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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 ≥ 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^2) and cisplatin (10.5 mg/m^2) 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 (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^2 and 2.1 mg/m^2 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/m2; 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

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

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

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

We hypothesized that nab-paclitaxel could be a good candidate for IP administration by PIPAC in patients with PC, as this route allows reduced systemic toxicity and increased intra-tumoral drug concentration. We expect that this local intervention might rebalance favorably PC immune environment, leading to a prolonged local control and potentially a survival benefit. As PIPAC procedure is commonly repeated three times, collecting PC samples before each

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

Inclusion	*Exclusion*
♦ 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 ≥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) contra-indications for laparoscopic surgery

♦ Not candidate for surgical cytoreduction and IP/HIPEC based on expert multidisciplinary board	♦ Known allergy to cisplatin or other platinum-containing compounds or to compounds of similar chemical or biologic composition of nab-paclitaxel
♦ 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.	♦ Severe organ dysfunction including: renal impairment (calculated GFR < 60 mL/min/1.73 m^2); myelosuppression (platelet count < 100.000/µl, hemoglobin < 9g/dl, neutrophil granulocytes < 1.500/ml); INR ≥ 2; hepatic impairment (serum total bilirubin ≥ 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
♦ ECOG 0, 1 or 2	♦ Pregnancy or breastfeeding, women who can become pregnant must ensure effective contraception
♦ Life expectancy > 3 months	♦ 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.

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, intraperintoaneal; 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^2, 15 mg/m^2, 25 mg/m^2, 37.5 mg/m^2, 52.5 mg/m^2 and 70 mg/m^2. 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 ≥33% (≥ 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 ≥33% (≥ 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 ≥ 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 ≥ 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 ($CD68^+$, $CD163^+$, $Tie2^+$), regulatory T cells ($Foxp3^+$), TILs ($CD8^+$), plasmacytoid dendritic cells ($BDCA2^+$), resident T cells ($CD103^+$), PD-L1/ PD1and 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^2 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^2[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^2 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^2
- 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**	**C1D0**	**C1D1**	**C1D2**	**C1D3**	**C1D10**	**C2D0**	**C2D1**	**C2D2**	**C2D3**	**C2D10**	**C3D0**	**C3D1**	**C3D2**	**C3D3**	**C3D10**	**CXD56[a]**	**Q3M**
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[b]	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[c]							x											
Concomitant Medication	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	
Hematology[d]	x[d]	x				x	x				x	x				x	x	
Serum Chemistry[d]	x[d]	x				x	x				x	x				x	x	
Coagulation[d]	x[d]																	
Serum Tumor biomarker[d]	x[d]						x					x					x	
Urine analysis[d]	x[d]																	
Pregnancy Test	(x)[e]	(x)					(x)					(x)						
Chest CT	x																x	
CT enterograph (CT-PCI score)	x											X[g]					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 plasmatic nab-paclitaxel)[h]			x	x														
QoL		x				x	x				x	x				x	x	
VAS[i]	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

[a] To be performed 56 days after the last PIPAC administration
[b] Neurological examination with pallesthesia and abdominal circumference only requested at screening visit
[c] For Dose Limiting Toxicities, refer to study outcomes section
[d] To be performed within 10 days prior to registration
[e] To be performed within 7 days prior to registration
[f] when available
[g] 3 days before in order to assess the PCI score before the next administration
[h] Blood samples for pharmacokinetic analysis will be performed at the following timepoints: Pre-dose 30 minutes [± 5 minutes], end of infusion [± 15 minutes], 1 hour [± 15 minutes], 4 hours [± 30 minutes], 24 hours [± 4 hours]. Samples collected at the first cycle of PIPAC for the two first patients treated for each dose level escalation.
[i] highest value of the day taken in bed

Data handling and monitoring

Data generation, transmission, archiving and analysis of personal data within this study, strictly follows Swiss legal requirements according to the federal law on data security, as well as the regulation on professional secrecy in clinical research. Prerequisite is the voluntary approval of the participant given by signing the informed consent prior start of participation of the clinical trial. Health related personal data captured during this project are strictly confidential and accessible only by investigators and authorized personnel. Coding will safeguard participants' confidentiality. Data management is performed by DFDL unit (Department of Oncology, HUG). Data monitoring is performed by UIC (Unité d'Investigation Clinique), a unit which is part of CRC (Centre de Recherche Clinique / CTU) at HUG (Hôpitaux

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/m2. 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 ≥ 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 (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.

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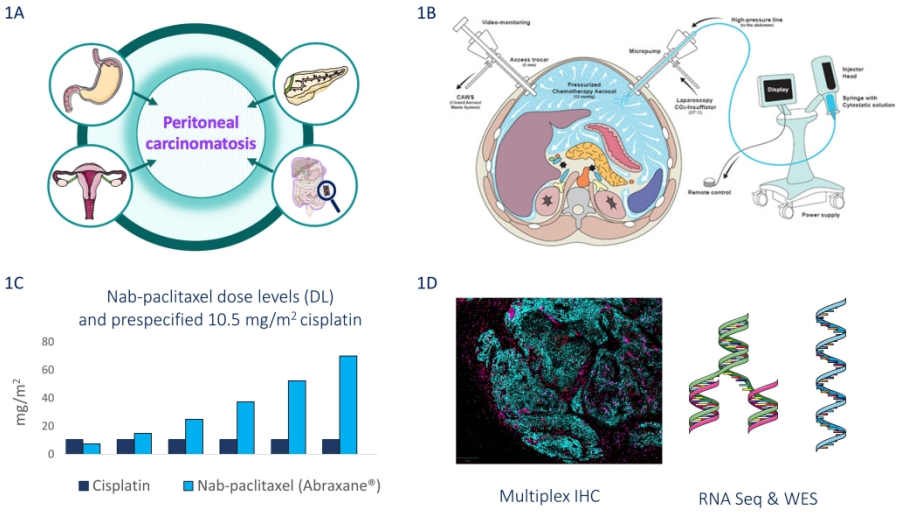
Figure 1. Nab-PIPAC Study design

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 sequnecing and whole exome sequencing



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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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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 ≥ 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^2) and cisplatin (10.5 mg/m^2) 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 (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^2 and 2.1 mg/m^2 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/m2; 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

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

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

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

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

immune environment, leading to a prolonged local control and potentially a survival benefit. As PIPAC procedure is commonly repeated three times, collecting PC samples before each 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)[38].

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

Inclusion	*Exclusion*
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 ≥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) contra-indications for laparoscopic surgery
Not candidate for surgical cytoreduction and IP/HIPEC based on	Known allergy to cisplatin or other platinum-containing compounds or to compounds of

expert multidisciplinary board	similar chemical or biologic composition of nab-paclitaxel
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.	Severe organ dysfunction including: renal impairment (calculated GFR < 60 mL/min/1.73 m^2); myelosuppression (platelet count < 100.000/µl, hemoglobin < 9g/dl, neutrophil granulocytes < 1.500/ml); INR ≥ 2; hepatic impairment (serum total bilirubin ≥ 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
ECOG 0, 1 or 2	Pregnancy or breastfeeding, women who can become pregnant must ensure effective contraception
Life expectancy > 3 months	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.

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, intraperintoaneal; 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^2, 15 mg/m^2, 25 mg/m^2, 37.5 mg/m^2, 52.5 mg/m^2 and 70 mg/m^2. 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[39]) 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 ≥33% (≥ 2/6) subjects experienced a DLT during the first cycle of treatment[40].
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 ≥33% (≥ 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 ≥ 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 ≥ 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

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)[42] 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[43];
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 ($CD68^+$, $CD163^+$, $Tie2^+$), regulatory T cells ($Foxp3^+$), TILs ($CD8^+$), plasmacytoid dendritic cells ($BDCA2^+$), resident T cells ($CD103^+$), PD-L1/ PD1and 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^2 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^2[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^2 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^2
- 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.

- **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**	**C1D0**	**C1D1**	**C1D2**	**C1D3**	**C1D10**	**C2D0**	**C2D1**	**C2D2**	**C2D3**	**C2D10**	**C3D0**	**C3D1**	**C3D2**	**C3D3**	**C3D10**	**CXD56[a]**	**Q3M**
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[b]	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[c]							x											
Concomitant Medication	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	
Hematology[d]	x[d]	x				x	x				x	x				x	x	
Serum Chemistry[d]	x[d]	x				x	x				x	x				x	x	
Coagulation[d]	x[d]																	
Serum Tumor biomarker[d]	x[d]						x					x					x	
Urine analysis[d]	x[d]																	
Pregnancy Test	(x)[e]	(x)					(x)					(x)						
Chest CT	x																x	
CT enterograph (CT-PCI score)	x											X[g]					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 plasmatic nab-paclitaxel)[h]			x	x													
QoL		x				x	x				x	x				x	x	
VAS[i]	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

[a] To be performed 56 days after the last PIPAC administration
[b] Neurological examination with pallesthesia and abdominal circumference only requested at screening visit
[c] For Dose Limiting Toxicities, refer to study outcomes section
[d] To be performed within 10 days prior to registration
[e] To be performed within 7 days prior to registration
[f] when available
[g] 3 days before in order to assess the PCI score before the next administration
[h] Blood samples for pharmacokinetic analysis will be performed at the following timepoints: Pre-dose 30 minutes [± 5 minutes], end of infusion [± 15 minutes], 1 hour [± 15 minutes], 4 hours [± 30 minutes], 24 hours [± 4 hours]. Samples collected at the first cycle of PIPAC for the two first patients treated for each dose level escalation.
[i] highest value of the day taken in bed

Data handling and monitoring

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

d'Investigation Clinique), a unit which is part of CRC (Centre de Recherche Clinique / CTU) at HUG (Hôpitaux 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)[39]. 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[39] 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)[39]. 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/m2. Overall response rate according to PRGS was 35% (7/21) with stable disease present in 35% (7/21)[46].

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 ≥ 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 (NCT04000906). Swiss National Clinical trial Portal (SNCTP000003129 via BASEC).
The clinical trial comes under category B (clinical trials of medicinal products).
Data sharing will follow ICMJE statements. All individual deidentified participant data collected during the trial (including data dictionary) will be shared following publication, no end date. Data will be shared for meta-analysis or any academic purpose. Related documents will be available (study protocol, ICF).

Ethics and dissemination

This study protocol (version 4.0 4.06.2021) and its amendements have been approved by the Commission cantonale d'éthique de la recherche de Genève (CCER) and 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. 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.

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Figure 1. Nab-PIPAC Study design

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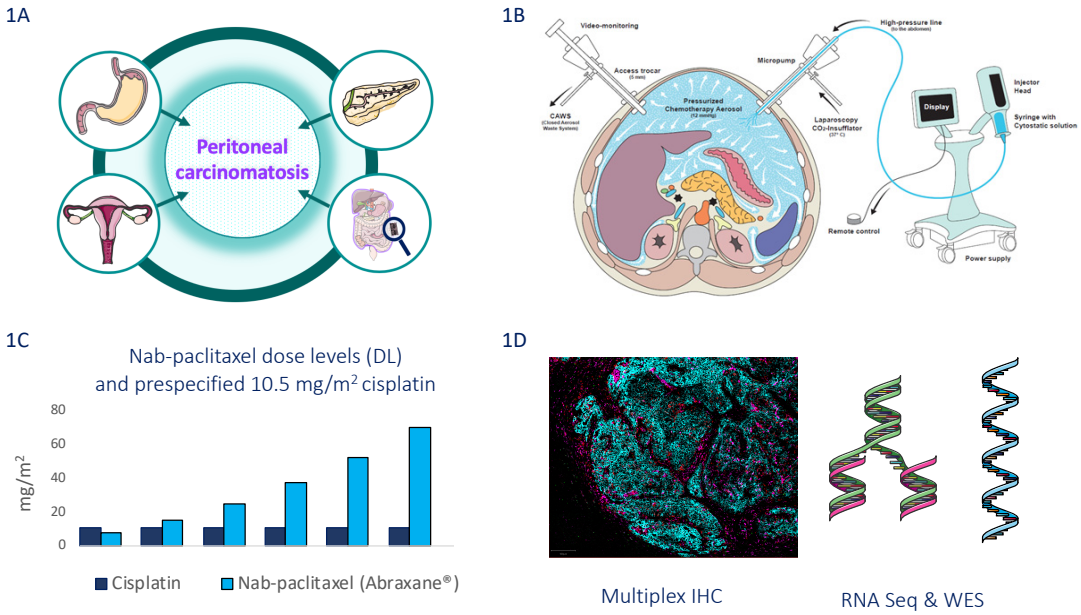

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