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Rationale of Emerging Antigen-Directed Strategies in Frontline ES-SCLC

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Dr. Ready:
Welcome to CE with GLC. I'm Dr. Neal Ready from Duke University. Today, I'll discuss the rationale for emerging antigen-directed strategies in first-line treatment for extensive-stage small cell lung cancer.

Here is a cartoon of a small cell lung cancer cell. I've illustrated the cell membrane with different molecules sticking out. There's TROP2, B7-H3, DLL3, SEZ6, and Fuc-GM1. These are all molecules that are expressed on most small cell lung cancer cells but not on most normal cells. This makes them a target for different mechanisms of action.

When we give an antibody against Fuc-GM1, such as an anti-fucosyl-GM1 now called atigotatug, the antibody can stick onto the tumor cell, as shown in this cartoon, and cause antibody-dependent cellular phagocytosis, where a phagocyte may attack the tumor cell; can cause antibody-dependent cell-mediated cytotoxicity, where a natural killer cell could attack the tumor cell. If there's enough antibody on the tumor cell, it can cause complement-dependent cytotoxicity.

And we know from clinical trials that if we block PD-1 on the T cell with nivolumab, then we get additive or synergistic activity with the anti-fucosyl-GM1 antibody.

The anti-fucosyl-GM1 antibody atigotatug is now combined in the same bag with nivolumab as a single anti-cancer product. This can be given in one infusion.

Antibody-drug conjugates are also really important, and there are several very interesting antibody-drug conjugates in clinical development against small cell lung cancer. I-DXd, which is ifinatamab deruxtecan, which is an antibody-drug conjugate of B7-H3, has been studied extensively in phase 2 trials and now in phase 3 trials. Here we see the deruxtecan toxin bound to the humanized anti-B7-H3 antibody, with 4 toxins per molecule. In patients with previously treated small cell lung cancer, there was a high degree of activity for that antibody-drug conjugate.

Tarlatamab has now been approved for the treatment of second-line small cell lung cancer. Tarlatamab is a bispecific antibody against CD3 and DLL3. What this does is it allows the bispecific antibody to attach to a T cell and also to a cancer cell and pull them in close proximity so that the T cells can activate, proliferate, and attack the cancer cell.

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So small cell lung cancer is mostly an immunologically cold tumor. So how do we turn a cold tumor into a hot tumor? This is potentially possible by targeting the molecules on the small cell lung cancer surface, and this can be with antibody therapy, antibody-drug conjugate therapy, bi- and trispecific antibodies, and even CAR-T cells, which is an active area of advanced research in small cell lung cancer.

Well, that's all the time I have today. I'm glad I've had this opportunity to share this information with you. Thank you for participating.

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