Personalised Treatment For Melanoma

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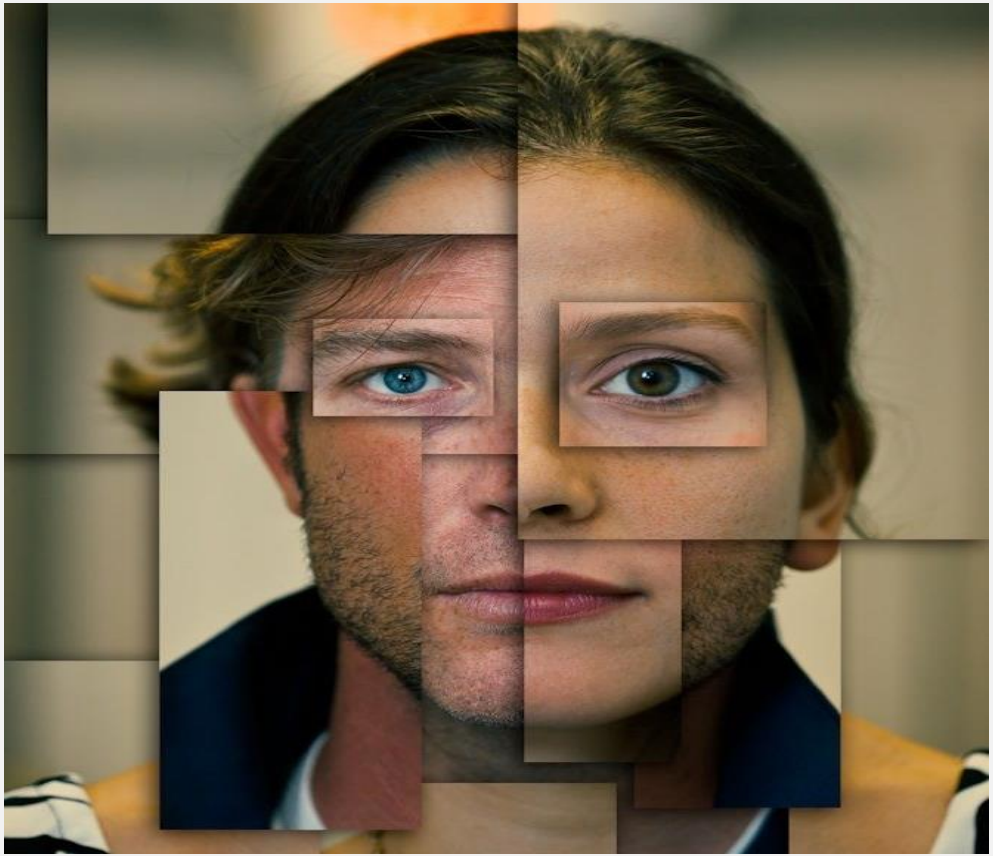
www.christie.nhs.uk/services/i-to-q/melanoma/

A personalised approach



Goals

- Advice or treatment personalised to the individual
- Decisions made in real time
- Dynamic - ongoing monitoring and decision making
- Evidence based

Definitions

- **Biomarker**: measurable marker of biological state or condition
- **Prognostic biomarker**: predicts outcome
- **Predictive biomarker**: predicts response to treatment

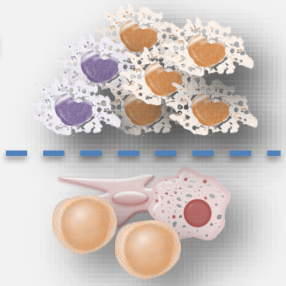
Prognostic And Predictive (Bio)markers For Stage IV Melanoma

1  Patient

- Age, sex, ECOG PS
- # of metastatic sites
- Microbiome
- Vitiligo
- Skin rash
- Immune toxicity

2  Blood

- LDH
- cfDNA

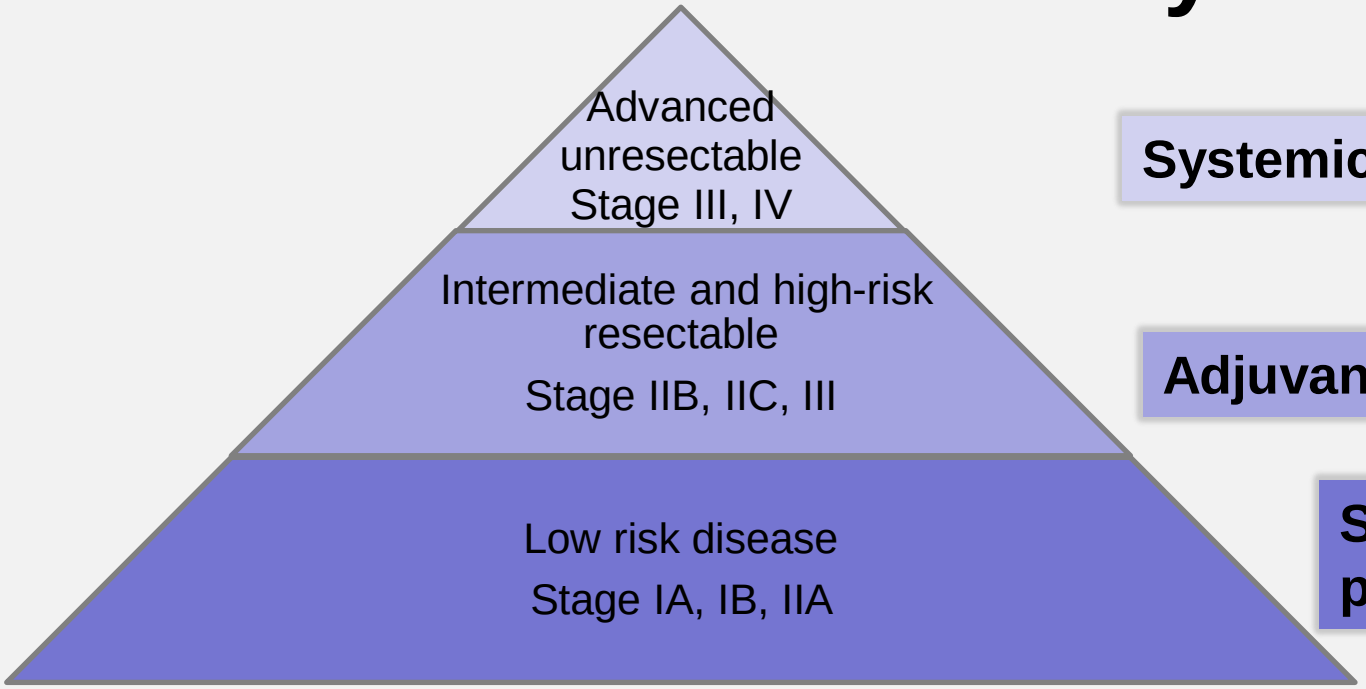
3  Tumour

Microenvironment

- BRAF, CKIT, NRAS
- PD-L1
- Neo-antigens
- TILs
- Inflamed phenotype
- Tregs

Baseline ***On treatment***

Distribution of Melanoma by Stage



Systemic Therapy

Adjuvant Therapy

Secondary prevention

The burden of low and intermediate disease dwarfs that of advanced melanoma

The Low Risk Paradox

		Queensland[2]	USA[3]
Thickness category	**5 year survival[1]**	**Cases n=13,006**	**Cases n=49,319**
0.01-1.00mm	97%	72%	72%
1.01-2.00mm	88%	14%	16%
2.01-4.00mm	74%	9%	8%
>4.00mm	56%	5%	4%

1 Shaikh et al, JNCI 2016; 2 Whiteman DC, et al. J Invest Dermatol 2015; 3 Landow et al. J Am Acad Dermatol. 2016

The Low Risk Paradox

		Queensland[2]		USA[3]	
Thickness category	**5 year survival[1]**	**Cases n=13,006**	**Deaths n=1,021**	**Cases n=49,319**	**Deaths n=3,660**
0.01-1.00mm	97%	72%	29%	72%	29%
1.01-2.00mm	88%	14%	27%	16%	27%
2.01-4.00mm	74%	9%	26%	8%	27%
>4.00mm	56%	5%	18%	4%	17%

1 Shaikh et al, JNCI 2016; 2 Whiteman DC, et al. J Invest Dermatol 2015; 3 Landow et al. J Am Acad Dermatol. 2016

Primary Melanoma

AJCC staging system

- Version 8 January 2018
- Snapshot in time based tumour appearance and stage

Molecular predictors

- Reflects the biology of the tumour?

Vitamin D

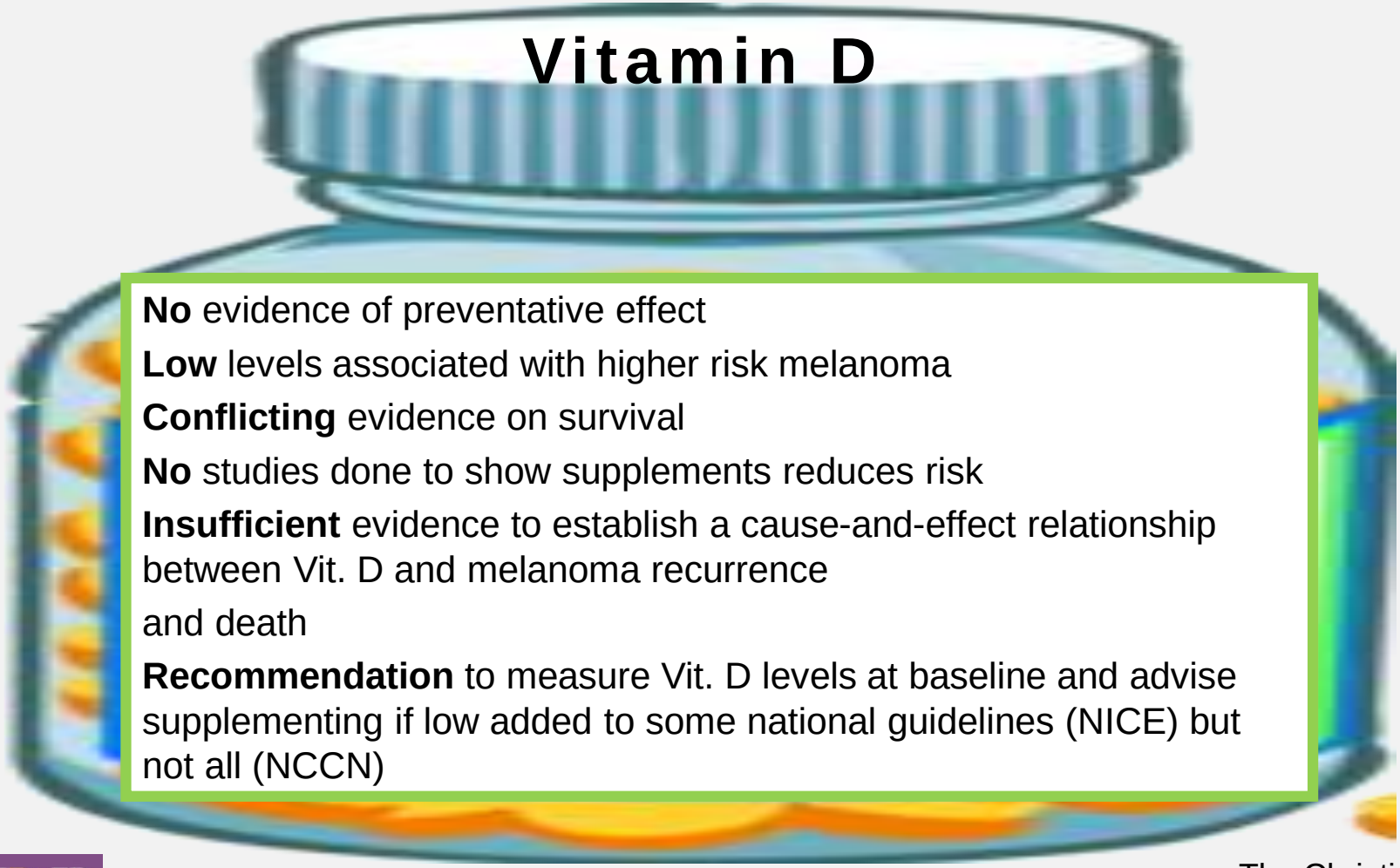
- Correlates with tumour risk

DecisionDX-Melanoma

- 31 gene signature
- Binary classification: Class-1 Low risk, Class-2 High risk
- Emerging evidence that it is an effective prognostic factor, needs further validation

1.Gerami et al. CCR 2015; 2.Gerami JAA Derm 2016; 3.Zager et al JCO 2016

Vitamin D



No evidence of preventative effect

Low levels associated with higher risk melanoma

Conflicting evidence on survival

No studies done to show supplements reduces risk

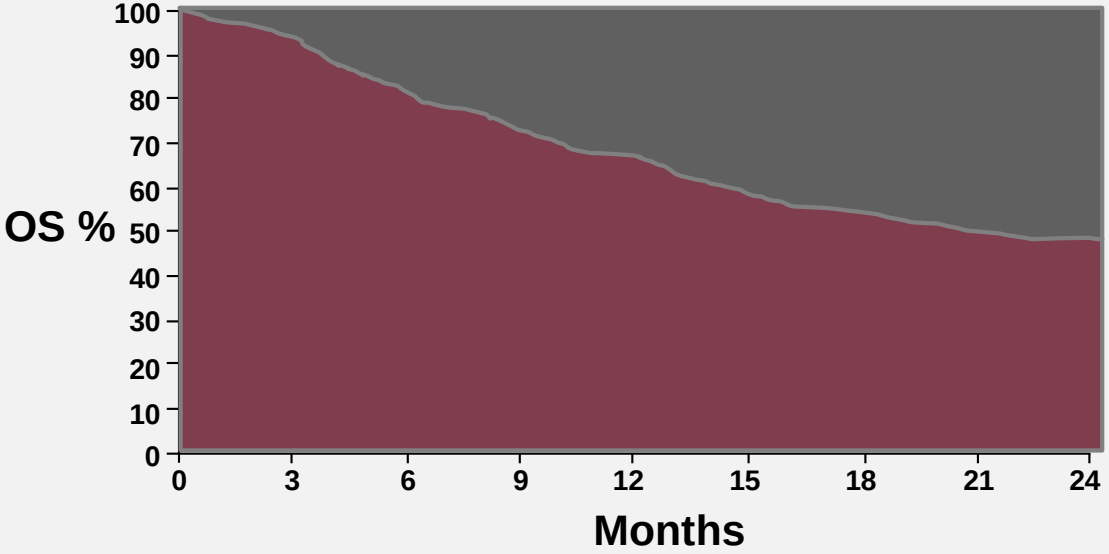
Insufficient evidence to establish a cause-and-effect relationship between Vit. D and melanoma recurrence

and death

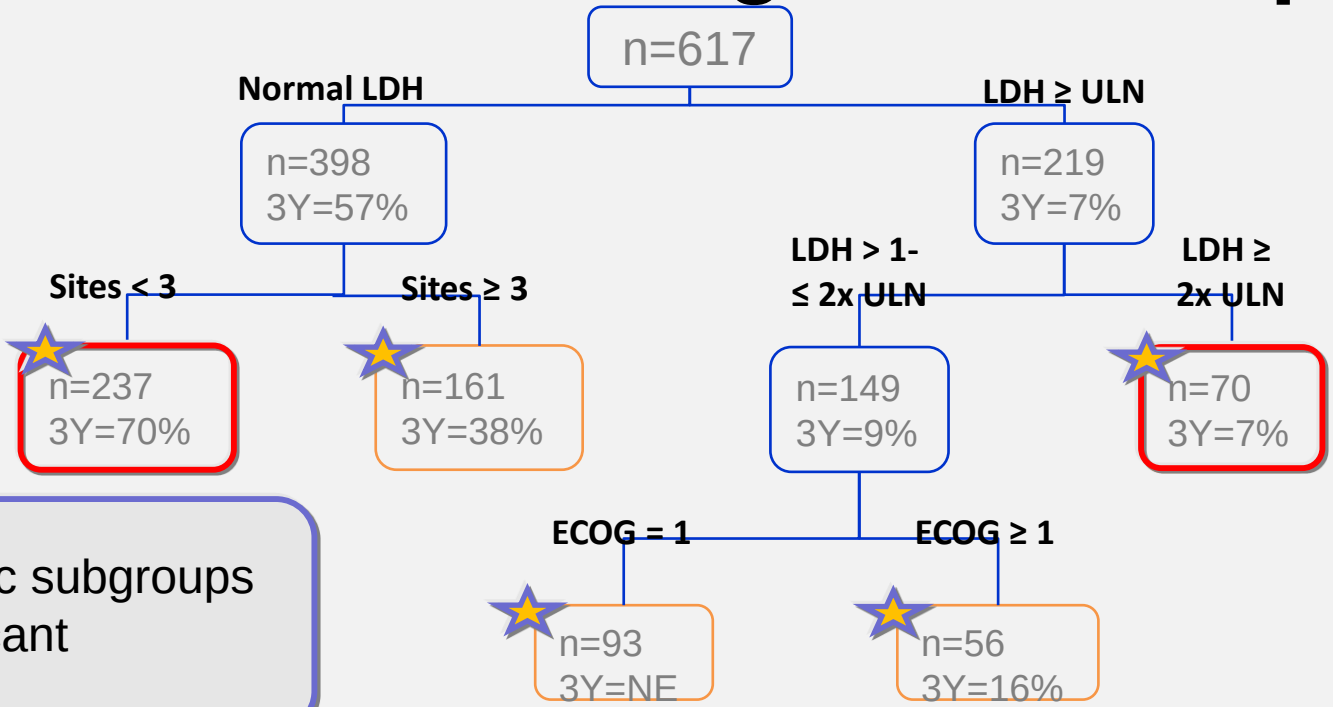
Recommendation to measure Vit. D levels at baseline and advise supplementing if low added to some national guidelines (NICE) but not all (NCCN)

We still need to improve our treatment

Overall Survival in advanced melanoma



Baseline Factors Influencing Outcome with Targeted Therapy

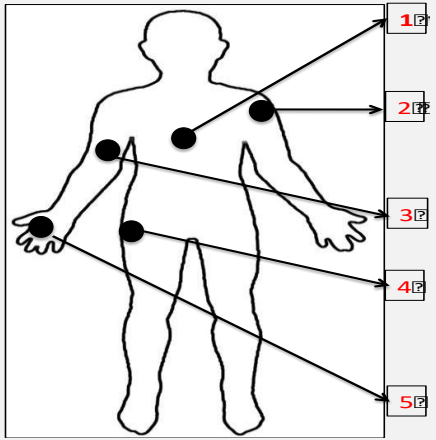


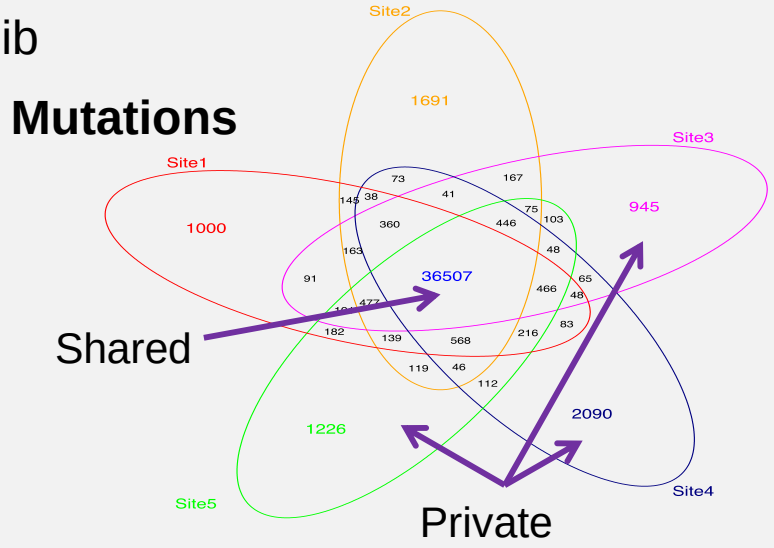
5 prognostic subgroups with significant differences

Adapted from:
GV. Long, SMR 2015, JCO 2016
K. Flaherty, ASCO 2016

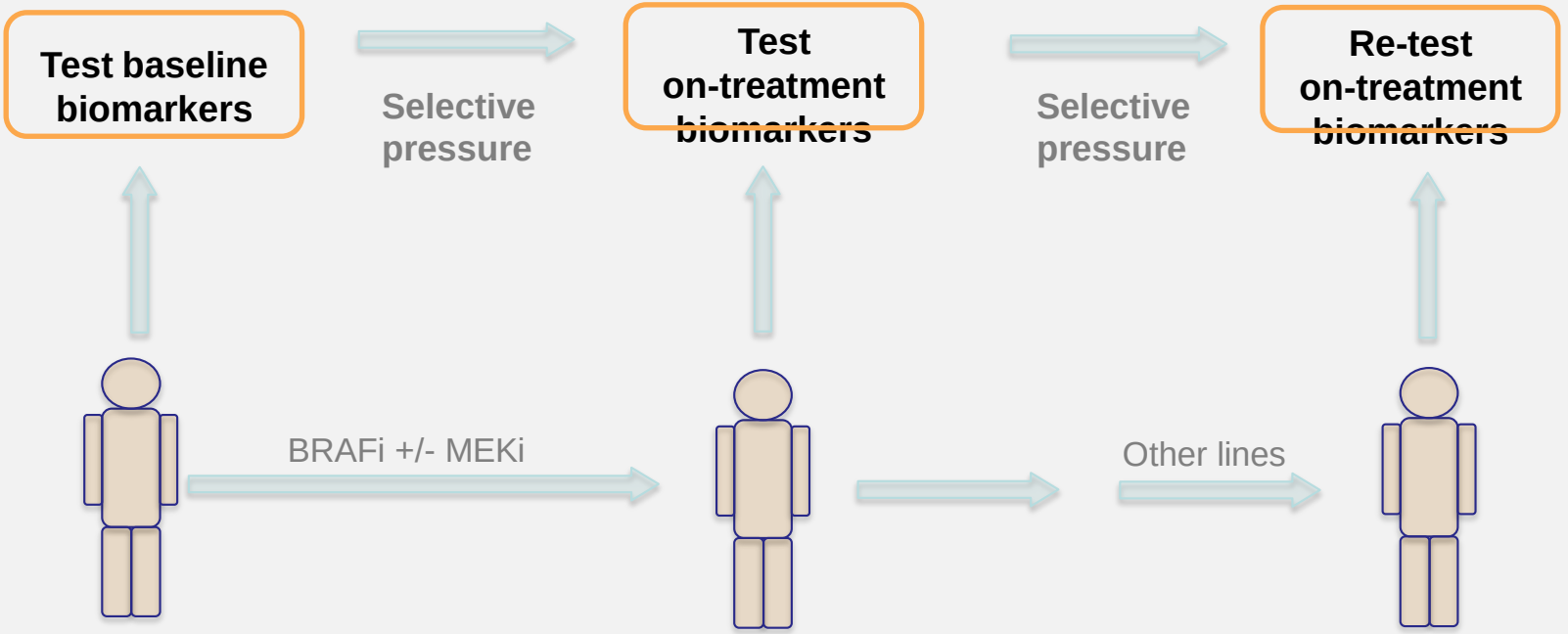
Mutations

- A 26-year-old male
- Surgery for thick ulcerated cutaneous melanoma
- Developed metastatic disease
- BRAF mutation, darafenib and trametinib
- Initial response then progression

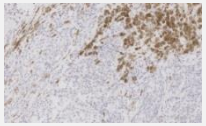




Clinical And Molecular Predictors Of Outcome For MAPKi



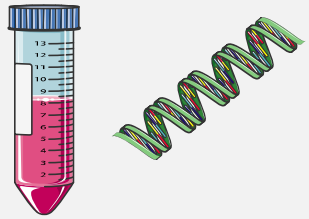
Personalised medicine platform in melanoma



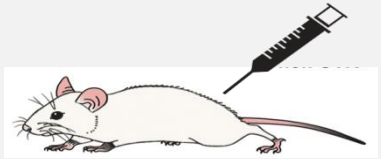
Pathology

Patient derived xenograft

Circulating tumour DNA (ctDNA)

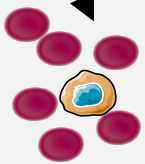


Sequential Samples



Circulating tumour cell derived xenograft

Cell lines

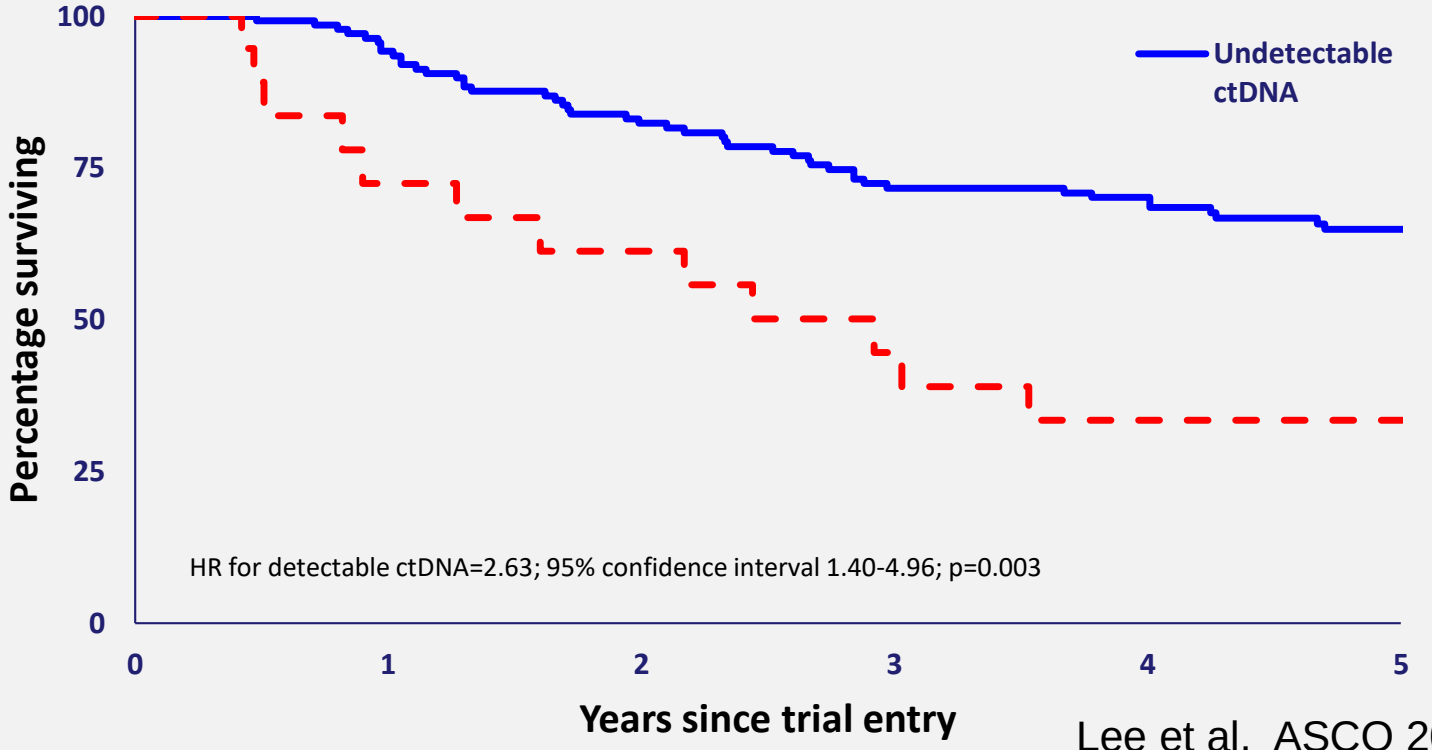


Circulating tumour cells

ctDNA is produced by tumour cells, it is not entirely clear how it enters the circulation. It is useful in many ways:

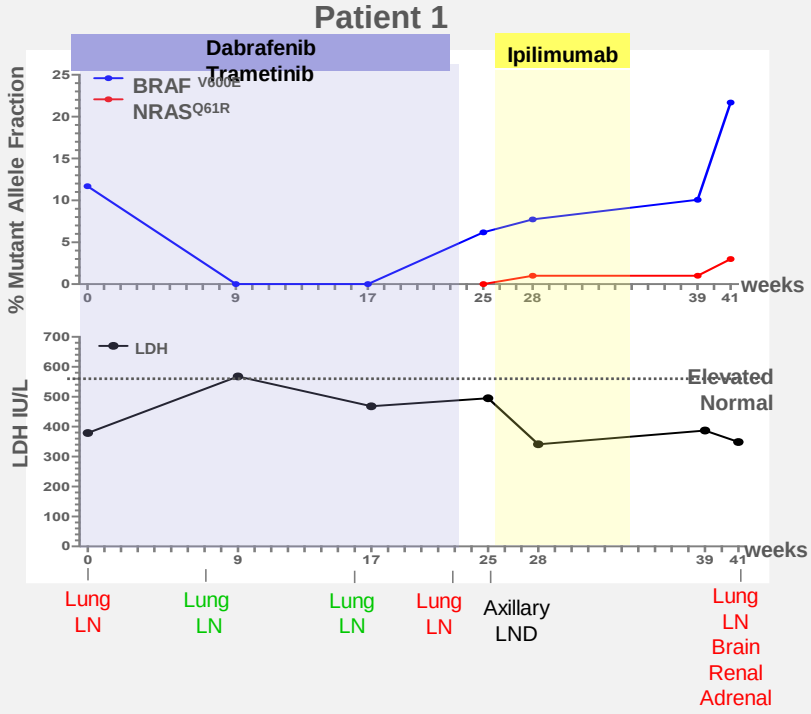
- As a **prognostic biomarker**
- To monitor **tumour activity/burden**
- As a b**iomarker of response** to therapy
- To identify **mechanisms of resistance**
- To characterise **tumour *heterogeneity*** (differences between tumour cells at separate sites in the same person)

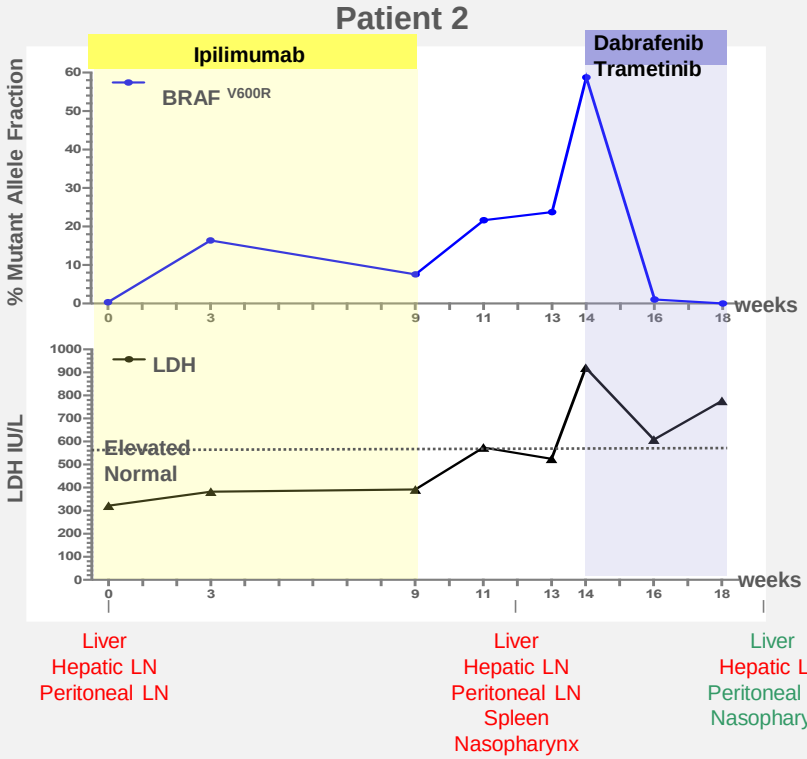
Predicting survival following surgery for high risk stage II/III melanoma



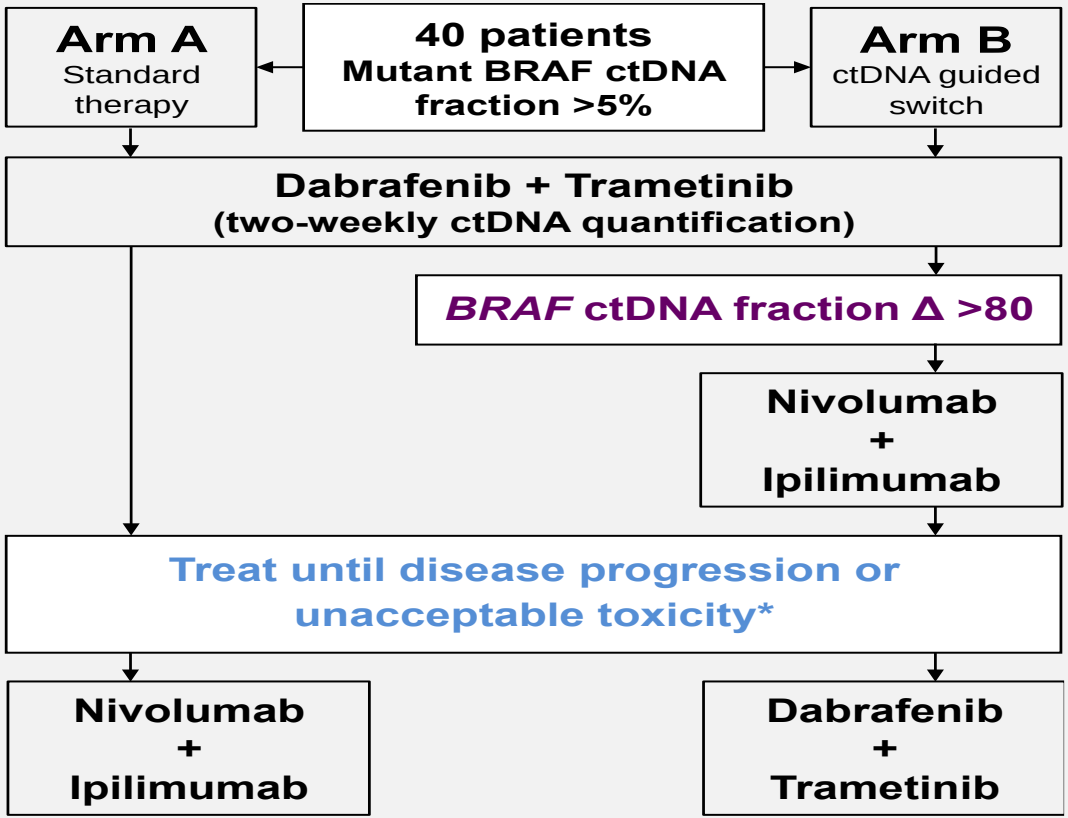
Lee et al. ASCO 2017

Circulating tumour DNA reveals patient responses to immunotherapy treatment





Trial Design



*If unacceptable toxicity on immunotherapy only switch to dabrafenib plus trame8nib if confirmed disease progression

Conclusion

Personalised treatment in melanoma

- Not yet standard of care
- Requires new skills – different MDT
- Resource intensive, but may be cost effective
- Huge potential to improve outcomes in adjuvant setting and advanced disease

Challenges

- Technology is ahead of treatment advances
  - Accessing novel drugs
  - Combining treatments
- Real time decision making