



Cardiac issues related to checkpoint inhibitors

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Conflicts of Interest disclosures for Michael S Ewer

- **Book royalties**
 - Cancer and the Heart
 - Ethical Challenges in Cancer Patients
- **Consultancies**
 - AstraZeneca
 - Bayer
 - Pharmacyclics
- **Character Actor—Houston Grand Opera**



Some basic concepts regarding checkpoint inhibitors

- **Programmed death (PD)**
 - **Programmed cell death** → cell death mediated by a program within the cell
- Programmed death-1 (PD-1) is a cell-surface immune checkpoint receptor on cytotoxic T cells.
 - Down-regulates the immune system
 - Promotes self tolerance by suppressing inflammatory activity.
- The PD-1 receptor has two ligands, programmed death ligand-1 and 2 (PD-L1 and PD-L 2)
- Upregulation of the PD-1 receptor plays a key role in the debilitating process of T-cell exhaustion, as well as being an important factor during the normal immune response to prevent autoimmunity.



Some basic concepts regarding checkpoint inhibitors

- Programmed death-1 (PD-1) prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells
- If we inhibit the ability to down-regulate the immune system (PD-1 inhibitors activate the immune system)
 - Inflammatory activity is enhanced, and →
 - Allows the immune system to attack tumors,
- Inhibitors are therefore used with varying success to treat some types of cancer

Some Checkpoint Inhibitors:

➡ Nivolumab (Opdivo)

- ➡ Acts by blocking a negative regulator of T-cell activation and response, thus allowing the immune system to attack the tumor;
 - ➡ Melanoma, non-small cell lung, renal cell

➡ Pembrolizumab (Keytruda)

- ➡ Targets the programmed cell death 1 (PD-1) receptor of lymphocytes
- ➡ Initially approved it to treat metastatic melanoma; now approved for any unresectable or metastatic solid tumor
 - ➡ First FDA approval based on tumor genetics rather than tissue type or tumor site

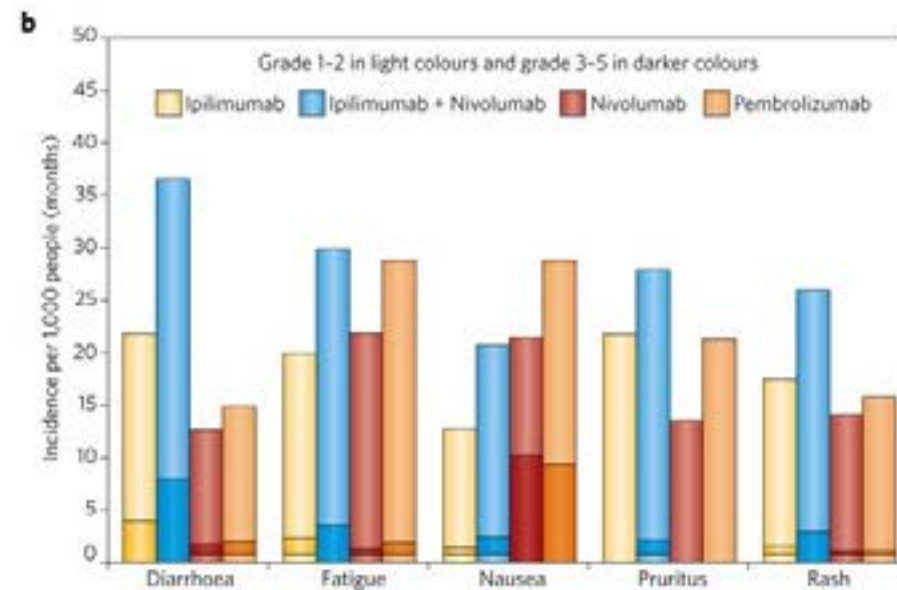
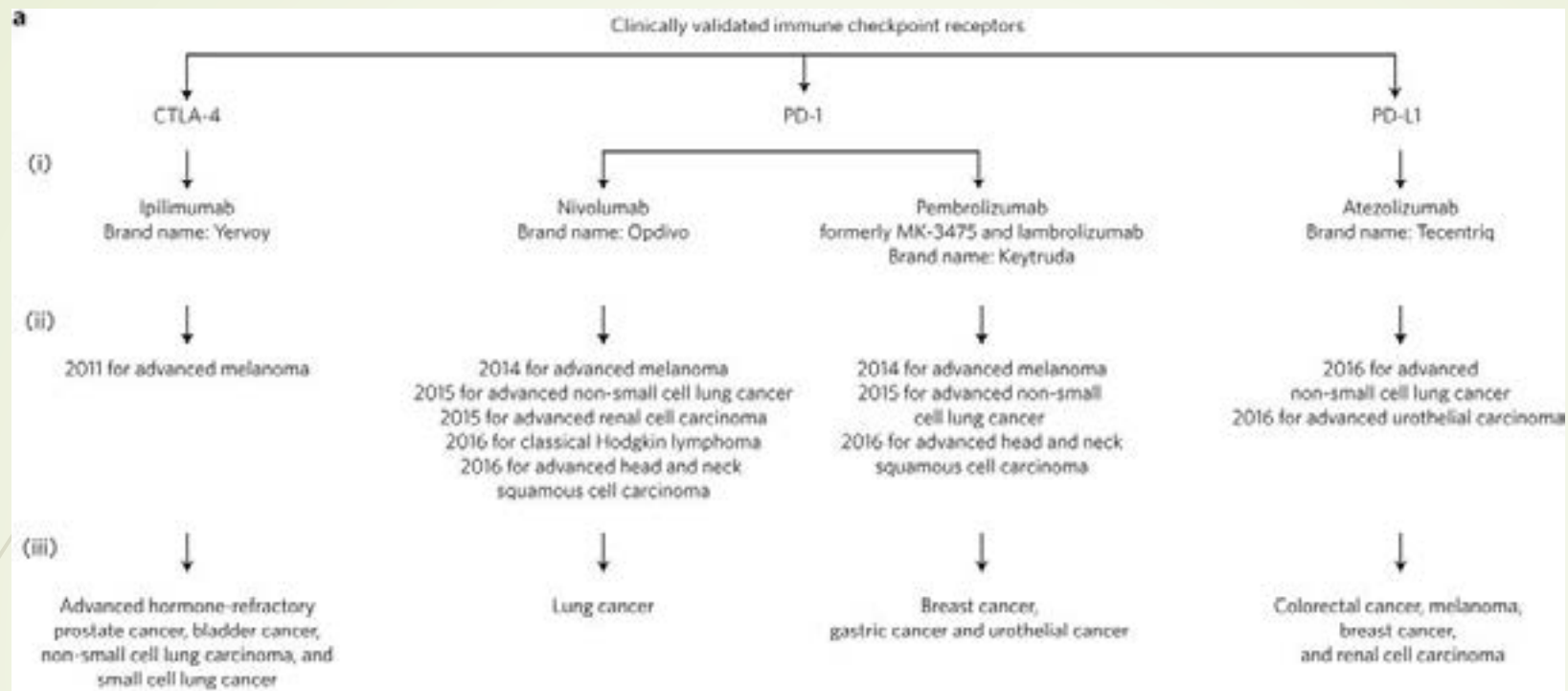
Some Checkpoint Inhibitors:

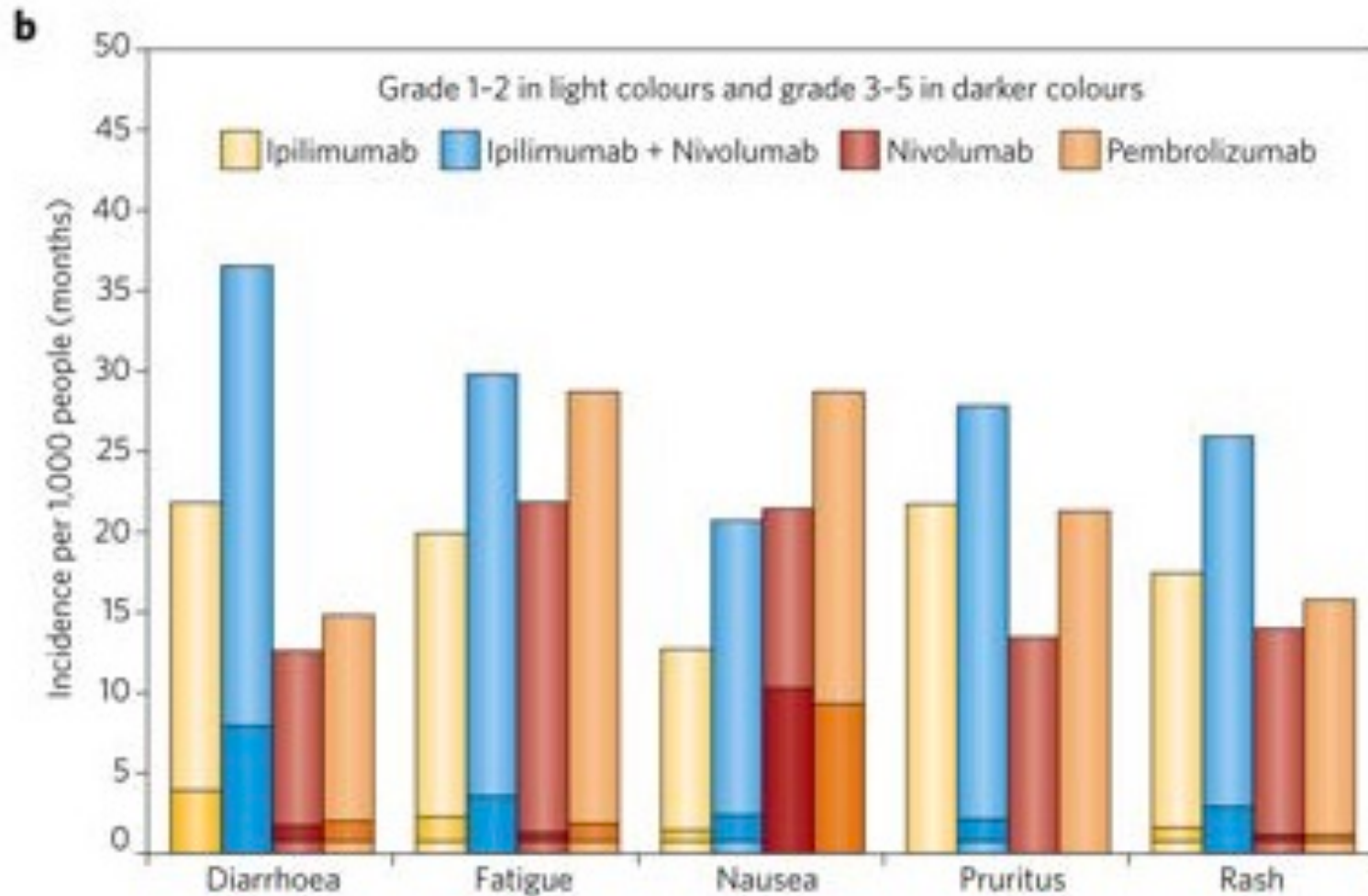
► Durvalumab (Imfinzi)

- Blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1) molecules. Approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who either have disease progression during or following platinum-containing chemotherapy or have progression within 12 months of adjuvant / neoadjuvant RX

► Ipilimumab (Yervoy)

- A monoclonal antibody that activates the immune system, targeting CTLA-4, a protein receptor that down-regulates the immune system.
- Indications: metastatic melanoma;
 - Studies ongoing for
 - small cell lung cancer
 - Bladdercancer
 - hormone-refractory prostate cancer





Non-cardiac (and more common than cardiac) side effects

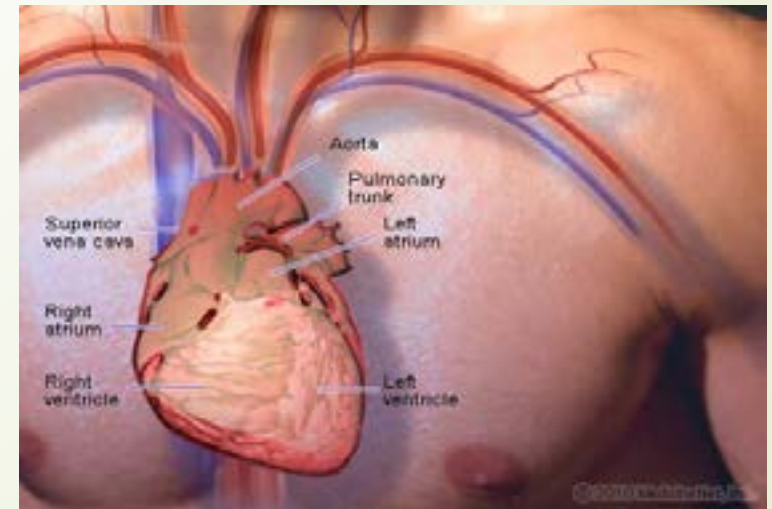
EVENT	RANGE (per month)	%/year (if one Yr. RX)	MOST COMMON IN
➤ Diarrhea:#	12-22	14-26	Ipilimumab
➤ Fatigue:#	20-29	24-35	Pembrolizumab
➤ Nausea:	12-29*	14-35	Pembrolizumab
➤ Pruritus:#	13-22	16-26	Ipilimumab
➤ Rash:#	14-22	17-26	Ipilimumab

*Grade 3-5 events of > 5% of treated patients

#More common when Ipilimumab and Nivolumab are given together


OK, but what do they do to the heart?

(SERIOUS EVENTS IN $\leq 1\%$)

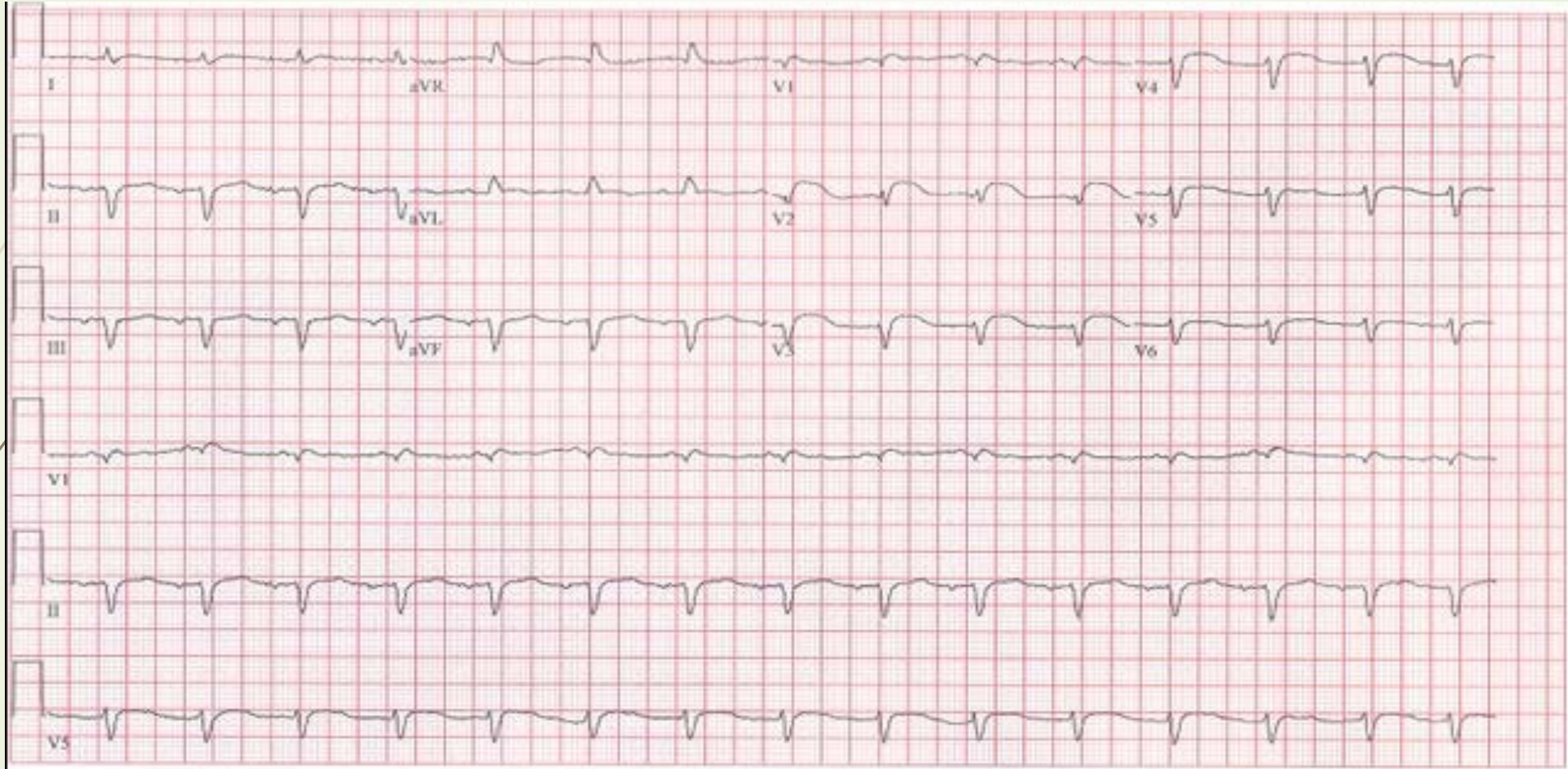




Case 1 (clear)

- 55 year old man with recurrent non-small cell lung cancer, on treatment with nivolumab.
 - Admitted with diabetic ketoacidosis, thought to be related to nivolumab. Troponin found to be 6, and was attributed to metabolic derangements.
 - Readmitted 3 weeks later with sustained VT and cardiogenic shock. Coronary angiogram was negative for CAD.
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Case 1 (clear)



Troponin 14.4; BNP E1009 (Courtesy of SM Ewer)

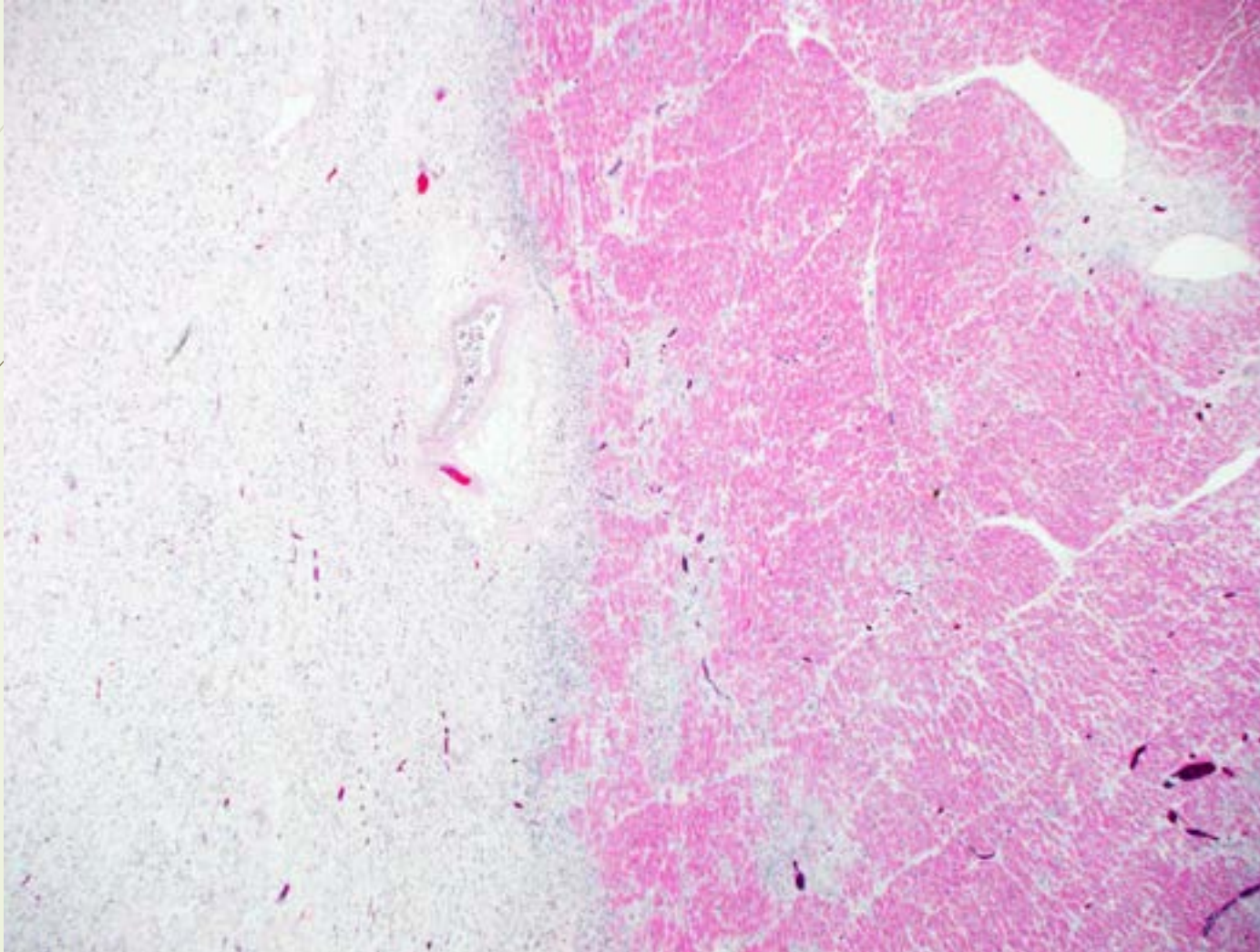


Case 1 (clear)



The patient deteriorates quickly and dies 24 hours after admission despite efforts to stabilize.

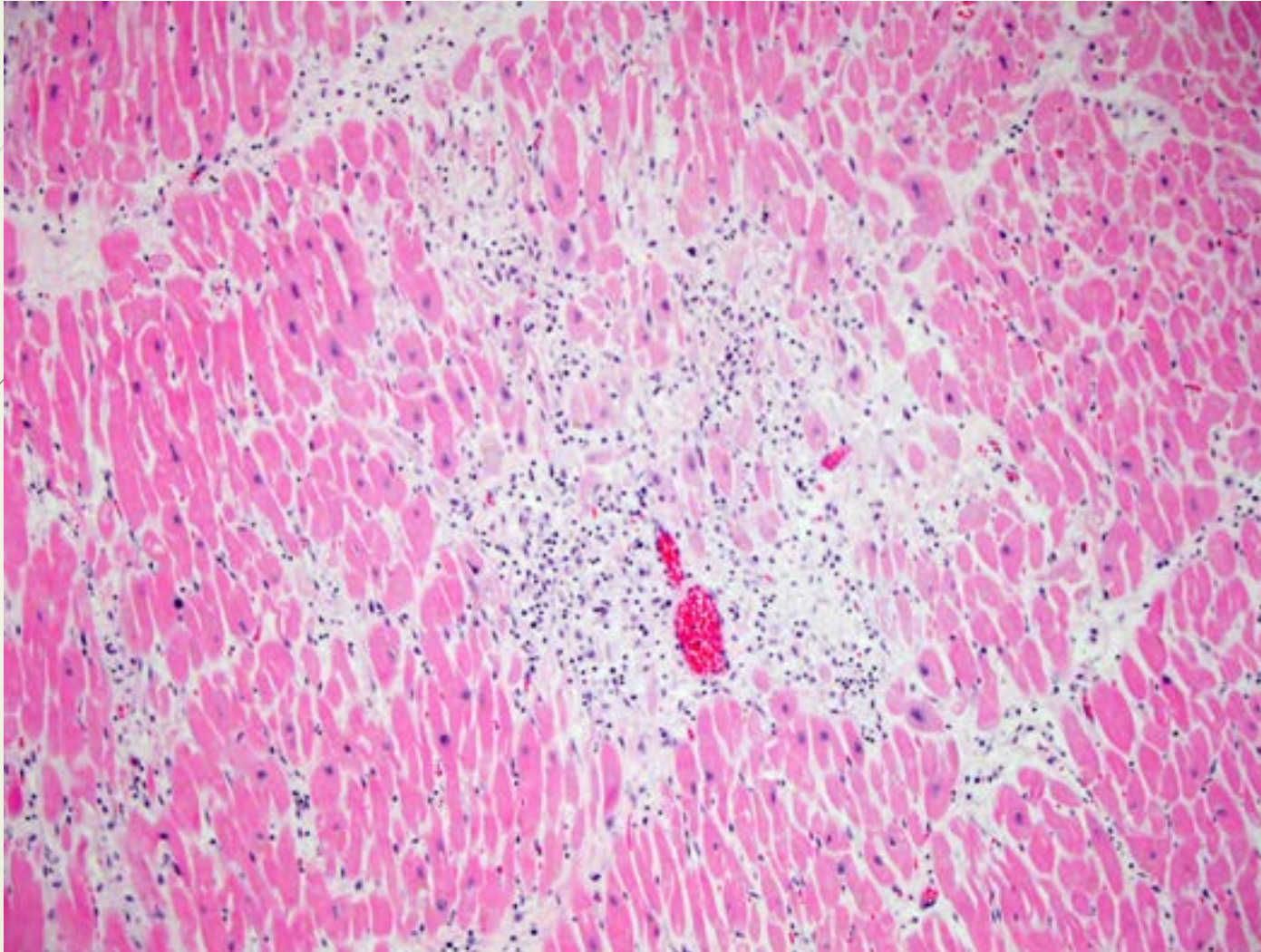
Case 1



Interventricular septum, demonstrating granulation tissue arising from extensive injury on the left and more intact myocardium on the right

(Image courtesy of SM Ewer)

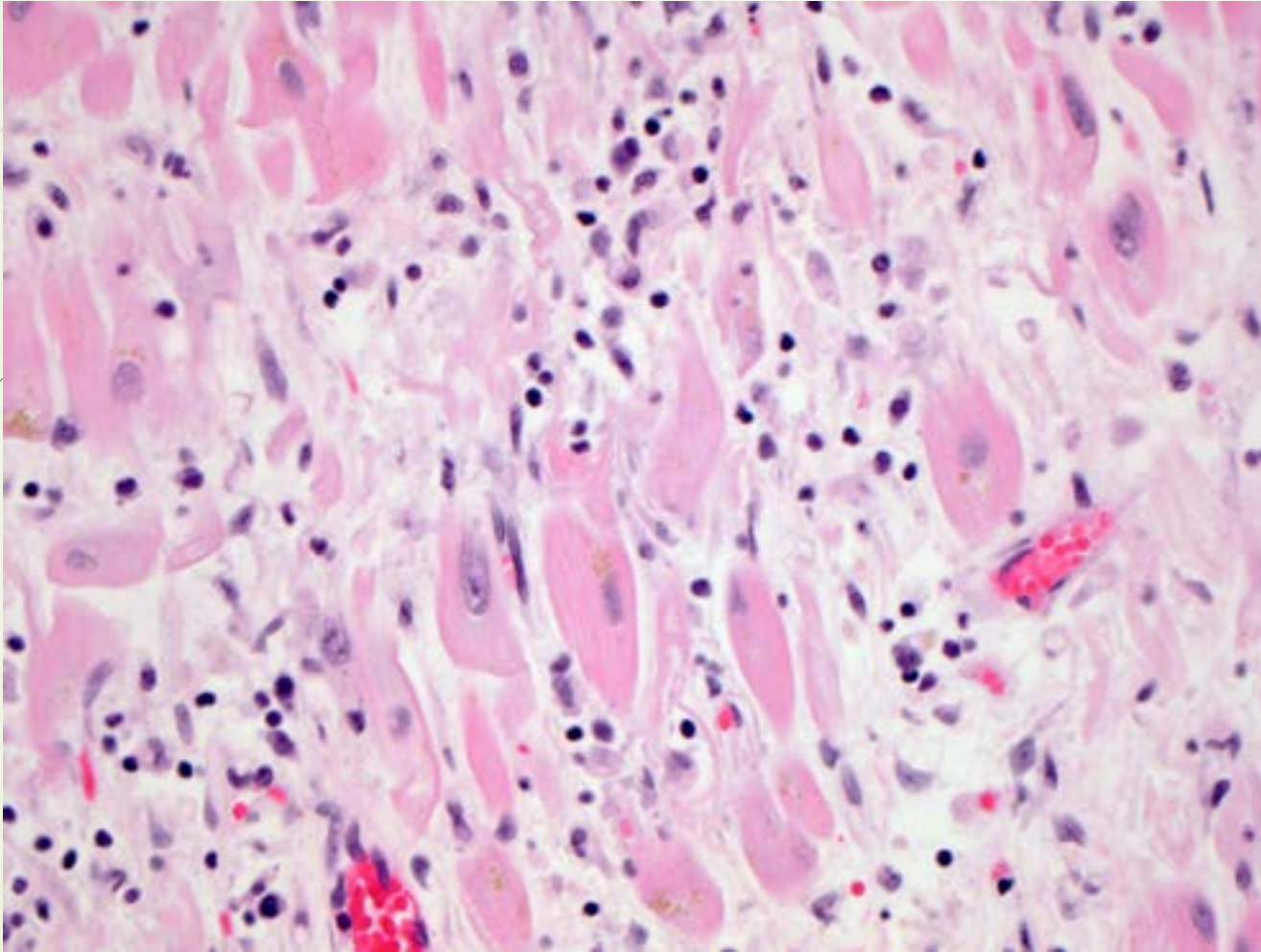
Case 1



Low power view
of myocardium

(Image courtesy of SM Ewer)

Case 1



High power view of myocardium

(Image courtesy of SM Ewer)

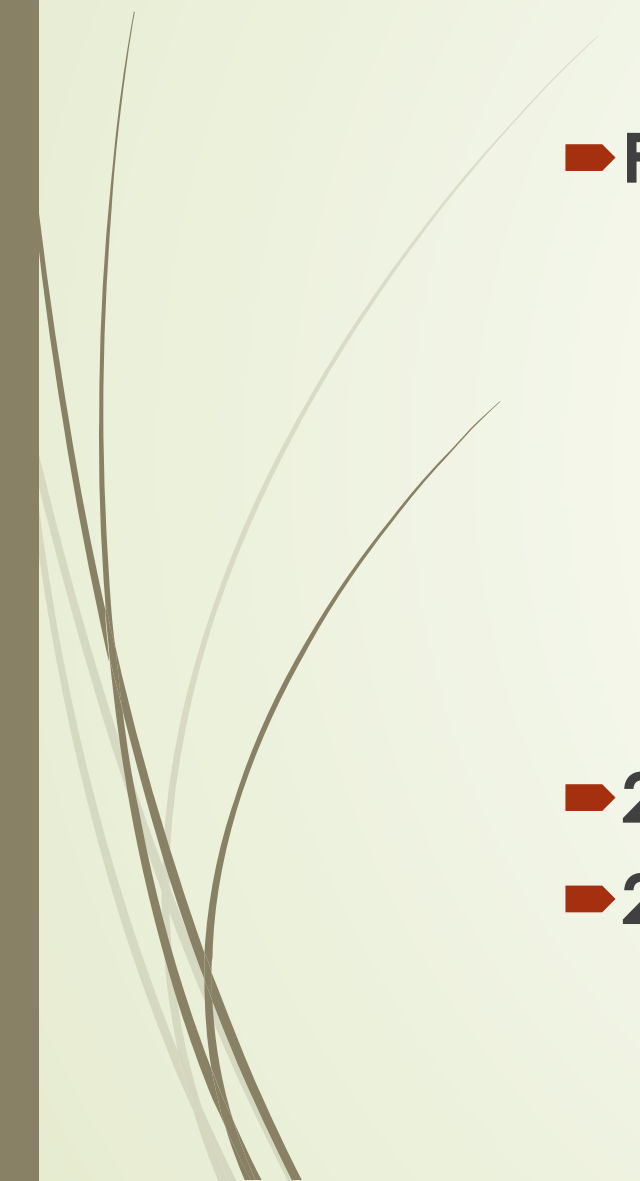


Case 2 (not clear)

- ➡ **Sixty-one year Asian female**
 - ➡ **No cardiac history; no cardiac medications**
 - ➡ **Cancer history:**
- 



Case 2 (not clear)

- **Prior treatment**
 - 5 fluorouracil
 - Additional therapy with cis-platin and radiation
 - Nivolumab
 - Erbitux
 - Taxanes
 - Steroids
 - **2016 found to have metastatic disease to the liver**
 - **2018 → new checkpoint inhibitor**
- 

Case 2 (not clear)

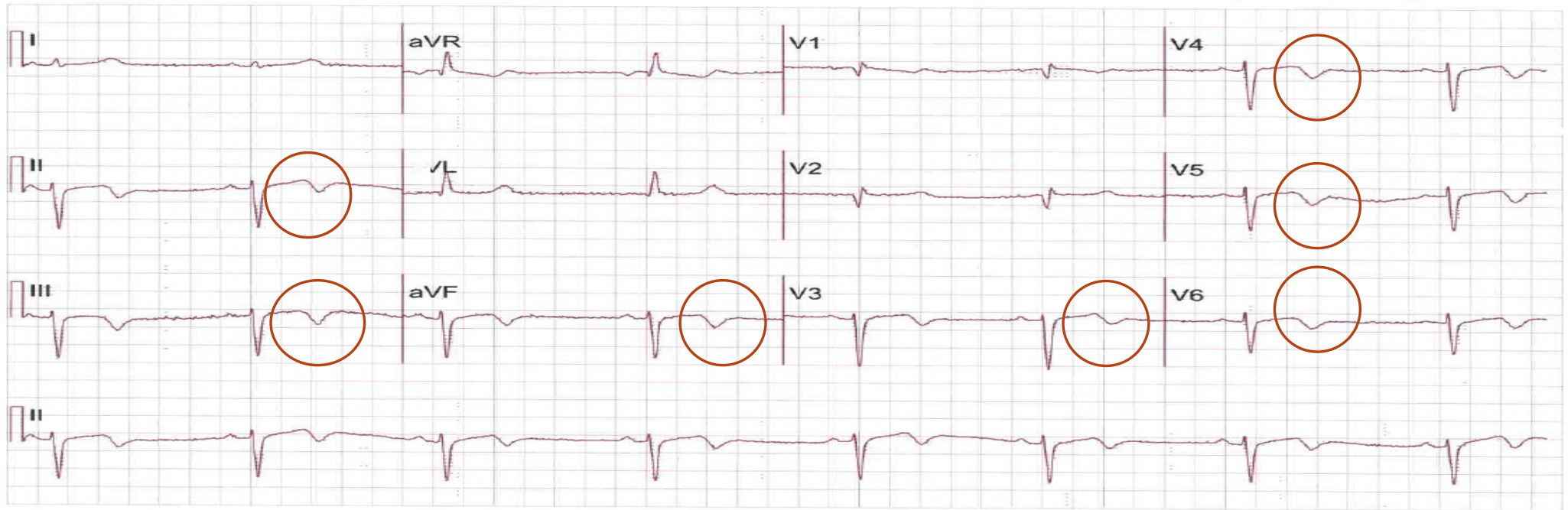
She was followed with electrocardiograms:

May 30, 2018 afternoon



Case 2 (not clear)

She was followed with electrocardiograms:
May 31, 2018 morning



What was going on in Patient 2?

- Troponin I was borderline elevated
- Patient was asymptomatic → (admitted for evaluation of CNS lesion)
- Could the ECG changes be related to CNS change?
- Could the ECG changes be related to stress-induced ischemia?
- **But, could the ECG changes be related to checkpoint inhibitor-related myocarditis?**
 - **How might we know?**



Until we have more information: (none of this is evidence-based)

- **Should we follow ECG?**
 - Probably reasonable to get a baseline ECG so we have something to compare follow-up studies; repeat ECG if:
 - Any cardiac signs or symptoms (change in activity, palpitations, chest pain etc.)
- **Should we follow troponin I?**
 - A single troponin may be prudent, but when? Reports suggest that after 1-2 weeks may be appropriate
- **Should we follow cardiac ultrasound?**
 - As with the anthracyclines, LVEF changes may be a late finding. Echo for symptoms

What are non-healthcare professionals reading?

➡ The New York Times (February 19, 2018)

- ➡ Reported that four patients, all of whom had a rare and aggressive form of ovarian cancer, were treated. The group included Oriana Sousa, a twenty-eight year old woman who lives in Marinha Grande, Portugal. Ms. Sousa who received nivolumab in 2015, and the report suggested a dramatic and unanticipated response
- ➡ They report others who also responded

What are healthcare professionals reading? (1)

(The response rates of patients treated with checkpoint inhibitors are, of course, not 100%)

- In the widely cited nivolumab melanoma trial, the 1- and 2-year survival rates were 62% and 43% respectively.*
- In a non-small cell lung cancer trial,[#] 17 of 117 patients had an objective response as assessed by an independent radiology review committee; importantly, 13 of the 17 had ongoing response throughout the trial.

*Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030

[#]Rizvi NA, et al. The Lancet 2015;16:257-265.

What are healthcare professionals reading? (2)

(The response rates of patients treated with checkpoint inhibitors are, of course, not 100%)

- Among 1861 patients with advanced melanoma:*
- 1257 previously treated; 604 treatment naïve
- Overall survival 11.4 months
- Three-year survival 22%
- Plateau in survival curve at three years at 21%
- Very important
- Are the 21% cured? Hopefully, and some say yes, but we still have to wait a while to convince others

What are healthcare professionals reading? (3)

(The response rates of patients treated with checkpoint inhibitors are, of course, not 100%)


- ➡ Advanced cutaneous squamous-cell cancer treated with Cemiplimab (PD-L1)*
 - ➡ Response: 13 of 26 in phase I (50%)
 - ➡ Response: 28 of 59 (47%) in metastatic (Phase II)
 - ➡ Median time to response: 2.3 months
 - ➡ Duration of response > 6 months: 57%
 - ➡ So 27% had a response of > 6 months

*Migden MR et al. NEJM June 4, 2018




And, bear in mind....

**Increasingly approved (by US
FDA) as first-line treatments**





What many will agree on (1):

1. Checkpoint inhibitors represent a giant step forward in the treatment of some cancers.
- 



What many will agree on (2):

2. Checkpoint inhibitors have the potential to induce long-term remission in some patients, but, just as with other oncologic interventions, we are not yet able to identify those who will benefit or those who will experience life-threatening adverse events. Algorithms and risk-factor guidance to predict who may be at increased risk for cardiotoxicity following exposure to checkpoint inhibitors are not yet available.

What many will agree on (3):

3. Cardiac adverse events exist in the form of myocardial inflammation, contractile dysfunction and dysrhythmia. In rare instances these events may be severe and can be fatal. The possibility exists that less severe cases may be overlooked
 - a. As with other forms of anti-cancer treatment that cause toxicity, the observed cardiac involvement may constitute a spectrum that varies from mild to severe. Further research will be of vital importance.



What many will agree on (4):

4. Much must still be learned regarding these agents; to some extent by giving these drugs after exhausting all standard treatments, we are shooting in the dark in our efforts to help very sick patients receive a medicine that might help them. Broader use as first-line agents and experience beyond clinical trials will provide vital information regarding both successes and failures of checkpoint inhibitor therapy.

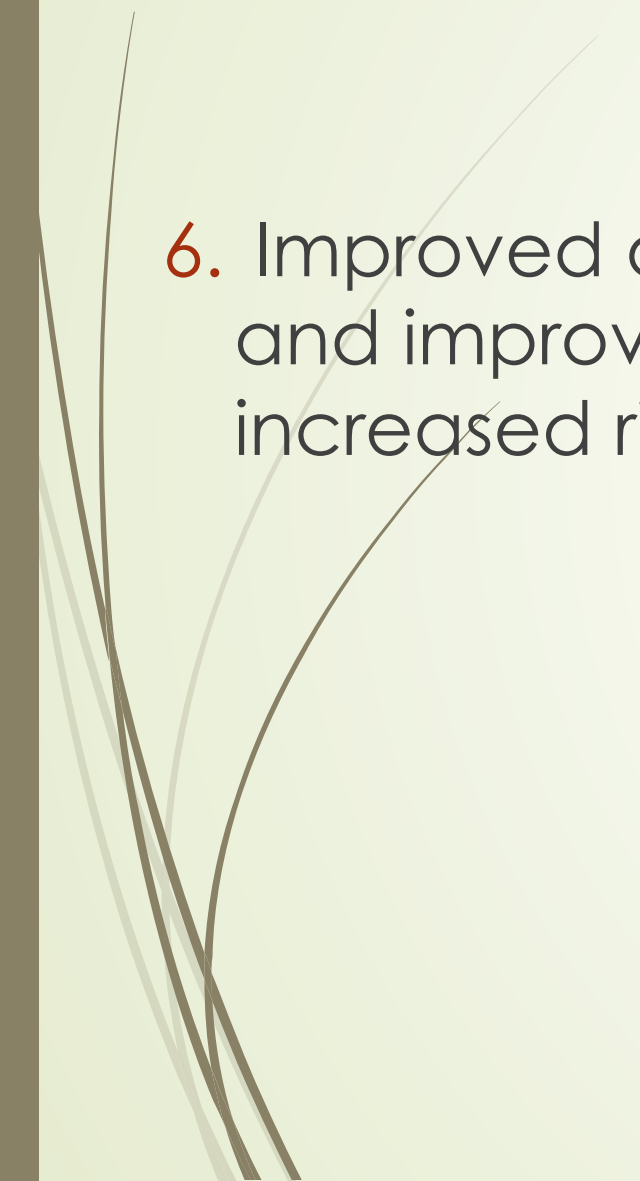


What many will agree on (5):

5. Treatment strategies for cardiac events have included high-dose corticosteroids, sometimes with the addition of mycophenolate, infliximab, and / or anti-thymocyte globulin. There are no broadly accepted guidelines for the management of these events and treatment remains empiric; no specific identifiable agent or antidote to reverse the process exists.



What many will agree on (6):

- 
6. Improved ability to identify subgroups of likely responders, and improved ability to identify those who may be at increased risk of adverse events is essential.

What many will agree on (7):

7. Checkpoint inhibitors are exceedingly costly, many costing more than \$100,000 for a course of treatment. Beyond efficacy and safety, future cost-effective analysis should provide estimates of cost for a quality life-year per patient.
 - a) At the present time, the cost of these agents is unaffordable for most individual patients. The drug costs are problematic for society, and are a matter for a serious public health debate regarding utilization in the absence of strong evidence for broader benefit among those undergoing treatment.

Immune Checkpoint Inhibitors

summary

- ▶ Pembrolizumab, nivolumab, ipilimumab
- ▶ Inhibit programmed cell death-1 (PD-1) pathways
- ▶ Used for metastatic lung cancer and melanoma and an increasing group of other malignancies
 - ▶ Cutaneous squamous cell cancer
 - ▶ GU / Gyn cancers
 - ▶ Endocrine cancers
- ▶ Increasingly used as first-line therapy
- ▶ Unleash T cells to help fight malignancy
- ▶ Associated with a broad array of autoimmune side effect, including potentially fatal myocarditis
- ▶ Treatment involves high-dose steroids +/- mycophenolate, infliximab or anti-thymocyte globulin



Thank you!