41st Annual Carrell-Krusen Neuromuscular Symposium
Case Presentation

Not your Typical Necrotizing Myopathy

Sarita Said-Said, MD
Afra Janarious, MD
Nita Chen, MD
Mari Perez-Rosendahl, MD
Tahseen Mozaffar, MD FAAN

University of California Irvine

History

- A 77 year-old man was in his normal state of health until two weeks after his first chemotherapy treatment for his stage IV melanoma, given on July 18.
- He was active, ambulatory, and planning a trip to North Carolina.
- August 8: Three weeks later, he began to experience droopy eyelids and fatigue.
- August 9: Came to emergency department with elevated liver enzymes and complaints of droopy eyelids, difficulty walking without sensory changes or bowel/bladder dysfunction. Admitted for evaluation.
- August 10: Hypercapnic respiratory failure, intubation.

History

Past Medical/ Surgical History:

Stage IV melanoma: excised previously
Primary basal cell carcinoma.

Social History:

Denies tobacco, OH or illicit drug use

Family History:

Mother has Myasthenia Gravis.
Father had Alzheimer's dementia.
No history of malignancies.

Medications upon admission:

Amlodipine.
Aspirin.
Pembrolizumab (single dose).

Initial Physical Exam

- **MS:** Alert, oriented.
- **CN:** non-fatigable bilateral ptosis; facial diplegia, tongue weakness; soft voice with mild dysarthria.
- **Motor:**
  - Neck flexor 4-/5
  - MRC (right/left): deltoids (3/4), biceps (3/4), triceps (3/4), hip flexor (4/4), knee extensor (4/4), knee flexor (4/4), dorsiflexion (4/4), plantar flexion (4/4).
  - NL: tone, bulk.
- **Sensory:** normal.
- **DTRs:** 2+ throughout.
- **Gait:** ambulatory.

Studies

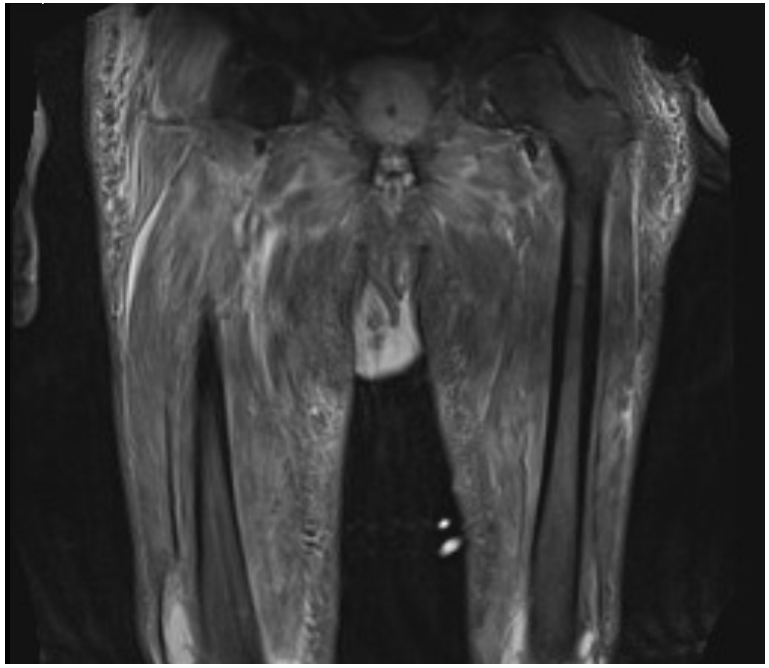
- AST 492 U/L, ALT 256 U/L, and **CPK 8284 U/L.**
- CXR (pre-intubation): normal
- CT head without contrast: normal.
- MRI of brain: negative for ischemia.
- PET/CT (a month prior):
    - FDG avid nodules in left forearm consistent with recurrent neoplasm. Widespread metastases.
    - FDG osseous lesion left tibia and right distal femur concerning for additional osseous metastases.

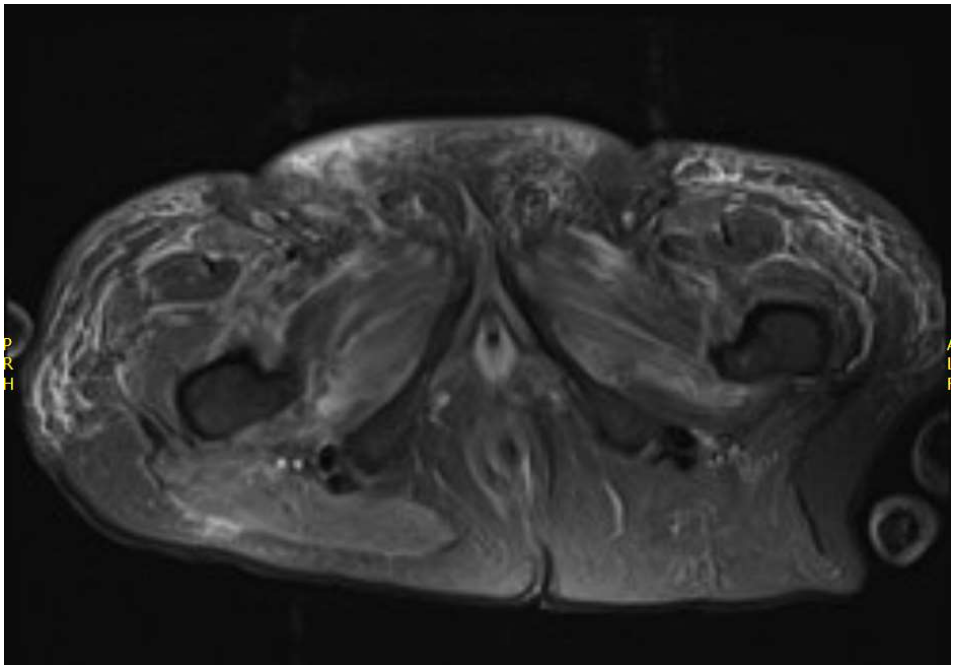
Differential?

What would you do?

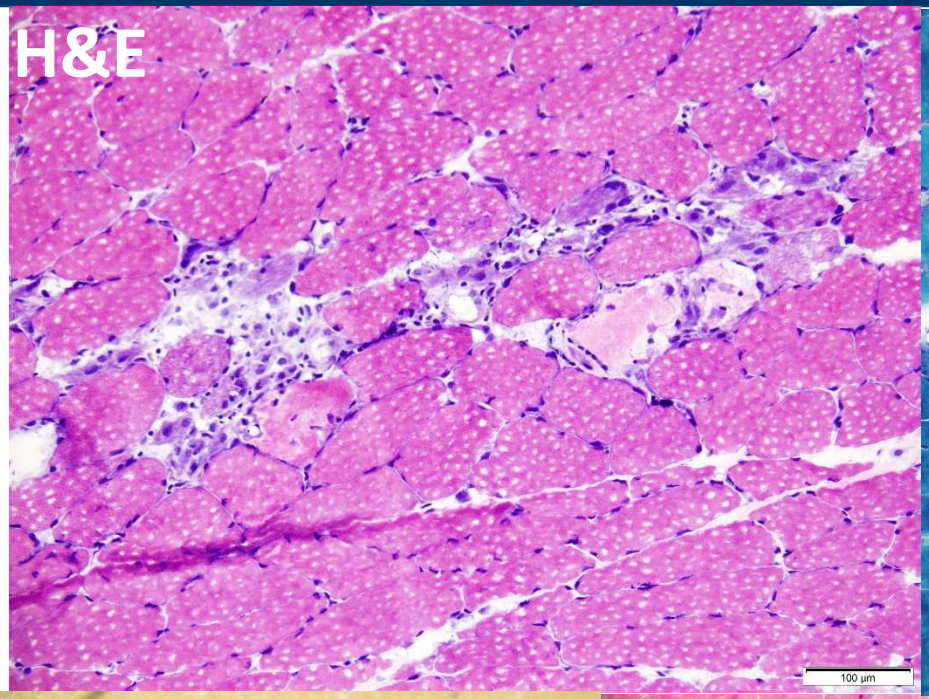
Interventions and other results

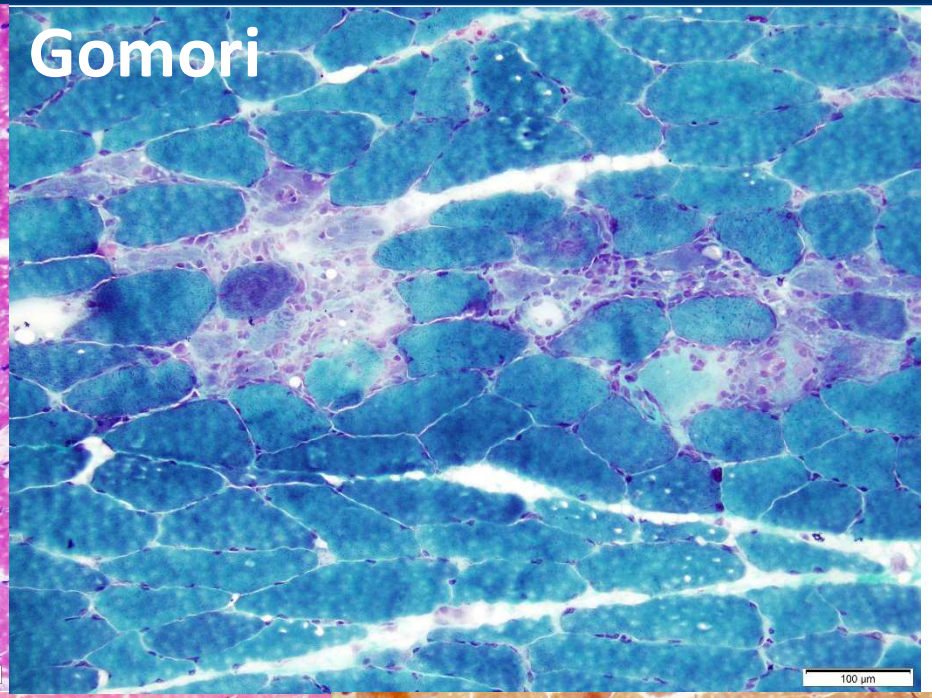
- AchR binding, blocking and modulating Abs: negative/normal.
- Myositis panel: MDA-5.
- Striated muscle Ab: 1:480
- MRI of the femur without contrast, bilateral:

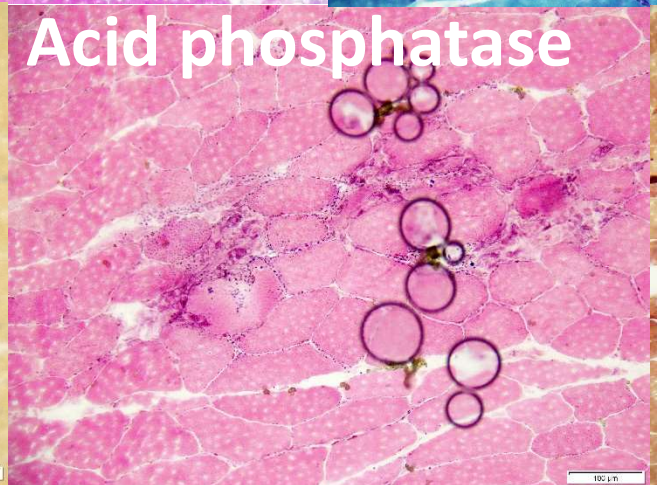


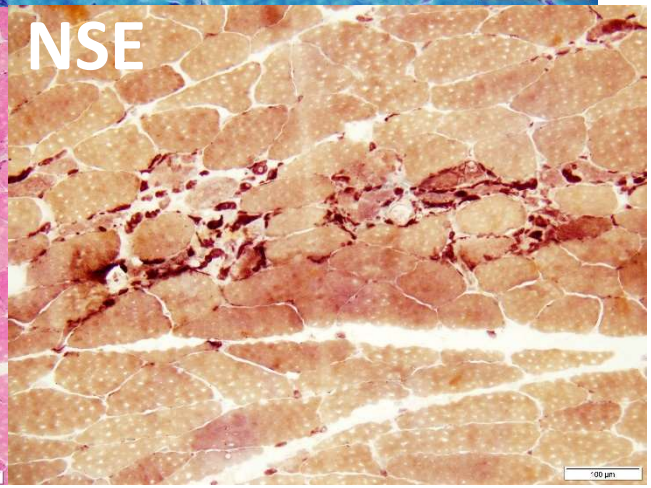


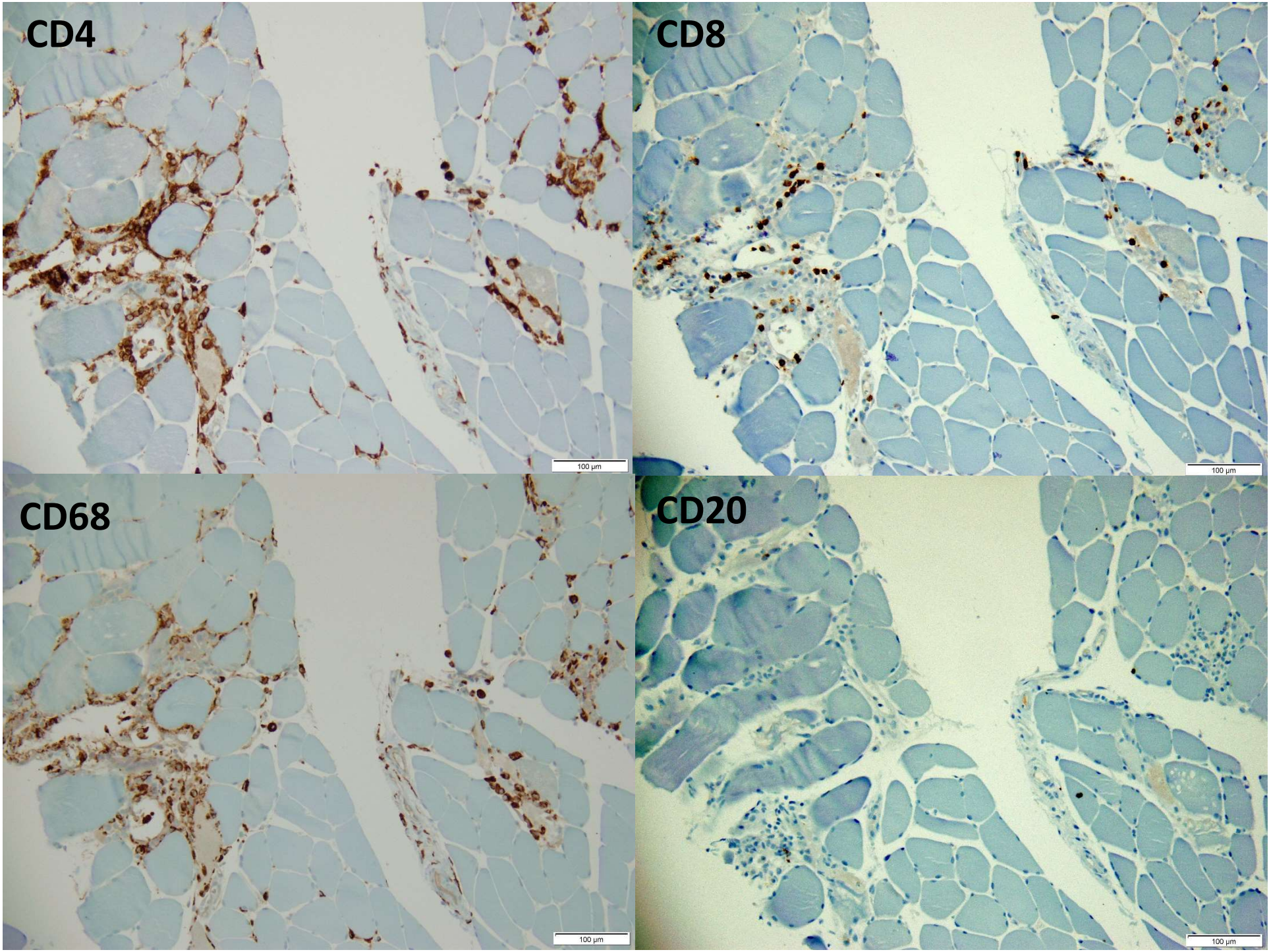
Muscle biopsy of the right vastus lateralis










CD4
CD8
CD68
CD20
100 µm
100 µm
100 µm
100 µm

Pembrolizumab-induced Autoimmune Necrotizing Myopathy

Management in hospital:

- Started combined therapy:
  - IV Ig 2g/kg over 5 days, and
  - IV methylprednisolone 1000mg daily for 6 days → prednisone 60mg

Outcomes:

- Labs, by day 5 of treatment: AST 36 U/L, ALT 130 U/L, CK 314.
- Slow improvement in strength, but admission complicated by Pseudomonas septicemia.
- At discharge (2 months later): G-tube for severe dysphagia, could stand momentarily, mRS 4.

Pembrolizumab-induced Autoimmune Necrotizing Myopathy

Teaching Points

Programmed cell death 1 (PD-1) is a immune check point in charge of maintaining self-tolerance and preventing uncontrolled inflammation.

PD-1 inhibitors unleash the immune response to tumors

They are among a class called autoimmune checkpoint inhibitors.

	Drugs	Cancer
PD-1 inhibitor	• **Pembrolizumab (Keytruda)** • **Nivolumab (Opdivo)** • **Cemiplimab (Libtayo)**	Melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Hodgkin lymphoma
PD-L1 inhibitor	• **Atezolizumab (Tecentriq)** • **Avelumab (Bavencio)** • **Durvalumab (Imfinzi)**	Bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma)

Pembrolizumab-induced Autoimmune Necrotizing Myopathy

- Autoimmune checkpoint inhibitors can cause various **immune related adverse events**.
- Most common adverse events affect the skin and GI tract (esophaghitis, gastritis, enteritis, colitis). Endocrine dysfunction has also been described.
- Neurologic complications are less frequent but reported in 3% of patients treated with PD-1 inhibitors. These can include seizure, polyneuropathy, headache, and myopathy.

Pembrolizumab-induced Autoimmune Necrotizing Myopathy

- In the case of myopathy, weakness evolves after 1-4 cycles
- Maximum severity 8-30 days after treatment
- Pattern: oculo-bulbar involvement common with proximal muscle weakness
- Laboratory evaluation reveals high CK, can find positive AChR antibodies in absence of RNS and single fiber abnormalities.
- We emphasize the importance of muscle biopsy in confirming diagnosis.

Pembrolizumab-induced Autoimmune Necrotizing Myopathy

Management:

- Discontinuation of the immune checkpoint inhibitor.
- Aggressive treatment: High dose intravenous steroids.
- IVIg or Plasma exchange can be added to steroids is most severe cases.

References

1. Touat, M., et al., *Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer.* Neurology, 2018. **91**(10): p. e985-e994.
2. American Cancer Society. “Immune checkpoint inhibitors to treat cancer”. Accessed at https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html on February 14, 2019.
3. Hartley, G.P., et al., *Programmed Cell Death Ligand 1 (PD-L1) Signaling Regulates Macrophage Proliferation and Activation.* Cancer Immunol Res, 2018. **6**(10): p. 1260-1273.
4. Haddox, C.L., et al., *Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm.* Ann Oncol, 2017. **28**(3): p. 673-675.
5. Liewluck, T., J.C. Kao, and M.L. Mauermann, *PD-1 Inhibitor-associated Myopathies: Emerging Immune-mediated Myopathies.* J Immunother, 2018. **41**(4): p. 208-211.
6. Zimmer, L., et al., *Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy.* Eur J Cancer, 2016. **60**: p. 210-25.

Thank You!