Editorial

TTF-1 and immune checkpoint therapy in non-small cell lung cancer

Matthew Gumbleton[1,2], Eric L. Snyder[2,3]

[1]Division of Oncology, Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [3]Department of Pathology, University of Utah, Salt Lake City, UT, USA

Correspondence to: Eric L. Snyder. Department of Pathology and Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Drive, Salt Lake City, UT, USA. Email: eric.snyder@hci.utah.edu.

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The treatment of non-small cell lung cancer (NSCLC) has undergone a major shift in recent years with the introduction of immune checkpoint inhibitors (ICIs) that target the programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis. These ICIs have shown remarkable efficacy treating patients with advanced NSCLC (1). Indeed, a current standard of care first-line therapy given to many patients with advanced, non-targetable, non-squamous NSCLC is now treatment with a PD-1/PD-L1 inhibitor in combination with pemetrexed and platinum chemotherapy (2).

Although this treatment strategy has shown promising results, including durable responses even after stopping treatment amongst a subset of patients, not all patients have a favorable response (3). There is therefore an urgent need for identification of biomarkers capable of predicting treatment response, thereby allowing a patient to select the most effective treatment strategy while avoiding therapeutics unlikely to provide benefit.

Thyroid transcription factor-1 (TTF-1), also known as NKX2-1, is a transcription factor required for morphogenesis and differentiation of the lung, thyroid and ventral forebrain (4,5). TTF-1 is expressed by the majority of non-squamous lung cancers, and is used as a diagnostic marker in this disease (6). In lung adenocarcinoma, loss of TTF-1 expression results in dedifferentiation and enhanced metastatic potential (7). As such, patients with TTF-1-negative lung adenocarcinoma have inferior survival compared to patients with TTF-1-positive disease (8,9). TTF-1 expression remains a prognostic indicator amongst patients treated with cytotoxic chemotherapy regimens—patients with TTF-1-positive non-squamous NSCLC have improved survival when treated with a platinum-based chemotherapy regimen compared to patients with TTF-1-negative tumors (10-12). However, as the current standard of care therapy for patients with advanced non-squamous NSCLC without a targetable mutation has changed in recent years to include an ICI, it has remained unknown if TTF-1 expression still affects patient outcomes when treated with modern chemoimmunotherapeutic regimens.

Ibusuki *et al.* begin to address this question through a retrospective analysis of 122 patients with advanced non-squamous NSCLC treated in the first-line setting with a pemetrexed-containing chemoimmunotherapy regimen at four different institutions in Japan (13). Here the authors demonstrate significantly improved progression-free survival (PFS) amongst patients with TTF-1-positive non-squamous NSCLC compared to those with TTF-1-negative disease. As TTF-1 expression can affect the histologic subtype it is not surprising that there are significantly fewer patients with lung adenocarcinoma in the TTF-1-negative cohort. Importantly, the authors are able to show that the PFS benefit remains when the analysis is restricted to patients

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with lung adenocarcinoma.

Although this paper demonstrates patients with non-squamous TTF-1-negative NSCLC treated with a first-line pemetrexed-containing chemoimmunotherapy regimen have a worse prognosis compared to patients with TTF-1-positive disease, further studies are needed to answer important outstanding questions. Is the improved PFS in TTF-1-positive disease seen in this study due to the effect of TTF-1 expression on treatment response, or is it because of the different underlying biology of TTF-1-positive vs negative disease as outlined above? Suggesting that TTF-1 indeed influences response to ICIs, a recent analysis of patients treated with ICI monotherapy demonstrated that patients with TTF-1-positive lung adenocarcinoma had improved survival compared to those with TTF-1-negative disease (14). Intriguingly, one study showed that TTF-1 can induce PD-L1/PD-L2 expression in human lung cancer cell lines, and that PD-L1 was expressed in a higher percent of TTF-1 positive tumors than TTF-1 negative tumors (15). However, TTF-1 is clearly not the only activator of PD-L1 expression, as not all TTF-1-positive tumors expressed PD-L1 (15), and Ibusuki *et al.* did not find a significant correlation between TTF-1 and PD-L1 expression in their cohort (13). Moreover, the survival benefit of TTF-1 expression described by Nakahama *et al.* remained when the analysis was restricted to only patients with PD-L1 positive tumors (14). Thus, further work is needed to understand how TTF-1 loss might mediate resistance to ICIs. As Ibusuki *et al.* highlight, the most important question raised by this work is whether patients with TTF-1-negative non-squamous NSCLC need different treatment compared to patients with TTF-1-positve disease, and it is encouraging that authors have planned a prospective clinical trial to address this question (13).

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References

1. 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.
2. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:497-530.
3. 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.
4. Kimura S, Hara Y, Pineau T, et al. The T/ebp null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. Genes Dev 1996;10:60-9.
5. Lazzaro D, Price M, de Felice M, et al. The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. Development 1991;113:1093-104.
6. Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. Am J Surg Pathol 2002;26:767-73.

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7. Winslow MM, Dayton TL, Verhaak RG, et al. Suppression of lung adenocarcinoma progression by Nkx2-1. Nature 2011;473:101-4.
8. Anagnostou VK, Syrigos KN, Bepler G, et al. Thyroid transcription factor 1 is an independent prognostic factor for patients with stage I lung adenocarcinoma. J Clin Oncol 2009;27:271-8.
9. Barlési F, Pinot D, Legoffic A, et al. Positive thyroid transcription factor 1 staining strongly correlates with survival of patients with adenocarcinoma of the lung. Br J Cancer 2005;93:450-2.
10. Takeuchi A, Oguri T, Yamashita Y, et al. Value of TTF-1 expression in non-squamous non-small-cell lung cancer for assessing docetaxel monotherapy after chemotherapy failure. Mol Clin Oncol 2020;13:9.
11. Fiala O, Pesek M, Skrickova J, et al. Thyroid transcription factor 1 expression is associated with outcome of patients with non-squamous non-small cell lung cancer treated with pemetrexed-based chemotherapy. Tumour Biol 2017;39:1010428317691186.
12. Grønberg BH, Lund-Iversen M, Strøm EH, et al. Associations between TS, TTF-1, FR-α, FPGS, and overall survival in patients with advanced non-small-cell lung cancer receiving pemetrexed plus carboplatin or gemcitabine plus carboplatin as first-line chemotherapy. J Thorac Oncol 2013;8:1255-64.
13. Ibusuki R, Yoneshima Y, Hashisako M, et al. Association of thyroid transcription factor-1 (TTF-1) expression with efficacy of PD-1/PD-L1 inhibitors plus pemetrexed and platinum chemotherapy in advanced non-squamous non-small cell lung cancer. Transl Lung Cancer Res 2022;11:2208-15.
14. Nakahama K, Kaneda H, Osawa M, et al. Association of thyroid transcription factor-1 with the efficacy of immune-checkpoint inhibitors in patients with advanced lung adenocarcinoma. Thorac Cancer 2022;13:2309-17.
15. Guo M, Tomoshige K, Meister M, et al. Gene signature driving invasive mucinous adenocarcinoma of the lung. EMBO Mol Med 2017;9:462-81.

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