Atezolizumab Oncology Development
Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

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Outline

• Introduce Roche/Genentech Pediatric Oncology Team
• Cancer Immunotherapy
• Atezolizumab Mechanism of Action
• Atezolizumab Adult Development
• Key Differences Between Adult and Pediatric Cancers
• Atezolizumab Pediatric Development
• Next Steps
Genentech/Roche Pediatric Oncology
Doing Now What Children Need Next

Vision  Provide children with unmet medical needs with innovative, safe, life-saving therapies

Goals
• Ensure early access to drugs for children with high unmet medical needs
• Improve pediatric patient care through pediatric product labeling
• Fulfill pediatric regulatory obligations to enable timely registrations

Team

31 dedicated individuals and growing. Research Scientists, Pediatric Oncologists, Clinical Pharmacologists, Safety Specialists, Regulatory, etc.
Cancer Immunotherapy

Checkpoint Inhibitors are Key Activators of Anti-cancer Immunity

Cancer Immunotherapy
Checkpoint Inhibitors are Key Activators of Anti-cancer Immunity

Atezolizumab Mechanism of Action

Humanized mAB inhibits binding of PD-L1 to PD-1 & B7.1

- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming

- Atezolizumab leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

• **~ 5000 patients** have received atezolizumab across clinical trials, as of February 2016

• The key safety risks associated with atezolizumab are immune-related events
  – Events include pneumonitis, hepatitis, colitis, endocrinopathies, and other immune-related events including meningitis / encephalitis, motor and sensory neuropathy, and pancreatitis
  – Immune-related events are generally grade 1 and 2 in nature and manageable with dose interruption and supportive care, including the use of systemic corticosteroids, where appropriate

• The safety profile appears similar between tumor types and suggests independence from the level of PD-L1 expression

• No apparent dose related trends in the incidence of AEs
Atezolizumab Adult Development
Demonstrates Activity Across Tumor Types

- Non-small cell lung cancer
- Small cell lung cancer
- Renal cell cancer
- Colorectal cancer
- Triple-negative breast cancer
- Melanoma
- Acute myeloid leukemia
- Myelo dysplastic syndrome
- Multiple myeloma
- Prostate cancer
- Metastatic urothelial cancer (FDA approval May 2016)
Atezolizumab Adult Development
Overall Survival Benefit in Patients with Non Small Cell Lung Cancer

Atezolizumab vs. Docetaxel for Patients with Previously Treated NSCLC (POPLAR)

- Median 9.7 months (95% CI, 8.6 -12.0)
- Median 12.6 months (95% CI, 9.7 -16.0)

HR 0.69 (95% CI, 0.52 - 0.92)
P value = 0.011

Minimum follow-up = 12 months

N = 287 Intent to Treat

Smith D, et al. ASCO 2016 [abstract 9028]
Atezolizumab Adult Development
Demonstrates Activity Across Subgroups of PD-L1 Expression Levels

NSCLC – POPLAR Study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Proportion</th>
<th>Proportion (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>16%</td>
<td>0.45</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>37%</td>
<td>0.50</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>68%</td>
<td>0.59</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>32%</td>
<td>0.88</td>
</tr>
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</table>

Hazard Ratio
In favor of atezolizumab ← 0.45 0.50 0.59 0.88 → In favor of docetaxel

Smith D, et al. ASCO 2016 [abstract 9028]
Cancer Immunotherapy

Biomarkers of Tumor Immunity in Adult vs Pediatric Cancers

1. Antigen release
2. Presence of Tumor Resident T cells
3. Infiltration of T cells into tumors
4. T cell recognition
5. T cell killing

- Adult cancers
- Pediatric cancers

Mutational Load

- Adult cancers
- Pediatric cancers

Presence of Tumor Resident T cells

PD-L1 Expression

Cancer Immunotherapy
Mutational Load Across Adult and Pediatric Tumor Types

Mutational Load

Adult cancers

Pediatric cancers

Somatic mutation prevalence
(number mutations per megabase)

1.0

0.1

0.01

0.001


* Additional Publications:


Cancer Immunotherapy
PD-L1 Expression in Adult and Pediatric Tumors

PD-L1 / PD-1 Pathway
Atezolizumab (aPD-L1)

T cell recognition

T cell killing

PD-L1 Expression

Adult cancers
Pediatric cancers

Colon Cancer
Rhabdomyosarcoma
Cancer Immunotherapy

Evidence of Pre-existing Immune Infiltrate in Adult and Pediatric Tumors

Infiltration of T cells into tumors

Presence of Tumor Resident T cells

↑ Adult cancers  ↑ Pediatric cancers

Colon Cancer

Rhabdomyosarcoma
Pediatric Biomarker Development

• Unselected pediatric population chosen for Phase I to ensure:
  – We did not prematurely exclude any children who could potentially benefit
  – We could collect robust data to optimize our biomarker understanding and development

• Planned evaluation of CD8⁺ T-cell infiltration PD-L1 expression, and antigen-specific T-cell responses in addition to other immune markers

• Biomarker findings will be utilized to guide amendments to the current protocol, and to the design of future studies
Atezolizumab Pediatric Development

Proactive Study Evaluating Multiple Tumor Types

Phase I/II: Single Arm Study Designed to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity & Preliminary Efficacy

- Age <30 yrs
- Relapsed, refractory pediatric solid tumors
- No known curative options
- IHC PD-L1 expression not required

Atezolizumab IV q3 weeks while experiencing clinical benefit

- Dose: < 18 years = 15 mg/kg *
- ≥18 years = 1200 mg

Primary Endpoints:
- PK
- Safety
- Efficacy: ORR (CR or PR), PFS

Secondary Efficacy Endpoints:
- DOR
- OS

Multiple Tumor Types:
- Known or Expected PD-L1 Pathway

IHC= Immunohistochemistry; PK=Pharmacokinetics; ORR= Overall Response Rate; CR= Complete Response; PR=Partial Response; PFS= Progression Free Survival; DOR= Duration of Response; OS= Overall Survival. * Maximum pediatric dose 1200mg.
Atezolizumab Pediatric Development
Gated Study Design

iMATRIX (Phase I/II)

**Gate 1**
PK/ Safety Check

**Gate 2**
Initial Response Assessment

**Gate 3**
Additional Response Assessment

**Pivotal**
Further gates for futility

**Efficacy Confirmation**

- First 5 patients enrolled ≥2 years of age
- Minimum of 20 patients
- Early PK and Safety Evaluation

- Will occur when tumor type cohort reaches ~10 patients
- Decision will be made whether or not to continue enrollment in that tumor type based on disease-specific criteria (for most tumor types 2 – 3/10 need to show an objective response)
- Retrospective biomarker analysis

Investigational sites: 24 sites (ITCC, EU, Israel), 10 sites (POETIC, US).
Atezolizumab Pediatric Development

Gated Study Status

iMATRIX (Phase I/II)

Gate 1
PK/Safety Check

Gate 2
Initial Response Assessment

Gate 3
Additional Response Assessment

Pivotal
Further gates for futility

• First Patient In (FPI), November 2015
• iDMC, March 2016
• iDMC, May 2016
• Preliminary Pharmacokinetic Data: exposure in pediatric patients is similar to exposure in adult patients
  - No recommended dose modifications at this time
• Robust Safety Monitoring Plan Ongoing
  - No study conduct changes recommended by iDMC at this time

As of June 1, 2016:

<table>
<thead>
<tr>
<th>Total Patients Enrolled</th>
<th>67</th>
</tr>
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<tbody>
<tr>
<td>Median Age</td>
<td>14 years</td>
</tr>
<tr>
<td>Age Range</td>
<td>2 – 29 years</td>
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<tr>
<td>Wilms’ Tumor, Rhabdomyosarcoma, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Soft Tissue Sarcoma, Osteosarcoma, Ewing Sarcoma &amp; Neuroblastoma</td>
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iDMC = independent Data Monitoring Committee.
Cancer Immunotherapy
Future Opportunities

Continue to collaborate and utilize latest research findings to support and prioritize the development of new therapies for children with high unmet needs.

1. Release of cancer cell antigens
   - Chemotherapy, Radiation therapy
   - Targeted therapy (BRAFi or MEKi)

2. Cancer antigen presentation
   - Vaccines, IFN-a, GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonist

3. Priming and activation
   - Anti-PD-L1, Anti-PD-1, Anti-CTLA-4
   - Anti-CD137 (agonist), Anti-OX40 (agonist)
   - Anti-CD27 (agonist), IL-2, IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CAR-T cells

7. Killing of cancer cells
   - Anti-PD-L1, Anti-PD-1
   - IDO inhibitors

**iMATRIX Trial Concept**

*Match Promising Molecules to Pediatric Patients with High Unmet Needs*

- **Molecule #1 Study**
  - PEDIATRIC Ph1 Study
  - Preclinical assessment for pediatric use

- **Molecule #2 Study**
  - PEDIATRIC Tumor A → Cross Tumor PK & Safety Assessment → Yes → P2 Cohort Expansion
  - PEDIATRIC Tumor B
  - PEDIATRIC Tumor C

- **Molecule #3 Study**
  - Efficacy Signal/Safety?
    - Yes → P2 Cohort Expansion
    - No → P2 Cohort Expansion

**ADULT**

- Ph1/2 Studies
- Ph3 – Disease 1
- Ph3 - Disease 2
- Ph3 – Disease 3
Key Conclusions & Next Steps

• Atezolizumab is a humanized, monoclonal antibody which binds to PD-L1 to restore the anti-tumor immunity mediated by T cells

• Atezolizumab is well tolerated and demonstrates clinical efficacy across tumor types & subgroups in adults

• Voluntary pediatric study of atezolizumab is ongoing as part of our iMATRIX platform which matches promising molecules to pediatric patients with high unmet medical needs
  - Rigorous and consistent PK, safety and efficacy assessment
  - Comprehensive biomarker evaluation
  - Strong collaboration with academic consortium and health authorities
THANK YOU
Increase in CD8 T Cells in Pseudoprogressing On-treatment Brain Lesions

CD8 IHC Quantification Across Samples

- Bx1. brain
- Bx2. thigh
- Bx3. small bowel
- Bx4. brain (Responding lesion)
- Bx5. brain (Responding lesion)
- Bx6. small bowel (Non-Responding lesion)

OHSU Collaboration: Single Patient IND