

PIPAC

FOR

GASTRIC CANCER PERITONEAL CARCINOMATOSIS



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Acknowledgement

FUNDING

**DoD E01 Award W81XWH-19-1-0225 (PI, 2019-2021) & Clinical Trials
Internal Funding Prioritization Committee Support**

“Discovery of Immune Biomarkers That Predict Response to a Novel Chimeric
Immuno-Oncolytic Virus Encoding Anti-PD-L1 in Gastric Cancer Peritoneal
Carcinomatosis”

Stand Up 2 Cancer Gastric Cancer Interception Grant (Site PI, 2020-2023)
“Early Detection of Diffuse and Intestinal Gastric Cancer”

Department of Surgery Start Up (PI, 2015-2020)
“Molecular Staging of Gastric Cancer” and
“Preclinical studies in evaluation of the safety and efficacy of oncolytic viruses in GI
cancers”

My Goal, our goal

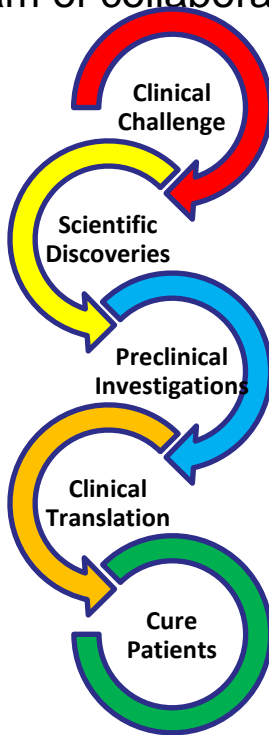
- *To eliminate deaths due to stomach cancer*
- *To bring the best of science and technology to improve quality of life and long-term survival for patients with stomach cancer peritoneal carcinomatosis*
- *Invite all of us to work together to reach this goal*

Teaming up to cure stomach cancer

- It takes vision, dedication and a team of collaborators to find a cure for stomach cancer



DoD Award Team



SU2C team



Aki Smith (@AkiStoCAN) | ...

No Life Should Be Lost to Stomach Cancer



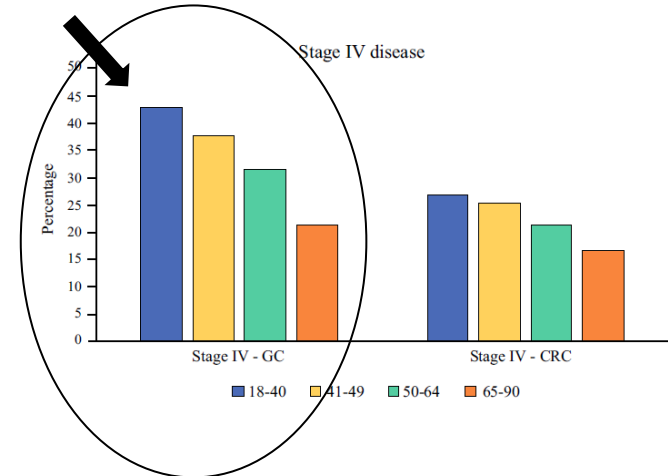
Adversely Impacts Young Adults

Disparate and Alarming Impact of Gastrointestinal Cancers in Young Adult Patients

Amir Khan, MD¹, Philip H. G. Ituarte, PhD¹, Mustafa Raouf, MD¹, Laleh Melstrom, MD¹, Haiqing Li, PhD², Yate-Ching Yuan, PhD², Lily Lai, MD¹, I. Benjamin Paz, MD¹, Ajay Goel, PhD³, Yuman Fong, MD¹, and Yanghee Woo, MD, FACS¹

- The average age of stomach cancer patient in U.S. is 68 years old
- But young (≤ 40 yo) GC patients are more likely to have more aggressive and treatment resistant tumors
- More than 40% of stomach cancer patients 18-40 yo present with Stage IV cancer
- **More likely to present with peritoneal metastases at the time of initial stomach cancer diagnosis: 32.1% vs. 14.1%**

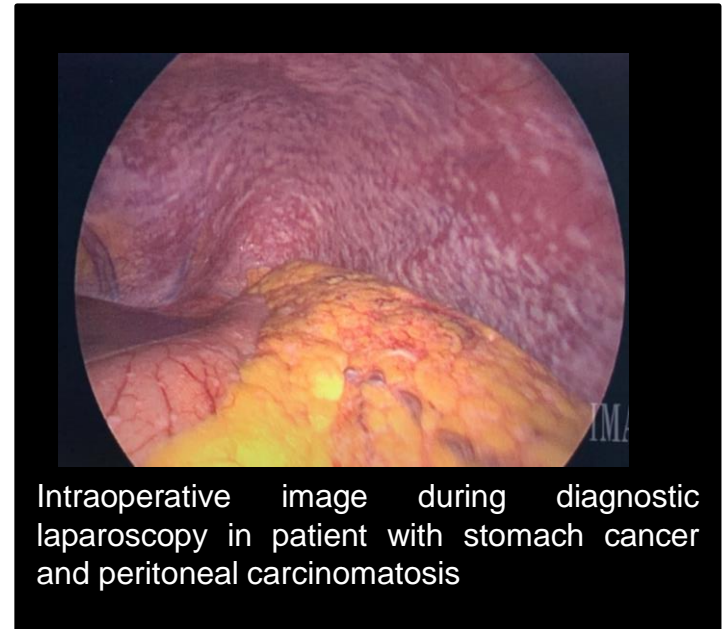
>40% of 18-40 yo with Stomach Cancer have Stage IV



Peritoneal Carcinomatosis

- **The peritoneum** is the most common site of recurrence or metastatic presentation of stomach cancer
- Tumors in the peritoneum are called peritoneal carcinomatosis and associated with myriad of complications
 - Accumulation of malignant ascites
 - Development of bowel obstruction
 - Pain, malnutrition and cachexia
- Standard of care is systemic chemotherapy, +/- Herceptin, immunotherapy
- Role of surgery is limited
- Not good enough and unacceptable

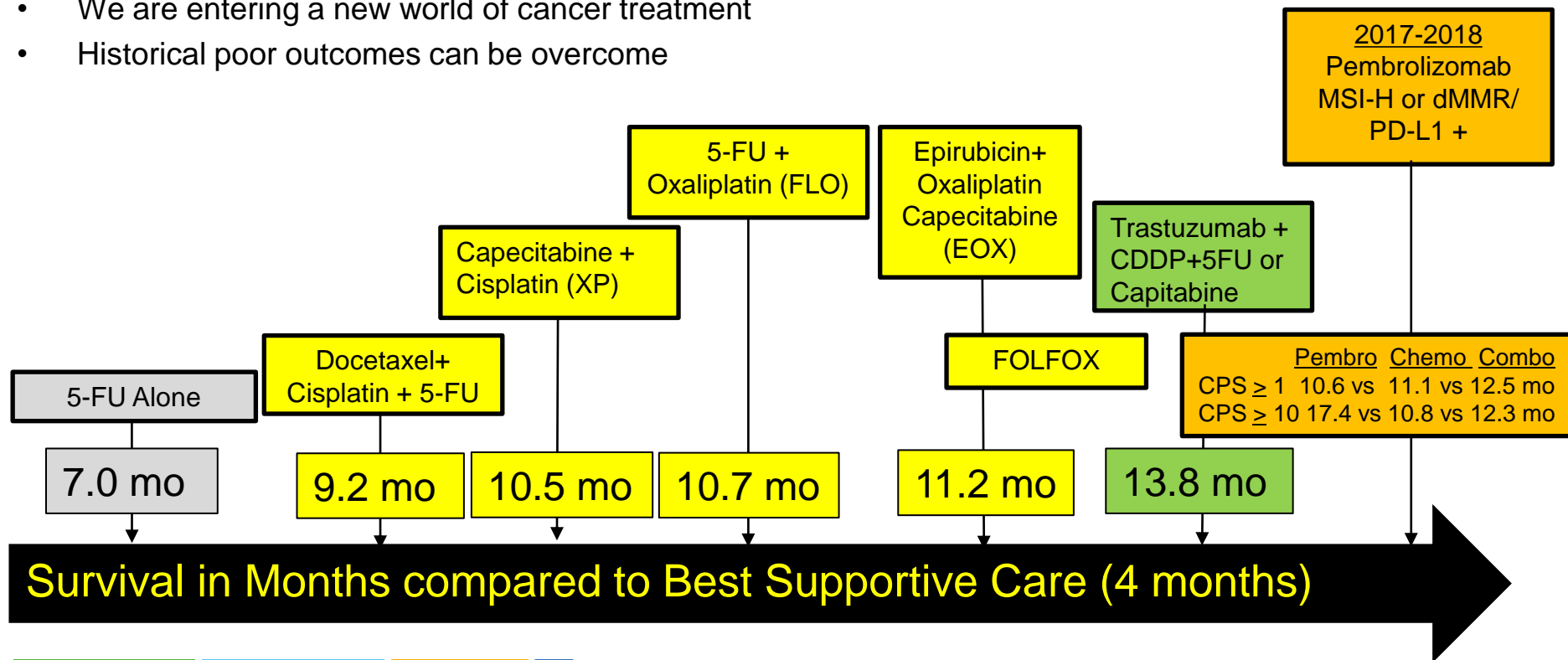
Primary	Syn	Met	Autopsy
GC	15%	>50%	60%



Intraoperative image during diagnostic laparoscopy in patient with stomach cancer and peritoneal carcinomatosis

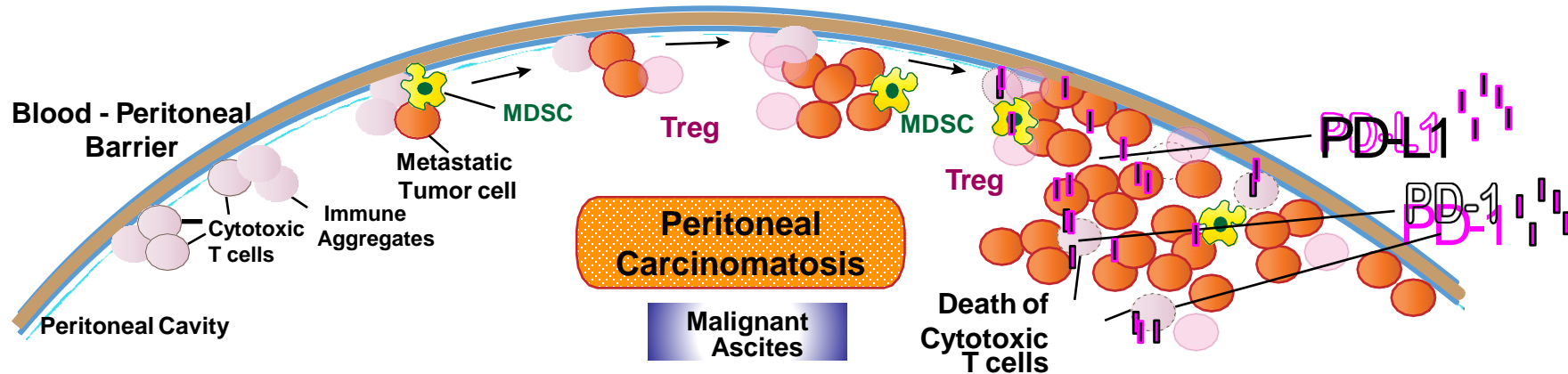
Progress Against Stage IV Stomach Cancer

- We are entering a new world of cancer treatment
- Historical poor outcomes can be overcome

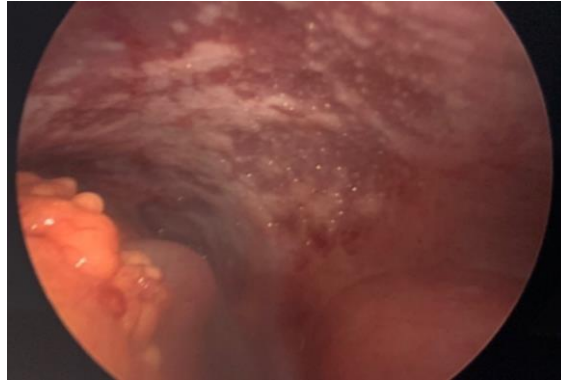
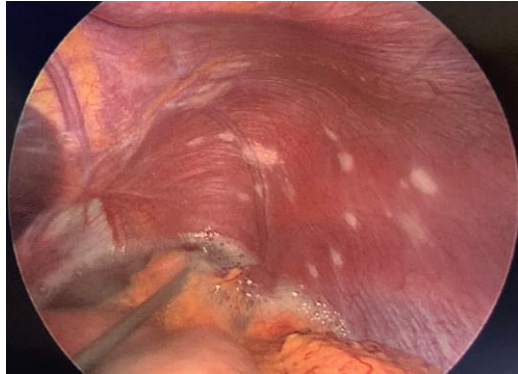


Barriers To Treatment of Peritoneal Carcinomatosis

- PC poses distinct therapeutic challenges
 - Diffuse nature of PC makes complete surgical resection ineffective, if not harmful
 - Tumor protective **blood-peritoneal barrier** and an **immunosuppressive environment** that prevent effective drug delivery and promote **drug resistance**
 - **Disease often not measurable → Patients do not qualify for clinical trials**
 - Thus, little is known about the effects of established drugs or novel therapies in PC patients



Regional Therapy for Peritoneal Carcinomatosis



IP

Intraperitoneal
Chemotherapy

HIPEC

Heated IP Chemotherapy

PIPAC

Pressurized Aerosolized IP
Chemo

PIPAC for Gastric Cancer Peritoneal Carcinomatosis

- What is PIPAC?
 - **P**ressurized **I**ntra**P**eritoneal **A**erosolized **C**hemotherapy
 - A laparoscopic approach of delivering chemotherapy (or other anti-cancer agents) to destroy cancer cells in the peritoneum
 - Uses a high-pressure drug delivery system **CapnoPen** that is **NOT YET FDA approved in U.S.**
- What is role of PIPAC in the treatment of stomach cancer patients in the U.S.?
 - In its **INVESTIGATIONAL PHASE**
 - Currently undergoing Phase I clinical trial

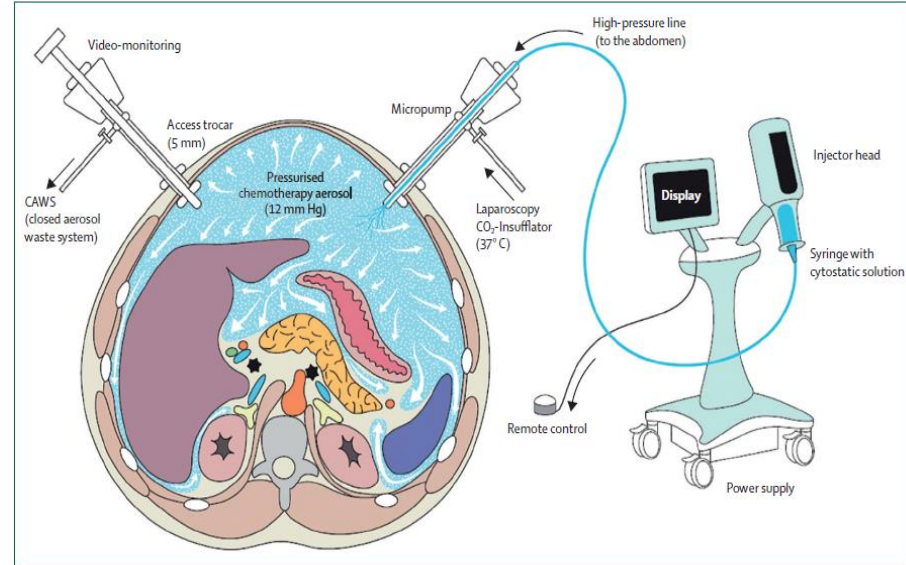


Figure 2: Schematic of PIPAC set-up

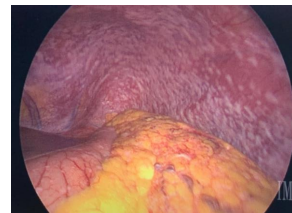
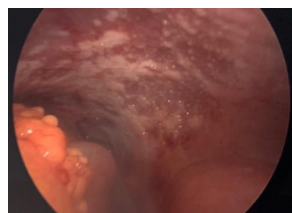
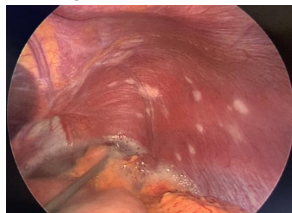
A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues¹⁸ with permission from *Médecine et Hygiène*. PIPAC=pressurized intraperitoneal aerosol chemotherapy.

Phase I Trial In U.S. – PIPAC Device Registry

- To evaluate the safety of the PIPAC device and the method of intraperitoneal delivery of combination chemotherapies by PIPAC

- Indications:

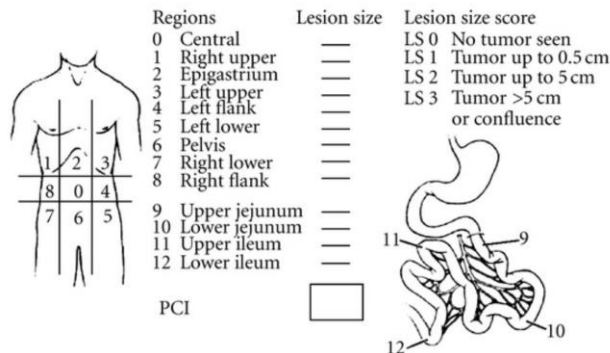
- Patients with PC from stomach, ovarian, colon and appendiceal cancers
- High burden of peritoneal disease
- Progressed on systemic therapy



- Laparoscopic procedure
- Short hospital stay ~24 hr
- Repeat 3 times

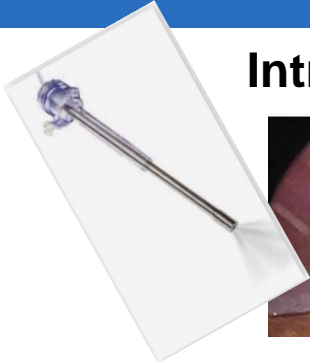
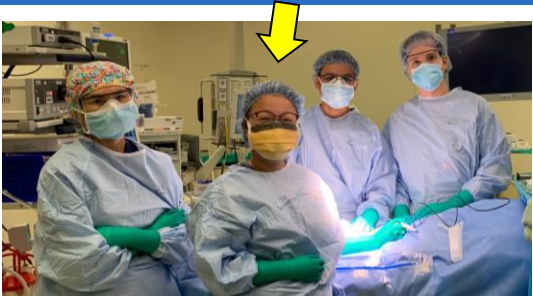


Cisplatin
Doxorubicin



Peritoneal Carcinomatosis Index (PCI) Score: 0 to 39

Minimally Invasive and Short Operative Time



Intra-abdominal view



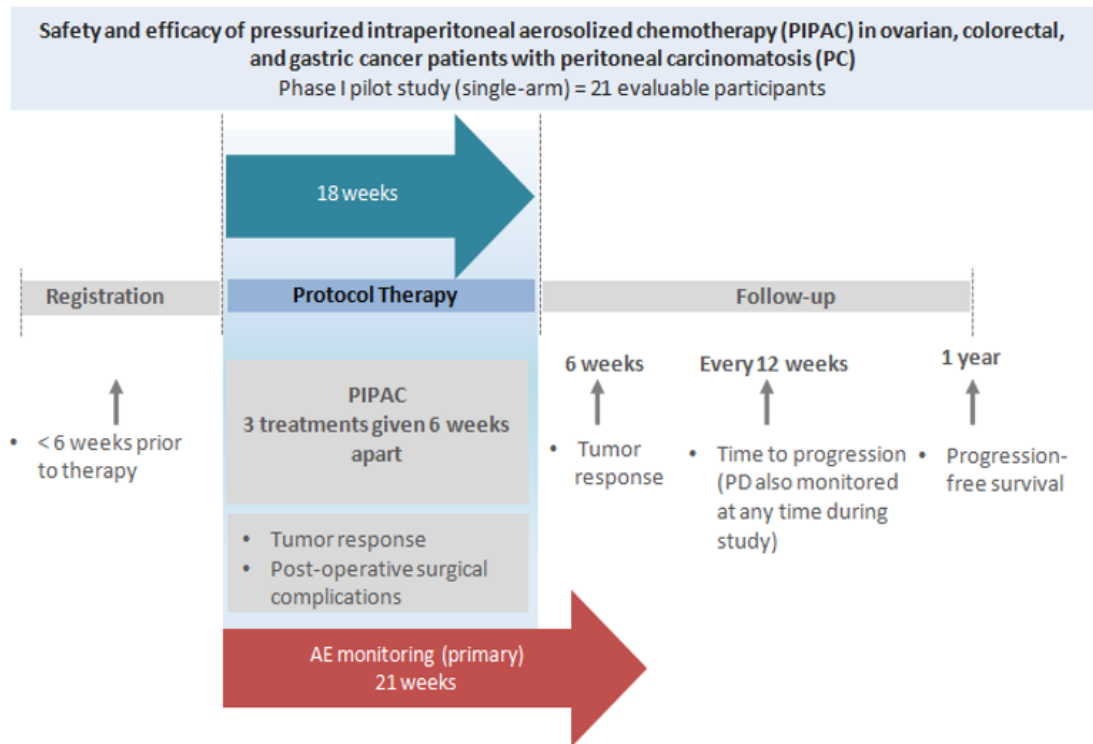
OR Setup



Extra-abdominal view

Phase I PIPAC Trial: Experimental Design

Experimental Design Schema



Evidence for PIPAC from International Experts



New Journal
Pleura and Peritoneum
 Official Journal of the International Society for the Study of Pleura and Peritoneum (ISSPP)
 Editor in Chief: Marc A. Reysaad
 Edited by: Irindice Bibaux, Waa Carlin, Ben Davidson, Marc Picard, Maher Tahiri, and Christian B. Tompfer



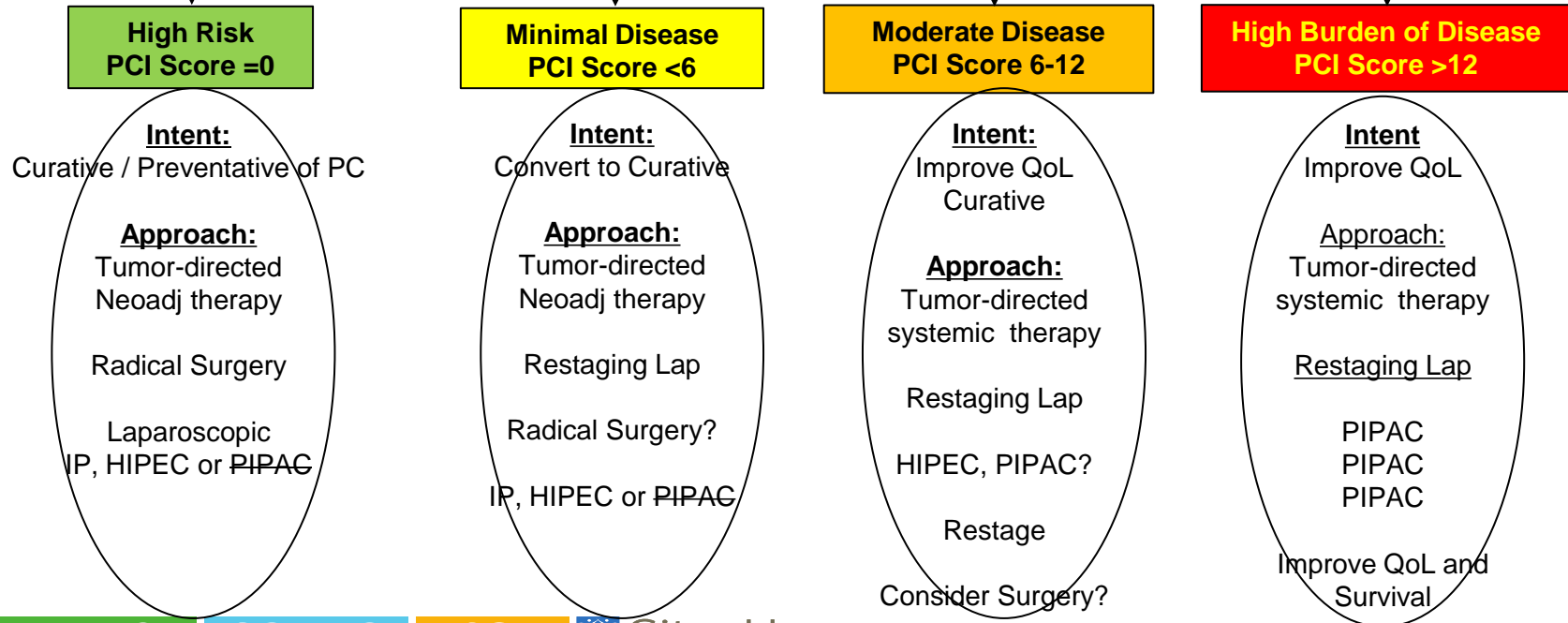
	Number of patients	±2 PIPAC	Peritoneal cancer index improvement	Assessment of response				Survival
				Histological	Regression score	RECIST	Other	
Ovarian								
PIPAC OV-1*	64	43/53 (81%)	26/34 (76%); 3rd PIPAC	ITT: 33/53 (62%) to 28/53 (72%); PP: 26/34 (76%) to 29/53 (89%)*	Gleix et al*	ITT: 33/53 (62%); PP: 16/31 (52%)*	-	OS: 331 days (mean; 95% CI 293-371); PFS: 134 days (mean; 122-168)
Templer and colleagues ⁵	21	8/10 (44%)	-	PP: 6/8 (75%)	Gleix et al*	-	-	442 days (mean)
Templer and colleagues ⁶	99	54/61 (89%)	24/50 (64%)	PP: 38/50 (76%)	Gleix et al*	-	-	143 months (median)
Gastric								
PIPAC GA-2 ²	25	12/25 (48%)	-	ITT: 9/25 (36%); PP: 9/12 (75%)	PRGS*	ITT: 10/25 (40%); PP: 10/13 (77%)	-	8.4±17 months (mean); PFS±12: 13-1±3-5
PIPAC GA-2 ¹	31	15/31 (48%)	-	PP: 9/15 (60%) to 21/23 (91%)	PRGS*	-	-	13 months (median); 3 year OS: 69%
Nadkarni and colleagues ⁵	25	17/24 (71%)	-	ITT: 13/24 (50%); PP: 13/17 (71%)	TRGS ²	-	-	15.4 months (median)
Sokol and colleagues ²⁰	24	14/24 (58%)	8/14 (57%)	PP: 10/14 (71%)	PRGS*	-	79% stable or decreased ascites	230 days (median; range 66-625; all 450 days); (median; 205-450; ±3 PIPAC)
Colorectal								
Dentoider and colleagues ⁸	17	14/17 (82%)	-	ITT: 12/17 (71%); PP: 12/14 (86%)	Dworak et al ¹⁶	-	-	15.7 months (median)
Pancreas								
Greenen and colleagues ⁵	5	5/5 (100%)	-	PP: 4/5 (80%)	PRGS*	-	-	14 months (median); 19-20 months (range)
Khosrawipour and colleagues ⁵	20	10/20 (50%)	-	PP: 7/10 (70%)	TRGS ²	-	-	36.6 weeks (95% CI 36.6-5.11)
Biliary tract								
Falkenstein and colleagues ⁵	13	5/11 (45%)	-	PP: 4/5 (80%)	PRGS*	-	-	85 days (median; 95% CI 59.2-110.4; overall)
Mesothelioma								
Giger-Pabst and colleagues ⁹	29	20/22 (91%)	-	PP: 15/20 (75%)	Dworak et al ¹⁶	-	-	26.6 months (median; 95% CI 9.5-43.7)
Various								
PIPAC OPC-1 ¹⁴	35	20/35 (56%)	-	ITT: 20/35 (57%); PP: 20/28 (71%)	PRGS*	-	-	-
PIPAC OPC-1 ¹⁵	35	30/35 (86%)	-	ITT: 20/35 (57%); PP: 20/28 (71%)	PRGS*	-	-	-
Aljona and colleagues ¹¹	73	45/73 (62%)	63% (95% CI 43-83%)	63% (95% CI 43-83%)	PRGS*	-	-	40-45 to with lymphatic vessel
Kruse and colleagues ¹²	71	39/71 (55%)	-	PP: 24/30 (80%)	PRGS*	-	-	13.80 months (median; 95% CI 9.2-18.0)
Total, weighted mean	552	455 (83%)	66.7%	PP: 73.7%; ITT: 57.4%	PRGS*	ITT: 56.4%; PP: 59.4%	-	11.80 months (median; 95% CI 9.2-18.0)

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; PIPAC, pleural/peritoneal intracavitary chemotherapy; PRGS, peritoneal regression grading system; TRGS, tumor regression grading system; PIPAC, pleural/peritoneal intracavitary chemotherapy; PFS, progression-free survival; ITT, intent-to-treat analysis; PP, per-protocol analysis; CI, confidence interval; OS, overall survival; PFS, progression-free survival; TRGS, tumor regression grading system; PIPAC, pleural/peritoneal intracavitary chemotherapy; PFS, progression-free survival.

- 42 Clinical Trials
 - Over 800 total patients
 - ~200 stomach cancer
 - Safe and feasible
 - 79% stable disease or decreased ascites
 - 10-20 months survival
 - May prolong survival
 - On-going trials in Europe and Singapore
- ❖ Phase I Device Registry trial open at COH (T. Dellinger, PI)

Role for Regional Therapy for Stomach Cancer

All GC patients with advanced stage disease should be cared for by a multidisciplinary team with a patient-tailored tumor-specific strategy



Summary

- Every patient with stomach cancer peritoneal carcinomatosis should be evaluated by a multidisciplinary team for potential regional treatment option
- Treatment strategies should be evidence based but we can always think outside the box and beyond standard of care
- Patient-tailored, tumor specific treatment strategy should be developed
 - Systemic therapy (chemotherapy +/- immunotherapy or targeted therapy)
 - Regional therapy with IP, HIPEC, or PIPAC should be considered on clinical trial or on an individualized patient bases
- PIPAC is INVESTIGATIONAL and undergoing safety evaluation in the United States
- Phase II PIPAC trial for patients with stomach cancer PC is planned at COH
- Many promising new therapies are under preclinical testing and clinical trials

Future of Novel GC PC Therapies

Translation of new drugs / strategies

- Numerous novel agents for cancer are under investigation
- Direct these novel discoveries for stomach cancer patient treatment
- Evaluate these novel agents for stomach cancer peritoneal carcinomatosis in preclinical setting (our laboratories)
- Conduct clinical trials for stomach cancer patients
- Development of better treatment strategies

Improve Stomach Cancer Outcome

Awareness

Advocacy

Funding

Awareness

Advocacy

Funding

Regional Therapy

Immunotherapy

Oncolytic
Viruses

CAR-T Therapy

Liquid biopsy

Plan: Bring best of science and technology to cure stomach cancer patients

Thank you for your dedication and advocacy!

PATIENTS & ADVOCATES



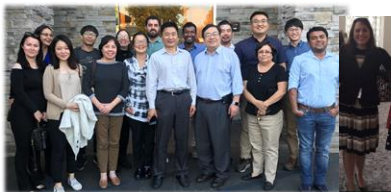
DONORS

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Mark Allen Ober

MENTORS

Drs. Yuman Fong, Larry Kwak, Benjamin Paz, Mark Hardy, MD and Woo Jin Hyung, MD

FONG-WARNER-HAHN-WOO LAB



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COH Core Facilities

Flow Cytometry
Small Animal and Small Animal Imaging
Pathology, Biostatistics, Integrated Genomics

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