First-in-human study of MALT1 inhibitor MPT-0118: Results from monotherapy dose escalation in advanced or metastatic refractory solid tumors

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**BACKGROUND**

- MALT1 protease is a promising target in aggressive lymphomas and for augmenting cancer immunotherapy in solid tumors.
- In preclinical models, MALT1 protease inhibition reprograms tumor-resident regulatory T cells (Treg), inducing interferon-gamma (IFN) expression and loss of immunosuppressive function in solid tumors.
- MPT-0118 is an orally bioavailable MALT1 inhibitor undergoing a phase 1 evaluation as monotherapy or in combination with pembrolizumab (pembro) (NCT04859777).

**METHOD**

- Part A trial enrolled eligible patients (pts) into escalating dose cohorts of MPT-0118 (Fig. 2).
- The primary study objectives were safety, tolerability, and determination of the recommended phase 2 dose (RP2D).
- Secondary and exploratory objectives included assessing pharmacokinetics (PK), biomarkers, and objective response rate (ORR) per RECIST v.1.1 and iRECIST.
- Paired biopsies were obtained during screening and after 8 days of treatment.

**RESULTS**

- **SAFETY / PK / TOLERABILITY**
  - 38% received prior immunotherapy
  - No dose-limiting toxicities (DLT) were observed.
  - All treatment-related adverse events (TRAЕ) were reversible (Tab. 1).

- **RESPONSE EVALUATION PER iRECIST**
  - Reduction of target lesion size in 3/13 patients (23%), stable disease (SD) in 5/13 (38%) after ≥ 2 treatment cycles.
  - Heavily pre-treated patient population.
  - Longest treatment 32 weeks: Breast Cancer patient; after cycle 3 (week 9) combination with pembrolizumab.

- **BIOMARKER ASSESSMENT**
  - Good tolerability and single-agent activity of MPT-0118 in cold tumors that poorly respond to checkpoint inhibitors.
  - No immune related toxicities.
  - RP2D of MPT-0118 at 200 mg/day based on PK and clinical observations.
  - Correlative biomarkers are consistent with proposed mode of action.
  - Evidence for reprogramming of tumor Tregs by MPT-0118.
  - Augmented CD8 T cell recruitment by MPT-0118 in all SD patients with evaluable paired biopsies.
  - Tregs in hgs due to fluidic treatment ex vivo with MPT-0118 (12-24 h) start producing increased amounts of IFN-γ.

- **CONCLUSIONS**
  - MPT-0118 decreased peritoneal target lesion in gastric cancer (GC) patient by ~20% (Fig. 5).
  - MPT-0118 enriched CD8 T cells in GC tissue 8 days after start of treatment (Fig. 5).
  - Augmented CD8 T cell recruitment by MPT-0118 in all SD patients with evaluable paired biopsies.
  - Tregs in hgs due to fluidic treatment ex vivo with MPT-0118 (12-24 h) start producing increased amounts of IFN-γ.

**ACKNOWLEDGMENTS**

This study was sponsored by Monopetos Therapeutics, Inc. Peter Keller is an employee and shareholder of Monopetos Therapeutics, Inc.

**REFERENCES**

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3. di Pilato M, et al., JTO 2023; doi: 10.1161/JTO.2023.050400
4. di Pilato M et al., JTO 2023; doi: 10.1161/JTO.2023.050400
5. di Pilato M et al., JTO 2023; doi: 10.1161/JTO.2023.050400

**TABLE 1:** Patient dosing and treatment-related adverse events (TRAЕ).

<table>
<thead>
<tr>
<th>MPT-0118 (mg/day)</th>
<th>Number of Pts</th>
<th>DLT</th>
<th>Pts with Grade ≥3 TRAE</th>
<th>No. Pts most common TRAE*</th>
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<tr>
<td>50</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>(neutrophil &amp; WBC count decreased) 1</td>
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<tr>
<td>150</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>200</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>(febrile neutropenia, hepatitis) 4</td>
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<tr>
<td>300</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>0</td>
<td>17</td>
<td>17</td>
</tr>
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*Di Pilato M et al., JIPO 2023, doi: 10.36401/JIPO-22-18

**REFERENCES**


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**FOOTNOTES**

1. The University of Texas MD Anderson Cancer Center, Houston, TX, USA, 2Massachusetts General Hospital, Boston, MA, USA, 3Columbia University Irving Medical Center, New York, NY, USA, 4Monopetos Therapeutics, Boston, MA, USA, 5Helmholtz Munich, Munich, Germany, 6Harvard Medical School, Boston, MA, USA, 7NEXT Oncology, San Antonio, TX, USA

**EXHIBITIONS**

- First-in-human study of MALT1 inhibitor MPT-0118: Results from monotherapy dose escalation in advanced or metastatic refractory solid tumors.

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