BACKGROUND

Deposition of arginase represents an important mechanism of immunosuppression and high plasma and tumor arginase (ARG) activity actively have been demonstrated in patients with a wide spectrum of tumors and correlated with a poor prognosis. Low arginase levels inhibit proliferation and activation of cytotoxic T and NK cells. Preclinical and clinical studies confirmed that synergistic interference with multiple mechanisms of immunosuppression resulted in a strongly improved antitumor efficacy. In this context, we have developed OAT-1746, a novel, potent and selective small molecular inhibitor of AR ligands and AR22 and evaluated its antitumor efficacy as a monotherapy and in combinations with gemcitabine and inhibitors of PD-L1 and ISO.

METHODS

The EC50 values were determined against AR1L2. M2-polarized, bone marrow-derived murine macrophages and CHL-2 cells transfected with human AR21 were used to assess the cell viability. The in vivo antitumor efficacy of the new agent was evaluated in mouse models after oral administration. Quantitative real-time PCR was used to determine inflammatory markers. The tumor growth assay was used to assess the tumor growth inhibition of OAT-1746 and OAT-1746 and arginine levels were determined at the indicated time points after the last dose.

RESULTS

- We have developed potent, selective, orally active inhibitors of AR1L2 and 2. Our lead compound OAT-1746 is a non-naturally-dual inhibition of AR1L2 with a potent cellular activity (Table 1).

- OAT-1746 demonstrated strong efficacy as a monotherapy in 3 syngeneic tumor models.

- Fig. 1. Activity of OAT-1746 against recombinant human (A), mouse (m) and rat (r) AR1L2 and AR22 and against AR1L2 in cell-based assay.

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- OAT-1746 exhibited a dose-dependent anti-tumor efficacy, which correlated with plasma and tumor arginase levels and significantly increased plasma arginase levels which were sustained for 24 h (Fig. 2).

- OAT-1746 significantly increased the antitumor efficacy of the PO-L1 + DOX/IRL21 dual immunotherapy in the CT26 model. Rescanning of the mice which completed the triple immunotherapy (OAT-1746 + PD-L1 + ISO) with CT26 cells resulted in a strongly suppressed tumor growth suggesting development of the antitumor immunity (Fig. 4).

- OAT-1746 exhibited a strong PO effect resulting in 4.7-fold increase of arginase levels in plasma and tumor (Fig. 4). The arginase plasma levels (500-700 uM) exceeded several fold the arginase concentration required for the maximal stimulation of CD2 cell proliferation (120 uM) determined in ex vivo assays.

CONCLUSIONS

- OAT-1746 is a highly active, selective dual inhibitor of AR1L2 and AR22 with a potent cellular activity.

- OAT-1746 exhibited good pharmacological properties and a significant antitumor activity in multiple tumor models as a monotherapy and in combinations.

- OAT-1746 significantly increased antitumor activity of immune checkpoint inhibitors (PD-L1 and ISO), with the triple immunotherapy demonstrating the best tumor control.

- OAT-1746 efficacy correlated with PO effects including inhibition of tumor arginase activity and 4.7-fold increase in plasma and tumor arginase levels.

- Induction of markers of T and NK cell activation in tumor microenvironment confirmed the reversal of ARG-mediated immunosuppression by OAT-1746.

- Based on these results, OAT-1746 was nominated for a clinical development as OAT-02.