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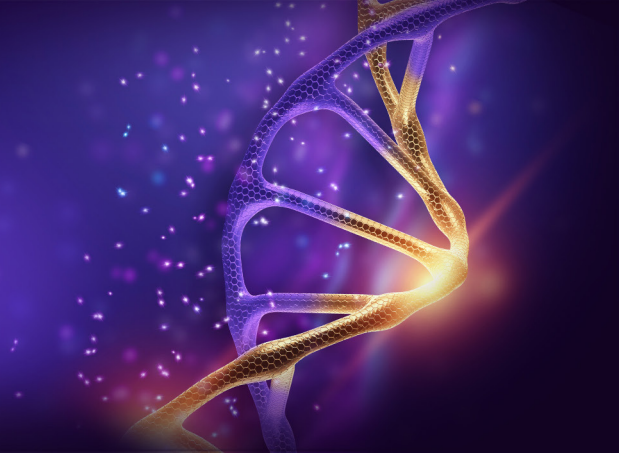
Inizio Advisory

SPOTLIGHT ON
Antibody Drug Conjugates (ADCs)



After the wave of immuno-oncology, antibody drug conjugates (ADCs) have been a transformational platform in Oncology that are redefining treatment strategies across tumors. This is reflected by the analyst projections of the ADC market opportunity to grow from $7B in 2022 to ~$17B by 2030, driven by organic growth or by mergers and acquisitions. Companies continue to add or expand their drug conjugate offerings to remain competitive. Key recent BD&L activities with drug conjugates include:

- Drug Partnership Deals: Merck-DSI (HER3, B7-H3 and CDH6 ADC), BioNTech-DualityBio (HER2, B7-H3 ADC), EMD Serono-Hengrui (CLDN 18.2 ADC), GSK-Hansoh (B7-H4 ADC), and BeiGene-DualityBio (Undiclosed target, preclinical)
- Innovative Drug Conjugate Technology Deals: Seagen-Nurix (Degrader antibody conjugates) and Amgen-Synaffix (GlycoConnect and Hydraspace)

ADCs continued to be in the spotlight at ESMO 2023, especially with breakthrough data being presented with ENHERTU in HER2 low breast cancer and pan-tumors, and PADCEV + pembrolizumab in L1 urothelial cancer. As this complex platform continues to fuel excitement around potential widespread application, it is imperative to understand their key value drivers and associated limitations.

VALUE DRIVERS

Targeted chemotherapy:
- ADCs offer target antigen specificity with controlled delivery of cytotoxic payload

Enhanced efficacy:
- Exhibit "Bystander Effect", thereby killing adjacent antigen negative tumor cells
  - Apart from the approved ADCs, PADCEV, ENHERTU, TRODELVY, other emerging ones w/ strong bystander effect incl. BAT8008 (TROP2 ADC) and BAT8009 (B7-H3 ADC)

Overcomes drug resistance:
- ADCs, such as datopotamab DXd and sacituzumab govitecan in NSCLC, continue to showcase potential in IO resistant sub-populations

Expanding the market potential:
- Potential to demonstrate activity in tumors with low target expression, addressing the issue of tumor heterogeneity
  - Trastuzumab DXd vs. chemo, HER2-Low Br Ca [OS@1yr 26.2 vs. 16.2mo, mPFS 8.8 vs 4.2 mo
  - Luveltamab tazevibulin (STRO-002) FR alpha R/R endometrial cancer, PR: 29% with FR alpha >25% & PR: 19% with FR alpha ≥1%

Synergistic combinations:
- Proven synergy with PD-(L)1i has potential to overcome resistance, increase sensitivity to PD-(L)1is, and improve outcomes
  - EV + Pembro (1L, UC) vs chemo: mOS 31.5 vs 16.1 mo
  - Dato DXd + Durva (1L TNBC): ORR 79%, mDoR 15.5 mo, mPFS 13.8 mo, irresp. of PD-L1 exp.

Flexibility for innovative drug conjugation:
- Potential to stimulate innate immune response by conjugation with IO payloads
  - BDC-1001, drug conjugate with TLR 7/8 agonist payload, PR 29% in HER2+ tumors
- Validated concept of drug conjugation drives innovation with peptide drug conjugates (TH1902), bicyclic conjugates (BT7480) etc

CHALLENGES

Off target toxicities:
- Antigen expression on healthy cells or payload associated toxicities such as ocular toxicity and peripheral neuropathy with auristatins, interstitial lung disease/pneumonitis with maytansines, compromise drug compliance.

Payload stability and release:
- Conjugation technology challenges with first gen ADCs lead to toxicity issues due to
  - Premature uncoupling of payload
  - Incomplete endocytosis

Tumor heterogeneity:
- Varying levels of antigens and/or sensitivity to chemo payloads (need for biomarker enrichment approaches)
- Variable tumor sensitivity to cytotoxic payload, may require alternate treatment strategies such as
  - Utilizing IO/targeted agent payloads for chemo-refractory RCC and melanoma
  - Binding to extradomain-B (EDB) fibronectin, an integral component of tumor stroma in pancreatic cancer (low tumor microenvironment penetration capacity), which avoids endocytosis

Manufacturing complexity and cost:
- ADC manufacturing requires a comprehensive portfolio of products and wide-ranging expertise in large molecule development, testing, and specialization

Development of resistance mechanisms:
- Acquired resistance to some of the approved ADCs, has been characterized with change in antigen expression or payload resistance that impacts treatment sequencing

EMERGING TRENDS

Apart from the ground-breaking results of PADCEV, ENHERTU, and datopotamab deruxtecan at ESMO 2023 following advances in the pipeline underscore the value proposition of drug conjugates to further deepen and expand their presence

Next Gen ADCs:
- Third gen ADCs with safer chemo payloads such as BNT323 utilize immune toxin conjugation technology that aid in rapid systemic clearance and efficient bystander killing
- Next gen iADCs utilizing immune stimulating payloads such as TLR 7/8 agonists such as SBT6050 and BDC1001 are in development
- Biparatopic ADCs binding to two epitopes on the same target induces deeper tumor cell death and also promotes effective killing of resistant cells while being less susceptible to resistance (e.g. zanidatamab zovodotin)

Novel drug conjugates:
- Innovative small format drug conjugates such as bicycle peptides, protein degrader conjugates, nanobody conjugates, and probody conjugates are expected to modulate the bioavailability (PK, half life, renal elimination), thereby minimizing toxicities

Expansion of therapeutic applicability of ADCs:
- Early stages – Enfortumab vedotin in cis-ineligible Neoadj MIBC showed pCR 34%
- Novel combinations – Beyond PD-1 combinations have potential to reverse resistance
  - VEGFi, HER2 TKIs, and CD47 agents may be alternate combo partners
  - ADC + ADC with different payloads, different targets offer potential to increase DoR and early response. TRODELVY + PADCEV (payloads with non-overlapping toxicities) in 2L+ mUC has shown ORR 71%

Sequential use of ADCs:
- Approval of ADCs in >1 line of therapy within a tumor such as urothelial and breast cancer necessitates the optimal sequencing strategy to mitigate cross resistance
  - Academic study with sequencing therapy data from two approved ADCs in HER2 negative Breast Ca (ENHERTU and TRODELVY) resulted in longer PFS with the switch in target vs rechallenge with same target 3.25 vs. 2.3 mo

Putnam has been a trusted strategic partner to several pharma companies investing in ADCs, providing comprehensive support from early-stage development to commercialization.

REFERENCES

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