Clinical and Humanistic Outcomes of BRAF Inhibitors in BRAF^{V600E} Mutant Metastatic Colorectal Cancer

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Background

- Around 8–10% of patients with metastatic colorectal cancer (mCRC) are known to harbor mutations in the BRAF^{V600E} gene
- This mutation is recognized as a poor prognostic factor for mCRC, with a median overall survival of 10-20 months[1,2]
- Thus, treatment of mCRC with BRAF^{V600E} mutations is an unmet need
- Several potential treatment options have been investigated for this subset of patients, including immune checkpoint inhibitors, VEGF inhibitors, BRAF inhibitors, MEK inhibitors, and various other small molecules
- We wanted to evaluate the treatment outcomes (clinical and humanistic) of BRAF inhibitors used alone or in combination with other agents in the management of patients with mCRC harboring BRAF^{V600E} mutations

Objective

- To evaluate the safety, efficacy, and humanistic outcomes of BRAF inhibitors when used to manage mCRC with BRAF^{V600E} mutations

Methodology

Eligibility Criteria

Facet	Inclusion	Exclusion
Population	Adult patients diagnosed with unresectable, metastatic, advanced, refractory, or late stage CRC, with BRAF^{V600E} mutations	• Non-human/ preclinical studies • No mCRC • Having CRC of other stages • mCRC without BRAF^{V600E} mutations
Intervention	BRAF inhibitors: Dabrafenib, Encorafenib, Vemurafenib	All other interventions
Comparator	All comparators	No exclusion based on comparators

Outcome	• Clinical outcome: Efficacy
	  ◦ Survival (OS, PFS)
	  ◦ Rx Response (ORR, DCR, CR, PR, PD, SD, DOR)
	  ◦ Time to objective disease progression
	• Clinical outcome: Safety
	  ◦ Overall AEs
	  ◦ Treatment-related AEs
	  ◦ ≥ grade 3 AEs
	  ◦ SAEs
	  ◦ Deaths due to AEs
	  ◦ Treatment discontinuation due to AEs
	• Humanistic outcomes
	  ◦ Quality of life through any validated tool
	  ◦ Pain and fatigue scores
	  ◦ Patient satisfaction, convenience and adherence
	  ◦ Caregiver burden
		• All other outcomes

Study design	RCTs, single-arm studies, observational studies, and RWE studies	• All other types of studies
Databases	• PubMed	

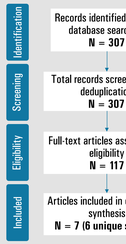
PubMed Search Strategy

Executed 07th Nov 2022

No	Terms	Hits
1	"Colorectal Neoplasms"[Mesh]	230,078
2	((((((((((advanced colorectal cancer) OR (unresectable colorectal cancer)) OR (metastatic colorectal cancer)) OR (refractory colorectal cancer)) OR (late-stage colorectal cancer)) OR (unresectable CRC)) OR (metastatic CRC)) OR (advanced late-stage CRC)) OR (refractory CRC)) OR (late-stage CRC)) OR (mCRC)	76,802
3	#1 OR #2	245,826
4	BRAFV600E	3,230
5	#3 AND #4	307

Note: Restrictions were not imposed on the search strategy; ineligible articles were manually screened out

Results



Records identified through database searching
N = 307

Total records screened after deduplication
N = 307

Records excluded, with reasons, **N = 190**
- Population not of interest, **N = 120**
- Study design not of interest, **N = 70**

Full-text articles assessed for eligibility
N = 117

Full-text articles excluded, with reasons, **N = 110**
- Population not of interest, **N = 13**
- Intervention not of interest, **N = 34**
- Outcomes not of interest, **N = 13**
- Study design not of interest, **N = 41**
- Full text not accessible, **N= 9**

Articles included in qualitative synthesis
N = 7 (6 unique studies)

- Publication disposition
  - Total articles included: 7
  - Total unique studies included: 6
- Patients disposition
  - Overall:1058 patients
  - Patients with BRAF^{V600E} mutant mCRC: 1027 patients
  - Range: 29 to 665
- Meta-analysis was not possible due to heterogeneity of data

Main Characteristics of the Included Studies [3-9]

No	Author, year	Study design	Overall sample size	BRAF^{V600E} mutation mCRC	BRAF inhibitor combinations	Treatment arms (N)	Males, N (%)	Females, N (%)	Age, Median (Range)	Primary site		
										Rt colon	Lt colon	Rectum
1	Corcoran RB, 2018	Phase 1 clinical trial	142	142	Dabrafenib: DP, DPT	DP (20) [Int]	9 (45%)	11 (55%)	58.0 (42-84)	14	4	2
						DPT (91) [Int]	33 (36%)	58 (64%)	60.0 (28-83)	57	19	15
						PT (31) [Comp]	13 (42%)	18 (58%)	57.0 (39-74)	16	10	5
2	Yu LF, 2022	Retrospective cohort (RWE)	40	29	Vemurafenib: VIC	Front-line therapy (11)	NR	NR	NR	NR		
						Subsequent VIC (29) [Int]	19 (66%)	10 (34%)	51 (14-78)	15	9	5
3	Kopetz S, 2021	RCT	100	100	Vemurafenib: VIC	VIC (50) [Int]	13 (26%)	37 (74%)	61.9 (30-82)	30	17	3
						IC (50) [Comp]	29 (58%)	21 (42%)	59.7 (34-82)	36	8	6
4	Guan W L, 2020	Retrospective cohort (RWE)	74	54	Vemurafenib: VIC	mCRC, BRAF^{V600E} (54)	32 (59%)	22 (41%)	48 (NR)	22	15	17
						VIC (8) [Int]	NR	NR	NR	NR		
						BFFx/ FFx/ RFr (13) [Comp]	NR	NR	NR	NR		
5	Huiberts S, 2021	Retrospective cohort (RWE)	37	37	Encorafenib: EC, ECB, ECA	Overall	13 (35%)	13 (35%)	59 (38-74)	NR		
						EC (17) [Int]	NR	NR	NR	NR		
						ECB (7) [Int]	NR	NR	NR	NR		
						ECA (13) [Int]	NR	NR	NR	NR		
6	Stintzing S, 2022	RCT	441	441	Encorafenib: EC	EC (220) [Int]	114 (55%)	94 (45%)	61 (30-91)	110	83	
						IC/CF (221) [Comp]	106 (45%)	127 (55%)	60 (27-91)	119	68	
7	Tabernero J, 2021	RCT	665	665	Encorafenib: EC, ECB	ECB (224) [Int]	105 (47%)	119 (53%)	62 (26-85)	126	79	
						EC (220) [Int]	114 (52%)	106 (48%)	61 (30-91)	110	83	
						IC/CF (221) [Comp]	94 (43%)	127 (57%)	60 (27-91)	119	68	

Note: RWE = real-world evidence; RCT = randomized controlled trial; mCRC = metastatic colorectal cancer; VIC = vemurafenib, irinotecan, cetuximab; IC = Irinotecan, cetuximab; EC = encorafenib, cetuximab; IC = Irinotecan, cetuximab; CF: cetuximab, FOLFIRI; BFFx = bevacizumab, FOLFIRI/FOLFOXIRI; FFx: FOLFIRI/FOLFOXIRI; RFr: regorafenib, fruquintinib; ECB = encorafenib, cetuximab, binimetinib; ECA = encorafenib, cetuximab, alpelisib; DP = dabrafenib, panitumumab; DPT = dabrafenib, panitumumab, trametinib; PT = panitumumab, trametinib; Int = Intervention; Comp = Comparator

Publication Information

Study Designs
- RCTs: 3 studies (BEACON study, BEACON re-analysis, SWOG S1406)
- Phase 1 trial: 1 study
- Retrospective cohort (RWE): 3 studies

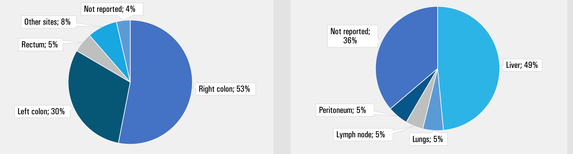
First Author Countries
- USA: 2 studies
- China: 2 studies
- Germany, Netherlands, Spain: 1 study each

Study Duration
- RCTs: 20 months; follow-up of 6-36 months
- RWE studies: 24 months to 96 months
- One study did not report study duration

Study Sponsor
- Pharmaceutical industry: 3 studies
- National research foundation: 3 studies
- One study did not report study sponsor details

mCRC Information

Primary Site



Metastasis Site

Intervention and Comparator

Drug	No of Studies	Combinations	Dose details
Dabrafenib	1	DP, DPT	Oral Dabrafenib (D): 150 mg BID Oral Trametinib (T): 1.5 mg once daily IV Panitumumab (P): 4.8 mg/kg to 6 mg/kg Q2W
Vemurafenib	3	VIC	Oral Vemurafenib (V): 480 mg/day to 960 mg/day IV Irinotecan (I): 180 mg/m^2 Q2W IV Cetuximab (C): 500 mg/m^2 Q2W
Encorafenib	3	EC, ECB, ECA	Oral Encorafenib (E): 100 mg to 450 mg QD Oral Binimetinib (B): 45 mg BID Oral Alpelisib (A): 100 mg to 300 mg QD IV Cetuximab (C): 400 mg/m^2 to 250 mg/m^2 weekly
Control	3 (4 articles)	PT IC, CF BFFx, FFx, RFr	IV Irinotecan (I): 180 mg/m^2 Q2W IV Cetuximab (C): 400 mg/m^2 to 250 mg/m^2 weekly FOLFIRI (F), FOLFOXIRI (Fx), Bevacizumab (B), Regorafenib (R), Fruquintinib (Fr): dose NR

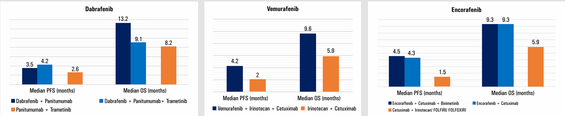
- 3 unique studies in 4 articles had non-BRAF inhibitor comparators
- 3 studies did not include non-BRAF comparators

Clinical Outcomes: Efficacy

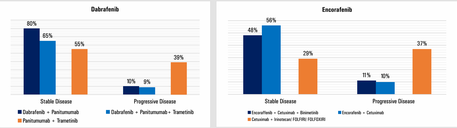
Dabrafenib
- Compared to non-dabrafenib combination therapy (PT; N = 31), dabrafenib combinations (DP, DPT; N = 20, 91 respectively) had:
  - Longer median OS and PFS
  - Higher ORR, CR, PR, and SD; lower PD; longer median DOR

Vemurafenib
- Compared to IC, VIC had: (N = 50 in each group):
  - Longer median OS and PFS
  - Higher ORR
- Compared to non-Vemurafenib combination therapies (BFFx, FFx, Rfr), VIC had (N = 8,2,3,8 respectively):
  - Marginally longer PFS (BFFx had longer PFS than VIC)
  - Marginally higher proportion of SD, and lower proportion of PD
- In 29 patients, VIC had an OS of 16.6 (95% CI 4.2-29.1) months and PFS of 5.8 (95% CI 3.8-7.7) months

Encorafenib
- Compared to non-encorafenib combination therapy (IC/ CF; N = 221), encorafenib combinations (ECB, EC; N = 224, 220 respectively) had:
  - Longer median OS and PFS
  - Higher ORR, CR, PR, and SD; lower PD
- In 37 patients treated with three encorafenib combinations (EC, ECB, ECA), SD was highest with ECA



Median PFS and OS: BRAF inhibitor combinations vs non-BRAF inhibitor combinations



Stable disease and Progressive disease: BRAF inhibitor combinations vs non-BRAF inhibitor combinations

Clinical Outcomes: Safety

- Only 4 studies reported safety outcomes
- Safety outcomes were largely similar between patients receiving BRAF inhibitor combination therapies and those receiving non-BRAF inhibitor combination therapies

	Any AE N (%)	Grade 3-4 AE N (%)	Serious AE N (%)	AE leading to discontinuation N (%)
Dabrafenib				
Dabrafenib + Panitumumab	20 (100%)	9 (45%)	6 (30%)	1 (5%)
Dabrafenib + Panitumumab + Trametinib	91 (100%)	64 (70%)	46 (51%)	16 (18%)
Panitumumab + Trametinib (Control)	50 (98%)	34 (67%)	23 (45%)	8 (16%)
Encorafenib				
Encorafenib + Cetuximab + Binimetinib	220 (99.1%)	146 (65.8%)	NR	13 (5.8%)
Encorafenib + Cetuximab	212 (98.1%)	124 (57.4%)	NR	11 (5.0%)
Cetuximab + Irinotecan/ FOLFIRI/ FOLFOXIRI (Control)	190 (98.4%)	124 (64.2%)	NR	10 (4.5%)

Humanistic Outcomes

- Only 1 study compared humanistic outcomes between [Encorafenib + Cetuximab] and [Cetuximab + Irinotecan/ FOLFIRI/ FOLFOXIRI]
- Statistically significant differences favoring Encorafenib + cetuximab (compared to control) were reported in:
  - EORTC QLQ-C30 (global health status; individual symptom scales)
  - FACT-C and FACT-G

Parameter	Mean difference (95% CI) between groups	p value
QLQ-C30 global health status	3.92 (0.26 to 7.57)	0.036
EORTC QLQ-C30 symptom scales		
Diarrhoea	-12.61 (-17.75 to -7.47)	< 0.0001
Nausea/ Vomiting	-4.62 (-7.75 to -1.48)	0.004
Loss of appetite	-6.72 (-12.07 to -1.38)	0.014
Constipation	-5.68 (-10.05 to -1.28)	0.012
FACT-G global health score	3.78 (1.0.5 to 6.50)	0.007
FACT-C physical well-being	1.62 (0.70 to 2.54)	< 0.001

Discussion

- All three BRAF inhibitors in combination with drugs acting through other mechanisms appear to improve survival (OS, PFS) and treatment response (ORR, PR, SD, lower PD) compared to combinations without BRAF inhibitors
- Oral route of administration is an added benefit compared to existing standard of care which are predominantly parenteral
- No new safety signals of interest were uncovered by the studies
- Quality of life was higher with encorafenib in one reported study
- Preliminary analysis suggests that BRAF inhibitor combinations have a role to improve efficacy, safety, and quality of life in mCRC patients with BRAF^{V600E} mutations: It is worthwhile exploring these combinations as earlier lines of therapy with larger trials

Limitations

- Search was limited to PubMed; databases like Embase were not included
- Meta-analysis was hindered by varying quality of reported data
- SLR protocol not prospectively registered with PROSPERO

Conclusion

- Use of BRAF inhibitor combinations show a trend towards improved efficacy, safety, and quality of life in mCRC patients with BRAF^{V600E} mutations

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