Lung Cancer

General Small Cell Lung Cancer

Immunotherapy for Small Cell Lung Cancer

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Dr. Stephen Liu: My name is Stephen Liu. I'm an associate professor and director of thoracic oncology at Georgetown University in Washington, DC. Small cell lung cancer is a particularly lethal subtype of lung cancer. It accounts for about 13% of new diagnoses, but represents a disproportionate number of lung cancer deaths. Our historic standard for this disease has been chemotherapy, platinum plus etoposide, this is not new treatment. This was first introduced in the 1970s, and it may seem like an effective treatment. It has a high initial response rate about 60%, about 10% of patients will have a complete response, but that benefit is transient. The progression free survival is limited to about four months. Meaning most patients will progress either during or shortly after chemotherapy. Survival had been limited to about eight to 10 months on average. Despite these shortcomings, this has been our standard treatment for small cell lung cancer for decades.

We simply have not been able to improve upon it. Despite many phase three trials, the first major advance for small cell lung cancer was immunotherapy. The initial signal came in the previously treated space where we saw exciting activity in Checkmate 032 the PD1 inhibitor nivolumab, given either alone or with a CTLA4 inhibitor Ipilimumab offered modest response rates around 10 to 20%, progression free survival rates that were unfortunately quite short, but impressive landmark survival rates. Meaning more patients were alive at the one year and the two year Mark. For example, the combination of nivolumab and ipilimumab had a two year survival rate of 26%. The number may seem low, but with any standard treatment in patients who've received many other treatments, that number would be quite close to zero. Based on the quality of these responses and the potential for durable survival. We saw the FDA approval of a

third line nivolumab monotherapy in August, 2018 and third line pembrolizumab monotherapy in June, 2019.

These are important approvals, but the problem is that only about one in five patients will receive third line treatment, which really limits the impact. So to increase that impact for these potentially transformative medications, we try to introduce immunotherapy earlier. Checkmate 331 was a randomized phase three trial comparing second line nivolumab versus standard Topotecan chemotherapy. Disappointingly, this was a negative trial. Nivolumab failed to improve survival over Topotecan. Even earlier, Checkmate 451 explored maintenance, immunotherapy, patients who completed chemotherapy and then immediately received immunotherapy before progression did not derive benefit. The use of nivolumab and ipilimumab as a maintenance treatment after chemotherapy did not improve survival over placebo. No, it was in the first line setting where we saw practice changing data. The first trial to explore this approach was Empower 133.

This was a randomized double blind placebo controlled phase three trial for patients with untreated extensive stage small cell lung cancer. In this study, all patients received standard chemotherapy with carboplatin and a etoposide and were randomized one-to-one to receive concurrent Atezolizmuab, which is a PDL1 antibody or placebo followed by maintenance Atezolizmuab or placebo. The co-primary endpoints were progression free survival and overall survival. And this was a positive trial meeting, both end points. We saw an improvement in progression free survival with a hazard ratio of 0.77. But most importantly, we saw an improvement in overall survival with a hazard ratio of 0.7. This translates to an improvement in survival and reduction in the risk of death, about 30%. This was the first improvement in survival we've seen in decades. And importantly it did not come at the cost of significant toxicity. We also saw improvements in patient quality of life.

And this landmark improvement led to the FDA approval of Atezolizmuab as part of the first line treatment for small cell lung cancer in March, 2019. We had waited almost four decades to see any improvement in survival. We waited less than a year to see the next improvement. When we saw the results of the Caspian trial. This was an open label phase three trial for patients with extensive stage small cell lung cancer. They were randomized to receive chemotherapy alone, chemotherapy with the PDL1 inhibitor durvalumab followed by maintenance durvalumab, or chemotherapy with durvalumab and the CTLA4 inhibitor tremelimumab, with durvalamab maintenance. What we saw was that the addition of durvalumab to chemotherapy improved survival. Here, the hazard ratio is 0.73 and survival curves that appear very similar to Empower 133 with Atezolizmuab. This led to the FDA approval of durvalumab in March, 2020, the third arm

of that trial, featuring durvalumab with tremelimumab unfortunately it did not meet its Survival endpoint.

The addition of tremelimumab increased toxicity, but did not offer gains in survival. In June, 2020, we also saw the results of Keynote 604, a randomized phase three trial of pembrolizumab, a PD1 antibody with chemotherapy. While pembrolizumab improved progression free survival, unfortunately it did not meet its survival endpoint. There was a trend towards improvement in survival, but it did not cross the predetermined threshold for positivity. This limits its clinical practice impact, but it validates the approach that the addition of immunotherapy to chemotherapy does improve outcomes. In an attempt to identify who are deriving that benefit, we explore different biomarkers. An important one is PDL1 expression, which is useful in non small cell lung cancer. PDL1 expression was explored in Caspian, in Empower 133, and in Keynote 604. And while PDL1 was detected on some tumor cells it did not prove useful in determining who derives that benefit.

PDL1 expression cannot be used to select patients for immunotherapy in small cell lung cancer. Tumor mutational burden is often explored in cancers as a predictive marker for immunotherapy benefit. Blood-based TMB was explored in Empower 133, but also did not serve a predictive role, whether it was low or high, regardless of cutoff, patients derive benefit from immunotherapy. Our current standard of care is to deliver concurrent Atezolizmuab or durvalumab with chemotherapy followed by Atezolizmuab or durvalumab maintenance treatment in an all comer approach.