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Preclinical assessment of a novel small molecule inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1)

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Introduction

iTeos leverages the science of the LICR to target the metabolism of the tumor microenvironment and develops small-molecule inhibitors. Tryptophan catabolism can suppress the anti-tumor immune response through expression of the rate-limiting enzyme IDO1. Local tryptophan reduction and metabolite production by the kynurenine pathway are associated with anergy/apoptosis of tumor-infiltrating lymphocytes. Two IDO1 inhibitors (Incyte INCB24360/NewLink NLG919) are currently tested in clinical trials for treatment of relapsed/refractory solid tumors but exhibit therapeutic limitations.

Methods/results

A primary HTS (176,000 compounds) led to the discovery of several confirmed hits. Medicinal chemistry optimization resulted in an original lead with nM potency in a relevant human blood assay, comparable to Incyte $IDO1_i$ (IC_{50} 890 ± 220 nM [iTeos $IDO1_i$] versus 970 ± 100 nM [Incyte $IDO1_i$] [N = 3 donors; Kyn ELISA]). For rodents & monkey, iTeos compound showed low clearance (9.9&1.9 mL/min/kg respectively), moderate-to-low protein binding (48&28%Fu respectively), a short half-life in rodents but long in monkey (1.1&12 h respectively), good oral availability (>75%), and no inhibition on five CYP450 isoforms). Good predictive values for human PK were obtained through allometric scaling. Quantification of the tryptophan metabolite kynurenine showed a significant decrease in mouse plasma after oral administration of the $IDO1_i$ in a dose response setting (45.3 ± 2.4 [iTeos $IDO1_i$] and 48.1% ± 3.0 [Incyte $IDO1_i$]; 2 h per os at 100 mg/kg compared to vehicle; N = 5 independent experiments). In a time-course experiment, inhibition of kynurenine production lasted 8 h (iTeos $IDO1_i$) compared to 16 h (Incyte $IDO1_i$), consistent with their respective rodent half-life. A comparable PD effect was observed in mouse tumor lysates. Monkey PD is ongoing. Preliminary data obtained with the Pan02 mouse tumor model showed significant survival benefit of the iTeos $IDO1_i$ in stand-alone and in combination with anti-CTLA4 treatment compared to vehicle or anti-CTLA4 in stand-alone respectively. 15 different human cancer types (60 samples each) were analyzed for IDO1 protein expression and allowed identification of several tumors with high expression.

Conclusions

iTeos' drug discovery efforts have delivered a selective IDO1 small-molecule inhibitor with novel scaffold suitable for *in vitro*/*in vivo* validation and with good predictive human PK (low clearance(<10% Q_H), long half-life (>20 h), high oral bioavailability).

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