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TOPIC PAPER

Design and rationale of a single-arm phase II study of neoadjuvant Durvalumab and Gemcitabine associated with Cisplatin or Carboplatin for upper urinary tract urothelial cancer: the iNDUCT trial (NCT04617756)

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Abstract

Background Upper urinary tract urothelial carcinoma (UTUC) is often locally advanced at initial diagnosis and is associated with high recurrence and mortality rates after radical nephroureterectomy (RNU). Adjuvant platinum-based chemotherapy has shown a recurrence-free survival benefit in a randomised phase III trial, while neoadjuvant treatment seems promising in retrospective series. On the contrary, little is known about the role of perioperative immunotherapy and its combination with chemotherapy for UTUC patients, although initial positive results have been published for muscle-invasive bladder cancer.

Study design and endpoints Against this backdrop, we are running a multi-centre single-arm phase 2 trial of neoadjuvant Durvalumab, a monoclonal antibody targeting programmed cell death ligand 1, combined with Gemcitabine and Cisplatin or Carboplatin for high-risk UTUC patients. The primary outcome is pathological complete response rate at RNU. Secondary endpoints include the partial pathological response rate, safety, as well as disease-free and overall survival. A biomarker analysis is also planned.

Patients and interventions Included patients must have a good performance status and harbour a non-metastatic UTUC, considered at high risk of progression, defined as either biopsy-proven high-grade disease or invasive features at imaging with or, more recently, without high-grade cytology at the multidisciplinary team discretion, as specified in the latest amendment. Enrolled patients receive 3 cycles of neoadjuvant immuno-chemotherapy before RNU, and the standard of care thereafter. The trial is registered as NCT04617756 and is supervised by an independent data monitoring committee.

Keywords Upper tract urothelial cancer · Nephroureterectomy · Neoadjuvant chemotherapy · Neoadjuvant immunotherapy · Durvalumab

Background

Upper urinary tract urothelial carcinoma (UTUC) represents approximately 5–10% of urothelial cancers (UCs) and is twice more common in male than female patients [1]. Around 60% of the patients present with a non-organ-confined disease at initial diagnosis [2]. The prognosis is poor, with 2 years recurrence-free survival rates ranging from 74% for clinically node-negative disease to 50% for clinically node-positive disease and 5 years cancer-specific survival ranging from 86.2% for pT1 disease to 38.8% for pT4 and/or N + disease [3–5]. Moreover, the current pre-operative staging and grading approaches are of suboptimal accuracy and the therapeutic strategy is determined on a risk-based approach, with radical nephroureterectomy (RNU) representing the standard of care for invasive, non-metastatic disease [6].

Nonetheless, the high post-surgical recurrence rates and cancer-specific mortality raise the need for perioperative systemic treatment to prolong cancer control in early phases and improve survival, an approach that is already the standard of care for muscle-invasive bladder urothelial cancer [7].

The practice-changing POUT randomised controlled trial (RCT), published in 2020, provided the first

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high-quality evidence in favour of adjuvant chemotherapy (AC) after radical RNU, showing a 55% risk reduction for disease recurrence or death [8]. No difference was observed to date in terms of overall survival (a secondary endpoint), after a 48-month follow-up (HR = 0.79, $p = 0.26$) [9].

In parallel, neoadjuvant chemotherapy (NAC) has a considerable potential for this disease, as it allows to treat patients before the deterioration of renal function related to the RNU, potentially expanding the proportion of those fit for Cisplatin-based therapy by 30% [10]. Results from retrospective series are encouraging in terms of pathological complete (pCR) and partial (pPR) response, with a potential survival benefit [11–14]. In addition, two prospective phase 2 studies have recently shown pCR rates ranging from 14 to 19% and pPR rates ranging from 60 to 63% [15, 16]. To date, several other trials are ongoing, including the European collaborative URANUS study, in which eligible patients are randomised either to NAC or to AC (NCT02969083).

In addition to chemotherapy, immunotherapy has revolutionised the treatment of Cisplatin-ineligible or progressive UC with the use of immune checkpoint inhibitors (ICIs), which are of interest also for maintenance approaches [17, 18]. Considering the immunotherapy application to the perioperative setting, there is conflicting evidence from phase 3 RCTs on the efficacy of adjuvant immunotherapy for high-risk UC after radical cystectomy or RNU. The IMvigor010 trial did not show any significant disease-free survival (DFS) benefit with the use of adjuvant Atezolizumab, while adjuvant Nivolumab has proven effective in the CheckMate 274 study [19, 20]. Moreover, the role of adjuvant Pembrolizumab is currently tested in the ongoing AMBASSADOR RCT (NCT03244384).

In the neoadjuvant setting, although Pembrolizumab and Atezolizumab have recently demonstrated high pCR rates in muscle-invasive bladder cancer (MIBC) patients undergoing radical cystectomy (RC) [21, 22], the PURE-02 feasibility study has shown discouraging results without any pCR at RNU for the use of single-agent neoadjuvant immunotherapy [23]. Thus, three other phase 2 studies are currently testing the role of neoadjuvant Durvalumab (SAKK06/17-NCT03406650), Pembrolizumab (NCT02365766) or Toripalimab (NCT04099589) in combination with chemotherapy for a mixed MIBC-UTUC population.

Against this backdrop, the objective of the unique iNDUCT trial (NCT04617756) is to explore the efficacy and the safety of neoadjuvant Durvalumab, a human immunoglobulin G1 kappa [IgG1κ] monoclonal antibody [mAb] targeting programmed cell death ligand 1 [PD-L1], combined with Gemcitabine and Cisplatin or Carboplatin prior to RNU, in terms of pCR and pPR, in patients with high-risk, localised, non-metastatic UTUC.

Study protocol

Study design and hypotheses

The iNDUCT trial is a non-commercial, open-label, phase 2, single-arm study aiming to enrol 50 patients affected by high-grade UTUC, who are candidates to RNU, sponsored by the Centre Hospitalier Universitaire de Nîmes, France. All included patients will receive neoadjuvant immunochemotherapy, consisting in Durvalumab and, according to the renal function, Gemcitabine and Cisplatin (Cohort 1) or Gemcitabine and Carboplatin (Cohort 2). An independent data and safety monitoring board has been established. The study hypothesis is that pCR rates will be higher than what is expected according to the literature, and namely ≥ 25% for Cohort 1 and ≥ 21% for Cohort 2 [11, 12].

Eligibility criteria

The main inclusion criterion is the diagnosis of a histologically or cytologically confirmed UTUC of the renal pelvis or of the ureter, considered at high risk of progression. To be enrolled, patients should have either (1) a biopsy-proven high-grade disease using ureteroscopy biopsy or (2) infiltrative features on imaging combined with a high-grade cytology. Due to slow accrual related to the multiple issues for obtaining pre-operative histology, an amendment has been submitted and accepted in June 2022, allowing the multidisciplinary team (MDT) to include the patient in the study based on the finding of infiltrative features at imaging only, in the absence of high-grade histology/cytology.

Furthermore, patients must have a good performance status (ECOG performance status of 0 or 1), a life expectancy > 1 year, no receipt of prior systemic therapies, no distant metastases (cM0), no more than a single regional lymph-node metastasis below 2 cm (cN0 or cN1), and an estimated glomerular filtration rate (eGFR) > 40 ml/min/1.73 m^2. Main exclusion criteria are patient refusal and serious cardiac, psychiatric, autoimmune, infectious or medical comorbidities.

Interventions

The study treatment consists in a neoadjuvant combination of Durvalumab (MEDI4736, AstraZeneca Laboratories, Courbevoie, France) and chemotherapy with Gemcitabine (Ely Lilly and Co., Lilly France, Neuilly-sur-Seine, France) and Cisplatin (Bristol-Myers Squibb Company, Princeton, New Jersey, USA) or Carboplatin (Bristol-Myers Squibb Company, Princeton, New Jersey, USA). Patients are assigned to Cohort 1 (Durvalumab 1500 mg

IV + Cisplatin 70 mg/m^2 IV + Gemcitabine 1000 mg/m^2 IV on days 1 and 8, every 3 weeks for 4 cycles) if the eGFR > 60 ml/min/1.73 m^2 and to Cohort 2 (Durvalumab 1500 mg IV + Carboplatin AUC4.5 + Gemcitabine 1000 mg/m2 IV on days 1 and 8, every 3 weeks for 4 cycles) if eGFR is in between 40 and 60 ml/min/1.73 m^2. Subsequently, the RNU is performed 4 (± 2) weeks after the last dose, according to best clinical practice (Fig. 1). Adjuvant chemotherapy is allowed within 90 days after surgery, for patients with the evidence of pT3-4 and/or pN + disease, while no further immunotherapy can be given post-operatively.

PD-L1 status will be assessed on both tumour cells and immune cells in the RNU tissue specimens from all patients enrolled in this study. An ancillary study will be performed on the surgical specimen to characterise the genomic aspects of the tumour and its environment, in order to search for predictive markers of clinical response and to deepen the understanding of the pathological mechanisms. In particular, the microsatellite instability (MSI) status, PD-L1, PD-L2, and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) expression in the tumour environment and in tumour cells will be assessed; CD8 + tumour-associated lymphocytes, CD3, CD68 (macrophages), and FOXP3 + regulatory T cells (T-reg) will be evaluated within the inflammatory infiltrate.

Endpoints

The primary endpoint is the pCR rate at RNU, defined as no residual sign of viable tumour cells in tissue samples removed during surgery after neoadjuvant treatment (ypT0). Secondary endpoints encompass the pPR rate (downstaging to ≤ ypT1N0M0), safety and tolerability of the treatment, as well as oncological outcomes including disease-free, bladder recurrence-free and overall survival at 2 years.

Sample size calculation

The two cohorts will be analysed separately. The objective is to assess whether the use of neoadjuvant immuno-chemotherapy results in pCR rate of ≥ 25% for Cohort 1 and ≥ 21% for Cohort 2. To achieve a two-sided test at the 5% level of significance, the overall sample size will consist in 25 patients for Cohort 1 (90% power) and 25 patients for Cohort 2 (80% power). With an estimated annual rate of inclusion per centre of 4 to 5, the inclusion phase of the study should take 18 months since the approval of the amendment.

Methods of data collection and analysis plan

Clinical observations will be recorded in the electronic case report form (eCRF) as the study progresses and inclusion will take place through a dedicated platform. The NCI Common Terminology Criteria for Adverse Events v5.0 will be

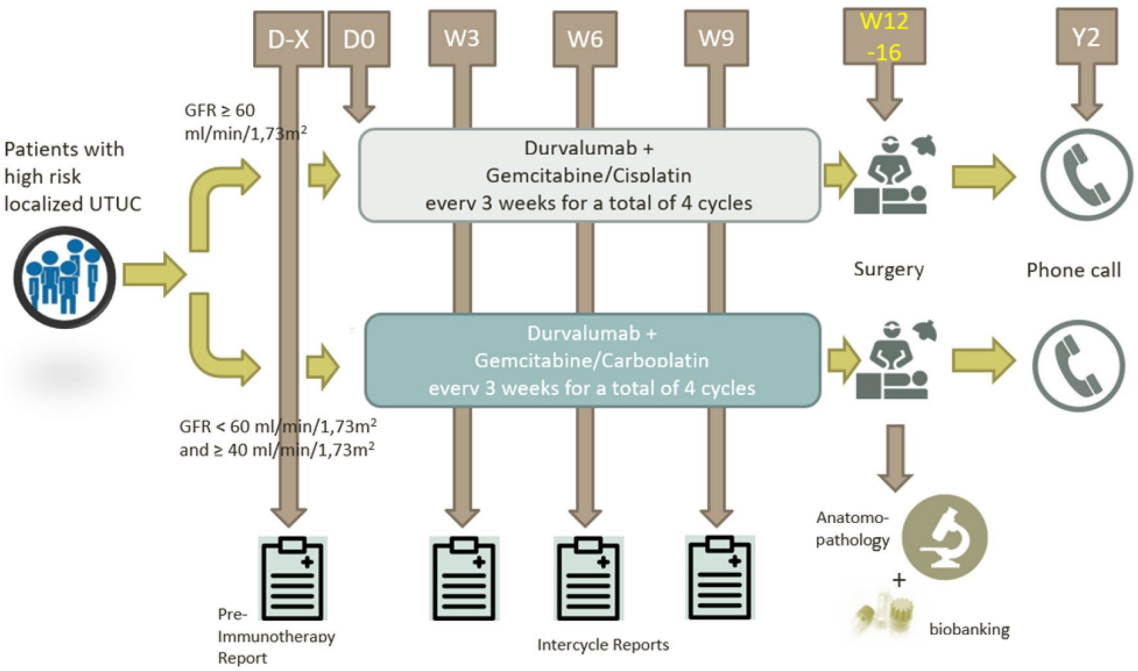

Fig. 1 Study flowchart. Legend: UTUC upper urinary tract urothelial cancer, GFR glomerular filtration rate, D-X screening phase, W week, Y year

adopted for adverse event reporting. Patients are followed up by the treating physician and survival outcomes will be collected 2 years after surgery. The primary endpoint will be analysed immediately after the inclusion period. All patients included in the study will also be included in the analysis, which will be performed in intention-to-treat (ITT). Patients not undergoing surgery for whatever reason will be considered non-responders in ITT analysis. The rate of pPR will be calculated on the subpopulation of patients with ureteroscopic biopsy at diagnosis. The demonstration of the efficacy of the treatment will allow to settle a phase III study in order to confirm these findings.

Accrual status

Accrual for iNDUCT started in September 2021. To date (February 2023), 23 patients have been enrolled, with a clear boost due to the modification of inclusion criteria detailed in the amendment. Currently, ten uro-oncologic French referral centres are recruiting under the sponsorship of the Centre Hospitalier Universitaire de Nîmes.

Discussion

The iNDUCT trial is a unique study designed to investigate the efficacy of combined neoadjuvant immuno-chemotherapy for high-risk UTUC, on the grounds of a growing scientific evidence supporting pre-operative treatment in this setting. Several aspects are of note.

First, to date, neoadjuvant treatments are not routinely recommended for high-risk UTUC, despite a strong rationale, encouraging data from both prospective single-arm studies [15, 16] and retrospective comparative studies and some similarities with the MIBC setting [6, 14]. On the one hand, approximately 30% of UTUC patients who are candidates for neoadjuvant Cisplatin-based chemotherapy will become ineligible after surgery, mainly due to renal insufficiency, therefore losing a therapeutic window to potentially cure this highly aggressive disease [10]. A broadened access to perioperative therapy is indubitably a strength of iNDUCT design. On the other hand, the limitations of the current pre-operative staging and risk prediction tools are likely to result in either undertreatment or overtreatment issues when employed to select patients for neoadjuvant treatments [24]. The possibility to include in iNDUCT unambiguous cases at imaging, in the absence of high-grade cytology/histology, meets clinical practice challenges in UTUC and will allow to consider broadened eligibility criteria for future studies. Also for these reasons, enrolment in a clinical trial is currently the best management option for high-risk UTUC patients.

Second, two recently published phase 3 trials on adjuvant immunotherapy for UC raise the question of the applicability to UTUC (Table 1). They were both designed before the POUT trial results became available. The CheckMate 274 trial has brought the first positive results for adjuvant ICI, while the similarly designed IMvigor010 did not meet its primary endpoint [19, 20]. As direct comparisons are lacking, we are not able to ascertain if these results are drug dependent or are due to the study design. Both studies enrolled mainly MIBC patients (from 79 to 93%) and the subgroup analysis of the UTUC cohort in the CheckMate 274 trial suggested a lower efficacy of adjuvant Nivolumab, with even a detrimental effect on disease-free survival, although this was not significant. A similar, not-significant trend was observed also in UTUC subgroup of IMvigor010 trial. Although these findings are not enough to infer a diminished efficacy of adjuvant immunotherapy in UTUC, they raise the need for further disease-specific investigation, especially considering that UTUC has shown some differences in genomic background from UC of the bladder [25, 26]. Interestingly, the predictive role of biomarkers for ICIs (notably PD-L1 expression and tumour mutational burden) has been tested extensively without any consistent and definitive results [22]. The identification of accurate predictors enhancing tailored therapy remains an unmet need [27].

Third, the association between chemotherapy and immunotherapy is a strength of the iNDUCT study design, given the consistent proportion of UC patients (30–45%) who did not respond to neoadjuvant single-agent ICI in several phase 1 or 2 studies, with dangerous delay in surgical treatment [21–23]. Moreover, subgroup analyses of CheckMate 274 and IMvigor010 have suggested that ICI could be more effective in patients previously treated with chemotherapy and the synergistic effect of these treatments remains a fascinating hypothesis in the neoadjuvant setting. Complementary information about this approach can be derived from phase 3 RCTs on unresectable/metastatic treatment-naïve urothelial disease (Table 1). In this population, the DANUBE trial has compared Durvalumab (with or without Tremelimumab) to the standard-of-care chemotherapy, failing to show a significant overall survival advantage for the investigational drug (HR = 0.85, 95% CI 0.72–1.02; $p = 0.075$). PD-L1 status was not a reliable predictor of response and crossover might have mitigated the treatment effect. Interestingly, disease responses were more frequent in the chemotherapy arm and more durable in the immunotherapy arm [28]. In addition, two phase 3 trials have compared immuno-chemotherapy to chemotherapy alone in populations similar to the DANUBE trial. Specifically, IMvigor130 has shown the superiority of Atezolizumab + chemotherapy versus chemotherapy alone in terms of progression-free survival but not of overall survival. KEYNOTE-361, which adopted a very

Table 1 Phase 3 randomised controlled trial of immunotherapy or immuno-chemotherapy including UTUC patients

Study	Setting	Design	*N*	Population	Treatment	Comparison	Outcomes	FU	Subgroup
IMvigor010 [16]	Adjuvant	RCT open label	809	ypT2-T4a/ypN + or pT3-T4a/pN + Tx naïve 52% Post-chemo 48% Cystectomy 93% NUT 7%	Atezolizumab 1200 mg q3w for 1y	Observation	DFS: 19.4 m vs 16.6 m (HR = 0.89, $p = 0.24$)	21.9 m	For UTUC, DFS HR = 1.25 (95% CI: 0.57–2.74)
CheckMate 274 [17]	Adjuvant	RCT double blind	709	ypT2-T4a/ypN + or pT3-T4a/pN + Post-chemo 43.4% Cystectomy 79.0% NUT 21.0%	Nivolumab 240 mg q2w for 1 y	PBO q2w for 1y	DFS: 20.8 vs 10.8 (HR 0.70, $p < 0.01$) OUT-RFS: HR = 0.72 (95% CI: 0.59–0.89)	20.9 m	For renal pelvis, DFS HR = 1.23 (CI: 0.67–2.23); for ureter HR = 1.56 (CI: 0.70–3.48)
DANUBE [22]	First-line, advanced, metastatic	RCT open label	1032	Advanced/metastatic urothelial cancer, MIBC 78.4%, UTUC 21.6%, M0 4.5%	Arm A: Durvalumab 1500 mg q4w OR Arm B: Durvalumab 1500 + Tremelimumab 75 mg q4w 4 cycles + Durvalumab maintenance	Arm C: Gem + Cis/Carbo q3w 6 cycles	OS: Arm A vs Arm C: HR = 0.99 (95% CI 0.83–1.17); Arm B vs Arm C: HR = 0.85 (95% CI 0.72–1.02)	41.2 m	For highPD-L1, Arm A vs Arm C OS HR = 0.89, $p = 0.3$)
KEYNOTE-361 [27]	First-line, advanced, metastatic	RCT open label	1010	Advanced/metastatic urothelial cancer, MIBC 79.2%, UTUC 20.8%, M0 6.3%	Arm A: Pembrolizumab 200 mg q3w 2y + Gem + Cis/Carbo q3w 6cycles Arm B: Pembrolizumab alone	Arm C: Gem + Cis/Carbo	PFS: Arm A 8.3 m vs Arm C 7.1 m(HR 0.78 $p < 0.01$, ns) OS: Arm A 17 m vs Arm C 14.3 m (HR 0.86, $p = 0.04$, ns)	31.7 m	
IMvigor130 [28]	First-line, advanced, metastatic	RCT double blind	1213	Advanced/metastatic urothelial cancer MIBC 73.5%, UTUC 25.7%, M0 10.6%	Arm A: Atezolizumab 1200 mg q3w + Gem + Cis/Carbo Arm B: Atezolizumab alone	Arm C: PBO + Gem + Cis/Carbo	PFS: Arm A 8.2 m vs Arm C 6.3 m (HR 0.82, $p = 0.007$) OS: Arm A 16 m vs Arm C 13.4 m (HR 0.83, $p = 0.03$)	31.7 m	

RCT randomised controlled trial, *Tx* treatment, *NUT* nephroureterectomy, *chemo* chemotherapy, *q* every, *w* week, *m* month, *y* year, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval, *UTUC* upper urinary tract urothelial cancer, *PBO* placebo, *OUT-RFS* survival free from recurrences outside the urothelial tract, *Gem* Gemcitabine, *Cis* Cisplatin, *Carbo* Carboplatin, *PFS* progression-free survival, *ns* not significant

strict criterion for statistical significance, failed to prove the superiority of Pembrolizumab + chemotherapy over chemotherapy alone; also here, treatment crossover could have influenced the result and the duration of the responses appeared longer for patients receiving immunotherapy [29, 30]. All in all, these results do not support immune-chemotherapy as a first-line treatment for metastatic UC.

Fourth, from a methodological perspective, the primary and secondary endpoints adopted for this phase 2 trial are adequate proxies of robust long-term oncologic results. Indeed, pCR has been consistently associated with disease recurrence and overall survival in MIBC patients and has been widely used as an endpoint in this setting [22, 31, 32]. In addition, 2-year DFS correlates with overall survival both in UTUC and MIBC [20, 33]. Of note, the choice of including a Carboplatin-based regimen (Cohort 2), for patients with suboptimal eGFR, mirrors the absence of heterogeneity in treatment effects described in the POUT trial and meets the needs of a large UTUC patient population unable to receive preferred agent Cisplatin [8, 10].

Fifth, from a speculative perspective, the early use of ICIs in the neoadjuvant setting with a greater tumour burden and possibly more tumour antigens could result in a highly sustained T-cell response, as previously shown for melanoma, for instance [19, 34]. However, these potential benefits with the use of neoadjuvant ICIs do not come without toxicity and adverse events. Although the phase 3 trials testing neoadjuvant ICIs have confirmed their acceptable toxicity profile, the benefits have to be carefully weighed against the risk in the curative pre-operative setting. Indeed, 18% of patients in the experimental group of CheckMate 274 trial discontinued Nivolumab, including 3 lethal cases due to pneumonitis or bowel perforation [20]. In addition, one toxicity-related death was registered in IMvigor010 [19].

It is noteworthy that there are currently many phase 2 or phase 3 trials investigating the interest of neoadjuvant immuno-chemotherapy for MIBC, including NCT03661320-ENERGIZE, NCT04209114-PIVOT-IO-009, NCT03924895-KEYNOTE-905/EV-303, NCT03924856-KEYNOTE 866, NCT03732677-NIAGARA, and NCT03472274-DUTRENEO, for example. Nonetheless, the corresponding results, whatever they are, will need to be confirmed in UTUC-specific trials and we believe that the iNDUCT trial will help for that matter by contributing to cast some new light on the best perioperative management for UTUC patients. Even if enrolment is not yet completed, the use of neoadjuvant Durvalumab in combination with chemotherapy does not seem to affect the perioperative outcomes of RNU and preliminary analyses are promising. We expect that mature study results will provide the basis to design a dedicated phase 3 RCT (iNDUCT-3) to compare neoadjuvant immuno-chemotherapy versus chemotherapy alone before RNU in UTUC patients.

Conclusions

Oncological outcomes of high-risk UTUC patients remain unsatisfactory and clinical trials represent the best treatment option to improve perioperative therapy results. Researchers in this field face several issues, among which are the relative rarity of the disease, its suboptimal pre-operative staging, and post-operative renal failure. On the grounds of a growing and up-to-date body of clinical evidence, the innovative iNDUCT phase 2 trial is investigating neoadjuvant immune-chemotherapy safety and efficacy in this setting.

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Author contributions GC was involved in manuscript writing, data collection or management, and data analysis. MR and NH were involved in protocol development, manuscript editing, data collection or management, and data analysis. TS was involved in protocol development and manuscript writing. LB contributed to protocol development, and data collection or management. TC contributed to protocol development, data collection or management, and data analysis. AM-L, CT, YN, and FA edited the manuscript. EX was responsible for protocol development and manuscript editing.

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Data availability This article has no original data to be made publicly available.

Declarations

Conflict of interest Morgan Rouprêt declares to be part of the advisory board for UroGen Pharma, Bristol-Myers Squibb, Janssen Pharmaceuticals, Astellas Pharma, Ipsen, and Cepheid; Constance Thibault for AAA, Astellas, AstraZeneca, Ipsen, Janssen, Pfizer, Merck, MSD, BMS, and Seagen; François Audenet for Astellas, Bristol-Myers Squibb, Ipsen, and Pfizer; Yann Neuzillet for Astellas, AstraZeneca, Bayer, BMS, Bouchara Recordati, Ferring, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, and Pfizer; and Nadine Houédé for Astra Zeneca, Bayer, Bristol-Myers Squibb, Janssen Pharmaceuticals, and Ipsen. Giorgio Calleris, Lyamin Bendjeddou, Thomas Seisen, Thierry Chevallier, Alexandra Masson-Lecomte, and Evanguelos Xylinas have no competing interests to declare that are relevant to the content of this article.

Informed consent This article does not report any personal data and requires no patient consent for publication. All patients enrolled in this study whose protocol is here presented have subscribed a written informed consent in accordance with applicable regulation and ethical standards.

Research involving human participants and ethics approval The present article consists in a narrative review of the literature and in the presentation of a study protocol; therefore, it does not directly involve human participants. The study protocol presented in this article was approved by the appropriate institutional ethics committee, "Comité de Protection des Personnes", and by the "Agence nationale de sécurité

du médicament et des produits de santé". The authors certify that the study whose protocol is here presented is being performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Trial registration number is NCT04617756 and it is supervised by an independent data monitoring committee.

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