# Genetics & Mutation - what this means for treatment type

CANCER RESEARCH UK

OXFORD CENTRE

# We live in an immunotherapy world…

But melanoma is still a genetic disease

## Whole-genome landscapes of major melanoma subtypes

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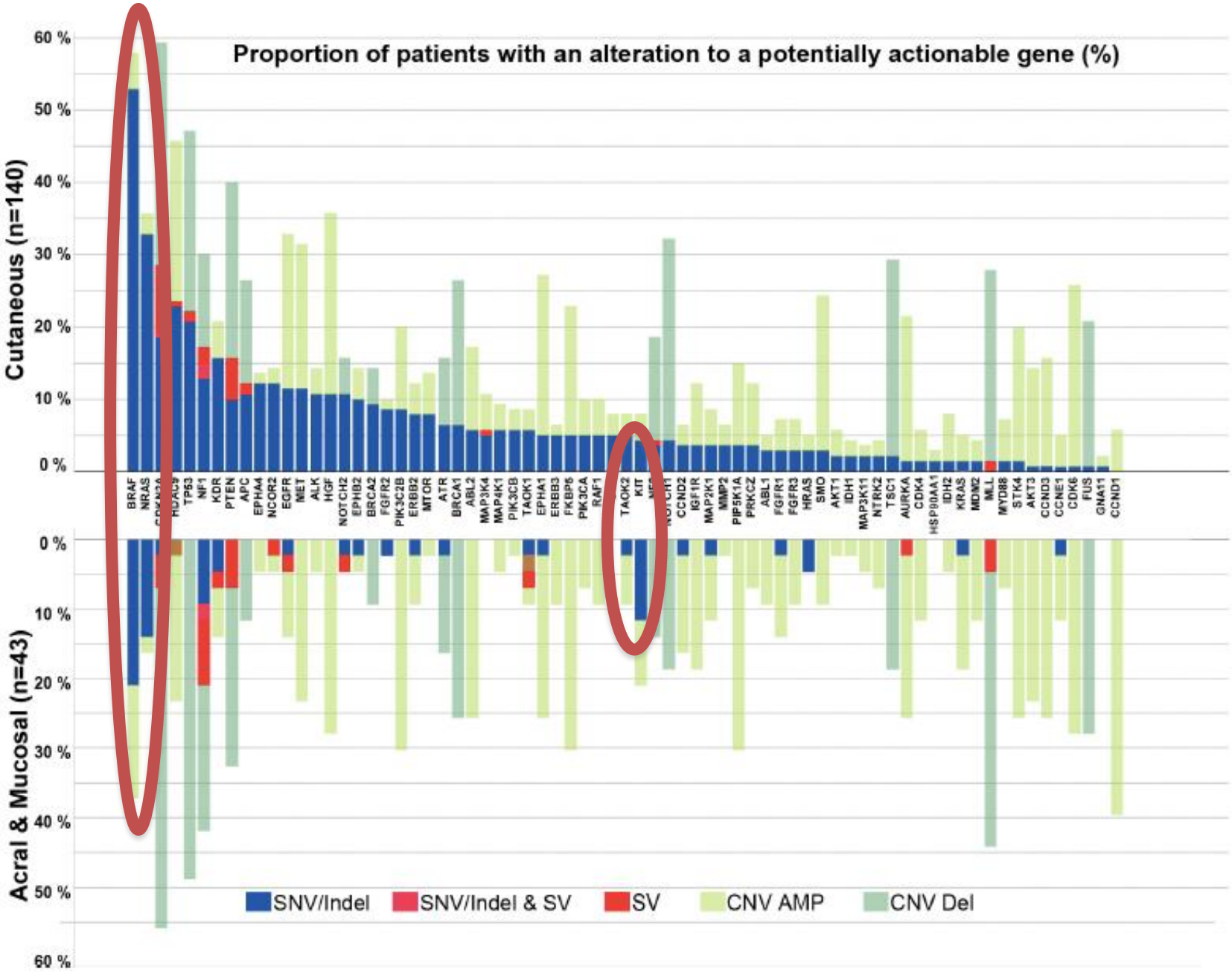

Proportion of patients with an alteration to a potentially actionable gene (%)
Cutaneous (n=140)
Acral & Mucosal (n=43)
60 %
50 %
40 %
30 %
20 %
10 %
0 %
BRAF
NRAS
TP53
NF1
KDR
PTEN
APC
EPHA4
NCOR2
EGFR
MET
ALK
HGF
NOTCH2
ERBB2
BRCA2
FGFR2
PIK3C2B
ERBB2
MTOR
ATR
BRCA1
ABL2
MAP3K4
MAP4K1
PIK3CB
TAOK1
EPHA1
ERBB3
FKBP5
PIK3CA
RAF1
TAOK2
KIT
CCND2
IGF1R
MAP2K1
MMP2
PIP5K1A
PRKCZ
ABL1
FGFR1
FGFR3
HRAS
SMO
AKT1
IDH1
MAP3K11
NTRK2
TSC1
AURKA
CDK4
HSP90AA1
IDH2
KRAS
MDM2
MLL
MYD88
STK4
AKT3
CCND3
CCNE1
CDK6
FUS
GNA11
CCND1
SNV/Indel
SNV/Indel & SV
SV
CNV AMP
CNV Del

# So what does it mean practically?

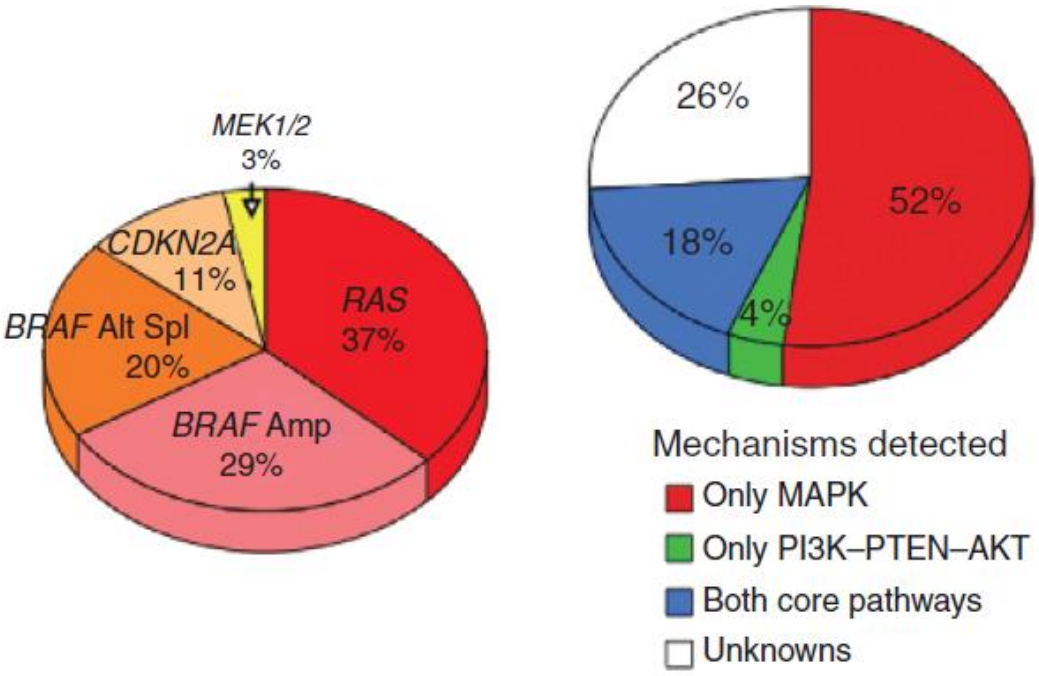
Or what to do if immunotherapy doesn't work?

BRAF mutant melanoma – BRAFi/MEKi
but are we using the drugs right?

NRAS mutation – can MEKi help?
NEMO trial

wt/wt disease – what are the options?
PACMEL, CDK4/6 with MEKi

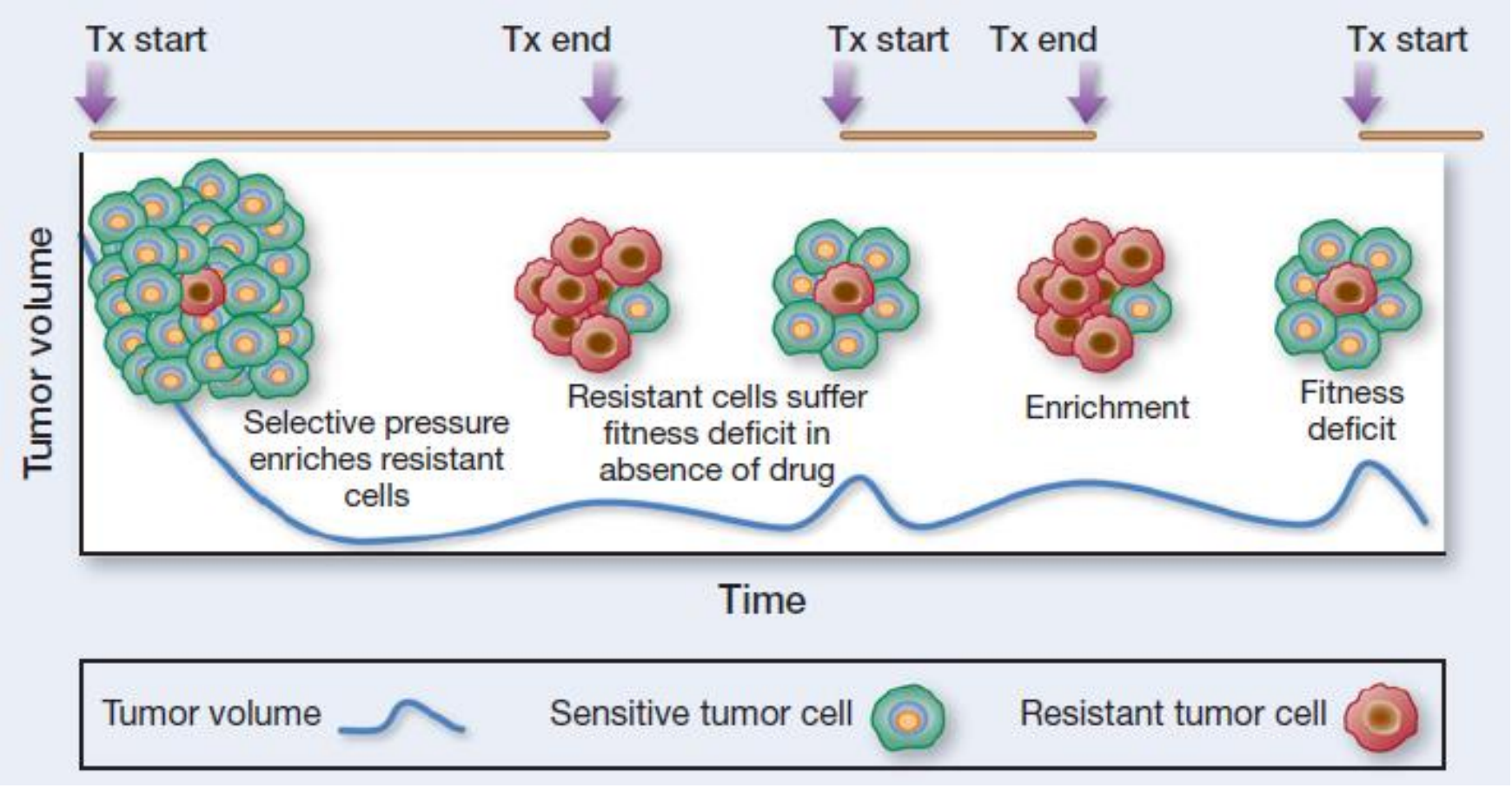
# Activating RAS mutations drive resistance to BRAF inhibitors in $BRAF^{V600mut}$ melanoma



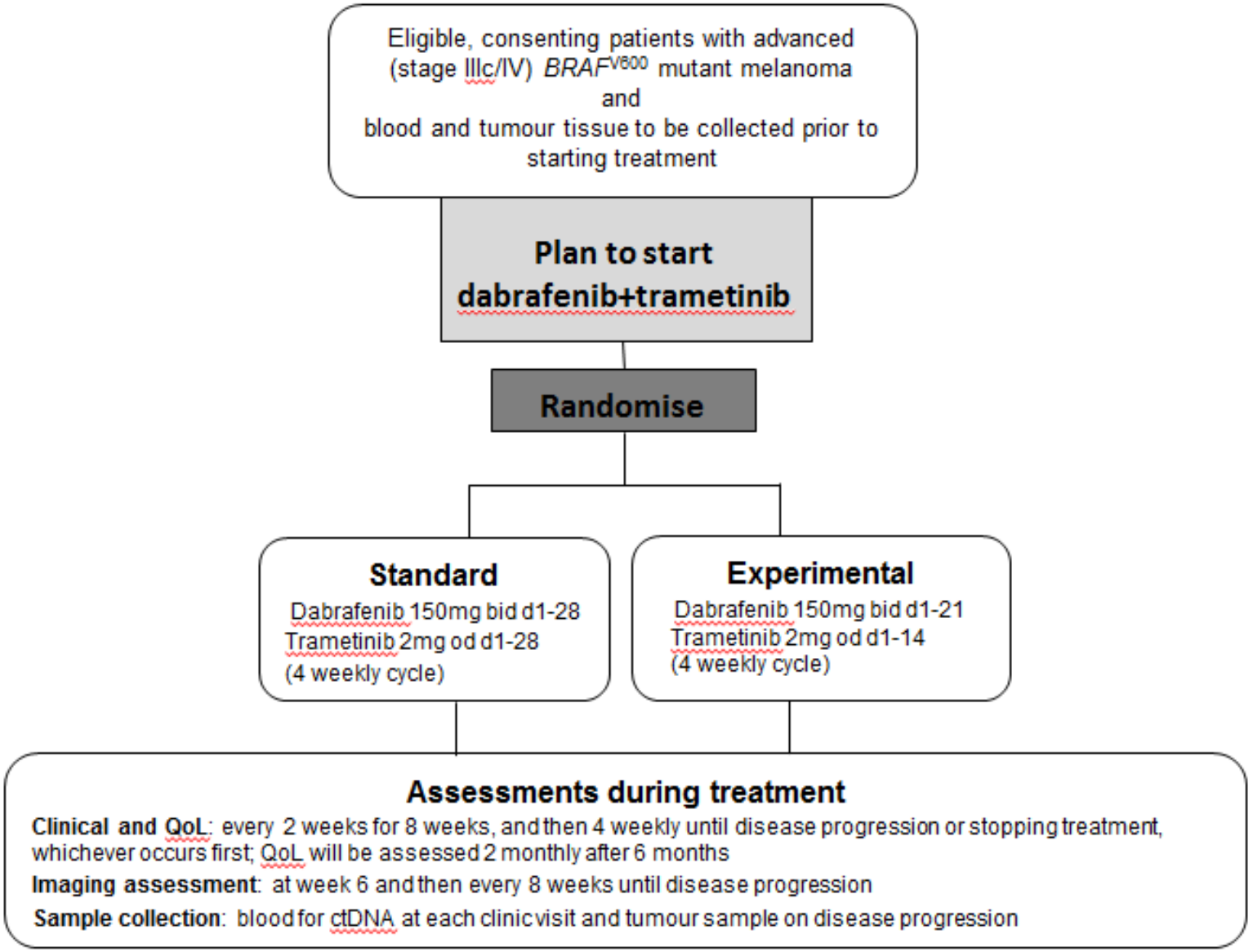

- *Shi et al. Cancer Discovery 2014*

# Alternating selective pressure will prevent the emergence of resistance

*Resistant cells suffer a fitness deficit in the absence of drug treatment*

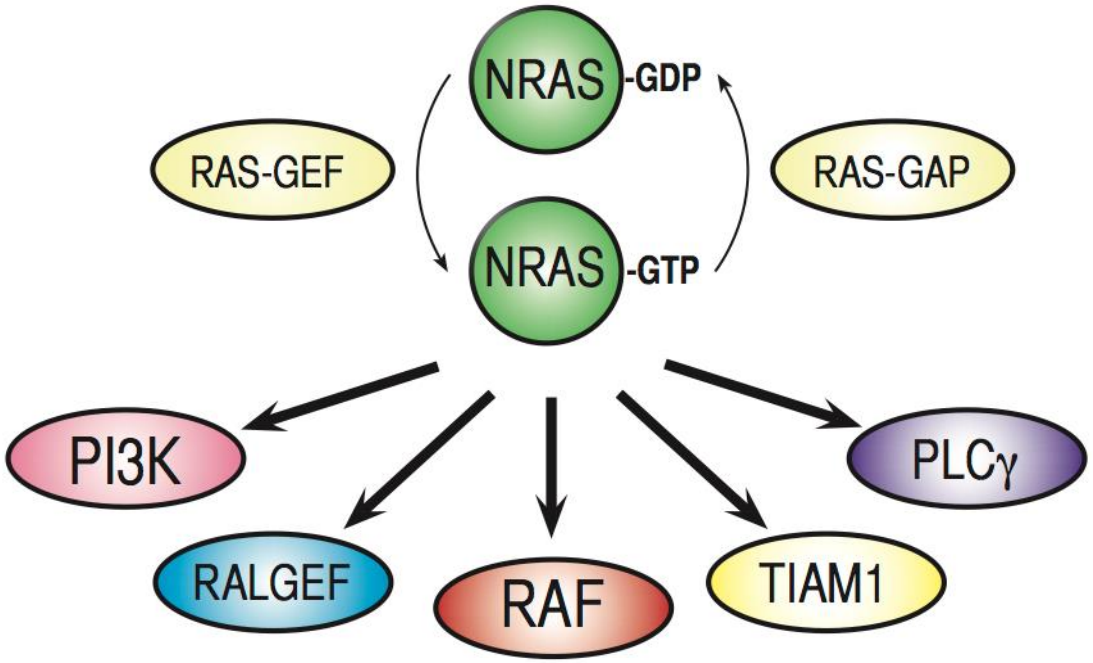


# INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of combination BRAF+MEK inhibitor treatment In patients with BRAF mutant unresectable or metastatic Melanoma



# How do we target RAS?

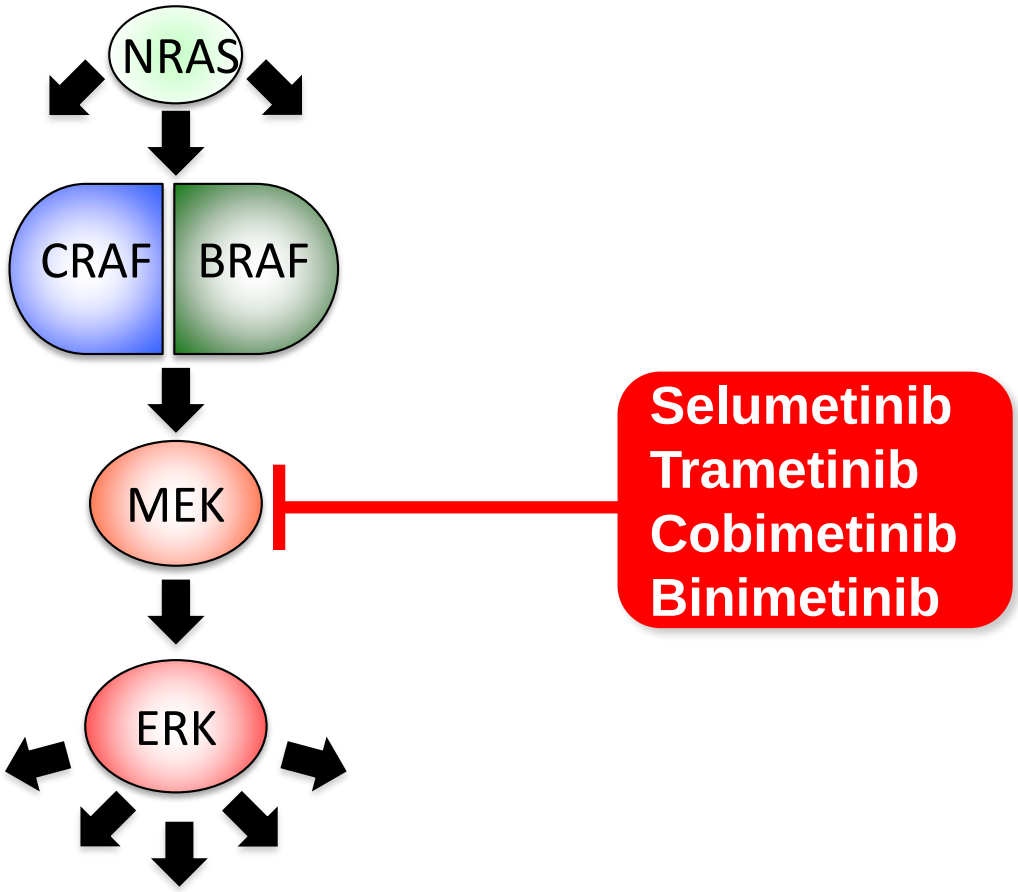
## Downstream signalling




Kelleher & McArthur, *The Cancer J*, 2012

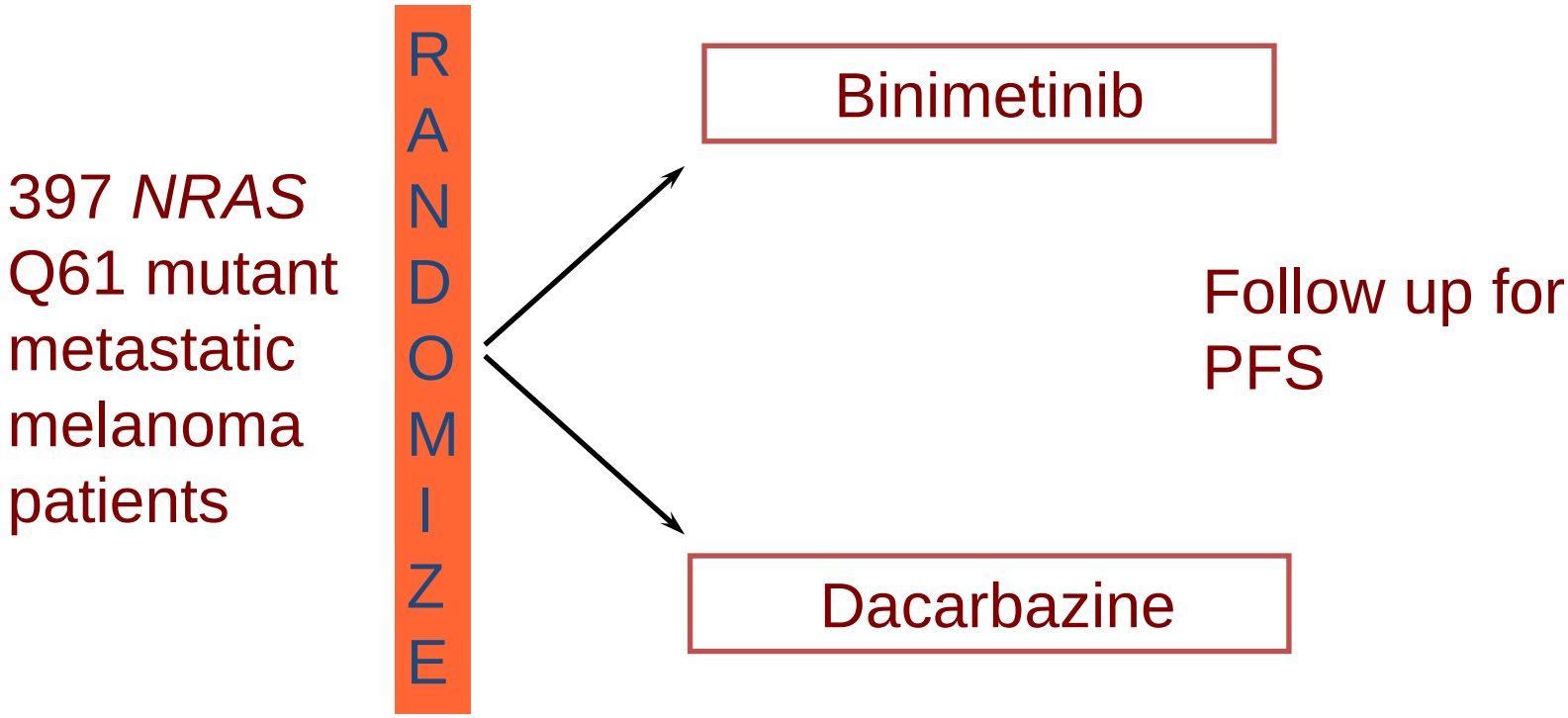
# How do we target RAS?

MEK Inhibition



# MEK Inhibition: Binimetinib

NEMO Trial

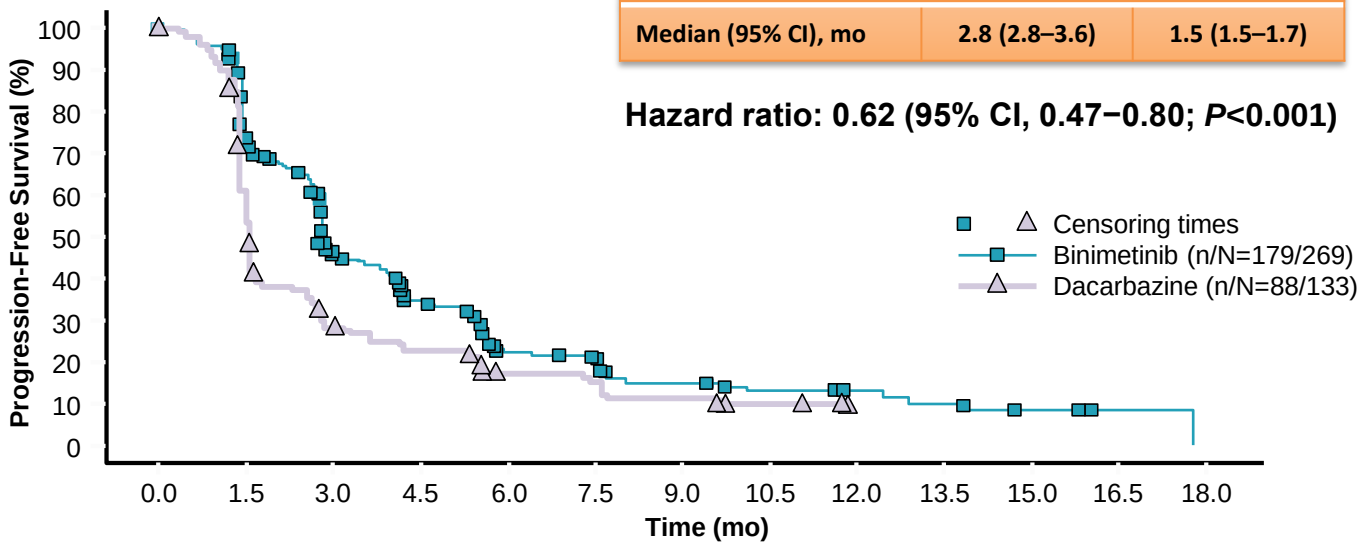


# MEK Inhibition: Binimetinib

## NEMO Trial – Progression Free Survival

| PFS | Binimetinib | Dacarbazine |
|---|---|---|
| Median (95% CI), mo | 2.8 (2.8–3.6) | 1.5 (1.5–1.7) |

**Hazard ratio: 0.62 (95% CI, 0.47−0.80; *P*<0.001)**



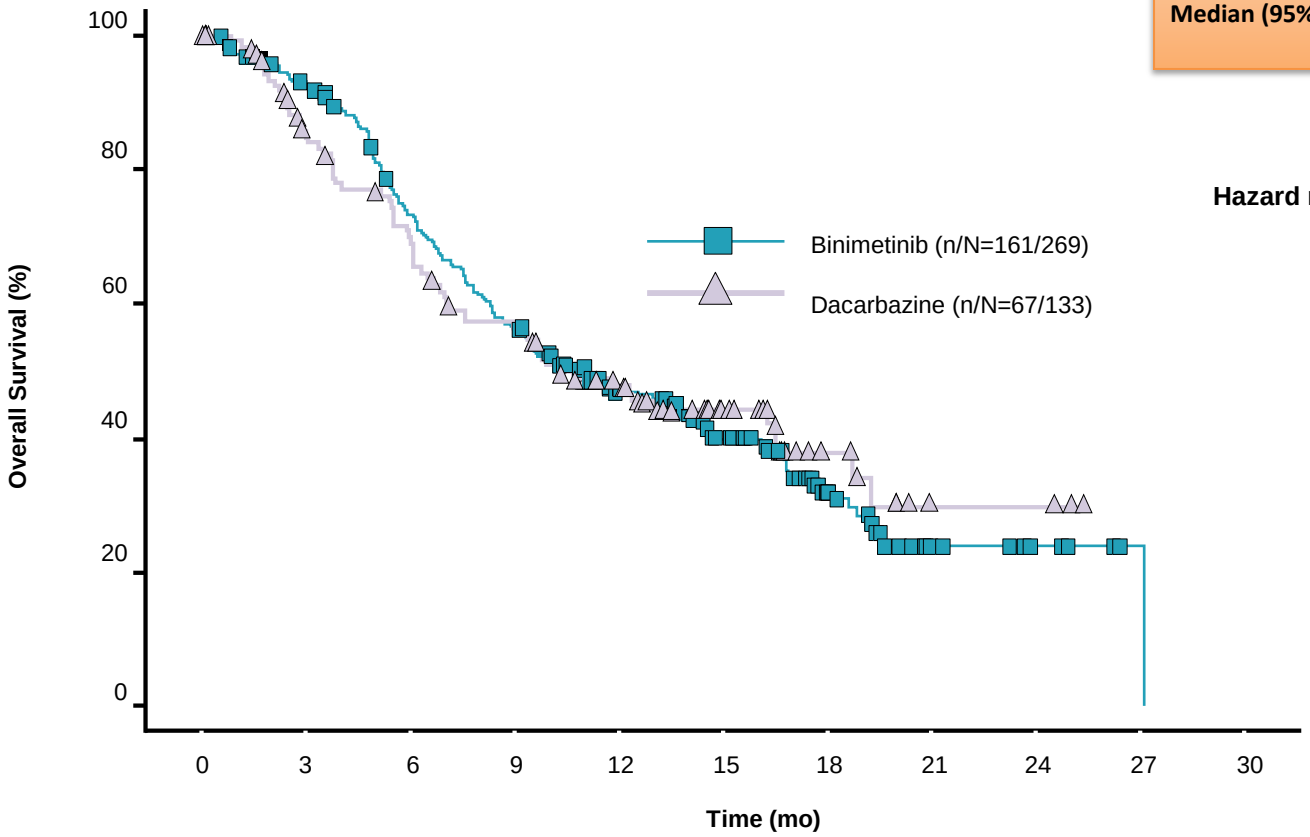

Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy, and ECOG performance status
AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; PFS=progression-free survival

# MEK Inhibition: Binimetinib

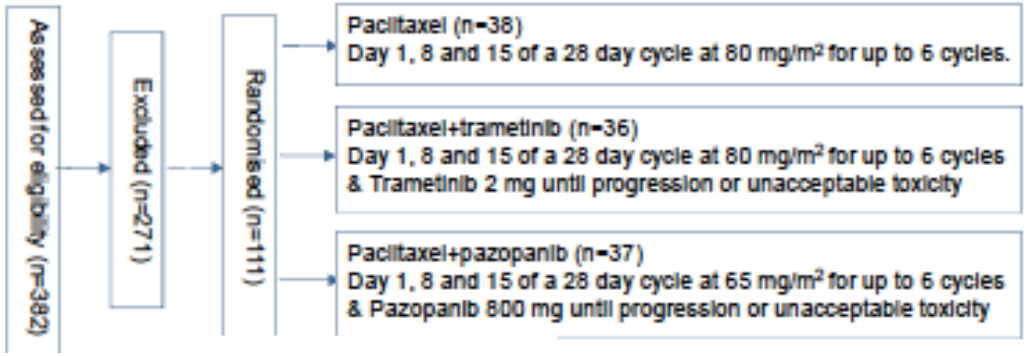
## NEMO Trial – Overall Survival

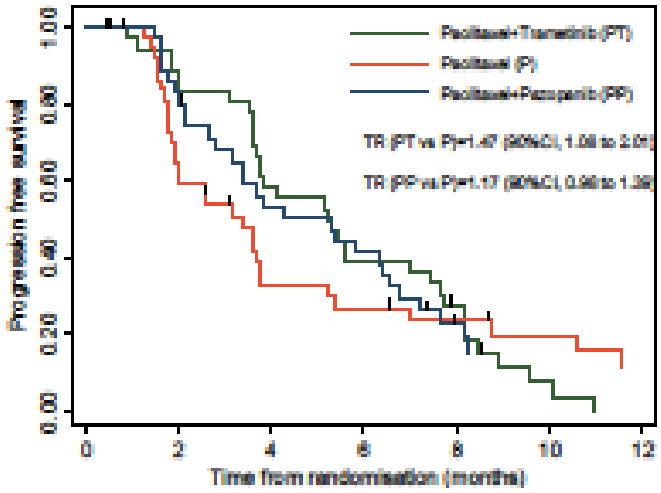
| Overall survival | Binimetinib | Dacarbazine |
|---|---|---|
| Median (95% CI), mo | 11.0 (8.9–13.6) | 10.1 (7.0–16.5) |

**Hazard ratio: 1.00 (95% CI, 0.75–1.33; *P*=0.499)**



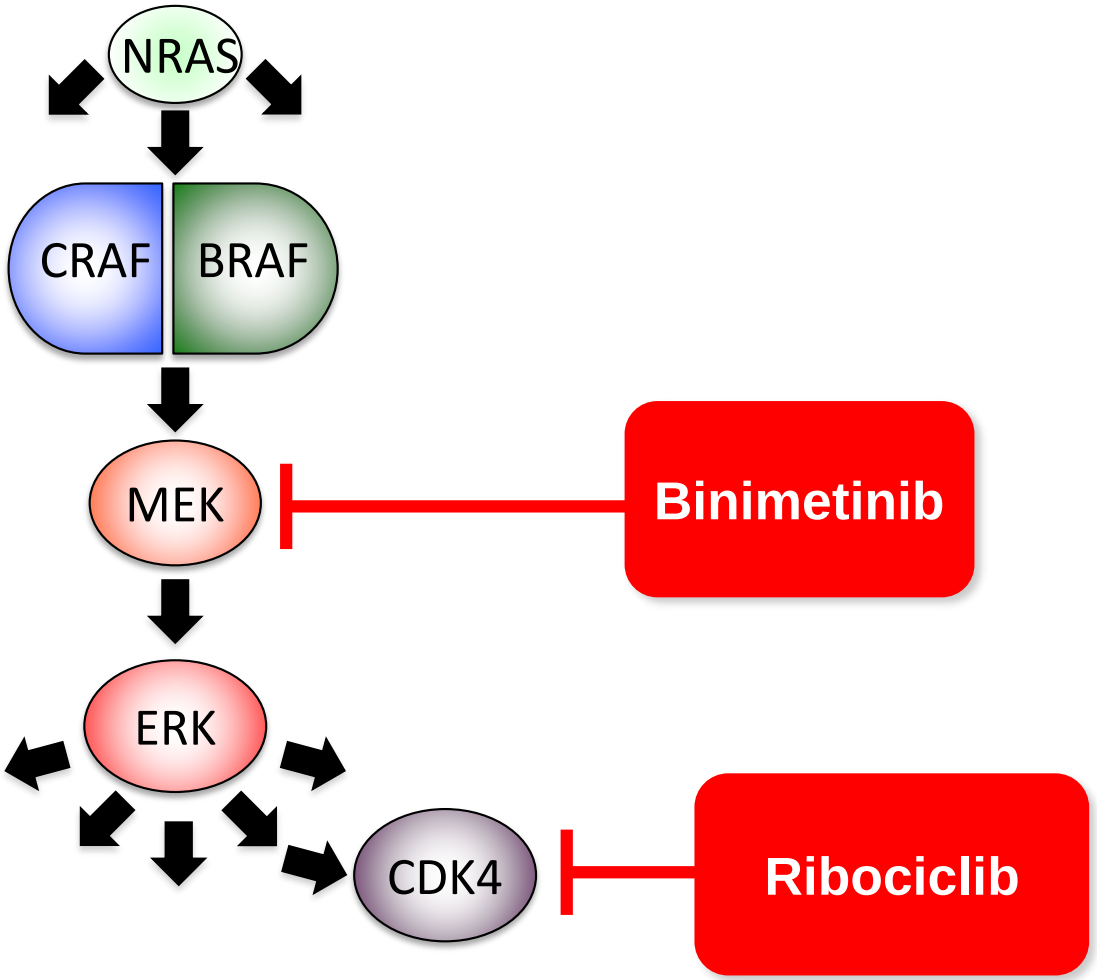
# PACMEL Trial



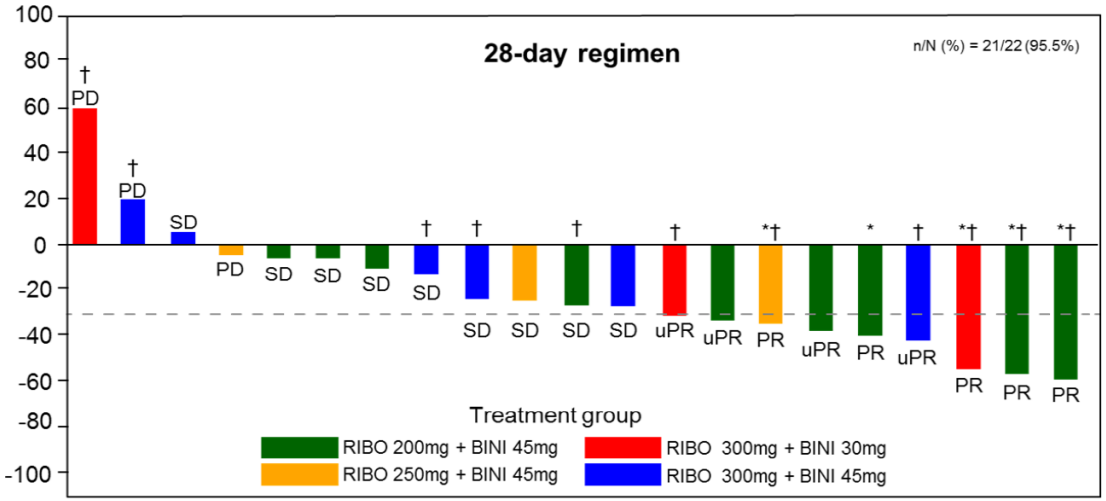

| Parameters | Paclitaxel (N=38) | Paclitaxel + trametinib (N=36) | Paclitaxel + pazopanib (N=37) |
|---|---|---|---|
| PFS (months) | | | |
| Median PFS (90% CI) | 3.4 (2.0 to 3.8) | 5.2 (3.7 to 7.0) | 5.3 (3.4 to 6.4) |
| PFS rate at 6 months | | | |
| Estimated % (90%CI) | 27 (16 to 40) | 39 (26 to 52) | 41 (28 to 55) |
| OS months | | | |
| Median OS (90% CI) | 13.7 (8.7 to -) | 9.3 (8.2 to 13.4) | 11.6 (8.0 to 16.2) |
| ORR | | | |
| Complete response | 2 | 0 | 0 |
| Partial response | 3 | 15 | 8 |
| Stable disease | 13 | 11 | 16 |
| Progression disease | 12 | 6 | 9 |
| Not-evaluable | 7 | 4 | 4 |
| Best overall response (CR+PR), n (%) | 5 (13) | 15 (42) p=0.01 | 8 (22) p=0.33 |

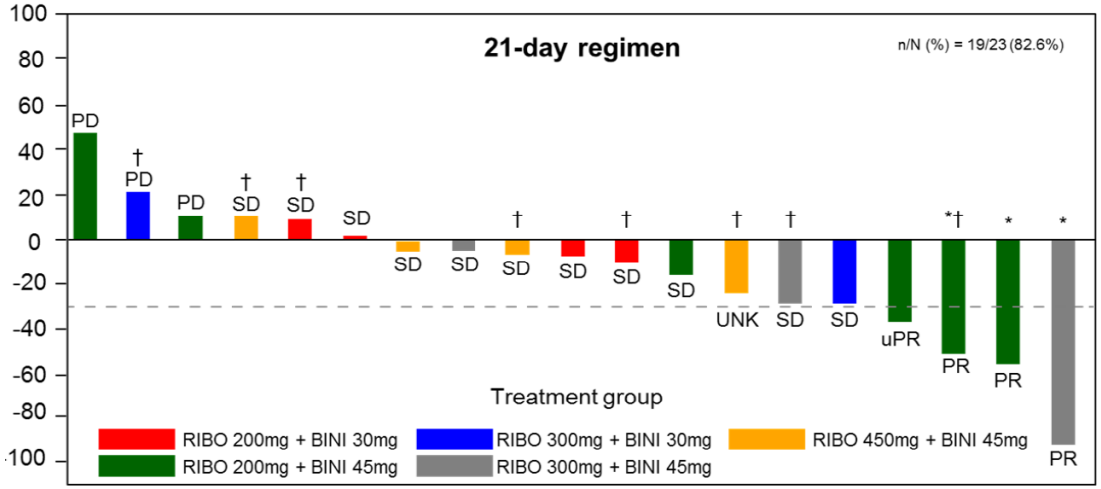
# MEK inhibition in NRAS mutant melanoma: attacking other nodes in the pathway



# MEK inhibition in NRAS mutant melanoma: attacking CDK4/6 too

| Response, n (%) | All 28-day Regimen Patients (n = 22) | All 21-day Regimen Patients (n = 23) |
|---|---|---|
| Evaluable patients | 22 | 22 |
| Complete response | 0 | 0 |
| Partial response (PR)<br>Confirmed PR<br>Unconfirmed PR | <br>5 (23)<br>4 (18) | <br>3 (14)<br>1 (5) |
| Stable disease | 9 (41) | 11 (50) |
| Progressive disease | 3 (14) | 4 (18) |
| Unknown | 1 (5) | 3 (14) |
| **Overall response rate[a]** | **9 (41)** | **4 (18)** |
| **Disease control rate[a]** | **18 (82)** | **15 (68)** |
| **Median PFS, months** | **6.7** | **4** |



# So what does it mean…

Despite immunotherapy tumour genotype is important

The AVAST-M trial data show that mutation type affects the natural history of melanoma

Treatment options are dictated by BRAF mutation status

We still need to find good options for NRAS mutant and wt/wt disease

Trials of immunotherapy with BRAF and/or MEK inhibitors are being done

Oxford Biomedical Research Centre

NHS National Institute for Health Research

NCRI National Cancer Research Institute

# Thanks for Listening

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

octo Oncology Clinical Trials Office

OCTRU Oxford Clinical Trials Research Unit

UKCRC Registered Clinical Trials Units

OCTRU is a UKCRC Registered Clinical Trials Unit
OCTRU is a joint venture between the Centre for Statistics in Medicine (CSM) and the Oncology Clinical Trials Office (OCTO) both based at the University of Oxford

CSM

Oxford University Hospitals NHS Trust