**Phase I study of MP0317, a FAP-dependent DARPin for tumor-localized CD40 activation in patients with advanced solid tumors**

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**Study objectives**

- **Primary**
  - Safety and tolerability
  - Recommended dose for expansion and combination study
- **Secondary**
  - PK
  - Antitumor activity
  - Preliminary clinical benefits

**Study design**

- Phase 1, open-label, multicenter, dose-escalation study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of MP0317 in neuroendocrine tumors in adult patients with advanced solid tumors (NCT03588886)

**Key takeaways**

**Hypothesis**

Tumor-localized CD40 agonism can overcome the limitations of systemic CD40 agonists (toxicities and low anti-tumor activity) by:

- Activating innate immune cells intratumorally

**Hypothesis confirmed in ongoing Phase 1 study**

- MP0317 has a favorable safety profile in 36 patients dosed with 0.03 mg/kg – 50 mg/kg (Q2W and Q4W schedules)
- Tumor biopsies show target occupancy and activation of APCs in B cell, plasma cell, and DC abundance, and IFN-γ production in the tumor microenvironment
- Increased serum levels of CXCL10 corroborate these findings

**The present data support planning of future combination studies**

**Proposed mechanism of action of MP0317**

- **Direct effects of MP0317**
  - MP0317 binds to FAP on CAFs and activates tumor-localized APCs
- **Indirect effects of MP0317**
  - Activating T cells and natural killer cells
  - Chemosensitizing peripheral immune cells in the tumor microenvironment
  - Target-localized activation of T and NK cells present within the TME

**Study status**

- **Study population**: 19 patients evaluable for safety/tolerability
- **Number of treatment-emergent adverse reactions (patients)**
  - Cohort 1: 0 (0)
  - Cohort 2: 0 (0)
  - Cohort 3: 1 (1)
  - Cohort 4: 3 (3)
  - Cohort 5a: 1 (1)
  - Cohort 5b: 1 (1)

**Characteristics of Patients (N=19)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>62 (35–79)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female (9 (47))</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>1 (17 (47))</td>
</tr>
<tr>
<td>Prior regimens, median (range)</td>
<td>0 (1–15)</td>
</tr>
<tr>
<td>Cancer type, n (%)</td>
<td>11 (31 %)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>7 (20 %)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2 (5 %)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>Breast</td>
<td>4 (11 %)</td>
</tr>
<tr>
<td>GIST</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>2 (5 %)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2 (5 %)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>Cervical</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>RCC</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>CCA</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>SCC</td>
<td>1 (2 %)</td>
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<tr>
<td>EOC</td>
<td>1 (2 %)</td>
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</table>

**Number of treatment-emergent adverse reactions (patients)**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>0 (0)</th>
<th>1 (1)</th>
<th>2 (2)</th>
<th>3 (3)</th>
<th>4 (4)</th>
<th>5 (5)</th>
<th>6 (6)</th>
<th>Total</th>
</tr>
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</table>

**Number of patients by cohort**

<table>
<thead>
<tr>
<th>Cohort no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>5a</th>
<th>5b</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td>00</td>
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</tr>
</tbody>
</table>

**Increased in CXCL10 serum levels post-MP0317 treatment**

Circulating CXCL10 in low dose cohorts (n=4) and circulating CXCL10 in higher dose cohort (n=13)

**Increased B, plasma and T follicular helper cell infiltration and IFNγ production in tumors post-MP0317 treatment**

- **MP0317 low dose cohort**
  - CXCL10 detected in tumor (n=0)
  - IFNγ detected in tumor (n=0)
  - CD4+ T cells detected in tumor (n=0)

- **MP0317 higher dose cohort**
  - CXCL10 detected in tumor (n=6)
  - IFNγ detected in tumor (n=6)
  - CD4+ T cells detected in tumor (n=6)

**Acknowledgments**

Representative multiplex immunofluorescence (1st image) displays a tumor-located and perivascular pattern in tumor biopsies showing MP0317 localization with FAP and CD40. TME analysis verified the presence of T cells (CD3+), and typical cells (DCs as CD11c+ and macrophages, lipid as CD68+ and F4/80 type as CD206+ CD11c+).

**Data cut-off**: 02 May 2023

**For any questions, please contact**: Hilde.DeWinter@molecularpartners.com

**At a statistically significant increase in DCs in tumors post-MP0317 treatment**

- **MP0317 low dose cohort**: not detected in tumor (n=0)
- **MP0317 higher dose cohort**: detected in tumor (n=6)

**Circulating CXCL10 in low dose cohorts (n=4)**

- **Basal**: 2000 (1900–2100)
- **C1D8**: 2000 (1900–2100)
- **C2D1**: 2000 (1900–2100)
- **C2D8**: 2000 (1900–2100)

**Circulating CXCL10 in higher dose cohort (n=13)**

- **Basal**: 2000 (1900–2100)
- **C1D8**: 2000 (1900–2100)
- **C2D1**: 2000 (1900–2100)
- **C2D8**: 2000 (1900–2100)