Editorial

First-line nivolumab (anti-PD-1) monotherapy in advanced NSCLC: the story of immune checkpoint inhibitors and "the sorcerers apprentice"

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Non-small cell lung cancer (NSCLC) has usually been thought to be a non-immunogenic tumor, because early studies with Bacillus Calmette-Guerin, interleukin-2, or interferon have failed to demonstrate any benefit in NSCLC. Recently, some studies indicated that immune mechanisms play a vital role in the origin and development of lung cancer, and the abnormality of immune checkpoints would be the chief culprit. Immune checkpoint-inhibitors have shown promising activity in several solid tumors, including NSCLC. But interfering with the complex immune system in tumor immunosurveillance can trigger not only long lasting responses, but also severe and sometimes irreversible immunological side effects, as seen with the first approved cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor ipilimumab. This reminds one of a famous German poem written by Johann Wolfgang von Goethe in the year 1797, where an apprentice takes the opportunity to "play a little" with some magic when his master wizard had gone out of the house. But the apprentice summoned some powerful spirits he couldn't actually control.

Better understanding of the immune system and identification of potential new targets in the immune checkpoint pathway has led to development of new compounds targeting programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1) or other immune checkpoint molecules with different efficacy and toxicity profiles.

In a phase I study of patients with solid tumors, nivolumab (1)—a fully human IgG4 monoclonal antibody—was given biweekly in escalated doses for up to 12 cycles over 2 years. In the NSCLC cohort of 129 heavily pretreated patients (55% receiving at least 3 prior lines of therapy) the overall response rate (ORR) was 17% with a median duration of response of 74 weeks (range, 6.1-133.9 weeks). The median survival was 9.9 months with 1- and 2-year survival rates of 42% and 24%, respectively. However, the median progression free survival (PFS) was only 2.3 months. Side effects included skin (20%), gastrointestinal (15%) and pulmonary (9%) toxicities, being the most commonly observed adverse events (AEs). A lower frequency of gastrointestinal toxicities (2%) was seen (grade 3/4) compared to ipilimumab (20%). However, pneumonitis was reported in 6% (8/129) of patients with two deaths (2). PD-L1 expression analysis was performed in 49% (63/129) of patients and was defined as expression in at least 5% of tumor cells on immunohistochemistry (IHC). PD-L1 positivity was found in 49% (31/63) of patients. The ORR in patients with PD-L1 positive and PD-L1 negative tumors was 16% and 13%, respectively, showing that PD-L1 status was not a good predictive marker in this study.

At the ASCO annual meeting 2014 new data have been presented for nivolumab monotherapy as 1st-line treatment compared to standard chemotherapy (3). In this study patients with squamous or non-squamous advanced NSCLC received nivolumab 3 mg/kg IV Q2W until progression or unacceptable toxicity. Primary endpoint was safety; secondary endpoints included ORR and PFS rate at 24 weeks. Interim analysis of the first 20 patients was presented showing a tolerable safety profile. It is notable that no pneumonitis occurred among those 20 patients. 20% experienced grade 3/4 toxicities, being mainly elevated liver enzymes. However,

only two patients discontinued treatment due to treatment related AEs. ORR was 30% with the median of duration not being reached. In this study no response was seen in those patients defined as PD-L1 negative. However, only 7 PD-L1 negative patients were treated so far. The effect of PD-L1 status might be different in those two studies, the reason for that remain unclear. The methods used to measure the expression of PD-L1 may be responsible. Also the baseline characteristics of included patients between the two studies, such as prior therapy or tumor stage, were different.

In conclusion, the experience with the PD1-inhibitor nivolumab is still preliminary. Response rates are promising even in heavily pretreated patients and are in the range of other PD1 and PD-L1 antibodies. It is noteworthy, that duration of responses is uncommonly long with these agents. However, the toxicity profile still remains to be defined in larger patient cohorts. Especially pneumonitis, which is a common side effect in many drugs (e.g., gefitinib, erlotinib, gemcitabine), needs to be monitored carefully, particularly when nivolumab is combined with other agents.

In general, many questions related to immunotherapy remain unanswered: is inhibition of PD1 or PD-L1 the better approach? What is the ideal schedule and duration of therapy, and should we combine immunotherapy with targeted therapies or chemotherapy? Is PD-L1 status a good predictor of efficacy? To answer these questions we have to wait for the results of several ongoing studies. Until that we may sometimes find ourselves in the position of the sorcerers apprentice from the above mentioned poem, when at the end he shouted for the big sorcerers help: "I have need of Thee! From the spirits that I called Sir, deliver me!"

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