

CHEMORES

TUMOUR CHEMOTHERAPY RESISTANCE



WELCOME!

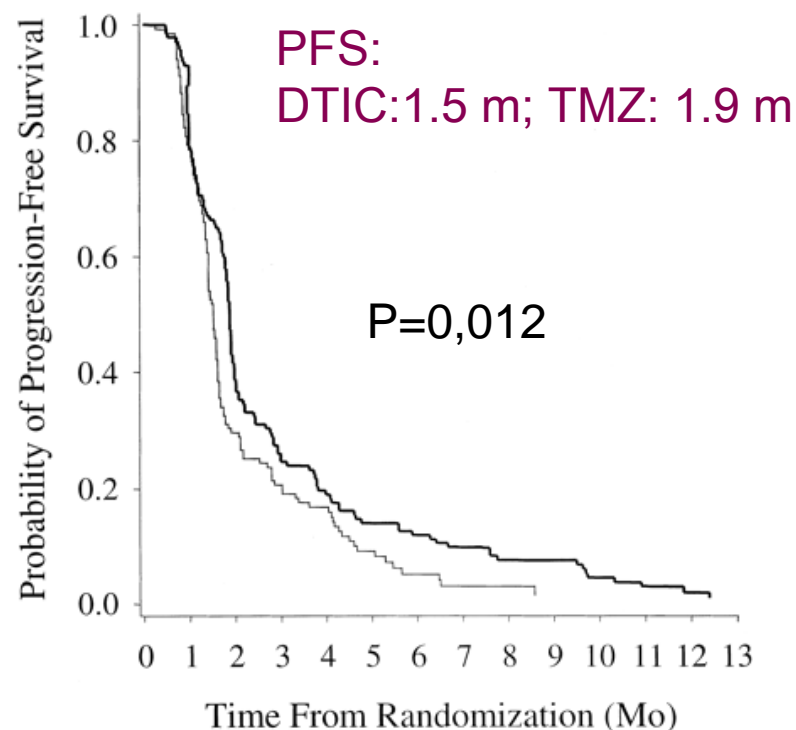
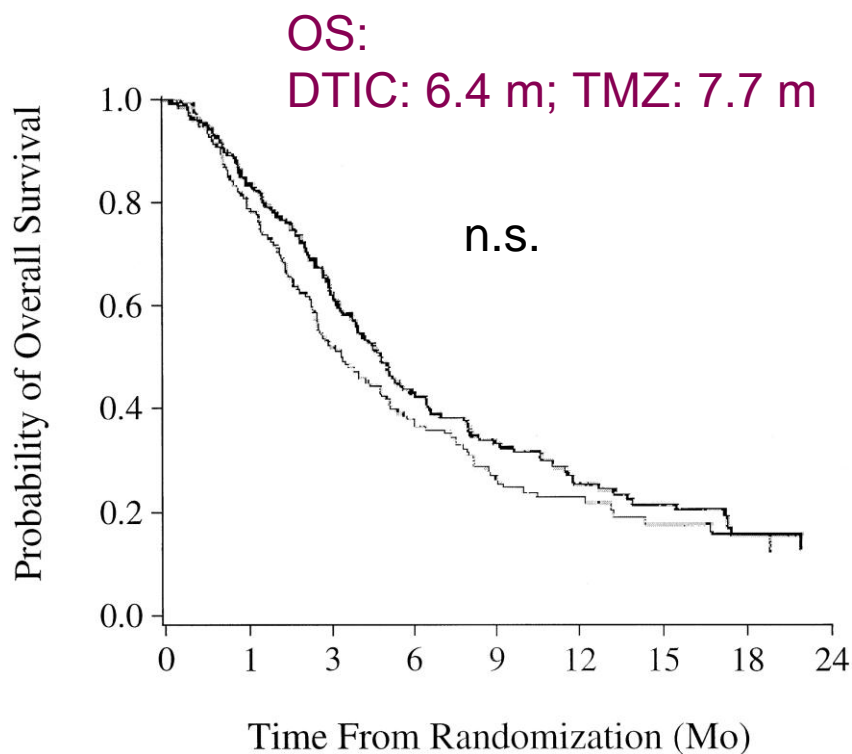


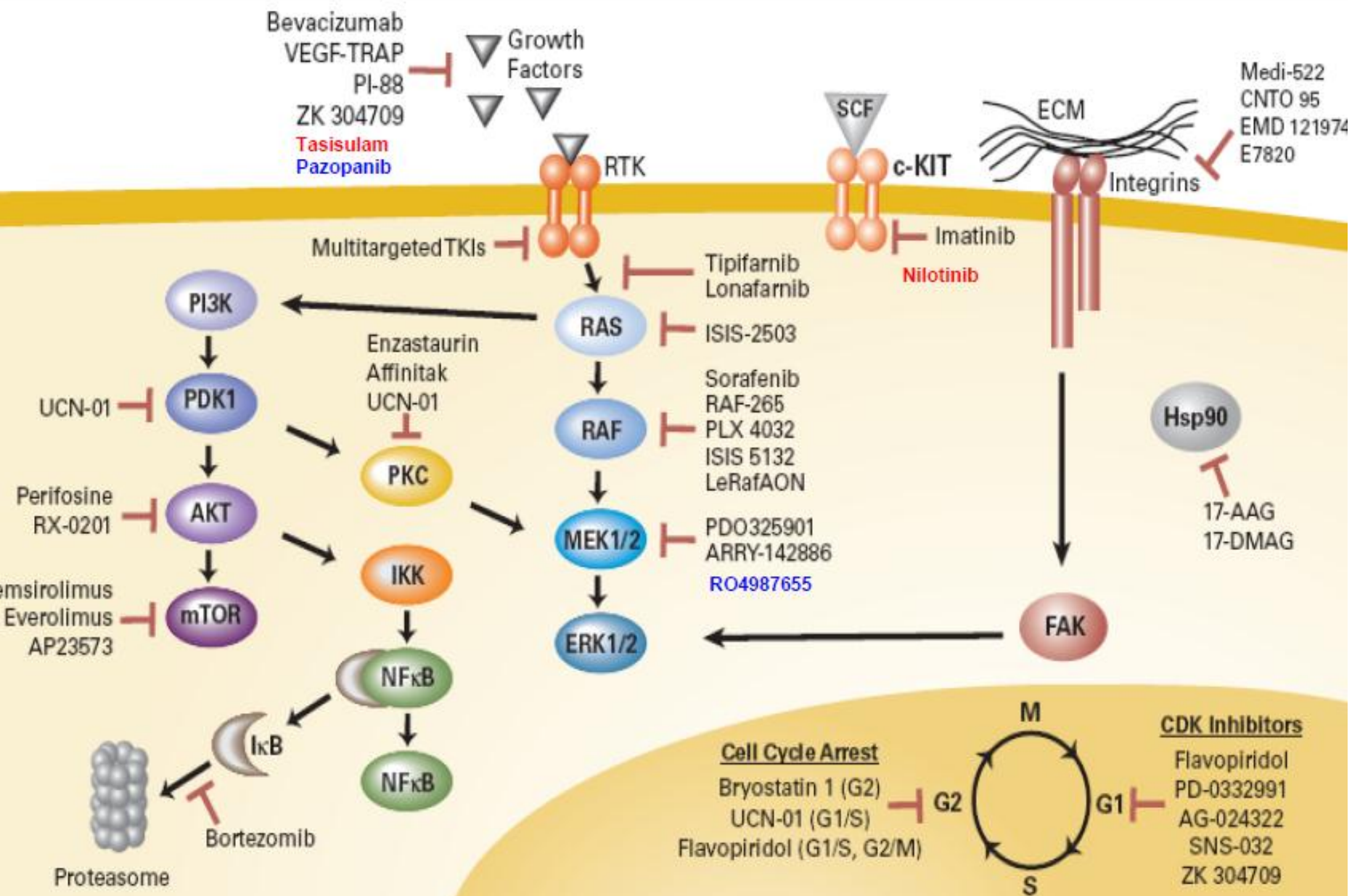
Randomized trial Stage IV melanoma: 1970s – DTIC 2000s – Temozolomide (TMZ)



Karolinska
Institutet

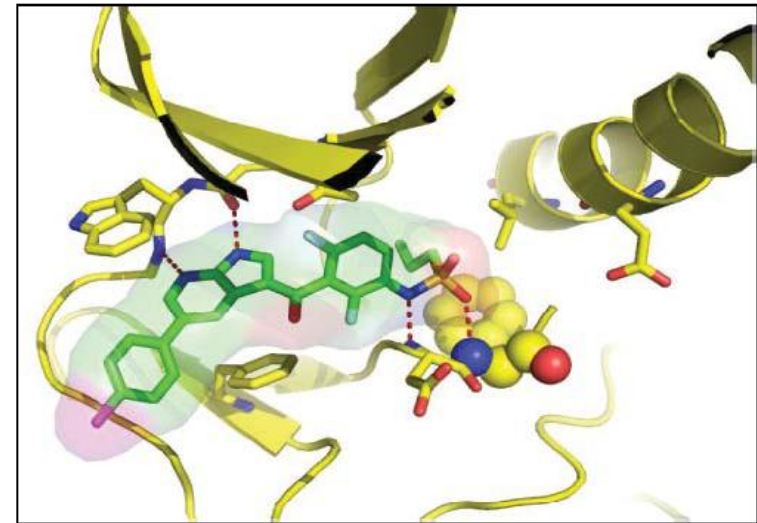
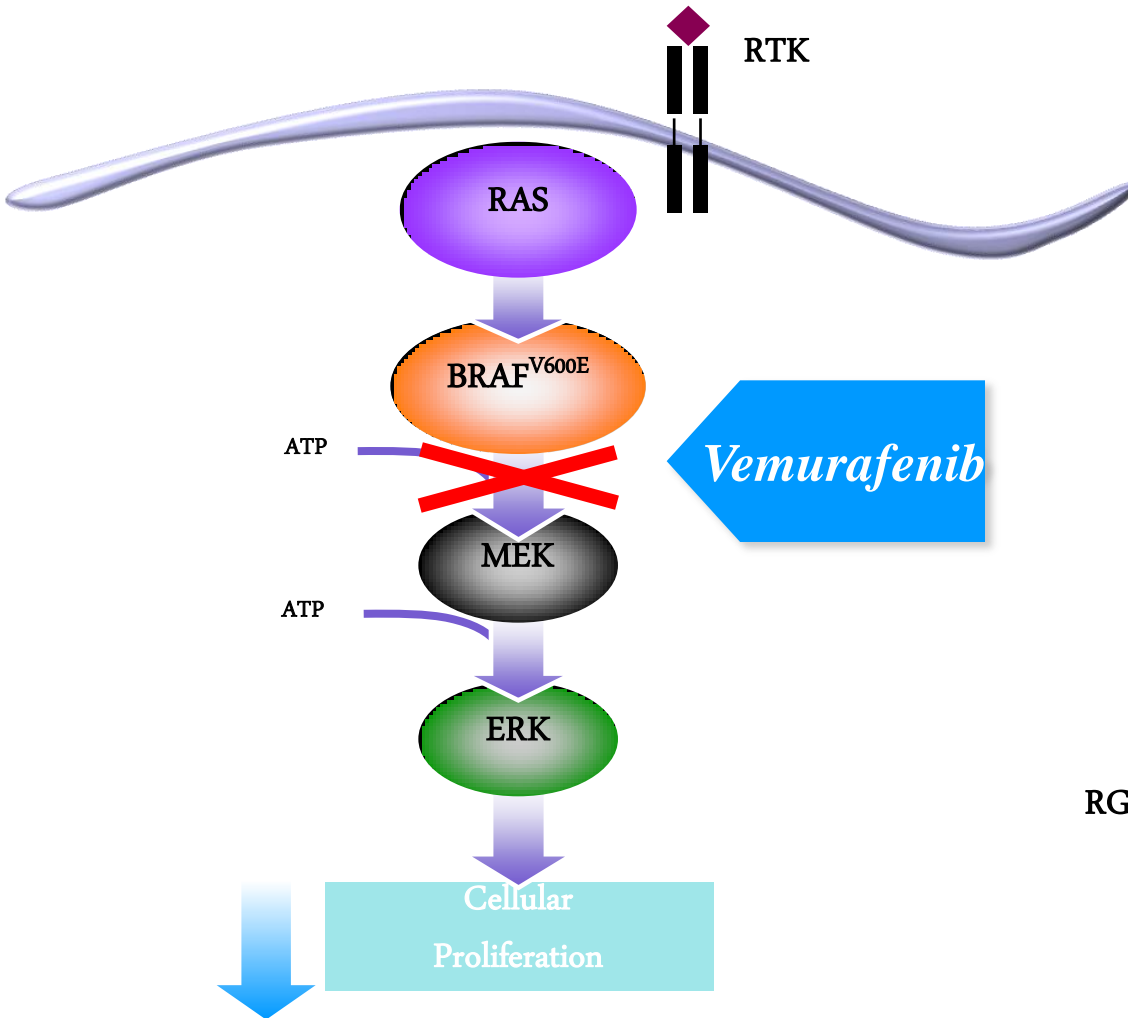
305 pat





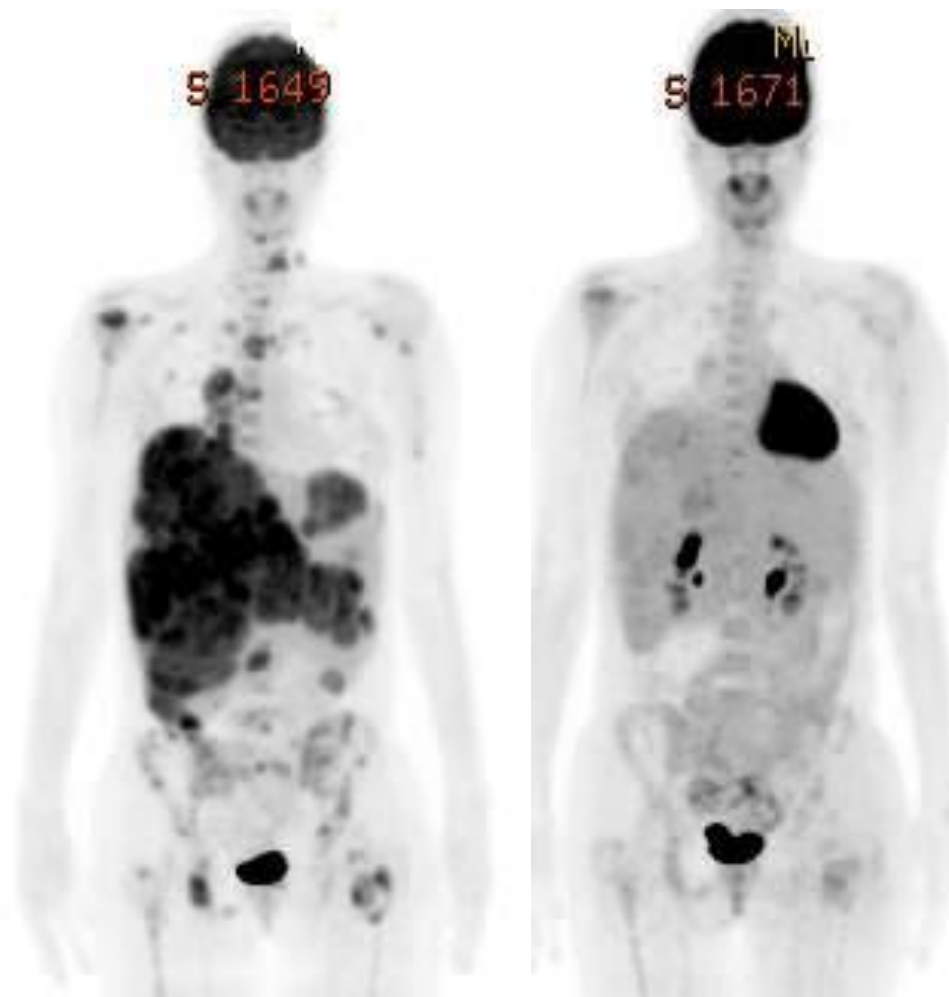
The Target: BRAF Kinase

An important mediator of cellular proliferation



RG7204 co-Structure with kinase domain of B-RAF^{V600E}

(Bollag *et al.*, Nature 2010)

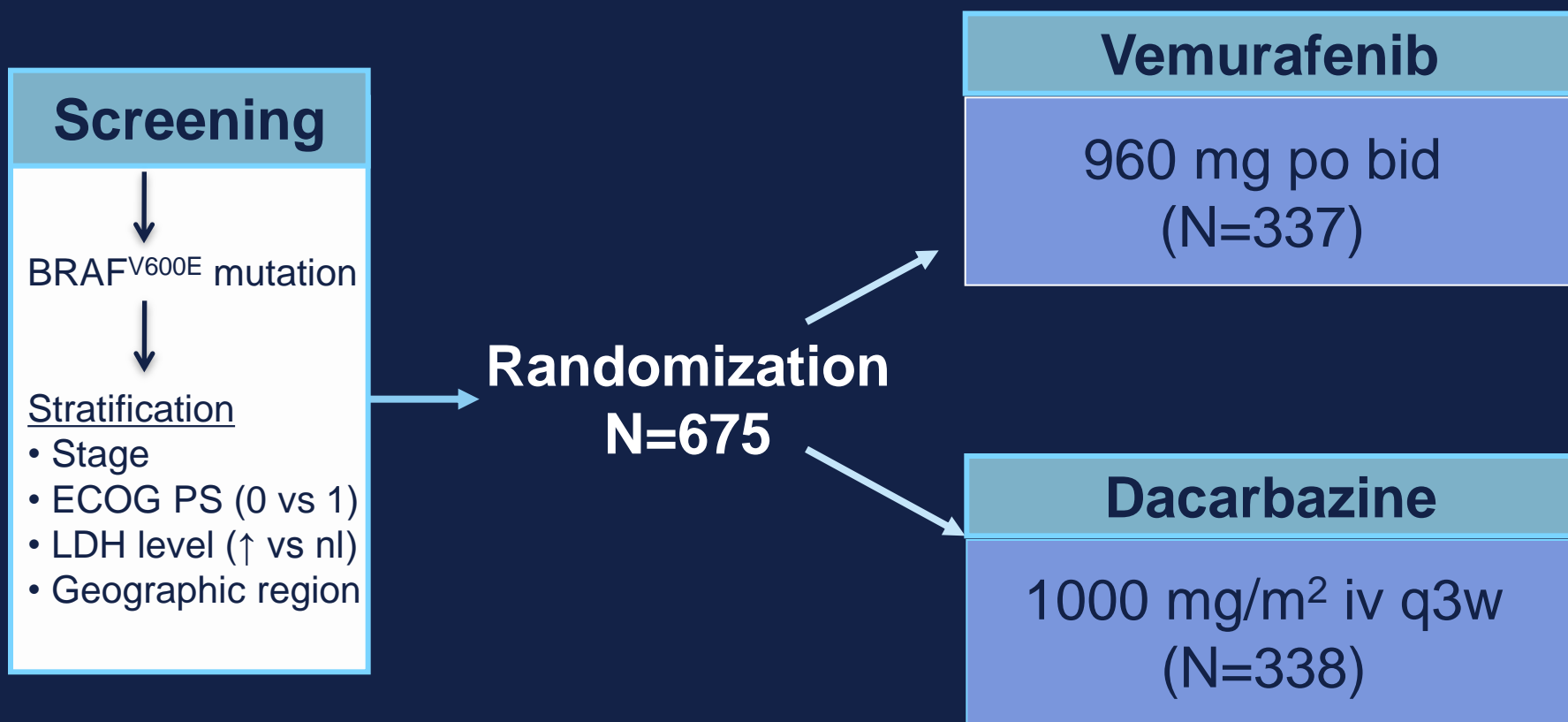


Baseline

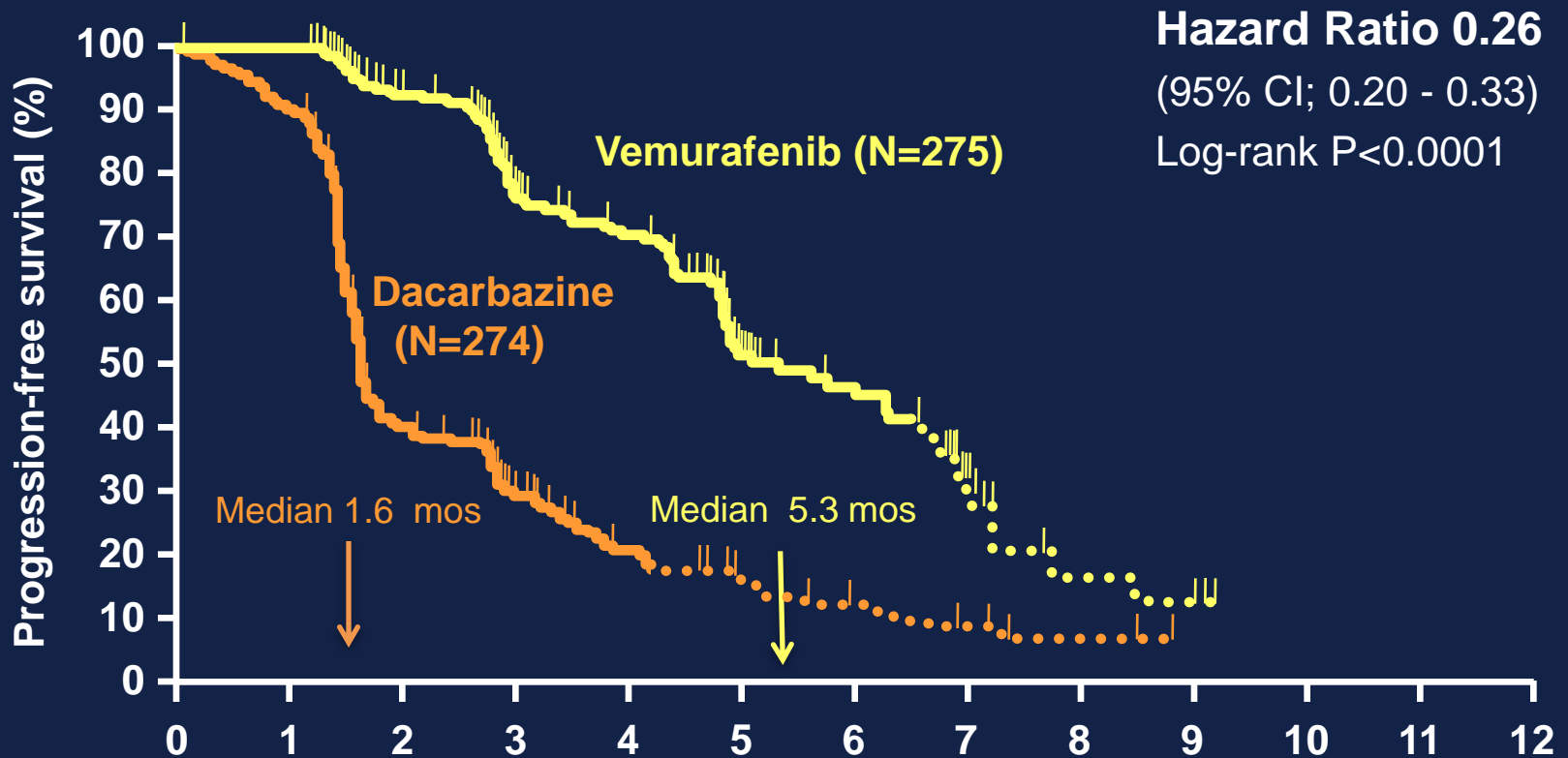
Day 15

PET Scan

Phase III BRIM3 Study design



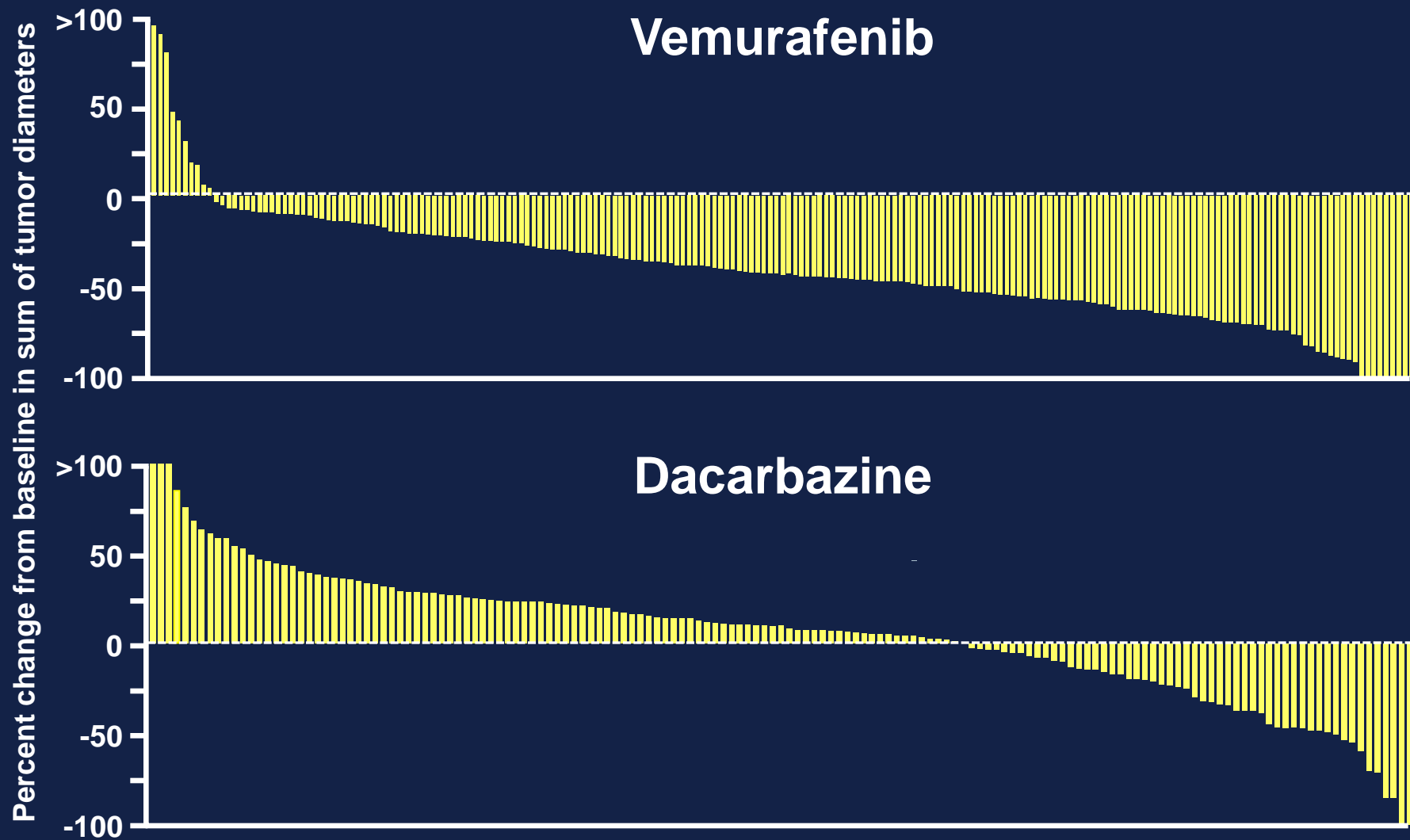
Progression-free survival (Dec 30, 2010 cutoff)



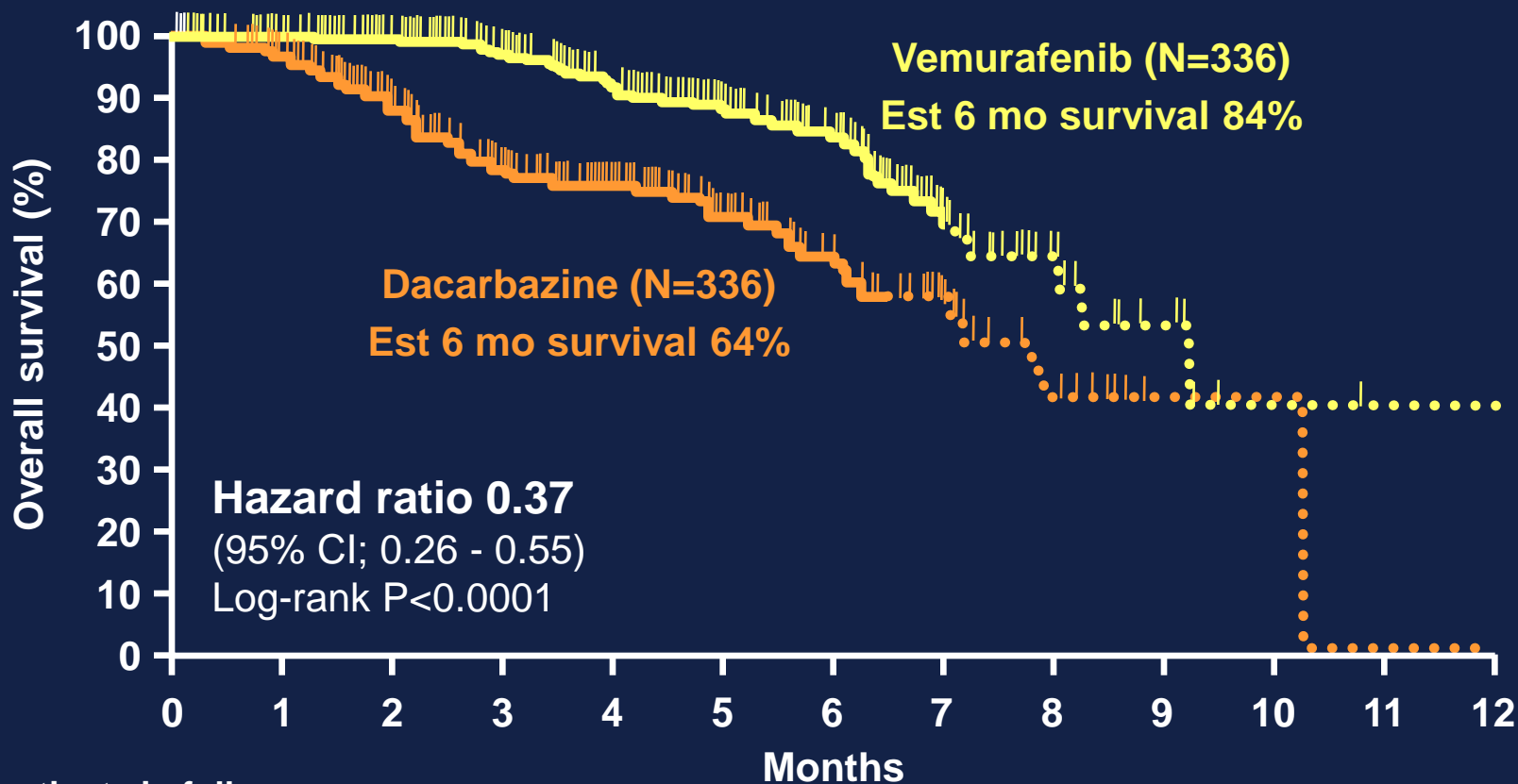
No. of patients in follow up

	0	1	2	3	4	5	6	7	8	9
Dacarbazine	274	213	85	48	28	16	10	6	3	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3

Maximal tumor shrinkage by individual patient



Overall survival (Dec 30, 2010 cutoff)



No. of patients in follow up

Dacarbazine	336	283	192	137	98	64	39	20	9	1	1
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1

Potential Mechanisms of Drug Resistance/Toxicity

Mechanism 1



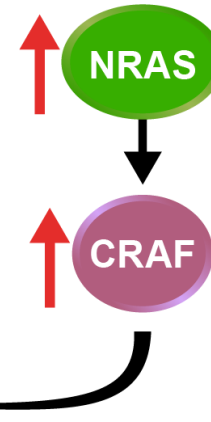
Alternative survival

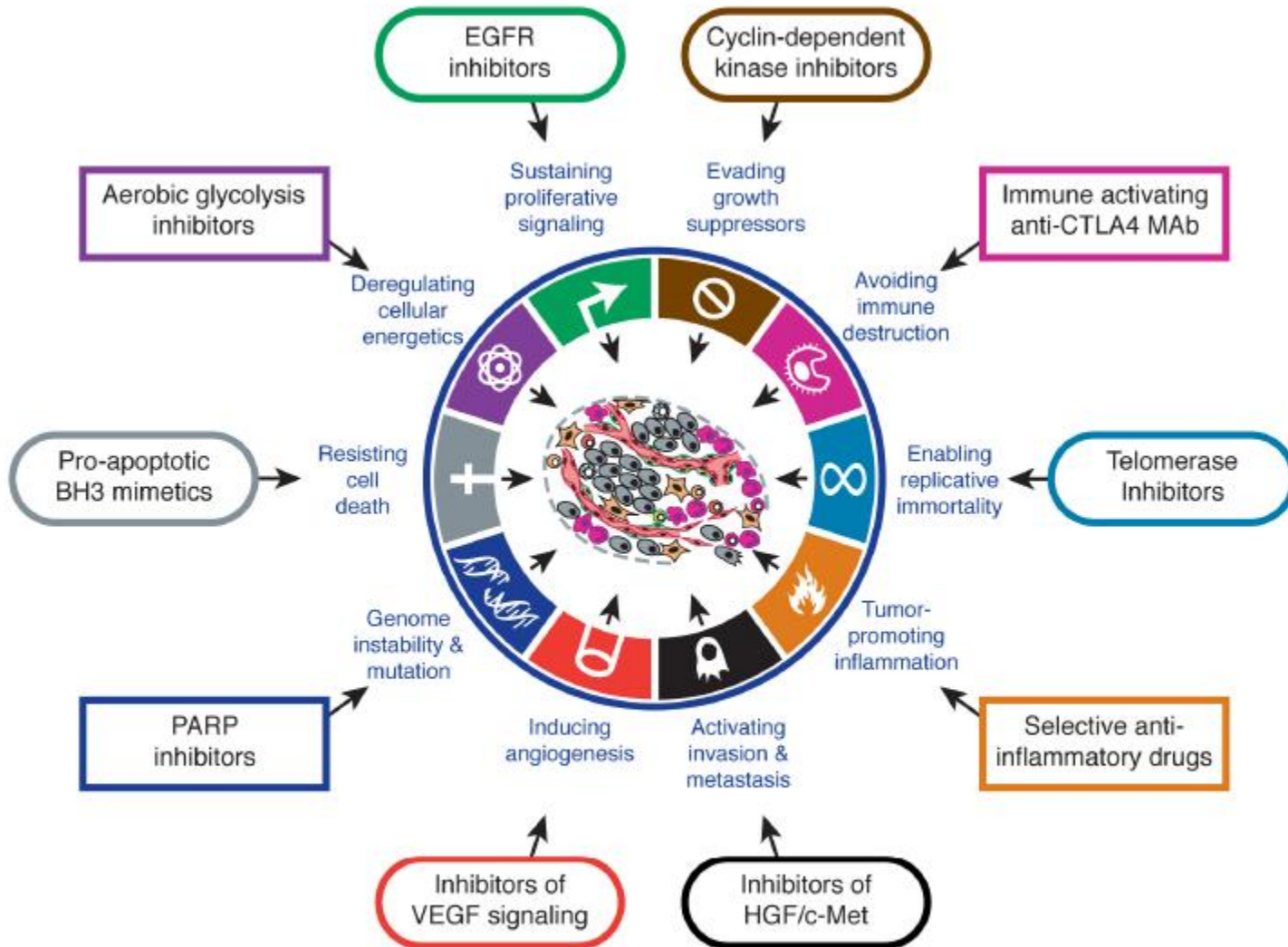
Mechanism 2

PLX4032



MAPK-dependent survival





Hanahan and Weinberg, 2011

”Personalized medicine”

