

Clinical Phase II Development of Resminostat, a Novel HDAC Inhibitor

R. Jankowsky, A. Mais, S.W. Henning, B. Hauns, B. Hentsch
4SC AG, Am Klopferspitz 19a, 82152-Planegg-Martinsried, Germany



About Resminostat

- Novel oral pan-HDAC inhibitor
- IC₅₀ values in low micro-molar range in cellular cancer models
- Excellent anti-tumor activity in *in vivo* cancer models
- Additive or synergistic activity in combination with established chemotherapeutic agents in cancer models
- Direct effect on the regulation of genes relevant to cancer therapy, e.g. thymidilate synthetase (TYMS)

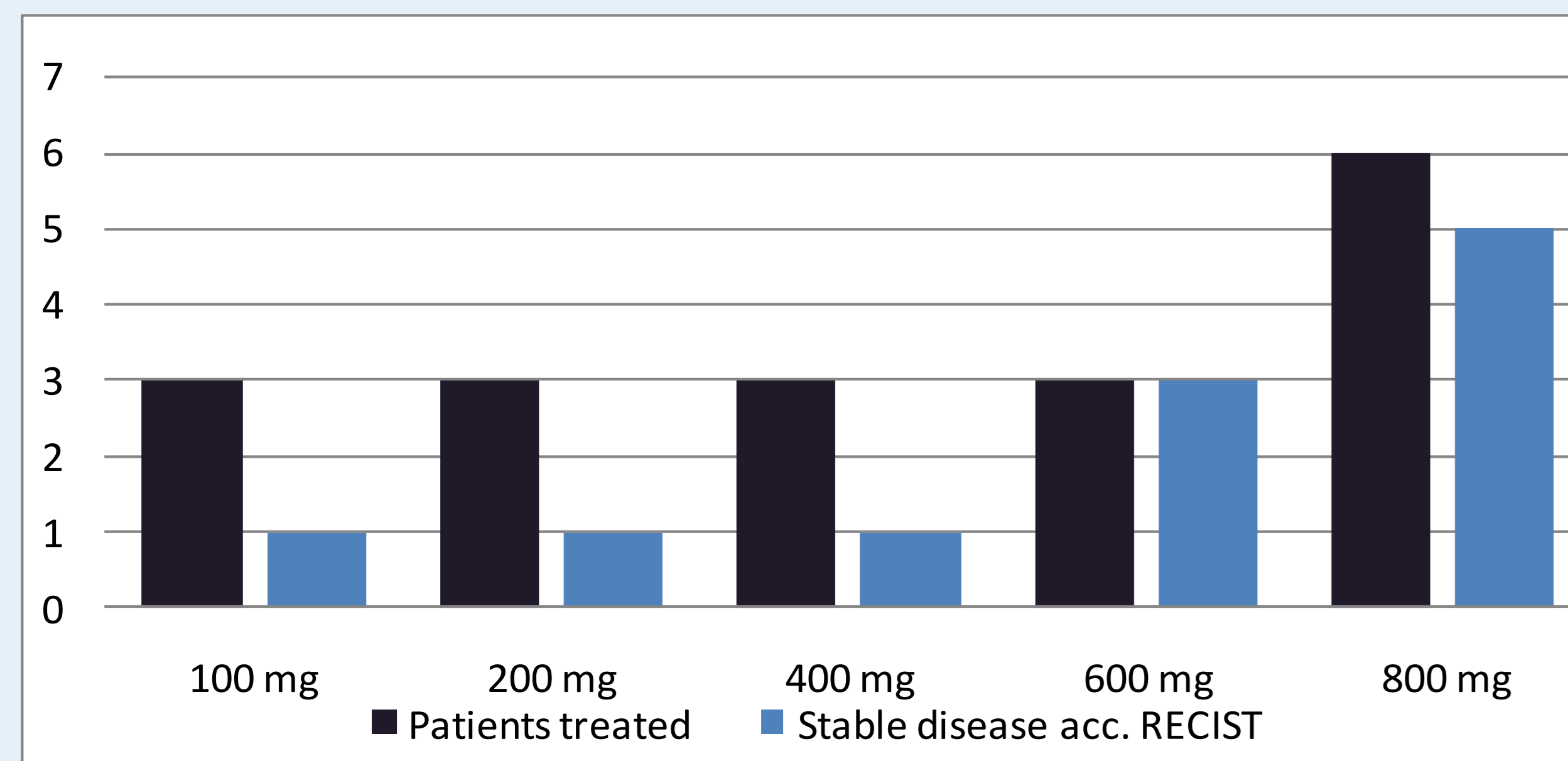
Phase I Study

STUDY DESIGN

- Open-label, inter-patient dose escalation study
- 5+9 days treatment schedule: 5 days of continuous once daily resminostat dosing, followed by 9 days rest period (14-day cycle)
- 19 patients treated with doses from 100 to 800 mg, heterogeneous population with advanced solid tumors

RESULTS

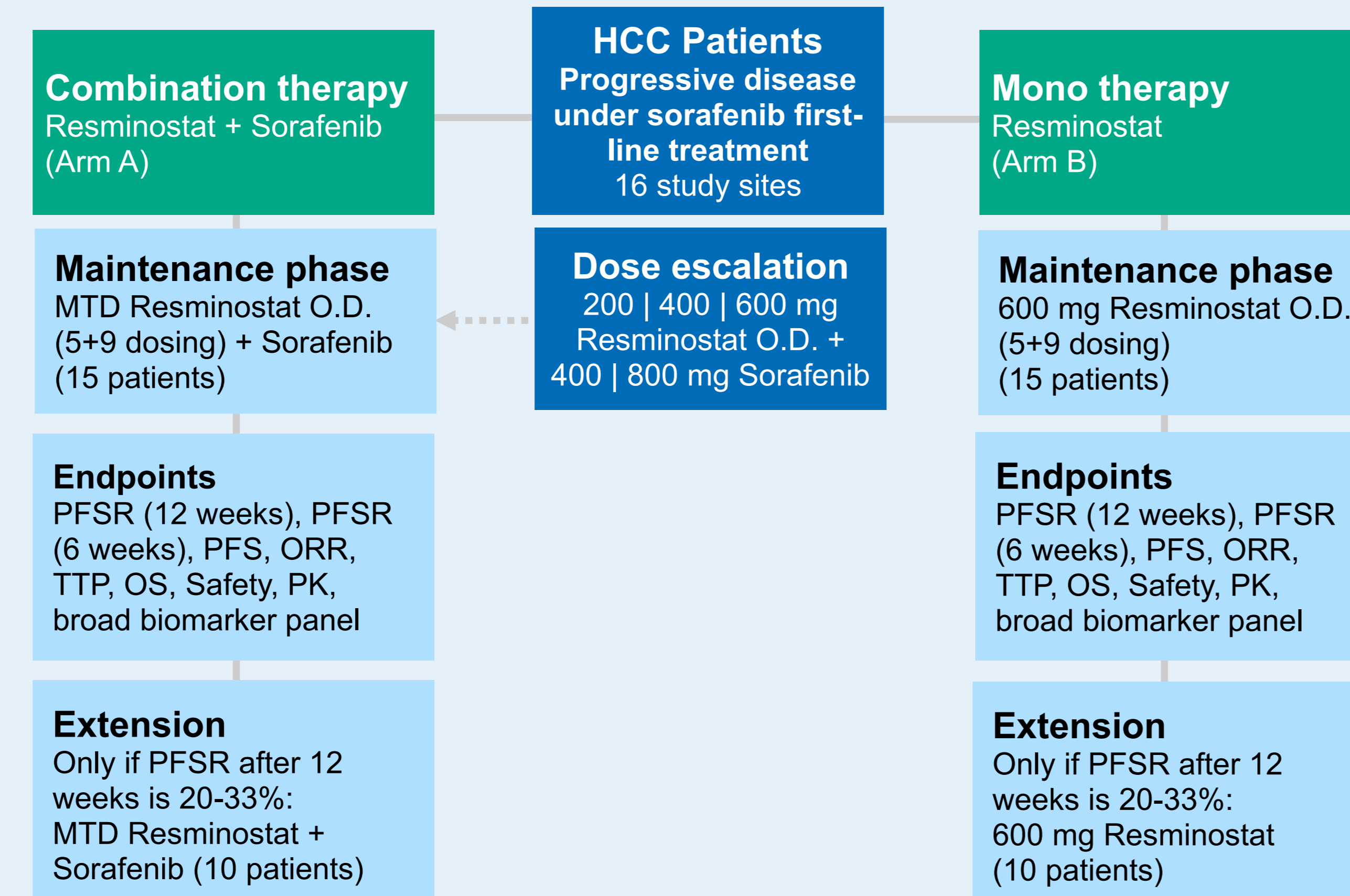
- Good bioavailability, high systemic exposure
- Term. plasma elimination half-life of about 3 hours, no accumulation
- Favourable safety profile: mainly mild to moderate gastrointestinal side effects and fatigue
- Stabilization of disease in >50% of patients treated:



- Biomarkers in patient plasma: consistent and dose dependent HDAC inhibition, histone acetylation and modulation of gene expression

Phase II Study in Hepatocellular Carcinoma The SHELTER Study

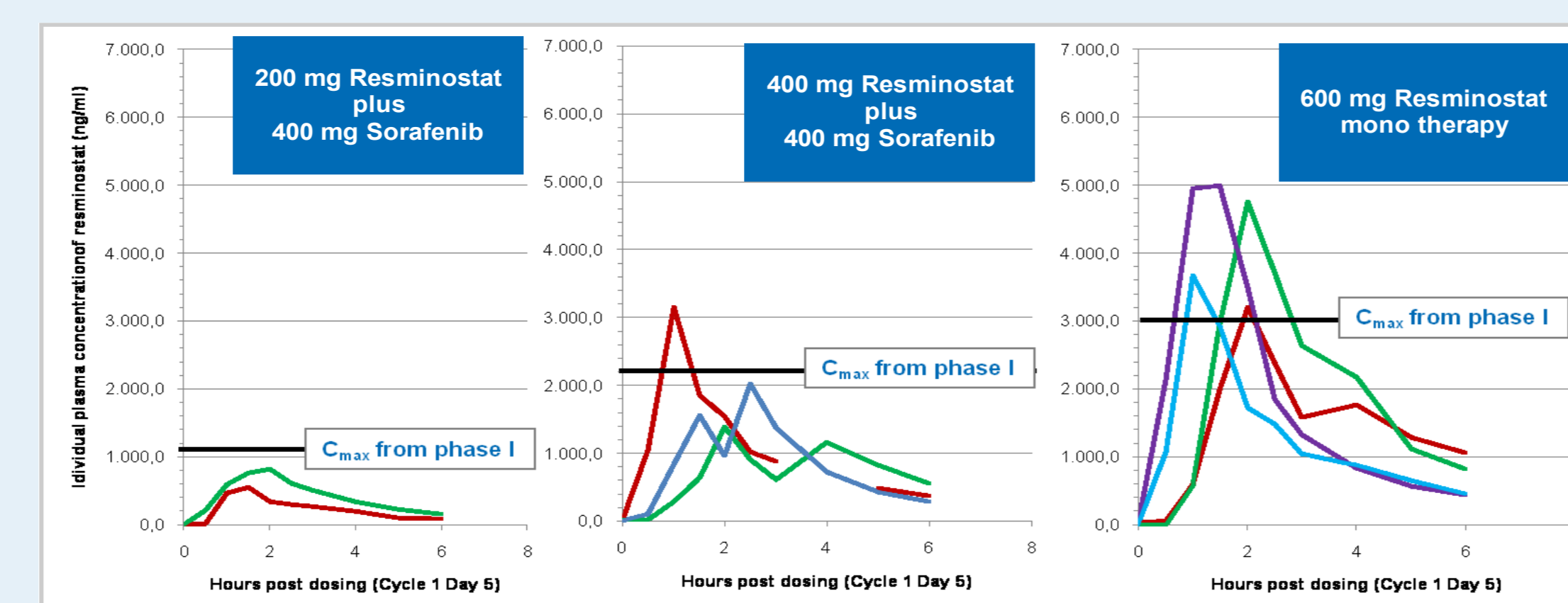
STUDY DESIGN



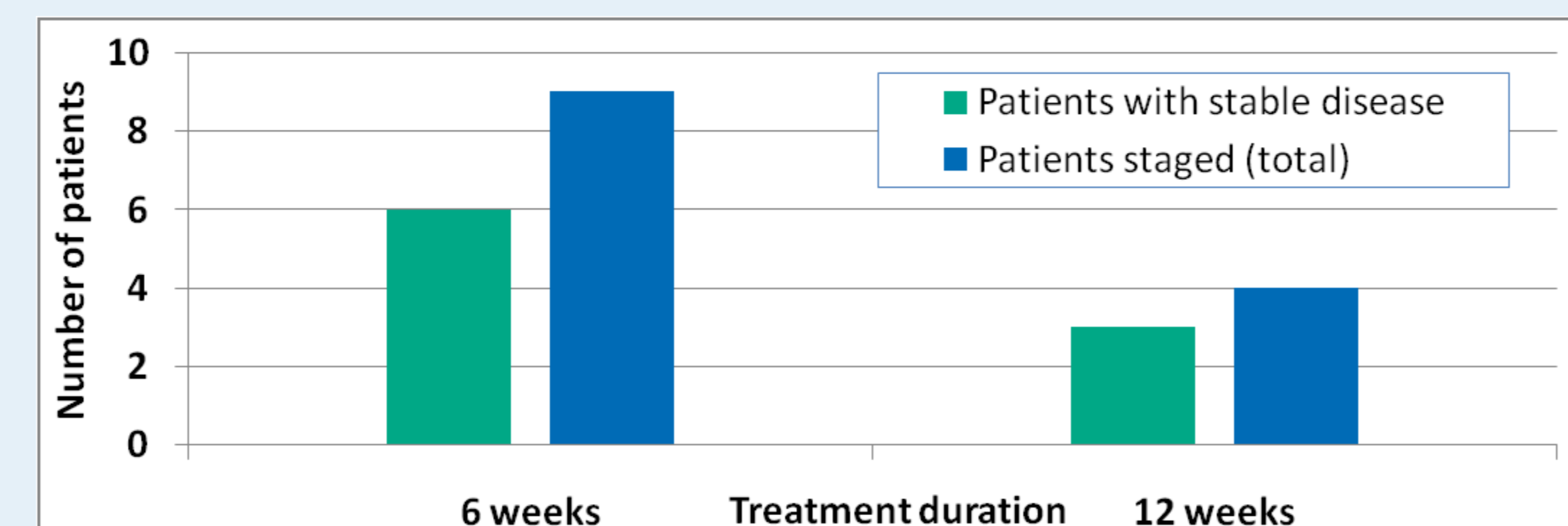
HCC, hepatocellular carcinoma. MTD, maximum tolerated dose. OS, overall survival. PFS, progression-free survival. PFSR, progression-free survival rate. PK, pharmacokinetics. TTP, time to progression. Study sites: actually recruiting 8 sites in Germany. Co-ordinating investigator Prof. Dr. Michael Bitzer, Tübingen. Additional sites are currently in approval process.

INITIAL RESULTS (first 9 patients)

- PK: Good oral bioavailability, dose proportionality of systemic resminostat exposure. No PK interference of resminostat exposure with sorafenib detected. c_{max} values comparable to phase I data:

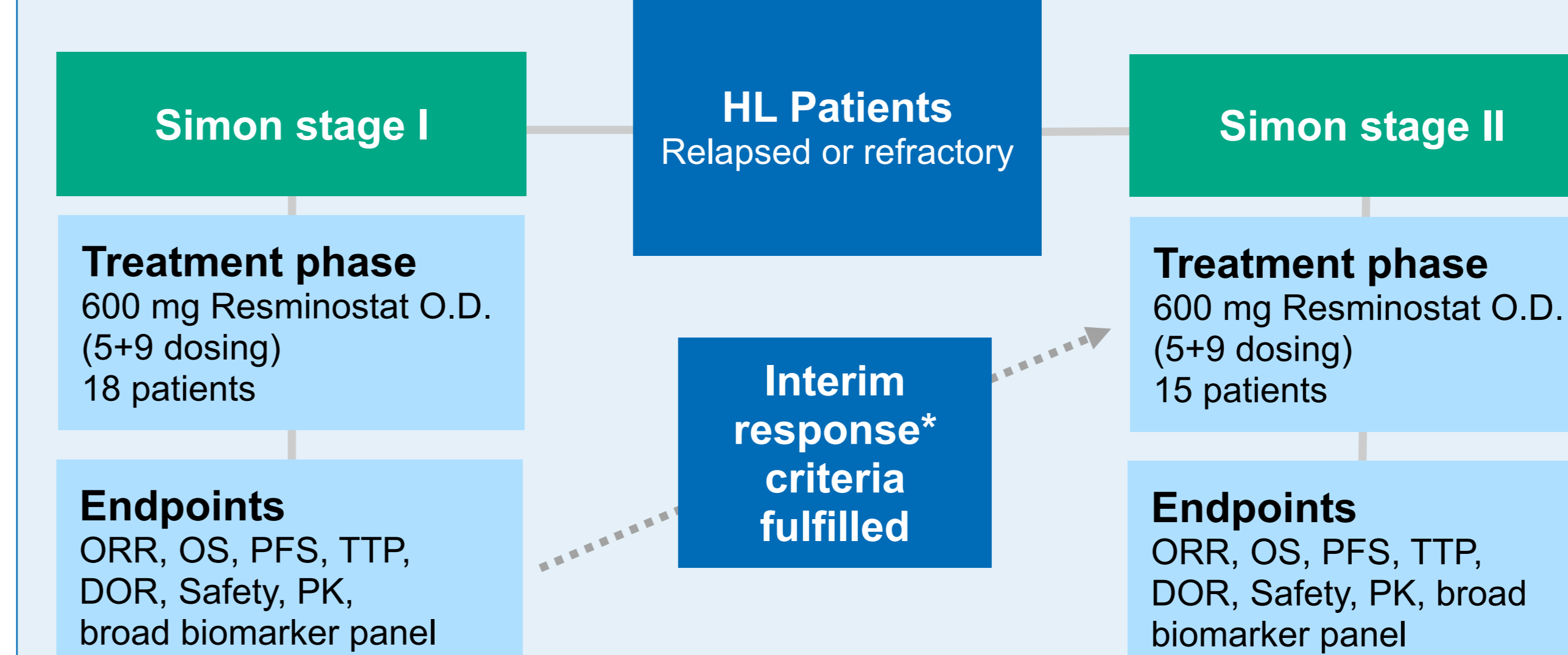


- Safety/adverse events: gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever (regardless of causality). Mild to moderate intensity.
- 6 out of 9 patients staged after 6 weeks (3 cycles) with stable disease (SD). 3 out of 4 patients staged after 12 weeks (6 cycles) with SD:



Phase II Study in Hodgkin's Lymphoma The SAPHIRE Study

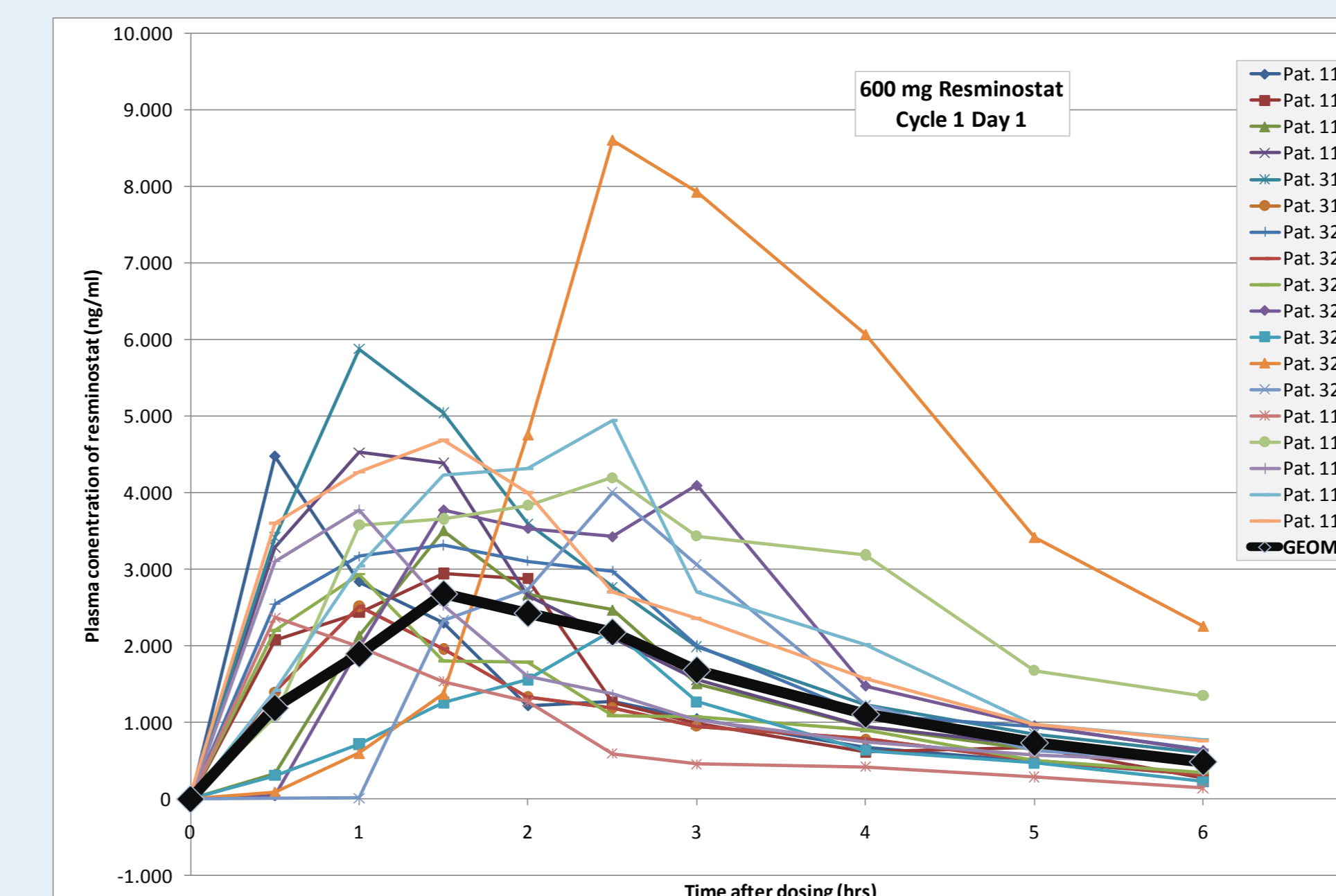
STUDY DESIGN



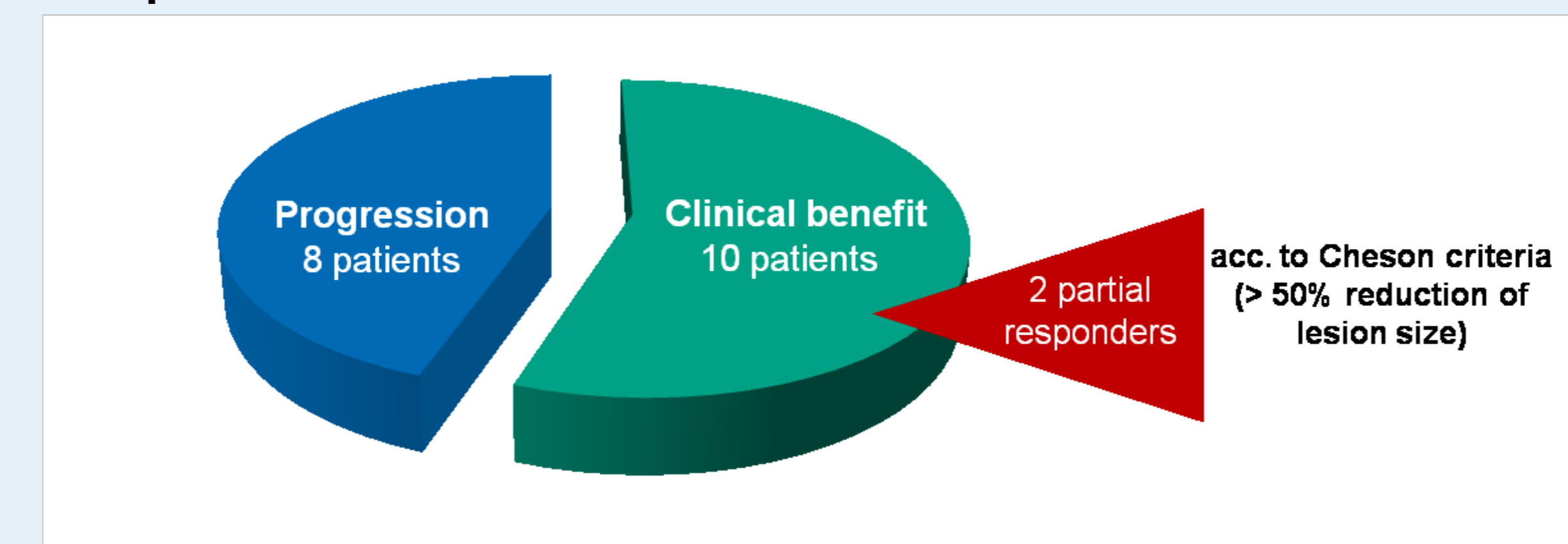
*Response criteria: CR, PR or PMR (functional metabolic improvement using PET > 25% change of sum of SUV_{max} acc. to EORTC) in ≥ 5 patients. HL, Hodgkin's Lymphoma. CR, complete response. ORR, overall response rate. OS, overall survival. PFS, progression-free survival. PFSR, progression-free survival rate. PK, pharmacokinetics. PR, partial response. PMR, partial metabolic response. TTP, time to progression. Study sites: 10 sites in Poland, Czech Republic and Romania. Co-ordinating investigator Prof. Dr. Jan Walewski, Warsaw.

INITIAL RESULTS (first 18 patients)

- PK: c_{max} values comparable to phase I data, similar to SHELTER data. PK characteristics of C1D1 comparable to C1D5. Good oral bioavailability, t_{max} between 1.6 hrs and 1.8 hrs:

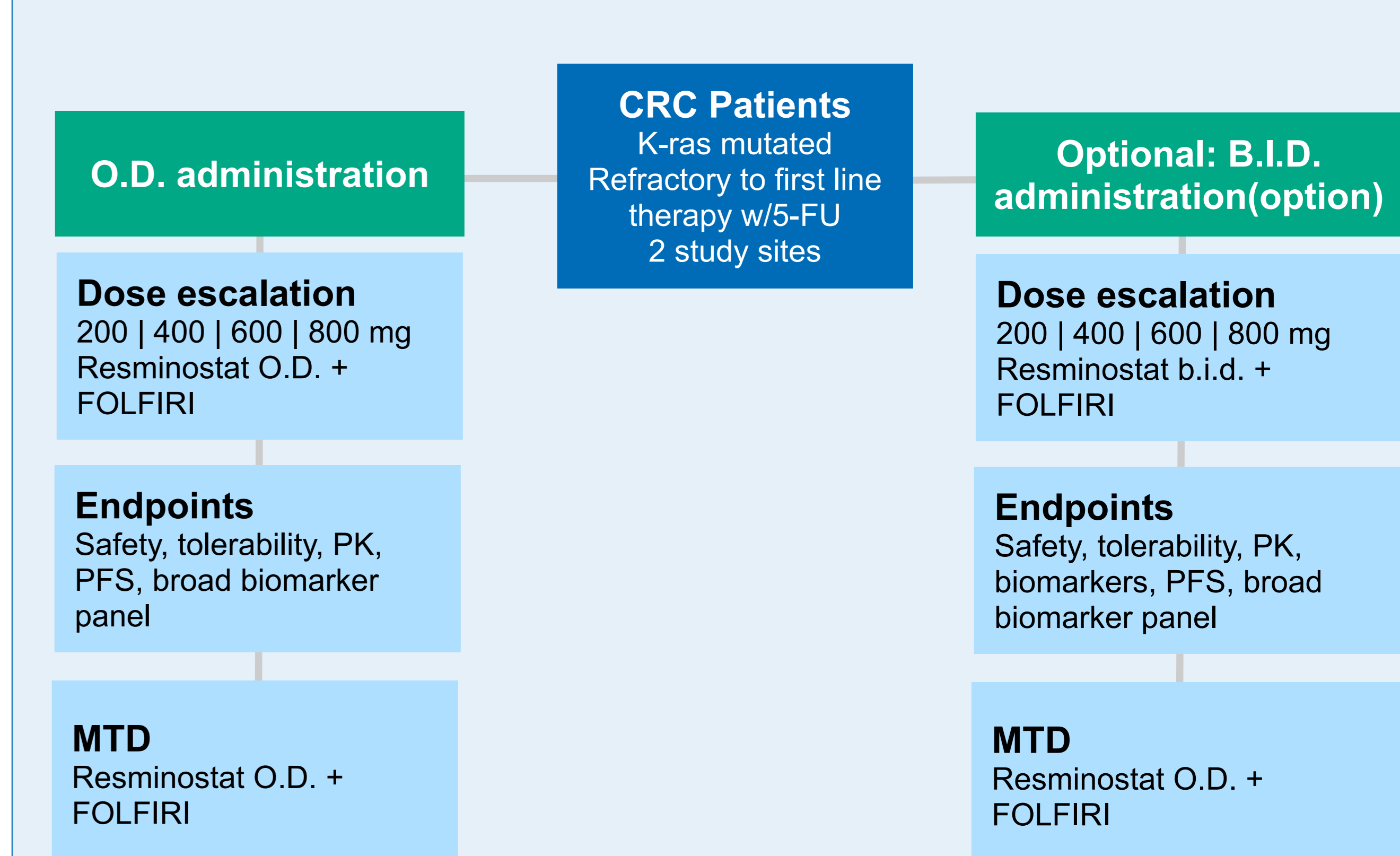


- Safety/adverse events: gastrointestinal toxicities (nausea, vomiting and stomach pain), mild to moderate. Some cases of thrombocytopenia and anemia, potentially associated with underlying disease.
- Efficacy: 10 out of 18 patients in Simon stage I showed clinical benefit. 2 patients had more than 50% reduction of lesion size.



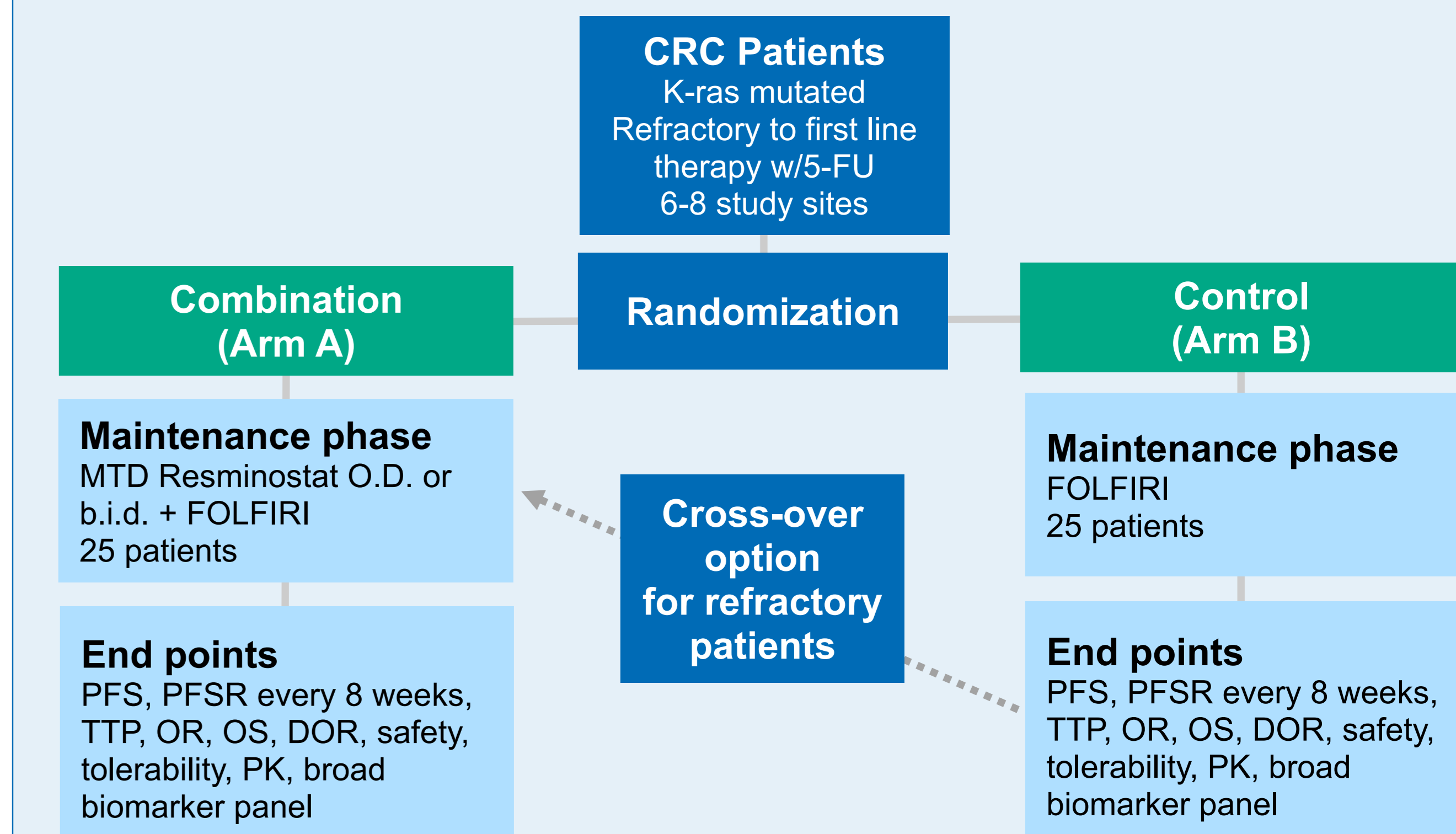
Phase II Study in Colorectal Carcinoma The SHORE Study

STUDY DESIGN – Dose Escalation Part



CRC, colorectal carcinoma. MTD, maximum tolerated dose. PFS, progression-free survival. PK, pharmacokinetics. Study sites: 2 sites in Germany. Co-ordinating investigator Dr. Stefan Bauer, Heidelberg.

STUDY DESIGN - Maintenance Part



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 sites: phase I sites plus further sites (currently being evaluated).

CURRENT STATUS

- Study is open for recruitment since October, 2010
- Patient screening has started

22nd EORTC-NCI-AACR symposium on "Molecular Targets and Cancer Therapeutics" Berlin, Germany, 16 - 19 November 2010 Poster #076