CLINICAL

Patient Selection for PIPAC

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Disclosures

- I do not have any relevant financial relationships.

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

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:

- PIPAC access for patients with limited financial resources or social support.

City of Hope

Peritoneal Metastasis: Treatment Background

- Aim is to preserve life and quality of life
- Multidisciplinary team including surgery, oncology, and palliative care
- Treatment is multimodal and must be tailored to individual patient, including:
  - Systemic chemotherapy
  - Cytoreductive surgery
  - Intraperitoneal chemotherapy (HIPEC, catheter-based, etc.)
  - Palliative surgery
  - Palliative/ supportive care for symptom management and quality of life
- Evidence on therapy of PM is generally low
- Evidence on therapy of PM is evolving rapidly

- PIPAC is a drug delivery system rather than a specific treatment

PIPAC: Evidence Available

	Registry	Phase 1	Phase 2	Randomized trial
Ovarian cancer	NCT03210298	NCT02475772	NCT02475772	PIPAC-OV3 (1)
			NCT02735928	**REF/2018/08/021223***
			NCT03304210	**REF/2018/08/021225#**
Gastric cancer	NCT03210298	NCT02475772	NCT01854255	PIPAC-Estok (2)
				PIPAC - AIO (3)
				PMGA-PIPAC (4)
Colorectal cancer	NCT03210298	NCT03294252	NCT03280511	PIPIRINOX (5)
		NCT03172416	NCT03246321	
HBP tumor	NCT03210298	NCT02475772		
Appendiceal cancer	NCT03210298	NCT02475772		
Pseudomyxoma Peritonei	NCT03210298	NCT02475772		
Malignant Peritoneal Mesothelioma	NCT03210298	NCT02475772		MESOTIP (6)
Peritoneal carcinomatosis			NCT02604784 NCT02320448	

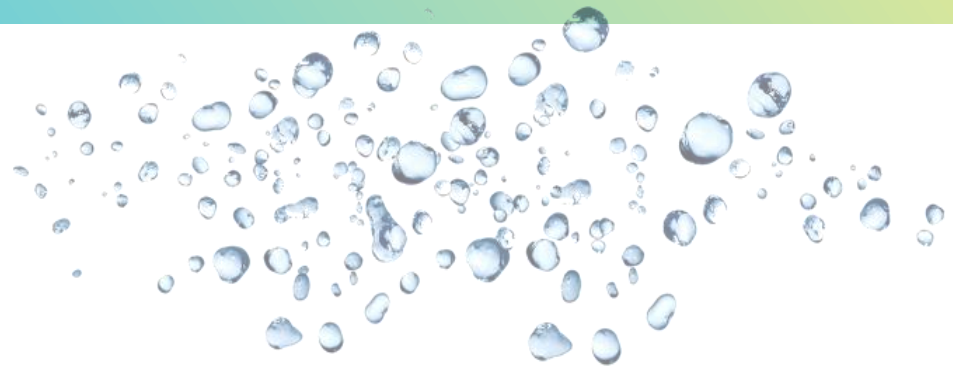
Legend	
	Trial completed
	Trial ongoing
	Trial planned

1. Bakrin N et al, Pleura Peritoneum 2018; 2. Eveno C et al, Pleura Peritoneum 2018; 3. Götze et al, Pleura Peritoneum 2018;
4. Rau B et al, under review; 5. Dumont F et al, under review; 6. Sgarbura O et al, approved 2019.

* REF/2018/08/021225 - S.P. Somashekhar, K.R. Ashwin, Amit Rauthan, Kumar C. Rohit., Pleura and Peritoneum 2018; 20180110

REF/2018/08/021223- S. P. Somashekhar, K. R. Ashwin,, Pleura and Peritoneum 2019; 20180111

PIPAC: What We Know



Available evidence (level IIB) shows that PIPAC is:

- ✓ Feasible
- ✓ Safe
- ✓ Well-tolerated

Preliminary oncological results are encouraging:

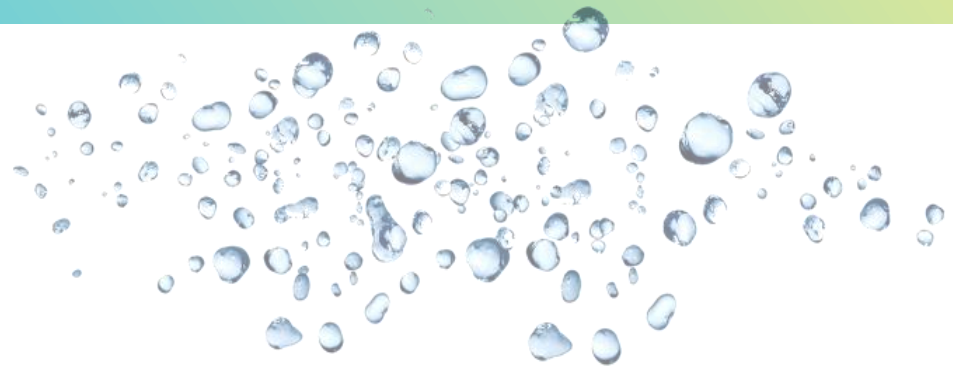
- RECIST
- Peritoneal regression score grading score (PRGS)
- Symptoms, Quality of life

Grass F et al, Br J Surg 2017; Tempfer CB et al, Arch Gyn Oncol 2018.

PIPAC: What We Do Not Know

- Everything else (no randomized trials published so far)

Contraindications



Absolute contraindications:

- No safe access to laparoscopy
- Bowel obstruction, total parenteral nutrition (TPN), NGT, venting Gtube
- Decompensated ascites
- Comorbidities that preclude general anesthesia
- Patient with resectable disease and candidate for cytoreductive surgery
- Patient at the end of life (not always clear prospectively)

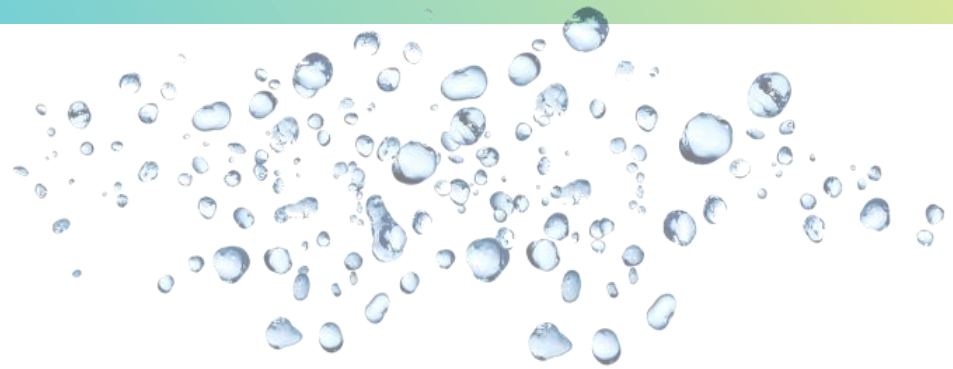
Relative contraindications:

- Extraperitoneal metastasis (Exception of Isolated Malignant Pleural Effusion)
- ECOG > 2
- Simultaneous intestinal anastomosis and PIPAC

Special Situations

- Prior cytoreductive surgery +/- HIPEC (sometimes ascites is helpful)
- Prior anaphylactic reaction to IP regimen
- Ostomy

Indications



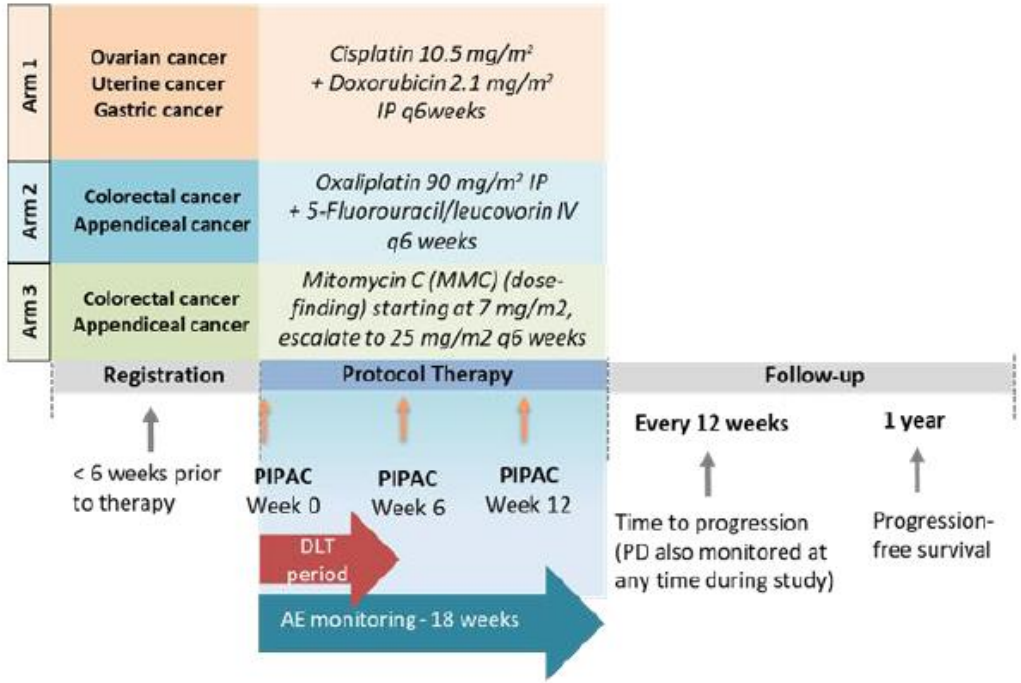
- Comparative studies are lacking
- Unable to make clear recommendations regarding indication
- PIPAC should only be performed within the framework of clinical studies
- However, there are many situations for patients with PM where no evidence-based therapy is available
- In these situations, "off-label" PIPAC therapy is legitimate since*:
  - Disease is life-threatening
  - No evidence-based therapy is available
  - PIPAC can induce regression of PM in the salvage situation

*In the United States, PIPAC is not FDA approved and cannot be recommended outside of a clinical trial. We have limited compassionate use cases to patients who have completed clinical trial with good response and no good alternative options.

American PIPAC Trial

EXPERIMENTAL DESIGN SCHEMA

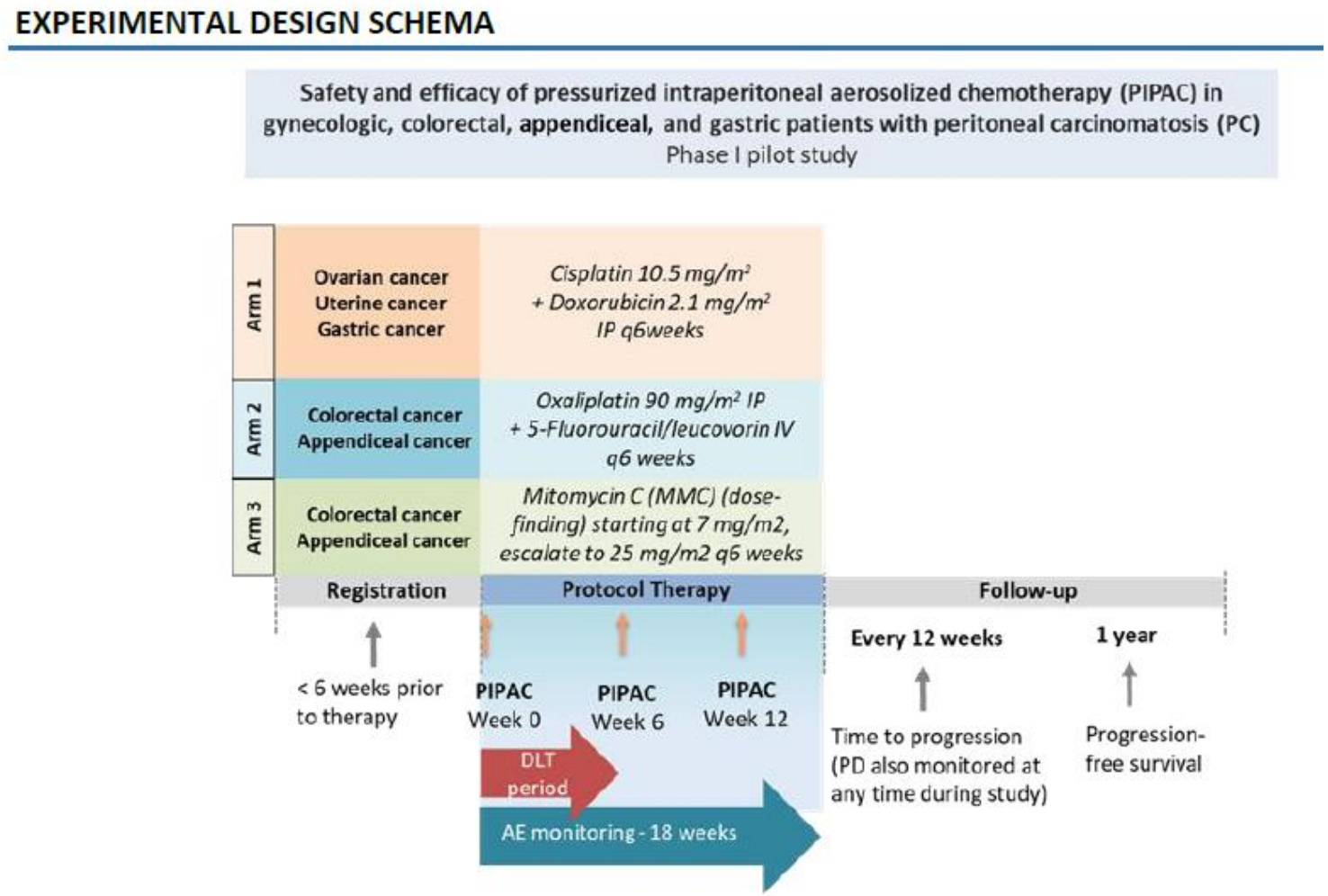
Safety and efficacy of pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in gynecologic, colorectal, appendiceal, and gastric patients with peritoneal carcinomatosis (PC)
Phase I pilot study



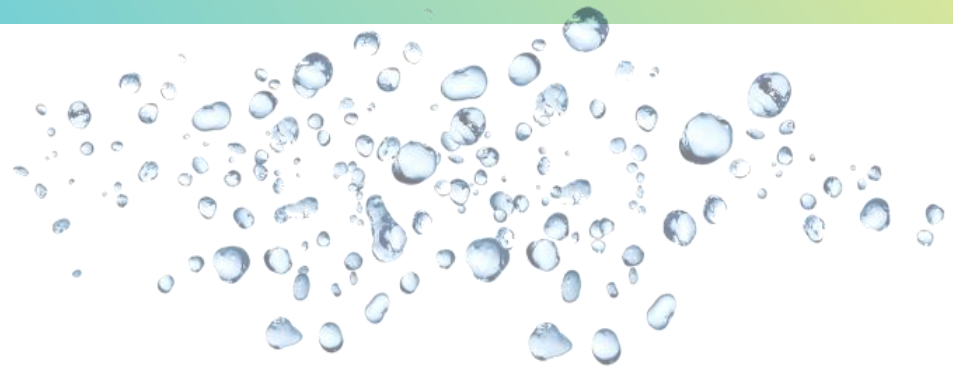
Arm 1-3 run in parallel, with safety rules determined independently, with the exception of any treatment-related death. See additional details for Arm 3, below.

American PIPAC Trial

- City of Hope, Mayo Jacksonville, Northwell



American PIPAC Trial



Inclusion Criteria

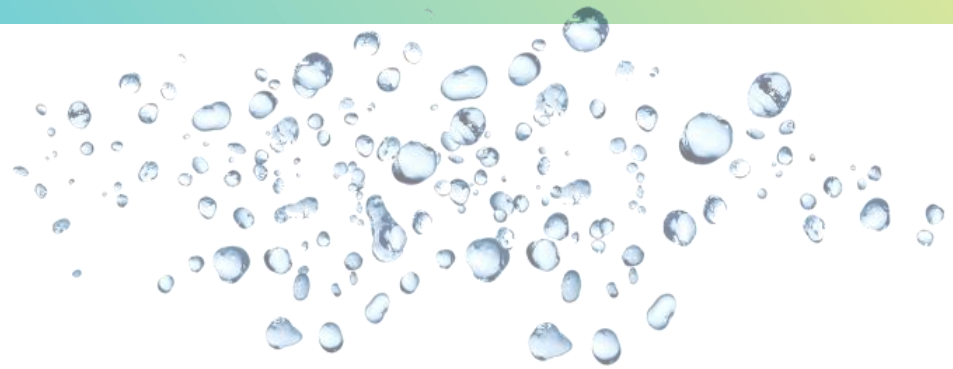
- Ability to obtain informed consent
- Age at least 18 years
- Histologically confirmed ovarian, uterine, gastric, appendiceal, colorectal with peritoneal metastasis
- ECOG at least 2
- No contraindications to laparoscopy
- Disease visible on EITHER cross-sectional imaging or laparoscopy

On laparoscopy their must be:

- Feasible access
- Room for aerosol
- No evidence of impending bowel obstruction
- No more than 5L ascites
- Unresectable disease/ not a candidate for CRS/ HIPEC

- **Diagnostic laparoscopy is key and should be performed prior to enrollment.**

American PIPAC Trial



Exclusion Criteria

- Gastric, colorectal, appendiceal: extraperitoneal disease

- Arm 1 (IP Doxorubicin/ cisplatin): Previous treatment w max cumulative dose anthracyclines
- Arm 2 (IP oxaliplatin): known DPD deficiency
- Arm 3 (IP Mitomycin C + IV FOLFIRI): Progression on FOLFIRI

- Bowel obstruction requiring NGT, venting PEG, TPN
- Platinum hypersensitivity or severe reaction to platinum
- Life expectancy less than 6 months
- Decompensated cirrhosis or portal vein thrombosis with ascites
- Uncontrolled intercurrent illness
- Pregnancy
- Major systemic infection

In Summary…

- Looking for patients with unresectable, but relatively low-volume peritoneal metastasis
- Peritoneal-only (peritoneal-dominant?)
- Even with “bidirectional” chemotherapy, some systemic therapy is compromised by giving PIPAC
- Histology is important, but probably less important than pattern of disease
- Bulky mesenteric and peritoneal metastasis unlikely to be sufficiently treated
- Must have space for safe laparoscopic access and for aerosol to circulate
- Patient must be fit for general anesthesia
- In the United States, generally must be a candidate for a trial

- Regimens, timing in disease trajectory, and timing with systemic therapy are areas of active investigation

Timing?????

Probably 2 ideal cohorts

1. Patients with moderate PCI that may be CRS/ HIPEC candidates

   ? Down-stage to CRS/ HIPEC

   ? Allow time to test pace of disease prior to CRS/ HIPEC

   -> Inutitive that this occurs in “bidirectional” fashion in conjunction with systemic chemotherapy

   -> Must determine ideal timing with systemic therapy

2. Palliative option for patients that are unlikely to be down-staged to CRS

   -> Can consider in absence of systemic chemotherapy

   -> Well tolerated, focus on quality of life

Ovarian Peritoneal Metastasis

Legend
HLE high level of evidence
Randomized trial planned

Upfront sitution	Systemic chemotherapy HLE	Always
	Cytoreductive surgery HIPEC (off-label) HLE	Resectable disease Good patient fitness
	PIPAC C/D (off-label) Neoadjuvant Setting[1] Combined IVand PIPAC Therapy[2]	Unresectable disease, under study conditions
Recurrence situation	Systemic chemotherapy HLE	Always (2nd line)
	PIPAC C/D (off-label)	Platin-resistant disease ≥ 3rd line situation Progress under chemotherapy Chemotherapy intolerance Therapy-refractory ascites Pleural effusion: combine PITAC
	Cytoreductive surgery HIPEC (off-label)	Limited disease DESKTOP II criteria

Legend
HLE high level of evidence
Randomized trial ongoing

Gastric Cancer Peritoneal Metastasis

Legend
HLE high level of evidence
Randomized trial planned

Prophylactic (high-risk)	Perioperative and Adjuvant chemotherapy HLE	Always indicated
	HIPEC (off-label)	Additional, under study conditions
	PIPAC C/D (off-label)	Additional, under study conditions
Upfront sitution	Systemic palliative chemotherapy HLE	Always indicated
	Cytoreductive surgery + HIPEC (off-label)	Limited disease (PCI ≤ 6) Good patient fitness PCI > 6: after downstaging only
	PIPAC C/D (off-label) Neoadjuvant Setting[1]	PCI > 6 Additional, under study conditions RCT
Palliative situation ≥ 2nd line situation	Systemic palliative chemotherapy	Indicated when good performance
	PIPAC C/D (off-label)	Therapy-refractory ascites Chemotherapy intolerance Progress under chemotherapy No pleural effusion RCT

Colorectal Peritoneal Metastasis

Legend
HLE high level of evidence
Phase II trial ongoing

Prophylactic (high-risk)	Adjuvant chemotherapy[HLE]	Always indicated
	HIPEC (which agent ?) (off-label)	Additional, under study conditions*
	PIPAC OX (off-label)	Additional, under study conditions
Upfront situation	Systemic palliative chemotherapy[HLE]	Always indicated
	Cytoreductive surgery[HLE] Additional HIPEC (which agent ?)# off-label	Limited disease (PCI < 15) Good patient fitness signet-ring histology- Caution B-raf Caution PCI ≥ 15: after downstaging only PCI 10-15
	PIPAC OX (off-label) Neoajuvant Setting[3] Concomittantly with systemic chemotherapy[2,4]	Additional, under study conditions
Recurrence/ ≥2nd line	Systemic palliative chemotherapy[HLE] PIPAC OX (off-label)	Always indicated Unresectable disease Therapy-refractory ascites Chemotherapy intolerance Progress under chemotherapy

Hepatobiliary-Pancreatic Peritoneal Metastasis

Legend
HLE high level of evidence
Randomized trial planned

Upfront sitution	Systemic palliative chemotherapy HLE	Always
	Cytoreductive surgery + HIPEC (off-label)	Limited disease Good patient fitness under study conditions
	PIPAC C/D (off-label)	Additional, under study conditions
Salvage situation	Systemic palliative chemotherapy (off-label)	Individual decision
	PIPAC C/D (off-label)	Therapy-refractory ascites Chemotherapy intolerance Progress under chemotherapy No massive disease No pleural effusion

Malignant Peritoneal Mesothelioma (MPM)

Legend
HLE high level of evidence
Randomized trial planned

Upfront sitution	Systemic palliative chemotherapy HLE	Always
	Cytoreductive surgery + HIPEC (off-label)	Limited disease Good patient fitness No sarcomatoid histology No pleural disease
	PIPAC C/D (off-label)	Additional, under study conditions, if unresectable disease RCT
Salvage situation	Systemic palliative chemotherapy (off-label)	Individual decision
	PIPAC C/D (off-label)	Therapy-refractory ascites Chemotherapy intolerance Progress under chemotherapy No massive disease Pleural effusion: combine with PITAC

Therapy of Isolated PM of Appendiceal Origin: Pseudomyxoma

Legend
HLE high level of evidence
Randomized trial planned

Upfront and salvage situation	Systemic palliative chemotherapy (off-label)	HAMN only Patient unfit for surgery Unresectable disease
	Cytoreductive surgery ± HIPEC (off-label)	LAMN or HAMN: Resectable disease Good patient fitness
	PIPAC C/D (off-label)	Unresectable disease Patient unfit for surgery

Appendiceal Adenocarcinoma Peritoneal Metastasis

Legend
HLE high level of evidence
Randomized trial ongoing

Prophylactic (high-risk)	Adjuvant chemotherapy (off-label)	In selected cases,
	(CRS) & HIPEC (off-label)	Additional, under study conditions
Upfront sitution	Systemic palliative chemotherapy (off-label)	Always
	Cytoreductive surgery ± HIPEC (off-label)	Good patient fitness Resectable disease Signet-ring histology ?
	PIPAC C/D (off-label)	Unresectable disease In addition to systemic Cx, individual decision
Salvage situation	Syst. palliative chemotherapy (off-label)	Indicated when good performance
	PIPAC C/D (off-label)	Unresectable disease Signet-ring histology Therapy-refractory ascites Chemotherapy intolerance Progress under chemotherapy No pleural effusion

PIPAC vs HIPEC

	Colorectal cancer		Gastric cancer		Ovarian cancer		Peritoneal mesothelioma		Biliary tract cancer		Appendiceal cancer	
	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC
High risk for peritoneal metastasis after primary tumour resection	USC	USC	USC	USC	–	–	–	–	?	?	–	–
Upfront or interval situation and resectable peritoneal metastasis	USC	PCI≤15	USC; PCI >6	USC; PCI ≤6	USC	+	USC	+	USC	USC	–	+
Synchronous or recurrent peritoneal metastasis as sole metastatic site and unresectable disease, or patient not eligible for extensive cytoreductive surgery or HIPEC and with 2nd or 3rd line of systemic chemotherapy	+	–	+	–	+	–	+	–	+	–	+	–
Refractory ascites	+	–	+	–	+	+/–	+	–	+	–	+	–
Systemic chemotherapy intolerance	+	–	+	–	+	–	+	–	+	–	+	–
Unfavourable histology	+*§	–*	+*§	–*	+†§	+†	+‡§	+/–‡	+§	–	+*§	–*

PIPAC=pressurised intraperitoneal aerosol chemotherapy. HIPEC=hyperthermic intraperitoneal chemotherapy. USC=under study condition. PCI=peritoneal cancer index. *Signet ring histology. †Clear cell carcinoma, undifferentiated ovarian cancer. ‡Sarcomatoid or biphasic peritoneal mesothelioma. §Unfavourable histology is an additional argument to introduce PIPAC earlier in the treatment strategy.

***Table 3*: Potential indications for the use of PIPAC and HIPEC**

Alyami , Hubner et al Lancet oncol 2019

PIPAC: Indications: Conclusion

- PIPAC is a promising palliative therapy in isolated PM when no evidence-based treatment is available.
- Possible indications:
  - PIPAC with cisplatin/ doxorubicin (PIPAC C/D):
    - ≥ 3rd line in ovarian cancer
    - ≥ 2nd line in gastric cancer
    - ≥ 2nd line situation in HBP cancer
    - recurrence in malignant peritoneal mesothelioma
    - intolerance/ side-effects of systemic chemotherapy
    - Deterioration of QOL on chemotherapy
    - ascites control in the platin-resistant situation
  - PIPAC with oxaliplatin (PIPAC OX):
    - salvage situation in colorectal cancer & other Peritoneal surface malignancy
- First randomized trials evaluating the effect of PIPAC C/D in isolated PM have been initiated.

1.Alyami M et al., EJSO 2019
2.Ploug et al. BMC Cancer (2020.
3.Girshally et al. WJSO (2016)
4.Alyami , Hubner et al Lancet oncol 2019

THANK YOU

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