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Friday, June 9, 2017

14:30 - 14:45 The -ibs and -abs of Advanced Melanoma

The –ibs and –abs of advanced melanoma

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Rotorua GP-CME 2017

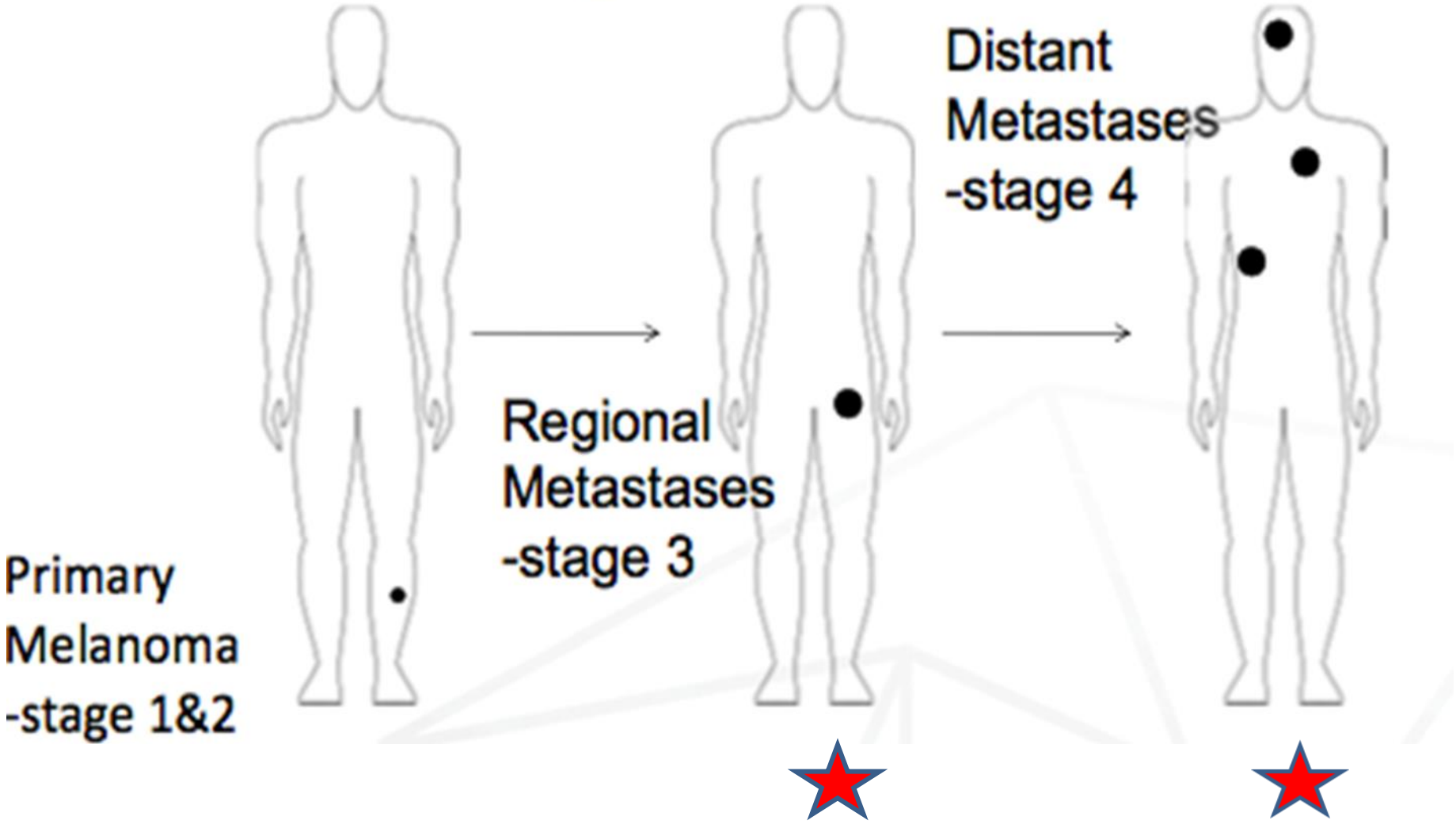
Key messages

- Advanced melanoma is bad, but treatable…
- …not with chemotherapy!
- With new systemic treatments these people live longer and better
- New treatments = new side effects
- Surgery still important
- Decision-making complex – all advanced melanoma patients should go through MDM

Outline

- Key features of advanced cutaneous melanoma
- Systemic therapies
  - Focus on immunotherapy
- Side effect recognition and management
- Summary and questions

Melanoma - stage defines treatment



Advanced melanoma

- Stage 3 (especially if inoperable) and stage 4
- 20% do not have a primary identified
- Disproportionately affects young people – but huge burden of disease in elderly
- Very morbid
  - Typically involves skin, nodes, lungs, liver, brain, bone, small bowel
- Historically life expectancy 6-12 months

Metastatic melanoma: goals of treatment

- Relief of symptoms
- Maintaining/improving quality of life
  - Avoiding toxicity/harm
- Slowing the progression of disease
- Improving survival
  - Now long-term remission is possible

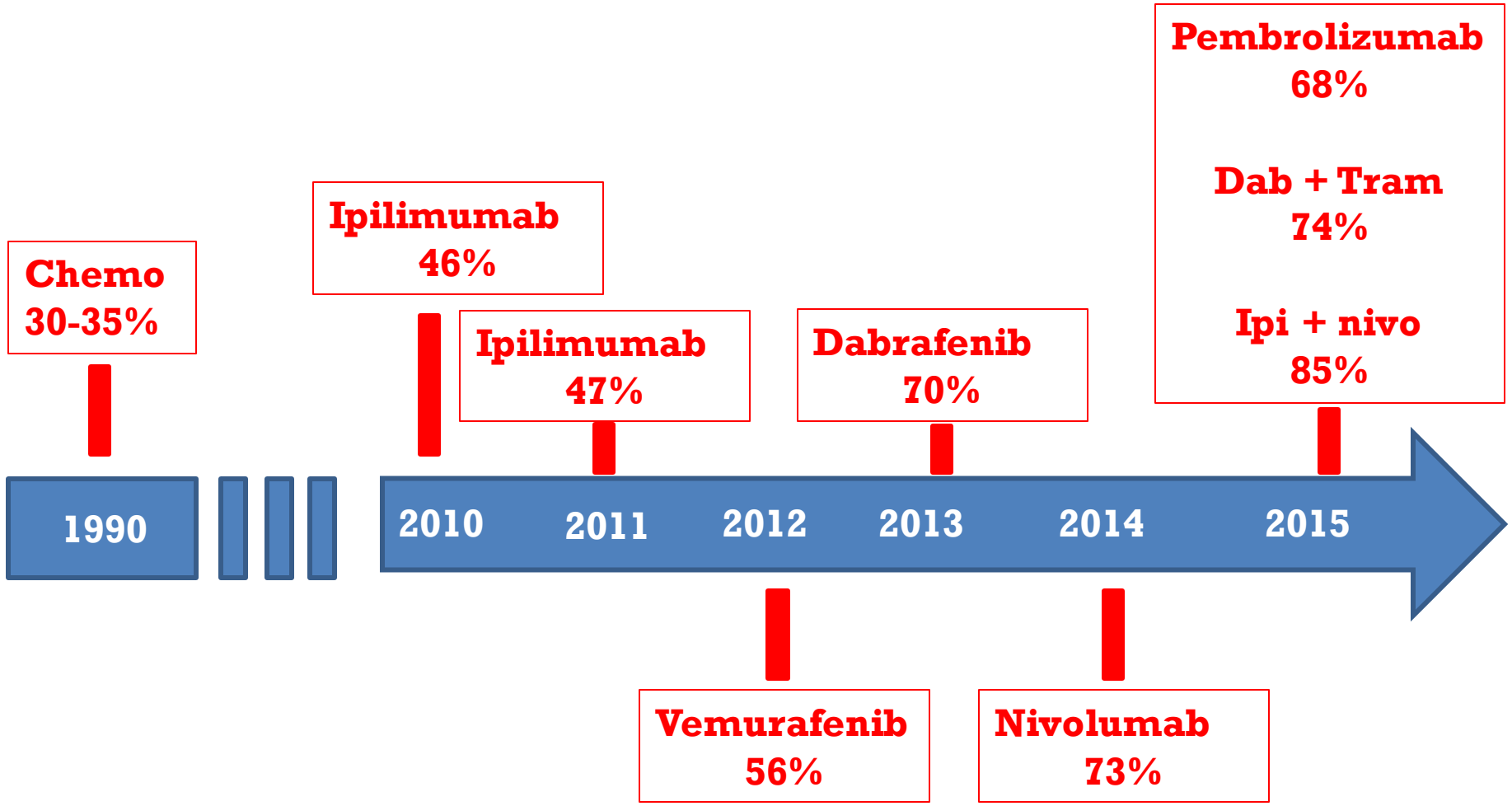
General principles/approach

- Local control important even in the setting of metastatic disease
- Metastasectomy needs to be carefully considered
  - Appropriate in highly selected patients
- PET-CT widely accepted as best staging
- A new symptom in a patient with previous high-risk melanoma is melanoma until proven otherwise
- Brain, bone, peritoneal mets do poorly

Metastatic melanoma: treatment

- Surgery still has a key role
  - Oligometastatic disease
  - Palliation of skin, soft tissue disease
  - Difficult disease sites eg brain, small bowel
- Radiotherapy
  - Brain, bone
- Chemotherapy (eg dacarbazine, cisplatin, paclitaxel)
  - Not particularly useful; we try to avoid

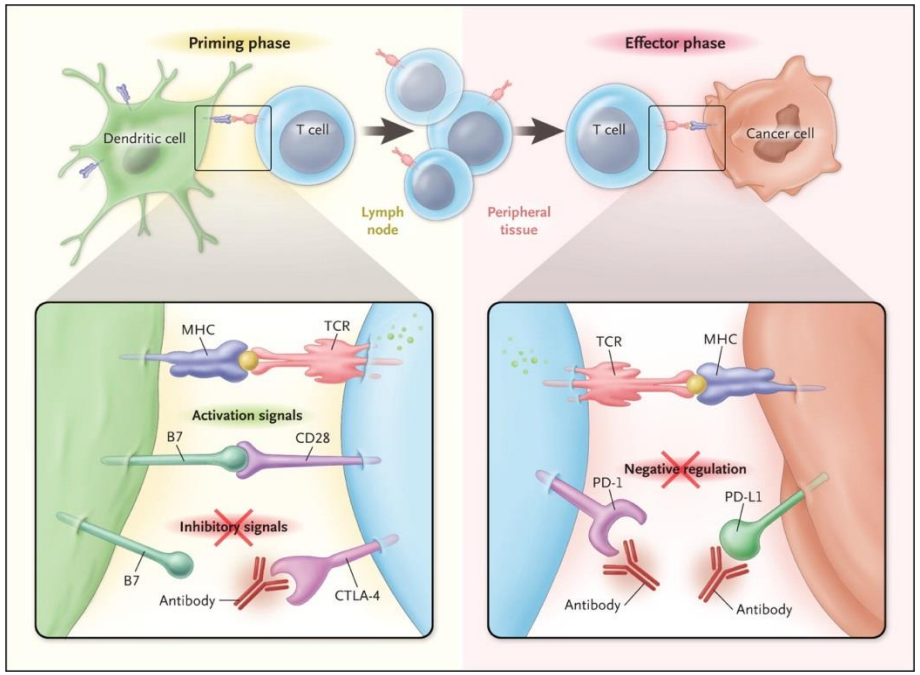
1 year overall survival



Systemic therapies in 2017

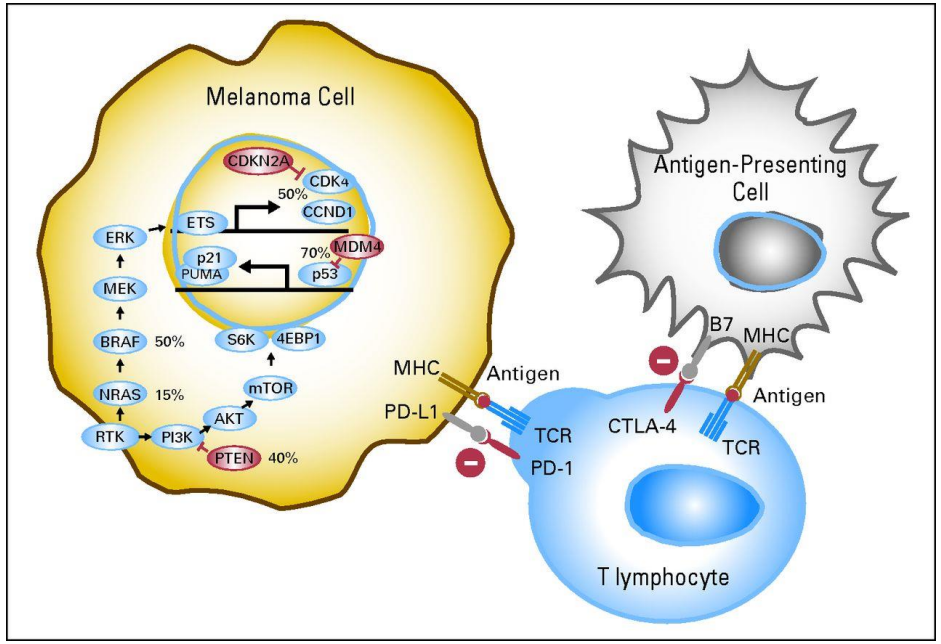
Checkpoint inhibitors **The '-abs'**
• Monoclonal antibodies • Can be used in anyone with adv melanoma • Intravenous, in cycles • Can take time to work • Response rates 40% but response enduring • Work in brain • Funded in NZ

BRAF/MEK inhibitors **The 'ibs'**
• Kinase inhibitors • Will only work if tumour has BRAF mutation • Oral, continuous • Benefit usually rapid • Response rates 80% but duration limited • Work in brain • Not funded in NZ



1. Immune checkpoint inhibition
Checkpoint is the physiological inhibitory signal on T cell activation

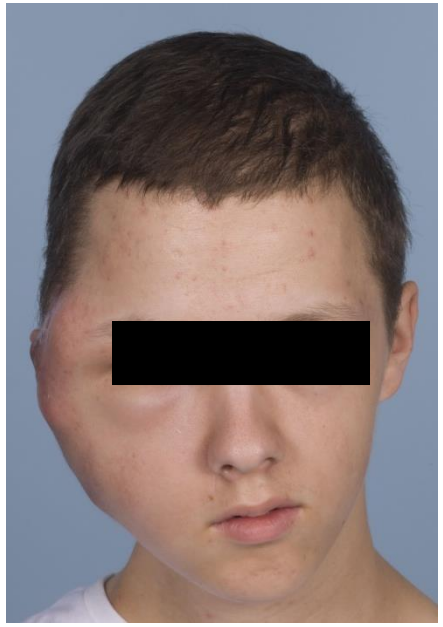
2. RAF/RAS/ERK signal transduction inhibition.
Inhibition of an abnormally activated ('oncogenic' pathway) caused by V600 mutation in BRAF gene. This is an acquired mutation, NOT germline

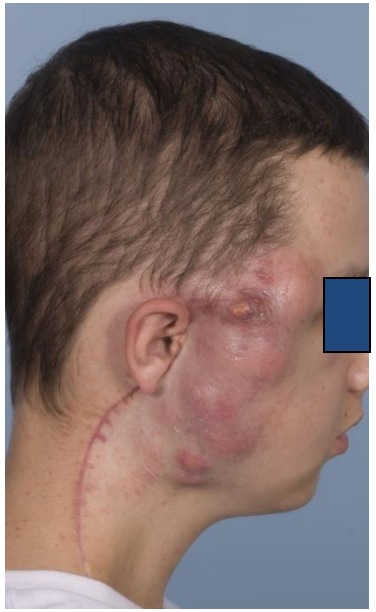


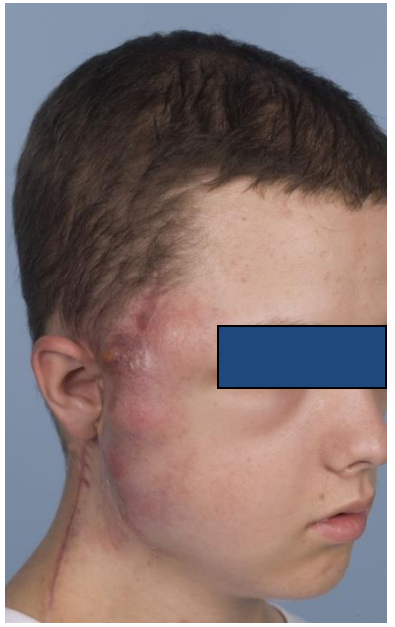
BRAF/MEK inhibitors in brief

- Dabrafenib/trametinib (Novartis) or vemurafenib/cobemetinib (Roche)
- Rapid tumour control in patients with BRAF mutant melanoma (approx 40%)
- Duration of control typically 12 months
- Resistance mechanisms multiple
- Side effects chronic but manageable
  - Skin, joint toxicity
- Expensive (approx $18K per month for combo)

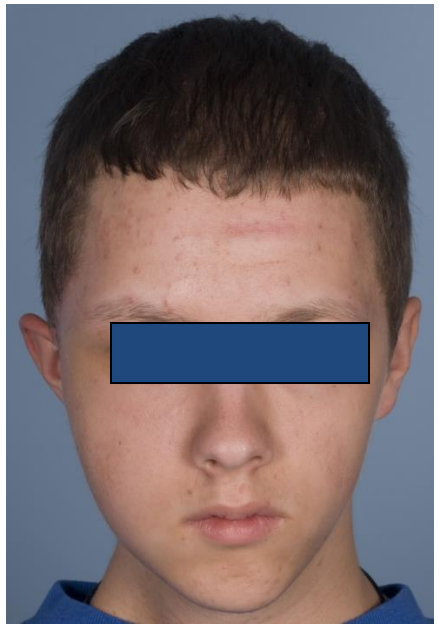
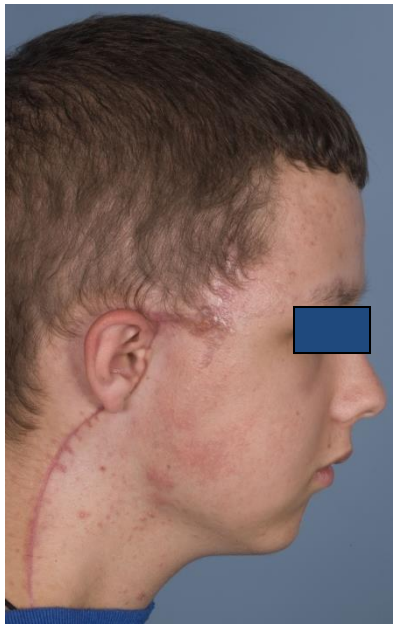
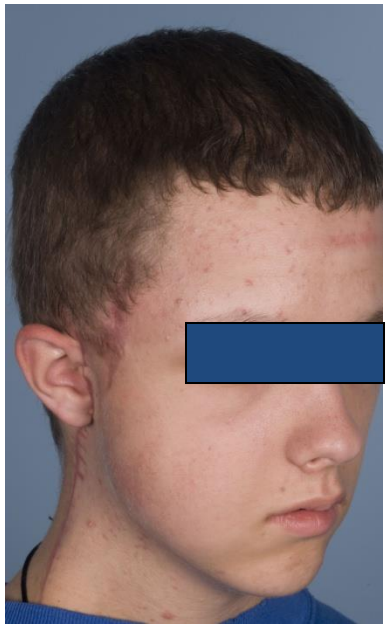
BRAF inhibitors offer rapid palliation







17 year old with advanced melanoma
parotid/face: before starting vemurafenib

After nine days of vemurafenib

Immune checkpoint inhibitors:
PD-1 inhibitors are a major breakthrough

- Pembrolizumab (Keytruda) and nivolumab (Opdivo)
- These drugs have the same efficacy and toxicity
- In NZ funded as monotherapy for patients with inoperable stage 3 or stage 4 melanoma, with measurable disease
- Can be used in combination with ipilimumab (CTLA-4 checkpoint inhibitor) for even better results; more toxicity

PD-1 inhibitors: efficacy

- "The median isn't the message"
- What are relevant measures of success?
  - Response/disease control rates
    - 30-40% and 60% respectively
    - 10% complete response
    - Responses very enduring
  - QOL
    - Not yet reported in depth
  - Survival

Milestones in melanoma survival: PD-1 inhibitors

Year	% alive
One	70
Two	57
Three	50
Four	34

PD-1 inhibitors in practice

- 30-60 min infusion every 2-3 weeks
- Average time to respond 8 weeks
- We sometimes see unusual response patterns ('pseudoprogression')
- Virtually no drug interactions but we avoid 'flu vaccine and systemic steroids unless absolutely necessary
- No concern about immunosuppression à la chemo – in fact we worry about the opposite!

PD-l inhibitor side effects

- Generally well tolerated
- Common and niggly:
  - Fatigue
  - Rash
  - Pruritis
  - Hypo and hyper-thyroidism
  - Sinusitis/rhinitis
  - Arthralgias
- Personal experience: fatigue in elderly can be debilitating

Immune Aes: the feared and the weird

- Pneumonitis
- Hepatitis
- Anything with '-itis'
  - Uveitis
  - Hypophysitis
  - Nephritis
  - Myocarditis
  - Encephalitis
- Early recognition key
- Usually treatable with high dose steroids

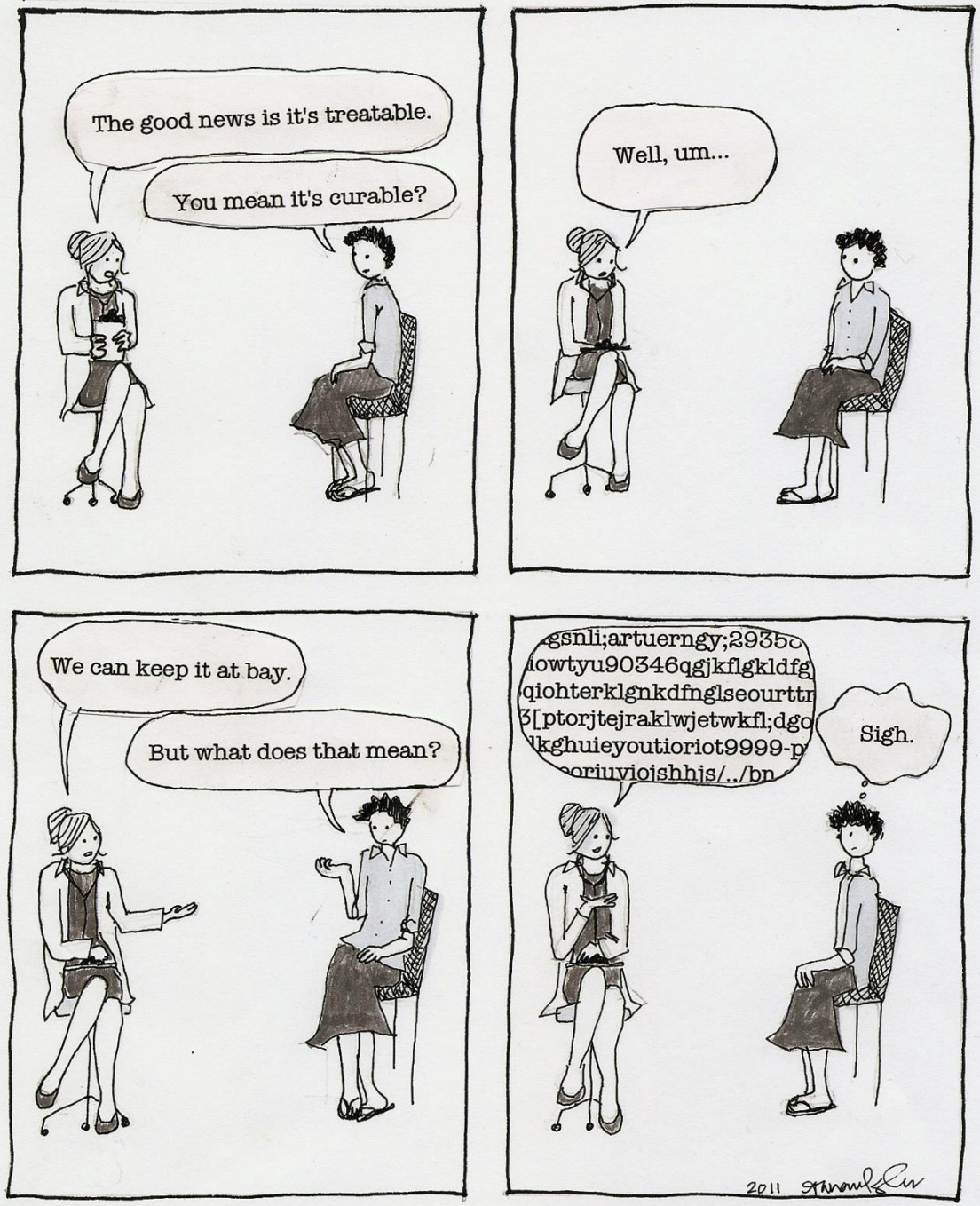
RED FLAG SYMPTOMS: DIARRHOEA, SOB, COUGH, NEUROLOGICAL

PD-1 inhibitors: unresolved questions

- Patient selection/predictors of benefit
- How to assess benefit
- Duration of treatment
- Efficacy in brain
- Optimal sequence with BRAF/MEK inhibitors
- How to integrate with surgery and radiotherapy
- Should we use them earlier eg in stage 3 disease?

The (near) future

- Defining the optimal sequence and timing of systemic therapies
- Adjuvant therapy for stage III and stage IV resected disease
- Combination approaches
  - Drugs including intra-lesional, vaccines
  - Surgery plus drugs
  - Radiation plus drugs
- New targets


The good news is it's treatable.
You mean it's curable?
Well, um...
We can keep it at bay.
But what does that mean?
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Sigh.
2011

Summary

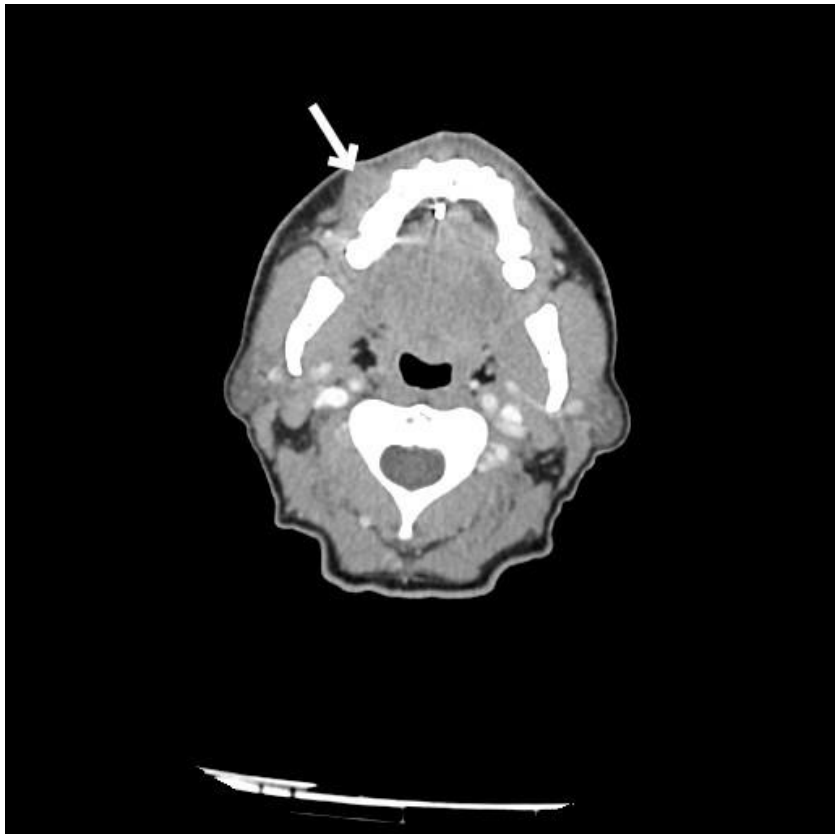
- We finally have treatments that alter the natural history of metastatic melanoma
- Immunotherapies offer long-term remission to patients with advanced melanoma
  - They bring new clinical dilemmas
- Management is becoming increasingly complex – there is still much to learn
- Access to clinical trials remains vital as cost remains a major issue

Example of response – case 1

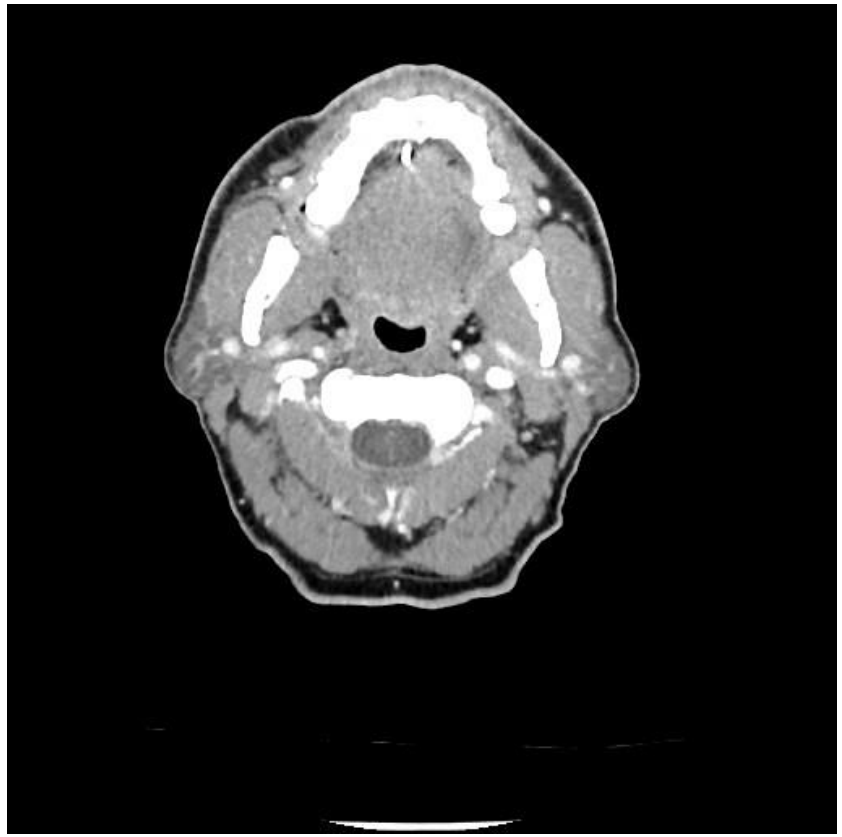
- 69 year old man
- History of 2 primary melanomas
- Widespread metastatic disease 2015 – nodes, soft tissues, bone, adrenal
- Commenced pembrolizumab Feb 2016

Maxillary mass

Feb 2016

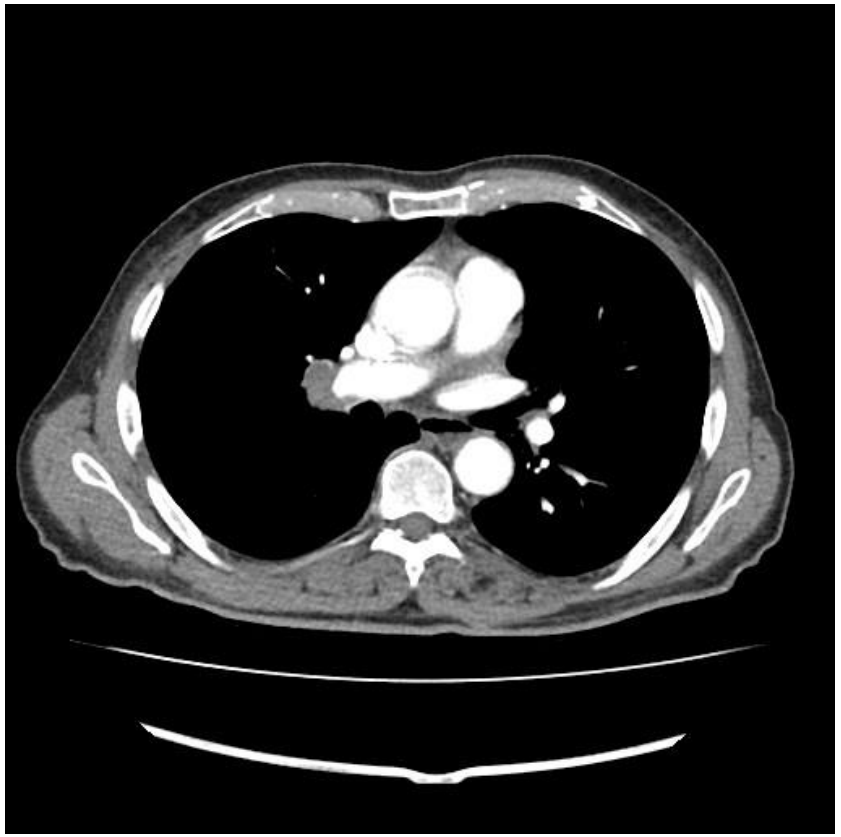


Nov 2016



Hilar lymphadenopathy

Feb 2016



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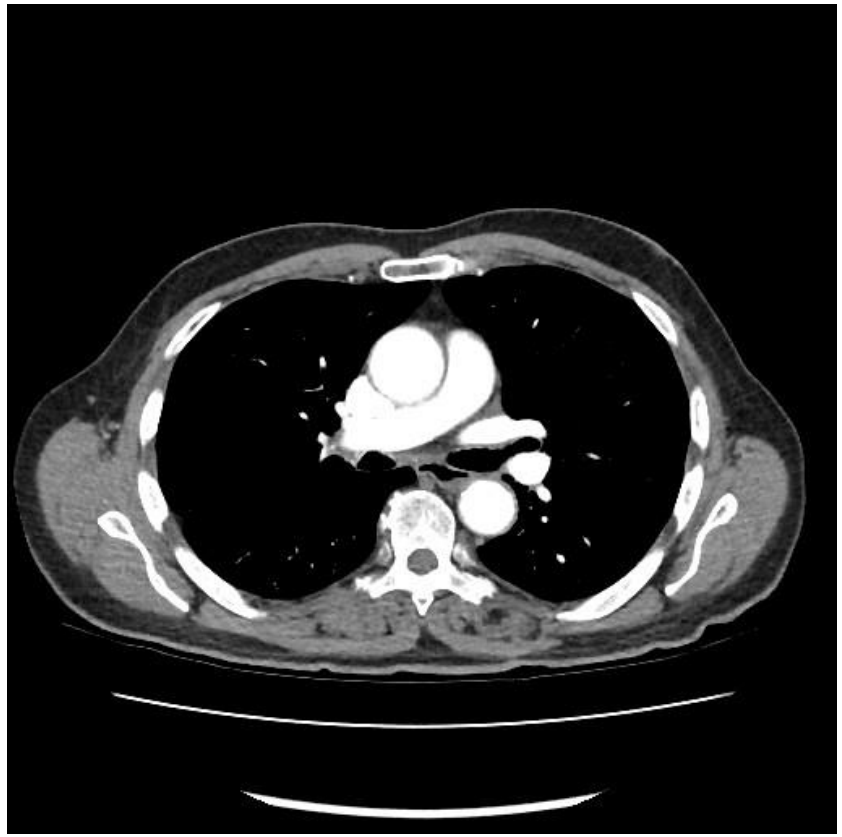
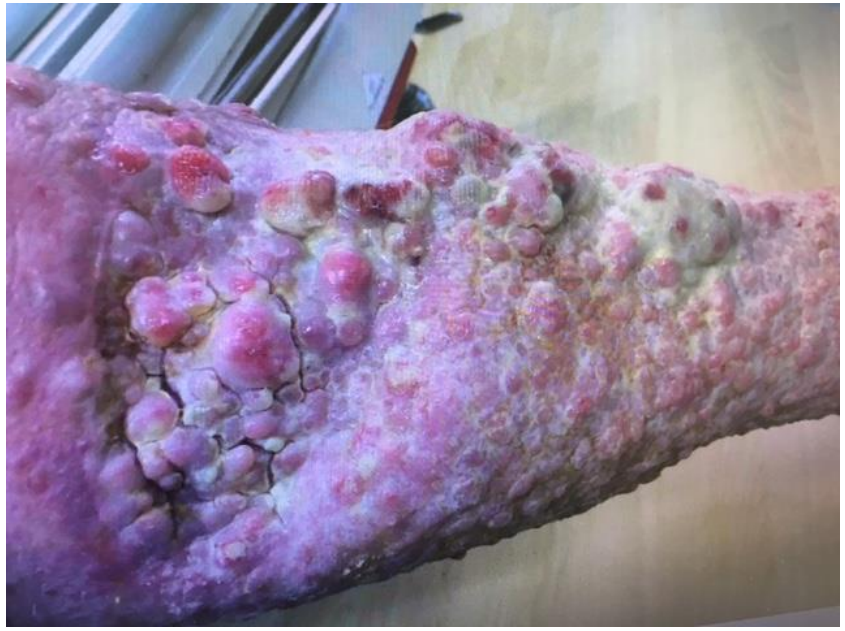


Example of response – case 2

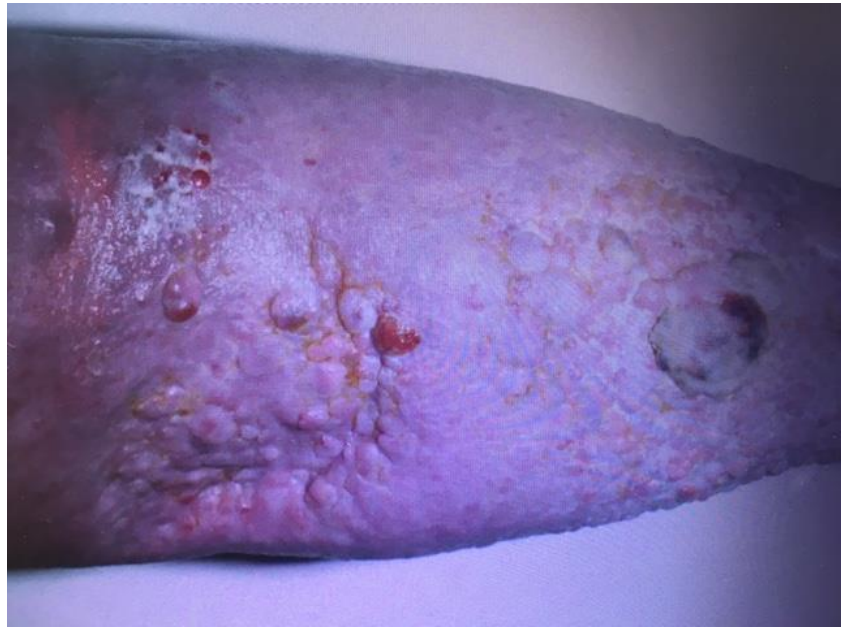
- 76 year old woman with extensive dermal/in-transit melanoma of leg
- No metastatic disease
- Recurrent sepsis; admission to ICU
- Commenced nivolumab September 2016

Responder 2

September 2016



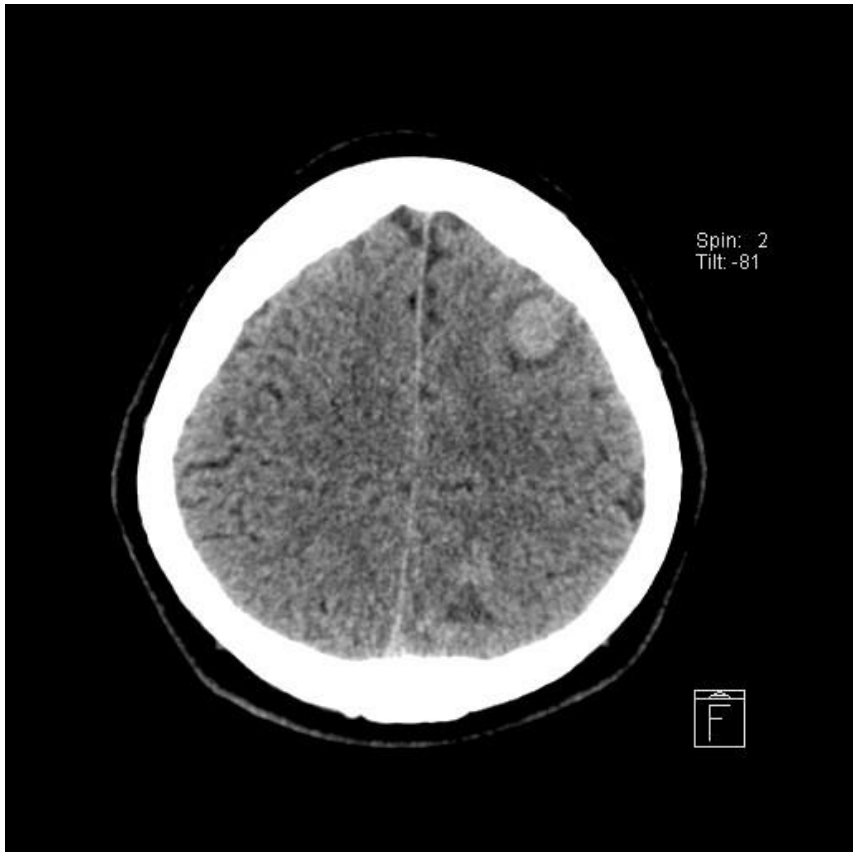
February 2017

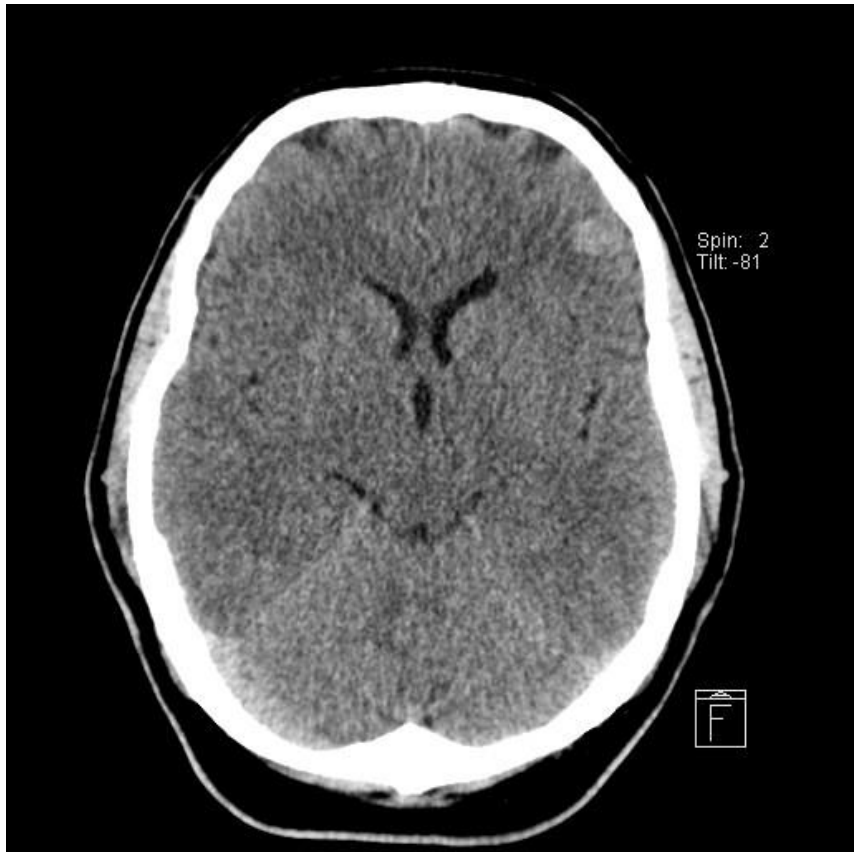


Non-responder – case 3

- 45 year old Maori man
- 2010 1.3mm melanoma, non-ulcerated, involving posterior left upper arm treated with excision biopsy. Declined wider excision and sentinel node biopsy.
- Jan 2016 Presented with a 7 cm left axillary mass that had been growing over the last three months. Fine needle aspiration confirmed melanoma.
- Feb 2016 CT-PET scan showed an 8 x 7 cm mass left axilla, smaller mass involving right axilla, multiple lung metastases ranging up to 2.1 cm and subcutaneous and bone metastases present (widespread).
- Feb 2016 Core biopsy left axilla confirmed melanoma, BRAF mutation present.
- Mar 2016 Commenced dabrafenib and trametinib
- Oct 2016 Progressive disease confirmed with lung lesion of 12 mm and progression in left axillary nodal disease. Changed to second line pembrolizumab.

Case 3 November 2016 (after 2 cycles pembro)



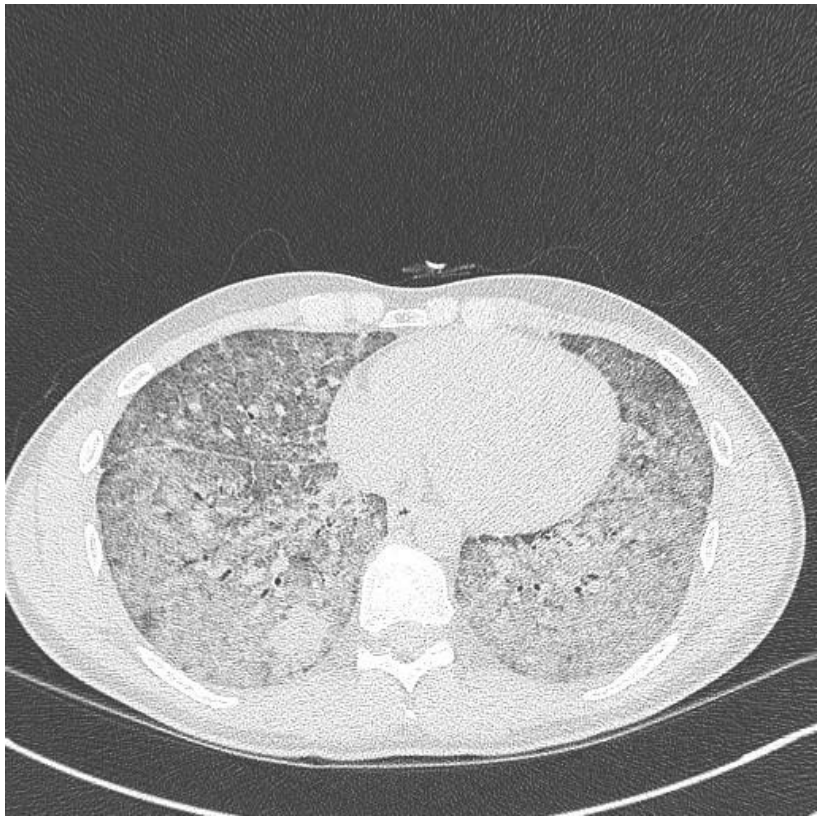


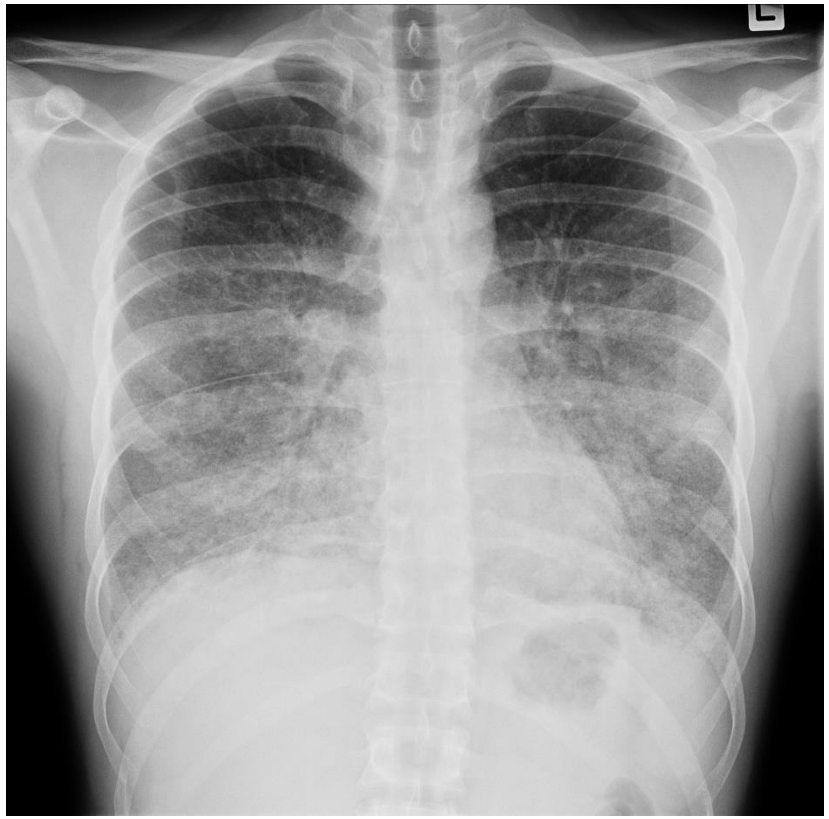
Case 3: non-responder

- PD in brain and axilla
- Completed whole brain RT Dec 2016
- Received 4 cycles pembro
- Treatment stopped early Feb 2017
- Died late Feb 2017

Case study of pneumonitis

- 30 year old male
- Metastatic melanoma to lungs, nodes
- Presented with dry cough after cycle 3 pembrolizumab
- Progressive axillary node
- Not hypoxic, no respiratory distress on admission





Pneumonitis

- Treated with high dose corticosteroids
- CPAP in intensive care
- Treated with infliximab
- Deteriorated and died despite treatment, 10 days after admission