The Royal Marsden NHS
NHS Foundation Trust

Precision Medicine in RCC and Clinical Trial Design

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Disclosures

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

Overview

- What is precision medicine?
- Are there any examples in kidney cancer?
- Why have advances in genomics not really impacted clinical practice?
- What are the clinical problems in this disease?
- How does this inform trial design?
- What does the future hold?

What is precision medicine?

- 'Integration of molecular profiling with clinicopathological parameters to select optimal treatments for individual patients'
- Often refers to drug treatments and use of genomic information for patient care
- In RCC,we have lots of drugs…
- …but all are cytokine, anti-VEGF or anti-mTOR

What is precision medicine?

- 'Integration of molecular profiling with clinicopathological parameters to select optimal treatments for individual patients'
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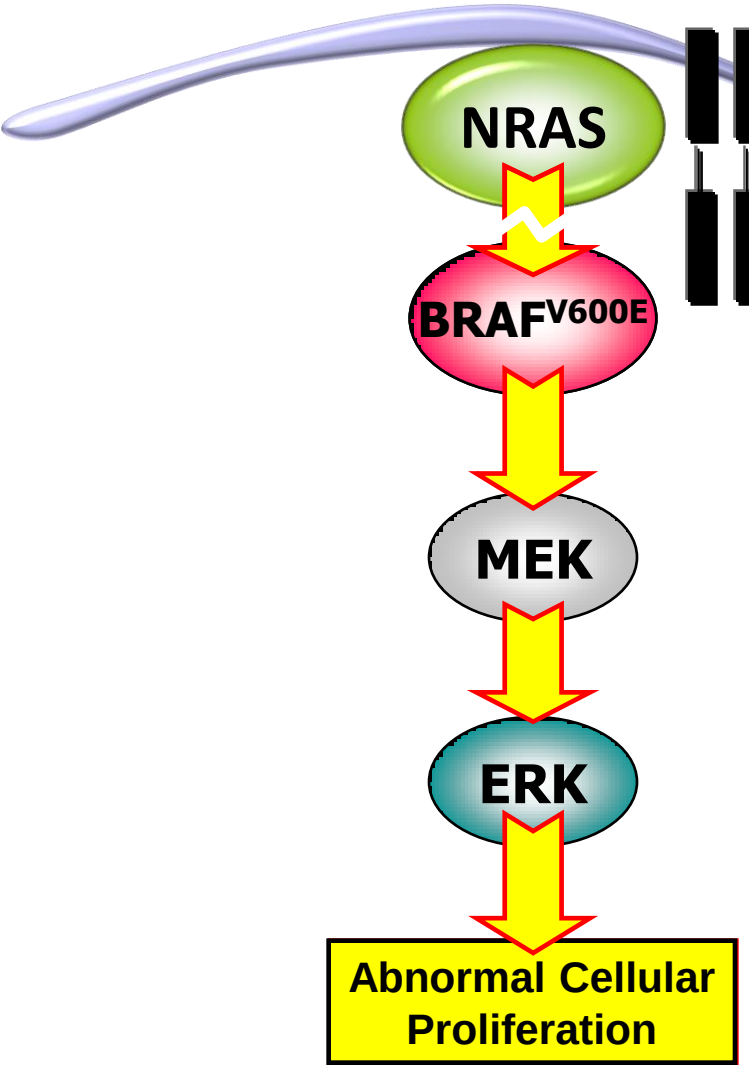
- In RCC,we have lots of drugs…
- …but all are cytokine, anti-VEGF or anti-mTOR
- **Molecular profiling has no routine clinical role in 2014 in kidney cancer**

Kidney Cancer Drug Therapy 2014

Neoadjuvant / Pre-operative	Adjuvant	1st Line Relapse	2nd Line Relapse	3rd Line Relapse
?	?	SUNITINIB PAZOPANIB IFN-α + BEVACIZUMAB TEMSIROLIMUS HD IL-2	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**

Precision Medicine in Melanoma 2014



KIT ~ 2%

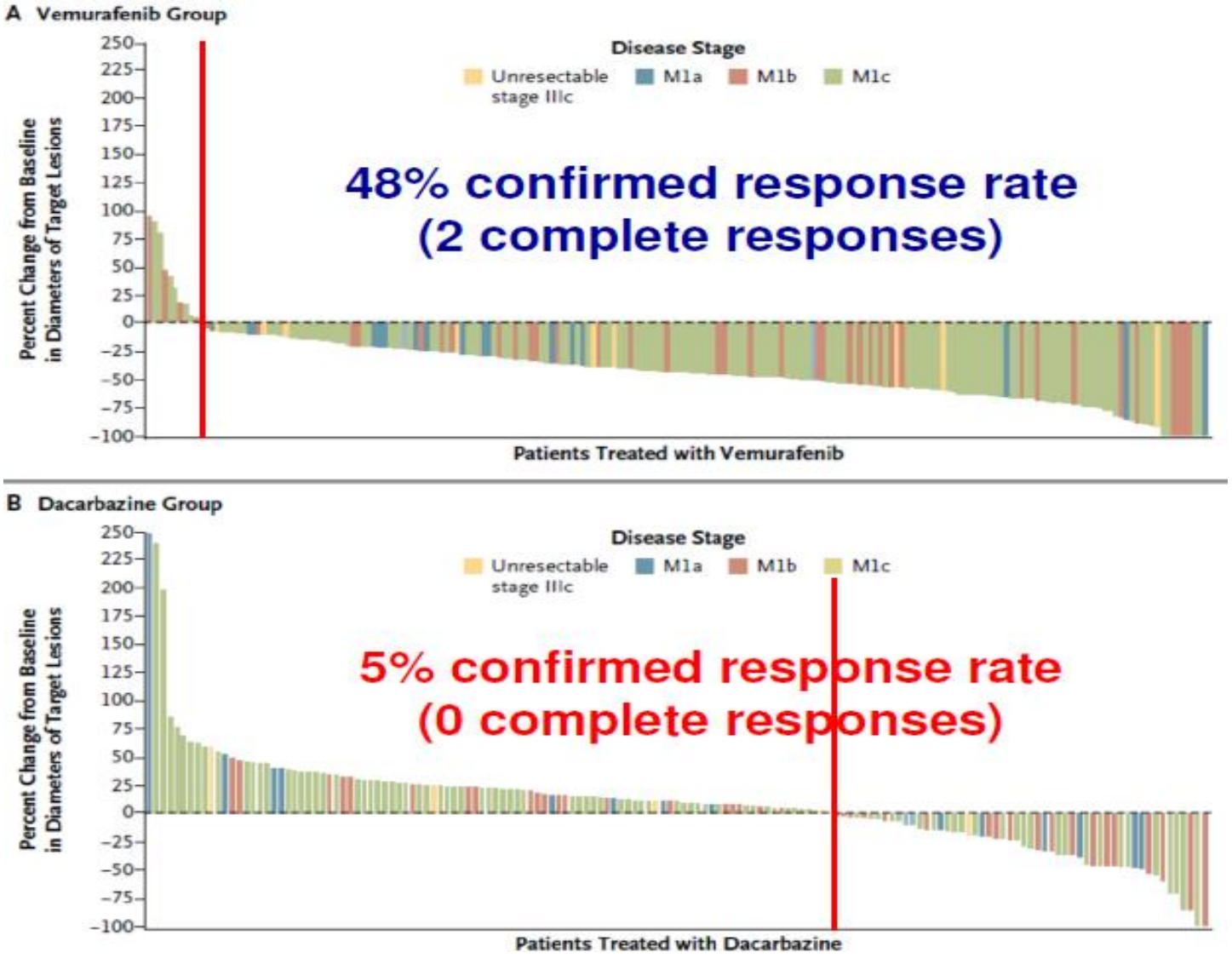
BRAF ~ 40%

NRAS ~ 20%

GNAQ ~ 2%

Curtin NEJM 2005; Curtin JCO 2006

Melanoma: Vemurafenib vs dacarbazine



Chapman NEJM 2011

What about RCC?

- Most patients with ccRCC will get some tumour shrinkage from anti-VEGF therapy
- (Waterfall plot not as dramatic as targeting BRAF in melanoma though)
- Biggest problem in both diseases is acquired resistance to targeted therapy
- A lot is already known about this biologically **in patients** with melanoma (little in RCC)
- Clinically though we have a good idea in RCC which patients will not do well on therapy

Why not more progress in RCC?

- RCC is **not** characterised by activating kinase mutations cf lung, melanoma, GIST etc
- Drug development for activating kinase mutations is tractable
- For tumour suppressor genes (which dominate RCC biology), targeting difficult
- Immunotherapy and anti-VEGF therapy act in the non-tumour compartment
- (NB No progress in developing predictive factors for these treatments in any tumour type)

What about mTORi in RCC?

- If mTORi are predominantly targeting the tumour compartment, you would expect tumours with activation of this pathway to be sensitive to therapy…

What about mTORi in RCC? RCTs:

- 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

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- TEM vs IFN vs TEM + IFN in poor risk 1st line
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OS WORSE ON TEM

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

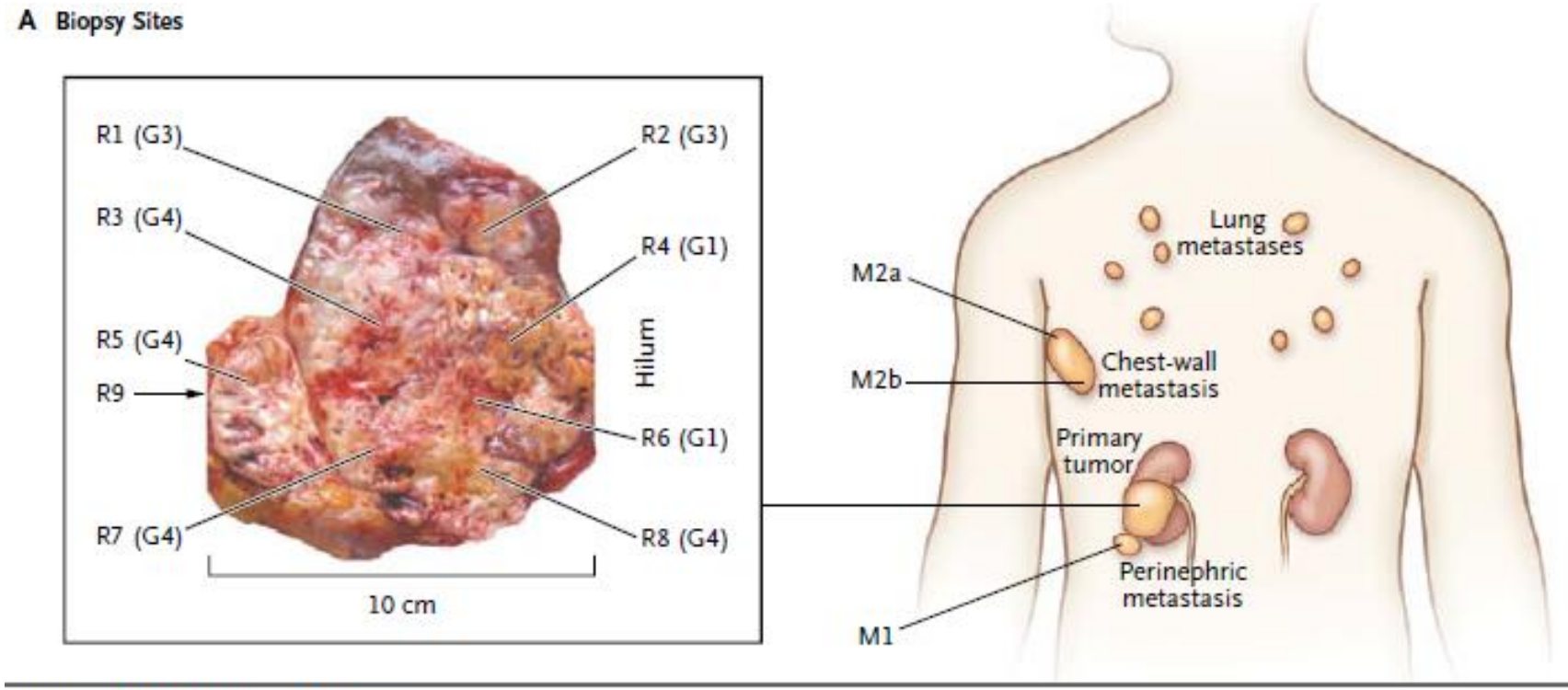
What about mTORi in RCC? RCTs:

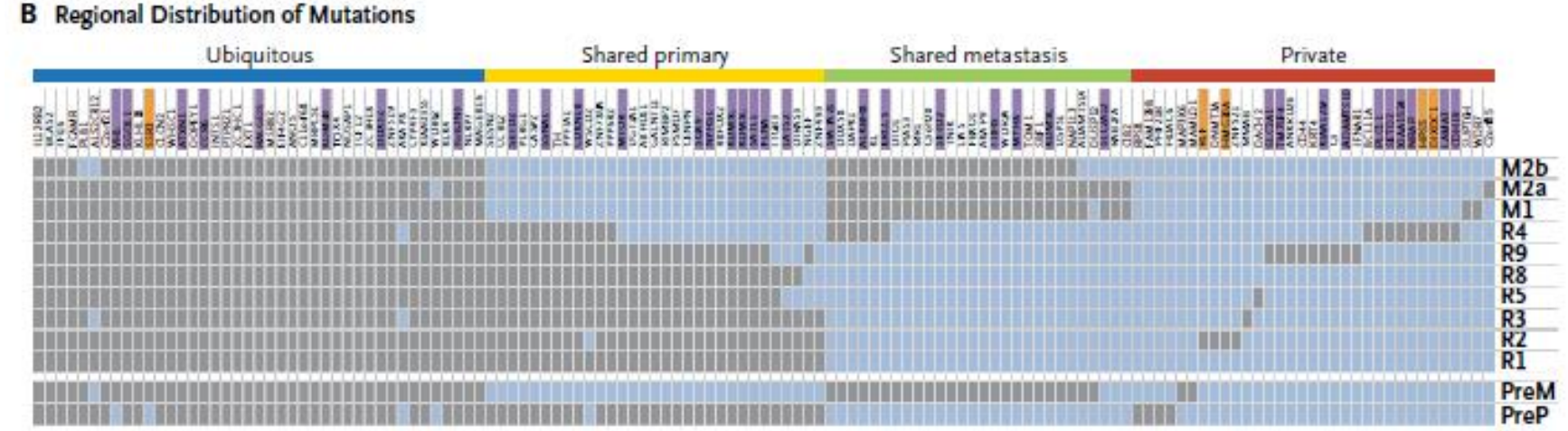
- TEM vs IFN vs TEM + IFN in poor risk 1st line
- *Choice of comparator arm controversial*
- *No other trials in poor risk group*
- *No yardstick for anti-VEGF activity*
- EVE vs placebo post sunitinib/sorafenib
- *Placebo control arm reasonable when trial recruited*

Hudes NEJM 2007; Motzer Lancet 2008

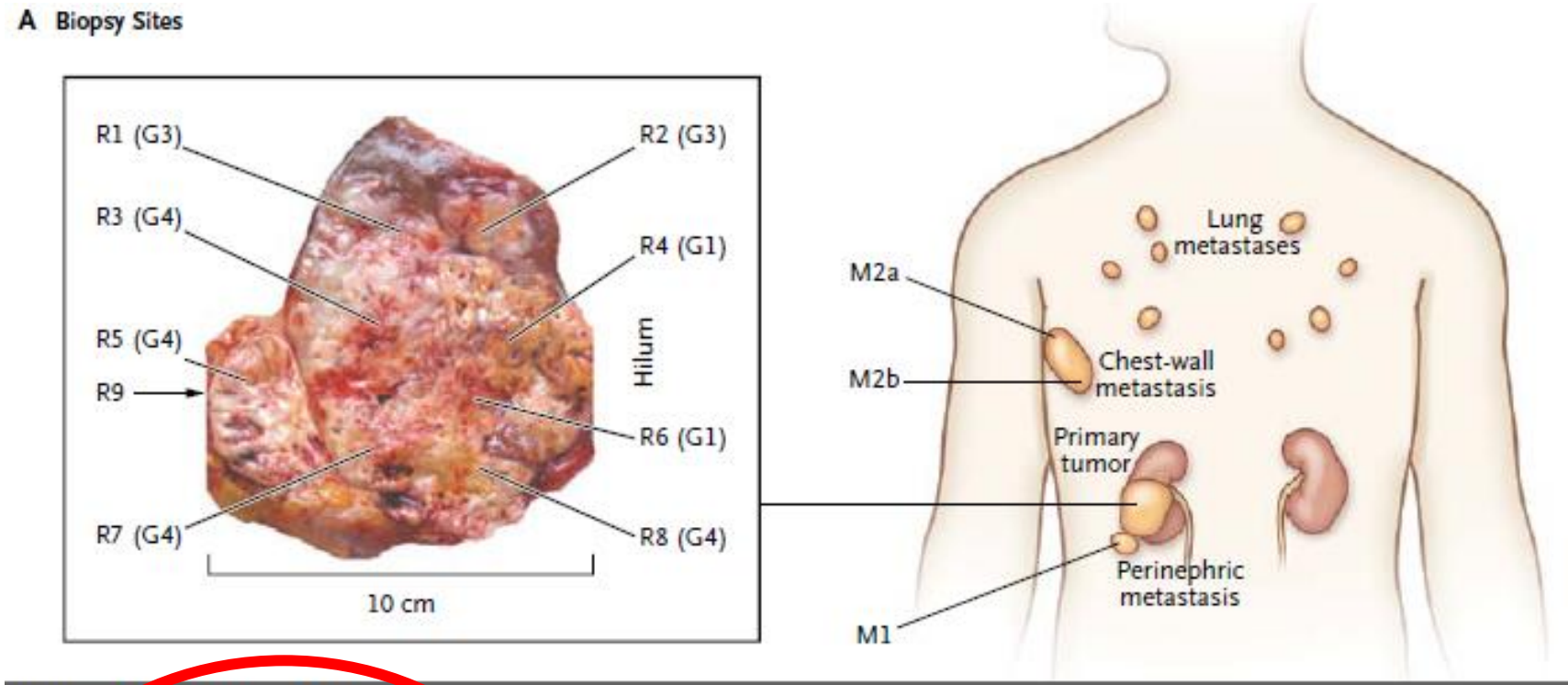
What about mTORi in RCC?

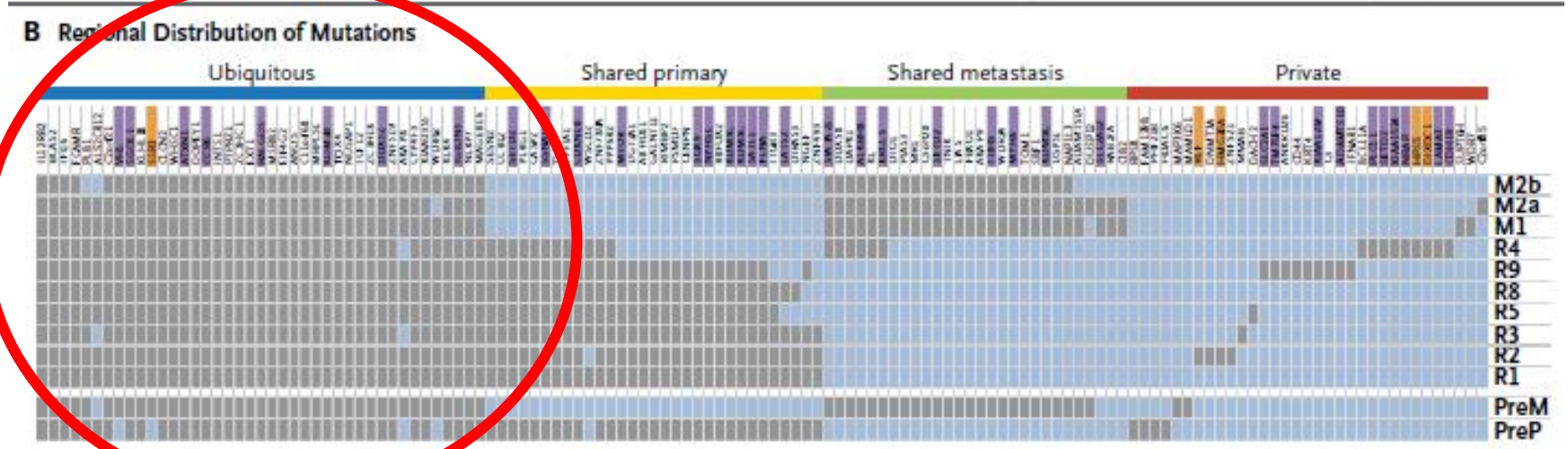
- If mTORi are predominantly targeting the tumour compartment, you would expect tumours with activation of this pathway to be sensitive to therapy
- Clearly, on average, this is not the case in comparison with anti-VEGF therapy
- How could this be explained?
- Is there a subset of molecularly defined patients that might benefit?





Gerlinger NEJM 2012





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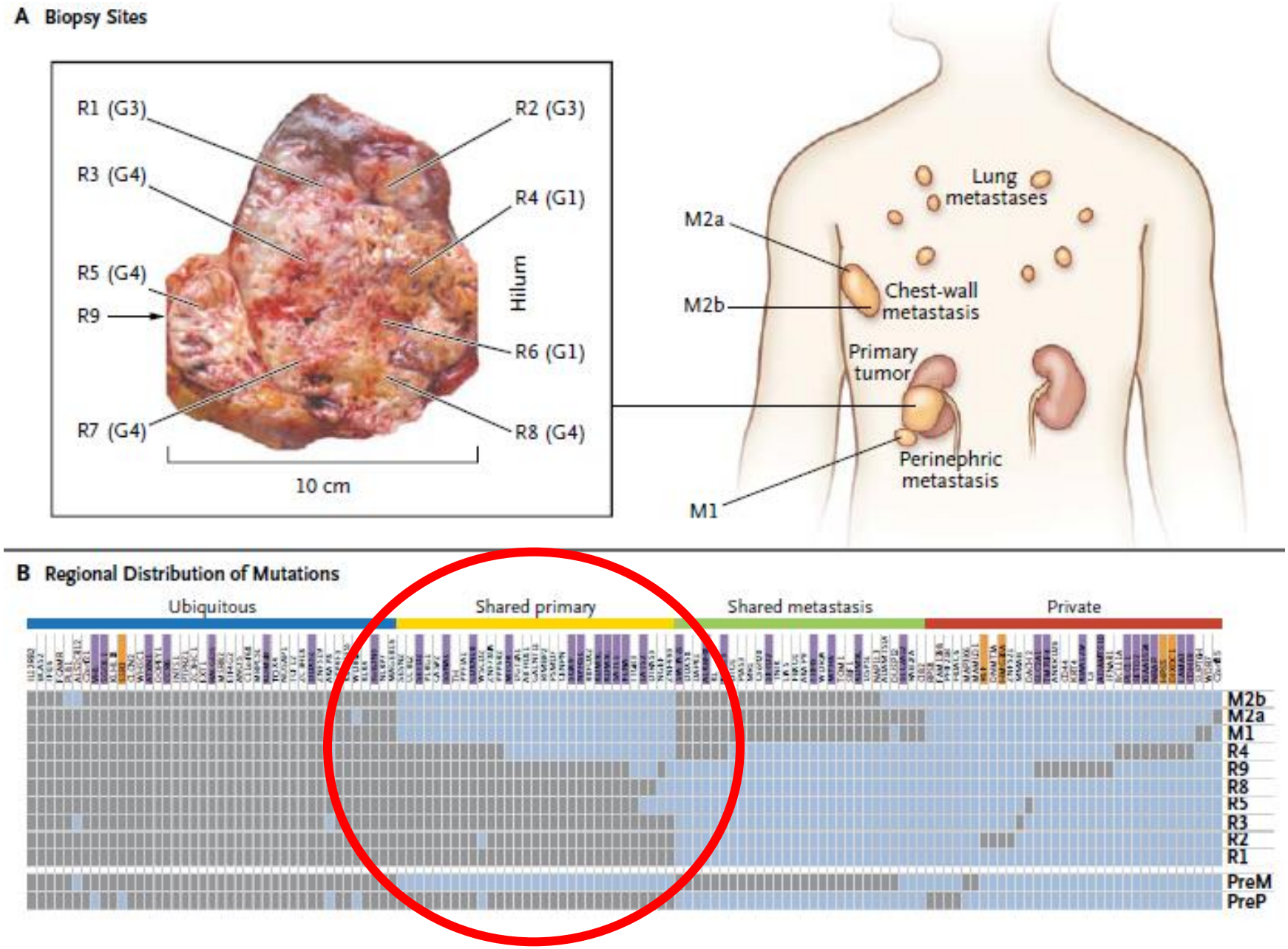

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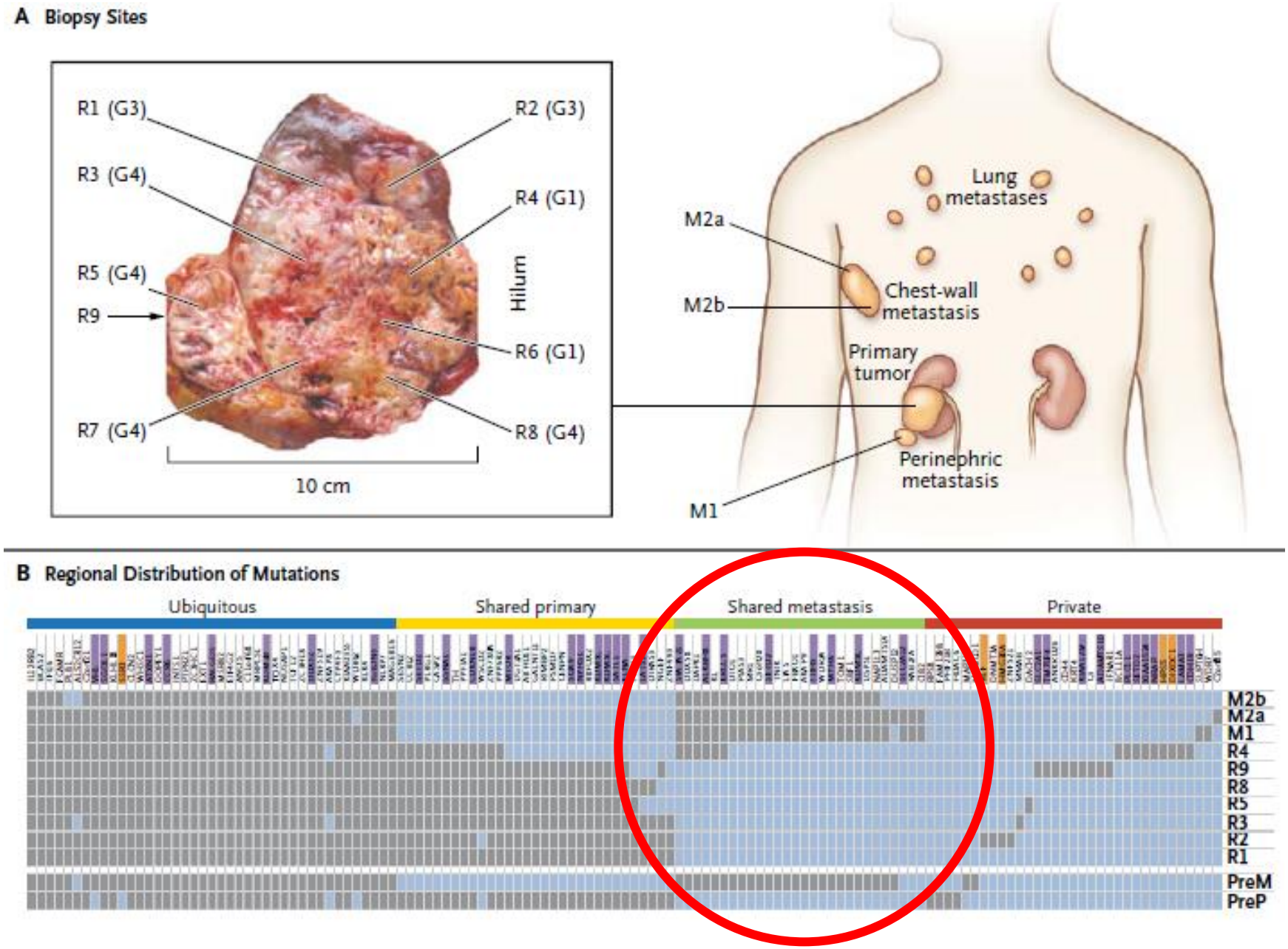

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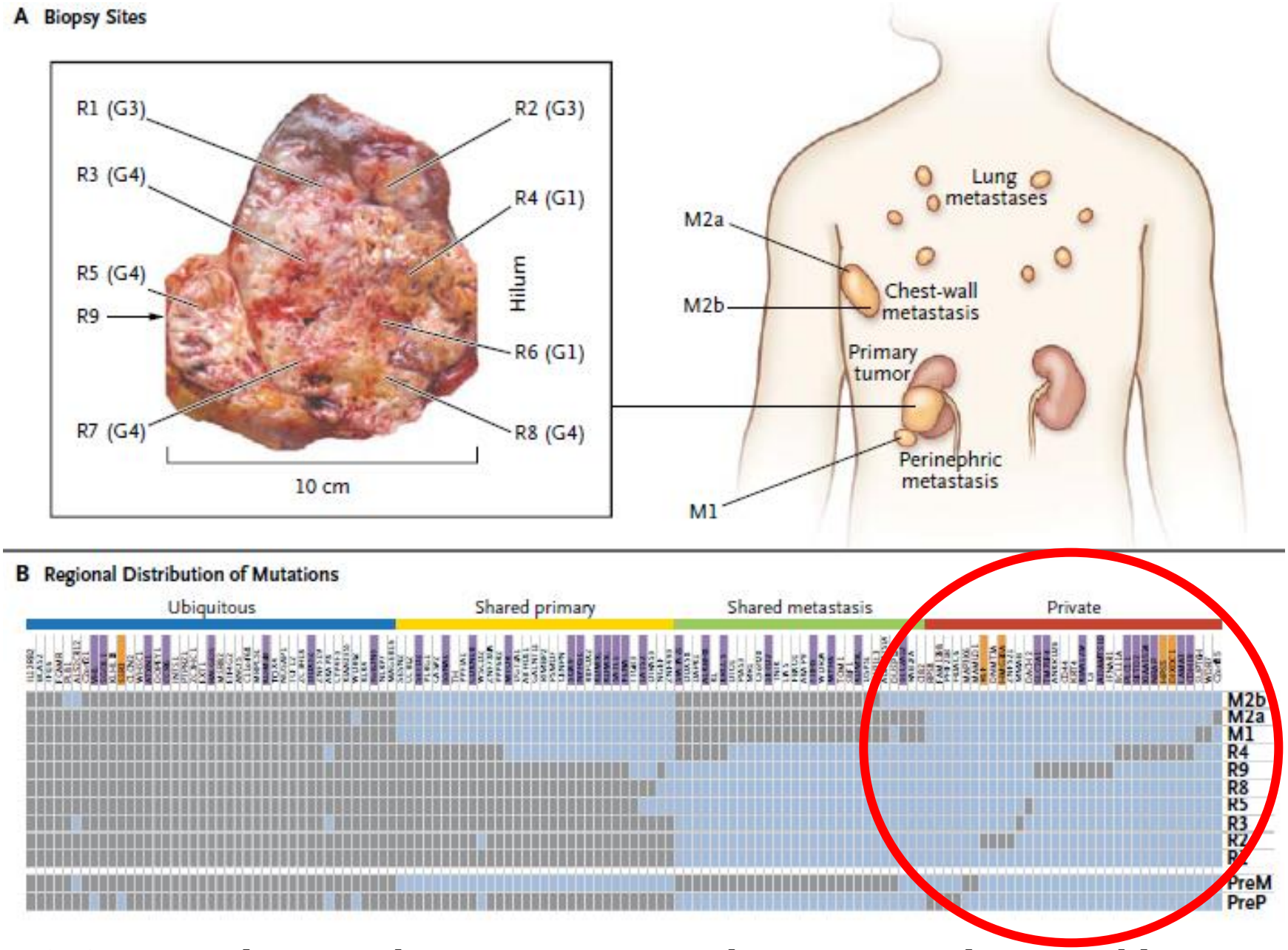
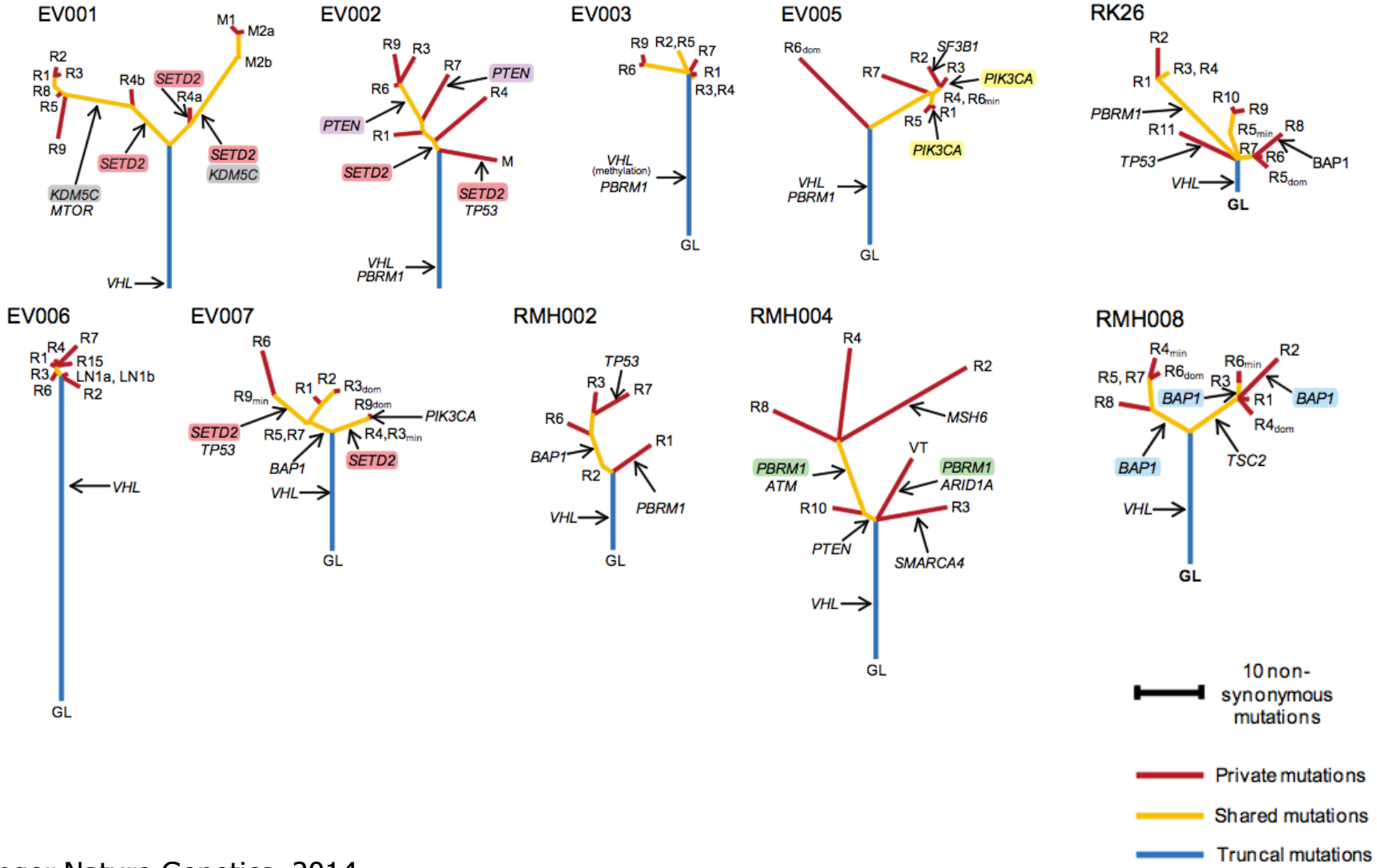


65% mutations are heterogeneous and not present in every biopsy

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

Target Trunks and Resolve Branches

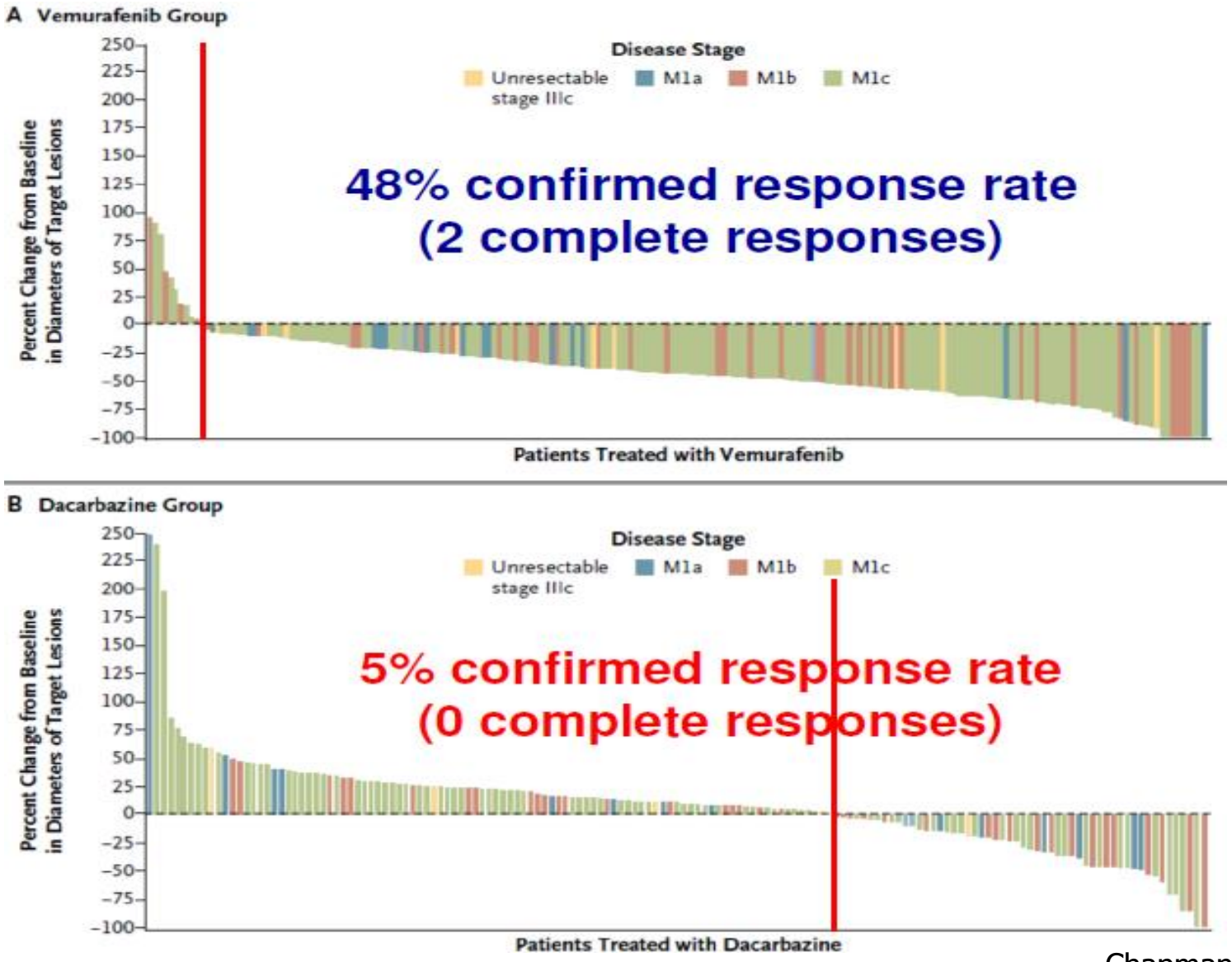
Branched Genetic Events Present in Some Cancer Cells not others
Dynamic during disease course

Monitor subclonal events to define drug resistance mechanisms

Trunk Genetic Events Present in Every Cancer Cell

DEFINE TRUNK DRIVERS

BRAF in Melanoma: 'Truncal Driver'



Chapman NEJM 2011

mTORi in RCC summary

- mTORi active in RCC but less (on average in unselected patients) than anti-VEGF therapy
- 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

What does this mean for clinical trial design?

- Relatively small 'tissue heavy' clinical trials are needed to understand these ideas better
- Need not involve drug therapy; disease evolution off therapy important too
- Our efforts to understand response and resistance to anti-VEGF and anti-mTOR therapy should continue
- We must also put the same efforts into investigating new drugs e.g. anti-PD1/PDL1

What does this mean for clinical trial design?

- We need to frame our trials so that we are addressing important clinical issues e.g.
- Sarcomatoid histology does badly
- Patients presenting with mRCC do badly
- Patients presenting with mRCC unsuitable for cytoreductive nephrectomy do badly
- Patients with non-clear cell RCC do badly
- Patients with limited benefit from anti-VEGF do badly

What does this mean for clinical trial design?

- We need to continue our engagement with industry to bring exciting drugs into RCC
- I would particularly highlight 2 trials
- Randomised phase 2: sunitinib vs MPDL3280A vs bevacizumab + MPDL3280A
- Well tolerated combination of drugs
- Cross-over to anti-PDL1 therapy is allowed
- Lack of cytoreductive nephrectomy allowed
- Sarcomatoid histology explicitly allowed

NCT01984242

What does this mean for clinical trial design?

- The '214' trial: sunitinib vs ipilimumab + nivolumab ~1000 patient phase 3
- Melanoma clinicians familiar with ipilimumab + nivolumab and the '067' trial of ipi vs nivo vs the combination
- In melanoma, ipilimumab alone can durably control melanoma in 15-20%
- Early efficacy suggests activity in 40-50%
- Ipilimumab + nivolumab in RCC early efficacy ~ 40%

NCT02231749

Conclusions

- Major increase in understanding of RCC biology (especially genomic) last ~10 years
- This has yet to translate into molecular predictive factors for treatment in the clinic
- Inherently, there are some differences in RCC biology that may partly explain this
- Extensive efforts are being made and should continue with newer agents, particularly checkpoint inhibitors
- Clinical trial design must reflect clinical issues as well as molecular predictive factors

Acknowledgements

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Thank you