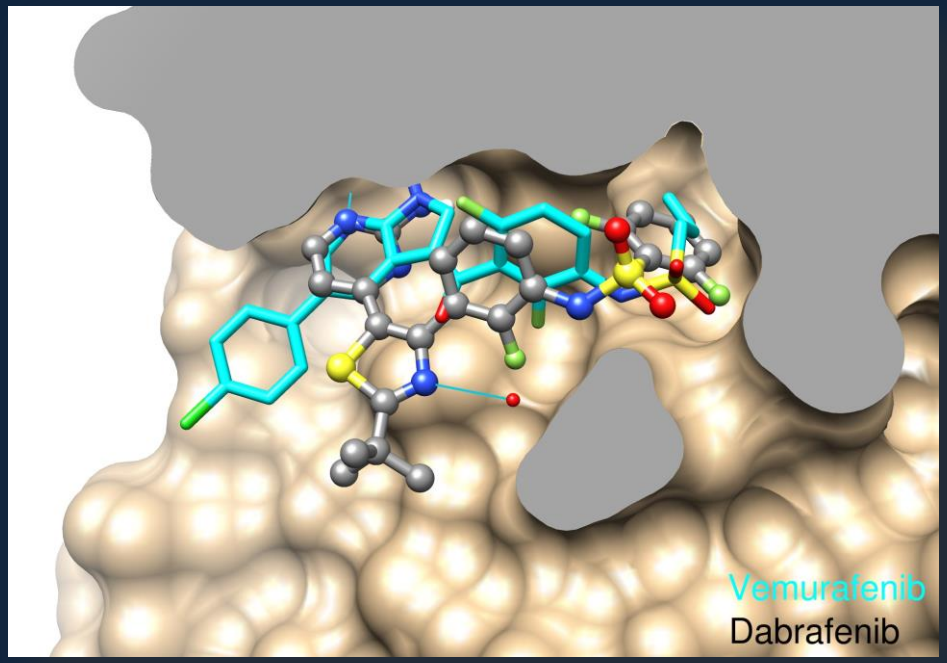
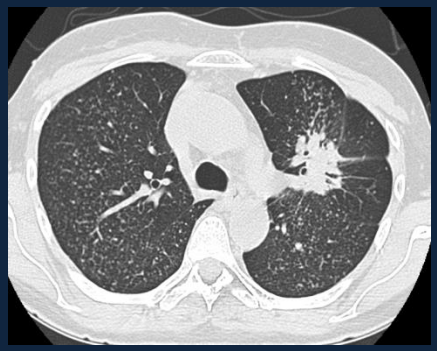
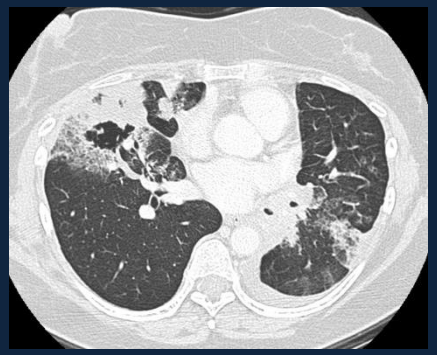
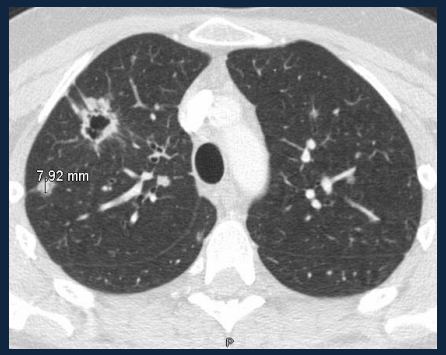
Solange Peters, MD-PhD
Cancer Center, Lausanne
Switzerland



BRAF IN NSCLC







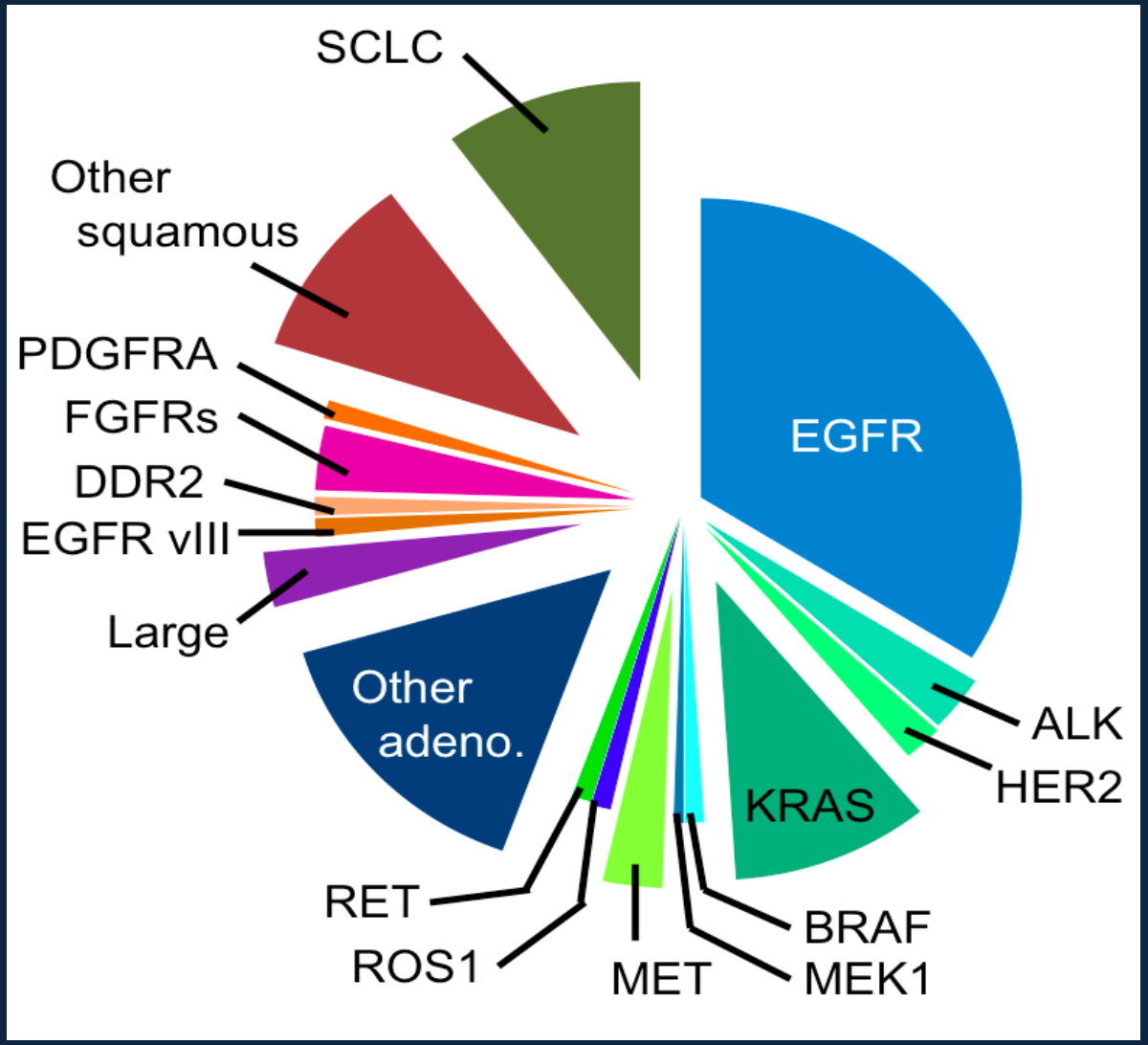
Disclosures

I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, MSD, Amgen, Clovis, Astellas and Tesaro, for which I received honoraria.

I declare no conflict of interest.

NSCLC Drivers



Courtesy Suda and Mitsudomi 2013

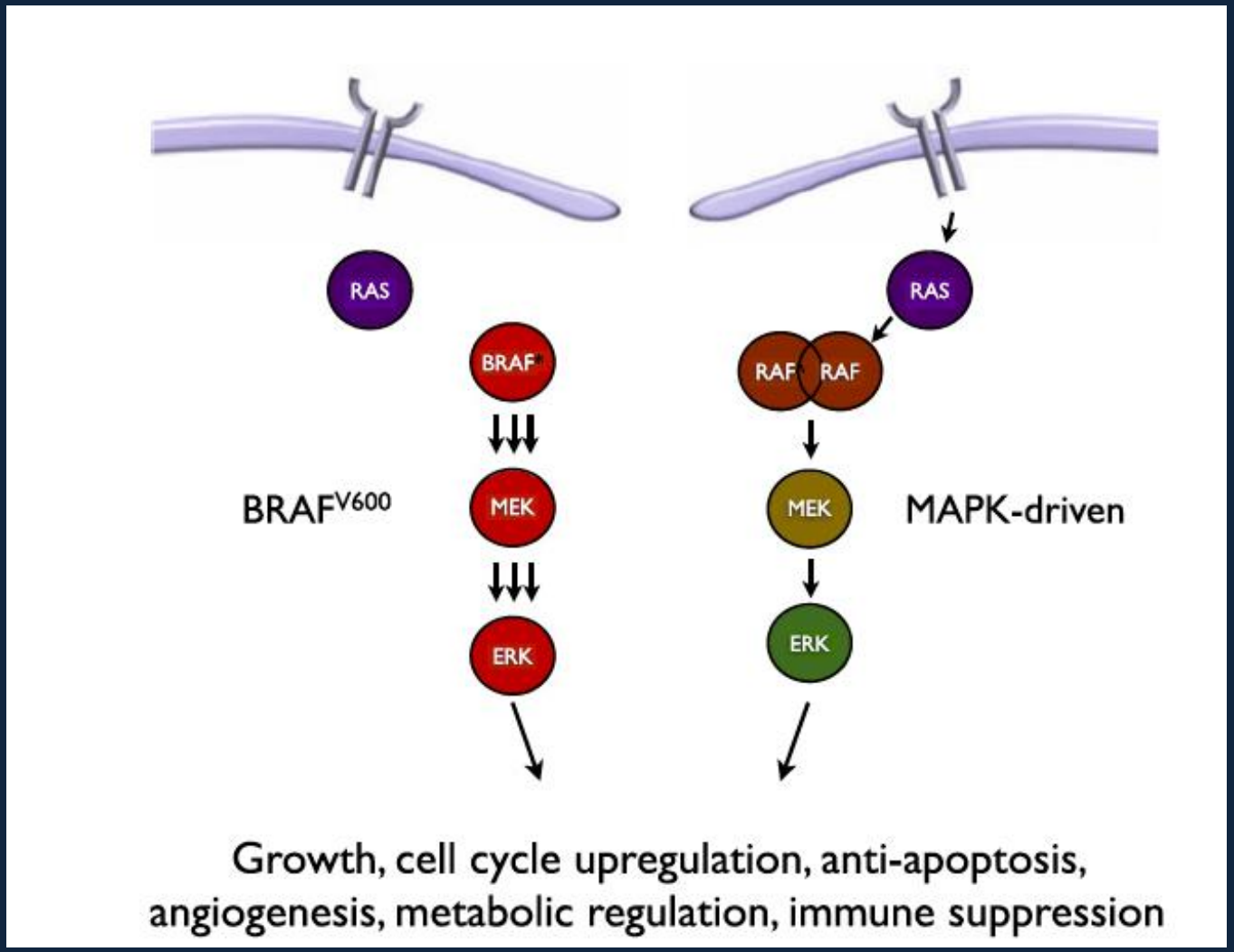
Definition of drivers?

Mouse models for *BRAF*-induced cancers

C. Pritchard[1], L. Carragher, V. Aldridge, S. Giblett, H. Jin, C. Foster, C. Andreadi and T. Kamata
Department of Biochemistry, Henry Wellcome Building, University of Leicester, Lancaster Road, Leicester LE1 7RH, U.K.

Cre-mediated activation in lung indicate that (V600E)BRAF mutation can drive tumour initiation and that its primary effect is to induce high levels of cyclin D1-mediated cell proliferation

Oncogenic vs canonical signalling



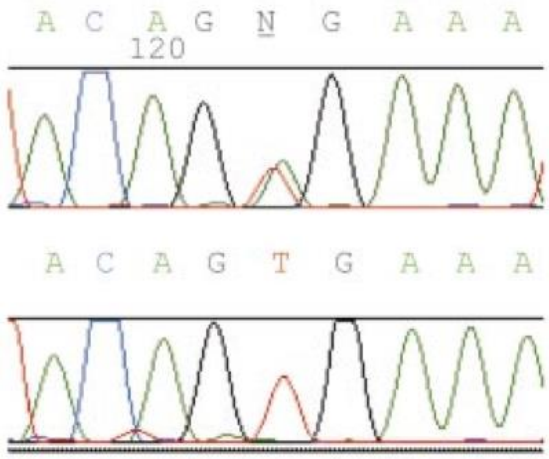
Sullivan , Eur J Cancer 2012

First evidences of BRAF ^{V600E} mutations

Davies H. & al. *Nature* 2002

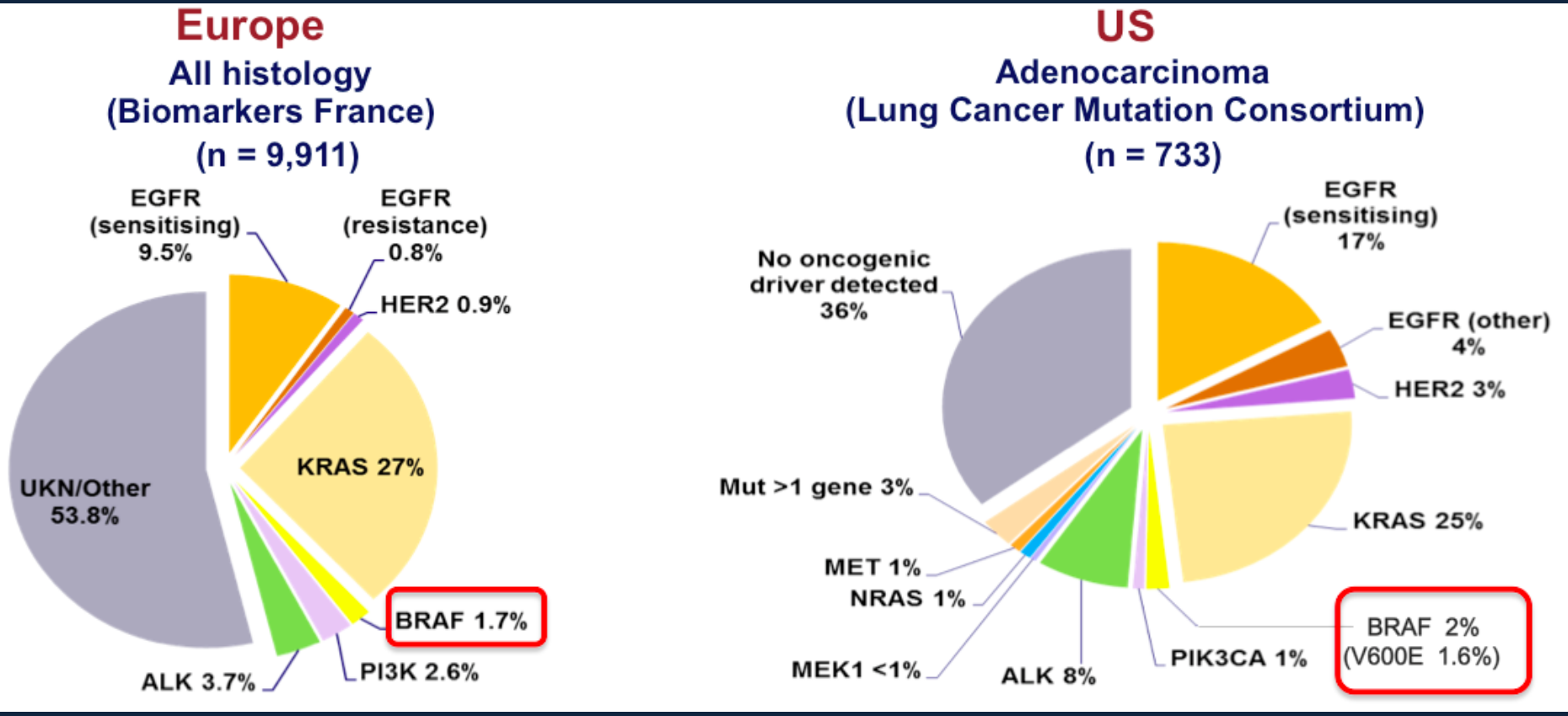
Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14], Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]



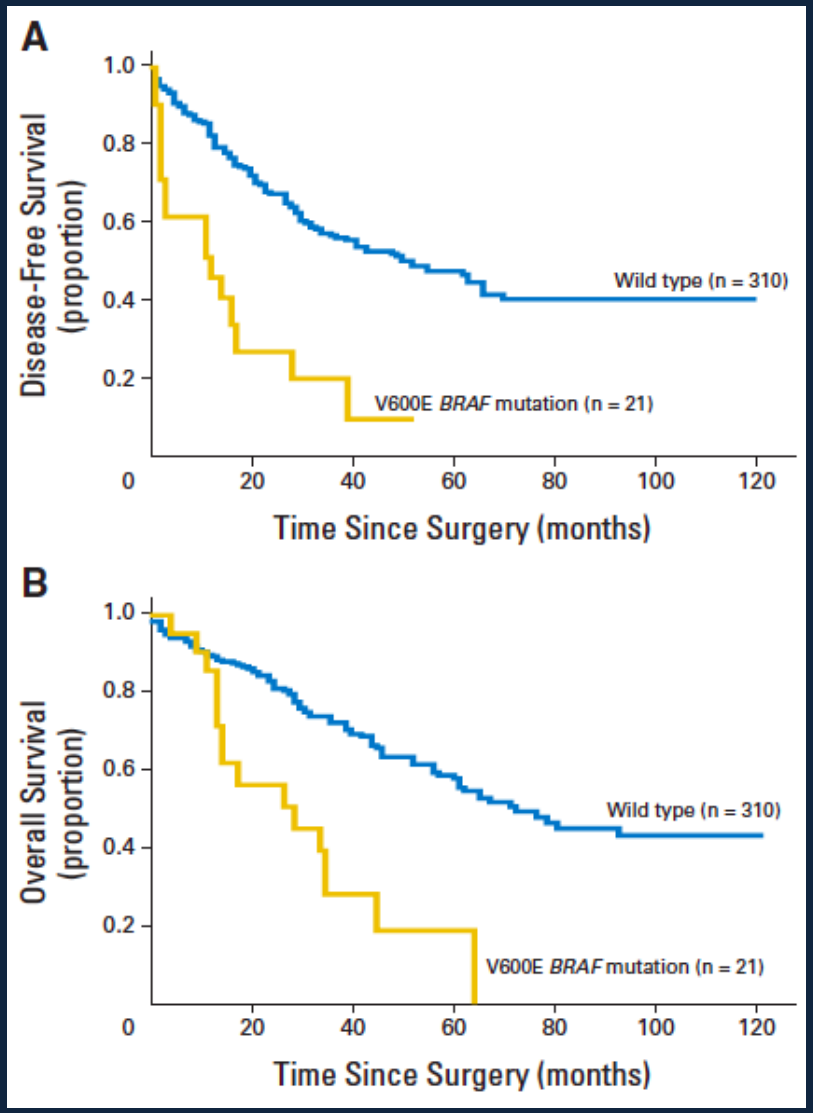
Cancers arise owing to the accumulation of mutations in critical genes that alter normal programmes of cell proliferation, differentiation and death. As the first stage of a systematic genome-wide screen for these genes, we have prioritized for analysis signalling pathways in which at least one gene is mutated in human cancer. The RAS–RAF–MEK–ERK–MAP kinase pathway mediates cellular responses to growth signals[1]. RAS is mutated to an oncogenic form in about 15% of human cancer. The three *RAF* genes code for cytoplasmic serine/threonine kinases that are regulated by binding RAS. Here we report *BRAF* somatic missense mutations in 66% of malignant melanomas and at lower frequency in a wide range of human cancers. All mutations are within the kinase domain, with a single substitution (V599E) accounting for 80%. Mutated BRAF proteins have elevated kinase activity and are transforming in NIH3T3 cells. Furthermore, RAS function is not required for the growth of cancer cell lines with the V599E mutation. As BRAF is a serine/threonine kinase that is commonly activated by somatic point mutation in human cancer, it may provide new therapeutic opportunities in malignant melanoma.

BRAF mutations in NSCLC



- **BRAF missense mutations in exons 11 or 15 are evidenced in 2-5% of NSCLC**
- **> 50% of NSCLC BRAF mutations are non-V600E (G469A (40%), D594G (10%))**
- **V600E mutations might be correlated to non-smoking habit while the contrary might hold true for exon 11 mutations**

BRAF-related prognosis in resected NSCLC



BRAF mutations in 36 ADCs (4.9%) and one SCC (0.3%). 56.8% were V600E, and 43.2% were non-V600E.

V600E mutations were significantly more prevalent in females and an aggressive micropapillary subtype with shorter disease-free and overall survival rate.

Marchetti JCO 2011

BRAF Mutated Lung Cancer: Clinical Features and Outcomes

	1	2	3	4	5	6
Country	US	Italian	US	US	US	Norway
Patients, n	697	1046	883	951	NA	979
BRAF n (%)	18 (3)	36 (3.5)	36 (4)	21 (2)	63 (NA)	17 (1.7) (AC 2.3)
V600E	50%	58%	50%	81%	57%	V600E only
Smoking	smokers	never smokers	no difference	smokers	smokers	71% (ex-) smokers
Survival	same	worse	same	same	same	NA
Comparator	EGFR/ALK / KRAS+	BRAF WT	BRAF/EGFR/ KRAS/ALK WT	other drivers	EGFR/KRAS+	NA

[1] Palk J Clin Oncol 2011 [2] Marchetti J Clin Oncol 2011 [3] Cardarella Clin Cancer Res 2013[4] Villaruz Cancer 2015, [5] Litvak J Thor Oncol 2014, [6] Brustugum Lung Cancer 2014

Clinical Characteristics and Course of 63 Patients with *BRAF* Mutant Lung Cancers

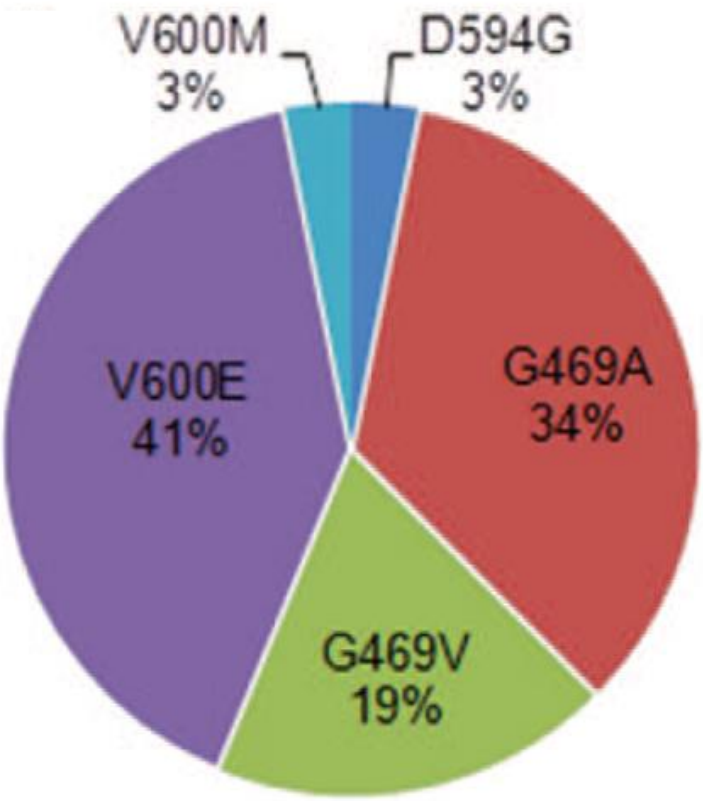
Anya M. Litvak, MD, Paul K. Paik, MD,* Kaitlin M. Woo, MS,† Camelia S. Sima, MD,† Matthew D. Hellmann, MD,* Maria E. Arcila, MD,‡ Marc Ladanyi, MD, PhD,‡ Charles M. Rudin, MD, PhD,* Mark G. Kris, MD,* and Gregory J. Riely, MD, PhD**

- V600 had a better survival than non-V600 (3-year OS: 24% versus 0%; $p < 0.001$).

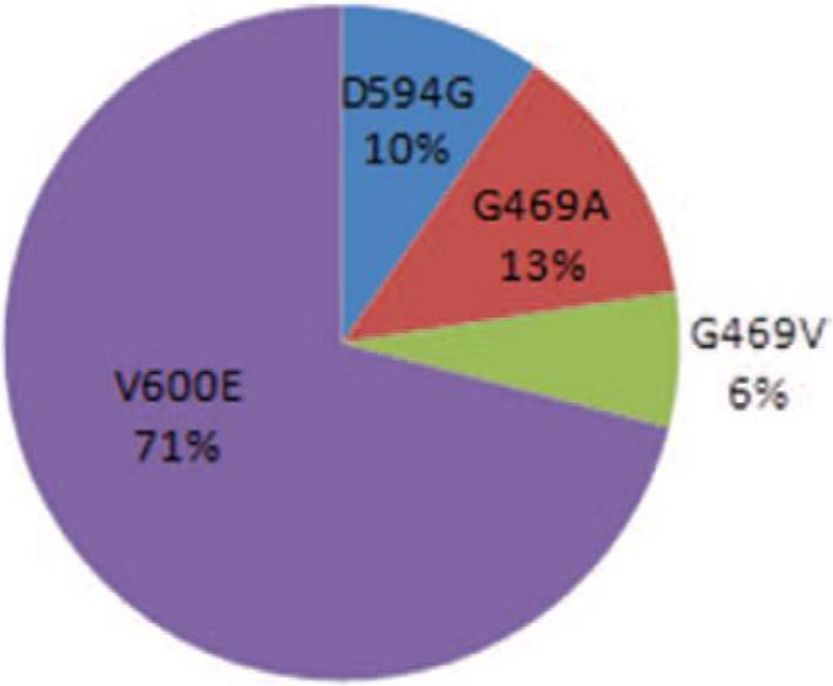
- Within the BRAF cohort, patients with V600E-mutated tumors had a shorter PFS to platinum-based chemotherapy compared with those with non-V600E mutations (4.1 vs. 8.9 months; NS)

BRAF mutation type according to tumour stage?

Stage I-IIIA

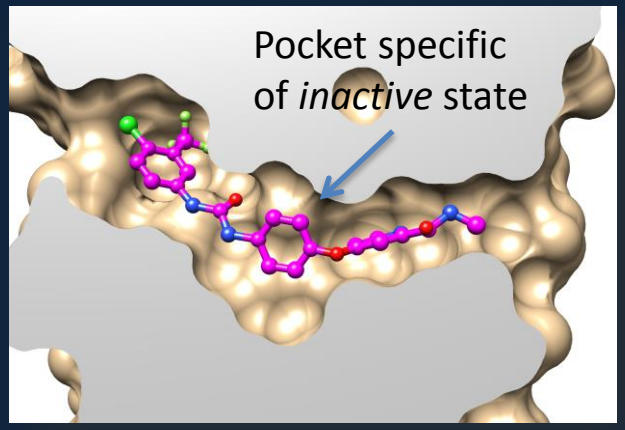


Stage IIIB/IV

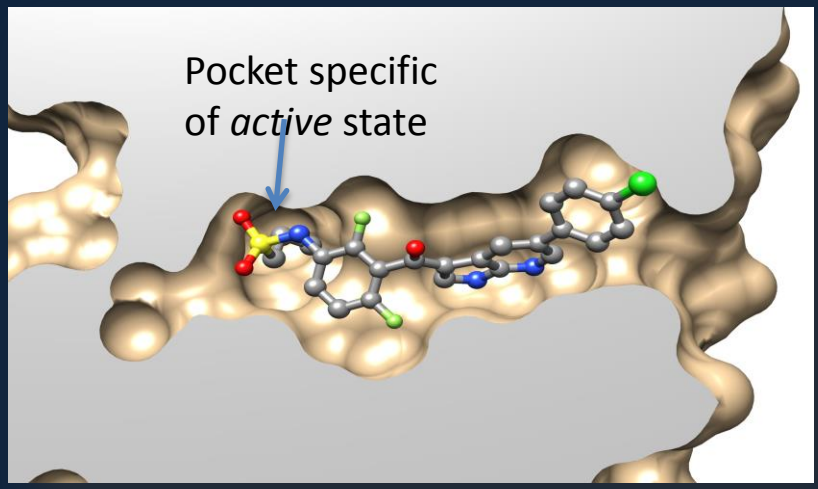


Litvak, J Thor Oncol 2014

BRAF type I and type II inhibitors are available



Sorafenib docked to BRAF WT



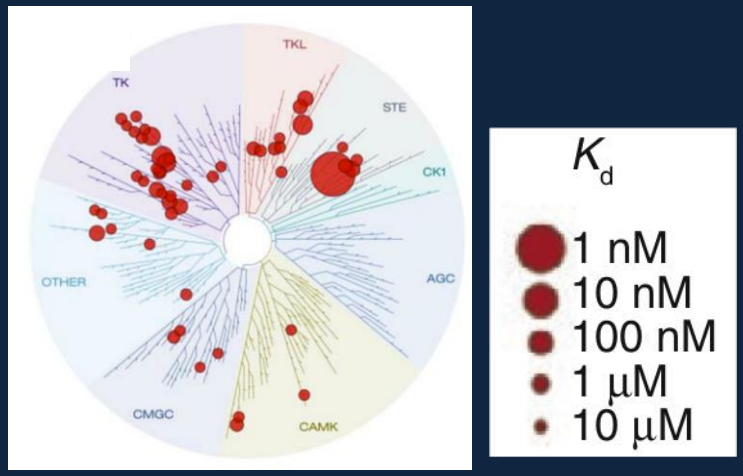
Vemurafenib docked to $BRAF^{V600E}$

Sorafenib stabilises the enzyme in inactive conformation of the kinase (Type 2-binding model), whereas the other inhibitors stabilise the enzyme with the DFG-loop in the ATP pocket (Type 1-binding model).

All of these inhibitors are less-potent inhibitors of RAF–MEK–ERK signalling in cells expressing wild-type BRAF and in fact paradoxically activate the pathway, especially in cells with activating RAS mutations.

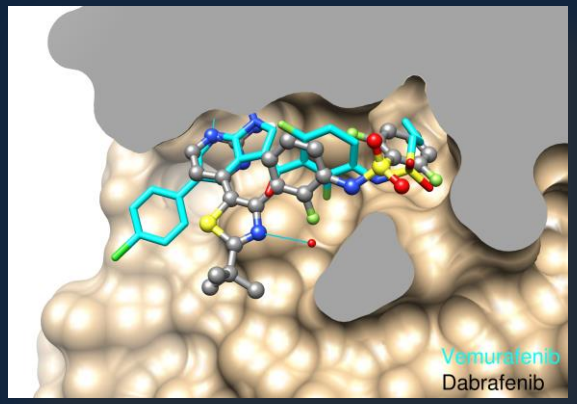
BRAF V600E type I inhibitors: Vemurafenib

- Vemurafenib is a first in class inhibitor targeting activated BRAF V600E kinase (type I inhibitor)
- Kinome specificity profile:



Davis & al. *Nat. Biotech.* 2011

- FDA and EMA approved: 2011/12



Target Kinase	IC50 (nM)
BRAF V600E	31
BRAF WT	100
CRAF	48

Bollag & al. *Nature* 2010

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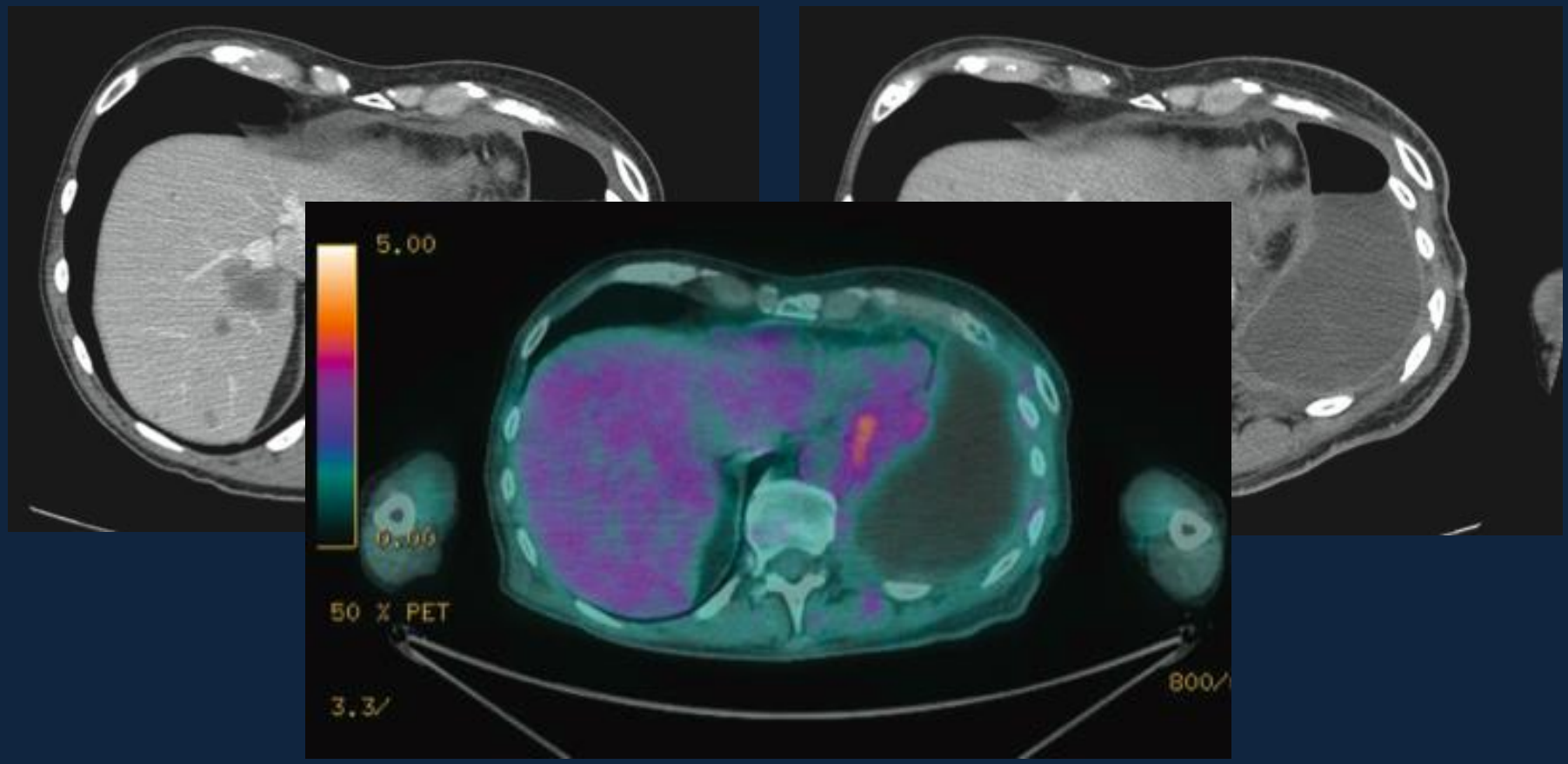
JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

Dramatic Response Induced by Vemurafenib in a *BRAF* V600E-Mutated Lung Adenocarcinoma



A Patient With BRAF V600E Lung Adenocarcinoma Responding to Vemurafenib

Oliver Gautschi, MD, Chantal Pauli, MD,† Klaus Strobel, MD,‡ Astrid Hirschmann,† Gert Printzen, MD,§ Stefan Aebi, MD,* and Joachim Diebold, MD†*

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Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Case report

BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib

Sara D. Robinson[a], Joyce A. O'Shaughnessy[a,b], C. Lance Cowey[a,b], Kartik Konduri[a,b,*]

[a] Baylor Charles A. Sammons Cancer Center, Baylor University Medical Center, 3410 Worth Street, Dallas, TX 75246, United States
[b] Texas Oncology, 3410 Worth Street, Dallas, TX 75246, United States

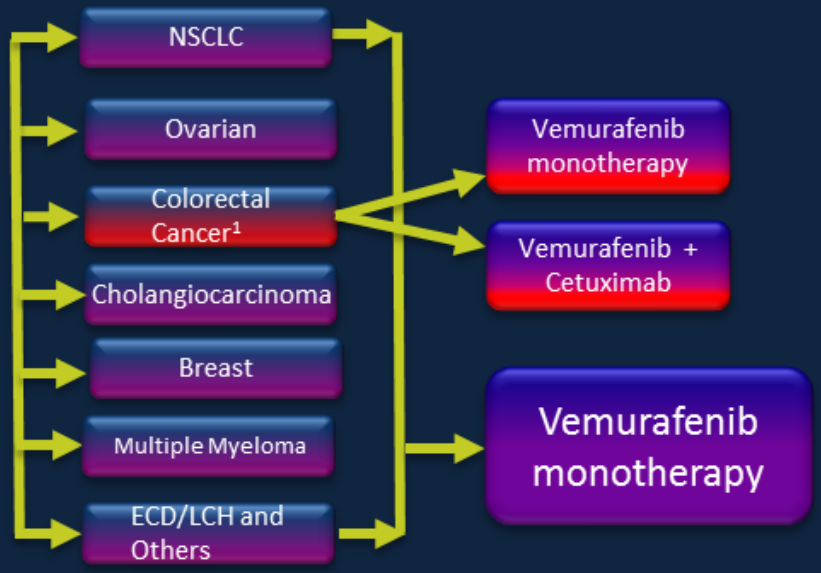
Lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib

Oliver Gautschi[a,*], Solange Peters[e], Vincent Zoete[e], Franziska Aebersold-Keller[b], Klaus Strobel[c], Bernhard Schwizer[d], Astrid Hirschmann[b], Olivier Michielin[e], Joachim Diebold[b]

VE-BASKET: A First-in-Kind, Phase 2, Histology-Independent "BASKET" Study of Vemurafenib in Non-melanoma Solid Tumors Harboring *BRAF*^{V600} Mutations

- Simon 2-stage adaptive design[1]

- 7 Cohorts (metastatic solid tumors and multiple myeloma)
- Up to 170 pts
- *BRAF*^{V600} positive (testing per local methods)
- **Vemurafenib** 960 mg BID orally
- **Primary Endpoint**: RR at Week 8
- **Secondary Endpoints**: PFS, TTP, BOR, TTR, DOR, CBR, OS, safety



ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung cancer.

- Primary endpoint: response rate at Week 8
- Secondary endpoints: PFS, TTP, BOR, TTR, DOR, CBR, OS, safety

1. Lin Y, Shih WJ. *Biometrics.* 2004;60(2):482-490.
2. Tabernero J et al. ASCO Meeting abstract #3518 to be presented Saturday, May 31, 2014.

Preliminary Change From Baseline[a]

Progressive disease

Stable disease

Partial response

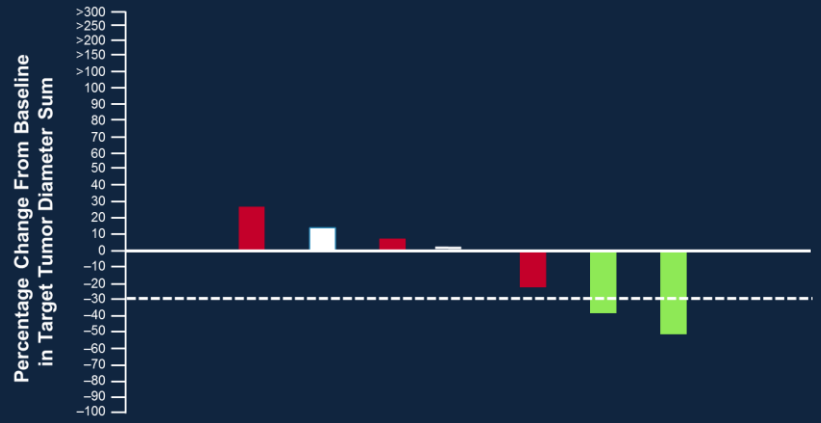
Complete response

Not evaluable

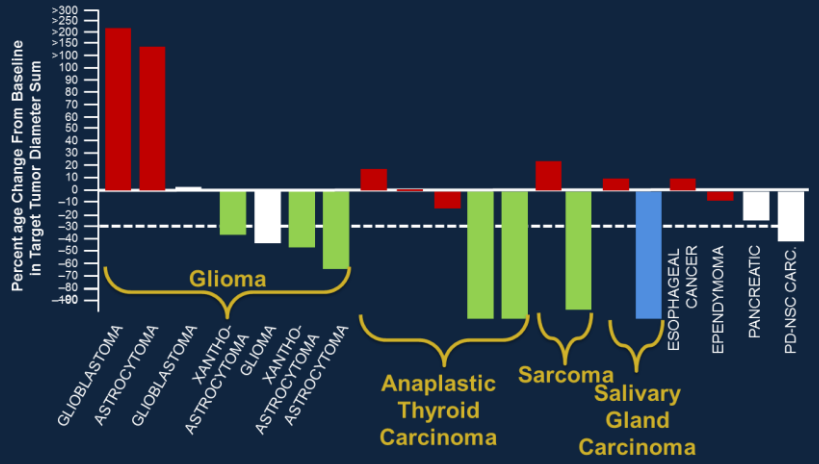
NSCLC

ECD/LCH

Cholangiocarcinoma



Other solid tumors



[a]Only includes patients who had measurable disease at baseline based on RECIST and at least 1 posttreatment evaluation.

ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung carcinoma; PD-NSC carc., poorly differentiated non-small cell carcinoma.

Presented by: David M. Hyman

Preliminary Efficacy Evaluation: Best Overall Response

Patients, n (%)	NSCLC (n=19)	CLC (n=7)[a]	ECD/LCH (n=11)[b]
Timing of Analysis	Best Confirmed Overall Response	Unconfirmed Preliminary Overall Response at Week 8	Best Confirmed Overall Response
Complete response	–	–	1 (9.1)
Partial response	8 (42.1)	–	3 (27.3)
Stable disease	6 (31.6)	4 (57.1)	6 (54.5)
Progressive disease	3 (15.8)	3 (42.9)	–
Not evaluable	2 (10.5)[c]	–	1 (9.1)[d]
Clinical benefit[e]	14 (73.7)	4 (57.1)	10 (90.9)
95% CI	48.8-90.9	18.4-90.1	58.7-99.8

CI, confidence interval; CLC, cholangiocarcinoma; CR, complete response; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NSCLC, non-small cell lung carcinoma; PR, partial response; SD, stable disease.

[a]Unconfirmed preliminary overall response at Week 8. In cohort 4 (CLC), 2 patients had a late response (PR) at Week 24 (unconfirmed) and Week 16 (confirmed).

[b]Table includes only patients who had measurable disease at baseline and at least 1 posttreatment evaluation based on RECIST.

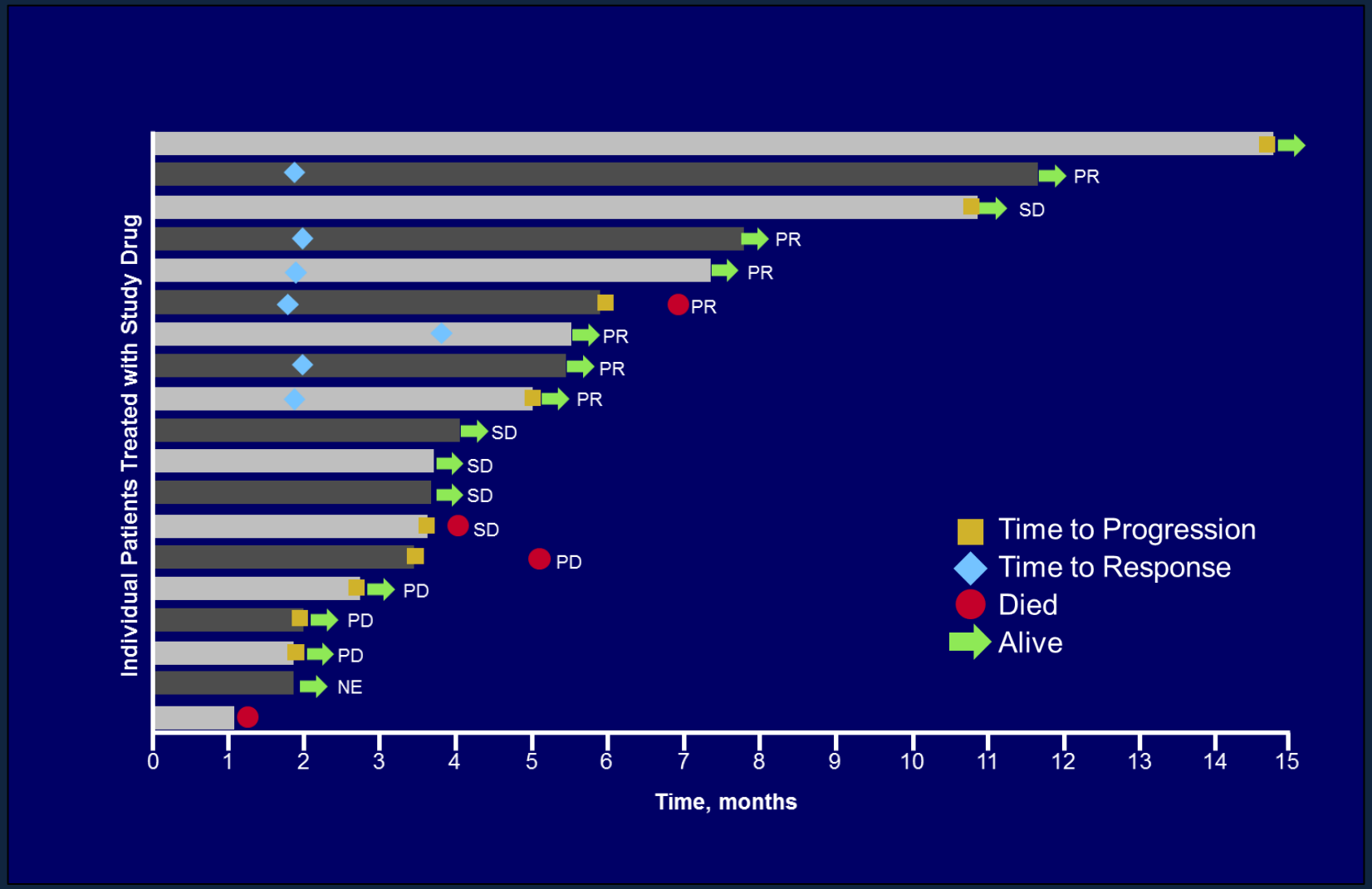
[c]1 patient died and 1 patient withdrew consent before Week 8 evaluation.

[d]Patient withdrew from study because of an adverse event before Week 8 evaluation.

[e]Clinical benefit = PR, CR, or SD.

Presented by: David M. Hyman

Time to Response and Progression



BRAF V600E type I inhibitors: Dabrafenib

Mode of Action

- Reversible, small molecule
- ATP competitive

Molecular Activity:

BRAF V600E: IC_{50} 0.65 nM

BRAF WT: IC_{50} 3.2 nM

Selectivity:

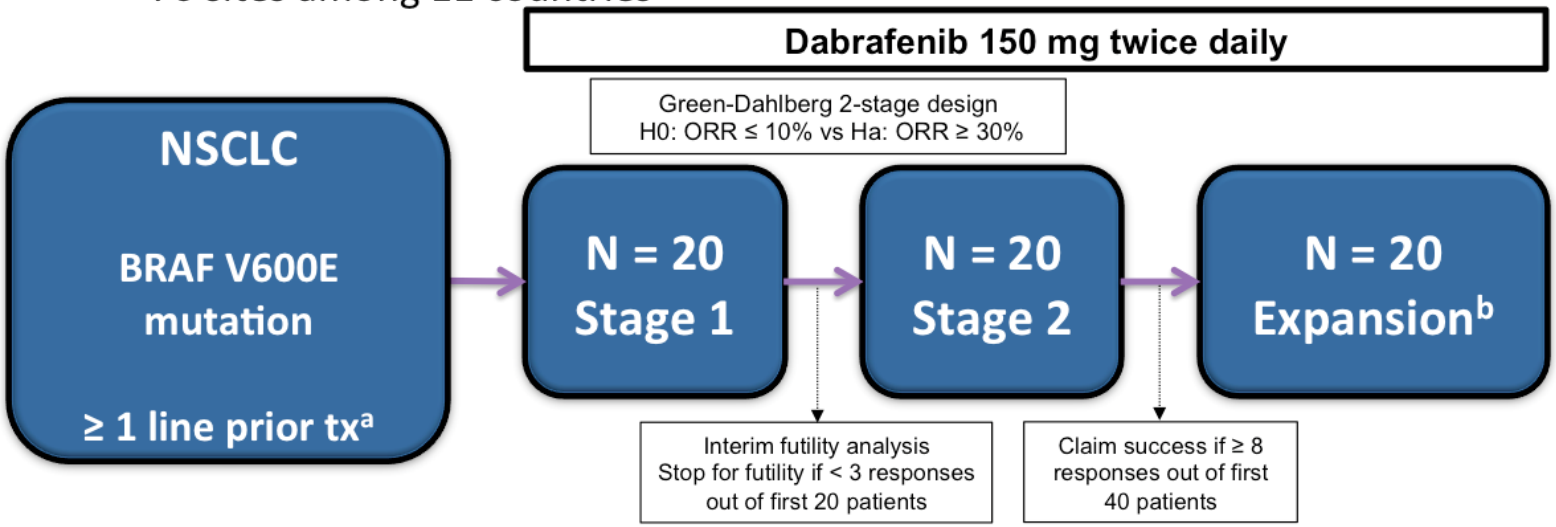
- IC_{50} of 10-100 nM against 8 of 282 human kinases

BRAF inhibitor phase 2 trial in NSCLC

MADRID 2014 ESMO congress

BRF113928: Study Design

- Single arm, phase 2, open label
- 70 sites among 11 countries



[a] Six first line patients enrolled under protocol Amendment 07

[b] Expansion phase was added with protocol Amendment 07 to provide better precision of ORR estimate with total of 78 ≥ 2nd line patients enrolled to increase probability of at least 60 with BRAF V600E mutation centrally confirmed

Planchard, ASCO 2014

BRAF inhibitor phase 2 trial in NSCLC

MADRID 2014 ESMO congress

BRF113928: Study Objectives

- **Primary objective**: Investigator-assessed ORR
- **Secondary objectives**: PFS, duration of response, overall survival (OS), safety, tolerability, and population pharmacokinetics
- **Analysis populations**:
  - Efficacy population (≥ 2nd line), N = 78
  - Safety population (All Treated), N = 84

		≥ 2nd Line (N = 78)
Age, years	Median (range)	66 (28-85)
Sex, (%)	Female/male	39 (50)/39 (50)
Race, n (%)	White	59 (76)
	Asian	17 (22)
	African American	2 (3)
ECOG PS at baseline, n (%)	0	16 (21)
	1	50 (64)
	2	12 (15)
Smoking history, n (%)	Never smoked	29 (37)
	Smoker ≤ 30 pack-years[a]	25 (32)
	Smoker > 30 pack-years[a]	24 (31)
Histology at initial diagnosis, (%)	Adenocarcinoma	75 (96)
	Other	3 (4)
Number of prior systemic regimens for metastatic disease, n (%)	1	40 (51)
	2	14 (18)
	≥ 3	24 (31)
Time since last progression, months (n = 71)	Median (range)	1.1 (0.2 – 6.8)

BRAF inhibitor phase 2 trial in NSCLC

MADRID 2014 ESMO congress

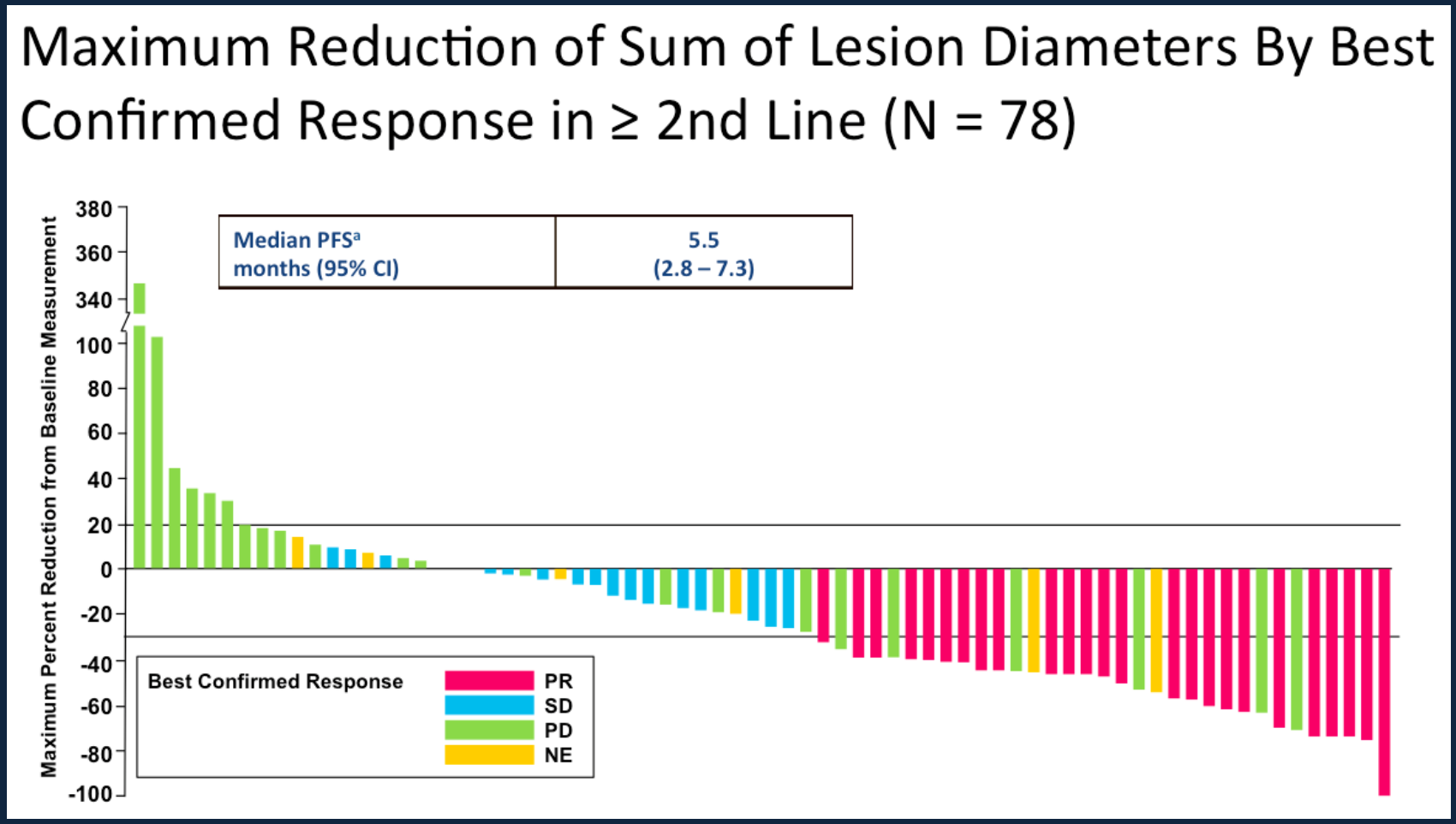
Investigator Assessed Best Confirmed Response For ≥ 2nd Line[a]

Best response	≥ 2nd Line (N = 78)
PR, n (%)	25 (32)
SD[b], n (%)	19 (24)
PD, n (%)	23 (29)
Not evaluable (NE), n (%)	11 (14)
Response rate (confirmed CR + PR)	32%
95% CI	(21.9–43.6)
Disease control rate (CR + PR + SD)	56%
95% CI	(44.7–67.6)

[a] 1st line subjects (n=6): 3=PR, 3=SD.

[b] SD is defined as meeting SD ≥ 12 weeks (planned time for the second post-baseline disease assessment).

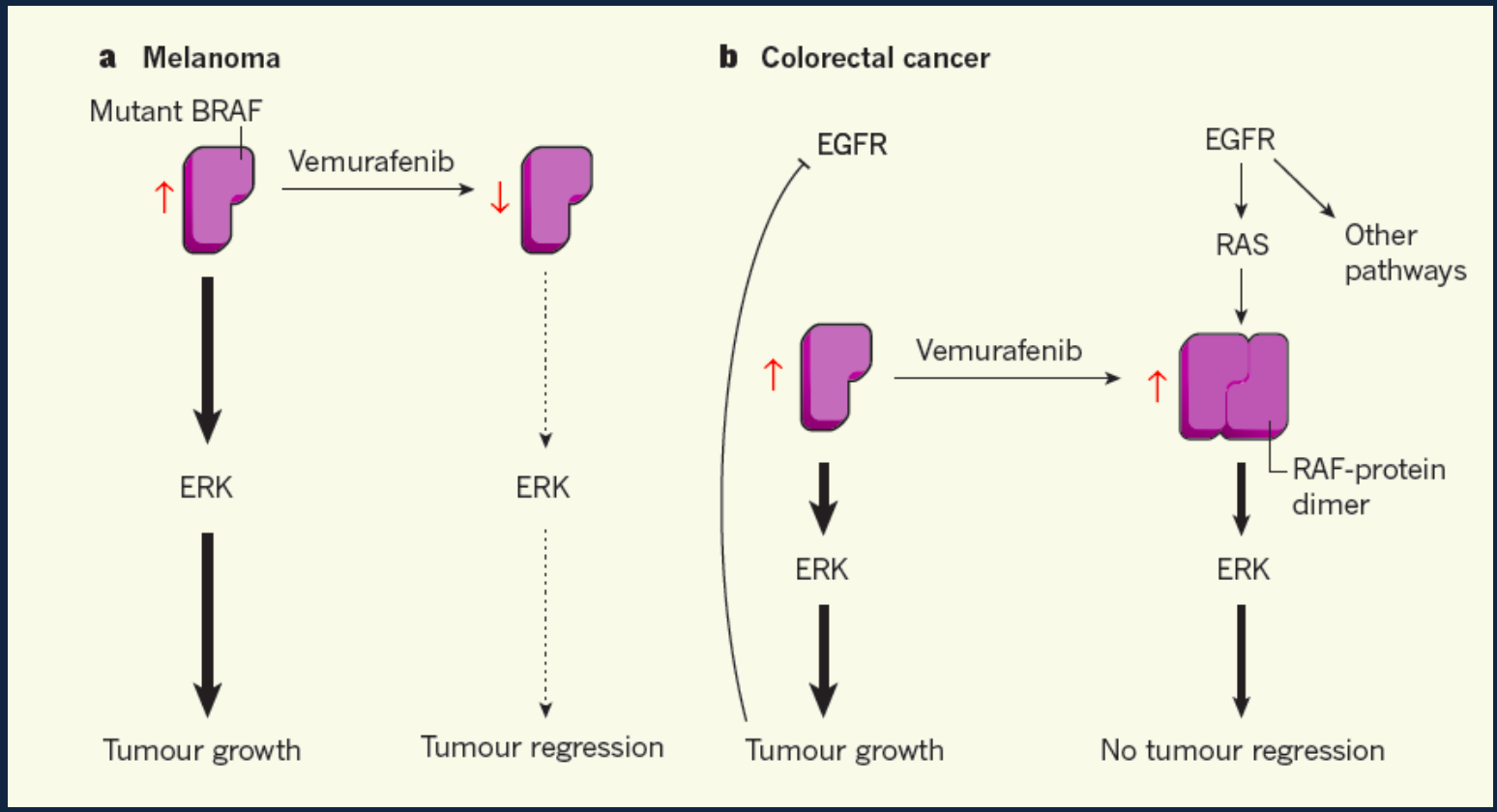
BRAF inhibitor phase 2 trial in NSCLC



Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

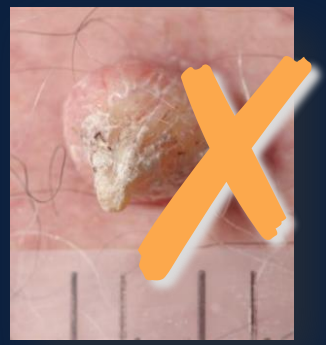
Anirudh Prahallad[1]*, Chong Sun[1]*, Sidong Huang[1]*, Federica Di Nicolantonio[2,3]*, Ramon Salazar[4], Davide Zecchin[2], Roderick L. Beijersbergen[1], Alberto Bardelli[2,3] & René Bernards[1]

- Inhibition of BRAF by vemurafenib « relieves » a negative feedback loop that keeps EGFR inactive
- Activated RAS causes resistance inducing RAF dimers formation



Janne, Nature 2012

Melanoma story:
V600E BRAF and MEK dual inhibition



RTK

Altered non melanoma cell

Oncogenic RAS

RAS

CRAF

WT BRAF

MEK

ERK

Cell survival & proliferation

Dabrafenib
Vemurafenib

Trametinib
Cobimetinib

RTK

Melanoma cell

RAS

BRAF V600E

MEK

ERK

Cell survival & proliferation

Improved PFS

Resistances:

- BRAF splice variant
- NRAS, MEK mutations
- COT…

BRAF resistance mechanisms in NSCLC?

Molecular Characterization of Acquired Resistance to the BRAF Inhibitor Dabrafenib in a Patient with *BRAF*-Mutant Non–Small-Cell Lung Cancer

Charles M. Rudin, MD, PhD, Kelvin Hong, MD,* and Michael Streit, MD†*

TABLE 1. Tumor Mutational Profiles Pretreatment and upon Disease Progression

	Mutations	
Gene	**Prestudy[a]**	**Progressive Disease[a]**
BRAF	V600E	V600E
CCND3	Amplification	Amplification
ARID1A	S90fs*11	S90fs*11
RB1	S807*	S807*
KRAS	—	G12D
TP53	—	R175H
CDKN2A	—	R24fs*20

[a] Both tumor biopsies were profiled using the Foundation One next-generation sequencing assay.

Rudin, JTO 2013

BRAF resistance mechanisms in NSCLC?

- Activation of signalling through HER-3 as a mechanism of resistance/refractoriness to BRAFi/MEKi?
- HER-3 pathway activation observed in patients?

➢ Combination of MEK or BRAF TKI and a pan-HER TKI? What can we achieve in the clinic?

Conclusions (1)

BRAF mutated NSCLC represent small distinct subgroups of oncogene addicted cancers with specific demographics and potentially outcomes

Prognostic feature BRAF mutations remain to be studied in large cohorts of patient

We identified some men and heavy smokers (up to 60 packs-year) suggesting that and BRAF testing should not be restricted to clinically defined subgroups

The targeted strategy against BRAF requires a prospective evaluation in large collaborative international clinical trials.
BRAF non-V600E mutated NSCLC treatment remains to be explored.

Conclusions (2) BRAF trials

A Phase II Study of the BRAF Inhibitor Dabrafenib as a single-agent and in combination with the MEK Inhibitor Trametinib in ongoing in Subjects With BRAF V600E NSCLC (NCT01336634)

A Phase Ib/II, multicenter, open-label, dose escalation study of LGX818 in combination with MEK162 in patients with BRAF V600 - dependent advanced solid tumors (NCT01543698) is recruiting

BASKET study (NCT01524978) of Vemurafenib with expansion phase in NSCLC ongoing

Several early phase 1 trials including RTKi (EGFR, HER1-3, MET) and BRAF TKIs as well as intremittent schedules ongoing

Thanks for your attention