Oxford Biomedical Research Centre

Oxford Radcliffe Hospitals NHS
NHS Trust

UNIVERSITY OF OXFORD

NHS
National Institute for Health Research

PLX4032 and follow up molecules

Mark Middleton
Oxford NIHR Biomedical Research Centre

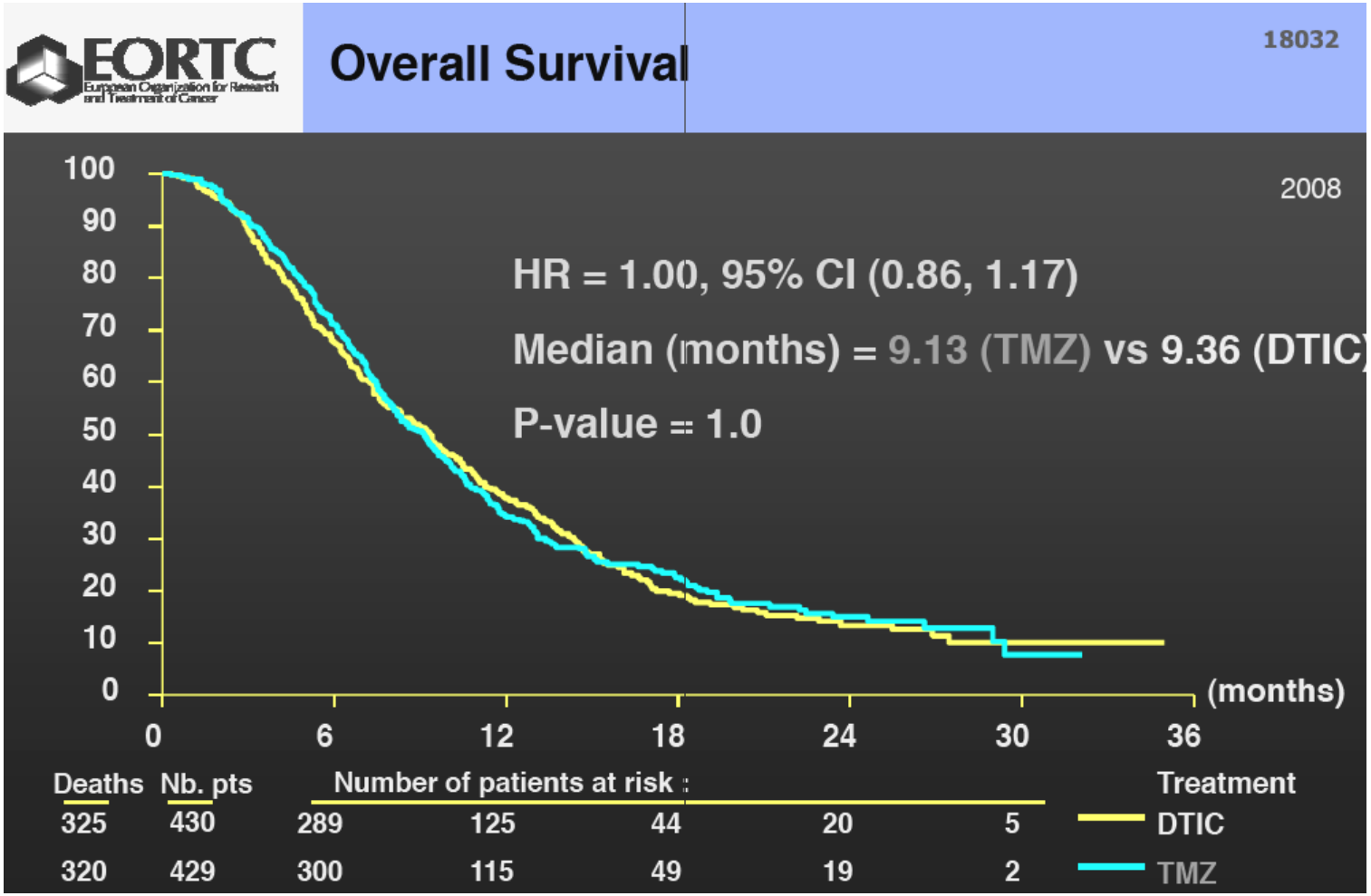
Disclosures

Research Funding	*Astrazeneca, GlaxoSmithKline, Sanofi*
Consultancy	*Astrazeneca, Roche, BMS, Clovis, Merck (Schering Plough)*
Speaker	*Roche, Merck, Astrazeneca, Orphans*
Swedish	

Approved Melanoma Treatment 2009

Stage 1, early stage 2	Surgery
Late stage 2	Surgery, IFN
Stage 3	Surgery, IFN
Stage 4	Surgery, DTIC, IL-2
CNS disease	Surgery, Radiation

DTIC vs. TMZ


EORTC
European Organization for Research and Treatment of Cancer
Overall Survival
18032
2008
HR = 1.00, 95% CI (0.86, 1.17)
Median (months) = 9.13 (TMZ) vs 9.36 (DTIC)
P-value = 1.0
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
(months)
Deaths
Nb. pts
Number of patients at risk :
Treatment
325
430
289
125
44
20
5
DTIC
320
429
300
115
49
19
2
TMZ

Failed registration trials

Metastatic Disease

Temozolomide (twice)

Combination chemotherapy

Histamine/IL-2/IFN

Oblimersen

Tremelimumab

Sorafenib

Elesclomol

Effective therapies?

Current Experimental Approaches

Resistance modification	PARP, MEK inhibition
Targeted agents	MEK, BRAF inhibitors
Immunotherapy	anti-CTLA-4, PD-1

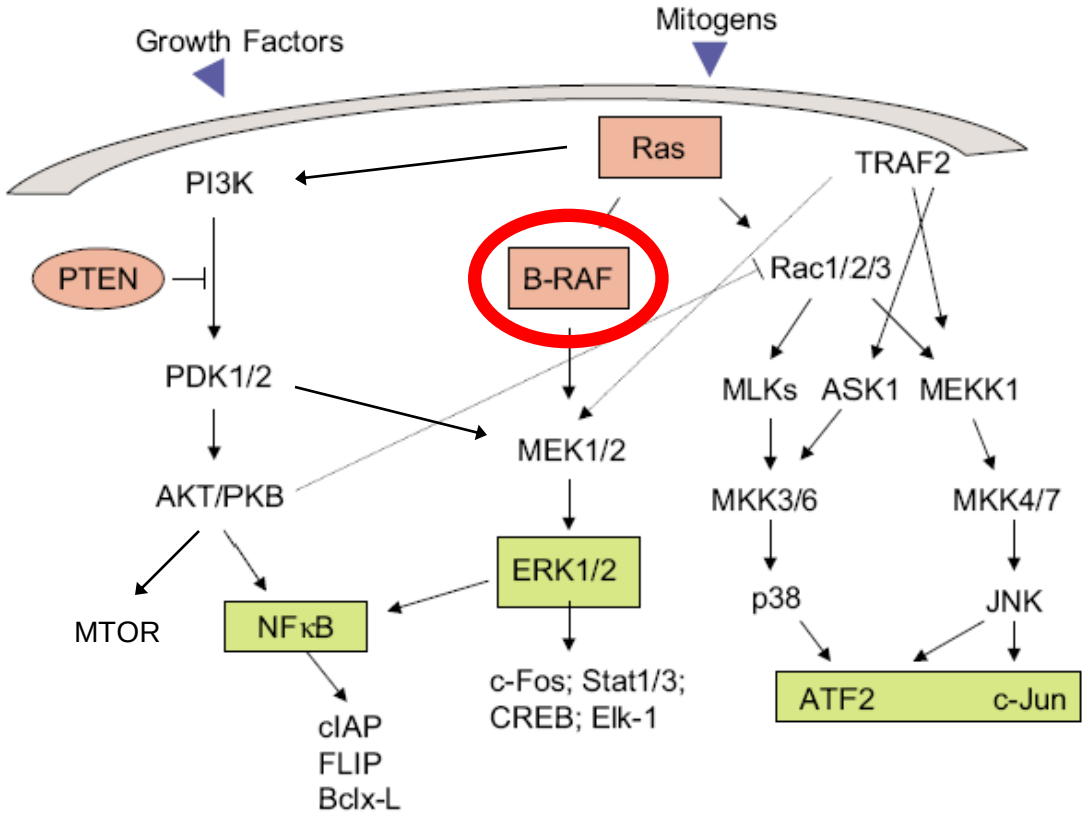
BRAF Inhibitors In Melanoma

Vemurafenib results published June 2011

GSK2118436 in late phase trials

Combination BRAF/MEK inhibition in the clinic

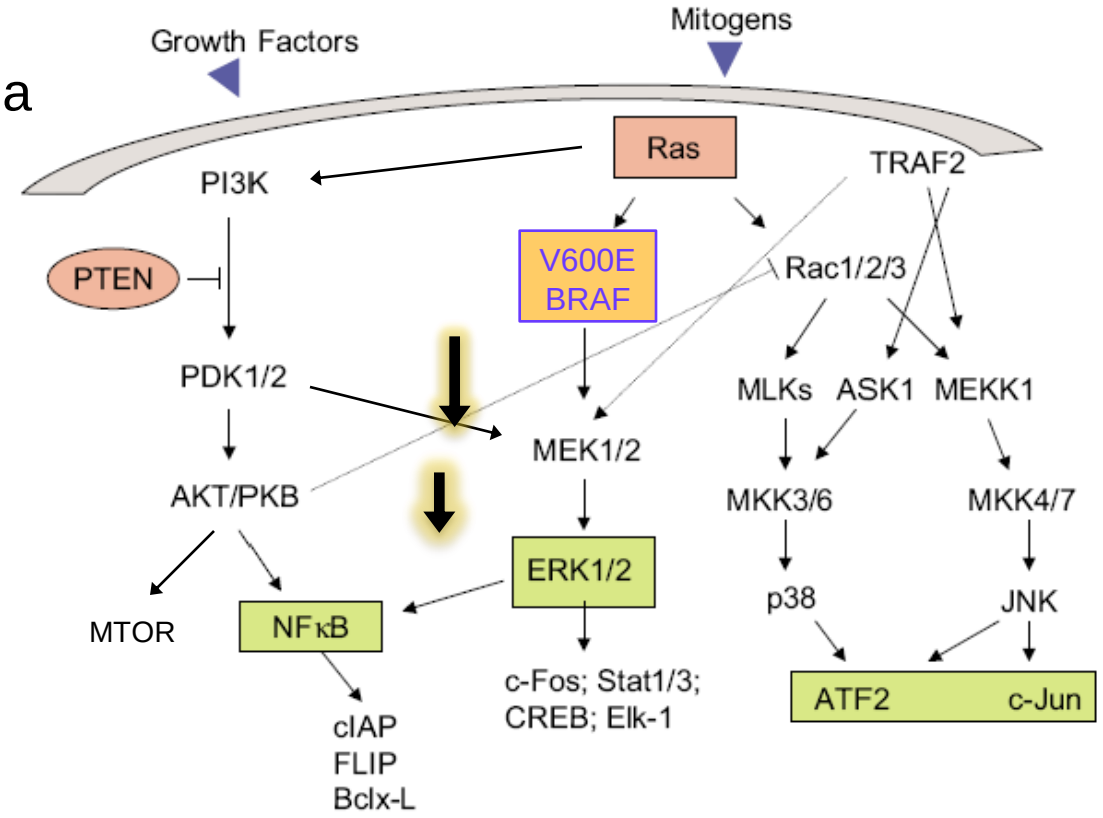
BRAF Inhibitors In Melanoma



Adapted from Ivanov Oncogene. 2003 May 19;22(20):3152-61.

BRAF Inhibitors In Melanoma

40% of melanoma



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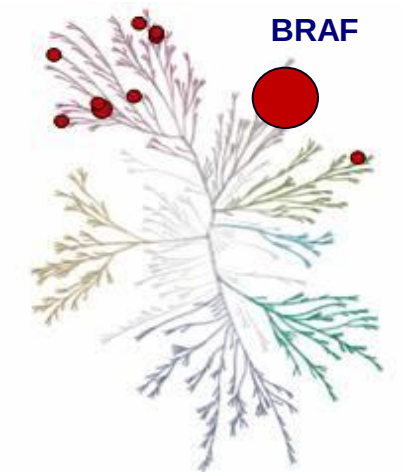
BRAF Inhibitors In Melanoma

Vemurafenib

A selective inhibitor of V600E mutated BRAF

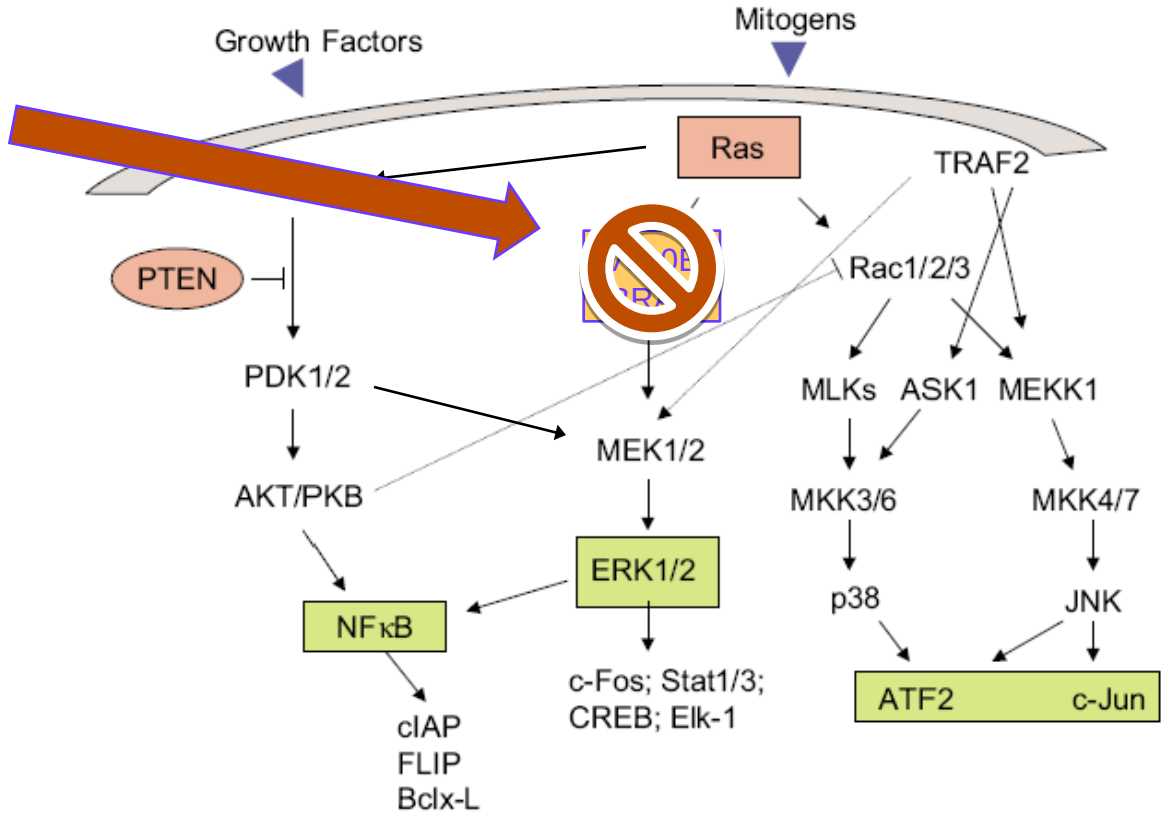


Selective in cellular assays

	Cell line	IC_{50} (nM)
V600E	A375	20
	COLO829	10
	COLO205	30
WT	SW620	>40,000
	SKMEL2	14,000

BRAF Inhibitors In Melanoma

Vemurafenib
PLX4032
RG7402



BRAF Inhibitors In Melanoma

GSK2118436

61 patients in phase 1 dose escalation trial (Kefford ASCO 2010)

70% response rate (18/30) in mutBRAF melanoma

Significant activity in CNS disease (80% response rate, Long ESMO 2010)

BRAF Inhibitors In Melanoma

GSK2118436

Phase 3 versus dacarbazine in progress

Phase 2 in CNS metastatic disease accruing

Combination with GSK1120212 in phase 1/2

BRAF Inhibitors In Melanoma

GSK2118436

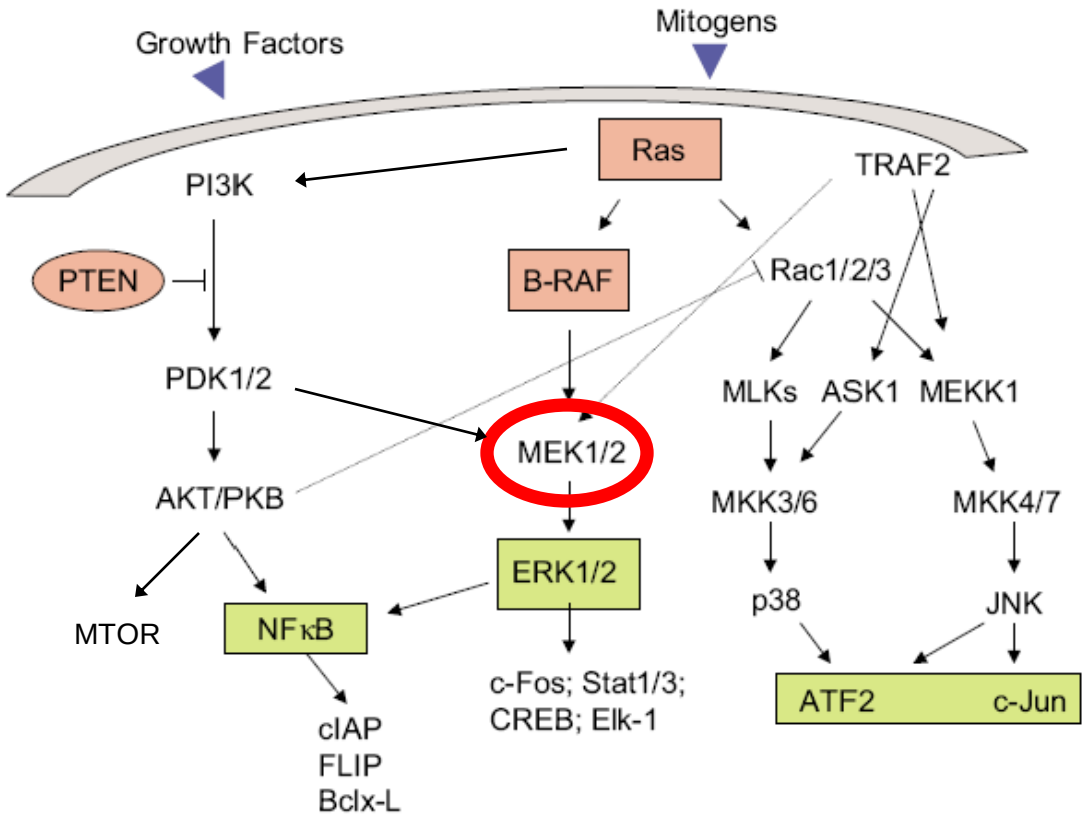
Phase 3 versus dacarbazine in progress

Phase 2 in CNS metastatic disease accruing

Combination with GSK1120212 in phase 1/2

- better tolerated than either agent alone
- impressive activity

MEK Inhibitors In Melanoma



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MEK Inhibitors In Melanoma

In the clinic are AZD6244, GSK1120212, RO4987655

Emerging single agent activity data

No results for combination trials yet

Several more agents in phase 1

MEK Inhibitors In Melanoma

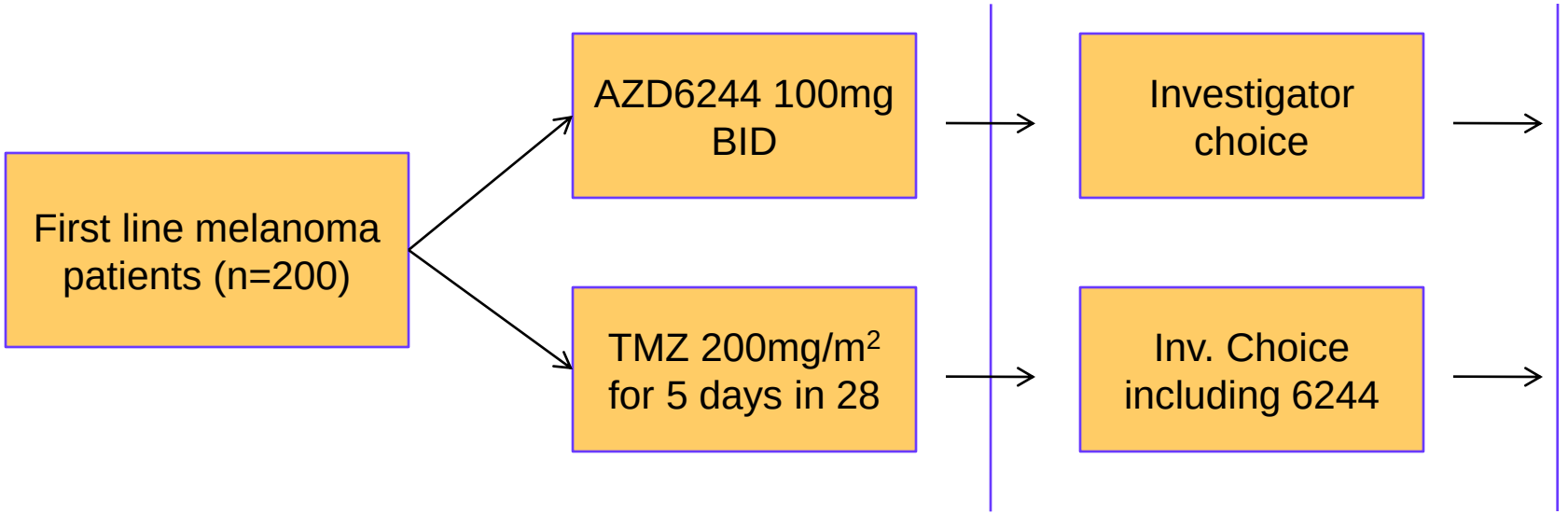
Single agent activity

Phase 2 trial of AZD6244 vs Temozolomide
(Dummer ASCO 2008)

First time in human trial of GSK1120212
(Infante ASCO 2010)

MEK Inhibitors In Melanoma

AZD6244 vs Temozolomide



Analysed as whole population, and BRAF+/wt and BRAF or NRAS mutant vs wt/wt

PFS (primary end-point)

Follow for OS

MEK Inhibitors In Melanoma

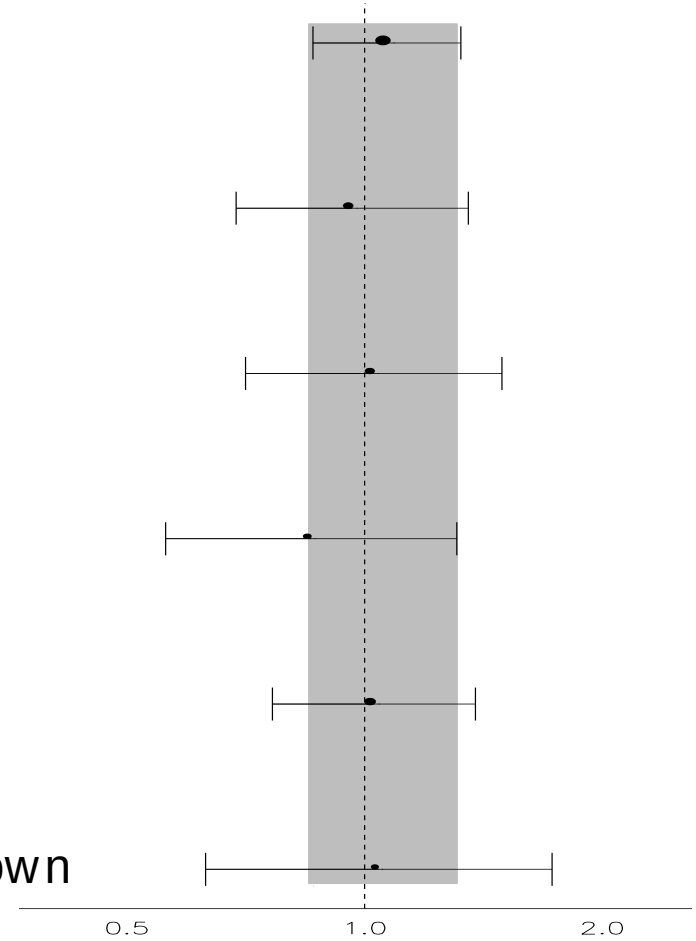
Single agent activity

Population*	Therapy	N	Responders (%)
Overall	AZD6244	104	11 (11)
	TMZ	96	13 (13)
BRAF+	AZD6244	45	7 (15)
	TMZ	28	4 (15)
BRAF/NRAS+	AZD6244	55	8 (14)
	TMZ	46	6 (13)

*Status ascertained in 158/200 pts

MEK Inhibitors In Melanoma

Progression Free Survival



Overall	1.07	(0.86,1.32)
BRAF negative	0.96	(0.69, 1.35)
BRAF positive	1.03	(0.71,1.49)
Mutation negative	0.86	(0.56, 1.31)
Mutation positive	1.03	(0.76, 1.38)
BRAF/mutation unknown	1.04	(0.63,1.73)

MEK Inhibitors In Melanoma

GSK1120212

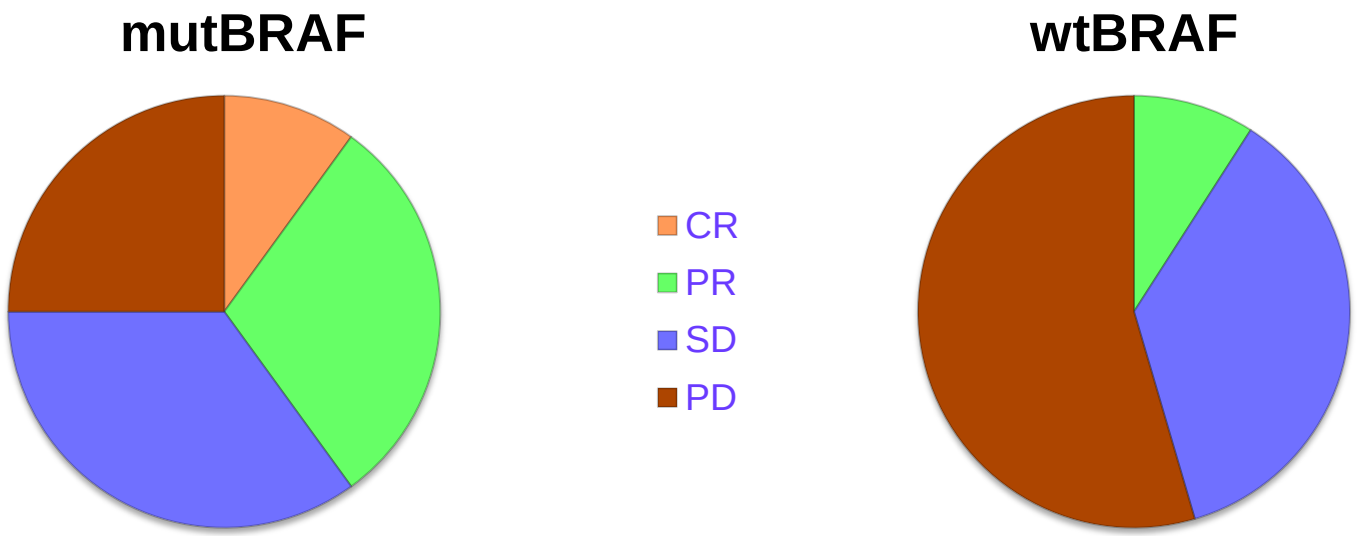
162 patients in phase 1 dose escalation trial

Expansion cohorts at RP2D including melanoma

Presented at ASCO annual meeting in 2010

MEK Inhibitors In Melanoma

GSK1120212 Response Rates

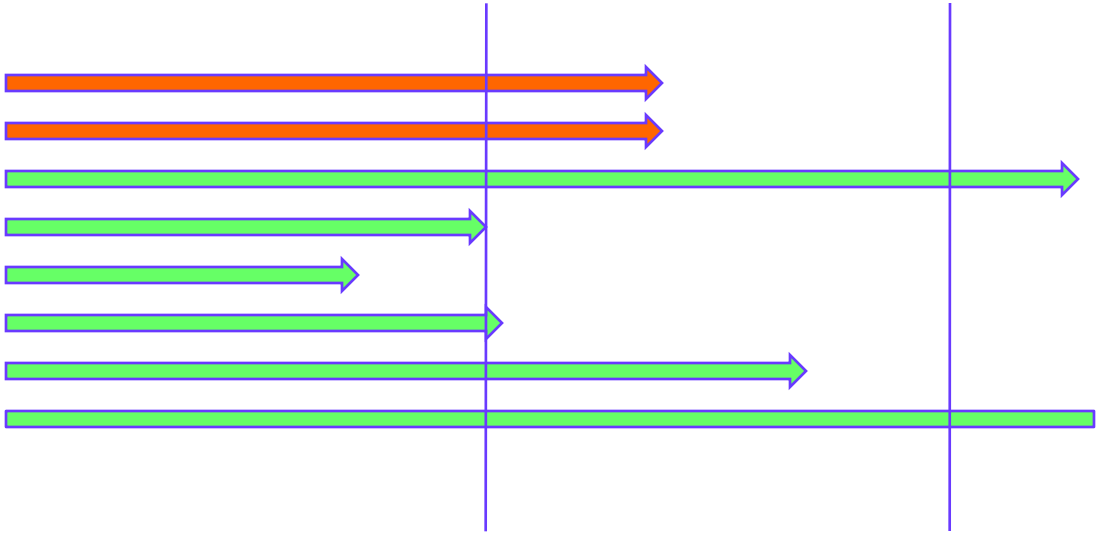


8/20 = 40%

2/22 = 9%

MEK Inhibitors In Melanoma

GSK1120212 Response Duration
mut BRAF Population



3 months 6 months

MEK Inhibitors In Melanoma

GSK1120212

Well-tolerated (grade 1-2, rash, diarrhoea, fatigue)

40% response rate in BRAF mutated melanoma

9% response rate in wt BRAF population

Phase 3 trial in mutated BRAF population in progress

MEK Inhibitors In Melanoma

RO4987655

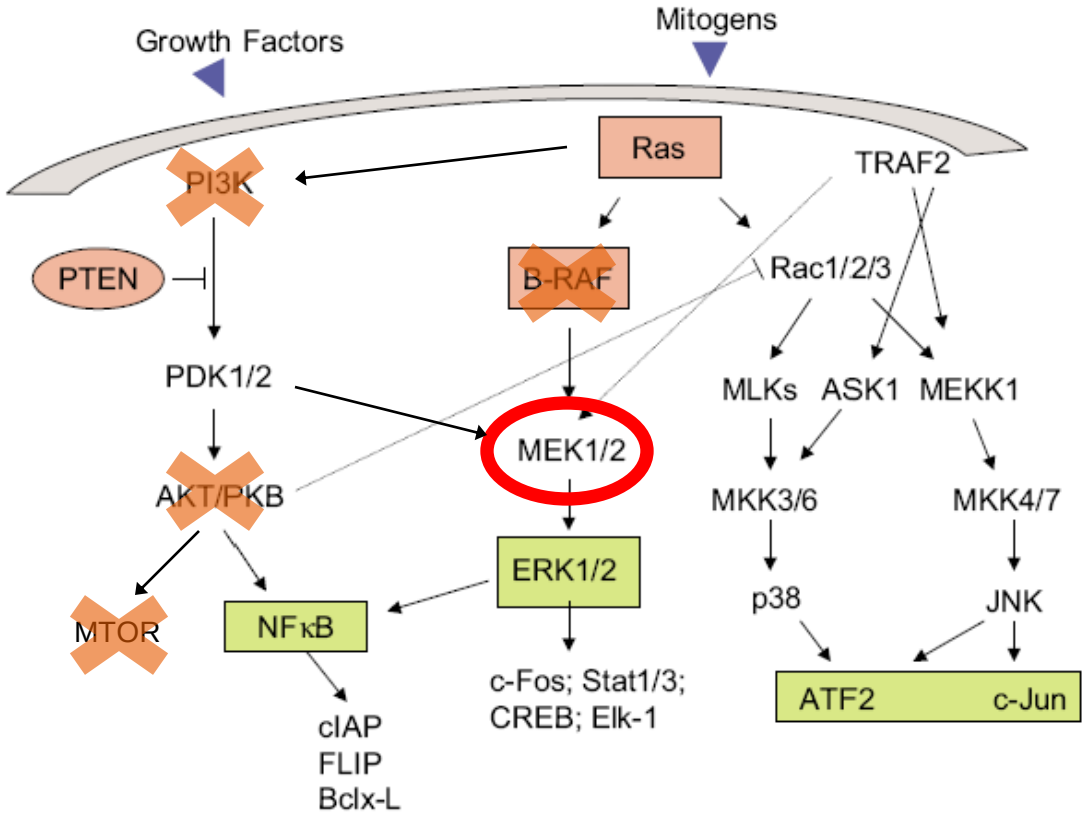
Completed phase 1 trials (Leijen, ASCO 2011)

Responses in melanoma

Rash, diarrhoea, oedema

Expansion in melanoma (V600E and wt), colorectal cancer (mutKRAS), NSCLC (mutNRAS)

MEK Inhibitors In Melanoma



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MEK Inhibitors In Melanoma

Combination Therapy

IGF-AKT-mTOR axis

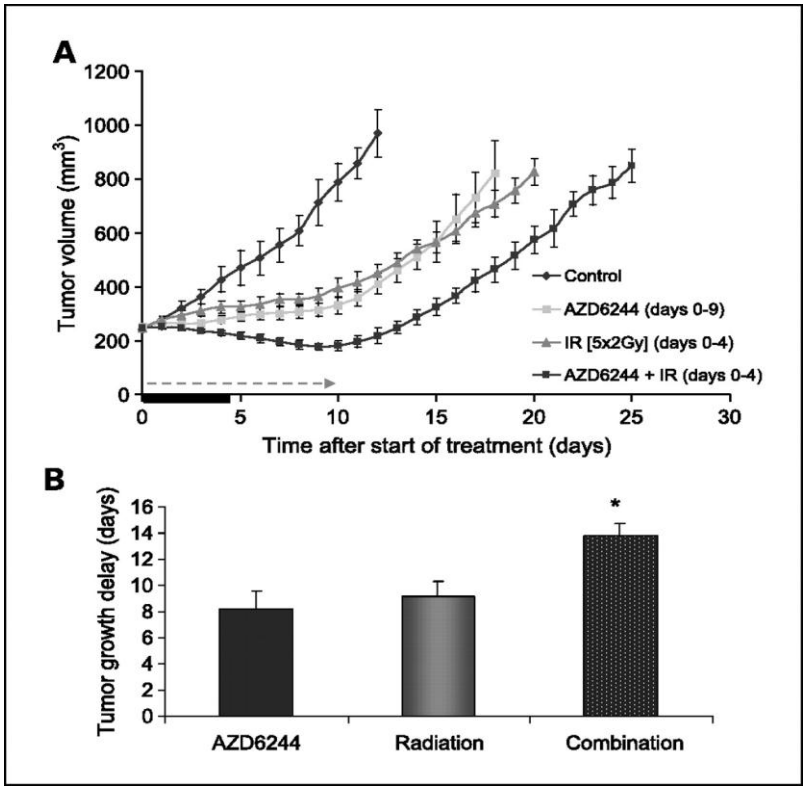
Dual MAPkinase pathway inhibition

Radiotherapy

Cytotoxic Chemotherapy

MEK Inhibitors as Radiosensitisers

AZD6244 and radiotherapy enhances the therapeutic response of HCT116 xenografts compared with either therapy alone.

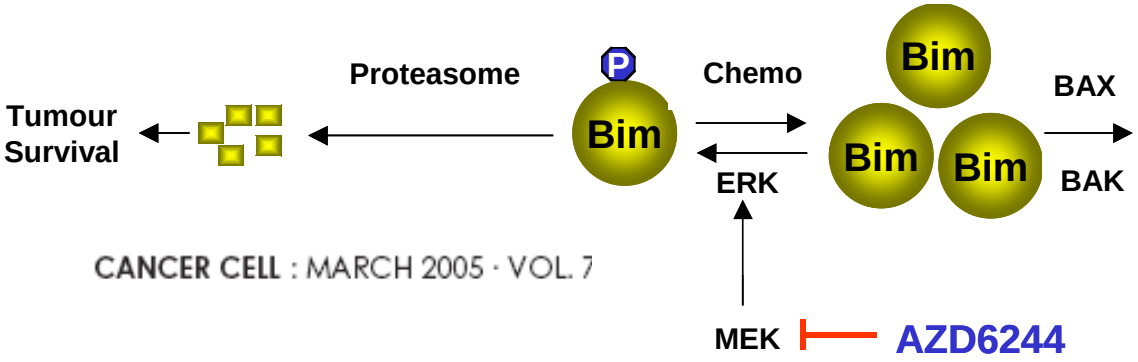


Shannon A M et al. Clin Cancer Res 2009;15:6619-6629

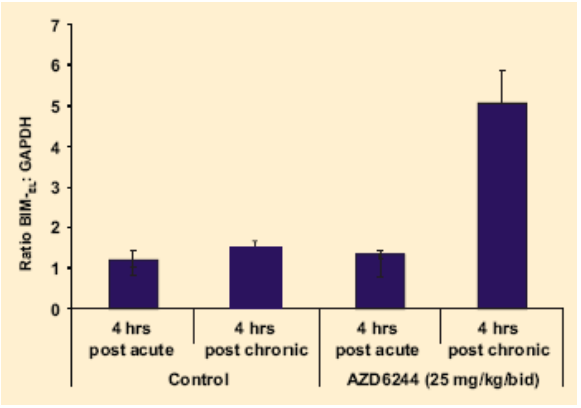
Clinical Cancer Research

MEKi as Chemosensitisers

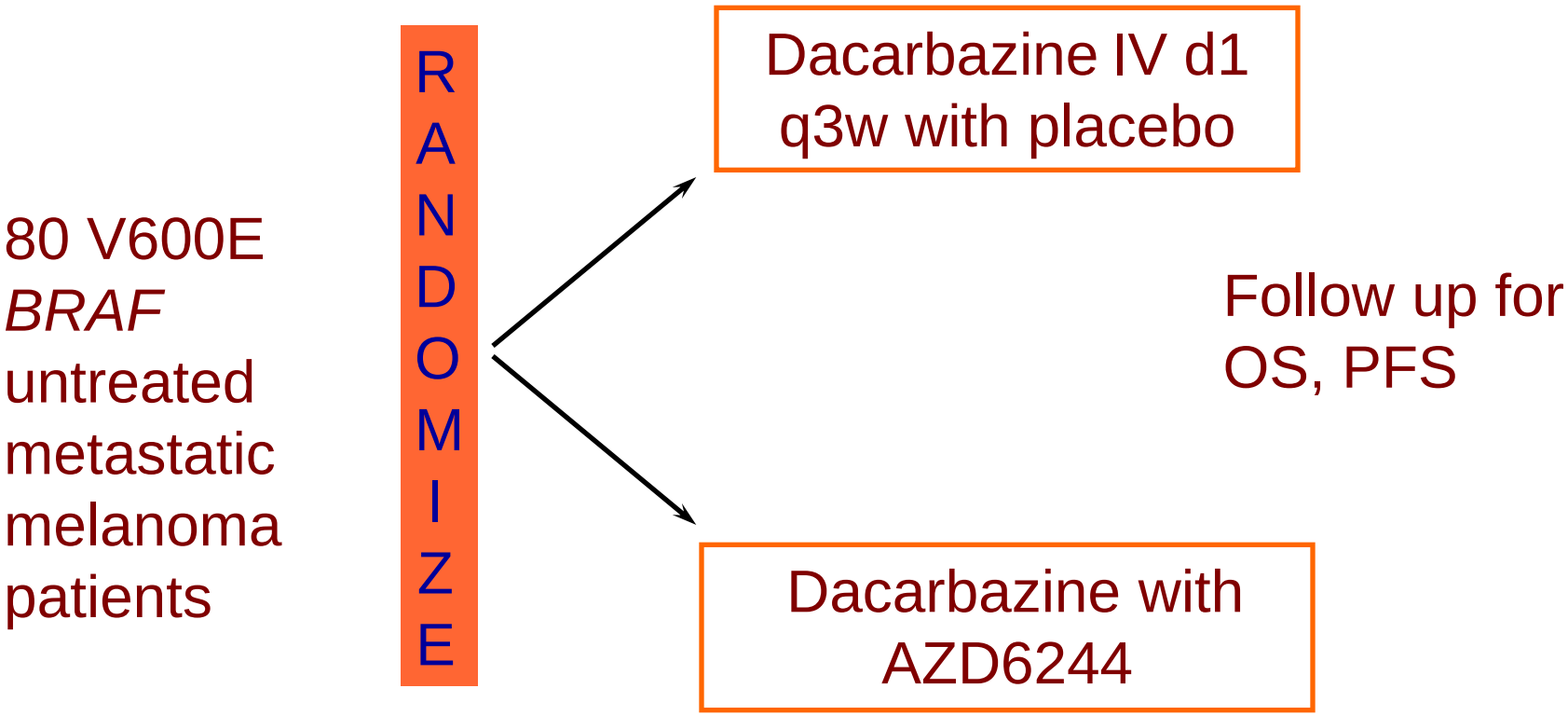
- ERK is highly active in melanoma cells, irrespective of BRAF status
- ERK phosphorylates the pro-apoptotic protein Bim, targeting it for proteasomal degradation
- ERK promotes Bim's dissociation from pro-survival proteins e.g. Mcl1
- MEK inhibition prevents the degradation of Bim enhancing chemotherapy induced cell death



CANCER CELL : MARCH 2005 · VOL. 7



MEKi as Chemosensitisers



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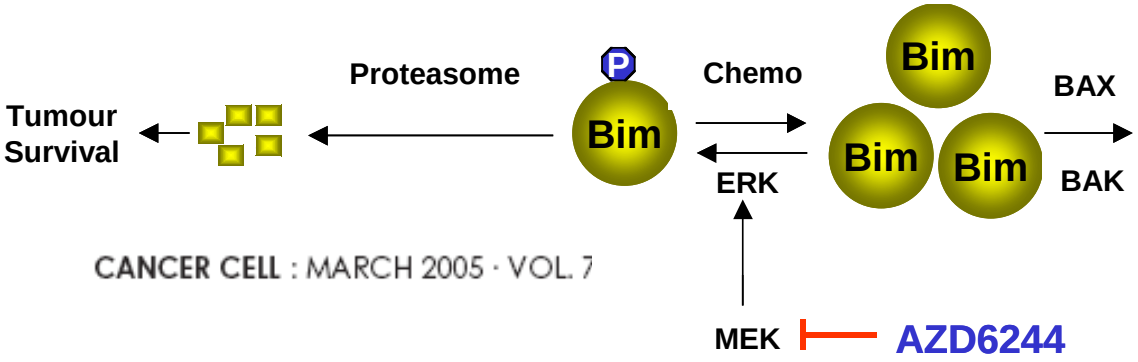
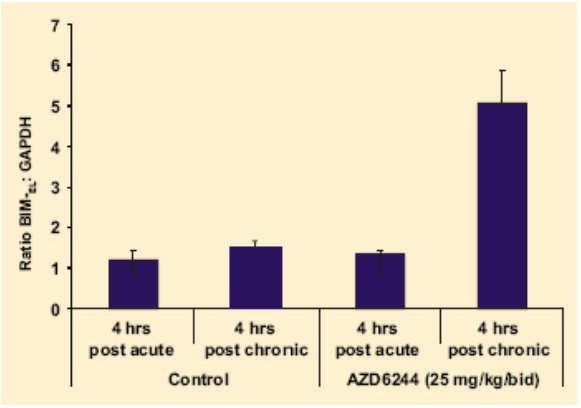
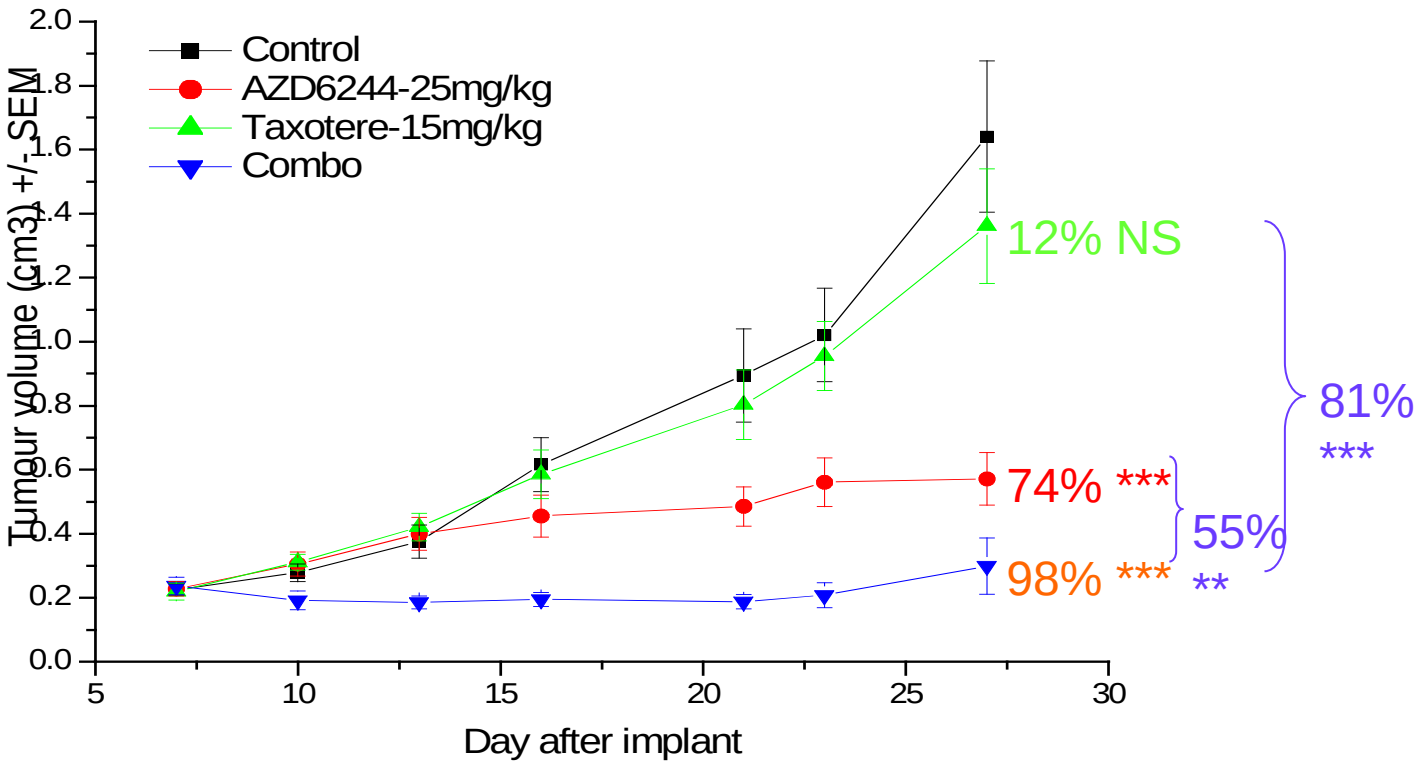


CANCER CELL : MARCH 2005 · VOL. 7



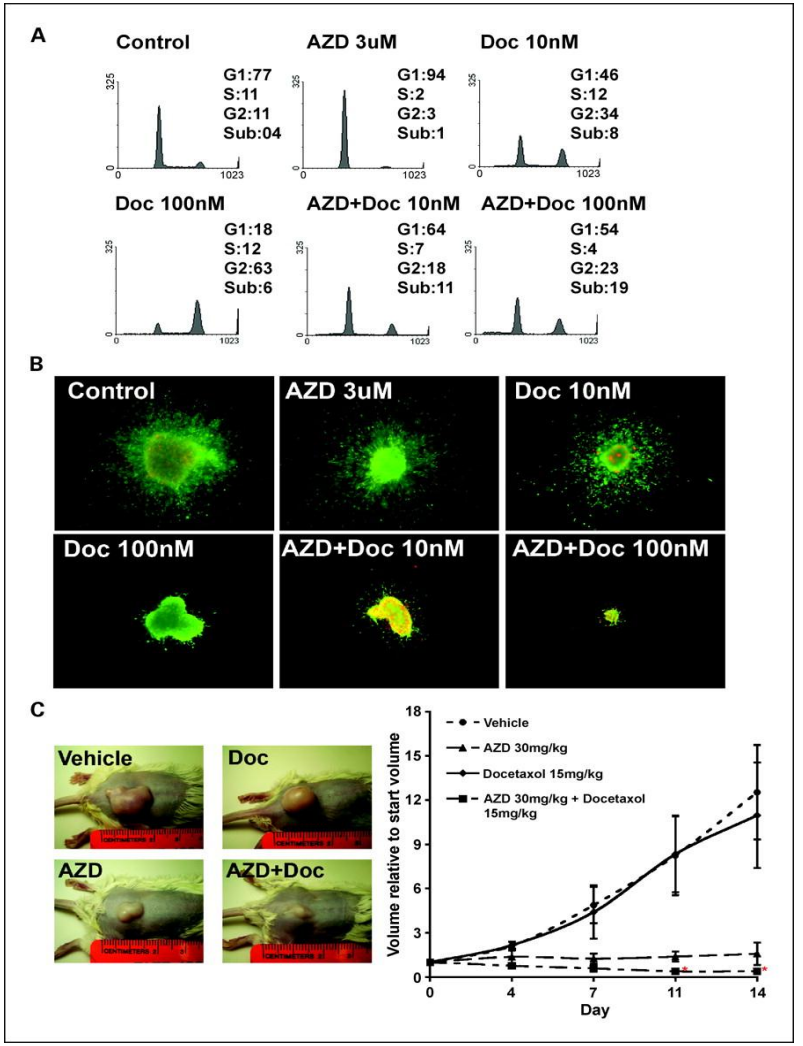
MEKi as Chemosensitisers

SW620 Xenograft - Kras mutant



MEKi as Chemosensitisers

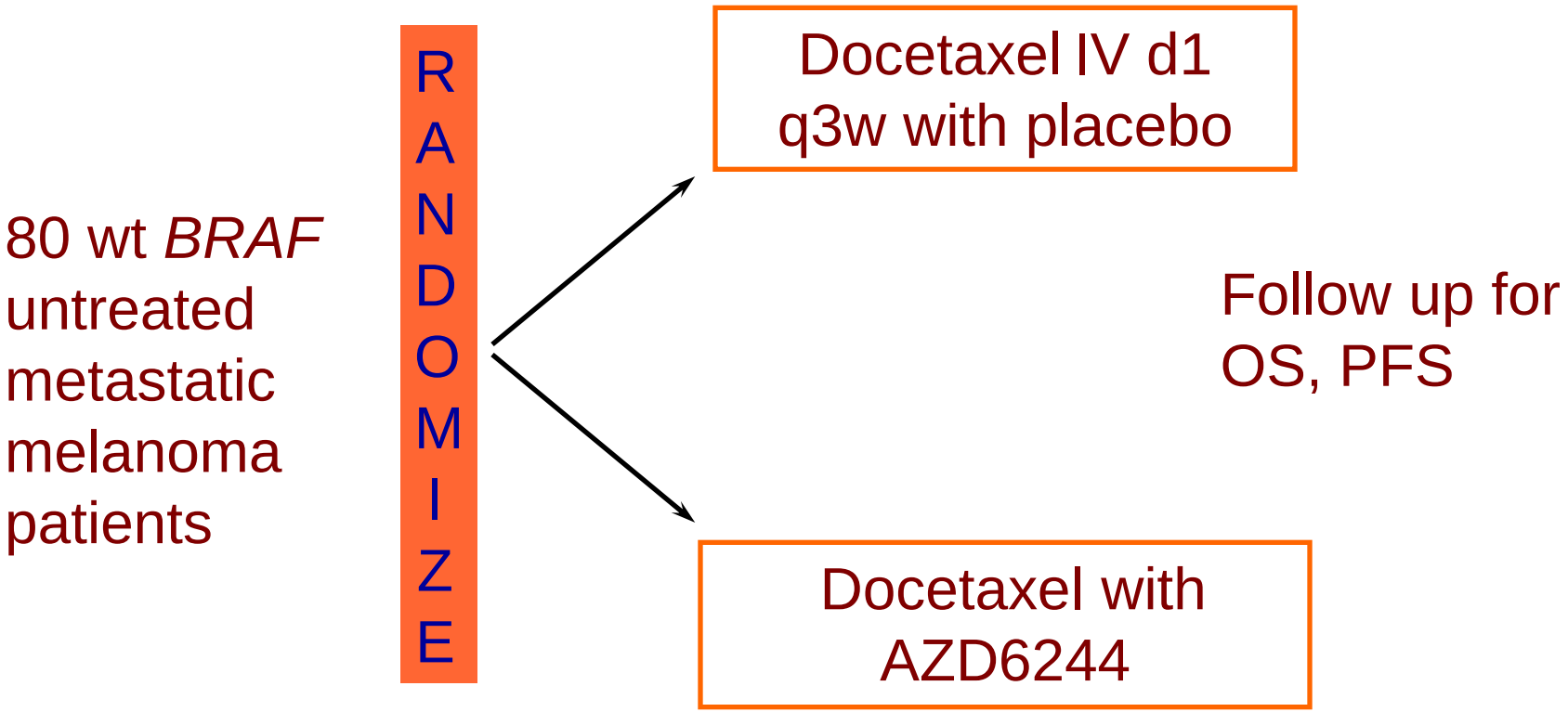
Docetaxel treatment enhances the antitumor activity of AZD6244 in both in vitro and in vivo melanoma models.



Haass N K et al. Clin Cancer Res 2008;14:230-239

Clinical Cancer Research

MEKi as Chemosensitisers



a study of the UK NCRI Melanoma Clinical Study Group

The Future For Melanoma

Metastatic Disease

Somatic mutation status will define therapeutic options

For symptomatic mut BRAF patients targeted agents are likely to be the treatments of choice

For wt BRAF patients ipilimumab has emerged as treatment of choice