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Exploring PICO Variations in Relapsed or Refractory DLBCL in the Context of the European Joint Clinical Assessment

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INTRODUCTION

- The EU Health Technology Assessment Regulation requires Member States to conduct a Joint Clinical Assessment (JCA) on the relative clinical effectiveness and safety of a new health technology. JCAs are central to the regulation and aim to streamline health technology assessments (HTAs) across the 27 EU countries. The overarching scope of the JCA process is an all-inclusive assessment that addresses the specific needs requested by each Member State. The population, intervention(s), comparator(s), outcome(s) (PICO) framework provides a standard format for defining the assessment scope[1]
- Though the practical guideline, D4.2 Scoping Process[2], provides an example of up to five PICOs consolidated, we anticipate that manufacturers may need to report on a greater number of PICOs in one submission.[1] Currently, most countries have different preferences for PICOs, including comparators (i.e. what is approved for use in their country), endpoints, and the relevant population. Multiple PICOs in one submission will have consequences for data presentation in the JCA
- Since the JCA process will become mandatory for oncology drugs in 2025, it is imperative to explore the implications of PICO variations. While the JCA aims to provide consolidated PICO requirements from all Member States, variations across countries could have implications for drug assessments

OBJECTIVES

- This review assessed HTA submissions in England, Germany, Ireland, Sweden and the Netherlands for variations in the PICO criteria in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

METHODS

- This study investigated variations in PICO criteria for drugs in R/R DLBCL across England four EU HTA bodies
- HTA reports in DLBCL published between 2020 and 2024 in the National Institute for Health and Care Excellence (NICE)[3] (reference HTA) were compared with four Member State national HTA bodies implementing the JCA process:
  - The Federal Joint Committee (Gemeinsamer Bundesausschuss, or G-BA; Germany)[4]
  - The National Centre for Pharmacoeconomics (NCPE; Ireland)[5]
  - The Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, or TLV; Sweden)[6]
  - The National Health Care Institute (Zorginstituut Nederland, or ZIN; the Netherlands)[7]
- A targeted review was conducted that examined publicly available HTA reports for six drugs in patients with R/R DLBCL after two or more lines of systemic therapy. To understand the potential PICO burden, the consolidated EU PICO for a hypothetical product (Molecule X) in R/R DLBCL were simulated. PICO information was extracted and analysed to identify 'unique PICO combinations' for these six drugs and assess the variations among the PICO combinations for the target Member States

Table 1. Consolidated PICO variations among four national HTA bodies (Member States implementing the JCA)*

Drug	Population		Intervention	Comparators	Outcomes	Variation in combinations
	Population	Line of treatment				
Epcoritamab	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	NA	▪ PFS ▪ OS ▪ ORR ▪ Mortality ▪ HRQL ▪ Safety	6
Loncastuximab tesirine	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	NA	▪ HRQL ▪ Safety ▪ Mortality ▪ Morbidity	4
Tisagenlecleucel	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ R-GDP ▪ R-GIFOX ▪ Axicabtagene ciloleucel ▪ Salvage chemotherapy followed by SCT on need basis	▪ OS ▪ PFS ▪ ORR ▪ HRQL ▪ Safety	20
Glofitamab	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	NA	▪ OS ▪ PFS ▪ CR ▪ Safety ▪ HRQL	5
Axicabtagene ciloleucel	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ GEM ▪ GEMOX ▪ R-ESHAP ▪ R-GDP ▪ Chemotherapy	▪ OS ▪ CR ▪ PFS ▪ ORR ▪ Safety	25

Key: CR, complete response; DLBCL, diffuse large B-cell lymphoma; GEM, gemcitabine and methylprednisolone, GEMOX, gemcitabine and oxaliplatin; HRQL, health-related quality of life; HTA health technology assessment; JCA, Joint Clinical Assessment; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PICO, population, intervention(s), comparator(s), outcome(s); R-ESHAP, rituximab, etoposide, methylprednisolone, high-dose cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-GIFOX, rituximab, gemcitabine, ifosfamide, oxaliplatin; R/R, relapsed or refractory; SCT, stem cell transplantation.
Note: None of the MS HTA bodies assessed Zanubrutinib in adult patients with R/R DLBCL.

RESULTS

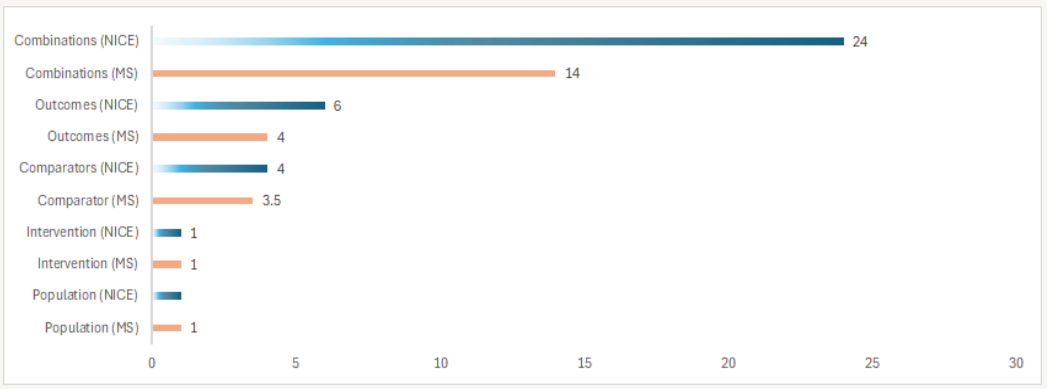
- The analysis demonstrated substantial disparities in PICO questions for several R/R DLBCL oncology drugs. Please refer to **Table 1** and **Table 2** for the PICO assessed for each drug
- Based on assessments among the Member States of interest, the anticipated number of consolidated PICO combinations for a product in R/R DLBCL after two or more lines of systemic therapy ranges from four to more than 20 (**Table 1**)
- Twenty or more PICO combinations are also accounted for by NICE, which can be a reflection on the PICO combinations possibly anticipated among EUnetHTA 21 countries (**Table 2**)

Table 2. PICOS criteria in NICE evaluations

Drug	Population		Intervention	Comparators	Outcomes	Variation in combinations
	Population	Line of treatment				
Epcoritamab	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ Pola + BR ▪ Axicabtagene ciloleucel ▪ Pixantrone ▪ Rituximab- based CIT regimens	▪ PFS ▪ TTD ▪ OS ▪ CR ▪ ORR	20
Loncastuximab tesirine	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ Chemotherapy, including RTX-based ▪ Pola + BR ▪ Pixantrone ▪ Axicabtagene ciloleucel ▪ Tafasitamab with lenalidomide	▪ OS ▪ PFS ▪ Response rates ▪ HRQL ▪ Safety	25
Glofitamab	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ Chemotherapy, including RTX-based therapy ▪ Pola+BR ▪ Pixantrone ▪ Axicabtagene ciloleucel ▪ Tafasitamab with lenalidomide	▪ CR rate ▪ PFS ▪ Safety ▪ HRQL ▪ ORR ▪ DOCR ▪ DOR	35
Axicabtagene ciloleucel	Adult patients with R/R DLBCL	After two or more lines of systemic therapy	Molecule X	▪ Salvage chemo ▪ Pola + BR ▪ Tafasitamab with lenalidomide	▪ EFS ▪ OS ▪ PFS ▪ ORR ▪ Safety ▪ HRQL ▪ DOR ▪ TTNT	24

Key: CIT, chemoimmunotherapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; EFS, event-free survival; HRQL, health-related quality of life; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PICOS, population, intervention(s), comparator(s), outcome(s), study design(s); Pola + BR, polatuzumab vedotin with bendamustine plus rituximab; R/R, relapsed or refractory; TTD, time to treatment discontinuation; TTNT, time to next treatment.

Figure 1. Average number of PICO combinations for the drugs investigated in patients with R/R DLBCL



Key: DLBCL, diffuse large B-cell lymphoma; MS, Member State; NICE, National Institute for Health and Care Excellence; PICO, population, intervention(s), comparator(s), outcome(s), study design(s); R/R, relapsed or refractory.

- Variation in the number of comparators and outcomes emerged as the key drivers, driving the differences in the PICO criteria (Figure 1)
- Another interesting finding is that none of the drugs assessed in this review had a consistent PICO across all four Member State countries, reflecting on the variation that is expected as the regulation continues

CONCLUSIONS

- The anticipated variation in PICO combinations for R/R DLBCL after two or more lines of systemic therapy highlight the challenges in attaining a consolidated approach during the JCA scoping phase. Therefore, early preparation and awareness of the anticipated scope, particularly around predicting and addressing PICOs, is the key for success
- However, the results of this study should be interpreted with caution, as the 'PICO development process' will also consider off-label comparators and greater numbers of countries than those that were assessed in this review
- It is anticipated that the PICO development process may be further complicated by national differences in healthcare systems and treatment guidelines[8], impacting market entry across multiple European countries
- Additional data requirements may be expected during the evaluation of therapies, potentially further delaying patient access within these nations[8]

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