Protocol Summary

Stereotactic body radiotherapy with or without Darolutamide for OligoRecurrent prostate cancer: a randomized phase II trial (DART)

Title of clinical trial	Stereotactic body radiotherapy with or without Darolutamide for OligoRecurrent prostate cancer: a randomized phase II trial
Short title/acronym	DART
Study phase	Phase II
Sponsor name	Ghent University Hospital
Study Coordinator	Piet Ost
EudraCT number	2019-004952-13
Medical condition under investigation	Hormone sensitive prostate cancer with biochemical progression after local therapy and PET-detected oligometastatic disease.
Purpose of trial	To evaluate the combination of SBRT plus darolutamide as compared to SBRT.
Primary objective	To compare metastasis-free survival (rPFS) between SBRT plus darolutamide and SBRT only for oligorecurrent PCa
Secondary objective(s)	• To describe the toxicity of both arms in patients with oligometastatic disease. • To determine local control after SBRT + darolutamide in patients with oligometastatic disease. • To assess biochemical relapse-free survival (BRFS) in both arms. • To assess clinical progression-free survival (PFS) in both arms. • To assess time to next systemic therapy in both arms • To assess CRPC-free survival in both arms • To assess PCa-specific and overall survival in both arms. • To assess quality of life in both arms.
Trial design	Multicenter, open-label, randomized phase II trial.
Treatment	SBRT +/- darolutamide 2x 300 mg bid
Randomization ratio	1:1
Number of subjects	124
Summary of eligibility criteria	<u>Inclusion criteria</u> • Histologically proven initial diagnosis of adenocarcinoma of the prostate • Biochemical relapse of PCa following radical local prostate treatment (radical prostatectomy (RP), primary radiotherapy or the combination of RP and prostate bed adjuvant/ salvage radiotherapy) according to the EAU guidelines 2018. • Following RP, patients with a biochemical relapse are eligible in case a metastatic relapse is detected even in the absence of prior postoperative prostate bed radiotherapy (adjuvant or salvage). In the absence of prior prostate bed radiotherapy, prostate bed radiotherapy is mandatory for all pT3a or higher or patients with a positive margin at time of RP. • For patients without prior RP that have a suspected local recurrence following primary radiotherapy, a biopsy should confirm local recurrence. Patients with a confirmed local

	recurrence and metastases are eligible in case they also undergo a local salvage therapy. • Metastatic relapse on PSMA PET-CT with a maximum of 5 metastases (any M1a, M1b or M1c). Concomitant diagnosis of N1 disease is allowed as long as all lesions are treated with SBRT and the total number of lesions does not exceed 5. PSMA positive lesions will be scored using the MI-RADS scoring system with lesions scored 4 or 5 considered positive19. • Asymptomatic for metastatic PCa • Age ≥18 years • WHO class 0-1 • Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial • Before patient registration/randomization, written informed consent must be given in accordance with to ICH/GCP, and national/local regulations. <u>Exclusion criteria</u> • Local relapse in the prostate gland or prostate bed not suitable for a local salvage treatment • Small cell carcinoma of the prostate • PSA doubling time >12 months • Serum testosterone level <50ng/dl or 1.7 nmol/L at time of randomization • Currently receiving ADT or PSA rise while on active treatment with ADT within the past 6 weeks • Spinal cord compression or impending spinal cord compression • Metastases in previously irradiated areas precluding safe delivery of SBRT • Contraindications to darolutamide • PSA rise while on active treatment with ADT (LHRH-agonist, LHRH-antagonist, anti-androgen or estrogen) • Previous treatment with cytotoxic agent for PCa • Treatment during the past month with products known to influence PSA levels (e.g. fluconazole, finasteride, corticosteroids,…) • Other active malignancy, except non-melanoma skin cancer or other malignancies with a documented disease-free survival for a minimum of 3 years.
Study duration	The accrual duration is 24 months, subjects will be followed for a minimal of 24 months following randomization of the last subject. The total study duration is thus projected to be 48 months.
Primary endpoint	Metastasis-free survival
Secondary endpoints	• Clinical progression-free survival • Biochemical relapse-free survival • Time to next systemic therapy • Castrate resistant-free survival • Prostate cancer-specific survival • Overall survival • Acute and late toxicity • Quality of life
Version & date of protocol	Version 1.1, November 20, 2020
Version & date of protocol amendments	Not applicable.