these tumors by for example spatial genomics may help us to understand what mechanisms are relevant in resistance to immunotherapy and how they should be targeted. This may also open more possibilities for biomarker-driven studies.

Nevertheless, we still face the issue that, to this day, there is no discriminating biomarker to predict clinical response to ICI on a patient level. When considering biomarker-driven studies, an effective biomarker should be able to distinguish whether a patient is a responder or a non-responder early in treatment. One could argue whether the described HUDSON trial was truly a "biomarker-directed", or if "target-directed" would be a more appropriate term. Another focus in biomarker-driven studies could be to shift more towards optimizing patient selection on an individual basis prior to treatment by for example using exhaled breath analysis with an electronic nose (eNose). An eNose is a non-invasive tool that recognizes the gas mixture from volatile organic compounds (VOCs) and classifies based on pattern recognition (24). Previously, the eNose could discriminate patients with NSCLC who benefit from PD-1 inhibitors from those who did not at baseline (25). However, to the best of our knowledge, no external validation studies have been conducted yet to support its practical use. Another possibility might lie in assessing the extent to which the immune system can be effectively stimulated early in treatment. For example, by testing the *ex vivo* stimulation of blood-derived lymphocytes at baseline, in which a mild stimulus resulted in a higher percentage of activated $CD8^+$ T-cells in responders compared to non-responders (26).

In conclusion, PD-L1 expression is the only clinically used biomarker in NSCLC. Extensive research is being conducted on new potential biomarkers. The aim is to progress towards stratifying treatments based on potential biomarkers across different patient cohorts. The HUDSON trial attempted to achieve this; however, their best treatment module (durvalumab-ceralasertib) in this setting was not the breakthrough discovery hoped for either and unfortunately, we have not reached the stage of biomarker-driven therapies yet. Ongoing research with new agents or studies in the neo-adjuvant setting may help us move forward to achieve this aim. Ultimately, non-invasive and accurate tools can distinguish at an early stage, and for example exhaled breath analysis may help us move forward towards a world with biomarker-driven therapies.

Table 2 Immunotherapy trials in advanced stage NSCLC on WCLC 2024

Trial	Treatment	Target	Treatment line	N	PD-L1	ORR [95% CI], %
ARTEMIDE-01	Rilvegostomig 750 mg	PD-1 & TIGIT	1st line; allowed ≤1 chemotherapy	31	1–49%	29 [14–48]
	Rilvegostomig 750 mg	PD-1 & TIGIT	1st line; allowed ≤1 chemotherapy	34	≥50%	61 [44–78]
	Rilvegostomig 1,500 mg	PD-1 & TIGIT	1st line; allowed ≤1 chemotherapy	30	≥50%	37 [20–56]
EVOKE-02	Sacituzumab govitecan + chemotherapy + pembrolizumab (non-squamous)	Trop-2 & PD-1	1st line	51	All	45 [31–60]
	Sacituzumab govitecan + chemotherapy + pembrolizumab (squamous)	Trop-2 & PD-1	1st line	41	All	39 [24–56]
HARMONi-2	Ivonescimab (AK112)	PD-1 & VEGF	1st line	189	≥1%	50.0 [42.8–57.2]
	Pembrolizumab	PD-1	1st line	200	≥1%	38.5 [31.7–45.6]
SHR-1701	SHR-1701 + chemotherapy followed by SHR-1701 + fluzoparib	PD-L1 & TGF-βRII followed by PD-L1 & TGF-βRII & PARPi	1st line	10–15†	UK	63–94† [UK]
Volrustomig	Volrustomig + chemotherapy (non-squamous)	PD-1 & CTLA-4	1st line	119	<1%‡	43.7 [UK]
	Volrustomig + chemotherapy (squamous)	PD-1 & CTLA-4	1st line	20	<1%§	65 [UK]
SAFFRON-301	Tislelizumab + sitravatinib	PD-1 & TYRO3/ACL/MERTK/ VEGFR2/KIT	≥2nd line	187	All	12.3 [8.0–17.9]
	Docetaxel	–	≥2nd line	190	All	12.6 [8.3–18.2]
IBI363	IBI363	PD-1 & IL-2	≥2nd line	134	All	20.8 [14.1–29.0]
QUILT-3.055	N-803 + CPI	IL-15/IL-15Rα superagonist & PD-1	3rd line	19	All	16 [UK]
	N-803 + CPI	IL-15/IL-15Rα superagonist & PD-1	2nd line	9	≥50%	0 [UK]
	N-803 + CPI	IL-15/IL-15Rα superagonist & PD-1	2nd line	20	All	5 [UK]
	N-803 + CPI	IL-15/IL-15Rα superagonist & PD-1	2nd and 3rd line	38	All	5 [UK]

†, 10 patients with a confirmed partial response (ORR, 63%); 15 patients with an unconfirmed partial response (ORR, 94%). ‡, in 90% of patients. §, in 50% of patients. NSCLC, non-small cell lung cancer; WCLC, World Conference on Lung Cancer; N, number of patients; PD-L1, programmed death-ligand 1; ORR, objective response rate; CI, confidence interval; PD-1, programmed cell death protein 1; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; Trop-2, trophoblast surface antigen 2; VEGF, vascular endothelial growth factor; TGF-βRII, transforming growth factor beta receptor type II; PARPi, poly(ADP-ribose) polymerase inhibitor; UK, unknown/ not mentioned; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; TYRO3, tyrosine-protein kinase receptor; ACL, ATP citrate lyase; MERTK, MER proto-oncogene, tyrosine kinase; CPI, checkpoint inhibitor; IL-2, interleukin-2; IL-15(Rα), interleukin-15 (receptor alpha).

Acknowledgments

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-24-966/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-966/coif). M.B.M.W. reports travel grants from AACR-BMS and NRS. T.J.N.H. reports research funds from Roche, BMS, and AZD. 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.

References

1. Zhang B, Liu Y, Zhou S, et al. Predictive effect of PD-L1 expression for immune checkpoint inhibitor (PD-1/PD-L1 inhibitors) treatment for non-small cell lung cancer: A meta-analysis. Int Immunopharmacol 2020;80:106214.
2. van de Haar J, Mankor JM, Hummelink K, et al. Combining Genomic Biomarkers to Guide Immunotherapy in Non-Small Cell Lung Cancer. Clin Cancer Res 2024;30:1307-18.
3. Besse B, Pons-Tostivint E, Park K, et al. Biomarker-directed targeted therapy plus durvalumab in advanced non-small-cell lung cancer: a phase 2 umbrella trial. Nat Med 2024;30:716-29.
4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
5. 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.
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
7. 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.
8. 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.
9. Carbone DP, Ciuleanu TE, Schenker M, et al. Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. J Immunother Cancer 2024;12:e008189.
10. 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.
11. Garon EB, Hellmann MD, Rizvi NA, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol 2019;37:2518-27.
12. 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.
13. 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.
14. Paz-Ares L, Vicente D, Tafreshi A, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus

Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol 2020;15:1657-69.
15. Herbst RS, Garon EB, Kim DW, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol 2021;16:1718-32.
16. Schoenfeld AJ, Antonia SJ, Awad MM, et al. Clinical definition of acquired resistance to immunotherapy in patients with metastatic non-small-cell lung cancer. Ann Oncol 2021;32:1597-607.
17. Mellman I, Chen DS, Powles T, et al. The cancer-immunity cycle: Indication, genotype, and immunotype. Immunity 2023;56:2188-205.
18. Pitt JM, Vétizou M, Daillère R, et al. Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors. Immunity 2016;44:1255-69.
19. Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 2019;20:572.
20. Ouma LO, Wason JMS, Zheng H, et al. Design and analysis of umbrella trials: Where do we stand? Front Med (Lausanne) 2022;9:1037439.
21. Ricciuti B, Recondo G, Spurr LF, et al. Impact of DNA Damage Response and Repair (DDR) Gene Mutations on Efficacy of PD-(L)1 Immune Checkpoint Inhibition in Non-Small Cell Lung Cancer. Clin Cancer Res 2020;26:4135-42.
22. Ayers M, Lunceford J, Nebozhyn M, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest 2017;127:2930-40.
23. Vokes NI, Galan Cobo A, Fernandez-Chas M, et al. ATM Mutations Associate with Distinct Co-Mutational Patterns and Therapeutic Vulnerabilities in NSCLC. Clin Cancer Res 2023;29:4958-72.
24. Farraia MV, Cavaleiro Rufo J, Paciência I, et al. The electronic nose technology in clinical diagnosis: A systematic review. Porto Biomed J 2019;4:e42.
25. Buma AIG, Muller M, de Vries R, et al. eNose analysis for early immunotherapy response monitoring in non-small cell lung cancer. Lung Cancer 2021;160:36-43.
26. Kievit H, Muntinghe-Wagenaar MB, Abdulahad WH, et al. Baseline Blood CD8(+) T Cell Activation Potency Discriminates Responders from Non-Responders to Immune Checkpoint Inhibition Combined with Stereotactic Radiotherapy in Non-Small-Cell Lung Cancer. Cancers (Basel) 2024;16:2592.

Cite this article as: Muntinghe-Wagenaar MB, Hiltermann TJN. Novel immune checkpoint inhibitor strategies in advanced non-small cell lung cancer: towards biomarker-driven therapies? Transl Lung Cancer Res 2025;14(2):328-333. doi: 10.21037/tlcr-24-966

