City of Hope

THIRD ANNUAL
ISSPP
Congress 2022

International Society for the Study of Pleura and Peritoneum

GASTRIC CANCERS

Systemic Therapy for Gastric Cancer Patients with Peritoneal Metastases

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City of Hope

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Consultant for J&J Ethicon, and Imugene, LTD.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products 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 Oncolytic Viruses, and CAR-T Cell in clinical trials will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Differences in treatment by ethnicity.
- Barriers to enrollment in clinical trials.

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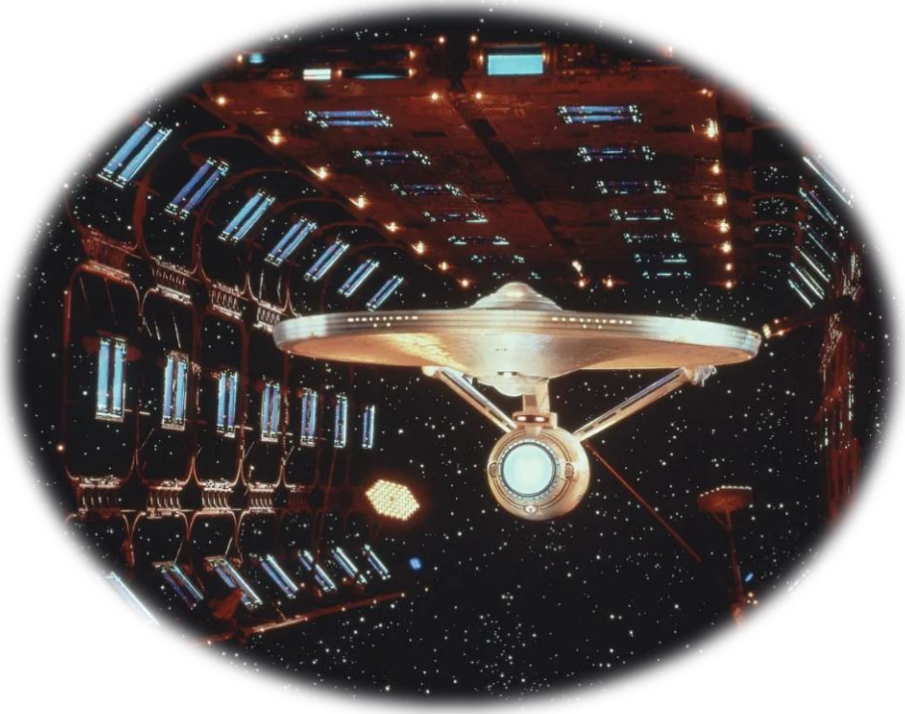
Space: the Final Frontier

USS Enterprise NCC-1701 - 1979



USS Enterprise NCC-1701-A - 1991

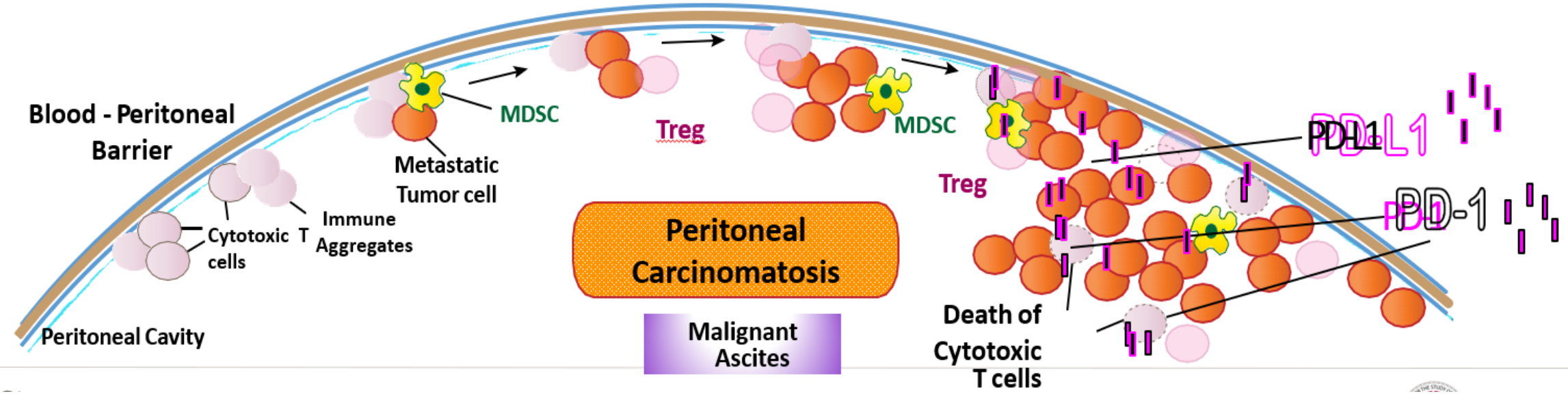
Space: the Final Frontier

These are the voyages of the starship *Enterprise*. Its five-year mission: to explore strange new worlds. To seek out new life and new civilizations. To boldly go where no ~~man~~ one has gone before!

The Peritoneum: The Final Frontier in Gastric Cancer

Peritoneum: the Final Frontier in Gastric Cancer Cure

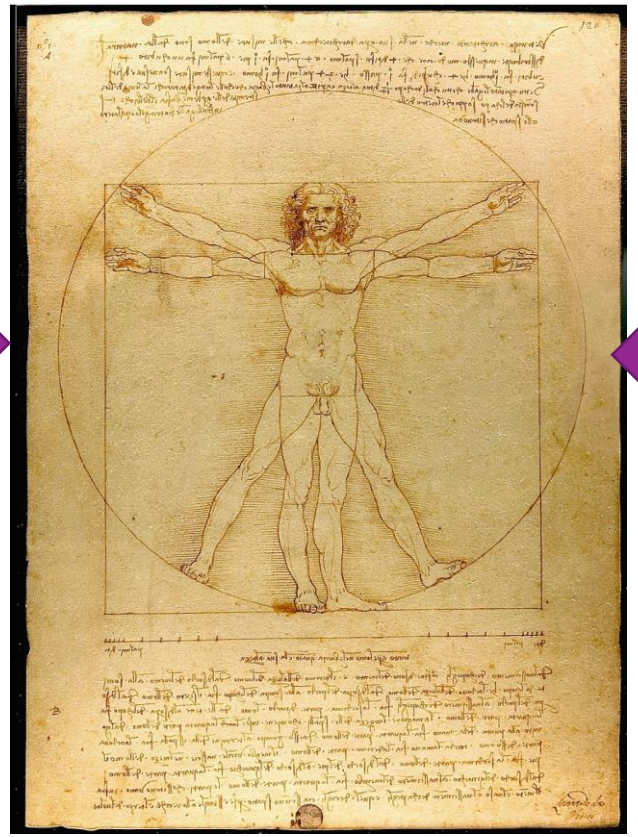
These are the ~~voyages~~ **investigations** of the starship ~~*Enterprise*~~ ***ISSPP - GC Collaborative*****.** Its five-year mission: to explore strange new worlds **of GC peritoneal metastases**. To seek out new ~~life~~ **cures** and new ~~civilizations~~ **curative strategies**. To boldly go where no ~~man~~ **systemic therapy** has gone before!



Systemic therapy for Gastric Cancer Peritoneal Metastases

"Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win."

-Sun Tzu, Art of War



"Strategy without tactics is the slowest route to victory. ***Tactics without strategy is the noise before defeat."***

-Sun Tzu, Art of War

JUST LIKE WE CANNOT SQUARE A CIRCLE, SYSTEMIC THERAPY ≠ CURE!

- Systemic therapy is one tactic in GC treatment … but alone it remains Noise Before Defeat against GCPM?

In Pursuit of More Cures for *All* Patients with Gastric Cancer

- Goal: to achieve long-term survival and to preserve or provide improved QoL
- By bringing the best of scientific discoveries and surgical innovation to GC care

Materials & Methods | More Curative Therapies | Multidisplinary Team

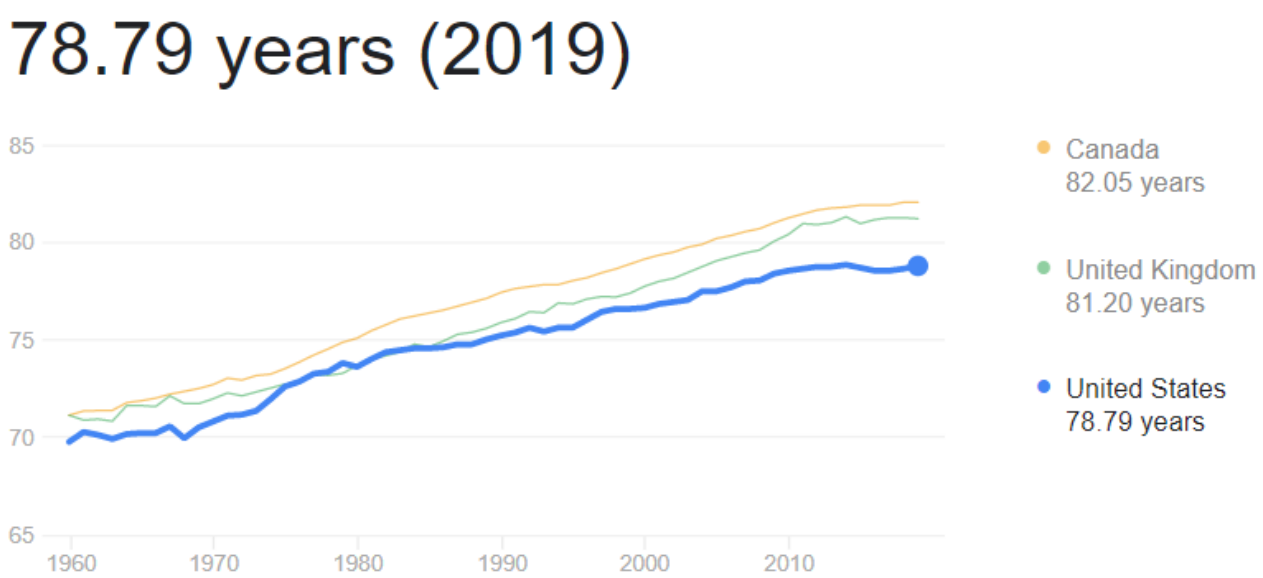
The diagnosis of GC begins patient's war to protect life.

Each of us enter the war in different battles with different tactics but each without a winning strategy

Life Years Lost to Gastric Cancer

***"If you know the enemy and know yourself, you need not fear the result of a hundred battles**. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle." – Sun Tzu in the Art of War*

Life Expectancy in the United States



- Average of 15.48 years of life lost / death due to GC
- Year of life lost per death was higher
  - Women (19.24 YLL per death),
  - >10 years of education (18.99 YLL per death)
  - clinical stage IV (17.44 YLL per death),
  - non-white (16.68 YLL per death)

https://datacommons.org/place/country/USA
Kim Y et al. Epidemiol Health. 2015; Kahn et al 2019; Li et al 2022

PM is Leading Cause of Therapeutic Failure in GC

PM is the most common site of distant metastases in GC

60%

at autopsy

Leading distant metastatic site at time of initial diagnosis

43%

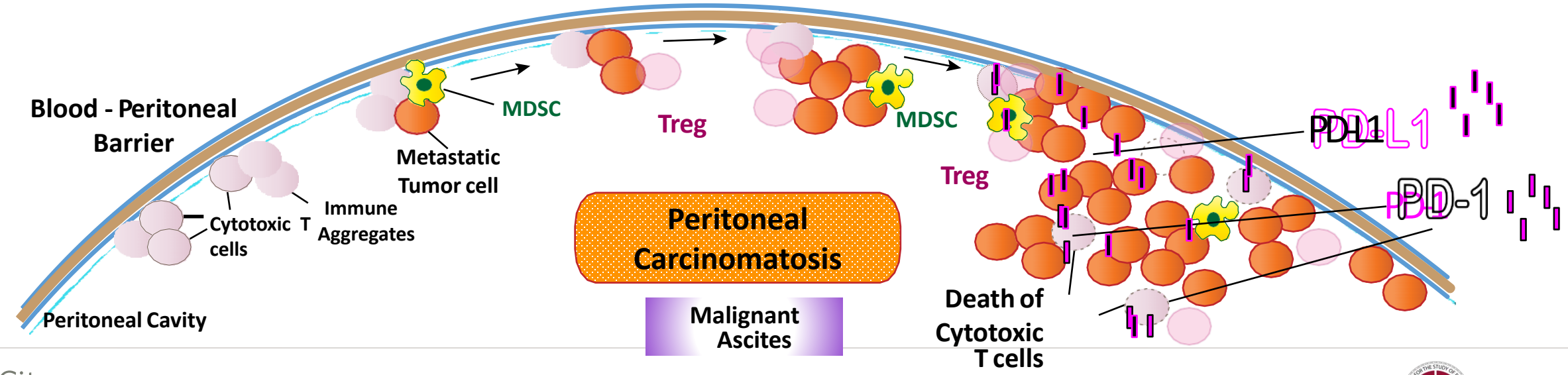
in the U.S. GC patients

Highest rate of recurrent disease occurs in the peritoneum

56%

after FLOT + gastrectomy with D2

OVERALL SURVIVAL = 3.3 TO 11.0 MONTHS



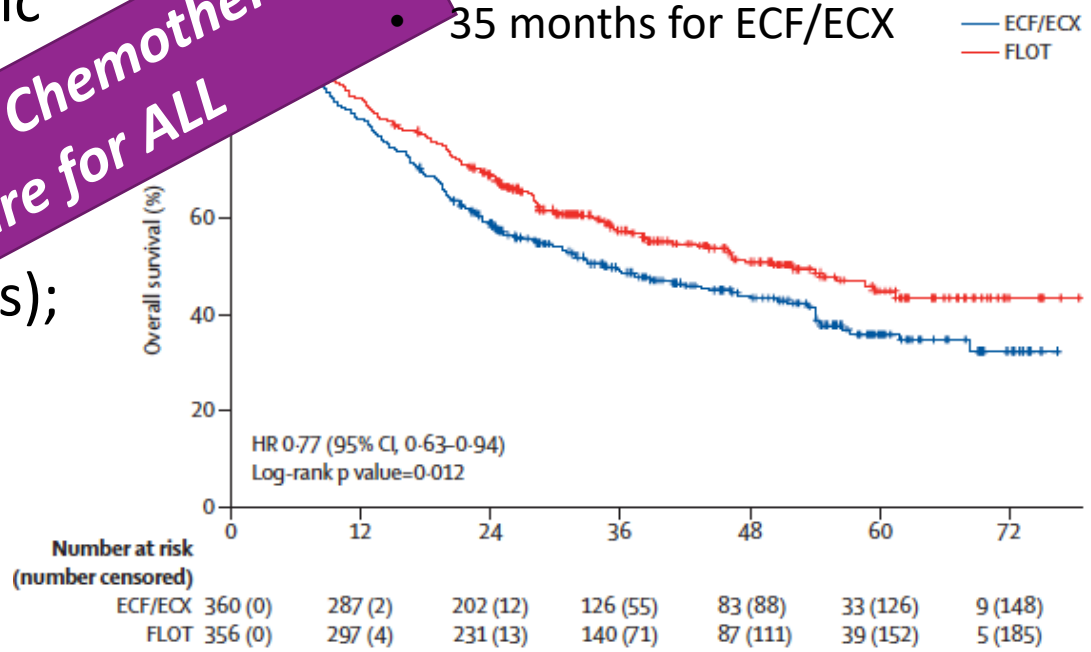
The FLOT4 Improves Survival Over ECF

- **Al-Batran et al. Lancet 2019**
  - N=716 locally advanced resectable gastric or GEJ cancers
  - Peri-op FLOT (8 cycles) vs. ECF (6
- 90% completed pre-op FLOT (4 eeks); but only 46% completed OT
- Better tolerated, ate (16% vs 6%)
- 85% R0 rate

Resection of the Primary plus Chemotherapy Does NOT Lead to Cure for ALL

Median OS

- 50 months for FLOT
- 35 months for ECF/ECX



Patterns of Recurrence with More P

- cT3-4 and/or cN+ (n=228) treated with periopFLOT-plus curative surgery (2009 – 2018)
- **89% of recurrence within firs**
- **Highest recurrence sit eal carcinomatosis (** while esophageal ca red mostly as metastasis to di ant organs (78%).
- The specific site of recurrence had no impact on overall survival time.
- Median OS = 61 mo; Median RFS = 42 mo.

Increasing rates of PM recurrence in GC with current therapies?

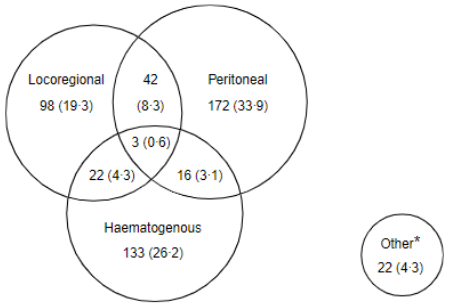


Fig. 1 Patterns of recurrence in 508 patients after curative resection. Values in parentheses are percentages. *Recurrence at the extra-abdominal lymph nodes

Article

Pat ival after
n 5-FU, Leucovorin, LOT) for Locally
tric Adenocarcinoma in tside Clinical Trials

s Verst [2], Jasmina Kuvendjiska [2], Peter Bronsert [3,4], Heiko Becker [5], and Birte Kulemann [2]

Table 2. Pattern of recurrence.

	Gastric Carcinoma (N = 97)	Esophageal Carcinoma (N = 131)	Total (N = 228)
Recurrence	36 (37%)	46 (35%)	82 (36%)
Time of recurrence after surgery (m)	9 (2–46)	9.5 (1–42)	9 (1–46)
Type of recurrence			
Local	3 (8%)	3 (7%)	6 (7%)
Local and distant metastasis	2 (6%)	4 (9%)	6 (7%)
Peritoneal carcinomatosis	20 (56%)	3 (7%)	23 (28%)
Hepatic metastasis	1 (3%)	11 (24%)	12 (14%)
Pulmonary metastasis	3 (8%)	7 (15%)	10 (12%)
Other location of metastasis	4 (11%)	11 (24%)	15 (18%)
Multiple distant metastasis	3 (8%)	7 (15%)	10 (12%)
Therapy of recurrence			
None	13 (36%)	7 (15%)	20 (24%)
Curative surgery	2 (6%)	4 (9%)	6 (7%)
Radiotherapy	0 (0%)	4 (9%)	4 (5%)
Chemotherapy	19 (53%)	23 (50%)	42 (51%)
Chemo- and radiotherapy	2 (6%)	8 (17%)	10 (12%)

T. Glatz et al J. Clin. Med. **2020**

Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial

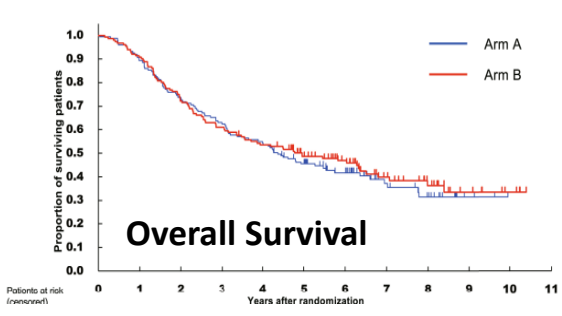
316 Randomized
20-75yrs
Type 4 or Large Type 3 GC
No Gross PM at Dx Lap

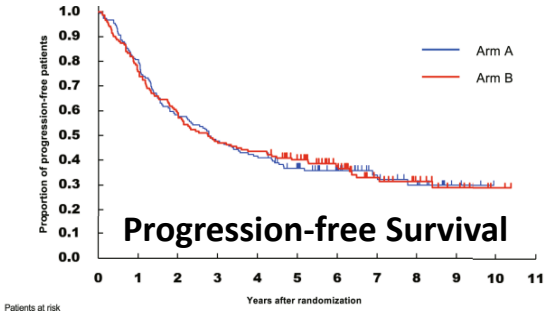
ARM
A

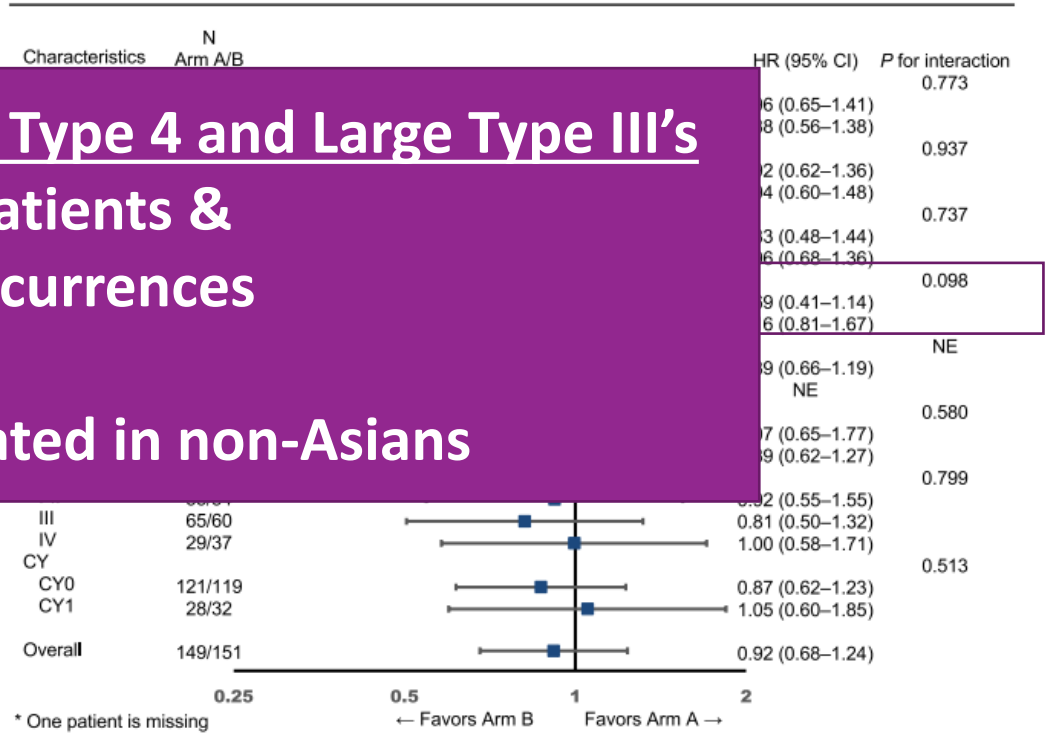
106 received adjuvar
70 completed
36 did not complet

Recurrence si

		(n = 91)
Lymph node	15	11
Peritoneum	68	73
Distant	15	11
Other	4	4







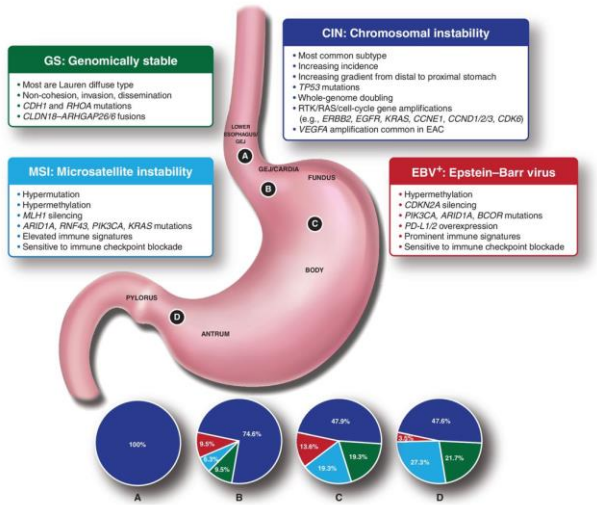
Peritoneal Recurrences in Bormann Type 4 and Large Type III's
45% - 48% of all patients &
75% -80% of the recurrences

***S1 + Cisplatin is less tolerated in non-Asians**

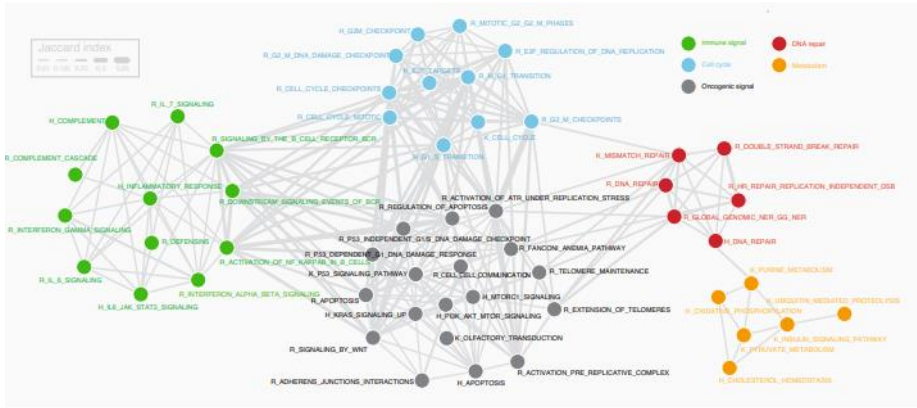
Y. Iwasaki et al. Gastric Cancer. 2021

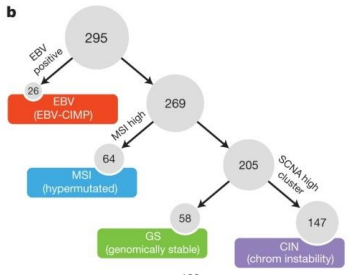
Molecular Heterogeneity of GC Reveals High Risk Profiles for PM

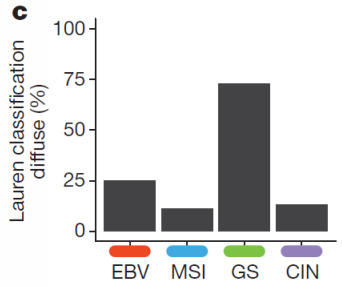
Understanding the Genomic Alteratons of Peritoneal Dissemination

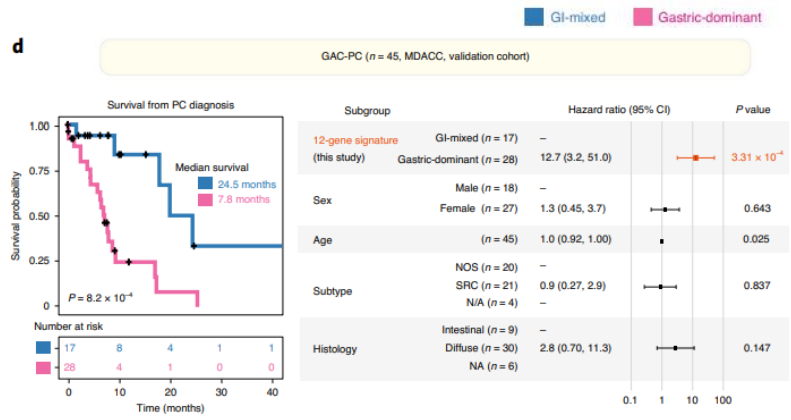


Classification	Subtypes of GCPM
• Bormann:	Type IV
• Lauren:	Diffuse Type
• Singapore-Duke:	Mesenchymal
• TCGA:	GS
• ACRG:	MSS/EMT
• Stromal/Vascular:	VM/I and VM







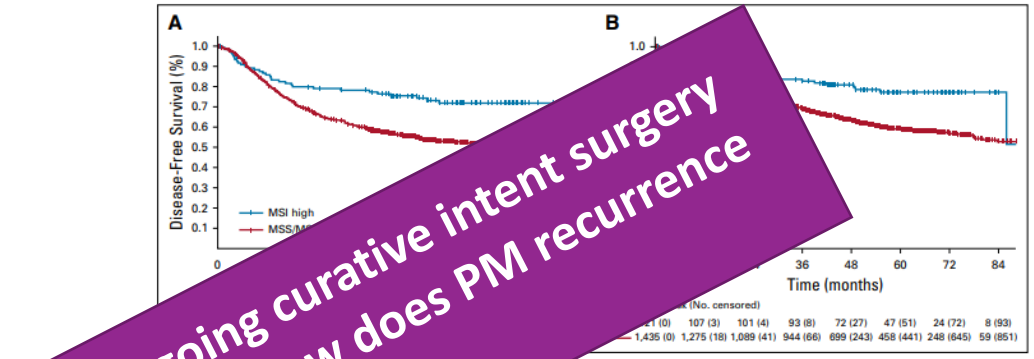


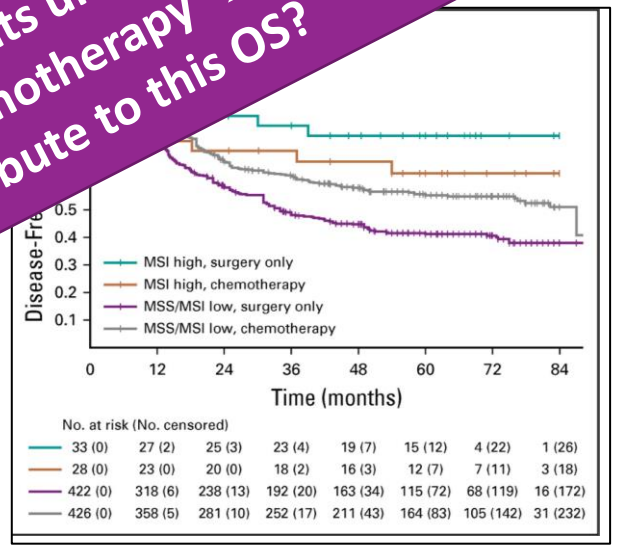
TCGA, Nature 2014; A Nagaraja et all Cancer Discovery. 2019; Chen Y et al. Cancers 2020; R. Wang et al. 2021;

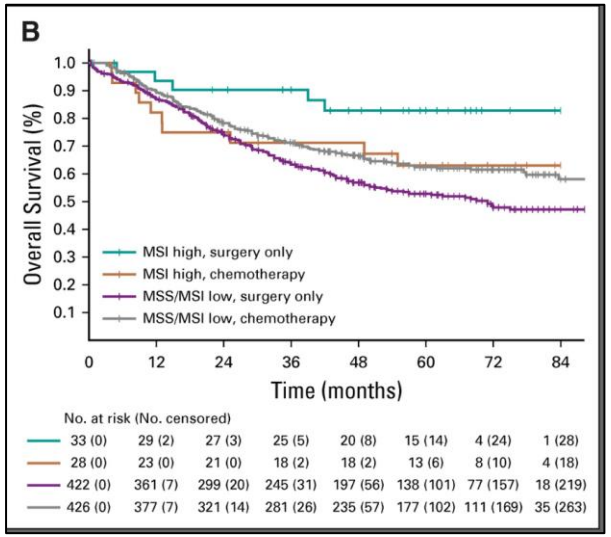
MSI Status Informs Chemo for Resectable GC

- **MAGIC, CLASSIC,** ARTIST, and ITACA-S trials (91.7% GC)
- MSI high: 121 (7.8%) – small %-age of pts
- MSI high is favorable prognostic factor
  - 72.8% 5-year DSF, 95% CI 63.8-80.7%) versus 52% CI 49.1%-55.1%)
  - Longer DSF: HR 1.88;95% CI, 1.1
    P=0.008)
- BEST SURVIVAL in M
  SURGERY ONL
- WORST SURVIA ients with
  SURGERY ONLY

MSI status can identify GC patients undergoing curative intent surgery who may not benefit from chemotherapy → How does PM recurrence contribute to this OS?







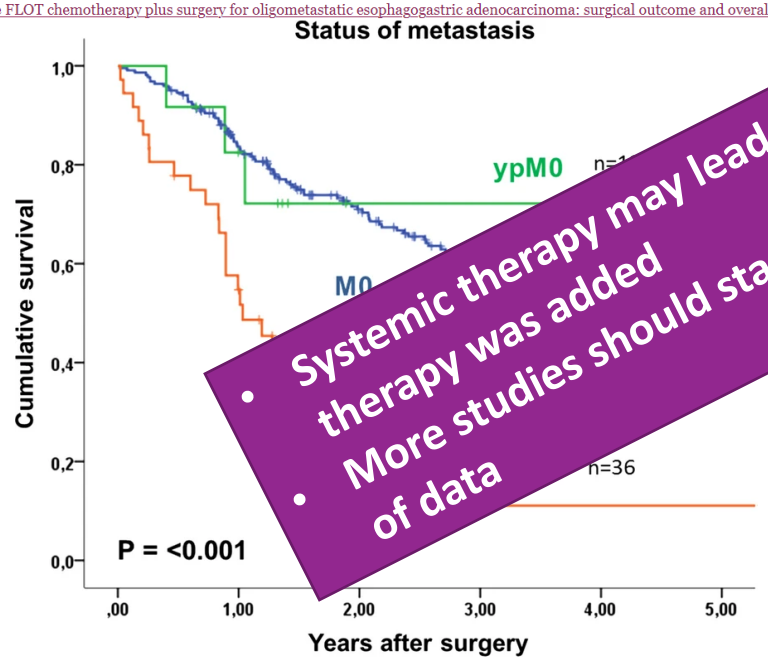
F. Pietrantonio et al. JCO 2019

Perioperative FLOT chemotherapy plus surgery for oligometastatic esophagogastric adenocarcinoma: surgical outcome and overall survival

Mira Runkel[1*], Rasmus Verst[1], Julia Spiegelberg[1], Stefan Fichtner-Feigl[1], Jens Hoeppner[1,2] and Torben Glatz[1,3]

Fig. 3

From: Perioperative FLOT chemotherapy plus surgery for oligometastatic esophagogastric adenocarcinoma: surgical outcome and overall survival



Kaplan Meier 5- year survival for patients with oligometastatic EGAC depending on status of metastases

- Systemic therapy may lead to curative intent surgery in GC with PM but regional therapy was added
- More studies should start to report and account for PM in design & interpretation of data

- N=31 GC of 48 total
- **84% GC patients had P**
- *Complete remi… …eoperative chemoth… …atients*

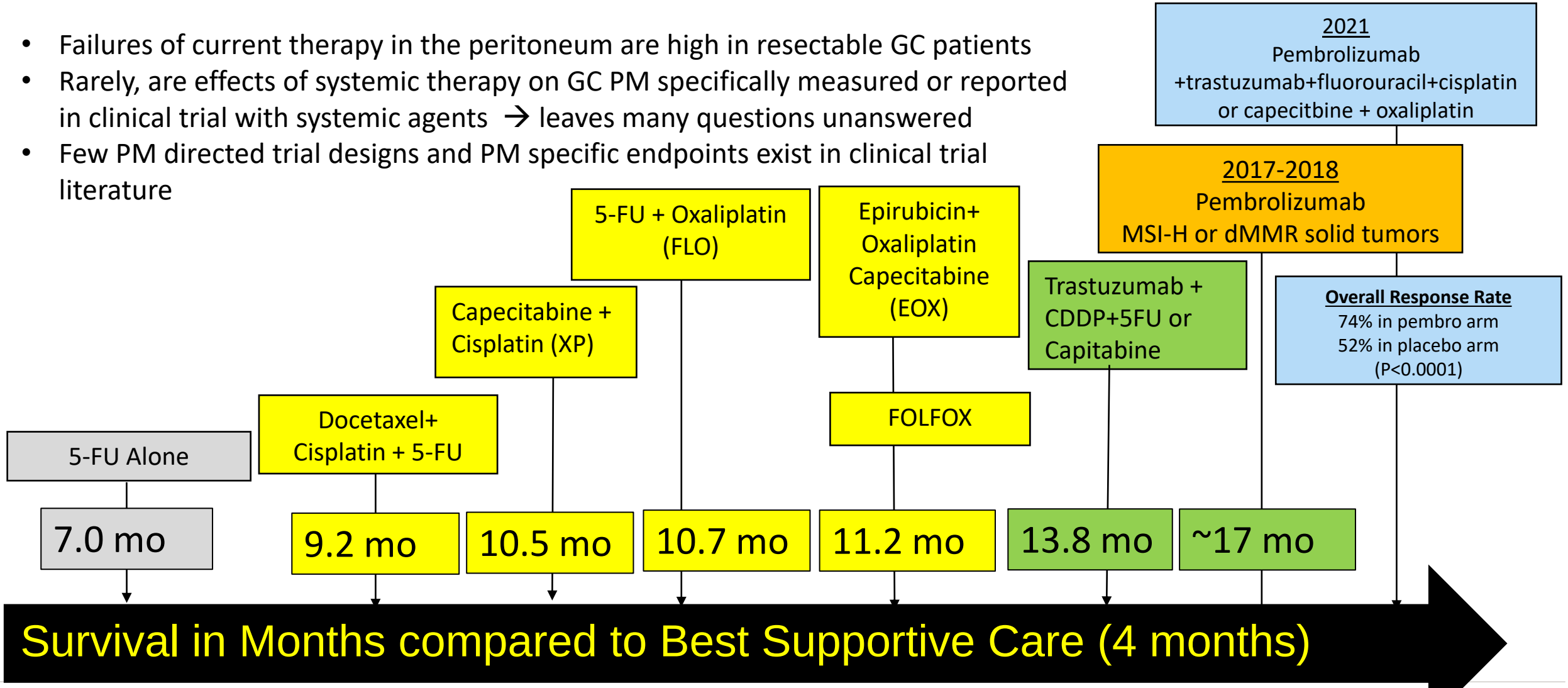
… patients (ypM0), 8 no evidence of … lesions, both during the preoperative staging … intraoperatively, and 4 patients with macroscopically suspected PC showed no histologic evidence of tumor cells after peritonectomy.

- Simultaneous resection of metastases: 68% of patients (n = 33)
- HIPEC was additionally carried out in 15 patients with peritoneal metastases after complete cytoreductive surgery.
- **Peritoneal recurrence 33% > hepatic (25%), local (8%), local and distant (17%), other (8%).**

M. Runkel et al. BMC Surgery 2021

Systemic Therapies in GC with PM

- Failures of current therapy in the peritoneum are high in resectable GC patients
- Rarely, are effects of systemic therapy on GC PM specifically measured or reported in clinical trial with systemic agents → leaves many questions unanswered
- Few PM directed trial designs and PM specific endpoints exist in clinical trial literature



Not a Curative Therapy nor Achieve Long-term Survival

Table 2. Summary of phase III trials conducted in Japan

Study	Treatment	n	RR (%)	Median PFS (months)	*P* value	MST (months)	*P* value
JCOG9205[14]	5-FU	106	11	1.9	—	7.1	—
	5-FU + cisplatin	104	34	3.9	<0.001	7.3	.34
	UFT + MMC	70	9	2.4	—	6.0	.11
JCOG9912[19]	5-FU	234	9	2.9	—	10.8	—
	Irinotecan + cisplatin	236	38	4.8	<0.001	12.3	.055
	S-1	234	28	4.2	0.001	11.4	<.001†
SPIRITS[21]	S-1	150	31	4.0	<0.001	11.0	.04
	S-1 + cisplatin	148	54	6.0		13.0	
GC0301/TOP002[22]	S-1	160	160	3.6*	0.16	10.5	.23
	S-1 + irinotecan	155	155	4.5*		12.8	

* Time to progression.
† Not inferior.
Abbreviations: RR = response rate; PFS = progression-free survival; MST = median survival time; UFT = uracil/tegafur; MMC = mitomycin-C

Table 1. Summary of recent phase III trials conducted in countries other than Japan

Author	Treatment	n	RR (%)	Median PFS (months)	*P* v		
Van Cutsem et al.[5]	5-FU + cisplatin	224	25	3.7*			
	5-FU + cisplatin + docetaxel	221	37	5.6*			
Kang et al.[9]	5-FU + cisplatin	156	29				
	Capecitabine + cisplatin	160	41				
Cunningham et al.[10]	ECF	263	38				—
	EOF	245					.69
	ECX	250				.9	.2
	EOX	244				11.2	.11
Ajani et al.[11]	5-FU + cisplatin	5				7.9	.198
	S-1 + cisplatin					8.6	
Al-Batran et al.[12]	5-FU + cisplatin + LV				.077	8.8	NS
	5-FU + L-OHP + LV					10.7	
Dank et al.[13]	5-FU + cisplatin			2	.088	8.7	.53
	Irinotecan + 5-FU + LV			5.0		9.0	

* Time to progression.
† Not inferior.
Abbreviations: RR = response rate; PFS = progression-free survival; M survival time; 5-FU = 5-fluorouracil; ECF = epirubicin/cisplatin/5-FU; EOF = epirubicin/oxaliplatin/5-FU; ECX = epirubicin/cisplatin/capecitabin = epirubicin/oxaliplatin/capecitabine; LV = leucovorin; NS = not significant

- Survival benefit is measured in months and less than a year OS
- Limit to Adding Additional Chemotherapy Due to Toxicity
- Survival after progression differ between Japan and rest of world?

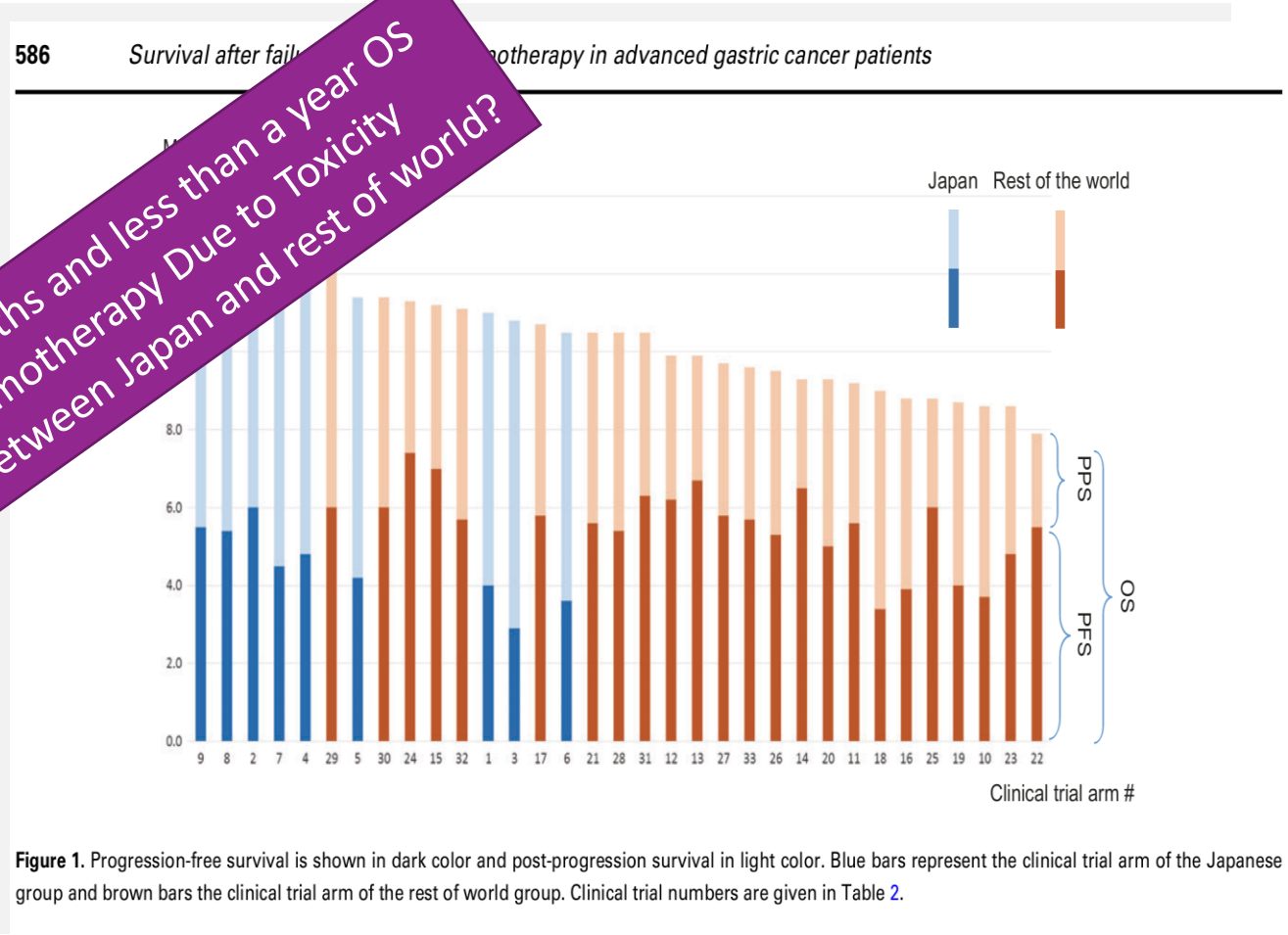


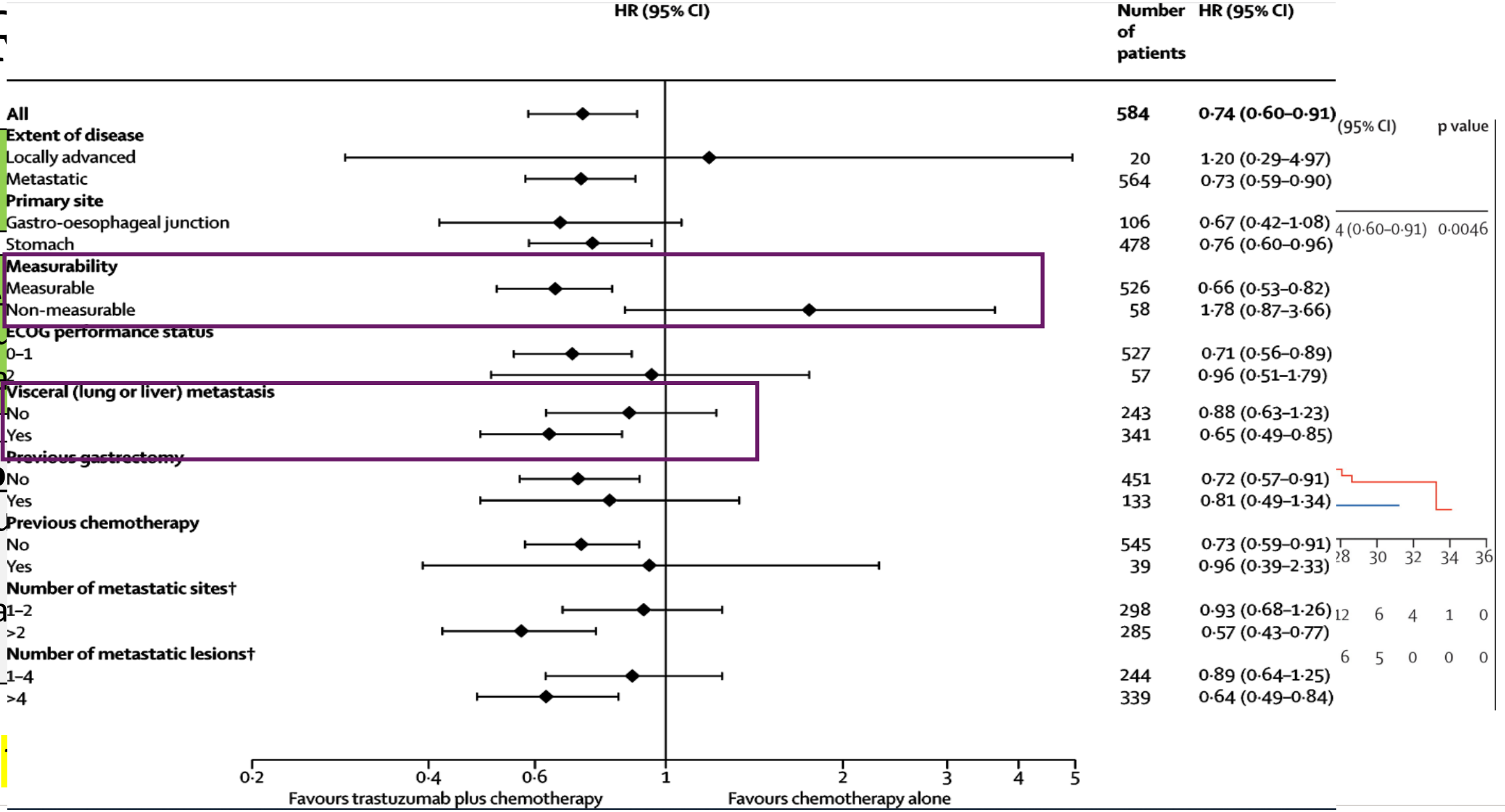
Figure 1. Progression-free survival is shown in dark color and post-progression survival in light color. Blue bars represent the clinical trial arm of the Japanese group and brown bars the clinical trial arm of the rest of world group. Clinical trial numbers are given in Table 2.

J. Cheng et al. Ther Adv Med Oncol 2019; A. Takashima et al. Gastroinest Cancer Res 2009

HEF

ToGA
Trastu
Cispla

Jacob
Trastu
Cispla



VEGFR2 Targeting Strategies

RAINBOW: Ramucirumab plus paclitaxel (n=330) vs Placebo plus pacelitaxel (n=335)

- Age=61 (25-84)
- Ethnicity = 4% black or other |63% white | 33% Asian
- Lauren type= Intestinal (44%) | Diffuse (35%)
- Peritoneal Metastases = 49% tx arm | 45% control arm
- Ascites present in 39% tx arm| 32% control arm
- Previously therapy = Triplet (25%)|Doublet (77%) |HER2 EGFR (9%)
- Previously surgery = Total (16%) | partial (24%)

- PFS/OS benefit of 1.5, 2.2 months → 47% Grade 3, 22% Grade 4, and 12% Grade 5

Second Line Treatment in VEGFR2+

RAINBOW Phase III (p=0.017)	**Median ORR/ PFS/ OS**
Ramucirumab +Paclitaxel	28%/ 4.4/ 9.6
Paclitaxel	16%/ 2.9/ 7.4

REGARD Phase III (p=0.047)	**Median ORR/ PFS/ OS**
Ramucirumab	3%/ 2.1/ 5.2
Placebo	3%/ 1.3/ 3.8

r 2nd Therapy

Fuchs CS et al. *Lancet*. 2014;
Wilke H et al. *Lancet Oncol*. 2014;
Fuchs CS et al. Lancet Oncology 2019

PD-1 Targeting Strategies

FDA approves pembrolizumab for adults and children with TMB-H solid tumors

- June 16, 2020→ for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067)
- A total of 102 patients (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb.
- The ORR for these patients was 29% (95% CI: 21,39), with a 4% complete response rate and 25% partial response rate. The median DoR was not reached, with 57% of patients having response durations ≥12 months and 50% of patients having response durations ≥24 months.

FDA grants accelerated approval to pembrolizumab for HER2-positive gastric cancer

- May 5, 2021→ interim analysis of 264 patients of on-going KEYNOTE-811 (NCT03615326) a multicenter, randomized, double-blind, placebo-controlled trial in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease.
- Patients were randomized (1:1) to receive pembrolizumab 200 mg or placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin
- Overall response rate: The ORR was 74% (95% CI 66, 82) in the pembrolizumab arm and 52% (95% CI 43, 61) in the placebo arm (p-value< 0.0001).

ASCO POST 2020

Survival Benefits Achieved With Pembrolizumab in MSI-H and CPS ≥ 10 Gastric/Gastroesophageal Junction Cancer


Joseph Chao, MD


Zev A. Wainberg, MD

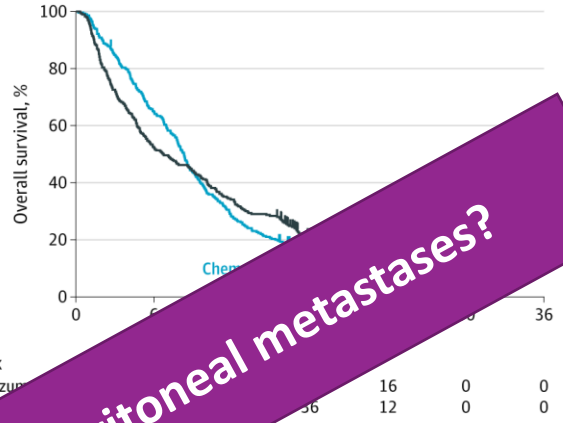
TABLE 1: Outcomes by Line of Therapy in Patients With MSI-H Disease

	KEYNOTE-062 (First-line pembrolizumab vs chemotherapy)	KEYNOTE-061 (≥ Second-line pembrolizumab v chemother	KEY
Objective response rate	57% vs 37%		
Median progression-free survival	11.2 vs 6.6 mo	17.8 vs	NR
Median overall survival	NR vs 8.5 mo	NR vs 8.1 mo	NR

HR = hazard ratio; mo = month; MSI-H = microsatellite instability–high; NR = not reached.

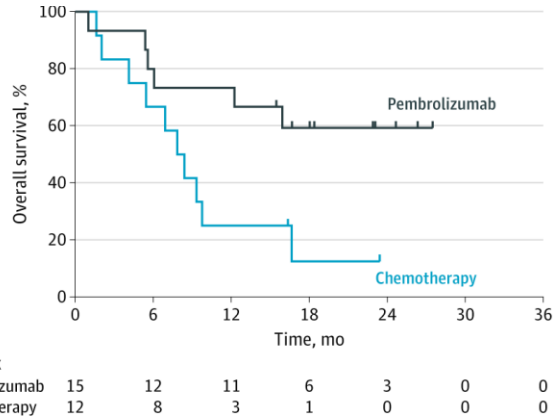
What is the response in peritoneal metastases?

ALL PATIENTS – KEYNOTE 061

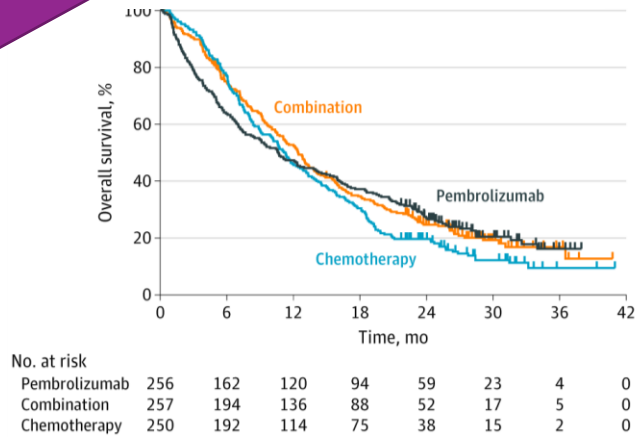


B Pat

MSI High – KEYNOTE 061

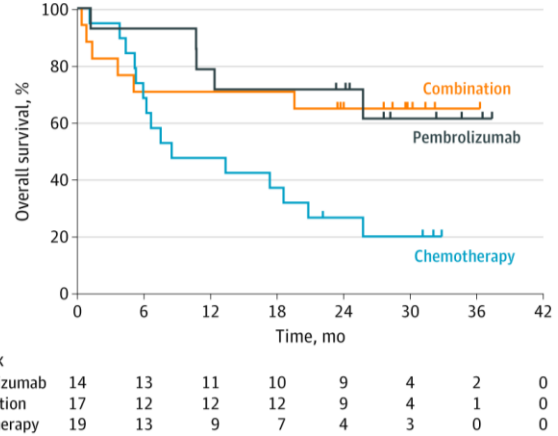


ATIENTS – KEYNOTE 062



D

MSI High – KEYNOTE 062



Shitara K et al. Lancet 2018. J. Chao et al. JAMA Oncol. 2021

Immune Checkpoint Targeting Strategies

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median age, years	63 (54-69)	62 (54-68)	62 (54-69)	61 (53-68)
<65	266 (56%)	286 (59%)	473 (60%)	488 (62%)
≥65	207 (44%)	196 (41%)	316 (40%)	304 (38%)
Sex				
Men	331 (70%)	349 (72%)	540 (68%)	560 (71%)
Women	142 (30%)	133 (28%)	249 (32%)	232 (29%)
Race				
Asian	119 (25%)	117 (24%)	186 (24%)	189 (24%)
White	328 (69%)	327 (68%)	556 (70%)	541 (68%)
American Indian or Alaska Native	10 (2%)	10 (2%)	12 (2%)	14 (2%)
Black or African American	2 (<1%)	7 (1%)	7 (1%)	11 (1%)
Other	14 (3%)	21 (4%)	28 (4%)	36 (5%)
Not reported	0	0	0	1 (<1%)
Region				
Asia	117 (25%)	111 (23%)	178 (23%)	178 (22%)
USA and Canada	67 (14%)	70 (15%)	131 (17%)	132 (17%)
Rest of world	289 (61%)	301 (62%)	480 (61%)	482 (61%)
ECOG performance status*				
0	194 (41%)	203 (42%)	326 (41%)	336 (42%)
1	279 (59%)	278 (58%)	462 (59%)	452 (57%)
2	0	0	1 (<1%)	3 (<1%)
Not reported	0	1 (<1%)	0	
Primary tumour location at initial diagnosis				
Gastric cancer	333 (70%)	334 (69%)		
Gastro-oesophageal junction cancer	84 (18%)	86 (18%)		
Oesophageal adenocarcinoma	56 (12%)			
Tumour cell PD-L1 expression				
<1%†				
≥1%				(16%)
Previous surgery				
Yes	97		(20%)	176 (22%)
No	376 (		629 (80%)	616 (78%)
Disease stage				
Metastatic	454 (96	461 (96%)	757 (96%)	756 (95%)
Locally advanced	16 (3%)	20 (4%)	27 (3%)	34 (4%)
Locally recurrent	3 (1%)	1 (<1%)	5 (1%)	2 (<1%)
Organs with metastases				
1	98 (21%)	105 (22%)	164 (21%)	183 (23%)
≥2	361 (76%)	362 (75%)	602 (76%)	583 (74%)

(Table 1 continues on next page)

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarci (CheckMate 649): a randomised, open-label

	Patients with a PD-L1 CPS of five or more		All randomly assi	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=48		
(Continued from previous page)				
Site of metastases				
Liver				40%)
Peritoneum				188 (24%)
CNS			1%)	0
			4%)	145 (18%) 136 (17%)
		413 (86%)		644 (82%) 656 (83%)
	171 (36%)	176 (37%)	272 (34%)	267 (34%)
	137 (29%)	141 (29%)	254 (32%)	273 (34%)
	37 (8%)	30 (6%)	58 (7%)	48 (6%)
Unknown	128 (27%)	135 (28%)	205 (26%)	204 (26%)
Microsatellite instability status				
Microsatellite stable	423 (89%)	423 (88%)	695 (88%)	682 (86%)
Microsatellite instability-high	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen§				
FOLFOX	237/468 (51%)	242/465 (52%)	422/782 (54%)	406/767 (53%)
XELOX	231/468 (49%)	223/465 (48%)	360/782 (46%)	361/767 (47%)

Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=capecitabine and oxaliplatin. *Based on case report form. All randomly assigned patients had ECOG performance status of 0 or 1 based on interactive response technology. †Includes indeterminate tumour cell PD-L1 expression. ‡Per WHO histological classification. §Patients who received at least one dose of the assigned treatment.

Table 1: Baseline characteristics

FDA APPROVES NIVO + combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic GC, GEJ cancer and esophageal adenocarcinoma

e 12-mo PFS rate for

% (95% CI 32–41) for NIVO + CHEMO
22% (18–26) for chemotherapy alone

D-L1 CPS ≥1 (B) -

- 34% (95% CI 30–38) for NIVO + CHEMO
- 22% (19–26) for chemotherapy alone

All randomly assigned patients (C)-

- 33% (95% CI 30–37) for NIVO + CHEMO
- 23% (20–27) for chemotherapy alone

12- month OS rate

PD-L1 CPS ≥5 (A) -

- 57% (95% CI 53–62) for NIVO + CHEMO
- 46% (42–51) for chemotherapy alone

PD-L1 CPS ≥1 (B) -

- 56% (95% CI 52–59) for NIVO + CHEMO
- 47% (43–51) for chemotherapy alone;

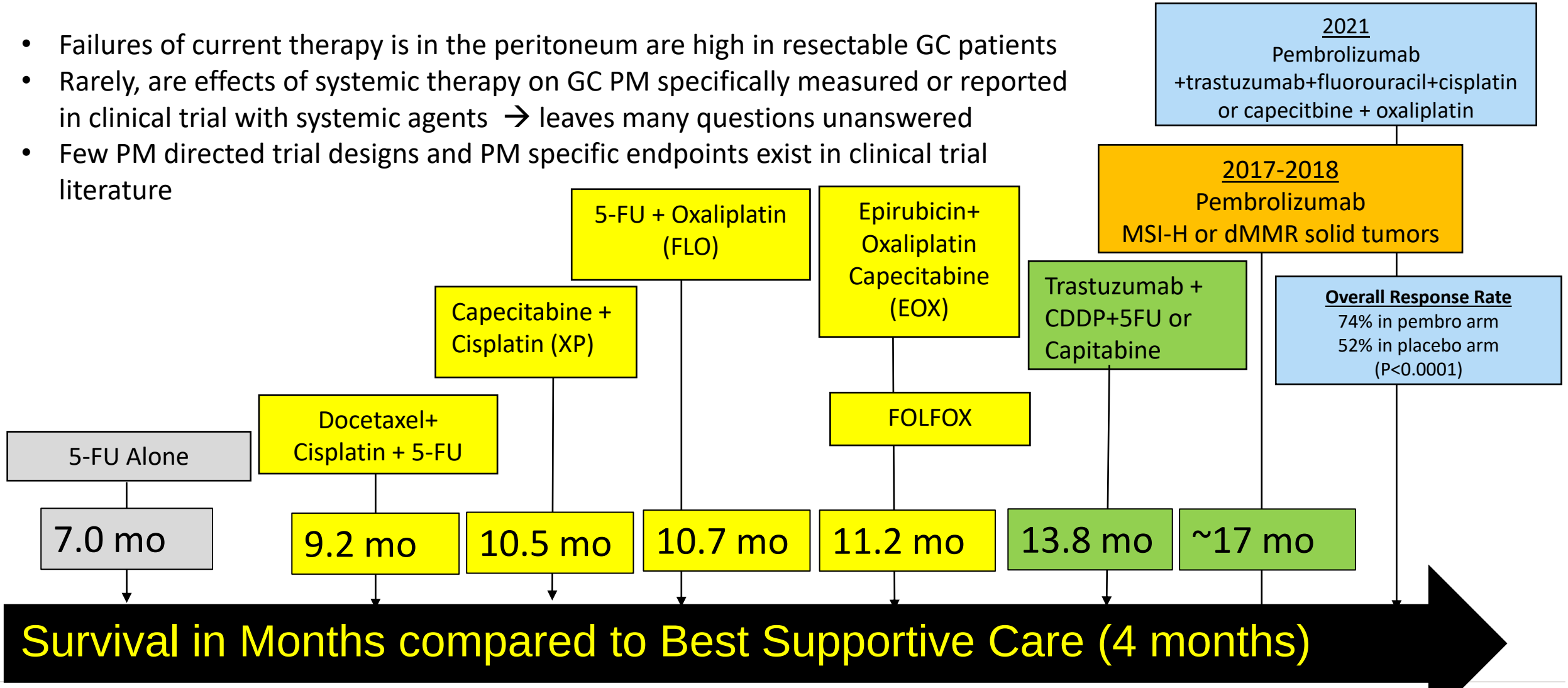
ALL randomly assigned patients (C) –

- 55% (95% CI 51–58) for NIVO + CHEMO
- 48% (44–51) for chemotherapy alone

Y. Janjigan et al. Lancet. 2021

Therapeutic Strategies in GC with PM?

- Failures of current therapy is in the peritoneum are high in resectable GC patients
- Rarely, are effects of systemic therapy on GC PM specifically measured or reported in clinical trial with systemic agents → leaves many questions unanswered
- Few PM directed trial designs and PM specific endpoints exist in clinical trial literature



Is Regional Therapy Another Tactic that is Needed in the Strategy to Win Our War Against GCPM? YES!

- ❑ **Intent: Cure or care**
- ❑ **Timing of Regional Therapy (First-line?, second-line?, Third-line)**
- ❑ **Regional Drug Selection**
- ❑ **Combination Dosing Schedule?**
- ❑ **Patient Selection-**
  - ❑ **Age**
  - ❑ **Performance status**
  - ❑ **Disease characteristics (primary tumor versus PM)**
  - ❑ **Histology, MSI status, TMB, Burden of PC/MA**
  - ❑ **Other Sites of Metastases**
- ❑ **Biomarkers of response**
- ❑ **What else can equip us for each battle to win the war against GCPM**

What will be our strategy to win this war?
How can we fight each battle without loss of life?

Diagnostic laparoscopy when safe and able: assess extent of disease, obtain tissue biopsy

High Risk Cytology +	Minimal Disease PCI Score <6	Moderate Disease PCI Score 6-12	High Burden Disease PCI Score >12

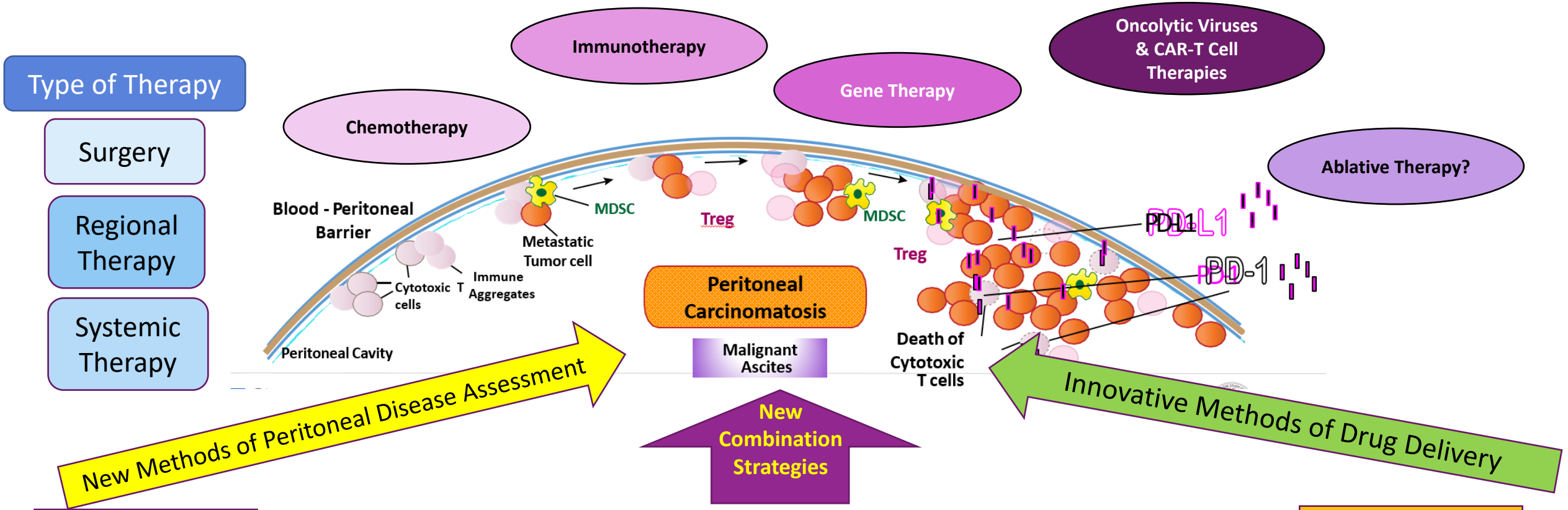
First Line: FOLFOX plus/minus Pembro/Herceptin/etc

Second Line: Paclitaxel + Ramucirumab

Primary Outcome: MTD, safety
Secondary Outcomes: OS, PFS
Goal: palliation versus curative (improve QoL versus prolong survival)

Exploratory Measures: peritoneal immuneTME changes over the course of therapy
Specimen collection: primary tumor, PM, peritoneal fluid, peripheral blood

Will Different Route of Delivery with Same Drugs Lead to a Cure of PM in GC? NO!



PM Specific Clinical Trial Designs?

Equip our battleships with the best of science and innovation for the cure and care of patients with GC PM

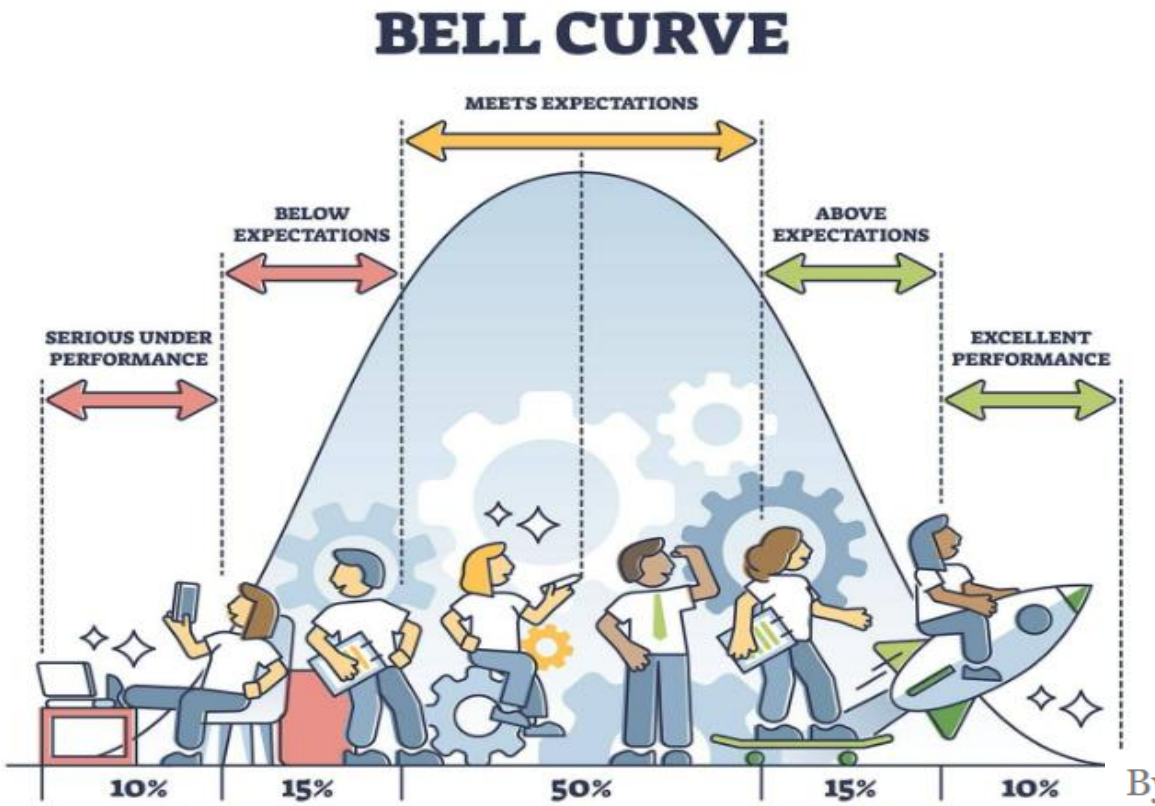
PM Specific Clinical Trial Endpoints

FINAL THOUGHTS

SURGERY

SYSTEMICCHEMO

IMMUNOTHERAPY



By Dr. Saul McLeod, published 2019

?

Thank you for your attention and participation!

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Join Together to Develop the New Strategies!

PATIENTS & ADVOCATES

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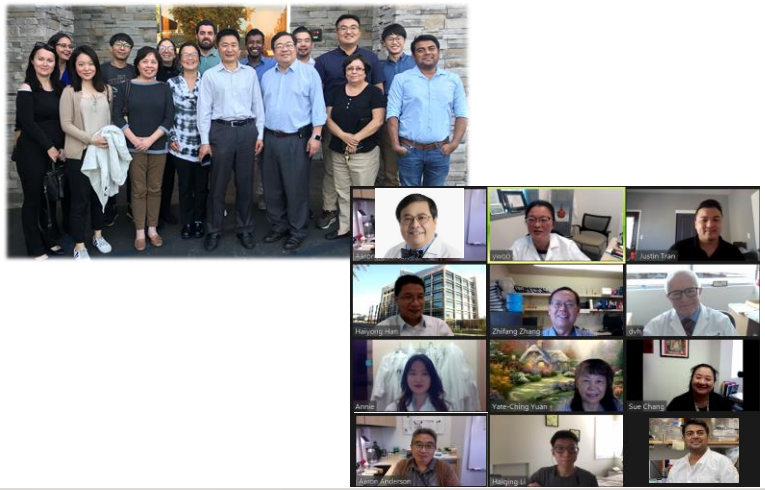
FONG-WOO LAB



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M Jung (Sweden)
And Growing…

ISSPP & the U.S PIPAC Consortium

BACK in 30 Minutes for the LAST GREAT DEBATE – Is there a role for REGIONAL DIRECTED THERAPIES in GASTRIC CANCER?

Wei Peng Yong MB ChB

PRO

Samuel Klempner, MD

Joseph Chao, MD

CON

Systemic Therapy Improves Survival

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

- fluorouracil (200 mg / m^2 / day) for 21 days.
- OS: HR for death, 0.75; 95% CI 0.60 to 0.93; P=0.009)
- PFS: HR for progression, 0.66; 95% CI 0.53 to 0.81; P<0.001)
- Recurrence in 24.4% versus 36.8 %
- 5-year survival rates:
  - 36.3 % (95 % CI 29.5 to 43.0%) perioperative-chemotherapy group vs
  - 23.0 percent (95% CI, 16.6 to 29.4 %)
- 86% completed neoadj; 55% adjuvant started and 42% completed 6 cycles

D. Cunningham et al. NEJM 2006

Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial

Sung Hoon Noh, Sook Ryun Park, Han-Kwang Yang, Hyun Cheol Chung, Ik-Joo Chung, Sang-Woon Kim, Hyung-Ho Kim, Jin-Hyuk Choi, Hoon-Kyo Kim, Wansik Yu, Jong Inn Lee, Dong Bok Shin, Jiafu Ji, Jen-Shi Chen, Yunni Lim, Stella Ha, Yung-Jue Bang*, on behalf of the CLASSIC trial investigators†*

- 61.1% (95% CI, 56.8% to 65.3%) in the surgery-only group. The HR for death in the S-1 group compared with the surgery-only group was 0.669 (95% CI, 0.540 to 0.828),
- Postoperative adjuvant S-1 alone reduced the risk of death by 33.1%
- Reduction in the risk of mortality is comparable with MAGIC trial and the Intergroup 0116 (INT-0116) trial.