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## Nab-PIPAC: A PHASE IB TRIAL OF INTRAPERITONEAL CISPLATIN AND NAB-PACLITAXEL ADMINISTERED BY PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN THE TREATMENT OF ADVANCED MALIGNANCIES CONFINED TO THE PERITONEAL CAVITY

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# Nab-PIPAC: A PHASE IB TRIAL OF INTRAPERITONEAL CISPLATIN AND NAB-PACLITAXEL ADMINISTERED BY PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN THE TREATMENT OF ADVANCED MALIGNANCIES CONFINED TO THE PERITONEAL CAVITY

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## Abstract

### *Introduction*

Intraperitoneal dissemination is a major problem resulting in very poor prognosis and a rapid marked deterioration in the quality of life of patients. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an emergent laparoscopic procedure aiming to maximize local efficacy and to reduce systemic side effects.

### *Methods and analysis*

Nab-PIPAC, a bicenter open label phase IB, aim to evaluate safety of nab-paclitaxel and cisplatin association using in patients with peritoneal carcinomatosis (PC) of gastric, pancreatic or ovarian origin as  $\geq 1$  prior line of systemic therapy. Using a 3+3 design, sequential intraperitoneal laparoscopic application of nab-paclitaxel (7.5, 15, 25, 37.5, 52.5 and 70 mg/m<sup>2</sup>) and cisplatin (10.5 mg/m<sup>2</sup>) through a nebulizer to a high-pressure injector at ambient temperature with a maximal upstream pressure of 300 psi. Treatment maintained for 30 minutes at a pressure of 12 mmHg and repeated q4-6 weeks intervals for 3 courses total. A total of 6 to 36 patients are expected, accrual is ongoing. Results are expected in 2024. The primary objective of Nab-PIPAC trial is to assess tolerability and safety of nab-paclitaxel and cisplatin combination administered intraperitoneally by PIPAC in patients with PC of gastric, pancreatic or ovarian origin. This study will determine maximum tolerated dose (MTD) and provide pharmacokinetic data.

### *Ethic and dissemination*

Ethical approval was obtained from the ethical committees of Geneva and Vaud (CCER-2018-01327). The study findings will be published in an open access, peer-reviewed journal and presented at relevant conferences and research meetings.

### *Trial registration*

The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04000906)  
Swiss National Clinical trial Portal (SNCTP000003129 via BASEC).

### Strengths and limitations of this study

- This is the first study that evaluate pressurized intraperitoneal aerosol of nab-paclitaxel and cisplatin intraperitoneal administration; it will determine MTD and provide pharmacokinetic data.
- This study includes quality-of-life assessments to investigate the clinical benefit of Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
- Within this population, the dose-limiting toxicity (DLT) assessment is challenged by peritoneal carcinomatosis (PC) symptoms.
- The efficacy assessment will be limited by small sample size and heterogeneity in tumor's organ origin of participants
- The study includes a translational research program to characterize longitudinal changes induced by PIPAC on tumor immune microenvironment in patients with PC

## Manuscript

### Introduction

Intraperitoneal (IP) dissemination of malignant tumors is a major problem in the management of digestive and gynecological cancers resulting in very poor prognosis and a rapid marked deterioration in the quality of life of these patients. Malignancies most likely to spread to the peritoneum include ovarian (60-70%), gastric (15-43%), colorectal (8-25%), pancreatic, peritoneal mesothelioma and pseudomyxoma peritonei[1].

Maintaining the quality of life of patients in palliative oncology is of great importance. Surgical and/or systemic treatments (intravenous chemotherapy) have limited efficacy in the palliation of symptoms related to PC at the cost of systemic toxicities, which are usually significant. Intravenous chemotherapy efficacy is usually short lived due to poor penetration into the peritoneal cavity. The role of IP chemotherapy is to maximize tumor penetration and optimize cell death while minimizing systemic toxicity[2]. IP chemotherapy is a recommended treatment for epithelial ovarian cancer in combination with maximal cytoreductive surgery and is the standard treatment of pseudomyxoma peritonei[3][4][5]. It has also been studied in several cancers of digestive origin[6].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a laparoscopic procedure used for the IP application of a pressurized aerolization of chemotherapy, hence optimizing therapeutic ratio of the substance administered between local and systemic concentrations, resulting in an improvement of local efficacy and reduction of systemic toxicity. Its application could be repeated at a four-six weeks' interval[7]. A phase I study aiming to report the maximal tolerated dose (MTD) of cisplatin and doxorubicin administered intraperitoneally by PIPAC has found that dose level of 10.5 mg/m<sup>2</sup> and 2.1 mg/m<sup>2</sup> of cisplatin and doxorubicin respectively[10]. A second phase 1 conducted in patients suffering from PC of gastrointestinal origin evaluated the safety and efficacy of oxaliplatin administered by PIPAC and found recommended phase II dose is 120 mg/m<sup>2</sup>; of note, in this study, 12.5% (3/24) patients developed acute pancreatitis as dose-limiting toxicity (DLT)[9][10]. Overall, PIPAC was shown to be feasible and safe in patients with refractory carcinomatosis of various origins, with a low incidence of reported serious adverse events (SAEs) (2-15%) and [11], surgery-related complications (12%)[8][12][13] and meaningful clinical benefit and histological response rate[8][12][13]. Laparoscopic access and repeatability were 83-100% and 38-82% respectively[14]. PIPAC was followed by a modest

1  
2  
3 and transitory inflammatory response, no hematological, renal or hepatic toxicity were  
4 observed even after repetitive administration[15]. Quality of life and symptoms were not  
5 impacted by PIPAC therapy[16]. The available evidence on PIPAC was summarized by a  
6 systematic review confirming its feasibility and tolerance profile[17]. With a standardized  
7 surgical approach and dedicated safety checklist, PIPAC could be safely introduced in  
8 clinical routine with minimal learning curve[18][19]. The overall tumor response ranged  
9 between 40 and 75% in peritoneal carcinomatosis of ovarian and gastric origin with three  
10 successive PIPAC cycles with cisplatin and doxorubicin [8][12][13]. Additionally, practice of  
11 this new drug administration method was studied within an international expert panel  
12 showing excellent standardization of PIPAC among expert centers opening the door for  
13 registries and multi-center studies[20].  
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15

16  
17 Classical chemotherapy components used intravenously for ovarian, gastric and pancreatic  
18 neoplasias belong to the taxane and platin cytostatic families. Nab-paclitaxel is a nanoparticle  
19 albumin-bound formulation of paclitaxel specifically designed to overcome the limitations of  
20 conventional paclitaxel formulations, including the barriers to effective drug delivery of  
21 highly lipophilic agents[21]. Nab-paclitaxel has fewer side effects, shows increased tumor  
22 cell cytotoxicity, and patients have higher overall response rates, compared with equal doses  
23 of solvent-based paclitaxel in many solid malignancies[22]. It has been studied intravenously  
24 in many solid tumors, including four phases II clinical trials for recurrent ovarian cancer  
25 [23][24][25][26] and in two phases II and a phase III trial for recurrent gastric  
26 adenocarcinoma[27][28][29][30]. IP administration of paclitaxel is a standard therapy for  
27 advanced epithelial ovarian carcinoma in North America[31], but the IP administration of  
28 Nab-paclitaxel has been little studied. IP administration of nab-paclitaxel has been evaluated  
29 in phase I trial in 27 patients with gynecologic and digestive PC, with an IP maximal  
30 tolerated dose (MTD) of 140 mg/m<sup>2</sup>. IP administration of nab-paclitaxel showed higher  
31 (~150 fold) peritoneal exposure to the drug compared with the plasma exposure with a low  
32 inter- and intra-patient variability[32].  
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36  
37 Preclinical reports have shown that nab-paclitaxel has an enhanced antitumoral activity due to  
38 its internalization through macropinocytosis by the macrophages of the tumor environment  
39 (TAMs) leading to anti-tumoral immunomodulatory effect[33]. Macropinocytosis is a form of  
40 endocytosis in which a large fluid-filled vesicle is pinched off from the cell membrane and  
41 brought into the interior of the cell. This is particularly relevant as peritoneal carcinomatosis  
42 from tumors highly infiltrated by TAMs have an especially poor prognosis, this hold true for  
43 pancreatic, gastric and ovarian carcinoma [34][35][36]. Tumor-associated macrophages  
44 (TAMs) may be polarized in two phenotypes: type M1 or type M2. TAMs of the M2 phenotype  
45 are known to promote tumor proliferation by suppressing anti-tumor immune reactions and  
46 inducing angiogenesis and are associated with a poor prognosis in numerous cancers[34]. On  
47 the contrary, a ratio favoring type M1 TAMs confers a better prognosis[37]. A mechanism of  
48 action of nab-paclitaxel recently identified in preclinical models of pancreatic cancers is its  
49 capacity to polarize TAMs toward M1 activation state. Nab-paclitaxel-mediated M1 induction  
50 might result in a positive feedback signaling, further promoting uptake of drug and enhancing  
51 its M1-activating effects in autocrine and paracrine fashions[22].  
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55 We hypothesized that nab-paclitaxel could be a good candidate for IP administration by PIPAC  
56 in patients with PC, as this route allows reduced systemic toxicity and increased intra-tumoral  
57 drug concentration. We expect that this local intervention might rebalance favorably PC  
58 immune environment, leading to a prolonged local control and potentially a survival benefit.  
59 As PIPAC procedure is commonly repeated three times, collecting PC samples before each  
60

procedure is a unique opportunity for longitudinal studies of changes in peritoneal tumor immune microenvironment upon exposure to *in situ* therapy.

## Methods and analysis

### *Trial design*

It is a prospective sequential open-label non-randomized multicentric conventional phase IB with a single dose escalation of the investigational drug (nab-paclitaxel, Abraxane®) performed in association with a prespecified cisplatin dose administered intraperitoneally by PIPAC (Figure 1).

### *Study population and recruitment*

This study is intended for patients with peritoneal carcinomas from neoplasias known to be sensitive to platin and/or taxane chemotherapy, who are in a palliative situation, due to peritoneal metastatic spreading, but still in good shape and would offer them an additional therapy that might improve their quality of life and potentially their survival. According to inclusion and exclusion criteria (Table 1), the study population will include all voluntary patients aged > 18 years, psychologically and physically able to follow the trial procedures and to give a written informed consent, suffering from peritoneal carcinomatosis, with limited extra-peritoneal metastases from pancreatic, oesogastric, ovarian cancers or primitive peritoneal mesothelioma, for whom standard therapies have been exhausted, or not feasible, or having residual disease following first line of therapy.

Recruitment of voluntary participants will be done during the oncological multidisciplinary tumor board (gyneco-oncology and gastro-intestinal oncology), the oncologic clinic and referral from private practice and other hospitals. Enrolment started in 2021 with 6 patients enrolled in the two first dose level (DL), expected trial completion year is 2023.

**Table 1. Inclusion / exclusion criteria for all participants**

<i>Inclusion</i>	<i>Exclusion</i>
◆ Informed Consent as documented by signature	◆ Predominant extra-peritoneal metastases at the discretion of the study team after discussion at the multidisciplinary tumor board
◆ Age $\geq 18$ years	◆ Bowel obstruction, active gastro-duodenal ulcer or ongoing abdominal infection (bacterial, viral or fungal)
◆ Who are psychologically able to follow the trial procedures	◆ Chemotherapy or surgery within the last two weeks prior to enrollment
◆ With peritoneal carcinomatosis from pancreatic, oesogastric, epithelial ovarian cancers or primitive peritoneal mesothelioma	◆ General or local (abdominal) contraindications for laparoscopic surgery



<p>◆ Not candidate for surgical cytoreduction and IP/HIPEC based on expert multidisciplinary board</p>	<p>◆ Known allergy to cisplatin or other platinum-containing compounds or to compounds of similar chemical or biologic composition of nab-paclitaxel</p>
<p>◆ Who received at least one line of chemotherapy and for whom standard therapies have been exhausted or not feasible. Patients with residual disease following the first line of therapy or following secondary debulking are eligible.</p>	<p>◆ Severe organ dysfunction including: renal impairment (calculated GFR &lt; 60 mL/min/1.73 m<sup>2</sup>); myelosuppression (platelet count &lt; 100.000/μl, hemoglobin &lt; 9g/dl, neutrophil granulocytes &lt; 1.500/ml); INR ≥ 2; hepatic impairment (serum total bilirubin ≥ 1.5 mg/dl, AST/ALT &gt;1.5 x ULN); severe respiratory or neurologic impairment (grade 3); severe myocardial insufficiency (NYHA class &gt;2), recent myocardial infarction, severe arrhythmias</p>
<p>◆ ECOG 0, 1 or 2</p>	<p>◆ Pregnancy or breastfeeding, women who can become pregnant must ensure effective contraception</p>
<p>◆ Life expectancy &gt; 3 months</p>	<p>◆ Known or suspected non-compliance, inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant</p> <p>• History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.</p>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group performance status scale; GFR, glomerular filtration rate; HIPEC, hyperthermic intraperitoneal chemotherapy; INR, International Normalized Ratio; IP, intraperitoneal; NYHA, New York Heart Association functional classification; ULN, upper limit of normal

### *Study location*

This study will be conducted at the Hôpitaux Universitaires de Genève (HUG) and Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland.

### *Determination of sample size*

The study design consists in a modified Fibonacci sequence (Nab-paclitaxel dose increase by 100%, 67%, 50%, 40%, and 33% for all the rest): 7.5 mg/m<sup>2</sup>, 15 mg/m<sup>2</sup>, 25 mg/m<sup>2</sup>, 37.5 mg/m<sup>2</sup>, 52.5 mg/m<sup>2</sup> and 70 mg/m<sup>2</sup>. Three patients are treated at each dose level (DL) until the first DLT in the first cycle of treatment (defined as grade 3 or 4, CTCAE version 5.0[38]) occurred. If one patient among the three of the first cohort experiences a DLT within 4 weeks from the first cycle of PIPAC, then an additional cohort of 3 patients is treated at the same DL. If no

patient among 3 or 1 among 6 experiences a DLT within 4 weeks from the first cycle of PIPAC, the dose is escalated. The MTD is (maximal tolerated dose) defined as the lowest dose level at which  $\geq 33\%$  ( $\geq 2/6$ ) subjects experienced a DLT during the first cycle of treatment[39].

Within each cohort, a timeframe after the first PIPAC procedure will be respected before starting the treatment of the next patient.

In the first cohort of a DL:

- The first two patients can be enrolled simultaneously in cycle 1, while the third patient could be included only after at least one of the previous patients has completed the DLT monitoring period without experiencing any DLT.
- In case only one patient was initially enrolled: The next 2 patients of the same cohort can be enrolled simultaneously only after the first patient has completed the DLT reporting period without experiencing a DLT. The next 2 patients of the same cohort should be enrolled sequentially, if the first patient experienced a DLT.

In the second cohort of a DL:

- If no DLT was experienced in the first cohort of 3 patients: 2 patients can be enrolled simultaneously, while the third patient should be included only when at least one of the previous patients has completed the DLT monitoring period without experiencing any DLT.
- If 1 DLT was experienced in the first cohort of 3 patients: the 3 planned patients of the second cohort should be enrolled sequentially.

According to the occurrence of a DLT, we are expecting enrollment of 6 to 36 patients.

### *Study outcomes*

#### Primary

The study seeks primarily to assess short-term safety and tolerability of the IP association of cisplatin and nab-paclitaxel administration by PIPAC and to determine the MTD of nab-paclitaxel administered IP by PIPAC in concomitance with cisplatin. MTD defined as the lowest dose level at which  $\geq 33\%$  ( $\geq 2/6$ ) of patients experience DLT in the first cycle of treatment in accordance to CTCAE criteria version 5.0[38]. DLT is defined as any CTCAE Grade 3 or 4 adverse event (AE) determined to be possibly, probably or definitely related to nab-paclitaxel and cisplatin IP administration.

DLTs define as:

#### **Hematologic**

- Febrile neutropenia grade  $>3$  for more than 7 days
- Platelet count decreased grade 3 or 4 for more than 7 days
- Thrombocytopenia requiring transfusion

#### **Non-hematologic**

- Any grade  $\geq 3$  non-hematological trial treatment-emergent adverse event (TEAE). Exception: non-clinically significant non-hematological laboratory findings
- Any treatment-related AE that leads to a delay of treatment in the start of cycle 2 of  $> 14$  days
- Abdominal pain grade  $\geq 3$  during more than 7 days and requiring opioides treatment. Pain will be estimated with visual analogic scale for pain (VAS). The highest VAS value of the day taken in bed will be recorded in the eCRF.

AE related to the primary tumor, such as progression of the disease will not be considered as DLTs.



Documentation of AE and SAE with predefined toxicity criteria will be applied using CTCAE version 5.0 criteria[38], documented before and after the first, second, and third course of treatment (D0/D10 of each cycle). Surgical complications will be assessed according to Clavien classification and comprehensive complication index (CCI)[40].

### Secondary

i) to report pharmacokinetic analysis of free plasmatic concentrations of nab-paclitaxel at pre-dose, end of infusion, H1, H4 and 24 hours after the first PIPAC treatment for the two first patients treated for each new DL

ii) to evaluate histological regression and objective tumor response rate (OTR) assessed according to peritoneal regression grade score system (PRGS)[41] at D1 of second and third PIPAC cycles. Histologic regression will be assessed by pathologic review of repeated peritoneal biopsies proceeded during laparoscopy before each PIPAC cycle, according to the new regression system for peritoneal cancer;

iii) to assess the objective response rate (ORR) and the clinical benefit rate (CBR), defined by revised RECIST version 1.1 criteria[42];

iv) to evaluate any benefit in QoL assessed by EORTC QLQ-C30 v3.0 and visual analogic scale for pain (VAS) questionnaires filled by the patient itself before (D0) and after (D10) each cycle of PIPAC application.

### Correlatives

i) to assess predictive relevance and reproducibility of radiological assessment of peritoneal carcinomatosis index (PCI) by abdominal CT enterography at screening and EOT visit, when available

ii) to evaluate of the impact of locally administered nab-paclitaxel and cisplatin on intratumoral immune response (spatial distribution of immune cell subsets) assessed by multispectral IHC; Assessment of the presence of TAMs (CD68<sup>+</sup>, CD163<sup>+</sup>, Tie2<sup>+</sup>), regulatory T cells (Foxp3<sup>+</sup>), TILs (CD8<sup>+</sup>), plasmacytoid dendritic cells (BDCA2<sup>+</sup>), resident T cells (CD103<sup>+</sup>), PD-L1/PD1 and other immune cells to be defined.

iii) to quantify gene expression by RNAseq, performed on formalin-fixed paraffin embedded (FFPE) tumor samples. Bioinformatic processing will be based on a standardised pipeline (bwa, edgeR); downstream analysis will include unsupervised hierarchical clustering for the discovery of underlying subgroups, differential expression analysis of matched samples before and during treatment and differential expression analysis between responders and non-responders. Gene expression information can also be used to deconvolute immune infiltrates (for example, CIBERSORT, TIMER), supplementing the immunohistochemical estimates.

iv) to evaluate potential predictive biomarkers using whole-exome sequencing performed on blood and FFPE tumor samples obtained before and during treatment and processed on a standardized pipeline (bcBio) for the identification of pathogenic variants (mutations) and copy number alterations (CNVkit). Mutational signatures can also be derived from exome data and have been associated with distinct biological processes, such as deficient DNA repair. We plan to compare the patterns of responders with non-responders in the hope of identifying candidate biomarkers. In addition, we will examine the changes that might have resulted from exposure to treatment, such as the expansion of potentially resistant clones.

Outcomes of interest include (a) the distribution of gene expression profiles, (b) the gene expression changes during treatment, (c) the gene expression differences between responders and non-responders, (d) mutational patterns (pathogenic variants, mutational signatures) predicting response, (e) sub-clonal changes in response to treatment, for example expansion of resistant clones and resistance mutations.

### *Study intervention*

#### Dose rationale

The choice of 10.5 mg/m<sup>2</sup> cisplatin dose has been based on the result of the recent phase I escalation dose of cisplatin and doxorubicin association administered IP by PIPAC[8]. The MTD dose in the phase I of IP nab-paclitaxel administration by catheterism was 140 mg/m<sup>2</sup>[32], we are expecting MTD at a lower dose for this phase I as PIPAC has an enhanced activity and penetration than conventional IP treatment. Cisplatin 10.5 mg/m<sup>2</sup> body surface in 150 ml NaCl 0,9% (concentration of 1mg/ml) and nab-paclitaxel (Abraxane®) in 150 ml NaCl 0,9% at escalating doses will be applied sequentially through a nebulizer (Capnopen®, Capnomed GmbH, Villigendorf, Germany) to a high-pressure injector (Accutron HP-D Injecteur, Medtron AG) with a flow rate of 0.6-0.7 ml/s and a median droplet size of 11 (3-15) µm at ambient temperature and at a maximal upstream pressure of 300 psi intraperitoneally. Treatment will be maintained for 30 minutes after administration at a pressure of 12 mmHg.

PIPAC will be performed only by gynaecologic or gastrointestinal surgeon who has already completed a special training and will be repeated q4-6 week's intervals for a total of 3 courses procedure. The length of stay in hospital for the PIPAC procedure is about 4 days.

#### PIPAC procedure[18]

- Intervention under general anesthesia
- Antibiotic prophylaxis with commercial cephalosporine administered during anesthetic induction
- Introduction of a 5mm optic after insufflation with Hasson technique
- Insufflation capnoperitoneum at 12 mmHg and insertion of 1 trocar of 10/12 for the nebulizer, 1 trocar for the camera and 1 working trocar (ascites removal, biopsies, peritonectomy).
- Removal of ascites and documentation of the volume and cytology
- Documentation of the peritoneal carcinomatosis index (surgical PCI score and Fagotti score for ovarian carcinoma)[43][44]
- 5 punch peritoneal biopsies in the 4 quadrants of the abdomen and 1 peritonectomy of several cm<sup>2</sup>
- Connection of the nebulizer (Capnopen®, Capnomed GmbH, Villigendorf, Germany) to a high-pressure injector (Accutron HP-D Injecteur, Medtron G) and insertion into the abdomen.
- Pressurized dose of cisplatin and nab-paclitaxel at escalating doses will be applied via the nebulizer and injector, with a flow rate of 0.6-0.7 ml/s
- Maximal upstream pressure of 300 psi.
- Treatment to be maintained for up to 30 minutes after administration at ambient temperature and a pressure of 12 mmHg.

### *Study assessment and schedule*

The study schedule is summarized in Table 2. Safety will be assessed by the surgeon at each medical visit before (D0) and after (D10) each PIPAC course and at the EOT visit by a dedicated oncology physician, with predefined toxicity criteria which will be documented according to the CTCAE version 5.0 criteria[38] and consigned in the patient file and electronic case report form (eCRF). Surgical complications will be assessed according to Clavien classification and comprehensive complication index (CCI)[40].

Sequence and duration of all study periods:

- **Screening phase (S, D-28):** will consist in checking that every candidate meets the inclusion criteria and does not have any exclusion criteria. The physician will explain the purpose, the design, the risk and benefit balance of the study and the necessity of a good compliance. All the procedures and tests for the screening phase mentioned in the flow chart must have been completed during the defined interval timeline of 28 following days.
- **Intervention phase (C1D1, C2D1 +/- 3, C3D1 +/-3):** During the intervention phase, each participant intends to have 3 cycles of PIPAC repeated at q4-6 week's intervals. Before each PIPAC cycle (D0), a pre-operative medical visit by the surgeon and laboratory tests will be performed. The estimated duration of the hospitalization is 4 days. After each cycle of PIPAC, a medical visit will be done at day 10 (D10) to evaluate the toxicity and report any TEAE assessed by using CTCAE criteria version 5.0[38], monitoring of vital signs and laboratory parameters and filling the QoL questionnaires (QLQ-C30 Version 3.0 and VAS scale). The highest VAS value of the day taken in bed will be recorded in the eCRF.
- **End of treatment visit (EOT, CXD56 +/-7):** will consist in a medical visit done 2 months after the last PIPAC cycle, with assessment of clinical and biological parameters, chest and CT enterography when available. TEAEs and QoL evaluation will be consigned by the physician in patient's file.
- **Expected duration of participant's participation:** from the screening phase till the EOT visit, the total participation time will be 6-8 months.

## Table 2. Study schedule

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visit Name	Screening	C1 D0	C1 D1	C1 D2	C1 D3	C1D 10	C2 D0	C2 D1	C2 D2	C2 D3	C2D 10	C3 D0	C3 D1	C3 D2	C3 D3	C3D 10	CXD 56 <sup>a</sup>	Q3 M
Scheduling Window	-28	-3				+/- 3	-3	+/-3			+/-3	-3	+/- 3			+/- 3	+/- 7	+/- 14
Patient Information & Consent	x																	
Demographics	x																	
Medical History	x																	
In- /Ex-Criteria	x																	
Physical Examination <sup>b</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG score	x	x				x	x				x	x				x	x	
AE/SAE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
DLT evaluation <sup>c</sup>							x											
Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology <sup>d</sup>	x <sup>d</sup>	x				x	x				x	x				x	x	
Serum Chemistry <sup>d</sup>	x <sup>d</sup>	x				x	x				x	x				x	x	
Coagulation <sup>d</sup>	x <sup>d</sup>																	
Serum Tumor biomarker <sup>d</sup>	x <sup>d</sup>						x					x						x
Urine analysis <sup>d</sup>	x <sup>d</sup>																	
Pregnancy Test	(x) <sup>e</sup>	(x)					(x)					(x)						
Chest CT	x																	x
CT enterography (CT-PCI score)	x											X <sup>g</sup>						x
ECG	x																	



Universitaires de Genève) and the Faculty of Medicine of Geneva University (UNIGE). UIC is certified ISO 9001/2008, and the unit guarantees best practices in the field of clinical data management. Data are physically stored in a relational database management system, using a deidentified dedicated clinical database management system software [secuTrial®]. All study documents will be archived on site for the minimum of at least 10 years after study termination. A risk-based monitoring will be conducted by the UIC and the frequency of monitoring visits will be determined by factors such as the frequency of subject visits and the site enrolment rate. Upon study completion, the Sponsor representative will visit the site to conduct a study termination visit. The source data/documents will be accessible to monitors and questions will be answered during monitoring.

### *Statistical analysis plan*

#### Participant Characteristics

Patient characteristics will be tabulated for visual comparison. For quantitative variables, the following descriptive statistics will be given: N, Mean and 95% confidence interval, Standard Deviation, Median and Interquartile range (for non-normally distributed); for qualitative variables, the Frequency and Percentage of patients within each category will be provided.

#### Adverse events

TEAEs and SAEs will be summarized by presenting the number and percentage of patients having any AE, having any event by body system and having each individual AE (incidence, relationship to Nab-PIPAC, severity according CTCAE version 5.0)[38]. AEs that result in death (other than disease progression), discontinuation or SAEs will be presented separately. Any other information, e.g. time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment will be listed for all participants.

#### Laboratory parameters

All laboratory results mentioned in the eCRF monitored at each planned visit which are not in line with the laboratory normal ranges and/or the CTCAE version 5.0 criteria[38] will be summarized by presenting shift tables using normal ranges, by presenting summary statistics of raw data and changes from baseline values (mean, median, standard deviation, range) and by flagging of notable values in data listings.

#### Vital signs

Vital signs at baseline and change from baseline will be summarized by changes from baseline values (mean, median, standard deviation, range) and by flagging of notable values in data listings.

The trial will end in case of more than one grade 5 event related to the Investigational product or to the study procedure (CTCAE version 5.0)[38]. Deaths due to progressive disease are not considered as grade 5 events. Patients who will prematurely withdraw from the study will be displayed and summarized by primary reason and treatment. No deviation(s) from the planned analyses will be justified.

A safety report will be performed 16 weeks after the last eligible patient has completed the last third cycle of PIPAC. Intent-to-treat (ITT) analysis will be performed on all patients who receive at least two cycles of PIPAC. The final efficacy analysis will be performed one year after the last eligible patient has completed the last follow-up visit. Survivals will be reported using Kaplan-Meier curves. A final report will be issued at the end of the trial. The statistical analysis will be conducted by a dedicated biostatistician.

### *Patient and Public Involvement*

No patient involved.



## Discussion

Recently, Ceelen et al reported results of their phase 1 evaluating the safety of nab-paclitaxel administration by PIPAC in patients with PC from ovarian, breast, gastric, hepatobiliary, or pancreatic origin. In this study, PIPAC was associated to concomitant systemic treatment in 65% of the twenty-one enrolled patients. Safety results were encouraging, with no major surgical complications or mortality and manageable hematological toxicity. Unless patients have known hepatobiliary functional impairment, the MTD and recommended phase II dose was defined as 140 mg/m<sup>2</sup>. Overall response rate according to PRGS was 35% (7/21) with stable disease present in 35% (7/21)[45].

In comparison to the phase I reported by Ceelen et al, our study varies in its inclusion criteria, definition of DLT and design. For instance, they excluded fatigue and abdominal symptoms (nausea and abdominal pain) from their definition of DLT, while we consider any grade  $\geq 3$  non-hematological TEAEs, including abdominal pain as a DLT. Further, they allowed systemic chemotherapy prior to and in between two PIPAC cycles, which is not the case in our study. Finally, their study investigated nab-paclitaxel monotherapy while we combine it with cisplatin. Such differences in the design are expected to lead to differences in the DLT between both studies.

## Registration and categorization of study

The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04000906)

Swiss National Clinical trial Portal (SNCTP000003129 via BASEC).

The clinical trial comes under category B (clinical trials of medicinal products).

## Ethics and dissemination

Approvals of the Commission cantonale d'éthique de la recherche de Genève (CCER), la Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD). The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH and the Swiss Law and Swiss regulatory authority's requirements.

Study findings will be published in an open access, peer-reviewed journal and presented at relevant conferences and research meetings.

## Authors' contributions

NL conceptualized the original study and drafted the manuscript. MH, ILG, MU, MD and FR contributed to refining the study design. UIC is the monitoring manager. MH, ILG, AD, FR, PP, CT, NM and MU critically revised the manuscript. NL was the principal investigator (2018-2019), ILG and AD are the current principal investigators (2019-2022). IL is the lead researcher. All authors have approved the final draft of the manuscript.

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**Competing interests**

None declared for IL, FR, MU, AD, PP, CT, MD and NM.

MH declares the following competing interests: ENCARE Consultant fee (institution); Nestlé; Research funding Capnomed Sponsoring of scientific meetings MSD; Fresenius Speaker honorary (institution); ERAS society Board member, chair education; ISSPP Board member, chair education.

For peer review only

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4 2015.  
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8 **Figure 1. Nab-PIPAC Study design**

9 1A. Peritoneal carcinomatosis from oesogastric, pancreatic, ovarian origin and primitive  
10 peritoneal mesothelioma; 1B. PIPAC procedure; 1C. 3+3 escalating dose level (DL) design;  
11 1D. Translational research using multiplex immunohistochemistry (IHC), RNA sequencing  
12 and whole exome sequencing  
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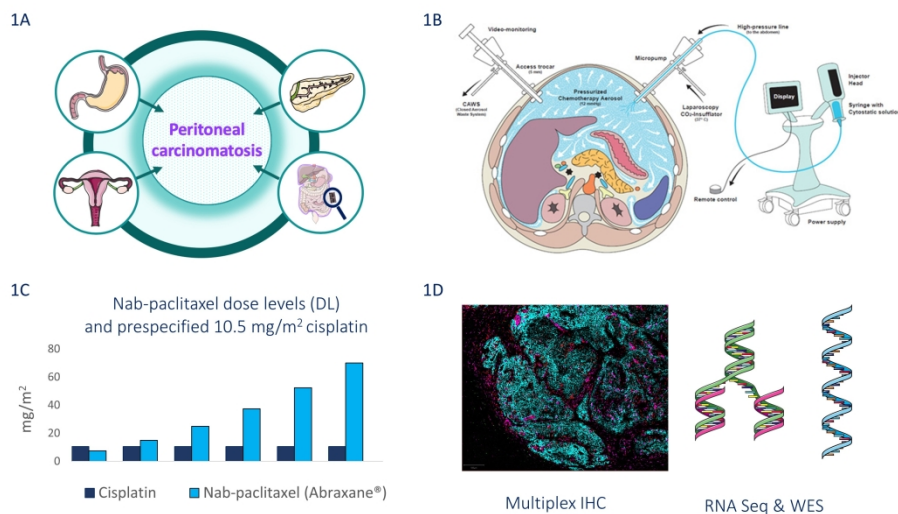


Figure 1. Nab-PIPAC Study design

1A. Peritoneal carcinomatosis from oesogastric, pancreatic, ovarian origin and primitive peritoneal mesothelioma; 1B. PIPAC procedure; 1C. 3+3 escalating dose level (DL) design; 1D. Translational research using multiplex immunohistochemistry (IHC), RNA sequencing and whole exome sequencing

338x190mm (300 x 300 DPI)

# BMJ Open

## Nab-PIPAC: A PHASE IB STUDY PROTOCOL OF INTRAPERITONEAL CISPLATIN AND NAB-PACLITAXEL ADMINISTERED BY PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN THE TREATMENT OF ADVANCED MALIGNANCIES CONFINED TO THE PERITONEAL CAVITY

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Keywords:	Gynaecological oncology < GYNAECOLOGY, Adult oncology < ONCOLOGY, Gastrointestinal tumours < ONCOLOGY

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Manuscripts

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3 1 **Nab-PIPAC: A PHASE IB STUDY PROTOCOL OF INTRAPERITONEAL**  
4 2 **CISPLATIN AND NAB-PACLITAXEL ADMINISTERED BY PRESSURIZED**  
5 3 **INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN THE**  
6 4 **TREATMENT OF ADVANCED MALIGNANCIES CONFINED TO THE**  
7 5 **PERITONEAL CAVITY**  
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33 27

34 28 **Abstract**

35 29 *Introduction*

36 30 Intraperitoneal dissemination is a major problem resulting in very poor prognosis and a rapid  
37 31 marked deterioration in the quality of life of patients. Pressurized intraperitoneal aerosol  
38 32 chemotherapy (PIPAC) is an emergent laparoscopic procedure aiming to maximize local  
39 33 efficacy and to reduce systemic side effects.

40 34 *Methods and analysis*

41 35 Nab-PIPAC, a bicenter open label phase IB, aim to evaluate safety of nab-paclitaxel and  
42 36 cisplatin association using in patients with peritoneal carcinomatosis (PC) of gastric,  
43 37 pancreatic or ovarian origin as  $\geq 1$  prior line of systemic therapy. Using a 3+3 design,  
44 38 sequential intraperitoneal laparoscopic application of nab-paclitaxel (7.5, 15, 25, 37.5, 52.5  
45 39 and 70 mg/m<sup>2</sup>) and cisplatin (10.5 mg/m<sup>2</sup>) through a nebulizer to a high-pressure injector at  
46 40 ambient temperature with a maximal upstream pressure of 300 psi. Treatment maintained for  
47 41 30 minutes at a pressure of 12 mmHg and repeated q4-6 weeks intervals for 3 courses total.  
48 42 A total of 6 to 36 patients are expected, accrual is ongoing. Results are expected in 2024.  
49 43 The primary objective of Nab-PIPAC trial is to assess tolerability and safety of nab-paclitaxel  
50 44 and cisplatin combination administered intraperitoneally by PIPAC in patients with PC of  
51 45 gastric, pancreatic or ovarian origin. This study will determine maximum tolerated dose (MTD)  
52 46 and provide pharmacokinetic data.

53 47 *Ethic and dissemination*

54 48 Ethical approval was obtained from the ethical committees of Geneva and Vaud (CCER-  
55 49 2018-01327). The study findings will be published in an open access, peer-reviewed journal  
56 50 and presented at relevant conferences and research meetings.  
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### *Trial registration*

The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04000906). Data sharing will follow ICMJE statements. Swiss National Clinical trial Portal (SNCTP000003129 via BASEC).

### **Strengths and limitations of this study**

- This is the first study that evaluate pressurized intraperitoneal aerosol of nab-paclitaxel and cisplatin intraperitoneal administration; it will determine MTD and provide pharmacokinetic data.
- This study includes quality-of-life assessments to investigate the clinical benefit of Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
- Within this population, the dose-limiting toxicity (DLT) assessment is challenged by peritoneal carcinomatosis (PC) symptoms.
- The efficacy assessment will be limited by small sample size and heterogeneity in tumor's organ origin of participants
- The study includes a translational research program to characterize longitudinal changes induced by PIPAC on tumor immune microenvironment in patients with PC

### **Manuscript**

#### **Introduction**

Intraperitoneal (IP) dissemination of malignant tumors is a major problem in the management of digestive and gynecological cancers resulting in very poor prognosis and a rapid marked deterioration in the quality of life of these patients. Malignancies most likely to spread to the peritoneum include ovarian (60-70%), gastric (15-43%), colorectal (8-25%), pancreatic, peritoneal mesothelioma and pseudomyxoma peritonei[1].

Maintaining the quality of life of patients in palliative oncology is of great importance. Surgical and/or systemic treatments (intravenous chemotherapy) have limited efficacy in the palliation of symptoms related to PC at the cost of systemic toxicities, which are usually significant. Intravenous chemotherapy efficacy is usually short lived due to poor penetration into the peritoneal cavity. The role of IP chemotherapy is to maximize tumor penetration and optimize cell death while minimizing systemic toxicity[2]. IP chemotherapy is a recommended treatment for epithelial ovarian cancer in combination with maximal cytoreductive surgery and is the standard treatment of pseudomyxoma peritonei[3][4][5]. It has also been studied in several cancers of digestive origin[6].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a laparoscopic procedure used for the IP application of a pressurized aerolization of chemotherapy, hence optimizing therapeutic ratio of the substance administered between local and systemic concentrations, resulting in an improvement of local efficacy and reduction of systemic toxicity. Its application could be repeated at a four-six weeks' interval[7]. A phase I study aiming to report the maximal tolerated dose (MTD) of cisplatin and doxorubicin administered intraperitoneally by PIPAC has found that dose level of 10.5 mg/m<sup>2</sup> and 2.1 mg/m<sup>2</sup> of cisplatin and doxorubicin respectively[8]. A second phase 1 conducted in patients suffering from PC of gastrointestinal origin evaluated the safety and efficacy of oxaliplatin administered by PIPAC and found recommended phase II dose is 120 mg/m<sup>2</sup>; of note, in this study, 12.5% (3/24) patients developed acute pancreatitis as dose-limiting toxicity (DLT)[8][9]. Overall, PIPAC was shown to be feasible and safe in patients with refractory carcinomatosis of various origins, with a low incidence of reported serious adverse events (SAEs) (2-15%) and [10], surgery-related complications (12%)[11][12][13] and meaningful

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3 101 clinical benefit and histological response rate[11][12][13]. Laparoscopic access and  
4 102 repeatability were 83-100% and 38-82% respectively[14]. PIPAC was followed by a modest  
5 103 and transitory inflammatory response, no hematological, renal or hepatic toxicity were  
6 104 observed even after repetitive administration[15]. Quality of life and symptoms were not  
7 105 impacted by PIPAC therapy[16]. The available evidence on PIPAC was summarized by a  
8 106 systematic review confirming its feasibility and tolerance profile[17]. With a standardized  
9 107 surgical approach and dedicated safety checklist, PIPAC could be safely introduced in  
10 108 clinical routine with minimal learning curve[18][19]. The overall tumor response ranged  
11 109 between 40 and 75% in peritoneal carcinomatosis of ovarian and gastric origin with three  
12 110 successive PIPAC cycles with cisplatin and doxorubicin [11][12][13]. Additionally, practice  
13 111 of this new drug administration method was studied within an international expert panel  
14 112 showing excellent standardization of PIPAC among expert centers opening the door for  
15 113 registries and multi-center studies[20].  
16 114

17 115 Classical chemotherapy components used intravenously for ovarian, gastric and pancreatic  
18 116 neoplasias belong to the taxane and platin cytostatic families. Nab-paclitaxel is a nanoparticle  
19 117 albumin-bound formulation of paclitaxel specifically designed to overcome the limitations of  
20 118 conventional paclitaxel formulations, including the barriers to effective drug delivery of  
21 119 highly lipophilic agents[21]. Nab-paclitaxel has fewer side effects, shows increased tumor  
22 120 cell cytotoxicity, and patients have higher overall response rates, compared with equal doses  
23 121 of solvent-based paclitaxel in many solid malignancies[22]. It has been studied intravenously  
24 122 in many solid tumors, including four phases II clinical trials for recurrent ovarian cancer  
25 123 [23][24][25][26] and in two phases II and a phase III trial for recurrent gastric  
26 124 adenocarcinoma[27][28][29][30]. IP administration of paclitaxel is a standard therapy for  
27 125 advanced epithelial ovarian carcinoma in North America[31], but the IP administration of  
28 126 Nab-paclitaxel has been little studied. IP administration of nab-paclitaxel has been evaluated  
29 127 in phase I trial in 27 patients with gynecologic and digestive PC, with an IP maximal  
30 128 tolerated dose (MTD) of 140 mg/m<sup>2</sup>. IP administration of nab-paclitaxel showed higher  
31 129 (~150 fold) peritoneal exposure to the drug compared with the plasma exposure with a low  
32 130 inter- and intra-patient variability[32].  
33 131

34 132 Preclinical reports have shown that nab-paclitaxel has an enhanced antitumoral activity due to  
35 133 its internalization through macropinocytosis by the macrophages of the tumor environment  
36 134 (TAMs) leading to anti-tumoral immunomodulatory effect[33]. Macropinocytosis is a form of  
37 135 endocytosis in which a large fluid-filled vesicle is pinched off from the cell membrane and  
38 136 brought into the interior of the cell. This is particularly relevant as peritoneal carcinomatosis  
39 137 from tumors highly infiltrated by TAMs have an especially poor prognosis, this hold true for  
40 138 pancreatic, gastric and ovarian carcinoma [34][35][36]. Tumor-associated macrophages  
41 139 (TAMs) may be polarized in two phenotypes: type M1 or type M2. TAMs of the M2 phenotype  
42 140 are known to promote tumor proliferation by suppressing anti-tumor immune reactions and  
43 141 inducing angiogenesis and are associated with a poor prognosis in numerous cancers[34]. On  
44 142 the contrary, a ratio favoring type M1 TAMs confers a better prognosis[37]. A mechanism of  
45 143 action of nab-paclitaxel recently identified in preclinical models of pancreatic cancers is its  
46 144 capacity to polarize TAMs toward M1 activation state. Nab-paclitaxel-mediated M1 induction  
47 145 might result in a positive feedback signaling, further promoting uptake of drug and enhancing  
48 146 its M1-activating effects in autocrine and paracrine fashions[22].  
49 147

50 148 We hypothesized that nab-paclitaxel could be a good candidate for IP administration by PIPAC  
51 149 in patients with PC, as this route allows reduced systemic toxicity and increased intra-tumoral  
52 150 drug concentration. We expect that this local intervention might rebalance favorably PC



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3 151 immune environment, leading to a prolonged local control and potentially a survival benefit.  
4 152 As PIPAC procedure is commonly repeated three times, collecting PC samples before each  
5 153 procedure is a unique opportunity for longitudinal studies of changes in peritoneal tumor  
6 154 immune microenvironment upon exposure to *in situ* therapy.  
7 155

## 9 156 **Methods and analysis**

### 10 157 *Trial design*

11 158 It is a prospective sequential open-label non-randomized multicentric conventional phase IB  
12 159 with a single dose escalation of the investigational drug (nab-paclitaxel, Abraxane®)  
13 160 performed in association with a prespecified cisplatin dose administered intraperitoneally by  
14 161 PIPAC (Figure 1)[38].  
15 162

### 16 163 *Study population and recruitment*

17 164 This study is intended for patients with peritoneal carcinomas from neoplasias known to be  
18 165 sensitive to platin and/or taxane chemotherapy, who are in a palliative situation, due to  
19 166 peritoneal metastatic spreading, but still in good shape and would offer them an additional  
20 167 therapy that might improve their quality of life and potentially their survival. According to  
21 168 inclusion and exclusion criteria (Table 1), the study population will include all voluntary  
22 169 patients aged > 18 years, psychologically and physically able to follow the trial procedures and  
23 170 to give a written informed consent, suffering from peritoneal carcinomatosis, with limited extra-  
24 171 peritoneal metastases from pancreatic, oesogastric, ovarian cancers or primitive peritoneal  
25 172 mesothelioma, for whom standard therapies have been exhausted, or not feasible, or having  
26 173 residual disease following first line of therapy.  
27 174

28 175 Recruitment of voluntary participants will be done during the oncological multidisciplinary  
29 176 tumor board (gyneco-oncology and gastro-intestinal oncology), the oncologic clinic and  
30 177 referral from private practice and other hospitals. Enrolment started in 2021 with 6 patients  
31 178 enrolled in the two first dose level (DL), expected trial completion year is 2023.  
32 179

33 180 **Table 1. Inclusion / exclusion criteria for all participants**  
34 181

<i>Inclusion</i>	<i>Exclusion</i>
<b>Informed Consent as documented by signature</b>	Predominant extra-peritoneal metastases at the discretion of the study team after discussion at the multidisciplinary tumor board
<b>Age ≥18 years</b>	Bowel obstruction, active gastro-duodenal ulcer or ongoing abdominal infection (bacterial, viral or fungal)
<b>Who are psychologically able to follow the trial procedures</b>	Chemotherapy or surgery within the last two weeks prior to enrollment
<b>With peritoneal carcinomatosis from pancreatic, oesogastric, epithelial ovarian cancers or primitive peritoneal mesothelioma</b>	General or local (abdominal) contra-indications for laparoscopic surgery
<b>Not candidate for surgical cytoreduction and IP/HIPEC based on</b>	Known allergy to cisplatin or other platinum-containing compounds or to compounds of

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	<b>expert multidisciplinary board</b>	similar chemical or biologic composition of nab-paclitaxel
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	<b>Who received at least one line of chemotherapy and for whom standard therapies have been exhausted or not feasible. Patients with residual disease following the first line of therapy or following secondary debulking are eligible.</b>	Severe organ dysfunction including: renal impairment (calculated GFR < 60 mL/min/1.73 m <sup>2</sup> ); myelosuppression (platelet count < 100.000/ $\mu$ l, hemoglobin < 9g/dl, neutrophil granulocytes < 1.500/ml); INR $\geq$ 2; hepatic impairment (serum total bilirubin $\geq$ 1.5 mg/dl, AST/ALT >1.5 x ULN); severe respiratory or neurologic impairment (grade 3); severe myocardial insufficiency (NYHA class >2), recent myocardial infarction, severe arrhythmias
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	<b>ECOG 0, 1 or 2</b>	Pregnancy or breastfeeding, women who can become pregnant must ensure effective contraception
	<b>Life expectancy &gt; 3 months</b>	Known or suspected non-compliance, inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant  History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

182 ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group performance status  
183 scale; GFR, glomerular filtration rate; HIPEC, hyperthermic intraperitoneal chemotherapy; INR, International Normalized Ratio; IP,  
184 intraperitoneal; NYHA, New York Heart Association functional classification; ULN, upper limit of normal

#### 185 186 *Study location*

187 This study will be conducted at the Hôpitaux Universitaires de Genève (HUG) and Centre  
188 Hospitalier Universitaire Vaudois (CHUV), Switzerland.

#### 189 190 *Determination of sample size*

191 The study design consists in a modified Fibonacci sequence (Nab-paclitaxel dose increase by  
192 100%, 67%, 50%, 40%, and 33% for all the rest): 7.5 mg/m<sup>2</sup>, 15 mg/m<sup>2</sup>, 25 mg/m<sup>2</sup>, 37.5 mg/m<sup>2</sup>,  
193 52.5 mg/m<sup>2</sup> and 70 mg/m<sup>2</sup>. Three patients are treated at each dose level (DL) until the first  
194 DLT in the first cycle of treatment (defined as grade 3 or 4, CTCAE version 5.0[39]) occurred.  
195 If one patient among the three of the first cohort experiences a DLT within 4 weeks from the  
196 first cycle of PIPAC, then an additional cohort of 3 patients is treated at the same DL. If no  
197 patient among 3 or 1 among 6 experiences a DLT within 4 weeks from the first cycle of PIPAC,  
198 the dose is escalated. The MTD is (maximal tolerated dose) defined as the lowest dose level at  
199 which  $\geq$ 33% ( $\geq$  2/6) subjects experienced a DLT during the first cycle of treatment[40].

200 Within each cohort, a timeframe after the first PIPAC procedure will be respected before  
201 starting the treatment of the next patient.

202 In the first cohort of a DL:

- The first two patients can be enrolled simultaneously in cycle 1, while the third patient could be included only after at least one of the previous patients has completed the DLT monitoring period without experiencing any DLT.
- In case only one patient was initially enrolled: The next 2 patients of the same cohort can be enrolled simultaneously only after the first patient has completed the DLT reporting period without experiencing a DLT. The next 2 patients of the same cohort should be enrolled sequentially, if the first patient experienced a DLT.

In the second cohort of a DL:

- If no DLT was experienced in the first cohort of 3 patients: 2 patients can be enrolled simultaneously, while the third patient should be included only when at least one of the previous patients has completed the DLT monitoring period without experiencing any DLT.
- If 1 DLT was experienced in the first cohort of 3 patients: the 3 planned patients of the second cohort should be enrolled sequentially.

According to the occurrence of a DLT, we are expecting enrollment of 6 to 36 patients.

### *Study outcomes*

#### Primary

The study seeks primarily to assess short-term safety and tolerability of the IP association of cisplatin and nab-paclitaxel administration by PIPAC and to determine the MTD of nab-paclitaxel administered IP by PIPAC in concomitance with cisplatin. MTD defined as the lowest dose level at which  $\geq 33\%$  ( $\geq 2/6$ ) of patients experience DLT in the first cycle of treatment in accordance to CTCAE criteria version 5.0[39]. DLT is defined as any CTCAE Grade 3 or 4 adverse event (AE) determined to be possibly, probably or definitely related to nab-paclitaxel and cisplatin IP administration.

DLTs define as:

#### ***Hematologic***

- Febrile neutropenia grade  $>3$  for more than 7 days
- Platelet count decreased grade 3 or 4 for more than 7 days
- Thrombocytopenia requiring transfusion

#### ***Non-hematologic***

- Any grade  $\geq 3$  non-hematological trial treatment-emergent adverse event (TEAE). Exception: non-clinically significant non-hematological laboratory findings
- Any treatment-related AE that leads to a delay of treatment in the start of cycle 2 of  $> 14$  days
- Abdominal pain grade  $\geq 3$  during more than 7 days and requiring opioides treatment. Pain will be estimated with visual analogic scale for pain (VAS). The highest VAS value of the day taken in bed will be recorded in the eCRF.

AE related to the primary tumor, such as progression of the disease will not be considered as DLTs.

Documentation of AE and SAE with predefined toxicity criteria will be applied using CTCAE version 5.0 criteria[38], documented before and after the first, second, and third course of treatment (D0/D10 of each cycle). Surgical complications will be assessed according to Clavien classification and comprehensive complication index (CCI)[41].

#### Secondary

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3 252 i) to report pharmacokinetic analysis of free plasmatic concentrations of nab-paclitaxel at pre-  
4 253 dose, end of infusion, H1, H4 and 24 hours after the first PIPAC treatment for the two first  
5 254 patients treated for each new DL  
6  
7 255 ii) to evaluate histological regression and objective tumor response rate (OTR) assessed  
8 256 according to peritoneal regression grade score system (PRGS)[42] at D1 of second and third  
9 257 PIPAC cycles. Histologic regression will be assessed by pathologic review of repeated  
10 258 peritoneal biopsies proceeded during laparoscopy before each PIPAC cycle, according to the  
11 259 new regression system for peritoneal cancer;  
12 260 iii) to assess the objective response rate (ORR) and the clinical benefit rate (CBR), defined by  
13 261 revised RECIST version 1.1 criteria[43];  
14 262 iv) to evaluate any benefit in QoL assessed by EORTC QLQ-C30 v3.0 and visual analogic  
15 263 scale for pain (VAS) questionnaires filled by the patient itself before (D0) and after (D10) each  
16 264 cycle of PIPAC application.  
17 265

### 18 265 19 266 Correlatives

- 20 267 i) to assess predictive relevance and reproducibility of radiological assessment of peritoneal  
21 268 carcinomatosis index (PCI) by abdominal CT enterography at screening and EOT visit, when  
22 269 available  
23 270 ii) to evaluate of the impact of locally administered nab-paclitaxel and cisplatin on intratumoral  
24 271 immune response (spatial distribution of immune cell subsets) assessed by multispectral IHC;  
25 272 Assessment of the presence of TAMs (CD68<sup>+</sup>, CD163<sup>+</sup>, Tie2<sup>+</sup>), regulatory T cells (Foxp3<sup>+</sup>),  
26 273 TILs (CD8<sup>+</sup>), plasmacytoid dendritic cells (BDCA2<sup>+</sup>), resident T cells (CD103<sup>+</sup>), PD-L1/  
27 274 PD1 and other immune cells to be defined.  
28 275 iii) to quantify gene expression by RNAseq, performed on formalin-fixed paraffin embedded  
29 276 (FFPE) tumor samples. Bioinformatic processing will be based on a standardised pipeline  
30 277 (bwa, edgeR); downstream analysis will include unsupervised hierarchical clustering for the  
31 278 discovery of underlying subgroups, differential expression analysis of matched samples before  
32 279 and during treatment and differential expression analysis between responders and non-  
33 280 responders. Gene expression information can also be used to deconvolute immune infiltrates  
34 281 (for example, CIBERSORT, TIMER), supplementing the immunohistochemical estimates.  
35 282 iv) to evaluate potential predictive biomarkers using whole-exome sequencing performed on  
36 283 blood and FFPE tumor samples obtained before and during treatment and processed on a  
37 284 standardized pipeline (bcbio) for the identification of pathogenic variants (mutations) and copy  
38 285 number alterations (CNVkit). Mutational signatures can also be derived from exome data and  
39 286 have been associated with distinct biological processes, such as deficient DNA repair. We plan  
40 287 to compare the patterns of responders with non-responders in the hope of identifying candidate  
41 288 biomarkers. In addition, we will examine the changes that might have resulted from exposure  
42 289 to treatment, such as the expansion of potentially resistant clones.  
43 290 Outcomes of interest include (a) the distribution of gene expression profiles, (b) the gene  
44 291 expression changes during treatment, (c) the gene expression differences between responders  
45 292 and non-responders, (d) mutational patterns (pathogenic variants, mutational signatures)  
46 293 predicting response, (e) sub-clonal changes in response to treatment, for example expansion of  
47 294 resistant clones and resistance mutations.  
48 295

### 49 296 Study intervention

#### 50 297 Dose rationale

51 298 The choice of 10.5 mg/m<sup>2</sup> cisplatin dose has been based on the result of the recent phase I  
52 299 escalation dose of cisplatin and doxorubicin association administered IP by PIPAC[8]. The  
53 300 MTD dose in the phase I of IP nab-paclitaxel administration by catheterism was 140  
54 301 mg/m<sup>2</sup>[32], we are expecting MTD at a lower dose for this phase I as PIPAC has an enhanced

activity and penetration than conventional IP treatment. Cisplatin 10.5 mg/m<sup>2</sup> body surface in 150 ml NaCl 0,9% (concentration of 1mg/ml) and nab-paclitaxel (Abraxane®) in 150 ml NaCl 0,9% at escalating doses will be applied sequentially through a nebulizer (Capnopen®, Capnomed GmbH, Villigendorf, Germany) to a high-pressure injector (Accutron HP-D Injecteur, Medtron AG) with a flow rate of 0.6-0.7 ml/s and a median droplet size of 11 (3-15) µm at ambient temperature and at a maximal upstream pressure of 300 psi intraperitoneally. Treatment will be maintained for 30 minutes after administration at a pressure of 12 mmHg.

PIPAC will be performed only by gynaecologic or gastrointestinal surgeon who has already completed a special training and will be repeated q4-6 week's intervals for a total of 3 courses procedure. The length of stay in hospital for the PIPAC procedure is about 4 days.

#### PIPAC procedure[18]

- Intervention under general anesthesia
- Antibiotic prophylaxis with commercial cephalosporine administered during anesthetic induction
- Introduction of a 5mm optic after insufflation with Hasson technique
- Insufflation capnoperitoneum at 12 mmHg and insertion of 1 trocar of 10/12 for the nebulizer, 1 trocar for the camera and 1 working trocar (ascites removal, biopsies, peritonectomy).
- Removal of ascites and documentation of the volume and cytology
- Documentation of the peritoneal carcinomatosis index (surgical PCI score and Fagotti score for ovarian carcinoma)[44][45]
- 5 punch peritoneal biopsies in the 4 quadrants of the abdomen and 1 peritonectomy of several cm<sup>2</sup>
- Connection of the nebulizer (Capnopen®, Capnomed GmbH, Villigendorf, Germany) to a high-pressure injector (Accutron HP-D Injecteur, Medtron G) and insertion into the abdomen.
- Pressurized dose of cisplatin and nab-paclitaxel at escalating doses will be applied via the nebulizer and injector, with a flow rate of 0.6-0.7 ml/s
- Maximal upstream pressure of 300 psi.
- Treatment to be maintained for up to 30 minutes after administration at ambient temperature and a pressure of 12 mmHg.

#### *Study assessment and schedule*

The study schedule is summarized in Table 2. Safety will be assessed by the surgeon at each medical visit before (D0) and after (D10) each PIPAC course and at the EOT visit by a dedicated oncology physician, with predefined toxicity criteria which will be documented according to the CTCAE version 5.0 criteria[39] and consigned in the patient file and electronic case report form (eCRF). Surgical complications will be assessed according to Clavien classification and comprehensive complication index (CCI)[41].

Sequence and duration of all study periods:

- **Screening phase (S, D-28):** will consist in checking that every candidate meets the inclusion criteria and does not have any exclusion criteria. The physician will explain the purpose, the design, the risk and benefit balance of the study and the necessity of a good compliance. All the procedures and tests for the screening phase mentioned in the flow chart must have been completed during the defined interval timeline of 28 following days.



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3 352 - **Intervention phase (C1D1, C2D1 +/- 3, C3D1 +/-3):** During the intervention phase,  
4 353 each participant intends to have 3 cycles of PIPAC repeated at q4-6 week's intervals.  
5 354 Before each PIPAC cycle (D0), a pre-operative medical visit by the surgeon and  
6 355 laboratory tests will be performed. The estimated duration of the hospitalization is 4  
7 356 days. After each cycle of PIPAC, a medical visit will be done at day 10 (D10) to  
8 357 evaluate the toxicity and report any TEAE assessed by using CTCAE criteria version  
9 358 5.0[38], monitoring of vital signs and laboratory parameters and filling the QoL  
10 359 questionnaires (QLQ-C30 Version 3.0 and VAS scale). The highest VAS value of the  
11 360 day taken in bed will be recorded in the eCRF.  
12 361 - **End of treatment visit (EOT, CXD56 +/-7):** will consist in a medical visit done 2  
13 362 months after the last PIPAC cycle, with assessment of clinical and biological  
14 363 parameters, chest and CT enterography when available. TEAEs and QoL evaluation  
15 364 will be consigned by the physician in patient's file.  
16 365 - **Expected duration of participant's participation:** from the screening phase till the  
17 366 EOT visit, the total participation time will be 6-8 months.  
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21 **Table 2. Study schedule**  
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Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visit Name	Screening	C1 D0	C1 D1	C1 D2	C1 D3	C1D 10	C2 D0	C2 D1	C2 D2	C2 D3	C2D 10	C3 D0	C3 D1	C3 D2	C3 D3	C3D 10	CXD 56 <sup>a</sup>	Q3 M
Scheduling Window	-28	-3				+/- 3	-3	+/-3			+/-3	-3	+/- 3			+/- 3	+/- 7	+/- 14
Patient Information & Consent	x																	
Demographics	x																	
Medical History	x																	
In- /Ex-Criteria	x																	
Physical Examination <sup>b</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG score	x	x				x	x				x	x				x	x	
AE/SAE	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
DLT evaluation <sup>c</sup>							x											
Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology <sup>d</sup>	x <sup>d</sup>	x				x	x				x	x				x	x	
Serum Chemistry <sup>d</sup>	x <sup>d</sup>	x				x	x				x	x				x	x	
Coagulation <sup>d</sup>	x <sup>d</sup>																	
Serum Tumor biomarker <sup>d</sup>	x <sup>d</sup>						x					x						x
Urine analysis <sup>d</sup>	x <sup>d</sup>																	
Pregnancy Test	(x) <sup>e</sup>	(x)					(x)					(x)						
Chest CT	x																	x
CT enterography (CT-PCI score)	x											X <sup>g</sup>						x
ECG	x																	

Ascite volume			x					x						x					
PIPAC			x					x						x					
Surgical PCI score			x					x						x					
Biopsies (standard & translational)			x					x						x					
Blood sampling (translational research)		x																	
PK (free plasmaic nab-paclitaxel) <sup>h</sup>			x	x															
QoL		x				x	x				x	x				x	x		
VAS <sup>i</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Survival status																			x
Pathology and Molecular analysis			x																
Disease status																			x

370 <sup>a</sup> To be performed 56 days after the last PIPAC administration

371 <sup>b</sup> Neurological examination with pallesthesia and abdominal circumference only requested at screening visit

372 <sup>c</sup> For Dose Limiting Toxicities, refer to study outcomes section

373 <sup>d</sup> To be performed within 10 days prior to registration

374 <sup>e</sup> To be performed within 7 days prior to registration

375 <sup>f</sup> when available

376 <sup>g</sup> 3 days before in order to assess the PCI score before the next administration

377 <sup>h</sup> Blood samples for pharmacokinetic analysis will be performed at the following timepoints: Pre-dose 30  
378 minutes [± 5 minutes], end of infusion [± 15 minutes], 1 hour [± 15 minutes], 4 hours [± 30 minutes], 24 hours  
379 [± 4 hours]. Samples collected at the first cycle of PIPAC for the two first patients treated for each dose level  
380 escalation.

381 <sup>i</sup> highest value of the day taken in bed

382

### 383 *Data handling and monitoring*

384 Data generation, transmission, archiving and analysis of personal data within this study, strictly  
385 follows Swiss legal requirements according to the federal law on data security, as well as the  
386 regulation on professional secrecy in clinical research. Prerequisite is the voluntary approval  
387 of the participant given by signing the informed consent prior start of participation of the  
388 clinical trial. Informed consent will be obtained by dedicated treating physicians or physician  
389 from the DFDL unit (Department of Oncology, HUG). Health related personal data captured  
390 during this project are strictly confidential and accessible only by investigators and authorized  
391 personnel. Coding will safeguard participants' confidentiality. Data management is performed  
392 by DFDL unit (Department of Oncology, HUG). Data monitoring is performed by UIC (Unité

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3 393 d'Investigation Clinique), a unit which is part of CRC (Centre de Recherche Clinique / CTU)  
4 394 at HUG (Hôpitaux Universitaires de Genève) and the Faculty of Medicine of Geneva  
5 395 University (UNIGE). UIC is certified ISO 9001/2008, and the unit guarantees best practices in  
6 396 the field of clinical data management. Data are physically stored in a relational database  
7 397 management system, using a deidentified dedicated clinical database management system  
8 398 software [secuTrial®]. All study documents will be archived on site for the minimum of at  
9 399 least 10 years after study termination. A risk-based monitoring will be conducted by the UIC  
10 400 and the frequency of monitoring visits will be determined by factors such as the frequency of  
11 401 subject visits and the site enrolment rate. Upon study completion, the Sponsor representative  
12 402 will visit the site to conduct a study termination visit. The source data/documents will be  
13 403 accessible to monitors and questions will be answered during monitoring.  
14 404

#### 17 405 *Statistical analysis plan*

##### 18 406 Participant Characteristics

19 407 Patient characteristics will be tabulated for visual comparison. For quantitative variables, the  
20 408 following descriptive statistics will be given: N, Mean and 95% confidence interval, Standard  
21 409 Deviation, Median and Interquartile range (for non-normally distributed); for qualitative  
22 410 variables, the Frequency and Percentage of patients within each category will be provided.

##### 24 411 Adverse events

25 412 TEAEs and SAEs will be summarized by presenting the number and percentage of patients  
26 413 having any AE, having any event by body system and having each individual AE (incidence,  
27 414 relationship to Nab-PIPAC, severity according CTCAE version 5.0)[39]. AEs that result in  
28 415 death (other than disease progression), discontinuation or SAEs will be presented separately.  
29 416 Any other information, e.g. time of onset, duration, resolution, action to be taken, assessment  
30 417 of intensity, relationship with study treatment will be listed for all participants.

##### 32 418 Laboratory parameters

33 419 All laboratory results mentioned in the eCRF monitored at each planned visit which are not in  
34 420 line with the laboratory normal ranges and/or the CTCAE version 5.0 criteria[39] will be  
35 421 summarized by presenting shift tables using normal ranges, by presenting summary statistics  
36 422 of raw data and changes from baseline values (mean, median, standard deviation, range) and  
37 423 by flagging of notable values in data listings.

##### 39 424 Vital signs

40 425 Vital signs at baseline and change from baseline will be summarized by changes from baseline  
41 426 values (mean, median, standard deviation, range) and by flagging of notable values in data  
42 427 listings.  
43 428

45 429 The trial will end in case of more than one grade 5 event related to the Investigational product  
46 430 or to the study procedure (CTCAE version 5.0)[39]. Deaths due to progressive disease are not  
47 431 considered as grade 5 events. Patients who will prematurely withdraw from the study will be  
48 432 displayed and summarized by primary reason and treatment. No deviation(s) from the planned  
49 433 analyses will be justified.  
50 434

52 435 A safety report will be performed 16 weeks after the last eligible patient has completed the last  
53 436 third cycle of PIPAC. Intent-to-treat (ITT) analysis will be performed on all patients who  
54 437 receive at least two cycles of PIPAC. The final efficacy analysis will be performed one year  
55 438 after the last eligible patient has completed the last follow-up visit. Survivals will be reported  
56 439 using Kaplan-Meier curves. A final report will be issued at the end of the trial. The statistical  
57 440 analysis will be conducted by a dedicated biostatistician.  
58 441

#### 59 441 *Patient and Public Involvement*

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3 443 No patient involved.  
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### 445 **Discussion**

446 Recently, Ceelen et al reported results of their phase 1 evaluating the safety of nab-paclitaxel  
447 administration by PIPAC in patients with PC from ovarian, breast, gastric, hepatobiliary, or  
448 pancreatic origin. In this study, PIPAC was associated to concomitant systemic treatment in  
449 65% of the twenty-one enrolled patients. Safety results were encouraging, with no major  
450 surgical complications or mortality and manageable hematological toxicity. Unless patients  
451 have known hepatobiliary functional impairment, the MTD and recommended phase II dose  
452 was defined as 140 mg/m<sup>2</sup>. Overall response rate according to PRGS was 35% (7/21) with  
453 stable disease present in 35% (7/21)[46].  
454

455 In comparison to the phase I reported by Ceelen et al, our study varies in its inclusion criteria,  
456 definition of DLT and design. For instance, they excluded fatigue and abdominal symptoms  
457 (nausea and abdominal pain) from their definition of DLT, while we consider any grade  $\geq 3$   
458 non-hematological TEAEs, including abdominal pain as a DLT. Further, they allowed systemic  
459 chemotherapy prior to and in between two PIPAC cycles, which is not the case in our study.  
460 Finally, their study investigated nab-paclitaxel monotherapy while we combine it with  
461 cisplatin. Such differences in the design are expected to lead to differences in the DLT between  
462 both studies.  
463

### 464 **Registration and categorization of study**

465 The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04000906). Swiss National Clinical  
466 trial Portal (SNCTP000003129 via BASEC).

467 The clinical trial comes under category B (clinical trials of medicinal products).

468 Data sharing will follow ICMJE statements. All individual deidentified participant data  
469 collected during the trial (including data dictionary) will be shared following publication, no  
470 end date. Data will be shared for meta-analysis or any academic purpose. Related documents  
471 will be available (study protocol, ICF).  
472

### 473 **Ethics and dissemination**

474 This study protocol (version 4.0 4.06.2021) and its amendments have been approved by the  
475 Commission cantonale d'éthique de la recherche de Genève (CCER) and  
476 la Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER-VD). The  
477 study will be carried out in accordance to the protocol and with principles enunciated in the  
478 current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP)  
479 issued by ICH and the Swiss Law and Swiss regulatory authority's requirements.  
480

481 Study findings will be published in an open access, peer-reviewed journal and presented at  
482 relevant conferences and research meetings.  
483

### 484 **Authors' contributions**

485 NL conceptualized the original study and drafted the manuscript. MH, ILG, MU, MD and FR  
486 contributed to refining the study design. MH, ILG, AD, FR, PP, CT, NM and MU critically  
487 revised the manuscript. NL was the principal investigator (2018-2019), ILG and AD are the  
488 current principal investigators (2019-2022). IL is the lead researcher. All authors have  
489 approved the final draft of the manuscript.  
490

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1  
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6 495 department of oncology (HUG), the department of oncology (CHUV) , the division of  
7 496 visceral surgery (CHUV), la fondation pour l’innovation sur le cancer et la biologie and the  
8 497 “Fond’action contre le cancer” foundation.  
9

10 498

11 499 **Competing interests**

12 500 None declared for IL, FR, MU, AD, PP, CT, MD and NM.

13 501 MH declares the following competing interests: ENCARE Consultant fee (institution);  
14 502 Nestlé; Research funding Capnomed Sponsoring of scientific meetings MSD; Fresenius  
15 503 Speaker honorary (institution); ERAS society Board member, chair education; ISSPP  
16 504 Board member, chair education.  
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9 **Figure 1. Nab-PIPAC Study design**

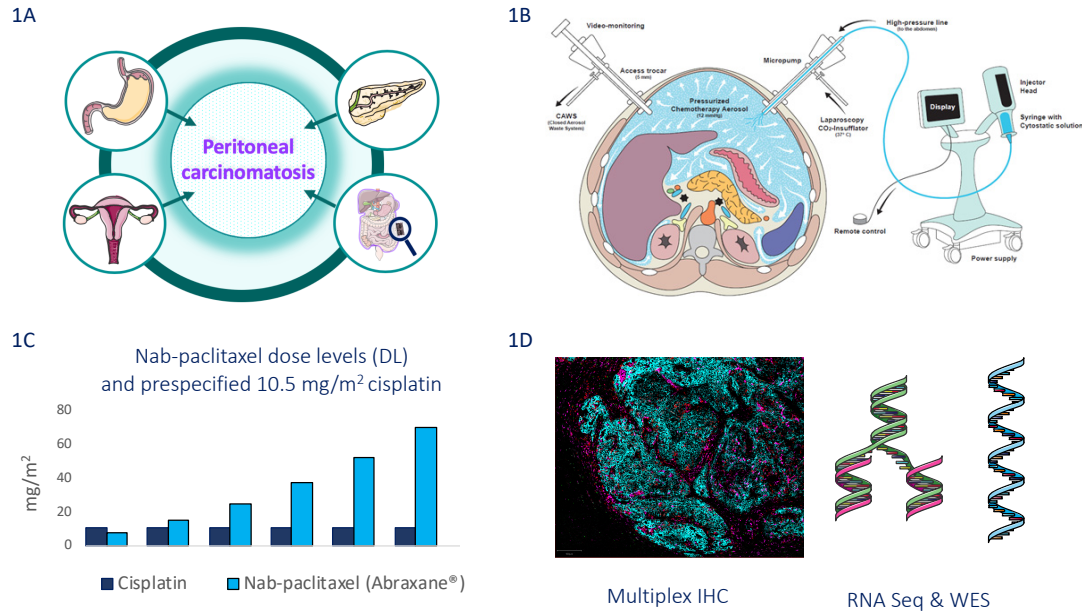
10 671 1A. Peritoneal carcinomatosis from oesogastric, pancreatic, ovarian origin and primitive  
11 672 peritoneal mesothelioma; 1B. PIPAC procedure; 1C. 3+3 escalating dose level (DL) design;  
12 673 1D. Translational research using multiplex immunohistochemistry (IHC), RNA sequencing  
13 674 and whole exome sequencing  
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For peer review only

**Figure 1. Nab-PIPAC Study design**

1A. Peritoneal carcinomatosis from oesogastric, pancreatic, ovarian origin and primitive peritoneal mesothelioma; 1B. PIPAC procedure; 1C. 3+3 escalating dose level (DL) design; 1D. Translational research using multiplex immunohistochemistry (IHC), RNA sequencing and whole exome sequencing



This figure was partly generated using PIPAC schema published in “Hübner, M., et al. PIPAC – Chimiothérapie intrapéritonéale vaporisée. Un traitement innovateur de la carcinose péritonéale”, Rev Med Suisse, Vol. 1, no. 479, 2015, pp. 1325–1330, and Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license