ICH E3 SYNOPSIS

Sponsor / Study Code
Sponsor-investigator: Dr. PhD Line Schmidt Tarpgaard, Department of Oncology, Odense University Hospital, Denmark
Study code: EudraCT 2019-002748-25

Active substance / Investigational product
Irinotecan, disulfiram and copper

Title of study
Repurposing disulfiram as treatment for irinotecan-resistant metastatic colorectal cancer – an investigator-initiated phase II trial

Investigators
Dr Line Schmidt Tarpgaard, Odense University Hospital, Denmark
Prof Per Pfeiffer, Odense University Hospital, Denmark

Study centres

- Odense University Hospital, Odense, Denmark

Publications
Dose-finding part presented at WCGIC 2021 (Line S. Tarpgaard et al.).
Phase II results presented as poster 405P at ESMO GI 2023 (Line S. Tarpgaard et al.).

Studied period (years)
Planned study period: October 2019 – October 2021 (inclusion) with additional follow-up.
Actual: First patient in October 2019; last patient last visit in 2023

Phase of development
Phase II, single-arm, open-label

Objectives

Primary objective
To assess the disease-control rate (DCR) at 18 weeks (complete response, partial response or stable disease ≥ 18 weeks) in patients with irinotecan-resistant metastatic colorectal cancer treated with irinotecan, disulfiram and copper.

Secondary objectives

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate (RR) according to RECIST v1.1
- Safety and tolerability (NCI CTCAE v5.0)
- Health-related quality of life (EORTC QLQ-C30)

- Exploratory association between tumour/blood biomarkers (cfDNA, CuET and others) and clinical outcome

Methodology

Investigator-initiated, non-randomised, single-arm phase II trial using Simon's two-stage Mini-max design. Patients received a 3-weekly regimen of irinotecan with continuous oral disulfiram and copper.

Treatment continued until radiological or clinical progression, unacceptable toxicity, withdrawal of consent, or investigator decision. Tumour assessments (CT scans) were performed every 9 weeks. Blood samples for biomarkers and quality of life questionnaires were collected at predefined timepoints (baseline, after cycle 3 and at end of treatment/progression).

Number of patients (planned and analysed)

- Planned: 15 patients in stage 1; if ≥1 patient achieved disease control at 18 weeks, an additional 10 patients in stage 2 (total 25).
- Actually included: 24 patients

All 24 patients received at least one cycle of study treatment and were included in the intention-to-treat (ITT) population and in the safety population.

Diagnosis and main inclusion criteria
Adult patients with non-resectable, metastatic colorectal adenocarcinoma and documented irinotecan-resistant disease.

Main inclusion criteria (summary)

- Age ≥ 18 years
- Histologically verified colorectal adenocarcinoma
- Non-resectable metastatic disease
- Measurable or non-measurable disease per RECIST v1.1
- WHO performance status 0–1 and life expectancy > 3 months
- Documented early progressive disease after ≥2 months of irinotecan (+/− fluoropyrimidines), on treatment or within 6 months after end of treatment
- Adequate haematological and organ function
- Willingness to abstain from alcohol during treatment and for 14 days after last disulfiram dose
- Written informed consent

Main exclusion criteria (summary)

- Known UGT1A1 polymorphism
- Known CNS metastases
- Relevant prior malignancy (with standard exceptions)
- Uncontrolled hypertension

- Significant comorbidity judged by investigator to interfere with the study
- Known allergy/intolerance to irinotecan, disulfiram or copper

Test treatment, dose and mode of administration

Irinotecan

- 250 mg/m² i.v., 30-minute infusion, every 3 weeks
- Individual dose escalation up to 300 and 350 mg/m² allowed in subsequent cycles if well tolerated; dose reductions in case of DLT.

Disulfiram and copper
After early dose-finding and schedule optimisation, the phase II regimen was:

- Disulfiram 400 mg/day plus copper 2 mg/day from day 1 to day 7
- Disulfiram 100–400 mg/day plus copper 2 mg/day from day 8 to day 14
- Treatment cycles repeated every 3 weeks

Disulfiram and copper were taken orally at home; compliance was monitored by patient interview and pill counts. Irinotecan was administered at the hospital.

No comparator arm or placebo was used.

Duration of treatment

Treatment cycles were repeated every 3 weeks until:

- Radiological or clinical disease progression,
- Unacceptable toxicity,
- Patient withdrawal of consent, or
- Investigator decision (including request for “chemo holiday” as per protocol).

Criteria for evaluation

Efficacy

- **Primary endpoint:** DCR at 18 weeks (CR + PR + SD ≥ 18 weeks)
- **Secondary endpoints:**
    - PFS (from inclusion to progression or death)
    - OS (from inclusion to death)
    - RR (CR + PR) per RECIST v1.1 in patients with measurable disease

Safety

- Adverse events graded according to NCI CTCAE v5.0
- Definition of DLTs pre-specified in protocol (haematologiske og non-haematologiske kriterier, inkl. Hy’s law for leverpåvirkning).

Quality of life / biomarkers

- EORTC QLQ-C30 at baseline, every third cycle and at end of treatment
- Serial blood samples (serum, plasma, full blood) for cfDNA and CuET and other biomarker analyses at baseline, after cycle 3 and at end of treatment/progression.

Statistical methods

Patients were analysed according to intention-to-treat. PFS and OS were estimated using the Kaplan–Meier method.

Sample size was based on **Simon's two-stage Mini-max design**:

- Null hypothesis: 18-week DCR ≤10 % (not clinically relevant).
- Alternative hypothesis: 18-week DCR = 30 %.
- One-sided $\alpha = 0.05$; $\beta = 0.20$ (80 % power).
- Stage 1: 15 patients. If 0/15 with disease control at 18 weeks → early termination.
- If ≥1/15 with disease control → additional 10 patients (total 25). If ≥5/25 with disease control → a DCR of 30 % could not be excluded.

Summary of results

Patient disposition and baseline characteristics

- Included / treated: 22 patients (ITT and safety populations)
- Median age: 67 years (range 48–78)
- Median number of prior systemic treatment lines: 4 (range 2–7)
- Median time from diagnosis of metastatic disease to inclusion: 43 months (range 12–93)

All patients had previously received irinotecan-containing therapy and had documented irinotecan-resistant disease.

Median number of cycles received: 3 (range 1–9). All patients discontinued treatment.

Efficacy

- **Disease-control rate at 18 weeks (primary endpoint):**
  - 3/24 patients (13 %) without progression at 18 weeks.
  - Predefined target of 30 % DCR was not met.
  -
- **Response rate:**
  - No RECIST complete or partial responses observed; best responses were stable disease or progression.
- **Progression-free survival:**
  - Median PFS: 2.3 months (95 % CI 1.9–3.8).
- **Overall survival:**
  - Median OS: 6.5 months (95 % CI 4.7–14.1).

Safety

All 22 patients were evaluable for safety.

- **Fatigue** was the most frequent AE:
    - 16/24 patients (15 grade 2, 1 grade 3).
- **Hypertension grade 3** was observed in 2 patients.
- No other grade 3–4 toxicities occurred frequently, and no treatment-related deaths were reported.

Overall, the regimen was **clinically manageable** with mainly fatigue and occasional hypertension as the dominant toxicities.

Quality of life / biomarkers

- EORTC QLQ-C30 was collected according to protocol; detailed analyses are planned and will be reported separately.
- Biomarker analyses (e.g. cfDNA, CuET) from serial blood samples are planned in collaboration with the Danish Cancer Society Research Center and will be reported in separate translational publications.

Conclusions

In heavily pretreated patients with irinotecan-resistant mCRC:

- The combination of irinotecan, disulfiram and copper was feasible and generally well tolerated, without unexpected safety signals.
- However, the predefined efficacy threshold was not reached: the 18-week disease-control rate was 13 %, and median PFS and OS remained limited.
- Irinotecan combined with disulfiram and copper cannot be recommended as a treatment option outside clinical trials in this setting.

No specific safety concerns warrant additional action or follow-up beyond routine pharmacovigilance