Abstract #354060: Evaluation of SN-38 PK profile in patients with RAS wild-type metastatic colorectal cancer treated with a combination of SCO-101 and FOLFIRI.

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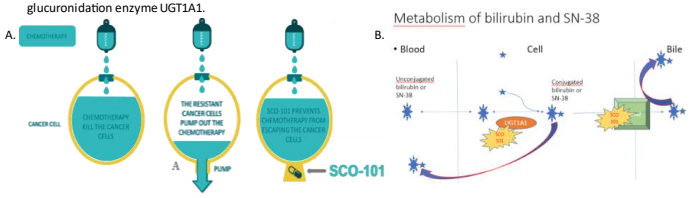
Background:

- The FOLFIRI regimen (5-fluorouracil, leucovorin and irinotecan) is a predominant treatment regimen for metastatic colorectal cancer. To optimize the benefit for the patients, it would be desirable to increase the efficacy of irinotecan by increasing the exposure of SN-38 (the active metabolite of irinotecan) to the cancer cells, while maintaining a good safety profile.
- The oral drug SCO-101, that is currently being developed by Scandion Oncology A/S, was tested in an early clinical trial (CORIST-trial, ClinicalTrials.gov identifier: NCT04247256). SCO-101 is an inhibitor of efflux pump ABCG2 and the glucuronidation enzyme UGT1A1.



Mechanisms of action: A: Inhibition of drug efflux pumps. **B: inhibition of UGT1A1**

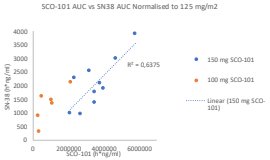
- The CORIST trial was set up to address the safety, tolerability, and efficacy of SCO101 given orally for 6 days followed by FOLFIRI at varying doses from day 5 to 7, in a biweekly schedule, in patients with metastatic colorectal cancer who have formerly been treated with FOLFIRI and afterwards progressed.
- The first part of the study was a dose-finding study, where the impact of SCO-101 on the pharmacokinetics (PK) of SN-38 was studied.

Methods:

- 12 patients from the dose-finding part of the CORIST study received 150 mg SCO-101 for 6 days a t 45 – 80% of the recommended dose of FOLFIRI.
- 6 patients received 100 mg SCO -101 for 6 days at 50% of the recommended dose of FOLFIRI.
- Blood for PK analysis was sampled from the patients at 1, 2, 4, 8, 24, 48, and 96 hours after treatment with FOLFIRI and SCO-101. The blood samples were analyzed for C_{max}, T½ and AUC (0-24h) of SCO-101, irinotecan and SN-38.

Results:

- Correlation between SCO-101 and SN -38 concentrations (SCO-101 AUC plasma level correlated with SN-38 AUC plasma level when normalized to 125 mg/m^2 dose).



Data from both RAS wild type and RAS mutated patients

SCO-101 changes the pharmacokinetic profile of SN-38

This brings therapy with SN-38 to new potentials by improving the safety/efficacy ratio

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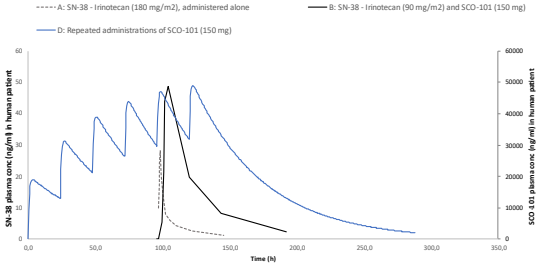
SCO-101 in combination with FOLFIRI (irinotecan) dramatically increases the exposure and halffe of SN-38, compared to irinotecan



Modelled PK data of the 12 patients who received 150 mg SCO -101

Addition of SCO-101:
- Increases the exposure of SN-38 with approximately 3-4-fold (AUC)
- Increases the half-life of SN-38 with approximately 2-fold

The dose finding part of the CORIST study included 6 patients with RAS wild-type tumors.

PK data of the 6 patients with RAS wt tumors normalized to 90 mg irinotecan dose	Irinotecan mg/m^2	T½ hours	Cmax ng/ml	AUC_0-24 h*ng/ml
SN-38 Standard	180 mg	11,7	40	385
SN-38 CORIST	90 mg	19	60	1415
Fold increase (CORIST vs Standard)	0,5	1,6	1,5	3,7

Conclusions:

SCO-101 in combination with FOLFIRI has demonstrated the ability to modulate the PK profile of SN-38 in mCRC patients with RAS wild-type tumors, by significantly increasing the halflife, the peak plasma concentration, and area under the curve of SN-38. The combined treatment was well tolerated, and the drug is now being tested for efficacy in the CORIST trial.

Future Directions for Research:

- Many new formulations of irinotecan/SN-38 have been developed in the recent years (nivyde, oncoral, sacizumab govitecan) that all modulate the plasma PK of SN-38 .
- SCO-101 modulate the PK of SN-38 thus potentially enhancing the therapeutical benefit by improved safety/efficacy ratio with irinotecan treatment.