

A health care system to meet our needs

The Power of Innovation

Shrinking Cancer: Revolutionary New Treatment of Brain Tumours
Dr Georgina Long,
Westmead Millennium Institute for Medical Research



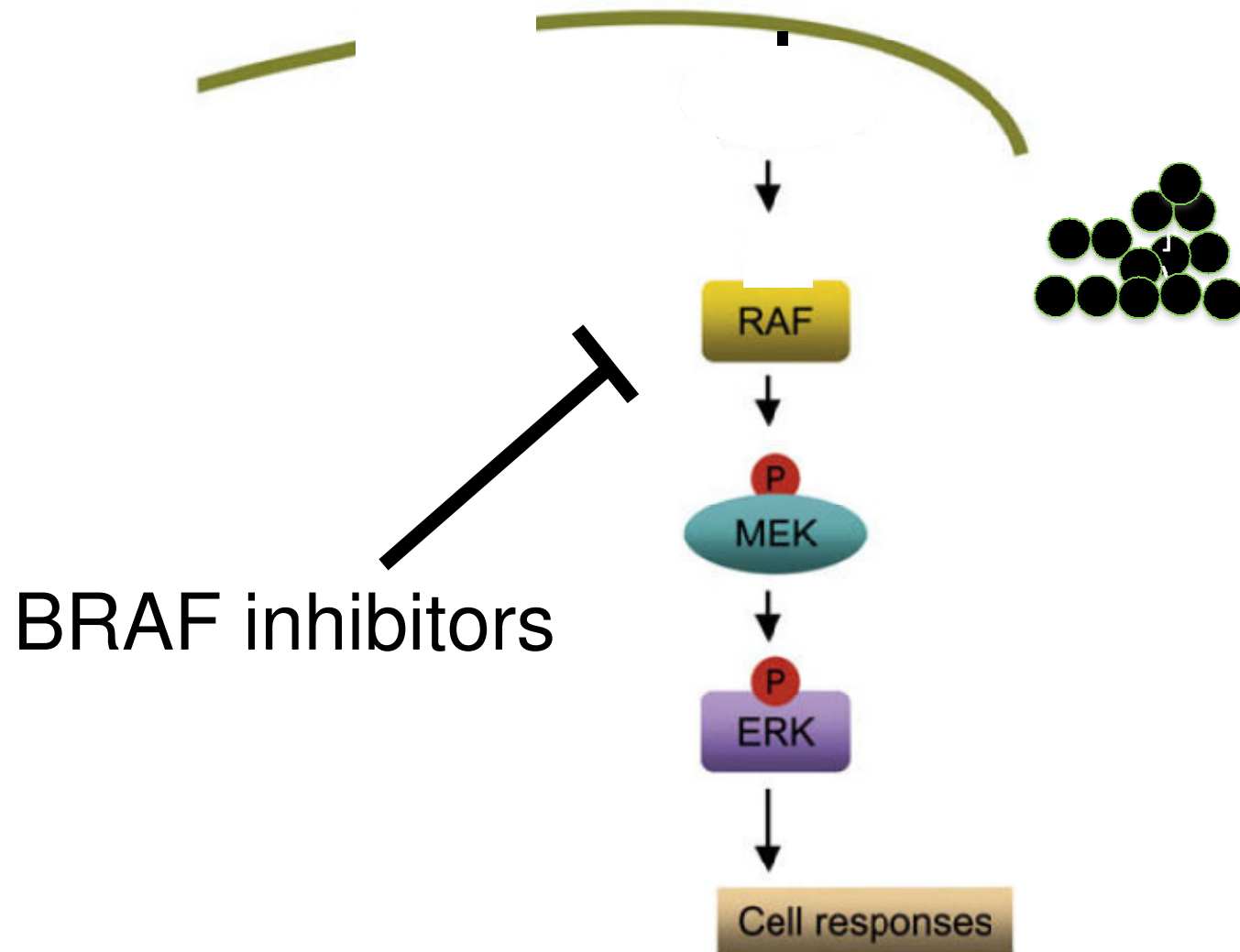
Health

Dr Georgina Long

Melanoma Institute Australia
Westmead Millenium Institute
Westmead Hospital
The University of Sydney

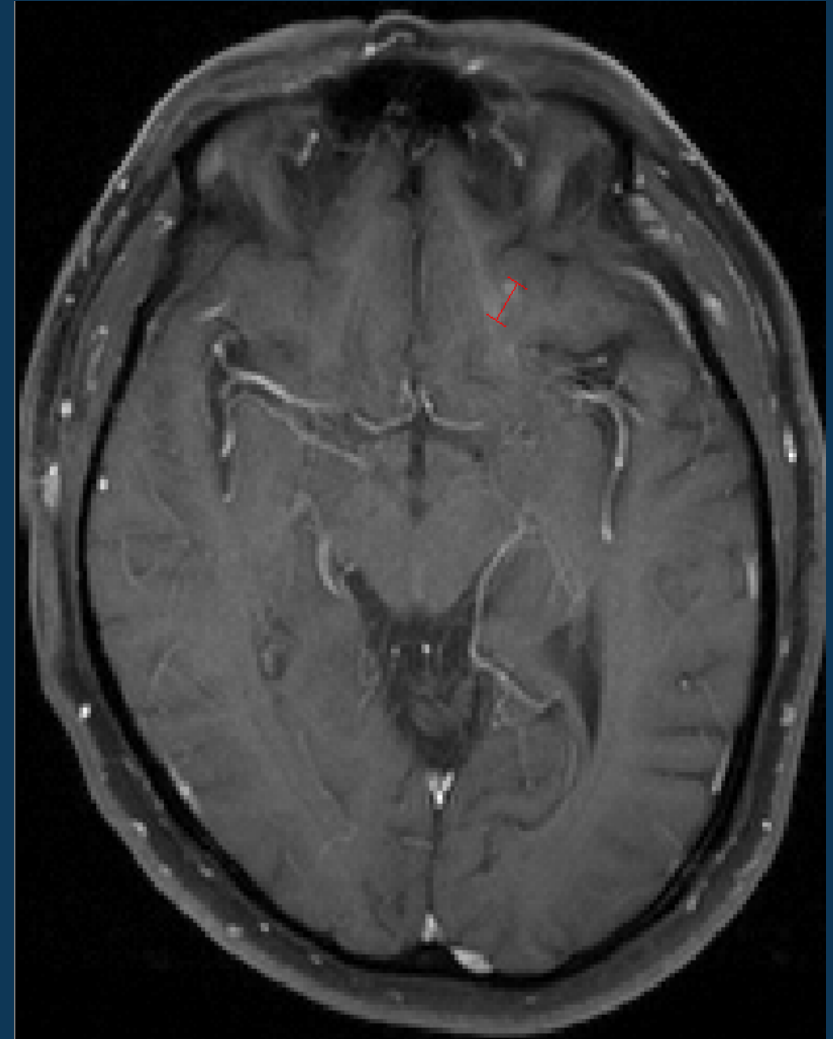
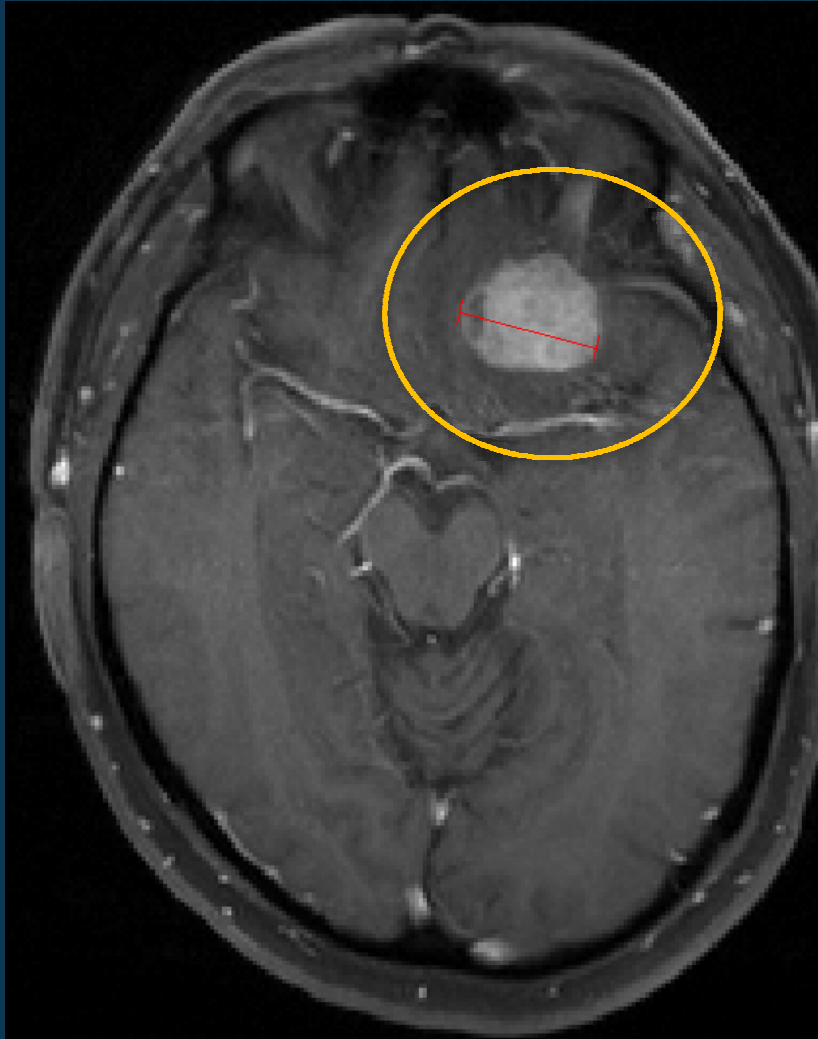


Mutated BRAF

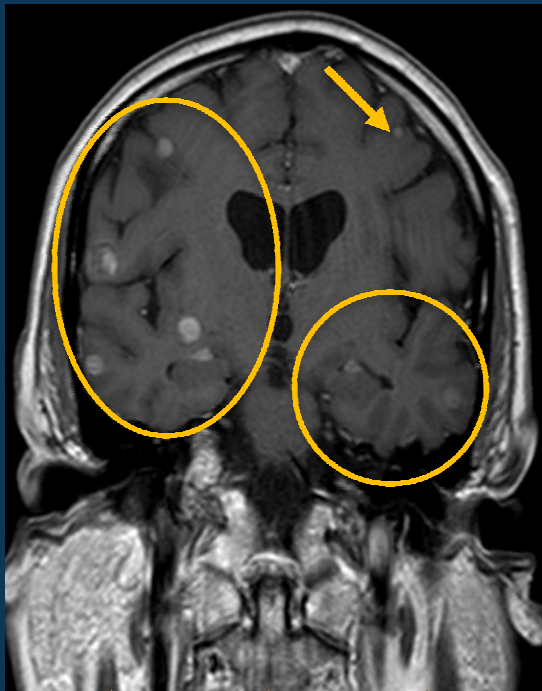


Cellular Proliferation, Survival, Migration

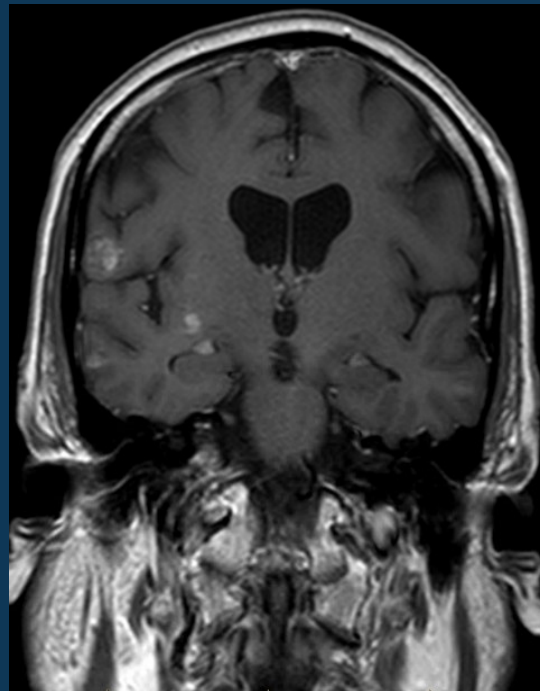
Dabrafenib Response in Brain



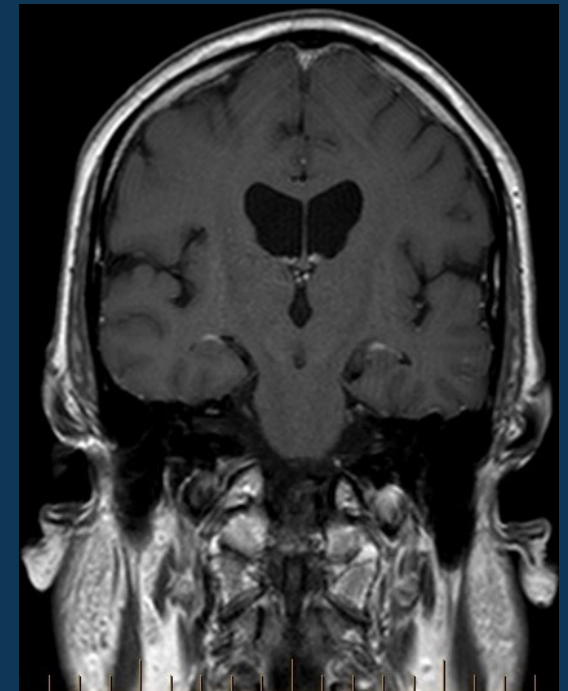
Dabrafenib Response in Brain



Baseline

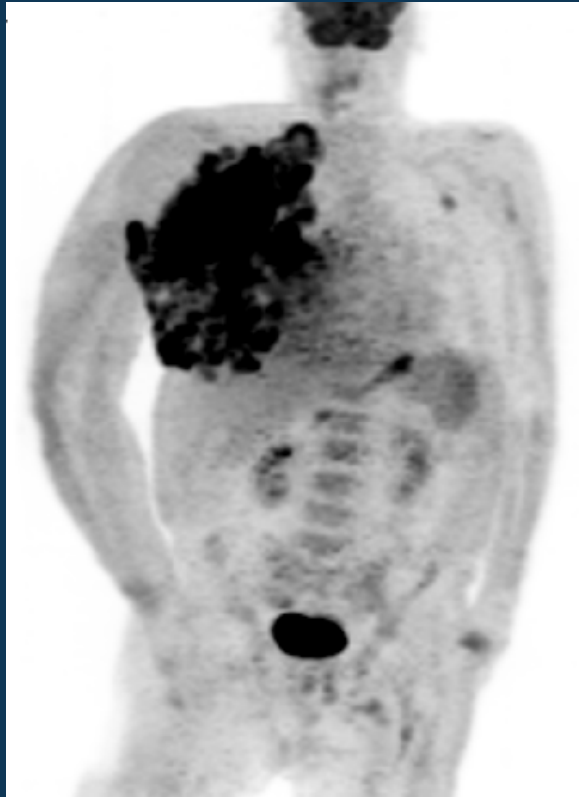


Week 4

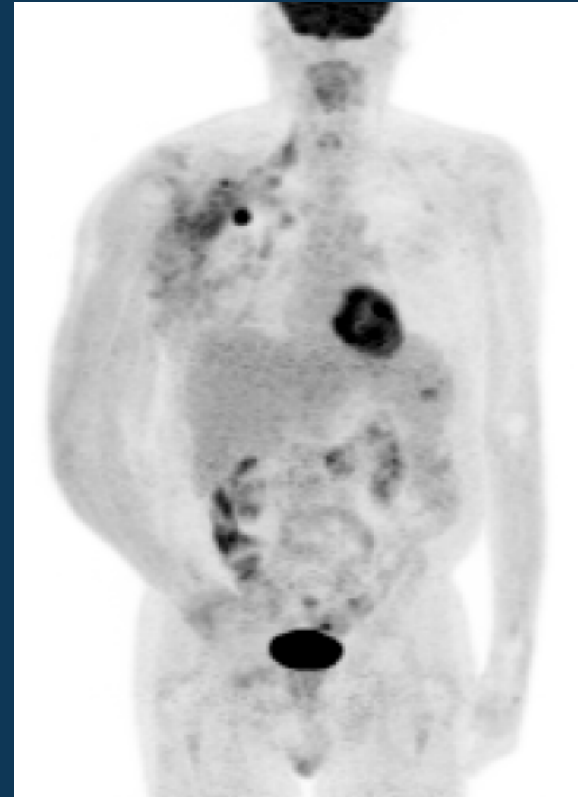


Week 10

Dabrafenib



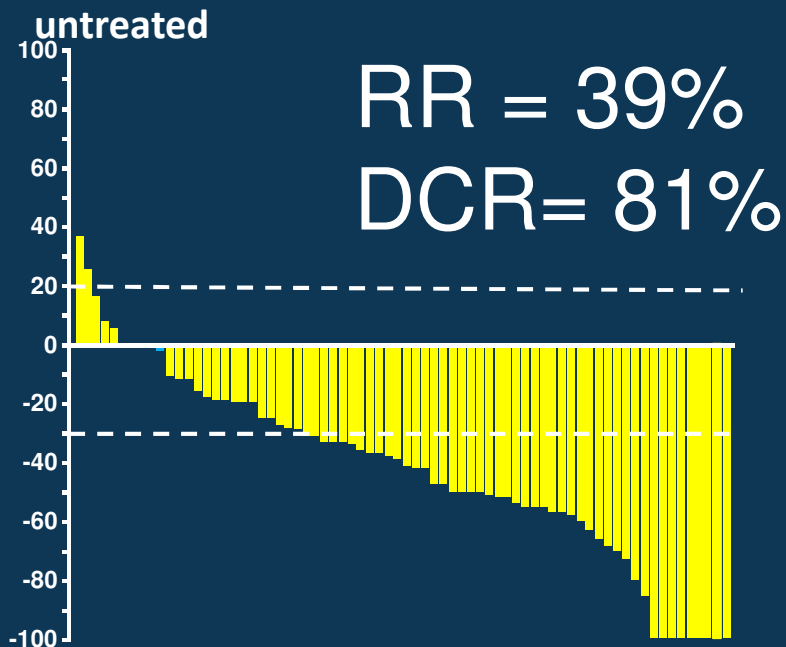
Baseline



Week 6

V600E Brain Response

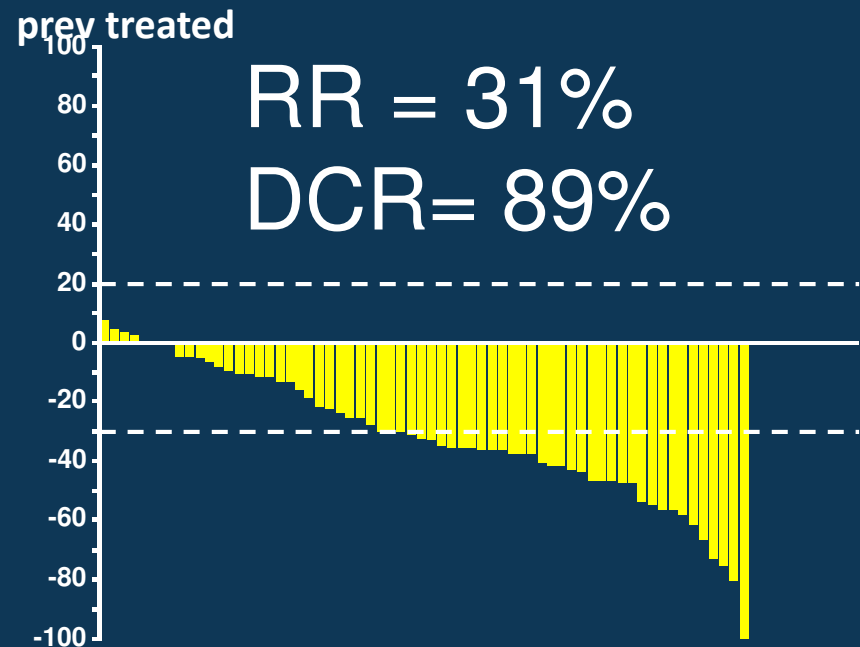
Cohort A



•Median duration of brain response: 20.1 wks

- ORR: 38%
- Overall DCR: 80%
- Median duration of response: 27.6 wks

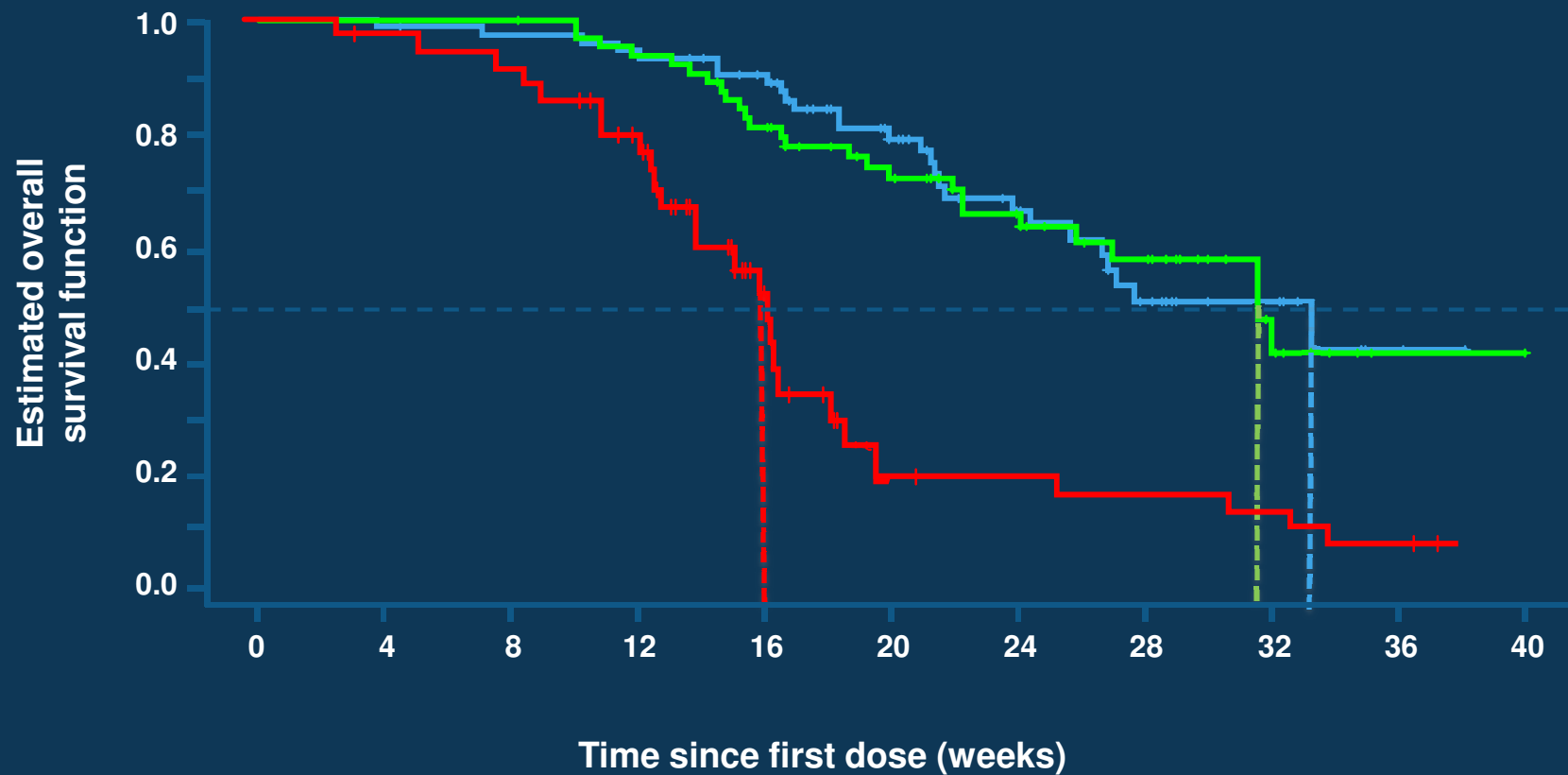
Cohort B



•Median duration of response: 28.1 wks

- ORR: 31%
- Overall DCR: 83%
- Median duration of response: 20.1 wks

Median Overall Survival



Adapted from Long GV et al Lancet Onc 2012

Innovation and Translation in Clinical Practice: Lessons from Melanoma and Targeted Therapies

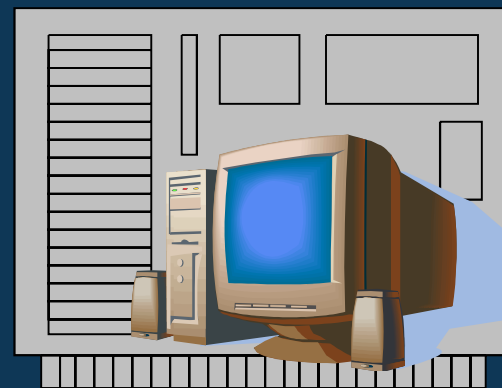
Disclosures

- Roche:
Advisory Boards
Honoraria
Research Support
- GSK:
Advisory Boards
Conference attendance
- Bristol Myers Squibb:
Advisory Board
- Novartis:
Advisory Board
- Amgen:
Advisory Board

Biospecimen Bank

	Av p.a.	Overall
Blood Banked	800	3655
Metastases Banked	220	2180
Primaries Banked	70	465

Research Database



MIA - 35 000 pt records

The Clinic



Clinical Trials
new drugs
new technology

Laboratories

Lesson 2: Multidisciplinary

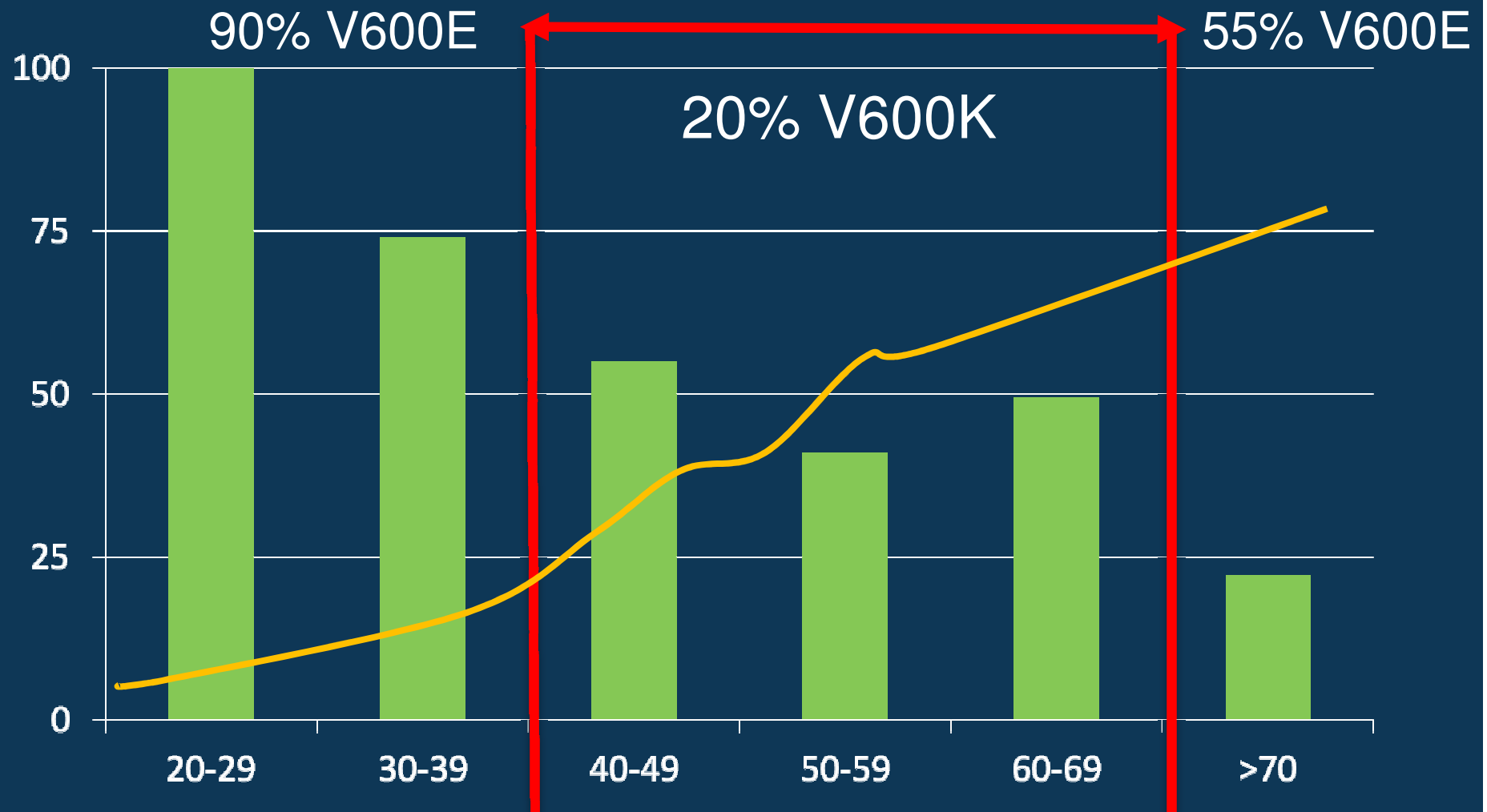


"We like to bring together people from radically different fields and wait for the friction to produce heat, light and magic. Sometimes it takes a while."

What BRAF testing should we perform as a Unit? Who pays?



BRAF Rate by Decade N=308

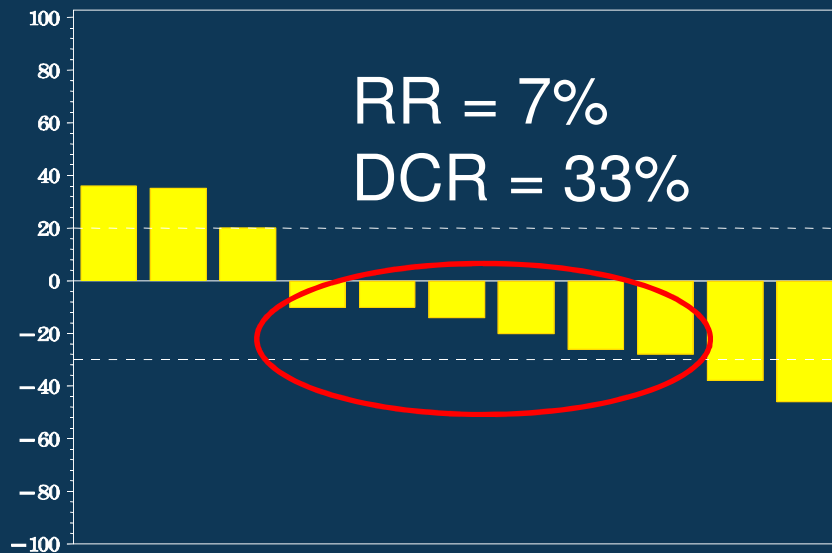


Dabrafenib Best unconfirmed response : V600K (BREAK-2)



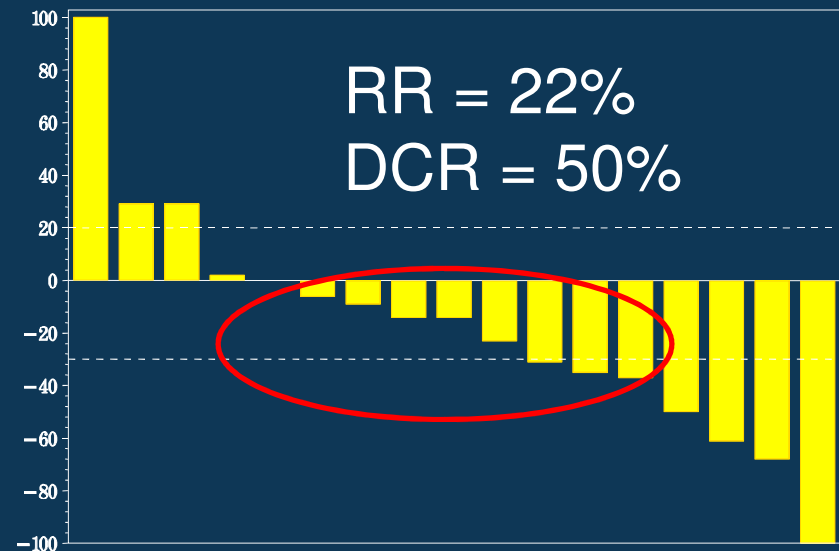
V600K Brain Response

Cohort A



ORR: 0%
Overall disease control rate: 33%

Cohort B



ORR: 28%
Overall disease control rate: 50%

Long et al Lan Onc 2012

Lesson 3: Tissue Banking Infrastructure Is Critical.....



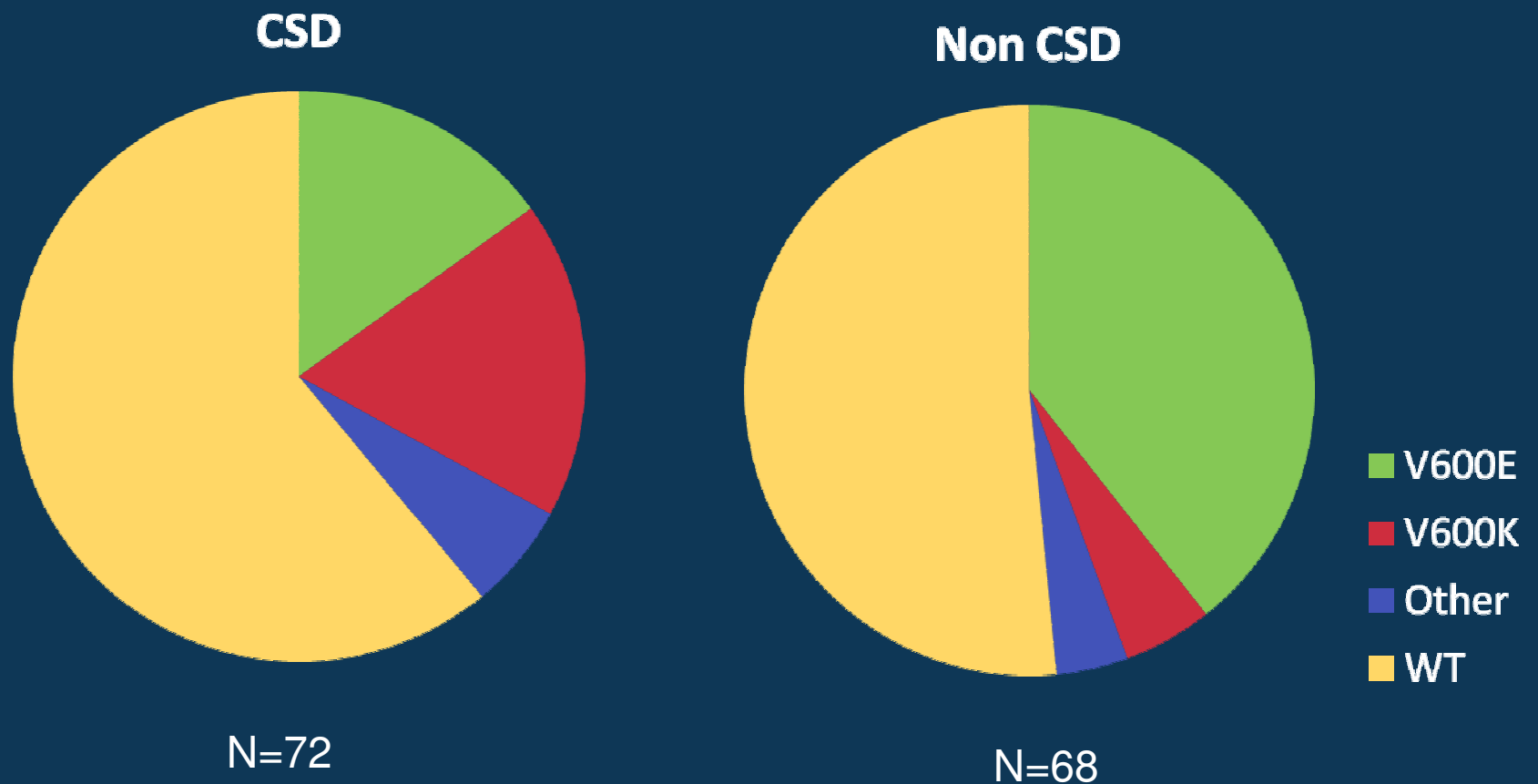
Lesson 4: ...is almost nothing without a pathologist



and high quality real-time clinical data

Chronic Sun Damage (CSD)

N=140 antecedent primary cutaneous melanoma



N=72

N=68

$P = 0.004$

Lesson 5: Novel Therapeutics



Sydney West Cancer Trials Centre
Westmead Hospital



Melanoma Institute Australia
Clinical Trials

Lancet

Dabrafenib
metastases
dose-escala

Lancet Oncology

Articles

Gerald S Falchook*, Georgina V Long, Michael Millward, Anna C P

Summary
Background Dabrafenib safety and tolerability especially those with

Dabrafenib in patients with Val600Glu or Val600Lys

BRAF-mutant melanoma metastatic to the brain

The NEW ENGLAND JOURNAL of MEDICINE

(BREAK-M



ORIGINAL ARTICLE

Georgina V Long, Uwe Tre
Caroline Robert, Alain Alg
Mary Guckert, Vicki Good

Summary
Background Brain m
their diagnosis is ty
mutant melanoma r

Survival in BRAF V600–Mutant Advanced Melanoma Treated with Vemurafenib

The NEW ENGLAND JOURNAL of MEDICINE

Jeffrey J
Rene Gonz
Gran
Stergios J. Mos
Richard Keffo
Karl D. Lewis,
H. Jeffrey
Keith

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffrey R. Infante, M.D., Adil Daud, M.D.,
Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D.,
Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D.,
Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D.,
Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D.,
Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I.,
Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H.,
Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D.,
Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

Lesson 6: Committed Surgeons





TEAM — Treat Excise Analyse Melanoma



Biopsy BEFORE
(-7 days)

PRE

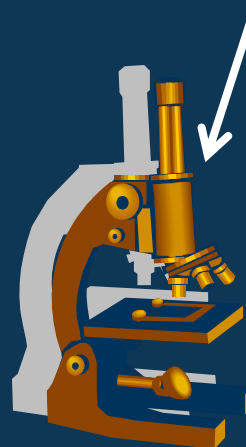
Treat with trial drug

Biopsy Early During
Treatment (7days)

EDT

Biopsy PROGRESSION

PROG



Examine for biomarkers of
response and resistance

Lesson 7: Withdraw From the Bank

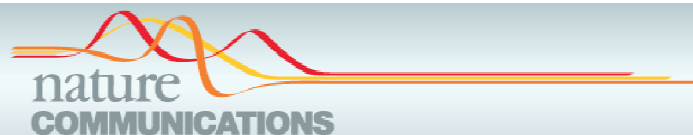


Lesson 8: Collaborate



The “TEAM” team

RESEARCH BRIEF



Published OnlineFirst on April 24, 2012; DOI:10.1158/1078-0432.CCR-12-0052

Published OnlineFirst December 12, 2011; DOI:10.1158/1078-0432.CCR-11-2479

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clinical
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research

Sele
into ^{18}F -labelled f
James (FDG-PET)
John f dabrafenib tr

Matteo S. Carlini
Alexander M. M
Richard F. Keffo

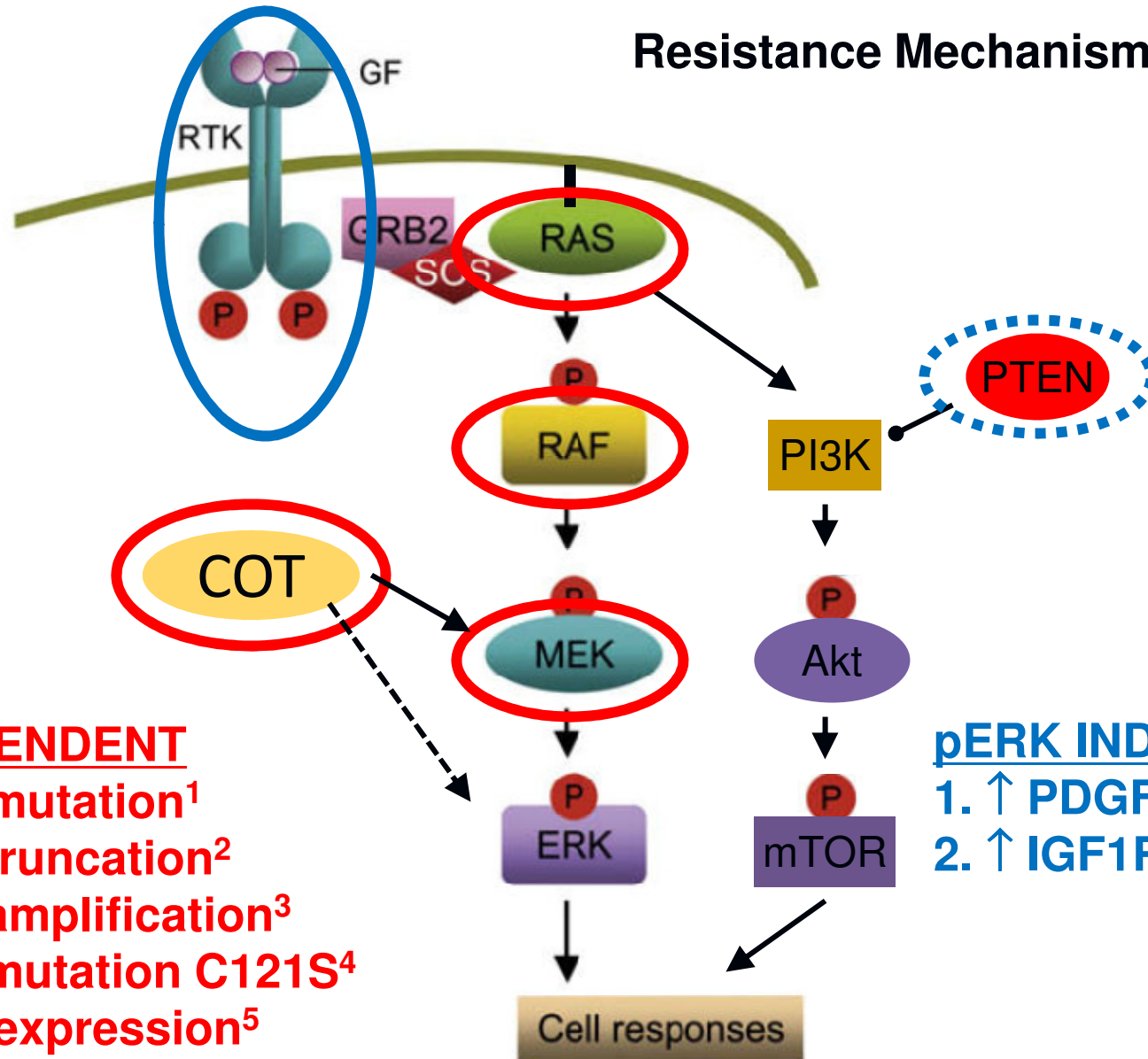
LETTER

doi:10.1038/nature10630

A novel recurrent mutation in *MITF* predisposes to familial and sporadic melanoma

Satoru Yokoyama^{1*}, Susan L. Woods^{2*}, Glen M. Boyle^{2*}, Lauren G. Aoude^{2*}, Stuart MacGregor^{2*}, Victoria Zismann^{3*}, Michael Gartside², Anne E. Cust⁴, Rizwan Haq¹, Mark Harland⁵, John C. Taylor⁵, David L. Duffy², Kelly Holohan², Ken Dutton-Regester², Jane M. Palmer², Vanessa Bonazzi², Mitchell S. Stark², Judith Symmons², Matthew H. Law², Christopher Schmidt², Cathy Lanagan², Linda O'Connor², Elizabeth A. Holland⁶, Helen Schmid⁶, Judith A. Maskiell⁷, Jodie Jetann⁸, Megan Ferguson⁸, Mark A. Jenkins⁷, Richard F. Kefford⁶, Graham G. Giles⁹, Bruce K. Armstrong⁴, Joanne F. Aitken⁸, John L. Hopper⁷, David C. Whiteman², Paul D. Pharoah¹⁰, Douglas F. Easton¹⁰, Alison M. Dunning¹⁰, Julia A. Newton-Bishop⁵, Grant W. Montgomery², Nicholas G. Martin², Graham J. Mann⁶, D. Timothy Bishop⁵, Hensin Tsao^{11*}, Jeffrey M. Trent^{3*}, David E. Fisher^{1*}, Nicholas K. Hayward^{2*} & Kevin M. Brown^{3,12*}

Resistance Mechanisms to BRAFi

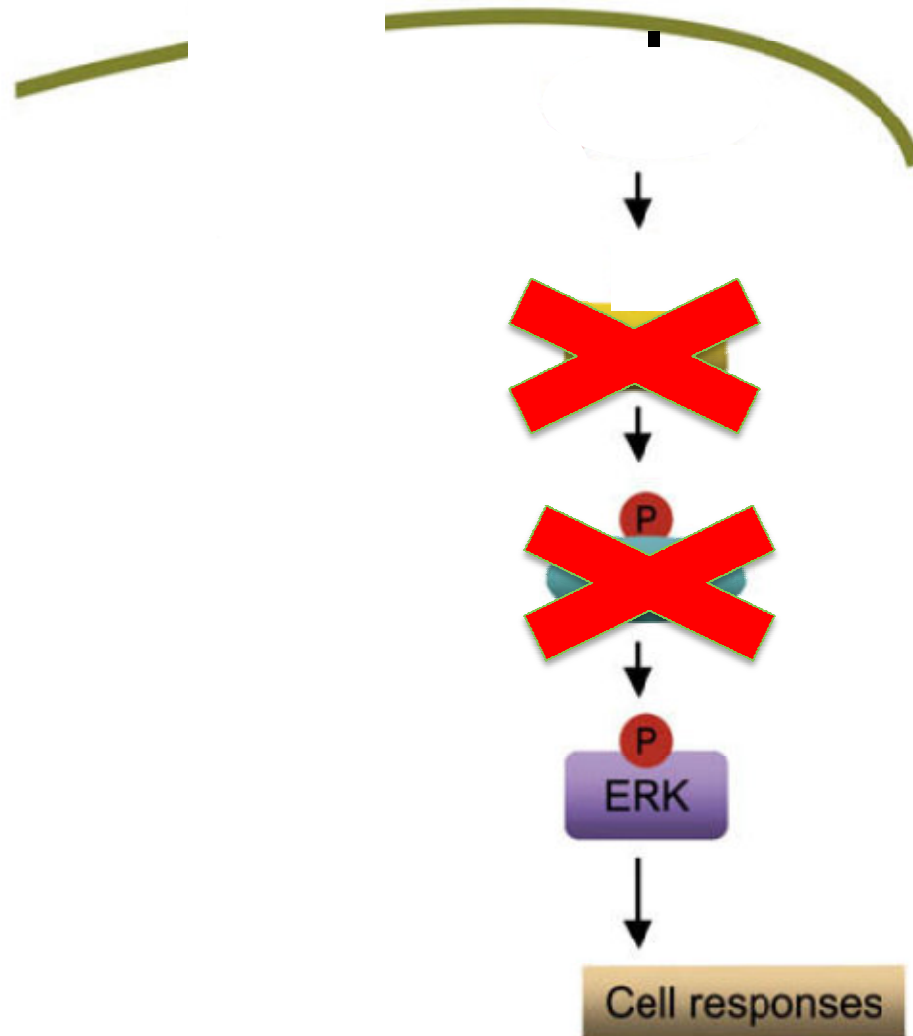


1. Nazarian R, Shi H, Wang Q, et al. Nature 2010; 468, 973-977.
2. Poulidakos PI, Persaud Y, Janakiraman M, et al Nature 2011;480:387-90.
3. Shi H, Moriceau G, Kong X, et al Nat Commun 3:724, 2012
4. Wagle N, Emery C, Berger MF, et al J Clin Oncol 29:3085-3096, 2011.
5. Johannessen CM, Boehm JS, Kim SY, et al. Nature 2010;468:968-72.
6. Villanueva J, Vultur A, Lee JT, et al. Cancer Cell 2010;18:683-95.

Lesson 9: Think ahead – what's next?

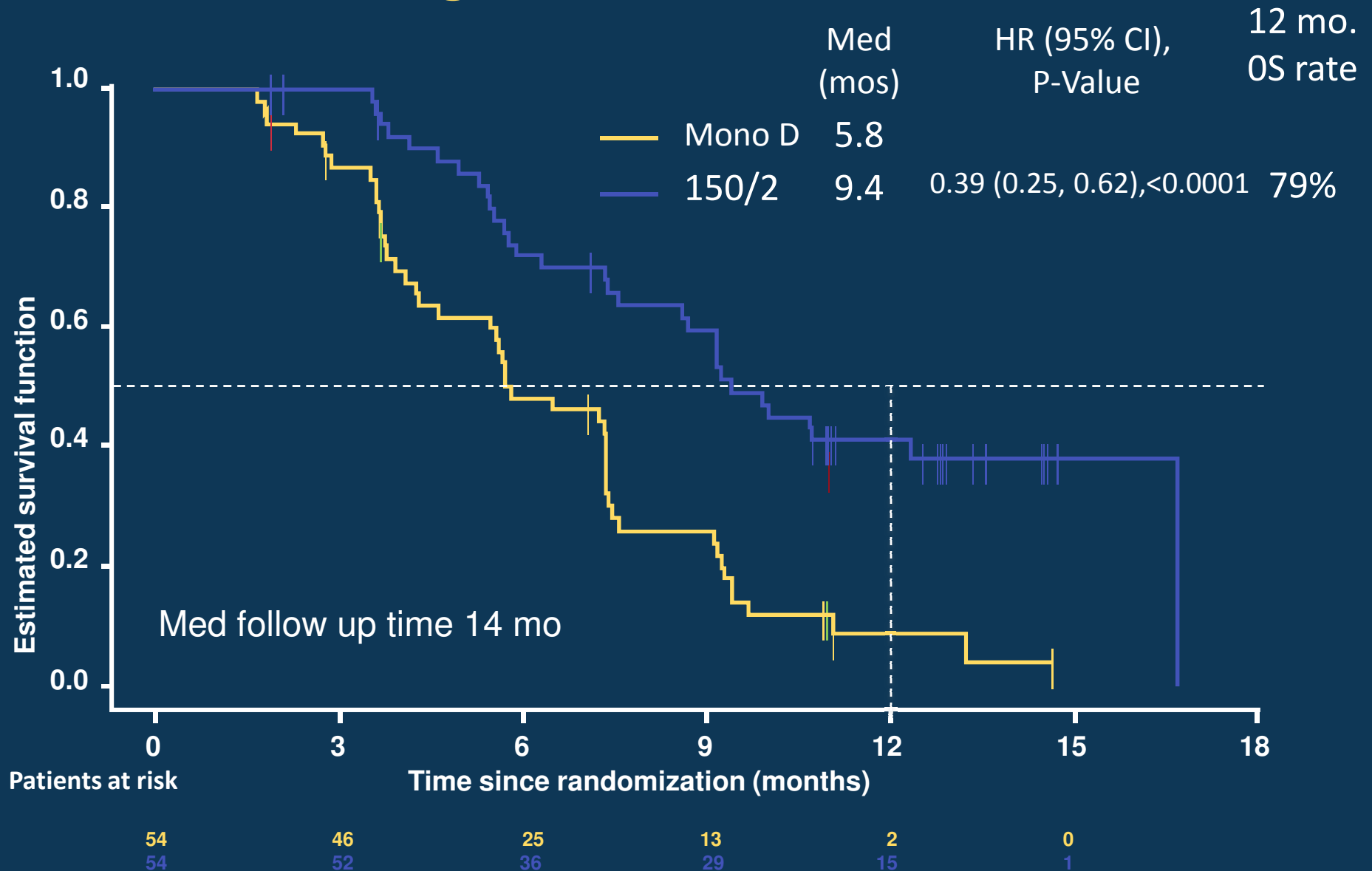


Mutated BRAF

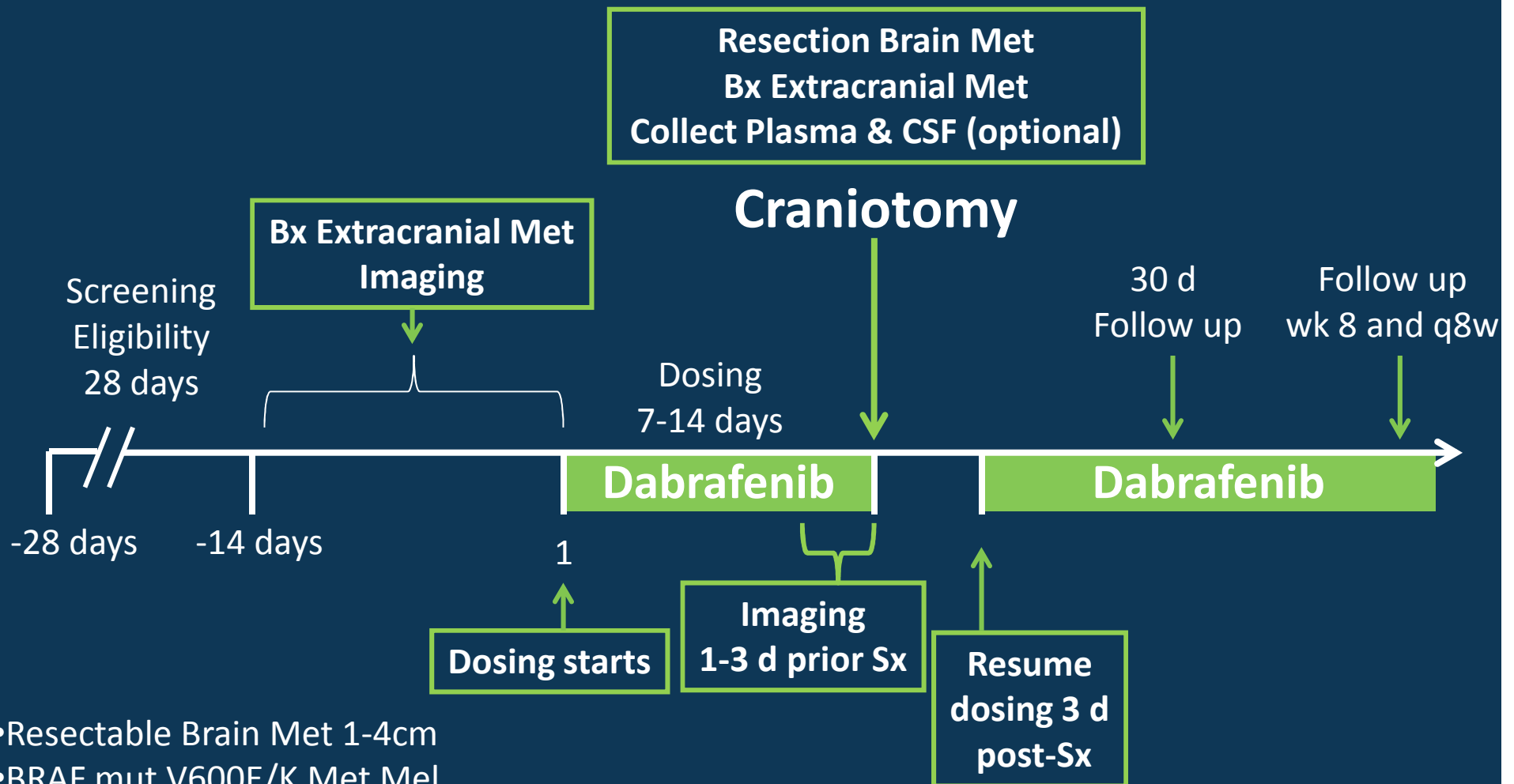


Cellular Proliferation, Survival, Migration

Progression-Free Survival



Neoadjuvant Dabrafenib - Study Schema



- Resectable Brain Met 1-4cm
- BRAF mut V600E/K Met Mel
- Other brain mets allowed

MIA Melanoma Genome Project

450 Melanoma Samples

Detailed clinicopathologic follow up

Cohort 4 = Primary and metastatic pairs



Cohort 1 = Primary melanoma

Cohort 2 = Lymph Nodes

Cohort 3 = brain metastases

- Whole genome sequencing
- RNA seq
- RNA gene expression array
- aCGH; DNA copy number
- Metabolomics, proteomic (iTRAQ)

Acknowledgements

- Patients and Families
- National and International Colleagues and Scientists working in Melanoma
- Westmead Millennium Institute/Melanoma Institute Australia/Westmead Hospital

Professor Rick Kefford, Vicky Wegener, Natalie Byrne, Arthur Clements, Pablo Fernandez-Penas, Alex Menzies, Matt Carlino, Jennifer O'Leary, Julie Howle, Deirdre d'Souza, Catriona McNeil, Sayed Ali, Lydia Visintin, Annie Maher, Mary Azer, Rob Zeilinski, Michael Hughes, Catherine Saunders

John Thompson, Peter Barry, Jonathon Stretch, Robyn Saw, Andrew Spillane, Kerwin Shannon, Michael Quinn, Raghwa Sharma, Richard Scolyer, Sandie Grierson, Candace Carter, Valarie Jakrot

