City of Hope

ISSPP

INTERNATIONAL SOCIETY FOR THE STUDY OF PLEURA AND PERITONEUM - 2018 -

**PIPAC – CLINICAL EVIDENCE**

# PIPAC in Ovarian Cancer


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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, 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

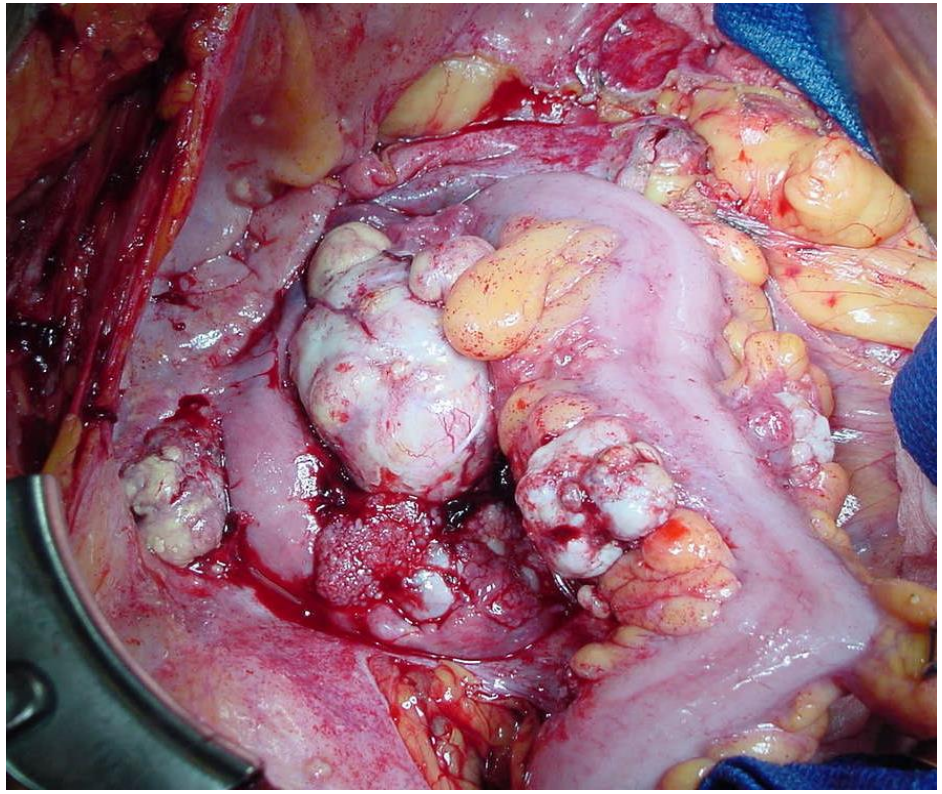
Review of Ovarian cancer PIPAC trials

Review of drug selection and dosages

Potential indications of PIPAC in ovarian cancer

# Ovarian cancer as a peritoneal surface malignancy

- Peritoneal cavity is the principal site of disease
- Malignant gastrointestinal obstruction
- Urinary obstruction
- Malignant ascites



*Parkin et al. Int J Cancer 2000; 94: 152.

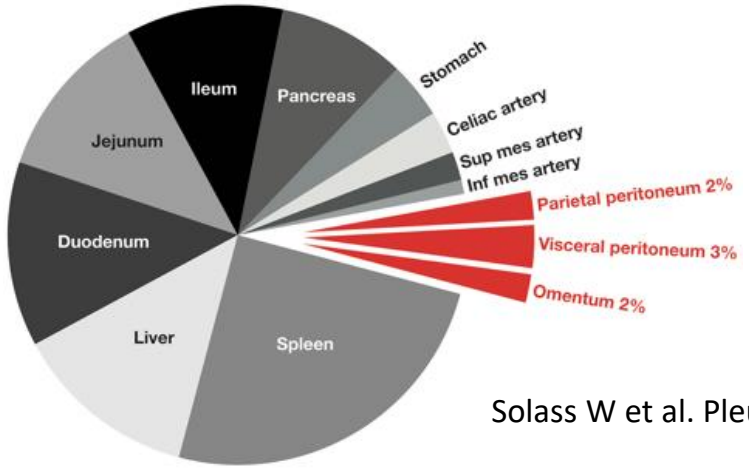
# Can regional therapies effectively treat peritoneal surface malignancies?

**Intraperitoneal chemotherapy**

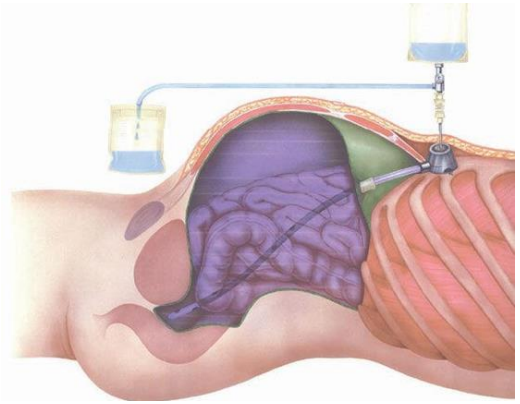
Exploit “direct” effect of drugs on tumors that are primarily peritoneal-based

**Pharmacokinetic advantage**

Poor vascular supply to peritoneum




Solass W et al. Pleura Peritoneum 2016



# Pharmacokinetic advantage of Intraperitoneal chemotherapy

1978 Seminal Paper: Some drugs have slow peritoneal clearance

- Certain drugs have lower peritoneal permeability than Plasma clearance
- These drugs can have greater concentration in the peritoneal space relative to what can be achieved with systemic administration

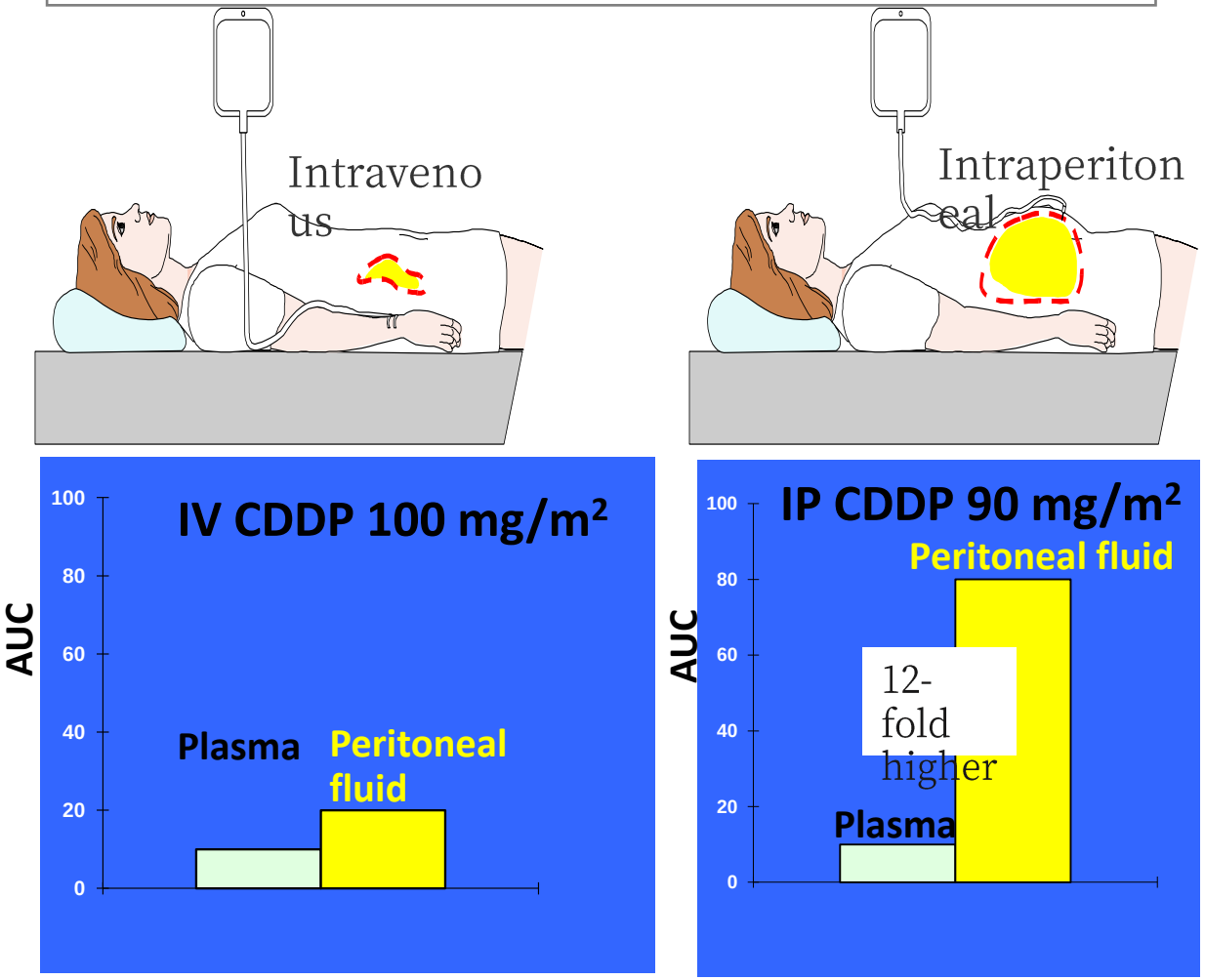
**Pharmacokinetic Rationale for Peritoneal Drug Administration in the Treatment of Ovarian Cancer** [1]

- The peak peritoneal [cisplatin] was 21-fold > plasma [cisplatin]
- Area Under the Peritoneal cisplatin elimination Curve was 12-fold higher than the Area Under the Plasma Curve.
- Neither of these ratios varied significantly with cisplatin dose.

...suggest there is 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 peritoneal tumors

Pharmacokinetics of **cisplatin** in plasma vs peritoneal fluid




High peritoneal to plasma ratios for peak cisplatin concentrations

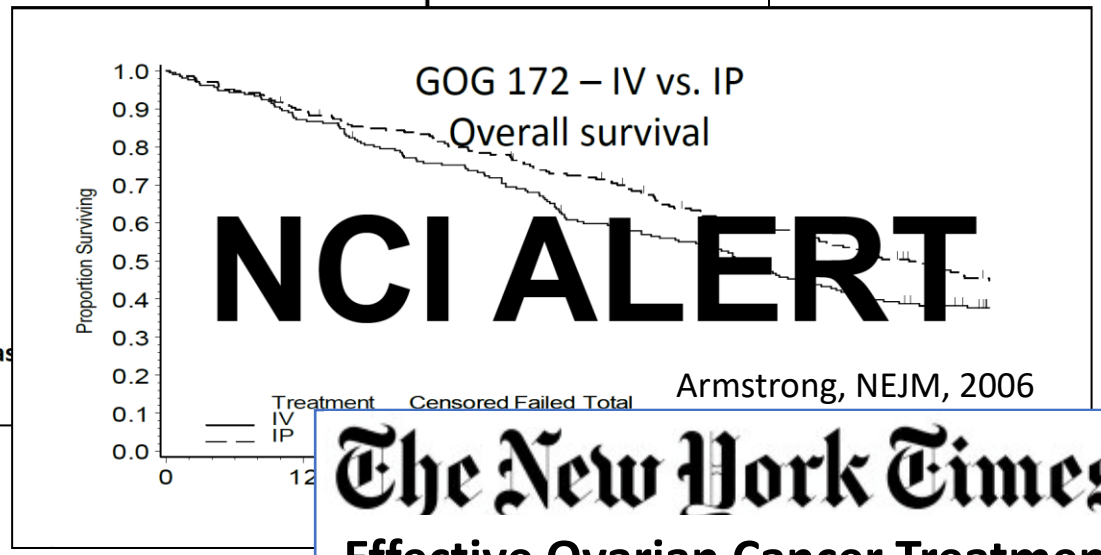
* Adapted from Howell SB et al. Ann Intern Med 97:845-851, 1982

# Intraperitoneal chemotherapy in ovarian cancer

**Treatment Hazard Ratios for Death**
**Intraperitoneal vs Intravenous Therapy**

| | Rel Haz | Var(ln(HR)) | IP regimen better | IV regimen better |
|---|---|---|---|---|
| SWOG/GOG–104 (1996) | 0.760 | 0.013 | | |
| GONO (2000) | 0.670 | | | |
| GOG–114/SWOG (2001) | 0.810 | | | |
| Taiwan (2001) | 1.130 | | | |
| EORTC–55875 (2003) | 0.820 | | | |
| GOG–172 (2005) | 0.710 | | | |

On average IP therapy had a 21.6% decreas
Hazard ratio 0.784 (95% CI 0.693 – 0.886)




Armstrong, NEJM, 2006

The New York Times

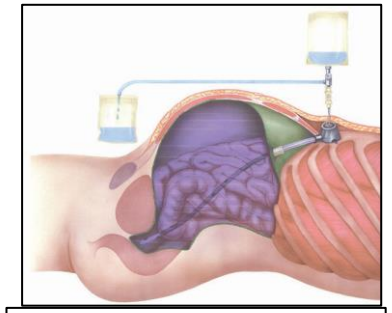
**Effective Ovarian Cancer Treatment Is Underused, Study Finds**

Nearly a decade later, doctors report that fewer than half
of ovarian cancer patients at
receiving the abdominal trea

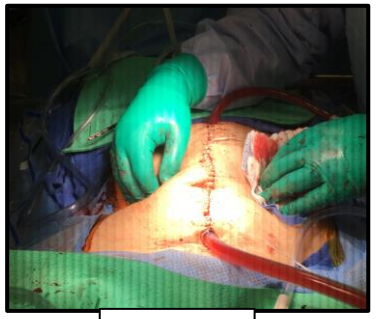
Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study

Joan L. Walker, MD[1]; Mark F. Brady, PhD[2]; Lari Wenzel, PhD[3]; Gini F. Fleming, MD[4]; Helen Q. Huang, MS[2]; Paul A. DiSilvestro, MD[5];

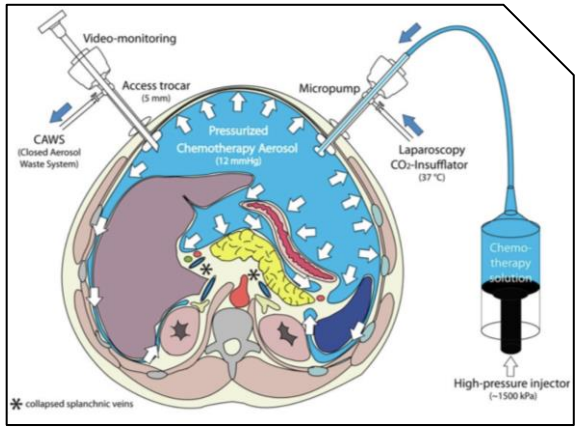
# Evolution of Intraperitoneal Chemotherapy in Ovarian Cancer

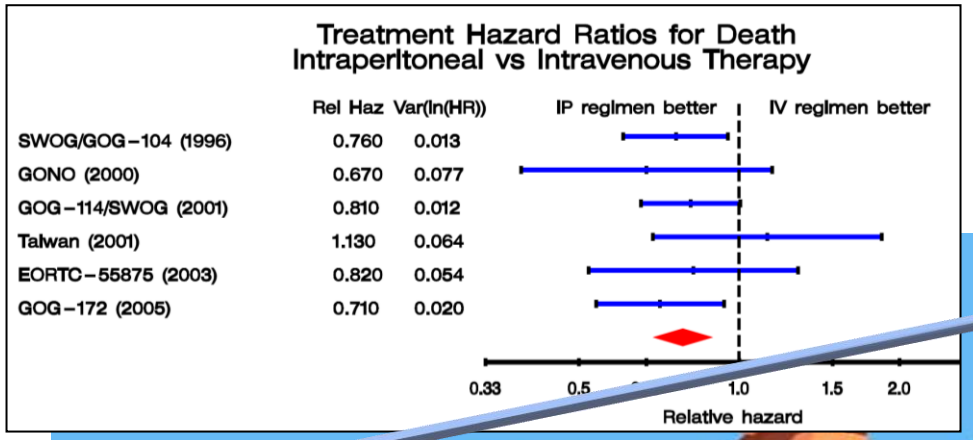


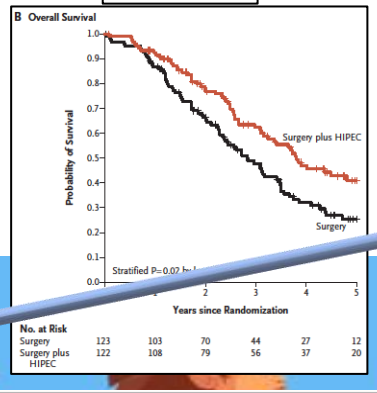
IP Chemotherapy



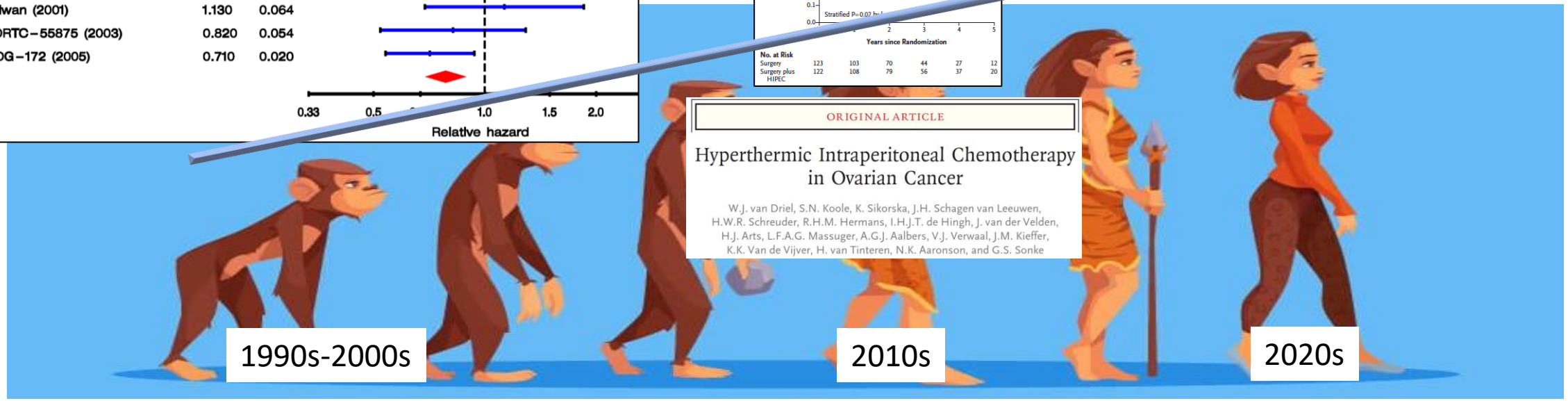
HIPEC




Does PIPAC have a role in ovarian cancer?

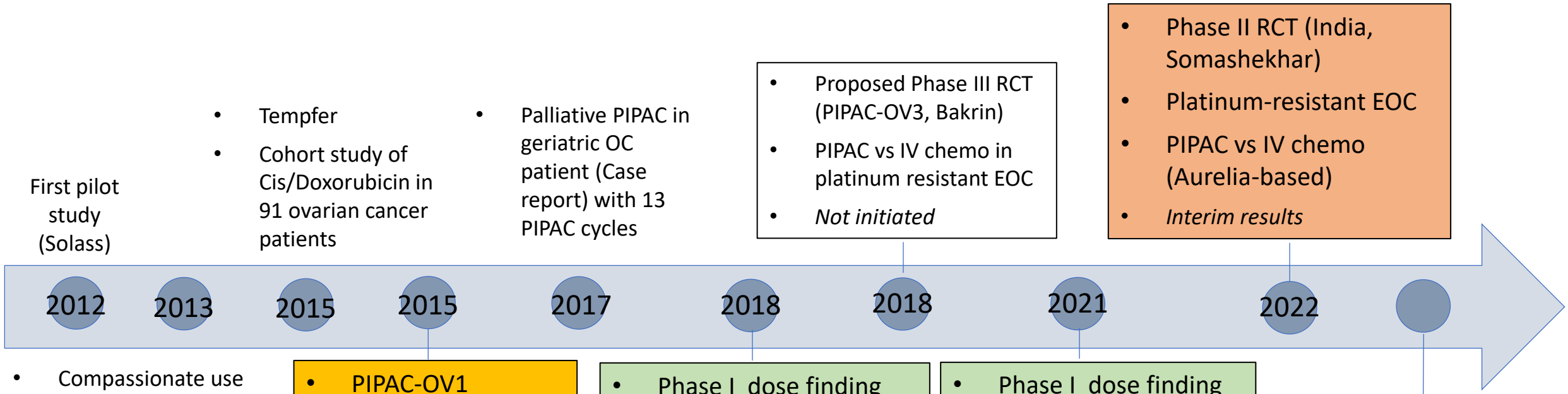



1990s-2000s

2010s

2020s

# PIPAC studies in ovarian cancer




First pilot study (Solass)

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

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

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

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

- Phase I dose finding study (Tempfer)
- Recurrent ovarian cancer (n=15)
- Cisplatin 7.5 mg/m2
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- Phase I-II, Single arm, n=50
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- Phase I, n=15
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Solass et al. *Surg Endosc.* 2012;26:1849–1855.
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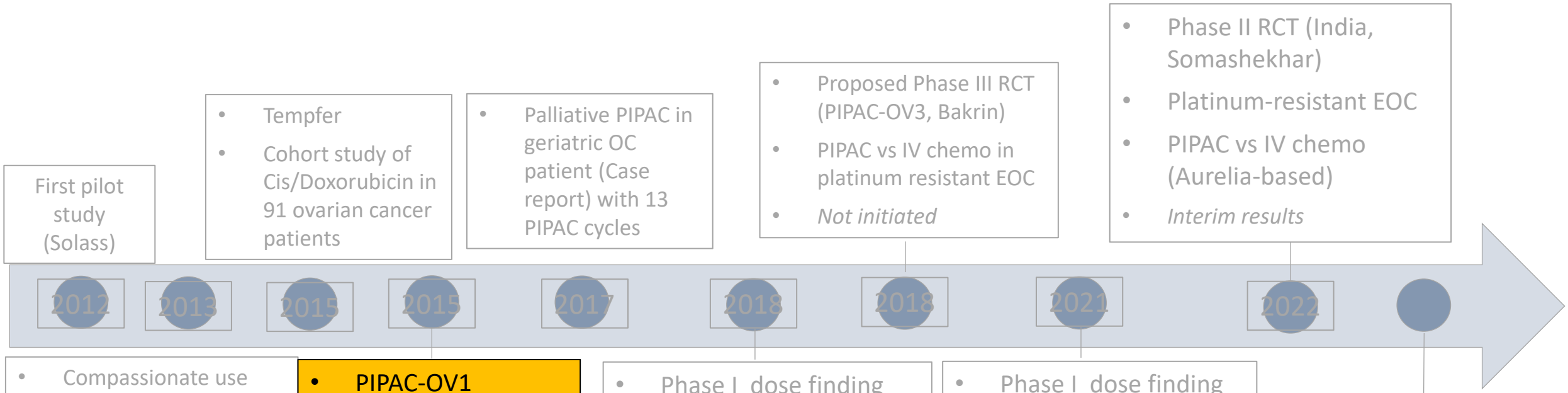
# PIPAC studies in ovarian cancer

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

PIPAC-OV1

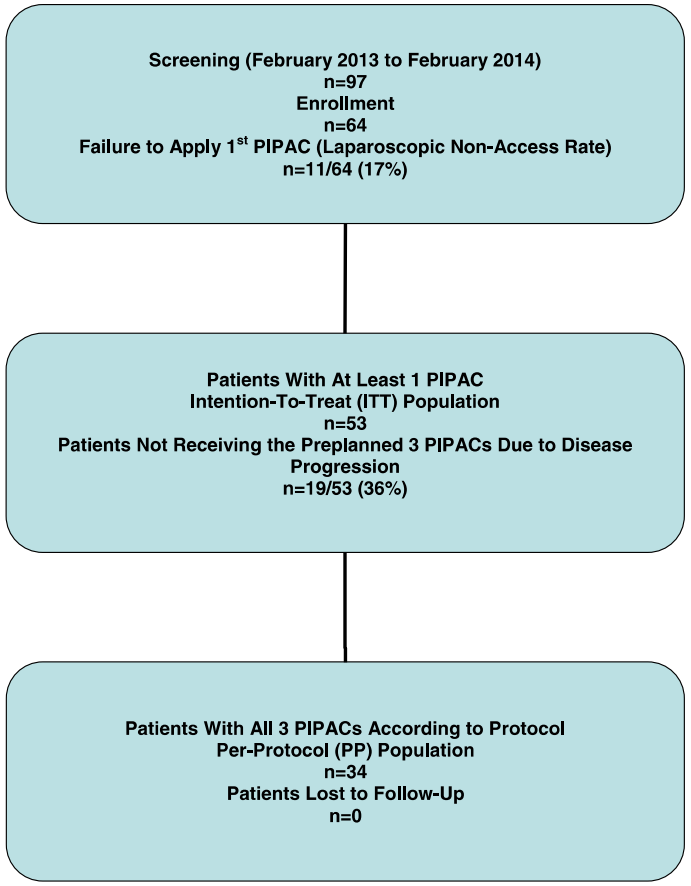



**Fig. 1.** Flow diagram of the patients' flow through the study.

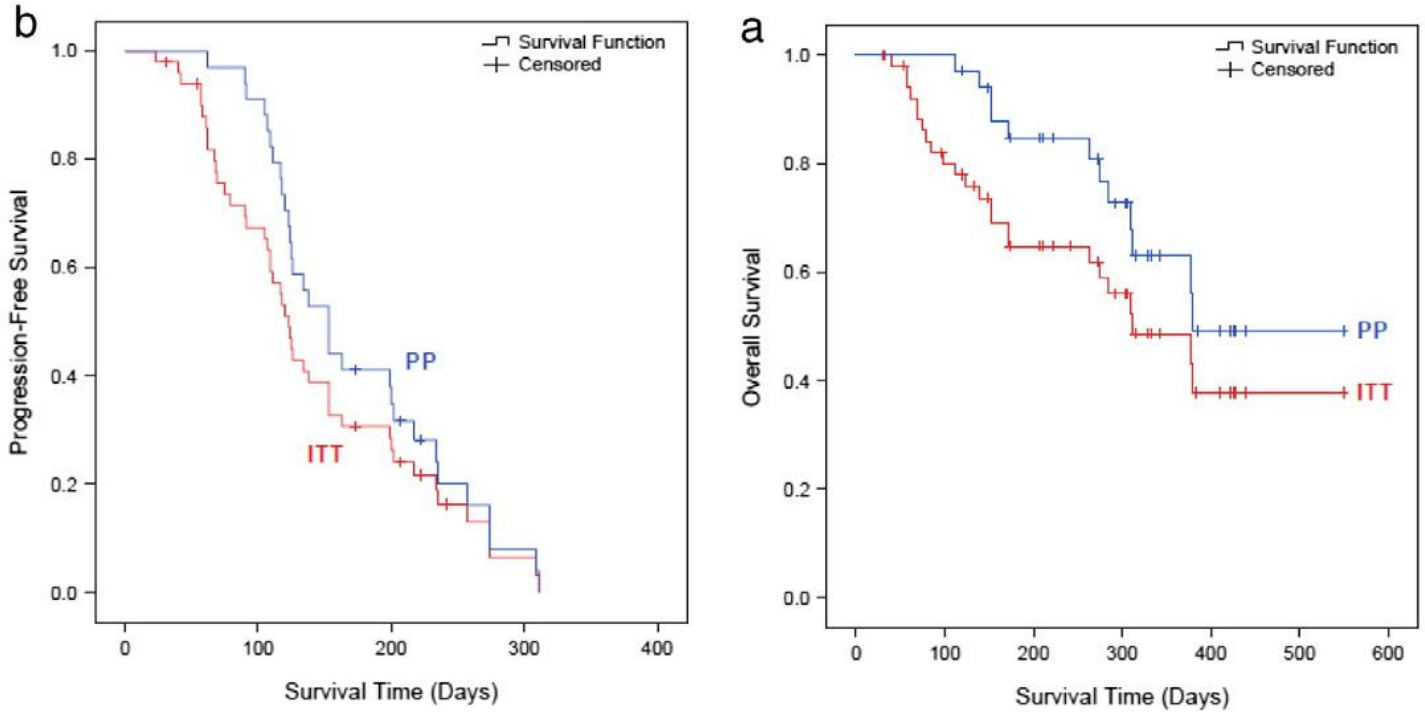
Patient characteristics of 53 women with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).

| 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) |

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

# First Phase II PIPAC study in platinum-resistant ovarian cancer – PFS and Response Rate

- PFS is ~ 5 months depending on how many cycles received
- Response rate: ~60% had a stable response, ~5% had partial response




| | Per protocol population | Intention to treat (ITT) population |
|---|---|---|
| # cycles PIPAC | 3 cycles | 1 cycle |
| PFS | 5.8 months | 4.8 months |
| OS | 13.5 months | 11.0 months |

For comparison: AURELIA –
PFS 6.7 mo. with Bevacizumab
OS 16.6 mo.

53 patients
- 62% clinical benefit rate with PIPAC (SD after 3 cycles or a PR)
- 3 patients had a partial response (5.7%), while the rest had a stable response.

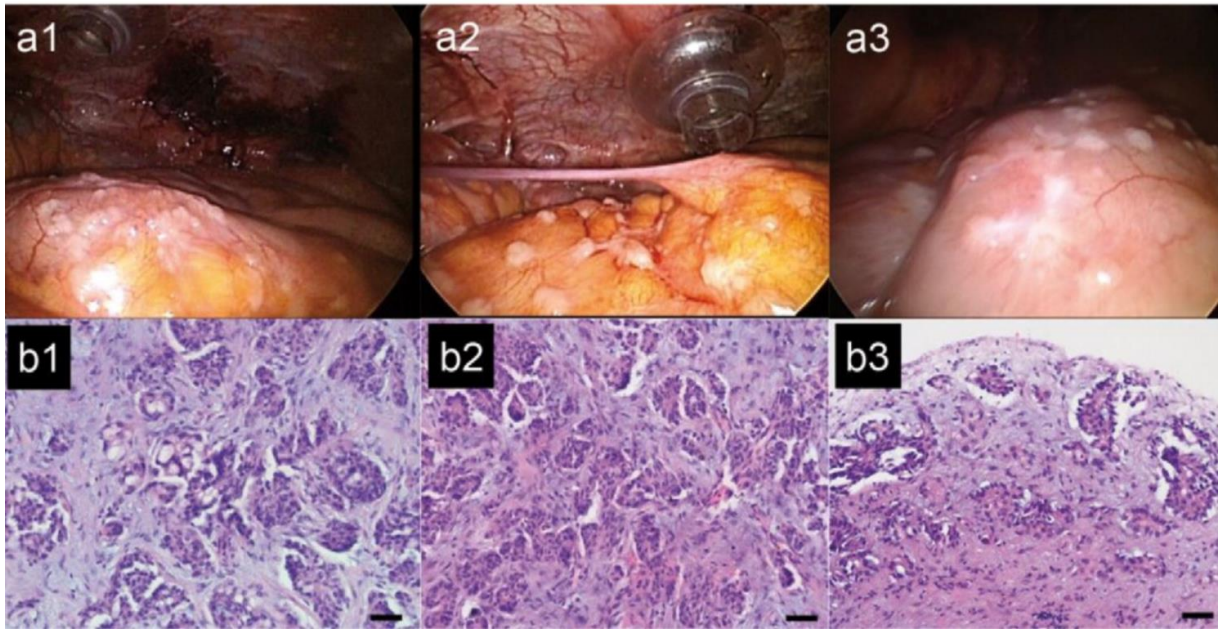
*C.B. Tempfer et al. / Gynecologic Oncology 137 (2015) 223–228*

# PIPAC-OV1 and histologic regression (PRGS), Quality of Life

Histologic Regression observed in ~75% of patients

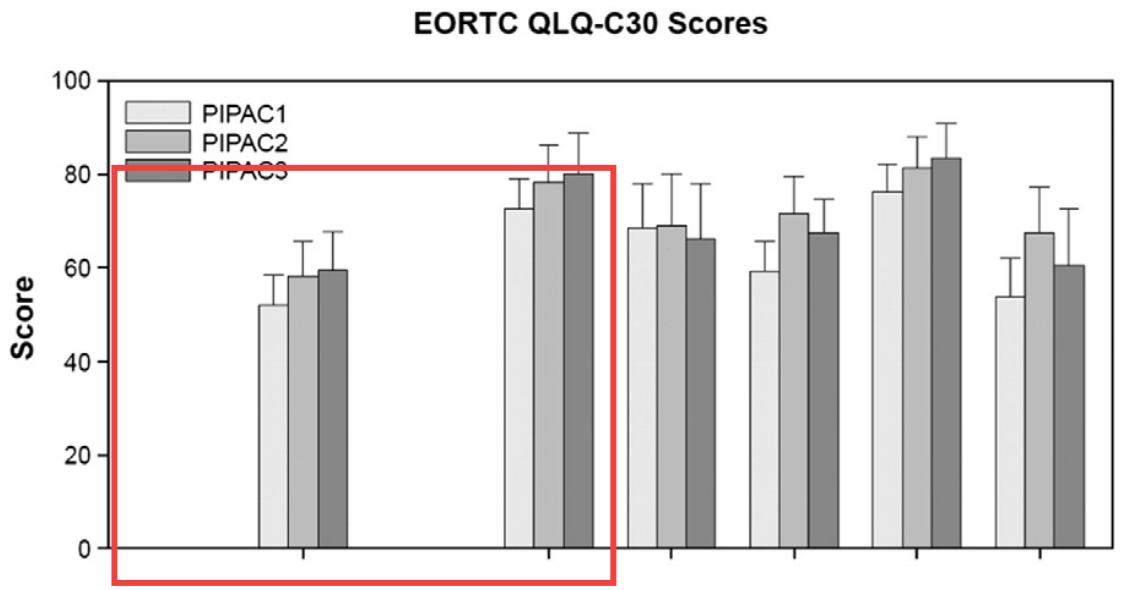
GI-related Quality of life improved after 1st PIPAC: Nausea/vomiting, appetite loss, constipation, diarrhea

## Histologic Regression




moderate or strong tumor regression on histology observed in 76% of patients who underwent 3 PIPAC cycles

## Quality of Life



# PIPAC-OV1 and Adverse Events

Abdominal pain and trocar hernia were most common G3 events, but still <5%

Other G3 AEs included bowel obstruction, hemorrhage, intraop bleeding, urosepsis (all 2%)

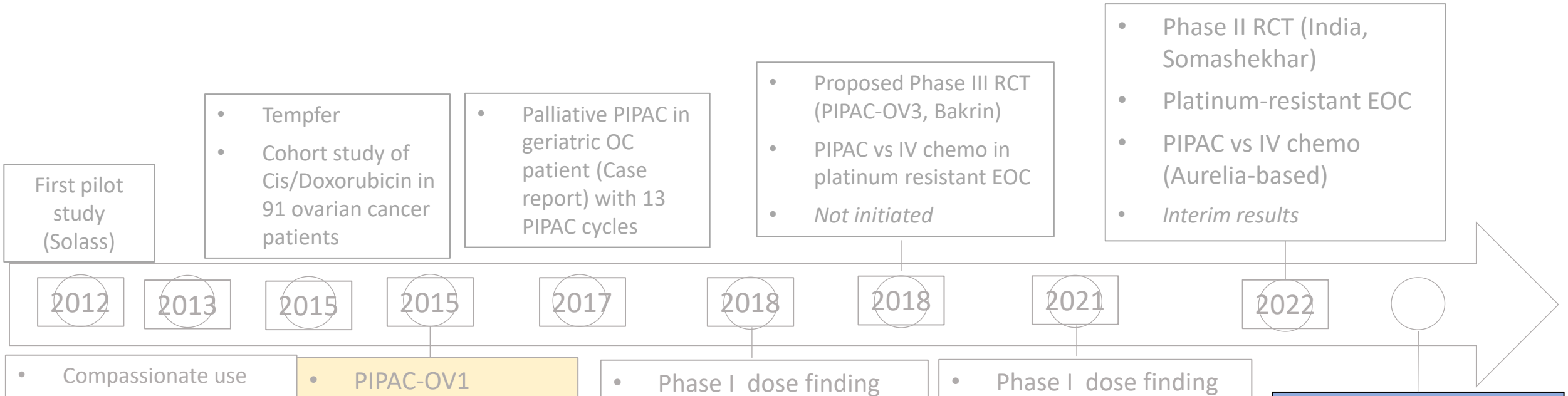
## Adverse events – PIPAC-OV1

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.

# PIPAC studies in ovarian cancer

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# Italian Phase II PIPAC study in Ovarian Cancer

Another Phase II trial in platinum-resistant EOC

## 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

Clinical Benefit Rate (CBR) according to RECIST/GCOG criteria after three cycles of PIPAC with PIPAC cisplatin and doxorubicin
[ Time Frame: 12-18 weeks ]

**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

**Cisplatin 10.5 mg/m2 + Doxorubicin 2.5 mg/m2**

## PARROT – flow diagram

Eligible patients: 43

Excluded:
- 3 patients: impossibility of access to the abdominal cavity

Patients enrolled: 40
- < 3 PIPAC courses: 22 (55.0%)
- ≥ 3 PIPAC courses: 18 (45.0%)

Overall PIPAC procedures: 98

Major post-operative complications: 2 (5%)
- Bowel occlusion: 2 pts

Intra-operative complications: 2 (5%)
- Bowel lesions: 2 pts

Median Follow-up: 30 mts (11-110)

# Italian Phase II – PIPAC platinum resistant EOC

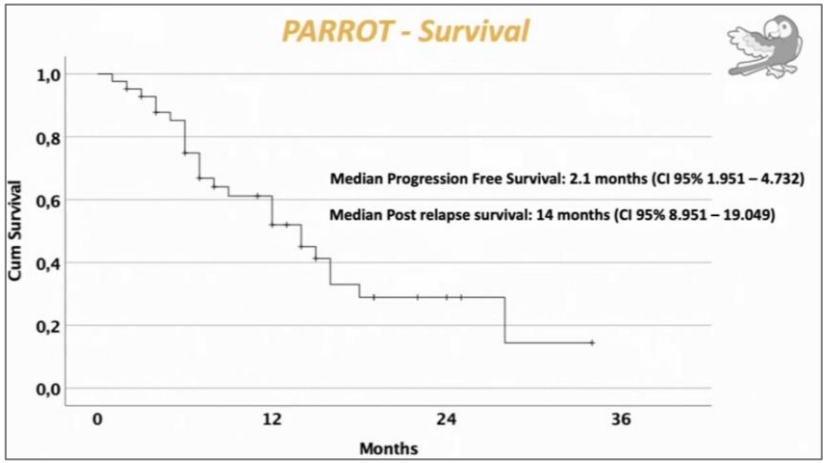
Response rate of 81%, PFS of 2.1 months, OS of 14 months

Compare to Tempfer Phase II:
RR ~60%, PFS ~5 months, OS of 11-13 months

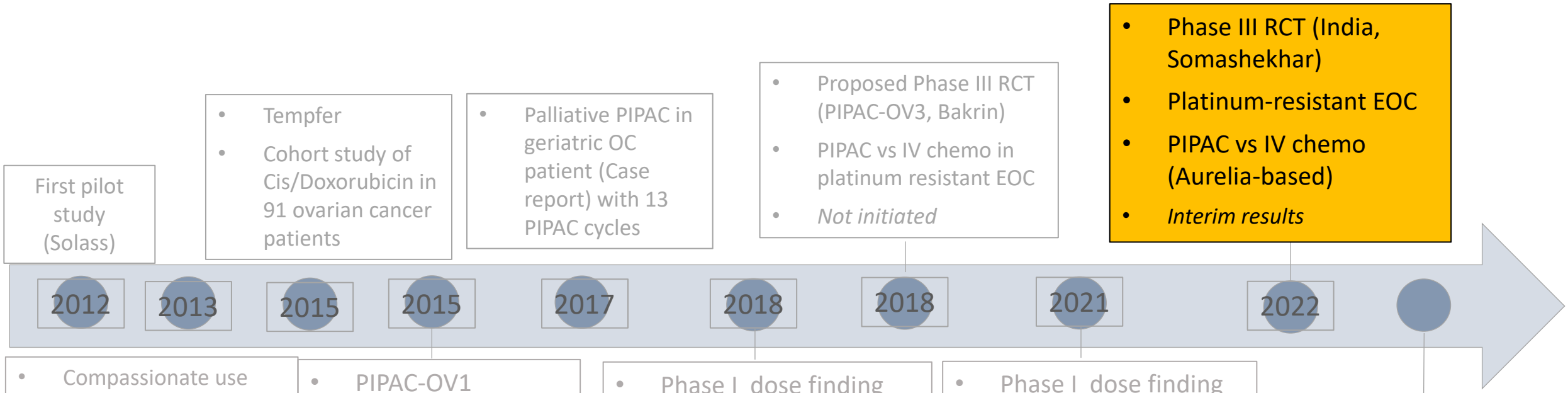
**PARROT (NCT02735928): PIPAC Applied to platinum-Resistance Recurrence of Ovarian Tumor**

| 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)<br>1<br>2 | <br>14 (35.0)<br>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) |

| Variable | N (%) |
|---|---|
| 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)<br>Partial response<br>Stable disease | 31 (56.7)<br>10 (32.3)<br>21 (67.7) |
| Overall Survival (months)(median)(range) | 14 (8-19) |



# PIPAC studies in ovarian cancer

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- Platinum-resistant EOC
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**2022**

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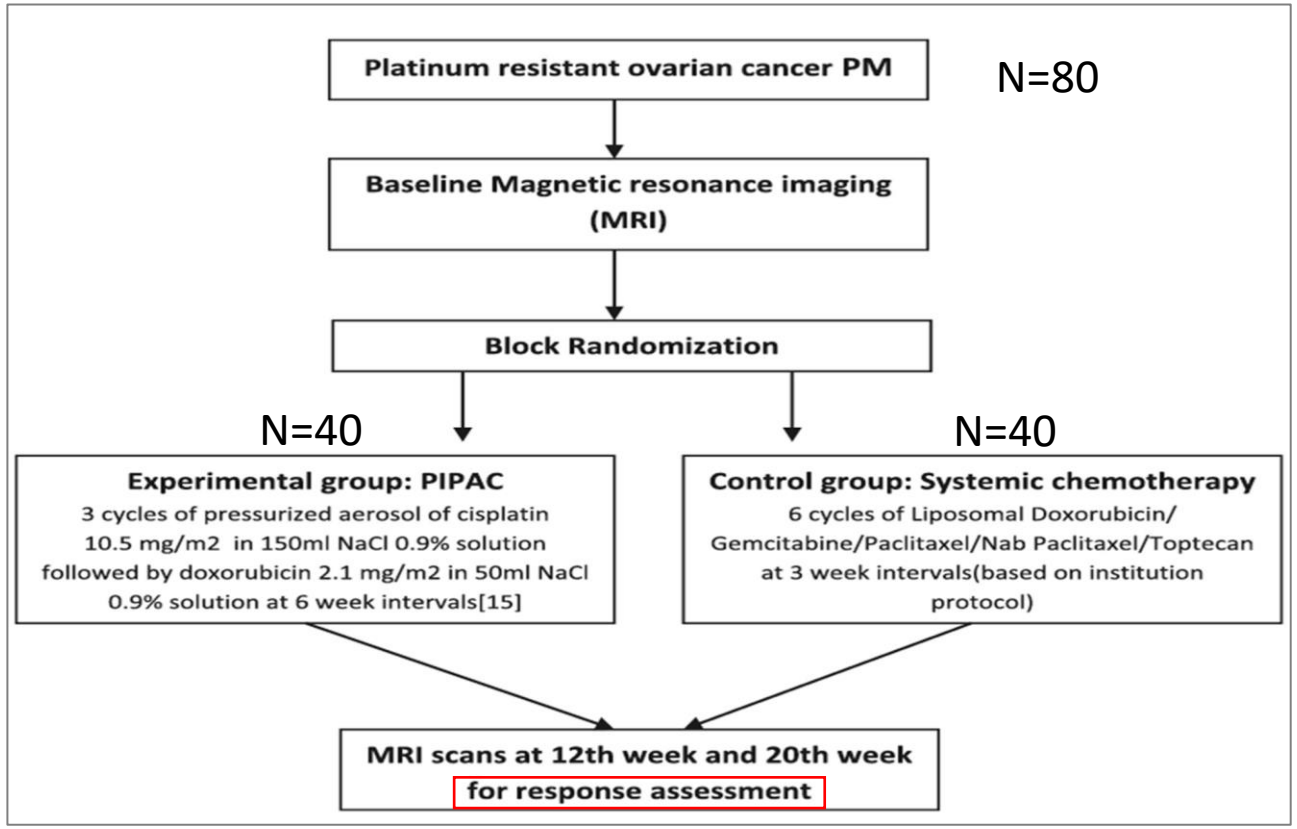
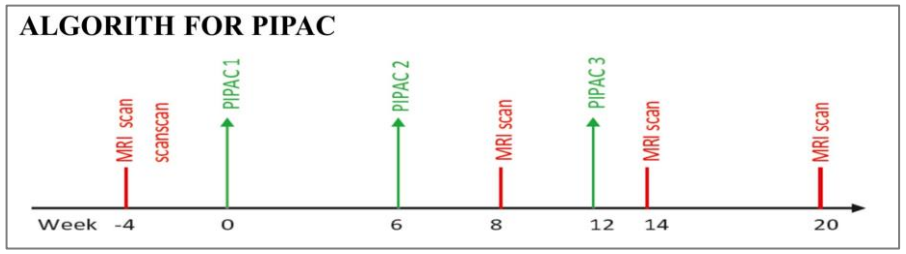
# First PIPAC randomized trial in platinum-resistant ovarian cancer

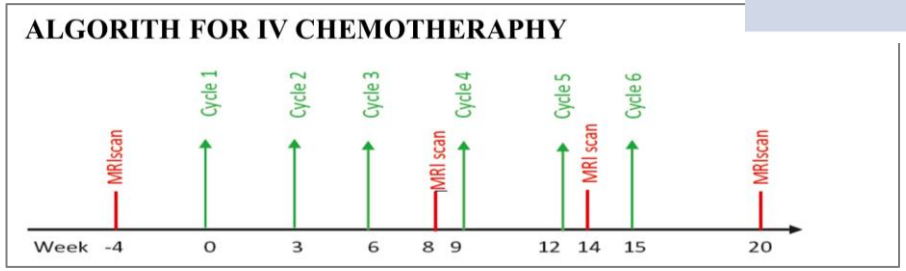
## PIPAC compared to AURELIA regimen




### Patient Characteristics

| | 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<br>2 PIPAC - 05<br>1 PIPAC - 05 | 6 CYCLES - 25<br>4 CYCLES - 10<br>3 CYCLES - 05 | ___ |

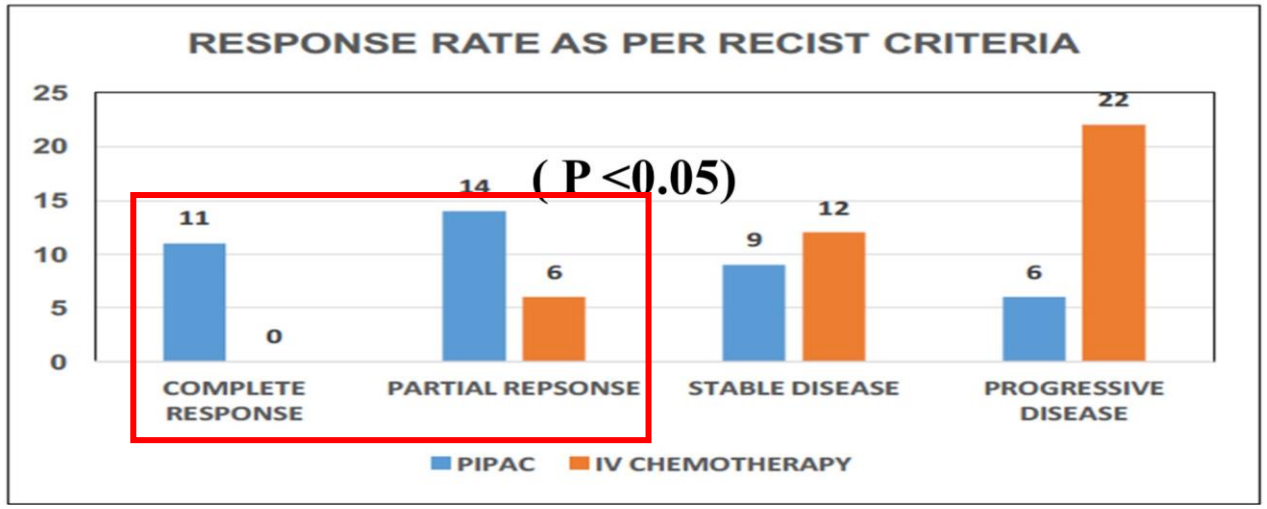



Somashekar SP et al ASCO 2022 Poster

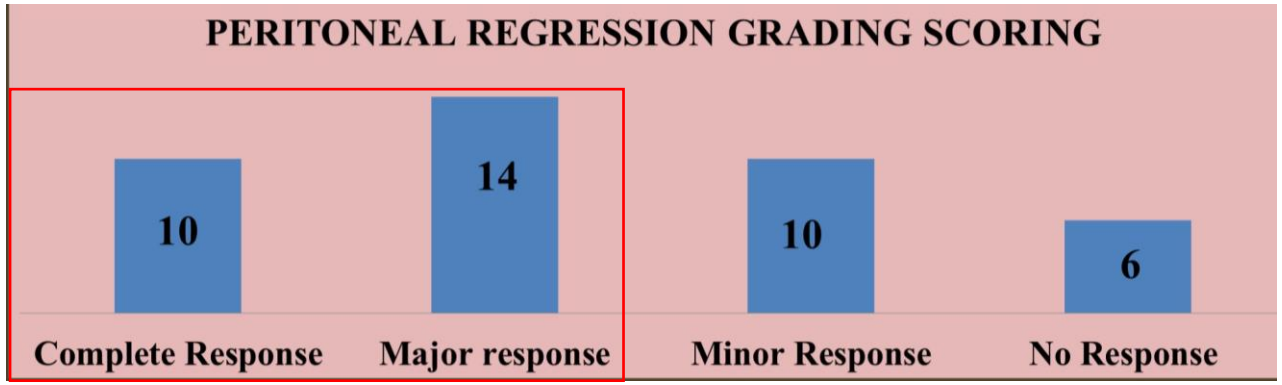
# First PIPAC randomized trial in platinum-resistant ovarian cancer

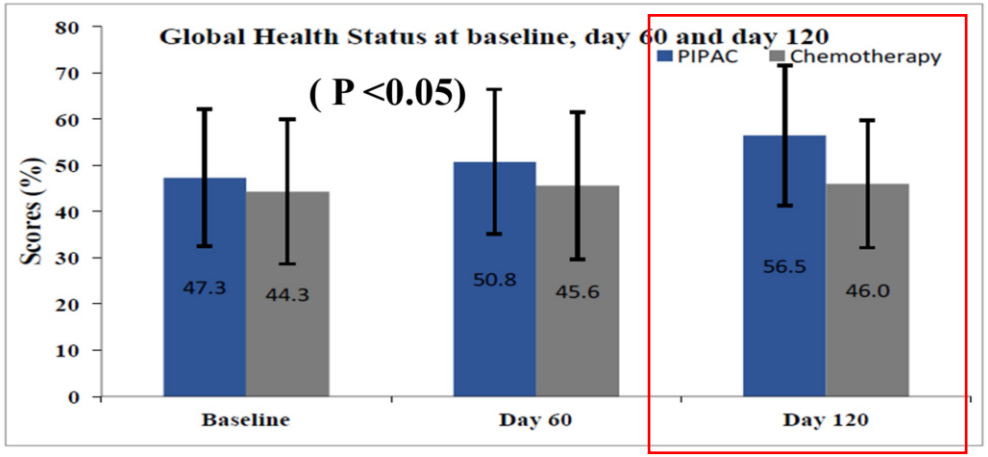
## PIPAC compared to AURELIA regimen




Response: MRI at week 12 and 20

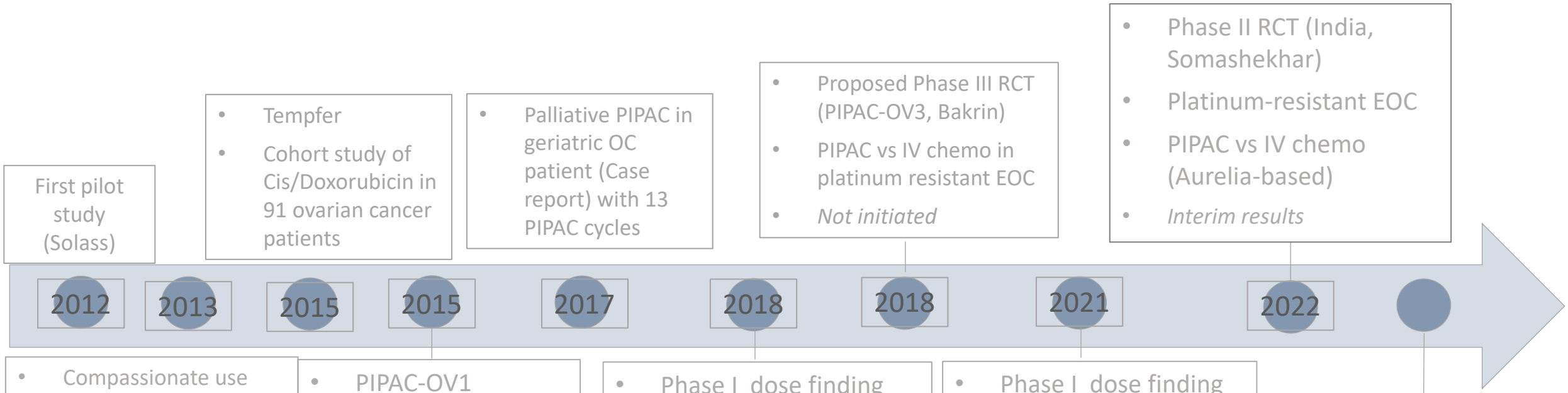
| Complications | (G1- G2 ) | | (G3) | |
|---|---|---|---|---|
| | PIPAC | IV | PIPAC | IV |
| Nausea/Vomiting | 9 | 9 | 0 | 3 |
| Pain | 9 | 13 | 0 | 2 |
| SSI | 3 | 0 | 0 | 0 |
| Cytopenia | 7 | 6 | 1(G3) | 5 |
| Mucositis | 0 | 12 | 0 | 5 |
| Neuropathy | 0 | 9 | 0 | 2 |
| Intra-operative Bleeding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

# First-line PIPAC after neoadjuvant chemotherapy in unresectable ovarian cancer




**2012**
- First pilot study (Solass)

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

**2015**
- PIPAC-OV1 (Tempfer)
- Phase II study
- Platinum resistant ovarian cancer
- N=64

**2017**
- Proposed Phase III RCT (PIPAC-OV3, Bakrin)
- PIPAC vs IV chemo in platinum resistant EOC
- *Not initiated*

**2018**
- Phase I dose finding study (Tempfer)
- Recurrent ovarian cancer (n=15)
- Cisplatin 7.5 mg/m2
- Doxorubicin 2.1 mg/m2

**2018**
- Phase I dose finding study (Robella)
- EOC (n=2), CRC, GC
- Cisplatin 30 mg/m2
- Doxorubicin 6 mg/m2

**2021**
- Phase II RCT (India, Somashekhar)
- Platinum-resistant EOC
- PIPAC vs IV chemo (Aurelia-based)
- *Interim results*

**2022**
- PARROT (Italy)
- Phase I-II, Single arm, n=50
- Platinum-resistant EOC
- *Ongoing, NCT02735928*

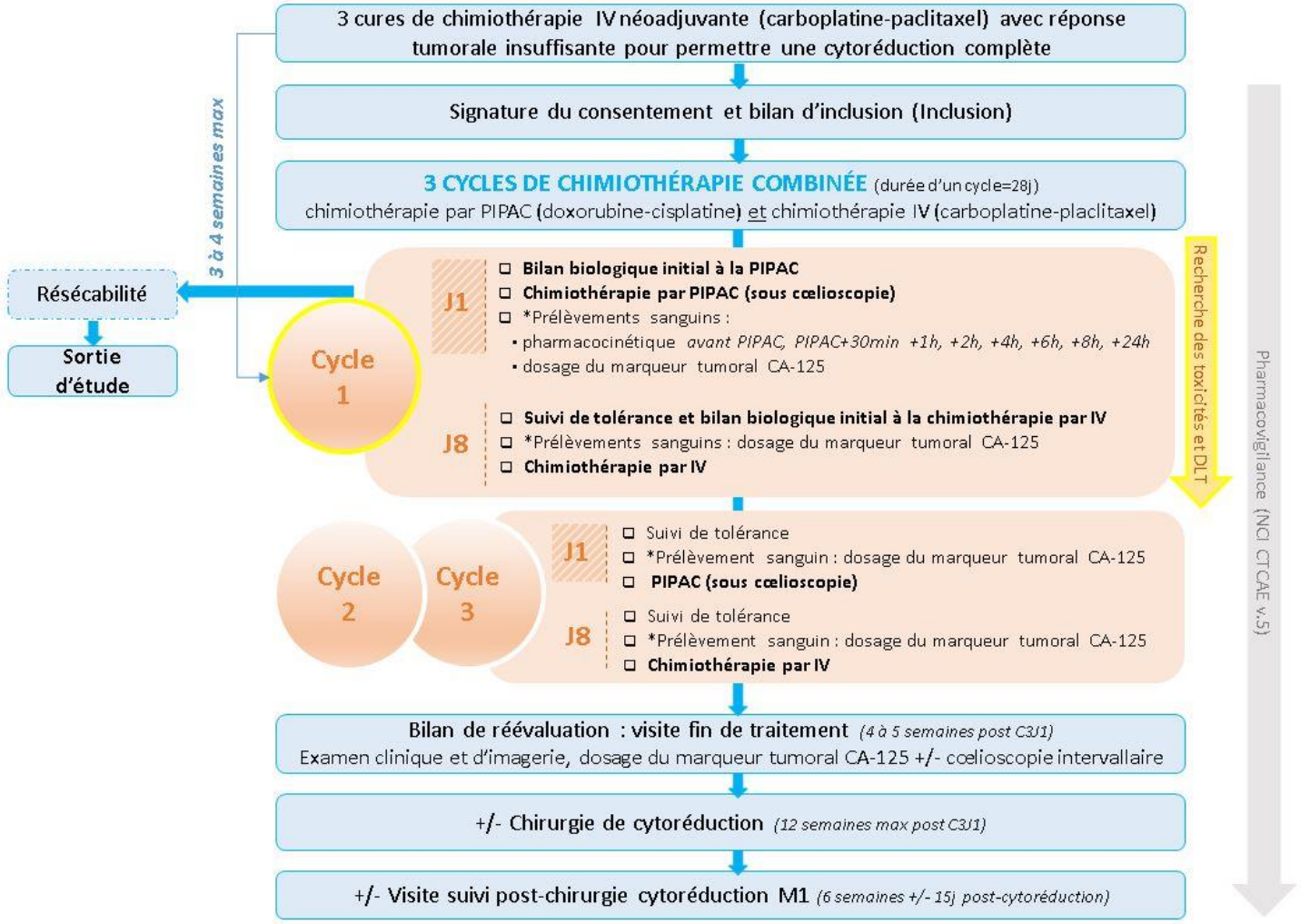
- PIPAC-OVA (France)
- Phase I, n=15
- First-line setting Neoadjuvant PIPAC
- *Ongoing NCT04811703*


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*

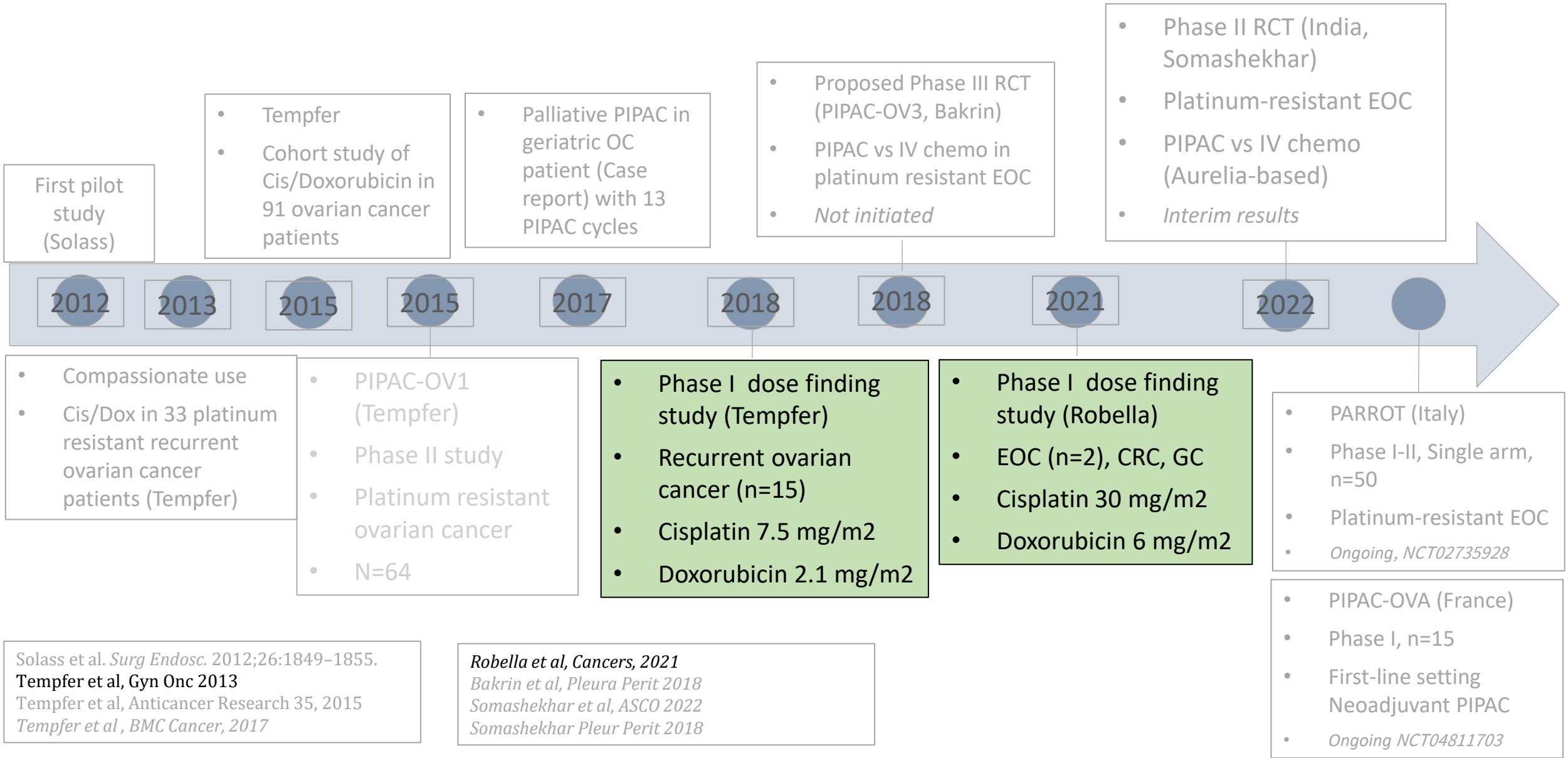
# PIPACOVA - Safety of PIPAC in combination with systemic chemotherapy in **first-line setting**

- **Phase I** dose escalation evaluating the addition of PIPAC (cis/dox) to systemic chemotherapy, for RP2D
- **Neoadjuvant** chemo x 3 cycles
- **Interval** Diagnostic laparoscopy
  - Surgically resectable → interval CRS
  - **Unresectable → PIPAC**
- D1 =PIPAC (cisplatin/doxorubicin)
- D8 = IV carbo/taxol
- **Dose escalation study**
  - 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)

# Dose finding studies in PIPAC ovarian cancer

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# Dose finding studies in ovarian cancer PIPAC

## Tempfer and Robella Studies

Tempfer Phase I Dose escalation study established SOC PIPAC dose of Cisplatin 10.5 mg/m2 + Doxorubicin 2.1 mg/m2

More recent Robella Phase I study escalated to higher dose levels, and found Cis 30 + Dox 6 safe, but only 3 EOC patients used

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,*]

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 |

N=15 EOC patients

**Cisplatin 10.5 mg/m2 + Doxorubicin 2.1 mg/m2**

**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]**

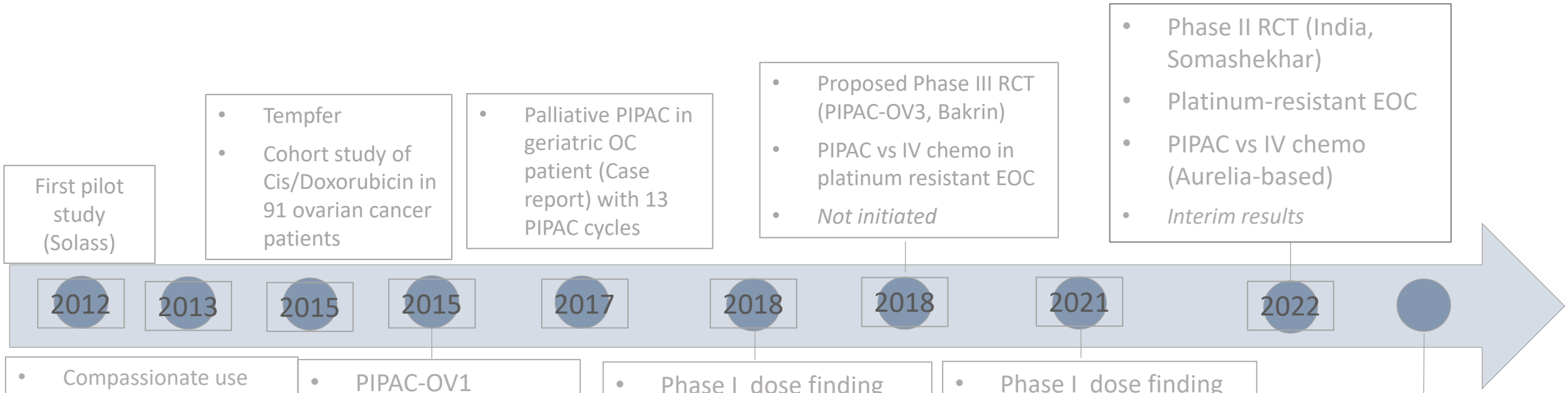
**Table 2.** Adverse events (CTCAE 4.03) according to dose level of Cisplatin and Doxorubicin.

| 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 | |

N=13, with 2 EOC patients

Cisplatin 30 mg/m2 + Doxorubicin 6 mg/m2

# Other drugs used in PIPAC ovarian cancer

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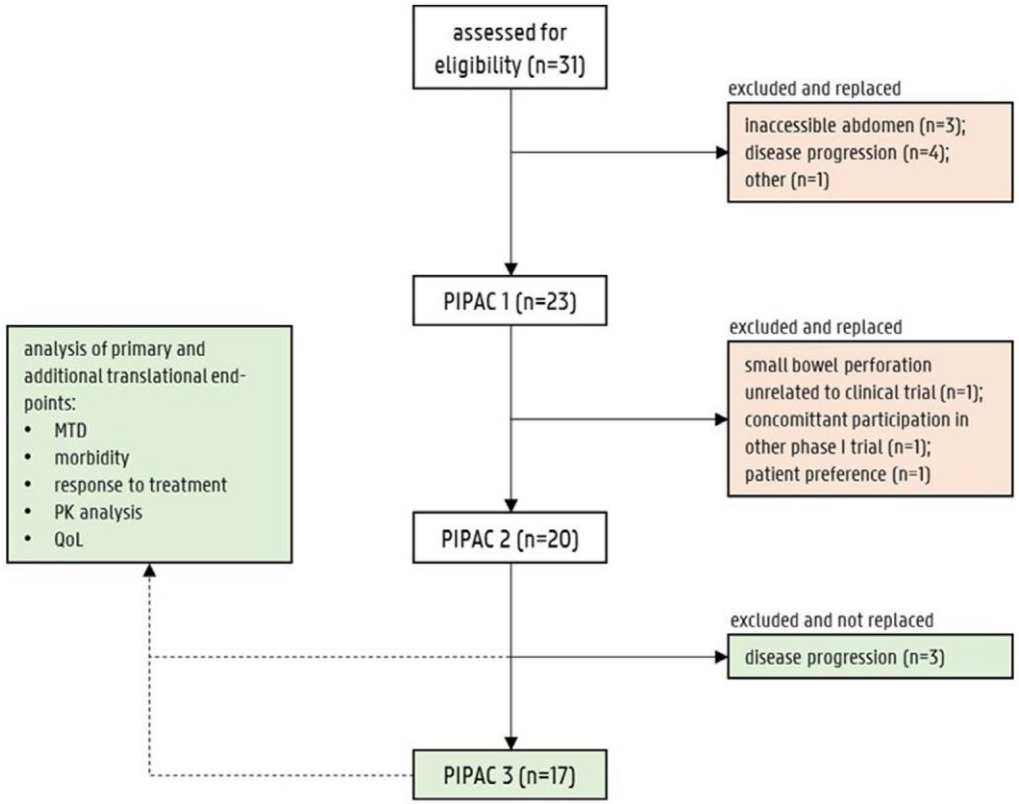
*Robella et al, Cancers, 2021*
*Bakrin et al, Pleura Perit 2018*
*Somashekhar et al, ASCO 2022*
*Somashekhar Pleur Perit 2018*

# First use of Nab-paclitaxel PIPAC in ovarian cancer – Dose escalation study

## 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]*




| | Overall (*n* = 20) | 35 mg/m² (*n* = 2) | 70 mg/m² (*n* = 2) | 90 mg/m² (*n* = 3) | 112.5 mg/m² (*n* = 3) | 140 mg/m² (*n* = 10) |
|---|---|---|---|---|---|---|
| Patient characteristics | | | | | | |
| Age (years) | 57 (49–65) | 64 | 68 | 52 | 59 | 51 |
| Gender (male, %) | 40 | 50 | - | 100 | 33 | 30 |
| BMI (kg/m²) | 23 (19–26) | 23 | 25 | 27 | 21 | 21 |
| PCI | 22 (12–31) | 35 | 24 | 17 | 20 | 21 |
| Concomitant systemic chemotherapy (%) | 65 | 50 | 50 | 67 | 67 | 70 |
| Cancer origin | | | | | | |
| Ovarian (%) | 20 | - | 50 | - | - | 30 |
| Gastric (%) | 55 | 50 | - | 33 | 100 | 60 |
| Pancreatic (%) | 5 | - | - | 33 | - | - |
| Breast (%) | 5 | 50 | - | - | - | - |
| Gallbladder (%) | 5 | - | - | 33 | - | - |
| Bile duct (%) | 5 | - | - | - | - | 10 |
| Unspecified upper GI (%) | 5 | - | 50 | - | - | - |

***Table 1*: Patient characteristics and cancer origin. Median (IQR) for age, body mass index (BMI) and peritoneal cancer index (PCI) at first PIPAC procedure. Overall PCI scoring is based on 16 patients. In four patients, the PCI could not be assessed due to extensive adhesions.**

**eBioMedicine 2022;82: 104151**
Published online 15 July 2022
https://doi.org/10.1016/j.ebiom.2022.104151

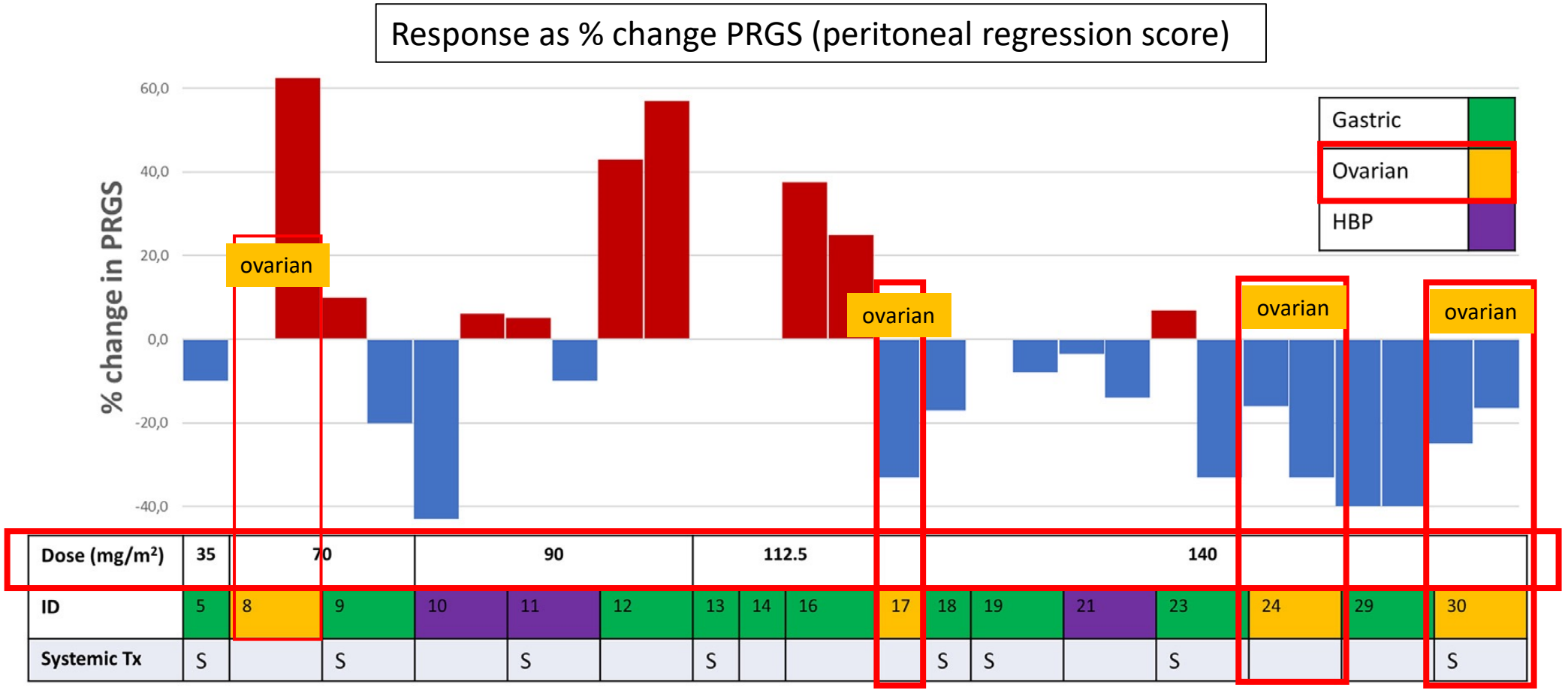
For comparison: Abraxane IV 125 mg/m2

# Response to Nab-paclitaxel PIPAC in ovarian cancer – Histologic regression

**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]*

Response as % change PRGS (peritoneal regression score)




eBioMedicine 2022;82: 104151
Published online 15 July 2022

# Nab-paclitaxel PIPAC – Toxicities

**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/m² (n=3) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 |
| **Hematological toxicity** | | | | | | | | | | |
| Thrombopenia | 0 | 0 | 1 | 0 | 1 | 1 | 2 | 0 | 3 | 0 |
| Leucopenia | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Neutropenia | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 4 | 0 |
| Anemia | 0 | 0 | 1 | 0 | 2 | 0 | 1 | 1 | 7 | 0 |
| **Liver toxicity** | | | | | | | | | | |
| Elevated AST | 0 | 0 | 2 | 0 | 3 | 0 | 2 | 0 | 4 | 0 |
| Elevated ALT | 0 | 0 | 2 | 0 | 3 | 0 | 2 | 0 | 3 | 0 |
| Elevated ALP | 0 | 0 | 2 | 0 | 1 | 0 | 2 | 0 | 4 | 0 |
| Elevated bilirubin | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| Elevated GGT | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 6 | 0 |
| **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/m² (n=3)** | |
| | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 | grade ≤2 | grade 3 |
| Infectious complications | | | | | | | | | | |
| Bacterial pneumonia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Skin infection (cellulitis) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin infection (abscess) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

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

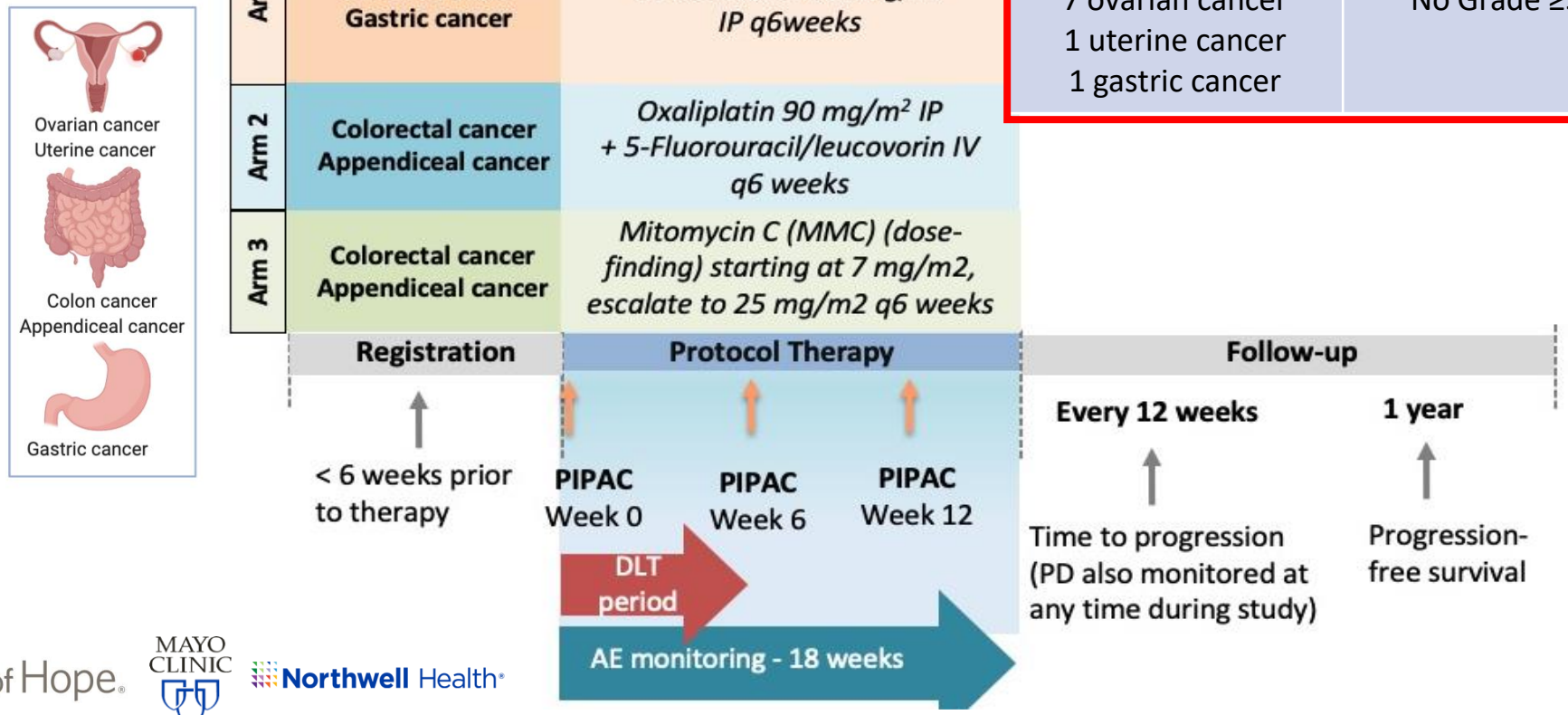
# Drug dosages in Ovarian Cancer PIPAC

| | Drug | Evidence | Publication | Multimodal therapy? |
|---|---|---|---|---|
| Recommended dose | Cisplatin 10.5mg/m2<br>Doxorubicin 2.1 mg/m2 | Phase I dose escalation study in EOC (3+3)<br>Three dose levels of Cis/doxo (mg/m2):<br>7.5/1.5<br>9.0/1.8<br>10.5/2.1 | Tempfer et al, Gyn Onc 2015 | No |
| Alternative | Cisplatin 30mg/m2<br>Doxorubicin 6 mg/m2 | Phase I dose escalation (model-based) in mixed cancers (EOC, CRC, GC)<br>Three dose levels of cis/doxo (mg/m2):<br>15/3<br>30/6<br>50/10 | Robella et al, Cancers, 2021 | Yes |
| Novel | Nab-Paclitaxel 140mg/m2<br><br>(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:
# *Interim Clinical results*

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

| Accrual to date | Safety | PIPAC completion rate (≥2 PIPACs) |
|---|---|---|
| N=9<br>7 ovarian cancer<br>1 uterine cancer<br>1 gastric cancer | No DLTs<br>No Grade ≥3 AEs | 63% |

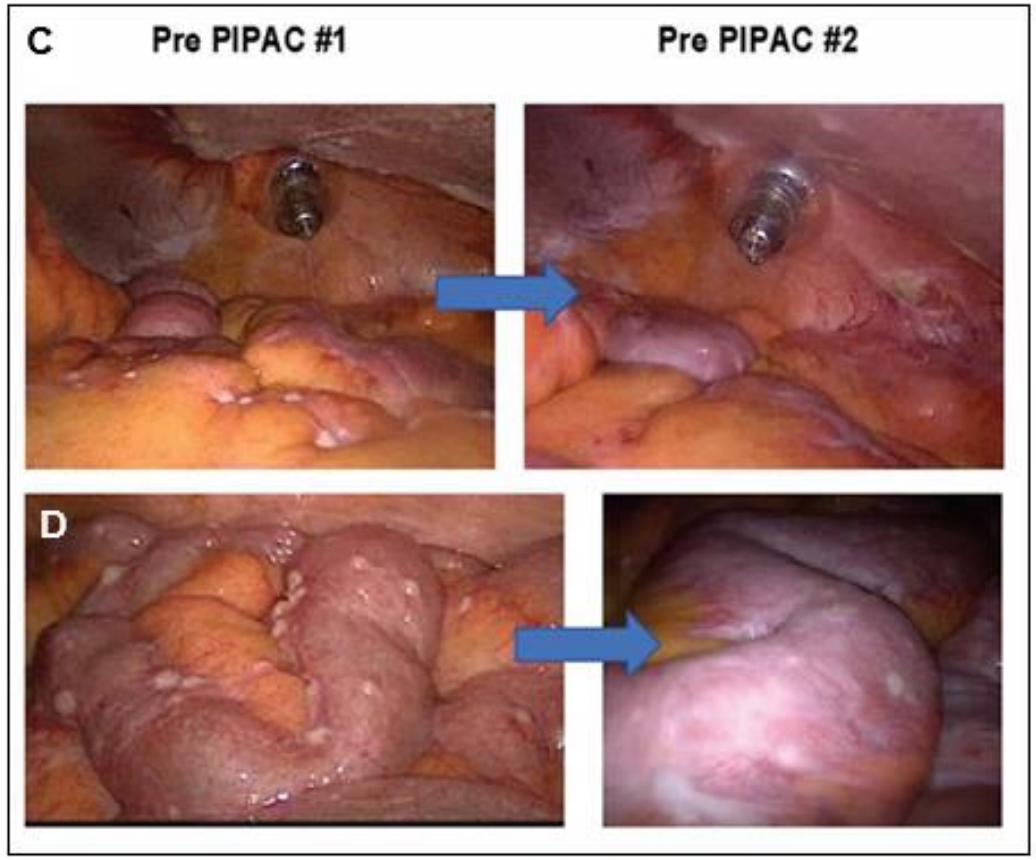



City of Hope · MAYO CLINIC · Northwell Health

Raoof et al, Ann Surg Onc, 2022

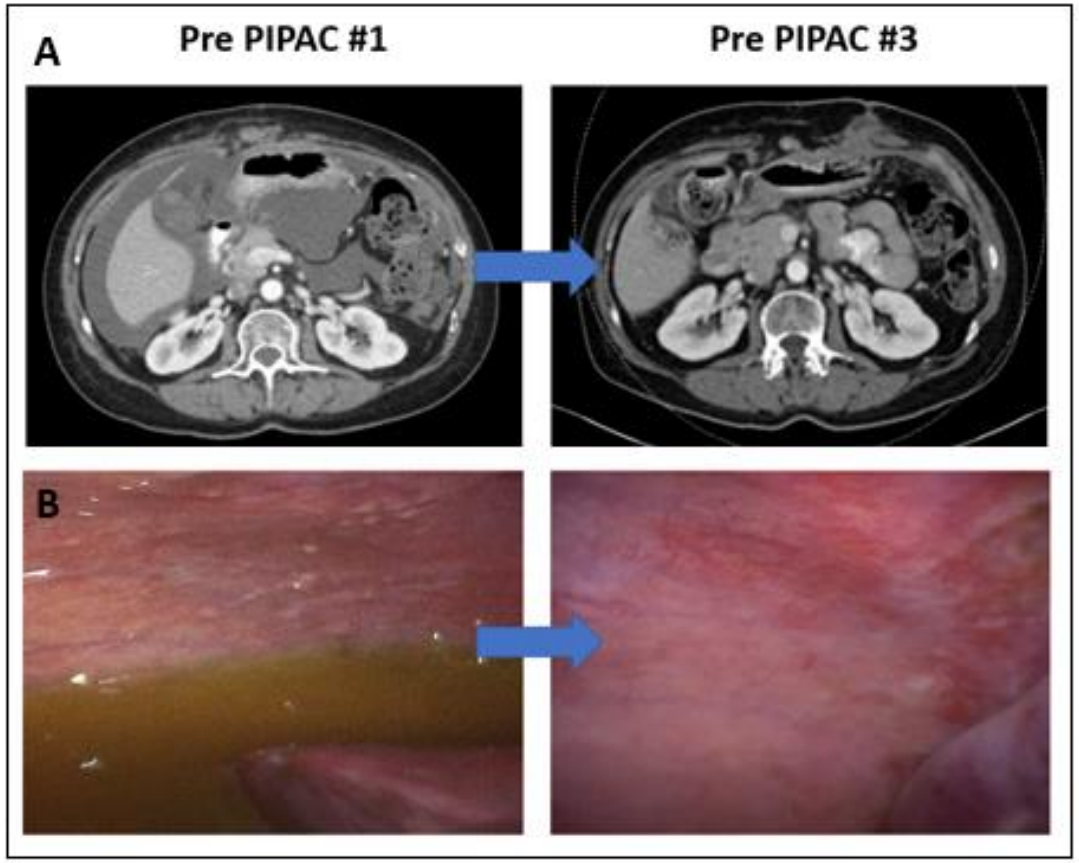
# PIPAC in Low Grade Serous (LGS) Ovarian cancer patients

*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.

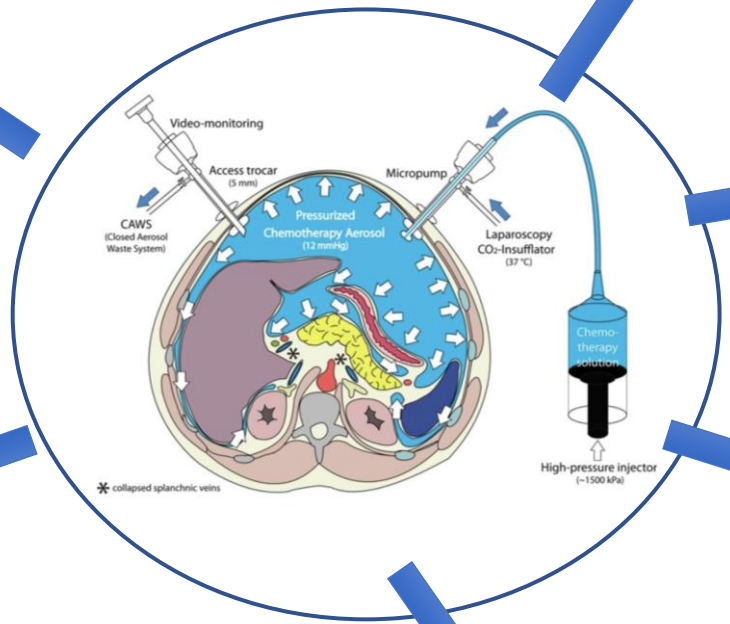
- CA125 = 367 → 32
- Peritoneal tumor regression by RECIST
- Resolution of Ascites

Dellinger et al, SSO virtual poster presentation, 2022

# Indications for PIPAC in ovarian cancer

Platinum-resistant ovarian cancer

Geriatric patients



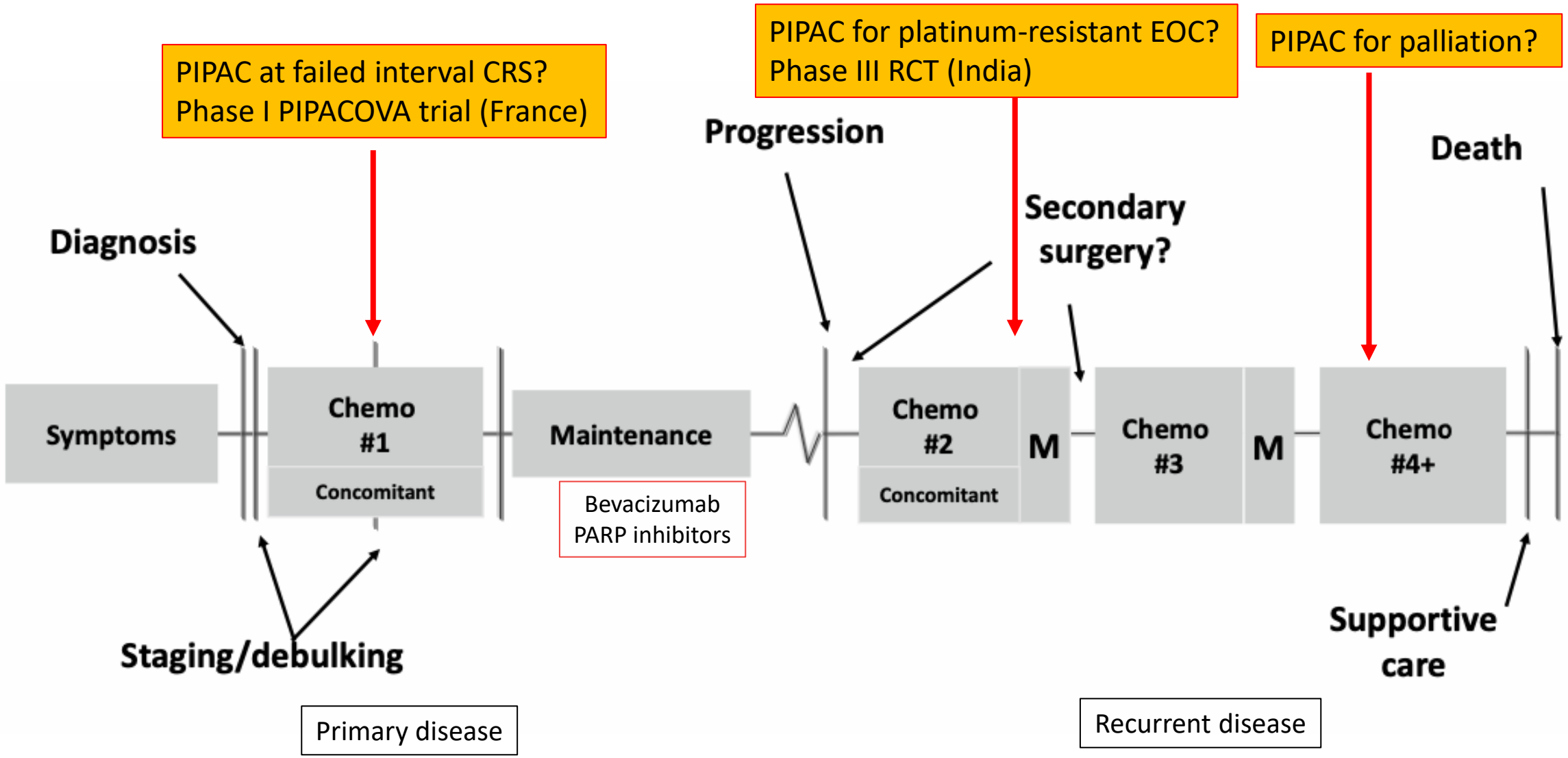

Systemic chemotherapy intolerance

*First-line setting:*
Adjunct to neoadjuvant IV chemo to enable optimal interval CRS?

Low-grade serous ovarian cancer?
Cancers with relative chemoresistance

Adjunct to 2nd line chemotherapy 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

Quality of life

Establish indications

Establish

optimal drug doses and combinations

Multimodal therapy

- IV chemo
- PARP inhibitors
- Bevacizumab
- Checkpoint inhibitors

Novel PIPAC drugs

- nab-paclitaxel
- Checkpoint inhibitors?

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