# Incidence and Management of Toxicities Associated with Checkpoint Inhibitors; Autoimmune Contraindications to Treatment

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# Disclosure Information
# David F. McDermott, MD

I have the following financial relationships to disclose:

Consultant for: Merck, Bristol-Myers Squibb, Genentech, Pfizer, Exelixis, Novartis, Array Biopharma, Easai

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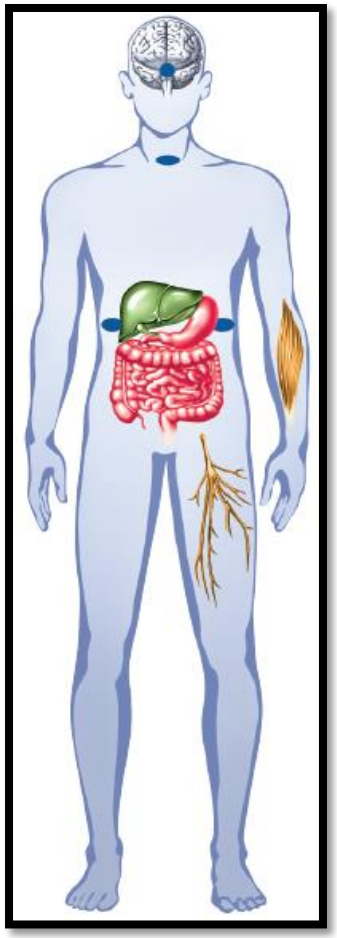
# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions in RCC

- Clinical
  - What is the proper duration of therapy?
  - How many responses are durable off therapy?
  - **Will toxicity management prove challenging?**
- Translational

# Toxicity with immunotherapy agents

Activation of the immune system against tumors can result in a novel spectrum of immune related Adverse Events (**irAEs**)[1]

- May be due to cytokine release by activated T cells[1]
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious[2]
- Requires prompt recognition and treatment[2]
- Requires patient and HCP education[3]



**irAEs occur in certain organ systems:[1]**

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

irAE = immune-related adverse event.

1. Amos SM, et al. *Blood*. 2011;118:499–509; 2. YERVOY immune-related adverse reactions management guide. October 2012. Available at https://www.yervoy.co.uk/Images/6682_IrAR%20management%20guide%20731EMEA12PM014.pdf. Accessed September 2014;
3. Chin K, et al. Poster presented at ESMO 2008 (abstr. 787P).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

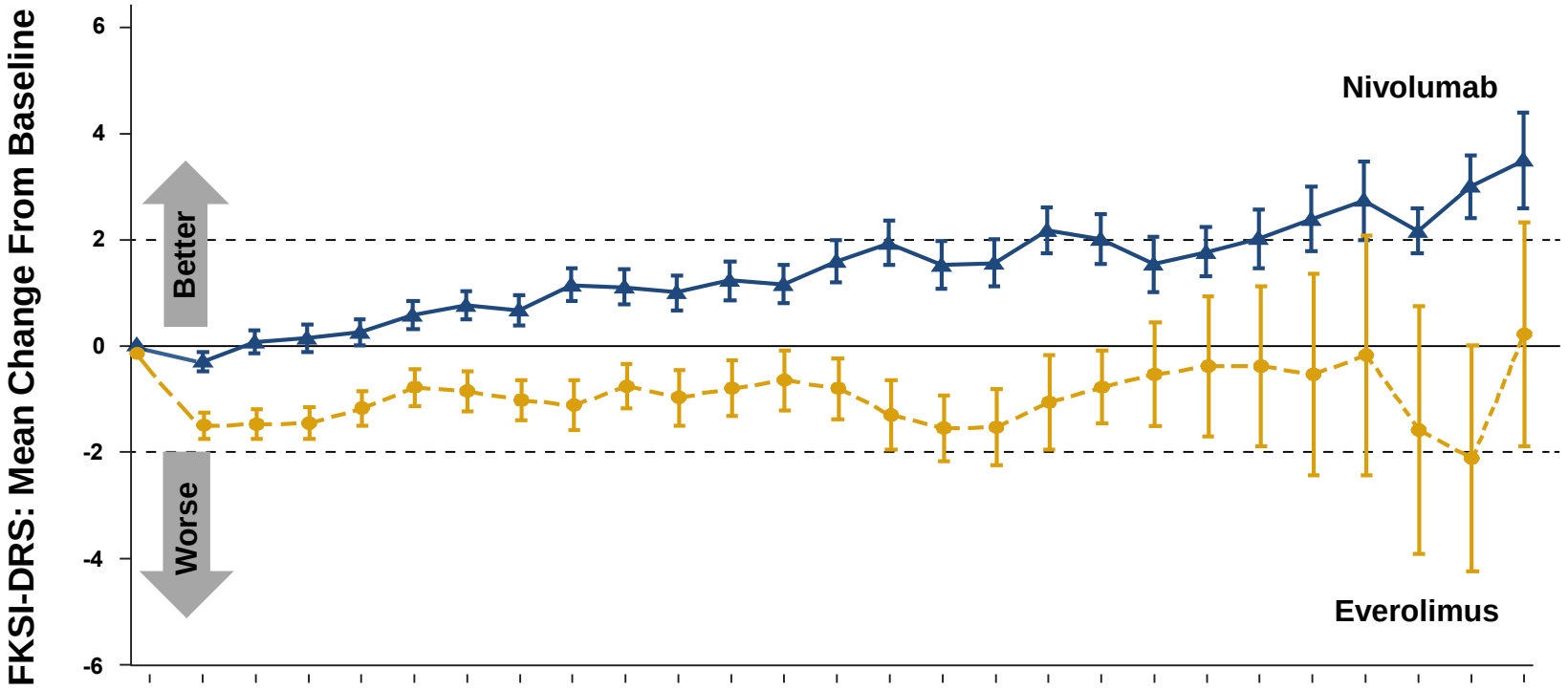
R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S.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

# 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 |

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

- A clinically meaningful and statistically significant improvement in QoL was seen with nivolumab versus everolimus for the duration of the study




No. of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 362 | 334 | 302 | 267 | 236 | 208 | 186 | 164 | 159 | 144 | 132 | 119 | 112 | 97 | 90 | 89 | 81 | 72 | 63 | 59 | 53 | 44 | 43 | 31 | 30 | 26 | 20 |
| Everolimus | 344 | 316 | 270 | 219 | 191 | 157 | 143 | 122 | 102 | 97 | 87 | 74 | 73 | 63 | 58 | 49 | 44 | 35 | 30 | 28 | 24 | 21 | 15 | 12 | 12 | 9 | 9 |

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

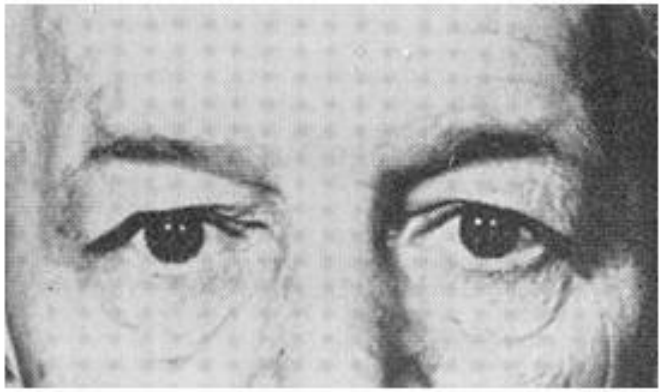
# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **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?

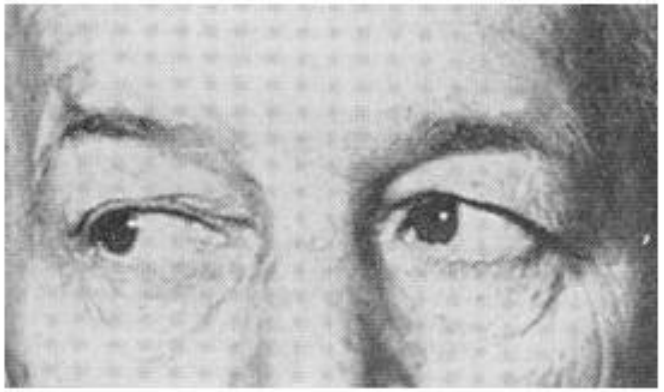
# Patient Case 1

- A 66-year-old male previously treated mRCC enrolled in a clinical trial of anti-PD-L1 Ab therapy
- Approximately 2 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.

"Look at me"



"Look to the right"



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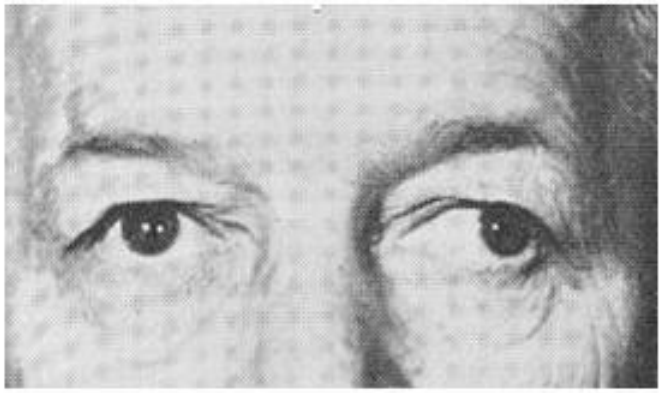
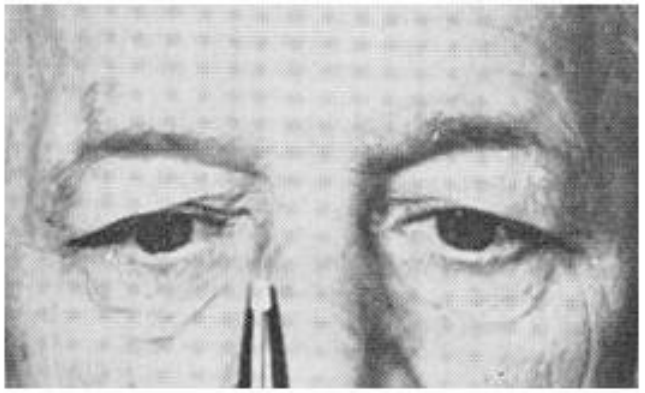


"Look at this object"



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

# Case Description: 65-Year-Old Male (continued)

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

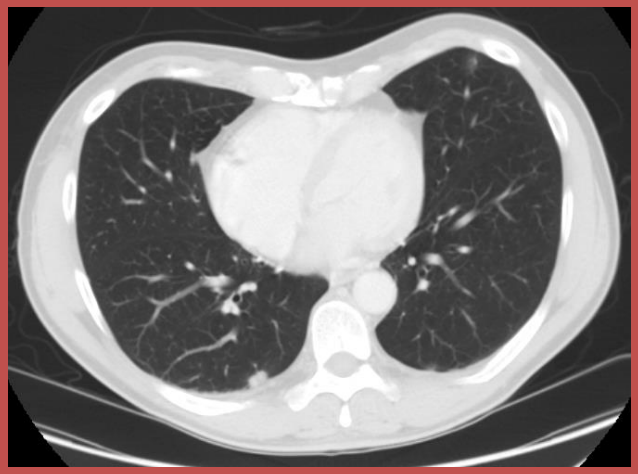
# Case Description: 65-Year-Old Male (continued)

- Neurologic symptoms resolved on steroids.
- Patient was taken off study, then developed disease progression 3 months later.
- Patient subsequently received VEGF TKI therapy.

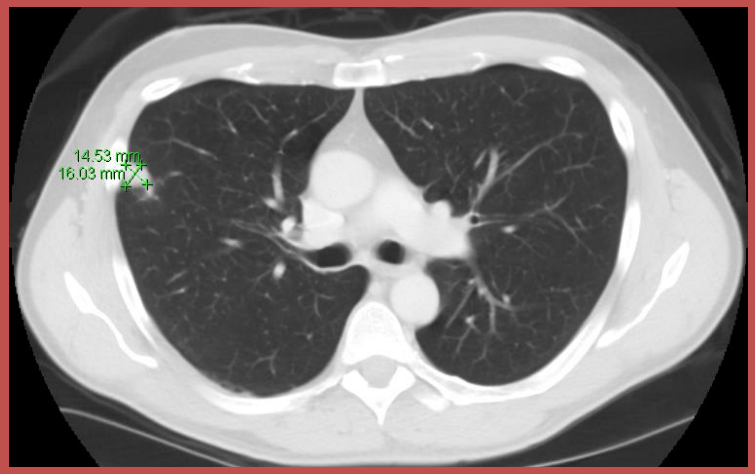
# Patient Case 2

- 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

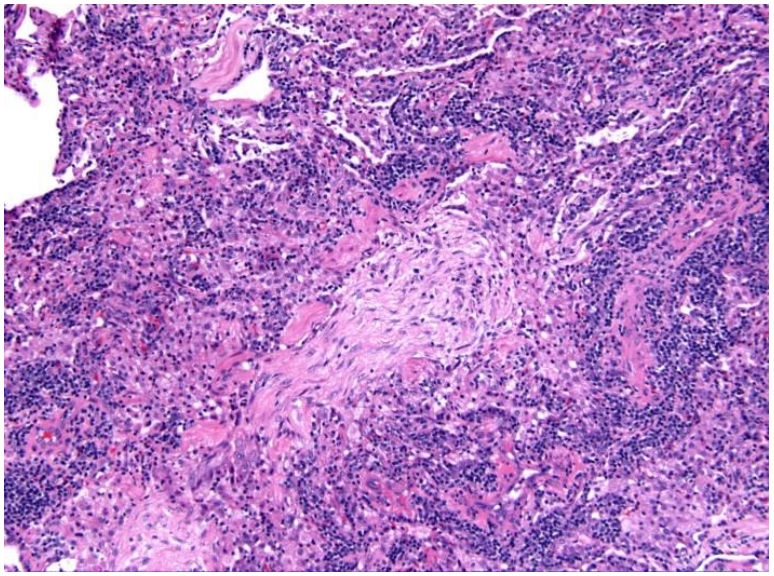


Subsequent Scan at Mo 8



# Patient Case

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



**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

# Patient Case

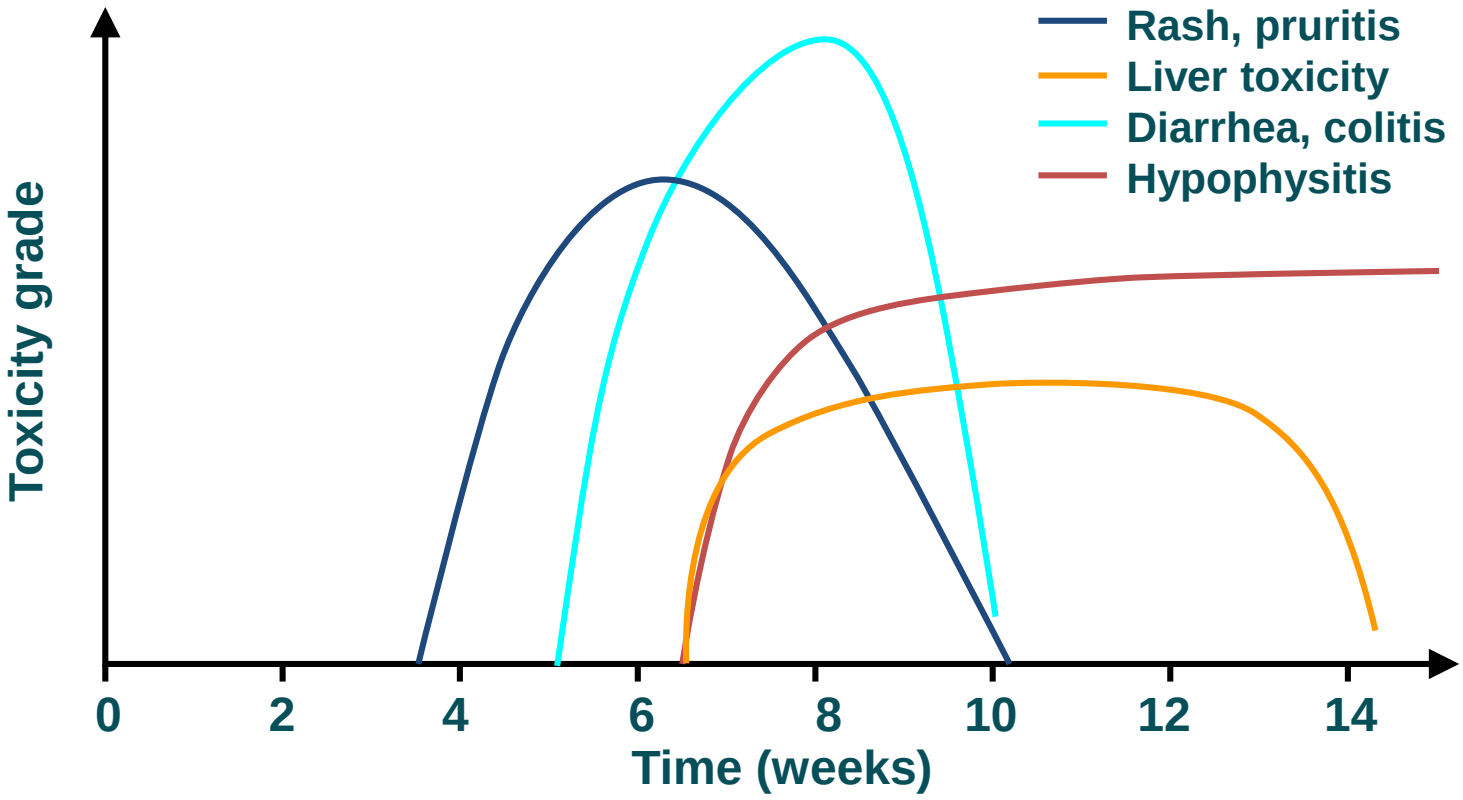
- Symptoms and lung lesions resolved with initiation of steroid therapy
- Nivolumab treatment was discontinued, and disease is currently stable off all therapy x 2 yrs

# 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?

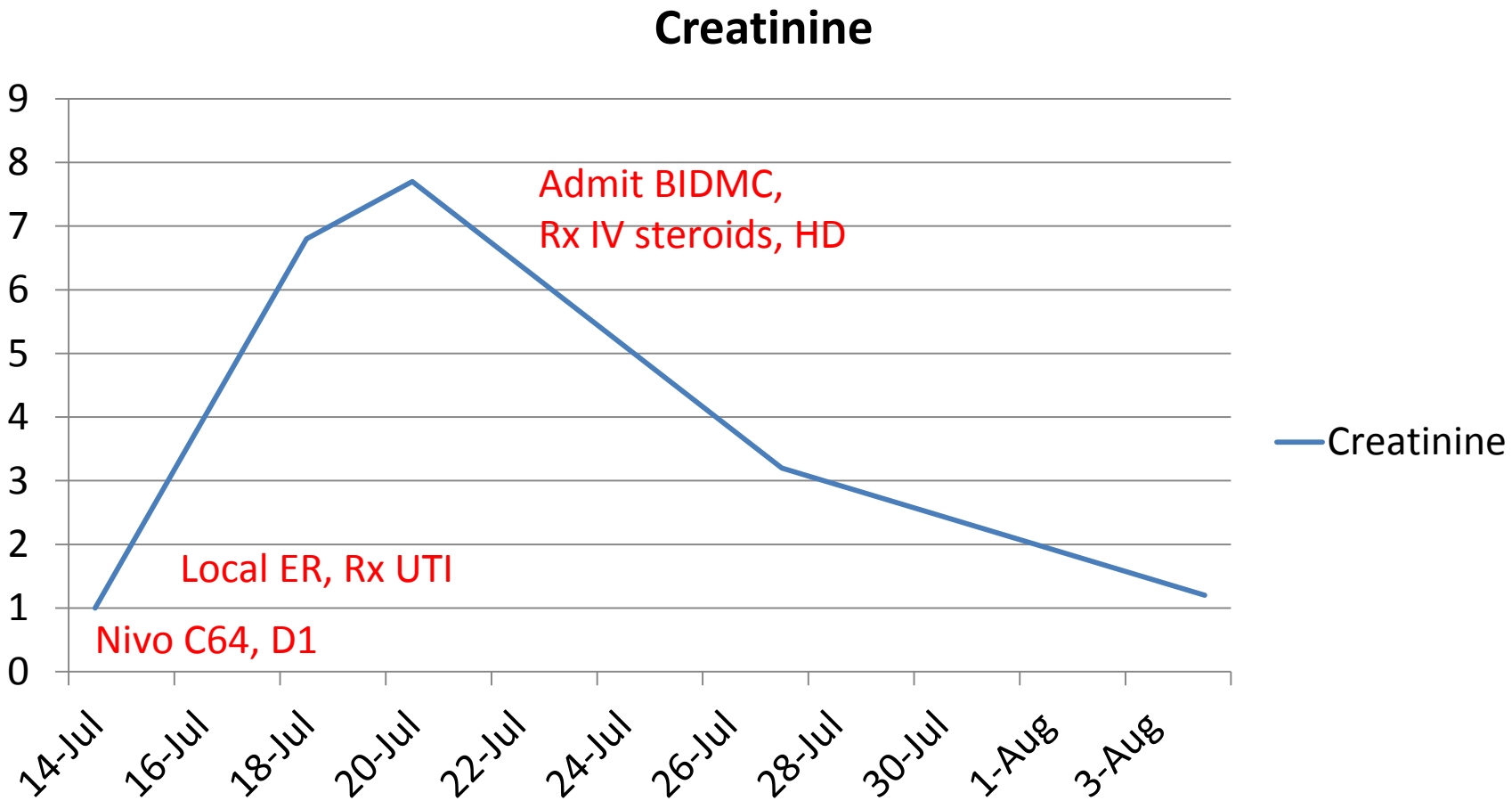
# Immune checkpoint inhibitors: immune-related adverse event (irAE) onset

- 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.

# Late PD-1 Toxicity?: Acute Renal Failure

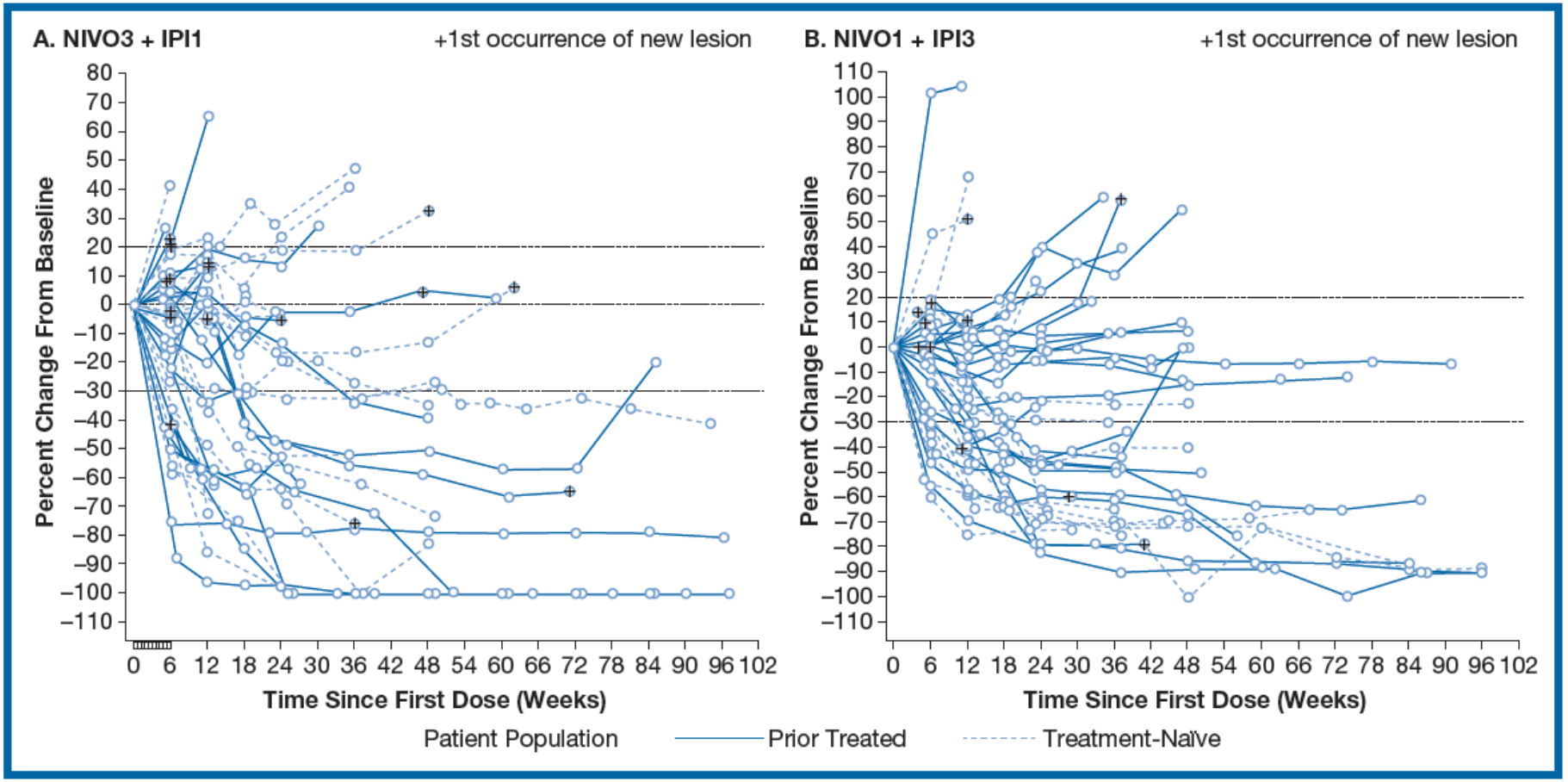



74 yo female, mRCC, s/p sunitinib, enrolled in Nivo P2 trial

# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

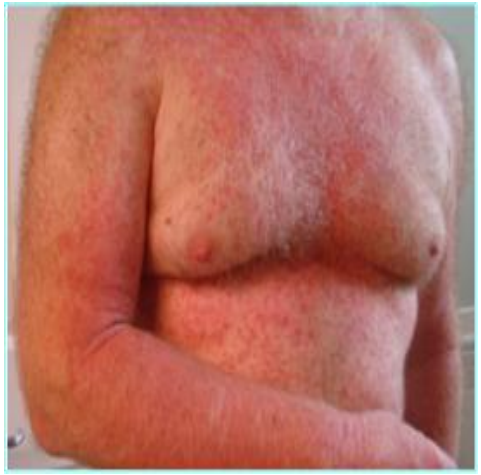
- **Will toxicity management prove challenging?**
  - Will rare but serious toxicities occur?
  - Will late toxicity emerge?
  - **Will certain toxicities make combinations difficult?**
    - (e.g. nephritis, hepatitis, pneumonitis)
  - Will history of autoimmunity limit application?

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



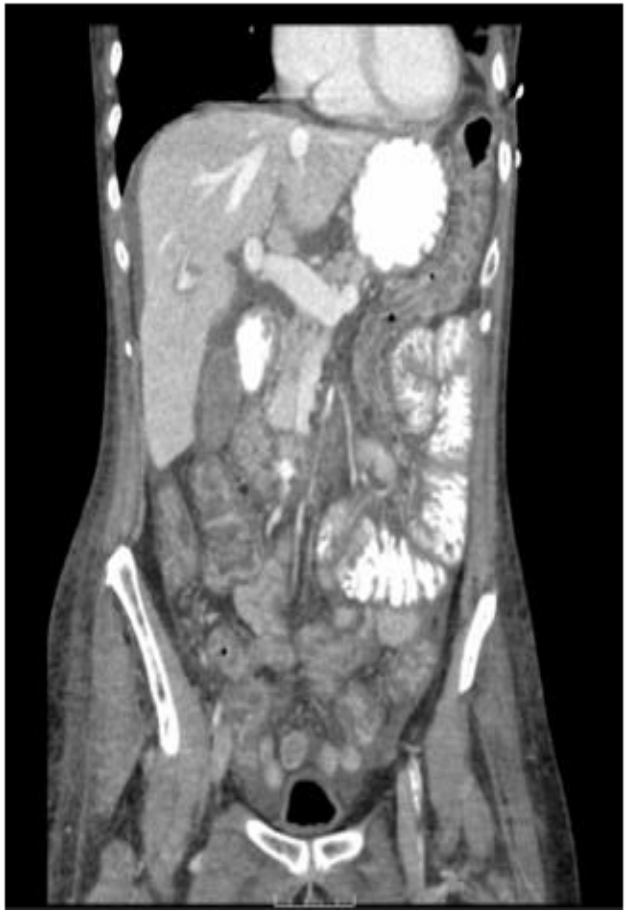

Hammers et al, ASCO 2015

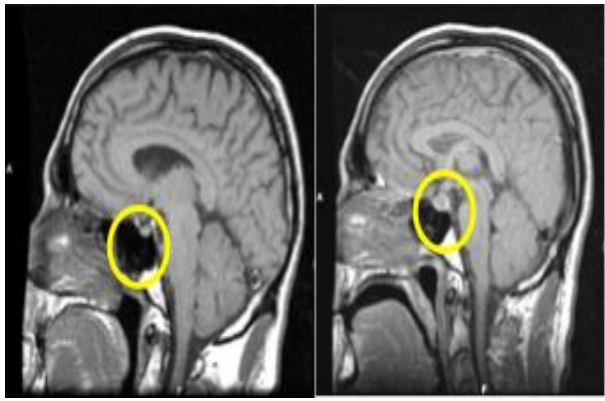
# Improving Immune Activation: The consequences-CTLA4 antibodies



Dermatitis

Colitis





Hypophysitis

**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 |

# 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?**

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

# 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 |

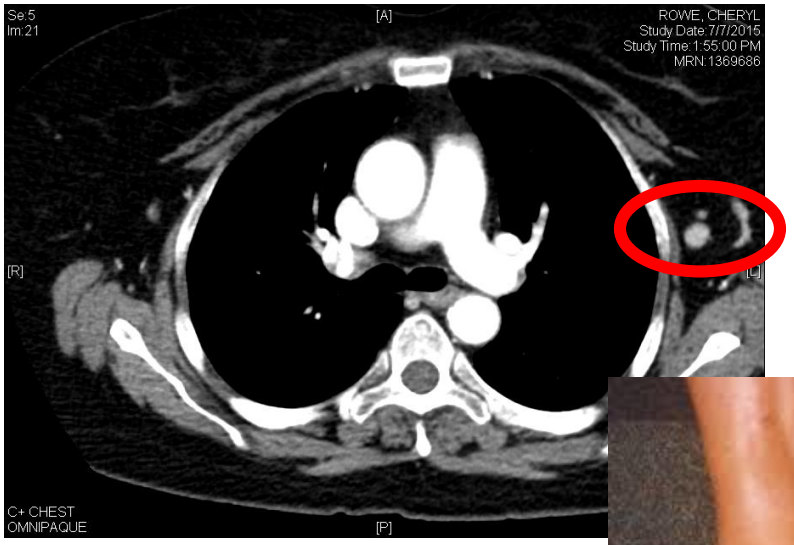
Abbreviations: CR, complete response; ellipses, none; PR, partial response; RA, rheumatoid arthritis; SD, stable disease.

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

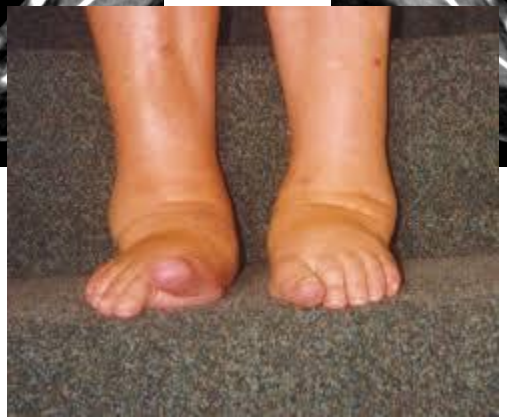
[b] Patient developed a chronic, inflammatory-appearing arthritis during nivolumab therapy that improved with use of low-dose steroids and hydroxychloroquine.

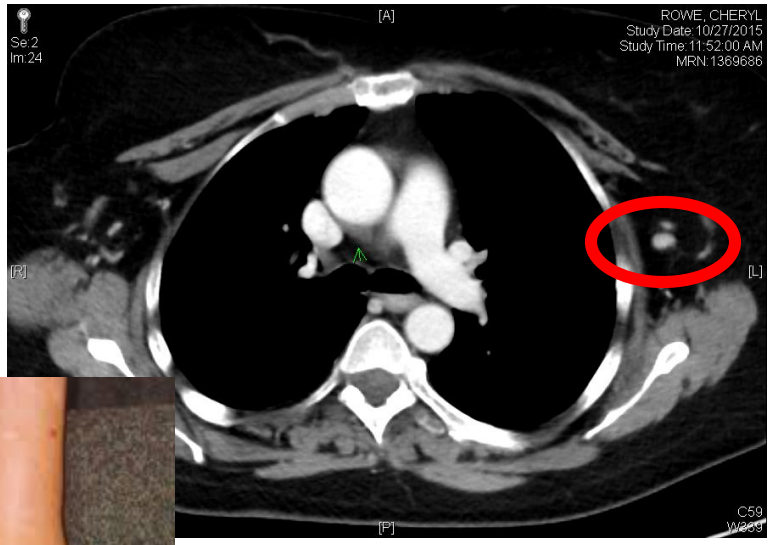
Johnson et al, JAMA Oncology 2015

# 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

# PD-1 Pathway Blockade Based ImmunoRx: Unanswered Questions

- **Will toxicity management prove challenging?**
  - **Not to the informed**
  - 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