Second-line systemic treatment outcomes for patients with metastatic BRAFV600E mutant colorectal cancer

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Introduction

- BRAF V600E mutations (BRAFmt) occur in about 10% of patients with metastatic colorectal cancer (mCRC)
- A BRAFmt renders the BRAF pathway constitutionally active, increasing kinase activity compared to BRAF wildtype by about 10-fold, stimulating cell growth, proliferation and migration
- A BRAFmt is a negative prognostic factor with multiple associations including older age, female gender, right-sided primary, deficient mismatch repair gene (dMMR) status, mucinous subtype and increased frequency of peritoneal metastases
- BRAF status is emerging as a predictive marker in mCRC with the combination of a BRAF inhibitor and an EGFR inhibitor +/- MEK inhibitor demonstrating improved survival outcomes in second- and third-line setting (BEACON[1] and SWOG 1406[2] trials)
- Irinotecan plus cetuximab was the control arm in both the above studies with a dismal response rate of 2-4% and progression free survival (PFS) of 2 months
- BRAF-targeted therapies have yet to be funded by the Pharmaceutical Benefits Scheme (PBS) for mCRC. The Pharmaceutical Benefits Advisory Committee has recently recommended encorafenib, a BRAF inhibitor, in combination with cetuximab to be listed on PBS for management of BRAFmt mCRC in second-line setting

Aims

- To compare the survival outcomes of Australian BRAFmt mCRC patients in the second-line setting, excluding those who received BRAF-targeted therapies

Methodology

- The Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) Registry, has prospectively captured BRAFmt status for mCRC patients
- Data from July 2009 - October 2020 was examined for patient characteristics, treatment and outcomes
- The primary endpoint was second-line treatment PFS
- Patients who received BRAF-targeted therapies, immunotherapy or other experimental approach were excluded
- Treatment groups analysed were:

1) Chemotherapy alone (includes fluoropyrimidine, irinotecan, oxaliplatin, TAS102 and combinations of these)
2) Chemotherapy (as above) plus bevacizumab
3) Chemotherapy (as above) plus EGFR inhibitor

Results

Figure 1: Consort Diagram

Results (cont.)

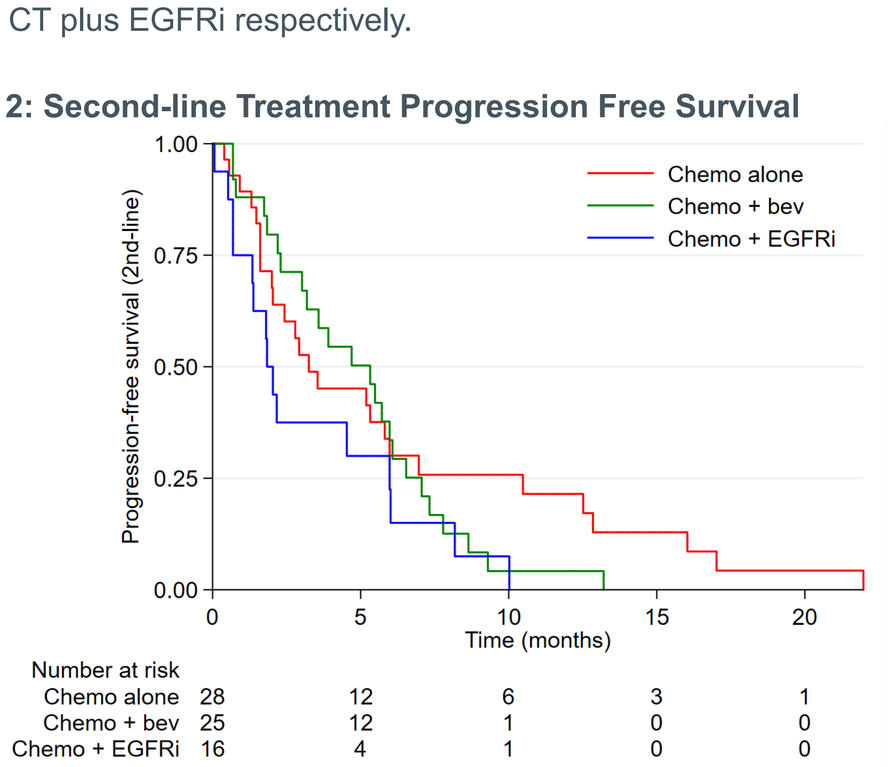
- 70 BRAFmt patients received second-line treatment, including chemotherapy (CT) alone (n=28), chemotherapy plus bevacizumab (BEV) (n=25) and chemotherapy plus EGFRi (n=17)
- The majority (n=50, 71%) received an irinotecan-based chemotherapy backbone

Table 1: Baseline clinicopathologic factors

	All treated patients (n=70)	CT alone (n=28)	CT + BEV (n=25)	CT + EGFRi (n=17)
Median age (range)	57.9 (24-85)	63.0 (28-85)	57.6 (24-77)	55.2 (29-83)
Female (%)	41 (59%)	20 (71%)	18 (72%)	3 (18%)
ECOG ≥ 2 (%)	7 (10%)	1 (4%)	2 (8%)	4 (17%)
Right side primary (%)	47 (67%)	18 (64%)	16 (64%)	11 (65%)
dMMR status (%)	8 (11%)	2 (7%)	5 (20%)	1 (6%)
1st line Oxaliplatin (%)	55 (79%)	22 (79%)	18 (72%)	15 (88%)
1st line Irinotecan (%)	12 (17%)	4 (14%)	6 (24%)	2 (12%)

- Median PFS was 3.3, 5.3 and 1.8 months for CT alone, CT plus BEV and CT plus EGFRi respectively.

Figure 2: Second-line Treatment Progression Free Survival



- In multivariate analysis (MVA), including CT alone, CT plus BEV and CT plus EGFRi, PFS when treated with CT plus EGFRi was similar to CT alone (HR 0.52, p=0.093) but **inferior** to CT plus bevacizumab (HR 2.31, p=0.03)
- In MVA, poor PFS was associated with age ≥ 65 years (HR 3.06, p=0.002) and ECOG ≥ 2 (HR 4.22, p=0.006)
- In MVA, poor PFS was **not** associated with a right sided primary (HR 1.93, p=0.071) or dMMR status (HR 1.19, p=0.69)
- Median overall survival was 8.7, 7.9 and 2.5 months for CT alone, CT plus BEV and CT plus EGFRi respectively (CT vs CT plus BEV, p=0.25; CT vs CT plus EGFRi; p=0.068; CT plus EGFRi vs CT plus BEV, p=0.008)

Conclusions

- Less than half of real-world BRAFmt mCRC patients received second-line therapy
- Limited benefit was derived from standard treatment options for BRAFmt mCRC in the second-line setting
- Patients who received chemotherapy plus an EGFRi had a poor PFS, comparable to those in the BEACON trial control arm (1.8 vs 1.5 months)
- Given these poor outcomes, wider access to BRAF targeted agents is urgently needed in the routine care setting

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