PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Lang, Noemie; Diciola, Antonella; Labidi-Galy, Intidhar; Ris, Frédéric; Di Marco, Mariagrazia; Mach, Nicolas; Petignat, Patrick; Toso, Christian; Undurraga, Manuela; HUBNER, Martin

VERSION 1 – REVIEW

REVIEWER	Paolo Sammartino Umberto I Policlinico di Roma, Pietro Valdoni
REVIEW RETURNED	30-Sep-2022

GENERAL COMMENTS	Interesting paper but the different disease included makes it more a pharmacological exercise than a study able to impact the outcome of completely different patients.

REVIEWER	Jessica Reid The University of Adelaide
REVIEW RETURNED	18-Nov-2022

GENERAL COMMENTS	Dear Dr Lang and Team, Congratulations on this well written PIPAC protocol combining nab-paclitaxel with cisplatin for patients with unresectable peritoneal disease. The nab-paclitaxel dose escalation methodology is rational and the toxicity measures are logical for this patient cohort. We have two minor points for your consideration. The first is that many centres are admitting PIPAC patients as day cases, or discharging the next day. It may be possible to reduce the 4 day window mentioned here for select patients. The second point relates to patients who experience favourable oncological results. Would you be able to offer those patients additional cycles beyond the protocol? This may disrupt the statistics for disease/survival status, but would be welcomed by patients and their families. We wish you all the best with this important study and look forward to viewing your results. Dr Jessica Reid PhD Dr Markus Trochsler MD MMIS FMH FRACS

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Paolo Sammartino, Umberto I Policlinico di Roma
Comments to the Author:
Interesting paper but the different disease included makes it more a pharmacological exercise than a study able to impact the outcome of completely different patients.

→ Response to Reviewer 1
Dear Dr Paolo Sammartino,
Thank you for considering our study protocol for review. The main aim of this phase 1 study is to determine the MTD and assess feasibility and toxicity of cisplatin and nab-paclitaxel administered by PIPAC. In this sense, we agree that phase 1 studies could be viewed as pharmacological exercises. Enrolling four different malignancies (ovarian, pancreatic, gastric and peritoneal mesothelioma), all known to be sensitive to taxanes and platinum, is not uncommon in phase 1 studies. We agree with Dr Paolo Sammartino that the number of participants per histopathology will be limited to formally be able to assess efficacy, however, if a positive signal is observed in a specific malignancy, it could provide rationale to pursue recruitment in an extension cohort.

Reviewer: 2
Dr. Jessica Reid, The University of Adelaide
Comments to the Author:
Dear Dr Lang and Team,

Congratulations on this well written PIPAC protocol combining nab-paclitaxel with cisplatin for patients with unresectable peritoneal disease. The nab-paclitaxel dose escalation methodology is rational and the toxicity measures are logical for this patient cohort.

We have two minor points for your consideration. The first is that many centres are admitting PIPAC patients as day cases, or discharging the next day. It may be possible to reduce the 4 day window mentioned here for select patients.
The second point relates to patients who experience favourable oncological results. Would you be able to offer those patients additional cycles beyond the protocol? This may disrupt the statistics for disease/survival status, but would be welcomed by patients and their families.

We wish you all the best with this important study and look forward to viewing your results.

Dr Jessica Reid PhD
Dr Markus Trochsler MD MMIS FMH FRACS

→ Response to Reviewer 2
Dear Dr Jessica Reid,
We are grateful for your encouraging and enthusiastic comments.
Regarding your two minor points for your consideration.
"The first is that many centres are admitting PIPAC patients as day cases, or discharging the next day. It may be possible to reduce the 4 day window mentioned here for select patients. The second point relates to patients who experience favourable oncological results. Would you be able to offer those patients additional cycles beyond the protocol? This may disrupt the statistics for disease/survival status, but would be welcomed by patients and their families."

We agree with first comment, length of hospital stay after routine PIPAC has been nowadays shorten (generally 24 hours, depending on post-surgery symptomatology). We will consider to amend hospital stay to 24/36 hours.
We are fully agreeing with the second point. An amendment that will allow to offer additional PIPAC cycles beyond protocol for clinically benefiting patients is on its way to be submitted to EC. In a phase 1 study, we are feeling that survival outcomes are less important than safety, efficacy (ORR) and in this view, we would agree to privilege patients clinical benefit.

VERSION 2 – REVIEW

REVIEWER	Jessica Reid The University of Adelaide
REVIEW RETURNED	09-Dec-2022

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.