Tumor Mutation Burden Does Not Predict Immunotherapy Response

Biomarker was not linked to response rates in two studies of Keytruda for lung cancer.

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A biomarker known as tumor mutational burden (TMB) was not associated with a greater likelihood of response to the checkpoint inhibitor Keytruda (pembrolizumab) in people with non-small-cell lung cancer (NSCLC), according to two studies presented this week at the World Conference on Lung Cancer (WCLC) in Barcelona.

Summarizing the study results, presenter Corey Langer, MD, of the University of Pennsylvania's Abramson Cancer Center, suggested that TMB is "not ready for prime time" as a predictor of treatment response.

Immunotherapy is a promising new approach in oncology, but it does not work equally well for all types of cancer or for all patients with a specific cancer type. Researchers are therefore exploring various biomarkers that might help identify individuals who are likely to respond well.

Keytruda is a PD-1 checkpoint inhibitor, a type of immunotherapy that helps the immune system fight cancer. PD-1 is a receptor on T cells that plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or its binding partner, known as PD-L1, can release the brakes and restore T-cell activity. People with higher levels of PD-L1 in their tumors tend to do better on checkpoint inhibitors, but this is not a reliable predictor of individual response.

Another biomarker candidate is tumor mutational burden, a measure of the number of genetic changes in a tumor. Studies have shown that so-called "hot" or inflamed tumors filled with immune cells are more susceptible to checkpoint inhibitors. Such tumors typically have a large number of mutations, sometimes called neoantigens, that attract T cells. Thus, researchers have hypothesized, measuring TMB might predict response.

This turned out not to be the case, however, in two clinical trials that compared Keytruda plus Alimta (pemetrexed) and carboplatin platinum-based chemotherapy versus standard-of-care chemotherapy alone in people with previously untreated metastatic nonsquamous NSCLC.

KEYNOTE-021 showed that the Keytruda combination regimen led to improvements in the overall

response rate and progression-free survival, which supported Food and Drug Administration accelerated approval. Keynote-189, a larger Phase III trial, confirmed these findings and also showed an improvement in overall survival, leading to regular full approval of the regimen. While people with the highest PD-L1 levels had the best responses, even those who tested negative for PD-L1 saw improved outcomes compared with chemotherapy alone.

In a follow-up analysis from Keynote-021, Langer and colleagues explored the relationship between TMB and outcomes in two study cohorts. Data on TMB as determined by whole-exome genetic sequencing was available for 44 participants treated with Keytruda plus chemotherapy and 26 of those randomized to chemotherapy alone, representing nearly half of the cohort populations.

TMB was not significantly associated with overall response rate, progression-free survival or overall survival in either the Keytruda plus chemotherapy or chemotherapy-only groups, Langer reported. There was also no correlation between TMB and PD-L1 levels.

“Among pembrolizumab plus chemotherapy-treated patients, [the] overall response rate was high in both the TMB low and high subgroups,” Langer said in a WCLC press release.

Marina Garassino, MD, of Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, presented findings from a similar analysis of participants in Keynote-089. In this study, 616 patients were randomly assigned to receive Keytruda plus chemotherapy or a placebo plus chemotherapy. Again, about half (293 people) had evaluable TMB data.

Here, too, TMB was not significantly associated with response in either treatment group. People treated with Keytruda plus chemotherapy had better overall response rates, progression-free survival and overall survival compared with the chemotherapy-only group regardless of whether their TMB score was above or below 175. People with high and low TMB had similar overall response rates (50% versus 40%, respectively), median progression-free survival (9.2 versus 9.0 months) and median overall survival (23.5 versus 20.2 months). Outcomes were also similar when using a TMB cutoff of 150 mutations.

“Tumor mutational burden was not significantly associated with efficacy of pembrolizumab plus chemotherapy or placebo plus chemotherapy as first-line therapy for metastatic nonsquamous NSCLC,” Garassino said. “Pembrolizumab plus chemotherapy had a similar overall survival benefit in the TMB-high and low subgroups.”

Given the lack of correlation between TMB scores and response rates in these trials, as well as the inconsistent association between PD-L1 levels and outcomes in people with different types of cancer, researchers are left searching for other biomarkers that could help select individuals who have the best chance of responding to checkpoint immunotherapy.

Speaking at a WCLC plenary session, Keith Kerr of the University of Aberdeen School of Medicine and Dentistry in Scotland concluded that “no single biomarker is going to provide the perfect solution” and that “combinations may be more powerful.” Whatever happens, he added, “please,

make it practical and affordable.”

Click here for the WCLC conference program. These studies were presented Sunday in the “Immuno Combinations as the Role of TMB” session.
