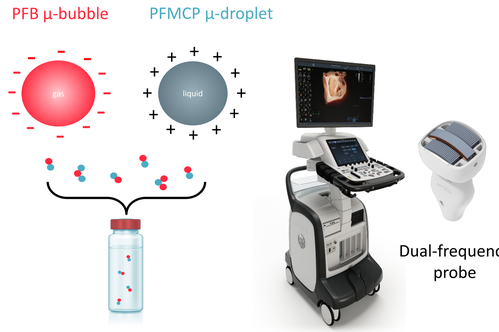
First-in-human study of acoustic cluster therapy (ACT) consisting of PS101 with chemotherapy and insonation in patients with liver metastases of colorectal cancer origin (NCT04021277)

Abstract 6221

Udai Banerji [1,2], Wing Yau [2], Mark O'Leary [2,1], Nigel Bush [1] Sumita Gurung [2], Amir Snapir [3], Melina Mühlenpfordt [3], Jeff Bamber [1,2] and Nina Tunariu [1,2]
[1] The Institute of Cancer Research [2] The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; [3] Exact Therapeutics AS, Oslo, Norway

Background

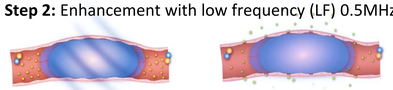


Step 1: Activation with high frequency (HF) 2-10MHz

Microclusters (PS101) are free floating in the capillary and HF ultrasound is applied for Activation.

Phase shift and ACT® bubble formation as a result of ultrasound activation.

Step 2: Enhancement with low frequency (LF) 0.5MHz



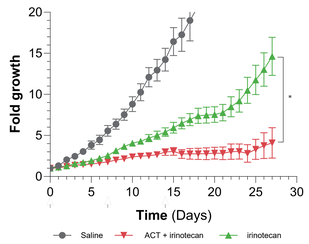
LF ultrasound is applied to the trapped ACT® bubble resulting in controlled oscillation.

Opening of vasculature, extravasation of co-administered drug resulting in Enhanced drug delivery.

Preclinical Experiments

Methods

- Human colorectal adenocarcinoma (SW620) xenografts were implanted subcutaneously into athymic nude mice
- Mice were enrolled into the study when tumour sizes reached ~90 mm^3
- The therapeutic efficacy of ACT with irinotecan (60 mg/kg i.p.) was investigated using three treatment sessions given on day 0, 7, and 14
- ACT treatment was performed with three back-to-back PS101 injections on each treatment day using 45 sec of high frequency ultrasound at 8 MHz at a mechanical index of 0.3 and low frequency exposure at 500 kHz with a mechanical index of 0.2



Results

- ACT induced a reduction in tumour volume from 14.6 (irinotecan), to 5.4 (ACT with irinotecan, p = 0.002)
- Median survival increased from 34 days (irinotecan) to 54 (ACT with irinotecan, p = 0.002)
- ACT with irinotecan induced an increase in the fraction of complete responders; from 7% to 26%

Conclusion

- ACT with irinotecan for the treatment of colorectal cancer showed a significant improvement in treatment response and survival

Methods

Study treatment:

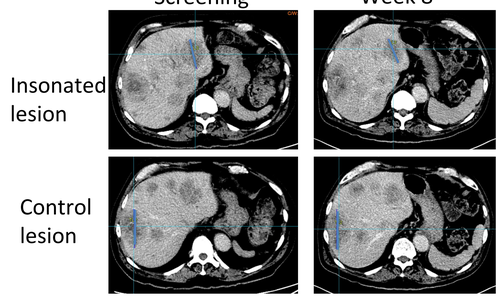
- up to 4 cycles of ACT treatment (3x IV bolus of PS101 + ultrasound) given concomitantly with FOLFOX (5-fluorouracil [5FU], leucovorin, oxaliplatin) or FOLFIRI (5-FU, leucovorin, irinotecan)
- Radiological evaluation of response based on Investigator and central assessment of the maximum diameter and volume of selected lesions at baseline and at 8 weeks from the start of treatment,
- % change in tumour diameters and volumes are the sum of measurements at 8 weeks minus baseline divided by baseline and multiplied by 100, calculated for each subject and averaged for the dose group.

Results

Population characteristics, treatment and toxicity

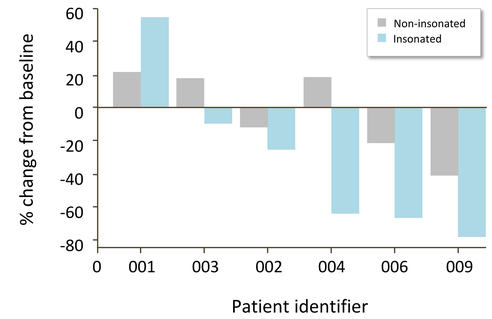
	20 ul/kg (n=3)	40 ul/kg (n = 5)	Overall (n = 8)
Age, years, mean (SD)	60 (17)	62 (5)	61 (10)
ECOG – 1, n (%)	3 (100%)	5 (100%)	8 (100%)
Cancer type – colorectal, n (%)	3 (100%)	5 (100%)	8 (100%)
Years since diagnosis of liver metastasis, mean (SD)	5.6 (2.1)	4.4 (3.1)	
Prior lines of chemotherapies, median	6	4	
Combined with FOLFOX/FOLFIRI, n/n	2/1	1/4	3/5
Dose limiting toxicity	0	0	0

Representative scans of patient receiving ACT



Results

Changes in sum of volumes of control and insonated lesion(s)*



Anti-tumour activity by independent central review
Volume data are average % change from baseline to 8 weeks (SD)

Conclusions

- Data from dose escalation do not show unexpected side effects from PS101 or ultrasound on its own or worsening the effects of chemotherapy
- In the six evaluable patients in the dose escalation cohort, compared to baseline there was a change in volume of -32% (-15% in diameter) in the insonated tumour Vs -3% (-1% in diameter) in the control, non-insonated tumour
- Preliminary data suggests that ACT is deliverable in an out-patient setting and that doses of PS101 are safe and hepatic metastasis can be visualized using microbubbles during chemotherapy
- Data from dose escalation provides proof of concept that insonated lesions show reduction in size of tumour greater than non-insonated lesions. This will be evaluated further in the ongoing expansion part of the ACTIVATE study
- The ACT technology is planned to be evaluated in a Phase 2 study in locally advanced pancreatic cancer - planned to start in 2024