An Open Label Phase 1b/2 Trial of TRC105 and Sorafenib in Patients with Advanced/Metastatic Hepatocellular Carcinoma (HCC)

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INTRODUCTION

TRC105 is a chimeric IgG1 monoclonal antibody that binds endoglin with high avidity (Kundt et al. 2013; Liu et al. 2013). Endoglin is a membrane receptor required for angiogenesis (Li 1999) that is also associated with telangiectasia and increased serum VEGF concentrations at its site of expression (Bockhorn et al. 2003; Davis et al. 2004). Sorafenib is an oral multikinase inhibitor targeting several receptor tyrosine kinases involved in angiogenesis and tumour progression (Nolan et al. 2013; Liu et al. 2013). TRC105 is recommended Phase 2 dose (Rosen 2012, Gordon et al. 2014, Karzai et al. 2015).

STUDY DESIGN

PRIOR COMPLETED TRIAL OF TRC105 AND SORAFENIB IN HCC

• In a study performed at the Clinical Center of the National Cancer Institute the combination of TRC105 and sorafenib was tolerable and the study proceeded per protocol to the maximum planned dose level of TRC105 (15 mg/kg every 2 weeks) in combination with 400 mg BID of sorafenib. Therefore, weekly dosing of TRC105 at 10 mg/kg was selected as RP2D. One patient with experienced DLT of grade 3 infusion related reaction from premedication. Therefore, weekly dosing of TRC105 at 10 mg/kg was continued with improved cancer survival (Duarte 2014).

RESULTS

SUMMARY OF SAFETY AND EFFICACY

Mean serum concentrations of TRC105 at 10 mg/kg exceeded the target concentration (7 ug/ml) in 5/17 patients. Mean trough concentrations decreased following weekly dosing of TRC105 at 10 mg/kg (44.7 ug/ml at 6 weeks). No meaningful increases in sorafenib plasma concentrations were observed in patients via fibrotic/cirrhotic liver disease. Sorafenib is an oral multikinase inhibitor targeting several receptor tyrosine kinases involved in angiogenesis and tumour progression (Nolan et al. 2013; Liu et al. 2013).

CONCLUSION

Adverse events characteristic of sorafenib were not increased in frequency or severity when the combination was administered at the recommended dose of TRC105. Mean serum concentrations of TRC105 at 10 mg/kg exceeded the target concentrations. However, TRC105 trough concentrations were lower in HCC patients compared with prior TRC105 studies in HCC and sorafenib, where hybrid dosing led to higher target concentrations. This may reflect increased target mediated clearance in HCC patients via fibrotic/cirrhotic liver disease. Treatment emergent ADA was observed more frequently in patients with HCC (76%) compared with mixed trials of TRC105 in other tumour types (e.g., RCC, sarcoma, and lung where ADA has been 7%) and may have influenced PK in individual patients. The combination of TRC105 and sorafenib continued to demonstrate encouraging signs of activity in a heterogeneous patient population with a reported response rate of 20% by RECIST, which is consistent with the response rate reported from the NCI site study, as well as > 50% reduction in alpha-fetoprotein (AFP) with therapy.

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