

# **Atezolizumab Oncology Development**

## **Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)**

Raphaël Rousseau, M.D., Ph.D.  
Global Head, Pediatric Oncology Drug Development Group  
Genentech, a member of the Roche Group  
South San Francisco



# Outline

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- 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

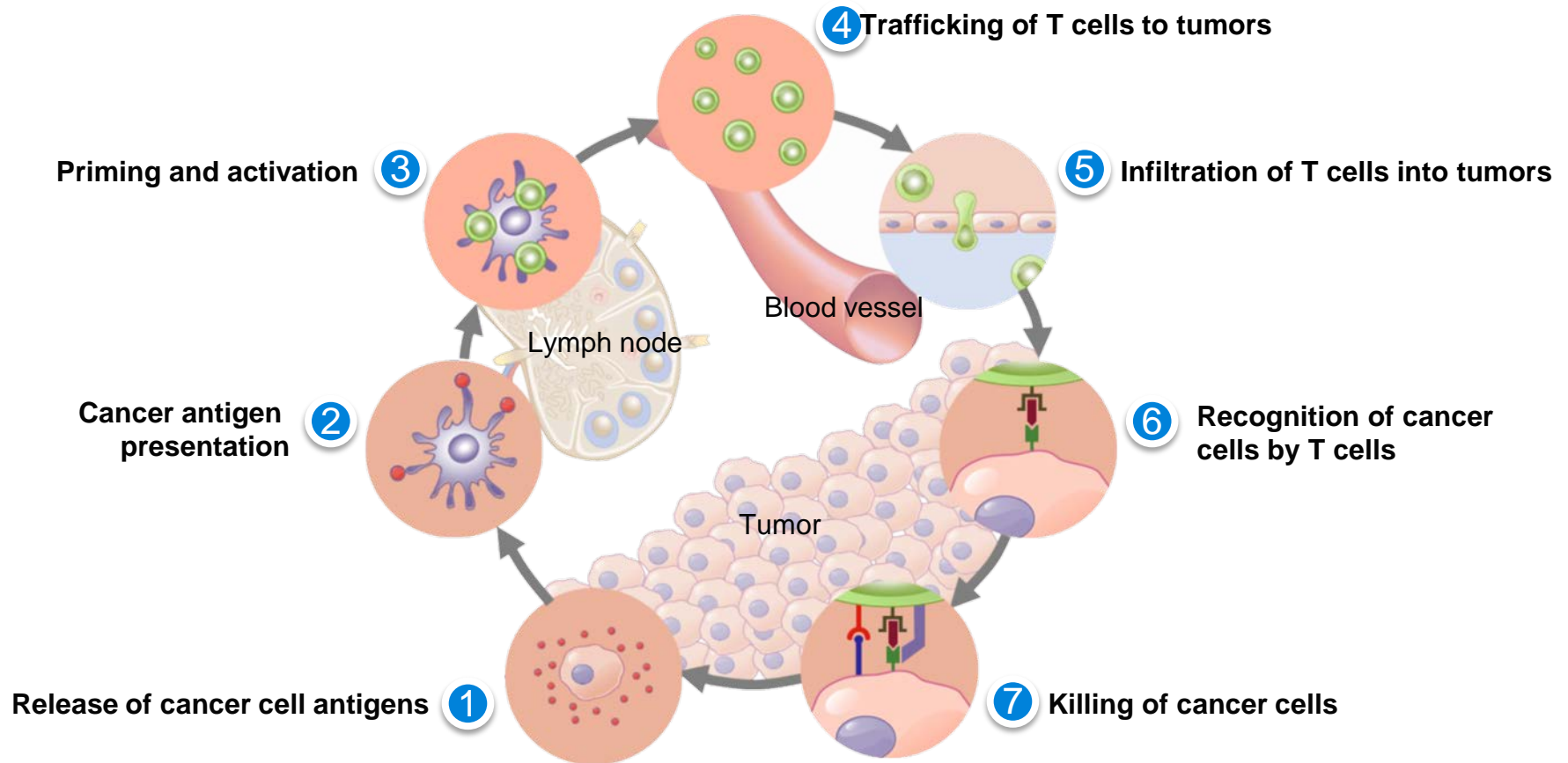
## Team



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

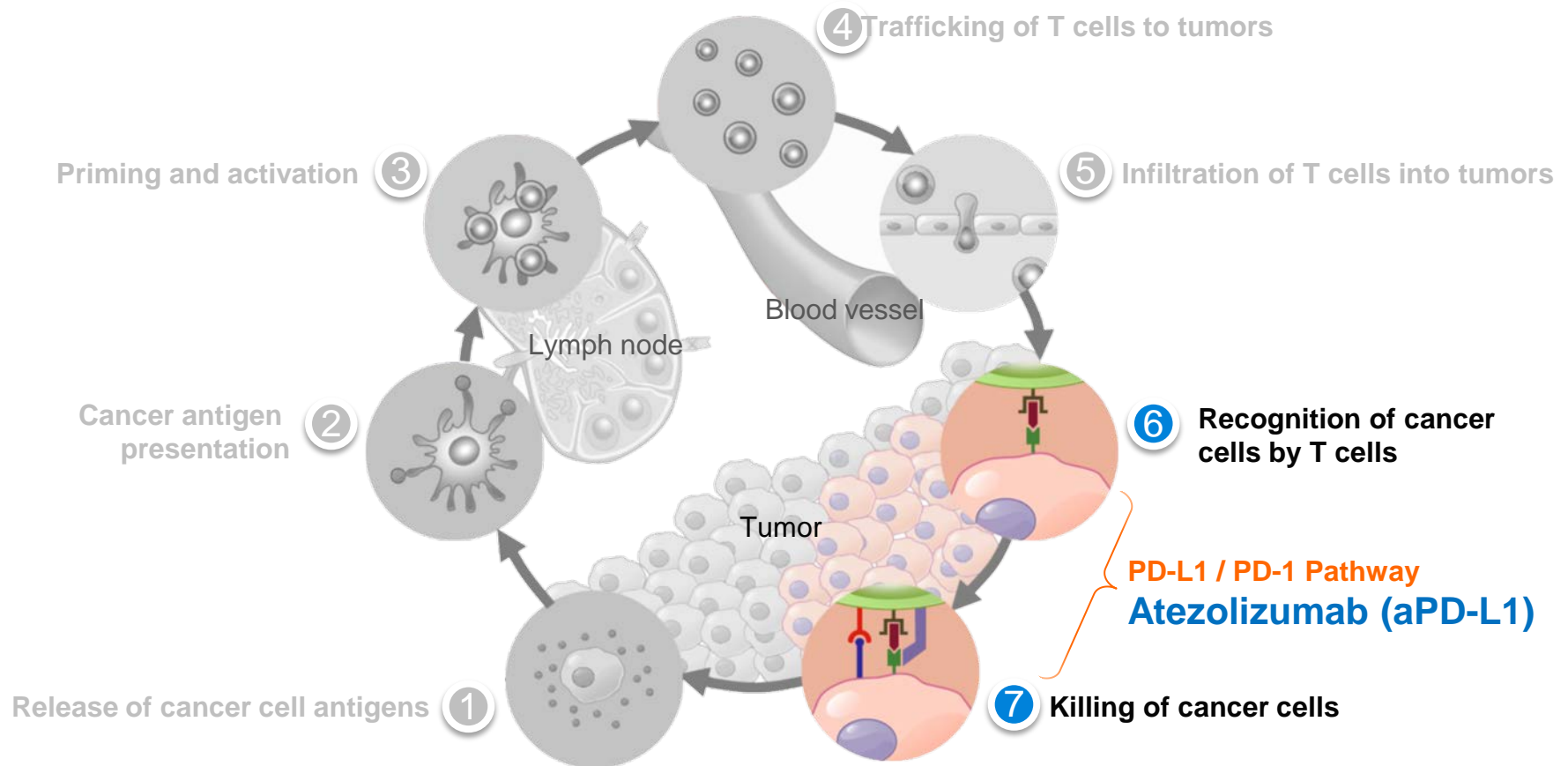
# Cancer Immunotherapy

*Checkpoint Inhibitors are Key Activators of Anti-cancer Immunity*



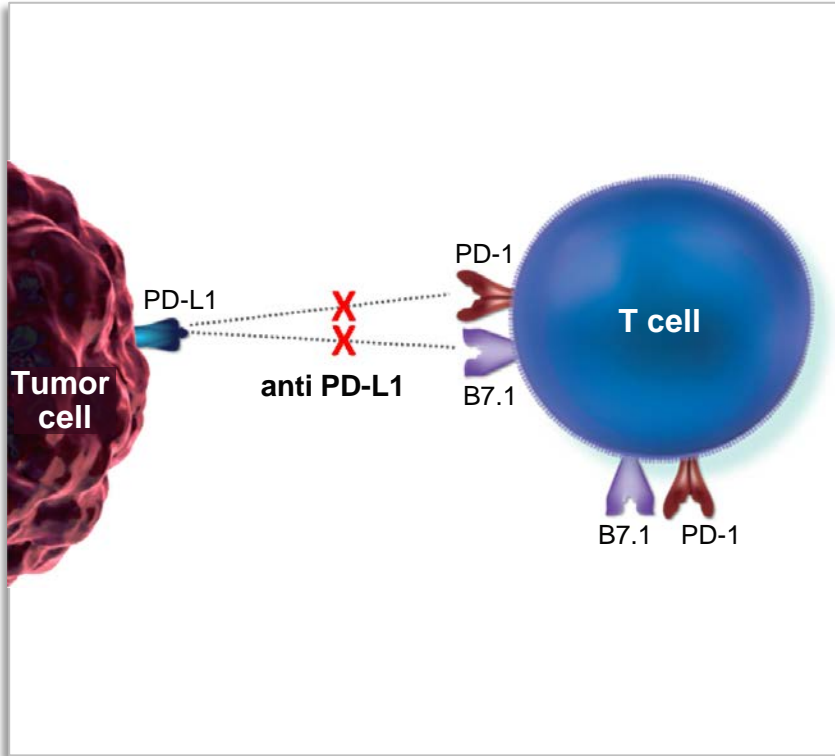
# Cancer Immunotherapy

*Checkpoint Inhibitors are Key Activators of Anti-cancer Immunity*

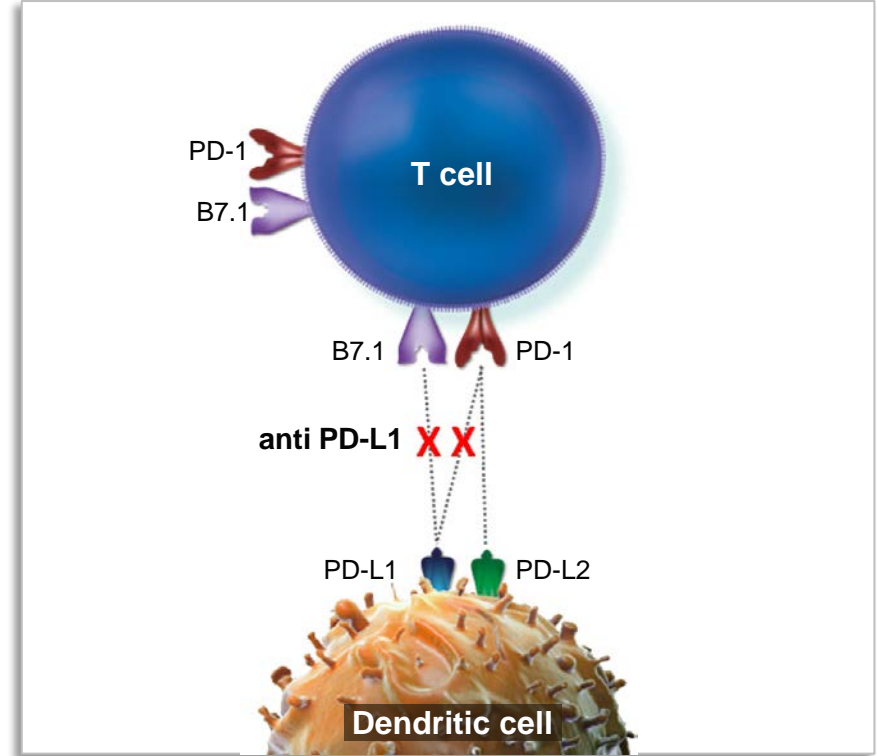


# Atezolizumab Mechanism of Action

*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

# Atezolizumab Adult Development

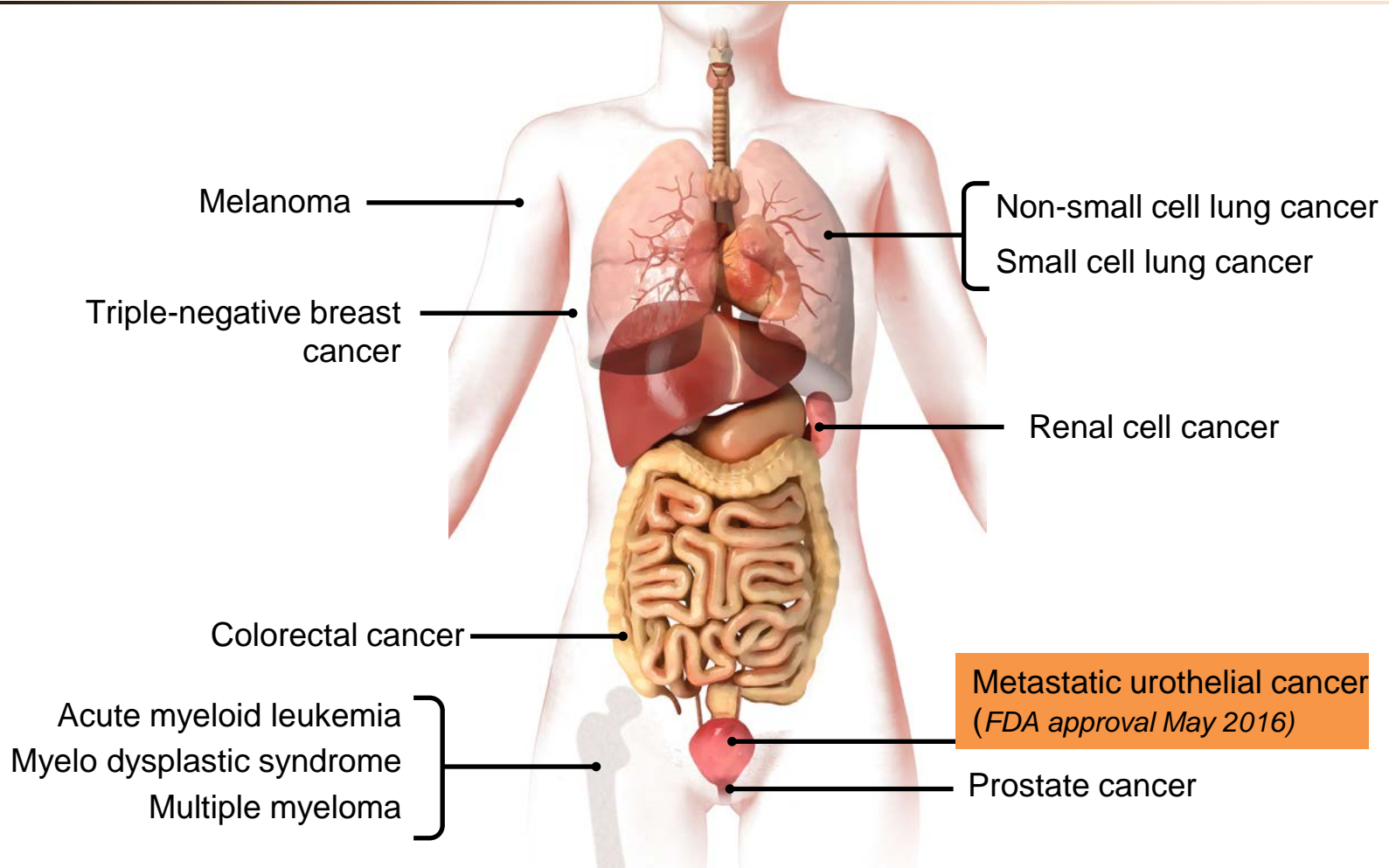
## *Acceptable Safety Profile Across Tumor Types*

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- ~ **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*

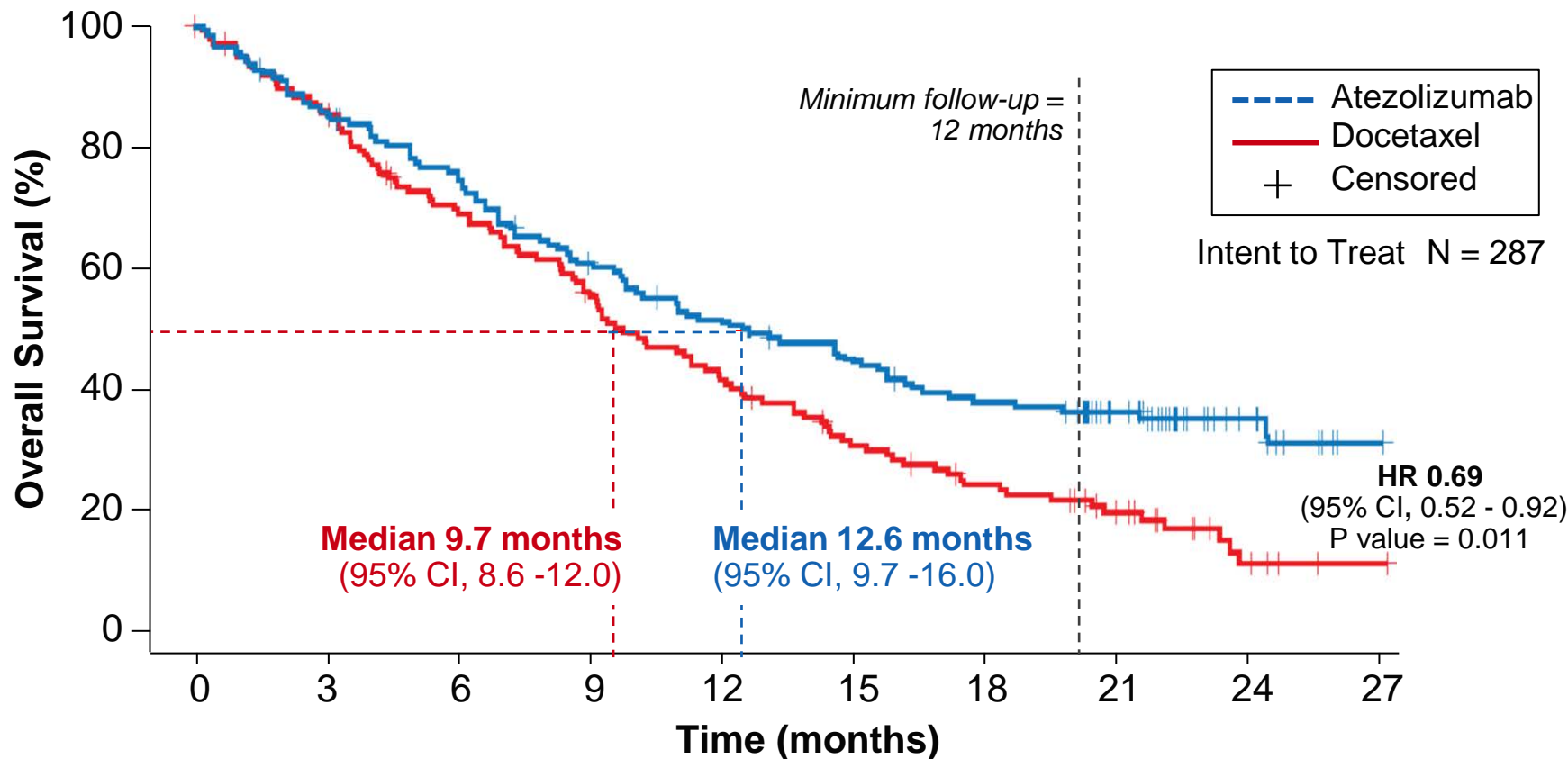




# Atezolizumab Adult Development

## Overall Survival Benefit in Patients with Non Small Cell Lung Cancer

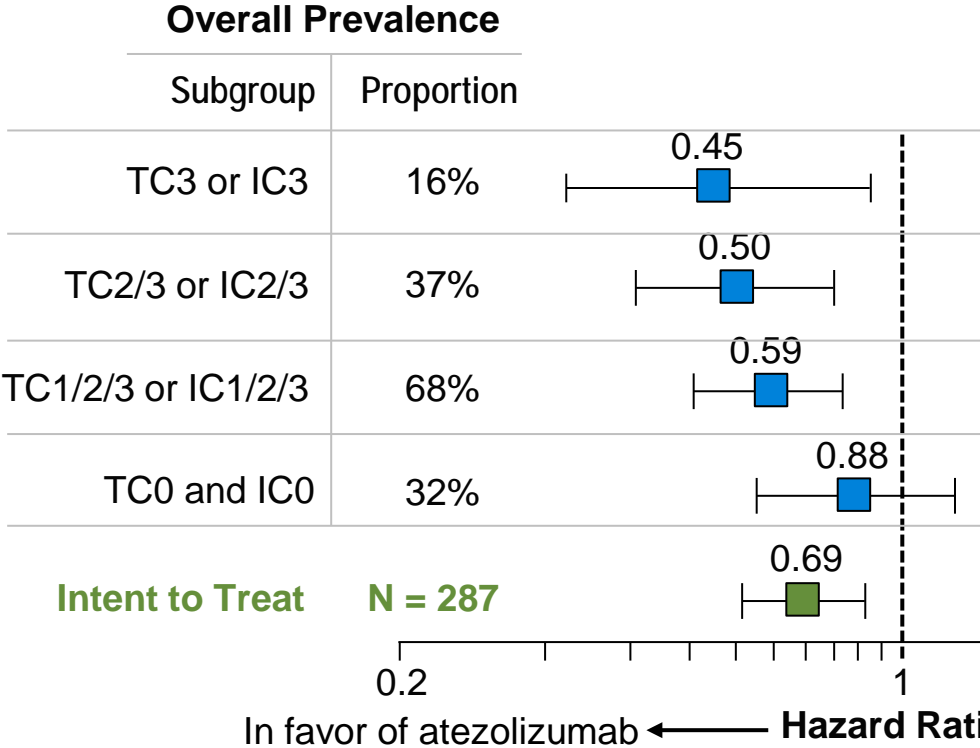
### Atezolizumab vs. Docetaxel for Patients with Previously Treated NSCLC (POPLAR)



# Atezolizumab Adult Development

*Demonstrates Activity Across Subgroups of PD-L1 Expression Levels*

## NSCLC – POPLAR Study



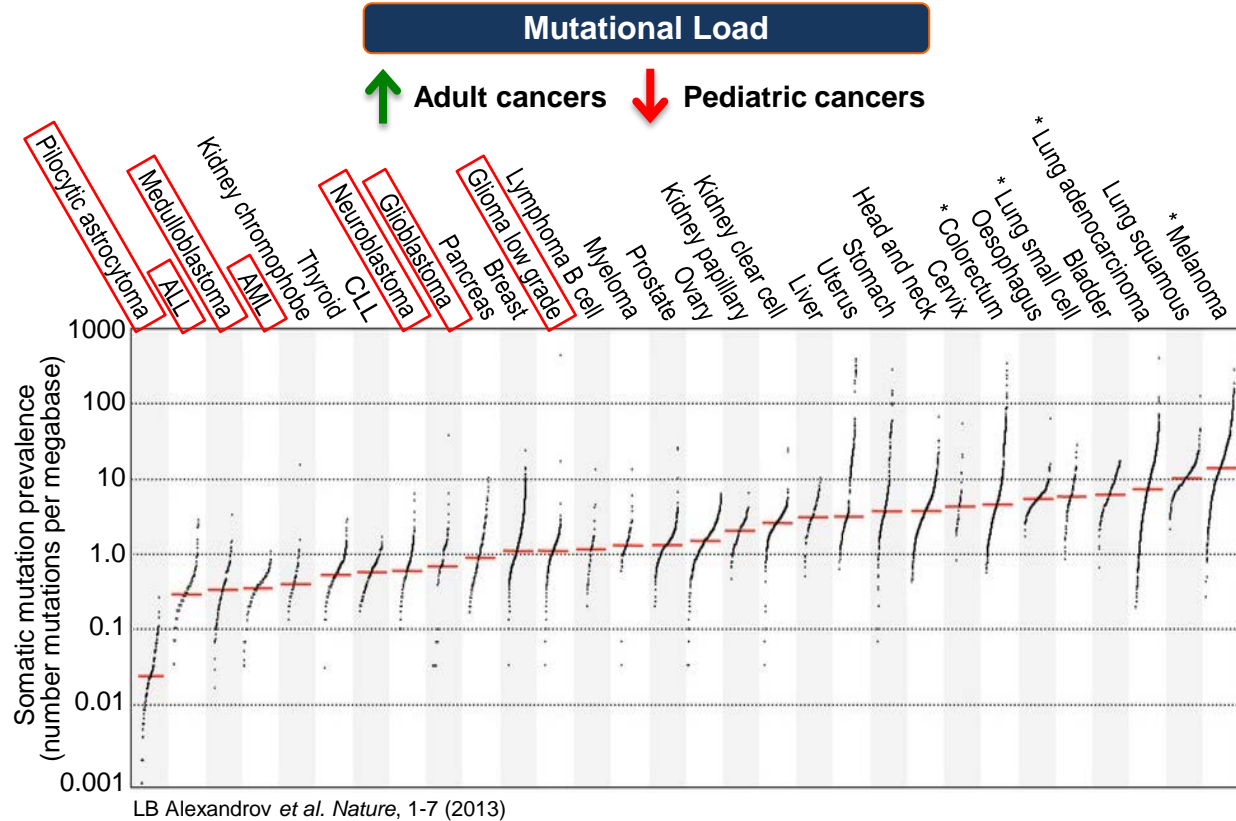
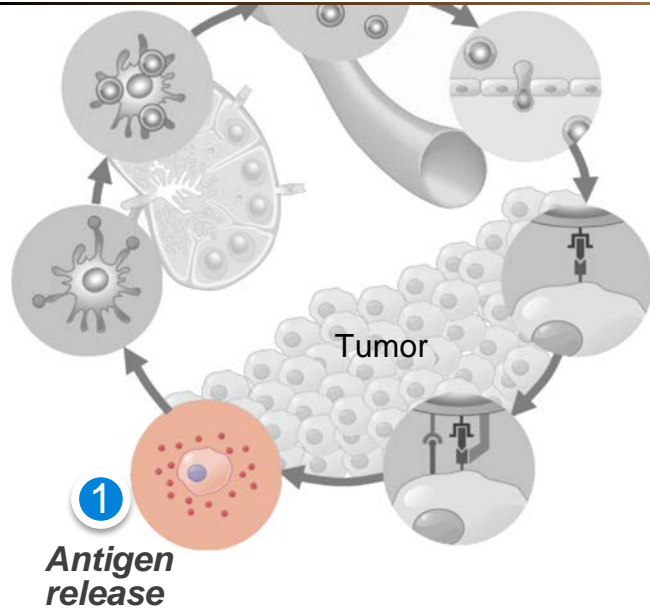
Tumor Cell		Immune Cell	
Score	% of PD-L1-expressing cells	Score	% of PD-L1-expressing cells
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

## Biomarkers of Tumor Immunity in Adult vs Pediatric Cancers



# Cancer Immunotherapy

## Mutational Load Across Adult and Pediatric Tumor Types



### \* Additional Publications:

**Lung adenocarcinoma:** McGranahan N, Furness AJS, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 10.1126/science.aaf490 (2016).

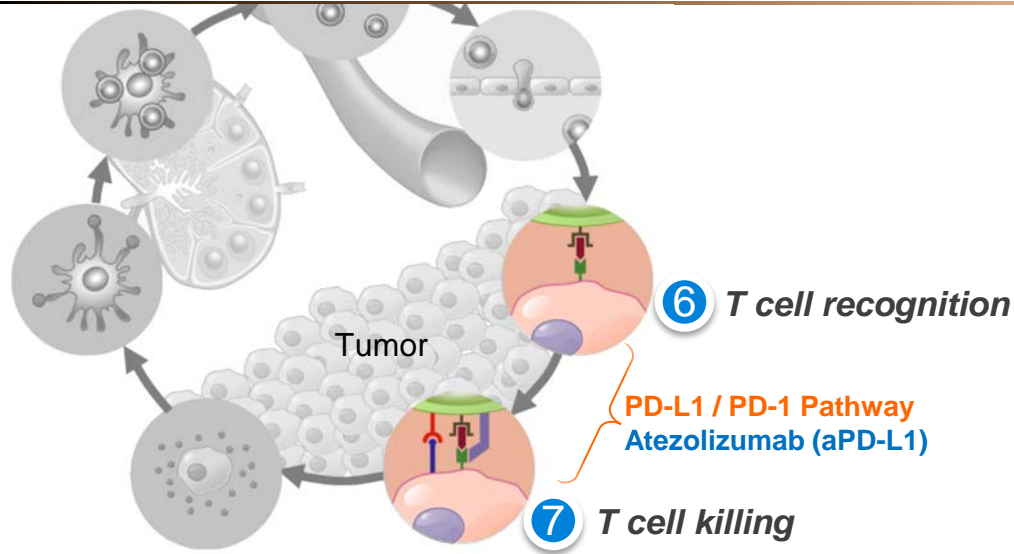
**Melanoma:** McGranahan N, Furness AJS, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 10.1126/science.aaf490 (2016) | Snyder A, Makarov V, Merghoub T. et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N. Engl. J. Med.* 2014;371:2189-2199 | Van Allen EM, Miao D, Schilling B, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science* 2015;350:207-21 | Hugo W, Zaretsky JM, Sun L, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell* 2016;165:35-44.

**Lung-small cell:** McGranahan N, Furness AJS, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 10.1126/science.aaf490 (2016).

**Colon:** 1. Le D. T., Uram J. N., Wang H. et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N. Engl. J. Med.* 2015;372:2509-2520.

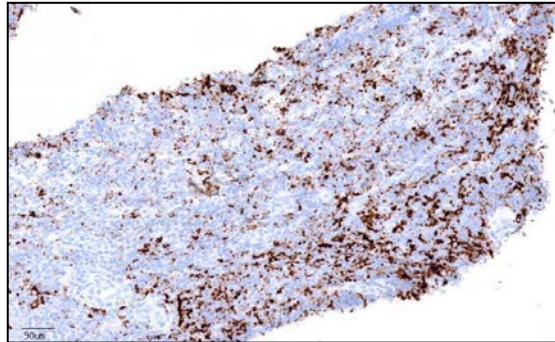
# Cancer Immunotherapy

## *PD-L1 Expression in Adult and Pediatric Tumors*

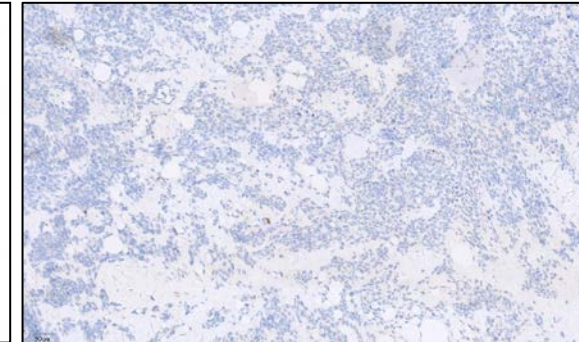


**PD-L1 Expression**

↑ Adult cancers    ↓ Pediatric cancers



Colon Cancer

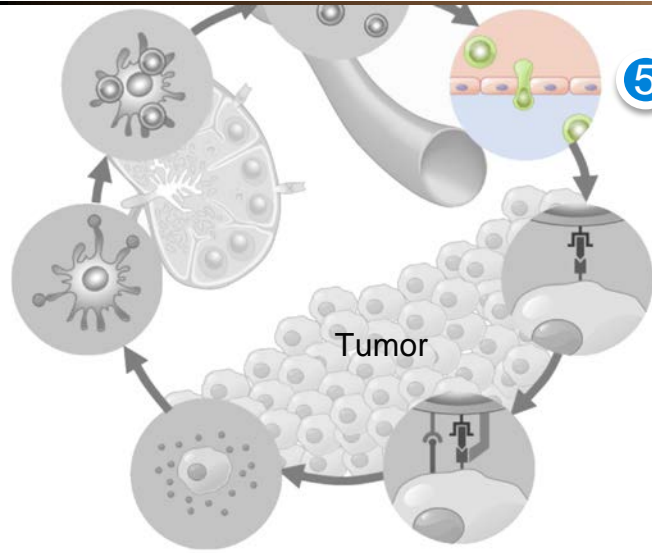


Rhabdomyosarcoma



# Cancer Immunotherapy

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



⑤ *Infiltration of T cells into tumors*

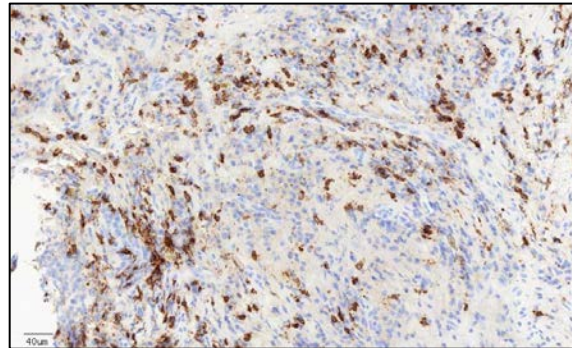
**Presence of Tumor Resident T cells**



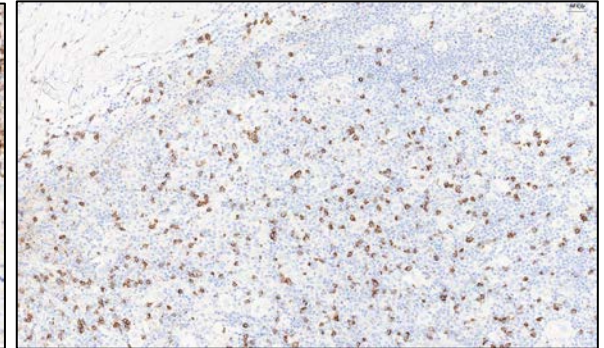
Adult cancers



Pediatric cancers



*Colon Cancer*



*Rhabdomyosarcoma*

# Atezolizumab Pediatric Development

## *Broad Spectrum Biomarker Research Ongoing*

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### **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<sup>+</sup> 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



# Atezolizumab Pediatric Development

## *Gated Study Design*

### iMATRIX (Phase I/II)

### Pivotal

**Gate 1**  
PK/ Safety Check

**Gate 2**  
Initial Response  
Assessment

**Gate 3**  
Additional Response  
Assessment

Further gates for futility

PK/Safety

Initial Response  
Assessment

Additional Response  
Assessment

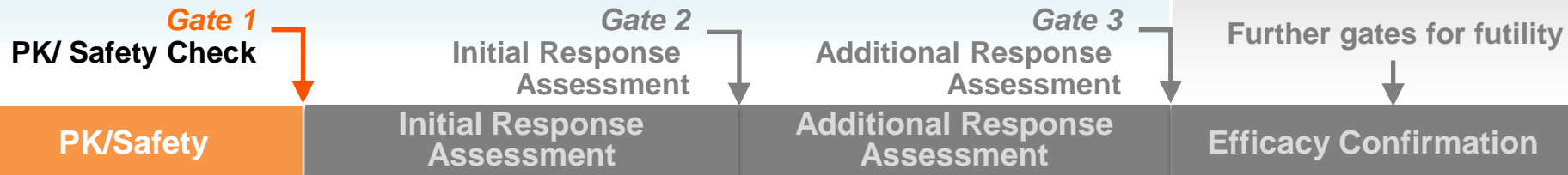
Efficacy Confirmation

- First 5 patients enrolled  $\geq 2$  years of age
- Minimum of 20 patients
- Early PK and Safety Evaluation
- Will occur when tumor type cohort reaches  $\sim 10$  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

# Atezolizumab Pediatric Development

## *Gated Study Status*

### iMATRIX (Phase I/II)



- 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:

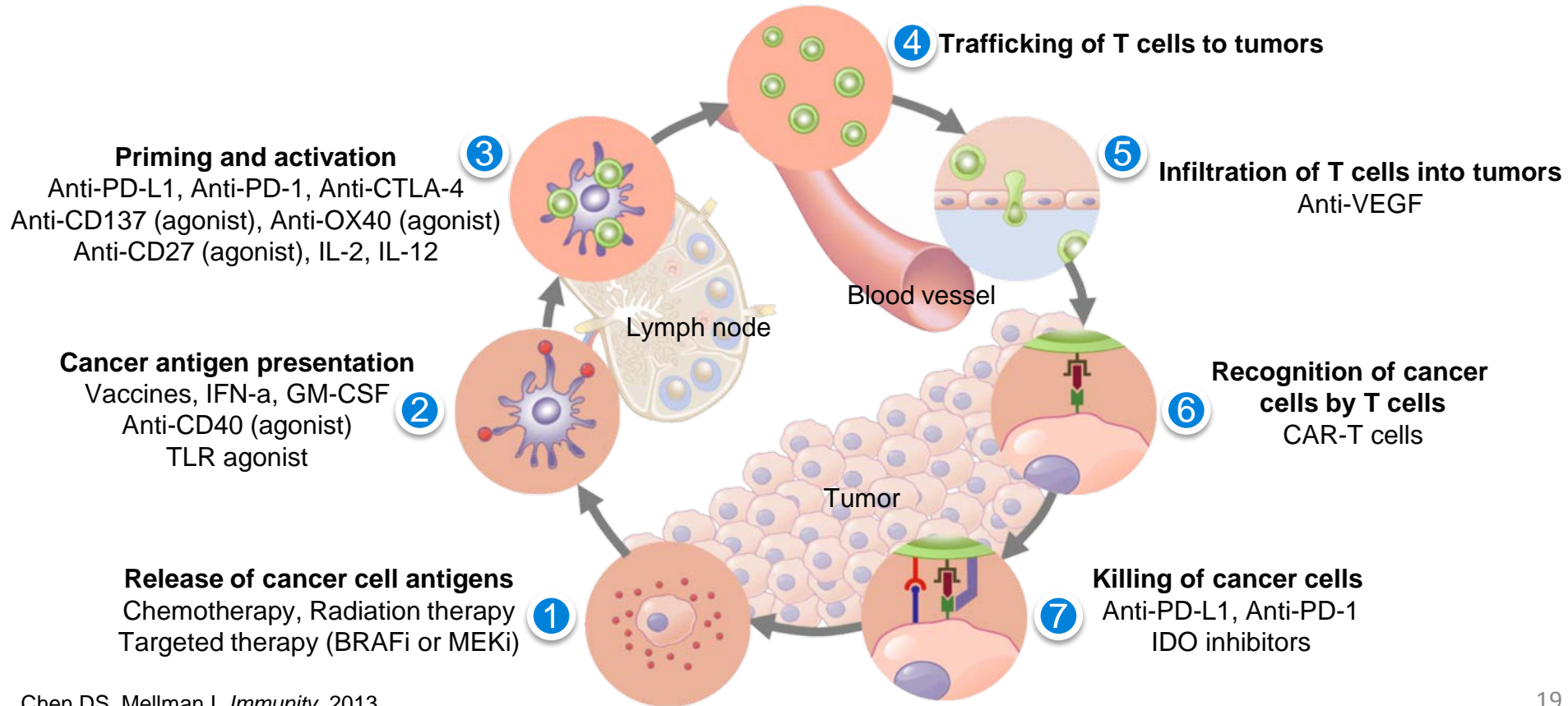
Total Patients Enrolled	67
Median Age	14 years
Age Range	2 – 29 years

Wilms' Tumor, Rhabdomyosarcoma, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Soft Tissue Sarcoma, Osteosarcoma, Ewing Sarcoma & Neuroblastoma

# Cancer Immunotherapy

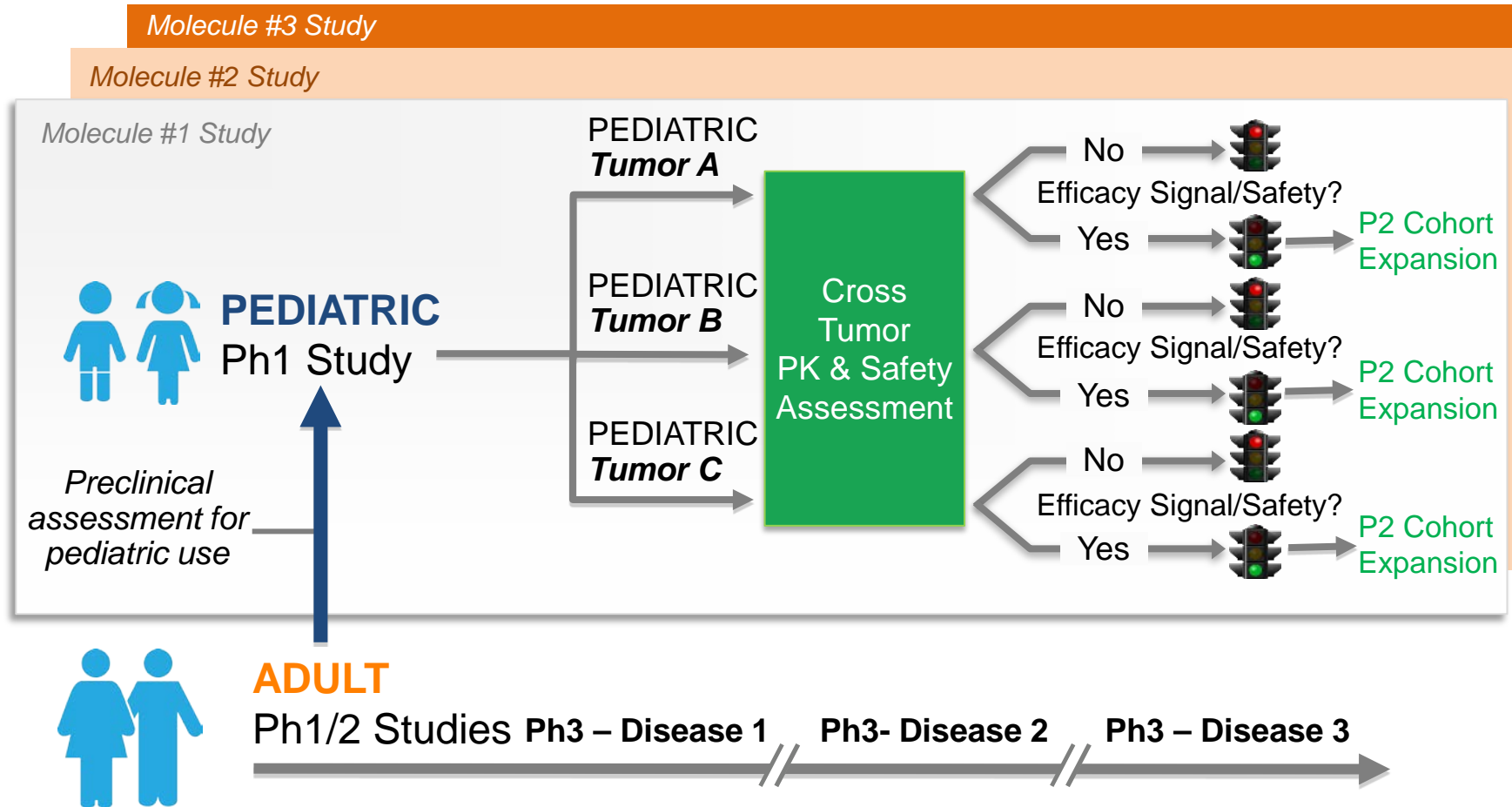
## *Future Opportunities*

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



# iMATRIX Trial Concept

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



# Key Conclusions & Next Steps

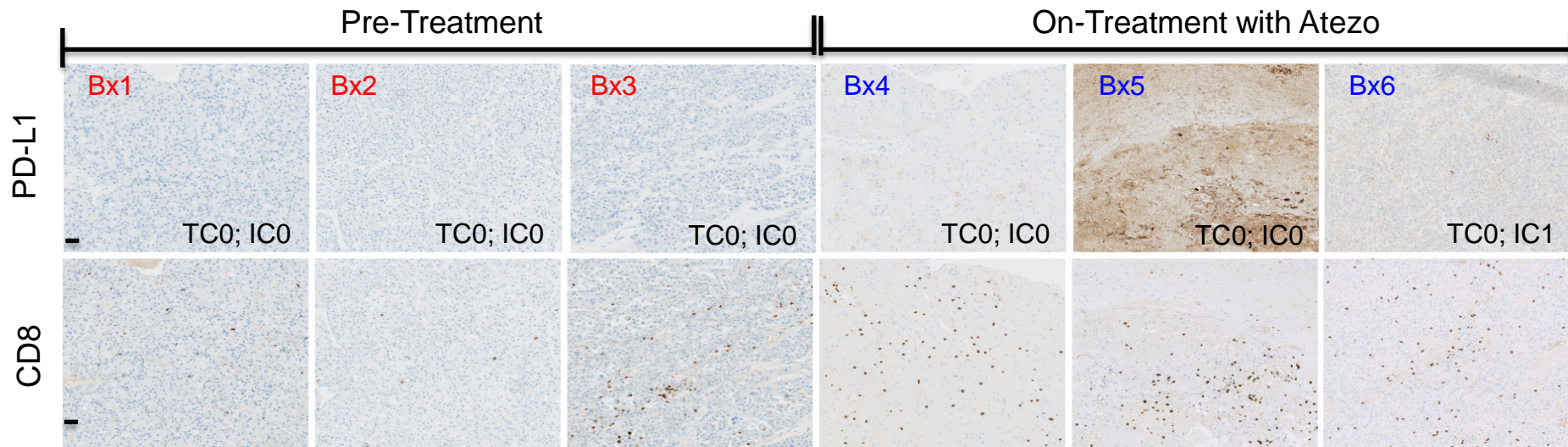
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- Atezolizumab is a humanized, monoclonal antibody which binds to PD-L1 to restore the anti-tumor immunity mediated by T cells
- Atezolizumab is well tolerated and demonstrates clinical efficacy across tumor types & subgroups in adults
- Voluntary 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

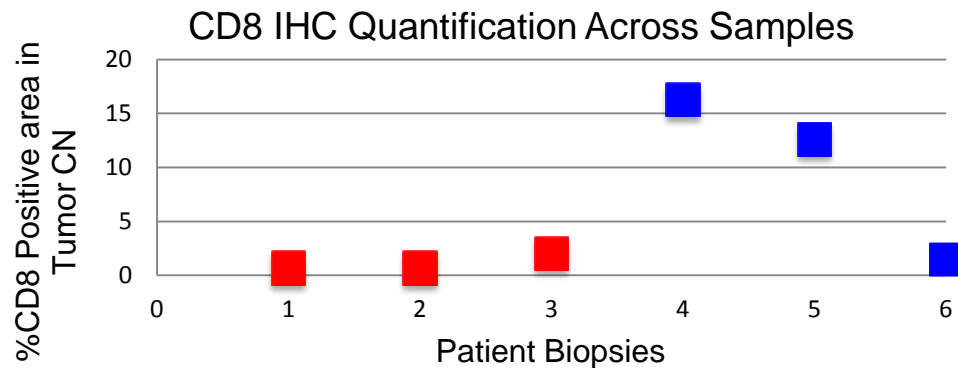
# THANK YOU

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# Increase in CD8 T Cells in Pseudoprogressing On-treatment Brain Lesions



Scale bars represent 50  $\mu$ m



- 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