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The Survival Ceiling in ES-SCLC: Why Checkpoint Blockade Alone Is Not Enough

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Dr. Ready:

Welcome to this educational activity with GLC. I'm Dr. Neal Ready from Duke University. Today, I'll discuss limitations of first-line chemoimmunotherapy in extensive-stage small cell lung cancer and emerging strategies to improve patient outcomes in this setting.

The first major breakthrough adding immune therapy to standard treatment in small cell lung cancer was IMpower133. This was a study in first-line extensive-stage small cell lung cancer where patients received standard chemotherapy with or without atezolizumab, both with the chemotherapy induction and during maintenance. The primary endpoints were overall survival and investigator-assessed progression-free survival.

The overall survival was significantly improved, and this had not been seen for 20 or 30 years in extensive-stage small cell lung cancer, with an improvement in median survival from 10.3 months to 12.3 months, which was considered both statistically significant and clinically meaningful.

The next important study was the CASPIAN study. This was another phase 3 trial. There were 3 arms: standard chemotherapy, standard chemotherapy with the PD-L1 antibody durvalumab, or chemotherapy, durvalumab, plus a CTLA-4 inhibitor, tremelimumab. The positive arm was the durvalumab and chemotherapy arm. In that arm, overall survival was meaningfully improved, and more importantly, we see impressive landmark survivals compared to standard chemotherapy at 2 and 3 years.

We've reviewed some of the important progress made in adding immune therapy to chemotherapy in first-line treatment of extensive-stage small cell lung cancer, but the results at this point, what we can offer patients, is not adequate. There's a lot more progress to be made.

Some of the things that have been standing in the way of immune therapy working in small cell lung cancer are difficulty with antigen presentation and recognition, where tumor cells do not express MHC-I, sometimes due to mutations and deletions; tumor microenvironment modulation, where cytokines such as VEGF and hypoxia can exclude T cells from the tumor microenvironment; tumor-induced immune suppression, where T-regulatory cells that get into the tumor microenvironment can directly inhibit the activity of T cells; and finally there are numerous immune inhibitory checkpoints. The common ones that you probably know about are PD-1, CTLA-4, and perhaps LAG-3, but there are many others, such as TIM-1, TIGIT, VISTA, BTLA, CD47, etc. So we have lots of different ways that the immune system can be inhibited, and now we need some strategies to overcome these problems.

So these are some of the ways of thinking about small cell lung cancer that may allow us to improve outcomes on top of what has already been done with the addition of immune therapy to chemotherapy. We know that different genes are modulated in small cell lung cancer compared to normal cells. This can lead to production of receptor tyrosine kinases on the cell surface, neuroendocrine signaling, and immune regulatory targets on the cell surface. All of these cellular changes can lead to potential ways that we can target small cell lung cancer.

While the standard therapies that we now have are meaningful, we have a long way to go, and we need to look for new targets and new mechanisms of action to continue to make progress in the treatment of small cell lung cancer.

Well my time is up, I hope you have found this brief overview helpful, and thanks for participating.

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