# Efficacy of BRAF Inhibitor FORE8394 in BRAF V600+ Patients

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## INTRODUCTION

### Unique Mechanism of Action

**FORE8394** is uniquely designed as a dimer breaker to target *BRAF* alterations

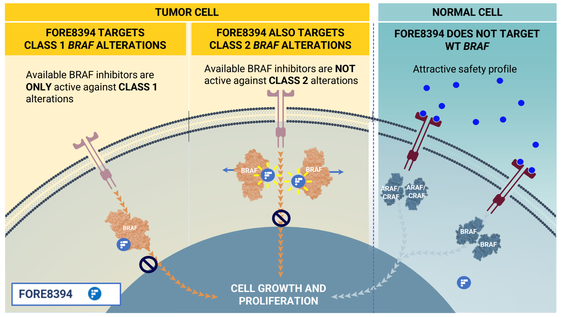
- Class 1 (V600), with phase 1/2a results, as presented here, **and**
- Class 2 and fusions[1]: complete response in melanoma AGK-BRAF fusion; remains on treatment ≥4 years

**FORE8394** avoids a key limitation of standard of care: paradoxical activation of MAPK signaling, resulting in[1-3]:

- Avoidance of secondary drug-related malignancies[2]
- Avoidance of specific resistance mechanisms[1,4]
- Conducive to combination therapy opportunities[5]
- Avoidance of the need for combination with a MEK inhibitor[1-3]

### FORE8394: Next-in-Class BRAF Inhibitor

Targets Class 1 and Class 2 *BRAF* alterations and avoids paradoxical MAPK activation[1, 5, 6]




## METHODS

**Study Design**

Phase 1/2a single-arm, open-label study in adults and children with advanced tumors with activating *BRAF* alterations (NCT02428712)[7]

As of July 31, 2022, 108 adults and children have received ≥1 dose of FORE8394 (safety analysis population)

**Eligibility Criteria**

- Key inclusion criteria
  - Solid and CNS tumors
  - Measurable disease defined by RECIST or RANO criteria
  - ECOG-PS of 0–1
  - Adequate hematologic, hepatic, and renal function[a]
- Key exclusion criteria included:
  - Participants receiving contraindicated medications such as inducers/inhibitors of CYP3A4 or agents contraindicated with cobicistat

**FORE8394 Dosing**

- Participants received oral FORE8394 900–3600 mg/d alone or with cobicistat (Tybost; CYP3A4/P-gp inhibitor) to increase exposure
- Based on the totality of the PK and clinical data, QD dosing was evaluated and resulted in the declaration of the RP2D of FORE8394 900 mg QD with cobicistat 150 mg QD

**Primary End Points**

- Safety, PK, RP2D
- ORR (CR+PR)

**Secondary End Points**

- CBR (CR+PR+SD ≥24 wk)
- DoR and PFS

**Subgroup Analyses Conducted for Efficacy: BRAF V600**

- ≥18 years of age
- Solid and CNS tumors
- ≥1 postbaseline assessment, as defined for mITT population for efficacy
- Documented *BRAF* V600 mutation
- Within this subgroup and based on potential similar mechanisms of resistance and coactivation of other driver pathways (eg, EGFR in CRC), efficacy was evaluated
  - Including patients who had not received prior BRAF or other MAPK-targeted therapies
  - Excluding those with CRC
- In addition, efficacy subset analyses by tumor type were conducted for more commonly enrolled populations (PTC, ATC, gliomas, ovarian cancer)

[a]ANC ≥1.5 × $10^9$/L, Hgb ≥9 g/dL, platelet count ≥100 × $10^9$/L, AST/ALT ≤2 × ULN, total bilirubin ≤1.5 × ULN or ≤2 × ULN if hepatic metastases/involvement, creatinine ≤1.5 × ULN or CrCl >50 mL/min.

## RESULTS

### Baseline Characteristics

**TABLE 1. Baseline Demographics and Clinical Characteristics**

| Characteristic | | Total population (N=108) | Adult V600+ mITT (N=51) |
|---|---|---|---|
| Sex | Male, n (%) | 57 (52.8) | 24 (47.1) |
| Age, y, median (range) | | 57 (4–86) | 61 (21–86) |
| Race, n (%) | Asian | 3 (2.8) | 1 (2.0) |
| | Black or African American | 5 (4.6) | 1 (2.0) |
| | White | 96 (88.9) | 48 (94.1) |
| | Missing | 4 (3.7) | 1 (2.0) |
| ECOG-PS, n (%) | 0 | 42 (38.9) | 20 (39.2) |
| | 1 | 61 (56.5) | 29 (59.9) |
| | >1 | 5 (4.6) | 2 (3.9) |
| Prior lines of therapies, n (%) | 0 | 20 (18.5) | 12 (23.5) |
| | 1 | 25 (23.1) | 12 (23.5) |
| | 2 | 16 (14.8) | 8 (15.7) |
| | 3 | 18 (16.7) | 7 (13.7) |
| | ≥4 | 29 (26.9) | 12 (23.5) |
| | **Prior MAPK-targeted therapies, n (%)** | | |
| | Any (MEK inhibitor, ERK, BRAF inhibitor) | 28 (25.9) | 17 (33.3) |
| | BRAF inhibitor | 23 (21.3) | 16 (31.3) |
| Prior radiation therapy, n (%) | Y | 59 (54.6) | 31 (60.8) |
| Prior checkpoint inhibitor therapy, n (%) | Y | 21 (19.4) | 11 (21.6) |
| *BRAF* mutational status, n (%) | **Class 1 variants** | 62 (57.4) | 51 (100) |
| | V600E | 58 (53.7) | 47 (92.2) |
| | Other[a] | 4 (3.7) | 4 (7.8) |
| | **Class 2 variants** | 19 (17.6) | 0 |
| | **Fusions** | 13 (12.0) | 0 |
| | **Other** | 5 (4.6) | 0 |

Total population includes all patients who received a dose of FORE8394; mITT includes all patients who were V600 positive.
[a]Includes V600K, V600M, V600R, and other mutations.

**FIGURE 1A. Histology of Tumors, Total Population (N=108)**

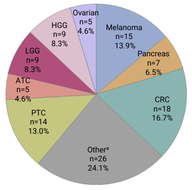
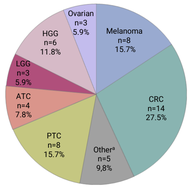



**FIGURE 1B. Histology of Tumors, mITT Adult V600+ Subset (N=51)**




[a]Other tumor types include neuroblastoma, non-small cell lung cancer, angiosarcoma, biliary tree, endometrium, gastric, Langerhans cell histiocytosis, lung, medullary thyroid cancer, prostate, pheochromocytoma, sarcoma, small bowel, thyroid, and unknown.
Note: Percentages were rounded up to 1 decimal place.

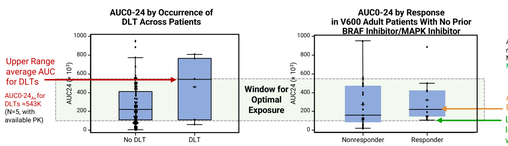
### Clinically relevant exposures were achieved, suggesting a wide therapeutic window

#### Pharmacokinetics

- 95/104 (91.3%) adult participants received 900 mg to 1800 mg total daily dose, divided QD to 3 times daily, and majority of responses occurred within this dose range
- Clinically relevant exposures were achieved across all dose levels with or without cobicistat
  - Includes lowest dose level of 450 mg twice daily without cobicistat
- Potentially wide therapeutic window

### Dose Declaration – FORE8394 900 mg QD With Cobicistat Achieves Targeted Therapeutic Window

**FIGURE 2. Exposure in Patients With DLT and Responders Provides Thresholds for Risk-Benefit**




- Exposures optimized and align with targeted therapeutic window based upon nonclinical and clinical data
- FORE8394 900 mg QD with cobicistat was declared as RP2D
  - 3/5 patients demonstrated confirmed partial response and remain on treatment, all with V600E glioma
  - No DLTs were observed in participants who have received the RP2D (n=6)
- Across all cohorts, DLTs included Grade 3 increased AST (n=1), ALT (n=1), blood bilirubin (n=2), and ALT and bilirubin (n=1)

### Safety: TEAEs

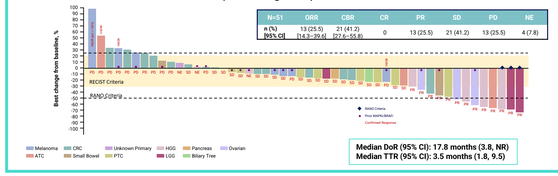
**TABLE 2. Summary of All TEAEs Reported in ≥20% of Participants or ≥Grade 3 in ≥5% of Participants, Irrespective of Tumor Type (N=108)**

| TEAEs, n (%) | All Grades | ≥Grade 3 |
|---|---|---|
| Participants with any TEAE | 105 (97.2) | 53 (49.1) |
| Participants with any treatment-emergent FORE8394-related AE | 84 (77.8) | 22 (20.4) |
| Patients with treatment-emergent cobicistat-related AE | 56 (51.9) | 16 (14.8) |
| Increased ALT | 43 (39.8) | 10 (9.3) |
| Increased AST | 38 (35.2) | 3 (2.8) |
| Fatigue | 35 (32.4) | 1 (0.9) |
| Nausea | 29 (26.9) | 2 (1.9) |
| Diarrhea | 24 (22.2) | 4 (3.7) |
| Vomiting | 22 (20.4) | 1 (0.9) |
| Increased bilirubin | 18 (16.7) | 7 (6.5) |

- Long-term tolerability was observed with 20 (18.5%) patients still being treated with FORE8394
- Symptomatic AEs were low grade and mild
- ALT, AST, or bilirubin changes were transient and manageable with dose interruption or modification
- 54.6% of participants interrupted FORE8394 owing to AEs, 7.4% had dose reduced
- Reasons for treatment discontinuation: 54 (50%) PD; 5 (4.6%) AEs
- Only 1 participant discontinued FORE8394 due to treatment-related AE (Grade 3 bilirubin)

### Efficacy: Adult Participants With *BRAF* V600 Mutation (mITT), N=51

**FIGURE 3. Waterfall Plot Showing Decrease in Tumor Burden in Adults With *BRAF* V600+ Advanced Solid and CNS Tumors (Including CRC)**




9 patients were excluded from mITT owing to lack of postbaseline scan. Data cutoff: July 31, 2022.
Includes 1 patient (not shown) with unscheduled postbaseline assessment for whom target lesion measurements are not available.
All patients were *BRAF* V600E unless otherwise specified.

- Of 3 participants with ovarian cancer, 3 had PR (DoR range, 9.2+ to 16.6+ months, ongoing); 2 had received prior BRAF inhibitor/MAPK-targeted treatments
- In addition, 1 participant with small bowel cancer who received prior BRAF inhibitor had PR
- Of 14 V600 participants with CRC, 1 had PR; 1 had SD for 28.6 months

### Efficacy: V600+ BRAF/MAPK-Naïve Population (mITT, excluding CRC), N=21

**FIGURE 4A. Waterfall Plot of Decrease in Tumor Burden in Each Participant**

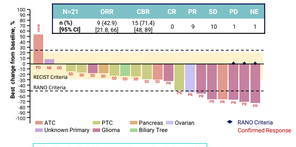
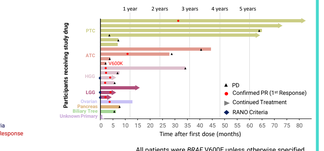



**FIGURE 4B. Duration of Treatment and Confirmed Response**



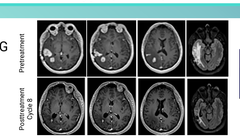

All patients were *BRAF* V600E unless otherwise specified.

Confirmed responses and durable benefit seen across multiple tumor types

### Efficacy: Subset Analyses by Tumor Types, V600+; BRAF Inhibitor/MAPK Inhibitor-naïve

**FIGURE 5. Glioma**

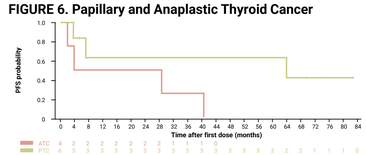
- Of the 7 with HGG or LGG
  - 6 PR
  - 1 SD for 15+ months
- HGG: all (N=4) had PR, with treatment up to 34 months




| | ORR, n (%) | CBR, n (%) | mPFS, mo | mTTR, mo | mDOR, mo |
|---|---|---|---|---|---|
| HGG | 4 (100) | 4 (100) | 6.7 [5.5–NE] | 1.9 [1.7–NE] | 4.7 [3.8–NE] |
| LGG | 2 (66.7) | 3 (100) | NR [NR–NR][a] | 2.7 [1.8–3.5][a] | NR [NR–NR][a] |

[a]Treatment for all 3 with LGG is ongoing

**FIGURE 6. Papillary and Anaplastic Thyroid Cancer**




| | ORR, n (%) | CBR, n (%) | mPFS, mo | mTTR, mo | mDOR, mo |
|---|---|---|---|---|---|
| PTC | 1 (16.7) | 4 (66.7) | 63.9 [3.6–NE] | 44.7 [31.2–NE] | NE [5.7–NE] |
| ATC | 1 (25.0) | 2 (50.0) | 16.1 [1.8–NE] | 10.8 [NE–NE] | 17.8 [NE–NE] |

- 6 participants with PTC:
  - Median PFS not reached
  - Median follow-up 5.6 years
  - 4 on treatment for 2+ years
- 2/4 with ATC received FORE8394 >2 years

## CONCLUSIONS

- FORE8394 achieved clinically relevant exposures with a favorably low rate of symptomatic AEs
- Encouraging response rates and durability of benefit were observed in multiple tumors
  - Durable PFS was demonstrated in BRAF inhibitor–/MAPK inhibitor–naïve patients with *BRAF* V600 PTC
  - A high proportion of participants with glioma demonstrated response, with 6/7 MAPK inhibitor–naïve patients demonstrating confirmed PRs
- Durability and tolerability support lack of paradoxical MAPK inhibitor pathway activation
- Overall, FORE8394 was well tolerated, with a clinically manageable safety profile
  - LFT changes were transient and manageable with dose interruption/modification
  - Current dose range achieves optimal efficacy while avoiding toxicity
- In 4Q 2022, Phase 2 Master Protocol will initiate NCT05503797—participants with BRAF fusions (CNS and solid tumors) and V600 positive recurrent primary CNS tumors

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## ACKNOWLEDGEMENTS

We thank Emil Samara, Robin McGarry, and Diane Mould for contributions to data analysis and interpretation.
Medical writing support was provided by PRECISIONscientia, Yardley, PA, USA.
Corresponding author: Dr Eric Sherman Email: shermane@mskcc.org
Dr Sherman was on an advisory board for Eisai, Roche, Regeneron, Exelixis, and Bayer, was a trial chair and PI with no financial interest for Novartis, a local PI for Regeneron and Eli Lilly, and was on a steering committee for Eli Lilly.

**Abbreviations:** AE, adverse event; AGK-BRAF, acylglycerol kinase–B-Raf proto-oncogene; ALT, alanine aminotransferase; ANC, absolute neutrophil count; ARAF, A-Raf proto-oncogene; AST, aspartate aminotransferase; ATC, anaplastic thyroid cancer; AUC0-24$_{ss}$, area under the curve average from time zero to 24 hours; BID, twice daily; BRAF, B-Raf Proto-oncogene, serine/threonine kinase; CBR, clinical benefit rate; CNS, central nervous system; CR, complete response; CRAF, Raf-1 proto-oncogene, serine/threonine kinase; CRC, colorectal cancer; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; DLT, dose-limiting toxicity; DoR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; Hgb, hemoglobin; HGG, high-grade glioma; LFT, liver function test; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; mDOR, median duration of response; MEK, mitogen-activated protein kinase kinase; mITT, modified intent-to-treat; mPFS, modified progression-free survival; mTTR, median time to response; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; P-gp, P-glycoprotein; PR, partial response; PTC, papillary thyroid carcinoma; QD, once daily; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; WT, wild-type.

Presented at the European Society for Medical Oncology Congress; September 9–13, 2022; Paris, France