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

NSCLCPROMODECK/RAFMEQ/ONCO/28785/28/FEB/2020

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MEQSEL™ (trametinib dimethyl sulfoxide)

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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 Rafinlar (dabrafenib) and Meqsel (trametinib) in advanced NSCLC

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Introduction to BRAF

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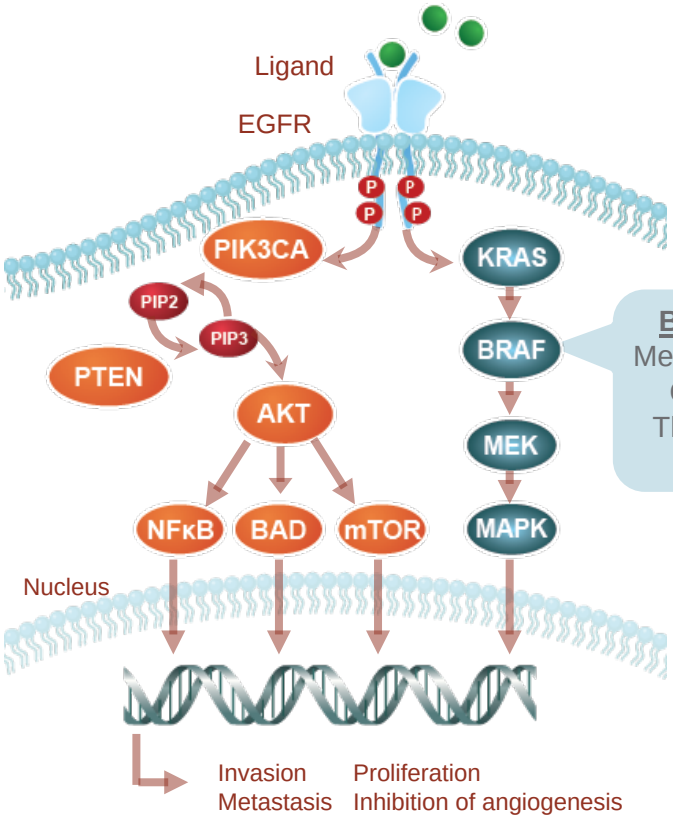
The RAS-RAF-MEK-ERK (MAPK) Pathway Plays a Key Role in Cell Proliferation

- 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:
Melanoma (50%-60%)
Colorectal (10%)
Thyroid (30%-50%)
NSCLC (2%)[4,5]

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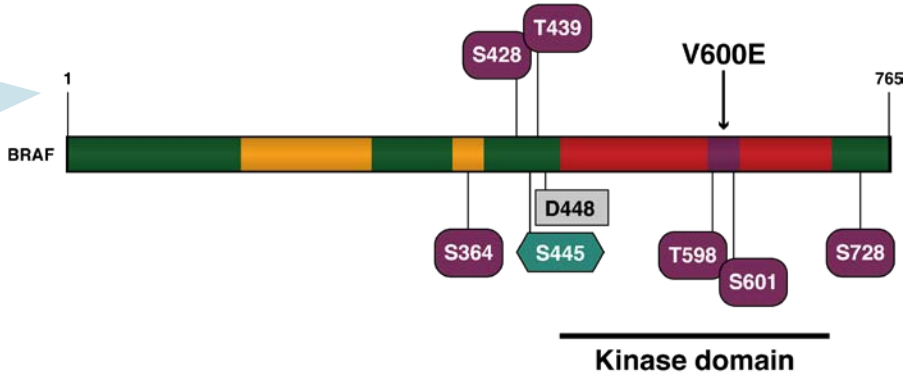
BRAF Mutations in NSCLC

- 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)



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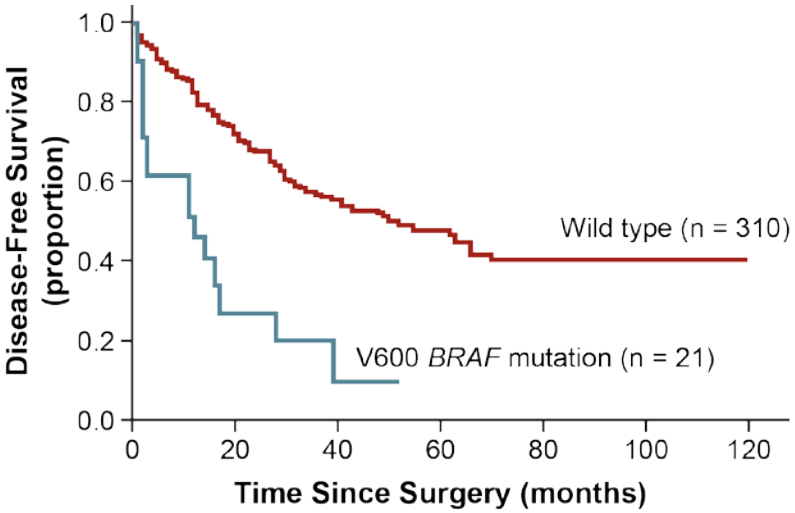
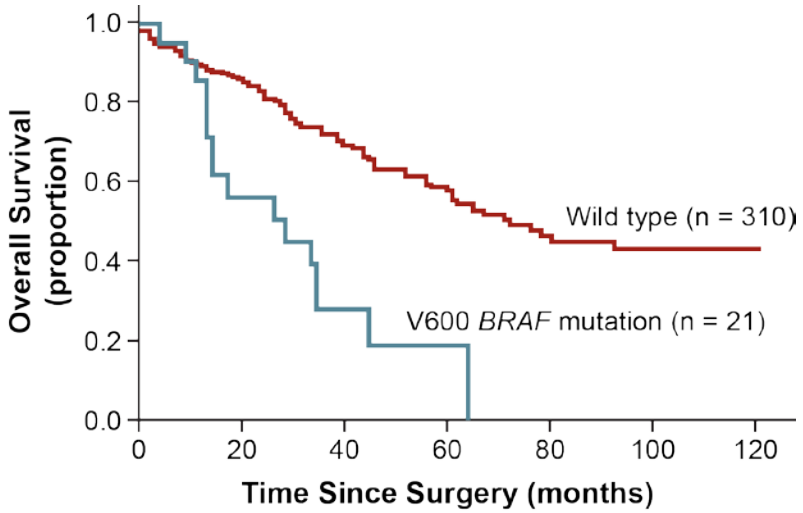
Patients With BRAF V600E Mutations Have Shorter Median DFS and OS Than Patients Without V600E Mutations[10]

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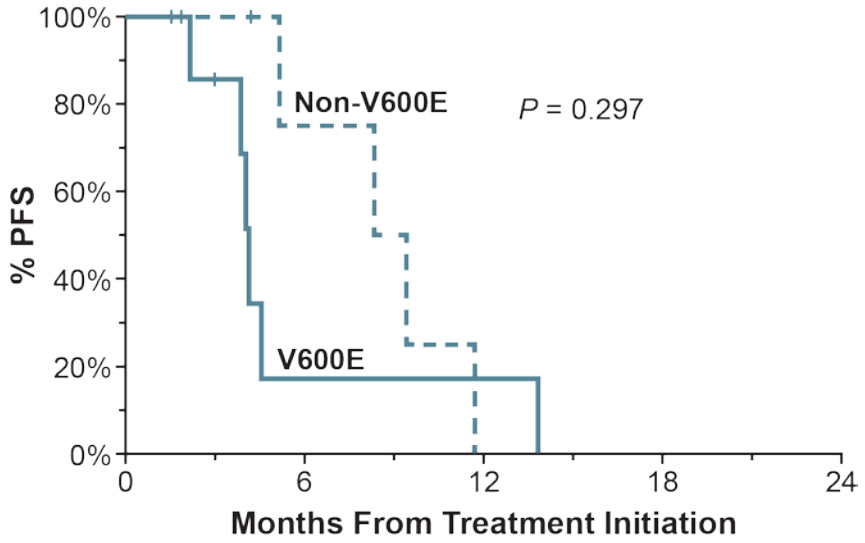
Outcomes in Patients With BRAF V600E+ NSCLC vs Patients With Wild-Type BRAF[8]

- 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

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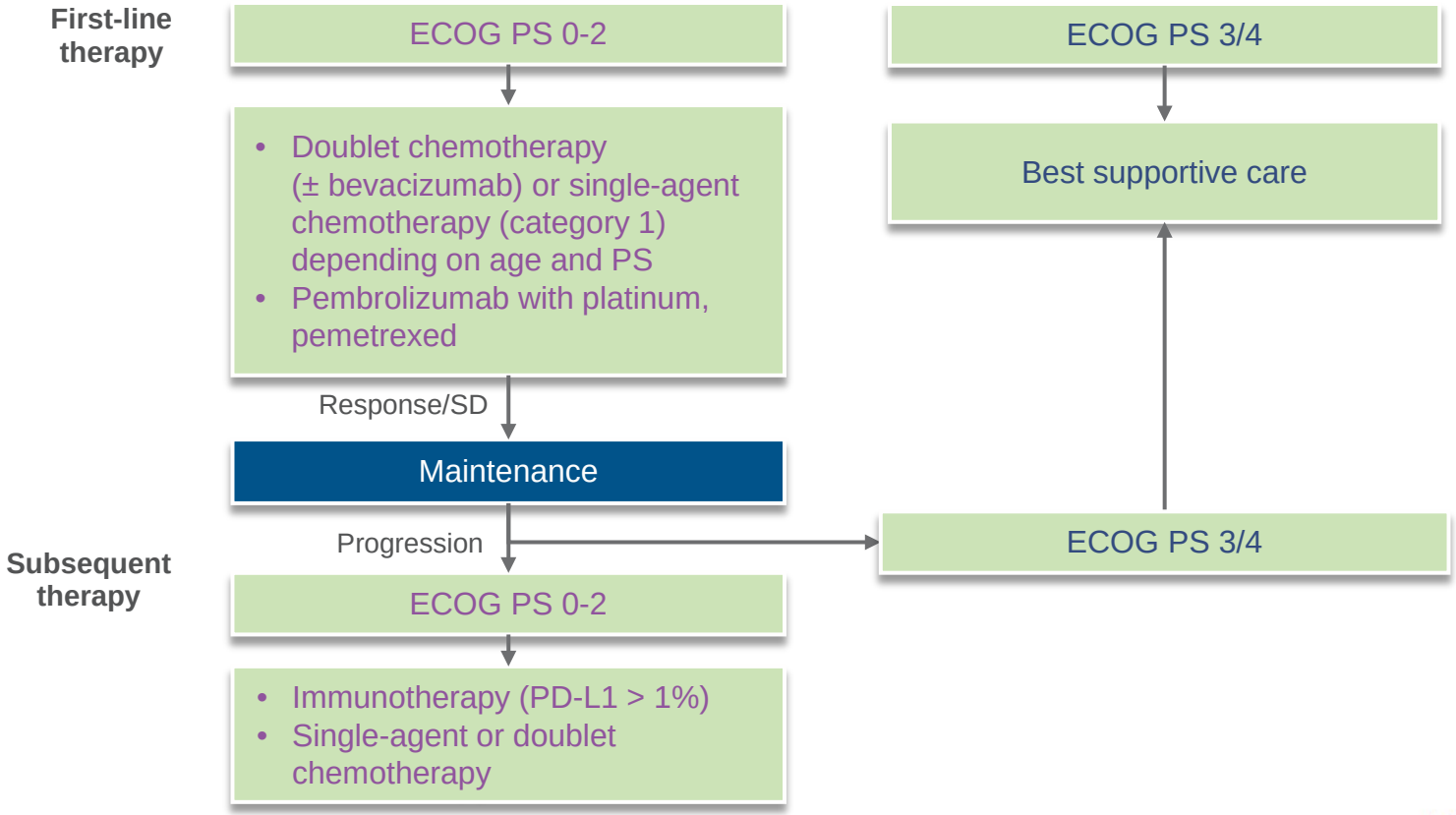
Patients With Nonsquamous NSCLC Without Mutated ALK, EGFR, or ROS1 Currently Receive Chemotherapy or Immunotherapy

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



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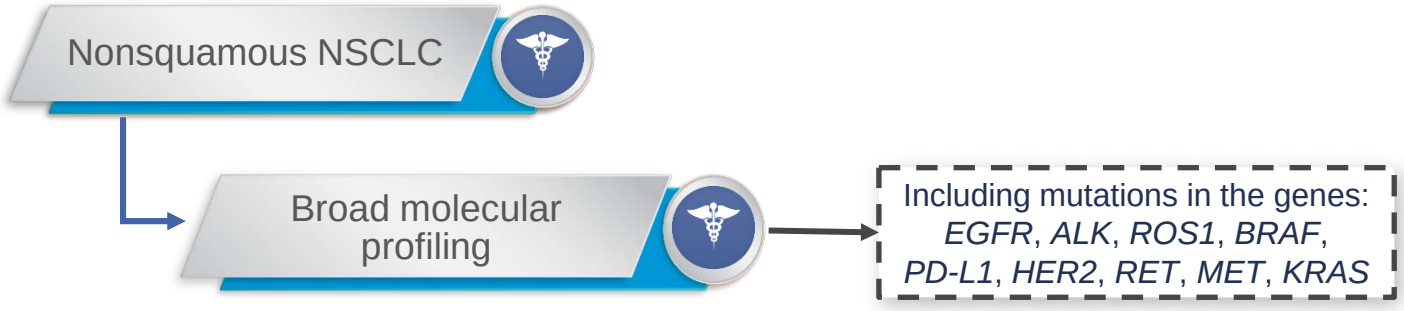
Broad Molecular Profiling Includes Identification of BRAF+ Patients

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



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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]

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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 Rafinlar + Meqsel

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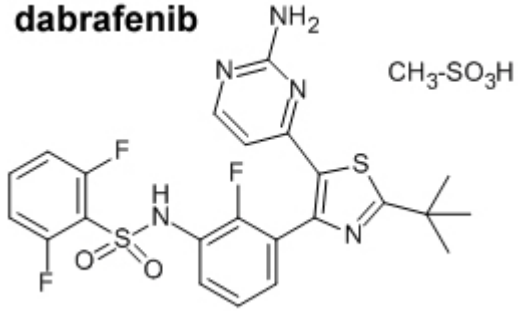
Rafinlar (dabrafenib) and Meqsel (trametinib) Target Different Kinases in the MAPK Pathway

Dabrafenib[14]

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

dabrafenib

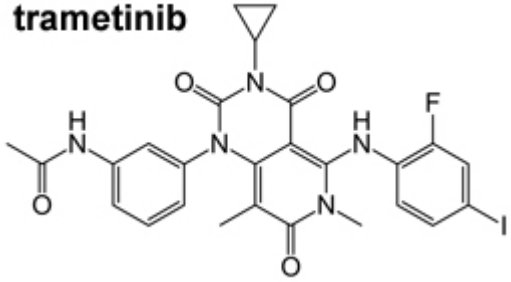


Target	IC_{50}
Wild-type BRAF	3.2 nM
BRAF V600E	0.6 nM

Trametinib[15]

Reversible, highly selective inhibitor of MEK1 and MEK2 kinase activity

trametinib



Target	IC_{50}
MEK1	0.7 nM
MEK2	0.9 nM

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Rafinlar (dabrafenib) and Meqsel (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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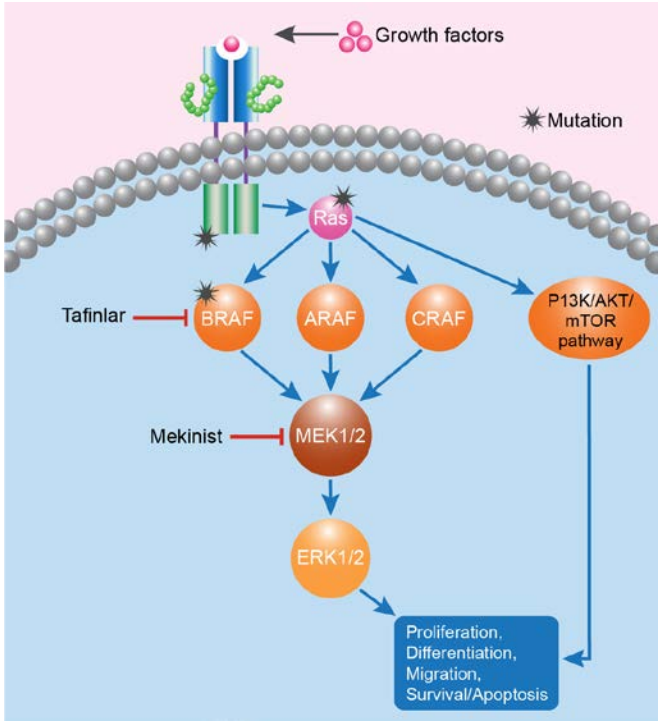
Rationale for Combination of Rafinlar (dabrafenib) and Meqsel (trametinib)



- 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 Rafinlar + Meqsel for the treatment of BRAF V600+ advanced melanoma[16,19,20]

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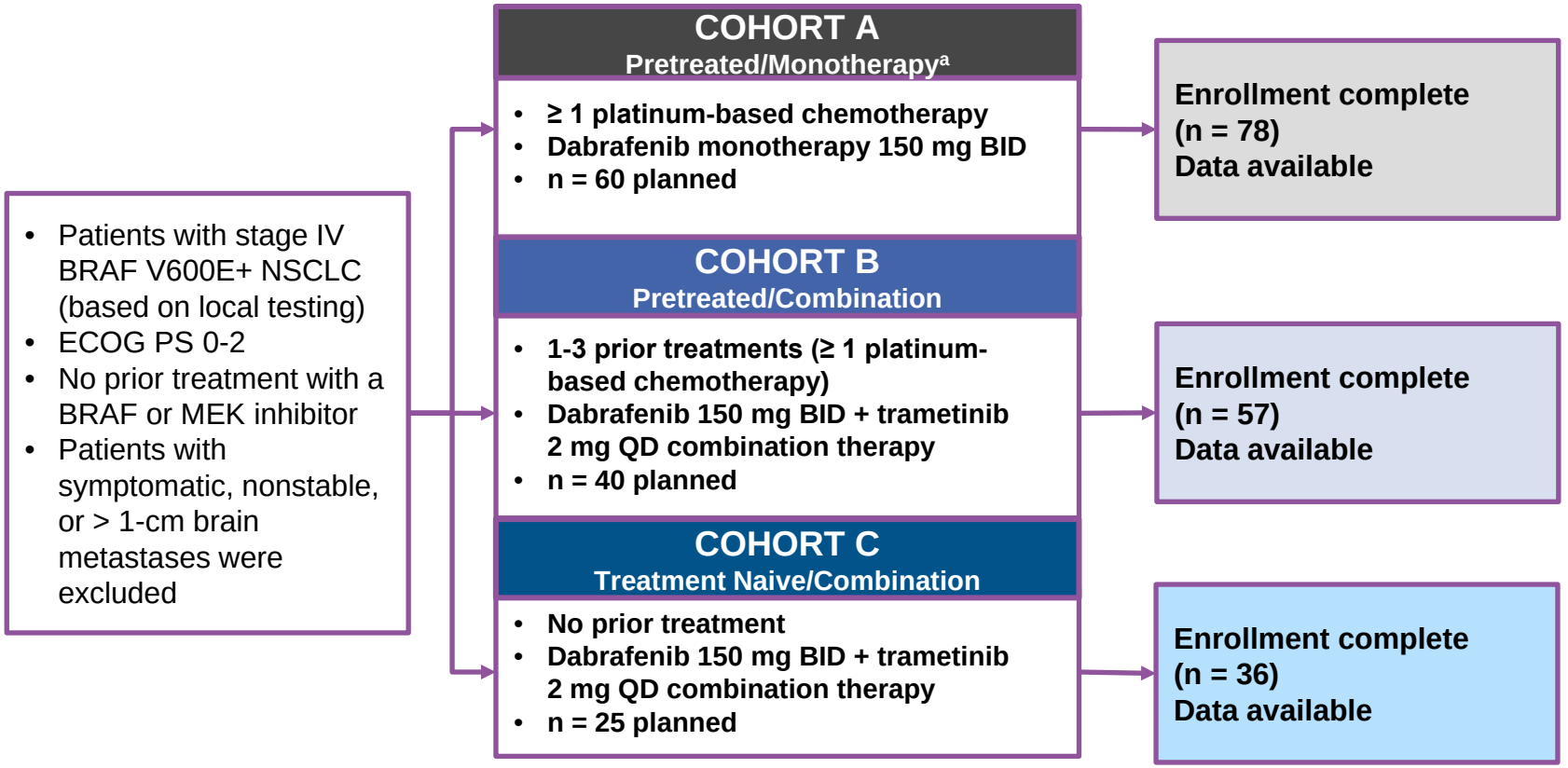
Phase 2 Study of Rafinlar (dabrafenib) + Meqsel (trametinib) in BRAF V600E+ NSCLC

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



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Rafinlar + Meqsel 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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Rafinlar (dabrafenib) + Meqsel (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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Rafinlar (dabrafenib) + Meqsel (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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Rafinlar (dabrafenib) + Meqsel (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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Rafinlar (dabrafenib) + Meqsel (trametinib) Phase 2 Study: Summary of Study Design and Patient Population[13,25,26]

- Phase 2 study of Rafinlar and Meqsel enrolled 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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Rafinlar (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) (95% CI), %	33 (23-45)
DCR (CR + PR + SD) (95% CI), %	58 (46-67)
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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Rafinlar (dabrafenib) + Meqsel (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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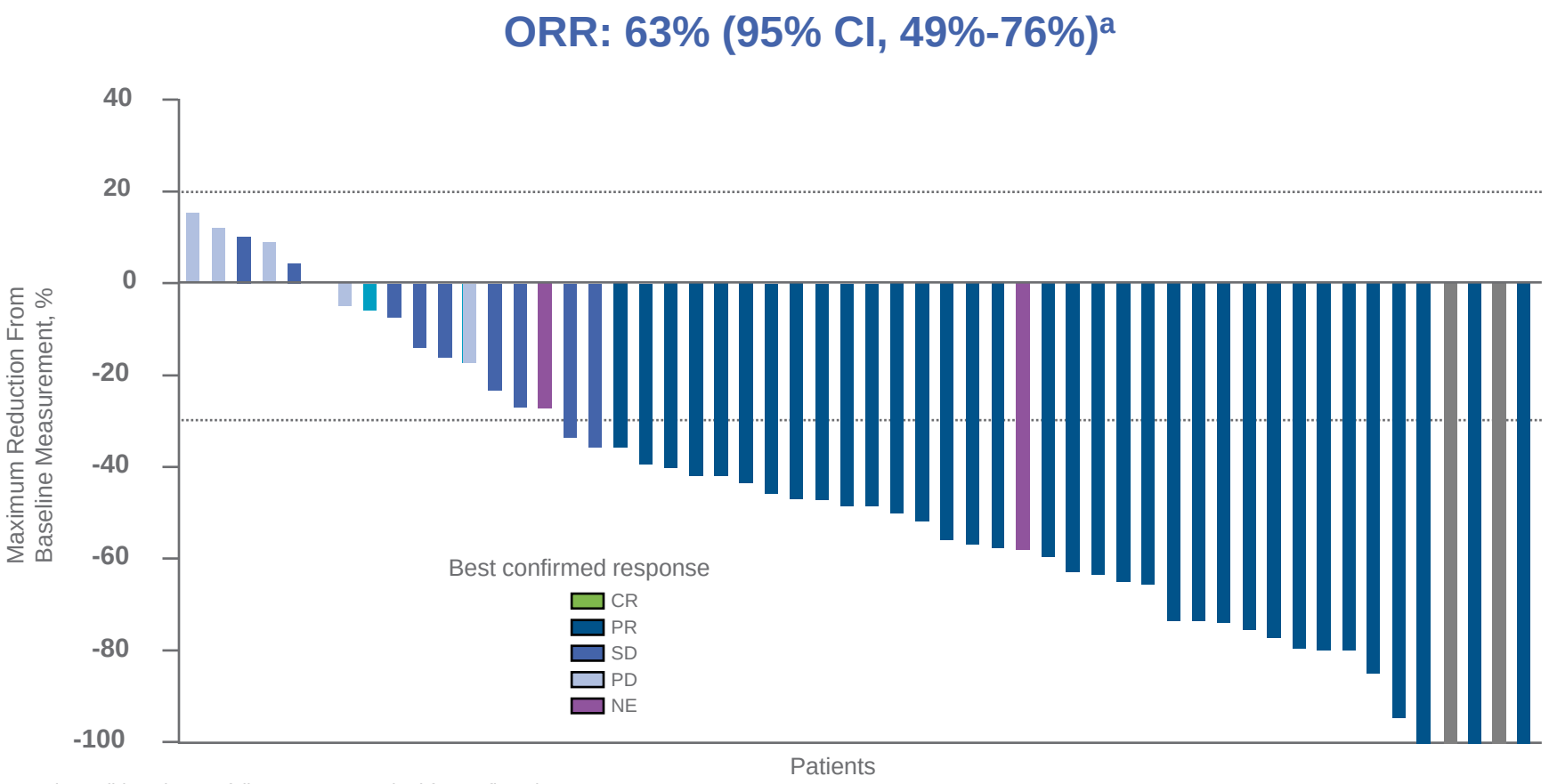
Results in Cohort B
The Majority of Patients in Cohort B Experienced Tumor Shrinkage[13]



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

[a] Data cutoff, October 7, 2015.

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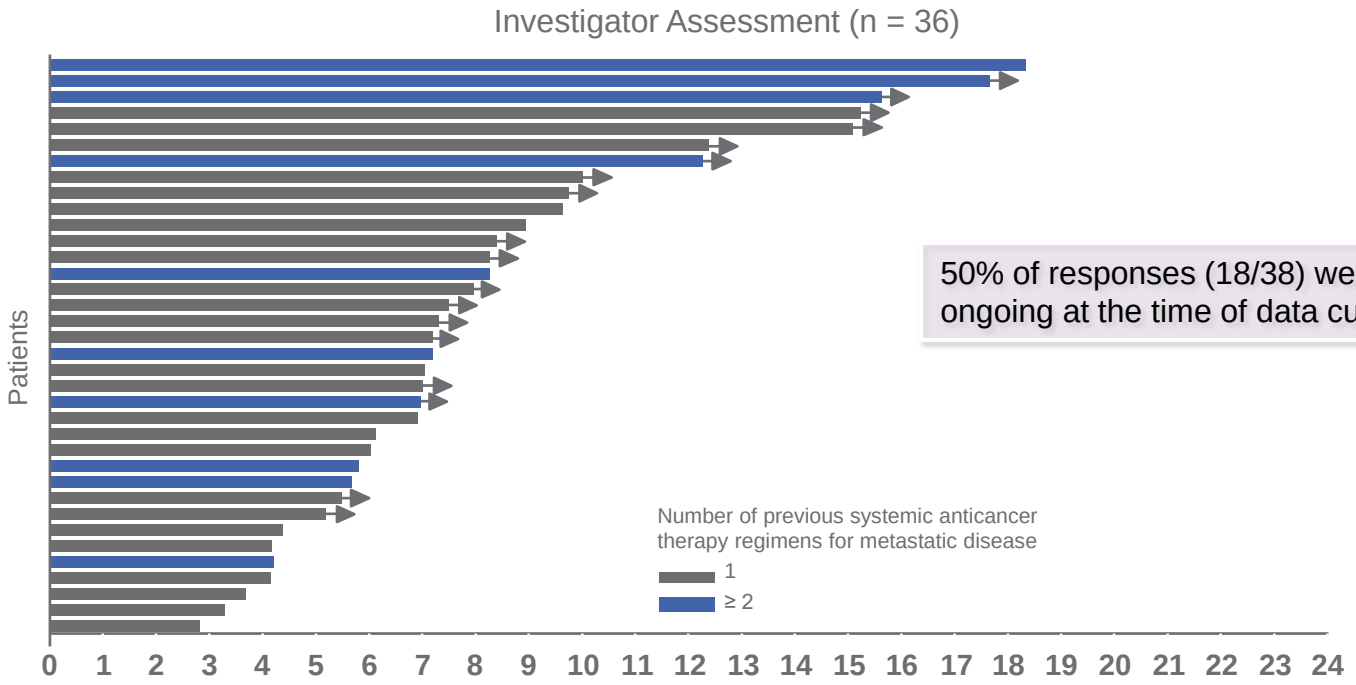
Results in Cohort B
Median DOR With the Combination Was 9 Months in Previously Treated Patients[13]

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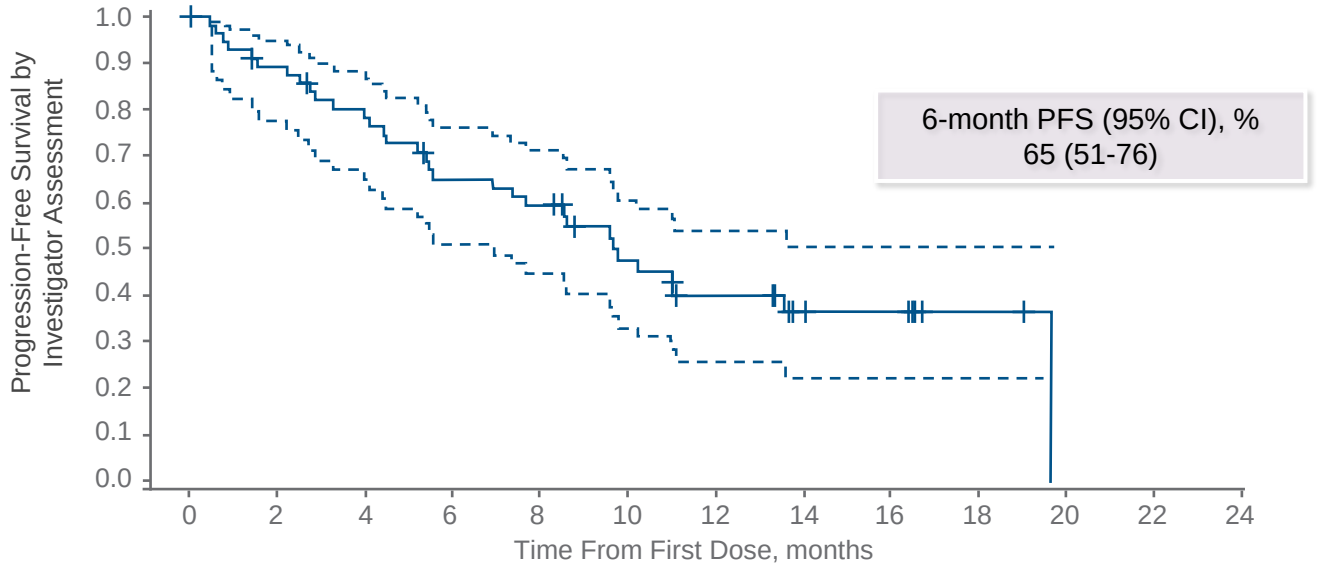
Results in Cohort B
Median PFS With the Combination Was Also ≈ 9 Months for Pretreated Patients[13a]

- 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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Rafinlar (dabrafenib) + Meqsel (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]

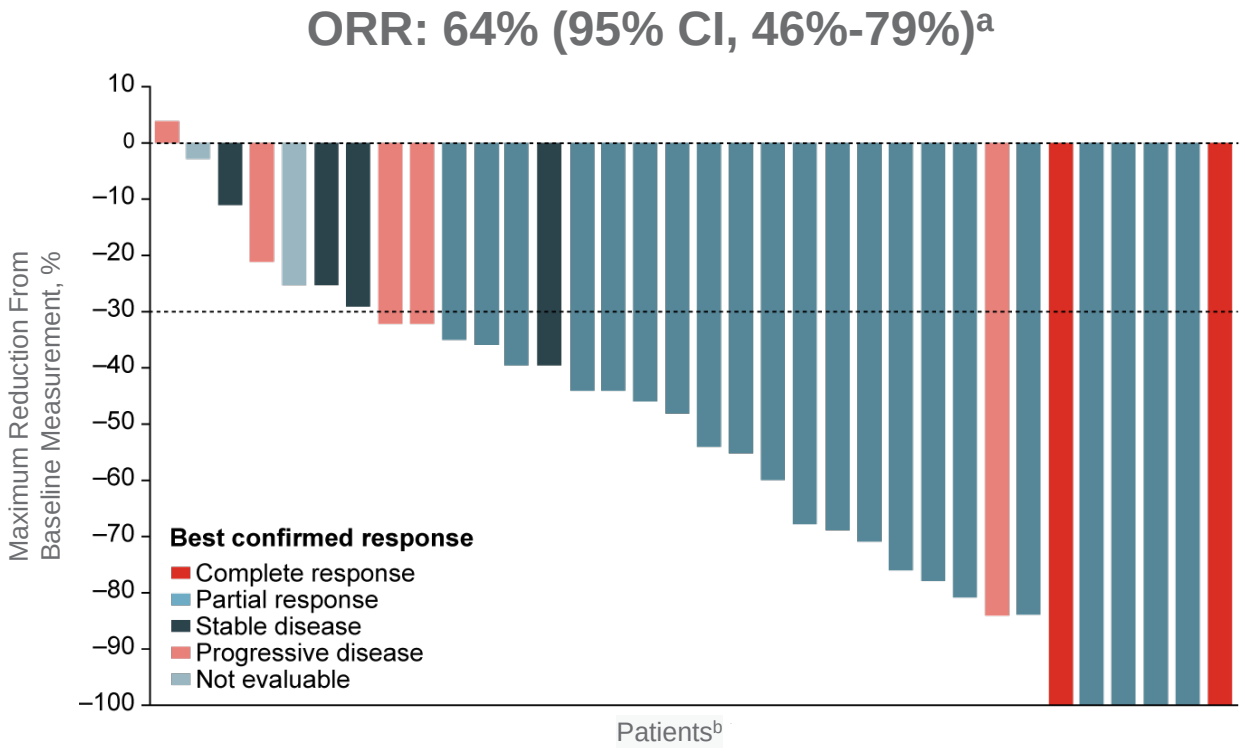

Image created based on Planchard D, et al. Lancet Oncol. 2017;18(10):1307-1316.

[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

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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

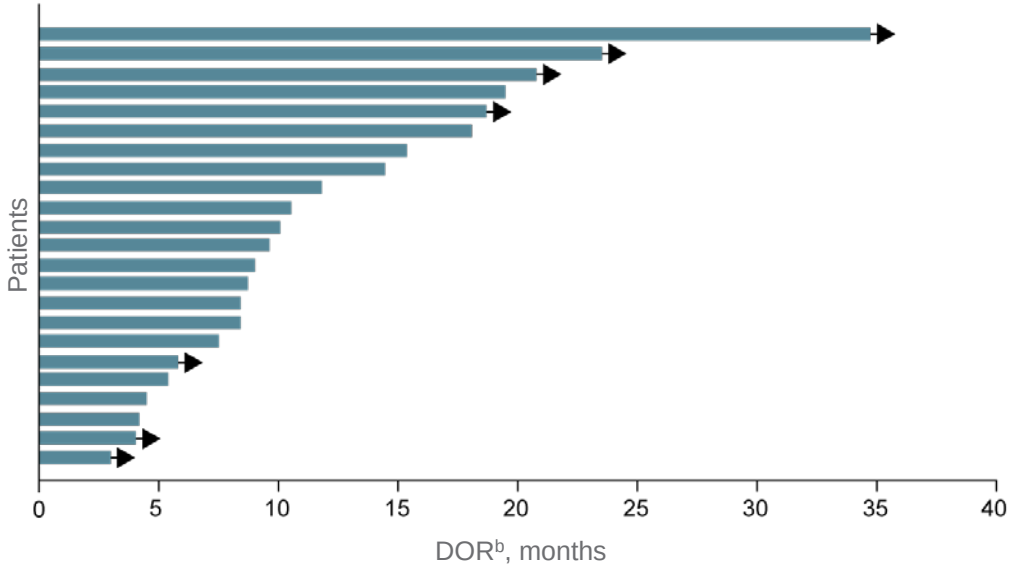

Image created based on Planchard D, et al. Lancet Oncol. 2017;18(10):1307-1316.

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

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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)

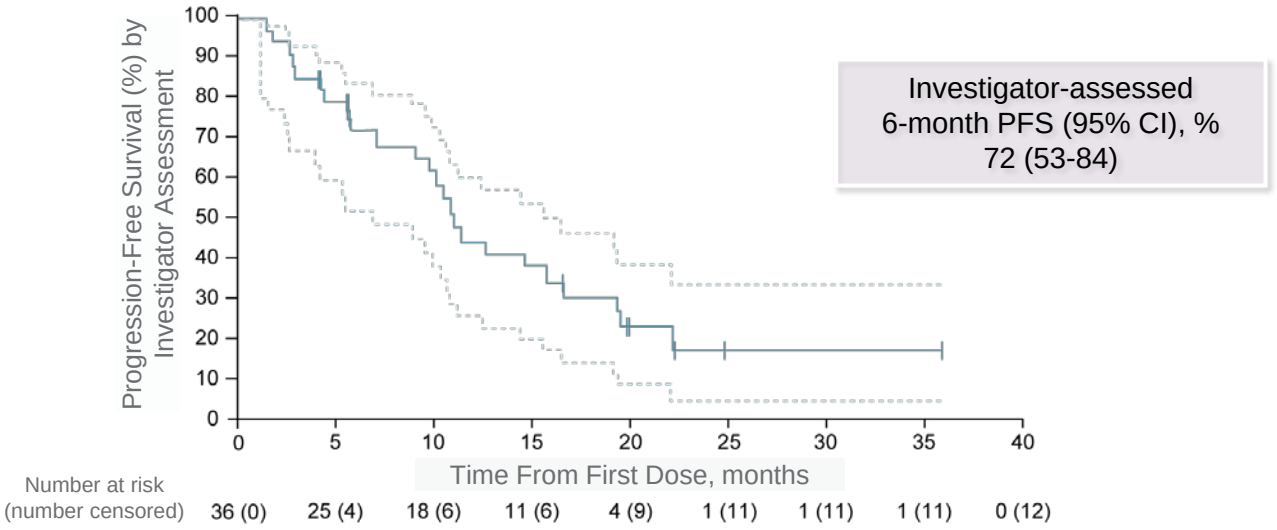

Image created based on Planchard D, et al. Lancet Oncol. 2017;18(10):1307-1316.

[a] Data cutoff, April 28, 2017.

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Rafinlar (dabrafenib) and Meqsel (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

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Safety Results in Cohort A
Rafinlar (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)

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Results in Cohort B
Safety Profile of Combined Rafinlar + Meqsel 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.

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Results in Cohort B
Safety Profile of Combined Rafinlar + Meqsel 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

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Safety Results in Cohort C Combined Rafinlar + Meqsel 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 Rafinlar (dabrafenib) + Meqsel (trametinib)[16,28]

1. **INTERRUPT TREATMENT** with Rafinlar if the patient's temperature is ≥38.5 ºC. Continue Meqsel at 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 Rafinlar (dabrafenib) + Meqsel (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) + Meqsel (trametinib) Dosing and Recommended Dose Reductions[16,17]

	Rafinlar (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 Rafinlar if unable to tolerate 50 mg orally twice daily	Permanently discontinue Meqsel if unable to tolerate 1 mg orally once daily

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

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Rafinlar (dabrafenib) + Meqsel (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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RAFINLAR® Presentation: Hard capsule: contains dabrafenib mesylate equivalent to 50 mg of dabrafenib. **Indications: Unresectable or metastatic melanoma** Rafinlar as a single agent for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation as detected by an appropriate test. Rafinlar in combination with Trametinib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation as detected by an appropriate test. **Advanced non-small cell lung cancer** Rafinlar 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. **Dosage and administration:** ♦**Adults:** Recommended dose either as monotherapy or in combination with Meqsel is 150 mg twice daily. ♦**Dose modifications:** Management of adverse reactions may require treatment interruption, dose reduction or treatment discontinuation. **Special populations:** ♦Children (<18 years): safety and efficacy not established. ♦Elderly (>65 years): no dose adjustment required. ♦Renal impairment: Mild or moderate: no dose adjustment required. Severe: should be used with caution. ♦Hepatic impairment: Mild: no dose adjustment required. Moderate or severe: should be used with caution. **Contraindications:** None. **Warnings and precautions:** ♦Pyrexia including severe rigors, dehydration and hypotension (including acute renal insufficiency) reported. Incidence and severity increased when used in combination with Meqsel. Monitoring serum creatinine and renal function. Serious non-infectious febrile events observed. For management of Pyrexia, dose modification guidelines should be followed. ♦**Cutaneous Squamous Cell Carcinoma (cuSCC) and new primary melanoma:** Skin examination prior, during, and for 6 months after discontinuation of treatment or until initiation of another anti-neoplastic therapy. ♦**Non-cutaneous secondary/recurrent malignancy:** Monitoring as clinically appropriate for up to 6 months after discontinuation of Tafinar® or until initiation of another anti-neoplastic therapy. ♦**Pancreatitis:** Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Close monitoring when re-starting Rafinlar. ♦**Uveitis:** Monitoring patients for visual signs and symptoms during therapy. **Dabrafenib in combination with trametinib:** ♦**Hemorrhage:** Hemorrhagic events, including major and fatal hemorrhagic events have occurred in patients taking Rafinlar in combination with Meqsel. **Women of child-bearing potential:** Use effective methods of contraception during therapy and for 4 weeks following discontinuation of Rafinlar. ♦Rafinlar may decrease the efficacy of hormonal contraceptives, use an alternate method of contraception. **Pregnancy:** Not recommended. **Breast-feeding:** Not recommended. **Fertility:** Potential risk for impaired spermatogenesis, which may be irreversible. **Adverse events with Rafinlar monotherapy in metastatic melanoma:**
Very common (≥10%): papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, pain in extremity, asthenia, chills, fatigue, pyrexia. Common (1 to 10%): nasopharyngitis, acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrheic keratosis, hypophosphataemia, hyperglycaemia, constipation, skin effects (actinic keratosis, skin lesion, dry skin, erythema, pruritus), photosensitivity reaction, influenza-like illness. **Uncommon (0.1 to 1%):** new primary melanoma, hypersensitivity, uveitis, pancreatitis, panniculitis, renal failure, acute renal failure. **Rare (0.01 to 0.1%):** tubulointerstitial nephritis. **Adverse events in combination with Meqsel in metastatic melanoma: Very common (≥10%):** urinary tract infection, nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, hypertension, haemorrhage, cough, abdominal pain, constipation, diarrhoea, nausea, vomiting, dry skin, pruritus, rash, dermatitis acneiform, arthralgia, myalgia, pain in extremity, fatigue, oedema peripheral, pyrexia, chills, asthenia, alanine aminotransferase increased, aspartate aminotransferase increased. **Common (1 to 10%):** cellulitis, folliculitis, paronychia, rash pustular, cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, papilloma including skin papilloma, seborrhoeic keratosis, acrochordon (skin tags), anaemia, thrombocytopenia, leukopenia, dehydration, hyperglycaemia, hyponatraemia, hypophosphataemia, vision blurred, visual impairment, ejection fraction decreased, bradycardia, hypotension, lymphoedema, dyspnoea, dry mouth, stomatitis, erythema, actinic keratosis, night sweats, hyperkeratosis, alopecia, palmar-plantar erythrodysaesthesia syndrome, skin lesion, hyperhidrosis, skin fissures, panniculitis, photosensitivity reaction, muscle spasms, blood creatine phosphokinase increased, renal failure, mucosal inflammation, influenza-like illness, face oedema, blood alkaline phosphatase increased, gamma-glutamyltransferase increased,. **Uncommon (0.1 to 1%):** new primary melanoma, hypersensitivity, chorioretinopathy, uveitis, retinal detachment, periorbital oedema, left ventricular dysfunction, cardiac failure, pneumonitis, interstitial lung disease, pancreatitis, rhabdomyolysis, nephritis, renal failure acute. Adverse drug reactions in combination with Meqsel in advanced non-small cell lung cancer: **Very common (≥10%):** neutropenia, hyponatraemia, headache, dizziness, haemorrhage, hypotension, nausea, vomiting, diarrhoea, decreased appetite, constipation, erythema, dry skin, rash, pruritus, hyperkeratosis incl. hyperkeratosis, actinic and seborrhoeic keratosis and keratosis pilaris, muscle spasms, arthralgia, myalgia, pyrexia, asthenia including fatigue and malaise, oedema (generalized and peripheral), chills, blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased. Common (1 to 10%): cutaneous squamous cell carcinoma, leukopenia, dehydration, detachment of retina/retinal pigment epithelium, ejection fraction decreased, hypertension, pulmonary embolism, pancreatitis acute, renal failure, tubulointerstitial nephritis.
For a complete list, consult full prescribing information. **Interactions:** ♦Caution with combination with strong inhibitors or inducers of CYP2C8 or CYP3A4. ♦Caution with drugs that affect gastric pH. ♦Rafinlar may induce CYP3A4, CYP2C9, CYP2B6, CYP2C8, CYP2C19, UGT and P-gp. Efficacy of medicinal products metabolized by these enzymes may be reduced. Monitoring recommended. **Packs:**28 capsules Before prescribing, please consult full prescribing information available from Novartis Healthcare Private Limited, Inspire BKC, Part of 601 & 701, Bandra Kurla Complex, Bandra (East), Mumbai – 400 051, Maharashtra, India. Tel +91 22 50243335/36, Fax +91 22 50243010. For the use of only registered medical practitioners or a hospital or a laboratory.
India BSS dated 5 Dec 19 based on international BSS dated 1 Jun 17 effective from 5 Dec 19.

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MEQSEL® **Presentation:** Film-coated tablets: contain trametinib equivalent to 0.5 mg. **Indications: Unresectable or metastatic melanoma** Meqsel in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Meqsel as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Meqsel as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy. **Advanced non-small cell lung cancer** Meqsel in combination with dabrafenib is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. **Dosage and administration:** ♦Adults: Recommended dose either as monotherapy or in combination with Rafinlar is 2 mg once daily. ♦Meqsel should be taken without food, with a full glass of water, at least 1 hour before or at least 2 hours after a meal. ♦When Meqsel is taken in combination with Rafinlar, the once-daily dose of Meqsel should be taken at the same time each day with either the morning or the evening dose of Rafinlar. ♦**Missed dose:** A missed dose should be taken only if it is more than 12 hours until the next scheduled dose. ♦**Dose modifications:** Management of adverse reactions may require treatment interruption, dose reduction or treatment discontinuation. Special populations: ♦**Children (< 18 years):** Safety and efficacy not established. ♦**Elderly (> 65 years):** No dose adjustment required. ♦**Renal impairment:** Mild or moderate: No dose adjustment required. **Severe:** Should be used with caution. ♦**Hepatic impairment: Mild:** No dose adjustment required. Moderate or severe: Should be used with caution. **Contraindications:** None. **Warnings and precautions:** ♦**Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction:** Cases of LVEF decrease reported. Should be used with caution when conditions could impair left ventricular function. All patients should be evaluated for LVEF prior to initiation of treatment with continued evaluation during treatment. Dose modification guidelines should be considered. ♦**Hemorrhage:** Hemorrhagic events, including major and fatal hemorrhagic events occurred in patients taking Meqsel as monotherapy and in combination with Rafinlar. ♦**Visual impairment:** Visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) observed. Not recommended for patients with history of RVO. Ophthalmological evaluation should be performed at baseline and during treatment. If retinal abnormalities observed, treatment should be interrupted immediately and referral to specialist should be considered. Permanent discontinuation of treatment if RVO occurs. ♦Rash: Observed in Meqsel monotherapy and in combination with Rafinlar. ♦**Deep vein thrombosis (DVT)/Pulmonary embolism (PE):** Can occur when used as monotherapy or in combination with Rafinlar. Patients should seek immediate medical care if they develop symptoms of DVT or PE. ♦**Pyrexia:** Pyrexia including severe rigors, dehydration and hypotension (including acute renal insufficiency) reported. Incidence and severity increased when Meqsel used in combination with Rafinlar. Monitoring serum creatinine and other evidence of renal function impairment during and following severe pyrexia events. Serious non-infectious febrile events observed. For management of pyrexia, dose modification guidelines should be followed. ♦**Colitis and Gastrointestinal perforation:** Colitis and gastrointestinal perforation, including fatal outcome, reported. Treatment with Meqsel as monotherapy or in combination with Rafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation. If patients develop symptoms of colitis and gastrointestinal perforation they should immediately seek medical care. **Pregnancy, lactation, females and males of reproductive potential** ♦**Pregnancy:** Meqsel can be harmful to the fetus. Pregnant women should be advised of the potential risk to the fetus. ♦**Lactation:** Nursing women should be advised of the potential risks to the child. ♦**Females and males of reproductive potential:** Sexually-active women should be advised to use effective contraception while on Meqsel and for at least 16 weeks after stopping it. Efficacy of oral or any other systemic hormonal contraceptives may be decreased; an effective alternative method of contraception should be used. Male patients (including those that have had a vasectomy) should be advised to use condoms while on Meqsel and for at least 16 weeks after stopping it. ♦**Infertility:** May impair human fertility. **Adverse events with Meqsel monotherapy in metastatic melanoma Very common (≥10%):** hypertension, hemorrhage, cough, dyspnea, diarrhea, nausea, vomiting, constipation, abdominal pain, dry mouth, rash, dermatitis acneiform, dry skin, pruritus, alopecia, fatigue, edema peripheral, pyrexia. **Common (1 to 10%):** hypersensitivity, folliculitis, paronychia, cellulitis, rash pustular, anemia, dehydration, vision blurred, periorbital edema, visual impairment, left ventricular dysfunction, ejection fraction decreased, bradycardia, lymphedema, epistaxis, pneumonitis, stomatitis, skin chapped, erythema, palmar-plantar erythrodysaesthesia syndrome, skin fissures, blood creatine phosphokinase increased, face edema, mucosal inflammation, asthenia, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased. **Uncommon (0.1 to 1%):** chorioretinopathy, retinal vein occlusion, papilledema, retinal detachment, cardiac failure, interstitial lung disease, gastrointestinal perforation, colitis, rhabdomyolysis. **Adverse events in combination with Rafinlar in metastatic melanoma Very common (≥10%):** urinary tract infection, nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, hypertension, hemorrhage, cough, abdominal pain, constipation, diarrhea, nausea, vomiting, dry skin, pruritus, rash, dermatitis acneiform, arthralgia, myalgia, pain in extremity, fatigue, edema peripheral, pyrexia, chills, asthenia, alanine aminotransferase increased, aspartate aminotransferase increased. **Common (1 to 10%):** cellulitis, folliculitis, paronychia, rash pustular, cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, papilloma including skin papilloma, seborrheic keratosis, acrochordon (skin tags), anemia, thrombocytopenia, leukopenia, dehydration, hyperglycemia, hyponatremia, hypophosphatemia, vision blurred, visual impairment, ejection fraction decreased, bradycardia, hypotension, lymphedema, dyspnea, dry mouth, stomatitis, erythema, actinic keratosis, night sweats, hyperkeratosis, alopecia, palmar-plantar erythrodysesthesia syndrome, skin lesion, hyperhidrosis, skin fissures, panniculitis, photosensitivity, muscle spasms, blood creatine phosphokinase increased, renal failure, mucosal inflammation, influenza-like illness, face edema, blood alkaline phosphatase increased, gamma-glutamyltransferase increased. **Uncommon (0.1 to 1%):** new primary melanoma, hypersensitivity, chorioretinopathy, uveitis, retinal detachment, periorbital edema, left ventricular dysfunction, cardiac failure, pneumonitis, interstitial lung disease, pancreatitis, gastrointestinal perforation, colitis, rhabdomyolysis, nephritis, renal failure acute. Adverse drug reactions in combination with Rafinlar in Stage III melanoma following complete resection **Very common (≥10%):** nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, hemorrhage, hypertension, cough, nausea, diarrhea, vomiting, abdominal pain, constipation, rash, dry skin, dermatitis acneiform, erythema, pruritus, arthralgia, myalgia, pain in extremity, muscle spasms, pyrexia, fatigue, chills, edema peripheral, influenza like illness, alanine aminotransferase increased, aspartate aminotransferase increased. **Common (1 to 10%):** uveitis, chorioretinopathy, retinal detachment, palmar-plantar erythrodysesthesia syndrome, alkaline phosphatase increased, ejection fraction decreased. **Uncommon (0.1 to 1%):** rhabdomyolysis, renal failure. Adverse drug reactions in combination with Rafinlar in advanced non-small cell lung cancer **Very common (≥10%):** neutropenia, hyponatremia, headache, dizziness, hemorrhage, hypotension, nausea, vomiting, diarrhea, decreased appetite, constipation, erythema, dry skin, rash, pruritus, hyperkeratosis incl. hyperkeratosis, actinic and seborrheic keratosis and keratosis pilaris, muscle spasms, arthralgia, myalgia, pyrexia, asthenia incl. fatigue and malaise, edema (generalized and peripheral), chills, blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased. **Common (1 to 10%):** cutaneous squamous cell carcinoma, leukopenia, dehydration, detachment of retina/retinal pigment epithelium, ejection fraction decreased, hypertension, pulmonary embolism, pancreatitis acute, renal failure, tubulointerstitial nephritis. Adverse drug reactions in combination with Rafinlar in locally advanced or metastatic anaplastic thyroid cancer (ATC) **Very common (≥10%):** neutropenia, anemia, leukopenia, hyperglycemia, decreased appetite, headache, dizziness, hemorrhage, cough, nausea, vomiting, diarrhea, constipation, dry mouth, rash, myalgia, arthralgia, fatigue, pyrexia, chills, edema, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased. **Common (1 to 10%):** hypophosphatemia, hyponatremia, detachment of retinal pigment epithelium, hypertension, rhabdomyolysis, ejection fraction decreased. For a complete list, consult full prescribing information. **Interactions:** None. **Packs:** 30 film-coated tablets

Before prescribing, please consult full prescribing information available from Novartis Healthcare Private Limited, Inspire BKC, Part of 601 & 701, Bandra Kurla Complex, Bandra (East), Mumbai – 400 051, Maharashtra, India. Tel +91 22 50243335/36, Fax +91 22 50243010. For the use of only registered medical practitioners or a hospital or a laboratory. India BSS dated 5 Dec 19 based on international BSS dated 12 Nov 18 effective from 5 Dec 19.

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