# Molecular correlates of *MAEA* expression in colorectal cancer (CRC)

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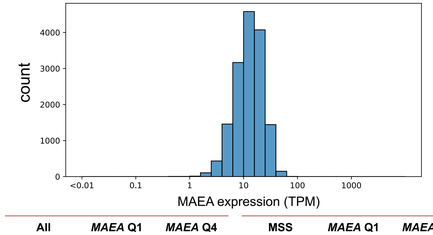
## Introduction

- Macrophage Erythroblast Attacher (MAEA) plays an important role in actin cytoskeleton rearrangement in macrophages and erythroid cells.
- We previously reported that MAEA suppresses migration, invasion and enhances chemosensitivity in CRC cell lines.
- Here we aimed to characterize the molecular features associated with *MAEA* gene expression in CRC.

## Methods

- A total of 14,416 CRC tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (Illumina Next Seq, 592 genes, or Illumina NovaSeq, WES) and RNA (Illumina NovaSeq, WTS) were analyzed.
- Top quartile transcripts per million (TPMs) for *MAEA* expression were considered high (Q4) while bottom quartile low (Q1) expression.
- Consensus molecular subtypes (CMS) were assessed using RNAseq.
- Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by QuantiSEQ.
- $X^2$/Fisher-Exact tests were used for comparison and significance was determined as *P*-value adjusted for multiple comparison (Q < 0.05).

## Distribution and Demographic

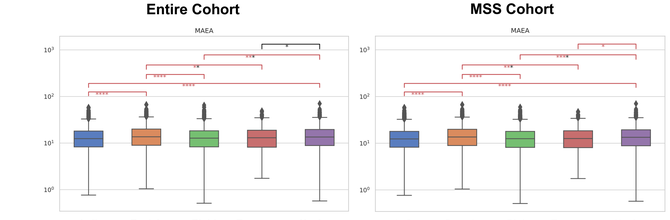



| All | *MAEA* Q1 | *MAEA* Q4 |
|---|---|---|
| Count (N) | 3697 | 3697 |
| Median Age (range) | 62.0 (15 - >89) | 63.0 (17 - >89) |
| Male | 53.8% | 54.6% |
| Female | 46.2% | 45.4% |

| MSS | *MAEA* Q1 | *MAEA* Q4 |
|---|---|---|
| Count (N) | 3631 | 3472 |
| Median Age (range) | 61.0 (15 - >89) | 62.0 (17 - >89) |
| Male | 54.4% | 54.9% |
| Female | 45.6% | 45.1% |

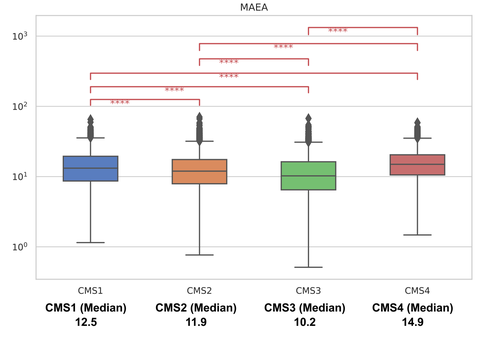
## Results

### Figure 1. Correlation between *MAEA* Expression and Primary Tumor Side.




Overall, *MAEA* expression was highest in rectal tumors (13.6 median TPM) followed by transverse and right-sided tumors (13.0 and 12.8, respectively) and lowest in left-sided tumors (12.5) ($P < 0.001$).
The same was observed in microsatellite stable (MSS) tumors when analyzed separately.

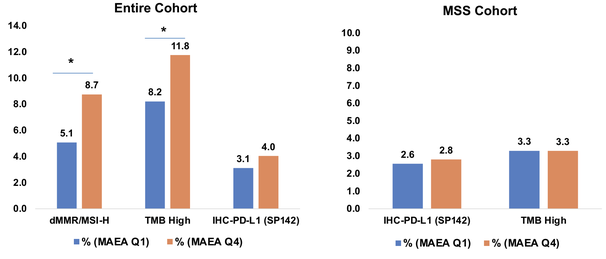
### Figure 2. Distribution of *MAEA* Tumor Expression According to CMS Subtypes (MSS Cohort).




In the MSS cohort, *MAEA* expression was the highest in CMS4 (14.9 median TPM) followed by CMS1 (12.5), CMS2 (11.9), and the lowest in CMS3 (10.3, all intergroup Q < 0.05).

### Figure 3. Association with Tumor Molecular Characteristics.

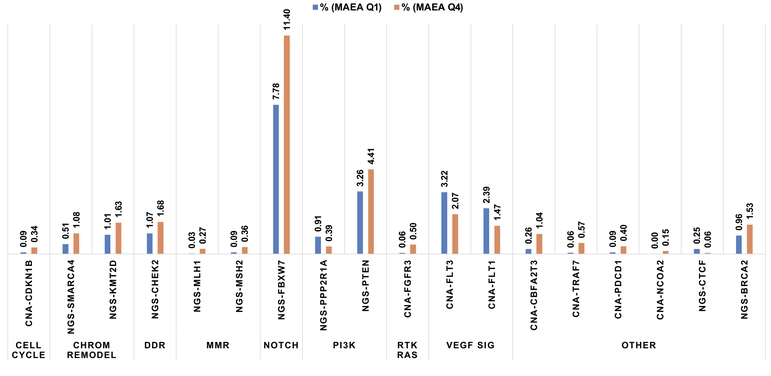
#### A. Immune Markers




* Q < 0.05; PDL-1 cutoff 2+ 5%

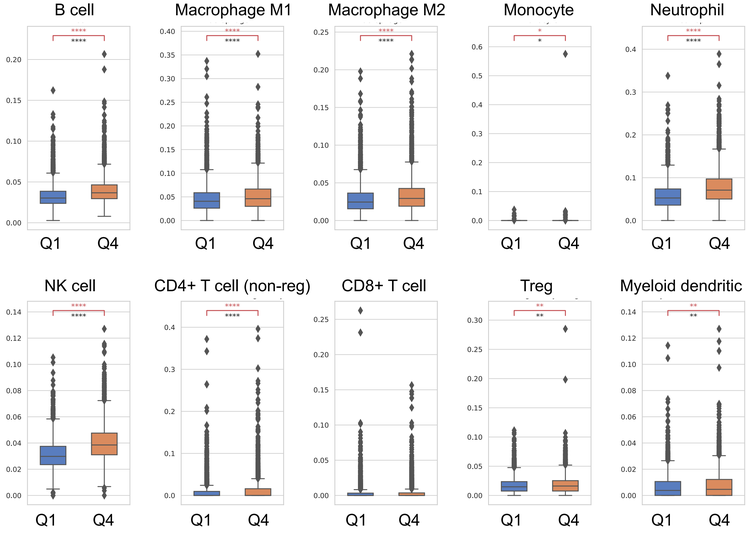
Overall, *MAEA* TPM were associated with higher tumor mutational burden (≥ 10 Mut/Mb) (11.8% vs. 8.2%) and dMMR/MSI-H (8.7% vs. 5.1%) (Q < 0.0001); however, the association with TMB was not observed in MSS tumors.

#### B. Mutations and CNA (MSS Cohort)




*MAEA* high was associated with lower mutation rates of *APC* and amplification of *FLT1*/*FLT3* while higher mutation rates of *ASXL1*, *KMT2A/C/D*, *SMARCA4*, *FBXW7*, *PTEN*, *RNF43*, *BRCA2*, *HNF1A* in the overall cohort (Q < 0.05).
In the MSS cohort, *FBXW7* mutation significance with *MAEA* high expression held true (Q < 0.05) while *MAEA* high expression trended to associate with higher mutation rates of *KMT2D*, *SMARCA4*, *PTEN*, *BRCA2* mutations, and a lower frequency of *FLT1*/*FLT3* CNA (*P* < 0.05 but Q > 0.05).

### Figure 4. TME Cell Infiltration According to *MAEA* Expression in MSS Tumors.




High *MAEA* was associated with higher immune CI in the TME, including B cells, macrophages (M1 and M2), neutrophils, NK cells, Tregs, CD4+ T cells and myeloid dendritic cells both in the overall cohort and in MSS tumors (fold change: 1.11-1.33, all Q < 0.001).

## CONCLUSIONS

**Our data show a strong association between *MAEA* gene expression and distinct molecular features (including CMS and immune biomarkers) and TME cell infiltration in CRC.**

**These findings suggest that targeting MAEA may have relevant clinical applications in selected CRC subgroups and MAEA may be an important player in determining the composition of the TME.**