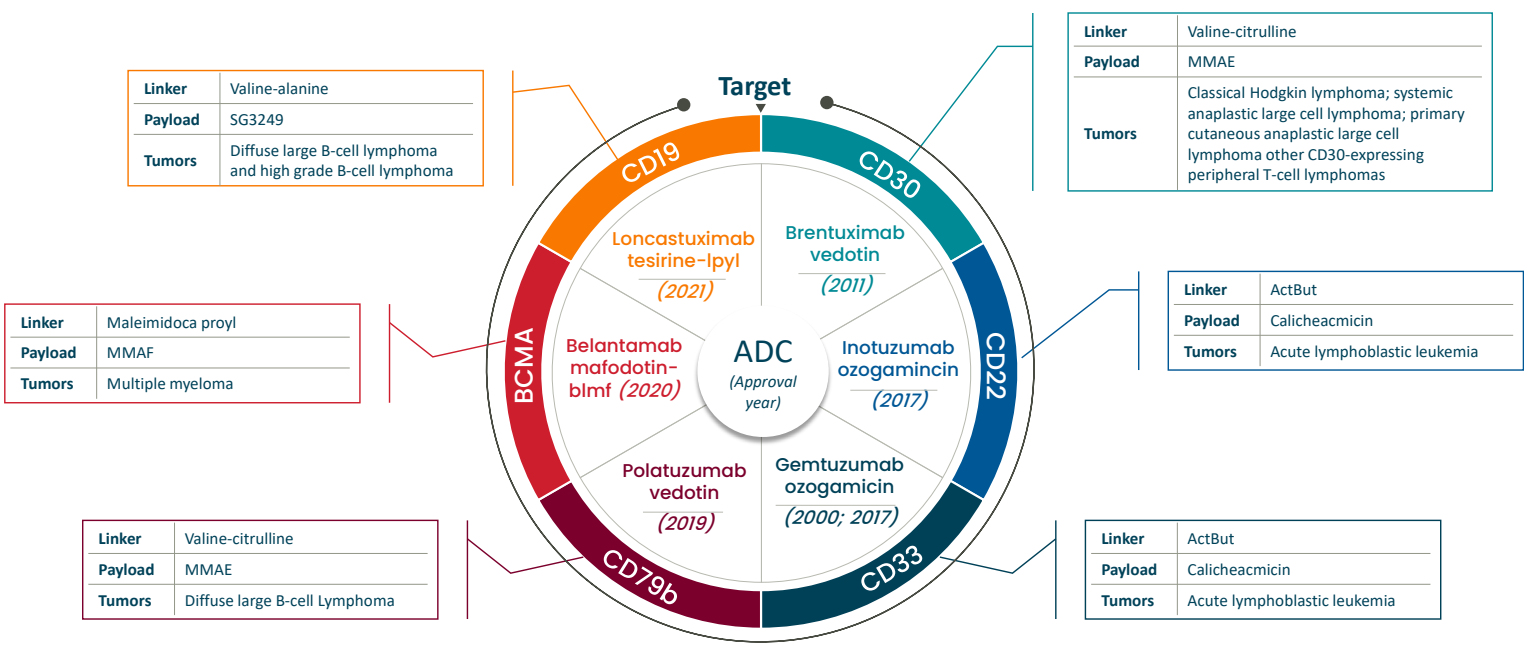
ASH 2021

Advances in Antibody-drug Conjugates(ADCs) for Hematological Malignancies

Conventional cancer treatments such as chemotherapy, radiotherapy, nanoparticulate-based targeted therapies, and immunotherapies have significant adverse events and patients can develop drug resistance.[1] Antibody-drug conjugate (ADC) class of drugs work like a guided missile composed of an antibody directed against the tumor antigen, a cytotoxic payload which is the effector component, and a linker. It binds to tumor cell antigen, gets internalized via endocytosis, and releases cytotoxic payload following lysosomal degradation. The cytotoxic payload then kills the tumor cell by apoptosis. ADCs are being developed with the goal of high tumor selectivity, increased drug tolerability, and limited drug resistance.[2]

Six ADCs have been approved for hematological malignancies[3] and contain 6 unique target antigens, 4 linkers, and 4 cytotoxic payloads.



Despite the approval of several ADCs, toxicity and drug resistance remain key challenges in developing an ADC. Gemtuzumab ozogamicin is an example of toxicity-associated limitations. Initially approved in 2000 for relapsed AML, it was voluntarily withdrawn in 2010 after trials failed to confirm benefit and demonstrated safety concerns, including early mortality and VOD. In 2017, US FDA approved it again based on new trials with a lower recommended dose and schedule of gemtuzumab ozogamicin than what the FDA approved previously in 2000, as well as a different patient population. Drug resistance is another concern in the development of ADCs. Preclinical studies have shown that patients can develop drug resistance against ADCs because of mutations in targeted cell surface antigens and/or a decrease in payload toxicity due to upregulation of drug efflux transporters.[5,6]

Research and development in ADCs is fast expanding and evolving, in both hematological malignancies and solid tumors. Most clinical trials are in lower phases with few reaching Phase III. ASH 2021 is expected to provide insights on a stimulating array of advancements in new target antigens, linkers, and payloads. One such ADC being evaluated is Zilovertamab vedotin (ZV), a first-in-class humanized mAb with a novel target ROR1, a type1 transmembrane protein. ROR1-expressing tumors have a high potential for self-renewal, exhibit increased survival and migration, and are associated with poor outcomes. Preclinical studies have shown that ZV can safely induce tumor shrinkage even with heterogenous ROR1 expression, thus suggesting that it may have reduced drug resistance in addition to a good safety profile. SmartAnalyst will closely monitor these developments at ASH 2021.

ASH 2021 Key Data Read Out

ADC	Target	Linker	Payload	Tumors	Developmental Phase
Zilovertamab Vedotin (MK-2140) (VLS-101)[7]	ROR1	Valine-citrulline	MMAE	Non-Hodgkin's lymphoma (FL, MZL, DLBCL, MCL, Richter transformation, Burkitt lymphoma, and T-cell-NHL), chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenstrom macroglobulinemia, acute lymphoblastic leukemia or acute myeloid leukemia	Phase I, FIH
Naratuximab emtansine[8]	CD37	SMCC (maleimide-derived thioether-based)	DM1	Follicular lymphoma, mantle cell lymphoma, and diffused large B-cell lymphoma	Phase II
IMGN632[9]	CD123	Peptide	DGN459	CD123+ acute myeloid leukemia	Phase Ib/II

References

1. M.-R. Nejadmoghaddam, A. Minai-Tehrani, R. Ghahremanzadeh, et al. Antibody-drug conjugates: Possibilities and challenges. Avicenna J Med Biotechnol. 2019;11(1):3–23.
2. A. Papachristos, N. Pippa, C. Demetzos, et al. Antibody-drug conjugates: a mini-review. The synopsis of two approved medicines. Drug Deliv. 2015;23(5):1662—1666.
3. A. Q. Dean, S. Luo, J. D. Twomey, et al. Targeting cancer with antibody-drug conjugates: Promises and challenges. mAbs. 2021;13(1):1951427.
4. C. M. Mckertish, V. Kayser. Advances and limitations of antibody drug conjugates for cancer. Biomedicines. 2021;9:872.
5. N. Joubert, A. Beck, C. Dumontet, et al. Antibody–drug conjugates: The last decade. Pharmaceuticals. 2020;13(9):245.
6. D. M. Collins, B. Bossenmaier, G. Kollmorgen, et al. Acquired resistance to antibody-drug conjugates. Cancers. 2019;11(3):394.
7. M. Wang, M. Mei, P. M. Barr, et al. Phase 1 Dose escalation and cohort expansion study of the anti-ROR1 antibody-drug conjugate Zilovertamab Vedotin (MK-2140) for the treatment of non-Hodgkin lymphoma [Abs#528]. In: ASH 2021; December 11-14; Atlanta, GA. Available at: https://ash.confex.com/ash/2021/webprogram/Paper148607.html.
8. M. Y. Levy, D. Jagadeesh, Z. Grudeva-Popova, Safety and efficacy of CD37-targeting Naratuximab Emtansine PLUS rituximab in diffuse large B-cell lymphoma and other non-Hodgkin'S B-cell lymphomas – a Phase 2 study [Abs#526]. In: ASH 2021; December 11-14; Atlanta, GA. Available at: https://ash.confex.com/ash/2021/webprogram/Paper145102.html.
9. N. Daver, A. Aribi, P. Montesinos, et al. Safety and efficacy from a Phase 1b/2 study of IMGN632 in combination with azacitidine and venetoclax for patients with CD123-positive acute myeloid leukemia [Abs#372]. In: ASH 2021; December 11-14; Atlanta, GA. Available at: https://ash.confex.com/ash/2021/webprogram/Paper146503.html.

SmartAnalyst will focus on the key presentations to help clients understand the advances in ADCs for hematological malignancies. Contact us to learn more

Please Contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile: +44-(0)-752-163-8242
Mobile: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, India)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel: 91-124-4313800

SmartAnalyst
An Ashfield Advisory Company