Activity of BRAF Inhibitor Plixorafenib (FORE8394) in Advanced Ovarian Cancer Harboring BRAF V600E Mutation

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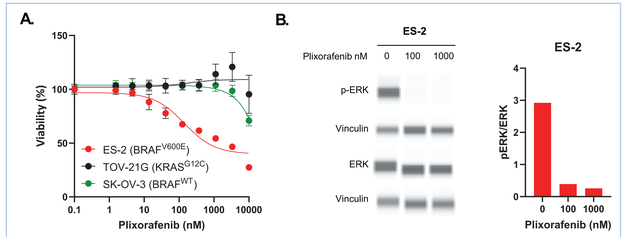
BACKGROUND

High Unmet Need for Ovarian Cancers

- BRAF gene alterations occur in 2% of high-grade and 5% of low-grade serous ovarian cancers.[1]
- Although currently available BRAF inhibitors are a potential treatment option for these patients, their use is limited by tolerability and the development of resistance.[2]

Plixorafenib

- A potent, orally available BRAFi that selectively targets V600 and non-V600 alterations through disruption of BRAF monomers and dimers.[3,4]
- Evades paradoxical MAPK pathway activation, eliminating the need for coadministration with a MEK inhibitor.[5]
- Designed to be highly selective and more tolerable than early-generation BRAFis.[2–4]
- In vitro, ES-2 human ovarian cancer cells with BRAF V600E mutations were sensitive to plixorafenib treatment.



Ovarian cancer cells with BRAF V600E mutations are sensitive to plixorafenib. (A) Cell viability assay was performed for 72 hours and analyzed using Cell-Titer Glo. (B) Western blot analysis of ES-2 cells showing p-ERK and ERK activity 18 hours after plixorafenib treatment.

METHODS

Study Description

- Phase 1/2a, open-label, single-arm, multicenter study (NCT02428712) to assess the safety, PK, and preliminary efficacy of oral plixorafenib 900–3600 mg/day with or without cobicistat[a] (PK enhancer) in children and adults with BRAF-altered solid tumors
  - Phase 1: 3+3 dose escalation in adults and children
  - Phase 2a: Consisted of a series of expanded-dose cohorts, accompanied by modeling, to identify the optimal dose in patients aged ≥10 years

Overall Patient Population[c] (N=113)

- 64 (57%) had BRAF V600 mutation
- 34 (30%) received ≥1 prior MAPK-targeted regimen

Key Eligibility Criteria[b]

- Histologically confirmed, advanced, unresectable solid tumors
- Measurable disease
- Intolerant to standard therapy or no standard therapy available
- No symptomatic brain metastases

Patients With Ovarian Cancer (n=5)

- 3 had a BRAF V600 mutation
  - 2 of 3 received ≥1 prior MAPK therapy
- 1 had a class II nonfusion, 1 had no BRAF alteration

BRAF V600 mutations were a prespecified efficacy subgroup

[a]Cobicistat is a CYP3A inhibitor used as a PK booster (with no anticancer effect) coadministered with plixorafenib in selected cohorts.
[b]During phase 1 of the study, BRAF alteration was not required for eligibility.
[c]All patients who received ≥1 dose of plixorafenib.

Abbreviations

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; ATC, anaplastic thyroid cancer; AUC, area under the curve; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BRAFi, BRAF inhibitor; BSA, body surface area; CBR, clinical benefit rate; CI, confidence interval; C_{max}, maximum serum concentration; CNS, central nervous system; CR, complete response; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; DOR, duration of response; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GBM, glioblastoma; GNT, glioneuronal tumor; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LFT, liver function test; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mDOR, median DOR; mITT, modified intent to treat; mPFS, median PFS; MR, minor response; MTC, medullary thyroid cancer; NCI-CH, neurodegenerative LCH; NGS, next-generation sequencing; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PTC, papillary thyroid carcinoma; QD, once daily; RP2D, recommended phase 2 dose; SAE, serious AE; SD, stable disease; TEAE, treatment-emergent AE; TTR, time to response; VAF, variant allele frequency.

Conflicts of Interest

JR, Grants/contracts: Blueprint Medicines, Merck Sharp & Dohme, 28D Bio, Consultant: Cancer Core Europe, Hummingbird, Yingli, Merus, Aadi, Fore Biotherapeutics (Fore Bio), Amgen, Monte Rosa, Debio, Incyte, BridgeBio, Vall d'Hebron Institute of Oncology/Cancer Core Europe. Meeting support: Loxo Oncology. Data safety monitoring/advisory board: Ellipses, Molecular Partners, iOncture, Sardona, Mekanistic, Amgen, Merus, Monte Rosa, Aadi, BridgeBio. Other: Cancer Core Europe, Symphogen, BioAlta, Pfizer, Kelun-Biotech, GSK, Taiho, Roche, Hummingbird, Yingli, Bicycle, Merus, Aadi, Fore Bio, Loxo Oncology, Hutchinson MediPharma, Ideaya, Amgen, Tango, Mirati, Limaeus, Monte Rosa, Kinnate, Debio, BioTheryX, Storm, BeiGene, MapKure, Relay, Novartis, Fusion Pharma, C4, Scorpion, Incyte, Fog, Tyra, Nuvectis, BridgeBio, 3H Pharmaceuticals, AstraZeneca, Vall d'Hebron Institute of Oncology/Cancer Core Europe. **FJ**: Employee and stock/stock options: Monte Rosa. Advisor: Fore Bio. **IK, MP, ATL, KW, SPS, PJ**: Employee: Fore Bio. **MdlF**: Advisory board: Fore Bio, Servier, Amfinart, Rigel. Research support: Caris. Board of Directors: Neuro-Oncology. Receipt of equipment, materials, drugs, medical writing, gifts or other services: Fore Bio. **EJS**: Grants: Fore Bio, Eli Lilly, Regeneron, Pure Tech Health. Personal fees: Affirmtrune, Eli Lilly. **FT**: Honoraria: Aptitude Health. Stock/stock options: Solarius, Sphinx Health Solutions Corp. **NAB**: Nothing to disclose. **CEA**: Grants/contracts: NCRUM, Bi, Baldrick's Foundation, The Leukaemia & Lymphoma Society. Consultant: Sobi, Elektra, DPhar. **NRA**: Honoraria: BMS. Meeting support: Loxo Oncology. Stock/stock options: Ivuroxa. **GM**: Consultant: Fore Bio. **RY**: Grants: Boehringer Ingelheim, Boundless Bio, Daiichi Sankyo, Pfizer. Personal fees: Revolution, Loxo@Lilly, Zai Lab. Grants and personal fees: Mirati.

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RESULTS

Baseline Characteristics

Demographics		Overall (N=113)	Ovarian Cancer (N=5)[a]
Age, y	Median (min, max)	57 (4, 86)	51 (25, 77)
Sex, n (%)	Female	54 (47.8)	5 (100)
	Male	59 (52.2)	0
Race, n (%)	White	101 (89.4)	4 (80.0)
	Black/African American	5 (4.4)	0
	Asian	3 (2.7)	0
	Missing	4 (3.5)	1 (20.0)
Ethnicity, n (%)	Hispanic or Latino	12 (10.6)	1 (20.0)
ECOG performance status, n (%)	0	43 (38.1)	1 (20.0)
	1	65 (57.5)	4 (80.0)
	≥2	5 (4.4)	0
Prior lines of therapy, n (%)	0	15 (13.3)	0
	1	28 (24.8)	1 (20.0)
	2	16 (14.2)	1 (20.0)
	3	17 (15.0)	0
	≥4	37 (32.7)	3 (60.0)
Prior MAPK-targeted therapies, n (%)	Any MAPK-targeted therapy	34 (30.1)	2 (40.0)
	>1 prior MAPKi[b]	13 (38.2)	1 (50.0)
	BRAFi[b]	24 (70.6)	1 (50.0)
BRAF mutation, n (%)	V600 (class I)	64 (56.6)	3 (60.0)
	V600E	60 (53.1)	3 (60.0)
	Other[c]	4 (3.5)	0
	Class II	36 (31.9)	1 (20.0)
	Fusion	17 (15.0)	0
	Nonfusions	19 (16.8)	1 (20.0)
	Class III	1 (0.9)	0

[a]1 (20.0%) patient with ovarian cancer did not have a documented BRAF alteration.
[b]Percentage is based on the total number of any MAPK-targeted therapy.
[c]Includes V600K and V600R variants.

- **Tumor type:** 99.1% solid tumors, including 5 (4.4%) ovarian; 1 (0.9%) patient with ND-LCH

Disposition

- 89.2 patient-years of cumulative plixorafenib exposure as of February 9, 2024
- 106 (93.8%) patients discontinued treatment due to RECIST/RANO-defined PD or clinical disease progression (n=87), patient withdrawal (n=9), AE (n=5; 1 discontinued due to treatment-related AE [grade 3 bilirubin; dose: 1800 mg BID with PK enhancer]), other reason (n=3), physician decision (n=1), or death (n=1).

Most Common Treatment-Emergent Adverse Events[a] in the Overall Population

		Overall (N=113)					RP2D (N=9)				
	Preferred term	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)	14 (12.4)	9 (8.0)	1 (0.9)	48 (42.5)	4 (44.4)	1 (11.1)	1 (11.1)	0	6 (66.7)
	Increased AST	26 (23.0)	13 (11.5)	3 (2.7)	0	42 (37.2)	4 (44.4)	1 (11.1)	0	0	5 (55.6)
	Increased blood bilirubin	4 (3.5)	8 (7.1)	8 (7.1)	0	20 (17.7)	0	1 (11.1)	0	0	1 (11.1)
	Hyponatremia	1 (0.9)	0	6 (5.3)	1 (0.9)	8 (7.1)	0	0	0	1 (11.1)	1 (11.1)
Symptomatic AEs	Fatigue	17 (15.0)	23 (20.4)	1 (0.9)	0	41 (36.3)	1 (11.1)	1 (11.1)	0	0	2 (22.2)
	Nausea	27 (23.9)	6 (5.3)	2 (1.8)	0	35 (31.0)	4 (44.4)	0	0	0	4 (44.4)
	Diarrhea	15 (13.3)	7 (6.2)	4 (3.5)	0	26 (23.0)	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

[a]≥20% any grade and/or ≥5% grade ≥3 TEAEs

- Among the most common TEAEs in the overall population, the majority of symptomatic AEs were grade 1 in severity.
- Ocular toxicities or secondary skin cancers associated with early BRAFis[2] were not observed.
  - Ocular TEAEs (ie, dry eye, blurred vision) were reported in <5% of patients.
- Grade 4 events were uncommon and no fatal treatment-related adverse events occurred.

Dose Evaluation

- Evaluated total daily doses 900–3600 mg with or without cobicistat 150 mg coadministered QD (PK enhancer that increased plixorafenib exposure 2- to 3-fold).
- Clinically relevant exposures and responses were observed across dose levels and with and without cobicistat, suggesting a broad therapeutic window.
- Based on the totality of the data for safety, PK, pharmacodynamics, and efficacy, the RP2D was determined to be 900 mg QD coadministered with cobicistat for ages ≥10 years.

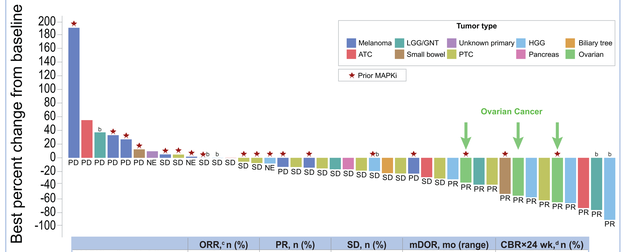
Efficacy in Patients With BRAF V600-Mutated Tumors

Excluding CRC and patients who received BSA-adjusted dosing

- ORR, n (%; 95% CI): 13/43 (30.2%; 17.2, 46.1); Median (range) DOR: 17.8 (3.7, 59.2) months
- Median (range) time to response: 3.6 (1.7, 81.2) months
- 1-year PFS rate: 32.6%; 2-year PFS rate: 16.3% (in the MAPKi-naïve subgroup: 1- and 2-year PFS were 45.8% and 29.2%, respectively)
- Antitumor activity was observed across various tumor types.
- Among the BRAF V600E mutant tumor types, ovarian cancers were of note, as 3/3 patients had PR.

Plixorafenib Best Percent Tumor Change From Baseline in BRAF V600 Adults (N=43, mITT)[a]

Excluding CRC due to known intrinsic resistance through EGFR pathway

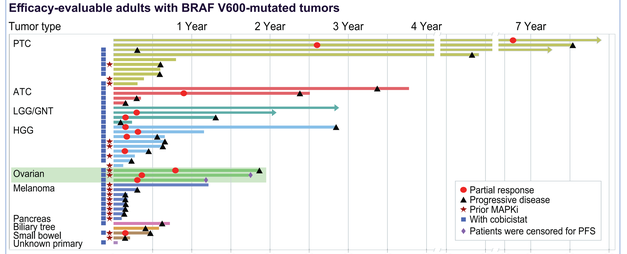


	ORR,[c] n (%)	PR, n (%)	SD, n (%)	mDOR, mo (range)	CBR×24 wk,[d] n (%)
MAPKi naïve (N=24)	10 (41.7)	10 (41.7)	11 (45.8)	17.8 (3.7, 59.2)	17 (70.8)
MAPKi pretreated (N=19)	3 (15.8)	3 (15.8)	7 (36.8)	12.9 (3.9, 16.6+)	7 (36.8)

[a]One patient was excluded due to the unavailability of postbaseline assessment target lesion measurement and best response was not evaluable.
[b]Reported per RANO criteria.
[c]All responses were confirmed.
[d]CBR: CR+PR+MR+(SD≥24 weeks).

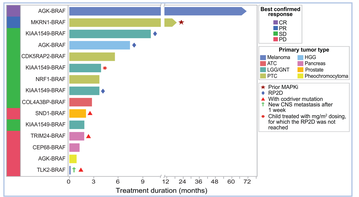
Plixorafenib Treatment Duration

Efficacy-evaluable adults with BRAF V600-mutated tumors



Efficacy in BRAF Fusion Tumors

- ORR: 14.3% (2/14) of adults
  - CR (1): melanoma, DOR 66.7+ months
  - PR (1): PTC, DOR 9.2+ months
  - SD: 7 (50%), lasting up to 7.5 months
  - 5 had PD (3 with co-occurring driver mutations).
- One pediatric patient with glioma receiving mg/m² dosing had SD.



Demographics, Safety, and Efficacy in Patients With Ovarian Cancer

- 5 patients with a median (min, max) age of 51.0 (25, 77) years
- 3 patients had BRAF V600 ovarian cancer (serous, papillary, low-grade serous), and their treatment outcomes are detailed here.
- 1 patient had a class II nonfusion and 1 patient had no documented BRAF alteration.
- All patients had received ≥1 prior line of treatment.
  - 2 of 3 patients with BRAF V600 mutations received prior MAPK-targeted therapy.
- Patients received doses ranging from 900–3600 mg of plixorafenib in combination with cobicistat.

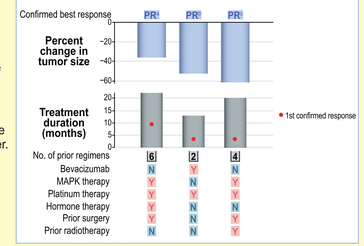
Safety (n=5)

- No patients with ovarian cancer experienced DLTs.
- 2 patients experienced grade 3 or 4 AEs, including transient increase in ALT, AST, or bilirubin.
  - These 2 patients experienced grade 3 SAEs of jugular vein thrombosis, nausea, renal failure, small intestinal obstruction, and vomiting (all assessed as not treatment related).
- There were no treatment discontinuations due to TEAEs in the 5 patients with ovarian cancer.

Efficacy: BRAF V600-Mutated Ovarian Cancer (n=3)

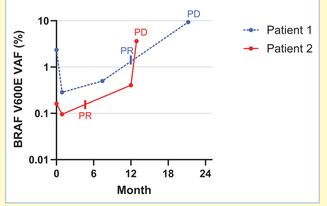
- All 3 patients had PR
- TTR: 3.5, 3.6, and 9.5 months
- DOR: 9.2, 12.9, and 16.6 months
- PFS: 12.7, 20.2, and 22.4 months

Efficacy and Treatment Duration by Patient



[a]Discontinued treatment due to radiographic disease progression.
[b]PR at last tumor assessment before discontinuing treatment approximately one month later due to disease progression.
[c]Discontinued treatment due to clinical disease progression.

Longitudinal ctDNA Analysis (Log Scale)



Translational Data

- 3/3 patients with BRAF V600-mutated ovarian cancer did not have any concurrent driver mutations (based upon documented local NGS testing results).
- Longitudinal ctDNA samples were available from 2 participants with BRAF V600-mutated ovarian cancer.
  - Both showed a decrease of BRAF V600E variant allelle fractions (VAFs) after 4 weeks of plixorafenib, indicating rapid molecular response to treatment.
  - % VAF increased to above pretreatment levels at the time of disease progression.

CONCLUSIONS

- Plixorafenib achieved clinically active exposures across dose levels, including with and without the PK booster.
- Plixorafenib demonstrated a favorable benefit risk profile, with ORR 32% in BRAF V600-mutated advanced solid tumors and low rate of symptomatic AEs.
- In patients with ovarian cancer:
  - No DLTs
  - 3/3 with BRAF V600-mutated ovarian cancer had PR, all with duration of response ≥9 months.
  - Molecular response was observed in 2/2 with available data.
- The Forte study, a basket study in tumors harboring BRAF V600 mutations or BRAF fusions, including patients with ovarian cancer, is currently ongoing (NCT05503797).