COMBINING A SAFE PI3KD INHIBITOR WITH CHEMOTHERAPY AND ANTI-PD1 IN IMMUNOTHERAPY-REFRACTORY NSCLC: A PROOF-OF-CONCEPT STUDY TO ALLOW CLINICAL TRIAL DESIGN

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Background Roginolisib (IOA-244) is a first in class allosteric modulator and non-ATP competitive PI3Kd inhibitor currently in a Phase 1 clinical study. In preclinical studies, roginolisib inhibits suppressive immune cells, such as Tregs and MDSC, while preserving proliferation and function of CD8 T cells.

A FIH (first-in-human) dose escalation study to assess safety, has determined that roginolisib is well tolerated at the 80 mg dose, shows signs of efficacy and induces phenotypic changes in the circulating immune cells. These effects were confirmed in a dose-expansion study focused on follicular lymphoma and uveal melanoma. As best response at the RP2D, anti-tumour activity was observed in follicular lymphoma (50% PR) and uveal melanoma patients (5% PR; 80% SD).

Methods In non-clinical studies, we have co-cultured tumour cells and matched PBMC derived from 10 NSCLC patients, of which 6 were refractory and 4 were responders to checkpoint inhibitors: we then evaluated roginolisib in combination with chemotherapy and immune-targeted therapy. As readout we used flow cytometry to assess immunophenotype after 3 days of co-culture and tumor cell death assay to evaluate the antitumoral activity of the immune cells.

Results In these models, we show that the addition of roginolisib to chemotherapy (carboplatin or gemcitabine) plus nivolumab specifically increased activated CD107a+/IFNγ+ CD8 T cells and M1-like macrophages, and concomitantly decreased Tregs, exhausted CTLA4+ CD8 T cells and MDSCs with an overall effect to increase the antitumoral immune response. In addition to that, evaluation of cytotoxicity towards tumor cells, revealed a strong synergistic effect of Roginolisib when combined with chemo-immunotherapy.

Conclusions These results encourage the further clinical development of Roginolisib in combination with checkpoint blockade inhibitor in relapsed/refractory NSCLC patients.

Ethics Approval The submitted study obtained ethical approved as specified below:

# ethical approval: IRB n. 73/2018, approved by local ethics committee of San Luigi Gonzaga Hospital, Orbassano (Italy)

Consent Written informed consent was obtained from the patients for publication of this abstract and any accompanying images.

A copy of the written consent is available for review by the Editor of this journal.

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