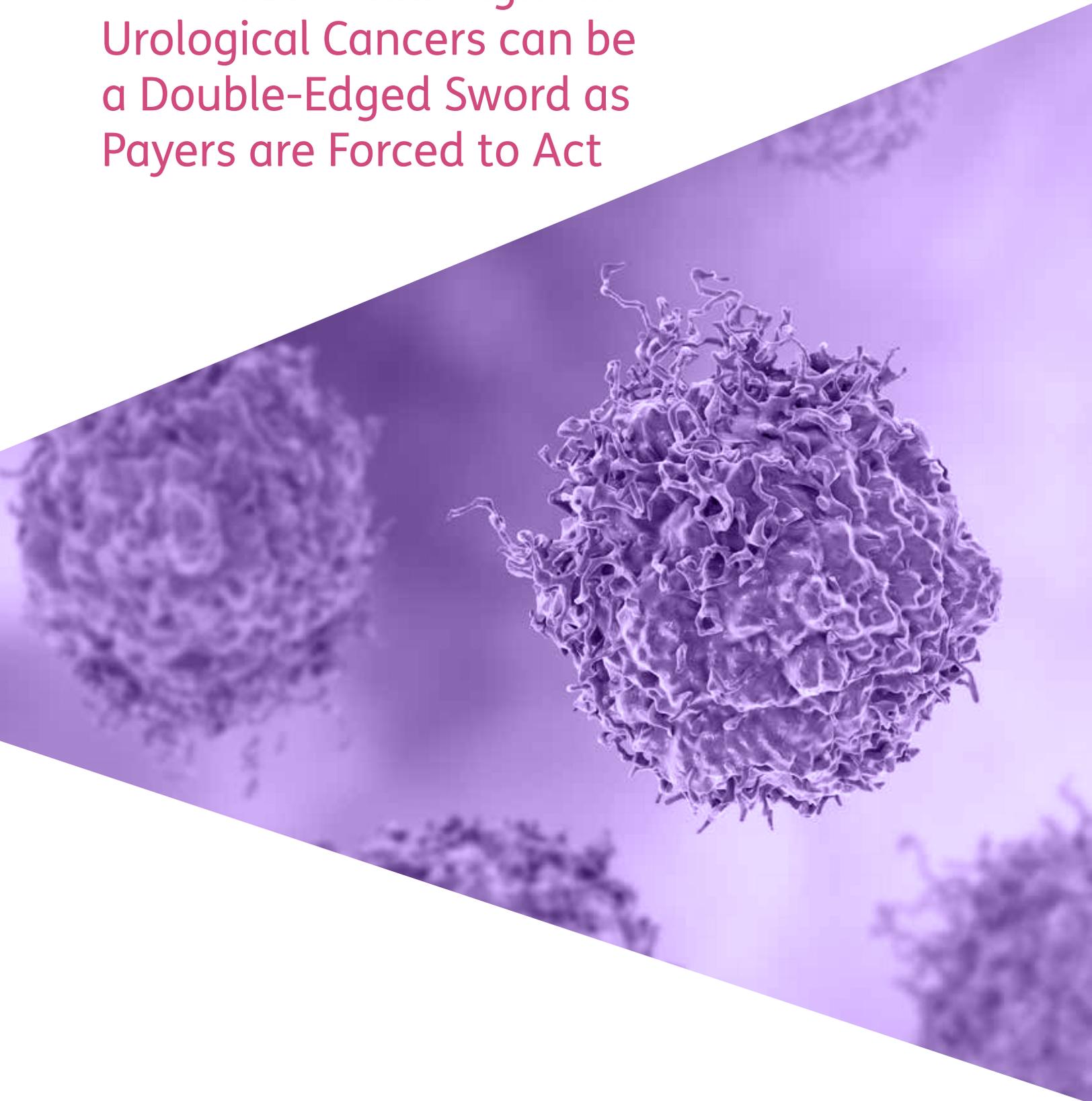


# Clinical Breakthroughs in Urological Cancers can be a Double-Edged Sword as Payers are Forced to Act





## Overview

The three urological cancers are undergoing tremendous changes in treatment practices as a result of new product launches and indication expansions. Checkpoint inhibitors in bladder cancer, combination regimens in renal cell carcinoma (RCC) and novel anti-androgens in early prostate cancer treatment lines have demonstrated patient benefit, increasing survival times and addressing major areas of unmet need. However, payers are concerned about the potential impact of these therapies due to their high costs and sometimes

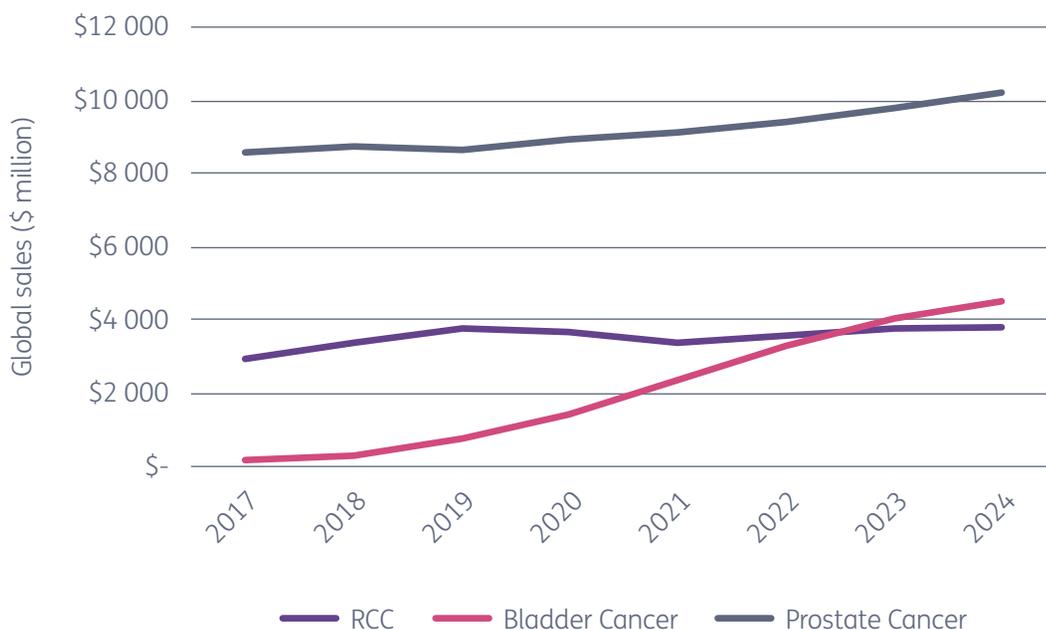
extended treatment durations. As a result, payers and health technology assessment (HTA) agencies have put these new treatments under scrutiny, with evidence requirements growing as the competition in each indication heats up. This white paper looks at the reimbursement restrictions payers around the US and EU have placed on these high-cost therapies, the changes in evidentiary and clinical trial evidence requirements, and future cost-control measures which are likely to be implemented to curb the total expenditure in these indications.

## Introduction

Over the past few years, several high-impact therapies have gained approvals and label expansions in bladder cancer, RCC and prostate cancer. Spend has been rising steadily within

the indications, with further increases expected as numerous expensive therapies, including combination treatments, enter the late-stage pipeline (see Figure 1).

**Figure 1: Global sales forecast for urological cancers, 2017–24**



Source: Datamonitor Healthcare, September 2018

## RCC

In RCC, Opdivo (nivolumab; Bristol-Myers Squibb/ Ono Pharmaceutical) and tyrosine kinase inhibitor (TKI) Cabometyx (cabozantinib; Exelixis/Ipsen) have gained approval in the second-line advanced treatment setting, with Opdivo also likely to gain a label expansion into the first-line setting. Furthermore, in an increasingly crowded market, developers are hoping that label expansion into the adjuvant setting or as part of a combination therapy will help to increase market share. Avastin (bevacizumab; Genentech/Roche/Chugai) and Inlyta (axitinib; Pfizer) are currently in clinical trials testing their efficacy in combination with pipeline programmed death-1 (PD-1)-targeted therapies, and Sutent (sunitinib; Pfizer) and Votrient (pazopanib; Novartis) are being investigated as adjuvant therapies to surgery in high-risk individuals.

### **German physician association payer:**

*“The increasing use of combinations: that is a big issue. In the past the surgical intervention was the most important issue for payers – it was the highest cost – and then the adjuvant treatment strategy became more popular and the interleukins were not too expensive, but then these new targeted agents were quite expensive, but the newest things – the combination therapy of two branded targeted therapies or PD-L1 inhibitors – that could then easily come to a price of €200,000 per patient per year.”*

## Prostate cancer

While the novel anti-androgens Zytiga (abiraterone acetate; Johnson & Johnson/AstraZeneca) and Xtandi (enzalutamide; Pfizer/Astellas) have been approved in metastatic castration-resistant prostate cancer (mCRPC) since 2012, the drugs have recently gained approvals in earlier treatment lines such as metastatic hormone-sensitive prostate cancer (mHSPC) and non-metastatic castration-resistant prostate cancer (nmCRPC). These lines not only represent larger patient numbers than mCRPC, but also require significantly longer treatment durations due to longer life expectancies and slower disease progression.

### **UK national payer:**

*“As you advance therapies from third line to first line, the numbers increase but the duration of treatment also increases. So, we know that there are going to be potentially big hikes in expenditure on prostate cancer drugs even if only one or two drugs get through, if they are earlier in the patient pathway.”*

## Bladder cancer

Bladder cancer has seen an influx of immunotherapy treatment, with five checkpoint inhibitors gaining approval in the second-line metastatic treatment setting, and Keytruda (pembrolizumab; Merck & Co) and Tecentriq (atezolizumab; Roche/Chugai) also gaining approval for first-line cisplatin-ineligible patients. Pressure on payers to fund these therapies is high considering the short life expectancies among metastatic patients, as well as the significant unmet need for new treatments that can improve outcomes in comparison to standard chemotherapy.

While payers are concerned about the rising cost of oncology treatment across the board, there are certain indications which capture the most payer attention due to their significant budget impacts. Of the urological cancers, payers express the most concern about the cost of prostate cancer treatment due to its high and growing prevalence, and the potential use of expensive novel androgens in early treatment lines where patients have historically been treated with cheap androgen deprivation therapy. Payers are less worried about the cost of bladder cancer and RCC due to their relatively smaller patient numbers in comparison to other solid tumours; however, they express considerable concern surrounding the budget impact of immunotherapies across the wider oncology setting.

### **US payer:**

*“Most payers are not really focused on bladder cancer, they are looking at other cancers that are more prevalent. However, because of the introduction of the immuno-oncology agents with bladder cancer, there are some looking at it in terms of clinical policy and making sure that those indications are in the policy.”*

## Several products have faced reimbursement hurdles in the EU

The national healthcare systems in the five major EU markets (France, Germany, Italy, Spain and the UK) employ various methods to control the budget impact of oncology drugs. HTA and reimbursement agencies require therapies to demonstrate an additional benefit over their appropriate comparator to gain favourable pricing and reimbursement recommendations. Within the uro-oncology

indications, there have been several cases in which therapies have failed to gain reimbursement or have been restricted to a specific subgroup of patients in which an additional benefit is deemed to be the most likely (see Figure 2). Furthermore, across the five major EU markets, companies are often required to concede on price to justify uncertainties in a therapy's evidence base.

**Figure 2: HTA setbacks within urological cancers across the five major EU markets**

Prostate Cancer		
Xofigo		NICE recommends Xofigo under the conditions of a patient access scheme (confidential discount), and restricts to docetaxel-ineligible
		Excluded from the high-cost reimbursement list, the liste-en-sus. Received an ASMR IV based on a minor impact on morbidity and mortality, and a lack of direct comparison with Zytiga
Zytiga		Rejected by NICE for mHSPC based on a lack of cost-effectiveness in comparison to docetaxel
Bladder cancer		
Opdivo		Not recommended by NICE in second-line metastatic patients based on a lack of Phase III data and a lack of cost-effectiveness
Keytruda/Tecentriq		No additional benefit rating by the G-BA in first-line cisplatin-ineligible patients based on a current lack of mature Phase III data
Tecentriq		Not recommended by AIFA for first or second line patients based on non-significant survival improvement in Phase III trial, and failure to provide a sufficient price decrease
RCC		
Avastin + IFN-alpha 2a		Excluded from the high-cost reimbursement list, the liste-en-sus. Received an ASMR IV based on an improvement in PFS, but a lack of comparator data vs Sutent or Votrient
Cabometyx		Recommended under the conditions of a patient access scheme (confidential discount)

Source: Datamonitor Healthcare, September 2018

Each HTA or reimbursement agency across the five major EU markets has its own set of specific processes and requirements. There are different conditions for clinical evidence, comparator treatments and health economic justifications. Furthermore, the influence of these assessments differs widely, with some agencies able to refuse national reimbursement, or to restrict reimbursement to a smaller patient group, and others primarily influencing price negotiations. In the UK, cost effectiveness is the main criterion that impacts decision-making. Therapies that fail to fall within predetermined cost-effectiveness thresholds risk rejection, restriction to a smaller subset of patients or reimbursement through the Cancer Drugs Fund (CDF). For example, the National Institute for Health and Care Excellence (NICE) has rejected several RCC drugs in the first and second lines, including Avastin and Torisel (tamsitrolimus; Pfizer) in the first line, Sutent in the second line, and Nexavar (sorafenib; Bayer/Amgen) in both lines. In all of these cases, the incremental cost-effectiveness ratios (ICERs) determined that the drugs were not a cost-effective use of NHS resources. In bladder cancer, neither Keytruda nor

Tecentriq have been recommended for routine commissioning in first-line cisplatin-ineligible patients, and are instead only available through the CDF. This decision was based on the drugs' high costs and the high level of uncertainty surrounding their clinical effectiveness, translating into ICERs above the £50,000 threshold for end-of-life drugs.

In France, one of the main hurdles for high-cost hospital-administered therapies, such as immunotherapies, is gaining inclusion on the *liste en sus*. Hospitals receive an extra payment at the national level for therapies included on this high-cost reimbursement list, beyond what would normally be reimbursed through the diagnosis-related group for inpatient use. However, gaining inclusion on the *liste en sus* is proving difficult, with drugs expected to gain either an additional medical benefit (ASMR) rating of III or better, or to have an appropriate comparator that is already included on the list. Examples of drugs that have failed to receive this additional funding and thus experience minimal uptake in France include Xofigo in second-line mCRPC, Avastin + IFN-alpha-2a in first-line RCC and Keytruda in first-line bladder cancer.

## Reimbursement controls are minimal for oncology drugs in the US

Access to oncology medicines is relatively unrestricted in the US, with payers required to reimburse the majority of therapies in line with their FDA labels. Exceptions to this rule occur within prostate cancer and RCC, where payers have formalized contracting agreements with specific manufacturers in return for drug pricing discounts/rebates. Through various mechanisms including prior authorizations, tier positioning and oncology pathways, Zytiga is recommended over Xtandi in mCRPC, and Sutent is recommended over alternative first-line TKIs in RCC. These contracts have been possible due to the willingness of the

manufacturers to provide rebates in exchange for preferential positioning, as well as due to the deemed therapeutic equivalence of the drugs. While contracting is not currently widespread within oncology, these cases could be a potential indicator of where things are headed in the future.

### **US payer:**

*“[Sutent] is our preferred [TKI inhibitor, with] about 15% or 20% [discount]. It is fairly significant given the price of these drugs. [...] We probably will have a few [contracted drugs], probably across indications and not just for renal, in the [next] 12 months or so.”*

## Payers are concerned about the budget impact of immunotherapies across oncology

With immunotherapies gaining approvals across multiple oncology indications, payers are concerned about the rising spend on these high-cost treatments, and suggest that further access controls may need to be implemented in the future. Price-volume and budget ceiling agreements are

becoming increasingly popular across France, Spain and Italy, and payers in other European countries may follow suit in the future. Further mechanisms could also include per-patient caps on pricing implemented for immunotherapies at an indication-by-indication level.

## Immunotherapy drugs present an opportunity for contracting, but payers await more competition

Immune checkpoint inhibitors present an attractive target for future contracting due to the high budget impact of the class. However, products must be deemed therapeutically equivalent across a wide breadth of indications before these practices can take place. Therapies that gain approvals in the most prevalent indications are expected to be at a significant advantage when it comes to contracting, as payers will be able to negotiate higher discounts across more expansive patient populations.

While the majority of payers agree that contracting for immunotherapies will likely occur in the future, there is currently a lack of consensus among payers in the US and Europe surrounding how these agreements will be implemented in each market. For example, in Germany, payers indicate that physicians will be financially incentivised to prescribe preferred therapies, but the final decision will reside

with the physician and there will be no penalties for choosing a non-preferred agent. In Spain, discounts, price-volume agreements or per-patient caps are expected to be offered to reimbursement authorities at the local level in exchange for preferential status.

### German regional payer:

*“Preferred agent, that could be, yes, but without any obligation, so the doctor at the end of the day is still the decision-maker.”*

### Italian local payer:

*“In the future, the kinds of tenders that we will do will perhaps consider two or three molecules, and if you have five or six in total, at least for the most common indications, they will be put at the same level and we will take two or three of them and not all of them. So, this is the future. We will consider the price, the side effects and efficacy.”*

**Figure 3: Future use of contracts/discount agreements for immunotherapies across the US and five major EU markets**

US	France	Germany	Italy	Spain	UK
✓	?	✓	✓	✓	✓

Source: Datamonitor Healthcare, September 2018

## Presenting evidence of value along the entire treatment pathway through sequencing studies is valued by payers

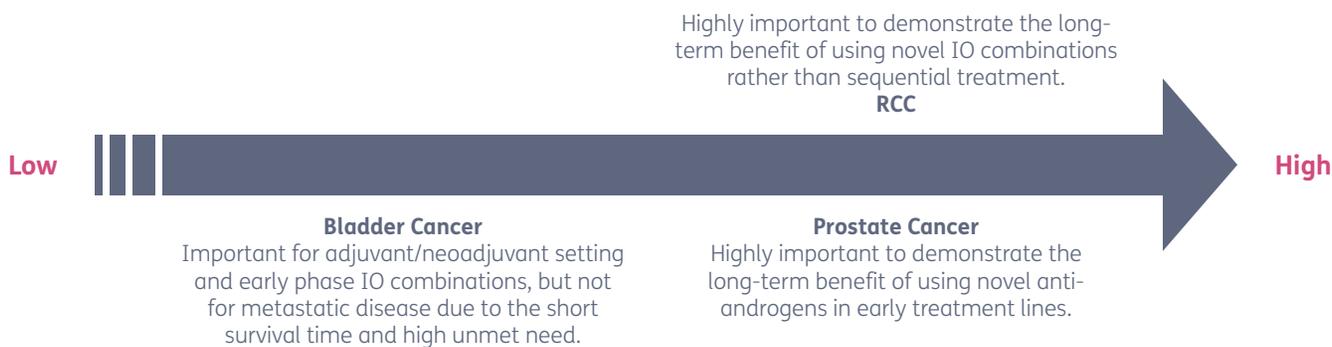
With the emergence of new expensive treatments within urological cancers, payers highlight the benefit of demonstrating value across the whole treatment pathway through sequencing studies. Payers are keen to understand the interplay between first-line and second-line therapies, as well as the impact of sequencing specific therapies on the overall survival of the patient. Payers acknowledge the complexities of executing sequencing trials, including following patients and maintaining records, as well as extracting clear-cut results, given the growing complexity of the treatment algorithm. Nevertheless,

they believe that attempting to adopt strategies to understand the long-term downstream effect will provide an advantage to manufacturers that choose to do so versus those that are focusing on shorter-term endpoints.

### **UK national payer:**

*“NICE would like to know what happens along the whole treatment pathway, ie if you have the new drug early on, and it has a big PFS difference, does that actually translate into a substantial OS difference once you have had all the other drugs along the pathway?”*

**Figure 4: Payer requirements for sequencing studies within urological cancers**



Source: Datamonitor Healthcare, September 2018

## Payers are beginning to consider intermediary endpoints due to the difficulties with conducting sequencing trials

Due to the difficulties with collecting long-term sequencing data, payers are beginning to consider intermediary endpoints such as second objective disease progression (PFS2) and time to subsequent therapy (TSST) as being supportive of a product's value proposition. One of the key questions for payers is whether the use of specialist therapies/combinations early in the treatment pathway may alter patients' response to subsequent treatment, and intermediary endpoints such as PFS2 and TSST can help with this. PFS2, which is defined as the time from randomization to objective tumor progression on the next line of treatment or death from any cause, is gaining importance for both

regulatory and reimbursement evaluations. TSST can be utilized as a proxy for PFS2 and has the benefit of being easier to measure. Given the increasing competition within these indications, manufacturers that invest in such evidence development could secure better positioning for their products in the treatment algorithm. However, payers highlight that these intermediary endpoints alone will not be sufficient to obtain a positive reimbursement or pricing assessment, and they must be considered in conjunction with harder endpoints.

### **Former French national payer:**

*“What is more important is sequencing, so if I use a product like Xtandi earlier on in the patient pathway, what do I use next, and if the PFS1 plus PFS2 is better than what I currently do – so basically what you should evaluate is does treating those patient populations earlier bring better outcomes?”*

## Combination treatments may present a particular challenge in the future, especially if developed by different manufacturers

With many high-cost combinations seeking approvals within urological cancers, payers are likely to implement new strategies to manage price negotiations in the future. The new tools will be used to ensure that the cost of individual components is lower when used in combination compared to use as a monotherapy, reducing the maximum net price that can be achieved.

Adding to the complexity of combination therapies are the various reimbursement hurdles that arise when components are produced by two different manufacturers, as payers lack the ability to bring both manufacturers into joint pricing negotiations. This is particularly relevant when one component of the combination wins approval for use with another agent that is already used in the indication. Payers also currently face the challenge of tracking the use of a drug alone or as a combination therapy, although some do report the ability to do so. Payers in EU countries expect new policies aimed at the pricing and reimbursement of combinations to emerge in the next one to three years that would enable them to manage price negotiations for combinations more effectively. Until then, Datamonitor Healthcare expects that fragmented strategies will be adopted at regional and local levels.

### **German physician association payer:**

*“The problem is just in Germany that we so far do not assess combination therapy at once together, as such, but just the new active ingredients that have come to the market – or just the new indication. [...] Then the next point would be that we just should reimburse combination therapies when they are positively rated by the G-BA, not when they get a no additional benefit rating. The third new step would be when they receive the positive benefit rating then they should be given a joint price negotiation for both combination therapies, when it is just coming from one manufacturer. And, if not, well then we would like to introduce indication-specific pricing for both agents in this combination therapy.”*

### **UK national payer:**

*“I think in the next year we will see a much greater focus on two things; how can the discussions between manufacturers be managed in order to potentially address this issue [of combinations], the second thing is I think NICE is beginning to look at whether it needs to look at its own rules or is this just a straightforward cost-effectiveness issue, is it all about the cost of the new drug A plus the incremental duration of baseline commissioning of drug B, and I think NICE is looking as to whether it needs to look at its rules about combination drugs.”*

## Editor's Note

This analysis comes from Datamonitor Healthcare's Pricing & Reimbursement reports. For full coverage please follow the links below:

- Datamonitor Healthcare's [Renal Cell Cancer Pricing, Reimbursement, and Access](#)
- Datamonitor Healthcare's [Prostate Cancer Pricing, Reimbursement, and Access](#)
- Datamonitor Healthcare's [Bladder Cancer Pricing, Reimbursement, and Access](#)

## About the Author

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Louisa produces disease pricing and reimbursement analysis across a range of different therapeutic areas, with primary focus in oncology. She is well-versed in the national and regional health technology assessment, pricing, and reimbursement policies in the US, Europe, Japan and Canada, and has in-depth knowledge of the payers' clinical trial and evidentiary requirements.

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