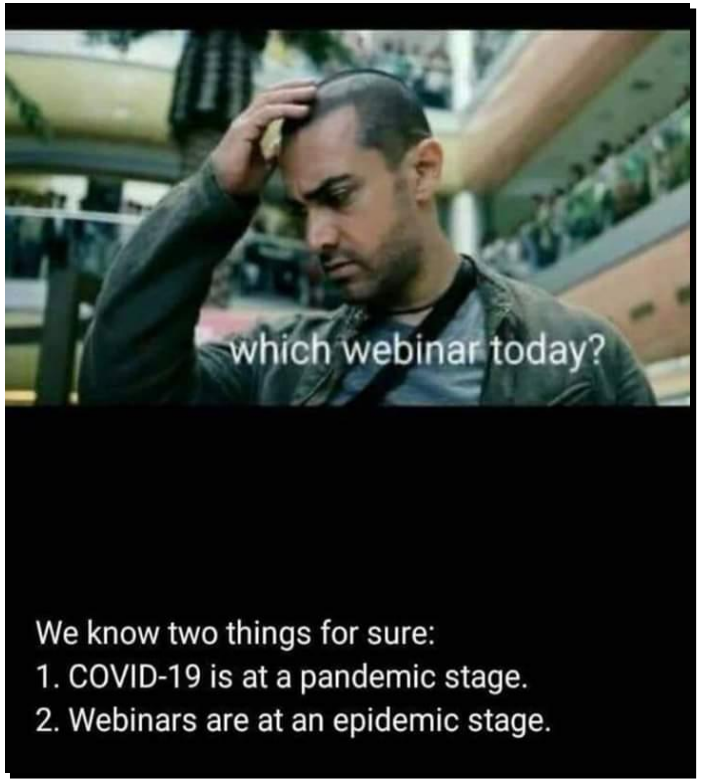
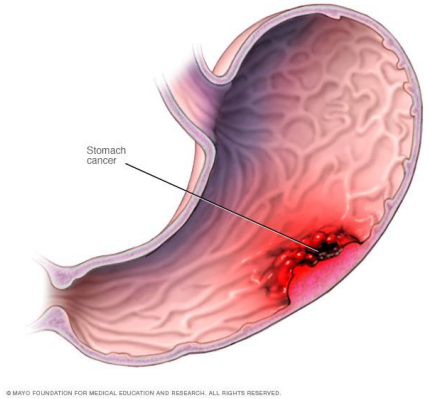
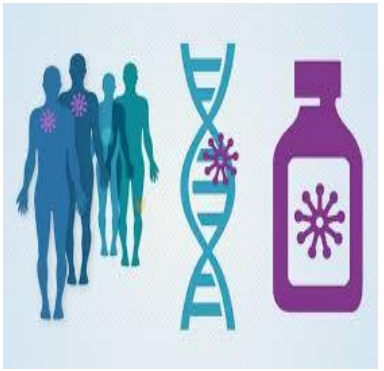


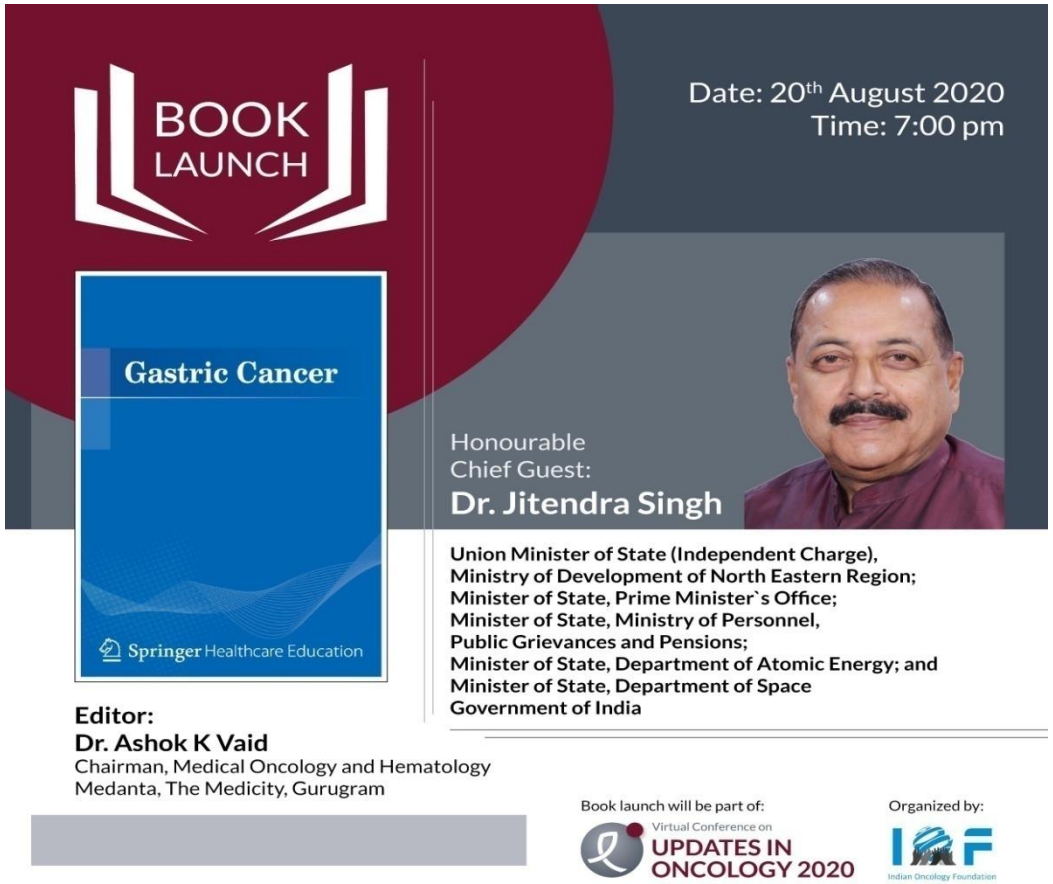
Targeted therapy in Gastric Cancer: Scarcity to plenty ; How and when to best use them?

Prof. (Dr) Ghanashyam Biswas, DM
Sparsh-AOI and Sum Hospital
Bhubaneswar, Odisha





Proud to be a part of this Journey



Chemotherapy and Targeted Treatment as Later Line Therapy 5.3

Dr. Ghanashyam Biswas

ABSTRACT

The development of progressive disease post first line therapy is seen in almost all the metastatic cancer patients. The implementation of second line therapeutic regimen in relatively fit patients is combination of taxane and ramucirumab or else alone. Thereafter only few patients remain as a candidate for later lines of therapy like apatinib, immunotherapy, or re-challenge of previously received treatment.

Keywords: Apatinib, immunotherapy, antiangiogenesis, vascular endothelial growth factor, 1000 Genome Project

INTRODUCTION

You beat cancer by how you live, why you live, and in the manner in which you live. Live your life by your own terms, not cancers'.

– Stuart Scott, anchor at ESPN and a cancer patient

The seeds for gastric adenocarcinoma management had been sown nearly two centuries earlier. It was during 1800s that Dr. John Jones, the first Professor of surgery at King's College, and an author of the first American textbook on surgery,

Dr. Ghanashyam Biswas, MD DM
Executive Director, Sparsh Hospital, Consultant Medical Oncology, American Oncologic Institute, Bhubaneshwar

Ashok K Vaid (ed.), *Gastric Cancer*

Stomach cancer facts

- **1/3** are detected early
- **2/3** will have metastatic disease at some point
- Incidence is decreasing in developed countries and more proximal cancers are reported
- A shift from distal to proximal as the site of disease has not been reported from India
- Intestinal type: Males , older age, prevalent in high-risk areas & linked to environmental factors.

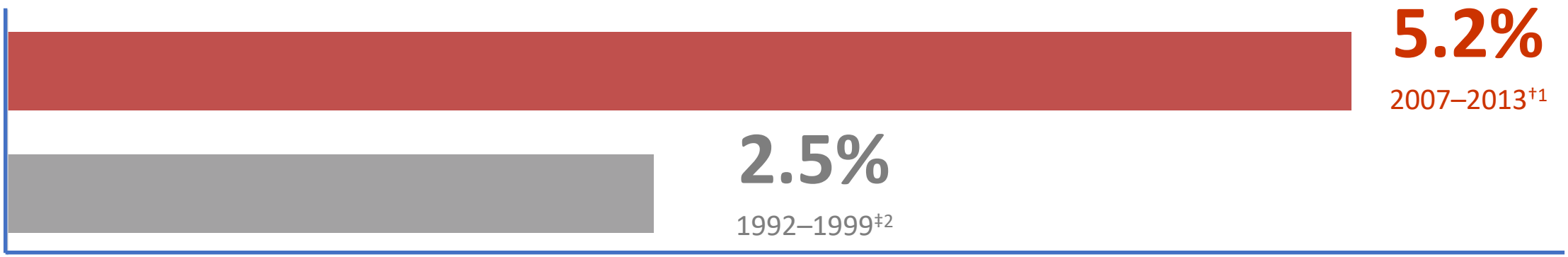
  Declining incidence in developing countries, HER2 (31.8%)
- Diffuse or infiltrative type: Both sexes, younger age and carries a worse prognosis. Rising incidence globally,

  HER2 (6.2%)

Gastric Cancer survival in the last two decades

Gastric Cancer Survival Rates: 2 Decades of "*improvements*"

5-Year Relative Survival Rates for Patients With Distant Gastric Cancer



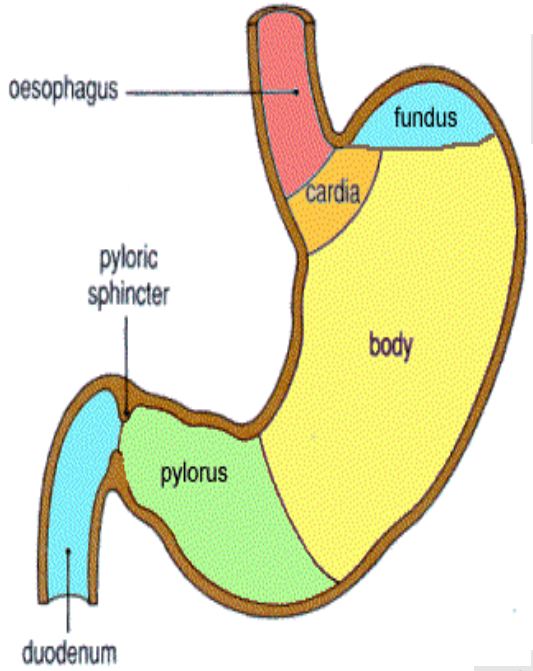
Howlader N, et al. SEER Cancer Statistics Review (CSR) 1975–2014. https://seer.cancer.gov/archive/csr/1975_2014. Accessed September 26, 2018.
Ries LAG, et al. SEER Cancer Statistics Review (CSR) 1975–2000. https://seer.cancer.gov/archive/csr/1975_2000. Accessed September 26, 2018.
Altekruse SF, et al. SEER Cancer Statistics Review (CSR) 1975–2007. https://seer.cancer.gov/archive/csr/1975_2007. Accessed September 26, 2018.
National Cancer Institute. Distant. SEER training modules Web site. https://training.seer.cancer.gov/staging/systems/summary/distant.html. Accessed September 26, 2018.

Genetic types of Gastric Cancers

CIN

Chromosomal instability

- Intestinal histology
- Aneuploidy
- RTK amplification
- *TP53* mutations
- HER2, EGFR, MET



EBV

High EBV burden
Extensive DNA hypermethylation

- Amplification of *PD-L1/2*
- *PIK3CA* mutations

GS

Genomically stable

- Diffuse histology, young age
- *CDH1, RHOA* mutations (mobility, adhesion)
- Sensitivity to m-TOR inhibitors in vitro

MSI

Microsatellite unstable

- Older age, High MSI
- Elevated mutation rate
- Hypermethylation (*MLH1*)

The cancer Genome Atlas Research Network, Nature 2014;513:202-9
Lei et al Gastroenterology 2013;145:554-565

Sorting Gastric Cancers

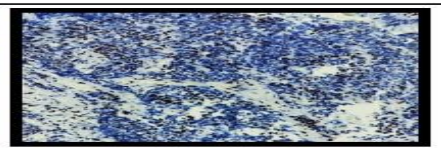
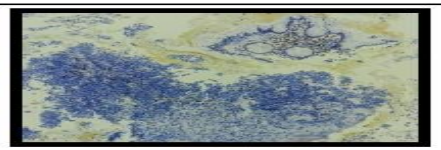
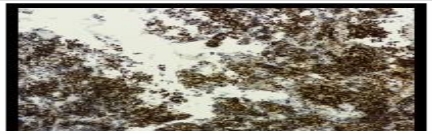
Table 3. TCGA Subtypes

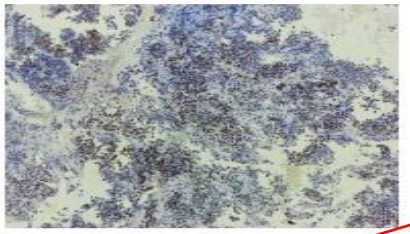
Subtypes	EBV-positive	MSI	GS	CIN
Frequency	8.8%	21.7%	19.7%	49.8%
Demographic	Male patients (81%)	Old age (median 72 years)	Young age (median 59 years)	No special
Histology			Diffuse histology	Intestinal histology
Main location	Fundus or body (62%)			Gastro-esophageal junction/cardia (65%)
Molecular alterations	EBV-CpG island methylator phenotype (CIMP)	Gastric-CIMP	*CDH1*, *RHOA* mutation	*TP53* mutation
	PD-L1/2, *JAK2* overexpression	Hypermutation in *TP53*, *PIK3CA*, *ERBB3*, *ARID1A*	*CLDN18-ARHGAP* fusion	RTK-RAS activation
	Mutation in *PIK3CA*, *ARID1A*, *BCOR*	*MLH1* silencing	Cell adhesion, angiogenesis pathways enriched	Mutations of *SMAD4* and *APC*
	CDKN2A silencing	Mitotic pathways activation	Rare *TP53* mutations	
	Immune cell signaling	Commune changes in the genes of CMHI		
	Rare *TP53* mutations			
Potential targets	PIK3CA, JAK2, PD-L1/PD-L2	PIK3CA, ERBB2/3, EGFR, PD-L1, MLH1 silencing	RHOA, CLDN18	RTKs, EGFR, VEGFA, CCNE1, CCND1, CDK6
Treatment reaction		No response to adjuvant chemotherapy		

Molecular Testing in Gastric Cancer

- Standard
  - HER2 (IHC or FISH, NGS for amplification)
  - MSI (variety of techniques)
  - PD-L1 (IHC, CPS)
  - NTRK (RNA fusion)
- Germline
  - CDH-1 and a long list of others (FAP, Lynch, etc)

Some real life reports (MSI)

Markers	Result	Image
hMSH-6(EP-49)	LOSS OF NUCLEAR EXPRESSION	
hMSH-2(RED2)	LOSS OF NUCLEAR EXPRESSION	
hMLH-1(GM011)	INTACT NUCLEAR EXPRESSION	

Markers	Result	Image
hPMS-2(EP-51)	INTACT NUCLEAR EXPRESSION	

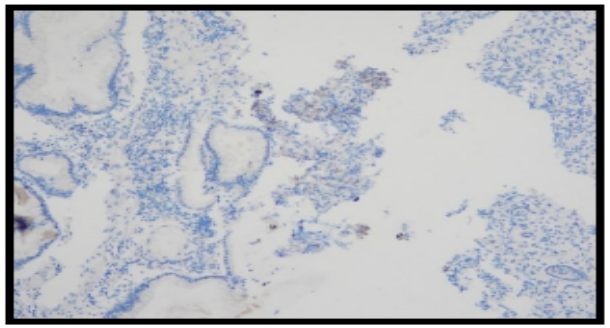
IHC INTERPRETATION AND RESULT

- Loss of nuclear expression of one or more MMR proteins: deficient mismatch repair (high probability of MSI-H)
- Loss of nuclear expression of MSH2 and MSH6: high probability of Lynch syndrome (sequencing and/or large deletion/duplication testing of germline MSH2 may be indicated, and, if negative, sequencing and/or large deletion/duplication testing of germline MSH6 may be indicated).

#There are exceptions to the above IHC interpretation. These results should not be considered in isolation and clinical correlation with genetic counselling is recommended to asses the need for germline testing.

- **(Reference: Colon and Rectum- Biomarkers Colon Biomarkers (v 1.2.0.0 - CAP Protocol).**

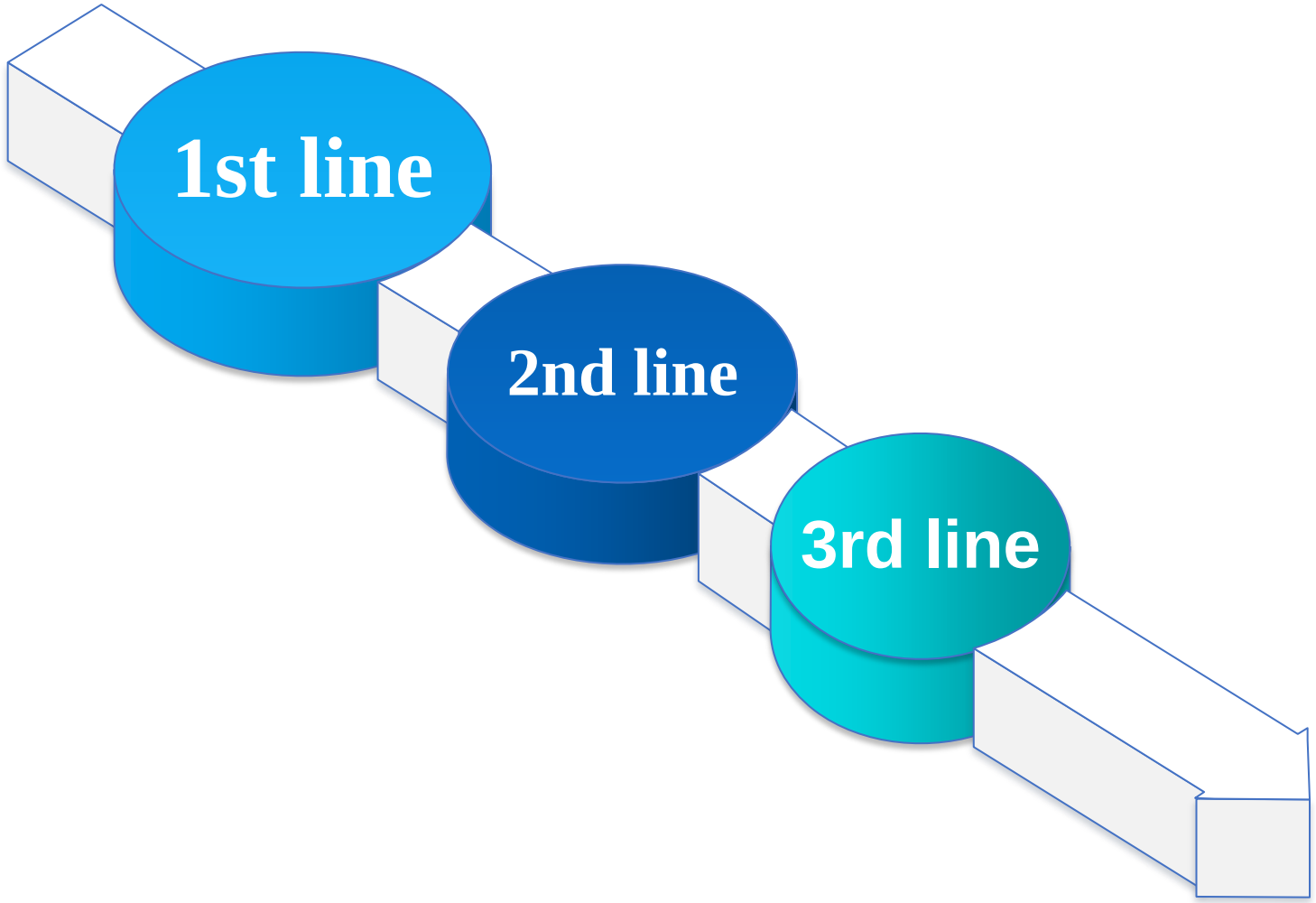
Some real life reports (CPS)

MARKERS (CLONES)	RESULT	IMAGES
PD-L1 (DAKO 22C3 pharmDx)	COMBINED POSITIVE SCORE:03%	

INTERPRETATION

1. Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages*) divided by the total viable tumor cells, multiplied by 100. Although the result of the calculation can exceed 100, the maximum score is defined as CPS 100.
2. Recurrent/ metastatic head and neck squamous cell carcinoma[1]:
   The specimen should be considered to have PD-L1 expression if CPS ≥ 1.
3. Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma[2]:
   The specimen should be considered to have PD-L1 expression if CPS ≥ 1.
4. Cervical cancer[3]:
   The specimen should be considered to have PD-L1 expression if CPS ≥ 1.
5. Urothelial cancer[4]:
   The specimen should be considered to have PD-L1expression if CPS ≥ 10.
6. Esophageal Squamous Cell Carcinoma [5]:
   CPS greater than or equal to 10 PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying esophageal squamous cell cancer patients for treatment with KEYTRUDA® (pembrolizumab).

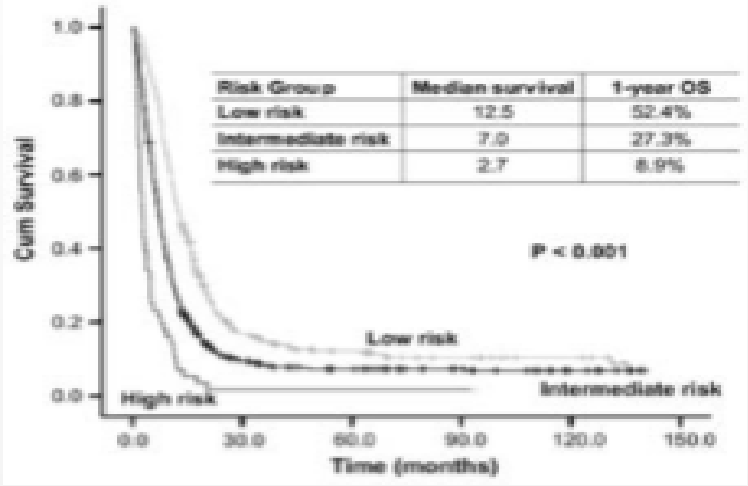
1st line treatment decision is key



Clinical prognostic factors

- **Among 1445 Asian** patients treated with different first-line regimens, the factors associated with worse OS:

✓ ECOG performance status ≥2
✓ bone metastases
✓ no prior gastrectomy
✓ ascites
✓ alkaline phosphatase >85 U/L
✓ albumin <3.6 g/dL

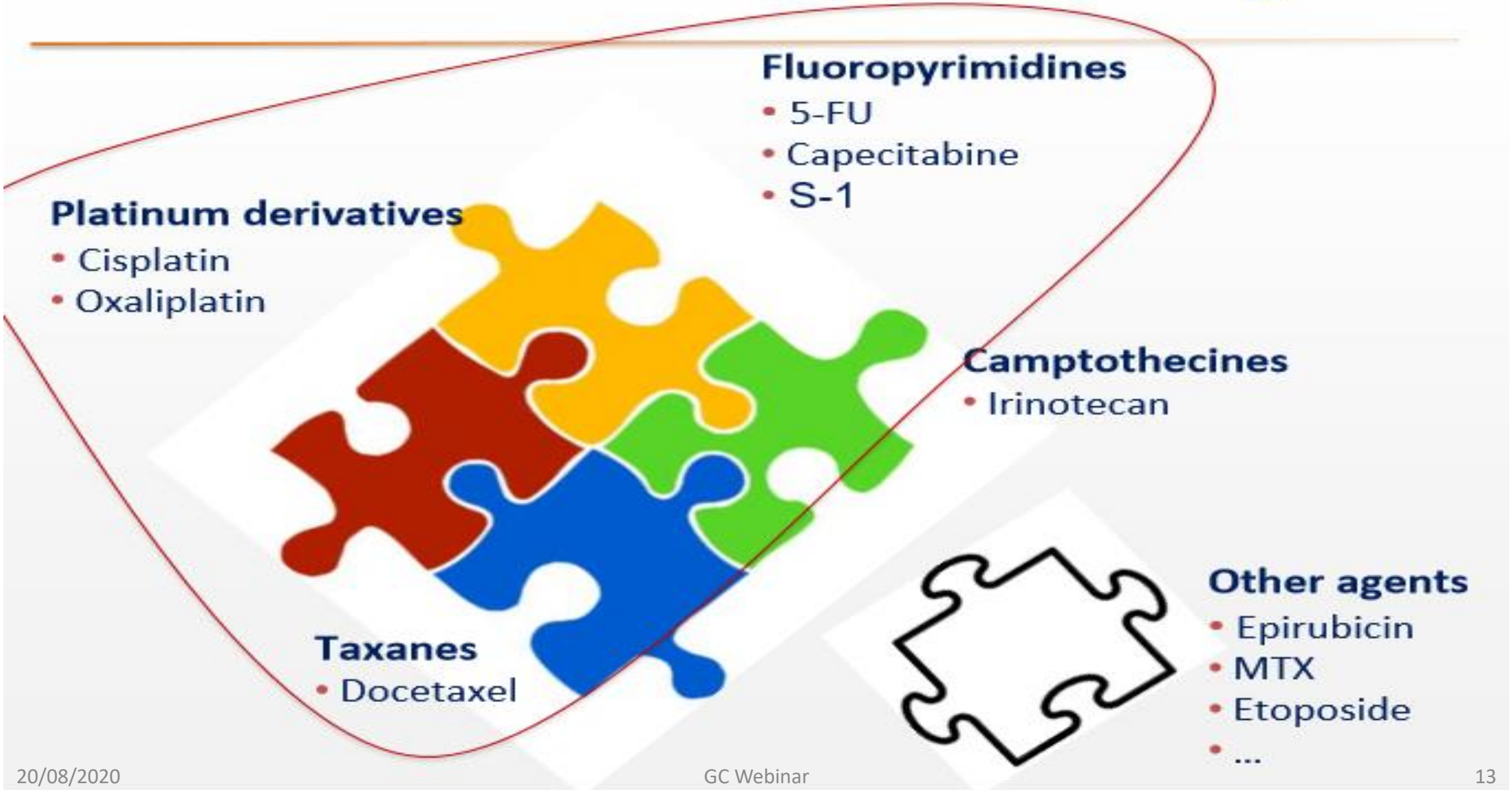


Good risk: 0-1 risk factors
Moderate risk: 2-4 risk factors
Poor risk: 5-6 risk factors

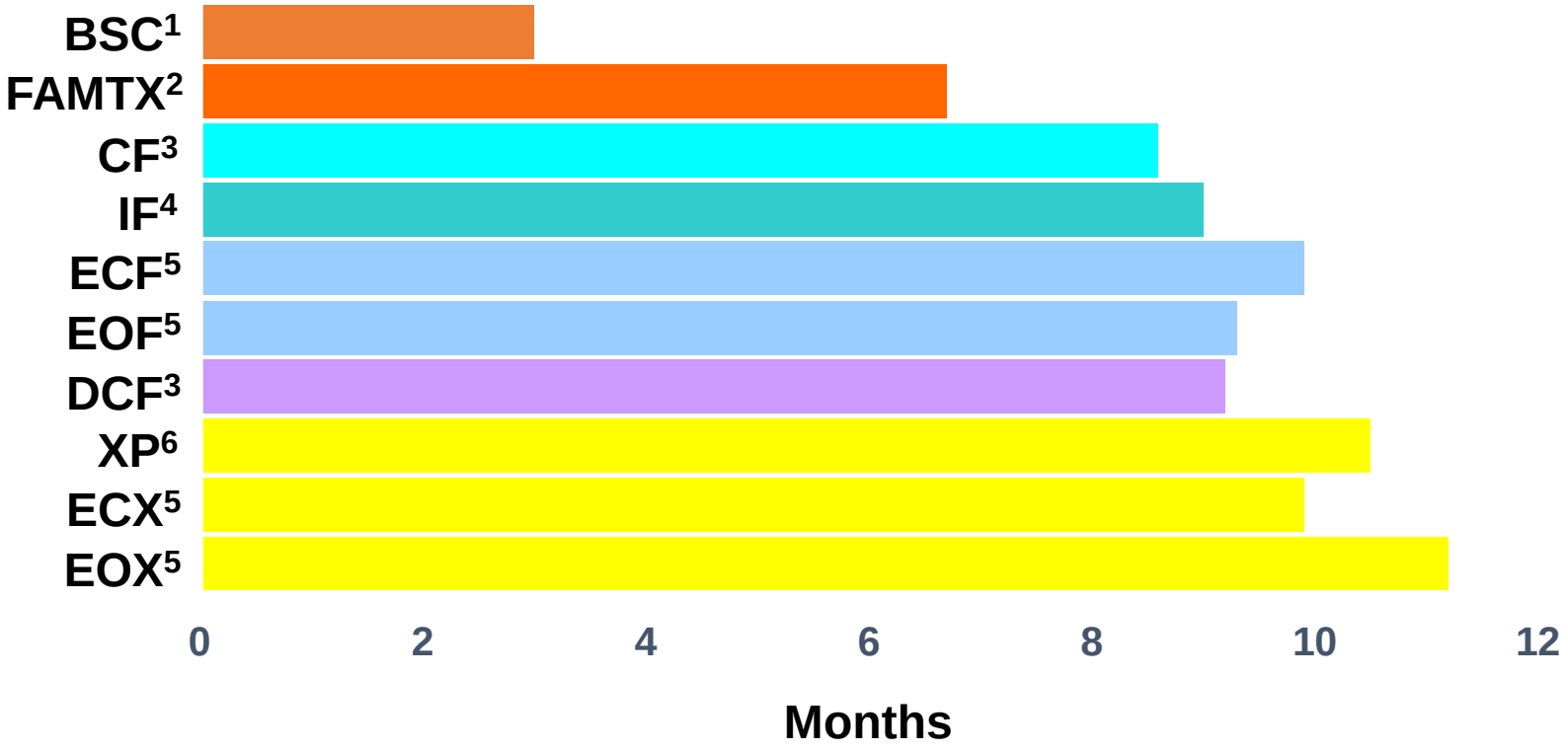
Lee J et al. Ann Oncol 2007

- Advanced Gastric Cancer (First line)
  - HER2 negative

First-line chemotherapy: active agents



Impact on survival of Cytotoxics in advanced Gastric Cancer



❖Cytotoxics: Modest impact: Median survival of doublets/triplets usually <12 mo

1. Murad et al. Cancer 1993; 2. Vanhoefer et al. J Clin Oncol 2000; 3. Van Cutsem et al. J Clin Oncol 2006
4. Dank et al. Ann Oncol 2008; 5. Cunningham et al. N Engl J Med 2008; 6. Kang et al. Ann Oncol 2009

Standard first line treatment of Gastric Cancer

	3-Drug Regimens				2-Drug Regimens			
	EOX/EOF[1]	ECX/ EOX[1]	DCF[2]	ECF[3]	XP[4]	FLO[5]	FOLFIRI[6]	S-1/Cis[7]
N	489	513	221	126	160	112	209	305
ORR, %	44	45	37	45	46	35	39	54
TTP, mo	6.7	6.5	5.6	7.4	5.6	5.8	5.3	6.0
OS, mo	10.4	10.9	9.2	8.9	10.5	10.7	9.5	13.0

1. Cunningham D, et al. N Engl J Med. 2008;358:36-46. 2. Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997. 3. Webb A, et al. J Clin Oncol. 1997;15:261-267
4. Kang YK, et al. Ann Oncol. 2009;20:666-673. 5. Al-Batran SE, et al. J Clin Oncol. 2008;26:1435-1442. 6. Guimbaud R, et al. J Clin Oncol. 2014;32:3520-3526.
7. Koizumi W, et al. Lancet Oncol. 2008;9:215-221.

Standard first line treatment of Gastric Cancer

Are Taxanes needed to achieve
the best results in advanced Gastric Cancer?

Study	n		OS, Months		PFS, Months		ORR	
V325[1]	445	DCF	9.2	HR 1.29 p 0.02	5.5	HR 1.47 p<0.001	37	p 0.01
		CF	8.6		3.7		25	
JCOG1013[2]	741	DCS1	14.2	HR 0.99 p 0.47	7.4	HR 0.99 p 0.92	59	p 0.5
		CS1	15.3		6.5		56	

[1]Van Cutsem E et al. JCO 2006. [2]Yamada Y et al. Lancet Gastroenterol Hepatol 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab[a] should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma
  (See Principles of Pathologic Review and Biomarker Testing [GAST-B])
  - Combination with fluoropyrimidine and platinum (category 1 in combination with cisplatin;[11] category 2A in combination with other platinum agents)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

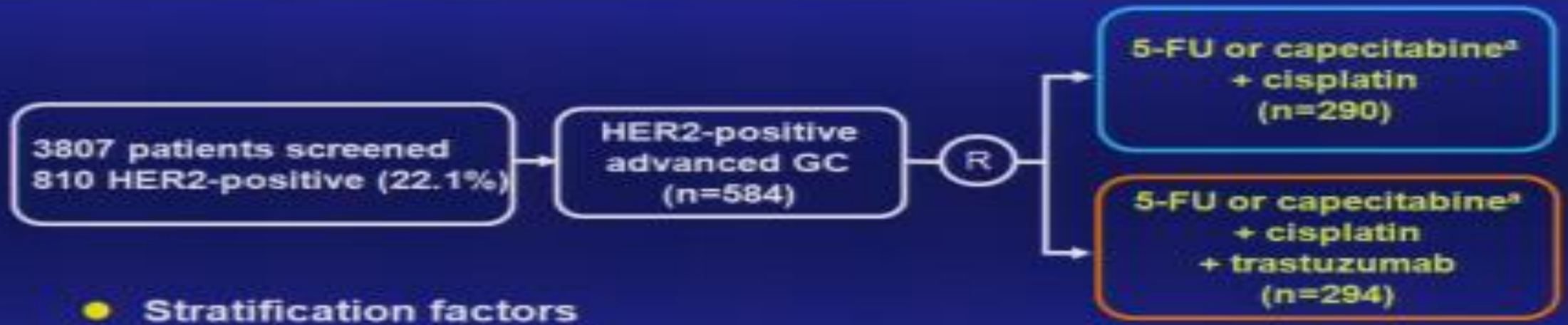
Preferred Regimens
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[12-14]
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and cisplatin[12, 15-17]

Other Recommended Regimens
- Fluorouracil[c,f] and irinotecan[18]
- Paclitaxel with cisplatin or carboplatin[19-21]
- Docetaxel with cisplatin[22,23]
- Fluoropyrimidine[16,24,25] (fluorouracil[c] or capecitabine)
- Docetaxel[26,27]
- Paclitaxel[28,29]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[c,30]
  - Docetaxel, oxaliplatin, and fluorouracil[31]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[32]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]
- ECF modifications (category 2B)[34,35]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

- Advanced Gastric Cancer (First line)
  - HER2 positive

ToGA trial design

Phase III, randomized, open-label, international, multicenter study



- **Stratification factors**
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

Van Cutsem E, et al. ASCO 2009 abstract 4509

ToGA study: trastuzumab global study

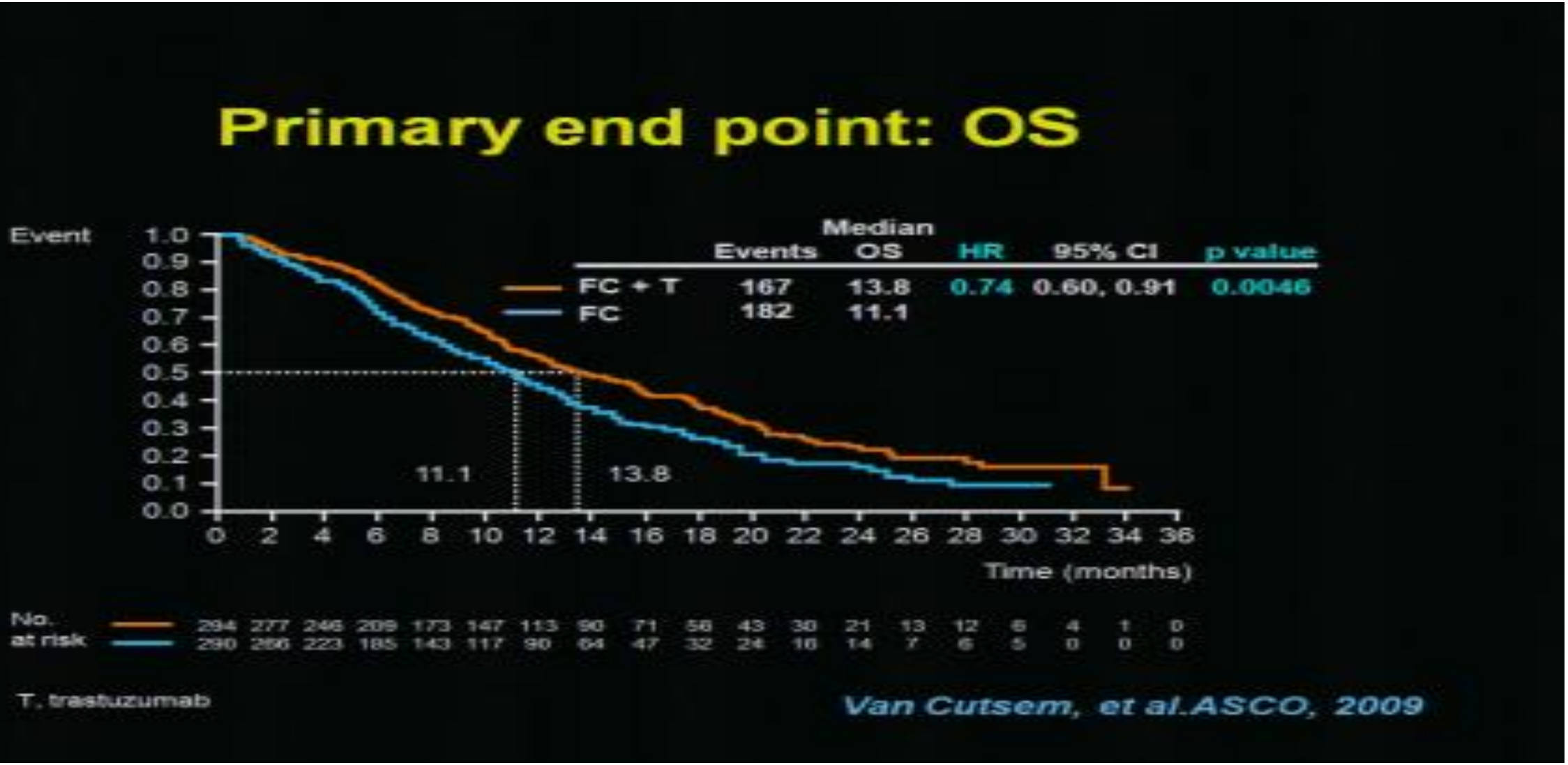
Required sample size = 584

Primary endpoint; Overall survival

Participants; 120 centers / 22 countries

Primary endpoint has met !

Primary end point: OS

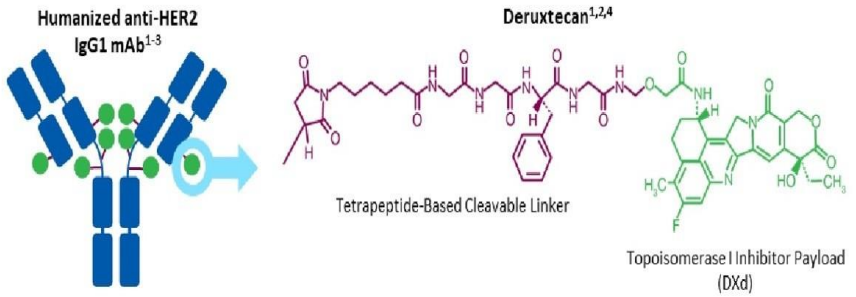


- Advanced Gastric Cancer (Second line)
  - HER2 positive

Trastuzumab deruxtecan (T-DXd)

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

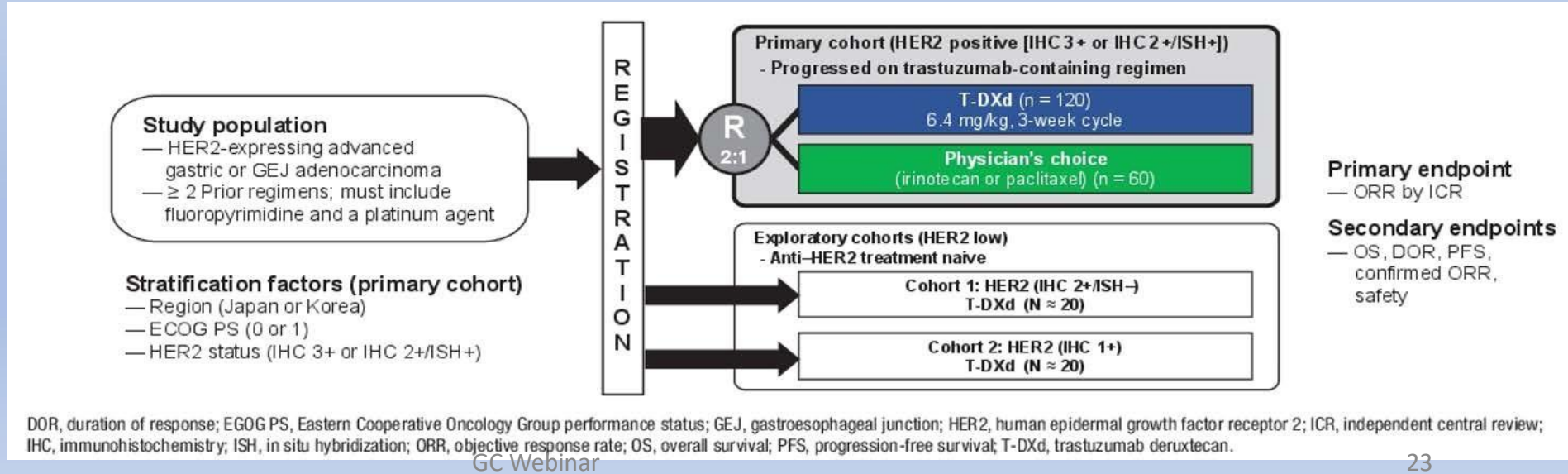


Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

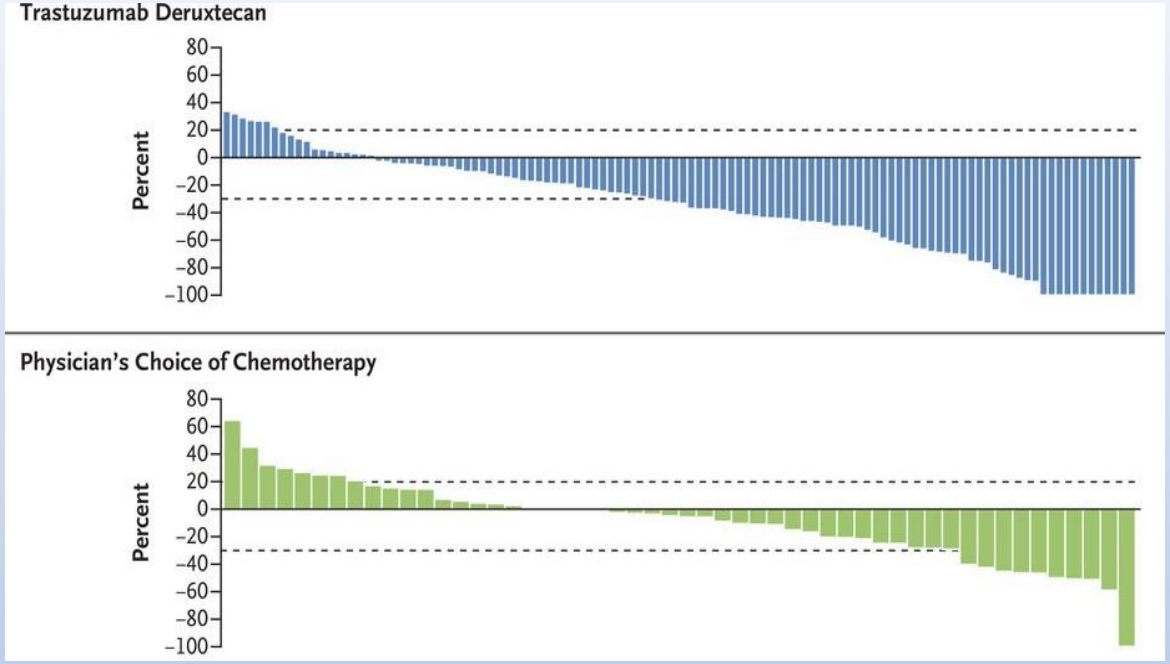


DOR, duration of response; EGOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Shitara K et al, NEJM 2020
382: 2419-2430

Courtesy of Crystal Denlinger, MD, F.A.C.P.

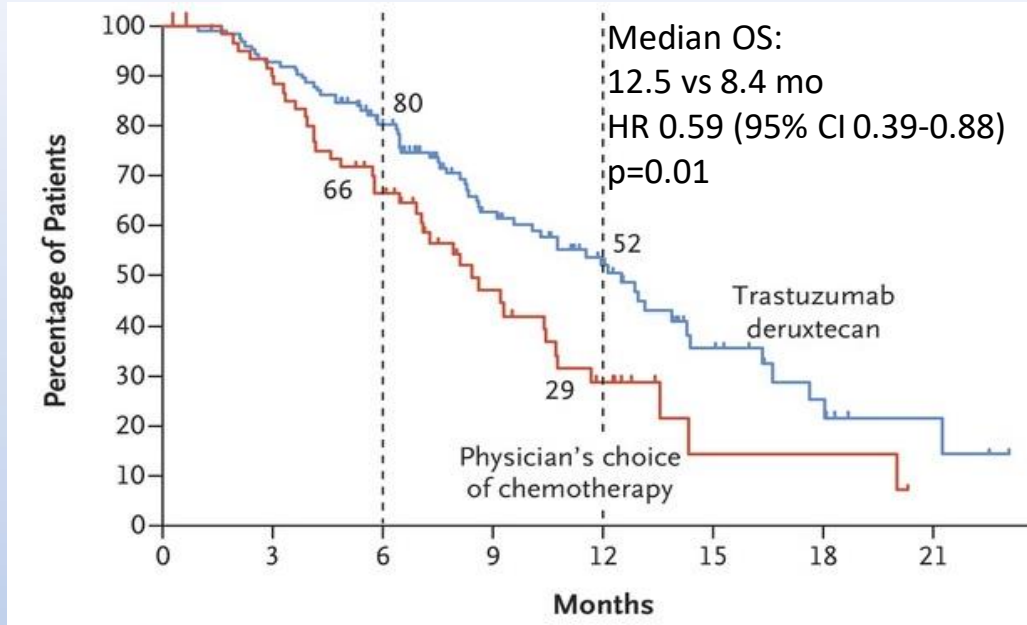
DESTINY-Gastric 01: A Potential Option for Refractory GEC?

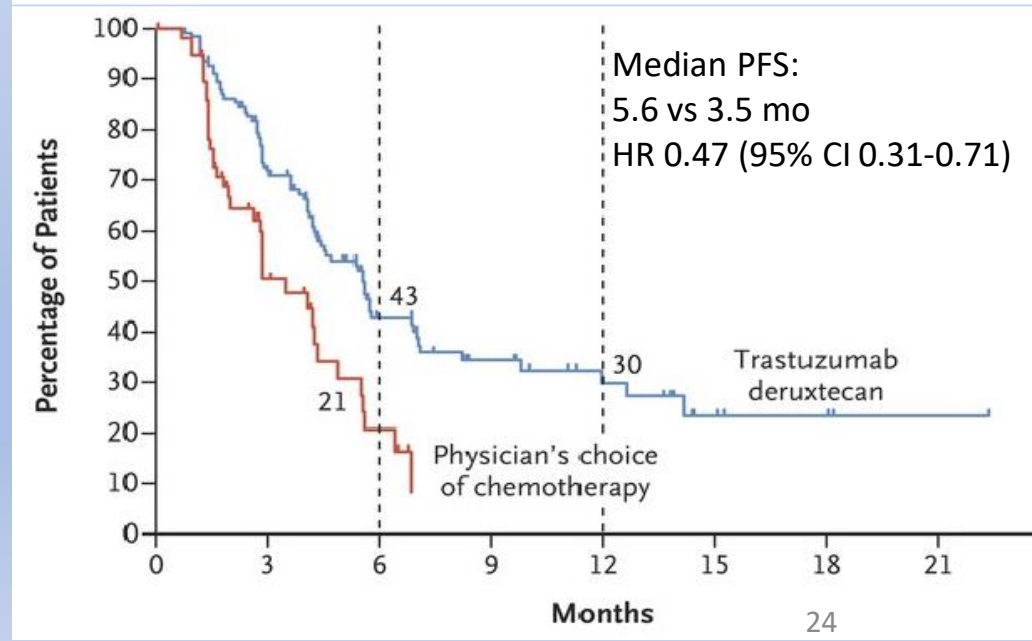


	T-DXd (n=119)	PC (n=56)
ORR	**51.3%**	**14.3%**
Confirmed ORR	**42.9%**	**12.5%**
CR	8.4%	0%
PR	34.5%	12.5%
SD	42.9%	50.0%

Disease control:

- T-DXd: 86% with median 11.3 mo
- PC: 62% with median 3.9 mo





Shitara et al, *NEJM* (2020), Slide courtesy of Yelena Jangigian

Courtesy of Crystal Denlinger, MD, F.A.C.P.

- Advanced Gastric Cancer (Second line)
  - Pre Ramucirumab
  - Post Ramucirumab

Standard Second Line Treatment Before Ramucirumab Trials

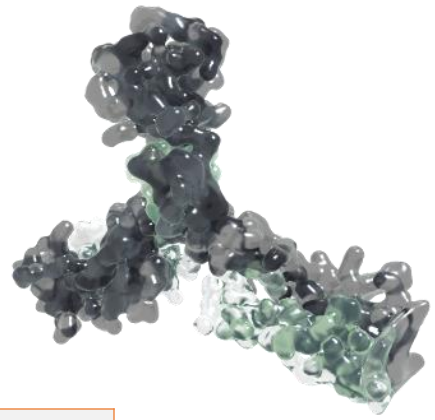
	n	medOS (months)	HR vs BSC (95%CI)	medPFS (Months)	ORR (%)	DC (%)
Docetaxel 75[1]	84	5.2	0.67 (0.49-0.92)	3.0	7	53
CPT-11[2]	21	4.0	0.48 (0.25-0.92)	2.5	0	53
CPT11/ Docetaxel[3]	133	5.2 /6.5	0.66 (0.48-0.89)	NR	8/11	43/38
Paclitaxel / CPT11[4]	219	9.5/8.4	NA	3.6/2.3	20.9/13.6	NR

[1]Ford The Lancet 2014.. [2]Thuss-Patience EJC 2011.. [3]Kang JCO 2012. [4]Hironaka JCO 2013


www.maadurgawallpaper.com

Ramucirumab offers two regimen choices for 2nd-line treatment of GC and GEJ

- Both phase III trials showed statistically significant improvements in survival and progression-free survival with ramucirumab[1,2]
  - For eligible patients, ramucirumab extends survival when combined with paclitaxel[2]
  - For patients who have progressed on first-line chemotherapy, ramucirumab extends survival vs best supportive care[1]



	Overall survival benefit	Progression-free survival benefit	Indication
REGARD[1]	✓	✓	Monotherapy
RAINBOW[2]	✓	✓	Combination therapy

1. Fuchs CS et al. *Lancet* 2014;383:31–39
2. Wilke H et al. *Lancet Oncol* 2014;15:1224–1235

RAM+PACLI vs PACLI: RAINBOW study

Generally Well Tolerated

RR 28% vs 16%
DCR 80% vs 63%

PS 0/1 to PS 2
10 mos vs 8.6 mos

Toxicity → RR/DCR → PS Deterioration

Adverse reactions occurring at incidence rate ε 5% and a ε 2% difference between arms in patients receiving CYRAMZA in combination with paclitaxel (RAINBOW).

Lancet Onco 2014 Oct;15(11):1224-35; Ann Oncol. 2016 Apr;27(4):673-9

Summary of efficacy of the RAINBOW and REGARD trials

	RAINBOW[1] Ramucirumab + paclitaxel (vs placebo + paclitaxel)	REGARD[2] Ramucirumab (vs placebo)
Number of patients	665	355
Overall survival (months)	9.6 (vs 7.4) (p=0.017)	5.2 (vs 3.8) (p=0.047)
Progression-free survival (months)	4.4 (vs 2.9) (p<0.0001)	2.1 (vs 1.3) (p<0.0001)

1 yr Survival in RAINBOW Ram+Pacli arm 40% vs Pacli 30%

1. Wilke H et al. *Lancet Oncol* 2014;15:1224–1235
2. Fuchs CS et al. *Lancet* 2014;383:31–39

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[36]
- Docetaxel (category 1)[26,27]
- Paclitaxel (category 1)[28,29,37]
- Irinotecan (category 1)[37-40]
- Trifluridine and tipiracil (category 1)[41]
  - For third-line or subsequent therapy
- Fluorouracil[c,f] and irinotecan[38,42,43]
- Pembrolizumab[g]
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[44,45]
  - For third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1[h,46]

Other Recommended Regimens
- Ramucirumab (category 1)[47]
- Irinotecan and cisplatin[13,48]
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Docetaxel and irinotecan (category 2B)[51]

Useful in Certain Circumstances
- Fluorouracil and irinotecan + ramucirumab (category 2B)[c,f,52]

- Advanced Gastric Cancer (Third line & beyond…)

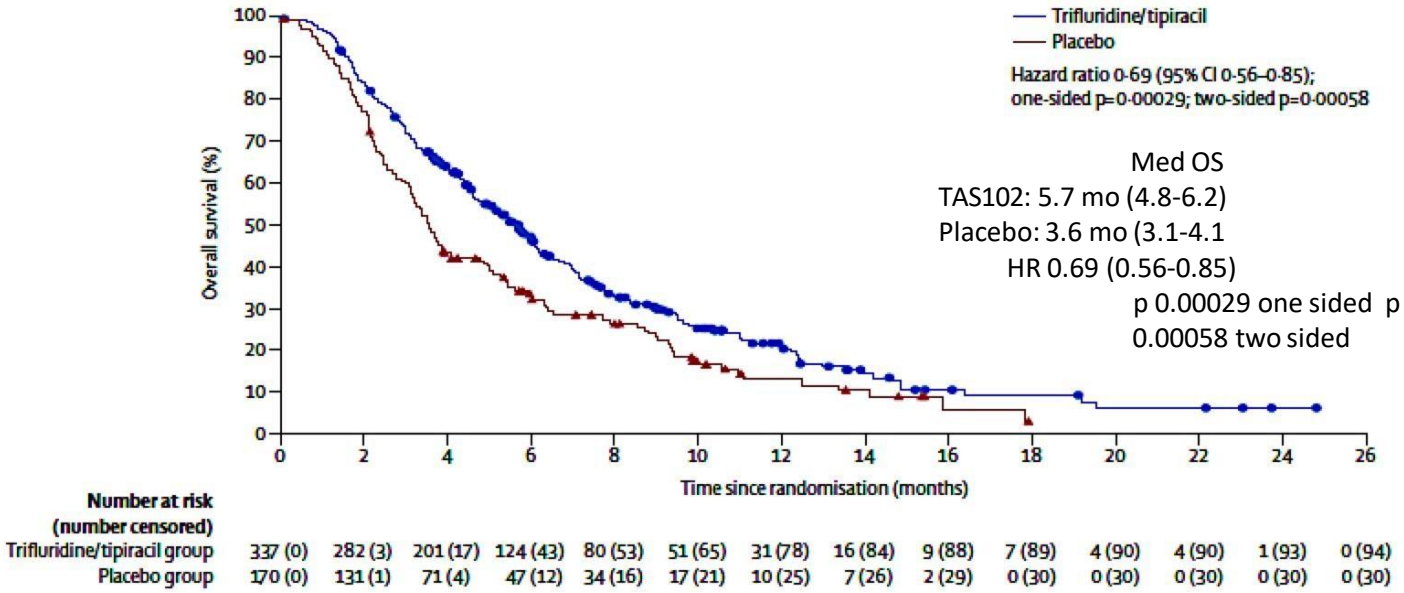
Third Line Treatment and Beyond….

- TAS 102 (Trifluridine/Tipiracil)
- Pembrolizumab (anti PD-1)
- Nivolumab (anti PD-1)
- Apatinib (Anti-VEGFR2) (* China)
- Dealer’s Choice

Third line treatment and beyond…TAS-102

Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial

Kohei Shitara, Toshihiko Doi, Mikhail Dvorkin, Wasat Mansoor, Hendrik-Tobias Arkenau, Aliaksandr Prokharau, Maria Alsina, Michele Ghidini, Catia Faustino, Vera Gorbunova, Edvard Zhavrid, Kazuhiro Nishikawa, Ayumu Hosokawa, Şuayib Yalçın, Kazumasa Fujitani, Giordano D Beretta, Eric Van Cutsem, Robert E Winkler, Lukas Makris, David H Ilson, Josep Tabernero



Med OS
TAS102: 5.7 mo (4.8-6.2)
Placebo: 3.6 mo (3.1-4.1
HR 0.69 (0.56-0.85)
p 0.00029 one sided p 0.00058 two sided

	Trifluridine/tipiracil group (n=337)	Placebo group (n=170)
(Continued from previous column)		
HER2 status		
Positive	67 (20%)	27 (16%)
Negative	207 (61%)	106 (62%)
Not assessed or unknown	63 (19%)	37 (22%)
Number of metastatic sites		
1–2	155 (46%)	72 (42%)
≥3	182 (54%)	98 (58%)
Peritoneal metastases	87 (26%)	53 (31%)
Previous gastrectomy	147 (44%)	74 (44%)
Number of previous chemotherapy regimens		
2	126 (37%)	64 (38%)
3	134 (40%)	60 (35%)
≥4	77 (23%)	46 (27%)
Previous systemic anticancer agents		
Platinum	337 (100%)	170 (100%)
Fluoropyrimidine	336 (>99%*)	170 (100%)
Taxane†	311 (92%)	148 (87%)
Irinotecan†	183 (54%)	98 (58%)
Ramucirumab	114 (34%)	55 (32%)
Anti-HER2 therapy	60 (18%)	24 (14%)
Immunotherapy (anti-PD-1 or anti-PD-L1)	25 (7%)	7 (4%)
Other	77 (23%)	41 (24%)

Shitara K et al Lancet Oncol 2018

Third line treatment and Beyond…Pembrolizumab

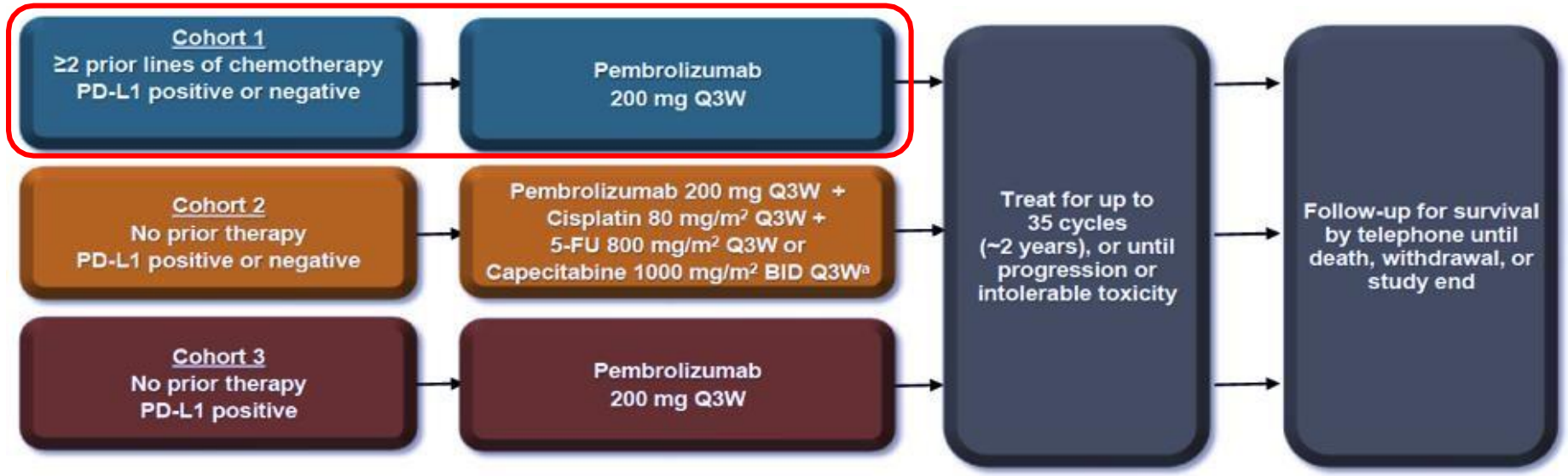
MADRID 2017 ESMO congress

KEYNOTE-059: Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Patients With Advanced Gastric or Gastroesophageal Cancer

JAMA Oncology | Original Investigation

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer

Phase 2 Clinical KEYNOTE-059 Trial



PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = the number of PD-L1–positive cells[b] (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100

Fuchs CS, et al. ASCO 2017. Abstract 4003.

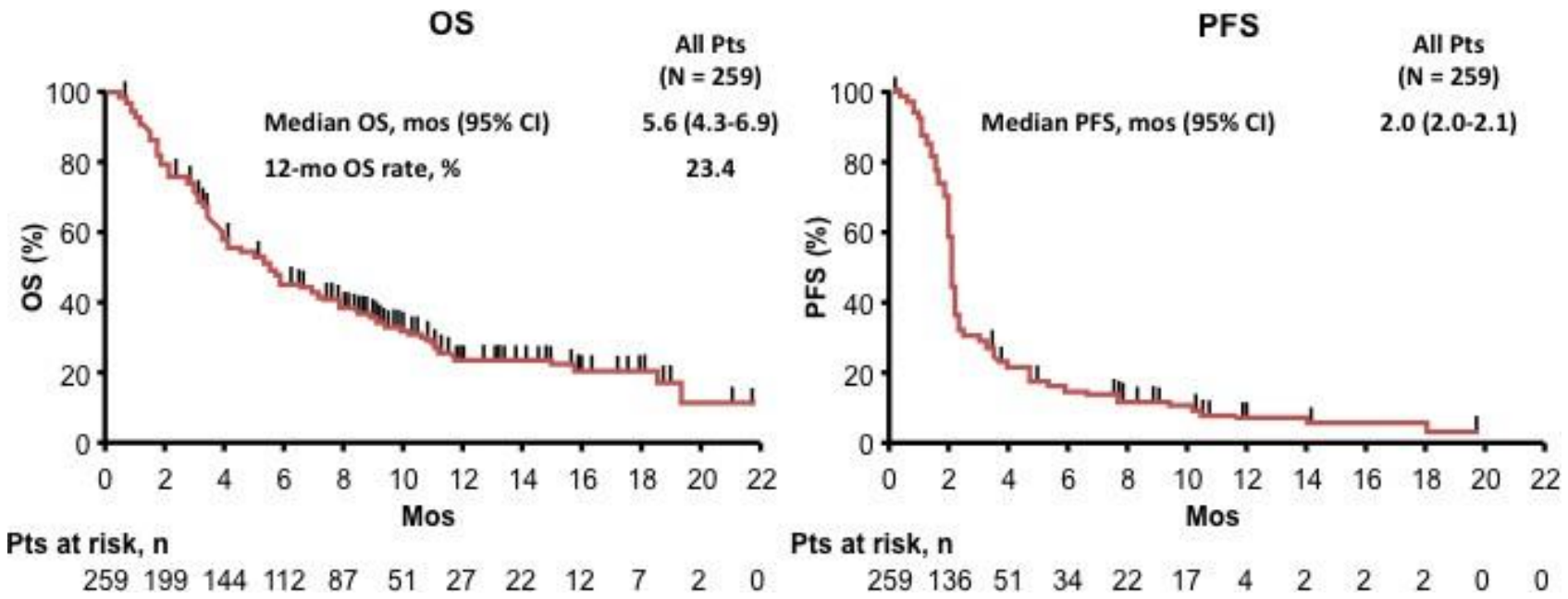
Fuchs CS, et al. JAMA Oncology 2018.

Third line treatment and beyond… Pembrolizumab

JAMA Oncology | Original Investigation

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer

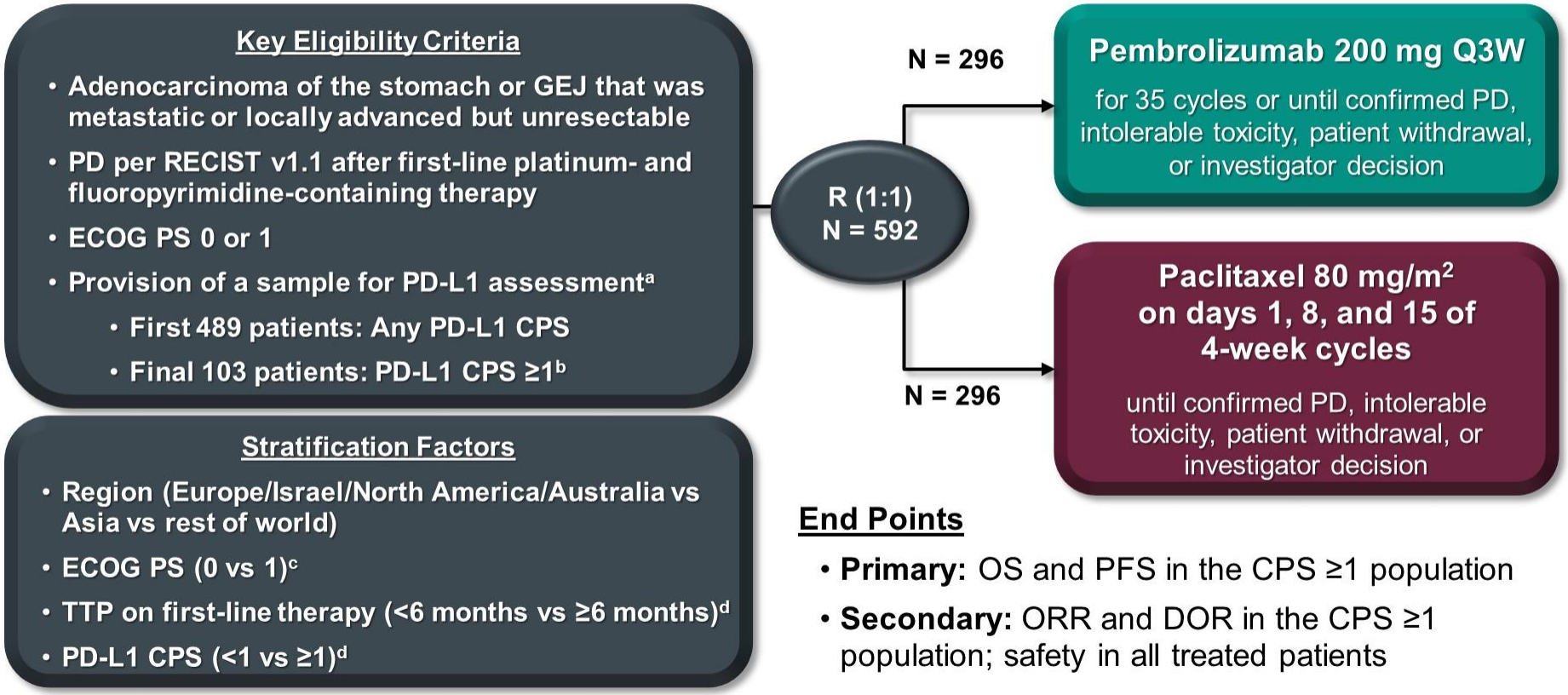
Phase 2 Clinical KEYNOTE-059 Trial



Objective Responses % (95% CI)	% (N = 259)
ORR	11.6 (8.0-16.1)
CR	2.3 (0.9-5.0)
PR	9.3 (6.0-13.5)
ED/NC	16.2 (11.9-21.3)
PD	56.0 (49.7-62.1)

Fuchs CS, et al. JAMA Oncology 2018.

KEYNOTE-061 Study Design (NCT02370498)



End Points

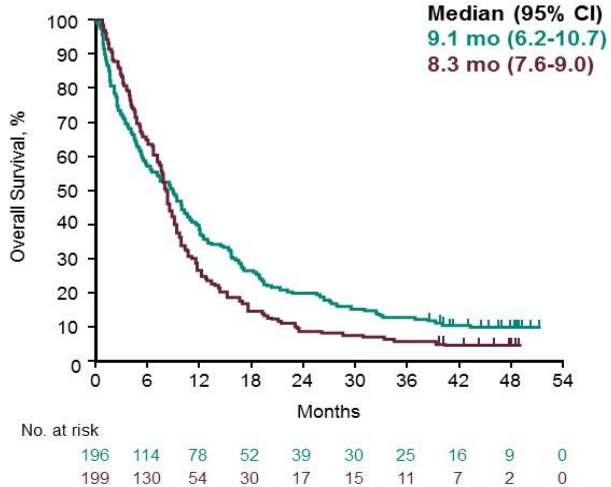
- **Primary:** OS and PFS in the CPS ≥1 population
- **Secondary:** ORR and DOR in the CPS ≥1 population; safety in all treated patients

[a]PD-L1 was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). Measured as CPS, defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100. [b]At the recommendation of the independent external monitoring committee. [c]First 125 patients only. [d]Final 467 patients only.

Overall Survival by CPS

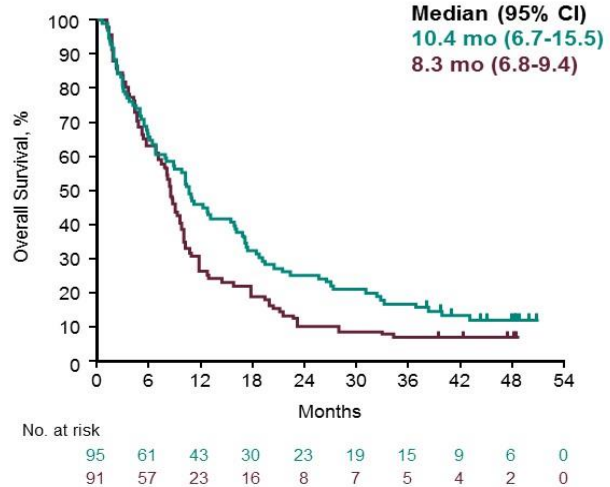
CPS ≥1

	Events/ Pts	HR (95% CI)
Pembrolizumab	176/196	0.81 (0.66-1.00)
Paclitaxel	190/199	



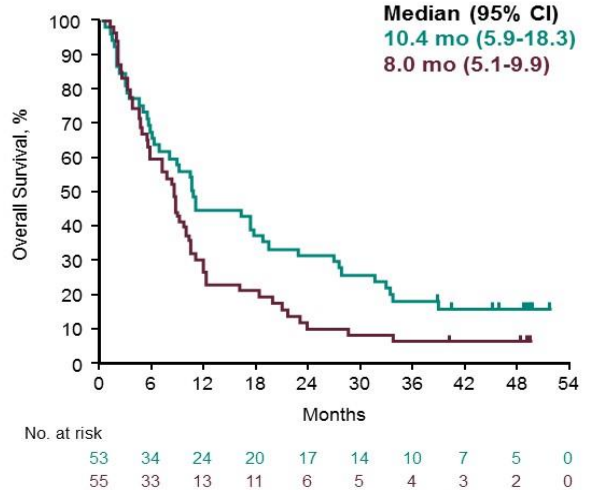
CPS ≥5

	Events/ Pts	HR (95% CI)
Pembrolizumab	84/95	0.72 (0.53-0.99)
Paclitaxel	86/91	



CPS ≥10

	Events/ Pts	HR (95% CI)
Pembrolizumab	44/53	0.69 (0.46-1.05)
Paclitaxel	51/55	

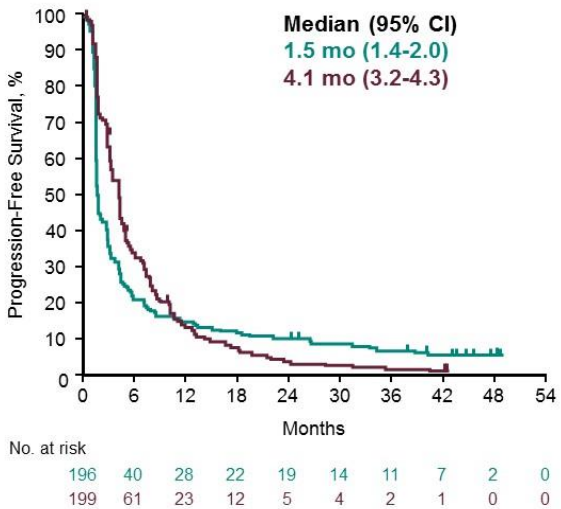


Data cutoff date: Oct 7, 2019.

Progression-Free Survival by CPS

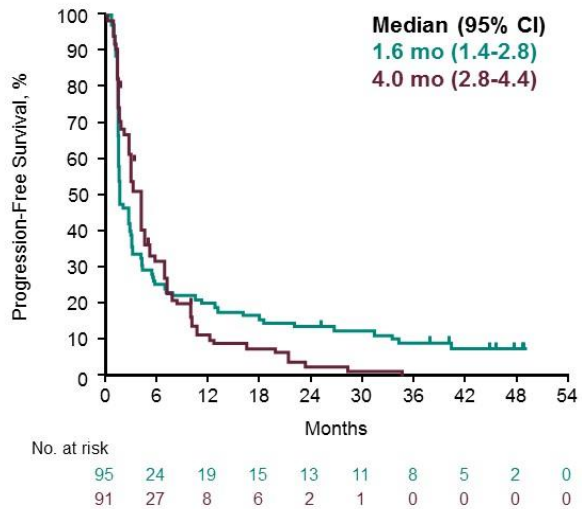
CPS ≥1

	Events/ Pts	HR (95% CI)
Pembrolizumab	185/196	1.25 (1.02-1.54)
Paclitaxel	192/199	



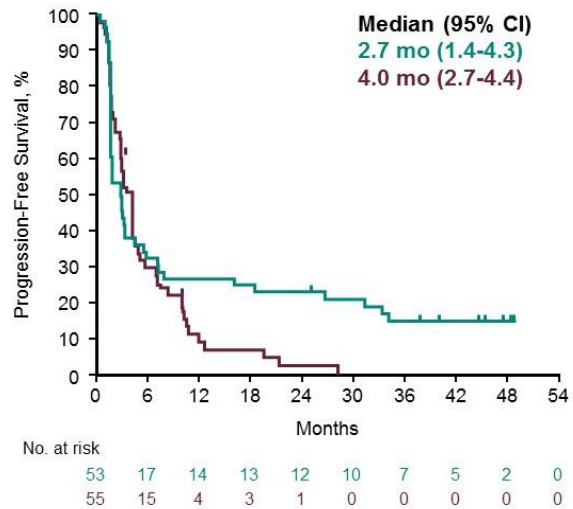
CPS ≥5

	Events/ Pts	HR (95% CI)
Pembrolizumab	87/95	0.98 (0.71-1.34)
Paclitaxel	87/91	



CPS ≥10

	Events/ Pts	HR (95% CI)
Pembrolizumab	45/53	0.79 (0.51-1.21)
Paclitaxel	52/55	



Data cutoff date: Oct 7, 2019.

Pembrolizumab in Advanced Gastric or Gastro-esophageal Cancer

- Accelerated approval of pembrolizumab monotherapy as third- or later- line therapy was based on the Phase II KEYNOTE-059 study
  - ORR: 11.6% (all patients); 15.5% (PD-L1-positive); 57% (MSI-high)

- Phase III KEYNOTE-061 trial of pembrolizumab versus paclitaxel as second-line therapy did not meet its primary endpoint of OS in patients with CPS ≥1
  - Median OS: Pembrolizumab 9.1 mo, paclitaxel 8.3 mo (HR 0.82; $p = 0.042$)

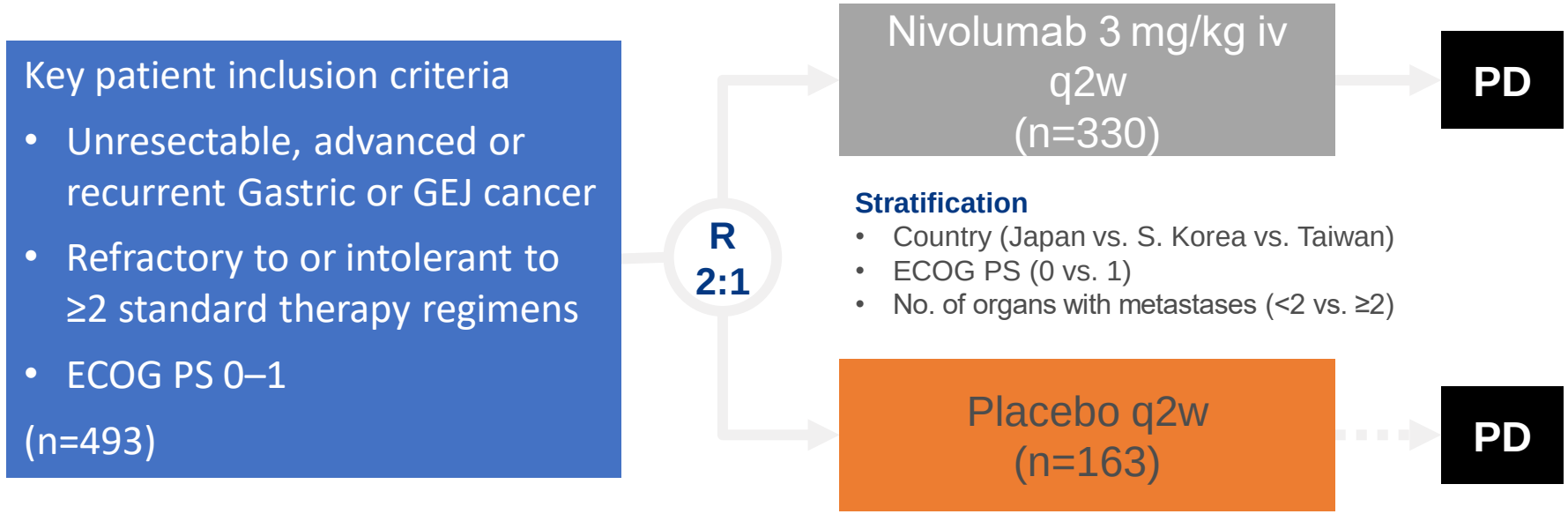
Fuchs C et al. *JAMA Oncol* 2018;4(5):e180013; Shitara K et al. *Lancet* 2018;392(10142):123-33; Tabernero J et al. *Proc ASCO* 2019;Abstract LBA4007. Shitara K et al. *Proc ESMO* 2019;Abstract LBA44.

Third line treatment and beyond… Nivolumab

A phase III study (ATTRACTION-2)

Study objective

- To evaluate the long-term efficacy and safety of nivolumab in patients with previously treated advanced Gastric or GEJ cancer



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

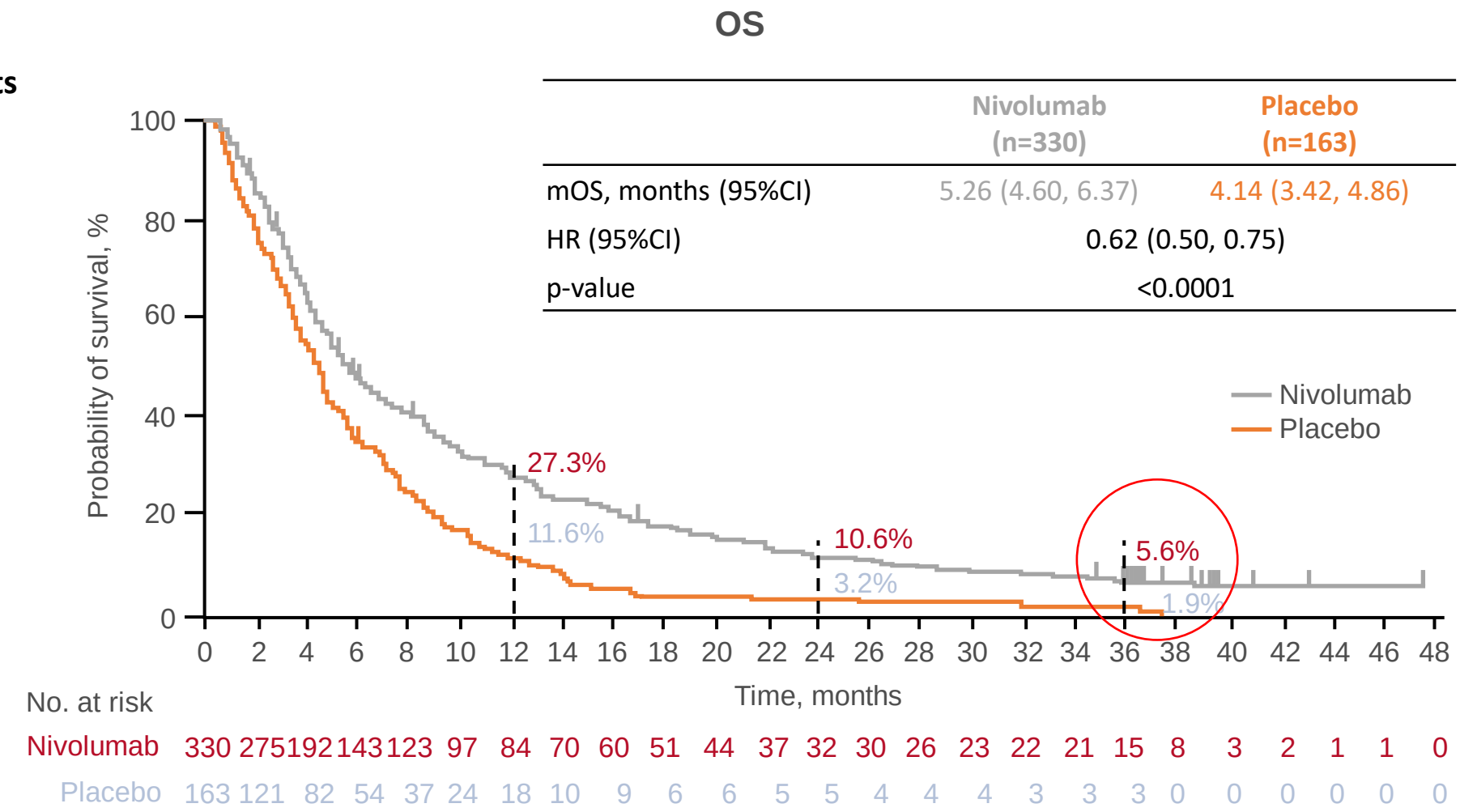
- PFS, BOR, ORR, TTR, DoR, DCR, safety

Chen L-T, et al. J Clin Oncol 2020;38(suppl):abstr 383

Third line treatment and beyond… Nivolumab

A phase III study (ATTRACTION-2)

Key results



Chen L-T, et al. J Clin Oncol 2020;38(suppl):abstr 383

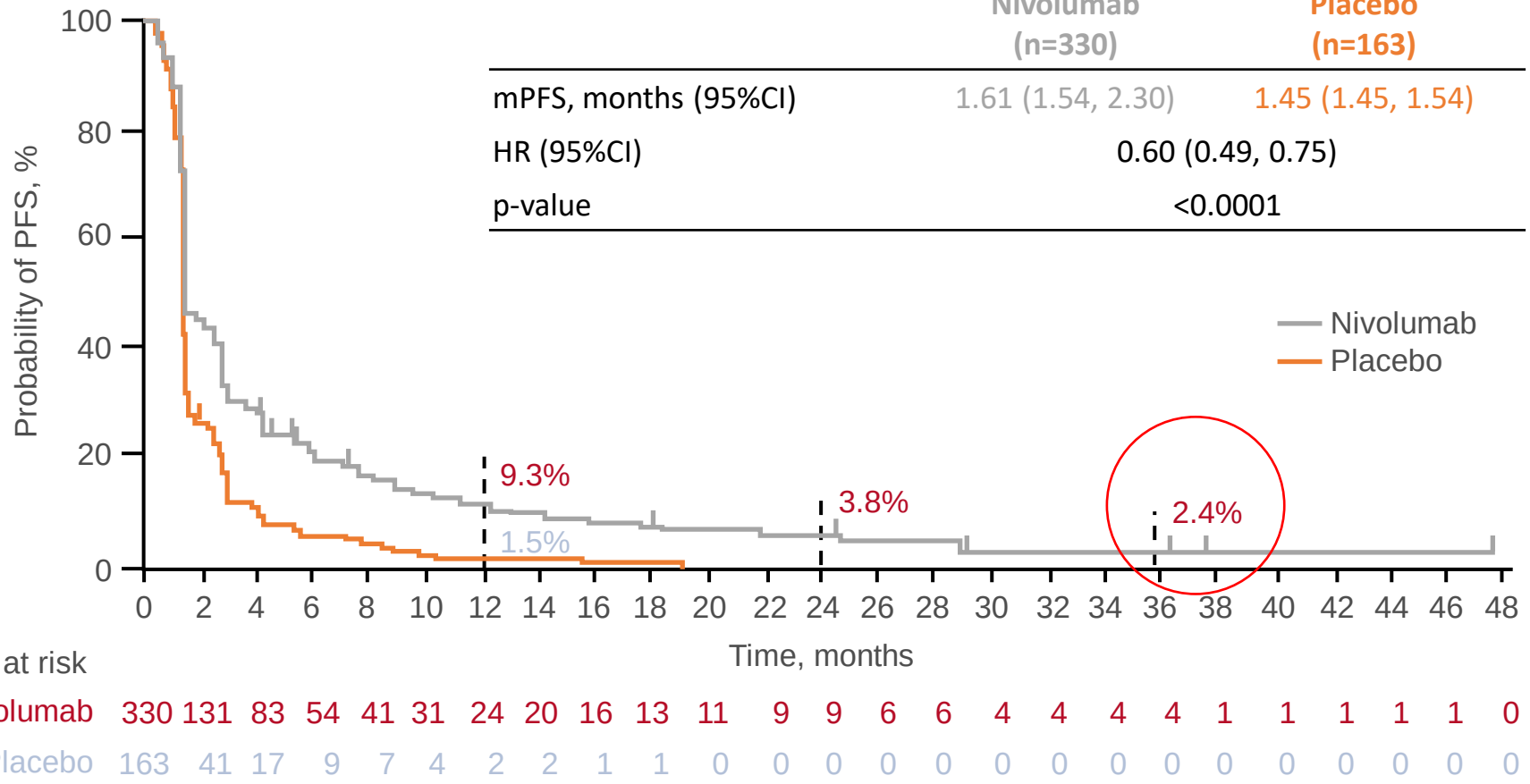
Third line treatment and beyond… Nivolumab

A phase III study (ATTRACTION-2)

Key results (cont.)

PFS

	Nivolumab (n=330)	Placebo (n=163)
mPFS, months (95%CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)
HR (95%CI)	0.60 (0.49, 0.75)	
p-value	<0.0001	

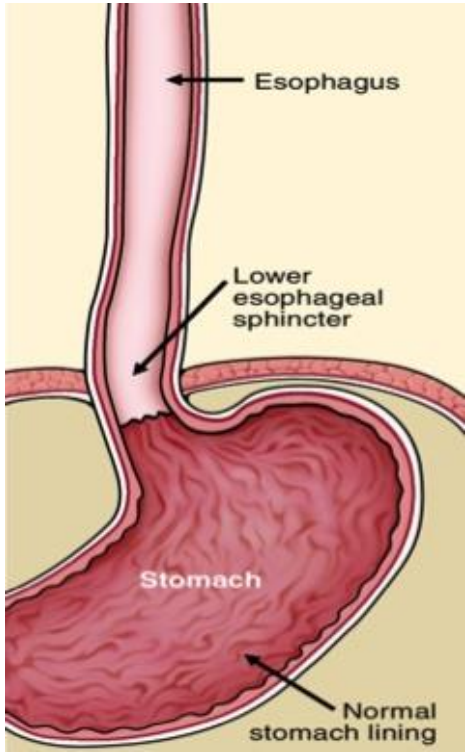


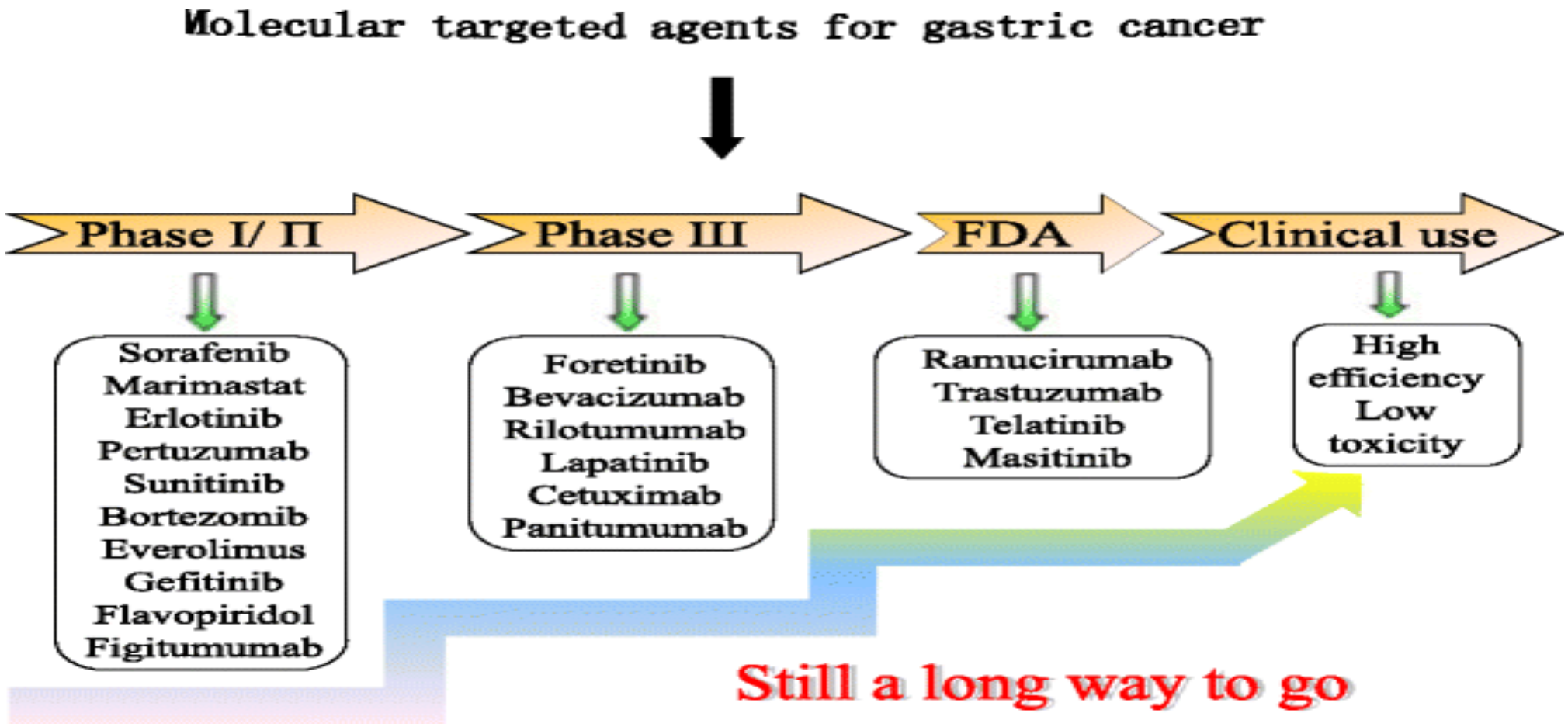
Chen L-T, et al. J Clin Oncol 2020;38(suppl):abstr 383

Other targets in Gastric Cancer

❖ Other targets

- EGFR
- mTOR
- cMET
- FGFR
- Claudine
- Stemcell: STAT3
- MMP9
- PARP
- …..




Molecular targeted agents for gastric cancer
Phase I/ Π
Phase III
FDA
Clinical use
Sorafenib
Marimastat
Erlotinib
Pertuzumab
Sunitinib
Bortezomib
Everolimus
Gefitinib
Flavopiridol
Figitumumab
Foretinib
Bevacizumab
Rilotumumab
Lapatinib
Cetuximab
Panitumumab
Ramucirumab
Trastuzumab
Telatinib
Masitinib
High efficiency
Low toxicity
Still a long way to go

Select Ongoing Biomarker-Based Trials in Gastric, GEJ, and Esophageal Cancers

Biomarker	Phase (NCT)	Population	Planned N	Agents and Comparisons
PD-L1/PD-1	III (NCT02494583)	Gastric/GEJ cancer (first line)	763	Pembrolizumab vs pembrolizumab + SoC chemo vs placebo + SoC chemo
	III (NCT04342910)	Gastric/GEJ cancer (second line)	550	Camrelizumab + afatinib vs paclitaxel or irinotecan
HER2 overexpression and HER2/neu (ERBB2) amplification	Phase III (NCT03615326)	Gastric/GEJ cancer (first line)	732	Trastuzumab + chemo + pembrolizumab vs trastuzumab+ chemo + placebo
	Phase II/III (NCT04082364)	Gastric/GEJ cancer (first line)	850	Cohort A: Margetuximab + MGA012; Cohort B: Margetuximab + MGA012 + chemo vs margetuzimab + MGD013 + chemo vs margetuzimab + chemo vs trastuzumab + chemo
EGFR overexpression	II (NCT03400592)	Gastric cancer (second line)	55	Nimotuzumab + irinotecan
Claudin 18.2	III (NCT03504397)	Gastric/GEJ cancer (first line)	550	Zolbetuzimab + mFOLFOX6 vs placebo + mFOLFOX6
FGFR2	III (NCT03694522)	Gastric cancer (first line)	548	Bemarituzumab + mFOLFOX6 vs placebo + mFOLFOX6
FGFR	II (NCT01719549)	Gastric cancer (second or third line)	19	Dovitinib

Lenvatinib plus pembrolizumab in patients with advanced gastric cancer in the first-line or second-line setting (EPOC1706): an open-label, single-arm, phase 2 trial

Akihito Kawazoe, Shota Fukuoka*, Yoshiaki Nakamura, Yasutoshi Kuboki, Masashi Wakabayashi, Shogo Nomura, Yuichi Mikamoto, Hikari Shima, Noriko Fujishiro, Tsukiko Higuchi, Akihiro Sato, Takeshi Kuwata, Kohei Shitara*

Summary

Background Pembrolizumab, an anti-PD-1 antibody, results in tumour response in around 15% of patients with advanced gastric cancer who have a PD-L1 combined positive score of at least 1. Lenvatinib, a multikinase inhibitor of VEGF receptors and other receptor tyrosine kinases, substantially decreased tumour-associated macrophages and increased infiltration of CD8 T cells, resulting in enhanced anti-tumour activity of PD-1 inhibitors in an in-vivo model. We aimed to assess the combination of lenvatinib plus pembrolizumab in patients with advanced gastric cancer in a phase 2 study.

Methods This study was an open-label, single-arm, phase 2 trial undertaken at the National Cancer Center Hospital East (Chiba, Japan). Eligible patients were aged 20 years or older and had metastatic or recurrent adenocarcinoma of the stomach or gastro-oesophageal junction, an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), irrespective of the number of previous lines of treatment. Patients received 20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks until disease progression, development of intolerable toxicity, or withdrawal of consent. The primary endpoint was objective response rate according to RECIST, analysed in all patients who were eligible and received protocol treatment at least once. The safety analysis included all those who received protocol treatment at least once, regardless of eligibility. This study is registered at ClinicalTrials.gov, NCT03609359, and enrolment is complete.

Findings Between Oct 15, 2018, and March 25, 2019, 29 patients were enrolled in the first-line or second-line settings. At data cutoff (March 20, 2020), the median follow-up was 12·6 months (IQR 10·5–14·3). 20 (69%, 95% CI 49–85) of 29 patients had an objective response. The most common grade 3 treatment-related adverse events were hypertension (in 11 [38%] patients), proteinuria (five [17%]), and platelet count decrease (two [7%]). No grade 4 treatment-related adverse events, serious treatment-related adverse events, or treatment-related deaths occurred.

Interpretation Lenvatinib plus pembrolizumab showed promising anti-tumour activity with an acceptable safety profile in patients with advanced gastric cancer. On the basis of these results, a confirmatory trial will be planned in the future.

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- To Conclude…

Validated Targets in GC

- HER2 (ToGA trial of Trastuzumab + Chemotherapy)
- VEGF (REGARD, RAINBOW trials with Ramucirumab)
- Checkpoint inhibitors (KEYNOTE -059 & ATTRACTION-2)

GC: Markers Negative

- 1st Line: Doublet chemo preferably (5FU or Cape/Platinum)
- 2nd Line: Ramucirumab + Paclitaxel/ Ramucirumab
- 3rd Line: Dealer's choice - TAS-102, Irinotecan , Apatinib, IO…

GC: HER2+

- 1st Line: Doublet chemo (5FU OR Cape/Platinum) + **Trastuzumab**
- 2nd Line: Ramucirumab + Paclitaxel/ Ramucirumab/New drug
- 3rd Line: Dealer's choice

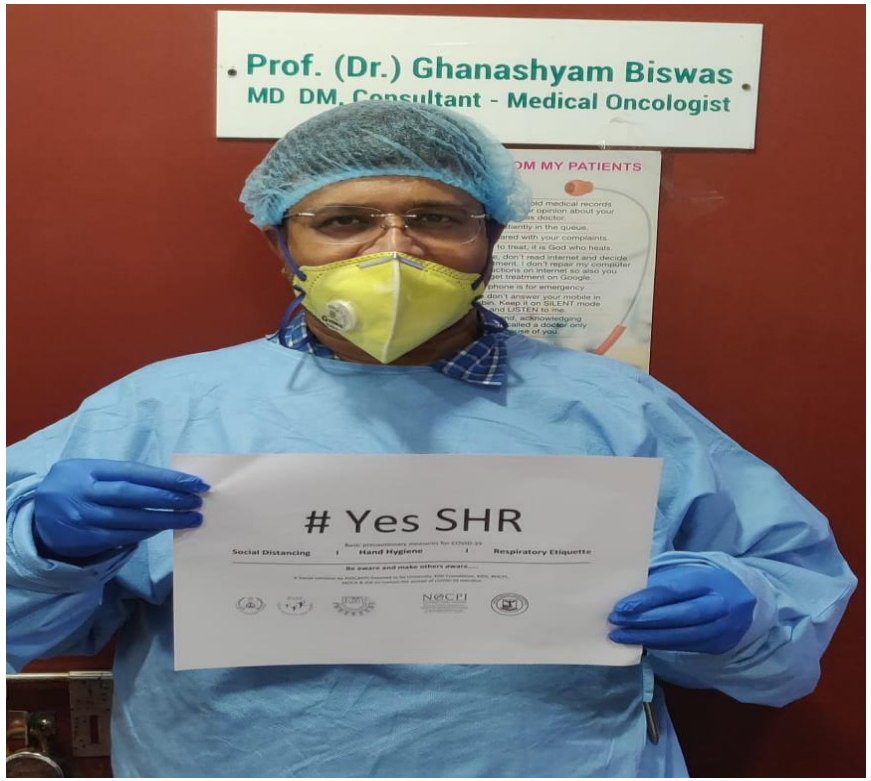
GC: MSI-H

- 1st Line: Doublet chemo (5FU/platinum)/ IO
- 2nd Line: IO
- 3rd Line: Dealer's choice including IO

GC: PD-L1 > 10 CPS

- 1st Line: Doublet chemo (5FU/platinum)/ IO
- 2nd Line: IO
- 3rd Line: Dealer's choice including IO

THANK YOU.


Prof. (Dr.) Ghanashyam Biswas
MD DM. Consultant - Medical Oncologist
Yes SHR
Social Distancing
Hand Hygiene
Respiratory Etiquette
Be aware and make others aware.....