Leukapheresis Collection Insights in Unstimulated Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving a Combination of Autologous Immunotherapy (AGS-003) and Sunitinib: From the Ongoing International ADAPT Phase 3 Trial Experience.

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Disclosures

• I am an Employee of Argos Therapeutics
Background- AGS-003

• A novel immunotherapy treating mRCC patients with primarily clear cell histology.
• An autologous, patient and tumor specific, cellular immunotherapy
  – designed to induce a memory T-cell response specific to a patient’s tumor antigens.
• To obtain the optimized dendritic-cells needed to manufacture AGS-003, a Leukapheresis collection is performed on unstimulated (unmobilized) pts.
• Monocytes isolated from a single Leukapheresis are matured into optimized dendritic cells, electroporated with autologous amplified tumor RNA and synthetic CD40L, then vialied and frozen prior to intradermal administration.
• A high quality, single Leukapheresis can deliver multiple years of treatment.
How is AGS-003 Produced for Each Patient?

- RNA that encodes autologous RCC antigens is isolated and amplified from a **small, fresh, viable, non-necrotic tumor sample (~200mg)** isolated during nephrectomy.
- Monocytes isolated from a **single leukapheresis** are differentiated into DCs.
- The mature DCs are **co-electroporated** with RCC and CD40L RNA, **vialled and frozen** for shipment.
- One production run yields **multiple years** of treatment per patient.
AGS-003 Contains Key Attributes Necessary for an Effective Immunotherapy

- Targets each patient’s disease-specific antigens, including mutated antigens
- Overcomes profound, baseline immune suppression that exists in advanced cancer
- Induces CD8+ CD28+ memory T cells known to correlate with good clinical outcome
- Minimal toxicity allows combinations with other therapies

Potentially Applicable to Wide Range of Cancers
ADAPT (AGS-003-007) Phase 3 Study Design

**Primary Endpoint**
To compare OS in subjects treated with AGS-003 in combination with standard targeted drug therapy (Arm A) versus standard targeted drug therapy alone (Arm B)

**Additional Endpoints**
- To compare progression-free survival (PFS) using RECIST 1.1 between study arms
- To compare objective tumor responses based on RECIST 1.1 between study arms
- To compare safety assessments between study arms
- To compare immunologic responses between study arms (T regs, MDSCs, memory T cells)

*Standard therapy initiates with sunitinib. Other therapies may be substituted for sunitinib intolerance or progression.*
Methods

• We performed a retrospective data analysis of all randomized patients from Feb 2013 through April 2015,
  – 374 pts were randomized
  – 249 pts. to the combination arm
  – 226 pts had a Leukapheresis collections performed
• 14 pts were not able to be collected due to early study withdrawal.

• All FDA-approved apheresis devices are eligible for Leukapheresis collections in the study.

• The desired target values for each collection are as follows:
  – Mononuclear cell yield > 3 x10⁹
  – Mono: Gran ratio > 3
  – RBC vol. < 7.5
Methods

• Review of the data from these Leukapheresis collections, and the pts clinical and lab findings, several parameters were found to impact the final product.

• Like other diseases affecting the kidneys, mRCC has the potential to alter RBC hematopoiesis causing shifts in EPO levels.
  – Lower EPO levels are consistent with anemia, sometimes microcytic in nature.

• Thrombocytosis and hypercalcemia has also been described in these pts.

• Metastatic RCC may also cause systemic inflammation, increasing plasma proteins and viscosity.
Results

• A total of 301 LCs have been performed and processed.
• All targets were met in 163 LC
• 138 LC had ≥ 1 parameter(s) that were below desired targets.
• Low Monos occurred in 43 collections
• 95 collections had high Grans.
• A review of the patients screening labs and clinical findings is conducted to identify potential modifications prior to each LC and communicated to the collection staff.
Results

- Initially the WBV processed requested a minimum of 2 TBV (10-12L). A review of collections with lower yields resulted in a wide range of actual WBV processed across all participating apheresis centers.

- As a result, the guidelines for collection were modified to process a minimum of 12L of WBV and an upper limit of 20L was set.

- In addition with the help from the Scientific Support Group at Terumo BCT we developed a decision pathway and prediction algorithm to use for all our collections.
  - The Decision Pathway and updated equipment and software settings were incorporated into the most recent version of the ADAPT Leukapheresis Manual with input from both the Clinical and Scientific Group at TerumoBCT and R&D group at Fresenius Kabi.
## Prediction Algorithm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono Yield x 10e9</td>
<td>3.0E+09</td>
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<tr>
<td>Mono CE2%</td>
<td>50</td>
</tr>
<tr>
<td>WBC pre- x10e3/µl</td>
<td>6.6</td>
</tr>
<tr>
<td>% Mono pre-</td>
<td>4.9</td>
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<tr>
<td>Inlet:AC Ratio</td>
<td>12</td>
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</tbody>
</table>

**Enter values in blue cells only!**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB volume to process</td>
<td>18553</td>
</tr>
<tr>
<td>Inlet Volume to process</td>
<td>20240</td>
</tr>
</tbody>
</table>

**Enter values in blue cells only!**
Results

ADAPT Leukapheresis Manual

Date: 03 February 2015
Leukapheresis Decision Pathway
## Lab Data

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Average Value</th>
<th>Average Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca+</td>
<td>9.3 g/dL</td>
<td>8.6 – 9.5 g/dL</td>
</tr>
<tr>
<td>Total Protein</td>
<td>7.2 g/dL</td>
<td>5.9 – 7.9 g/dL</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>27.8 mg/L</td>
<td>14.8 – 58.2 mg/L</td>
</tr>
<tr>
<td>WBC</td>
<td>7.9 x10³/µl</td>
<td>3.0 – 8.4 x10³/µl</td>
</tr>
<tr>
<td>% Monocytes</td>
<td>7.0 %</td>
<td>3.9 – 8.7 %</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.2 g/dL</td>
<td>10.9 – 13.1 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38 %</td>
<td>34 – 40 %</td>
</tr>
<tr>
<td>Platelets</td>
<td>321 x10³/µl</td>
<td>180 – 500 x10³/µl</td>
</tr>
<tr>
<td>MCH</td>
<td>27.9 pg</td>
<td>27.8 – 33.1 pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.3 g/dL</td>
<td>32.2 – 33.2 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>86.4 fL</td>
<td>85.7 – 101.1 fL</td>
</tr>
</tbody>
</table>
Next Steps

• We expect to close the enrollment to the study in early summer
• All apheresis data will be analyzed and published in late 2016.
• Revision of our prediction algorithm
• Develop an automated tool for the evaluation and recommendations using the current decision pathway
Conclusion

• Patient and tumor-specific cellular immunotherapy represents an important potential advance in treating pts with a variety of mutations and malignancies.

• Identifying factors which impact the successful collection of MNC for cellular immunotherapy manufacturing will be integral to future research and treatment success.

• A review of patient clinical, lab, and Leukapheresis collection results from the ADAPT study has provided data to create a prediction algorithm and decision pathway to improve collections specific to the available type of apheresis equipment and software version.

• Additional information on all remaining Leukapheresis collections will be collected through the completion of the ADAPT study to monitor trends and provide ongoing validation of the current guidelines.
Acknowledgements

Thanks To Our

- Apheresis Centers
- Manufacturing Team at Argos
- Scientific Affairs Group at Argos
- The Scientific Support Group at Terumo BCT
- Fresenius KABI R&D Group