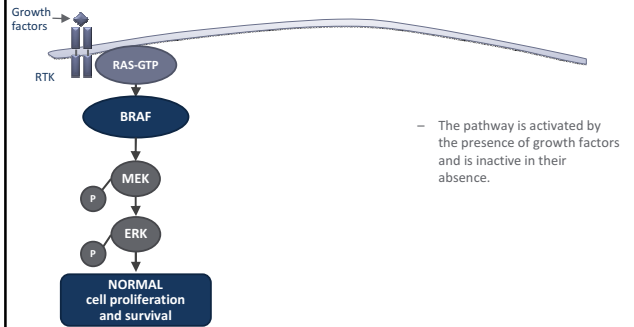


BRAF & Zelboraf in Metastatic Melanoma

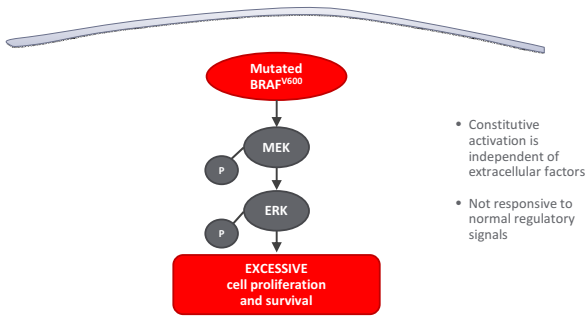
Dr. Ruth Achten
Patholoog-Anatoom
Jessa Ziekenhuis Hasselt

Normal RAS–RAF Pathway Signaling controls cell proliferation and survival



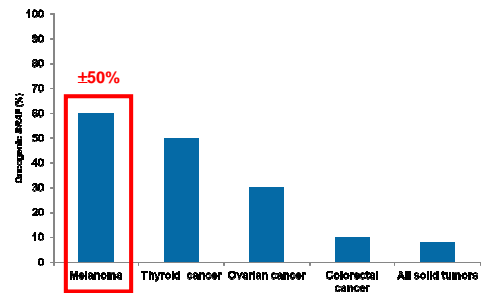
RTK = receptor tyrosine kinase; GTP = guanosine triphosphate; ERK = extracellular signal-related kinase; MEK = MAP (mitogen-activated protein).

Oncogenic RAS–RAF Pathway Signaling leads to excessive cell proliferation and survival

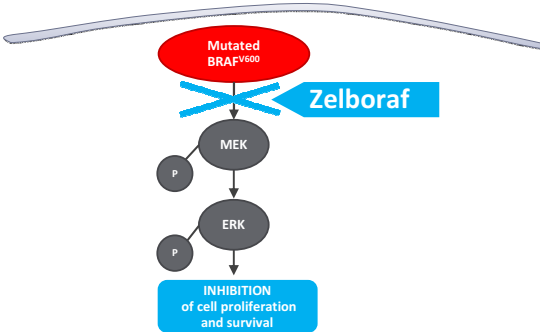


RTK = receptor tyrosine kinase; GTP = guanosine triphosphate; ERK = extracellular signal-related kinase; MEK = MAP (mitogen-activated protein).

Mutated BRAF is frequently identified in cancer^{39,42-47}

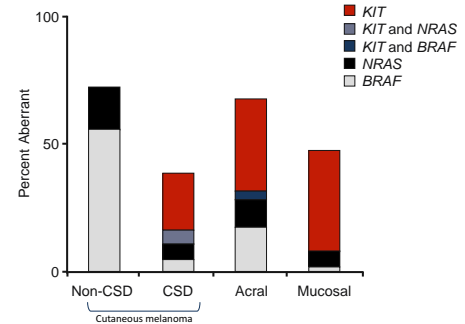


Oncogenic RAS–RAF Pathway Signaling inhibited by Zelboraf



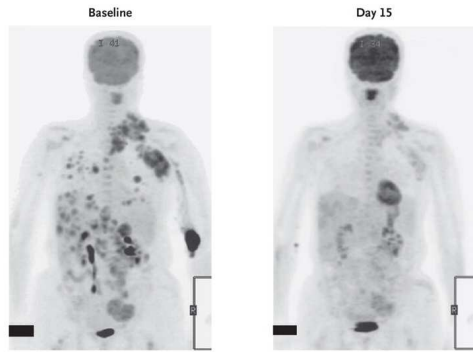
BRAF = rapidly accelerated fibrosarcoma oncogene B; ERK = extracellular signal-regulated kinase; GTP = guanosine triphosphate; MEK = mitogen-activated protein kinase (MAPK) or ERK kinase; P = phosphate; RTK = receptor tyrosine kinase.

Distribution of Genetic Alterations in BRAF, NRAS, and KIT by Primary Site & UV exposure



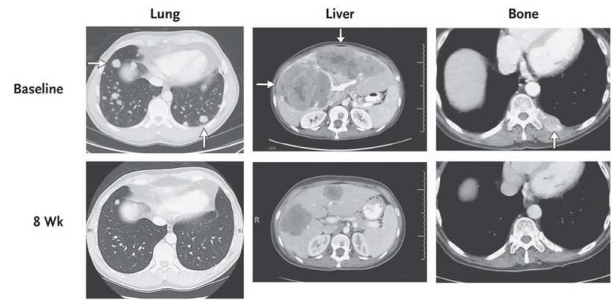
CSD: chronic sun damaged
Non-CSD: intermittent sun exposure

Phase I: Early FDG-PET Responses on Zelboraf



FDG = F-18-fluorodeoxyglucose; PET = positron emission tomography.
9 Falherby KT, et al. N Engl J Med 2010;363:809-19

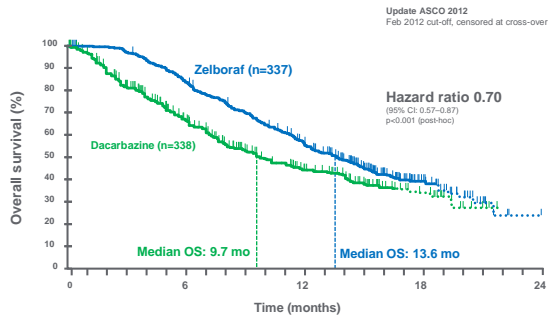
Phase I: Regression of Distant Metastases



Computer tomography revealed regression of lung, liver and bone metastases following 8 weeks Zelboraf treatment (with each pair of images shown for a different patient)

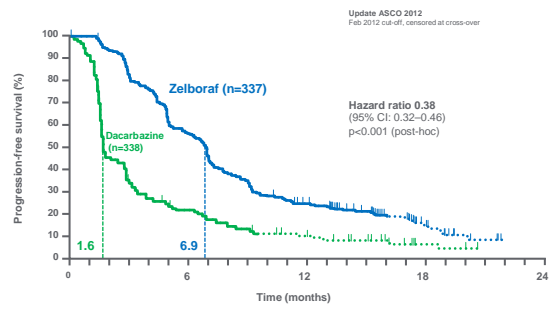
9 Falherby KT, et al. N Engl J Med 2010;363:809-19

Phase III: Unprecedented Survival benefit in BRAF mutation positive metastatic melanoma versus chemotherapy



14 Chapman et al. Abstract 8502, Oral Abstract session, J Clin Oncol 30, ASCO 2012.

Phase III: > 5 month longer without progression of disease



14 Chapman et al. Abstract 8502, Oral Abstract session, J Clin Oncol 30, ASCO 2012.

Consistent Survival Data across Zelboraf Clinical Trial Program versus Meta-Analysis 2008

	Korn et al. 2008 ⁶	Phase I ^{9,11} (extension cohort)	Phase II BRIM-2 ^{12,10}	Phase III BRIM-3 ^{10,14}	
Population	Previously treated (n=116) ⁶	Previously treated (24) untreated (8)	Previously treated (n=132)	Previously untreated (n=337)	
Median PFS (months)	1.7	> 7	6.7	5.3	6.9
Median OS (months)	6.2	13.8	15.9	-	13.6
12-month survival rate	25%	50%	58%	-	56%

9 Falherby KT, et al. N Engl J Med 2010;363:809-19
10 Soeman J et al. N Engl J Med 2012;366(8):707-714.
12 Zelboraf (vemurafenib) Summary of Product Characteristics Feb 2012.
14 Chapman et al. Abstract 8502, J Clin Oncol 30, oral presentation ASCO 2012.
11 McVittur A, oral presentation ESMO 2011

Note: Zelboraf Clinical Trial population limited to BRAF V600 mutation-positive melanoma