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EUROPEAN LUNG CANCER CONFERENCE 2016

NEW MOLECULAR TARGETS OF INTEREST: BRAF

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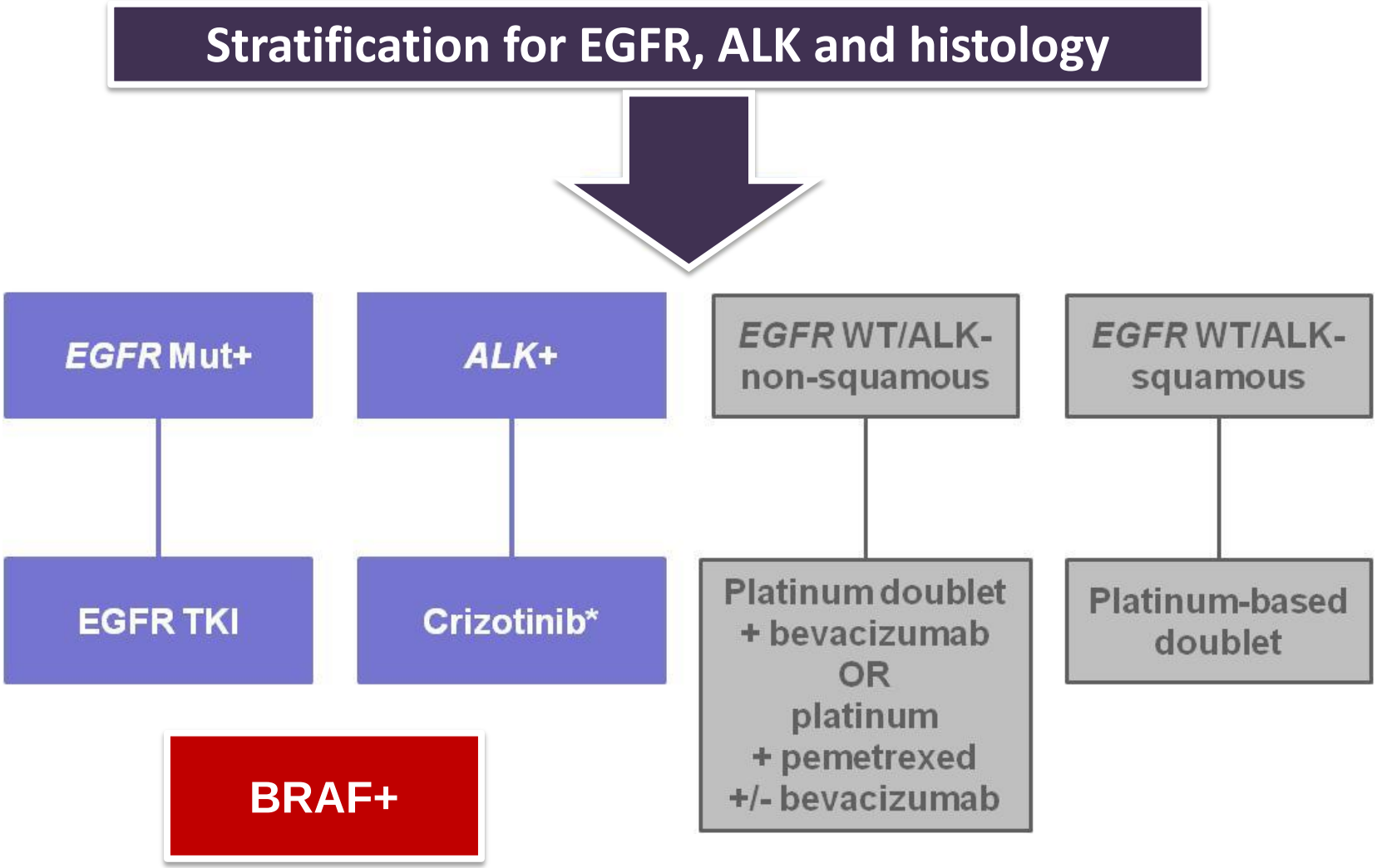
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

DISCLOSURE SLIDE

AstraZeneca, BMS, Clovis, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Boehringer Ingelheim,

Great advances have been made in lung cancer therapy



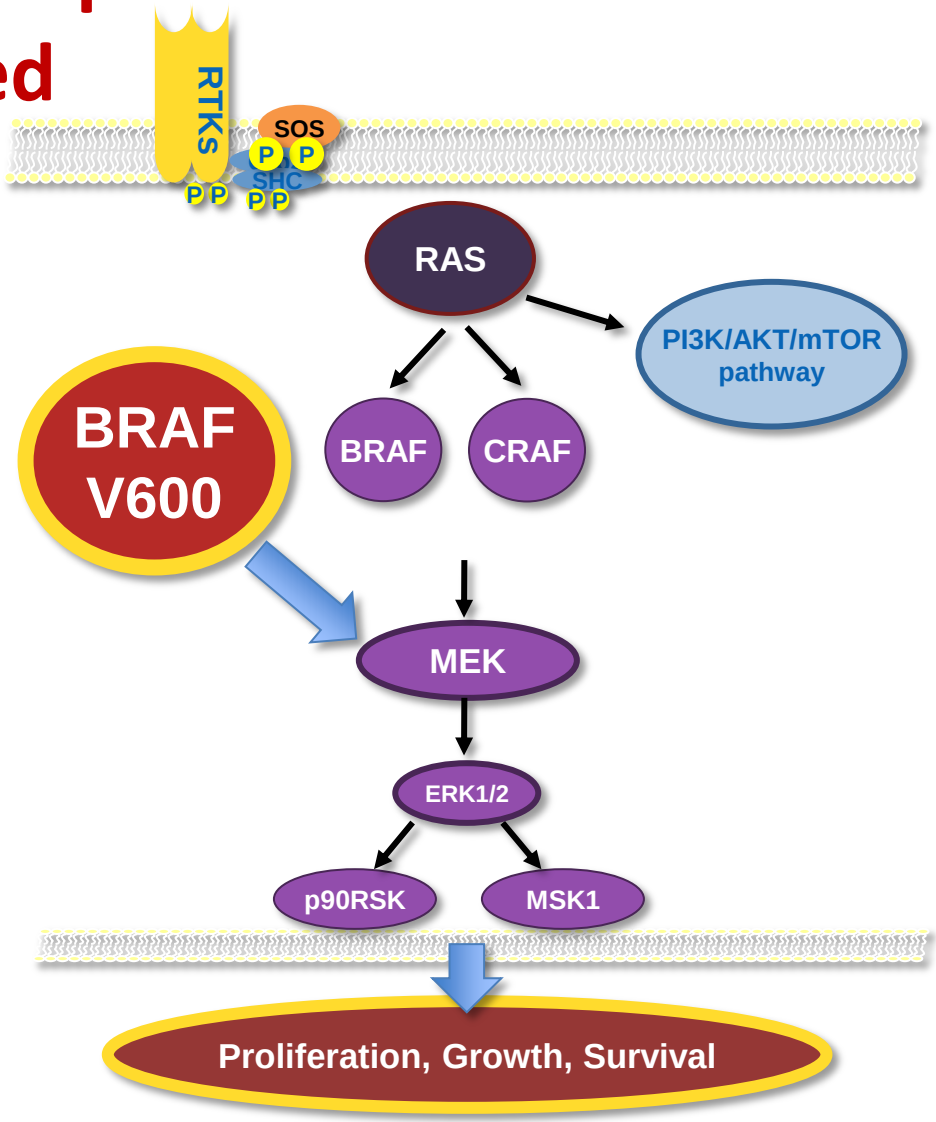
BRAF plays a key role in cell proliferation and oncogenesis when mutated

Wild Type

In normal cells BRAF activity is regulated by mitogens such as growth factors, cytokines & hormones

***Oncogenesis**

By contrast, oncogenic BRAF is constitutively active and stimulates the MAPK pathway and cell growth independently of mitogenic activation



changes valine (V) residue at position 600 to glutamic acid (E) referred to as **V600E**

BRAF 593 DFGLATVKSRWSGSHQF--EQLSGSILWMAPE

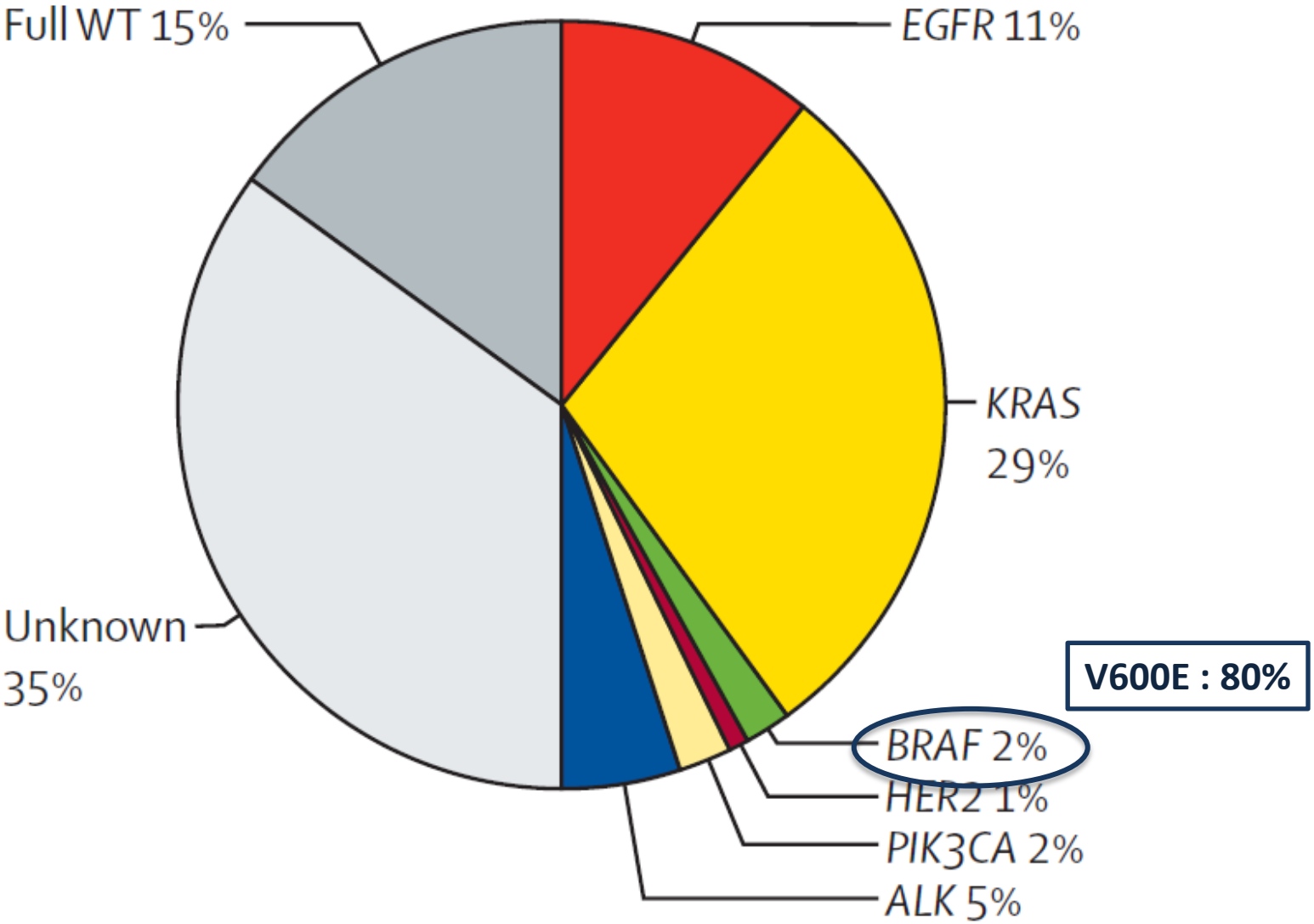
BRAF mutations in diverse cancers

Cancer	BRAF mutation frequency	Comments
Cholangiocarcinoma	3%–22%	*BRAF* V600E (60%) *BRAF* V600D (13%) Other codons (27%)
Chronic lymphocytic leukemia	2.8%	
Colorectal cancer	5%–15%	*BRAF* V600E
MSI unstable	27.8%–51.8%	
MSI stable	5%–7.5%	
Erdheim-Chester disease	54%	*BRAF* V600E
Ganglioglioma	43%	*BRAF* V600E
GIST	2%–13%	*BRAF* V600E
Glioblastoma	1.7%	*BRAF V600E*
Hairy cell leukemia	~100%	*BRAF* V600E
Kidney cancer	3%	*BRAF* V600E (85%) Other codons (5%)
Lung cancer adenocarcinoma	3%	*BRAF* V600E (50%) *BRAF* G469A (39%) *BRAF* D594G (11%)
Langerhans cell histiocytosis	25%–38%	*BRAF* V600E
Melanoma	~60%	*BRAF* V600E (80%) *BRAF* V600K (8%) *BRAF* V600R (1%) Other codons (10%)
Multiple myeloma	~6%	*BRAF* V600E (38%) Other codons (62%)
Ovarian cancer	35%–60%	*BRAF* V600E
Serous borderline	44.6%–71%	
Low-grade serous	5.3%–14%	
Pancreatic cancer	1%–16%	Schultz et al reported all mutations detected were non-*BRAF* V600E (112). COSMIC reported ~55% of BRAF mutations were *BRAF* V600E.
Pilocystic astrocytoma	70%–80%	*BRAF-KIAA1549* fusion
Pleomorphic xanthoastrocytoma	66%	*BRAF* V600E
Prostate cancer	1.6%	*BRAF* V600E (<1%) *BRAF* V600X (84%)
Papillary thyroid cancer	30%–80%	*BRAF* V600E

Michelle L. Turski et al, Mol cancer ther 2016

Frequency of genetic alterations

1-year nationwide programme in France



from 18 679 analysed samples

F.Barlesi et al, lancet 2016

Summary of Clinicopathologic Features of BRAF-Mutant Lung Adenocarcinomas

	Paik et al (2011)	Marchetti et al (2011)	Carderella et al (2013)	Lung cancer consortium
Setting	Single US institution	Multiple Italian institutions	Single US institution	Multiple US institutions
Patients, n	697	739	883	951
BRAF mutant, n (%)	18 (3)	36 (5)	36 (4)	21 (2)
Stage, n (%)	Stages I-IIIA: 8 (44) Stages IIIB-IV: 10 (56)[b]	Stages I-III: 34 (94) Stage IV: 2 (6)	Stages I-III: 11 (31) Stage IV: 25 (69)	Stage IV: 21 (100)[b]
Comparator group	*EGFR*-mutant, *KRAS*-mutant, and *ALK*-rearranged lung adenocarcinomas	*BRAF* wild-type lung adenocarcinomas	*BRAF/EGFR/KRAS/ALK* wild-type lung adenocarcinomas	Patients with known genotype for 10 oncogenic drivers
Associated clinical features	No differences in age or sex; *BRAF* mutations more likely in whites	V600E mutations more common in females	No differences in age or sex	Differences in age between patients with *ALK* rearrangements and in sex between patients with *EGFR* mutations
Associated smoking status	*BRAF* mutations more likely in current/former smokers	V600E more common in never smokers; non-V600E clusively mokers	No differences in smoking history	*BRAF* mutations more likely in current/former smokers *FR*, ic subgroups
BRAF genotypes, n (%)	V600E: 9 (50) Non-V600E: 9 (50)	V600E: 21 (58) Non-V600E: 15 (42)	V600E: 18 (50) Non-V600E: 18 (50)	V600E: 17 (81) Non-V600E: 4 (19)
Associated clinical outcome	No OS differences in stage IIIB/IV patients	V600E-mutant tumors associated with inferior DFS and OS postoperatively	No OS differences	No OS differences

V600E: 50%

V600E: 58%

V600E: 50%

V600E: 81%

Liza C. Villaruz et al, cancer 2014

BRAF genes stratified by clinical characteristics

(Biomarkers France)

	BRAF		
	Mutation*	Wild-type	Unknown
Number (%)	262 (1%)	13 644 (73%)	4773 (26%)
Age (median)	65·9	64·7	65·7
Sex‡			
Male	160 (61%)	8881 (65%)	2906 (61%)
Female	101 (39%)	4686 (34%)	1834 (38%)
Ethnic origin			
Asian	0	72 (1%)	36 (2%)
Other	150 (100%)	5800 (99%)	1853 (98%)
Smoking history			
Never	41 (25%)	1229 (18%)	503 (22%)
Former	63 (38%)	2887 (42%)	915 (40%)
Current	60 (37%)	2709 (40%)	864 (38%)

F.Barlesi et al, lancet 2016

Clinical Features and Outcome of BRAF-Mutated NSCLC Patients

First author	Paik	Marchetti	Ille	Carderella	Luk	Litvak	Brustugun	Villaruz
Country	United States	Italy	France	United States	Australia	United States	Norway	United States
Year	2011	2011	2013	2013	2014	2014	2014	2015
Patients (n)	697	1046	450	883	273	63	979	951
B	18	37	4	36	7	3 (	1	2
V600E (%)							NA	
Smokers (%)								
V600E	100	52[a]	57	72	100	57	71	76
Non-V600E	100	100[a]	89	89	100	43	NA	100
Female (%)								
V600E	78	76[a]	52	56	75	53	59	53
Non-V600E	44	7[a]	26	50	33	56	NA	25
V600E (n)								
Early stage (I and II)	3 (33%)[b]	11 (52%)[a]	6 (29%)	3 (17%)	NA	11 (31%)	6 (35%)	5 (31%)[c]
Advanced stage (III and IV)	6 (67%)[b]	10 (48%)[a]	15 (71%)	15 (83%)	NA	25 (69%)	11 (65%)	11 (69%)[c]
Non-V600E (n)								
Early stage (I and II)	5 (56%)[b]	12 (80%)[a]	8 (42%)	2 (11%)	NA	10 (37%)	NA	1 (25%)
Advanced stage (III and IV)	4 (44%)[b]	3 (20%)[a]	11 (58%)	16 (89%)	NA	17 (63%)	NA	3 (75%)
Survival outcome[d]								
BRAF mutant vs. wt	Same[e]	Same	NA	Same	NA	Same[f]	NA	Same[g]
V600E vs. wt	NA	Worse	NA	NA	NA	NA	Same	NA
Non-V600E vs. wt	NA	Same	NA	NA	NA	NA	NA	NA
V600E vs. non-V600E	NA	Worse	Worse	Same[h]	NA	Better[i]	NA	NA

Smokers %

100% 52% 57% 72% 100% 57% 71% 76%

Tu Nguyen-Ngoc et al, JTO 2015

Identifying BRAF+ patients remains a challenge despite ESMO/NCCN testing recommendations

- Widespread adoption of BRAF screening in NSCLC as recommended by professional guidelines still has room for improvement

ESMO Consensus[1]

At the 2nd ESMO consensus conference on lung cancer, experts recommended BRAF testing in patients with demographic risk factors (e.g. minimal or remote smoking history) whose tumours have tested negative for EGFR mutation and ALK [III, A]

"While mutations are not entirely mutually exclusive, the incidence of disease characterized by 'double mutations' is <1% making this a logical and cost-effective approach."[1]

NCCN Treatment Guidelines[2]

2015 NCCN Guidelines strongly endorses broader molecular profiling to identify rare driver mutations using multiplex/NGS (next-generation sequencing) to ensure that patients receive the most appropriate treatments

Next-generation sequencing (NGS), also known as high-throughput sequencing, describes a number of different high throughput modern DNA sequencing with clinical applications.

Sources: K. M. Kerr et. al, *Annals of Oncology* 25: 1681–1690, 2014; 2015 20th Annual NCCN Non-Small Cell Lung Cancer Treatment Guidelines

BRAF V600E mutation is a prognostic indicator for shorter survival

NSCLC who received radical resection of a primary NSCLC

Predictors of Survival

Stage I-IV BRAF+ NSCLC Adenocarcinoma[1]

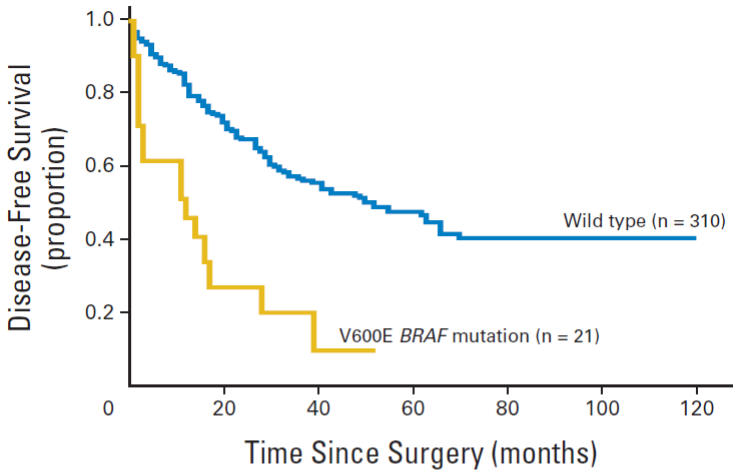
- Disease stage and BRAF V600E mutation were found to be the **only independent and significant factors to predict both DFS and OS***

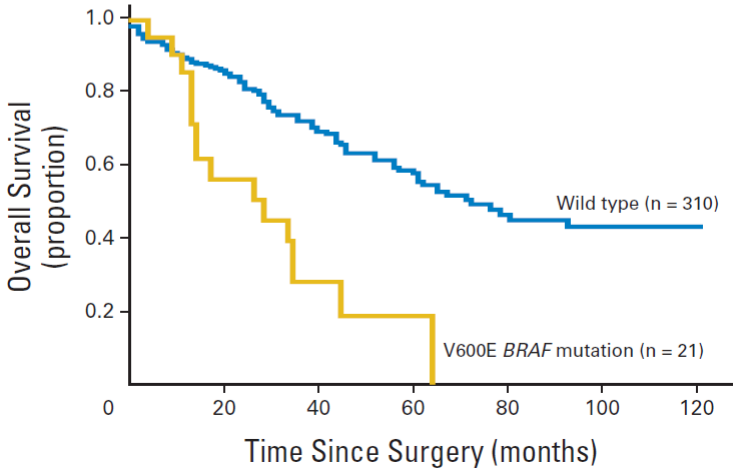
**results remained consistent across univariate and additional subgroup analysis of study population*

Multivariate Overall Survival Analysis 331 Patients With Lung ADC

Variable	Category	HR	95% CI	P-value
Smoking	Never smoker/Smoker	1.09	.56-2.09	NS
Sex	Female/Male	1.2	0.63-2.27	NS
Non-V600E	Mutated/wild type	1.46	.46-4.64	NS
V600E	**Mutated/wild type**	**2.18**	**1.17-4.04**	**0.014**
Stage	III + IV/I + II	2.92	1.95-4.37	< .001

NS = not significant





Sources: 1. Antonio Marchetti et al. JCO 2011;29:3574-3579; 2. Stephanie Cardarella et al. Clin Cancer Res 2013;19:4532-4540

BRAF V600E mutation is a prognostic indicator for lower response rates and shorter survival

Advanced NSCLC with BRAF mutations and wild-type tumors

Stage IIIB-IV Prognosis

Survival of V600E vs. Wild Type On 1st Line Platinum-Based Chemo

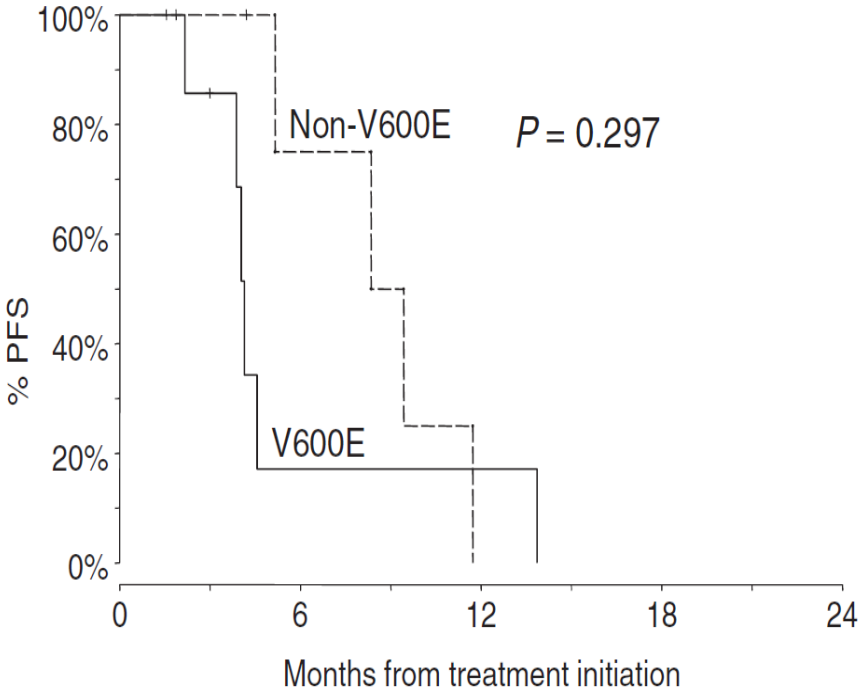
- **Stage IIIB-IV BRAF V600E NSCLC** patients were found to have lower ORR, PFS, and OS than wild-type patients

Note: BRAF V600E ORR, PFS, and OS was also lower than BRAF non-V600E patients

Chemotherapy refers to first-line platinum-based combination chemotherapy

Stage IIIB-IV NSCLC Clinical Outcomes[2]

Endpoint	*Wild-Type (n=79)*	***BRAF V600E (n=12)***
ORR	48%	**29%**
Median PFS (mon)	6.7	**4.1**
Median OS (mon)	15.9	**10.8**
Treatment	Majority received chemo	



Sources: 1. Antonio Marchetti et al. JCO 2011;29:3574-3579; 2. Stephanie Cardarella et al. Clin Cancer Res 2013;19:4532-4540

BRAF NSCLC patients respond poorly to currently approved therapies

BRAF Interim Outcomes from French NSCLC Registry

Setting	Study	Line of Therapy	Total (N)	Efficacy Outcomes			
				N	TTF (Mean), months	N	ORR, %
Registry (France)	Barlesi 2015	1L	55	22	**3.4**	35	**14.3**
		2L	38	7	**3.2**	21	**4.8**

TTF: time to failure; ORR: overall response rate

- Interim outcomes from an ongoing collaboration with IFCT (Intergroupe Francophone de Cancérologie Thoracique) to assess outcomes associated with BRAF V600E mutation
  - Time to treatment failure was less than 4 months
  - Overall response rates in 1st line were <15% and <5% in 2nd line[1]

Sources: 1. Barlesi et al. ASCO Abstract 8000 2013

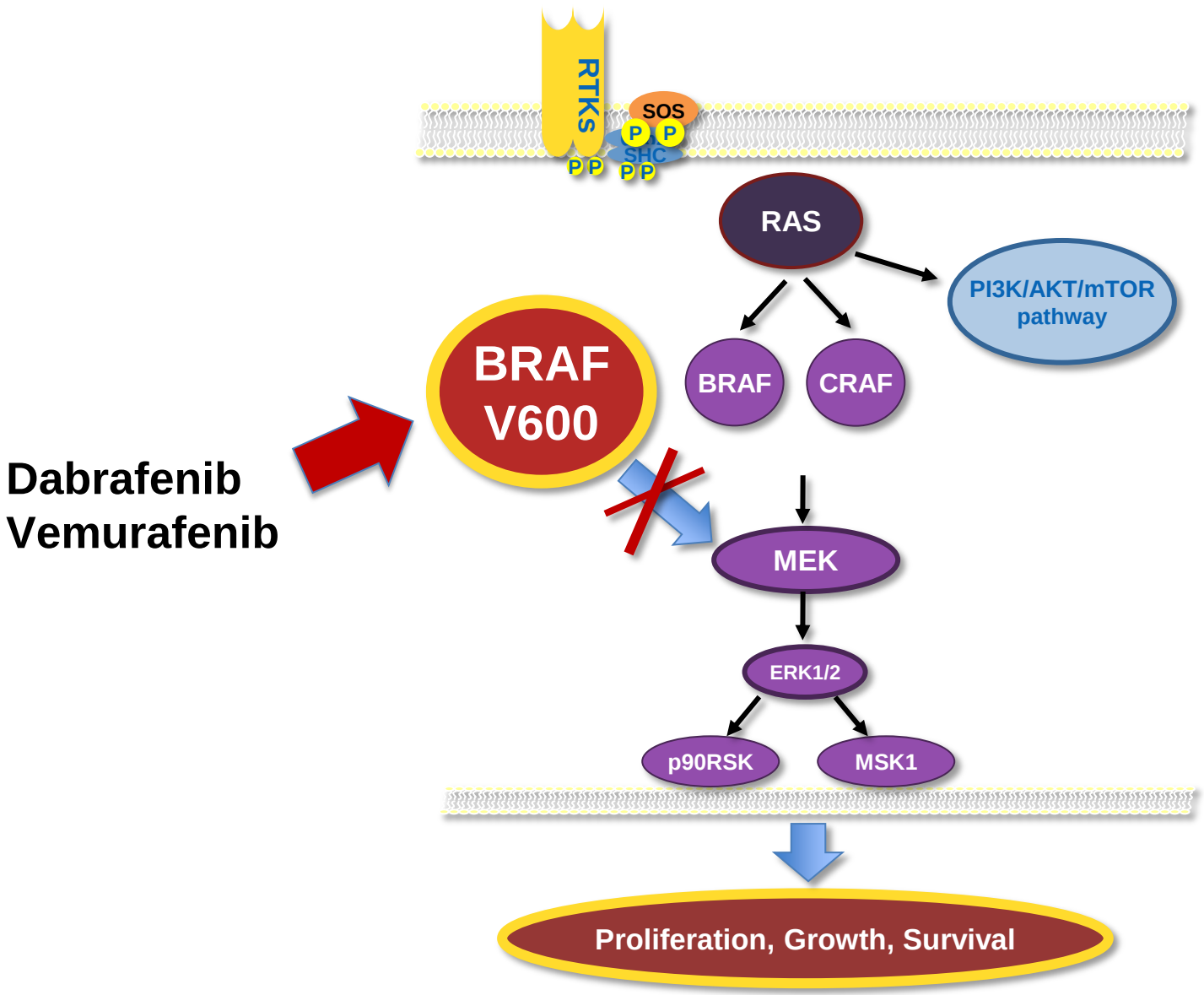
Previously Treated Non–Small-Cell Lung

- Docetaxel, erlotinib, Pemetrexed (non-squamous) for the second-line treatment of advanced NSCLC

	Erlotinib vs placebo[2]		DOCETAXELvs PEMETREXED[1]	
	Erlotinib (n = 488)	Placebo (n = 243)	**DOCETAXEL (n = 288)**	PEMETREXED (n = 283)
ORR	**8,9%**	<1%	**8,8%**	**9,1%**
Median PFS, months	**2.2**	1.8	**2,9**	**2,9**
HR (95% CI) P-value	0.62 (0.51-0,74),P<0,001		0-19.5	0-18.2
Median OS, months	6,7	4,7	7,9	8,3
HR (95% CI) *P*-value	0.70 (0.58 to 0.85); P<0.001		0.99 (0.8-1,20), P: NS	

2.Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123–32.
1. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22(9): 1589–97

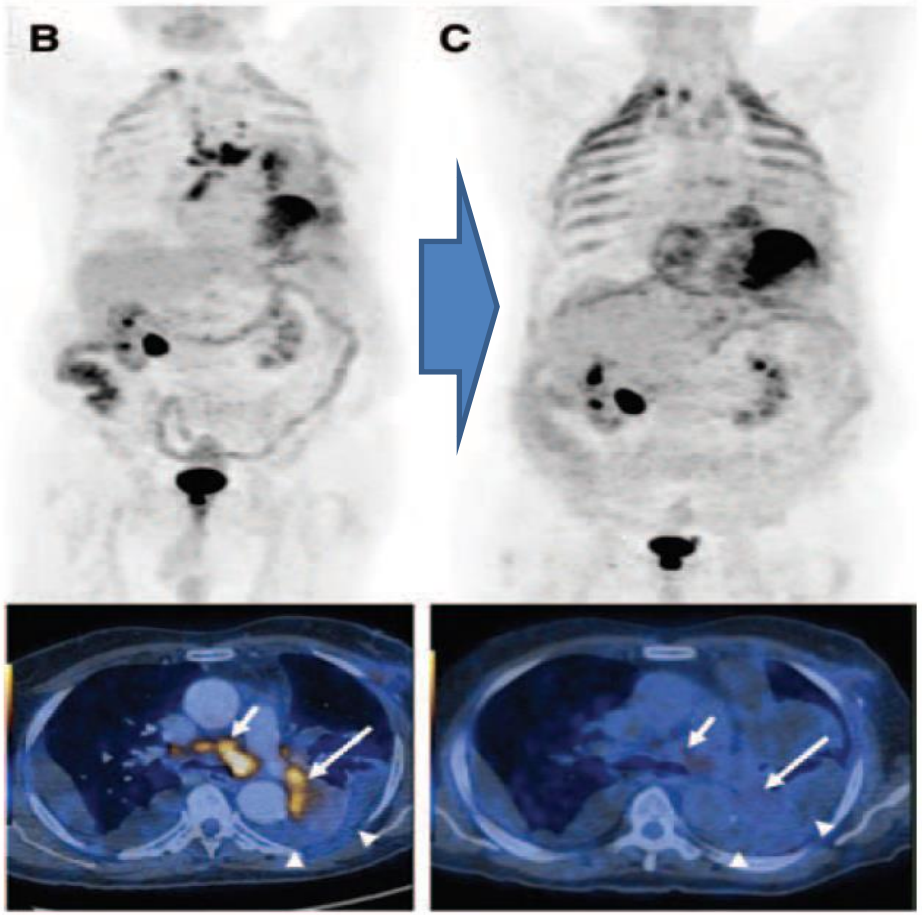
Inhibition of BRAF V600 Kinase



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†*

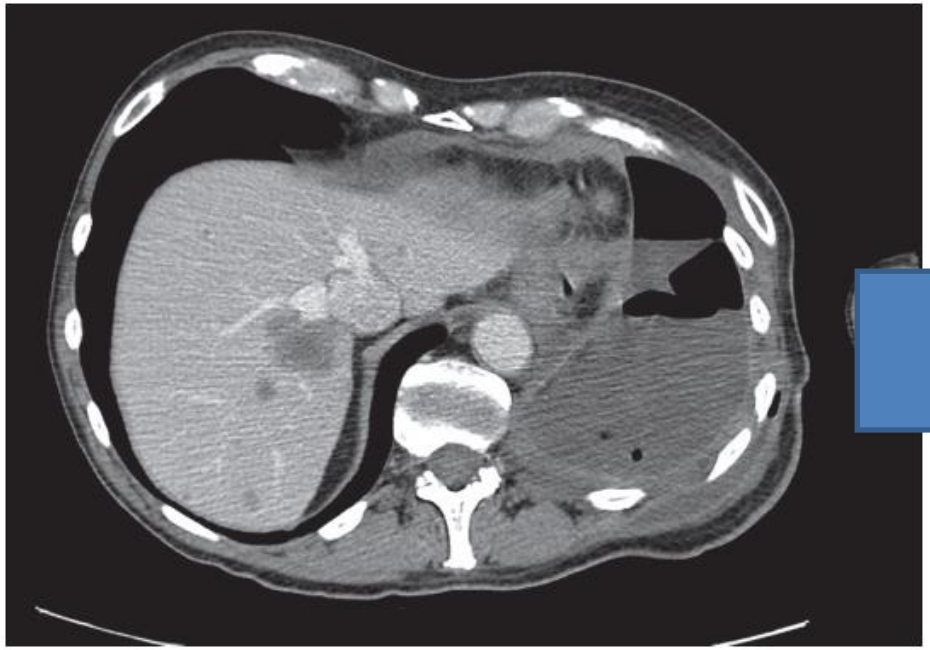
First report of a patient with V600E-NSCLC responding to vemurafenib

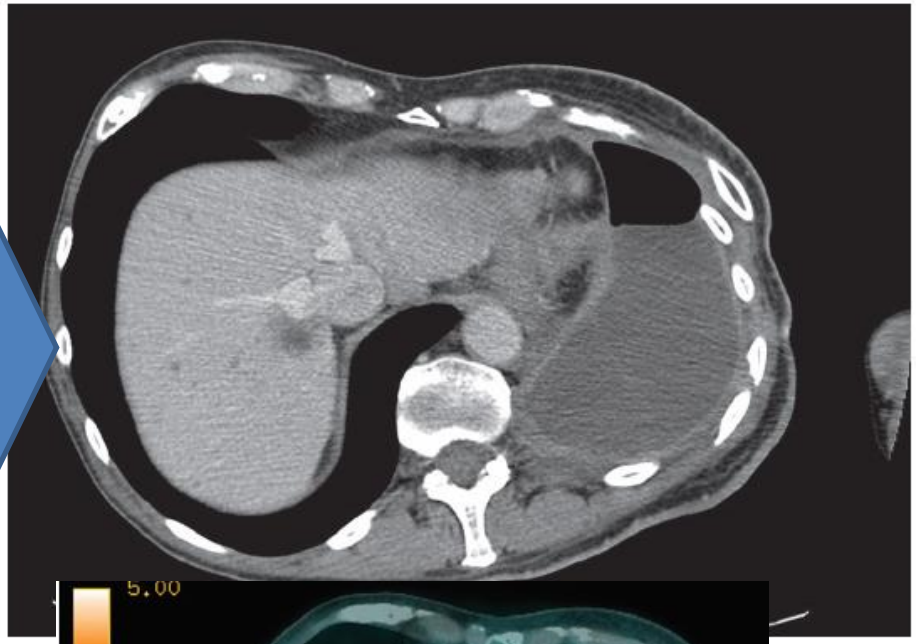


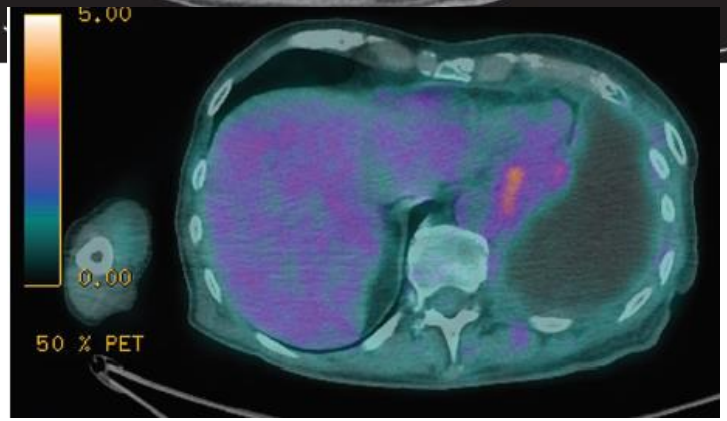
JTO 2012

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

6 weeks of treatment



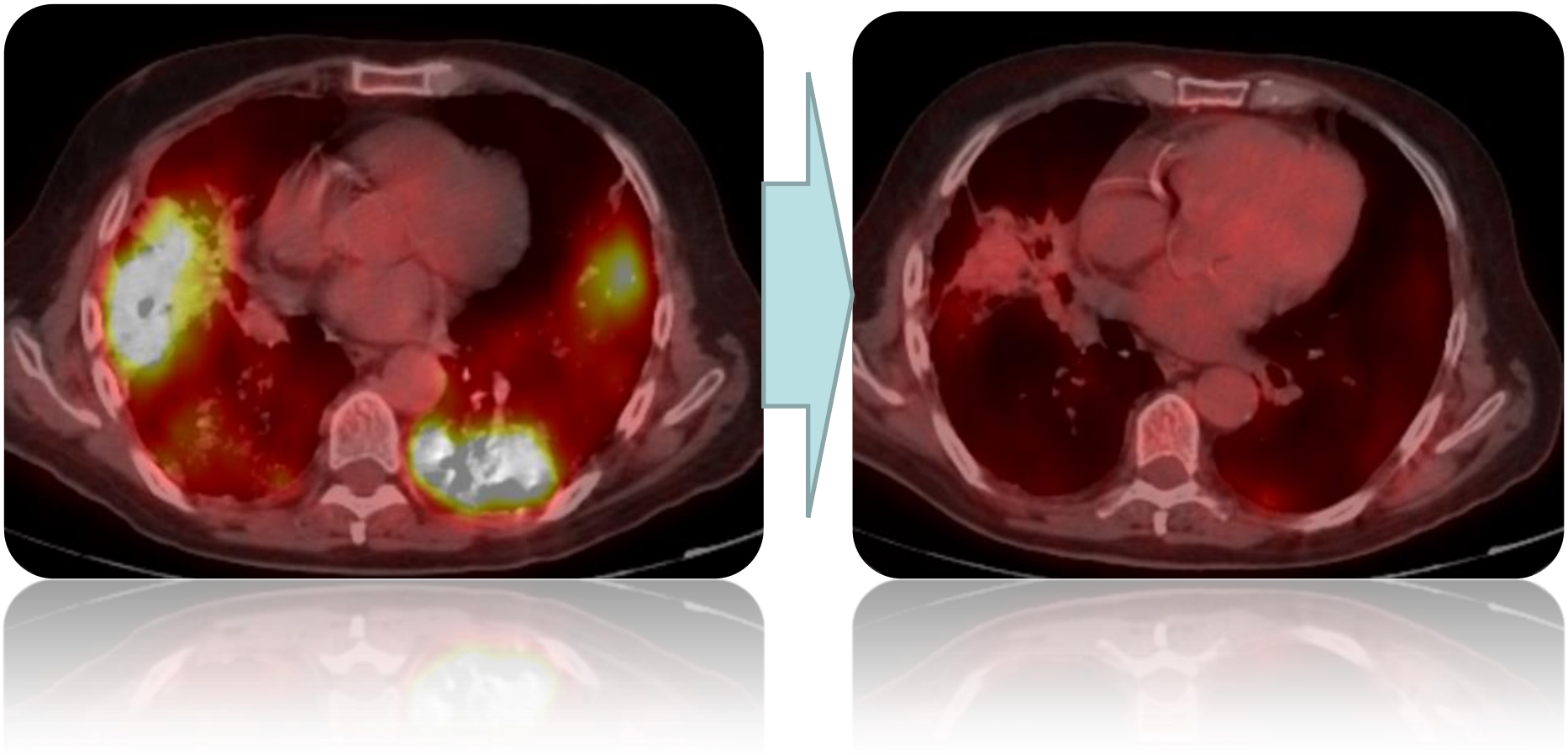




Off-label vemurafenib started in September 2012 at a dose of 960 mg administered twice per day

Solange Peters et al, JCO 2013

BRAF V600E and Vemurafenib



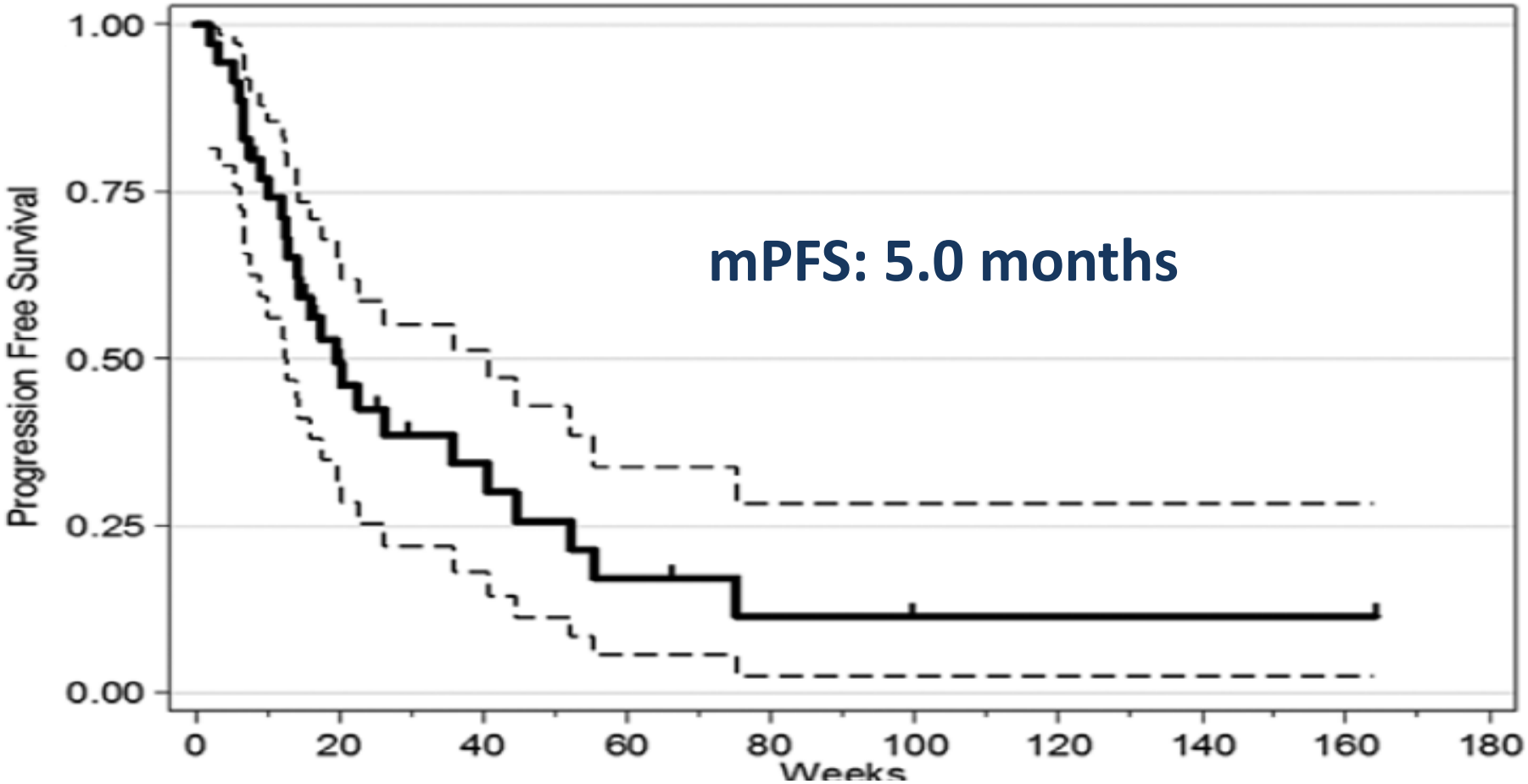
B.Besse, Gustave Roussy

Targeted Therapy for Patients with BRAF-Mutant Lung Cancer Results from the European EURAF Cohort

Sample size (N)	35
BRAF inhibitor therapy	35 (100%)
BRAF inhibitors and lines (total)	39
Vemurafenib	29
Dabrafenib	9
Sorafenib	1
Sequential BRAF inhibitors	
No	31 (89%)
Yes	4 (11%): 3× vemurafenib → dabrafenib and 1× sorafenib → vemurafenib
BRAF inhibitor used in	
First line	5 (14%)
Further lines	30 (86%)

Oliver Gautschi et al, JTO 2014

Survival with BRAF therapy



overall survival : 10.8 months

Oliver Gautschi et al, JTO 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

Characteristic	NSCLC (N=20)	Colorectal Cancer		Multiple Myeloma (N=5)	Cholangiocarcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)	Other† (N=27)
		Received Vemurafenib (N=10)	Received Vemurafenib + Cetuximab (N=27)					
Sex — no. (%)								
Male	14 (70)	5 (50)	10 (37)	4 (80)	3 (38)	7 (39)	4 (57)	9 (33)
Female	6 (30)	5 (50)	17 (63)	1 (20)	5 (62)	11 (61)	3 (43)	18 (67)
Yr of age — median (range)	61 (48–83)	59 (49–64)	63 (45–81)	64 (58–68)	53 (37–66)	64 (35–83)	65 (55–81)	55 (18–77)
ECOG performance status†								
0 or 1	16 (80)	10 (100)	25 (93)	4 (80)	7 (88)	15 (83)	4 (57)	22 (81)
≥2	4 (20)	0	2 (7)	1 (20)	1 (12)	3 (17)	3 (43)	5 (19)
Prior systemic therapies — no. (%)‡								
Any	19 (95)	10 (100)	27 (100)	5 (100)	8 (100)	11 (61)	7 (100)	21 (78)
None	1 (5)	0	0	0	0	7 (39)	0	6 (22)
1	10 (50)	1 (10)	5 (19)	0	2 (25)	2 (11)	5 (71)	6 (22)
2	4 (20)	2 (20)	11 (41)	2 (40)	1 (12)	7 (39)	1 (14)	5 (19)
≥3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Prior radiation — no. (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BRAF V600 mutation — no. (%)								
V600E	18 (90)	8 (80)	24 (89)	5 (100)	7 (88)	17 (94)	7 (100)	25 (93)
V600G	1 (5)	0	0	0	0	0	0	2 (7)
V600 unknown	1 (5)	2 (20)	3 (11)	0	1 (12)	1 (6)	0	0

%V600E	90%	80%	89%	100%	88%	94%	100%	93%

David M. Hyman et al, NEJM 2015

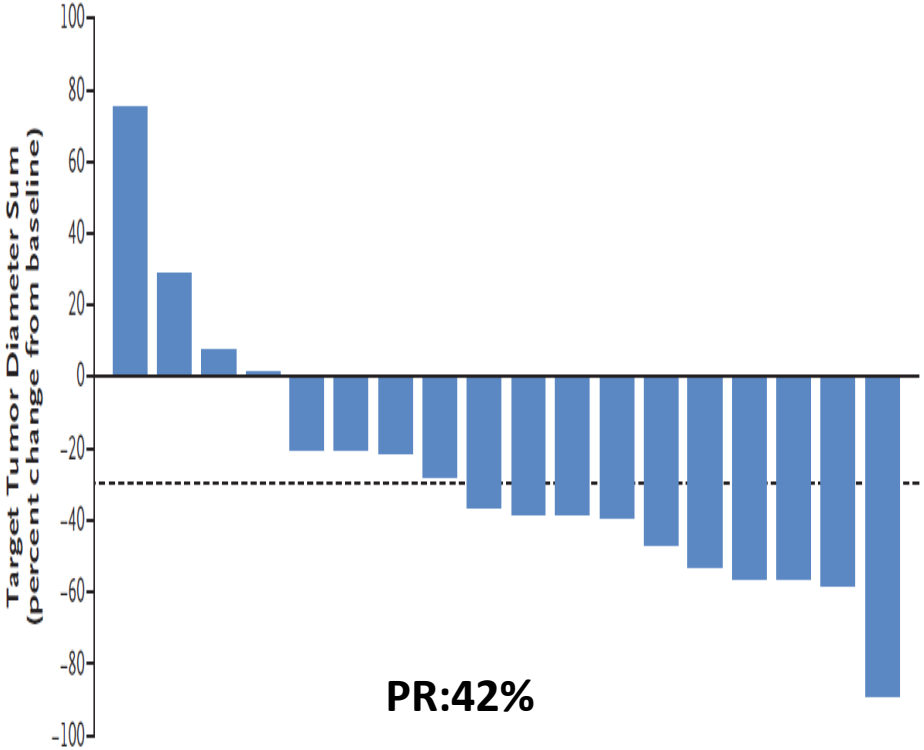
Preliminary Best Response

Variable	NSCLC (N=20)	Colorectal Cancer	
		Vemurafenib (N=10)	Vemurafenib + Cetuximab (N= 27)
Patients with ≥1 postbaseline assessment — no.	19	10	26
Complete response — no. (%)	0	0	0
Partial response — no. (%)	8 (42)	0	1 (4)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)
Missing data — no. (%)†	1 (5)	0	0
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]

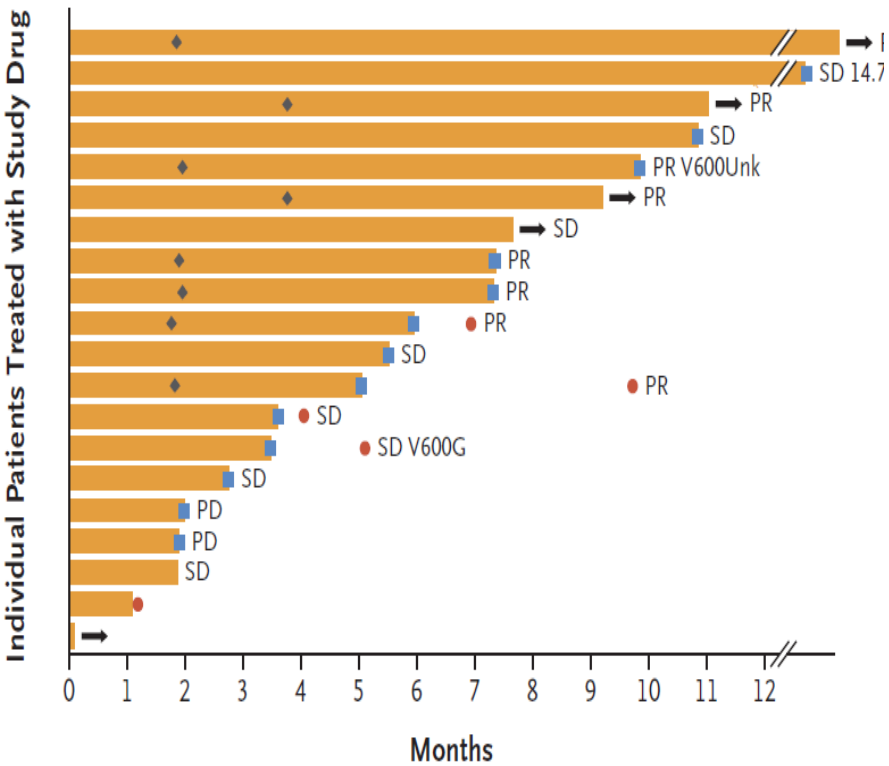
David M. Hyman et al, NEJM 2015

BASCKET Trial: Vemurafenib in Multiple Non-melanoma cancers with BRAF V600 Mutations

Maximum Percent Change



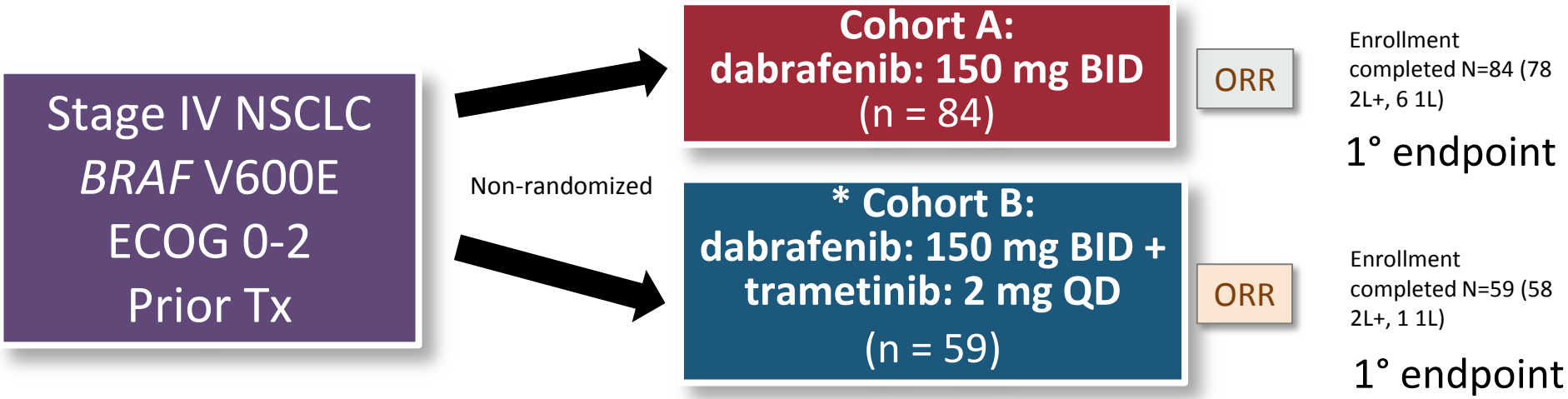
Time to Events



mPFS: 7.3 months (95% CI, 3.5 to 10.8)

David M. Hyman et al, NEJM 2015

Phase II BRAF+ NSCLC trial design



* Prior Tx limited to 1-3 lines

Statistical Assumptions:

- **2L Cohort A**: Primary , Original (n=40) 92.6% power to detect 30% ORR. Per FDA guidance expanded to 60 pts, ORR of 30% @95% CI(18.9%, 43.2%). To achieve 60 evaluable, enrolled 78 $2L^+$ pts. Included 6 1L pts.
  - Secondary PFS, OS, safety and tolerability, pop PK
- **2L Cohort B**: Primary, 92.2% power to detect 55% ORR. To achieve 40 evaluable, enrolled 59. Included 1 1L.
  - Secondary PFS, OS, safety and tolerability, pop PK

Patient Population (Cohort A)

		≥ 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)

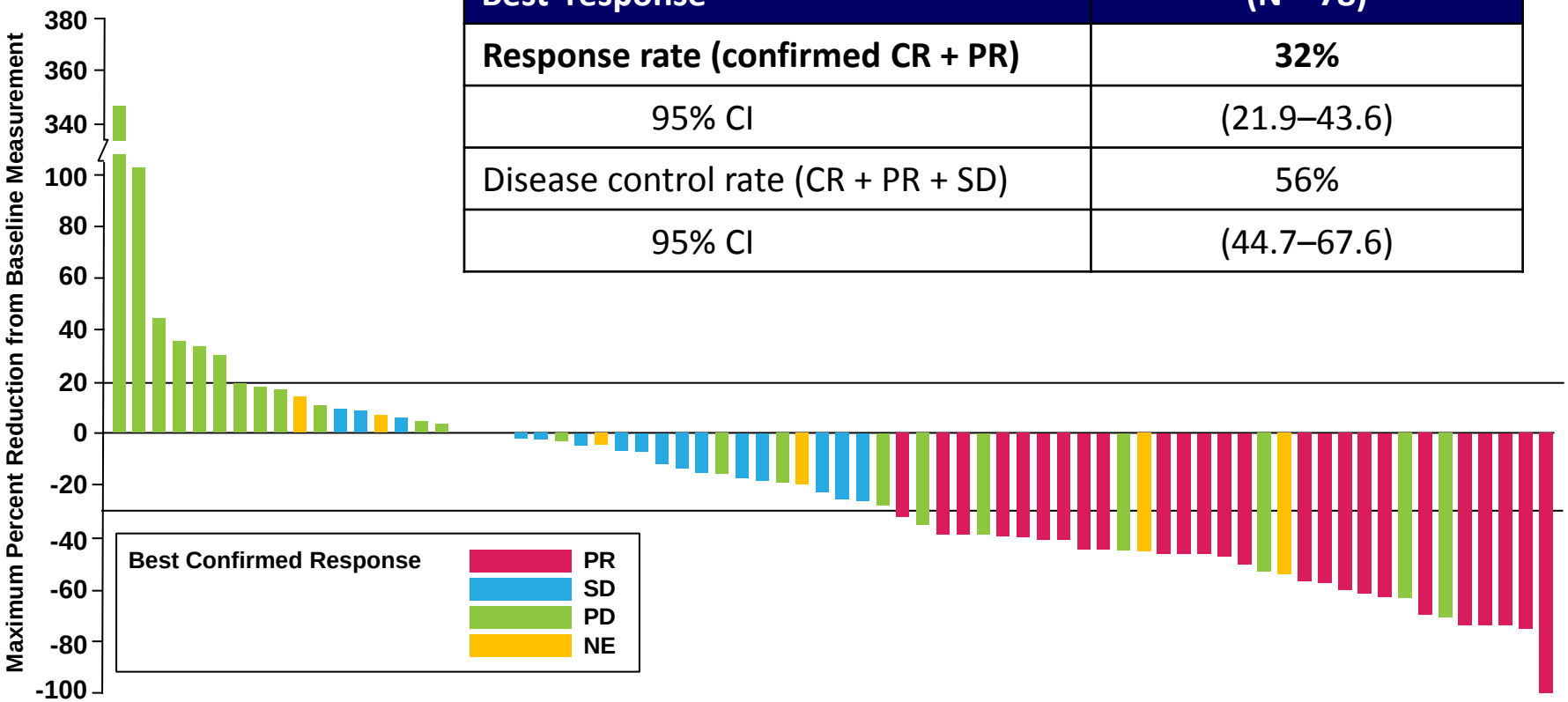
[a] Among 49 smokers, 3 current smokers, and 46 former smokers.

 Presented by David. Planchard et al

D.Planchard et al, ESMO 2014

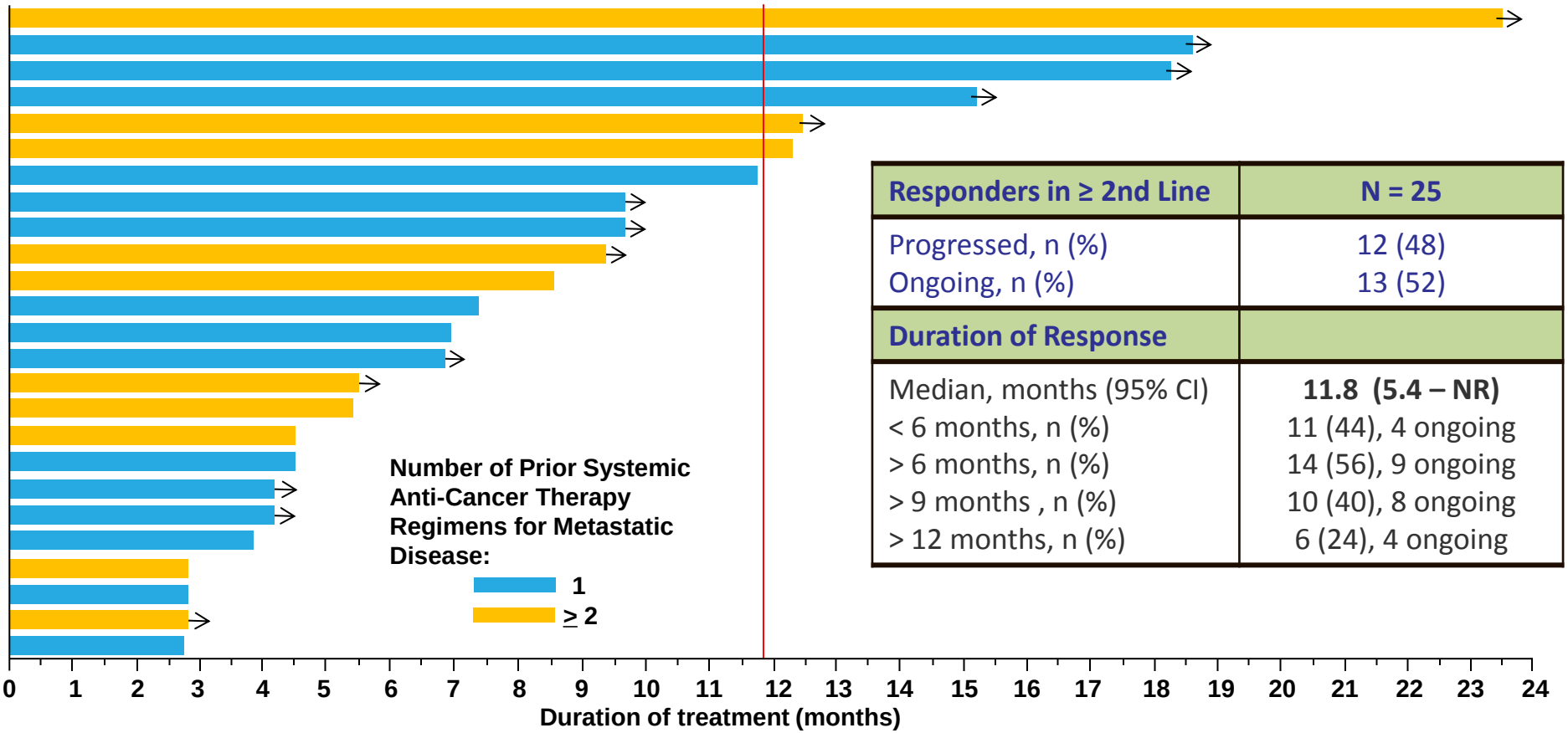
Dabrafenib (Cohort A): Maximum Reduction (N = 78)

Best response	≥ 2nd Line (N = 78)
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)



D.Planchard et al, ESMO 2014, lancet onco

Duration of Investigator Assessed Response in ≥ 2nd Line (n = 25)



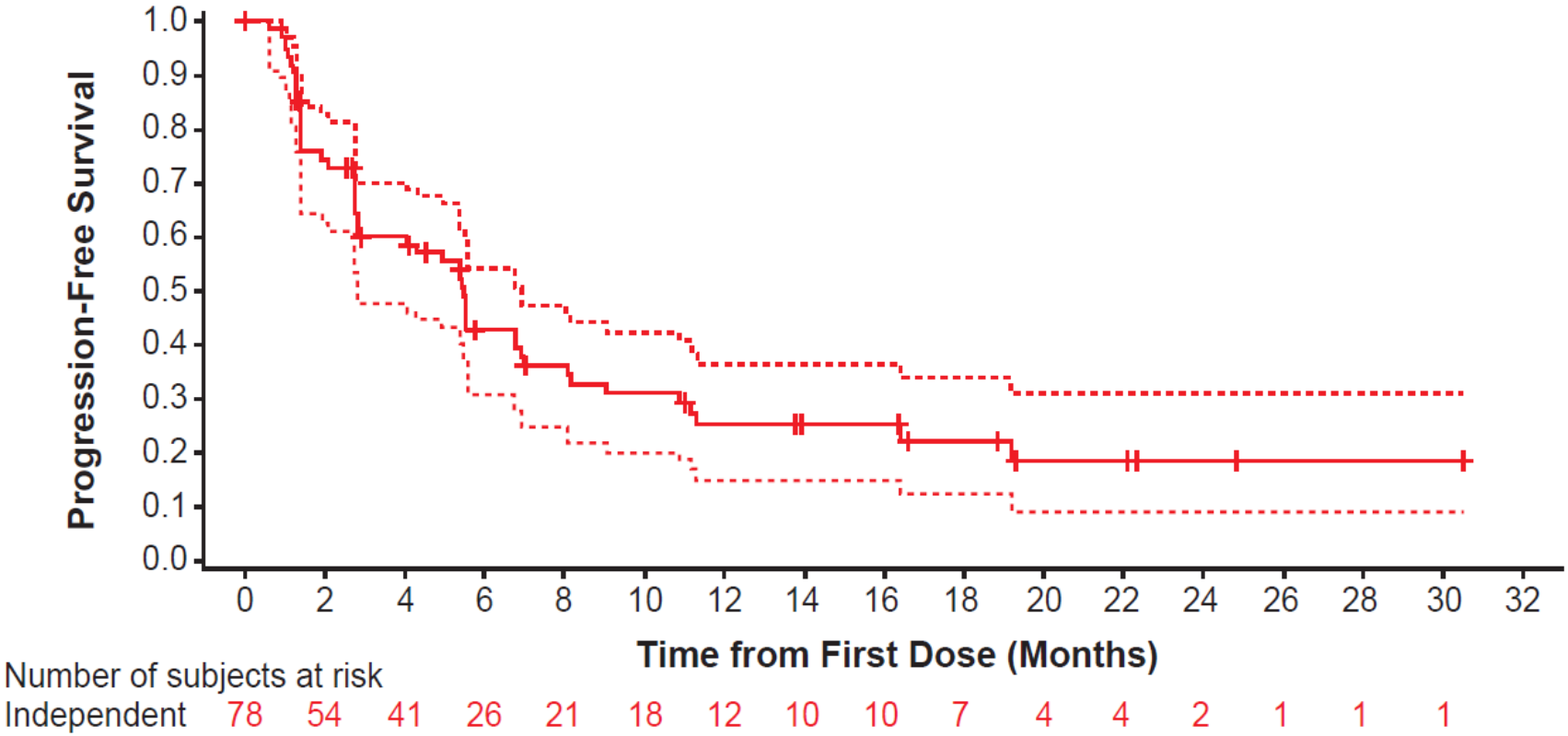
Responders in ≥ 2nd Line	N = 25
Progressed, n (%)	12 (48)
Ongoing, n (%)	13 (52)
Duration of Response	
Median, months (95% CI)	**11.8 (5.4 – NR)**
< 6 months, n (%)	11 (44), 4 ongoing
> 6 months, n (%)	14 (56), 9 ongoing
> 9 months , n (%)	10 (40), 8 ongoing
> 12 months, n (%)	6 (24), 4 ongoing

[a] 62% of patients progressed or died.

Presented by David. Planchard et al

D.Planchard et al, ESMO 2014

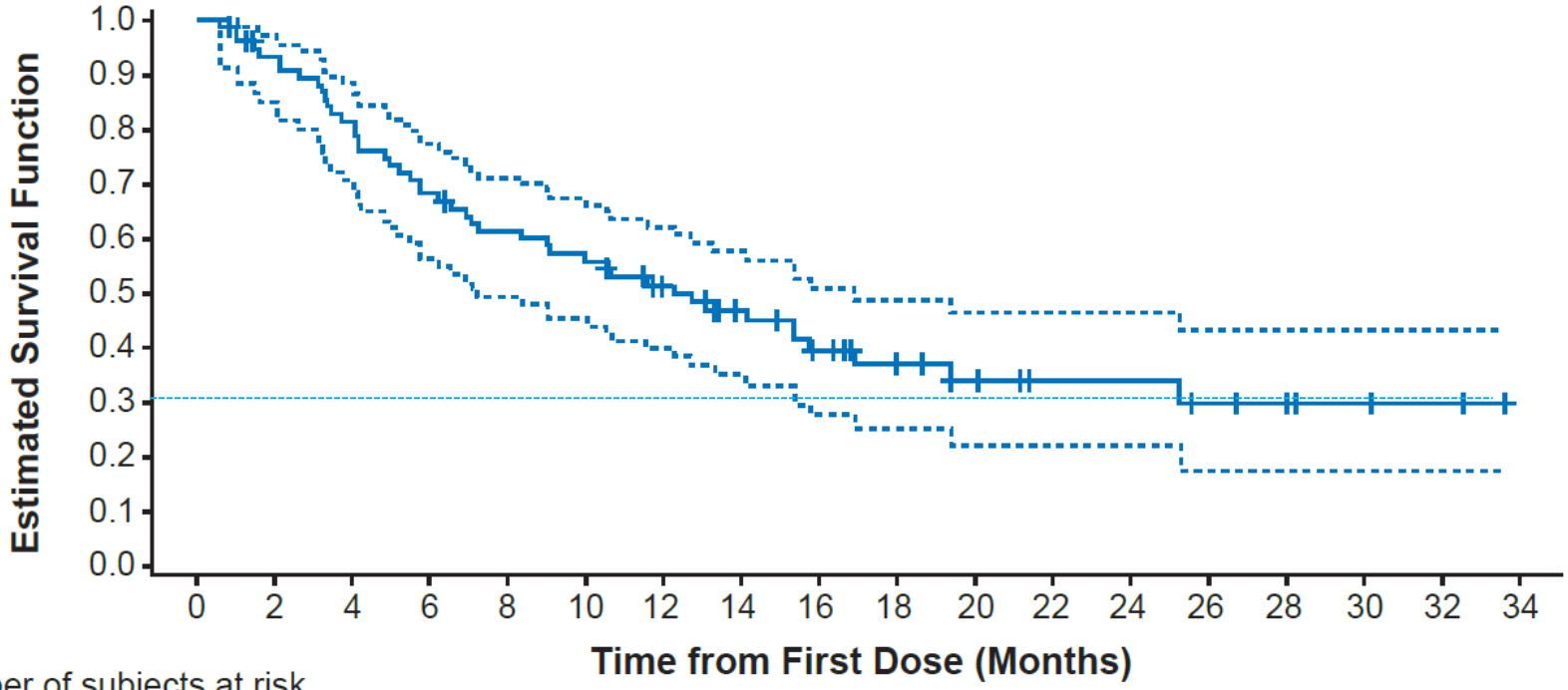
Progression-Free Survival (independent review)



PFS: 5.5 months (95% CI, 2.8 to 6.9)

D.Planchard et al, lancet onco 2016

Overall Survival



Number of subjects at risk

Overall Survival	78	70	61	51	45	42	33	26	20	14	11	8	8	6	5	3	2	0

mOS of 12.7 months

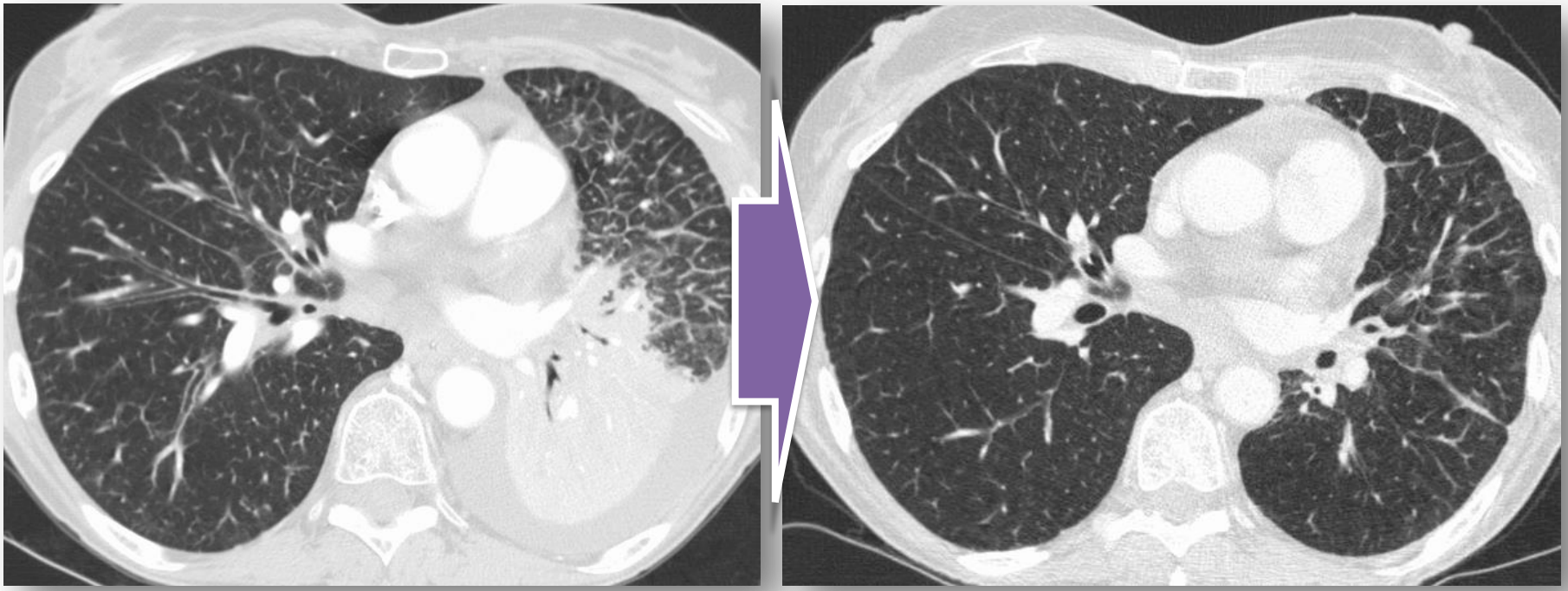
D.Planchard et al, lancet onco 2016

Case study

Dabrafenib Activity in BRAF V600E NSCLC

- 72 year old white female, 2nd line, former smoker, 10 pack years (stop in1985)
- ECOG PS2
- Adenocarcinoma, BRAFV600E, T3N3M1b (pleural, pulmonary, lymph nodes)
- Progression after one line of platinum-pemetrexed

October 2012 | **+ 6 weeks of Dabrafenib**



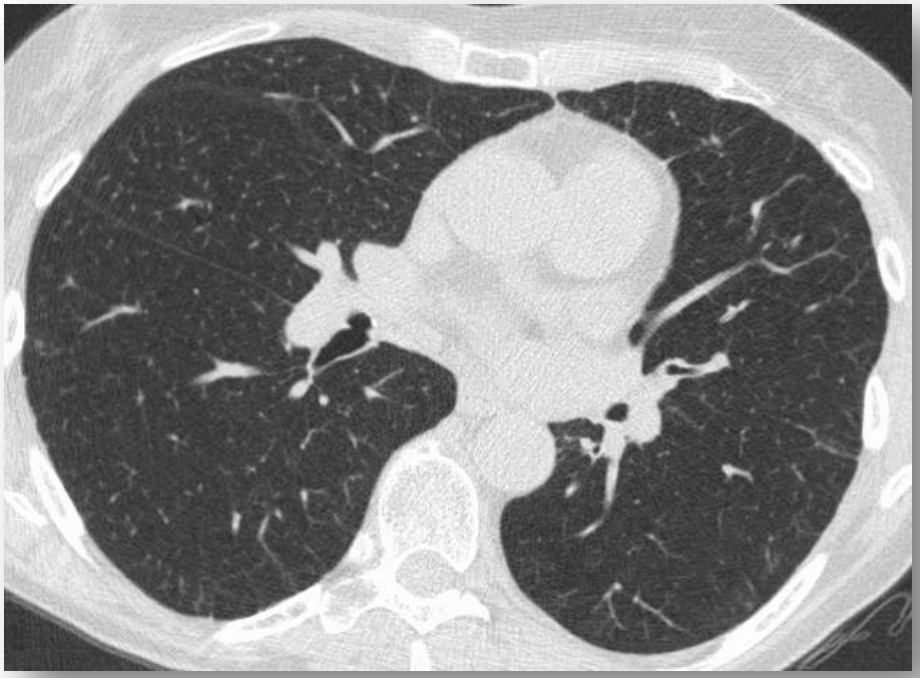
Baseline CT-Scan | **ECOG PS0**

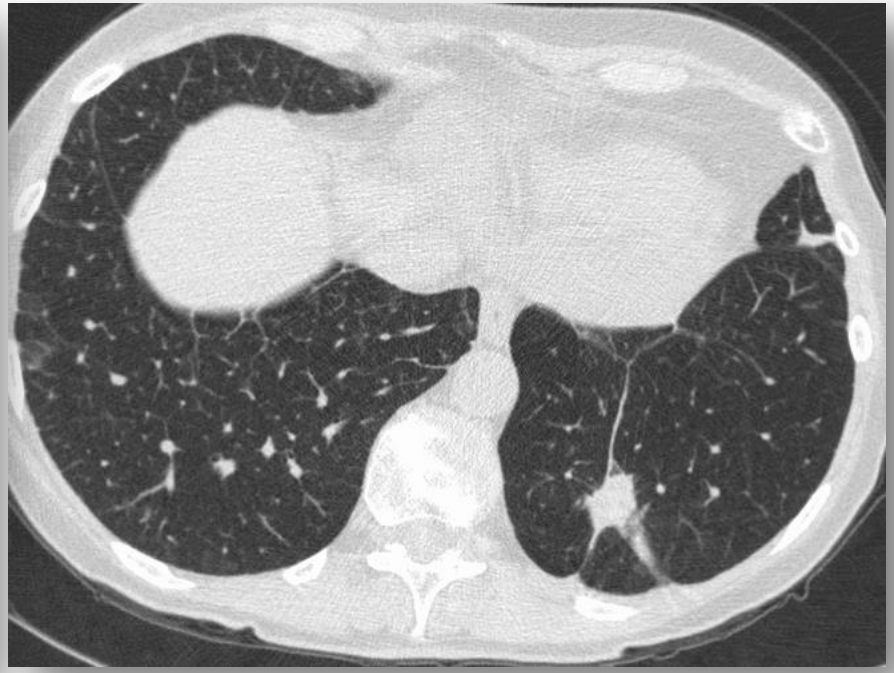
J. Mazieres et al, Hôpital Larrey CHU Toulouse

D.Planchard et al, ESMO 2014

- ECOG PS:0
- Asymptomatic
- Very good safety profile (rare episodes of fever)

September 2014





- Unique residual disease in the lower left lung
- Discussion for a local treatment 2 years after the start of dabrafenib

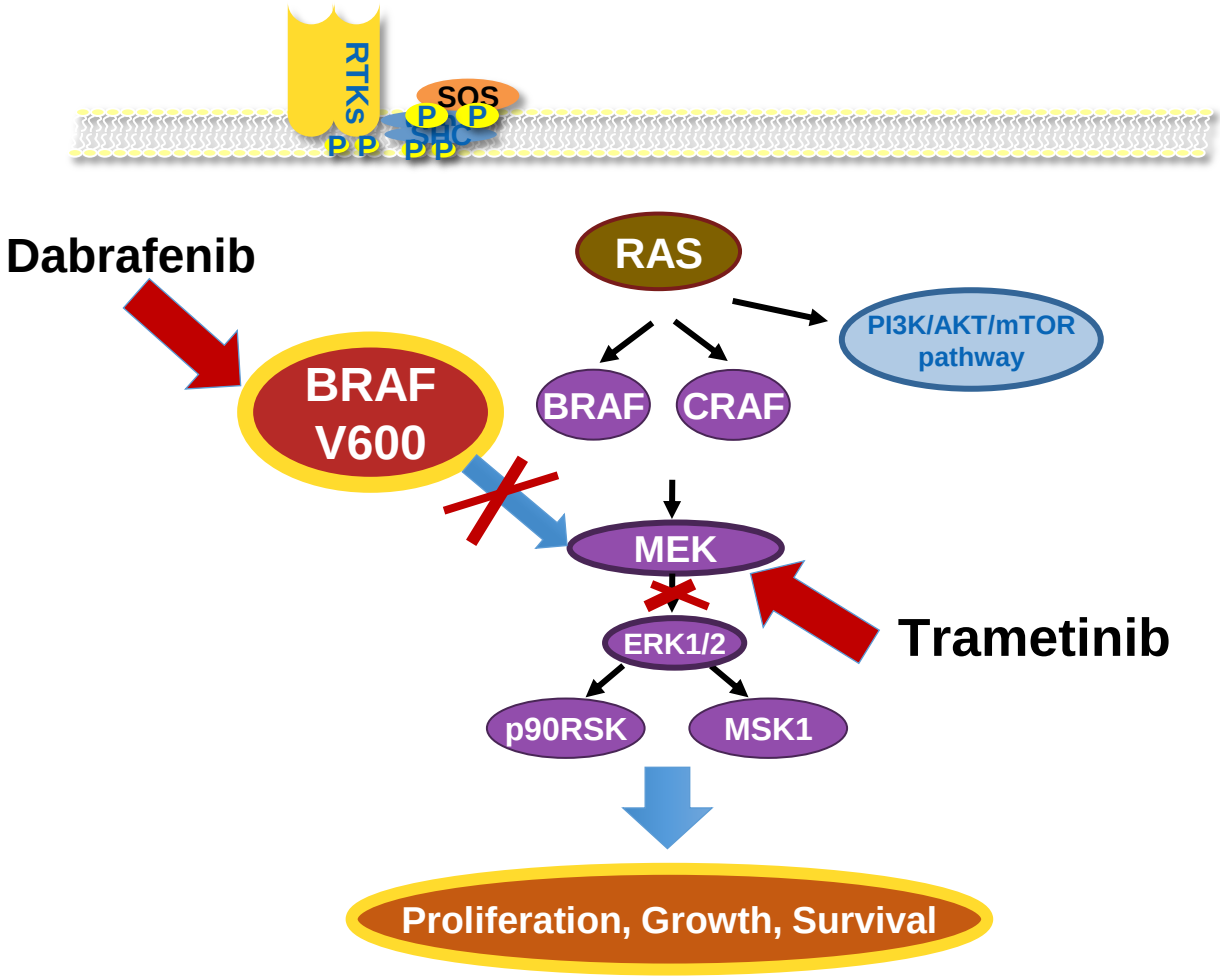
Dabrafenib Inhibits BRAF V600 Kinase and Trametinib Inhibits Downstream MEK Signaling

<u>Dabrafenib mode of action</u>

- Reversible, small molecule
- BRAF inhibitor
- ATP competitive
- BRAF V600E: IC_{50} 0.65 nM

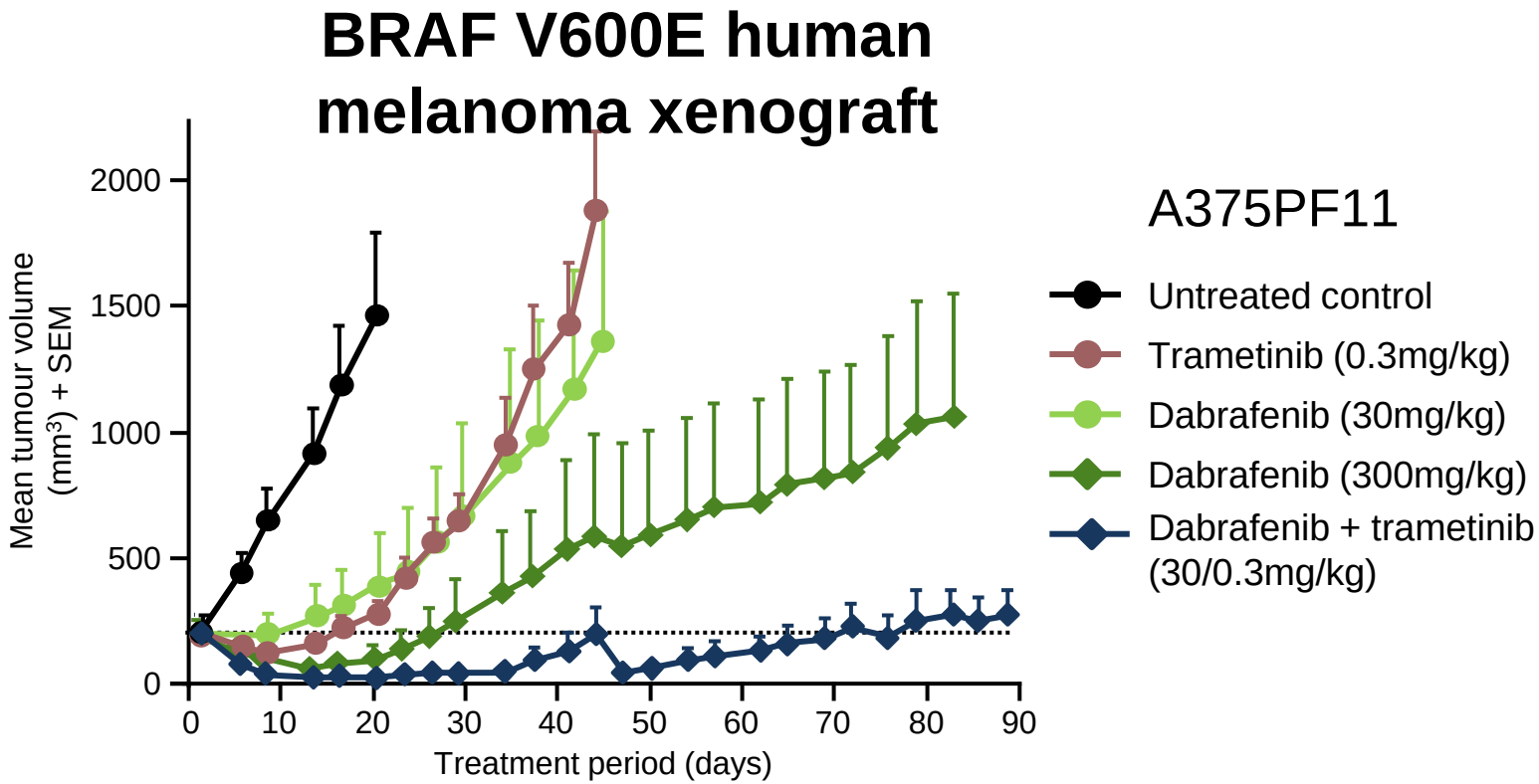
<u>Trametinib mode of action</u>

- Reversible, small molecule
- MEK1 and MEK2 allosteric inhibitor
- MEK1 and MEK2: IC_{50} 0.7 and 0.9 nM



Davies H, et al. *Nature.* 2002;417:949-954; Platz A, et al. *Mol Oncol.* 2008;1:395-405; Karasarides M, et al. *Oncogene.* 2004;23:6292-6298; Long, et al. *N Engl J Med.* 2014;371:1877; Gilmartin et al *Clin Cancer Res* 2011;17:989.

Enhanced antitumour activity with BRAF/MEK inhibitor combination



Greater reduction in tumour volume than seen with either single agent:
$p \leq 0.05$ *vs* dabrafenib (30mg/kg) or trametinib (0.3mg/kg) at Day 19

Infante J, *et al.* Oral presented at ASCO 2011; data on file.

SEM=standard error of the mean

In unresectable or metastatic melanoma, D+T has shown consistent long-term OS in three randomized studies

- 38% long-term survival at 3 years in a randomized trial[2]

	STUDY 220[2]		COMBI-D[1]		COMBI-V[1]	
	Dabrafenib + Trametinib (n = 54)	Dabrafenib monotherapy (n = 54)	**Dabrafenib + Trametinib (n = 211)**	Dabrafenib monotherapy (n = 212)	**Dabrafenib + Trametinib (n = 352)**	Vemurafenib monotherapy (n = 352)
ORR	**76%**	54%	**69%**	53%	**64%**	51%
Median PFS, months	9.4	5.8	11	8.8	11.4	7.3
Median OS, months	25	20.2	25.1	18.7	25.6	18.0
HR (95% CI) *P*-value	0.77 (0.49-1.21)		0.71 (0.55-0.92) .011		0.66 (0.53-0.81) < .001	

Tafinlar® (dabrafenib) and Mekinist®(trametinib) : first approved (FDA and EMA) combination of oral targeted therapies indicated for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations

Sources: 1. (dabrafenib) [summary of product characteristics]. West Sussex, UK: Novartis Europharm Limited; 2015.; 2. Daud A, et al. J Clin Oncol. 2015;33:[abstract 9036]; 3. Johnson DB, et al. J Clin Oncol. 2014;32:3697-3704.

D+T: Patient Population (cohort B)

		All Treated (N = 33)
Age, years	Median (range)	66 (49-88)
Sex, (%)	Female/male	21 (64)/12 (36)
Race,[a] n (%)	White	27 (82)
	Asian	3 (9)
	African American/Mixed	2 (6)
ECOG PS at baseline, n (%)	0 or 1	31 (94)
	2	2 (6)
Smoking history,[b] n (%)	Never smoked	9 (27)
	≤ 30 pack-years	13 (39)
	> 30 pack-years	10 (30)
Number of prior systemic regimens for metastatic disease,[c] n (%)	1	19 (58)
	2	6 (18)
	3	5 (15)

[a]One patient had missing race data; [b] One patient had missing smoking history information; [c] Three patients had missing information for prior systemic regimen for metastatic disease.

D.Planchard et al, ASCO 2015

Cohort B (Dabrafenib+Trametinib): interim results

- **Efficacy of D+T (Cohort B) at interim analysis was numerically superior to dabrafenib monotherapy (Cohort A) when <u>indirectly</u> compared across cohorts**
- Similar benefit observed in B*RAF* V600 metastatic melanoma; D+T demonstrated significantly superior anti-tumor activity *vs.* BRAF inhibitor monotherapy*

	Monotherapy	**D+T Combination**
	D[#] (primary analysis; N=78)	D+T[&] (interim analysis; N=24)
Investigator Assessed ORR (95% CI)	32% (21.9%, 43.6%)	**63% (40.6%, 81.2%)**
IRC Assessed ORR (95% CI)	23% (14.3%, 34.0%)	**68% (45.1%, 86.1%); N=22[1]**

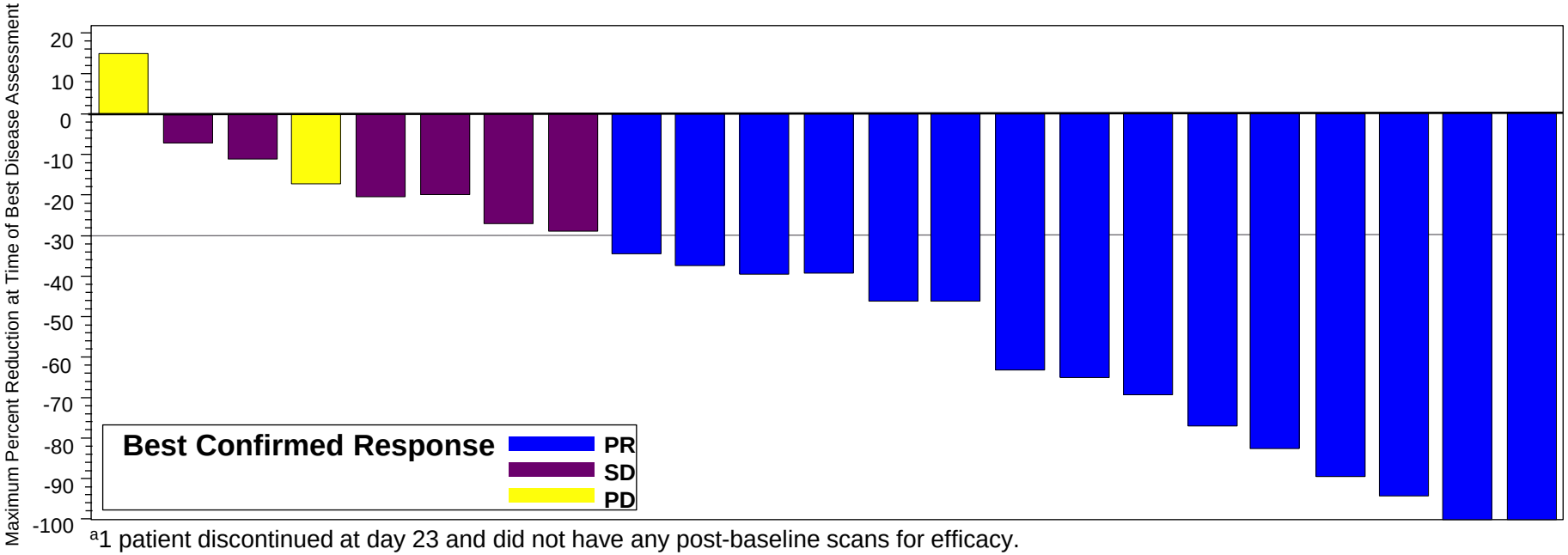
1. Excludes two subjects who did not have scans available for IRC review

D+T, Dabrafenib + Trametinib; D, Dabrafenib
ORR, Overall Response Rate; IRC, Independent Review Committee

**Flaherty, NEJM 2012; Long, NEJM 2014; Robert, NEJM 2014; [#] Planchard ESMO 2014; [&] Planchard ASCO 2015*

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 24[a])

ORR : 63%

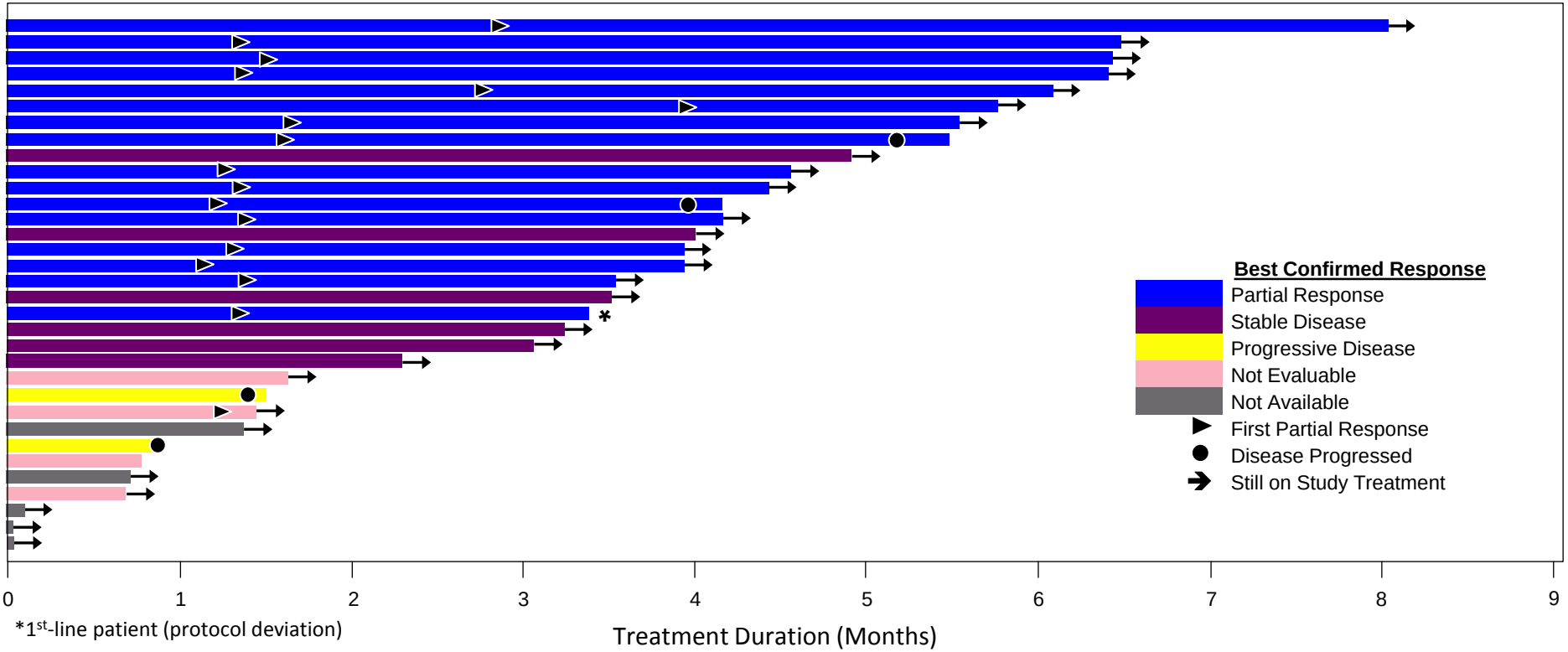


[a]1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

- The median duration of response was not reached

D.Planchard et al, ASCO 2015

Duration of Treatment for All Enrolled Patients in the Interim Analysis (n = 33)



- Median time on study treatment (dabrafenib and trametinib) = 108 days (range,1 to 244 days)

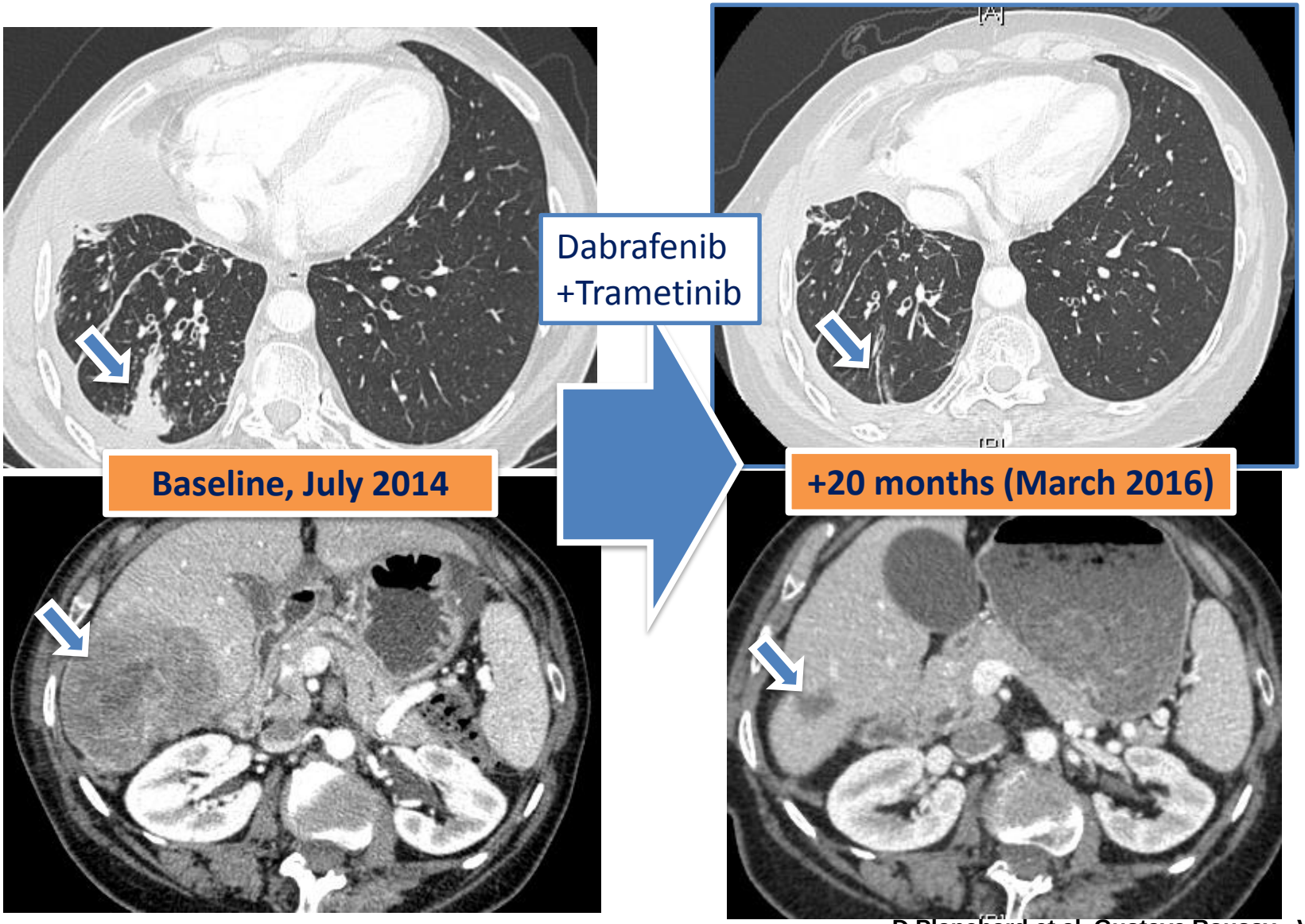
D.Planchard et al, ASCO 2015

Dabrafenib and Trametinib in BRAF V600E NSCLC

Case study - 61 year old women, never smoker.

Adenocarcinoma with pleural effusion, liver metastases, 4st line (CDDP-Pem, Docetaxel, Gemzar)

PR on week 6 with 54% reduction (confirmed and still response 73%, +20months)



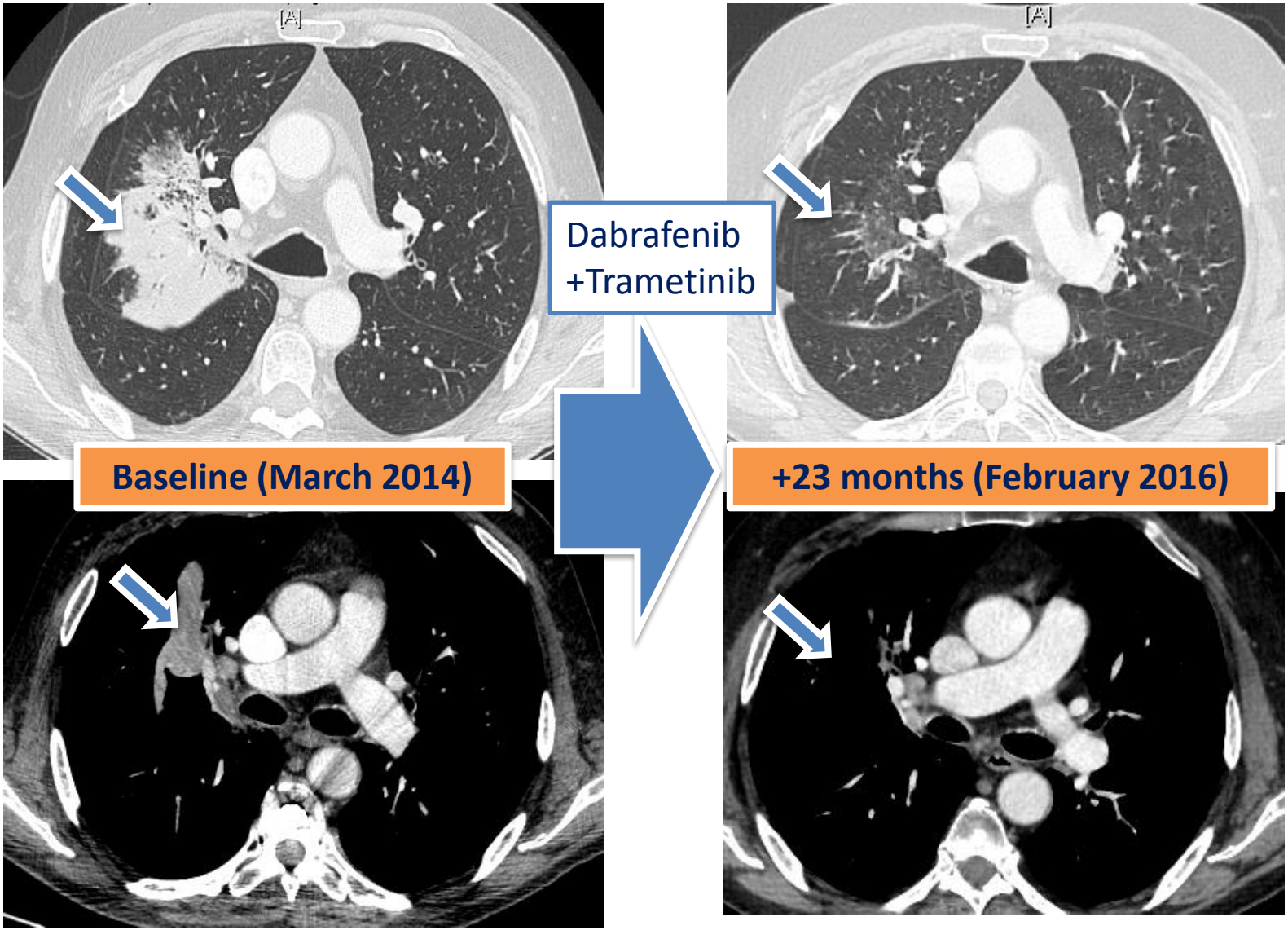
D.Planchard et al, Gustave Roussy - Villejuif

Dabrafenib and Trametinib in BRAF V600E NSCLC

Case study - 59 year old men, former smoker, 70 pack years.

Adenocarcinoma with irradiated brain metastases, 2nd line (1st line Carboplatin + Pemetrexed)

PR on week 6 with 70% reduction (confirmed and still response, -80% +23months)



D.Planchard et al, Gustave Roussy - Villejuif

Adverse events of D±T generally consistent with known safety profile to date

- Safety profile of D+T was consistent with that observed in melanoma population; no new safety trends noted

Adverse Event, n (%)*	D (N=84)	D+T (N=33)
Pyrexia	30 (36%)	13 (39%)
Diarrhea	14 (17%)	11 (33%)
Nausea	23 (27%)	11 (33%)
Vomiting	17 (20%)	11 (33%)
Decreased appetite	24 (29%)	8 (24%)
Asthenia	25 (30%)	7 (21%)
Cough	22 (26%)	7 (21%)
Edema peripheral	2 (2%)	7 (21%)
Rash	17 (20%)	7 (21%)

* Note: Non-randomized safety data

* Note: Non-randomized safety data

US FDA has supported pathway to registration based on the Phase II study

July 2015: Based on interim findings from the ongoing clinical trial, the FDA granted dabrafenib + trametinib Breakthough Therapy Designation for metastatic BRAF V600E NSCLC

FDA Guidance on D+T Trial Design & Submission

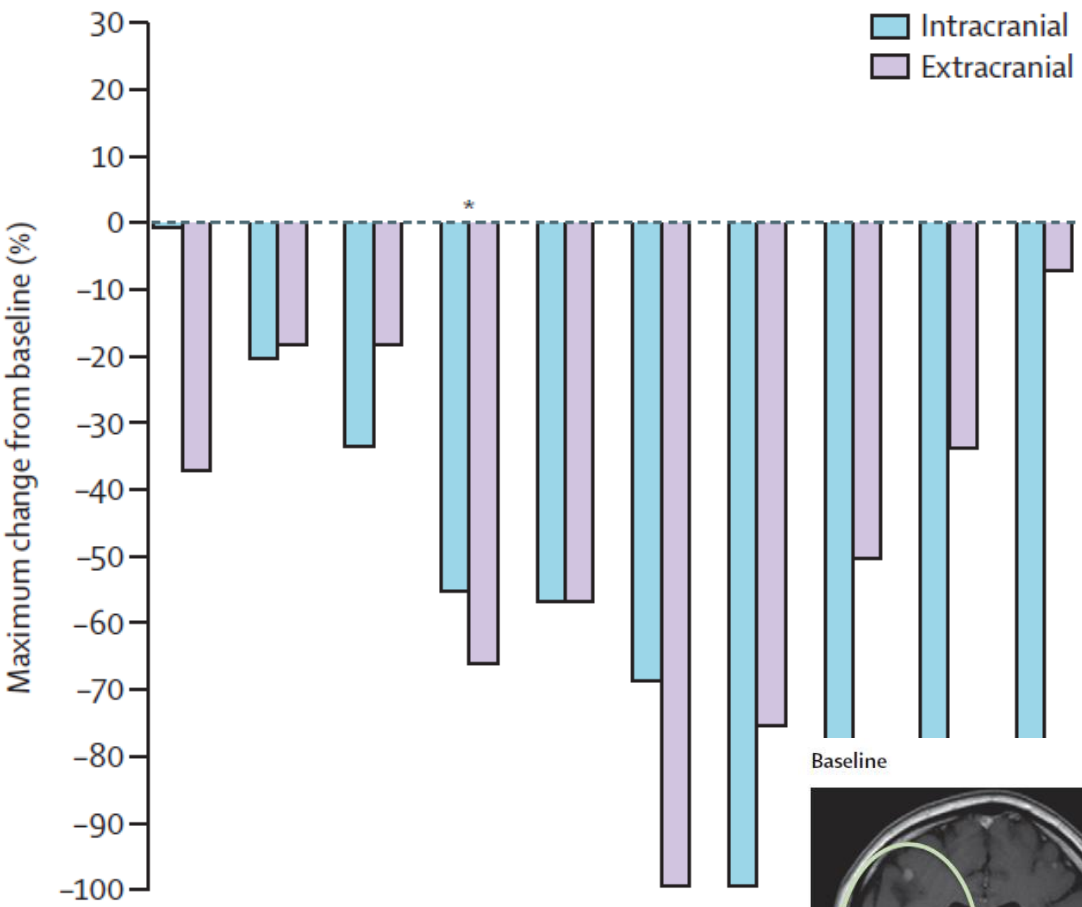
- **Study Design:** Single-arm study with a 50% ORR (lower bound of the CI ~35%) and ≥6 months follow-up on all patients could support a sNDA filing for a line agnostic BRAF V600E NSCLC indication
- **Line Agnostic Filing:** Agreed it may be infeasible to conduct a randomized trial in 1st line; not in a position to comment on ability of the 1st line cohort (Cohort C) to support an indication

Expected Patient Enrollment at Time of Submission

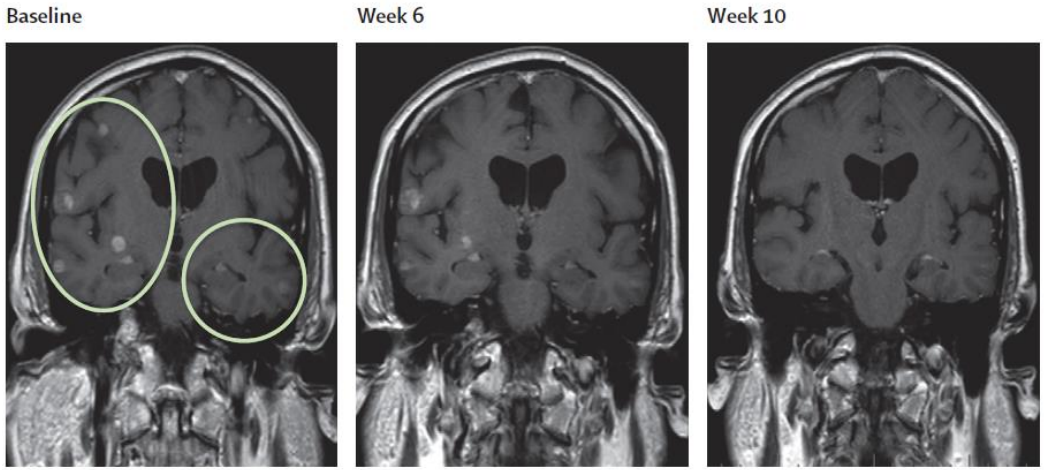
Cohort	N
A (Monotherapy)	84
B (D+T Combo 2nd Line)	59
C (D+T Combo 1st Line)	~14

Note: 70 NSCLC trial sites have been open globally for over 3 years with only ~150 patients enrolled

Melanoma and untreated brain (phase I Dabrafenib)



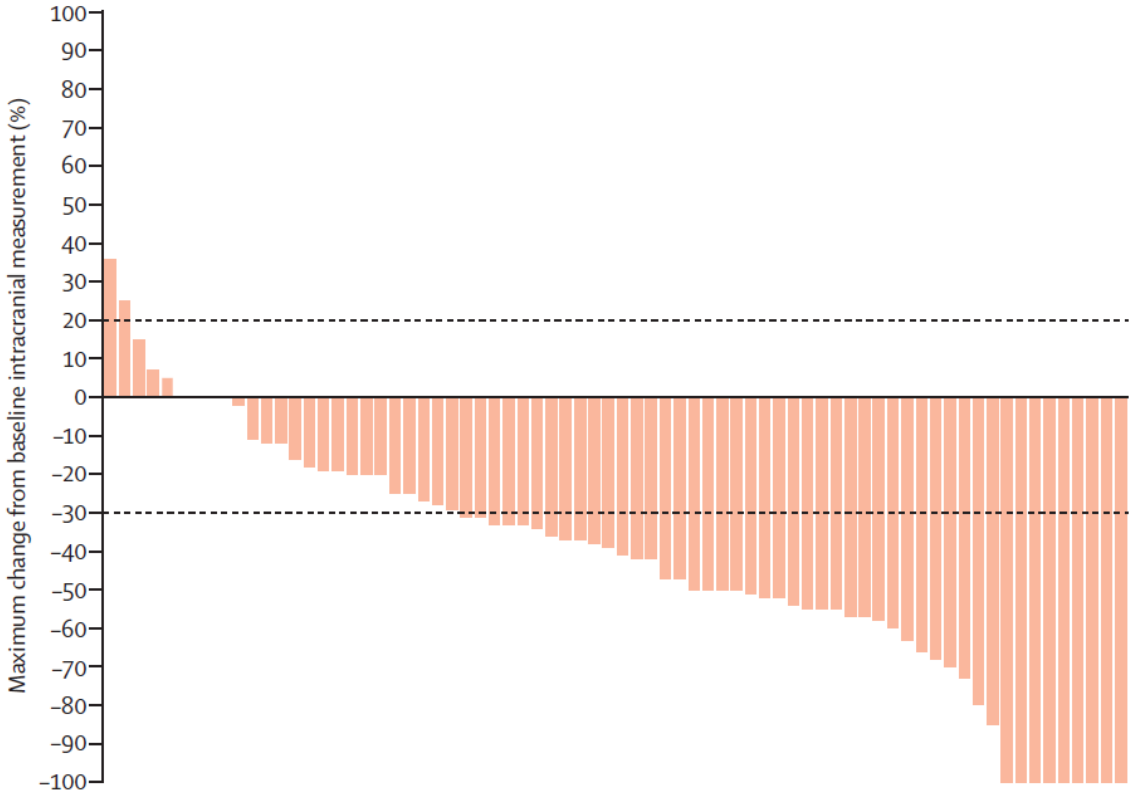
Change in intracranial and extracranial tumour size in the ten patients with Val600 BRAF-mutant



Gerald S Falchook et al, lancet 2012

Melanoma Val600E or Val600K brain metastatic (BREAK-MB):

Multicenter, open-label, phase 2 trial (Dabrafenib)



	A	B
Val600Glu BRAF mutant	74	65
Overall intracranial response (CR+PR)	29 (39·2%, 28·0–51·2%)	20 (30·8%, 19·9–43·4%)
Intracranial disease control (CR+PR+SD)*	60 (81·1%, 70·3–89·3%)	58 (89·2%, 79·1–95·6%)
Intracranial CR	2 (3%)	0
Intracranial PR	27 (36%)	20 (31%)
Intracranial SD	31 (42%)	38 (58%)
Intracranial PD	9 (12%)	5 (8%)
Not assessable	5 (7%)†	2 (3%)‡
Overall response (CR+PR)§	28 (37·8%, 26·8–49·9%)	20 (30·8%, 19·9–43·5%)
Overall disease control (CR+PR+SD)	59 (79·7%, 68·8–88·2%)	54 (83·1%, 71·7–91·2%)
6-month survival estimate (%)	61% (46·7–73·2%)	61% (46·3–72·7%)

cohort A had not received previous local treatment for brain metastases
cohort B had progressive brain metastases after previous local treatments

Georgina V Long et al, lancet onco 2012

Mechanims of resistance…

- BRAF-V600E copy-number gain and overexpression

- Expression of a splice variant form of BRAF-V600E

- Activating NRAS and MEK mutations, KRAS mutation

- Increased formation of eIF4F eukaryotic translation initiation complex

- Overexpression of antiapoptotic molecules, such as BCL2A1

- Overexpression of transcription factors such as c-FOS, NR4A1, NR4A2, MITF, and NF-κB

Warren Fiskus et al, Annual Review of Medicine 2016

Summary

- **BRAF V600E NSCLC** is a rare disease (2%)

- BRAF should testing in pts EGFR and ALK wild type

- **D + T (for Tafinlar® and Mekinist®)** demonstrated clinically meaningful anti-tumor activity with higher ORR when compared indirectly with dabrafenib or Vemurafenib in BRAF V600E NSCLC

-**Safety profile** is manageable and generally consistent with previous studies in melanoma

-**Next step**: immunotherapy is tempting, and clinical trials testing these combinations are ongoing in melanoma

-**Strong need** to better characterize resistance mechanisms in NSCLC

THANK YOU!

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