Clinical Updates for Advaxis’ Pipeline of \( Lm \)-based Immunotherapies in Oncology

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**Lm Platform Designed to Trigger Strong Immune Responses against Targeted Antigens**

### Three Core Components

- **Attenuated Lm**
- **Carrier Vector**
- **Fusion protein**
- **tLLO**
- **Tumor-Associated Antigen**

### Comprehensive Immune Activity

- **Listeria monocytogenes (Lm) bacteria**
  - Carrier vector; irreversibly attenuated\(^\text{(1)}\)
  - Tropism to spleen, lymph nodes, liver, lung, primary tumor & metastasis
  - Well understood and manageable safety profile, to date

- **tLLO**
  - Adjuvant properties
  - Neutralize Tregs & MDSCs protecting the tumor

- **Diverse tumor-associated antigens**
  - Viral antigens (HPV+)
  - Cancer type-specific (PSA, HOT)
  - Patient-specific neoantigens (NEO)
  - Powerful CD8+ T cell response and antigen spreading

Legend: MDSC myeloid-derived suppressor cell | TAA tumor associated antigen | tLLO truncated fragment of listeriolysin O | Treg regulatory T cell.

Note: (1) attenuation renders the bacteria “harmless” to administrate.
**Lm Technology™: Overview – Harnessing Unique Life Cycle of Lm in APCs**

1. Lm-based vector is phagocytosed by APC
2. Some Lm escape the phagosome and enter the cytosol
3. Secreted tLLO-TAA fusion proteins are degraded by proteasomes into peptides for presentation by the MHC class I pathway
4. Lm that do not escape the phagosome are killed in the phagolysosome. Expressed tLLO-TAA fusion proteins are degraded into peptides that enter the MHC class II pathway
5. Recognition of surface peptide-MHC complexes by TAA-specific CD4+ (MHC II) and CD8+ (MHC I) T cells leads to their activation and differentiation into T cell effectors

Legend: APC antigen-presenting cell | Lm Listeria monocytogenes | MHC major histocompatibility complex | TAA tumor-associated antigen | tLLO, truncated listeriolysin O.
**Lm effects on primary tumor and establishment of metastases**

Canine osteosarcoma with T cell infiltration after ADXS-HER2 therapy

Frequency of metastases and tumor weight after a combination of one preventive and two therapeutic immunizations in BALB/c mice injected with 4T1 tumor cells

Krupar R et al., Advaxis Meeting_AACR 2016; Phee H. et al., European Neoantigen Summit, 2018; Kim SH et al., Cancer Res 2009, 69:5860; Mason NJ et al., CCR, 2016, 22

Disease-free survival in dogs with osteosarcoma without preexisting metastatic disease treated with ADXS-HER-2 and historical controls
Combination with Checkpoints and Co-Stims May Improve Outcomes

**Checkpoint Inhibitors:**
- PD-1/PD-L1
- CTLA-4
- TIGIT

**Co-stimulatory agonists:**
- CD137/41BB
- OX40
- GITR

**TME acting agents:**
- CSF1R
- HDAC1 inhibitor
- CCR8
- PEG rHuPH20(1)

**Standard-of-care regimens:**
- Chemotherapy
- Radiation

CPI, checkpoint inhibitor; TME, tumor micro-environment. (1) In collaboration with Halozyme.

Selected Examples

**Checkpoints and Co-Stims**

- **AXAL + aPD-1**
- **AXAL + aGITR**
- **AXAL + aOX-40**

**Tumor Volume (mm³)**

- Days after tumor implantation

**PBS**
- Isotype control
- AXAL
- AXAL + aCTLA4 (50µg)
- AXAL + aCD137 (200µg)

**PEG rHuPH20**
- Isotype control
- AXAL
- AXAL + aCTLA4 (50µg)
- AXAL + aCD137 (200µg)

**Mkrtichyan M et al., J Immunotherapy Ca, 2013, 1:15; Shrimali R et al., J Immunotherapy Ca, 2017, 5:64; Kosoff RE et al., SITC Annual Meeting 2016**
Our Development Strategy

The Past…

Asset Centric

- ADXS-HPV
  - HPV+ cancers: cervical, anal & head and neck
- ADXS-HER2
  - Breast cancer and sarcomas
- ADXS-PSA
  - Advanced prostate cancer
- ADXS-NEO
  - Personalized multi-neoantigen immunotherapy
    - TMB approach: NSCLC > CRC > head and neck
- ADXS-HOT (n >10)
  - Off-the-shelf, tumor type-specific immunotherapy
  - > 10 discrete constructs have been designed

The Present…

Disease/Patient Centric

- ADXS-PSA:
  - KN-046: Phase 1/2 monotherapy data and combination data with Keytruda in Metastatic Castration Resistant Prostate Cancer - Completed
- ADXS-504:
  - Phase 1/2 monotherapy data in prostate cancer patients with biochemical recurrence after radical therapy – IST
- ADXS-503:
  - Phase 1/2 monotherapy data and combination data with Keytruda in NSCLC – Ongoing

PoC studies with monotherapy in late stage patients with high tumor burden

Prolong PFS/OS by selecting pts in earlier stages of the disease and by using combination therapy
Positioning of ADXS-PSA in the Prostate Cancer Treatment Landscape

**ADXS-PSA** expresses a truncated fragment of the listeriolysin (tLLO) fused to human PSA.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>Non-metastatic</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Castration</td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
KEYNOTE-046 ± Pembrolizumab in mCRPC

ClinicalTrials.gov Identifier: NCT02325557

Title: A Phase 1/2 Dose-Escalation and Safety Study of ADXS31-142 Alone and in Combination With Pembrolizumab in Patients With Previously Treated Metastatic Castration-Resistant Prostate Cancer

Trial design:

<table>
<thead>
<tr>
<th>Safety Phase</th>
<th>Efficacy Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part A</td>
<td>Part B</td>
</tr>
<tr>
<td>ADXS-PSA Monotherapy Dose Escalation 3+3 Design</td>
<td>ADXS-503 + aPD1 antibody Dose Determination</td>
</tr>
<tr>
<td>1x10^10 CFU of ADXS-PSA (n = 4)</td>
<td>1x10^10 CFU of ADXS-PSA + pembrolizumab (200mg)</td>
</tr>
<tr>
<td>Part B Expansion</td>
<td>Part B Expansion</td>
</tr>
<tr>
<td>ADXS-503 + aPD1 antibody Expansion</td>
<td>ADXS-503 + aPD1 antibody Expansion</td>
</tr>
<tr>
<td>5x10^9 CFU of ADXS-PSA (n = 3)</td>
<td>1x10^9 CFU of ADXS-PSA + pembrolizumab (200mg)</td>
</tr>
</tbody>
</table>

• 12-week dosing cycle
• 3x PSA every 3 weeks (wk 1, 4, 7)
• For up to 24 months or until disease progression or discontinuation.

• 12-week dosing cycle
• 3x PSA every 3 weeks (wk 1, 4, 7)
• 4x Pembrolizumab every 3 weeks (wk 1, 4, 7, 10)
• For up to 24 months or until disease progression or discontinuation

n = 14
n = 37

- Keynote-046 PhI/II study
  - Parts A - ADXS-PSA Monotherapy
  - Part B - ADXS-PSA 1x10^9 CFU +/- 200mg pembrolizumab established as R2PD

- Part B-combination might be associated with prolonged survival
  - MSI-H negative status
  - visceral metastases ~30%
  - prior chemotherapy ~60%
  - prior NGHAs ~90%

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Overall</td>
<td>37</td>
<td>16</td>
<td>33.7</td>
<td>15.4-33.6</td>
</tr>
<tr>
<td>No prior docetaxel</td>
<td>17</td>
<td>3</td>
<td>NR</td>
<td>15.1-NR</td>
</tr>
<tr>
<td>Post-docetaxel</td>
<td>20</td>
<td>13</td>
<td>16.0</td>
<td>6.4-34.6</td>
</tr>
<tr>
<td>Prior visceral mets</td>
<td>11</td>
<td>6</td>
<td>16.4</td>
<td>4.0-NR</td>
</tr>
<tr>
<td>No visceral mets</td>
<td>26</td>
<td>10</td>
<td>33.7</td>
<td>15.1-NR</td>
</tr>
</tbody>
</table>

Legend: CFU Colony-Forming Unit | NGHA next generation hormonal agent | R2PD recommended phase 2 dose.
**ADXS-HOT PROGRAM**

Targeting Multiple Hotspots, OFAs and CTAs Increases Patient Applicability and Clinical Activity Potential

Hotspot mutations have demonstrated **pre-clinical activity** in Advaxis’ *Lm* Technology

ADXS-HOT constructs target both public, or shared, hotspot neoantigens and multiple proprietary tumor associated antigen targets, including oncofetal antigens (OFAs) and cancer testis antigens (CTAs)

- Over 10 drug candidates designed using this approach
- CD8 + T cell activity vs. hotspot mutations has been documented in a personalized neoantigen vaccine program, ADXS-NEO

**Coverage of nearly 100%**

ADXS-HOT constructs can include **over 30 antigen targets** and are designed to allow for multiple shots on goal to control the tumor in nearly all patients

**Antigen spreading could further increase the potential number of targets**

Can be used as **monotherapy and/or in combination** with other cancer treatments like checkpoint inhibitors

Off-the-shelf and available for patients to start treatment immediately

Manufactured in bulk with good stability keeping cost of goods low vs. “individualized” products

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1. Data on file, Advaxis, Inc. 2019
HOT ADXS-503 in metastatic NSCLC

Off-The-Shelf \textit{Lm}-vector Designed to Trigger Strong Anti-Tumoral Immune Responses with Targeted Antigens

\textbf{ADXS-503} expresses a truncated fragment of the listeriolyisin (tLLO) fused to highly prevalent antigens in cancer genes:

\textbf{11 hot spots in:} KRAS, EGFR, U2AF1, BRAF, PIK3CA and TP53

\textbf{11 oncofetal & cancer testis:} CEACAM5, STEAP1, RNF43, MAGE A6, NYESO1, GAGE1

\begin{itemize}
  \item Disease Control by Tumor Volume CT26 Model
  \item Specific T-cell responses and antigen spreading after infusion of ADXS-NEO in MSS CRC patient with KRAS G12A (Hit Rate 73-90% at W5 and W8)
\end{itemize}

Data on file, Advaxis, Inc. 2019; Hecht JR et.al., AACR Annual Meeting, 2019
ADXS-503 ± Pembrolizumab in recurrent & first line therapy of NSCLC

Title: A Phase 1/2, Open-Label Study of ADXS-503 Alone and in Combination with Pembrolizumab in Subjects with Metastatic Squamous or Non-Squamous Non-Small Cell Lung Cancer

Endpoints:
- Primary
  - Tolerability/ Safety
  - RP2D recommended phase 2 dose
- Secondary
  - Clinical activity
  - Exploratory
    - Immunological

Preliminary Results
- Part A, in monotherapy and Part B, in combination with Pembrolizumab
  - Completed Part A (n=7)
    - No dose limiting toxicities observed
    - Most AEs were grade 1-2 chills, fever and nausea; reversible and manageable
    - SD observed in 3 pts
  - Currently enrolling patients in Part B (n=2)
    - Safe and tolerable in 2 pts treated at DL-1
    - One SD and one PR observed
  - Immune-correlative work in progress

Safety Phase
- Part A
  - ADXS-503 Monotherapy Dose Escalation 3+3 Design
  - 5x10⁶ CFU of ADXS-503 (DL2)
  - 1x10⁶ CFU of ADXS-503 (DL1)
  - Refractory setting
  - Up to 3 lines prior therapy permitted
  - Enrollment irrespective of EGFR/ALK mutation status or PD-L1 expression
  - n = 6-12

- Part B
  - ADXS-503 + aPD1 antibody Dose Escalation 3+3 Design
  - 5x10⁶ CFU of ADXS-503 (DL2) + anti-PD1 antibody
  - 1x10⁶ CFU of ADXS-503 (DL1) + anti-PD1 antibody

Efficacy Phase
- Part B
  - ADXS-503 + aPD1 antibody

- Part C
  - ADXS-503 + aPD1 antibody

Legend: CFU Colony-Forming Unit | DL dose level | NSCLC non-small cell lung cancer | RP2D recommended phase 2 dose | DL dose level.

ClinicalTrials.gov Identifier: NCT03847519

Legends: CFU Colony-Forming Unit | DL dose level | NSCLC non-small cell lung cancer | RP2D recommended phase 2 dose | DL dose level.
ADXS-504 expresses a truncated fragment of the listeriolyisin (tLLO) fused to highly prevalent antigens in cancer genes:

14 hot spots in:
CHEK2, RGPD8, ANKRD36C, SPOP, AR

10 oncofetal & cancer testis in:
PSA, PSMA, STEAP, SART3, RNF43, PAGE4, CEACAM5, SSX2, MAGEA4

HOT ADXS-504 in the Prostate Cancer Treatment Landscape
ADXS-504 in Biochemically Recurrent Prostate Cancer

Title: A Phase 1 Study of ADXS-504, a Cancer Type Specific Immunotherapy in Subjects with Biochemically Recurrent Prostate Cancer

Trial design:

<table>
<thead>
<tr>
<th>Safety Phase</th>
<th>Part A – Low risk</th>
<th>Part B – High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADXS-504 Monotherapy*</td>
<td>5x10^8 CFU of ADXS-504 (DL2)</td>
<td>ADXS-504* + GnRH antagonist**</td>
</tr>
<tr>
<td>Dose Escalation 3+3 Design</td>
<td>1x10^8 CFU of ADXS-504 (DL1) + GnRH antagonist</td>
<td>5x10^8 CFU of ADXS-504 (DL2) + GnRH antagonist</td>
</tr>
<tr>
<td>1x10^8 CFU of ADXS-504 (DL1)</td>
<td>n = 9-18</td>
<td>n = 9-18</td>
</tr>
</tbody>
</table>

Endpoints:

- **Primary**
  - Tolerability/ Safety
- **Secondary**
  - PSA response
- **Exploratory**
  - rPFS
  - PSADT
  - Immunological

Potential benefits:

- To delay progression after radical prostatectomy/ radiotherapy
  - Low risk patients: monotherapy
  - High risk patients: combination with degarelix (gonadotropin-releasing hormone (GnRH) receptor antagonist)\(^{(1)}\)
- To delay ADT hormone therapy and decrease long term toxicity, e.g., sarcopenia, insulin insensitivity, fractures, CVD, weight gain, etc.

Notes: * Dosing schedule: q4w for 6 doses | ** Dosing schedule: 4 doses only | (1) Alternative GnRH could be used.
Legend: ADT androgen deprivation therapy.
Our gratitude…

To our patients and their families

To our experts

**ADXS-PSA**
Dr. Mark N. Stein, Columbia University
Dr. Naomi Haas, UPenn
Dr. Lawrence Fong, UCSF
Dr. Ronald Tutrone, Chesapeake, MD
Dr. Anthony Mega, Rhode Island Hospital
Dr. Elaine T. Lam, U. Colorado University

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