2023 ASCO® ANNUAL MEETING

Safety & Efficacy of the Novel BRAF Inhibitor FORE8394 in Patients with Advanced Solid & CNS Tumors

Results from a Phase 1/2a Study

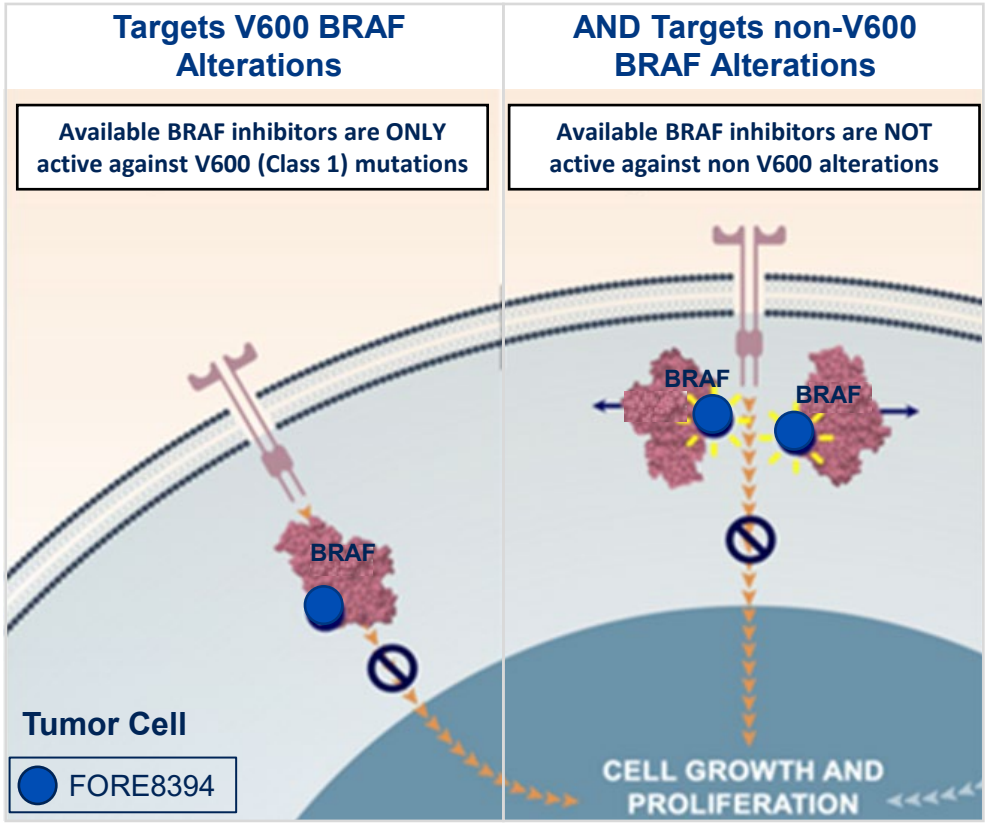
De La Fuente MI,[1] Sherman EJ,[2] Yaeger R,[1] Tsai FY-C,[3] Janku F,[4] Butowski NA,[5] Allen CE,[6] Ammakkanavar NR,[7] Taylor JW,[5] Samara E,[8] Mould DR,[9] Michelson G,[10] Kline I,[11] Paz M,[11] Tussay-Lindenberg A,[11] Wang K,[11] Peacock Shepherd S,[11] Jiang P,[11] Ahnert JR[4]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]HonorHealth Research Institute, Scottsdale, AZ; [4]MD Anderson Cancer Center, Houston, TX; [5]University of California, San Francisco, San Francisco, CA; [6]Baylor College of Medicine Texas Children's Cancer Center, Houston, TX; [7]Community Health Network, Cancer Center, Anderson, IN; [8]Pharma Polaris International Consulting Inc, San Marino, CA; [9]Projections Research Inc, Phoenixville, PA; [10]Audentes Consulting LLC, Fairfax, CA; [11]Fore Biotherapeutics Inc., Philadelphia, PA

Plixorafenib (FORE8394): A Novel BRAF-Inhibitor

- Investigational, potent, oral BRAF-inhibitor
- Specific activity against mutant BRAF in comparison to all wild type RAF proteins (including BRAF and CRAF).
- Targets mutated BRAF monomers and homodimers and BRAF-CRAF heterodimers without inducing RAF dimer formation
- Does not result in paradoxical activation of MAPK pathway
- Available BRAF-inhibitors target mutated BRAF monomers

Plixorafenib (FORE8394)



BRAF, v-raf murine sarcoma viral oncogene homolog B1; MAPK, mitogen-activated protein kinases; MEK, mitogen-activated protein kinase

Phase 1/2a Study Design

Key Objectives

- RP2D
- Safety
- PK
- Efficacy in BRAF Class 1 or 2, ≥1 post-baseline assessment (mITT)

Key Inclusion Criteria

- Adults / children
- Advanced unresectable solid tumors
- No available standard therapy

Dose Escalation (3+3 Design) & Extension

- Patients with advanced cancer or LCH
  - Escalation & extension: 57 adults
  - Escalation: 4 pediatric patients (3-17 years)[1]

Dose Optimization & Extension

- Patients aged ≥10 y with BRAF-altered tumors
  - Dose Optimization (n=48)
  - CNS Tumors Extension (n=4)

Treatment / Assessments

- Until progression / unmanageable toxicity
- Total daily doses of FORE8394 (fasted) 900-3600 mg & 500-1000 mg/m^2
- CYP3A inhibitor cobicistat[2] as PK booster
- Tumor assessments (RECIST v1.1/RANO)
  - Every 2 cycles in first year
  - Every 2-4 cycles after first year
- Skin and Eye exams

BRAF, v-raf murine sarcoma viral oncogene homolog B1
mITT: modified intent-to-treat population
[1]Closed prior to determination of RP2D, with 2 dose levels (n=3; n=1). As RP2D was not determined for BSA-adjusted dosing, efficacy data for these patients will be reported separately.
[2]Cobicistat (Tybost®) was administered at 150 mg QD.
All tables / graphs in this slide deck were developed based on ASCO TLFs (run date 08 May 2023) unless stated otherwise.
Data cutoff date: March 31, 2023

Baseline Demographics & Disposition

- 113 patients received FORE8394
- 12 patients (10.6%) still on treatment
- 101 patients (89.4%) discontinued treatment
  - Disease progression* 65 (57.5%)
  - Clinical progression 18 (16%)
  - Withdrawal 9 (8%)
  - Adverse events 4 (3.5%)
    - Drug-related (n=1)
    - Underlying disease-related (n=3)
- 11 patients (9.7%) treated ≥ 2 years
- 80 patient-years of FORE8394 exposure

* *By RECIST or RANO tumor assessment criteria*

Demographics	n (%)
Age	
<18 years	5 (4.4%)
18 to <65 years	66 (58.4%)
≥65 years	42 (37.2%)
Sex	
Male	59 (52.2%)
Female	54 (47.8%)
Race	
White/Caucasian	101 (89.4%)
Black/African-American	5 (4.4%)
Asian	3 (2.7%)
Missing	4 (3.5%)
Ethnicity	
Hispanic or Latino	12 (10.6%)
Not Hispanic/Latino	99 (87.6%)
Missing	2 (1.8%)

ECOG Performance Score	n (%)
0	43 (38.1%)
1	65 (57.5%)
≥2	5 (4.4%)
CNS Metastases	**n (%)**
Solid Tumors (n=90)	12 (13.3%)
Prior Treatment	**n (%)**
Number of Lines[1]	
0	15 (13.3%)
1	28 (24.8%)
2	17 (15.0%)
3	16 (14.2%)
≥4-10	37 (32.7%)
Prior Treatment Type	
MAPK-inhibitor[2]	33 (29.2%)
BRAF-inhibitor	24 (21.2%)
Checkpoint inhibitor	30 (26.5%)

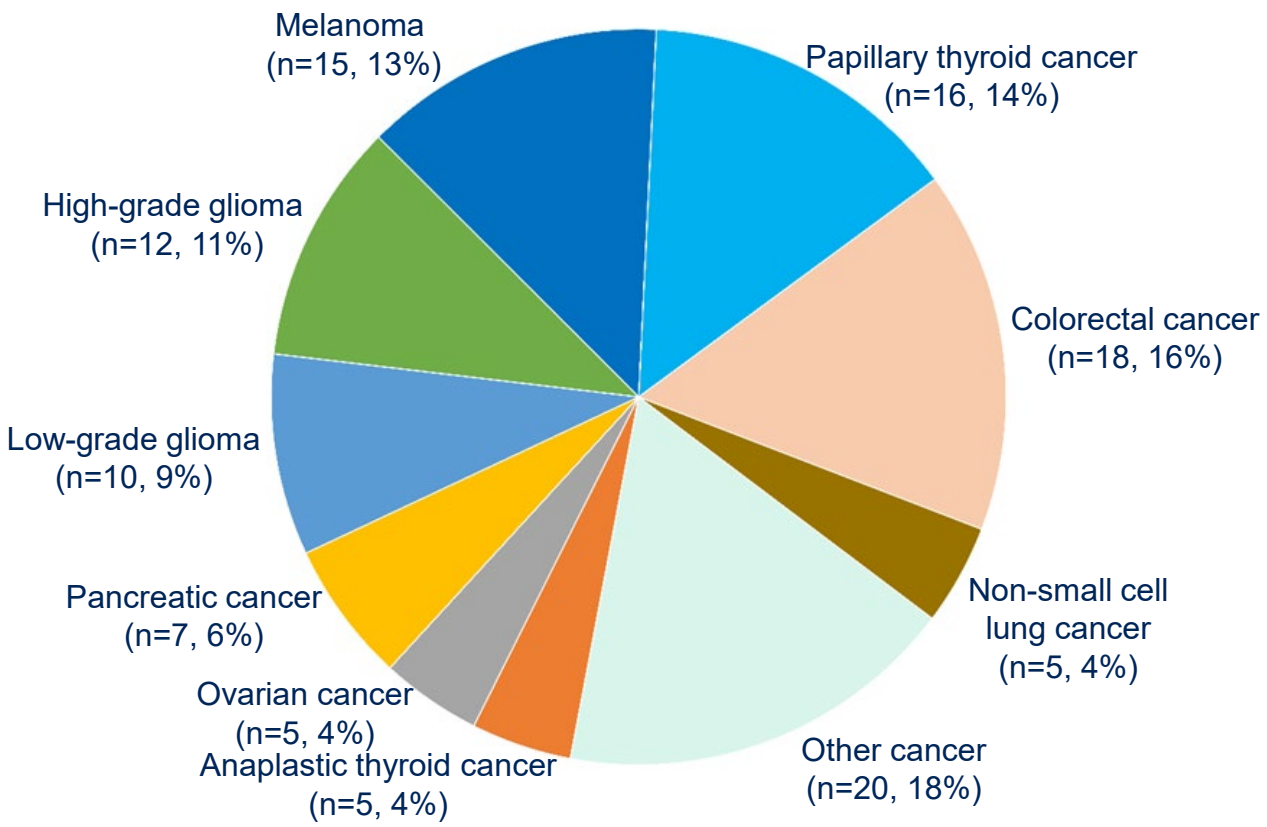
[1] *For locally advanced or metastatic disease*
[2] *Includes patients who received a BRAF inhibitor*

Tumor Distribution by BRAF Alteration and Type

BRAF Alteration	n (%)
Class 1	64 (56.6%)
V600E	60 (53.1%)
V600K	3 (2.7%)
V600R	1 (0.9%)
Class 2	36 (31.9%)
Non-fusion	19 (16.8%)
Fusion	17 (15.0%)
Class 3	1 (0.9%)
Other[1]	3 (2.7%)
No documented BRAF alteration[2]	9 (8.0%)

[1] 1 P708A point mutation, 1 amplification, 1 intragenic deletion
[2] BRAF alterations were not required for inclusion in Phase 1 component

Histology of Tumors (N =113)



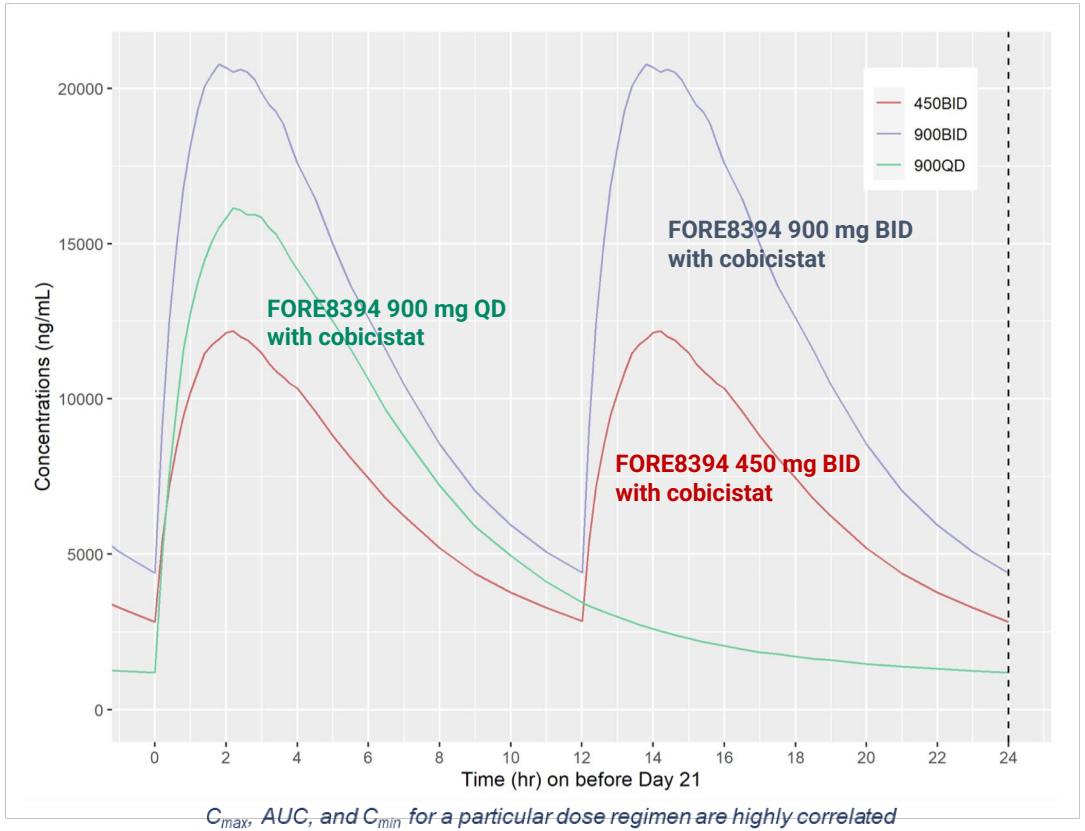
Selection of the Recommended Phase 2 Dose (RP2D)

- **Safety**
  - No DLTs at <1500 mg/day
  - The one FORE8394 discontinuation due to related AE occurred at the highest dose (3600 mg/day)
- **Efficacy**
  - Responses occurred across dose levels
  - No increase at > 900 mg/day
- **PK:** Higher steady state C_{max} with comparable AUC achieved with QD vs. BID dosing
- Addition of CYP3A inhibitor cobicistat and QD dosing provide the **most convenient regimen** for patients

Presented in more detail in poster #3106

PK modeling – Source: Nonmem version 7.5.1 (Icon development solutions, Dublin Ireland)
Methods – DR Mould, RN Upton "Basic Concepts in Population Modeling, Simulation and Model-Based Drug Development - Part 2: Introduction to Pharmacokinetic Modeling Methods" Clin. Pharmacol. Ther. Pharmacomet. and Systems Pharmacol. 2, e38 2013

Steady-State Concentration-Time Profile of FORE8394 900-1800 mg/day with Cobicistat



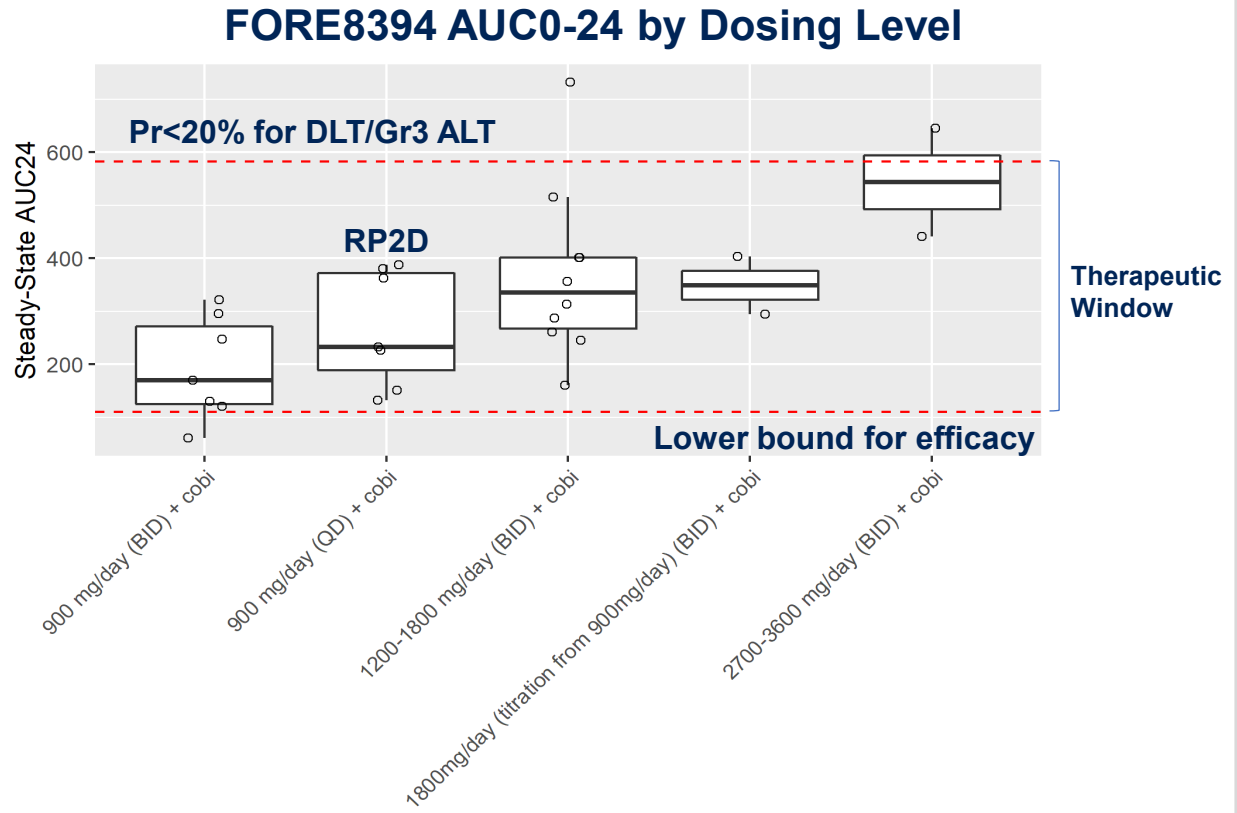
C_{max}, AUC, and C_{min} for a particular dose regimen are highly correlated

Simulated exposures are shown

Therapeutic Window Achieved with FORE8394 900 mg QD + Cobicistat

- FORE8394 900 mg QD + cobicistat provided
  - Exposure within therapeutic window
  - Minimized adverse events
  - Best clinical response
- Declared the RP2D

Presented in more detail in poster #3106



Therapeutic window is defined by the lowest exposure with objective clinical response (lower bound) and the probability < 20% of ≥ Grade 3 increased ALT (upper bound).

TEAEs in ≥20% All Grades and/or ≥5% Grade ≥3 of Patients

	Preferred Term	All Dose Levels (N=113)					RP2D (n=9)				
		G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	Any Grade n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	Any Grade n (%)
Lab Abnormality AEs	Increased ALT	24 (21.2%)	13 (11.5%)	9 (8.0%)	1 (0.9%)	47 (41.6%)	4 (44.4%)	1 (11.1%)	1 (11.0%)	0	6 (66.7%)
	Increased AST	25 (22.1%)	13 (11.5%)	3 (2.7%)	0	41 (36.3%)	4 (44.4%)	1 (11.1%)	0	0	5 (55.6%)
	Increased blood bilirubin	4 (3.5%)	9 (8.0%)	8 (7.1%)	0	21 (18.6%)	0	1 (11.1%)	0	0	1 (11.1%)
Symptomatic AEs	Fatigue	16 (14.2%)	22 (19.5%)	1 (0.9%)	0	39 (34.5%)	1 (11.1%)	1 (11.0%)	0	0	2 (22.2%)
	Nausea	26 (23.0%)	6 (5.3%)	2 (1.8%)	0	34 (30.1%)	3 (33.3%)	0	0	0	3 (33.3%)
	Diarrhea	15 (13.3%)	6 (5.3%)	4 (3.5%)	0	25 (22.1%)	2 (22.2%)	0	0	0	2 (22.2%)
	Vomiting	11 (9.7%)	11 (9.7%)	1 (0.9%)	0	23 (20.4%)	0	0	0	0	0

Safety Profile Supports Durable Tolerability with a Low Frequency of ≥Grade 2 Symptomatic Adverse Events

RAF Inhibitor Known Toxicities, Contrasted with FORE8394 TEAEs

Including Safety Relative to Approved MEK Inhibitor Combinations

Dabrafenib / Trametinib Common Events (≥ 20%)*

Treatment-Emergent Adverse Events	All		Grade 3 & 4	
	Dabr/Tram	FORE8394	Dabr/Tram	FORE8394
Pyrexia	55%	7%	4.9%	0
Fatigue	50%	35%†	5%	0.9%†
Nausea	40%	30%	1.5%	1.8%
Rash	40%	12%†	2.4%	0†
Chills	30%	1%	0.5%	0
Headache	30%	15%	1.5%	1.8%
Hemorrhage	29%	9%†	4.4%	1.8%†
Cough	29%	14%†	0	0†
Vomiting	27%	20%	1.5%	0.9%
Constipation	27%	17%	0	0
Diarrhea	26%	22%	2.9%	3.5%
Myalgia	24%	11%†	0.5%	2.7%†
Arthralgia	23%	12%	0.5%	1.8%
Peripheral edema	22%	12%†	0	0.9%†

**Taflinar US Prescribing Information, Table 14, 3/2023*

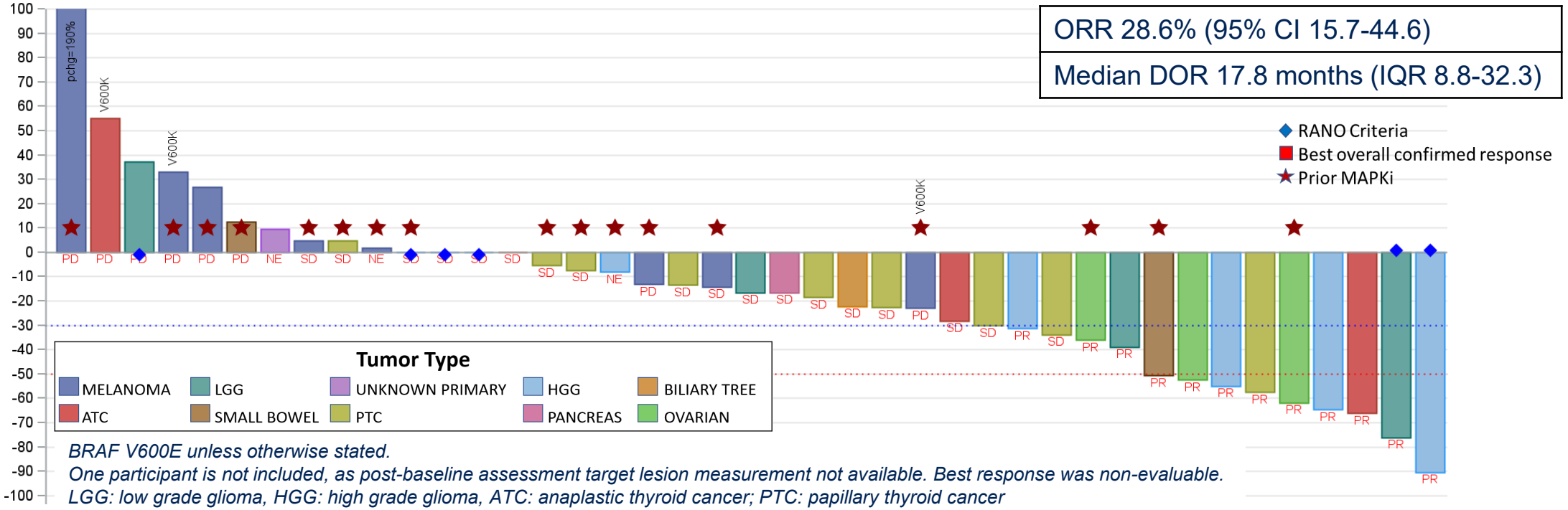
†*Combined incidence for the TEAEs listed in the Taflinar USPI*

- **Rash & pyrexia:** Grade 1 only; none led to FORE8394 reductions
- **Ocular:** no uveitis or retinal detachment based on TEAE and eye exams
- **Cardiovascular:** no TEAE of left ventricular ejection fraction reduction
- **Lack of paradoxical MAPK pathway activation:** no related events of hyperkeratosis or secondary skin cancers

FORE8394 has a unique and favorable safety profile within the RAF inhibitor class

FORE8394 Best Percent Tumor Change from Baseline in V600+ Adults (N=42, mITT)

Excluding CRC Due to Known Intrinsic Resistance Through EGFR Pathway



BRAF V600E unless otherwise stated.
One participant is not included, as post-baseline assessment target lesion measurement not available. Best response was non-evaluable.
LGG: low grade glioma, HGG: high grade glioma, ATC: anaplastic thyroid cancer; PTC: papillary thyroid cancer

MAPKi Naive

V600 Mutated Tumors (n = Naive)	ORR n (%)	CBRx24w n (%)
Primary CNS tumors (10)	6 (60%)	7 (70%)
Ovarian cancer (1)	1 (100%)	1 (100%)
Papillary thyroid cancer (6)	1 (16.7%)	4 (66.7%)
Anaplastic thyroid cancer (4)	1 (25%)	2 (50%)

MAPKi Pretreated

V600 Mutated Tumors (n = Pretreated)	ORR n (%)	CBRx24w n (%)
Primary CNS tumors (3)	0	1 (33.3%)
Ovarian cancer (2)	2 (100%)	2 (100%)
Small bowel cancer (2)	1 (50%)	1 (50%)
Papillary thyroid cancer (3)	0	0
Melanoma (8)	0	1 (12.5%)

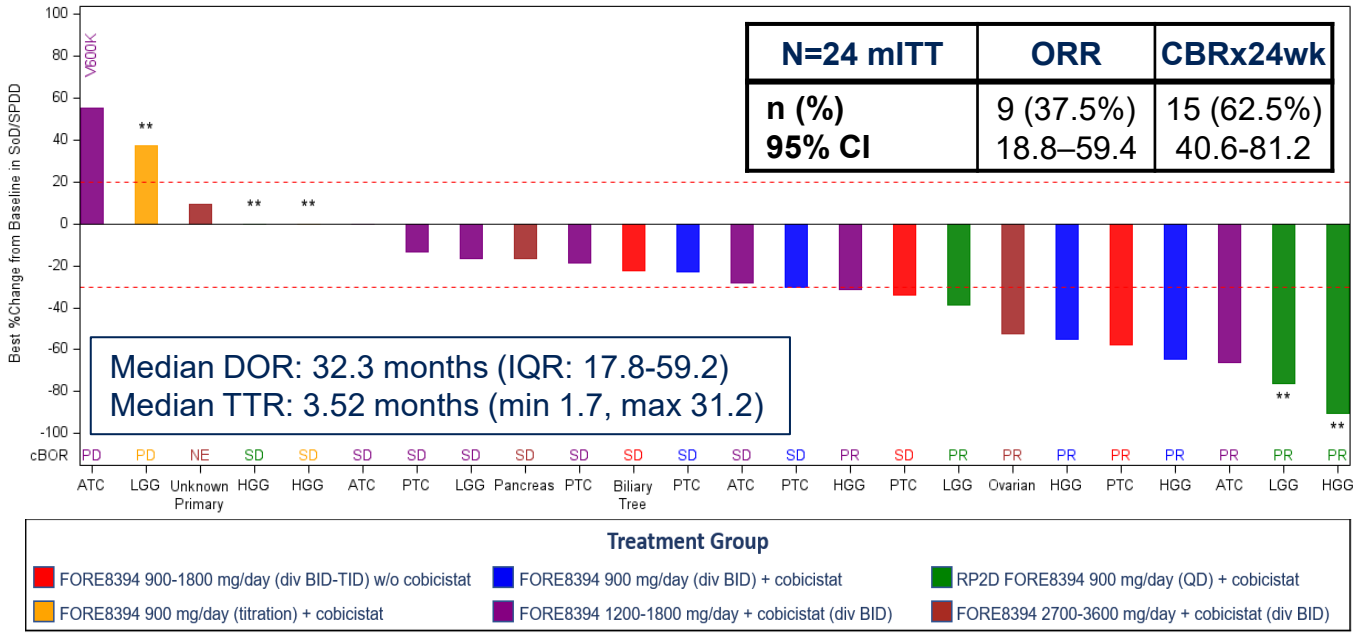
3/3 confirmed PR in ovarian cancer. One with 6 prior lines of therapy, of which 4 included RAF, MEK, and/or ERK inhibitor, with documented PD.

MAPKi pretreated V600+ (N=18)
ORR 16.7%, mDOR=12.9 months

Tables include representative tumor types.
n=0 for tumor types not shown in both tables.

Efficacy in MAPKi Naïve V600+ Population, Including CNS Tumors

Best Change in Tumor Size by Treatment Groups



N=24 mITT	ORR	CBRx24wk
n (%)	9 (37.5%)	15 (62.5%)
95% CI	18.8–59.4	40.6-81.2

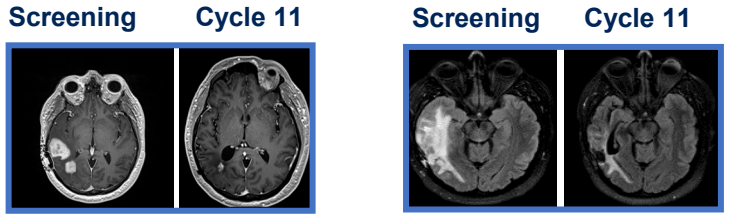
N=24	CR	PR	SD	PD	NE
n (%)	0	9 (37.5)	12 (50)	2 (8.3)	1 (4.2)

Responses Occurred Across Treatment Groups

*** Subject was assessed by RANO criteria*
cBOR: Confirmed Best Overall Response
Excludes CRC due to intrinsic resistance through EGFR pathway, and mg/m2-dosed pts, as RP2D not determined

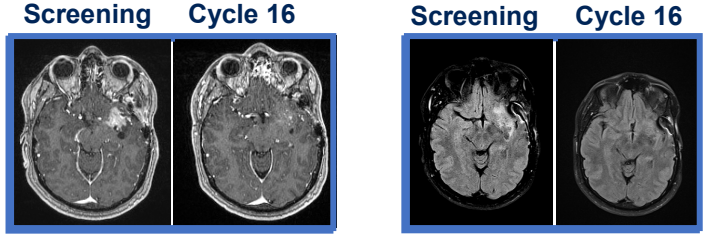
47-year-old male with recurrent WHO G4 V600E+ glioblastoma

- S/p resection & RT with concurrent temozolomide (TMZ), 5 adjuvant cycles (presented with disease progression)
- Treated with FORE8934 900 mg QD + cobicistat (4-wk cycles)
- PR by RANO at 3.7 months
- Continues treatment 13.8+ months



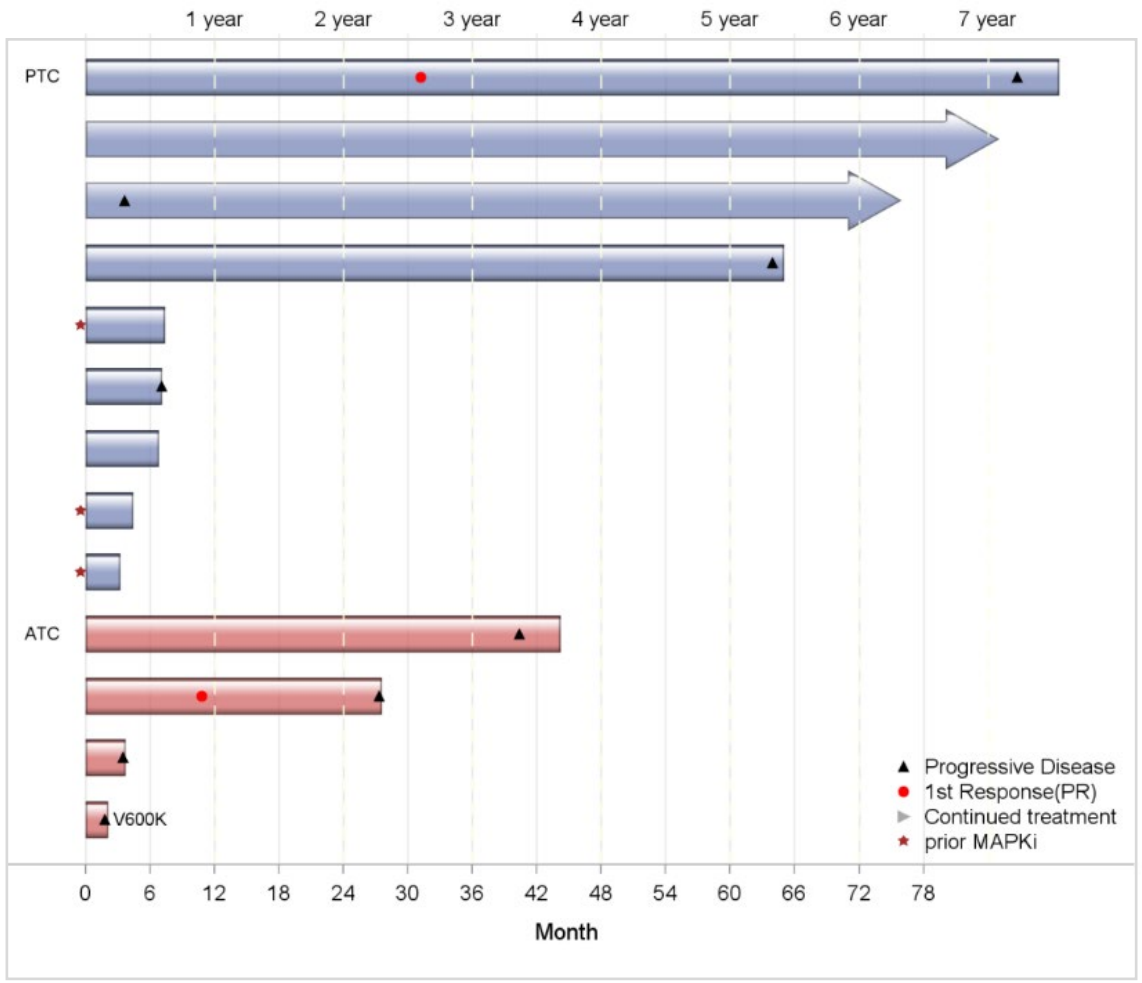
37-year-old male with recurrent V600E+ xanthoastrocytoma

- Dx'd 14 years ago, s/p 2 resections, RT with concurrent TMZ, followed by TMZ cycles. POD, with a 3rd resection
- Treated with FORE8934 900 mg QD + cobicistat
- PR after 1.8 months
- Continues treatment 19+ months

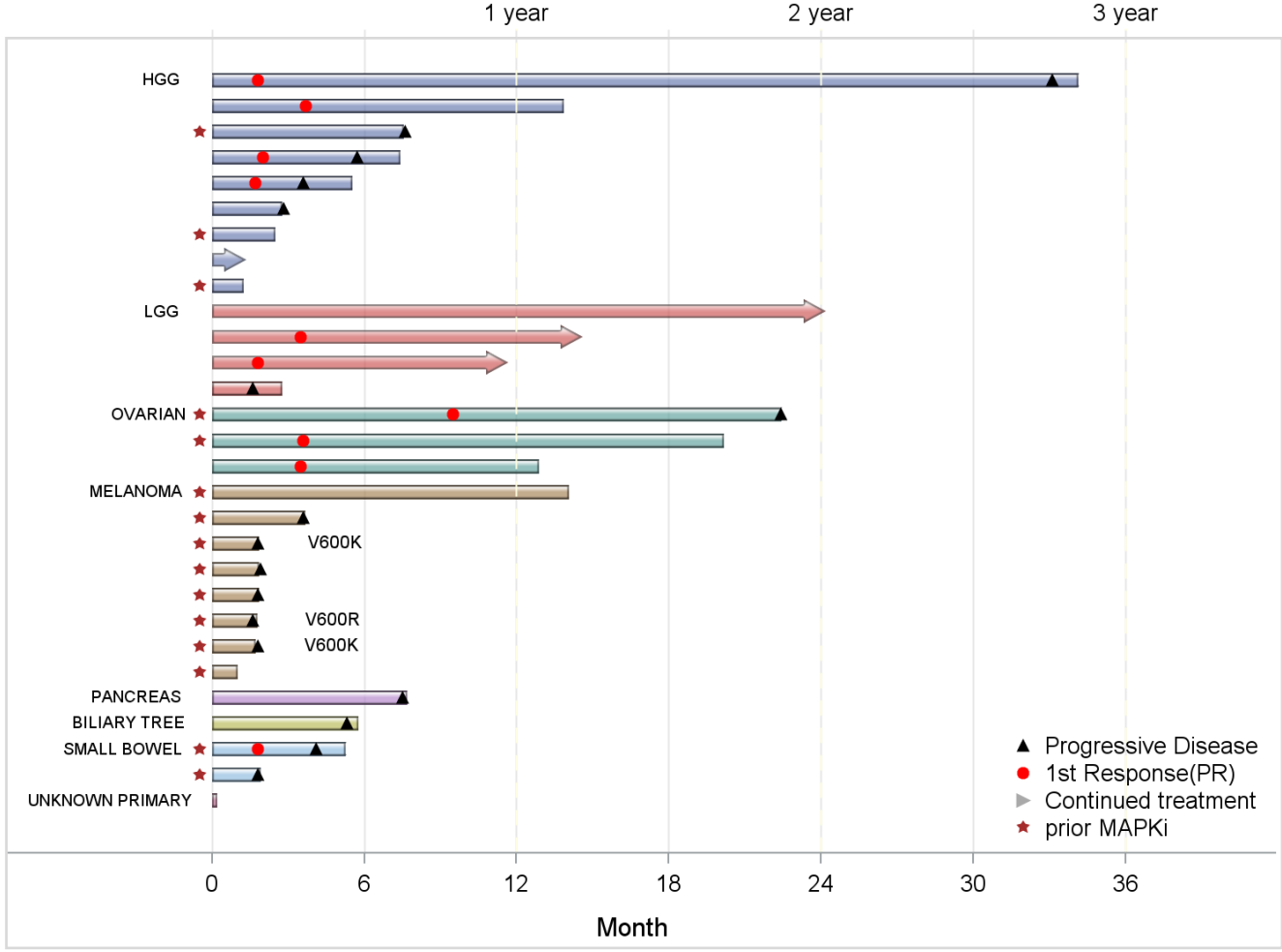


FORE8394 Treatment Duration Up to 7 Years in Patients with V600+ Tumors

Thyroid Cancers

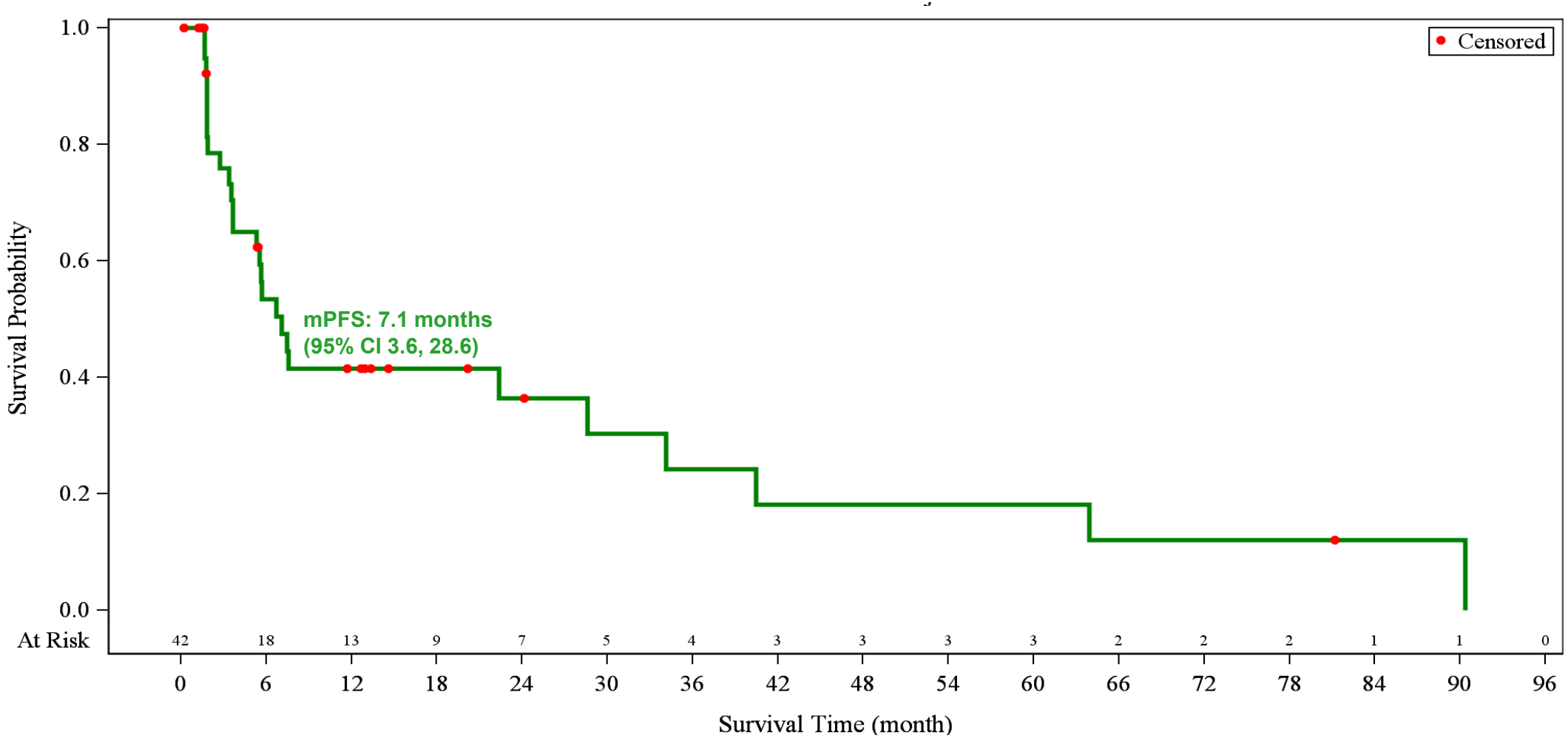


Non-Thyroid Malignancies



PRESENTED BY: Macarena de la Fuente, M.D.

Progression-Free Survival: MAPKi-Naïve & MAPKi-Pretreated V600+ Subsets

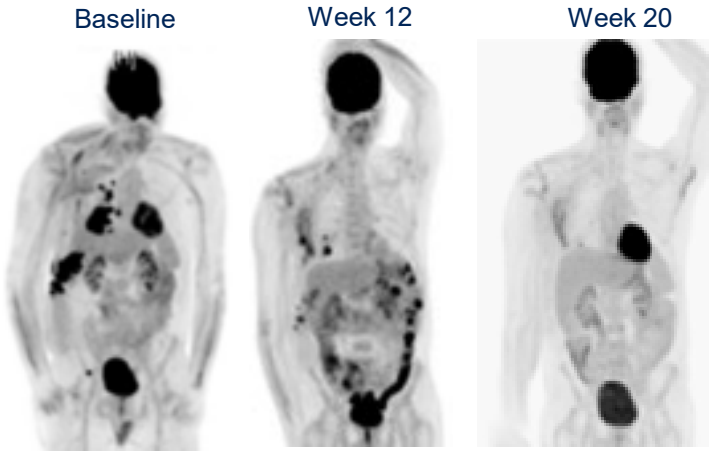


Efficacy evaluable population with at least one post-baseline assessment
Excludes CRC (Due to Intrinsic Resistance) and Phase 1 – Peds (mg/m^2) cohorts (n=4) as escalation closed prior to RP2D

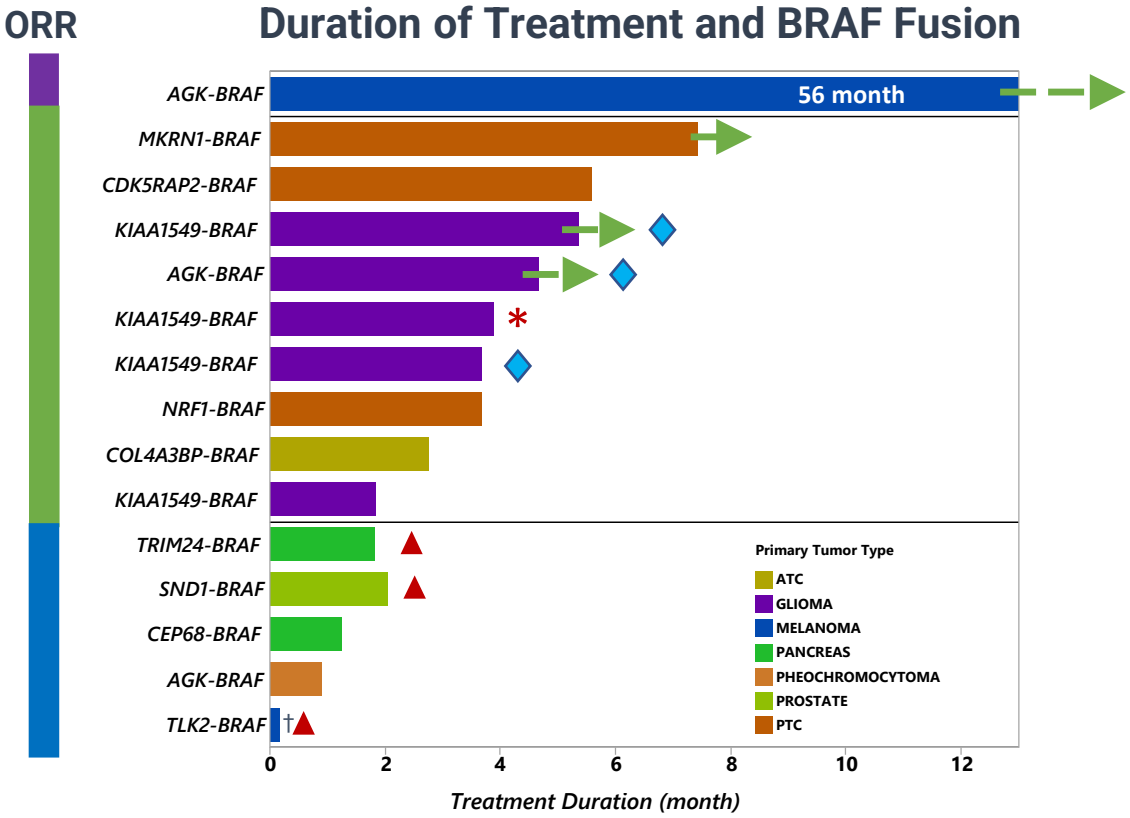
Efficacy in Solid Tumors with BRAF Fusions

- **Of the 14 efficacy-evaluable adults with BRAF fusions**
  - 1 CR (DOR 55.5 months), 8 SD, and 5 PD
  - Of 8 with SD, 4 with glioma, 4 with thyroid cancer
  - 4 remain on treatment: 2 with glioma who received the RP2D, 1 melanoma (CR), and 1 thyroid cancer
  - 3/5 patients with PD had co-occurring driver mutation
  - 1 pediatric patient (BSA-adjusted dosing; n=1) had SD

AGK-BRAF fused metastatic melanoma,
3 prior lines of therapy: pembro, nivo/ipi, ipi



1st dose: 23 March 2018; CR by week 20; treatment is ongoing



ORR CR SD PD

Treatment ongoing

With co-occurrent driver mutation

RP2D

* Also shown is the single patient with BRAF fusion in the mg/m^2 subgroup, which provided suboptimal exposures (AUC0-24 was 25% of target threshold)

† New CNS metastasis after 1 week

Conclusions

Summary

- Durable long-term tolerability
  - Symptomatic Grade 3 AEs were infrequent (of the most common: G3 was ≤3.5%)
    - None were G4 or dose-limiting
    - Only 1 discontinuation due to treatment-related AE
  - Minimal toxicities relative to approved BRAF inhibitors
  - Fever and skin abnormalities were infrequent; no ocular toxicities were detected
  - No signs of paradoxical MAPK pathway activation
- Promising single-agent activity against BRAF altered tumors including primary CNS tumors
- PK and efficacy/safety data fully support the RP2D of 900 QD with cobicistat 150 mg QD

Future Directions

- Phase 2 Forte basket study (NCT05503797) is ongoing
- To evaluate FORE8394 900 mg QD with cobicistat 150 mg QD in patients ≥10 years old with
  - Recurrent primary CNS tumors harboring BRAF V600E mutations
  - Advanced or metastatic solid tumors (excluding colorectal or pancreatic adenocarcinoma) or primary CNS tumors harboring BRAF fusions with no co-occurring driver mutation

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- Patients & their families
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