IMP761, a novel anti-LAG-3 agonist antibody for the treatment of auto-immune diseases

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Disclosures:

Conflict of interest: None
**IMP761 vs Auto-immune diseases: Mode of action**

- **Current therapies:** fighting the symptoms by treating inflammation (e.g. anti-TNF)
- **Future direction:** fighting the root cause of auto-immune diseases (activation of anti-self T cells)

**IMP761 (anti-LAG-3 agonist):**
- Down-regulates TCR signaling
- Blocks the activation of self-reactive memory T cells
IMP761 Inhibits human T cell proliferation and activation \textit{in vitro}

**Proliferation of (CFSE$^{\text{low}}$) CD8$^+$ T cells**

\begin{align*}
\text{CEF} & \quad \% \text{ of proliferating CD8}^+ \text{ T cells} \\
36.3\% & \quad 3.7\% \\
\text{CEF + IMP761} & \quad 8.6\% \\
\end{align*}

Mean of inhibition \( 50.5\% \)

**Activation of (CD25$^+$) CD8$^+$ T cells**

\begin{align*}
\text{CEF} & \quad \% \text{ of activated CD8}^+ \text{ T cells} \\
36.3\% & \quad 3.7\% \\
\text{CEF + IMP761} & \quad 8.6\% \\
\end{align*}

Mean of inhibition \( 38.3\% \)

Proliferation to CEF (CMV + influenza + EBV peptides)
Delayed-type hypersensitivity model in cynomolgus monkey

Study Design

<table>
<thead>
<tr>
<th>BCG1</th>
<th>BCG2</th>
<th>Tuberculin test 1</th>
<th>IMP761/PBS</th>
<th>Tuberculin test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-45</td>
<td>D-30</td>
<td>D-15/-13</td>
<td>D0</td>
<td>D1/3</td>
</tr>
</tbody>
</table>

Pharmacokinetics

0.3 mg/kg: 1,367 ng/ml
0.03 mg/kg: 165 ng/ml

Median [IMP761] at 24h:
- 0.03 mg/kg: 165 ng/ml
- 0.3 mg/kg: 1,367 ng/ml

Immunofluorescence staining

Inflammatory T cells infiltration at Tuberculin test site before and after IMP761/PBS injection

Tuberculin test 1

PBS

IMP761

Tuberculin test 2
IMP761 inhibits inflammatory T cell infiltration \textit{in vivo}

T cell infiltration
Inflammatory T cell infiltration at tuberculin site injection before compared to after treatment

IMP761 is able to inhibit significantly T cell infiltration of an antigen-specific intradermal reaction

\textbf{Multivariate analysis}

\textbf{PERMANOVA} **

% CD3\(^+\) cell infiltration
% CD4\(^+\) cell infiltration
% CD8\(^+\) cell infiltration
% Erythema size

IMP761 (mg/kg)
0.03 0.3
PBS

median

IMP761 0.3 mg/kg
PBS

IMP761 (mg/kg)
0.03 0.3
PBS

IMP761 inhibits inflammatory T cell infiltration \textit{in vivo}
Conclusions

• **The Goal:** a more targeted therapeutic approach for AID

• **The Target:** the self-peptide-specific “exhausted” memory T cells harboring LAG-3

• **The Tool:** IMP761, an agonistic LAG-3-specific mAb down-modulating self-peptide-induced TCR signaling

• **The Evidences:**
  - *in vitro* inhibition of peptide-induced human T cell proliferation and activation
  - *in vivo* down-modulation of an antigen-induced inflammatory T cell infiltration in a new NHP model

• **The Status:** Cell line development ongoing and GMP manufacturing preparations underway in order to progress to clinical development