**GEN1042 (DuoBody®-CD40x4-1BB), a novel, agonistic bispecific antibody**

- **GEN1042 combines targeting and conditional activation of CD40 and 1BB on immune cells to enhance priming and bioactivation of human specific immunity.**
  - Strengthens the adaptive cell (CD8+ T cells) innate immune response, induces DC maturation, and enhances Th1 polarization, proliferation, and cytokine activity in vitro.
  - As a single-agent monotherapy, GEN1042 showed biology and early clinical activity with a manageable safety profile in patients with advanced cutaneous in the dose-finding part of the ongoing phase 1/2 trial (NCT04889287).
- The distinct and complementary mechanisms of action of GEN1042 support its clinical investigation as a combination partner to improve current standard of care across a range of solid tumors.
  - Preliminary data suggest that the magnitude of immune response generated by GEN1042 treatment can be amplified by co-administration of a RIL 1 inhibitor.
- Additional combinations with chemotherapies (CT) are being pursued to further enhance antitumor responses by increasing antigen release and PD-L1 expression.

**Pharmacological characterization of bispecific GEN1042**

- **Objective:** To investigate the pharmacological properties of GEN1042 in murine and human models.
- **Methods:** In vitro and in vivo assays were performed to determine the binding and functional properties of GEN1042.
- **Results:** GEN1042 demonstrated specific binding and pharmacological activity in both murine and human cell lines.

**Safety and Preliminary Efficacy of GEN1042 (DuoBody®-CD40x4-1BB) Combination Therapy in Patients With Advanced Solid Tumors**

- **Study Design:** A phase 1/2 open-label trial investigating GEN1042 in combination with pemtuzumab (pCTx).
- **Patient Population:** Patients with advanced solid tumors who failed standard of care.
- **Endpoints:** Safety, tolerability, and preliminary efficacy.

**Results:**

- **Safety:** No DLTs were reported.
- **Efficacy:**
  - 4 patients with HRGSC received GEN1042 + PEM + CTX; 1 patient had a partial response (PR).
  - 4 patients with NSCLC received GEN1042 + PEM + CTX; 2 patients had a partial response (PR).

**Conclusions:**

- GEN1042 has potential as a novel, synergistic approach for combination therapy in advanced solid tumors.
- Further studies are needed to fully evaluate the safety and efficacy of GEN1042 in combination with other agents.

**References**

- Ignacio Mekelis, MD, PhD. *Eduardo Grande, MD*, *Maria J. de Miguel*, MD, PhD.*
- Melissa Johnson, MD, *Vesna Barnard, MD*, *Victor Miro, MD*, PhD.
- Annette Wolter, PhD. *Heather Adams, MD*, *Dolun Yenel, MD*, *Giuseppe Russo, PhD*, *F. Javier Salas, MD*, PhD. *Jay X. Stemberg*, DO.
- Takeshi Aoyama, PhD. *Tomoyuki Goto*, ABD.
- Uğur Şahin, MD, PhD.
- Jay Steinberg, DO.
- Enriqueta Felip:

**Table of Related Adverse Events (≥10% of Patients) by Grade**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<td>Fatigue</td>
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<td>7.7%</td>
<td>11.5%</td>
<td>11.5%</td>
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<tr>
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<tr>
<td>Fatigue</td>
<td>7.7%</td>
<td>7.7%</td>
<td>11.5%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

**PD activity in HRGSC was consistent with GEN1042-mediated immune activation**

- **PD activity was evaluated on day 7 post treatment with GEN1042 + PEM + CTX + S-100**
- **Combination therapy in patients with HRGSC:**
  - Evaluation of protein expression (cytotoxicity) and of TARC (IL-17A AFC/PAC)
  - Observation of TARC (IL-17A AFC/PAC) activity in HRGSC cells, and in 4-color & 5-color cycle profiles

**Clinical benefit observed in patients with HRGSC receiving GEN1042 + PEM + CTX**

- 4 patients with HRGSC treated with GEN1042 + PEM + CTX + S-100 were evaluated for PD activity.
- Early preliminary data show that GEN1042 combination therapy induced deep responses in patients with HRGSC at first scan, which were sustained over time.
- Responses were seen in tumors with both low and high PD-L1 expression; all 4 patients were HPV negative.