Lung Cancer

General Non Small Cell Lung Cancer

Leading Treatment Options for Patients with Negative Tumor PD-L1

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Dr. Stephen Liu: My name is Stephen Liu, associate professor of medicine and director of thoracic oncology at Georgetown University in Washington, DC, for patients with metastatic non small cell lung cancer that does not harbor dry [inaudible] our current standard of care is immunotherapy. Multiple trials have shown that immunotherapy based treatment offers a significant survival advantage over chemotherapy alone. Using chemotherapy alone in the absence of a contraindication is simply no longer good enough and below our standard of care. The challenge is that there are several different strategies we can use to deliver immunotherapy. So how do we choose which regimen is appropriate? Our decision is first informed by expression of the protein PD-L1 on tumor cells. This is performed by a test called immunohistochemistry, done on a tissue specimen, not blood. If PD-L1 is positive or detected, we have one set of options. If PD-L1 is negative or not known, we have a different set of options, though. There is some overlap.

For PD-L1 negative tumors, the approved options are immunotherapy combinations. Most commonly used are combining a PD1 or PD-L1 antibody given intravenously with standard chemotherapy. The specific regimen is informed by the histology. The subtype of non small cell lung cancer. The most common is non-squamous non small cell lung cancer, primarily adenocarcinoma or large cell carcinoma. For this subset, the combination of carboplatin, pemetrexed and pembrolizumab, a PD1 inhibitor, is a commonly used and effective regimen that offers a survival benefit over standard chemotherapy. This was based on the large phase three randomized Keynote 189 trial with the addition of pembrolizumab to chemotherapy improved survival, doubling the median overall survival, and improving the one year survival rate from 49% to 69%. it's

benefit was seen across PD-L1 subtypes, including PD-L1 negative, with the hazard ratio of 0.59.

Another FDA approved regimen comes from the Empower 130 trial. This explore the combination of carboplatin and NAB paclitaxel given with the PD-L1 inhibitor Atezolizmuab. Here, the addition of Atezolizmuab chemotherapy improves survival, has a ratio is 0.79. It's difficult to compare across trials, but the important difference between these two studies are the chemotherapy backbones, as these have different toxicity profiles, different pros and cons. And so it is good to have multiple options. The Empower 150 trial looked at a four drug regimen, carboplatin, paclitaxel, the anti VEGF antibody bevacizumab, and the anti PD-L1 antibody Atezolizmuab. This also improves survival. Here, the hazard ratio is 0.78 and encouraging regimen in different subsets of lung cancer, including patients whose cancers have shredded the liver, a subset of patients where outcomes have historically not been as good. For squamous histology, there are different regimens used.

Here, the phase three Keynote 407 trial looked at a combination of chemotherapy with carboplatin and either paclitaxel or NAB paclitaxel, given with either pembrolizumab or placebo. Here, we saw that the addition of immunotherapy, pembrolizumab to chemotherapy in squamous lung cancer, also improved survival. Hazard ratio here is 0.64. Another interesting combination is dual Checkpoint Blockade with ipilimamab a CTLA4 antibody and nivolumab, a PD1 inhibitor. In patients with tumors that are PD-L1 negative, this combination improved survival. The hazard ratio was 0.64, with a median survival of 17 months and quite impressive duration of response of 18 months. Technically this is only approved for PD-L1 positive tumors and so use in PD-L1 negative non small cell lung cancer is off label use, but I do think it is reasonable and supported by the data. The most recently approved regimen is based on the phase three Checkmate 9LA trial.

This trial explore the combination of nivolumab, ipilumumab and chemotherapy, but the chemotherapy was only given for two cycles and stopped early. The phase three trial was for patients whose tumors did not express mutations or rearrangements in EGFR and ALK, but was across PD-L1 subsets and for all histology. This was a positive trial, the combination of nivolumab, ipilimumab, and two cycles of chemotherapy compared to standard chemotherapy, improved survival with a hazard ratio of 0.69 across major subtypes, including squamous histology and across PD-L1 cutoffs, including negative. As expected, there was more toxicity. 47% of patients had a grade three adverse event and about one in five patients had to stop due to toxicity. At the same time, because the

chemotherapy was limited to two cycles, there was less myelosuppression, likely reflecting the lack of cumulative toxicity of the bone there.

Overall immunotherapy should be part of our standard approach for all patients with driver negative, non small cell lung cancer, including PD-L1 negative tumors. Saving immunotherapy for later is not an appropriate response, but we do have multiple options which could include dual checkpoint blockade, or combination chemo, immunotherapy strategies. Selection of a specific regimen needs to be individualized based on specific clinical circumstances, comorbidities, and certainly patient input. So a clinical trial with novel combinations may also be an option for some patients.