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HTA138

Evidence Strategy Starts Early: Integrating HTA Needs Through PICO Simulation in Metastatic Castration-resistant Prostate Cancer

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KEY FINDINGS & CONCLUSIONS

- The participating countries proposed multiple, non-overlapping PICO scenarios, reflecting alignment on core trial parameters but variation in subgroup and comparator expectations, highlighting the complexity of national HTA requirements.
- Disease-specific challenges including population heterogeneity and evolving comparators suggest the need for regular stakeholder engagement and scenario testing.
- Early mapping of such variations provides a basis for further PICO refinement, gap analysis, and prioritization of evidence to support the overall EU JCA strategy.

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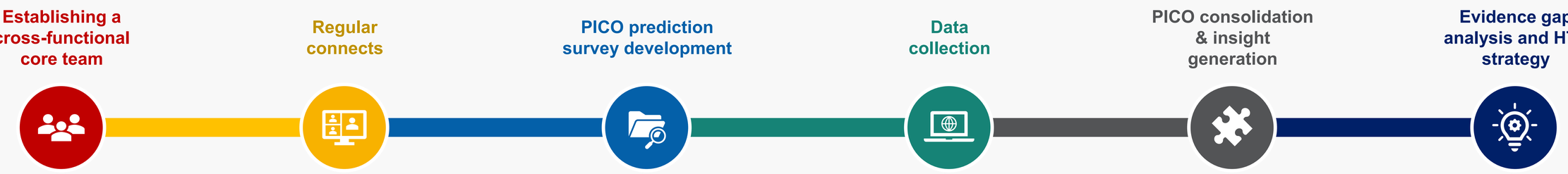
INTRODUCTION

- With the implementation of the European Joint Clinical Assessment (EU JCA) in 2025 for all oncology and advanced therapy medicinal products (ATMPs), the EU is moving towards a centralized clinical assessment process—aiming to harmonize clinical value evaluation across Member States before national pricing and reimbursement decisions[1,2].
- The PICO (Population, Intervention, Comparator, Outcomes) framework lies at the core of this process, defining the scope and structure of evidence appraisal[2]. However, given the diversity of clinical practice and comparator use, considerable variability in PICO expectations is anticipated across countries[3-6].
- For health technology developers (HTDs), early anticipation and alignment with these potential PICO scenarios is essential to inform trial design, evidence generation, and overall EU JCA preparedness[4].
- Therefore, we aimed to explore and evaluate potential PICO scenarios through a cross-country simulation exercise, supporting EU JCA readiness for a treatment under development for heavily pre-treated mCRPC patients.

METHODS

- An overview of the methodology for the PICO simulation exercise is provided in **Figure 1**.
- An online PICO prediction survey was conducted with colleagues from Germany, France, Italy, Spain, and the Nordics to understand their perspectives on the relevance of the clinical trial design and base-case PICO, and to elicit alternative relevant PICO scenarios.
- The planned clinical trial design for the investigational treatment served as the foundation for this exercise, and its corresponding PICO was defined as the base-case PICO:
  - **Patient population (P)**: Adult males with advanced mCRPC who have received multiple lines of prior systemic therapies
  - **Intervention (I)**: Investigational agent 'X'
  - **Comparators (C)**: Investigator's choice of standard of care, including androgen receptor pathway inhibitors, taxane-based chemotherapy, or other approved treatment options (e.g., cellular immunotherapy or targeted radionuclide therapy)
  - **Outcomes (O)**: Efficacy endpoints (radiographic progression-free survival; overall survival; progression-free survival; response rates etc.), quality of life, safety & tolerability
- The survey questionnaire included a mix of structured and open-text questions to capture both standardized responses and free-text reflections, ensuring comprehensive coverage of country perspectives.
- Respondents represented country affiliates from Health Economics & Outcomes Research (HEOR) and Market Access functions, with experience in national Health Technology Assessment (HTA) submissions. The responses were aligned with their local cross-functional teams (e.g., Medical Affairs) to ensure that the feedback reflected broader perspective from country teams.
- Based on the insights obtained through the survey, multiple alternative scenarios were developed, primarily reflecting population variations and currently approved comparator options across participating countries.

Figure 1. Description of overall methodology adopted for the PICO simulation exercise and insight generation



RESULTS & DISCUSSION

PICO survey results

- Substantial heterogeneity was observed among the PICO inputs received from countries, leading to identification of eight alternative consolidated PICO scenarios with limited overlap across markets.
- Three of the eight PICO scenarios were based on alternative relevant comparators, whereas the remaining five PICOs reflected patient population variations in terms of mutation status (n=2) or subgroups based on metastasis (n=1), functional status (n=1), and previously failed therapies (n=1).
- While there was a general alignment to the base-case outcomes across most markets, overall survival was the only endpoint considered most relevant by all the countries, emphasizing its central role in demonstrating clinical benefit for HTA evaluations.

Table 1. Summary of consolidated PICO scenarios

#	Patient population	Comparator(s)	Number of countries*
Alternative PICOs based on base-case population			
1	• Base-case population	• CABA, ENZA, ABI	1
2	• Base-case population	• Base-case except Sipuleucel- T	1
3	• Base-case population	• CABA + PRED or PRDL • BSC	1
Alternative PICOs based on base-case population variations/subgroups			
4	• Patients with symptomatic bone metastasis and no visceral metastasis	• ^{223}Ra dichloride	3
5	• Patients with ECOG PS >2	• Base-case comparators	1
6	• Patients with +ve BRCA 1/2 mutations	• OLA, OLA + ABI	1
7	• Patients with +ve BRCA mutation must have received prior PARP inhibitors	• Base-case comparators	1
8	• Patients who have failed all established therapies	• Base-case comparators	1

*Note: Above eight PICOs represent variations or subgroups derived from the base-case PICO provided in the survey. Exact country-level attribution to specific PICOs has been anonymized to maintain confidentiality.

Abbreviations: ^{223}Ra: Radium-223; ABI: Abiraterone; BRCA: BReast CAncer susceptibility gene; BSC: Best supportive care; CABA: Cabazitaxel; ECOG PS: Eastern Cooperative Oncology Group performance status; ENZA: Enzalutamide; OLA: Olaparib; PARP: Poly (ADP-ribose) Polymerase; PRED: Prednisone; PRDL: Prednisolone

Learnings & next steps

- While the base-case PICO was broadly considered clinically relevant, individual countries proposed multiple additional PICOs to reflect their national HTA expectations, mainly related to subgroup definitions and comparator selection.
- Heterogeneity across countries largely reflected differences in national clinical practice, treatment sequencing, and reimbursement environments, which influence the definition of clinically relevant subpopulations and available standard-of-care comparators. This observation is consistent with findings from a previous PICO simulation in mCRPC that also reported substantial cross-country variation in PICOs and HTA expectations[3].
- When extrapolated to all EU27 Member States, the number of anticipated PICOs is expected to rise considerably, highlighting the challenge for HTDs to generate comprehensive evidence packages that address diverse HTA comparator requirements.
- As a next step, a structured evidence gap analysis and EU JCA strategy will be developed to guide future readiness activities:
  - **PICO-level evidence mapping**: Evaluate the likelihood and rationale for each anticipated JCA PICO, map existing and planned evidence, and identify outstanding data gaps.
  - **Evidence gap prioritization**: Rank identified evidence gaps based on feasibility, expected impact on JCA outcomes, and alignment with the overall asset strategy.
  - **Comprehensive EU JCA strategy**: Define evidence-generation or justification needs for each PICO, assess access implications, and finalize an actionable strategy in collaboration with relevant cross-functional stakeholders.

Limitations/challenges

- **Feasibility of implementing alternate PICOs**: Some proposed scenarios may not be practical to operationalize within the scope or timelines of the pivotal clinical program, necessitating complementary real-world evidence (RWE) or secondary evidence strategies.
- **Survey response window and depth of feedback**: A two-week data collection period constrained the level of detail and cross-functional discussion possible at the affiliate level.
- **Dynamic development environment**: As clinical protocols, treatment landscapes, and EU JCA procedures continue to evolve, the current PICOs are expected to be refined through subsequent PICO exercises and iterative updates aligned with the finalized EU JCA scope at the time of submission.
- **Potential internal perspective bias**: Feedback represents internal affiliate and functional expert viewpoints, which may differ from official HTA assessment frameworks or national evaluation practices.

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Disclosures

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