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 Severson¹, Wendy Kellner², Aleksandra Franovic³, Nichol Miller¹, Eric Murphy⁴, Eric Martin⁵, Richard Williams¹

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

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

Clinical data was available for a subset of patients.
Pan panel and paired RNA seq De-identified data was utilized from the Tempus database containing 55,000+ solid tumor patients with tumor tissue profiling via the Tempus xT assay (Ipsigen DNA-seq panel and paired RNA-seq).

Co-occuring MAPK mutations:
- More common in BRAF Class II & III than Class I

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 (Ipsigen 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 II, III and with derived TTD were included in the TTD analyses regardless of BRAF detection date

RESULTS

<table>
<thead>
<tr>
<th>BRAF Class</th>
<th># of Patients</th>
<th>% of Patients Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>702</td>
<td>1.3</td>
</tr>
<tr>
<td>Class II</td>
<td>456</td>
<td>0.8</td>
</tr>
<tr>
<td>Class III</td>
<td>1,161</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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

Tumor Mutation Burden & Microsatellite Instability
Colorectal:
- 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.
- 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.

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).