PDG79

WAS THE EVIDENCE BASE FOR YESCARTA AND KYMRIAH SUFFICIENT TO JUSTIFY THEIR COST AND SECURE PATIENT ACCESS ACROSS FIVE MARKETS?

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Introduction/objective

- High-cost CAR-T immunotherapies, specifically Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel), are becoming more widely available worldwide.
- Due to the extremely high financial impact of these therapies and limited clinical data available at launch, the evidence base for Yescarta and Kymriah are coming under intense scrutiny by payers.
- This study aims to determine whether the evidence for Kymriah and Yescarta for the diffuse large B-cell lymphoma (DLBCL) indication was sufficient to secure a positive outcome from HTA bodies in Europe and the USA, and specifically how gaps in the current evidence are linked to access restrictions and mitigation strategies.

Methods

- NICE (England & Wales), G-BA (Germany), TLV (Sweden), *ICER* (USA) and TC (France) HTA reports were identified for Yescarta and Kymriah in diffuse large B-cell lymphoma (DLBCL).
- The above agencies were selected to provide a mix of those driven primarily by cost-effectiveness (NICE, TLC and *ICER*) vs. clinical evidence (G-BA and TC).
- The identified HTA reports were assessed to understand whether the clinical and economic evidence was sufficient at launch to secure reimbursement.
- Sources of clinical and cost-effectiveness uncertainty were identified, and HTA body recommendations to address these gaps were compared across the five countries.

Results

- Despite the high treatment costs, patients can access these treatments in all countries selected, albeit with varying levels of assessment outcomes (Table 1). For example, the TC determined that Yescarta added moderate clinical value (ASMR III), whereas the GB-A assessed there to be a non-quantifiable added benefit.
- Prominent evidence gaps were identified for both Yescarta and Kymriah. The primary clinical concerns were similar for both drugs in the five countries, primarily being:
  1) the lack of certainty in treatment response, long-term OS and PFS data
  2) the lack of comparative data generated by single-arm studies (Tables 2 and 3).
- Of the HTA bodies that consider cost-effectiveness, only NICE produced an ICER estimation for both drugs (despite a high level of uncertainty); for Kymriah, the level of uncertainty was so high that the TLV and *ICER* could not produce an ICER estimate.
- NICE, G-BA, TLV and the TC require additional evidence to be gathered to demonstrate both drugs' long-term clinical value and cost-effectiveness (Tables 2 and 3).

Table 1: Assessment outcomes for Yescarta and Kymriah in five selected countries

Country	Yescarta	Kymriah
England	Recommended with no restrictions within CDF (ICER: £50k - £100k / QALY)	Recommended with no restrictions within CDF (ICER: £43k - £55.4k / QALY)
Germany	Non-quantifiable added benefit	Non-quantifiable added benefit
Sweden	ICER: SEK 1m – 1.4m	ICER: Non-calculable
USA	Moderate certainty of a small or substantial net health benefit* (ICER: $136k / QALY)	Moderate certainty of a small or substantial net health benefit* (ICER: Non-calculable)
France	SMR: Important ASMR: III	SMR: Important ASMR: IV

* Against standard chemotherapy

Table 2: Clinical and cost-effectiveness uncertainty for Yescarta (DLBCL)

Key: ICER calculated | ICER too uncertain

Countries	Clinical uncertainty: Treatment response	Clinical uncertainty: Long term survival	Clinical uncertainty: Long term side effects	Clinical uncertainty: Relative efficacy and side-effects against comparator	Cost-effectiveness uncertainty	Mitigation Strategy
NICE		✓		✓	Immature survival data; Cost of treating side effect (IVIG treatment for B-cell aplasia)	Incorporated into the CDF until further trial data and RWE from use in NHS becomes available to reduce the level of uncertainty regarding the CE ratio
ICER		✓	✓	✓	Outcome discount rate; standardised mortality ratio; Cost of treating side effect (IVIG treatment for B-cell aplasia)	Policy recommendations including outcomes-based pricing arrangements and creation of CAR-T patient registry; 'Affordability and Access Alert' raised (significant risk of budget impact threshold being exceeded)
TLV	✓	✓		✓	Cure proportion; mortality risk	Recommends continuous monitoring of use for future re-evaluation
G-BA	✓	✓		✓	N/A	Reassessment before May 2022; 60-month data from ZUMA-1 study, indirect comparisons and observational studies to be submitted in this time
TC		✓	✓	✓	N/A	Annual re-assessment based on further clinical trials, post-authorisation efficacy studies and RWE from ATUs

Table 3: Clinical and cost-effectiveness uncertainty for Kymriah (DLBCL)

Key: ICER calculated | ICER too uncertain

Countries	Clinical uncertainty: Treatment response	Clinical uncertainty: Long term survival	Clinical uncertainty: Long term side effects	Clinical uncertainty: Relative efficacy and side-effects against comparator	Cost-effectiveness uncertainty	Mitigation Strategy
NICE		✓		✓	Immature survival data; Cost of treating side effect (IVIG treatment for B-cell aplasia)	CDF until further data from JULIET study and RWE from use in NHS
ICER		✓	✓	✓	Too much uncertainty	Policy recommendations including outcomes-based pricing arrangements and creation of CAR-T patient registry
TLV	✓	✓	✓	✓	Too much uncertainty	Recommends continuous monitoring of use for future re-evaluation
G-BA	✓	✓		✓	N/A	Reassessment before March 2022; further JULIET study data, indirect comparisons and observational studies to be submitted in this time
TC	✓	✓	✓	✓	N/A	Annual re-assessment based on further data from JULIET study, post-authorisation efficacy studies and RWE from ATUs

Discussion and conclusions

- The fact that both Yescarta and Kymriah have widespread access, despite significant uncertainty in clinical evidence and cost-effectiveness (where relevant), is largely reflective of the high unmet need in DLBCL, the willingness of payers to access CAR-T therapies and the high level of innovation perceived
- For both drugs, HTA bodies are recommending that re-assessment occurs when more clinical and economic data (from clinical trials, country-specific real world evidence and indirect comparisons) becomes available
- It is clear that the HTA bodies recognised the high level of unmet need and also the limited data available at launch from the single armed clinical trials. Reducing this uncertainty over the longer term is key to demonstrate the true clinical and economic value of Yescarta and Kymriah

ATU=Temporary authorisations for use; CDF=Cancer Drugs Fund; CE=Cost-effectiveness; DLBCL=Diffuse Large B Cell Lymphoma; G-BA= Federal Joint Committee; HTA-Health technology assessment; IVIG=Intravenous Immunoglobulin; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; OS=Overall survival; PFS=Progression-free survival; RWE= Real world evidence; TC=Transparency Committee; TLV=Dental and Pharmaceutical Benefits Agency

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