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A Phase 1 Clinical Trial Evaluating Monotherapy With Exarafenib (KIN-2787), a Highly Selective Pan-RAF Inhibitor, in *BRAF*-Altered Solid Tumors and *NRAS*-Mutant Melanoma

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Disclosure Information

Alexander I. Spira, MD, PhD

I have the following relevant financial relationships to disclose:

Employee of: No relationships to disclose

Consultant for: Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo, Astra Zeneca, Regeneron, Lilly, Black Diamond Therapeutics, Array BioPharma, AstraZeneca/MedImmune, Merck, Bristol-Myers Squibb, Blueprint Medicines

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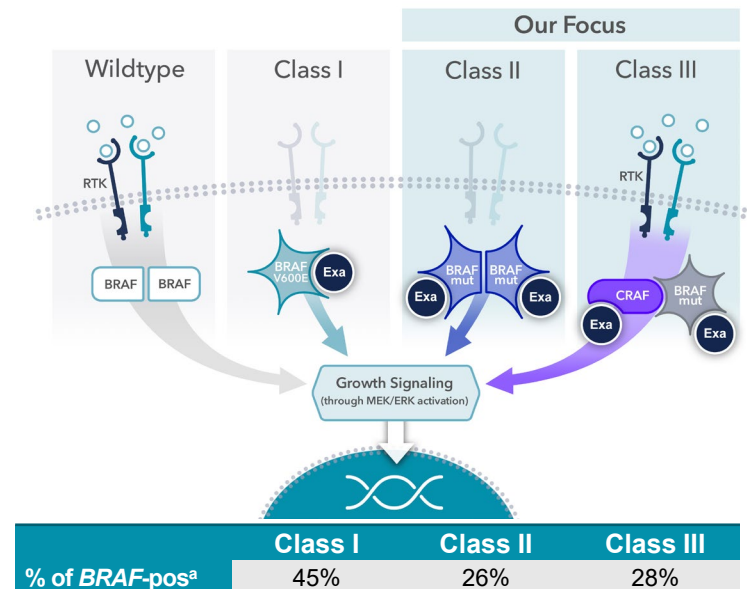
My additional financial relationship disclosures are:

Leadership at: NEXT Oncology Virginia

Patients With Tumors Harboring *BRAF* Class II/III Alterations Represent a Broad Population With Significant Unmet Need^{1,2}

- *BRAF* Class II/III alterations comprise more than half of oncogenic *BRAF* alterations^{1,a}
 - Estimated to occur in 2.1% of solid tumors²
 - Most common in NSCLC, CRC, melanoma, and prostate cancer²
- *BRAF* Class II/III alterations are associated with poorer clinical outcomes²
 - mOS was shorter for pts with NSCLC or melanoma with Class II/III vs Class I alterations¹
- There are no approved targeted therapies for tumors with *BRAF* Class II & III alterations^{1,2}
 - Novel *BRAF*-targeted strategies are also needed for *NRAS*^{mut} melanoma, which is refractory to Class I inhibitors^{3,4}

Classes of *BRAF* Alterations in Cancer^{1,2}



^a Based on a real-world analysis of 5896 pts with metastatic/advanced cancers harboring *BRAF* alterations from a clinical databased of 160,000+ pts profiled by the Guardant360[®] assay. Multiple *BRAF* alterations were identified in 1.8% of pts (107/5896). ^b Median OS from metastatic diagnosis of NSCLC (n=938) or melanoma (n=333).

Abbreviations: BRAF, B-Raf serine/threonine protein kinase; CRAF, also known as Raf-1; CRC, colorectal cancer; ERK, extracellular signal-regulated kinase; Exa, exarafenib; MEK, mitogen-activated protein kinase; mut, mutation; mOS, median overall survival; NRAS^{mut}, neuroblastoma ras viral oncogene homolog mutated; NSCLC, non-small cell lung cancer; pos, positive; pts, patients; Raf, serine/threonine kinase; RTK, receptor tyrosine kinase.

1. Severson P, et al. Poster presented at: 2022 AACR Annual Meeting; April 8–13; New Orleans, LA. Abstract 4122. 2. Severson P, et al. Poster presented at: ESMO Targeted Anticancer Therapies Congress 2022. March 7–8 [Virtual]. Abstract 40P. 3. Dorard C, et al. *Nat Commun.* 2017;8:15262. 4. Echevarria-Vargas IM, Villanueva J. *Melanoma Manag.* 2017;4(4):183–186.

Exarafenib Is a Pan-RAF Inhibitor Designed to Target *BRAF* Class II/III Alterations and *NRAS*^{mut} Melanoma

Exarafenib Addresses Key Factors Critical for Successful Pan-RAF Inhibition

1 High selectivity

- Kinome profiling of >600 kinases demonstrated very high selectivity for RAF family kinases

2 Broad coverage of *BRAF* Class II & III alterations

- Potent inhibition of MAPK signaling in *BRAF* Class II- & III-driven cell lines with selectivity over wildtype *BRAF*

3 Equipotent inhibition of RAF kinases

- Equal inhibition across both RAF kinases in the dimer, reducing potential for paradoxical activation

4 Optimized PK profile

- High aqueous solubility, significant plasma-free fraction (~7%) enables robust exposures and target coverage

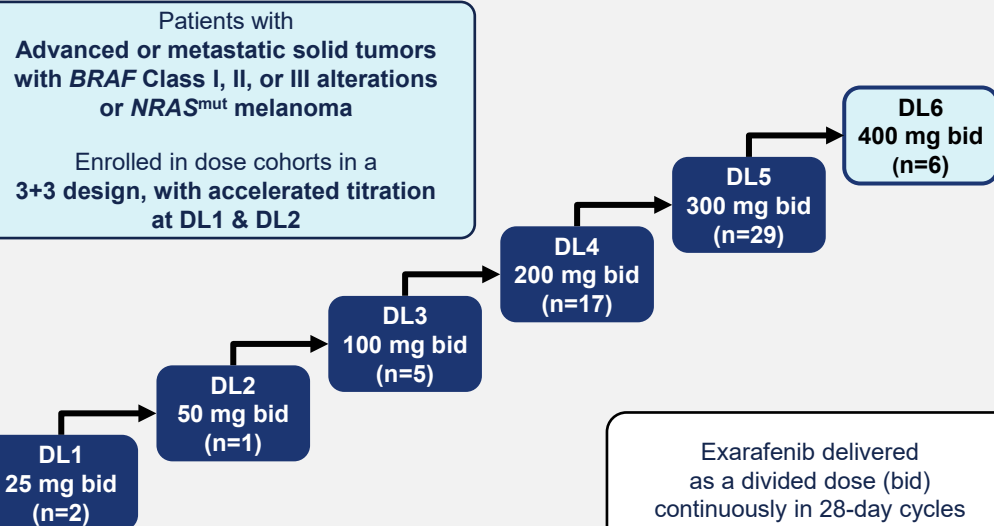
Exarafenib is a highly selective pan-RAF inhibitor that targets RAF dimer signaling while minimizing paradoxical activation of MAPK in wildtype signaling

KN-8701: A First-in-Human Phase 1/1b Study Evaluating KIN-2787 in Adult Patients With *BRAF* and *NRAS* Mutation-Positive Solid Tumors^{1,2}

Part A1: Monotherapy Dose Escalation Schema

60 patients in safety population across 6 dose levels

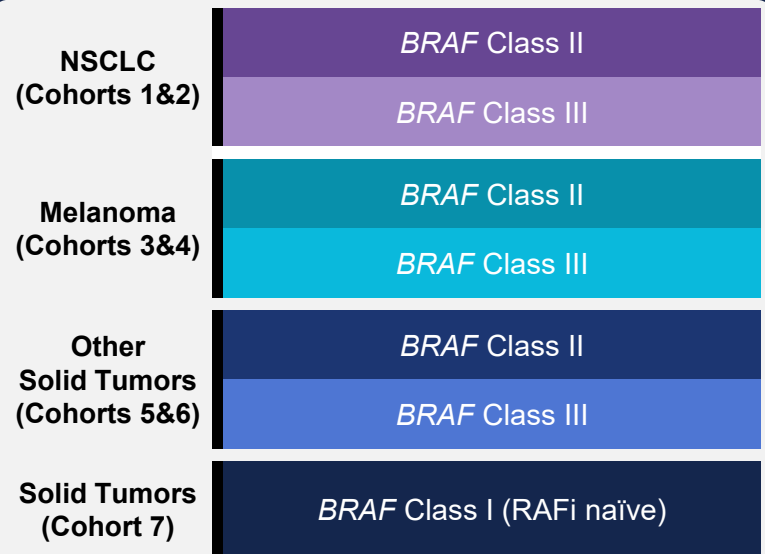
49 patients are efficacy evaluable



Part B: Monotherapy Dose Expansion

Separates *BRAF* Class II & Class III

Adds *BRAF* Class I RAFi-naïve patients



Patients with solid tumors with *BRAF* Class I mutations pretreated with RAFi and patients with *NRAS*^{mut} melanoma continue to enroll in KN-8701 Part A2, a dose escalation study evaluating exarafenib + binimetinib

KN-8701 Part A1: Dose Escalation to Determine Safety and Pharmacokinetic Properties of Exarafenib Monotherapy^{1,2}

Part A1: Monotherapy Dose Escalation

Enrolled Cohorts

Patients with
Advanced or metastatic solid tumors
with *BRAF* Class I, II, or III alterations
or *NRAS*^{mut} melanoma

Enrolled in dose cohorts in a
3+3 design, with accelerated titration
at DL1 & DL2

DL1
25 mg bid
(n=2)

DL2
50 mg bid
(n=1)

DL3
100 mg bid
(n=5)

DL4
200 mg bid
(n=17)

DL5
300 mg bid
(n=29)

DL6
400 mg bid
(n=6)

Exarafenib delivered
as a divided dose (bid)
continuously in 28-day cycles

Objectives and Assessments

Primary Objectives

- Determine safety and tolerability of exarafenib monotherapy, including DLTs
- Identify MTD and dose for subsequent investigation

Secondary Objective

- Characterize **PK properties** and effect of food on exarafenib including T_{max} , C_{max} , and AUC

Assessments

- DLT assessment period is 28 days
- Tumor assessments (per RECIST v1.1) every 2 cycles (8 weeks)

Baseline Demographics and Disease Characteristics

Baseline demographics	Patients (N=60) ^a
Age, median (range)	63 (33–84)
Male, n (%)	33 (55.0)
Race, n (%)	
American Indian or Alaska Native	0
Asian	4 (6.7)
Black	1 (1.7)
Native Hawaiian or Pacific Islander	0
White	43 (71.7)
Other	4 (6.7)
Not reported	8 (13.3)
Ethnicity, n (%)	
Hispanic or Latino	2 (3.3)
Non-Hispanic or Latino	49 (81.7)
Not reported	9 (15.0)

Disease characteristics	Patients (N=60) ^a
Prior therapies, median (range)	3 (1–11)
ECOG PS, n (%)	
0	20 (33.3)
1	38 (63.3)
2	2 (3.3)
<i>BRAF</i> / <i>NRAS</i> alteration, n (%)	
<i>BRAF</i> Class I	25 (41.7)
<i>BRAF</i> Class II	8 (13.3)
<i>BRAF</i> Class III	18 (30.0)
<i>NRAS</i>	9 (15.0)
Tumor type, n (%)	
CRC	20 (33.3)
Melanoma	17 (28.3)
NSCLC	11 (18.3)
Biliary	3 (5.0)
Thyroid (papillary)	3 (5.0)
Others ^b	6 (10.0)

^a Analyses based on February 28, 2023, data cutoff. ^b Spindle cell sarcoma, appendiceal carcinoma, GIST, breast cancer, skin SCC (apocrine), and ampullary (n=1 each).

Abbreviations: *BRAF*, B-Raf serine/threonine protein kinase; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GIST, gastrointestinal stromal tumors; *NRAS*, neuroblastoma ras viral oncogene homolog; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma.

Data on File. Kinnate Biopharma [2023].

Exarafenib Was Well Tolerated Among Patients With Solid Tumors With *BRAF* or *NRAS* Alterations

- 2 DLTs occurred at the 400-mg dose level (Gr 3 acneiform rash, Gr 3 macular rash)
- Relative dose intensity was 97% across all DLs
 - Dose interruptions occurred in 16% of pts across all DLs, and 20% of pts at DL5 (300 mg bid)
 - Dose reductions occurred in 14% of pts across all DLs and at DL5 (300 mg bid)

2 pts (3.3%) discontinued exarafenib due to TRAEs

- TRAEs occurred in 73.3% of pts across all DLs and in 79.3% of pts treated at DL5 (300 mg bid)
 - Most TRAEs were Gr 1/2
 - Gr 3/4 TRAEs occurred in 18.3% of pts and treatment-related SAEs occurred in 8.3% of pts (12 events)
 - The most common TRAEs were rash, dermatitis acneiform, increased AST, increased ALT, and nausea

The MTD of exarafenib 300 mg bid (DL5) was selected for dose expansion (Part B)

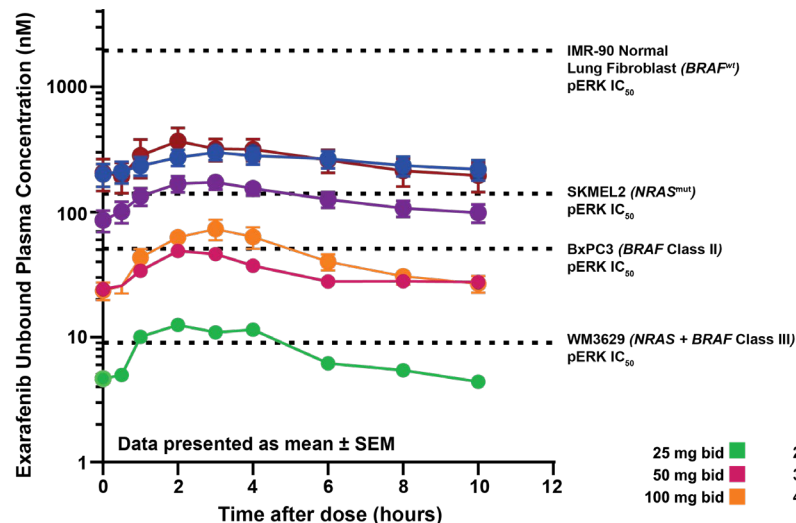
TRAEs (≥5%) in the Safety Population (N=60)^{a,b}

TRAEs	Any Grade	Grade 3/4
Any TRAE	44 (73.3%)	11 (18.3%)
Gastrointestinal disorders		
Nausea	10 (16.7%)	0
Vomiting	5 (8.3%)	0
Oral pain	3 (5.0%)	0
General disorders		
Fatigue	8 (13.3%)	0
Asthenia	5 (8.3%)	0
Laboratory investigations		
AST increased	11 (18.3%)	4 (6.7%)
ALT increased	10 (16.7%)	5 (8.3%)
Blood alkaline phosphatase increased	3 (5.0%)	0
Blood bilirubin increased	3 (5.0%)	0
Blood creatine phosphokinase increased	4 (6.7%)	0
Metabolism and nutrition disorders		
Decreased appetite	6 (10.0%)	0
Musculoskeletal and connective tissue disorders		
Myalgia	4 (6.7%)	0
Nervous system disorders		
Dizziness	3 (5.0%)	0
Skin and subcutaneous tissue disorders		
Rash (any) ^c	18 (30.0%)	1 (1.7%)
Dermatitis acneiform	13 (21.7%)	2 (3.3%)
Pruritus	9 (15.0%)	0

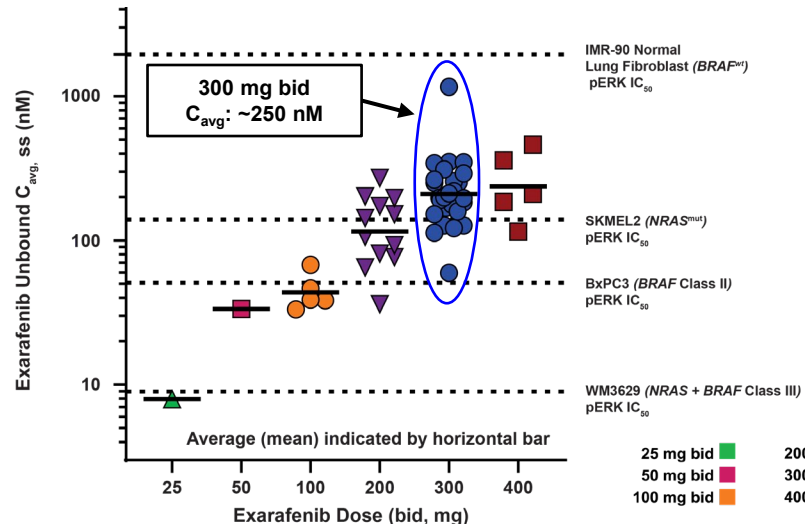
^a Analyses based on February 28, 2023 data cutoff. ^b The safety population included pts treated with exarafenib across all dose levels. ^c Includes rash, rash macular, rash papular, rash maculopapular, and rash morbilliform. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; DL, dose level; DLT, dose-limiting toxicity; Gr, grade; MTD, maximum tolerated dose; NRAS, neuroblastoma ras viral oncogene homolog; pts, patients; SAE, serious adverse event; TRAE, treatment-related adverse event. Data on File. Kinnate Biopharma [2023].

Pharmacokinetic Analyses Demonstrate Dose Proportional Exposure With Exarafenib

Unbound Exarafenib Exposures at Steady State^a (nM; All Dose Levels)



Unbound Average Steady-State Exarafenib Exposure^a (nM; All Dose Levels)



Exarafenib had a half-life of ~8 hours and exhibited near-linear pharmacokinetics across dose levels

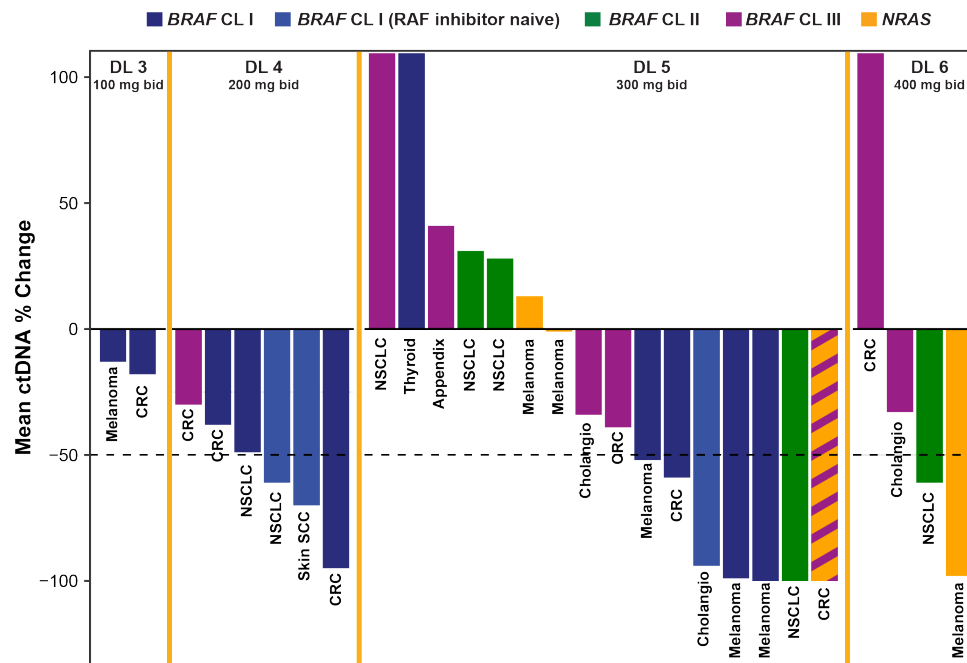
^a Analyses based on March 16, 2023, data cutoff.

Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; *BRAF*^{wt}, BRAF, B-Raf serine/threonine protein kinase wildtype; BxPC3, pancreas adenocarcinoma human cell line; $C_{avg,ss}$, average concentration; IC₅₀, half maximal inhibitory concentration; IMR-90, human embryonic lung fibroblasts; *NRAS*^{mut}, neuroblastoma ras viral oncogene homolog mutated; pERK, phosphorylated extracellular signal-regulated kinase; RAF, serine/threonine protein kinase; SEM, standard error of the mean; SKMEL2, human malignant melanoma cell line; ss, steady state; WM3629, metastatic human melanoma cell line.

Data on File. Kinnate Biopharma [2023].

Exarafenib Achieved Molecular Responses Across Cancer Types and Genetic Alterations

Mean Change in ctDNA Levels From Baseline^{a,b}



- 20/28 (71%) pts evaluable for molecular response had decreases in mean ctDNA levels
- 12/28 (43%) pts had a molecular response, including 3 pts with a complete molecular response

Patients With Molecular Responses (>50% decrease in ctDNA)

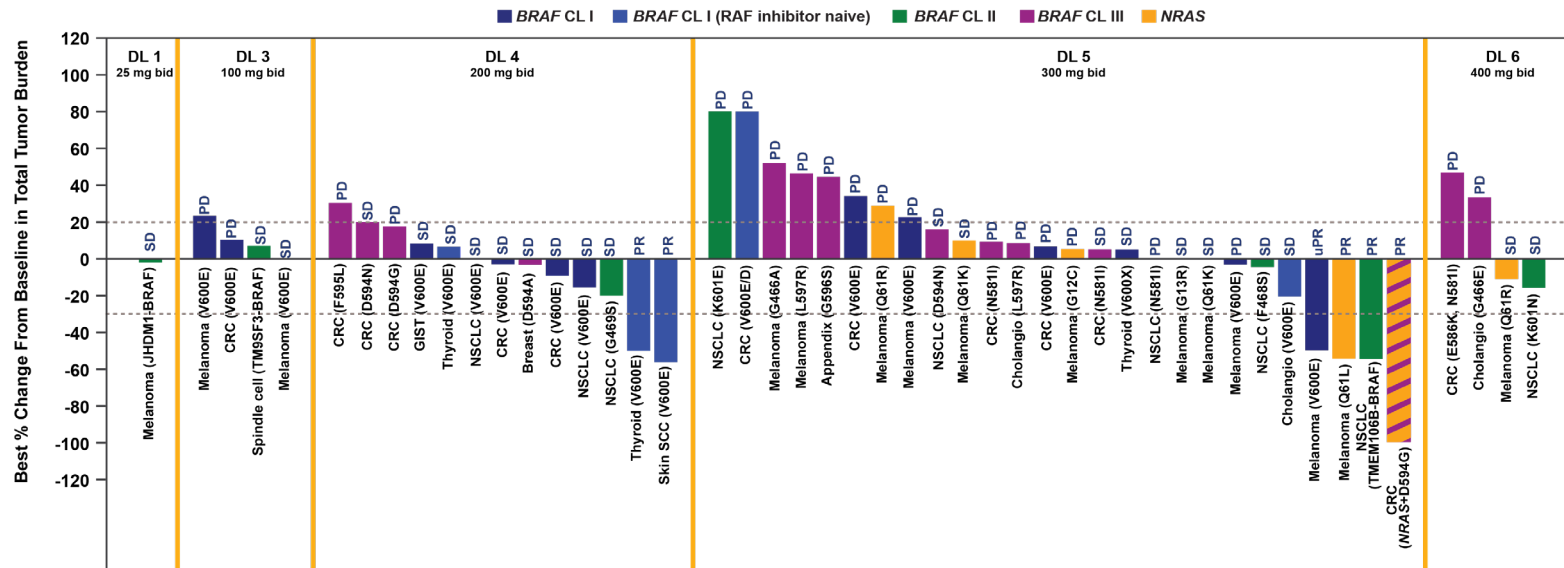
Population	No. of responders % (n/N)	Cancer types
BRAF Class I	62 (8/13)	NSCLC, CRC, skin SCC, melanoma, cholangio
BRAF Class II	50 (2/4)	NSCLC
NRAS	50 (1/2)	Melanoma
NRAS + BRAF Class III	100 (1/1)	CRC

^a Analyses based on March 17, 2023, data cutoff. ^b Change was calculated from baseline to C2D1 or C3D1.

Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; C2D1, cycle 2 day 1; C3D1, cycle 3 day 1; CL, class; Cholangio, cholangiocarcinoma; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DNA, deoxyribonucleic acid; DL, dose level; Mel, melanoma; NSCLC, non-small cell lung cancer; NRAS, neuroblastoma ras viral oncogene homolog; pts, patients; RAF, serine/threonine protein kinase; SCC, squamous cell carcinoma. Data on File. Kinntate Biopharma [2023].

Responses With Exarafenib Monotherapy in Patients With Solid Tumors Harboring *BRAF* or *NRAS* Alterations

Response With Exarafenib Monotherapy by Dose Level and Genetic Alteration^{a-d}



12/26 (46%) pts treated at DL5 (300 mg bid) experienced clinical benefit (4 had PR/uPR; 8 had SD)

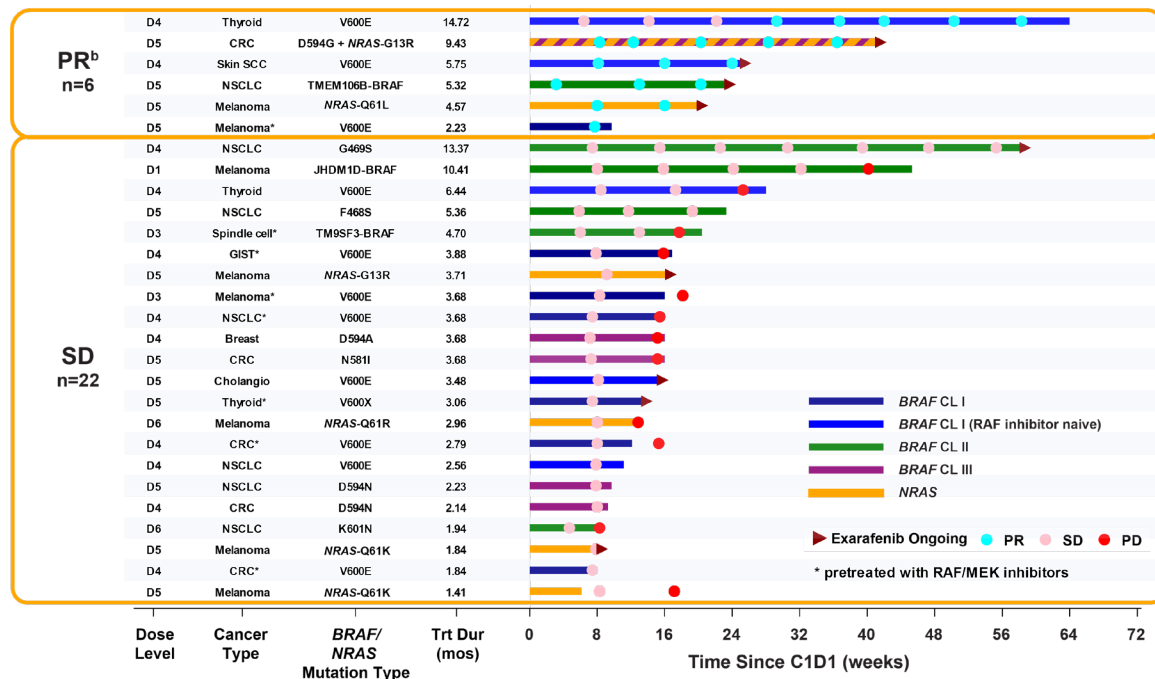
^a Analyses based on February 28, 2023, data cutoff. ^b Efficacy evaluable population includes all participants with documented *BRAF* (or melanoma with *NRAS*) genomic alterations who received at least 1 dose of exarafenib and had ≥ 1 measurable lesion at baseline for disease response assessment and at least 1 post-baseline efficacy assessment per RECIST v1.1. ^c One pt (DL1, 25 mg bid) was not included as pt had a baseline measurable lesion, but had PD based on appearance of a new lesion prior to post-baseline assessment (no percentages could be calculated). ^d Pts were included in the DL at which they achieved or confirmed their best response.

Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; CL, class; CRC, colorectal cancer; DL, dose level; GIST, gastrointestinal stromal tumor; MEK, mitogen-activated protein kinase kinase; NRAS, neuroblastoma ras viral oncogene homolog; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; pt, patient; RAF, serine/threonine protein kinase; RECIST, Response Evaluation Criteria in Solid Tumours; SCC, squamous cell carcinoma; SD, stable disease; uPR, unconfirmed PR.

Data on File. Kinnate Biopharma [2023].

Responses Were Durable With Exarafenib Monotherapy Across Tumor Types and Genetic Alterations

Duration of Treatment Among Patients With Clinical Benefit^a



- Response rates at DL5 (300 mg bid):
 - BRAF Class II: 33% (1/3)
 - NRAS: 29% (2/7)
- Mean duration of therapy:
 - Pts with PR: 7.0 mos
 - Pts with SD: 4.0 mos
- Treatment is ongoing for 4 of 6 responders

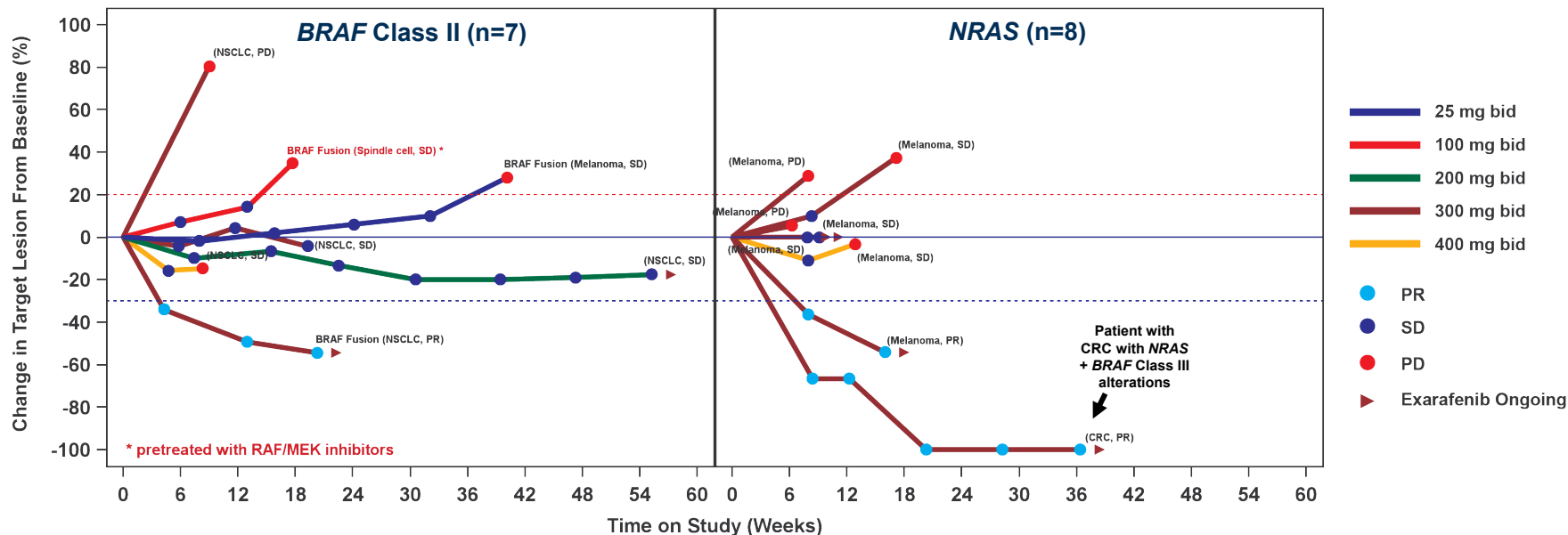
^a Analyses based on February 28, 2023, data cutoff. ^b There were 6 partial responses, 5 of which were confirmed.

Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; C1D1, cycle 1 day 1; CL, class; Cholangio, cholangiocarcinoma; CRC, colorectal cancer; DL, dose level; dur, duration; GIST, gastrointestinal stromal tumor; MEK, mitogen-activated protein kinase kinase; mos, months; NRAS, neuroblastoma ras viral oncogene homolog; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; pts, patients; RAF, serine/threonine protein kinase; SCC, squamous cell carcinoma; SD, stable disease; Trt, treatment.

Data on File. Kinnta Biopharma [2023].

Rapid and Prolonged Responses Occurred Among Patients With *BRAF* Class II or *NRAS* Alterations

Target Lesion Assessment Among Patients With *BRAF* Class II and/or *NRAS* Alterations^{a,b}



3 of 15 patients with *BRAF* Class II or *NRAS* alterations achieved a PR in <12 weeks of exarafenib therapy

^a Analyses based on February 28, 2023, data cutoff. ^b Target tumor reduction may not match best overall response assessment, which takes into consideration nontarget lesions and the observations of new lesions as per RECIST v1.1. Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; CL, class; CRC, colorectal cancer; MEK, mitogen-activated protein kinase kinase; NRAS, neuroblastoma ras viral oncogene homolog; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RAF, serine/threonine protein kinase; SD, stable disease. Data on File. Kinnate Biopharma [2023].

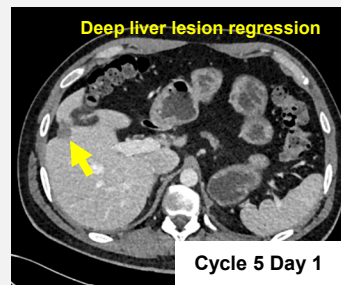
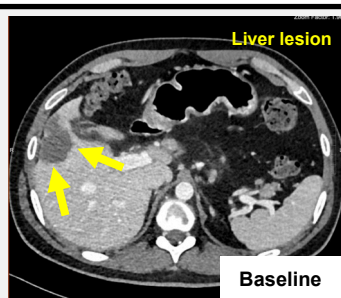
Patient Data Provide Rationale for Investigation of Exarafenib Monotherapy in Challenging Settings

NSCLC^a

BRAF Class II Fusion

DL6 (400 mg bid) → DL5 (300 mg bid)

- **PR** on first scan with rapid response (34% reduction on 2 target lesions)
- Dose reduced after drug interruption due to rash
- **PR** confirmed on 2nd and 3rd scans (54% reduction on target lesions; significant reductions on nontarget lesions)
- Complete molecular response by C3D1
- Exarafenib treatment ongoing after ~5 months



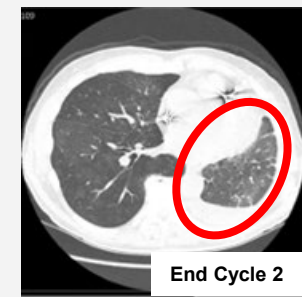
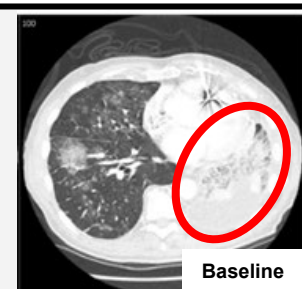
Sustained response after dose reduction to 300 mg bid

NSCLC^b

BRAF Class II SNV (G469S)

DL4 (200 mg bid)

- Weaned off supplemental oxygen after 2 weeks of treatment (87% to 100% O₂ saturation)
- Significant reduction in nontarget disease
- Prolonged **SD** (20% reduction on target lesions) on 7 successive scans
- Exarafenib treatment ongoing after 13+ months



Prolonged tumor control at a suboptimal dose

^a Pt received pembrolizumab, pemetrexed, cisplatin, and cabozantinib. ^b Pt received pembrolizumab, pemetrexed, and carboplatin.

Abbreviations: bid, twice daily; BRAF, B-Raf serine/threonine protein kinase; C3D1, cycle 3 day 1; DL, dose level; NSCLC, non-small cell lung cancer; PR, partial response; pt, patient; SD, stable disease; SNV, single nucleotide variant. Data on File. Kinnate Biopharma [2023].

Conclusions

- Exarafenib exhibited dose-linear pharmacokinetics and reached steady-state unbound exposures exceeding those required for target coverage
- Exarafenib monotherapy was well-tolerated by patients with solid tumors harboring *BRAF* Class I, II, or III alterations or *NRAS*^{mut} melanoma
 - DLTs at 400 mg bid included Grade 3 acneiform rash and Grade 3 macular rash
 - The most common toxicities were skin-related, including rashes, dermatitis acneiform, and pruritis
- Exarafenib monotherapy yielded meaningful clinical activity in a heavily pretreated population of patients with a variety of tumor types
 - Responses were rapid and durable, with activity observed in patients with tumors harboring *BRAF* Class II/III and/or *NRAS* alterations

Exarafenib 300 mg bid will be evaluated in cohorts of patients with NSCLC, melanoma, or other solid tumors harboring *BRAF* Class I/II/III alterations in Part B of the KN-8701 study

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ANNUAL MEETING

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**Thank you for your attention.
Questions?**