Oxford University Hospitals NHS
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Systemic treatment for malignant melanoma

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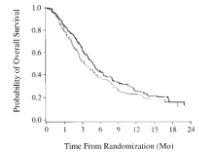
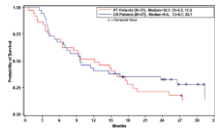
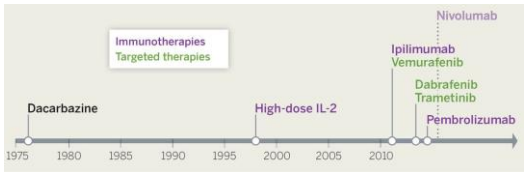
Metastatic melanoma

- Historically very treatment refractory
  - Median survival <12 months
- Chemotherapy traditional treatment until ~2005
  - Dacarbazine
  - Temozolamide
  - Paclitaxel





Metastatic melanoma - progress

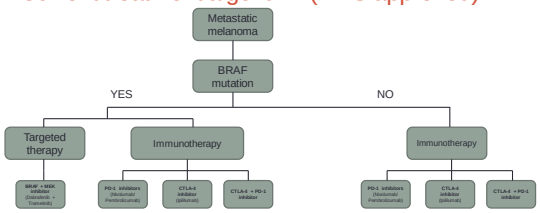


Breakthroughs

- Two significant discoveries
  - 1) "driver" BRAF mutation
  - 2) Immunogenicity

James Allison and Tasuku Honjo

Current treatment algorithm (NHS approved)

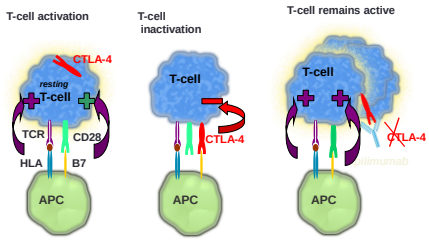


Typically

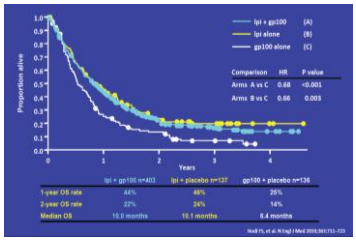
- Immunotherapy first
  - PD-1 followed by CTLA-4 inhibitor
  - Combination for young and fit patients
- Targeted treatment second (for those with BRAF mutation)

IMMUNOTHERAPY

CTLA4 inhibitors (Ipilimumab)



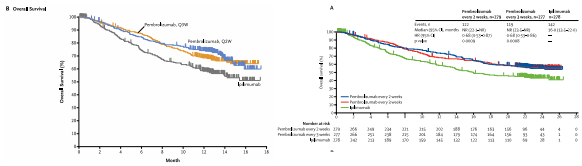
Hodi et al, NEJM, 2010, 363:711-723



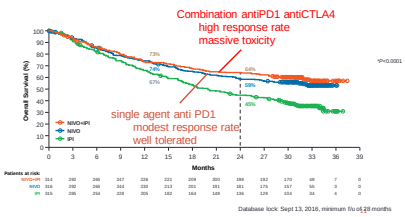
4 x doses
3 weeks apart

PD-1 inhibitors (Pembrolizumab and Nivolumab) - 2015

Ongoing dosing
Every 3 weeks



PD-1 and CTLA-4 inhibitors in combination

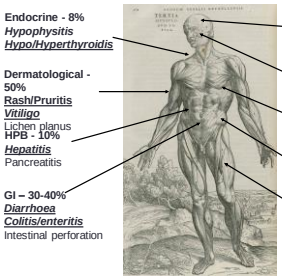


Safety Summary

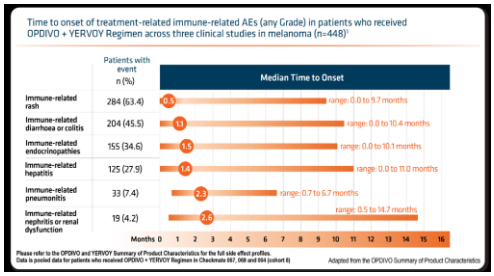
- With an additional 19 months of follow-up, safety was consistent with the initial report[1]

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

Immune-related adverse events (irAEs)



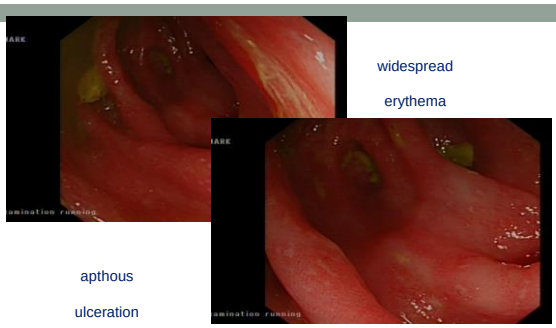
Immune related toxicity - time to



Immune mediated colitis

- Usual onset ~ after 6 weeks
- 10% with ipilimumab, 1-2% with PD1 inhibitors
- Risk of perforation, death

- Management
  - G1: Monitor
  - ≥ G2: Prednisolone 1mg/kg/day
  - Send stool for C.Diff and MC&S
  - Consider flexible sigmoidoscopy/colonoscopy
  - Retreat when improves to Grade 1
  - Escalate to infliximab if not improving

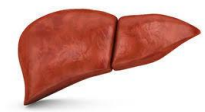


widespread erythema

apthous ulceration

Hepatitis

- ALT/AST elevations
- 8-12 weeks after treatment
- Usually asymptomatic



- Treatment:
  - ≥ G2: Prednisolone 1mg/kg
  - ≥ G3: Steroids + consider stopping permanently
- If not improving
  - Mycophenolate Mofetil
  - ATG

Endocrinopathies

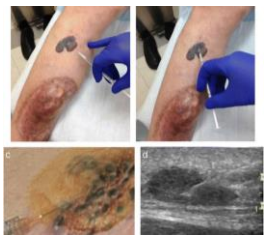
- Thyroid:
  - "Graves like" hyperthyroidism
  - Hypothyroidism
    - Primary (often manifests as thyroiditis progressing to hypothyroidism
    - Secondary (due to hypophysitis)
    - Check T4, TSH
    - Replace if symtomatic
- Pituitary (hypophysitis)
  - Low TSH, ACTH Cortisol
  - Cortisol preferably 9am
  - Caution if am cortisol <150
  - Replace with oral hydrocortisone
  - Check in any patient with fatigue
- Adrenal insufficiency
  - Low cortisol
  - Replace in hypophysitis
  - Higher dose steroids if unwell
- Type 1 Diabetes Mellitus
  - Rare (0.2%)
  - Can present as DKA

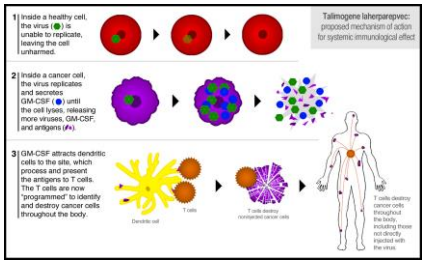
Other toxicities

- Renal
  - Acute interstitial nephritis
- Neurological
  - 1-2%
  - Guillain-Barre
  - Autoimmune encephalitits
- Cardiovascular
  - Myocarditis
- Pneumonitis
  - 5%
  - Can manifest as radiation recall
- Haematological
  - Cytopenias
- Rash
  - Topical steroids
- Rheumatological
  - Inflammatory arthritis

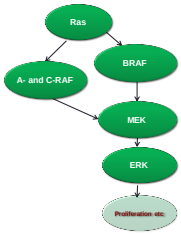
T-VEC (Talimogene laherparepvec)

- Oncolytic virus (engineered HSV-1virus)
  - Deletion of ICP34.5 gene (eliminate neuropathogenecity)
  - Addition of GM-CSF gene
- Two mechanisms of action
  - Preferential infection of tumour cells (local effects)
  - Presentation of tumour antigens to surrounding T-Cells (systemic effects)
- Response rates 40%



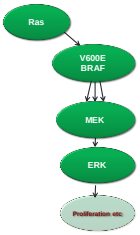


TARGETED THERAPY



MAPK pathway

Adapted from Mark Middleton



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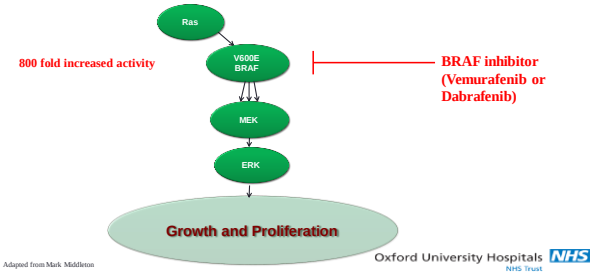

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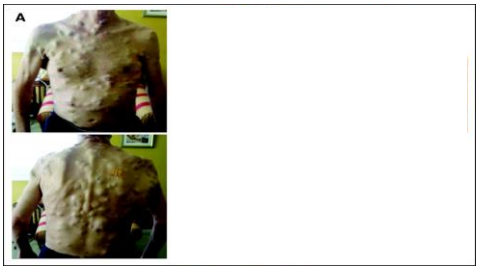
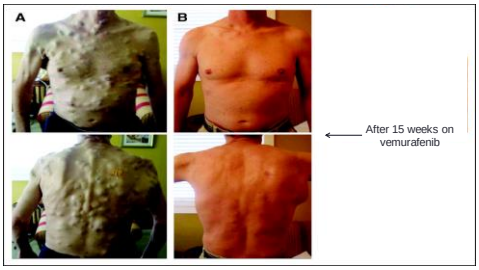


Wagle N et al. JCO 2011;29:3085-3096

JOURNAL of CLINICAL ONCOLOGY ASCO



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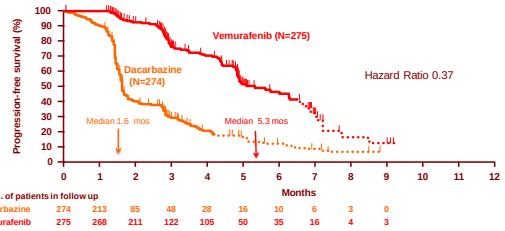
BRIM 3: Progression-free survival



Chapman PB, *et al. N Engl J Med* 2011 Jun 5

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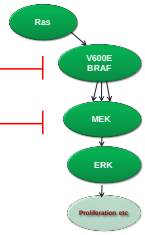
Minimising toxicity and delaying development of resistance

Combination treatment with BRAF inhibitor and MEK inhibitor



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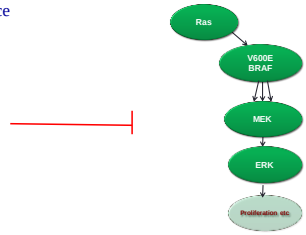
Minimising toxicity and delaying development of resistance

Trametinib

Cobimetenib

Binimetenib

Selumetinib



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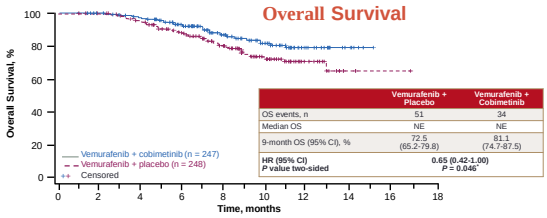


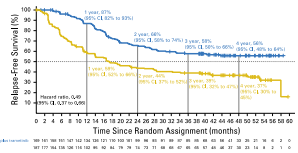
CI, confidence interval; NE, not estimable. Data Cutoff: May 9, 2014

* Descriptive p-value. Did not cross the pre-specified stopping boundary for the interim analysis (boundary p <0.00000037)

Larkin, et al New England Journal of Medicine 2014, 371; 20 – slide from ESMO presentation 2014

Adjuvant BRAF/MEK inhibition

- Dabrafenib/Trametinib
  - 12 months
  - Improvements in PFS and OS
  - Standard of care for resected stage III melanoma



BRAF inhibitors - indications

- Usually second line
- First line in high volume, highly symptomatic cases
  - Can be used in patients with very poor performance status
  - Can work in days
  - Therapeutic window much larger compared to chemotherapy
- Make sure all patients with metastatic melanoma have a BRAF result

BRAF inhibitor toxicities

- Photosensitivity (vemurafenib)
- Fevers (dabrafenib)
- Skin reactions
  - Squamoproliferative lesions
  - Hyperkeratosis
  - Various rashes…
- Arthralgias/Myalgias/Fatigue
- QTc prolongation
- Renal /Liver dysfunction (rare)
- Retinal vein occlusion

Greatly reduced when combined with MEK inhibitor

BRAF inhibitor toxicities - Management

- If in doubt: Stop treatment
  - Symptoms usually resolve within days
  - Cancer wont progress rapidly (patients may need some reassurance)
- Specific treatments
  - Skin
    - Emolients.
    - SCC's: Resection (often shave)
  - Fevers:
    - Consider steroids in severe cases
  - All others:
    - Stop treatment and wait to resolve
    - Consider dose reduction

Treatment of brain metastases

- Medical
  - BRAF/MEK inhibitors
    - Can cross blood brain barrier
  - Immunotherapy
    - Combination immunotherapy active in asymptomatic disease
    - Single agents generally not effective
    - No role in symptomatic brain lesions
- Surgery
- Stereotactic radiotherapy
- Whole Brain Radiotherapy
  - Rarely used nowadays
- Surgery/RT indicated for patients responding elsewhere apart from the brain
- Medical treatment does not have to stop

Relevant issues for palliative care

- Prolonged toxicity (particularly with immunotherapy)
- Effective treatments with large therapeutic windows
  - Potential to treat frailer patients
  - BRAF/MEK inhibitors can be effective in ECOG >2
- Treatments can offer effective palliation
- Survivorship
- Managing patient expectations
- Palliative support for patients on active treatment

Case report GB

- 44 year old male
- Married, 10 year old son
- BRAF mutant melanoma
- Metastatic disease at presentation
  - Liver
  - Bone
  - Nodes
- Commenced combination immunotherapy Sept 2018

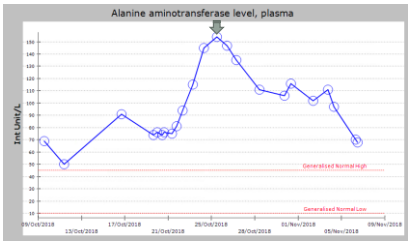
GB

- Completed 2 cycles
- Unwell
  - Drowsiness
  - Elevated LFTs
  - Calcium of 4.5
- Restaged October ‘18
  - Progressive liver mets with ascites
  - Subcutaneous metastases
  - New bone lesions
  - New, large volume nodal metastases
- PS 4
  - Reduced GCS
  - Unable to speak
  - Able to swallow…
- No improvement in steroids or zolendronic acid
- Commenced end of life care
  - Syringe driver

GB

- Long discussion with wife re: Dabrafenib and trametinib
- Low expectations, “nothing to lose”
- Consented on the basis of best interests
- Commenced Dabrafenib and Trametinib

Dabrafenib/Trametinib



GB

- Clinical improvement within days
  - Woke up
  - Speaking clearly
  - Eating/drinking
  - Wife amazed
  - Vicar even more amazed
- However
  - Highly anxious
  - Very oedematous
  - Limited mobility
  - Numerous falls
  - Far from discharge
  - Staph sepsis (req long line)

GB

- Transferred to Sue Ryder
- Still actively treated
- Numerous issues
  - Treatment for sepsis
  - Poor mobility
  - Very anxious
  - Hasn't told his son about his diagnosis
  - Active or palliative care??
  - Goals of care?
  - Patients and families expectations?
  - What did we (oncologists) expect from this treatment?
- Currently
  - Complications to dealt with on a case by case basis
    - Reversible?
    - Appropriate?

GB

- More cases likely as treatments improve
  - Melanoma
  - Lung
- Blurring of boundaries between active and palliative care

Thank you