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Background

Resminostat (4SC-201) is a novel oral pan-HDAC inhibitor under clinical evaluation as mono or part of a combination therapy for solid and hematological malignancies. Here, we describe first data of a phase II study (the SHELTER study) to evaluate the safety, tolerability and therapeutic activity of resminostat in patients with HCC exhibiting progressive disease under sorafenib first-line sorafenib therapy.

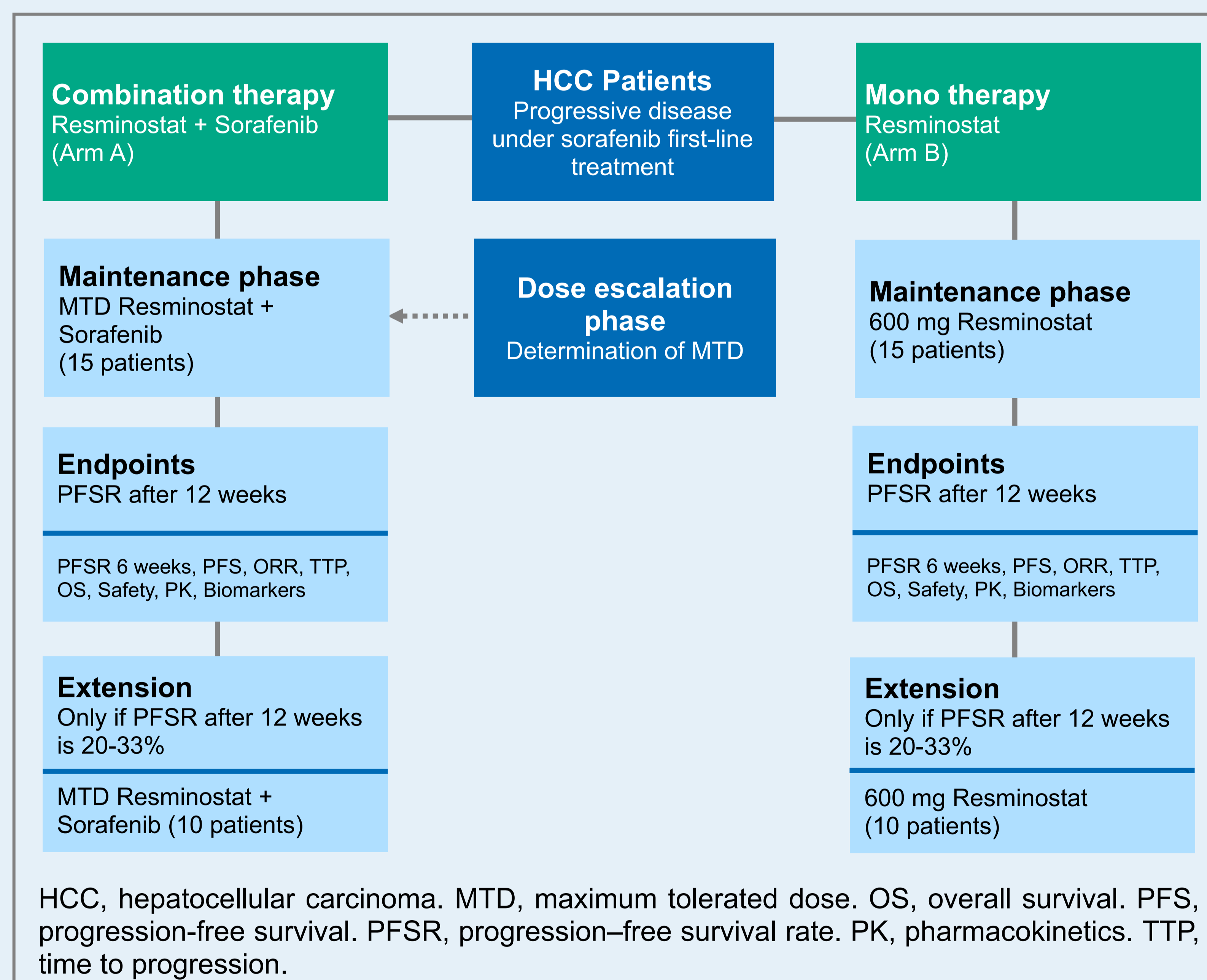
Methods

PATIENT CHARACTERISTICS

- Advanced HCC
- Progressive disease under sorafenib first-line treatment
- Child-Pugh Index A or B (maximum 7)
- Sorafenib-intolerant patients are excluded

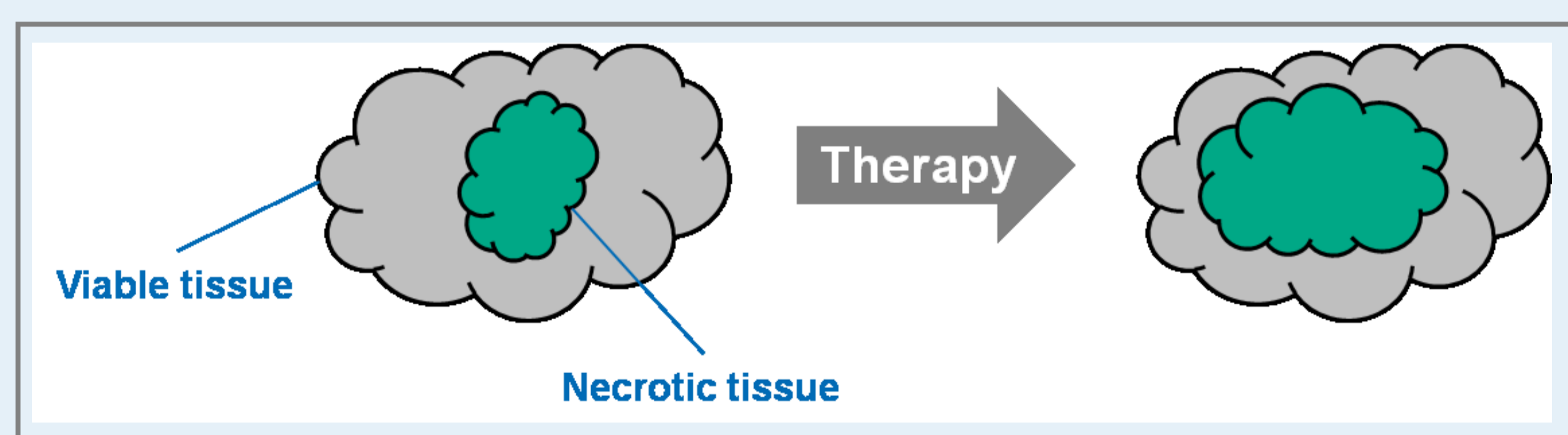
STUDY DESIGN

- Arm A: combination therapy of resminostat plus sorafenib with precedent dose escalation phase (3+3 design, up to 600 mg resminostat and up to 800 mg sorafenib).
- Arm B: mono therapy of resminostat (600 mg).
- 14-day cycles, consisting of 5 days with resminostat dosing, followed by 9 days rest. In combination therapy, sorafenib is given daily throughout the study.
- Primary endpoint: Progression-Free Survival Rate (PFSR) after 12 weeks (6 cycles), detected by MRT-based imaging. Secondary endpoints: PFSR 6 weeks, PFS, ORR, TTP, OS, Safety, PK, Biomarkers (see Figure).
- Number of patients: 15 per arm plus dose escalation phase for combination therapy, totalling an estimate of about 45 patients. 10 further patients may be added per arm in case the observed PFSR is between 20 and 33%.



IMAGING

- HCC lesions may become partly necrotic upon therapy, thus viable and necrotic areas have to be discriminated.
- In the SHELTER study, target lesions are therefore analyzed using contrast-enhanced MRT according to AASLD criteria suggested by Llovet et al. (Panel of Experts in HCC Design Clinical Trials; J Natl Cancer Inst 2008).



STUDY SITES

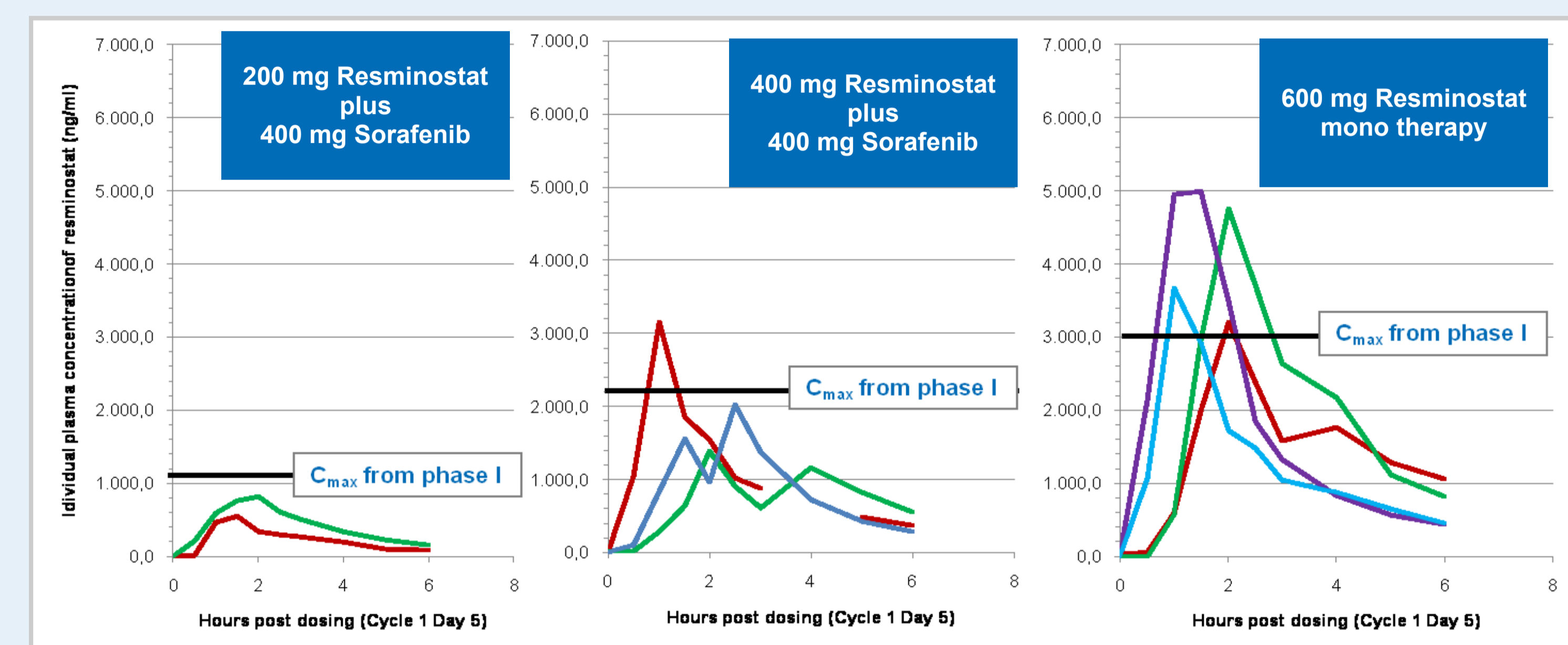
- Universitätsklinik Tübingen, Prof. M. Bitzer (Coordinating Investigator)
- Klinikum Rechts der Isar, München, Prof. M. Ebert
- Universitätsklinik Heidelberg, Dr. T. Ganten
- Universitätsklinik Mainz, Dr. M. Wörns
- Universitätsklinik Halle/S., Dr. M. Dollinger
- Universitätsklinik Essen, Profs. M.E. Scheulen, G. Gerken
- Onkologischer Schwerpunkt Berlin, Dr. A. Kirsch
- Universitätsklinikum Hamburg-Eppendorf, Dr. H. Wege (approval pending)

Results

- Data from first 9 patients are presented here.
- Status of dose escalation phase:
 - Dose level I, 200 mg Resminostat + 400 mg Sorafenib completed
 - Dose level II, 400 mg Resminostat + 400 mg Sorafenib completed
 - Dose level III, 600 mg Resminostat + 400 mg Sorafenib ongoing (data not shown)

INITIAL PHARMACOKINETICS DATA

- Good oral bioavailability.
- Dose proportionality of systemic resminostat exposure observed so far.
- C_{max} values comparable to phase I data.
- No PK interference of resminostat exposure with sorafenib detected.

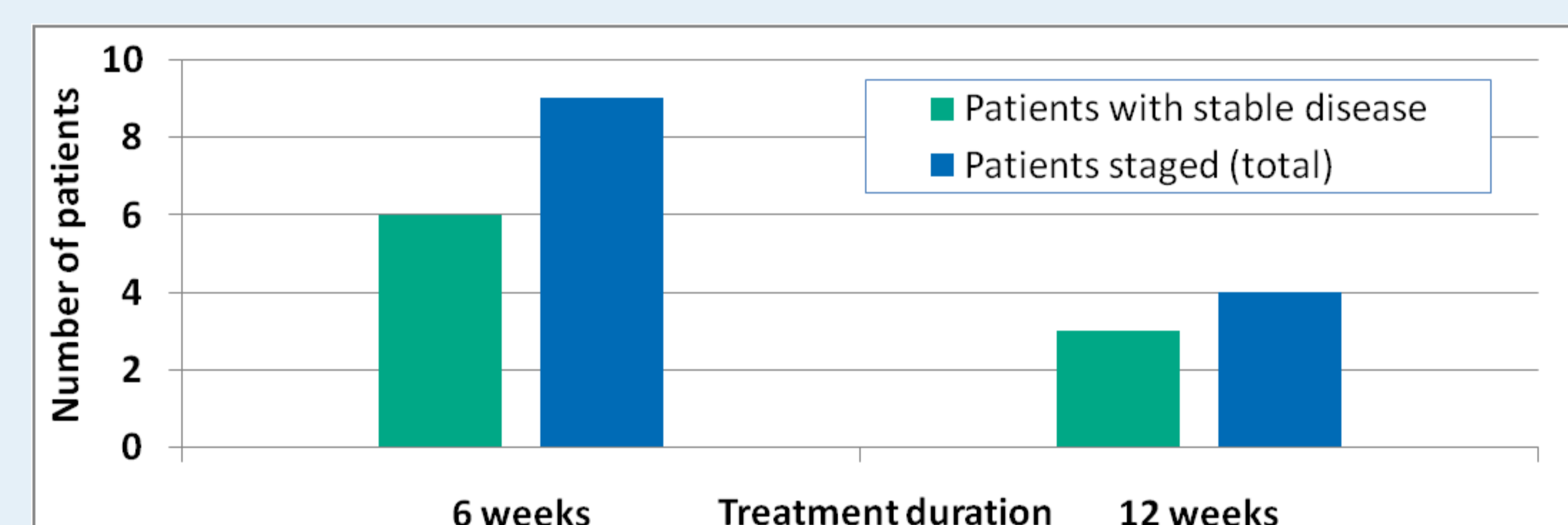


INITIAL SAFETY DATA

- Regardless of causality, adverse events evaluated so far included gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever.
- Mild to moderate intensity of adverse events reported.

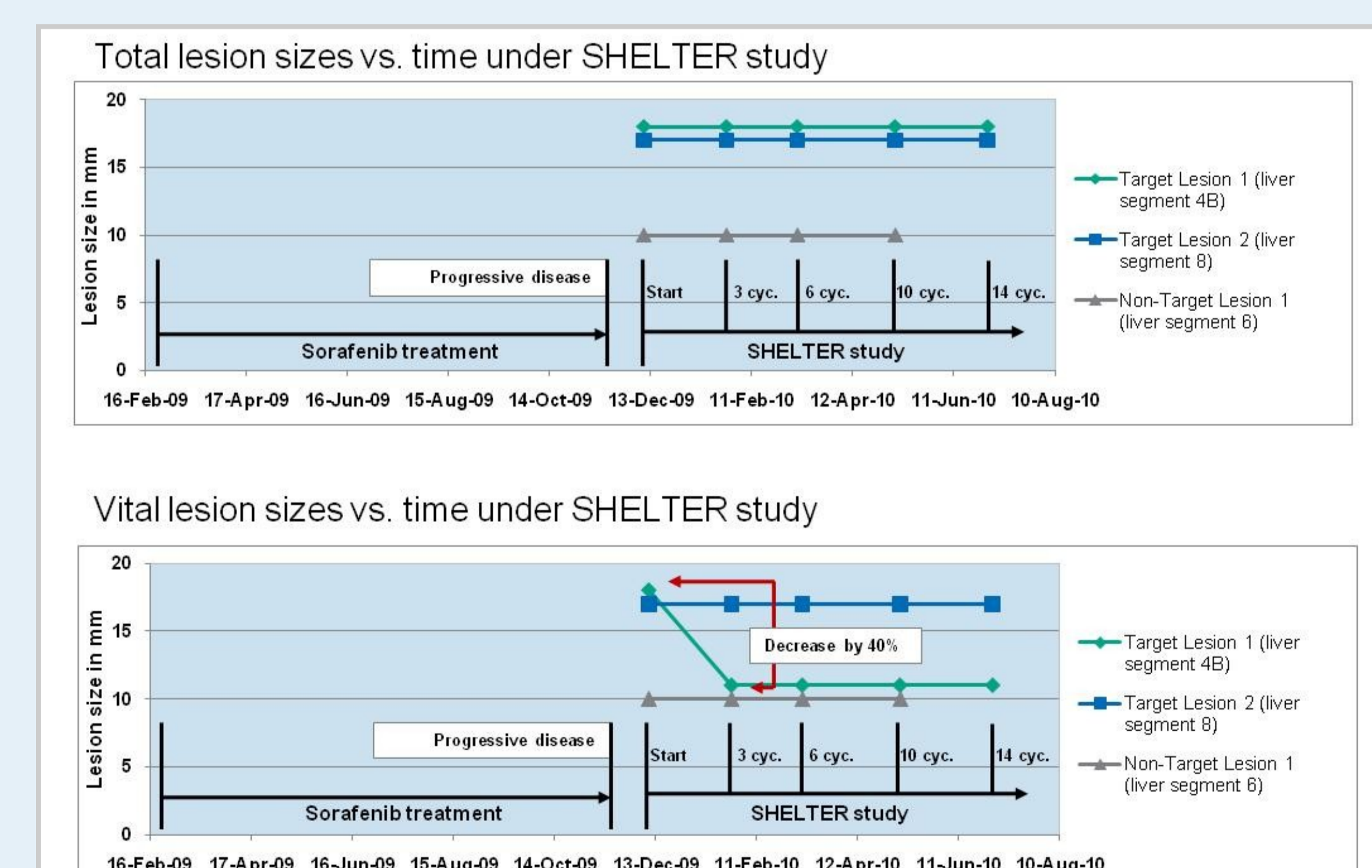
INITIAL DATA ON THERAPEUTIC ACTIVITY

- 6 out of 9 patients staged after 6 weeks (3 cycles) showed stable disease.
- 3 out of 4 patients staged after 12 weeks (6 cycles) showed stable disease.



CASE STUDY

- 64-year-old male patient, primary HCC diagnosis in 2008.
- Sorafenib treatment from Feb, 2009 to Nov, 2009. Progressive disease in Nov, 2009.
- Start in SHELTER study in Dec, 2009: 400 mg resminostat plus 400 mg sorafenib.
- Treatment duration with resminostat/sorafenib combination: 18 cycles (36 weeks).
- Patient was progression-free from treatment start until cycle 18, with 40% decrease in one target lesion (viable tissue). Progression observed after 18 cycles first.



Conclusions

- Preliminary data from the SHELTER study in HCC patients show a good safety and tolerability profile of resminostat, either in mono therapy or in combination therapy with sorafenib.
- The systemic exposure of resminostat is favourable and comparable to phase I data. No pharmacokinetic interaction with sorafenib was observed so far.
- A considerable number of patients showed stable disease after 3 or 6 treatment cycles. In certain cases, patients remained stable for more than 12 weeks treatment.
- Resminostat could open an option for the urgently needed improvement of the second line HCC therapy. In particular, the introduction of an epigenetic mode of action appears to be promising.
- For further information, log on to www.hcc-perspektive.de