First-in-human administration of CEB-01, a novel drug delivery implant matrix, in patients with recurrent or locally advanced retroperitoneal soft tissue sarcoma (RPS) after surgery. Preliminary safety and pharmacokinetics report

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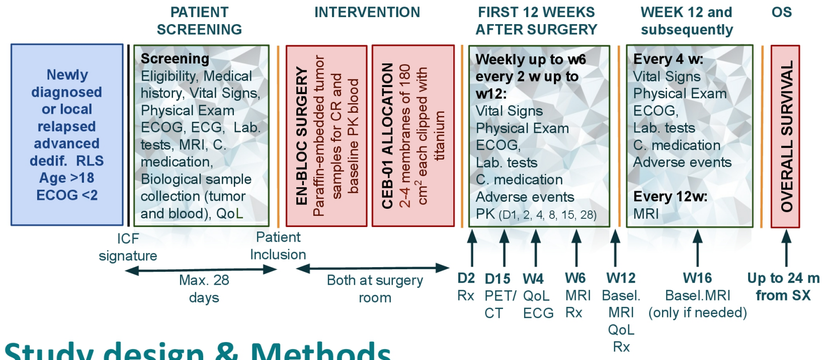
Background

- Currently, local recurrence after radical surgery (SX) is frequent and a major cause of death in retroperitoneal soft tissue sarcoma (RPS) patients[1]. About 41–50% will develop locally recurrent disease within 5 years[1].
- We hypothetized that locally delivered chemotherapy (CHT) by CEB-01 placed in the surgical bed during SX may increase local control and survival in RPS patients with reduced systemic toxicity.

CEB-01 membrane

- Biocompatible and biodegradable membrane of poly lactic-co-glycolic acid (PLGA) nanofibers loaded with the anti-tumour drug SN-38[2].



Study design & Methods

- This is a multicentre, open label, first-in-human phase 1 trial comprising a dose-escalation phase (3 cohorts with total SN-38 doses of 9, 18 and 36 mg respectively), followed by an expansion cohort at the recommended phase 2 dose (RP2D).
- Recurrent or locally advanced RPS patients candidates for local surgery, with no option of systemic treatment, age ≥18 years old, ECOG < 2, life expectancy > 6 months, and normal organ function are eligible. Tumor size >50 mm at staging.
- Primary objective is to determine RP2D, defined as the dose level at which less than 33% of patients present dose limiting toxicity (DLT) in a minimum of 6 at-risk patients during the first two weeks after SX. DLT is defined as any Grade ≥3 toxicity.
- Secondary objectives include safety, time to recurrence, biomarkers, pharmacokinetics (PK) and quality of life (QoL). Here we report preliminary safety, and PK data for the initial patients enrolled.

CONCLUSIONS

- CEB-01 biocompatible and resorbable implant matrix loaded with SN38 (9mg) is safe upon first human administrations in RPS patients, with scarce low grade Adverse Events and Toxicities.
- Preliminary PK indicates low, prolonged, systemic SN-38 exposure as expected.
- After a median follow-up of 16 (range 9-32) weeks from SX all patients were disease-free.

Figure 1. Surgical statistics

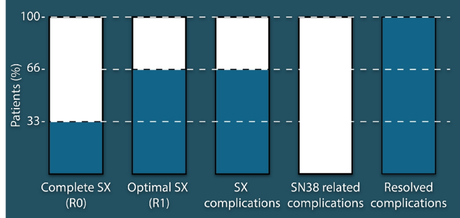
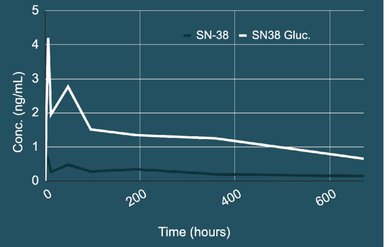


Figure 2. SN38 PK analysis in blood samples



Future Directions for Research

- Currently the second cohort (18 mg SN-38) of CEB-01-RLS trial is open for recruitment.
- Evaluate CEB-01 efficacy for local control of RPS in phase 2 trials.
- Clinical trials in other cancer types in wich control of local recurrence is of utmost relevance such as glioblastoma.

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Results

Table 1. Baseline Characteristics

Characteristic (continuous)		mean (SD)
age (years)		71.7 (5.9)
Tumor diameter (mm)		192 (144.1)
Characteristic (categorical)		**N (%)**
Sex	Male	3 (100%)
Histology	Liposarcoma	3 (100%)
Primary stage	III	2 (66%)
	uk	1 (33%)
Grade at diagnose	2	1 (33%)
	3	1 (33%)
	uk	1 (33%)
Tumor Location (resected)	Retroperitoneum	3 (100%)
	Suprarenal glands	1 (33%)
	Kidney	1 (33%)
	other	1 (33%)
Metastasis	no	3 (100%)
Prior SX/RT	no	3 (100%)

- First cohort of 9 mg SN-38 was completed in feb 2021, with the inclusion of three patients with dedifferentiated liposarcoma, (grade 2-3) Patients were male, age 65 to 76, with ECOG of 0-1 (Table 1). Optimal SX were performed for recurrent disease (1 patient) or locally advanced disease (2 patients) with complete (R0) and optimal (R1) outcomes (Fig. 1). There were no surgical complications attributed to the SN-38 treatment. One patient suffered from grade 2 (Dindo Clavien classification) intestinal subocclusion and other from grade 1 pneumoperitoneum due to SX complication resolved with medical treatment.
- Frequency and severity of adverse events (AE) was low (Table 2). All the patients presented transitory abdominal discomfort and seroma. Only one treatment related AE (TRAE) consisting of alopecia grade 1 was reported. There were no DLTs observed during the first administrations of CEB-01 (9 mg SN38).
- SN38 and its glucuronidated SN-38 systemic levels were low, reaching a peak (Cmax) of 0.76 and 4.2 ng/mL at 2 and 6 hours respectively, and were detectable 27 days after CEB-01 implantation in the surgical bed, at 0.1 and 0.6 ng/mL respectively (Fig. 2).

Table 2. Adverse events classified by frequency and severity

Event	Grade	n (%)	Related to CEB-01	SAE	DLT
Seroma	1	3 (100%)	no	no	no
Depression	1	2 (66%)	no	no	no
Diarrhea	1	2 (66%)	no	no	no
Hiccups	1	2 (66%)	no	no	no
Nausea	1	2 (66%)	no	no	no
Vomiting	1	2 (66%)	no	no	no
Alkaline phosphatase increased	3	1 (33%)	no	no	no
Catheter related infection	3	1 (33%)	no	no	no
Hypomagnesemia	3	1 (33%)	no	no	no
Pneumonia	3	1 (33%)	no	YES	no
Pneumoperitoneum	3	1 (33%)	no	YES	no
ALT increased	2	1 (33%)	no	no	no
Anemia	2	1 (33%)	no	no	no
AST increased	2	1 (33%)	no	no	no
Hypoalbuminemia	2	1 (33%)	no	no	no
Pleural effusion	2	1 (33%)	no	no	no
abdominal disconfort	1	1 (33%)	no	no	no
Alopecia	1	1 (33%)	YES	no	no
Cough	1	1 (33%)	no	no	no
Creatinine increased	1	1 (33%)	no	no	no
Fatigue	1	1 (33%)	no	no	no
Back discomfort	1	1 (33%)	no	no	no
Left thigh Hypoesthesia	1	1 (33%)	no	no	no
Limbs edema	1	1 (33%)	no	no	no
Pain	1	1 (33%)	no	no	no
Paresthesia	1	1 (33%)	no	no	no
Peripheral sensory neuropathy	1	1 (33%)	no	no	no
Platelet count decreased	1	1 (33%)	uk	no	no
Rash acneiform	1	1 (33%)	no	no	no
Weight loss	1	1 (33%)	no	no	no

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