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Dabrafenib in patients with BRAF V600E-mutant Advanced Non-Small Cell Lung Cancer (NSCLC): a multicenter, open-label, phase 2 trial (BRF113928)

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Dabrafenib Inhibits BRAF V600 Kinase

Mode of Action

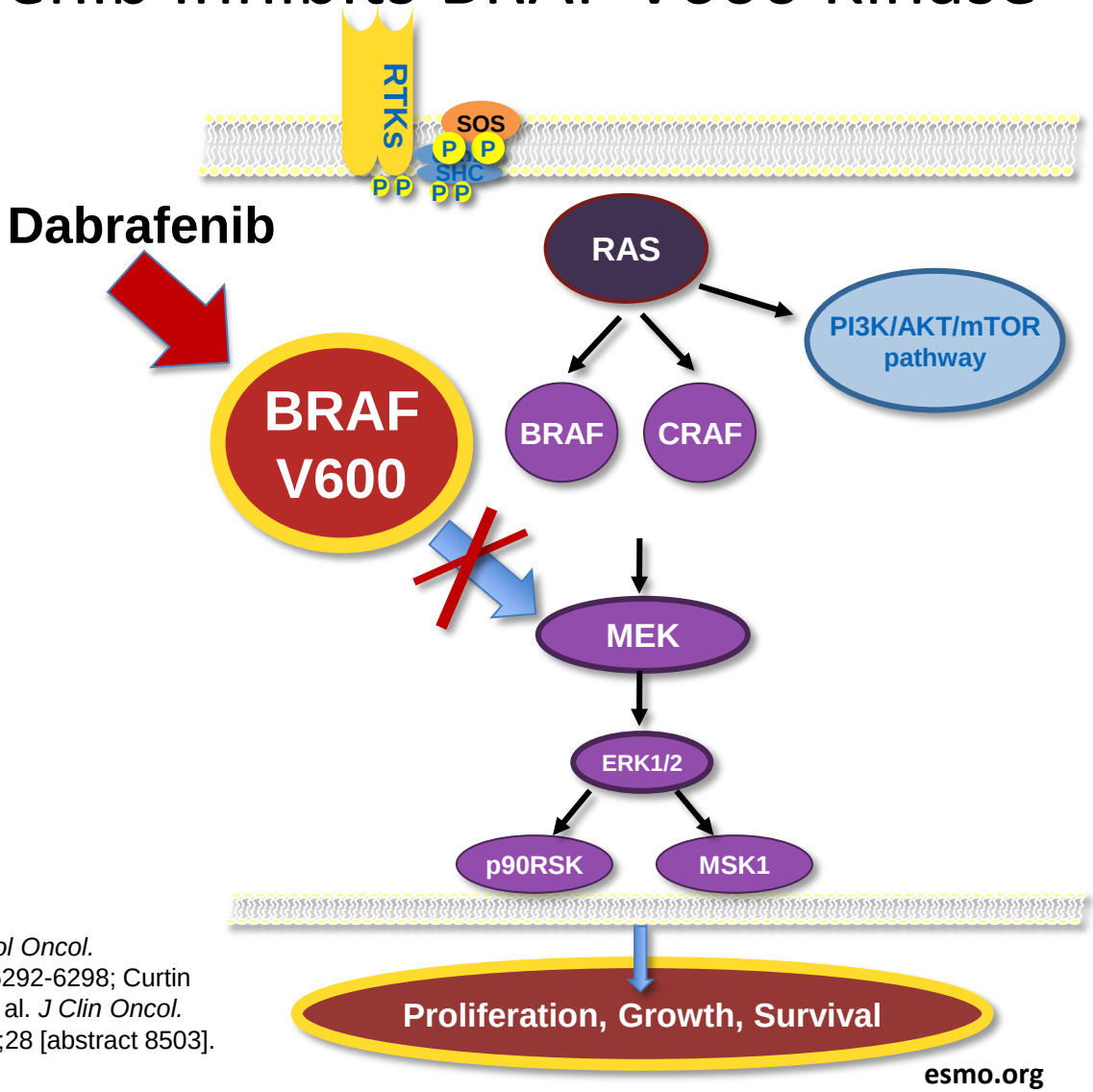
- Reversible, small molecule BRAF inhibitor
- ATP competitive

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

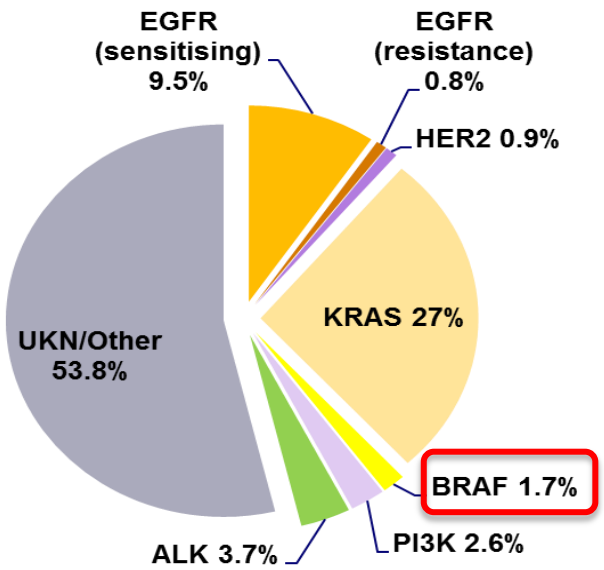


Davies H, et al. *Nature.* 2002;417:949-954; Platz A, et al. *Mol Oncol.* 2008;1:395-405; Karasarides M, et al. *Oncogene.* 2004;23:6292-6298; Curtin JA, et al. *N Engl J Med.* 2005;353:2135-2147; Flaherty K, et al. *J Clin Oncol.* 2009;27 [abstract 9000]; Kefford R, et al. *J Clin Oncol.* 2010;28 [abstract 8503].

BRAF Mutation in NSCLC

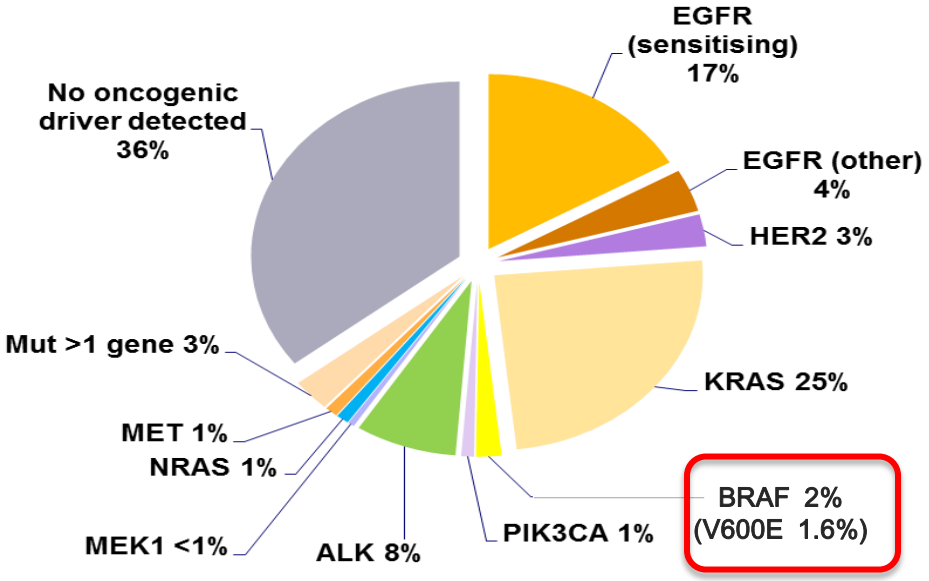
Europe[1]

All histology
(Biomarkers France)
(n = 9,911)



US[2]

Adenocarcinoma
(Lung Cancer Mutation Consortium)
(n = 733)

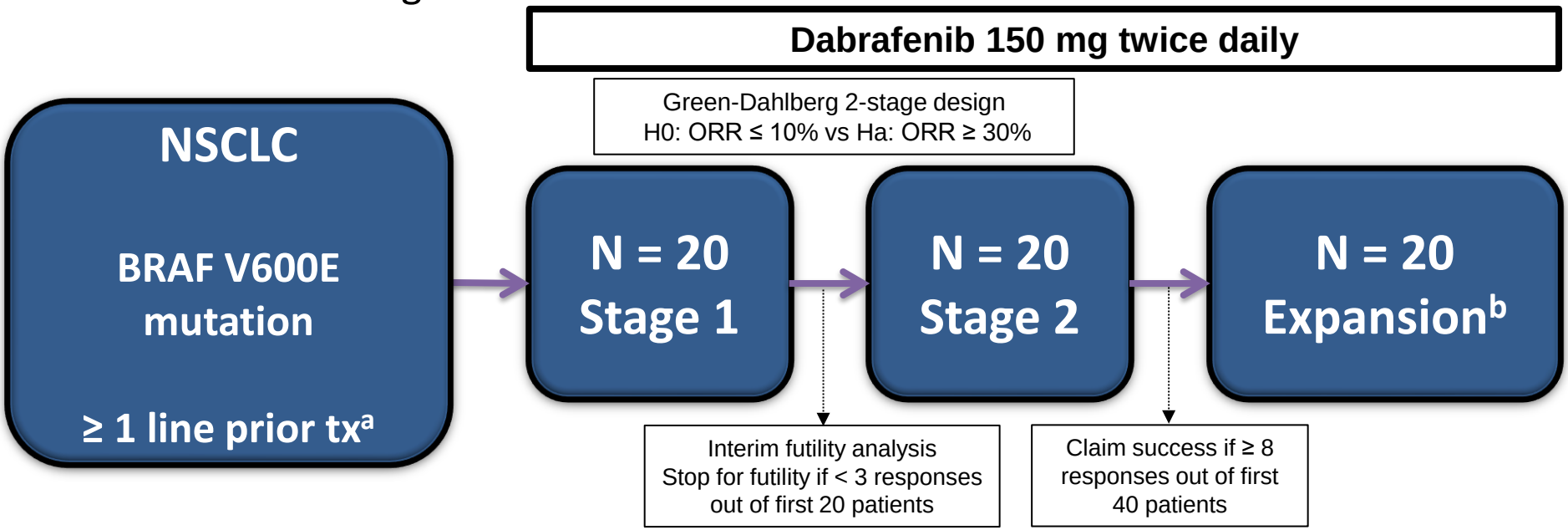


- NSCLC with BRAF V600E mutations have histologic features suggestive of an aggressive tumor[3]
- Patients with BRAF V600E mutation demonstrate less favorable outcomes with platinum based chemotherapy[3, 4]

1. F.Barlesi et al, ASCO 2013
2. Mark G. Kris et al, JAMA 2014
3. A Marchetti et al, JCO 2011
4. S Cardella et al, CCR 2013

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

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

Key Inclusion and Exclusion Criteria

- Inclusion:
  - Stage IV NSCLC
  - Measurable disease according to RECIST 1.1
  - Presence of BRAF V600E mutation (based on local testing)
  - Prior progression on systemic chemotherapy
  - ECOG PS 0-2

- Exclusion:
  - History of cancer within the past 5 years
  - Previous treatment with BRAF or MEK inhibitor
  - Symptomatic, nonstable, or > 1 cm brain mets

Study Treatment Status, 30 April 2014

	≥ 2nd Line, n (%) (N = 78)
On study treatment	19 (24)
Discontinued from study treatment:	59 (76)
Disease progression	46 (59)
Adverse event	5 (6)
Decision by subject	5 (6)
Investigator discretion	2 (3)
Protocol deviation[a]	1 (1)

[a] Patient failed to comply with study visits and was eventually discontinued by investigator for non-compliance.

Patient Population

		≥ 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.

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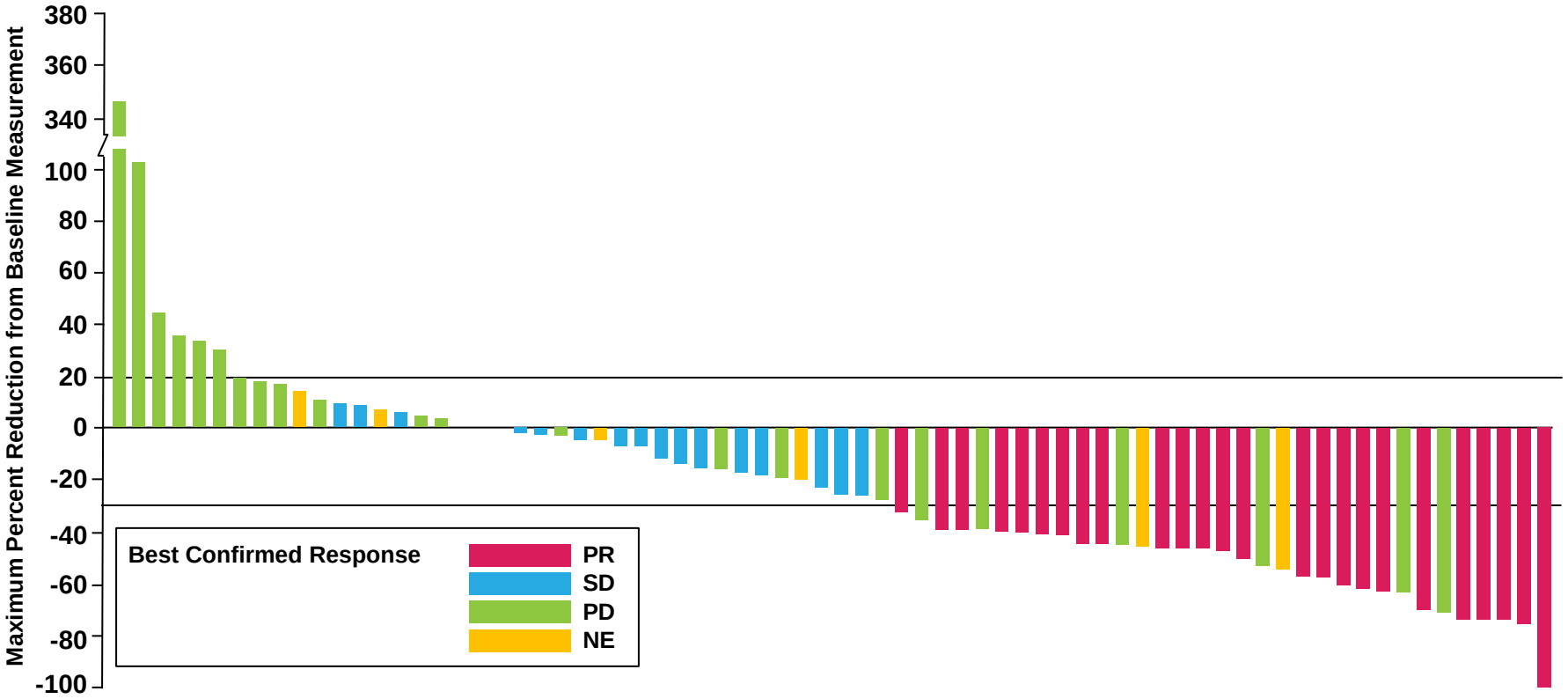
Investigator Assessed Best Confirmed Response For ≥ 2nd Line[a]

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)

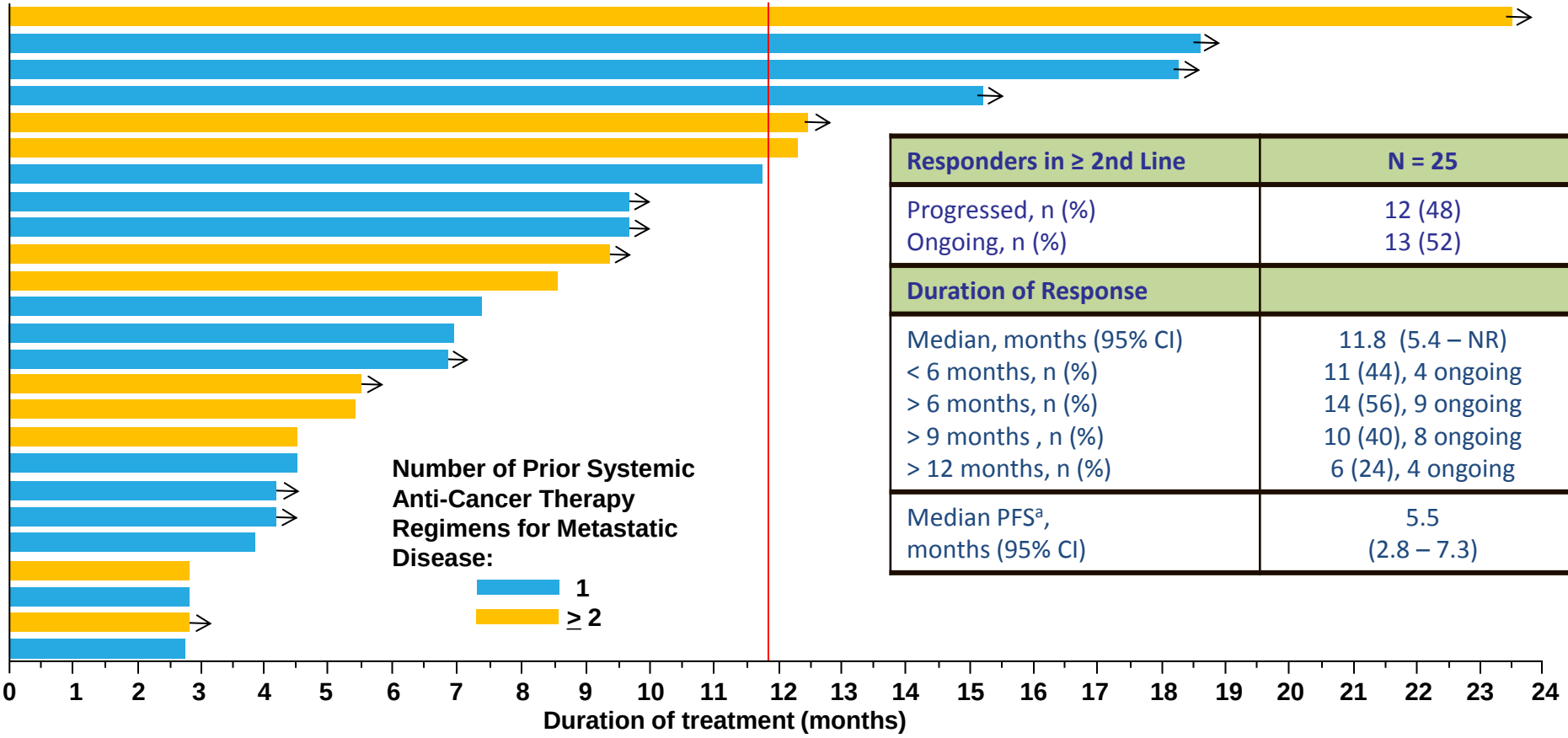
[a] 1st line subjects (n=6): 3=PR, 3=SD.

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

Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 78)



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
Median PFS[a], months (95% CI)	5.5 (2.8 – 7.3)

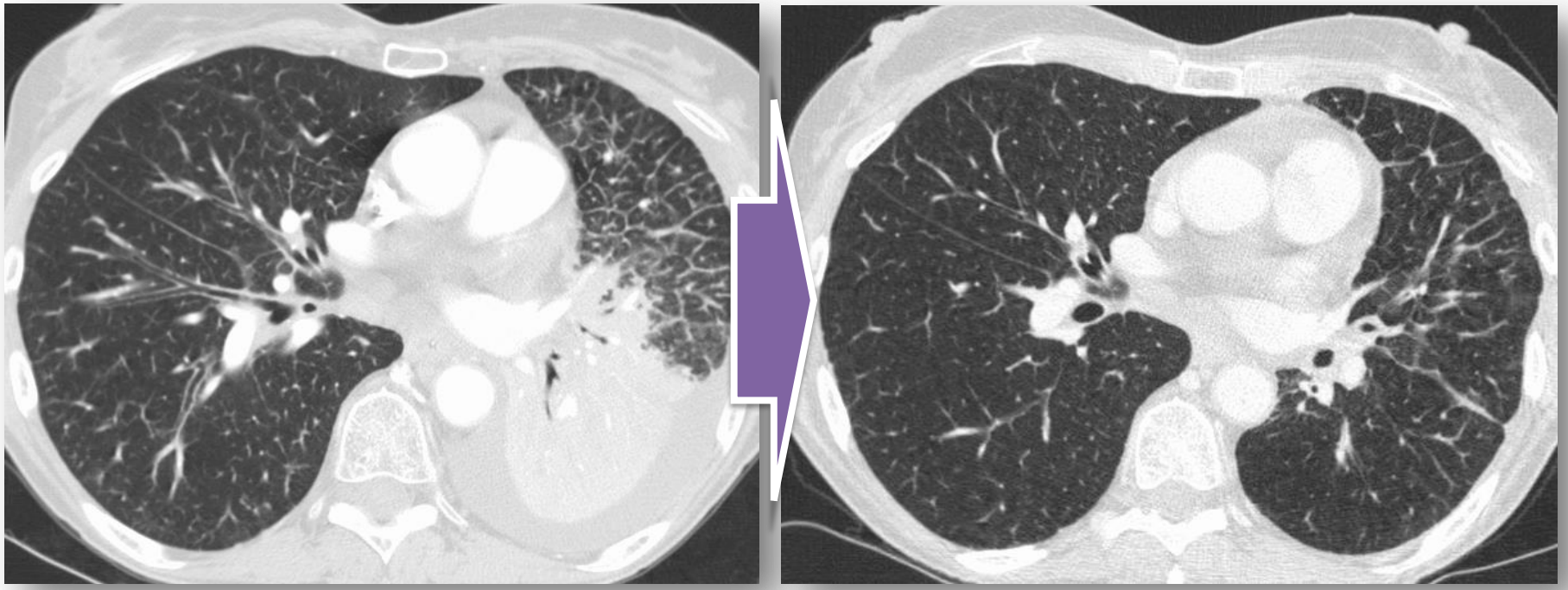
[a] 62% of patients progressed or died.

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

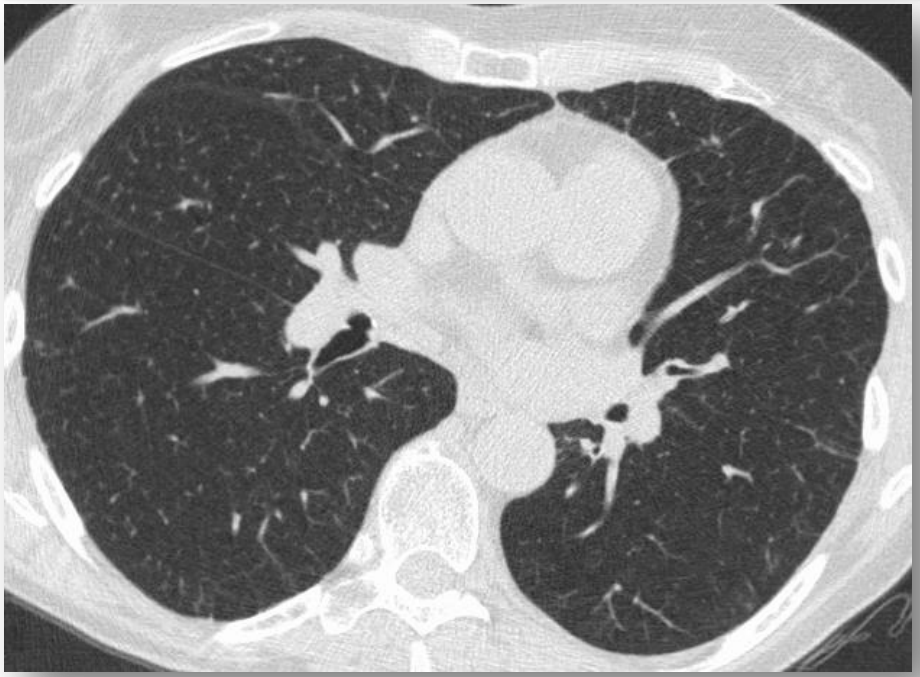
October 2012 → **+ 6 weeks of Dabrafenib**

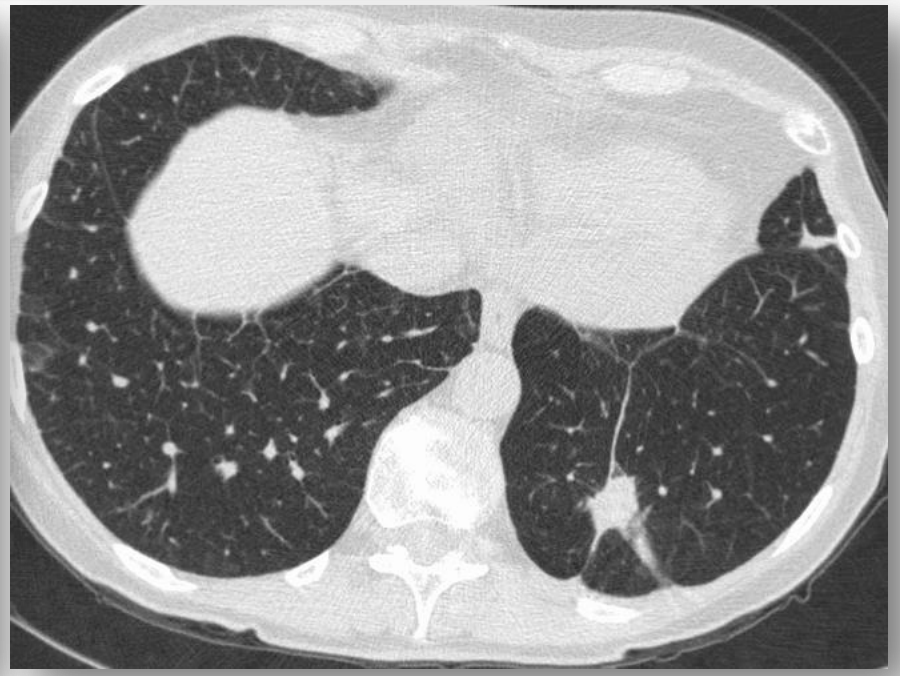


Baseline CT-Scan → **ECOG PS0**

- 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

Baseline Status by Independent Review for ≥ 2nd Line Patients[a]

Baseline Status (per RECIST 1.1)	≥ 2nd Line, n (%) (N=78)
Measurable disease	64 (82)
Non-measurable disease only	13 (17)
Unknown[b]	1 (1)

[a] Out of 6 first line patients, 2 had non-measurable disease by independent review

[b] One patient's lesion data not available for independent review at this time.

Independent Review Best Confirmed Response For ≥ 2nd Line[a] Patients with Measurable Disease at Baseline

Independent Review	
Best response	**N = 64**
PR, n (%)	18 (28)
SD[c], n (%)	15 (23)
PD, n (%)	23 (36)
Not evaluable	8 (13)
Response rate (confirmed CR + PR)	28%
95% CI	(17.6–40.8)
Disease control rate (CR + PR + SD)	51%
95% CI	(38.7–64.3)

[a] First line patients (n=6): PR = 3; SD = 1; non-measurable disease at baseline = 2.

[b] Investigator assessed best confirmed response for ≥ 2nd line patients.

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

Independent Review Best Confirmed Response For ≥ 2nd Line[a] Patients with Measurable Disease at Baseline

Independent Review			Investigator Assessed
Best response	**N = 64**		**N = 78[b]**
PR, n (%)	18 (28)		25 (32)
SD[c], n (%)	15 (23)		19 (24)
PD, n (%)	23 (36)		23 (29)
Not evaluable	8 (13)		11 (14)
Response rate (confirmed CR + PR)	28%		32%
95% CI	(17.6–40.8)		(21.9–43.6)
Disease control rate (CR + PR + SD)	51%		56%
95% CI	(38.7–64.3)		(44.7–67.6)

[a] First line patients (n=6): PR = 3; SD = 1; non-measurable disease at baseline = 2.

[b] Investigator assessed best confirmed response for ≥ 2nd line patients.

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

Adverse Event Overview

Best Response	No. of Patients All Treated, n (%) (N = 84)
Any adverse event (AE)	83 (99)[a]
Max grade 3 Max grade 4 Max grade 5	33 (39) 4 (5) 1 (1)
AEs related to study treatment	77 (92)
Any serious AE (SAE) Fatal SAEs SAEs related to study treatment	35 (42) 1 (1) 24 (29)
AEs leading to study treatment discontinuation	5 (6)
AEs leading to dose reduction	15 (18)
AEs leading to dose interruption	36 (43)

[a] One patient with no reported AEs stopped study drug 13 days after first dose for PD.

Most Common Adverse Events (≥ 20%)

Category	AE	No. of Patients All Treated (N = 84)	
		All n (%)	≥ Grade 3 n (%)
General	Pyrexia	30 (36)	2 (2)
	Asthenia	25 (30)	4 (5)[a]
	Decreased appetite	24 (29)	1 (1)
	Cough	22 (26)	0
	Fatigue	22 (26)	1 (1)
	Alopecia	18 (21)	0
Skin	Hyperkeratosis	25 (30)	1 (1)
	Skin papilloma	22 (26)	0
	Dry skin	19 (23)	0
Digestive	Nausea	23 (27)	1 (1)

[a] Includes one Grade 4 event.

Serious Adverse Events

SAE	No. of Patients All Treated, n (%) (N = 84)
Any	35 (42)
Fatal (Grade 5): hemorrhage intracranial	1 (1)
≥ 2 patients	
Cutaneous squamous cell carcinoma	10 (12)
Pyrexia	5 (6)
Basal cell carcinoma	4 (5)
Ejection fraction decreased	2 (2)
Pneumonia	2 (2)

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Summary & Conclusions

- Dabrafenib is the first drug of its class to demonstrate clinically meaningful antitumor activity with durable objective responses in BRAF V600E mutated NSCLC in a prospective clinical trial:
  - ORR = 32%, and DCR = 56%
  - Median DoR = 11.8 months with 48% responders progressed
  - Median PFS = 5.5 months with 62% patients progressed or died

- Safety profile is manageable and generally consistent with previous studies in melanoma:
  - Most common (> 25%) AEs were pyrexia, asthenia, hyperkeratosis, decreased appetite, nausea, cough, fatigue, and skin papilloma
  - Cutaneous squamous-cell carcinomas and keratoacanthoma reported in 18%

- A second cohort investigating dabrafenib + trametinib combination therapy is actively recruiting

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