# Role of Regional Therapy (HIPEC/PIPAC/IP CHEMO) for Gastric Cancer Peritoneal Carcinomatosis


**Yanghee Woo, MD FACS**
**Debbie's Dream Foundation Webinar**
**Gastric Cancer Work Group / Peritoneal Surface Malignancies**
**Associate Professor of Surgery**
**City of Hope, Duarte CA, USA**

# Disclosures


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"

Medical Advisor

Hope for Stomach Cancer / Debbie's Dream Foundation

CONSULTANT

Ethicon, Auris, Verb

# Opportunities to Improve Survival in GC PC patients

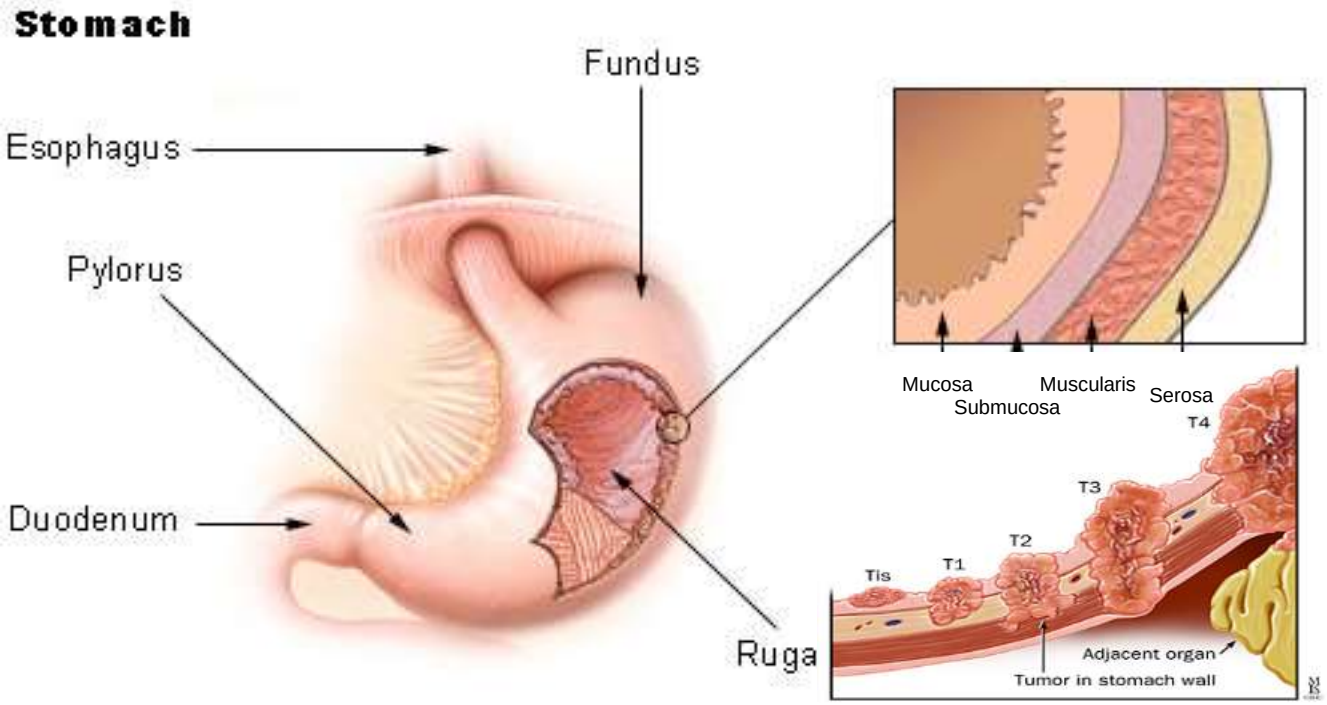
- What is stomach cancer peritoneal carcinomatosis?
- What are the peritoneal carcinomatosis directed therapies in gastric cancer?
- How, when and who of IP /HIPEC/ PIPAC?
  - Intraperitoneal chemotherapy
  - Hyperthermic Intraperitoneal Chemotherapy
  - Pressurized Intraperitoneal Aerosolized Chemotherathy
- How do we select the right therapy for the right GC PC patients?
- How can we do more to achieve a cure for all GC patients?

# No Life Should Be Lost to Stomach Cancer

# What is Gastric (Stomach) Cancer ?

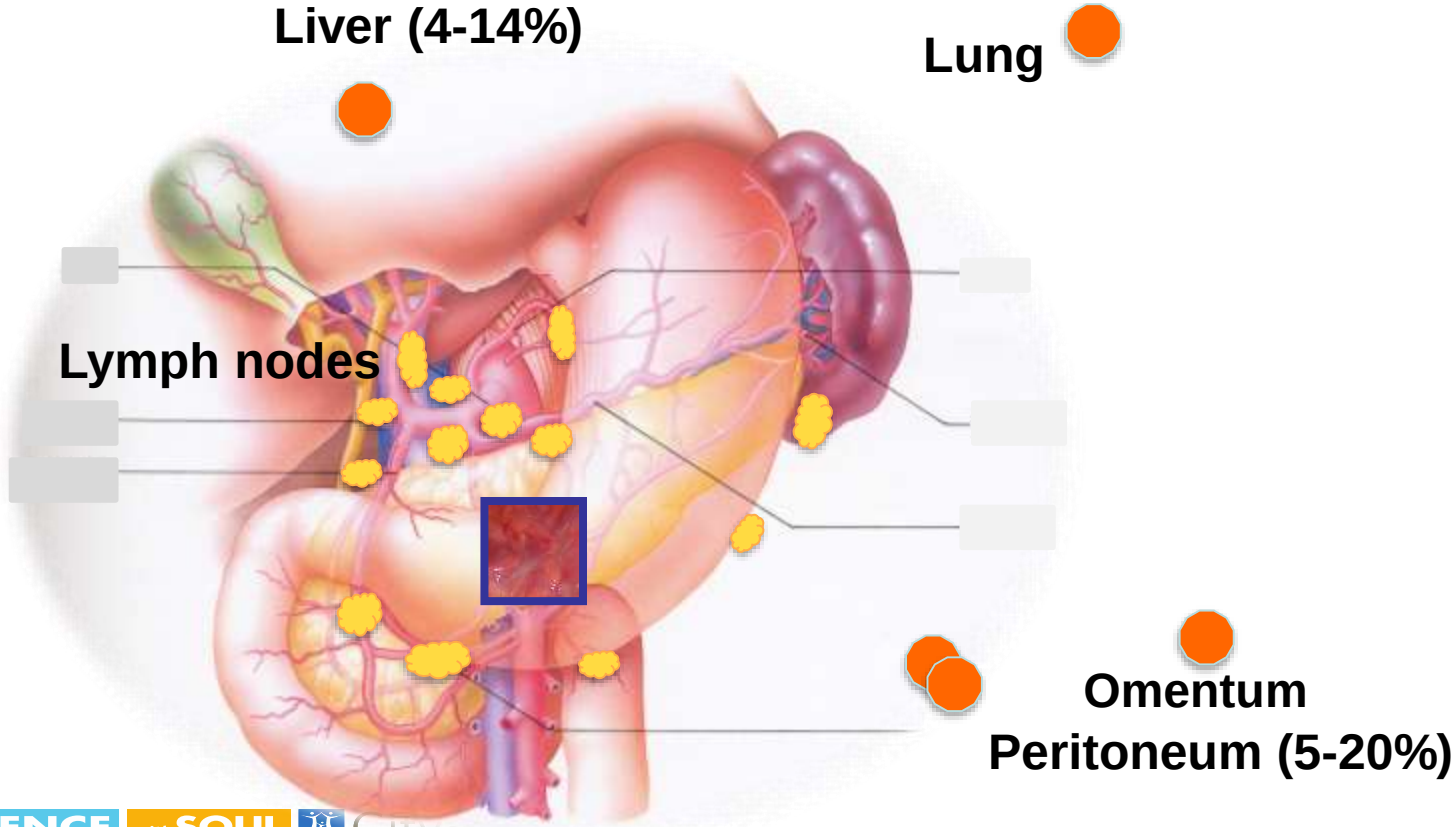
Malignant tumor that arises in the wall of the stomach anywhere from the junction of the esophagus and stomach the (EGJ) and the pylorus (the most distal portion of the stomach)

# If Left Untreated Gastric Cancer Invades




Cancer cells invade the inner layers of the stomach outward

# …and Spread to LNs and Other Organs



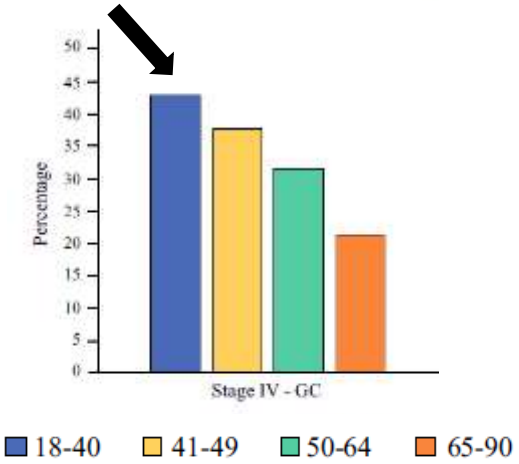
# Peritoneal Carcinomatosis

- Tumors in the peritoneum are called peritoneal carcinomatosis (PC) and associated with many complications
  - Accumulation of malignant ascites
  - Development of bowel obstruction
  - Pain, malnutrition and cachexia
  - Can lead to deaths in weeks to months
- More than 40% of stomach cancer patients 18-40 yo present with Stage IV cancer
- YA are likely to present with PC at the time of initial stomach cancer diagnosis: 32.1% vs. 14.1%

| Primary | Syn | Recur | Autopsy |
|---|---|---|---|
| GC | 15% | >50% | 60% |

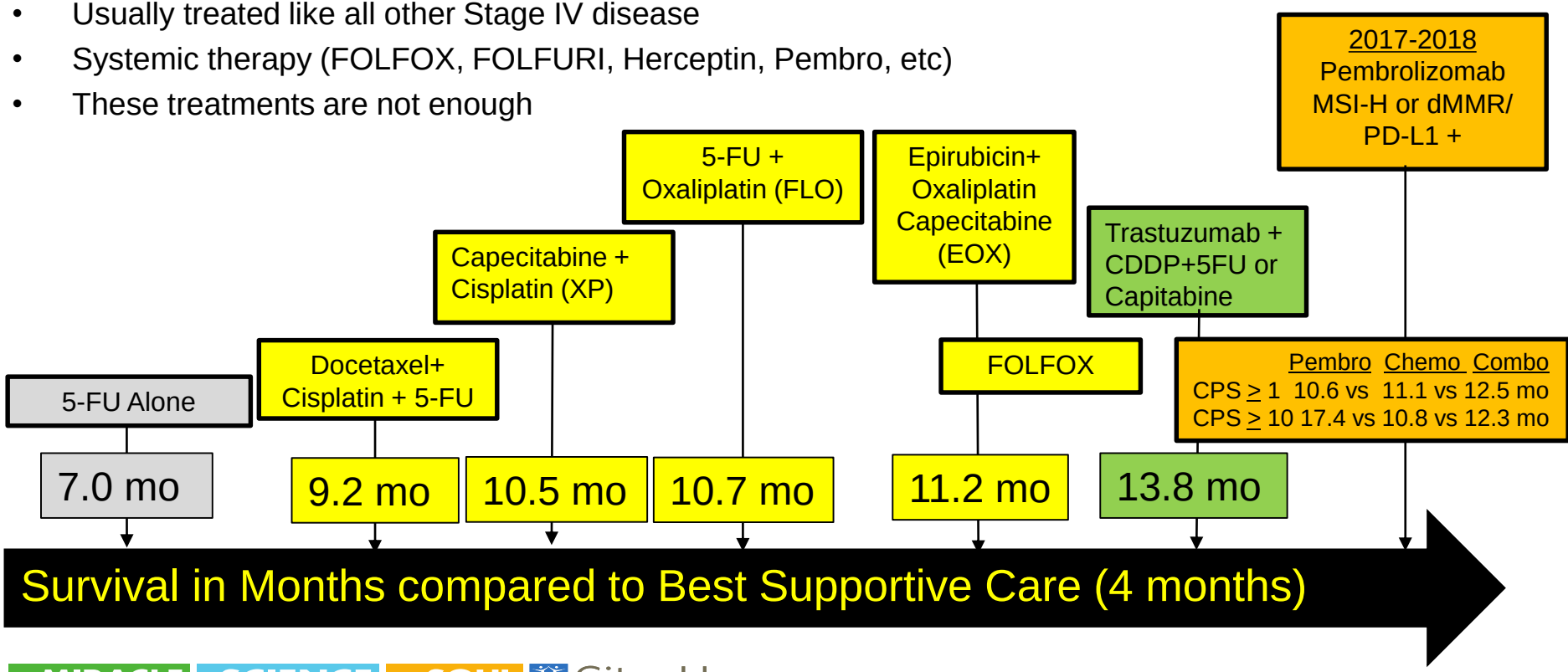
**Disparate and Alarming Impact of Gastrointestinal Cancers in Young Adult Patients**

Amir Khan, MD[1], Philip H. G. Duarte, PhD[1], Mostafa Raoof, MD[1], Laleh Melstrom, MD[1], Baiqing Li, PhD[2], Yate-Ching Yuan, PhD[2], Lily Lai, MD[1], I. Benjamin Paz, MD[1], Ajay Goel, PhD[1], Yanmin Feng, MD[1], and Yanghee Woo, MD, FACS[1]



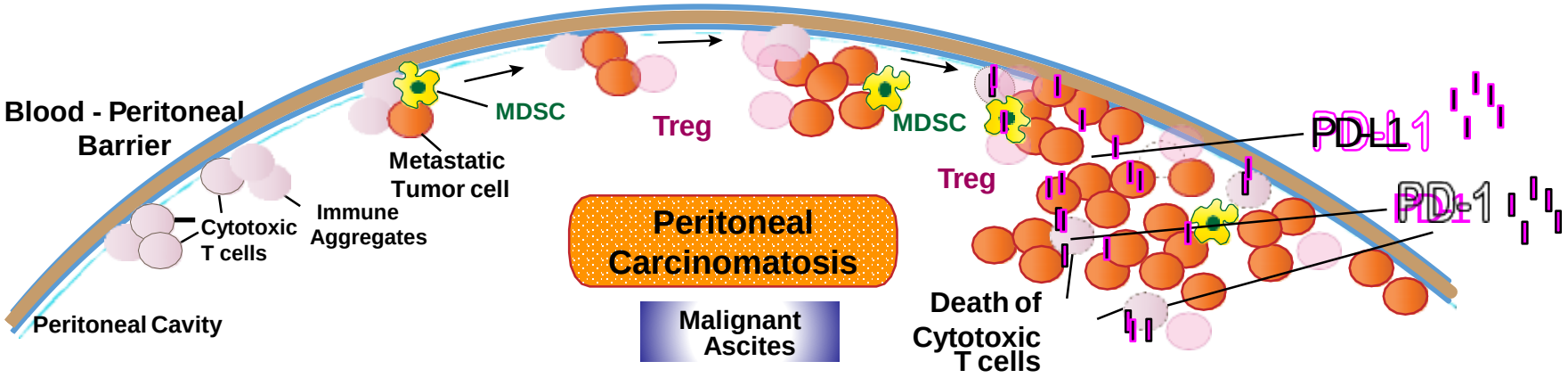
# Treatment Strategies for Peritoneal Carcinomatosis

- Usually treated like all other Stage IV disease
- Systemic therapy (FOLFOX, FOLFURI, Herceptin, Pembro, etc)
- These treatments are not enough



# Rationale for Peritoneum Directed Therapy

- PC poses distinct therapeutic challenges
  - Tumor protective **blood-peritoneal barrier** and an **immunosuppressive environment that** prevent effective drug delivery and promote **drug resistance**
  - Diffuse nature of PC makes complete surgical resection ineffective, if not harmful
  - **Disease often not measurable → Patients do not qualify for clinical trials**

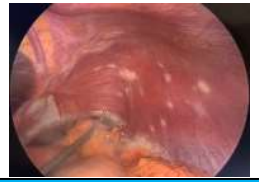


# Rationale and Goals of Peritoneum Directed Therapy

- Goals of care
  - Decrease tumor burden and improve symptoms from complications such as malignant ascites
  - Complete eradication of tumor in the peritoneum to improve survival (combination of therapies)

- Rationale:
  - To bypass or penetrate the blood-peritoneal barrier: Intraperitoneal chemotherapy can achieve higher concentrations in the peritoneal tumor
  - Heated chemotherapy can penetrate tumor better
  - Repeated dosing is possible and more effective
  - Cytoreductive surgery can have high risk of complications – reserved for those with chance of complete clearance of all tumors
  - Treatment approaches: systemic, intraperitoneal, normal versus heated versus pressurized, cytoreductive surgery or no surgery, what are the best combinations?

# Peritoneal Directed Therapy: Lessons from Past Trials



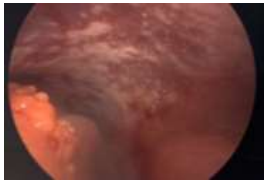
## IP
Intraperitoneal Chemotherapy

Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial

- Trials have failed to demonstrate clear survival benefit IP + IV versus IV alone
- However, responses were encouraging in patients with MA
- **Suggested improved survival with IP in high ascites patients**

Goals of Care
Palliative
Preventative
Curative ?

- Combination of IV plus IP maybe better
- Earlier treatment of PC is better
- Heated has advantages
- Better strategies are needed



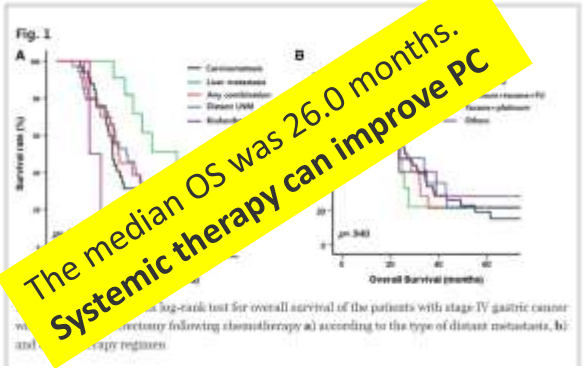
## HIPEC + CRS
Heated IP Chemotherapy

- 30 years of clinical trials failed to achieve survival benefit for single dose HIPEC in most
- Chemo agents, dosing, timing is varied across the trials
- **Benefits patients with occult disease and for improvement of 4 months**

# Lessons from Practice-based on Trials

## Systemic chemo plus CRS

Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy

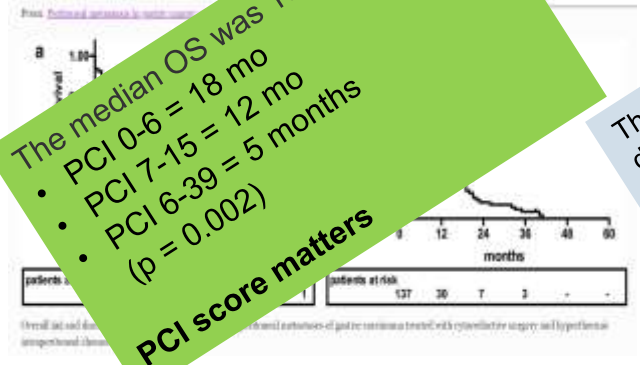



The median OS was 26.0 months.
**Systemic therapy can improve PC**

Beom, SH et al. BMC Cancer, 2018
South Korea

## Systemic chemo plus One HIPEC (one or two chemo agents) plus CRS

Peritoneal metastasis in gastric cancer: results from the German database



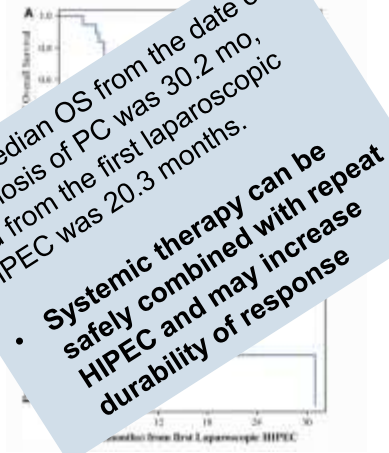

The median OS was 13.0 months.
- PCI 0-6 = 18 mo
- PCI 7-15 = 12 mo
- PCI 6-39 = 5 months
(p = 0.002)

**PCI score matters**

Rau, B et al. Gastric Cancer, 2019
Germany

## Systemic chemo plus **repeat** HIPEC (two chemo agents) 5 of 19 CRS

Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Positive Peritoneal Cytology in Patients with Gastric Adenocarcinoma




The median OS from the date of diagnosis of PC was 30.2 mo, and from the first laparoscopic HIPEC was 20.3 months.

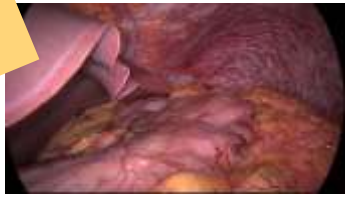
- **Systemic therapy can be safely combined with repeat HIPEC and may increase durability of response**

Badgewell, B et al. ASO, 2020

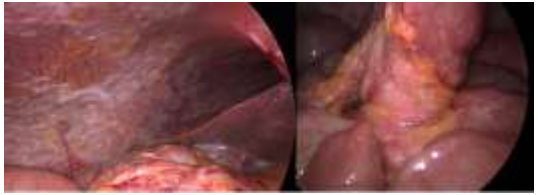
# Have We Optimized Our PC Treatment Strategy

Poorly Diff, diffuse, SRC, HER2 (2+); PD-L1 CPS 5

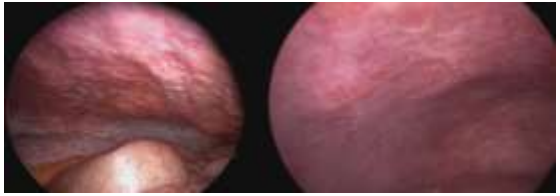
PreTreatment
Jan 2020



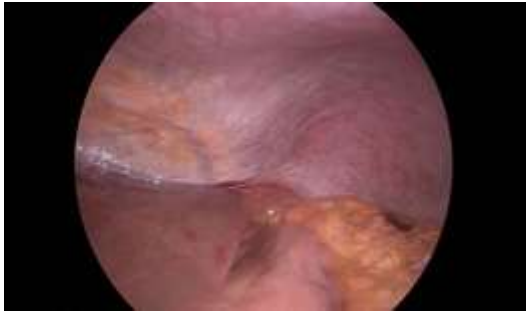
FOLFOX/Herceptin/Pembro
May 2020



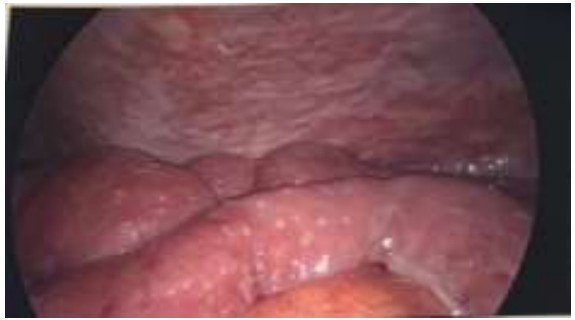
Systemic Plus HIPEC#2
August 2020



Systemic Plus HIPEC#3
October 2020



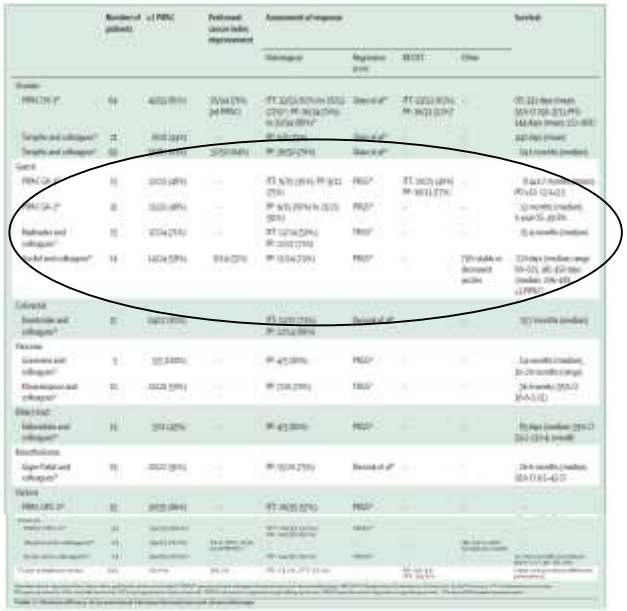
FOLFIRI / Herceptin / Pembro;
November 2020



**No HIPEC for 3 months**

# Evidence for PIPAC from International Experts

Pleura and Peritoneum



- 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)**

# PIPAC for Gastric Cancer Peritoneal Carcinomatosis

- Exactly, 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 INVESTIVATIONAL PHASE
  - Currently undergoing Phase I clinical trial

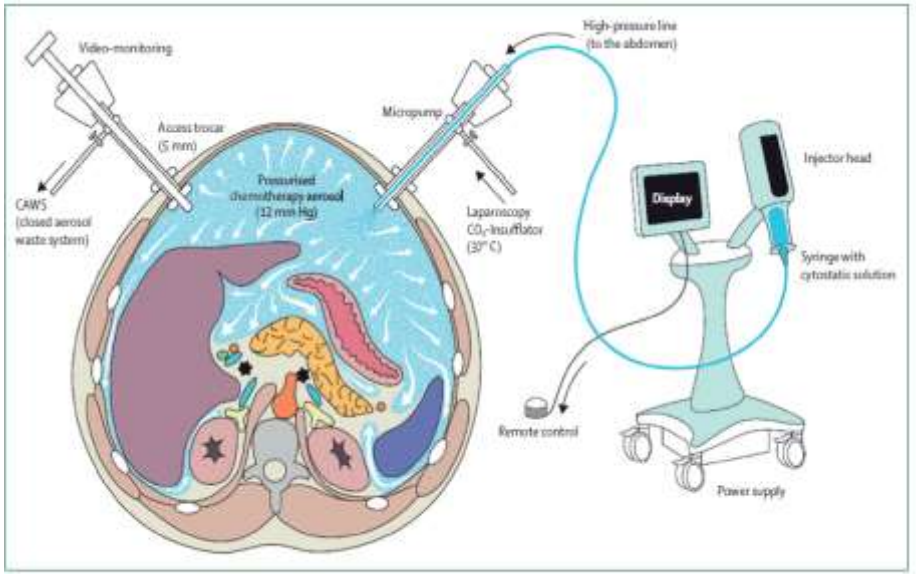
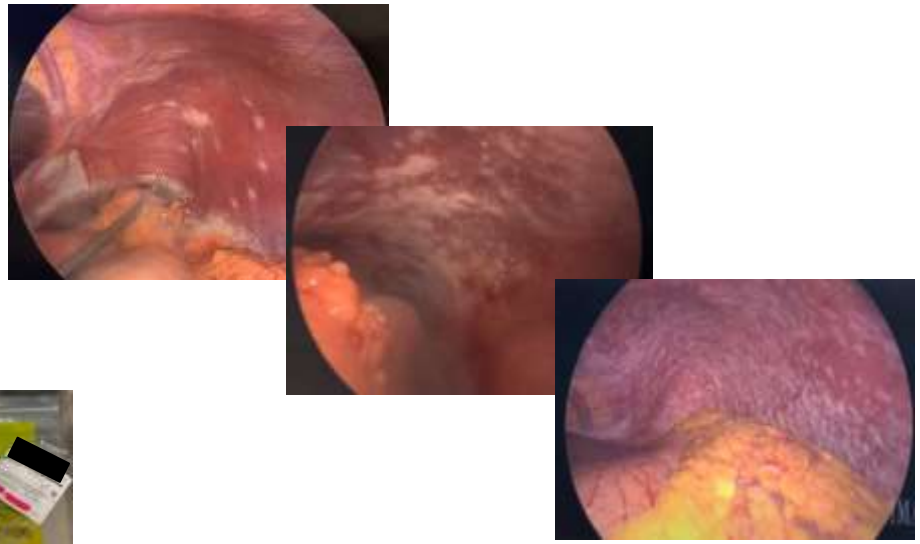



Figure 2: Schematic of PIPAC set-up
A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues[9] with permission from Médicine et Hygiène. PIPAC=pressurised 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

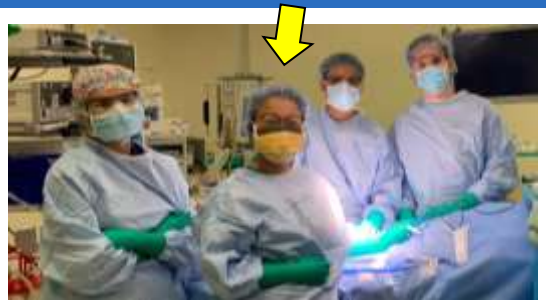


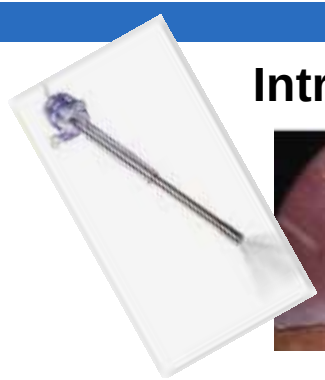
**Peritoneal Carcinomatosis Index (PCI) Score: 0 to 39**

Cisplatin

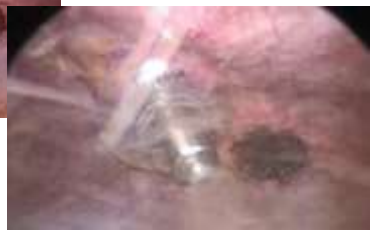
Doxorubicin

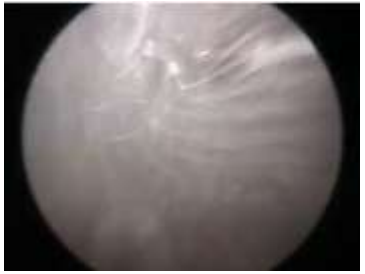
# Minimally Invasive and Short Operative Time

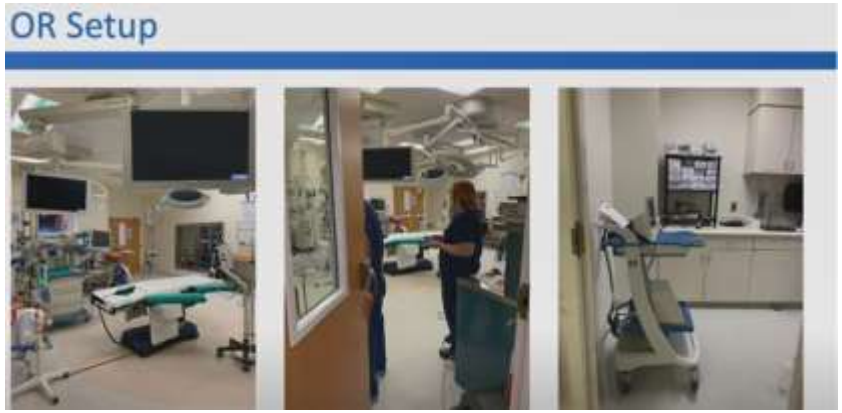




Intra-abdominal view

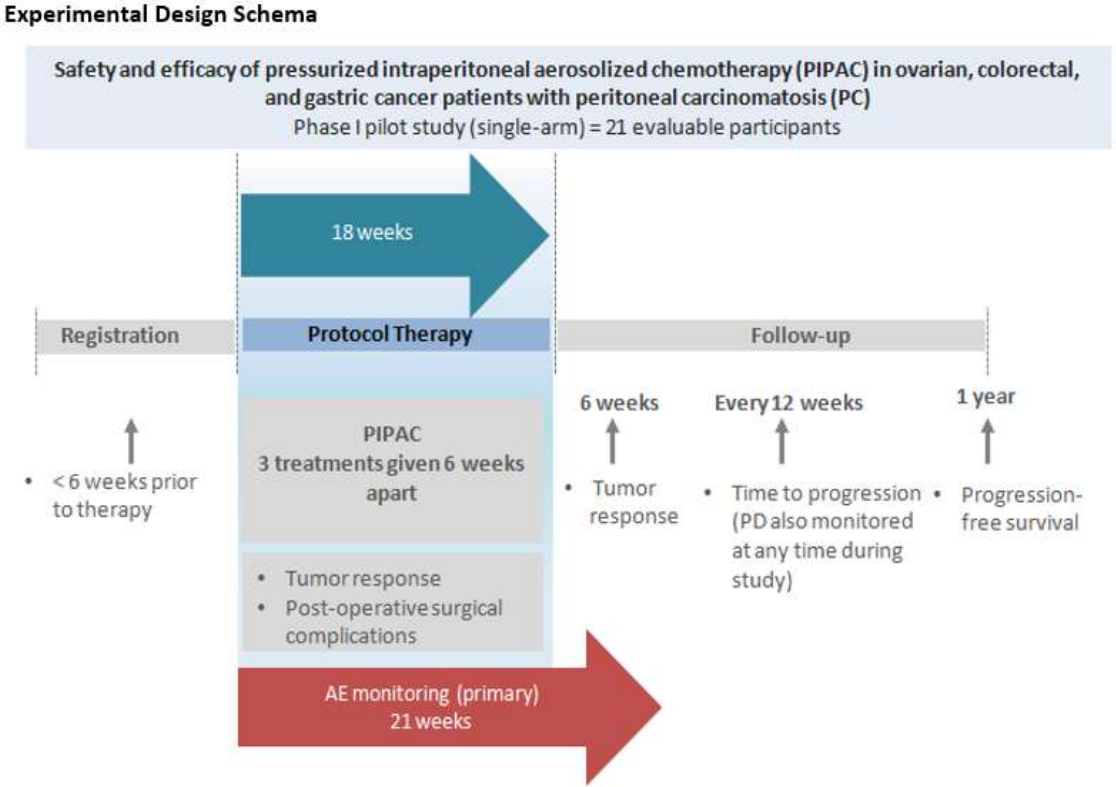




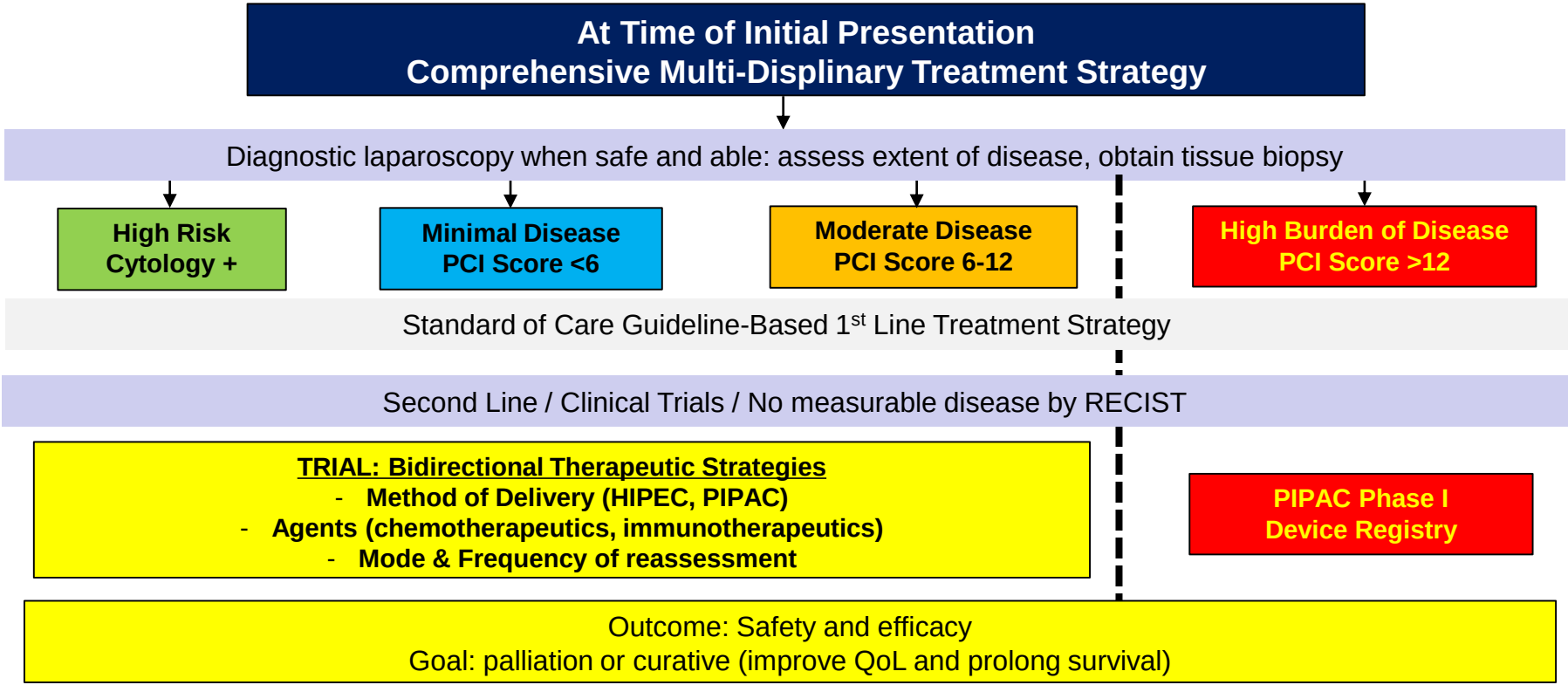



Extra-abdominal view

# Phase I PIPAC Trial: Experimental Design



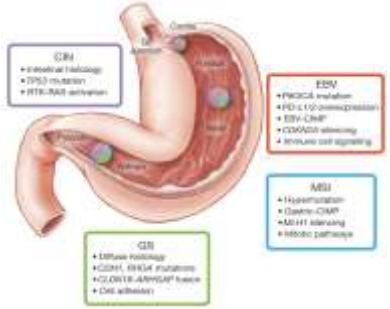
# Potential Role for Regional Therapy in GC PC

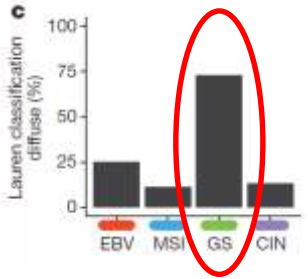


# Let's Summarize the Clinical Realm of GC PC

- Every patient with GC PC should be evaluated by a multidisplinary team for potential regional treatment option
- Patient-tailored, tumor specific treatment strategy should be developed
- Standard of care is not enough
- Clinical trials of novel therapies and strategies should be considered based on patient's tumor specific molecular profiles
- Regional therapy with IP, HIPEC, or PIPAC can be considered on clinical trial or on an individualized patient bases (expert centers, experienced surgeons)
  - HIPEC for stomach cancer in clinical trials; and used in clinical practice in select settings
  - PIPAC is INVESTIGATIONAL and undergoing safety evaluation in the United States
  - Phase II trials of efficacy of regional therapy for stomach cancer is planned at COH
- We are striving to bring novel and more effective treatments for GC PC patients

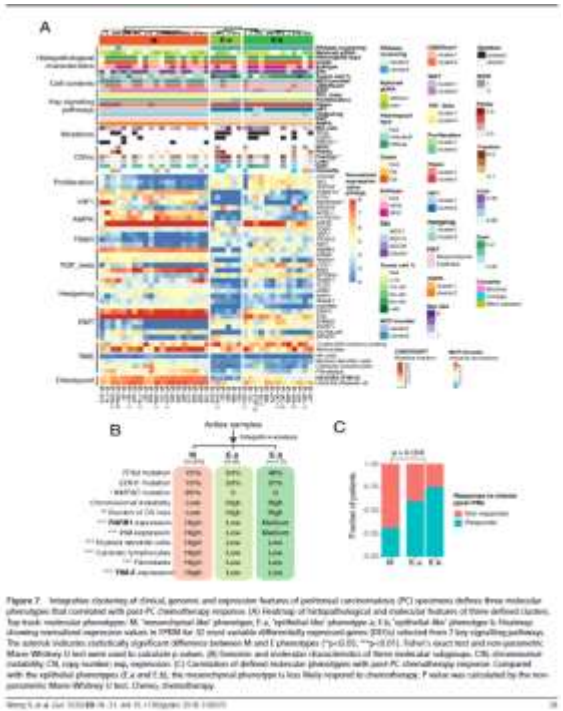
# Precision Oncology for GC PC Patient-Tailored Treatment





Nature 2014;513:202-209




Gut 2020;69:18-31

# Current Clinical Trials Open to Accrual at COH

| Protocol No. | Allows RECIST Non-measurable disease? | Most Novel Therapeutic Agents being tested IMMUNOTHERAPIES | PI Name | Sponsor | Line of Therapy |
|---|---|---|---|---|---|
| 20244 | **No** | **A Phase 2a, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma** | J. Chao | Leap Therapeutics | 1L and 2L cohorts |
| 19311 | **Yes (during dose escalation)** | **A Global Phase I Study: Bispecific T-cell Engager AMG199 in Subjects with MUC17-positive GC** | J. Chao | AMGEN | ≥ 3L |
| 20052 | **Yes (during dose escalation)** | **A Global Phase I Study: Bispecific T-cell Engager AMG910 in Subjects with CLDN18.2-positive GC** | J. Chao | Amgen | ≥ 3L |
| 18289 | **Yes** | **A Phase 3, Global Multi-center, Double Blind, Randomized Efficacy Study of IMAB362 Plus mFOLFOX6 compared with Placebo plus mFOLFOX6 as First Line Treatment of subjects with Claudin (CLDN)18.2+, HER2-, locally advanced unresecatble or mGC or mGEJ AdenoCa** | J Chao | Astellas Pharm | 1L |
| 19572 | **No** | **A Phase 2/3 Trial to Evaluate Margetuximab in combo with INCMGA00012 and Chemo or MGD013 and chemo in patients with mGC or locally adv, treatment-naïve HER2+ GC or GEJ AdenoCA** | J. Chao | Macrogenics | 1L |
| 17450 | **No** | **PHII-162, NCI#10066: A Phase ½ Study of Olaparib in combo with ramucirumab in mGC and GEJ AdenoCa** | J. Chao | ETCTN / NCI | ≥ 2L |
| 18069 | **Yes** | **A Phase 1b/2 Trial of the IRX-2 Regimen and Pembro in AGC and Adv GEJ adenoCA** | J. Chao | COH | ≥ 3L |

# 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**

# Gastric Cancer Workgroup at City of Hope

The GCWG at COH is a multidisplinary team of experts in GC / GEJ.
We strive to provide the best quality of life and long-term survival for our patients.
Our goal is to eliminate deaths due to stomach cancer nationally and worldwide.













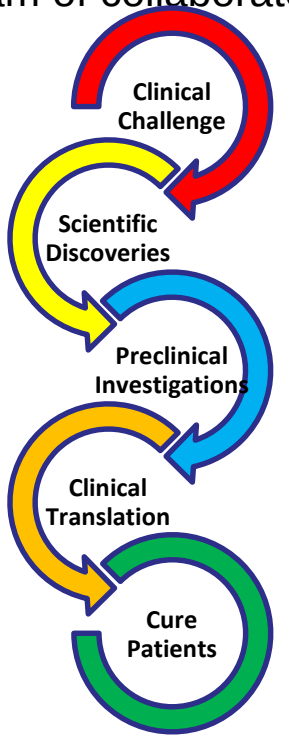


the MIRACLE of SCIENCE with SOUL City of Hope®

# 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**

Ale Smith (@AleStraCAN) |

the MIRACLE of SCIENCE with SOUL City of Hope tgen Penn Medicine MGH

# We are committed

- ***To eliminate deaths due to stomach cancer (gastric cancer, GC)***
- ***To bring the best of science and technology to improve quality of life and long-term survival for patients with GC***
- ***To develop more effective diagnostic and therapeutic strategies for gastric cancer peritoneal carcinomatosis (GC PC)***

# Thank you for your dedication and advocacy!

PATIENTS & ADVOCATES

DONORS

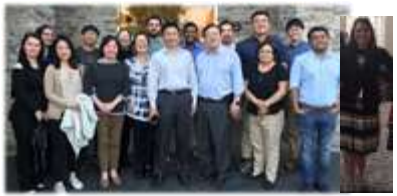
Eugene and Catherine Ohr Foundation

Mark Allen Ober

MENTORS

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

FONG-WARNER-HAHN-WOO LAB



GASTRIC CANCER WORKGROUP

J Chao, J Lin, Y Chen, L. Melstrom, B. Paz, S Yoon, G Idos, M J Sullivan, S Buga, M Raoof

PSM WORKGROUP

COH/TGEN CO-INVESTIGATORS

D Von Hoff, H Han, YC Yuan, H Li, M Li, S Priceman, S Forman, C Behrendt, SC Cha

COH Core Facilities

Flow Cytometry

Small Animal and Small Animal Imaging

Pathology, Biostatistics, Integrated Genomics

STAND U2C GC TEAM

J Chao (COH), S. Klempner, A Chan (MGH), S Yoon (MSKCC), S. Rhyeum (UPenn), D Catenacci (U Chicago), H. Lee (Samsung)

Stomach Cancer Task Force

JH Hwang (Stanford U), H Koh (Harvard U), R. Huang (Stanford U), etc

G6+ INTERNATIONAL GC TEAM

WJ Hyung, TI Son, YM Kim (S. Korea)

Y. Hu, G. Li, K Yang (China)

K. Obama, T. Nishigori (Japan)

N. Okabe, T. Kinoshita (Japan)

A. Guner (Turkey)

J Deciderio, A Marano (Italy), A Navaar (Chile)

A. Takasashi (Mexico)

And Growing…

*Email: ywoo@coh.org or cell: 626-482-7660*

the MIRACLE of SCIENCE with SOUL City of Hope