Efficacy and safety of dendrimer-enhanced (DEP) cabazitaxel (CTX-SPL9111) in advanced esophago-gastric cancers in a phase 1/2 trial

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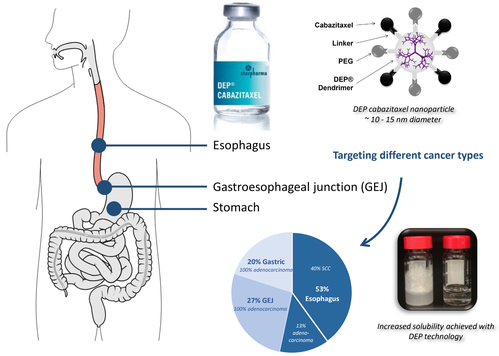
Background

- Advanced esophago-gastric cancers (EGC):
  - significant unmet medical need, very poor prognosis, limited available treatments
  - progress rapidly with 1-year survival rate of only 20%[1,2]
- DEP cabazitaxel:
  - novel, patented, poly-L-lysine dendrimer nanoparticle with polyethylene glycol (PEG), and cabazitaxel covalently attached via a hydrolysable linker
  - highly water-soluble, does not contain surfactants (detergents) so does not require routine pre-medication with steroids, H2 antagonists or antihistamines, unlike conventional formulations of cabazitaxel that contain polysorbate 80
  - DEP nanoparticle size restricts it to blood volume, but allows extravasation through leaky tumor vasculature[3], enabling sustained delivery of cytotoxic drugs within the tumor microenvironment
- Standard cabazitaxel is widely used for treatment of metastatic castrate-resistant prostate cancer (mCRPC), but is not indicated for use in other tumor types
- Objectives of this Phase 1/2 trial were to assess preliminary efficacy and safety of DEP cabazitaxel in patients with advanced, metastatic solid cancers
- We present the efficacy and safety of DEP cabazitaxel in a cohort of locally advanced and metastatic EGC patients recruited to the Phase 2 part of this trial
- Phase 1 dose escalation and efficacy in mCRPC patients was presented previously[4]



DEP cabazitaxel nanoparticle ~ 10 - 15 nm diameter

Targeting different cancer types

Patients' cancer primary distribution

Increased solubility achieved with DEP technology

Methods

- Patients with RECIST 1.1 measurable advanced EGC (squamous cell carcinoma [SCC] and adenocarcinoma) were enrolled to receive open label DEP cabazitaxel
- DEP cabazitaxel, equivalent to 20 mg/m^2 cabazitaxel (recommended dose), administered intravenously (IV, ~60 min infusion), once every 21 days (3-weekly)
- Antitumor activity assessed by RECIST v1.1 and, where applicable, tumor biomarker levels such as CEA and CA 19-9; safety assessed by physical and hematological examinations, and adverse events graded according to CTCAE v4.03

KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
• Patients with advanced or metastatic solid tumors • Measurable disease or evaluable tumor marker • 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 < 100×109/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-tumor therapy ≤ 30 days or 5 half-lives prior to dosing

EU Clinical Trials Register EudraCT: 2017-003424-76

Results

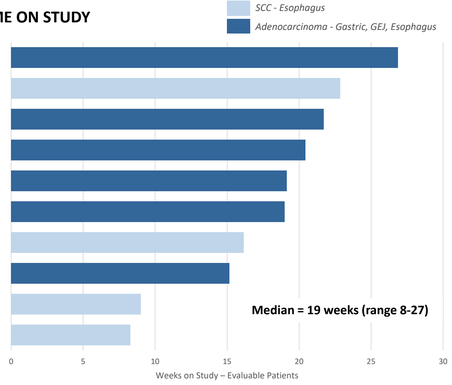
PATIENT BASELINE CHARACTERISTICS		All (N=15)	Adenocarcinoma (N=9)	Squamous Cell Carcinoma (N=6)
Age (years)	Median (Range)	61 (25 – 73)	60 (25 – 70)	68 (50 – 73)
Sex (% (n))	Male	67% (10)	67% (6)	67% (4)
	Female	33% (5)	33% (3)	33% (2)
Race (% (n))	Asian	13% (2)	11% (1)	17% (1)
	Black	7% (1)	0	17% (1)
	Black - Arabic	7% (1)	11% (1)	0
	Caucasian	67% (10)	78% (7)	50% (3)
	Not specified	7% (1)	0	17% (1)
Prior no. lines (incl neoadjuvant / adjuvant) (% (n))	1	53% (8)	67% (6)	33% (2)
	2	27% (4)	22% (2)	33% (2)
	≥3	20% (3)	11% (1)	33% (2)
Selected prior chemo-therapeutic / biologic agents (% (n))	Oxaliplatin	60% (9)	89% (8)	7% (1)
	Cisplatin	27% (4)	11% (1)	50% (3)
	Taxane	27% (4)	22% (2)	33% (2)
	Anti PD-1/PD-L1	27% (4)	0	67% (4)
Definitive Treatment (curative intent) (% (n))	**Yes**	**47% (7)**	**22% (2)**	**83% (5)**
	FLOT + surgery	7% (1)	11% (1)	0
	ECX + surgery	7% (1)	11% (1)	0
	CRT	27% (4)	0	67% (4)
	CRT + surgery	7% (1)	0	17% (1)
	No (metastatic at diagnosis)	**53% (8)**	**78% (7)**	**17% (1)**

FLOT (chemotherapy) + surgery = 5-FU + leucovorin + oxaliplatin + docetaxel + gastrectomy
ECX (chemotherapy) + surgery = epirubicin + cisplatin + capecitabine + esophagectomy
CRT = chemoradiotherapy (fluoropyrimidine / paclitaxel + platinum) + 50.4 Gy radiotherapy
CRT + surgery = carboplatin + paclitaxel + 40.4 Gy RT + esophagectomy

KEY OUTCOMES

- EGC patients received a median of 4.5 DEP cabazitaxel cycles (range 1-7)
- No routine steroid, antihistamine or H2 antagonist pretreatment
- Patients' prior anti-cancer therapy: median of 1 line and median of 6 cycles
- Overall ORR in evaluable patients was 30%, overall DCR was 80%
  - Partial responses (PR) in both adenocarcinoma and SCC subtypes
  - Stable disease (SD) for up to 27 weeks and PR for up to 17 weeks in evaluable EGC patients
- Median progression free survival (PFS) (all enrolled) was 4.0 months
- Median Overall Survival (OS) (all enrolled) was 8.6 months

TIME ON STUDY



PHASE 2 ESOPHAGO-GASTRIC CANCER COHORT EFFICACY OVERVIEW

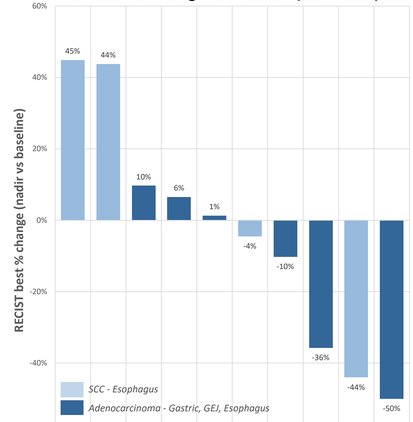
DEP Cabazitaxel					
Tumor type	**Evaluable***	**Disease Control Rate (RECIST)**	**Objective Response Rate (ORR)**	**Median PFS (months)**	**Median OS (months)**
Esophageal / GEJ / Gastric (N=15)	**10**	**80%**	**30%**	**4.0**	**8.6**
Adenocarcinoma (N=9)	6	100%	33%	4.1	ND
SCC (N=6)	4	50%	25%	2.9	ND

**Evaluable = received ≥ 1 dose of DEP cabazitaxel and had a CT scan at ≥ 8 weeks*
ORR, objective response rate (CR+PR)
DCR, disease control rate (CR+PR+SD)
ND, not determined

Unsolicited investigator reports of improvements in patient Quality of Life (QoL) factors included:

- Reduced cancer-related pain and opiate usage
- Improved performance status
- Weight gain

Best % Reduction in Tumor Target Lesion Size (RECIST 1.1)



Primary tumor location	E	E	G	E	GEJ	E	GEJ	E	E	GEJ
Sub-type	SCC	SCC	Ad.	Ad.	Ad.	SCC	Ad.	Ad.	SCC	Ad.
Metastatic at diagnosis	N	N	N	Y	Y	N	Y	Y	N	N
1st line Best Response of PD	N	N	N	Y	N	N	N	Y	Y	N
Prior chemo lines	3	3	2	1	3	1	1	1	1	2
Prior anti-PD-1 / PD-L1	Y	Y	N	N	N	Y	N	N	Y	N
Best % Reduction in Tumor Biomarkers (where applicable)										
CEA	0%	0%	0%	-67%	N/A	-50%	-40%	N/A	-20%	N/A
CA 19-9	9%	-33%	38%	-81%	>100%	-35%	-77%	-99%	-5%	-11%

PD = Progressive Disease
CEA = carcinoembryonic antigen
CA 19-9 = cancer antigen 19-9 / carbohydrate antigen 19-9

SAFETY OVERVIEW

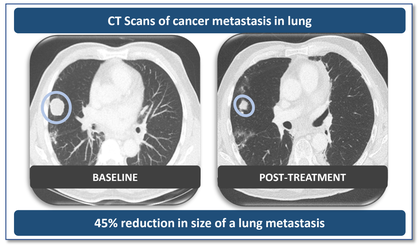
- DEP cabazitaxel was well-tolerated, with mostly Grade 1 (62.9%) / moderate (20%, Grade 2) treatment-related adverse events (TRAEs), with few ≥ severe (grade 3) events
- Limited myelosuppression, including ≥ severe (grade 3) neutropenia – only 1 pt had G-CSF treatment, 1 patient had secondary G-CSF prophylaxis
- Of severe TRAEs (G3/4; 17%) most (80%) were observed in 2 patients, including neutropenia, anemia, thrombocytopenia, fistula, sepsis, elevated liver enzymes
- TRAEs were like those observed for standard cabazitaxel treatment

DEP Cabazitaxel Treatment-related Adverse Events (% of all TRAEs) in EGC patients			
Grade 1	Grade 2	Grade 3	Grade 4
63%	20%	7%	10%

Treatment-Related Adverse Events (Most Extreme Grade) Experienced by ≥ 10% Patients or ≥ Grade 3 (N=15)					
System Organ Class MedDRA Preferred Term	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and Lymphatic System Disorders					
Anemia	7 (47)	1 (7)	4 (27)	2 (13)	
Neutropenia	7 (47)	2 (13)	1 (7)	1 (7)	3 (20)
Thrombocytopenia	2 (13)	1 (7)		1 (7)	
Gastrointestinal Disorders					
Esophago-pulmonary fistula	1 (7)				1 (7)
Nausea	5 (33)	5 (33)			
Vomiting	3 (20)	2 (13)	1 (7)		
General Disorders and Administration Site Conditions					
Fatigue	5 (33)	4 (27)	1 (7)		
Infections and infestations					
Sepsis	1 (7)				1 (7)
Investigations					
Alanine aminotransferase (ALT) increased	2 (13)	1 (7)			1 (7)
Aspartate aminotransferase (AST) increased	3 (20)	2 (13)			1 (7)
White blood cell count decreased	2 (13)		1 (7)	1 (7)	
Nervous system Disorders					
Peripheral neuropathy	9 (60)	5 (33)	3 (20)	1 (7)	
Skin and Subcutaneous Tissue Disorders					
Nail distrophy	2 (13)	2 (13)			

CASE REPORT: 73-year-old man with Stage IV esophageal SCC

- Developed multiple new lung metastases within 3 months of completing an initial course of chemoradiotherapy with curative intent (first line)
- Achieved partial response following 5 cycles of DEP cabazitaxel:
  - 44% overall decrease in tumor burden
  - 45% reduction in size of a lung metastasis
  - Disease control maintained for 24 weeks



DEP CABAZITAXEL MONOTHERAPY (Q3W DOSE REGIMEN)

HIGHLY ENCOURAGING ANTI-TUMOR ACTIVITY IN ADVANCED ESOPHAGO-GASTRIC CANCERS OF BOTH ADENOCARCINOMA AND SCC HISTOLOGY

- durable responses in esophageal, GEJ and gastric cancers
- concomitant tumor biomarker reductions

WELL-TOLERATED IN ADVANCED CANCER PATIENTS WITH HIGH-RISK CLINICAL FEATURES INCLUDING POOR NUTRITIONAL STATUS

- mostly mild / moderate TRAEs
- limited myelosuppression, lack of need for G-CSF treatment or prophylaxis
- no severe hypersensitivity even in the absence of routine steroid, H2 antagonist and antihistamine premedication

Conclusion

DEP cabazitaxel administered as a monotherapy, once every 3 weeks exhibited highly encouraging anti-tumor activity in >1L, advanced EG cancers:

- multiple anatomic locations (esophagus, GEJ and stomach)
- different histological sub-types: adenocarcinoma and SCC
- included many patients who were refractory to 1st line therapy
- achieved excellent efficacy responses:
  - median progression-free survival (PFS) of 4.0 months
  - median overall survival (OS) of 8.6 months
  - 30% ORR and 80% DCR in evaluable patients

The DEP cabazitaxel results compare very favorably to standard-of-care paclitaxel treatment in patients with esophageal or gastro-esophageal junction cancers, with DEP cabazitaxel achieving a more than 50% longer median PFS and a 29% longer median OS than paclitaxel administered weekly as a second-line treatment[5]. The DEP cabazitaxel efficacy results in advanced EGC patients, along with highly encouraging efficacy results in patients with mCRPC and platinum-resistant ovarian cancer, indicate the promising clinical potential of DEP cabazitaxel in a range of cancer types, including cancers for which conventional cabazitaxel is not indicated[6].

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