Abstract 561: Molecular Characteristics and Clinical Outcomes of Breast Cancer with *HRAS* Mutations

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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)

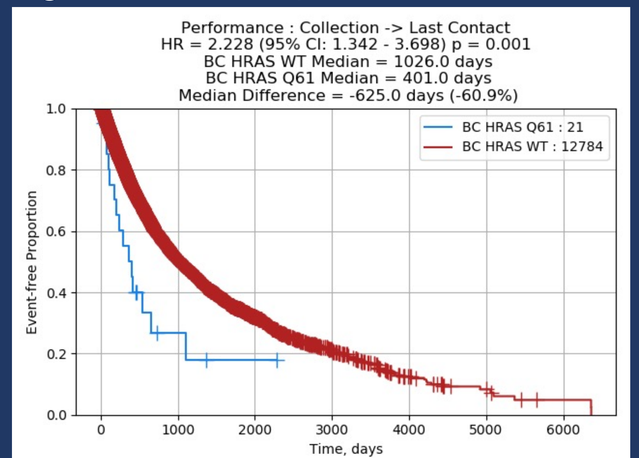
Methods:

- **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

	All HRASmut (*n*=70)			
Mutation type	Q61	G12	G13	Other/Likely pathogenic
Cases with alterations	29 (41.4%)	20 (28.6%)	17 (24.3%)	4 (0.6%)

Figure 1: OS data for Q61-Mutated HRASmut



Take-Home Points:

1) HRASmut were mutually exclusive with HER2+ BC
2) PIK3CA was significantly co-mutated with HRASmut
3) *HRAS* may represent a new therapeutic target

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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<.05) but less TP53 mutations (50% vs 84.9%, q<.05**), higher expression of PD-L1** (41.2% vs 10.8%, p<.05) and **androgen receptor** (AR, 45.8% vs 24.4%, p<.05), and more frequent ARv7 fusions (20.7% vs 4.3%, p<.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