Cancer research and post-mortem studies

Independent Cancer Patients' Voice Autumn Workshop

7 September 2012

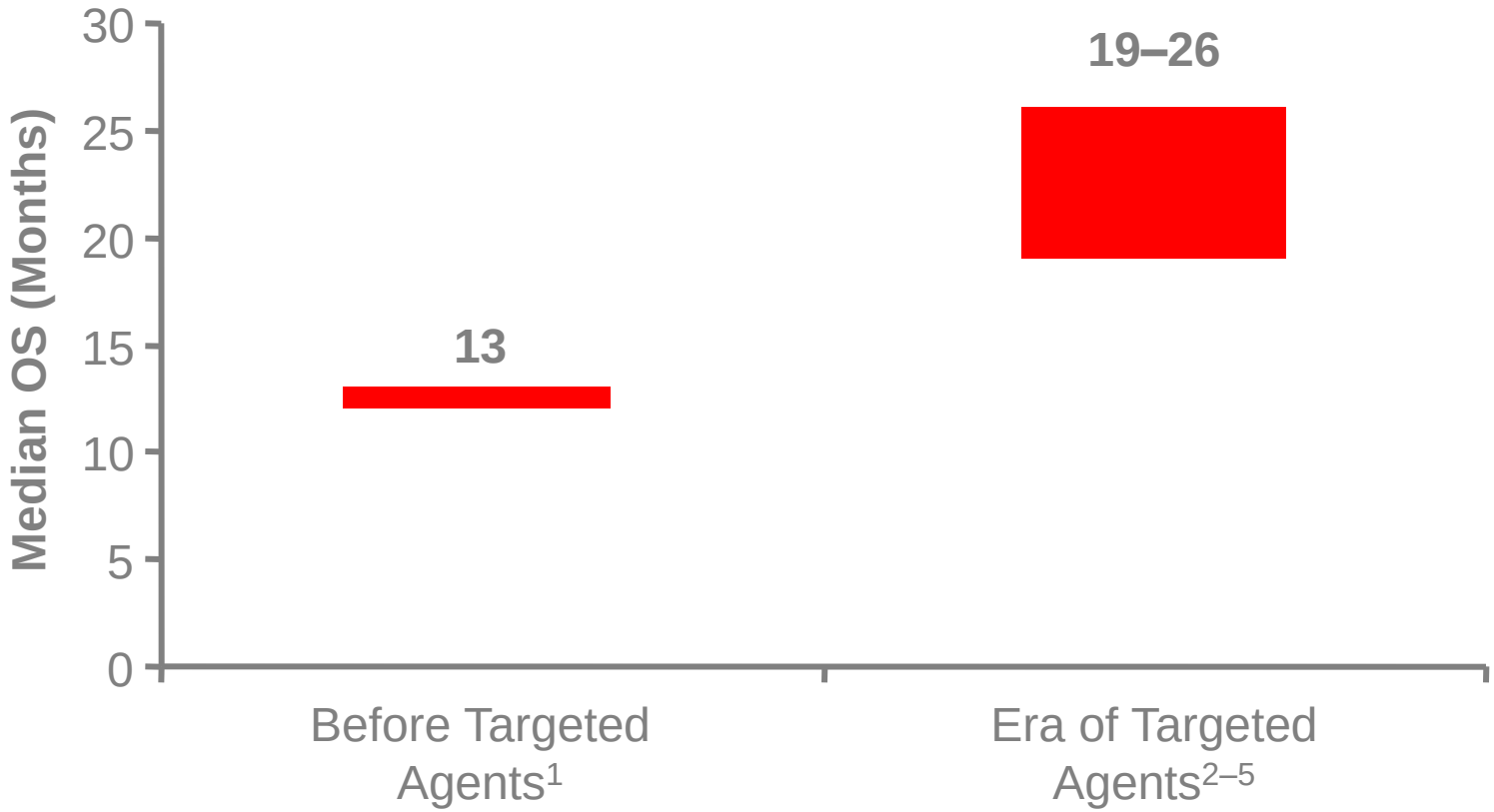
Dr Rosalie Fisher

Clinical Research Fellow, Royal Marsden Hospital

Introduction

- Major explosion in knowledge of cancer biology last decade
- Major therapeutic advances in ‘targeted’ therapies
- Progress uneven though; some targeted therapies have marginal benefits
- Limitations of chronic oral palliative treatments have become clear

Survival improvements with targeted agents in kidney cancer



1. Coppin C, et al. Cochrane Collaboration, 2006; 2. Escudier B, et al. *N Engl J Med* 2007; 3. Bayer Healthcare. Nexavar® (sorafenib) Summary of Product Characteristics, 2008; 4. Escudier B, et al. *Lancet* 2007; 5. Motzer RJ, et al. *J Clin Oncol* 2009

Challenges for Targeted Therapies to Treat Cancer

- Resistance: innate, acquired, speed of progression, heterogeneity of mechanism (?)
- Patient selection for drug therapy
- Intratumour heterogeneity as a potential challenge for treatment selection and resistance
- Translating benefit in advanced setting to curative (i.e. adjuvant) setting

How can we improve patient outcomes in 2012?

- Find new treatments
  - More potent drugs
  - New targets
  - New (or old?!) modes of therapy - chemo/immuno

- Use our existing ones better
  - Sequences/combinations/schedules
  - Understanding mechanisms of resistance
  - **Selection of patients for treatment**

What is our aim?

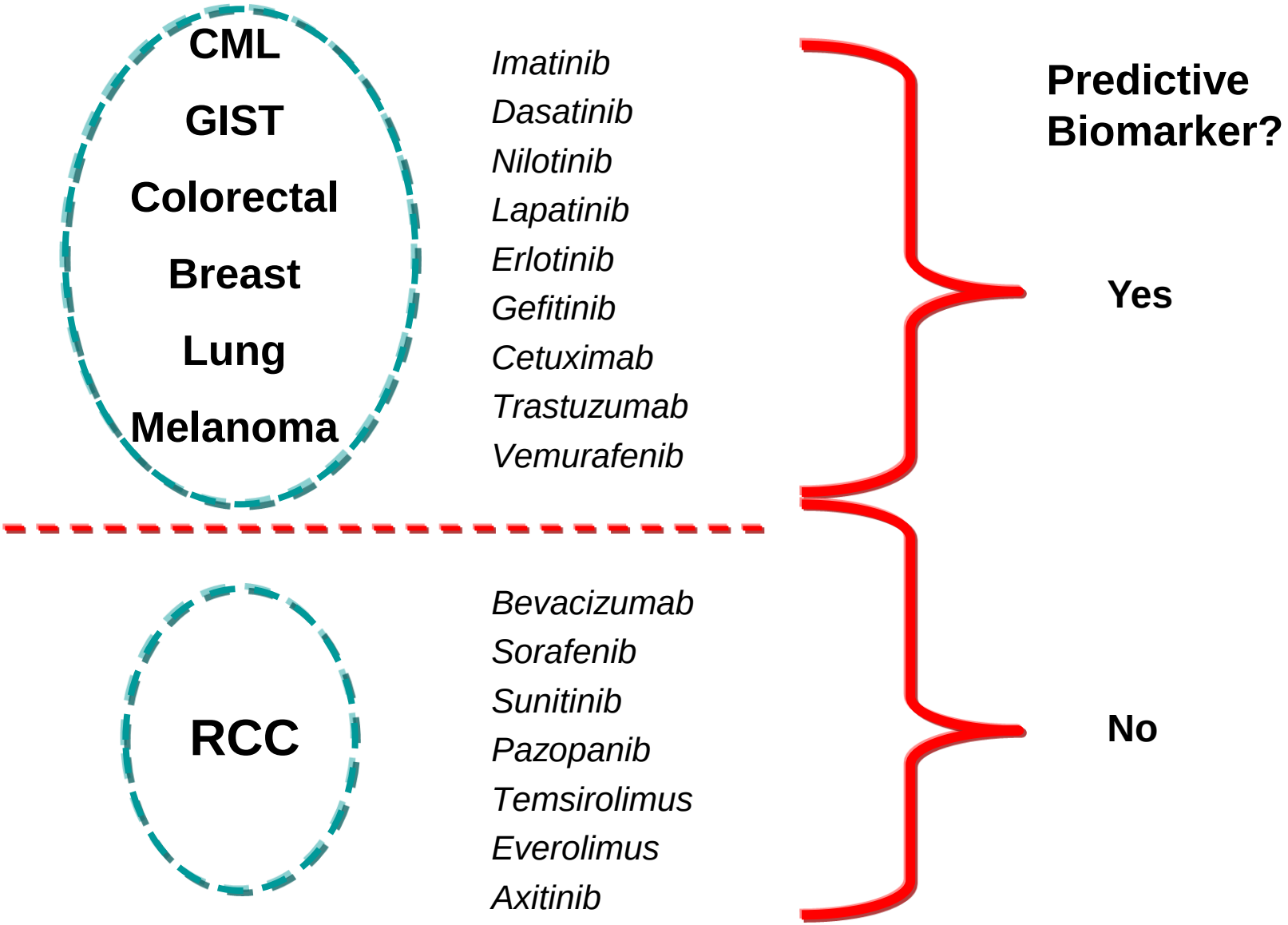
➡ Personalised medicine

- Treating the right person with the right treatment at the right time

- Ideally based on precise and reproducible molecular (genetic) factors which provide prognostic information and predict for response and resistance to treatment

- Hopefully associated with improved outcomes (cure?)

Targeted Agents to Treat Cancer 2012



What is a biomarker?

- A measurable parameter indicative of important clinical events, such as:
  - Cancer onset
  - Recurrence
  - Progression
  - Death

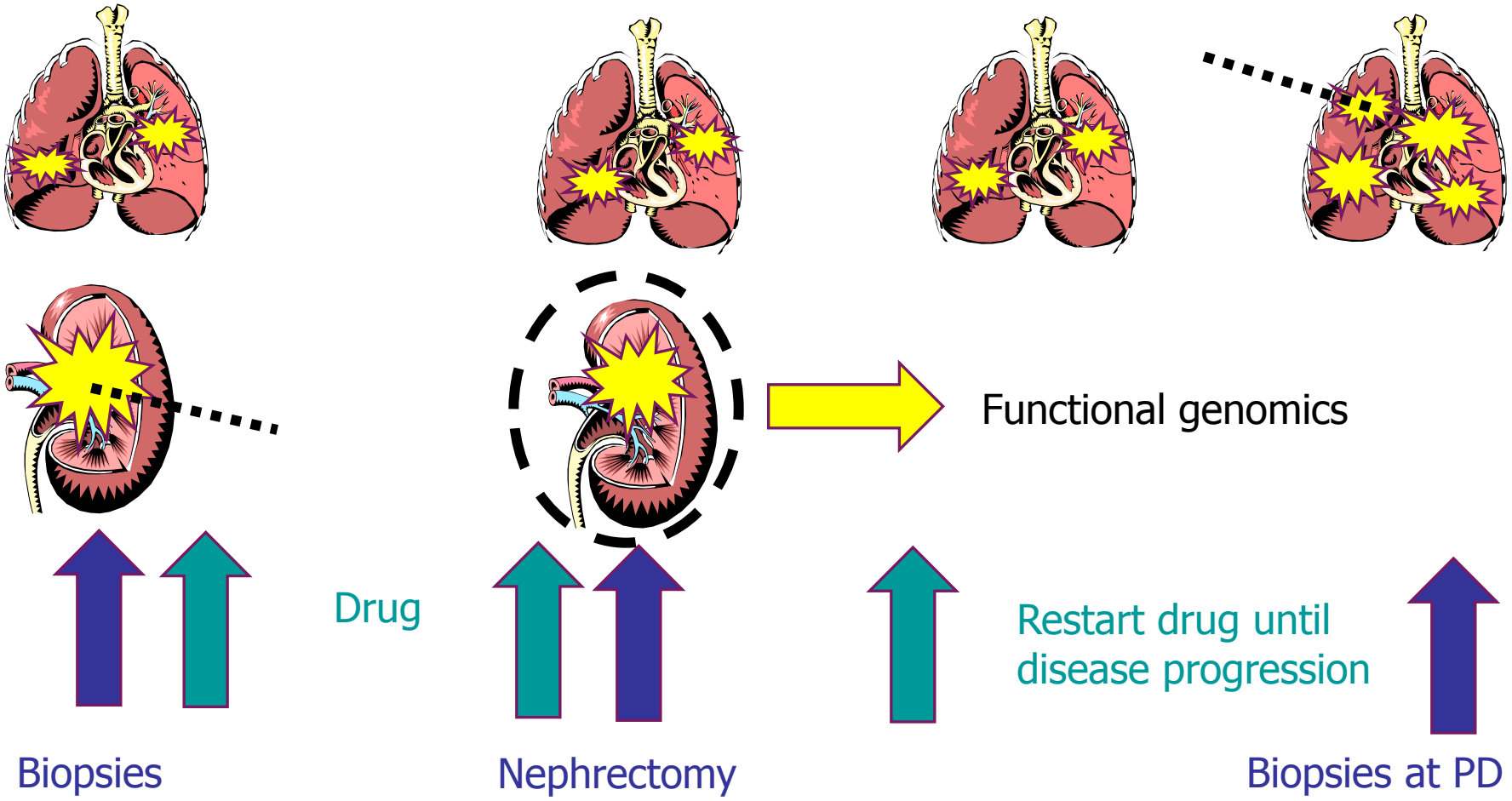
- Biomarkers can be molecular, cellular, functional

Why are there no biomarkers in clinical use in kidney cancer?

- Lack of tissue collection and translational endpoints in drug registration trials
- Drugs may act on non-tumour components, such as blood vessels
- Disease heterogeneity – is a single biopsy representative?

PREDICT Clinical Trial Design

Patients presenting with metastatic RCC planned for debulking nephrectomy as part of routine care



The Intratumour Heterogeneity Question

- A fundamental question for personalised medicine:
- What drives the development of metastatic disease and what is the molecular relationship between primary and secondary tumours?
- We were worried that image-guided biopsies of large tumours might not be representative of the entire primary, never mind the burden of metastatic disease
- So we set out to investigate this in patients 1 to 4

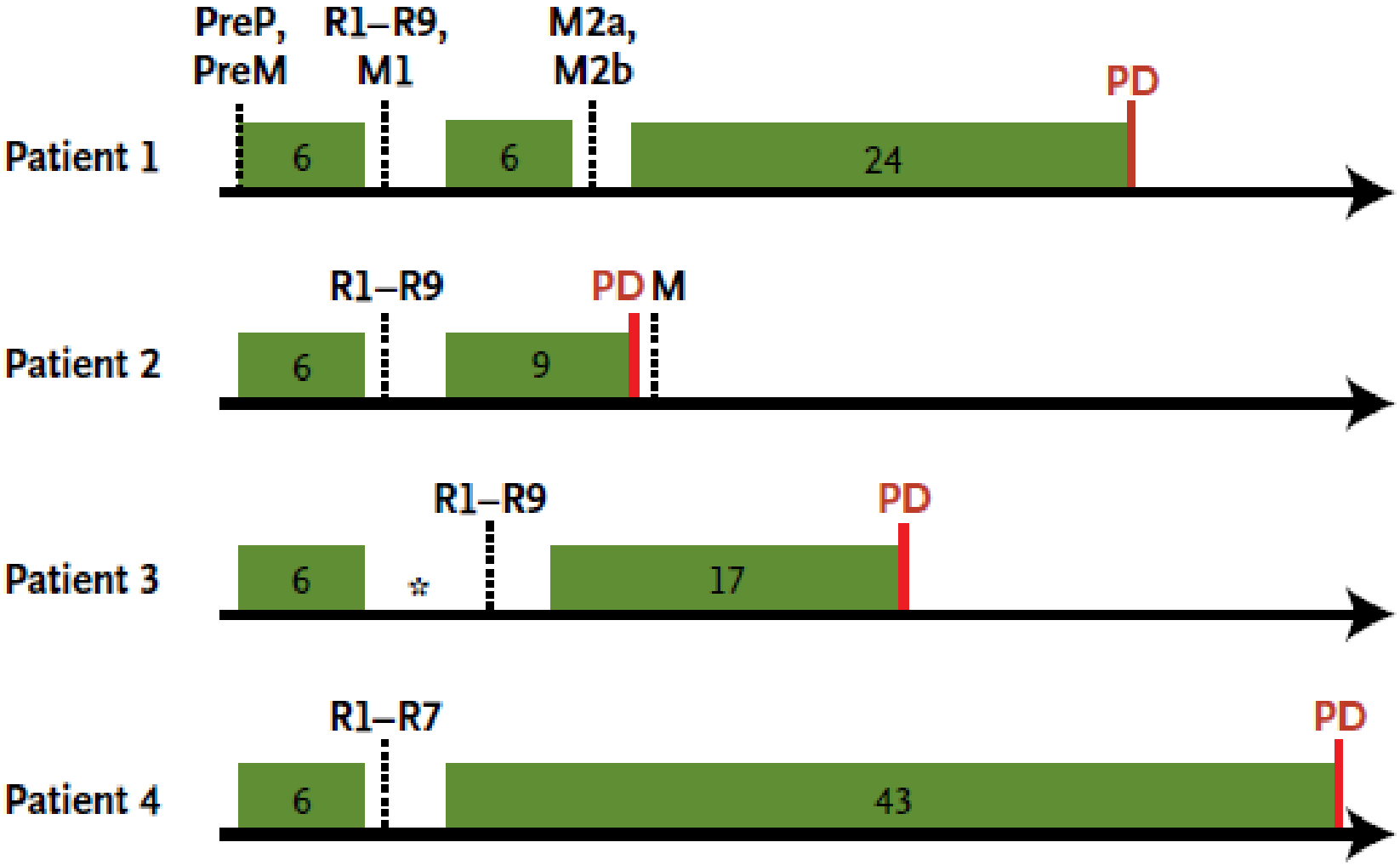
Intratumour Heterogeneity

The NEW ENGLAND JOURNAL of MEDICINE

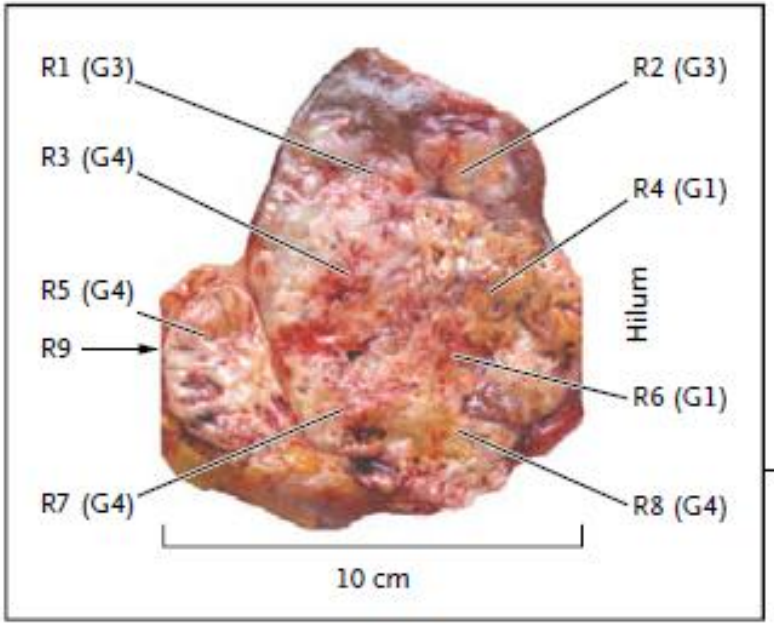
ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

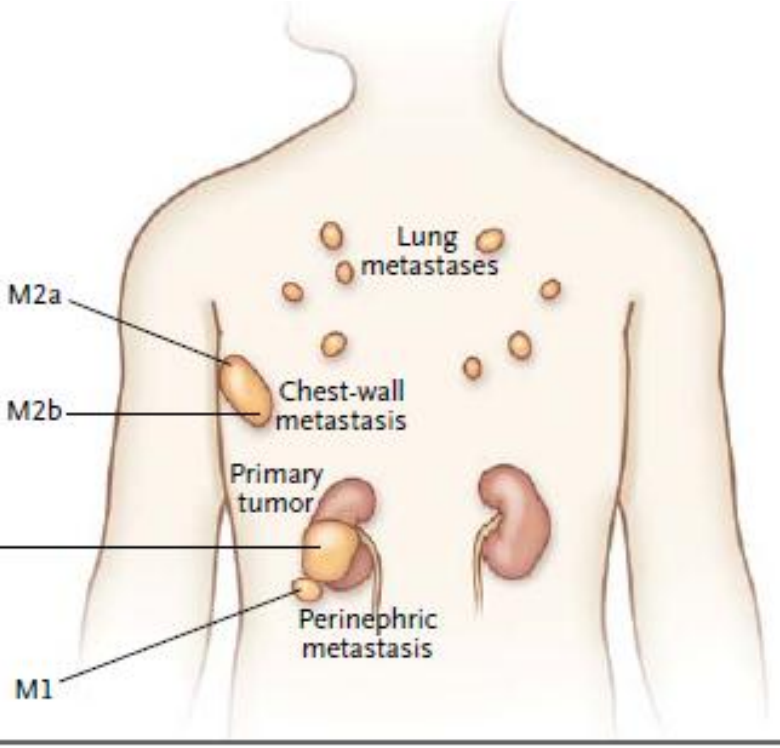
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

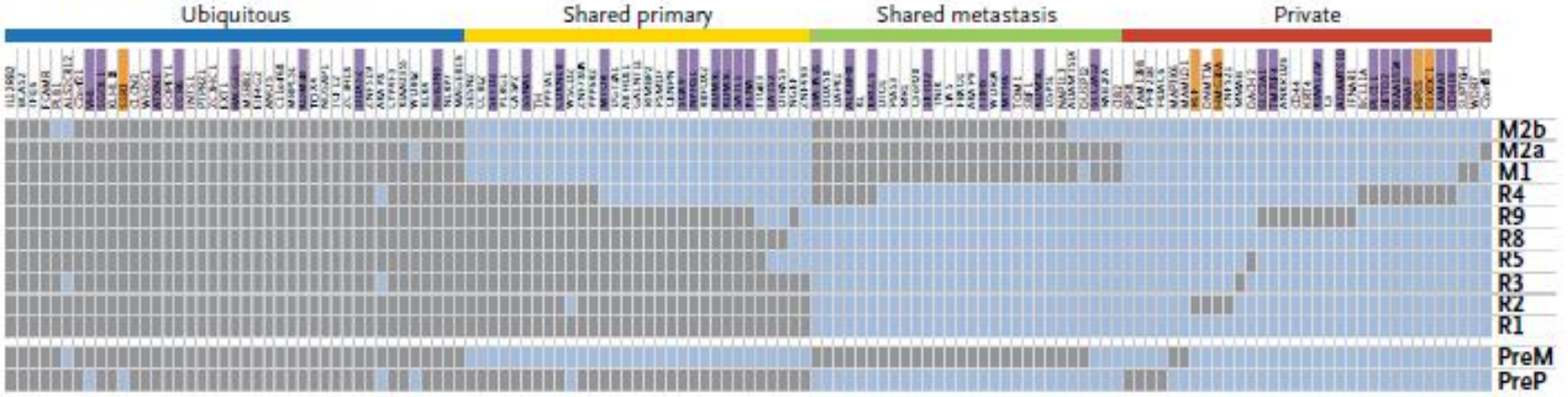

PreP,
PreM
R1–R9,
M1
M2a,
M2b
PD
Patient 1
6
6
24
R1–R9
PD M
Patient 2
6
9
R1–R9
PD
Patient 3
6
17
R1–R7
PD
Patient 4
6
43

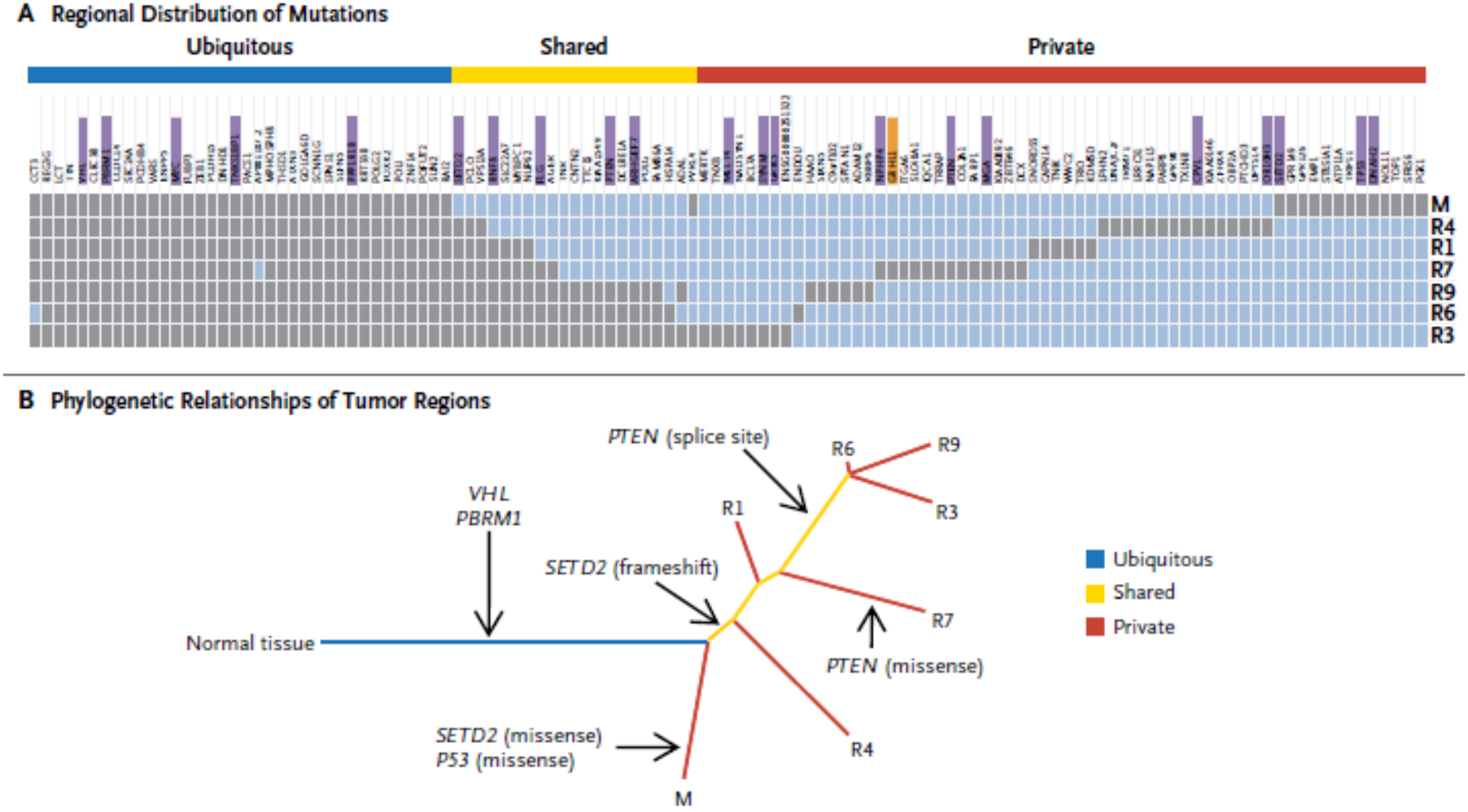
A Biopsy Sites





B Regional Distribution of Mutations




A Regional Distribution of Mutations
Ubiquitous
Shared
Private
M
R4
R1
R7
R9
R6
R3
B Phylogenetic Relationships of Tumor Regions
PTEN (splice site)
R6
R9
VHL
PBRM1
R1
R3
SETD2 (frameshift)
R7
Normal tissue
PTEN (missense)
SETD2 (missense)
P53 (missense)
R4
M
Ubiquitous
Shared
Private

Intra-tumour heterogeneity: speculation

- Relevance to other tumour types?
- Implications for personalised medicine
- Differences in small vs large tumours
- Prognostic and predictive relevance uncertain
- Study of primary and metastatic sites within an individual patient is key

Tissue donation by living patients

- Allows longitudional analysis of tumour sites, spatially and temporally separated
- Use of tissue which is surplus to diagnostic and clinical requirements
- Use of tissue which is obtained purely for research purposes

Challenges associated with tissue collection in living patients

- Multiple samples from one tumour – increased biopsy risk
- Metastatic sites may be technically difficult to access
- Patients with advanced cancer may be unwell
- Cost to patients – time, travel, expenses
- Huge collaborative effort – nurse, tissue collector, research fellow, radiologist, surgeon, pathologist, scientists

Access to fresh tumour tissue in a post-mortem study

- Would allow multi-region sampling within larger tumours, and sampling of all metastatic sites, aiming to:
  - Analyse the extent of intra-tumour heterogeneity within and between tumour sites
  - Establish a model of tumour progression
  - Determine whether these influence clinical outcomes

- Potentially even small patient numbers would yield clinically meaningful information

Practical considerations

- Consent
  - Pre-mortem
- Individual and family beliefs surrounding death and burial customs
- Time and place of death
- Availability of post-mortem analysis
- Type and amount of tissue sampled

Discussion points

- Individualised consent/research protocol, discussed prior to patient death – is this practical?
- How would this proposal be received by patients/families/advocacy groups/ethics committees?
- Is it realistic to bring about a change in post-mortem practices?

Acknowledgements

- Dr James Larkin
- Professor Charles Swanton
- Professor Martin Gore
- Independent Cancer Patients' Voice