POINT / COUNTER

Should checkpoint inhibitors be limited in the front-line NSCLC setting based on PD-L1 expression?

POINT

PD-L1 expression should guide selection of patients for clinical trials in the front-line setting.


Tarek Mekhail

Immunotherapy, specifically nivolumab (Opdivo, Bristol-Myers Squibb), has been approved in the second line for squamous non–small cell lung cancer based on the results from the CheckMate 017 trial. In that trial, patients assigned nivolumab achieved a median OS of 9.2 months, whereas the median OS in the docetaxel arm was 6 months (HR = 0.59; 95% CI, 0.44-0.79). The benefit associated with nivolumab persisted regardless of PD-L1 expression levels.

However, the CheckMate 057 trial in patients with adenocarcinoma demonstrated similar results with some intriguing findings regarding the correlation of response and PFS based on PD-L1 expression. PD-L1 positivity at 1%, 5% and 10% expression levels appeared associated with benefit from nivolumab.

Further, the study published on pembrolizumab (Keytruda, Merck) in *The New England Journal of Medicine* showed significant improvement in response rates for a selected population with PD-L1 expression of more than 50% compared with lower response rates for patients with less PD-L1 expression.

In selection for patients with more treatment options — such as patients in the first-line setting — the bar is higher. I suspect this may partially explain why checkpoint inhibitors have not been approved for adenocarcinoma where we have more treatment options.

This also applies to front-line treatment, where the treatment options and combination of treatments are much more abundant than the second- or third-line settings. Consequently, it is harder to prove efficacy in the front-line setting compared with standard treatment.

When the bar is higher and there are more options, selection has to be more restricted to patients who have a higher chance of responding to treatment based on endpoints that are harder to reach. PD-L1 expression can help define the patient population appropriate for treatment.

None of the checkpoint inhibitors are currently approved in the front-line setting. With these parameters, we should select the population based on PD-L1 expression provided the evidence we have so far. Although PD-L1 expression testing has not yet been standardized, I believe more evidence is yet to come.

References:

Garon EB, et al. *N Engl J Med*. 2015;doi:10.1056/NEJMoa1501824.

The following were presented at ASCO Annual Meeting; May 29-June 2, 2015; Chicago:

Paz-Ares LG, et al. Abstract LBA109.

Spigel DL, et al. Abstract 8009.

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COUNTER

Certain patients with non–small cell lung cancer may derive benefit from immunotherapy in the first-line setting regardless of biomarker expression.


Laura Q. M. Chow

The recent data on the anti-PD-1 antibody, nivolumab (Opdivo, Bristol-Myers Squibb) — in the squamous population (CheckMate 017) and non-squamous population (CheckMate 057) — highlight the high efficacy, low toxicity and substantial clinical benefits of the PD-1 checkpoint inhibitors in the second-line setting in advanced/metastatic NSCLC when compared with docetaxel chemotherapy, regardless of PD-L1 expression. However, impressive data from Garon and colleagues published in *The New England Journal of Medicine* also demonstrate that the anti–PD-1 antibody pembrolizumab (Keytruda, Merck) had impressive sustained responses and high clinical benefit in selected highly expressing PD-L1–positive patients (> 50% via immunohistochemistry). The use of PD-L1 as a selective biomarker, varying methods for detection and cut-offs levels have been vigorously debated and have been an area of substantial controversy in the second-line setting.

In the first-line setting where platinum-based cytotoxic chemotherapy has had a firm established role with known response rates, PFS and OS, biomarkers for molecular drivers (eg, *EGFR* and *ALK* gene mutations) have been successful for selecting patients who may derive even greater benefit in this setting than from chemotherapy. The impressive tolerability and substantial benefit of the PD-1 checkpoint inhibitors in the second-line setting has led to high enthusiasm for use of these agents in the first-line setting. However, the role of PD-L1 as a biomarker to select responders to immunotherapy in the first-line setting and the benefits of immunotherapy when compared with chemotherapy are still pending data from current ongoing clinical trials. In the clinical management of NSCLC, there are many patients for whom tolerance to the toxicities of cytotoxic chemotherapy would be challenging —the extreme elderly, the frail, less fit patients, those with have a high risk for infection, those with conflicting comorbidities, and some patients who may have a strong philosophical opposition to chemotherapy. These patients may potentially derive some benefit with PD-1 checkpoint immunotherapy in the first-line setting regardless of biomarker status due to the differing and potentially lower toxicity profile of the immune checkpoint inhibitors.

It is clear that immunotherapy with a checkpoint inhibitor is an exciting new option that hopefully many patients with lung cancer may see in their treatment algorithm, whether they are biomarker selected or not, regardless of the line of therapy.

References:

Garon EB, et al. *N Engl J Med*. 2015;doi:10.1056/NEJMoa1501824.

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