Dose optimization of novel BRAF inhibitor FORE8394 based on PK and efficacy results

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Abstract Number 3106

FORE8394 900 mg QD with cobicistat has been supported as the recommended Phase 2 dose for the treatment of BRAF-altered advanced malignancies based on frequency of DLTs, overall tolerability, efficacy, and pharmacokinetic data.

INTRODUCTION

- Traditionally, determining the dose of cytotoxic chemotherapy drugs was based on identifying the maximum tolerated dose. However, with the advent of targeted therapies, the US FDA recommends that dose optimization be routinely performed early in drug development as targeted therapies demonstrate different dose-response relationships compared to cytotoxic chemotherapy.
- Dose optimization identifies a dose that preserves clinical benefit with optimal tolerability. It avoids exposing patients to a dosage regimen that is poorly tolerated or adversely impacts functioning and quality of life. This in turn may impact treatment adherence,[1] which is commonly observed with the traditional maximal tolerated dose paradigm.
- FORE8394 is a next-generation, orally available, small-molecule, selective inhibitor of class 1 (V600) and class 2 (non-V600), BRAF alterations.
- FORE8394 avoids a key limitation of approved BRAF inhibitors: paradoxical activation of MAPK signaling, resulting in:
  - Avoidance of secondary drug-related malignancies,[2] specific resistance mechanisms,[3,4] and need for combination of FORE8394 with a MEK inhibitor[2,3,5]
  - Favorable profile for combination therapies[6]

OBJECTIVE

In line with guidance from the Project Optimus of the US FDA, we aimed to identify the optimal recommended phase 2 dose (RP2D) for FORE8394 using integrated pharmacokinetics (PK), safety and efficacy data, and exposure-response modeling.

METHODS

Study Design

- Single-arm, open-label study in patients with advanced solid or CNS tumors with BRAF alterations (NCT02428712).[7]
- Phase 1 3+3 Dose Escalation Design: A) adults; B) 3-17 years of age with BSA-adjusted dosing
- Phase 2a: ≥10 years of age. Phase 2a was amended to enable dose optimization.

As of March 31, 2023, 113 patients have received ≥1 dose of FORE8394 (safety analysis population) Efficacy analysis population (mITT): Class 1 or 2 BRAF alteration and ≥1 post-baseline assessment

Eligibility Criteria

Key inclusion criteria
- Measurable disease by RECIST or RANO criteria
- ECOG-PS of 0–1
- Adequate hematologic, hepatic, and renal function

Key exclusion criteria
- Symptomatic brain metastases, baseline brain MRI was not required
- Refractory nausea/vomiting; unable to swallow

Dosing

- FORE8394 continuous dosing under fasting conditions on 28-day cycles until disease progression
- Evaluated a wide range of doses (900–3600 mg/d) and schedules with and without cobicistat (a CYP3A inhibitor)

Main outcome measures

- Pharmacokinetics (PK) was evaluated after single and repeated dosing
- Plasma concentration-time data for FORE8394 were analyzed by noncompartmental methods
- Plasma concentration-time data were analyzed to determine the population PK of FORE8394, in addition to simulations to inform dose selection
- Efficacy endpoints included confirmed response by RECIST 1.1 or RANO criteria.
- Major subgroups were based on BRAF status, prior MAPK-targeted therapy, and similar mechanisms of resistance.

BRAF= B-Raf gene; CYP3A= cytochrome P450, family 3, subfamily A; ECOG-PS= ECOG Scale of Performance status; MAPK= MAPK signaling pathway; mITT= modified intention-to-treat; MRI= magnetic resonance imaging; RANO= Response Assessment in Neuro-Oncology criteria; RECIST=Response Evaluation Criteria In Solid Tumors.

RESULTS

Baseline Clinical Characteristics

- Of the 113 participants, more males than females were enrolled (n=59 [52.2%])
- White population was the largest race group (n=101 [89.4%])
- Median (range) age of the patients was 57 (4–86) years
- Majority of patients were pretreated with ≥2 prior lines of treatment (n=70 [61.9%])
- 18 (15.9%) had colorectal cancer, which is known to have intrinsic resistance
- 33 (29.2%) had received a prior MAPK inhibitor, including 24 with a prior BRAF inhibitor
- Other tumor types reported in ≥10% were glioma (n=22 [19.4%]), thyroid cancer (n=21[18.6%]), and melanoma (n=15 [13.3%])

Table 1. Baseline Clinical Characteristics

Characteristic		Total population (N=113)
ECOG-PS, n (%)*	0	43 (38.1)
	1	65 (57.5)
	2	5 (4.4)
Prior lines of therapies, n (%)	0	15 (13.3)
	1	28 (24.8)
	2	17 (15.0)
	3	16 (14.2)
	≥4	37 (32.7)
Prior MAPKi-targeted therapies, n (%)	Any MAPK targeted therapy	33 (29.2)
Prior BRAFi, n (%)	Included a BRAF inhibitor	24 (21.2)
Prior immune checkpoint inhibitor, n (%)	Y	30 (26.5)
BRAF mutational status, n (%)	**Class 1 variants**	**64 (56.6)**
	V600E	60 (53.1)
	V600K and V600R	4 (3.6)
	Class 2 variants	**36 (31.9)**
	Fusions	17 (15.0)
	Class 3 variants	**1 (0.9)**
	Other**	**3 (2.7)**
	No BRAF alteration	**9 (8.0)**

*Earlier version of the protocol allowed patients with ECOG 2. 5 patients with ECOG 2 were included in the trial. ** Other (P708A, AMP, and intragenic deletion)

Source: ASCO Output Table 1 and Table 2 (run date 08 May 2023)

FORE8394 Exposure and Safety Profile

- Total of 80.4 patient-years of exposure, with consistent manageable safety profile. 12 (10.6%) are still on treatment as of March 31, 2023. Most common reasons for discontinuation are progressive disease (n=65 [57.5%]) and clinical progression (n=18 [15.9%]).
- One discontinuation due to FORE8394-related AE occurred with 3600 mg/day + cobicistat
- A total of 17 patients have been treated with FORE8394 for 1 year; of which 11 patients have been treated for 2 years or more.

Table 2. Treatment-Emergent Adverse Events ≥ Grade 3 (≥ 5% of All Events)

	Preferred Term	All Dose Levels (N=113) (Up to 4x the total daily dose of RP2D) G3 n (%)	All Dose Levels (N=113) (Up to 4x the total daily dose of RP2D) G4 n (%)	RP2D (n=9) FORE8394 900 mg QD with cobicistat G3 n (%)	RP2D (n=9) FORE8394 900 mg QD with cobicistat G4 n (%)
Abnormal Laboratory AEs	Increased ALT	9 (8.0%)	1 (0.9%)	1 (11%)	0
	Increased AST	3 (2.7%)	0	0	0
	Increased blood bilirubin	8 (7.1%)	0	0	0
Symptomatic AEs	Fatigue	1(0.9%)	0	0	0
	Nausea	2 (1.8%)	0	0	0
	Diarrhea	4 (3.5%)	0	0	0
	Vomiting	1 (0.9%)	0	0	0

Source: ASCO Table 7 & Table 11 (run date 08 May 2023)

FORE8394 Pharmacokinetics (PK)

- Exposure ($AUC_{0\text{-}6}$) increased with dose with less than proportional increase at >900 mg BID (FIG 1)
- Higher C_{max} and comparable AUC were achieved with QD vs BID (FIG 2)
- Cobicistat, a PK enhancer for FORE8394, increased FORE8394 exposure 2- to 3-fold (FIG 1 & 3).
- Based on the PK and safety profile, a flat-fixed dose paradigm was selected for adults and children
  - C_{max} and AUC were comparable in both populations.
  - Population PK analysis of pooled data from 123 children and adults in this study and a phase 1 PK study suggest comparable FORE8394 PK characteristics that are neither affected by age (4–86 years) or body weight (18–132 kg) (FIG 4).
  - No unexpected safety concerns identified in studied pediatric population
- Clinically relevant exposures were achieved with pERK suppression (FIG 5) and a wide therapeutic window. FORE8394 900 mg QD + cobicistat provides targeted efficacious exposures (FIG 6).

Figure 1: FORE8394 AUC on D15 across clinically relevant range ±cobicistat

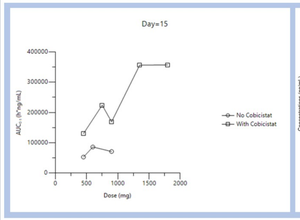


Figure 2: Concentration-time profiles for FORE8394 with cobicistat QD

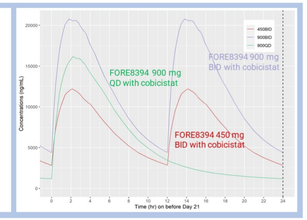


Figure 3: Effect of cobicistat, a CYP3A inhibitor, on FORE8394 exposure

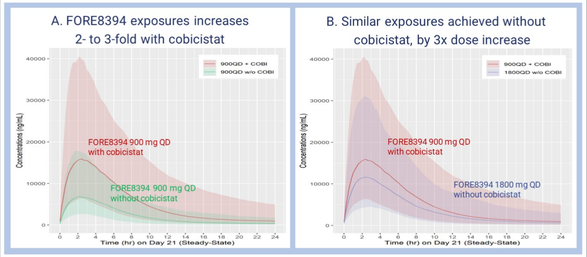


Figure 4. AUC is not weight-dependent, supporting fixed dosing in children

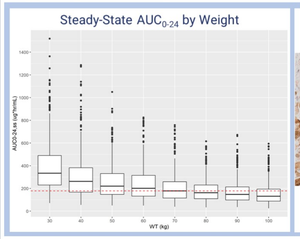


Figure 5. FORE8394 PD effect on pERK in patient w/ BRAF G466R

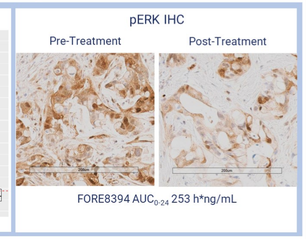


Figure 6. Therapeutic window achieved with FORE8394 900 mg/day + cobicistat

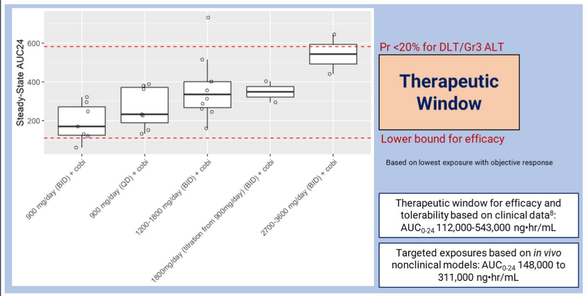


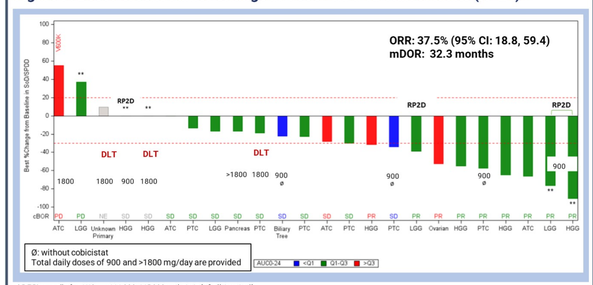
Table 3. Summary of Safety and Efficacy (N=109)

Assigned Regimen	Safety[1]	Efficacy (mITT)	Efficacy MAPKi naïve V600*
Total daily dose FORE8394[1]	**≥Grade 3 TEAE**	**ORR**	**ORR**
900–1800 mg	9/18 (50%)	1/13 (8%)	1/3 (33%)
900 mg + cobi	12/33 (36%)	7/28 (25%)	5/10 (50%)
450 mg BID + cobi	4/11 (36%)	4/10 (40%)	2/4 (50%)
900 mg QD + cobi	**4/9 (44%)**	**3/8 (38%)**	**3 /4 (75%)**
900 mg /day + titration[2]	4/13 (31%)	0/10 (0%)	0/2 (0%)
1200–1800 mg + cobi	28/49 (57%)	4/37 (11%)	2/8 (25%)
2700–3600 mg + cobi	6/9 (67%)	2/8 (25%)	1/3 (33%)

[1] Does not include pts ≤17 years with mg/m² dosing (n=4), as Phase 1 for this regimen was completed prior to RP2D and in general provided lower-than-targeted exposures.
[2] FORE8394 was gradually increased to a maximum of 900 mg BID with cobicistat based on individual tolerability.
* Except CRC; cobi= cobicistat; MAPKi= MAPK signaling pathway inhibitors; mITT= modified indented to treat; ORR= objective response rate; TEAE= treatment-emergent adverse event.
Source: ASCO Output Table 27 and Inhouse orr_v600_MAPKiNaiv_exCRC.rtf (run date 08 May 2023)

No Increase in Efficacy at Higher Exposures or Doses

Figure 7: Best Percent Tumor Change in V600+ MAPKi-Naïve Adults (N=24)*



25-75% quartile for $AUC_{0\text{-}24}$: 111,000-445,000 ng*hr/mL (of all treated)
Source: ASCO Table 18 (run date 08 May 2023)
*Excludes CRC due to intrinsic resistance through the EGFR pathway

Efficacy

- Responses were observed at all doses.
- Objective response rate (ORR) was greatest with FORE8394 900 mg QD + cobicistat (Table 3), with no increase at higher doses or at higher exposures (FIG 7).

Rationale for Selection of RP2D

FORE8394 900 mg QD + cobicistat: declared as the RP2D based upon the totality of the data:

- ✓ Measurable clinical responses - 12 of 14 responses occurred with 900-1800 mg/day
- ✓ No DLT at total daily doses of FORE8394 <1500 mg
- ✓ Increase in frequency of ≥Grade 3 TEAEs was observed at higher doses
- ✓ Exposures further support that these doses achieve the optimal therapeutic window

CONCLUSIONS

- FORE8394 900 mg QD + cobicistat achieved targeted efficacious exposures with robust antitumor activity and favorable safety and is the optimal dose for further development.
- This dose optimization is consistent with current guidelines.
- **A Phase 2 study (NCT05503797) at the RP2D is ongoing for the treatment of recurrent V600E BRAF-mutated primary CNS tumors and advanced solid or CNS tumors with BRAF fusions.**

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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.

Presented at the American Society of Clinical Oncology Annual Meeting; June 2–6, 2023; Chicago, IL, USA