Lost in PICO? A simulation of the EU HTA scoping process

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ISPOR poster code: PT28
Poster presented at ISPOR Europe 2023
12-15 November 2023 in Copenhagen, DK.

OBJECTIVES

The joint clinical assessment (JCA) according to Regulation (EU) 2021/2282 will initially be implemented for oncology drugs and ATMPs from January 2025. All JCA procedures are commenced by the scoping process: The formulation of a member state-specific research question, represented as individual PICO schemes. Patient population, intervention, comparator, and study endpoints to measure the outcome are determined by the authorities as basis for clinical evaluation. Given the diversity of standards of care in Europe, multiple PICOs can be demanded. By simulating an EU HTA-like scoping process as of today, this analysis aims to assess the risk of receiving numerous PICOs.

METHODS

To determine the potential heterogeneity of PICO schemes, completed national HTA assessments from the "EU big 6" member states were compared regarding several oncology drugs. The PICO schemes for osimertinib (subsequently presented), venetoclax and pembrolizumab were extracted from the available national HTA reports and subsequently consolidated using the process described in the EUnetHTA 21 deliverable D4.2. In addition, the results of this analysis were then compared to the results of the EUnetHTA 21 PICO exercise for Pluvicto® to understand the factors influencing the HTA authorities in a PICO scoping process under realistic conditions.

RESULTS

PICO scoping Pluvicto® (EUnetHTA 21)

1. PICO survey: 8 Member States

2. PICO consolidation: Black Box

Central uncertainties

- Which member states did participate?
- Were the steps of deliverable D4.2 strictly applied?
- What role did political pressure of individual member states play ?
- How were patients and clinical experts involved, and what was the impact?

3. Final PICO scope:

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6
P	Label population[1], with bone metastases and no visceral metastasis	Label population[1], been treated with AR inhibitors and one line of taxans, suitable for cabazitaxel	Label population[1], with BRCA 1/2 mutation	Label population[1], not suitable for chemo or have been treated with docetaxel/ cabazitaxel or have no further therapy options	Label population[1]	Label population[1]
I	Pluvicto®	Pluvicto®	Pluvicto®	Pluvicto®	Pluvicto®	Pluvicto®
C	Radium-223	Cabazitaxel	Olaparib	BSC	Cabazitaxel ⊖ Abiraterone + prednisolon ⊖ Enzalutamide ⊖ Apalutamide ⊖ Olaparib ⊖ Radium-223 ⊖ BSC	Cabazitaxel ⊖ Abiraterone + prednisolone/ prednison ⊖ Enzalutamide
O	Outcomes	Outcomes	Outcomes	Outcomes	Outcomes	Outcomes

(1) Pluvicto® in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistantprostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane based chemotherapy.

PICO scoping Osimertinib (SKC)

1. PICO survey: DE, FR, IT, PL, NL

2a. PICO consolidation: List PICO requirements per MS

	DE	DE	FR	IT	PL	NL
P	Label population[2], suitable for adjuvant platin-based chemo	Label population[2], not suitable for adjuvant platin-based chemo[3]	Label population[2]	Label population[2]	Label population[2]	Label population[2]
I	Osimertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib	Osimertinib
C	Watchful waiting ⊖ Systemic antineoplastic therapy as prescribed	Watchful waiting	Watchful waiting	Watchful waiting	Watchful waiting	Watchful waiting
O	German outcome requirements	German outcome requirements	French outcome requirements	Italian outcome requirements	Polish outcome requirements	Dutch outcome requirements

2b. PICO consolidation : Select comparators and assign PICOs per population

	DE	DE	FR	IT	PL	NL
P	Label population[2], suitable for adjuvant platin-based chemo	Label population[2], not suitable for adjuvant platin-based chemo	Label population[2]	Label population[2]	Label population[2]	Label population[2]
C	Watchful waiting ⊖ Systemic antineoplastic therapy as prescribed	Watchful waiting	Watchful waiting	Watchful waiting	Watchful waiting	Watchful waiting

3. Final PICO scope:

	PICO 1	PICO 2	PICO 3
P	Label population[2], suitable for adjuvant platin-based chemo	Label population[2], not suitable for adjuvant platin-based chemo	Label population[2]
I	Osimertinib	Osimertinib	Osimertinib
C	Watchful waiting ⊖ Systemic antineoplastic therapy as prescribed	Watchful waiting	Watchful waiting
O	Outcome requirements from all MS	Outcome requirements from all MS	Outcome requirements from all MS

(2) Osimertinib as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA nonsmall cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Limitations and uncertainties:

National HTA reports usually do not include a transparent PICO scheme as it is common for GER. For osimertinib only 5/6 HTA reports were evaluable (excluding Spain). The potential translation of a placebo comparator into watchful waiting, BSC or a combination of both as a PICO comparator is subject to interpretation. A retrospective extraction of the PICOs from HTA report might differ from an actual proactive scoping process. Comparability with Pluvicto® is limited due to the difference in indication.

Abb.: AR: Androgen receptor; BSC: Best Supportive Care; Chemo: chemotherapy; EU: European Union; HTA: Health Technology Assessment; HTD: Health Technology Developer; JCA: Joint Clinical Assessment PICO: Patient, Intervention Comparator, Outcome; ⊖:OR conjunction.

Conclusion & Discussion

Extracting PICO schemes from available HTA reports from Germany, France, Italy, Poland, Netherlands and Poland and applying the PICO consolidation steps from EUnetHTA 21 deliverable D4.2 resulted in 3 PICOs (from 5 countries) for osimertinib, 1 PICO for (from 6 countries) venetoclax and 2 PICOs (from 6 countries) for pembrolizumab. Comparing these results with the EUnetHTA 21 PICO exercise for the oncologic product Pluvicto®, the following conclusions can be drawn:

- Strictly applying the consolidation rules appears to lead to potentially fewer PICOs than the Pluvicto® exercise, suggesting that **the process is likely more political than it is logical**.
- Therefore, **anticipating and preparing PICOs**, especially considering the **demands of influential countries like Germany** will be crucial for a favorable JCA outcome of a specific product.
- In addition, evaluating the **strategic implications of receiving disadvantageous comparators** (price anchors) and **populations** (subpopulations for which no evidence may be available) in the JCA which might then be brought also into national HTA procedures will be essential.

The presented analysis emphasizes the importance for HTDs of initializing strategic, structural and operative preparations for the upcoming EU HTA process, both in general and product specific.

All analyses have been generated by data from SKC's proprietary MAIS (Market Access Intelligence System = MAIS) database. This database contains and links information on completed and ongoing benefit assessments according to §35a SGB V of the German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). The MAIS-database records and evaluates relevant information from the dossier, the benefit assessment by IQWiG or the G-BA, the G-BA resolution as well as the Lauer-Taxe. It also contains an up-to-date overview of all procedures and their status.

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