PERSONALIZED THERAPY TO FURTHER IMPROVE OUTCOMES IN PATIENTS WITH BRAF MUTATED mNSCLC

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Objectives

- Understand the role of BRAF in metastatic NSCLC
- Gain awareness of BRAF testing methods and the diagnosis of BRAF+ NSCLC
- Review the clinical data for dabrafenib and trametinib in advanced NSCLC

Introduction to BRAF

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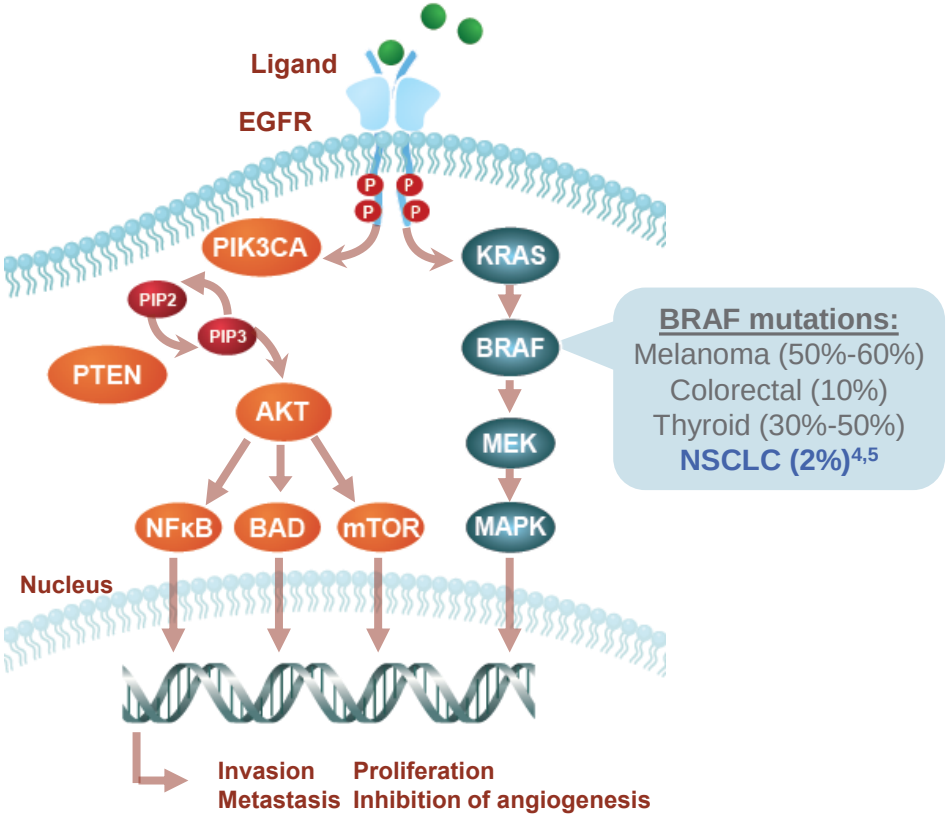
The RAS-RAF-MEK-ERK (MAPK) Pathway Plays a Key Role in Cell Proliferation

- The mitogen-activated protein kinase (MAPK) pathway regulates cell signaling from transmembrane growth factor receptors, leading to cell proliferation[1-3]
- Oncogenic mutations in the MAPK pathway, including BRAF kinase mutations, have been reported in a number of human cancers, including NSCLC[2]
- BRAF mutations result in constitutive BRAF activation and uncontrolled signaling via the MAPK pathway[1]

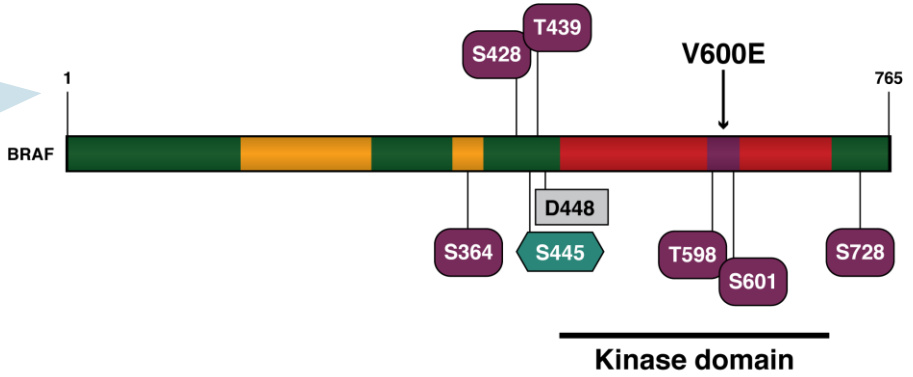


BRAF Mutations in NSCLC

- BRAF mutations occur in ≈ 1% to 4% of all NSCLC adenocarcinomas[4-8]
- BRAF mutations typically do not overlap with other common mutations in NSCLC (eg, KRAS, EGFR, ALK)[9]
- In contrast to other oncogenic drivers in NSCLC, key patient characteristics/indicators for BRAF-mutated NSCLC have not been well characterized
  - BRAF mutations do not appear to correlate strongly with age, sex, stage at diagnosis, or smoking status. However, some studies suggest that patients with BRAF mutations are more likely to be female or have a history of smoking[7,10]

BRAF V600E is the most common BRAF mutation in NSCLC[7]

- Occurs in about 50% to 70% of cases
- Caused by a point mutation in the BRAF kinase domain at position 600—a valine (V) is changed to glutamic acid (E)



Types of BRAF Mutations

- Although V600E is the most common BRAF mutation in NSCLC, occurring in ≈ 50% to 70% of BRAF+ cases, other mutations in BRAF have been identified[7,10]
- Diversity of BRAF mutations has important implications
  - Different strategies may be required for the targeted treatment of NSCLC bearing V600, non-V600, and/or inactivating BRAF mutations
- In a retrospective analysis of 1046 NSCLC tumors, BRAF mutations were present in 4.9% of adenocarcinomas; 21 of 37 BRAF mutations (56.7%) were V600E, and 15 (43.3%) were non-V600E mutations[10]

BRAF Mutations Detected in 37 NSCLC Tumors[10]				
V600E	K601N	D594G	W604R	K601E
L597R	G606A	L597V	G606V	G469V
L597Q	G466V	V600L	G469A	

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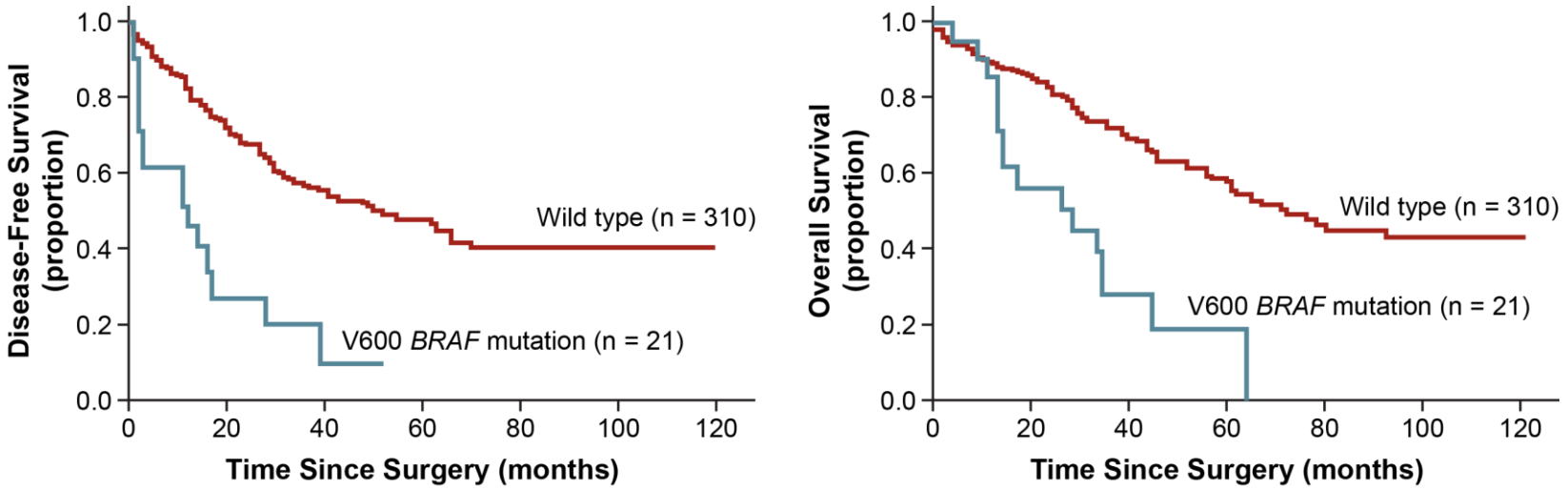
Patients With BRAF V600E Mutations Have Shorter Median DFS and OS Than Patients Without V600E Mutations[10]

- BRAF V600E+ NSCLC has histological features suggestive of an aggressive tumor
- Patients with advanced BRAF V600E+ NSCLC have worse outcomes with platinum-based chemotherapy, including ORR, PFS, and OS, than wild-type patients and patients with non-V600E mutations



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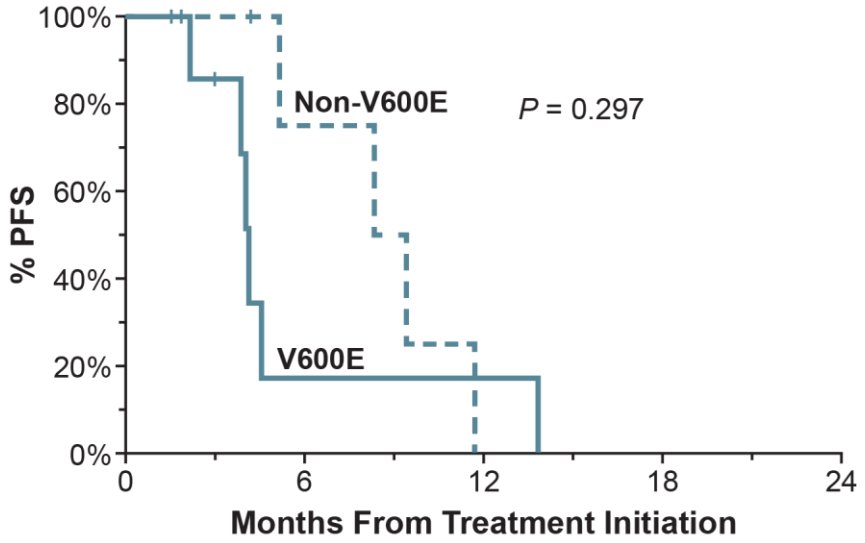
Outcomes in Patients With BRAF V600E+ NSCLC vs Patients With Wild-Type BRAF[8]

- Patients with advanced BRAF V600E+ NSCLC have worse outcomes with platinum-based chemotherapy, including ORR, PFS, and OS, than wild-type patients and patients with non-V600E mutations

PFS for BRAF V600E–Mutant vs Wild-Type NSCLC With First-Line Platinum-Based Chemotherapy



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Clinical Outcomes in Patients With NSCLC on First-Line Platinum-Based Chemotherapy

Endpoint	Wild Type (n = 79)	BRAF V600E (n = 7)
ORR, %	48	29
Median PFS, mo	6.7	4.1
Median OS, mo	15.9	10.8
Treatment	Majority received chemotherapy	

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Treatment Remains Suboptimal for Patients With BRAF V600+ NSCLC

Approximately one-third of patients remain untreated[5]

- 33% of patients with BRAF V600+ NSCLC receive best supportive care first line
- 57% received best supportive care second line

Doublet chemotherapy is the most common treatment option in BRAF+ NSCLC[5]

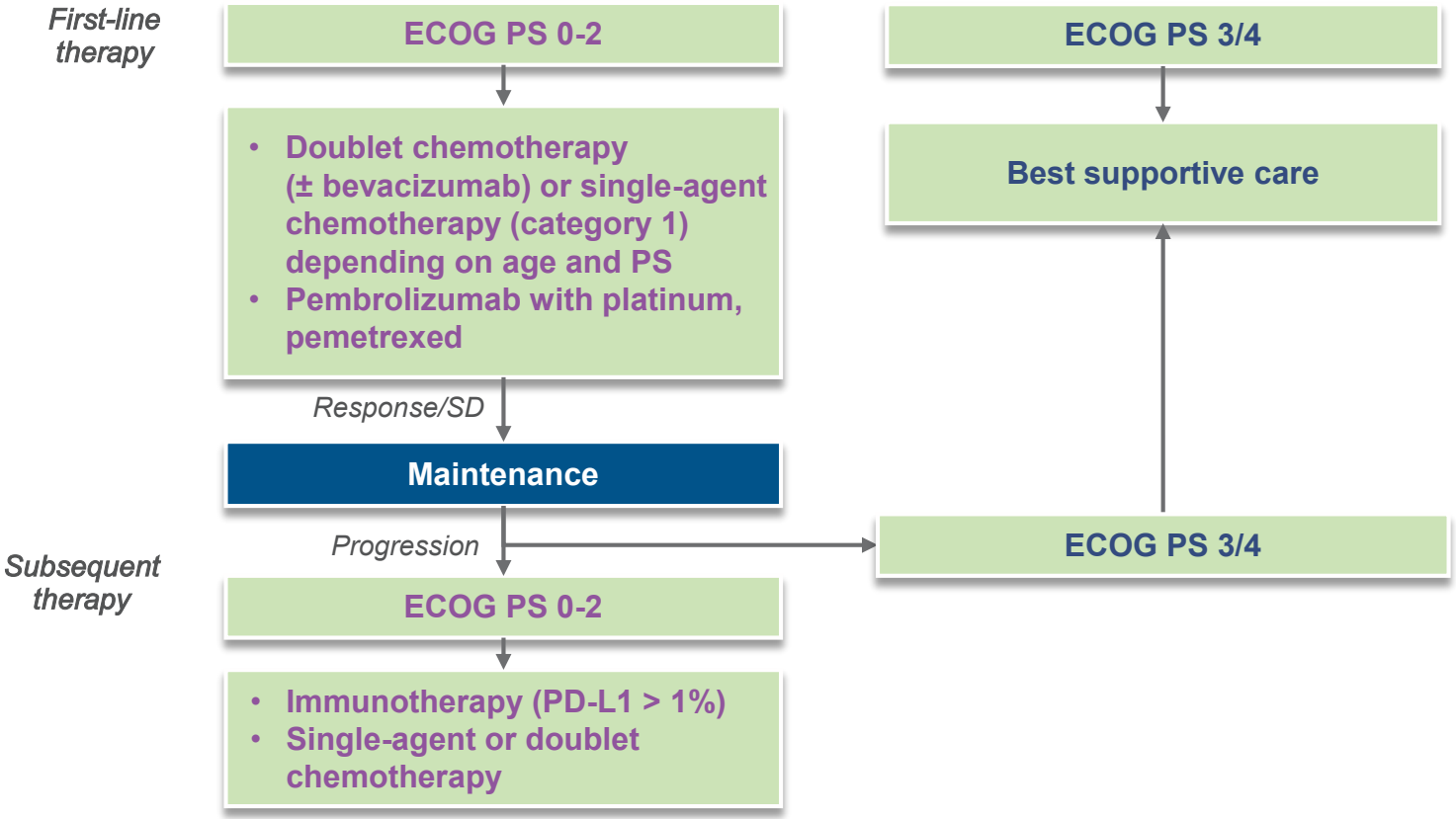
- A French registry study showed that 52% of patients with a BRAF mutation received doublet chemotherapy (n = 146)

In patients with driver mutations, targeted therapy can help patients live longer[4]

- Patients identified with a mutation driver not receiving targeted therapy lived 1 year shorter than those who were identified with actionable drivers and treated with targeted therapy

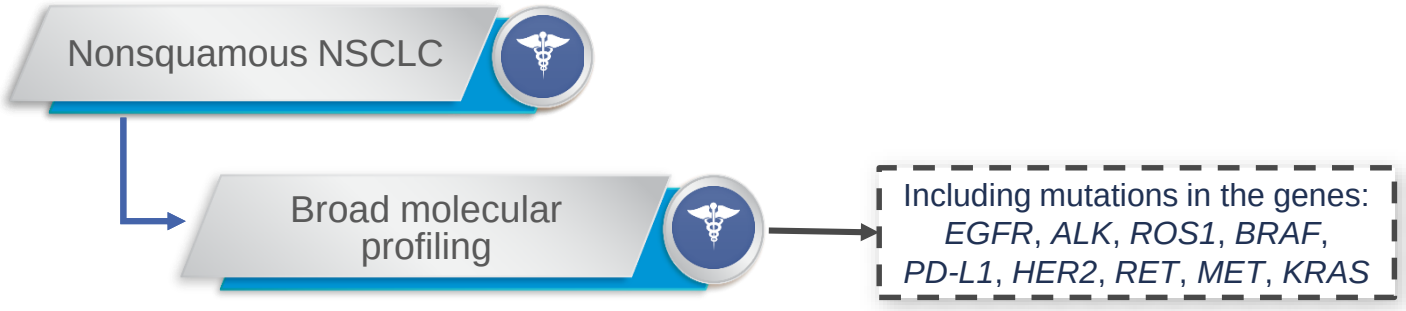
Patients With Nonsquamous NSCLC Without Mutated ALK, EGFR, or ROS1 Currently Receive Chemotherapy or Immunotherapy

Summary of Current Treatment Guidelines for Advanced or Metastatic Disease[11,12]



Broad Molecular Profiling Includes Identification of BRAF+ Patients

- Historical approach encourages serial testing with companion diagnostics
- Current testing paradigm favors broad molecular profiling for all patients[11]



Current NSCLC Treatment Guidelines Prioritize Precision Medicine

ESMO Consensus[12]

The most recent ESMO clinical practice guidelines recommend **broader molecular profiling to identify rare driver mutations, including BRAF, using multiplex/NGS (next-generation sequencing)** to ensure that patients receive the most appropriate treatments

NCCN Treatment Guidelines[11]

2018 NCCN Guidelines **strongly endorse broader molecular profiling to identify rare driver mutations using multiplex/NGS (next-generation sequencing)** to ensure that patients receive the most appropriate treatments

- EGFR, BRAF, ALK, and ROS1, are currently recommended by NCCN guidelines as the minimum assessment of potential genetic alterations
- Broad molecular profiling can be achieved by companion diagnostic NGS technologies[11]

Up-Front BRAF Testing Is Needed to Quickly and Efficiently Identify Patients

- Up-front BRAF testing is essential for patients with advanced NSCLC because
  - BRAF does not appear to correlate with any clinical risk factors (eg, age, sex, smoking history) [7,10]
  - BRAF+ NSCLC may be more aggressive than lung cancers with other mutations or histologies[10]
  - Targeting BRAF mutations has demonstrated clinical efficacy in patients with BRAF V600+ NSCLC[13]

Broader molecular profiling can help identify more actionable drivers, such as BRAF V600E, earlier

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Clinical Data of dabrafenib + trametinib

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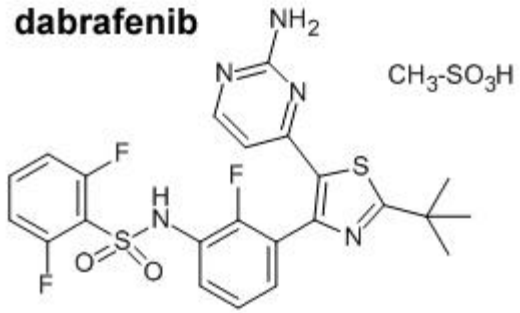
Dabrafenib and Trametinib Target Different Kinases in the MAPK Pathway

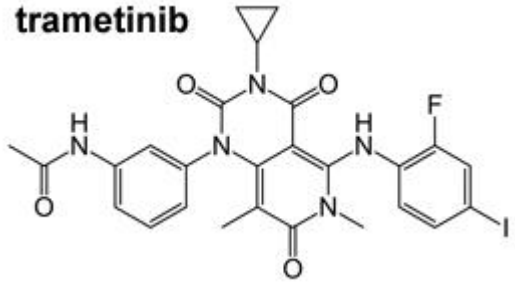
Dabrafenib[14]

Reversible, potent selective inhibitor of RAF kinases, including BRAF V600 and particularly BRAF V600E and V600K



Trametinib[15]

Reversible, highly selective inhibitor of MEK1 and MEK2 kinase activity



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Dabrafenib and Trametinib are Approved for the Treatment of BRAF V600+ NSCLC[16-17]

DCGI Approved Indication

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

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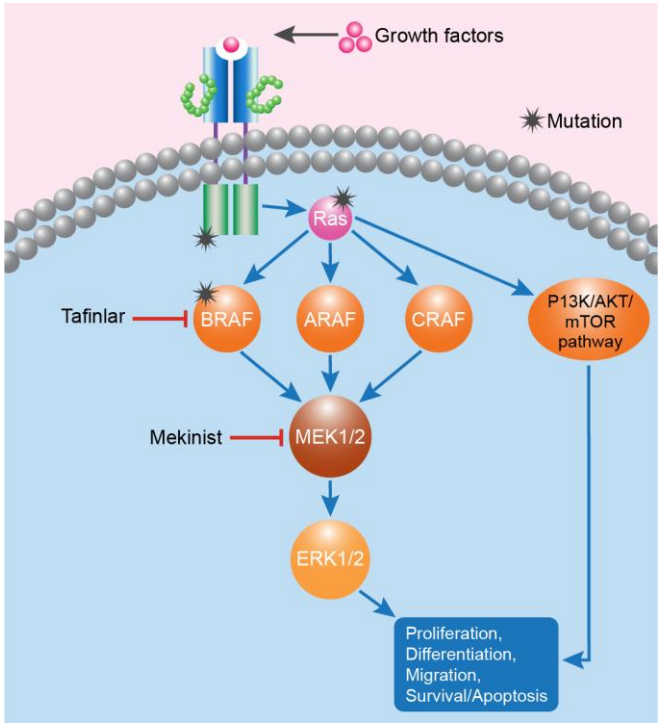
Rationale for Combination of Dabrafenib + Trametinib



- Combination therapies that target multiple portions of the MAPK pathway have been developed to overcome resistance to BRAF inhibitor monotherapy[18]
- In NSCLC and melanoma, compared with BRAF inhibition alone, BRAF and MEK inhibition has been shown to[13]
  - Synergistically inhibit the MAPK pathway in BRAF V600E+ cell lines
  - Delay resistance to BRAF inhibitors in animal models
  - Inhibit cancer growth more effectively than dabrafenib alone in clinical trials, leading to approval of dabrafenib + trametinibfor the treatment of BRAF V600+ advanced melanoma[16,19,20]

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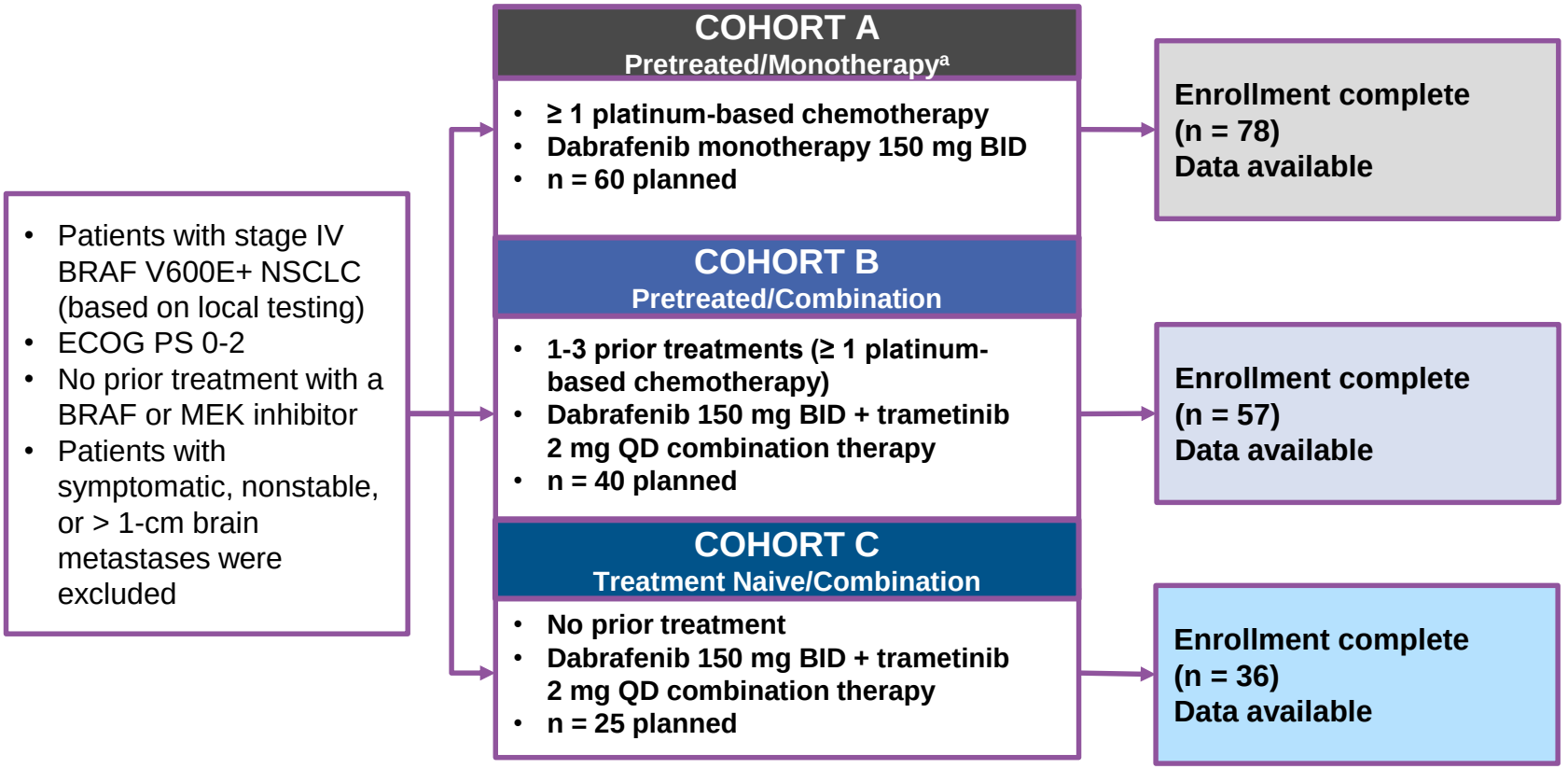
Phase 2 Study of Dabrafenib + Trametinib in BRAF V600E+ NSCLC

BRF113928 Study Design: a Multicohort, Nonrandomized, Open-Label, Phase 2 Study[13,25,26]



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Dabrafenib + Trametinib in BRAF V600E+ NSCLC: Study Endpoints[25]

Primary Endpoint

- **Investigator-assessed ORR**
  - **All responses had to be confirmed based on RECIST v1.1**
  - **Independent review committee was also used**

Secondary Endpoints

- **PFS**
- **DOR**
- **OS**
- **Safety**
- **Population pharmacokinetics**

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Dabrafenib + Trametinib in BRAF V600E+ NSCLC: Patient Cohort A[25]

Patient Population	Cohort A (n = 78)
Age, median (range), years	66 (28-85)
Sex, n (%)	
Female/male	39 (50)/39 (50)
Race, n (%)	
White	59 (76)
Asian	17 (22)
Black	2 (3)
ECOG PS at baseline, n (%)	
0/1/2	16 (21)/50 (64)/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 diagnosis, n (%)	
Adenocarcinoma	75 (96)
Other	3 (4)
Prior systemic regimens for metastatic disease, n (%)	
1	40 (51)
2	14 (18)
≥ 3	24 (31)

Two-thirds of patients were current or former smokers

Nearly all patients had adenocarcinoma histology

Almost half the patients were in second line and beyond

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

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Dabrafenib + Trametinib in BRAF V600E+ NSCLC: Patient Cohort B[13]

Patient Population	Cohort B n = 57
Age, median (range), years	64 (58-71)
Sex, n (%)	
Male/female	29 (51)/28 (49)
Race, n (%)	
White	49 (86)
Black	2 (4)
Asian	4 (7)
Other	2 (4)
ECOG PS, n (%)	
0/1/2	17 (30)/35 (61)/5 (9)
Histology at initial diagnosis, n (%)	
Adenocarcinoma	56 (98)
Large cell	1 (2)
Smoking history, n (%)	
Never smoker	16 (28)
Former smoker	35 (61)
Current smoker	6 (11)
Prior systemic regimens for metastatic disease, n (%)	
1	38 (67)
2-3	19 (33)

Nearly all patients had adenocarcinoma histology

Three-quarters of patients were current or former smokers

One-third of patients received > 2 previous lines of chemotherapy

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Dabrafenib + Trametinib in BRAF V600E+ NSCLC: Patient Cohort C[26]

Patient Population	Cohort C n = 36
Age, median (range), years	67 (62-74)
Sex, n (%)	
Male/female	14 (39)/22 (61)
Race, n (%)	
White	30 (83)
Native American or other Pacific Islander	1 (3)
Black or African American	1 (3)
Asian	3 (8)
Missing	1 (3)
ECOG PS, n (%)	
0/1/2	13 (36)/22 (61)/1 (3)
Histology at initial diagnosis, n (%)	
Adenocarcinoma	32 (89)
Adenosquamous carcinoma (predominantly adenocarcinoma)	1 (3)
Adenosquamous carcinoma (predominantly SCC)	1 (3)
Large-cell carcinoma	1 (3)
NSCLC not otherwise specified	1 (3)
Smoking history, n (%)	
Never	10 (28)
Current	5 (14)
Former	21 (58)

Nearly all patients had adenocarcinoma histology

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Dabrafenib + Trametinib Phase 2 Study: Summary of Study Design and Patient Population[13,25,26]

- Phase 2 study of dabrafenib and trametinibenrolled 169 patients with stage IV BRAF V600E+ NSCLC (based on local testing)
  - The primary endpoint was investigator-assessed ORR
- Patients who had no prior treatment with a BRAF or MEK inhibitor were enrolled in 3 cohorts
  - Cohort A (n = 78): Pretreated patients received dabrafenib monotherapy 150 mg BID
  - Cohort B (n = 57): Pretreated patients received dabrafenib 150 mg BID + trametinib 2 mg QD
  - Cohort C (n = 36): Treatment-naive patients received dabrafenib 150 mg BID + trametinib 2 mg QD
- The majority of patients enrolled had adenocarcinoma and were current/former smokers

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Dabrafenib Monotherapy in Previously Treated Advanced BRAF V600E+ NSCLC[25]

Investigator-Assessed Efficacy Results in Cohort A[a]

Endpoint	n = 78
Best response, n (%) CR PR SD PD Not evaluable	 0 26 (33) 19 (24) 23 (29) 10 (13)
ORR (confirmed CR + PR) (%	26 (33)
DCR (CR + PR + SD) %	45 (58)
DOR, median (95% CI), months	9.6 (5.4-15.2)
PFS, median (95% CI), months[b]	5.5 (2.8-6.9)
OS, median (95% CI), months	12.7 (7.3-16.9)

[a] Data cutoff, November 21, 2014; [b] Independent review.

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Dabrafenib + Trametinib in Previously Treated Advanced BRAF V600E+ NSCLC[13]

Efficacy Results in Cohort B[a]

Endpoint	Investigator Assessment (n = 57)	Independent Assessment (n = 57)
Best response, n (%)		
CR	2 (4)	0
PR	34 (60)	36 (63)
SD[b]	9 (16)	4 (7)
PD	7 (12)	8 (14)
Non-CR/non-PD[c]	0	3 (5)
Not evaluable	5 (9)	6 (11)
ORR (CR + PR), n (%) [95% CI]	36 (63) [49-76]	36 (63) [49-76]
DCR, n (%) [95% CI]	45 (79) [66-89]	43 (75) [62-86]
DOR, median (95% CI), months[a]	9.0 (6.9-18.3)	9.0 (5.8-17.6)

- At the time of data cutoff, treatment was ongoing for 39% of patients (22 of 57)

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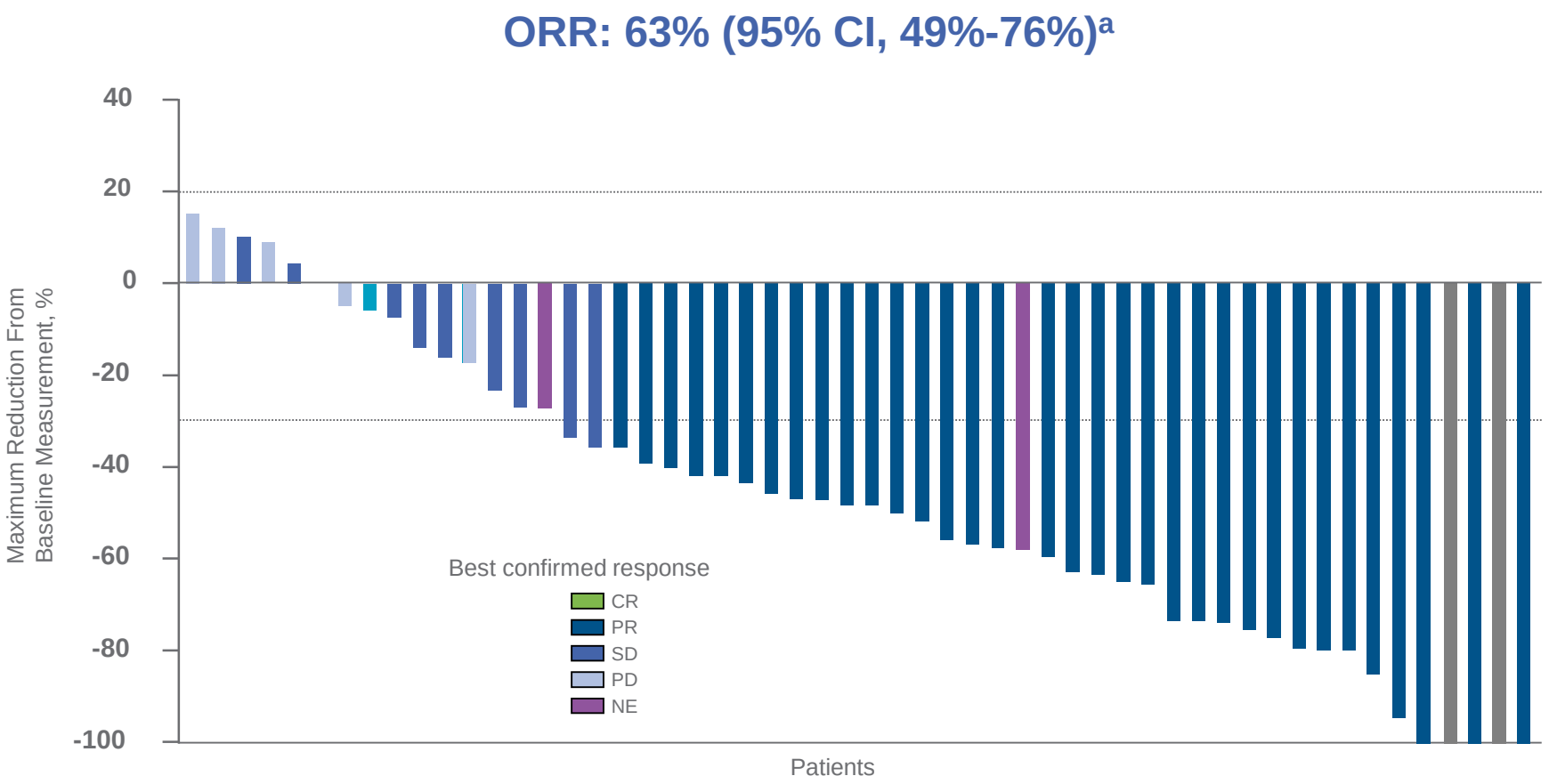
Results in Cohort B
The Majority of Patients in Cohort B Experienced Tumor Shrinkage[13]



NE patients did not have a follow-up scan required for confirmation.

[a] Data cutoff, October 7, 2015.

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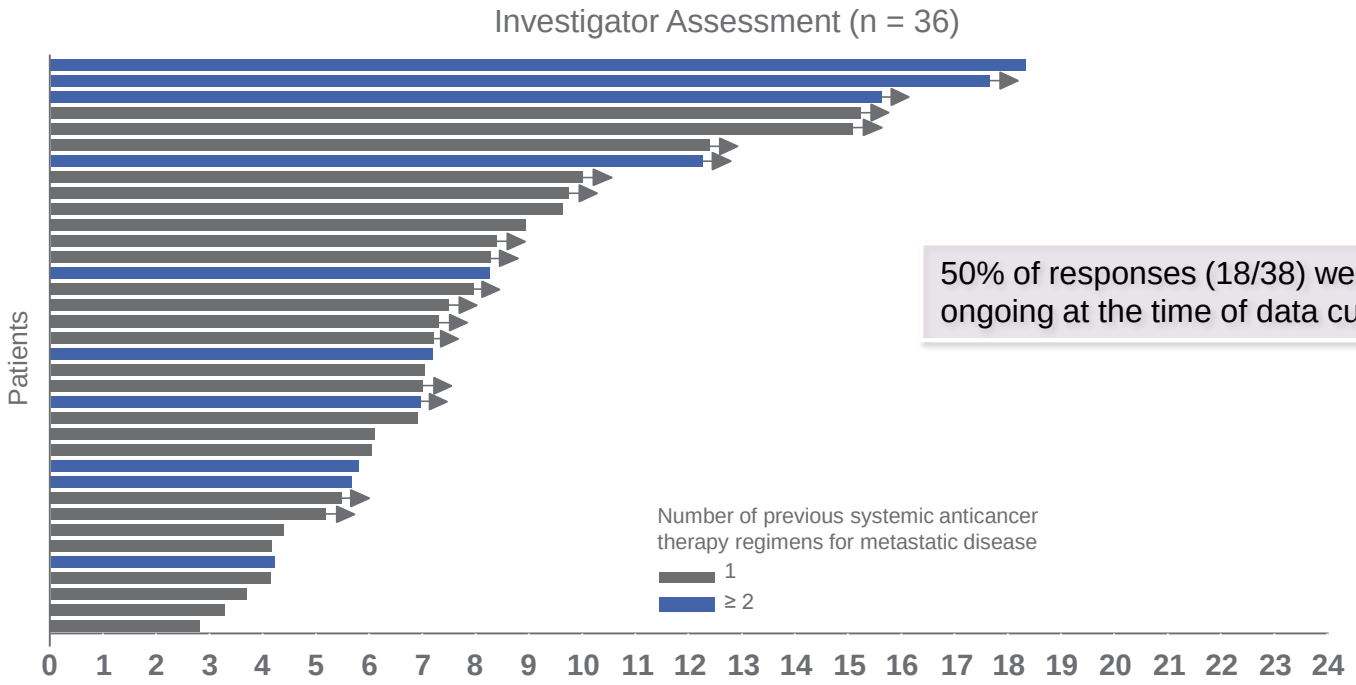
Results in Cohort B
Median DOR With the Combination Was 9 Months in Previously Treated Patients[13]

	Investigator n = 38	Independent n = 36
DOR, median (95% CI), months[a]	9.0 (6.9-18.3)	9.0 (5.8-17.6)



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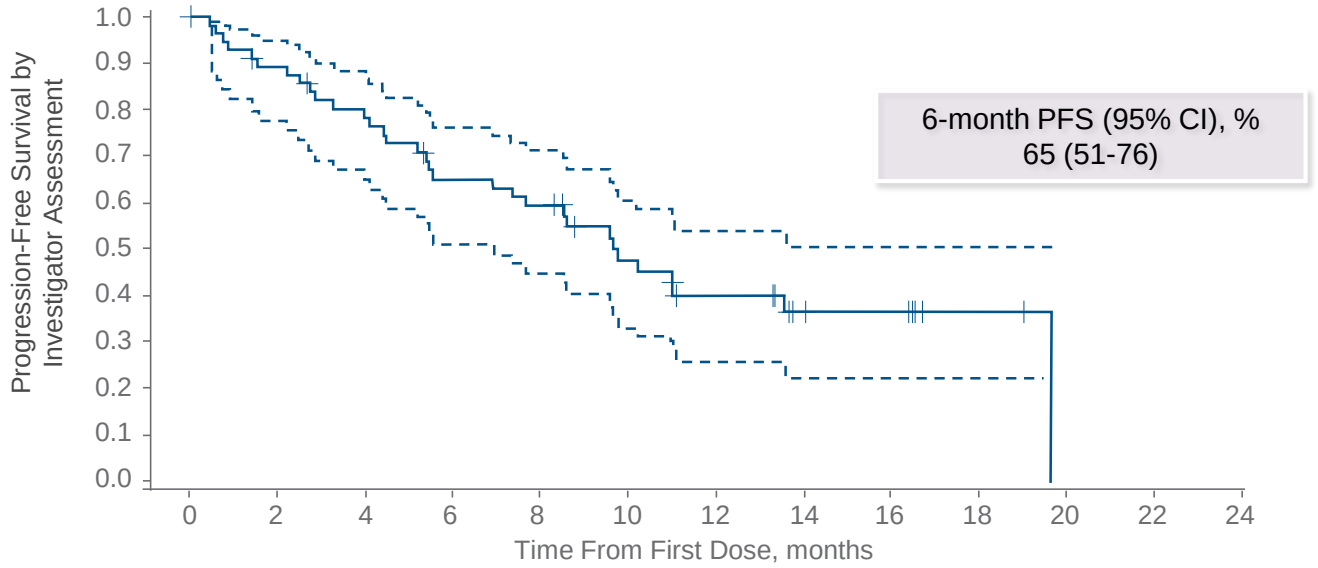
Results in Cohort B
Median PFS With the Combination Was Also ≈ 9 Months for Pretreated Patients[13a]

- PFS with combination therapy was almost double what has been reported with dabrafenib monotherapy (9.7 mo vs 5.5 mo)

	Investigator	Independent
PFS, median (95% CI), mo	9.7 (6.9-19.6)	8.6 (5.2-19.1)
Number of progressions or deaths, n (%)	32 (56)	34 (60)



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[a] Data cutoff, August 8, 2016.

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Dabrafenib + Trametinib in Previously Untreated Advanced BRAF V600E+ NSCLC[26]

Efficacy Results in Cohort C

Endpoint	Investigator Assessment (n = 36)	Independent Assessment (n = 36)
Best response, n (%)		
CR	2 (6)	2 (6)
PR	21 (58)	21 (58)
SD[b]	4 (11)	3 (8)
PD	5 (14)	7 (19)
Not evaluable	4 (11)	3 (8)
ORR (CR + PR), n (%) [95% CI]	23 (64) [46-79]	23 (64) [46-79]
DCR, n (%) [95% CI]	27 (75) [58-88]	26 (72) [55-86]
DOR, median (95% CI), months[a]	10.4 (8.3-17.9)	15.2 (7.8-23.5)

- At the time of data cutoff[a], treatment was ongoing for 31% of patients (11 of 36)

[a] Data cutoff, April 28, 2017

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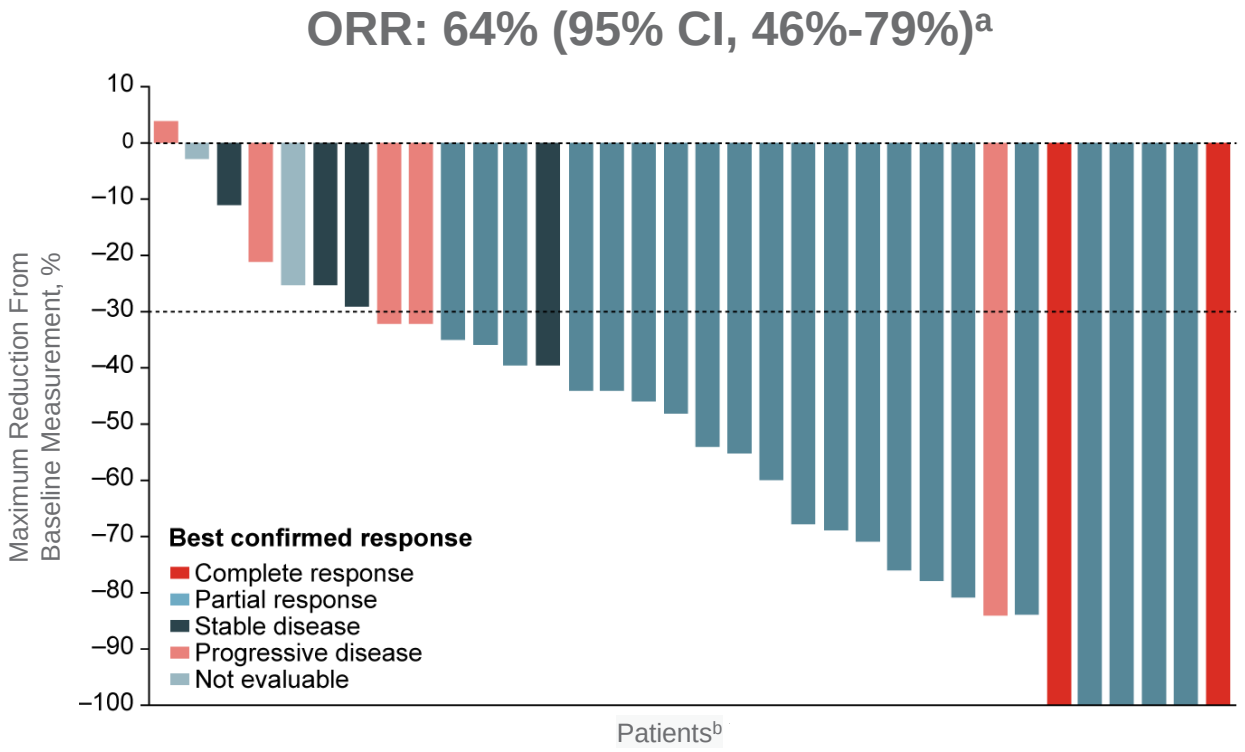
Results in Cohort C
The Majority of Patients in Cohort C Experienced Tumor Shrinkage[26]



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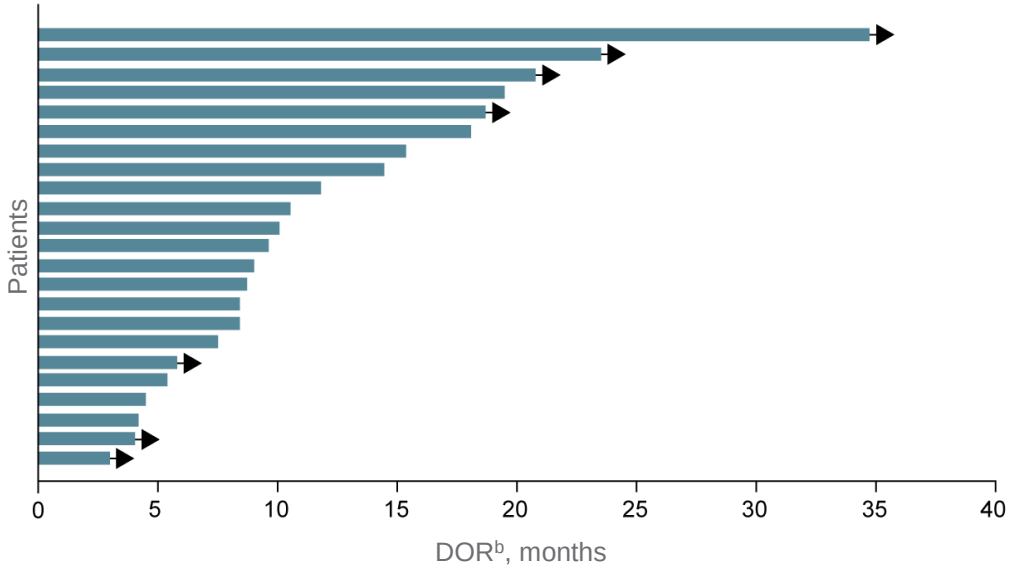
[a] Data cutoff, April 28, 2017; [b] Two patients initially enrolled in cohort B were not included because they did not have a post-baseline assessment of target lesions

Results in Cohort C
Median DOR With the Combination by Investigator Assessment Was 10.4 Months in Previously Untreated Patients[26]

- The number of patients with confirmed overall response was 23 (64%, 95% CI: 46-79)

	Investigator n = 36[a]	Independent n = 36[a]
DOR, median (95% CI), months[a]	10.4 (8.3-17.9)	15.2 (7.8-23.5)

[a]Patients with confirmed response, n = 23



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Arrows indicate censored patients with follow-up ongoing.
[a] Data cutoff, April 28, 2017; [b] Investigator assessed (n = 36)

Results in Cohort C
Median PFS With the Combination by Investigator Assessment Was 10.9 Months for Untreated Patients[26a]

- PFS with combination therapy was double what has been reported with dabrafenib monotherapy (10.9 mo vs 5.5 mo)

	Investigator n = 36	Independent n = 36
PFS, median (95% CI), months	10.9 (7.0-16.6)	14.6 (7.0-22.1)

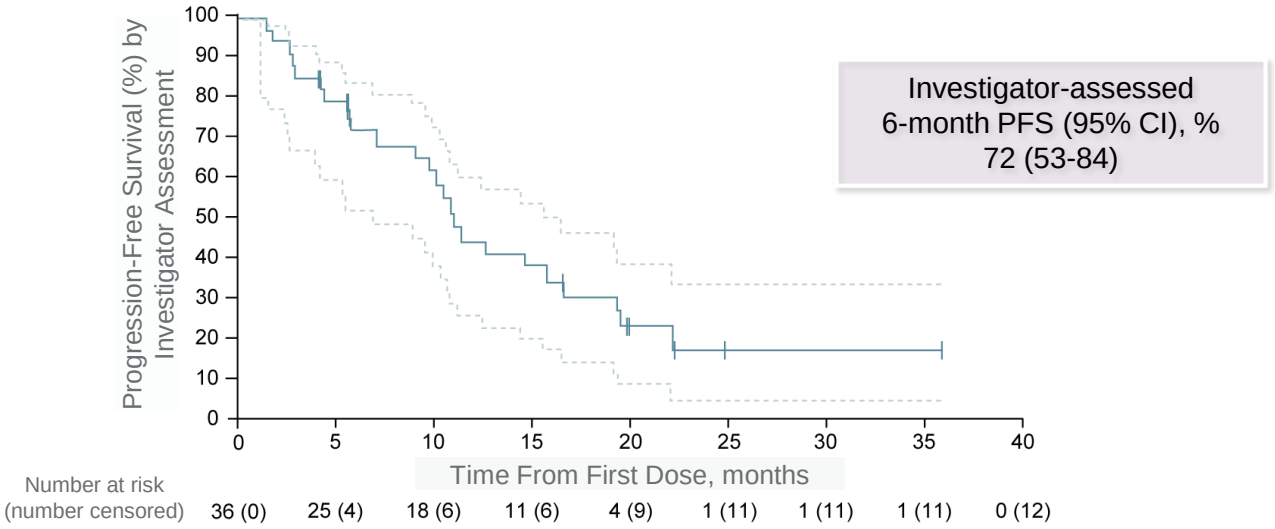

Image created based on Planchard D, et al. Lancet Oncol. 2017;18(10):1307-1316.

[a] Data cutoff, April 28, 2017.

Dabrafenib + Trametinib Phase 2 Study: Efficacy Summary[13,25,26]

- Dabrafenib + trametinib was more effective than dabrafenib alone in patients with previously treated BRAF V600E+ NSCLC: ORR and PFS were nearly doubled

Endpoint per Investigator Assessment	Cohort A Dabrafenib Monotherapy (n = 78)	Cohort B Dabrafenib + Trametinib Previously Treated (n = 57)	Cohort C Dabrafenib + Trametinib Previously Untreated (n = 36)
ORR[a] (95% CI), %	33 (23-45)	63 (49-76)	64 (46-79)
DCR[a] (95% CI), %	58 (46-67)	79 (66-87)	75 (58-88)
PFS[a], median (95% CI), mo	5.5 (3.4-7.3)	9.7 (6.9-19.6)	10.9 (7.0-16.6)
DOR[a], median (95% CI), mo	9.6 (5.4-15.2)	9.0 (6.9-18.3)	10.4 (8.3-17.9)

[a]All endpoints reported are as per investigator assessment

Safety Results in Cohort A Dabrafenib Monotherapy in BRAF V600E+ NSCLC[25]

Most Common AEs (≥ 20%), n (%)	Grade 1/2	Grade 3/4
General		
Pyrexia	28 (33)	2 (2)
Asthenia	21 (25)	4 (5)
Hyperkeratosis	24 (29)	1 (1)
Decreased appetite	23 (27)	1 (1)
Cough	22 (26)	0
Fatigue	21 (25)	1 (1)
Skin		
Skin papilloma	22 (26)	0
Dry skin	19 (23)	0
Alopecia	18 (21)	0
Digestive		
Nausea	22 (26)	1 (1)

Results in Cohort B
Safety Profile of Combined Dabrafenib + Trametinib in BRAF V600E+ NSCLC[27]

AE Overview (n = 57)	All Grades n (%)	Grade 3/4 n (%)
AEs	56 (98)	24/4 (49)
Suspected to be drug related	51 (89)	16/2 (32)
Serious AEs	32 (56)	16/4 (35)
Suspected to be drug related	19 (33)	9/2 (19)
Fatal serious AEs	4 (7)	—
Suspected to be drug related	0	—
AEs leading to discontinuation	8 (14)[a]	4/0 (7)
AEs leading to dose reduction	20 (35)	8/1 (16)
AEs requiring dose interruption/delay	35 (61)	17/3 (35)

- Nearly all patients experienced ≥ 1 AE (98%), and almost half (49%) had a grade 3/4 AE
- However, there was a low discontinuation rate due to AEs (14%)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted once in each of those categories.

[a] One patient discontinued trametinib due to an AE but remained on study receiving dabrafenib only.

Results in Cohort B
Safety Profile of Combined Dabrafenib + Trametinib in Previously Treated BRAF V600E+ NSCLC[13]

AEs ≥ 20%, n (%)	Grade 1/2	Grade 3
General		
Pyrexia	25 (44)	1 (2)
Asthenia	16 (28)	2 (4)
Decreased appetite	17 (30)	0
Chills	12 (21)	1 (2)
Peripheral edema	13 (23)	0
Cough	12 (21)	0
Skin		
Dry skin	14 (25)	1 (2)
Rash	11 (19)	1 (2)
Digestive		
Nausea	23 (40)	0
Vomiting	20 (35)	0
Diarrhea	18 (32)	1 (2)

Pyrexia was the most common AE (46% of patients); however, only 2% had grade 3 pyrexia

- SAEs were reported in 32 patients (56%)
- SAEs in ≥ 2 patients (4%) were pyrexia (16%), anemia (5%), and 4% each for confusional state, decreased appetite, hemoptysis, hypercalcemia, nausea, skin squamous cell carcinoma
- Fatal AEs occurred in 4 patients (retroperitoneal hemorrhage, subarachnoid hemorrhage, respiratory distress, and neoplasm progression), but all were considered unrelated to study medication

Safety Results in Cohort C Combined Dabrafenib + Trametinib in Previously Untreated BRAF V600E+ NSCLC[26]

Most Common AEs (≥ 20%), n (%)	Grade 1/2	Grade 3
General		
Pyrexia	19 (53)	4 (11)
Fatigue	13 (36)	0
Peripheral edema	13 (36)	0
Decreased appetite	12 (33)	0
Chills	9 (25)	0
Headache	9 (25)	0
Dizziness	8 (22)	0
Cough	8 (22)	0
Skin		
Dry skin	12 (33)	0
Digestive		
Nausea	20 (56)	0
Diarrhea	12 (33)	1 (3)
Vomiting	9 (25)	3 (8)

Pyrexia was the most common AE (64% of patients)

- All patients had at least one AE of any grade
- SAEs in ≥ 2 patients included ALT increase (14%), pyrexia (11%), AST increase (8%), and ejection fraction decrease (8%)
- AEs led to permanent discontinuation, dose interruption or delay, and dose reduction in 22%, 75%, and 39% of patients, respectively
- One fatal AE was reported (cardiorespiratory arrest), but was considered unrelated to study medication

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3 Steps for Pyrexia Management in Patients Treated With Dabrafenib + Trametinib

1. **INTERRUPT TREATMENT** with dabrafenib if the patient's temperature is ≥38.5 ºC. Continue trametinibat the same dose
2. **INITIATE ANTIPYRETICS** such as ibuprofen or acetaminophen/paracetamol
3. **CONSIDER ORAL CORTICOSTEROIDS** in those instances in which antipyretics are insufficient

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Pyrexia Management Protocol for Patients Treated With Dabrafenib + Trametinib

ANY EVENT
- Clinical evaluation for infection and hypersensitivity
- Laboratory work-up
- Hydration as required

First event
- Administer antipyretic treatment if clinically indicated
- Interrupt dabrafenib (if on combination therapy, trametinib may continue)
- Once pyrexia resolves to baseline, restart dabrafenib at the same dose level
- If fever was associated with dehydration, hypotension, or renal insufficiency, reduce dabrafenib by 1 dose level

Second event
- Same as for first event and consider oral corticosteroids (ie, prednisone 10 mg) for ≥ 5 days or as clinically indicated

Subsequent events
- Interrupt dabrafenib
- Once pyrexia resolves to baseline, restart dabrafenib (consider 1-level dose reduction)
- Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia
- If corticosteroids have been tapered and pyrexia recurs, restart steroids
- If corticosteroids cannot be tapered or escalating doses are required, consult medical monitor

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RAFINLAR® (dabrafenib mesylate) MEQSEL™ (trametinib dimethyl sulfoxide)

Dabrafenib + Trametinib) Dosing and Recommended Dose Reductions[16,17]

	dabrafenib (dabrafenib)	Mekinst (trametinib)
Starting dose	150 mg (2 × 75 mg) twice daily (morning and evening)	2 mg once daily
First dose reduction	100 mg twice daily	1.5 mg once daily
Second dose reduction	75 mg twice daily	1 mg once daily
Third dose reduction (combination only)	50 mg twice daily	1 mg once daily
Subsequent modification	Permanently discontinue dabrafenib if unable to tolerate 50 mg orally twice daily	Permanently discontinue trametinibif unable to tolerate 1 mg orally once daily

- trametinibshould be take at the same time each day with either the morning dose **OR** evening dose of dabrafenib
- Both dabrafenib and trametinibshould be taken without food at least 1 hour before or 2 hours after a meal

Dabrafenib + Trametinib Phase 2 Study: Safety Summary

- The safety profile of dabrafenib + trametinib was manageable and similar to that previously reported in melanoma studies
- The most common AEs across all cohorts were pyrexia, GI-related toxicities, and skin reactions[16,28]
- Pyrexia was the most frequently observed AE across all cohorts[16,28]
  - Occurred in 33% of patients in cohort A (grades 1/2), 46% of patients in cohort B (all grades), and 64% of patients in cohort C (all grades)
  - Pyrexia events were managed with a pyrexia management protocol

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THANKYOU