Efficacy and Safety of Oxaliplatin/ Capecitabine Based Chemotherapy plus Bevacizumab as First-line Treatment for Advanced Colorectal Cancer (CRC): a Systematic Review and Meta-analysis

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INTRODUCTION

- Colorectal cancer (CRC) is a leading cause of cancer-related deaths.[1]
- Current 1st line for CRC therapy usually consists of 5-Fluorouracil (5-FU) based combination chemotherapy along with a targeted antibody against VEGF or EGFR.[2]
- The combination of 5-FU with Oxaliplatin (FOLFOX) is a commonly used treatment regimen for CRC.
- Capecitabine is an oral prodrug of 5-FU.[2]
- The combination of capecitabine with oxaliplatin (XELOX) has been shown to be non-inferior to the FOLFOX regimen, albeit with slightly increased toxicity.[3]

OBJECTIVE

To evaluate the efficacy and safety of oxaliplatin or capecitabine - based chemotherapy plus bevacizumab as first-line treatment for advanced CRC.

MATERIAL AND METHODS

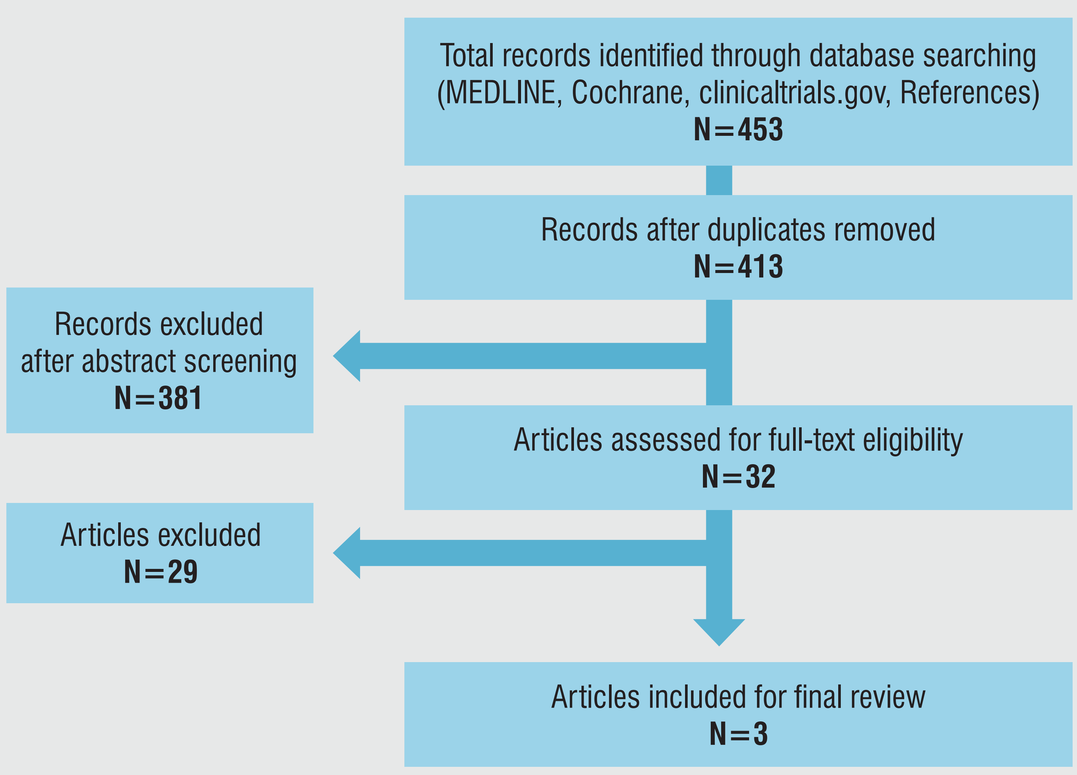
- Literature searches were conducted in MEDLINE, Embase, the Cochrane Library, and clinicaltrials.gov. No language or date restrictions were imposed.
- In addition, references of included studies were searched for relevant studies.
- All randomized controlled trials (RCTs) examining the efficacy and safety of oxaliplatin/capecitabine based chemotherapy plus bevacizumab in adult patients with advanced CRC were included.

Outcomes:

- **Primary:** overall survival (OS) and progression free survival (PFS).
- **Secondary:** response rate, complete response, partial response, stable disease, progressive disease, disease control, and adverse events.

- Two authors independently selected papers, extracted data and assessed quality.
- Study quality of included trials were assessed using the Cochrane Risk of Bias Tool.

RESULTS



- A total of 3 RCTs involving a total of 1993 patients were included in this meta-analysis.
- A total of 997 Patients received Oxaliplatin/capecitabine based chemotherapy, and a total of 996 Patients received comparators.
- Overall, the risk of bias of included trials was low.
- Most common adverse events reported with bevacizumab included bleeding, hypertension, and venous thromboembolic events.

Overall survival

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	27	140	14	140	25.6%	2.15 (1.07, 4.30)
Saltz 2008	420	699	455	701	43.5%	0.81 (0.66, 1.01)
Tebutt 2010	42	114	38	108	30.9%	1.07 (0.62, 1.86)
Total (95% CI)		**953**		**949**	**100.0%**	**1.14 (0.68, 1.92)**
Total events	489		607			

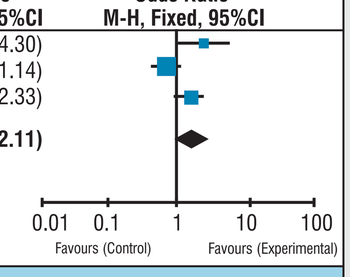
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.28$, df = 2 (P = 0.03); $I^2 = 73\%$
Test for overall effect: Z = 0.49 (P = 0.63)

The **overall survival** was between OCB regimen (Oxliplatin/capecitabine based chemotherapy plus bevacizumab) and other chemotherapy regimen
(Odds Ratio [OR] = 1.14, 95% CI 0.68 to 1.92, 3 trials)

Overall response

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	27	140	14	140	24.1%	2.15 (1.07, 4.30)
Saltz 2008	328	699	343	701	43.8%	0.92 (0.75, 1.14)
Tebutt 2010	56	147	43	143	32.1%	1.43 (0.88, 2.33)
Total (95% CI)		**986**		**994**	**100.0%**	**1.30 (0.80, 2.11)**
Total events	411		400			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 7.10$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 1.07 (P = 0.28)

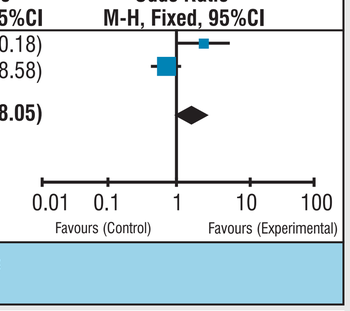


The **overall response** was higher with OCB regimen than other comparators
(OR = 1.30, 95% CI 0.80 to 2.11, 3 trials)

Complete response

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	3	140	2	140	66.3%	1.51 (0.25, 0.18)
Tebutt 2010	3	147	1	142	33.7%	2.94 (0.30, 28.58)
Total (95% CI)		**287**		**282**	**100.0%**	**1.99 (0.49, 8.05)**
Total events	6		3			

Heterogeneity: $Chi^2 = 0.20$, df = 1 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 0.97 (P = 0.33)

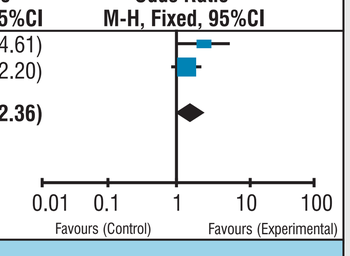


The **complete response** was higher with OCB regimen than other comparators
(OR = 1.99, 95% CI 0.49 to 8.05, 2 trials)

Partial response

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	24	140	12	140	26.7%	2.21 (1.06, 4.61)
Tebutt 2010	53	147	47	142	73.3%	1.34 (0.82, 2.20)
Total (95% CI)		**287**		**282**	**100.0%**	**1.57 (1.05, 2.36)**
Total events	77		54			

Heterogeneity: $Chi^2 = 1.21$, df = 1 (P = 0.27); $I^2 = 17\%$
Test for overall effect: Z = 2.18 (P = 0.03)

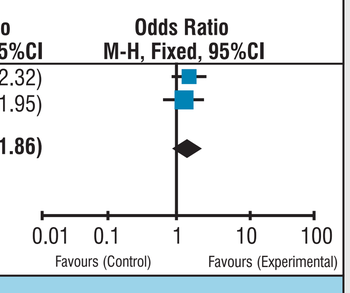


The **partial response** was higher with OCB regimen than other comparators
(OR = 1.57, 95% CI 1.05 to 2.36, 2 trials)

Stable Disease

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	77	140	67	147	47.5%	1.46 (0.92, 2.32)
Tebutt 2010	80	147	70	142	52.5%	1.23 (0.77, 1.95)
Total (95% CI)		**287**		**289**	**100.0%**	**1.34 (0.96, 1.86)**
Total events	157		137			

Heterogeneity: $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 1.74 (P = 0.08)

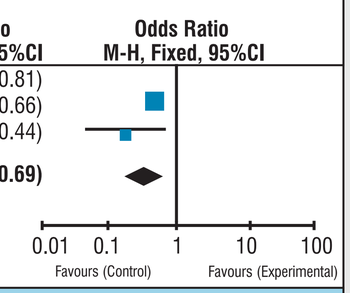


OCB regimen showed higher **stable disease** than other comparators
(OR = 1.34, 95% CI 0.96 to 1.86, 3 trials)

Progression Disease

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Cunnigham 2013	14	140	30	140	31.1%	0.41 (0.21, 0.81)
Saltz 2008	366	699	472	701	49.9%	0.53 (0.43, 0.66)
Tebutt 2010	4	142	24	147	19.0%	0.15 (0.05, 0.44)
Total (95% CI)		**981**		**988**	**100.0%**	**0.38 (0.21, 0.69)**
Total events	384		526			

Heterogeneity: $Tau^2 = 0.17$, $Chi^2 = 5.51$, df = 2 (P = 0.06); $I^2 = 64\%$
Test for overall effect: Z = 3.17 (P = 0.002)



OCB regimen showed lower **progressive disease** than other comparators
(OR = 0.38, 95% CI 0.21 to 0.69, 3 trials)

DISCUSSION

- Despite advances in the treatment of metastatic CRC (mCRC), most patients have a poor prognosis.[4]
- Since many patients may not prefer, or are not candidates for aggressive treatment regimens, effort should be put to identify efficacious but less toxic chemotherapeutic regimens.[4]
- Bevacizumab is a humanized, IgG monoclonal antibody against VEGF-A which does not have significant activity as monotherapy.[4]
- When given as part of combination chemotherapy, bevacizumab has shown good activity, and its ADRs are not serious enough to lower QoL.[4]
- Bevacizumab also has been shown to improve progression-free survival and overall survival when added to chemotherapy in first line and second-line treatment settings.[5]
- International guidelines recommend 5-FU or capecitabine with or without bevacizumab as first line treatment for patients with mCRC for whom more intensive treatment is not appropriate.[5]
- When bevacizumab was combined with fluorouracil/ folinic acid plus oxaliplatin (FOLFOX-4) in the second-line setting, there were significant benefits in OS, PFS an RR.[6]

CONCLUSION

Bevacizumab plus Oxaliplatin/capecitabine based chemotherapy showed improvement in OS and RR as compared to other chemotherapy in patients with advanced CRC.

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Poster presented at ISPOR 22nd Annual International Meeting, May 20-24, 2017, Boston, MA, USA