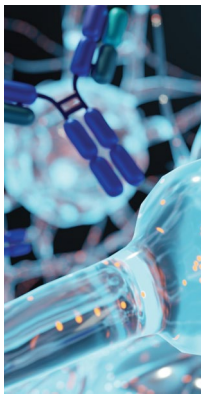
INSTITUTE @PRECISION™



AN INDUSTRY BRIEF FROM INSTITUTE@PRECISION

HEOR Value Demonstration for Antibody-Drug Conjugates

Ross Maclean, MD | *Global HEOR & Access Consulting, Precision AQ*

The Institute@Precision is part of Precision Medicine Group, an ecosystem of organizations spanning discovery to commercialization, purpose-built for precision.

PRECISION MEDICINE GROUP®

PRECISION for medicine®

PRECISION AQ™

Introduction

Antibody drug conjugates (ADCs) celebrate 25 years of U.S. regulatory approval this year and are widely regarded as a major scientific and medical advance in oncology, offering hope to many people who are struggling to overcome serious, often late-stage cancers that have proven resistant to existing treatment options.

The Health Economics & Outcomes Research (HEOR) team at Precision AQ has supported many of these ADCs, dating back to 2008. Over nearly two decades, we have published over 900 HEOR articles in support of innovative health technologies. This brief article offers a summary of our work related to ADCs, identifying three recurring themes from over 30 of these peer reviewed publications to provide biopharma innovators with insights on critical strategies and tactics to embed into launch preparation and successful commercialization.

Theme 1:

A clearly articulated unmet medical need (UMN) is the starting point for appreciating the potential place-in-therapy and value of a new treatment such as an ADC.

One could argue that in the case of ADCs, given regulatory approval in a cancer indication for which there is clinical urgency to treat, clinician adoption and use will be inevitable and robust. However, approval of drug and existence of clinical need alone are not sufficient to drive adoption. Other stakeholders such as financial risk-bearing payers and HTA authorities will take a more objective, population-level view to put the new ADC in context, necessitating focused evidence generation to capture the UMN from an epidemiological, clinical, humanistic and economic perspective.

Case Study: Hospitalizations for Older Patients with Acute Myeloid Leukemia (AML): Demonstrating the intensity and cost of Inpatient Treatment

Challenge: In advance of the launch of an ADC for older adults with AML the manufacturer wanted to demonstrate the cost of the current standard of care.

Response: Characterize the costs and length of stay (LOS) for hospitalizations among older adults with AML in the US.

Outcome: Medicare inpatient data were analyzed on hospitalizations in people with AML as a principal or secondary diagnosis (ICD-9 205.0), grouping patients by Diagnosis Related Group (DRG) for reimbursement. Across over 12,500 AML cases the average LOS was 13.6 days of which ~2,200 people had an ICU stay (mean ICU LOS of 9.6 days), chemotherapy was administered in 29.1% of hospitalization (associated with lower ICU use at 12.6%). Overall, DRG-based costs varied widely from ~$10k up to $98k.

Key Takeaway for ADC Developers: AML treatment in older adults is resource-intensive and costly, regardless of chemotherapy administration. The low ICU usage in many chemotherapy hospitalizations suggests that outpatient management may be feasible for some patients, potentially reducing costs and improving patient experience.

Theme 2:

Manufacturers must assess and describe the health and economic value of a new treatment must from the perspective of multiple stakeholders.

Our research has shown that the most effective demonstrations of health and economic value define value broadly, measuring and incorporating how different stakeholder groups assess value and weigh the tradeoffs inherent in any treatment option:

- **The patient:** As the individual coping with the illness and the recipient of ADC treatment, their perspective on treatment attributes is important as they weigh important tradeoffs between survival, treatment side effects, return to better health and function, and the practical issues inherent in receiving treatment.
- **The clinician:** The provider perspective of treatment options is also important, with conventional priorities being patient survival, tumor removal or destruction, and improvement in tumor-related signs, symptoms, and overall quality-of-life. However, on occasion, the order of these priorities may differ to those of the patient and his/her family.
- **Comparative effectiveness:** Even with exciting new treatments with novel mechanisms of action, there is still a need to compare to the existing standard of care, including how the anticipated outcomes relate to different care models.

Case study: Measuring and conveying the importance of patient perspectives on drug attributes and treatment selection

Situation: Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) have few good options after first-line therapy fails; some newer options include ADC and CAR T-cell therapies. Yet second-line treatments have tradeoffs between survival, adverse events, and return to function.

Challenge: To demonstrate to hematology oncologists how patients choose between hypothetical treatment profiles defined by different treatment attributes, specifically how patients trade off efficacy, safety and quality of life.

Response: A survey method called a "discrete choice experiment" asked 224 patients with DLBCL from the U.S. and Europe to trade off five different treatment-level attributes: (i) probability of 1-year survival, (ii) the risk of severe cytokine release syndrome (CRS), (iii) the risk of severe neurological toxicities, (iv) the risk of severe infection, and (v) the time to return to pre-treatment functioning

> Safety concerns, including dose selection and toxicity,can derail ADC development programs. Learn more in our white paper by Nicholas Richardson, DO, MPH, Precision for Medicine's VP of Clinical Development and former FDA Deputy Director of the Division of Hematologic Malignancies 2

Outcome: The increase in one-year survival probability was the most influential factor (61% of decision weight) driving patient choice followed by avoiding risks of CRS and neurological toxicities. Patients required a 13–14% increase in one-year survival probability to offset acceptance of these serious adverse event risks.

Key Takeaway for ADC Developers: The results suggest that patients are willing to accept substantial risks (like CRS, neurological toxicities) if the survival gain is meaningful.

Theme 3:

Communication between the biopharma innovator and payer stakeholders is critical to understanding the place-in-therapy and value of a new treatment.

Regarding ADC place-in-therapy, safe and appropriate use is of paramount importance. To that end, there is ongoing need to continue to advance communication channels between the ADC manufacturer and the payer/HTA authority.

This includes several insights pertinent to the biopharma HEOR, Access and Medical capabilities:

- All data are local; there remains strong demand to replicate studies and RWE across markets and populations, including different insurers. Even the most compelling evidence can struggle to be accepted if it is viewed as not being applicable to the population for which the payer bears risk.
- There is demand for data (and methods) to reliably and accurately extrapolate endpoints from short-term trials to longer-term, real-world effectiveness. To that end, the advent of tokenization to allow linkage of data across disparate sources such as from clinical trials to real-world data, and the emergence of wearable health technologies to capture health metrics in real-time both offer great potential.
- There is a growing need to develop novel methods to generate real-world insights, such as expert elicitation.
- In cancers for which there are many treatment options, there is a need to understand and quantify the different options and outcomes by line-of-therapy. This necessitates advancing the methods and application of Treatment Sequencing Models.

Case Study: The role of a comparative effectiveness analysis in informing treatment selection.

Situation: Patients, clinicians, and payers have a vested interest in understanding how different treatment options compare. This is true in all care settings, especially in situations where there is an absence of a head-to-head trial for competing therapies, as in many cancer trials.

Challenge: In people with relapsing/refractory large B-cell lymphoma (R/R LBCL) with two competing autologous anti-CD19 CAR T-cell therapies, the manufacturer of the second-to-market product wanted to offer a response to the inevitable question: "Of the anti-CD19 CAR T-cell therapies, which one is better?"

Response: Estimate the relative efficacy and safety of Rx A vs. Rx B in patients with R/R LBCL using a matching-adjusted indirect comparison (MAIC) method. Individual patient-level data from the Rx A trial were compared to published aggregate data from the Rx B trial.

Outcome: From an efficacy perspective, Rx A showed higher ORR and CR, but differences were not statistically significant. However, Rx A demonstrated statistically significant improvements in OS and PFS. Duration of response (DoR) favored Rx A but was not statistically significant. From a safety perspective, Rx A had

higher rates of grade ≥3 CRS and neurological events compared to Rx B. In scenario analyses with expanded safety cohorts, these differences were less pronounced.

Key Takeaway for ADC Developers: Treatment A may offer better survival outcomes (OS and PFS) than Rx B, though safety concerns, particularly neurological events, remain higher with Rx A, though improvements over time are noted. No significant differences in response rates were found, highlighting the need for further comparative studies.

Conclusion

The benefit:risk profile of many ADC drugs offers an important treatment option to cancer patients, many of whom are facing late-stage cancers with few promising treatment options. One perspective on the three themes shared above is that quantifying UMN, comparative clinical effectiveness and economic value, and addressing the real-world evidence needs of different stakeholders is foundation to all novel, transformational and/or disruptive health technologies, including ADC.

An alternative view offers a call-to-action for ADC developers:

- Recognize and prepare evidence for the "conventional" value demonstration challenges yet also consider how "novel sources of value" described by Lakdawalla et al may offer potential to capture the value of a new treatment.
- Embrace the potential for real-world data to address ADC concerns such as toxicity and tolerability by the conduct of patient-centered surveys on attitudes towards the attributes of new treatments.
- Advance the use of treatment sequencing models where ADCs are used in later lines of therapy.
- Given the intention of many ADC to move from later to front line therapy, this will raise payer attention as greater use will drive higher spend. The ADC team can prepare for the increased scrutiny by prioritizing real-world evidence generation including patient and clinician ADC treatment experience and real-world effectiveness.

In summary, ADC present value demonstration needs like other novel drugs yet with incremental expectations, all of which can be met with an HEOR and Access Consulting partner that has experience in oncology and ADC.

About the Author

Ross Maclean, MD, is a global health economics and market access leader with 35+ years of experience in HEOR, health policy, and pharmaceutical strategy. He drives innovation and cross-functional collaboration at Precision AQ—advancing access, shaping value strategies, and aligning global healthcare systems to deliver meaningful patient outcomes.

References

Theme 1 case study

Sacks N, Cyr P, Noone J, Miller D, Louie A. Hospitalizations for older patients with acute myeloid leukemia: In patient treatment is intensive and costly. Value in Health. 2016; 19(3): A246.

Theme 2 case study

Birch K, Snider JT, Chiu K, Baumgardner J, Wade SW, Shah GL. Patient preferences for treatment in relapsed/refractory diffuse large B-cell lymphoma: a discrete choice experiment. Future Oncology. 2022;18(25): 2791-2804

Theme 3 case study

Oluwole OO, Chen JM, Chan K, Patel AR, Jansen JP, Keeping S, Locke FL. ABCL-289: Matching-Adjusted Indirect Comparison (MAIC) of Axicabtagene Ciloleucel (Axi-Cel) and Lisocabtagene Maraleucel (Liso-Cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) After Two or More Prior Lines of Therapy. Clinical Lymphoma Myeloma and Leukemia. 2021; 21, S388.

Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in Health. 2018;21(2):131–139. doi:10.1016/j.jval.2017.12.007

To learn more about Precision AQ, visit

www.precisionaq.com

PRECISION AQ™