What's coming up at EHA 2021?

Beyond Autologous CAR-Ts: Why is the New Wave of Cell Therapies in B-cell Lymphomas Inevitable?

The first wave of innovative cell therapies has been game-changing in the management of many hard-to-treat relapsed and refractory B-cell malignancies. Four autologous CD19 targeting CAR-Ts (Kymriah, Yescarta, Tecartus and Breyanzi) with various constructs are approved and have shown remarkable benefits in high unmet need R/R patient segments of lymphomas such as DLBCL, MCL, and FL.

Despite tremendous success, there are several limitations with autologous CAR-Ts that stymie their wider use and realization of their true potential. The major barriers are:

- logistic challenges that delay therapy initiation
- resistance to auto CD19 CAR-T therapies; clonal escape or development of CD19 negative clones
- health of T-cells from heavily pretreated patients
- high cost and resource utilization

Extensive clinical activity is ongoing to address these challenges. The new phase of promising cell therapies under development includes key new approaches like '***off-the-shelf***' CD19 allogeneic CAR-Ts with nearly no vein-to-vein time, allogeneic CD19 CAR NK cells, and exploration of alternative antigen beyond CD19 or dual bispecific antigen targeting CAR-Ts.

Exciting new data is being presented at ASCO and EHA 2021 showcasing some of these approaches in B-cell malignancies. The key abstracts and products to watch out for are allogeneic CAR-Ts (CTX110, PBCAR0191, ALLO-501/501A), new or bispecific CAR-Ts (CD20 CAR-T, C-CAR039), and NK CAR cells.

The Tale of Two Targets: Where do Bispecific Fit in B-cell Lymphoma Treatment?

Blinatumomab is only bispecific antibody targeting CD19 and CD3 approved to treat R/R ALL. Bispecific antibodies are now being studied in virtually all the key heme malignancies targeting increased efficacy over monospecific antibodies. The bispecifics are considered one of the most promising '***off-the-shelf***' modalities, perceived to be comparable to CAR-T cell therapy for the treatment of R/R lymphomas, but with less side effects e.g. CRS and neurotoxicity especially for T-cell engaging bispecifics.

Future clinical data will guide how bispecific CAR-Ts vs. bispecific antibodies will play out in hematologic malignancies, with attention to:

- The right patient selection for bispecifics
- The right sequencing of therapies against the same target
- The right combinations to maximize outcomes

Multiple studies are reading out at ASCO and EHA 2021 with noteworthy examples including CD20 x CD3 dual targeting (mosunetuzumab, glofitamab, and epcoritamab), novel ROR1 x CD3 (NVG-111), and CD19 x CD20 that can potentially offer options for patient ineligible or resistant to CAR-T therapies.

ADCs in B-cell Lymphomas

Antibody-drug conjugates (ADCs) is a rapidly evolving unique class of agents that incorporates cytotoxic payloads, covalently linked to a monoclonal antibody. More than 10 ADCs are already approved in multiple hematologic malignancies including lymphomas, with the recent approvals of polatuzumab vedotin and loncastuximab tesirine in DLBCL.

Like bispecifics, the ADCs may provide a readily available therapy in R/R lymphomas. There are numerous ADC trials in lymphoma evaluating diverse payloads, TAA selection, advanced linkers, optimizing DAR, alternative dosing schedules, optimizing patient selection, identifying potential biomarkers, and use as monotherapy or in combination to maximize the therapeutic index of ADCs.

ADCs are targeting both established and novel targets such as CD19, CD37, CD25, CD70, or ROR1. Questions remain on how the ADCs will be best utilized:

- Will there be a shift of 'easier-to-use' ADCs in the earlier lines of therapy and an impact on therapy sequencing?
- Which combinations of ADCs with novel agents such as bispecifics or current SoCs will add clinical value?
- What will be the basis of modality selection for the same target (such as CD19) in lymphomas?

At ASCO and EHA 2021, there will be presentations highlighting the new data for ADCs such as loncastuximab tesirine, polatuzumab vedotin, and brentuximab vedotin.

We look forward to assessing the impact of the data presented on CAR-Ts, bispecific antibodies, and ADCs in hematologic malignancies at EHA 2021.

SmartAnalyst is helping clients interpret the data presented at EHA 2021 (June 9-17) and the implications on their clinical development programs and go-to-market strategies. Contact us to learn more

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