

FRI-078

THE POTENT PAN-CASPASE INHIBITOR IDN-7314 DOES NOT AFFECT TUMOR GROWTH RATE NOR DOES IT ANTAGONIZE THE EFFICACY OF SORAFENIB IN MODELS OF HEPATOCELLULAR CARCINOMA

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Background and Aims: IDN-7314 is a potent, orally active pan-caspase inhibitor that is a close structural analogue of emricascan, (IDN-6556), which is in Phase 2 clinical development. Caspases are enzymes that are critically involved in apoptosis. Apoptosis and caspase activity are elevated in many liver diseases and are closely associated with disease severity and progression. There is a longstanding theoretical concern regarding caspase inhibition and cancer potentiation. To investigate this potential in preexisting tumors, we studied the effect of IDN-7314 with and without sorafenib in cellular and in vivo models of hepatocellular carcinoma, (HCC).

Methods: The effect of IDN-7314 was evaluated in the human hepatoma cell line PLC/PRF/5 for its effects on cell viability and compared with sorafenib using cisplatin as a positive control. Combination studies were conducted with IDN-7314 and sorafenib to evaluate potential synergy/antagonism in tissue culture. In vivo studies were conducted in female BALB/c nude mice bearing PLC/PRF/5 tumors. Mice (10/group) were treated (QD) with either vehicle; IDN-7314 (10 mg/kg, po); sorafenib (10 mg/kg, po) or IDN-7314 (10 mg/kg, po) plus sorafenib (10 mg/kg, po). Treatment began when tumor volume reached ~200 mm³ and was continued for 21 days. LC/MS/MS was used to quantify tumor levels of IDN-7314.

Results: In cell culture studies, IDN-7314 alone had no effect on the viability of PLC/PRF/5 cells at any concentration up to the maximum dose of 30 μ M. In combination studies, IDN-7314 (0.37 to 30 μ M) did not antagonize the efficacy of sorafenib (IC₅₀ ~4 μ M) in tissue culture. In vivo, the tumor growth rate in the IDN-7314 cohort was not different than that observed in placebo-treated animals. When dosed in combination with sorafenib, IDN-7314 did not antagonize the efficacy of sorafenib. Intratumoral levels of IDN-7314 at the end of study were ~10–100-fold above the in vitro IC₅₀s against caspases.

Conclusions: These results demonstrate that inhibition of caspases by IDN-7314 does not affect the chemotherapeutic activity of sorafenib in models of HCC. Importantly, administration of IDN-7314 also did not affect the growth rate of established tumors. To our knowledge this is the first reported study of a pan caspase inhibitor in an in vivo model of HCC and provides experimental evidence that directly addresses theoretical concerns regarding caspase inhibition and cancer promotion.