#4122

Occurrence of BRAF class II and III alterations is common across solid tumors and is associated with inferior clinical outcomes in NSCLC and melanoma

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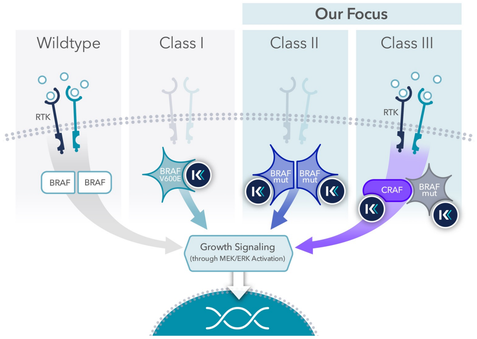
BACKGROUND

Three classes of BRAF alteration/mutation:

- **Class I** - kinase active signaling of BRAF mutant monomers
- **Class II** - kinase active signaling of BRAF mutant homodimers
- **Class III** - kinase impaired BRAF that signals through RAS-dependent, BRAF mutant / RAF wild-type heterodimers



- There are no approved targeted therapies for patients with BRAF Class II or Class III alterations.

➢ **KIN-2787** is a clinical stage, small molecule pan-RAF inhibitor designed to inhibit all classes of BRAF mutations.

Class	BRAF Alterations
Class I	$V600^{E/K/R/G/M/V/L/A/D}$
Class II	$Q257^{R}$, $P367^{L/S}$, $E451^{Q}$, $I463^{S}$, $G464^{V/E/R/A}$, $G469^{A/R/V/S}$, $V471^{F}$, $L485^{F/W}$ $N486\_A489^{delinsK}$, $N486\_P490^{del}$ $T488\_P492^{del}$, $K499^{E}$, $L505^{H/F}$, $L525^{R}$, $E586^{K}$, $L597^{R/V/Q/S}$, $E586^{K}$, $T599^{ir}$, $T599^{dup}$, $V600\_K601delinsE$, $K601^{E/N/Q/T}$
Class III	$F247^{L}$, $D287^{H}$, $G466^{V/E/A/R}$, $S467^{L}$, $G469^{E}$, $K483^{E}$, $R558^{Q}$, $N581^{I/Y/S/T/K}$, $D594^{N/E/G/H/A/Y/V}$, $F595^{L}$, $G596^{R/C/D/V}$, $T599^{k}$

METHODS

GuardantINFORM™ de-identified clinical genomic research database spanning 3/2014 thru 6/2021:

- 160,000+ patients with advanced/metastatic cancer profiled by the Guardant360® assay
- Over 80% of cases linked to treatment and procedural data
- Survival data is sourced from third party providers and aggregated with administrative claims data

Analysis of BRAF Class I, II, & III to explore:

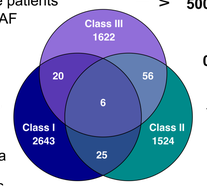
- Pan-cancer prevalence (count, % of ctDNA positive, % of BRAF positive)
- Patient characteristics in NSCLC
- Treatment landscape in NSCLC
- Real-world overall survival measured from time of metastatic diagnosis in NSCLC and Melanoma
  - Includes all BRAF Class I, II or III patients regardless of BRAF detection date
  - Patients without known death date censored at their date of last know claim activity
  - Cohorts compared pairwise with logrank test

RESULTS

Prevalence by Class (Pan-Cancer)

BRAF Class	No. of Patients	% of ctDNA Positive	% of BRAF Positive
I only	2,643	1.9	44.8
II only	1,524	1.1	25.8
III only	1,622	1.1	27.5
Multiple	107	0.1	1.8

- **55%** of BRAF positive patients (3,253/5,896) have Class II or Class III
- **2.3%** of all ctDNA positive patients (3,253/142,609) have BRAF Class II or Class III
- Cancer types with more than 100 Class II or III:
  - NSCLC, Colorectal, Breast, Prostate, Melanoma, Cholangiocarcinoma



- In most of the tumor types tested by ctDNA analysis, BRAF Class II and Class III are more common than Class I (*e.g.*, NSCLC, Breast, Prostate, Cholangiocarcinoma, Pancreatic, Gastric Adenocarcinoma, Ovarian, etc.).
- Occurrence of multiple BRAF alterations of distinct classes within a single patient sample is rare (0.1% of ctDNA positive patients).
- In this large study of liquid biopsy-derived genomic data, BRAF Class II and Class III alterations are present across a variety of tumor types.

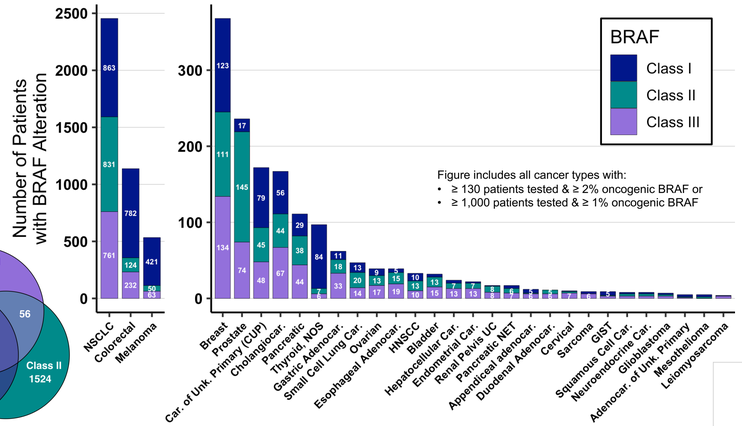
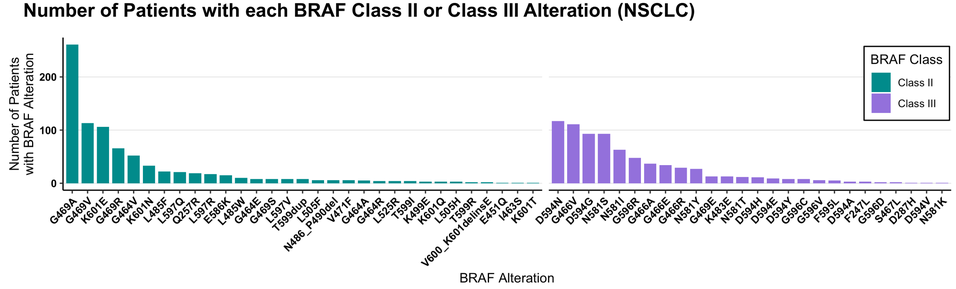


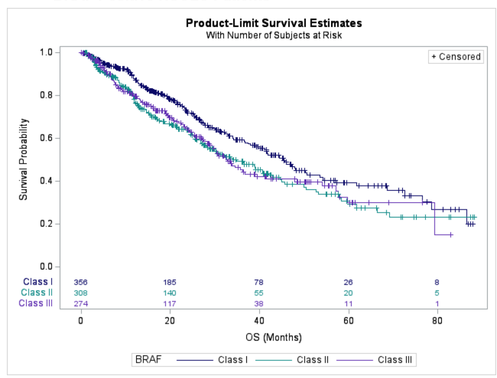
Figure includes all cancer types with:
- ≥ 130 patients tested & ≥ 2% oncogenic BRAF or
- ≥ 1,000 patients tested & ≥ 1% oncogenic BRAF

Number of Patients with each BRAF Class II or Class III Alteration (NSCLC)

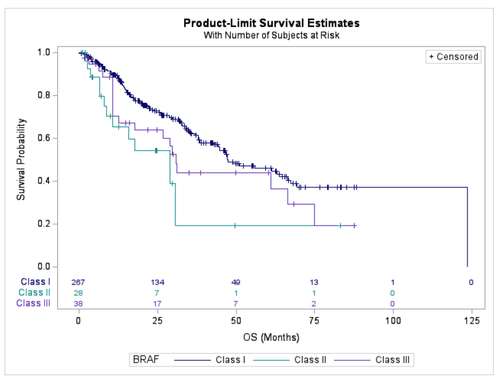


Real-World Overall Survival from Time of Metastatic Diagnosis (NSCLC, Melanoma)

BRAF Positive NSCLC Patients



BRAF Positive Melanoma Patients



- NSCLC and Melanoma patients with BRAF Class II or III had shorter median overall survival compared to patients with Class I.
  - Analyses include all patients with survival data and BRAF positive test regardless of BRAF detection date.
  - Patients with multiple classes of BRAF alteration were excluded from the analyses.

Cohort	Median OS from Metastatic Diagnosis, Months (%95 CI)			Unadjusted P-value (pairwise logrank test)		
	Class I	Class II	Class III	I vs II	I vs III	II vs III
NSCLC (n=938)	44.8 (37.5, 52.8)	34.4 (27.5, 41.5)	32.3 (28.4, 40.9)	0.006	0.0126	0.6611
Melanoma (n=333)	46.5 (42.3, 65.5)	28.5 (8.6, 30.3)	30.5 (12.5, 73.8)	0.0008	0.0165	0.6529

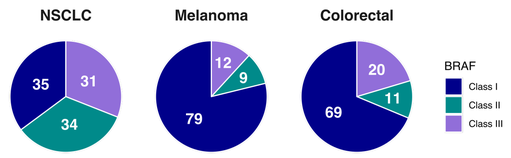
Patient Characteristics (NSCLC)

Parameters			BRAF Class			
			Class I	Class II	Class III	
Total Number			845	810	743	P-value
Age		Mean	68.61	70.10	69.37	0.0142
		Std Deviation	11.01	9.70	10.47	
		Median (range)	70 (23-85)	70 (42-85)	70 (41-85)	
Gender	Female	Frequency	476	410	371	0.0176
		Percent (%)	56.33	50.62	49.93	
	Male	Frequency	369	400	372	
		Percent (%)	43.67	49.38	50.07	
Vital Status	Unknown or Still Alive	Frequency	513	442	405	0.0144
		Percent (%)	60.71	54.57	54.41	
	Date of Death Known	Frequency	332	368	338	
		Percent (%)	39.29	45.43	45.49	
Smoking Status	Ever Tobacco Product User	Frequency	462	559	509	<0.0001
		Percent (%)	54.67	69.01	68.51	
	Unknown	Frequency	383	251	234	
		Percent (%)	45.33	30.99	31.49	

Note: Patients with multiple BRAF alterations across functional classes were excluded from the summary of characteristics. F test and Chi-squared test were used to compare means and frequencies respectively.

In BRAF Positive NSCLC:
- Class I has higher frequency of female versus male
- History of tobacco use is higher in Class II and Class III compared to Class I

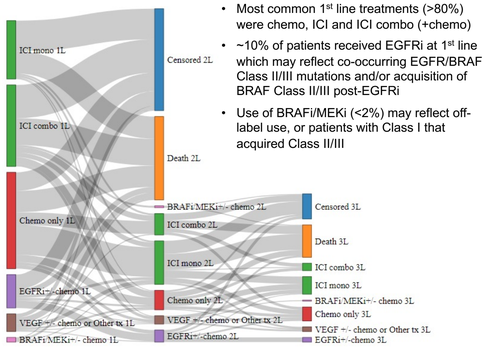
Percent of Oncogenic BRAF Alterations



- BRAF Class II and Class III accounted for 65%, 21% and 31% of oncogenic BRAF mutations in NSCLC, Melanoma and Colorectal cancer, respectively

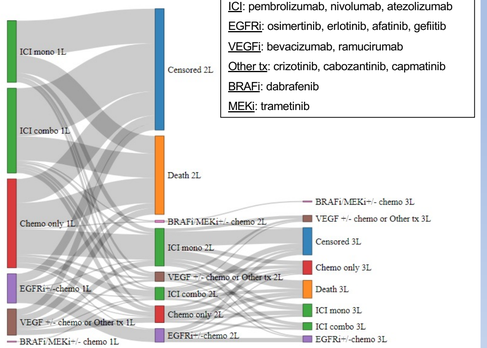
Treatment Landscapes (NSCLC)

BRAF Class II (N=315)



Treatment landscapes of patients with BRAF Class II or III regardless of BRAF detection date:
- Most common 1st line treatments (>80%) were chemo, ICI and ICI combo (+chemo)
- ~10% of patients received EGFRi at 1st line which may reflect co-occurring EGFR/BRAF Class II/III mutations and/or acquisition of BRAF Class II/III post-EGFRi
- Use of BRAFi/MEKi (<2%) may reflect off-label use, or patients with Class I that acquired Class II/III

BRAF Class III (N=279)



Chemo: carboplatin, pemetrexed, paclitaxel, etc.
ICI: pembrolizumab, nivolumab, atezolizumab
EGFRi: osimertinib, erlotinib, afatinib, gefiitib
VEGFi: bevacizumab, ramucirumab
Other tx: crizotinib, cabozantinib, capmatinib
BRAFi: dabrafenib
MEKi: trametinib

SUMMARY

- The analysis identified more than 3,250 cancer patients with BRAF Class II or Class III alterations which were detected by ctDNA profiling with the Guardant360® assay.
  - BRAF Class II and Class III were present in 55% of all patients with oncogenic BRAF alterations in the database
  - BRAF Class II and Class III were more common than Class I in most of the tumor types tested
- Compared to Class I, NSCLC patients with BRAF Class II and III were more likely to have a history of tobacco use.
- In BRAF Class II and Class III NSCLC, chemotherapy and immune checkpoint inhibitors +/- chemotherapy were the most common 1st line treatments.
- NSCLC and melanoma patients with BRAF Class II and Class III alterations had shorter overall survival compared to Class I and represent a population that could benefit from novel targeted therapies
- A clinical trial of the pan-RAF inhibitor **KIN-2787** is open to participants with BRAF and/or NRAS mutation-positive solid tumors (NCT04913285). See posters #2674 & #CT248 for more information on KIN-2787.