Background: Invariant natural killer T-cells (iNKTs) share features of innate cells (NK-like) and T-cells. The importance of this relatively rare lymphocyte subset has generated increased interest due to its dual ability to have a direct cytotoxic effect on CD1d-expressing tumors and its ability to induce long-lasting antitumor CD8 T-cell responses mediated by cross priming and licensing of dendritic cells. Various clinical approaches involving the use of allogeneic iNKT cells are in development; here we describe an initial clinical study with IMM60, a synthetically derived agonist of iNKT cells which is formulated in a liposome (PORT-2). In preclinical studies, IMM-60 treatment results in maturation of DCs and B cells and potent stimulation of iNKT cell-derived IFN-g. In efficacy studies, IMM60 demonstrated monotherapy activity in PD-1 resistant models, (e.g., B16-F10), and upregulation of PD-L1 expression on cancer cells as a consequence of its priming effect.

Methods: IMP-MEL is an open-label first-in-human phase 1/2 study, currently enrolling adult subjects with advanced NSCLC and melanoma. IMM60-containing liposomes were administered IV Q3W at 3 escalating dose levels for 6 doses. The study seeks to assess the safety and efficacy of IMM-60 alone, as well as in combination with a PD-1 inhibitor. Pharmacodynamic analyses were performed, including circulating cytokines and flow cytometry.

Results: Six patients with advanced melanoma (n=3) or NSCLC (n=3) have been enrolled in the monotherapy dose cohorts, having a median of 4.5 prior therapies (min 2, max 5). The drug was well tolerated with no treatment-related SAEs or Grade 3-5 adverse events to date. Cytokine analysis and flow cytometry of pre- and on-study blood samples revealed evidence of iNKT activation as well as NK and dendritic cell activation. [MP1] One patient achieved >50% reduction in select target and non-target lesions. The MTD has not been reached.

Conclusions: This trial provides early proof of concept for using a small molecule iNKT agonist to promote both innate and adaptive immune responses. PORT-2 (liposomal IMM60) is well tolerated at 1 and 3 mg/m². Pharmacodynamic measurements support a broad immune mechanism. Once the Phase 2 dose is defined the trial is designed to accrue six Phase 2 arms testing PORT-2 alone or combined with a PD-1 inhibitor, compared to PD-1 inhibitor monotherapy. Further data on pharmacokinetics and biopsy analyses will be presented.

Ethics Approval: This University of Oxford study has received ethical approval by a UK Research Ethics Committee, approval number 20/SC/0367. All participants provided informed consent before taking part in this clinical trial.