JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Renal Cell Carcinoma

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Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

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Learning Objectives

- Differentiate between early and late adverse effects associated with immunotherapeutic agents.
- Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management.
- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

Goals

- Summarize data on currently available immunotherapeutic agents for renal cell carcinoma
- Identify appropriate management of immune-related dermatitis and arthritis.

Renal Cell Carcinoma

- 63,000 new cases of renal cancer in United States each year
  - ~30% diagnosed with locally advanced or metastatic disease
  - ~40% develop metastasis after primary surgical resection for localized RCC
- Median age at diagnosis 64 years
- 80%–90% of RCC are clear cell carcinomas
- Hallmark of RCC is increased angiogenesis
  - Increased VEGF signaling
  - mTOR activity
- Anti-VEGF and mTOR targeted therapy have been standard therapy for previously untreated patients with metastatic renal cell carcinoma

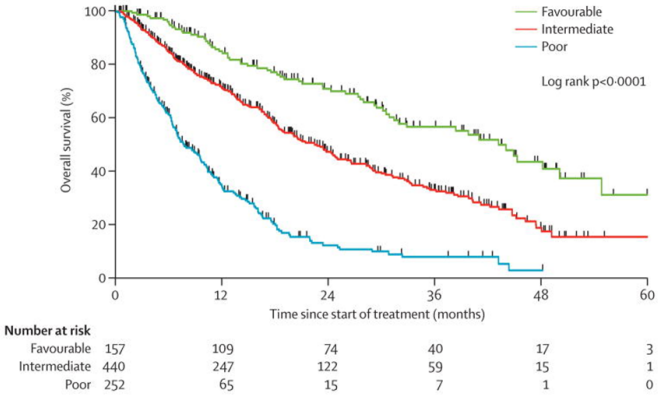
RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor; mTOR = mammalian target of rapamycin.

Atkins MB, et al. (2017). *Annals of Oncology*, *28*(7), 1484–1494. https://doi.org/10.1093/annonc/mdx151

International Metastatic Renal Cell Database Consortium (IMDC) Criteria: Prognostic Risk Stratification

Prognostic Factors

- Less than 1 year from time of diagnosis to systemic therapy
- Performance status < 80% (Karnofsky)
- Hemoglobin < LLN
- Calcium > ULN
- Neutrophil > ULN
- Platelets > ULN



Risk Groups and Prognosis

Risk factors	Prognosis	Median survival
0	Favorable	43 months
1–2	Intermediate	23 months
3–6	Poor	8 months

LLN = lower limit of normal; ULN = upper limit of normal

Heng, D. Y. C., et al. (2013). The Lancet. Oncology, 14(2), 141–8. https://doi.org/10.1016/S1470-2045(12)70559-4

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model

Prognostic Factors

- Less than one year from time of diagnosis to systemic therapy
- Performance status < 80% (Karnofsky)
- LDH > 1.5 ULN
- Calcium > ULN
- Hemoglobin < LLN

Prognostic Risk Groups

Risk Factors	Prognosis
0	Favorable
1–2	Intermediate
3–5	Poor

LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal

Motzer, R. J., et al. (2009). Journal of Clinical Oncology, 27(22), 3584–90. https://doi.org/10.1200/JCO.2008.20.1293

Approved Immunotherapy

- **11/2015** nivolumab, based on CheckMate 025
  - Advanced RCC for patients who have received prior antiangiogenic therapy
  - Dose: 240 mg IV over 30 minutes every 2 weeks, OR
    480 mg IV over 30 minutes every 4 weeks
- **4/16/18** nivolumab and ipilimumab in combination, based on CheckMate 214
  - First-line treatment of intermediate or poor risk advanced renal cell carcinoma
  - Dosing
    - Nivolumab, 3 mg/kg, followed by ipilimumab, 1 mg/kg, on the same day every 3 weeks for 4 doses
    - Followed by nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks

Phase III CheckMate 025 Study: Nivolumab vs. Everolimus in Patients Who Had Received Prior Antiangiogenic Therapy for Advanced Renal Cell Carcinoma

	Nivolumab 3 mg/kg q2w (n = 410)	Everolimus 10 mg/d (n = 411)
Median overall survival	25.0 mo (95% CI = 21.7–not estimable)	19.6 mo (95% CI = 17.6–23.1)
Objective response rate	21.5%	3.9%
Median time to response	3 mo (range, 1.4–13)	3.7 mo (range, 1.5–11.2)
Median duration of response	23.0 mo (range, 12–not estimable)	13.7 mo (range, 8.3–21.9)

Motzer RJ, et al. *N Engl J Med* 2015;373:1803-13 (original study)
Nivolumab Prescribing Information 3.2018 updated results.

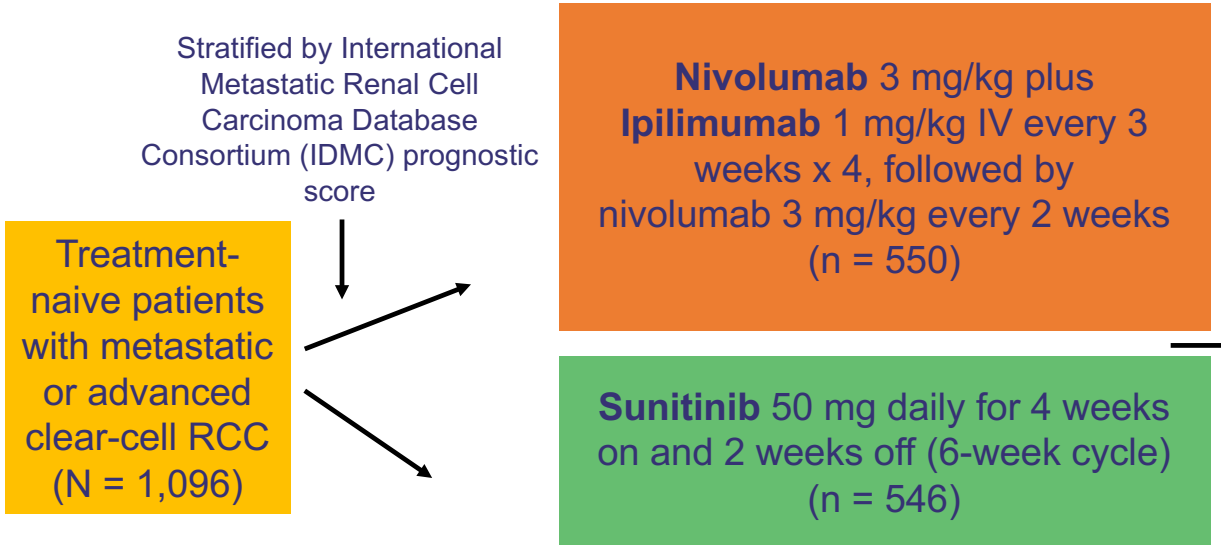
Unclear if Patients with RCC Respond to Treatment Beyond Progression

- CheckMate 025 study: advanced renal cell carcinoma treated with nivolumab
  - 48% of patients with progressive disease by RECIST criteria were treated beyond progression (at least 4 more weeks)
  - 14% of patients had 30% or more decreased tumor burden
  - Median OS for patients treated beyond progression: 28.1 months vs. 15.3 months for patients not treated beyond progression
- FDA re-analysis of CheckMate 025 data:
  - Only 5 of the 171 patients treated beyond radiographic progression (2.9%) achieved a PR following an initial RECIST-defined progression
- Responses beyond progressive disease are rare, yet some patients may derive clinical benefit that is not reflected by radiographic assessments

RECIST = Response Evaluation Criteria in Solid Tumors.

Escudier B., et al. *J Clin Oncol* 2016; 34 (15 Suppl): abstr 4509; Weinstock C., et al. *J Clin Oncol* 2016; 34 (15 suppl): abstr 4508

Phase III CheckMate 214: Ipilimumab/Nivolumab vs. Sunitinib In First-Line Clear Cell Advanced Renal Cell Carcinoma



Response for IDMC intermediate/poor risk
Minimum follow up: 17.5 months

%	ORR	CR	PR	SD	PD
Nivo + Ipi (n = 425)	42	9	32	31	20
Sunitinib (n = 422)	27	1	25	45	17

Treatment continued until progression or unacceptable toxicity

CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; SD = stable disease.

Motzer, R. J., et al. (2018). New England Journal of Medicine, NEJMoa1712126. https://doi.org/10.1056/NEJMoa1712126

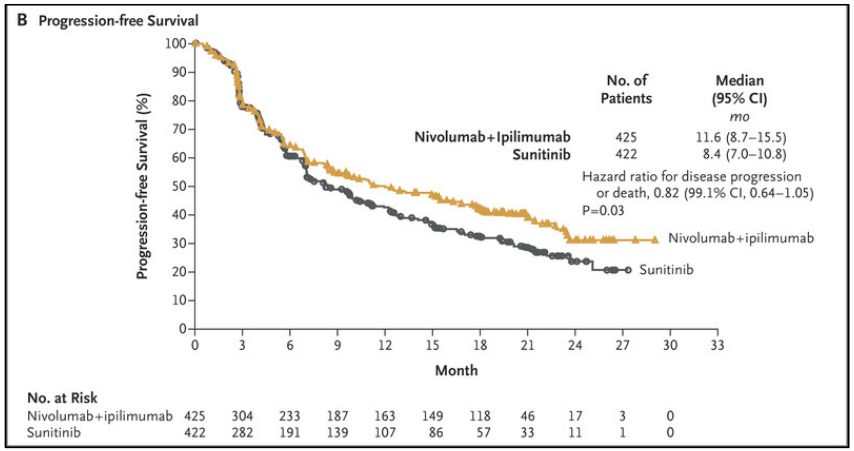
Phase III CheckMate 214: Nivo/Ipi Significantly Improved Overall Survival for IMDC intermediate/poor-risk RCC

Median Progression-Free Survival

Nivo + Ipi (n = 425): 11. 6 months

Sunitinib (n = 422): 8.4 months

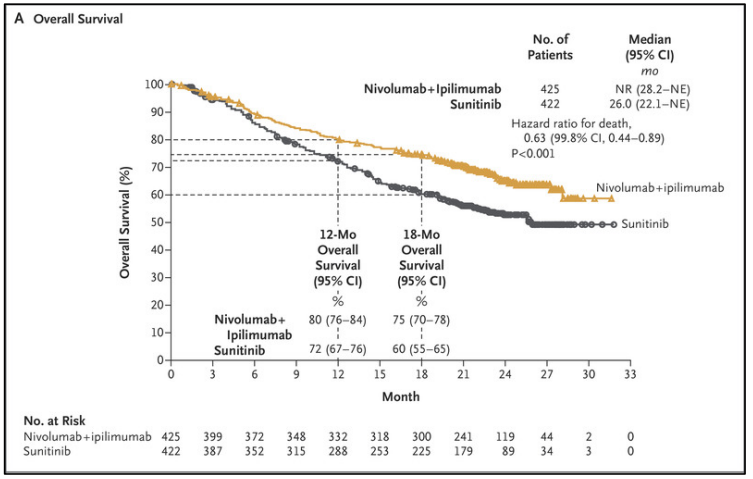
Median duration of response not reached



Median Overall Survival

Nivo + Ipi (n = 425): Not reached

Sunitinib (n = 422): 26 months



IMDC = International Metastatic Renal Cell Carcinoma Database; RCC = renal cell carcinoma.

Motzer, R. J., et al. (2018). New England Journal of Medicine, NEJMoa1712126. https://doi.org/10.1056/NEJMoa1712126

Checkmate 214: Key Takeaways

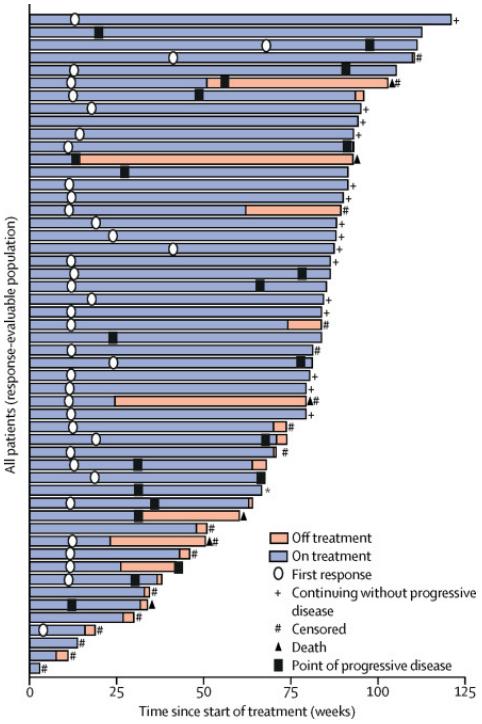
- Favorable risk disease tended to have lower PD-L1 expression and responded better to sunitinib (S) than nivolumab + ipilimumab (N+I): ORR 52% vs. 29%, respectively
- Intermediate- and poor-risk disease responded better to N+I than sunitinib regardless of PD-L1 expression, however best response to N+I was when tumor PD-L1 expression ≥ 1%
  - PD-L1 < 1%: ORR 37% (N+I) vs. 28% (S)
  - PD-L1 ≥ 1%: ORR 58% (N+I) vs. 22% (S)
- Drug-related AEs occurred in 93% of patients treated with N+I
  - Grade 3–4: 46%
  - Discontinued drug due to AE: 22%
- Drug-related AEs occurred in 97% treated with S
  - Grade 3–4: 63%
  - Discontinued drug due to AE: 12%

ORR = overall response rate.

Motzer, R. J., et al. (2018). New England Journal of Medicine, NEJMoa1712126. https://doi.org/10.1056/NEJMoa1712126

Phase I Trial: Axitinib/Pembrolizumab In Patients With Advanced Renal Cell Cancer

- Axitinib 5 mg po bid and pembrolizumab 2 mg/kg IV q3w
- N = 52
- ORR 73%
- More than 90% of patients has some tumor shrinkage
- Median progression-free survival > 20 months
- Grade 3–4 toxicity: 65%
  - Most frequent AEs: Hypertension, diarrhea, fatigue, increased AST/ALT, hypothyroidism
- KEYNOTE-426: Phase III trial accruing which compares axitinib 5 mg po bid plus pembrolizumab 200 mg IV q3w with sunitinib 50 mg/d for 4 weeks; off 2 weeks.



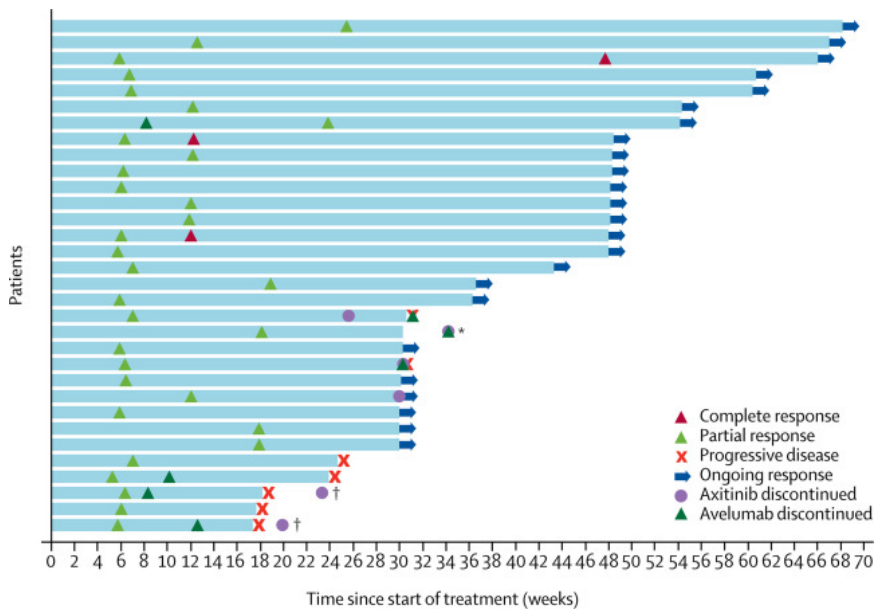
Choueiri, T. K., et al. (2018). The Lancet. Oncology, 0(0). https://doi.org/10.1016/S1470-2045(18)30107-4

IMmotion151: Phase III Trial Of Atezolizumab and Bevacizumab Compared With Sunitinib

- n = 915 patients
- Randomized to one of 2 arms:
  - Atezolizumab at 1,200 mg IV and bevacizumab 15 mg/kg IV q3w until loss of clinical benefit or unacceptable toxicity
  - Sunitinib 50 mg/d po for 4 weeks followed by 2 weeks rest until loss of clinical benefit or unacceptable toxicity
- Median PFS
  - 11.2 months with the combination vs. 7.7 months with sunitinib
- OS data are immature and the median has not been reached in either study arm
- Grade 3–4 adverse events:
  - Atezolizumab/bevacizumab: 40%
  - Sunitinib: 54%

Phase Ib JAVELIN Renal 100: Avelumab Plus Axitinib As First-line Therapy in Patients With Advanced Clear-Cell Renal-Cell Carcinoma

- Axitinib 5 mg po bid x 7 days followed by avelumab 10 mg/kg IV every 2 weeks and axitinib 5 mg po bid
- N = 55
- ORR 58%
- Most frequent AE
  - Hypertension, increased ALT, amylase, lipase and hand-foot syndrome
  - A phase 3 trial is assessing avelumab and axitinib compared with sunitinib monotherapy



Choueiri, T. K., et al. (2018). The Lancet. Oncology, 0(0). https://doi.org/10.1016/S1470-2045(18)30107-4

KEYNOTE-564: Phase III Trial Evaluating Pembrolizumab As Adjuvant Therapy For Renal Cell Carcinoma

- Phase III randomized, double-blind, placebo-controlled phase III trial
- Evaluate the efficacy and tolerability of pembrolizumab as adjuvant therapy in pts with RCC who have T2 grade 4, T3, T4, N (+), or stage M1 with no evidence of disease (M1 NED) following nephrectomy and/or metastasectomy
- ~950 pts will be randomly assigned in a 1:1 ratio between 2 cohorts
  - Pembrolizumab 200 mg every 3 weeks by intravenous infusion, or placebo, continued for up to 17 cycles (~1 year) or until disease recurrence or treatment discontinuation
  - Placebo

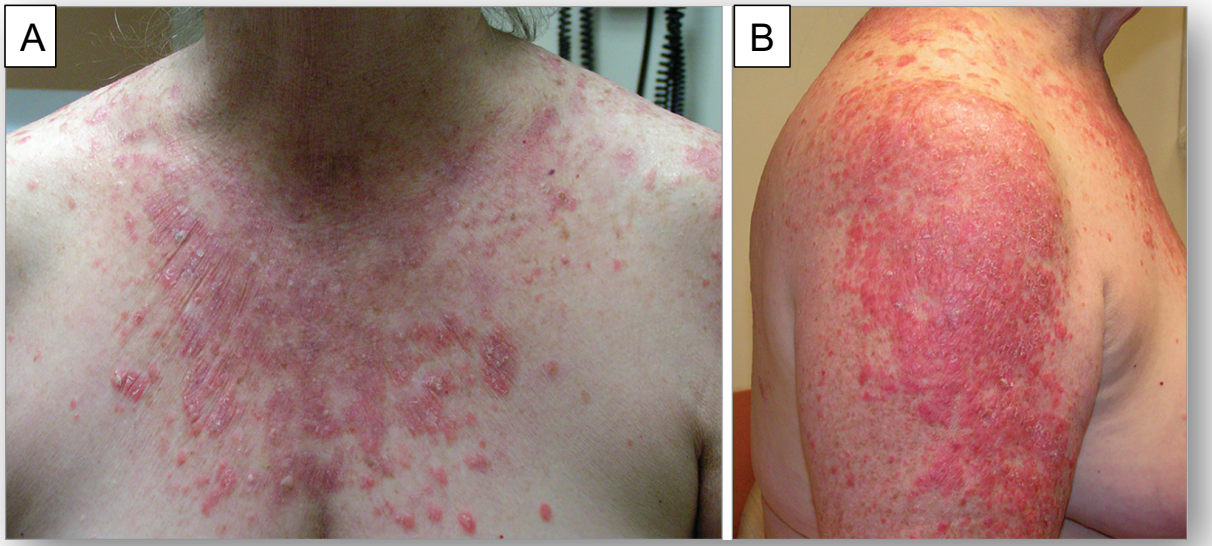
Choueiri, T.K. et al. (2017). Annals of Oncology, 28 (suppl_5): v295-v329. 10.1093/annonc/mdx371

Case Study

- TB is a 67-year-old female diagnosed with stage II clear-cell renal cell carcinoma who underwent laparoscopic left nephrectomy and had no evidence of disease after surgery
- One year later, she developed lower back pain
  - CT (chest, abdomen, pelvis): lytic lesion T10, several lung nodules and a pre-sacral mass consistent with metastatic disease
- She is treated with sunitinib for 10 months until progressive disease in the lungs
- Her doctor recommends nivolumab for second-line therapy

Case Study (cont.)

- TB presents to clinic for cycle 3 nivolumab
- She reports that she has developed a rash



A. Macular papular eruption with predilection sites on photoexposed areas of the chest

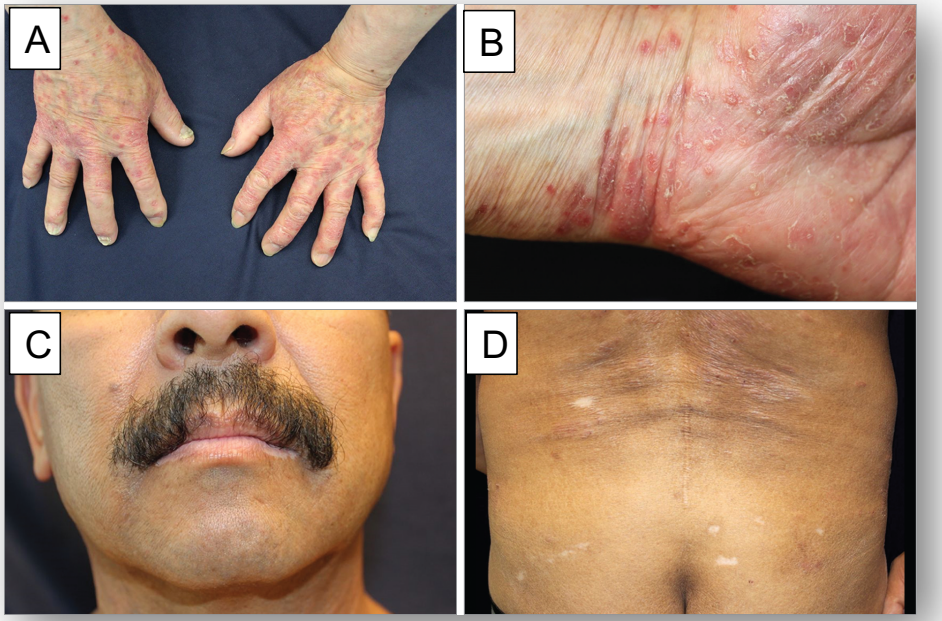
B. Macular papular eruption with predilection sites on photoexposed areas of the arm

Sanlorenzo M, et al. *JAMA Dermatology* 2015;151:1206-12.

Immune-Related Dermatitis

Symptoms	Differential Diagnosis
• Rash (excluding bullous skin formations) • Dry skin • Pruritus • Maculopapular rash • Skin hypopigmentation	• Infectious rash (e.g., viral exanthem, zoster) • Scabies • Contact dermatitis

Examples of IO-Induced Rash



A. Macular papular eruption

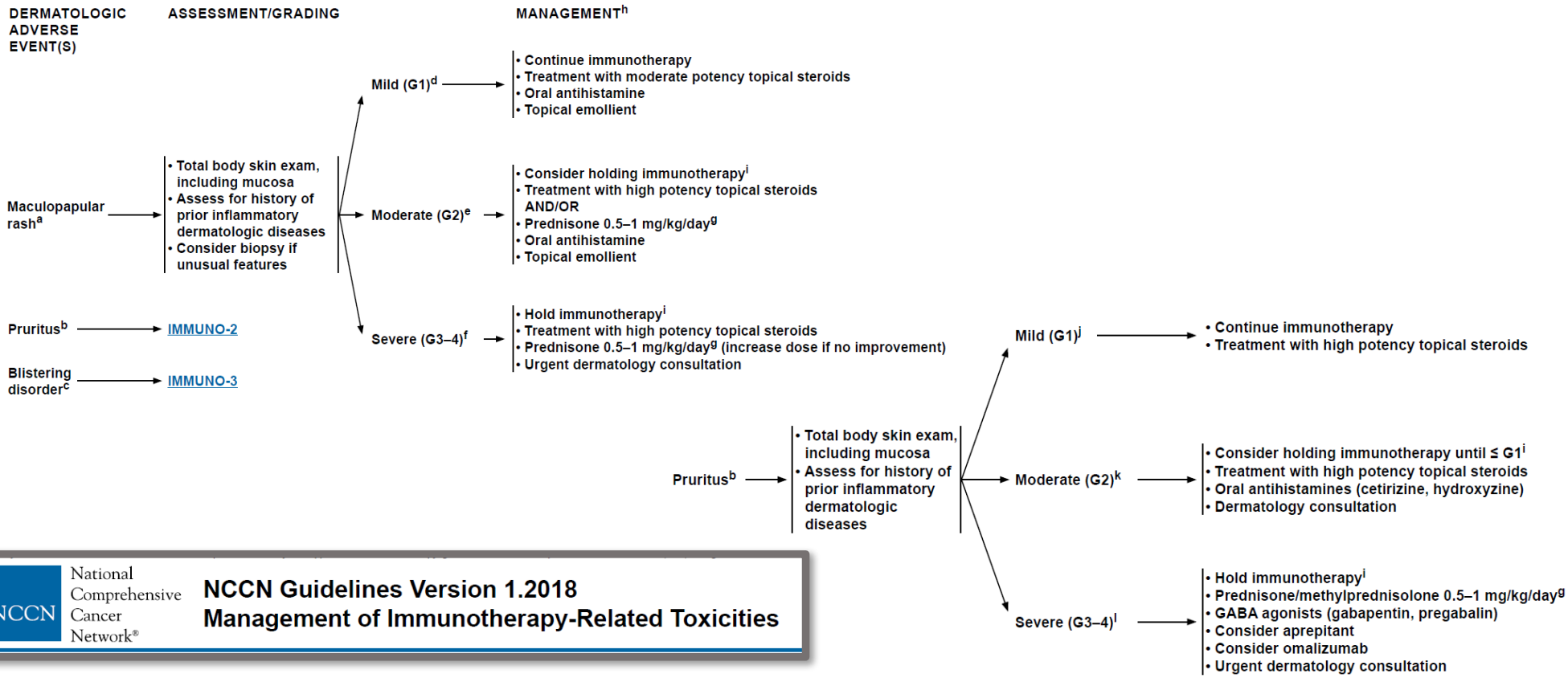
B. Macular papular eruption

C. Vitiligo/hypopigmentation of the lips

D. Scaly papular eruption with hypopigmentation

IO = immuno-oncology.

Management: Dermatitis

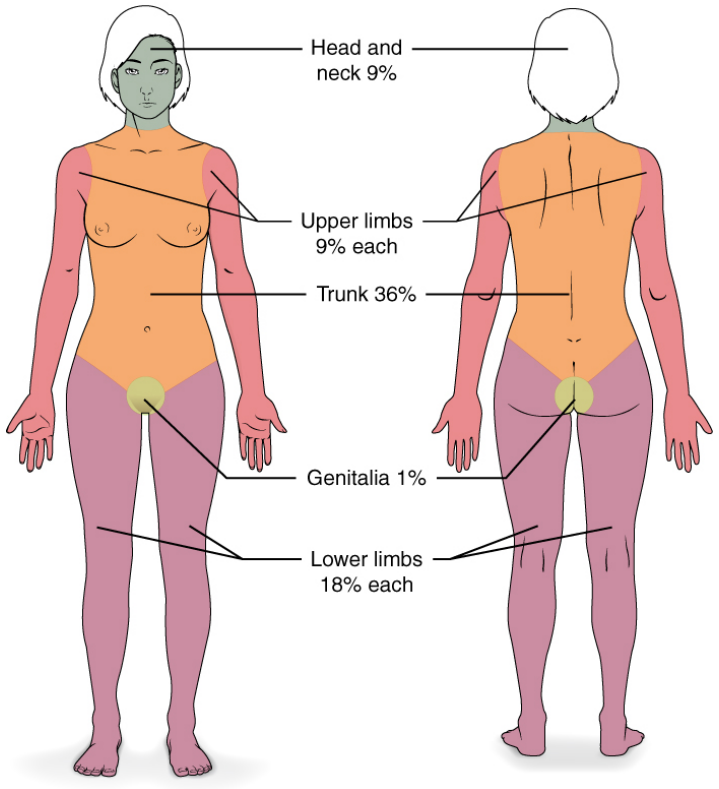


National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

Case Study (cont.)

- TB had a rash on both arms, chest, and trunk
  - Grade 3: 54% BSA based on rule of nines
- Nivolumab stopped for grade 3 toxicity
- Treated with
  - Topical triamcinolone 0.1% ointment
  - Prednisone 1 mg/kg/d
  - Sulfamethoxazole and trimethoprim daily for PCP prophylaxis
  - H2 antagonist for GI prophylaxis
- Rash started to improve within 1 week
- Steroid taper began after rash began to improve



BSA = body surface area; PCP = *Pneumocystis jiroveciii* pneumonia.

Audience Response Question

When can you restart immunotherapy after immune-related dermatitis?

A. When rash resolves and steroid taper is completed
B. When rash resolves and steroid dose 20 mg/d or less
C. When rash resolves and steroid dose 10 mg/d or less
D. When the rash resolves regardless of steroid dose
E. Unsure

Case Study (cont.)

- Nivolumab restarted 4 weeks later after rash resolved and steroids tapered to 10 mg/d
- Imaging at 18 weeks demonstrated partial response
- Nivolumab continued. At 24 weeks, TB reported joint pain and swelling in both knees. She reported that her knees felt “stiff” in the morning when she woke up.
- TB was referred to rheumatology

Presentation and Diagnosis of Immune-Related Inflammatory Arthritis

5.1 Inflammatory arthritis

Definition: A disorder characterized by inflammation of the joints

Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.

Diagnostic work-up

G1

- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine
- Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate
- Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing

G2

- Complete history and examination as above; laboratory tests as above
- Consider US ± MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)
- Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks

G3-4

- As for G2
- Seek rheumatologist advice and review

Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

CRP = c-reactive protein; CCP = anti-cyclic citrullinated peptide antibodies; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ANA = anti-nuclear antibodies.

Brahmer, J. R., et al. (2018). *Journal of Clinical Oncology*, JCO.2017.77.638. https://doi.org/10.1200/JCO.2017.77.6385

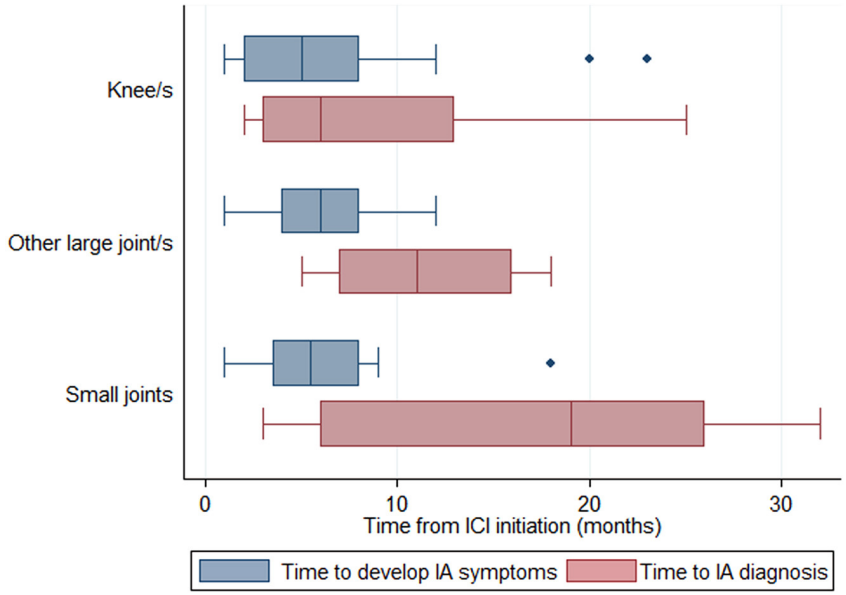
Management of Immune-Related Inflammatory Arthritis

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.

Brahmer, J. R., et al. (2018). *Journal of Clinical Oncology*, JCO.2017.77.638. https://doi.org/10.1200/JCO.2017.77.6385

Delay in Diagnosis of Immune-Related Inflammatory Arthritis

- Average time from patient-reported initial development of joint symptoms to diagnosis of inflammatory arthritis (IA): 5.2 months
- Few patients are positive for auto-antibodies, so important to make clinical diagnosis



Cappelli, L. C., et al. (2018). Seminars in Arthritis and Rheumatism. https://doi.org/10.1016/J.SEMARTHRIT.2018.02.011

Case Study (cont.)

- Rheumatologist evaluated TB and diagnosed inflammatory arthritis of both knees
  - B knee joint swelling
  - C-reactive protein: 5
  - CCP, RF, ANA negative
- Treated with prednisone 20 mg/d with rapid response
- Tapered to 10 mg/d one week later and restarted nivolumab

CCP = anti-cyclic citrullinated peptide antibodies; RF = rheumatoid factor; ANA = anti-nuclear antibodies

Summary

- Metastatic renal cell carcinoma has a dismal prognosis and new treatments are needed to improve upon standard of care
- Nivolumab improves survival when compared to everolimus in patients who had received prior antiangiogenic therapy
- Combination therapy with nivolumab and ipilimumab significantly improved overall survival for patients with intermediate/poor-risk RCC in the first-line setting
- Immune checkpoint inhibitor monotherapy is well tolerated, combination therapy has more side effects than monotherapy but better tolerated than sunitinib
- Emerging data with combination of immune checkpoint inhibitors and anti-angiogenesis drugs are promising, yet high rate of adverse effects

Audience Response Question

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