**Immunotherapeutic effects of the TYK2 inhibitor SAR-20351 in syngeneic tumor models**

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**Abstract**

SAR-20351 inhibits cytokine signaling pathways dependent upon TYK2 and JAK1 in whole blood, with excellent selectivity over other validated signaling pathways. SAR-20351 was selected for further development following in vitro studies. It was shown to potently inhibit human peripheral blood mononuclear cell (PBMC) cytokine signaling in whole blood and tumor microenvironment in a range of syngeneic tumor models. SAR-20351 results in significant control of solid tumor growth and the microenvironment, which reverses the immune checkpoint signaling of solid tumors.

**Table 1**: Inhibition of STAT phosphorylation (pS/T) following cytokine stimulation of murine A20 lymphocytes in whole blood: IC50 (nM) ± SD.

<table>
<thead>
<tr>
<th>Model</th>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>CD43 ↑</th>
<th>CD3 ↑</th>
<th>CD8 ↑</th>
<th>MDSCs ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>A20</td>
<td>Monotherapy</td>
<td>10</td>
<td>86 ± 12</td>
<td>91 ± 3</td>
<td>238 ± 24</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>A20</td>
<td>Combination</td>
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<td>93 ± 8</td>
</tr>
</tbody>
</table>

**Figure 1**: Volume of PANC02 tumors implanted subcutaneously in C57BL/6 mice treated with SAR-20351 (10 mg/kg PO bid). A: vehicle control (100% T/C). B: SAR-20351 (50 mg/kg PO bid). C: combination with 5-FU (50 mg/kg PO bid). D: combination with 5-FU (50 mg/kg PO bid). E: combination with 5-FU (50 mg/kg PO bid).

**Figure 2**: Normalised lymph node cytokine mRNA expression in SAR-20351 treated and untreated mice. A: CD43 (Glycolipid). B: CD3 (Glycolipid). C: CD8 (Glycolipid). D: MDSCs (Glycolipid). E: combination with 5-FU (50 mg/kg PO bid). F: combination with 5-FU (50 mg/kg PO bid). G: combination with 5-FU (50 mg/kg PO bid).


**Effect of SAR-20351 on A20 tumor size in xenograft model:**

SAR-20351 was well tolerated and showed significant reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 50% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 30% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 40% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 50% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 60% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 70% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 80% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 90% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 100% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 110% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 120% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 130% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 140% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 150% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 160% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 170% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 180% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 190% reduction in tumor size compared to vehicle control. SAR-20351 (50 mg/kg PO bid) resulted in a 200% reduction in tumor size compared to vehicle control.

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**Conclusion and Future Directions:**

- SAR-20351 is a potent, selective, JAK/STAT inhibitor of TYK2 and reduces JAK/STAT phosphorylation downstream of cytokine stimulation in human tumors and human whole blood.
- In a range of tumor models, SAR-20351 is well tolerated and inhibits tumor growth when dosed orally in xenograft models.
- SAR-20351 is selective when co-treated with other therapeutic agents, suggesting that it is selective over JAK1 and JAK2, and that this is a key factor in tumor inhibition.
- SAR-20351 results in reduced cytokine production in tumors and the tumor microenvironment, including tumor necrosis factor-α (TNF-α) and IL-6, which are known to promote tumor growth and metastasis.
- SAR-20351 results in significant control of solid tumor growth and the microenvironment, which reverses the immune checkpoint signaling of solid tumors.
- SAR-20351 has been selected as a candidate for further preclinical development.

**References**

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