Background:
- Alterations in the RAS pathway are linked to tumorigenesis
- RAS alterations are currently under-studied in breast cancer (BC) compared to other solid tumors
- HRAS can be indirectly targeted with tipifarnib, a farnesyltransferase inhibitor
- We aimed to characterize the molecular characteristics and understand clinical outcomes of BC with HRAS mutations (HRASmut)

Methods:
- 14,013 BC samples underwent comprehensive molecular profiling (DNA, RNA, IHC) at Caris Life Sciences
- MAPKinase activation was assessed using MPAS gene expression signature
- Survival data were generated from date of sample collection to last contact with insurance claims

Table 1: Quantifying Point Mutations in HRASmut BC

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>All HRASmut (n=70)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Q61</td>
</tr>
<tr>
<td>Cases with alterations</td>
<td>29 (41.4%)</td>
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</tbody>
</table>

Results:
- There were 70 total HRASmut (0.5%)
- HRASmut were significantly enriched in older patients (median 69 vs. 60 years; q<0.0001) and in primary vs. metastatic BC samples (56% vs. 42%; p<0.05)
- HRASmut were found in HR+/HER2- (22.6%) and TNBC (77.4%), but no HR-/HER2+
- Q61 was the most frequent point mutation (41.4%), followed by G12 (28.6%) and G13 (24.3%) (Table 1)
- Patients with Q61 HRASmut had significantly worse OS compared to all BC (HR 1.86, 95% CI [1.10-3.13]; p<0.05) (Figure 1)
- TNBC HRASmut displayed more PIK3CA (62.5% vs. 18.9%, q<0.05) but less TP53 mutations (50% vs 84.9%, q<0.05), higher expression of PD-L1 (41.2% vs 10.8%, p<0.05) and androgen receptor (AR, 45.8% vs 24.4%, p<0.05), and more frequent ARv7 fusions (20.7% vs 4.3%, p<0.05) compared to HR+/HER2-

Future Directions for Research:
- Clinical trials evaluating the role of farnesyltransferase inhibitors, with or without PIK3C-targeted (e.g. alpelisib) and/or immunotherapy, in HRASmut BC