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Real-World Clinical Genomic Analysis of Patients with BRAF Mutated Cancers Identifies BRAF Class II and III as a Population of Unmet Medical Need

Paul Severson[1], Wendy Kellner[2], Aleksandra Franovic[1], Nichol Miller[1], Eric Murphy[3], Eric Martin[3], Richard Williams[1]

[1] Kinnate Biopharma Inc., San Diego, CA, [2] Tempus Labs Inc., Chicago, IL, [3] Former Employee of Kinnate Biopharma Inc.

ESMO TAT Targeted Anticancer Therapies

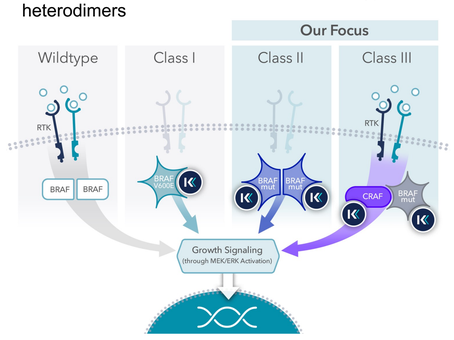
KINNATE BIOPHARMA

TEMPUS

BACKGROUND

Three classes of BRAF 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 targeted therapies approved for patients with BRAF Class II or Class III mutations.

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

Class	BRAF Mutations
Class I	$V600^{E/K/D/G/R}$
Class II	$Q257^{R}$, $G464^{V/E/R/A}$, $G469^{A/R/V}$, $V471^{F}$, $L485^{F}$, $K499^{E}$, $L505^{H}$, $L597^{R/V/Q/S}$, V600_K601delinsE, $E586^{K}$, N486_P490del, $T599^{Ins}$, V600_K601delinsEE, V600_K601delinsEQ, P490_Q494del, $K601^{E/N/T}$, fusions
Class III	$N581^{I/Y/S/T}$, $G466^{V/E/A/R}$, $K483^{E}$, $F595^{L}$, $D594^{N/E/G/H}$, $G469^{E}$, $G596^{R/C/D/V}$, $S467^{L}$

METHODS

De-identified data was utilized from the Tempus database containing 55,000+ solid tumor patients with **tumor tissue** profiling via the Tempus xT assay (648-gene DNA-seq panel and paired RNA-seq).

Clinical data was available for a subset of patients. Pan-cancer analysis of BRAF Class I, II, & III explored:

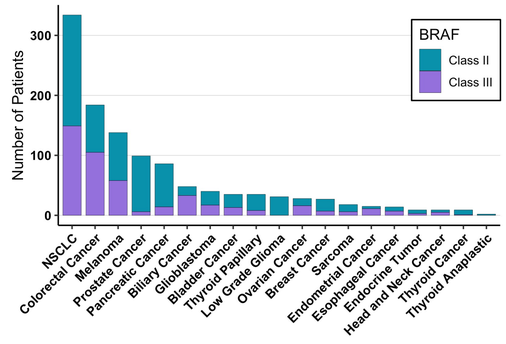
- Prevalence, Cancer Stage, Treatment Landscape
- Co-occurrence with RAS, NF1, PD-L1 gene expression (via RNA-seq), Tumor mutation burden (TMB), and Microsatellite instability (MSI)
- Real-world Treatment Outcomes
  - Time to Treatment Discontinuation (TTD)
    - All patients with BRAF Class I, II, III and with derived TTD were included in the TTD analyses regardless of BRAF detection date

RESULTS

Prevalence

- Out of more than 55,000 solid tumor patients, ~1,160 patients had BRAF Class II or III mutations
- Cancer types with abundant BRAF Class II or III mutations included: NSCLC, CRC, Melanoma, Prostate

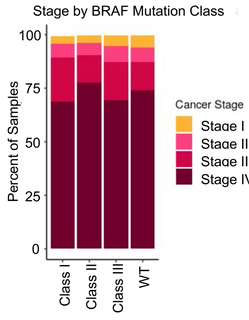
BRAF Class	# of Patients	% of Patients Tested
Class II	702	1.3
Class III	459	0.8
Class II or III	**1,161**	**2.1**



Cancer Stage

Similar distribution of stages across BRAF classes

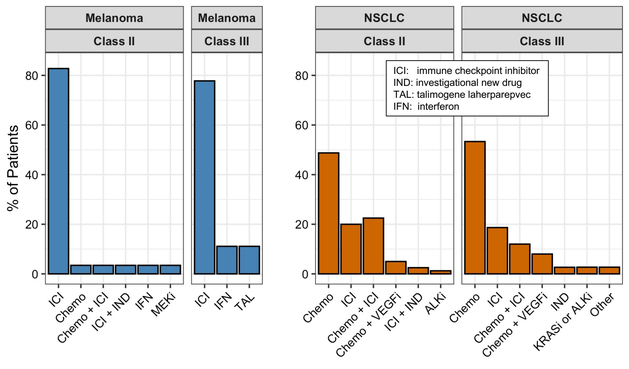
- ~70% stage IV
- ~90% stage III – IV



1st Line Treatment Landscape

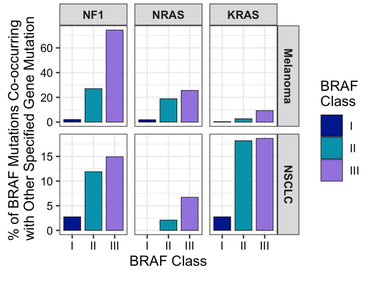
In patients with BRAF Class II or III:

- Chemo and/or immune checkpoint inhibitors was most common
- Use of targeted therapy was rare



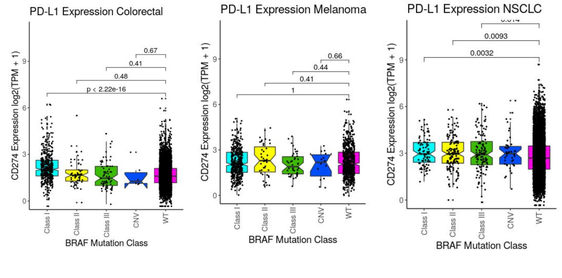
Co-occurring MAPK Mutations

More common in BRAF Class II & III than Class I



PD-L1 Gene Expression across BRAF Classes

BRAF Class I CRC have a trend toward higher PD-L1



Tumor Mutation Burden & Microsatellite Instability

Colorectal

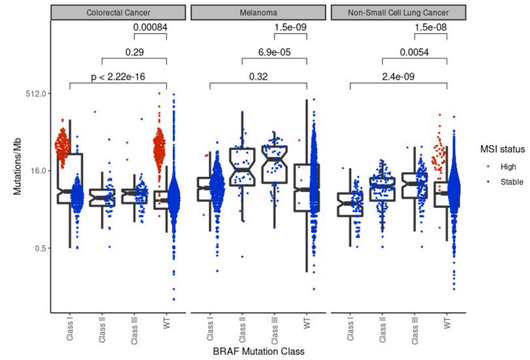
- BRAF Class I has two subgroups:
  - MSI high and TMB high
  - MSI stable and TMB moderate

Melanoma

- MSI generally stable across classes
- Median TMB increases with BRAF Class
  - Trend: Class I < Class II < Class III

NSCLC

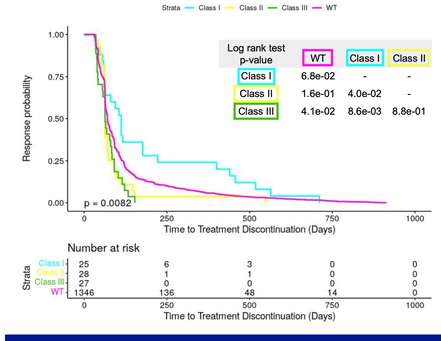
- MSI generally stable across classes
- Median TMB increases with BRAF Class
  - Trend: Class I < Class II < Class III



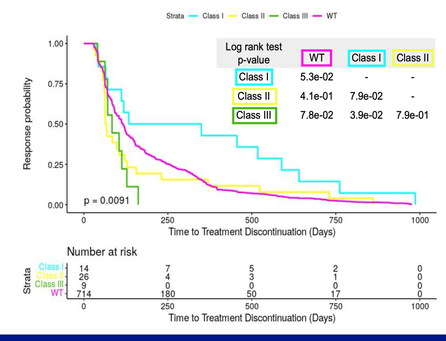
NSCLC Real-world Outcomes: Time to Treatment Discontinuation

- NSCLC Patients with BRAF Class II or III discontinued 1st line treatments sooner than patients with Class I. The same trend was observed with second line treatments.
- A shorter TTD suggests that patients with BRAF Class II and Class III experienced less benefit and/or less tolerability with the therapies used in these cohorts.

NSCLC 1st Line TTD across BRAF Classes



NSCLC 2nd Line TTD across BRAF Classes



SUMMARY

➢ **Real-world clinical genomic analysis** identified **~1,160 solid tumor patients** with **BRAF Class II** or **Class III** mutations.

➢ **BRAF Class II and Class III mutations** are associated with **distinct tumor characteristics** from Class I such as more frequent concurrent RAS and NF1 mutations (melanoma, NSCLC), higher TMB (melanoma, NSCLC), and inferior real-world outcomes (NSCLC).

➢ This analysis suggests that solid tumor patients with BRAF Class II or Class III mutations represent a substantial population with an unmet need for safe and effective therapies.

➢ A **clinical trial** of the **pan-RAF inhibitor KIN-2787** is open and enrolling **adult solid tumor patients** with **BRAF Class I, II, III** mutations and **NRAS mutant melanoma** (NCT04913285).