EUnetHTA 21

Consolidated PICO

PICO EXERCISE II - EBVALLO TABELECLEUCEL

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	**14/09/2023**	Publication final consolidated PICOs

Disclaimer

This document describes a test run for the definition of PICOs for an assessment of a medicinal product. This exercise aimed at testing and improving the process developed within EUnetHTA21. As such, it has no relevance and no consequences for national assessments of medicinal products.

Furthermore, heterogeneity in terms of wording and presentation between the 3 exercises was expected.

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The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group actively wrote the deliverable, the entire EUnetHTA 21 consortium was involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) reviewed and discussed several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) endorsed the final deliverable prior to publication.

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LIST OF ABBREVIATIONS

CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
EUnetHTA	European Network of Health Technology Assessment
GL	Guideline
HOG	Hands-on Group
HTA	Health Technology Assessment
HTAb	Health Technology Assessment Body
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MD	Medical Devices
MP	Medicinal Products
PICO	Population, Intervention, Comparators and Outcomes
SOP	Standard Operating Procedure

1 INTRODUCTION

On 17 September 2021, the European Health and Digital Executive Agency (HaDEA) signed the Service Contract for the Provision of Joint Health Technology Assessment (HTA) Work Supporting the Continuation of EU Cooperation on HTA. The contract will run for 24 months, and until 16 September 2023. EUnetHTA 21 work will build on the achievements and lessons learned from the EUnetHTA Joint Actions and focus on supporting a future EU HTA system under the HTA Regulation. For all EUnetHTA 21 deliverables the future EU HTA Regulation will serve as a basis.

As part of this work the consortium have taken part in project work on developing PICO questions, based on methods developed during the service contract.

2 METHODOLOGICAL APPROACH

> "*The starting point for every assessment of a health technology is the scoping phase. During the scoping phase, an important goal is the definition of a concise research question that should be answered by the assessment. The PICO framework provides a standard format for the definition of a research question. Within the PICO framework, research questions are defined using (at minimum) the following components: Population (P), Intervention (I), Comparators (C) and Outcomes (O). Countries may differ in the exact PICO question they need to be answered. Therefore, during the scoping phase of EUnetHTA 21 agreement on the PICO questions should be reached.*"[1]

Despite multiple acquisition efforts by EUnetHTA 21, no medicinal product was submitted for the Joint Clinical Assessment work under EUnetHTA 21 contract. Regardless, EUnetHTA 21 has as one of its objectives to test the guidelines developed. To allow testing of procedures and gaining experience on JCA for medicinal products, EUnetHTA has conducted three PICO exercises. These exercises were very important as the D4.2 scoping guideline was one of the guidelines which would require the most capacity building. Furthermore, after these exercises the D4.2 scoping guideline went under revision to implement the relevant learnings.

The PICO exercises were conducted on medicinal products which already obtained a positive CHMP opinion. Therefore, no confidential data was used.

The production focussed on the scoping phase, i.e., to perform three JCA without a HTD submission. A JCA without submission still allowed to apply lessons learned within the development of the templates and methodological deliverables developed under the EUnetHTA 21 service contract. Within the given timeframe three scoping procedures without submission were conducted.

The below section provides a brief summary of the conducted scoping procedure.

3 PICO 2 – EBVALLO (TABELECLEUCEL)

Name of Product: Ebvallo (tabelecleucel)
Company: Atara Biotherapeutics Ireland Limited
Date of CHMP & MA: 13.10.2022 more information here.
Indication: Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

[1] EUnetHTA 21 D4.2 Deliverable https://www.eunethta.eu/d4-2/

Date of PICO survey: 09 - 23.01. 2023
Number of MS participated: 10
Number of associated HTAb participated: 3
Consolidated PICOs: 5 PICOs (1 in the full population and 4 in subpopulations)
CSCQ validation: 28 April 2023

4 CONSOLIDATED PICOS

Below you can find the five consolidated PICOs, which were validated by the EUnetHTA 21 CSCQ.

PICO 1: Full population	
Population	Adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.
Intervention	Tabelecleucel
Comparator	Individualized treatment, which may include: • 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
Outcome	see outcomes table
Abbreviations: CHOP - cylophosphamide, doxorubicine, vincristine, predniso(lo)ne; ACVBP **-** doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; DA-EPOCH - dose adjusted etoposide, prednisone, vincristine, doxorubicine, cyclophosphamide; R-DHAP – rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; (R-)GemOx - (rituximab), gemcitabine, oxaliplatin; (R)-Benda: rituximab, bendamustine; BSC - best supportive care.	

PICO 2: Subpopulation	
Population	Adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received rituximab and who are **ineligible for chemotherapy.**
Intervention	Tabelecleucel
Comparator	BSC
Outcome	see outcomes table
Abbreviations: BSC - best supportive care.	

PICO 3: Subpopulation	
Population	Adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) **after a haematopoietic stem cell transplantation**, who have received **rituximab** and are **eligible for chemotherapy.**
Intervetion	Tabelecleucel
Comparator	CHO(E)P +/- rituximab
Outcome	see outcomes table
Abbreviations: CHO(E)P – cyclophosphamide, doxorubicine, (etoposide), predniso(lo)ne.	

PICO 4: Subpopulation	
Population	Adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) **after a solid organ transplantation**, who have received at least one prior therapy and are **eligible for chemotherapy.**
Intervention	Tabelecleucel
Comparator	Individualized treatment. The following comparators are deemed appropriate: • CHO(E)P ± rituximab (-21) • cyclophosphamide + prednisolone ± rituximab • (R-)CE • HD-MTX ± rituximab • ProMACE CytaBOM
Outcome	see outcomes table
Abbreviations: CHO(E)P - cyclophosphamide, doxorubicine, vincristine, (etoposide), predniso(lo)ne; (R-)CE - (rituximab +) carboplatin, etoposid; HD-MTX - High dose methotrexate; ProMACE CytaBOM - prednisone + methotrexate + doxorubicine + cyclophosphamide + etoposide + cytarabine + bleomycine + vincristine+ methotrexate	

PICO 5: Subpopulation	
Population	Adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) **after a solid organ transplantation,** who have received at least one prior therapy and are **eligible for chemotherapy**.
Intervention	Tabelecleucel
Comparator	Any of the following alternative[1] chemotherapy-regimens: • CHO(E)P ± rituximab (-21) (cyclophosphamide, doxorubicine, vincristine, predniso(lo)ne) **OR** • cyclophosphamide + prednisolone ± rituximab **OR** • c(R-)CE **OR** • HD-MTX ± rituximab **OR** • ProMACE CytaBOM
Outcome	see outcomes table
Abbreviations: CHO(E)P - cyclophosphamide, doxorubicine, vincristine, (etoposide), predniso(lo)ne; (R-)CE - (rituximab +) carboplatin + etoposid; HD-MTX - High dose methotrexate; ProMACE CytoBOM - prednisone + methotrexate + doxorubicine + cyclophosphamide + etoposide + cytarabine + bleomycine + vincristine+ methotrexate	

[1]Compared to the first chemotherapy-regimen

Outcomes

• Overall survival
• Disease specific survival
• Symptoms like:
  - Symptomatic lymphadenopathy
  - B symptoms (fever, nights sweats, unintentional weight loss)
  - Infections
  - Viremia
• Overall response rate (partial and complete response)
• Treatment response (incl. overall response rate; partial response and complete response, including PET)
• Duration of response
• PFS
• EFS (including initiation of new treatments)
• Quality of life measured preferably by the EORTC QLQ C30, EORTC PR 25, FACT-P
• Health status measured by the EQ-5D
• Any other patient-centered outcome, assessed by generic or disease specific patient-reported outcome measures.
• Adverse events (in total)
• Serious adverse events (SAE)
• Severe adverse events (grade ≥ 3)
• Discontinuation due to adverse events
• Adverse events of special interest (AESI) e.g. GvHD occurrence, transplant rejection (allograft loss/rejection episodes)

Abbreviations: PET – Positron Emission Tomography; PFS – progression-free survival; EFS – event-free survival; EORTC-QLQ - European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire; FACT-P – Functional Assessment of Cancer Therapy – Prostate; EQ-5D – European Quality of Life 5 Dimensions; GvHD – Graft-versus-host disease