

Background on Current Mechanistic Understanding of Common Toxicities

ACI™: A Focus on Toxicity Management

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Disclosures

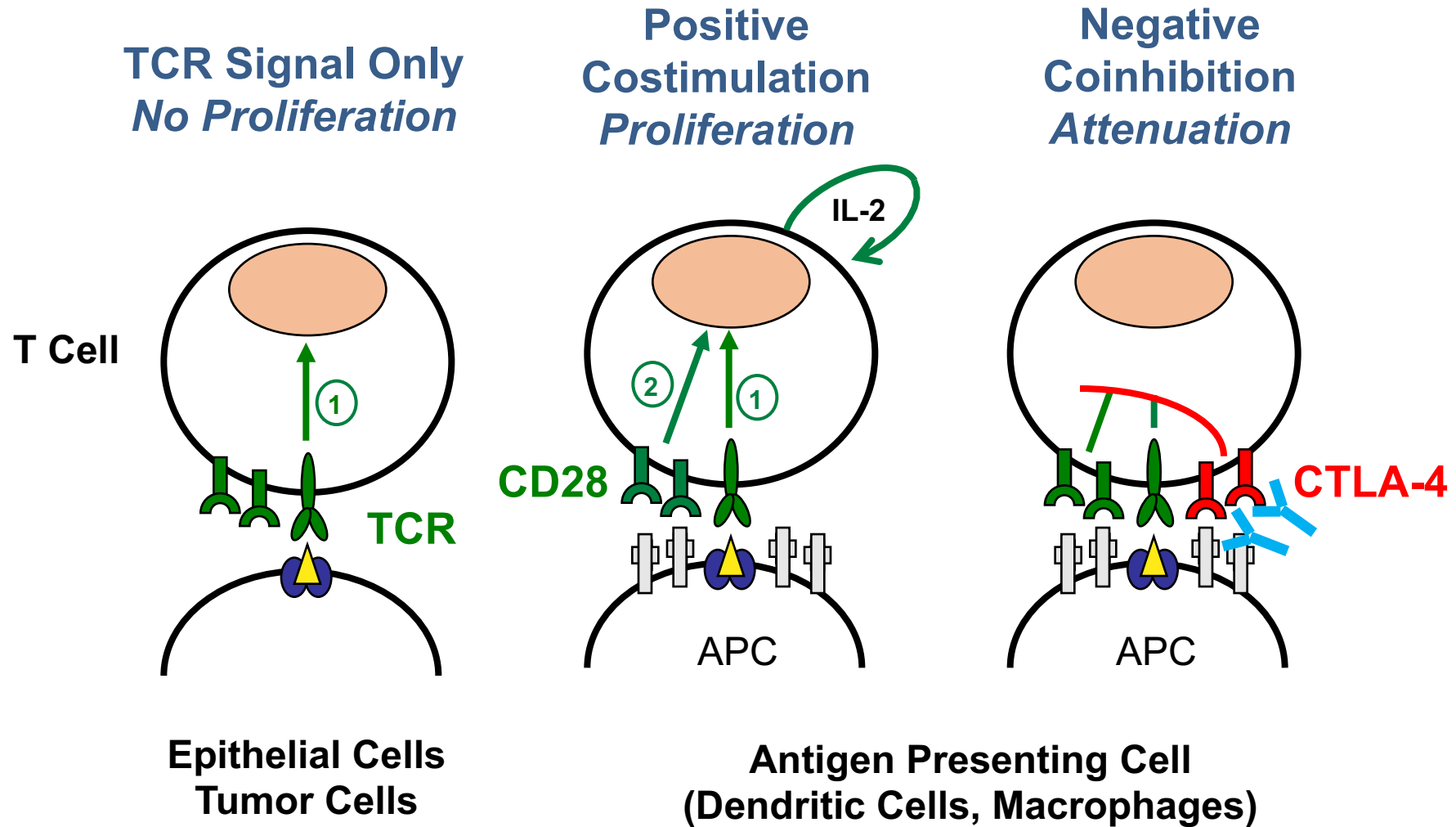
- **Consulting or Advisory Role:** Amgen, Apricity Health, Bayer, Bristol-Myers Squibb, Cancer Expert Now, Dendreon, Janssen Oncology, Javelin Oncology, Kahr Bio, and MD Education Limited
- **Research Funding:** AstraZeneca
- **Other (Joint Scientific Committee):** Amgen, Janssen Oncology, and Polaris

Immunotherapies

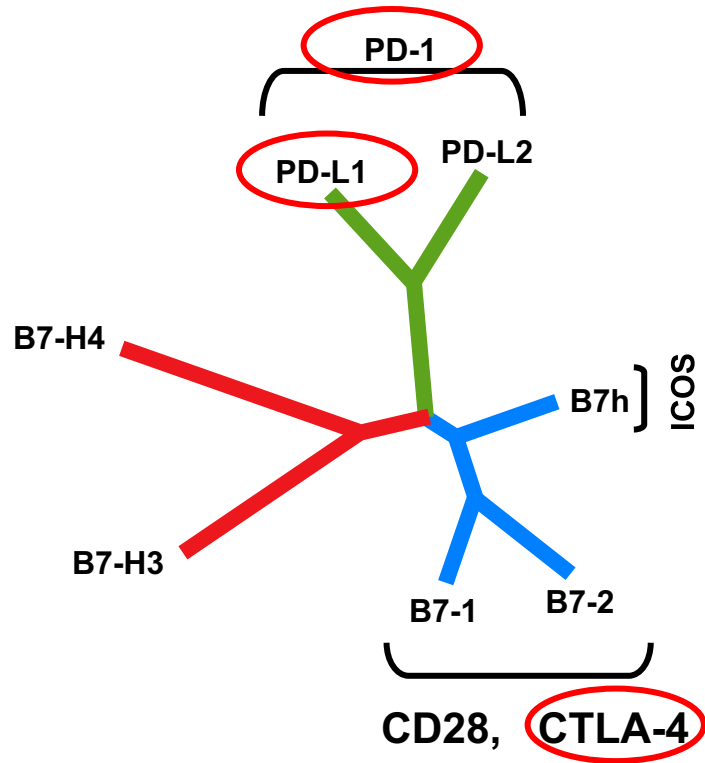
Not all the same!

- **Vaccines**
 - Directs immune system to focus on tumor antigen(s)
- **Cellular therapies**
 - CAR T cells target the tumor cells
- **Immune checkpoint therapies**
 - Increases T cell activation and function

New Understanding of T Cell Regulation: Positive / Negative Signals Govern Responses



2018: Nobel Prize in Physiology or Medicine



Zang X et al., *Proc Natl Acad Sci* 2003



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James P. Allison



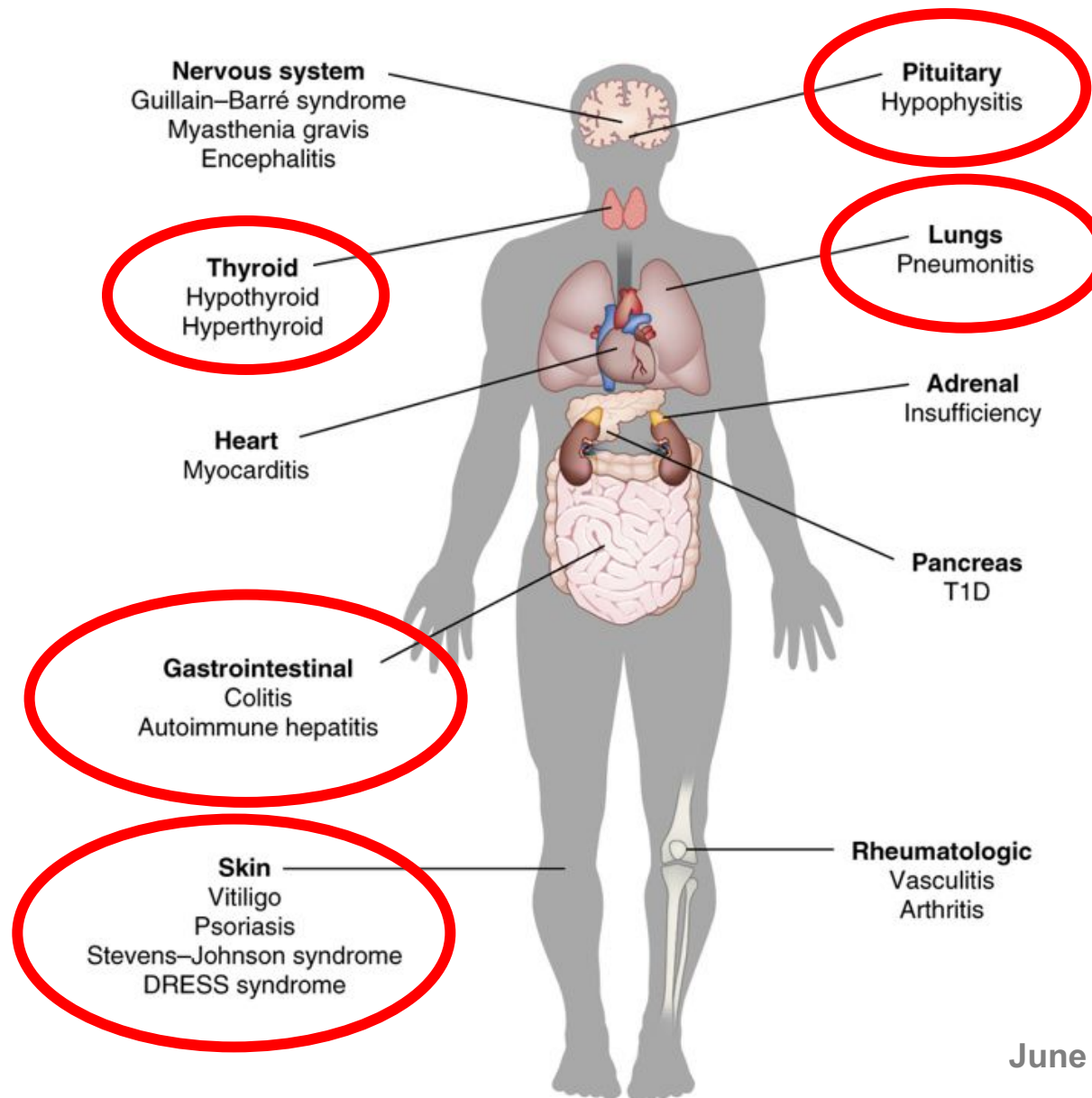
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Tasuku Honjo

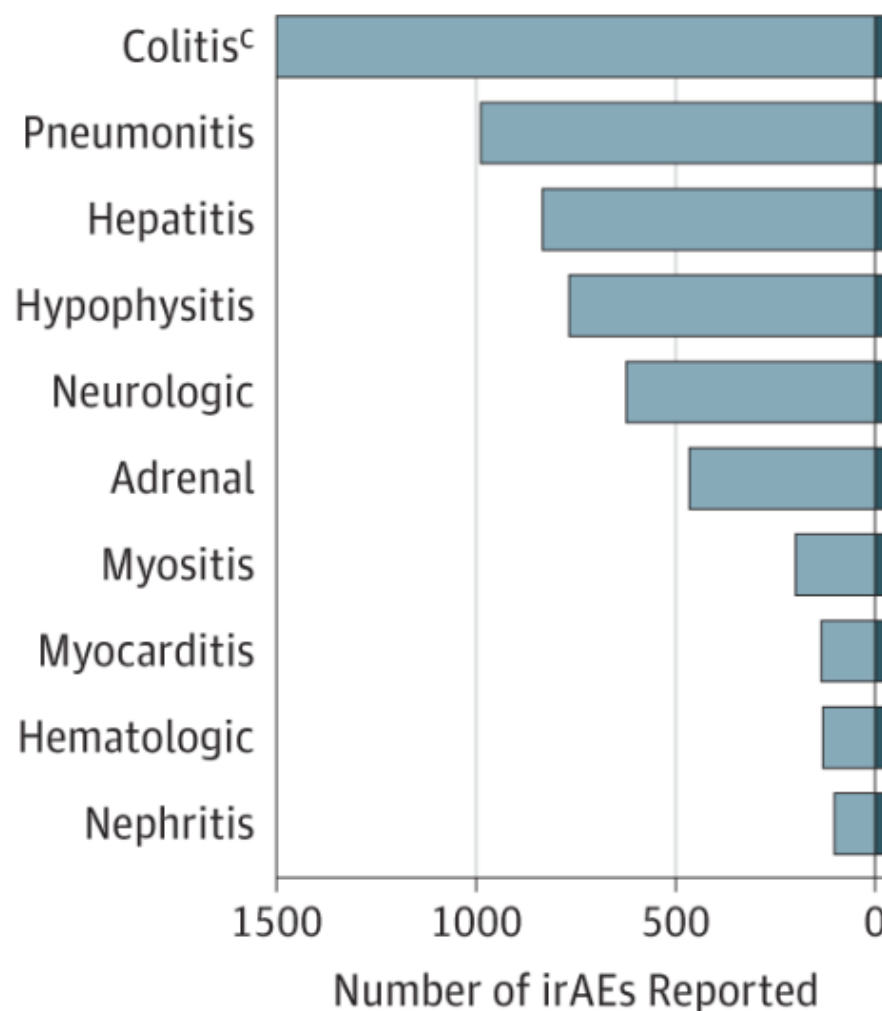
Differences Between Anti-CTLA-4 and Anti-PD-1

Anti-CTLA-4	Anti-PD-1
<ul style="list-style-type: none">• Targets CD28 pathway	<ul style="list-style-type: none">• Targets TCR pathway
<ul style="list-style-type: none">• Works mainly on T cell priming	<ul style="list-style-type: none">• Works mainly on exhausted T cells
<ul style="list-style-type: none">• Expands clonal diversity	<ul style="list-style-type: none">• Does not expand clonal diversity
<ul style="list-style-type: none">• Primarily effects CD4 T cells	<ul style="list-style-type: none">• Primarily effects CD8 T cells
<ul style="list-style-type: none">• Can move T cells into “cold” tumors	<ul style="list-style-type: none">• Cannot move T cells into “cold” tumors
<ul style="list-style-type: none">• Responses often slow	<ul style="list-style-type: none">• Responses usually rapid
<ul style="list-style-type: none">• More adverse events	<ul style="list-style-type: none">• Less adverse events
<ul style="list-style-type: none">• Disease recurrence after response rare	<ul style="list-style-type: none">• Disease recurrence after response significant

Organ-Specific Immune-Related Adverse Events (irAEs)



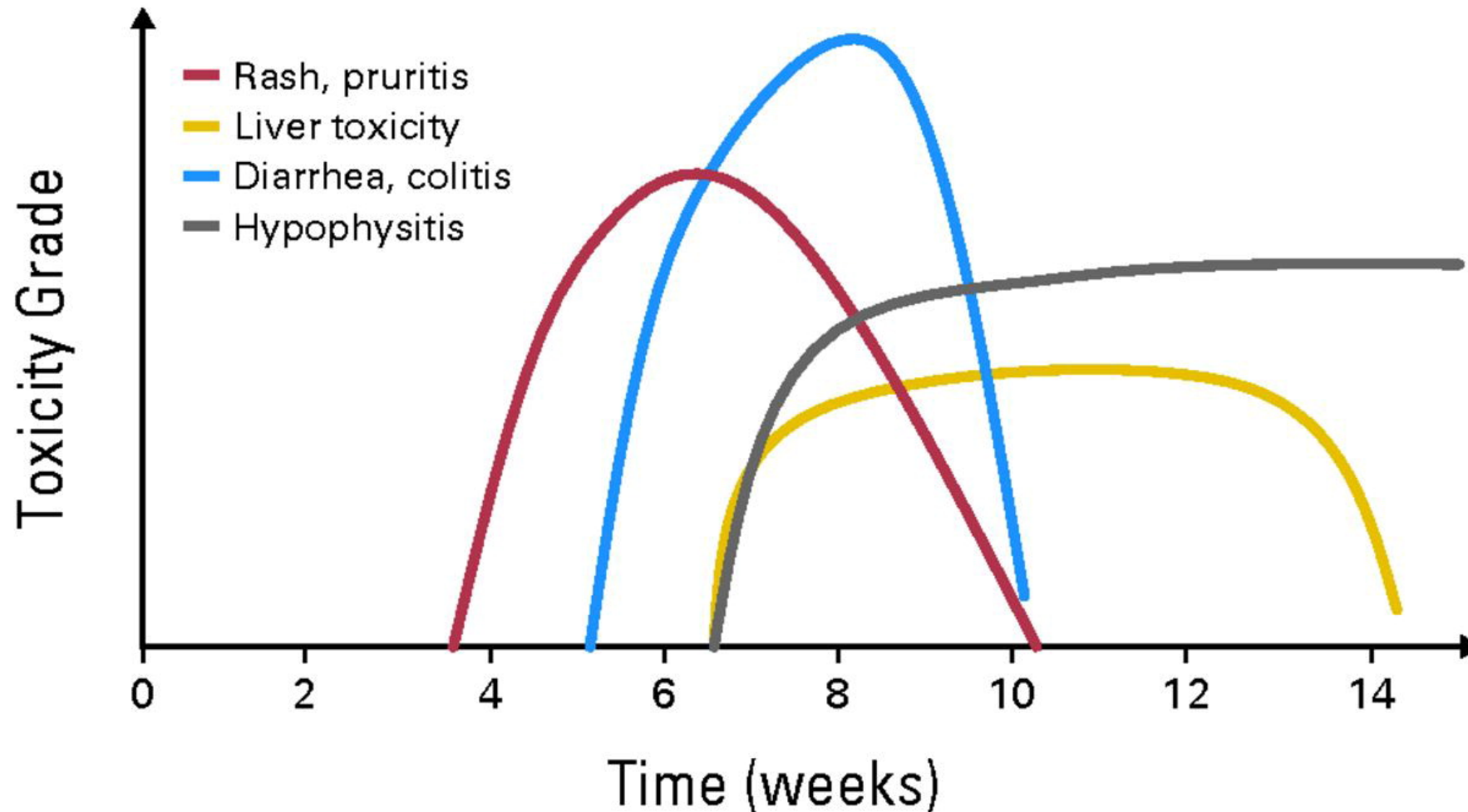
Cases and Fatality Rates for Different Types of irAEs



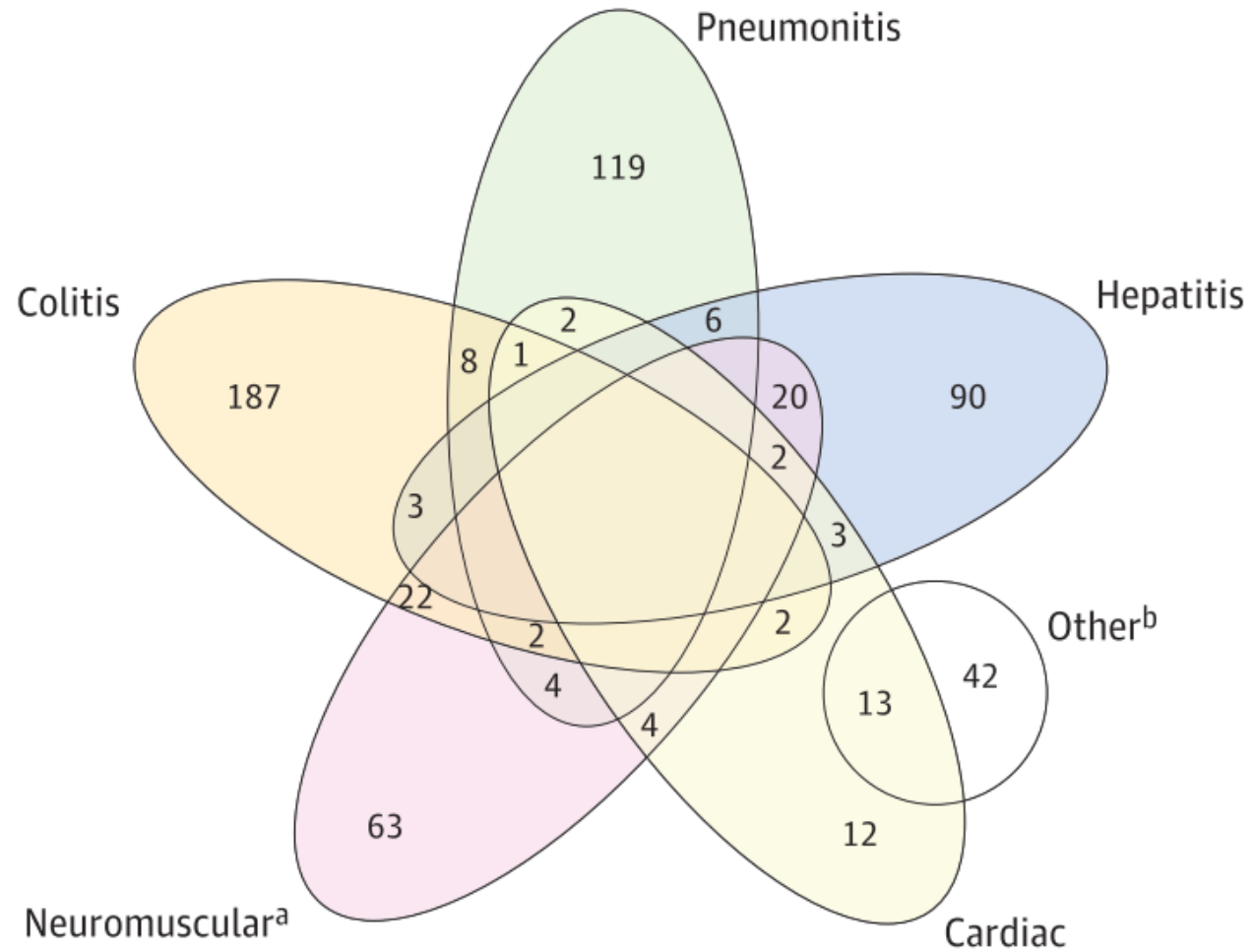
Immune-Related Colitis / Diarrhea



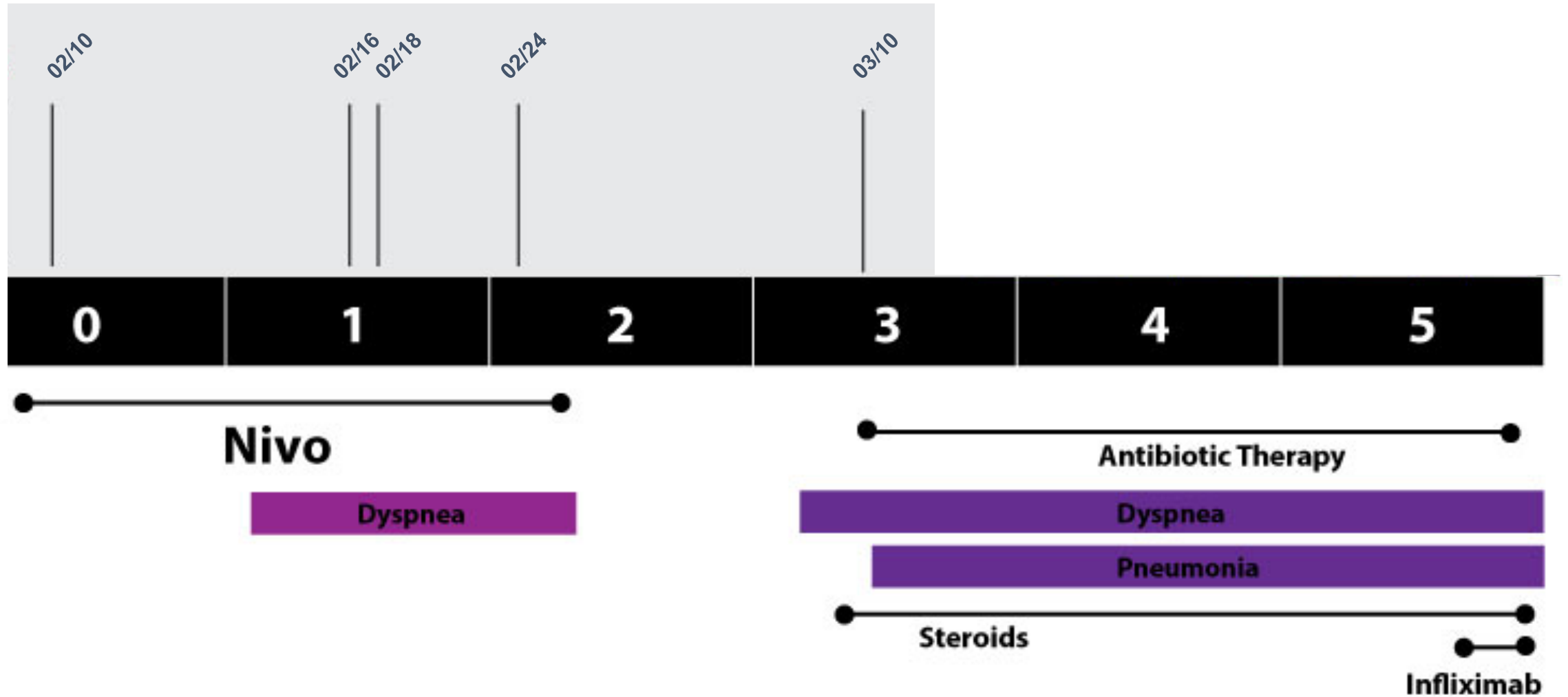
Kinetics of Appearance of irAEs



Co-Occurring Fatal irAEs



Immune-Related Pneumonitis

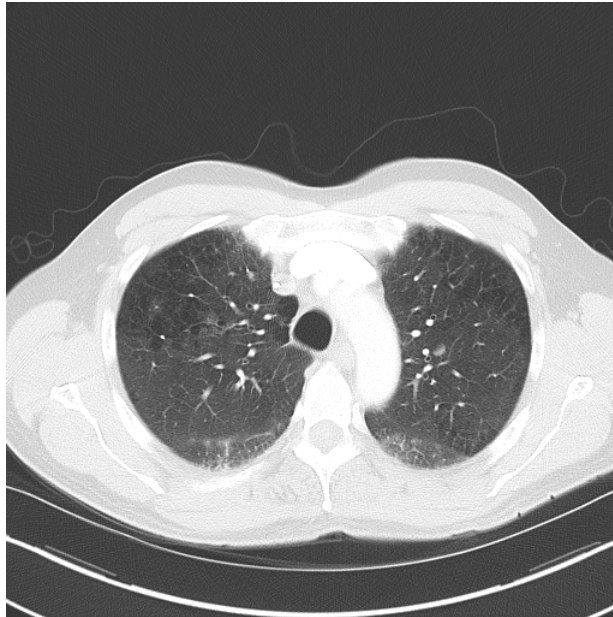


Monday Morning Quarterback

02/05/2015



02/18/2015



03/11/2015



Safety Considerations

- **irAEs appear to be under-reported**
- **Early recognition / intervention with immunosuppressive agents**
 - **Medical team**
 - **Patient / Family**
 - **Laboratory tests**
 - **Consult teams**

Additional Safety Considerations

- **Super Users**
 - Research nurses, Advanced practice providers, Physicians
- **Weekly team meetings**
- **Standardization:**
 - Algorithms
 - Pharmacy order sets
- **Handouts to patients**

Management of irAEs: ASCO Guidelines

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ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network



Management of irAEs: SITC Guidelines

Open access

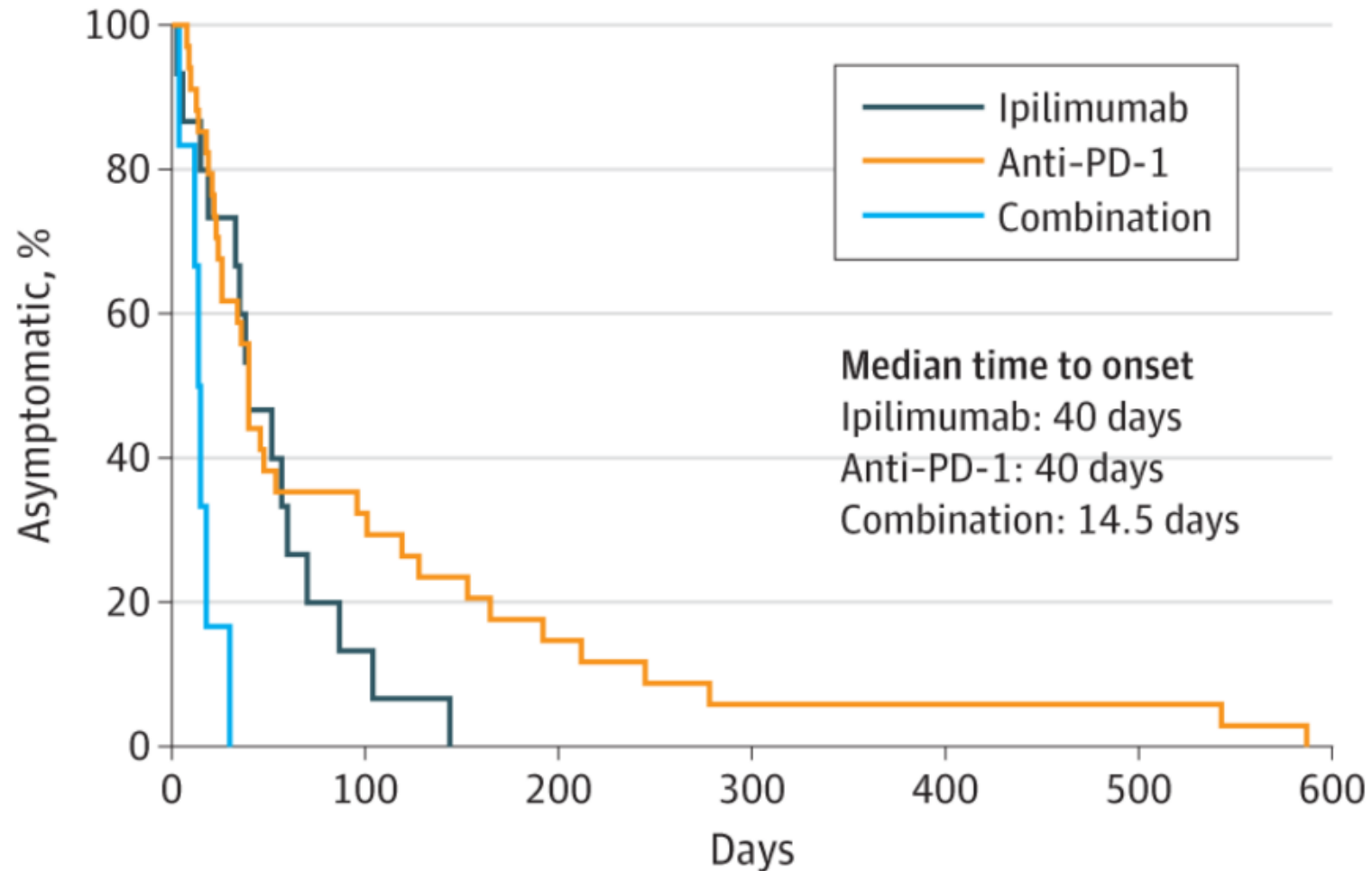
Position article and guidelines



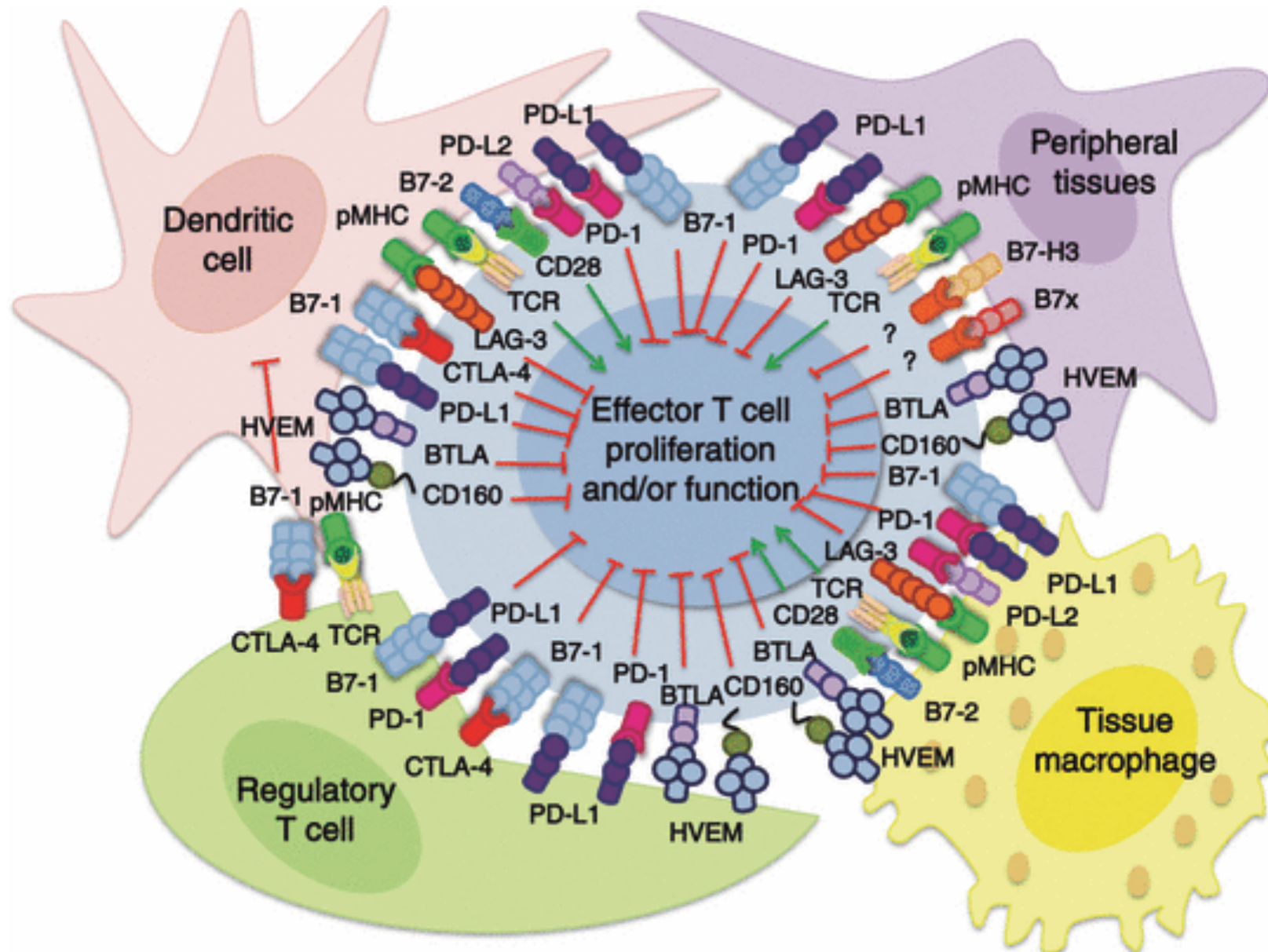
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,¹ Hamzah Abu-Sbeih,² Paolo Antonio Ascierto ,³ Jill Brufsky,⁴ Laura C Cappelli,⁵ Frank B Cortazar,^{6,7} David E Gerber,⁸ Lamy Hamad,⁹ Eric Hansen,¹⁰ Douglas B Johnson,¹¹ Mario E Lacouture,¹² Gregory A Masters,¹³ Jarushka Naidoo,^{1,14} Michele Nanni,¹⁰ Miguel-Angel Perales,¹² Igor Puzanov,¹⁰ Bianca D Santomaso,¹⁵ Satish P Shanbhag,^{5,16} Rajeev Sharma,¹⁰ Dimitra Skondra,¹⁷ Jeffrey A Sosman,¹⁸ Michelle Turner,¹ Marc S Ernstoff  ¹⁹

Time to Symptom Onset for irAEs



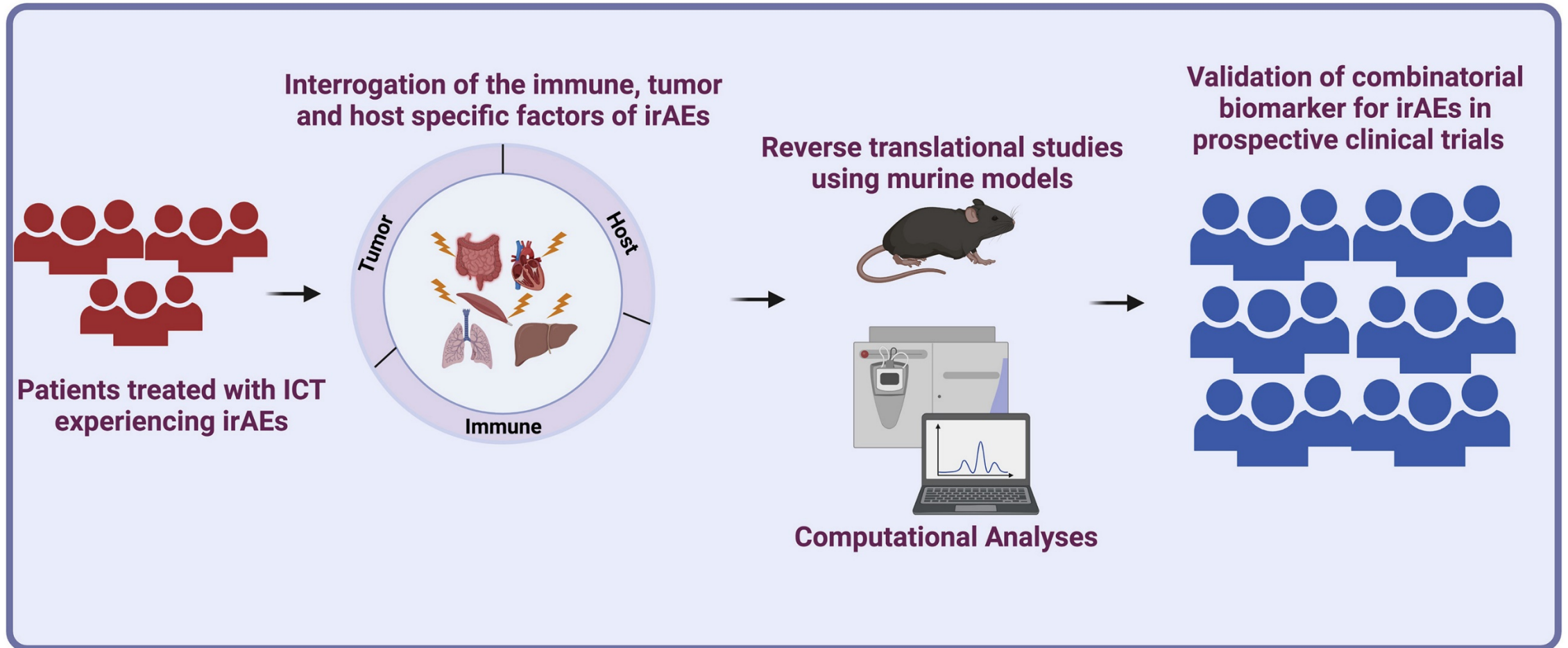
Novel Immunotherapy Targets



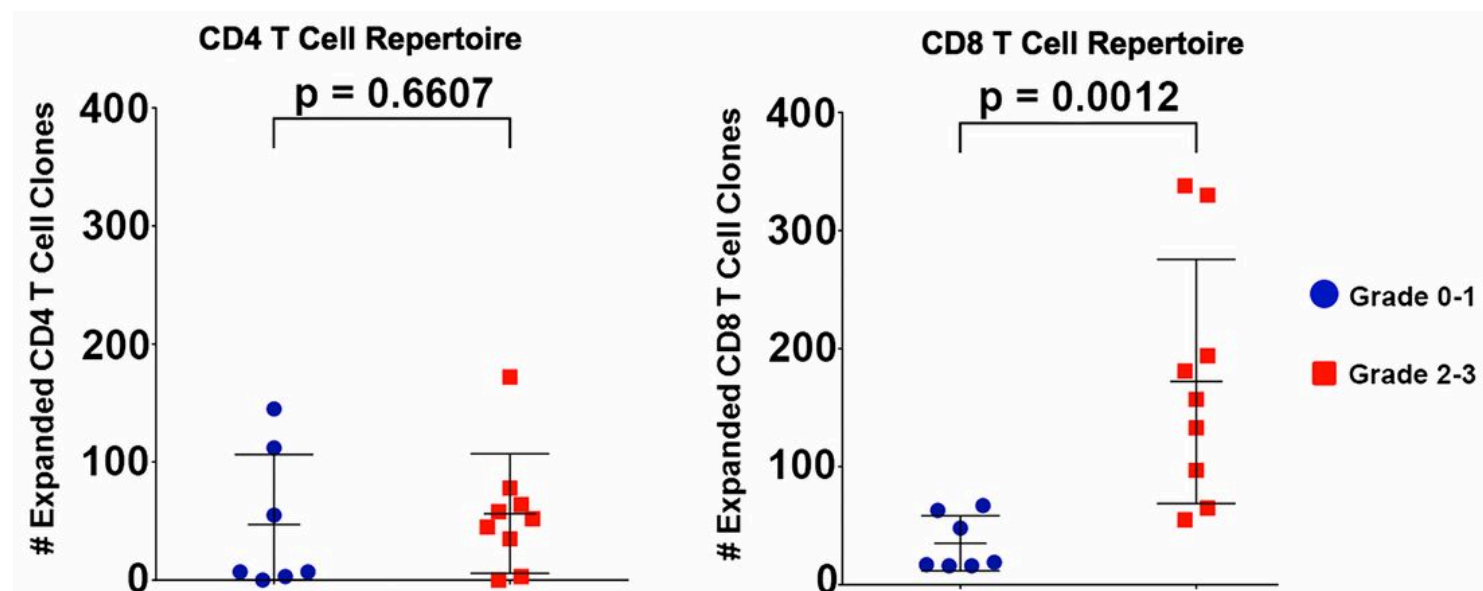
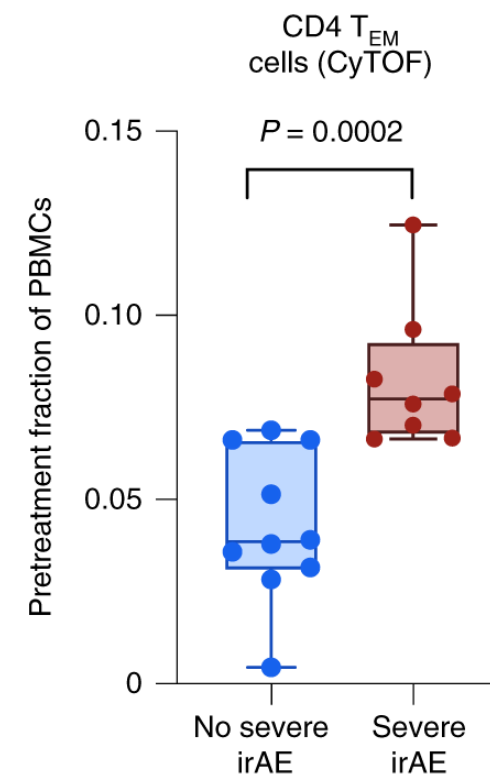
Overall Goals

- ***Early*** identification of vulnerable patients
- ***Prompt*** intervention with specific therapies
- Understanding disease ***biology*** to develop novel treatment strategies

Path Forward: Developing Mechanistic Understanding of irAEs



T Cell Subsets in Systemic Circulation Associated with irAEs

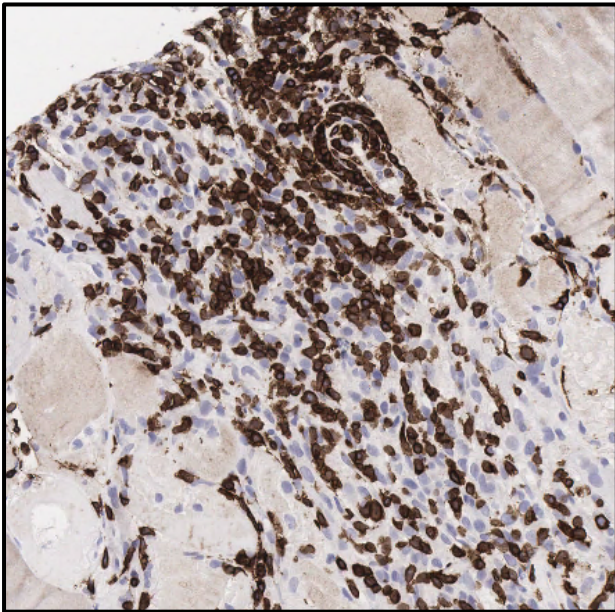
Subudhi SK et al., *Proc Natl Acad Sci U S A* 2016

Lozano AX et al., *Nat Med* 2022

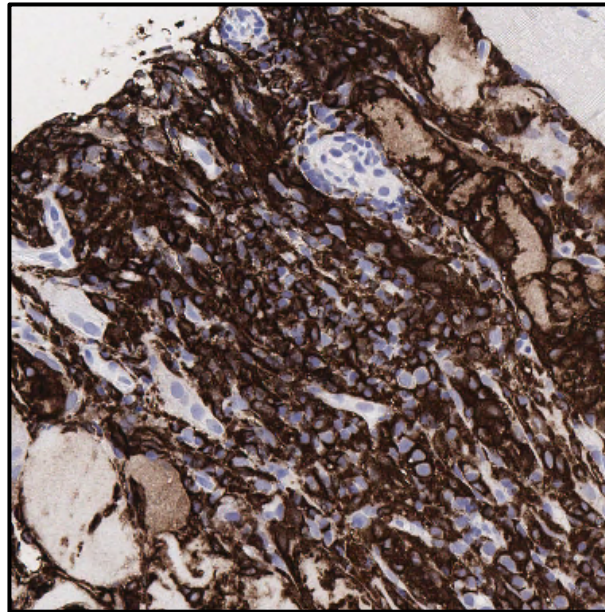
T Cells, B Cells, and Myeloid Cells Can Contribute to irAEs

Skeletal Muscle

T Cells (CD3)



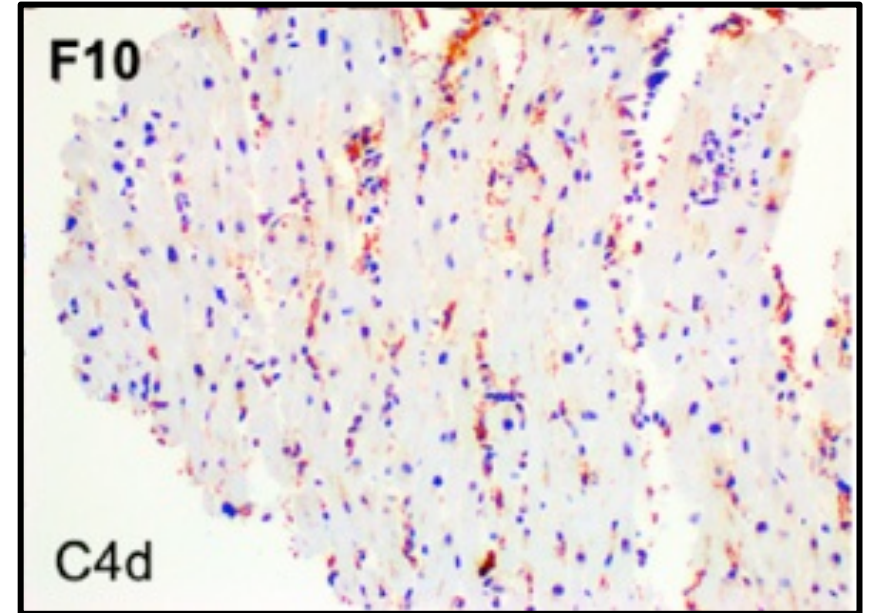
Myeloid Cells (CD163)



Siddiqui BA and Palaskas NL (unpublished)

Cardiac Muscle

C4d



Balanescu DV et al., *Cardiovasc Path* 2020

Rechallenge After Toxicity Induces Durable Responses

Grade 3 Colitis / Diarrhea

Grade 2 Arthralgia

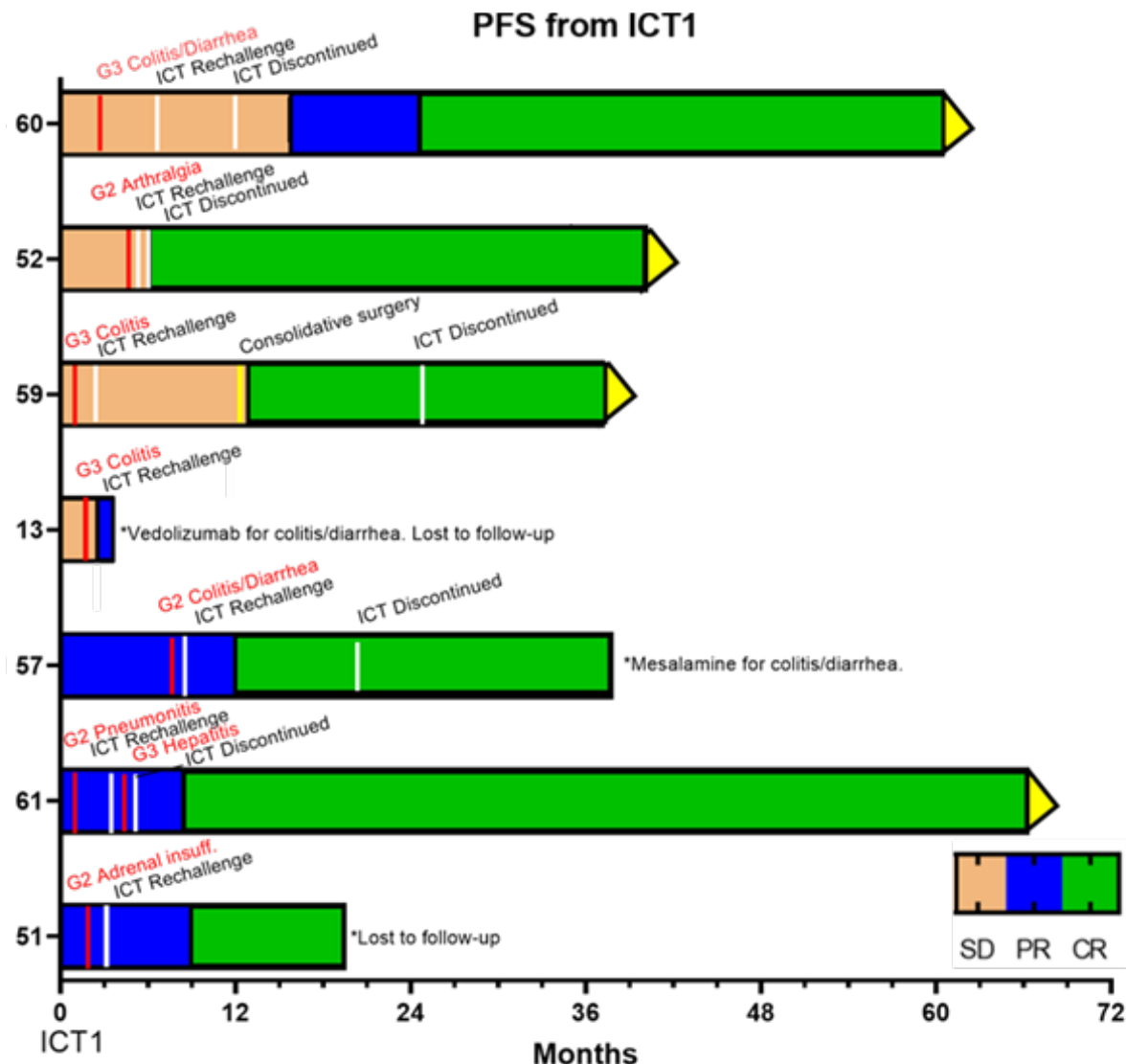
Grade 3 Colitis / Diarrhea

Grade 3 Colitis / Diarrhea

Grade 2 Colitis / Diarrhea

Grade 2 Pneumonitis / Grade 3 Hepatitis

Grade 2 Adrenal Insufficiency



Acknowledgements

Our Patients

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