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A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients

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Summary

Background—Activation of the vascular endothelial growth factor receptor (VEGFR) and the oncogenic Src pathway has been implicated in the development of castration-resistant prostate cancer (CRPC) in preclinical models. Cediranib and dasatinib are multi-kinase inhibitors targeting VEGFR and Src respectively. Phase II studies of cediranib and dasatinib in CRPC have shown single agent activity.

Methods—Docetaxel-pretreated CRPC patients were randomized to arm A: cediranib alone (20 mg/day) versus arm B: cediranib (20 mg/day) plus dasatinib (100 mg/day) given orally on 4-week cycles. Primary endpoint was 12-week progression-free survival (PFS) as per the Prostate Cancer Clinical Trials Working Group (PCWG2). Patient reported outcomes were evaluated using Functional Assessment of Cancer Therapy- Prostate (FACT-P) and Present Pain Intensity (PPI) scales. Correlative studies of bone turnover markers (BTM), including bone alkaline phosphate (BAP) and serum beta-C telopeptide (B-CTx) were serially assayed.

Results—A total of 22 patients, 11 per arm, were enrolled. Baseline demographics were similar in both arms. Median number of cycles =4 in arm A (range 1–12) and 2 in arm B (range 1–9). Twelve-week PFS was 73 % in arm A versus 18 % in arm B (p=0.03). Median PFS in months (arm A versus B) was: 5.2 versus 2.6 (95 % CI: 1.9–6.5 versus 1.4-not reached). Most common grade 3 toxicities were hypertension, anemia and thrombocytopenia in arm A and hypertension, diarrhea and fatigue in arm B. One treatment-related death (retroperitoneal hemorrhage) was seen in arm A. FACT-P and PPI scores did not significantly change in either arm. No correlation between BTM and PFS was seen in either arm.

Conclusions—Although limited by small numbers, this randomized study showed that the combination of VEGFR and Src targeted therapy did not result in improved efficacy and may be associated with a worse outcome than VEGFR targeted therapy alone in patients with CRPC.

Keywords

Cediranib; Dasatinib; Castration resistant prostate cancer; Quality of life; Bone turnover marker

Introduction

Over the last few years, treatment options for patients with castration-resistant prostate cancer (CRPC) have evolved from older generation antiandrogens and chemotherapy to now include novel androgen receptor signaling inhibitors, next-generation taxanes, as well as immunotherapy. Docetaxel, cabazitaxel, enzalutamide, abiraterone acetate, radium-223 and

sipuleucel-T have all been associated with improved overall survival in randomized clinical trials in metastatic CRPC patients [1–9]. Despite the approval of these novel agents, resistance is inevitable and new treatment approaches are needed, highlighting the impact of new drug development in the cancer setting.

Preclinical data have demonstrated that the Vascular Endothelial Growth Factor (VEGF) and the proto-oncogene tyrosine-protein kinase Src may play a crucial role in the development and progression of prostate cancer [10–14], both through a Src-related activation of the MAPK, PI3K/AKT/mTOR and STAT3 signaling pathways [15, 16] and direct hormonal control of angiogenesis in the early stages of prostate carcinogenesis [17, 18]. Importantly, VEGF and Src have been shown to be instrumental in osteoclast function and bone formation [19–22]. In particular, osteoclast and osteoblast proliferation and consequent bone remodeling has been associated with alteration of mineral homeostasis and bone architecture through the effects of several cytokines, such as VEGF, generated by tumor cells. [23, 24]. Additionally, expression of Src induces rearrangements of the actin cytoskeleton and regulates the structure and organization of podosomes, actin-rich protrusions, which coordinate extracellular matrix degradation with cell motility, to facilitate normal cell migration through tissue microenvironments [19]. Furthermore, previous data have shown a proangiogenic role of Src through hypoxia-driven VEGF induction [16, 25]. Previous in vivo studies have shown statistically significant tumor growth inhibition with cediranib, a VEGF receptor inhibitor, in combination with saracatinib, a dual-specific inhibitor of Src and Abl, as compared to treatment with either single agent alone in lung cancer xenograft models [26]. In the phase I setting, the combination of saracatinib and cediranib was well tolerated and demonstrated disease control [27, 28]. Therefore, targeting both angiogenesis and Src appears to be a rational therapeutic strategy for patients with advanced prostate cancer.

Cediranib (AZD2171 maleate, Recentin™; AstraZeneca) is an orally available, potent inhibitor of VEGF receptor tyrosine kinases (RTKs) -1, –2 and –3, and has also shown activity against c-kit and platelet-derived growth factor receptors (PDGFR) with effects on cell migration and invasion [29–31]. In preclinical models of prostate cancer expressing PDGF-D, previously shown to have an oncogenic activity in prostate cancer progression and to be associated with tumor stage and Gleason grade [32, 33], cediranib has exhibited intraosseous growth reduction [34]. In the clinical setting, cediranib has been safely administrated both as a single agent and in combination with either platinum-based chemotherapy or other targeted agents in patients with advanced cancer, and has demonstrated modest clinical benefit in specific tumor types such as prostate and renal cell cancer [35–42]. Recent results from a randomized, double-blind phase III study have shown that cediranib both in combination with concurrent platinum-based chemotherapy as well as maintenance post chemotherapy, increased PFS and OS in patients with recurrent ovarian carcinoma [43]. Additional studies are evaluating the safety, tolerability and efficacy of cediranib in several tumor types (clinicaltrials.gov).

Dasatinib (SPRYCEL; Bristol-Myers Squibb) is an oral protein tyrosine kinase (PTK) inhibitor with specificity for BCR-ABL, c-Src, c-kit, PDGFRβ, and EPHA2 [44]. It is currently indicated for the treatment of chronic phase (CP) Philadelphia chromosome-

positive (Ph+) chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) [45, 46]. In the preclinical setting, dasatinib has shown decreased cellular proliferation, migration, and invasion in prostate cancer tumor cells, as well as inhibition of tumor growth and lymph node metastases in both androgen-sensitive and androgen-resistant orthotopic nude mouse models, resulting in inhibition of activated Src Family Kinases (SFKs) expression [47, 48]. Additionally, dasatinib has been shown to reduce osteoclast activity [49, 50]. In the prostate cancer setting, dasatinib has been investigated in several phase I and II clinical trials both as a single agent and in combination with chemotherapy or other targeted therapies, with variable results with regards to tolerability and efficacy but with promising bone activity with reduction or normalization of markers of bone metabolism such as urinary N-telopeptide and bone alkaline phosphatase (BAP) and stabilization of bone metastases [51–55].

The combination of cediranib and another Src inhibitor, saracatinib, (AZD0530; AstraZeneca) has been tested in a phase I clinical trial of patients with advanced solid tumors [27]. In this study, the combination exhibited a favorable toxicity profile with hypertension as the most common adverse event and promising preliminary evidence of efficacy with stable disease, as per RECIST version 1, observed in 22 out of 35 (63 %) evaluable patients [27].

The purpose of this randomized phase II clinical trial was to evaluate the clinical activity of cediranib with or without dasatinib in CRPC patients whose disease had progressed on first-line docetaxel-based chemotherapy.

Materials and methods

Study objectives

The primary objective of this study was to determine and compare the efficacy of cediranib versus cediranib and dasatinib in patients with metastatic CRPC utilizing progression free survival (PFS) as per the Prostate Cancer Clinical Trials Working Group (PCWG2), which includes a compilation of prostate-specific antigen (PSA), bone scan, and CT-scan assessments [56]. The secondary objectives were: safety and tolerability confirmation as well as objective response rate analysis of cediranib with or without dasatinib; symptom assessment using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire [57] and the present pain intensity (PPI) scale from the McGill-Melzack questionnaire [58], and correlative biomarkers analysis, such as evaluation of bone turnover markers, including beta C-telopeptide (β-CTX) and bone-specific alkaline phosphatase (BAP). Full protocol is available in Appendix 1 of supplementary material.

Patients and eligibility criteria

Eligible patients included men with castration-resistant, histologically confirmed prostate cancer previously treated with docetaxel and who had a European Cooperative Oncology Group Performance Status (ECOG PS)≤2, estimated life expectancy greater than 3 months, and adequate marrow and organ functions [absolute neutrophil count≥1.5 × 10^9/L; Hb>90 g/L; Platelets≥100 × 10^9/L; INR ≤1.3; Total bilirubin ≤1.25 × institutional upper limit of

normal (ULN); AST (SGOT)/ALT (SGPT) ≤2 × ULN or <5 × ULN if clearly attributable to liver metastasis; Creatinine ≤ ULN and calculated creatinine clearance (≥60 mL/min/1.73 m^2 for patients with creatinine level above institutional normal); urine dipstick for protein of less than +1; for dipsticks of +1 or more, 24-h urine collection for protein is necessary and should be <1 g/24 h]. Following docetaxel, patients may have had any number of chemotherapy regimens. Prior surgery, radiotherapy, radioisotopes, hormonal therapy, and targeted therapies other than angiogenesis, Src or FAK inhibitors were allowed upon appropriate washout period (3 to 4 weeks depending on the treatment). Presence of measurable, or non-measurable metastatic disease as defined by RECIST 1.0 [59], and clinical and/or radiological confirmation of disease progression on or after docetaxel treatment were mandatory. Patients with elevation of PSA alone without radiographic evidence of measurable or non-measurable disease were not eligible.

Study design, treatment and evaluation of clinical activity

This randomized, multicenter, phase II study was supported by the US National Cancer Institute, and approved by each center's Institutional Review Board and all patients provided written informed consent.

At baseline, all patients underwent history and physical examination, blood evaluation and appropriate diagnostic imaging. To assess Quality of Life (QoL), patients also completed both FACT-P and PPI questionnaires [57, 58]. Upon registration, patients were randomized to receive either single agent oral cediranib at 20 mg once daily or cediranib 20 mg once daily in combination with oral dasatinib at 100 mg once daily, continuously on a 28-day cycle. Treatment response, according to RECIST, was evaluated every 12 weeks [59]. Best overall response was defined as the best response recorded from the start of the treatment until disease progression/recurrence. PPI and FACT-P questionnaires were undertaken at the beginning of each cycle. A reduction of at least 2 points in the PPI total score or 50 % in analgesic use from baseline and an improvement of 10 % (a sustained 16-point or greater improvement from baseline on consecutive measurements) in the FACT-P total score defined treatment-related pain and QoL response [60].

Bone turnover biomarkers

As a secondary objective, plasma bone turnover markers (BTM) beta C-telopeptide (β-CTX) and bone-specific alkaline phosphatase (BAP) were evaluated at baseline as well as at the end of cycles 1 and 3, using Elecsys β-crossLaps immunoassay (Roche Diagnostic, Indianapolis, IN) and Access Ostase immunoassay (Beckman Coulter, Brea CA) respectively, according to manufacturers' procedures. β-CTX is a specific resorption marker of degradation of bone type I collagen by osteoclasts, while BAP is a bone formation marker reflecting osteoblast activation. Our hypothesis was that β-CTX would decrease, while BAP would increase as a result of treatment in both arms, with a more pronounced effect when cediranib was given in combination with dasatinib.

Sequencing analysis

Tumor DNA, isolated from formalin-fixed paraffin-embedded (FFPE) archived samples, was characterized by Next Generation Sequencing (NGS) using either a customized

Sequenom panel (PMH version 1.0, 23 genes, 279 mutations) on the Sequenom MassARRAY platform, or the commercially available Illumina MiSeq TruSeq Amplicon Cancer Panel (version 2.0, 48 genes, 212 amplicons, ≥500× coverage) on the Illumina MiSeq personal genome sequencer. Selected FFPE samples with insufficient DNA quantity to perform MiSeq analysis were genotyped using the Sequenom platform. All the analyses were performed in the Clinical Laboratory Improvement Amendments (CLIA)-certified University Health Network (UHN) Advanced Molecular Diagnostics Laboratory (AMDL).

Statistical analysis

Initially, this randomized phase II study aimed to enroll a total of 50 patients (25 patients per arm) to demonstrate a 30 % absolute improvement in the proportion of patients who were progression-free at 12 weeks in the combination group as compared to single agent cediranib (estimating an improvement from 30 to 60 %). Unfortunately the study was closed prematurely due to discontinued supply of cediranib. Fisher's Exact test was used to compare the 12-week PFS proportions between the two treatment arms. Descriptive statistics were used for other aspects of the trial.

Results

Patients data

Between October 2010 and July 2012, 22 men with CRPC, 11 per arm, were recruited in seven centers of the three participating Consortia (Fig. 1). All patients were included in the analysis for 12-week PFS as per PCWG2. Patient characteristics were similar across the two treatment arms (Table 1) with most having a good ECOG performance status. Approximately half of the patients had target lesions (55 % in arm A and 45 % on arm B). Baseline pain, assessed by a score≥2 on the PPI scale, appeared to be slightly more prominent in patients enrolled in the combination arm.

Treatment administration

At the time of the data cut-off for final analysis (April 2013), all patients had completed treatment. In patients treated with cediranib alone (arm A), a total of 51 cycles with a median of 4 cycles (range, 1 to 12) were delivered, compared to a total of 31 cycles, with a median of 2 cycles (range, 1 to 9 cycles) for patients treated in the cediranib/dasatinib combination arm (arm B). During cycle 1, most of the patients in arm A (81 %) received cediranib at a dose intensity of over 80 % compared to the combination group (cediranib: 54 %, dasatinib 64 %). A similar trend was maintained in the subsequent cycles. The most common reasons of treatment discontinuation, which occurred in 55 % of patients in arm A and in 64 % of patients in arm B, were either progression of disease or consent withdrawal. One patient in arm A and two patients in arm B discontinued treatment because of adverse events (Fig. 1). After treatment discontinuation, 63 % of the patients enrolled in arm A underwent additional treatment (chemotherapy: 5 patients, radiotherapy: 2 patients), while 27 % of the patients treated with the combination study (arm B) received further therapy (chemotherapy: 1 patient, surgery: 2 patients).

Safety

The entire patient population enrolled in this study (*n*=22) was evaluable for safety profile. The majority of the adverse events were considered mild or moderate and clinically manageable as summarized in Table 2. The most common drug-related adverse events of all grades in both arms were diarrhea, fatigue, hypertension, and nausea. In arm A, drug-related severe (grade≥3) adverse events included hypertension, anemia and thrombocytopenia, all seen in 27 % of patients, and retroperitoneal hemorrhage (grade 5), which occurred in one patient. In arm B severe adverse events included diarrhea and hypertension, described in 27 % of patients, fatigue, and lower and upper gastrointestinal hemorrhage (all grade 3), which occurred in 18 % of patients. The grade 5 drug-related hemorrhagic event that occurred in arm A was in a 75 year-old man with extensive bone metastases, and comorbidities including hypertension and atrial fibrillation on anticoagulant therapy, who showed confirmed prolonged stable disease on cediranib. Prior to the serious adverse event, the patient tolerated full dose cediranib with no major adverse events for a total of 10 months. During cycle 12, after the first dose of cediranib, the patient experienced grade 2 thrombocytopenia, for which treatment was held for 7 days prior to hospital admission where the patient was found to have grade 3 anemia, grade 3 thrombocytopenia, grade 3 proteinuria, grade 3 retroperitoneal hemorrhage with consequent grade 3 sinus tachycardia. All these events were deemed as probably related to study medication and possibly related to disease and concomitant medications, which included low-molecular weight heparin, acetylsalicylic acid (ASA), and nonsteroidal antiinflammatory drug (NSAID) the patient received prior and during the hospitalization.

Objective response and progression free survival

Five patients (45%) in arm A and six patients (54 %) in arm B had measurable disease by RECIST. No patient had a complete (CR) or partial response (PR). All patients, 11 per arm, with target and non-target lesions were evaluable for response (best overall response). More patients in arm A presented with stable disease (SD) as best response as compared to arm B (77 % versus 22 %, respectively), while progression disease (PD) was observed more frequently in arm B (45 % versus 18% in arm A, respectively). As per PCWG2 criteria, twelve-week PFS was observed in 8 patients (73 %) in arm A and in 2 patients (18 %) in arm B (Fig. 2a). As shown in Fig. 2b, median PFS estimates were 6.4 months (95 % CI: 1.9 - not reached) in arm A and 2.6 months (95 % CI: 1.4 – not reached) in arm B (*P*=0.28).

Correlative studies

Pain and quality of life—To assess the impact of cediranib single agent versus the combination of cediranib plus dasatinib on advanced CRPC patients who progressed on docetaxel chemotherapy, FACT-P and PPI questionnaires were evaluated at baseline and after every cycle during treatment. As displayed in Fig. 3, no statistically significant differences were seen in QoL between baseline and cycles 2 and 3 in either arm. The results were also confirmed over time in those patients who continued the treatment beyond cycle 3 (data not shown). Comparable results were observed for the pain assessment, with a trend of pain worsening in the combination arm as compared to single agent cediranib (Supplementary Fig. 1).

Drug effects on bone turnover markers—To evaluate the effects of cediranib alone or the combination of cediranib plus dasatinib on bone, levels of β-CTX and BAP in cycle 2 were compared to baseline. As shown in Fig. 4a, β-CTX was reduced in six out of nine (67 %) patients in arm A, and in seven of 11 (64 %) patients in arm B. Additionally, serum BAP, a bone formation marker, was significantly increased in arm B as compared with cediranib alone as indicated in Fig. 4b (P=0.04). These data are consistent with the effects of VEGFR and/or Src inhibition on bone resorption and formation, despite no correlation being seen between bone turnover biomarker response and 12-week PFS.

Molecular profiling analysis—To gain further insight into the tumor characteristics of this patient population, archival tumor samples were molecularly profiled. Although all patients' specimens were available for the analysis, five out of 20 samples were not tested due to insufficient DNA quantity. Fifteen samples were sequenced by either MiSeq (8 samples), or Sequenom (7 samples) because of low DNA quantity. One of the samples genotyped with the customized Sequenom panel presented *EGFR* and *KIT* mutations in the tumor, while 42% of samples tested with MiSeq were found to have mutations in the related genes: *HNF1A*, *SMARCB1*, *TP53*, and *APC*. Median DNA quantity from all FFPE samples was 0.015 μg/μL (range 0.00005–0.208 μg/μL). Three patients in arm A and one patient in arm B harbored mutation in their archival tumor tissue. The average number of mutations detected by MiSeq was 0.5 per patient (range 0–2), while for Sequnom was 0.42 (range 0–3). Within the mutations detected, the ones found in *HNF1A* and *SMARCB1* genes presented unknown functional impact and have never been described before. Although rarely described in prostate cancer, this analysis enabled identification of potentially druggable mutations frequently described in other malignancies. Molecular profiling results are described in Supplementary Tables 1 and 2.

Discussion

This multicenter, randomized phase II study was interrupted prematurely because of the termination of cediranib clinical development at the US National Cancer Institute and subsequent lack of drug availability. However, despite the small sample size, our study showed no benefit to the combination of cediranib and dasatinib in CRPC patients progressing after docetaxel despite the fact that preclinical and clinical data of VEGFR and Src inhibition have demonstrated a crucial role for these kinases in cancer and promising activity in prostate cancer and several other tumor types [27, 61–64].

In our study, the median PFS of patients treated with cediranib alone appeared similar or better than values observed in other large phase II and III trials of docetaxelnaïve or -resistant CRPC patients [4, 65, 66]. These findings may be explained by the presence of a selected patient population with good performance status, and may not be fully representative of the overall docetaxel-resistant CRPC population. Taken into consideration the small sample size, our study suggests that the combination of cediranib and dasatinib may be associated with worse outcome than cediranib therapy alone in patients with CRPC. Although the number of severe adverse events did not significantly differ between arms A and B, more patients in arm B found the combination of the two agents difficult to tolerate and dropped out of the study early, thus limiting the interpretation of the outcome

comparison. This is in keeping with recent data that have shown that VEGF and Src inhibitors in combination may result in increased toxicity profile requiring frequent dose reduction or dose interruption [27]. Unfortunately, at the time the study was initially designed, tolerability of such a combination appeared acceptable [28] and no clinically significant effect of cediranib on the steady-state PK of saracatinib had been observed [67].

Preclinical studies have described Src-related androgen-independent growth during advanced stages of disease, with dasatinib-sensitive high Src activity prostate cancer cell lines exhibiting low androgen receptor activity [68, 69]. This provides evidence of a potential effect of dasatinib in CRPC, particularly in those lacking androgen receptor activity. However, despite promising preclinical data, clinical results of Src inhibitors in CRPC have been disappointing, with limited antitumor activity observed in a phase II study of single agent dasatinib in chemotherapy-resistant patients [54], and a large randomized phase III trial (READY), in which the addition of dasatinib to docetaxel-based chemotherapy did not improve overall survival [55]. Our data are consistent with previous findings and suggest that other unknown mechanisms, such as pathways activation or signaling cross-talk, may drive the growth of tumor cell and play a role in the bone remodeling processes [70].

In contrast with the lack of antitumor activity in the clinical setting, dasatinib appears to have important bone-protecting properties in patients with prostate cancer. Dasatinib has direct activity on osteoblast differentiation and osteoclast inhibition altering the tumor microenvironment [50, 71, 72]. Our pharmacodynamic results strengthen the previous data demonstrating the ability of Src as well as VEGF to influence osteoblast and osteoclast activity [73–76].

Although phase III studies evaluating the effects of various inhibitors of angiogenesis, such as bevacizumab and aflibercept have been disappointing [65, 77], in our study, single agent cediranib appeared to have some activity with 73 % of patients in arm A experiencing a PFS of twelve weeks or higher. These results may represent the consequence of a multi kinase inhibition of cediranib as compared to the selective VEGFR target of both bevacizumab and aflibercept, or the natural history of the disease in a selected group of patients [78].

Despite in this study most of the toxicities were considered clinically manageable in both arms, increased drug-related hemorrhagic events were seen when cediranib was combined with dasatinib, and tolerability was an important issue, with only half of the patients being able to receive both agents beyond cycle 1. Angiogenesis is often dysregulated in cancer and antiangiogenic molecules are now standard of treatment for several types of malignancies [79]. Activation of Src has been associated with both positive and negative regulation of VEGFR expression, with secondary inhibitory effects on permeability, endothelial cell differentiation and migration [80–84]. This activity may result in an overlapping antiangiogenic effect that can potentially explain the increased toxicity observed in our study, suggesting the need for a vigilant and prudent strategy for further combination treatment. In our study, the higher rate of adverse events likely contributed to treatment delays and dose reductions, which may have led to an underestimate of the activity of the combination.

In this study we attempted to profile patients' archival tumor tissue to better understand the molecular characteristics of this disease. In a few specimens a druggable pathway was identified, but the small sample size study limited the ability to perform any correlation of genotypes with clinical outcome.

Despite our small sample size, this study showed no evidence of a beneficial effect of adding the Src inhibitor dasatinib to a VEGF inhibitor, cediranib and a negative interaction effect of this combination of drugs in CRPC cannot be definitively ruled out.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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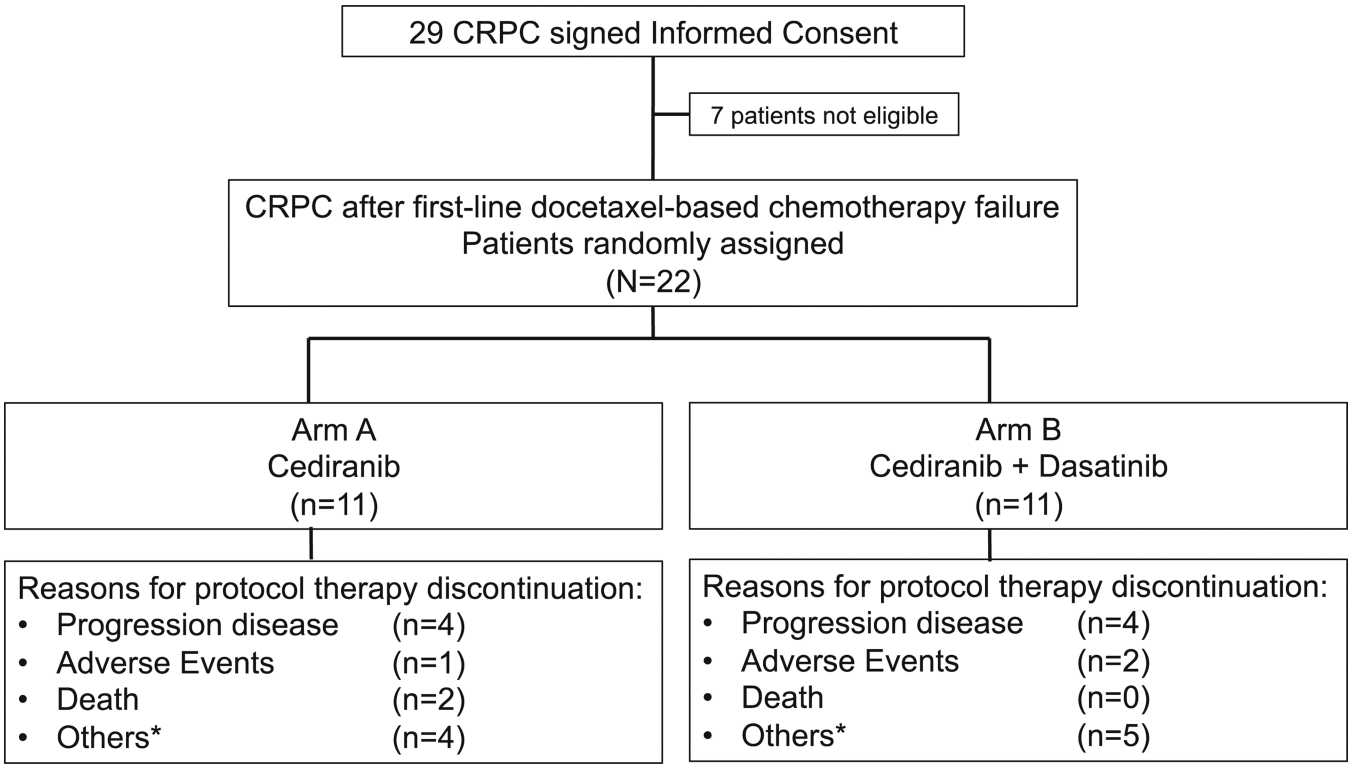

Fig. 1.
Study diagram. CRPC: castration resistant prostate cancer

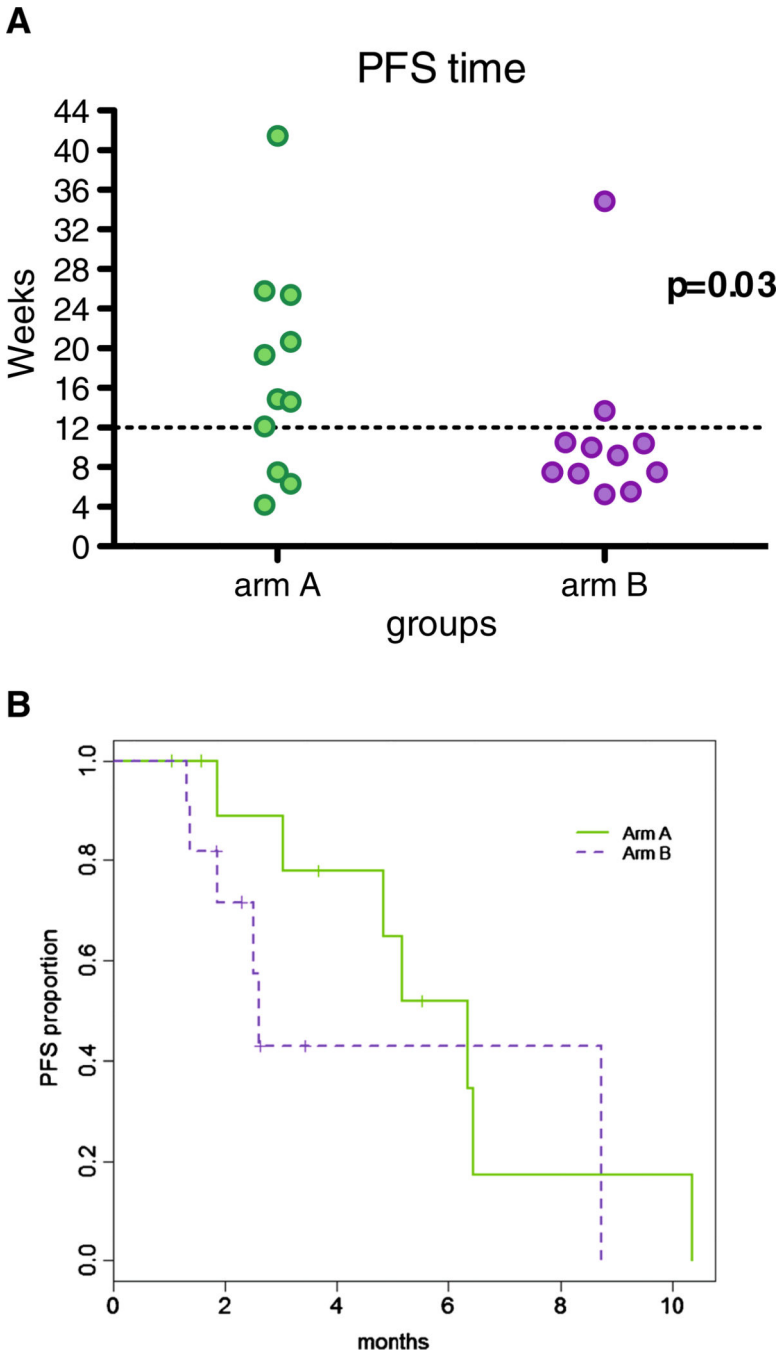

Fig. 2.
Twelve-week PFS as per PCWG2 criteria (A) and median PFS time

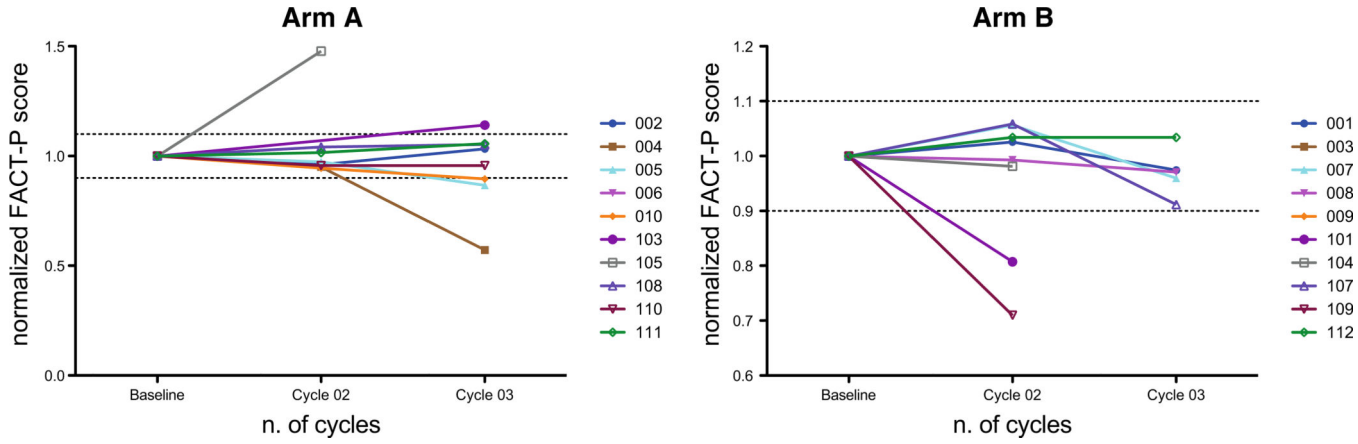

Fig. 3.

Quality of Life (QoL) as assessed by FACT-P score in CRPC patients treated with cediranib single agent or cediranib/dasatinib in combination. Dash-lines indicate the 10 % cut-off to identify deterioration (≥10 %) or improvement (<10 %) in QoL

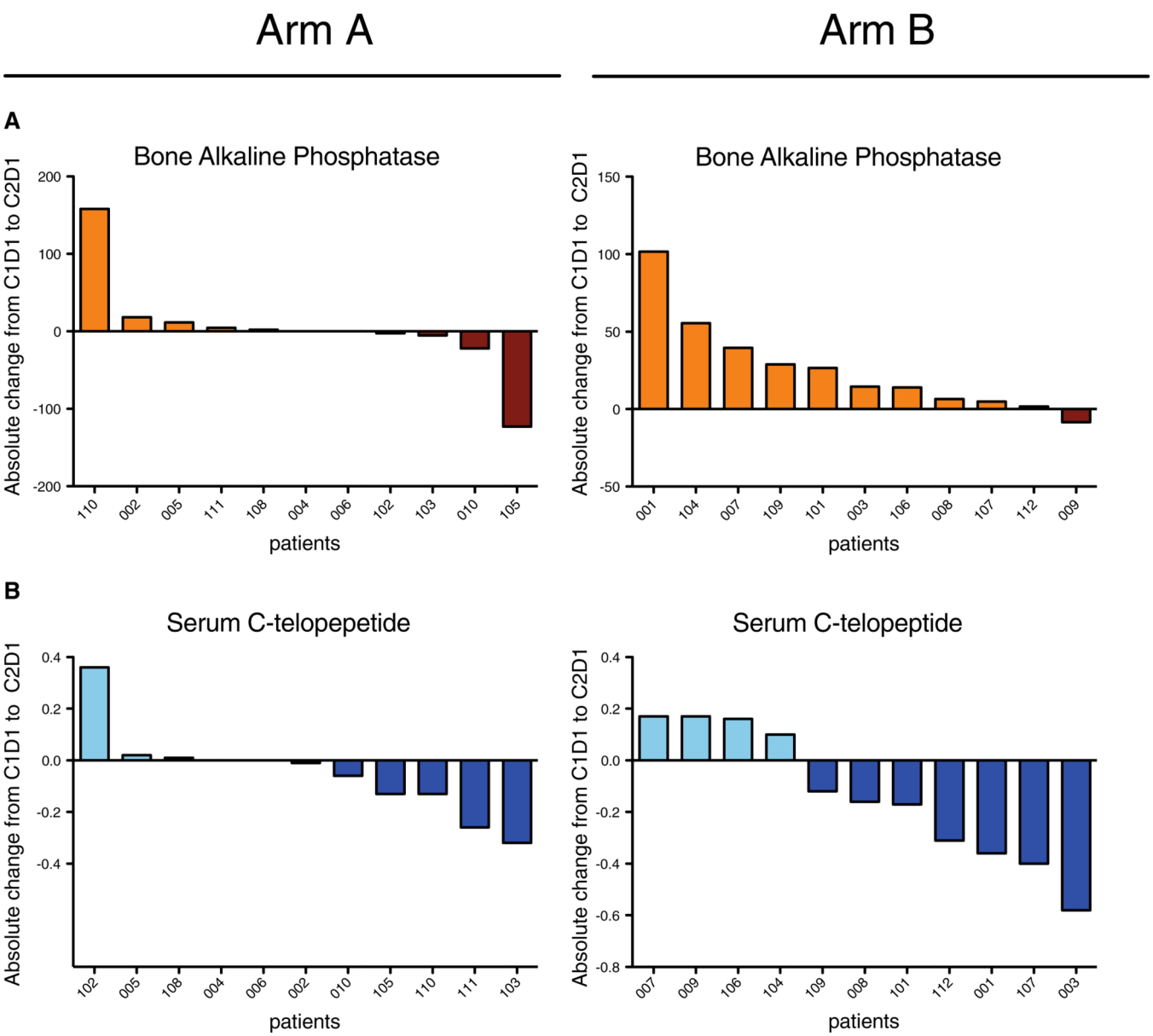

Fig. 4.

Changes of β C-telopeptide and serum bone-specific alkaline phosphate assessed between Cycle1 Day1 and Cycle2 Day1 in CRPC patients treated with either cediranib single agent or cediranib/dasatinib in combination

Table 1

Baseline characteristics by treatment group

Patients' Characteristics		**Arm A (*n*=11)**	**Arm B (*n*=11)**
Median Age (range)		71 (61–86)	66 (51–74)
ECOG PS	0 : 1 : 2	2 : 7 : 1	1 : 10 : 0
Prior Treatments	Adjuvant Chemotherapy	1	3
	Palliative Chemotherapy	11	11
	Radiotherapy	8	11
Median Serum PSA ng/ml (range)		361 (9.1–2451)	389 (47.6–2177)
Median Hb g/dL (range)		110 (9.4–130)	114 (12.7–137)
Median LDH U/L (range)		410 (151–504)	231 (139–1442)
Median ALP U/L (range)		260 (86–626)	131 (73, 1490)
Extent of disease (%)	Bone metastases	90	90
	Visceral disease	64	64
	Measurable lesions	55	45
Pain (%) score ≥2 on PPI scale		36	73

Table 2

Possibly-related treatment adverse events

Any		Arm A (*N*=11)		Arm B (*N*=11)	
		All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Gastrointestinal disorders	Diarrhea	7 (64 %)	1 (9 %)	7 (67 %)	3 (27 %)
	Nausea/vomiting	3 (27 %)	0	9 (82 %)	0
	Reflux	1 (9 %)	0	0	0
	Oral mucositis	1 (9 %)	0	4 (36 %)	1 (9 %)
Cardiovascular disorders	Hypertension	6 (54 %)	3 (27 %)	6 (54 %)	3 (27 %)
	Bradycardia/tachycardia	2 (18 %)	1 (9 %)	0	0
	ECG QT prolongation	1 (9 %)	0	2 (18 %)	0
	Hemorrhage	1 (9 %)	1* (9 %)	4 (36 %)	2 (18 %)
Asthenia or Fatigue		4 (36 %)	1 (9 %)	6 (54 %)	2 (18 %)
Fever		0	0	1 (9 %)	0
Electrolytes abnormalities		7 (64 %)	0	5 (45 %)	0
Bone Marrow:	Anemia	3 (27 %)	1 (9 %)	1 (9 %)	0
	Leucopenia/Neutropenia	5 (45 %)	0	5 (45 %)	0
	Thrombocytopenia	5 (45 %)	2 (18 %)	1 (9 %)	0
Edema		1 (9 %)	0	0	0
Endocrine disorders	Hypothyroidism	2 (18 %)	0	3 (27 %)	0
Alopecia		0	0	2 (18 %)	0
Urinary system	Proteinuria	3 (27 %)	1 (9 %)	3 (27 %)	0
	Hematuria	1 (9 %)	0	0	0
	Creatinine alteration	1 (9 %)	0	0	0
Nervous system		0	0	2 (18 %)	0
Liver function test alteration		3 (27 %)	0	4 (26 %)	0
Pain		4 (36 %)	0	7 (64 %)	2 (18 %)
Respiratory	Dyspnea/cough	2 (18 %)	0	3 (27 %)	0
Headache		2 (18 %)	0	3 (27 %)	0
Musculoskeletal		4 (36 %)	0	2 (18 %)	0
Appetite Disorders		8 (73 %)	0	11 (100 %)	0

Any	Arm A (*N*=11)		Arm B (*N*=11)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Others	7 (64 %)	0	11 (100 %)	0

* G5 retroperitoneal hemorrhage event