

A Phase I/II Study of Resminostat, an Oral Histone Deacetylase Inhibitor (HDACi), in Combination with FOLFIRI as Second-Line Treatment in KRAS Mutated Colorectal Cancer (CRC) patients - the SHORE Study



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Background

Resminostat

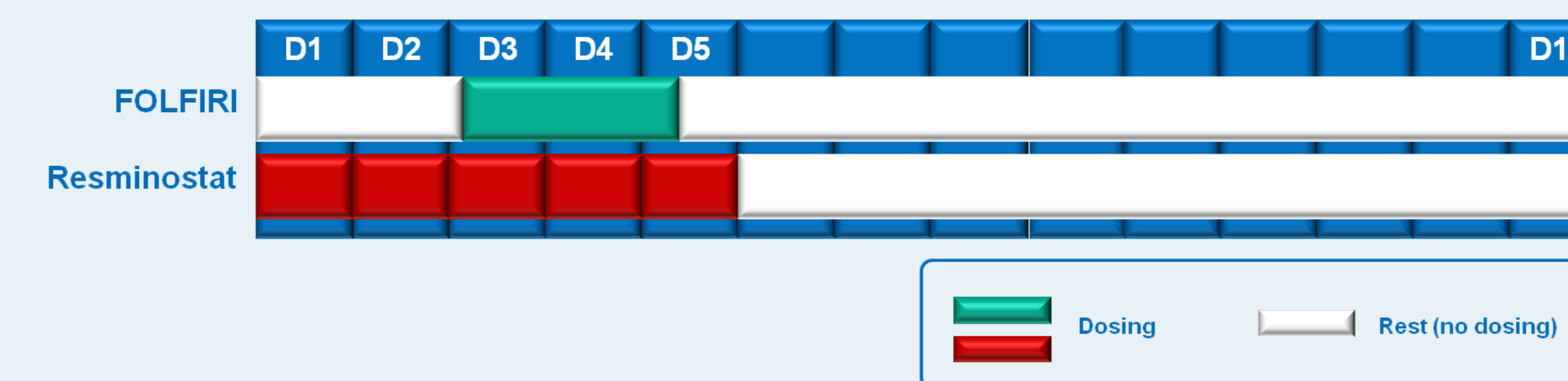
- Novel oral pan-HDAC inhibitor.
- In clinical development for several cancer indications: hepatocellular carcinoma, Hodgkin's lymphoma and colorectal carcinoma.
- Inhibition of HDAC enzymes at sub-micromolar concentrations.
- IC₅₀ values in cellular cancer models in the low micro-molar range.
- Anti-tumour activity in various *in vivo* cancer models, covering a broad range of oncological indications.
- Considerable additive or synergistic effects in combination with other chemotherapeutics *in vitro* and *in vivo*. Synergistic action on several colon cancer cell lines with 5-FU and the active metabolite of irinotecan (SN-38). Strong combination effects with SN-38 in a HCT116 *in vivo* model.
- Direct effect on the regulation of genes relevant to cancer therapy, e.g. thymidylate synthase (TYMS), being responsible for 5-FU therapy resistance.
- Favourable safety profile in a phase I study in cancer patients.
- Stabilization of a considerable number of cancer patients in the phase I study.

Resminostat in CRC

- Overexpression of class I HDAC enzymes is common in patients with colorectal cancer (CRC), this overexpression is linked to poor prognosis of such patients.
- Resminostat effectively inhibits class I HDACs, among them the cancer cell survival factor HDAC-2.
- About 40% of all CRC patients bear KRAS-mutated tumours, these patients are excluded from EGFR inhibitor therapy. Thus, the need for new treatment has arisen for CRC patients carrying mutated KRAS genes.
- The SHORE study addresses this medical need for patients with KRAS mutated CRC.

Study Design

- The SHORE study evaluates resminostat in combination with FOLFIRI in patients with KRAS mutated CRC in the second therapy line with regard to safety, tolerability and efficacy.
- Eligible patients: KRAS mutated CRC having failed a prior first-line therapy with 5-FU alone or in combination, no previous irinotecan therapy
- Resminostat is given once daily for 5 consecutive days, followed by 9 days rest ("5+9" scheme), resulting in treatment cycles of 14 days. On days 3 and 4 of each cycle, standard FOLFIRI regimen is administered:



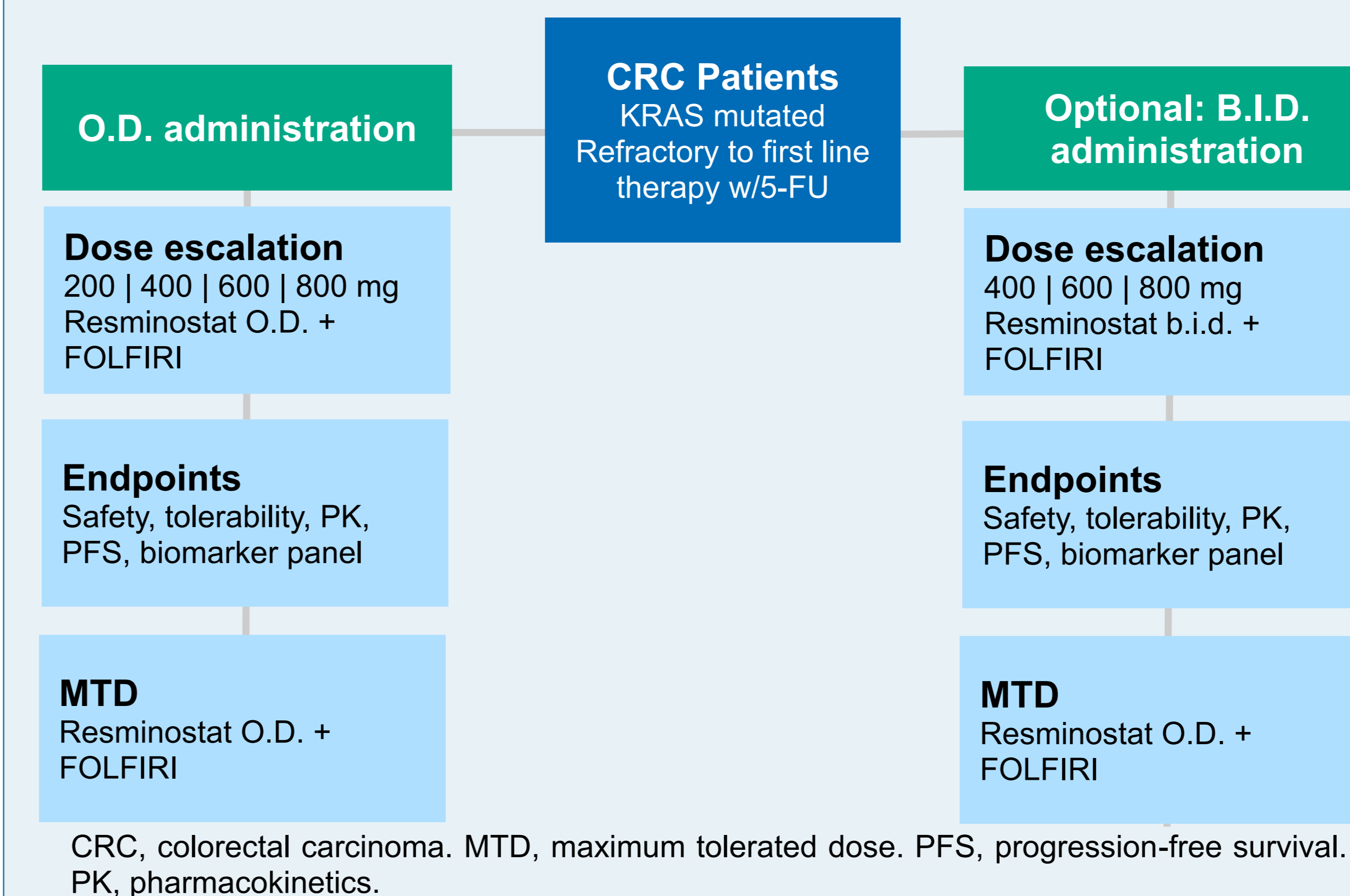
- Staging according to RECIST criteria is performed every eight weeks. Patients who benefit from the treatment can stay on treatment for an unlimited period.
- The SHORE study comprises two parts:
 - Phase I part for the determination of the maximum tolerated dose (MTD) of the resminostat/FOLFIRI combination
 - Phase II part (subsequent to phase I part)

Endpoint	Phase I Part	Phase II Part
Primary endpoint	Maximum tolerated dose (MTD) of resminostat in combination with FOLFIRI (safety, tolerability and pharmacokinetics)	Progression-free survival (PFS)
Secondary endpoints	PFS, PFS rate (PFSR) every 8 weeks, time to progression (TTP), number of objective responses (OR), overall survival (OS), duration of response (DOR), biomarkers (HDAC enzyme inhibition, histone acetylation, gene expression profiling, protein biomarkers)	PFSR every 8 weeks, TTP, OR, OS, DOR, safety and tolerability, pharmacokinetics, biomarkers (HDAC enzyme inhibition, histone acetylation, gene expression profiling, protein biomarkers)

Study Design

Phase I part

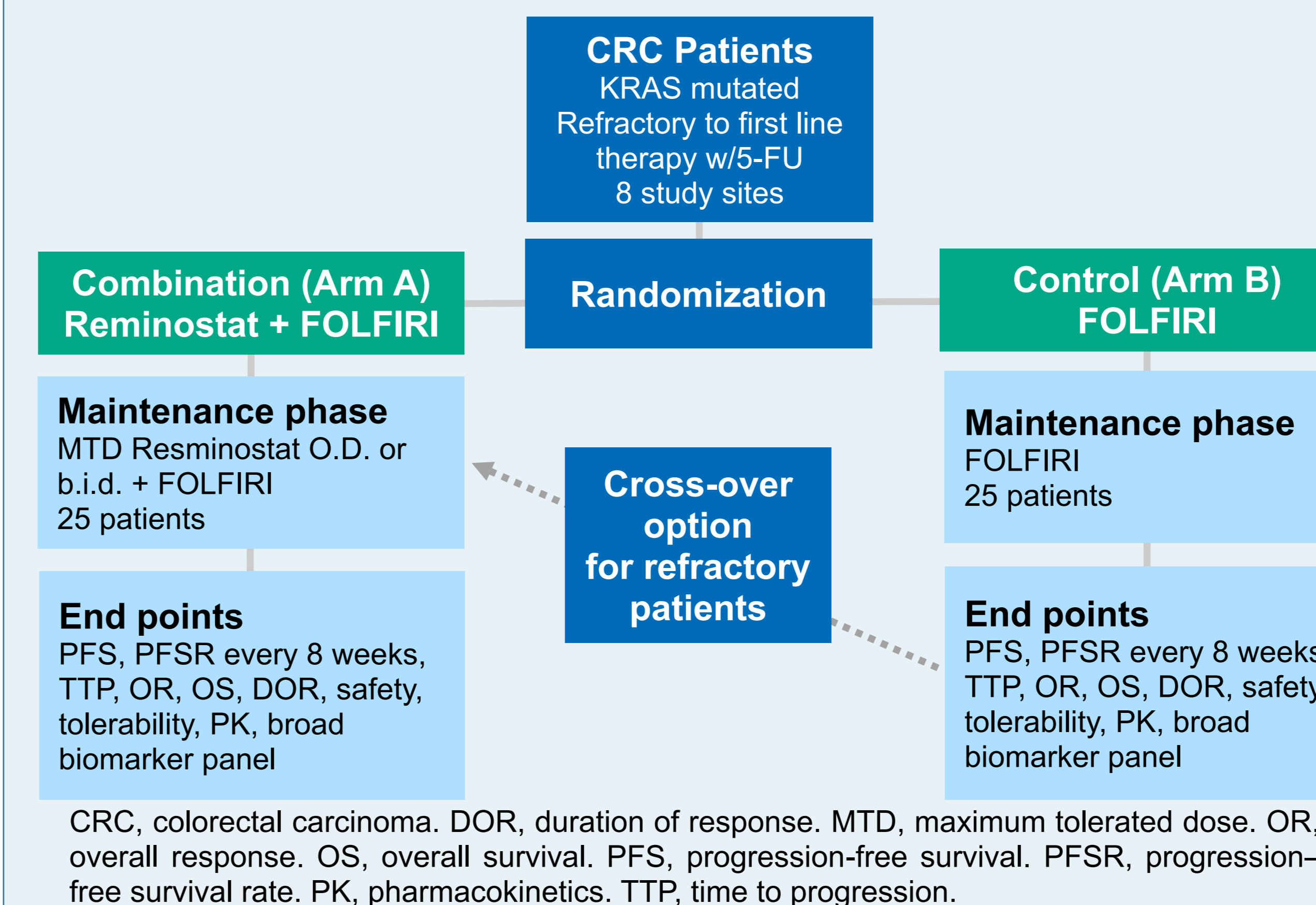
- 3+3 dose escalation
- 200 - 800 mg resminostat (O.D. administration) + FOLFIRI
- Option: B.I.D. administration for resminostat



CRC, colorectal carcinoma. MTD, maximum tolerated dose. PFS, progression-free survival. PK, pharmacokinetics.

Phase II part

- 2-arm, randomised
- Arm A: MTD Resminostat + FOLFIRI, 25 patients
- Arm B: FOLFIRI alone (control arm), 25 patients



CRC, colorectal carcinoma. DOR, duration of response. MTD, maximum tolerated dose. OR, overall response. OS, overall survival. PFS, progression-free survival. PFSR, progression-free survival rate. PK, pharmacokinetics. TTP, time to progression.

Study Status

- The phase I part (dose escalation) is currently in progress:

Dose level	Status
200 mg Resminostat (O.D.) + FOLFIRI	Finalised (3 patients enrolled)
400 mg Resminostat (O.D.) + FOLFIRI	In progress
600 mg Resminostat (O.D.) + FOLFIRI	Pending
800 mg Resminostat (O.D.) + FOLFIRI	Pending

- The combination of 200 mg Resminostat and FOLFIRI was well tolerated. No dose-limiting toxicity (DLT) was observed.
- Side effects on the first dose level were in line with expectations, including mainly gastrointestinal events. According to preliminary analysis, these effects can be attributed to the FOLFIRI regimen. A detailed analysis of the side effects is in progress.

Summary and Outlook

- Resminostat has the potential to considerably improve the treatment options for CRC patients, due to the novel and innovative epigenetic mode of action (HDAC inhibition).
- Due to its HDAC-inhibitory properties, resminostat is in particular promising as a combination partner for other chemotherapeutics. This combination approach is pursued in the SHORE study, using the combination with the established FOLFIRI regimen.
- The SHORE study addresses a high medical need in CRC, namely for patients with KRAS mutated tumours.
- The SHORE study is currently in the phase I part, the dose escalation is ongoing. The phase II part is in preparation, study sites are currently under evaluation.