Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methods

– Complete list of eligibility criteria

Inclusion criteria

Eligible patients were adults who had:

- a World Health Organization performance status of ≤1;
- histological or cytological proof of peritoneal metastases of a nonappendiceal colorectal adenocarcinoma with ≤50% of malignant cells being signet ring cells;
- resectable disease determined by computed tomography (CT) and a peritoneal cancer index (PCI)[1] of ≤20 at diagnostic laparoscopy or laparotomy;
- no evidence of systemic (e.g. liver, lung) colorectal metastases within three months prior to enrolment;
- no systemic therapy for colorectal cancer within six months prior to enrolment;
- no contraindications for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), determined by the treating surgical oncologist;
- no previous CRS-(HIPEC);
- no concurrent malignancies that interfere with the planned trial treatment or the prognosis of resected colorectal peritoneal metastases;

Exclusion criteria

Patients were excluded in case of any contraindication for the planned perioperative systemic therapy, determined by the treating medical oncologist, e.g.:

- inadequate bone marrow, renal, or liver functions (e.g. hemoglobin <6.0 mmol/L, neutrophils <1.5 x 10^9/L, platelets <100 x 10^9/L, serum creatinine >1.5 x upper limit of normal [ULN], creatinine clearance <30 ml/min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);
- previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan, to such an extent that the medical oncologist could not consider the patient eligible for the planned systemic therapy;
- dehydropyrimidine dehydrogenase deficiency;
- serious active infections;
- severe diarrhea;
- stomatitis or ulceration of the mouth and gastrointestinal tract;
- recent major cardiovascular events;
- unstable or uncompensated respiratory or cardiac disease;
- bleeding diathesis or coagulopathy;
- pregnancy or lactation.

– Doses, routes, and schedules of perioperative systemic regimens

CAPOX-bevacizumab

Four three-weekly neoadjuvant and four-three weekly adjuvant cycles of oral capecitabine (1000 mg/m^2 body surface area [BSA], twice daily on days 1-14) and intravenous oxaliplatin (130 mg/m^2 BSA on day 1), with intravenous bevacizumab (7.5 mg/kg of body weight on day 1) added to the first three neoadjuvant cycles.

FOLFOX-bevacizumab

Six two-weekly neoadjuvant and six two-weekly adjuvant cycles of intravenous 5-fluorouracil (400 mg/m^2 BSA bolus on day 1 followed by 2400 mg/m^2 BSA continuous infusion on days 1-2), intravenous leucovorin (400 mg/m^2 BSA on day 1), and intravenous oxaliplatin (85 mg/m^2 BSA on day 1), with intravenous bevacizumab (5 mg/kg of body weight on day 1) added to the first four neoadjuvant cycles.

FOLFIRI-bevacizumab

Six two-weekly neoadjuvant cycles of intravenous 5-fluorouracil (400 mg/m^2 BSA bolus on day 1 followed by 2400 mg/m^2 BSA continuous infusion on days 1-2), intravenous leucovorin (400 mg/m^2 BSA on day 1), and intravenous irinotecan (180 mg/m^2 BSA on day 1), with intravenous bevacizumab (5 mg/kg of body weight on day 1) added to the first four neoadjuvant cycles, followed by either four three-weekly adjuvant cycles of oral capecitabine (1000 mg/m^2 BSA, twice daily on days 1-14) or six two-weekly adjuvant cycles of 5-fluorouracil (400 mg/m^2 BSA bolus on day 1 followed by 2400 mg/m^2 BSA continuous infusion on days 1-2) with leucovorin (400 mg/m^2 BSA on day 1).

– Cytoreductive surgery and HIPEC according to the Dutch protocol

After explorative laparotomy, CRS was only performed if the PCI was ≤20 and macroscopic complete CRS was deemed achievable. Only after macroscopic complete CRS (i.e. a completeness of cytoreduction [CC] score of 0 or an R-1 resection depending on the local classification used),[1,2] HIPEC was performed at 41-42 °C using the open technique with either mitomycin C (35 mg/m^2, 90 minutes) or oxaliplatin (460 mg/m^2, 30 minutes) with intravenous leucovorin (20 mg/m^2, 10 minutes) and 5-fluorouracil (400 mg/m^2, 15 minutes) according to local protocol.[3] Both regimens were allowed, since a recent systematic review showed that no meaningful survival comparison between these regimens could be made.[4] HIPEC regimens or doses were not adjusted based on previous systemic therapies.

– Central radiologic and pathological review

After completion of the present phase 2 trial, the investigators collected all baseline CTs, restaging CTs, and resected specimens of patients in the experimental arm. Radiologic and pathological response to neoadjuvant treatment were both evaluated by two independent assessors blinded to clinical outcomes. Radiologic response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) and the radiologic PCI.[1,5] When in situ, the primary tumor was not included in the radiologic PCI. Pathological response was classified according to Mandard tumor regression grading (TRG) and the Peritoneal Regression Grading Score (PRGS).[6,7]

Radiologic response

Response according to RECIST was classified as complete response, partial response, stable disease, progressive disease, or non-evaluable.[5] Analogue to RECIST, response according to radiologic PCI was classified as complete response (i.e. disappearance of all peritoneal lesions), partial response (i.e. ≥30% decrease of PCI), stable disease (i.e. <30% decrease or <20% increase of PCI), progressive disease (i.e. ≥20% increase of PCI), or non-evaluable. For both classifications, an objective radiologic response was defined as complete or partial response.

Pathological response

Mandard TRG was classified as TRG1 (i.e. no residual cancer cells), TRG2 (i.e. rare residual cancer cells scattered through fibrosis), TRG3 (i.e. increased residual cancer cells, but predominant fibrosis), TRG4 (i.e. residual cancer cells outgrowing fibrosis), TRG5 (i.e. no regressive features), or non-evaluable.[6] PRGS was classified as PRGS1 (i.e. no residual cancer cells), PRGS2 (i.e. major regressive features, few residual cancer cells), PRGS3 (i.e. minor regressive features, predominance of residual cancer cells), PRGS4 (i.e. no regressive changes), or non-evaluable.[7] In patients whose primary tumor was resected during cytoreductive surgery, separate regression scores were determined for all three tumor components (i.e. peritoneal metastases, primary tumor, and locoregional lymph nodes). In these patients, the overall response was based on the mean regression score in all tumor components. In patients with a previously resected primary tumor, the overall response was based on the regression score in peritoneal metastases only. When multiple peritoneal metastases were resected, a mean regression score was determined for all peritoneal metastases together. Major pathological response was defined as TRG1 or TRG2.

eTable 1. Comparison of baseline characteristics in the intention-to-treat and the modified intention-to-treat populations.

	Intention-to-treat population				Modified intention-to-treat population			
Variable	**Experimental (n=40)**	**Control (n=40)**	**Total (n=80)**	**p-value**	**Experimental (n=37)**	**Control (n=42)**	**Total (n=79)**	**p-value**
Sex, *n* (%)								
Male	19 (48)	24 (60)	43 (54)	0.26	18 (49)	25 (60)	43 (54)	0.33
Female	21 (53)	16 (40)	37 (46)		19 (51)	17 (40)	36 (46)	
Age in years, mean (SD)	60 (11)	64 (10)	62 (10)	0.05	59 (11)	64 (10)	62 (10)	0.03
WHO performance score, *n* (%)								
0	30 (75)	33 (83)	63 (79)	0.59	27 (73)	35 (83)	62 (78)	0.33
1	9 (23)	7 (18)	16 (20)		9 (24)	7 (17)	16 (20)	
2	1 (3)[a]	0 (0)	1 (1)[a]		1 (3)[a]	0 (0)	1 (1)[a]	
Primary tumor location, *n* (%)								
Proximal colon[b]	17 (43)	14 (35)	31 (39)	0.74	16 (43)	15 (36)	31 (39)	0.71
Distal colon[c]	21 (53)	25 (63)	46 (58)		19 (51)	26 (62)	45 (57)	
Rectum	1 (3)	1 (3)	2 (3)		1 (3)	1 (2)	2 (3)	
Multiple	1 (3)	0 (0)	1 (1)		1 (3)	0 (0)	1 (1)	
Histology, *n* (%)								
Non-mucinous adenocarcinoma	37 (93)	37 (93)	74 (93)	>0.99	34 (92)	39 (93)	73 (92)	0.87
Mucinous adenocarcinoma	3 (8)	3 (8)	6 (8)		3 (8)	3 (7)	6 (8)	
Primary tumor status, *n* (%)								
Resected	29 (73)	23 (58)	52 (65)	0.16	27 (73)	25 (60)	52 (66)	0.21
In situ	11 (28)	17 (43)	28 (35)		10 (27)	17 (40)	27 (34)	
T-stage of primary tumor[d], *n* (%)								
T_{0-3}	18 (45)	21 (53)	39 (49)	0.80	16 (43)	23 (55)	39 (49)	0.48
T_4	21 (53)	19 (48)	40 (50)		21 (57)	19 (45)	40 (51)	
Unknown	1 (3)[e]	0 (0)	1 (1)[e]		0 (0)	0 (0)	0 (0)	
N-stage of primary tumor[d], *n* (%)								
N_0	14 (35)	15 (38)	29 (36)	0.25	13 (35)	16 (38)	29 (37)	0.39
N_1	17 (43)	11 (28)	28 (35)		16 (43)	12 (29)	28 (35)	
N_2	8 (20)	14 (35)	22 (28)		8 (22)	14 (33)	22 (28)	
Unknown	1 (3)[e]	0 (0)	1 (1)[e]		0 (0)	0 (0)	0 (0)	
Previous systemic chemotherapy for colorectal cancer, *n* (%)								
No	29 (73)	31 (78)	60 (75)	0.61	27 (73)	32 (76)	59 (75)	0.74
Adjuvant: a fluoropyrimidine with oxaliplatin	9 (23)	9 (23)	18 (23)		9 (24)	9 (21)	18 (23)	
Adjuvant: fluoropyrimidine monotherapy	2 (5)	0 (0)	2 (3)		1 (3)	1 (2)	2 (3)	

(continued)	Intention-to-treat population				Modified intention-to-treat population			
Variable	**Experimental (n=40)**	**Control (n=40)**	**Total (n=80)**	**p-value**	**Experimental (n=37)**	**Control (n=42)**	**Total (n=79)**	**p-value**
For metastatic disease	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Previous resection of extraperitoneal colorectal metastases, *n* (%)								
No	37 (93)	40 (100)	77 (96)	0.24	34 (92)	42 (100)	76 (96)	0.10
Yes	3 (8)	0 (0)	3 (4)		3 (8)	0 (0)	3 (4)	
Onset of PM, *n* (%)								
Synchronous	21 (53)	24 (60)	45 (56)	0.50	20 (54)	24 (57)	44 (56)	0.78
Metachronous	19 (48)	16 (40)	35 (44)		17 (46)	18 (43)	35 (44)	
Months from primary diagnosis to synchronous PM, median (range)	1 (0-2)	1 (0-2)	1 (0-2)	0.78	1 (0-2)	1 (0-2)	1 (0-2)	0.90
Months from primary diagnosis to metachronous PM, median (range)	14 (4-44)	20 (7-48)	19 (4-48)	0.32	14 (4-44)	21 (7-48)	19 (4-48)	0.08
Months from diagnosis of PM to trial enrolment, median (range)	1 (0-4)	1 (0-4)	1 (0-4)	0.41	1 (0-4)	1 (0-4)	1 (0-4)	0.37
Baseline PCI, median (range)	3 (0[f]-15)	5 (0[g]-18)	4 (0-18)	0.06	3 (0[f]-15)	5 (0[g]-18)	5 (0-18)	0.10
Modality of determining baseline PCI, *n* (%)								
Laparoscopy	25 (63)[h]	34 (85)	59 (74)[h]	0.03	22 (59)[h]	36 (86)	58 (73)[h]	0.01
Laparotomy	14 (35)[h]	6 (15)	20 (25)[h]		14 (38)[h]	6 (14)	20 (25)[h]	
Centre of determining baseline PCI, *n* (%)								
Trial center	18 (45)[h]	24 (60)	42 (53)[h]	0.22	18 (49)[h]	25 (60)	43 (54)[h]	0.40
Referring center	21 (53)[h]	16 (40)	37 (46)[h]		18 (49)[h]	17 (40)	35 (44)[h]	
Planned HIPEC regimen, *n* (%)								
Mitomycin C	32 (80)	32 (80)	64 (80)	>0.99	30 (81)	34 (81)	64 (81)	0.99
Oxaliplatin	8 (20)	8 (20)	16 (20)		7 (19)	8 (19)	15 (19)	

HIPEC hyperthermic intraperitoneal chemotherapy; *PCI* peritoneal cancer index; *PM* peritoneal metastases *SD* standard deviation; *WHO* world health organization; [a]due to severe obesity; [b]caecum, ascending colon, hepatic flexure, transverse colon; [c]splenic flexure, descending colon, sigmoid, rectosigmoid; [d]pathological stage used for patients whose primary tumor was previously resected or patients in the control arm whose primary tumor was resected during upfront cytoreductive surgery, clinical stage used for patients in the experimental arm whose primary tumor was still in situ or patients in the control arm whose primary tumor was not resected during upfront cytoreductive surgery; [e]in one patient, clinical T-stage and clinical N-stage could not be adequately determined on baseline radiology; [f]2 patients in the experimental arm had a baseline PCI of 0; [g]3 patients in the control arm had a baseline PCI of 0; [h]in one patient, resectability was not determined by laparoscopy or laparotomy, but by radiology only.

eTable 2. Baseline characteristics of the CRS-HIPEC population.

Variable	Experimental (n=33)	Control (n=36)	Total (n=69)
Sex, *n* (%)			
Male	14 (42)	22 (61)	36 (52)
Female	19 (58)	14 (39)	33 (48)
Age in years, mean (SD)	60 (11)	64 (10)	62 (10)
WHO performance score, *n* (%)			
0	25 (76)	31 (86)	56 (81)
1	7 (21)	5 (14)	12 (17)
2	1 (3)[a]	0 (0)	1 (1)[a]
Primary tumor location, *n* (%)			
Proximal colon[b]	14 (42)	11 (31)	25 (36)
Distal colon[c]	17 (52)	24 (67)	41 (59)
Rectum	1 (3)	1 (3)	2 (3)
Multiple	1 (3)	0 (0)	1 (1)
Histology, *n* (%)			
Non-mucinous adenocarcinoma	32 (97)	33 (92)	65 (94)
Mucinous adenocarcinoma	1 (3)	3 (8)	4 (6)
Primary tumor status, *n* (%)			
Resected	26 (79)	23 (64)	49 (71)
In situ	7 (21)	13 (36)	20 (29)
T-stage of primary tumor[d], *n* (%)			
$T_{0\text{-}3}$	13 (39)	22 (61)	35 (51)
T_4	20 (61)	14 (39)	34 (49)
N-stage of primary tumor[d], *n* (%)			
N_0	12 (36)	12 (33)	24 (35)
N_1	13 (39)	10 (28)	23 (33)
N_2	8 (24)	14 (39)	22 (32)
Previous systemic chemotherapy for colorectal cancer, *n* (%)			
No	23 (70)	26 (72)	49 (71)
Adjuvant: a fluoropyrimidine with oxaliplatin	9 (27)	9 (25)	18 (26)
Adjuvant: fluoropyrimidine monotherapy	1 (3)	1 (3)	2 (3)
For metastatic disease	0 (0)	0 (0)	0 (0)
Previous resection of extraperitoneal colorectal metastases, *n* (%)			
No	30 (91)	36 (100)	66 (96)
Yes	3 (9)	0 (0)	3 (4)
Onset of PM, *n* (%)			
Synchronous	17 (52)	19 (53)	36 (52)
Metachronous	16 (48)	17 (47)	33 (48)
Months from primary diagnosis to synchronous PM, median (range)	0 (0-2)	1 (0-2)	1 (0-2)
Months from primary diagnosis to metachronous PM, median (range)	14 (4-44)	20 (7-48)	19 (4-48)
Months from diagnosis of PM to trial enrolment, median (range)	1 (0-4)	1 (0-4)	1 (0-4)
Baseline PCI, median (range)	3 (0-14)	5 (0-18)	4 (0-18)
Modality of determining baseline PCI, *n* (%)			
Laparoscopy	19 (58)[e]	31 (86)	50 (72)[e]
Laparotomy	13 (39)[e]	5 (14)	18 (26)[e]
Centre of determining baseline PCI, *n* (%)			
Trial center	17 (52)[e]	22 (61)	39 (57)[e]
Referring center	15 (45)[e]	14 (39)	29 (42)[e]
Planned HIPEC regimen, *n* (%)			
Mitomycin C	26 (79)	29 (81)	55 (80)
Oxaliplatin	7 (21)	7 (19)	14 (20)

CRS cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy; *PCI* peritoneal cancer index; *PM* peritoneal metastases; *SD* standard deviation; *WHO* world health organization; [a]due to severe obesity; [b]caecum, ascending colon, hepatic flexure, transverse colon; [c]splenic flexure, descending colon, sigmoid, rectosigmoid; [d]pathological stage used for patients whose primary tumor was previously resected or patients in the control arm whose primary tumor was resected during upfront cytoreductive surgery, clinical stage used for patients in the experimental arm

whose primary tumor was still in situ or patients in the control arm whose primary tumor was not resected during upfront cytoreductive surgery; [e]in one patient, resectability was not determined by laparoscopy or laparotomy, but by radiology only.

eTable 3. Intraoperative and postoperative characteristics of the CRS-HIPEC population, including details of Clavien-Dindo grade ≥3 postoperative morbidity and reoperations.

Intraoperative characteristics				
Variable	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**	**p-value**
PCI, median (range)	4 (0-14)	11 (0-20)	8 (0-20)	0.004
Primary tumor resection, *n* (%)				0.17
Yes	7 (21)	13 (36)	20 (29)	
No	26 (79)	23 (64)	49 (71)	
Bowel anastomosis, *n* (%)				0.20
Yes	17 (52)	24 (67)	41 (59)	
No	16 (48)	12 (33)	28 (41)	
Ostomy formation, *n* (%)				0.006
Yes	6 (18)	18 (50)	24 (35)	
No	27 (82)	18 (50)	45 (65)	
Operating time in minutes, mean (SD)	344 (94)	372 (132)	359 (115)	0.32
HIPEC regimen, *n* (%)				0.64
Mitomycin C	28 (85)	29 (81)	57 (83)	
Oxaliplatin	5 (15)	7 (19)	12 (17)	
Postoperative characteristics				
Variable	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**	**p-value**
Initial hospital stay in days, median (IQR)	8 (7-16)	12 (8-21)	10 (7-16)	0.09
Readmission, *n* (%)				0.06
Yes	6 (18)	14 (39)	20 (29)	
No	27 (82)	22 (61)	49 (71)	
Reoperation, *n* (%)				0.68
Yes	6 (18)	8 (22)	14 (20)	
No	27 (82)	28 (78)	55 (80)	
Any Clavien-Dindo grade ≥2 postoperative morbidity, *n* (%)				0.01
Yes	16 (48)	28 (78)	44 (64)	
No	17 (52)	8 (22)	25 (36)	
Any Clavien-Dindo grade ≥3 postoperative morbidity, *n* (%)				0.17
Yes	7 (21)	13 (36)	20 (29)	
No	26 (79)	23 (64)	49 (71)	
Any Clavien-Dindo grade 4 postoperative morbidity, *n* (%)				0.57
Yes	3 (9)	2 (6)	5 (7)	
No	30 (91)	34 (94)	64 (93)	
Details of Clavien-Dindo grade ≥3 postoperative morbidity[a]				
Adverse event, *n* (%)	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**	**p-value[b]**
Anastomotic leakage, grade 3	1 (3[c])/(6[d])	3 (8[c])/(13[d])	4 (6[c])/(10[d])	NA
Anastomotic leakage, grade 4	1 (3[c])/(6[d])	0 (0)	1 (1[c])/(2[d])	NA
Intra-abdominal abscess, grade 3	0 (0)	2 (6)	2 (3)	NA
Intra-abdominal abscess, grade 4	2 (6)	1 (3)	3 (4)	NA
Asystole, grade 4	0 (0)	1 (3)	1 (1)	NA
Fascia dehiscence, grade 3	1 (3)	2 (6)	3 (4)	NA
Ileus, grade 3	1 (3)	1 (3)	2 (3)	NA
Gastroparesis, grade 3	1 (3)	2 (6)	3 (4)	NA
Pneumothorax, grade 3	0 (0)	1 (3)	1 (1)	NA
Postoperative hemorrhage, grade 3	0 (0)	1 (3)	1 (1)	NA
Colonic fistula, grade 3	0 (0)	1 (3)	1 (1)	NA
Luxation double J catheter, grade 3	1 (3)	0 (0)	1 (1)	NA

Reoperations[e]				
Adverse event, *n* (%)	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**	**p-value[b]**
Anastomotic leakage, grade 3	1 (3[c])/(6[d])	3 (8[c])/(13[d])	4 (6[c])/(10[d])	NA
Reoperations[e] (continued)				
Adverse event, *n* (%)	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**	**p-value[b]**
Anastomotic leakage, grade 4	1 (3[c])/(6[d])	0 (0)	1 (1[c])/(2[d])	NA
Intra-abdominal abscess, grade 3	0 (0)	1 (2)	1 (1)	NA
Intra-abdominal abscess, grade 4	2 (6)	1 (1)	3 (4)	NA
Fascia dehiscence, grade 3	1 (3)	2 (5)	3 (4)	NA
Ileus, grade 3	1 (3)	0 (0)	1 (1)	NA
Postoperative hemorrhage, grade 3	0 (0)	1 (1)	1 (1)	NA
Bowel perforation, grade 3	0 (0)	1 (1)	1 (1)	NA

CRS cytoreductive surgery; *HIPEC* hyperthermic intraperitoneal chemotherapy; *IQR* interquartile range; *NA* not applicable; *PCI* peritoneal cancer index; *SD* standard deviation; [a]as multiple Clavien-Dindo grade ≥3 adverse events could have occurred in one patient, numbers may not add up to the total number of patients with any Clavien-Dindo grade ≥3 postoperative morbidity; [b]due to low numbers, no comparison was made between both arms; [c]percentage of all patients; [d]percentage of patients with a bowel anastomosis; [e]as multiple reoperations could have been performed in one patient, numbers may not add up to the total number of patients with a reoperation.

eTable 4. Details of Clavien-Dindo grade 2 postoperative morbidity in the modified intention-to-treat (i.e. surgical) and the CRS-HIPEC population.

	Modified intention-to-treat population			CRS-HIPEC population		
Adverse event, *n* (%)	**Experimental (n=37)**	**Control (n=42)**	**Total (n=79)**	**Experimental (n=33)**	**Control (n=36)**	**Total (n=69)**
Gastroparesis	2 (5)	8 (19)	10 (13)	2 (6)	7 (19)	9 (13)
Pneumonia	3 (8)	4 (10)	7 (9)	3 (9)	4 (11)	7 (10)
Urinary tract infection	2 (5)	3 (7)	5 (6)	2 (6)	3 (8)	5 (7)
Wound infection	1 (3)	4 (10)	5 (6)	1 (3)	3 (8)	4 (6)
Intra-abdominal abscess	1 (3)	3 (7)	4 (5)	1 (3)	3 (8)	4 (6)
Ileus	2 (5)	3 (7)	5 (6)	1 (3)	2 (6)	3 (4)
Anastomotic leakage	1 (3[a])/(6[b])	0 (0)	1 (1[a])/(2[b])	1 (3[a])/(6[b])	0 (0)	1 (1[a])/(2[b])
Bowel perforation	0 (0)	1 (2)	1 (1)	0 (0)	1 (3)	1 (1)
Pneumothorax	1 (3)	0 (0)	1 (1)	1 (3)	0 (0)	1 (1)
Thromboembolic event	0 (0)	1 (2)	1 (1)	0 (0)	1 (3)	1 (1)
Infected hematoma	0 (0)	1 (2)	1 (1)	0 (0)	1 (3)	1 (1)
Urinary retention	0 (0)	1 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Delirium	1 (3)	0 (0)	1 (1)	1 (3)	0 (0)	1 (1)

CRS-HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; multiple Clavien-Dindo grade 2 adverse events could have occurred in one patient; [a]percentage of all patients; [b]percentage of patients with a bowel anastomosis.

eTable 5. Details of CTCAE grade 2 systemic therapy-related toxicity in the experimental arm.

Adverse event, *n* (%)	Experimental (n=37)
Diarrhea	10 (27)
Nausea/vomiting	9 (24)
Peripheral neuropathy	8 (22)
Abdominal pain	2 (5)
Colonic perforation	1 (3)
Constipation	2 (5)
Mucosal infection	1 (3)
Anorexia	1 (3)
Phlebitis	1 (3)
Laryngospasm	1 (3)
Allergic reaction	5 (14)
Dysgeusia	1 (3)
Skin ulceration	1 (3)
Chest pain – cardiac	1 (3)
Hypertension	1 (3)
Dizziness	1 (3)
Thromboembolic event	1 (3)
Stroke	1 (3)
Pancreatitis	1 (3)
Lung infection	1 (3)
Fatigue	5 (14)
Chronic kidney disease	1 (3)
Fever	1 (3)
Depression	1 (3)
Vaginal hemorrhage	1 (3)
Hiccups	1 (3)
Ascites	1 (3)
Anxiety	1 (3)
Increased urinary frequency	1 (3)
Neutrophil count decreased	1 (3)
Hypokalemia	1 (3)
Platelet count decreased	1 (3)
Alanine aminotransferase increased	1 (3)

CTCAE common terminology criteria for adverse events; multiple CTCAE grade 2 adverse events could have occurred in one patient.

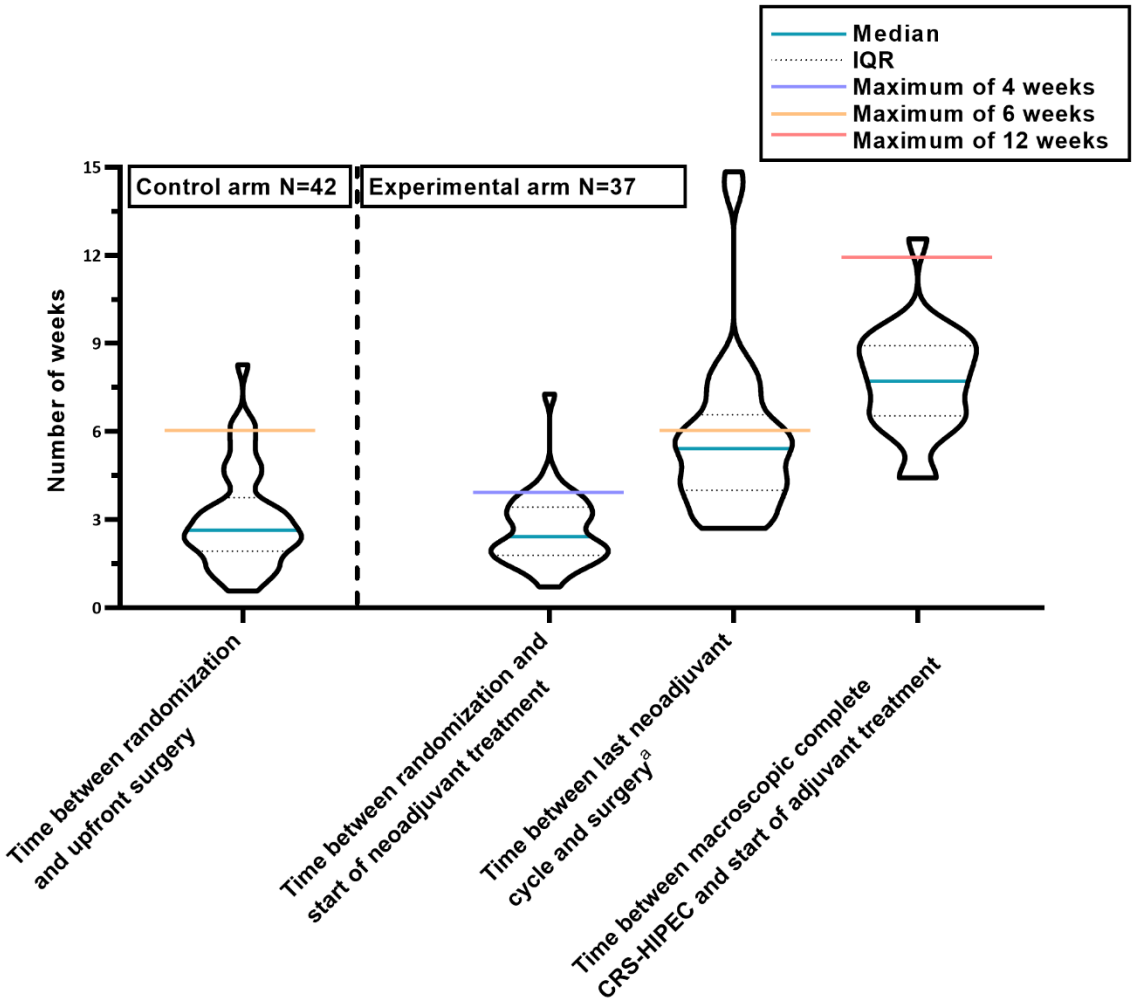
eTable 6. Details of central review of radiologic and pathological response to neoadjuvant treatment.

	Tumor characteristics		Central radiologic review					Central pathological review									
ID	Onset of peritoneal metastases	Primary tumor status	RECIST	PCI at baseline CT	PCI at restaging CT	PCI difference (%)	PCI response	No. of resected specimens sent to pathology		Peritoneal metastases		Primary tumor		Locoregional lymph nodes		Overall response	
								Total	Tumor-positive (%)	TRG	PR GS	TRG	PR GS	TRG	PR GS	TRG	PR GS
1	Synchronous	In situ	SD	6	4	-33%	PR	7	3 (43%)	3	2	4	3	3	2	3	2
2	Metachronous	Resected	NE[a]	17	1	-94%	NE[a]	6	2 (33%)	2	2	NA	NA	NA	NA	2	2
3	Synchronous	In situ	NE	0	0	0%	SD	7	2 (29%)	3	2	3	2	4	3	3	2
4	Metachronous	Resected	SD	9	8	11%	SD	13	12 (92%)	4	3	NA	NA	NA	NA	4	3
5	Synchronous	Resected	PR	3	3	0%	SD	3	1 (33%)	3	2	NA	NA	NA	NA	3	2
6	Synchronous	In situ	NE	17	21	+24%	PD[b]	5[c]	4 (80%)[c]	3[c]	2[c]	3[c]	2[c]	4[c]	3[c]	3[c]	2[c]
7	Metachronous	Resected	CR	4	0	-100%	CR	6	2 (33%)	4	3	NA	NA	NA	NA	4	3
8	Synchronous	In situ	SD	4	4	0%	SD	10	8 (80%)	5	4	3	2	4	3	4	3
9	Synchronous	Resected	NE	4	3	-25%	SD	8	0 (0%)	1	1	NA	NA	NA	NA	1	1
10	Metachronous	Resected	NE	1	1	0%	SD	2	1 (50%)	3	2	NA	NA	NA	NA	3	2
11	Synchronous	In situ	NE	4	1	-75%	PR	1[d]	1 (100%)[d]	NE[d]	NE[d]	3	2	3	2	3	2
12	Synchronous	Resected	NE[e]	1	1	0%	NE[e]	4	0 (0%)	1	1	NA	NA	NA	NA	1	1
13	Synchronous	In situ	NE	5	24	+380%	PD	0[f]	0[f]	NE[f]	NE[f]	NE[f]	NE[f]	NE[f]	NE[f]	NE[f]	NE[f]
14	Metachronous	Resected	NE	3	3	0%	SD	7	4 (57%)	2	2	NA	NA	NA	NA	2	2
15	Synchronous	In situ	NE	12	12	0%	SD	10	5 (50%)	3	3	2	2	3	2	3	2
16	Synchronous	Resected	NE	20	7	-65%	PR	7	0 (0%)	1	1	NA	NA	NA	NA	1	1
17	Metachronous	Resected	NE[e]	10	6	-40%	NE[e]	9	0 (0%)	NE[g]	NE[g]	NA	NA	NA	NA	NE[g]	NE[g]
18	Synchronous	In situ	NE	17	7	-59%	PR	10	8 (80%)	3	2	4	3	3	2	3	2
19	Synchronous	Resected	SD	10	10	0%	SD	7	0 (0%)	1	1	NA	NA	NA	NA	1	1
20	Synchronous	Resected	NE	11	9	-18%	SD	7	0 (0%)	1	1	NA	NA	NA	NA	1	1
21	Synchronous	In situ	NE	8	8	0%	SD	3[h]	3 (100%)[h]	5[h]	4[h]	NE[h]	NE[h]	NE[h]	NE[h]	5[h]	4[h]
22	Synchronous	In situ	SD	5	5	0%	SD	5	3 (60%)	2	2	1	1	1	1	1	1
23	Metachronous	Resected	SD	3	3	0%	SD	2	0 (0%)	1	1	NA	NA	NA	NA	1	1
24	Metachronous	Resected	NE	8	8	0%	SD	5	0 (0%)	1	1	NA	NA	NA	NA	1	1
25	Synchronous	Resected	NE	7	4	-43%	PR	7	0 (0%)	1	1	NA	NA	NA	NA	1	1
26	Synchronous	Resected	NE	11	10	-9%	SD	7	7 (100%)	4	3	NA	NA	NA	NA	4	3
27	Metachronous	Resected	SD	5	4	-20%	SD	7	1 (14%)	4	3	NA	NA	NA	NA	4	3
28	Synchronous	Resected	NE	12	10	-17%	SD	11	1 (9%)	3	2	NA	NA	NA	NA	3	2
29	Metachronous	Resected	SD	4	4	0%	SD	4	2 (50%)	5	4	NA	NA	NA	NA	5	4
30	Synchronous	Resected	NE[e]	8	8	-75%	NE[e]	21	2 (10%)	3	2	NA	NA	NA	NA	3	2

	Tumor characteristics		Central radiological review					Central pathological review									
ID	**Onset of peritoneal metastases**	**Primary tumor status**	**RECIST**	**PCI at baseline CT**	**PCI at restaging CT**	**PCI difference (%)**	**PCI response**	**No. of resected specimens sent to pathology**		**Peritoneal metastases**		**Primary tumor**		**Locoregional lymph nodes**		**Overall response**	
								Total	**Tumor-positive (%)**	**TRG**	**PRGS**	**TRG**	**PRGS**	**TRG**	**PRGS**	**TRG**	**PRGS**
31	Metachronous	Resected	SD	4	4	0%	SD	9	5 (56%)	4	3	NA	NA	NA	NA	4	3
32	Metachronous	Resected	SD	6	6	0%	SD	9	5 (56%)	5	4	NA	NA	NA	NA	5	4
33	Metachronous	Resected	SD	4	3	-25%	SD	2	1 (50%)	3	2	NA	NA	NA	NA	3	2
34	Metachronous	Resected	NE	12	12	0%	SD	3[h]	3 (100%)[h]	5[h]	4[h]	NA	NA	NA	NA	5[h]	4[h]
35	Synchronous	Resected	NE	8	6	-25%	SD	8	2 (25%)	2	2	NA	NA	NA	NA	2	2
36	Synchronous	Resected	NE[e]	2	0	-100%	NE[e]	18	1 (6%)	2	2	NA	NA	NA	NA	2	2
37	Metachronous	Resected	NE	3	1	-67%	PR	11	1 (9%)	3	2	NA	NA	NA	NA	3	2

CR complete response; *CT* computed tomography; *NA* not applicable; *NE* non-evaluable; *PCI* peritoneal cancer index; *PD* progressive disease; *PR* partial response; *PRGS* peritoneal regression grading score; *RECIST* response evaluation criteria in solid tumors; *SD* stable disease; *TRG* tumor regression grade (Mandard); [a]patient had resection of symptomatic ovarian metastases (and several other lesions) between baseline CT and enrolment, and was therefore classified as non-evaluable; [b]classified as stable disease by the treating physicians; [c]patient did not undergo cytoreductive surgery due to extensive peritoneal disease, but had palliative primary tumor resection and peritoneal biopsies for response assessment; [d]only the primary tumor was sent to pathology, as patient had no suspected peritoneal lesions during cytoreductive surgery (despite having pathologically proven peritoneal metastases before enrolment); [e]patient had an (emergency) resection of the primary tumor (± biopsy or biopsies of peritoneal metastases) between baseline CT and enrolment, and was therefore classified as non-evaluable; [f]patient did not undergo cytoreductive surgery due to extensive peritoneal disease and severe progression during neoadjuvant treatment, and had no palliative primary tumor resection or peritoneal biopsies for response assessment; [g]although patient had a strong suspicion of metachronous colorectal peritoneal metastases (on imaging and during laparoscopy) before enrolment and no residual cancer cells in all resected specimens during cytoreductive surgery, central pathological review revealed that the peritoneal metastases were not pathologically proven before enrolment, and pathological regression was therefore classified as non-evaluable rather than TRG1 or PRGS1; [h]patient did not undergo cytoreductive surgery due to extensive peritoneal disease, but had peritoneal biopsies for response assessment.

eFigure. Violin plots of the ability to administer trial treatments within predetermined time frames.



CRS-HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; *IQR* interquartile range; [a]included seven patients who prematurely terminated neoadjuvant treatment and consequently had to wait at least six weeks for surgery given the recent administration of bevacizumab.

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