# Best Practices: PD1/PDL1 Toxicity Management

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# Disclosures

- Rachael Morgan – No actual or potential conflicts of interest in regard to this presentation

- Jenna Houranieh - No actual or potential conflicts of interest in regard to this presentation

# Learning Objectives

- Develop strategies to manage common adverse effects of immunotherapies
- Recognize challenges in treating patients with adverse effects on immunotherapeutic agents
- Discuss the potential role of a pharmacist in management of patients on immunotherapy

# Educational Need/Practice Gap

## Traditional Chemotherapy

- Nausea/Vomiting
- Myelosuppression
- Alopecia
- Mucositis

## Immunotherapy

- Dermatitis
- Colitis
- Pneumonitis
- Hepatitis

# Educational Need/Practice Gap

## Traditional Chemotherapy

- Rash
- Diarrhea
- Hepatotoxicity

## Radiotherapy

- Fibrosis

## Immunotherapy

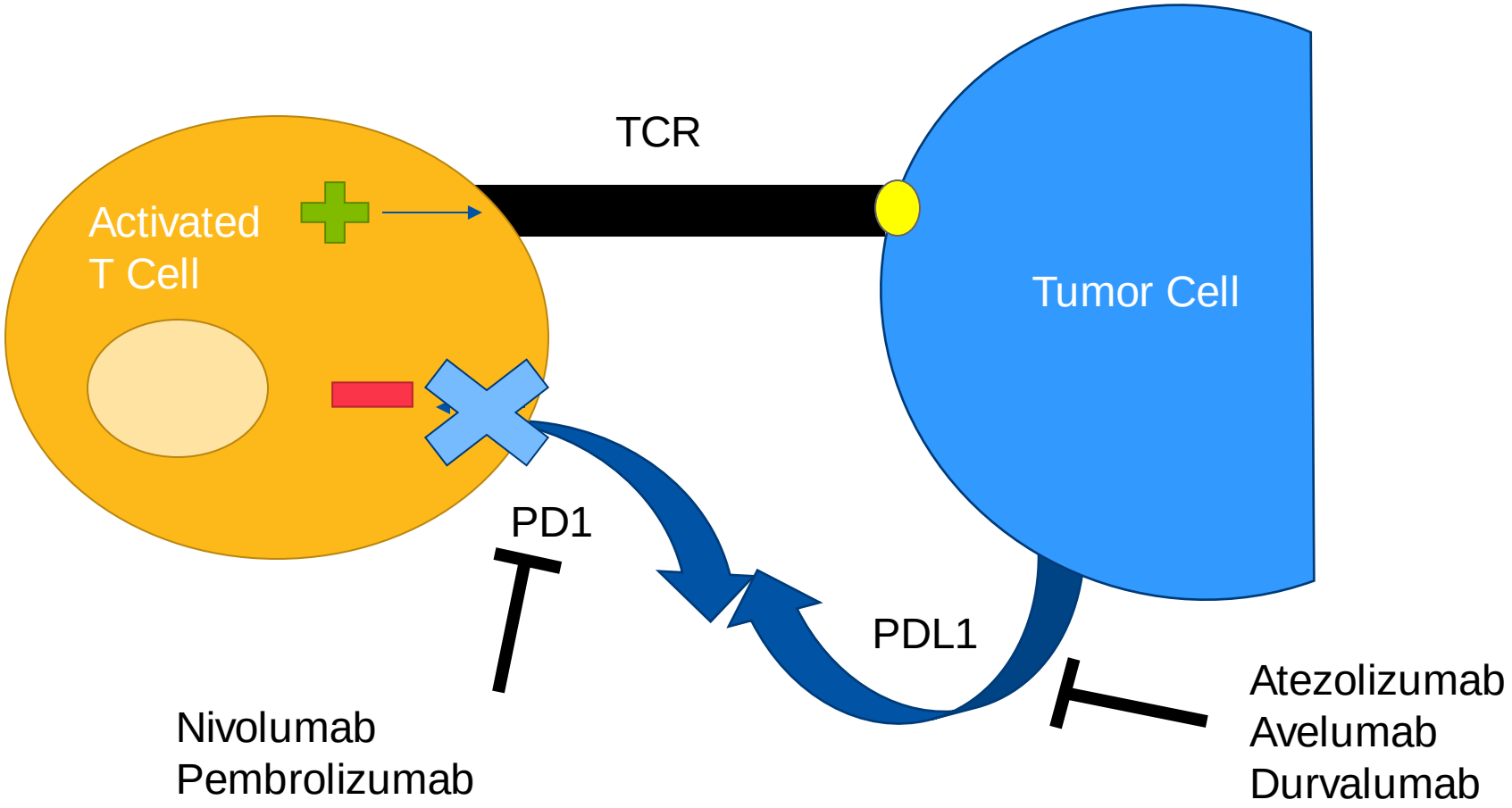
- Dermatitis
- Colitis
- Hepatitis
- Pneumonitis
- Neurological complications

# Immunotherapy vs. Chemotherapy

| | Immunotherapy | Chemotherapy |
|---|---|---|
| Mechanism of Action | Enhanced anti-tumor activity | Direct killing of tumor cells |
| Target | Immune Cells (T Cells) | Rapidly dividing tumor cells |
| Onset of Activity | Gradual (4-6 months) | Immediate |
| Duration of Activity | Long after treatments ends | While drug remains in the body |
| Adaptability to mutations | Yes | No |
| Toxicities | Less | More |

Chen, D., & Mellman, I. *Immunity.* 2013 Jul 25;39(1):1-10.

# PD1/PDL1 Inhibition




TCR: T cell Receptor
PD(L): Programed Death (Ligand)

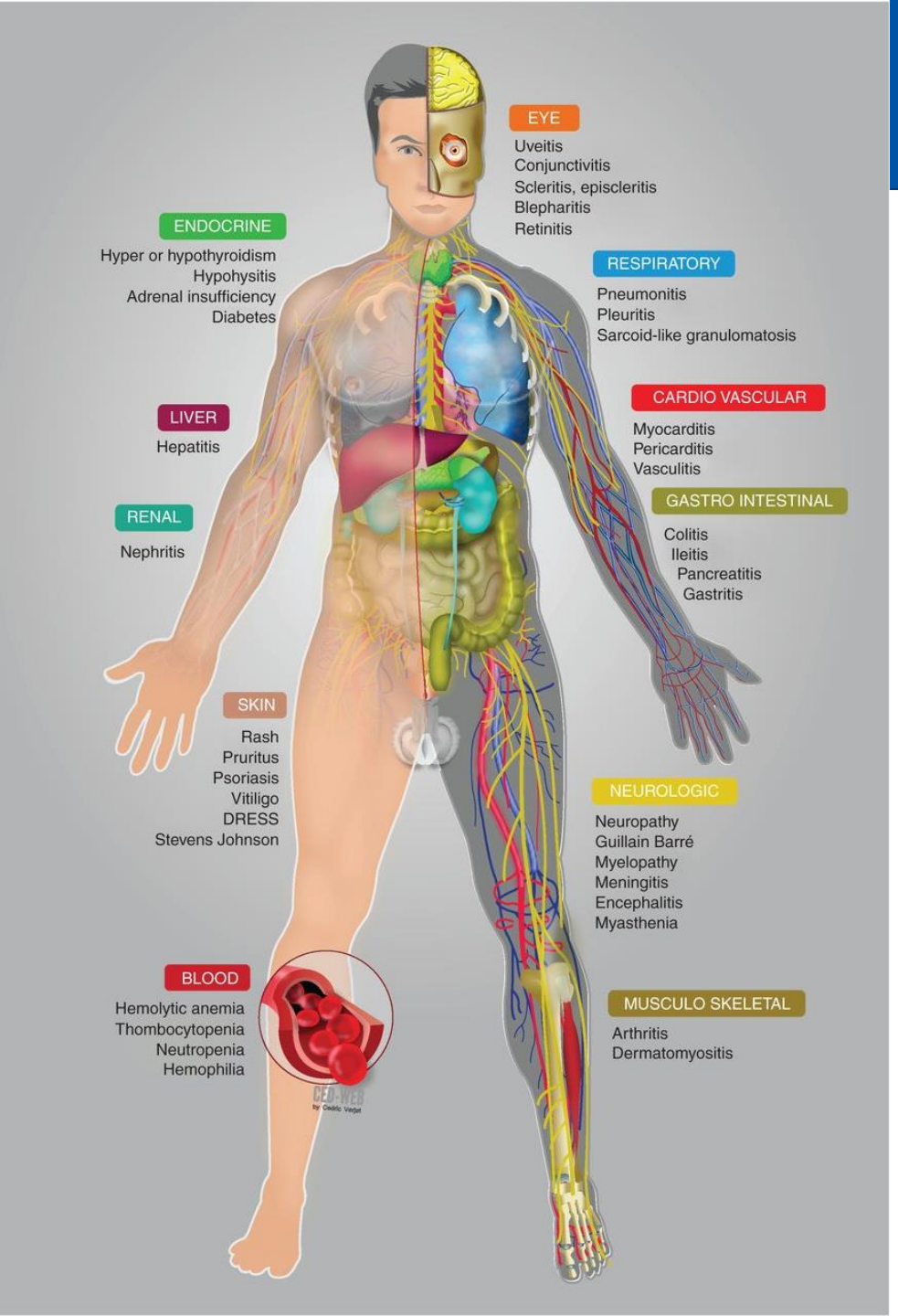
Pardoll DM. *Nat Rev Cancer.* 2012 Mar 22;12(4): 252–264.

# Pharmacokinetics

| Checkpoint Inhibitor | Elimination Half life |
|---|---|
| Ipilimumab | 15.4 days |
| Nivolumab | ~25 days |
| Pembrolizumab | 22 days |
| Atezolizumab | 27 days |
| Avelumab | 6.1 days |
| Durvalumab | ~28 days |

*Package inserts for respective agents.*

# Immune-Related Adverse Events




- Any organ can be affected
- Varying frequencies

Champiat, S, et al. *Ann Oncol.* 2016 Apr;27(4):559-74

# Immune Related Adverse Events (irAE)

| Organs Affected by Immunotherapy | Manifestations |
|---|---|
| Skin | Pruritus, vitiligo, maculopapular rash, lichenoid deposits |
| Gastrointestinal | Diarrhea, nausea/vomiting, bowel perforation, pancreatitis, gastritis |
| Liver | Hepatitis, transaminitis |
| Endocrine | Thyroiditis (hypo, hyper), hypophysitis, pan hypopituitarism, adrenal failure, Type I DM |
| Pulmonary | Pneumonitis, ARDS, acute interstitial pneumonia, pleuritis |
| Renal | Nephritis, renal insufficiency |

# Immune Related Adverse Events (irAE)

| Organs Less Commonly Affected by Immunotherapy | Manifestations |
|---|---|
| Cardiovascular | Myocarditis, pericarditis, vasculitis |
| Musculoskeletal | Arthralgias, myalgias, inflammatory arthritis |
| Ocular | Uveitis, iritis, conjunctivitis, scleritis, blepharitis |
| Neurologic | Peripheral neuropathy, temporal arteritis, aseptic meningitis, Guillain-Barré syndrome, myasthenia gravis, transverse myelitis, encephalitis |
| Hematologic | Hemolytic anemia, immune thrombocytopenia, hemorrhagic risk |

# Management of irAEs By Grade

| Severity-CTCAE Grade | Ambulatory versus inpatient care | Corticosteroids | Other Immuno-suppressant drugs | Immunotherapy |
|---|---|---|---|---|
| 1 | Ambulatory | Not recommended | Not recommended | Continue |
| 2 | Ambulatory | Topical steroids or systemic steroids PO 0.5-1 mg/kg/day | Not recommended | Hold<br>Resume upon resolution |
| 3 | Inpatient hospitalization | Systemic PO/IV 1-2 mg/kg/day for 3 days then reduce to 1mg/kg/day and taper over 4-6 wks. | • Consider if unresolved in 48-72 hours (infliximab)<br>• Organ specialist referral | Hold<br>Resume only if benefit outweighs risk |
| 4 | Inpatient Hospitalization, may consider ICU | Systemic IV Methylprednisolone 1-2 mg/kg/day for 3 days then reduce to 1mg/kg/day | • Consider if unresolved in 3-5 days<br>• Organ specialist referral Advised | Permanently discontinue |

Champiat, S, et al. *Ann Oncol.* 2016 Apr;27(4):559-74.;
Brahmer, J., et al. *J Clin Oncol.* 2018 Jun 10;36(17):1714-68.

# Case 1: RG

- RG is 52 yo veteran with a PMH of **ulcerative colitis** and multifocal hepatocellular carcinoma s/p TACE x 2 in 2018.
- Multifocal recurrence with rising AFP by July 2019 not amenable to liver directed therapies. He completed 4 months of sorafenib. AFP increased from 36 to 145 and imaging demonstrated progression in the liver as well as new painful skeletal mets to L1 + L5 requiring palliative XRT.
- He tolerated sorafenib poorly 2/2 to diarrhea which resolved with discontinuing therapy. His ECOG PS is 0. He works as an airplane mechanic. Childs Pugh B7. He presents to oncology clinic to discuss next steps in therapy.

| Date | AFP | Intervention |
|---|---|---|
| 12/10/2019 | 145.4 | Bone mets in L1 + L5, received XRT<br>MRI demonstrating progression in liver |
| 8/27/2019 | 35.9 | Started sorafenib |
| 7/9/2019 | 20.6 | MRI demonstrating progression |
| 5/2/2019 | 12.3 | - |
| 03/13/2019 | 2.2 | - |
| 12/06/2018 | 18.0 | TACE #2 |
| 09/10/2018 | 92.3 | TACE #1 |

# Case 1: Audience Response

- Would you consider treating RG with a checkpoint inhibitor for second line therapy for his progressive HCC taking his PMH into consideration?
  A. Yes, I see no concerns
  B. No, he has a history of UC which would be a contraindication
  C. I'm not sure, I need more information

# Autoimmune disease (AID) and Immunotherapy

- ICI's have an adverse effect profile that often mimics autoimmune disorders
- Lack of clinically useful biomarkers to preemptively identify patients who will experience severe irAEs
- Are all pre-existing autoimmune conditions contraindications to immunotherapy use?
  - Excluded from the approval studies
  - Real world/post marketing experience
  - Does the cancer/indication for use matter?
    - Melanoma without targetable mutations vs 3rd line therapy for head and neck ca?
    - I.e. is it worth the risk?
  - Does the autoimmune condition matter?
    - MS vs RA
    - IBD vs psoriatic arthritis

# ICI use in patient's with underlying AID

Table 2.
Retrospective Case Series Evaluating ICI Use in Patients With AID

**Table 2. Retrospective Case Series Evaluating ICI Use in Patients With AID**

| Study | N[a] | Tumor | ICI | AID | Treatment for AID[b] | ORR | AID Flare Rate[c] | irAE Rate[d] | D D |
|---|---|---|---|---|---|---|---|---|---|
| Tison et al[40] | 112 | Melanoma (59%)<br>NSCLC (35%)<br>Other (6%) | PD-1/PD-L1 in 85% of patients | Ps/PsA, RA, IBD, SA, SLE, PMR/TA | 22% | Melanoma: 48%<br>NSCLC: 54% | 42%<br>Gr 3/4: 13% | 38%<br>Gr 3–5: 16% | |
| Leonardi et al[41] | 56 | NSCLC | PD-1/PD-L1 | RA, PMR/TA, Scleroderma, Ps/PsA, Thyroiditis, IBD, MG, MS | 20% | 22% | 23%<br>Gr 3/4: 4% | 38%<br>Gr 3/4: 10% | |
| Menzies et al[42] | 52 | Melanoma | PD-1 | RA, PMR, SS, ITP, Ps, IBD, GBS, MG, Thyroiditis, SLE | 38% | 33% | 38%<br>Gr 3/4: 6% | 29%<br>Gr 3/4: 10% | |
| Danlos et al[43] | 45 | Melanoma (80%)<br>NSCLC (13%)<br>Other (7%) | PD-1 | Vitiligo, Ps/PsA, Thyroiditis, RA, ITP, SA, MS, MG, PMR, PAN, Sarcoidosis, T1 DM | 16% | 38% | 24% | 22% | |
| Johnson et al[44] | 29 | Melanoma | Ipilimumab | RA, Ps, Thyroiditis, MS, IBD, SLE, Sarcoidosis | 41% | 21% | 24% | 31%<br>Gr 3–5: 31% | |
| Gutzmer et al[45] | 19 | Melanoma | PD-1 | Ps/PsA, RA, Vasculitis, PMR, SA, Sarcoidosis, IBD, GBS, MS, MG, Thyroiditis | 32% | 32% | 42% | 16% | |
| Richter et al[46] | 16 | Melanoma<br>NSCLC<br>NHL | PD-1 (69%)<br>Ipilimumab (31%) | RA, PMR, Sarcoidosis, SLE, Vasculitis | 44% | Not stated | 6% | 38%<br>Gr 3/4: 25% | |
| Lee et al[47] | 8 | Melanoma | Ipilimumab | RA | 87.5% | 50% | 75%<br>Gr 3/4: 25% | 50%<br>Gr 3/4: 50% | |

Abbreviations: AID, autoimmune disease; GBS, Guillain-Barré syndrome; Gr, grade; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitor; irAE, immunotherapy-related adve idiopathic thrombocytopenic purpura; MG, myasthenia gravis; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; ORR, objective response rate; PAN, p PMR, polymyalgia rheumatica; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SA, spondylosing arthropathy; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; T1 DI mellitus; TA, temporal arteritis.
[a]Includes only patients in the study with preexisting autoimmune disease.
[b]Percentage of patients on baseline chronic immunosuppression for treatment of an AID at time of ICI initiation.
[c]Percentage of the intention-to-treat population.
[d]Excludes immunotherapy-related events that were felt to be an exacerbation of the patient's underlying autoimmune disorder.
[e]Percentage of the intention-to-treat population that permanently discontinued therapy for either AID exacerbation or irAEs.

Kennedy LC, et al. *JNCCN*. 2019 Jun 1;17(6):750-7.

# Baseline Immunosuppression and ICI use

- Will baseline immunosuppression at the time of ICI initiation or need to treat an irAE decrease the efficacy of the ICI?
  - Retrospective analysis of ICI therapy in patients with NSCLC with a baseline dose of ≥10 mg/d vs < 10mg/d of prednisone revealed lower response rates, progression-free survival, and overall survival with those treated > 10mg/d.
  - In Tison et al, patients with an irAE or autoimmune exacerbation had longer progression-free and overall survival, but the initiation of steroids for treatment reversed this benefit.
  - However, Leonardi et al reported no correlation between steroid initiation for toxicity and progression-free or overall survival, and 3 of the other case series noted no correlation between development of irAE or autoimmune exacerbation and disease response

# Considerations with pre-existing AID

Table 3.

Patients With Preexisting Autoimmune Disease and Cancer

**Table 3. Patients With Preexisting Autoimmune Disease and Cancer**

| ICIs May Be Considered | Avoid ICIs |
|---|---|
| 1. Consult with appropriate autoimmune subspecialist | 1. Autoimmune neurologic or neuromuscular disease |
| 2. Low level of or no immunosuppression with good control of underlying autoimmune disorder | 2. Life-threatening autoimmune disease |
| 3. Patient informed consent | 3. Patients with poor control of autoimmune disease OR requiring high doses of immunosuppressants for control |

Abbreviation: ICI, immune checkpoint inhibitor.

Kennedy LC, et al. *JNCCN*. 2019 Jun 1;17(6):750-7.

# RG's UC history:

- Followed by GI service for "ulcerative colitis with pancolitis"
  - "He was on metronidazole for over 20 yrs and mercaptopurine for over 10 yrs to maintain his UC."
  - History of requiring prednisone:
    - "Patient remembers long steroid taper from prednisone 60 mg.
    - Reports last flare was about 4 years ago".
  - Hasn't required any medications for his UC in the last 3 years.

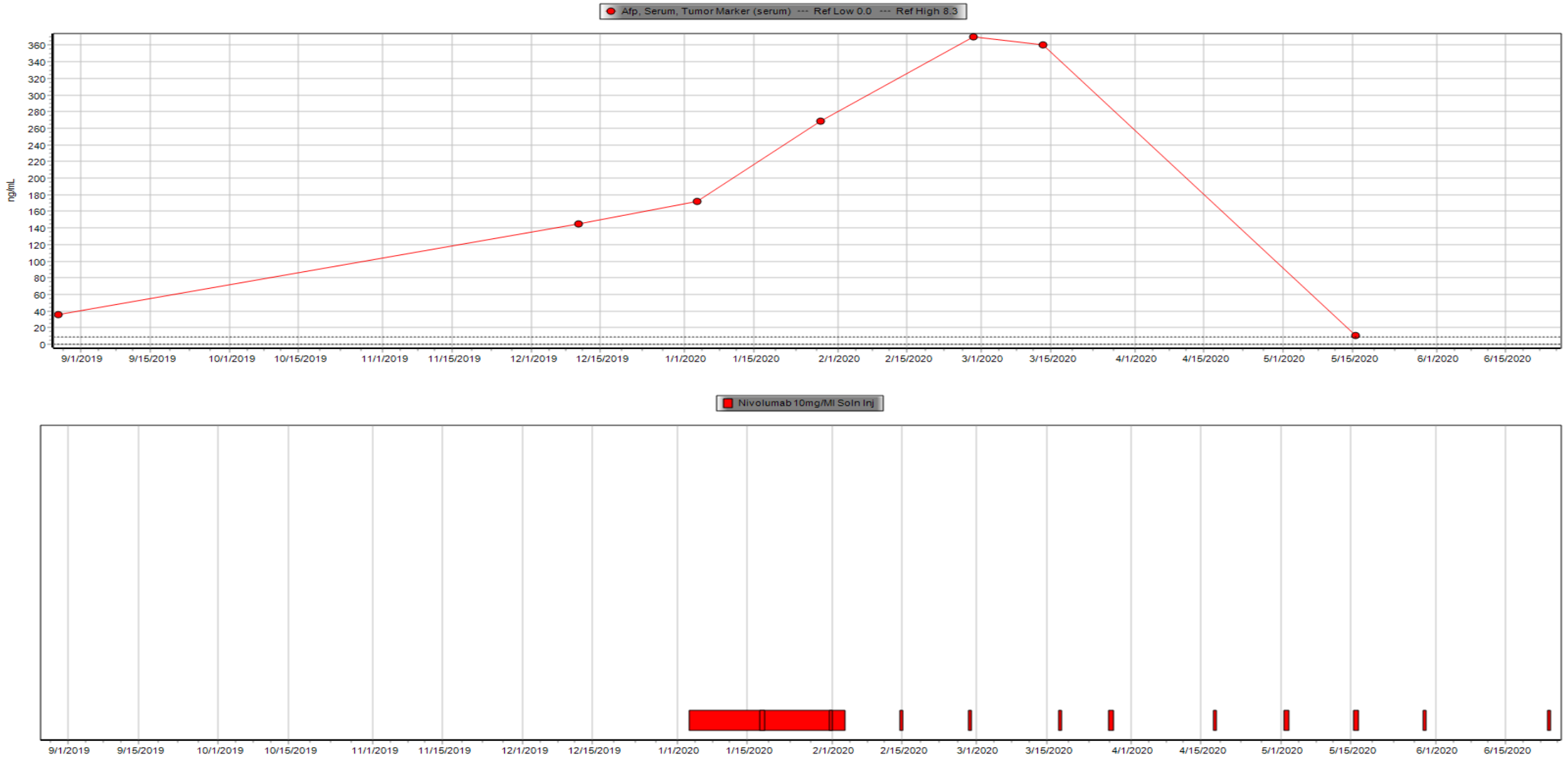
# RG case continued:

- Risk/benefits discussed, and GI consulted. Informed consent to proceed with nivolumab.
- After 5 months of nivolumab he had a clear/demonstrable benefit. AFP improved; MRI liver improved.
- Unfortunately has now developed moderate diarrhea after the 12th dose of nivolumab with 6-8 non-bloody stools/day over the course of 1 week despite loperamide use.
- Nivolumab was held and PO prednisone 1mg/kg was started. Diarrhea initially improved for the first week, but then reoccurred with tapering and was now considered severe with blood in stool.
- GI was consulted and they recommended admission for IV steroids and colonoscopy.

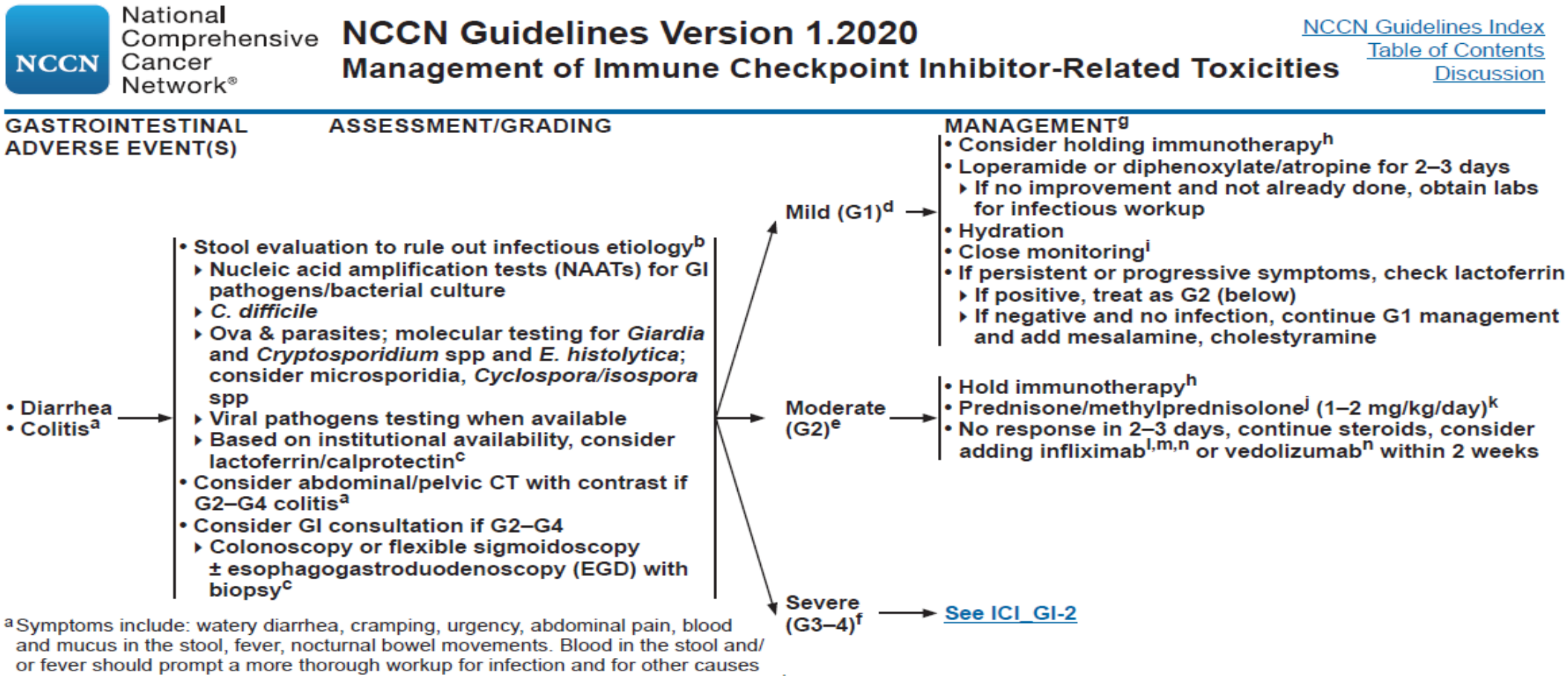
- MICROSCOPIC EXAM/DIAGNOSIS:
- Colon, random biopsies:
- -Active colitis with cryptitis, crypt abscesses, crypt atrophy and dropout; findings compatible with anti PD-1 colitis (see comment).
- -No evidence of CMV identified (immunohistochemical stain negative).

- Comment: **The clinical history of ulcerative colitis as well as nivolumab therapy is noted. There can be considerable histologic overlap between ulcerative colitis and anti PD-1 associated colitis. Therefore, further correlation with clinical impression is required**. The presence of crypt atrophy as well as the somewhat less than prominent lymphoplasmacytic infiltrate are features that are more suggestive of anti PD-1 associated colitis over active inflammatory bowel disease.

# RG's Response to Nivolumab



# NCCN ICI Diarrhea/Colitis Recommendations




Management of Immunotherapy-Related Toxicities. *NCCN Guidelines.* Version 1.2020.

# NCCN ICI Diarrhea/Colitis Recommendations



National Comprehensive Cancer Network®

## NCCN Guidelines Version 1.2020
## Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

| GRADING | MANAGEMENT[g] |
|---|---|
| Severe (G3–4)[f] diarrhea or colitis | • G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity[h]<br>• G4: Permanently discontinue immunotherapy agent responsible for toxicity[h]<br>• Consider inpatient care for provision of supportive care<br>• Intravenous (IV) methylprednisolone[j] (1–2 mg/kg/day)[k]<br>▸ No response in 2 days, continue steroids, strongly consider adding infliximab[l,m,n] or vedolizumab[n] within 2 weeks[o] |

[f] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).

Management of Immunotherapy-Related Toxicities. *NCCN Guidelines.* Version 1.2020.

# Vedolizumab

- Vedolizumab is an anti-integrin α4β7 antibody with gut-specific immunosuppressive effects i.e the immunity in extra-intestinal tissues remains intact

- Retrospective review of 7 patients who received ipi or nivo alone or in combination for advanced melanoma (*n* = 6) or non-small cell lung cancer (*n* = 1) and received vedolizumab for ICI colitis

Bergqvist V, et al. *Cancer Immunol Immunother*. 2017 May;66(5):581-92.

# Vedolizumab

- Case report of pt with melanoma who was able to successfully continue therapy with pembrolizumab after vedolizumab controlled her colitis

- Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor-induced colitis: a multi-center study
  - 28 patients refractory to steroids and/or infliximab
  - Twenty-four patients (86%) achieved and sustained clinical remission

Frohne CC, et al. *J Immunother Cancer*. 2019 Jan 6;7(1):1.
Abu-Sbeih H, et al. *J Immunother Cancer.* 2018 Dec 5;6(1):142.

# RG case continued:

- In conjunction with GI
  - RG started on vedolizumab along with prednisone taper:
    - Vedolizumab 0,2,6 weeks, then q 8 weeks
    - Slow prednisone taper with plan to be off by week 5
  - Plan is to restart nivolumab at the same time as week 6 (dose 3 ) of vedolizumab assuming diarrhea continues to improve

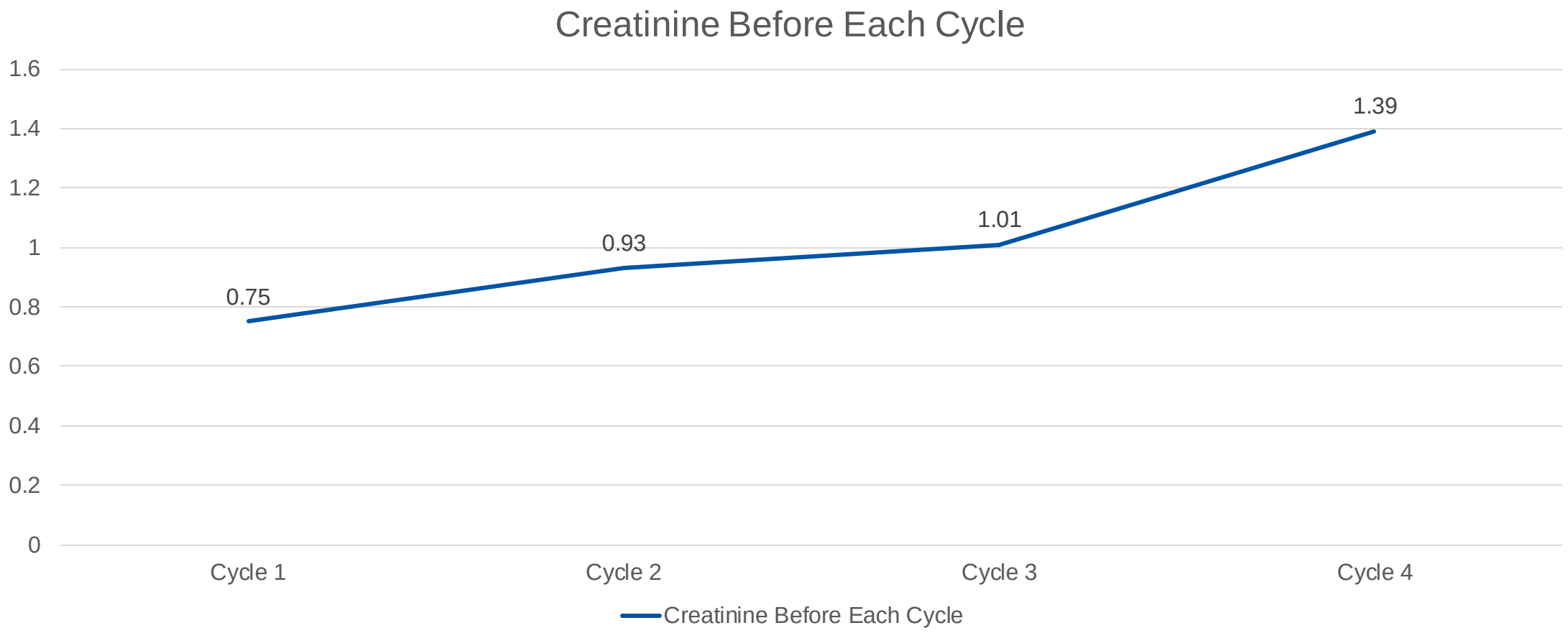
# Take home points:

- Preexisting autoimmune disorders are not an absolute contraindication to ICI therapy, but use of ICIs in these patients merits a thoughtful approach.
- A multidisciplinary discussion should occur between the oncologist, autoimmune specialists, and other team providers.
- A balance of the risks and benefits to the patient, the availability of alternative therapies, and patient preferences should be considered.
- The mechanism of action of immunosuppressive therapy should be considered with the most targeted form of treatment being used when possible.

# Case 2: Combination chemo-immunotherapy Who's to blame?

- CF is a 44yo who was diagnosed with NSCLC 4 months ago
- NSCLC
  - Adenocarcinoma
  - PDL1 2%
  - EGFR/ALK/ROS1/BRAF negative
- Treatment history
  - s/p Carboplatin/Pemetrexed/Pembrolizumab x3 cycles

# Today her creatinine is elevated at 1.39

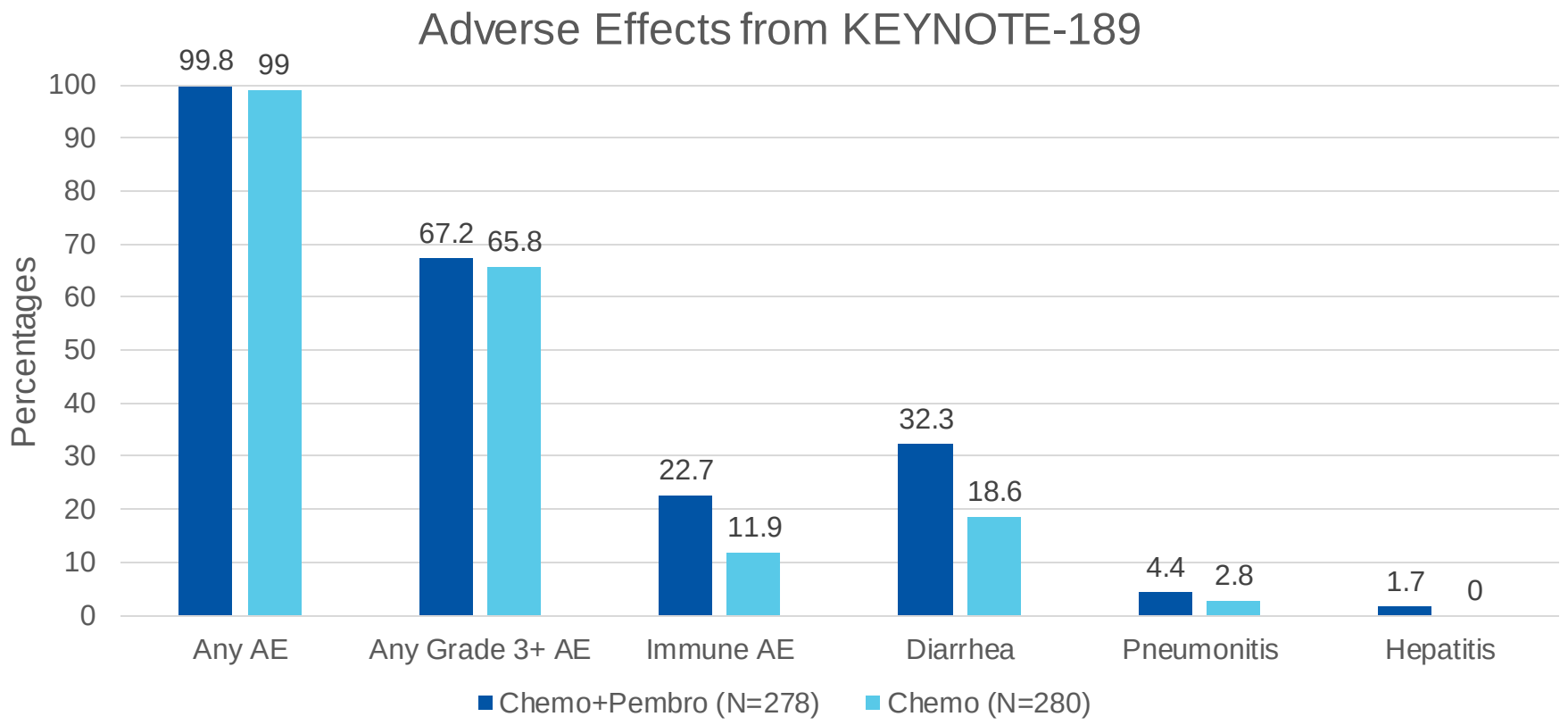


# Case 2: Audience Response

- Which of the following do you think could be to blame for her elevated creatinine?
  A. Carboplatin
  B. Pemetrexed
  C. Pembrolizumab
  D. None of the above
  E. All of the above

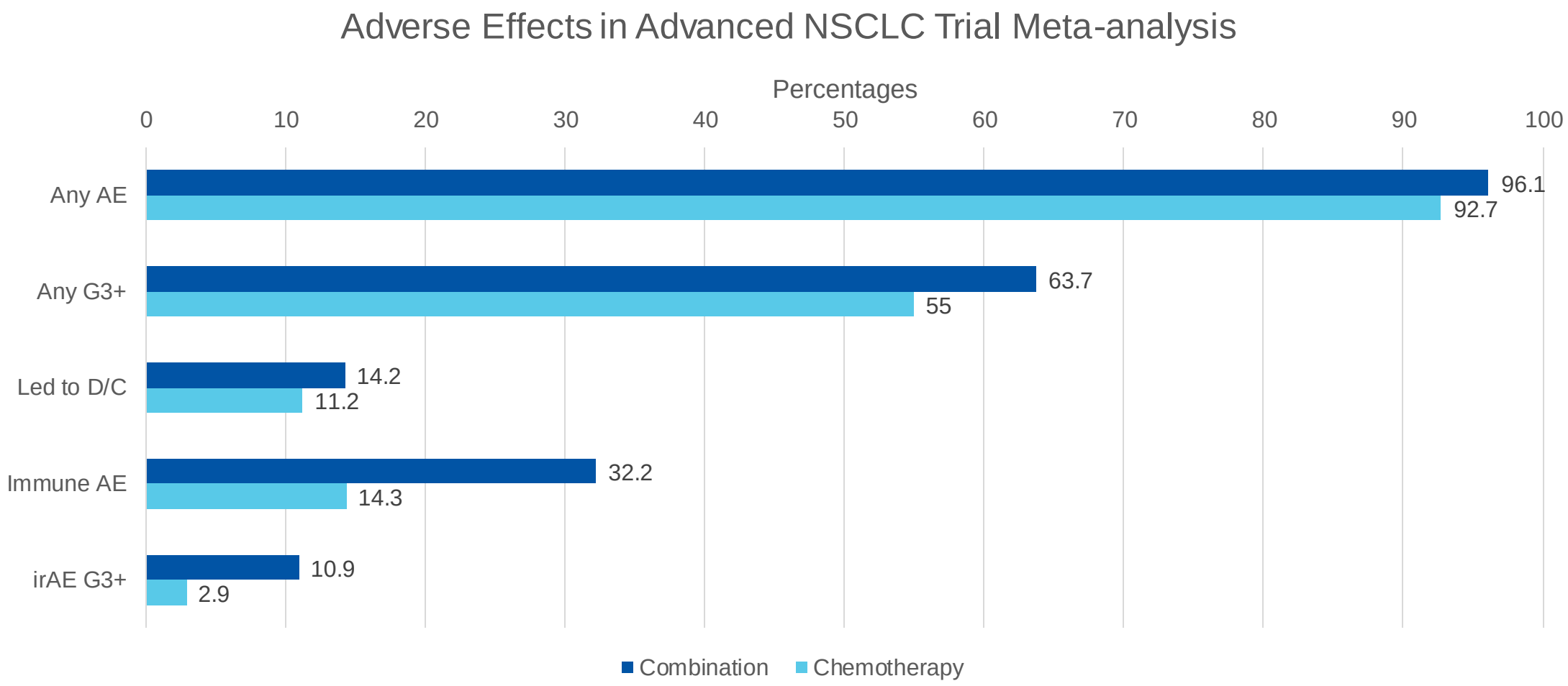
# Chemotherapy + Immunotherapy

Carboplatin + Pemetrexed + Pembrolizumab every 3 weeks x 4 doses




Paz-Ares L et al. *NEJM.* 2018;379:2040-51.

# Chemotherapy + Immunotherapy: Meta-analysis




Zhou Y et al. *J Immunother Cancer.* 2018;6:155.

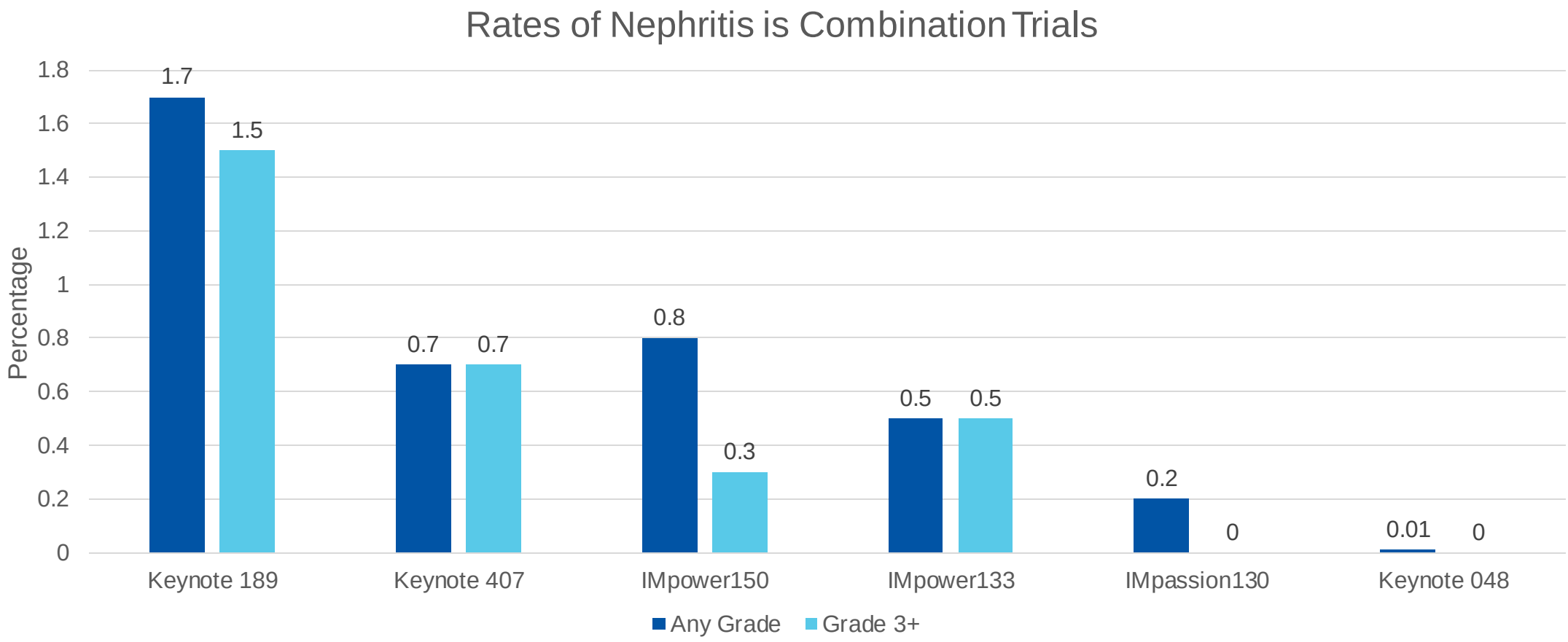
# Immune-mediated Effects on the Kidney

- Acute Kidney Injury
  - Acute tubulointerstisial nephritis (ATIN), alone or with
    - Acute tubular injury or glomerular disease
- Proteinuria
- Electrolyte abnormalities

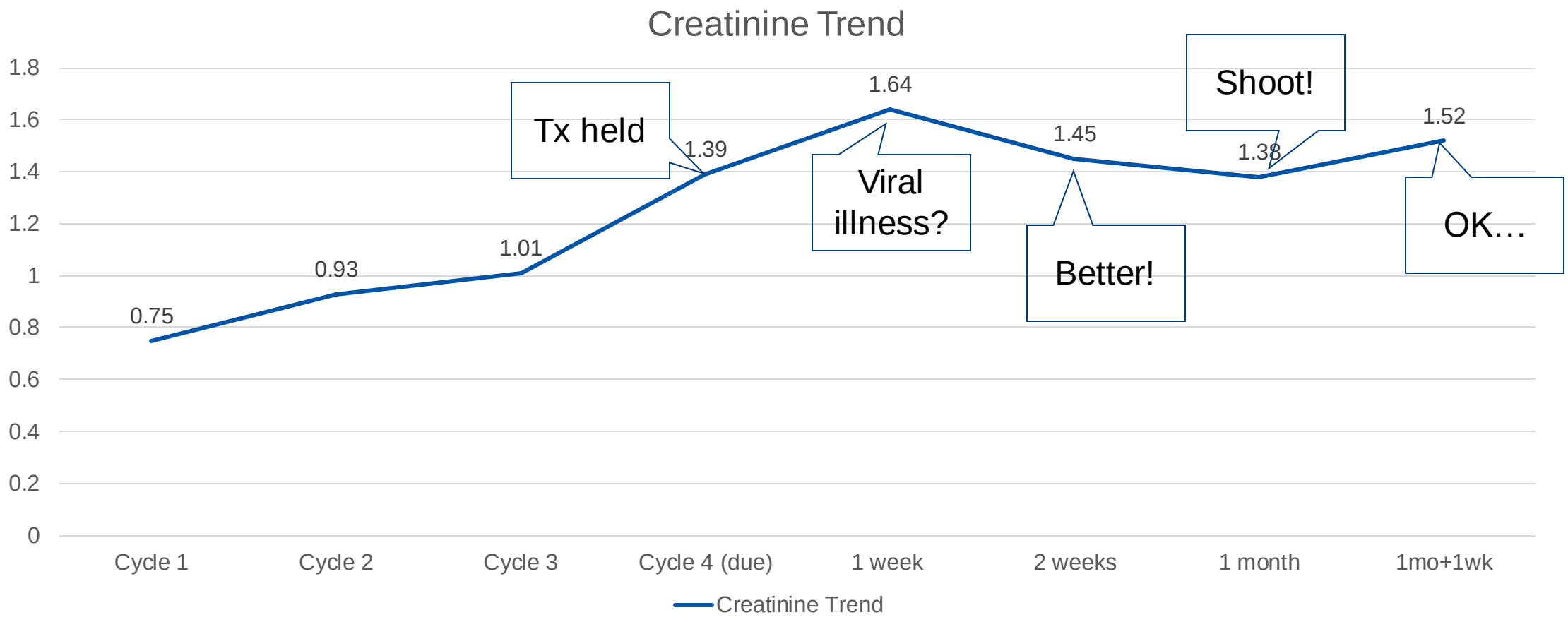
- Rates
  - ~2% monotherapy, ~5% in combination with other immunotherapy

Perazella MA et al. *Kidney Int.* 2020 Jan;97(1):62-74.

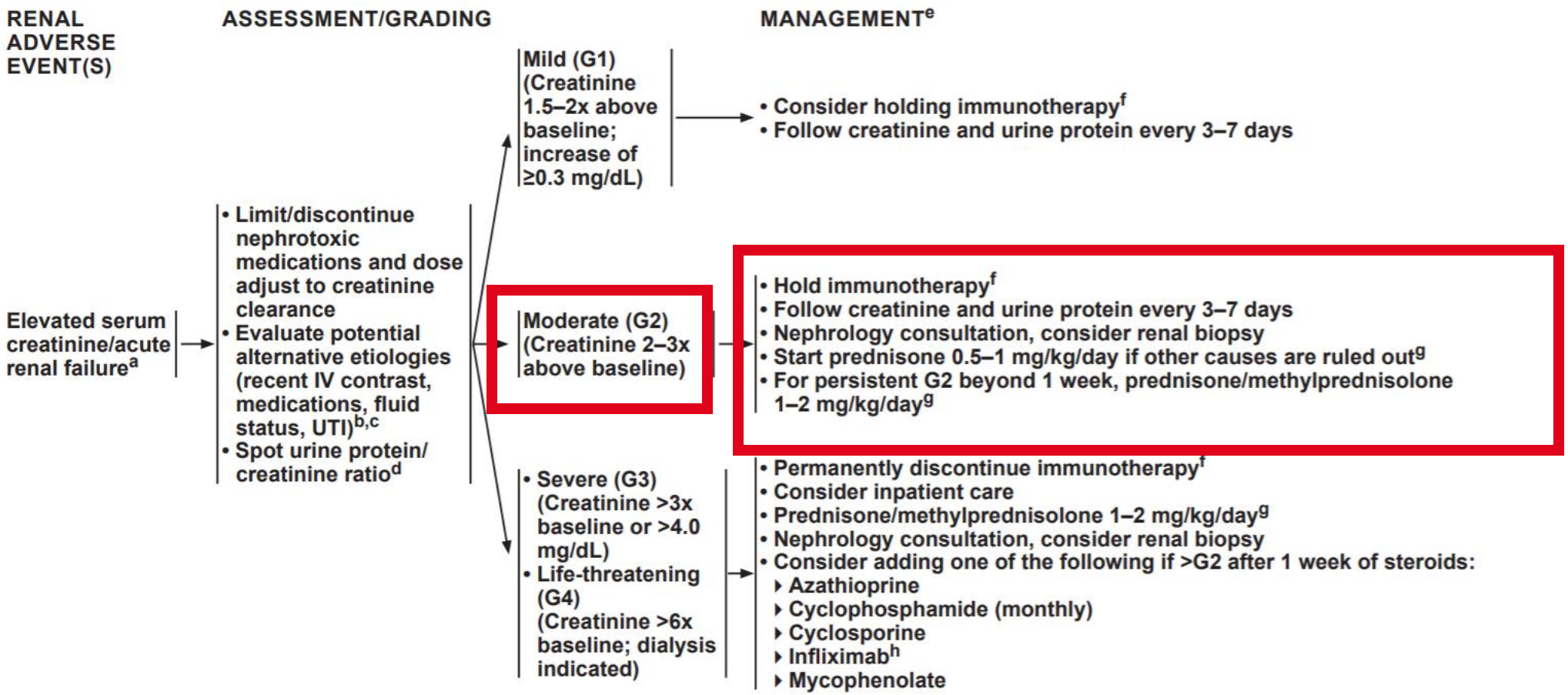
# Nephritis with Immuno-Chemotherapy



# CF continued



# NCCN Guidelines: Renal Toxicity

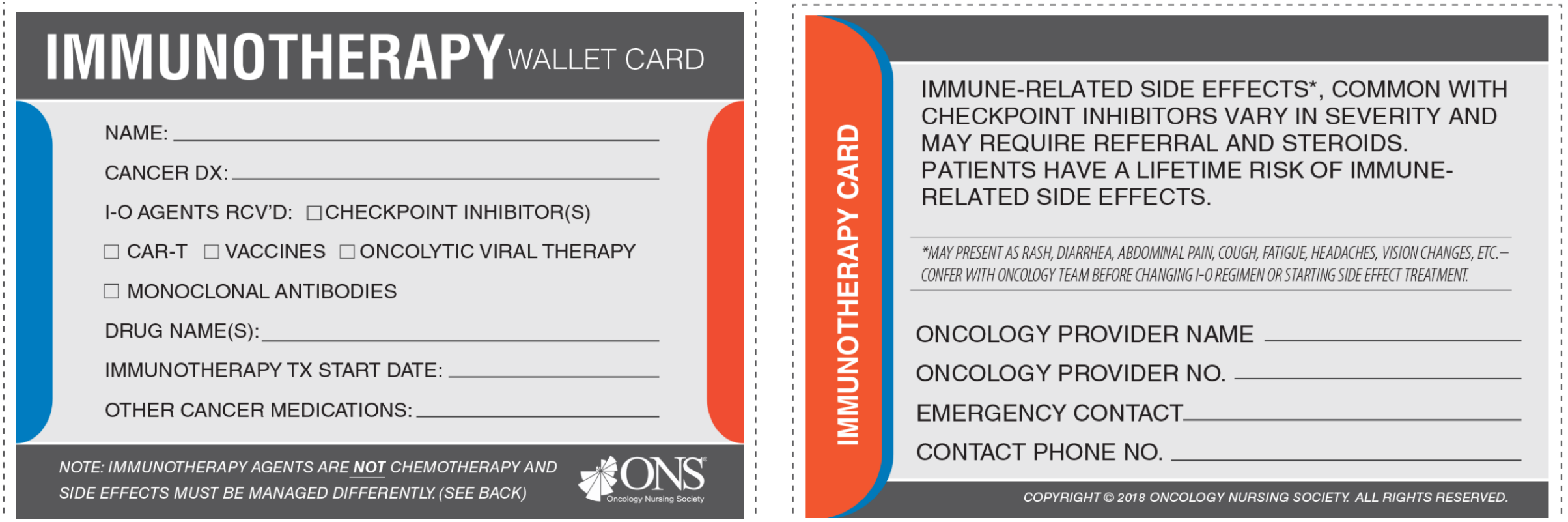



Management of Immunotherapy-Related Toxicities. *NCCN Guidelines.* Version 1.2020.

# How can the pharmacist help?

- Patient education and patient wallet card
  - Example of wallet card via ONS
  - NCCN patient education guide for immunotherapy side effects
- Education of non-oncology providers and pharmacists
  - Identification of immunotherapy agents
  - Common side effects
  - Basic management
- Know your resources

# ONS Patient Wallet Card



## IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

I-O AGENTS RCV'D: ☐ CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

*NOTE: IMMUNOTHERAPY AGENTS ARE **NOT** CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)*

ONS Oncology Nursing Society

IMMUNOTHERAPY CARD

IMMUNE-RELATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

**MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.– CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.*

ONCOLOGY PROVIDER NAME _____

ONCOLOGY PROVIDER NO. _____

EMERGENCY CONTACT _____

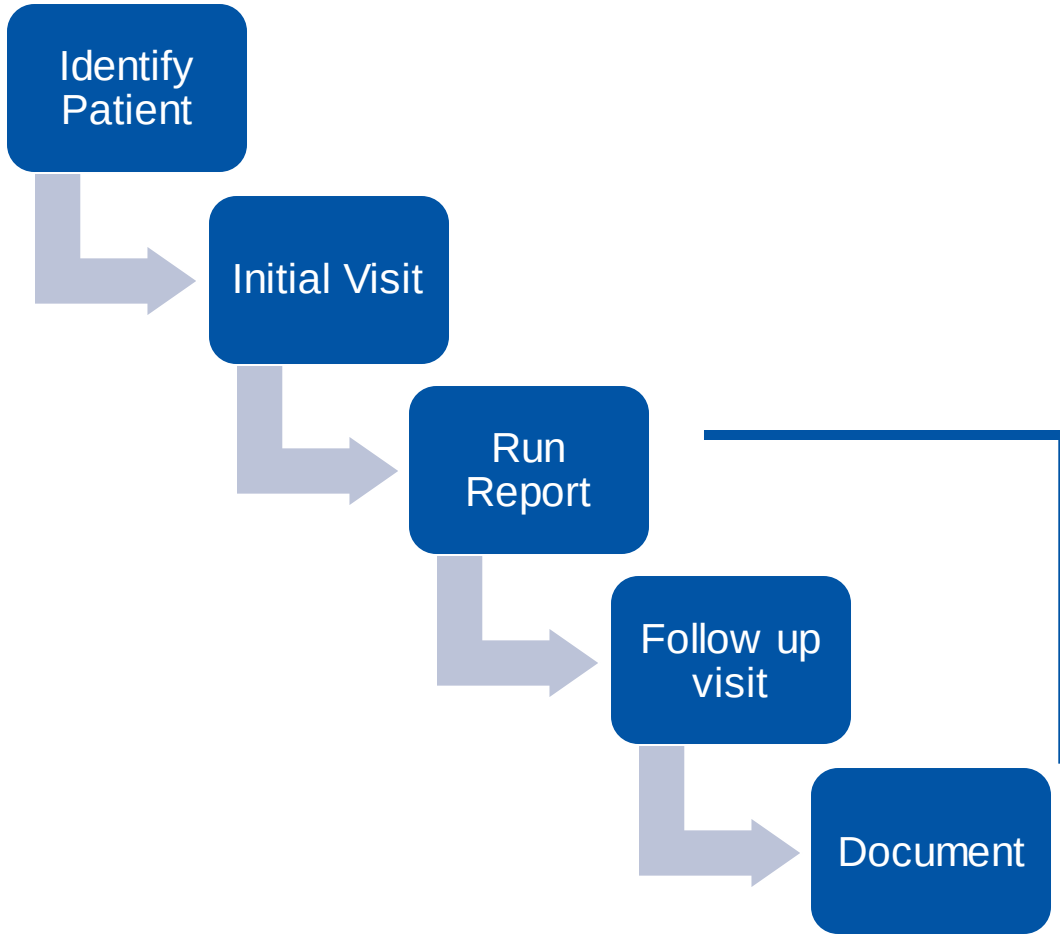
CONTACT PHONE NO. _____

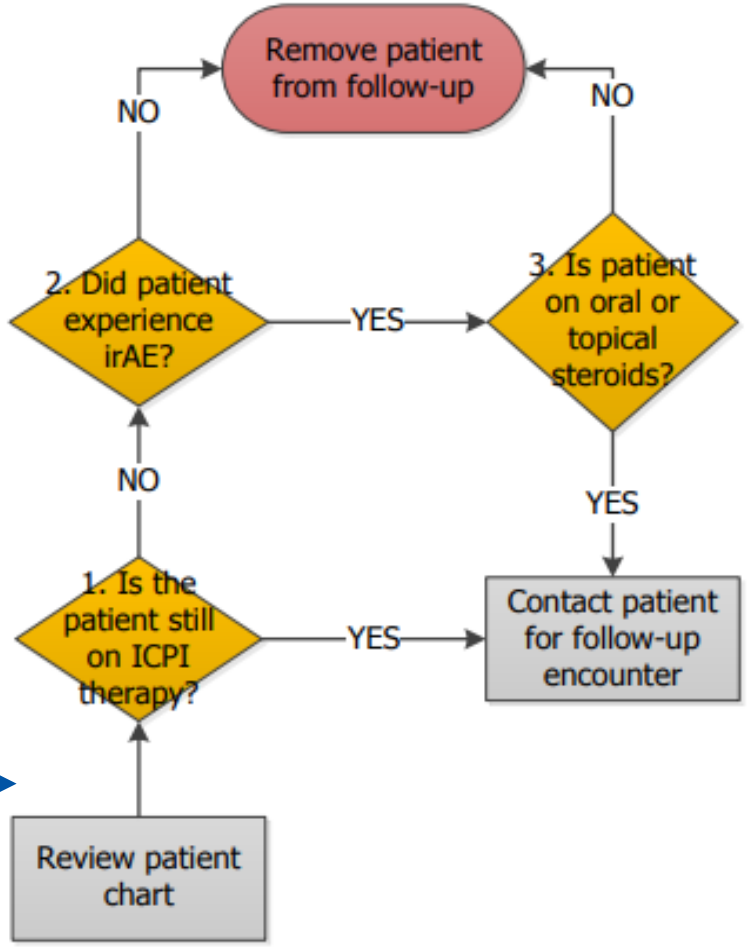
# Immunotherapy Check Ins

- University of Wisconsin Carbone Cancer Center
- Aims
  - Ensure patient and caregiver education
  - Continuous monitoring of immune related adverse events
- Possible Outcomes
  - Early identification and treatment of toxicity

Renna CE et al. *J Oncol Pharm Pract.* 2019 Jun:25(4):954-60.

# Workflow




Renna CE et al. *J Oncol Pharm Pract.* 2019 Jun:25(4):954-60.

# Take Home Points

- Immune checkpoint inhibitors aren't without some serious side effects
- Know
  - Who to treat
  - What side effects to look for
  - How to treat common side effects
    - Where to find less common management
- Get Creative!
  - How can you further help your patients?