PIPAC – Clinical Evidence

PIPAC in Colorectal and Appendiceal Cancer

Mustafa Raoof, MD, MS

Assistant Professor

Division of Surgical Oncology

Department of Surgery

Department of Cancer Genetics and Epigenetics

City of Hope

Disclosures

- I do not have any relevant disclosures.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label or investigational use of Mitomycin C, Oxaliplatin, and 5-FU will be discussed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Inclusion of patients in PIPAC trial should ensure racial and ethnic representation.
- Patients with peritoneal metastases are often considered end-stage with poor prognosis. There is implicit bias against treatment that points to nihilism about the disease.

OPC 1 and 2

DE GRUYTER

Pleura and Peritoneum 2020; 20200109

Signe Bremholm Ellebæk*, Martin Graversen, Sönke Detlefsen, Lars Lundell, Claus W. Fristrup, Per Pfeiffer and Michael B. Mortensen

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)-directed treatment of peritoneal metastasis in end-stage colo-rectal cancer patients

OPC 1 and 2

Table 1: Baseline demographic data.

Number of patients	24
Number of procedures	75
Age: years, median (range)	64 (40–80)
Performance status	
0	7 (29%)
1	14 (58%)
2	3 (13%)
Gender	
M/F	13/11
Chemotherapy	
Neoadjuvant[a]	4 (17%)
Adjuvant[b]	10 (42%)
Palliative[c]	22 (91%)
Bidirectional treatment[d]	3 (12.5%)
PCI score (median, range)	
PCI when ≥ 11 regions evaluated ($n = 16$)	14.8 (1–30)
PCI when < 11 regions evaluated ($n = 8$)	2.6 (1–8)
PCI total	10.7 (1–30)
Ascites	
Yes (%)	7 (29%)
Median, range (mL)	50 (10–2700)

[a]Four patients received neoadjuvant chemotherapy prior to primary colorectal cancer surgery. [b]Ten patients received adjuvant chemotherapy after primary colorectal cancer surgery. [c]Two patients did not want to receive systemic chemotherapy. [d]Tree patients received bidirectional treatment (PIPAC and systemic palliative chemotherapy).

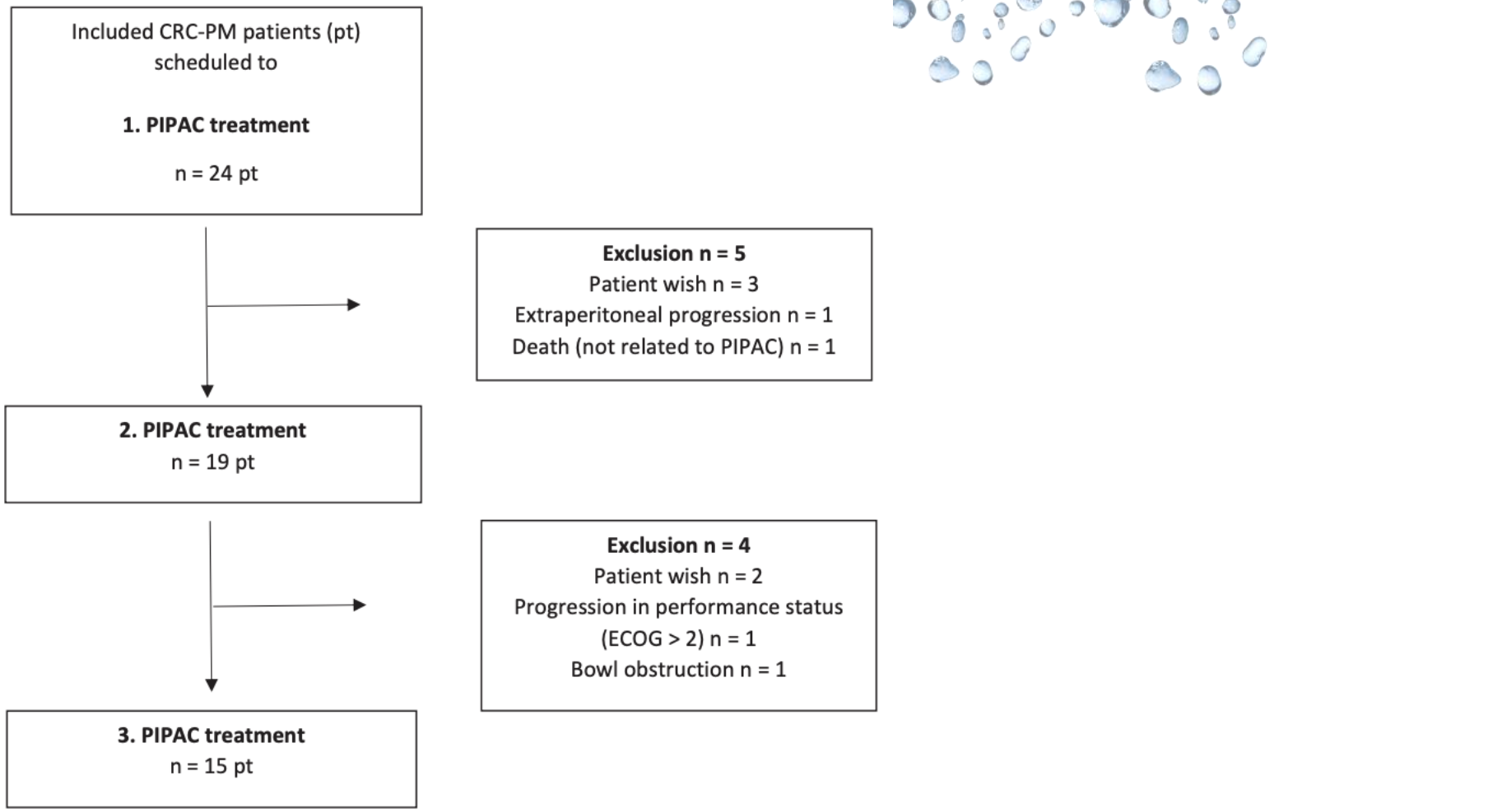
Chemotherapy:

14 patients had completed first-line

6 patients had completed second-line

2 patients had completed third-line

OPC 1 and 2


Included CRC-PM patients (pt) scheduled to
1. PIPAC treatment
n = 24 pt
Exclusion n = 5
Patient wish n = 3
Extraperitoneal progression n = 1
Death (not related to PIPAC) n = 1
2. PIPAC treatment
n = 19 pt
Exclusion n = 4
Patient wish n = 2
Progression in performance status (ECOG > 2) n = 1
Bowl obstruction n = 1
3. PIPAC treatment
n = 15 pt

OPC 1 and 2

Table 2: Peritoneal Regression Grading Score (PRGS 1–4), at baseline (i.e. before PIPAC 1) compared to the situation immediately before the third PIPAC procedure ($n = 15$).

Patient no.	PIPAC 1 PRGS (highest/mean)	PIPAC3 PRGS (highest/mean)	Histological response[a]
1	4/2.0	1/1.0	+
2	2/2.0	2/1.5	+
3	1/1.0	1/1.0	±
4	2/1.5	2/1.5	±
5	2/2.0	1/1.0	+ (CR)
6	2/1.75	2/1.25	+
7	3/2.0	2/1.67	+
8	2/1.0	1/1.0	+
9	3/3.0	1/1.0	+ (CR)
10	3/2.0	3/2.0	±
11	2/1.25	1/1.0	+ (CR)
12	2/1.33	1/1.0	+ (CR)
13	2/1.5	4/2.5	–
14	1/1.0	1/1.0	±
15	2/2.0	2/1.25	+

[a] +, regression; –, progression; ±, stable disease according to PRGS; CR, complete response (PRGS 1 + non-malign cytology).

Does histologic response correlate with survival??

OPC 1 and 2

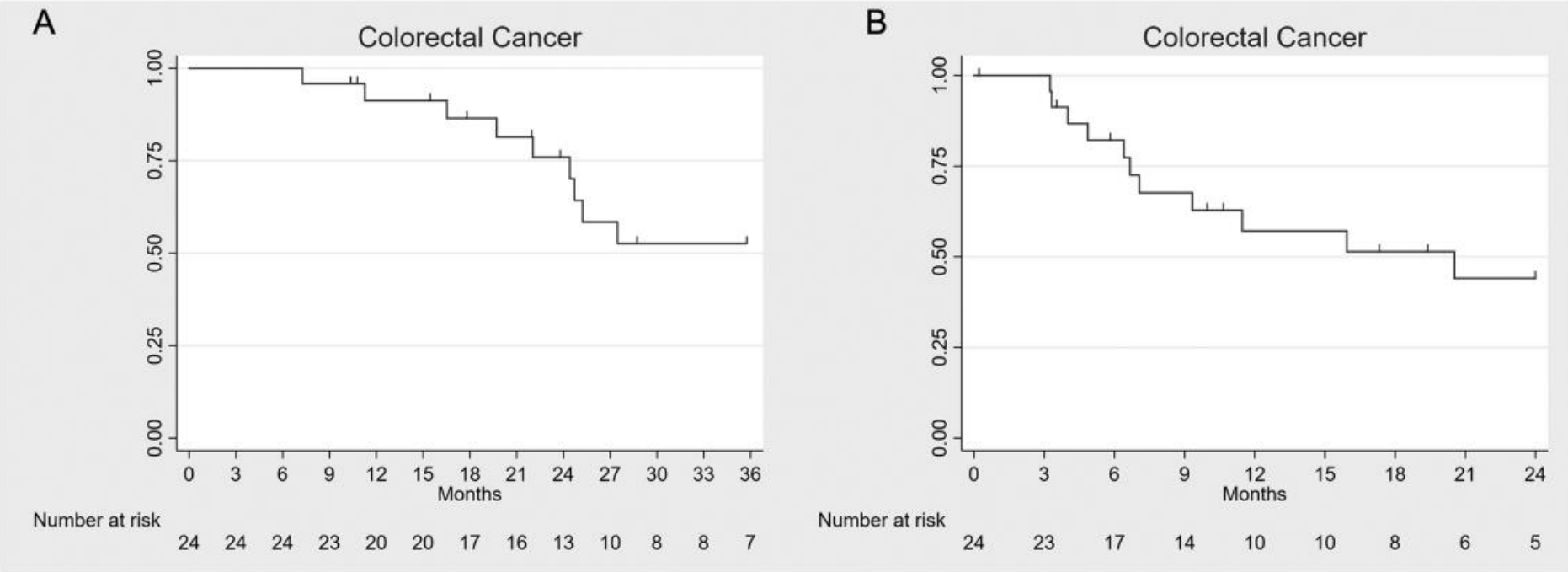


Figure 3: Kaplan–Meier survival plots in colorectal cancer patients with peritoneal metastasis subjected to PIPAC treatment. Survival from diagnosis of PM (A) and from the first PIPAC procedure (B).

Median survival:
37.6 (range 7.3– 48.9) months from the time of PM diagnosis
20.5 (range 0.1–34.7) months following the start of the first PIPAC session

PIPOX

European Journal of Cancer 140 (2020) 37–44

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic approach using pressurised intraperitoneal aerosol chemotherapy for advanced peritoneal metastases of gastrointestinal tract cancers

Frédéric Dumont [a,*], Christophe Passot [b], Jean-Luc Raoul [c], Vahan Kepenekian [d], Bénédicte Lelièvre [e], Michelle Boisdron-Celle [b], Sandrine Hiret [c], Hélène Senellart [c], Francois Pein [f], Audrey Blanc-Lapierre [g], Judith Raimbourg [c], Emilie Thibaudeau [a], Olivier Glehen [d], BIG-RENAPE Networks

3+3 Dose Escalation Study

DLT assessment period also included a potential systemic chemotherapy session between two PIPACs sessions, and any AEs related to systemic chemotherapy were necessarily included in the limiting toxicity.

PIPOX

Table 1
Characteristics of patients, tumours and treatment.

Characteristics	All	Dose 90 mg/m^2	Dose 140 mg/m^2
	N = 10	N = 6	N = 4
Median age, years (range)	56 (42–66)	58 (50–66)	53.5 (42–59)
Primary cancer (n)			
Gastric	3	3	0
Small bowel	2	0	2
Colorectal	5	3	2
BRAF mutated if primary colorectal cancer (n)	0	0	0
KRAS mutated if primary colorectal cancer (n)	2	1	1
Previous number of systemic chemotherapy cycles, median (range)	8.5 (6–36)	9.5 (6–36)	7 (6–13)
Previous number of systemic chemotherapy lines, median (range)	1 (1–3)	1 (1–3)	1.5 (1–3)
Interval between systemic chemotherapy and PIPAC (n)	2	1	1
Initial median PCI (range)	22 (14–31)	24.5 (19–29)	20 (14–31)
Number of PIPAC procedures, median (range)	3.5 (1–5)	3 (2–5)	4 (1–5)

PIPOX

Final median PCI, (range)	16.5 (3 −31)
Histologic regression score	
PRGS 1 (complete response), n (%)	1
PRGS 2 (major response), n (%)	1
PRGS 3 (minor response), n (%)	3
PRGS 4 (no response), n (%)	0
PRGS not assessable	1
PRGS heterogeneous	4
Number of complete cytoreduction CC0 and HIPEC (n)	2

PIPOX

Table 2
Adverse events during treatment period.

Adverse events	PIPAC with oxaliplatin 90 mg/m^2 n = 19		PIPAC with oxaliplatin 140 mg/m^2 n = 13	
	Grade I/II n	Grade III/IV n	Grade I/II n	Grade III/IV n
Related to chemotherapy (IV or IP)				
Abdominal pain	6	0	2	0
Anorexia	1	0	2	0
Nausea/vomiting	6	1	1	1
Fatigue	6	0	3	0
Stomatitis	0	0	1	0
Constipation	1	0	0	0
Cutaneous toxicity	4	0	0	0
Peripheral neuropathy	4	0	1	1
Dysarthria/dysgeusia	0	0	4	0
Dyspnoea	1	0	0	0
Allergic reaction	1	0	0	1
Thoracic pain	1	0	0	0
Neutropenia	0	0	1	2
Anaemia	3	0	3	0
Thrombopenia	1	0	0	0
Hepatobiliary disorders	0	0	1	0
Related to PIPAC surgical procedure				
Urinary retention	1	0	1	0
Intraoperative haemorrhage	0	1	0	0
Colonic fistula	0	0	1	0
Wound complications	2	1	0	0

- 2 DLTs at 140 mg/m^2
- No DLT at 90 mg/m^2
- RP2D: 90 mg/m^2

PIPOX

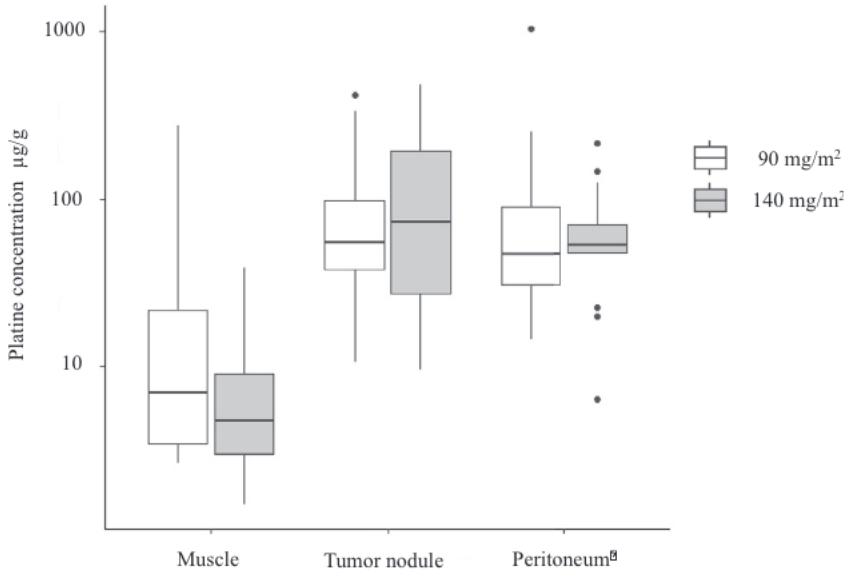


Fig. 2. Total platinum concentration in tissue samples. Results represent concentrations of total platinum per microgram of dried tissue. White boxplots represent concentrations for the 90 mg/m^2 dose and grey boxplots for the 140 mg/m^2 dose. Analyses were performed on 99 tissue samples (33 tumours nodules, 33 healthy peritoneum and 33 muscles). Horizontal bars, means; vertical bars, standard deviation.

PIPAC-OX

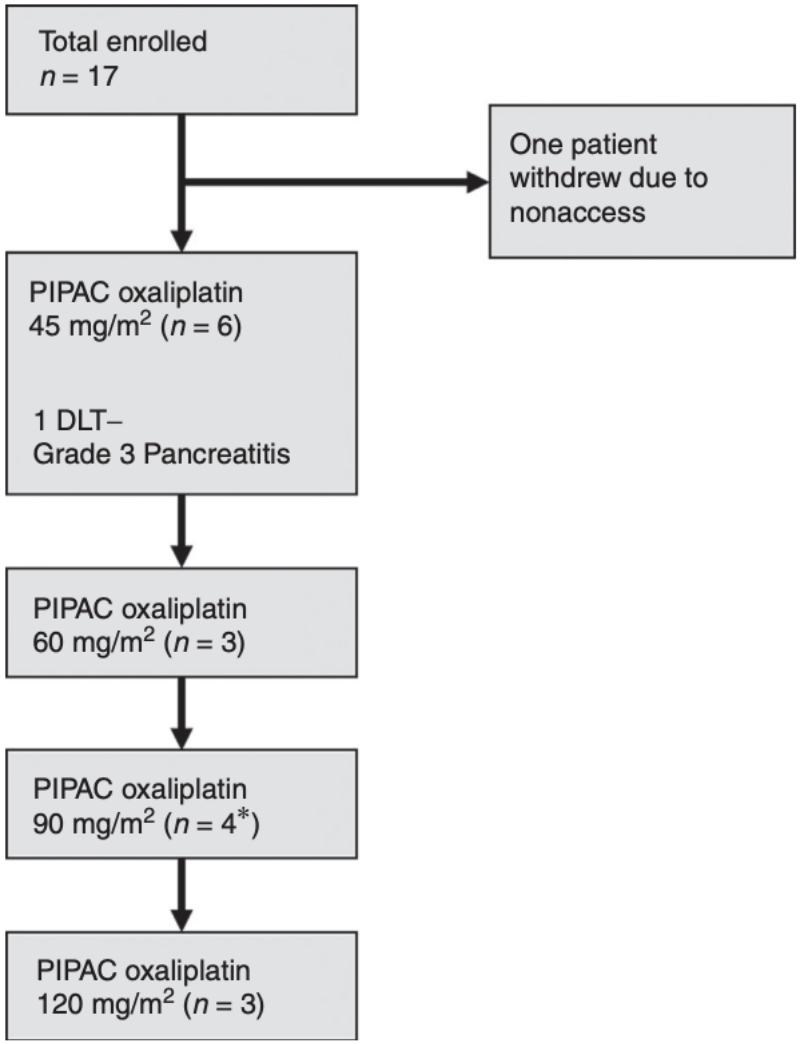
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

PIPAC-OX: A Phase I Study of Oxaliplatin-Based Pressurized Intraperitoneal Aerosol Chemotherapy in Patients with Peritoneal Metastases

Guowei Kim[1,2,3], Hon Lyn Tan[2,4], Raghav Sundar[2,4,5], Bettina Lieske[1,2,3], Cheng Ean Chee[2,4], Jingshan Ho[4], Asim Shabbir[1,2,3], Maria V. Babak[6,7], Wee Han Ang[6,8], Boon Cher Goh[2,4,9], Wei Peng Yong[4,9], Lingzhi Wang[2,9], and Jimmy B.Y. So[1,2,3]

3+3 Dose Escalation Study

PIPAC-OX


Total enrolled
n = 17
One patient withdrew due to nonaccess
PIPAC oxaliplatin
45 mg/m2 (n = 6)
1 DLT–
Grade 3 Pancreatitis
PIPAC oxaliplatin
60 mg/m2 (n = 3)
PIPAC oxaliplatin
90 mg/m2 (n = 4*)
PIPAC oxaliplatin
120 mg/m2 (n = 3)

PIPAC-OX

Table 1. Demographics and characteristics of all 16 patients.

Variable	Value
Age (years), median (range)	62 (51–75)
Gender (%)	
Male	11 (68.7)
Female	5 (31.3)
Ethnicity (%)	
Chinese	9 (56.3)
Malay	1 (6.3)
Indian	1 (6.3)
Others	5 (31.3)
ECOG performance status (%)	
0	4 (25.0)
1	10 (62.5)
2	2 (12.5)
Origin of primary tumor (%)	
Gastric	8 (50.0)
Colorectal	5 (31.3)
Gallbladder	1 (6.3)
Pancreas	1 (6.3)
Appendix	1 (6.3)
Primary tumor previously resected (%)	8 (50.0)
Previous lines of systemic therapy (%)	
1	9 (56.3)
2	3 (18.8)
3	2 (12.5)
≥4	2 (12.5)
Extraperitoneal metastasis at baseline (%)	3 (18.8)[a]
Pre-PIPAC PCI score, median (range)	17 (0–39)
Ascites at first PIPAC (%)	
Absent	5 (31.3)
Present	11 (68.8)
Ascites volume (mL) at first PIPAC, median (range)	340 (0–4,800)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PCI, peritoneal cancer index.
[a]One patient had bone, another lung, and the third patient, liver metastases.

PIPAC-OX

Table 2. Treatment-related AEs after PIPAC oxaliplatin administration in 16 patients, 24 PIPAC procedures.

		Dose level											
	Total events Patients: $n = 16$ PIPACs: $n = 24$	45 mg/m^2 Patients: $n = 6$ PIPACs: $n = 9$			60 mg/m^2 Patients: $n = 3$ PIPACs: $n = 4$			90 mg/m^2 Patients: $n = 4$ PIPACs: $n = 7$			120 mg/m^2 Patients: $n = 3$ PIPACs: $n = 4$		
Adverse event		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Pancreatitis	3 (12.5%)		1* (11.1%)	1# (11.1%)					1 (14.3%)				
Abdominal pain	2 (8.3%)	1* (11.1%)						1 (14.3%)					
Fever	1 (4.2%)	1# (11.1%)											
Fatigue	1 (4.2%)		1 (11.1%)										
Vomiting	1 (4.2%)							1 (14.3%)					
Total	8 (33.3%)	2 (22.2%)	2 (22.2%)	1 (11.1%)				2 (28.6%)	1 (14.3%)				

* #These complications occurred in the same patients.

Pancreatitis occurred 1, 7, and 9 days after PIPAC administration in the 3 patients

PIPAC-OX

Table 3. Clinical outcomes of the 16 patients (24 PIPAC procedures).

Variable	Value
Number of PIPACs per patient (%)	
1	8 (50.0)
2	8 (50.0)
Operation time (minutes), $n = 24$, median (range)	110 (68–169)
Peritoneal cancer index for patients who underwent two PIPACs, $n = 8$, median (range)	
1st PIPAC	15.0 (7–39)
2nd PIPAC	12.0 (8–39)
Ascites volume (mL) for patients who underwent two PIPACs, $n = 8$, median (range)	
1st PIPAC	225 (0–4,000)
2nd PIPAC	275 (0–2,200)
RECIST score after 1st PIPAC, $n = 16$ (%)	
Stable disease	10 (62.5)
Progressive disease	6 (37.5)
RECIST score after 2nd PIPAC, $n = 6$[a] (%)	
Stable disease	3 (50.0)
Progressive disease	3 (50.0)
PRGS for patients who underwent two PIPACs, $n = 7$[b], median (range)	
1st PIPAC	2.5 (1–3)
2nd PIPAC	2.0 (1–3)

[a]One patient died from rapid disease progression before RECIST scoring could be performed post PIPAC. Cross-sectional imaging for the other patient was performed overseas and unavailable for RECIST scoring.
[b]PRGS could not be obtained for 1 patient who had extensive peritoneal adhesions, precluding safe biopsies.

PIPAC-OX

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1st PIPAC	225 (0–4,000)
2nd PIPAC	275 (0–2,200)
RECIST score after 1st PIPAC, $n = 16$ (%)	
Stable disease	10 (62.5)
Progressive disease	6 (37.5)
RECIST score after 2nd PIPAC, $n = 6$[a] (%)	
Stable disease	3 (50.0)
Progressive disease	3 (50.0)
PRGS for patients who underwent two PIPACs, $n = 7$[b], median (range)	
1st PIPAC	2.5 (1–3)
2nd PIPAC	2.0 (1–3)

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[b]PRGS could not be obtained for 1 patient who had extensive peritoneal adhesions, precluding safe biopsies.

RP2D for PIPAC oxaliplatin at 120 mg/m^2

Italian Phase 1

cancers

MDPI

https://www.mdpi.com/journal/cancers

Article

A Phase I Dose Escalation Study of Oxaliplatin, Cisplatin and Doxorubicin Applied as PIPAC in Patients with Peritoneal Carcinomatosis

Manuela Robella [1,*], Michele De Simone [1], Paola Berchialla [2], Monica Argenziano [3], Alice Borsano [1], Shoeb Ansari [3], Ornella Abollino [3], Eleonora Ficiarà [4], Armando Cinquegrana [1], Roberta Cavalli [3] and Marco Vaira [1]

1 Unit of Surgical Oncology, Candiolo Cancer Institute, FPO—IRCCS, 10060 Candiolo, Italy; michele.desimone@ircc.it (M.D.S.); alice.borsano@ircc.it (A.B.); armando.cinquegrana@ircc.it (A.C.); marco.vaira@ircc.it (M.V.)

2 Department of Clinical and Biological Sciences, University of Torino, 10126 Torino, Italy; paola.berchialla@unito.it

3 Department of Drug Science and Technology, University of Torino, 10125 Torino, Italy; monica.argenziano@unito.it (M.A.); shoebanwarmohammedkhawja.ansari@unito.it (S.A.); ornella.abollino@unito.it (O.A.); roberta.cavalli@unito.it (R.C.)

4 Department of Neuroscience, University of Torino, 10126 Torino, Italy; eleonora.ficiara@unito.it

* Correspondence: manuela.robella@ircc.it; Tel.: +39-0119933630

CRM model: Cohort 1 – 100, Cohort 2 – 135, Cohort 3 – 155

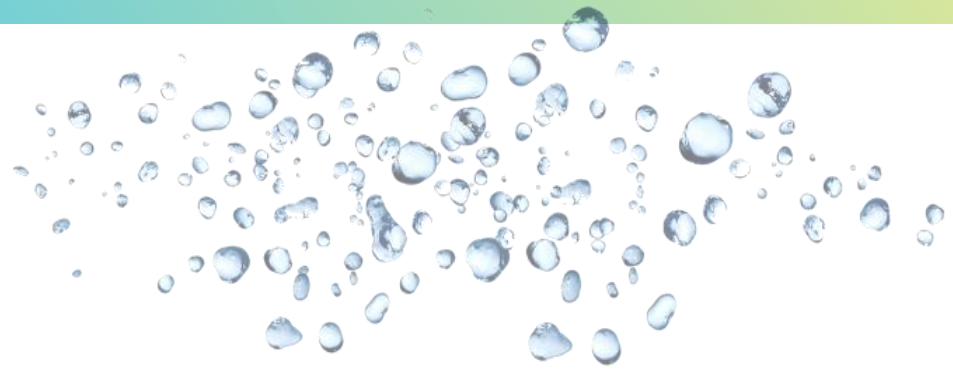
Italian Phase 1

Table 1. Demographic clinical and perioperative features of patients.

Variable	*n* = 13
Age (y), mean (range)	62.2 (34–79)
Females	9 (69%)
ECOG Performance Status	
0	5 (38%)
1	7 (54%)
2	1 (8%)
ASA Score	
1	0 (0%)
2	7 (54%)
3	6 (46%)
Body Surface Area, mean (range)	1.74 (1.32–2.12)
Histology	
EOC	2 (16%)
CRC	5 (38%)
GC	5 (38%)
PMP	1 (8%)
Prior Surgical Score	
1	5 (38%)
2	5 (38%)
3	3 (24%)
PCI, mean (range)	14 (6–24)
Ascites	
No	8 (62%)
Yes	5 (38%)
0–500 mL	4 (32%)
>500 mL	1 (8%)
Operative time (min), mean (range)	91 (55–125)

EOC = epithelial ovarian cancer; CRC = colorectal cancer; GC = gastric cancer; PMP = pseudomyxoma peritonei.

Italian Phase 1

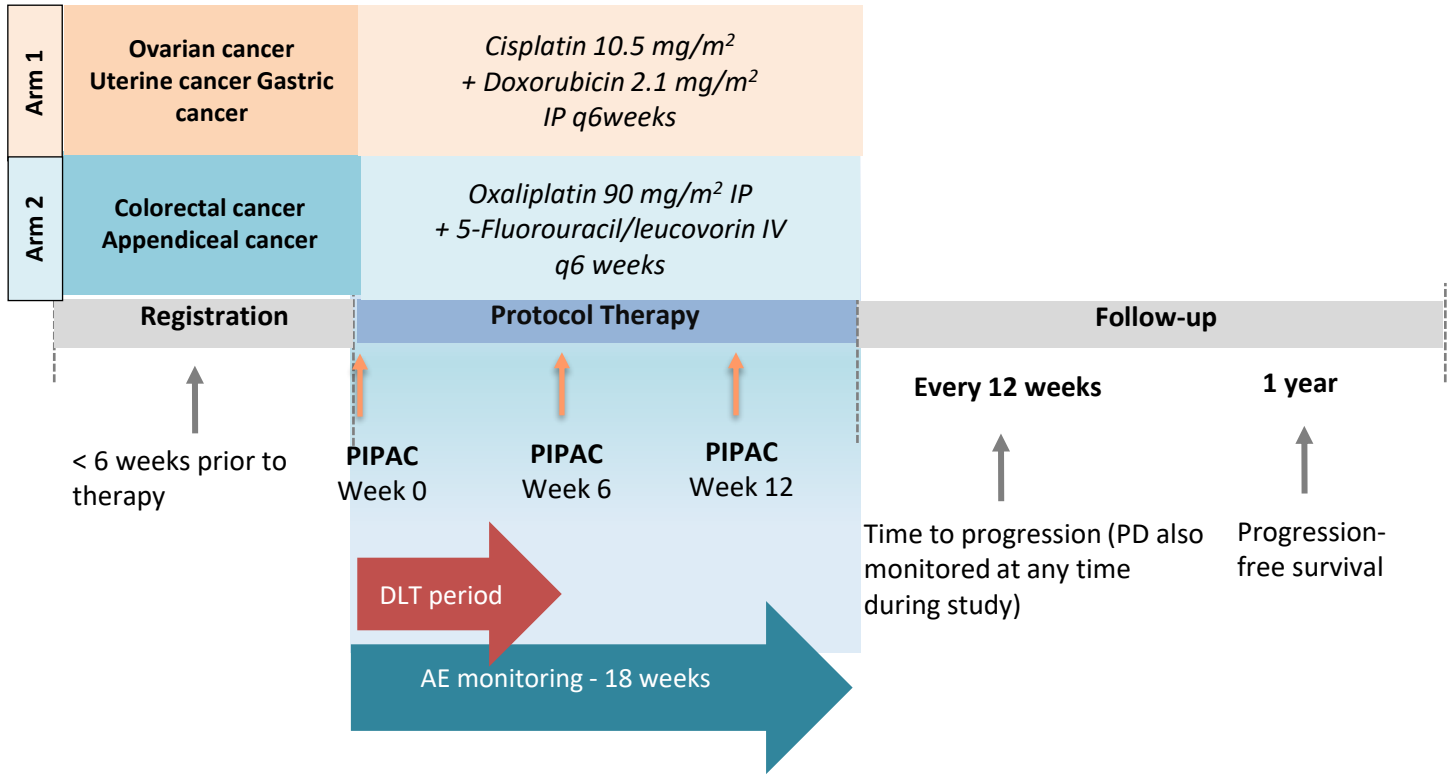


No DLT was observed to 135 mg/m^2

RP2D for single agent PIPAC 135 mg/m^2

US-Collaborative Arm 2

Safety and efficacy of pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in gynecologic, colorectal, and gastric patients with PC - Phase I pilot study



US PIPAC Collaborative

- City of Hope
- Northwell
- Mayo Clinic

Status:
Arm 1: Enrolling
Arm 2: Accrual Complete

US-Collaborative Arm 2

Table 1. Summary Statistics	
Characteristic	N = 12[1]
Age	60 (46, 62)
Gender	
Female	5 (42%)
Male	7 (58%)
Race	
Asian	1 (8.3%)
Non Disclosed	1 (8.3%)
Pacific Islander	1 (8.3%)
White	9 (75%)
Ethnicity	
Hispanic or Latino	1 (8.3%)
Non-Hispanic or Non-Latino	11 (92%)
ECOG	
0	8 (67%)
1	4 (33%)
Site	
Appendiceal	4 (33%)
Colorectal	8 (67%)
PCI	28 (19, 32)
Diagnosis to treatment (Days)	476 (309, 560)
Prior lines of chemotherapy*	2 (2, 3)

[1]Median (Inter-quartile range). *n=11

Feasibility: Of the 11 patients that have completed protocol therapy, 6 (55%) completed three PIPACs and 7 completed at least 2 (64%) PIPACs.

US-Collaborative Arm 2

Safety: No DLT or surgical complication occurred

Table 2. Summary of Adverse Events*

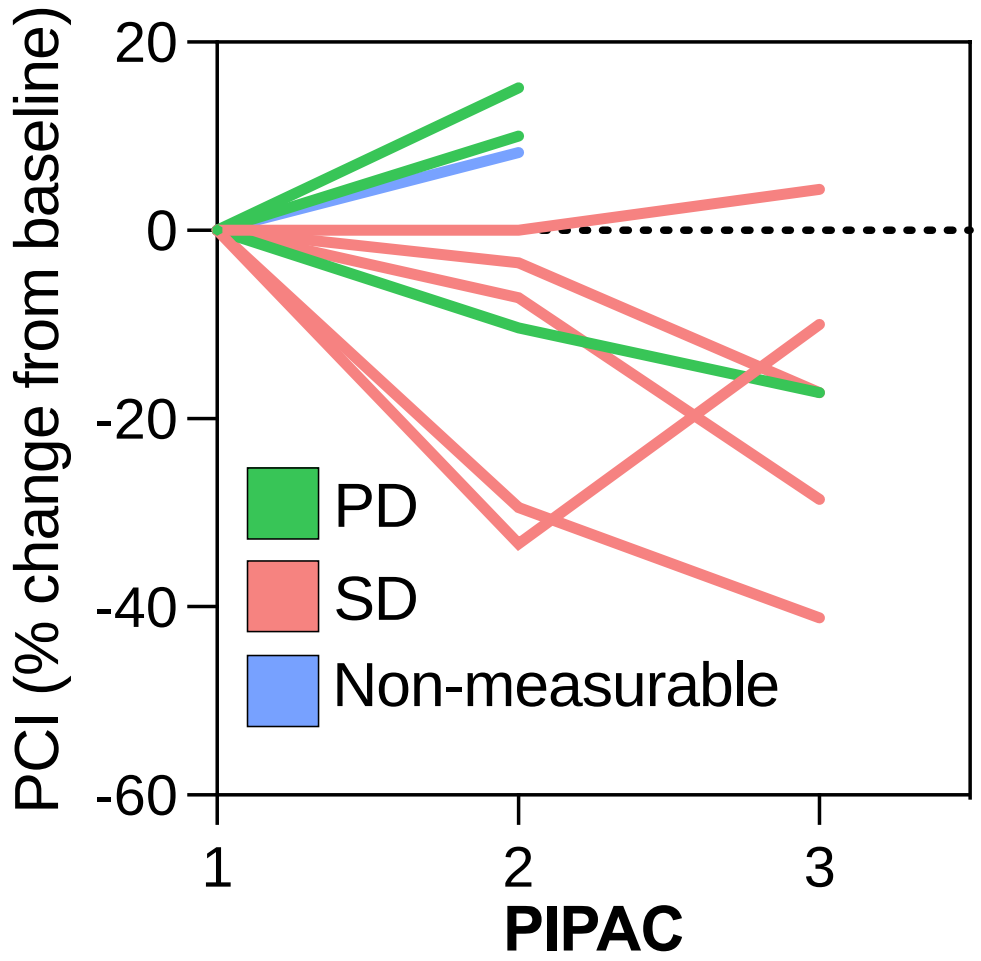
AE	Gr 1	Gr 2	Gr3
Abdominal pain	3	1	1
Anemia	1		1
Fatigue	1	1	
Constipation	3	1	
Nausea	3	1	
Vomiting	3	1	
Hypophosphatemia		1	
Hypotension		1	
Ileus		1	
Thrombocytopenia		1	
Bloating	1		
Dizziness	1		
Generalized muscle weakness	1		
Hypernatremia	1		
Hypoalbuminemia	1		
Hypocalcemia	1		
Hypokalemia	1		
Hyponatremia	1		
Muscle cramp	1		
Noncardiac chest pain	1		
Urine output decreased	1		
Leukopenia	1		
Abdominal distension	2		
Anorexia	2		
Diarrhea	2		

*definite, possible or probable

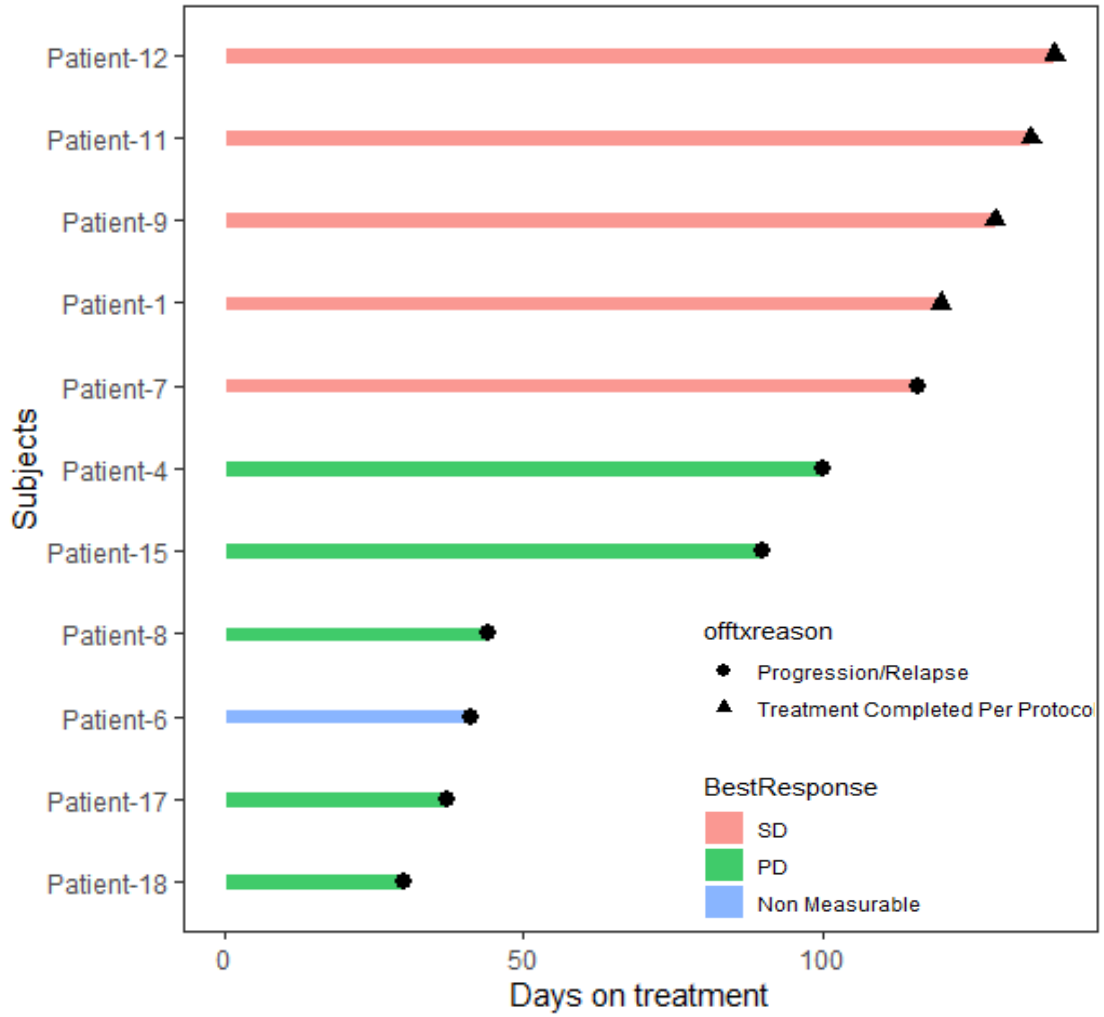
US-Collaborative Arm 2

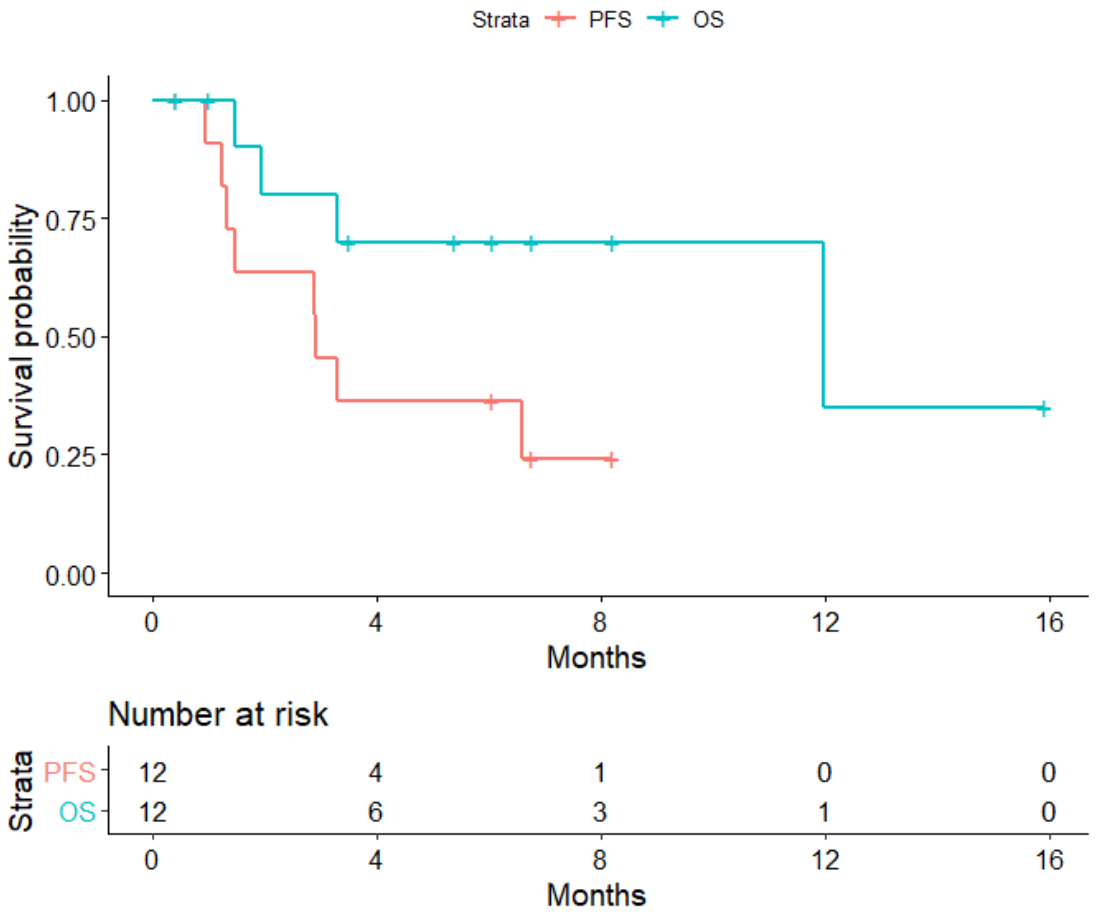
Efficacy: 2/11 (18%) underwent optimal cytoreduction/ HIPEC.

Table 3. Efficacy Statistics	
Best Response	N = 11
Radiographic – RECIST	
SD	5 (45%)
PD	5 (45%)
Non-Measurable	1 (9.1%)
Laparoscopic – PCI	
Decrease	5 (45%)
Stable	1 (9.1%)
Increase or only 1 PIPAC	5 (45%)



US-Collaborative Arm 2





US-Collaborative Arm 3

Arm 3: Safety and efficacy of Mitomycin C (MMC) PIPAC for the treatment of peritoneal metastasis in colorectal/ appendiceal cancer in combination with systemic chemotherapy

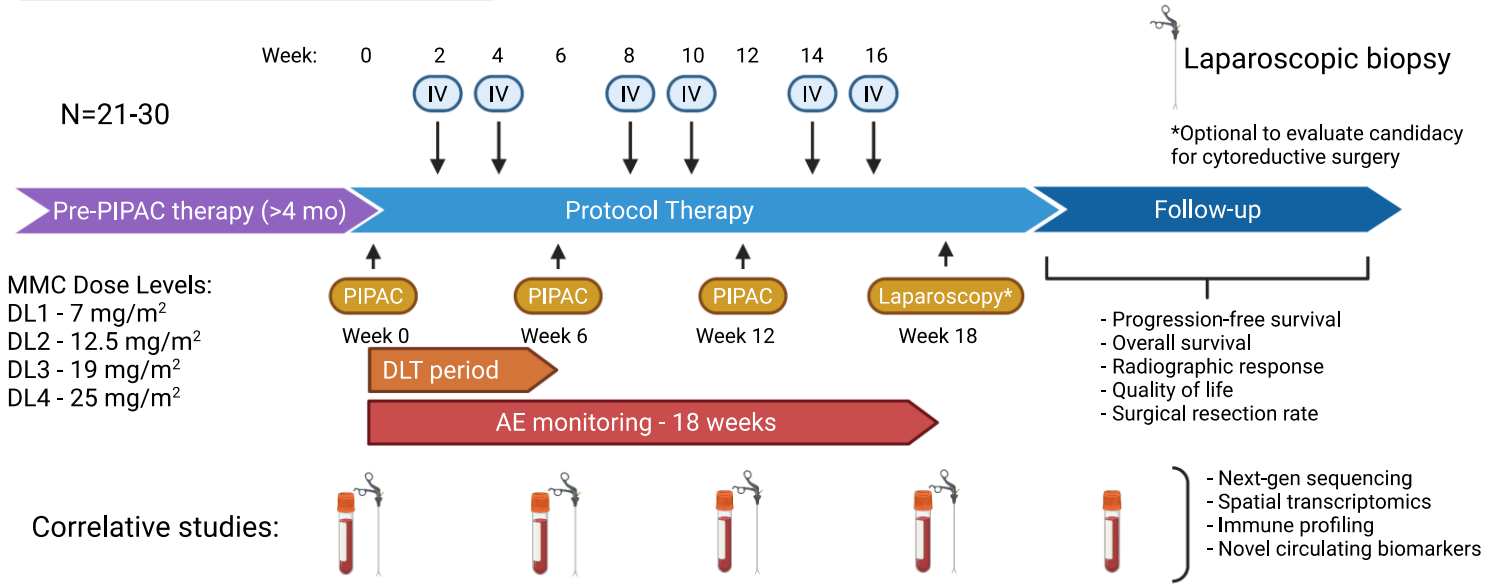
Key Eligibility:
- Colorectal/ Appendiceal peritoneal metastases
- Not candidates for upfront resection
- No extraperitoneal metastases
- At least 4 months of first/ second line standard of care chemotherapy
- ECOG < 2
- No bowel obstruction

Pre-PIPAC Standard-of-care Systemic Therapy

• Cytotoxic: FOLFOX/ FOLFIRI / FOLFOXIRI
• +/- Biologic: anti-EGFR (for left sided, KRAS-WT); anti-VEGF (for others)

PIPAC plus System therapy with:

• Cytotoxic: FOLFIRI
• PIPAC: Mitomycin C



US PIPAC Collaborative

City of Hope

Northwell

Mayo Clinic

Status: Open to Accrual

Phase 2/3 trials – Curated March 2022

NCT no. (phase)	Title/acronym	Malignancy types	PIPAC regimen	Primary outcomes measure	Dates	Location
NCT03294252 (phase 1/2)	PIPOX[57,58]	Stomach Small bowel Colorectal	Systemic: fluorouracil and leucovorin PIPAC: oxaliplatin	Maximum tolerated dose	9/2019–6/2021	France
NCT03100708 (phase 2)	PIPAC-01[59]	Ovarian Gastric Pancreatic Primary peritoneal Colorectal	Cisplatin + doxorubicin in ovarian, gastric, pancreatic cancer and primary peritoneal cancer Oxaliplatin in colorectal cancer	OS	4/2016–4/2021	Germany
NCT04065139 (phase 2)	PIPAC EstoK 01[60]	Gastric	Doxorubicin + cisplatin	PFS	9/2019–9/2022	France
NCT02735928 (phase 2)	PARROT[61]	Ovarian	Cisplatin + doxorubicin	Clinical Benefit rate	1/2016–10/2021	Italy
NCT03280511 (phase 2)	PIPAC-OPC3[52]	Colorectal	Oxaliplatin	PFS	12/2017–3/2025	Denmark
NCT03868228 (phase 2)	Pilot study assessing the efficacy of oxaliplatin-based PIPAC for the treatment of colorectal peritoneal metastases[62]	Colorectal	Oxaliplatin	PFS	2/2019–9/2021	United Kingdom
NCT04595929 (phase 2)	GASPACCO[63]	Gastric	Radical gastrectomy with intraoperative PIPAC using cisplatin + doxorubicin	OS	2/2020–1/2029	Russian Federation
NCT03875144 (phase 2)	MESOTIP[64]	Mesothelioma	Cisplatin + doxorubicin	OS	8/2020–12/2024	France
NCT04122885 (phase 2)	IMMUNOPAC[66]	Ovarian Gastric Colorectal	Oxaliplatin	OS	10/2019–9/2022	Germany

SUMMARY

- Oxaliplatin: RP2D with concurrent systemic therapy: 90 mg/m^2
  - Further Studies are Needed because systemic was not standardized
- Oxaliplatin: RP2D without concurrent systemic therapy: 120 – 135 mg/m^2
  - Could be higher
- Mitomycin C with concurrent FOLFIRI: Trial ongoing
- Efficacy: Trials ongoing and results awaited