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ASH 2024:

Technological & Manufacturing Innovations: CAR T-Cell Therapy

Innovative therapies with novel mechanisms of action (MOA) were among the most exciting topics at the American Society of Hematology (ASH) 66th Annual Meeting and Exposition. In our final installment recapping ASH 2024, we cover major abstracts that revealed the potential of new scientific approaches, including new constructs and MOAs that improve the performance of CAR T-cell therapy. We also dive into the manufacturing advancements that have the potential to revolutionize the landscape of cancer treatment.

Novel Constructs and Mechanisms of Action

Innovative CAR constructs and mechanisms of action were key highlights at ASH, offering new ways to enhance the precision, efficiency, and safety of CAR T-cell therapies. These approaches aim to target a broader range of tumor antigens, improve therapeutic outcomes, and address safety concerns associated with traditional CAR designs.

- **Anitocabtagene Autoleucel (anito-cel) in relapsed/refractory (r/r) Multiple Myeloma[1]:** Preliminary data from the phase II iMMagine-1 trial demonstrated a remarkable 97% overall response rate (ORR) and 62% complete response rate (CR) in patients with fourth-line or later multiple myeloma. With a 12-month progression-free survival (PFS) of 78.5%, this therapy stands out for its manageable safety profile, as no delayed neurotoxicity or immune effector cell-associated neurotoxicity syndrome (ICANS) were reported—potentially setting it apart from other BCMA-targeted CAR T-cell competitors in this space. Additionally, a unique feature of anito-cel is its novel D-domain binder. The construct helps provide high transduction efficiency, low tonic signaling, and a fast off-rate, which is thought to contribute to enhanced malignant cell elimination while minimizing prolonged inflammation.

- **Arlocabtagene Autoleucel (arlo-cel) in r/r Multiple Myeloma[2]:** Updated findings from Cohort A of the phase I MM-001 trial demonstrated an 87% ORR (CR: 53%) and a median PFS of 18.3 months. By targeting GPRC5D, this therapy offers an exciting new mechanism of action among CAR T-cell therapy agents for fourth-line or later multiple myeloma patients. Importantly, no delayed parkinsonism, Gullain-Barré syndrome or cranial nerve palsy were observed, adding to the arlo-cel's safety profile.

Long-Term Insights in CAR T-Cell Therapy

CAR T-cell therapy continues to redefine the treatment of hematologic malignancies, with multiple long-term follow-up and real-world evidence studies presented during the conference.

- **Axicabtagene Ciloleucel (Yescarta) in r/r FL and Marginal Zone Lymphoma (MZL)[3]:** In a 5-year follow-up from ZUMA-5, Yescarta achieved a 90% ORR (CR: 75%) among all treated patients. The 5-year median PFS was 62.2 months, and the estimated overall survival (OS) rate was 69% overall. The findings continue to solidify Yescarta's role as a transformative therapy for relapsed/refractory indolent NHL.

- **Lisocabtagene Maraleucel (Breyanzi) in r/r LBCL[4]:** Long-term follow-up of the TRANSCEND trial showcased median OS of 27.5 months and a 5-year OS rate of 38.1%, rising to 56% in patients achieving complete remission. These results underline the curative potential of Breyanzi in LBCL.

- **Comparative Real-World Outcomes of CD19 CAR T-cell Therapies in LBCL[5]:** A real-world study of 501 patients with r/r LBCL compared outcomes of three CD19-directed CAR T-cell therapies—Breyanzi, Kymriah, and Yescarta—across centers in the USA and Israel from April 2016 to January 2024. Breyanzi demonstrated comparable PFS and OS to Yescarta, while Kymriah was associated with comparatively inferior efficacy in the second line setting. In terms of safety, Breyanzi was found to have the most favorable safety profile, with lower rates of cytokine release syndrome (CRS) and ICANS compared to the other two products. These findings are consistent with previously understood data and offer further confirmation for the application of CAR T-cell therapy in real-world clinical practice.

Rapid Manufacturing

Reducing manufacturing times for CAR T-cell therapies was a key focus at ASH. Emerging technologies are revolutionizing CAR T-cell manufacturing processes by significantly shortening production times from weeks to just a few days, enabling faster patient access to these life-saving therapies.

- **Zamtocabtagene Autoleucel (zamto-cel) in r/r diffuse large B-cell lymphoma (DLBCL)[6]:** The DALY II USA Phase II study assessed zamto-cel, a non-cryopreserved CD20-CD19 targeted CAR T-cell therapy, in patients with relapsed/refractory DLBCL. The therapy demonstrated a 72.8% ORR and a 50.8% CR, with a 12-month PFS of 42% and OS of 72%. Unlike currently approved CAR T-cell therapies, zamto-cel is administered as a fresh product with a quick vein-to-vein time of 14 days. With no patients requiring bridging therapy in clinical trials, zamto-cel offers a promising option for high-risk r/r DLBCL patients.

- **Rapcabtagene Autoleucel (rapca-cel) in r/r DLBCL[7]:** In the phase II trial, rapca-cel, a CD19-targeted CAR T-cell therapy, achieved an 88.3% ORR (CR: 65%) and a 12-month OS of 83%. While rapca-cel's rapid T-Charge technology platform, capable of manufacturing cell product in as little as 2 days, offers logistical benefits, the entire preparation process spans several days, potentially limiting the overall impact of its manufacturing speed. This is particularly notable given that 60% of patients required bridging therapy in the trial. However, despite these challenges, rapca-cel delivers exceptional efficacy with an accelerated

manufacturing process, reinforcing its value as an innovative treatment for patients with r/r DLBCL.

- **GC012F/AZD0120 in Multiple Myeloma[8]:** The study evaluating GC012F/AZD0120, an autologous BCMA/CD19 dual-targeting FasTCAR T-cell therapy for elderly patients with newly diagnosed multiple myeloma (NDMM), demonstrated promising results. In the phase I trial, all eight treated patients achieved a 100% ORR, with 62.5% achieving CR, and all patients also became minimal residual disease (MRD) negative. The therapy showed a favorable safety profile, with mild CRS in 50% of patients, suggesting that age should not be a barrier to effective treatment for this patient population. Additionally, the ability for FasTCAR technology to manufacture T-cells in just a few days, further accelerates access to therapy for patients.

Decentralized Manufacturing

Another groundbreaking approach highlighted at ASH was decentralized manufacturing, which shifts production from centralized facilities to strategically located sites closer to patients. This model has the potential to streamline logistics, reduce costs, and accelerate therapy delivery.

- **GLPG5101 in r/r Non-Hodgkin Lymphoma (NHL)[9]:** The ATALANTA-1 study evaluated GLPG5101, a fresh, stem-like, early memory CD19 CAR T-cell therapy, in patients with relapsed/refractory non-Hodgkin lymphoma. The therapy demonstrated high efficacy, with an ORR of 88% and a CR of 83% across all subtypes. GLPG5101 stands out due to its decentralized manufacturing process and a quick median vein-to-vein time of just 7 days, enabling faster and more efficient delivery of cells. Of note, this decentralized approach on a rapid timeline effectively eliminated the need for product cryopreservation and bridging therapy for patients.

Induced Pluripotent Stem Cell (iPSC)-Derived T-cells

A particularly exciting area of preclinical research at ASH showcased the use of induced pluripotent stem cells (iPSCs) to develop T-cell therapies. IPSCs are generated from adult somatic cells that have been reprogrammed to regain their pluripotent state.[10,11] IPSCs offer a unique advantage in that they can theoretically grow almost indefinitely, making them an effective source for generating genetically engineered immune cells, including T-cells, with the ability to introduce enhanced therapeutic functions, such as CAR-based antigen targeting. Allogeneic "off-the-shelf" iPSC-derived T-cell therapies could overcome the challenges associated with traditional CAR T treatments by providing a scalable and cost-effective solution, with the potential for genetic modification to promote hypo-immunogenicity and enhanced anti-tumor activity. With advancements in good manufacturing practices, safety protocols, and scalability, iPSC-based therapies hold the promise of standardized, clinically viable treatments, paving the way for broader patient access in the future.

Closing Thoughts - ASH 2024

The ASH 2024 meeting showcased groundbreaking advancements in the field of cell and gene therapies, highlighting their transformative potential in the treatment of hematologic malignancies, genetic disorders, and rare disease. At the same time, the discussions shed light on crucial hurdles that must be addressed to fully realize this potential – including access, safety risks, and the complexities of scaling these therapies into real-world clinical practice. These challenges call for collaborative

efforts across the healthcare ecosystem to ensure these innovative treatments can benefit patients.

As the science continues to evolve, the promise of cell and gene therapies is not just limited to extending survival but also to fundamentally altering the trajectory of disease once thought untreatable. These innovations are poised to redefine clinical practice and reshape treatment paradigms. It is an exciting time in hematology, with a future brimming with possibilities for patients and clinicians alike.

1. Freeman CL, Dhakal B, Kaur G, et al. Phase 2 registrational study of anitocabtagene autoleucel for the treatment of patients with relapsed and/or refractory multiple myeloma: preliminary results from the iMMagine-1 trial. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #1031.
2. Bal S, Anderson LD, Nadeem O, et al. Efficacy and safety with extended follow-up in a phase 1 study of BMS-986393, a G Protein-Coupled Receptor Class C Group 5 Member D (GPRC5D)-targeted CAR T cell therapy, in patients (pts) with heavily pretreated relapsed/refractory (RR) multiple myeloma (MM). Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #922.
3. Neelapu SS, Chavez JC, Sehgal AR, et al. 5-Year Follow-up Analysis from ZUMA-5: A Phase 2 Trial of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #864.
4. Abramson J, Palomba M, Gordon L, et al. Five-Year Survival of Patients (pts) from Transcend NHL 001 (TRANSCEND) Supports Curative Potential of Lisocabtagene Maraleucel (liso-cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL). Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #3125.
5. Deschenes-Simard X, Bromberg M, Devlin S, et al. Comparative Real-World Outcomes of Commercial CD19-Directed CAR T-Cell Therapies in Large B-Cell Lymphoma. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #3752.
6. Shah N, Maziarz R, Jacobson C, et al. Interim Results from a Phase 2 Pivotal Study (DALY II USA) of Tandem CD20-CD19-Directed Non-Cryopreserved CAR-T Cells - Zamtocabtagene Autoleucel (Zamto-Cel) in Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #68.
7. Riedell PA, Kwon M, Flinn IW, et al. Rapcabtagene Autoleucel (YTB323) in Patients (Pts) with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL): Phase II Trial Clinical Update. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #67.
8. Du J, Qiang W, Lu J, et al. Autologous B Cell Maturation Antigen (BCMA) and CD19 Dual Targeting Fastcar-T Cells (GC012F/AZD0120) As First-Line Therapy for Elderly Patients with Newly Diagnosed Multiple Myeloma Patients. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #2072.
9. Kersten M, Saevels K, Willems E, et al. Atalanta-1: A Phase 1/2 Trial of GLPG5101, a Fresh, Stem-like, Early Memory CD19 CAR T-Cell Therapy with a 7-Day Vein-to-Vein Time, for the Treatment of Relapsed/Refractory Non-Hodgkin Lymphoma. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #93.
10. Netsrithong R, Garcia-Perez L, Themeli M. Engineered T cells from induced pluripotent stem cells: from research towards clinical implementation. *Front Immunol.* 2024 Jan 12;14:1325209.
11. Ye L, Swingen C, Zhang J. Induced pluripotent stem cells and their potential for basic and clinical sciences. *Curr Cardiol Rev*. 2013 Feb 1;9(1):63-72.