Evaluating PICOs Requested by EU Member States During Scoping for EU HTA Versus Those Covered in Actual HTAs

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INTRODUCTION

On 12 January 2025, European Union (EU) Joint Clinical Assessment (JCA) came into force, with the aim of standardising and streamlining the clinical evaluation of new oncology drugs and advanced therapy medicinal products (ATMPs) across the EU.[1] As part of the JCA process, a PICO (Population, Intervention, Comparator, Outcome) survey is conducted with EU member states to ensure that the scope of the assessment meets their needs.[2]

In 2023, EUnetHTA 21 conducted scoping surveys with EU member states for three products:

- PLUVICTO® (lutetium [^{177}Lu] vipivotide tetraxetan), a radiopharmaceutical, for prostate-specific membrane antigen positive, metastatic, castration-resistant, prostate cancer (PSMA+ mCRPC)[3]
- EBVALLO® (tabelecleucel), an ATMP used to treat adults and children with Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD)[4]
- POMBILITI™ (cipaglucosidase alfa), initially designated as an orphan drug (designation withdrawn at the time of marketing authorisation), used to treat adults with late-onset Pompe disease[5]

All three products had already obtained a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (EMA).[3-5]

OBJECTIVE

We aimed to assess the alignment between PICOs identified in EUnetHTA 21 scoping surveys for PLUVICTO®, EBVALLO® and POMBILITI™ published in 2023, versus PICOs considered in the actual health technology assessments (HTAs) of these products across different member states.

METHODS

Published HTAs for PLUVICTO®, EBVALLO® and POMBILITI™ from across EU member states, were identified using GlobalData Plc's Drug Pricing (POLI) and HTA database (up to April 10, 2025).[6] Published HTAs were reviewed, translated where appropriate, and PICOs covered in the HTAs were extracted into a data summary sheet. Similarities and differences between the HTA PICOs across member states were reconciled and consolidated following guidance published by the EU member state HTA Coordination Group (HTA CG).[2] Actual PICOs were compared to the consolidated PICOs identified in the EUnetHTA 21 scoping exercise.

RESULTS

In total, 8 HTAs for PLUVICTO®, 6 HTAs for EBVALLO®, and 7 HTAs for POMBILITI™ were identified across twelve member states: Austria, Czechia, Denmark, Finland, France, Germany, Ireland, Norway, Poland, Portugal, Romania, and Spain (**Table 1**).

Table 1 Actual HTAs identified for PLUVICTO®, EBVALLO® and POMBILITI™

Product	Markets												Number of HTAs included
	Austria	Czechia	Denmark	Finland	France	Germany	Ireland	Italy*	Norway	Poland	Portugal	Romania	Spain	
PLUVICTO®				✓	✓	✓	✓	✓	✓	✓		✓	✓	8/9
EBVALLO®			✓	✓	✓	✓		✓		✓			✓	6/7
POMBILITI™	✓	✓	✓		✓	✓		✓			✓		✓	7/8

*Italy excluded due to insufficient detail on PICOs utilised during the assessment

After consolidation, 5 PICOs were identified from actual HTAs for PLUVICTO® compared to 6 identified in the EUnetHTA 21 scoping exercise (**Table 2**). PICOs from EUnetHTA 21 were well aligned with actual HTAs; however, EUnetHTA 21 did not to consolidate "individual therapy" or "physician's choice" of therapy for the full population.

For EBVALLO®, 3 PICOs were included in actual HTAs compared to 5 in the EUnetHTA 21 scoping exercise (**Table 3**). This was due to HTAs not focussing on specific individual comparators as they all considered there to be no clear standard of care for patients and therefore individualised therapy was considered appropriate and therefore no separate subpopulations for patients who might be eligible or ineligible for chemotherapy.

For POMBILITI™, 6 PICOs were included in actual HTAs compared to 9 PICOs identified in the EUnetHTA 21 scoping exercise (**Table 4**). Although there was alignment in terms of populations (ERT-naïve or experienced), EUnetHTA also specified best supportive care (BSC) that was not included as a comparator in any actual HTAs and had several separate comparators for the full population.

The EUnetHTA 21 scoping exercise also prespecified a wider range of outcomes than was included in actual HTAs; however, this may be due to HTAs reacting to outcomes included in the trial and the submission.

In general, PICOs identified by the EUnetHTA 21 scoping exercises covered PICOs from actual HTAs; however, several PICOs identified in the scoping exercise were not assessed by HTAs, potentially resulting in over-scoping, particularly for orphan drugs where limited clinical data are available. For example, the Phase 3 ALLELE clinical study for EBVALLO® only included 43 patients who failed standard care therapy, for which 5 different PICOs were requested by EUnetHTA. Actual HTAs appear to have taken a more pragmatic perspective.

It should be noted that fewer PICOs in actual HTAs may be due to the limited number of published HTAs and because PICOs were estimated *post-hoc* after the HTA was published rather than *a priori*.

Table 2 Comparison between actual HTAs for PLUVICTO® vs consolidated PICOs from EUnetHTA 21

PLUVICTO® PICOs from actual HTAs					PLUVICTO® consolidated PICOs from EUnetHTA 21					
PICO 1 (subpopulation)	**PICO 2 (subpopulation)**	**PICO 3 (subpopulation)**	**PICO 4 (subpopulation)**	**PICO 5 (full population)**	**PICO 1 (subpopulation)**	**PICO 2 (subpopulation)**	**PICO 3 (subpopulation)**	**PICO 4 (subpopulation)**	**PICO 5 (full population)**	**PICO 6 (full population)**
Adult patients with progressive PSMA-positive mCRPC with symptomatic bone metastases and no extensive visceral metastases	Adult patients with progressive PSMA-positive mCRPC eligible for further taxane treatment (following previous treatment with docetaxel)	Adult patients with progressive PSMA-positive mCRPC with a *BRCA 1/2* mutation	Adult patients with progressive PSMA-positive mCRPC not eligible for further taxane treatment	Adult patients with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy	Adult patients with progressive PSMA-positive mCRPC with symptomatic bone metastases and no known visceral metastasis who have been treated with AR pathway inhibition and taxane-based chemotherapy	Adult patients with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and one previous line of taxane-based chemotherapy and who are suitable for cabazitaxel	Adult patients with *BRCA 1/2*-mutated with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy	Adult patients with progressive PSMA-positive mCRPC who are not suitable for chemotherapy or have been treated with docetaxel as 1L and cabazitaxel as 2L or patients who have taken all available treatments to their own clinical condition	Adult patients with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy	Adult patients with progressive PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy
^{177}Lu vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibitors					PLUVICTO					
Radium-223	Cabazitaxel in combination with standard of care (SoC)	Olaparib	BSC	Patient-specific therapy; abiraterone+prednisone/ prednisolone, or enzalutamide, or cabazitaxel, or olaparib (for *BRCA 1/2* mutation), or BSC, taking into account the previous therapy.	Radium-223*	Cabazitaxel*	Olaparib*	BSC	Individualized treatment, taking into account previous therapies, with selection of abiraterone+prednisone/ prednisolone*, enzalutamide*, cabazitaxel*	Physician choice for control arm, with at least cabazitaxel*, or abiraterone+prednisone/ prednisolone*, or enzalutamide*, or apalutamide*, or olaparib*, or Radium-223*, or BSC
Overall survival (OS); Progression free survival (PFS); Treatment response; Evolution of electrocorticography (ECOG); Radiological, clinical and biological (total serum prostate-specific antigen [PSA]) assessment; Pain (BPI-SF); Quality of life (QoL): EQ-5D-3L; EQ-5D-VAS; Functional Assessment of Cancer Therapy – Prostate (FACT-P); Duration of treatment; All-causality and treatment-related adverse events (AEs); Serious adverse events (SAEs); SAE CTCAE Grade 3 or 4; Treatment discontinuations; Symptomatic skeletal-related events, Deaths					OS; Radiological tumour assessment (including overall response rate [ORR] and duration of response [DoR]), PFS (radiological, clinical or PSA) by investigator and blinded independent central review (ICR); Symptomatic skeletal event (including time to first skeletal event); PSA levels; Pain measured by a patient-reported outcome (PRO) measure such as a numeric rating scale or a visual analogue scale (VAS); Fatigue; Health-related QoL measured preferably by generic and disease specific questionnaires i.e. EORTC QLQ C30 plus, if possible; EORTC PR25 or FACT-P; FACT-G; Health status measured preferably by EQ-5D-5L; Any other patient centred outcome measured by PRO measures; AEs; SAEs; SAEs (Grade ≥ 3); Discontinuation and interruption due to AEs; AESIs; SUSARs					

*ADT is the standard in the treatment of prostate cancer relapse or metastatic disease.

Table 3 Comparison between actual HTAs for EBVALLO® vs consolidated PICOs from EUnetHTA 21

EBVALLO® PICOs from actual HTAs			EBVALLO® consolidated PICOs from EUnetHTA 21					
PICO 1 (subpopulation)	**PICO 2 (subpopulation)**	**PICO 3 (full population)**	**PICO 1 (subpopulation)**	**PICO 2 (subpopulation)**	**PICO 3 (subpopulation)**	**PICO 4 (subpopulation)**	**PICO 5 (full population)**	
Patients who had prior solid organ transplant (SOT)	Patients who had prior haematopoietic stem cell transplantation (HSCT)	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy after a solid organ transplantation, who have received at least one prior therapy and are eligible for chemotherapy	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy after a solid organ transplantation, who have received at least one prior therapy and are eligible for chemotherapy	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy after a haematopoietic stem cell transplantation, who have received rituximab and are eligible for chemotherapy	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy who have received rituximab and who are ineligible for chemotherapy	Adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received ≥ 1 prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate	
Tabelecleucel			Tabelecleucel					
Patient individualised therapy as there is no clear standard of care (which may include various chemotherapy regimens +/- rituximab, rituximab monotherapy, BSC, and/ or other options e.g., transplants, infusions, clinical trials of novel therapies)			Any of the following alternative (compared to the first chemotherapy-regimen) chemotherapy-regimens: CHO(E)P ± rituximab (-21) (cyclophosphamide, doxorubicine, vincristine, prednisoi(lo)ne), or cyclophosphamide + prednisolone ± rituximab, or c(R-)CE, HD-MTX ± rituximab, ProMACE CytaBOM	Individualized treatment. The following comparators are deemed appropriate: CHO(E)P ± rituximab (-21), cyclophosphamide + prednisolone ± rituximab, (R-)CE, HD-MTX ± rituximab, ProMACE CytaBOM	CHO(E)P ± rituximab	BSC	Individualized treatment CHOP (including CHOP 21) ± rituximab, ACVBP ± rituximab, cyclophosphamide ± rituximab, cyclophosphamide + vincristine + prednisone ± rituximab, DA-EPOCH ± rituximab, R-DHAP, R-ICE, (R)-GemOx; (R)-Benda-Polatuzumab vedotin; methotrexat ± rituximab; BSC	
OS; Treatment response (ORR; PR and CR); DoR; PFS; Symptoms; QoL; Health status (EQ-5D); AEs (total); SAEs; Discontinuation due to AEs; Adverse events of special interest (AESIs) e.g. Graft-versus-host disease (GvHD) occurrence; Transplant rejection (allograft loss/rejection episodes)			OS; Disease specific survival; Symptoms like symptomatic lymphadenopathy, B symptoms (fever, nights sweats, unintentional weight loss, infections, viremia; ORR (partial and complete response); Treatment response (ORR, partial response [PR] and complete response [CR], including PET); DoR; PFS; Event-free survival (EFS; including initiation of new treatments); QoL measured preferably by the EORTC QLQ C30; EORTC PR 25; FACT-P; Health status measured by the EQ-5D; Any other patient-centred outcome, assessed by generic or disease specific patient-reported outcome measures; AEs (total); SAEs; SAEs (Grade ≥ 3), Discontinuation due to AEs; AESI e.g. GvHD occurrence; Transplant rejection (allograft loss/rejection episodes)					

Table 4 Comparison between actual HTAs for POMBILITI™ vs consolidated PICOs from EUnetHTA 21

POMBILITI™ PICOs from actual HTAs						POMBILITI™ consolidated PICOs from EUnetHTA 21								
PICO 1 (subpopulation)	**PICO 2 (subpopulation)**	**PICO 3 (subpopulation)**	**PICO 4 (subpopulation)**	**PICO 5 (full population)**	**PICO 6 (full population)**	**PICO 1 (subpopulation)**	**PICO 2 (subpopulation)**	**PICO 3 (subpopulation)**	**PICO 4 (subpopulation)**	**PICO 5 (subpopulation)**	**PICO 6 (full population)**	**PICO 7 (full population)**	**PICO 8 (full population)**	**PICO 9 (full population)**
Adult patients with late-onset Pompe disease who are ERT-experienced	Adult patients with late-onset Pompe disease who are ERT-experienced	Adult patients with late-onset Pompe disease, who are ERT-naive	Adult patients with late-onset Pompe disease, who are ERT-naive	Adult patients with late-stage Pompe disease	Adult patients with late-stage Pompe disease	Adult patients with late onset Pompe disease, who are ERT-experienced	Adult patients with late onset Pompe disease, who are ERT-experienced	Adult patients with late onset Pompe disease, who are ERT-naive	Adult patients with late onset Pompe disease, who are ERT-naive	Adult patients with late onset Pompe disease, who are ERT-naive	Adult patients with late onset Pompe disease	Adult patients with late onset Pompe disease	Adult patients with late onset Pompe disease	Adult patients with late onset Pompe disease
Cipaglucosidase alfa in combination with miglustat						Cipaglucosidase alfa in combination with miglustat								
Avalglucosidase alfa	Alglucosidase alfa	Avalglucosidase alfa	Alglucosidase alfa	Alglucosidase alfa	Avalglucosidase alfa **AND** alglucosidase alfa	Avalglucosidase alfa	Alglucosidase alfa	BSC	Avalglucosidase alfa	Alglucosidase alfa	Avalglucosidase alfa	Alglucosidase alfa	BSC	Physician's choice for control arm, with at least: Alglucosidase alfa or avalglucosidase alfa
6-Minute Walk Test (6MWT); Forced Vital Capacity as a percentage of predicted (FVC%); EQ-5D-5L/VAS; Mortality; Rasch-built Pompe-specific activity (R-PAct) scale/Patient-Reported Outcomes Measurement Information System (PROMIS); Subject Global Impression of Change (SGIC); AEs; SAEs; Discontinuation due to AEs						OS; Ventilator-free survival; Changes in mobility (including measurement by 6MWT and documented use of wheelchair); Changes in respiratory function (including measurement by FVC in sitting and upright positions); Changes in muscle strength (by validated scales); Changes in motor function (by validated scales, e.g. quick motor function test); Respiratory symptomatology associated with Pompe disease; Gastrointestinal symptomatology associated with Pompe disease; QoL (as assessed using disease-specific (preferably) and/or generic questionnaires); Health status (measured preferably by the EQ-5D); Patient-reported outcomes to include R-PAct scale, and any other patient-centred outcome assessed by means of a patient-reported outcome measure; AEs (including hypersensitivity, infusion reactions, immunogenicity); SAEs; Severe AEs; Discontinuation and interruption of treatment due to AEs; Mortality due to AEs								

CONCLUSIONS

PICOs included in actual HTAs were predicted by the EUnetHTA 21 scoping exercise; however, there may be over-scoping of PICOs due to a comprehensive scoping process and the requirement to meet all member states' needs. This may place an unnecessary burden on manufacturers preparing to respond to irrelevant PICOs or an inability to respond to specific PICOs due to limitations in the clinical trial data. Manufacturer input into the scoping could be beneficial to ensure alignment on PICOs prior to EU JCA.

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Abbreviations: ATMP: Advanced therapy medicinal product, BSC: Best supportive care, CHMP: Committee for Medicinal Products for Human Use, EBV+ PTLD: Epstein-Barr virus positive post-transplant lymphoproliferative disease, EMA: European Medicines Agency, ERT: Enzyme replacement therapy, EU: European Union, EUnetHTA: European Network for Health Technology Assessment, HTA: Health Technology Assessment, HTA CG: HTA Coordination Group, JCA: Joint Clinical Assessment, PICO: Population, Intervention, Comparator, Outcome, PSMA: Prostate-Specific Membrane Antigen