IMP-MEL: A phase 1 first-in-human dose-finding study of a novel invariant natural killer T-cell agonist (iNKT) IMM60 in advanced melanoma and non-small-cell lung cancer (NSCLC)

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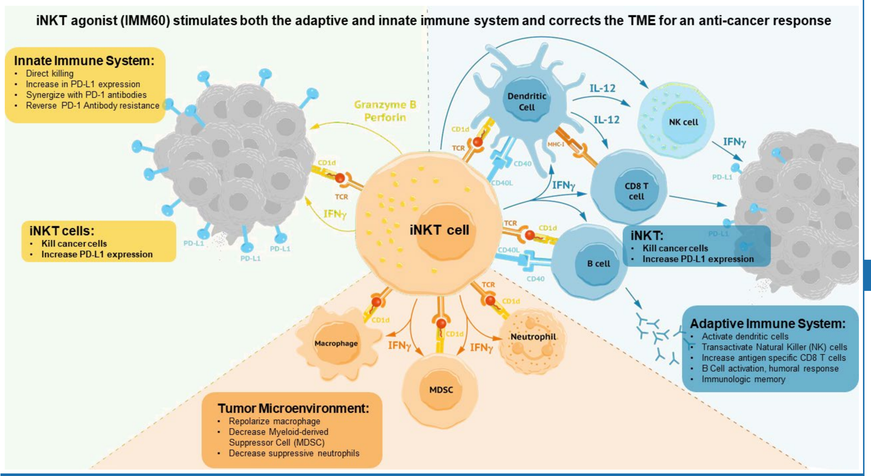
BACKGROUND

- IMM60 (PORT-2) is a synthetic derivative of α-galceramide formulated into a liposome
- IMM60 is a potent agonist of invariant natural killer T-cells (iNKTs) which leads to activation of the innate and adaptive immune systems, and down regulation of the suppressive tumor microenvironment
- In preclinical studies, IMM60 has demonstrated monotherapy activity in PD-1 resistant models
- IMM60 upregulates PD-L1 expression on cancer cells and may overcome resistance to anti-PD-1 antibody therapy (**Figure 1**)

Figure 1: IMM60 (PORT-2) Mechanism of Action



METHODS

- Phase 1 is a 3 + 3 design starting with IMM60 monotherapy at doses 1mg, 3mg and 9mg/m^2
- IMM60 at 3 and 9mg/m^2 will also be evaluated in combination with pembrolizumab 200 mg
- IMM60 is administered IV every 3 weeks x 6 cycles
- Patients were evaluated for safety, biopsies and blood were taken before and during treatment

STUDY POPULATION

8 patients have been treated as of Nov 3, 2022, including 1 each in the 9 mg/m^2 IMM60 monotherapy and 3 mg/m^2 IMM60 + pembrolizumab combination cohorts. Data for 6 patients evaluable as of the clinical cutoff date are reported herein.

Eligibility

- Melanoma and NSCLC patients progressing through prior immunotherapy (and platinum-based chemotherapy for NSCLC patients)
- Measurable disease per RECIST 1.1
- ECOG 0-1
- Demographics and baseline characteristics are summarized in **Table 1**

Table 1: Demographics and Baseline Characteristics (n=6)*

Tumor type	2 Melanoma 4 NSCLC
Median age (min/max)	64 (41,79)
Gender	33% Female 66% Male
Median prior therapies (min/max)	5 (3,7)
Prior PD-1 therapy	100%
Performance status	50% ECOG 0 50% ECOG 1

**Clinical Data Snapshot: September 14, 2022*
EudraCT Number: 2020-001351-41

EXPOSURE AND SAFETY

Exposure

- A total of 27 IMM60 infusions have been administered to 6 patients at 1 mg/m^2 and 3 mg/m^2 doses, with a median of 4 doses per patient
- The MTD has not been reached

Safety

- No SAEs or Dose Limiting Toxicities have been observed
- 5/6 patients (83%) experienced at least 1 AE considered to be related to IMM60; these related AEs were low grade and manageable (Table 2)

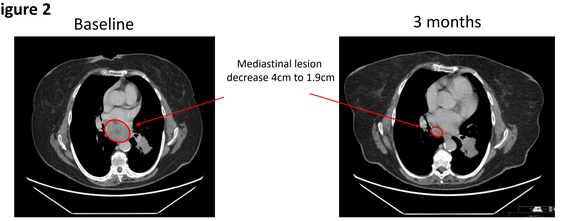
Table 2: Adverse Events related to IMM60 (n=6)

Adverse Event	Grade 1	Grade 2	Grade 3-5
Dizziness	1 (17%)	0	0
Fatigue	0	1 (17%)	0
Flu-like symptoms	1 (17%)	0	0
Hair Loss	1 (17%)	0	0
Headache	1 (17%)	0	0
Hypertension	0	1 (17%)	0
Vomiting	1 (17%)	0	0

CLINICAL ACTIVITY

- One patient (3 mg/m^2) achieved >50% reduction in a 4 cm mediastinal lesion (**Figure 2**), and resolution of 2.2 cm lesion in the small bowel mesentery as well as multiple pathologic lymph nodes (the RECIST best response was Stable Disease)

Figure 2



BLOOD BIOMARKERS

- Serum cytokine analysis and flow cytometry was analyzed from samples take prior to treatment and then at 4 hrs, 24hrs and 1 week
- MCP-1 (**Figure 3**) and IP-10 (**Figure 4**) showed increases in most subjects, no increases in IL-6, IL-4 and IL-10
- iNKTs downregulate their TCR when the agonist binds to the receptor, indicating activation of the iNKT (**Figure 5**).
- Increase in CD86+ B cells which is associated with tumor-specific antigen presentation[a] (**Figure 6**)

Figure 3

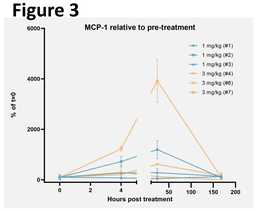


Figure 4

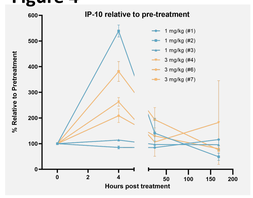


Figure 5

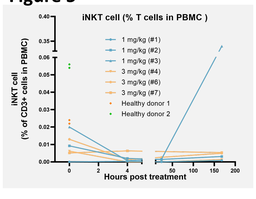
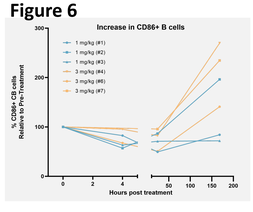


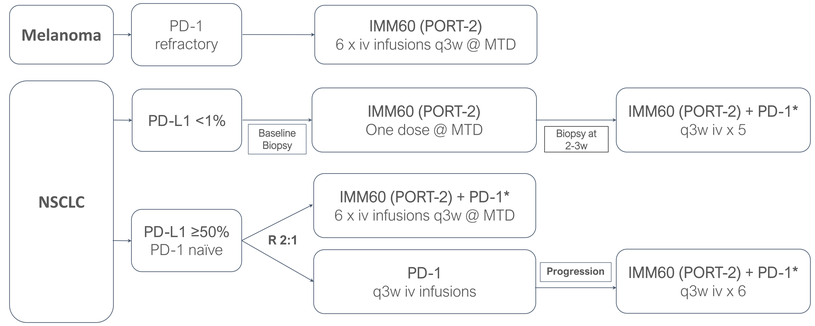
Figure 6



PLANNED PHASE 2

- A Phase 2 study (IMPORT-201) is planned to further evaluate IMM60 (PORT-2) in melanoma and NSCLC, both as a monotherapy and in combination with a PD-1 inhibitor versus PD-1 inhibitor monotherapy (**Figure 5**)

Figure 5: IMPORT-201 Study Schema



** PD-1 maintenance dosing may continue q3w for a total of 2 years*

CONCLUSIONS

- This trial provides early proof of concept using a small molecule iNKT agonist formulated in a liposome
- Liposomal IMM60 (PORT-2) is well tolerated at 1 and 3 mg/m^2 with preliminary evidence of clinical activity as a monotherapy
- Serum biomarker analysis provide evidence of iNKT activation, as well as increases in antigen-presenting B cells following treatment with PORT-2
  - High CD86+ B-cells in tumors correlate with favorable outcome and response to checkpoint inhibitors; changes in circulating levels will need to be studied further as a potential surrogate markers of immune response
- Once the Recommended Phase 2 Dose (RP2D) is defined, a multi-national Phase 2 study will be initiated, including 4 arms testing PORT-2 alone or combined with a PD-1 inhibitor, compared to PD-1 inhibitor monotherapy.

References

[a] Wennhold et al., Cancer Immunol Res 2021;9:1098-108.

ACKNOWLEDGMENTS

We extend our gratitude to the patients, their families, and the University of Oxford site staff members who are making this trial possible.

Link to poster