

# 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

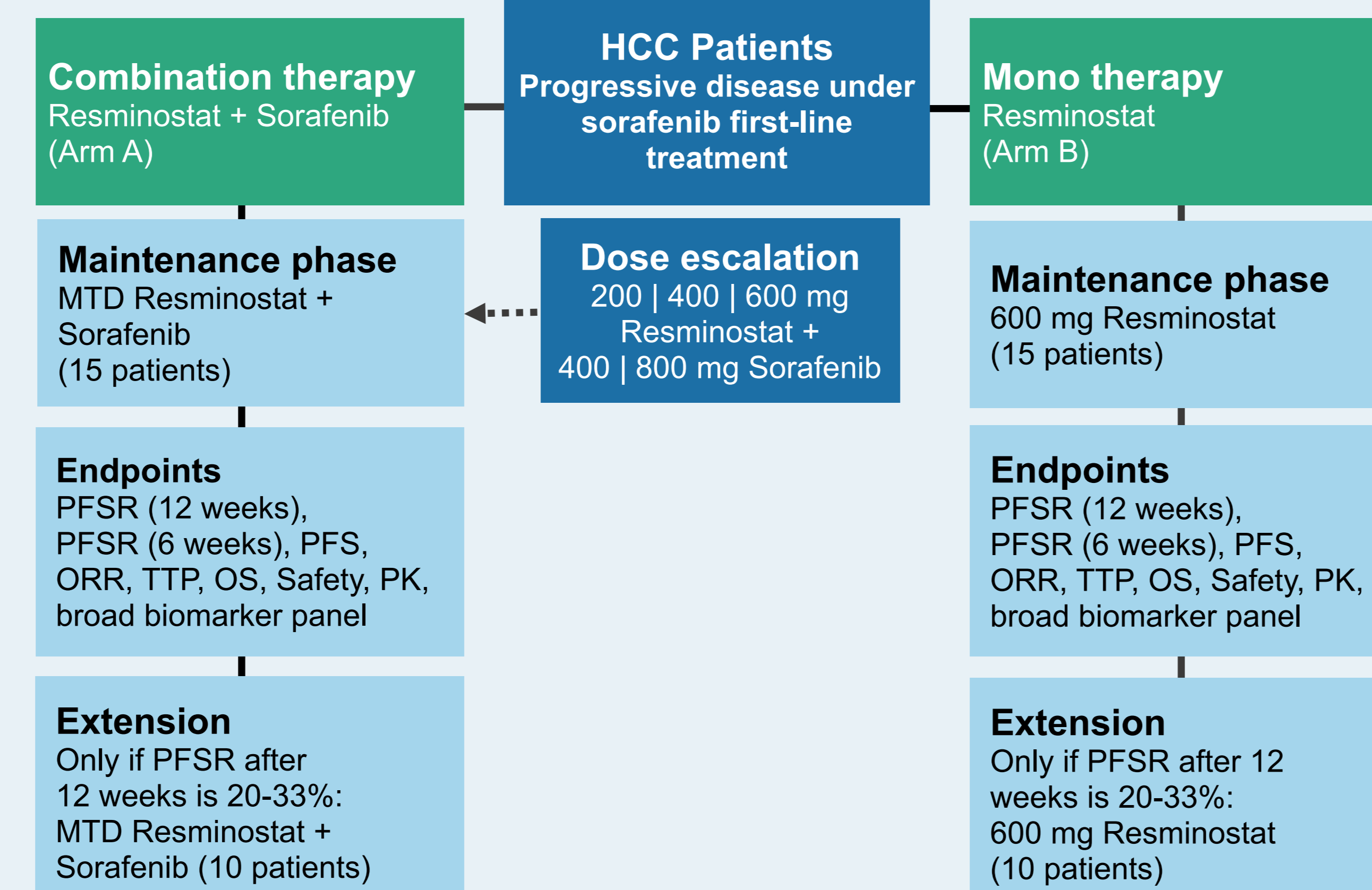
- Resminostat is a novel oral pan-HDAC inhibitor in clinical development for a variety of cancer indications.
- IC<sub>50</sub> values in cellular cancer models are in the low micro-molar range.
- There is excellent anti-tumor activity in *in vivo* cancer models.
- Additive or synergistic activity in 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 portion of patients could be stabilized under resminostat treatment.
- The SHELTER study evaluates safety, tolerability and efficacy in patients with HCC exhibiting progressive disease under sorafenib first-line therapy.

### Methods

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

### Methods

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



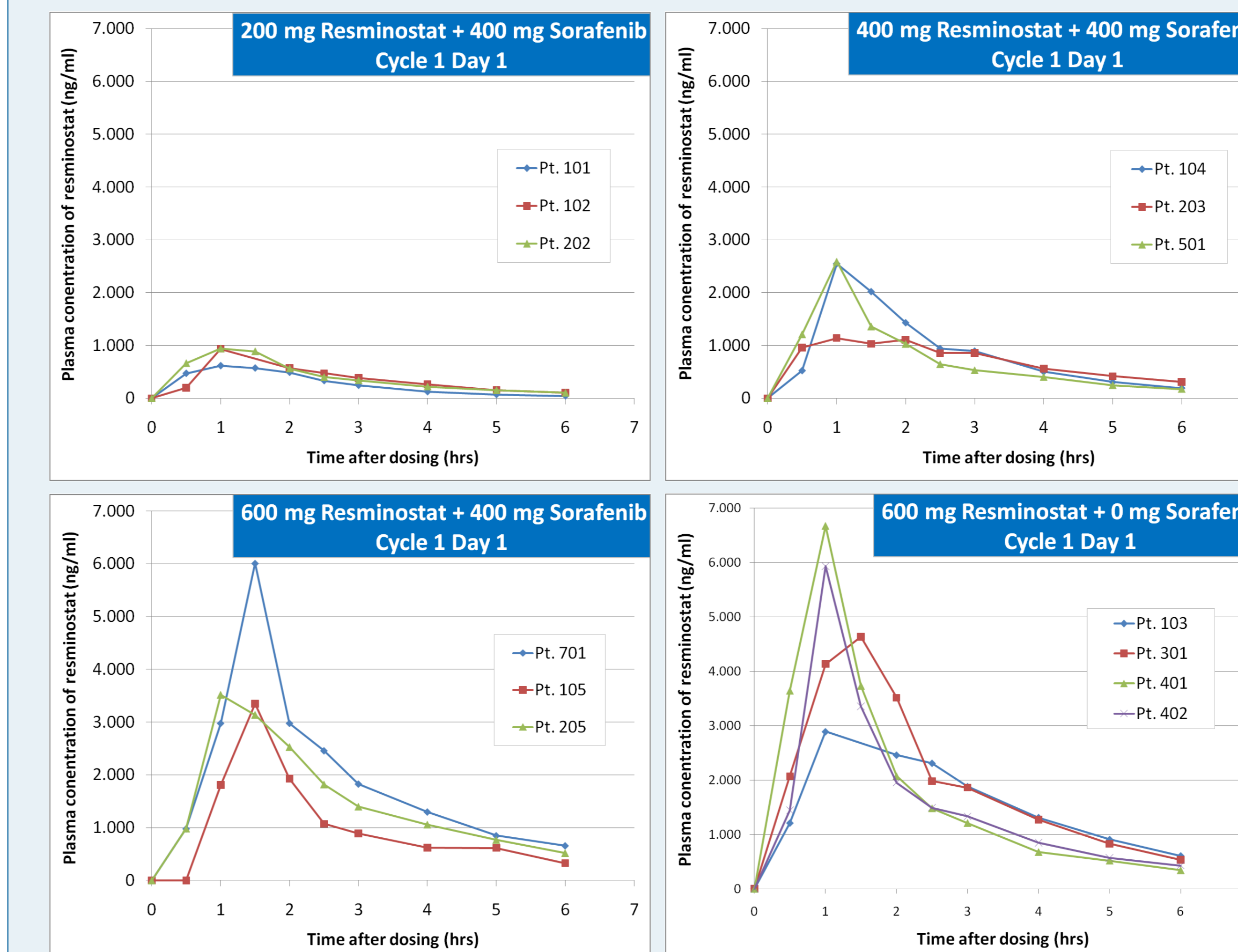
HCC, hepatocellular carcinoma. MTD, maximum tolerated dose. OS, overall survival. PFS, progression-free survival. PFSR, progression-free survival rate. PK, pharmacokinetics. TTP, time to progression.

### Patients Treated

- To date, 17 patients have been treated. Out of them, 4 patients are currently under treatment.
- The majority of patients has been treated for 12 weeks.
- Due to medical benefit, 4 patients have been treated for 20 weeks. One patient was under treatment for 36 weeks.

### 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.

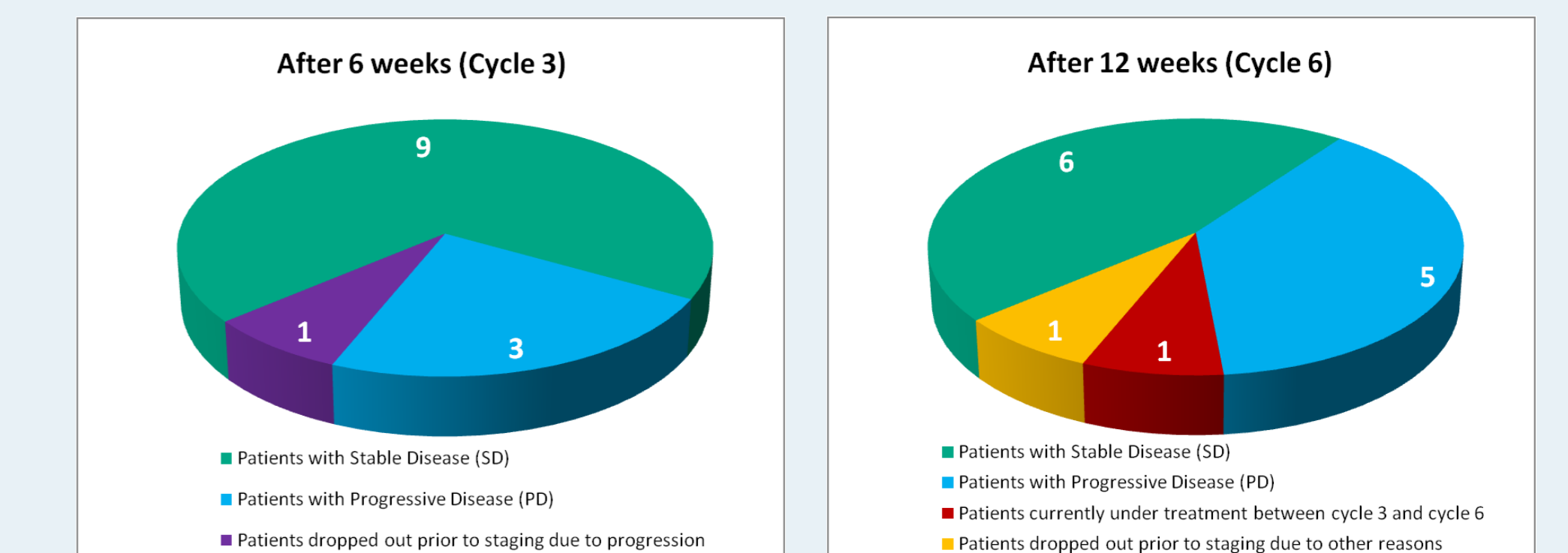


### Initial Safety Data

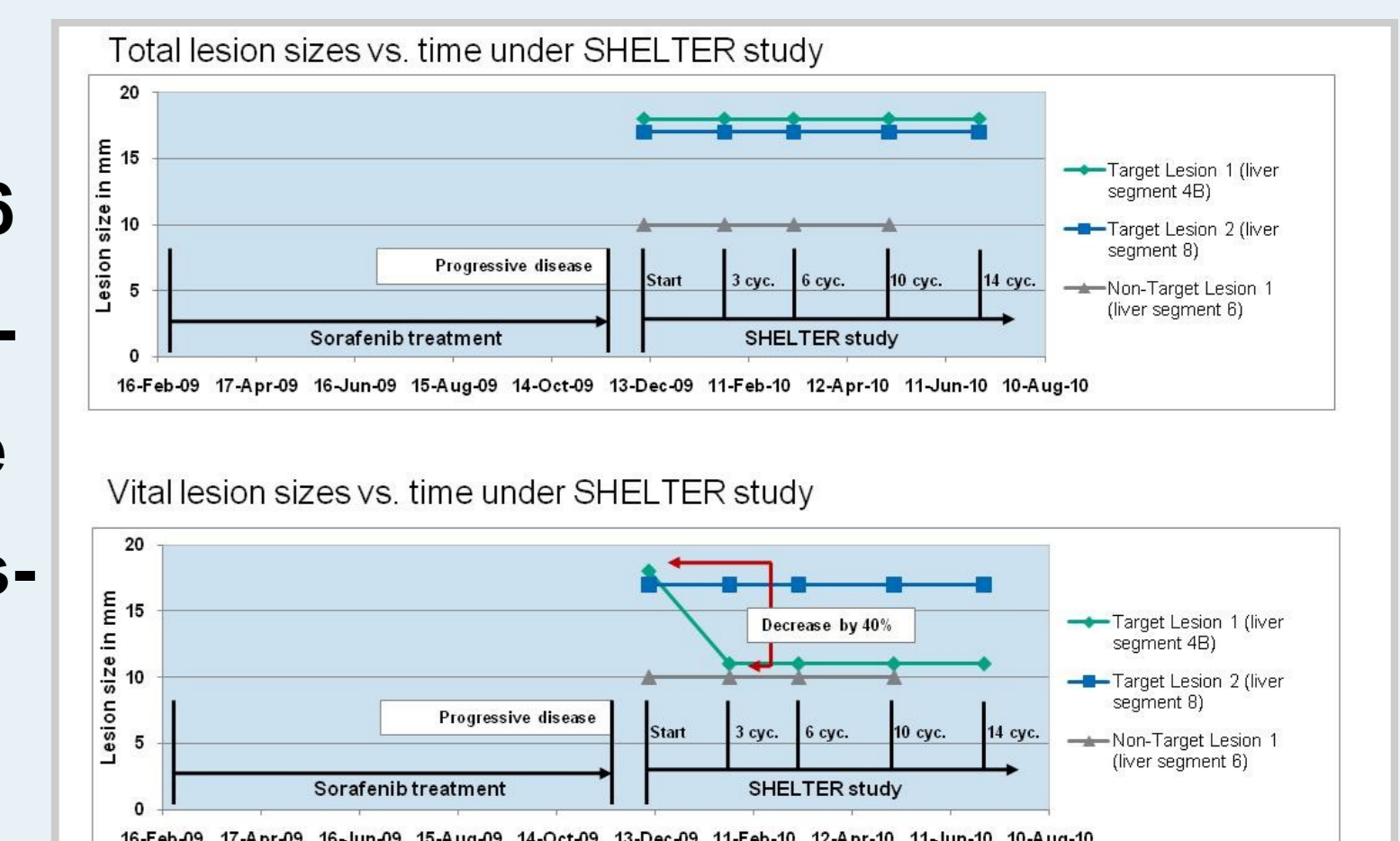
- The majority of adverse events included gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever (\*), all of those were of mild to moderate intensity.
- Further events included ascites, transient troponin I elevation, incarcerated hernia, QT prolongation in association with T wave abnormality, insult, anemia, detachment of retina, thrombosis and bleeding (\*). These events occurred only once in single patients and were at least partly attributable to the underlying disease.
- (\* The data on adverse events are preliminary and are currently being analyzed, also with respect to their relationship to the study medication.

### Initial Clinical Activity Data

- Irrespective of the received study medication, 9 out of 12 patients staged after 6 weeks (3 cycles) showed stable disease (SD). One patient left the study prior to the 6 weeks staging due to progressive disease (PD). The interim PFSR at 6 weeks is 69% (9 SD out of 13 patients).
- Out of the 9 patients with SD at cycle 3, 7 patients have been staged after 12 weeks so far. 1 patient is awaiting cycle 6 staging, 1 patient has dropped out due to other reasons. Regardless of the received dose, 6 out of those 7 patients staged after 12 weeks (6 cycles) had SD. Together with the 4 patients with PD at cycle 3, this yields an interim PFSR at 12 weeks of 54%.



- Case study:** 64-year-old male patient, primary HCC diagnosis in 2008. Sorafenib treatment from Feb, 2009 to Nov, 2009. PD 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 18 cycles (36 weeks). Patient was progression-free until cycle 18. One target lesion displayed a decrease by 40% in 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.