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Platinum Priority – Editorial

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Are Biomarker-driven Inclusion and Symptom Control Endpoints the Future of Phase 3 Trials in Metastatic Castration-resistant Prostate Cancer? Lessons from COMET-2

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The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) is ever-changing, with several new drugs approved for this setting in the last years, including docetaxel, cabazitaxel, enzalutamide, abiraterone, radium-223, and sipuleucel-T, and more therapies such as PARP inhibitors are currently being tested in phase 3 trials [1]. An often forgotten perspective is that a substantial number of oncological drugs reach phase 3 trials, but fail this late stage of clinical development at a high price for the industry, society, and patients [2].

In this issue of *European Urology*, Basch and colleagues [3] present results from the COMET-2 trial comparing cabozantinib with mitoxantrone plus prednisone for men with symptomatic mCRPC who previously experienced progression on docetaxel and either abiraterone or enzalutamide. The intervention was preceded by optimization of opioid analgesia. The primary endpoint of this trial was the rate of pain response at week 6 and confirmed at week 12, defined as a $\geq$30% decrease from baseline assessed using the Brief Pain Inventory Short Form without an increase in daily opiate use, use of a new opiate analgesic type, or clinical pain progression [3]. Although cabozantinib showed promising pain-relief results in the early phase 2 trials [4], the COMET-2 trial is a negative study with only a 2% difference in pain response observed favoring cabozantinib (95% confidence interval −16% to 11%; $p = 0.8$).

While these are disappointing results, it is important to view them in the context of the trial set-up. First, accrual to COMET-2 was carried out in parallel with the COMET-1 trial, which failed to show an overall survival (OS) benefit of cabozantinib versus prednisone for men with mCRPC previously treated with docetaxel and abiraterone and/or enzalutamide [5]. As a result, the COMET-2 trial was closed early. Only 119 men out of the planned 246 were included, making this a heavily underpowered study. Second, the patient cohort for COMET-2 consisted of men with late-stage symptomatic mCRPC. Most of the patients included had received five or more types of anticancer agents excluding androgen deprivation therapy, resulting in heterogeneous tumor mutation patterns. For this reason, it is not possible to conclude that cabozantinib does not have pain-relief activity in any subset of patients with mCRPC. However, if pain relief with cabozantinib could be shown in a subset of patients, would the urologic oncology community take this treatment to heart? The problem lies in the accompanying adverse events (AEs). Some 70% of the cabozantinib-treated patients in COMET-2 experienced grade 3/4 AEs. This can be attributed in part to the late stage of mCRPC and the general cancer-specific morbidity that these patients are bound to experience; however, 17% discontinued cabozantinib and 87% required a dose reduction or treatment interruption because of AEs.

Overall, results from the COMET-1 and COMET-2 trials are not encouraging for the role of cabozantinib in mCRPC in terms of either survival or palliative outcomes. Nonetheless, the article by Basch and colleagues provides important insights into the conduct of oncology trials assessing symptom control via patient-reported outcomes, for which

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the authors should be commended. We can only echo the authors' opinion on pain palliation being an unmet need for patients with mCRPC. Only mitoxantrone and samarium-153 have formal indications for pain palliation on the basis of results from randomized clinical trials designed to estimate pain palliation [6–8], whereas docetaxel, abiraterone, enzalutamide, and radium-223 have demonstrated pain relief as secondary endpoints in clinical trials designed to detect a survival benefit. Therefore, sound trial designs that assess symptom relief and include patients with symptomatic disease, mimicking real-world daily clinical settings, for future drug trials as proposed by the authors is important.

With the vast number of new drugs approved for the mCRPC setting, most phase 3 trials now only include men with very late-stage mCRPC and dissimilar genomic profiles. The strategy to systematically administer drugs to an unselected patient group is one of the main reasons for trial failure [2]. In this era of precision oncology, future studies identifying predictive biomarkers using a sound methodological framework are highly warranted [9]. It is our hope that new predictive biomarkers will allow biomarker-driven drug trials for meaningful patient selection, avoid unnecessary inclusion of nonresponders, increase drug efficacy, and reduce the number of failed phase 3 trials.

In summary, Basch et al. [3] share results from the COMET-2 trial. We applaud the authors' efforts to address an unmet clinical need of pain relief in the mCRPC setting; unfortunately, the trial did not show a benefit of cabozantinib versus mitoxantrone and prednisone in this regard. However, the authors do provide interesting insights into incorporating symptom control assessments in phase 3 trial designs, and the failure of both COMET-1 and COMET-2 highlights the importance of rethinking the framework for how we should conduct drug trials in the future to better benefit our patients.

Conflicts of interest: Peter B. Østergren has received speaker honoraria from Astellas Pharma A/S, Ferring Pharmaceuticals, and IPSEN; consultant honoraria from Astellas Pharma A/S; and advisory board member honoraria from IPSEN. Teemu J. Murtola has received consultancy fees from Astellas Pharma A/S, Ferring Pharmaceuticals, and Janssen Pharmaceutica, and speaker honoraria from Astellas Pharma A/S and Janssen Pharmaceutica. Mikkel Fode is an advisory board member for Astellas Pharma A/S and has received speaker honoraria from Astellas Pharma A/S and Ferring Pharmaceuticals.

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