FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in mCRC: final results of the phase II randomized MOMA trial by GONO

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On behalf of the GONO (Gruppo Oncologico del Nord Ovest, Italy) investigators

O-017

Introduction and objective

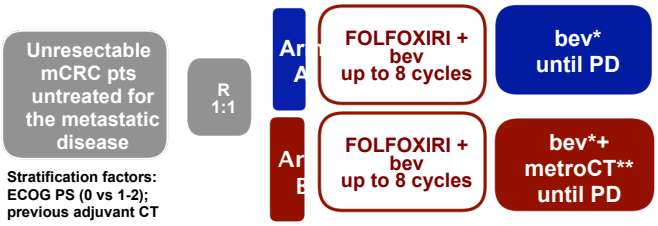
Although alternating induction and maintenance phases is a common strategy in mCRC, the optimal duration of induction therapy is an open issue.

When MOMA trial was designed, the role of maintenance with bev plus fluoropyrimidine (and optimal schedule) was still under investigation in phase III trials.

Clinical studies demonstrated that metroCT (i.e. the administration of low doses of anti-neoplastic drugs without drug-free intervals) acts targeting tumor angiogenesis and suggested a possible synergism with anti-vascular endothelial growth factor (VEGF) agents.

Kerbel et al, Nat Rev Cancer 2004; Pasquier et al, Nat Rev Clin Oncol 2010; Dellapasqua et al, J Clin Oncol 2008; Allegrini et al, Angiogenesis 2012; Bocci et al, Cancer Res 2002; Bocci et al, Nat Rev Clin Oncol 2014.

MOMA study is a phase II randomized trial, aiming at comparing the efficacy in terms of PFS of two different maintenance strategies: bev alone vs bev plus metroCT following 4 months-induction with FOLFOXIRI plus bev.



Stratification factors: ECOG PS (0 vs 1-2); previous adjuvant CT

Maintenance schedule:
*bev= 7,5 mg/kg every 3 weeks;
**metroCT = capecitabine 500 mg/tid + cyclophosphamide 50 mg/day.

Patients and Methods

Key eligibility criteria

- Histologically proven adenocarcinoma
- Unresectable mCRC not previously treated for metastatic disease
- At least one measurable lesion according to RECIST 1.1
- Age 18-75
- ECOG PS ≤ 2 (ECOG PS = 0 if age = 71-75 years)
- Adjuvant oxa-containing CT allowed if >12 mos elapsed between the end of adjuvant and relapse.

Statistics

Primary endpoint: Progression-Free Survival

- Null hypothesis – median PFS : 11 mos
- Alternative hypothesis – HR : 0.75 in favour of arm B
- 1-sided alpha error: 0.15, Beta error: 0.20
- Design: Rubistein and Korn

173 events required.

222 patients (111 per arm) to be randomized.

Study population

From to May 2012 to March 2015, 232 pts were randomized in 16 Italian centers

Characteristic, % patients	bev arm N = 117	bev+metroCT arm N = 115	Overall N = 232
Sex (M / F)	60% / 40%	56% / 44%	58% / 42%
Median Age (range)	61 (23 – 74)	62 (31 – 74)	61 (23 – 74)
ECOG PS (0 / 1-2)	85% / 15%	86% / 14%	85% / 15%
Synchronous Metastases (Y / N)	81% / 19%	83% / 17%	82% / 18%
Prior Adjuvant CT (Y / N)	14% / 86%	9% / 91%	11% / 89%
Primary Tumor Site (right / left / rectum)	32% / 32% / 36%	42% / 32% / 26%	37% / 32%/ 31%
Number Metastatic Sites (1 / >1)	37% / 63%	50% / 50%	43% / 57%
Liver Only Disease (Y / N)	28% / 72%	35% / 65%	31%/ 69%
Resected Primary (Y / N)	59% / 41%	53% / 47%	56% / 44%
Mutational status:			
RAS BRAF wt	18%	13%	15%
RAS mut	66%	63%	65%
BRAF mut	7%	10%	9%
NA	9%	14%	11%

Results

Secondary endpoint – Response and resection rate

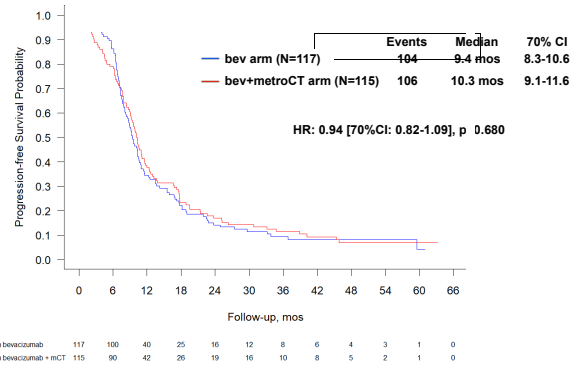
Best Response, %	bev arm N = 117	bev+metroCT arm N = 115	Overall N = 232
Complete Response	3%	3%	3%
Partial Response	65%	55%	60%
Response Rate	68%	58%	63%
Stable Disease	26%	30%	28%
Disease Control Rate	94%	88%	91%
Progressive Disease	2%	5%	3%
Not Assessed	4%	7%	6%

patients, %	bev arm N = 117	bev+metroCT arm N = 115	Overall N = 232
Secondary surgery with radical intent	25%	24%	25%
R0 secondary surgery	18%	16%	17%

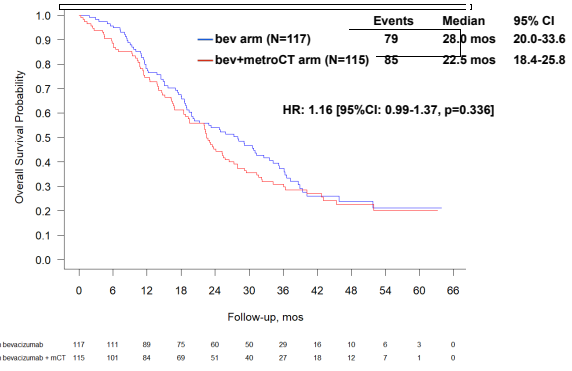
Liver-only subgroup	N = 33	N = 40	N= 73
Secondary surgery with radical intent	55%	45%	49%
R0 secondary surgery	39%	30%	34%

Results

Primary endpoint – Progression-Free Survival



Secondary endpoint – Overall Survival



Secondary endpoint – Safety profile

Induction phase

G3/4 adverse events, % patients	bev arm N = 116	bev+metroCT arm N = 115	Overall N = 231
Nausea	2.6%	3.5%	3.0%
Vomiting	0.9%	6.1%	3.5%
Diarrhea	11.2%	15.6%	13.4%
Stomatitis	3.5%	4.4%	3.9%
Neutropenia	59.5%	50.4%	55.0%
Febrile neutropenia	13.8%	8.7%	11.3%
Neurotoxicity	0.9%	1.7%	1.3%
Asthenia	12.9%	8.7%	10.8%
Anorexia	4.3%	6.1%	5.2%
Hypertension	5.2%	1.7%	3.5%
Venous Thrombosis	1.7%	5.2%	3.5%

Maintenance phase

G3/4 adverse events, % patients	bev arm N = 88	bev+metroCT arm N = 79	p
Neutropenia	0%	3.9%	0.062
Hand-foot syndrome	0%	9.1%	**0.004**
Hypertension	4.5%	3.9%	0.836

Treatment after PD

152 (72%) out of 210 patients with progression event received a treatment after PD.

	bev arm N = 117	bev+metroCT arm N = 115	Overall N=232
2nd-line therapy	N=84	N=68	N=152
FOLFOXIRI + bev	51 (61%)	40 (60%)	91 (60%)
FOLFOX/FOLFIRI + bev	16 (20%)	15 (22%)	31 (20%)
FOLFOX/FOLFIRI	2 (2%)	4 (6%)	6 (4%)
5FU + bev	3 (3%)	1 (1%)	4 (3%)
FOLFIRI + aflibercept	2 (2%)	4 (6%)	6 (4%)
FOLFIRI/FOLFOX + anti-EGFR	3 (4%)	3 (4%)	6 (4%)
Anti-EGFR alone	2 (2%)	0	2 (1%)
Other	5 (6%)	1 (1%)	6 (4%)

Main grade 3/4 adverse events occurring during the reintroduction of FOLFOXIRI plus bev were neutropenia (19%), diarrhea (9%), stomatitis (3%), vomiting (2%), and hypertension (1%).

Conclusions

The addition of metroCT to maintenance with bev does not significantly improve PFS or OS of mCRC patients.
Activity results of FOLFOXIRI plus bev are confirmed with a shorter treatment duration (4-months) in a population with high prevalence of *RAS and BRAF* mutant mCRC patients.
Re-introduction of FOLFOXIRI plus bev was feasible and associated with a favourable safety profile.

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