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# Management and Mitigation of irAEs for Immunotherapy Prescribers

John M. Kaczmar, MD

Assistant Professor

Division of Hematology/Oncology, MUSC Hollings Cancer Center

AMERICAN ACADEMY OF EMERGENCY MEDICINE

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# Disclosures

- I have no disclosures
- I will be discussing non-FDA approved indications during my presentation.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

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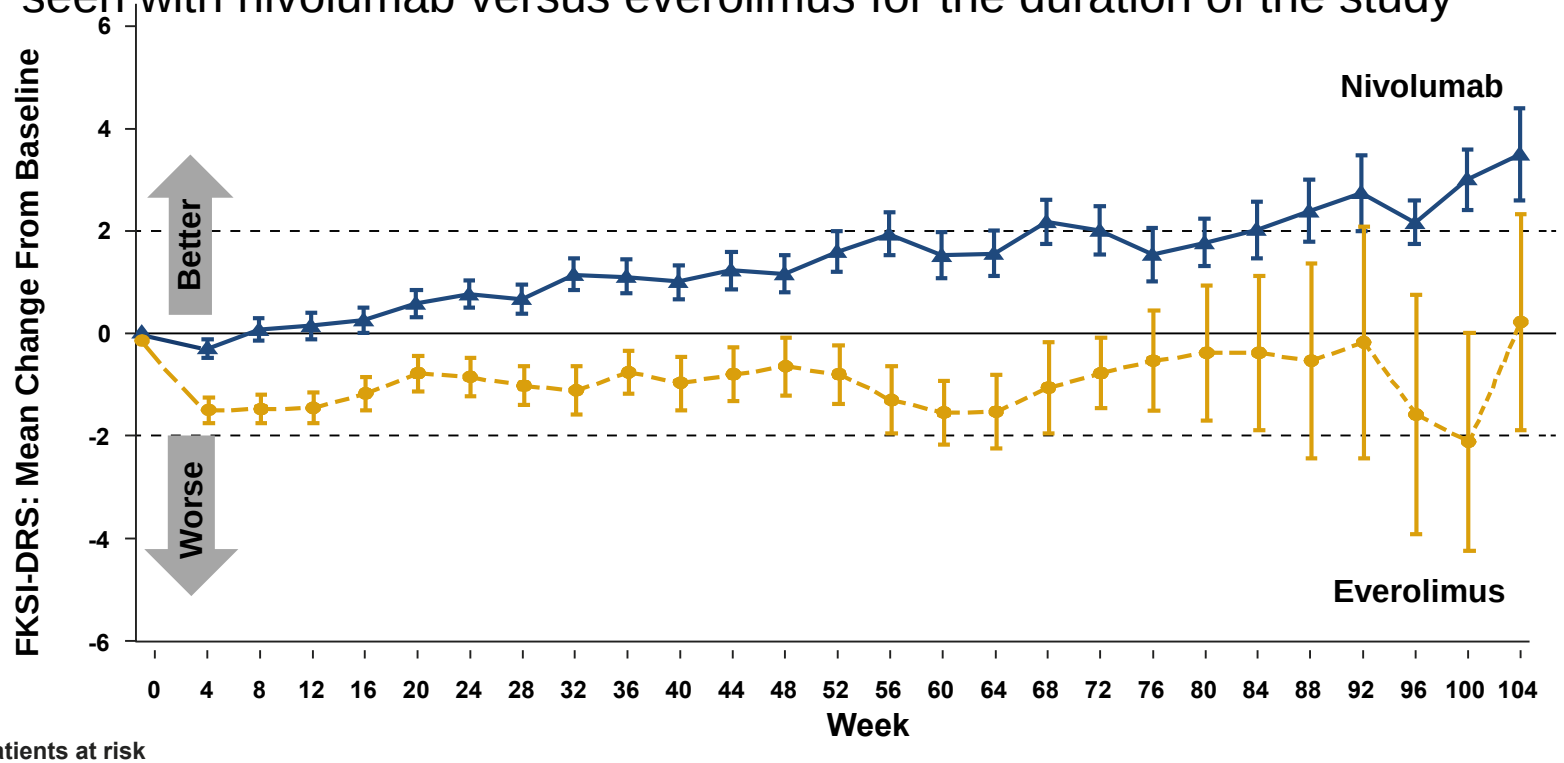
# Change from baseline in quality of life scores on FKSI-DRS

- QoL assessed using Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) scoring algorithm
- A clinically meaningful and statistically significant improvement in QoL was seen with nivolumab versus everolimus for the duration of the study

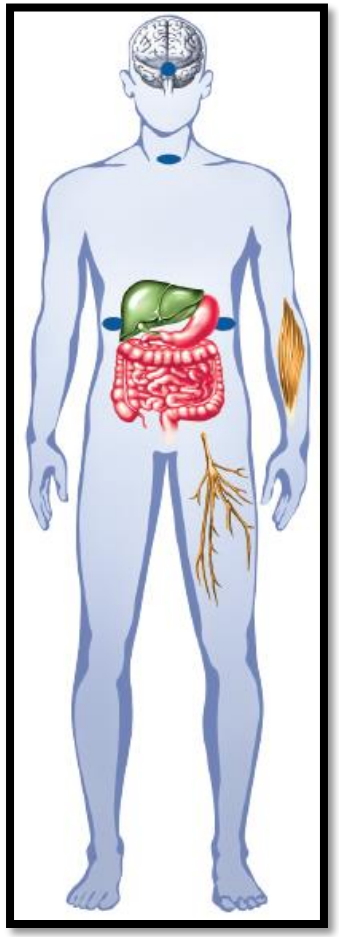



Questionnaire completion rate: ≥80% during the first year of follow-up

# Toxicity with immunotherapy agents

Activation of the immune system against tumors can result in a novel spectrum of immune-related Adverse Events (**irAEs**)

- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious
- Requires prompt recognition and treatment
- Requires patient and HCP education



**irAEs can occur in most organ systems:**

- Skin
- Endocrine system
- Renal system
- Liver
- Gastrointestinal tract
- Nervous system
- Eyes
- Respiratory system
- Hematopoietic cells
- Musculoskeletal

# Treatment-related AEs occurring in ≥10% of patients in either arm

| Event | Nivolumab N = 406 | | Everolimus N = 397 | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| **Treatment-related AEs, %** | 79 | 19 | 88 | 37 |
| **Fatigue** | 33 | 2 | 34 | 3 |
| **Nausea** | 14 | <1 | 17 | 1 |
| **Pruritus** | 14 | 0 | 10 | 0 |
| **Diarrhea** | 12 | 1 | 21 | 1 |
| **Decreased appetite** | 12 | <1 | 21 | 1 |
| **Rash** | 10 | <1 | 20 | 1 |
| **Cough** | 9 | 0 | 19 | 0 |
| **Anemia** | 8 | 2 | 24 | 8 |
| **Dyspnea** | 7 | 1 | 13 | <1 |
| **Edema peripheral** | 4 | 0 | 14 | <1 |
| **Pneumonitis** | 4 | 1 | 15 | 3 |
| **Mucosal inflammation** | 3 | 0 | 19 | 3 |
| **Dysgeusia** | 3 | 0 | 13 | 0 |
| **Hyperglycemia** | 2 | 1 | 12 | 4 |
| **Stomatitis** | 2 | 0 | 29 | 4 |
| **Hypertriglyceridemia** | 1 | 0 | 16 | 5 |
| **Epistaxis** | 1 | 0 | 10 | 0 |

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# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - **Will rare but serious toxicities occur?**
  - Will late toxicity emerge?
  - Will certain toxicities make combinations difficult?
  - Will history of autoimmunity limit application?

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# Case Study #1

- A 66-year-old male previously treated mRCC enrolled in a clinical trial of anti-PD-L1 Ab therapy
- Approximately two weeks after his second dose of anti-PD-L1 antibody, he presented with sudden onset of double vision, along with a 10-day history of muscle pain and weakness, joint aches and generalized malaise.
- Neurologic exam was notable for near complete opthalmoplegia, fatigability of his deltoids, otherwise non-focal. Labs were notable for transaminitis and myositis.

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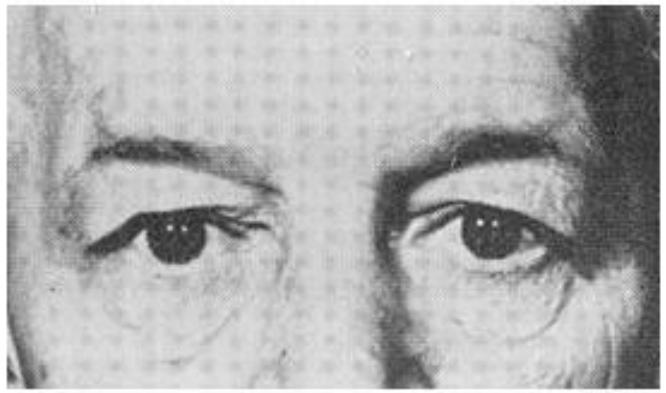
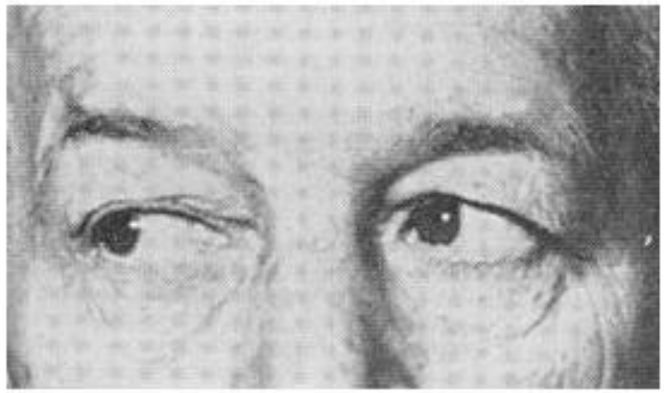
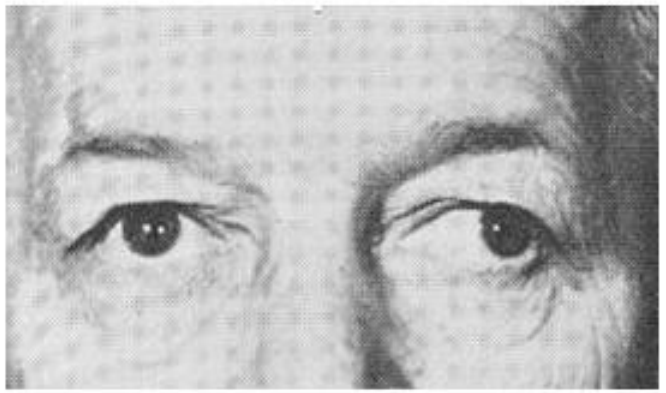
"Look at me"



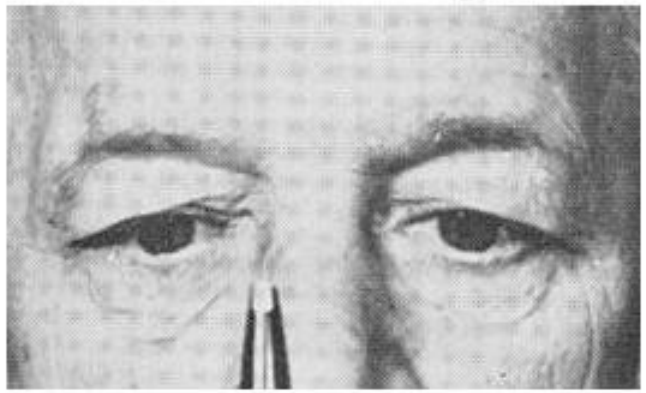
"Look to the right"



"Look to the left"



"Look at this object"



http://www.etsu.edu/com/medicalmystery/IOP.aspx

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# Case Description: 66-Year-Old Male (continued)

- This patient was diagnosed with drug-induced myasthenia gravis by serologic testing:
  - Clinical trial related labs: Antibody titer detected in pretreatment sample at lower level.

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# Case Description: 66-Year-Old Male (continued)

- Neurologic symptoms resolved on steroids.
- Patient was taken off study, then developed disease progression three months later.
- Patient subsequently received VEGF TKI therapy.

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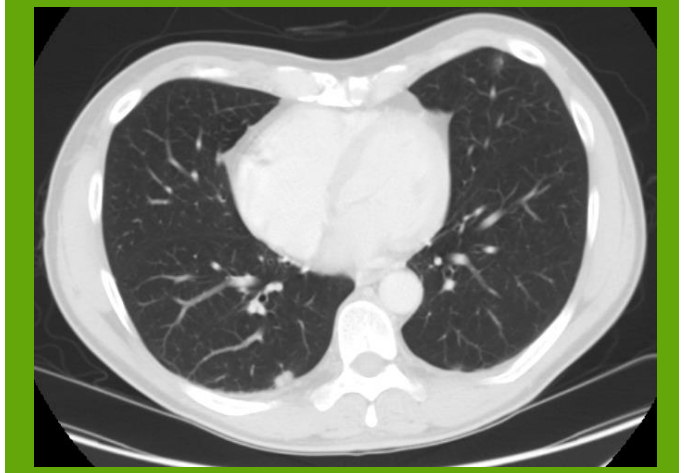
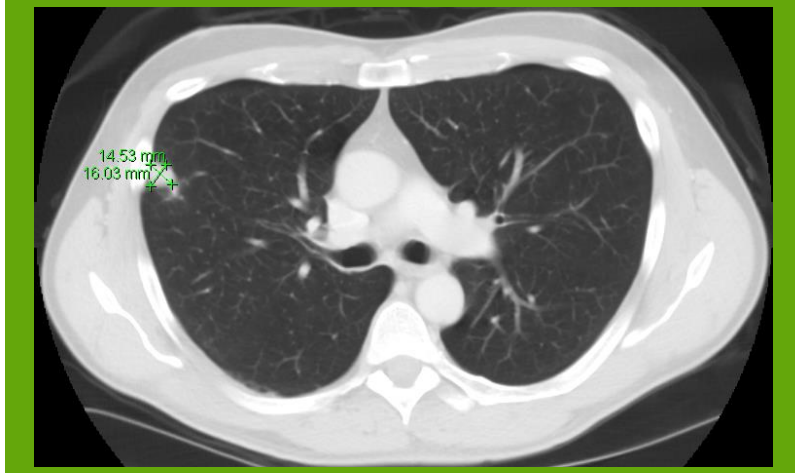
# Case Study #2

- A 56-yr-old male with stage 4 RCC was treated with high dose IL-2
- After progression, he was enrolled in clinical trial for nivolimab at 3 mg/kg
  - Patient developed a dry cough and came in for an exam

Scan at Mo 6



Subsequent Scan at Mo 8



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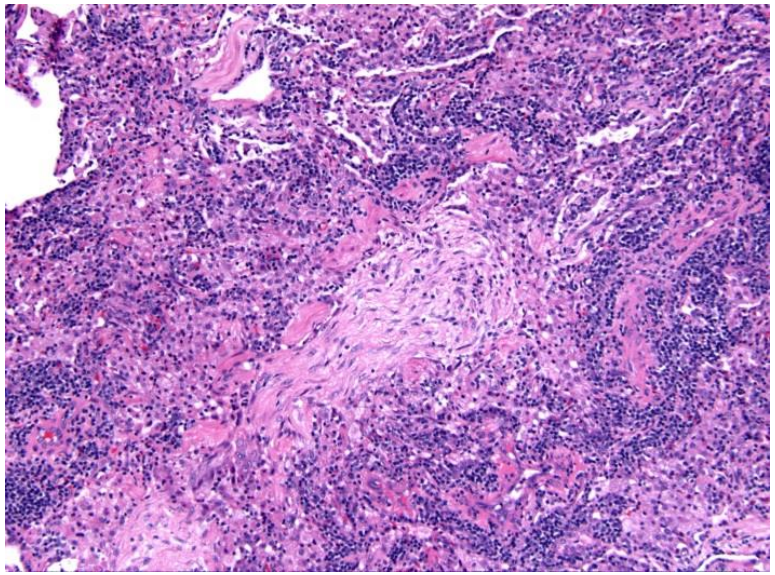
# Case Study #2

- Patient underwent biopsy to confirm disease progression
  - Biopsy suggested bronchiolitis obliterans



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## Patient underwent biopsy to confirm disease progression, and the biopsy suggested bronchiolitis obliterans.

## How would you manage this patient?

1. Continue nivolumab and start steroid treatment.
2. Continue nivolumab and start broad-spectrum antibiotics.
3. Discontinue nivolumab and start steroid treatment.
4. Discontinue nivolumab and start broad-spectrum antibiotics.

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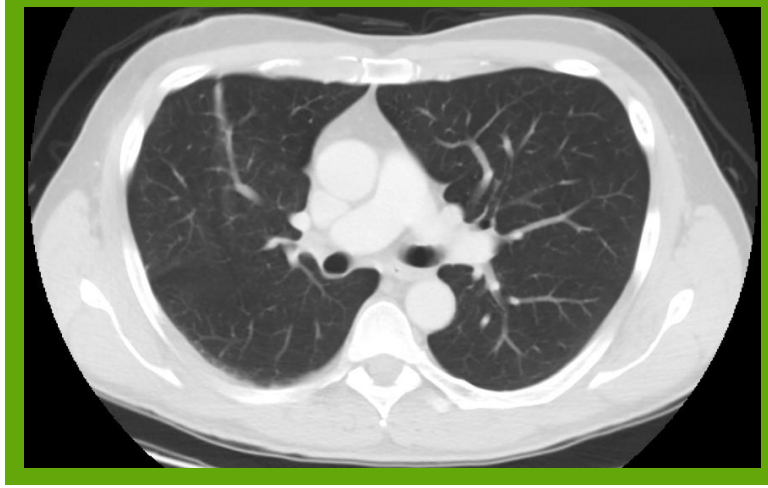
# Case Study #2

- Symptoms and lung lesions resolved with initiation of steroid therapy
- Nivolumab treatment was discontinued, and disease is currently stable off all therapy x two years

Lung Lesions Resolved



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# SITC consensus recommendations

**Table 2** General guidance for corticosteroid management of immune-related adverse events

| Grade of immune-related AE (CTCAE/equivalent) | Corticosteroid management | Additional notes |
|---|---|---|
| 1 | • Corticosteroids not usually indicated | • Continue immunotherapy |
| 2 | • If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication.<br>• If IV required, start methylprednisolone 0.5-1 mg/kg/day IV<br>• If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day<br>• Once improved to ≤grade 1 AE, start 4–6 week steroid taper | • Hold immunotherapy during corticosteroid use<br>• Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis |
| 3 | • Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)<br>• If no improvement in 2–3 days, add additional/alternative immune suppressant<br>• Once improved to ≤ grade 1, start 4–6-week steroid taper<br>• Provide supportive treatment as needed | • Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy<br>• Consider intravenous corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis<br>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) |
| 4 | • Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)<br>• If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab<br>• Provide supportive care as needed | • Discontinue immunotherapy<br>• Continue intravenous corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis<br>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) |

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event



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# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - Will rare but serious toxicities occur?
  - **Will late toxicity emerge?**
  - Will certain toxicities make combinations difficult?
  - Will history of autoimmunity limit application?

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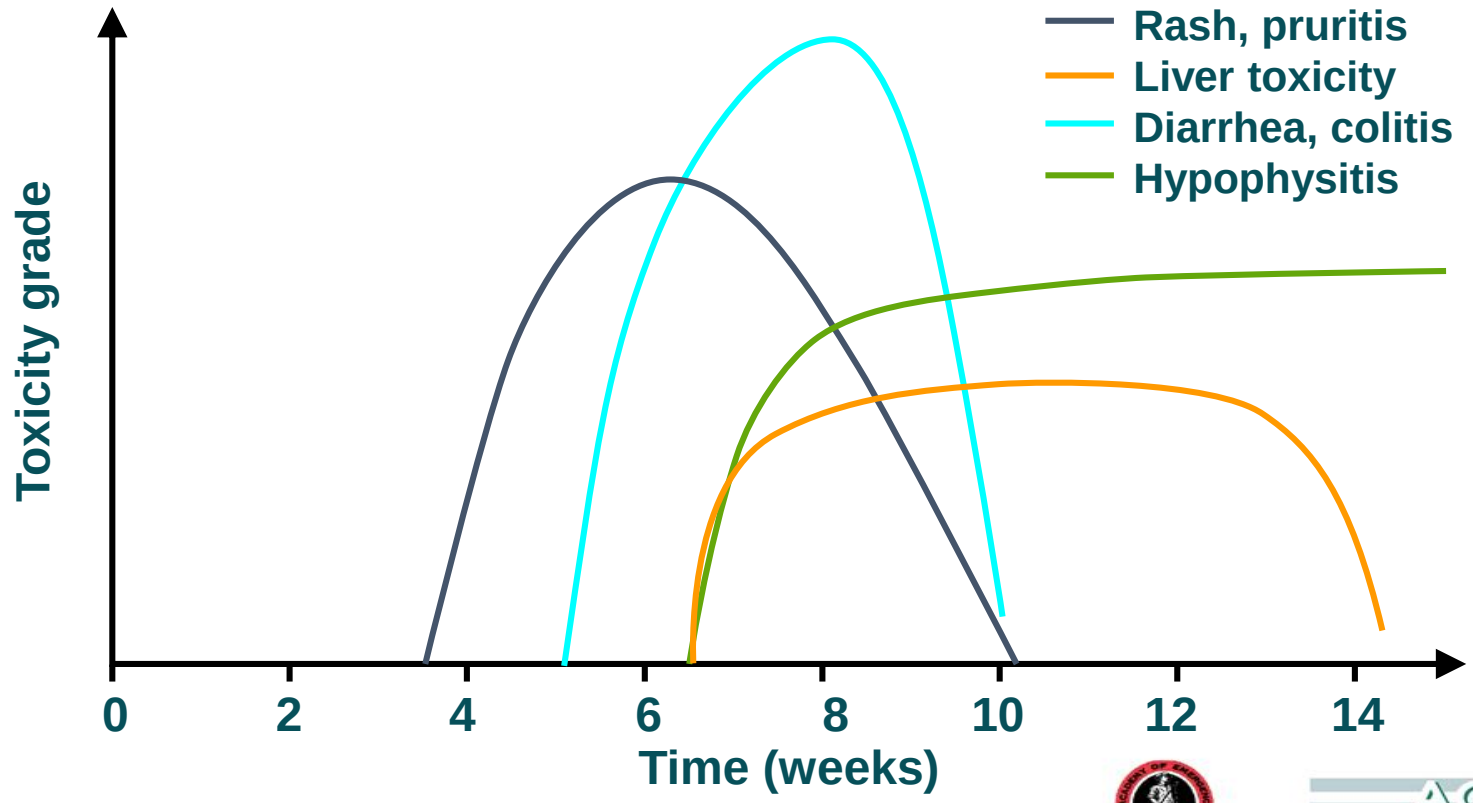
# Immune checkpoint inhibitors: immune-related adverse event (irAE) onset

- Each irAE has different kinetics of onset
- Rash first, followed by colitis, hypophysitis and finally hepatitis




Weber JS, et al. *J Clin Oncol.* 2012;30:2691–2697.

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# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - Will rare but serious toxicities occur?
  - Will late toxicity emerge?
  - **Will certain toxicities make combinations difficult?**
    - (e.g. nephritis, hepatitis, pneumonitis)
  - Will history of autoimmunity limit application?

# Distribution of irAEs in CTLA-4 vs. PD-1 vs. PD-L1 antibodies

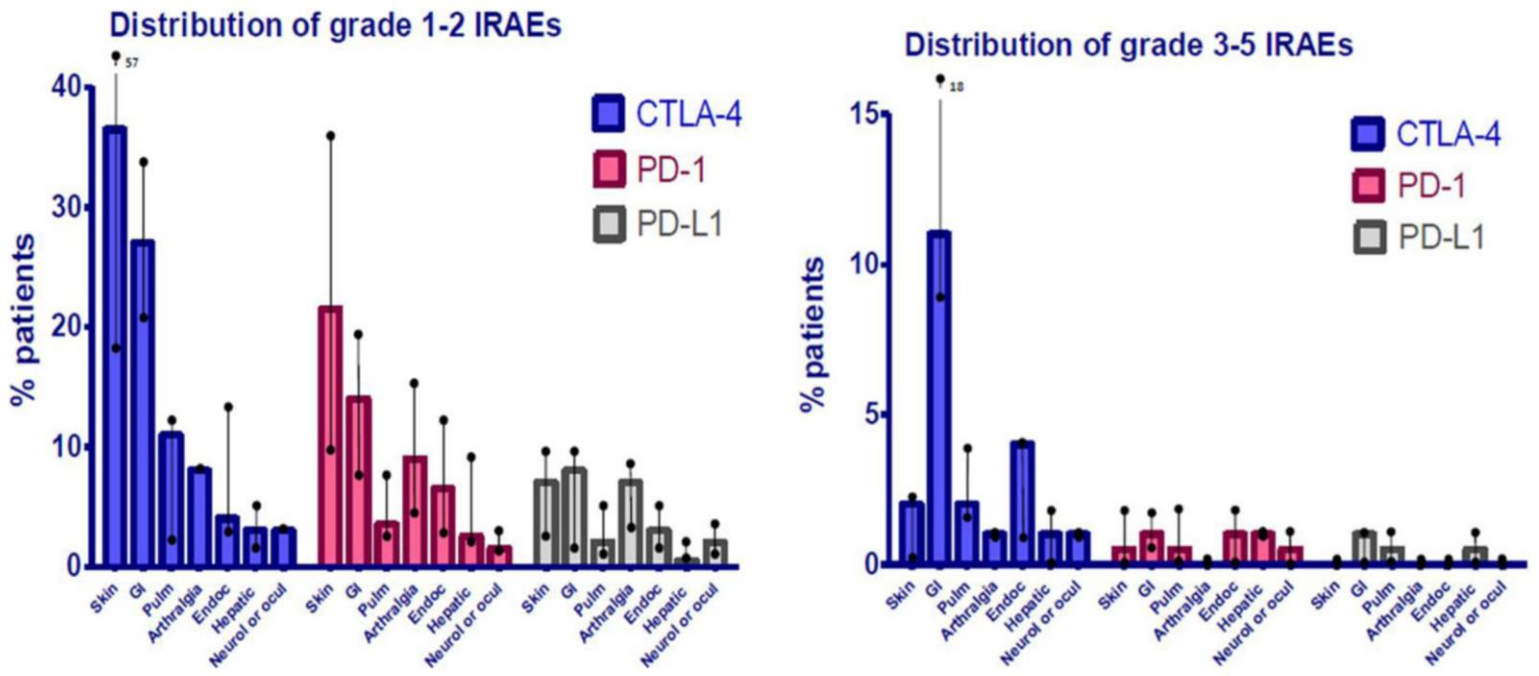
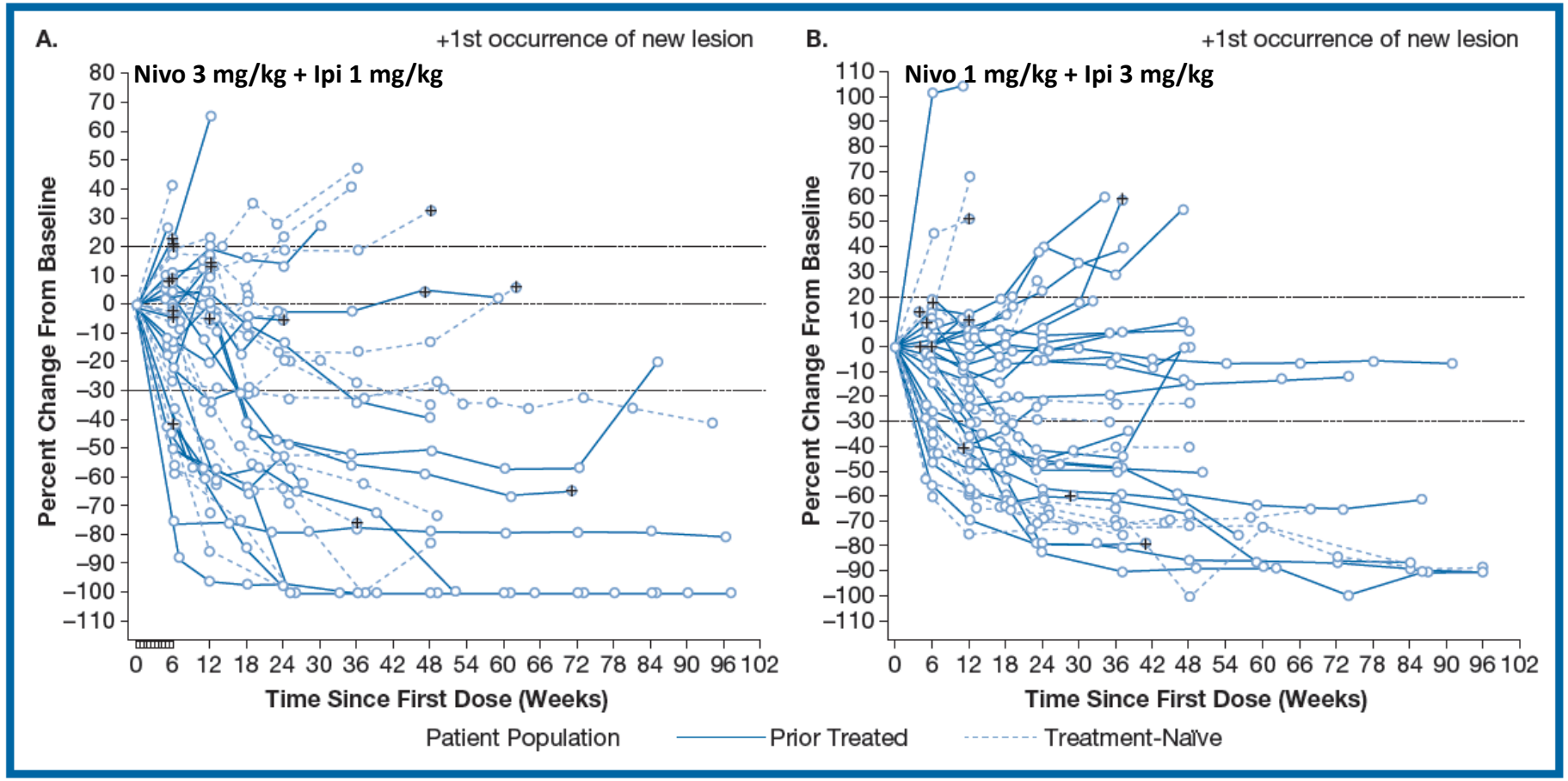



**Fig. 1** Distribution of mild and severe immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy. [Adapted from [88]]

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95

# PD-1 + CTLA-4 Blockade
# RCC Results: Tumor burden




Hammers et al, ASCO 2015

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbé, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, and J. Larkin

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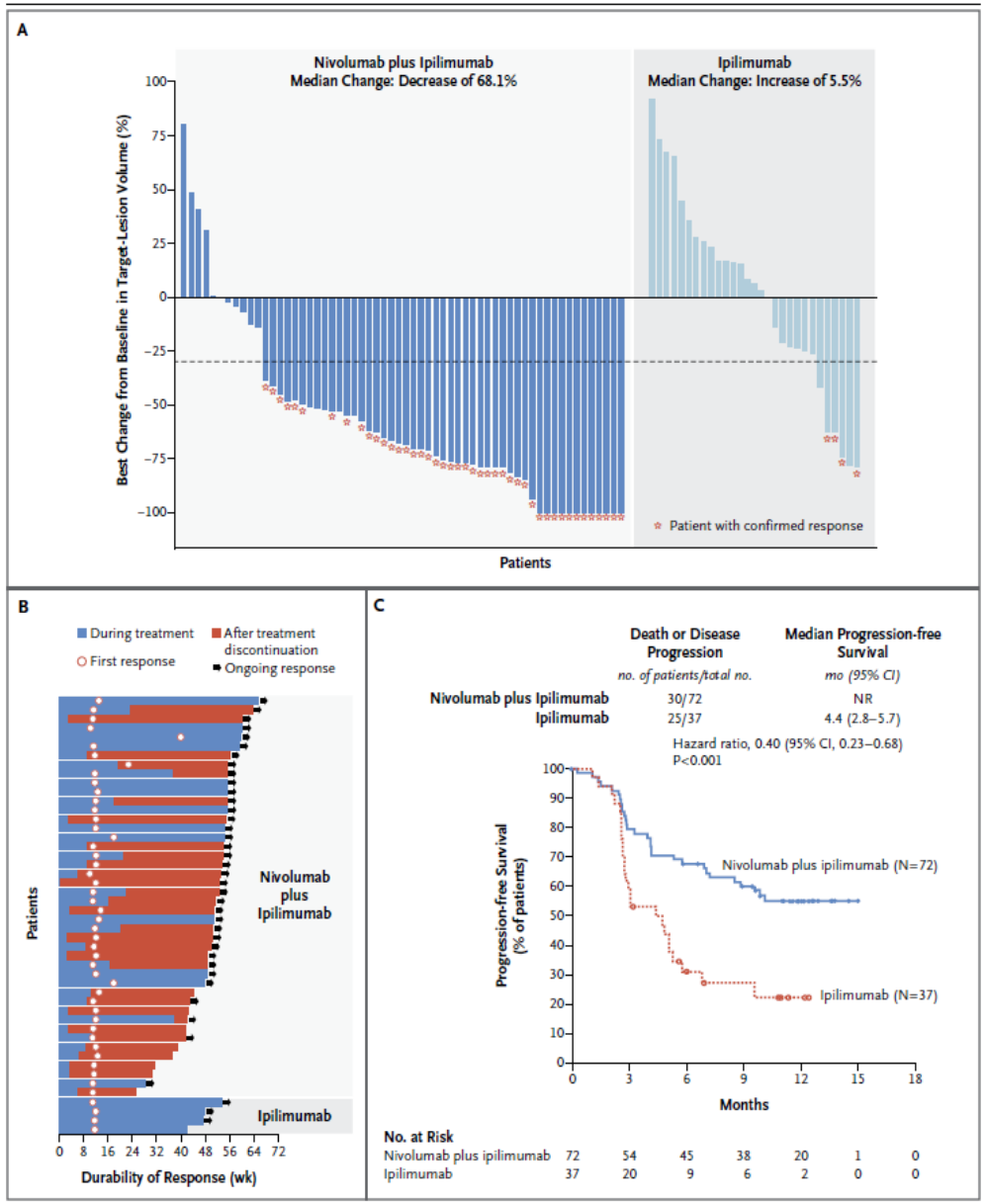
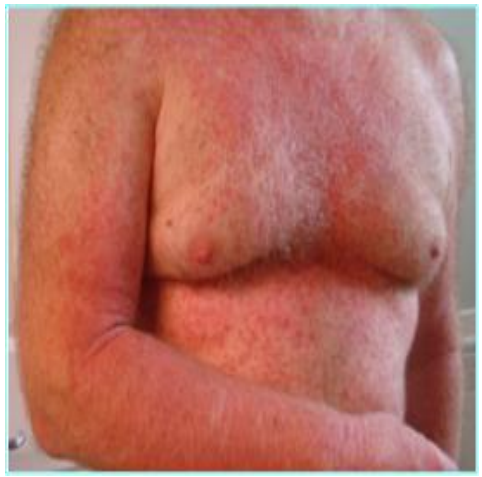
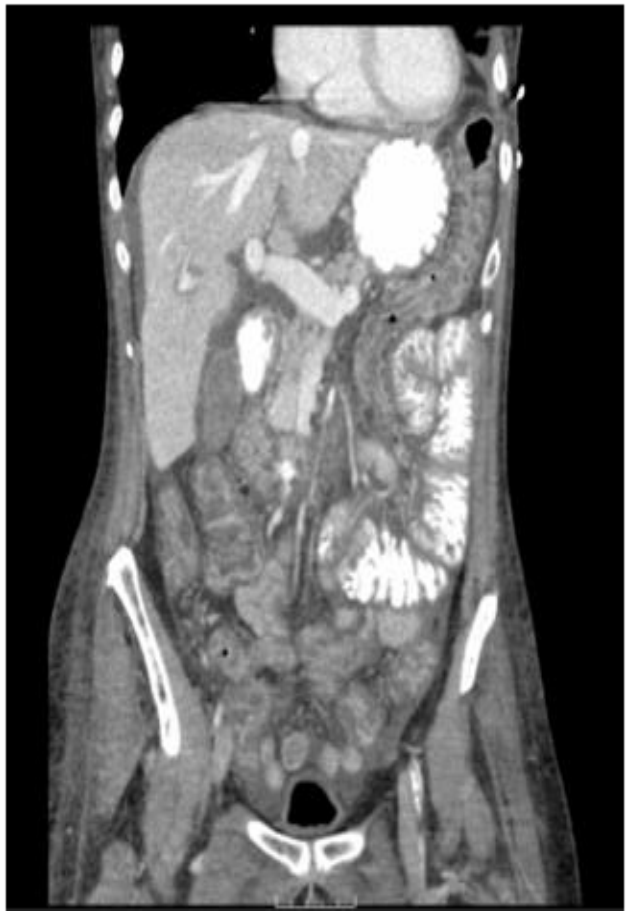

A
Nivolumab plus Ipilimumab
Median Change: Decrease of 68.1%
Ipilimumab
Median Change: Increase of 5.5%
Best Change from Baseline in Target-Lesion Volume (%)
100
75
50
25
0
−25
−50
−75
−100
Patient with confirmed response
Patients
B
During treatment
After treatment discontinuation
First response
Ongoing response
Nivolumab plus Ipilimumab
Ipilimumab
Patients
0 8 16 24 32 40 48 56 64 72
Durability of Response (wk)
C
Death or Disease Progression
Median Progression-free Survival
no. of patients/total no.
mo (95% CI)
Nivolumab plus Ipilimumab 30/72 NR
Ipilimumab 25/37 4.4 (2.8–5.7)
Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001
Progression-free Survival (% of patients)
100
90
80
70
60
50
40
30
20
10
0
Nivolumab plus ipilimumab (N=72)
Ipilimumab (N=37)
0 3 6 9 12 15 18
Months
No. at Risk
Nivolumab plus ipilimumab 72 54 45 38 20 1 0
Ipilimumab 37 20 9 6 2 0 0

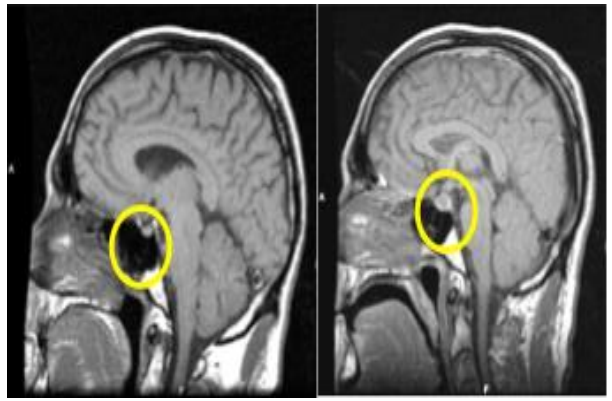
# Improving Immune Activation: The Consequences - CTLA4 Antibodies



Dermatitis

Colitis





Hypophysitis

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# Consequences Continued

**Table 2. Treatment-Related Adverse Events.***

| Event | Nivolumab plus Ipilimumab (N=313) | | Nivolumab (N=313) | | Ipilimumab (N=311) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients with event (percent)* | | | | | |
| Any treatment-related adverse event | 300 (96) | 184 (59) | 270 (86) | 67 (21) | 268 (86) | 86 (28) |
| Rash | 93 (30) | 10 (3) | 72 (23) | 1 (<1) | 68 (22) | 5 (2) |
| Pruritus | 112 (35) | 6 (2) | 67 (21) | 1 (<1) | 113 (36) | 1 (<1) |
| Vitiligo | 28 (9) | 0 | 29 (9) | 1 (<1) | 16 (5) | 0 |
| Maculopapular rash | 38 (12) | 6 (2) | 15 (5) | 2 (1) | 38 (12) | 1 (<1) |
| Fatigue | 119 (38) | 13 (4) | 114 (36) | 3 (1) | 89 (29) | 3 (1) |
| Asthenia | 30 (10) | 1 (<1) | 25 (8) | 1 (<1) | 17 (5) | 2 (1) |
| Pyrexia | 60 (19) | 2 (1) | 21 (7) | 0 | 21 (7) | 1 (<1) |
| Diarrhea | 142 (45) | 29 (9) | 67 (21) | 9 (3) | 105 (34) | 18 (6) |
| Nausea | 88 (28) | 7 (2) | 41 (13) | 0 | 51 (16) | 2 (1) |
| Vomiting | 48 (15) | 7 (2) | 22 (7) | 1 (<1) | 24 (8) | 1 (<1) |
| Abdominal pain | 26 (8) | 1 (<1) | 18 (6) | 0 | 28 (9) | 2 (1) |
| Colitis | 40 (13) | 26 (8) | 7 (2) | 3 (1) | 35 (11) | 24 (8) |
| Headache | 35 (11) | 2 (1) | 24 (8) | 0 | 25 (8) | 1 (<1) |
| Arthralgia | 43 (14) | 2 (1) | 31 (10) | 1 (<1) | 22 (7) | 0 |
| Increased lipase level | 44 (14) | 34 (11) | 27 (9) | 14 (4) | 18 (6) | 12 (4) |
| Increased amylase level | 26 (8) | 9 (3) | 20 (6) | 6 (2) | 15 (5) | 4 (1) |
| Increased aspartate aminotransferase level | 51 (16) | 19 (6) | 14 (4) | 3 (1) | 12 (4) | 2 (1) |
| Increased alanine aminotransferase level | 60 (19) | 27 (9) | 13 (4) | 4 (1) | 12 (4) | 5 (2) |
| Decreased weight | 19 (6) | 0 | 10 (3) | 0 | 4 (1) | 1 (<1) |
| Hypothyroidism | 53 (17) | 1 (<1) | 33 (11) | 0 | 14 (5) | 0 |
| Hyperthyroidism | 35 (11) | 3 (1) | 14 (4) | 0 | 3 (1) | 0 |
| Hypophysitis | 23 (7) | 5 (2) | 2 (1) | 1 (<1) | 12 (4) | 5 (2) |
| Decreased appetite | 60 (19) | 4 (1) | 36 (12) | 0 | 41 (13) | 1 (<1) |
| Cough | 25 (8) | 0 | 19 (6) | 2 (1) | 15 (5) | 0 |
| Dyspnea | 36 (12) | 3 (1) | 19 (6) | 1 (<1) | 12 (4) | 0 |
| Pneumonitis | 22 (7) | 3 (1) | 5 (2) | 1 (<1) | 5 (2) | 1 (<1) |
| Treatment-related adverse event leading to discontinuation | 123 (39) | 95 (30) | 37 (12) | 24 (8) | 49 (16) | 43 (14) |

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**Table 4. Select Adverse Events and Their Management with Immunomodulatory Medication (IMM), According to Organ Category.**

| Organ Category | Nivolumab plus Ipilimumab (N=94) | | | | Ipilimumab (N=46) | | | |
|---|---|---|---|---|---|---|---|---|
| | Reported Adverse Event | Treatment with IMM | Resolution of Event after Treatment with IMM | Median Time to Resolution | Reported Adverse Event | Treatment with IMM | Resolution of Event after Treatment with IMM | Median Time to Resolution |
| | *no. of patients* | *no. of patients/total no. (%)* | | *wk (95% CI)* | *no. of patients* | *no. of patients/total no. (%)* | | *wk (95% CI)* |
| Skin | | | | | | | | |
| Any grade | 67 | 41/67 (61) | 24/35 (69) | 18.6 (9.3–35.1) | 26 | 13/26 (50) | 11/13 (85) | 8.6 (3.3–22.0) |
| Grade 3 or 4 | 9 | 9/9 (100) | 8/9 (89) | 6.1 (0.9–24.1) | 0 | 0 | 0 | NE |
| Gastrointestinal | | | | | | | | |
| Any grade | 48 | 31/48 (65) | [illegible] | 4.7 (3.0–6.7) | 17 | 11/17 (65) | 7/9 (78) | 5.0 (1.4–12.1) |
| Grade 3 or 4 | 20 | 17/20 (85) | 15/17 (88) | 4.3 (1.4–10.7) | 5 | 5/5 (100) | 4/5 (80) | 3.6 (0.7–5.0) |
| Endocrine† | | | | | | | | |
| Any grade | 32 | 14/32 (44) | 2/14 (14) | NE (NE–NE) | 8 | 3/8 (38) | 1/3 (33) | NE (0.9–NE) |
| Grade 3 or 4 | 5 | 4/5 (80) | 1/4 (25) | NE (5.6–NE) | 2 | 2/2 (100) | 1/2 (50) | NE (0.9–NE) |
| Hepatic | | | | | | | | |
| Any grade | 26 | 13/26 (50) | 11/13 (85) | 14.1 [illegible] | 2 | 0/2 | 0 | NE |
| Grade 3 or 4 | 14 | 12/14 (86) | 10/12 (83) | 8.3 (2.1–14.1) | 0 | 0 | 0 | NE |
| Pulmonary | | | | | | | | |
| Any grade | 11 | 8/11 (73) | 6/8 (75) | 6.1 (0.3–9.0) | 2 | 2/2 (100) | 2/2 (100) | 3.2 (2.9–3.6) |
| Grade 3 or 4 | 3 | 3/3 (100) | 2/3 (67) | 9.0 (0.3–9.0) | 1 | 1/1 (100) | 1/1 (100) | 3.6 (NE–NE) |
| Renal | | | | | | | | |
| Any grade | 3 | 2/3 (67) | 2/2 (100) | 0.4 (0.3–0.6) | 1 | 0/1 | 0 | NE |
| Grade 3 or 4 | 1 | 1/1 (100) | 1/1 (100) | 0.6 (NE–NE) | 0 | 0 | 0 | NE |

# Anti-CTLA4 dosing and tolerability

| | Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks (n=38) | | | Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (n=39) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| Any event | 17 (45%) | 13 (34%) | 1 (3%) | 15 (38%) | 11 (28%) | 2 (5%) |
| Pruritus | 9 (24%) | 0 | 0 | 5 (13%) | 0 | 0 |
| Diarrhoea | 7 (18%) | 1 (3%) | 0 | 8 (21%) | 0 | 0 |
| Nausea | 6 (16%) | 0 | 0 | 5 (13%) | 1 (3%) | 0 |
| Fatigue | 5 (13%) | 1 (3%) | 0 | 8 (21%) | 1 (3%) | 0 |
| Increased amylase | 5 (13%) | 1 (3%) | 0 | 0 | 0 | 0 |
| Maculopapular rash | 5 (13%) | 0 | 0 | 3 (8%) | 1 (3%) | 0 |
| Pyrexia | 5 (13%) | 0 | 0 | 2 (5%) | 0 | 0 |
| Rash | 5 (13%) | 1 (3%) | 0 | 3 (8%) | 1 (3%) | 0 |
| Arthralgia | 4 (11%) | 0 | 0 | 0 | 0 | 0 |
| Decreased appetite | 4 (11%) | 0 | 0 | 5 (13%) | 0 | 0 |
| Anaemia | 3 (8%) | 0 | 0 | 2 (5%) | 1 (3%) | 0 |
| Increased lipase | 3 (8%) | 2 (5%) | 1 (3%) | 0 | 0 | 0 |
| Dyspnoea | 2 (5%) | 1 (3%) | 0 | 0 | 0 | 0 |
| Pneumonitis | 2 (5%) | 2 (5%) | 0 | 1 (3%) | 1 (3%) | 0 |
| Vomiting | 2 (5%) | 0 | 0 | 2 (5%) | 1 (3%) | 0 |
| Acute kidney injury | 1 (3%) | 1 (3%) | 0 | 0 | 0 | 0 |
| Increased alanine aminotransferase | 1 (3%) | 0 | 0 | 0 | 1 (3%) | 0 |
| Increased aspartate aminotransferase | 1 (3%) | 0 | 0 | 0 | 1 (3%) | 0 |
| Increased blood creatinine | 1 (3%) | 1 (3%) | 0 | 3 (8%) | 0 | 0 |
| Pancreatitis | 1 (3%) | 1 (3%) | 0 | 0 | 0 | 0 |
| Reduced lymphocyte count | 1 (3%) | 1 (3%) | 0 | 1 (3%) | 0 | 0 |

Hellman et. al Lancet Oncology 2017; 18:31-41

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# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - Will rare but serious toxicities occur?
  - Will late toxicity emerge?
  - Will certain toxicities make combinations difficult?
  - **Will history of autoimmunity limit application?**

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ADVANCES IN Cancer IMMUNOTHERAPY™

Original Investigation

# Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Douglas B. Johnson, MD; Ryan J. Sullivan, MD; Patrick A. Ott, MD, PhD; Matteo S. Carlino, MBBS; Nikhil I. Khushalani, MD; Fei Ye, PhD; Alexander Guminski, MD, PhD; Igor Puzanov, MD; Donald P. Lawrence, MD; Elizabeth I. Buchbinder, MD; Tejaswi Mudigonda, BS; Kristen Spencer, DO; Carolin Bender, MD; Jenny Lee, MBBS; Howard L. Kaufman, MD; Alexander M. Menzies, MBBS; Jessica C. Hassel, MD; Janice M. Mehnert, MD; Jeffrey A. Sosman, MD; Georgina V. Long, MBBS; Joseph I. Clark, MD

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Original Investigation

# Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Table 2. Autoimmune Exacerbations and Grade 3 to 5 Immune-Related Adverse Events

| Patient No. | Baseline Condition | Autoimmune Exacerbation | Treatment | Immune-Related Adverse Event | Treatment | Outcome Notes |
|---|---|---|---|---|---|---|
| 2 | Sarcoidosis | ... | ... | Glaucoma | Ocular steroids | |
| 3 | RA | Joint pain | As for hypophysitis | Hypophysitis | Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg | Durable CR |
| 4 | RA | ... | ... | Thyroiditis | Prednisone 1 mg/kg tapered over 2 wk | |
| 5 | Psoriasis | Worsening plaques | As for colitis | Colitis | Methylprednisolone 2 mg/kg tapered over 6 wk | After 1 dose |
| 6 | Psoriasis, Graves disease | ... | ... | Hypophysitis | Prednisone 30 mg ×1 wk, transition to hydrocortisone over 5 d | PR |
| 8 | RA, polymyalgia rheumatica | Joint pain, myalgias | Prednisone 30 mg/d tapered over 1 mo | ... | ... | After 3 d |
| 9 | RA | Joint pain | Prednisone 15 mg/d down to 10 mg | ... | ... | After 7 mo |
| 11 | Transverse myelitis | ... | ... | Colitis | Prednisone 1 mg/kg tapered over 8 wk | |
| 12 | Crohn disease | ... | ... | Colitis | Methylprednisolone 1 mg/kg tapered over 8 wk | After 1 dose |
| 14 | Ulcerative colitis | Diarrhea, disease flare | Infliximab, dexamethasone 2 mg daily[a] | ... | ... | PR |
| 15 | Inflammatory arthritis[b] | Joint pain | As for colitis | Colitis | Prednisone 1 mg/kg tapered over 4 wk, infliximab | ... |
| 20 | Psoriasis | ... | ... | Hypophysitis | Prednisone 50 mg ×1 dose, then 5 mg daily | ... |
| 23 | Sarcoidosis | Hypercalcemia, renal insufficiency | Prednisone 25 mg/d, tapered to 20 mg after 4 wk | ... | ... | Ongoing SD |
| 24 | RA | Joint pain | Prednisone 10 mg/d, now receiving 8 mg/d | ... | ... | Ongoing PR |
| 28 | Psoriasis | ... | ... | Presumed colitis grade 5 | Methylprednisolone 1 mg/kg | Patient died |

Abbreviations: CR, complete response; ellipses, none; PR, partial response; RA, rheumatoid arthritis; SD, stable disease.

[a] Receiving dexamethasone for brain metastases; infliximab was added with onset of diarrhea.

[b] Patient developed a chronic, inflammatory-appearing arthritis during nivolumab therapy that improved with use of low-dose steroids and hydroxychloroquine.

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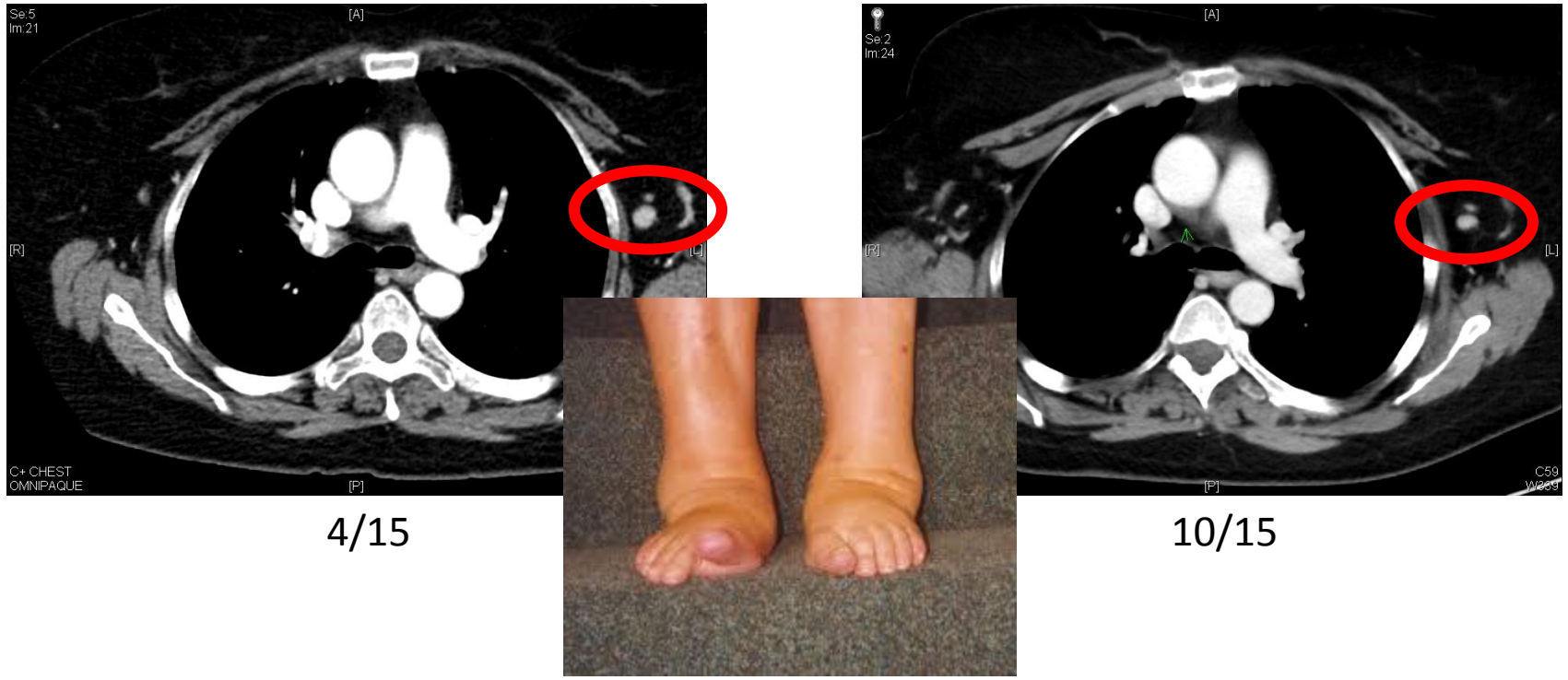
Johnson et al, JAMA Oncology 2015

# PD-1 Blockade in Patient with Autoimmune Disease




4/15

10/15

62 y.o. female, met melanoma, psoriatic arthritis S/P HD IL-2
4/15 - PD-1 (pembro) x 4 doses
7/15 – CTs = SD, PA flared, pembrolizumab held, rx – apremilast
10/15 – CT = MR, PA improved, plan = observation

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# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - **Not to the informed/vigilant**
  - Will rare but serious toxicities occur?
    - YES
  - Will late toxicity emerge?
    - YES
  - Will certain toxicities make combinations difficult?
    - Probably
  - Will history of autoimmunity limit application?
    - Yes, in some cases

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