

ClinicalTrials.gov (NCT03172416)

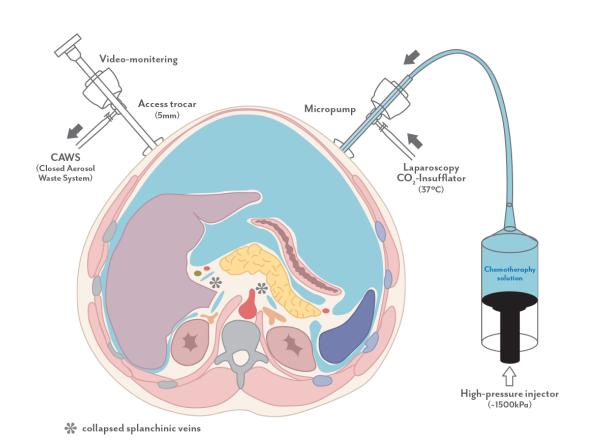
Protocol paper in press: Pleura and Peritoneum

Phase 1 Study of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Oxaliplatin in Patients with Peritoneal Carcinomatosis

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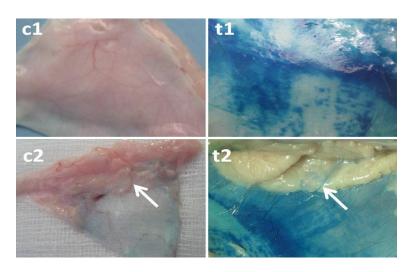
Background - Treatment for Peritoneal Carcinomatosis

- Palliative systemic chemotherapy
- HIPEC + CRS
- IP Chemo
- Immunotherapy
- PIPAC

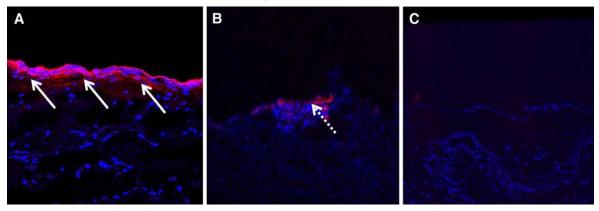


Why PIPAC?

Wide distribution (aerosol >liquids)



Better drug penetration (than IP chemotherapy)



- Less systemic side effects (than systemic chemotherapy)
- Direct assessment of response (with laparoscopy)

Current status of PIPAC

- PIPAC has only been used with:
 - Cisplatin + Doxorubicin
 - Oxaliplatin
- Limited pK data on these drugs delivered via PIPAC available
- Doses used in clinical trials derived arbitrarily (20% of HIPEC dose)

Aim

 To determine the safety profile and tolerability of PIPAC with oxaliplatin

Study Design

- Prospective, single arm, phase I study
- 3 + 3 dose escalation
- 2 PIPAC procedures per patient, 6 weeks apart

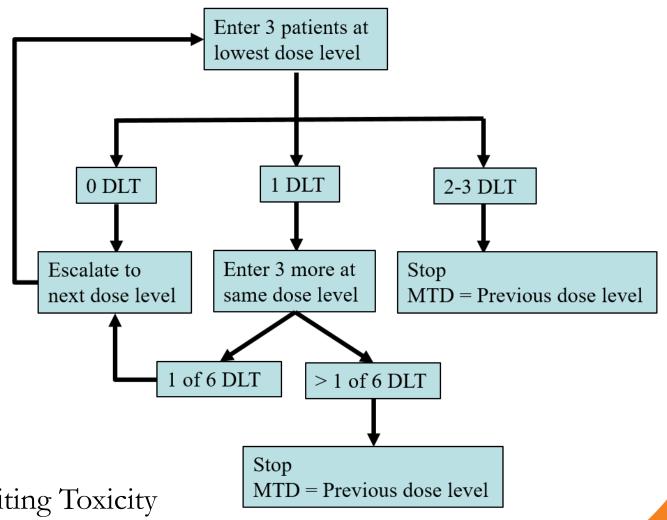
Inclusion Criteria

- Gastric and colorectal cancer patients with peritoneal metastasis on peritoneal cytology/histology
- Patients with predominant peritoneal carcinomatosis, where further systemic chemotherapy is not indicated or tolerated
- ECOG performance status 0-3
- Expected survival >3 months

DOSE ESCALATION SCHEDULE

| Dose Level | Dose of Study Drug | Minimum Number of Patients |
|------------|-----------------------|----------------------------|
| 1 | 45mg/m ² | 3 |
| 2 | 60mg/m ² | 3 |
| 3 | 90mg/m ² | 3 |
| 4 | 120mg/m ² | 3 |
| 5 | 150mg/m ² | 3 |

Escalation Decision Guide



DLT = Dose Limiting Toxicity
MTD = Maximum Tolerable Dose

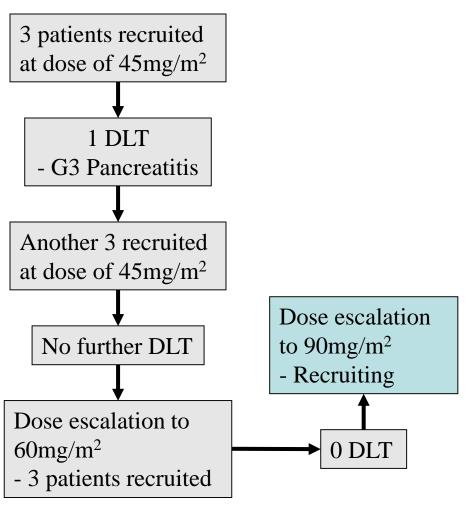
Primary Endpoints - Adverse events

- Surgical
 - Clavien-Dindo classification
- Chemotherapy
 - Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
 - Dose-limiting toxicities (DLT): **Grade 3 or higher** toxicity during the first 28 days after PIPAC

Secondary Endpoints

- 1. Clinical response PCI, RECIST v1.1
- **2. Pathological response** Histology (PRGS)
- 3. pK profiling ICP-MS
- **4. QoL assessment** EORTC QLQ-C30
- 5. Correlative studies
 - Patient samples (blood, urine, peritoneal tumour cells, and peritoneal fluid)

Current status



- 10 patients recruited
 - 1 patient dropped out due to non-access of the abdomen
- n=9
 - 3 female
- 3 with CLR cancer
 - 2 had primary tumour resected previously
- 6 with Gastric cancer
 - 3 had primary tumour resected previously
- Median age 58 years (range 51 65)
- 13 PIPAC procedures
- Mean PCI score: 13 (range 1 − 28)
- Mean operating time: 103 mins (68 146)

Summary of All Adverse Events and Grades

Cohort

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Adverse events (1)

No surgical morbidity

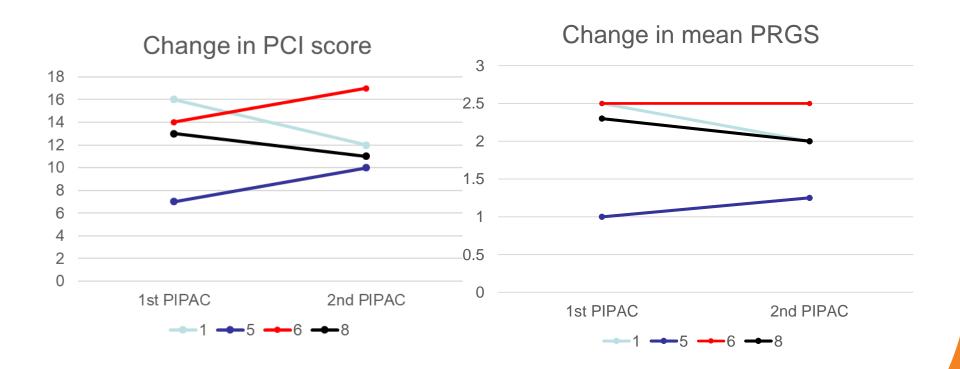
On day 6 and day 9 after PIPAC administration

| | Event | Number of events in all grades | Grade 3 and above |
|---|---------------------|--------------------------------|----------------------|
| | Abdominal pain | 2(22.2%) | 0 (0.0%) |
| | Amylase increased | 2 (22.2%) | 1(11.1%) |
| | Anemia | 2 (22.2%) | 1(11.1%) |
| | Anorexia | 1(11.1%) | 0 (0.0%) |
| | Fatigue | 1(11.1%) | 0 (0.0%) |
| | Fever | 1(11.1%) | 0 (0.0%) |
| | Hypokalemia | 1(11.1%) | 1(11.1%) |
| | Hypotension | 1(11.1%) | 0 (0.0%) |
| | Lipase increased | 2 (22.2%) | 2 (22.2%) |
| | Neuropathy | 2 (22.2%) | 0 (0.0%) |
| | Pancreatitis | 2 (22.2%) | 1(11.1%) |
| _ | Vomiting | 3 (33.3%) | 0 (0.0%) |
| | Genital Edema | 1 (11.1%) | 0 (0.0%) |
| | Pleural Effusion | 1 (11.1%) | 1 (11.1%) |
| | Ascites | 1 (11.1%) | 1 (11.1%) |
| | Weight Loss | 1 (11.1%) | 0 (0.0%) |

Clinical response

- 5 had stable disease
- 4 patients had progressive disease
 - 3 patients developed new malignant pleural effusion
 - 1 patient had worsening of liver metastasis

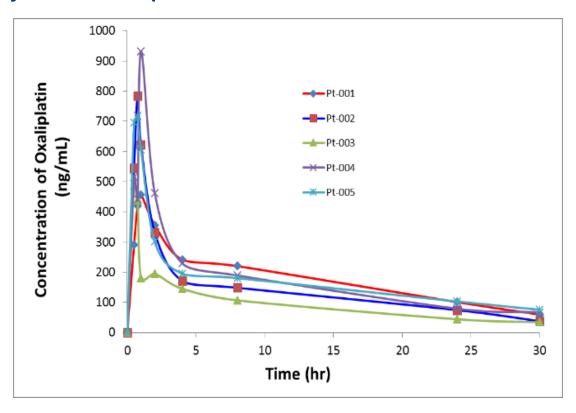
PCI and PRGS scores for 4 patients who underwent two PIPAC procedures



Reasons for not undergoing 2nd PIPAC procedure

- 1 SD but medically unfit due to refractory ascites and severe malnutrition
- 1 SD but decided to switch to another trial (immunotherapy)
- 2 due to PD
- 1 withdrew from trial

Preliminary Plasma pK data: n = 5, all dosed at 45mg/m²



- Mean plasma Cmax 675.7 (202) ng/mL
 - about half of those in i.v. infusion at the same dose*
- T_{1/2} 13.9 (2.5) hrs
- AUC 5515.9 (1445.0) hr*ng/mL

*FDA's Clinical Pharmacology and Biopharmaceutics Review 2008, NDA 21-492 SE8-s008

Conclusion

- PIPAC with oxaliplatin even at low doses may be associated with acute pancreatitis
- PIPAC is associated with minimal surgical complications
- PIPAC alone may not be adequate in the treatment of metastatic disease









