Consensus Molecular Subtyping of Colorectal Cancer Demonstrates Cetuximab Benefit in Right sided CMS2 Tumors, and Pembrolizumab Benefit in MSS CMS1 Tumors.

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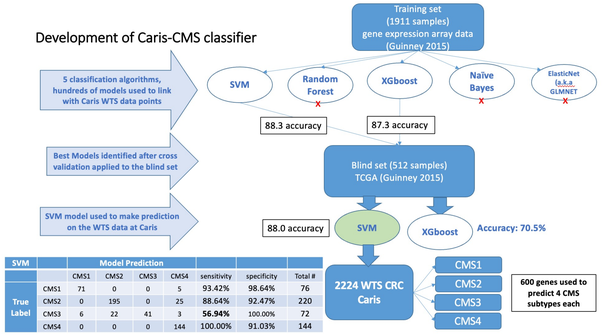
Background

- Consensus Molecular Subtypes (CMS) of colorectal cancer (CRC) were first developed in 2015 using microarray-based assays but are not widely used clinically.
- We developed a Caris CMS classifier on whole transcriptome sequencing data (WTS) with high concordance with the previously established CMS pipeline (Guinney et al 2015)
- We applied the Caris CMS classifier to a large clinic-genomic database of CRC to investigate the utility of CMS classification in identifying patients that may respond well to therapies commonly used in CRC.

Methods

- Next-generation sequencing (NGS) of DNA (592-gene or whole exome) and WTS was tested on CRC patient samples (n = 12,788) at a CLIA-certified lab (Caris Life Sciences, Phoenix, AZ).
- Caris CMS classifier was trained against the original CMS datasets using a classic SVM model and cross-validated for optimization of the SVM parameters.
- Possible overtraining was evaluated by predicting CMS from an independent blinded dataset (TCGA, N = 512) with an accuracy of 88.3%.
- Real-world overall survival was obtained from insurance claims and calculated from tissue collection to last contact (OS); time on treatment (TOT) was from first to last of treatment time.
- Kaplan-Meier estimates were calculated for molecularly defined cohorts. Significance was determined as p of < 0.05.

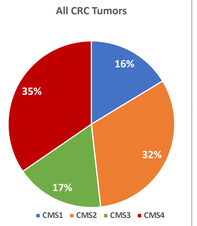


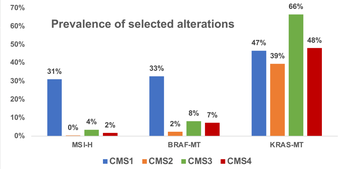
SVM		Model Prediction						
		CMS1	CMS2	CMS3	CMS4	sensitivity	specificity	Total #
True Label	CMS1	71	0	0	5	93.42%	98.64%	76
	CMS2	0	195	0	25	88.64%	92.47%	220
	CMS3	6	22	41	3	**56.94%**	100.00%	72
	CMS4	0	0	0	144	100.00%	91.03%	144

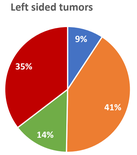
Results

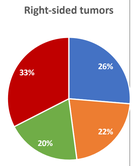
1. Patient Characteristics: A total of 12,788 CRC tumors were investigated

	CMS1 (2088)	CMS2 (4079)	CMS3 (2199)	CMS4 (4422)
Female	1074 (51%)	1728 (42%)	1062 (48%)	1975 (45%)
Male	1014 (49%)	2351 (58%)	1137 (52%)	2447 (55%)
Age <45	182 (9%)	371(9%)	181(8%)	472(11%)
Age 45-64	818 (39%)	1979 (49%)	1046 (48%)	2169 (49%)
Age>=65	1088 (52%)	1729 (42%)	972 (44%)	1781 (40%)





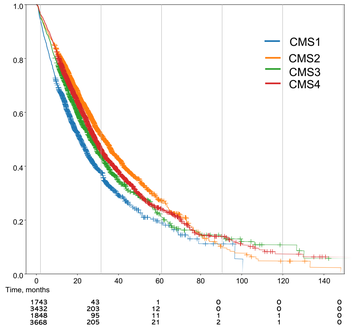




2. Prognosis of CRC stratified by CMS

- Consistent with previous reports, CMS2 was associated with the longest mOS, followed by CMS4, CMS3 and CMS1

End point: Median rwOS (Tissue collection to Last Contact)		
	OS (m)	95% Confidence Interval (m)
CMS1	21.4	19.8-23
CMS2	33	31.1-35.1
CMS3	26.4	24.9-28.8
CMS4	28.6	27.5-30.1

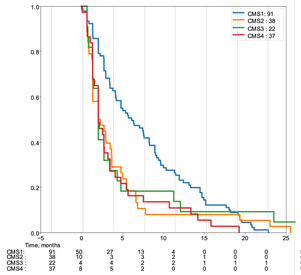


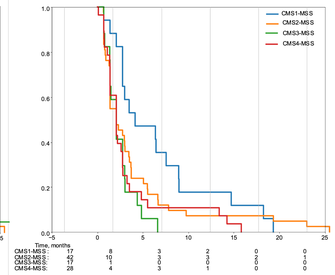
Results

3. Outcome of Immune Checkpoint Inhibitors in CMS1-4

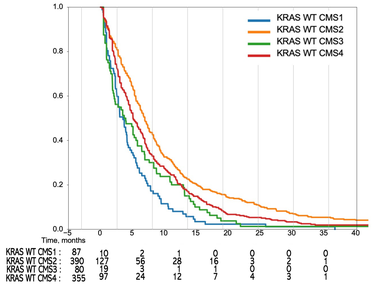
- As expected, CMS1 CRC tumors had the best outcome when treated with pembrolizumab compared to other CMS groups
- Very interestingly, in microsatellite stable (MSS) tumors treated with pembrolizumab, CMS1 had longer TOT than CMS2 , CMS3 and CMS4.
- Comparing CMS1 to CMS2-4 grouped together, HR: 0.58; CI: 0.34-0.97, p = 0.035.

End point: Median Pembrolizumab Time-On-Treatment (TOT)					
	CRC tumors			MSS-CRC tumors	
	mTOT (m)	95% Confidence Interval (m)		mTOT (m)	95% Confidence Interval (m)
CMS1	6.2	4.2-8.3	CMS1-MSS	4.2	2.8-8.9
CMS2	2.1	1.4-3.7	CMS2-MSS	2.1	1.4-3
CMS3	2.1	1.4-3.5	CMS3-MSS	2.1	3
CMS4	2.1	1.6-3.2	CMS4-MSS	2.1	2.8





4. Outcome of EGFR monoclonal antibodies (cetuximab/panitumumab) in KRAS- Wild Type CMS1-4 Tumors



End point: Median Cetuximab/Panitumumab Time-On-Treatment (TOT)		
	TOT (m)	95% Confidence Interval (m)
CMS1	3.5	2.5-4.1
CMS2	6.99	6.2-7.6
CMS3	3.9	2-5.8
CMS4	5.1	4.6-6.2

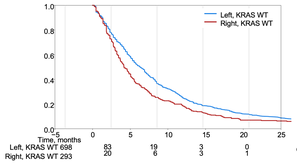
- CMS2 was associated with significantly longer TOT compared to CMS1, 3 and 4

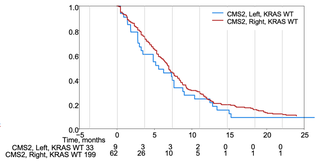
Results

4. CMS2 imbalance in sidedness and cetuximab/panitumab benefit

- As expected, left-sided KRAS WT CRC showed longer mTOT on cetuximab than right-sided tumors.
- Interestingly, CMS2 showed similar mTOT from the left and the right.
- Notably, CMS2 comprises 41% of left-sided tumors and only 22$ of right-sided tumors, potentially underlying the TOT difference between left and right.

End point: Median Cetuximab/Panitumumab Time-On-Treatment (TOT)					
	KRAS WT CRC tumors			CMS2 KRAS WT CRC tumors	
	mTOT (m)	95% Confidence Interval (m)		mTOT (m)	95% Confidence Interval (m)
Left-sided	6.3	5.5-6.9	Left-sided	6.9	6-7.7
Right-sided	4.2	3.7-4.8	Right-sided	5.6	3-7.6





Conclusions

- A Whole-Transcriptome-Sequencing based CMS classifier allows for investigation in a large real-world clinic-genomic database.
- We found that MSS CMS1 CRC's may derive benefit from immunotherapy.
- Additionally, CMS2 subgroup of right-sided tumors may derive benefit from cetuximab.
- Routine CMS subgrouping of CRC provides important treatment associations that should be further investigated.

References

- Guinney 2015, Nat Med
- Hoon 2022, JNCI J Natl Cancer Inst

Acknowledgements

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