PIPAC – CLINICAL EVIDENCE

PIPAC in Ovarian Cancer

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Disclosures

- I have no 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.

The off-label or investigational use of Cisplatin, Doxorubicin, Nab-Paclitaxel 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:

- Various international studies completed and ongoing, which have enrolled Asian, European, Hispanic patients.

PIPAC in gynecologic cancers

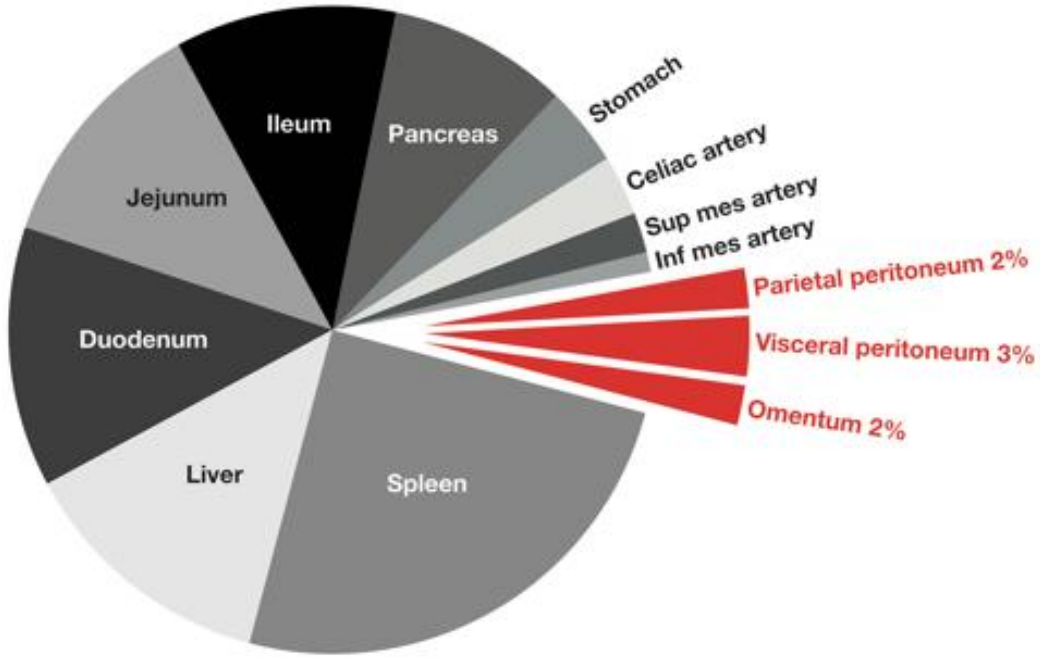
Review of Ovarian cancer PIPAC trials

Review of drug selection and dosages

Potential indications of PIPAC in ovarian cancer

Ovarian cancer as a peritoneal surface malignancy

- The peritoneal cavity is the principal site of disease in ovarian cancer
- Peritoneal carcinomatosis
- Malignant gastrointestinal obstruction
- Urinary obstruction
- Malignant ascites



Poor vascular supply to peritoneum

Splanchnic flow represents about 25% of cardiac output.
Peritoneal blood flow represents only 1-2% of cardiac output

Intraperitoneal chemotherapy in ovarian cancer

Pharmacokinetic Rationale for Peritoneal Drug Administration in the Treatment of Ovarian Cancer [1]

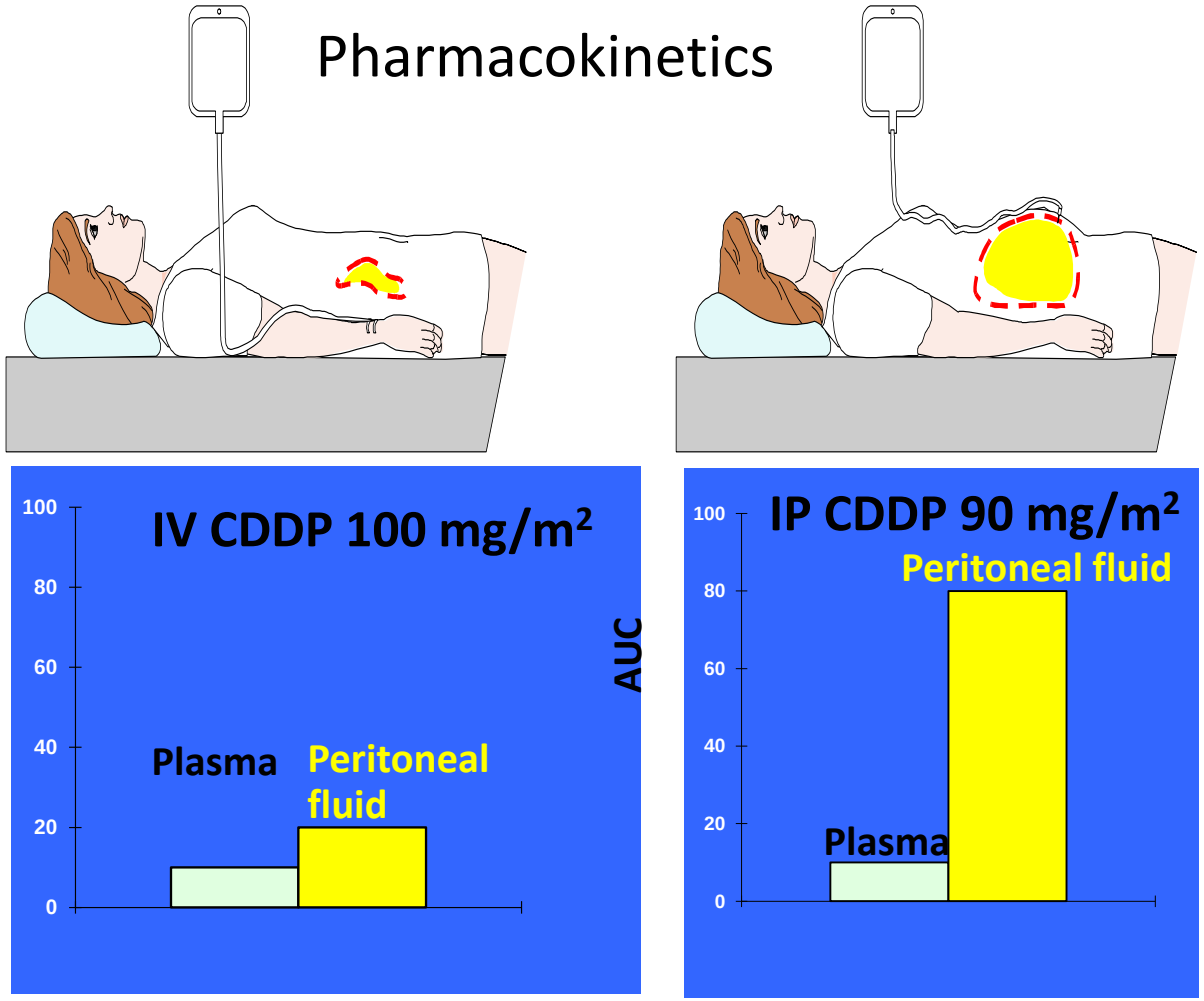
Robert L. Dedrick,[2,*] Charles E. Myers,[3] Peter M. Bungay,[2] and Vincent T. DeVita, Jr [3,4]

SUMMARY

Evidence from the peritoneal dialysis literature suggests that the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than plasma clearance. Pharmacokinetic calculations indicate that such drugs administered ip in large volumes are expected to maintain a significantly greater concentration in the peritoneal space than in the plasma. This concentration difference offers a potentially exploitable biochemical advantage in the treatment of patients with presumed microscopic residual ovarian cancer confined to the peritoneal cavity.

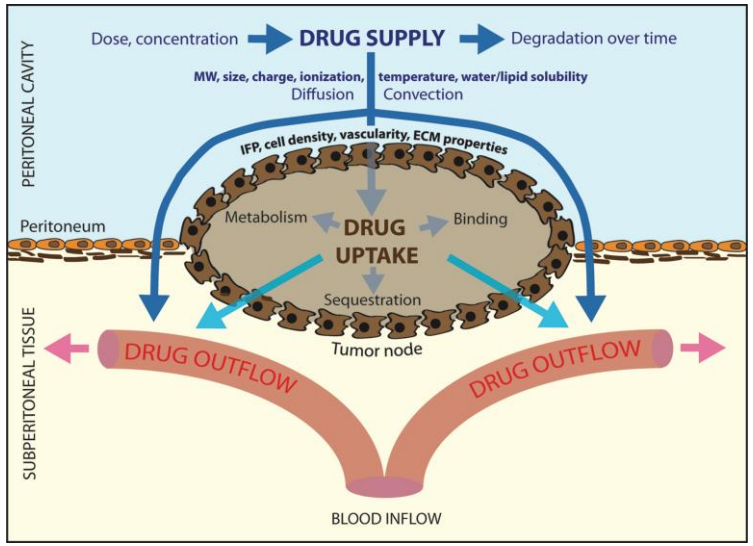
IP chemotherapy increases the dose intensity to the tumor

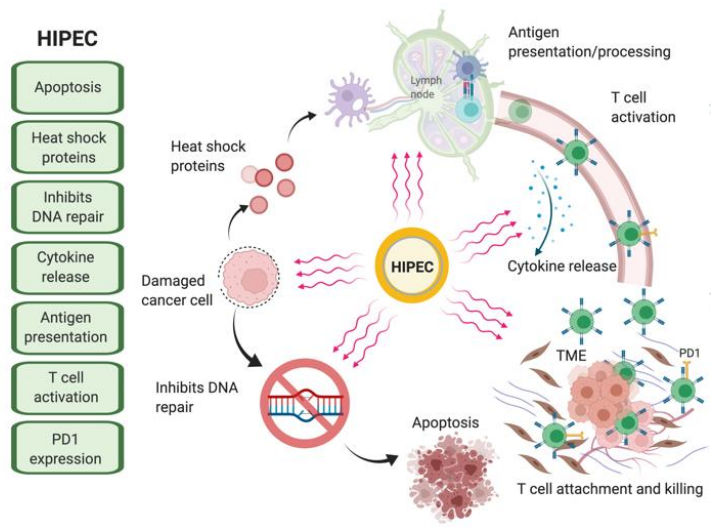
Pharmacokinetics



High peritoneal to plasma ratios for peak concentrations

Therapy related	Drug related	Tumour tissue related
Dose	Molecular weight	Permeability
Temperature	Ionic charge	Vascularity
Carrier fluid	Membrane binding	Interstitial fluid pressure (IFP)
Volume of carrier fluid	Solubility	Cell density
Intra-abdominal pressure	Diffusivity	Extracellular matrix composition
Vaso-active agents		
Surfactant use		
Duration		



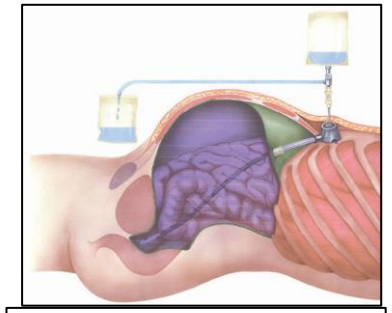


Optimizing Intraperitoneal chemotherapy delivery

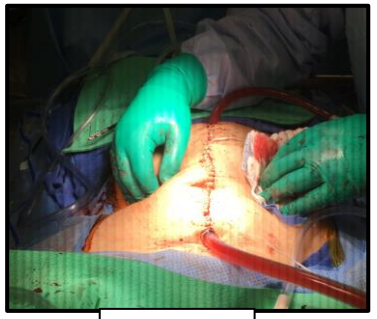
W. Ceelen, Pleura Perit, 2017

Dellinger, Gyn Onc, 2022

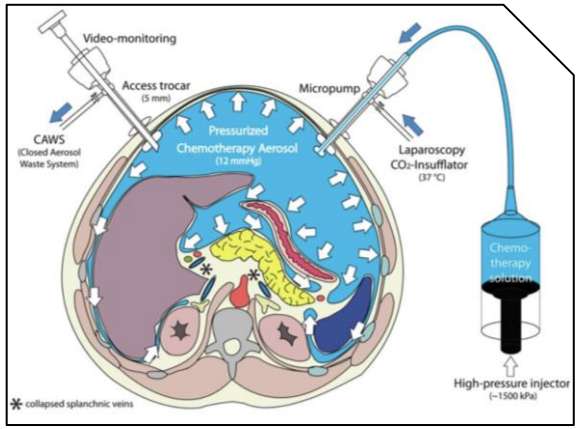
Evolution of Intraperitoneal Chemotherapy in Ovarian Cancer



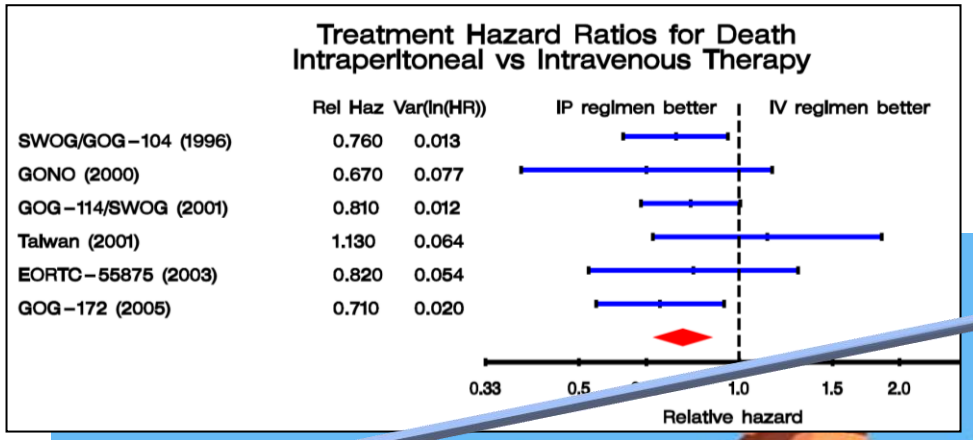
IP Chemotherapy

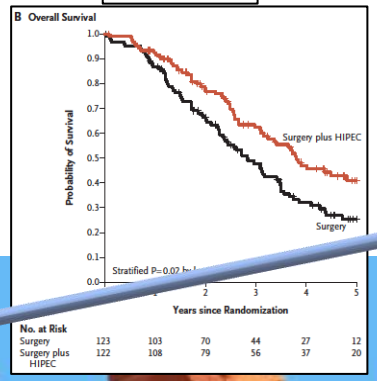


HIPEC

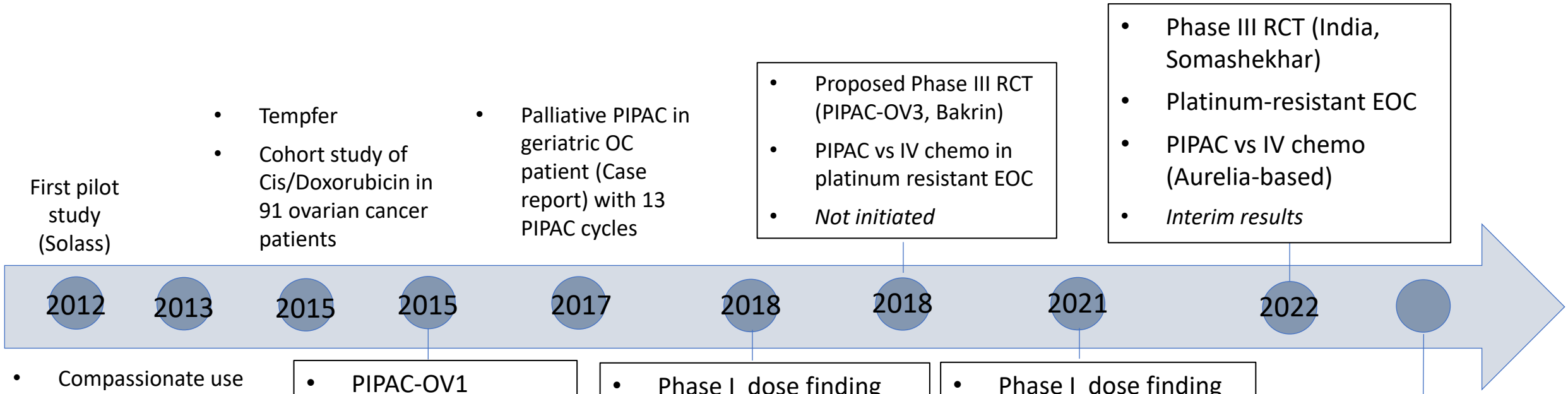


PIPAC





PIPAC studies in ovarian cancer



2012 — First pilot study (Solass)

- Compassionate use
- Cis/Dox in 33 platinum resistant recurrent ovarian cancer patients (Tempfer)

2013

- Tempfer
- Cohort study of Cis/Doxorubicin in 91 ovarian cancer patients

2015

- Palliative PIPAC in geriatric OC patient (Case report) with 13 PIPAC cycles

2015

- PIPAC-OV1 (Tempfer)
- Phase II study
- Platinum resistant ovarian cancer
- N=64

2017

2018

- Phase I dose finding study (Tempfer)
- Recurrent ovarian cancer (n=15)
- Cisplatin 7.5 mg/m2
- Doxorubicin 2.1 mg/m2

2018

- Proposed Phase III RCT (PIPAC-OV3, Bakrin)
- PIPAC vs IV chemo in platinum resistant EOC
- *Not initiated*

2021

- Phase I dose finding study (Robella)
- EOC (n=2), CRC, GC
- Cisplatin 30 mg/m2
- Doxorubicin 6 mg/m2

2022

- Phase III RCT (India, Somashekhar)
- Platinum-resistant EOC
- PIPAC vs IV chemo (Aurelia-based)
- *Interim results*

- PARROT (Italy)
- Phase I-II, Single arm, n=50
- Platinum-resistant EOC
- *Ongoing, NCT02735928*

- PIPAC-OVA (France)
- Phase I, n=15
- First-line setting Neoadjuvant PIPAC
- *Ongoing NCT04811703*

Solass et al. *Surg Endosc.* 2012;26:1849–1855.
Tempfer et al, Gyn Onc 2013
Tempfer et al, Anticancer Research 35, 2015
Tempfer et al , BMC Cancer, 2017

Robella et al, Cancers, 2021
Bakrin et al, Pleura Perit 2018
Somashekhar et al, ASCO 2022
Somashekhar Pleur Perit 2018

Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study

C.B. Tempfer et al. / Gynecologic Oncology 137 (2015) 223–228

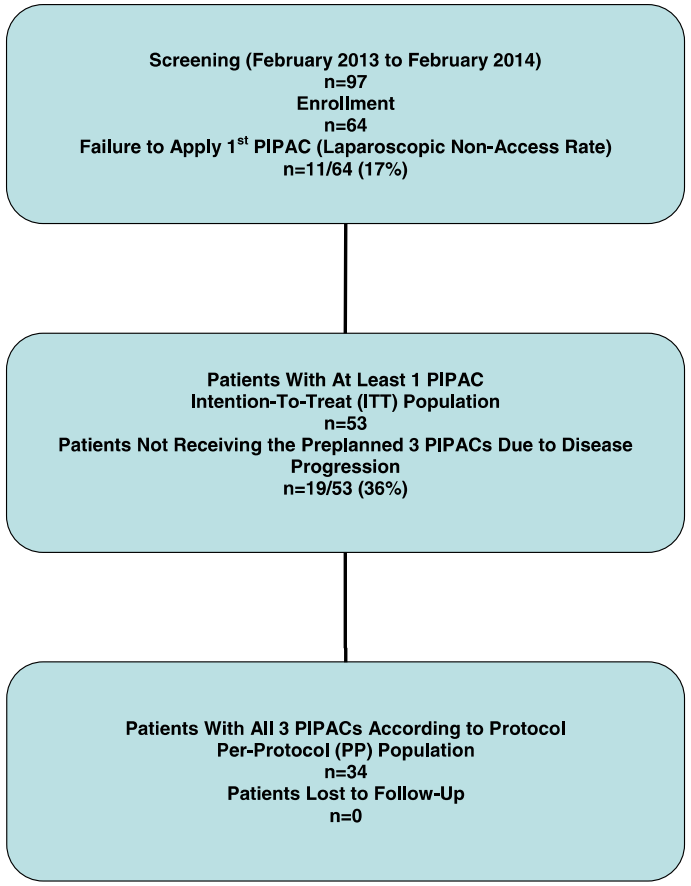
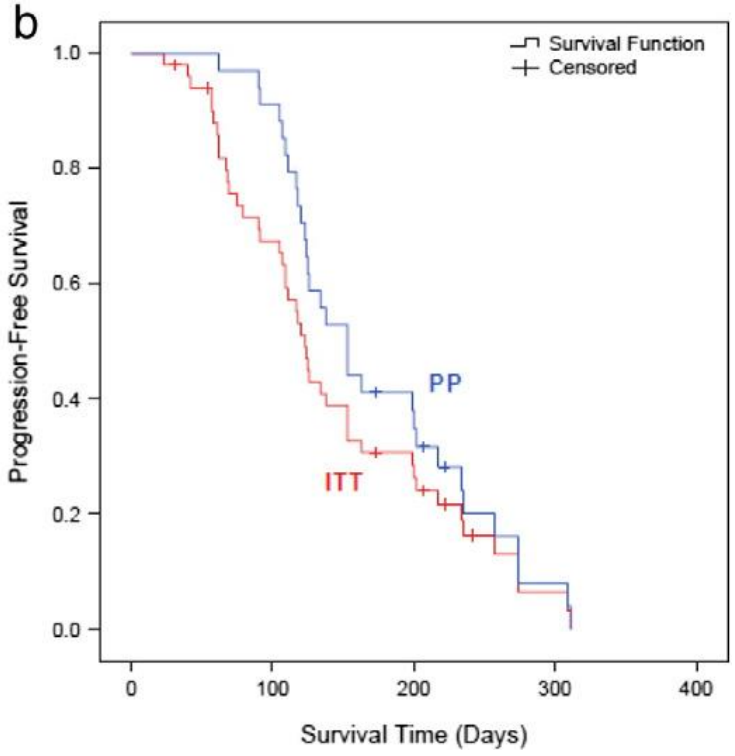


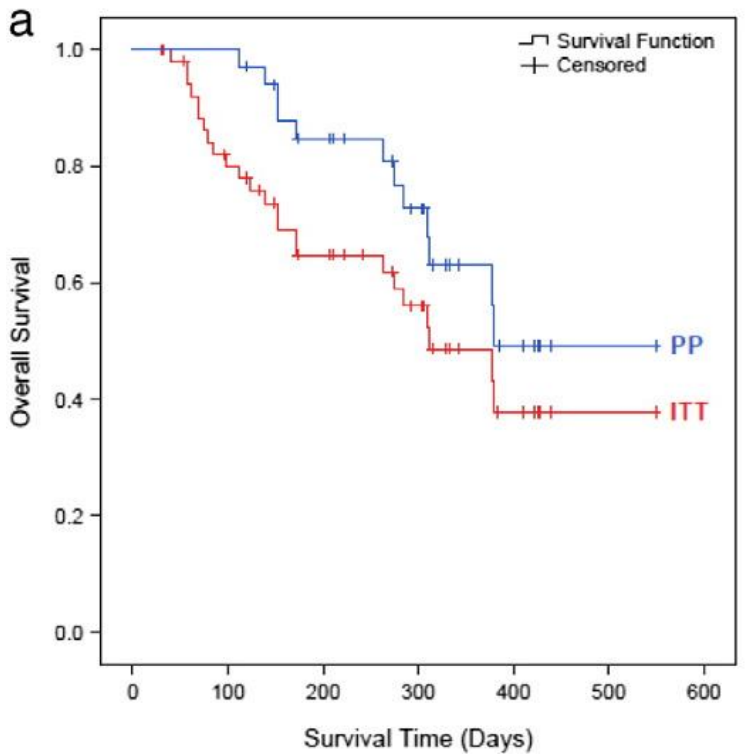
Fig. 1. Flow diagram of the patients' flow through the study.

Patient characteristics of 53 women with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Patient characteristic	Variable
Number of patients	53
Age (years; mean, ± SD)	62 (± 10)
ECOG performance score	
0	32 (60%)
1	20 (38%)
2	0
3	1 (2%)
Previous chemotherapy regimens (median, range)	3 (2, 8)
Previous radiation	None
Presence of pleural effusion	5/53 (9%)
Presence of ascites	22/53 (42%)
Ascites volume (ml; median, range)	483 (0, 4500)
PCI (mean, ± SD)	16.3 (± 9.9)
Serum CA 125 (U/ml; mean, ± SD)	1558 (± 3964)

PIPAC-OV1 results



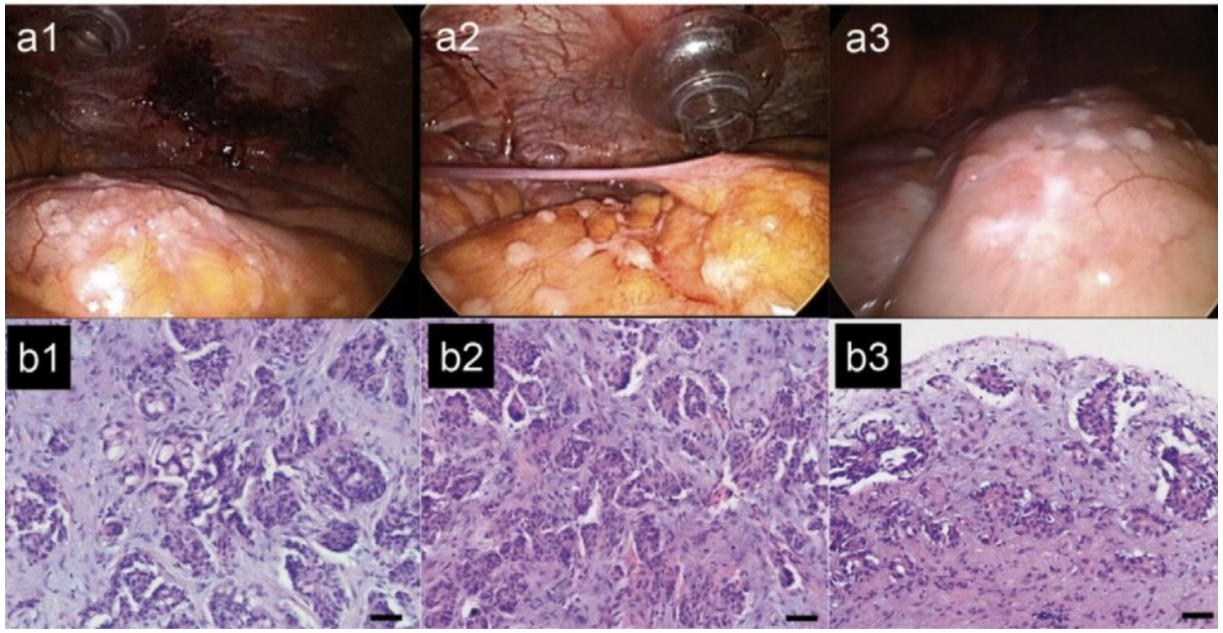


- PP – 3 cycles PIPAC
- ITT – 1 cycle PIPAC
- PFS –
  - PP – 5.8 months
  - ITT – 4.8 mo
- OS –
  - PP – 13.5 mo
  - ITT - 11.0 mo

AURELIA – PFS 6.7 mo w/ Bev
OS 16.6 mo

Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study

C.B. Tempfer et al. / Gynecologic Oncology 137 (2015) 223–228



Adverse events – PIPAC-OV1

Acute and chronic adverse events in 53 patients undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Adverse event	Grade 1	Grade 2	Grade 3
Trocar hernia	0	0	2 (4%)
Abdominal pain	53/53 (100%)	0	2 (4%)
Bowel obstruction	0	0	1 (2%)
Hemorrhage	0	0	1 (2%)
Intraoperative bleeding	0	0	1 (2%)
Cystitis	0	1 (2%)	0
Urosepsis	0	0	1 (2%)
Cardiac	6 (11%)	0	0
Neurological	1 (2%)	0	0
Renal	1 (2%)	1 (2%)	0
Pulmonary	0	5 (9%)	0
Inflammatory[a]	10 (19%)	25 (47%)	0

[a] Increase of C-reactive protein.

53 patients
- 62% clinical benefit rate with PIPAC (SD after 3 cycles or a PR)
- moderate or strong tumor regression on histology observed in 76% of patients who underwent 3 PIPAC cycles
- 3 patients had a partial response (5.7%), while the rest had a stable response.

Dose finding studies in ovarian cancer PIPAC

A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis

Clemens B. Tempfer [a], Urs Giger-Pabst [b], Veronika Seebacher [c], Miriam Petersen [d], Askin Dogan [a], Günther A. Rezniczek [a,*]

N=15 EOC patients

Grade 1 or higher adverse events at least "possibly" related to PIPAC treatment.

Adverse event	Dose level/adverse event grade								
	Cisplatin 7.5 mg/m² Doxorubicin 1.5 mg/m² Patients: n = 3 PIPACs: n = 9			Cisplatin 9.0 mg/m² Doxorubicin 1.8 mg/m² Patients: n = 7 PIPACs: n = 13			Cisplatin 10.5 mg/m² Doxorubicin 2.1 mg/m² Patients: n = 5 PIPACs: n = 12		
	1	2	3	1	2	3	1	2	3
Colon perforation			1						
Pain	3	3		4			7	1	
Vomiting		1		3					
Dyspnea		1							
Fatigue	4			7			8		
Appetite loss	1			2			3		
Nausea	3			6	1				
Sleep disorder	1			5			2		
Abdominal bulge	1								
Shivering	1								
Infection					1		1		
Obstipation				2					
Fever				2					
Night sweating				2					
Diarrhea				2	1		2		
Dizziness							2		
Visual problems				1					
Foot numbness				1					
Total	14	5	1	37	3	0	25	1	0

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]

N=13, with 2 EOC patients

Table 2. Adverse events (CTCAE 4.03) according to dose level of Cisplatin and Doxorubicin.

Adverse Event	CDDP 15 mg/m² + DXR 3 mg/m²			CDDP 30 mg/m² + DXR 6 mg/m²			CDDP 50 mg/m² + DXR 10 mg/m²
	Pt 1	Pt 2	Pt 3	Pt 1	Pt 2	Pt 3	Pt 1
Pain					3	2	
Nausea						3	1
Emesis						3	
Ileus						3	
Anemia						3	
Hypokalemia						1	

Italian Phase II PIPAC study in Ovarian Cancer

PARROT (NCT02735928): PIPAC Applied to platinum-Resistance Recurrence of Ovarian Tumor

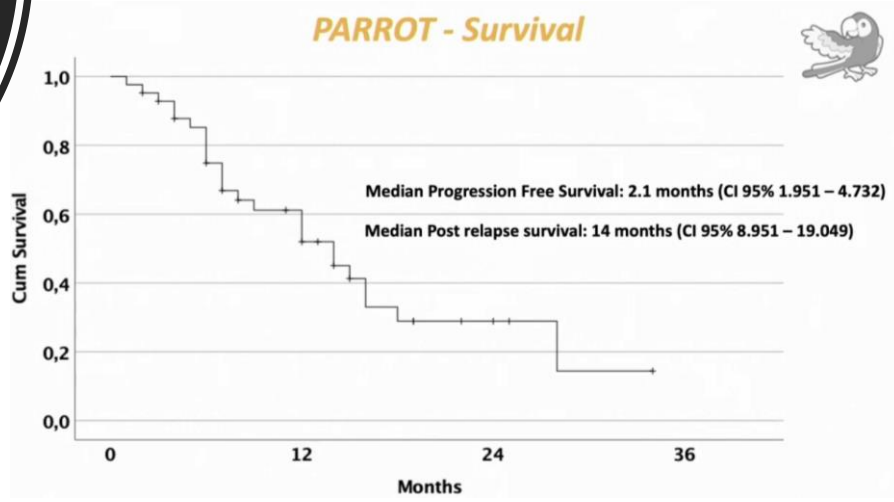
Eligibility
Platinum-resistance recurrent epithelial ovarian cancer "with less than 2 previous regimens of chemotherapy"

Primary end-point
To evaluate the clinical benefit rate (CBR) of PIPAC

Study Design
Open label, non-randomized, single-arm, repeated single dose study to explore the efficacy, safety, and pharmakokinetics of cisplatin and doxorubicin when given as a PIPAC to resistant AEOC

Trial Group: *50 patients*

Investigational product, dosage, and mode of administration
Cisplatin 10 mg/m2 in 150 ml NaCl 0,9% q6 weeks, applied intraperitoneally as pressurized aerosol (PIPAC) followed by doxorubicin at a dose of 2.5 mg/m2 body surface in a 50 ml NaCl 0.9% solution will be applied via a nebulizer immediately

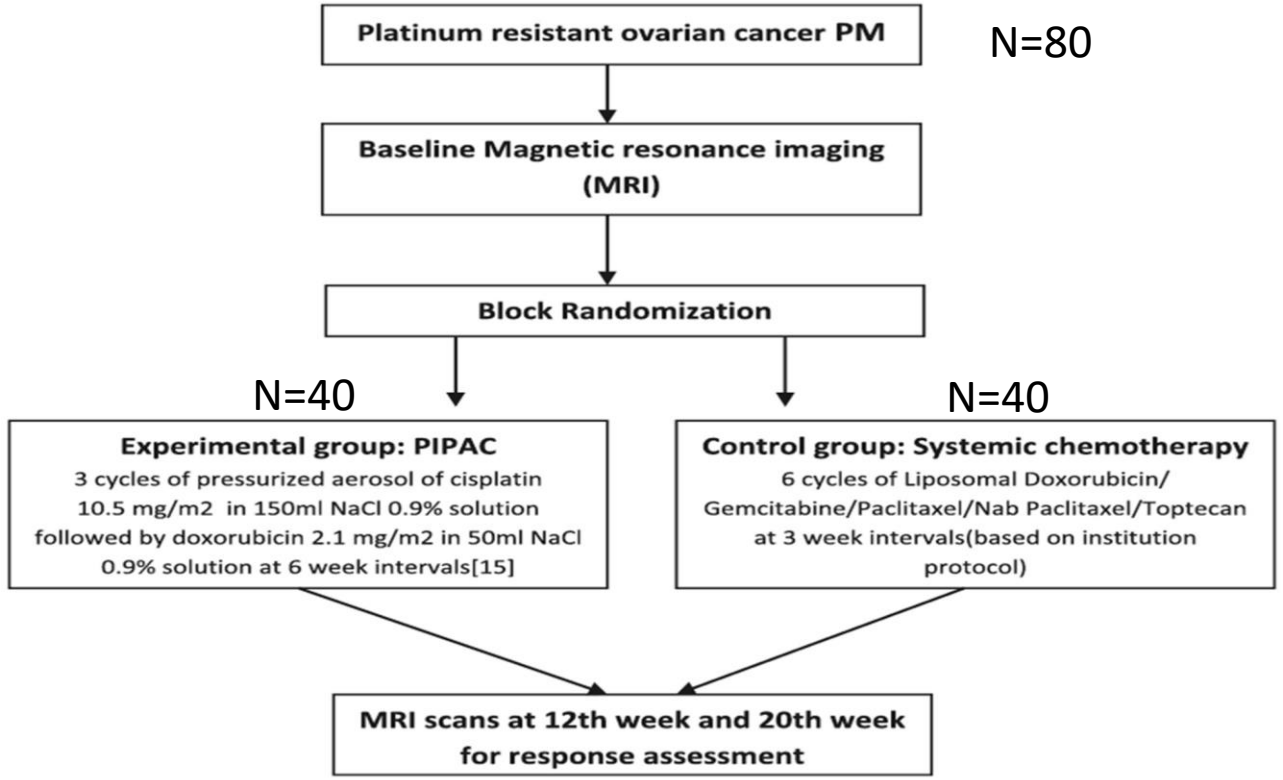


Variable	N (%)
All cases	43
PIPAC procedures	98
Age (median) (range)	56 (34-70)
BMI	23 (18-45)
PS – ECOG (median)(range)	1 (0-2)
Previous CHT regimen (Inclusion criteria) 1 2	 14 (35.0) 26 (65.0)
Fagotti's score (median) (range)	10 (8-12)
Ascites > 1000cc	8 (20.0)
Serum CA 125 (median) (range)	189 (16-6909)
Feasibility rate	*40/43 (93.0)*
PIPAC cycles (median)(range)	3 (1-9)

All cases	40
Hospital Stay (median)(range)	2 (2-10)
Overall Benefit (%)	31/38 (81.5)
CTCAE > 2 (%)	2/38 (5.2)
Mortality (30 days)	0
Pathological response (evaluable cases) Partial response Stable disease	31 (56.7) 10 (32.3) 21 (67.7)
Overall Survival (months)(median)(range)	14 (8-19)

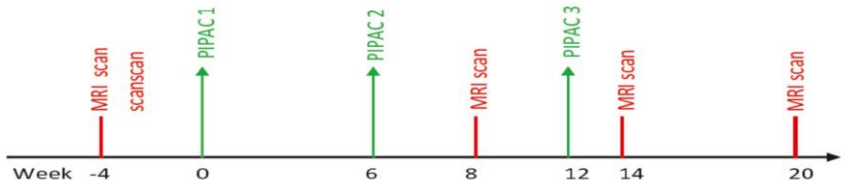
PIPAC randomized trial in platinum-resistant ovarian cancer

PIPAC compared to AURELIA regimen

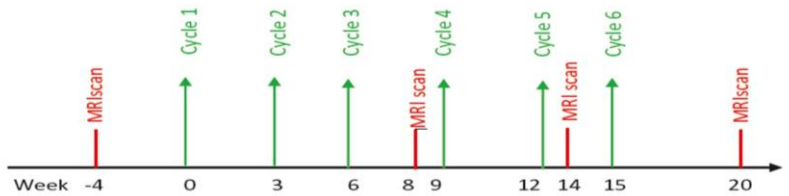


	PIPAC N=40	IV Chemo (N=40)	P – Value
Age (years)	55.5 ± 9.4	54.3± 6.7	0.128
ECOG			
0	08	08	
1	20	24	0.423
2	12	08	
Previous Surgery			
1	21	22	0.231
2	19	18	
Systemic Chemotherapy			
2nd line	24	21	
>2nd line	16	19	0.746
Serum CA 125 IU/ml	220± 15.4	235± 12.7	0.230
PCI	23.5± 8.7	18.4± 7.5	0.460
No of cycles	3 PIPAC - 30 2 PIPAC - 05 1 PIPAC - 05	6 CYCLES - 25 4 CYCLES - 10 3 CYCLES - 05	___

ALGORITH FOR PIPAC



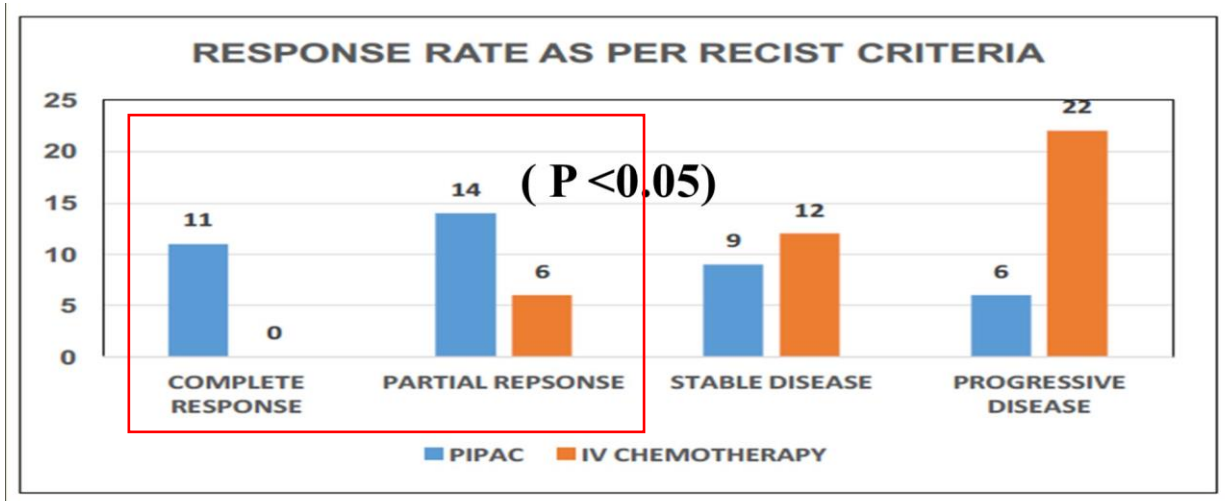
ALGORITH FOR IV CHEMOTHERAPHY



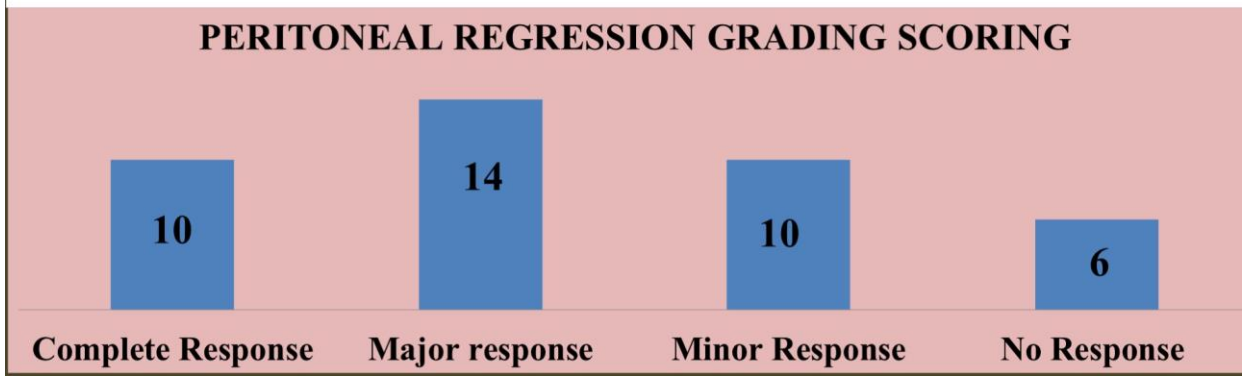
Somashekar SP et al ASCO 2022 Poster

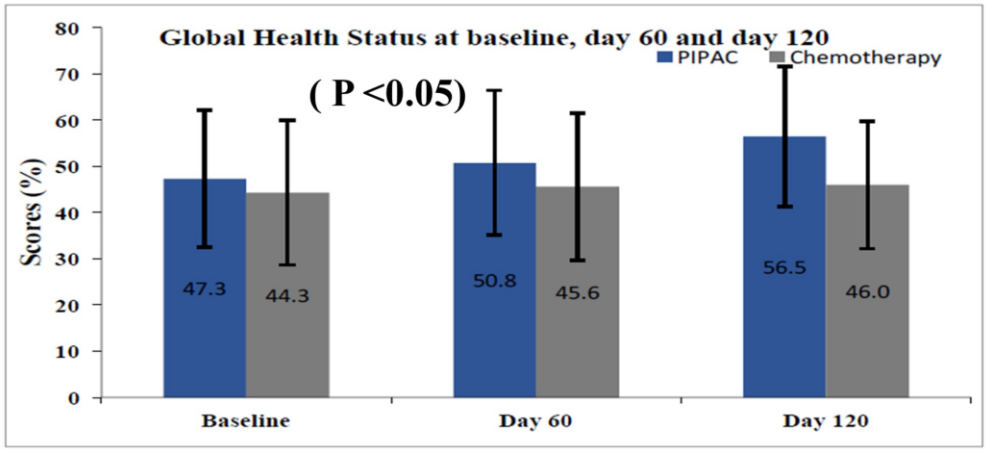
PIPAC randomized trialin platinum-resistant ovarian cancer

PIPAC compared to AURELIA regimen



Complications	(G1- G2)		(G3)	
	PIPAC	IV	PIPAC	IV
Nausea/Vomiting	9	9	0	3
Pain	9	13	0	2
SSI	3	0	0	0
Cytopenia	7	6	1(G3)	5
Mucositis	0	12	0	5
Neuropathy	0	9	0	2
Intra-operative Bleeding	0	0	1 (G3)	0
Bowel Perforation	0	0	2(G3)	0
Port Site Metastasis	0	0	1(G3)	0

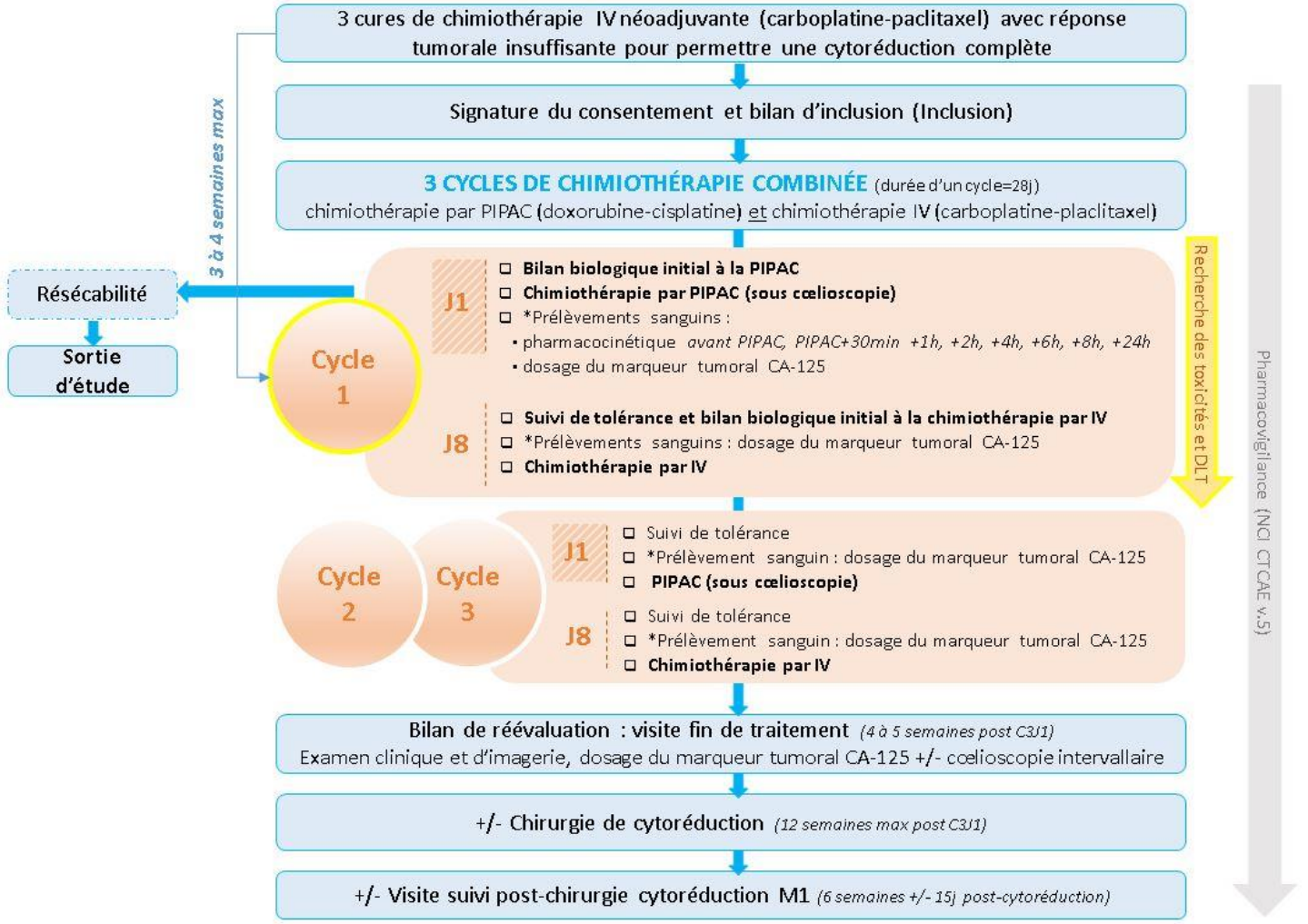




Somashekar SP et al ASCO 2022 Poster

PIPACOVA - Safety of PIPAC in combination with systemic chemotherapy in first-line setting

- Phase I dose escalation evaluating the addition of PIPAC (cis/dox) to systemic chemotherapy, for RP2D
- Neoadjuvant chemo x 3 cycles
- Diagnostic laparoscopy
  - Surgically resectable → interval CRS
  - Unresectable → PIPAC
- D1 =PIPAC (cisplatin/doxorubicin)
- D8 = IV carbo/taxol
- Dose escalation
  - Cisplatin 10.5 → 31.5 mg/m2
  - Doxorubicin 2.1 → 6.3 mg/m2
- Hospices Civils de Lyon | N=15 | Recruiting
- ClinicalTrials.gov Identifier: NCT04811703



Frankinet, Bakrin, Benoit, CHU Lyon (protocol courtesy of N Bakrin)

Nab-paclitaxel PIPAC in ovarian cancer

Phase I study of intraperitoneal aerosolized nanoparticle albumin based paclitaxel (NAB-PTX) for unresectable peritoneal metastases

Wim Ceelen,[a,b,c,1] Louis Sandra,[d,1] Leen Van de Sande,[c,1] Martin Graversen,[e] Michael Bau Mortensen,[e] An Vermeulen,[d] Elke Gasthuys,[d] Dries Reynders,[f] Sarah Cosyns,[c] Anne Hoorens,[g] and Wouter Willaert [a,c]*

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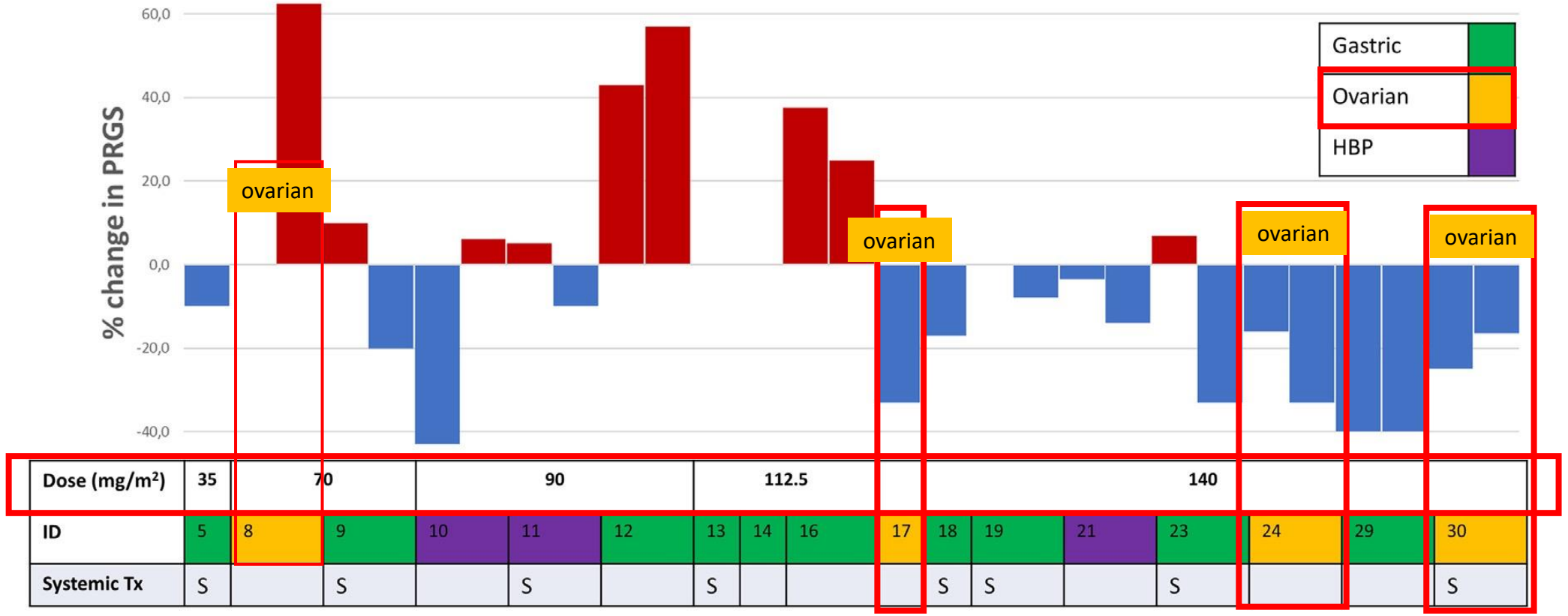


Phase I study of intraperitoneal aerosolized nanoparticle albumin based paclitaxel (NAB-PTX) for unresectable peritoneal metastases

Adverse event	35 mg/m² (n=2)		70 mg/m² (n=2)		90 mg/m² (n=3)		112.5 mg/m² (n=3)		140 mg
	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2
Hematological toxicity									
Thrombopenia	0	1	0	1	1	1	2	0	3
Leucopenia	0	0	0	1	0	1	1	0	1
Neutropenia	0	0	0	1	0	1	1	0	4
Anemia	0	1	0	2	0	1	1	1	7
Liver toxicity									
Elevated AST	2	0	0	3	0	2	2	0	4
Elevated ALT	2	0	0	3	0	2	2	0	3
Elevated ALP	2	0	0	1	0	2	2	0	4
Elevated bilirubin	0	0	0	1	0	0	0	0	2
Elevated GGT	1	0	0	0	0	2	2	0	6
Glucose and electrolyte disorders									
Adverse event	**35 mg/m² (n=2)**		**70 mg/m² (n=2)**		**90 mg/m² (n=3)**		**112.5 mg/m² (n=3)**		**140 mg**
	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2	grade 3	grade ≤2
Infectious complications									
Bacterial pneumonia	0	0	0	0	0	0	1	0	0
Skin infection (cellulitis)	0	0	0	0	0	0	0	0	0
Skin infection (abscess)	0	0	0	0	0	0	1	0	0

Nab-paclitaxel PIPAC – Toxicities

Toxicities at highest dose levels:
anemia, liver toxicities, wound infections

Clinical safety of PIPAC in ovarian cancer

	Main primary	Number of patients	Number of PIPAC	Non-access	≥2 PIPAC	Surgical complications from first PIPAC	Adverse events (CTCAE 4.0)		
							Grade 3	Grade 4	Grade 5
Prospective									
PIPAC OV-1[47]	Ovarian	64	130	11/64 (17%)	43/53 (81%)	4/53 (8%)	8/53 (15%)	0/53	0/53
Retrospective									
Tempfer and colleagues[50]	Ovarian	21	34	3/21 (14%)	8/18 (44%)	3/18 (17%)	3/18 (17%)	2/18 (11%)	0/18
Tempfer and colleagues[51]	Ovarian	99	252	17/99 (17%)	50/82 (61%)	5/82 (6%)*	17/82 (21%)	3/82 (37%)	0/82

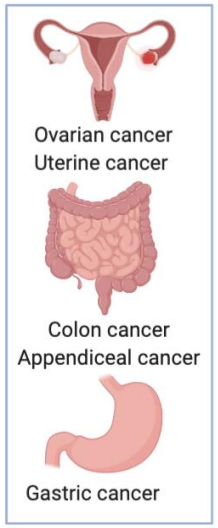
Alyami et al, Lancet Oncology

Drug dosages in Ovarian Cancer PIPAC

	Drug	Evidence	Publication	Multimodal therapy?
Recommended dose	Cisplatin 10.5mg/m2 Doxorubicin 2.1 mg/m2	Phase I dose escalation study in EOC (3+3) Three dose levels of Cis/doxo: 7.5/1.5 9.0/1.8 10.5/2.1	Tempfer et al, Gyn Onc 2015	No
Alternative	Cisplatin 30mg/m2 Doxorubicin 6 mg/m2	Phase I dose escalation (model-based) in mixed cancers (EOC, CRC, GC) Three dose levels of cis/doxo: 15/3 30/6 50/10	Robella et al, Cancers, 2021	Yes
Novel	Nab-Paclitaxel 140mg/m2 (112.5 mg/m2)	Phase I dose escalation in mixed cancers (n=4 EOC)	W. Ceelen, Ebiomedicine, 2022	Yes

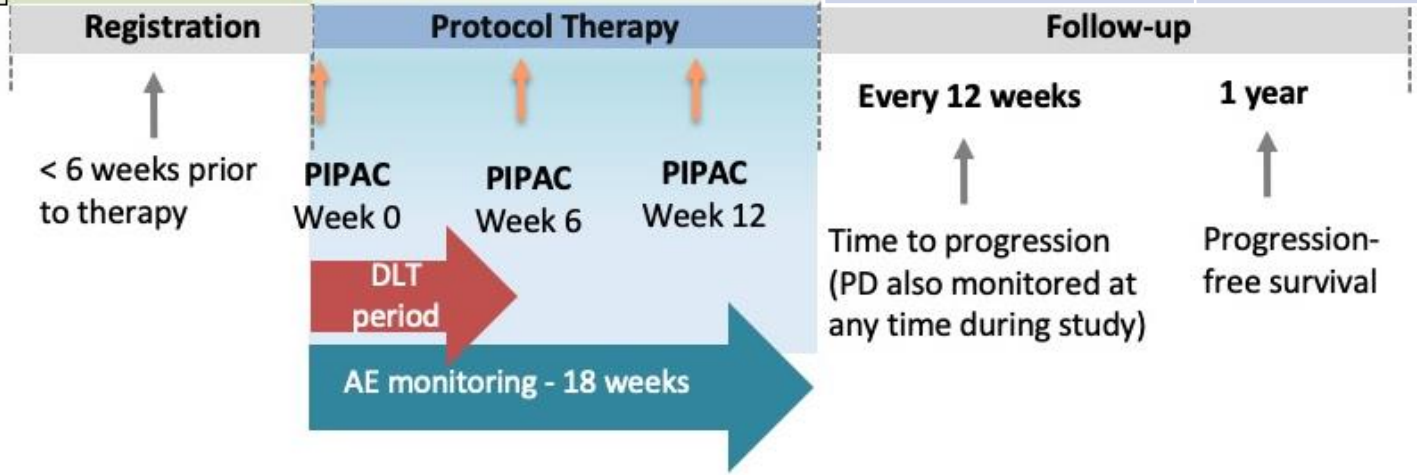
U.S. PIPAC Phase I Clinical trial: *NCT04329494*

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*

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		Yes (FOLFIRI)



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Northwell Health

MAYO CLINIC

Raoof et al, Ann Surg Onc, 2022

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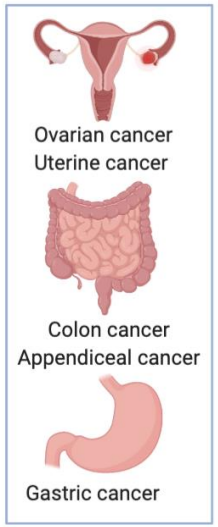


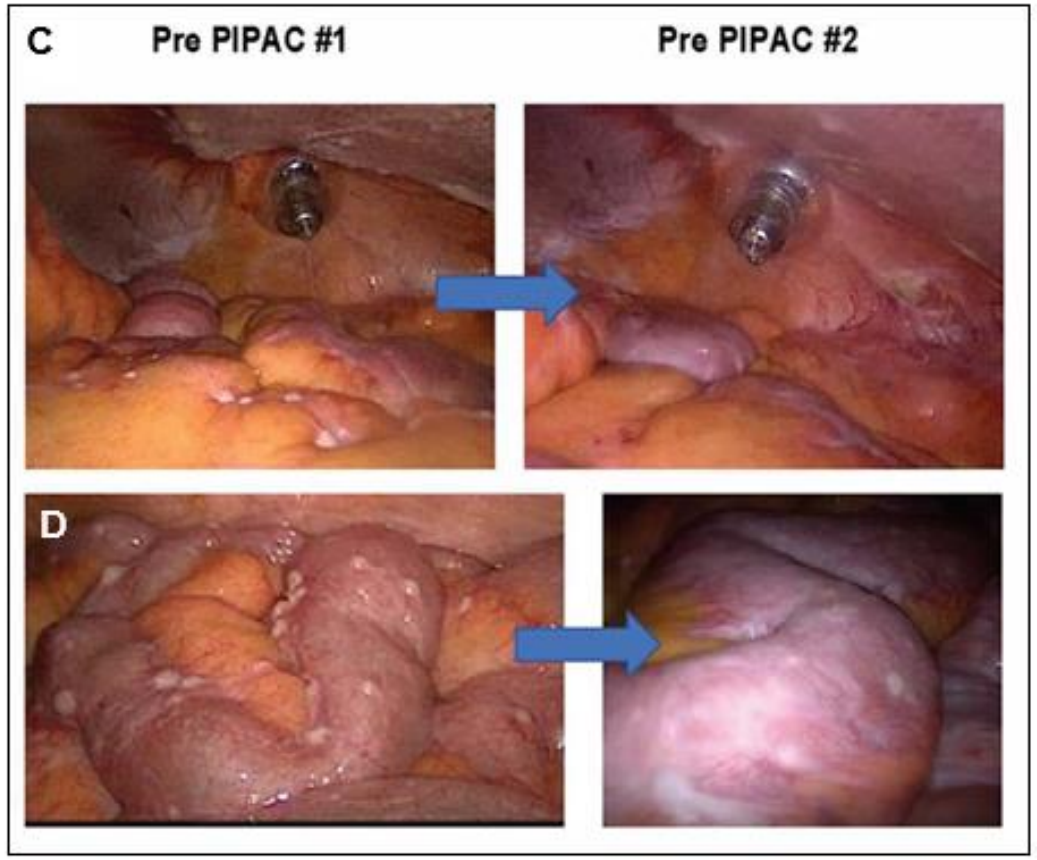
			Accrual to date	Safety	PIPAC completion rate (≥2 PIPACs)
Arm 1	Ovarian cancer Uterine cancer Gastric cancer	*Cisplatin 10.5 mg/m² + Doxorubicin 2.1 mg/m² IP q6weeks*	N=9 7 ovarian cancer 1 uterine caner 1 gastric cancer	No DLTs No Grade ≥3 AEs	63%
Arm 2	Colorectal cancer Appendiceal cancer	*Oxaliplatin 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)

City of Hope · Northwell Health · MAYO CLINIC

Raoof et al, Ann Surg Onc, 2022

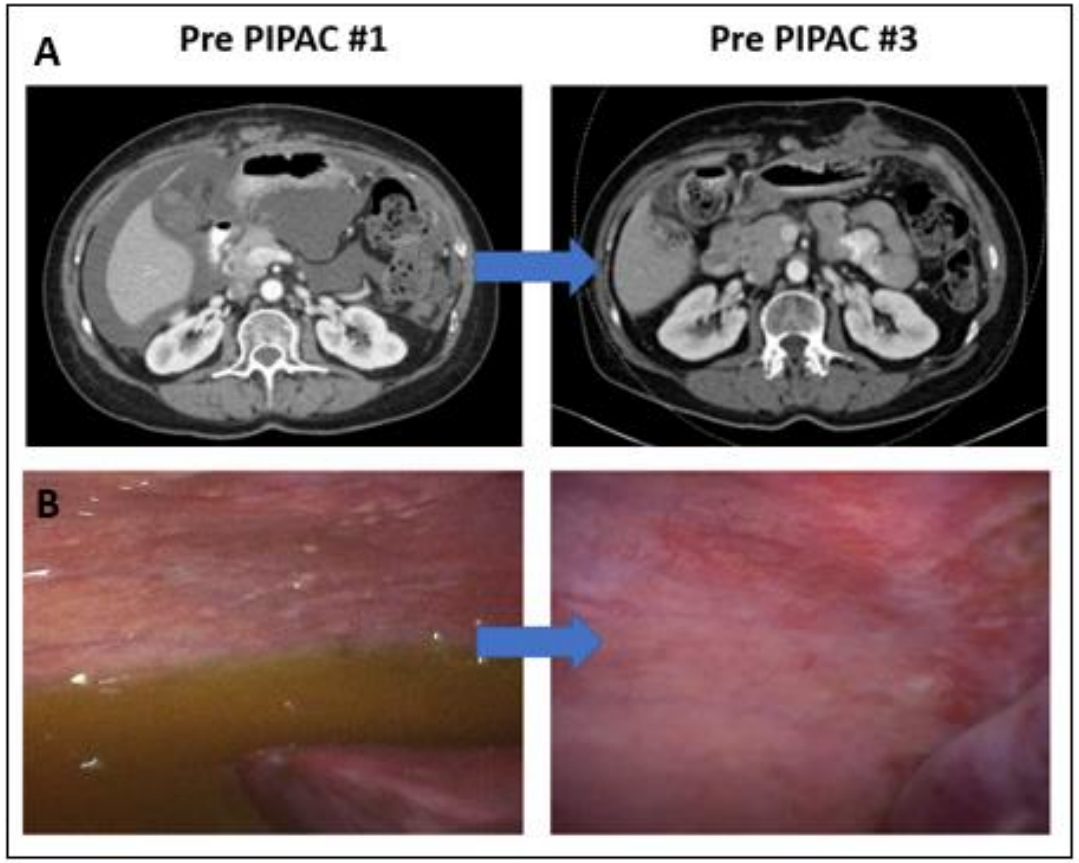
PIPAC in Low Grade Serous (LGS) Ovarian cancer patients

NCT04329494



68 yo F with Stage IV LGS metastatic to lung and liver, heavily pretreated with 10 prior lines

- Improved Peritoneal carcinomatosis index (PCI) 20 → PCI 14



59 yo F with Stage IIIC LGS, heavily pretreated with 5 prior lines.

- CA125 = 367 → 32
- Peritoneal tumor regression by RECIST
- Resolution of Ascites

Dellinger et al, SSO virtual poster presentation, 2022

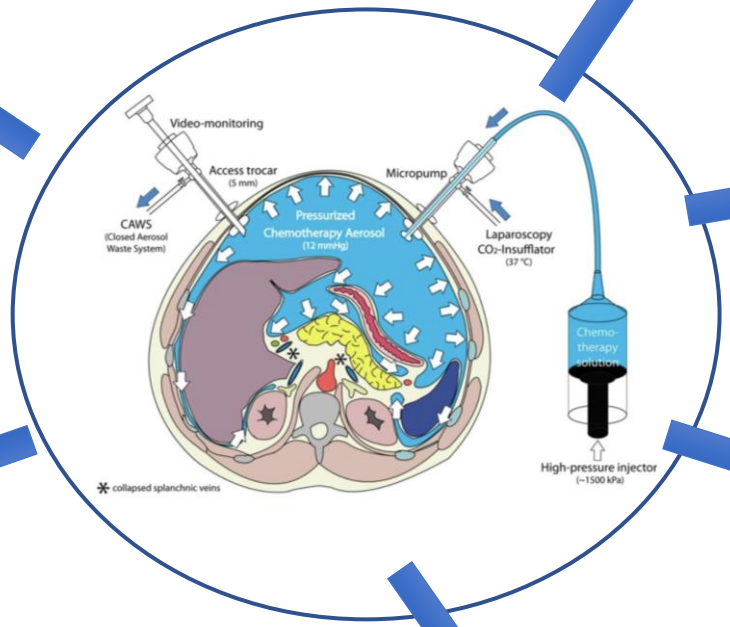
Indications for PIPAC in ovarian cancer

Platinum-resistant ovarian cancer

Geriatric patients

Systemic chemotherapy intolerance

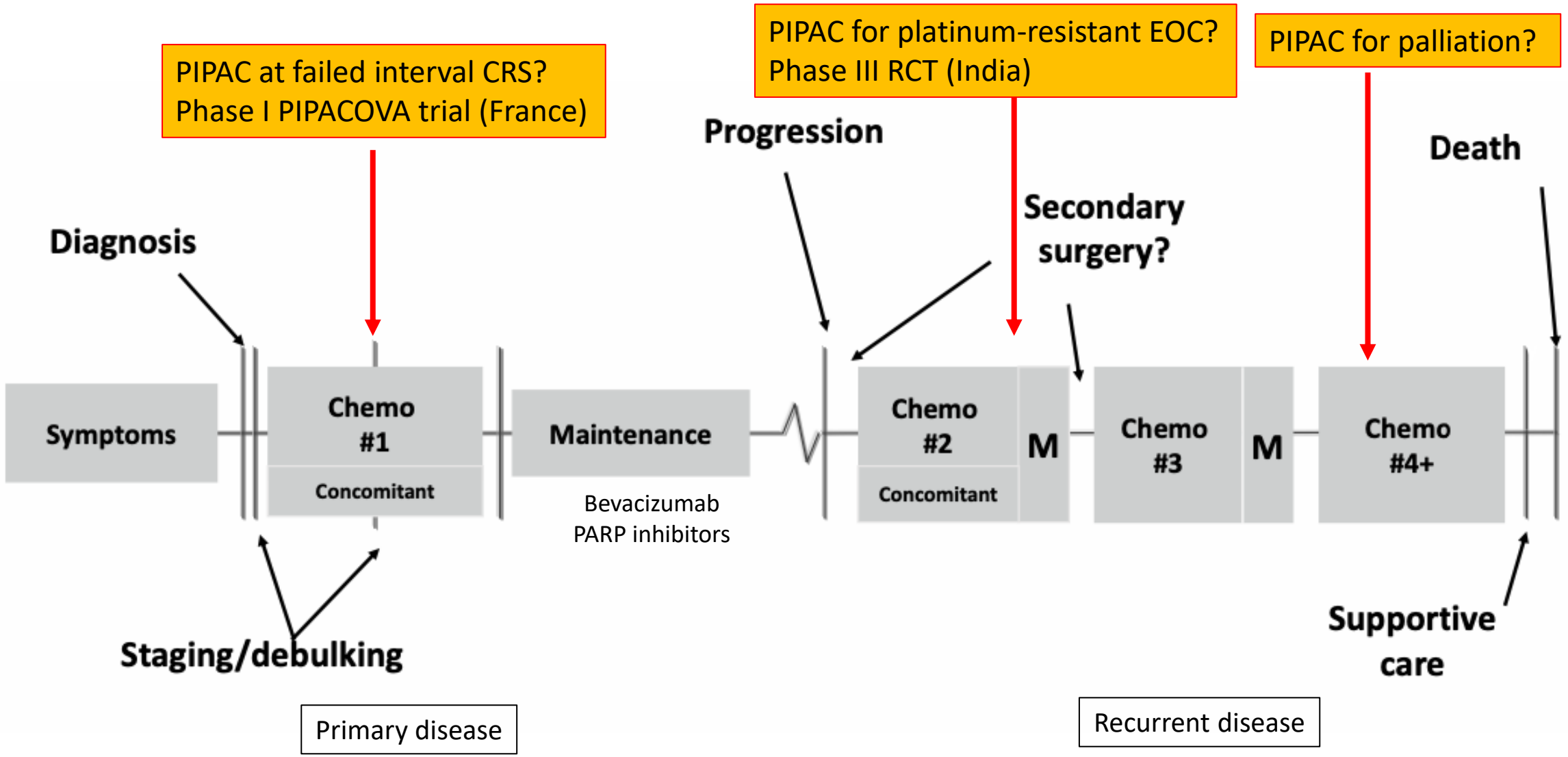
Adjunct to neoadjuvant IV chemo to enable optimal interval CRS?



Low-grade serous ovarian cancer?

Adjunct to 2nd line IV therapy with partial response, but residual peritoneal mets?

Potential PIPAC indications in Treatment paradigm in ovarian cancer



PIPAC in ovarian cancer

Experimental in the U.S.

- Clinical trial participation

Well tolerated with low toxicity profile

Recurrent ovarian cancer patients who seek less toxic alternatives to systemic chemotherapies

Establish indications

Establish optimal drug doses and combinations

Multimodal therapy

- IV chemo
- PARP inhibitors
- Bevacizumab
- Checkpoint inhibitors

Quality of life

Novel PIPAC drugs

- nab-paclitaxel
- Checkpoint inhibitors?

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