Dana-Farber Cancer Institute

Lessons from Non-Renal Immune-Related Adverse Events: Learning from Our Mistakes

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Disclosures

- Consulting: D.E. Shaw Research
- Advisory Board: Mallinckrodt Pharmaceuticals
- DSMB: FortVita
- Patent: Use of Atezolizumab for Patients with Alveolar Soft Part Sarcoma

Learning from Our Mistakes

Themes in the toxicity of immune checkpoint inhibitor therapy

1. **Mechanisms** · *of immune checkpoint blockade*
2. **Immune-related adverse events** · *toxicity as iatrogenic autoimmunity*
3. **A sentinel toxicity** · *ICI myocarditis and cardiac events*
4. **Building the evidence base** · *a national irAE biorepository*
5. **Special populations** · *patients excluded from registration trials*

PART 1

Mechanisms of immune checkpoint blockade

The biology of CTLA-4 and PD-1, and why their inhibition mobilizes T cells against the tumor.

CTLA-4 and PD-1 act at distinct stages and sites

Their differing biology underlies distinct patterns of efficacy and immune-related toxicity.

CTLA-4

early activation · secondary lymphoid tissue

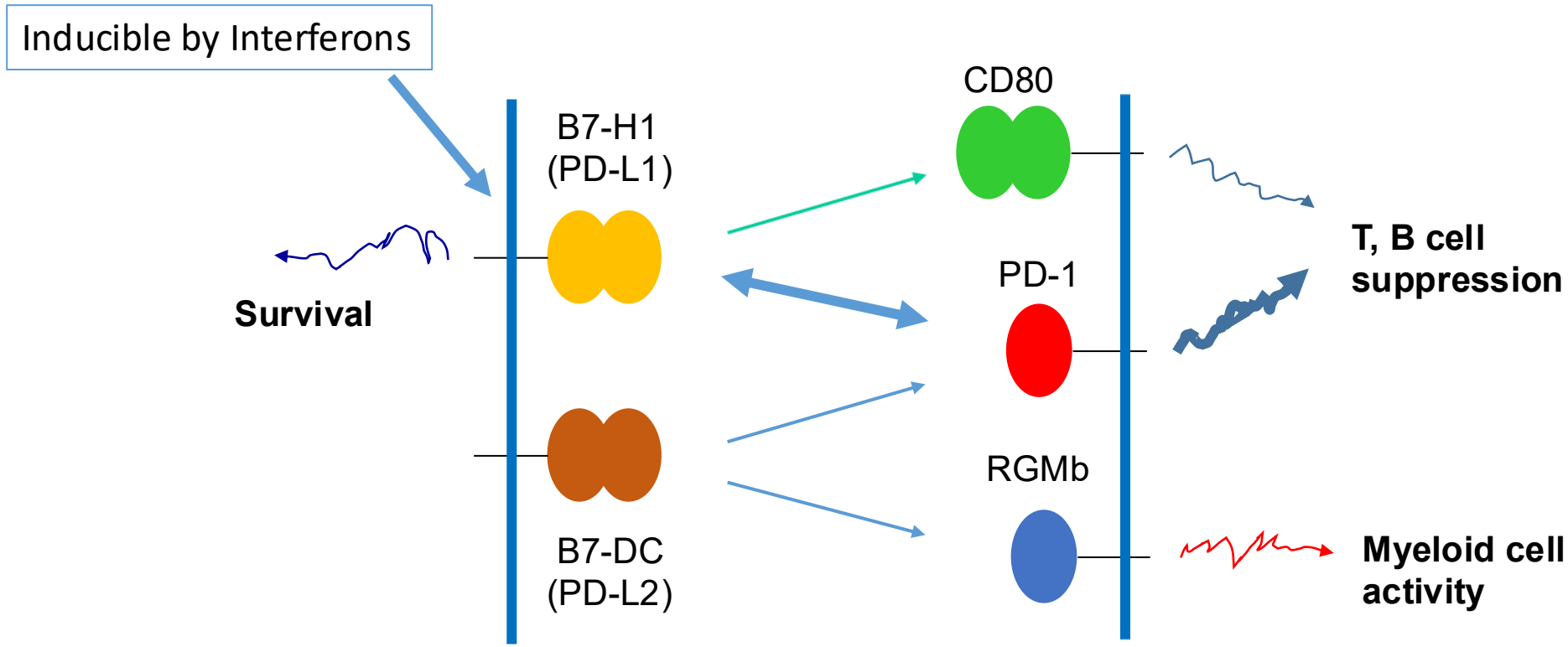
- Regulates the amplitude of early T-cell activation
- Outcompetes CD28 for the B7 ligands (CD80/CD86)
- Constitutively expressed on regulatory T cells
- Central checkpoint

PD-1

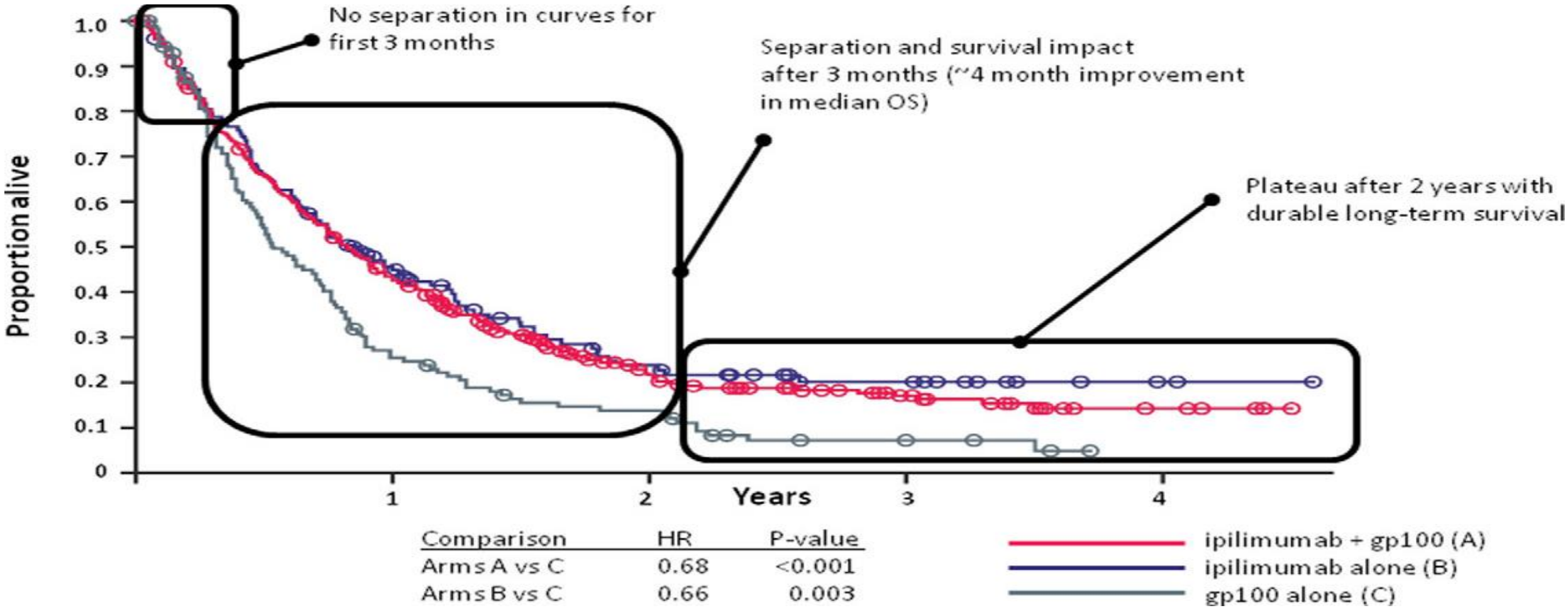
effector phase · peripheral tissue and tumor

- Attenuates activated T cells in peripheral tissue
- Engaged by PD-L1/PD-L2 in the tumor microenvironment
- Associated with T-cell exhaustion
- Peripheral checkpoint

The PD-L1/PD-1 Pathway



Obtained with permission from M. Sznol



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

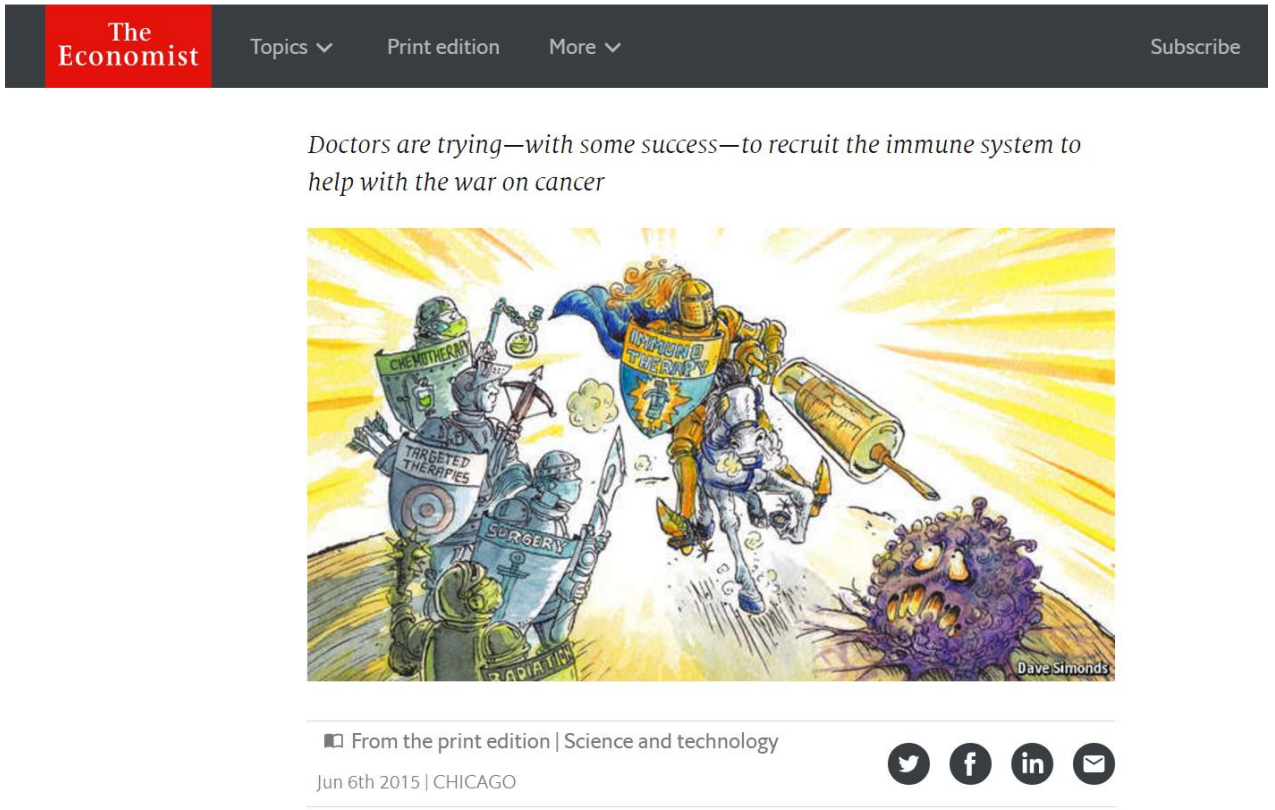
Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- Melanoma
- Renal cancer (clear cell and non-clear cell)
- NSCLC – adenocarcinoma and squamous cell
- Head and neck cancer
- Hodgkin Lymphoma
- Bladder Cancer
- Merkel Cell
- Gastric and GE junction
- Mismatch repair deficient tumors
- Hepatocellular carcinoma
- Cutaneous Squamous Cell Cancer
- Small cell lung cancer
- Triple negative breast cancer
- Primary Mediastinal B-Cell Lymphoma
- Mesothelioma
- Alveolar Soft Part Sarcoma
- Nasopharyngeal Cancer
- Ovarian Cancer
- Diffuse large B-cell lymphoma
- Follicular lymphoma

Minimal to no activity to single agents:

- Microsatellite Stable Prostate Cancer
- Microsatellite Stable Colorectal Cancer
- Multiple Myeloma
- Microsatellite Stable Pancreatic Cancer



Antitumor efficacy and autoimmune toxicity share a mechanism

Blocking the checkpoints that maintain tolerance predictably generates immune-related adverse events.

Antitumor immunity

Durable, occasionally curative responses across more than 20 malignancies.

shared mechanism

Autoimmune toxicity

Immune-related adverse events affecting virtually any organ system.

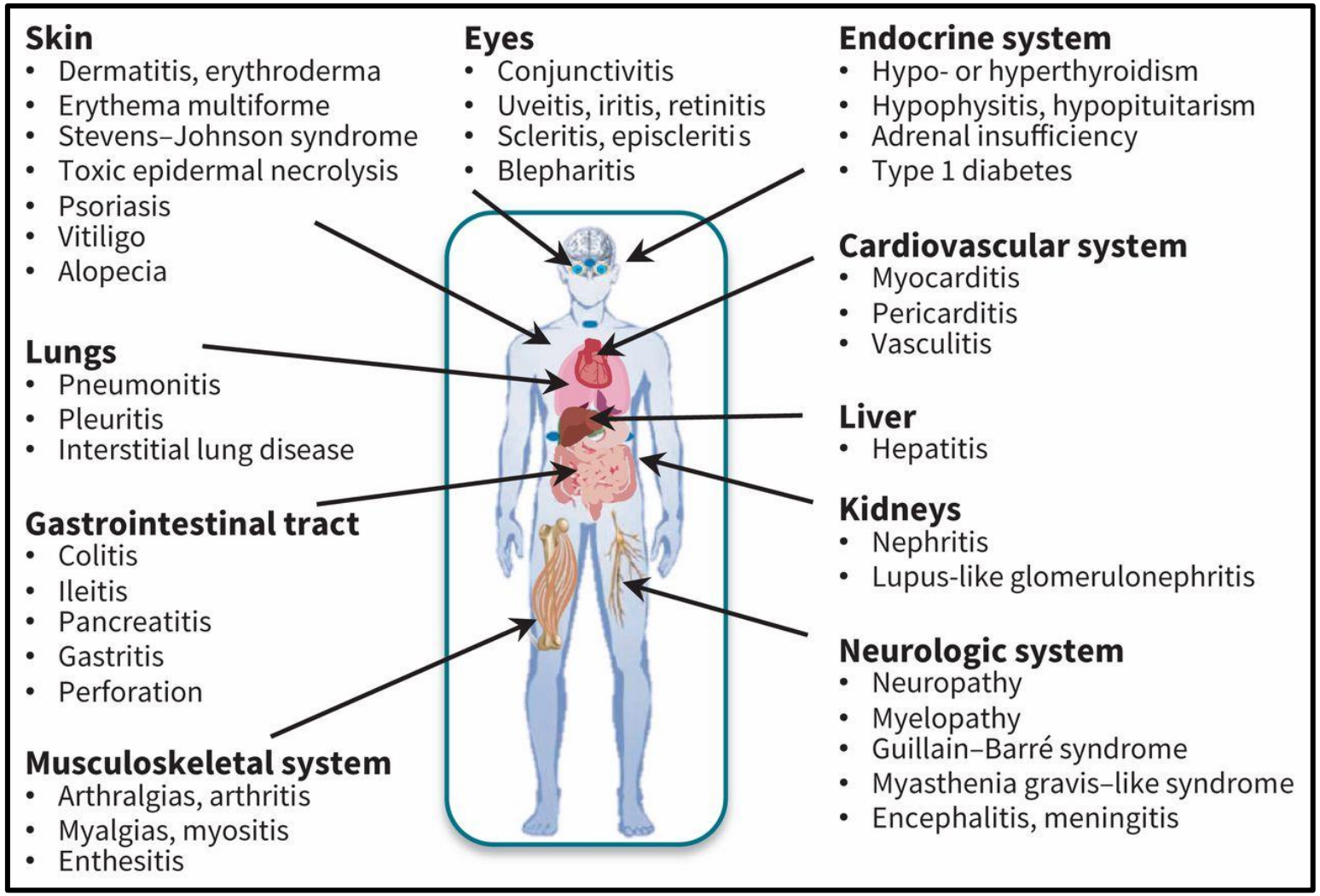
PART 2

Immune-related adverse events

Toxicity as iatrogenic autoimmunity, and the patient as a model of self-tolerance.

Immune Related Adverse Events (IrAEs)

- Can involve almost any system in the body (occur in up to 59%)
- Some are fatal
- Most are low grade disrupting QOL but can be long lasting
- irAEs differ from chemotherapy toxicities



Varricchi et al. 2017. ESMO; Thapa et al. 2019. ASCO

Figure: Khashayar Esfahani et al. CMAJ 2019;191:E40-E46

Correlations between first cycle toxicity and overall survival in patients with rare cancers treated with immune checkpoint inhibitors (NCI/SWOG S1609)

Methods:

S1609 trial (NCT02834013)

- SWOG/NCTN/NCI-sponsored
- Basket design (53 baskets)
- Nivolumab (240mg q2w) + Ipilimumab (1mg/kg q6w)
- Open at > 1000 sites
- Enrolled 798 patients

irAE = treatment-related (per treating physician) AE per CTCAEv5

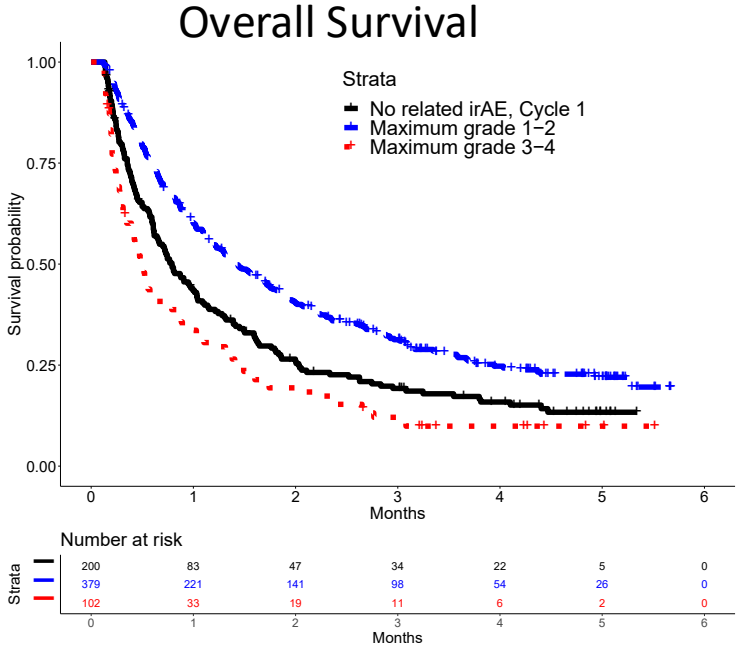
Analyses

- Landmark based on end of cycle 1 (day 42)
- Analyzed n = 681
- Kaplan-Meier, Cox regression
  - Stratified by basket

Among patients with rare cancers, grade of irAE in the *first* cycle of therapy was prognostic for overall survival.

Compared to no irAE:

- grade 1-2 was associated with longer survival
- Grade 3-4 was associated with shorter survival



Othus M. *et al*. *JNCI*. 2024

Corticosteroid exposure near ICI initiation and overall survival

Independent of the event prompting them, systemic glucocorticoids given near treatment start track with worse overall survival.

51%

shorter overall survival when systemic corticosteroids are given within one month of ICI initiation.

- 39,258 ICI recipients (Mass General Brigham), validated in the population-level TriNetX cohort
- Higher glucocorticoid dose and longer duration were associated with worse overall survival
- The association held regardless of indication — autoimmune control, palliation, or irAE treatment
- Observational analysis; residual confounding by disease burden cannot be excluded

Wan, Semenov, et al. JAMA Network Open 2026 (Mass General Brigham and TriNetX cohorts).

The human as a knockout animal model

- Immune-related AEs may have relevance both for mitigation of the AE and for the study of autoimmune disease
- Treatment and management of an adverse event induced by ICIs may teach us something about the corresponding autoimmune disorder and vice versa?
- Samples (blood, tissue, etc.) from adverse events on trial can be shared to examine commonalities between patients who exhibit the adverse event in question

Goals of Translational Studies

(1)Identify at-risk Patients

a) Clinical risk factors

i. History of heart disease?

b) Biomarker risk stratification

i. HLA haplotype?

ii. Tumor neoantigens?

(2)Prevent harm or mitigation risk of IO therapies

(3)Understand pathobiology of given irAE

PART 3

A sentinel toxicity: ICI myocarditis

Myocarditis and major adverse cardiac events — a rare toxicity that reshaped monitoring and adjudication.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

SUMMARY

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with

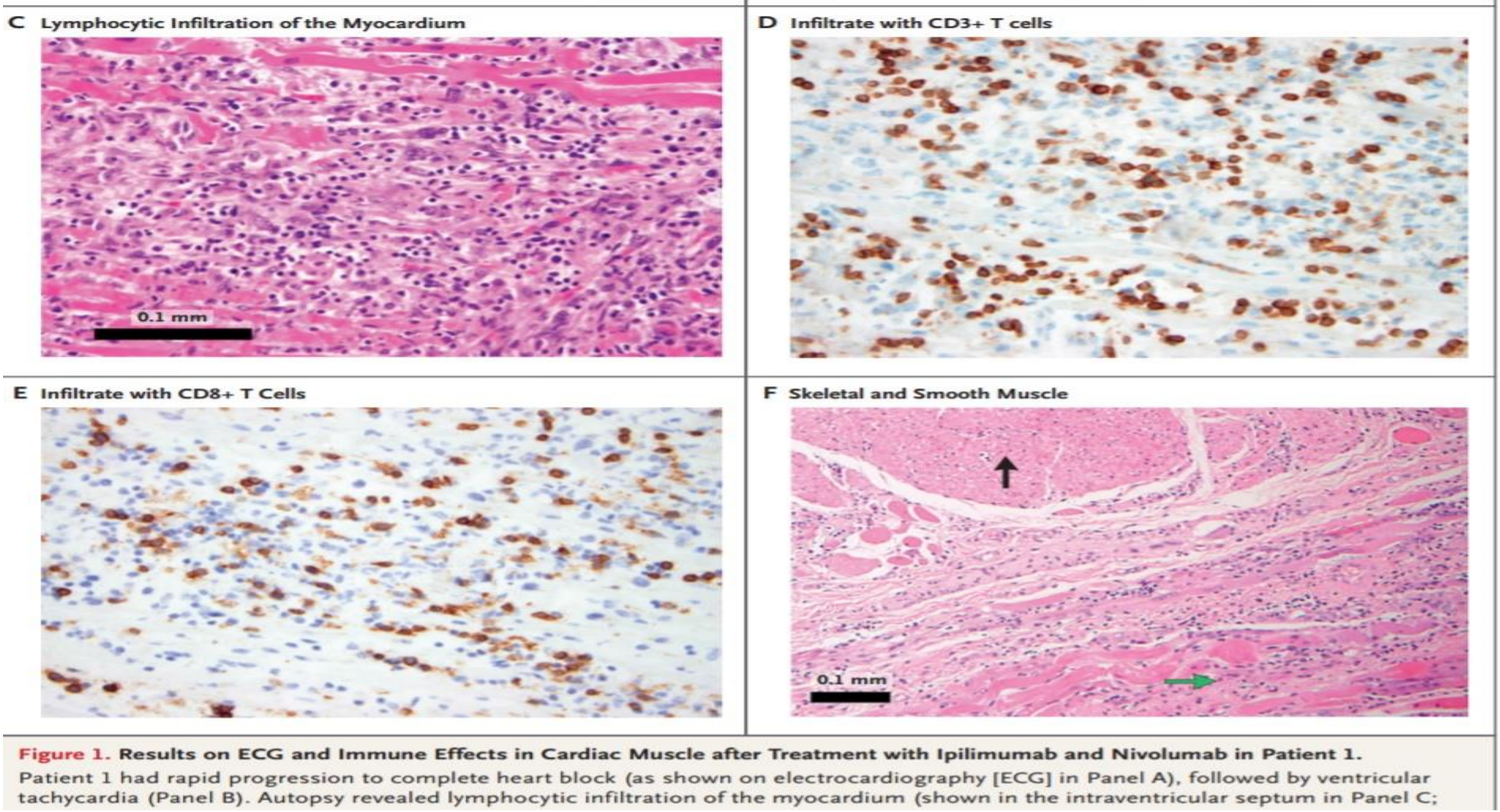
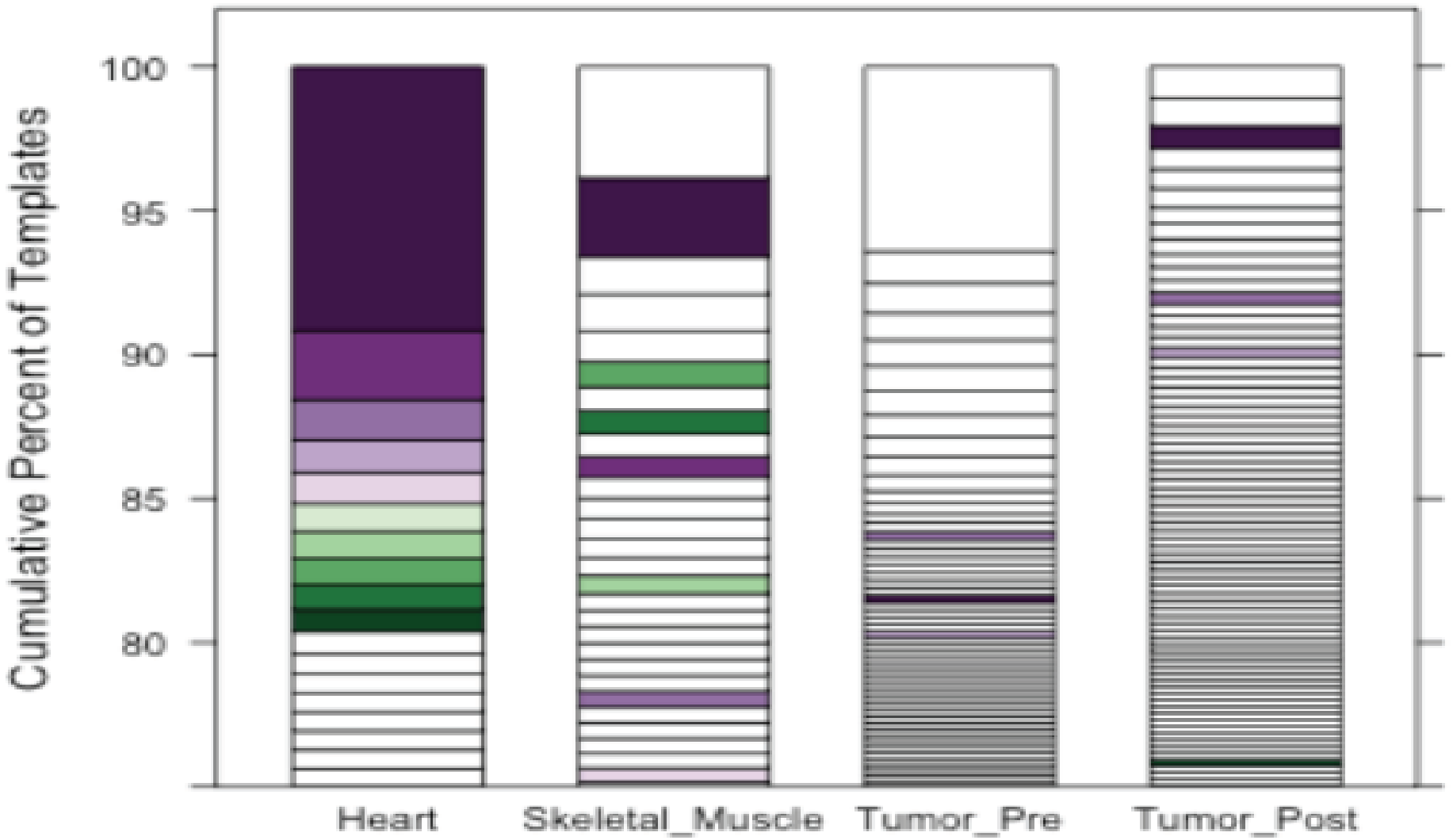


Figure 1. Results on ECG and Immune Effects in Cardiac Muscle after Treatment with Ipilimumab and Nivolumab in Patient 1.
Patient 1 had rapid progression to complete heart block (as shown on electrocardiography [ECG] in Panel A), followed by ventricular tachycardia (Panel B). Autopsy revealed lymphocytic infiltration of the myocardium (shown in the intraventricular septum in Panel C;

Johnson *et al. NEJM.* 2016



Johnson *et al. NEJM.* 2016

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Abstract # 2508

Major adverse cardiac events (MACE) with immune checkpoint inhibitor (ICI)-based therapies for cancer: A pooled analysis of investigational clinical trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP) in the United States and Canada

Abdul Rafeh Naqash MD, Melissa Y.Y. Moey MD MSc, Xiao-Wei Cherie Tan MD, Mehak Laharwal MD, Vanessa Hill, Nagabhishek Moka MD, Shanda Finnigan MPH, James Murray PhD, Douglas B. Johnson MD, Javid J. Moslehi MD, Elad Sharon MD MPH

OU Health | Stephenson Cancer Center

NIH NATIONAL CANCER INSTITUTE

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

Study Objectives

- CTEP Serious Adverse Event Reporting System (CTEP-SAERS)
  - Report on **patterns** and **outcomes** of ICI-MACE
  - Define incidence of ICI-MACE in the context of **type of anti- PD(L)-1** based anti-cancer therapy
  - Identify unique co-occurring **non-cardiac irAEs**

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

Key Eligibility

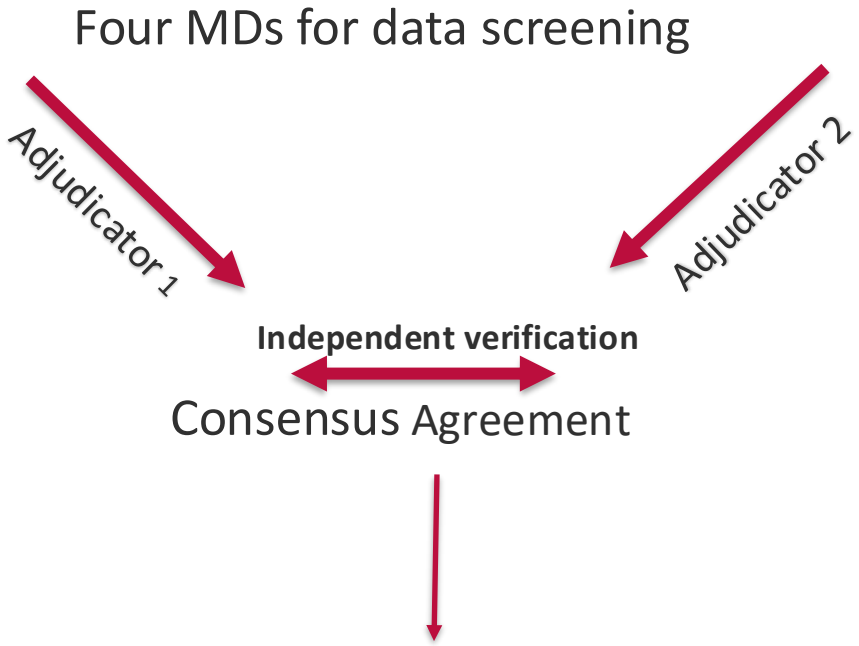
- ICI-based trials (06/2015 to 12/2019)
- ICIs : Monotherapy i.e., anti-PD-(L)1 alone

  or

  in combination with other anti-cancer therapies
  - Anti-CTLA-4
  - Other IO therapies
  - Antibody Drug Conjugates or Epigenetic therapy
  - Chemotherapy
  - Targeted Therapies
  - Multi-agent therapy (Chemo +/- TKI +/- IO etc.)
  - Radiation (RT) or Chemotherapy+ RT

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

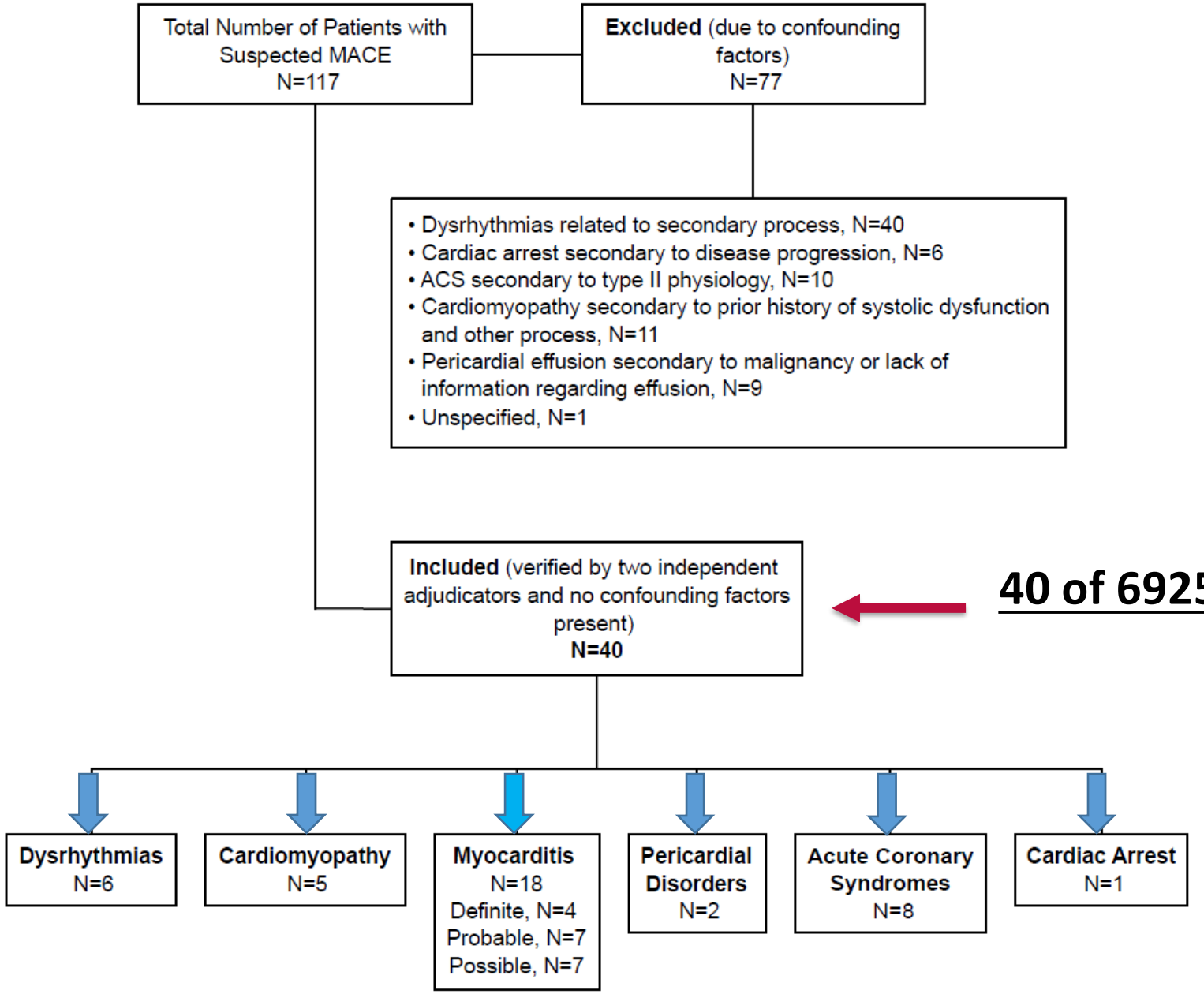
Methods



- **107** ICI-based clinical trials
  1 Pilot
  26 Phase-1
  9 Phase-1/2,
  44 Phase-2,
  9 Phase-2/3
  18 Phase-3 studies

- Distinct participants in intervention arms = **6,925**

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022



40 of 6925 ≈ 0.6% incidence

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

Incidence of MACE with anti-PD-(L)1-based anti-cancer therapies

- Incidence of MACE with **single-agent** anti-PD-(L)1 was **0.47%**

- For different **anti-PD–(L)1-based combinations**, the incidence of MACE was:
  - **0.90%** with anti-PD-(L)1+ anti-CTLA-4
  - **2.1%** with anti-PD-(L)1 + targeted therapies
  - **0.83%** with anti-PD-(L)1 + chemotherapy

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

Conclusions

- First ever pooled analysis of ICI clinical trials evaluating MACE
  - **0.6%** incidence of MACE
  - Myocarditis was the most common MACE (**45%)**
  - **65%** with MACE had other non-cardiac irAEs concurrently

- ICI-MACE have **heterogeneous presentations** and often associated with a **poor prognosis**
  - Timely identification and intervention are **critical**
  - **Multidisciplinary** approach

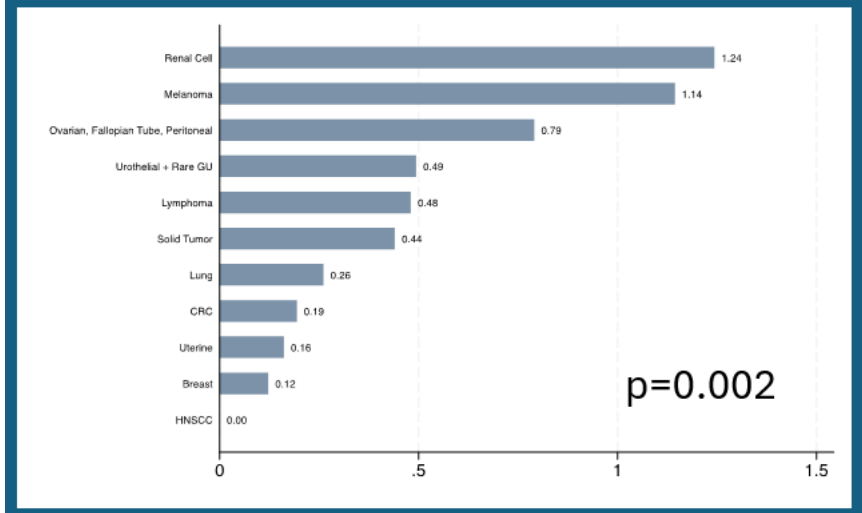
- Type of combination therapy may influence specific **MACE risk and incidence**
  - Better characterization of MACE with anti-PD-(L)1 based combination therapies

Naqash *et al. JCO.* 2022
Naqash *et al.* ASCO. 2022

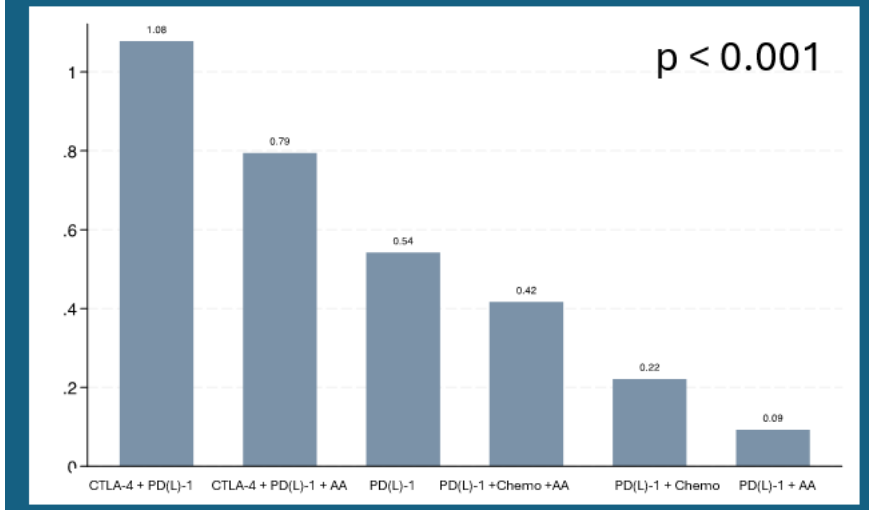
177 Individuals Identified with Diabetes Related AEs

CPI DM	New Onset T2DM	Exacerbation of T2DM	Steroid – Associated DM*	Medication Non-compliance	Other cause of acidosis
72	5	19	51	10	20

* Either steroid exacerbation of underlying DM or new onset steroid induced hyperglycemia



Cumulative incidence of CPI-DM per 100 persons treated with each cancer type if more than 500 subjects treated with that cancer



Cumulative incidence of CPI-DM per 100 persons treated with each therapy type if more than 500 subjects treated with that therapy.

Quandt *et al.* JAMA Onc 2026

Hepatitis

Autoimmune hepatitis

- Interface hepatitis, plasma cell rich
- ANA, anti-smooth muscle, anti-LKM1 positive
- Elevated IgG
- Chronic and relapsing
- Lifelong maintenance, relapse on withdrawal

ICI hepatitis

- Panlobular, CD8-predominant, granulomas described
- Usually seronegative
- IgG typically normal
- Acute and usually monophasic
- Induction and taper. Mycophenolate second line, not infliximab

Zen Y, Yeh MM. Mod Pathol. 2018;31(6):965-973.

Colitis

Inflammatory bowel disease

- Architectural distortion and basal plasmacytosis
- Chronic, with a relapsing course
- ASCA and pANCA of some diagnostic use
- Biologics given as maintenance
- Onset over months to years

ICI colitis

- Acute neutrophilic cryptitis with crypt apoptosis
- Chronicity features usually absent early
- Serology unhelpful. CMV must be excluded
- Infliximab or vedolizumab as a short course
- Onset in weeks, and it can be fulminant

Chen JH, Pezhouh MK, Lauwers GY, Masia R. Am J Surg Pathol. 2017;41(5):643-654.

Myocarditis

Viral myocarditis

- Lymphocytic infiltrate following a viral prodrome
- Often self-limited
- Supportive care and heart failure therapy
- Immunosuppression of uncertain benefit
- No characteristic overlap syndrome

ICI myocarditis

- Clonal T cells shared between tumor, myocardium, and skeletal muscle
- Case fatality historically 40% to 50%
- Immediate high-dose corticosteroids on troponin and symptoms
- Abatacept has a rationale that makes no sense in the viral disease
- Overlaps with myositis and myasthenia

Johnson DB, Balko JM, Compton ML, et al. N Engl J Med. 2016;375(18):1749-1755.

The same pattern in the kidney

ICI-associated interstitial nephritis is not drug-induced AIN with a new culprit.

Classic drug-induced AIN

- Latency of days to a few weeks
- Fever, rash, and eosinophilia when present at all
- Eosinophiluria of some historical use
- Resolves with withdrawal of the culprit
- Steroids optional and debated

ICI-associated AIN

- Median latency of 16 weeks, IQR 8 to 32
- The classic triad is usually absent
- Early steroids change recovery: adjusted OR 2.09 within 3 days
- The PPI association may be mechanistic: blockade unmasking latent drug-specific T cells.

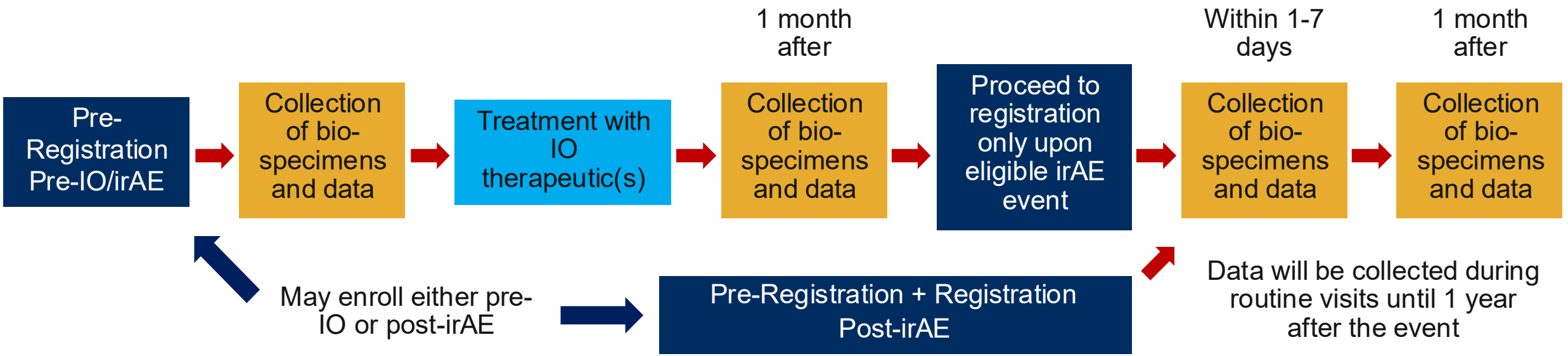
Gupta S, Short SAP, Sise ME, et al. J Immunother Cancer. 2021;9:e003467.

PART 4

Building the evidence base

A national biorepository (A151804) for the prospective study of immune-related adverse events.

A151804
Establishment of a National Biorepository to Advance Studies of Immune- Related Adverse Events



IO agents of interest

- CTLA-4 inhibitors
  - Ipilimumab, Tremelimumab
- PD-1 inhibitors
  - Cemiplimab, Dostarlimab, Nivolumab, Pembrolizumab, Tislelizumab
- PD-L1 inhibitors
  - Atezolizumab, avelumab, durvalumab
- Other
  - Relatlimab

irAEs of interest

- Myocarditis
- Colitis
- Hepatitis
- Nephritis
- Myositis
- Pneumonitis
- Meningitis/Encephalitis
- Dermatitis
- Endocrinopathies
- Other rheumatologic
- Hematologic cytopenias
- Pancreatitis
- Rare infections
- Hyperprogression

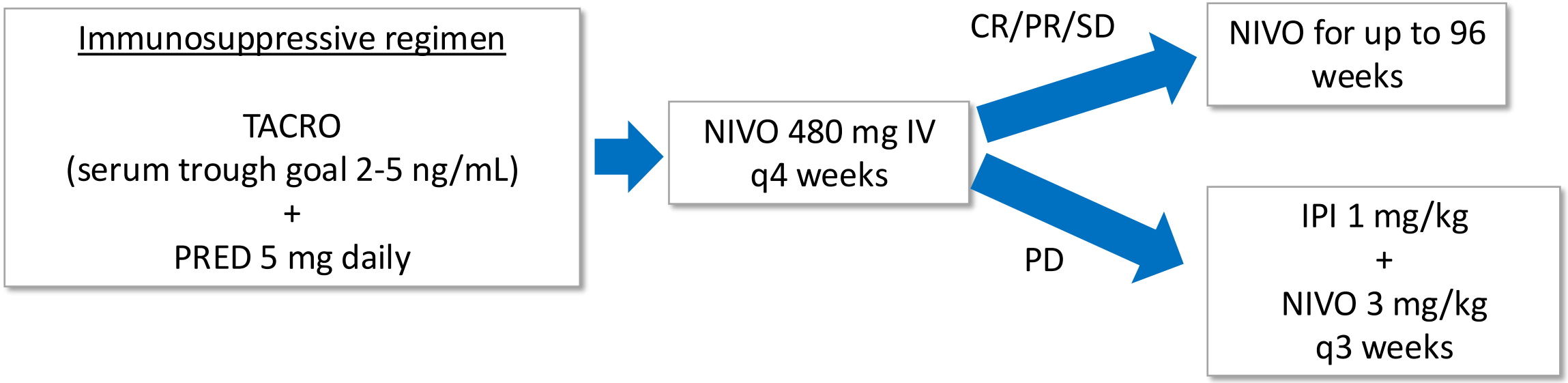
PART 5

Special populations

Patients excluded from registration trials: HIV, solid-organ transplantation, autoimmune disease, pregnancy, and rechallenge.

- Special Populations
  - Solid Organ Allografts
  - Pre-Existing Autoimmune Disease
  - Patients Requiring Rechallenge

Study of Nivolumab in Patients with Renal Allografts



CR, complete response; SD, stable disease; PD, progressive disease; PR, partial response

NCT03816332; ETCTN10214

Schenk KM et al. *Journal of Clinical Oncology*. 2024

Objectives

- Primary composite: complete or partial response (CR, PR) or stable disease* without allograft loss at 16 weeks on NIVO (Simon's 2-stage: 2/9 → 16)
- Secondary: ORR, PFS, OS
- Exploratory:
  - Immunological changes in the tumor microenvironment
  - Donor-derived cell-free DNA levels as early marker of allograft rejection
  - Histopathological characteristics of rejecting/rejected allografts

* per RECIST v.1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Schenk KM et al. *Journal of Clinical Oncology.* 2024

NIVO alone is insufficient to mediate tumor regression in kidney transplant recipients

- 8 of 8 (100%) evaluable pts with CSCC, MCC or MEL had progressive disease on NIVO alone
- 1 patient had allograft loss

		NIVO		CD8+ IHC (0-3+)*	
Pt ID	**Diagnosis**	Tumor response	Allograft loss	TACRO + PRED	TACRO + PRED+ NIVO
1	MCC	PD	N	1	1
2	CSCC	PD	N	1	2
3	MCC	PD	N	1	0
4	CSCC	PD	N	1	ND
5	CSCC	PD	N	1	ND
6	CSCC	PD	N	3	2
7	MEL	PD	Y	1	1
8	CSCC	PD	N	1	ND

*infiltrate was graded as none (0), mild (1), moderate (2), or severe (3). Taube, et al. *Sci Trans Med* 2012

CSCC, cutaneous squamous cell carcinoma; IHC, immunohistochemistry; MCC, Merkel cell carcinoma; MEL, melanoma; ND, not done; PD, progressive disease

Schenk KM et al. *Journal of Clinical Oncology*. 2024

IPI + NIVO: Complete tumor regression in 2/6 patients

- Marked tumor regression by 6 weeks in 2 patients (33%) with eventual complete response (CR)
- Progressive disease (PD) in 4 patients (67%)
- 2 patients with treatment-related allograft loss

		NIVO		CD8+ IHC (0-3+)*		IPI + NIVO	
Pt ID	**Diagnosis**	Tumor response	Allograft loss	TACRO + PRED	TACRO + PRED+ NIVO	Tumor response	Allograft loss
1	MCC	PD	N	1	1	PD	N
2	CSCC	PD	N	1	2	CR	N
3	MCC	PD	N	1	0	PD	Y
4	CSCC	PD	N	1	ND	PD	N
5	CSCC	PD	N	1	ND	N/A	N/A
6	CSCC	PD	N	3	2	CR	Y
7	MEL	PD	Y	1	1	PD	N
8	CSCC	PD	N	1	ND	N/A	N/A

*infiltrate was graded as none (0), mild (1), moderate (2), or severe (3). Taube, et al. *Sci Trans Med* 2012
CR, complete remission; ND, not done; N/A, not applicable

Schenk KM et al. *Journal of Clinical Oncology*. 2024

Cemiplimab for Kidney Transplant Recipients With Advanced Cutaneous Squamous Cell Carcinoma

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DOI https://doi.org/10.1200/JCO.23.01498

ABSTRACT

PURPOSE Cemiplimab is approved for treating locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC). Solid organ transplant recipients have been excluded from immunotherapy trials, given concern for allograft rejection despite their increased risk of skin cancers. Chronic immunosuppression is necessary to prevent organ rejection but may attenuate antitumor response with PD-1 inhibitors.

METHODS We report a phase I study of cemiplimab for kidney transplant recipients (KTRs) with advanced CSCC. After cross-taper to a mammalian target of rapamycin (mTOR) inhibitor and pulsed dose corticosteroids (prednisone 40 mg once daily, the day before and on days 1-3 of each cycle, followed by 20 mg once daily on days 4-6, then 10 mg once daily until the day before each subsequent cycle), patients received cemiplimab 350 mg intravenously once every 3 weeks for up to 2 years and were assessed for response every 8 weeks. The primary end point was the rate of kidney rejection, with key secondary end points including rate and duration of response, and survival.

RESULTS Twelve patients were treated. No kidney rejection or loss was observed. A response to cemiplimab was observed in five of 11 evaluable patients (46%; 90% CI, 22 to 73), including two with durable responses beyond a year. Median follow-up was 6.8 months (range, 0.7-29.8). Treatment-related grade 3 or greater adverse events occurred in five patients (42%), including diarrhea, infection, and metabolic disturbances. One patient died of angioedema and anaphylaxis attributed to mTOR inhibitor cross-taper.

CONCLUSION mTOR inhibitor and corticosteroids represent a favorable immunosuppressive

ACCOMPANYING CONTENT

Editorial, p. 981

Appendix

Protocol

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J Clin Oncol 42:1021-1030

View Online Article

2022 ASCO® ANNUAL MEETING

Safety and Efficacy of Immune Checkpoint Inhibitors in Solid Organ Transplant Recipients: A Systematic Review and Individual Patient Data Meta-Analysis.

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Results: Patient Characteristics

Characteristic	Overall N = 331	No Rejection N = 213	Rejection N = 118
Country			
USA	181 (55%)	118 (65%)	63 (35%)
Others	150 (45%)	95 (63%)	55 (34%)
Age (Mean ,Q1, Q3)	62 (54, 68)	62 (55, 68)	61 (51, 68)
Sex			
M	257 (78%)	166 (65%)	91 (35%)
F	71 (21%)	45 (63%)	26 (37%)
ICI Class			
PD-1	262 (76%)	159 (61%)	103 (39%)
PD-L1	22 (6.4%)	22 (100%)	0 (0%)
CTLA-4	16 (4.9%)	12 (75%)	4 (25%)
PD-1 + CTLA-4	27 (6.7%)	18 (67%)	9 (37%)
ICI administration			
Post Transplant	214 (65%)	127 (59%)	87 (41%)
Pre Transplant	116 (35%)	86 (74%)	30 (26%)
ICI Line			
First	94 (30%)	58 (62%)	36 (38%)
Second	70 (22%)	32 (46%)	38 (54%)
Third+	45 (7.9%)	34 (76%)	11 (34%)
Not Reported	102 (32%)	78 (76%)	24 (34%)

Al Zyoud *et al.* ASCO. 2025

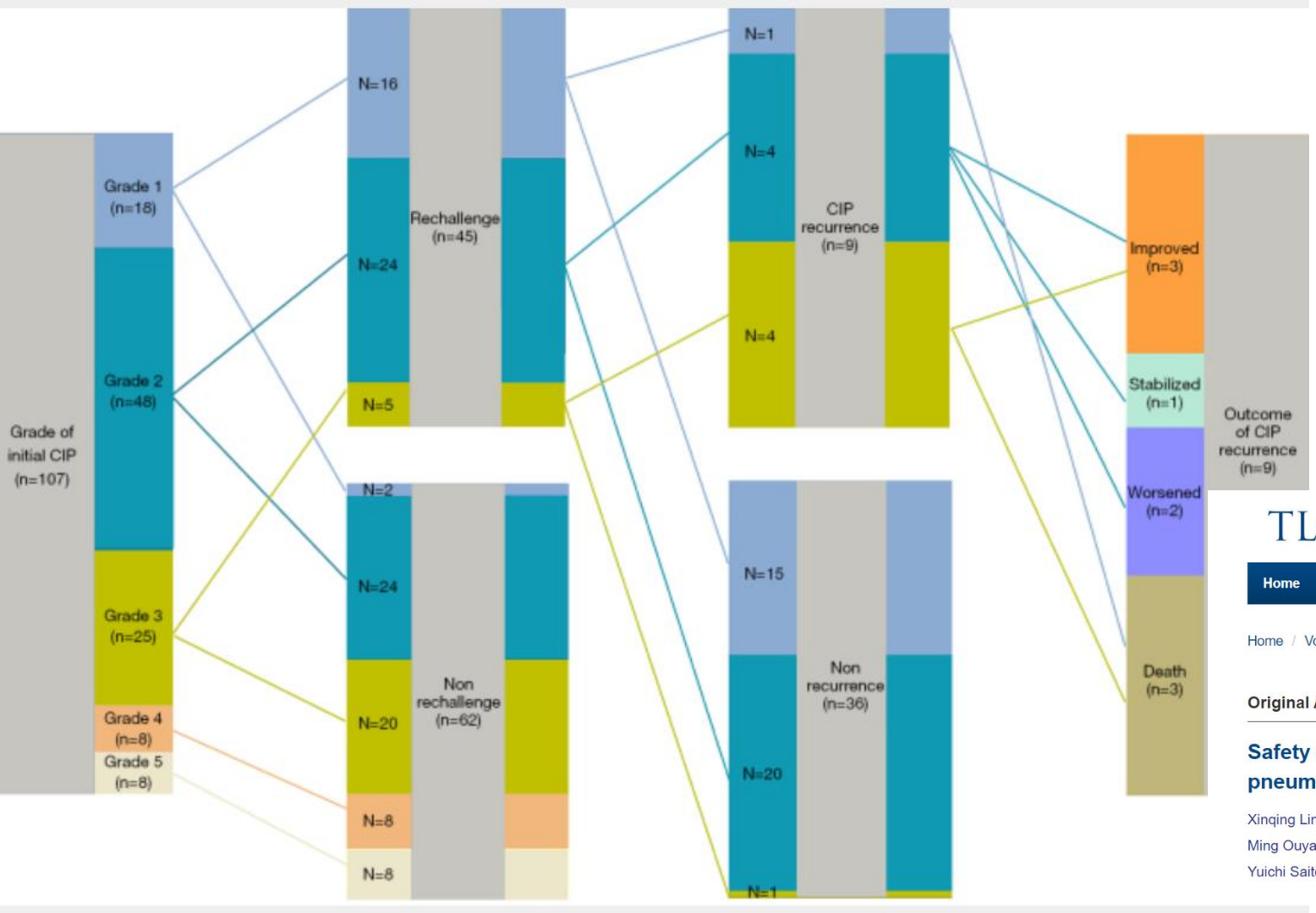
- Special Populations
  - Solid Organ Allografts
  - Pre-Existing Autoimmune Disease
  - Patients Requiring Rechallenge

NCI-10204: AIM-NIVO
NIVO in AutoImmune Disorders and advanced Malignancies
PI: Hussein Tawbi (MDACC), Elad Sharon (DFCI), Cathy Dumbrava (MDACC)

- **Dermatomyositis/Systemic Sclerosis-** Stanford University, NIH, JHU
  - ✓ Lorinda Chung, Ami Shah, Tamiko Katsumoto, Andy Mammen, David Fiorentino (Rheum)
- **Rheumatoid Arthritis (RA)-** Johns Hopkins University
  - ✓ Laura Cappelli, Bing Bingham (Rheum)
  - ✓ Julie Brahmer (Onc)
- **Sjogren's Syndrome-** NIH Clinical Center, DFCI
  - ✓ Blake Warner (Oral Pathology), Sarthak Gupta (Rheum)
  - ✓ Elad Sharon (Onc)
- **Systemic Lupus Erythematosis (SLE)-** MDACC and Emory
  - ✓ Maria Suarez-Almazor, Noha Abdelwahab, Ignacio Sanz, Arezou Khosroshahi (Rheum)
  - ✓ Cathy Dumbrava, Hussein Tawbi (Onc)
- **Inflammatory Bowel Disease (IBD)**- MGH, DFCI
  - ✓ Michael Dougan (GI)
  - ✓ Patrick Ott (Onc), Elad Sharon (Onc)
- **Psoriasis & Psoriatic Arthritis**- DFCI, MDACC
  - ✓ Nicole LeBoeuf (Derm)
  - ✓ Elad Sharon, Mehmet Altan (Onc)
- **Basket Cohort** including Polymyalgia Rheumatica/Giant Cell Arteritis (PMR/GCA)- BWH, DFCI, NIH Clinical Center
  - ✓ Deepak Rao, Lydia Gedmintas (Rheum)
  - ✓ Sarthak Gupta, Marianna Kaplan (Rheum)
  - ✓ Elad Sharon (Onc)
- **Multiple Sclerosis (MS)**-Yale and NINDS
  - ✓ David Hafler, Sarah Wesley, Daniel Reich (Neurology)
  - ✓ Harriet Kluger, Mario Sznol, Elad Sharon (Onc)

- Special Populations
  - Solid Organ Allografts
  - Pre-Existing Autoimmune Disease
  - Patients Requiring Rechallenge

Rechallenge of Lung Cancer Cohort after ICI Pneumonitis



Out of 45 rechallenged, 9 had recurrence of pneumonitis, 11 had other irAEs

TLCR Translational Lung Cancer Research
An open access journal focusing on closing the gap between "bench and bedside"
4 Impact Factor | 7.2 CiteScore

Original Article

Check for updates

Safety and efficacy of immunotherapy rechallenge following checkpoint inhibitor-related pneumonitis in advanced lung cancer patients: a retrospective multi-center cohort study

Xinqing Lin[1#], Haiyi Deng[1#], Tianqing Chu[2#], Likun Chen[3], Yilin Yang[1], Guihuan Qiu[1], Xiaohong Xie[1], Yinyin Qin[1], Ming Liu[1], Zhanhong Xie[1], Ming Ouyang[1], Shiyue Li[1], Yong Song[4], Francesco Petrella[5,6], Marko Jakopovic[7,8], Nikolaos Tsoukalas[9], Piergiorgio Solli[10], Taichiro Goto[11], Yuichi Saito[12], Chengzhi Zhou[1]

Was this an irAE?

> *The differential diagnosis of an irAE is rarely trivial, and subspecialty expertise is often essential.*

EXAMPLE: DIARRHEA

Non-immune causes
Infectious; caused by other anti-cancer agents in combination

ICI-mediated causes
ICI colitis · ICI microscopic colitis · ICI pancreatic exocrine insufficiency · ICI celiac disease

Confirmation
Flexible sigmoidoscopy, colonoscopy, and other targeted tests can help establish the diagnosis

Rechallenge: An Individualized Approach

Adverse-event nature
What was the irAE? How severe? How did it respond to treatment?

Therapy setting
Was treatment effective prior to the irAE?

Likelihood of benefit
What are the chances of further benefit from continued therapy?

Alternatives
What other options exist for this patient?

PRACTICAL EXAMPLES

Endocrine toxicity:

Treatment through thyroid dysfunction, adrenal insufficiency, or ir-diabetes is generally acceptable, with only a minimal pause required.

Combination IO:

If combination therapy was used prior to the irAE (e.g. nivo/ipi, nivo/relatlimab), rechallenge often involves only one agent.

Need & Nature: a Shorthand for Rechallenge

NEED
for rechallenge of IO

- Context of the patient's prior therapy
- Adjuvant / neoadjuvant? Following chemoradiation? Metastatic?
- Availability of alternative options
- Did the patient respond to prior IO?

NATURE
of the prior irAE

- What was the nature of the adverse event?
- How difficult was it to control?
- What was the immunosuppressive regimen required?

Conclusions

Immunotherapy is an Extraordinary Clinical Advance
Immunotherapy has transformed cancer care, but real challenges remain

irAEs are a Roadblock to Therapeutic Success
Immune-related adverse events are a primary obstacle to broader patient benefit

irAE Research has Many Applications
Expand access to novel therapies in unique populations · target therapy to sensitive patients · illuminate resistance mechanisms · serve as a tool in drug development · improve disease management · provide insight into cognate autoimmune diseases

Shared Analytic Toolkit
The same molecular and analytic tools can study both irAEs and immunotherapy response

Every Patient Counts
Each enrolled patient can contribute to the study of response, resistance, and irAEs

Sharing Samples & Data
Openness to data sharing helps improve outcomes and generate innovation in oncology

Thank you

Questions & discussion

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