

Mechanisms of resistance: what have we learned from melanoma

Richard Marais

richard.marais@cruk.manchester.ac.uk

www.cruk.manchester.ac.uk



CANCER
RESEARCH
UK

MANCHESTER
INSTITUTE



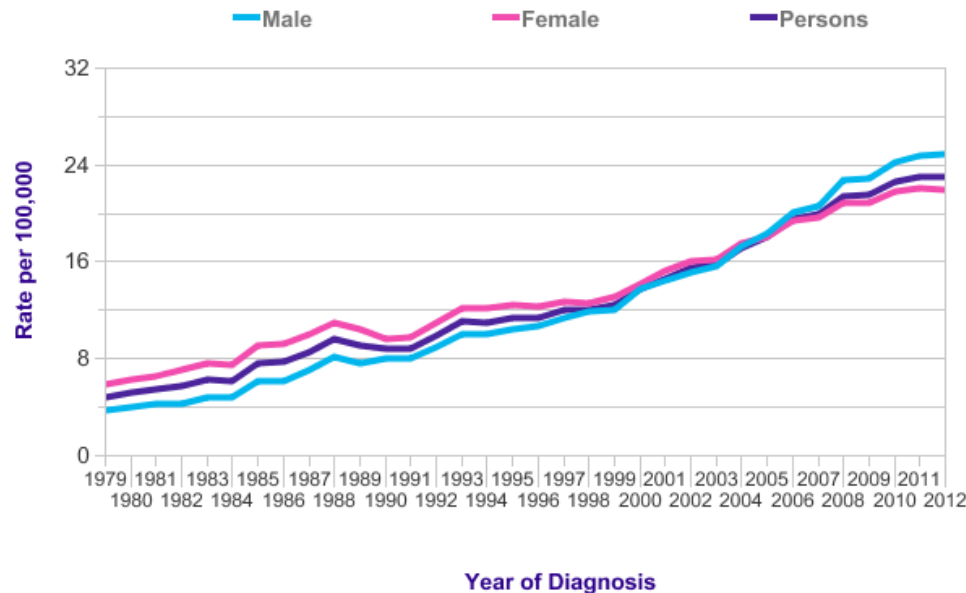
The University of Manchester

Follow us on:



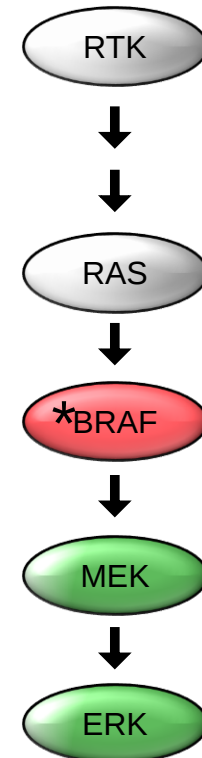
Melanoma

- Melanoma, a potentially deadly skin cancer
- EU: >100,000 cases; >22,000 deaths
 - incidence doubles every 10 years

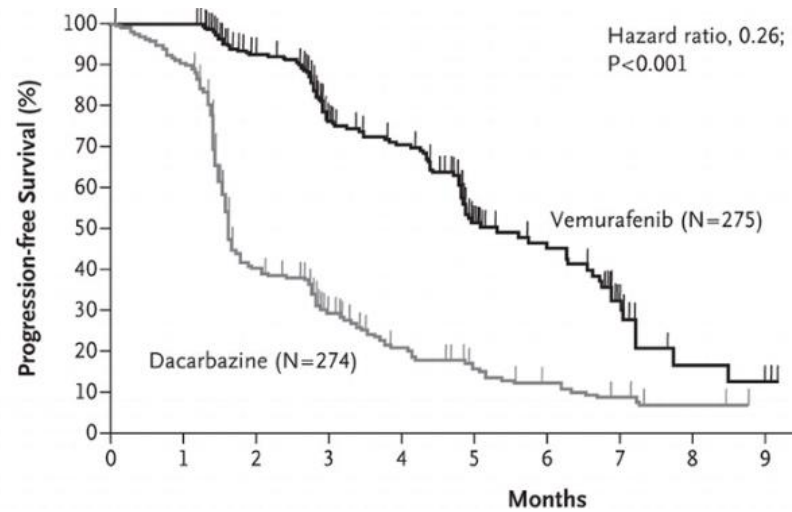
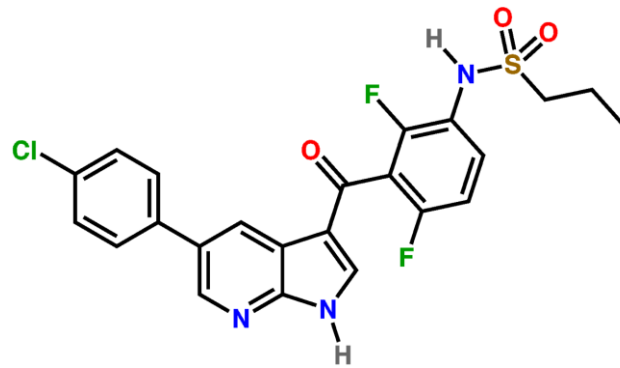


Mutations of the *BRAF* gene in human cancer

Helen Davies^{1,2}, Graham R. Bignell^{1,2}, Charles Cox^{1,2}, Philip Stephens^{1,2}, Sarah Edkins¹, Sheila Clegg¹, Jon Teague¹, Hayley Woffendin¹, Mathew J. Garnett³, William Bottomley¹, Neil Davis¹, Ed Dicks¹, Rebecca Ewing¹, Yvonne Floyd¹, Kristian Gray¹, Sarah Hall¹, Rachel Hawes¹, Jaime Hughes¹, Vivian Kosmidou¹, Andrew Menzies¹, Catherine Mould¹, Adrian Parker¹, Claire Stevens¹, Stephen Watt¹, Steven Hooper³, Rebecca Wilson³, Hiran Jayatilake⁴, Barry A. Gusterson⁵, Colin Cooper⁶, Janet Shipley⁶, Darren Hargrave⁷, Katherine Pritchard-Jones⁷, Norman Maitland⁸, Georgia Chenevix-Trench⁹, Gregory J. Riggins¹⁰, Darell D. Bigner¹⁰, Giuseppe Palmieri¹¹, Antonio Cossu¹², Adrienne Flanagan¹³, Andrew Nicholson¹⁴, Judy W. C. Ho¹⁵, Suet Y. Leung¹⁶, Siu T. Yuen¹⁶, Barbara L. Weber¹⁷, Hilliard F. Seigler¹⁸, Timothy L. Darrow¹⁸, Hugh Paterson³, Richard Marais³, Christopher J. Marshall³, Richard Wooster^{1,6}, Michael R. Stratton^{1,4} & P. Andrew Futreal¹

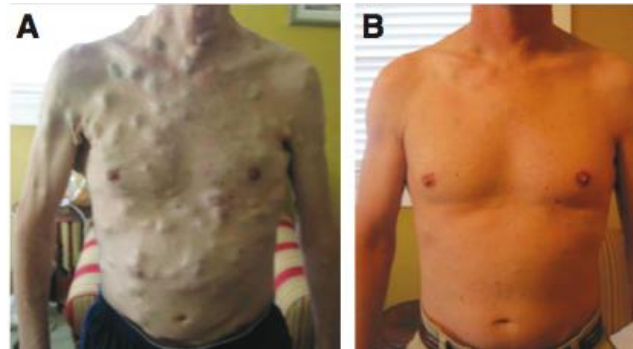


BRAF is mutated in ~45% melanoma

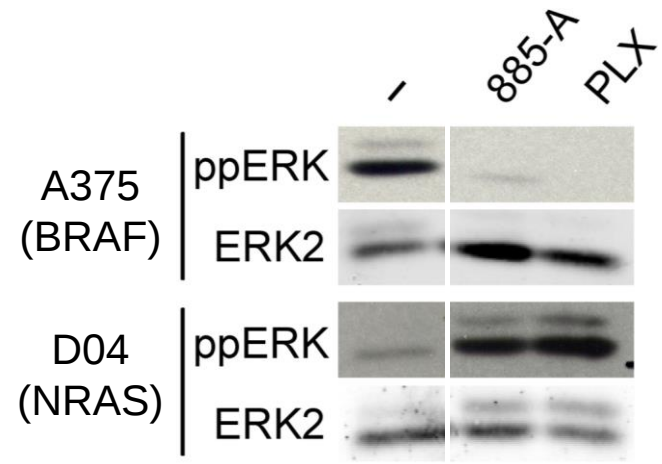
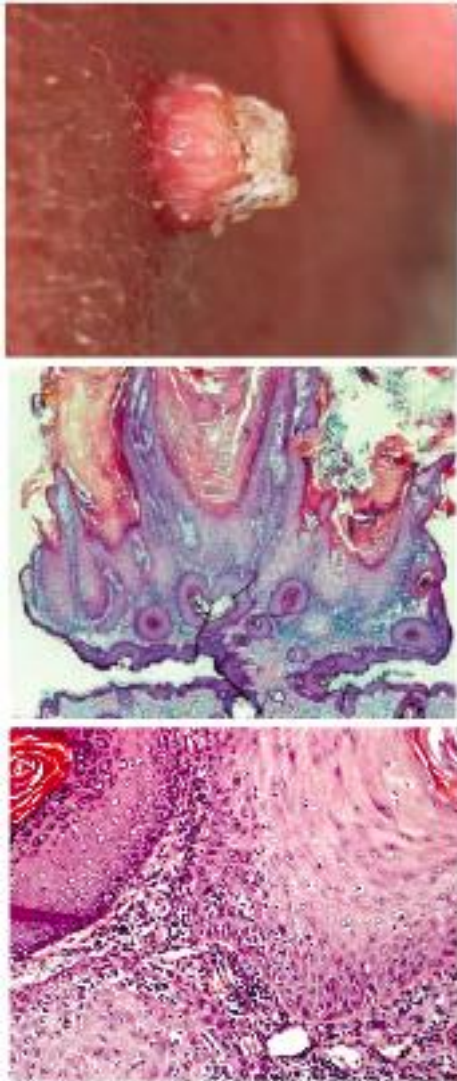


Pre-treatment

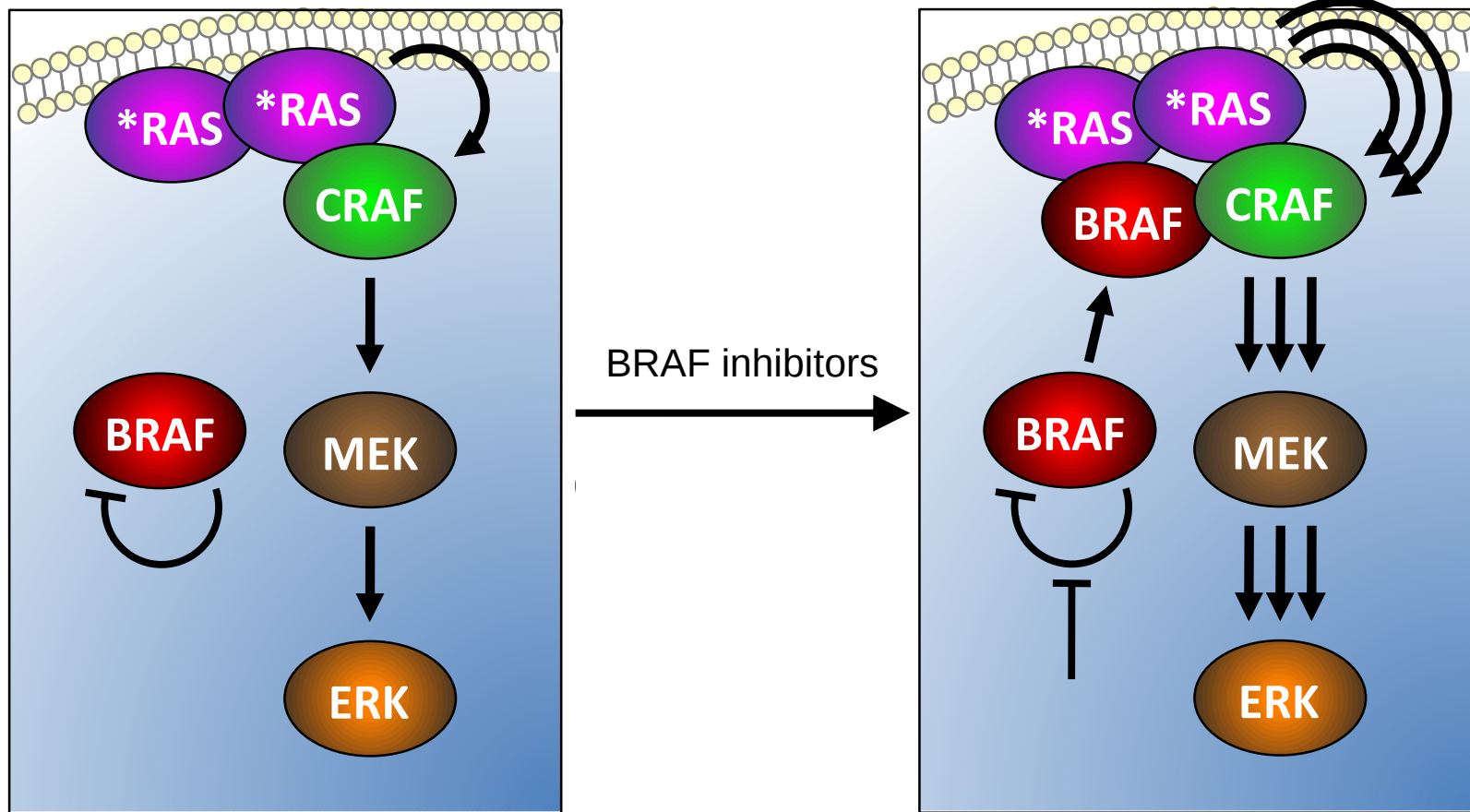
15 weeks



Flaherty et al (2010) *NEJM*, Chapman et al (2011) *NEJM*

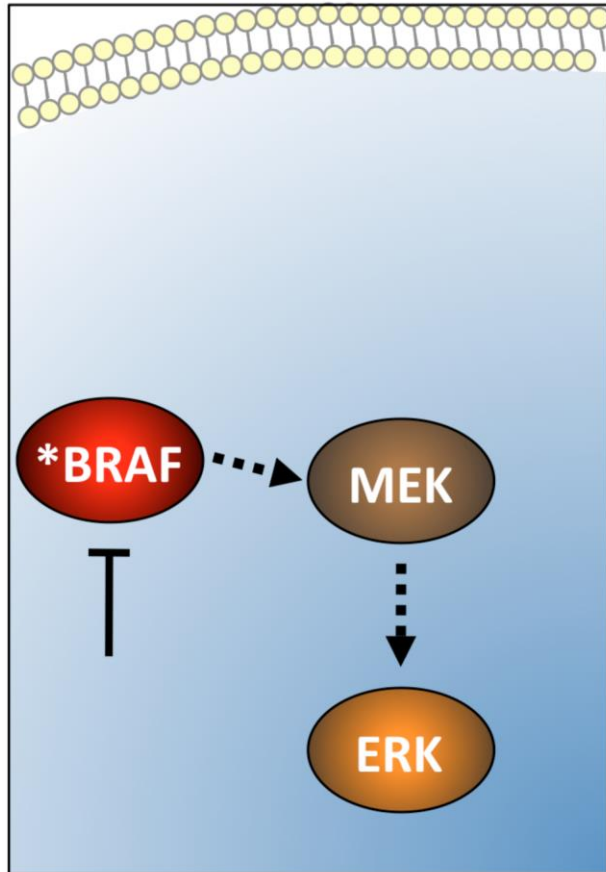


Su et al, NEJM 2012
Heidorn et al, Cell 2012

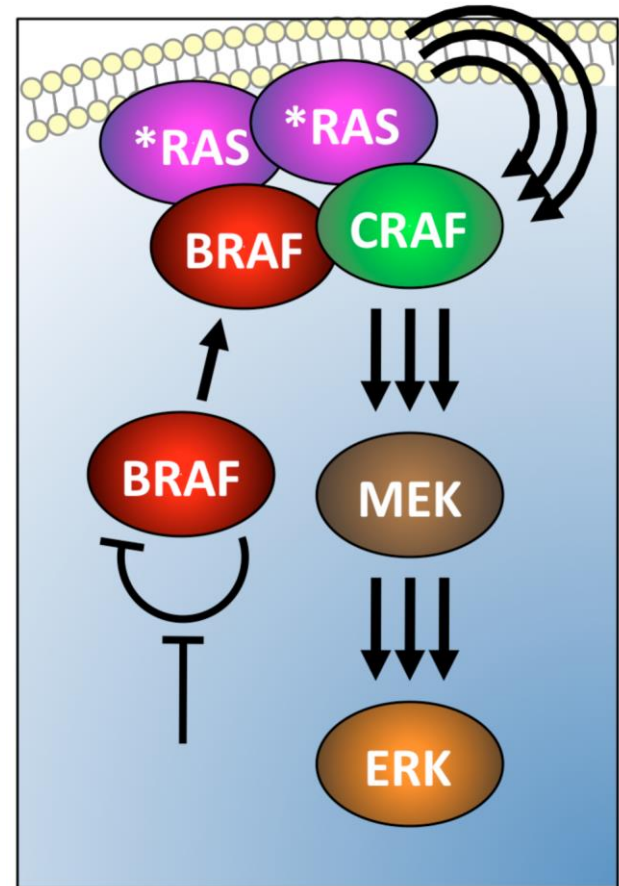


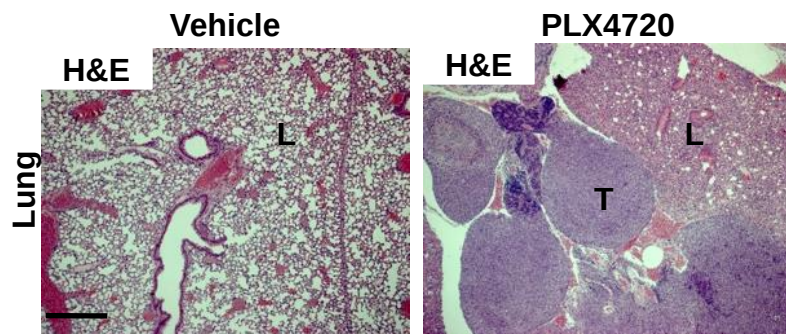
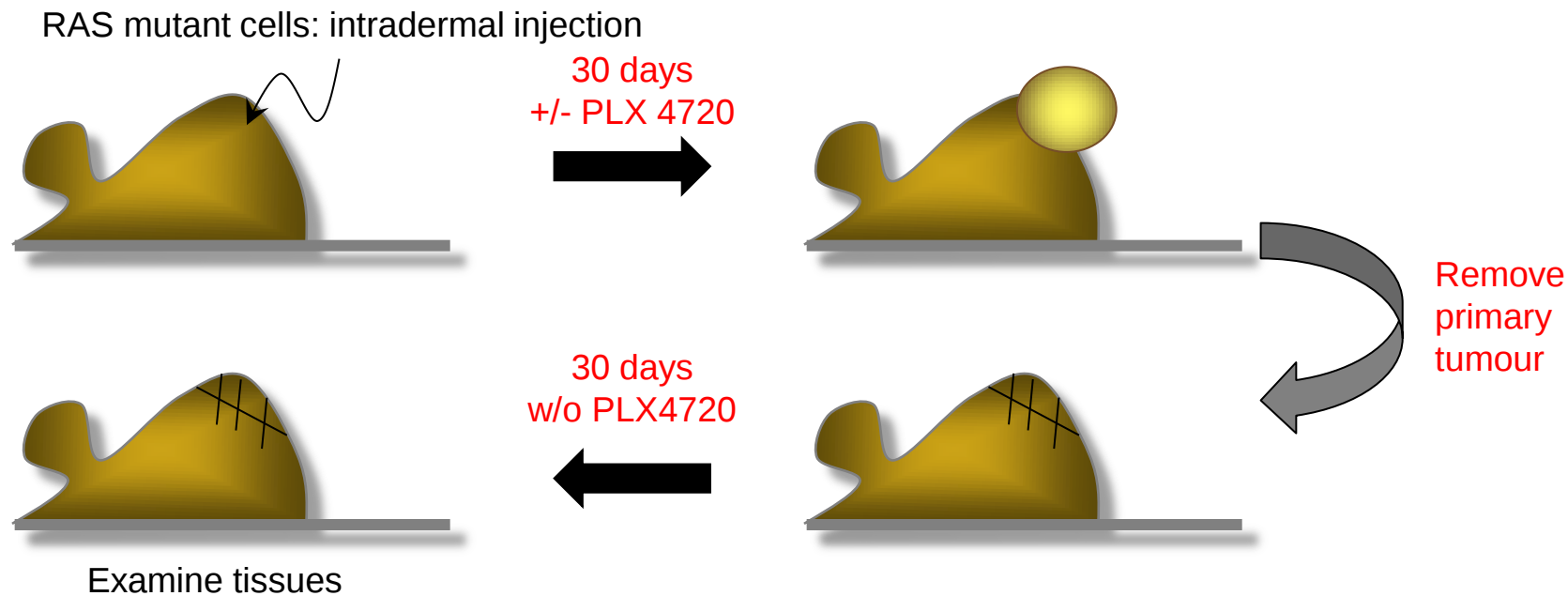
Heidorn et al (2010) *Cell*
 Hatzivassiliou et al (2010) *Nature*
 Poulikakos et al (2010) *Nature*

melanoma cell



keratinocyte



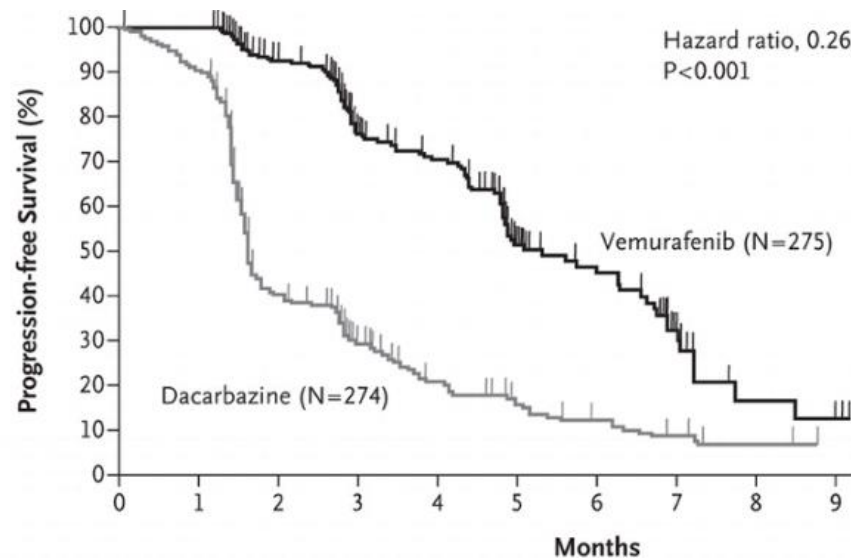
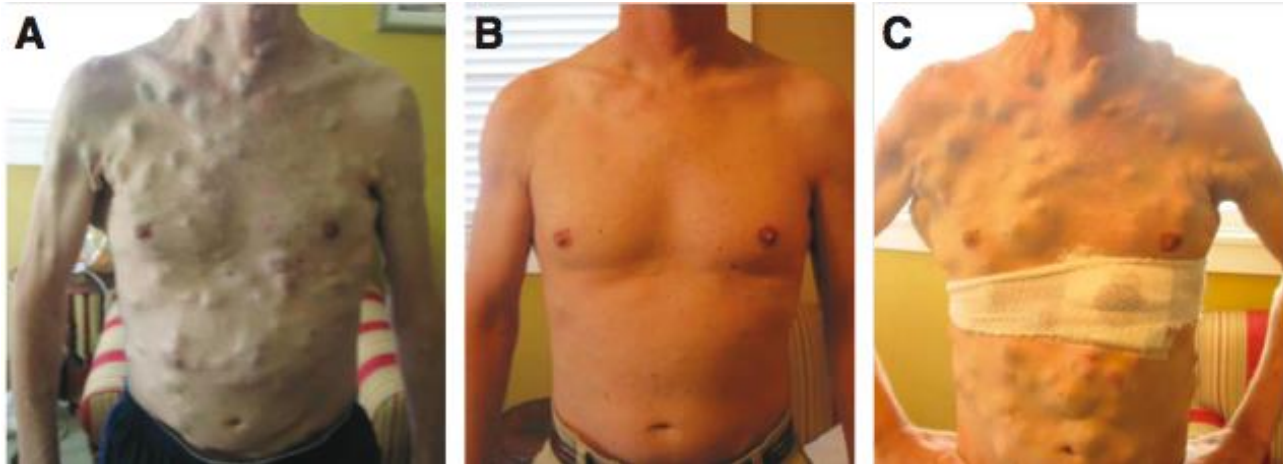


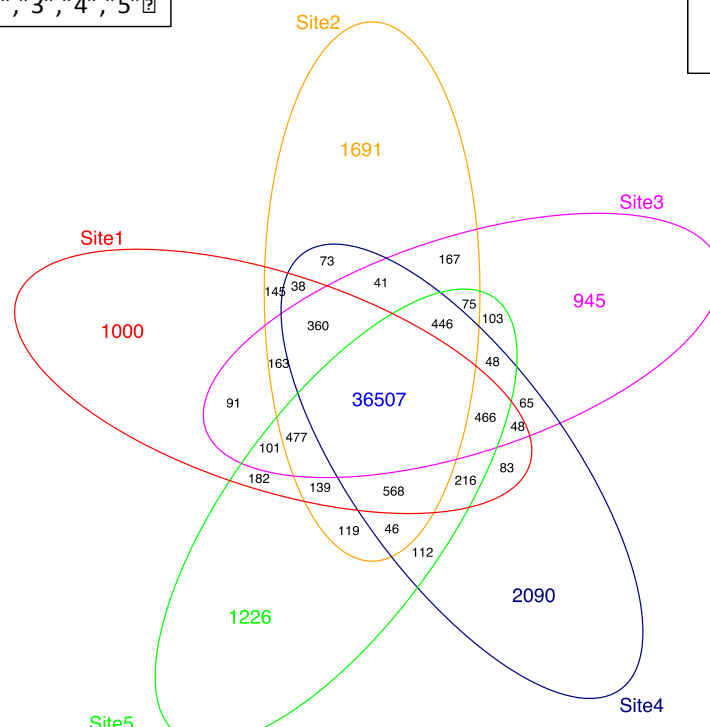
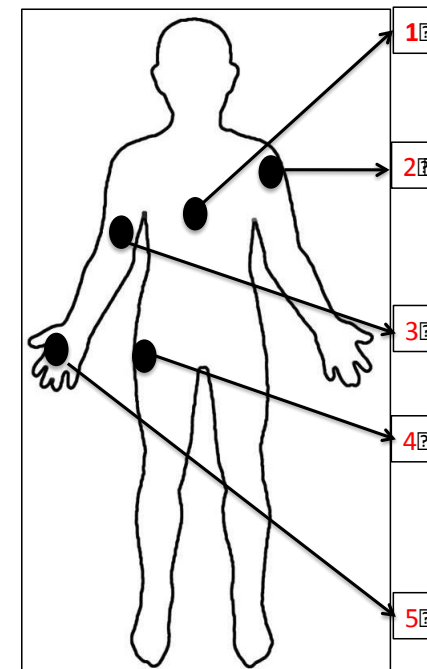
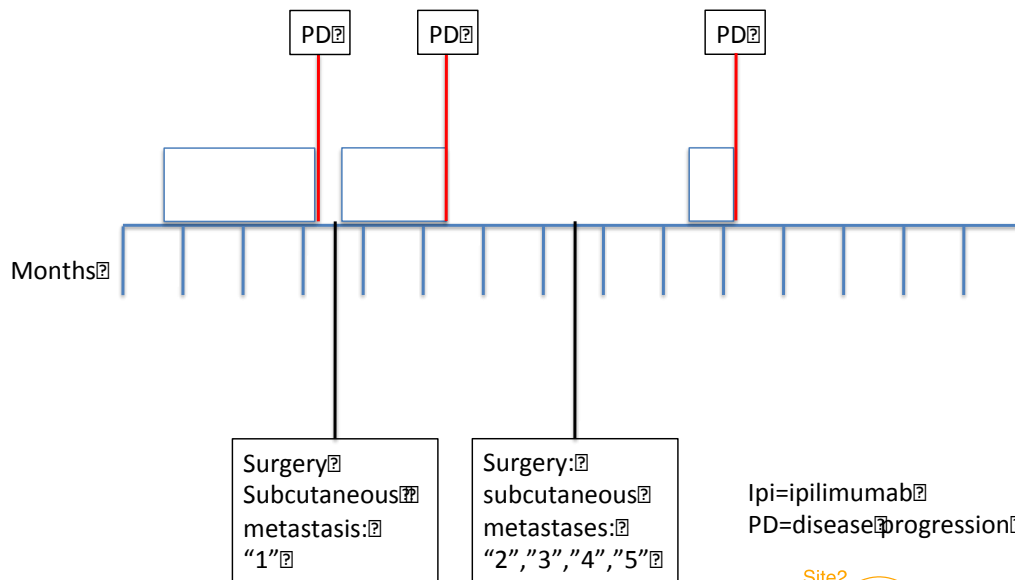
Sanchez-Loarden et al (2014) *Science Signaling*

Pre-treatment

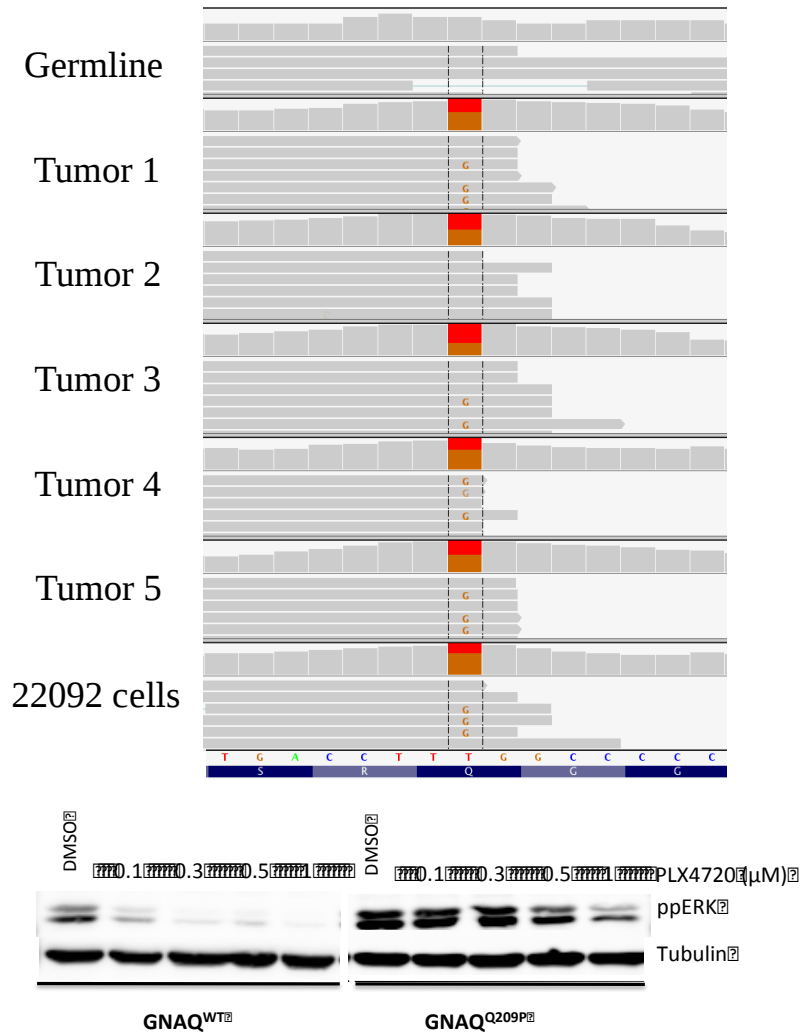
15 weeks

23 weeks

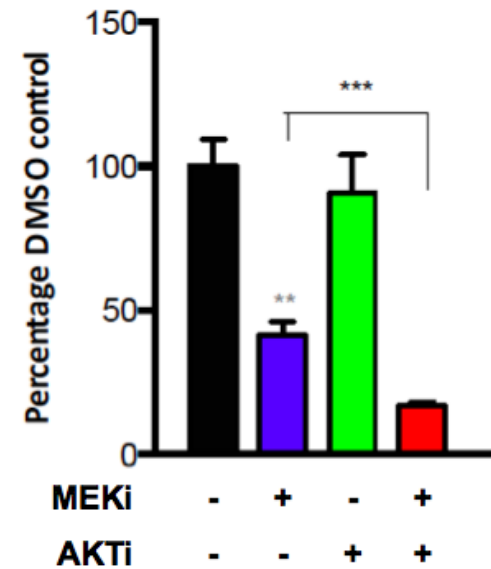
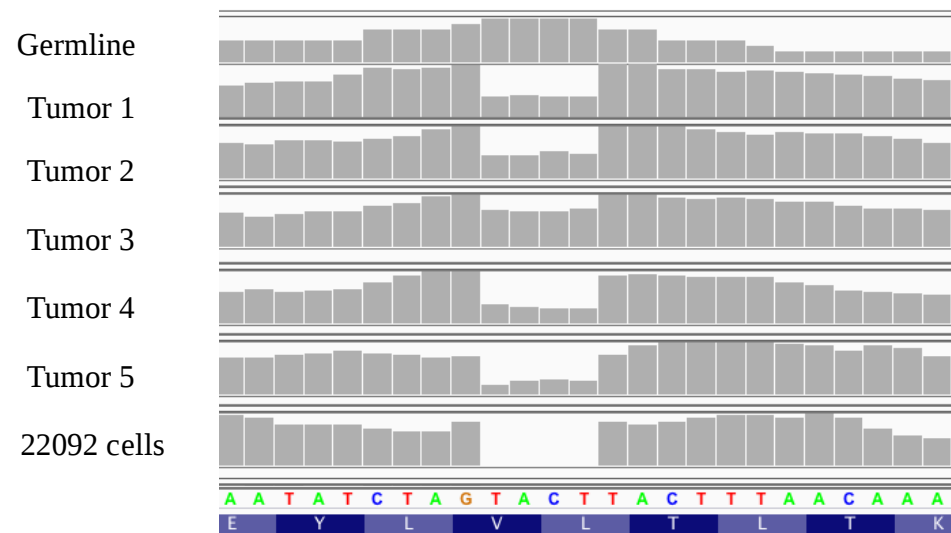


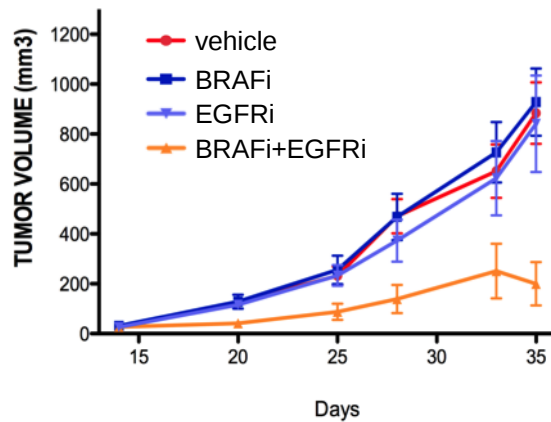
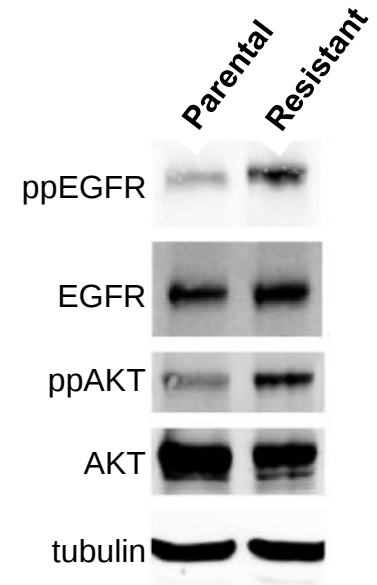
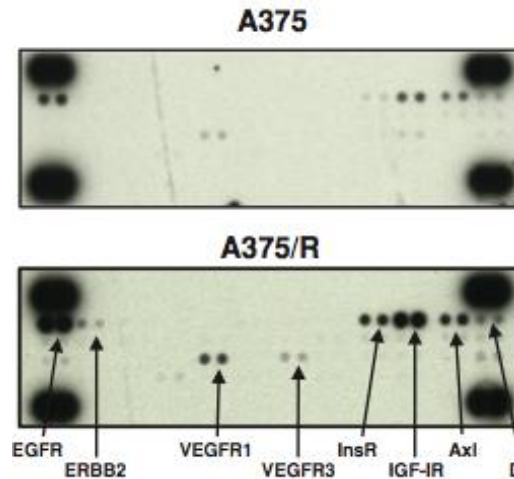
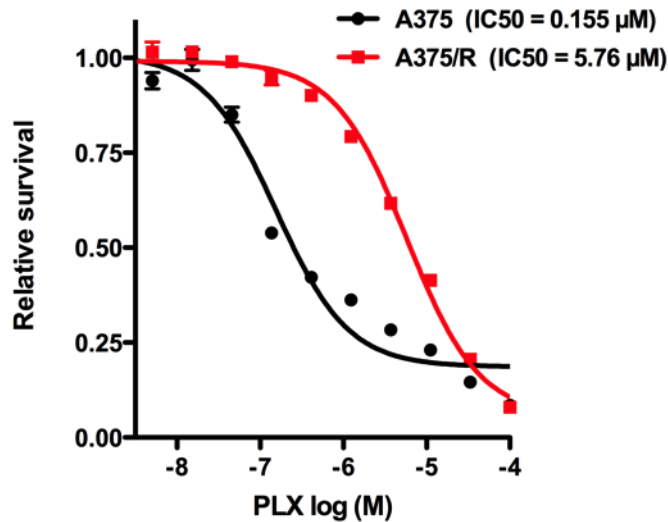


GNAQ (Q209P)



PTEN (indel)

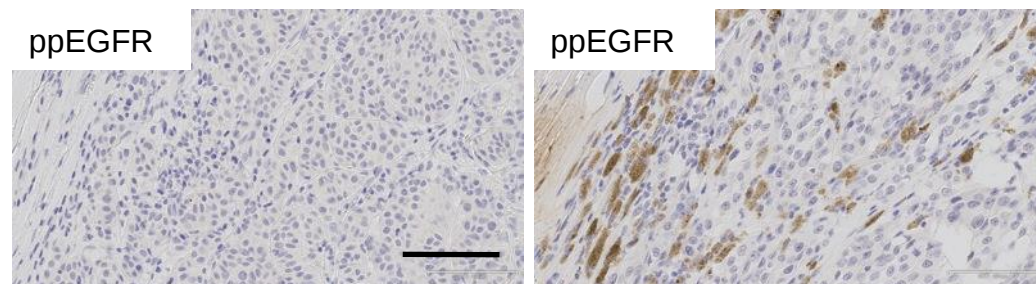


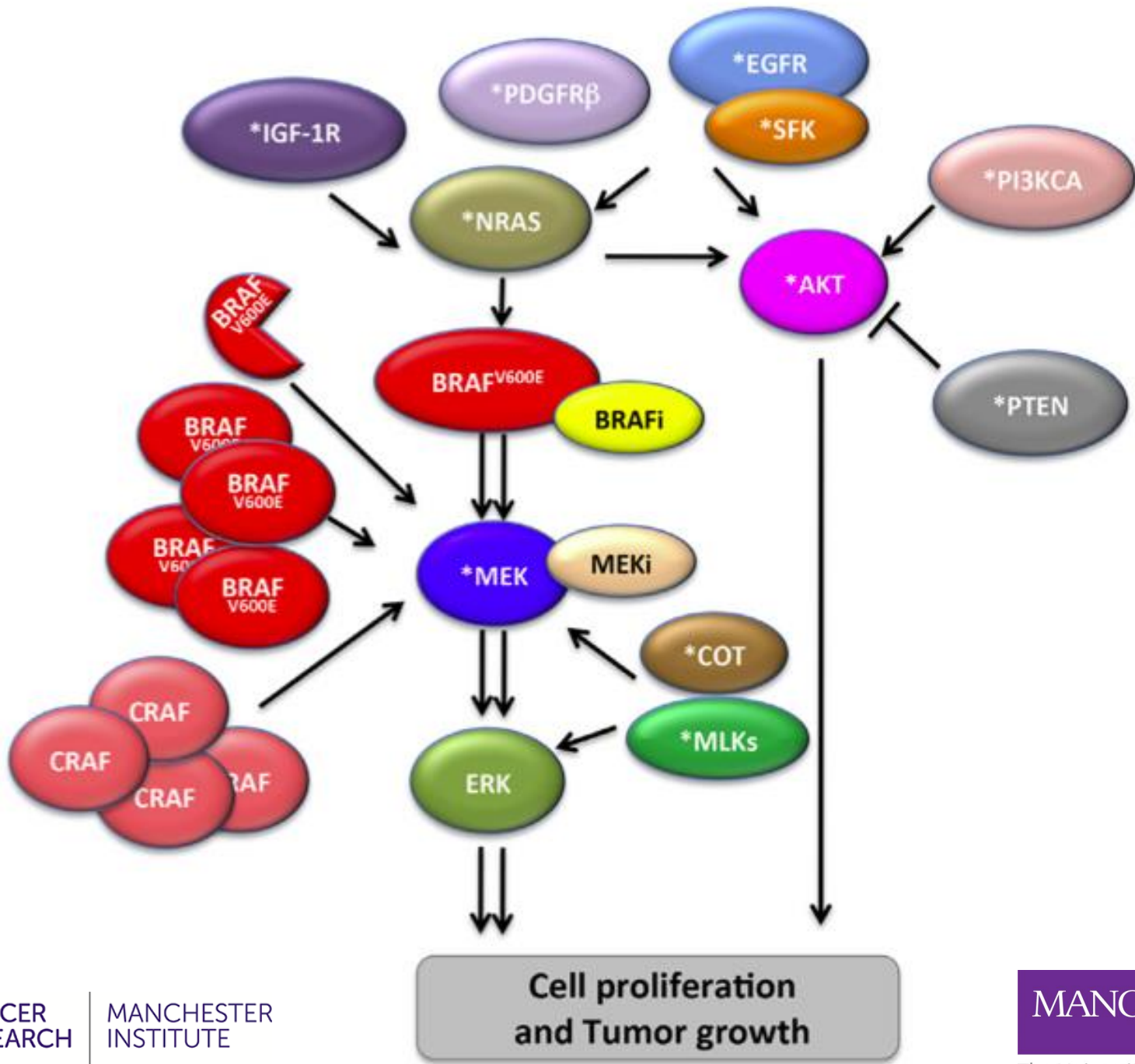


- 27 year old male
- stage IV malignant melanoma
- BRAF^{E600} mutation
- Vemurafenib: primary resistance

Pre-treatment

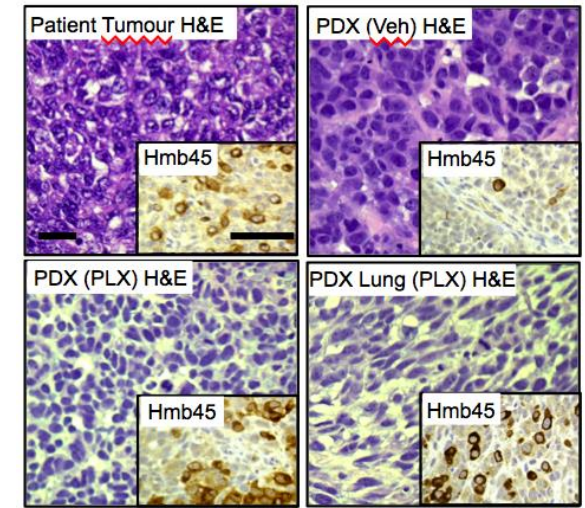
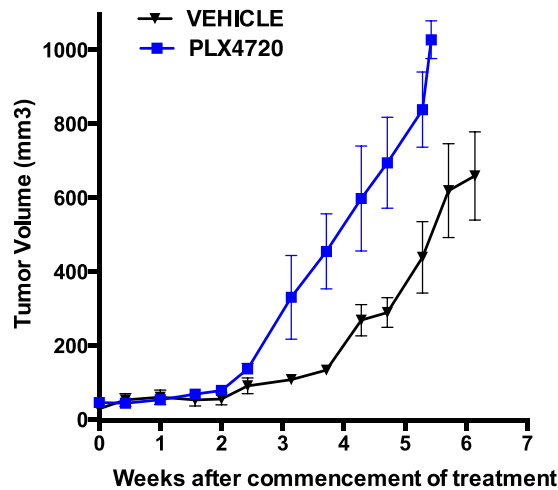
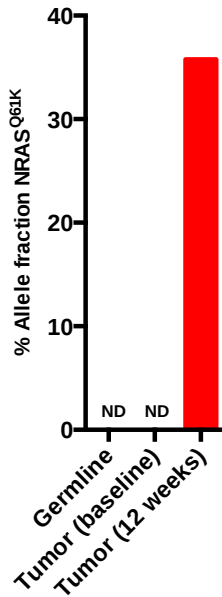
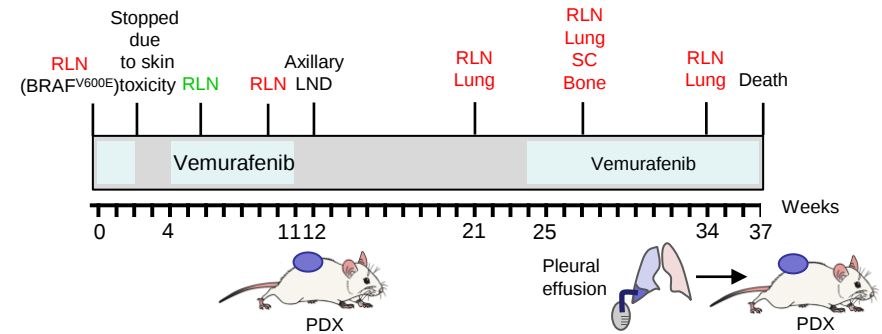
Vemurafenib-resistant



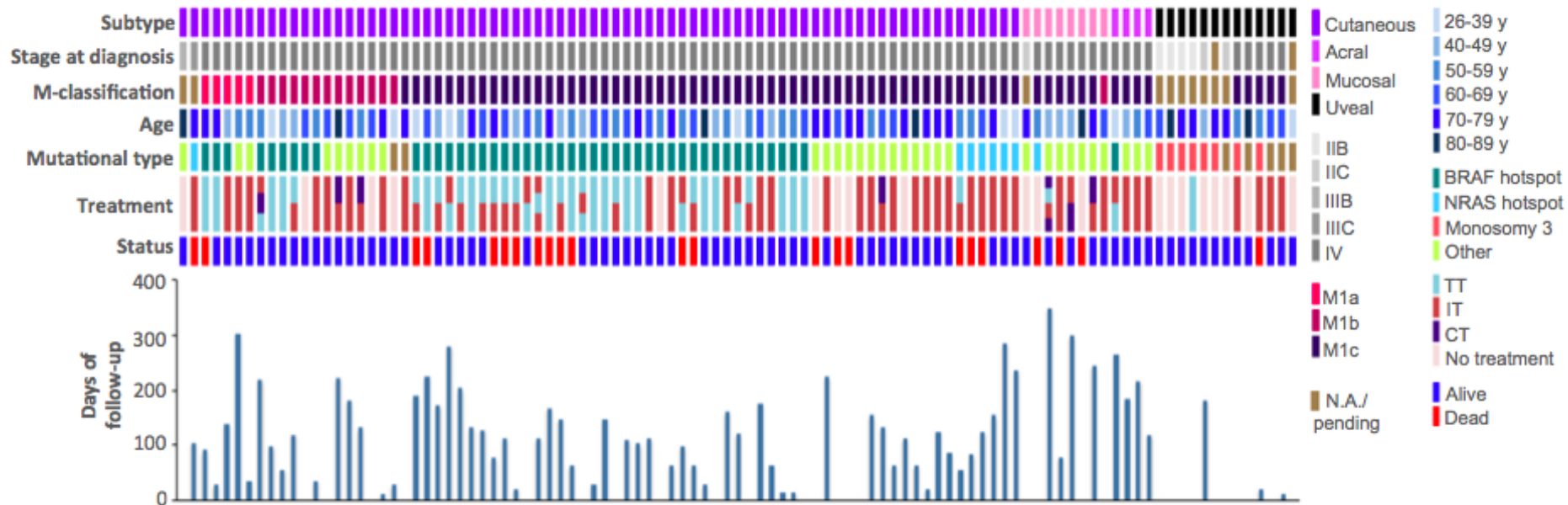


Case study

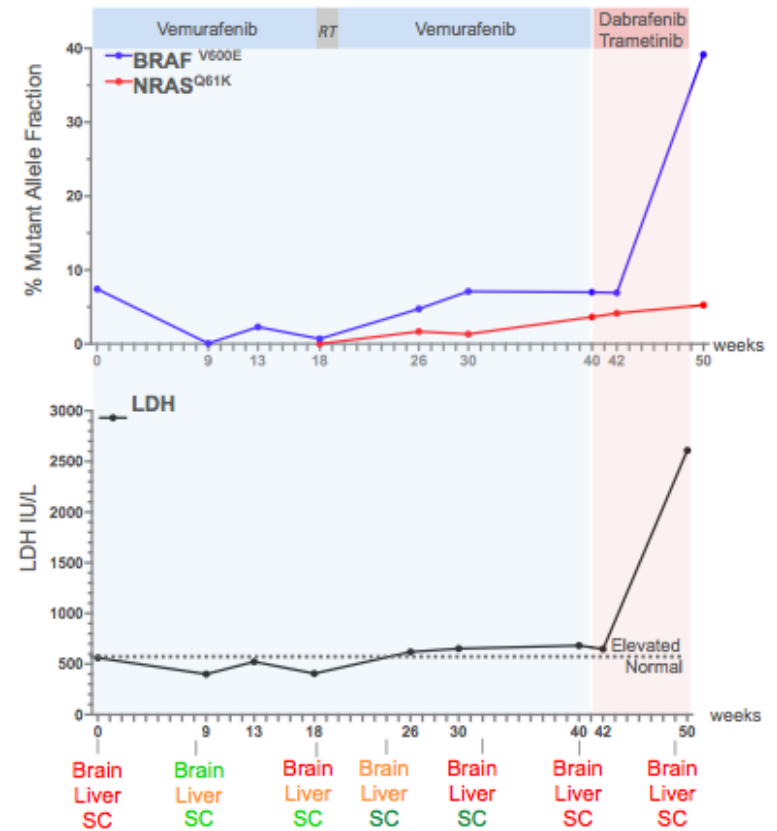
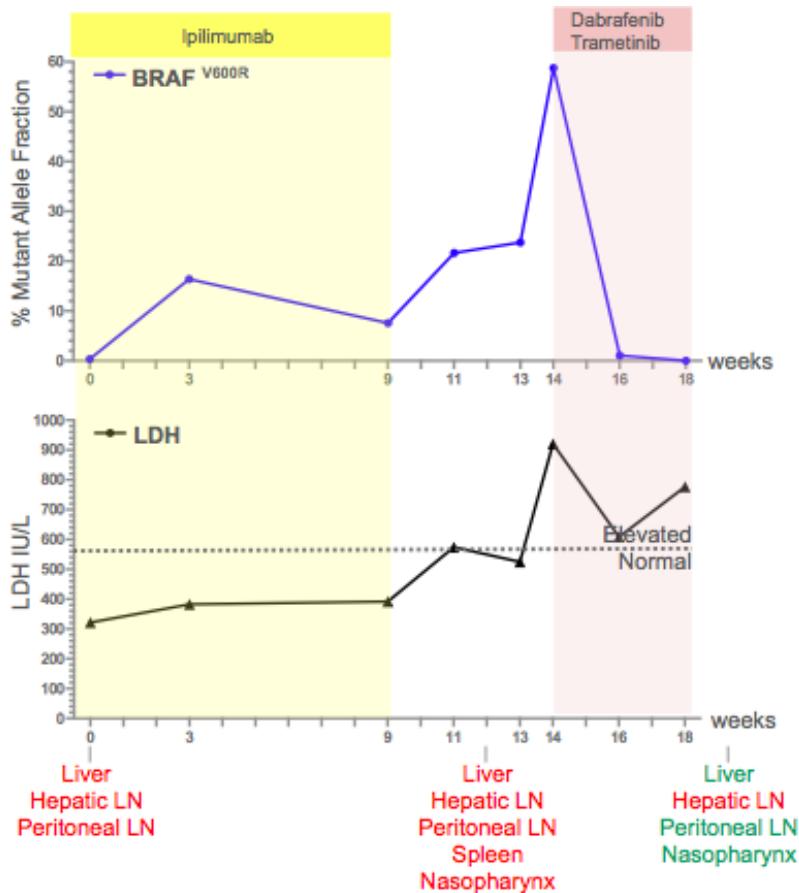
- Male – 40s
- Primary melanoma: dorsum of hand
- 15 years later: unresectable right axillary metastatic melanoma
- BRAF positive
- Vemurafenib for tumour reduction
- Surgery at 12 weeks
- Aggressive disease



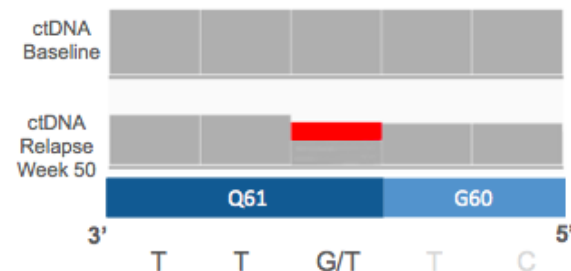
Circulating tumour DNA



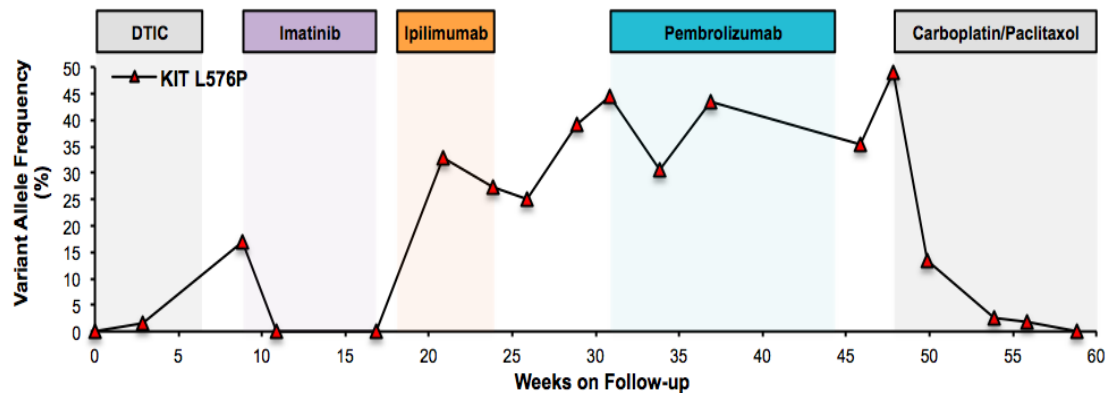
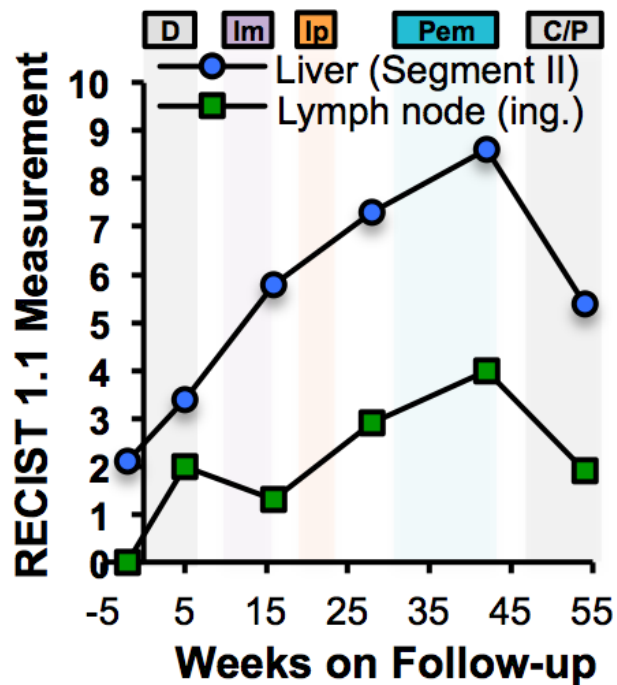
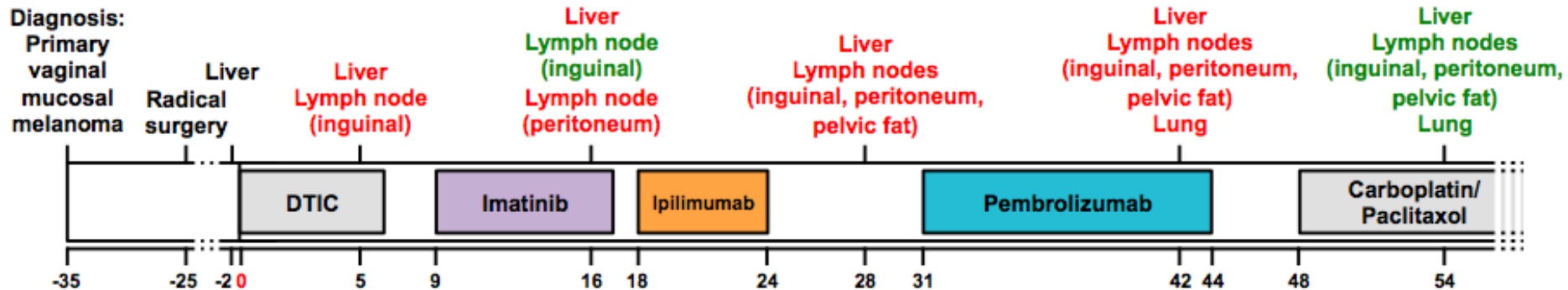
Circulating tumour DNA



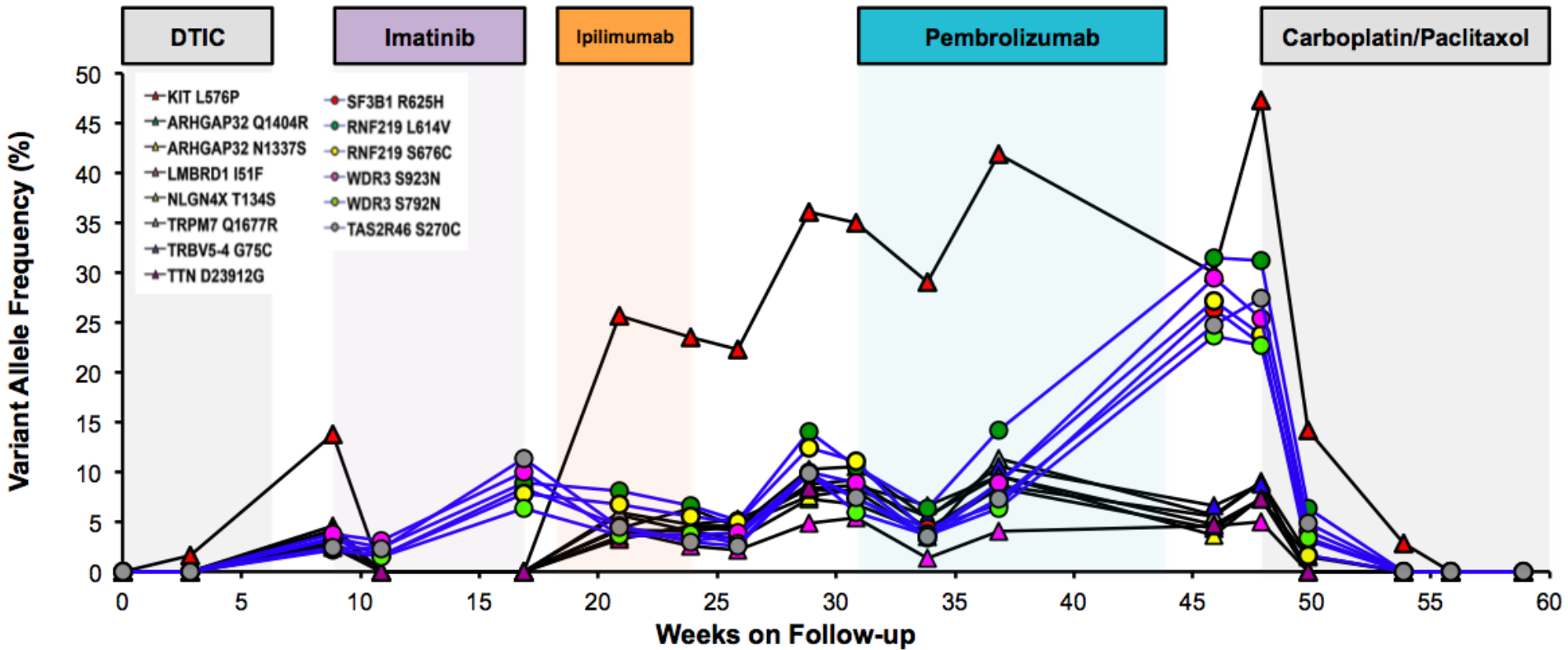
NRAS CAA > AAA (Q61K)



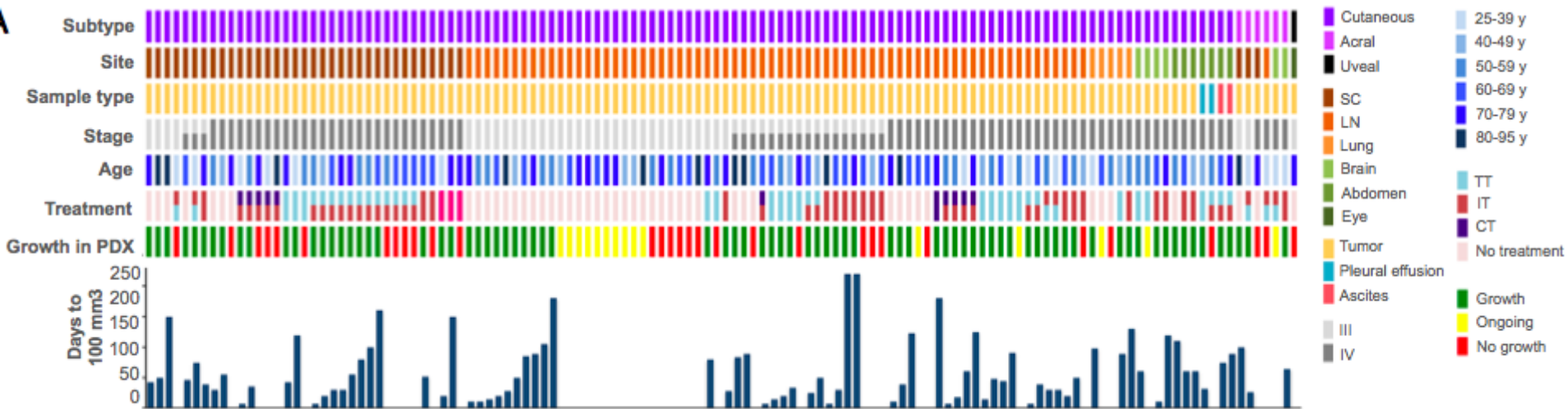
Circulating tumour DNA



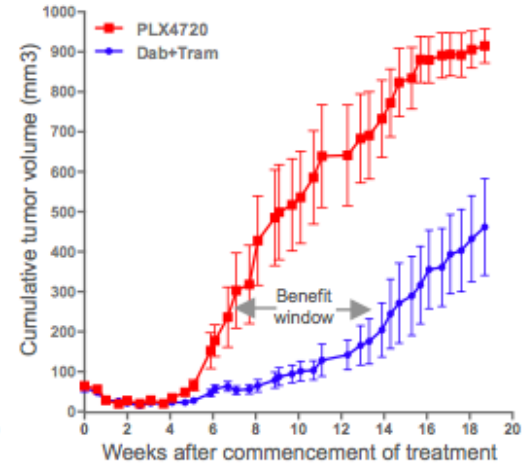
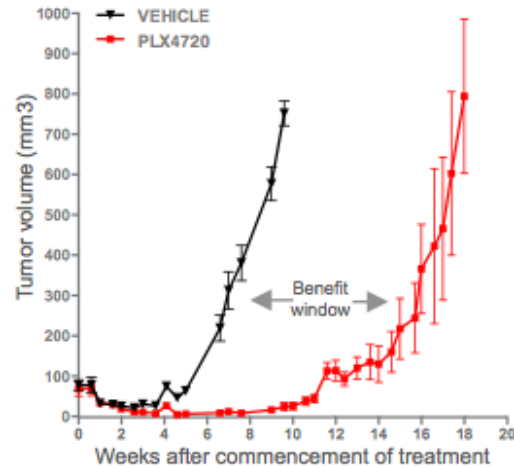
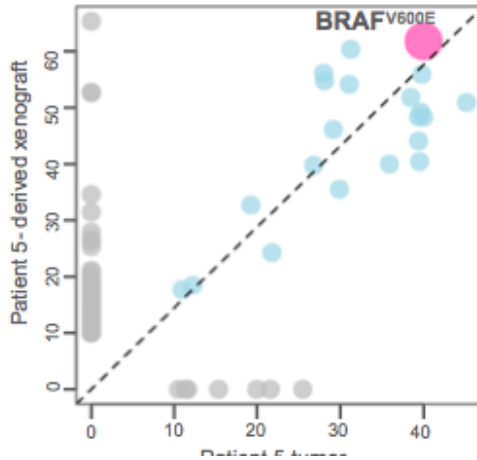
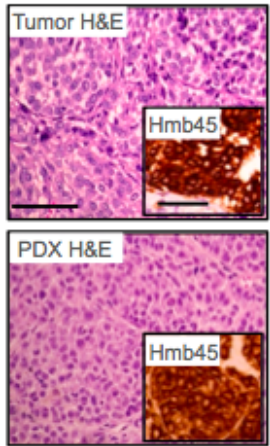
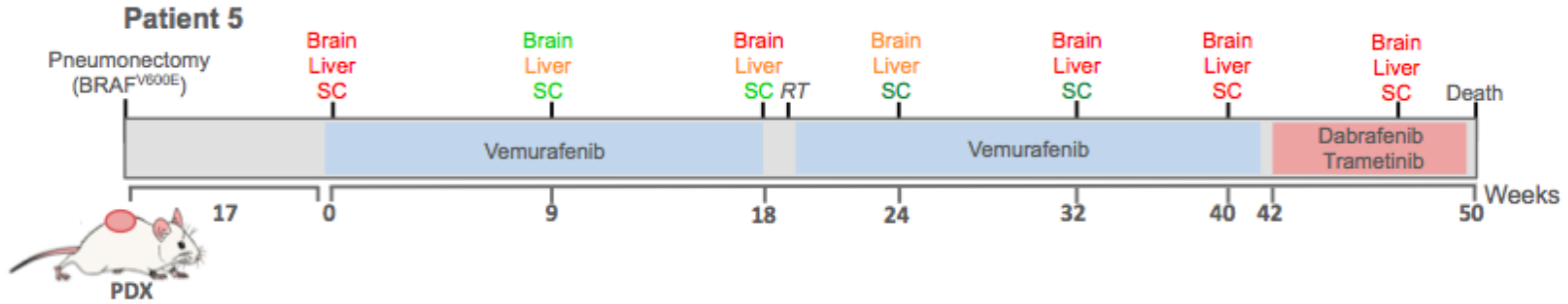
Circulating tumour DNA

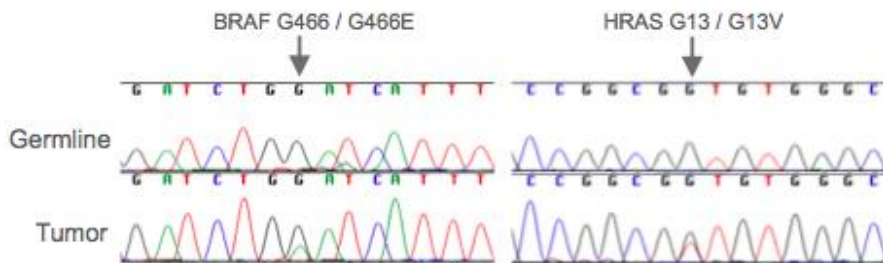
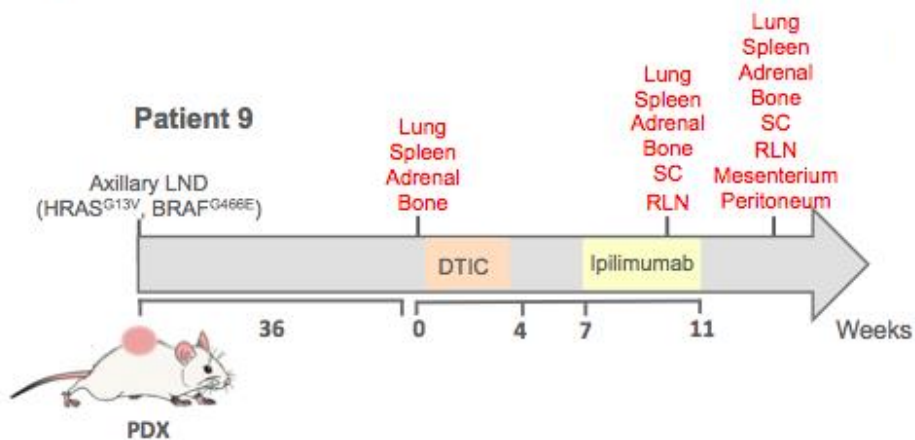


Patient derived xenografts

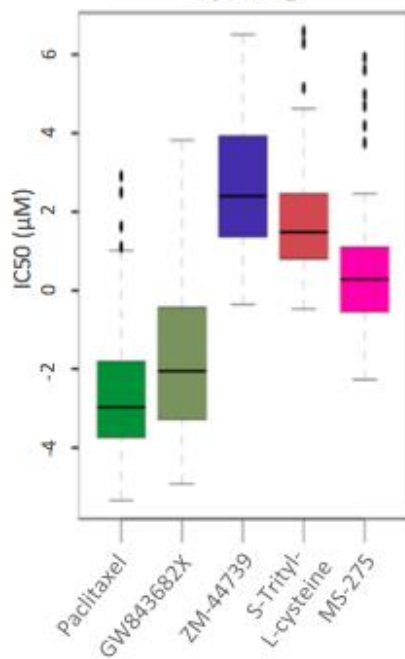


Patient derived xenografts

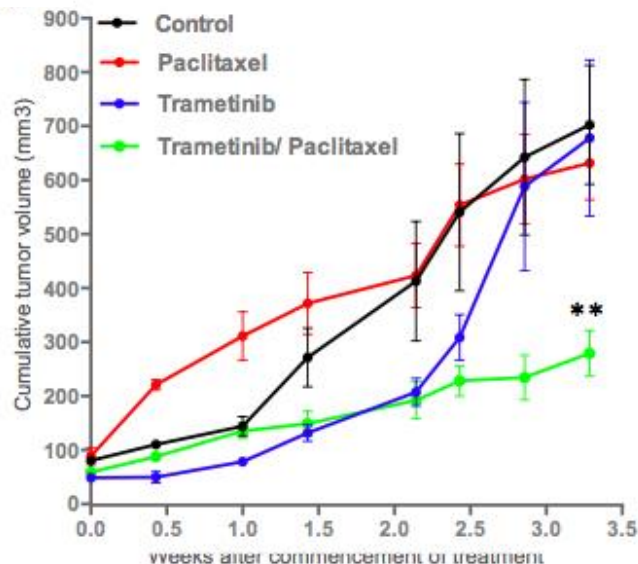
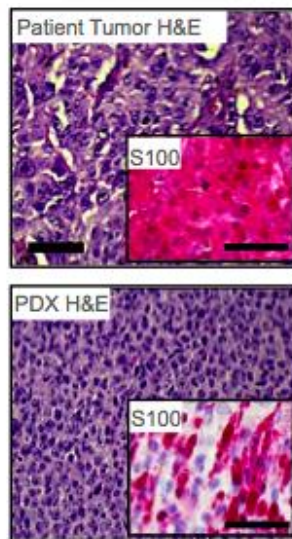
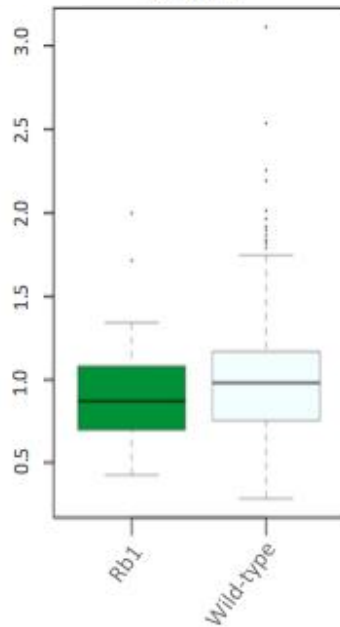




Top 5 drugs



Paclitaxel



PACMEL

Paclitaxel +/- GSK1120212 or Pazopanib in Melanoma - PACMEL

A randomised phase 2 study of paclitaxel with or without GSK1120212 or pazopanib in advanced wt BRAF melanoma

Specialty

Cancer

Portfolio Eligibility

Adopted non-commercial study

ISRCTN 43327231
EudraCT 2011-002545-35
MREC N° 11/SC/0458
UKCRN ID 12095
WHO ID

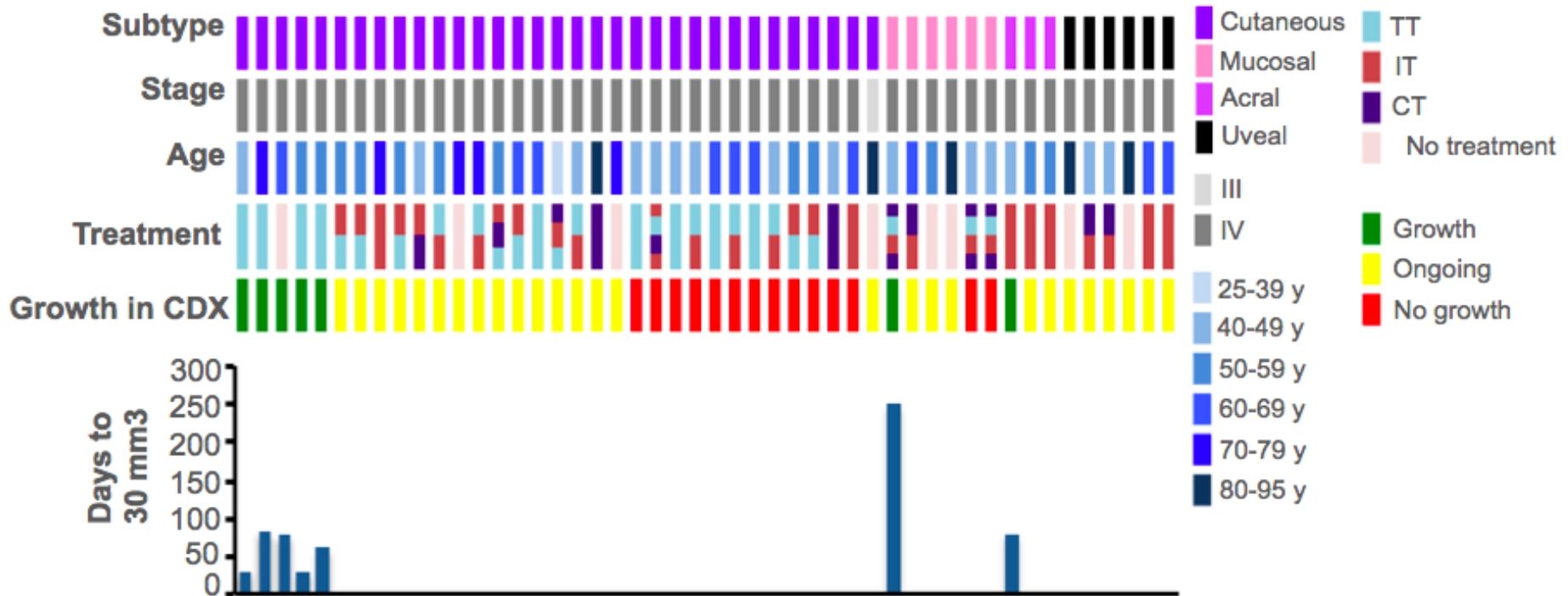
Research Summary

This is a randomised multi-centre study. 120 patients (forty in each of 3 arms) with melanoma will be randomly assigned to receive treatment with paclitaxel chemotherapy or the same drug along with GSK1120212 (a new medicine) or Pazopanib. To take part the patient's melanoma must have a normal BRAF gene (at V600), which is about 60% of people with melanoma. This can be checked on a sample of the patient's tumour (usually one that has already been taken as part of their treatment). Prior to the randomised part of the study, 16 patients took part in the dose-escalation phase of the trial to establish the best dose of GSK1120212 and paclitaxel in combination.

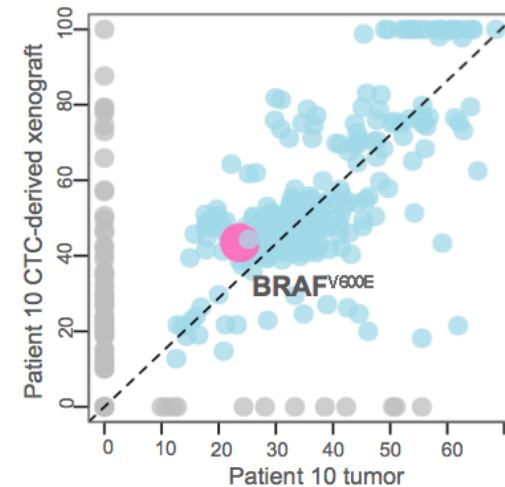
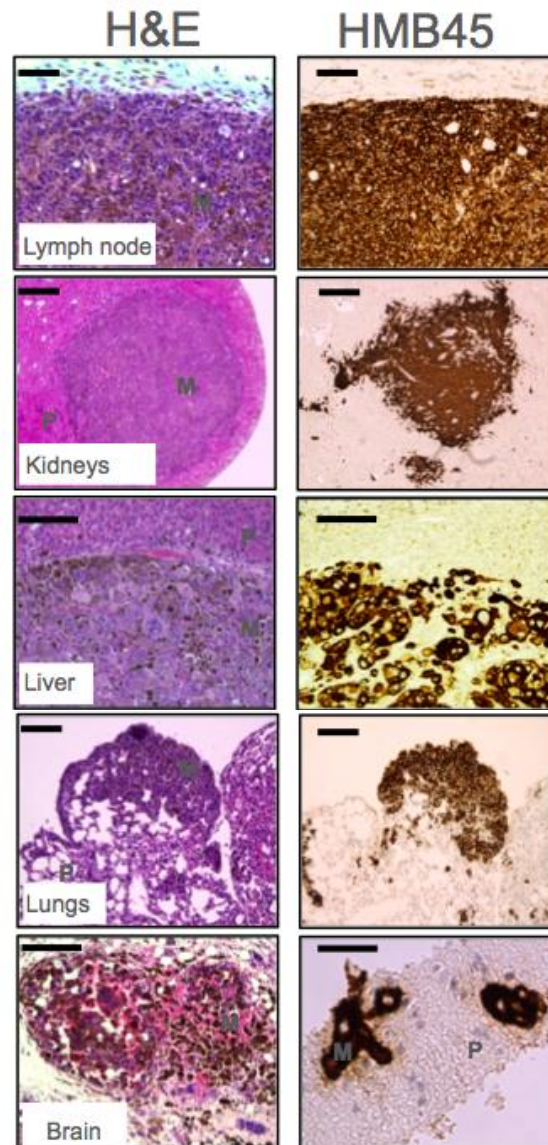
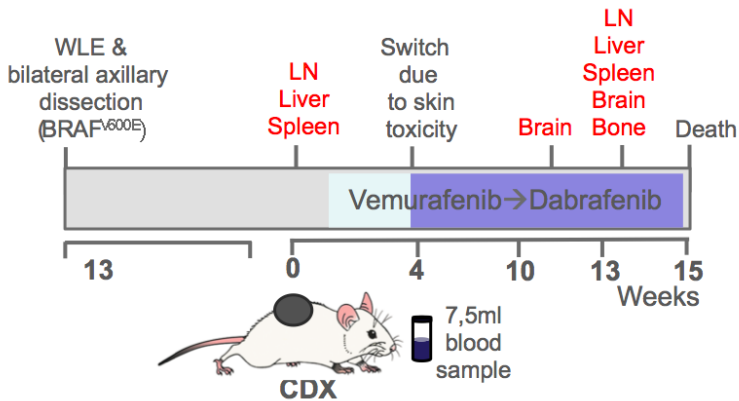
Study Type	Interventional
Design Type	Treatment
Disease(s)	Melanoma
Phase	II

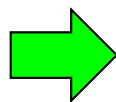
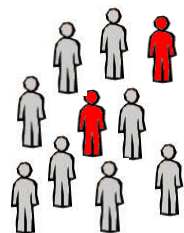
Current Status	Open
Closure Date	31/01/2016
Global Sample Size	120
Global Recruitment to Date	80%

Circulating tumour cell derived xenografts

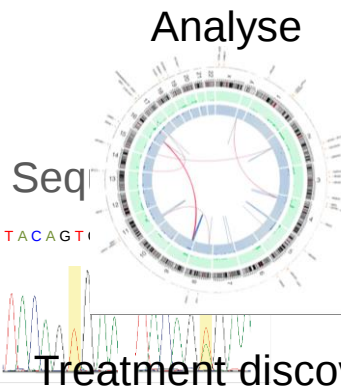
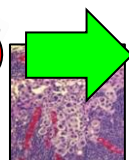


Circulating tumour cell derived xenografts

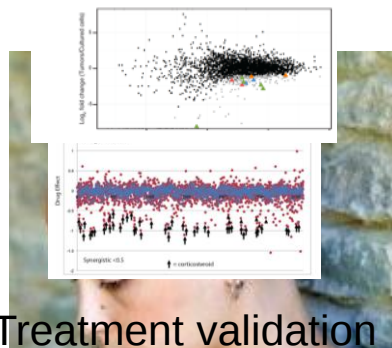




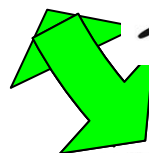
Clinical assessment/
pathology
Tumour



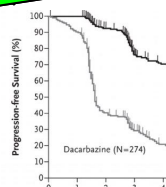
Treatment discovery



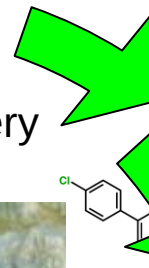
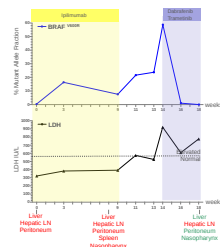
Treatment validation



Relapse

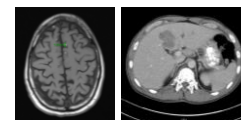
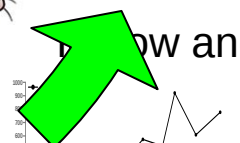
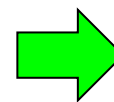
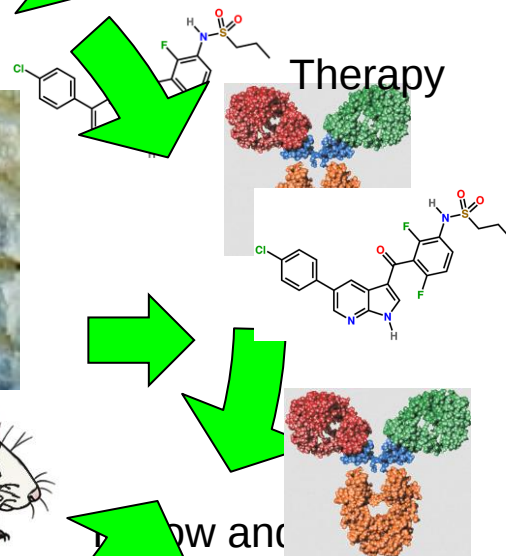


Follow



Therapy

Therapy



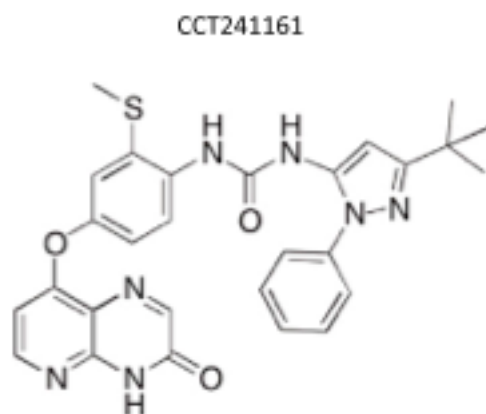
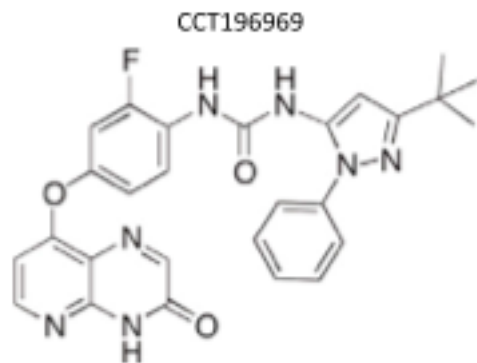
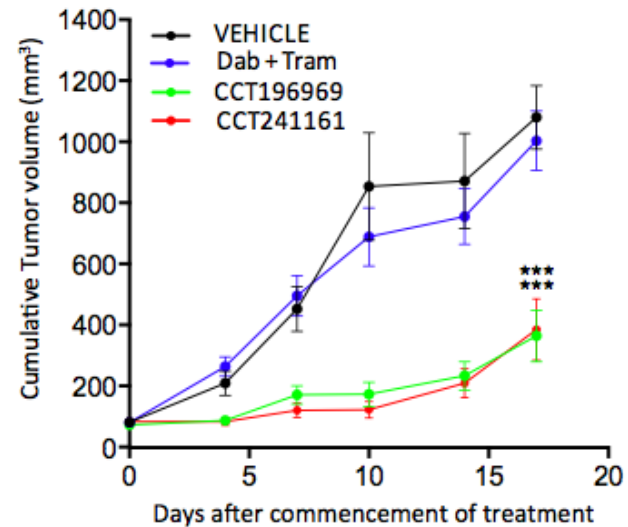
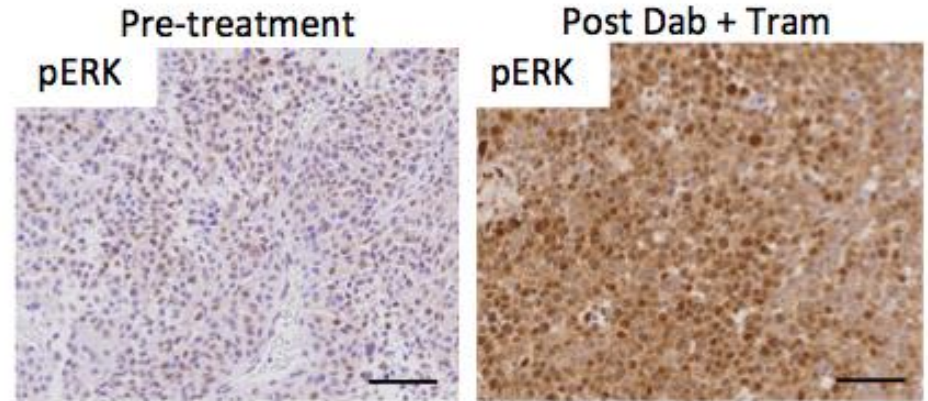
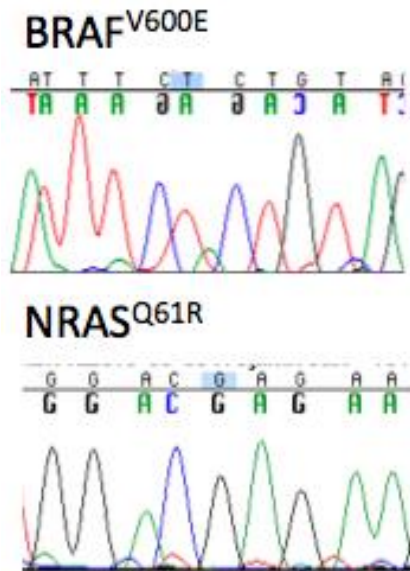


Table 1. IC₅₀ Values of CCT196969 and CCT241161

Kinase	CCT196969 (μM)	CCT241161 (μM)
BRAF	0.1	0.03
V600E-BRAF	0.04	0.015
CRAF	0.01	0.006
MEK1	>10	>10
COT	>10	>10

Case study

- Patient with stage IV BRAF mutant melanoma
- Dabrafenib plus trametinib
- Relapsed after only 5 months



Basilea Pharma Inks License Agreement For Novel PanRAF Kinase Inhibitors

4/1/2015 1:38 AM ET

Basilea Pharma ([BPMUF.PK](#)) Wednesday said it has entered into a license agreement for novel panRAF kinase inhibitors with a consortium of organizations including The Institute of Cancer Research, London, Cancer Research Technology, the Wellcome Trust and The University of Manchester.

The agreement grants Basilea exclusive global rights to develop, manufacture and commercialize novel panRAF kinase inhibitors which originate from research at The Institute of Cancer Research by scientists funded by Cancer Research UK and the Wellcome Trust.

RAF kinases play an important role in tumor cell proliferation. The oral, small molecule panRAF inhibitors target BRAF and other growth pathways relied upon by resistant tumor cells.

Funding



wellcometrust

ICR The Institute of
Cancer Research

A horizontal bar consisting of four colored squares: yellow, orange, pink, and red.

Collaborators



THE ROYAL
MARSDEN



The Christie

TOWARDS A FUTURE WITHOUT CANCER



- Melanoma Unit, The Royal Marsden Hospital
- Martin Gore, James Larkin
- Melanoma Unit, The Christie Hospital
- Paul Lorigan, Emma Dean

Collaborators



- **Caroline Springer**
- **Dan Niculescu-Duvaz, Alfonso Zambon, Ion Niculescu-Duvaz, Lawrence Davies, Filipa Lopes**
- Delphine Ménard, Bart Suijkerbuijk, Leslie Ogilvie, Douglas Hedley, Frank Friedlos, Natasha Preece, Laura Johnson, Rob McLeary, Helen Manne, Arnaut Nourry, Esteban Roman-Vella, Zhora Ali
- Stephen Whittaker, Ruth Kirk, Neus Cantarino (Richard Marais)
- **David Barford, Paul Wan** (Structural Biology)
- Flo Reynaud (Clinical Pharma and Trials Team)

- Nathalie Dhomen (The Netherlands)
- Franziska Baenke (Germany), Kelly Brooks (Australia), Alessio Cannistraci (Italy), Jasper Cook (UK), Elena Galvani (Italy), Caroline Gaudy (France), Gabriela Gremel (Austria), Kate Hogan (UK), Megan Grant (UK), Romina Girotti (Argentina), Koorosh Korfi (Iran), Rebecca Lee (UK), Gianpiero Di Leva (Italy), Amit Mandal (India), Clare McManus (UK), Marina Parry (UK), Grazia Saturno (Italy), Matthew Smith (UK), HaoRan Tang (China), Amaya Viros (Spain), Sally Wood (UK)
- Martin Cook (UK)
- Adele Green (Australia)





9 – 12 July 2016 | Manchester, UK

24th Biennial Congress of the
**European Association
for Cancer Research**

From Basic Research to Precision Medicine



SAVE THE DATE

