Clinical Trial Protocol

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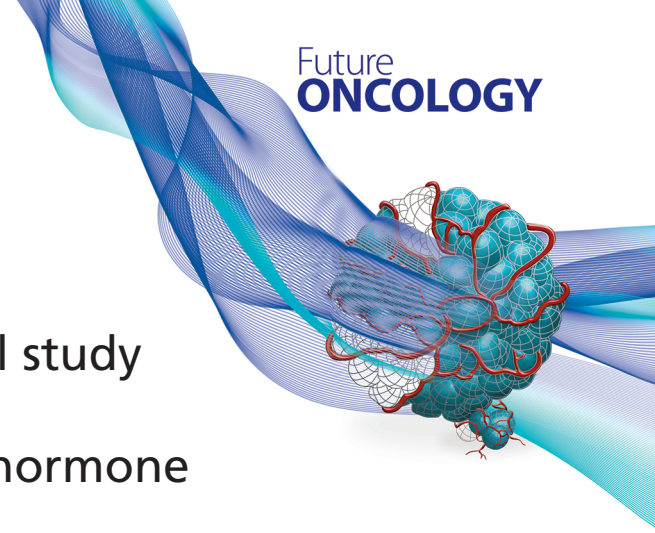

A phase III, randomized, open-label study (CONTACT-02) of cabozantinib plus atezolizumab versus second novel hormone therapy in patients with metastatic castration-resistant prostate cancer

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Cabozantinib inhibits multiple receptor tyrosine kinases, including the TAM kinase family, and may enhance response to immune checkpoint inhibitors. One cohort of the ongoing phase Ib COSMIC-021 study (NCT03170960) evaluating cabozantinib plus the PD-L1 inhibitor atezolizumab in men with metastatic castration-resistant prostate cancer (mCRPC) that has progressed in soft tissue on/after enzalutamide and/or abiraterone treatment for metastatic disease has shown promising efficacy. Here, we describe the rationale and design of a phase III trial of cabozantinib plus atezolizumab versus a second novel hormone therapy (NHT) in patients who have previously received an NHT for mCRPC, metastatic castration-sensitive PC or nonmetastatic CRPC and have measurable visceral disease and/or extrapelvic adenopathy – a population with a significant unmet need for treatment options.

Clinical Trial Registration: NCT04446117 (ClinicalTrials.gov).

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Metastatic prostate cancer is incurable, and patients who have metastatic disease have a 5-year survival rate of 31% [1]. Approximately two-thirds of men with radiographically localized disease are cured with definitive localized therapy

(radical prostatectomy and/or radiotherapy), but the remainder will experience recurrence associated with rising serum prostate-specific antigen (PSA) levels, and most will eventually develop metastatic disease. Some patients may also develop metastatic prostate cancer without prior history of localized prostate cancer, a condition known as *de novo* metastatic prostate cancer. Typically, prostate cancer responds initially to androgen deprivation therapy (ADT) with or without novel androgen receptor targeting agents (ARTAs), such as abiraterone, enzalutamide, darolutamide or apalutamide; or chemotherapy with docetaxel. However, disease progression is almost universal, and gives rise to metastatic castration-resistant prostate cancer (mCRPC). While the overall survival (OS) in men with mCRPC has increased since the introduction of newer ARTAs, the presence of visceral metastasis in men with mCRPC is associated with a particularly poor prognosis, especially in the setting of liver involvement [2,3].

Systemic treatment options for patients with mCRPC now include chemotherapy (docetaxel and cabazitaxel); immunotherapy with sipuleucel-T or pembrolizumab; ARTAs including abiraterone, enzalutamide, apalutamide and darolutamide (comprising the novel hormonal therapies [NHTs]); radionuclide therapy (radium 223 and 177 lutetium PSMA 617 [currently unapproved]) [4,5]; and poly(ADP-ribose) polymerase (PARP) inhibitors, including olaparib and rucaparib [4,6–17]. However, none of these treatments are curative. On the basis of data from multiple trials in the mCRPC setting where NHT was used pre-docetaxel, the risk of death was reduced by 29% with treatment with enzalutamide versus placebo [6] and 20% with treatment with abiraterone plus prednisone versus prednisone alone [11]. With the movement of NHTs to earlier settings of metastatic castration-sensitive prostate cancer (mCSPC) or nonmetastatic CRPC (nmCRPC), many patients with new-onset mCRPC will most likely have already been treated with an NHT. On the basis of results of the registration trials of abiraterone and/or enzalutamide in the pre-docetaxel mCRPC setting, the median OS after disease progression on abiraterone or enzalutamide was approximately 15 months [6,18]. Consequently, there remains a significant unmet need to develop effective novel treatments and combinations to treat patients with metastatic prostate cancer who have experienced disease progression on an NHT.

Here we describe the study design of the randomized, phase III, open-label CONTACT-02 trial (NCT04446117), which is evaluating the safety and efficacy of cabozantinib plus atezolizumab compared with a second NHT monotherapy (abiraterone or enzalutamide) in adult patients with mCRPC and disease progression on an NHT.

Rationale

Prostate cancer has been shown to be associated with an immune-suppressive tumor microenvironment (TME). Studies have demonstrated that cytokines, such as VEGF, IL-10 and TGF-β, drive the recruitment of Tregs and immunosuppressive M2 macrophages, and prevent the infiltration, proliferation and activation of CD8-positive ($CD8^+$) T cells within the prostate cancer TME [19,20]. Indeed, the population of tumor-infiltrating lymphocytes within surgical prostate cancer specimens consists primarily of $CD4^+FOXP3^+CD25^+$ Treg lymphocytes [21,22] and M2 macrophages, which have both been directly correlated with worse prognosis [19,23]. Hence, a strategy to promote an immune-permissive TME could be a promising therapeutic approach.

Immune checkpoint inhibitors (ICIs) are of particular interest in prostate cancer. Some preclinical and clinical studies have found high expression of PD-1/PD-L1/2 within prostate tumors [24,25], including those deemed enzalutamide resistant [26,27]. However, more recent data have shown that metastatic prostate lesions have limited expression of PD-1 and PD-L1 [28]. To date, studies of ICI monotherapy or combinations of ICIs in patients with mCRPC have shown only limited clinical benefit. A phase III trial assessing ipilimumab versus placebo following radiotherapy in patients with mCRPC previously treated with docetaxel initially did not meet the primary end point of OS [29]. Similar outcomes were reported in another phase III trial with ipilimumab in patients with mCRPC who were asymptomatic or had minimally symptomatic disease and had not received prior chemotherapy [13]. It was concluded that limited benefit may be experienced in a small subset of patients without visceral disease [13,29]. However, in a preplanned long-term analysis, OS favored ipilimumab plus radiotherapy versus placebo plus radiotherapy for patients with post-docetaxel mCRPC [30]. The results from two cohorts of patients with mCRPC (cohort 1: those who had progressed after NHT but had not received chemotherapy; cohort 2: those who had progressed after chemotherapy) from a phase II trial (NCT02985957; CheckMate 650) evaluating nivolumab plus ipilimumab demonstrated clinical activity for this combination, but again, benefit was mostly restricted to a subpopulation of patients with high PD-L1 expression. Moreover, the regimen had to be discontinued due to toxicity in 50% of patients in cohort 1 and 44% of patients in cohort 2 [31]. Pembrolizumab has also been evaluated in mCRPC. In the multicohort phase II KEYNOTE-199 study (NCT02787005) undertaken in men with mCRPC who previously progressed following docetaxel and targeted endocrine therapy, pembrolizumab monotherapy

resulted in very modest antitumor activity in patients with Response Evaluation Criteria in Solid Tumors (RECIST)-measurable PD-L1-positive and PD-L1-negative disease, and in those with bone-predominant disease irrespective of PD-L1 expression. The greatest clinical benefit was observed in patients with bone-predominant disease [32]. Cohorts 4 and 5 of this study evaluated a combination of pembrolizumab plus enzalutamide after progression on enzalutamide in patients with RECIST-measurable or bone-predominant nonmeasurable disease. While the safety profile was acceptable, again only modest antitumor activity was observed [33]. More recently, a phase I trial of atezolizumab in patients with mCRPC that had progressed on sipuleucel-T or enzalutamide reported limited efficacy. While there was some evidence of disease control, the data suggested that a combinatorial approach may be required [34]. Taken together, these data suggest that ICI monotherapy may only be beneficial for a small subset of patients [13,35–38]. This likely reflects the immunologically cold nature of mCRPC, a cancer that has minimal $CD8^+$ T-cell infiltrates [28,39]. In addition, recent evidence suggests the refractoriness of metastatic prostate cancer to ICIs, such as atezolizumab, possibly related to a novel mechanism of immune evasion present in these cells that involves the glyoxalase–methylglyoxal axis [40].

A growing body of evidence, however, supports the use of receptor tyrosine kinase (RTK) inhibitors in combination with ICIs as a novel treatment strategy for solid tumors [41–46]. The TAM kinase family of RTKs, which comprises Tyro3, Axl and Mer, is a particularly attractive target. Aberrant TAM receptor signaling has been implicated in tumorigenesis, and TAM receptors are overexpressed in numerous cancers (reviewed in Graham *et al.* [47]). Tumor progression and metastasis have been linked to TAM kinase expression on innate immune cells, which likely contributes to immune escape mechanisms and tumor cell dissemination [48–50]. TAM kinases also regulate immune responses [51–54] by downregulating inflammation, possibly through their expression on myeloid-derived suppressor cells [55], and can promote a suppressive TME through their effects on proinflammatory IFN-gamma-activated (M1) macrophages [56,57]. All three TAM kinases have been implicated in promoting resistance to ICIs [58–60], potentially through their contribution to creating an immunosuppressive TME (reviewed in [61]), their ability to upregulate PD-L1 on tumor cells [62], and their involvement in the epithelial-to-mesenchymal transition in cancer [63]. Several preclinical studies give credence to the efficacy of combining a TAM kinase inhibitor with ICIs. In a murine model of pancreatic cancer, the inhibition of Axl resulted in increased infiltration of natural killer and $CD8^+$ T cells in the TME and improved response to immunotherapy [55]. Another study demonstrated that Axl inhibition induced an antitumor response by reprogramming the immunologic microenvironment and enhancing the activation and function of tumor-infiltrating $CD4^+$ and $CD8^+$ T cells. The effect was further potentiated by PD-1 blockade [63].

Tyro3, Axl and Mer are all overexpressed in prostate cancer [64–67], and Axl has been shown to be involved in cancer invasion, proliferation and metastasis [64,65]. Axl expression has also been associated with tumor cell dormancy in prostate cancer [68], and it has been suggested that targeting Axl could help resensitize such dormant cells to immunotherapy or chemotherapy [69]. Consequently, the combination of a TAM kinase inhibitor with ICIs is a promising therapeutic strategy in patients with mCRPC.

Cabozantinib is a RTK inhibitor with activity against a broad range of targets, including TAM kinases, VEGF receptors, MET, RET, c-KIT and FLT3 [70,71]. Cabozantinib as a single agent has been approved for renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) in USA and Europe [44,72–77] and also for progressive, metastatic medullary thyroid cancer [78–80]. Preclinical studies have shown that cabozantinib promotes an immune-permissive environment that consists of decreased numbers of functional Tregs, increased cytokine production by effector T cells, and suppression of myeloid-derived suppressor cell-promoting cytokines [81–83]. In this regard, cabozantinib has been shown to be efficacious in combination with ICIs in various solid tumors including HCC, urothelial carcinoma, non-small-cell lung cancer and RCC [84–86]. Recent results from the phase III CheckMate 9ER study reported significantly improved progression-free survival (PFS), OS and objective response rate (ORR) with cabozantinib in combination with nivolumab compared with sunitinib as a first-line therapy for patients with metastatic RCC [76]. On the basis of these results, the US FDA approved the combination of nivolumab [87] and cabozantinib [72] as a first-line treatment for patients with metastatic RCC.

In the setting of prostate cancer, a phase III randomized, double-blind, controlled study (COMET-1; NCT01605227) of cabozantinib versus prednisone was conducted in 1028 men with bone-metastasized CRPC who had been treated previously with docetaxel and at least one NHT [88]. Although this study did not demonstrate a statistically significant improvement in OS with cabozantinib monotherapy, median OS was numerically higher in those patients who received cabozantinib (11 vs 9.8 months; hazard ratio [HR] 0.90; 95% confidence interval [CI]: 0.76, 1.06; stratified log-rank p = 0.213). Notably, there was a statistically significant improvement in the

investigator-assessed median radiographic PFS (rPFS) in the cabozantinib arm (5.6 vs 2.8 months; HR 0.48; 95% CI: 0.40, 0.57; stratified log-rank $p < 0.0001$). The bone scan response at week 12 was also significantly improved in the cabozantinib arm (42 vs 3%; stratified Cochran–Mantel–Haenszel $p < 0.001$). Improvements in circulating tumor cell conversion, bone biomarkers and time to symptomatic skeletal events incidence were also observed in this study following treatment with cabozantinib. Additionally, while this phase III randomized study of cabozantinib versus prednisone in patients with progressive, heavily pretreated mCRPC found no OS benefit of cabozantinib compared with prednisone in the overall population, there was a higher OS rate with cabozantinib for patients with visceral metastases compared with those without [88].

Results from the ongoing phase Ib open-label study COSMIC-021 (NCT03170960) assessing the combination of cabozantinib and atezolizumab in multiple solid tumors have recently been published and demonstrate the encouraging clinical activity in patients with RCC [89]. Cohort 6 of this study is evaluating the combination of cabozantinib plus atezolizumab in patients with mCRPC who received prior NHT. Results from the cohort of patients who had mCRPC (n = 44) demonstrated that the combination was safe and tolerable. Furthermore, clinically meaningful activity and durable responses were observed [90,91]. In all patients (n = 44), the ORR was 32%, with two patients achieving a complete response and 12 a partial response; the disease control rate was 80% and duration of response was 8.3 months (range: 2.8–9.8). In patients (n = 36) with measurable visceral disease or extrapelvic lymph node metastasis, ORR was 33%. In total, 34 patients had postbaseline PSA data, of whom 17 (50%) had a decrease in PSA [91]. These results were especially promising, as single-agent cabozantinib or atezolizumab have shown limited benefit in patients with mCRPC, and these data further support the potential synergistic effect of the combination of ICI and cabozantinib [37,88]. On the basis of these encouraging data, the phase III CONTACT-02 trial was initiated.

CONTACT-02 study design

This randomized, open-label, controlled phase III study (NCT04446117) evaluates the efficacy and safety of cabozantinib plus atezolizumab versus a second NHT (abiraterone or enzalutamide) in patients with mCRPC who previously received one NHT to treat mCSPC, nmCRPC or mCRPC. The study is being conducted in accordance with the protocol, the International Conference on Harmonization good clinical practice guidelines, and applicable regulations and guidelines governing clinical study conduct and ethical principles consistent with the Declaration of Helsinki. The protocol, any amendments and the informed consent form must be approved by the appropriate Institutional Review Boards or Ethics Committees. All patients must provide written informed consent prior to initiation of any screening or study-specific procedures.

A schematic of the study design is shown in Figure 1. Approximately 580 eligible patients will be randomized 1:1 (n∼290 in each arm) to receive cabozantinib plus atezolizumab or second NHT, respectively. Randomization will be stratified by the following factors: liver metastasis (yes vs no), prior docetaxel for mCSPC (yes vs no) and diagnosis at time of first NHT (mCRPC vs nmCRPC vs mCSPC). Patients randomized to the experimental arm will receive oral cabozantinib at a dose of 40 mg (two tablets, 20 mg each) once daily plus intravenous atezolizumab at a dose of 1200 mg once every 3 weeks. Those patients randomized to the control arm will receive either oral abiraterone at a dose of 1000 mg, once daily, plus 5 mg oral prednisone, twice daily or 160 mg oral enzalutamide, once daily. Dose reductions of cabozantinib will be allowed at two levels: 20 mg daily, and 20 mg every other day. Dose interruptions and/or reductions of cabozantinib, or delays of atezolizumab for the management of adverse events (AEs) may occur at any time and independently at the discretion of the investigator (no dose reductions of atezolizumab allowed). Dose interruptions and reductions of NHTs due to AEs will be allowed as per local prescribing information, at the discretion of the investigator.

Patients will remain on study until they are no longer clinically benefiting per the investigator's clinical judgment or develop unacceptable toxicity, or withdraw consent. Radiographic disease progression, one of the primary end points, is not a criterion for discontinuation of the protocol treatment until one of the above criteria is met. No crossover among treatment arms will be allowed. Long-term access to study drug will be available to patients who derive clinical benefit from treatment even after the completion of the study. During this maintenance phase, patients will continue to receive the study treatment to which they were randomized and will continue to undergo periodic safety and tumor assessments every 12 weeks.

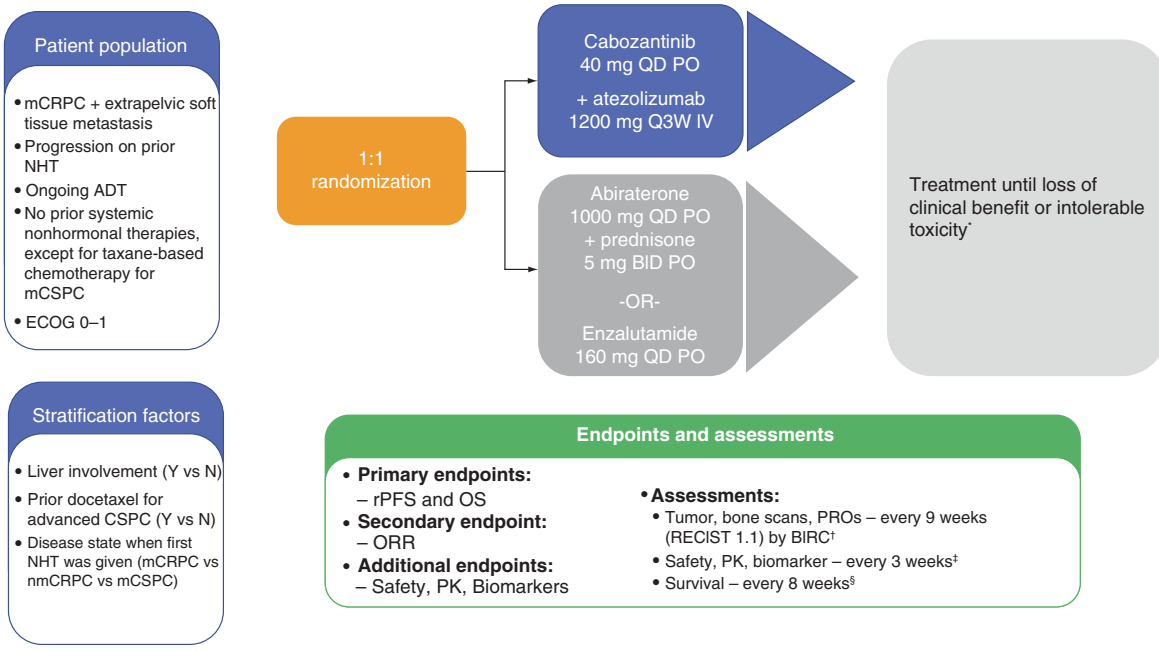

Figure 1. CONTACT-02 study design.
*Patients may be treated beyond radiographic progression if there is a clinical benefit per investigator assessment.
†Every 9 weeks for the first 28 weeks, then every 12 weeks thereafter.
‡Including 2 visits (30 and 100 days) following study discontinuation.
§Following study discontinuation, until death or withdrawal of consent.
ADT: Androgen deprivation therapy; BID: Twice daily; BIRC: Blinded independent radiology committee; ECOG: Eastern Cooperative Oncology Group; IV: Intravenously; mCRPC: Metastatic castration-resistant prostate cancer; mCSPC: Metastatic castration-sensitive prostate cancer; N: No; NHT: Novel hormonal therapy; nmCRPC: Nonmetastatic castration-resistant prostate cancer; ORR: Objective response rate; OS: Overall survival; PK: Pharmacokinetics; PO: Orally; PRO: Patient-reported outcome; Q3W: Every 3 weeks; QD: Daily; RECIST: Response Evaluation Criteria in Solid Tumor; rPFS: Radiographic progression-free survival; Y: Yes.

End points

The primary end points of this study are rPFS per RECIST 1.1 as determined by a blinded independent radiology committee (BIRC) and OS. rPFS is defined as the time from randomization to radiographic soft tissue disease progression per RECIST 1.1 (as informed by computed tomography [CT]/MRI) or death from any cause. OS is defined as time from randomization until death from any cause. ORR, a secondary end point, is defined as the proportion of patients for whom the best overall response was complete response or partial response, per RECIST 1.1 as assessed by the BIRC and confirmed by a subsequent visit ≥28 days later. Additional secondary end points will include PSA response rate ≥50%, duration of response, duration of rPFS (according to soft tissue progression per RECIST 1.1 informed via CT/MRI, or bone progression determined as per Prostate Cancer Working Group 3 criteria and determined via a bone scan), time to PSA progression, safety, the pharmacokinetics (PK) of cabozantinib, anti-atezolizumab antibodies, time to symptomatic skeletal events, time to pain progression, time to chemotherapy, health-related quality of life (HRQOL) scores and healthcare resource utilization. Biomarker analyses will also be conducted to explore the correlation between immune cell, tumor cell or plasma biomarkers with clinical outcome.

Eligibility

The main inclusion/exclusion criteria for this study are provided in Table 1. Males aged ≥18 years with histologically confirmed adenocarcinoma of the prostate, ECOG PS of 0 or 1, and measurable extrapelvic metastatic disease (per RECIST 1.1) will be enrolled. Patients must have had prior treatment with one and only one NHT for locally advanced or metastatic castration-sensitive disease, nonmetastatic or metastatic castration-resistant prostate cancer, and have biochemically and/or radiographically progressed on that NHT (regardless of the clinical state the NHT was used for). Patients should have undergone surgical or medical castration and have a serum testosterone level of ≤50 ng/dl (≤1.73 nmol/l) at the time of screening to maintain castration. Eligible patients may have received

Table 1. Key inclusion/exclusion criteria.

Key inclusion criteria
• Histologically confirmed adenocarcinoma of the prostate
• Prior treatment with 1 NHT for locally advanced CSPC (stage T3 or T4), mCSPC, nmCRPC and/or mCRPC
• Biochemical or radiographic progression on previous NHT
• Bilateral orchiectomy or ongoing ADT with a gonadotropin-releasing hormone, with serum testosterone ≤50 ng/dl at screening
• Measurable extrapelvic disease per investigator assessment
• Progressive disease defined as either
– Rising PSA (≥2 ng/ml [2 μg/l] within 1 year; 2 increasing values at 3–4 consecutive assessments with at least 7 days between assessments)
– Soft tissue disease progression per radiographic imaging (computed tomography/MRI)
• ECOG performance status 0–1
• Adequate organ and marrow function
Key exclusion criteria
• Patients with bone-only metastatic disease
• Any prior nonhormonal systemic therapy initiated for treatment of mCRPC
• Receipt of abiraterone within <1 week, cyproterone acetate <10 days, or ARTAs <2 weeks of randomization
• Receipt of radiation therapy within 4 weeks (<2 weeks for bone metastases) of randomization
• Known brain metastases or cranial epidural disease, unless adequately treated/removed and clinically stable for at least 4 weeks prior to randomization
• Systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization
• Uncontrolled, significant infection or illness

ADT: Androgen deprivation therapy; ARTA: Androgen receptor-targeted agent; CRPC: Castration-resistant prostate cancer; CSPC: Castration-sensitive prostate cancer; ECOG, Eastern Cooperative Oncology Group; mCRPC: Metastatic castration-resistant prostate cancer; mCSPC: Metastatic castration-sensitive prostate cancer; NHT: Novel hormone therapy; nmCRPC: Nonmetastatic castration-resistant prostate cancer; PSA: Prostate-specific antigen.

prior docetaxel for CSPC but not for mCRPC. Key exclusion criteria include: any prior nonhormonal systemic anti-cancer therapy for the treatment of mCRPC; treatment with abiraterone within 1 week, cyproterone within 10 days, or NHT within 2 weeks of randomization; bone-only disease; and pelvic node-only disease.

Assessments

Disease progression (rPFS) and response rates (ORR) will be assessed by a BIRC via radiographic imaging (CT of chest and CT/MRI of the abdomen/pelvis [and additional disease sites as needed]) per RECIST 1.1, and bone scan per Prostate Cancer Working Group 3. Tumor assessments will be conducted at screening and every 9 weeks following randomization through week 28; thereafter, tumor assessments will be undertaken every 12 weeks. Serum PSA levels will be collected at screening, prior to the first dose of study drug, and then routinely at each scheduled imaging visit. Survival will be assessed through the second follow-up visit (~100 days post-discontinuation) and every 8 weeks thereafter until death or withdrawal of consent.

Safety assessments will be conducted every 3 weeks and will include AE review, physical examination and collection of vital signs, laboratory parameters and performance status. The grade, seriousness and relationship to study treatment (including immune-relatedness) will be assessed by the investigator; the grading of AEs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5. Following discontinuation of study treatment, patients will be followed for safety assessments at >30 days and again at ~100 days.

Blood samples from patients within the experimental arm will be collected at baseline and predose at routine safety visits for analysis of serum concentrations of cabozantinib, as well as the population PK and exposure–response relationship of cabozantinib in combination with atezolizumab. Tumor tissue and blood will also be collected for exploratory plasma, serum, and cellular biomarker analyses of study drug target expression levels, immunogenicity, immune cell profiling, plasma biomarkers, circulating tumor cells/DNA and tumor-site specific characteristics.

Patient-reported outcomes of HRQOL scores will be assessed at baseline and on scheduled imaging days using the EuroQol Health questionnaire (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30). Pain will be assessed through self-reporting using an 11-point (from 0 to 10) numeric rating scale measuring worst pain in the last week, with 0 representing 'no pain' and 10 representing 'pain as bad as you can imagine'. Symptomatic skeletal events will be continually assessed throughout the study and during the follow-up period.

Statistical analyses

The primary rPFS analysis will be done in the PFS intent-to-treat population, which will consist of the first 300 patients who are randomized. This population may be extended to 400 patients if necessary, to reach the required

number of events. Other efficacy analyses will be conducted on the intent-to-treat population, which consists of all randomized patients. Safety analyses will be conducted on all patients who receive any amount of study drug.

The primary efficacy analyses of this study are rPFS (determined by BIRC per RECIST 1.1) and duration of OS in patients treated with cabozantinib in combination with atezolizumab (the experimental arm) versus second NHT (the control arm). If the null hypothesis of no difference between arms is rejected for either OS or rPFS in favor of the combination arm, treatment with cabozantinib in combination with atezolizumab will be considered to be superior to treatment with second NHT. Kaplan–Meier methodology will be used to descriptively summarize rPFS and OS and comparisons between arms will be made using a stratified log-rank test. A stratified Cox proportional hazards model will be used to estimate HRs, and stratification will be based on the same factors used for randomization.

The study is designed to provide adequate power (90%) for the two efficacy end points. However, a smaller sample size is required to provide reasonable power for rPFS testing compared with that needed for OS estimations. This may result in the number of events necessary to trigger the primary rPFS analysis occurring marginally before the study is fully accrued. Consequently, to reduce potential bias such as shorter progression times if rPFS is evaluated in the larger sample size required for estimation of OS, our study will utilize the 'trial within a trial' design [92]. This will allow a longer, more robust follow-up with fewer patients than is necessary for OS determination.

Two planned interim analyses for OS will be conducted that will include all randomized patients. The first will occur at the time of primary rPFS analysis, estimated to be at approximately the 32% information fraction for OS. The second is planned for when the approximate 76% information fraction is reached. If the null hypothesis of no difference is rejected at either planned interim OS analysis in favor of the experimental arm, no further testing will be conducted for OS.

The global COVID-19 pandemic or any unforeseen event may affect the required milestone intervals for this study (estimated to be ~21 months for rPFS and 37 months for OS), as well as enrollment numbers. Consequently, the sample size may be increased by an additional 25% if a data review suggests that the COVID-19 pandemic has resulted in increased rates of study dropout or noncompliance such that the evaluation of the study end points may be undermined.

Study sites

Patient enrollment is planned at ~285 sites in 27 countries in Europe, North and South America and the Asia Pacific region.

Summary & conclusion

Metastatic prostate cancer is a leading cause of cancer-related death worldwide. There remains a significant unmet need for efficacious therapies in patients with mCRPC who have received prior NHT with extrapelvic disease.

Cabozantinib is an inhibitor of multiple RTKs, including TAM kinases, VEGFRs, Met, and c-KIT, that has been approved for RCC and HCC (in patients previously treated with sorafenib). Preclinical studies have shown that cabozantinib promotes an immune-permissive environment and may work synergistically with ICIs to improve tumor responses [37]. The combination of cabozantinib plus atezolizumab, discussed here, has previously shown meaningful clinical activity as well as a tolerable safety profile in patients with locally advanced or metastatic solid tumors [91]. Cohort 6 of the ongoing phase Ib open-label COSMIC-021 study is evaluating cabozantinib plus atezolizumab in patients with mCRPC who received prior NHT. An ORR of 32% was observed for all evaluated patients (n = 44), with two patients achieving a complete response; the duration of response was 8.3 months (range: 2.8–9.8). For patients with 'high-risk' disease (measurable visceral and/or extrapelvic lymph node metastases) the ORR was 33% [91].

Evidence from both preclinical and clinical studies suggests a potential synergistic effect of cabozantinib plus atezolizumab on tumor responses and provides strong rationale for their combined use clinically. The CONTACT-02 trial will evaluate the efficacy and safety of cabozantinib plus atezolizumab compared with a second NHT alone in adult patients with mCRPC. Additional insights into the potential benefits of the cabozantinib and atezolizumab combination will be gleaned from the assessment of biomarkers and HRQOL outcomes. Given the tolerable safety profiles previously observed with the combination of cabozantinib and ICIs, this study may be particularly well suited to men with good performance status who wish to avoid treatment with chemotherapy or those who are deemed unable to tolerate chemotherapy-associated toxicities.

Trial status

The trial protocol version is 2.0. First person in was in October 2020; last person in is estimated to be in July 2022.

Executive summary

Introduction

- Metastatic prostate cancer is incurable, and patients who have new metastatic disease have a 5-year survival rate of 31%.
- The presence of visceral metastasis and/or extra-pelvic soft tissue metastasis in men with metastatic castration-resistant prostate cancer (mCRPC) is associated with a particularly poor prognosis.
- Novel hormone therapies (NHT) are often now used in earlier treatment settings, hence many patients with mCRPC may have already received an NHT.
- There remains a significant unmet need to develop effective novel treatments and combinations to treat patients with mCRPC who have experienced disease progression on an NHT.

Rationale

- Prostate cancer is associated with an immune-suppressive tumor microenvironment (TME), hence strategies that promote an immune-permissive TME could be a promising therapeutic approach.
- While immune checkpoint inhibitor (ICI) monotherapy has only shown limited clinical benefit, evidence suggests that the combination of ICIs with receptor tyrosine kinases (RTK) is a promising strategy.
- The TAM kinase family, which comprises Tyro3, Axl and Mer, is a particularly attractive target.
- Tyro3, Axl, and Mer are all overexpressed in prostate cancer and all three TAM kinases have been implicated in promoting resistance to ICIs, potentially through their contribution to creating an immune-suppressive TME.
- Preclinical data in murine models of cancer have demonstrated that a combination of a TAM kinase inhibitor plus ICI was efficacious and indicated that there may be a synergistic effect between the two inhibitors.
- Cabozantinib, an inhibitor of multiple RTKs, including TAM kinases, VEGFRs, Met and c-KIT, has been approved for renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC; in patients previously treated with sorafenib).
- Cabozantinib has shown to be efficacious in combination with ICIs in various solid tumors including HCC, RCC and non-small-cell lung cancer.
- Cohort 6 of the ongoing phase Ib open-label study COSMIC-021 (NCT03170960) is evaluating the combination of cabozantinib plus atezolizumab in patients with mCRPC who received prior NHT.
- This combination resulted in promising efficacy, even in patients with 'high-risk' disease (measurable visceral disease or extrapelvic lymph node metastasis), and was seen to be safe and tolerable.

CONTACT-02 study design

- This is a randomized, open-label, controlled phase III study (NCT04446117) evaluating the efficacy and safety of cabozantinib plus atezolizumab versus a second NHT (abiraterone or enzalutamide) in patients with mCRPC who previously received one NHT to treat metastatic castration-sensitive prostate cancer, nonmetastatic CRPC or mCRPC.
- Eligible patients are adult males with histologically confirmed adenocarcinoma of the prostate, measurable extrapelvic metastatic disease (per RECIST 1.1), an Eastern Cooperative Oncology Group performance status of $\leq$1, who have had prior treatment with one, and only one, NHT for locally advanced or metastatic castration-sensitive or castration-resistant prostate cancer (either M0 or M1), and have biochemically and/or radiographically progressed on that NHT.
- The primary objectives of this study are to determine radiographic progression-free survival (rPFS) per RECIST 1.1, as determined by a blinded independent radiology committee, and overall survival.
- Secondary end points include: overall response rate, prostate-specific antigen (PSA) response rate $\geq$50%, duration of response, duration of rPFS, time to PSA progression, safety and pharmacokinetics of cabozantinib.
- Approximately 580 eligible patients will be randomized 1:1 (n = 290 in each arm) to receive oral cabozantinib (40 mg, once daily) plus intravenous atezolizumab (1200 mg once every 3 weeks) or second NHT (oral abiraterone [1000 mg, once daily], plus 5 mg oral prednisone, twice daily, or oral enzalutamide [160 mg, once daily]), respectively.
- Patients will remain on study until they are no longer clinically benefiting per the investigator's clinical judgment, develop unacceptable toxicity or withdraw consent.
- No crossover among treatment arms will be allowed. Long-term access to study drug will be available to patients who derive clinical benefit from treatment even after the completion of the study.
- This study may be particularly well suited to men with good performance status who wish to avoid treatment with chemotherapy or those who are deemed unable to tolerate chemotherapy-associated toxicities.
- Patient enrollment is planned at ~285 sites in 27 countries in Europe, North and South America and the Asia Pacific region.

Author contributions

N Agarwal made a significant contribution to conceptualization of the trial, design, entry criteria site selection and assumptions, with input from A Azad, J Carles, S Chowdhury, B MacGregor, AS Merseberger, S Oudard, S Pal, F Saad, A Soares. A Panneerselvam

provided full statistical support. N Mohamed was involved in literature support and provided substantial input on study design, writing of the protocol and the subsequent amendments, construction of the case report form, data review and approach to safety assessment. F Wang was involved with trial conceptualization, design, population selection, entry criteria, site selection, writing of the protocol and the subsequent amendments, construction of the case report form and medical monitoring. All authors were involved in drafting and reviewing the manuscript and provided approval of the final version.

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Ethics approval and consent to participate

This study protocol is in accordance with and was based on the Helsinki Declaration. Ethics approval was obtained from Advarra. Freely given written informed consent will be obtained from every subject prior to his participation in this clinical trial.

Data sharing statement

There are no restrictions regarding access to the resultant trial data for the investigators. The datasets generated, used, and analyzed during the trial will be available from the corresponding author upon reasonable request.

Open access

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