Combining anti-BRAF and anti-MEK with translation inhibitors

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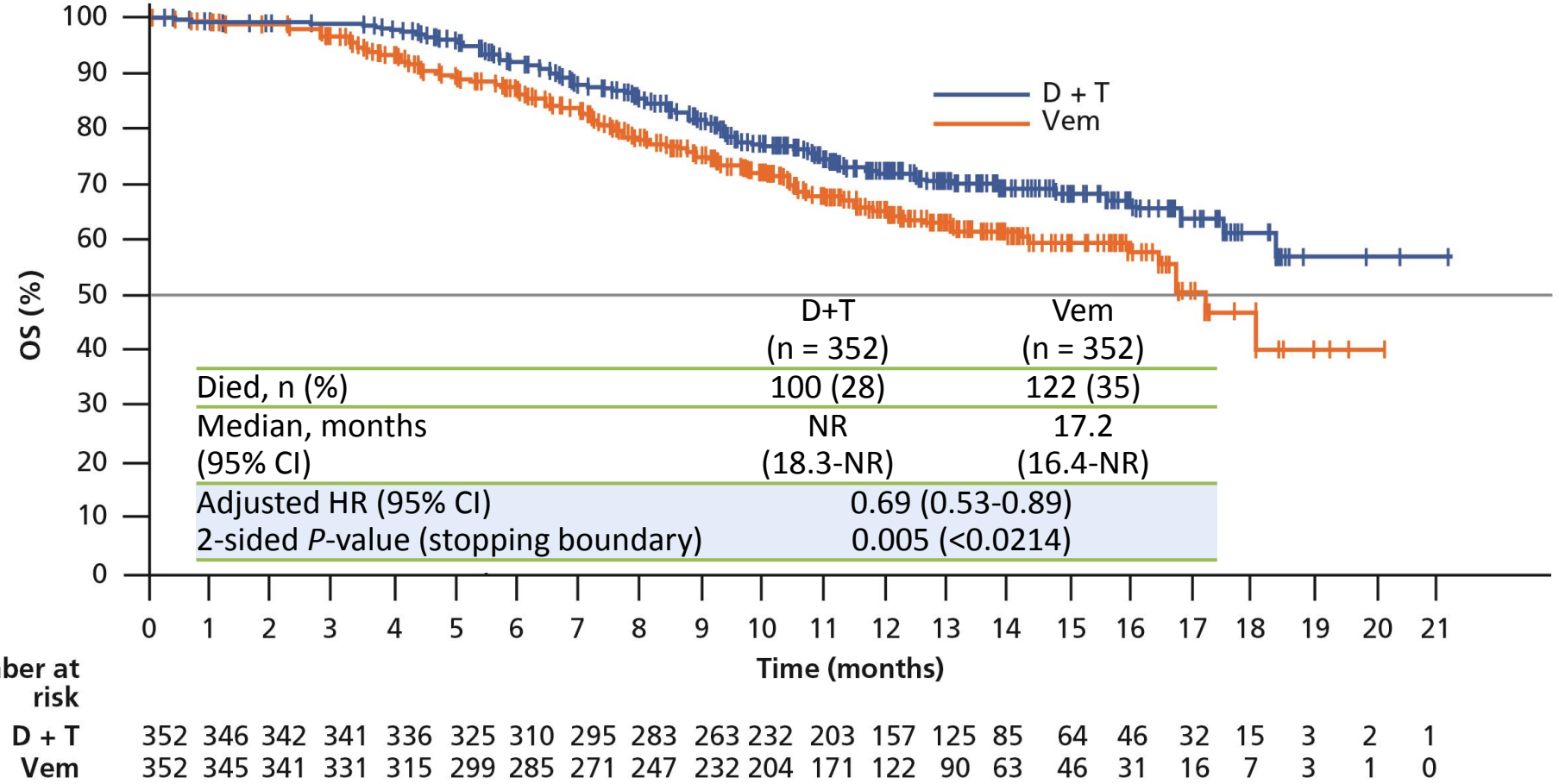
France

COMBI-v study
Overall Survival



	D+T (n = 352)	Vem (n = 352)
Died, n (%)	100 (28)	122 (35)
Median, months (95% CI)	NR (18.3-NR)	17.2 (16.4-NR)
Adjusted HR (95% CI)	0.69 (0.53-0.89)	
2-sided *P*-value (stopping boundary)	0.005 (<0.0214)	

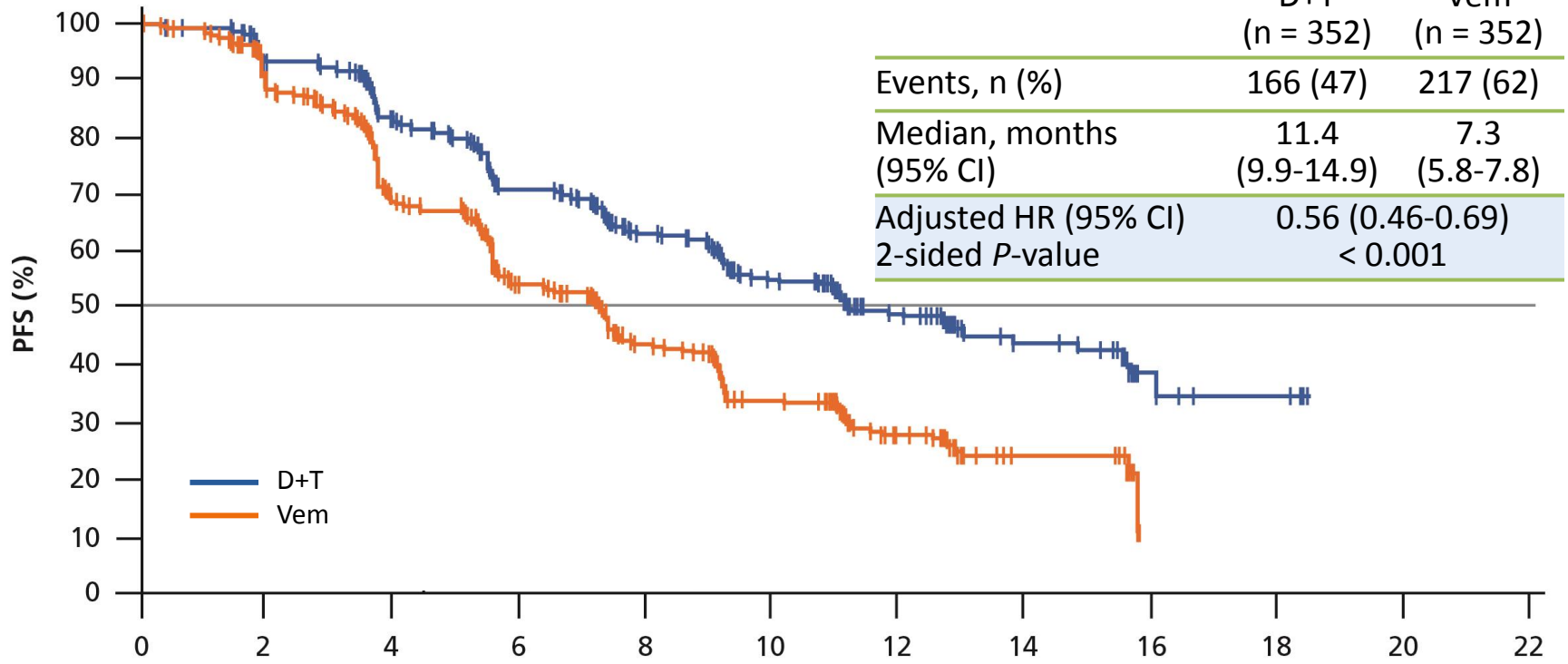
Number at risk																						
D + T	352	346	342	341	336	325	310	295	283	263	232	203	157	125	85	64	46	32	15	3	2	1
Vem	352	345	341	331	315	299	285	271	247	232	204	171	122	90	63	46	31	16	7	3	1	0

D + T, dabrafenib + trametinib; Vem, vemurafenib

Median Follow-up: D + T = 11 months and Vem = 10 months

C ROBERT et al ESMO 2014

Progression-Free Survival

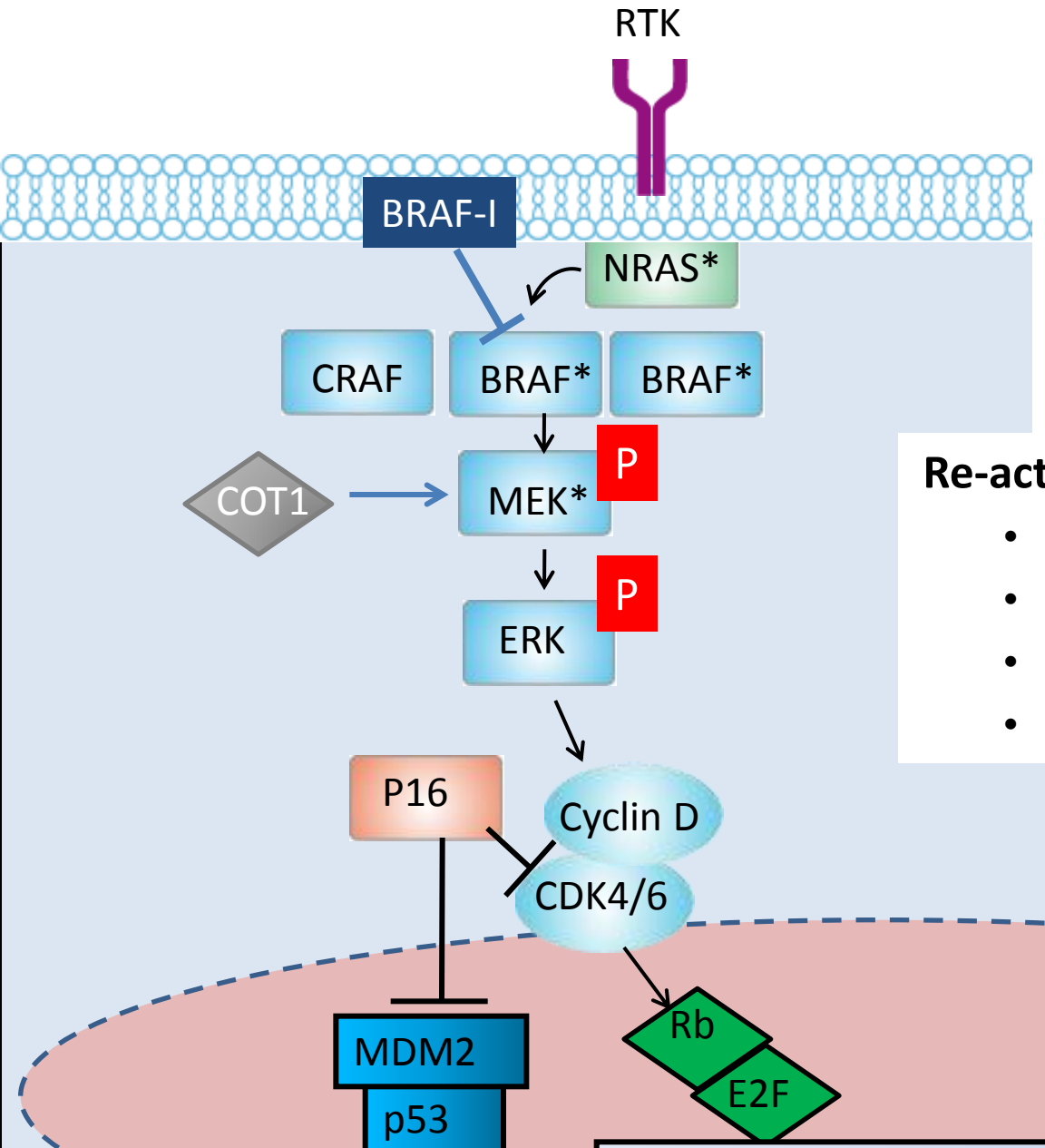


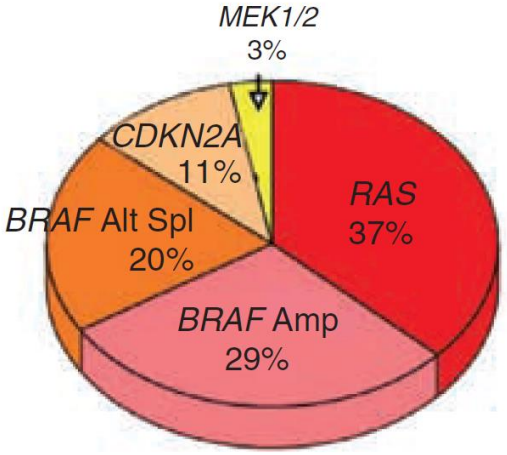
	D+T (n = 352)	Vem (n = 352)
Events, n (%)	166 (47)	217 (62)
Median, months (95% CI)	11.4 (9.9-14.9)	7.3 (5.8-7.8)
Adjusted HR (95% CI)	0.56 (0.46-0.69)	
2-sided *P*-value	< 0.001	

Number at risk												
D + T	352	310	270	228	194	142	83	39	10	7	0	0
Vem	352	279	214	161	121	83	45	11	0	0	0	0

D + T, dabrafenib + trametinib; Vem, vemurafenib

C ROBERT et al ESMO 2014



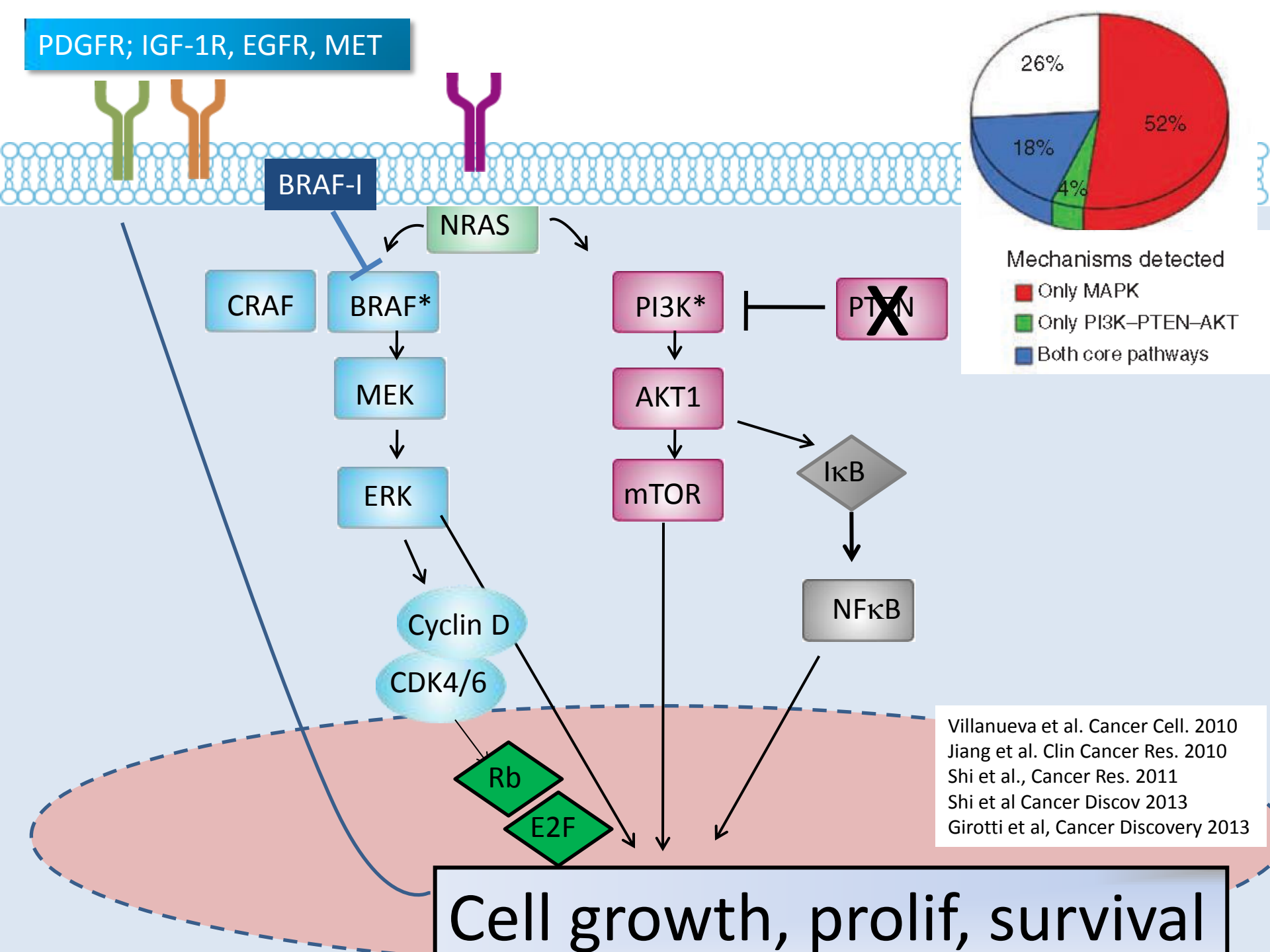


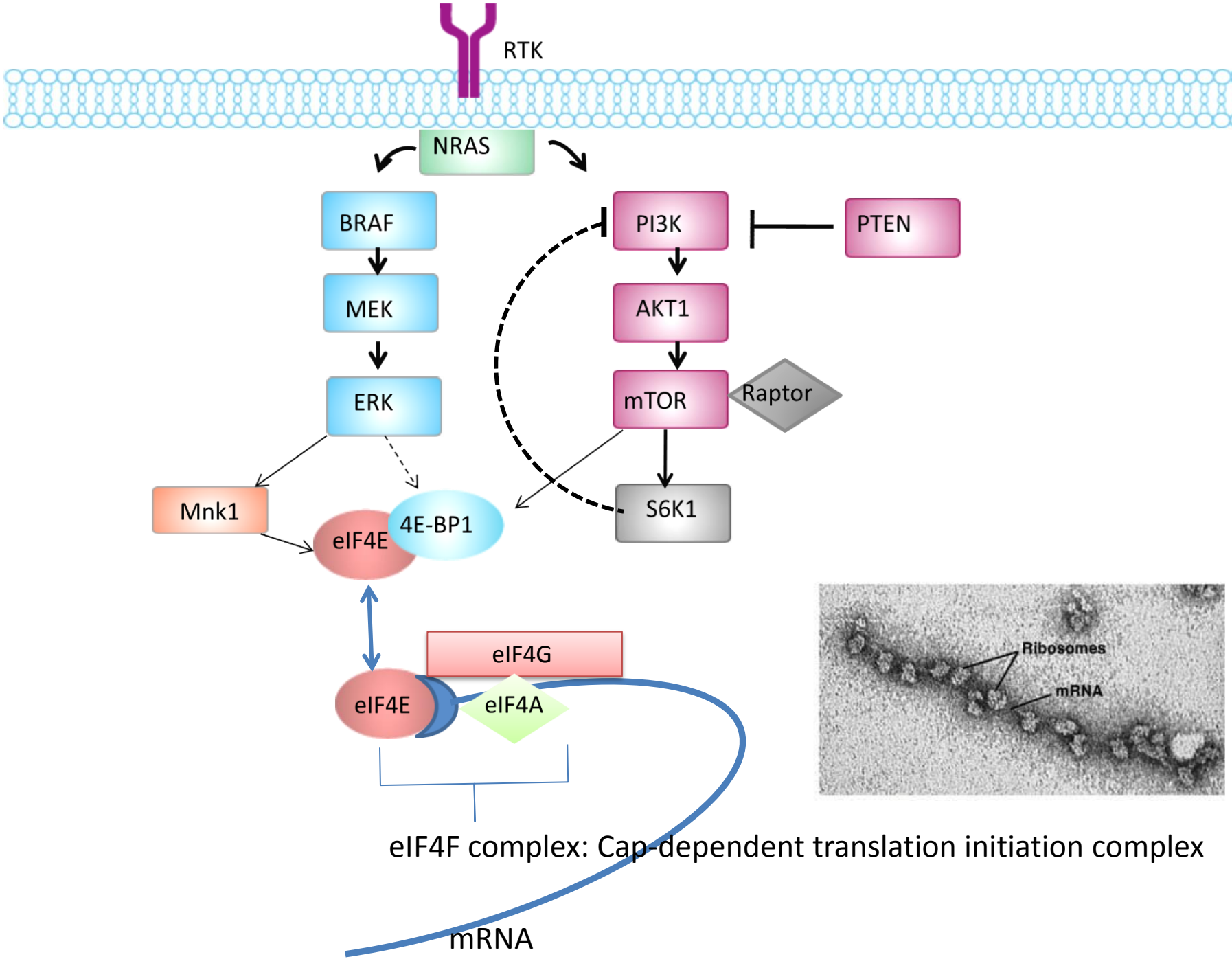
Re-activation of the MAPK pathway

- Splice variants of BRAF
- Raf proteins dimerization
- NRAS or MEK mutation
- COT activation

Poulikakos et al Nature 2010
Nazarian et al.. Nature. 2010
Johannessen et al. Nature. 2010
Poulikakos et al. Nature. 2011
Wagle et al. J Clin Oncol. 2011
Lito Cancer Cell 2012
Shi et al. Cancer Discovery 2013

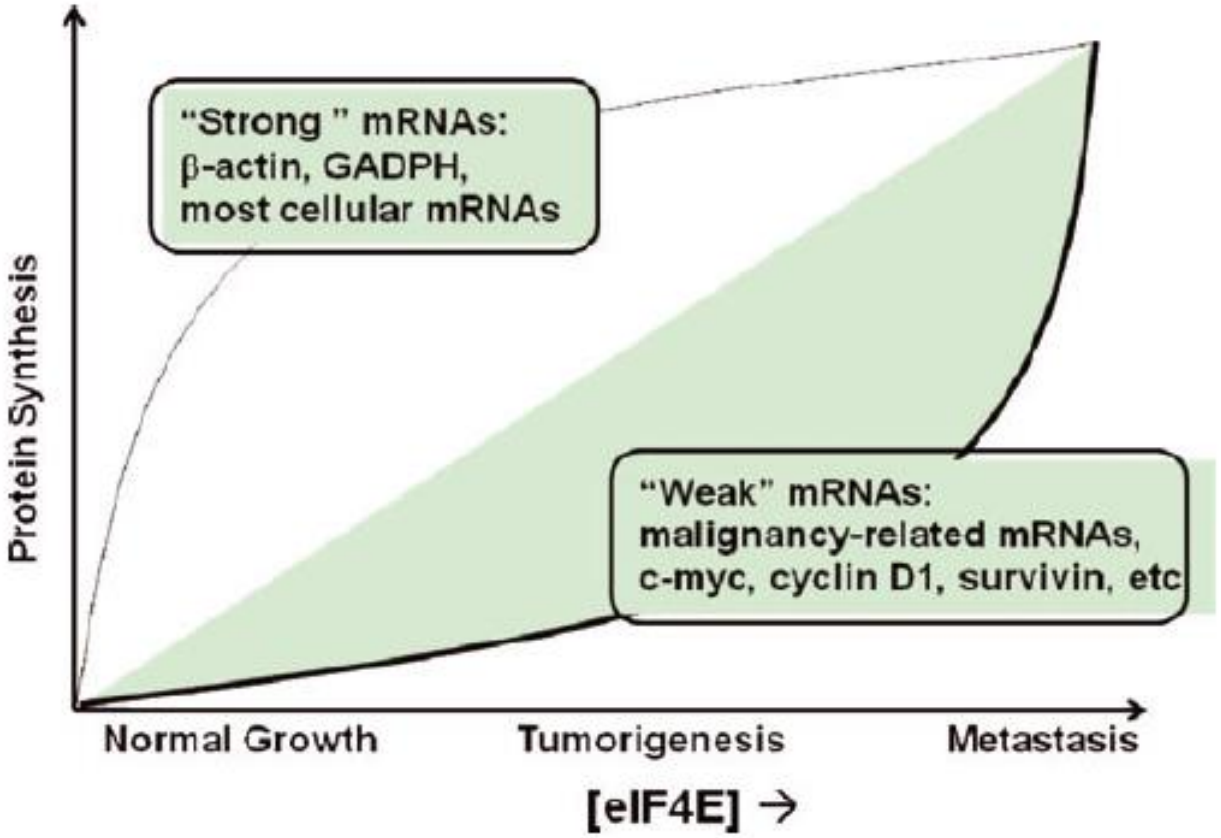
Cell growth, prolif, survival


PDGFR; IGF-1R, EGFR, MET
BRAF-I
NRAS
CRAF
BRAF*
MEK
ERK
PI3K*
PTEN
AKT1
mTOR
IκB
NFκB
Cyclin D
CDK4/6
Rb
E2F
Cell growth, prolif, survival
26%
52%
18%
4%
Mechanisms detected
Only MAPK
Only PI3K–PTEN–AKT
Both core pathways
Villanueva et al. Cancer Cell. 2010
Jiang et al. Clin Cancer Res. 2010
Shi et al., Cancer Res. 2011
Shi et al Cancer Discov 2013
Girotti et al, Cancer Discovery 2013

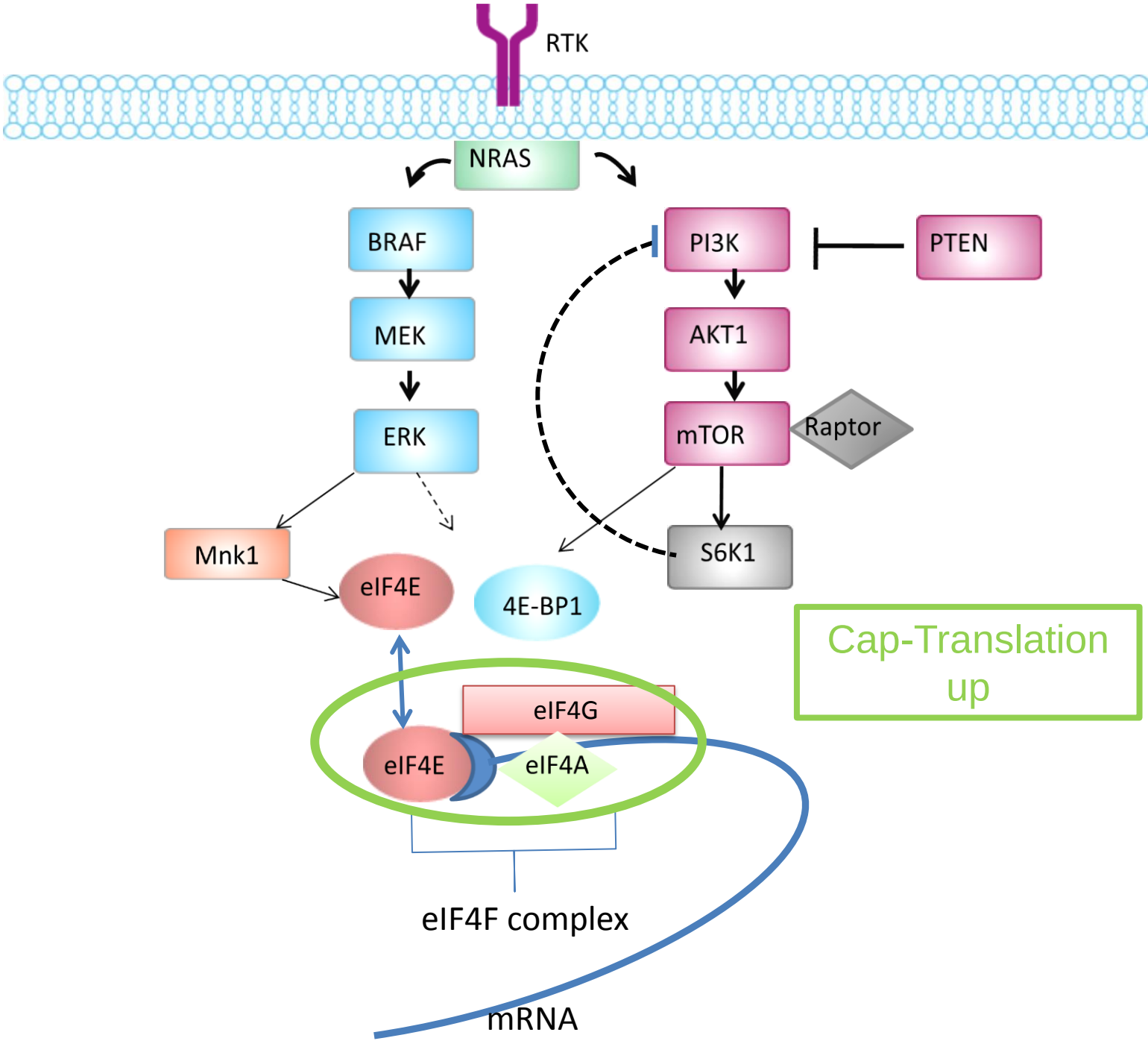


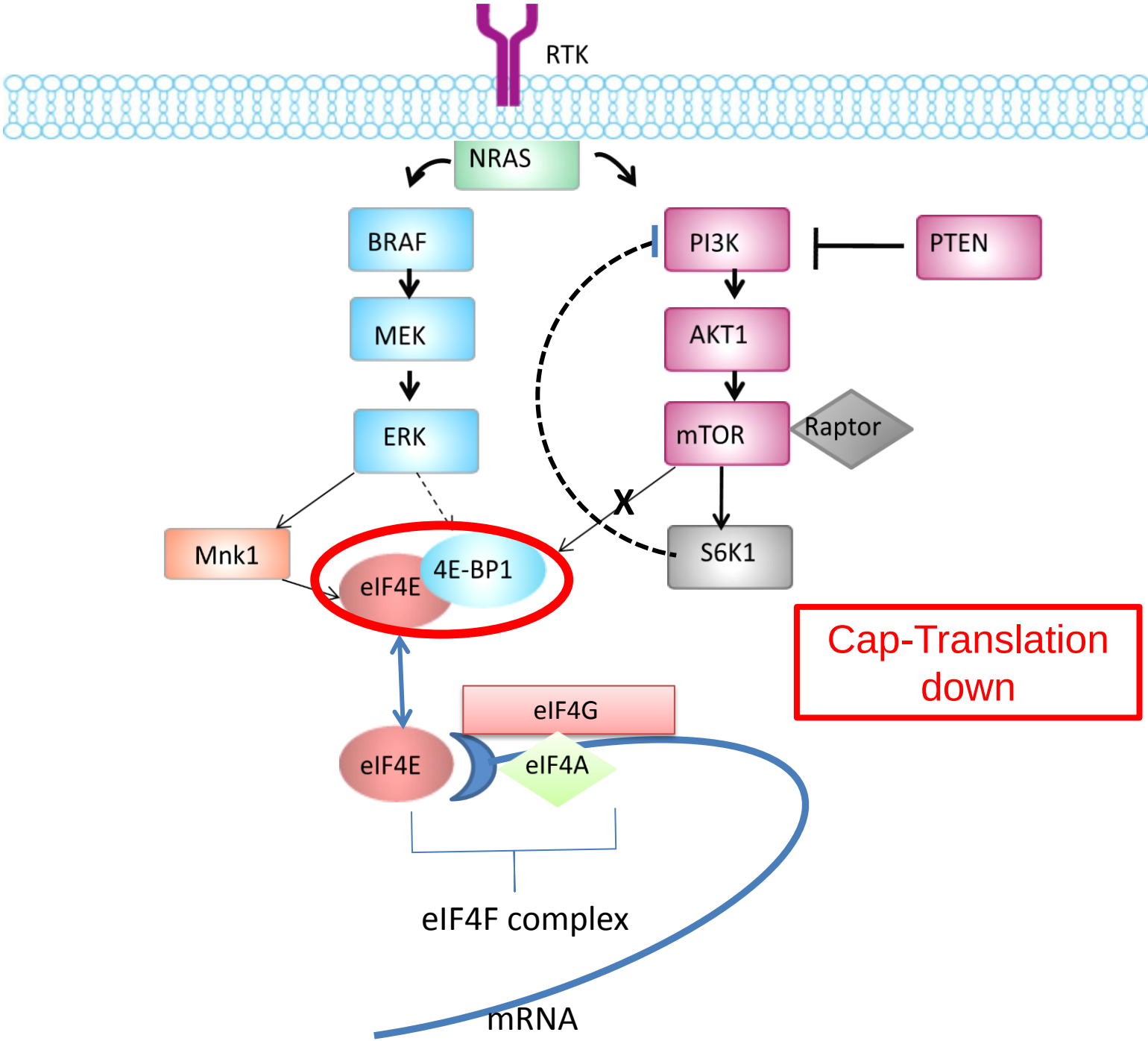
eIF4F complex: Cap-dependent translation initiation complex

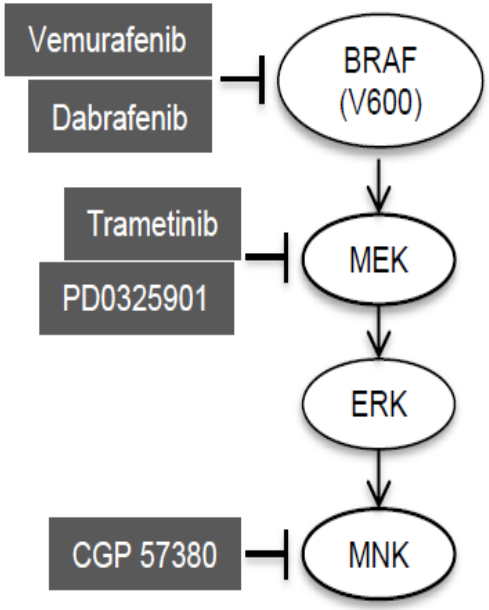
mRNA dependence of the eIF4F complex is variable

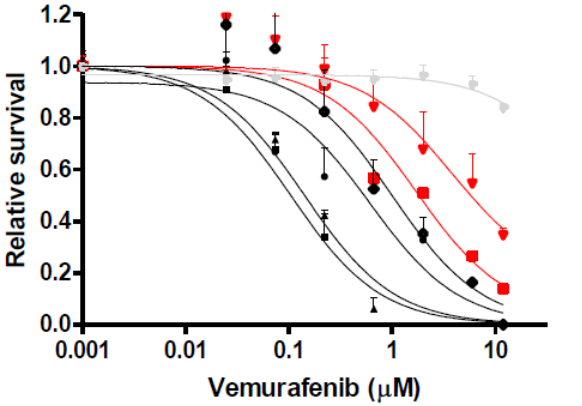


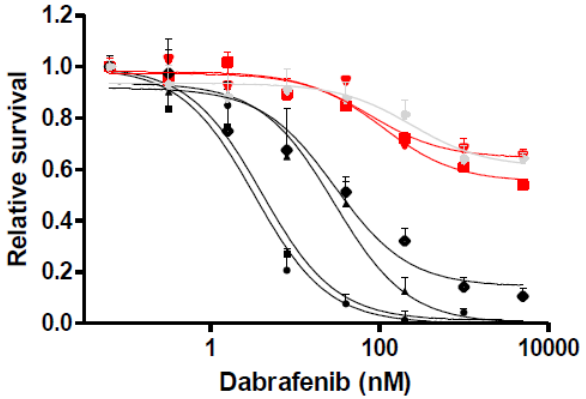
Jia et al Med Res Rev 2012

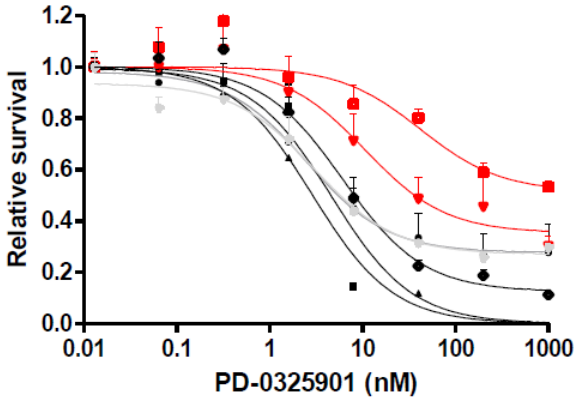

RTK
NRAS
BRAF
MEK
ERK
PI3K
PTEN
AKT1
mTOR
Raptor
S6K1
Mnk1
eIF4E
4E-BP1
eIF4G
eIF4E
eIF4A
eIF4F complex
mRNA
Cap-Translation up

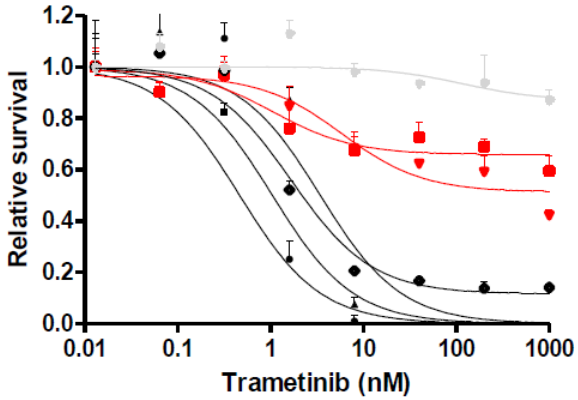

RTK
NRAS
BRAF
MEK
ERK
PI3K
PTEN
AKT1
mTOR
Raptor
S6K1
Mnk1
eIF4E
4E-BP1
eIF4G
eIF4E
eIF4A
eIF4F complex
mRNA
Cap-Translation down

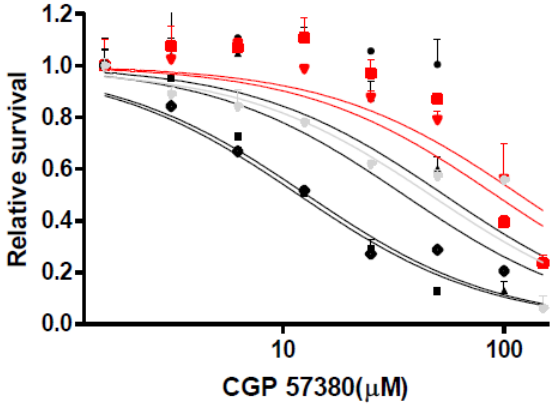


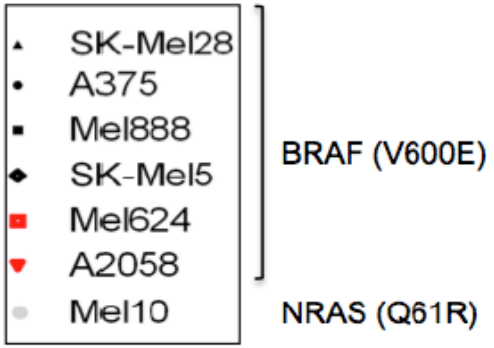




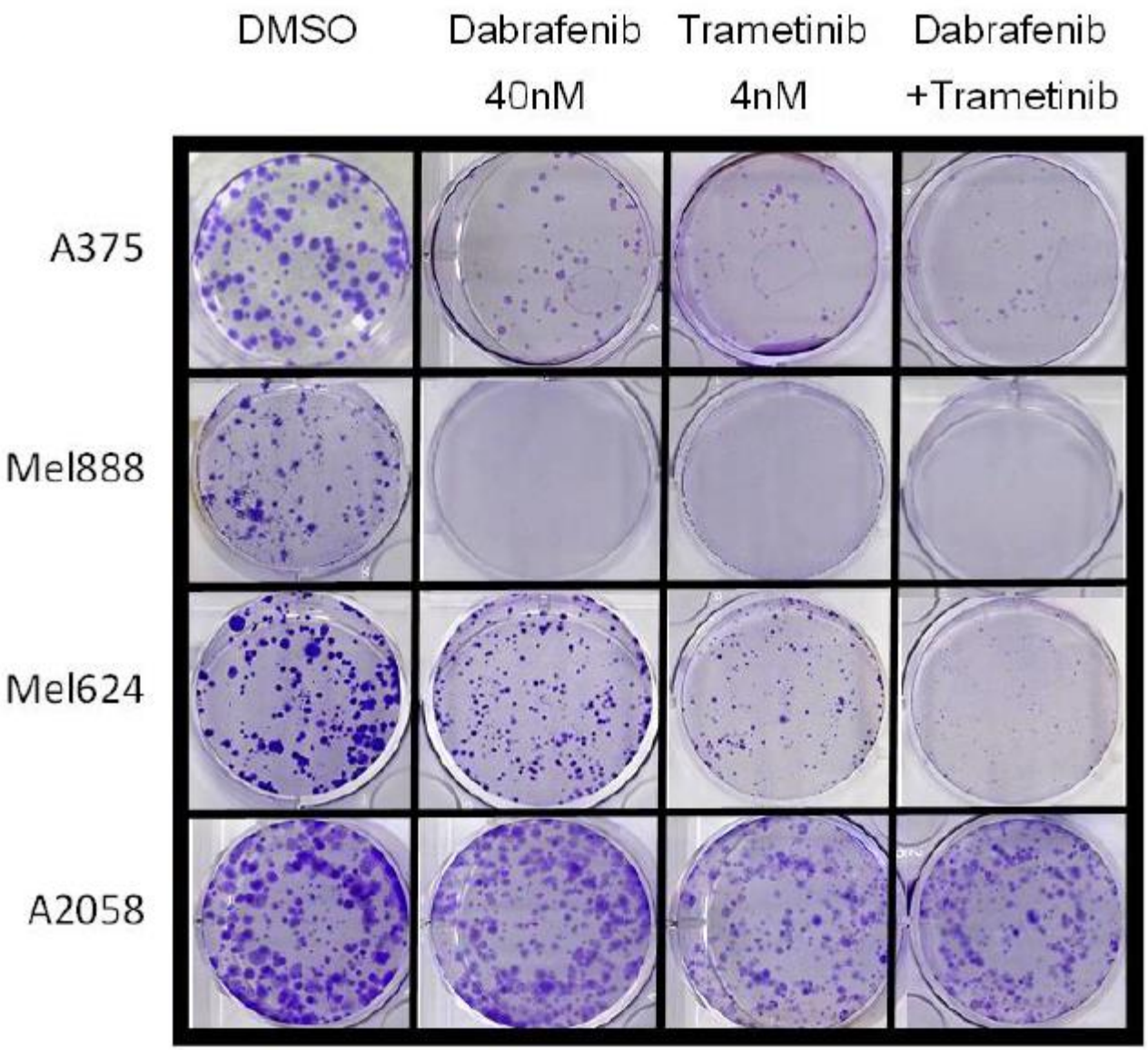




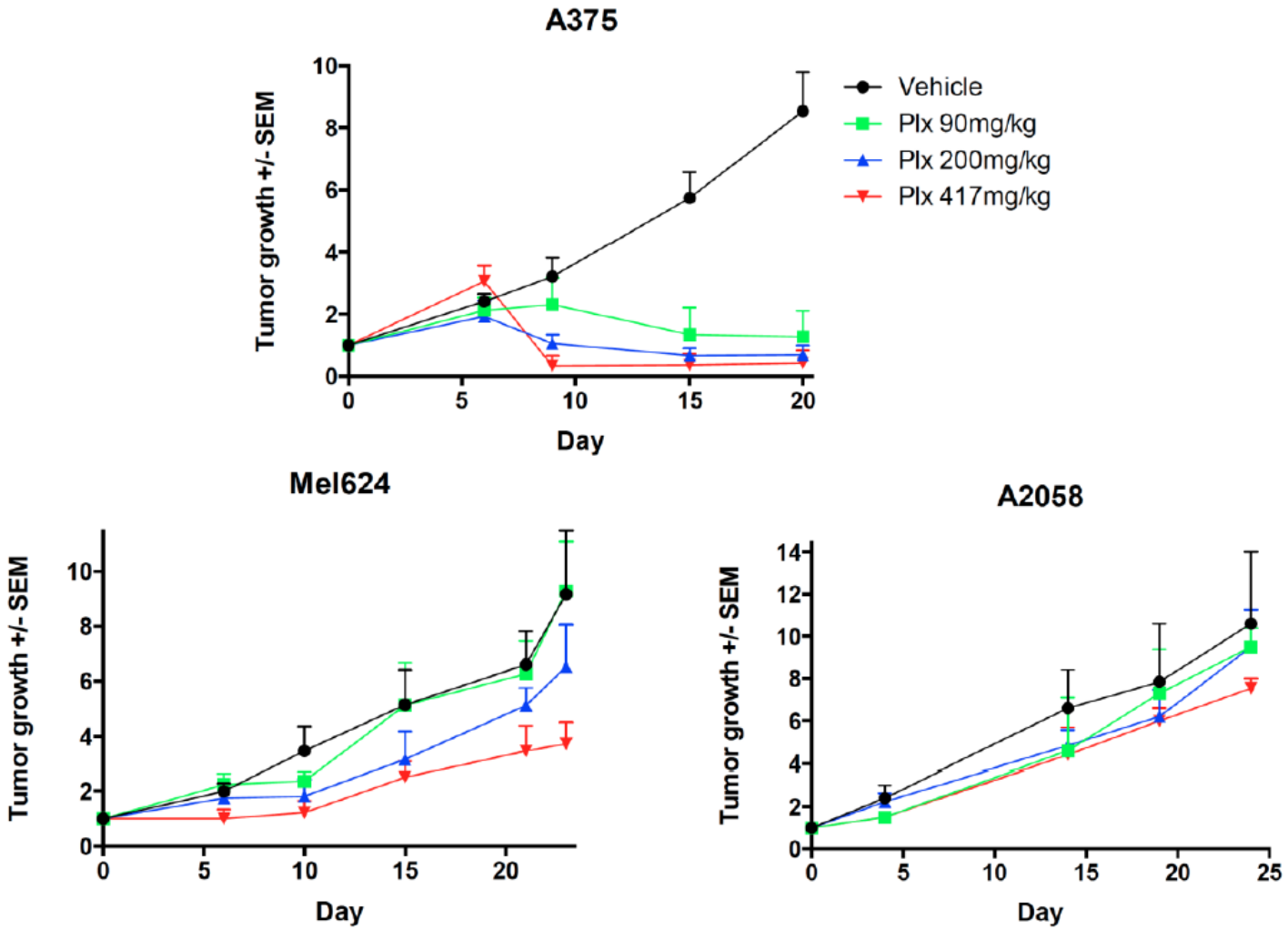




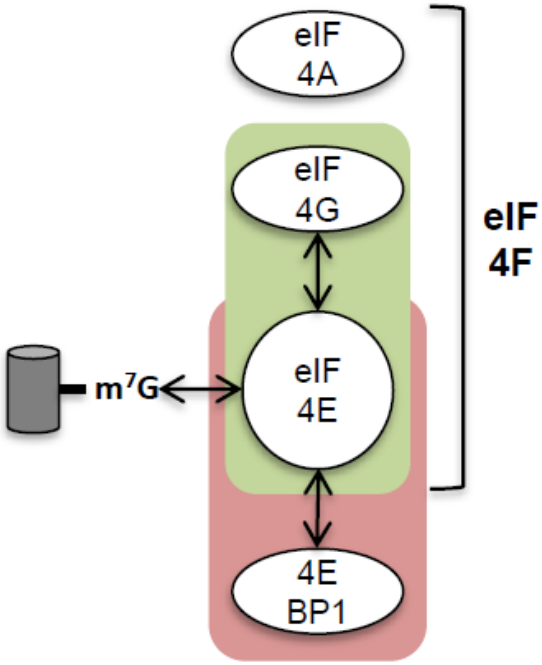
Mel624	A2058
TP53; CDK4; CTNNB1; FGFR4	MAP2K1; PTEN; TP53; STK11


DMSO
Dabrafenib 40nM
Trametinib 4nM
Dabrafenib +Trametinib
A375
Mel888
Mel624
A2058

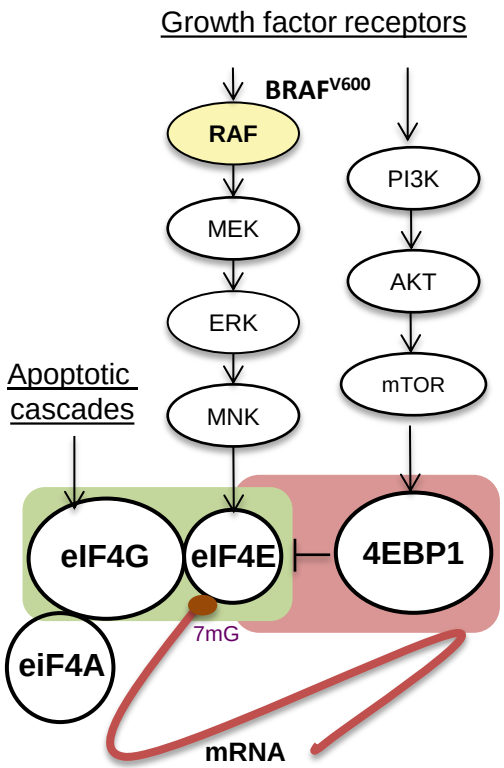
Xenograft models

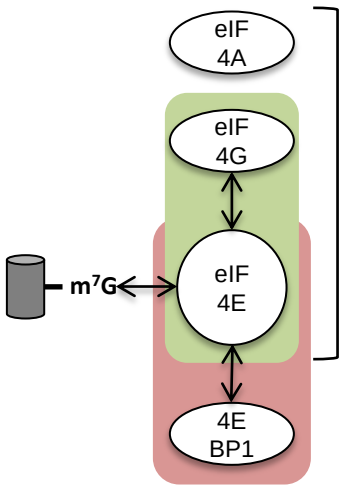


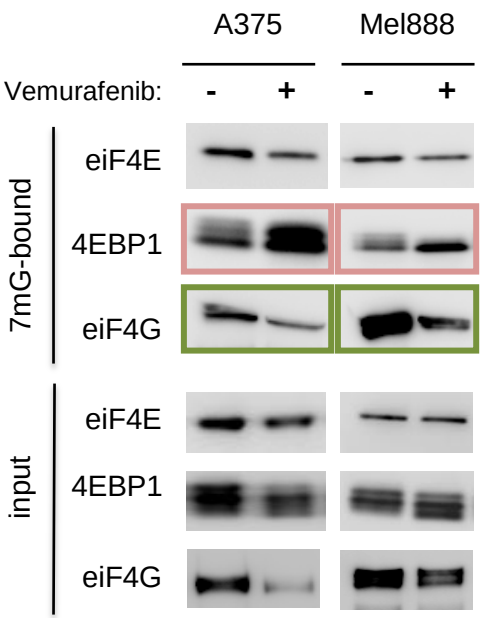
Cap-binding assay:
Capture of eIF4E and its ligands on synthetic m7GTP-sepharose beads



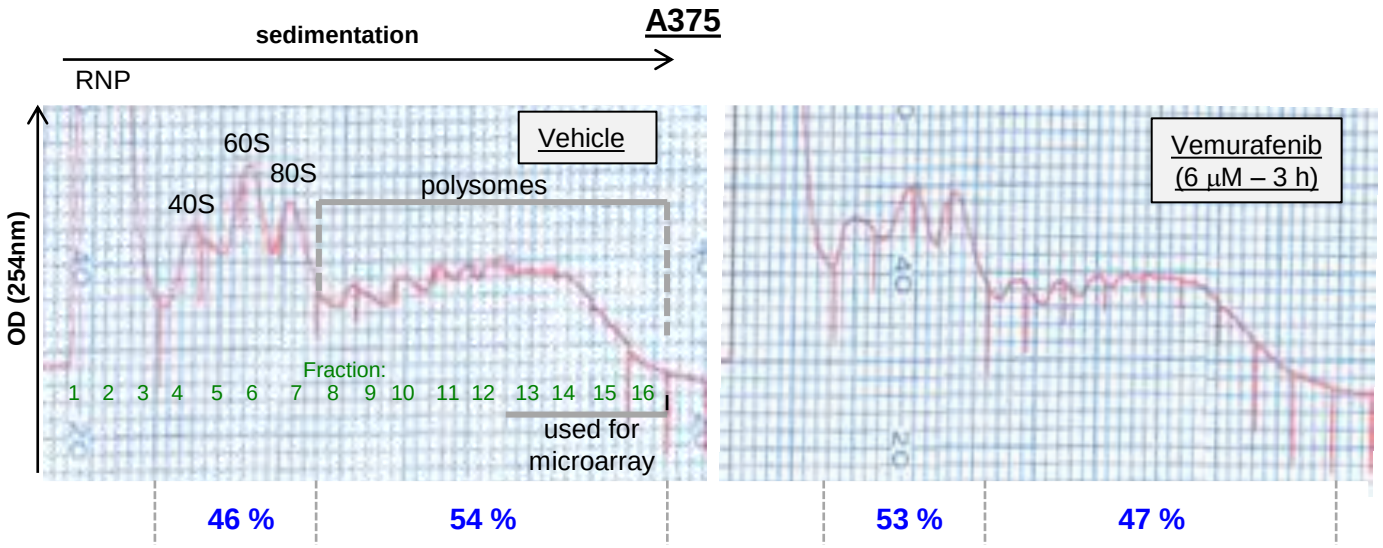
Vemurafenib leads to a decrease in the formation of the eIF4F complex

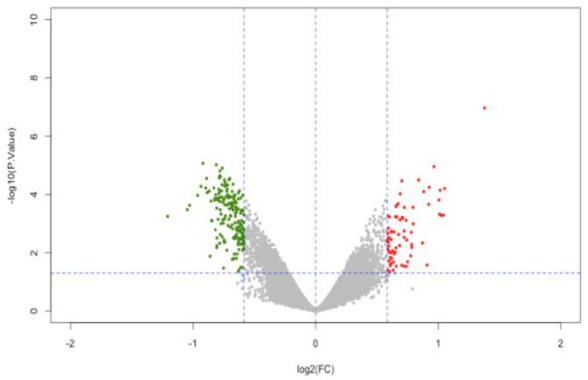






Vemurafenib does not lead to a general decrease in protein synthesis but to specific regulation of mRNA translation





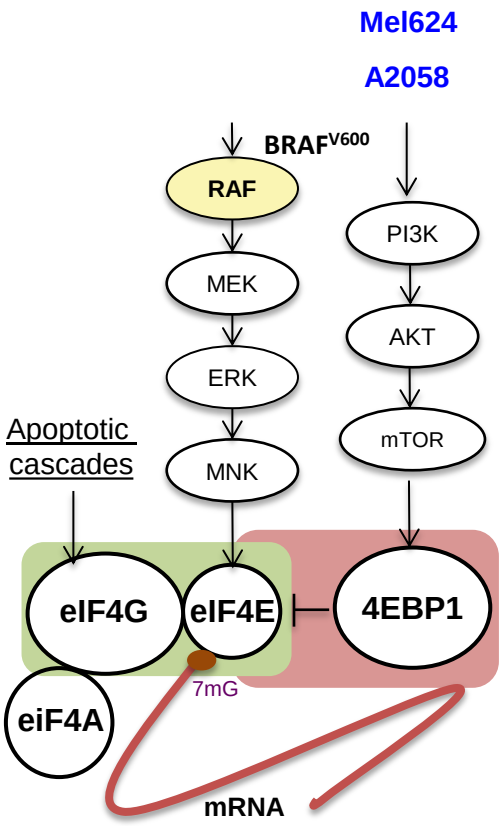
Downregulated TOP mRNAs

EEF1G
EEF1A1
EIF3F
RPS14
RPS18
RPS4X
HNRNPA1
TPT1
RPS10P7
RPS3
RPS3A
RPL13A
RPL7A
RPL21P44

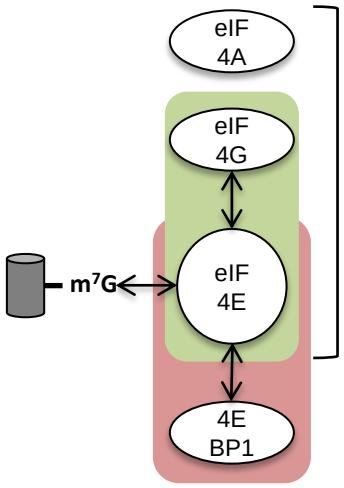
Other downregulated mRNAs encoding ribosomal proteins and translation factors

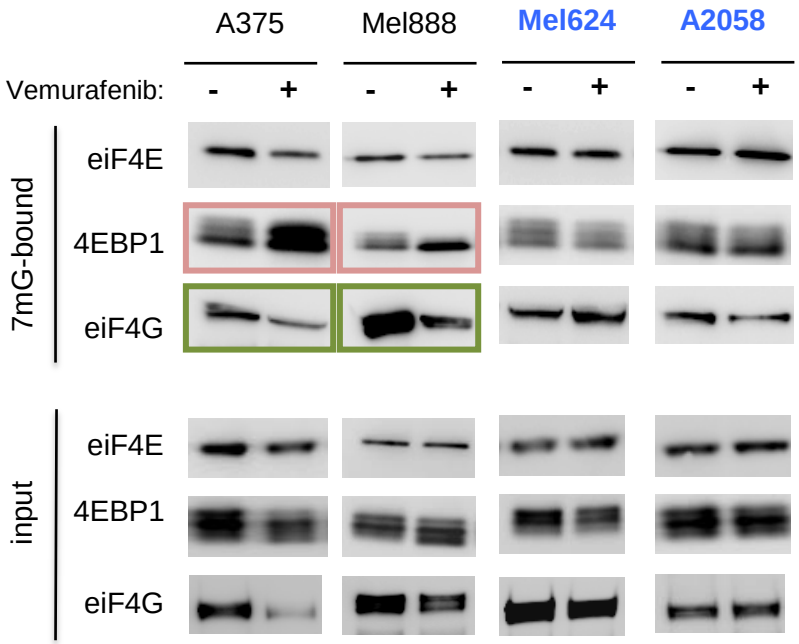
EIF3L
RPS6
RPSA
RPS8
RPSAP52
RPL13
RPL10
RPL10L
RPL13AP3
RPL3

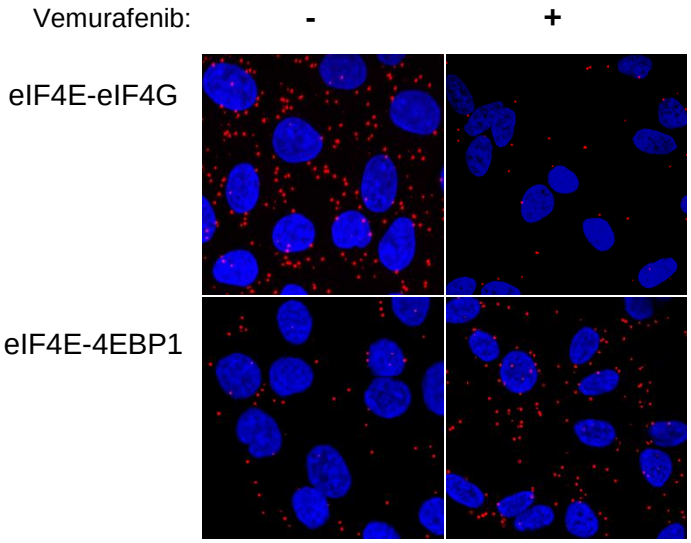
The persistance of the eIF4F complex is associated with resistance to Vemurafenib



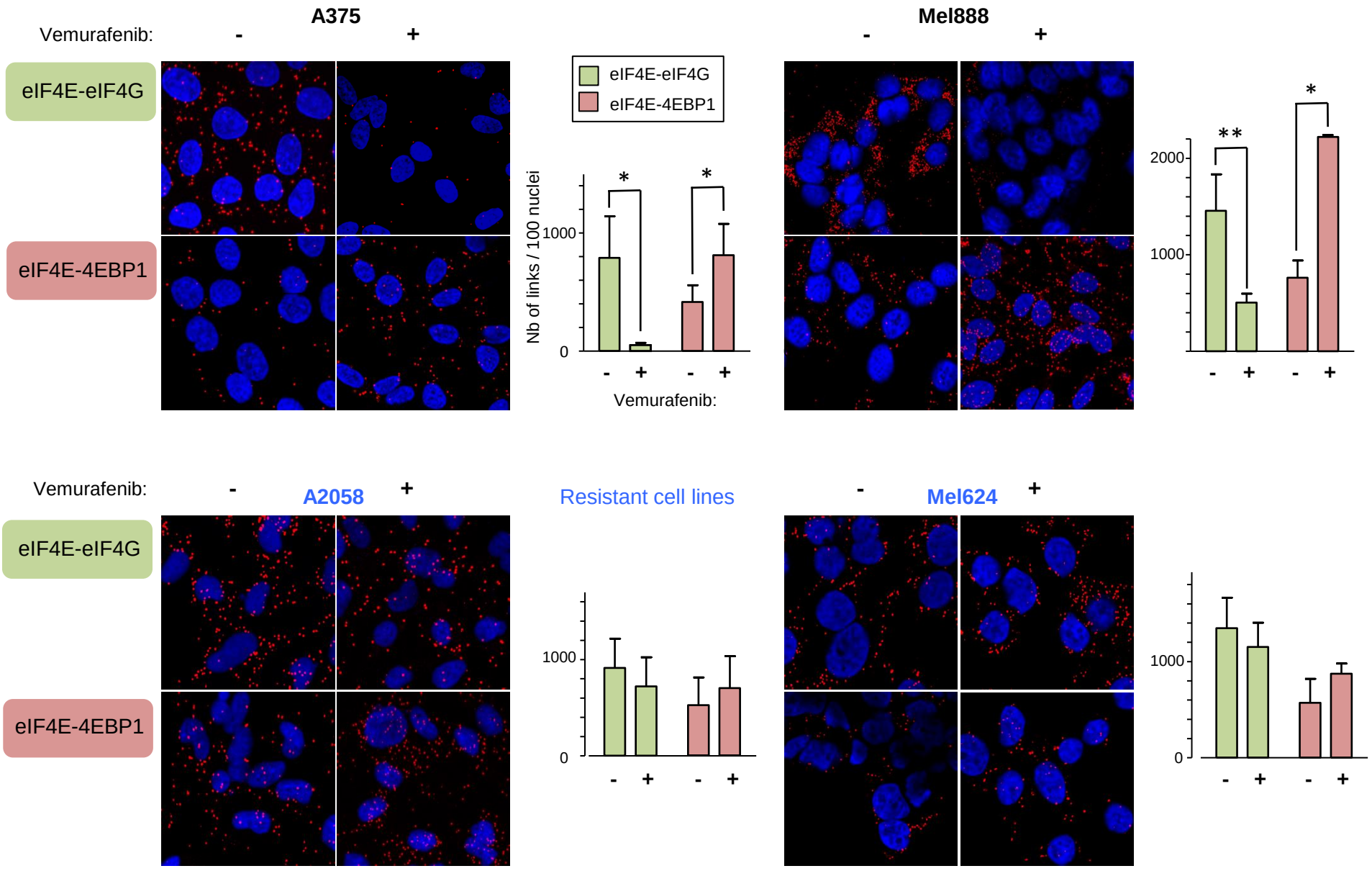
Cap-binding assay



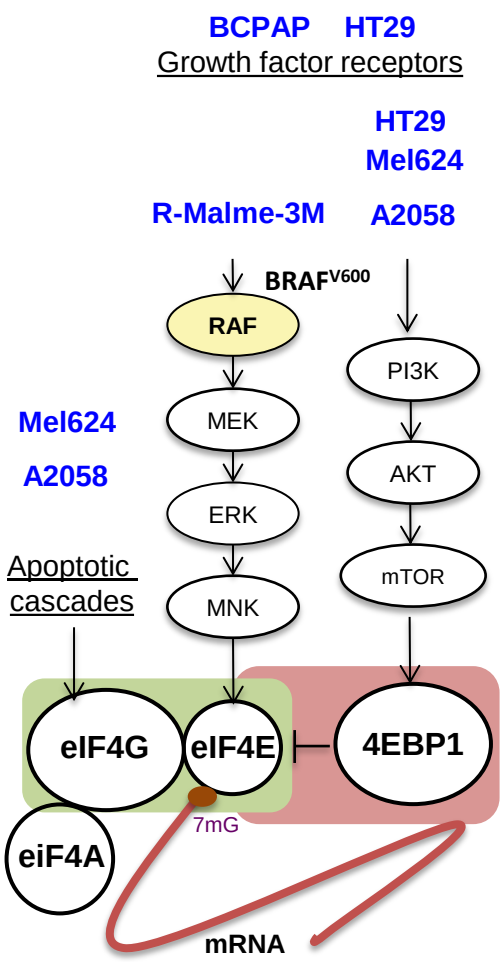


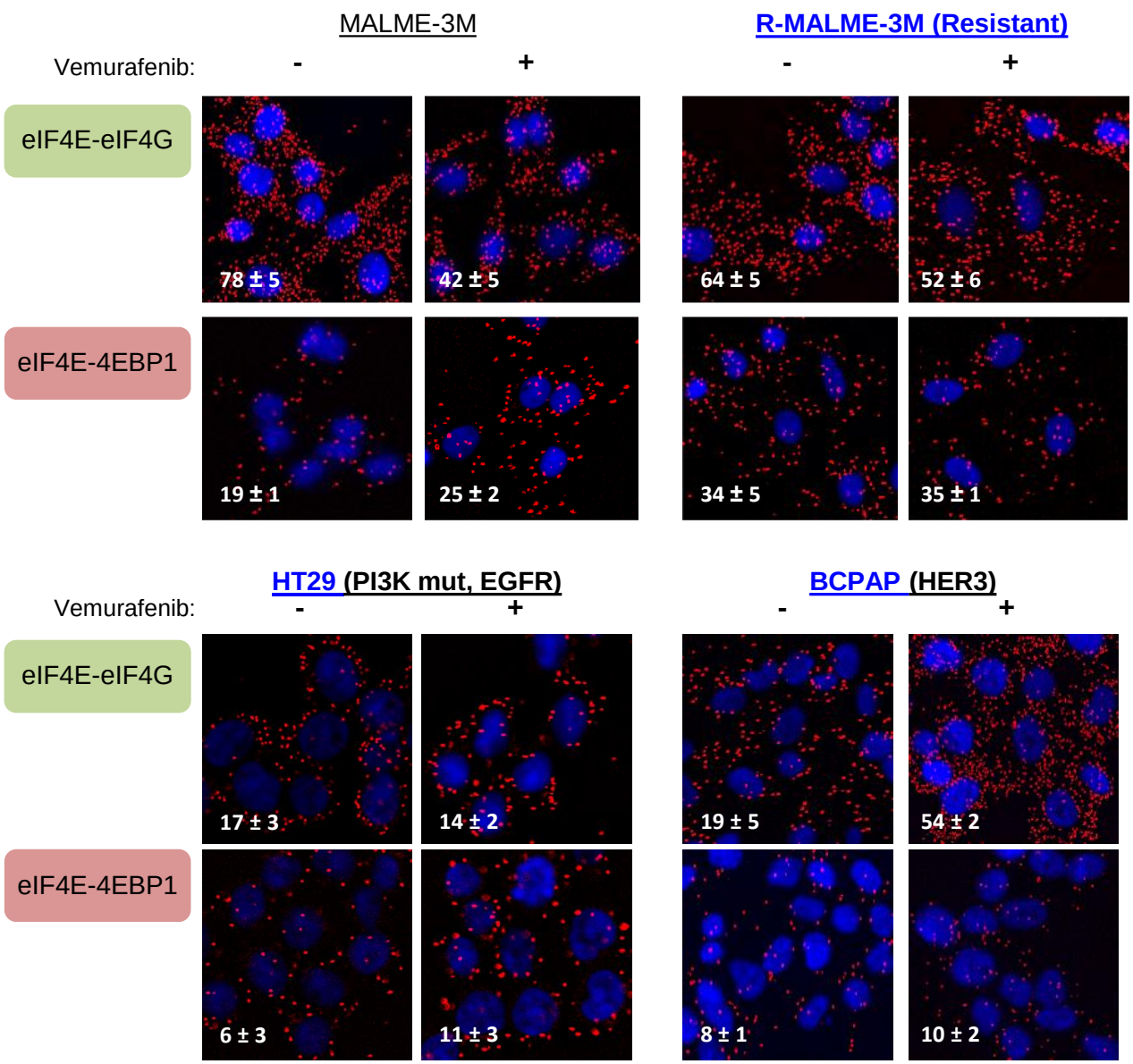

Vemurafenib:
-
+
eIF4E-eIF4G
eIF4E-4EBP1

The formation of the eIF4F complex is associated with resistance to Vemurafenib

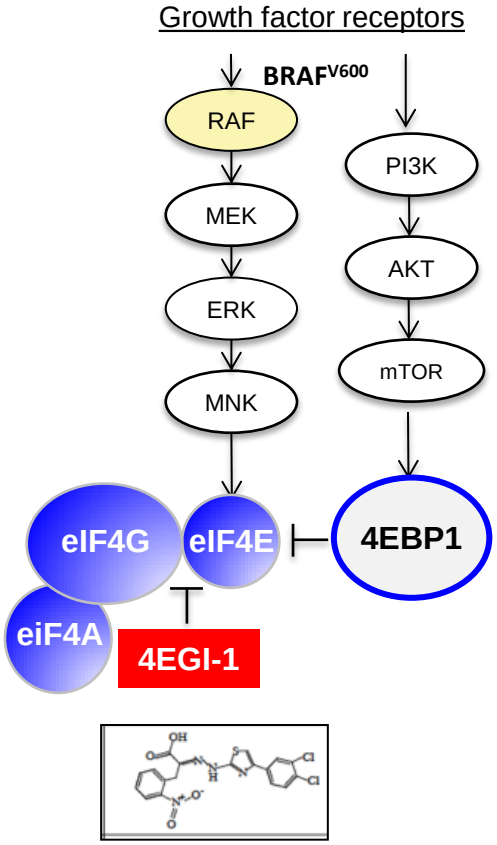


The formation of the eIF4F complex is associated with multiple mechanisms of resistance to Vemurafenib

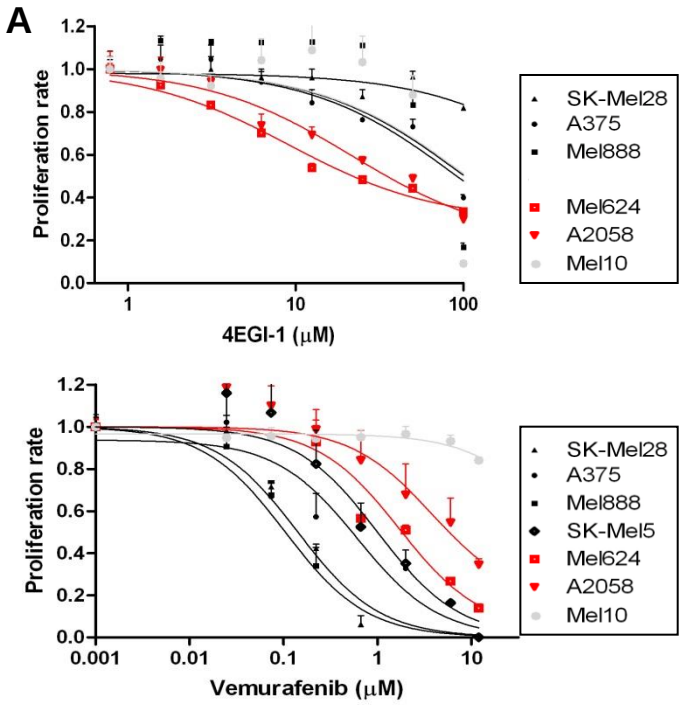


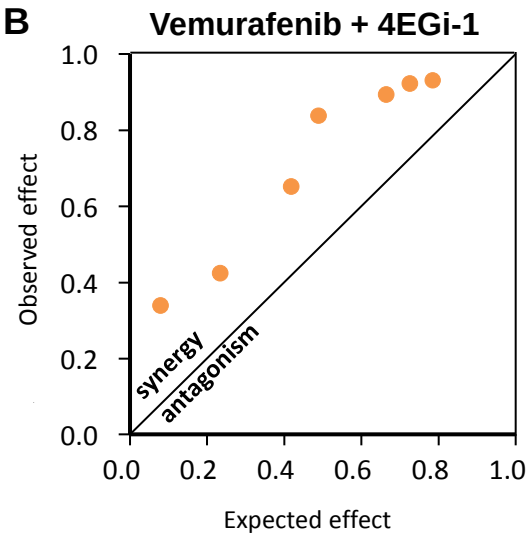


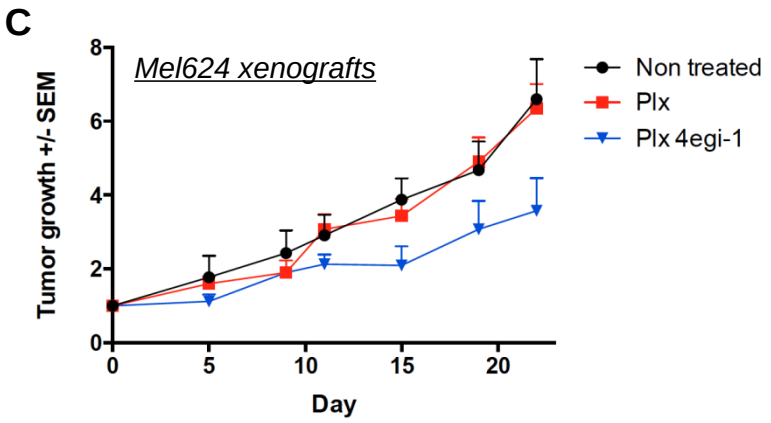
The formation of the eIF4F complex is directly involved in the sensitivity to vemurafenib

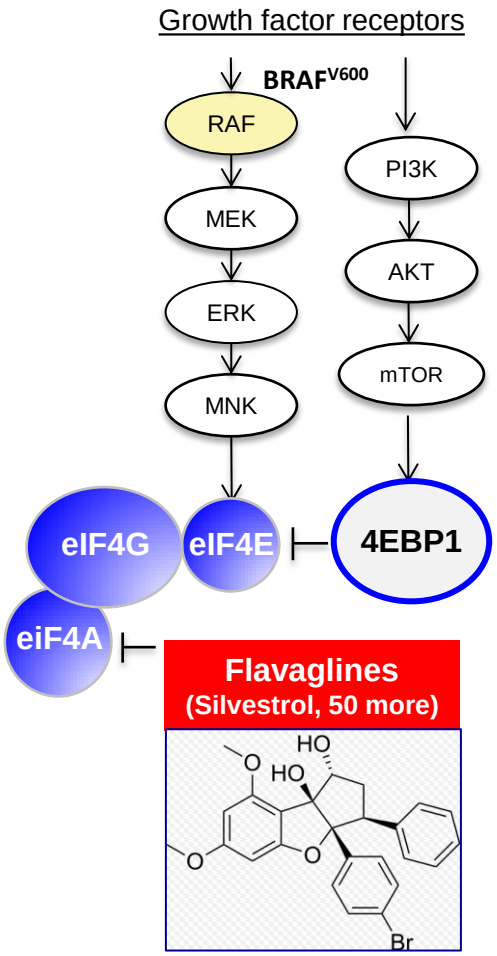


Moerke et al., Cell 2007

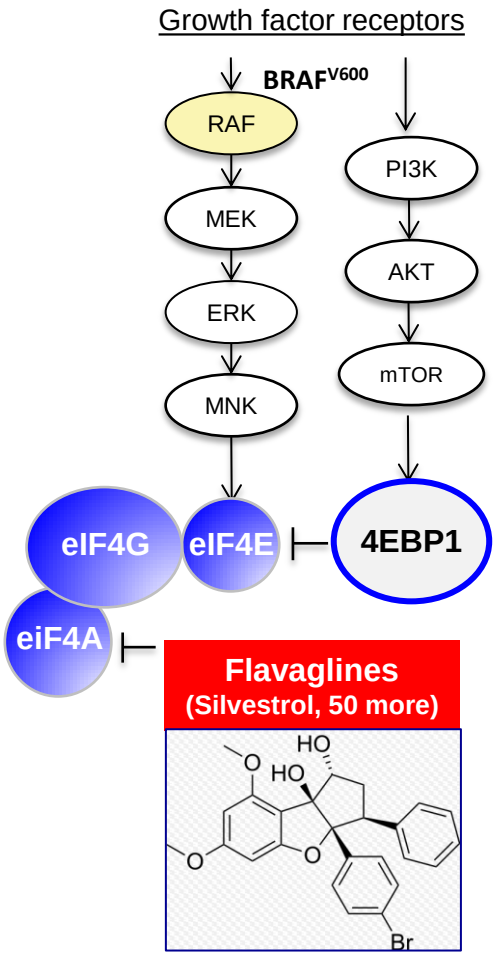


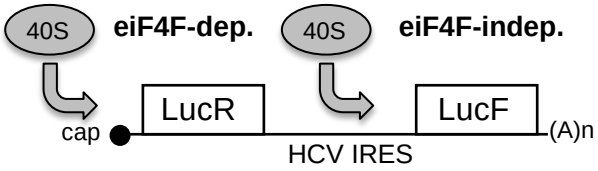






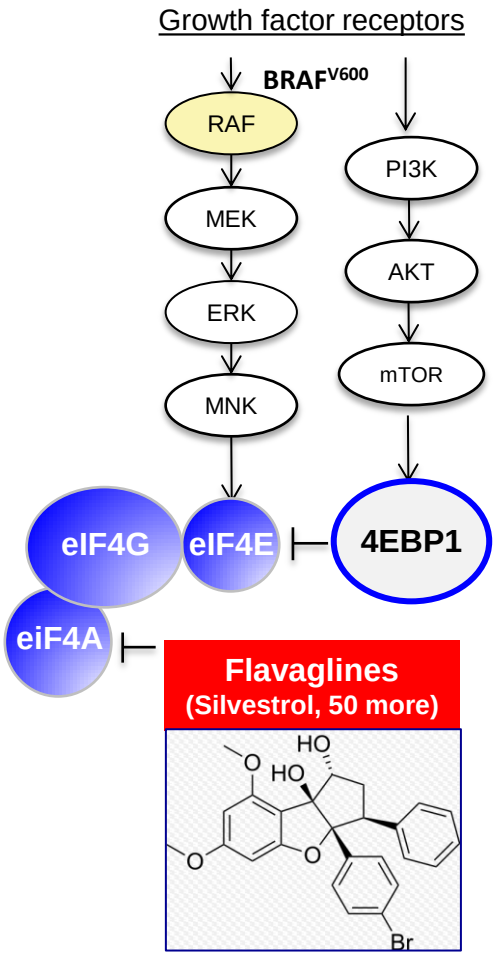
Collab: L. Desaubry (Strasbourg)

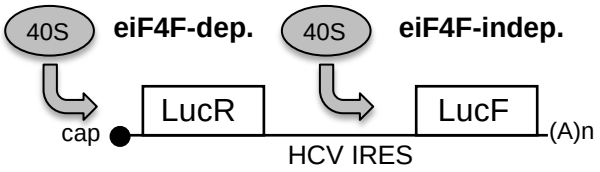


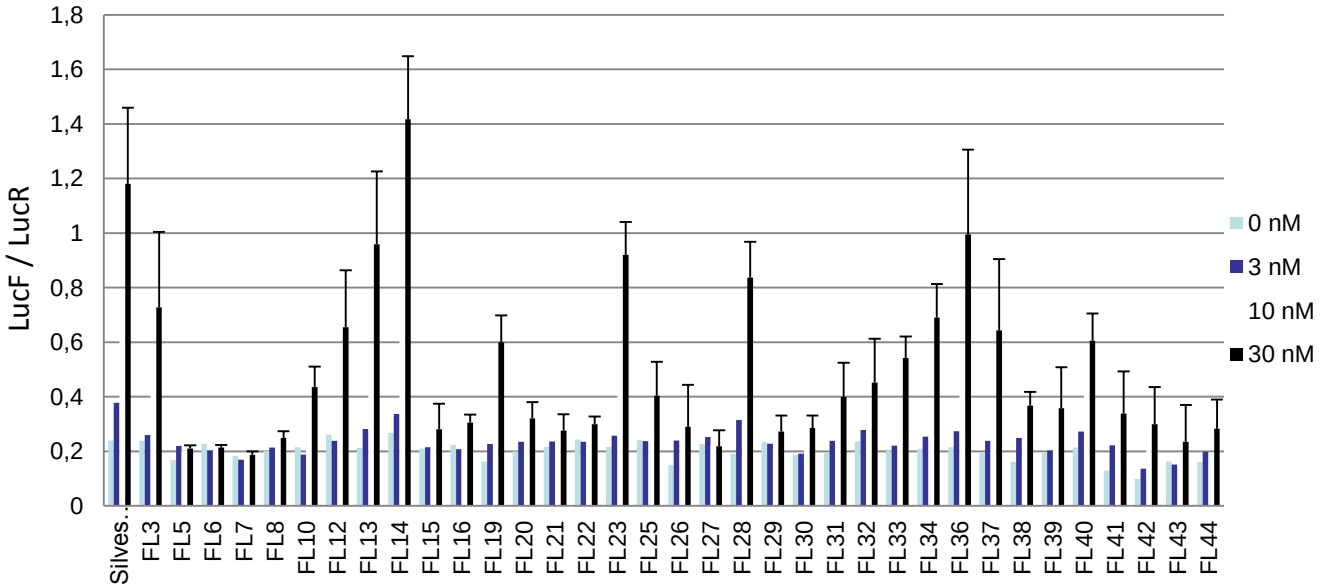


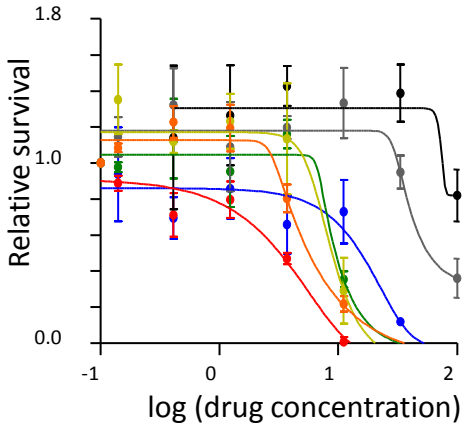
Collab: L. Desaubry (Strasbourg)

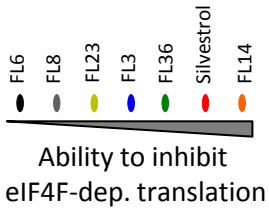
The ability of flavaglines derivatives to inhibit eIF4F-dependent translation correlates with their ability to inhibit cell proliferation





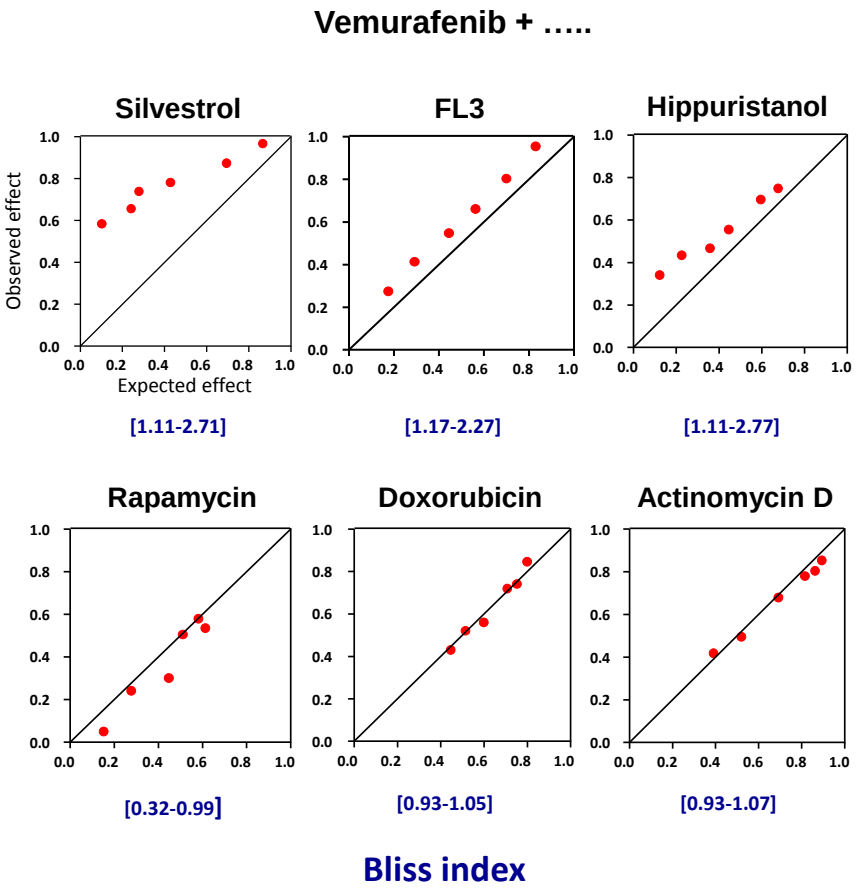


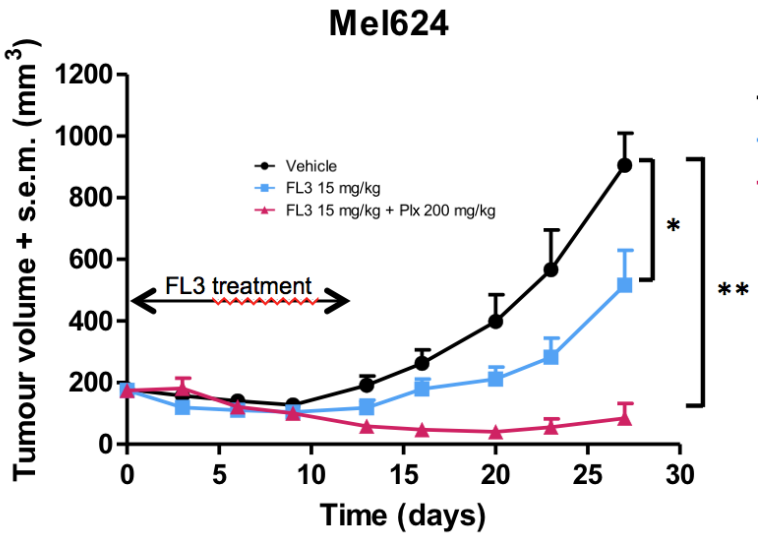




Collab: L. Desaubry (Strasbourg)

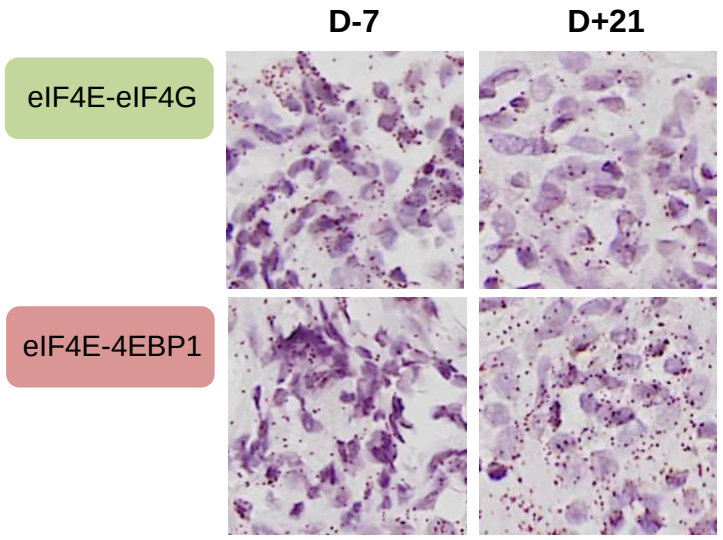
Vemurafenib and eIF4A inhibitors have a synergistic effect on cell proliferation and tumor growth



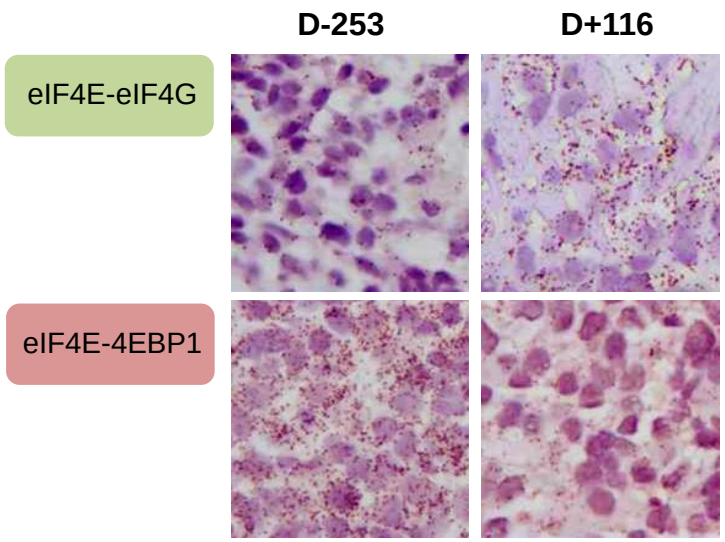


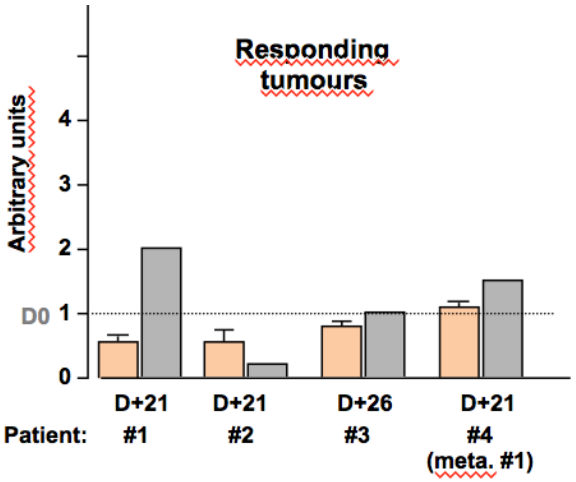
Increase of eIF4F complex formation is associated with resistance to anti-BRAF in patients

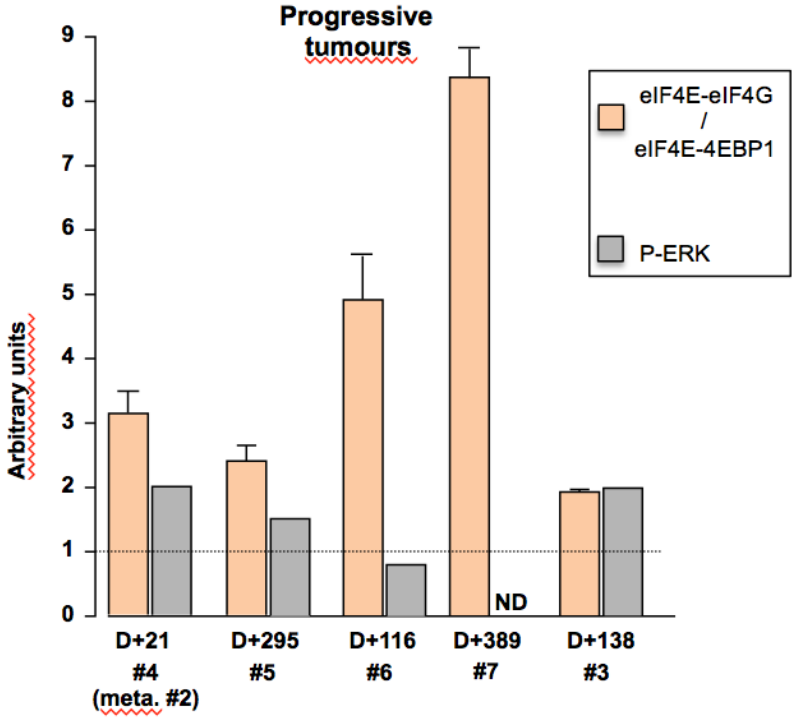
Patient #1 (Responding tumour)



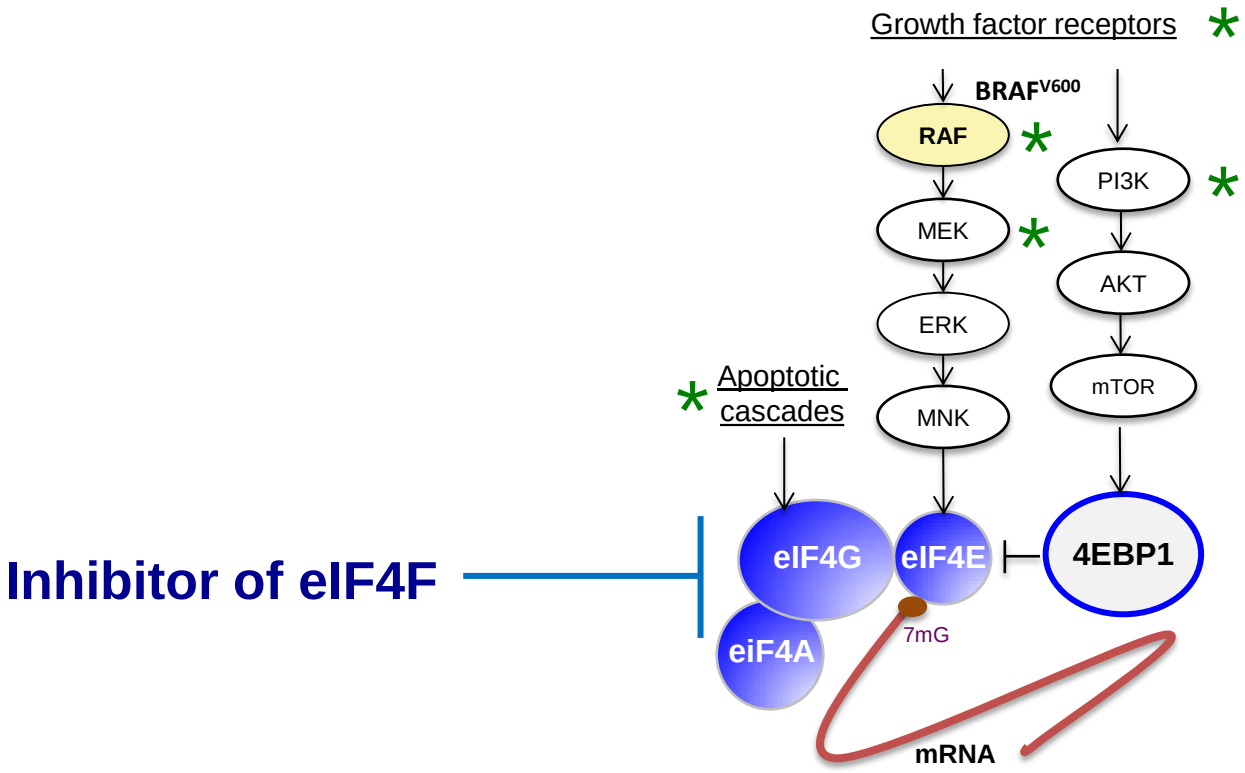
Patient #6 (Progressive tumour)







eIF4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies



Boussemart, Malka-Mahieu, Girault et al., Nature 2014

LETTER

doi:10.1038/nature13572

eIF4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies

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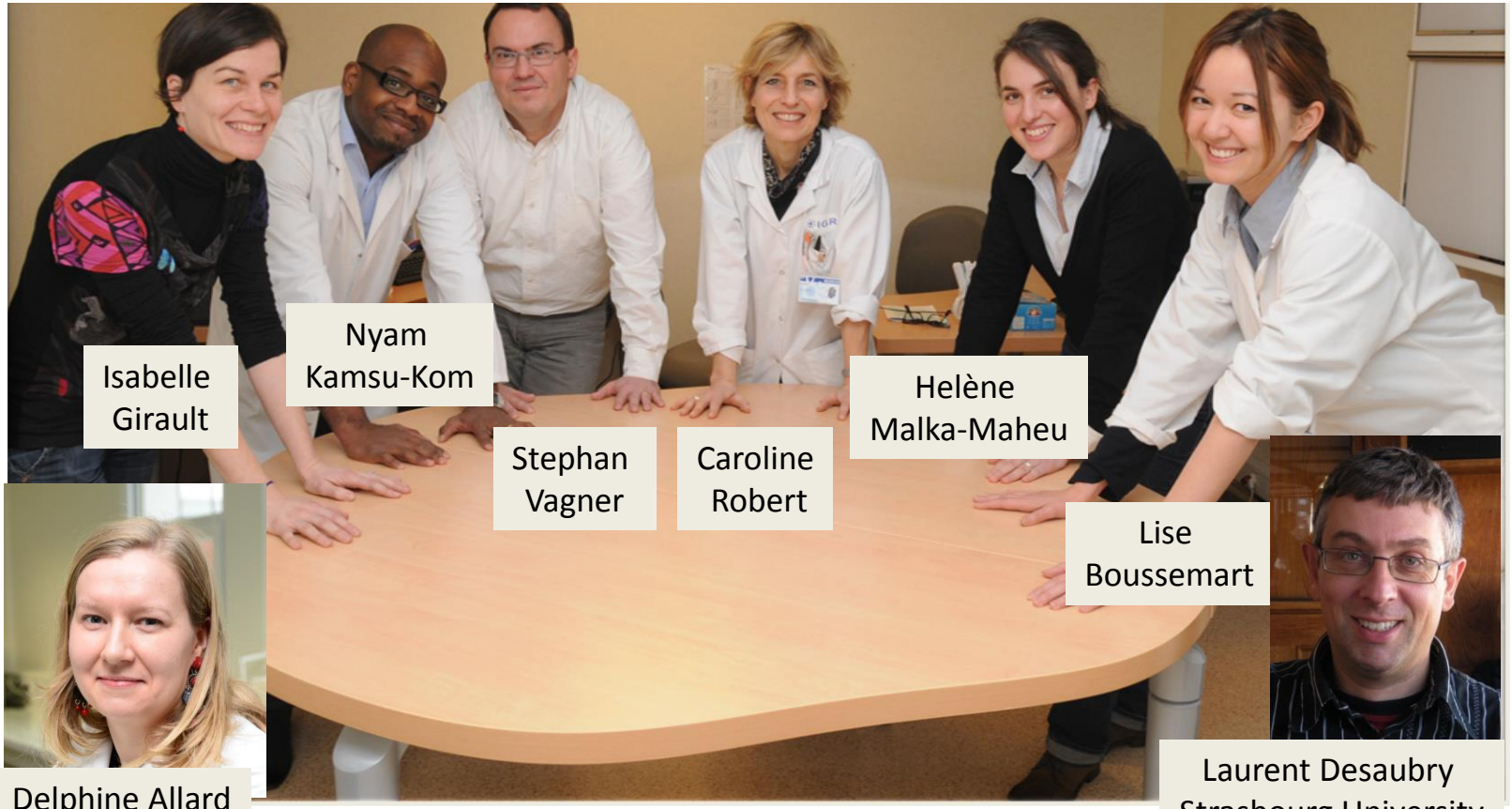

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