**Background**

- RAS mutations are associated with worse prognosis than RAS wild type tumors in metastatic colorectal cancer (mCRC).
- RAS mutations predict resistance to anti-EGFR therapy in mCRC.
- RAS amplification (RASª) results in activation of the EGFR pathway and is associated with anti-EGFR resistance in preclinical models.
- There are no reports on the impact of the presence or degree of amplification, as identified by next generation sequencing (NGS), on anti-EGFR therapy response.

**Methods**

- **Foundation Medicine (FM).** We investigated the FM database for RASª in CRC and characterized this population's demographics and tumor genomic profile.
- Gene amplification was defined as gene copy number (CN) of ≥2 copies per tumor (CN ≥2).
- **City of Hope (COH).** We reviewed a single center molecular database (2015-2018) cases analyzed by FM of mCRC and described the prevalence of RAS amplification, associated patient characteristics, and their response to anti-EGFR therapy.

**Results**

**FM Cohort:** Population Characteristics & Co-Existant Genomic Alterations in RAS Amplified Cases

**FM Cohort:** Case # | Age (Years) | Sex | KRAS CN | RAS SV Status | BRAF SV Status | Prior OX or IRI Resistance | Anti-EGFR Regimen | Anti-EGFR Initiated After Sample Collection | Best Response | PFS/Months | RAS Amplitations: COH Experience with Anti-EGFR Therapy
---|---|---|---|---|---|---|---|---|---|---|---|---
1 | 53 | Female | Left | 13 | WT | NA | Yes | FOI/Ft & Pmabs (1st Line) | SD | 4 |
2 | 53 | Male | Right | 20 | WT | OX & IRI resistant | Yes | FOI/Ft & Pmabs (3rd Line) | PD | 2 |
3 | 50 | Female | Left | 25 | WT | OX & IRI Resistant | Yes | FOI/Ft & Pmabs (2nd Line) | PD | 2 | 7 |
4 | 31 | Male | Left | 29 | WT | IRI & Cmba (3rd Line) | Yes | FOI/Ft & Pmabs (3rd Line) | PD | 2 | 2.5 |
5 | 56 | Male | Left | 30 | WT | OX & IRI Resistant | Yes | FOI/Ft & Pmabs (2nd Line) | PD | 2 | 5 |
6 | 53 | Female | Right | 42 | WT | OX & IRI Resistant | No | FOI/Ft & Pmabs (2nd Line) | PD | 3.5 |
7 | 36 | Male | Left | 54 | WT | OX & IRI Resistant | No | FOI/Ft & Pmabs (4th Line) | PD | 2 | 0.5 |
8 | 62 | Female | Left | 7 | KRAS G12S, WT | OX Exposed | No Anti-EGFR Regime | NA | NA | NA |
9 | 61 | Male | Left | 8 | KRAS G12S, WT | OX & IRI Resistant | No Anti-EGFR Regime | NA | NA | NA |
10 | 38 | Female | Left | 8 | WT | OX & IRI Resistant | No Anti-EGFR Regime | NA | NA | NA |
11 | 50 | Female | Left | 13 | KRAS G12S, WT | OX & IRI Resistant | No Anti-EGFR Regime | NA | NA | NA |
12 | 71 | Male | Left | 39 | WT | OX Exposed | No Anti-EGFR Regime | NA | NA | NA |
13 | 46 | Female | Left | 79 | WT | OX & IRI Exposed | No Anti-EGFR Regime | NA | NA | NA |

Abbreviations: M: male; F: female; mCRC: metastatic colorectal cancer; n: number; CN: copy number; SV: short variant (point mutation or indel); Amps: amplifications; "Type" of CRRC cases=21315. median age 58, gender: M (11668) 54.4%

**FM Cohort:** Frequency of Genomic Alternations in mCRC

- **RAS Amplifications:**
  - **FM Cohort:** Total 120 Cases: RAS Amplified: 43 (35.8%); RAS-Amplified w/ CN ≥2: 24 (20%); RAS-Amplified w/ CN ≥2 & OX Resistance: 9 (7.5%); RAS-Amplified w/ CN ≥2 & IRI Resistance: 9 (7.5%); RAS-Amplified w/ CN ≥2 & Both: 2 (1.7%; RAS-Amplified w/ CN ≥2 & Anti-EGFR resistance: 9 (7.5%)

**FM Cohort:** Frequency of MSI-H, RAS & BRAF in Overall and RAS-Amplified Population

- **Frequency of MSI-H, RAS & BRAF Short variant Mutations in RAS- Amplified Population**

**Conclusions**

- NGS identifies RAS (≥2 CN) and RASª in 1.5% and 0.6% of CRC, respectively.
- RASª tumors occurred predominantly in the left colon in a single institute cohort.
- RASª tumors are NRAS, generally lack RAS/WT short variant mutations, and predict for resistance to anti-EGFR therapy.
- Our data suggests that tumors with elevated RAS-CN may not drive a significant benefit from anti-EGFR therapy.
- The data support the potential relevance of 20-CN cut-off for the exclusion of pts from anti-EGFR, or at least in guiding the sequencing of anti-EGFR therapy.
- Additional validation through the retrospective analysis of completed phase II and III anti-EGFR clinical trials could provide support for our findings.

**References**