Histology independent indications in oncology

The BRAF Story

Yibing Yan PhD Roche / Genentech

- Introduction
  - the discovery

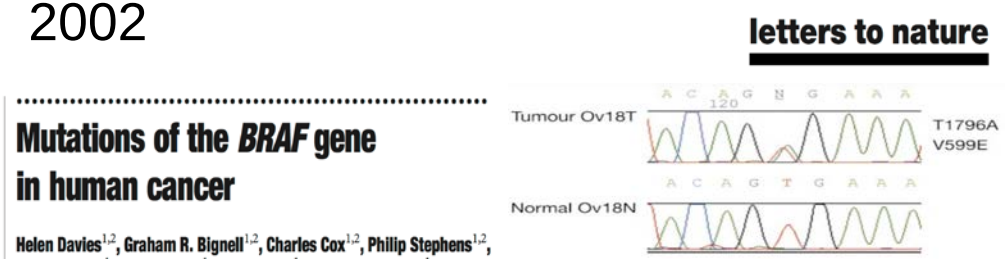
- Case study in BRAF mutant melanoma
  - heterogeneity within the tumour
  - variability over time

- Heterogeneity between histo/organs
  - VE-BASKET and beyond

Discovery of BRAF V600 mutation

Oncogenic mutations

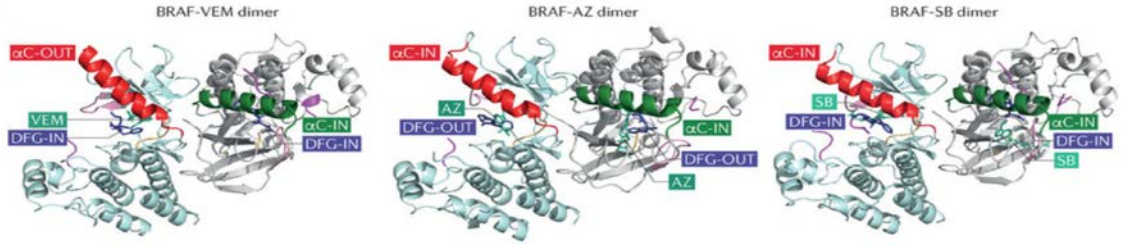
2002



Oncogenic mutation specific drugs

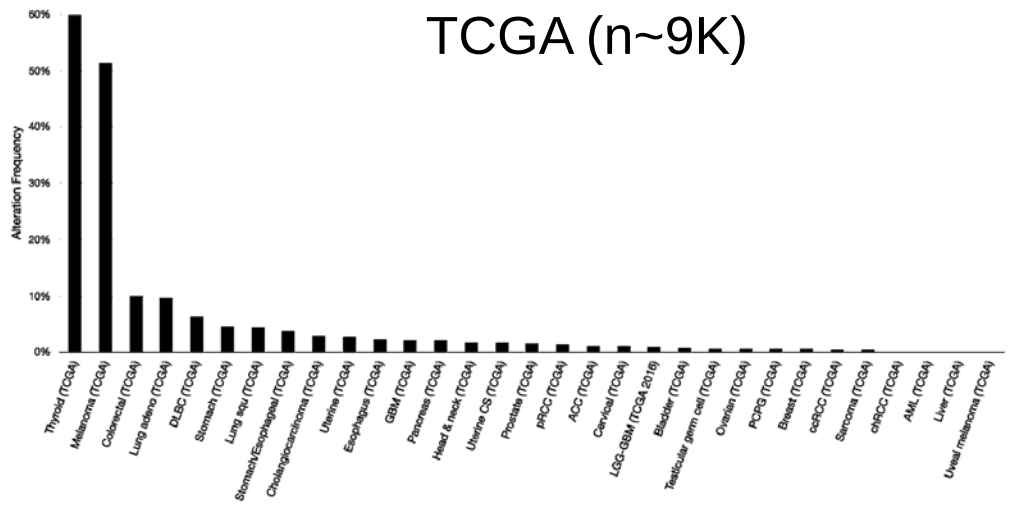
2011

And more to come …

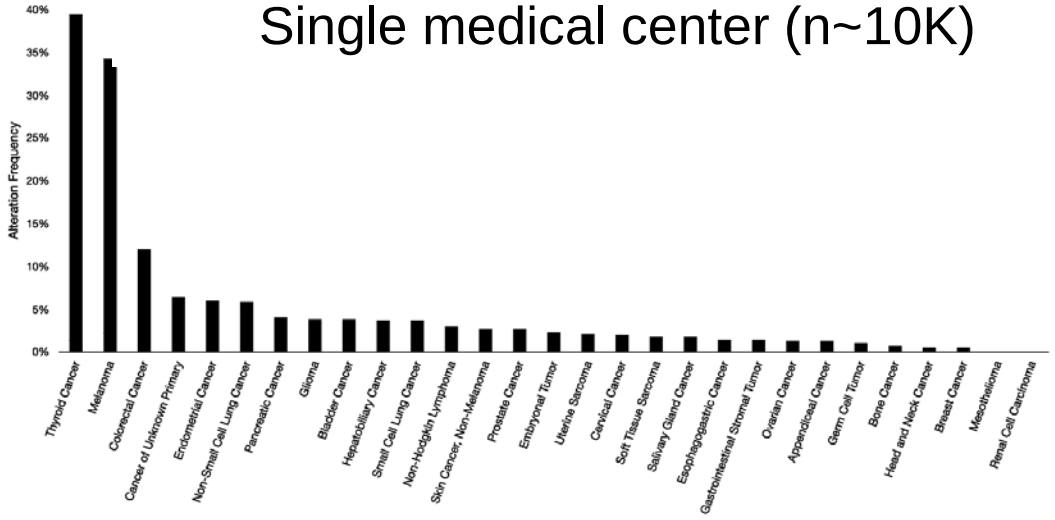


BRAF V600 mutations across oncology

TCGA (n~9K)

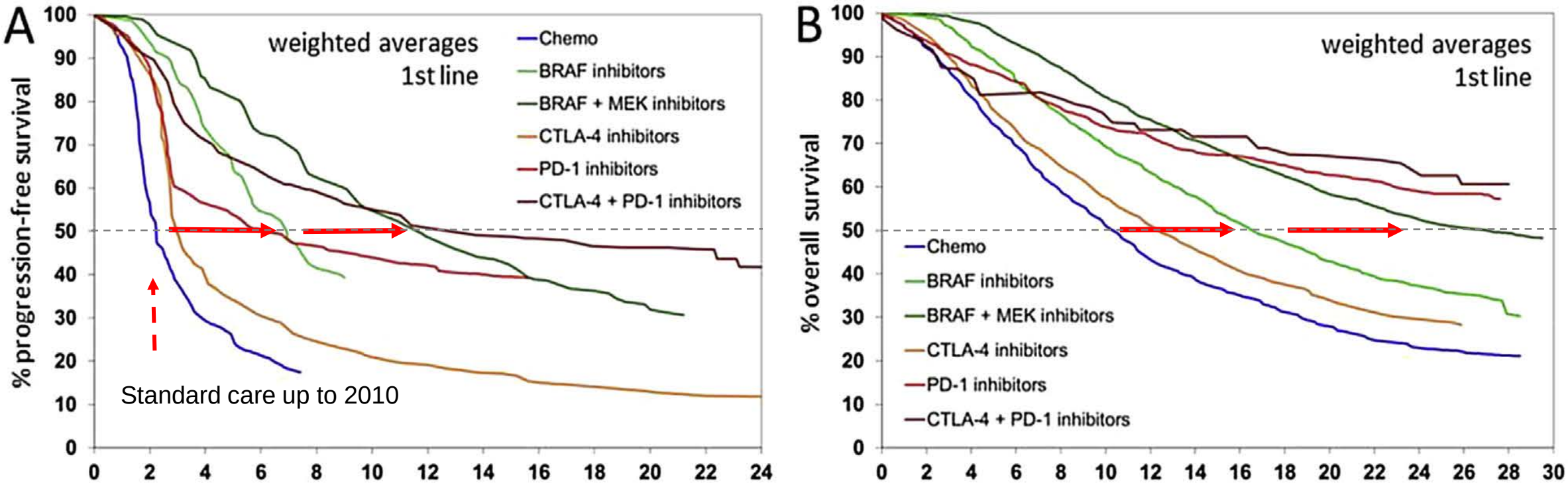


Single medical center (n~10K)



This discussion focuses on exon 15, activating BRAF V600 mutations

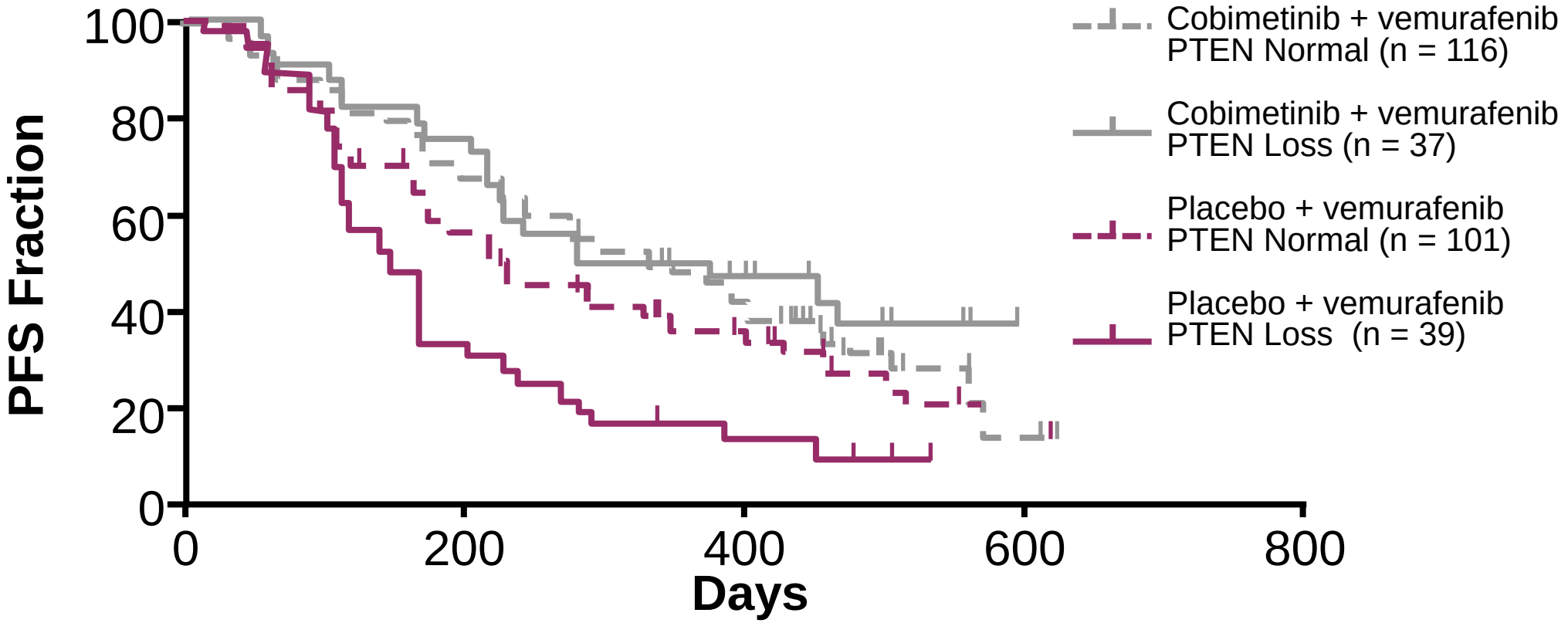
Introduction of BRAF inhibition improved survival of melanoma patients (tale of tails…)



Mean survival curves (A: PFS; B: OS) by weighted averaging of Kaplan-Meier curves of first line melanoma patients treated in clinical trials.

Selma Ugurel, et al; European Journal of Cancer 83 (2017) 247e25

BRAF Inhibition - heterogeneity of tumour genetic alterations



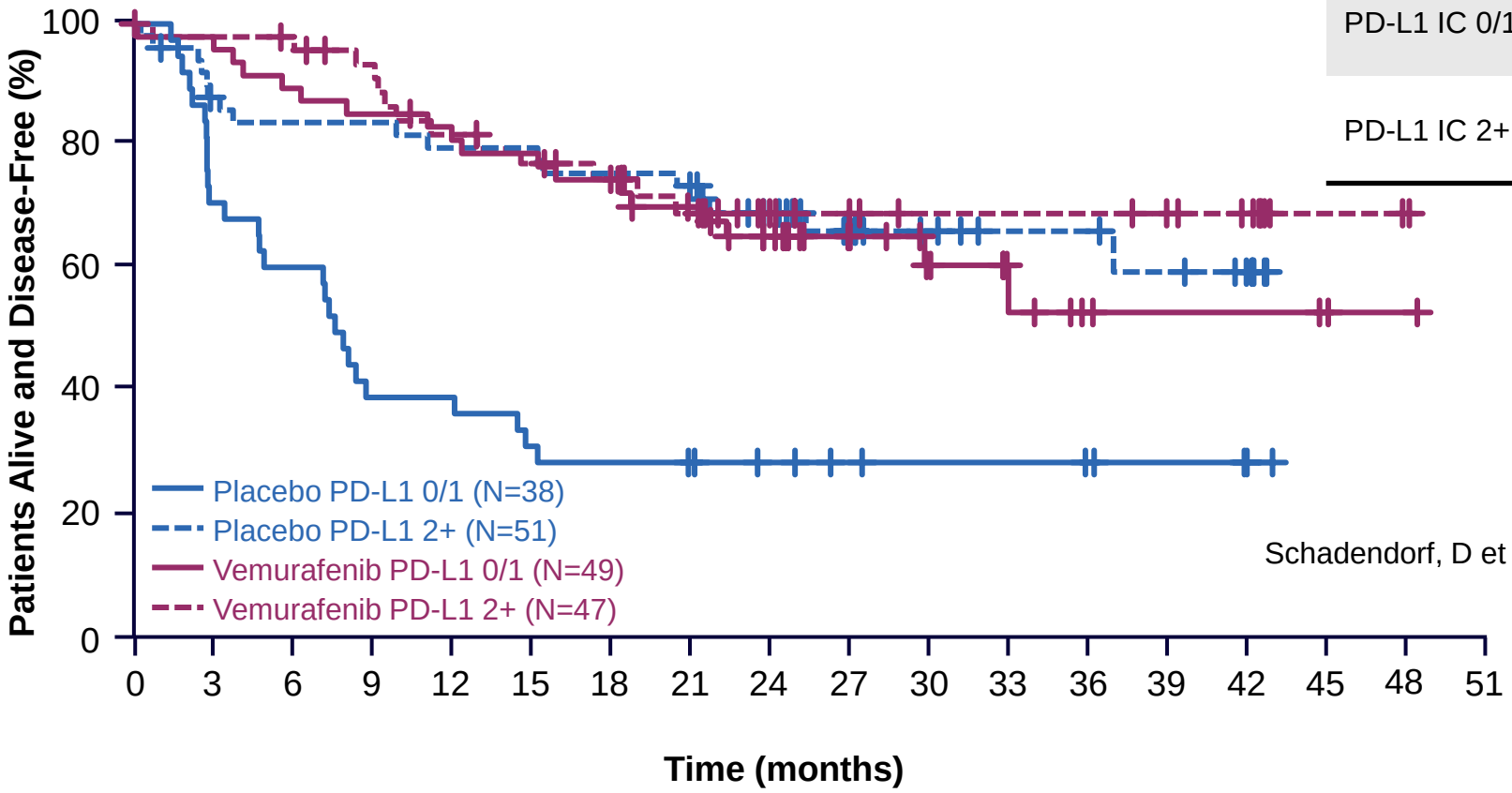
PTEN loss affected PFS and OS in patients treated with BRAFi, not MEKi + BRAFi
(From retrospective exploratory analysis of CoBRIM)

Yan, Y et al, EADO 2016

BRAF Inhibition - heterogeneity of tumour immune contextures

Adjuvant vemurafenib improved DFS in patients with melanoma expressing low PD-L1 (From retrospective exploratory analysis of BRIM8)

	Arm	mDFS (Months)	DFS HR (95% CI)
PD-L1 IC 0/1	Pbo	7.7	0.33 (0.18-0.59)
	Vem	NR	
PD-L1 IC 2+	Pbo	NR	0.85 (0.4-1.75)
	Vem	NR	



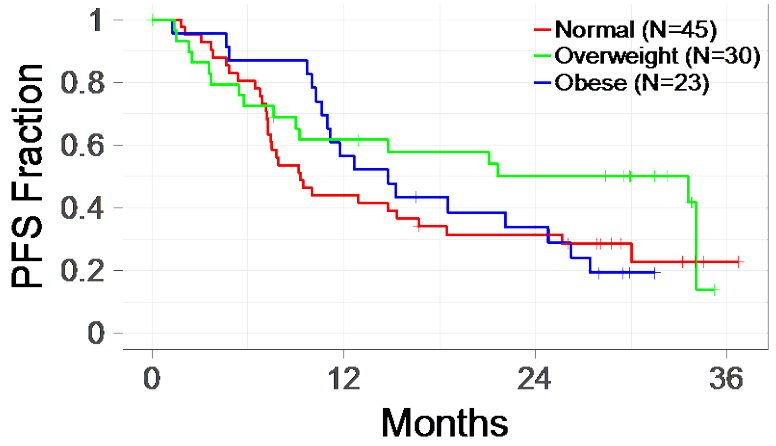
Schadendorf, D et al; Dec 2017 MelanomaBridges, Naples, Italy

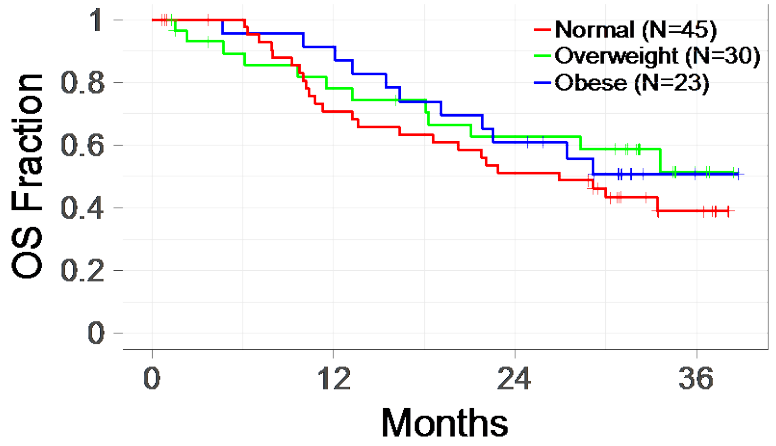
CI, confidence interval; DFS, disease-fee survival; HR, hazard ratio; NR, not reached; Pbo, placebo; PD-L1, programmed death ligand 1; Vem, vemurafenib.

BRAF Inhibition – heterogeneity in host metabolic profiles

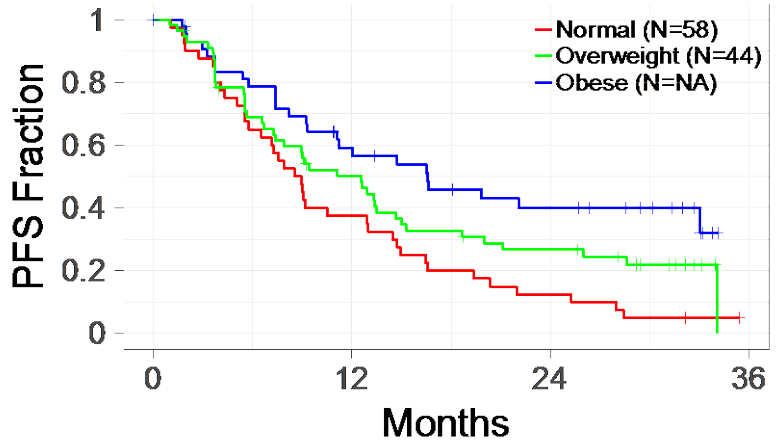
Influence of BMI on BRAF inhibitor sensitivity (From retrospective exploratory analysis of CoBRIM)

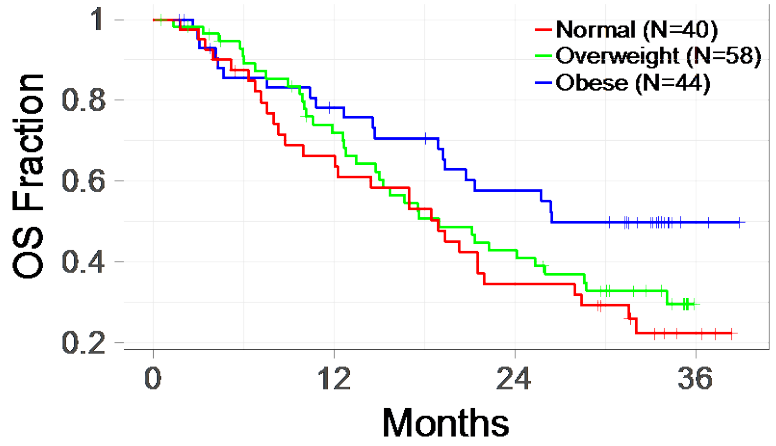
female





male

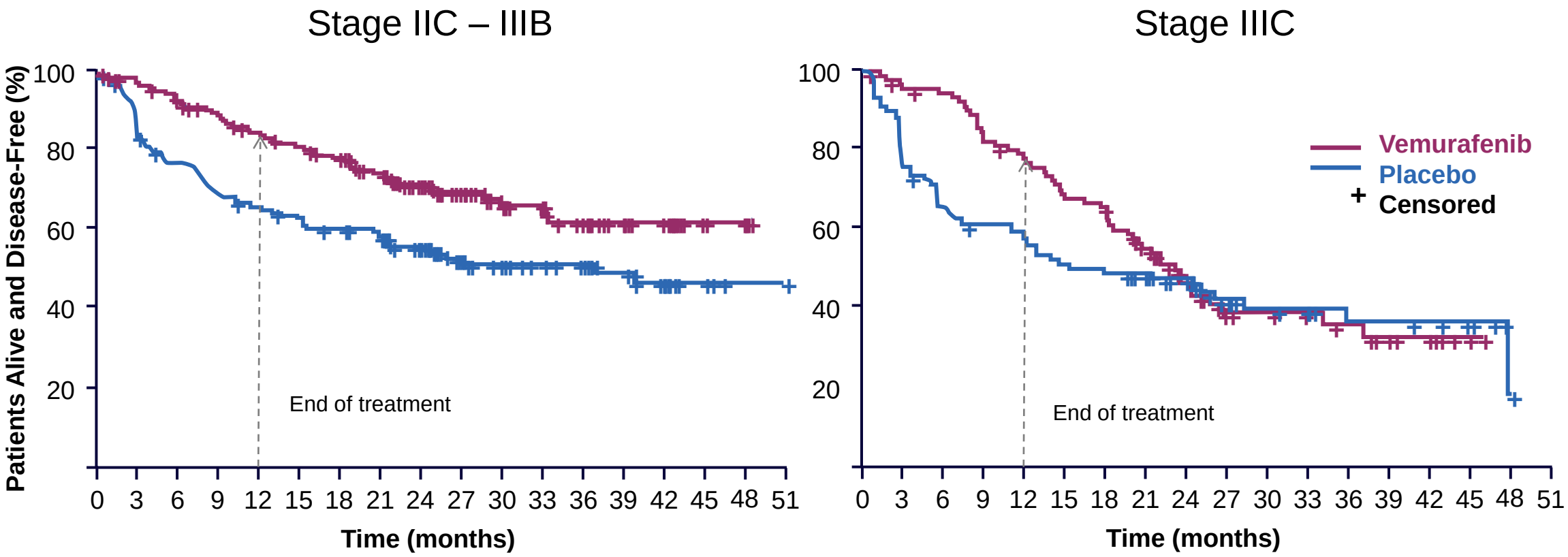




Jennifer M, et al; Lancet Oncology, 2017, accepted for publication

BRAF Inhibition - variability over time

Time = progressive disease stages



DFS of patients after one year adjuvant vemurafenib treatment in different disease stages (BRIM8)

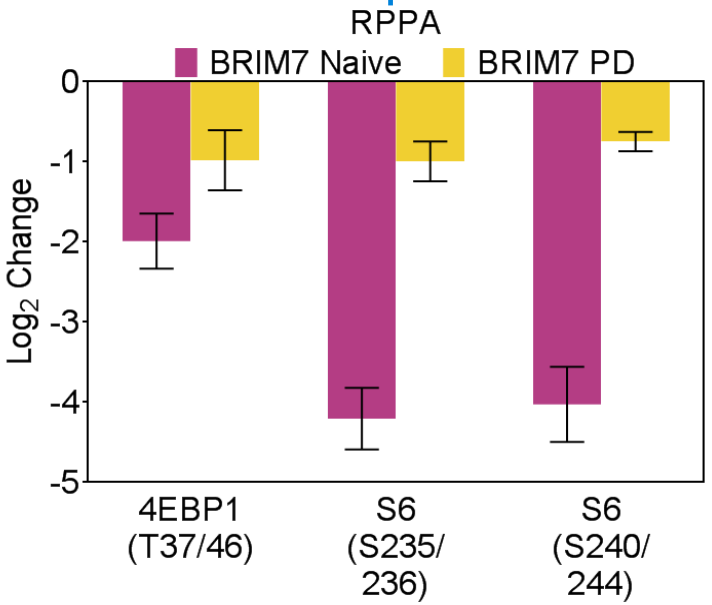
Karl Lewis et al, ESMO 2017

DFS, disease-free survival;

BRAF Inhibition - variability over time

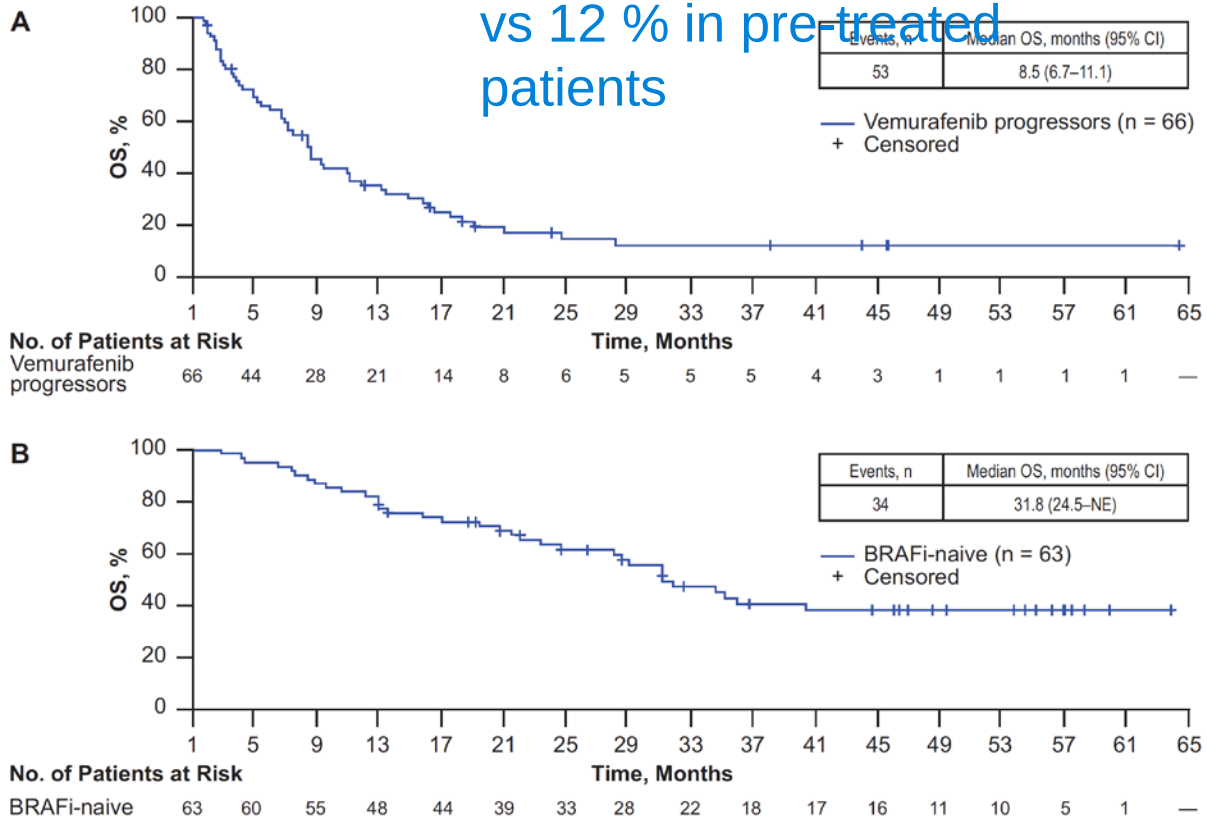
Time = successive lines of treatment

Pharmacodynamics (BRIM7):
Deeper pathway inhibition in BRAFi-naïve patients



Yan, Y et al; ESMO 2014

5 year OS (BRIM7):
39 % in BRAFi-naïve patients
vs 12 % in pre-treated patients



Daud, A et al; 2017 SMR congress

PD, vemurafenib progressor

Parameters of tumour sensitivity (VE-BASKET)

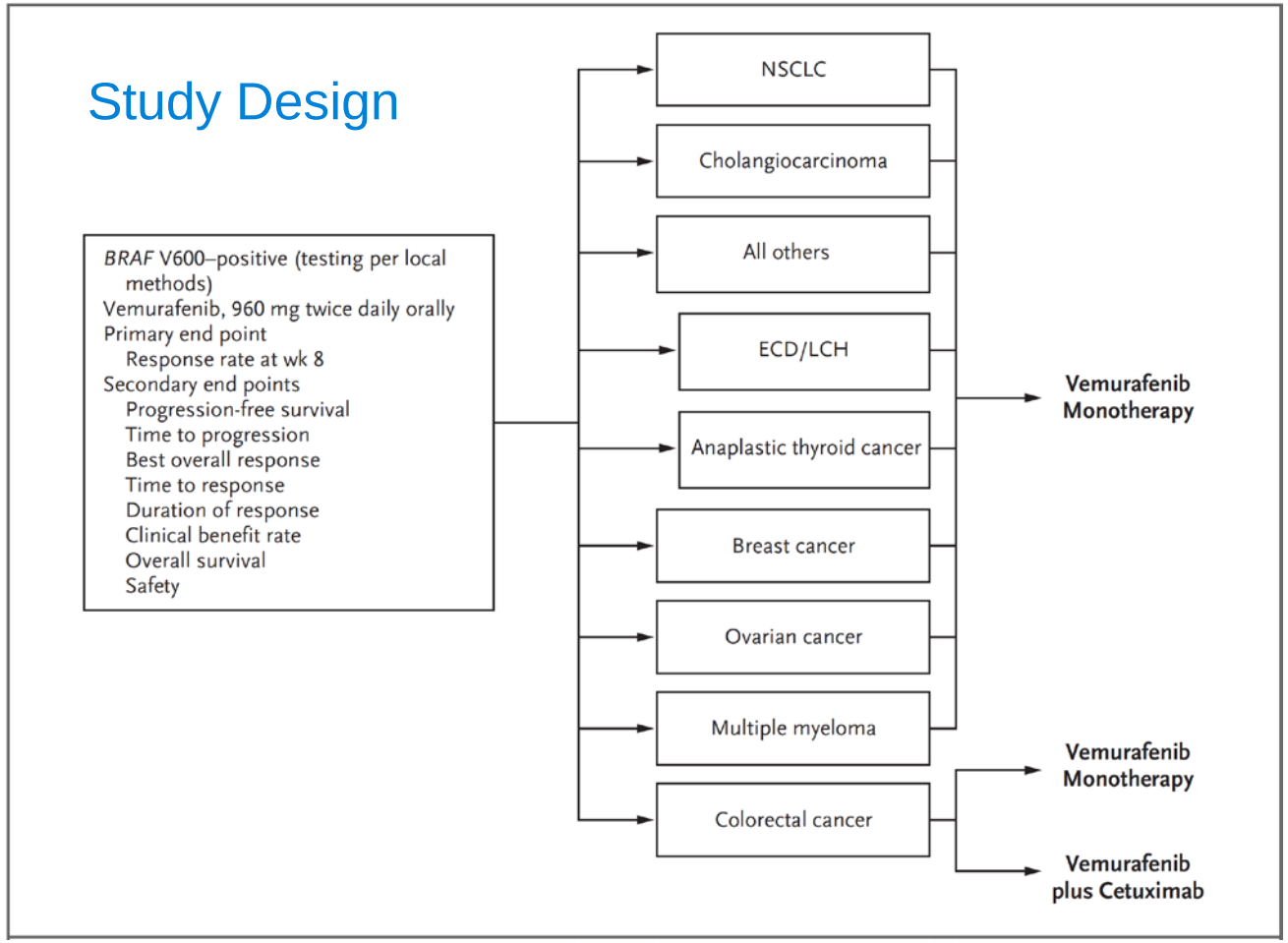
VE-BASKET: a histology-independent, flexible, early phase 2 study of vemurafenib in patients with non-melanoma cancers harboring
BRAF V600 mutations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

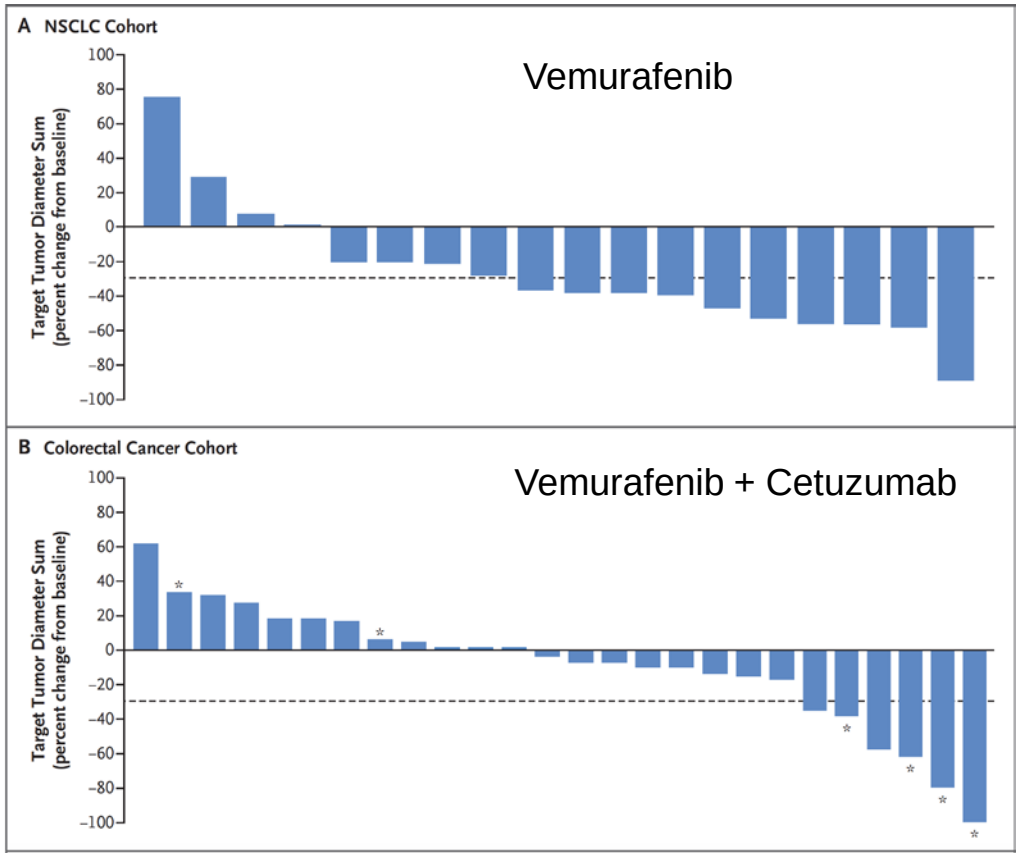
David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

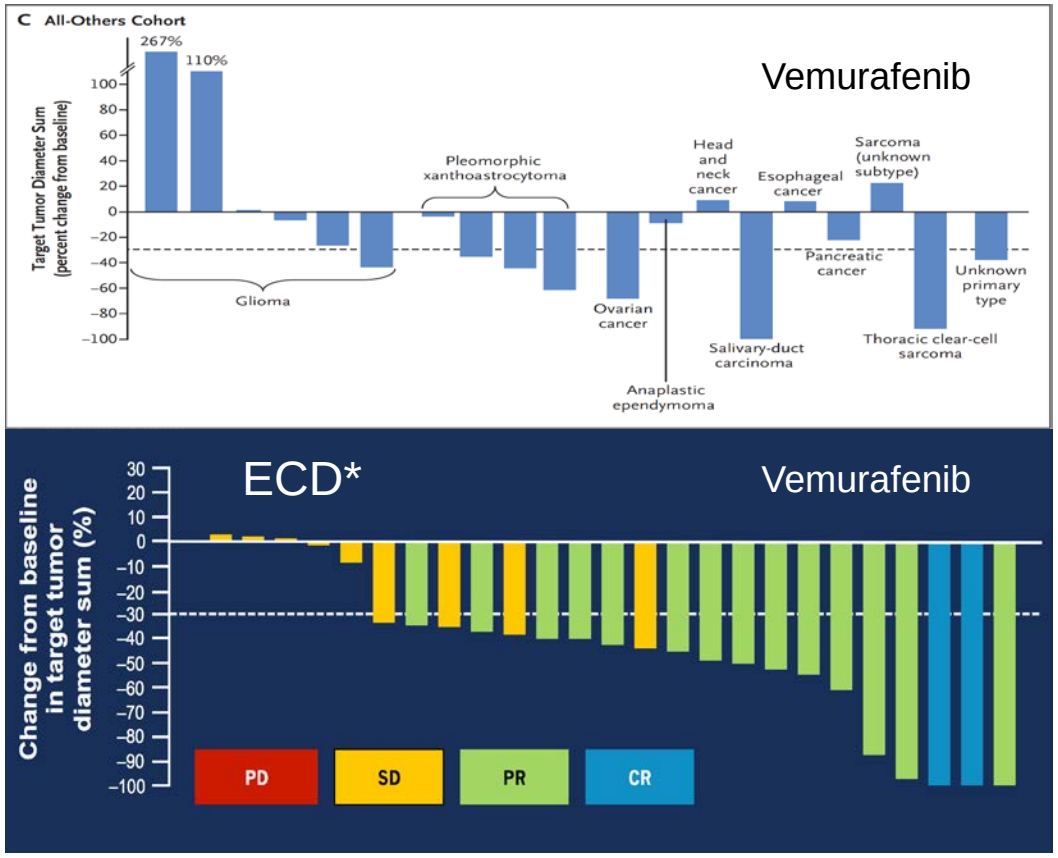


Hyman, DM et al, NEJM 373;8 August 20, 2015

Parameters of tumour sensitivity (VE-BASKET)

Percent change from baseline by RECIST1.1





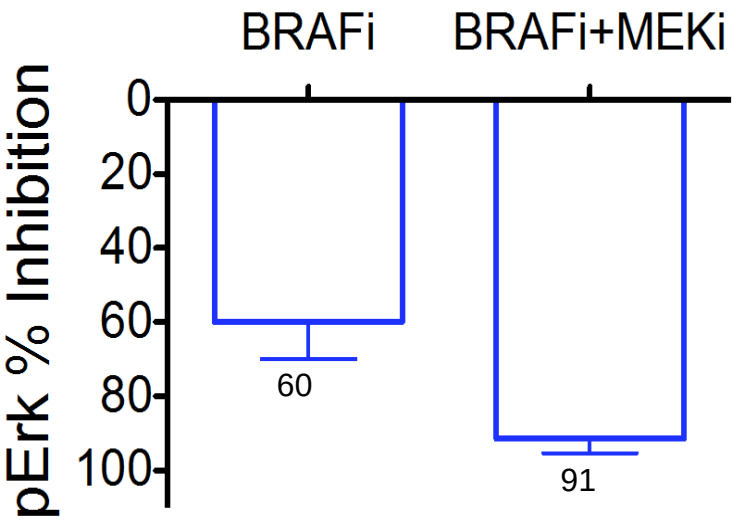
The histologic context is an important determinant of response in BRAF V600–mutated cancers

*ECD: Erdheim–Chester disease, approval in US was based on VE-BASKET

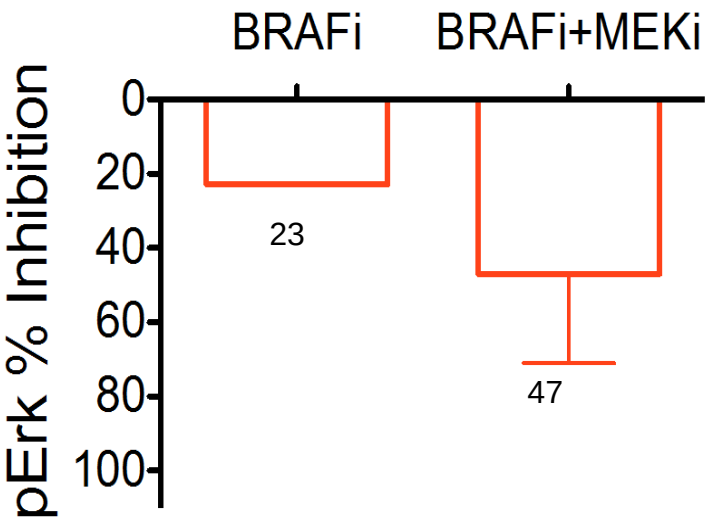
Hyman, DM et al, NEJM 373;8 August 20, 2015 Diamond, E et al, ASH 2016

Pharmacodynamics - heterogeneity between histo/organs

BRAF V600 mutant melanoma[1]



BRAF V600 mutant CRC[2,3]

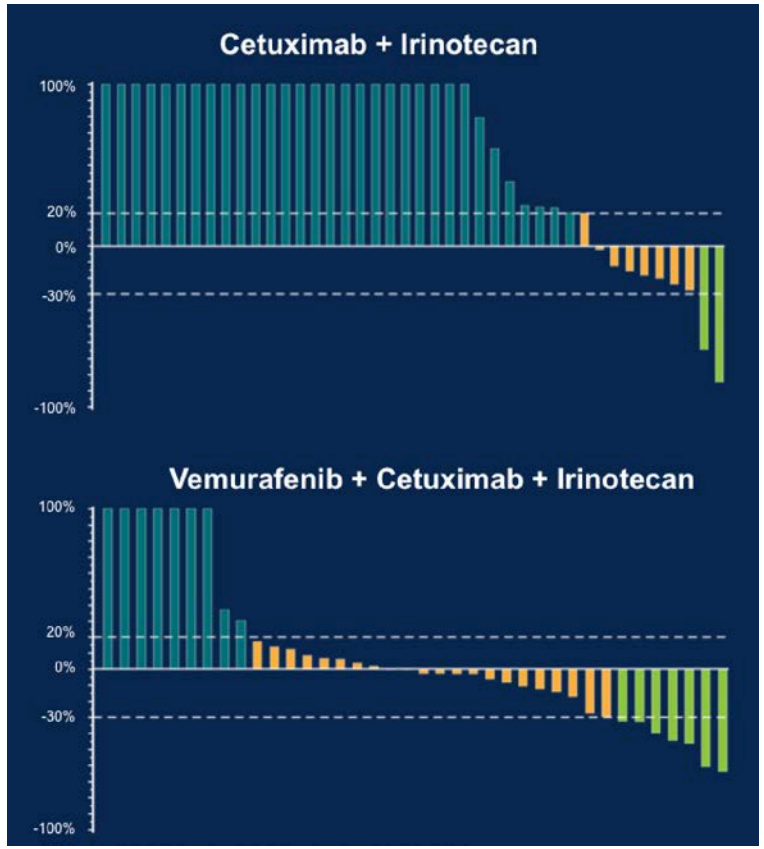


Different degrees of MAPK pathway (pErk) inhibition in melanoma and CRC

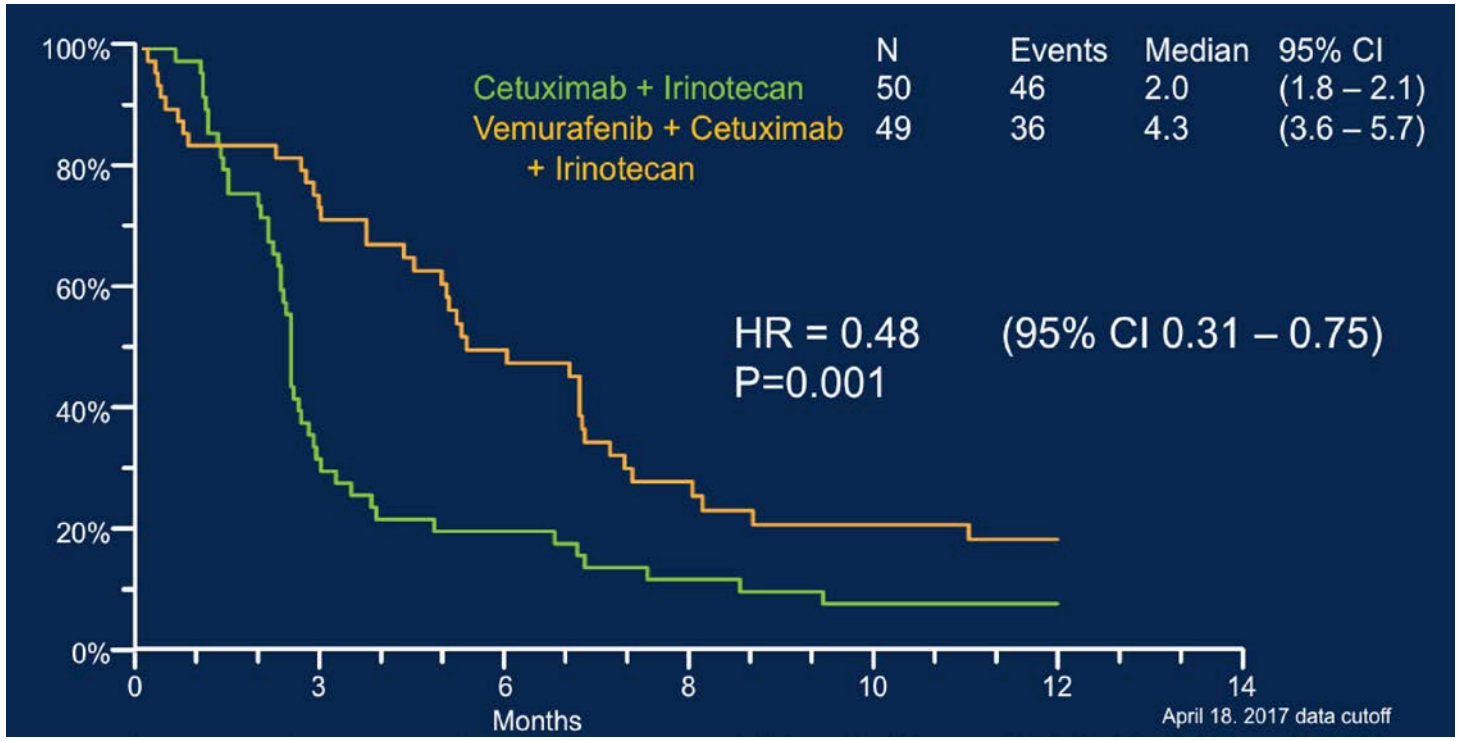
1. Yan, Y et al; ESMO 2014

2. Corcoran, RB et al; JCO 2015.63.2471
3. Sanz-Garcia, E et al; Ann Onco 28: 2648–2657, 2017

BRAF inhibition - integral part of BRAF CRC treatment?



BRAFi + EGFRi + Chemo improved PFS in BRAF CRC (SWOG140



Response and disease control rates were also higher in the vemurafenib arm (16% versus 4% and 67% versus 22%, respectively)

Scott Kopetz et al, ASCO 2017

Summary

- BRAF V600 mutations are driver mutations in many cancers
- Effective BRAF inhibition lead to significant improvement in long term survival in some indications
    - Tumour sensitivity to BRAF inhibition in same tumour type can be influenced by
        - Tumour genetic alterations, immune contextures or host metabolic profiles
        - Disease stages and line of treatments
- The histologic context is an important determinant of response in BRAF V600–mutated cancers
    - BRAF inhibition could still be an integral part of treatment even in histo-type that itself had insufficient activity