CLINICAL

U.S. PIPAC Trials

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City of Hope

Disclosures

- I have no 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 Cisplatin, Doxorubicin, Oxaliplatin 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:

- The ethnic and racial make-up of City of Hope trial participants, and how **consents** have been translated into **multiple languages** and are therefore, readily available for non-English speaking participants.
- The number of **obese** patients (by BMI) of our trial participants, and their **geographic** locations, which are known biases in healthcare.

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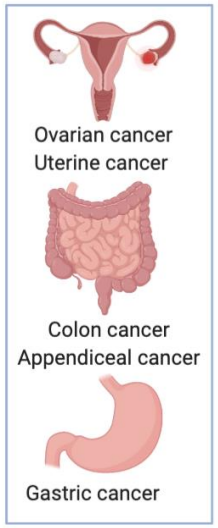
Overview – U.S. PIPAC trials

- Phase I trial in ovarian, uterine, gastric, colorectal, and appendiceal cancer
  - Feasibility of PIPAC in the U.S.
  - Dose-finding study of Mitomycin C in colorectal/appendiceal cancer
- Phase I trial in cholangiocarcinoma
- Translational studies
- Quality of Life Studies

U.S. PIPAC Phase I Clinical trial: *NCT04329494*

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



Arm 1	**Ovarian cancer Uterine cancer Gastric cancer**	*Cisplatin 10.5 mg/m² + Doxorubicin 2.1 mg/m² IP q6weeks*
Arm 2	**Colorectal cancer Appendiceal cancer**	*Oxaliplatin 90 mg/m² IP + 5-Fluorouracil/leucovorin IV q6 weeks*
Arm 3	**Colorectal cancer Appendiceal cancer**	*Mitomycin C (MMC) (dose-finding) starting at 7 mg/m2, escalate to 25 mg/m2 q6 weeks*

Registration

< 6 weeks prior to therapy

Protocol Therapy

PIPAC Week 0

PIPAC Week 6

PIPAC Week 12

DLT period

AE monitoring - 18 weeks

Follow-up

Every 12 weeks

Time to progression (PD also monitored at any time during study)

1 year

Progression-free survival

Disease	Eligibility	Multimodal therapy
Ovarian cancer Uterine cancer	Recurrent ovarian cancer with peritoneal mets Extraperitoneal mets allowed	no
Colorectal cancer Appendiceal	No extraperitoneal mets Failed at least one prior chemo line	no
Colorectal cancer Appendiceal cancer	At least 4 months of 1st/2nd line SOC chemotherapy	Yes (FOLFIRI)

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MAYO CLINIC

Raoof et al, Ann Surg Onc, 2022

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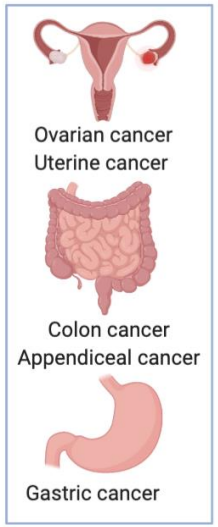

			Accrual to date	Safety	PIPAC completion rate (≥2 PIPACs)
Arm 1	Ovarian cancer Uterine cancer Gastric cancer	*Cisplatin 10.5 mg/m² + Doxorubicin 2.1 mg/m² IP q6weeks*	N=9 7 ovarian cancer 1 uterine caner 1 gastric cancer	No DLTs No Grade ≥3 AEs	63%
Arm 2	Colorectal cancer Appendiceal cancer	*Oxaliplatin 90 mg/m² IP + 5-Fluorouracil/leucovorin IV q6 weeks*	N=13 Arm completed	No DLTs 2 Grade 3 AEs (anemia, abdominal pain	64%
Arm 3	Colorectal cancer Appendiceal cancer	*Mitomycin C (MMC) (dose-finding) starting at 7 mg/m2, escalate to 25 mg/m2 q6 weeks*	N=5 Dose escalation study with Multimodal therapy	Pending (no DLTs to date)	Pending (100% to date)

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Raoof et al, Ann Surg Onc, 2022

Safety and efficacy of PIPAC in appendiceal and colorectal cancer patients with peritoneal metastases: A first-in-US phase I study

(US PIPAC Collaborative)

Mustafa Raoof*[1], Richard L. Whelan*[2], Paul Henry Frankel[1], Yujie Cui[1], Marwan Fakih[1], Joseph Chao[1], Dean Lim[1], Yanghee Woo[1], Isaac Benjamin Paz[1], Michael Lew[1], Mihaela C. Cristea[1], Lorna Rodriguez-Rodriguez[1], Yuman Fong[1], Wiebke Solass[3], Rebecca Meera Thomas[2], Sue Chang[1], Andrew M. Blakely[4], Danielle Deperalta[2], Marc A. Reymond[3], Amit Merchea*[5], Thanh Hue Dellinger*[1]

[1]City of Hope Cancer Center, [2]Northwell Health, [3]University of Tübingen, [4]NCI, [5]Mayo Clinic –Jacksonville (*Correspondence)

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Arm 2 Baseline characteristics

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:

PIPAC completion rate:

- 6 (55%) ≥ 3 cycles
- 7 (64%) ≥2 PIPACs

of 11 patients who completed protocol therapy

Safety:

- no DLTs
- no surgical complications

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

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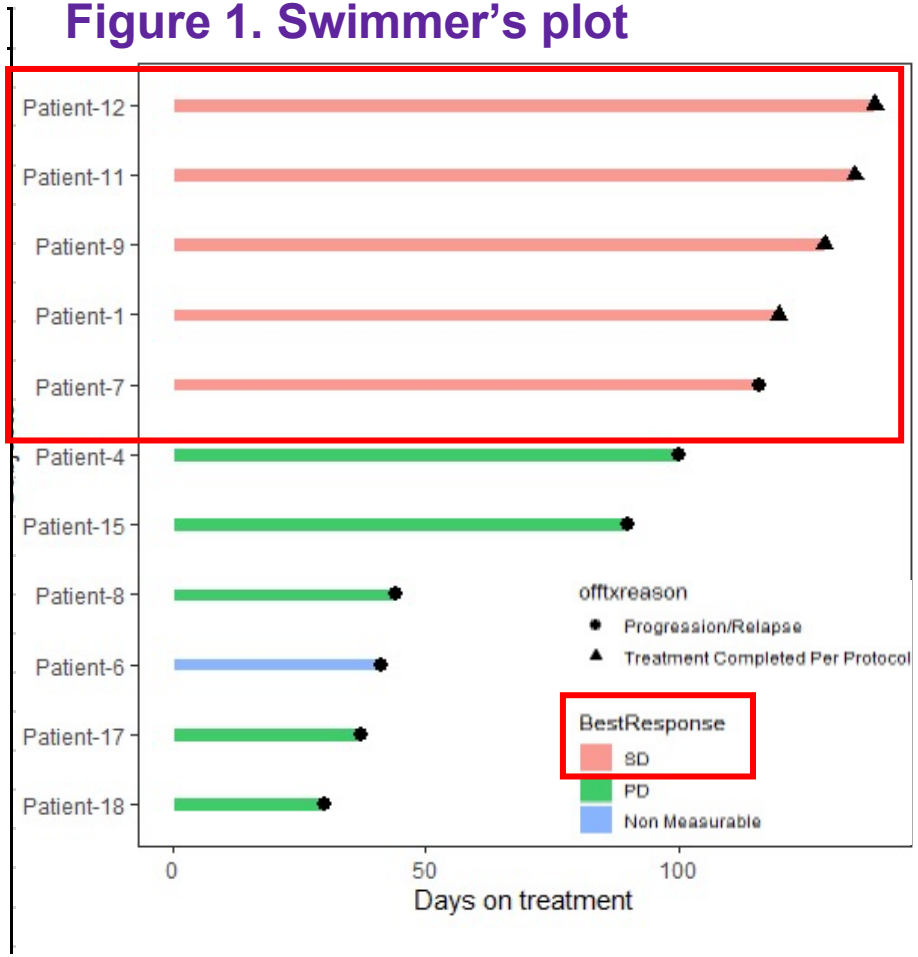
Figure 1. Swimmer's plot



- **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%)

Figure 2. Response Correlation

(RECIST vs. Laparoscopic PCI)

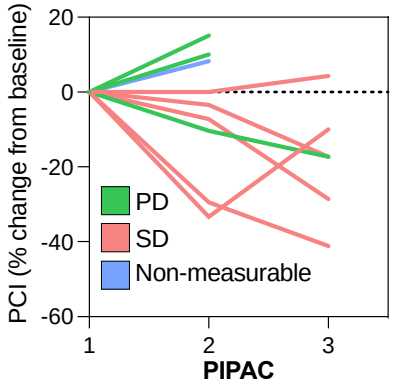
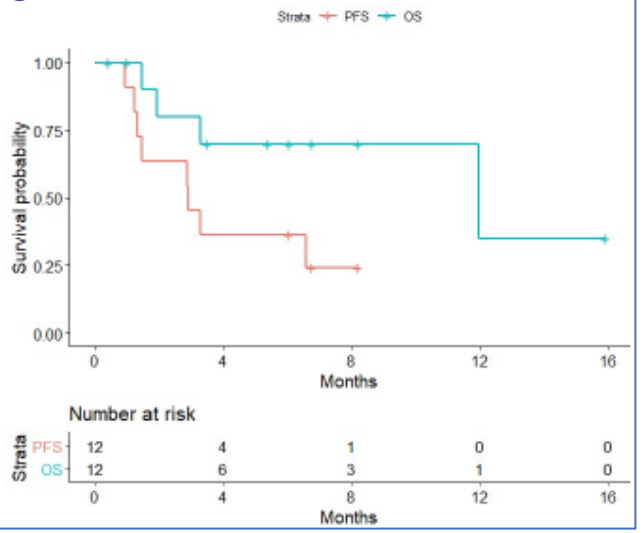


Figure 3. Survival



U.S. PIPAC Phase I Clinical trial: *Novel PIPAC chemotherapies – Mitomycin C*

DE GRUYTER Pleura and Peritoneum 2022; aop

Multicenter dose-escalation Phase I trial of mitomycin C pressurized intraperitoneal aerosolized chemotherapy in combination with systemic chemotherapy for appendiceal and colorectal peritoneal metastases: rationale and design

Mustafa Raoof*, Kevin M. Sullivan, Paul H. Frankel, Marwan Fakih, Timothy W. Synold, Dean Lim, Yanghee Woo, Isaac Benjamin Paz, Yuman Fong, Rebecca Meera Thomas, Sue Chang, Melissa Eng, Raechelle Tinsley, Richard L. Whelan, Danielle Deperalta, Marc A. Reymond, Jeremy Jones, Amit Merchea and Thanh H. Dellinger*

Table 1: Dose finding Phase I studies of PIPAC.

Trial	Oxaliplatin dose	Patients	Toxicities	Efficacy
PIPOX [16, 17]	90 mg/m^2 MTD	10	No DLT at MTD	All patients at least minor response by PGRS
PIPAC-OX [11]	120 mg/m^2 RP2D	16	No AEs at RP2D	PCI decrease from 15 to 12, and PRGS from 2.5 to 2.0.
Robella et al. [12]	135 mg/m^2 RP2D	6	Grade 1–2 abdominal pain	Not assessed

MTD, maximum tolerated dose; DLT, dose limiting toxicities; PRGS, peritoneal regression grading score; RP2D, recommended Phase II dose; AE, adverse events; PCI, peritoneal carcinomatosis index.

Raoof et al, Pleura Perit 2022

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Rationale for Mitomycin C

- Active HIPEC drug
- Direct cytotoxic effect after short exposure, thus a good IP drug
- Large molecular weight that allows for high exposure to peritoneal surface
- Water soluble, rapidly cleared

Multi-modal therapy:
PIPAC + systemic chemotherapy

- PIPAC MMC + FOLFIRI

First-line adjuvant setting:
at least 4 months of standard of care chemotherapy (FOLFIRI, FOLFOX, FOLFOXFIRI) in 1st or 2nd line setting

Raoof et al, Pleura Perit 2022

PIPAC drugs in CRC

Summary of chemotherapeutic agents and their Phase I studies of their use in PIPAC for CRC patients with PM.

	Oxaliplatin	Mitomycin C	Irinotecan[a]
IV dose, mg/m^2	85	10	120–185
HIPEC dose, mg/m^2	200–460	10-35 [30]	200
PIPAC dose, mg/m^2	120 [11]	1.5–7 [32, 34]	20 [32, 33]
	90 [17]		
	135 [12]		
	92 [b]		
Dose-escalation Phase I Study	Yes	No	No
RP2D	90–135 mg/m^2	n/a	n/a
Efficacy	16.4% partial response	n/a	n/a
	20.3% stable response (RECIST)		
Grade ≥ 3 Toxicity	Pancreatitis, neutropenia, allergic reaction, pain, nausea, peripheral neuropathy	n/a	n/a

[a]In 2018 international survey, only one center used Irinotecan PIPAC [33]. [b]arbitrary dose. RP2D, recommended Phase II dose; IV, intravenous; HIPEC, hyperthermic intraperitoneal chemotherapy; PIPAC, pressurized intraperitoneal aerosolized chemotherapy; RECIST 1.1, Response Evaluation Criteria in Solid Tumors.

- Mitomycin C efficacy or optimal dose is not yet established
- Previously reported doses:
  - 1.5mg/m2 in 50 mL NS for platinum-allergic patients, or
  - 7mg/m2 (based on a preclinical animal study using 14 mg MMC/50mL NS)

Raoof et al, Pleura Perit 2022

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

Key Eligibility:
- Colorectal or Appendiceal peritoneal carcinomatosis (PC)
- 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

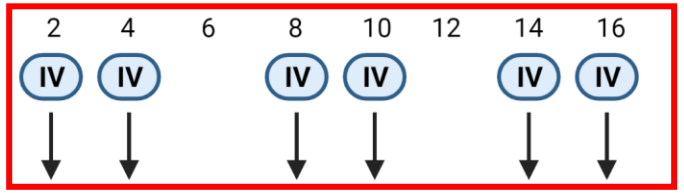
Pre-PIPAC Standard-of-care Systemic Therapy

- 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

N=21-30



Laparoscopic biopsy

*Optional to evaluate candidacy for cytoreductive surgery

Pre-PIPAC therapy (>4 mo) → Protocol Therapy → Follow-up

PIPAC Week 0 | PIPAC Week 6 | PIPAC Week 12 | Laparoscopy* Week 18

DLT period

AE monitoring - 18 weeks

MMC Dose Levels:
DL1 - 7 mg/m^2
DL2 - 12.5 mg/m^2
DL3 - 19 mg/m^2
DL4 - 25 mg/m^2

- Progression-free survival
- Overall survival
- Radiographic response
- Quality of life
- Surgical resection rate

Correlative studies:

- Next-gen sequencing
- Spatial transcriptomics
- Immune profiling
- Novel circulating biomarkers

MMC dose-escalation study

Inclusion	Exclusion
Documented informed consent	Extraperitoneal metastatic disease
Age ≥ 18 years	Progression on both first- and second-line systemic chemotherapy; progression on irinotecan-based chemotherapy
Histologically confirmed appendiceal or colorectal carcinoma	Bowel obstruction requiring nasogastric or gastrostomy tube
No contraindications for laparoscopy	Life expectancy of less than 6 months
Visible peritoneal disease on cross sectional imaging or on laparoscopy	Ascites due to liver cirrhosis or portal vein thrombosis
At least 4 months of standard of care systemic chemotherapy (e.g. FOLFOX, FOLFIRI, FOLFOXIRI). If irinotecan-based chemotherapy was used the patients should not have progression on irinotecan-based chemotherapy	Simultaneous tumor-debulking with gastrointestinal resection
	Uncontrolled current cardiac or renal comorbidity, myelosuppression, or hepatic impairment
	Exclusive total parenteral nutrition

Dose level	Dose	Expected N (evaluable)	Comments
DL 1	7 mg/m^2	3	Assuming no DLTs
DL 2	12.5 mg/m^2	3	Assuming no DLTs
DL 3	19 mg/m^2	3	Assuming no DLTs
DL 4	25 mg/m^2	3+3	Assuming at most 1 DLT

- Maximum dose level of 25 mg/m$_2$
- systemic exposure of MMC after HIPEC 40 mg/m$_2$ is approximately equivalent to 15–20 mg/m$_2$ IV
- we desired to achieve a maximum dose level less than maximum HIPEC doses.

U.S. PIPAC Translational studies

City of Hope · Northwell Health · Mayo Clinic

Pharmacokinetics

Tim Synold, PhD

Whole exome sequencing

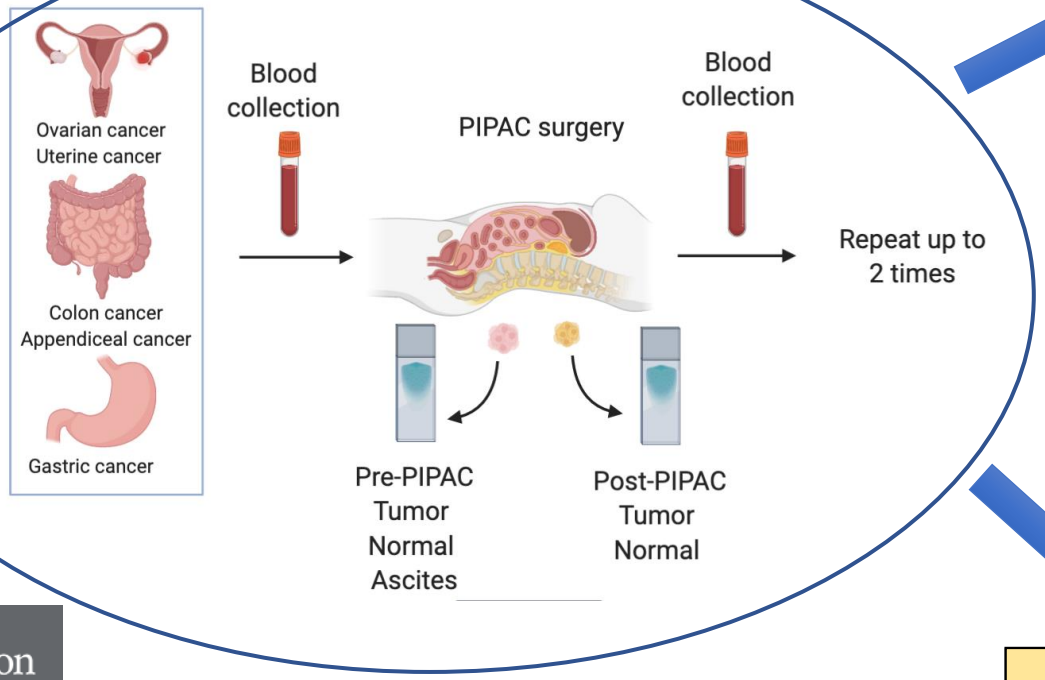
tgen

Muhammed Murtaza, PhD

Circulating Tumor DNA

Single Cell Omics

Andrea Bild, PhD



Mustafa Raoof, MD

Tumor Organoids

Immune Correlatives

- Blood and Fresh Tumor samples

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Pharmacogenomics

Andrew Blakely, MD

NIH NATIONAL CANCER INSTITUTE

Quality of Life Studies in U.S. PIPAC trials

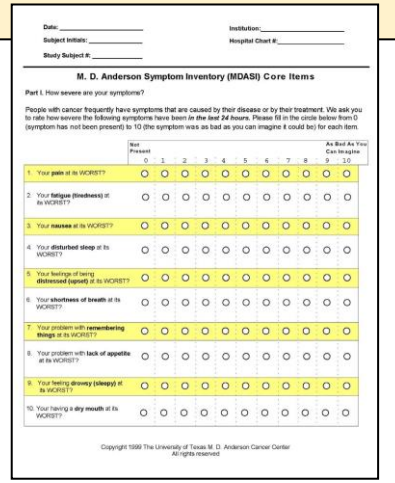
Functional status

- Vivofit® 4 wristband pedometer
- Functional status, as measured by the number of daily steps before and after treatments ()
- continuously assessed until the end of protocol therapy
- The device follows activity progress 24/7
- Vivofit will be worn continuously
- Steps data are wirelessly synced by pressing a button
- steps data will transmit to a study database.

Virginia Sun, PhD

Patient-reported Outcomes (PROs)

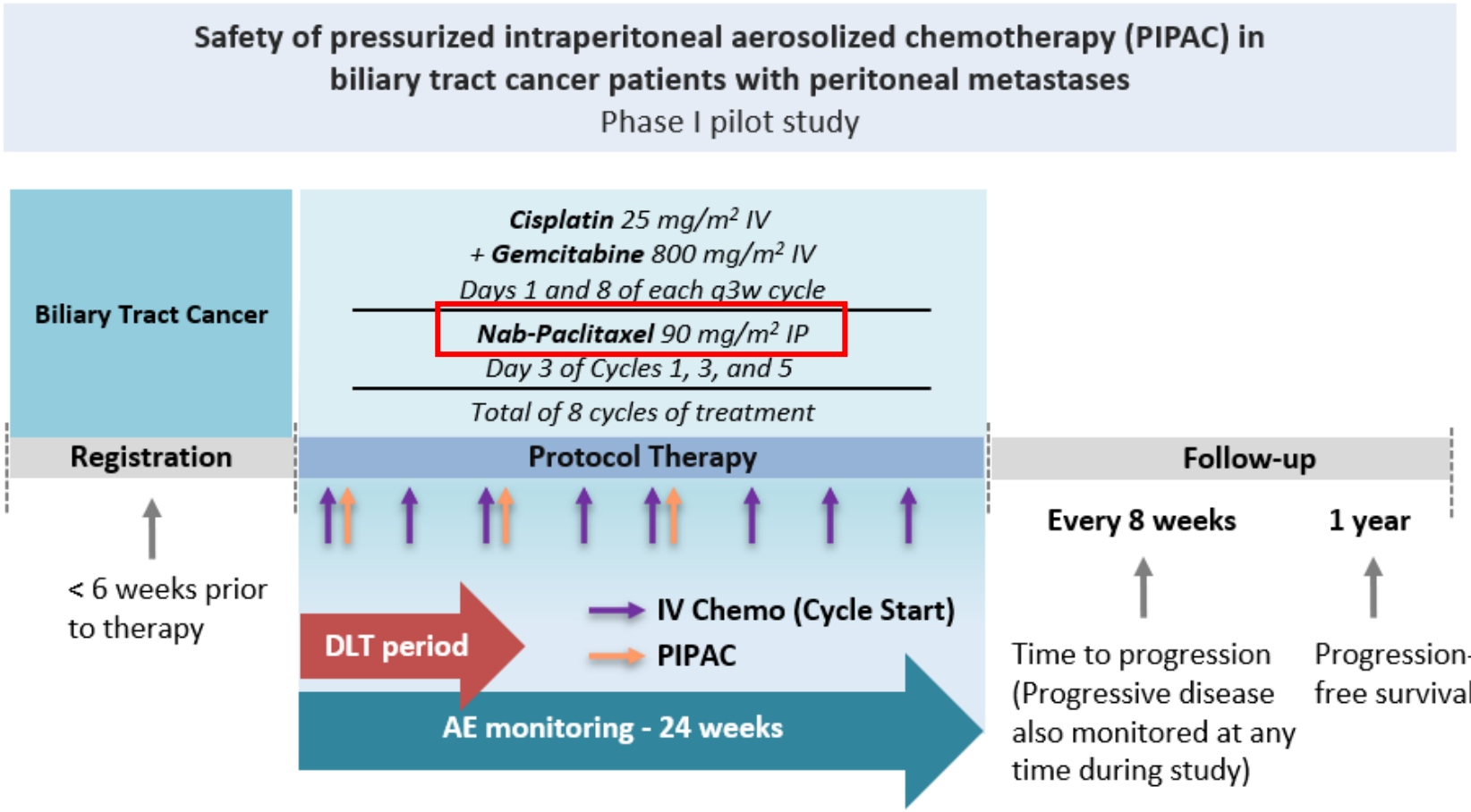
- **QoL**
- Quality of life assessments:
  - Patient-reported health state/quality of life and symptoms before treatment and at 0, 6 and 12and 18 weeks
- EQ-5D-5L
- MD Anderson Symptom Inventory (MDASI).



M. D. Anderson Symptom Inventory (MDASI) Core Items

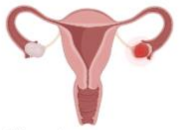
Sun et al, 2017; Sun et al, 2019

Safety of pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in biliary tract cancer patients with peritoneal metastases

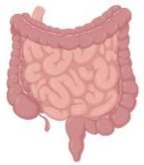


NCT05285358
PI: M. Raoof

U.S. PIPAC multi-institutional trial

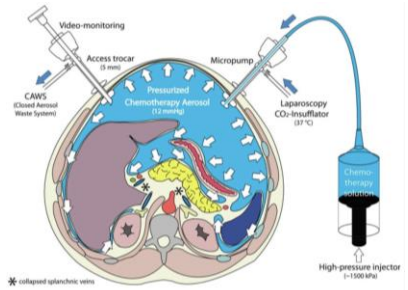


Ovarian cancer
Uterine cancer



Colon cancer
Appendiceal cancer

Gastric cancer



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Correlative studies

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