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IMI2 777492 – PIONEER

Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the Power of Big Data in EuRope

WP6 – HTA regulator-payer integration

D6.1 – Characterization and mapping of regulator and payer evidence challenges in PCa

efpia

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Due date	31 Oct 2022
Delivery date	28 Oct 2022
Deliverable type	R
Dissemination level	Public

Description of Work	Version	Date
	V1.0	28 Oct 2022

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Document History

Version	Date	Description
V1.0	28 Oct 2022	First Draft and Final Version

Publishable Summary

Prostate cancer therapies have advanced significantly over the past 10 years. However, despite many receiving marketing authorisations across Europe, patients may still face inequalities in accessing these new treatments as reimbursement decision making comes down to country-level health technology assessments (HTAs). How individual countries assess health technology benefit varies widely, with some countries traditionally focussing on cost-effectiveness to drive decisions (e.g., England, Sweden), while others place greater value on comparative clinical benefit with less emphasis on cost assessment (e.g., Germany, France), or instead focus on healthcare budget impact/containment (e.g., Spain). This diversity in product value assessment can lead to variation in final recommendations for national reimbursement, which in turn can impact patient access to new treatments.

In 2018 the European Innovative Medicines Initiative began the PIONEER program which aims to use big data to address key knowledge gaps related to the screening, diagnosis, and treatment of prostate cancer patients to ensure optimal care for all affected European men[1]. PIONEER plans to standardise and integrate existing 'big data' from sources such as clinical trials and electronic health records into a single, innovative data platform, which will then be used to improve prostate cancer outcomes and health system efficiency. As part of this program, PIONEER working group members undertook a survey of HTA challenges contributors had faced in recent HTAs to inform the database design. This activity found misalignment between clinical trials and HTA body evidence requirements, with HTA reports flagging issues such as uncertainty in survival outcomes (especially with early lines of treatment), use of intermediate versus hard endpoints, lack of current data for older comparator treatments, evidence for companion diagnostics, validity of observational data, validity of post hoc analyses, and differences in pivotal trial and label populations as common critiques made in HTA. Members also foresee that evidence challenges will continue to grow as the treatment landscape for prostate cancer continues to evolve rapidly, including more targeted therapies and treatments for earlier indications, and new treatments come to market with more innovative evidence packages.

To understand how HTA uncertainties might impact patient access to new prostate cancer treatments, and the potential utility of the PIONEER database to HTA, we undertook a detailed analysis of HTA reports published between 2019 and 2021 to investigate:

1. The challenges faced by new prostate cancer therapies in HTA following EMA approval over the last 10 years; and,
2. Inequalities in patient access to these therapies across European healthcare systems.

By understanding past HTA challenges we hoped to provide insight for future prostate cancer treatments and identify potential application of PIONEER data to support successful HTA, particularly as the EU moves towards joint clinical and health technology assessment[2].

Aim of the deliverable

With this deliverable, we try to understand how HTA uncertainties impact patient access to new prostate cancer treatments. This is done by exploring past HTA challenges and through a comparative analysis of inequalities across European healthcare systems. By understanding past challenges, insights can be provided for future prostate cancer treatments and for the potential of PIONEER data to support HTA decisions.

Methods

A detailed analysis of HTA reports published between 2019 and 2021 was performed. In particular, this was to assess the challenges faced by new prostate cancer therapies in HTA following EMA approval over the last

10 years and the inequalities in patient access to these therapies across European countries. IQVIA HTA Accelerator was used to identify HTA reports for new prostate cancer therapies published by key European HTA bodies between January 2019 and July 19, 2021. Relevant HTA reports (available in the public domain) were reviewed to determine HTA recommendation (positive, conditional, or negative recommendation), and key decision drivers (positive and negative critiques). Extraction of findings from HTA reports was based on a subjective assessment and interpretation, which may be a limitation, however this was undertaken in a systematic way to minimise any bias.

Information analysed across reports included:
- Decision drivers and outcomes of HTAs
- Extent of HTA recommendation variation across populations reviewed
- Key critiques of study design and clinical outcomes, and how these uncertainties impacted the HTA recommendation
- Role of RWE in HTA recommendations
- Differences in evidence requirements between different HTA agencies

Results

Recent advances in advanced prostate cancer therapy

Several new products for the treatment of advanced prostate cancer have been developed over the past decade. These have included treatments for multiple patient segments, including metastatic hormone-sensitive prostate cancer (mHSPC), nonmetastatic castration-resistant prostate cancer (nmCRPC), chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) and post-chemotherapy mCRPC, and offer improved clinical outcomes compared with previously available therapies. These have included Zytiga (abiraterone acetate), Erleada (apalutamide) and Xtandi (enzalutamide) for the treatment of mHSPC, Xtandi, Erleada and Nubeqa (darolutamide) for nmCRPC, Zytiga, Xtandi and Lynparza (olaparib) for chemotherapy-naïve mCRPC, and Zytiga, Jevtana (cabazitaxel), Xtandi and Xofigo (radium-223 dichloride) for post-chemotherapy mCRPC. These drugs have received European Medicines Agency (EMA) authorisation across multiple indications and, generally, been endorsed for use by the European Society for Medical Oncology (ESMO) based on magnitude of clinical benefit (MCB) scores of three or four (Figure 1).

Figure 1: Overview of EMA marketing authorisation decisions, and corresponding ESMO-MCBS score[a] (where available), for new prostate cancer therapies over the past decade

Treatment (approval date) ESMO-MCBS score[a3]	**mHSPC**	**nmCRPC**	**Chemo-naïve mCRPC**	**Post-chemo mCRPC**
Erleada[4] (apalutamide)	Erleada + ADT (27 Jan 2020) ESMO-MCBS: 4	Erleada + ADT (14 Jan 2019) ESMO-MCBS: 3	Not currently indicated	Not currently indicated
Jevtana[5] (cabazitaxel)	Not currently indicated	Not currently indicated	Not currently indicated	Jevtana + prednisone/ prednisolone (17 Mar 2011) ESMO-MCBS: 3
Nubeqa[6] (darolutamide)	Not currently indicated	Nubeqa + ADT (27 Mar 2020) ESMO-MCBS: 3[3]	Not currently indicated	Not currently indicated
Xtandi[7]	Xtandi + ADT	Xtandi + ADT	Xtandi	Xtandi

(enzalutamide)	(30 April 2021) ESMO-MCBS: 3	(23 Oct 2018) ESMO-MCBS: 3	(28 Nov 2014) ESMO-MCBS: 4	(21 Jun 2013) ESMO-MCBS: 4
Xofigo[8] (radium-223 dichloride)	Not currently indicated	Not currently indicated	Not currently indicated	Xofigo ± LHRH analogue (13 Nov 2013)[b] ESMO-MCBS: 5
Zytiga[9] (abiraterone acetate)	Zytiga + prednisone/ prednisolone + ADT (15 Nov 2017)[c] ESMO-MCBS: 4	Not currently indicated	Zytiga + prednisone/ prednisolone (18 Dec 2012) ESMO-MCBS: 4	Zytiga + prednisone/ prednisolone (5 Sep 2011) ESMO-MCBS: 4
Lynparza[10] (olaparib)	Not currently indicated	Not currently indicated	Lynparza monotherapy (3 Nov 2020)[d] ESMO-MCBS: 3	Not currently indicated

[a]ESMO-MCBS grading highlights treatments which substantially improve the duration of survival and/or the quality of life of patients with cancer and aims to distinguish them from trials demonstrating more limited and sometimes even marginal benefits to facilitate improved decision-making; for non-curative settings treatments are scored on a scale of 1 (lowest benefit) to 5 (greatest benefit)[3]
[b]mCRPC with symptomatic bone metastases and no known visceral metastases
[c]Newly diagnosed high risk mHSPC
[d]mCRPC with BRCA1/2-mutations (germline and/or somatic)
Abbreviations: ESMO, European Society for Medical Oncology; MCBS, magnitude of clinical benefit; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; N/A, not available; nmCRPC, nonmetastatic castration-resistant prostate cancer

Is there a gap between regulatory approval of new prostate cancer therapies and patient access, and why?

IQVIA's HTA Accelerator[11] was used to identify HTA reports for new prostate cancer therapies published by key European HTA bodies between January 2019 and July 19, 2021. Relevant HTA reports (available in the public domain) were reviewed to determine HTA recommendation (positive, conditional, or negative recommendation), and key decision drivers (positive and negative critiques). Extraction of findings from HTA reports was based on a subjective assessment and interpretation, which may be a limitation, however this was undertaken in a systematic way to minimise any bias.

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Access to prostate cancer therapies is variable

Broadly, many healthcare systems across Europe provide some level of access to, or reimbursement of, prostate cancer therapies approved between 2019 and 2021. However, comparison across countries revealed some inequality in patient access as reimbursement for new treatments varied (Figure 2). For example, the broadest reimbursement for new prostate cancer therapies was provided in Germany, Italy, and France, with most EMA-approved treatments fully reimbursed across all indications thereby providing patients with access to many treatment options. In contrast, Sweden and the Netherlands often applied conditions to the reimbursement of new prostate cancer therapies, thereby potentially restricting access. Furthermore, some countries, such as Poland, Ireland, and Portugal, provide reimbursement for only about half of new prostate cancer therapies, substantially restricting access options for patients.

In this assessment no single treatment, or patient segment, appeared to receive a greater proportion of

reimbursement restrictions compared with the others. However, countries with a cost-effectiveness focus to their HTA were more likely to decide not to reimburse, or only provide conditional reimbursement than countries using other HTA approaches (Figure 2). Negative or conditional recommendations from HTA bodies were often linked with reimbursement restrictions, reflecting uncertainty by HTA bodies in the value the new drugs could offer.

Figure 2: Reimbursement status of EMA-approved prostate cancer therapies across European countries (as of 30 June 2021, for countries included in the HTA outcomes analysis shown in Figure 3)

Country	Xtandi	Xtandi	Zytiga	Zytiga	Erleada	Xofigo	Zytiga	Xtandi	Erleada	Xtandi	Lynparza	Nubeqa	Jevtana
	Chemo-naïve mCRPC	Post-chemo mCRPC	Chemo-naïve mCRPC	Post-chemo mCRPC	nmCRPC	Post-chemo mCRPC	mHSPC	mHSPC	mHSPC	nmCRPC	Chemo-naïve mCRPC	nmCRPC	Post-chemo mCRPC
Germany[12]	P	P	P	P	P	P	P	P	P	P	P	P	P
Italy (CE)[a13]	P	P	P	P	P	P	P	P	P	P	P		P
France[14]	P	P	P	P	P	P	P	P	P	P	P	P	P
Belgium[15]	P	P	P	P	P	P	P	P	P	P	P	X	P
Denmark (CE)[a16]	P	P	P	P	P		P	P	P	P	P	P	P
Norway (CE)[17]	P	P	P	P	P	P	P	P	P	P		P	X
Spain[b18]	P	P	P	P	P	P	P		P	X	X	P	P
Bulgaria[19]	P	P	P	P	P	X	P	P	P	P	P	X	P
Finland (CE)[20]	P	P	P	P	P	X	P	P	P	P	P	P	X
Poland (CE)[21]	P	P	P	P	X	P	X	X	X	P	X	X	P
England (CE)[b22]	P	P	P	P	P	P		P	P	X	X	P	P
Scotland (CE)[b23]	P	P	P	P	X	P	P		X	X	X	P	P
Sweden (CE)[24]	P	P	P	P	P	P	P	P	P	P	P	P	P
Netherlands (CE)[25]	P	P	P	P	P	P	P	P	P	P	P		P
Ireland (CE)[26]	P	P	P	P	P	P	X	X	X	X	X	X	P
Portugal[27]	X	X	X	X	P	P	X	X	P	X	P	P	P

Table key	Not reimbursed	Fully reimbursed	Conditional reimbursement	Data not publicly available

Note: this table is sorted by countries with overall highest reimbursement at the top, and products with highest reimbursement at the left.

[a]Denmark and Italy started CE analysis in 2021 however prostate cancer treatments were reviewed prior to this

[b]Indication-specific data available.

Abbreviations: CE, cost-effectiveness market; chemo, chemotherapy; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer

Figure 3: Overview of HTA recommendations for prostate cancer therapies between 2019 and 2021

Country	Xtandi	Xtandi	Zytiga	Zytiga	Erleada	Xofigo	Zytiga	Xtandi	Erleada	Xtandi	Lynparza	Nubeqa	Jevtana
	Chemo-naïve mCRPC	Post-chemo mCRPC	Chemo-naïve mCRPC	Post-chemo mCRPC	nmCRPC	Post-chemo mCRPC	mHSPC	mHSPC	mHSPC	nmCRPC	Chemo-naïve mCRPC	nmCRPC	Post-chemo mCRPC
Germany	P	P	P	P	P	X	P		X	P	P	P	P
Italy (CE)[a]		P	P	P			X						X
France	P	P	P	P	P	P	P		P	P		P	P
Belgium													P
Denmark (CE)[a]					P		X			P		P	
Norway (CE)													
Spain[b]					P		P		P	X		P	
Bulgaria						X							
Finland (CE)													
Poland (CE)	P	P	X	P	P				X	P		P	P
England (CE)[b]	P	P	P	P		P		P		X		P	P
Scotland (CE)[b]	P	P	P	P	X	P	P		X	X		P	P
Sweden (CE)	P	P	P	P	P		P		P	X		P	
Netherlands (CE)				P									P
Ireland (CE)	X	X				X							
Portugal	P	P	P	P	P	P							

Table key	Negative recommendation	Positive recommendation	Conditional recommendation	No recommendation stated in report	No published review

[a]Denmark and Italy started CE analysis in 2021 however prostate cancer treatments were reviewed prior to this

[b]Indication-specific data available

Abbreviations: CE, cost-effectiveness market; chemo, chemotherapy; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer.

Note: For this analysis, all positive, restricted, negative and no recommendation were included for all EU countries where HTA publications were available as of 19 July 2021. No added benefit and less added benefit ratings from the G-BA in Germany, and service medical rendu (SMR) insufficient or amelioration du service medical rendu (ASMR) V rating from the Commission de la Transparence in France, are coded as a negative recommendation and impacts pricing but does not negatively impact patient access. For NICE the final guidance was used.

Source: IQVIA HTA Accelerator[11]

Patient access to new prostate cancer therapies is unequal and often delayed

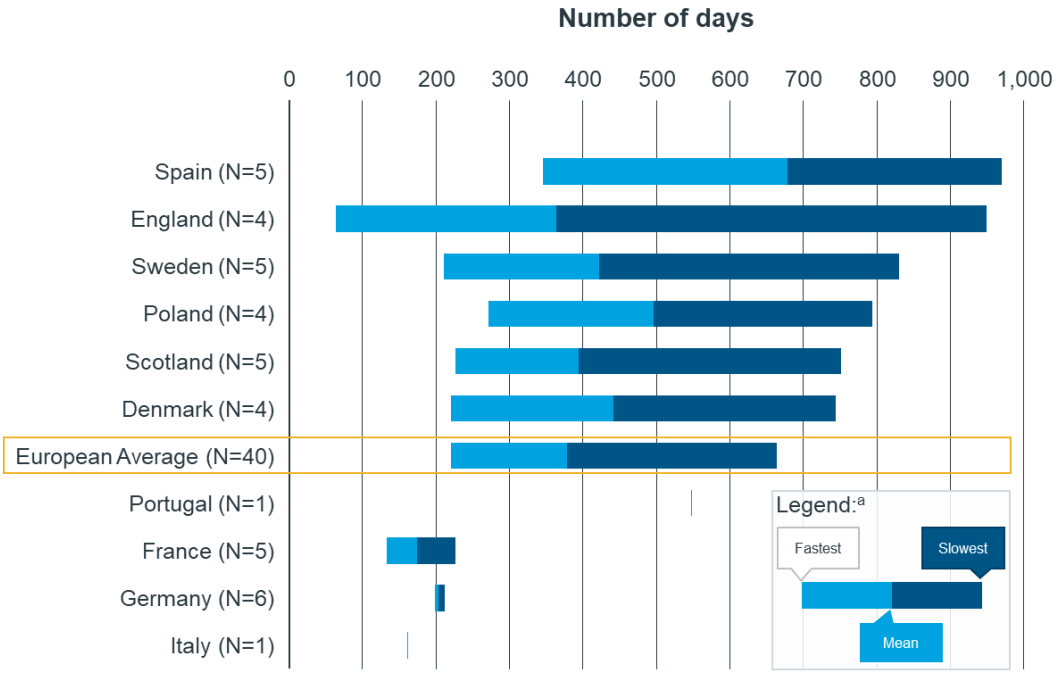
Comparing EMA approved indications and subsequent country HTA recommendations (between 2019 and 2021) revealed recommendations for use of new prostate cancer therapies was variable across countries. A greater willingness to recommend use of new therapies was observed in some countries, such as France (10 positive recommendations), Germany (8 positive recommendations), and Sweden (7 positive recommendations). In contrast, a substantial number of negative, conditional, or no recommendation, assessment outcomes were observed across the other European countries for which HTA reports were available (Figure 3).

Variation was observed in time from EMA approval to first HTA recommendation across countries, putting patients in countries with longer HTA decision times at a disadvantage when accessing new prostate cancer treatments. On average across European countries HTA recommendations were received approximately 400 days after EMA approval (Figure 4). Some assessments in Bulgaria (Xofigo in post-chemotherapy mCRPC), Poland (Xtandi in post-chemotherapy mCRPC) and Portugal (Xtandi and Zytiga in chemotherapy-naïve mCRPC) took approximately 4 to 7 years and were excluded from the analysis as outliers. Details of time from EMA approval to manufacturer reimbursement application were not publicly available for these decisions therefore it was not possible to understand the cause of these long decision times.

Even with the outliers excluded from the analysis, substantial variance remained for the average time taken for HTA recommendations across countries, ranging from 162 days to 679 days. Germany (N=6), France (N=5) and Italy (N=1) tended to have the shortest assessment times (around 180 days), while Spain (N=5), Poland (N=4) and Portugal (N=1) took noticeably longer (≥500 days). Average assessment times in England (N=4), Sweden (N=5), Scotland (N=5) and Denmark (N=4) were close to the overall average, however England had the greatest variation in time taken for HTA (from 64 to 949 days). Generally, we observed that assessment timelines were shortest in countries with potentially large target patient populations (e.g., Germany, France, Italy; with the exception of Spain), and longer in countries with smaller populations.

Two factors can contribute to the time taken for a HTA recommendation to be reached: 1) time between regulatory marketing authorisation and HTA submission/process start; and, 2) time between HTA submission and decision. Furthermore, in some countries (e.g., England) the HTA process can start before regulatory approval, while in other markets it can take >1 year for the HTA to start (note, this may also be driven by the marketing authorisation holder). However, HTA start dates and reimbursement dates are not published in many countries which limited our analyses, and due to a lack of data it was not feasible to determine which of these time components drove the variation in HTA decision times.

Figure 4: Average time (days) from EMA approval to date of first HTA decision/recommendation for prostate cancer therapies assessed 2019–2021 (excluding outliers; the chart is sorted by the longest maximum time from top to bottom)



[a]Note for chart legend: The chart is sorted by the longest maximum time from top to bottom. The left edge of the light blue segment represents the fastest time. The border from light to dark blue represent the average time. The right edge of the dark blue segment represents longest time. The average bar shows average of fastest, overall average and average of slowest decision. For Portugal and Italy, only one data point is available in each country. For this analysis only the first positive/ conditional recommendation has been considered and time to recommendation is the time from the date of EMA approval to date of first HTA decision; the analysis excluded assessments in Bulgaria (Xofigo in post-chemotherapy mCRPC), Poland (Xtandi in post-chemotherapy mCRPC) and Portugal (Xtandi and Zytiga in chemotherapy-naïve mCRPC) identified as outliers.
Source: IQVIA HTA Accelerator[11]

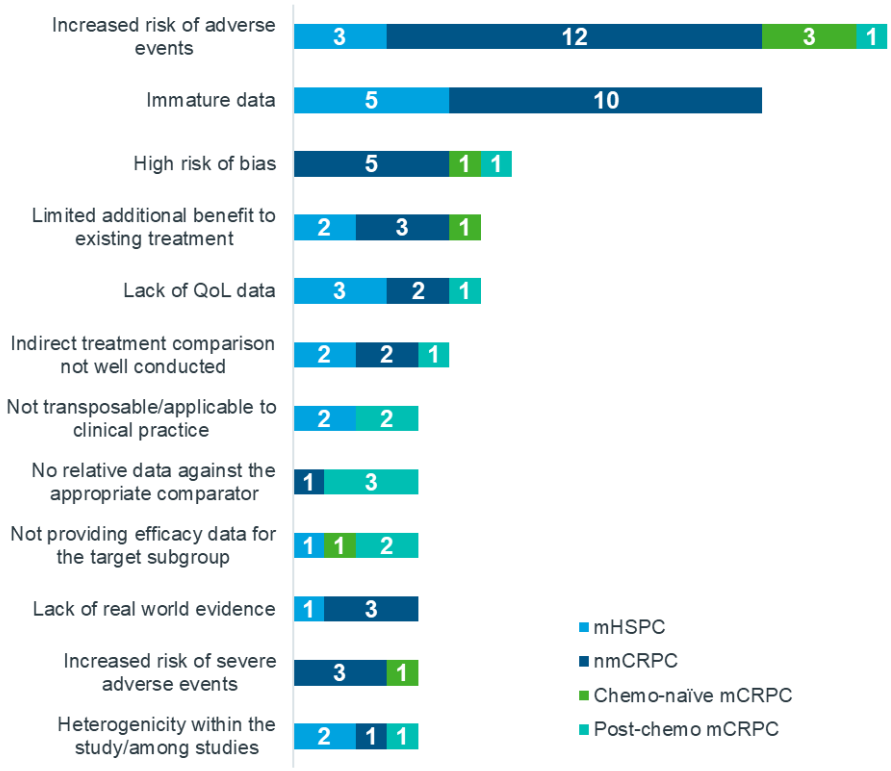
Increased risk of adverse events, immature data, high risk of bias, limited additional benefit to existing treatment and lack of QoL data were frequent HTA challenges

Uncertainty around the clinical benefit of new prostate cancer therapies was a key issue in HTA body assessment of clinical evidence. The top five clinical critiques for new treatments were increased risk of adverse events (vs. comparator), immature data, high risk of bias, limited additional benefit to existing treatment, and lack of QoL data (Figure 5).

Increased risk of adverse events was critiqued by most European HTA bodies, especially by the G-BA and IQWiG (Germany), HAS (France), and Medicinrådet (Denmark), however this was not a key driver of negative recommendations. Instead, immature overall survival was the most common reason underlying negative or conditional HTA recommendations across all countries. Furthermore, immature clinical trial data, in general, was critiqued most frequently by NICE (England), SMC (Scotland) and the G-BA (Germany) as a key reason impacting the level of benefit awarded to new prostate cancer treatments. This observation suggests that while regulatory agencies, and clinical bodies, were willing to award marketing authorization for the new prostate cancer therapies based on available clinical trial evidence this was not equally acceptable to HTA bodies, who often found the data insufficient to support full recommendation. Other critiques of clinical evidence cited in HTA reports shown in

Figure 5 were generally sporadic across the different markets.

Figure 5: Key clinical evidence critiques cited in HTA recommendations, regardless of outcome, for prostate cancer therapies (2019–2021)[a]



[a]Research focussed on prostate cancer therapies reviewed over the past 2 years (2019 – 2021), however for completeness Zytiga HTA records from 2018 were also included
Abbreviations: HTA, health technology assessment; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; QoL, quality of life.
Source: IQVIA HTA Accelerator[11]

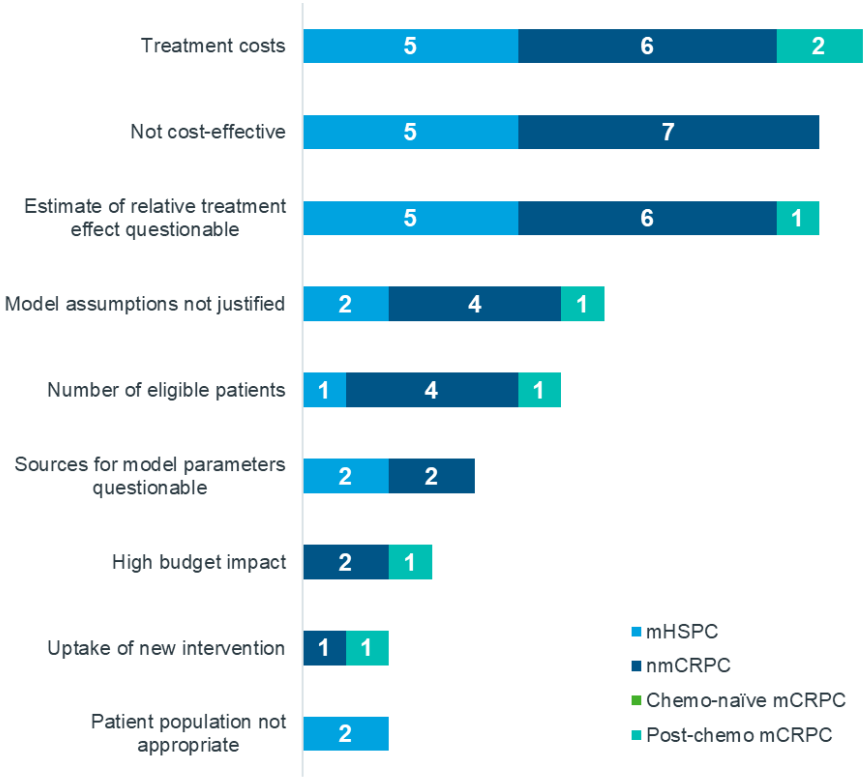
Uncertainty of clinical benefit in HTA led to criticism of treatment costs and health economic analyses, which negatively impacted HTA recommendations

Treatment costs, a lack of cost effectiveness, questionable estimate of relative treatment effect, model assumptions used provided for HTA not justified, and the number of eligible patients were the top five economic critiques cited in HTA outcomes for new prostate cancer treatments (Figure 6).

In those countries which focus on cost-effectiveness (e.g, England, Sweden, Denmark, Poland) a lack of demonstrated overall survival benefit, and/or immature clinical trial data in general, translated into the product not being deemed cost effective in ~60% (7/12) of negative or conditional prostate cancer therapy HTA recommendations assessed. This judgement, which linked directly to uncertainty in the clinical benefit observed in the clinical critiques, then impacted HTA recommendations, potentially limiting patient access to the new treatments.

In addition, HTA bodies often mentioned concerns about a lack of significant benefit in indirect treatment comparison, sources for model parameters questionable, inappropriate choice of comparator, economic model assumptions or design not justified, high budget impact, and use of an inappropriate patient population in economic comparisons as reasons underlying negative or conditional recommendations.

Figure 6: Key economic critiques cited in HTA recommendations, regardless of outcome, for prostate cancer therapies (2019–2021)[a]



[a]Research focussed on prostate cancer therapies reviewed over the past 2 years (2019 – 2021), however for completeness Zytiga HTA records from 2018 were also included
Abbreviations: HTA, health technology assessment; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer.
Source: IQVIA HTA Accelerator[11]

HTA bodies also stated immature clinical trial data, lack of demonstrated survival benefit, and use of clinical response endpoints (e.g., progression-free survival [PFS] or metastasis-free survival [MFS]) as a surrogate for overall survival, as key reasons underlying their uncertainty in the clinical benefit demonstrated by new prostate therapies. Again, these comments in HTA reports illustrate a disparity in acceptance of different elements of clinical evidence as a demonstration of clinical benefit between regulatory bodies and clinicians, and HTA bodies, with the later tending to be more critical of the clinical trial evidence.

Can real-world data help bridge the evidence requirements of EMA and HTA?

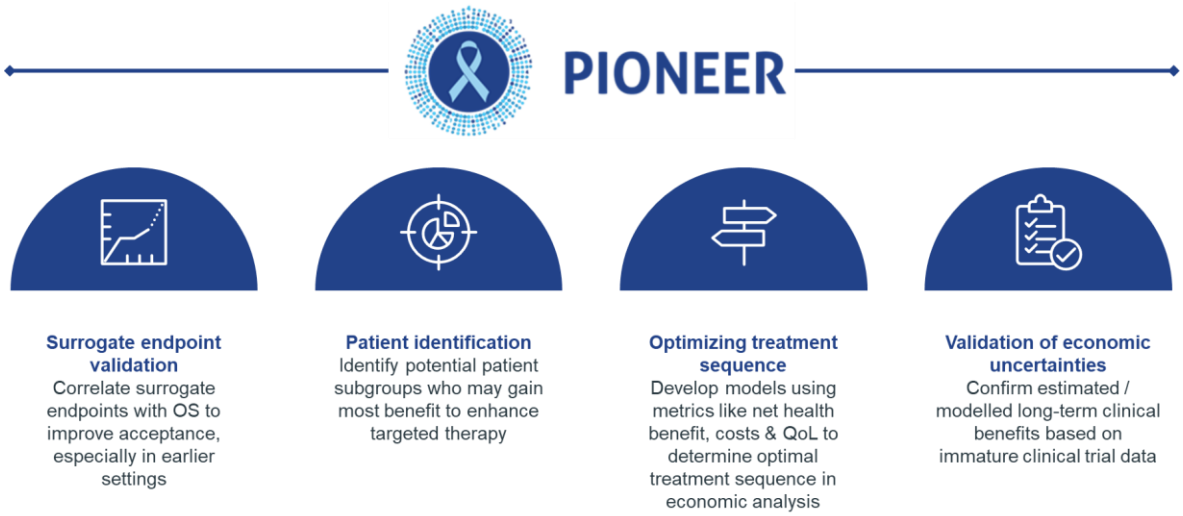
We found that evidence-based challenges or economic/price-based challenges from HTA bodies in their assessment of approved prostate cancer therapies contributed to potential access inequalities. Uncertainty in the benefit/risk of new treatments (immature data, use of surrogate endpoints in the absence of mature overall survival, unclear identification of patient groups with greatest benefit) and ambiguity in economic assessments were key critiques that led to HTA restrictions on patient access. In addition, variation in the mechanics of HTA across different European markets affected the speed with which HTA recommendations were delivered, again contributing to inequality in patient access to new prostate cancer treatments. Many of

the same issues identified here were also recognised in a report commissioned by the EFPIA in 2020[28] which found highly variable patient access to new oncology therapies and variation in time to market access across countries due to a number of factors including differences in evidence requirements across Europe, lack of clarity on national requirements, evidence gaps, and misalignment on value and price.

Our analysis suggests that to improve patient access marketing authorisation holders need to close the gap in evidence required by regulatory and HTA bodies, for example by providing clinical evidence acceptable to both, or by improving HTA certainty in clinical benefit by supplementing the evidence package with complementary data. This is likely to become increasingly important as the EU moves towards joint clinical and health technology assessment under the new EU Health Technology Assessment regulation[2].

The PIONEER program[1] could play a key role to play in bridging these data gaps. One objective is for PIONEER to empower meaningful improvement in health-economic outcomes across the European healthcare landscape[1]. Our assessment of recent European HTA of new prostate cancer therapies has identified three key areas where PIONEER data could strengthen HTA evidence packages for new treatments: 1) surrogate endpoint validation; 2) patient targeting; 3) optimisation of treatment sequencing assumptions in economic analyses; 4) validation of economic uncertainties (Figure 7).

Figure 7: Recommendations for PIONEER contribution to HTA evidence packages



Overall survival, which HTA bodies often see as a gold standard for clinical benefit, is often not available at the point of HTA and regulatory approval may instead rely on clinical trial endpoints that quantify disease response (e.g., PFS/radiographic PFS, MFS). However, HTA bodies often view these endpoints as surrogates with uncertain correlation with overall survival. Utilising PIONEER real world data to demonstrate surrogate endpoints correlate with overall survival in different patient segments could help to improve acceptance of these endpoints as part of HTA of new prostate cancer therapies. This could be an important goal to support early access for patients to innovative cancer therapies.

PIONEER may also be a useful data source to validate the optimal treatment sequence used in prostate cancer economic assessments, and to help identify potential patient subgroups who may gain most benefit thus enhancing targeted therapy. Identifying potential patient subgroups for targeted therapy using PIONEER data could build on a recent study-a-thon which assessed selection criteria and long-term outcomes of patients with prostate cancer who were on a watchful waiting management approach[29]. Potentially the prediction models developed in this study-a-thon could be used to identify patients who are highly likely to benefit from targeted treatment instead of using a watchful waiting approach. Furthermore, we hypothesise that the PIONEER framework could be extended to develop models that utilize metrics like net health/clinical benefit, costs, quality of life, and distributive cost-effectiveness analysis to determine the optimal treatment sequence

in prostate cancer treatment. Such real-world data analysis could enhance economic modelling to provide HTA bodies with greater confidence in future outcomes.

Uncertainty in economic evaluations may also be eased by using PIONEER data to validate estimated/modelled long-term clinical benefits based on immature clinical trial data. For example, leveraging PIONEER data to demonstrate that the level of data maturity does not substantially impact clinical endpoints (for example, demonstrating that more mature overall survival Kaplan-Meier curves match extrapolated overall survival).

Beyond supporting or enhancing economic evaluations, we foresee that PIONEER data may improve understanding of prostate cancer treatment and outcomes. For example, the database may be able to answer questions about treatment patterns, such as whether there are substantial differences in treatment patterns for advanced prostate cancer across European countries, and then whether these differences lead to differences in patient outcomes. When combined with analysis similar to that performed here, PIONEER data may also be able to investigate whether differences in speed of reimbursement decisions for new treatments potentially impacted treatment patterns and patient outcomes. PIONEER data may also be able to answer specific questions about the effectiveness of prostate cancer therapies in the real-world, or provide insight into how significant world-wide events, such as the COVID-19 pandemic, may have affected prostate cancer treatment.

Conclusion

Overall, HTA bodies in many countries across Europe recommend some level of access to new prostate cancer therapies, however variability across individual countries was observed. As often seen in wider oncology, the most common objection raised in European HTA review of new prostate cancer therapies were a lack of clinical trial data maturity and a lack of cost-effectiveness, generating uncertainty around perceived benefit to patients and the healthcare system. This uncertainty may then impact patient access. Similar payer critiques are not uncommon in the wider oncology field, reflecting a discrepancy in the evidence requirements of regulatory agencies and HTA bodies.

This prompts the question of what might be done to bridge this gap and ease HTA of new prostate cancer therapies to provide access for patients and improve clinical outcomes. It is anticipated that the PIONEER database will be a valuable source of real-world data to strengthen evidence packages for new prostate cancer therapies, particularly as European joint clinical assessment is introduced, to support patient access to new treatments.

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Acknowledgement

The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under Grant Agreement n° 777492. This Joint Undertaking receives the support from the European Union's Horizon 2020 research and innovation programme and EFPIA.