CLINICAL PRACTICE

Multimodal Therapy and PIPAC

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Disclosures

- Grant/Research Support from AstraZeneca.
- Consultant for Adagene, AstraZeneca, Eisai, Genentech, and Merck.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label or investigational use of Cisplatin, Doxorubicin, Nab-paclitaxel, and Oxaliplatin will be discussed.

Why Add PIPAC to Multimodal Therapy?

- May overcome systemic chemotherapy drug resistance[1]
  - Up to 98% of systemic chemotherapy never reaches the peritoneum: low vascularization, peritoneal–plasma barrier[1]
- Improved peritoneal coverage compared to conventional lavage[2]
- Improved drug uptake yield compared to hyperthermic intraperitoneal chemotherapy (HIPEC)[3]
- Quality of life may be maintained or improved[4, 5]

1. Nadiradze et al. *Cancers (Basel)* 2019 2. Solaß et al. *Surg Endosc* 2012 3. Davigo et al. *Int J Hyperthermia* 2020 4. Taibi et al. *Surg Oncol* 2020 5. Li et al. *Pleura Peritoneum* 2022

Multimodal Therapy and PIPAC

PIPAC may be combined with:

- Systemic chemotherapy
- Targeted therapy (e.g., VEGF[R] inhibition)
- Curative-intent surgery: cytoreductive surgery (CRS) ± HIPEC

PIPAC with Oxaliplatin + Systemic 5-Fluorouracil/ Leucovorin: Colorectal/Appendiceal Cancer

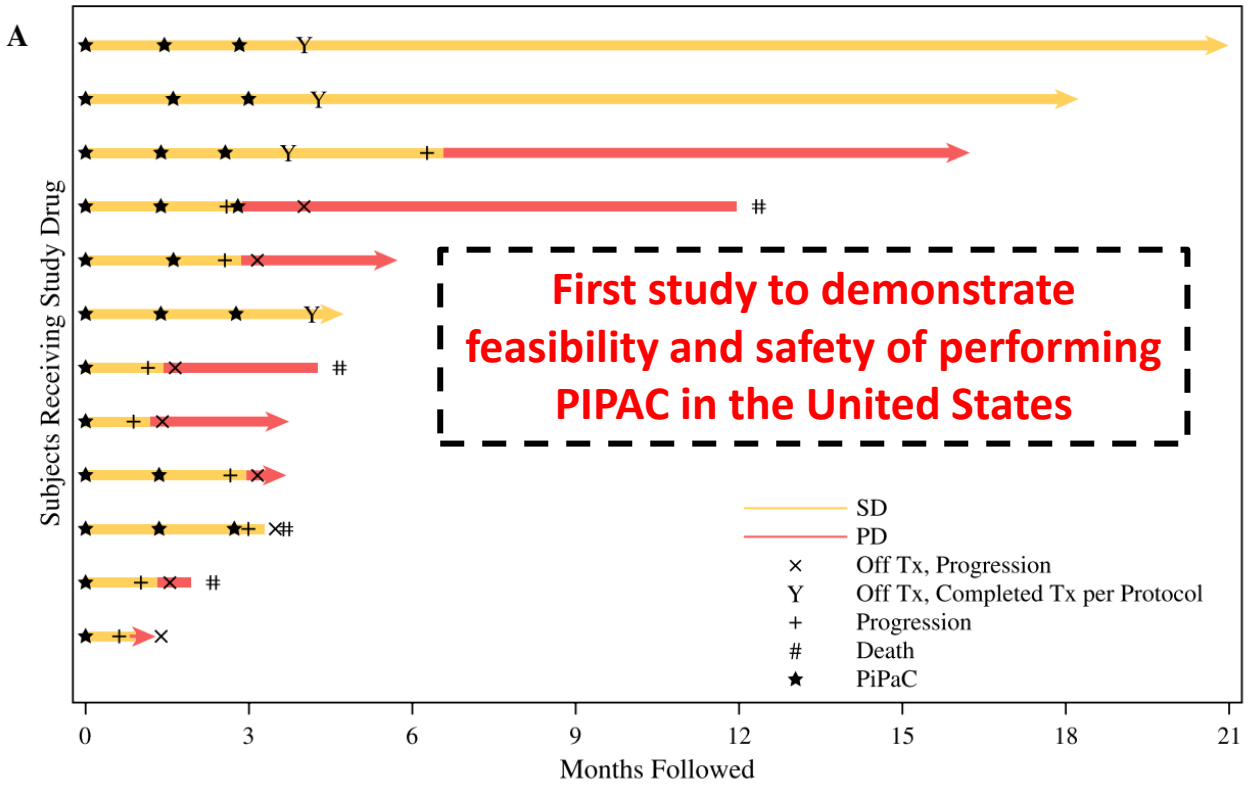
- Colorectal and appendiceal adenocarcinomas with peritoneal metastases (N=12)
  - Refractory to systemic oxaliplatin
  - All MSS, low TMB, 5 KRAS mutant
- PIPAC with oxaliplatin (up to 3 cycles)
  - Systemic 5-fluorouracil/leucovorin added after first PIPAC
  - 2 PIPAC cycles: 58%
  - 3 PIPAC cycles: 50%
- No surgical complications or DLTs
- CTCAE toxicities:
  - Grade 1: 58%
  - Grade 2: 33%
  - Grade 3: 17%
- No significant difference in AEs between Cycle 1 and Cycle 2

PIPAC with Oxaliplatin + Systemic 5-Fluorouracil/ Leucovorin: Colorectal/Appendiceal Cancer

TABLE 3 Response to oxaliplatin PIPAC with systemic therapy

	Best response	$N = 12$
Conversion to CRS-HIPEC	Yes	2 (17%)
	No	10 (83%)
Radiographic (RECIST)	SD	6 (50%)
	PD	6 (50%)
Laparoscopic (PCI)	Decrease	6 (50%)
	PD or only one PIPAC	6 (50%)
Histologic (PRGS, mean)	Decrease	5 (42%)
	SD	2 (17%)
	PD or only one PIPAC	5 (42%)

CRS-HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *RECIST* Response Evaluation Criteria in Solid Tumors, *PCI* peritoneal carcinomatosis index, *PRGS* peritoneal regression grading system, *SD* stable disease, *PD* progressive disease

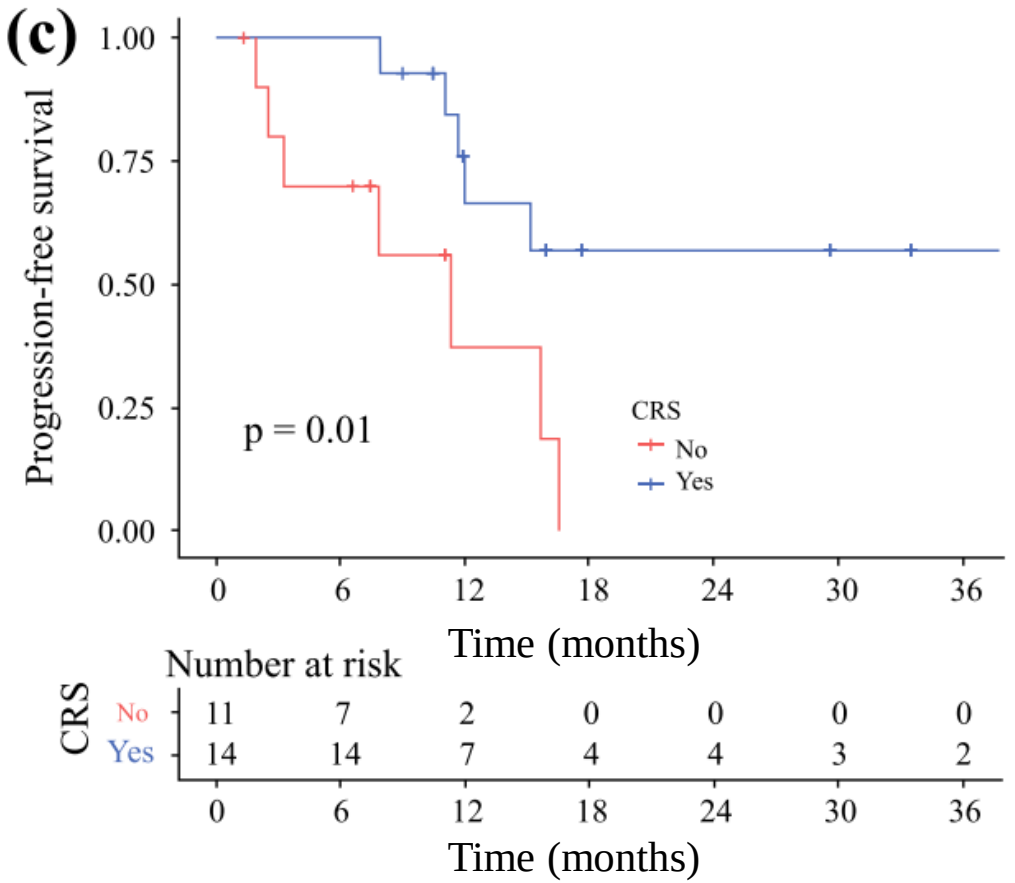


PIPAC with Cisplatin/Doxorubicin + Systemic Chemotherapy: Mesothelioma

- Nonresectable malignant peritoneal mesothelioma (N=26)
  - 20 patients upfront unresectable; 6 patients with recurrence after prior CRS
  - Patients with extraperitoneal metastases excluded
- PIPAC with cisplatin/doxorubicin plus systemic chemotherapy
  - Chemotherapy options: platinum and/or pemetrexed, gemcitabine
- 50% of patients received ≥3 instances of PIPAC
- Severe toxicities in only 2 patients (digestive perforation linked to tumor shrinkage)
- No PIPAC-related deaths

PIPAC with Cisplatin/Doxorubicin + Systemic Chemotherapy + Surgery: Mesothelioma

- 14 of 26 patients received subsequent CRS + HIPEC (including 11 initially unresectable patients)
  - Complete resection: 13 patients
- Progression-free survival significantly improved for patients who received surgery
  - 33.5 months vs 7.4 months
  - HR 0.18; 95% CI 0.06-0.755; p<0.001

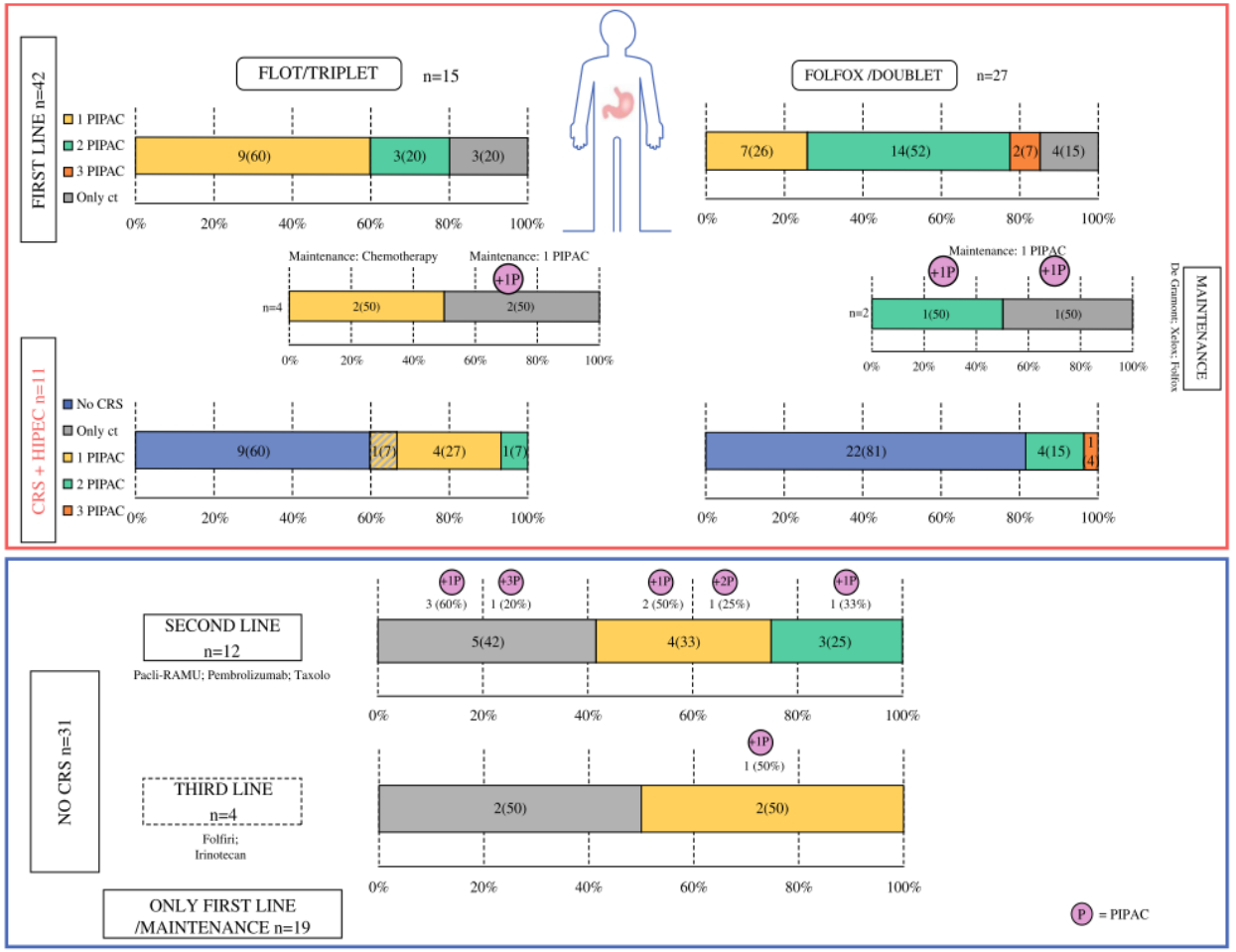


PIPAC with Cisplatin/Doxorubicin + Systemic Chemotherapy: Gastric Cancer

- Gastric cancer with synchronous peritoneal metastases (N=42)
  - Patients with extraperitoneal metastases excluded
- Various bi-directional treatment combinations
  - Most patients received systemic chemotherapy before and after PIPAC
- 59.5% of patients received ≥2 instances of PIPAC
- No re-operations or treatment-related deaths
  - CTCAE toxicities ≥grade 3 in only 2% of patients
  - No Clavien-Dindo complications >grade 3a

PIPAC with Cisplatin/Doxorubicin + Systemic Chemotherapy + Surgery: Gastric Cancer

- 11 of 42 patients underwent curative-intent surgery following PIPAC + systemic chemotherapy
  - HIPEC added: 7 cases
  - Multivisceral resection: 5 cases
- No surgery-related deaths; no Clavien-Dindo complications >grade 3a
- R0 resection: 9 patients
- R1 resection: 2 patients
- Complete pathological response: 3 patients



PIPAC with Cisplatin/Doxorubicin + D2 Gastrectomy: Gastric Cancer

- Gastric adenocarcinoma (N=21)
- High risk of recurrence:
  - Poorly cohesive subtype with predominance of signet-ring cells
  - Clinical stage ≥T3 and/or ≥N2
  - Pre-operative positive peritoneal cytology
- Laparoscopic D2 gastrectomy followed by PIPAC
  - Pre-operative chemotherapy: 95%
  - Post-operative chemotherapy: 71%
- Most AEs were grade 1-2
- Grade 3 treatment-related AEs:
  - Neutropenia (n=1)
  - Abdominal pain (n=1)
  - Other GI disorder (n=1)
- Grade 3b surgical complications:
  - Post-operative anastomotic leakage (n=1)
  - Late duodenal blowout (n=1)
- No procedure-related deaths

PIPAC + Systemic Chemotherapy ± Bevacizumab

- Gastric, colorectal, or ovarian cancer with peritoneal metastases (N=134)
- PIPAC with cisplatin/doxorubicin or oxaliplatin
  - Bevacizumab (bev) added: 26 patients
  - Median of 3 instances of PIPAC
- Major complications in bev arm:
  - Bowel obstruction (n=2)
  - Hematoma (n=1)
  - Severe hypersensitivity reaction to platinum compound (n=1)

30-day outcomes	Bev (n=26)	Non-Bev (n=108)	p-value
All-grade morbidity, %	14.8	9.4	0.147
Grade 3-4 post-operative complications, %	4.5	3.2	0.521
Mortality, %	0	5.5	--

PIPAC + Systemic Chemotherapy ± Ramucirumab

- Gastric cancer with peritoneal metastases (N=50)
  - Ramucirumab-containing regimen ≤6 weeks prior to PIPAC: 45% of patients
- PIPAC with cisplatin/doxorubicin
  - 2 instances of PIPAC: 50%
  - 3 instances of PIPAC: 26%
- Overall postoperative morbidity: 11%
- Severe surgical complications: 5.6%
  - Grade 3a (n=1)
  - Grade 3b (n=4)
- Severe postoperative complications in ramucirumab arm:
  - Surgical site infection (n=1)
  - Bowel perforation (n=1)
  - Urinary infection/acute abdomen (n=1)

TABLE 5 | Effect of ramucirumab (RAM) addition to pre-PIPAC chemotherapy (CTx) on postoperative complication rates and length of stay (LOS).

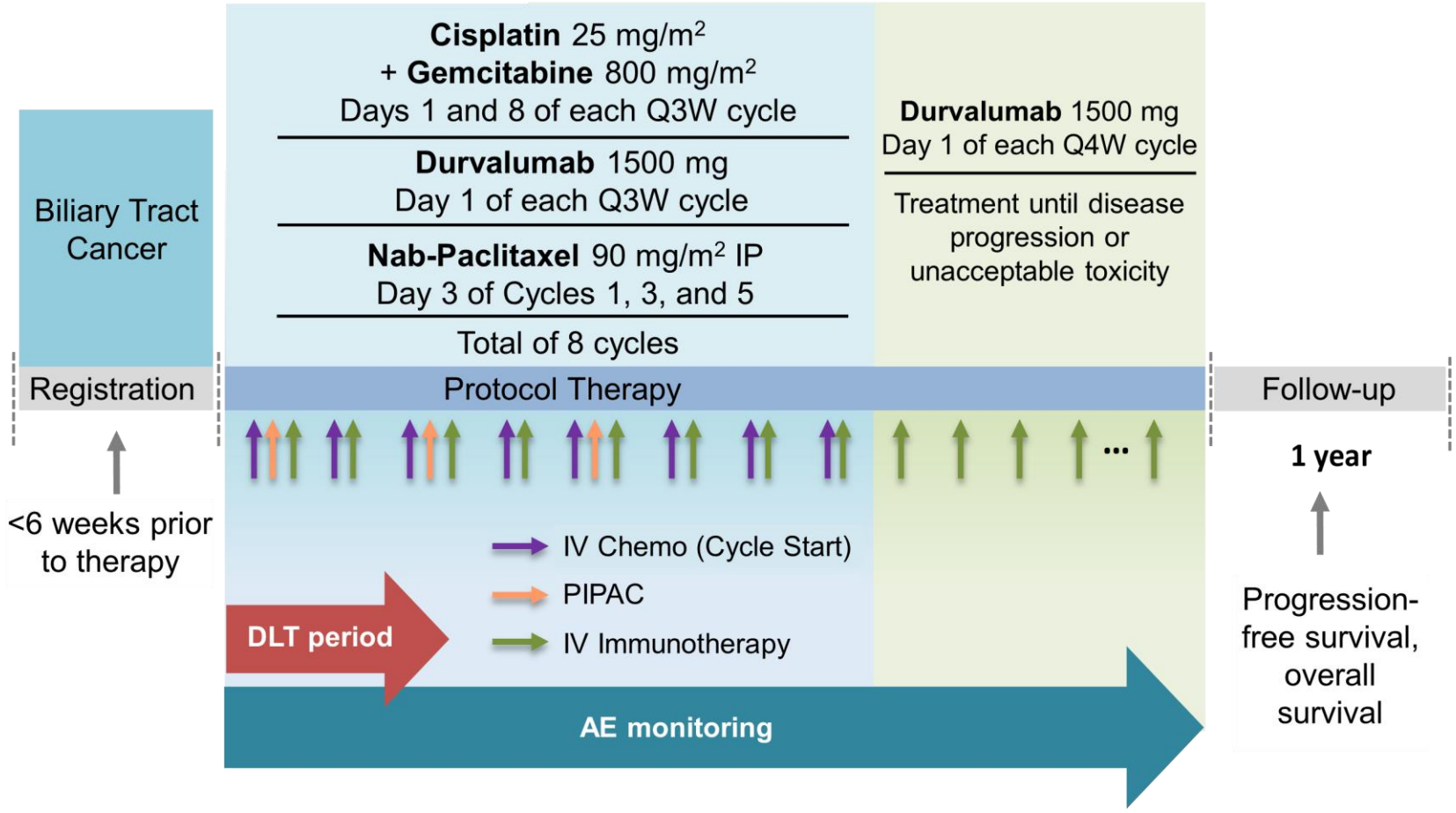
	CTx - RAM ***(n = 42)***	**CTx + RAM** ***(n = 35)***	***p-value***
Overall morbidity	4 (10%)	3 (9%)	1.000
Severe complication	2 (5%)	3 (9%)	0.654
LOS (median, min-max)	3 (2-6)	3 (2-43)	0.211

Severe complications are classified as Clavien-Dindo ≥3a.

Ongoing Multimodal Therapy Trials

ClinicalTrials.gov ID	Diagnosis	Treatment Plan
NCT05644249	Gastric cancer	PIPAC with cisplatin/doxorubicin + FOLFOX
NCT05303714	Gastric cancer	PIPAC with cisplatin/doxorubicin + FOLFOX vs FOLFOX
NCT03875144	Mesothelioma	PIPAC with cisplatin/doxorubicin + cisplatin/pemetrexed vs cisplatin/pemetrexed
NCT04811703	Ovarian cancer	PIPAC with cisplatin/doxorubicin + carboplatin/paclitaxel
NCT05371223	Pancreatic cancer	PIPAC with nab-paclitaxel + nab-paclitaxel/gemcitabine
NCT06295094	Gastric cancer	PIPAC with cisplatin/doxorubicin + D2 gastrectomy vs D2 gastrectomy
NCT05285358	Biliary tract cancer	PIPAC with nab-paclitaxel + gemcitabine/cisplatin + durvalumab

Pressurized Intraperitoneal Aerosolized Nab-Paclitaxel in Combination with Gemcitabine, Cisplatin, and Durvalumab for the Treatment of Biliary Tract Cancer Patients with Peritoneal Metastases (NCT05285358)



Conclusions

- Multimodal therapy with PIPAC is feasible and safe in patients with a variety of tumor types
  - Few surgical complications
  - Some patients may become eligible for curative-intent surgery
- Unanswered questions:
  - Which treatment modalities are best suited for combination with PIPAC?
  - Optimal schedule for administration?
- **Randomized trials to more fully demonstrate feasibility, safety, and efficacy of PIPAC in the United States are needed**