Efficacy and Safety of Dendrimer-Enhanced (DEP®) Cabazitaxel (CTX-SPL9111) in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) in a Phase 1/2 Trial

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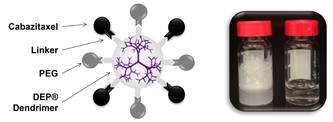
Background

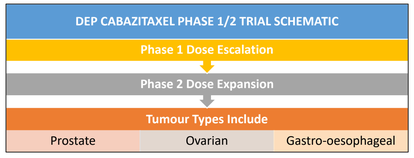
- Cabazitaxel is widely used in the treatment of prostate cancer
- Conventional formulations of cabazitaxel contain polysorbate 80 requiring routine pre-medication with steroids
- DEP® cabazitaxel is a novel, patented, highly water-soluble, poly-L-lysine dendrimer nanoparticle modified with polyethylene glycol (PEG) with cabazitaxel covalently linked via a hydrolysable linker; no pre-medication is required
- Dendrimer size restricts them to blood volume, enabling sustained delivery of cytotoxic drugs, but allows extravasation through leaky tumour vasculature[1]
- Superior preclinical efficacy of DEP® cabazitaxel compared with conventional cabazitaxel encouraged this Phase 1/2 clinical trial in patients with advanced solid tumours, including mCRPC



Representation of DEP® cabazitaxel components (left) and example of increased solubility of a drug substance achieved with DEP® technology

Methods

- Primary objective to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of DEP® cabazitaxel
- Intravenous (IV, ~60 min infusion) dosing once every 21 days
- Patients included prostate, ovarian, cholangiocarcinoma, and pancreatic cancer
- Dose (expressed as mg/m^2 cabazitaxel), was escalated to study the safety profile and identify a recommended phase 2 dose (RP2D) for expansion cohorts to explore preliminary efficacy
- No routine premedication with steroids or antihistamines (H1 or H2)
- Intra-patient dose escalation allowed in Phase 1, following confirmation of tolerability of next higher dose



KEY ELIGIBILITY CRITERIA

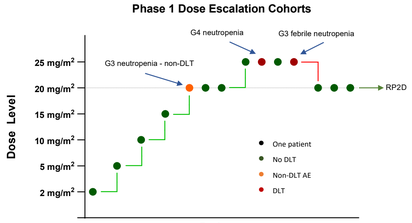
Inclusion Criteria	Exclusion Criteria

• Patients with advanced or metastatic solid tumours
• Measurable disease or evaluable tumour marker
• Prostate cancer patients:
  • Progressive disease per Prostate Cancer Working Group 3 (PCWG3) guidelines, with ≥1 of:
  • Prostate specific antigen (PSA): rising and ≥10 ng/mL at screening;
  • Soft tissue disease progression
  • Bone progression
• Eastern Cooperative Oncology Group (ECOG) performance status 0-1
• Life expectancy ≥12 weeks
	• Symptomatic brain metastases or untreated spinal cord compression
	• Absolute neutrophil count (ANC) <1.5×10^9/L; platelet count <100×10^9/L; haemoglobin <10 g/dL
	• Bilirubin >ULN, or AST or ALT >1.5 x ULN
	• Concurrent or planned treatment with inhibitors/inducers of CYP3A4/5
	• Symptomatic grade 1 or ≥ grade 2 peripheral neuropathy (PN)
	• Anti-tumour therapy ≤30 days or 5 half-lives prior to dosing

EU Clinical Trials Register EudraCT: 2017-003424-76

Results

PHASE 1 DOSE ESCALATION OVERVIEW

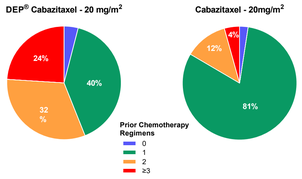


- Patients treated with up to 15 cycles of DEP® cabazitaxel
- Adverse events (AEs) were mild to moderate, similar in character to those reported for standard cabazitaxel, although no hypersensitivity or alopecia was seen
- Neutropenia, nausea, decreased appetite and fatigue were observed in >1 patient
- Encouraging efficacy signals observed in a range of tumour types, incl. mCRPC, ovarian, cholangiocarcinoma; one mCRPC patient had SD >47 weeks, PSA reduction of 79%

PHASE 2 PROSTATE CANCER COHORT

Phase 2 mCRPC Cohort Baseline Characteristics		Phase 2 mCRPC Cohort (N=25)
Age, years	Mean (Range)	73.1 (58-83)
Soft Tissue Disease (RECIST 1.1), % (n)	Any	68% (17)
	Measurable	56% (14)
	Non-measurable only	12% (3)
	Nodal metastases	40% (10)
	Visceral metastases	36% (9)
Bone Metastases, % (n)	Any	84% (21)
	1 to 4	40% (10)
	>4	44% (11)
	Only bone metastases	28% (7)
PSA, % (n)	PSA ≥ 10 ng/mL	88% (22)
Prior Systemic Cancer Treatments, % (n)	**Docetaxel**	
	Any	96% (24)
	1 to 5 cycles	16% (4)
	6 cycles	48% (12)
	7 to 12 cycles	20% (5)
	>12 cycles	12% (3)
	Cabazitaxel	
	Any	20% (5)
	<10 cycles	4% (1)
	10 cycles	16% (4)
	2nd Generation ASTIs	
	Any	100% (25)
	1	68% (17)
	2	32% (8)
	Radiopharmaceutical	24% (6)
Lowest Pre-dose Neutrophil Count (×10^9/L) (Screening or C1D1), % (n)	<4.0	68% (17)
	1.5 to <2.0	8% (2)
	2.0 to <3.0	36% (9)
	3.0 to <4.0	24% (6)
	>4.0	32% (8)

mCRPC patients treated with DEP® cabazitaxel were heavily pre-treated. Compared with published data for cabazitaxel[2], they were ~6 times more likely to have received ≥3 regimens of chemotherapy prior to study entry, and >3 times more likely to have received ≥2 regimens.[2]

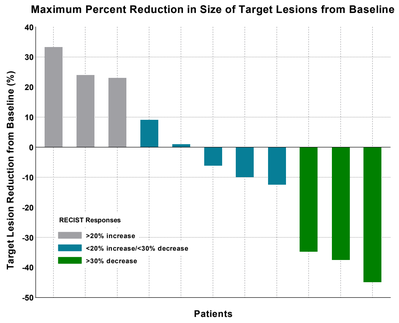


Number of prior chemotherapy regimens for patients in the Phase 2 mCRPC cohort vs trial of conventional cabazitaxel[2]

PHASE 2 PROSTATE CANCER COHORT EFFICACY OVERVIEW

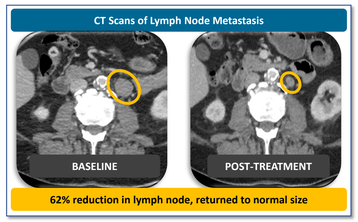
Efficacy Responses in Evaluable Patients		Phase 2 mCRPC Cohort Evaluable* Patients (N=22)
Soft Tissue Disease (RECIST 1.1)	**RECIST Evaluable, N**	**14**
	ORR evaluable (measurable), N	11
	ORR, % (n/N)	18.2% (2/11)
	DCR, % (n/N)	71.4% (10/14)
	Best RECIST Response	
	Confirmed PR, % (n/N)	18.2% (2/11)
	SD, % (n/N)	57.1% (8/14)
	PR, SD ≥18 weeks	50.0% (7/14)
PSA	**PSA Evaluable, N**	**21**
	Any PSA Decrease from Baseline, % (n/N)	90.5% (19/21)
	PSA Decrease ≥50% from baseline, % (n/N)	52.4% (11/21)
Bone Disease (PCWG3)	**Bone Disease Evaluable, N**	**18**
	No progression or improved, % (n/N)	83.3% (15/18)
Combined Responses (Soft Tissue, PSA, Bone)	≥1 response, % (n/N)	100% (22/22)
	All 3 responses, % (n/N)	66.7% (6/9)

* Evaluable = received ≥1 dose DEP® cabazitaxel and had an applicable efficacy assessment conducted post-treatment
ORR, objective response rate ([CR+PR]/ORR evaluable)
DCR, disease control rate ([CR+PR+SD]/RECIST evaluable)
CR, complete response
PR, partial response
SD, stable disease (includes non-CR and non-PD)

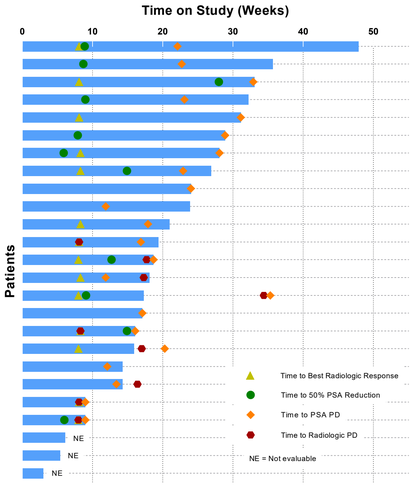


CASE REPORT: 80-year-old man with Stage IV mCRPC

- Progressed following 33 cycles / months of 3 different anticancer therapies
- 87% reduction in PSA
- PR, 62% reduction in size of lymph node, returned to normal size
- No G-CSF support required, despite low neutrophil count at baseline
- Notable absence of: neutropenia, anemia, thrombocytopenia

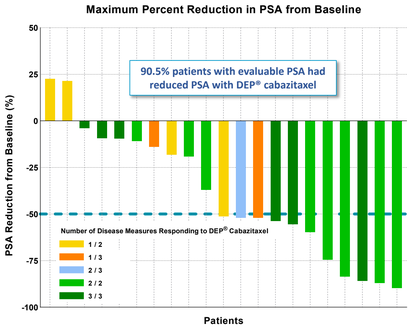


Time on Study
- Median treatment duration was 5 cycles (range 1-12)
- Median time on study 18.4 weeks
- Median composite progression free survival (PFS, time to first of PSA or radiologic progression, or death) was 3.9 months



Time on study, showing time to best radiologic or PSA responses, and time to radiologic or PSA PD

- 2 patients stayed on treatment through radiologic progression due to clinical benefit (e.g., improved bony pain, investigator report)



Maximum reduction in PSA vs baseline by patient; and number of disease measures (PSA, soft tissue, bone) responding to treatment with DEP® cabazitaxel (excl. 1 patient with 2/2 responses but baseline PSA < 10 ng/mL)

PHASE 2 PROSTATE CANCER COHORT SAFETY OVERVIEW

- For this heavily pre-treated cohort, the majority of treatment-related AEs (TRAEs) were mild to moderate, and have been reported for standard cabazitaxel

Grade 1	Grade 2	Grade 3	Grade 4
68.7%	23.8%	7.0%	0.5%

Adverse Event	Number of Patients with Treatment-Related Adverse Events (≥10%) (N=25)				
System Organ Class MedDRA Preferred Term	All n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and Lymphatic System Disorders					
Anemia	10 (40)	6 (24)	3 (12)	1 (4)	
Leukopenia	3 (12)		1 (4)	2 (8)	
Lymphopenia	4 (16)	2 (8)	2 (8)		
Neutropenia	9 (36)	4 (16)	1 (4)	3 (12)	1 (4)
Thrombocytopenia	5 (20)	3 (12)	2 (8)		
Gastrointestinal Disorders					
Constipation	7 (28)	5 (20)	2 (8)		
Diarrhea	12 (48)	10 (40)	1 (4)	1 (4)	
Nausea	11 (44)	10 (40)		1 (4)	
Vomiting	6 (24)	3 (12)	1 (4)	2 (8)	
General Disorders and Administration Site Conditions					
Fatigue	14 (56)	8 (32)	5 (20)	1 (4)	
Investigations					
ALT Increased	3 (12)	3 (12)			
AST Increased	5 (20)	4 (16)	1 (4)		
Weight Decreased	3 (12)	2 (8)	1 (4)		
Metabolism and Nutrition Disorders					
Decreased appetite	6 (24)	6 (24)			
Nervous System Disorders					
Neuropathy peripheral	17 (68)	4 (16)	11 (44)	2 (8)	
Renal and Urinary Disorders					
Hematuria	3 (12)	2 (8)	1 (4)		
Respiratory, Thoracic and Mediastinal Disorders					
Epistaxis	3 (12)	3 (12)			

Conclusions

DEP® cabazitaxel in heavily pre-treated mCRPC patients:

- demonstrated highly encouraging anti-tumour activity, including RECIST partial response for >45 weeks, and stable or improved bone disease for up to 45 weeks
- 100% of evaluable patients achieved a response in ≥1 measure of efficacy
- 52% of patients evaluable for PSA achieved PSA reduction ≥50% from baseline
- 68% of patients evaluable for 2 or 3 efficacy measures achieved a response for all evaluable measures
- did not require routine steroid pre-medication or daily oral steroid
- was generally well-tolerated, with AEs similar in character to those observed with standard cabazitaxel

Despite many patients being at an increased risk of neutropenic complications (older age, low baseline neutrophil count)[3], the incidence of laboratory detected Grade 3/4 neutropenia was low (7.5%), and secondary prophylactic use of G-CSF was only required by 2 patients.

Strong indicators of efficacy, including multiple PRs, have also been observed in heavily pre-treated patients with platinum resistant ovarian cancer, and other relapsed and refractory cancers, including oesophageal squamous cell carcinoma and gastro-oesophageal junction adenocarcinoma.

DEP® cabazitaxel is a promising, novel formulation of cabazitaxel that has multiple potential benefits over standard cabazitaxel and warrants further clinical development.

DEP® cabazitaxel in this cohort of heavily pre-treated mCRPC patients compared with published data for standard cabazitaxel:

PFS (median)

DEP® Cabazitaxel (20 mg/m^2) (N=25)	Cabazitaxel[2] (20 mg/m^2) (N=598*)	Cabazitaxel[2] (25 mg/m^2) (N=602*)	Cabazitaxel[4] (25 mg/m^2) (N=378*)
3.9 months	2.9 months	3.5 months	2.8 months

PFS = Composite endpoint from date of randomization to date of first tumour progression, PSA progression, or death. Note that the Jevtana studies[2,3] also included pain progression
* Intent-to-treat (ITT) populations

Grade 3/4 TRAEs

DEP® Cabazitaxel (20 mg/m^2) (N=25)	Cabazitaxel[2] (20 mg/m^2) (N=580†)	Cabazitaxel[2] (25 mg/m^2) (N=595†)
7.5%	39.7%	54.5%

† Safety populations (received at least 1 dose)

Severe bone marrow toxicities

Bone Marrow Toxicity	DEP® Cabazitaxel (20 mg/m^2) (N=25)	Cabazitaxel[*2] (20 mg/m^2) (N=580†)
Neutropenia* ≥ grade 3	16.0%	41.8%
Febrile neutropenia ≥ grade 3	0%	2.1%
Thrombocytopenia* ≥ grade 3	0%	2.6%
Neutropenic infection / sepsis	0%	2.1%

* Lab detected neutropenia or thrombocytopenia, regardless of whether or not event was reported as an AE
† Safety population (received at least 1 dose)

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2. Eisenberger, M, et al. *J Clin Oncol*, 2017;35(28):3198-206
3. Heidenreich, A, et al. *Eur J Cancer*, 2014;50:1090-9
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Presenting Author Conflict of Interest Declaration
RJ is coordinating or local PI for clinical studies sponsored by commercial entities Starpharma, AstraZeneca, Bayer, BioNTech, BMS, Boehringer, G1 Therapeutics, Genentech, Genmab, H3 Biomedicine, Orion, Roche and Sanofi.

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