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Class II and III BRAF mutations represent molecularly distinct subgroups of MMR proficient CRC and are associated with benefit from EGFR blockade

Ibrahim Halil Sahin[1], Joanne Xiu[2], Moh'd M. Khushman[3], Emily Palumbo[2], Benjamin Adam Weinberg[4], Mehmet Akce[5], Aatur D. Singhi[1], Phoenix D. Bell[1], Anup Kasi[6], Anthony F. Shields[7], Matthew James Oberley[2], George W. Sledge Jr[2]., John Paul Y.C. Shen[8], Anwaar Saeed`, Mohamedtaki Tejani [9]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA; [2]Caris Life Sciences, Phoenix, AZ; [3]Washington University in St. Louis, Siteman Cancer Center, St. Louis, MO; [4]Lombardi Comprehensive Cancer Center at Georgetown University, [5]University of Alabama at Birmingham, [6]University of Kansas Cancer Center, [7]Barbara Ann Karmanos Cancer Institute, Detroit, MI; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9] Advent Health Cancer Institute

Significance and Background

✳BRAF mutations represent a highly heterogeneous group of molecular alterations seen in colorectal cancer (CRC).

✳ Class I BRAF mutation (V600) render aggressive biology to CRC and poor response to EGFR blockade therapy.

✳ Currently there are limited data on clinical and molecular features of class II and III BRAF mutations and their response to EGFR blockade therapy.

✳ In this study, we investigated the clinical and molecular characteristics of BRAF mutation classes and their impact on clinical outcomes in a large cohort of patients with mismatch proficient-microsatellite stable CRC.

Methods

✳ A total of 18,575 pMMR/MSS CRC specimens were profiled by next-generation sequencing (592-gene, NextSeq; WES, WTS NovaSeq) (Caris Life Sciences, Phoenix, AZ).

✳ BRAF mutations were detected by NGS and classified using published literature (Sahin et al. JCO OP 2021).

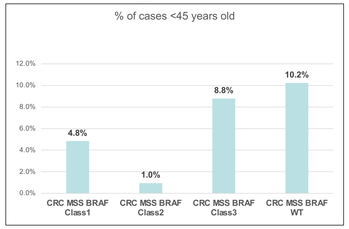
✳ Interferon gamma signature (Cristescu et al. 2018) and MAPK pathway activity score (MPAS) (Wagle et al 2018) were calculated using RNA expression data (TPM: Transcript per million).

✳ Real-world overall survival information was obtained from insurance claims and calculated from tissue collection to last contact, while post-treatment survival from first of treatment to last contact.

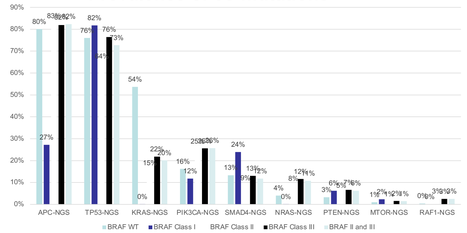
✳ Kaplan-Meier estimates were calculated for molecularly defined cohorts using Cox-proportional hazard analysis. Significance was determined as p values of <0.05.

Results

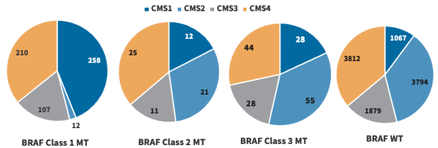
- **Patient age distribution**

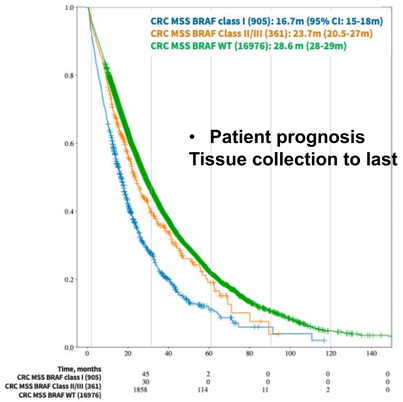


- **Prevalence of co-mutations**

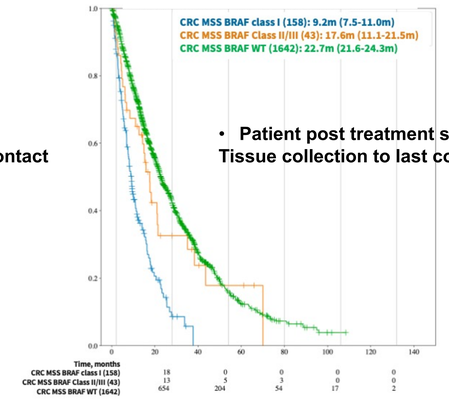


- **Enrichment of CMS1 in BRAF class 1 mutants**





- **Patient prognosis Tissue collection to last contact**



- **Patient post treatment survival Tissue collection to last contact**

✳ A total of 930,105, and 262 patients with class I, II, and III BRAF mts were identified. Patients with class III BRAF mts were significantly more common among younger pts (age<45) compared to class I and class II (8.8% vs. 4.8% vs. 1.0 % respectively; P<0.05).

✳ Class I BRAF mts were significantly enriched with (CMS1) (Class I, II and III: 44% vs. 17% vs. 18%) while class II and III BRAF mts were more often CMS2 subtype (canonical) compared to class I (2%, 30% and 35%, p<0.05).

✳ Class I BRAF and KRAS/NRAS mts were mutually exclusive, while KRAS mts incidences were 15% and 22% for class II and class III, and NRAS mts incidence were 8% and 12%, respectively.

✳ MPAS score was significantly lower for class III (-0.32, arbitrary unit) compared to Class I (p<0.05), but similar in class I and class II mutants (1.3 versus 1.38).

✳ Patients with class II and III mts had significantly better overall survival compared to patients with class I mts (HR=0.69 CI: 0.597-0.804 p<0.0001) and slightly worse overall survival compared to wild-type BRAF pts. (HR; 0.85 CI: 0.74-0.96 P=0.011).

✳ Among patients treated with anti-EGFR, patients with class II and III BRAF mts had significantly better post-anti-EGFR survival compared to class I BRAF mts (HR 0.498 CI 0.32-0.766 P=0.001 and similar survival compared to those with BRAF wild-type (P=0.21).

Conclusion

✳ Patient with class II and III BRAF mutations may have improved outcomes with EGFR blockade.

✳ Class II and III BRAF mutants represent a distinct biological subgroup of pMMR CRC

✳ Class III BRAF mts have lower MAPK activation, consistent with the pattern of kinase-dead mutations.

✳ Class II mutant have increased MAPK activation confirming their biological distinction from class III BRAF mutants ((Yao et al Nature 2017, Yeager et al Clin. Cancer Res 2019).

References

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