Targeting TRPV6 Oncochannel for the Treatment of Pancreatic Cancer: A Phase I Trial Experience.

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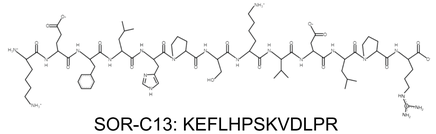
BACKGROUND

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 pancreatic cancer. 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. Results on the 2 patients with advanced pancreatic cancer are presented in this poster. Overall Phase I clinical trial results have been presented at AACR general meeting 2016.



SOR-C13: KEFLHPSKVDLPR

Methods

Clinical trial methods

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

TRPV6 mRNA Expression: Human TRPV6 and β-actin mRNA levels in tumor tissues were determined in 19 pancreatic biopsies (TissueScan Pancreatic Cancer cDNA Array, OriGene Technologies). For mRNA expression, two-step reverse-transcriptase quantitative PCR (RT-qPCR) using TRPV6 TaqMan® primers and probe sets (Life Technologies) were used. Determination of gene expression levels was done to the specifications outlined in the MIQE guidelines (4). A TRPV6 RNA standard curve was prepared for absolute quantification of the TRPV6 mRNA in each pancreatic biopsy.

RESULTS

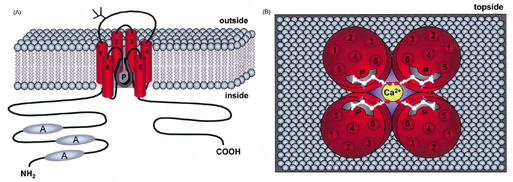
Pancreatic Cancer Patient Characteristics

Pt	Demographic/Type	Previous treatment
304	49 years, Black, Female Stage IV metastatic carcinoma	IMRT/Tomotherapy plus chemoradiation with Folfirinox, (ii) Carboplatin/gemcitabine/Tarceva (iii) Abraxane/Gemcitabine, (iv) IMRT/Tomotherapy;
312	70 years, White, Male Stage IV Metastatic carcinoma	(i) Folfirinox; (ii) gemcitabine and Abraxane; and, (iii) Xeloda

Pharmacokinetics

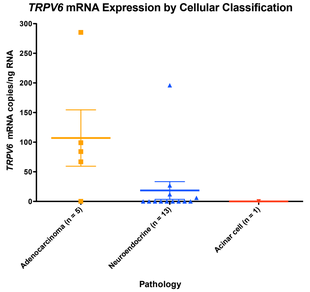
No evidence of accumulation after multiple doses. At highest dose, $t_{1/2}$ ~ 2-3 min, C_{max} = 1150 ng/mL @ 45 min P.I., AUC = 1134 ng hr/mL (means).

TRPV6 Channel



den Dekker, 2003

TRPV6 mRNA expression



Significant difference (p = 0.0304) in the mean of *TRPV6* mRNA copies/ng RNA in 5 adenocarcinoma (107 ± 48) and the 13 neuroendocrine (19 ± 15). The one acinar cell biopsy had 0 copies/ng of TRPV6.

TEAE in pancreatic patients

TEAE	Cohort	GRADE
Pt 304: alanine aminotransferase increased and aspartate aminotransferase increased, which persisted for >21 days. Possibly related to the study drug leading to patient's withdrawal after 4 cycles	4	3
Pt 312: Grade 3 pneumonia	6	3

Overall: Thirteen subjects (56.5%) with a total of 18 Grade 3 TEAEs. 5 drug-related grade 3 TEAEs (cohort) possibly related to the drug: urticaria (1); AlaAT & AspAT elevated (4); headache (4); hypokalemia (5). No Grade 4 TEAEs observed.

Drug-related Serious Adverse Events

None were observed

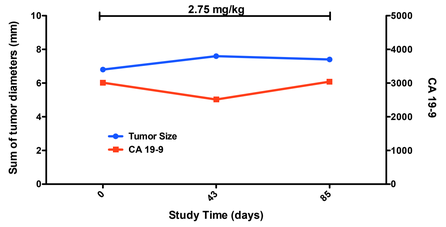
Overall Patient Safety

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

Cohort (Subject)	DLT	Dose/ Infusion	Resolu-tion	Drug Related ?
1 (101, 103)	Gr 2 Serum Ca^{+2} ⇓ asymptomatic	5.5 mg/kg/ 20min	4 - <24 h	Yes
2 (105)	Gr 2 Serum Ca^{+2} ⇓ asymptomatic	2.75 mg/kg/ 20min	4 - <24 h	Yes
4 (201)	Gr 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)	Gr 3 anemia	6.2 mg/ kg/90min		No
6 (316)	Gr 2 Atrial Fibrillation	6.2 mg/ kg/90min		No

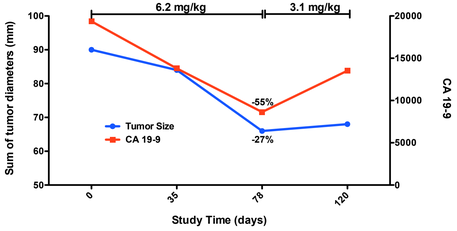
Pancreatic adenocarcinoma SOR-C13 tumor effect vs Biomarker levels

Patient 304- Tumour Size vs Time and Dose



Subject 304 had stable disease over 4 cycles (12 weeks) of SOR-C13 treatment at a dose of 2.75 mg/kg. The level of the CA 19-9 pancreatic tumor biomarker returned to baseline after an initial 16% reduction after 2 cycles of treatment.

Patient 312- Tumour Size vs Time and Dose



Subject 312 (KRAS mutation) had a 27% reduction in tumor size after 4 cycles of treatment at 6.2 mg/kg of SOR-C13. The reduction in tumor size corresponded with a 55% decrease in CA 19-9. A dose dependent effect was observed when the tumor started to grow after dose reduction to 3.1 mg/kg for cycle 3 because of pneumonia (not a drug related DLT).

DISCUSSION/CONCLUSION

No drug-related SAEs were observed in this study. Grade 3 elevated liver enzymes TEAEs were observed in 2 patients possibly linked to the drug. However, this continued for weeks after drug cessation. Urticaria was mitigated by pre-treatment with antihistamine, and hypocalcemia by calcium and vitamin D supplementation before each dosing. Occurrence of hypokalemia is not understood at this time. The safe range of the SOR-C13 is 4.13 – 6.2 mg/kg.

PK data indicate rapid clearance from the blood compartment after the infusion. Long-term (>3d) accumulation of SOR-C13 at the tumor sites, observed in xenograft studies (5), appears to mitigate this.

TRPV6 is highly expressed at the mRNA level in pancreatic adenocarcinomas.

Stable disease (SD) was observed in 55% of subjects after 2 cycles of treatment and in 2/2 of the pancreatic cancer patients, with SD lasting 12 weeks (subject 304) and 23 weeks (subject 312).

SOR-C13 treatment at 6.2 mg/kg reduced pancreatic tumor size, and correlated with a decrease in CA 19-9 in subject 312.

Further development of SOR-C13 in pancreatic cancer patients is warranted.

ACKNOWLEGEMENTS

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