The Royal Marsden NHS
NHS Foundation Trust

Targeting the PI3K/AKT/mTOR Pathway in Renal Cell Carcinoma

Signalling Pathways in Cancer
2014

James Larkin PhD FRCP
Royal Marsden Hospital

Disclosures

- Research funding: Pfizer and Novartis
- Consultancy (non-remunerated): Pfizer, Novartis, GSK, BMS, Roche, Merck

Overview

- Progress in advanced RCC 2007-2014
- Randomised trials of mTORi in RCC
- How can the role of mTORi in RCC be expanded?
- Predictive biomarkers for mTORi
- Intratumour heterogeneity: implications for predictive biomarkers

Progress in Advanced Kidney Cancer 2007-2014

Neoadjuvant / Pre-operative	Adjuvant	1st Line Relapse	2nd Line Relapse	3rd Line Relapse
?	?	SUNITINIB PAZOPANIB IFN-α + BEVACIZUMAB TEMSIROLIMUS	EVEROLIMUS (post-VEGFR-TKI) AXITINIB (post-VEGFR-TKI/ immunoRx) SORAFENIB (post-immunoRx) SUNITINIB (post-immunoRx) PAZOPANIB (post-immunoRx)	SORAFENIB (post-VEFGR-TKI + mTORi) EVEROLIMUS (post-VEGFR-TKI x2)
		Median PFS 9 months	**Median PFS 4-5 months**	**Median PFS 4-5 months**

Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1st line
- EVE vs sunitinib 1st line
- EVE + BEV vs IFN + BEV 1st line
- TEM + BEV vs IFN + BEV 1st line
- EVE vs placebo post sunitinib/sorafenib
- TEM vs sorafenib post sunitinib

Hudes NEJM 2007; Motzer Lancet 2008 and ASCO 2013; Hutson JCO 2013; Rini JCO 2013; Ravaud ASCO 2013

Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1st line
- EVE vs sunitinib 1st line NEGATIVE
- EVE + BEV vs IFN + BEV 1st line NEGATIVE
- TEM + BEV vs IFN + BEV 1st line NEGATIVE
- EVE vs placebo post sunitinib/sorafenib
- TEM vs sorafenib post sunitinib

Hudes NEJM 2007; Motzer Lancet 2008 and ASCO 2013; Hutson JCO 2013; Rini JCO 2013; Ravaud ASCO 2013

Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1st line
- EVE vs sunitinib 1st line
- EVE + BEV vs IFN + BEV 1st line
- TEM + BEV vs IFN + BEV 1st line
- EVE vs placebo post sunitinib/sorafenib
- TEM vs sorafenib post sunitinib

NEGATIVE

NEGATIVE

NEGATIVE

OS WORSE ON TEM

Hudes NEJM 2007; Motzer Lancet 2008 and ASCO 2013; Hutson JCO 2013; Rini JCO 2013; Ravaud ASCO 2013

Randomised trials of mTORi in RCC

- TEM vs IFN vs TEM + IFN in poor risk 1st line
- *Choice of comparator arm controversial*
- *No other trials in poor risk group*
- *No yardstick for anti-VEGF activity*
- EVE vs placebo post sunitinib/sorafenib
- *Placebo control arm reasonable when trial recruited*

Hudes NEJM 2007; Motzer Lancet 2008

mTORi have a diminishing role in RCC

- How can this be reversed?
- Increase dose? Neither EVE or TEM are given at MDT in RCC so possible, but not likely
- Use other inhibitors of pathway e.g. PI3K or dual TORC inhibitors: also possible and RP2 studies of GDC0980 and AZD2014 open
- Combinations? In RCC to date these result in increased toxicity and reduced dose

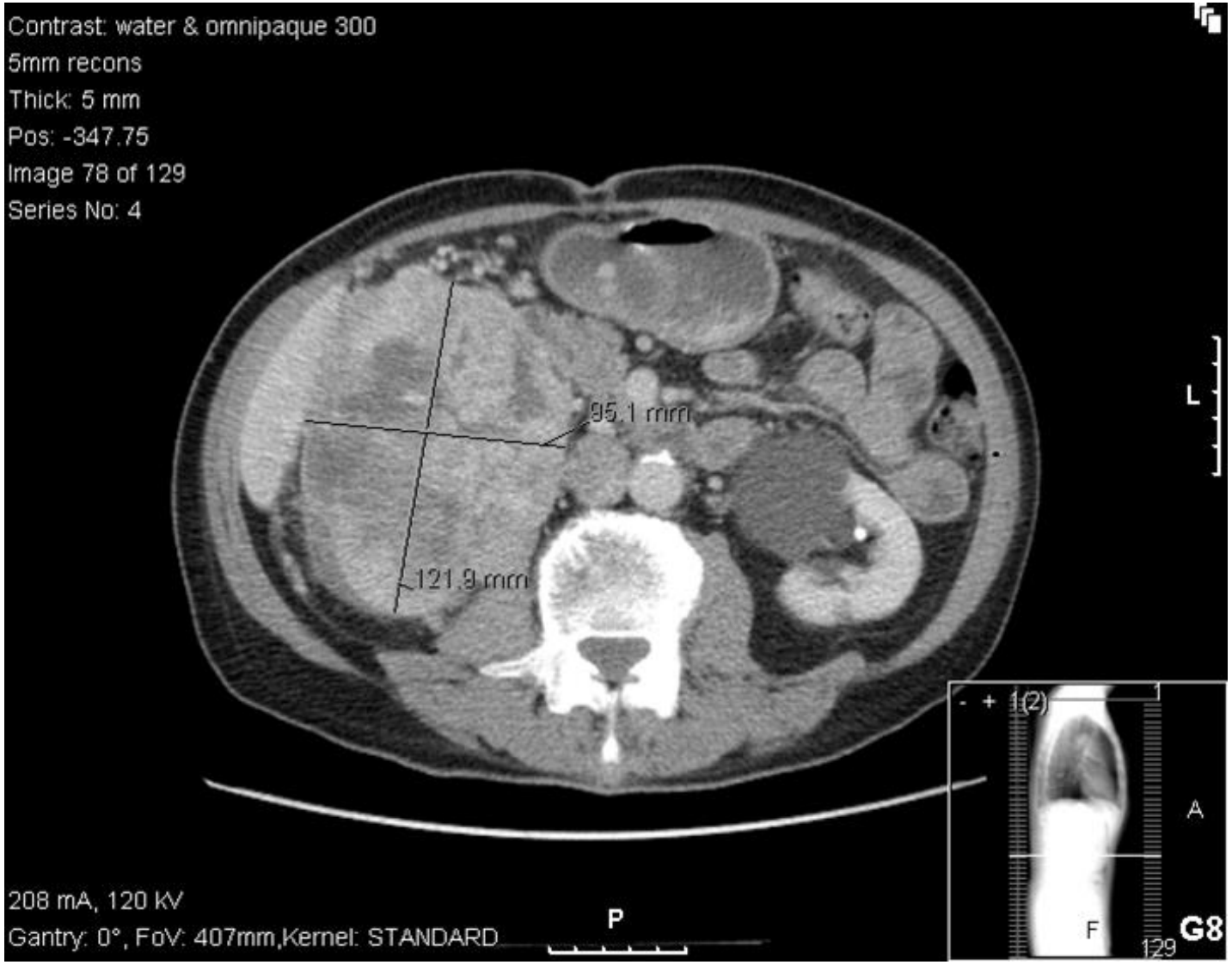
mTORi have a diminishing role in RCC

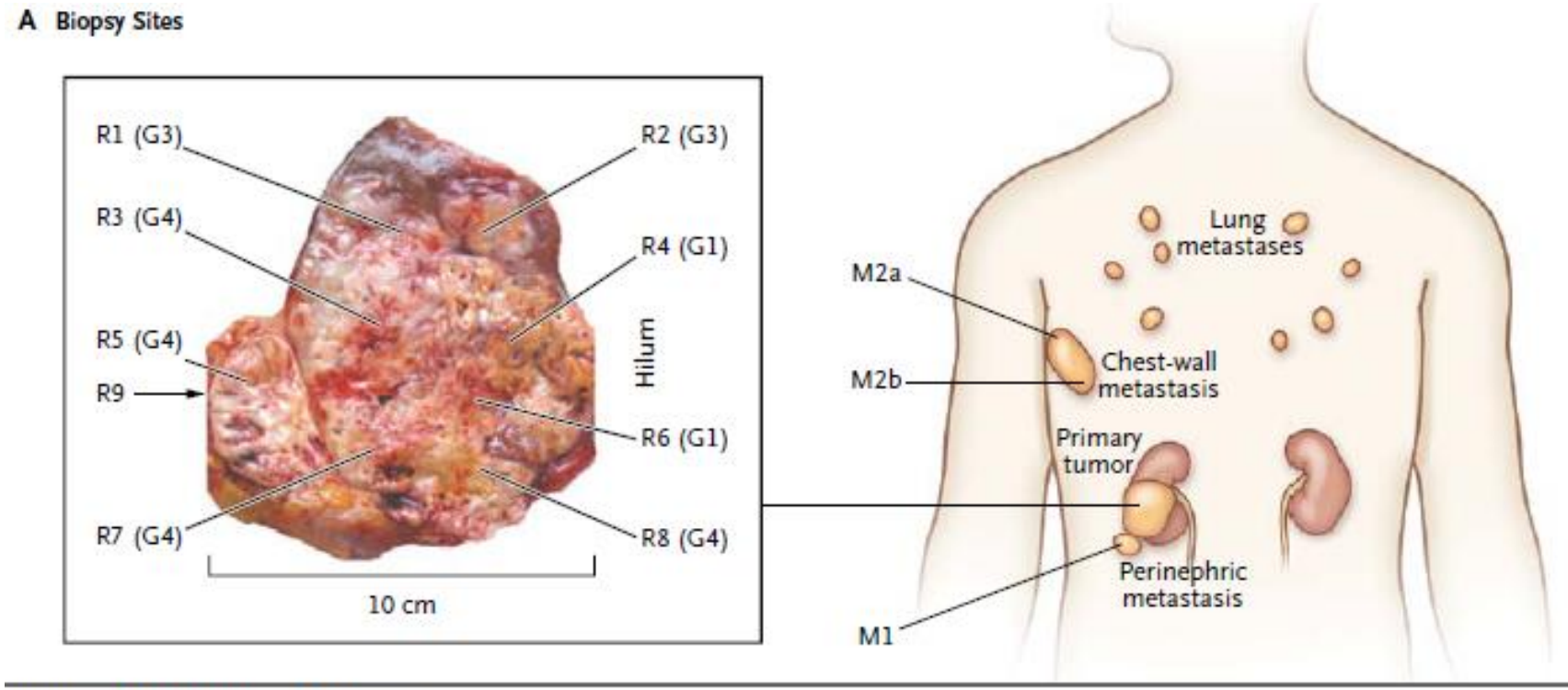
- How can this be reversed?
- Define predictive biomarkers
- Non-clear cell histology is a clinical candidate
- This is not homogeneous: papillary, chromophobe, medullary, collecting duct etc
- Sunitinib is active in papillary / chromophobe
- Our group became interested in trying to develop predictive markers in clear cell RCC for anti-VEGF and mTORi a few years ago…

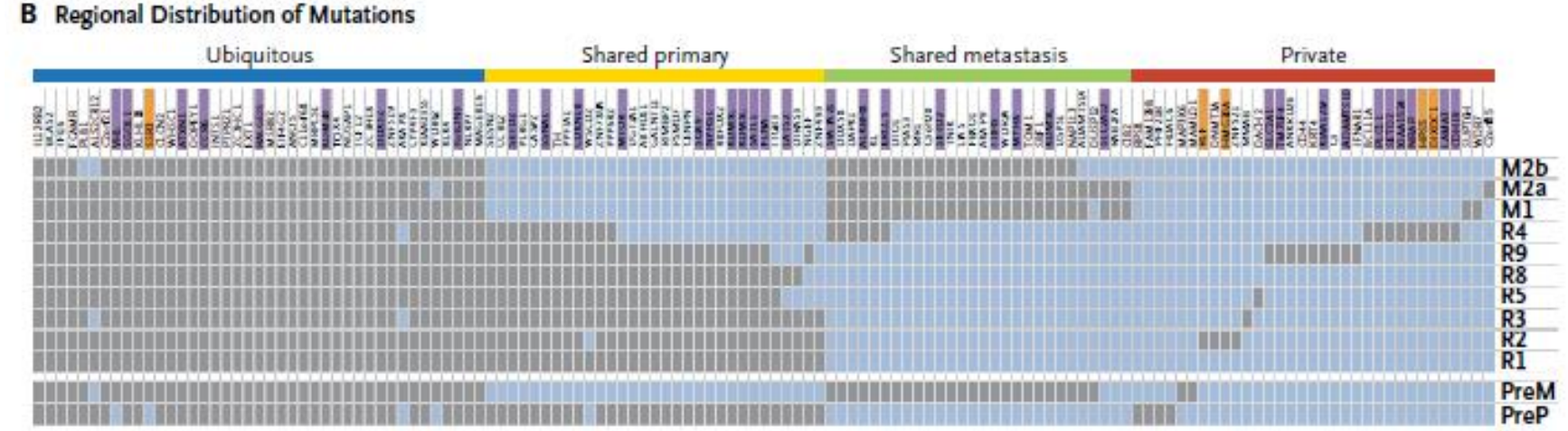
The Intratumour Heterogeneity Question

- A fundamental question for personalised medicine:
- Does the putative driver identified from tissue x at time y really drive the metastatic disease in the patient in front of you in the clinic?
- Are image-guided biopsies of large tumours representative of the entire primary, never mind metastatic disease?
- We set out to investigate this

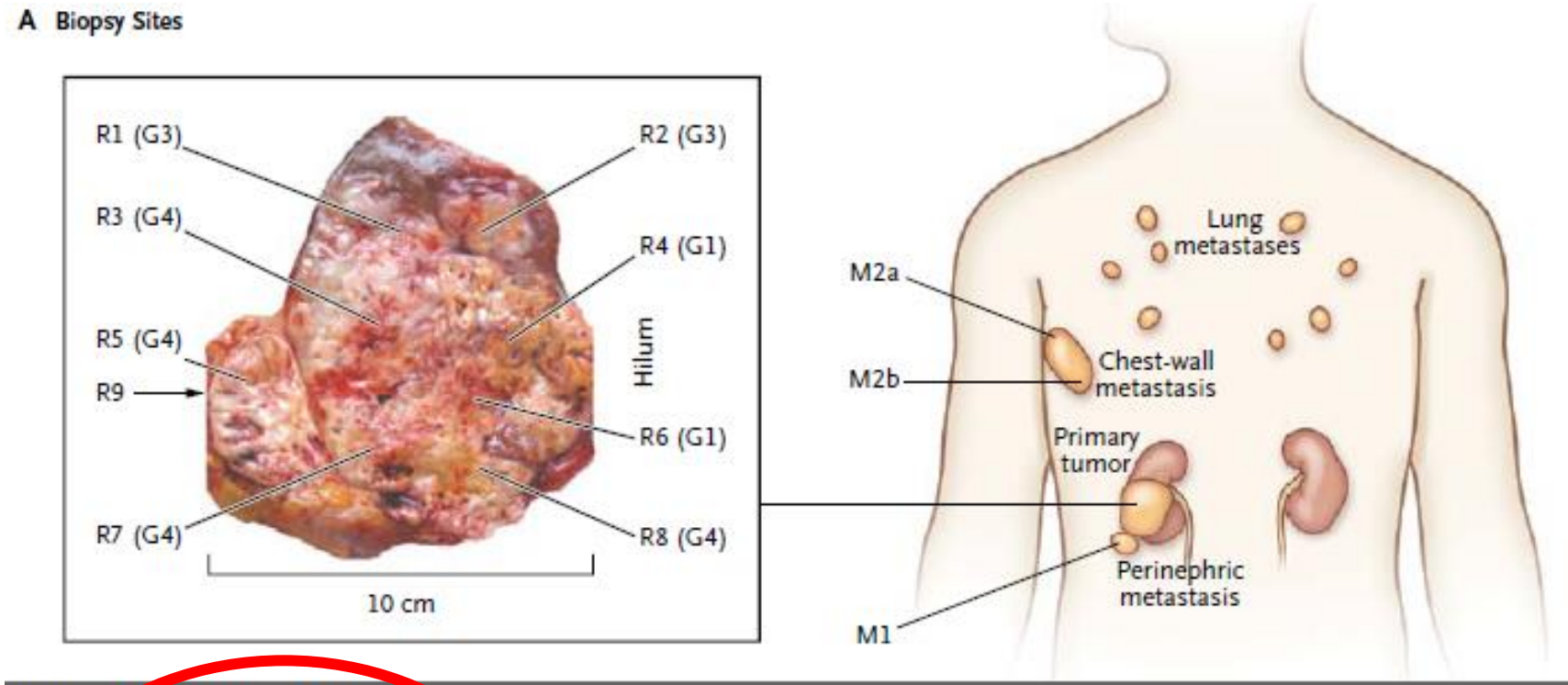
Radiographic Intratumour Heterogeneity

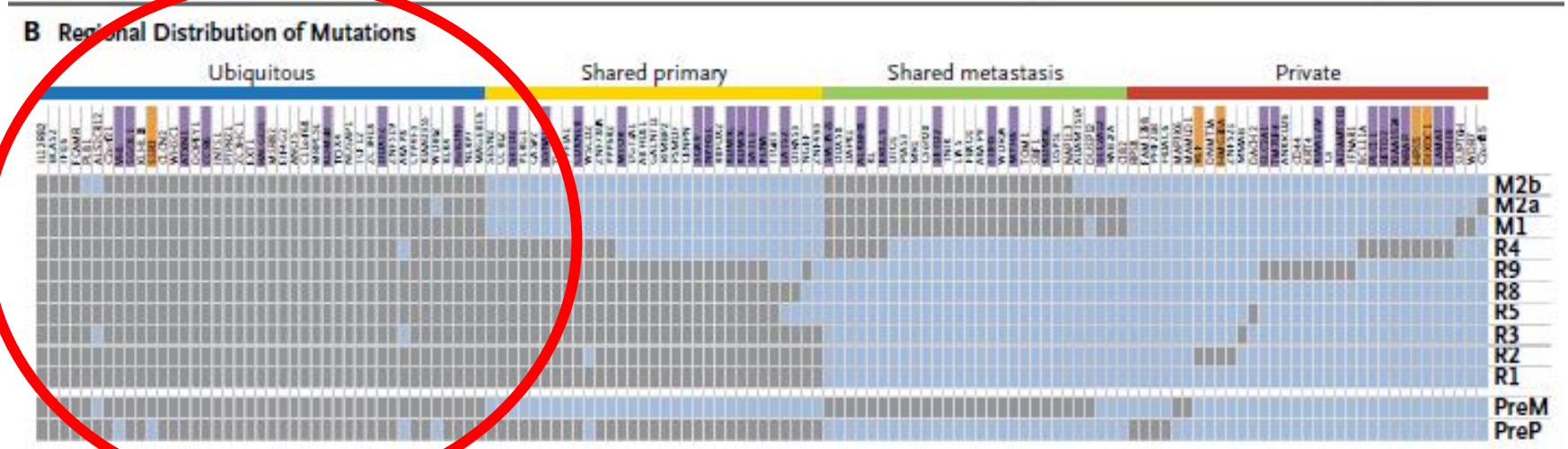




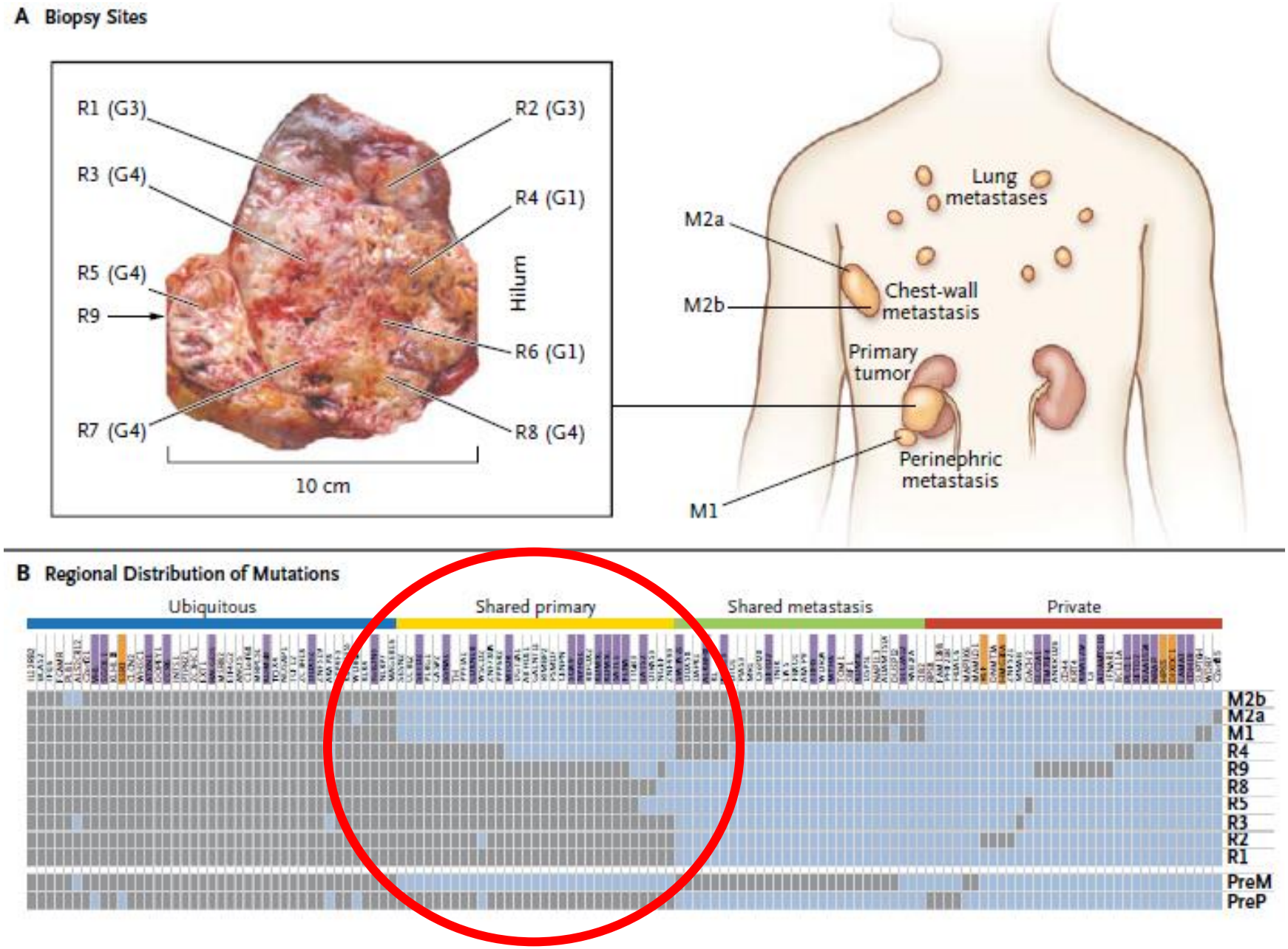


Gerlinger NEJM 2012

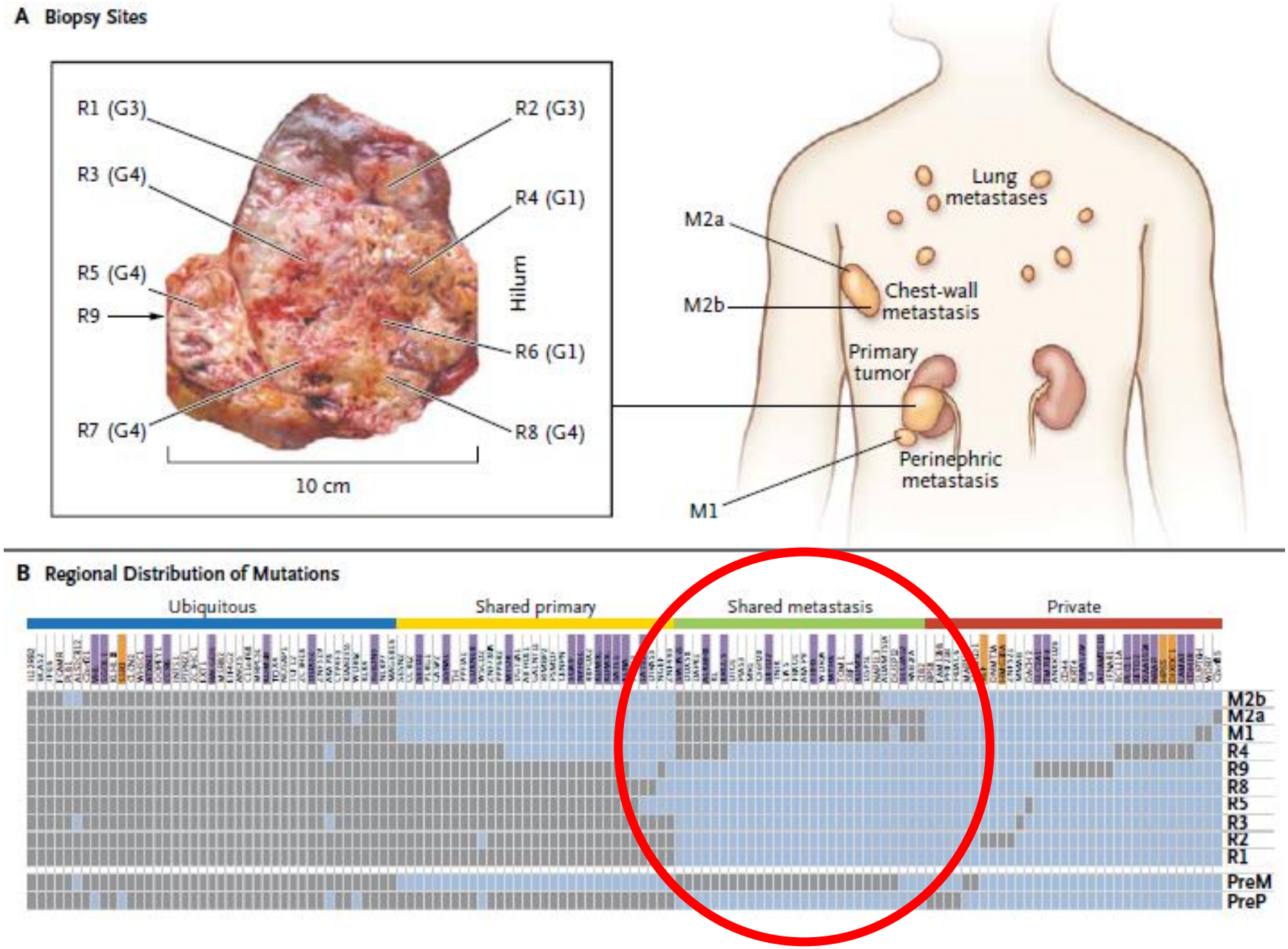




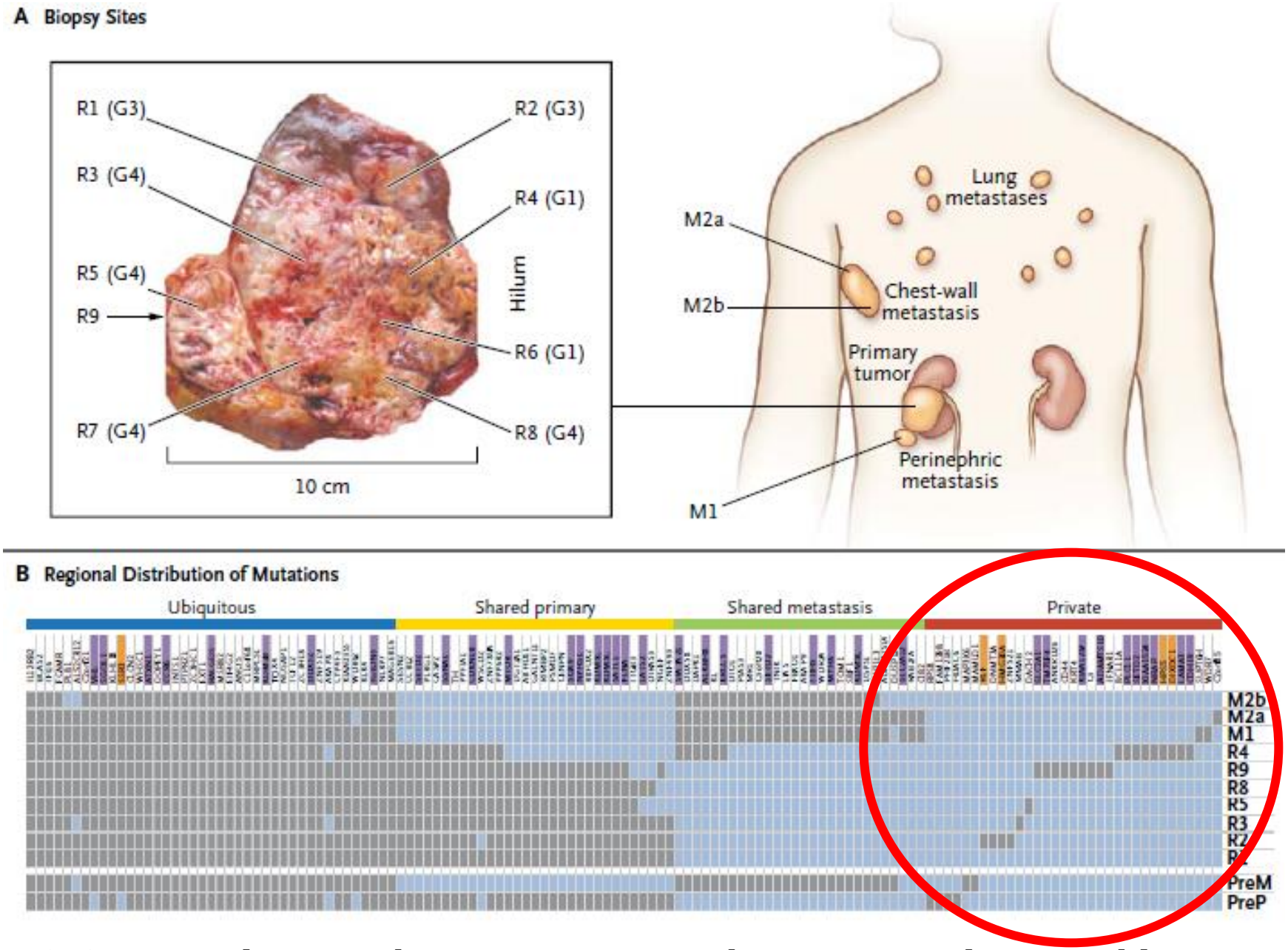
Gerlinger NEJM 2012



Gerlinger NEJM 2012

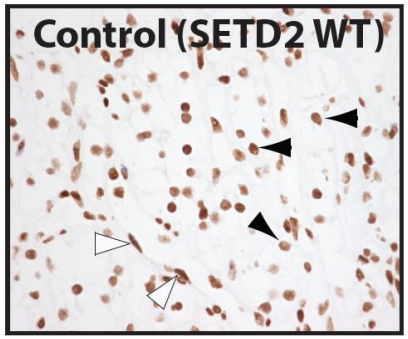


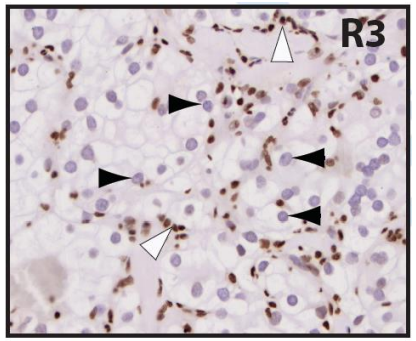
Gerlinger NEJM 2012

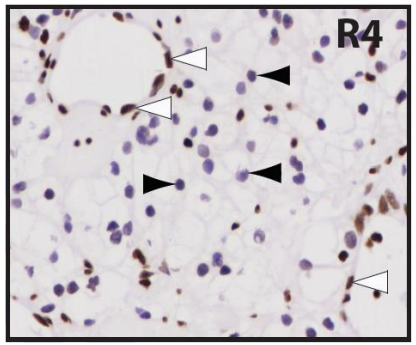


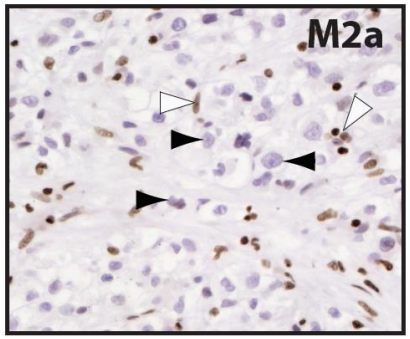
65% mutations are heterogeneous and not present in every biopsy

Evidence for Parallel Evolution
SETD2 Loss of Function: H3K36 tri-methylation

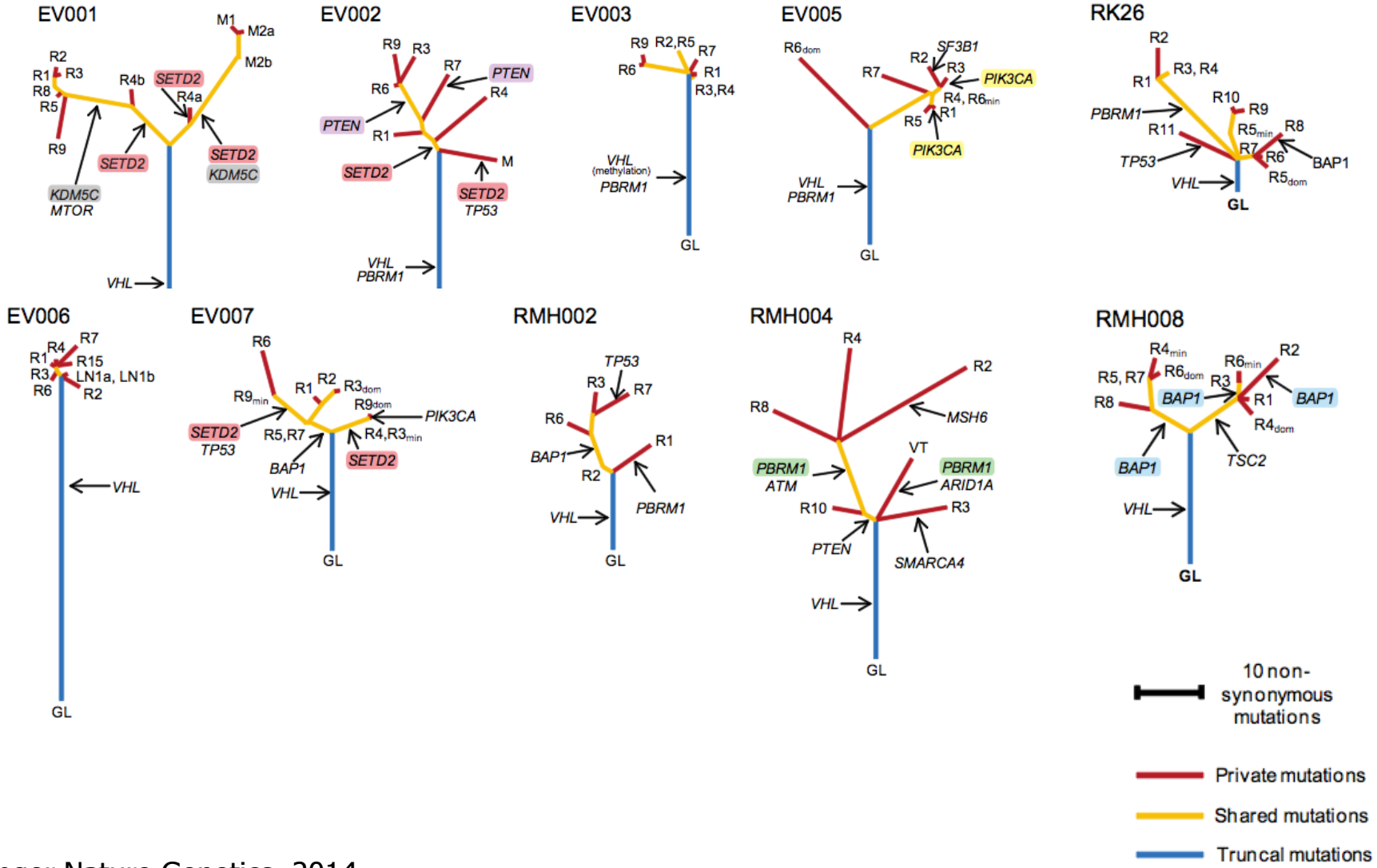








Branched Evolution in ccRCC



Gerlinger Nature Genetics 2014

Branched Evolution in ccRCC

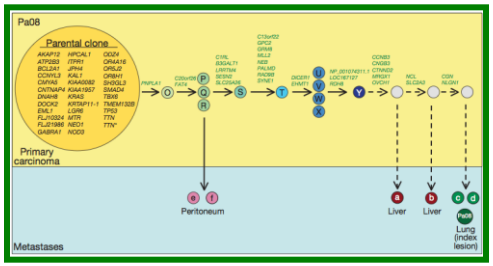
Table 1 Comparison of driver mutation prevalence in ccRCC samples

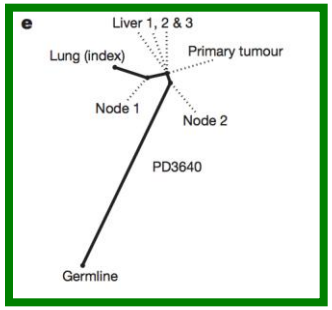
	Prevalence in TCGA samples (n = 218 samples)	Prevalence in all M-seq samples (n = 79 samples)	Prevalence in cases based on M-seq (n = 10 cases)	Prevalence cases/prevalence M-seq samples
PBRM1	42%	39%	60%	1.5
SETD2	18%	27%	30%	1.1
BAP1	21%	24%	40%	1.7
KDM5C	7%	11%	10%	0.9
TP53	5%	5%	40%	8.0
ATM	3%	4%	10%	2.5
ARID1A	6%	1%	10%	10.0
PTEN	5%	10%	20%	2.0
MTOR	9%	8%	10%	1.3
PIK3CA	3%	4%	20%	5.0
TSC2	2%	4%	10%	2.5
PI3K-mTOR pathway	18%	28%	60%	2.2

Gerlinger Nature Genetics 2014

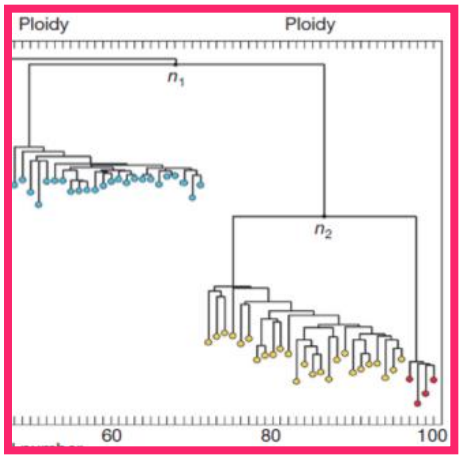
Branched Evolution in Cancer

Pancreas (Yachida/Campbell 2010)

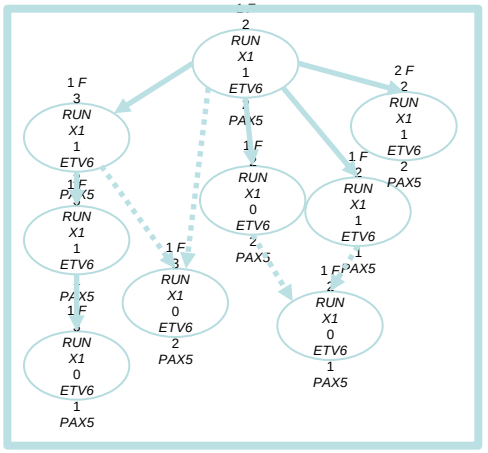




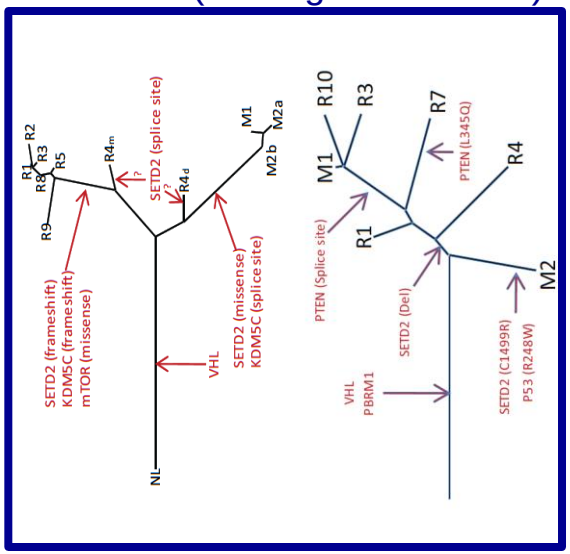
Breast (Navin 2011. Shah 2009)



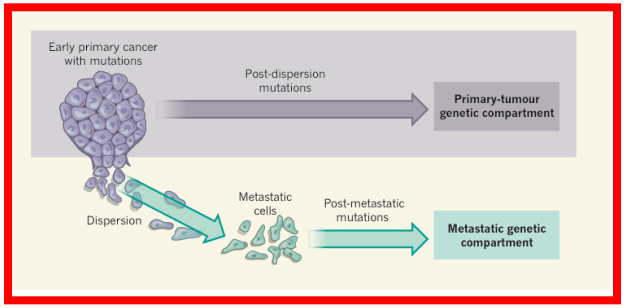
ALL (Enver and Greaves 2011)

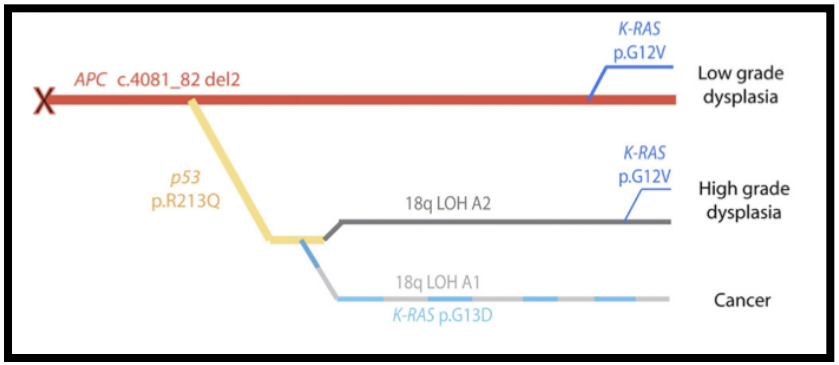


Renal (Gerlinger et al 2012)



Medulloblastoma
(Wu et al 2012)





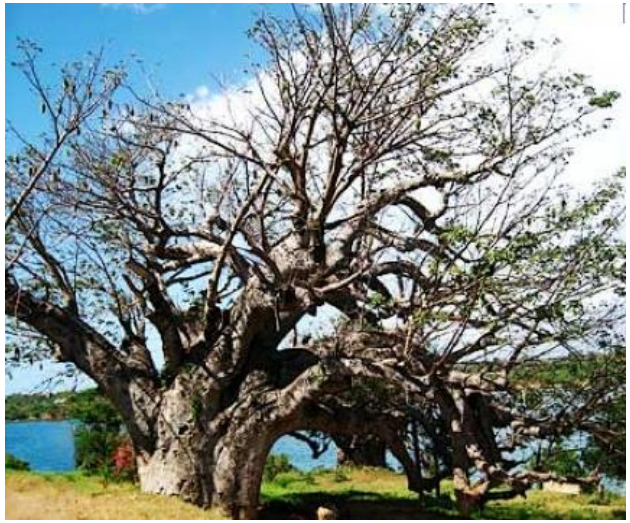
Colon Adenoma-Carcinoma
(Thirlwell et al 2010)

Clonal Architecture as a Biomarker?

Palm

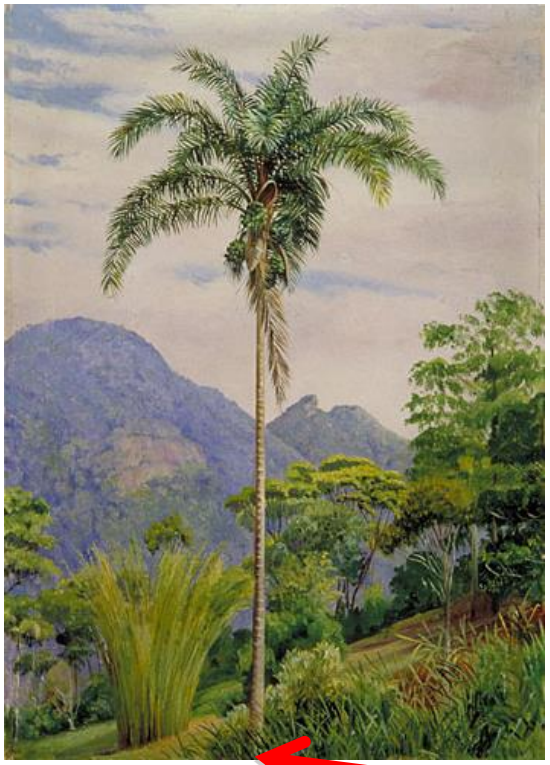
Chestnut

Baobab Tree



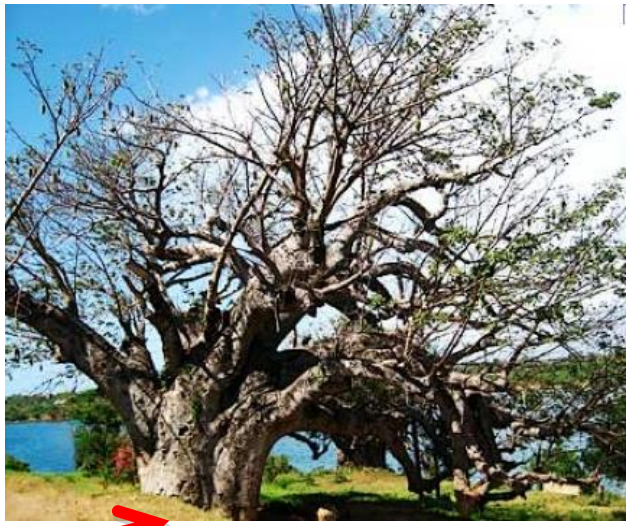
Clonal Architecture as a Biomarker?

Palm



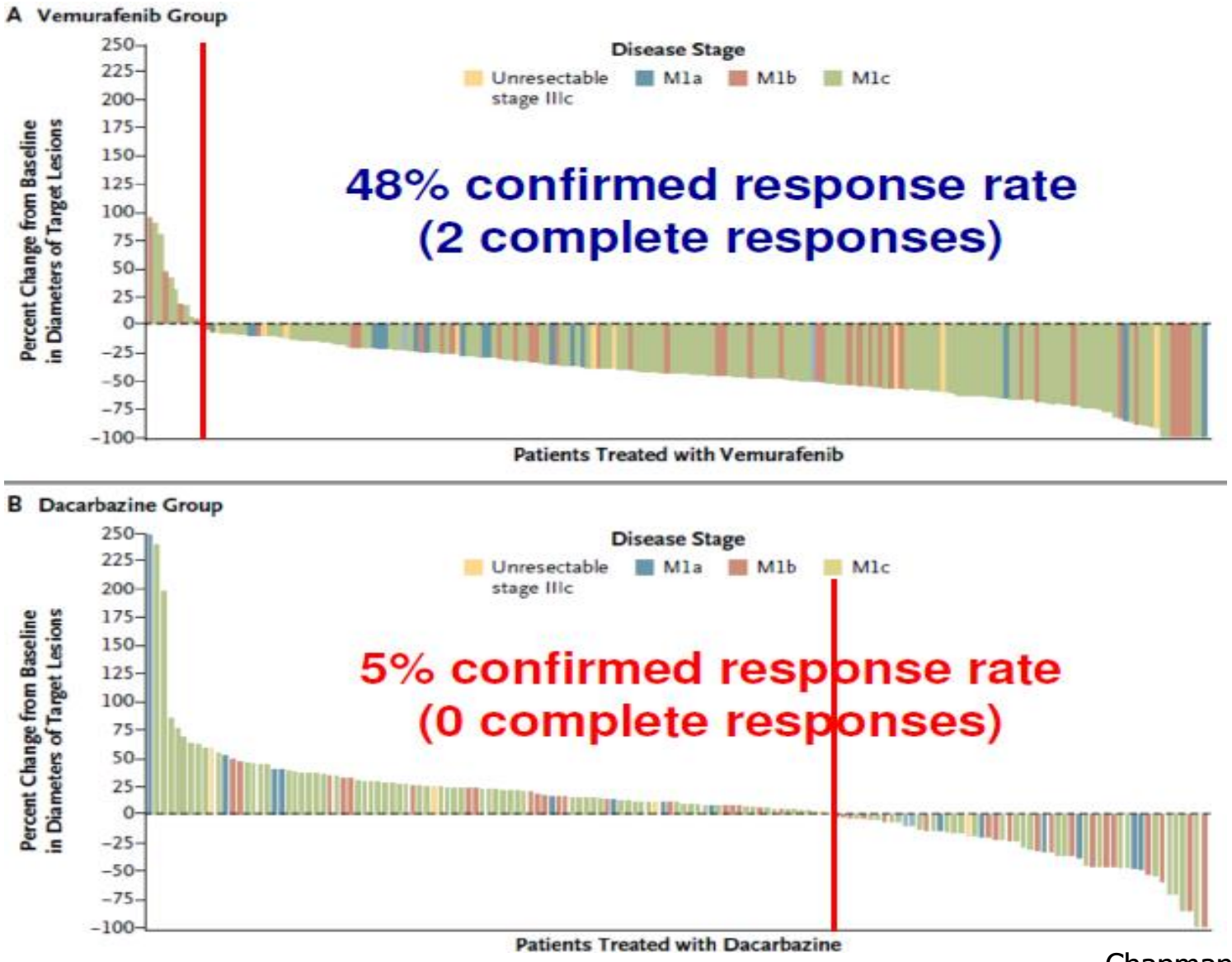
Chestnut

Baobab Tree



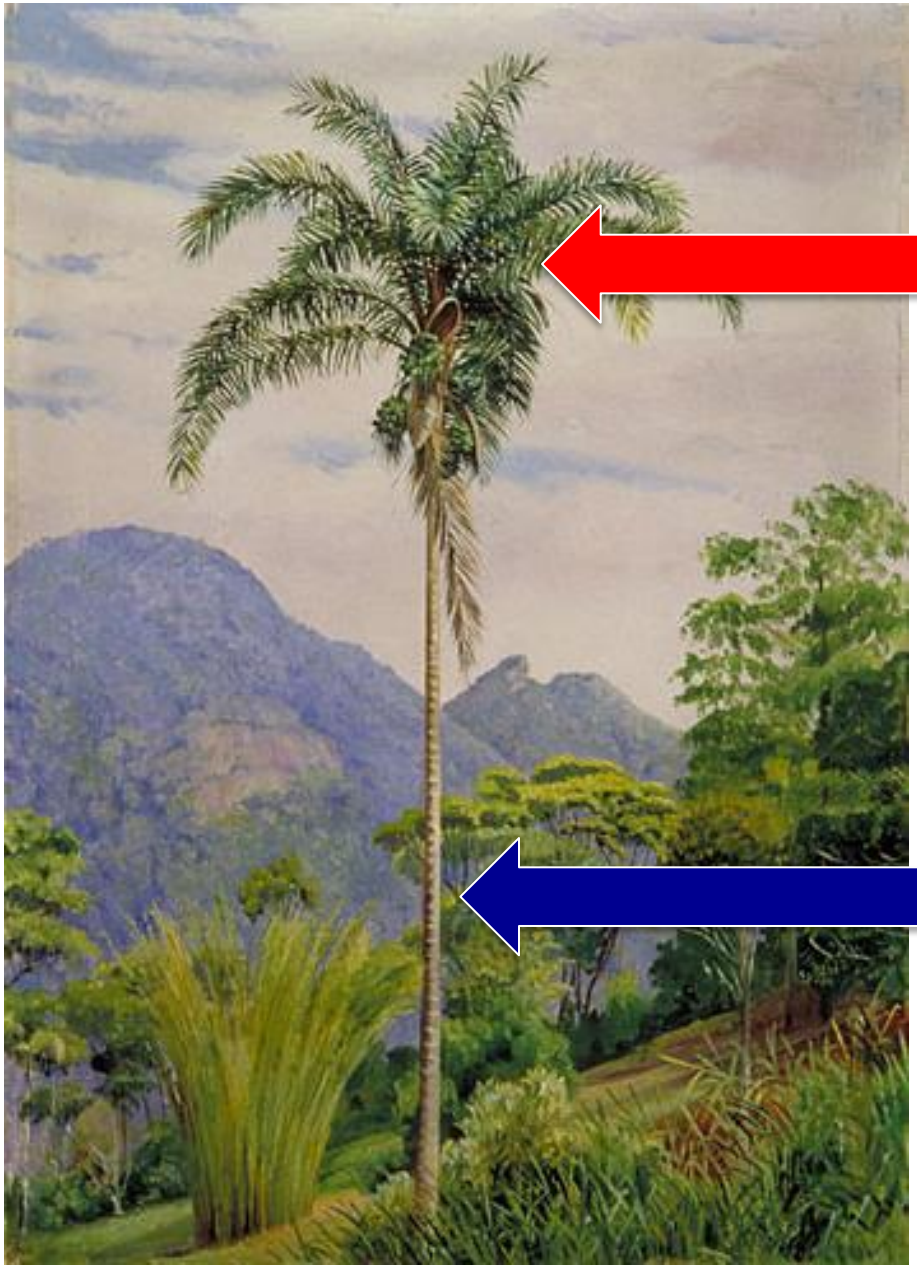
Successful Biomarkers eg EGFR/KRAS/HER2/BRAF
Trunk not branches?

BRAF in Melanoma: 'Truncal Driver'



Chapman NEJM 2011

Target Tumour Phylogenetic Trunks and Resolve Branches



Branched Genetic Events Present in Some Cancer Cells not others
Dynamic during disease course

Monitor subclonal events to define drug resistance mechanisms

Trunk Genetic Events Present in Every Cancer Cell

DEFINE TRUNK DRIVERS

Conclusions

- mTORi active in RCC but less (on average in unselected patients) than anti-VEGF therapy
- No predictive biomarkers for drugs in RCC
- mTOR pathway aberrations not infrequent
- Are they 'truncal drivers' though?
- Further study, particularly of metastatic sites / non-invasive technologies needed
- Understanding this could transform the use of mTORi in RCC

Acknowledgements

- Professor Charles Swanton
- Professor Martin Gore
- Professor David Nicol
- Dr Lisa Pickering
- Dr Steve Hazell
- Dr Marco Gerlinger
- Renal Cancer Clinical Trials Team,
  Royal Marsden Hospital, led by Sister Lynda Pyle
- Our patients and their families

Thank you