Patient Cases: Immunotherapy or Targeted Therapy for Oncogene Addicted Melanoma?

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NHS Foundation Trust

BRAF Mutant Melanoma: Immunotherapy or Targeted Therapy 1st Line?

James Larkin FRCP PhD

Disclosures

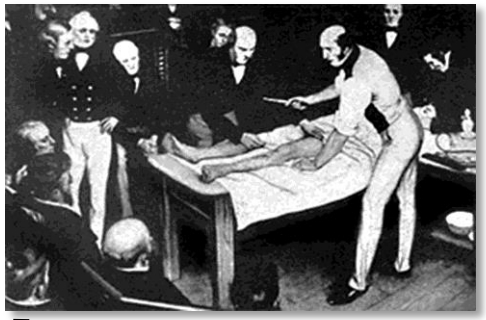
- Research support: BMS, MSD, Novartis, Pfizer

- Consultancy (all non-remunerated): BMS, GSK, MSD, Pfizer, Novartis, Roche/Genentech

Overview

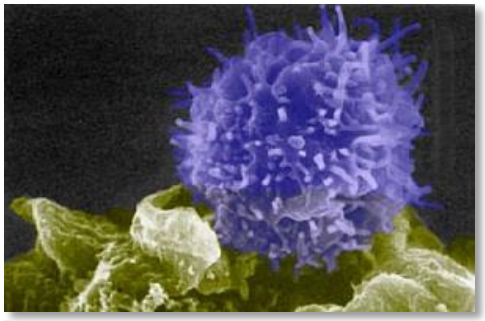
- What options do we have?
- Cases of 2 patients I have treated in 2014
- Selecting BRAF targeted vs immunotherapy
- Some urban myths
- Speculating on the future…
    - better immunotherapies
    - better BRAF targeted therapy
    - what will this mean?

Melanoma Therapy 1846 - 2014

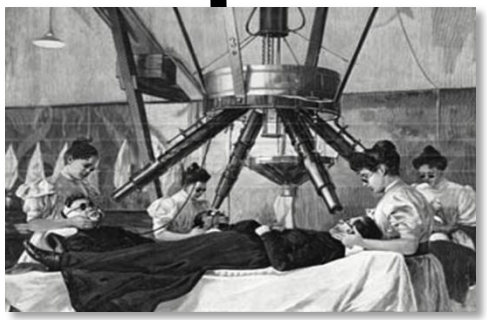


Surgery
1846

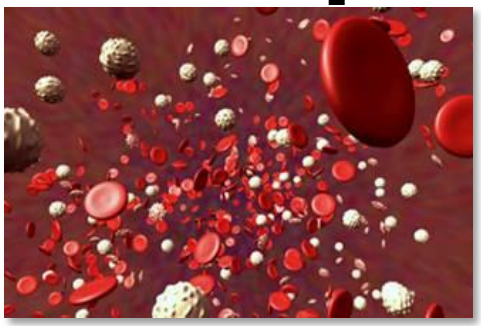
Cytotoxic Chemotherapy
1946



Checkpoint Inhibitors
Ipilimumab 2011
Nivolumab 2014
Pembrolizumab 2014



Radiation Therapy
1901



Cytokines
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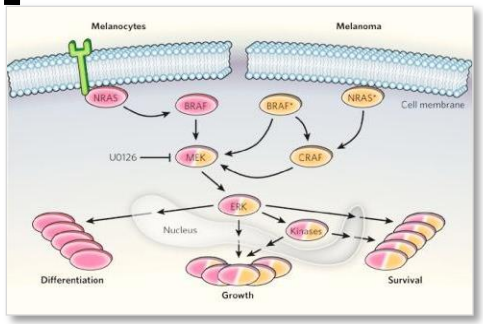

Targeted Therapy
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Trametinib 2013
Dabrafenib 2013

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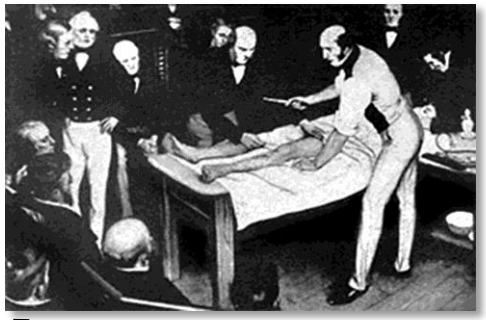

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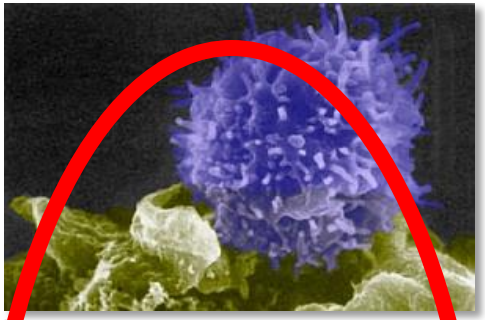

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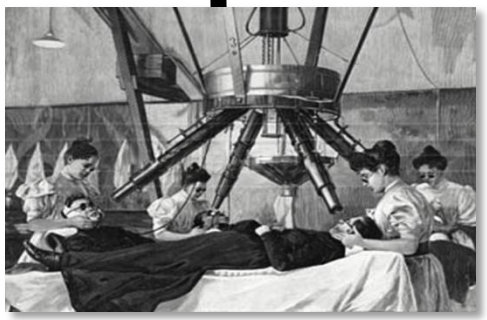

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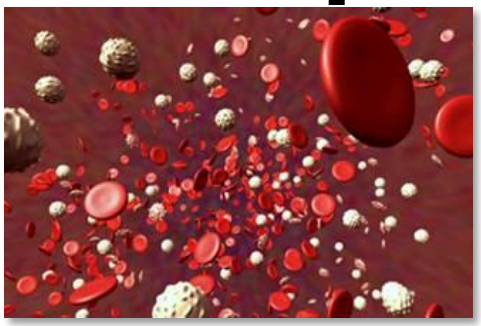

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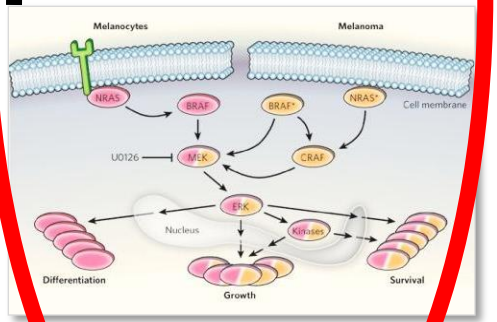

Targeted Therapy
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What I am going to talk about

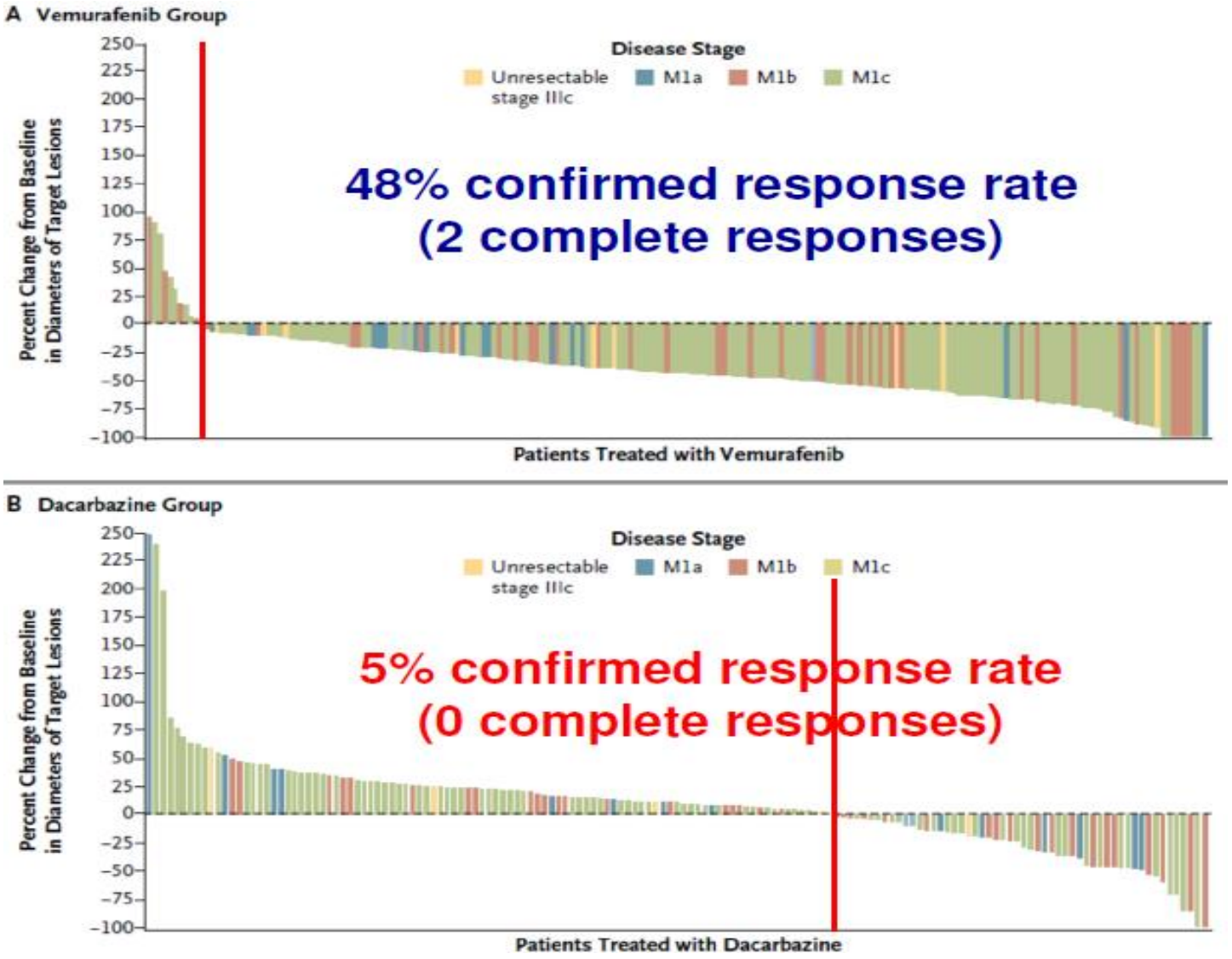
- BRAF targeted therapy vs checkpoint inhibition for the 1st line treatment of advanced BRAF mutant melanoma
- Practical approach to the patient in the clinic based on evidence and experience
- Principally, licensed BRAF targeted therapies and the anti-CTLA4 agent ipilimumab
- Some thoughts at the end though on other checkpoint inhibitors

What I am not going to talk about

- Access / reimbursement / regulatory factors
- i.e. I will assume access to licensed drugs
- Question of BRAFi vs BRAFi+MEKi
- Please attend Presidential Symposium 2 for new data and discussion: Monday 4pm
- Cytokines or non-checkpoint inhibitor immunotherapies

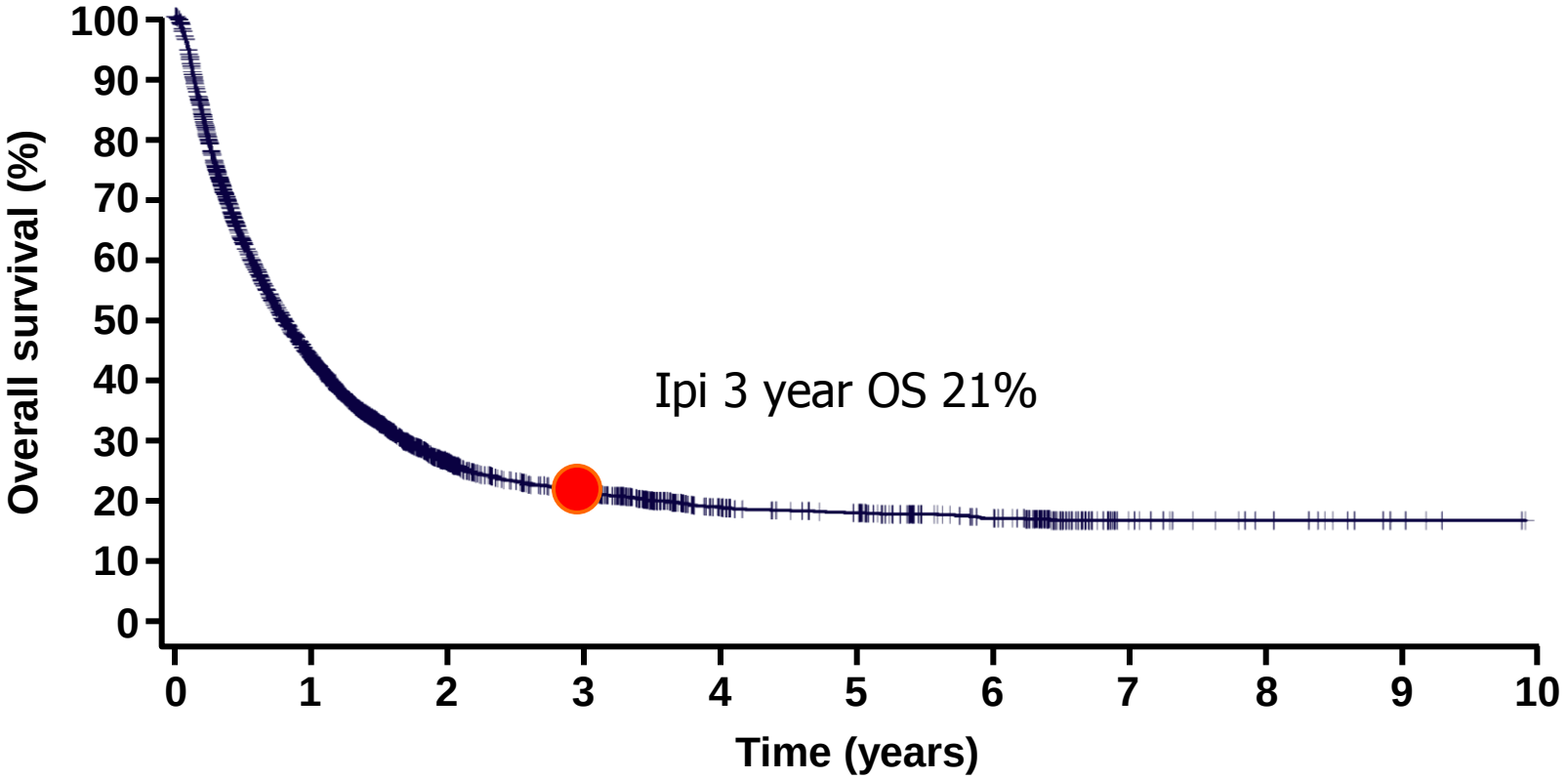
What have we got to offer our patients?

BRIM-3: Vemurafenib vs dacarbazine



Chapman NEJM 2011

Ipilimumab: survival in 4846 patients



Schadendorf ECCO 2013

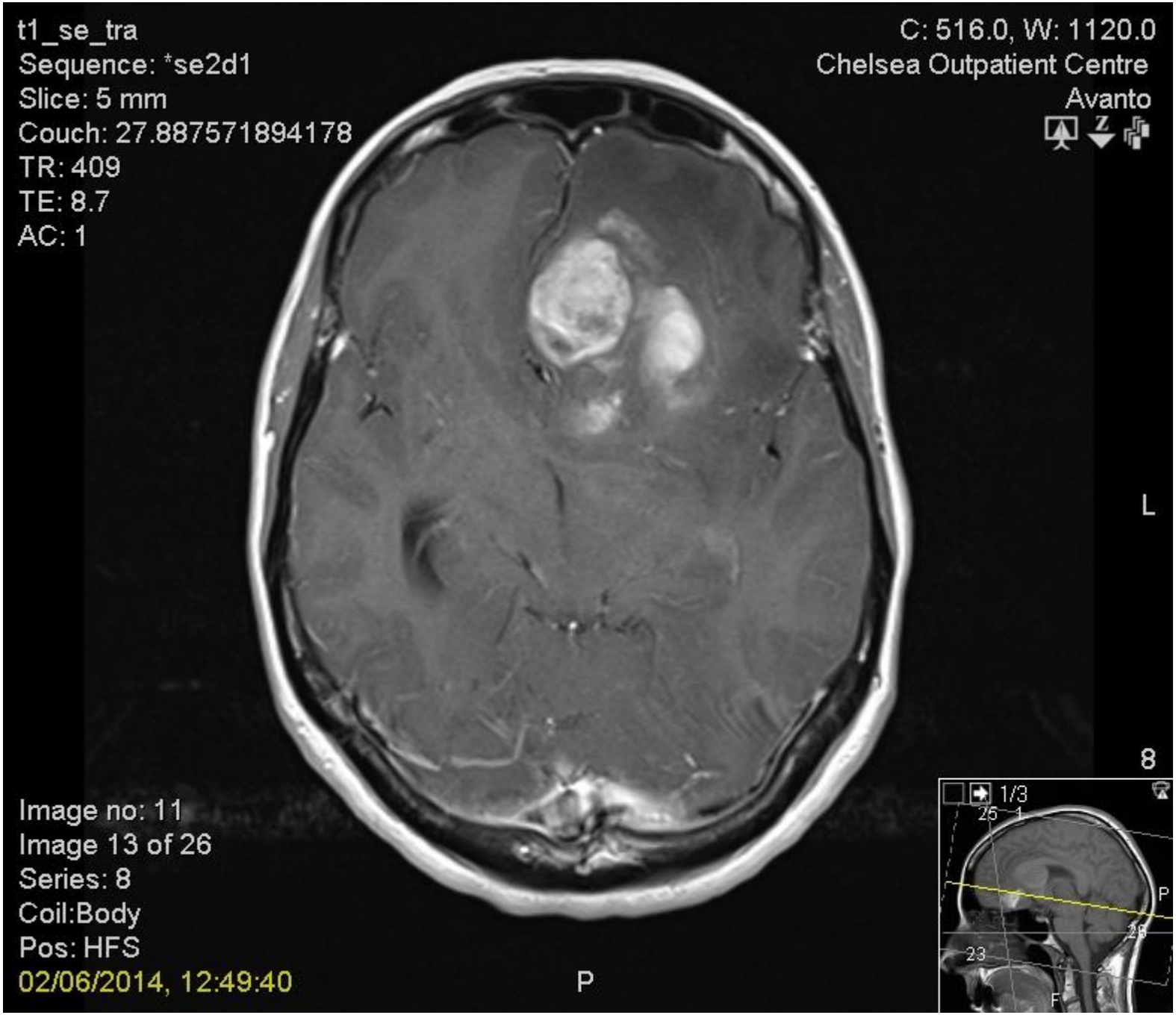
Case 1

Case 1

- 53 yo female
- Early 2013 2.8mm melanoma lower abdomen
- Late 2013 palpable contralateral groin LN: resected
- PMH Hashimoto's thyroiditis Rx T4 150mcg od
- BRAF V600 mutant; CT thorax/abdomen/pelvis clear

Case 1

- Surveillance imaging at 3 months recommended
- March 2014 staging CT: nodules R lung, L buttock, R breast
- Patient well
- Observation recommended
- June 2014: dizzy and confused
- Admitted to hospital for brain imaging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Case 1

- MR brain:
- 'Large right frontal mass with extensive mass effect, significant midline shift to the right and subfalcine herniation with hydrocephalus, significant displacement and effacement of the left lateral ventricle and effacement of the third ventricle, with dilatation of the right lateral ventricle and temporal horn. Risk of herniation at the level of the tentorium.'
- What now?
- BRAFi, ipilimumab, RT or surgery?

Case 1

- Urgent craniotomy and resection R frontal mass
- 2 weeks later: PS 0, LDH normal, off steroids
- CT: Modest progression from March
- MR brain:
- 'Residual enhancing tissue abutting the frontal horn of the left lateral ventricle and this has the appearance of residual or recurrent disease. Elsewhere in the brain, there are multiple new enhancing lesions (at least 4) which have the appearance of metastases and have developed since previous MRI. These is situated in the posterior right frontal (2 lesions), left frontal and left parietal lobes.'
- What now?
- BRAFi, ipilimumab, RT?

Case 1

- Options discussed with patient
- Focus on efficacy, toxicity, schedule
- Patient very keen to avoid whole brain RT
- 4 cycles of ipilimumab delivered June to August 2014
- No toxicity, LDH normal, PS excellent throughout
- Outcome of restaging scans not available at time of writing

Case 1: Points for discussion

- Brain imaging should have been part of surveillance
- Metastatic disease should very rarely (if ever) be observed when active drugs are available
- Disease tempo allowed delivery of ipi without symptomatic deterioration (with the benefit of hindsight)
- Ipi can be active in the setting of CNS disease
- WBRT avoided; can be considered for salvage
- BRAFi also reserved for salvage

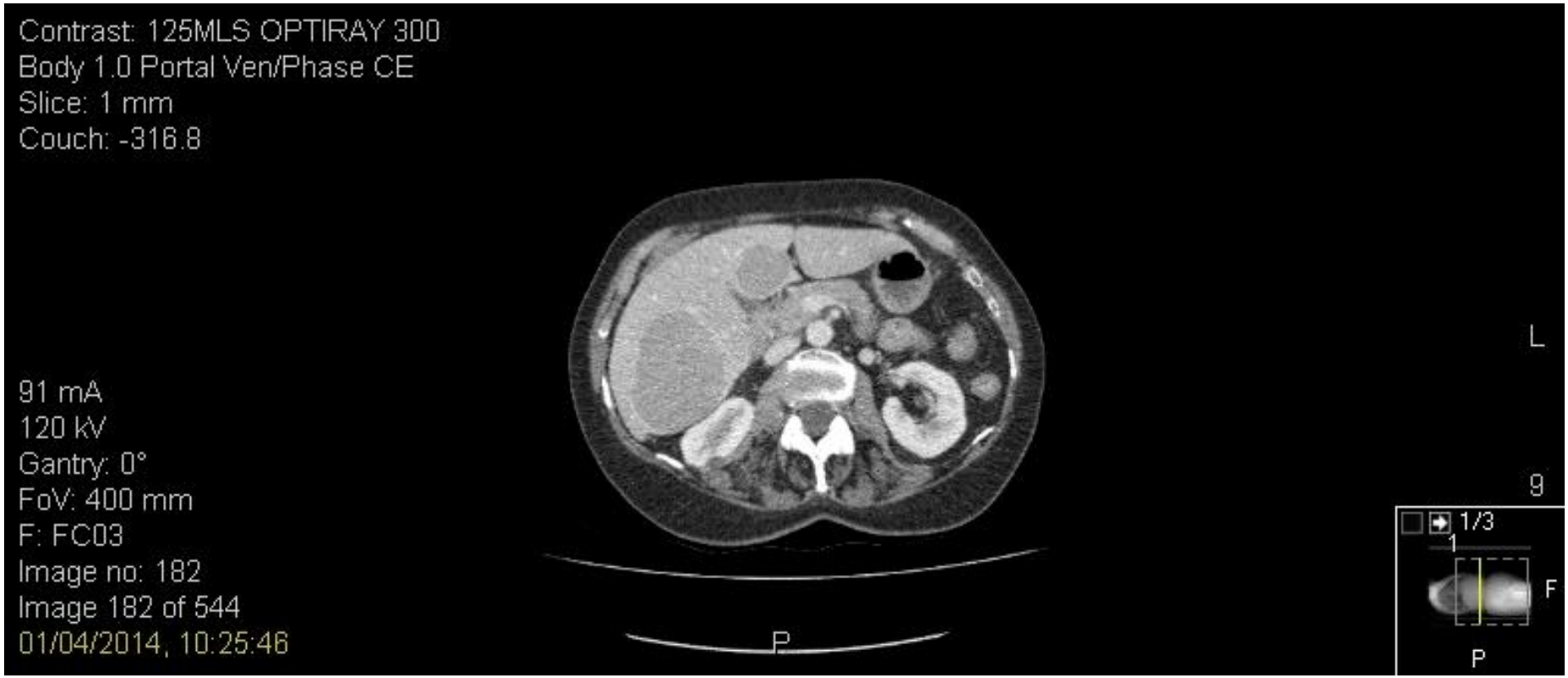
Case 2

Case 2

- 20 yo female
- Early 2013 3.8mm ulcerated 6 mitoses / HPF VGP melanoma excised from back
- Positive SLN both axillae
- Completion lymphadenectomy both axillae
- Referred to Royal Marsden Hospital
- October 2013 CT trunk + MR head normal
- Jan 2014 s/c mass L axilla = melanoma BRAF V600E mutant

Case 2

- Rapid development of abdominal pain, further s/c masses and headaches
- CT thorax/abdomen/pelvis: widespread metastatic disease: liver, peritoneum, LNs, s/c
- MRI brain: multiple <5mm parenchymal brain metastases with meningeal enhancement
- LDH ~5x ULN
- ECOG PS 1
- Management?
- Ipilimumab? BRAFi? Brain RT?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Case 2

- Started vemurafenib
- 10 days later: G1 rash, G1 arthralgia but s/c nodules had disappeared
- 8 week scan: PR throughout, LDH normal
- 16 week scan: PR throughout but brain PD; PS 1
- Vemurafenib stopped; ipilimumab #1 given
- Clinical decline and death 3 weeks later

Case 2: Points for discussion

- This type of presentation is not very common
- It is not rare either though
- Unlikely with this disease tempo that there would be sufficient time for ipi to work
- Use of BRAFi the only treatment with a realistic chance of controlling the disease
- This illustrates the limitations of currently approved therapies:
- Excellent initial response to BRAFi but limited period of disease control and no benefit from ipi
- Addressing this is the challenge for the future

What information do we need to select patients for targeted and immunotherapies?

Therapy schedule

Disease tempo

Chance of success

Patient preference

Disease distribution

Performance status

Need for rapid response

Adverse events

Ipilimumab vs BRAF inhibitor

	Anti-CTLA4 (Ipilimumab)	**BRAFi (Vemu/Dab)**
Given how?	Brief course intravenous	Continuous daily oral
Side effects?	Temporary	Chronic
Severity?	Mild to moderate but severe ~10%	Mild to moderate; rarely severe
Prolonged disease control?	Possible	Unknown
Tumour shrinkage	Slow	Rapid
Salvage 'bad' disease?	No	Yes
Who benefits?	~15% across the board	Almost all with BRAF mutation

Some urban myths…

- Myth #1: Ipilimumab is toxic and difficult to use

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- Myth #3: There is no 'tail on the curve' for targeted therapy in melanoma

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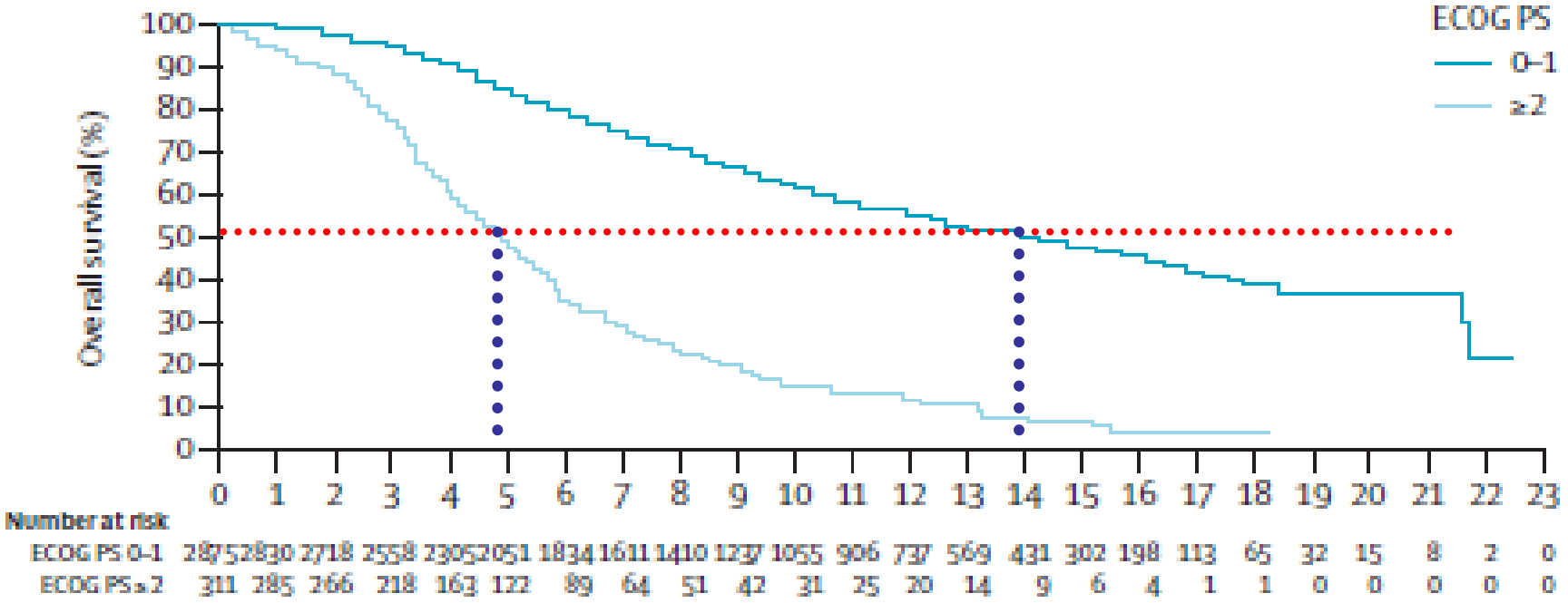
- Myth #2: Targeted therapy should be reserved only for high tempo symptomatic disease
- JL: Targeted therapy works in all patients with the mutation and better in patients with good biology disease
- Myth #3: There is no 'tail on the curve' for targeted therapy in melanoma
- JL: We simply do not know this yet

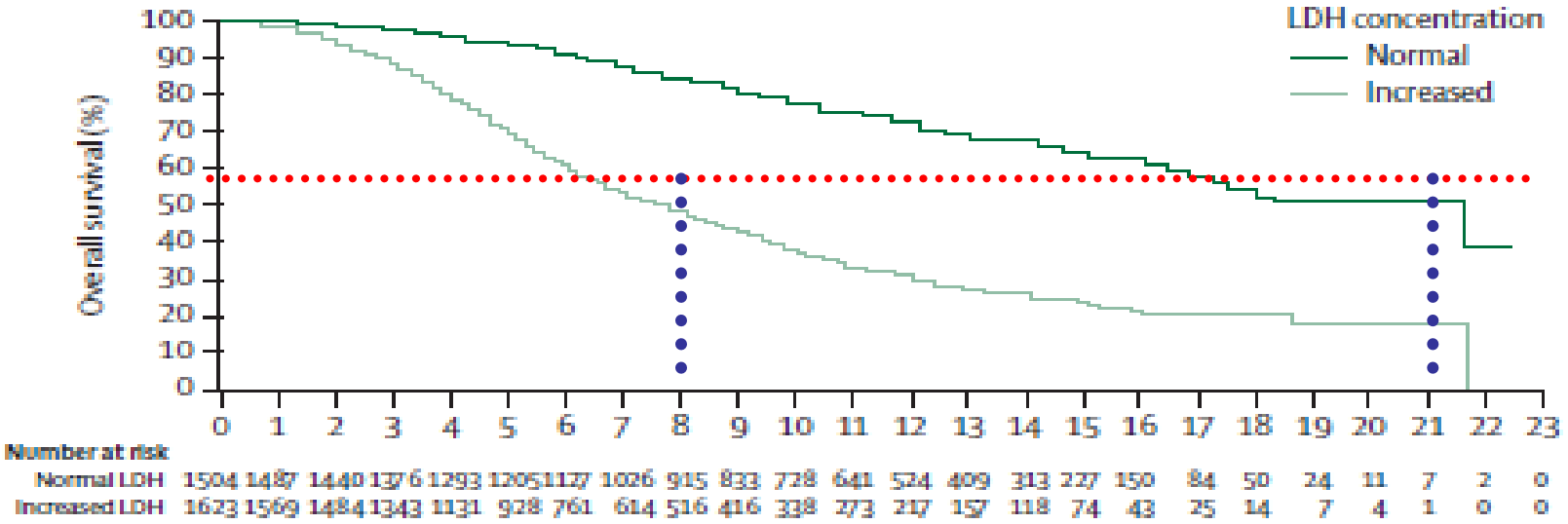
Vemurafenib: better in good biology disease

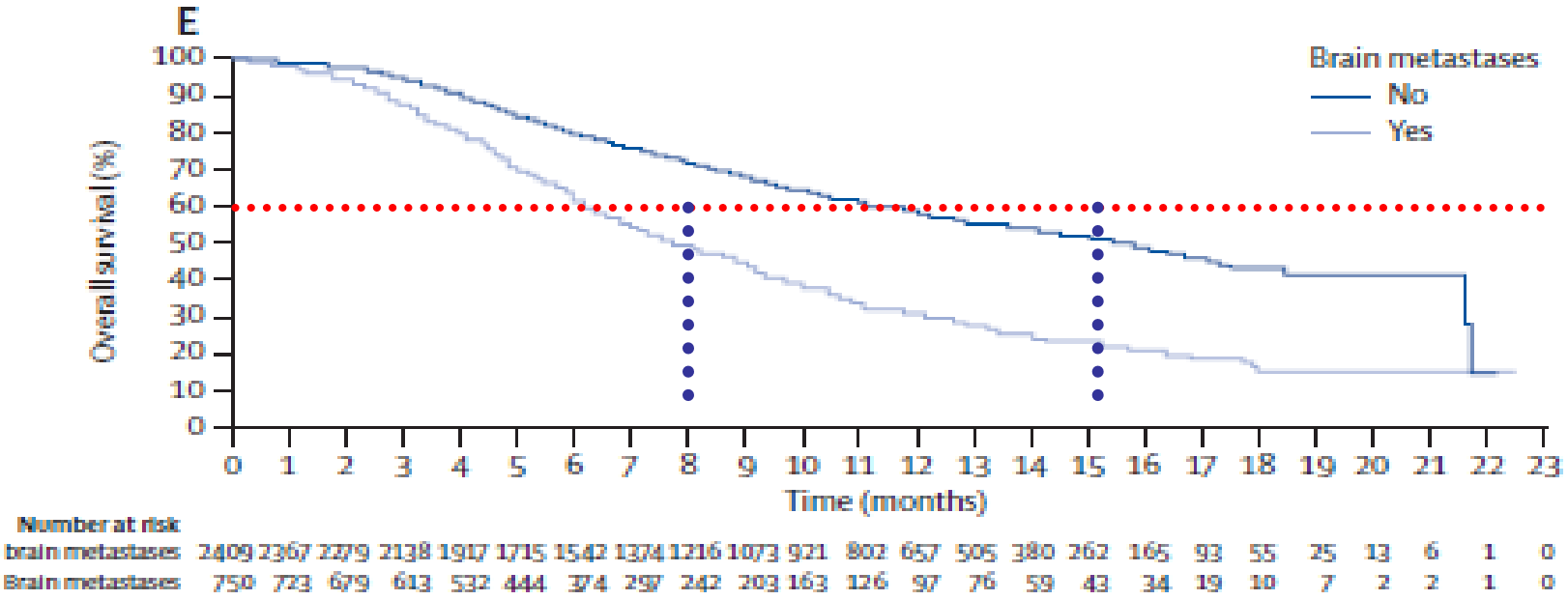


Vemurafenib safety study: 3222 patients with BRAF mutant melanoma; ‘real world’ setting

Larkin Lancet Oncol 2014

Vemurafenib: better in good biology disease





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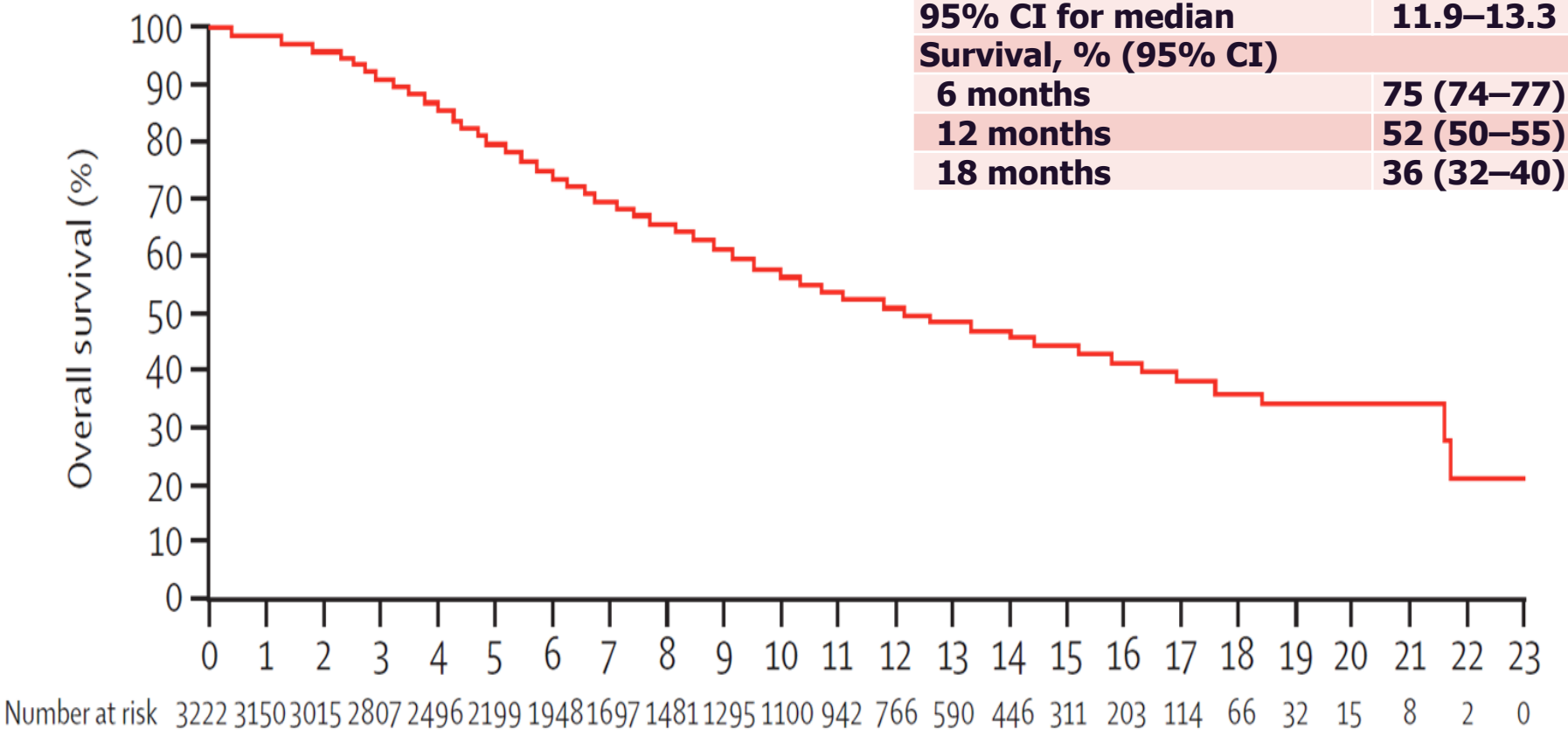
Vemurafenib: tail on the curve?

	N=3222
Median OS, months	**12**
95% CI for median	**11.9–13.3**
Survival, % (95% CI)	
6 months	**75 (74–77)**
12 months	**52 (50–55)**
18 months	**36 (32–40)**



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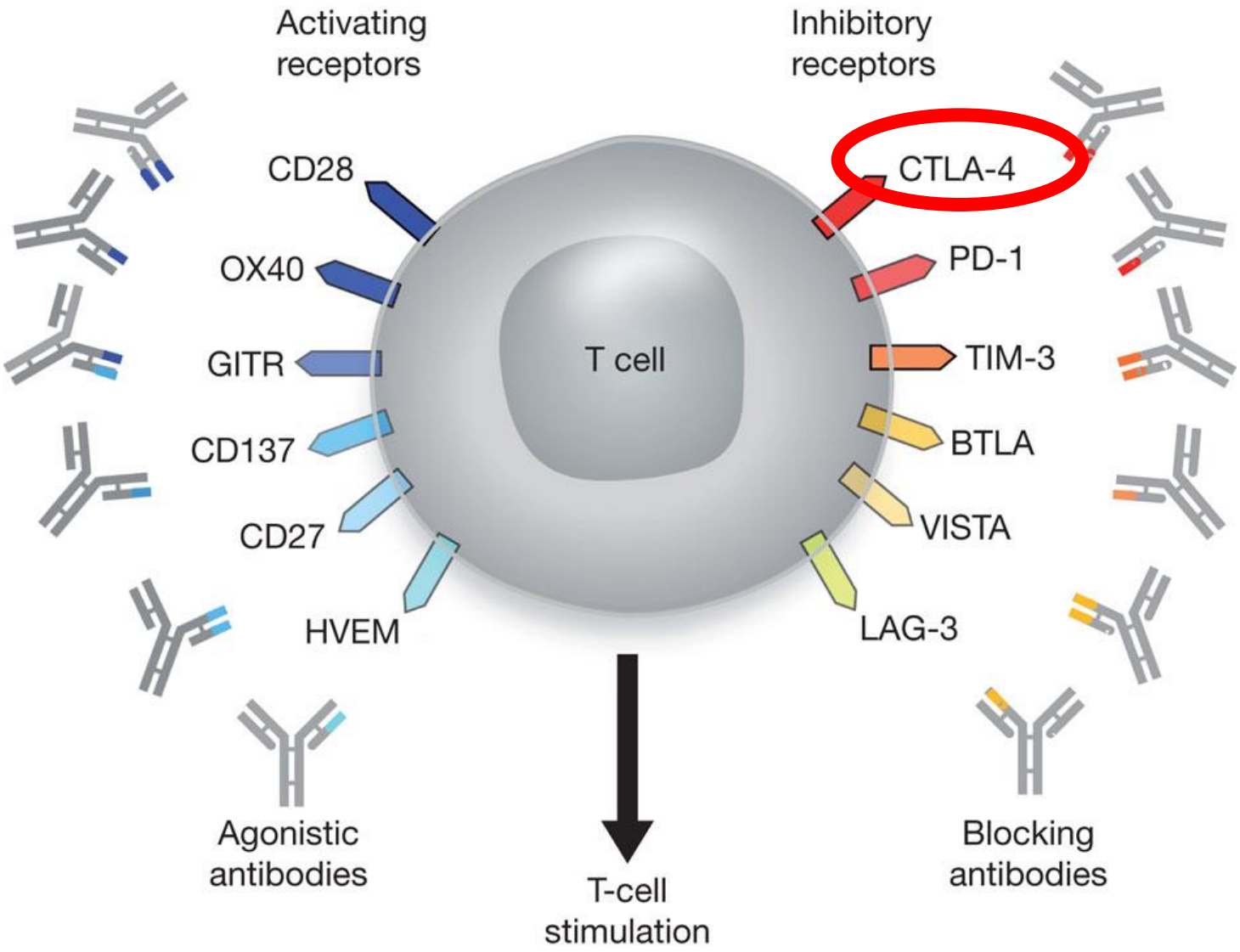
Checkpoint inhibitors: ipi is only the first…



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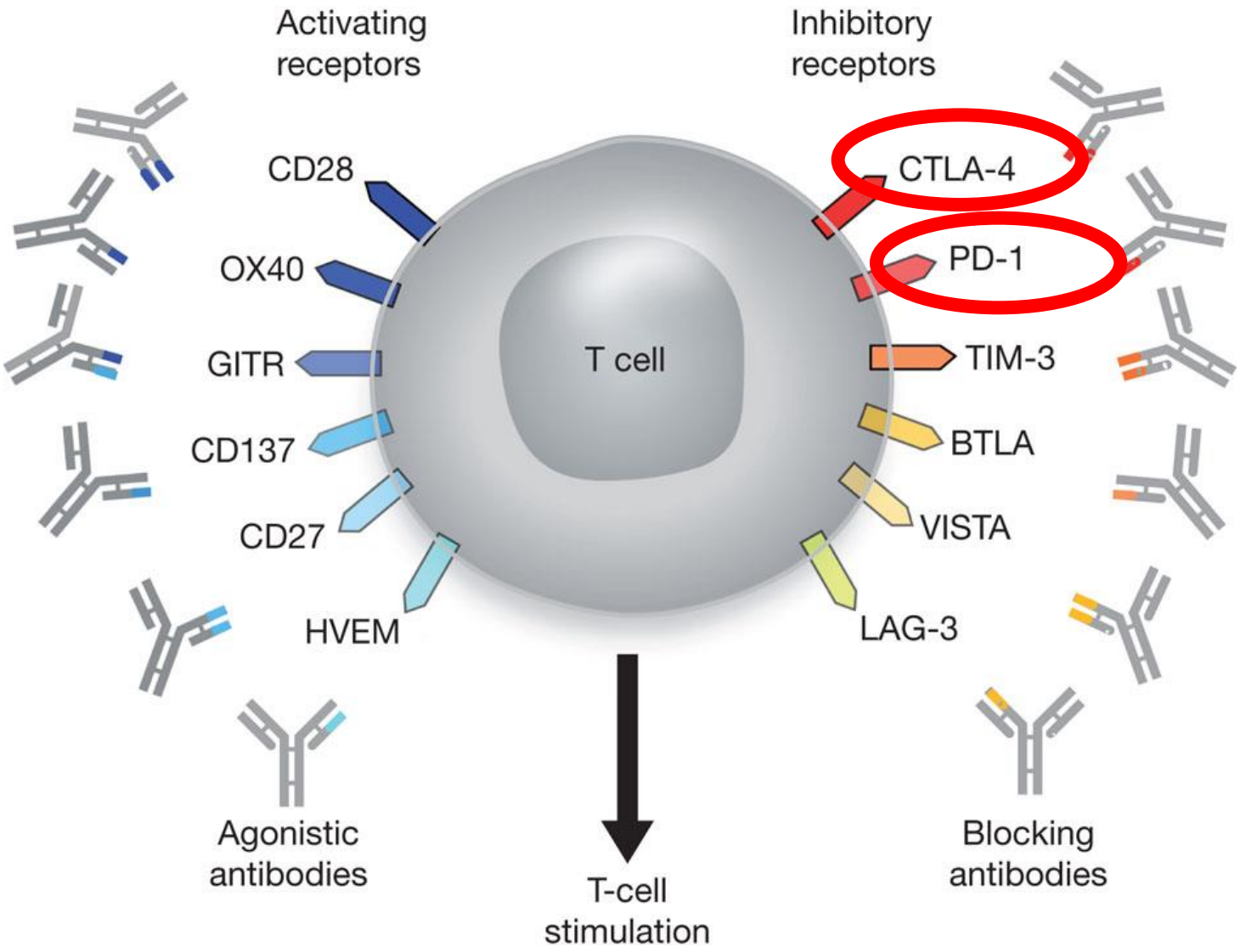
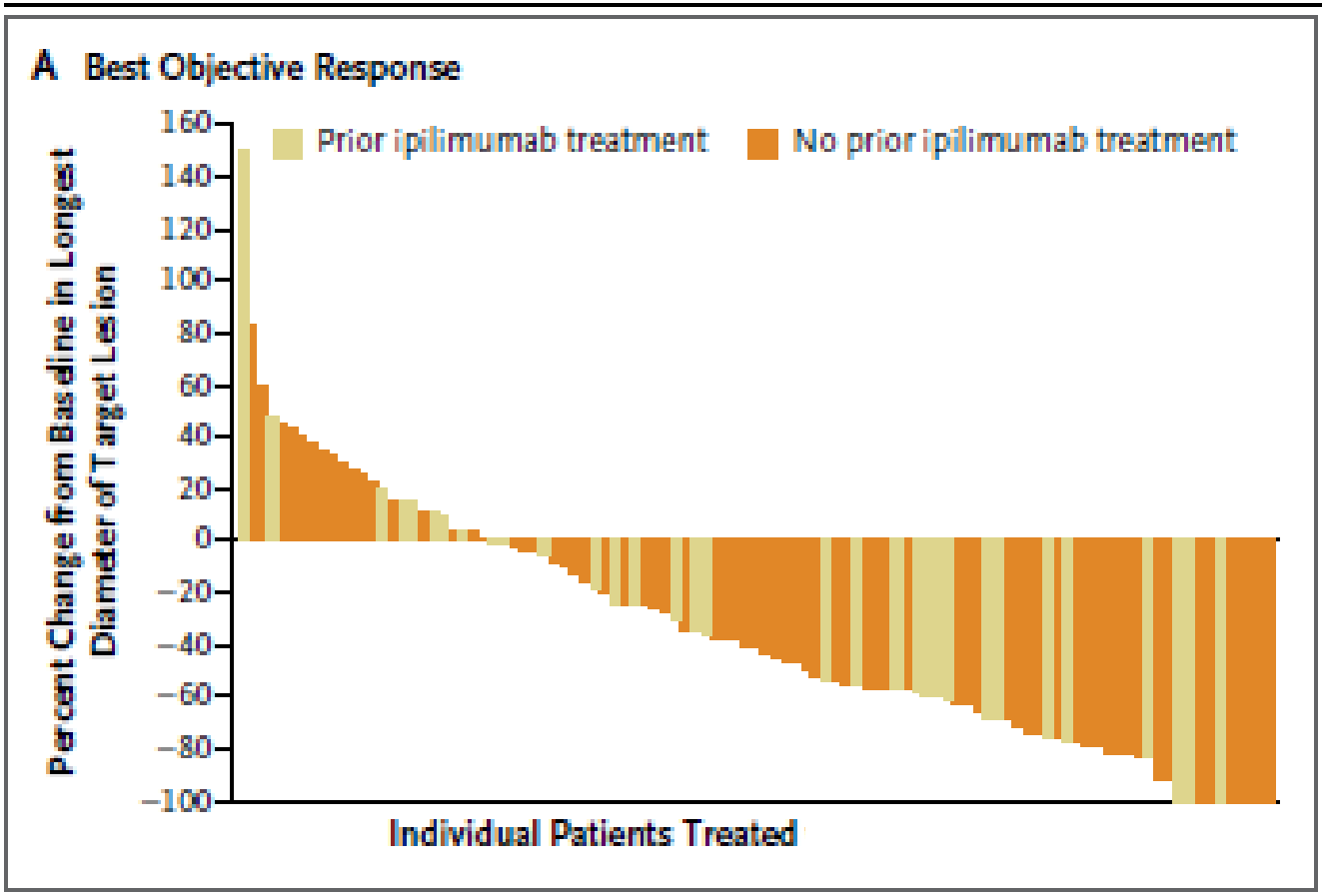


Pembrolizumab phase 1 cutaneous melanoma



Hamid NEJM 2013

Nivo + ipi phase 1 cutaneous melanoma

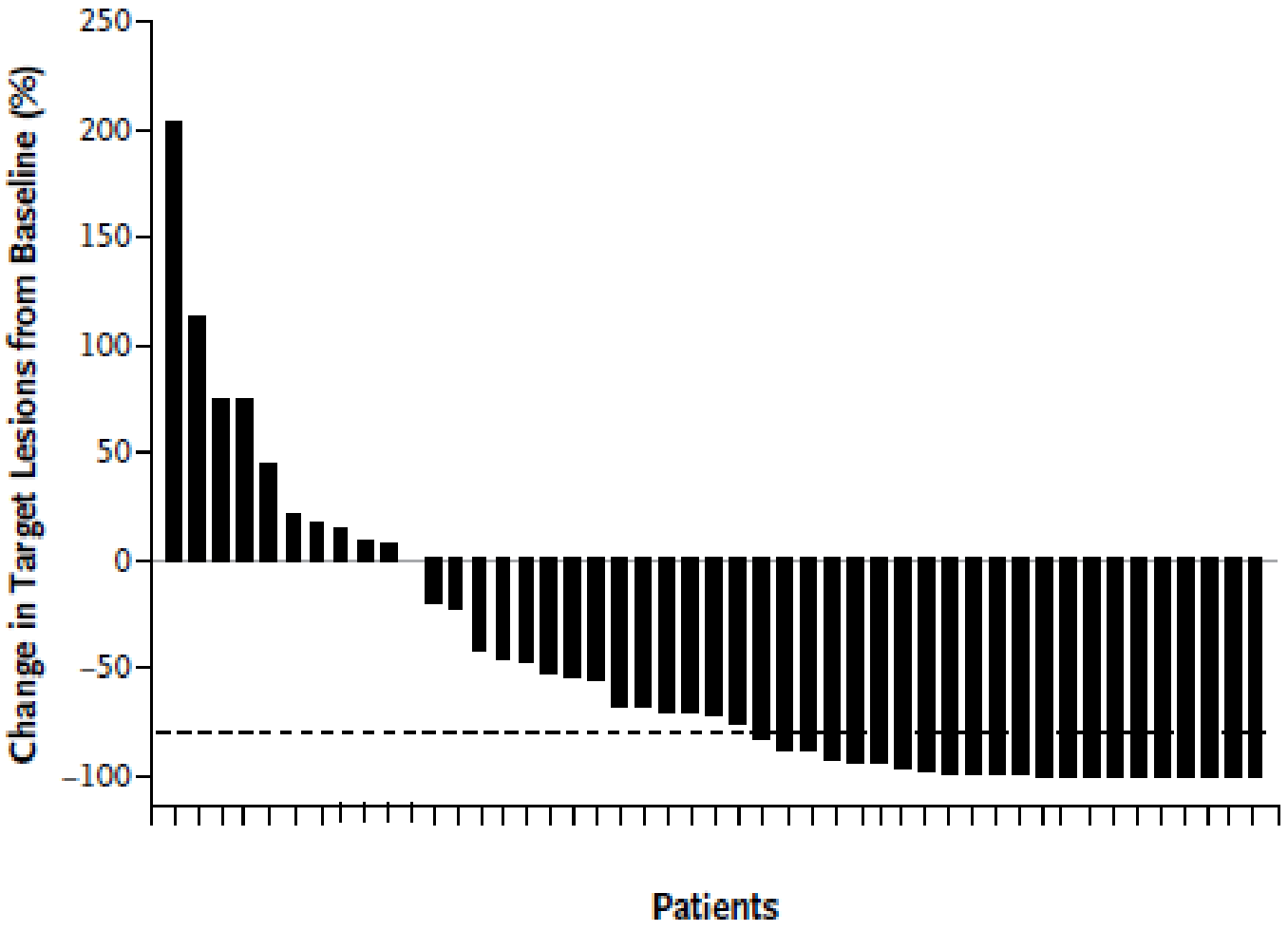
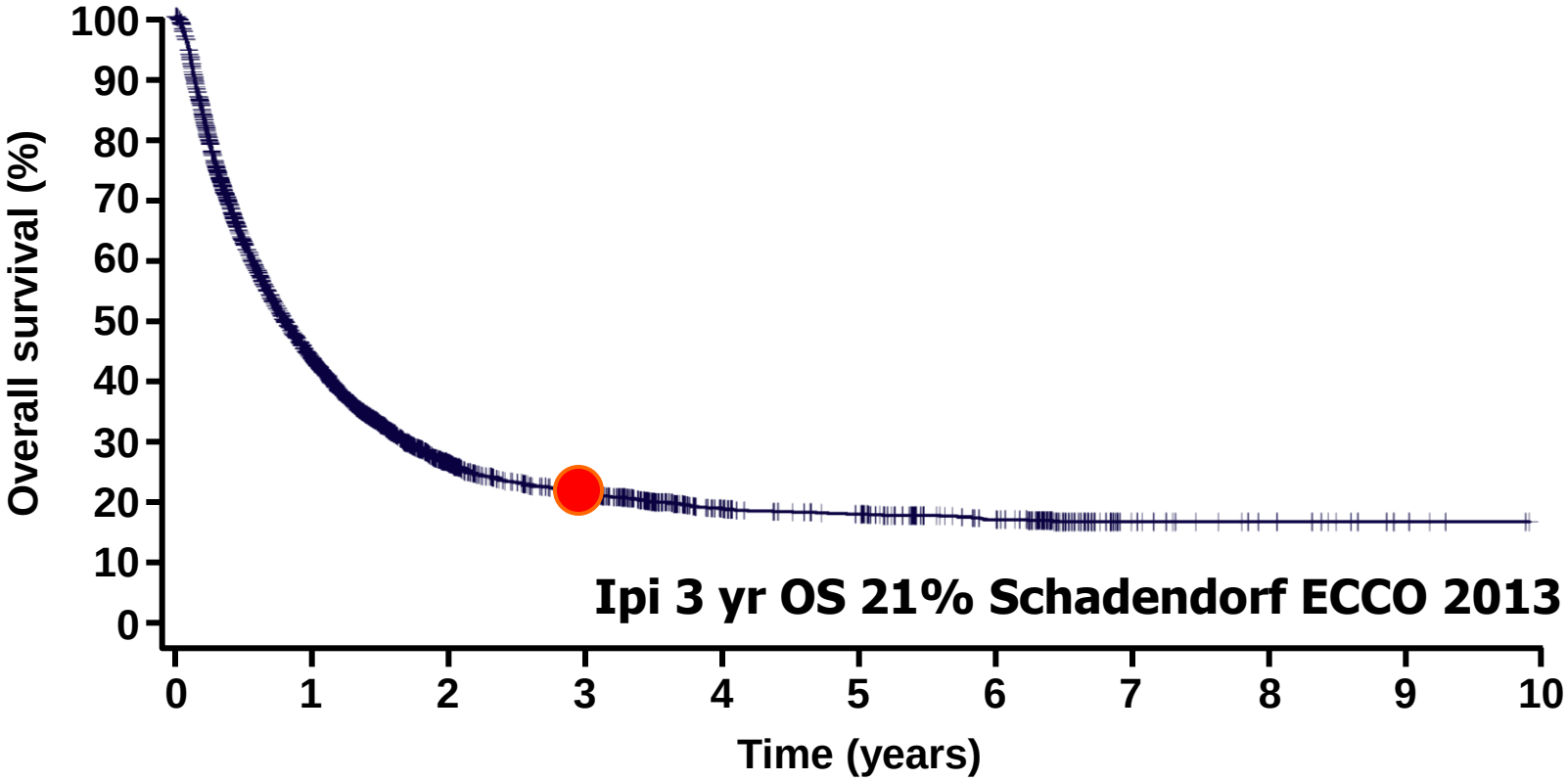


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Wolchok NEJM 2013

Pooled OS analysis including Expanded Access Programme data: 4846 patients



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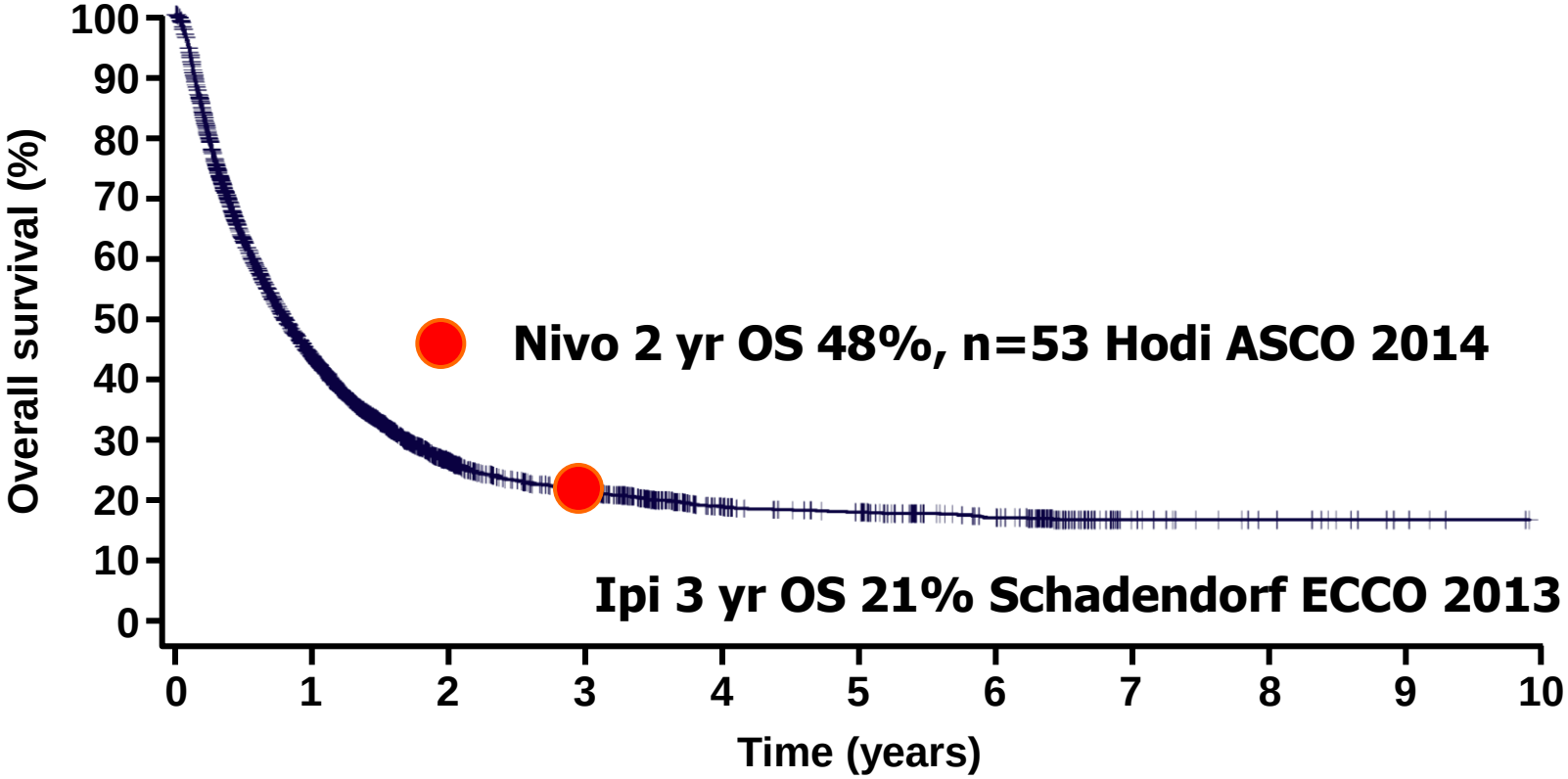

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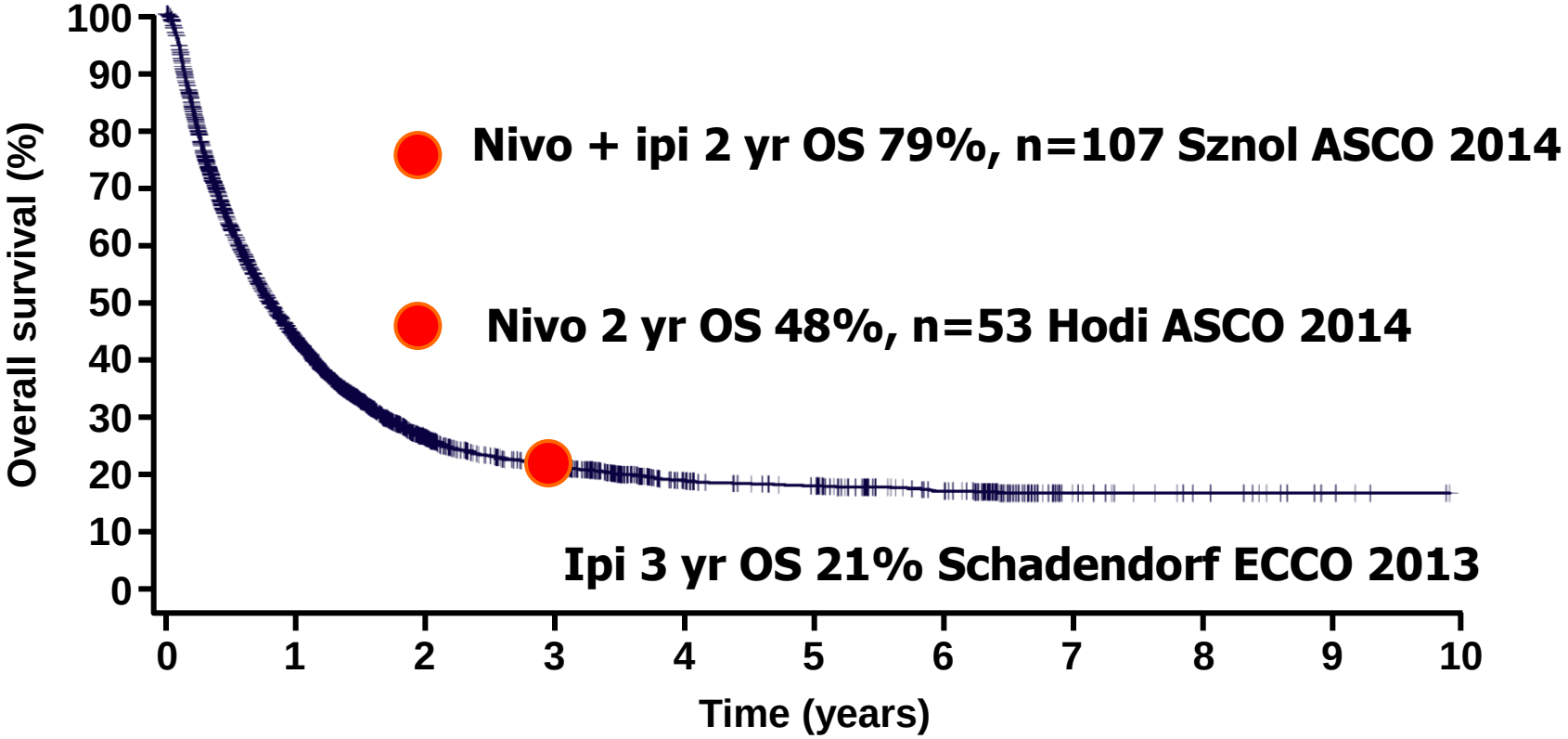

Anti-CTLA4 vs anti-PD1

	Ipilimumab	**Nivo/pembro**
Given how?	Brief course intravenous	Prolonged course intravenous
Side effects?	Temporary	Chronic
Severity?	Mild to moderate but severe ~10%	Generally mild
Prolonged disease control?	Possible	Unknown; perhaps?
Tumour shrinkage	Slow	Can be rapid
Salvage 'bad' disease?	No	Unknown; perhaps?
Who benefits?	~15% across the board	~35% across the board

Speculation on the future

- BRAF targeted therapies and checkpoint inhibitors will share more characteristics than now
- i.e. higher response rate, quicker onset and ability to salvage 'bad' disease for immunotherapy, more durable responses for BRAF targeted therapies
- Schedules will be different
- Combinations of drugs will be used more
- We will be able to define better which patients to treat with each drug

Conclusions

- Clinicians need to be familiar with the different characteristics of targeted and immunotherapies

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- Clinicians need to be familiar with the different characteristics of targeted and immunotherapies
- **This is not a competition; we need to use both to best serve our patients**
- Patient involvement in decision making critical
- Major progress in melanoma 2009-2014
- We must maintain this momentum and aim for prolonged disease control in the majority of patients
- Continued high clinical trial recruitment is needed to do this

Thank you