**Background** Phosphoinositide 3-kinase delta (PI3Kd) inhibitors are used to treat lymphomas but safety concerns and limited target selectivity complicate their wider application. More recently, the potential for PI3Kd inhibition in solid tumors has become appreciated, through both the modulation of T cell responses and direct anti-tumor activity. Here we report the exploration of IOA-244/MSC2360844, a non-ATP-competitive PI3Kd inhibitor, for the treatment of solid tumors.

**Methods** To harness the differentiation of IOA-244 from other PI3Kd inhibitors, we have performed molecular dynamic and protein dynamic studies, as well as in-cell kinase assay where we compared structural and selectivity features of IOA-244 with other inhibitors. Then, to investigate the tumor intrinsic and extrinsic properties of IOA-244, we performed patient-derived xenograft models, in vitro proliferation assay and in vivo syngeneic tumor models. Here, we tested IOA-244 in monotherapy or in combination with checkpoint blockade inhibitors.

**Results** Molecular dynamics and protein dynamics studies highlighted that, opposite to other inhibitors, IOA-244 binding to PI3Kd causes a bending of the C-terminal kα12 helix inwards towards the ATP binding pocket, overall resulting in the stabilisation of the inactive form of PI3Kd. Based on this unique binding mode, IOA-244 showed very selectivity when tested against a large set of other kinases, enzymes and receptors. IOA-244 inhibited the in vitro growth of cancer cells expressing high levels of PI3Kd, as well as of patient-derived xenografts of melanoma and mesothelioma, suggesting that there are cancer cell-intrinsic effects of IOA-244. Importantly, IOA-244 inhibits Treg proliferation while having limited anti-proliferative effects on conventional CD4+ T cells and no effect on CD8+ T cells, highlighting immune-modulatory properties that can be exploited in solid tumors. Indeed, in CT26 colorectal and LL2 lung cancer model IOA-244 sensitised the tumours to anti-PD(L)-1 treatment, with similar activity in the Pan-02 and A20 syngeneic mouse models. In these models IOA-244 also reshaped the tumour-infiltrating cells, favouring infiltration of CD8 and NK cells, while decreasing suppressive cells. IOA-244 presented no significant safety concerns in animal and in vitro toxicity studies and is currently in clinical Phase 1 evaluation for lymphoma and solid tumors. In this study, IOA-244 treatment in cancer patients showed unprecedented tolerability and clinical benefit, particularly in patients with metastatic uveal melanoma.

**Conclusions** In conclusion, thanks to its unique structural and selectivity features, IOA-244 represent a first in class PI3Kd inhibitor, with an exceptional safety profile.