

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

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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-1negative 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

with lung adenocarcinoma.

Although this paper demonstrates patients with nonsquamous TTF-1-negative NSCLC treated with a firstline 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 nonsquamous 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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Footnote

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References

- 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.
- 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.
- 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.
- 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.
- Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. Am J Surg Pathol 2002;26:767-73.

Gumbleton and Snyder. TTF-1 and immune checkpoint therapy

- Winslow MM, Dayton TL, Verhaak RG, et al. Suppression of lung adenocarcinoma progression by Nkx2-1. Nature 2011;473:101-4.
- 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.
- 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.
- 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.
- 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.

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- 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.
- 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.
- Nakahama K, Kaneda H, Osawa M, et al. Association of thyroid transcription factor-1 with the efficacy of immunecheckpoint inhibitors in patients with advanced lung adenocarcinoma. Thorac Cancer 2022;13:2309-17.
- Guo M, Tomoshige K, Meister M, et al. Gene signature driving invasive mucinous adenocarcinoma of the lung. EMBO Mol Med 2017;9:462-81.

400