Buy

Kinnate Biopharma Inc. (KNTE)

Framing the upcoming Phase 1 KIN-2787 data; Reiterate Buy

KNTE	12m Price Target: **$29.00**	Price: **$11.73**	Upside: **147.2%**

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Initial KIN-8701 data coming into scope; risk/reward biased to the upside, in our view. KNTE's Phase 1 study of KIN-2787 (pan-RAF inhibitor) in *BRAF*-mutant solid tumors is underway with initial monotherapy data set to read out in 4Q22. Recall that this trial will enroll approximately 115 patients with Class I, II, or III *BRAF* cancers with the dose escalation portion focusing on safety, PK/PD, and initial sign of activity in order to inform the dose for the subsequent dose expansion portion of the study. Ahead of the data, we think that investors are primarily looking for signs of activity in Class II and III tumors for which there is currently no approved therapy. The company has also expanded the study to include a combination portion with binimetinib (MEK inhibitor). While success in Class II and III *BRAF* tumors has historically been limited, we are encouraged by the preclinical evidence suggesting KIN-2787's differentiation versus competing assets, namely the drug's selective kinome profile via radiometric kinase inhibition assays and superior aqueous solubility, and competitor Day One's (DAWN, not covered) early clinical success in a rare pediatric indication with *BRAF* fusions (link). With the stock having pulled back meaningfully (along with other targeted oncology names) over the past year, we think KNTE shares are set up well heading into the read out, with both the bar for safety (comparable to the standard of care) and efficacy (ORR of 25-30%+) being attainable mostly in Class II vs. Class III tumors, in our view. We reiterate our Buy rating and $29 price target ahead of the upcoming readout.

Key Data

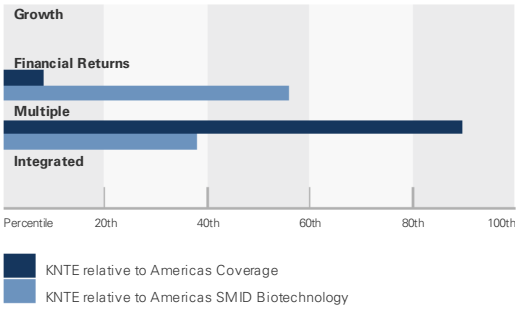
Market cap: $516.1mn
Enterprise value: $296.4mn
3m ADTV: $1.8mn
United States
Americas SMID Biotechnology
M&A Rank: 3

GS Forecast

	12/21	12/22E	12/23E	12/24E
Revenue ($ mn)	0.0	0.0	0.0	0.0
EBITDA ($ mn)	(90.0)	(113.5)	(123.8)	(133.2)
EBIT ($ mn)	(90.1)	(113.8)	(125.2)	(133.4)
EPS ($)	(2.06)	(2.31)	(2.28)	(2.30)
P/E (X)	NM	NM	NM	NM
EV/EBITDA (X)	NM	NM	NM	NM
FCF yield (%)	(6.4)	(16.7)	(15.4)	(16.2)
Dividend yield (%)	0.0	0.0	0.0	0.0
Net debt/EBITDA (X)	–	–	–	–

	6/22	9/22E	12/22E	3/23E
EPS ($)	(0.62)	(0.64)	(0.61)	(0.54)

GS Factor Profile



Source: Company data, Goldman Sachs Research estimates. See disclosures for details.

Portfolio Manager Summary

Risk/reward biased to an upside potential with positive KIN-2787 Phase 1 to be likely. KNTE will report initial monotherapy

Buy

Kinnate Biopharma Inc. (KNTE)

Rating since Dec 28, 2020

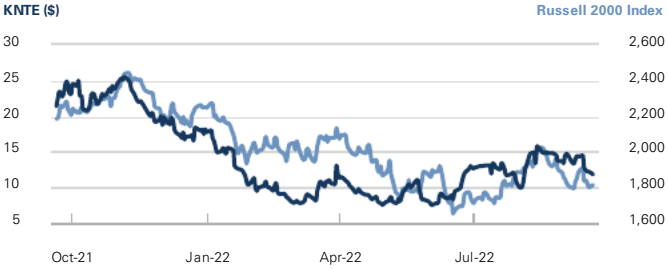
Ratios & Valuation

	12/21	12/22E	12/23E	12/24E
P/E (X)	NM	NM	NM	NM
EV/EBITDA (X)	NM	NM	NM	NM
EV/sales (X)	–	–	–	–
FCF yield (%)	(6.4)	(16.7)	(15.4)	(16.2)
EV/DACF (X)	NM	NM	NM	NM
CROCI (%)	(65.0)	(41.2)	(38.8)	(37.6)
ROE (%)	(25.2)	(28.6)	(29.3)	(31.3)
Net debt/EBITDA (X)	–	–	–	–
Net debt/equity (%)	(46.9)	(55.0)	(30.0)	(43.5)
Interest cover (X)	–	–	–	–
Inventory days	–	–	–	–
Receivable days	–	–	–	–
Days payable outstanding	NM	NM	NM	NM

Growth & Margins (%)

	12/21	12/22E	12/23E	12/24E
Total revenue growth	NM	NM	NM	NM
EBITDA growth	(150.6)	(26.1)	(9.1)	(7.5)
EPS growth	61.0	(12.3)	1.4	(1.0)
DPS growth	NM	NM	NM	NM
Gross margin	NM	NM	NM	NM
EBIT margin	NM	NM	NM	NM

Price Performance



	3m	6m	12m
Absolute	25.3%	8.6%	(50.5)%
Rel. to the Russell 2000 Index	15.1%	25.0%	(38.9)%

Source: FactSet. Price as of 19 Sep 2022 close.

Income Statement ($ mn)

	12/21	12/22E	12/23E	12/24E
Total revenue	0.0	0.0	0.0	0.0
Cost of goods sold	0.0	0.0	0.0	0.0
SG&A	(22.9)	(30.4)	(33.5)	(36.1)
R&D	(67.2)	(83.4)	(91.8)	(97.3)
Other operating inc./(exp.)	–	–	–	–
EBITDA	**(90.0)**	**(113.5)**	**(123.8)**	**(133.2)**
Depreciation & amortization	(0.1)	(0.3)	(1.4)	(0.2)
EBIT	**(90.1)**	**(113.8)**	**(125.2)**	**(133.4)**
Net interest inc./(exp.)	2.3	1.5	4.3	0.4
Income/(loss) from associates	–	–	–	–
Pre-tax profit	**(89.8)**	**(111.8)**	**(120.9)**	**(133.0)**
Provision for taxes	0.0	0.0	0.0	0.0
Minority interest	–	–	–	–
Preferred dividends	–	–	–	–
Net inc. (pre-exceptionals)	**(89.8)**	**(111.8)**	**(120.9)**	**(133.0)**
Net inc. (post-exceptionals)	**(89.8)**	**(111.8)**	**(120.9)**	**(133.0)**
EPS (basic, pre-except) ($)	**(2.06)**	**(2.31)**	**(2.28)**	**(2.30)**
EPS (diluted, pre-except) ($)	**(2.06)**	**(2.31)**	**(2.28)**	**(2.30)**
EPS (ex-ESO exp., dil.) ($)	**--**	**--**	**--**	**--**
DPS ($)	–	–	–	–
Div. payout ratio (%)	0.0	0.0	0.0	0.0
Wtd avg shares out. (basic) (mn)	43.6	48.3	53.0	57.8
Wtd avg shares out. (diluted) (mn)	43.6	48.3	53.0	57.8

Balance Sheet ($ mn)

	12/21	12/22E	12/23E	12/24E
Cash & cash equivalents	149.7	254.7	108.7	211.7
Accounts receivable	0.0	0.0	0.0	0.0
Inventory	–	–	–	–
Other current assets	109.0	203.1	253.4	278.5
Total current assets	**258.7**	**457.9**	**362.1**	**490.2**
Net PP&E	1.0	7.1	6.2	6.1
Net intangibles	–	–	–	–
Total investments	105.4	46.6	46.6	46.6
Other long-term assets	1.8	3.1	3.1	3.1
Total assets	**366.9**	**514.7**	**417.9**	**546.0**
Accounts payable	3.1	2.1	2.5	2.8
Short-term debt	–	–	–	–
Current lease liabilities	–	0.8	0.8	0.8
Other current liabilities	9.2	9.5	13.2	16.5
Total current liabilities	**12.4**	**12.4**	**16.6**	**20.1**
Long-term debt	–	–	–	–
Non-current lease liabilities	–	3.7	3.7	3.7
Other long-term liabilities	–	–	–	–
Total long-term liabilities	**0.0**	**3.7**	**3.7**	**3.7**
Total liabilities	**12.4**	**16.2**	**20.3**	**23.8**
Preferred shares	–	–	–	–
Total common equity	**319.5**	**463.5**	**362.7**	**487.2**
Minority interest	35.0	35.0	35.0	35.0
Total liabilities & equity	**366.9**	**514.7**	**417.9**	**546.0**
BVPS ($)	7.33	9.59	6.84	8.43

Cash Flow ($ mn)

	12/21	12/22E	12/23E	12/24E
Net income	(89.8)	(111.8)	(120.9)	(133.0)
D&A add-back	0.1	0.3	1.4	0.2
Minority interest add-back	–	–	–	–
Net (inc)/dec working capital	1.6	(0.9)	3.8	3.5
Others	15.1	19.8	20.0	20.0
Cash flow from operations	**(71.1)**	**(91.8)**	**(95.6)**	**(109.3)**
Capital expenditures	(0.8)	(2.7)	(0.4)	(0.2)
Acquisitions	–	–	–	–
Divestitures	--	–	--	--
Others	(179.8)	(38.8)	(50.0)	(25.0)
Cash flow from investing	**(180.6)**	**(41.5)**	**(50.4)**	**(25.2)**
Dividends paid	–	–	–	–
Share issuance/(repurchase)	--	237.5	--	237.5
Inc/(dec) in debt	--	--	--	--
Others	36.2	0.8	–	–
Cash flow from financing	**36.2**	**238.3**	**0.0**	**237.5**
Total cash flow	**(215.4)**	**105.1**	**(146.1)**	**103.1**
Free cash flow	(71.8)	(94.4)	(96.1)	(109.4)
Free cash flow per share (basic) ($)	(1.65)	(1.95)	(1.81)	(1.89)

Source: Company data, Goldman Sachs Research estimates.

data of KIN-2787 (a pan-RAF inhibitor) in cancer patients harboring *BRAF* Class I, II, and III mutations (~4% of all tumors), though interest will likely be focused on its initial efficacy in *BRAF* Class II & III population. Three BRAF inhibitors have been approved by the FDA (sales were ~$2bn in 2021), but they lack meaningful efficacy (just an 11.7% response rate) in Class II & III *BRAF* patients (~50% of all *BRAF* mutations), leaving a significant unmet need for this population with an attractive commercial opportunity available to KNTE and competitors (we estimate an initial addressable market of 21,000 NSCLC and 6,000 melanoma patients). In addition, targeting *BRAF* Class II & III mutated cancers through inhibiting BRAF dimers have been validated in both preclinical and clinical settings, though the earlier development of *BRAF* Class II & III targeted kinase inhibitors were not successful possibly due to poor pharmacological properties, leading to a suboptimal safety and efficacy profile. In our view, KIN-2787's optimized PK properties (high selectivity, high solubility, low protein binding, absence of pathway rebound, etc.) are differentiated from several key competing assets, which positions KIN-2787 well as a potential best-in-class drug for Class II and III mutations. Importantly, the FDA recently approved Novartis' (NVS, covered by Keyur Parekh) dabrafenib in combination with trametinib as a tumor-agnostic therapy for *BRAF* V600E-mutated (Class I) cancers for adults and pediatrics (ages 6+), thereby opening significant market potential for KNTE's KIN-2787 in all *BRAF* Class II and III tumors if the data should be positive. Overall, we think the Phase 1 monotherapy study is likely to be positive, which creates asymmetrical upside potential for KNTE shares (40%-50% vs. -20% to -30%). We remain Buy rated with a 12-month price target of $29.

1. We estimate the Phase 1 monotherapy of KIN-2787 will likely show an ORR of ~25% in a mix of Class II & III *BRAF* patients. We compared the preclinical and clinical efficacy, safety, and PK/PD data for multiple approved kinase inhibitors and pipeline candidates, and we see KIN-2787's optimized pharmacological properties as differentiated from prior *BRAF* Class II and III inhibitors that failed and, importantly, its preclinical safety and tolerability profile are generally in-line with approved kinase inhibitors. Accordingly, we think the preclinical dose-exposure profile of KIN-2787 potentially favors an optimal exposure and target engagement in human. An analysis of BRAF/MEK inhibition-associates AEs implicated KIN-2787 will likely have certain class-effect AEs but with a severity of mild-to-moderate. Additionally, based on recent data of tovorafenib (DayOne, not covered) and a meta-analysis of response rates for the approved BRAF inhibitors, our base case (60% probability) assumes that the trial is likely to achieve an overall ORR of ~25% in Class II (more likely to show responses) and III (less likely to show responses) mutated solid tumors with favorable safety/tolerability profile. In our view, we see this safety and efficacy profile could enable KIN-2787 to quickly enter the expansion study with a potential of accelerated approval using a single arm Phase 2 study.

2. Significant unmet needs leaves a meaningful commercial opportunity to KIN-2787. Our analyses of the RAF landscape indicates that the three approved BRAF inhibitors generated roughly $2bn global sales in 2021 while addressing only ~50% of *BRAF*-mutated population. The total addressable market for KIN-2787 will initially focus on NSCLC and melanoma patients with *BRAF* Class II & III mutations (~21,000 and ~6,000 patients, respectively). Additionally, the recent tumor-agnostic approval of

dabrafenib in *BRAF* V600E-mutated cancers (Class I) poses significant market expansion opportunity to KIN-2787 in a setting of *BRAF* Class II & III tumor agnostic treatment if the Phase 1 data meets our bull case (25% probability) - 30%+ ORR in both Class II and III mutated patients.

3. Possible expansion opportunity through combination with MEK inhibitors. Our analyses suggest that the combination of BRAF and MEK inhibitors would generally increase responses rates while also hit certain safety limits as MEK inhibitors are generally less tolerated with various safety AEs. A potentially favorable safety/tolerability profile of KIN-2787 - no cardiac/ocular events and mild-to-moderate skin/GI toxicities, could enable its combination therapy with MEK inhibitors, further boosting its commercialization opportunity.

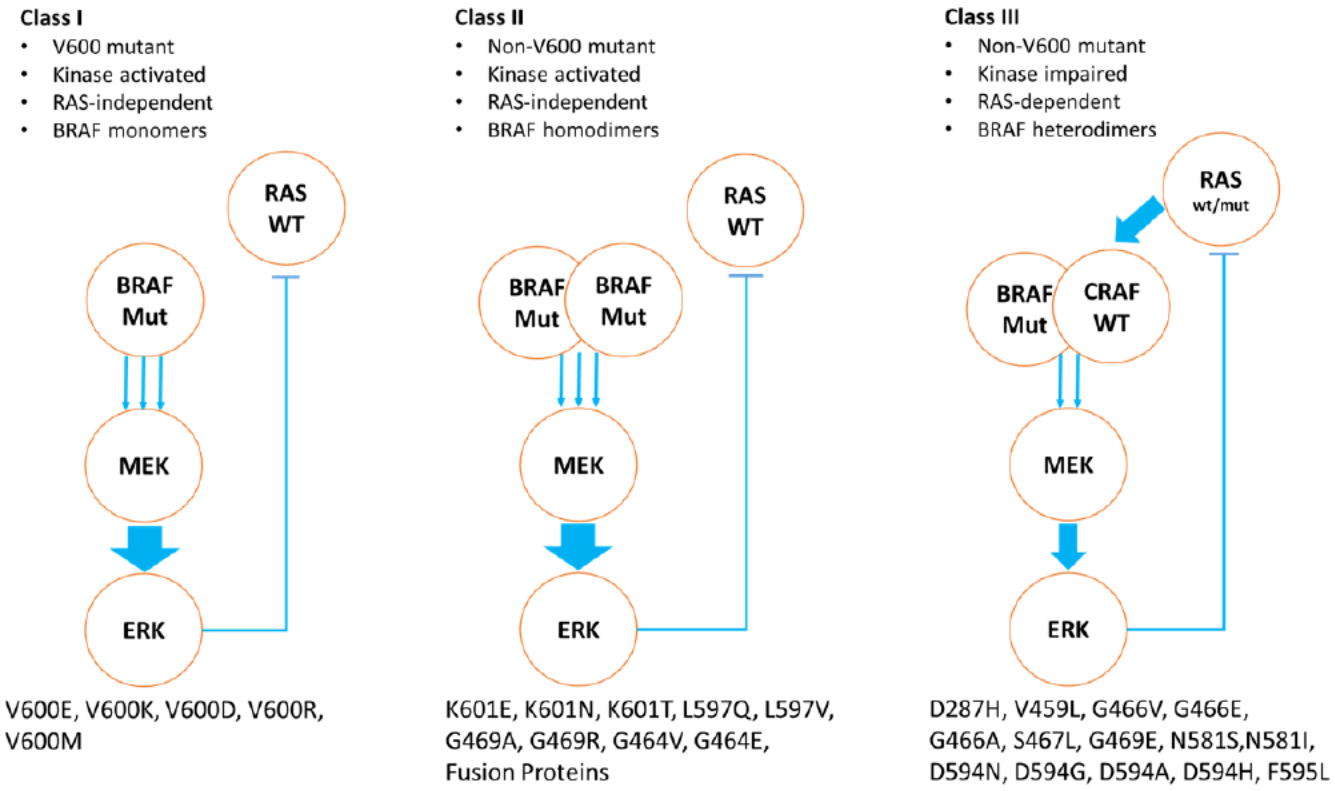
BRAF Class I, II, & III mutations in cancers

The RAF kinase family consists of ARAF, BRAF, and CRAF. Physiologically, RAF kinases activate MAPK signaling as a homodimer or heterodimer. In terms of frequency, *ARAF* and *CRAF* mutations are relatively uncommon while *BRAF* mutations are often seen in cancer patients.

The development of many types of cancers is related to mutations in the *BRAF* proto-oncogene gene (*BRAF*). *BRAF* is found on chromosome 7 and encodes the BRAF protein. While all RAF proteins phosphorylate components of the MAPK proliferation pathway MEK1 and MEK2, BRAF has been shown to have the strongest activation capacity. As such, the mitogen activated protein kinase (MAPK) / extracellular signal-related kinases (ERK) signaling pathway is stimulated and regulates cell proliferation, differentiation and apoptosis in response to a multitude of factors (e.g. hormones, environmental stressors, extracellular stimuli, etc.).

Mutations in *BRAF* are found in many types of cancer and the mutations are classified into three distinct classes according to their properties and activation pathways (see exhibit below). Although the mechanism of how the mutations induce malignancy differs with regard to their interactions with the MAPK pathway, they are all known to activate MEK/ERK phosphorylation. On the whole, nearly 7% of human cancers are associated with mutations in *BRAF*.

Exhibit 1: BRAF Class I, II, and III mutations and signaling pathways



Source: Goldman Sachs Global Investment Research

Class I *BRAF* mutations

Class I *BRAF* mutations are related to amino acid residue 600 and includes the *BRAF* V600E mutations (glutamic acid [E][E] substituted for valine [V]). *BRAF* V600mut acts as a monomer in an RAS-independent manner and constitutively activates ERK by phosphorylation. Of note, more than 90% of observed *BRAF* mutations are V600E mutations (See here). It has been structurally shown that *BRAF* with V600E mutation forms a salt-bridge with residue K507 and stabilizes the active form, which is normally adopted allosterically only upon dimerization of the wild type.

Class II *BRAF* mutations

In Class II, BRAF activation and signal transduction involves mutations beyond those at V600 including K601E, L597Q, and G469A. Strong kinase activation is regulated by dimers of mutant *BRAF*, independently of RAS. Class II mutations are mainly located in the activation segment (K601, L597) or P-loop (G464, G469), and the mutations in this location block the self-inhibitory mechanism of the kinase activity. Interestingly, it has been demonstrated that 13% of *BRAF* mutations found in 8,405 non-small cell lung cancer patients are G469 mutations (Class II; see here). Class II mutations exhibit lower ERK phosphorylation activity than *BRAF* V600E mutation (Class I) although in recently conducted studies, patients with Class I and Class II *BRAF* mutations showed similar poor median overall survival (OS) and disease-free survival (link). It is important to note, however that the molecular mechanism of the function of Class II is less studied than both Class I and III mutations.

Class III *BRAF* mutations

Class III mutations are kinase-impaired, meaning the mutation either has impaired kinase activity or is "kinase-dead" with low kinase activity as compared to wild type *BRAF*, and consists of *BRAF* non-600 mutant and formation of a heterodimer with wild type CRAF. In Class III mutations, the signal is transferred downstream in the presence of mutant RAS. Class III mutations are located in the P-loop (G466), catalytic loop (N581), or DFG motif (D594, G596). In melanoma, myeloma, and colorectal cancer, patients with *BRAF* mutations at residue D594 have a better prognosis and longer overall survival than those with the V600E mutation.

Epidemiology

Two recent studies have estimated the prevalence of *BRAF* mutations in various cancers. In an independent study examining *BRAF* mutations across human cancers in a cohort of 114,662 patients who received comprehensive genomics profiling using next-generation sequencing, 4,517 had a pathogenic or presumed pathogenic *BRAF* mutation (3.9% of the cohort). Of the 4,517 pathogenic or presumed *BRAF*-mutated patients, 1,271 were seen in melanoma, which represented 39.7% of all melanomas sequenced - the highest rate of all tumor types. In terms of prevalence at class levels, Class I mutations were seen overall in 2,841 patients (62.1% of *BRAF* mutations, 2.4% of total cancers). Class II mutations were seen in 746 tumors (16.5% of *BRAF* mutant, 0.7% of total), and Class III mutations were seen in 801 tumors (17.7% of *BRAF*, 0.7% of total; see study here).

In another study (see here), KNTE collaborated with Guardant (covered by Matt Sykes) to evaluate *RAF* clinico-genomics in more than 160,000 patients as 25% of the patients harboring a *BRAF* Class I mutation can develop acquired resistance to the approved BRAF inhibitors through Class II & III mutations and/or RAS mutation. Moreover, 6% of Stage III & IV NSCLC patients have *BRAF* mutations, of which >55% are *BRAF* Class II & III mutations. For Stage III & IV melanoma, 50% of melanoma patients harbor *BRAF* mutations, and ~25% of which are *BRAF* Class II & III mutations.

The study also showed in NSCLC and melanoma, RAS mutations only coexist with *BRAF* Class II & III mutations but not with Class I mutation, and ~13-14% or ~22-23% of *BRAF* Class II and III mutated patients harbor RAS mutations, respectively.

Exhibit 2: Epidemiology of BRAF mutations in cancers

Study Name	Jeff et al.	Guardant
N	114662	160000+
BRAF mutations in all cancers	3.9%	~3.7%
BRAF Class I in BRAF-mutated cancers	62.1%	44.8%
BRAF Class II in BRAF-mutated cancers	16.5%	25.8%
BRAF Class III in BRAF-mutated cancers	17.7%	27.5%
Acquried resistance in BRAF Class I mutated cancers	N/A	25%
BRAF mutations by cancer types	Melanoma (39.7%), thyroid (33.3%), small intestinal malignancies (8.9%), colorectal (8.7%), NSCLC (4.1%)	NSCLC, colorectal, melanoma (by # of patients)
BRAF Class I mutations by cancer types	Thyroid (97.6%), colorectal (79.1%), melanoma (77.5%)	Melanoma (79%), colorectal (69%), NSCLC (35%)
BRAF Class II mutations by cancer types	NSCLC (34.2%), small intestinal (27.3%), melanoma (12.6%)	NSCLC (34%), colorectal (11%), melanoma (9%)
BRAF Class III mutations by cancer types	Small intestinal (50.0%), NSCLC (30.7%), colorectal (13.4%)	NSCLC (31%), colorectal (20%), melanoma (12%)

Source: Company data, Data compiled by Goldman Sachs Global Investment Research

The current treatment paradigm for *BRAF*-mutated cancers

Marketed BRAF and MEK1/2 inhibitors and their applications

There have been multiple RAF and MEK inhibitors developed over the years primarily directed at V600 mutant tumors. Vemurafenib was developed after a Phase I study showed that a response rate of up to 81% was observed for *BRAF* V600E-mutated melanoma patients given the BRAF inhibitor. This compared exceedingly well versus the 10% to 20% response rates for non-targeted therapies that were approved for the treatment of melanoma. On the heels of vemurafenib, another BRAF inhibitor that proved to be efficacious in treating *BRAF* V600E-mutated melanoma patients was dabrafenib, which received FDA approval for the treatment of patients with melanoma having the *BRAF* V600E mutation.

More recently, dabrafenib in combination with trametinib was approved by the FDA as a tumor-agnostic therapy for *BRAF* V600E-mutated cancers for adults and pediatrics (ages 6+). Encorafenib, another approved BRAF V600E/K inhibitor, showed a mPFS of 14.9 months, mOS of 33.6 months, 63% ORR (8% CR, 55% PR) used in combination with binimetinib treating *BRAF* V600E/K unresectable or metastatic melanoma versus mPFS of 7.3 months, mOS of 16.9 months, 40% ORR (6% CR, 35% PR) for vemurafenib in a head-to-head Phase 3 study.

Other approved drugs that act as BRAF inhibitors but are not specifically approved for *BRAF*mut cancers include regorafenib, which is approved for colorectal cancer and gastrointestinal stromal tumors.

There currently are four approved MEK inhibitors including trametinib, binimetinib, cobimetinib, and selumetinib with others in development including pimasertib, refametinib, and mirdametinib (PD-0325901).

Originally, trametinib was approved on the basis of results from a Phase III trial which included 322 melanoma patients who harbored either *BRAF* V600E, *BRAF* V600K, or both mutations. The patients were randomized to receive either chemotherapy (namely

paclitaxel or dacarbazine) or trametinib. Patients receiving trametinib had a superior PFS as compared with patients receiving chemotherapy, with a median PFS of 4.8 months versus 1.5 months, respectively. Two other MEK1/2 inhibitors, cobimetinib and binimetinib, were approved to treat *BRAF* V600E/K melanoma only in combination with vemurafenib and encorafenib, respectively.

With respect to sales of approved BRAF V600E and MEK inhibitors, in 2021, dabrafenib/trametinib has worldwide sales of $1.7B, encorafenib had sales of $136M, binimetinib had worldwide/US sales of $155M, and vemurafenib achieved sales of $218M (2016).

Exhibit 3: Approved BRAF inhibitors and their applications

Drug Name	Brand Name	Company	Targets	Approximate IC50 for BRAF	Development Status	Indications / Stage of Development	Comments
Vemurafenib	Zelboraf	Genentech	BRAF V600E, BRAF, RAF1, ARAF, SRMS, TNK2, FGR, MAP3K5	31 nmol/L (BRAF V600E) 100 nm (BRAF)	Approved for BRAF V600E	Unresectable or metastatic melanoma with BRAF V600E mutation	-
Dabrafenib	Tafinlar, Rafinlar	NVS	BRAF V600E, BRAF V600D, BRAF V600K, BRAF, RAF1	1.84 nm (BRAF V600E) 3.2 nmol/L (BRAF)	Approved for BRAF V600E	- Single agent for unresectable or metastatic melanoma with BRAF V600E mutation - In combination with trametinib for unresectable or metastatic melanoma with BRAF V600E/K mutation	Recent tumor-agnostic accelerated approval for adult and pediatric (>6 YoA) cancers with BRAF V600E mutation
Encorafenib	Braftovi	PFE	BRAF V600E, wild-type BRAF, CRAF	0.35 nM (BRAF V600E), 0.47nM (wild-type BRAF), 0.3nM (CRAF)	Approved for BRAF V600E or V600K	-Melanoma with BRAF V600E/K in combination with binimetinib -CRC with BRAF V600E in combination with cetuximab	-
Trametinib	Mekinist	NVS	MEK1/2	N/A	Approved for BRAF V600E and V600K	Single agent or in combination with dabrafenib for unresectable or metastatic melanoma with BRAF 600E/K mutation	-
Cobimetinib	Cotellic	Genentech	MEK1/2	N/A	Approved for BRAF V600E or V600K	In combination with vemurafenib in unresectable or metastatic melanoma with BRAF V600E/K	-
Binimetinib	Mektovi	PFE	MEK1/2	N/A	Approved for BRAF V600E or V600K	In combination with encorafenib in unresectable or metastatic melanoma with BRAF V600E/K	-
Selumetinib	Koselugo	AZN	MEK1/2	N/A	Approved but not related to BRAF aberrations	Pediatric patients (2 YoA+) with neuroofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)	-
Sorafenib	Nexavar	BAYRY	BRAF, KDR, PDGFRA, PDGFRB, KIT, FLT4, FLT3, RET, RAF1, FLAT1	38 nmol/L (BRAF V600E) 25 nmol/L (BRAF)	Approved but not related to BRAF aberrations	- Unresectable hepatocellular carcinoma - Advanced renal cell carcinoma - Locally recurrent, or metastatic, progressive differentiated thyroid cancer	Also in Phase II trial for BRAF-mutant (excluding BRAF V600 mutations) solid tumors - Not validated clinically as an effective BRAF inhibitor
Regorafenib	Stivarga□	BAYRY	BRAF, FLT1, KDR, FLT4, KIT, TEK, PDGFRA, PDGFRB, FGFR1, FGFR2, NTKR1, MAPK11, ABL1	19 nmol/L (BRAF V600E) 28 nmol/L (BRAF)	Approved but not related to BRAF aberrations	- Metastatic colorectal cancer - Locally advanced, unresectable or metastatic GIST	- Also in Phase II trial for BRAF- or RAS-mutant colorectal cancer - Not validated clinically as an effective BRAF inhibitor
Pazopanib	Votrient	GSK	BRAF, FLT1, KDR, FLT4, KIT, TEK, PDGFRA, PDGFRB, KIT, FGFR1, FGFR3, CSFIR, LCK, ITK	410 nmol/L (BRAF)	Approved but not related to BRAF aberrations	-Advanced renal cell carcinoma - Advanced soft tissue sarcoma	- Also in Phase I trial in combination with dabrafenib for BRAF-mutant advanced malignant tumors - Less effective at inhibition of BRAF V600E; at 1umol/L can achieve ~80% inhibition of wild-type BRAF versus only 40% inhibition of BRAF V600E - Not validated clinically as an effective BRAF inihibtor

Source: Company data, FDA labels, Goldman Sachs Global Investment Research

Significant unmet needs still remain for ***BRAF*** Class II and III mutated cancer patients - solving for paradoxical activation

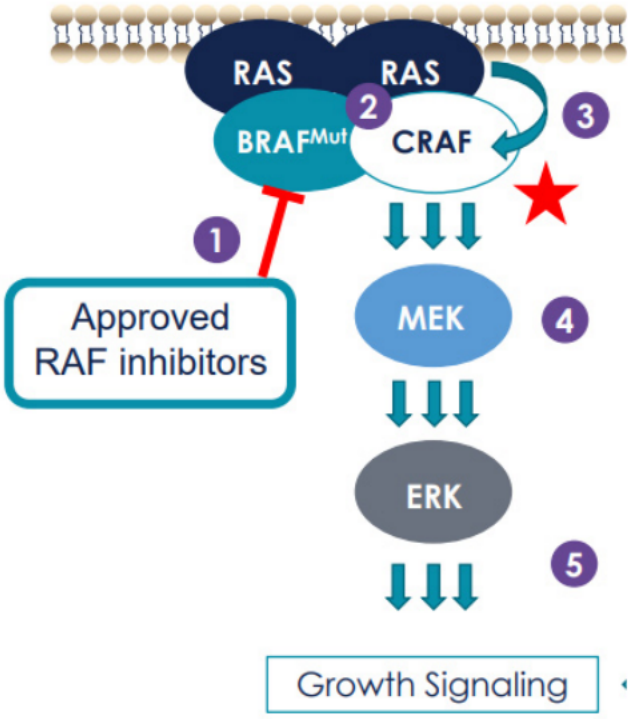
Though the approved BRAF and MEK1/2 inhibitors have demonstrated robust clinical efficacy (e.g., dabrafenib potently inhibiting *BRAF* V600E and achieving significant tumor regression with increased survival for melanoma patients) the clinical benefits of these drugs are limited to cancers with *BRAF* V600 mutations that function as monomers vs. *BRAF* Class II & III mutations that function as dimers. Importantly, *BRAF* Class II & III mutations (accounts for ~50% of *BRAF* mutations) are not only resistant to these approved BRAF inhibitors because in the context of dimer vs. monomer, the paradoxical activation of BRAF induced by the approved BRAF inhibitors also further diminishes their clinical efficacy with even worse safety (incidence of squamous cell carcinoma) and disease burden.

Paradoxical activation results from BRAF having an altered drug binding site due to either asymmetric dimerization or CRAF in heterodimer. Therefore, the inhibition of BRAF homo or heterodimers require a molecule to be able to bind to and inhibit second kinase active site. More specifically, RAF inhibitors have structural difference in terms of

the binding mode of the RAF kinases. With Type I & II RAF inhibitors (alpha C-IN/DFG-IN, alpha C-IN/DFG-out), they bind to the kinase in alpha C-IN mode, which doesn't obstruct the binding to another protomer in the dimer. However, the type 1.5 molecules (dabrafenib, encorafenib, vemurafenib) binds the first protomer in the mode of alpha C-OUT, which precludes the other protomer to bind the RAF inhibitor. With the heterologous dimerization and transactivation, the second protomer will activate the RAS-RAF-MEK pathway, leading to diminished inhibition or paradoxical activation of BRAF.

Additionally, about 25% of currently treated *BRAF* Class I mutation patients could develop acquired resistance to the approved BRAF inhibitors through *BRAF* Class II & III mutations or other pathways.

Exhibit 4: Illustration of paradoxical activation induced by approved BRAF inhibitors



Source: Company data

The *BRAF* Class II & III inhibitor development landscape

Multiple drug candidates (see below exhibit) are in preclinical/clinical development for targeting *BRAF* Class II & III mutated cancers. We highlight several key competing assets to KIN-2787, including BGB-3245 (Phase 1, SpringWorks/BeiGene), belvarafenib (Phase 2, Hanmi/Genentech), and tovorafenib (Phase 1/2, DayOne).

Exhibit 5: Pipeline candidates targeting BRAF Class II or Class III mutated solid tumors

Drug Name	Company	MOA	Administration Route	NCT #	Stage	N	Indication	Regimen	Start Date	Primary Completion Date	Comments
BGB-3245	MapKure (SpringWorks/BeiGene)	RAF fusion and dimer inhibitor	Oral	NCT04249843	Ph1	168	RAF mutant solid tumors	Monotherapy	Feb '22	May '23	Topline results in 2Q22
Lifirafenib	SpringWorks/BeiGene	RAF dimer inhibitor	Oral	NCT03905148	Ph1/2	105	KRASm NSCLC and endometrial cancer	Combination with mirdametinib (MEKi)	May '19	Mar '24	Initial results in 2Q22
				NCT02610361	Ph1	131	B-RAF, N-RAS, or K-RAS mutation positive solid tumor	Monotherapy	Nov '13	Oct '17	Results published in 2020
				NCT03641586	Ph1	42	Chinese patients with B-RAF, N-RAS, or K-RAS mutation positive solid tumor	Monotherapy	Oct '15	Dec '16	Completed in 2019
Belvarafenib	Hanmi/Genentech	RAF dimer inhibitor	Oral	NCT04835805	Ph1	98	NRAS-mutant advanced melanoma with prior anti-PD-1/PD-L1 therapy	Monotherapy or combination with cobimetinib +/- atezolizumab	May '21	Nov '24	-
				NCT04589845	Ph2	770	BRAF class II mutant or fusion-positive tumors and BRAF class III mutant-positive tumors	Monotherapy or combination	Jan '21	Sep '32	-
				NCT03284502	Ph1	140	KRASm NSCLC, pancreatic, RASm CRC, RAS/RAFm solid tumors, KRAS G13Dm CRC, BRAF V600m CRC, NRASm melanoma, BRAF Class II/III or fusions solid tumors	Combination with cobimetinib or cetuximab	May '17	Sep '23	-
				NCT03118817	Ph1	65	BRAF, KRAS or NRAS Mutant Solid Cancers	Monotherapy	May '17	Feb '20	Completed in 2020
				NCT02405065	Ph1	72	BRAF, KRAS or NRAS Mutant Solid Cancers	Monotherapy	Jan '15	Jan '17	Completed in 2018
RG6344	Roche	RAF dimer inhibitor	Oral	ISRCTN13713551	Ph1	292	BRAF V600-mutated solid tumours or melanoma	Monotherapy or combination with cobimetinib	Nov '21	Mar '24	-
KIN-2787	Kinnate	Pan-RAF inhibitor	Oral	NCT04913285	Ph1	155	BRAFm (Class II/III for dose expansion) solid tumors or NRASm melanoma	Monotherapy for BRAFm and combination with binimetinib for NRASm melanoma	Aug '21	Mar '24	Topline monotherapy results in 4Q22, combination in 1H22
LXH254	Novartis	CRAF inhibitor	Oral	NCT04417621	Ph2	320	BRAF V600m or NRASm melanoma	Combination with LTT462 (ERK1/2), trametinib (MEK), ribociclib (CDK4/6)	Oct '20	Nov '22	-
				NCT02974725	Ph1	241	KRAS/BRAFm NSCLC or NRASm melanoma	Combination with LTT462 (ERK1/2), trametinib (MEK), ribociclib (CDK4/6)	Feb '17	Nov '22	-
				NCT03333343	Ph1	105	EGFRm NSCLC	Combination with EGF816	Jan '18	Nov '22	-
				NCT04294160	Ph1	350	BRAF V600m CRC	Combination with LTT462 and dabrafenib	Jul '20	Jun '24	-
				NCT02607813	Ph1	142	MAPKm solid tumors, KRASm NSCLC, NRASm melanoma	Monotherapy or combination with PDR001 (aPD1)	Jan '16	Feb '22	Completed in 2022
Tovorafenib (DAY 101)	DayOne	Pan-RAF inhibitor	Oral	NCT04775485	Ph2	60	Pediatrics with BRAFm low-grade gliomas	Monotherapy	Mar '21	Mar '23	Topline data in 1Q23
				NCT04985604	Ph1/2	168	RAS/RAF/MEK/ERKm solid tumors in 12+ YoA patients	Monotherapy or combination with pimasertib	Jul '21	Jul '25	1st patient dosed in May '22
				NCT03429803	Ph1	44	Children with low-grade gliomas and RAS/RAF/MEK/ERKm solid tumors	Monotherapy	Feb '18	Dec '24	Investigator-sponsored trial
				NCT01425008	Ph1	149	Metastatic melanoma	Monotherapy	Sep '11	Apr '17	Completed in 2018
				NCT02327169	Ph1	81	KRAS/BRAF non-V600m solid tumors	Combination with MLN0128 (mTORC 1/2), alisertib (aurora), paclitaxel, cetuximab, irnotecan	Jan '15	Jul '18	Completed in 2018
				NCT02723006	Ph1	22	BRAF V600m or NRASm solid tumors	Combination with aPD1 (nivolumab, ipilimumab)	Jun '16	May '18	Terminated in 2018
FORE-8394	Fore Bio	BRAF class I/II inhibitor	Oral	NCT02428712	Ph1/2	100	BRAF V600m glioma and BRAF non-V600m solid tumors	Monotherapy	Apr '15	Feb '22	-
				NCT02012231	Ph1	5	BRAF-mutated melanoma, BRAF-mutated non-melanoma solid tumors, and BRAF-mutated classical hairy cell leukemia	Monotherapy	Feb '14	Sep '14	Terminated in 2015
JZP815	Jazz Pharmaceuticals	Pan-RAF inhibitor	Oral	Preclinical							IND filing in '22
BDTX-4933	Black Diamond	BRAF inhibitor (brain penentrant)	Oral	Preclinical							IND filing in 1H23
Pan-RAF prorgam	Deciphera	Pan-RAF inhibitor	Oral	Preclinical							Candidate selection in 2022
QLH11906	Qilu Pharma	Pan-RAF inhibitor	Oral	Preclinical							-
VS-6766	Verastem Oncology	RAF/MEK dual inhibitor	Oral	NCT04625270	Ph2	100	Low-grade serous ovarian cancer with and without a KRAS mutation	Monotherapy or combination with defactinib	Dec '20	Jun '23	-
				NCT05074810	Ph1/2	53	KRAS G12C NSCLC	Combination with sotorasib	Mar '22	Dec '23	-
				NCT04620330	Ph2	100	KRASm NSCLC	Monotherapy or combination with defactinib	Dec '20	Mar '23	-
CFT1946	C4 Therapeutics	BRAF bifunctional degrader	Oral	Preclinical							IND filing and Ph1 initiation in 2H22
Ulixertinib	BioMed Valley Discoveries	ERK1/2 inhibitor	Oral	NCT04488003	Ph2	528	BRAFm CRC (G469, L485, L597, Class II, non-V600)	Monotherapy	Nov '20	Aug '23	-
LY3009120	Eli Lilly	Pan-RAF inhibitor	Oral	NCT02014116	Ph1	51	Solid tumors	Monotherapy	Nov '13	Apr '17	Terminated in 2018
RO5126766	Chugai Pharma	RAF/MEK dual inhibitor	Oral	NCT00773526	Ph1	52	Solid tumors	Monotherapy	Nov '08	Sep '11	Completed in 2011
BMS-908662	BMS	Pan-RAF inhibitor	Oral	NCT01086267	Ph1/2	17	KRAS/BRAF V600m CRC	Monotherapy or combination with cetuximab	Jul '10	Aug '11	Completed in 2011
				NCT01245556	Ph1	8	BRAF V600m melanoma	Monotherapy or combination with ipilimumab	Jan '11	Nov '12	Completed in 2012
ASN003	Asana BioSciences	RAF/PI3K dual inhibitor	Oral	NCT02961283	Ph1	24	BRAF V600 or PIK3CAm NSCLC	Monotherapy	Oct '16	Feb '19	Terminated in 2019

Note: grey - terminated or inactive pipeline candidates

Source: Company data, clinicaltrials.gov, Goldman Sachs Global Investment Research

MapKure (SpringWorks/BeiGene, SWTX/BGNE, covered by Corinne Jenkins/Ziyi Chen): BGB-3245. BGB-3245 was evaluated in preclinical studies against a list of RAF inhibitors including vemurafenib, dabrafenib, and others, and higher activity against resistance mutations was observed. BGB-3245 is currently being developed in a Phase 1 study by MapKure, which is jointly owned by BeiGene and SpringWorks. BeiGene has the rights to the drug in Asia ex Japan.

In a Phase 1 dose escalation study (NCT04249843), 38 patients were enrolled with a median age of 57 years (range: 31-83) and a median of 5 prior lines of therapies (range: 0-10). 71.1% of the patients harbored RAF mutations (*BRAF* V600E, *BRAF* fusion) and the rest of patients have RAS mutations. BGB-3245 showed an ORR of 24% (n=6/25) with 3 cPR (2 NRASm melanoma + 1 *BRAF* V600E LGSOC) and 3 uPR (2 *BRAF* V600E melanoma and 1 *KRAS* appendiceal cancer). With respect to *BRAF* Class II mutations, for 6 *BRAF* fusion and 1 *BRAF* Class II mutated cancers, no responses were observed with 4 patients achieving SD and 3 having PD though we note that SWTX did not disclose the dose levels tested. From a safety perspective, BGB-3245 was generally safe and well tolerated with 11.8% G3+ TRAEs including 5.9% G3+ maculopapular rash, which we view as consistent with MAPK pathway inhibitors.

Updated data from the Phase 1 dose escalation part will be presented at a medical conference in 2H22 with SWTX expecting to determine a RP2D as well.

In preclinical studies, BGB-3245 showed consistent inhibition of MAPK (RAF-MEK-ERK) pathway without obvious pathway rebound across different cancer cell lines (melanoma, thyroid, colon). In *in vivo* studies, BGB-3245 showed consistent tumor growth inhibition across PDX models (*BRAF* V600E colon cancer, *BRAF* K601E CRC, *BRAF*/*NRAS*m CRC). Of note, in a melanoma PDX model with *AGK-BRAF* fusion, BGB-3245 at 10 mg/kg QD demonstrated 100% tumor reduction around day 30.

Roche (Genentech)/Hanmi (covered by Keyur Parekh/Sangsoo Kim): belvarafenib. Belvarafenib is a RAF dimer inhibitor being investigated in multiple Phase 1 and Phase 2 studies as a monotherapy or in combination with MEK1/2 inhibitors or other drugs. In two Phase 1 monotherapy studies (dose escalation, NCT02405065; dose expansion, NCT03118817), belvarafenib showed ORRs of 10.5% and 11.9% for *KRAS* and *BRAF* V600E mutated cancers in the escalation and expansion trials, respectively. With respect to safety of belvarafenib as a single agent, 21.6% of patients had G3+ TRAEs at 450 mg BID (RP2D), including 5.4% dermatitis acneiform, 2.7% rash, and 2.7% vomiting. Overall, 5.4% (n=4/63) of patients discontinued the studies due to AEs. As for PK/PD, belvarafenib of 450 mg BID had a half-life of 41.2 hrs, Cmax of 3,213.8 ug/L, and AUC(0-24) of 68,914.7 ug*hr/L.

Interestingly, in two Phase 1 combination studies (NCT04835805, NCT04589845) of belvarafenib with cobimetinib (MEK1/2 inhibitor) in patients with RAS or RAF mutated solid tumors, the combination therapy achieved encouraging ORRs of 35.7% (5/14) and 26.3% (5/19) in *BRAF* Class II & III solid tumors and *NRAS*-mutated melanoma, respectively. Specifically, in 6 melanoma patients with *BRAF* Class II & III mutations, the combination therapy achieved 50% PR, and 2 NSCLC patients harboring *BRAF* Class II & III mutations had a PR (100%).

DayOne (not covered): tovorafenib. Tovorafenib is being developed in multiple Phase 1 and Phase 2 trials with a focus on pediatric patients with *BRAF*-mutated low-grade gliomas. The company recently announced preliminary data from a Phase 2 study for tovorafenib as a monotherapy in pediatric patients with *BRAF* fusion or *BRAF* V600E low-grade glioma. Encouraging efficacy was observed with an ORR of 64% (60% in *BRAF* fusion and 100% in *BRAF* V600E). With respect to safety, tovorafenib led to

several G3+ TRAEs, including 12% rash, 8% blood creatine phosphokinase increased, and 8% anemia. Additionally, tovorafenib showed PK/PD properties with a half-life of 67 hrs, Tmax of 2 hrs, and mean accumulation of 2.6 times with Q2D dosing for 21 days. DayOne plans to report the topline data of this study in 1Q23.

Moreover, the company is currently evaluating the clinical efficacy/safety of tovorafenib in a Phase 1/2 study (NCT04985604) for patients with *RAS*/*RAF*/*MEK*/*ERK* mutations solid tumors in patients age 12 and older. The first patient was dosed in May 2022.

Exhibit 6: Early stage efficacy of RAF inhibitors in Class II and III patients

Drug Name		BGB-3245	Belvarafenib		Tovorafenib (DAY101)	Lifirafenib		Naporafenib (LXH254)	LY3009120	
Company		MapKure (SpringWorks/BeiGene)	Hanmi/Genentech		Day One	SpringWorks/BeiGene		Novartis	Eli Lilly	
MOA		RAF fusion and dimer inhibitor	Pan-RAF inhibitor		Pan-RAF inhibitor	RAF dimer inhibitor		CRAF inhibitor	Pan-RAF inhibitor	
NCT #		NCT04249843	NCT02405065	NCT03118817	NCT04775485	NCT02610361		NCT02607813	NCT02014116	
Stage		Ph1 dose escalation	Ph1 dose escalation	Ph1 dose expans ion	Phase 2 (pivotal)	Ph1 dose escalation	Ph1 dose expansion	Ph1	Ph1 dose escalation	Ph1 dose expansion
Dose		N/A	50, 100, 200 mg QD; 200, 300, 450, 650, 800 mg BID	450 mg BID	420 mg/m2 QW	5, 10, 20, 30, 40, 50, and 60 mg QD	30 mg QD	100, 200, 300, 400, 800, 1200 mg QD, 200, 400, 600 mg BID	50, 100, 200, 300, 400, 500, 600, 700 mg BID	300 mg BID
N		38	72	63	140, pivotal arm: 25	35	96	81	35	16
Baseline	Median age	57 (31-83)	58 (31-78)	57 (24-75)	8 (3-18)	59 (33-77)	63 (20-82)	57 (24-90)	59 (24-82)	63.5 (41-78)
	ECOG 0/1 PS	63.2%/34.2%	22.2%/72.2%/5.6%	41.3%/33.3%	N/A	34.3%/65.7%	34.4%/65.6%	34.6%/65.4%	37.1%/62.9%	1 8.8%/81.3%
	Tumor type	34.2% gastrointestinal, 23.7% skin, 10.5% female genitourinary, 10.5% lung, 7.9% thyroid	58.3% CRC, 34.7% melanoma, 2.8% NSCLC	31.8% CRC, 27.0% melanoma, 14.3% PDAC, 4.8% NSCLC	recurrent/progressive low-grade glioma	37.1% CRC, 25.7% NSCLC, 14.3% melanoma	35.4% CRC, 18.8% melanoma, 10.4% NSCLC	21% lung, 16% colon, 16% ovary, 9.9% melanoma	9 CRC, 9 NSCLC, 5 PDAC, 12 others (liver, breast, CCA)	10 NSCLC, 6 others (melanoma, breast)
	Tumor stage III/IV	13.2%/86.8%	N/A	N/A	N/A	11.4%/88.6%	15.6%/83.3%	48.1% I-III, 39.5% IV	100%	
	Mutation type	71.1% RAF (BRAF V600E, fusion, etc), 28.9% RAS	41.7% KRAS, 40.3% BRAF (V600E), 19.4% NRAS	47/6% KRAS, 31.8% BRAF (V600E), 22.2% NRAS	84% KIAA1549-BRAF fusion, 16% BRAF V600E	20% BRAF V600, 5.7% other BRAF, 57.1% KRAS, 11.4% NRAS	41.7% BRAF V600, 2.1% other BRAF, 40.6% KRAS, 3.1% NRAS	25 BRAF (V600E), 22 KRAS, 12 NRAS	18 KRAS, 7 BRAF (V600), 1 NRAS	5 KRAS, 6 BRAF (V600), 5 NRAS
	Prior therapy	Median of 5 (0-10)	Median 2, 32% >=3	Median 2, 33.3% 3-5	Median >=3 (56%)	Median 3 (no prior BRAFi)	Meidan 3 (12.5% prior BRAFi)	2-5, 63%	Median >=2 (89%)	Median >=2 (69%)
Efficacy	Evaluable # of patients	25	67	57	22 (20 BRAF fusion, 2 BRAF V600E)	119		81	51	
	ORR	24% (6/25)	10.5% (7/67)	11.9% (7/57)	Overall: 64% (95% CI: 41-83), BRAF fusion:60%, BRAF V600E: 100%	9.2% (11/119)		2.5% (2/81)	0	
	CR	0	0	0	0	1% (1 CR): in BRAF V600E melanoma		0	0	
	PR	24% (6/25): 3 cPR (NRAS Q61K and NRAS G12S melanoma, BRAF V600E LGSOC) + 3 uPR (2 BRAF V600E melanoma, KRAS G12D appendiceal)	10.5% (7/67): 3 cPR + 4 uPR in KRAS/NRAS/BRAF V600E 1 sarcoma, 5 melanoma, 1 GIST	11.9% (7/57): 4 cPR + 3 uPR in KRAS/NRAS/BRAF V600E 4 melanoma, 2 CRC, 1 bladder	13/22 (59%) PR, 1/22 (5%) uPR	8.4% (10 PR): 5 in BRAF V600E melanoma, 1 in BRAFm thyroid, 1 in BRAF V600E LGSOC, 1 in BRAFm NSCLC, 2 in KRASm endometrial and codon 12-mut NSCLC		2.5% (2/81) confirmed PR (KRASm ovarian, BRAFm other): 1 at 300 mg QD, 1 at 400 mg QD	0	
	SD	40% (10/25): 4/7 SD in BRAF fusion/class II	40% (27/67)	21% (12/57)	6/22 (27%) SD	50.4% (60/119)		34.6% (28/81)	8 SD	

Source: Company data, Goldman Sachs Global Investment Research

Exhibit 7: Clinical safety and PK/PD data comparison of RAF inhibitors in Class II and III patients

Drug Name		BGB-3245	Belvarafenib		Tovorafenib (DAY101)	Lifirafenib		Naporafenib (LXH254)	LY3009120	
Company		MapKure (SpringWorks/BeiGene)	Hanmi/Genentech		Day One	SpringWorks/BeiGene		Novartis	Eli Lilly	
MOA		RAF fusion and dimer inhibitor	Pan-RAF inhibitor		Pan-RAF inhibitor	RAF dimer inhibitor		CRAF inhibitor	Pan-RAF inhibitor	
NCT #		NCT04249843	NCT02405065	NCT03118817	NCT04775485	NCT02610361		NCT02607813	NCT02014116	
Stage		Ph1 dose escalation	Ph1 dose escalation	Ph1 dose expansion	Phase 2 (pivotal)	Ph1 dose escalation	Ph1 dose expansion	Ph1	Ph1 dose escalation	Ph1 dose expansion
Dose		N/A	50, 100, 200 mg QD; 200, 300, 450, 650, 800 mg BID	450 mg BID	420 mg/m2 QW	5, 10, 20, 30, 40, 50, and 60 mg QD	30 mg QD	100, 200, 300, 400, 800, 1200 mg QD, 200, 400, 600 mg BID	50, 100, 200, 300, 400, 500, 600, 700 mg BID	300 mg BID
N		38	72	63	140, pivotal arm: 25	35	96	81	35	16
Baseline	Median age	57 (31-83)	58 (31-78)	57 (24-75)	8 (3-18)	59 (33-77)	63 (20-82)	57 (24-90)	59 (24-82)	63.5 (41-78)
	ECOG 0/1 PS	63.2%/34.2%	22.2%/72.2%/5.6%	41.3%/33.3%	N/A	34.3%/65.7%	34.4%/65.6%	34.6%/65.4%	37.1%/62.9%	18.8%/81.3%
	Tumor type	34.2% gastrointestinal, 23.7% skin, 10.5% female genitourinary, 10.5% lung, 7.9% thyroid	58.3% CRC, 34.7% melanoma, 2.8% NSCLC	31.8% CRC, 27.0% melano ma, 14.3% PDAC, 4.8% NSCLC	recurrent/progressive low-grade glioma	37.1% CRC, 25.7% NSCLC, 14.3% melanoma	35.4% CRC, 18.8% melanoma, 10.4% NSCLC	21% lung, 16% colon, 16% ovary, 9.9% melanoma	9 CRC, 9 NSCLC, 5 PDAC, 12 others (liver, breast, CCA)	10 NSCLC, 6 others (melanoma, breast)
	Tumor stage III/IV	13.2%/86.8%	N/A	N/A	N/A	11.4%/88.6%	15.6%/83.3%	48.1% I-III, 39.5% IV	100%	
	Mutation type	71.1% RAF (BRAF V600E, fusion, etc), 28.9% RAS	41.7% KRAS, 40.3% BRAF (V600E), 19.4% NRAS	47/6% KRAS, 31.8% BRAF (V600E), 22.2% NRAS	84% KIAA1549-BRAF fusion, 16% BRAF V600E	20% BRAF V600, 5.7% other BRAF, 57.1% KRAS, 11.4% NRAS	41.7% BRAF V600, 2.1% other BRAF, 40.6% KRAS, 3.1% NRAS	25 BRAF (V600E), 22 KRAS, 12 NRAS	18 KRAS, 7 BRAF, 1 NRAS	5 KRAS, 6 BRAF, 5 NRAS
	Prior therapy	Median of 5 (0-10)	Median 2, 32% >=3	Median 2, 33.3% 3-5	Median >=3 (56%)	Median 3 (no prior BRAFi)	Meidan 3 (12.5% prior BRAFi)	2-5, 63%	Median >=2 (89%)	Median >=2 (69%)
Safety	G3+ TRAEs	11.8% G3+ TRAEs: 5.9% rash maculopapular	For both Ph1, 26 (19.3%) G3+: dermatitis acneiform (3%), rash (3%), vomiting (1.5%), dyspepsia (1.5%)	16 (21.6%) G3+: dermatitis acneiform (5.4%). Rash (2.7%), vomiting (2.7%)	Rash (12%), blood creatine phosphokinase increased (8%), and anemia (8%)	Thrombocytopenia (14.3%), hypertension (11.4%), and fatigue (11.4%)	Hypertension (8.3%) and fatigue (7.3%)	18.5% all G3+: Rash (2.5%), fatigue (2.5%), myalgia (2.5%), nausea (1.2%), vomiting (1.2%)	7 patients had G3 TRAEs (stomatitis, fatigue, pain, increased alanine aminotransferase, increased aspartate aminotransferase, increased bilirubin, arthralgia, myalgia, dermatitis acneiform)	
	DLTs	N/A	200 mg BID: G3 rash; 650 mg BID: G3 rash maculo-papular; 800 mg BID: G3 rash and G2 dermatitis aceniform	No DLTs	N/A	6 reversible DLTs (G3 increased ALT, G4 thrombocytopenia), 5 DLT at 40+ mg QD	N/A	600 mg BID: G3 neuralgia, G3 pruritus, G3 maculopapular rash; 1200 mg QD: G4 decreased platelet count	2 DLTs at 300 mg BID (G2 blurred vision, G3 dermatitis acneiform), 2 DLTs at 400 mg BID (G2/G3 ALT increase), 4 DLTs at 500 mg BID (G3 pain, G3 stomatitis, G3 arthralgia, G3 myalgia)	300 mg BID: 1 GLET (G3 myalgia)
	Discontinuation		For both Ph1, 13 (9.6%) discontinuation (9 [6.7%] due to G3+ AEs)	4 (5.4%) discontinuation	No discontinuation due to TRAEs	5 patients (14.3%)	19 patients (19.5%), including 2 patients had G3+ TRAE thrombocytopenia	2 (2.5%) discontinued dur to G2 colitis at 200 mg and G3 pneumonitis at 600 mg BID	2 patients discontinued due to myalgia (300 and 500 mg BID)	
	AE of special interest		For both Ph1, 37% dermatitis acneiform, 23.7% rash, 22.2% pruritus	46% dermatitis acneiform, 24.3% pruritus, 21.6% rash	Blood creatine phosphokinase increased, hair color changes, anemia, aspartate aminotransferase increased, vomiting, rash	42.9% dermatitis aceneiform	No cutaneous SCC or keratoacanthoma	58% rash, 21% fatigue, 18.5% nausea, 12.3% vomiting, 11.15 myalgia	Fatigue (29%), nausea (24%), dermatitis acneiform (20%), decreased appetitie (14%), maculopapular rash (14%)\	
PK/PD	Half-life	N/A	At 450 mg BID: 41.2 hr		67 hrs	15-59 hrs	N/A	Mouse: 1.4 hrs, rat: 3.9 hrs, dog: 7.8 hrs	3.1-9.9 hrs (predicted 6 hrs)	
	Cmax		At 450 mg BID: 3213.8 ug/L		Tmax 2 hr	At cycle 2 day 1, 30 mg (RP2D), 2583 ng/mL		At cycle 1 day 15, 3210 ng/mL	At 300 mg BID, ~1000 ng/mL	
	AUC(0-24)		At 450 mg BID: 68914.7 ug*hr/L		Mean accumulation of 2.6 times with Q2D dosing for 21 days	At cycle 2 day 1, 30 mg (RP2D), 47947 hr*ng/mL		At cycle 1 day 15, 28100 ng*hr/mL	N/A	

Source: Company data, Goldman Sachs Global Investment Research

Discontinued pipeline candidates targeting ***BRAF*** Class II & III mutations - key highlights

Novartis (NVS, covered by Keyur Parekh): naporafenib (LXH254). Naporafenib was initially developed as a selective BRAF and CRAF inhibitor, targeting *BRAF* Class II & III mutated cancers. During the discovery phase, naporafenib was optimized to have a balance between its physicochemical properties (e.g., solubility, Clint [human liver microsomes]) with cellular potency through modifying the electrons of the ring system of the compound.Naporafenib showed a pMEK EC50 of 14 nM in Calu-6 cell line with a human max clearance (Clint) of 13.5 uL/min/mg. Naporafenib is slightly soluble in water with a solubility of 20 uM and cLogP of 3.5. In addition, naporafenib showed ~98% human plasma protein binding (3.7% unbound fraction) with as a half-life of 8 hrs.

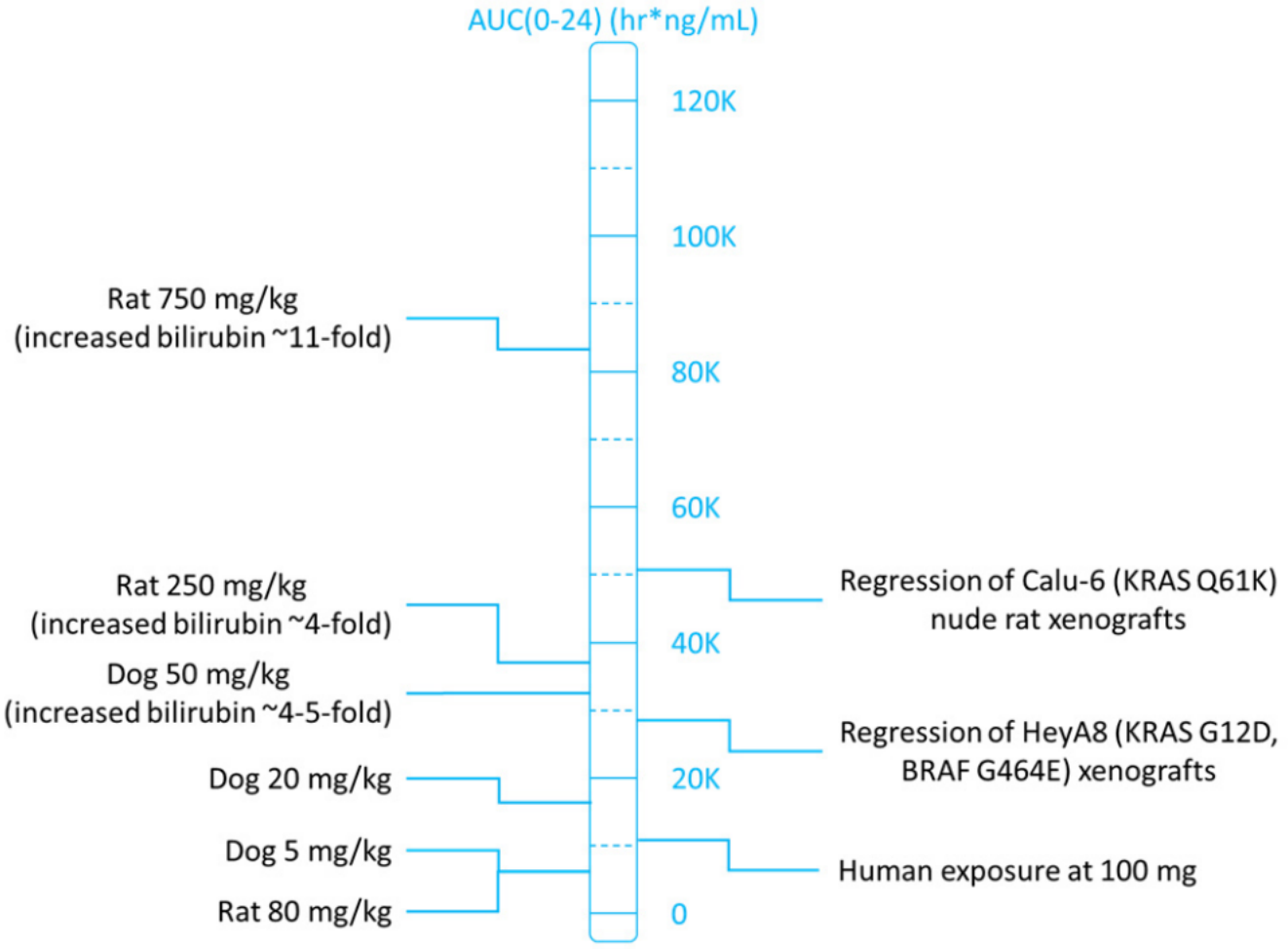
In *in vivo* studies using Calu-6 xenograft in rats, naporafenib at 35 mg/kg QD showed 91% tumor growth inhibition (AUC, 25,210 nM*h) and 56% tumor volume regression when the dose was increased to 150 mg/kg QD (AUC, 216,680 nM*h). However, in our view, naporafenib demonstrated a relatively narrow therapeutic window (see exhibit below) with observed bilirubin increases (due to UGT1A1 inhibition, IC50 of 130 nM) and skin toxicities in GLP toxicology study.

Though naporafenib showed promising preclinical activity against *BRAF* Class II & III mutated tumors, in a Phase 1 clinical study in patients with *BRAF* V600E, *KRAF*, and *NRAF* mutates solid tumors (NCT02607813), naporafenib's clinical benefits were

disappointing. Specifically, only 2 out of 81 patients achieved a PR (2.5% ORR/PR) as the rest of patients had stable disease (34.6%) or progressive disease. With respect to safety, naporafenib resulted in 18.5% G3+ TRAEs, including 2.5% rash, 2.5% fatigue, 2.5% myalgia, 1.2% nausea, and 1.2% rate of vomiting. Naporafenib at 600 mg BID also showed 3 DLTs (G3 neuralgia, pruritus, maculopapular rash) and 1 case of G4 decreased platelet count DLT at 1,200 mg QD. In addition, 400 mg BID was deemed to be the minimal clinically efficacious dose.

In its 1Q22 earnings report, NVS removed naporafenib from its pipeline without citing specific reasons, which is not unexpected considering the limited efficacy that was observed in both the monotherapy and combination settings.

Exhibit 8: Dose-exposure-toxicity-efficacy thermal diagram for naporafenib



Source: Company data

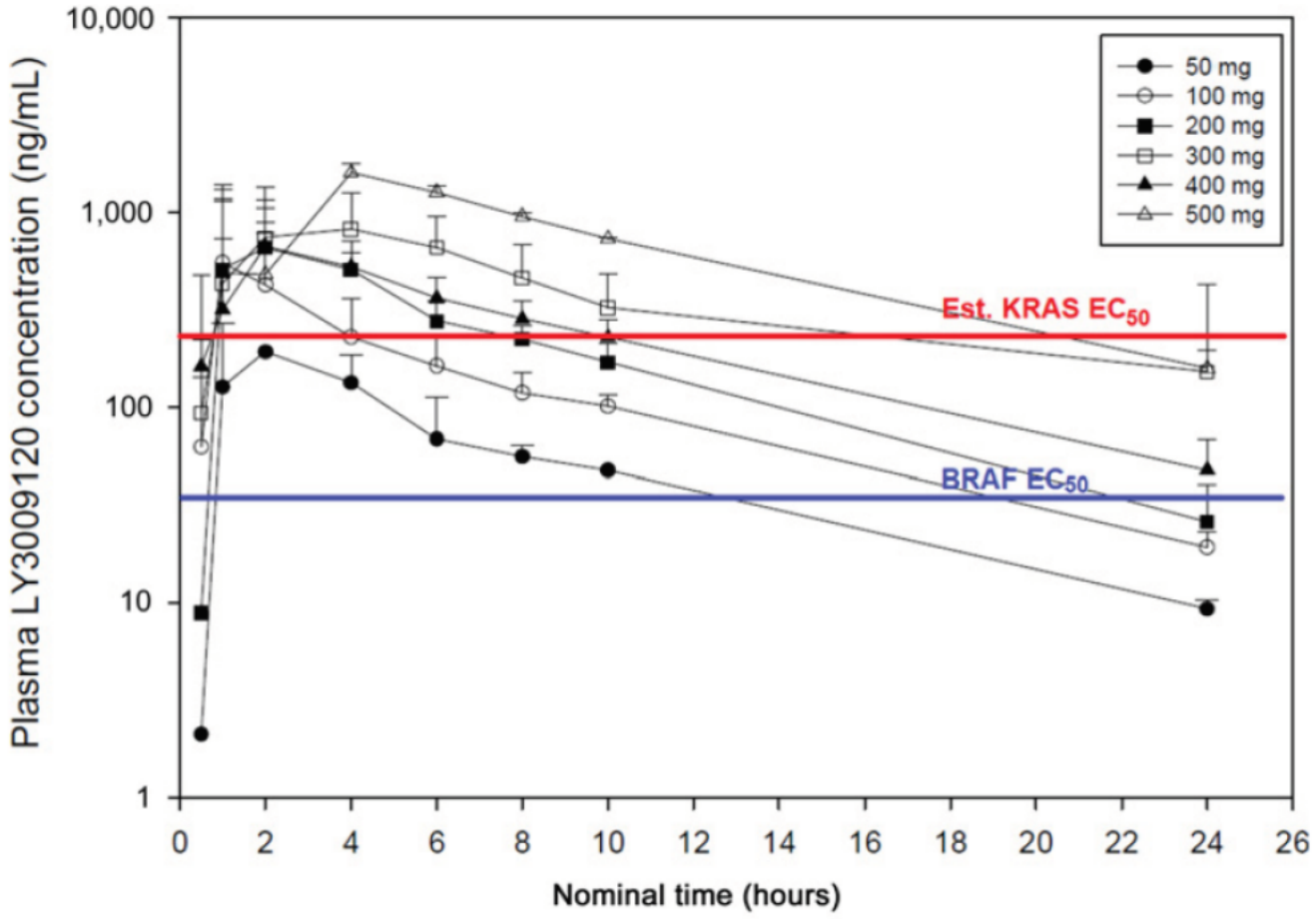
Eli Lilly (LLY, covered by Chris Shibutani): LY3009120. LY3009120 is a pan-RAF and dimer inhibitor and was evaluated in Phase 1 dose escalation (n=35) and expansion (n=16) studies (NCT02014116) in cancer patients. Various dose levels (50 mg to 700 mg BID) of LY3009120 were evaluated in the escalation part, and 300 mg BID was selected for the expansion portion. In addition, most patients in both parts harbor *KRAS* and *BRAF* mutations.

In the Phase 1 study, LY3009120 proved to berelatively toxic with 6 patients

experiencing 8 DLTs in the escalation part (300 mg to 500 mg BID), including G2 blurred vision, G3 dermatitis acneiform, G3 arthralgia, G3 myalgia, G3 pain, G3 stomatitis, and G2/3 ALT increase. In the expansion study, 1 patient had dose-limiting equivalent toxicity of G3 myalgia at 300 mg BID.

Disappointingly, no responses (CR or PR) were reported in the study. A best of response of SD was achieved in 8 patients albeit the exposure at 300 mg BID was above the preclinical efficacious concentration (EC50). The mPFS in the expansion study was 1.8 months (1.3-7.2). With respect to the PK/PD profile of LY3009120 following single or multiple doses, Tmax ranged from 1-10 hrs, and half-life was from 3.1 to 9.9 hrs across all cohorts.

Exhibit 9: PK of LY30099120 following single dose administration



Source: Company data

Base on the preclinical and clinical data of LY30099120, LLY concluded the best explanation for the lack of efficacy of LY30099120 is that, despite reasonable plasma exposure levels, no target engagement in the tumor environment was observed, which was possibly due to insufficient time for target coverage because of its short half-life. Besides the short half-life, we think the poor selectivity and safety profile could also have led to the lack of observed efficacy.

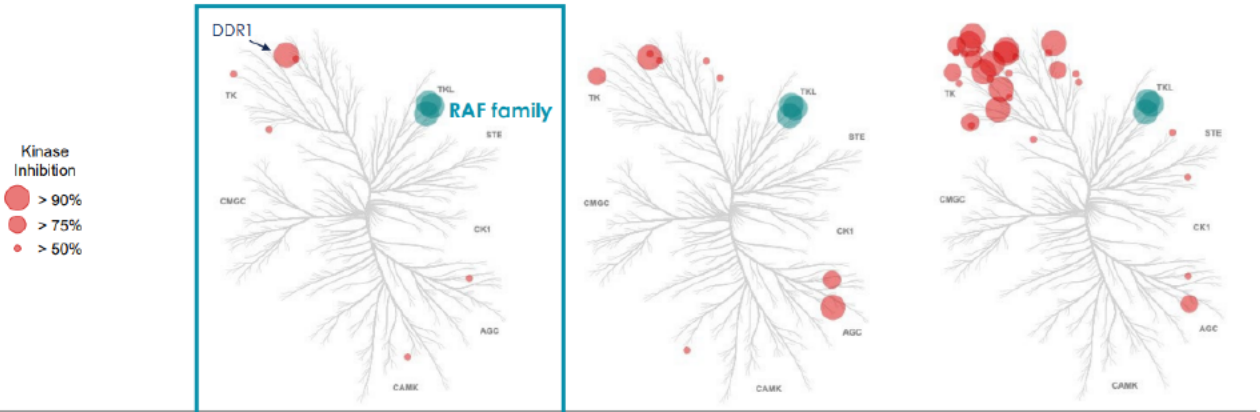
KIN-2787: MOA could drive differentiation vs. competing assets

One of the key issues with the currently approved BRAF inhibitors is that they will typically inhibit only one of the BRAF protomers in the dimer. As a result, the uninhibited molecule is activated and paradoxically leads to MAPK pathway activation, which is known as "pathway rebound". The pathway rebound can lead to harmful side effects and simultaneously limit the efficacy of the RAF inhibitor. To address these issues, KIN-2787 has been designed to inhibit both molecules of the dimer simultaneously, regardless of the specific dimer molecule variants.

High selectivity and potency: Of note, KIN-2787 demonstrated a selective kinome profile via radiometric kinase inhibition assays. KIN-2787 inhibits ARAF, BRAF, and CRAF with minimal off-target inhibition. In early studies, the company used ERK signaling as a measure of MAPK activation and, as seen in the exhibits below, KIN-2787 was able to activate MAPK at a lower level compared to ROG's cobimetinib and NVS's LXH254 seen with the higher level of ERK signaling in cells expressing wild type BRAF.

Based on this, we think the asset's ability to inhibit signaling in Class II and Class III mutations while minimally impacting WT could differentiate it compared to other drugs in development.

Exhibit 10: Selectivity compatison



Non-RAF Kinase Inhibition	Kinnate KIN-2787	Novartis LXH-254	Hanmi / Genentech Belvarafenib
# inhibited > 50%	7	10	42
# inhibited > 75%	1	5	23
# inhibited > 90%	1	2	14

Source: Company data

Exhibit 11: BRAF activity comparisons in multiple cell lines

Mutant BRAF Class	Cell Line	BRAF / MAPK Pathway Alteration(s)	Roche Cobimetinib EC50 (nM)	Pfizer Binimetinib EC50 (nM)	Novartis LXH254 EC50 (nM)	Hanmi/Genentech Belvarafemib EC50 (nM)	Kinnate KIN-2787 EC50 (nM)
I	A375	BRAF V600E	4	7	171	67	**67**
I	Colo800	BRAF V600E	N/A	6	242	108	**112**
II	BxPC3	BRAF indel	6	3	32	42	**51**
II	OV90	BRAF indel	2	4	24	22	**26**
II	H2405	BRAF indel	2	6	5	8	**10**
III	WM3629	BRAF D594G / NRAS G12D	3	5	6	4	**9**
III	CAL12T	BRAF G466V	4	3	19	41	**18**
WT	MiaPaCa-2	BRAF WT / KRAS G12C	9	N/A	357	N/A	**517**
WT	CHL-1	BRAF WT / NRAS WT	5	5	291	443	**580**
WT	NCI-H358	BRAF WT / KRAS G12C	N/A	1	153	303	**351**
WT	BJ	Wild type	N/A	31	486	2923	**7963**

Source: Company data, Goldman Sachs Global Investment Research

Optimized pharmacological properties: In terms of specific drug properties, we note that aqueous solubility is a focus in the category given its ability to improve drug absorption and potency. KIN-2787 has demonstrated higher aqueous solubility compared to LXH254, which also expected to improve the drug's exposure. KIN-2787 demonstrated close to three times area under the curve (AUC) compared to LXH254 (1,123 ng*h/mL vs. 3,335 ng*h/mL), which could increase its target engagement.

Exhibit 12: Improved physicochemical properties of KIN-2787

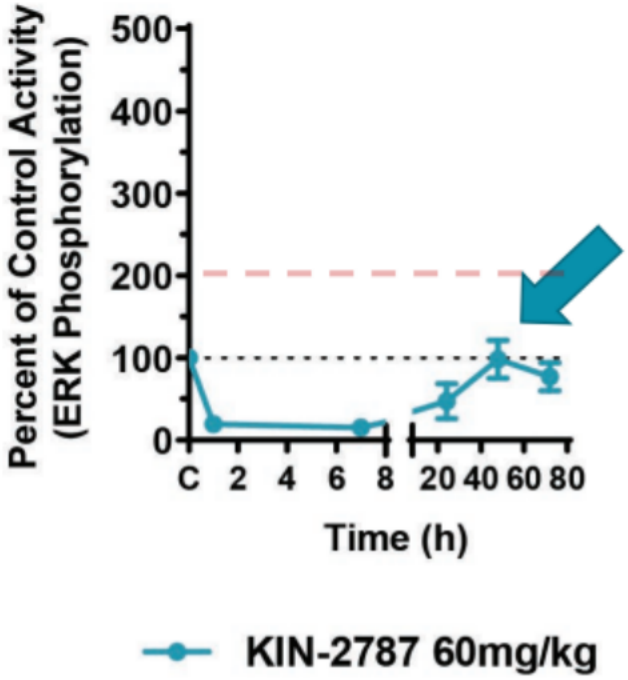
Feature	Parameter	Novartis LXH254	Hanmi/Genentech Belvarafemib	Kinnate KIN-2787
In vitro drug solubility	**Aqueous Solubility (uM)** pH = 7.4 pH=4.5 pH=2.0	 **8** **7** **50**	 **0.1** **0.4** **266**	 **29** **196** **312**
In vivo mouse pharmacology	**100 mg/kg per oral dose** Clearance (mL/min/kg) AUC / dose (ng*h/mL)	 **10** **1123**	 **N/A**	 **8** **3335**
Human plasma free fraction (%)	N/A	**<1**	**<1**	**7**

Source: Company data

Improved exposure: In human tumor cell xenografts, KIN002787 was dosed daily in tumor models with *BRAF* Class I, *BRAF* Class II, and *BRAF* Class III mutations compared to LXH254 and vehicle. While the two assets demonstrated similar tumor volume responses, we note that KIN-2787 was dosed up to 60 mg/kg/day whereas LXH254 was dosed at 200 mg/kg/day which represents >4x more free drug exposure vs. the highest clinical dose at 600 mg BID.

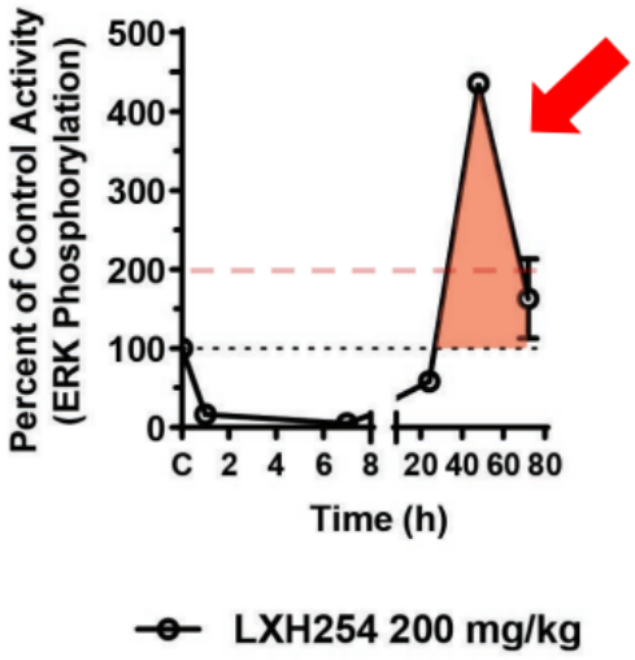
Absence of pathway rebound: In additional cancer cell line xenografts (with *BRAF* Class III mutation), phosphorylated ERK was evaluated as a measure of MAPK pathway signaling. As seen below, ERK phosphorylation was inhibited around one hour after a 60 mg/kg dose of KIN-2787, and maintained at seven hours. At ~24 hours after administration, ERK phosphorylation partially recovered and fully recovered at ~48 hours (100% BL). Alternatively, LXH254 treatment at 200 mg/kg led to pathway rebound of ERK phosphorylation at 48 hours after treatment (>400% BL).

Exhibit 13: In vivo ERK activity of KIN-2787



Source: Company data

Exhibit 14: In vivo ERK activity of LXH254



Source: Company data

Clinical efficacy and safety expectations for KIN-2787

Selecting a universe for a novel drug

In terms of a potential framework to assess KIN-2787's initial efficacy and safety profile, we first look to multiple approved BRAF-targeted inhibitors, including but not limited to: Novartis's (NVS; covered by Keyur Parekh) Tafinlar, Daiichi-Sankyo (4568:JP; covered by Akinori Ueda) and Genentech's (subsidiary of ROG:VX, covered by Keyur Parekh) Zelboraf, and Pfizer's (PFE; covered by Chris Shibutani) Braftovi, which are therapies approved for patients with Class I *BRAF* mutations. Tafinlar is approved for melanoma, NSCLC, and anaplastic thyroid cancer. Zelboraf is approved for melanoma, and Braftovi is approved in melanoma and CRC. In addition, we analyzed preliminary efficacy of several competing assets and retrospective meta-analyses of approved BRAF therapies.

While KNTE is targeting patients with Class II or Class III *BRAF* mutations who are not currently indicated for approved therapies, the approved BRAF inhibitors validate the clinical rationale for targeting BRAF in these aforementioned cancers. While we do not see these therapies as direct competitors given the different mutation population that KNTE is targeting, we view them as the closest available benchmarks to KIN-2787.

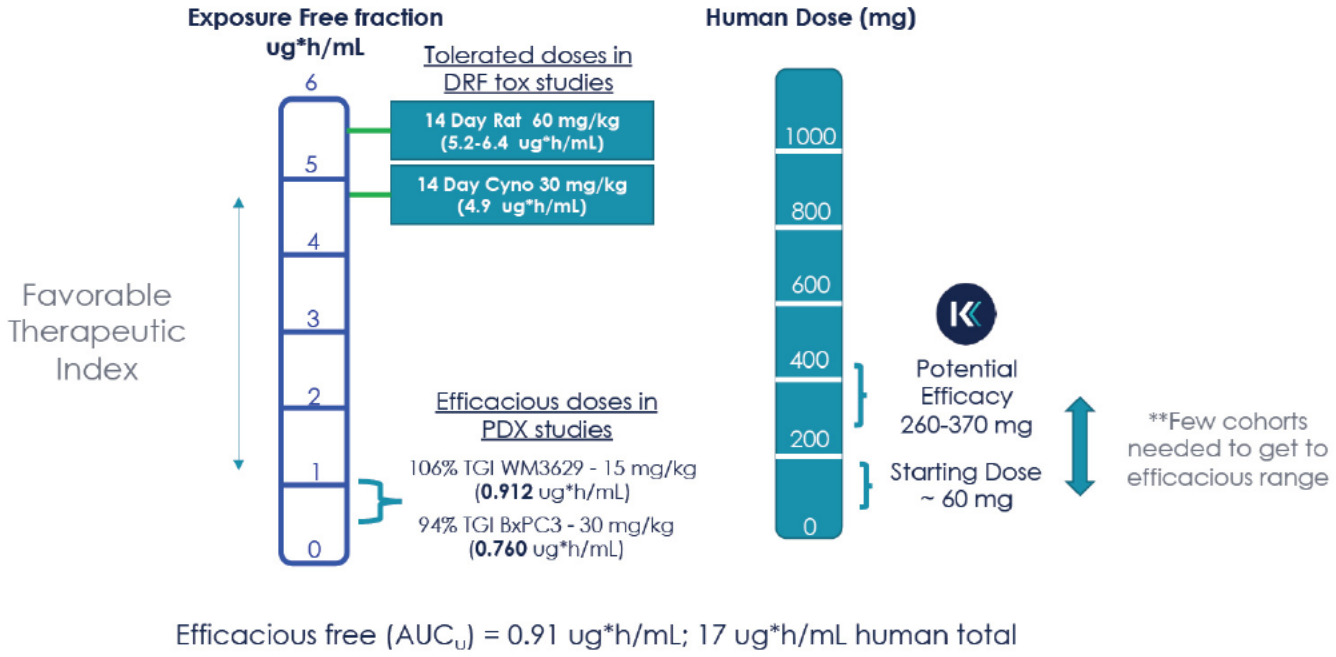
Additionally, we note that the company may pursue cancers with Class I mutations (naive or acquired resistance) eventually, which would provide upside to our estimates. We currently ascribe a 40% PoS to KIN-2787 in a monotherapy setting, which we would consider revisiting on the basis of the upcoming Phase 1 results.

Dosing - forming the basis for safety and efficacy

In preclinical DRF-tox studies, a 60 mg/kg dose was tolerated in a 14-day rat study (5.2-6.4 ug*h/mL) and a 30 mg/kg dose was tolerated in a 14-day cyno study (4.9 ug*h/mL), both of which considerably exceeded the predicted efficacious doses based on exposure levels observed in patient sample xenograft preclinical studies. The company is planning to start the in-human dose escalation at 60 mg, with the potential predicted efficacy range being between 260 mg - 370 mg, which is in line with our estimation (based on estimated allometric scaling). We note that the therapeutic index (maximal tolerated exposure divided by minimal efficacious exposure) in the preclinical DRF-tox study is ~5-8, which is considered to be relatively narrow whereas empirically above 10 is generally thought to be a wide therapeutic window.

Importantly, we think the optimized pharmacological properties (improved solubility, selectivity, protein binding) of KIN-2787 could potentially overcome the drawbacks of this relatively narrow therapeutic window, thereby enabling it to achieve optimal exposure and target engagement.

Exhibit 15: Company estimated human therapeutic index



Source: Company data

A commonly used class comparator is NVS's developmental pan-RAF inhibitor LXH254. By examining the available preclinical and clinical data for LXH254, we can see that exposures associated with efficacious preclinical doses were >2x than the max unbound free-drug fraction exposure shown in the clinic, thereby potentially explaining why the clinical data from this program were underwhelming.

We detail the steps in this calculation in the exhibit below.

Exhibit 16: LXH254 pre-clinical data to clinical AUCs

LXH 254	
AUC for highest clinical dose (1,200 mg)	**79,300 ng/ml*h**
Unbound fraction in plasma is ~3.7% for humans	
Corrected for human free fraction	**2,934 ng/ml*h**
Exposure at 150 mg/kg in Calu-6 human tumor xenografts in rats	216,800 nM*h
Unit correction based on weight of molecule of 502.5 g/mol & L to ml	
Exposure at 150 mg/kg in Calu-6 human tumor xenografts in rats	108,882 ng/mL*h
Unbound fraction in plasma is ~6.0% for rats	
Corrected for rat free fraction	**6,533 ng / ml*h**
Pre-clinical AUC / max clinical AUC	**2.2x**

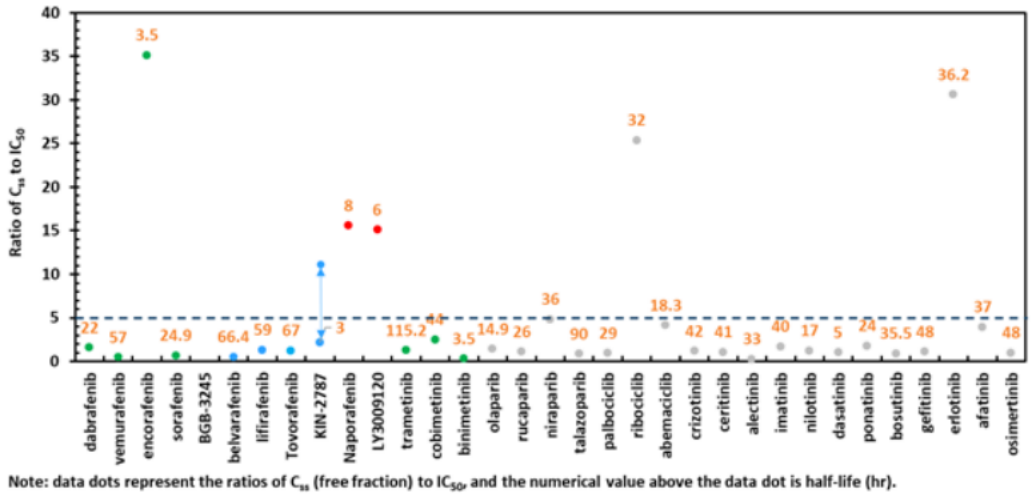
Source: Company data, Goldman Sachs Global Investment Research

In contrast, KIN-2787 exhibits a greater degree of human plasma free-drug fraction (7%) as well as higher solubility at physiologically-relevant pH levels. We believe these attributes will enable KIN-2787 to achieve sufficient physiological exposure levels that may lead to a higher probability for anti-tumor responses. Beyond these exposure issues, LXH254 also lags KIN-2787 on the basis of its potential for ERK pathway rebound, which may further support -2787's potential for pronounced and durable responses.

Additionally, we analyzed the PK profiles (steady-state free drug concentration, Css; IC_{50}; and the ratio of Css/IC50) of multiple kinase inhibitors (both approved and pipeline candidates), and results show that the estimated KIN-2787 steady state free drug exposure - Css/IC50 ratios range from 2 (at minimal efficacious dose) to 10 (at maximal tolerated dose). We see this is generally in-line with other approved kinase inhibitors (below 5, exception for encorafenib, ribociclib, and erlotinib) while two failed assets, naporafenib and LY3009120, exhibit ~15-time Css to IC_{50} at their minimal efficacious doses, which is a possible reason for their poor safety profiles.

With respect to half-life, we note a relatively short half-life of KIN-2787 (predicted human $t_{1/2}$ of ~3 hrs) whereas a longer half-life would be more favorable to achieve optimal target engagement and exposure at lower doses. Importantly, in our view, KIN-2787 could still be efficacious with a favorable safety/tolerability profile considering the following reasons: 1) the high selectivity of KIN-2787 reduces off-target toxicities; 2) lower protein binding and higher solubility/bioavailability increase plasma exposures and potentially target engagement in tumor environment; 3) though a shorter half-life may require higher doses to achieve equivalent efficacious exposures, leading to more toxicities due to higher Cmax, the identified toxicities (skin and GI tox) in the preclincial tox studies are mostly driven by exposure than Cmax (mostly related to cardiac toxicity), and therefore a balanced efficacy-safety profile can still be achieved; and 4) the lack of pathway rebound and limited activity of KIN-2787 in wild-type *BRAF* cells could potentially reduce skin-related toxicities and improve efficacy.

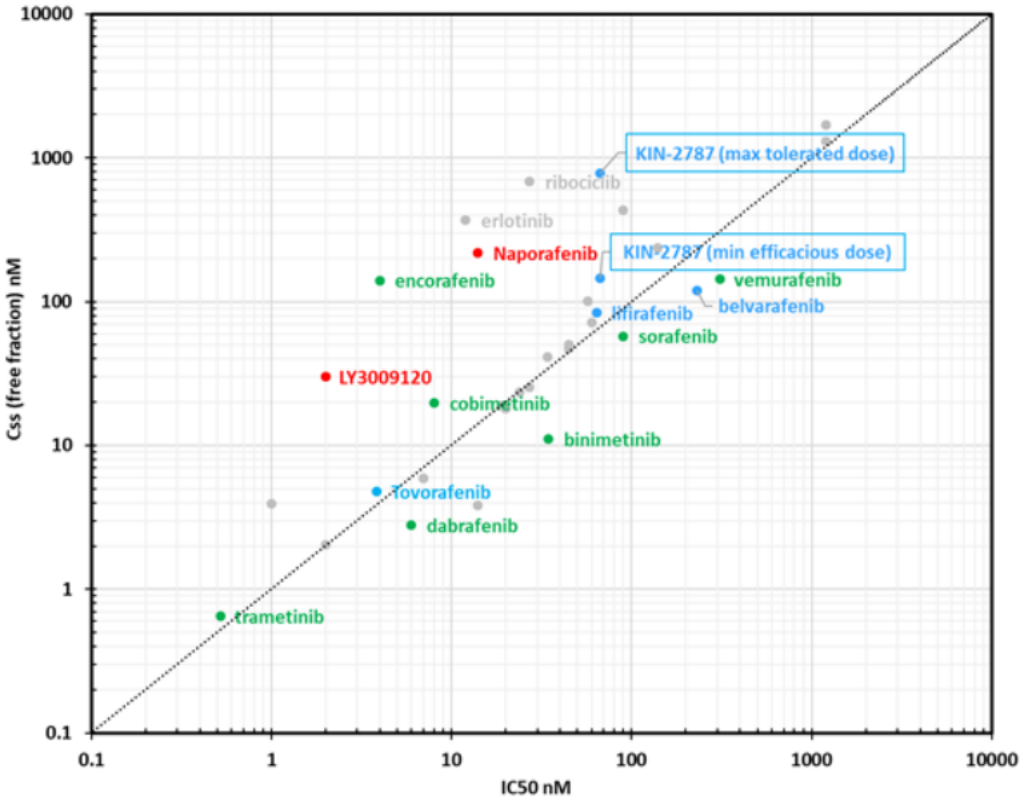
Exhibit 17: PK analyses of kinase inhibitors - Css/IC50, half-life



Note: data dots represent the ratios of C_{ss} (free fraction) to IC_{50}, and the numerical value above the data dot is half-life (hr).

Source: Goldman Sachs Global Investment Research

Exhibit 18: Correlation between Css and IC50 of kinase inhibitors



Source: Goldman Sachs Global Investment Research

Exhibit 19: Detailed PK data of kinase inhibitors

Target	Drug	Dose mg	Regimen	$t_{1/2}$ hr	AUCtau ng.h/mL	Cave ng/mL	fup unitless	fCave ng/mL	MW g/mol	fCave nM	IC_{50} nM	Css/IC_{50} unitless	Cell Line	MTD mg	Approved Regimen	Approved Indications	GLP Toxicology/Pharmacology
BRAF	dabrafenib	150	BID	8-22	4341	361.75	0.004	1.45	519.56	2.79	6	1.57	Colo205	ND	Monotherapy or combination with trametinib	Melanoma with BRAF V600E/K and NSCLC with BRAF V600E	Dog: cardiovascular AE at 5 times the human exposure at the recommended dose
BRAF	vemurafenib	960	BID	57	601000	50083.33	0.0014	70.12	489.92	143.12	309	0.46	Colo205	960	Monotherapy	Nelanoma and Erdheim-Chester disease with BRAF V600E	Mice: dose dependent cutaneous squamous cell carcinomas
BRAF	encorafenib	450	QD	3.5	13100	545.83	0.139	75.87	540.01	140.5	4	35.12	A375	450	Combination with binimetinib	Melanoma with BRAF V600E/K, CRC with BRAF V600E	Rats: hyperplasia and hyperkeratosis in the stomach at 14 times the human exposure at the 450 mg clinical dose
BRAF	sorafenib	400	BID	24.9	64300	5358.333	0.005	26.792	464.83	57.6	90	0.64	MB231	400	Monotherapy	Hepatocellular carcinoma, Renal cell carcinoma, thyroid cancer	N/A
BRAF	BGB-3245												N/A				
BRAF	belvarafenib	450	BID	41.2	68914.7	5742.89	0.01	57.4	478.93	119.91	230	0.52	A375	800	N/A	N/A	N/A
BRAF	lifirafenib	30	QD	15-59	47947	1997.79	0.02	40.0	478.42	83.52	64	1.30	A375	40	N/A	N/A	N/A
BRAF	Tovorafenib	450 mg/m2	QW	67	3450	246.43	0.0098	2.4	506.29	4.77	3.83	1.25	M27	N/A	N/A	N/A	N/A
BRAF	KIN-2787	15 mg/kg	BID	2-3	N/A	N/A	0.07	75.8	521	145.55	67	2.17	A375	60	N/A	N/A	Rats/cyno: tolerated exposure at 5.3-5.7 times of efficacious exposure
BRAF	Naporafenib	400	BID	8	35500	2958.33	0.037	109.5	502.5	217.83	14	15.56	Calu6	600	N/A	N/A	Dogs: body weight, increased bilirubin, soft feces/diarrhea at similar exposure at human efficacious dose
BRAF	LY3009120	300	BID	6	8460	705.00	0.0182	12.8	424.52	30.22	2	15.11	M12	300	N/A	N/A	N/A
MEK1/2	trametinib	2	QD	93.6-115.2	370	15.42	0.026	0.4	615.39	0.65	0.52	1.25	Colo205	3	Monotherapy or combination with dabrafenib	Melanoma with BRAF V600E/K and NSCLC with BRAF V600E	N/A
MEK1/2	cobimetinib	60	QD	44	4340	180.83	0.0583	10.54	531.32	19.84	8	2.48	Colo205	60	Combination with vemurafenib	Melanoma with BRAF V600E/K	N/A
MEK1/2	binimetinib	45	BID	3.5	2103	175.25	0.028	4.91	441.23	11.12	34.4	0.32	Colo205	60	Combination with encorafenib	Melanoma with BRAF V600E/K	N/A
PARP	olaparib	300	BID	14.9	49000	4083.33	0.18	735	434.47	1691.71	1200	1.41	ES7	400	Monotherapy or combination with bevacizumab	Ovarian, breast, pancreatic, prostate	N/A
PARP	rucaparib	600	BID	26	16900	1408.33	0.3	422.5	323.37	1306.55	1200	1.09	ES7	ND	Monotherapy	Ovarian, prostate	N/A
PARP	niraparib	300	QD	36	19700	820.83	0.17	139.54	320.4	435.52	90	4.84	CAPAN-1	300	Monotherapy	Ovarian, fallopian tube, peritoneal cancer	Dogs: cardiovascular AE at 0.5-5.8 times the unbound Cmax at steadt-state in human at the recommeded dose
PARP	talazoparib	1	QD	90	208	8.67	0.26	2.25	380.35	5.92	7	0.85	ES7	1	Monotherapy	Breast cancer	N/A
CDK4/6	palbociclib	125	QD	29	1863	77.63	0.147	11.41	447.55	25.5	27	0.94	EFM-19	125	Combination with aromatase inhibitor or fulvestrant	Breast cancer	N/A
CDK4/6	ribociclib	600	QD	32	23800	991.67	0.3	297.5	434.54	684.63	27	25.36	-	900	Combination with aromatase inhibitor or fulvestrant	Breast cancer	Dogs: QTc interval prolongation at an exposure similar in human at the recommended dose of 600 mg, premature ventricular contractions at 5 times the anticipated clinical Cmax
CDK4/6	abemaciclib	200	BID	18.3	3844	320.33	0.03	9.61	506.61	18.97	19	4.14	EFM-19	200	Combination with endocrine, aromatase inhibitor, fulvestrant or monotherapy	Breast cancer	Mice: retinal atrophy of the eyes at 10 times the exposure at the maximum recommended dose (for rats is 5 times the exposure)
ALK	crizotinib	250	BID	42	4166	347.17	0.093	32.29	450.34	71.69	60	1.19	Karpas299	250	Monotherapy	NSCLC, ALCL	N/A
ALK	ceritinib	750	QD	41	22590	941.25	0.028	26.36	558.14	47.22	45	1.05	Karpas299	750	Monotherapy	NSCLC	Rats: pancreatic focal acinar cell atrophy at 1.5 times the human exposure at the recommended dose, bile duct necrosis at 5% of the human exposure
ALK	alectinib	600	BID	33	7450	620.83	0.003	1.86	482.62	3.86	14	0.28	Karpas299	ND	Monotherapy	NSCLC	N/A
ABL	imatinib	400	QD	18-40	56400	2350	0.05	117.5	493.6	238.05	140	1.7	K562	NR	Monotherapy	Ph + CML	N/A
ABL	nilotinib	400	BID	17	16400	1366.67	0.016	21.87	529.52	41.29	34	1.21	K562	400	Monotherapy	Ph + CML	N/A
ABL	dasatinib	100	QD	3-5	396	16.5	0.06	0.99	488.01	2.03	2	1.02	K562	180	Monotherapy	Ph + CML	N/A
ABL	ponatinib	45	QD	24	1296	54	1	54	532.56	101.4	57	1.78	Ba/F3	45	Monotherapy	Ph + CML	N/A
ABL	bosutinib	500	QD	35.5	3650	152.08	0.063	9.58	530.45	18.06	20	0.9	K562	500	Monotherapy	Ph + CML	N/A
EGFR	gefitinib	250	QD	48	5900	245.83	0.091	22.37	446.9	50.06	45	1.11	HCC827	750	Monotherapy	NSCLC	N/A
EGFR	erlotinib	150	QD	36.2	41300	1720.83	0.084	144.55	393.44	367.4	12	30.62	H3255	150	Monotherapy or combination with gemcitabine	NSCLC, pancreatic	N/A
EGFR	afatinib	40	QD	37	920	38.33	0.05	1.92	485.94	3.94	1	3.94	HCC827	55	Monotherapy	NSCLC	N/A
EGFR	osimertinib	80	QD	48	5594	233.08	0.05	11.65	499.62	23.33	24	0.97	H1975	NR	Monotherapy	NSCLC	Rats: lens fiber degeneration at exposures 0.2 times the human exposure (2-year study)

Abbreviations are as follows: mg, milligram dose; QD/BID, daily or twice daily dosing; $t_{1/2}$, mean half-life (otherwise noted); AUCtau, area under the plasma concentration-time curve over the dosing interval, at steady-state; Cave, average plasma concentration; fup, fraction unbound drug in plasma; fCave, free Cave; IC50, concentration resulting in 50% target inhibition in vitro (cell potency); MW, molecular weight; MTD, maximum tolerated dose.

Source: Goldman Sachs Global Investment Research

Safety: anticipating class effect AEs and other considerations

In terms of safety, the most common ≥Grade 3 treatment-emergent adverse events for approved RAF family kinase inhibitors in dose-escalation settings are hypertension, fatigue, rash, creatine phosphokinase elevation, cutaneous squamous-cell carcinoma, cytopenia and hypoalbuminaemia. **While cytopenia and hypoalbuminaemia were AEs of note in preclinical toxicology studies for KIN-2787**, we view hypoalbuminaemia as more of an abnormal lab value and do not think that it will be a material event in the clinic. The company will monitor all AEs known to arise with Class I inhibitors for the

FDA, but noted it expects safety to be comparatively better on the whole.

From a broader perspective, in a study comparing vemurafenib against dacarbazine in melanoma with *BRAF* V600E mutation, adverse events led to dose modification or interruption in 129 of 336 (38%) of patients in the vemurafenib group and in 44 of 282 patients (16%) in the dacarbazine group. We have listed below on-label adverse events seen with the current standard of care (Zelboraf) in melanoma patients who have failed at least one prior systemic therapy (link). We also note that Zelboraf's safety profile is comparable to other on-market drugs, such as NVS's Mekinist.

Additionally, we list the associated AEs with approved BRAF and MEK inhibitors and possibly mechanistic explanation from several studies.

Dermatological events: As for BRAF and MEK inhibitors, the most frequent cutaneous side effects include rash, itching, dry skin, hair loss, photosensitivity reaction, keratinocytic proliferation and panniculitis. Specifically, rash was most often observed for vemurafenib/cobimetinib and was less common for dabrafenib/trametinib and for encorafenib/binimetinib. Generally, cutaneous side effects are usually well treatable and often do not immediately lead to dose reduction or discontinuation of therapy.

GI events: GI toxicities are commonly seen during therapy with BRAF and MEK inhibitors, including diarrhea, nausea, and vomiting. Studies have shown that frequencies of GI AE are higher for the combination of BRAF and MEK inhibitors compared with either monotherapy though the underlying pathophysiological mechanisms are still not completely understood. A possible explanation could be related to that the MAPK pathway is activated via EGFR in GI normal mucosa, and this pathway is a negative regulator of chloride secretion. Clinical research suggests that Grades 1 and 2 diarrhea may be managed with antidiarrheal medications, and in Grade 3+ cases, BRAFi/MEKi therapy should be withheld in addition to symptomatic treatment. Often those common GI adverse reactions resolve within a few days after cessation of treatment.

General disorders and hematological events: Fever and fatigue are very frequent with BRAFi+MEKi therapy while the Grade 3+ fever rate remains below 5%. Studies suggest that fever usually can be treated with medications and supportive care with a treatment holiday of few days for BRAF and MEK inhibitors. In addition, a full dose schedule can often be resumed after fever is resolved.

Cardiovascular events: Cardiovascular side effects have been described for BRAF and MEK inhibitors including QT-prolongation, cardiomyopathy with reduced pump function, and hypertension. QT prolongation is mainly an issue in treatment with vemurafenib (3-7%), which was dose dependent. Grade 3+ QT interval prolongation occurred in 1% of patients treated with vemurafenib monotherapy or with vemurafenib/cobimetinib. Interestingly, these QT prolongation AEs were not seen with dabrafenib or encorafenib, and research suggests this could be due to an additional fluorinated phenyl ring. In addition, most of the cardiac side effects can be adequately managed and are reversible with frequent monitoring.

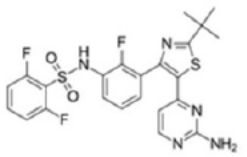
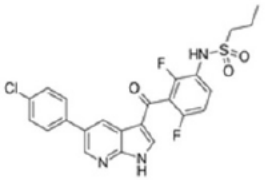
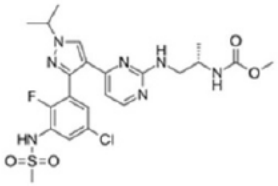
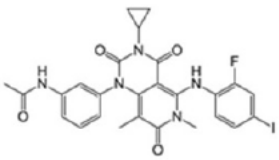
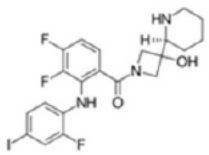
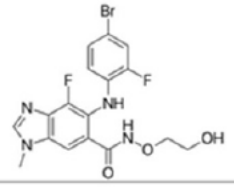
Ocular events: Serous neuroretinal detachment (SND) is a regular AE during treatment

with BRAF and MEK inhibitors. Importantly, SND associated with BRAF and MEK inhibitors is often asymptomatic, but may rarely cause transient blurred vision. Clinical studies suggest that during treatment, ophthalmologic checks including OCT should be performed depending on visual disturbances.

Renal events: Combination of BRAF and MEK inhibitors can cause renal impairment, mostly as an increase of serum creatinine. Acute renal failure or electrolyte disorders have been observed for all combination therapies. Dose interruption of BRAF and MEK inhibitors should be implemented to resolve renal AEs, and BRAFi + MEKi can reintroduced after improvement of renal function at a lower dose.

Overall, we think that any marginal improvement to the frequency of the listed AEs with no alarming additions, would be considered a positive result for KIN-2787. Further, we think that a dose modification or interruption of less than 25% would be an acceptable result.

Exhibit 20: Structural and PK properties of approved BRAF and MEK inhibitors

	Dabrafenib / Trametinib	Vemurafenib / Cobimetinib	Encorafenib / Binimetinib
BRAF Inhibitors **Dab.** (GSK2118436) **/** **Vem.** (PLX4032,RG7204) **/** **Enc.** (LGX818)			
	RP2D: **150 mg td** (MTD not reached) * BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.9 h** Time to steady-state ($t_{max,ss}$): **14 d** $AUC_{0\text{-}24,ss}$: **4.3 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **1478 ng/mL** (37 %CV_b) Clearance (CL/F): **17.3 L/h** (nc) Elimination half-life (t½): **8.4 h** (nc)	RP2D: **960 mg td** (=MTD) BCS class: IV (low permeability, low solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): ~**4 h** Time to steady-state ($t_{max,ss}$): **15-22** d $AUC_{0\text{-}8,ss}$: **380.2 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **56,700 ng/mL** (38 %CV_b) Clearance (CL/F): **1.2 L/h** (32 CV_b%) Elimin. half-life (t½): **56 h** [30-120]	RP2D: **300 mg od** (MTD: 450 mg od) BCS class: *nr* Food effect: None (Intake with/without food) Absorption (t_{max}): **2.0 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}24,ss}$: **12.3 h*µg/mL** (med.) $C_{max,ss}$: **3100 ng/mL** (med.) Clearance (CL/F): **24.4 L/h** (med.) Elimination half-life (t½):**6.3 h** [3.7-8.1]
MEK Inhibitors **Tra.** (GSK1210212) **/** **Cob.** (RG7420) **/** **Bin.** (MEK162)			
	RP2D: **2 mg od** (MTD: 3 mg od) BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.5 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}24,ss}$: **0.4 h*µg/mL** (22 %CV_b) $C_{max,ss}$: **22 ng/mL** (28 %CV_b) Clearance (CL/F): **5.4 L/h** (nc) Elimination half-life (t½): **90 h** [58-183]	RP2D: **60 mg od** (d1-21 q4w) (=MTD) BCS class I: (high permeability, high solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): **2.4 h** Time to steady-state ($t_{max,ss}$): **10 d** $AUC_{0\text{-}24,ss}$: **4.3 h*µg/mL** (61 %CV_b) $C_{max,ss}$: **273 ng/mL** (60 CV_b%) Clearance (CL/F): **13.8 L/h** (61% CV) Elimination half-life (t½): **44 h** [23-69]	RP2D: **45 mg td** (MTD: 60 mg td) BCS class: *nr* Food effect: none (Intake with/without food) Absorption (t_{max}): **2.0 h** (1.5 h at 60 mg td) Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0\text{-}8,ss}$: **1.5 h*µg/mL** (nc) $C_{max,ss}$: **273 ng/mL** (65 %CV_b) Clearance (CL/F): *nr* Elimination half-life (t½): **8.7 h** (nc)

* no-dose-limiting toxicity recorded at 300 mg td

Source: doi.org/10.1136/esmoopen-2019-000491

Exhibit 21: G3+ treatment-related AEs of three approved BRAF inhibitors

Tafinlar (dabrafenib)		Zelboraf (vemurafenib)		Braftovi (encorafenib) + binimetinib	
Grade 3+ AEs	Grade 3+ (%)	Grade 3+ AEs	Grade 3+ (%)	Grade 3+ AEs	Grade 3+ (%)
Hyperglycemia	6%	Cutaneous SCC	22%	Increased Gamma Glutamyl Transferase	11%
Hypophosphatemia	6%	GGT	12%	Increased ALT	6%
suSCC	4%	Rash	8%	Hyperglycemia	5%
Pyrexia	3%	Arthralgia	4%	Abdominal pain	4%
Back pain	3%	Photosensitivity reaction	3%	Pyrexia	4%
Palmar-plantar erythrodysesthesia syndrome	2%	Gamma-glutamyltransferase increased	3%	Increased Creatinine	4%
Constipation	2%	ALT	3%	Hyponatremia	4%
Hyponatremia	2%	Alkaline phosphatase	3%	Anemia	4%
Hyperkeratosis	1%	Rash maculo-papular	2%	Dizziness	3%
Arthralgia	1%	Fatigue	2%	Hemorrhage	3%
		Nausea	2%	Fatigue	3%
		Bilirubin	2%	Neutropenia	3%
		Pruritus	1%	Increased AST	3%
		Hyperkeratosis	1%	Headache	2%
		Vomiting	1%	Nausea	2%
				Vomiting	2%
				Lymphopenia	2%
				Hyperkeratosis	1%
				Rash	1%
				Pruritus	1%
				Peripheral neuropathy	1%
				Arthralgia	1%
				Pain in extremity	1%
				Hypermagnesemia	1%

Source: FDA labels

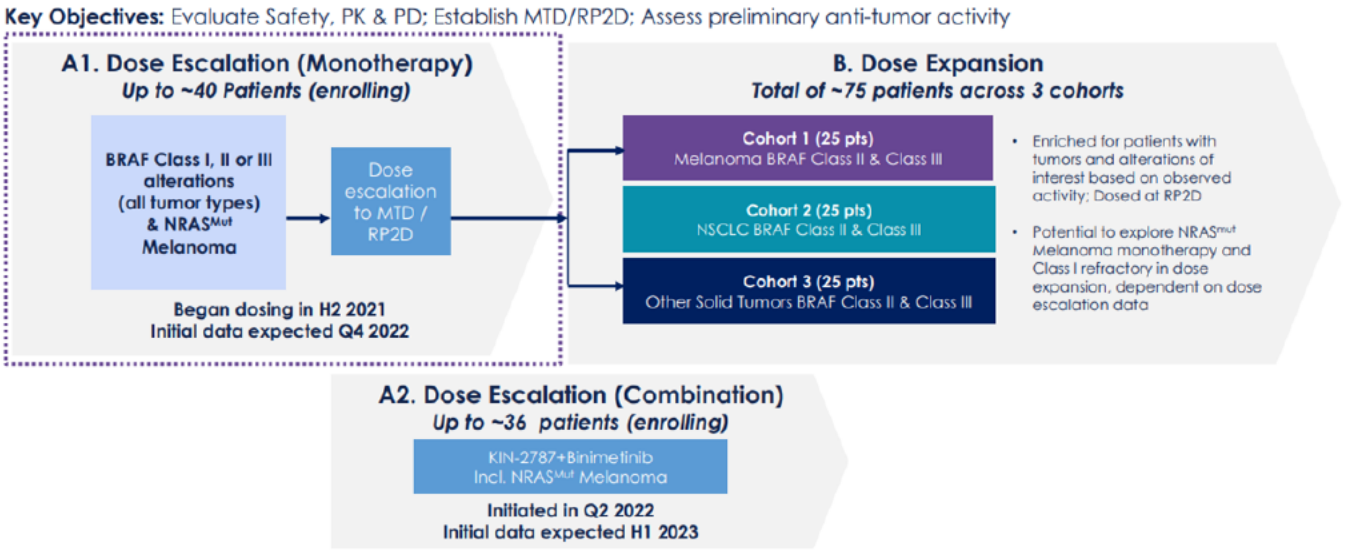
Monotherapy Efficacy: looking for 20-25% ORR in dose escalation

Trial design: The Phase 1 study of KIN-2787 will enroll patients with *BRAF*-driven advanced or metastatic tumors. This study will enroll ~115 patients with Class I, II, or III *BRAF* mutant cancer (with a cap on the number of Class I patients to be enrolled), and the interest remains on the clinical activity towards *BRAF* Class II & III mutated solid tumors and overcoming mechanisms of resistance to the first-generation BRAFi for Class I mutation. The dose escalation part will focus on safety, PK/PD, and preliminary activity and inform the dose for the subsequent dose expansion portion (*BRAF* Class II & III NSCLC and melanoma). Importantly, the previously announced initiation of the combination study marked that a combination of pre-specified criteria (e.g., safety) has been met based on the ongoing monotherapy study.

In the dose expansion portion of the study, patients with *BRAF* Class II or Class III mutations will be enrolled in: 1) Cohort 1: melanoma, 2) Cohort 2: NSCLC, or 3) Cohort 3: other solid tumors. The cohorts will include ~25 patients each (see below).

In addition, the Phase 1 trial should allow KNTE to determine an appropriate Phase 2 dose and schedule. As of now and pending positive Phase 1 clinical trial data, the company plans to engage with the FDA after the Phase 1 data to discuss one or more potential Phase 2 trials, which could be registration-enabling.

Exhibit 22: Phase 1 trial design



Source: Company data

Efficacy benchmark. In terms of a clinical bar for response rates in a monotherapy setting, we look to similar Phase I dose-escalation studies of RAF family kinase inhibitor's in later-line patients. While Class II and III doesn't have a directly-related precedent (Class II & III selective BRAF inhibitor) to benchmark against in a monotherapy setting for NSCLC and melanoma, we highlight the following studies and a meta-analysis as the closest comparable evaluations to establish expectations for potential efficacy:

- **Tovorafenib** (DAY101, pan-RAF inhibitor) monotherapy achieved 64% ORR in *BRAF*-mutant pediatric patients with recurrent/progressive low-grade glioma. Specifically, a 60% ORR (all PRs) was observed in 20 *BRAF* Class II fusion patients, and 100% ORR was reported in 2 *BRAF* V600E patients.
- A **meta-analysis** (link) of responses in 238 *BRAF* Class II & III cancer patients who were treated with BRAFi and/or MEKi, and EGFRi therapies demonstrate 40.7% and 12.7% response rates in Class II and III population, respectively, **which suggests the former is more likely to respond to a treatment such as KIN-2787 than the latter.** In addition, mPFS was 4.6 months and 2.1 months for Class II and III patients, respectively. Specifically, approved BRAF inhibitors achieved 11.7% response rate in Class II & III population, and approved MEK inhibitors had 37.9% response rate. Importantly, the combination of BRAFi and MEKi further improved the response rate to 50.8%.
- Single agent dabrafenib was initially tested in *BRAF* V600E mutated NSCLC. This Phase 2 study included 84 patients, 78 pre-treated and 6 untreated patients. A 33% objective response rate (ORR) to dabrafenib was observed in the pre-treated group with a further 24% categorized as stable disease. Further, the median progression free survival was 5.5 months (link).
- In the Phase III monotherapy dose-escalation and expansion study of binimetinib (NEMO trial), the clinical effect of binimetinib on *NRAS*-mutant melanoma was

observed. Binimetinib was compared with chemotherapy in patients with unresectable or metastatic melanoma with an *NRAS* mutation. The ORR was higher in the binimetinib arm, 15.2% versus the dacarbazine arm, which showed 6.8% (link).

- In the study of lifirafenib in patients with solid tumors, of the 53 patients with *BRAF* mutations, 1 achieved a complete response (1.9%) and 8 achieved a partial response (15.1%; link). We view lifrafenib as a close comparable for KIN-2787 and highlight further data in the exhibit below.
- In the dose-escalation study of CH5126766, a novel MEK-pan-RAF inhibitor, seven of 26 (27%) response-evaluable patients in the basket expansion achieved objective responses (link).

Taking into account response rates in prior comparable settings and the lack of details on patient baseline characteristics and mix of Class II and III tumor types, we think that **an ORR of 30%+ in a mix of *BRAF* Class II & III patients would be a positive result** by investors. Further, if the company were to achieve **a ~25% ORR, we think this would widely be viewed as an acceptable result**. Finally, **an ORR of less than 20% would most likely be viewed as a disappointing result**.

Addressable market and GS estimates

We ascribe risk-adjusted credit for KIN-2787 in NSCLC and melanoma, which are the initial patient populations on which KNTE is focusing. In the US, there are ~241k NSCLC patients with Stage IIIb/IV active disease and ~9k of these have a *BRAF* mutation. Of these patients we estimate ~4.8k have a Class II/III mutation and are diagnosed, which we see as the addressable population (EU: ~5k; JPN: ~3.5k). In melanoma, there are ~38k patients with Stage IV active disease and ~12k with a *BRAF* mutation. Of these patients, we estimate ~2.2k have a Class II/III mutation and are diagnosed, which we see as the addressable market (EU: ~1.7k; JPN: ~120).

Further, we assume initial launch pricing of $175k per year, increasing 2% annually, which is in line with recently approved kinase inhibitors. In a NSCLC population, we assume a duration of 11 months given Tafinlar's (dabrafenib) mDoR of 9.9 months in previously treated patients and 12.6 months in patients treated with Tafinlar + Mekinist (trametinib). In the melanoma population, we assume duration of therapy of 7 months based on data from comparable drugs in this population. We assign a probability of success (PoS) of 40% to both populations in our model.

Exhibit 23: WAC prices of approved BRAF and MEK inhibitors

Brand Name	Drug Name	Strength	Package Size	WAC Price	Dose	Frequency	Cost per Year
Zelboraf	vemurafenib	240mg	112	$ 5,316.90	960mg	BID	$ 127,605.60
Tafinlar	dabrafenib	50mg	120	$ 12,489.08	150mg	BID	$ 149,868.96
Braftovi	encorafenib	75mg	90	$ 6,686.86	450mg	QD	$ 160,484.64
Mekinist	trametinib	2mg	30	$ 13,559.71	2mg	QD	$ 162,716.52
Cotellic	cobimetinib	20mg	63	$ 7,355.22	20mg	21 days in a 28-day cycle	$ 88,262.64
Mektovi	binimetinib	15mg	180	$ 13,121.37	45mg	BID	$ 157,456.44
						Average	$ 151,626.43

Average price excludes Cotellic

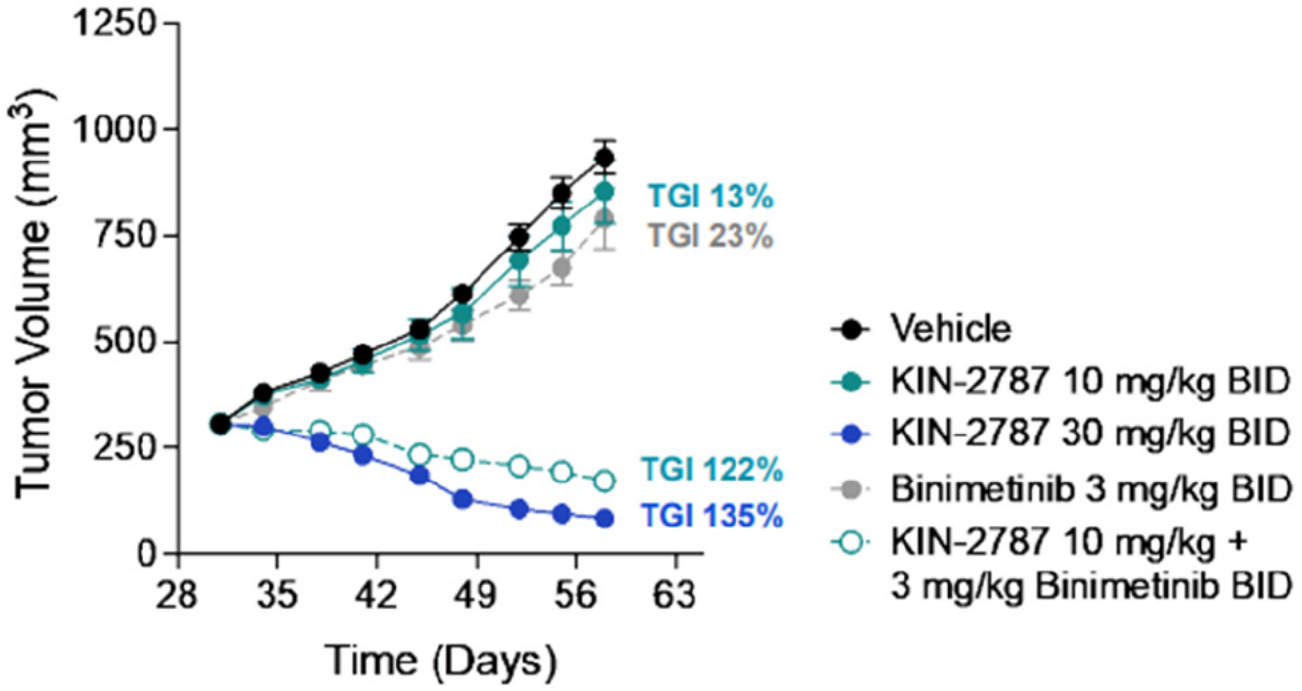
Source: PriceRx, Goldman Sachs Global Investment Research

RAF KIN-2787 + binimetinib combination

While the upcoming data (part A1) will be assessing KIN-2787 in a monotherapy setting, KNTE is also expanding the Phase 1 KIN-8701 study evaluating KIN-2787 to include a combination portion (Part A2) with the MEKi binimetinib (sold as Mektovi) in patients with *NRAS*mut melanoma. Currently approved Class I BRAF inhibitors do not have activity in *NRAS*mut melanoma and are not approved for Class II/III *BRAF*mut tumors. Binimetinib was selected as a combination agent based on its prior monotherapy performance in this indication, which the company believes could be improved with KIN-2787.

In our view, this combination makes sense as the synergy with binimetinib may potentially enable deeper and more sustained target coverage than monotherapy alone. Furthermore, preclinical data shows that KIN-2787 plus binimetinib combination treatment demonstrated meaningful tumor reductions and enhances anti-tumor activity compared to monotherapy (see exhibit below).

Exhibit 24: Potential for synergy in vitro and suggestive in vivo in NRAS, BRAF WT Melanoma



Source: Company data

Scenario analyses

Base on our aforementioned clinical benchmarks, we outlined the potential outcomes of the upcoming Phase 1 KIN-2787 monotherapy trial as below.

Base Case (60% probability)

KIN-2787 achieves an ORR of ~25% in a mix of *BRAF* Class II & III patients treated at various dose levels, and KIN-2787 is well tolerated with no new safety concerns (cardiac tox, ocular tox, etc.) other than mild-to-moderate skin-related toxicities, GI events, increased bilirubin, anemia, etc. PK/PD of KIN-2787 shows optimal exposure and high target engagement with a potential to further increase doses.

Stock reaction: Should the Phase 1 study achieve the efficacy and safety profile as described above, we think KNTE shares would increase 40%-50% from current levels as early efficacy is currently a focus for investors given KNTE's data would likely be first to target at *BRAF* Class II and III solid tumor patients with no direct cooperators.

Bull Case (25% probability)

KIN-2787 achieves an ORR of 30%+ in a mix of *BRAF* Class II & III patients treated at various dose levels, and KIN-2787 is well tolerated with no new safety concerns (cardiac tox, ocular tox, etc.) other than mild-to-moderate skin-related toxicities, GI events, increased bilirubin, anemia, etc. PK/PD of KIN-2787 shows optimal exposure and full target engagement.

Stock reaction: Should the Phase 1 study achieve the efficacy and safety profile as described above, we think KNTE shares would increase 80%-100% from current levels with similar stock movement as DAWN's recent ~+100% price reaction post its tovarafenib positive data in a rare pediatric indication.

Bear Case (15% probability)

KIN-2787 achieves an ORR less than 20% in a mix of *BRAF* Class II & III patients treated at the highest dose level, and KIN-2787 is less tolerated with new safety concerns (cardiac tox, ocular tox, etc.) other than moderate-to-severe skin-related toxicities, GI events, increased bilirubin, anemia, etc. PK/PD of KIN-2787 shows sub-optimal exposure and poor target engagement.

Stock reaction: Should the Phase 1 study shows the efficacy and safety profile as described above, we think KNTE shares would drop 20%-30% from current levels considering investors would likely put discount on KIN-2787 given lowered market penetration for monotherapy as well as raise questions on KNTE's kinases discovery platform.

Next steps

If successful, we expect KIN-2787 will move into the dose expansion phase of the trial. In the dose expansion portion, we expect thereto be 3 cohorts of roughly 25 patients each. The cohorts will likely be made up of: (i) Melanoma (*BRAF* Class II or Class III mutations), (ii) NSCLC (*BRAF* Class II or III mutations) and (iii) Other solid tumors (*BRAF* Class II or Class III mutations). To note, the dose expansion will add additional US sites and selected high impact EU and Asia Pacific centers.

KOL feedback indicates encouraging opportunity

We discussed KIN-2787 and other BRAF inhibitors targeting Class II and III mutations with a KOL at a largely, high volume academic hospital to understand clinicians' views on the current *BRAF* Class II and III cancer treatment landscape. The KOL recognizes significant unmet needs of the cancer patients harboring Class II and III *BRAF* (~50% of all *BRAF* mutations) as currently available therapies have limited efficacy.

1. KOL agrees that targeting BRAF dimers is valid. The KOL thinks targeting BRAF dimers through inhibition of the dimers or dimerization of BRAF/CRAF are promising, potentially achieving clinical benefits for Class II and III *BRAF* patients. More important, the KOL views targeting Class II *BRAF* cancers could potentially have higher clinical benefits as most Class II *BRAF* mutations are oncogenes while Class III *BRAF* may not be a driver for cancers. In line with our analyses, cancer patients harboring Class II *BRAF* showed higher efficacy compared to Class III *BRAF* when patients were treated by BRAF and/or MEK inhibitors.

2. KOL views KIN-2787's optimized pharmacological properties as likely to have an impact in the clinic. In line with our view, the KOL thinks the lack of efficacy of naporafenib could be attributed to the imbalance between exposure and safety. In KOL's

opinion, naporafenib's PK exposure was inefficient due to its relatively poor tolerability at higher doses. Additionally, the KOL addressed the need of adequate dosing to prevent paradoxical activation. As for KIN-2787, the KOL thinks the improved solubility, bioavailability, plasma free fraction could be clinically meaningful to improve efficacy and reduce toxicity. We note the KOL reiterated the importance of selecting right patient population as the inhibition of Class II BRAF kinases would likely show more clinical benefits compared to Class III BRAF kinases. In addition, the KOL thinks skin and GI toxicities associated with BRAF and/or MEK inhibitors are reversible and manageable while it may require dose interruption and/or reduction.

3. KOL views 25%-30% ORR as positive, potentially supporting further clinical development. Consistent with our expectations, the KOL think an ORR of 25%-30% would be positive for KIN-2787 to advance its clinical development. Importantly, the KOL noted the combination of BRAF and MEK inhibitors would be more applicable in clinical practice and beneficial to patients. Additionally, the KOL thinks Day One's tovorafenib data in rare pediatric brain tumors is interesting with the caveat of translating its efficacy into a class effect and other solid tumors.

Valuation and risks

We are Buy rated on KNTE. Our 12-month price target of $29 is based on a discounted cash flow (DCF) valuation analysis, assuming a 16% discount rate and terminal growth rate of 4%. Key risks: (-) worse-than-expected clinical data for KIN-2787 and KIN-3248; better-than-expected data from competitors in the indications that KNTE is pursuing; and launch execution and net pricing are worse than expected.

Disclosure Appendix

Reg AC

We, Paul Choi, Xiangyu (Roderick) Ma, Ph.D. and Cade Kruse, hereby certify that all of the views expressed in this report accurately reflect our personal views about the subject company or companies and its or their securities. We also certify that no part of our compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

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Growth is based on a stock's forward-looking sales growth, EBITDA growth and EPS growth (for financial stocks, only EPS and sales growth), with a higher percentile indicating a higher growth company. **Financial Returns** is based on a stock's forward-looking ROE, ROCE and CROCI (for financial stocks, only ROE), with a higher percentile indicating a company with higher financial returns. **Multiple** is based on a stock's forward-looking P/E, P/B, price/dividend (P/D), EV/EBITDA, EV/FCF and EV/Debt Adjusted Cash Flow (DACF) (for financial stocks, only P/E, P/B and P/D), with a higher percentile indicating a stock trading at a higher multiple. The **Integrated** percentile is calculated as the average of the Growth percentile, Financial Returns percentile and (100% - Multiple percentile).

Financial Returns and Multiple use the Goldman Sachs analyst forecasts at the fiscal year-end at least three quarters in the future. Growth uses inputs for the fiscal year at least seven quarters in the future compared with the year at least three quarters in the future (on a per-share basis for all metrics).

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	Buy	Hold	Sell	Buy	Hold	Sell
Global	50%	35%	15%	65%	58%	45%

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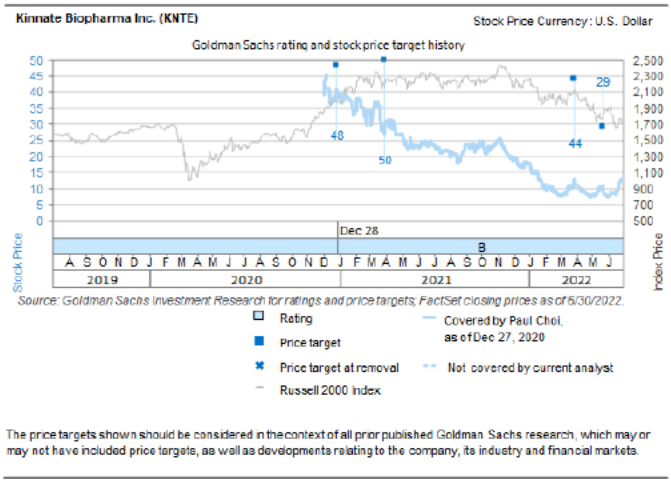
Price target and rating history chart(s)



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