

RAS and RAF signalling in melanoma: from biology to therapy

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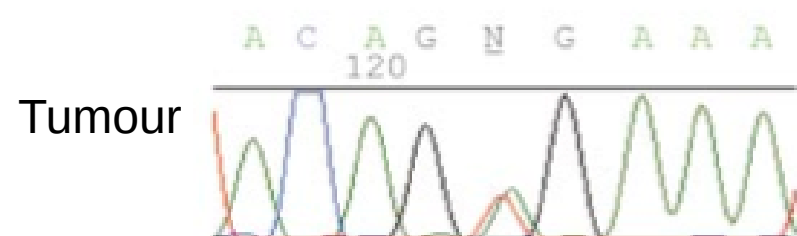
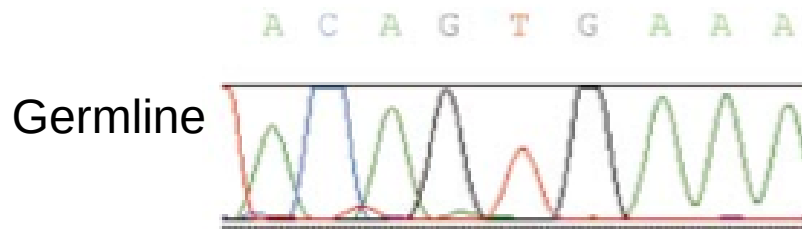
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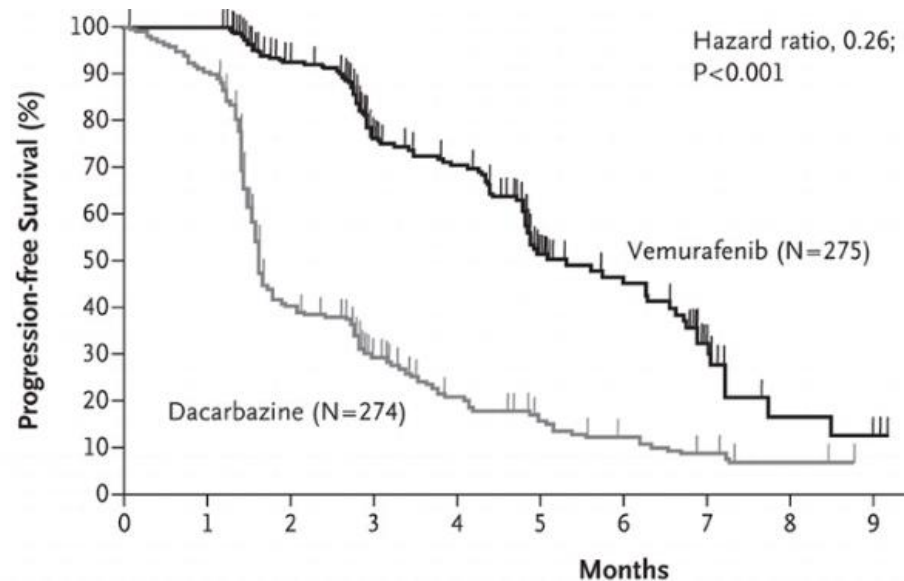
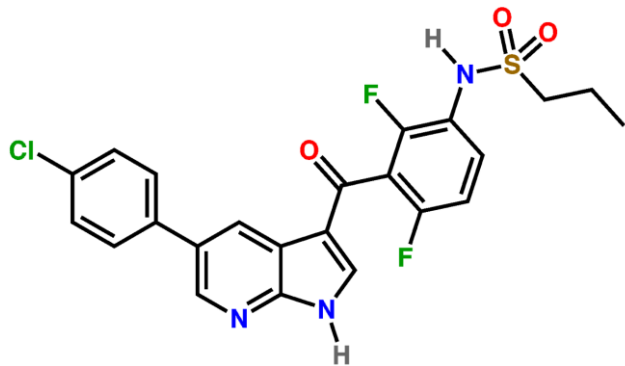
Melanoma



- Melanoma, a potentially deadly skin cancer
- EU: >100,000 cases; >22,000 deaths
 - incidence doubles every 10 years
- ~80% of cases cured by surgery (early diagnosis)
- ~20% of cases are metastatic malignant disease
 - Median survival 6-9 months; 5 year survival 5-10%
- BRAF mutations in ~45% of cases (V600E)



Vemurafenib in melanoma patients

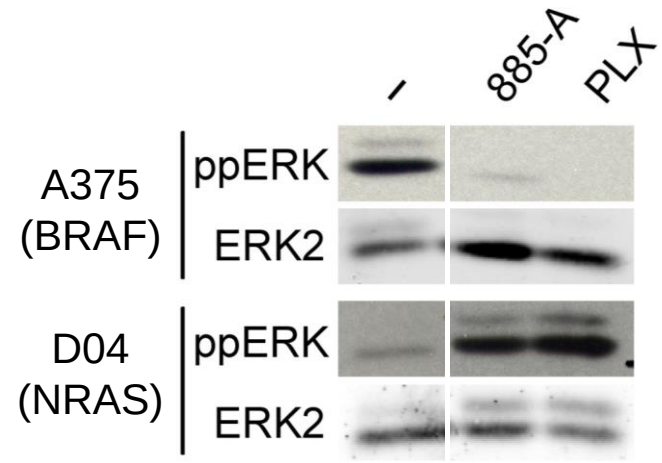
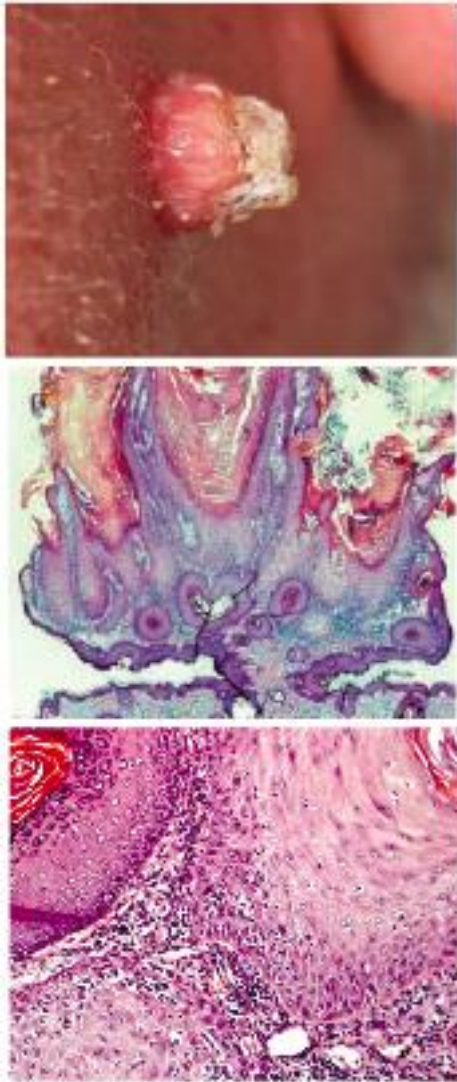


Flaherty et al (2010) *NEJM*, Chapman et al (2011) *NEJM*

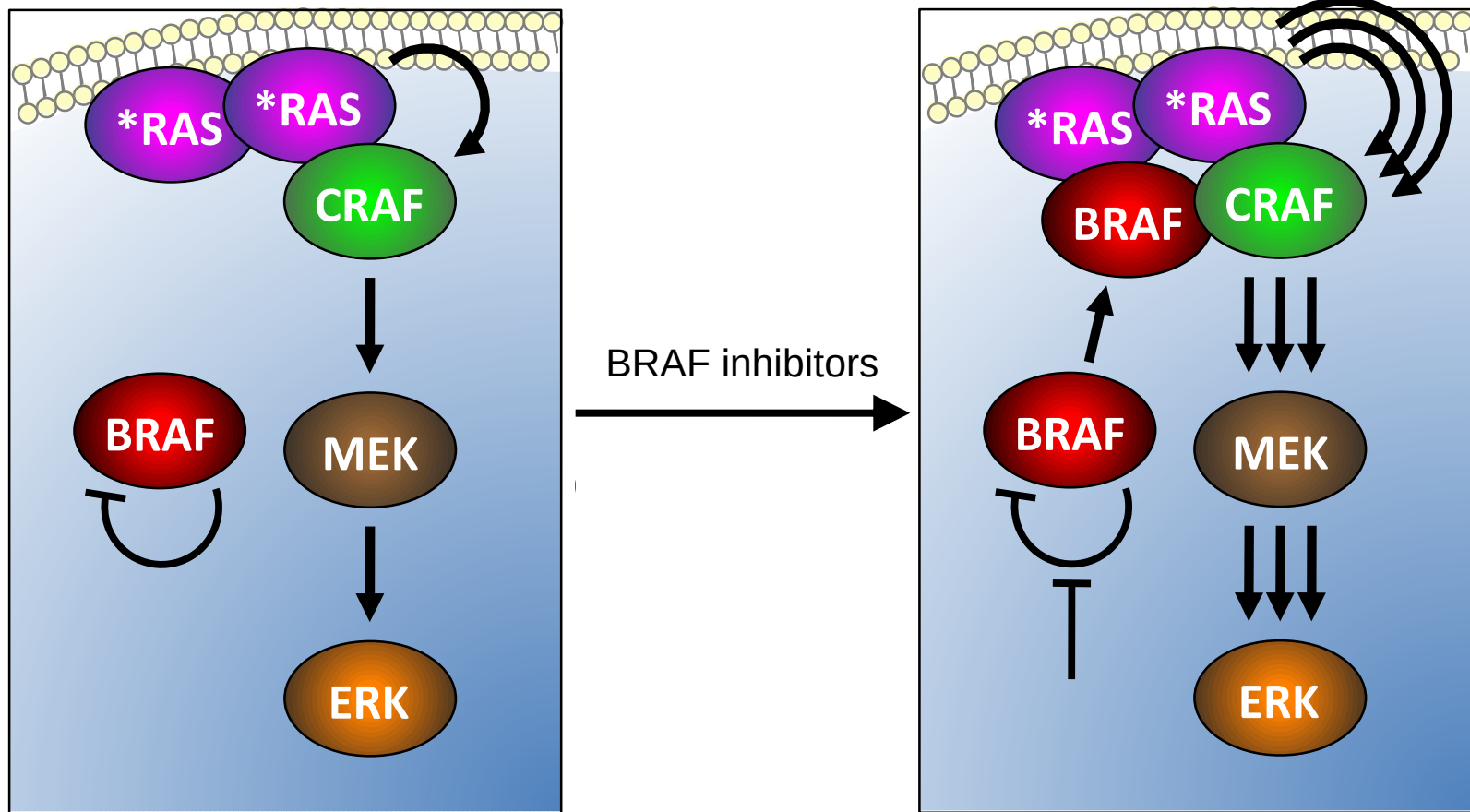
Pre-treatment

15 weeks



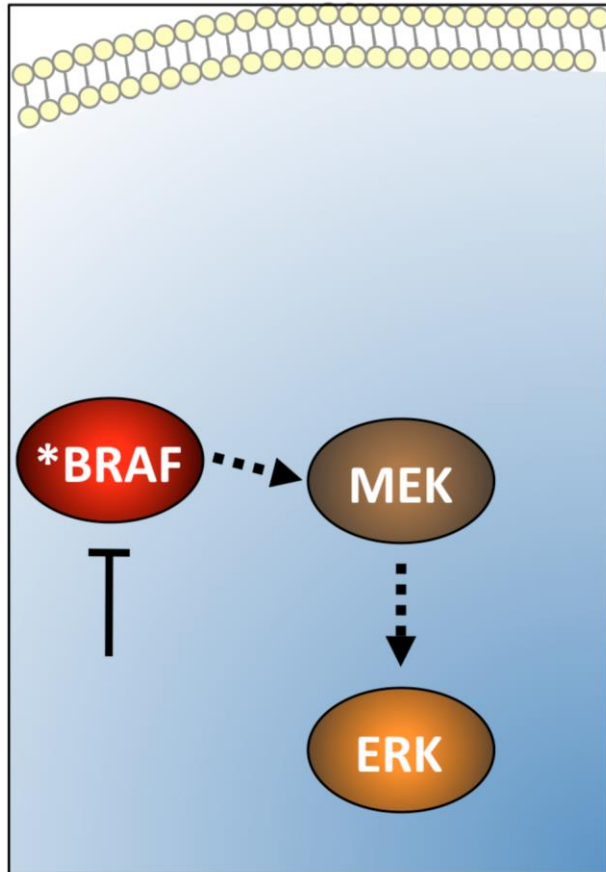


Su et al, NEJM 2012
Heidorn et al, Cell 2012

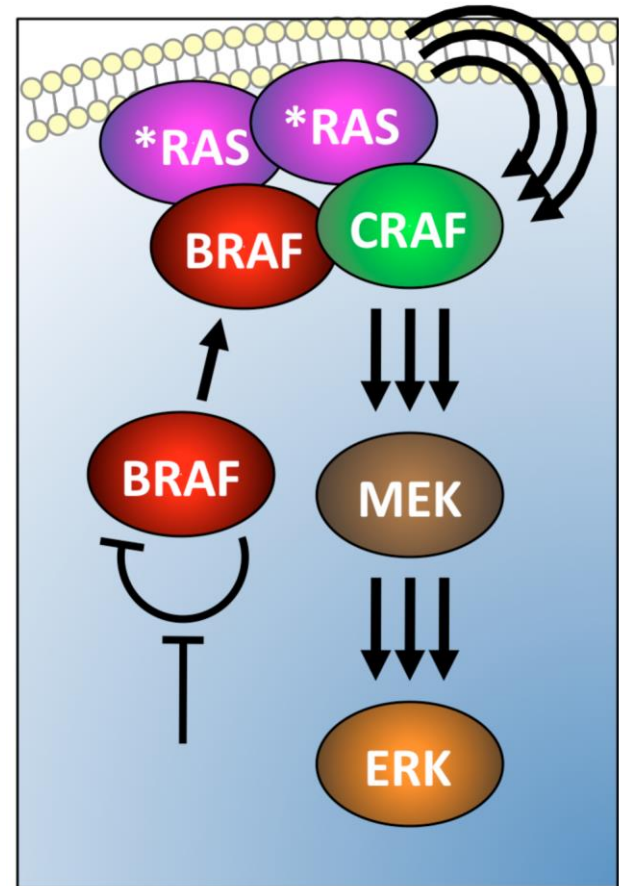


Heidorn et al (2010) *Cell*
 Hatzivassiliou et al (2010) *Nature*
 Poulikakos et al (2010) *Nature*

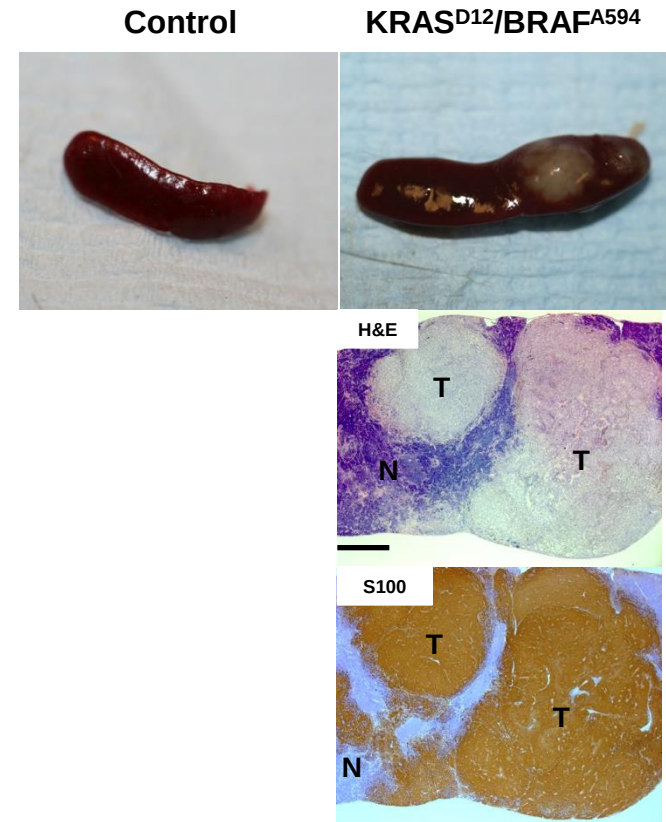
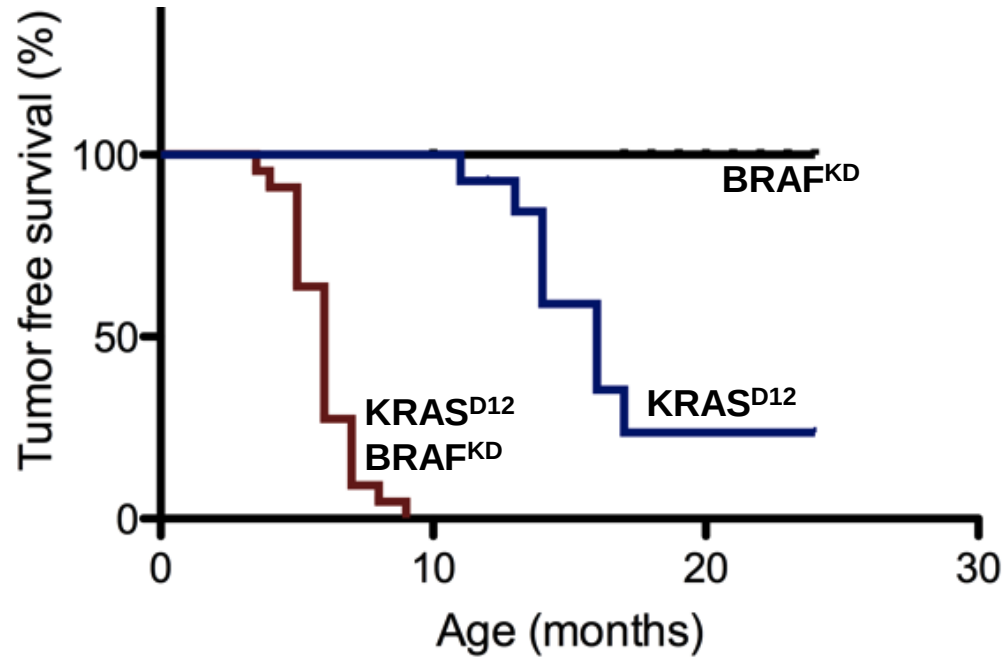
melanoma cell



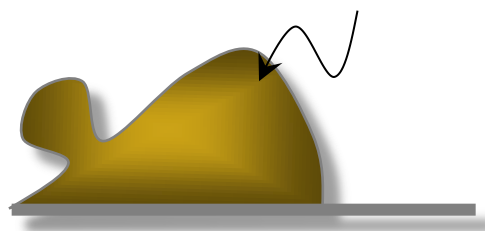
keratinocyte



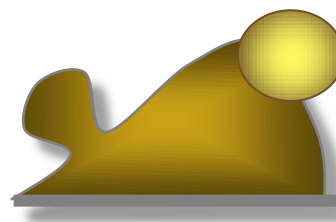
The RAF paradox induces metastasis



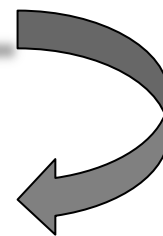
RAS mutant cells: intradermal injection



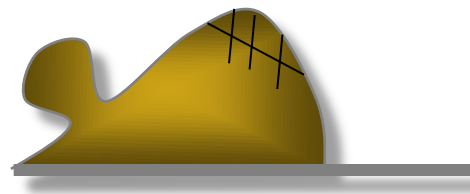
30 days
+/- PLX 4720



Remove
primary
tumour



30 days
w/o PLX4720



Examine tissues

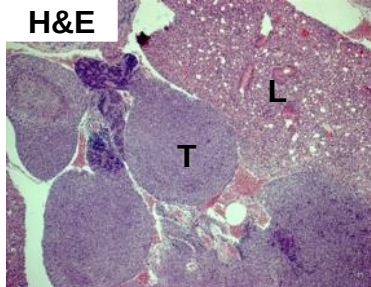
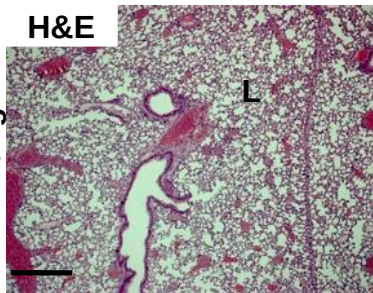
Vehicle

PLX4720

H&E

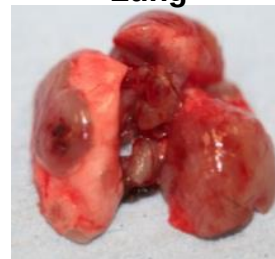
H&E

Lung

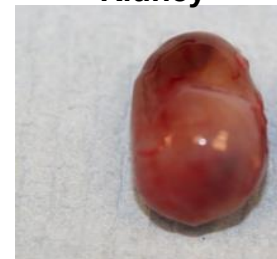


PLX4720 mice

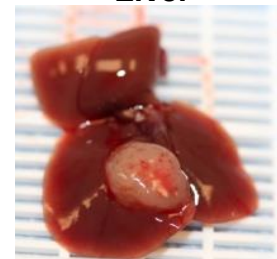
Lung



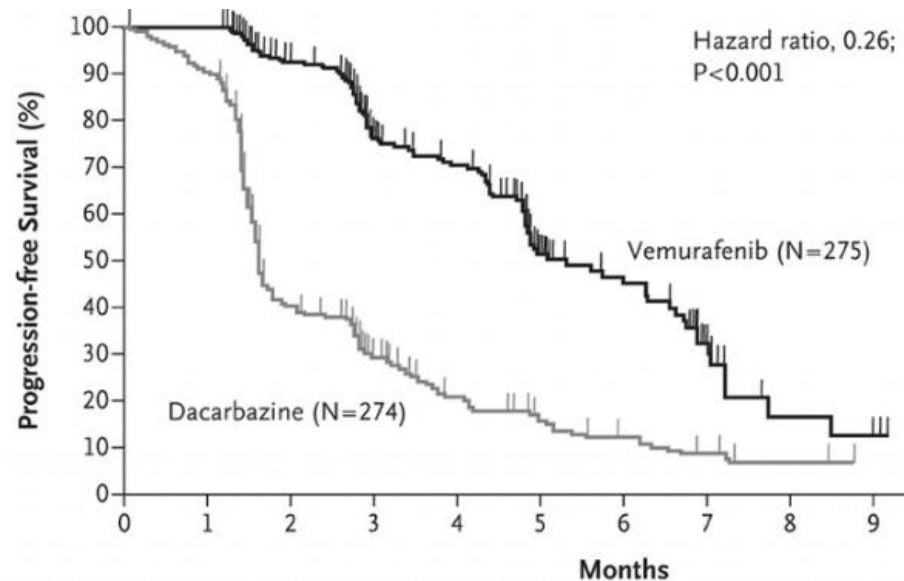
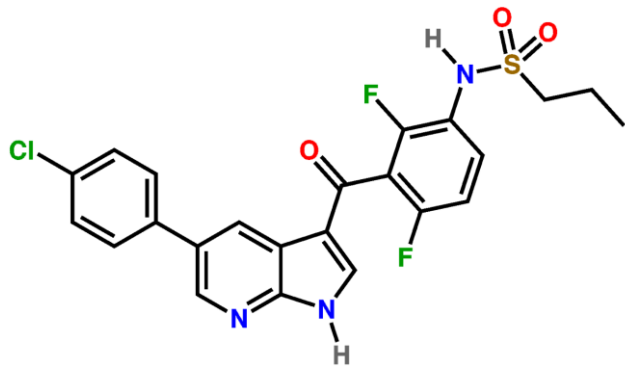
Kidney



Liver

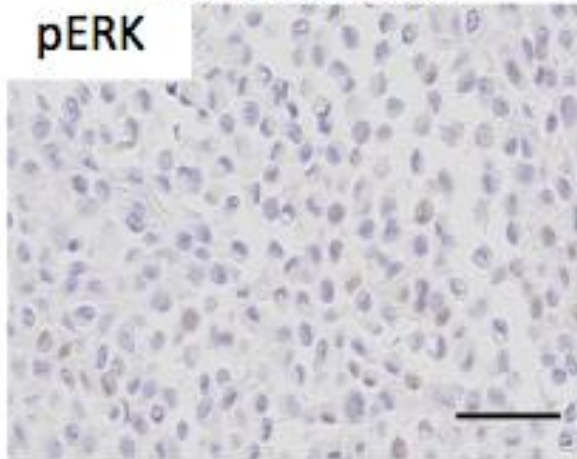


Vemurafenib in melanoma patients

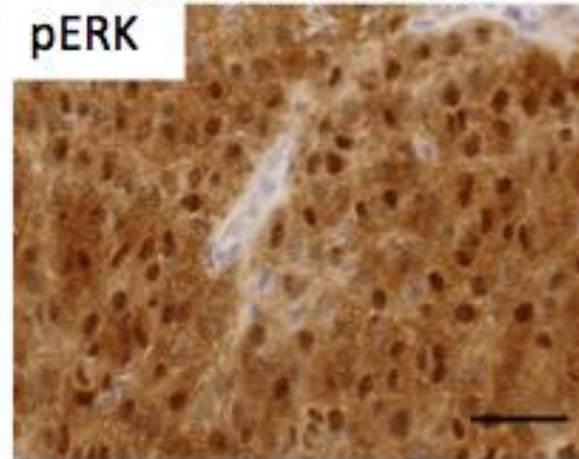


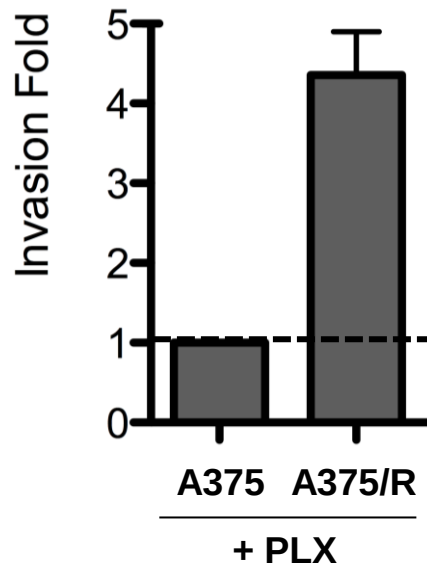
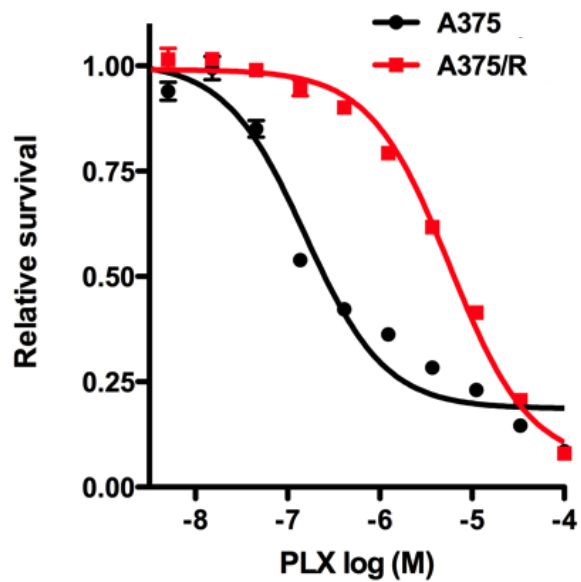
Flaherty et al (2010) *NEJM*, Chapman et al (2011) *NEJM*

Pre-treatment
pERK

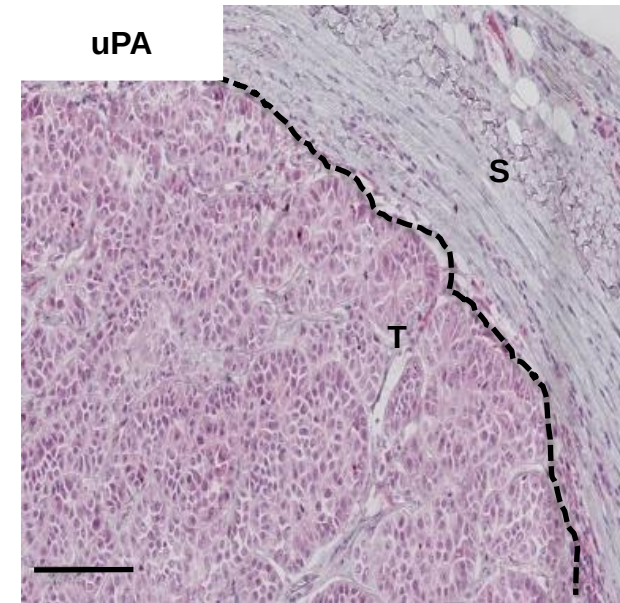


Post-vemurafenib
pERK

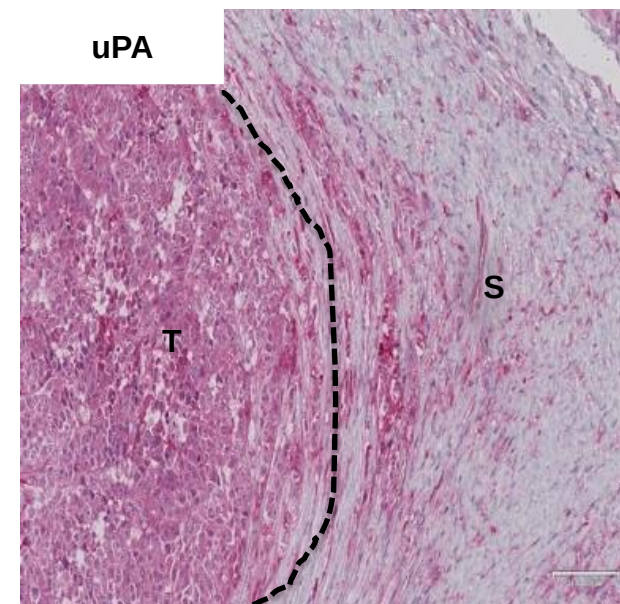




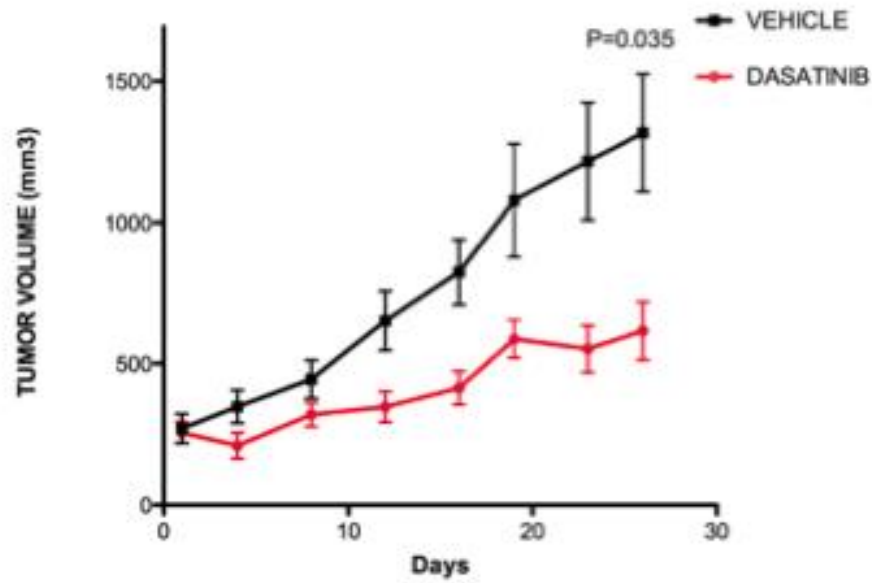
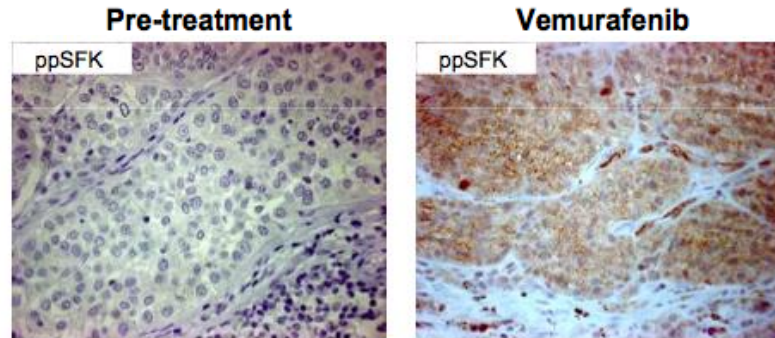
Pre-treatment

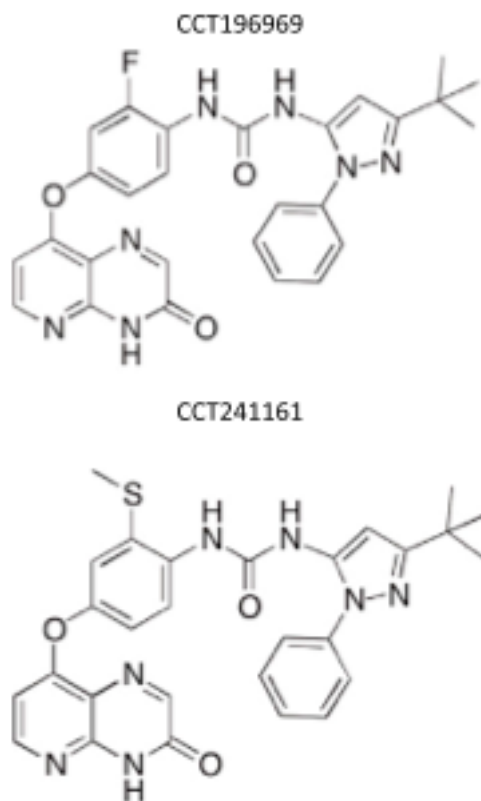


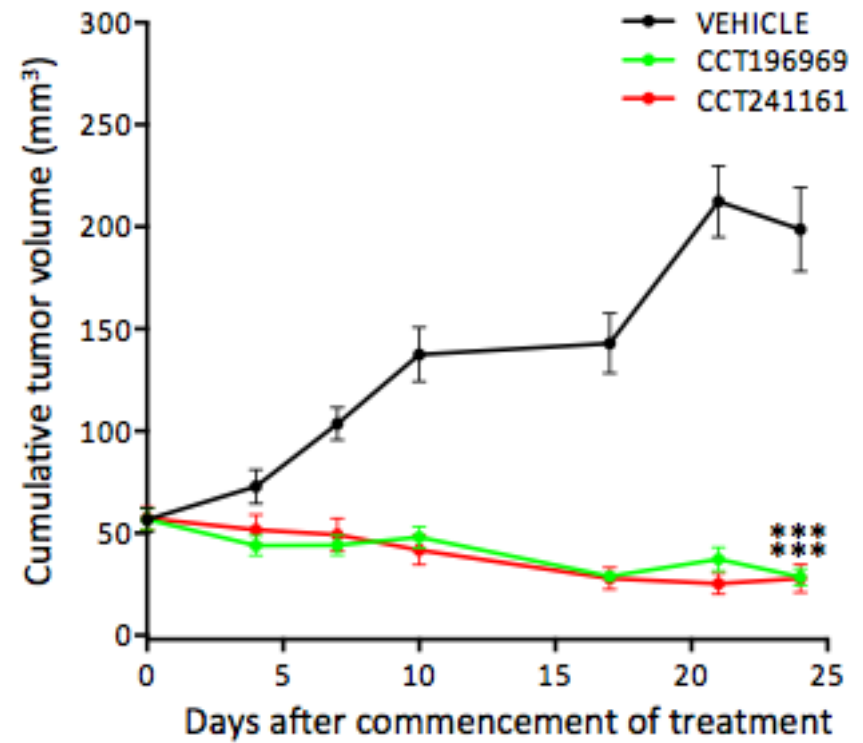
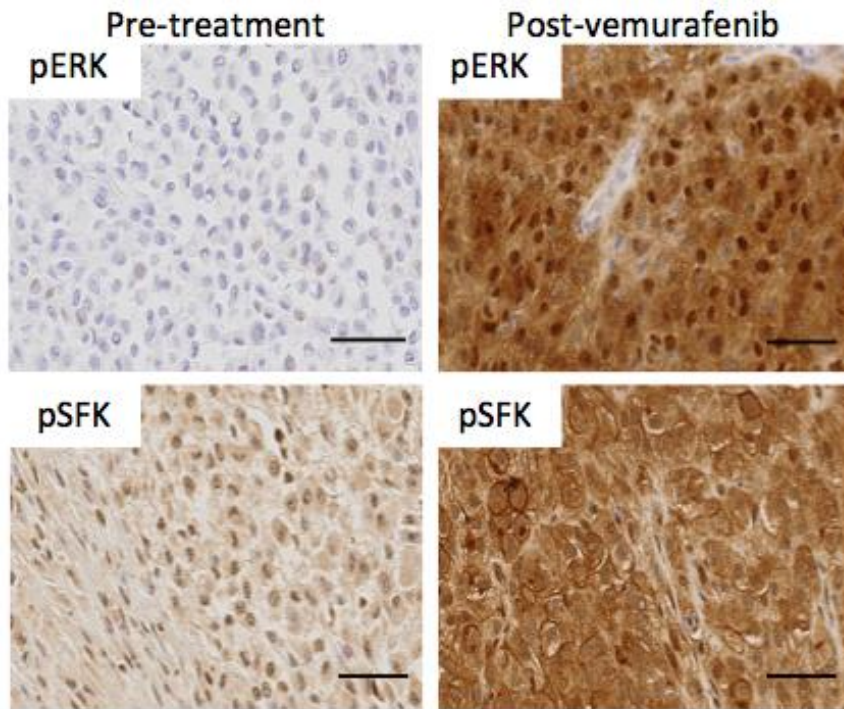
Vemurafenib

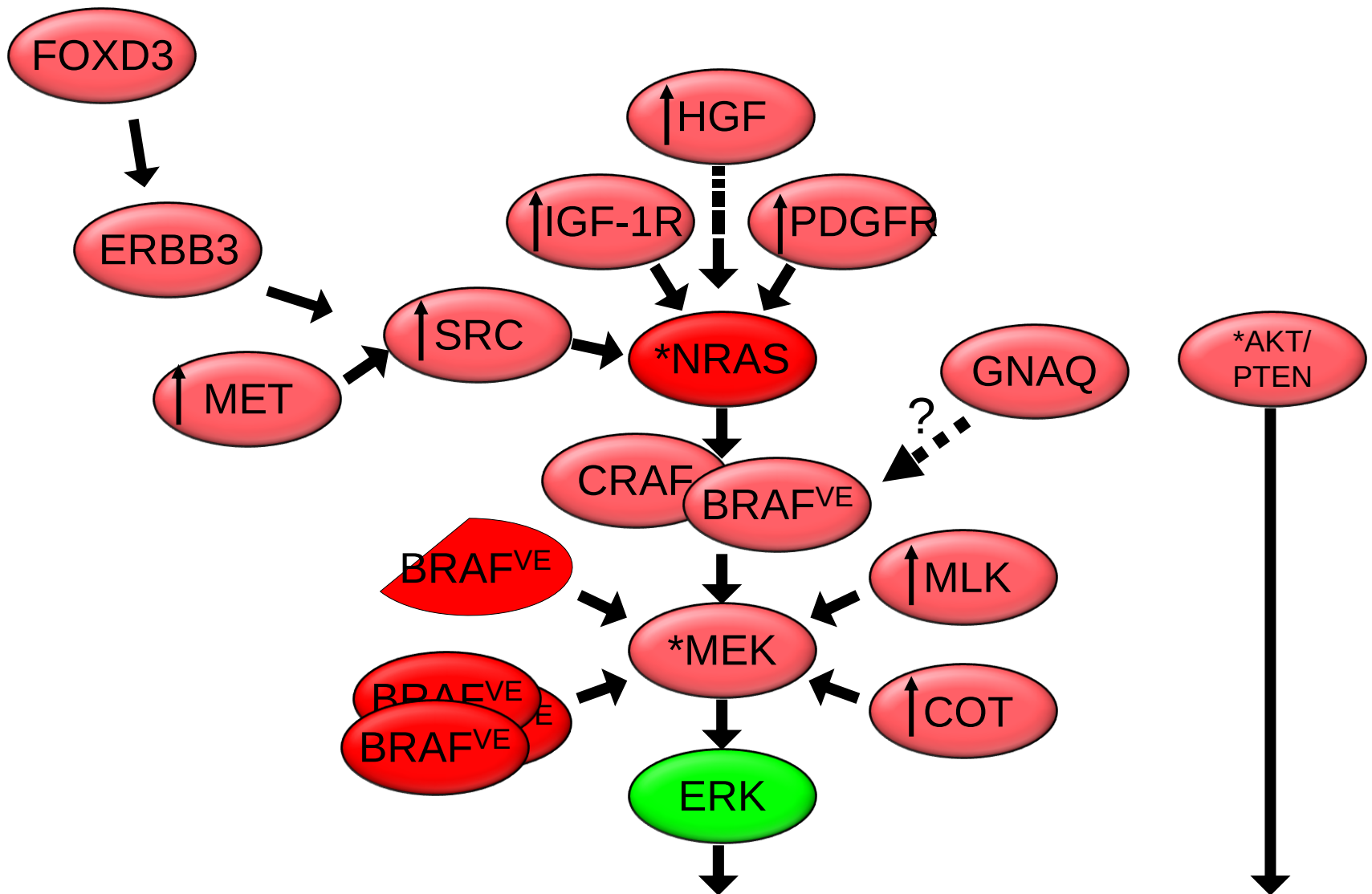


SFK are reactivated in patients

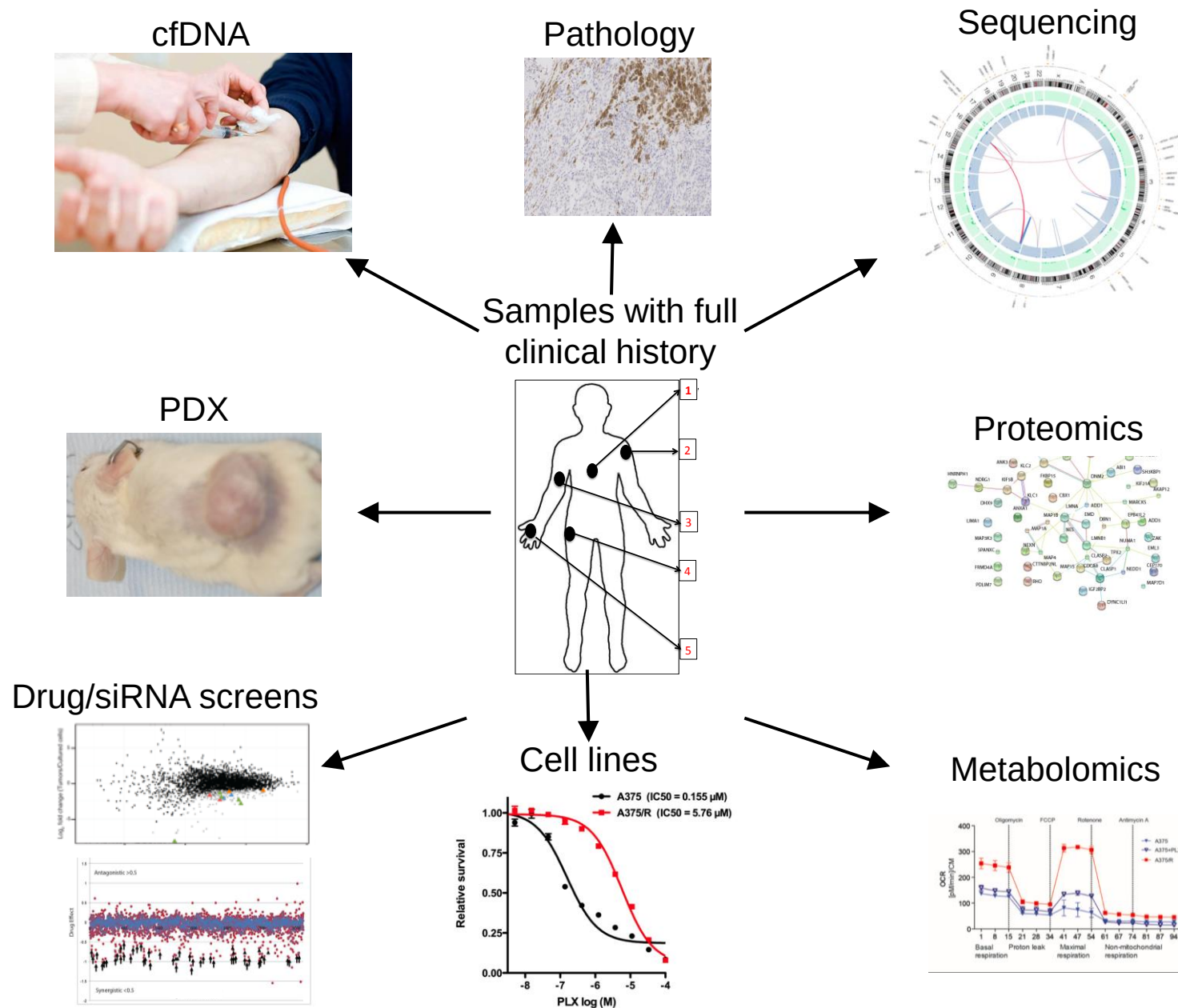








Precision Medicine for Melanoma



Conclusions

- BRAF is a driver oncogene in melanoma
- BRAF inhibitors increase overall and progression-free survival
 - resistance
 - metastasis in resistant tumours
- Precision medicine

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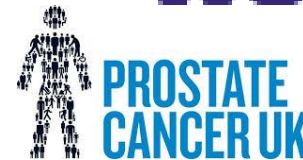
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