Clinico-Molecular Real-World Data Demonstrates Prognostic Significance of a Three-Gene Biomarker for Colorectal Liver Oligometastases

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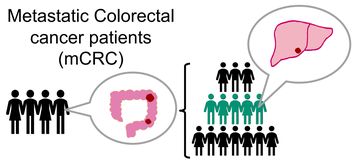
INTRODUCTION



Colorectal liver oligometastases (CLO)

Eligible to undergo curative intent resection for improved survival

Three-gene prognostic biomarker – Previously described (PMID: 31221662)

- *RAS (KRAS/NRAS)*
- *SMAD4*
- *TP53*

Heterogenous population

- Poor prognostic stratification
- 5-year survival rate of 25-58% (PMID: 20590894)

We validate the prognostication of this three-gene biomarker, discovered by Vauthey et al, in a CLO real world data (RWD) cohort

METHODS

CLO Patients (N = 276)

Molecular profiling with Tempus xT assay*

Inclusion Criteria:

- Curative intent liver resections with negative or unknown surgical margins
- Tumor samples collected from the colon or liver
- Metastasis to only the liver at time of sample collection
- Minimum 30 days follow up post resection

Retrospective, De-identified Clinico-molecular Real-World Data (RWD) of CLO patients

Assess prognostic value:

- Real-world time to progression (rwTTP)
- Cox proportional hazard model

Gene mutations:

- Continuous variable (genes mutated 0-3)
- Categorical variable

Controlling for:

- Neoadjuvant therapy
- Adjuvant therapy
- Meta vs. synchronous colorectal cancer

*Tempus xT solid tumor assay - DNA-seq of 595-648 genes at 500x coverage

Variable	Value	N (%)	1 yr progression rate
Metastasis timing	Synchronous	189 (68.5%)	52.9
	Metachronous	87 (31.5%)	66.5
Sample collection site	Colon/rectum	51 (18.5%)	55.7
	Liver	225 (81.5%)	57.7
Neoadjuvant therapy	No	160 (58.0%)	45.7
	Yes	116 (42.0%)	70.9
Adjuvant therapy	No	107 (38.8%)	47.8
	Yes	169 (61.2%)	60.8

Table 1: Overview of patient population. Synchronous diagnoses were defined as primary and metastatic diagnoses within 12 months.

SUMMARY

- A novel clinico-molecular RWD cohort allowed independent rwTTP validation of a three-gene biomarker in the CLO setting. This RWD cohort can be leveraged for further biomarker discover and validation.
- Although future prospective studies are warranted, the significance of the three-gene biomarker as a prognostic factor suggests that mutation status of *RAS*, *SMAD4*, and *TP53* may be helpful to guide treatment decisions surrounding curative surgery.

RESULTS

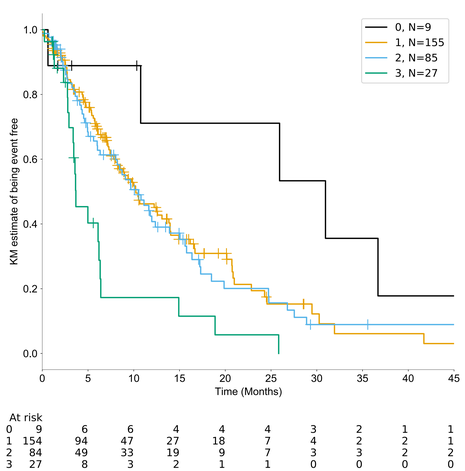


Figure 1: KM curves representing rwTTP based on the number of genes in which a patient has any variants reported among *RAS* (*NRAS* or *KRAS*), *TP53*, and *SMAD4*, which ranges from 0 to 3. Median rwTTP for 3 mutations is 3.7 months, 2 mutations is 10.5 months, 1 mutation is 10.2 months, and 0 mutations is 31.0 months.

Covariate	HR (95% CI)	p-value	N
3-gene biomarker (continuous)	1.42 (1.15-1.77)	0.001	276
3 mutations vs. 2 mutations	2.47 (1.44-4.22)	0.001	112
3 mutations vs. 1 mutation	2.55 (1.54-4.22)	<0.001	182
3 mutations vs. 1 or 2 mutations	2.51 (1.55-4.05)	<0.001	267
3 mutations vs. 0 mutations	10.6 (2.2-50.8)	0.003	36

Table 2: Multivariate analysis of the three-gene biomarker as a continuous variable or pairwise combinations. CoxPH models were fit while controlling for neoadjuvant therapy, adjuvant therapy, and metachronous vs. synchronous colorectal cancer.

Acknowledgements: We thank Amrita A. Iyer, Ph.D, for poster preparation & review.

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Variable	HR (95% CI)	p-value	N
3-gene biomarker (continuous)	1.40 (1.14-1.73)	0.002	276
3 mutations vs. 2 mutations	2.14 (1.27-3.60)	0.004	112
3 mutations vs. 1 mutations	2.34 (1.43-3.83)	<0.001	182
3 mutations vs. 0 mutations	8.31 (1.86-37)	0.006	36
RAS	1.10 (0.81-1.48)	0.57	276
SMAD4	1.64 (1.15-2.33)	0.006	276
TP53	1.45 (0.995-2.12)	0.053	276
Neoadjuvant therapy	1.80 (1.33-2.44)	<0.001	276
Adjuvant therapy	1.27 (0.90-1.80)	0.17	276
Synchronous vs. metachronous	1.14 (0.82-1.56)	0.44	276

Table 3: Univariate analysis of the main variables and interest and relevant confounders.

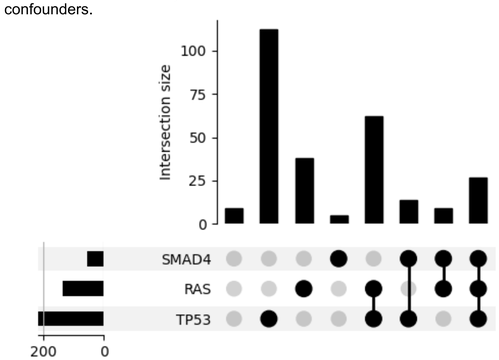

Figure 2: Upset plot showing the mutational frequency for each gene in the three-gene biomarker and frequency of co-mutations within this set. *SMAD4* is mutated in 55 patients total, *RAS* in 136, and *TP53* in 215.

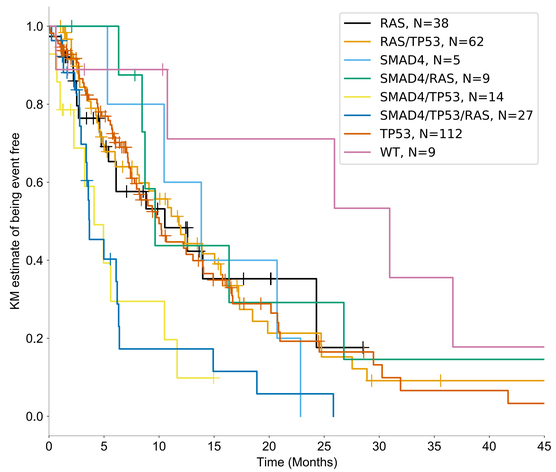

Figure 3: KM curves representing rwTTP for mutations in each gene in the three-gene biomarker independently, with all combinations of double mutants, with all three genes mutated, and with none of the genes mutated (WT). Total at risk counts do not add up to the full cohort size of 276 because two patients progressed on their anchor date.

DISCUSSION

- This study is limited by its retrospective design with RWD, which resulted in missing data on clinical covariates of interest, lack of control over sample acquisition methods, and insufficient prospective follow up to evaluate overall survival.
- The general CLO population is notably more homogenous than the resectable metastatic CRC population on key prognostic factors such as *BRAF* mutations and MSI status. Only 2.9% of patients in this RWD cohort have *BRAF* mutations and only 1.1% are MSI-high, demonstrating that research on additional prognostic markers is of high importance.
- This RWD cohort shows interesting differences from the Vauthey study. First, the RWD cohort suggests similar outcomes among the 1 and 2 gene mutation subgroups. Second, the RWD cohort suggests a weaker association between RAS mutation and outcome, independent of the mutation count. While further studies are needed to fully validate the three-gene biomarker, the combined mutational status of *RAS*, *TP53* and *SMAD4* has now been shown in two independent cohorts to be a potential novel prognostic factor for CLO patients.