Editorial

A mighty oak in the rapidly expanding field of checkpoint inhibition for NSCLC

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In the Lancet issue of last December Rittmeyer and colleagues reported the primary efficacy analysis of another landmark immunotherapy study (1): the randomized phase 3 OAK trial comparing atezolizumab (n=425), an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, with docetaxel (n=425) for patients with squamous or adenocarcinomatous non-small cell lung cancer (NSCLC) progressing after one or more platinum-based combination regimens. Atezolizumab was better tolerated and resulted in a significantly improved median overall survival of 13.8 versus 9.6 months in the ITT population [hazard ratio (HR) 0.73; 95% confidence interval (CI), 0.62–0.87]. These results corroborate the findings of the large randomised phase 2 POPLAR trial published in March 2016, which also showed a survival benefit for atezolizumab (n=144) compared with docetaxel (n=143) in the same setting (12.6 *vs.* 9.7 months; HR 0.73; CI, 0.53–0.99; P=0.04) (2).

Of course, immunotherapy for pretreated NSCLC patients is nothing new, since two PD-1 inhibitors, nivolumab and pembrolizumab are already in routine clinical use after demonstrating a clear survival benefit compared to docetaxel in squamous (3) and non-squamous (4) or in PD-L1 expressing (≥1% on tumor cells) NSCLC (5) respectively. In fact, all NSCLC trials investigating immune checkpoint inhibitors against chemotherapy in the second line so far have been positive with similar results, namely response rates of ca. 15–20% and an overall survival benefit of ca. 3–4 months. So, which are the new aspects with atezolizumab?

To begin with, atezolizumab becomes the first PD-L1 inhibitor with unambiguous positive data for second-line NSCLC treatment. Furthermore, in the OAK trial atezolizumab demonstrated an improved overall survival in three patient subgroups without clear benefit in previous studies: patients with treated CNS metastases at baseline (HR 0.54; CI, 0.31–0.94), never smokers (HR 0.71; CI, 0.47–1.08, with a cautionary note owing to the large CI) and PD-L1 negative patients (HR 0.75; CI, 0.59–0.96), albeit less than in cases with high PD-L1 expression (≥50% on tumor cells or ≥10% on tumor infiltrating immune cells, TC3/IC3; HR 0.41; CI, 0.27–0.64). Interestingly, the group of PD-L1 negative patients is smaller with the PD-L1 diagnostic assay employed in the OAK trial due to a different cut-off (<1% expression on both tumor and immune cells *vs.* on tumor cells only in the nivolumab and pembrolizumab trials), even though the PD-L1 antibody used with atezolizumab is per se less efficient for the detection of PD-L1 on tumor cells (clone SP142 *vs.* clones 28-8 and 22C3, respectively) (6). Moreover, atezolizumab in the OAK trial was associated with a lower frequency of specific immune mediated adverse events, like rash, diarrhea and pneumonitis, than observed with nivolumab and pembrolizumab in the respective phase 3 studies (<2% *vs.* generally 3–9%) (1,3-5). Hypothetically, the apparently improved tolerability of atezolizumab could

result from its different mode of action: direct targeting of the PD-L1 presumably blocks both the PD-L1/PD-1 and PD-L1/B7-1 interactions, which enhances immune responses more than the inhibition of PD-1 alone (7,8), while leaving the PD-L2/PD-1 interaction intact, which reduces the risk of autoimmunity (9).

Overall, the results of the OAK trial are a significant step forward, but several issues remain unsolved. Upon treatment with atezolizumab every second NSCLC patient will have refractory disease i.e., continuous tumor progression and a dismal prognosis with expected survival below 1 year (1). At the same time, the broad administration of immunotherapy instead of docetaxel to these patients regardless of PD-L1 status in accordance with the compelling evidence from the OAK trial will further increase the already difficult-to-bear costs of cancer immunotherapy (10). Is there a way to define those patients destined to achieve long-term benefit or even cure? Will the median survival of 20.5 months (HR 0.41; CI, 0.27–0.64) for patients with a high PD-L1 expression (TC3/IC3) in the OAK trial translate to a substantial five-year survival rate? A better understanding of the underlying immunobiology is urgently needed as it will pave the way for accurate predictive markers to guide application of existing drugs (11) as well as accelerate the development of more effective therapeutic strategies, be it novel compounds or combination regimens (12). The main problem with PD-L1 are not just its many different implementations, which render comparisons between the results of various checkpoint inhibitor trials and their application to everyday practice problematic (6), but its fundamental inability as a single marker to summarize the relevant biological complexity. Examples of more sophisticated approaches include a multiparametric characterization of several host and tumor factors crucial for anticancer immunity termed "the cancer immunogram" (13) as well as a comprehensive transcriptomic profiling of the tumor and its microenvironment to assess prognosis and predict response to various treatments (14).

Which will be the role of chemotherapy in the treatment of NSCLC beyond the first line now? In the first place, it is indispensable for patients with contraindications to checkpoint inhibitors like preexisting autoimmunity and interstitial lung disease as well as for patients under immunosuppression, who are unlikely to respond. In addition, patients with oncogene-driven NSCLC have benefited less from immunotherapy in the various checkpoint inhibitors trials (1,3-5), so chemotherapy is generally preferred after tyrosine-kinase inhibitor failure regardless of PD-L1 expression, which is often high in these cases, but caused by constitutive oncogenic signaling rather than induced by tumor-infiltrating lymphocytes (15). Finally, in a recent retrospective analysis up to 10% of patients—mostly elderly, aged over 65—showed a paradoxical stimulation of tumor growth on institution of treatment with checkpoint inhibitors, probably because of altered immune function due to immunosenescence, that necessitates an early switch to chemotherapy (16).

This pattern of "hyperprogressive disease" was an unexpected discovery that came into light only after large-scale administration of immune checkpoint inhibitors and somehow disturbs the deep optimism sparked by their introduction some years ago (17). Even more worrisome is the fact that our initial hope for definite cure of a substantial patient fraction through immunotherapy remains unfulfilled and slowly degrades into a mere prolongation of median survival intervals with each new drug at hardly sustainable costs. Nonetheless, immunooncology is definitely the most rapidly expanding and promising field of cancer medicine today, continuously outperforming and displacing traditional therapeutic approaches in an ever growing number of tumor entities and indications. Its ultimate challenge remains to facilitate and predict long-term survival.

The programmed death of chemotherapy in NSCLC has already begun (18), but the road will be long. And however reassuring a shelter this oak might be, let us keep in mind that our destination, the programmed death of the NSCLC itself, is not on the horizon yet.

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Footnote

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