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ONCORAL

ADVANCING CHEMOTHERAPY

CMO Carl Bjartmar

January 2021

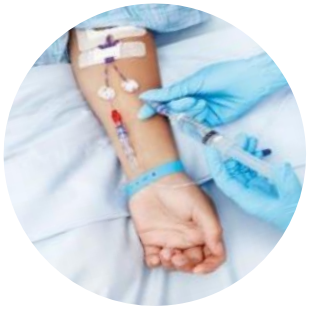
I.V. **IRINOTECAN** IS AN ESTABLISHED CHEMOTHERAPY

IRINOTECAN

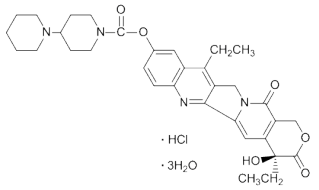
- **Established chemotherapy** with recognized anti-tumor effect (typically as high-dose IV infusion)
- **Approved for** metastatic colorectal and pancreatic cancer, and for gastric cancer in Japan (off-label use US/EU)
- **Demonstrated** clinical benefits and used in other solid cancer indications

IV BOLUS INFUSION

TODAY



Irinotecan Hydrochloride (IV)



ORAL, DAILY DOSING

TOMORROW

Oncoral is a novel oral formulation of irinotecan for daily dosing

Irinotecan (tablet formulation) solid composition with enteric coating

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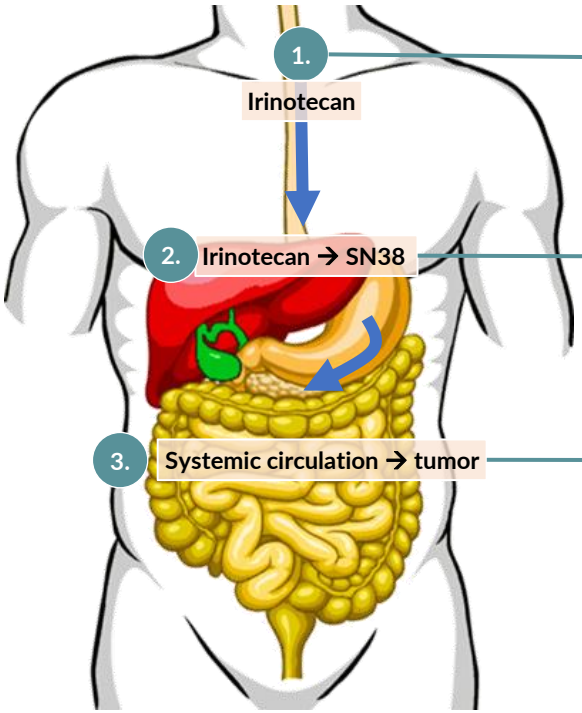
NEW ORAL **IRINOTECAN TABLET** FORMULATION



ONCORAL – mode of action

1. Oral administration of irinotecan in a tablet

2. Conversion of irinotecan in the liver to the active metabolite SN38, which is 100-1,000 more cytotoxic than irinotecan

3. SN38 reaches the tumor through systemic circulation and inhibits Topoisomerase 1 to exert its cytotoxic effect via prevention of DNA replication

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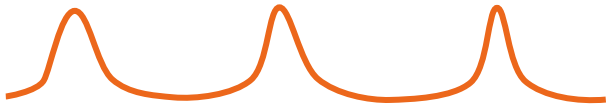
ORAL, DAILY DOSING: OPTIMIZING EFFICACY AND TOLERABILITY

	TODAY **TOLERABILITY TRADE-OFF** (IV BOLUS IRINOTECAN INFUSION) 	TOMORROW **OPTIMIZING EFFICACY AND TOLERABILITY** (POTENTIAL OF ORAL, DAILY DOSING) 
Efficacy	Sub-optimal treatment outcomes for many cancer types	Improved efficacy driven by favorable, dosing-related, pharmacokinetic and pharmacodynamic profile
Tolerability	Hematological toxicity common, 30% severe or life threatening. Gastrointestinal adverse events common	Improved tolerability, less severe side effects, and possibility to manage toxicity by flexible dosing
Convenience	Time spent on uncomfortable hospital IV administration	Reduced burden and increased comfort of home administration
Costs	Staff and equipment allocated to hospital IV administration	Cost-effective home dosing with less hospital visits

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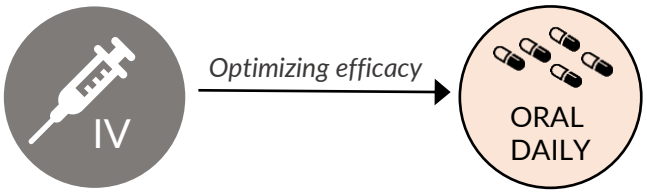
OPTIMIZING **EFFICACY**

OPTIMIZING EFFICACY BY DAILY DOSING

- After oral administration, 5-fold more irinotecan is converted to the active metabolite SN-38 compared to after IV infusion[1]
- Metronomic chemotherapy – frequent low dose administration – appears clinically beneficial in a broad range of tumors[2]
- Frequent dosing can optimize the chance that tumor cells are exposed to SN-38 during the susceptible S-phase of the cell cycle, maximizing anti-tumor effect



PROOF-OF-PRINCIPLE

- **Pre-clinical:** Metronomic dosing of irinotecan on xenografts in mice were more effective than the usual higher dose [3,4]
- **Clinical:** Positive clinical results with frequent dosing in pediatric and adult patients which progressed on standard therapy, incl. IV irinotecan[1,4,5]
- **Oncoral:** Phase 1 results indicated activity (stable disease) even in patients previously treated with IV irinotecan[1]
- **Daily chemotherapy** is in practice only possible with a tablet for home treatment

Refs: 1) Kumler et al 2018 2) Lien et al 2013 3) Houghton et al 1995 4) Furman et al 1999 5) Perez et al 2004

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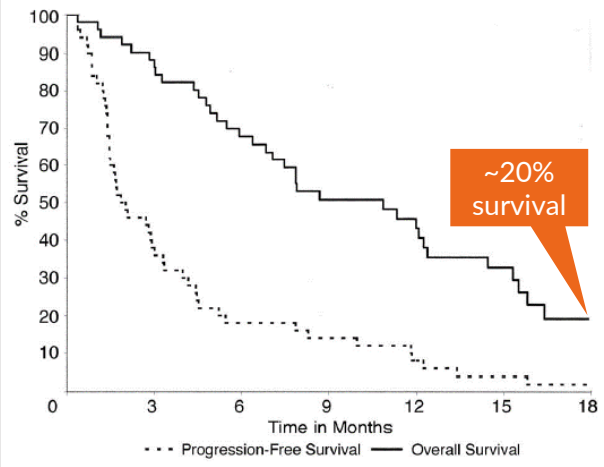
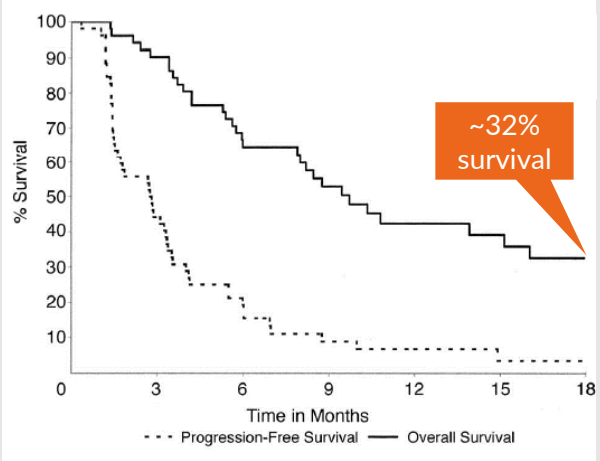
IMPROVED OVERALL SURVIVAL WITH MORE FREQUENT DOSING

STUDY COMPARING IRINOTECAN DOSING EVERY THIRD WEEK VS. WEEKLY DOSING[1]

Dosing every 3 weeks (IV)



Weekly dosing (IV)



Conclusions

Overall survival improved from 20% with irinotecan dosing every 3 weeks to 32% with weekly dosing

Study in patients with metastatic refractory breast cancer, N=103

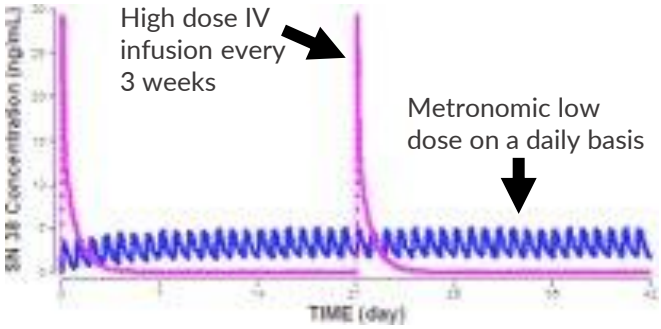
1) *Perez et al. J Clin Oncol 2004: Randomized Phase II Study of Two Irinotecan Schedules for Patients With Metastatic Breast Cancer Refractory to an Anthracycline, a Taxane, or Both*

OPTIMIZING **TOLERABILITY**

OPTIMIZING TOLERABILITY BY DAILY DOSING

- Bolus IV infusions of irinotecan are associated with toxicity
- Most patients experience gastrointestinal and haematological side effects, approximately 30% severe or life-threatening (grade 3 or 4) [1]
- Metronomic dosing may reduce peak related toxicity and complications compared to high-dose infusions
- Oral daily administration brings the opportunity to adjust dosing quickly in case of acute toxicity

Plasma levels (y-axis) of the active irinotecan metabolite SN38 (schematic)



PROOF-OF-PRINCIPLE

- **Pre-clinical:** Metronomic irinotecan dosing of xenografts in mice were less toxic than more intense schedules[2,3]
- **Clinical:** More frequent, low-dose, irinotecan regimens showed improved tolerability in several clinical studies[3,4]
- **Oncoral Phase 1 results[5]:**
  - ✓ Oncoral was well tolerated and safe with no unexpected side-effects
  - ✓ Hematological toxicities mild to moderate (grade 1 or 2)

Refs: 1) Camptosar prescribing information *2) Houghton et al 1995 3) Furman et al 1999 4) Perez et al 2004 5) Kumler et al 2018*

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CLINICAL DEVELOPMENT

MOVING ONCORAL INTO PHASE 2

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PHASE 1 – ENCOURAGING CLINICAL RESULTS

PHASE 1 SINGLE AGENT STUDY[1]

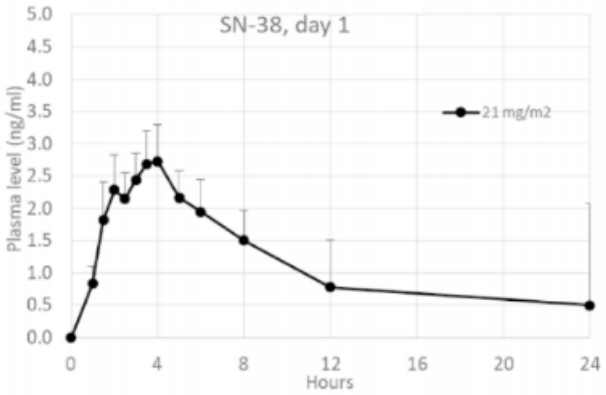
Study:

Dose escalating, open label, single center
25 patients with metastatic or unresectable solid tumors

Key results:

- Hematological toxicities were few and all mild (grade 1) to moderate (grade 2)
- Pharmaco-Kinetic (PK) data showed consistent daily exposures during treatment at days 1 and 14 with no drug accumulation
- The active metabolite, SN-38, interpatient variability was in the same range as for IV administration

Pharmacokinetic plasma profiles of SN-38
(mean values, n=15)



PHASE 1 COMBINATION STUDY[2]

Study:

Open label, single center
14 patients with metastatic or unresectable solid tumors

Key results:

The combination of Oncoral with another oral chemotherapy, demonstrated reassuring tolerability which could enable an all-oral chemotherapy combination

1) Kümler et al. Cancer Chemother Pharmacol. 2019 Jan;83(1):169-178, 2) Kümler et al. Cancer Chemother Pharmacol. 2019 Aug;84(2):441-446.

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PHASE 2 – STUDY IN PREPARATION

OVERALL OBJECTIVE OF PHASE 2 STUDY:

- Establish clinical proof-of-concept in metastatic gastric cancer
  - Potential orphan drug designation
  - Clinical guidelines support efficacy of irinotecan
  - Potential for subsequent label expansion to other solid tumor indications
- Generate compelling Phase 2 data package for further development

Type of study	Randomized controlled, multicentre, multinational study of: Oncoral + Standard of Care vs. Standard of Care
Endpoints	**Primary:** Progression Free Survival **Secondary:** Response rate, PK, safety and OS data in a follow up analysis
No. of patients	Approximately 100 patients
Study period	H2 2021 – 2024

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ONCORAL SCIENTIFIC ADVISORY BOARD

Prof Josep Tabernero, MD, PhD

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Prof Eric Van Cutsem, MD, PhD

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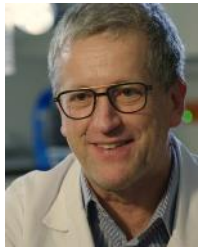
Co-founded ESMO GI/World Congress on GI Cancer. Serves/served on the board/committee of ESMO, ASCO, ENET, EORTC, ECCO, ESDO



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Chairs the NCCN committee for gastroesophageal cancers

Prof Jeff Evans, MD

Professor of Translational Cancer Research and Clinical Lead of the Institute of Cancer Sciences, University of Glasgow

Member of the NCRN Upper GI Cancer Pancreatic Cancer and Gastro-Oesophageal Cancer sub-groups

Joint view that Oncoral would be an important treatment option for cancer patients, especially in later disease stages

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