PARIS 2022 ESMO congress

FOLFOX/FOLFIRI plus either bevacizumab or panitumumab in patients with initially unresectable colorectal liver metastases and left-sided and *RAS*/*BRAFV600E* wild-type tumour

Randomised phase III CAIRO5 study of the Dutch Colorectal Cancer Group

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DECLARATION OF INTERESTS

Marinde Bond has no conflicts of interest to declare.

Colorectal cancer liver metastases (CRLM)

- Initially resectable CRLM
  → local treatment (e.g. resection, ablation)

- Initially unresectable but potentially resectable CRLM after downsizing
  → induction systemic treatment

- Permanently unresectable CRLM
  → palliative systemic treatment

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Colorectal cancer liver metastases (CRLM)

Unresolved issues

- No consensus on criteria for (un)resectability of CRLM
- No consensus on optimal systemic induction regimen in potentially resectable CRLM
- Retrospective studies in unselected metastatic patients and most prospective studies in CRLM patients are hampered by
  - absent or varying criteria for unresectability
  - lack of long-term outcome of liver resections
  - heterogeneity in study populations, trial design, use of *RAS/BRAF* mutation status

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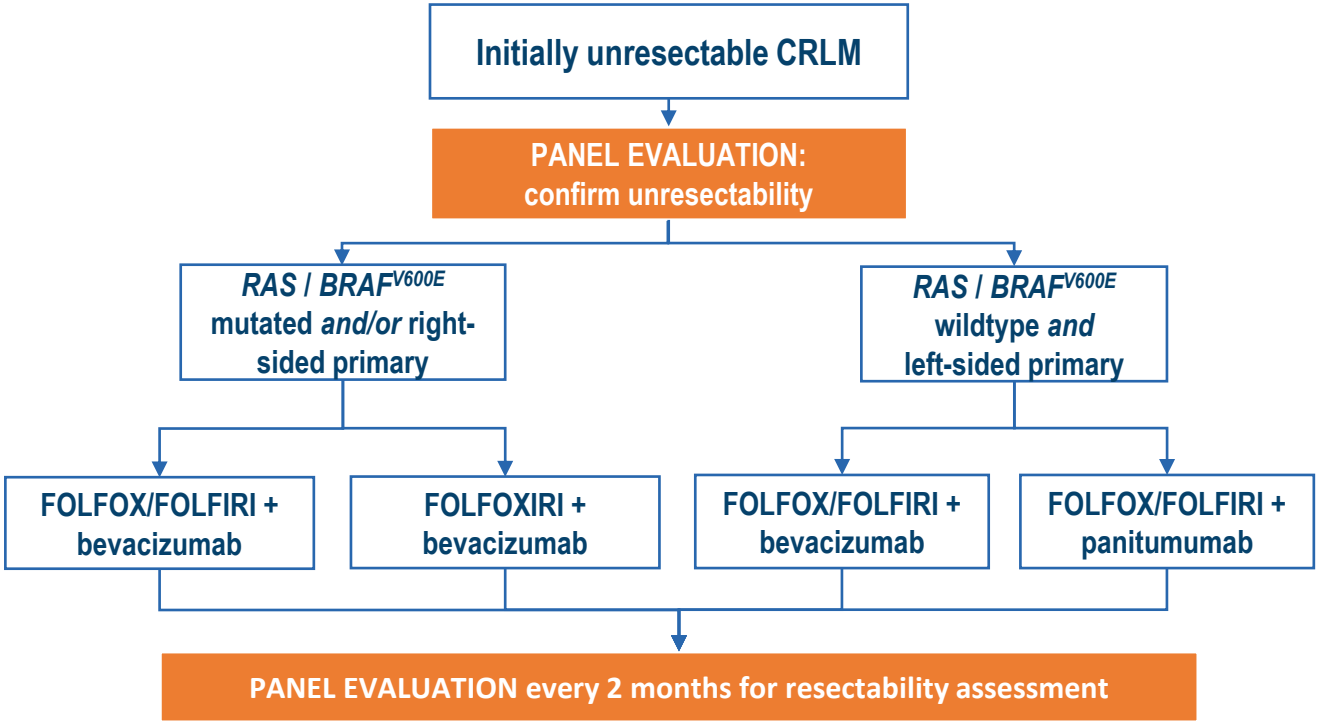
Reviewed in Bolhuis K. et al. Eur J Cancer 2020

CAIRO5: prospective randomised comparison of currently most active systemic regimens in defined subgroups of patients with initially unresectable CRLM



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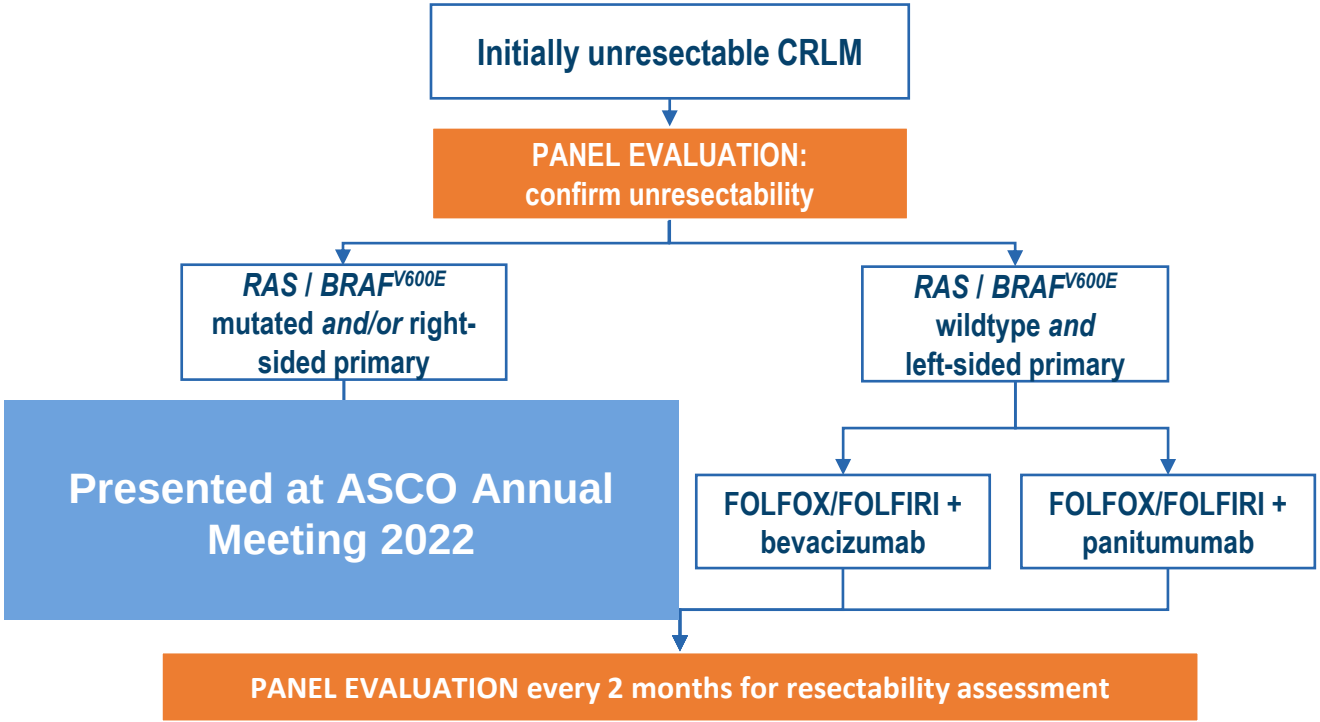
CAIRO5: prospective randomised comparison of currently most active systemic regimens in defined subgroups of patients with initially unresectable CRLM



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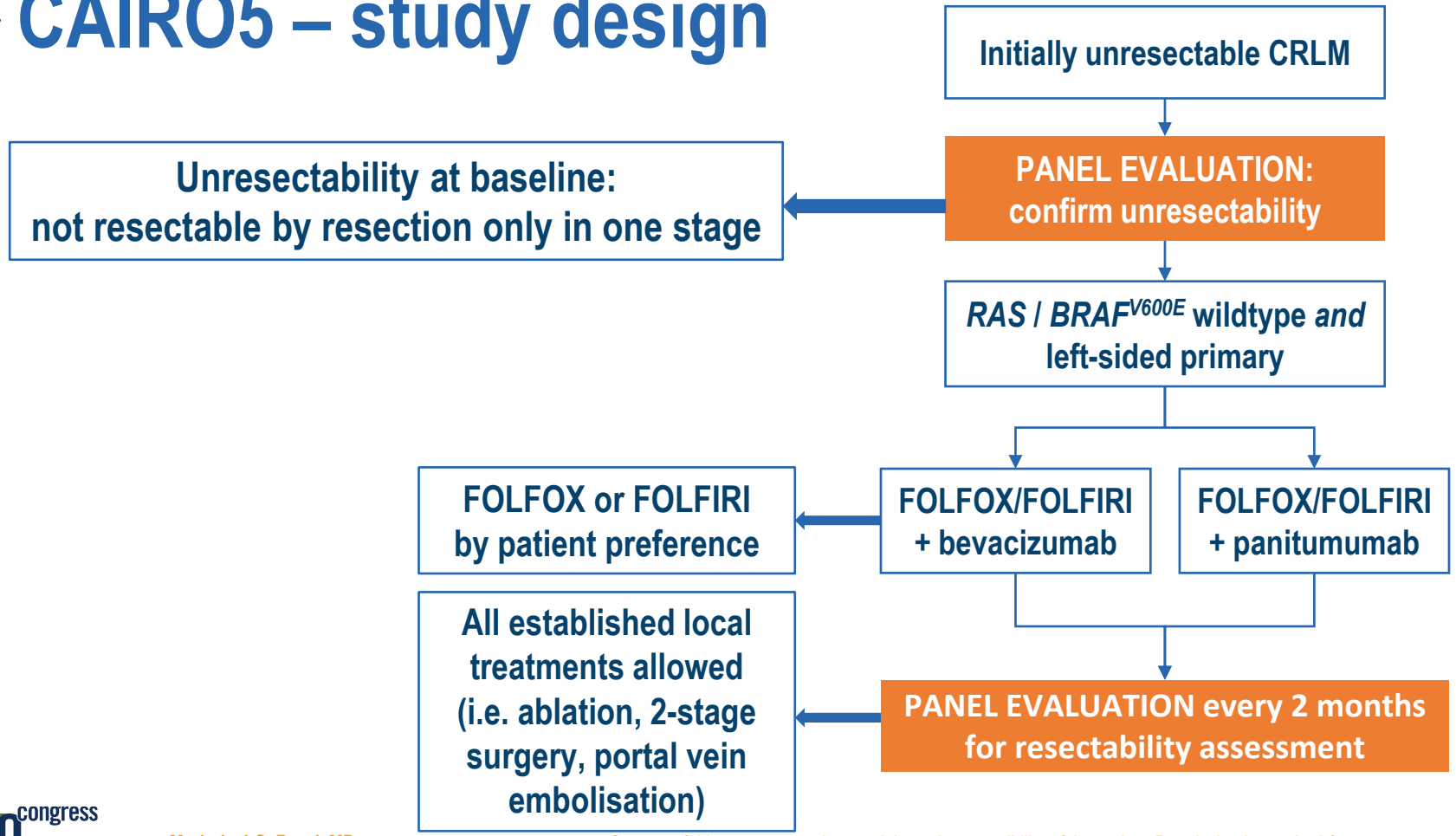
CAIRO5 – study design



CAIRO5 – study design

Primary endpoint: PFS

Secondary endpoints: OS, ORR, toxicity, R0/1 resection rates, postoperative morbidity.

Exploratory endpoint: Depth of response

Stratification parameters:

potentially resectable vs permanently unresectable (panel)

serum LDH (normal vs abnormal)

choice oxaliplatin vs irinotecan

Statistics:

256 events, HR 0.70 for PFS, 80% power 2-sided log-rank test at 5%,

assuming a median PFS of 11.6 months for doublet chemo+bevacizumab

CAIRO5 – eligibility criteria

- Metastatic colorectal cancer with previously untreated liver-only metastases
- Metastases not resectable with resection in one stage as defined by expert panel
- Patients with small (≤ 1 cm) extrahepatic lesions that are not clearly suspicious of metastases are eligible
- Left-sided primary tumour and *RAS/BRAF*^{V600E} wild-type tumour
- WHO performance status 0-1, age ≥ 18 years
- Eligible for study procedures (systemic regimens, local treatments)
- Primary tumour, if in situ, should be resectable
- Written informed consent

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CAIRO5 – liver expert panel

- Evaluation of CT scans at baseline and follow-up (and MRI if available) of all patients for (un)resectability by liver expert panel (15 liver surgeons and 3 abdominal radiologists).

- CT scans were uploaded online in a program designed to share patient imaging in a safe and privacy-respecting manner.

- Panel procedure: CT scans were reviewed by 1 radiologist and 3 liver surgeons. If no consensus per CT scan evaluation among 3 liver surgeons, then evaluation by 2 extra liver surgeons and decision by majority vote.

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CAIRO5 – liver expert panel

Panel procedure and outcome	
Number of CT scan evaluations (n)	533
Turn-around time CT scan evaluations (median, IQR)	6 days (3-9)
Consensus on (un)resectability at baseline evaluation	67%
Consensus on (un)resectability at follow-up evaluation	42%

Consensus = 3 liver surgeons of panel made same recommendation.

In case no consensus was reached, an additional 2 liver surgeons were included, followed by majority vote.

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CAIRO5 – systemic regimens

- Bevacizumab 5 mg/kg i.v.
- Panitumumab 6 mg/kg i.v.
- FOLFOX/FOLFIRI
  - oxaliplatin 85 mg/m^2 or irinotecan 180 mg/m^2 with LV 400 mg/m^2 in 120 min
  - bolus 5-FU 400 mg/m^2, infusional 5-FU 2400 mg/m^2 in 46h

- All cycles q 2 weeks for a maximum of 12 cycles, thereafter maintenance with 5-FU + LV + targeted therapy until disease progression.

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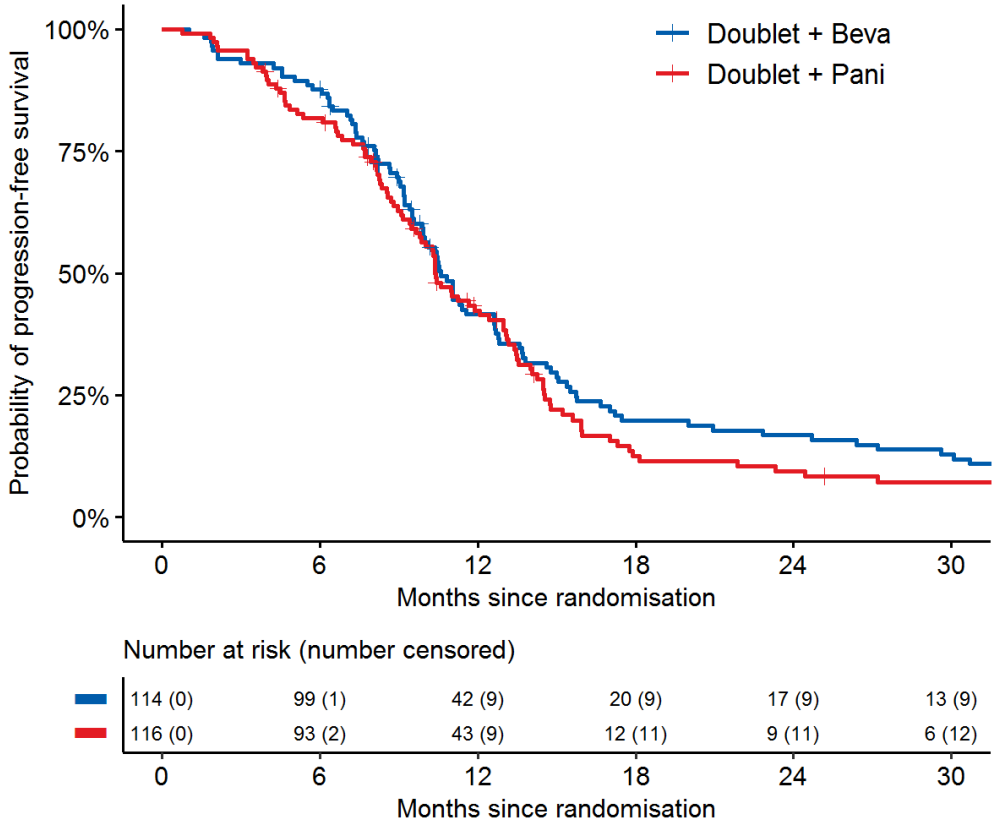
CAIRO5 – study design, accrual

- In patients receiving local treatment, a maximum of 12 systemic treatment cycles (before + after local treatment) was recommended, however without targeted therapy after local treatment.
- Protocol amendment in 2017 excluded patients with *BRAF*^{V600E} mutated and/or right-sided primary tumour, at that time 14 such patients had been included.
- 236 patients were randomised between Nov 2014 – March 2022 in 43 centres, 6 ineligible patients were excluded, resulting in 230 evaluable patients.
- Data Safety Monitoring Board advised to close the study prematurely in March 2022 for futility.

CAIRO5 – patient characteristics

	FOLFOX/FOLFIRI + bevacizumab	FOLFOX/FOLFIRI + panitumumab
n	114	116
Male gender	61%	63%
Age (median, range)	59 (53-67)	60 (52-69)
WHO PS 0	65%	59%
Right-sided primary	4%	5%
BRAF^{V600E} mutation	4%	3%
Synchronous metastases	88%	92%
Prior adjuvant chemotherapy	4%	3%
Median number of CRLM	12 (8-18)	12 (8-22)
Normal serum LDH	46%	45%
Preference for oxaliplatin	89%	92%
Potentially resectable CRLM (panel)	82%	83%

CAIRO5 – progression free survival



Median follow-up 44 months, 197 events

Median PFS:

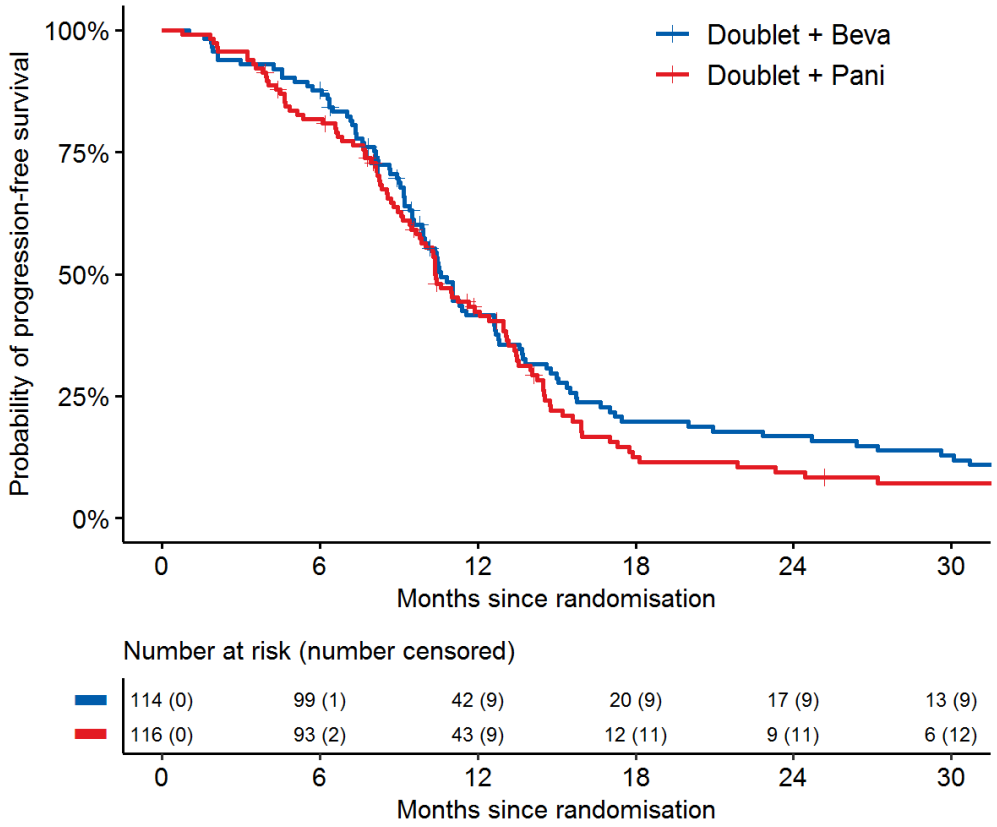
FOLFOX/FOLFIRI + bevacizumab 10.6 months

FOLFOX/FOLFIRI + panitumumab 10.3 months

HR 1.12, 95% CI 0.84 - 1.50, p = 0.44

Data on overall survival not yet mature.

CAIRO5 – progression free survival



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HR 1.12, 95% CI 0.84 - 1.50, p = 0.44

Data on overall survival not yet mature.

Per-protocol analysis (excluding 14 pts with *BRAF* mutation and/or right-sided primary):

FOLFOX/FOLFIRI + bevacizumab 10.8 months
FOLFOX/FOLFIRI + panitumumab 10.4 months
HR 1.12, 95% CI 0.83 - 1.52, p = 0.45

CAIRO5 – systemic treatment

	FOLFOX/FOLFIRI + bevacizumab	FOLFOX/FOLFIRI + panitumumab	
n	114	116	
Number of cycles (median, IQR) [1]	7 (5-10)	6 (5-9)	
Overall response rate	52%	76%	p<0.001
Median depth of response [2]	33%	49%	p<0.001
Grade ≥ 3 adverse events	52%	69%	p=0.01
skin toxicity	1%	25%	p<0.001
hypertension	18%	7%	p=0.02
diarrhoea	4%	16%	p=0.01
death [3]	0%	1.7% (n=2)	

[1] Excluding maintenance cycles and any adjuvant chemotherapy.
[2] Relative change in the sum of longest diameters of RECIST target lesions at the nadir compared with baseline.
[3] Cause of death: cardiac arrest and pulmonary embolism.

CAIRO5 – local treatment

	FOLFOX/FOLFIRI + bevacizumab	FOLFOX/FOLFIRI + panitumumab	
n	114	116	
Resection +/- ablation rate	68%	67%	p=1
postoperative complications	42%	41%	p=1
Clavien Dindo grade ≥3	21%	14%	p=0.30
grade 5 (death) [1]	0.9% (n=1)	0.9% (n=1)	
Number of induction cycles (median, IQR)	6 (5-8)	6 (5-9)	
Adjuvant chemotherapy	36%	42%	
R0/1 resection +/- ablation rate	58%	56%	p=0.79

[1] Cause of death: arm C multi-organ failure, arm D abdominal sepsis.

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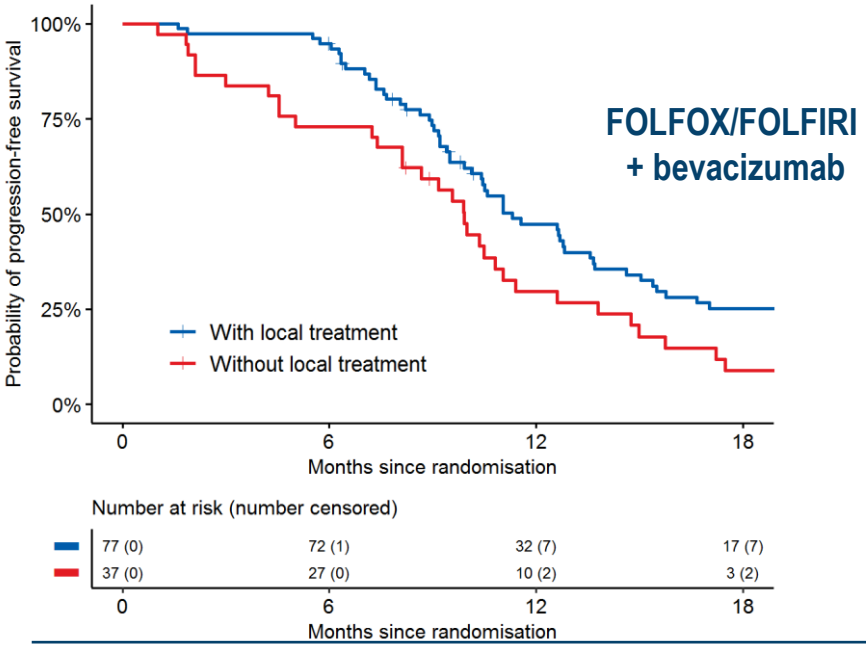
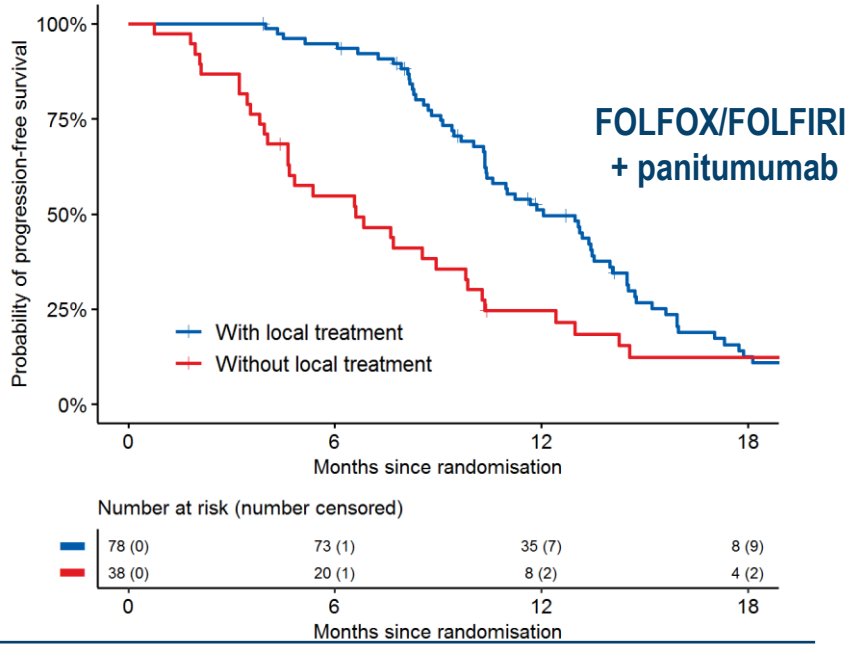
CAIRO5 – outcome of resections ± ablation





Median PFS	without local treatment	with local treatment	
FOLFOX/FOLFIRI + bevacizumab	9.9 months	11.3 months	HR 0.54, p<0.001
FOLFOX/FOLFIRI + panitumumab	6.6 months	12.1 months	HR 0.54, p<0.001

Conclusions

- CAIRO5 is the first randomised study that prospectively evaluates systemic induction regimens in patients with initially unresectable CRLM according to predefined criteria by a central liver expert panel.

- There is no difference in median PFS between the addition of either bevacizumab or panitumumab to FOLFOX/FOLFIRI in first-line treatment of patients with initially unresectable colorectal cancer liver metastases and left-sided and *RAS*/*BRAF*^{V600E} wild-type tumour.

- The addition of panitumumab is associated with more toxicity, and significantly increases response rate and depth of response which however does not translate in an increased local treatment rate of CRLM.

- The use of a liver expert panel is feasible and allows the selection of an increased number of patients who are eligible for local treatment with curative intent.

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