A Phase 1/2 Study of Dendrimer-Enhanced (DEP®) SN38 (SN38-SPL9111 / DEP® Irinotecan) in Patients with Advanced Solid Tumours

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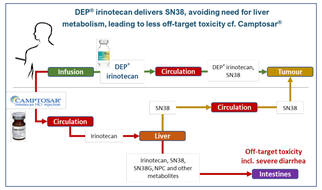
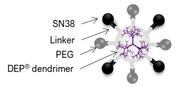
Background

- DEP® irinotecan, also called DEP® SN38, is a novel, patented, highly water-soluble, poly-L-lysine dendrimer nanoparticle modified with polyethylene glycol (PEG) with SN38 covalently linked via a hydrolysable linker.
- The dendrimer size limits it to circulatory system and, via extravasation through leaky tumour vasculature, they accumulate in tumour tissue providing increased tumour targeting and sustained delivery of cytotoxic drugs[1].
- Irinotecan, widely used in advanced colorectal (CRC) and other gastrointestinal (GI) cancers, is associated with significant cholinergic toxicity and life-threatening diarrhoea, both FDA "Black Box" warnings.
- Irinotecan requires complex conversion in the liver to the active moiety, SN38, with high interpatient plasma levels varying greatly.
- Following encouraging preclinical efficacy of DEP® irinotecan compared with irinotecan (see poster C167), this Phase 1/2 clinical trial was initiated in patients with advanced solid tumours, including CRC and platinum-resistant ovarian cancer.
- Phase 1 objective was to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of DEP® irinotecan (DEP® SN38). Phase 2 objectives included preliminary efficacy as defined by RECIST v1.1 and serum tumour biomarkers, and further safety and tolerability assessment.



Methods

- DEP® irinotecan administration: intravenous (IV, ~60 min infusion) dosing once every 14 (Q2W) or 21 (Q3W) days; administered as mg/m² SN38
- 5-FU (fluorouracil)/LV (leucovorin) administration: as per modified De Gramont protocol[2].
- Patients included advanced colorectal, ovarian, breast, pancreas, lung, upper GI cancers.
- Dose was escalated to study the safety profile and identify a recommended phase 2 dose (RP2D / RD) for expansion cohorts.



DEP® Irinotecan nanoparticle ~ 10 - 15 nm

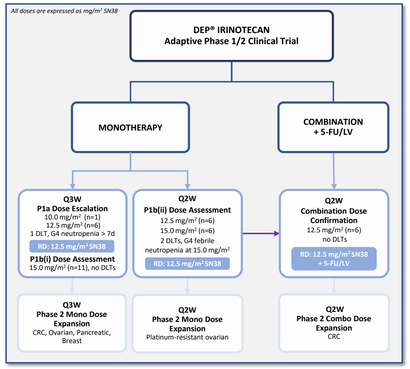
KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
• Patients with advanced or metastatic solid tumours, including CRC and platinum resistant high-grade serous ovarian carcinoma (HGSOC) • Measurable or evaluable disease • Eastern Cooperative Oncology Group (ECOG) performance status 0-1 • Life expectancy ≥ 12 weeks	• Uncontrolled brain metastases or spinal cord compression • UGT1A1*28 homozygous/congenital deficiency only in Phase 1 cohorts • DPD deficiency by standard genotypic testing for 5-FU/LV combination treatment • History of active bowel obstruction or inflammatory or acute GI disorders with diarrhea as major symptom

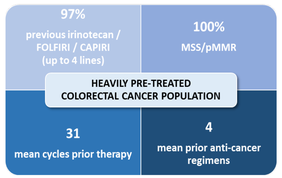
EU Clinical Trials Register EudraCT: 2019-001318-40

Results

DEP® IRINOTECAN RECOMMENDED DOSE (RD): 12.5 mg/m² SN38 MONOTHERAPY and 5-FU/LV COMBINATION THERAPY

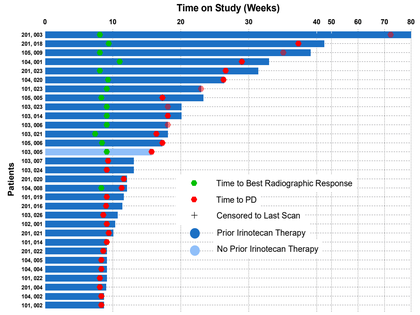


COLORECTAL PATIENTS OVERVIEW



- 95% had prior cancer surgery; 68% radiotherapy
- **DEP® irinotecan monotherapy**: Mean age: 59 years old (35-78)
- **DEP® irinotecan 5-FU/LV combination therapy**: Mean age: 52 years old (31-77) cohort; ongoing patients including several first assessment CT scans pending

COLORECTAL PATIENTS: EFFICACY OVERVIEW



COLORECTAL PATIENTS: EFFICACY OVERVIEW

Efficacy Response in Evaluable Patients		
DEP® irinotecan Monotherapy, Q3W, Q2W (N=38)	RECIST Evaluable, N	31
	DCR (n)	48% (15)
	ORR (n)	0% (0)
	Duration of response	up to 72 weeks
DEP® irinotecan combination with 5FU/LV, Q2W (N=17)	RECIST Evaluable, N	5
	DCR (n)	100% (5)
	ORR (n)	20% (1)
	Duration of response	up to 35 weeks

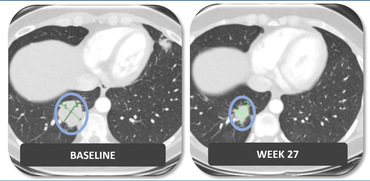
Evaluable: patients who received ≥ 1 dose DEP® irinotecan and a CT scan at ≥ ~Week 8 after first dose.
ORR: Objective Response Rate (CR+PR/ORR evaluable)
DCR: Disease Control Rate (CR+PR+SD/RECIST evaluable)

- Durable efficacy responses of up to 72 weeks for monotherapy and up to 35 weeks after DEP® irinotecan / 5-FU/LV combination therapy *(Note: 12 patients continuing on study treatment, including many pending 1st assessment CT scans)*

CASE REPORT: 38-year-old woman with Stage IV CRC

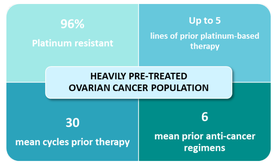
- 2 prior lines of therapy, 16 cycles including irinotecan-based therapy that was very poorly tolerated
- Received DEP® irinotecan (12.5 mg/m² SN38) + 5-FU/LV, Q2W, 17 cycles to date *(Note: patient ongoing in study)*
- Durable anti-tumour response for ~35 weeks, including Partial Response
- 74% reduction in CEA tumour biomarker
- DEP® irinotecan / 5-FU/LV combination treatment extremely well tolerated, especially a distinct lack of severe GI toxicity

CT Scans of Lung Metastasis (right lower lobe medial)



31.3% reduction in target lesion

OVARIAN PATIENTS OVERVIEW



- High grade serous ovarian cancer
- 96% had prior cancer surgery; 13% radiotherapy
- **DEP® irinotecan monotherapy**: Mean age: 62 years old (42-74)

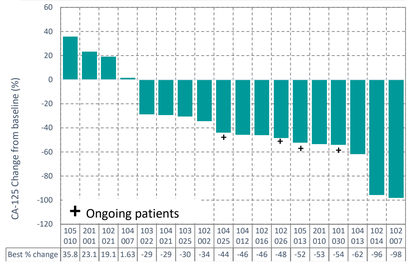
OVARIAN PATIENTS: EFFICACY OVERVIEW

Efficacy Response in Evaluable Patients		Total	Q2W	Q3W
DEP® irinotecan Monotherapy	Treated, N	23	8	15
	RECIST Evaluable, N	18	7	11
	ORR (n)	22% (4)	43% (3)	9% (1)
	DCR (n)	72% (13)	100% (7)	55% (6)
	Duration of response	up to 45 weeks	up to 45 weeks	≥ 27 weeks

Evaluable Patients: patients who received ≥ 1 dose DEP® irinotecan and a CT scan at ≥ ~Week 8 after first dose.
ORR: Objective Response Rate (CR+PR/ORR evaluable)
DCR: Disease Control Rate (CR+PR+SD/RECIST evaluable)

- Durable responses for up to 45 weeks, including 43% ORR and 100% DCR in very heavily pre-treated, platinum-resistant ovarian cancer patients treated with DEP® irinotecan Q2W; compares favorably to standard-of-care agent treatments e.g., paclitaxel, topotecan, gemcitabine, pegylated liposomal doxorubicin, which reported ORRs of ~9 to 16%[4-6] *(Note: patients continuing on study treatment).*
- Up to ~60% reduction in tumour size
- Complete resolution of soft-tissue tumour and tumour-related ascites in a patient with concomitant reduction in CA-125 to near non-measurable levels

CA-125 biomarker - up to 98% reduction in 75% patients



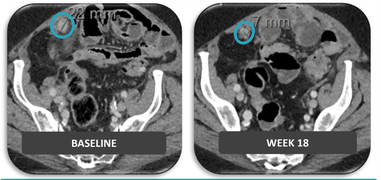
CASE REPORT: 71-year-old woman with Stage IV HGSOC

- 5 prior lines of therapy and 37 cycles
- DEP® irinotecan monotherapy, Q2W, 12.5mg/m2 SN38 - 12 cycles

(Note: patient ongoing in study)

- Efficacy responses:
  - Durable tumour response for > 27 weeks, PR
  - 52% reduction in CA-125 marker

CT Scans of Metastasis (Peritoneal deposit in RIF)



68% reduction in target lesion

DEP® IRINOTECAN SAFETY OVERVIEW

DEP® irinotecan treated patients: monotherapy (N= 95) and combination therapy (N=17); > 630 dose cycles administered

- Majority of treatment-related adverse events (TRAEs) mild and moderate
- Significantly fewer ≥ grade 3 (severe) TRAEs compared to (cf.) conventional irinotecan; 11% vs ~53-74% irinotecan monotherapy, 5-FU/LV combination therapy[3]
- No cholinergic symptoms, 0% vs ~47% pts irinotecan
- Neutropenia uneventful; managed with G-CSF
- No new TRAEs with DEP® irinotecan cf. irinotecan
- At least 2 patients have continued DEP® irinotecan treatment through radiologic disease progression due to clinical benefit, and particularly excellent tolerability

DEP® Irinotecan Treatment-related Adverse Events (% of all TRAEs)			
Grade 1	Grade 2	Grade 3	Grade 4
66%	23%	8%	3%

Number (%) of Patients with Treatment-Related Adverse Events (most severe event) ≥ 10% patients (N=112)				
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					
Anaemia	34 (30)	11 (10)	16 (14)	7 (6)	
Leukopenia	21 (19)	8 (7)	4 (4)	7 (5)	2 (2)
Lymphopenia	12 (11)	6 (5)	5 (4)	1 (1)	
Neutropenia	63 (56)	17 (15)	8 (7)	19 (17)	19 (17)
Thrombocytopenia	19 (17)	16 (14)	3 (3)		
Gastrointestinal Disorders					
Abdominal pain	14 (13)	13 (12)	1 (1)		
Constipation	14 (13)	9 (8)	5 (4)		
Diarrhoea	42 (38)	30 (27)	12 (11)		
Nausea	76 (68)	50 (45)	24 (21)	2 (2)	
Vomiting	40 (36)	32 (29)	7 (6)	1 (1)	
General Disorders and Administration Site Conditions					
Fatigue	51 (45)	28 (25)	19 (17)	4 (4)	
Investigations					
Alanine Aminotransferase (ALT) Increased	19 (17)	15 (13)	2 (2)	2 (2)	
Aspartate Aminotransferase (AST) Increased	20 (18)	14 (13)	4 (4)	2 (2)	
Blood bilirubin increased	12 (11)	9 (8)	3 (3)		
Metabolism and Nutrition Disorders					
Decreased Appetite	19 (17)	13 (12)	6 (5)		
Skin and Subcutaneous Tissue Disorders					
Alopecia	64 (57)	24 (21)	40 (36)		
Rash	14 (13)	14 (13)			

GI toxicity is significantly less severe with DEP® irinotecan e.g., CRC monotherapy treatment		
TRAE	DEP® Irinotecan mCRC pts (N=38)	Conventional Irinotecan (Camptosar®)[3] mCRC pts (N=316)
	Grade 3 / 4	Grade 3 / 4
Diarrhea	0	22%
Nausea	2.6%	12.7%
Vomiting	0	14%

DEP® irinotecan - well tolerated in UGT1A1*28 homozygous mutant patients who are at risk of increased systemic exposure to SN38

- 15 UGT1A1*28 patients: DEP® irinotecan monotherapy (12) or combination (3) in Phase 2 dose expansion cohorts
- DEP® irinotecan started at 8 mg/m² SN38, 11 escalated to 10 mg/m² (n=7), and then 12.5 mg/m² (n=4) SN38 to date
- Well tolerated, no significant toxicities, including no severe diarrhea, vomiting or nausea
- Efficacy signals observed in at least 6 patients, including stable disease for ≥ 36 weeks

(Note: several patients are ongoing in the trial, and pending 1st assessment scan)

DEP® IRINOTECAN MONOTHERAPY OR 5-FU/LV COMBINATION THERAPY

HIGHLY ENCOURAGING ANTI-TUMOUR ACTIVITY IN HEAVILY PRE-TREATED PATIENTS WITH ADVANCED SOLID TUMOURS

- Durable anti-tumour responses in CRC, HGS ovarian and other tumour types

EXCELLENT SAFETY AND TOLERABILITY – SIGNIFICANTLY IMPROVED COMPARED WITH CONVENTIONAL IRINOTECAN

- Distinct lack of severe GI toxicity, including life-threatening diarrhoea; 0% cf. ~ 20%
- No cholinergic symptoms 0% cf. ~ 47%
- Very well tolerated in patients who could not tolerate conventional irinotecan

Efficacy responses observed in other tumour types

Tumour Type	DCR (SD+PR+CR)	Duration of Response
Breast (N=5)	100%	≥ 63 wks
Lung (N=2)	100%	≥ 27 weeks
Upper gastric (N=4)	50%	≥ 18 weeks
Pancreatic (N=9)	44%	≥ 36 weeks

Conclusions

DEP® irinotecan (DEP® SN38) is a novel dendrimer formulation that delivers SN38, irinotecan's active moiety, and exhibits encouraging anti-tumour activity, as well as superior tolerability over conventional irinotecan, with these data supporting further clinical development. These interim results support the promising clinical utility of DEP® irinotecan and its potential for application in both colorectal and platinum-resistant ovarian cancers

Acknowledgements

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