# Methylthioadenosine Phosphorylase (*MTAP*) Genomic Loss in *ERBB2* Amplified and Mutated Metastatic Breast Cancer (4206)

A Sivapiragasam[1], KA McGregor[2], ES Sokol[2], N Danziger[2], JS Ross[1,2]

1. Upstate Medical University, Syracuse, NY, USA; 2. Foundation Medicine, Cambridge, MA, USA

## ABSTRACT

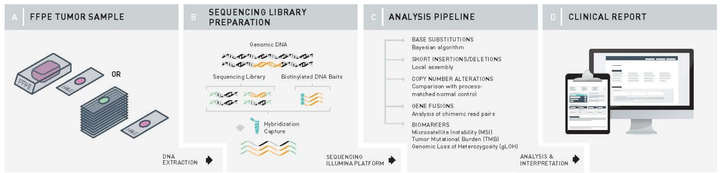
**Background**: *MTAP* loss has emerged as a potential biomarker for novel PRMT5 inhibitors in a variety of malignancies. We queried whether *MTAP* GA loss would impact the genomic alteration (GA) landscape in clinically advanced *ERBB2* altered MBC

**Methods:** 1,644 ERBB2 amplified or mutated clinically advanced MBC underwent hybrid-capture based comprehensive genomic profiling to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 95 loci. PD-L1 expression was determined by IHC (Ventana SP142 or Dako 22C3).

**Results:** 50 (3%) of *ERBB2* altered MBC featured MTAP loss (*MTAP*-) and 1,594 (97%) were *MTAP* intact (*MTAP*+). Ages were similar in both groups as were the GA/tumor when the co-deleted *CDKN2A/B* GA were excluded in the comparison. Co-deleted *CDKN2A/B* was far more common in *MTAP*- *ERBB2*+ cases (P<.0001). *MTAP*+ *ERBB2*+ MBC featured a lower frequency of *ERBB2*amp and a higher frequency of *ERBB2*mut than the *MTAP*- *ERBB2*+ cases (p=.07). *PIK3CA* mutations were more frequent in *MTAP*+ cases (P=.03) whereas both *BRCA1* and *BRAF* GA were more frequent in *MTAP*- cases (both P=.02). Biomarker GA impacting immune checkpoint inhibitor treatment efficacy and resistance were mostly similar in both *MTAP*- and *MTAP*+ cases although PD-L1 expression was significantly more frequent in the *MTAP*- *ERBB2*+ cases (P<.0001).

**Conclusions:** Deletion of *MTAP*, a biomarker linked to selection of PRMT5 drugs in clinical trials employing a synthetic lethality mechanism is rare in *ERBB2* altered MBC. Further study of the potential to employ PRMT5 inhibitors in patients with *ERBB2* driven MBC that has become refractory to anti-HER2 treatments appears warranted.

## MATERIALS AND METHODS



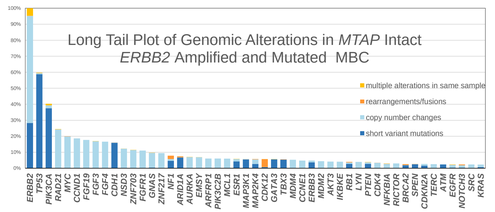

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes of known or likely functional significance were assessed
- Tumor mutational burden (TMB) calculated from 0.8 Mb sequenced DNA
- PD-L1 expression was measured by IHC (Dako22C3)

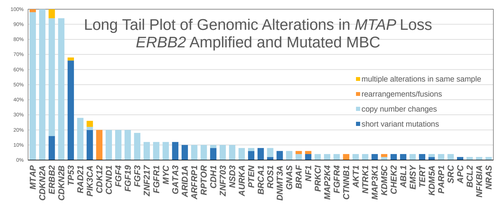
## RESULTS

### Clinical and Genomic Comparisons

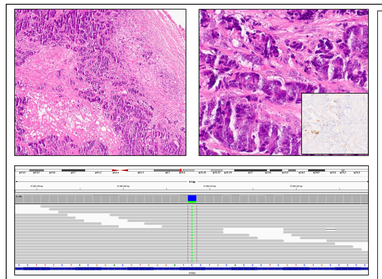
| | *MTAP* Loss | *MTAP* Intact | P Value |
|---|---|---|---|
| Cases | 50 | 1594 | |
| Age (range in years) | 59 (32-85) | 58 (21-89+) | NS |
| **ERBB2 Status** | | | |
| ERBB2 amplified | 78% | 67% | NS |
| ERBB2 sequence mutation | 16% | 28% | =.07 |
| Both | 6% | 5% | NS |
| **Endocrine Rx Related** | | | |
| CDH1 | 10% | 16% | NS |
| ESR1 | 0% | 6% | NS |
| AR | 0% | 2% | NS |
| **Cell Cycle Regulation** | | | |
| CDKN2A/B | 100%/94% | 26%/11% | <.0001 |
| CCND1 | 20% | 19% | NS |
| CDK4/6 | 0% | 4%/2% | NS |
| **MTOR GA** | | | |
| PIK3CA | 26% | 40% | =.03 |
| PTEN | 8% | 4% | NS |
| NF1 | 6% | 8% | NS |
| **HRD Related** | | | |
| BRCA1 | 8% | 2% | =.02 |
| BRCA2 | 0% | 3% | NS |
| PALB2 | 2% | 1% | NS |
| ATM | 2% | 3% | NS |
| **Other Kinase targets** | | | |
| FGFR1 | 12% | 11% | NS |
| FGFR2 | 0% | 2% | NS |
| EGFR | 0% | 2% | NS |
| KIT | 0% | 1% | NS |
| MET | 0% | 1% | NS |
| BRAF | 6% | 1% | =.02 |
| **IO Drug Biomarkers** | | | |
| MSI High | 0% | <1% | NS |
| TMB Median | 3.8 | 3.8 | NS |
| TMB > 10 mut/Mb | 16% | 14% | NS |
| TMB > 20 mut/Mb | 4% | 4% | NS |
| PD-L1 IHC Positive | 10% | 5% | <.0001 |
| CD274 (PD-L1) amp | 0% | 1% | NS |
| PBRM1 GA | 0% | 1% | NS |
| STK11 GA | 0% | 1% | NS |
| MDM2 amp | 2% | 4% | NS |

- 50 (3%) of *ERBB2* altered MBC featured MTAP loss (*MTAP*-) and 1,594 (97%) were *MTAP* intact (*MTAP*+)
- Ages were similar in both groups as were the GA/tumor when the co-deleted *CDKN2A/B* GA were excluded
- Co-deleted *CDKN2A/B* was far more common in *MTAP*- *ERBB2*+ cases (P<.0001)
- *MTAP*+ *ERBB2*+ MBC featured a lower frequency of *ERBB2*amp and a higher frequency of *ERBB2*mut than the *MTAP*- *ERBB2*+ cases (p=.07)
- *PIK3CA* mutations were more frequent in *MTAP*+ cases (P=.03) whereas both *BRCA1* and *BRAF* GA were more frequent in *MTAP*- cases (both P=.02)
- Biomarker GA impacting immune checkpoint inhibitor treatment efficacy and resistance were mostly similar in both *MTAP*- and *MTAP*+ cases although PD-L1 expression was significantly more frequent in the *MTAP*- *ERBB2*+ cases (P<.0001)

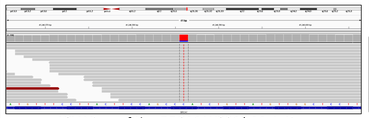


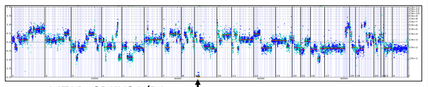

## CASES



IGV View of the *ERBB2* S310Y Mutation

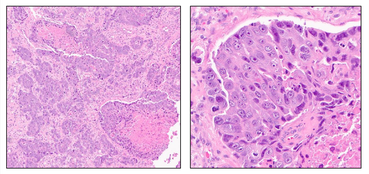


IGV View of the *BRCA1* W321* Mutation

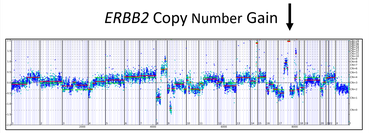


*MTAP*, *CDKN2A/B* Loss

Metastatic triple negative breast cancer to a supraclavicular lymph node. The inset shows a 5% immunocyte score and a 0% tumor cell score for PD-L1 expression. On CGP, this tumor featured loss of *MTAP* and *CDKN2A/B*. Although *ERBB2* was not amplified, there was an extracellular domain *ERBB2* sequence mutation (S310Y). In addition, there was a *BRCA1* W321* mutation which was predicted to be germline and a *TP53* E336* mutation. The tumor was MS stable and had a low TMB of 5 mutations/Mb. In the current study, *BRCA1* mutations were significantly more frequent in the *MTAP* loss MBC. In addition to potential use of PARP inhibitors and anti-HER2 targeted therapies, this patient would also be eligible for novel clinical trials for drugs such as PRMT5 and MAT2A inhibitors exploiting the *MTAP* loss.



*ERBB2* Copy Number Gain



Metastatic high grade breast cancer to the brain in a 58-year-old woman. IHC staining revealed this tumor to be ER/PR negative and HER2 3+ positive. IHC staining for PD-L1 expression was negative. On CGP, this tumor was MS stable and had a low TMB of just 3 mutations/Mb. The HER2 3+ IHC was confirmed with the highly amplified *ERBB2* copy number at 40 copies. The *MTAP*, *CDKN2A* and *CDKN2B* loss is also seen in the copy number plot. There was also a potentially targetable *PIK3CA* H1047R mutation and amplification of *AKT1* and *RAD21*. The *PIK3CA* is an approved target of the PIK3CA inhibitor alpelisib in ER+ breast cancer but is not an approved target for HER2+ MBC. At 3%, *MTAP* loss was uncommon in *ERBB2* amplified MBC and not significantly different from the *MTAP* loss frequency in *ERBB2* unamplified MBC. Whether targeting the arginine accumulation in *MTAP* depleted MBC will be a useful strategy for MBC treatment remains to be proven in future clinical trials.

## CONCLUSIONS

- Deletion of *MTAP*, a biomarker linked to selection of PRMT5 drugs in clinical trials employing a synthetic lethality mechanism is rare in *ERBB2* altered MBC
- Further study of the potential to employ PRMT5 inhibitors in patients with *ERBB2* driven MBC that has become refractory to anti-HER2 treatments appears warranted



Contact jross@foundationmedicine.com for permissions and further inquiries.