iSBTc Oncology Biologics Development Primer
February 28-29, 2008
Dendritic Cell Based Products

RNA electroporated CD14-derived Dendritic Cells
Overview

• Introduction to DCs and Arcelis™
• Issue 1: Non-Clinical Package
• Issue 2: Phase 1 Considerations
• Issue 3: Translational Package
• Issue 4: Product Optimization
• Issue 5: Suitable Study Designs
• Issue 6: Combination Therapy
• Issue 7: cGMP Manufacturing
• Discussion
Dendritic cells (DCs):

- Link between innate and adaptive immunity
- Organize and transfer information from the outside world to the cells of the adaptive immune system
- Versatile controller of the immune system
- Peripheral monocyte or bone-marrow-derived
- Immature - self tolerance
- Mature – induction of antigen specific immunity
- Impaired DC function leads to or associated with:
  - Autoimmunity: lupus, arthritis, psoriasis
  - Allergy
  - Cancer
Dendritic Cell – T-cell:
Interaction between innate and adaptive immunity facilitated by IL-12

The interaction between dendritic cells (DCs) and T cells involves three signals

*Expert Reviews in Molecular Medicine © 2002 Cambridge University Press*
Present Use of DCs in Clinical Studies

- Various strategies of differentiation
- Various loading strategies
  - Passive vs. active
  - Peptides, RNA, DNA constructs
- Various clinical administration strategies
  - Intradermal
  - Intranodal
  - Subcutaneous
  - Intravenous
Argos Autologous RNA-Loaded Dendritic Cell Immunotherapy: Arcelis™

• Powerful Antigen Presenting Platform
  – *Monocyte-derived dendritic cells* (DCs)

• Effective Antigen Amplification Platform
  – *RNA-based*
  – Polyvalent
  – Captures “private mutations’

• Advanced Processes
  – *Centralized manufacturing*
  – Automated, functionally closed

• Ability to induce effective CD8 response without the need to activate CD4+ compartment (HIV)
Arcelis™ Platform Overview

**Clinical Site**
- Small Amount of Tumor Cell or Pathogen
- Leukapheresis

**Centralized Manufacturing Facility**
- Tumor Cell or Pathogen → Amplified RNA
- Monocytes
  - Partially Mature Dendritic Cell
- Formulated for Direct Injection
- Mature Dendritic Cell
- Partially Mature Dendritic Cell

**In Body**
- Mature Dendritic Cell → Lymph Node
- Mature Dendritic Cell + T-cell
- Antigen-Specific T-cell
- Pathogen-infected or tumor cell
Arcelis™ Platform in Three Clinical Settings

• Renal Cell Carcinoma (RCC)
  – Single agent
  – Combination with TKI

• Chronic Lymphocytic Leukemia (CLL)
  – Hematologic tumor

• Human Immunodeficiency Virus (HIV)
  – Infectious disease
Issue 1: Non-Clinical Package
Issue 1: Non-Clinical Package
Chemistry Manufacturing Controls

- Celltherapy not a “well defined drug”
- Product defined through process and controls
- Product Characterization
  - In-process QC
  - Sterility
  - Phenotypic Characterization
  - Viability
  - Stability
  - Release
  - Controlled Storage
  - Controlled Shipment
Issue 1: Non-Clinical Package
Chemistry Manufacturing Controls

• Translate academic bench research into a GMP compliant manufacturing process
  – Academia ➔ Development Stage Manufacturing
  – Local ➔ Central
  – Fresh Leukapheresis ➔ Day old
  – Conventional Cell-culture ➔ Functionally closed
  – Experience/Art ➔ Standardized/Reproducible
Current Processing Overview - Oncology

**Tumor Collection**
- Isolate Tumor Total RNA
- Synthesize, Amplify, & Purify cDNA
- Produce & Purify IVT RNA

**Leukapheresis Collection**
- Isolate Monocytes (Elutriation)
- Freeze Cells
- Cryogenic Storage
  - Thaw & Culture Cells to Produce Immature Dendritic Cells
  - Add Maturation Media
  - Culture
    - Harvest Mature Dendritic Cells & Load with RNA Antigen
    - Culture

**Plasma Collection**
- Plasma Heat Inactivation & Processing

**Plasma Heat Inactivation & Processing**
- Harvest, Formulate, & Freeze Final Product

**Cellular Collection**
- Harvest Mature Dendritic Cells & Load with RNA Antigen
Issue 1: Non-Clinical Package
Toxicology

- Autologous product
- Conventional test not applicable
- Lack of adequate animal models
- Academic Human Data specific to the product
  - Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. 2003; 63(9): 2127-33

- Collective Published Evidence in the field
  - The first 1000 dendritic cell vaccinees. Cancer Invest. 2003; 21(6): 873-86
Issue 2: Phase 1 Considerations
Issue 2: Phase 1 Considerations

• Choice of clinical setting - RCC
  – Tumor type
    • “susceptible to immunotherapy”
    • Only curative treatment: High dose IL-2
  – Extent of tumor
    • Adjuvant vs. MRD vs. bulky
    • Primary removed per standard of care
  – Medical Need and Market Potential
    • 2004: chemo/radio-resistant, just IFN and IL-2
  – Pre-existing evidence
    • Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. 2003; 63(9): 2127-33
    • Comparison of “academic” product and data with “corporate” data
Issue 2: Phase 1 Considerations

- Endpoints
  - Safety
    - Dose: Conventional dose escalation/MTD not applicable
    - General CTCAE
    - Special considerations re: auto-immunity
      - Lab panel: RF, ANA, etc.
      - Renal function: contra-lateral kidney in place
  - Biologic activity
    - Large volume IM blood draws for ELISpot
    - IM leukapheresis
  - Clinical activity
    - Indicator lesion(s) – RECIST
    - Survival endpoints
A PHASE I/II STUDY IN PATIENTS WITH STAGE IV RENAL CELL CARCINOMA (RCC) VACCINATED WITH AUTOLOGOUS DENDRITIC CELLS (DCS) TRANSFECTED WITH AUTOLOGOUS AMPLIFIED TUMOR-DERIVED mRNA

JJ Knox, DK Ornstein, WK Rathmell, MK Wong, M Jewett, LH Finke, F Miesowicz, CA Nicolette, G Batist
Completed Phase 1/2 RCC Trial - Design

Dosing Regimen:
• 5 x every 2 weeks
• 4 x every 4 weeks
• Every 12 weeks until progression
• Follow up for survival

1st line standard of care

Nephrectomy (Nx)

Recovery RNA prod.

DC prod.

Leukapheresis (Lx)

D

D

D

D

D

D

D

D

D
Phase I/II RCC Study - Safety

- No autoimmune AEs, No kidney function impairment
- No drug related SAEs and no drug related Grade III or IV AEs
- 88% of all AEs were Grade I or II
  - 54% of AEs were related to MB-002
  - 95% of MB-002 related AEs were due to injection site reactions

<table>
<thead>
<tr>
<th>Drug Related Adverse event</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>General/administration site (i.e., injection site rxn, axillary pain, fatigue, flu-like illness)</td>
<td>70%</td>
</tr>
<tr>
<td>Skin/subcutaneous tissue (i.e., rash, pruritis, urticaria)</td>
<td>30%</td>
</tr>
<tr>
<td>Musculoskeletal (i.e., arthralgia, stiffness)</td>
<td>20%</td>
</tr>
<tr>
<td>Nervous system (i.e., headache)</td>
<td>10%</td>
</tr>
<tr>
<td>Lymph Node pain</td>
<td>5%</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>5%</td>
</tr>
</tbody>
</table>
Phase I/II RCC Study – Clinical Activity

• Clinical Endpoints
  – Predominantly stable disease
  – No confirmed objective response
  – Disease stabilization upon induction treatment in 5 out 6 subjects who experienced progression between Dx and start of treatment
Phase I/II RCC Study - Activity

- Immune Response (ELISPOT)
  - RCC patients were deficient in T cell IFN-γ and IL-2 production pre-treatment
  - Patients recovered some but not all immune deficiency
  - MB-002 treatment induced an increase in tumor antigen-specific* T cells in 8 of 12 Pts
  - 7 of 12 patients had response to more than one RCC biology relevant antigens post-treatment
### RCC Study - Activity

<table>
<thead>
<tr>
<th></th>
<th>Arcelis</th>
<th>IFN alone</th>
<th>Nexavar</th>
<th>Sutent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominant MSKCC score</strong></td>
<td>0-2</td>
<td>0-2</td>
<td>0-2</td>
<td>0-2</td>
</tr>
<tr>
<td>**Progression-free survival</td>
<td>6.9</td>
<td>4.1</td>
<td>5.7</td>
<td>11</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Median overall survival</td>
<td>24.7</td>
<td>11.1</td>
<td>17.8</td>
<td>TBD</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Side-effect profile</strong></td>
<td>No serious side effects</td>
<td>Fatigue, Depression</td>
<td>GI, skin toxicities</td>
<td>Hematologic, GI toxicities</td>
</tr>
</tbody>
</table>
Report Card: First Corporate Study

• Signals of clinical activity
  – PD to SD
  – PFS and OS

• Cytokine maturation product has incomplete biologic activity
  – IL-2 but no IFN-γ

• Feasibility
  – Central manufacturing
  – Central immune monitoring
Lessons Learned: First Corporate Study

- RCC induces profound immune suppression
- **Healthy volunteer material, although essential for process development and qualification work has limitations**
- Further translational research needed to tackle RCC impact on immune system
- **Further product optimization needed for full biologic activity in the RCC advanced stage background**
Issue 3: Translational Package
Issue 3: Translational Package

• Multiple procurement protocols –
  Non-Treatment Studies
  – Tissue
  – Blood draws & Leukapheresis
    • RCC: No systemic treatment, TKI
    • HIV: pre-ART and on ART
    • CLL: Leukemia cells vs. healthy monocytes

• PoP studies
  – VHL typing and immune response mapping
Issue 4: Product Optimization
Arcelis™
Three Generations of Products

1st Generation
Academic Product
- Total tumor RNA
- Passive transfection

2nd Generation
MB-002
- Amplified total tumor mRNA
- Active electroporation
- Cytokine maturation

3rd Generation
AGS-003
- Amplified total tumor mRNA
- Active electroporation
- PME CD40L maturation
- Elutra FT improved monocytes

Immature DCs
Mature DCs
Dendritic Cell – T-cell:
Interaction between innate and adaptive immunity facilitated by IL-12

The interaction between dendritic cells (DCs) and T cells involves three signals

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press
Issue 4: Product Optimization

• Rational
  – Immune monitoring told us that cytokine maturation process does not yield the full biologic activity when applied to RCC subjects
  – Safety and clinical data quite encouraging

• Action taken
  – Take CD40L co-stimulation into the manufacturing process and optimize maturation and loading protocol
  – Cut turn around time
  – Move to functionally closed systems
  – Start robotized manufacturing program

• Implementation
  – Tech Transfer and qualification
  – Regulatory submission
Issue 5: Suitable Study Designs
Issue 5: Suitable Study Designs

1. Confirmation of biologic rational
   - When going back to the clinic, first confirm that with the PME-CD40L product shows desired biologic activity: IL-2 & IFN-γ by ELISpot
   - Confirm similar safety profile
   - Build on legacy data from previous studies

2. Conserve resources in a VC funded start-up environment
   a. Start with a small PoP sample with a strict go/no-go criterion for in vivo biologic activity
   b. Adapt to single stage or two stage phase 2 design

3. Collect information on accepted oncology clinical endpoints
   - RECIST endpoints
   - PFS, OS
AGS-003-004

A PHASE I/II STUDY TESTING THE BIOLOGIC ACTIVITY AND SAFETY OF AGS-003 AS AN IMMUNOTHERAPEUTIC IN SUBJECTS WITH NEWLY DIAGNOSED ADVANCED STAGE RENAL CELL CARCINOMA (RCC)
AGS-003-004
Study Overview

• Step I:
  – Objective:
    > 5/8 subjects with polyvalent IL-2 and IFN-γ immune monitoring AND safety similar to first study

• Step II:
  – Two stage design
    • 18 + 17
  – Objective:
    • 3 PR / 18
    • 5 PR / 35
    • Monitor pertinent accepted clinical endpoints
    • Continue thorough immune monitoring
## SUMMARY OF IMMUNE MONITORING DATA

### Pre-Vaccination

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>F</td>
<td>-</td>
<td>F,G</td>
<td>G,S,F</td>
<td>F</td>
<td>G,F,S</td>
<td>E,G</td>
<td>-</td>
</tr>
<tr>
<td>002</td>
<td>-</td>
<td>-</td>
<td>S</td>
<td>F,S</td>
<td>S</td>
<td>G,F</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>003</td>
<td>-</td>
<td>S</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>S,F</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>F</td>
<td>S,F</td>
<td>S,F</td>
<td>-</td>
</tr>
<tr>
<td>005</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>S,G,T,F</td>
<td>S,G,F</td>
</tr>
</tbody>
</table>

### Post-Vaccination

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
<th>IFN-$\gamma$</th>
<th>IL-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>F</td>
<td>-</td>
<td>F,G</td>
<td>G,S,F</td>
<td>F</td>
<td>G,F,S</td>
<td>E,G</td>
<td>-</td>
</tr>
<tr>
<td>002</td>
<td>-</td>
<td>-</td>
<td>S</td>
<td>F,S</td>
<td>S</td>
<td>G,F</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>003</td>
<td>-</td>
<td>S</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>S,F</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>F</td>
<td>S,F</td>
<td>S,F</td>
<td>-</td>
</tr>
<tr>
<td>005</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>S,G,T,F</td>
<td>S,G,F</td>
</tr>
</tbody>
</table>

### AGS-003

**Immune Monitoring: First data with AGS-003**

### MB-002
AGS-003-004
Study Overview (Step II)

• Open-label, multi-center, two-stage, Phase I/II single agent clinical study
• Subjects with newly diagnosed metastatic clear cell RCC
• Primary endpoints:
  – Clinical response: PR and CR (RECIST)
  – Immune response
• Secondary endpoints:
  – Overall and progression free survival (RECIST)
  – AGS-003 production feasibility
  – Safety
  – Exploratory assays of T cell functionality and AGS-003 immunogenicity
Issue 6: Combination Therapy
Arcelis TKI Combination - Rationale

- SORAFENIB BUT NOT SUNITINIB INHIBITS HUMAN T-CELL FUNCTION (iSBTc Oct 2007)
- Supported by four independent groups
  - Immatics (Germany)
  - Cleveland Clinic
  - Dana Farber
  - Argos (leukapheresis material from TKI treated patients and in vitro studies)
- Arcelis / Sunitinib combination
  - First protocol to clear FDA and Health Canada
Dual Track Ph II Clinical Study Program:
- Newly diagnosed advanced stage RCC -

Single Agent first line (2 Stage “Simon Design”)

<table>
<thead>
<tr>
<th>Induction Phase</th>
<th>Booster Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Repeat every 3 months</td>
</tr>
<tr>
<td>AGS alone</td>
<td>Arcelis™ i.d.</td>
</tr>
<tr>
<td>AGS/TKI combo</td>
<td></td>
</tr>
</tbody>
</table>

Combination with Sunitinib first line (Singe stage design)

<table>
<thead>
<tr>
<th>Induction Phase</th>
<th>Booster Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Repeat every 3 months</td>
</tr>
<tr>
<td>TKI alone</td>
<td>Sunitinib QD 4 weeks, 2 weeks off</td>
</tr>
<tr>
<td>AGS/TKI combo</td>
<td>Arcelis™ i.d.</td>
</tr>
</tbody>
</table>

Nx - nephrectomy  - Arcelis™ Dosing

Argos Therapeutics
AGS-003-006

A Phase II Study Testing the Safety and Activity of AGS-003 as an Immunotherapeutic in Subjects with Newly Diagnosed Advanced Stage Renal Cell Carcinoma in Combination with Sunitinib
Arcelis TKI Combination - Design

- Multi-center single stage Phase II Study
- Centers in US and Canada
  - Plenty of very supportive interaction with FDA and Health Canada leading up to the IND and CTA submissions
- Newly diagnosed RCC or metachronous metastatic disease
  - Leukapheresis prior or after surgery
  - RNA from nephrectomy or metastectomy specimen
  - Cycled into Sunitinib (at reconstitution and prior to leuk drop)
- Requires a DMC
Issue 7: cGMP Manufacturing
Milestones in Process Development

1st Generation
Academic Product
- fresh monocytes
- open cell culture
- little GC

2nd Generation
MB-002
- day old monocytes
- flask culture
- establish GMP quality systems
- 12 weeks turn around
- establish clinical development & regulatory departments
- SOPs, practices, standards

3rd Generation
AGS-003
- PME CD40L process
- bag culture
- functionally closed systems

Robotized Automation
- more functionally closed systems
- modular, scalable manufacturing units

Immature DCs

Mature DCs
Automated Manufacturing Process

Clinical Site

Small tumor/virus sample → Leukapheresis

Centralized Manufacturing Facility

RNA Extraction/Amplification → Amplified RNA

Cellular Processing, Formulation, & Fill

Monocyte Isolation → Intradermal Injection
RNA Automated Processing
Conclusions
Case Studies: Lessons and Issues
Autologous RNA loaded DCs – Arcelis™

• Key Strategic Decisions
  – Are cooked fresh every morning
  – Stick to your biologic hypothesis
  – Ask every day: “what made us put this into the clinic?”

• Impact of Regulatory Interactions
  – Crucial and enabling

• Financial Considerations: Projected Costs vs. Reality
  – Cost: Follow press releases of companies in this space
  BUT
  – Personalized celltherapy can be done now!

• Lessons Learned
  – Immune monitoring
  – Limitations of healthy volunteer material
  – Single agent vs. combination in present day oncology
Acknowledgments

- Clinical Investigators
- Healthy volunteers and patients on the non-treatment protocols
  - Samples, leukaphereses
- Patients and their families on the clinical studies
- Scientific founders and investors
- iSBTc allowing us to present