A Phase I open-label, dose escalation study of a novel peptide (SOR-C13) antagonistic to the TRPV6 ion channel in patients with advanced solid tumor cancers.

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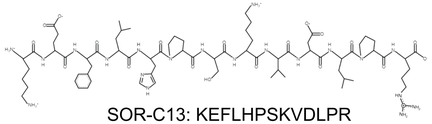
BACKGROUND

SOR-C13 is a first-in-man, selective, peptide inhibitor of Transient Receptor Potential Vanilloid 6 (TRPV6) calcium oncochannel. TRPV6 is highly elevated in carcinomas including prostate, breast, lung and ovary and is correlated with poor outcomes. TRPV6-mediated Ca^{2+} entry is responsible for maintaining a high proliferation rate, increasing cell survival and apoptosis resistance through calcineurin/NFAT pathways (1, 2, 3). Since SOR-C13 blocks TRPV6-mediated Ca^{2+} influx it was evaluated as a single agent in patients with late-stage carcinoma.



SOR-C13: KEFLHPSKVDLPR

Study Design

Objectives:

Primary:

- Assess safety and tolerability of SOR-C13 in subjects with advanced carcinomas commonly known to express the TRPV6 channel (NCT01578564).

Secondary:

- Evaluate PK/PD and measurement of tumor response

Methods

- Sequential, dose-escalating cohorts (3+3 design).
- Schedule: One 21-day cycle of treatment consisting of SOR-C13 for 3d on/4d off, 3d on/11d off.
- Doses: 1.375, 2.75, 4.13 and 6.2 mg/kg - i.v. infusion initially over 20 min (Cohorts 1 & 2) then 90 min (Cohorts 3 - 6).
- Dose limiting toxicity (DLT): any ≥ Grade 3 toxicity, or ≥ Grade 2 hypocalcemia over the first 21-day cycle of SOR-C13 treatment. Toxicity was assessed according to NCI CTCAE version 4.0.

Patient Population

- Patients aged ≥18 with advanced solid carcinomas refractory to all standard treatments.

RESULTS

Patient Characteristics

Characteristic		Overall (N=23)
		n (%)
Median Age, years (range)		58.6 (29 – 78)
Gender	Female	16 (69.6%)
ECOG Performance Status	0	8 (34.8%)
	1	15 (65.2%)
No. prior anticancer therapies	0 -1	0
	>1	23 (100%)
Ovarian 4; NSCLC 3, colon 4; breast 1; peritoneal 1; esophageal 1; pancreatic 2; uterine 1; GI stromal 1; prostate 1; parotid 1, nasopharyngeal 1; adenoid cystic 1		

Patient Safety

Six (26.1%) Dose Limiting Toxicities (N=23)

Cohort (Subject)	DLT	Dose/ Infusion	Resolu-tion	Drug Related ?
1 (101, 103)	Grd 2 Serum Ca^{+2} ⇓ asymptomatic	5.5 mg/kg/ 20min	4 - <24 h	Yes
2 (105)	Grd 2 Serum Ca^{+2} ⇓ asymptomatic	2.75 mg/kg/ 20min	4 - <24 h	Yes
4 (201)	Grd 2 Serum Ca^{+2} ⇓ asymptomatic	2.75 mg/kg/ 90min	4 - <24 h	Yes
No further grade 2 hypocalcemia observed after Calcium/Vit D supplementation				
6 (311)	Grd 3 anemia	6.2 mg/ kg/90min		NO
6 (316)	Grd 2 Atrial Fibrillation	6.2 mg/ kg/90min		NO

Drug-related Serious Adverse Events

None were observed

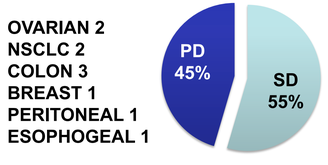
185 Treatment Emergent Adverse Events (N=23) MedDRA Preferred Term: Most Common TEAEs

TEAE	GRADE %				Total %
	1	2	3	4	
Fatigue	13.0	21.7	4.3		39.2
Hypoalbuminemia	30.4	4.3			34.8
Anemia	8.7	17.4	8.7		34.8
Urinary tract infection	13.0	17.4			30.4
Transient Blood Ca drop	4.3	21.7			26.1
Nausea	21.7				21.7
Constipation	13.0	8.7			21.7
Asp AT elevated	13.0	4.3	4.3		21.7
Lower appetite	13.0	4.3			17.4
Cough	4.3	13.0			17.4
Blood Alkaline P'tase	8.7	8.7			17.4
Ala AT elevated	4.3	4.3	8.7		17.4
Diarrhoea	13.0				13.0
Hypercalcemia	13.0				13.0
Hyperkalemia	13.0				13.0
Hypocalcemia	13.0				13.0

5 drug-related grade 3 TEAEs (cohort): uticaria (1); Ala AT & AspAT elevated (4); headache (4); hypokalemia (5). No Grade 4 TEAEs observed.

Clinical Response after 2 cycles (N=22)

PD = Progressive Disease; SD = Stable Disease.



OVARIAN 2
NSCLC 2
COLON 3
BREAST 1
PERITONEAL 1
ESOPHOGEAL 1

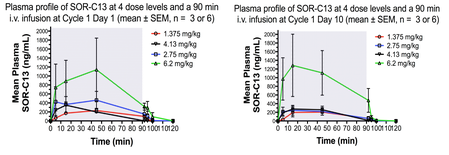
PANCREATIC 2
OVARIAN 2
COLON 1
UTERINE 1
GI STROMAL 1
PROSTATE 1
PAROTID 1
NASO-PHARYNGEAL 1
NSCLC 1
ADENOID CYSTIC 1

Particular interest:

- F, 63y, Stage IV, Adenoid cystic adenocarcinoma, tongue, PFS 54 wks (4.13 mg/kg, 90 min)—safe & well tolerated.
- M, 70y, Advanced Pancreatic adenocarcinoma, 27% reduction in tumor volume and 55% reduction in CA 19-9 (6.2 mg/kg, 90 min) after cycle 4. Increase in tumor & CA 19-9 when dose reduced due to non-drug related pneumonia (3.1 mg/kg)

Pharmacokinetics

No evidence of accumulation after multiple doses. At highest dose, $t_{1/2}$ ~ 2-3 min, C_{max} = 1150 ng/mL @ 45 min P.I., AUC = 1134 ng hr/mL

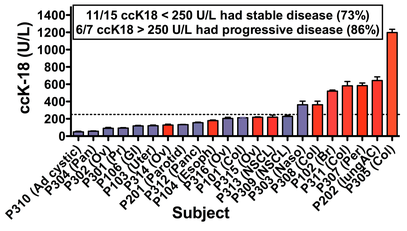


Infusion period shaded

Pharmacodynamics

Apoptosis biomarker ccK18 was monitored during treatment. Basal levels were associated with Stable Disease after Cycle 2.

Ranked basal ccK18 (U/L). Red = PD; Blue = SD



DISCUSSION

There were no drug-related SAEs observed in this study. Of TEAEs, Grade 3 elevated liver enzymes were observed in 2 patients and possibly linked to the drug, however, this continued for weeks after drug cessation. Uticaria was mitigated by pre-treatment with antihistamine. The appearance of hypokalemia is not understood at this time. An MTD was not reached but a safe range can be reported as 4.13 – 6.2 mg/kg. Stable disease was observed in 55% of subjects after 2 cycles of treatment.

PK data indicate rapid clearance from the blood compartment after cessation of the infusion. Long-term (>3d) accumulation of SOR-C13 at the tumor sites, observed in xenograft studies (4), appears to mitigate this.

Apoptosis biomarker ccK18 was <250 U/L for 73% of subjects who developed stable disease after 2 cycles while 86% of subjects with ccK18 > 250 U/L showed progressive disease (p = 0.02).

CONCLUSIONS

SOR-C13 was safe and well tolerated in subjects with advanced solid tumors of epithelial origin and demonstrates potential activity in these subjects. Further development of is warranted.

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