Sorafenib with or without everolimus in patients with unresectable hepatocellular carcinoma (HCC): A randomized multicenter phase II trial (SAKK 77/08 and SASL 29)

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Background: Sorafenib (S), a multitargeted tyrosine kinase inhibitor, has become standard of care for first-line systemic treatment of advanced HCC. Everolimus (E) is a potent inhibitor of the mTOR, a pathway frequently up-regulated in HCC. In preclinical HCC-models, S+E has additive effects compared to S. The objective of this trial was to investigate the antitumor activity of combined treatment with S+E.

Methods: Patients (pts) with unresectable or metastatic HCC and Child-Pugh ≤7 liver dysfunction were randomly assigned to receive daily S 800 mg alone or S 800 mg + E 5 mg until progression or unacceptable toxicity. The primary endpoint was progression free survival at 12 weeks (PFS12). In the S+E arm a PFS12 of ≤ 55% was considered uninteresting and promising if ≥ 75% using a Fleming’s single-stage design with 90% power and 5% significance level. The S arm was used for calibration. Secondary endpoints included response rate, PFS, TTP, OS, duration of disease stabilization (DS), safety and quality of life (QoL) assessments.

Results: 106 pts were randomized; 46 pts received S and 60 pts S+E. 93 pts are evaluable for the primary endpoint, 105 pts for the safety analysis. Main reasons for stopping therapy were: progressive disease (S: 64%; S+E: 51%), toxicity (S: 21%; S+E: 28%), or death 5% (both arms). PFS12 rate was 70% in S (95% CI: 54-83) and 68% in S+E (95% CI: 53-81). Response rate was 0% in S arm and 10% in S+E arm. Median PFS was 6.6 vs. 5.7, median TTP was 7.6 vs. 6.3, median DS 6.7 vs. 6.7, and median OS 10 vs. 12 months in the S vs. S+E arm. Activation of Hepatitis C virus was observed in 3 pts in each arm. No re-activation of Hepatitis B virus infection occurred. Grade 3 and 4 adverse events occurred in 72% (S) and in 86% (S+E). Pts
receiving S+E had worse QoL scores over time compared to pts receiving S with significant differences for physical well-being and mood.

**Conclusions:** Addition of a reduced dose of E to full doses of S is feasible, equally effective, but more toxic than S alone. Phase III testing of S 800 mg + E 5 mg daily appears not warranted in patients with unselected advanced HCC.

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