

Clinical Update of the SHELTER Study:

A Phase I/II Trial of HDAC Inhibitor Resminostat in Patients with Sorafenib-Resistant Hepatocellular Carcinoma (HCC)



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Background

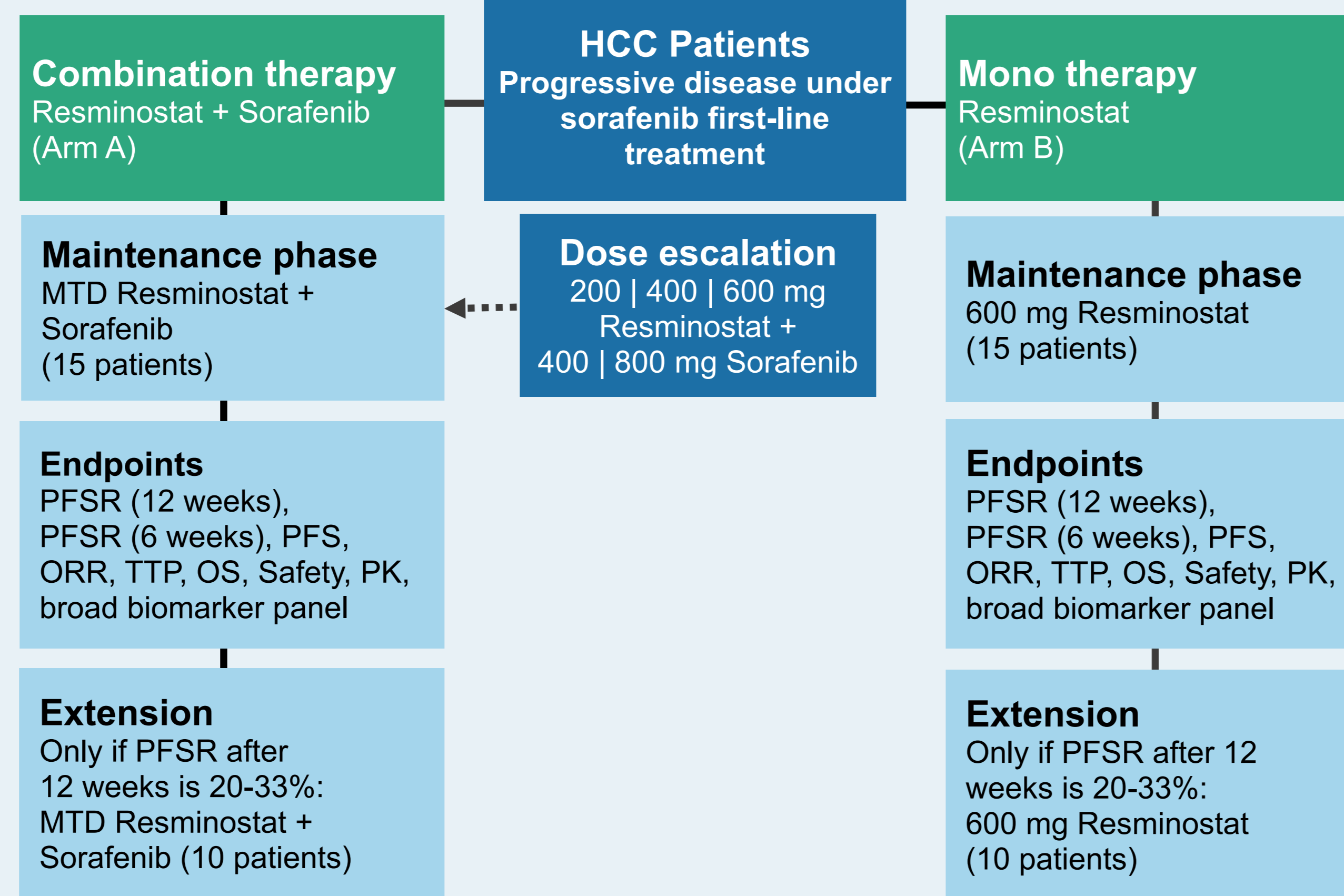
- Resminostat (4SC-201) is a novel oral pan-HDAC inhibitor in clinical development for several cancer indications.
- IC₅₀ values in cellular cancer models are in the low micro-molar range.
- There is broad anti-tumour activity in *in vivo* cancer models.
- Additive or synergistic activity in combination with established chemotherapeutic agents was proven in cancer models.
- Resminostat has a direct effect on the regulation of genes relevant to cancer therapy, e.g. thymidylate synthase (TYMS).
- A phase I study in cancer patients revealed a favourable safety profile. A remarkable number of patients could be stabilised under resminostat treatment.
- The SHELTER study evaluates safety, tolerability and efficacy in HCC patients exhibiting progressive disease under sorafenib first-line therapy.

Methods

- Sorafenib-refractory patients with radiologically proven progress under sorafenib pre-treatment are included, suffering from advanced HCC BCLC stages B or C.
- Resminostat is given once daily for 5 consecutive days, followed by 9 days rest ("5+9" scheme), resulting in treatment cycles of 14 days.
- Multi-center open-label trial, two-arm parallel group design:
 - Arm A:** resminostat in combination with sorafenib (given twice daily throughout the treatment) at the maximum tolerated dose (MTD). A precedent dose escalation phase for the determination of the MTD with 200 mg | 400 mg | 600 mg resminostat plus 400 mg | 800 mg sorafenib is conducted.
 - Arm B:** once-daily oral administration of 600 mg resminostat.
- The main study period is 12 weeks. Patients who benefit from the treatment can stay on treatment for an unlimited period.

Methods

- Radiological imaging is performed after 6 and 12 weeks treatment, using dynamic contrast-enhanced magnetic resonance tomography (DCE-MRT). Analysis of the DCE-MRT images is performed according to AASLD/EASL criteria for the differentiation of vital and total lesion size.
- Primary endpoint: progression-free survival rate at 12 weeks.
- Secondary endpoints: PFSR at 6 weeks, PFS, safety, tolerability, overall response rate, time to progression, overall survival, assessment of pharmacokinetics and biomarkers.
- Study sites: 8 sites in Germany and 7 sites in Italy.



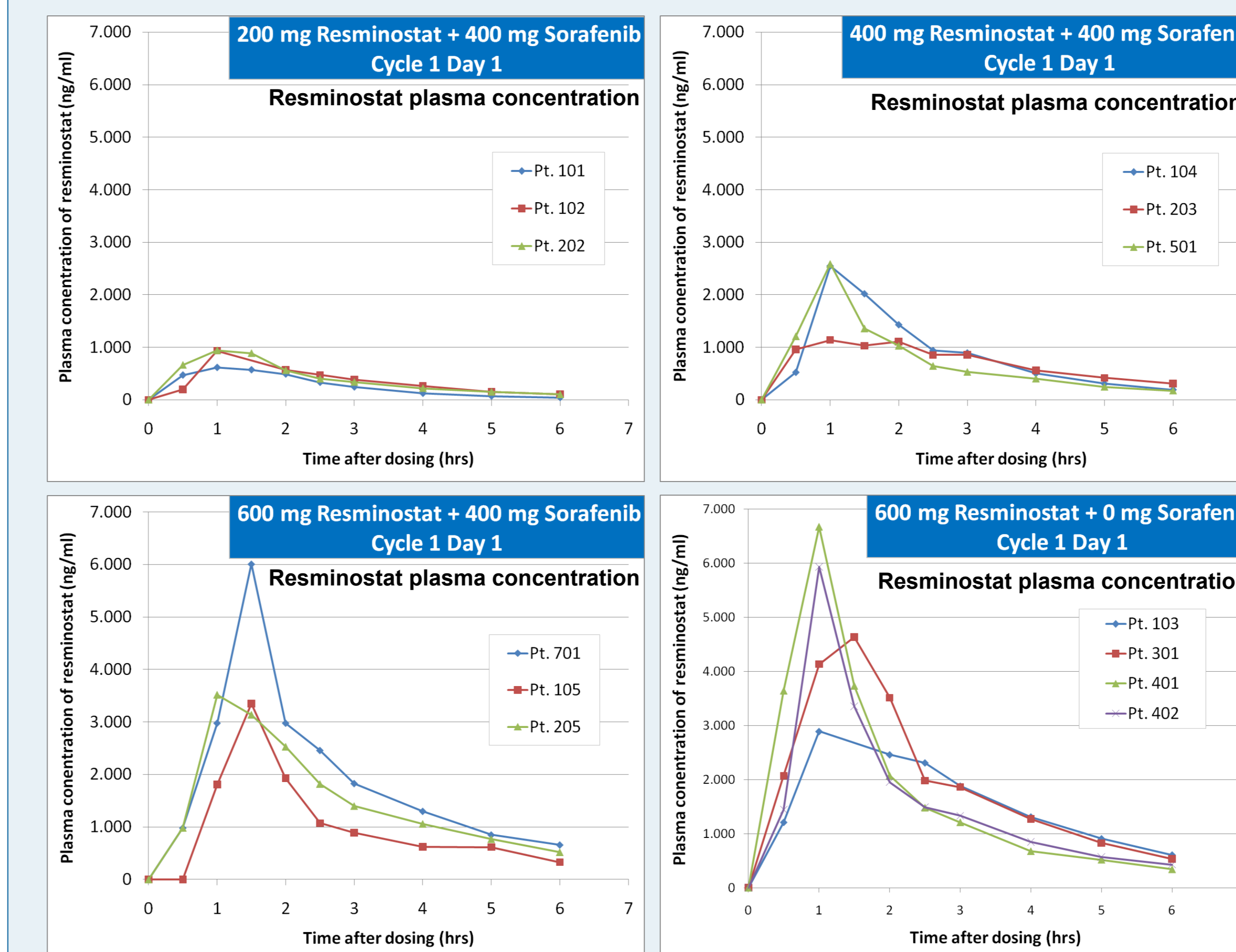
HCC, hepatocellular carcinoma; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFSR, progression-free survival rate; PK, pharmacokinetics; TTP, time to progression.

Patients Treated

- To date, 25 patients have been treated.
- On average, the patients were treated for about 12 weeks.
- Due to medical benefit, several patients have been treated for 20 weeks and more. Two patients were under treatment for at least 36 weeks.
- Dose levels 1, 2 and 3 of the combination treatment (200-600 mg resminostat plus 400 mg sorafenib) were successfully administered, and these levels were well tolerated. Dose level 4 (600 mg resminostat plus 800 mg sorafenib) is currently in progress.

Initial Pharmacokinetics Data

- The systemic resminostat exposure was in good correlation with the dose administered.
- The AUC (0-6 h) values increased dose-dependently, with values of 10.5 h*mg/l (for 600 mg resminostat mono) and 9.0 h*mg/l (for 600 mg resminostat plus 400 mg sorafenib combo).
- No PK interference of resminostat with sorafenib was detected.
- Resminostat plasma exposure (preliminary data):

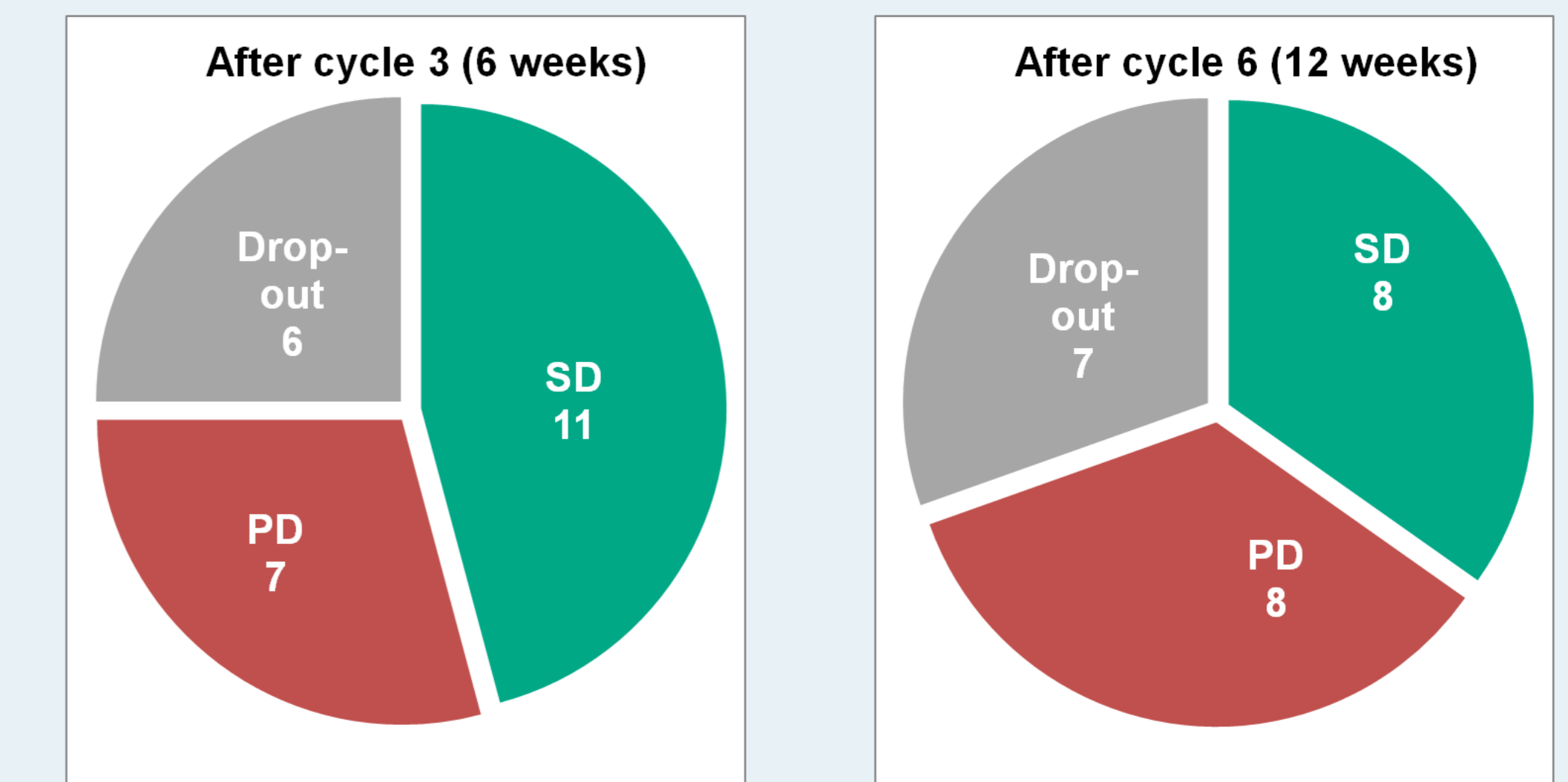


Initial Safety Data

- The majority of adverse events included gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever, all of those were of mild to moderate intensity (*).
- Most of the SAEs were singular and included transient troponin I elevation, incarcerated hernia, QT prolongation in association with T wave abnormality, insult, anemia, detachment of retina, thrombosis, bleeding, kidney failure and cholangitis (*); these events occurred only once in single patients and were at least partly attributable to the underlying disease. Ascites occurred several times, supposed to be caused by the underlying disease.

(*) The data on adverse events are preliminary and are currently being analysed, also with respect to their relationship to the study medication.

Initial Clinical Activity Data



SD, Stable Disease; PD, Progressive Disease; Drop-out, Patients who have left the study due to other reasons

- PFS rate after 3 cycles (6 weeks) = 61%**
Of the 25 patients recruited, 11 patients had stable disease after 6 weeks; 7 patients had progressive disease at this time point. 6 patients have dropped out prior to week 6 staging due to other reasons, and one patient is awaiting staging after 6 weeks.
- PFS rate after 6 cycles (12 weeks) = 50%**
8 patients had stable disease after 12 weeks, and 8 patients had progressive disease (7 patients with progressive disease after 6 weeks are included in this number). One patient has dropped out due to other reasons, one patient has developed progressive disease after 12 weeks, and one patient is awaiting staging after 12 weeks.
- Case study: decrease in vital lesion size during treatment**
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 with 400 mg resminostat plus 400 mg sorafenib. Treatment duration with resminostat/sorafenib combination was 36 weeks, along with good long-term tolerability. The patient was progression-free for 36 weeks. One target lesion displayed a decrease by 40% in the vital lesion size.

Conclusions

- The preliminary clinical data show the favourable PK and safety profile of resminostat.
- The initial data on the clinical activity of resminostat are promising with regard to a new second line treatment option in HCC, potentially overcoming resistance to sorafenib.