



**Lung Cancer Video Library**  
**General Non Small Cell Lung Cancer**  
**Current Status of Tumor Mutational Burden, 2020**

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Dr. Charu Aggarwal: We will talk about blood-based tumor mutational burden today. There has been a lot of interest in tumor mutation burden over all. As a predictive biomarker for response to immunotherapy. Previously using tissue TMB we have seen superior outcomes with immunotherapy versus chemotherapy for patients that have high tissue TMB both in non small cell lung cancer and in melanoma. Most recently blood based TMB has become interesting because it offers a minimally invasive way to ascertain patient's tumor mutation burden, especially in those patients receiving immunotherapy.

Previously blood based TMB greater than 16 mutations per mega base has been shown to predict for response to immunotherapy alone. In a study that was published in Nature Medicine by Dr. Kundera and colleagues as well as combination anti PDL 1 and CTL 4 combination on the MYSTIC trial as presented by Dr. Peters as well as Dr. Risbee, and updated at the last meeting at the World Conference of Lung Cancer in 2019. What they showed was that patients that had a TMB greater than 16 tended to have superior outcomes and perhaps even a subset of patients that had TMB greater than 20 had a slightly better outcome to combination immunotherapy. But is this really true for patients that receive chemo immunotherapy?

In a study that we conducted at Penn Medicine, we showed that patients who had high TMB, again in the blood, as defined as greater than 16 mutations per mega base, using a 500 gene panel, using a more specialized Research Assay that's not currently available clinically. We were able to sort of dissect our population into two groups those that were greater than 16 or less than 16 mutations per mega base, and we did see that patients who had this higher tumor mutational burden tended to have superior



outcomes with either immunotherapy alone or combination chemo immunotherapy which is currently the standard for most patients that have PDL 1 expression, less than 50 percent. We saw this for response rate. We saw this for progression free survival, and there were trends for overall survival although our numbers were not big enough to really discern these differences as the median overall survival were quite long.

There's also been interest in looking at other mutations. So we looked at RB2, Exon 20, we looked at [inaudible] level which is an emerging biomarker, P1 and P10. We also found that these mutations tended to cluster in patients that did not receive a durable benefit from immunotherapy and these are findings that I think need to be validated in a larger clinical trial. There are certainly many more reports of [inaudible] level, as well as keep at P10 being negative predictors of response to immuno therapy so perhaps we could come up with a composite score of TMB in combination with these negative predictive mutations that can really help us figure out which patients are destined to best benefit from immunotherapy. And which patients may benefit from a chemotherapy based approach. I think these are things that we need to look at in further prospective clinical trials.