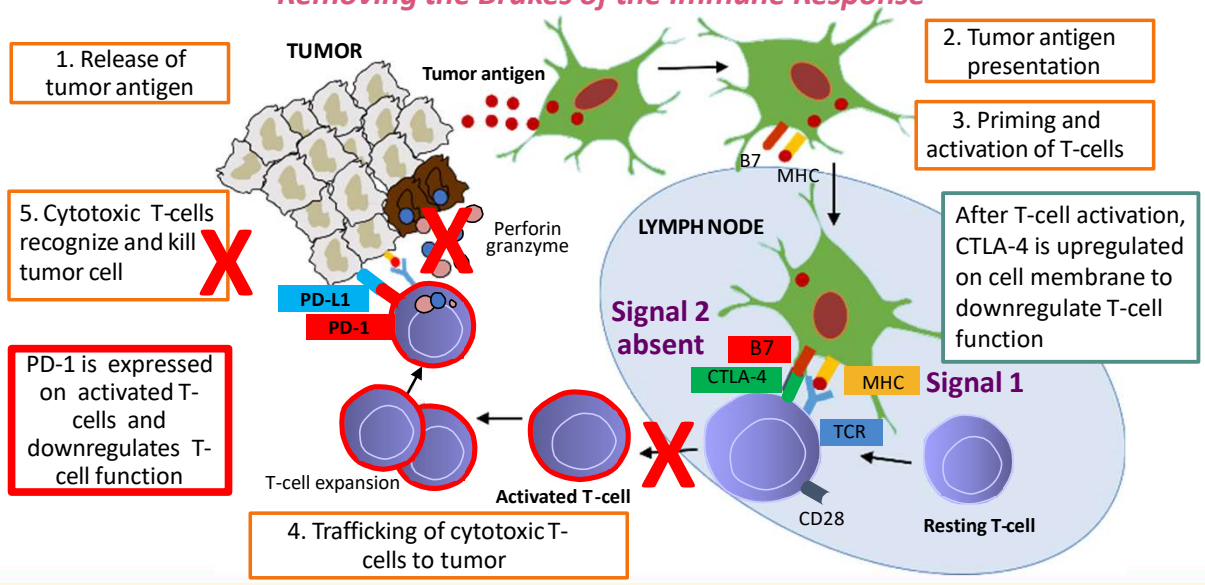
Learning Objectives

1. Assess the clinical efficacy, unique response patterns, and safety profiles associated with checkpoint inhibitors in various types of cancers.
2. Evaluate the signs and symptoms of immune-related adverse events (irAEs) associated with checkpoint inhibitors and understand how to differentiate them from other etiologies.
3. Review recent ASCO/NCCN guidelines for the management of irAEs and apply these recommendations to optimize patient care.
4. Using a case-based approach, discuss strategies oncology nurses can employ to overcome real-world challenges to the early recognition and appropriate management of irAEs.

Checkpoint Blockade

Removing the Brakes of the Immune Response



Adapted from Chen DS, Mellman I. *Immunity*. 2013.

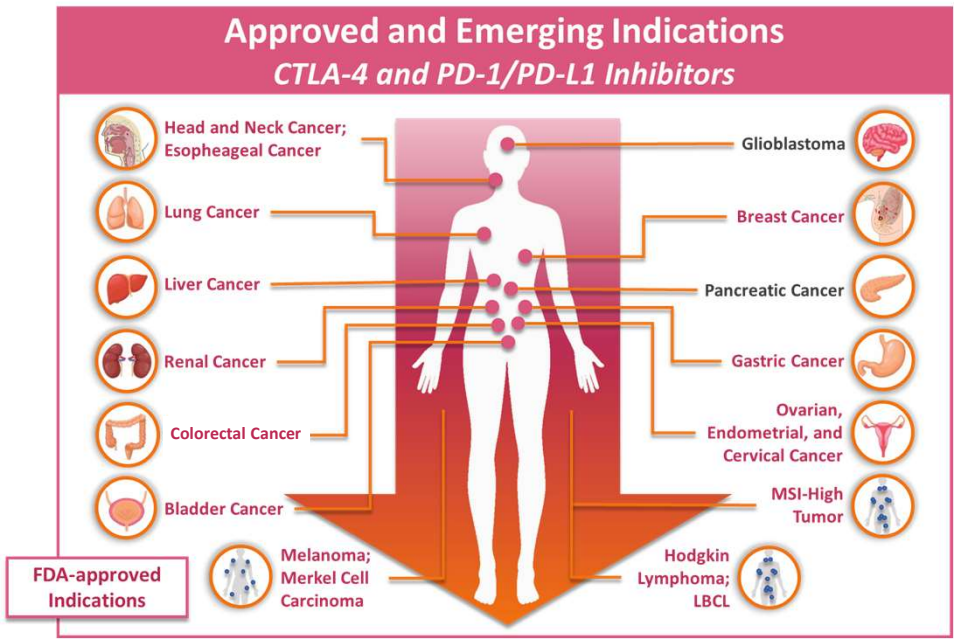
CTLA-4 and PD-1/PD-L1 Inhibitors

FDA-approved Agents as of January 2020

Class	Agents
Anti–CTLA-4	• Ipilimumab (Human IgG1 mAb) • Tremelimumab* (Human IgG2 mAb)
Anti–PD-1	• Nivolumab (Human IgG4 mAb) • Pembrolizumab (Humanized IgG4 mAb) • Cemiplimab (Humanized IgG4 mAb)
Anti–PD-L1	• Atezolizumab (Humanized IgG1 mAb) • Avelumab (Human IgG1 mAb) • Durvalumab (Human IgG1 mAb)

**orphan drug status for malignant mesothelioma and small-cell lung cancer*

FDA Prescribing Information.



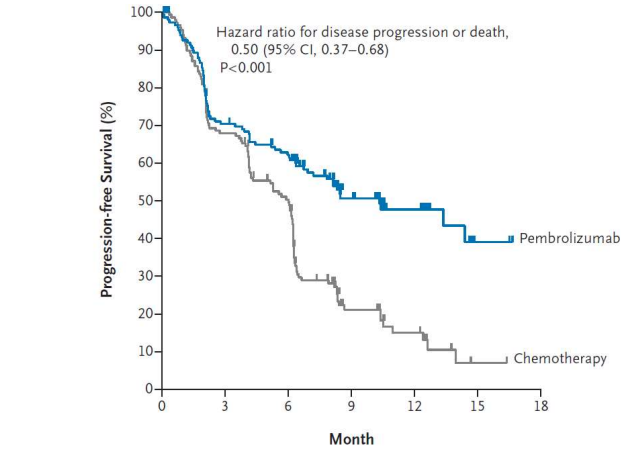
Adapted from: McIntyre P. *Cancerworld*. 2016.

Immune Therapy vs Cytotoxic Therapy

	Immune Therapy	Cytotoxic Therapy
Mechanism of action	Enhance anti-tumor immunity	Direct tumor cell kill
Target	Immune cells	Rapidly dividing cancer cells
Mechanism of toxicity	Loss of immunologic tolerance to self-antigens	• Off-target cytotoxicity • Drug specific toxicities from metabolism/metabolites
Onset of toxicity	Unpredictable	Predictable
Duration of response	Durable/Prolonged	Limited
Supportive care measures	Targets immune system	Targets adverse effect

Chen DS, Mellman I. *Immunity*. 2013; Dimberu PM, Leonhardt RM. *Yale J Biol Med*. 2011; Villadolid J, Amin A. *Transl Lung Cancer Res*. 2015; http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/how-chemotherapy-drugs-work.

Durable Responses in IO vs. Chemotherapy



Reck M, et al. *N Engl J Med*. 2016.

Immune-related Adverse Events (irAEs)

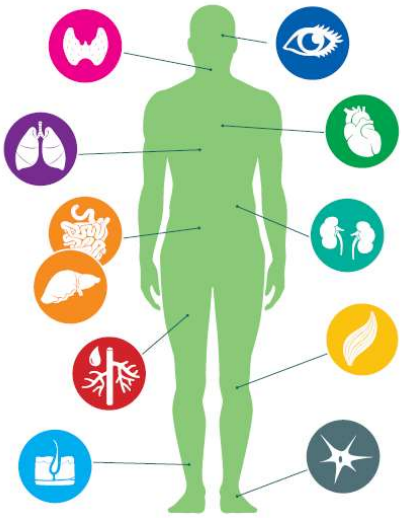
- Any toxicity with a potential immune-mediated etiology that may or may not require use of an immune-modulating therapy (e.g., steroids) after other diagnoses have been excluded
- The nomenclature for organs afflicted with inflammation usually includes the suffix "-itis"
  - Thyroiditis (inflammation of the thyroid)
  - Pneumonitis (inflammation of the lungs)
  - Colitis (inflammation of the colon)
  - Pancreatitis (inflammation of the pancreas)

Maughan BL, et al. *Front Oncol.* 2017.

Organs Affected By irAEs

Common

- Skin
- Thyroid gland
- Lung
- Colon
- Liver

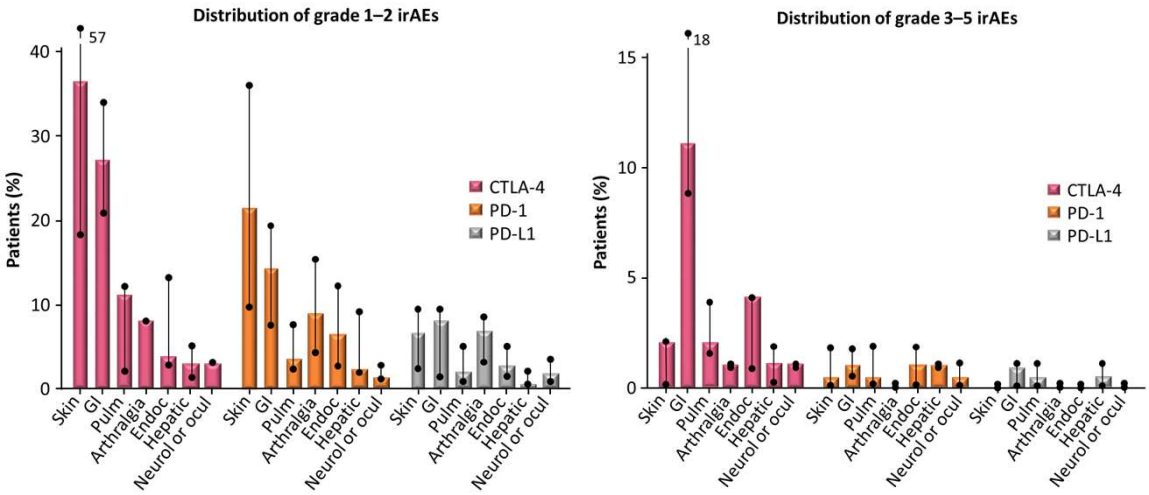


Uncommon/Rare

- Pancreas
- Kidney
- Heart
- Muscle/soft tissue
- Eye
- Hematologic system

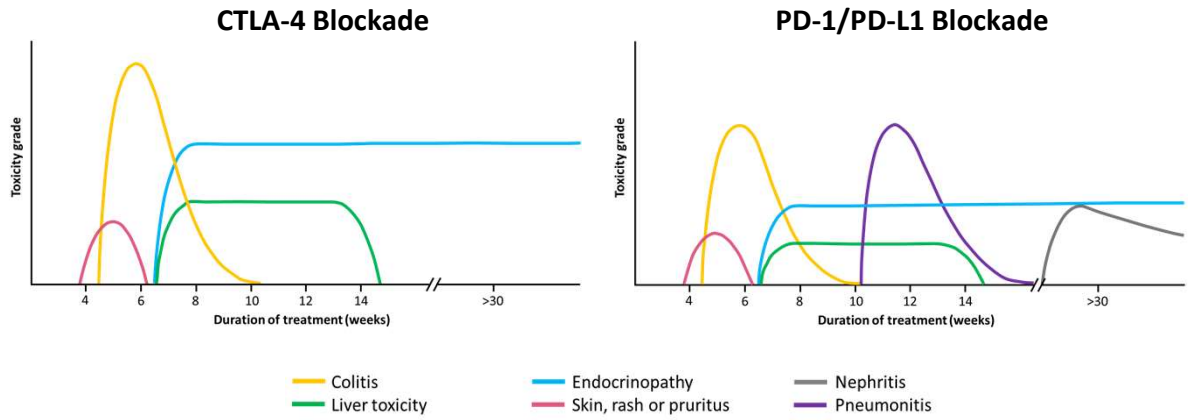
Brahmer JR, et al. *J Clin Oncol.* 2018.

Distribution of irAEs in IO Therapy



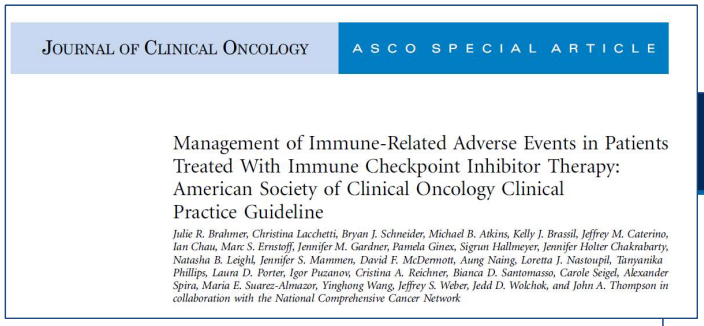
Adapted from Brahmer JR, et al. *J Clin Oncol*. 2018.

Median Time to Resolution of irAEs



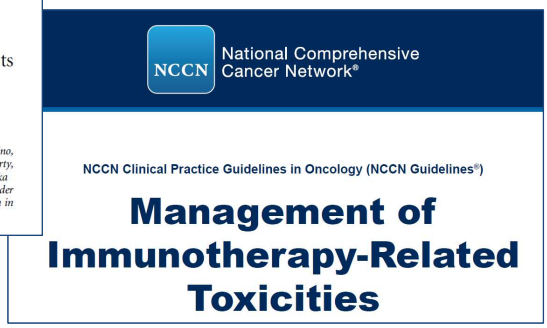
Adapted from Martins F, et al. *Nat Rev Clin Oncol*. 2019.

Managing irAEs
2018 ASCO/NCCN Guidelines


JOURNAL OF CLINICAL ONCOLOGY 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. Reichmer, 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


NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Brahmer JR, et al. *J Clin Oncol.* 2018;
NCCN. Management of Immunotherapy-Related Toxicities. Version 1.2020.

Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0

Descriptive terminology to "quantify" the severity of an adverse event (AE)/side effect of treatment.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death related to AE

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Case Study

JT is a 70-year-old male never smoker. He is a South African native who works as an endocrinologist in a private practice. He is an avid marathon runner.

In 2012, JT developed a SOB. CTs of the chest, abdomen, and pelvis were performed and showed a LUL nodule. A PET scan confirmed LUL with no other sites of disease.

He underwent a VATS resection of LUL.

- Pathology: squamous cell carcinoma, approximately 3 cm, all nodes (-)
- Molecular: p53 (+), EGFR, ALK, BRAF (-)

JT is followed yearly with scans

Case Study

In 2015, a routine CT showed a right renal mass. An MRI of the abdomen confirmed a suspicious lesion. JT underwent a left total nephrectomy.

- Pathology: metastatic squamous cell carcinoma

Case Study

In September 2015, JT enrolled in a phase II study of pembrolizumab after curative intent treatment for oligometastatic non–small-cell lung cancer (NSCLC).

When seen in clinic for cycle 5 of pembrolizumab, he notes bilateral hand “stiffness” that is worse in the morning but not affecting activities of daily living.

Differential diagnoses?

- Metastases
- Joint erosion
- Arthritis

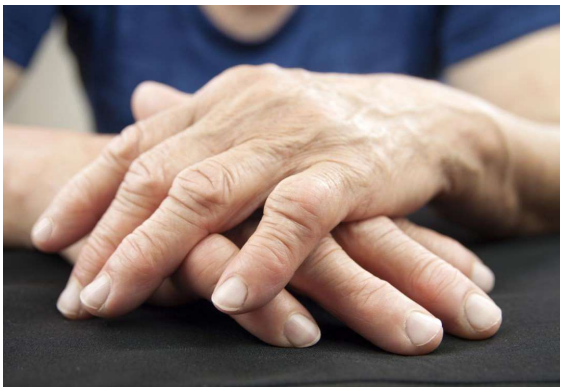
Arthralgias

Incidence: (2%–12%)

- More common in anti–PD-1
- Often exacerbation of pre-existing arthritis

Management

- NSAIDS/APAP
- Prednisone
- Refer to rheumatology



JT was managed with naproxen as needed.

Image from: Nall R, et al. *Medical News Today*. 2017. Haanen JBAG, et al. *Ann Oncol*. 2017.

Case Study

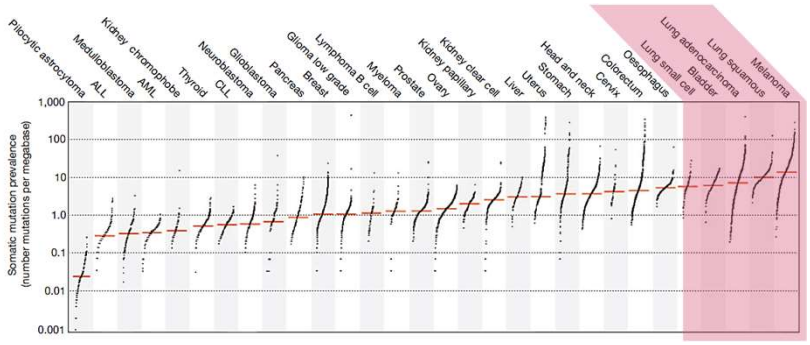
JT completed the pembrolizumab oligometastases study in July 2016, but 4 months later, a PET scan confirmed recurrence in the renal fossa.

A biopsy of the left retroperitoneal lesion was completed.

- Pathology: metastatic squamous cell carcinoma
- Molecular: P53 (+), PD-L1 (-), TMB high

Mutational Burden
A Changing Paradigm

Tumor mutational burden—measurement of mutations carried by tumor cells; a predictive biomarker being studied to evaluate its association with response to immunotherapy



Highest prevalence of mutations ⟺ **Highest benefit** from immune checkpoint inhibitors

Alexandrov LB, et al. *Nature*. 2013; Langer C, et al. *WCLC*. 2019. Abstract OA04.05; Garassino M, et al. *WCLC*. 2019. Abstract OA04.06.

Mutational Burden
A Changing Paradigm

2019: KEYNOTE 021/189 data shows no association with tumor mutational burden.

Alexandrov LB, et al. *Nature*. 2013; Langer C, et al. *WCLC*. 2019. Abstract OA04.05.

Case Study

Plan: Chemo vs. I/O therapy?

In December 2016, atezolizumab IV every 3 weeks was initiated.

Patient Complaints/Issues While Receiving Atezolizumab

- Xerosis, Pruritus, Xerostomia, Taste Alterations
- Hypothyroidism
- Dyspepsia
- Diplopia
- Ongoing: Arthritis

Case Study

JT was seen in clinic prior to cycle 4 of atezolizumab. He complains of dry mouth/taste alterations and pruritic skin.

Xerostomia/Taste Alterations
Differential Diagnoses

- Parotid blockage—parotiditis
- Dehydration
- Medication
- Hypothyroidism

Pruritic Skin
Differential Diagnoses

- Dry skin
- Contact dermatitis
- Allergy
- Medications

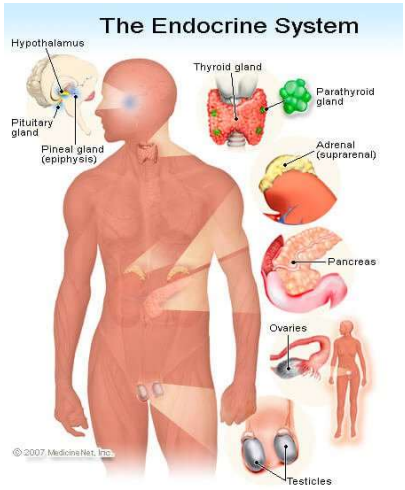
Cutaneous irAE
Pruritus, Xerosis, Xerostomia, Taste Alterations

- Incidence: 13%–20% PD-1
- Affects QOL
- Management
  - Topical emollients
  - Topical steroids
  - Oral antihistamines
  - Avoid irritants
  - Avoid sun exposure
  - Grade 2–3: prednisone 1 mg/kg

JT managed symptoms with hydration, thick emollients, and gum. After trying to avoid steroids, he started a steroid taper and remained on 10 mg prednisone daily for several months.

Phillips GS, et al. *JAMA Dermatol.* 2019; Haanen JBAG, et al. *Ann Oncol*. 2017.

Endocrinopathies



- Thyroid dysfunction
  - Hypothyroid
  - Hyperthyroid
  - Thyroiditis
- Adrenal insufficiency (rare)
- Hypophysitis
- Diabetes mellitus type 1

Brahmer JR, et al. *J Clin Oncol.* 2018; www.medicinenet.com/script/main/art.asp?articlekey=25210.

Endocrinopathies
Hypothyroidism

- Incidence: up to 16%
- Differential diagnoses
  - After obtaining TFTs, unlikely to have a diagnosis other then hyper/hypothyroidism
- JT was not symptomatic; incidental finding on routine blood work (check TSH prior to each visit)

Haanen JBAG, et al. *Ann Oncol*. 2017.

Case Study

JT started levothyroxine (based on 2017 guidelines, not 2018 guidelines), and managed on own.

ENDOCRINE THYROID TSH	
Latest Ref Rng & Units 0.27–4.20 uIU/mL	
3/16/2017	3.96
4/13/2017	4.62 (H)
5/4/2017	4.93 (H)
9/15/2017	5.19 (H)
11/7/2017	4.97 (H)
11/21/2017	6.77 (H)
11/28/2017	6.56 (H)
12/5/2017	2.85
12/12/2017	2.57
12/19/2017	3.54

GI
irAE—Dyspepsia

- Upper GI toxicity much less common
- Most common → diarrhea: combo (26-45%); CTLA-4 (30-40%); PD-1 (≤19%)
- Treatment: steroids with possible additional immunosuppression if refractory (i.e., infliximab)

JT managed the dyspepsia with omeprazole 20 mg daily.

NCCN. Management of Immunotherapy-Related Toxicities. Version 1.2020;
Brahmer JR, et al. *J Clin Oncol.* 2018; Grover S, et al. *Am Soc Clin Oncol Educ Book*. 2018.

Case Study

JT was seen in clinic prior to cycle 6 and noted binocular diplopia at night when watching TV.

Binocular Diplopia
Differential Diagnoses

- Brain metastases
- Nerve palsy
- Strabismus from thyroid disease
- MG
- Stroke

Neurologic Disorders
Rare

- Incidence: 1%
- Many different disorders → Guillain-Barré syndrome, MG, peripheral neuropathy, encephalitis
- Treatment: steroids 1 mg/kg and then wean

Haanen JBAG, et al. *Ann Oncol*. 2017; NCCN. Management of Immunotherapy-Related Toxicities. Version 1.2020.

Case Study

JT had an MRI (-) for lesions. Neuro-ophthalmology ordered a single-fiber EMG, which confirmed ocular MG.

At the time, JT was on steroids for pruritis, which helped x 1 week, then returned. Neuro-ophthalmology instructed him to patch one eye as needed for symptomatic relief.

Case Study

JT refused chemo and enrolled in a phase 1b/2 study assessing safety and anti-tumor activity of AMG 820 in combination with pembrolizumab in select advanced solid tumors. A comprehensive metabolic panel was checked at every visit.

GENERAL CHEMISTRIES Latest Ref Rng & Units	CREATININE 0.64–1.27 mg/dL
7/11/2017	1.24
9/1/2017	1.45 (H)
9/7/2017	1.31 (H)
9/15/2017	1.50 (H)
9/28/2017	1.42 (H)
10/5/2017	1.27

Differential diagnoses?

- Dehydration
- Medications
- Hypercalcemia
- Recent IV contrast

Case Study
Nephritis

- Incidence: ~2%–5%
- Management: Grade 1 can hold ICI or observe

Creatinine was never higher than 1.52. JT continued ICI treatment, received IVFs with treatment, consulted pharmacy, and followed a renal diet.

Puzanov I, et al. *J ImmunoTher Cancer*. 2017; Brahmer JR, et al. *J Clin Oncol.* 2018; Haanen JBAG, et al. *Ann Oncol*. 2017.

Case Study

Four months later, a follow-up CT showed PD in RP LN, liver, with increasing left pleural effusion. JT was started on carbo/nab-paclitaxel.

When he had been off ICI therapy x 5 months, he complained of worsening fatigue and weakness.

Differential Diagnoses?

- Chemotherapy induced
- Thyroid disorder
- Depression
- Medications
- Anemia

Case Study

JT requested that his testosterone level be tested.

TESTOSTERONE		
Latest Ref Rng & Units	10/5/2017	
Testosterone	193–740 ng/dL	82 (L)
Free Testosterone	47–244 pg/mL	7 (L)

Case Study

JT was diagnosed with secondary hypogonadism, which has an incidence of approximately 7.5% and is managed with HRT.

He was referred to urology who prescribed testosterone gel, which would be required lifelong.

Byun DJ, et al. *Nat Rev Endocrinol*. 2017.

Case Study
Further Treatment

- **March 2018**—PD; given nivolumab
- **October 2018**—PD; given pembrolizumab + xrt on RadVax clinical trial (SBRT to right lung)
- **February 2019**—PD; enrolled in phase 1 viagenpumatucel + nivolumab
- **July 2019 to present**—on ipilimumab/nivolumab
- **July 15 and August 9, 2019**—underwent radioembolization to liver lesions

Case Study
Presently

Currently, JT has a creatinine of 1.3; receives HRT for hypogonadism and hypothyroidism, and suffers from xerostomia, pruritis, diplopia, and fatigue (worst symptom—especially after SIR-spheres).

Medications

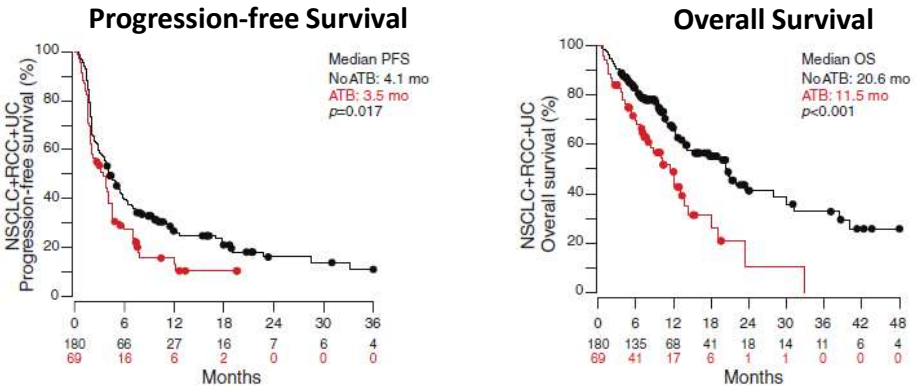
- Atorvastatin 20 mg daily
- Fluocinonide 0.05% BID
- Levothyroxine 88 mcg daily
- Megestrol
- Meloxicam 7.5 mg BID
- Omeprazole 20 mg daily
- Prednisone 10 mg daily
- Testosterone gel 1.62% transdermal daily
- Zolpidem 10 mg qhs
- _____
- Meds in 2012: atorvastatin, zolpidem

What Else Could Impact IO Therapy Efficacy?

- We know that treating with steroids for irAEs does not worsen outcomes
  - Treating with steroids for other indications was excluded from prior studies
  - Remains an open question
- Gut microbiome may be an important factor predicting response to immunotherapy
  - Patients with cancer frequently receive antibiotics
  - Could antibiotics decrease efficacy?

Routy B, et al. *Science*. 2018.

Impact of Antibiotics on PD-1 Response



Need to consider indication for antibiotics. Sometimes patients need treatment!

Routy B, et al. *Science*. 2018.

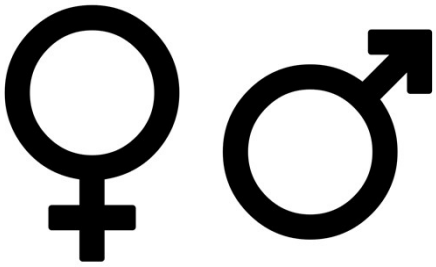
Probiotics
Good or Bad?

- Small study—46 patients
- Probiotics are associated with lower gut microbiome diversity
- Diets high in added sugars and processed meat were negatively associated with these bacteria.
- Eating fiber has better outcomes
  - Five times as likely to respond to anti–PD-1 treatment compared to patients who consumed a low-fiber diet.

Spencer CN, et al. AACR Annual Meeting. 2019. Abstract 2838/24.

Does Patient's SEX Impact Efficacy?

- Meta-analysis of 11,351 patients
- HR= 0.72 in males
- HR = 0.86 in females
- *P*=0.0019



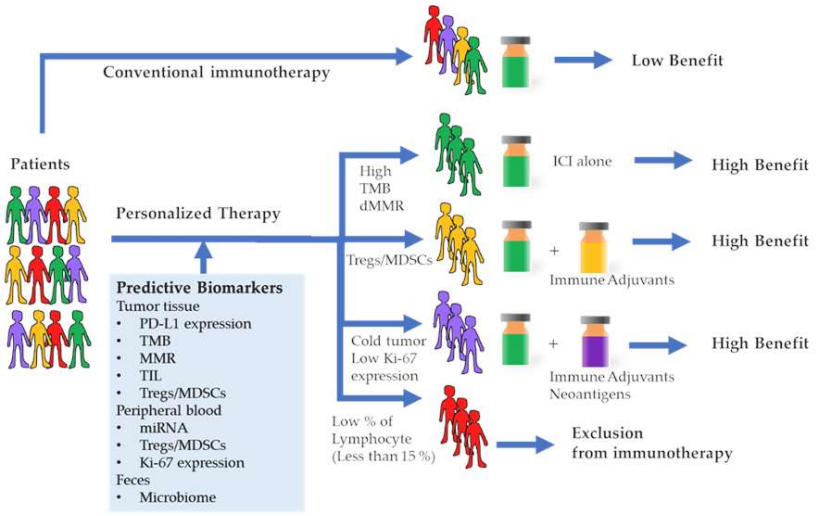
Conforti F, et al. *Lancet Oncol*. 2018.

Personalized Cancer Immunotherapy?

- Success in the majority of patients is limited by a low response rate, high treatment cost, and treatment-related toxicity.
- Need to identify predictive and prognostic biomarkers to select the patients who are most likely to benefit from, and respond well to, these therapies.
- *"Cancer immunogram"*

Shindo Y, et al. *Cancers* (Basel). 2019.

Cancer IO Outcomes Based on Biomarkers



Shindo Y, et al. *Cancers* (Basel). 2019.

Are irAEs Associated with Improved Clinical Outcomes?

NSCLC Patients

	HR (95% CI)	*P*
PFS (unadjusted model)		
# of irAEs (+1)	0.81 (0.65-1.01)	0.067
PFS (adjusted model)		
# of irAEs (+1)	0.75 (0.56-0.99)	0.043

Melanoma Patients

irAE Status and Treatment Arm	RFS, HR (95% CI)	*P*
Any irAE		
Placebo	1	
Pembro without/before irAE	0.62 (0.49-0.78)	0.03
Pembro after irAE onset	0.37 (0.24-0.57)	
Any severe irAE		
Placebo	1	
Pembro without/before irAE	0.55 (0.44-0.68)	0.43
Pembro after irAE onset	0.78 (0.32-0.91)	

Lisberg A, et al. *Cancer Immunol.* 2018; Eggermont AM, et al. *JAMA Oncol*. 2020.

DIRE

- Defined as new irAEs manifesting ≥90 days after discontinuation of immunotherapy
- Systematic review from 2008 to 2018 to determine the median data safety reporting window from existing IO clinical trials
- 23 cases identified
- Median off-treatment interval to DIRE was 6 months (range: 3–28)
- Median cumulative immunotherapy exposure was 4 doses (range: 3–42)
- Involvement included endocrine, neurologic, GI, pulmonary, cardiac, rheumatologic, and dermatologic irAEs

Couey MA, et al. *J Immunother Cancer*. 2019.

DIRE
Impact on Nursing

- Not recognizing symptoms can impact patient morbidity
- Early recognition is crucial as irAEs are generally manageable with prompt initiation of treatment
- DIRE should be considered in the differential diagnosis of patients presenting with illnesses of unclear etiology regardless of what treatment they are on

Couey MA, et al. *J Immunother Cancer*. 2019.

Conclusions

- Immunotherapy can induce durable responses and can result in prolonged OS
- Immune-related adverse events are a unique spectrum of adverse events that can mimic other disease processes; irAEs need to be considered as differential diagnosis in any patient receiving checkpoint inhibition
- Early recognition and effective management of irAEs is crucial to optimal use of checkpoint inhibitors
- The overarching principle of medical management is STEROIDS

Notes

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Couey MA, Bell RB, Patel AA, et al. Delayed immune-related events (DIRE) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance. *J Immunother Cancer*. 2019;7(1):165.

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