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Evaluating neoadjuvant options in synchronous non-resectable mCRC, RAS mutated or right-sided RAS wild type: A Real-World perspective

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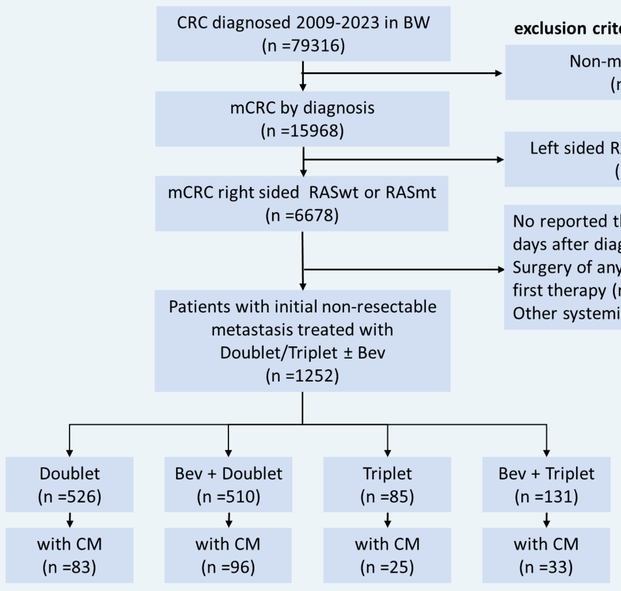
Background

- Treatment of metastatic colorectal cancer (mCRC) remains challenging, especially in primarily unresectable cases with synchronous metastases, RAS mutations, or right-sided tumors
- While several RCTs have compared triplet to doublet chemotherapy (CTx), the real-world effectiveness of these regimens is less clear. Bevacizumab (Bev) has shown benefits in trials, but its impact in broader populations needs further investigation
- **Aim:** Using data from the Baden-Wuerttemberg Cancer Registry, we evaluated real-world outcomes, focusing on triplet vs. doublet CTx and the use of Bev

Methods

- **Study type**: retrospective cancer registry study
- **Data source**: Baden-Wuerttemberg Cancer Registry (BWCR), Germany
- **Patients**: non-resectable synchronous mCRC (RAS-mutated or right-sided RAS wild-type), diagnosed 2009-2023
- **Treatment arms**: Triplet vs Doublet +/- Bevacizumab
- **Endpoints**:
  - Primary – Overall survival (OS), overall response (ORR)
  - Secondary – surgical resection rate, residual disease status
- **Statistics**: Fisher's exact/chi-square test; Kaplan-Meier and Cox models
- **Parameter Adjustment:** propensity score weighting (PSW)

Fig. 1: Consort Diagram



CM in the diagram denotes complete metastasectomy

Results

Table 1: Patient characteristics

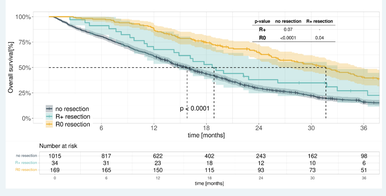
	Overall	Bev + Doublet	Bev + Triplet	Doublet	Triplet
cofactors					
n	1252	510 (40.7)	131 (10.5)	526 (42.0)	85 (6.8)
Age - mean (SD)	65.23 (10.99)	65.86 (10.68)	57.69 (11.56)	67.41 (10.12)	59.54 (10.33)
Sex					
m	736 (58.8)	283 (55.5)	72 (55.0)	326 (62.0)	55 (64.7)
w	516 (41.2)	227 (44.5)	59 (45.0)	200 (38.0)	30 (35.3)
ECOG					
0	363 (49.3)	155 (51.3)	59 (65.6)	118 (41.0)	31 (55.4)
1	284 (38.6)	117 (38.7)	27 (30.0)	119 (41.3)	21 (37.5)
2-4	89 (12.1)	30 (9.9)	4 (4.4)	51 (17.7)	4 (7.1)
M-Stage					
M1a	556 (44.6)	237 (46.7)	54 (41.2)	229 (43.8)	36 (42.4)
M1b	391 (31.4)	156 (30.8)	48 (36.6)	152 (29.1)	35 (41.2)
M1c	299 (24.0)	114 (22.5)	29 (22.1)	142 (27.2)	14 (16.5)

Table 2: Treatment response, metastasectomy rates, and residual disease status stratified by type of systemic therapy

	Overall	Bev + Doublet	Bev + Triplet	Doublet	Triplet
cofactors					
n	1252	510 (40.7)	131 (10.5)	526 (42.0)	85 (6.8)
objective response					
stable disease	246 (33.3)	108 (34.4)	31 (35.6)	82 (28.9)	25 (47.2)
progress	257 (34.8)	102 (32.5)	23 (26.4)	120 (42.3)	12 (22.6)
partial response	216 (29.3)	98 (31.2)	29 (33.3)	75 (26.4)	14 (26.4)
complete response	19 (2.6)	6 (1.9)	4 (4.6)	7 (2.5)	2 (3.8)
Metastasectomy					
no	1015 (81.1)	414 (81.2)	98 (74.8)	443 (84.2)	60 (70.6)
yes	237 (18.9)	96 (18.8)	33 (25.2)	83 (15.8)	25 (29.4)
Pat. (with metastasectomy)					
R+	34 (16.7)	10 (12.7)	5 (17.2)	15 (20.5)	4 (18.2)
R0	169 (83.3)	69 (87.3)	24 (82.8)	58 (79.5)	18 (81.8)

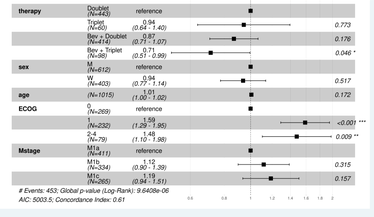
- **Response:**
  - Progression: highest with Doublet(42 %), lowest with Bev+Triplet (26 %)
  - Highest ORR: Bev+Triplet (37.9%) and Bev+Doublet (33.1%) (p<0.001)
- **Metastasectomy:**
  - Patients in the Triplet groups were most frequently resected (p=0.002)
  - with numerically highest R0 resection rates (p=0.71)

Fig 2: Impact of R0-metastasectomy



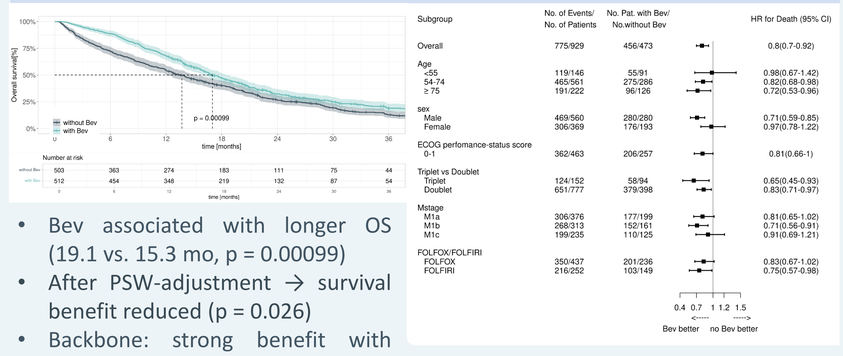
- **R0 resection**: mOS 44.6 mo
- **CTx only**: mOS 17.0 mo

Fig 3: Non-resectable Metastasis



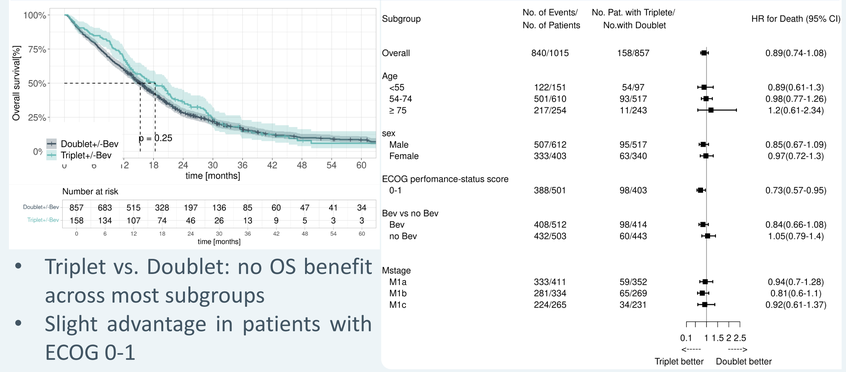
ECOG drives outcomes more than CTx- choice

Fig 4: Impact of Bevacizumab



- Bev associated with longer OS (19.1 vs. 15.3 mo, p = 0.00099)
- After PSW-adjustment → survival benefit reduced (p = 0.026)
- Backbone: strong benefit with FOLFIRI, reduced with FOLFOX

Fig 5: Triplet vs Doublet



- Triplet vs. Doublet: no OS benefit across most subgroups
- Slight advantage in patients with ECOG 0-1

Discussion

- **R0 metastasectomy** is a key prognostic factor in right-sided and/or RAS-mutated mCRC
- **Triplet chemotherapy** slightly increases resectability but does not improve survival vs. doublet
- **Bevacizumab** enhances response and tumor control, but has limited effect on long-term survival

Conclusion

- Results support **therapy de-escalation** when appropriate
- Real-world data provide important guidance for clinical decisions

Conflict of interest : No conflict of interest

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