Evoluzione delle strategie terapeutiche nel carcinoma gastrico: attualità e prospettive future

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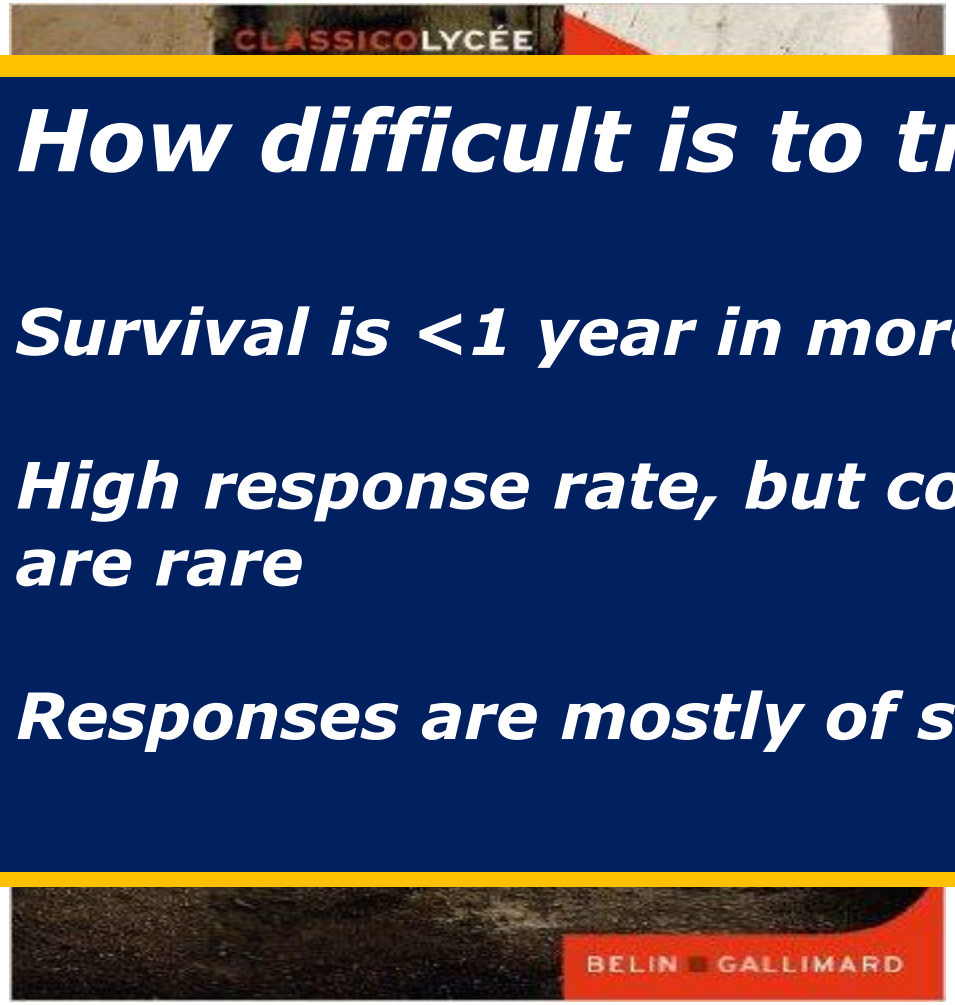
DELLA CAMPANIA
LUIGI VANVITELLI

Treatment of metastatic gastric cancer
The challenge



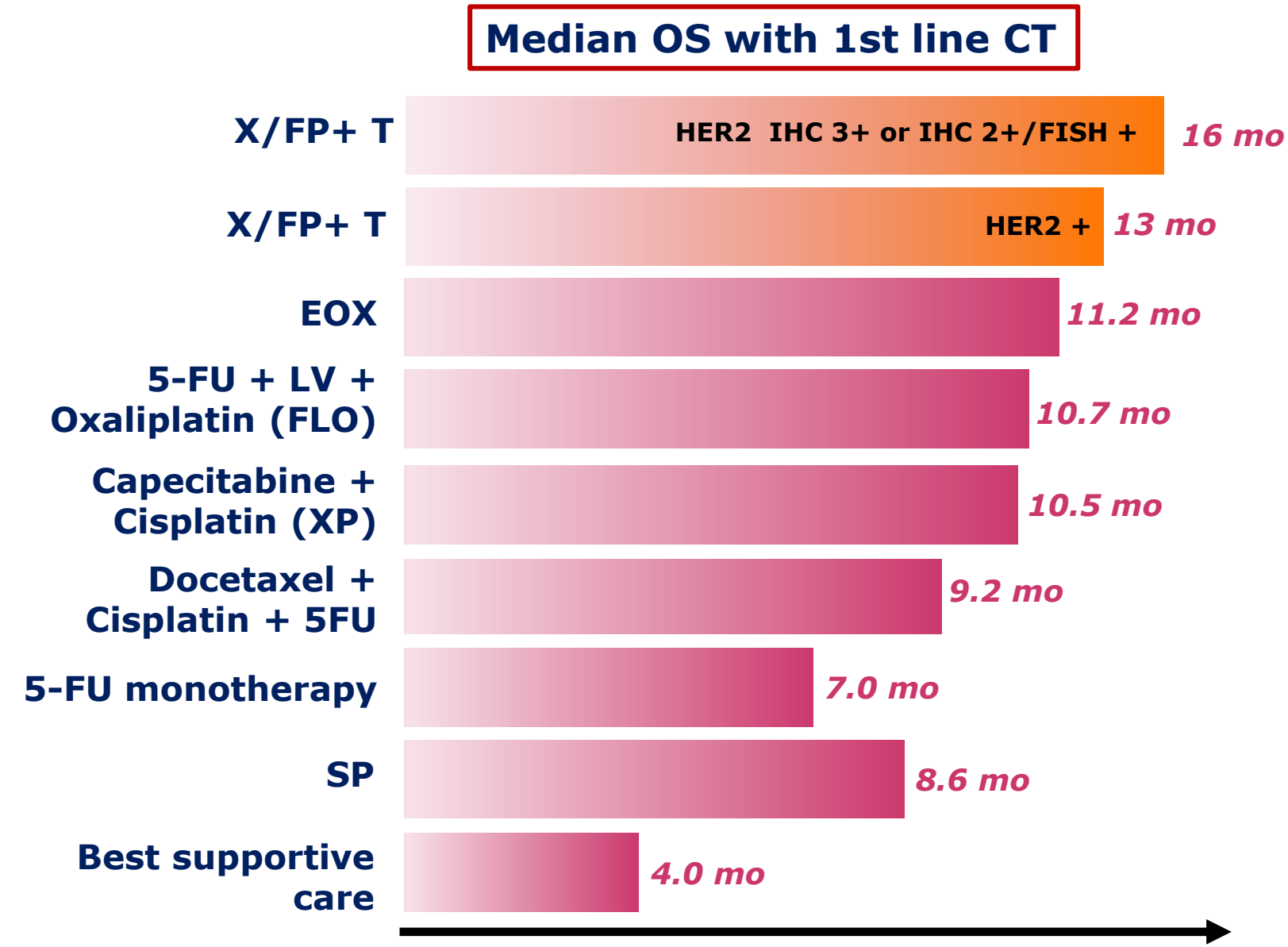
How difficult is to treat metastatic GC?

Survival is <1 year in more than half of patients

High response rate, but complete responses to CT are rare

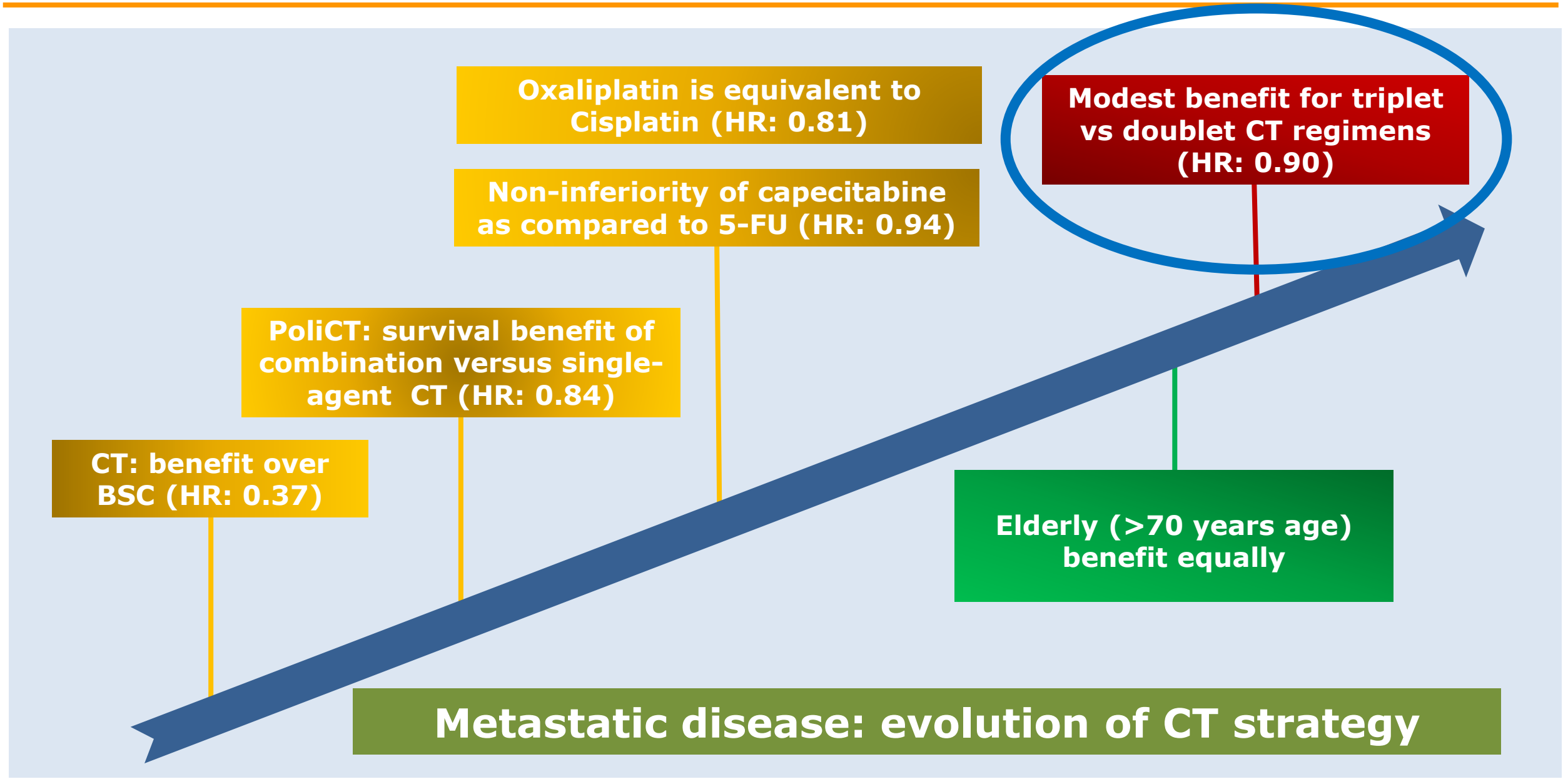
Responses are mostly of short duration

In mGC setting CT is the backbone of treatment but…
…limited progress with chemotherapy alone



CT plateau!

Metastatic setting treatment
What we know from clinical research…



Is the more the better?
Triplet or Doublet CT in Advanced Gastric Cancer?

Toxicity grade 3 or 4	Triplet			Doublet				
...but toxicity?	*N*	Total	%	*N*	Total	%	RR	95 % CI
Hematologic toxicity								
Anemia	106	840	12.6	121	823	14.7	0.86	0.68–1.09
Neutropenia	543	1006	54.0	470	986	47.7	1.07	0.92–1.23
Neutropenic fever	46	385	11.9	46	367	12.5	0.95	0.50–1.82
Thrombocytopenia	61	986	6.2	37	962	3.8	1.57[a]	1.06–2.31
Non-hematologic toxicity								
Fatigue	50	331	15.1	52	316	16.5	0.91	0.64–1.29
Infection	64	630	10.2	40	629	6.4	1.60[a]	1.09–2.33
Mucositis	59	607	9.7	28	591	4.7	2.20[a]	1.00–4.86
Nausea	85	665	12.8	63	648	9.7	1.34	0.98–1.82
Vomiting	84	728	11.5	81	716	11.3	1.04	0.78–1.38
Diarrhea	114	1260	9.0	98	1244	7.9	0.98	0.60–1.61
Toxicity-related deaths	68	1069	6.4	54	1052	5.1	1.24	0.89–1.74

Mohammad NH, Cancer Metastasis Rev 2015

Is the more the better?
Triplet or Doublet CT in Advanced Gastric Cancer?

165 pts with AGC treated with poliCT treated from 2012 through 2016

Med Oncol (2017) 34:186
DOI 10.1007/s12032-017-1046-7

ORIGINAL PAPER

Efficacy of a triplet and doublet-based chemotherapy as first-line therapy in patients with HER2-negative metastatic gastric cancer: a retrospective analysis from the clinical practice

Maria Maddalena Laterza[1] · Luca Pompella[1] · Angelica Petrillo[1] · Giuseppe Tirino[1] · Annalisa Pappalardo[1] · Michele Orditura[1] · Teresa Troiani[1] · Fortunato Ciardiello[1] · Natale Di Martino[2] · Ferdinando De Vita[1]

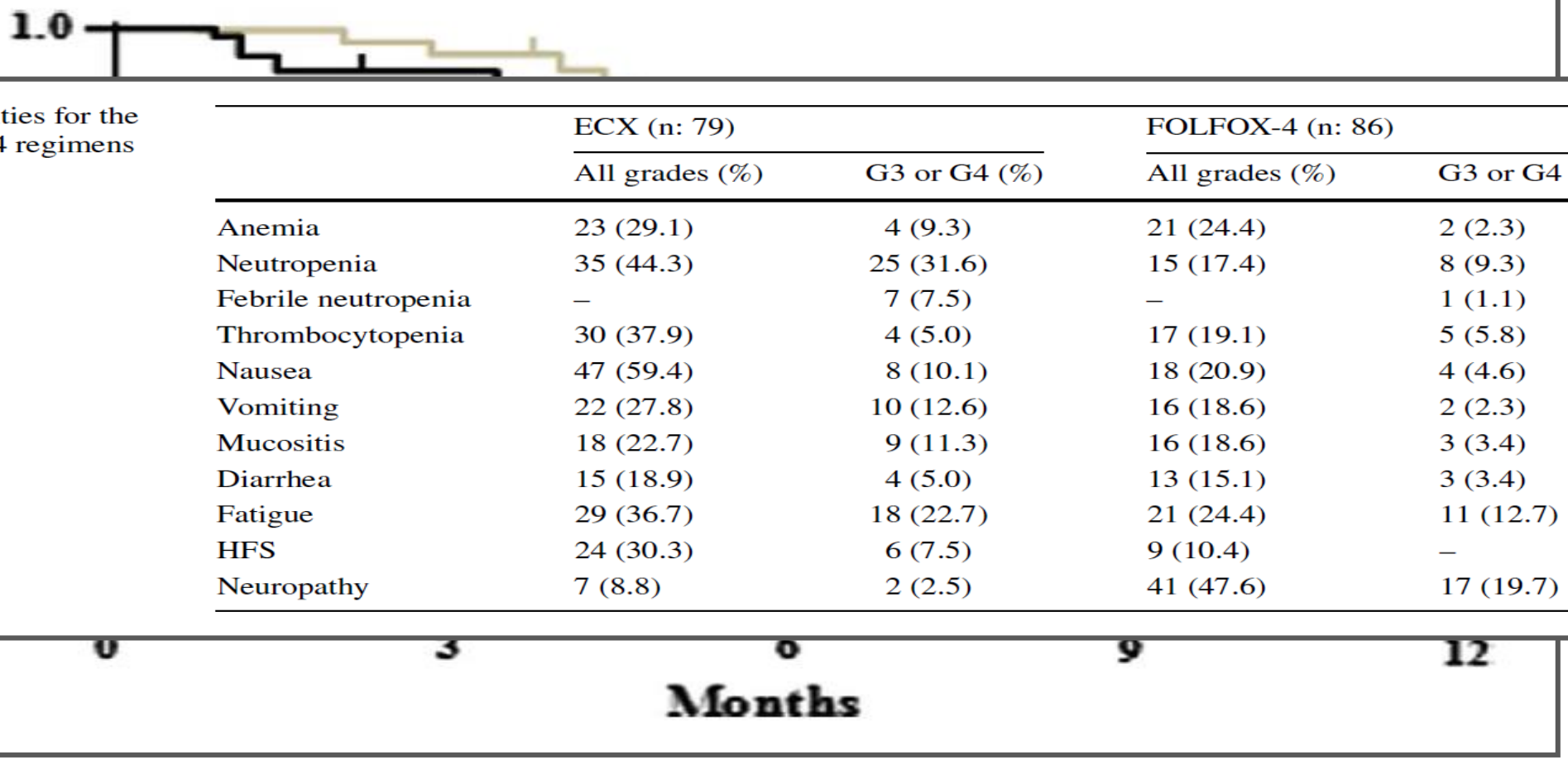


Table 2 Main toxicities for the ECX and FOLFOX-4 regimens

	ECX (n: 79)		FOLFOX-4 (n: 86)	
	All grades (%)	G3 or G4 (%)	All grades (%)	G3 or G4 (%)
Anemia	23 (29.1)	4 (9.3)	21 (24.4)	2 (2.3)
Neutropenia	35 (44.3)	25 (31.6)	15 (17.4)	8 (9.3)
Febrile neutropenia	–	7 (7.5)	–	1 (1.1)
Thrombocytopenia	30 (37.9)	4 (5.0)	17 (19.1)	5 (5.8)
Nausea	47 (59.4)	8 (10.1)	18 (20.9)	4 (4.6)
Vomiting	22 (27.8)	10 (12.6)	16 (18.6)	2 (2.3)
Mucositis	18 (22.7)	9 (11.3)	16 (18.6)	3 (3.4)
Diarrhea	15 (18.9)	4 (5.0)	13 (15.1)	3 (3.4)
Fatigue	29 (36.7)	18 (22.7)	21 (24.4)	11 (12.7)
HFS	24 (30.3)	6 (7.5)	9 (10.4)	–
Neuropathy	7 (8.8)	2 (2.5)	41 (47.6)	17 (19.7)

Laterza MM & De Vita F, Med Oncol 2017

Anthracyclines: which benefit?
No more Epirubicin!

Cancer Metastasis Rev (2015) 34:429–441
DOI 10.1007/s10555-015-9576-y

CLINICAL

Optimal first-line chemotherapeutic t
with locally advanced or metastatic es
triplet *versus* doublet chemotherapy: a
review and meta-analysis

Gastric Cancer
DOI 10.1007/s10120-017-0718-5

ORIGINAL ARTICLE

Anthracycline-based triplets do not improve the efficacy

VOLUME 35 · NUMBER 4 · FEBRUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

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Ga …

Doublet CT is preferred based on benefit risk-ratio

Study or Subgroup	Log HR	SE	Triplet regimen	Total	Do
1.1.1 Fluoropyrimidine-based					
Van Cutsem 2015	-0.4902	0.1614	DTX+Ox+FPyr	175	DTX+Ox
Douglass 1984	-0.3935	0.2211	Doxo+MMC+5-FU	48	Doxo+MMC
Roth 2007	-0.1434	0.2412	DTX+Cis+5-FU	41	DTX+Cis
Ajani 2005	0.1892	0.1614	DTX+Cis+5-FU	79	DTX+Cis
Subtotal (95% CI)				343	
Heterogeneity: Chi² = 8.12, df = 3 (P = 0.04); I² = 63%					
Test for overall effect: Z = 2.34 (P = 0.02)					
1.1.2 Cisplatinum-based					
Roth 1999	-0.3039	0.1499	Epi+Cis+5-FU	54	Epi+5-FU
Park 2008	-0.1805	0.3628	Cis+Iri+5-FU+Lv	45	Iri+5-FU+Lv
Subtotal (95% CI)				99	
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%					
Test for overall effect: Z = 2.06 (P = 0.04)					
1.1.3 Taxane-based					
Wang 2015	-0.3422	0.1591	DTX+Cis+5-FU	121	Cis+5-FU
Van Cutsem 2006	-0.235	0.1199	DTX+Cis+5-FU	227	Cis+5-FU
Al-Batran 2013	-0.1847	0.2202	DTX+Ox+5-FU+Lv	112	Ox+5-FU+Lv
Subtotal (95% CI)				460	
Heterogeneity: Chi² = 0.43, df = 2 (P = 0.81); I² = 0%					
Test for overall effect: Z = 2.96 (P = 0.003)					
1.1.4 MMC-based					
Koizumi 2004	-0.2129	0.2766	5-DFUR+Cis+MMC	33	5-DFUR+Cis
Cullinan 1985	0.0446	0.1975	5-FU+Doxo+MMC	51	5-FU+Doxo
Subtotal (95% CI)				84	
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%					
Test for overall effect: Z = 0.26 (P = 0.79)					
1.1.5 Anthracyclin-based					
KRGCGC 1992	-0.5635	0.3805	Epi+Cis+5-FU	31	Cis+5-FU
Kim 2001	-0.1956	0.3428	Epi+Cis+5-FU	60	Cis+5-FU
Subtotal (95% CI)				91	
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%					
Test for overall effect: Z = 1.42 (P = 0.16)					
1.1.6 Other					
Thuss-Patience 2005	-0.4463	0.2237	Epi+Cis+5-FU	45	DTX+5-FU
Li 2011	0.0032	0.2538	PTX+Cis+5-FU	46	Cis+5-FU+Lv
Guimbaud 2014	0.0083	0.1095	Epi+Cis+Cap	269	Iri+5-FU+Lv
Van Hoefer 2000	0.0234	0.1258	5-FU+Doxo+MTX	133	Cis+5-FU
Van Hoefer 2000	0.0508	0.1272	5-FU+Doxo+MTX	133	Eto+5-FU+Lv
Roth 2007	0.0738	0.242	Epi+Cis+5-FU	40	DTX+Cis
Kim 1993	0.282	0.1755	Doxo+MMC+5-FU	110	Cis+5-FU
Subtotal (95% CI)				720	
Heterogeneity: Chi² = 3.36, df = 6 (P = 0.76); I² = 0%					
Test for overall effect: Z = 0.67 (P = 0.51)					
Total (95% CI)				1797	
Heterogeneity: Chi² = 26.82, df = 19 (P = 0.11); I² = 29%					
Test for overall effect: Z = 2.70 (P = 0.007)					
Test for subgroup differences: Chi² = 13.72, df = 5 (P = 0.02), I² = 63.6%					

Mohammad NH, Cancer Metastasis Rev 2015

		Anthracycline-based triplet	
		Total (%)	Grade 3–4 (%)
		65.7	7.7
		57.0	32.0
		8.6	
		23.4	3.0
		38.2	4.9
		43.2	5.5
		33.0	2.7
		66.9	5.5
		27.1	3.0
		66.0	4.0
		61.7	
		16.3	0.9
		8.0	1.5
		6.7	0.6
		1.7	0
		11.1	6.7
		31.0	
Death due to toxicity	0.6	0.3	

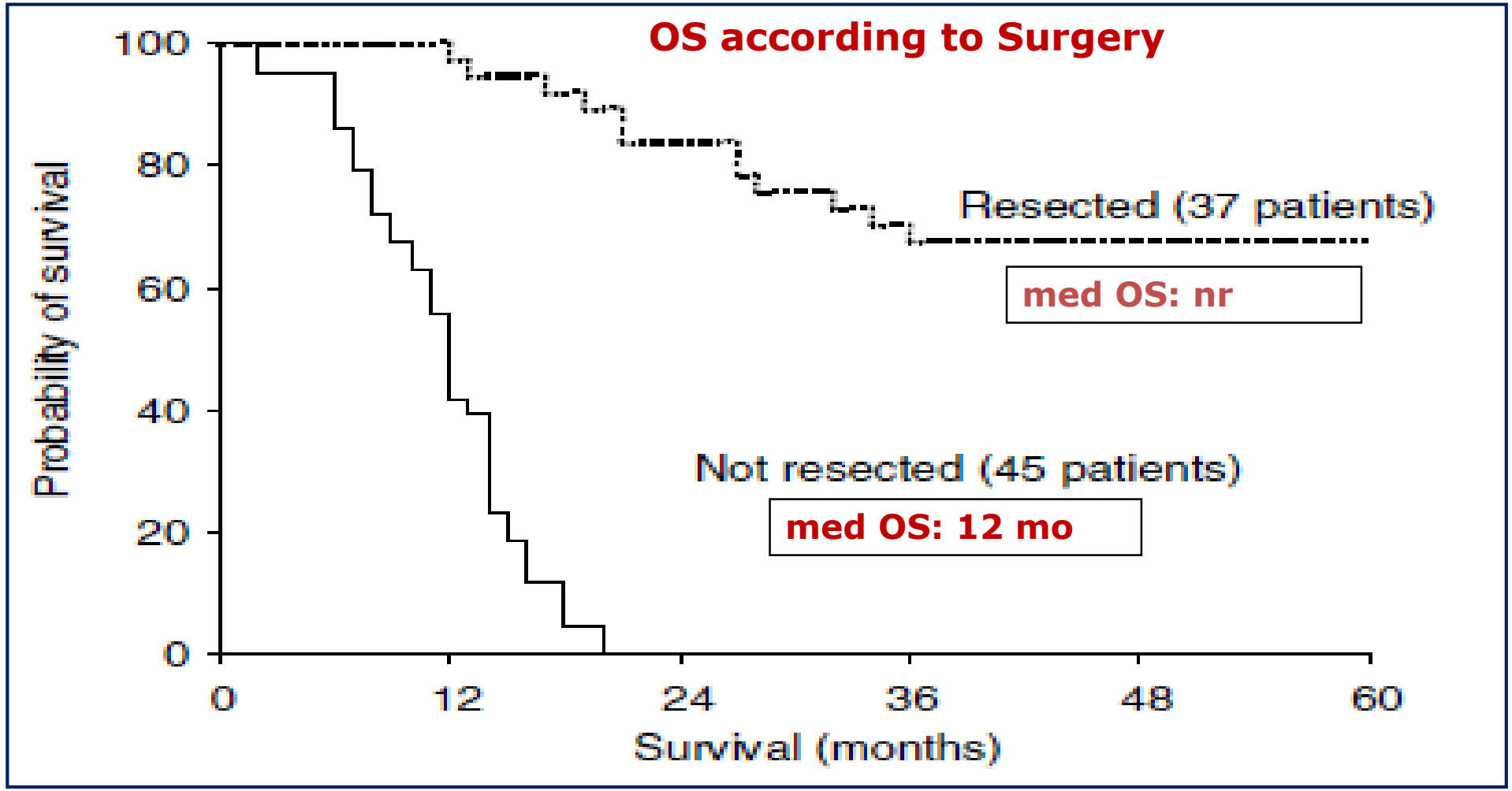
Carmona-Bayonas A, Gastric Cancer 2017

When triplet CT in Advanced Gastric Cancer?
...*when needs high antitumor activity*

LOCALLY ADVANCED UNRESECTABLE OR BORDERLINE RESECTABLE DISEASE

British Journal of Cancer (2004) 90, 1521 – 1525
© 2004 Cancer Research UK All rights reserved 0007 – 0920/04 $25.00
www.bjcancer.com

High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione, and filgastrim in patients with locally advanced, unresectable gastric cancer: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD)



Cascinu S, Br J Cancer 2004

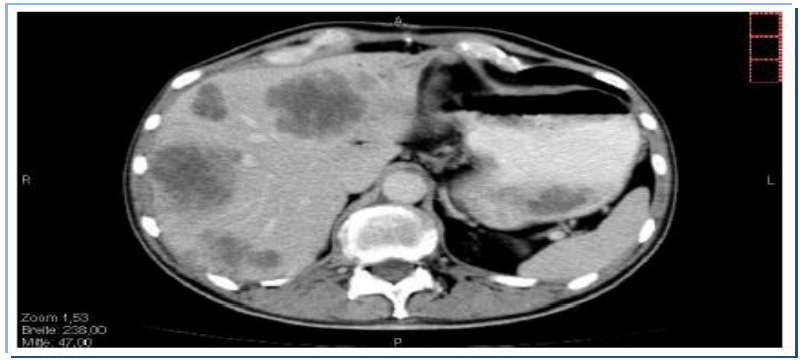
When triplet CT in Advanced Gastric Cancer?
...*when needs high antitumor activity*

Cancer Metastasis Rev (2015) 34:429–441
DOI 10.1007/s10555-015-9576-y

CLINICAL

Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

HIGH TUMOR BURDEN
HIGH SYMPTOM BURDEN



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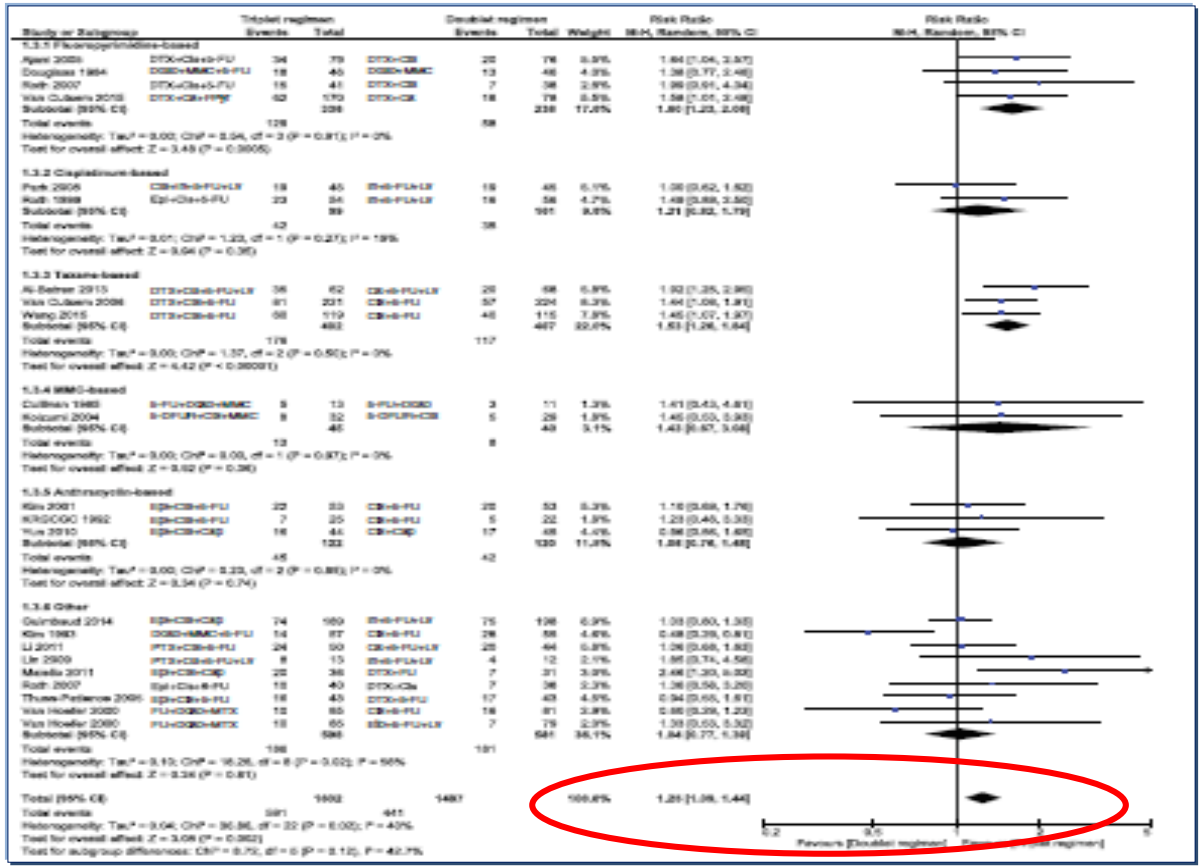
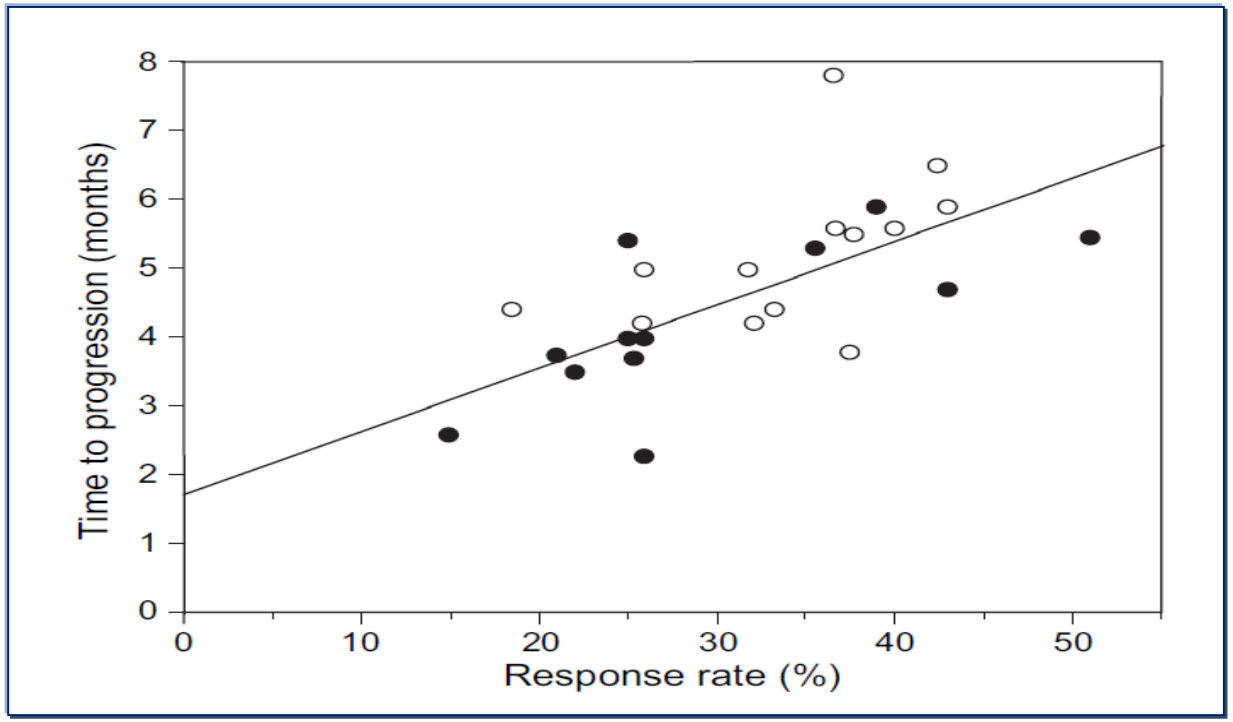


Mohammad NH,Cancer Metastasis Review 2015



Ichikawa W,Ann Oncol 2006

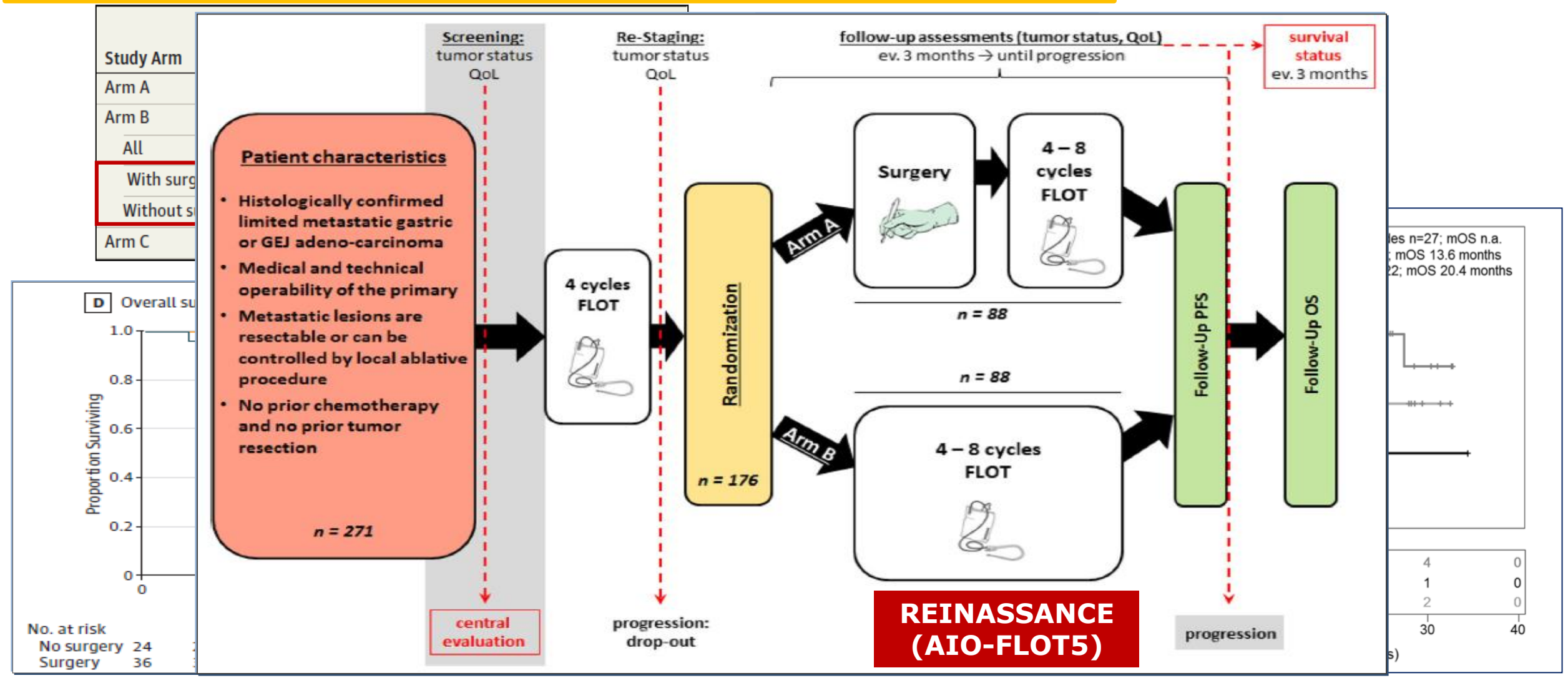
When triplet CT in Advanced Gastric Cancer?
...*when needs high antitumor activity*

Research

JAMA Oncology | Original Investigation

Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer
The AIO-FLOT3 Trial

Metastatic disease with the potential for conversion surgery



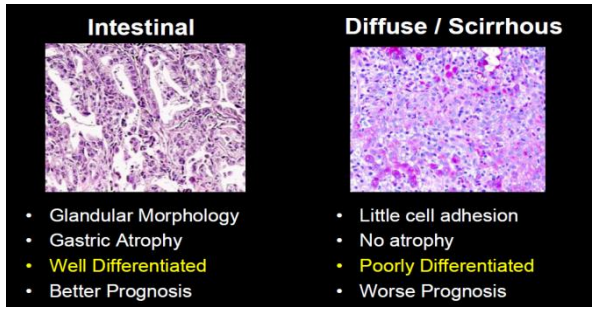
Al-Batran SE,JAMA Oncology 2017

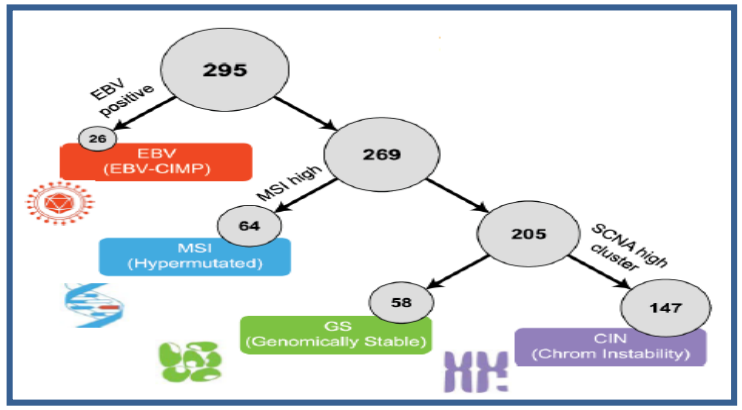
Target-oriented phase II/III trials in GC
Not a success story!

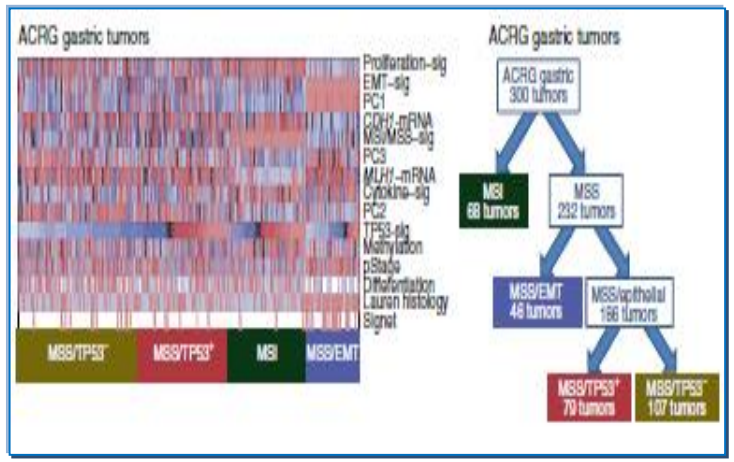
Trial	Phase	Setting	Target	Arms	N Patients	Primary Endpoint	Result
ToGA	III	1st line	HER2+	CF/CX ± Trastuzumab	594	OS	Positive
JACOB	III	1st line	HER2+	CF/CX+ Trastuzumab ± Pertuzumab	780	OS	Negative
GATSBY	II/III	2nd line	HER2+	Taxanes ± TDM-1	345	OS	Negative
LOGIC	III	1st line	HER2+	CapeOX ± Lapatinib	545	OS	Negative
TyTAN	III	2nd line	HER2+	Paclitaxel ± Lapatinib	261	OS	Negative
EXPAND	III	1st line	EGFR (unselected)	CX ± Cetuximab	894	PFS	Negative
REAL-3	III	1st line	EGFR (unselected)	EOC ± Panitumumab	553	OS	Negative
METGastric	III	1st line	MET+	Folfox ± Onartuzumab	562	OS	Negative
RILOMET-1	III	1st line	MET+	ECX ± Rilotumumab	609	OS	Negative
SHINE	II	2nd line	FGFGR2+	Paclitaxel ± AZD4546	71	PFS	Negative
FAST	IIb	1st line	CLDN18.2+	EOX ± Claudiximab	161	PFS	Positive
AVAGAST	III	1st line	VEGF	CX ± Bevacizumab	774	OS	Negative
AVATAR	III	1st line	VEGF	CX ± Bevacizumab	202	OS	Negative
REGARD	III	2nd line	VEGFR2	Ramucirumab vs. Placebo	355	OS	Positive
RAINBOW	III	2nd line	VEGFR2	Paclitaxel ± Ramucirumab	665	OS	Positive
RAINFALL	III	1st line	VEGFR2	CX± Ramucirumab	645	PFS	Positive

Petrillo A & De Vita F, Int J Mol Siences 2018

Why so disappointing results?
Genomic heterogeneity as a potential barrier to precision medicine







Evidence of GC heterogeneity
From histological to molecular classifications of GC

a TCGA

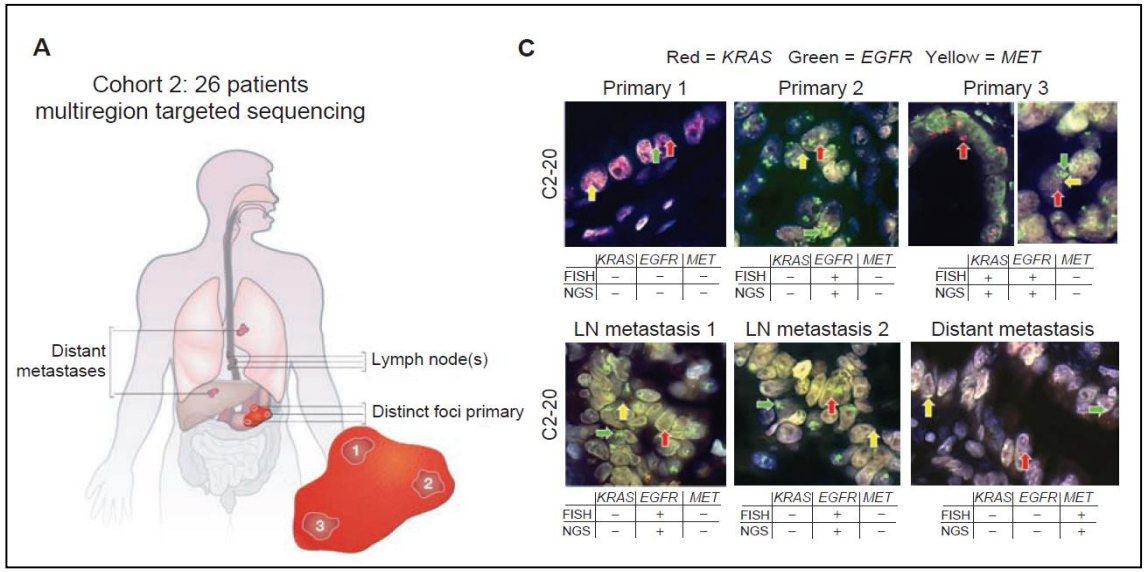
Subtype	EBV⁺ (9%)	MSI-high (22%)	Genomically stable (20%)	CIN (50%)
Molecular alterations	• *PIK3CA* mutations • *CDKN2A* silencing • *JAK2* amplification • PDL1 and PDL2 amplification	• *MLH1* silencing • Hypermutation of targetable oncoproteins	• *RHOA* mutations • *CDH1* mutations • Most diffuse type	• RTK amplification and overexpression • *TP53* mutations • Aneuploidy

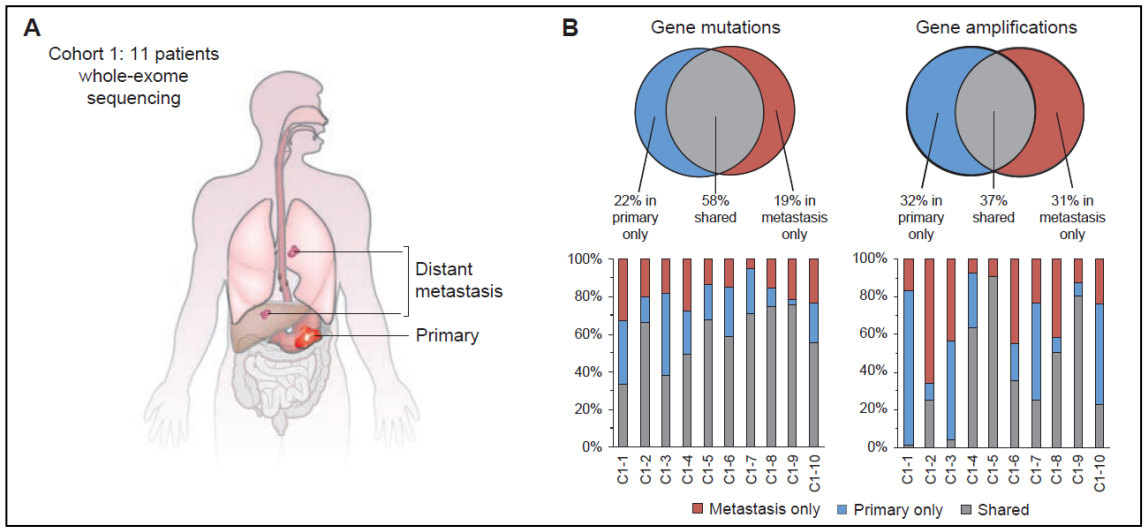
b ACRG

Subtype	MSS/*TP53*⁺ (26%)	MSI-high (23%)	MSS/EMT (15%)	MSS/*TP53*⁻ (36%)
Molecular alterations	• Frequent mutations in *APC*, *ARID1A*, *PI3KCA* and *SMAD4* • Intact *TP53*	• Hypermutation • Frequent mutations in *KRAS*, *PI3K*, *PTEN*, *MTOR*, *ALK* and *ARID1A*	• Low mutational load • Loss of *CDH1* • Most diffuse type	• *TP53* mutation • RTK amplification • Overexpression of *HER2*, *EGFR*, *CCNE1*, *CCND1*, *GATA6* and *MYC*
Clinical phenotypes	• EBV⁺ • Intermediate-risk prognosis • Intermediate risk of recurrence	• Best prognosis • Low risk of recurrence • Commonly diagnosed at early stage	• Worst prognosis • High risk of recurrence • Late stage III–IV	• Intermediate-risk prognosis • Intermediate risk of recurrence

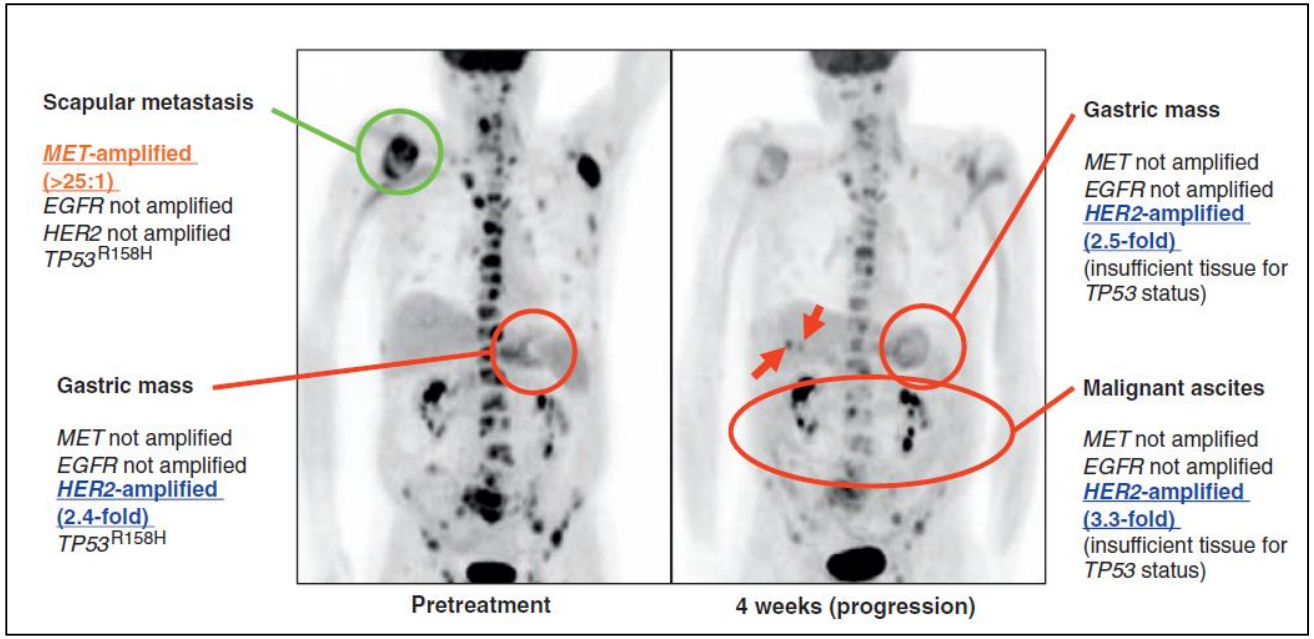
USA Cancer Genome Atlas (TCGA), 2014 Nature; Cristescu R, Nature Medicine 2015

Why so disappointing results?
Genomic heterogeneity as a potential barrier to precision medicine





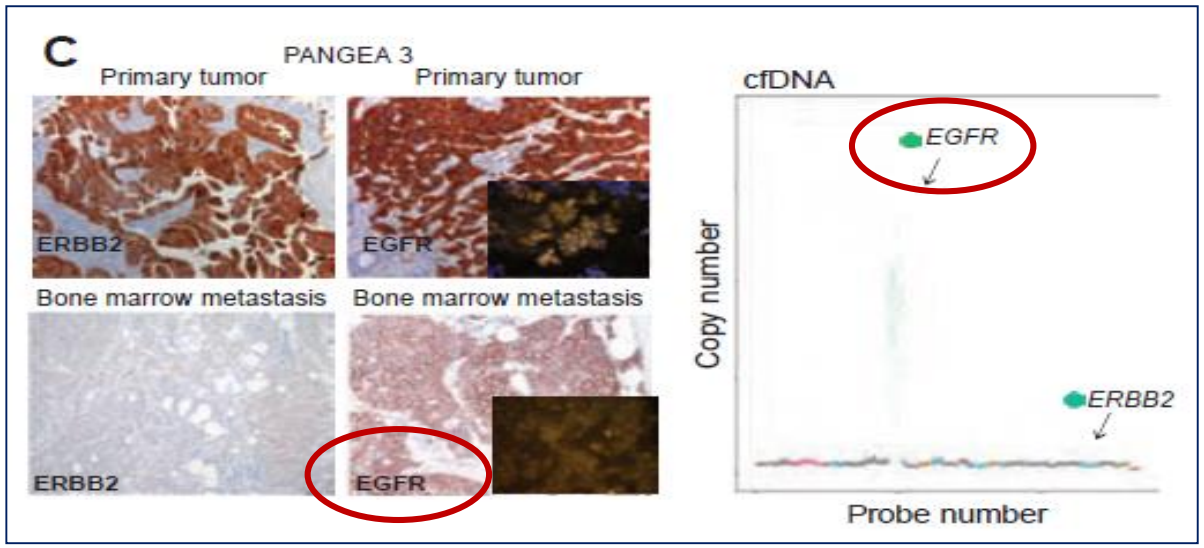
GC is a genomically heterogeneous disease: sampling a single site of the disease can never fully assess the clonal complexity of multisite metastatic disease in patients

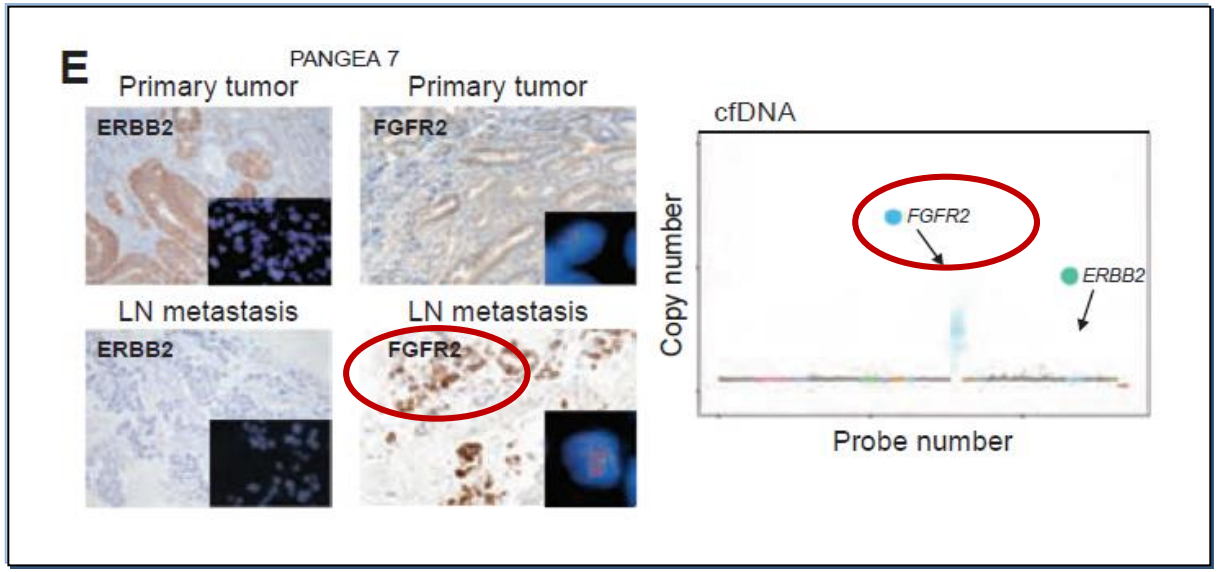


Pectasides E, Cancer Discovery 2018
Kwak EL, Cancer Discovery 2015

Liquid biopsies to measure tumor heterogeneity

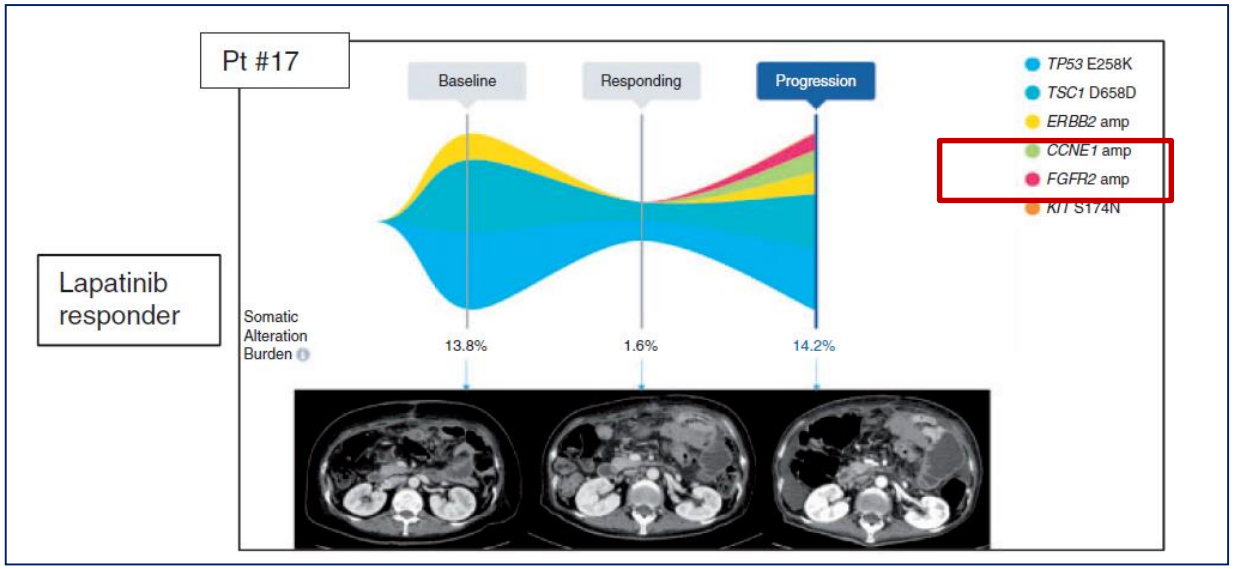
Discrepant biomarker profiling between paired PT, metastasis, and circulating cell-free DNA

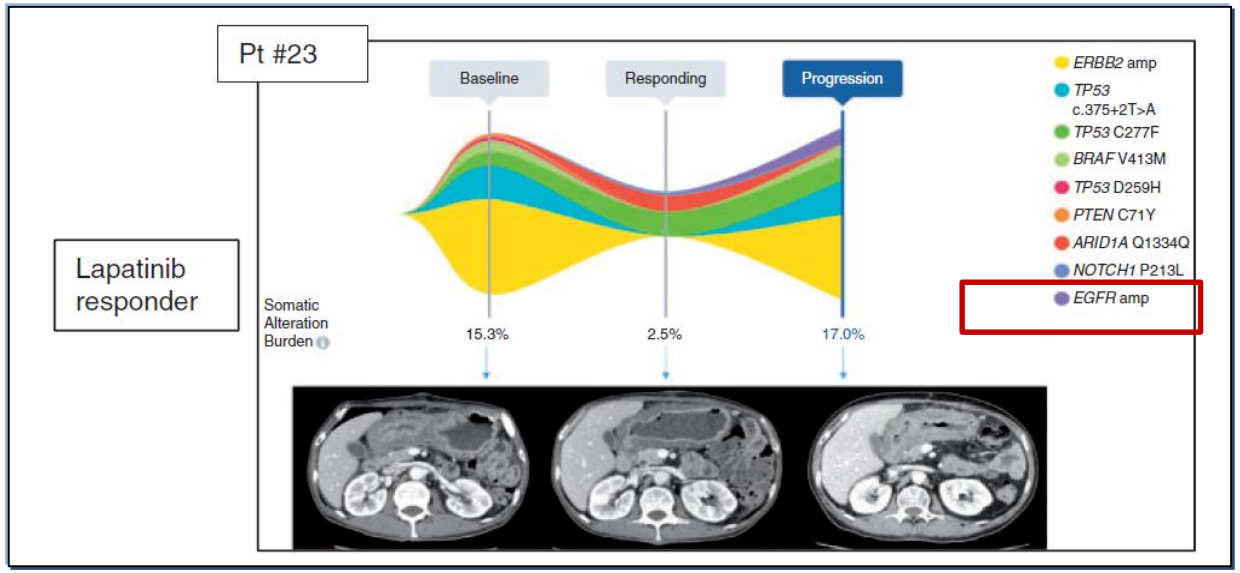




Pectasides E, Cancer Discovery 2018

Changes in plasma-detected genomic alterations are associated with Lapatinib sensitivity and/or resistance





Kim ST, Ann Oncol 2018

Why so disappointing results?
Pts selection: rethinking anti-EGFR development


Articles

Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial

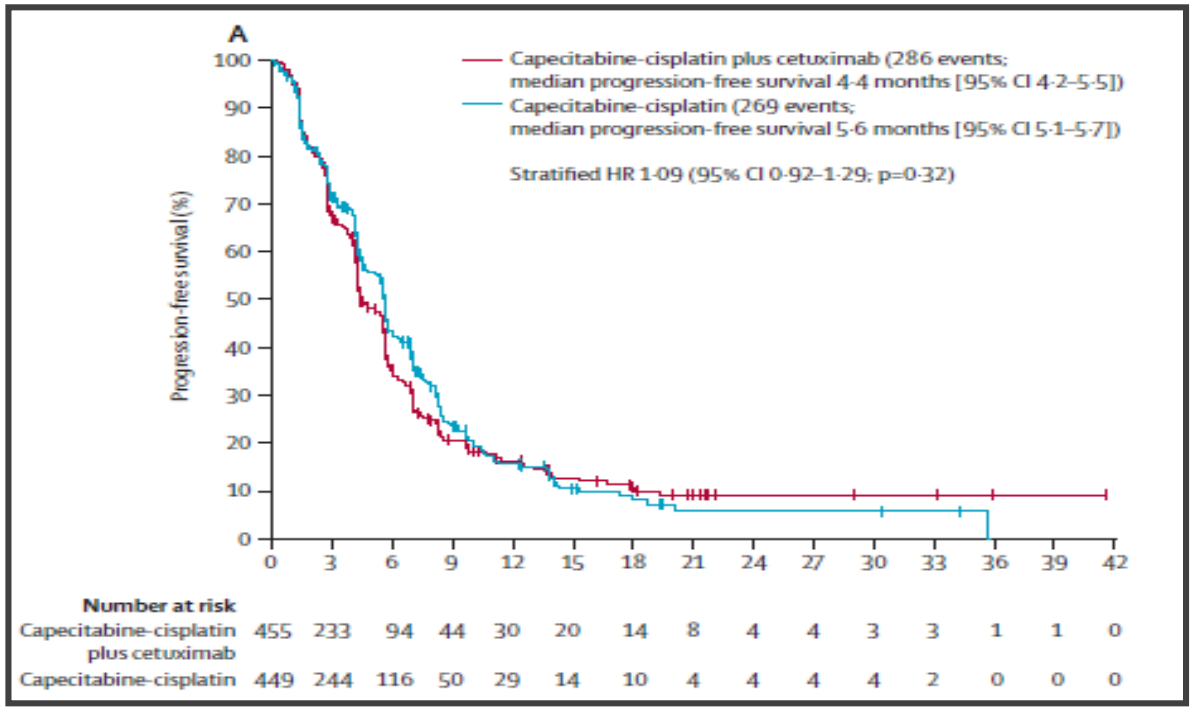
Targeted agents in a targeted population?


Articles

Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial

EXPAND Study

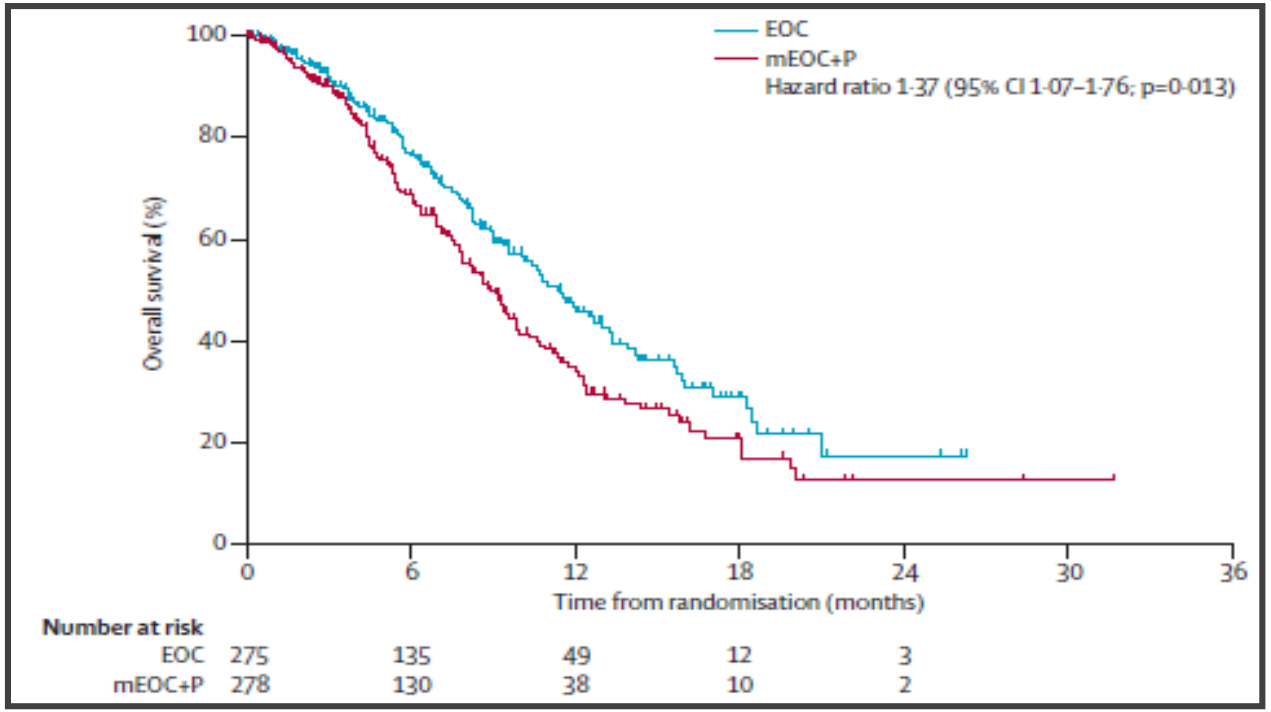
XP vs X + cetuximab



Lordick F, Lancet Oncol 2013

REAL 3 Study

EOX vs mEOX + panitumumab

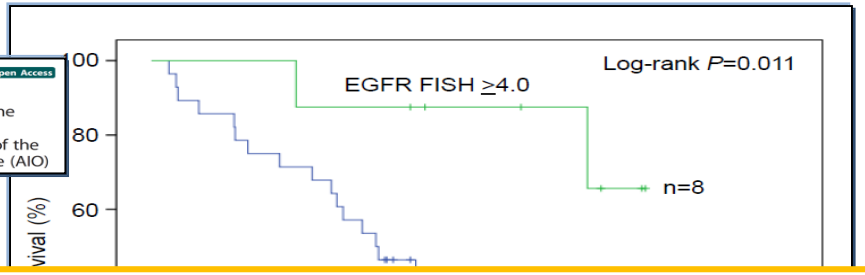


Waddel T, Lancet Oncol 2013

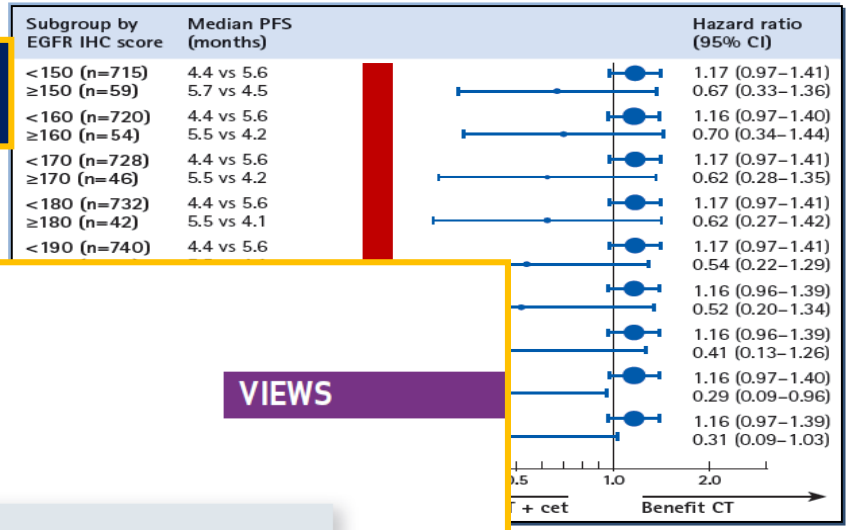
Why so disappointing results?
Pts selection: rethinking anti-EGFR development

RESEARCH ARTICLE Open Access

Biomarker analysis of cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric and oesophago-gastric junction cancer: results from a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO)



Highest expressing tumors clearly under-represented in anti-EGFR trials



VIEWS

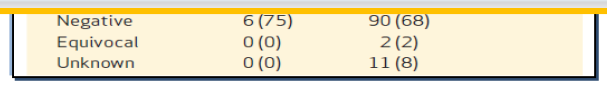
IN THE SPOTLIGHT

EGFR Amplification as a Target in Gastroesophageal Adenocarcinoma: Do Anti-EGFR Therapies Deserve a Second Chance?

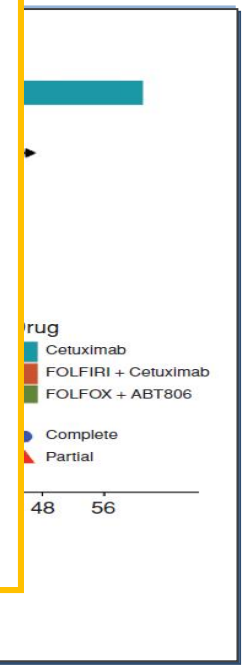
John H. Strickler

Summary: Anti-EGFR therapies have failed to improve survival for unselected patients with metastatic gastroesophageal cancer, but in a subset of patients, *EGFR* amplification may predict treatment benefit. Maron and colleagues report the clinical activity of anti-EGFR therapies in a cohort of patients with *EGFR*-amplified metastatic gastroesophageal cancer and utilize serial blood and tumor tissue collection to identify molecular drivers of treatment sensitivity and resistance. Their insights offer a path to overcome technical limitations associated with *EGFR* amplification and facilitate molecularly targeted therapeutic strategies. *Cancer Discov; 8(6); 679–81. ©2018 AACR.*

See related article by Maron et al., p. 696 (6).



DCR: 100% (7/7)
Med PFS: 10 mo



Lordick F, ASCO 2013; Luber B,BMC Cancer 2011; Maron SB, Cancer Discovery 2018

Metastatic setting treatment
Sequential treatment improves outcome

Lancet Oncol 2009; 10: 903–12

Is there a role for second-line chemotherapy in advanced gastric cancer?

Robert Wesolowski, Chan Lee, Richard Kim

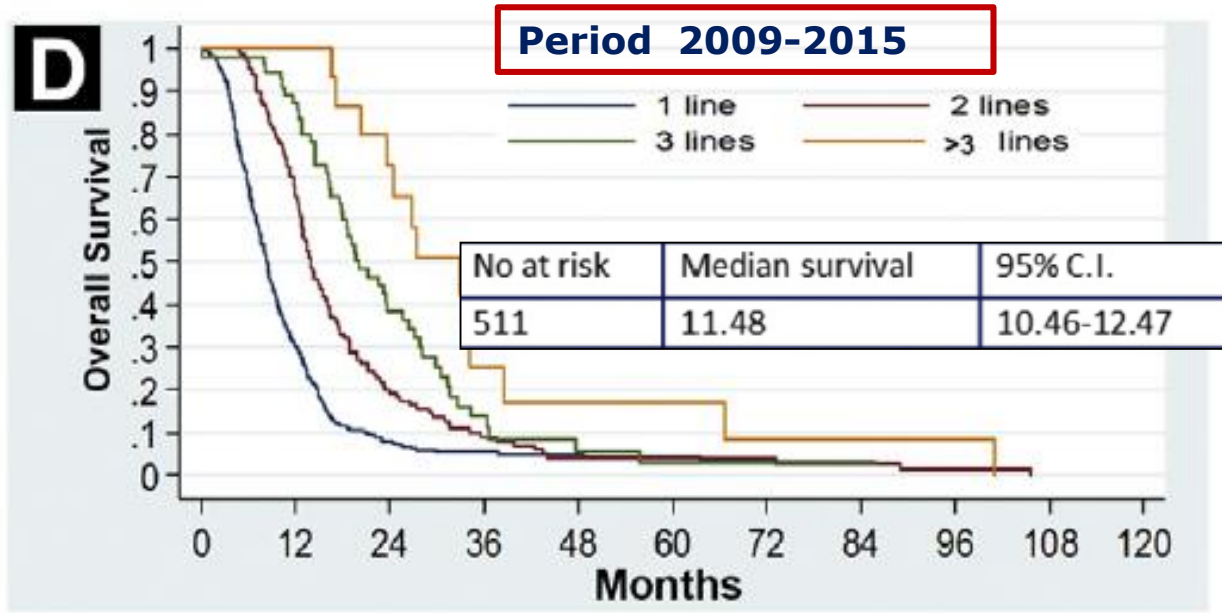
Real-world evidence of pts receiving second and third-line CT

Therapy	*USA*	*UK*	*ITALY*
2nd line	42%	39%	39%
3nd line	18%	15%	14%

Third-line therapy in RAINBOW trial

Asian pts: 69%

Non-Asian pts: 38%



Chemotherapy line	No at risk	No of events	Median Survival (m)	95% C.I.
1 only	311	286	8.32	7.57-9.05
2 only	130	119	13.95	12.90-15.89
3 only	55	48	20.10	17.60-25.76
>3	15	13	33.03	20.30-38.55

Hess LM, Gastric Cancer, 2016; Davidson M, Clin Colorectal Cancer 2018; Fanotto V, Oncologist 2018

Sequential treatment improves outcome of mGC pts
REGARD and RAINBOW suggest the 2nd line standard treatment

Articles

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

REGARD and RAINBOW trials

Articles

Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

Studies	Treatment	OS (mo)	HR OS	Delta (mo)	PFS (mo)	HR PFS	Delta (mo)	ORR (%)	DCR (%)
REGARD *2013*	Ramucirumab BSC	5.2* 3.8	0.77	+1.4	2.1* 1.3	0.48	+0.8	3 3	49* 23
RAINBOW *2014*	Ramucirumab + Paclitaxel Paclitaxel	9.6* 7.3	0.80	+2.3	4.4* 2.8	0.63	+1.6	28* 16	80* 64

***statistically significant**

Fuchs CS, Lancet Oncol 2014

Wilke H, Lancet Oncol 2014

The clinical relevance of Ramucirumab data

Real world data: The RAMoss study

Targeted Oncology
https://doi.org/10.1007/s11523-018-0562-5
ORIGINAL RESEARCH ARTICLE

Ramucirumab as Second-Line Therapy in Metastatic Gastric Cancer: Real-World Data from the RAMoss Study

Maria Di Bartolomeo[1] · Monica Niger[1] · Giuseppe Tirino[2] · Angelica Petrillo[2] · Rosa Berenato[1] · Maria Maddalena Laterza[2] · Filippo Pietrantonio[1] · Federica Morano[1] · Maria Antista[1] · Sara Lonardi[3] · Lorenzo Fornaro[4] · Stefano Tamberi[5] · Elisa Giommoni[6] · Alberto Zaniboni[7] · Lorenza Rimassa[8] · Gianluca Tomasello[9] · Teodoro Sava[10] · Massimiliano Spada[11] · Tiziana Latiano[12] · Alessandro Bittoni[13] · Alessandro Bertolini[14] · Ilaria Proserpio[15] · Katia Bruna Bencardino[16] · Francesco Graziano[17] · Giordano Beretta[18] · Salvatore Galdy[19] · Jole Ventriglia[2] · Simone Scagnoli[20] · Andrea Spallanzani[21] · Raffaella Longarini[22] · Ferdinando De Vita[2]

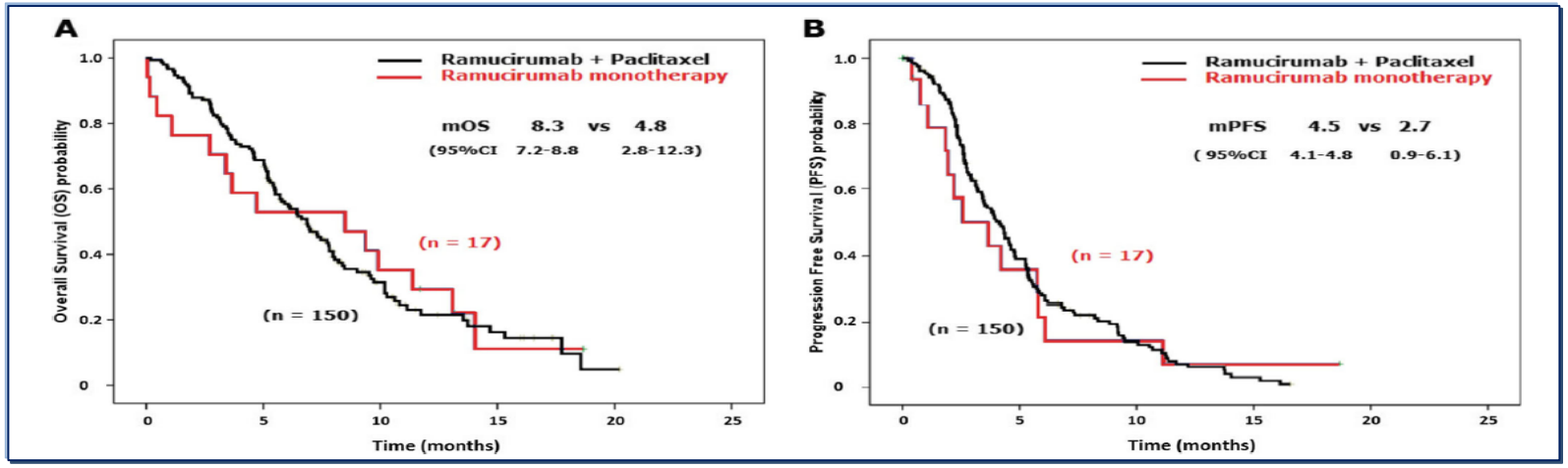


Table 2 Adverse events

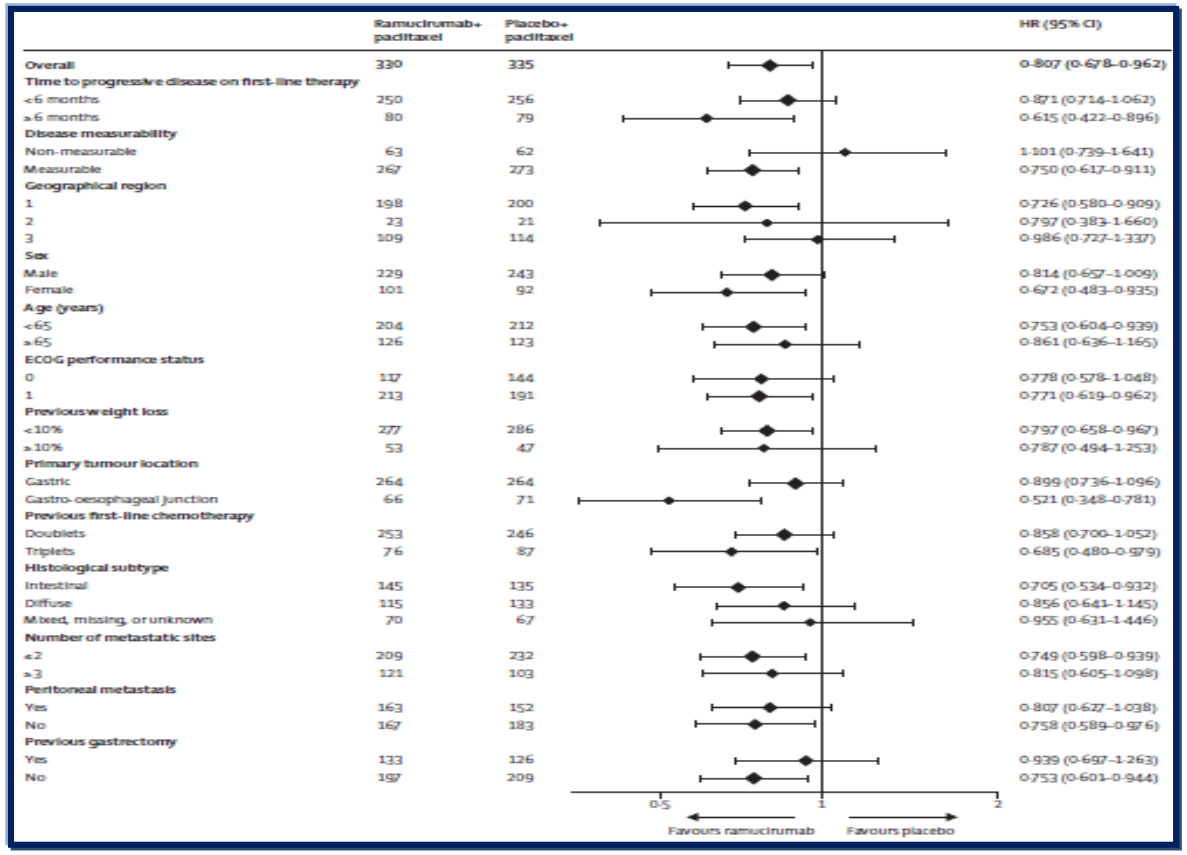
	No. (%)
G1/G2	
Neutrophil count decreased	25 (14.9)
Nervous system disorders	44 (26.3)
Fatigue	46 (27.5)
Nausea	13 (7.7)
Vomiting	7 (4.1)
Diarrhea	19 (11.3)
Bleeding	10 (5.9)
Hypertension	6 (3.5)
Proteinuria	1 (0.6)
Anemia	19 (11.3)
G3/G4	
Neutropenia	9 (5.4)
Bleeding	3 (1.8)
Fatigue	1 (0.6)
Hypertension	1 (0.6)

Outcomes	° *RAINBOW WESTERN PTS*	^*RAMoss (RAM+PTX)*
mOS (mo)	**8.6**	**8.3**
mPFS (mo)	**4.2**	**4.5**
ORR (%)	**26.8**	**20.3**
DCR (%)	**76.8**	**59.7**
Neutropenia G3/4	**32.1%**	**5.3%**
Severe bleeding G3/4	**4.6%**	**2.4%**

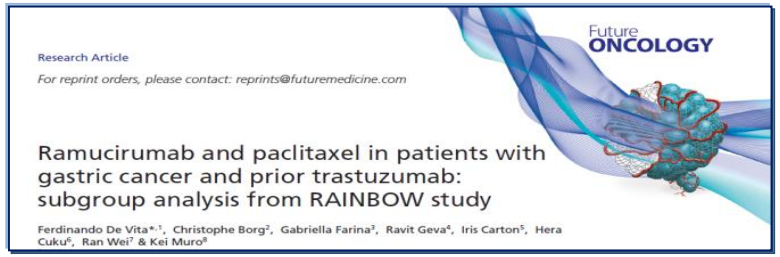
Di Bartolomeo M & De Vita F, Targeted Oncol 2018

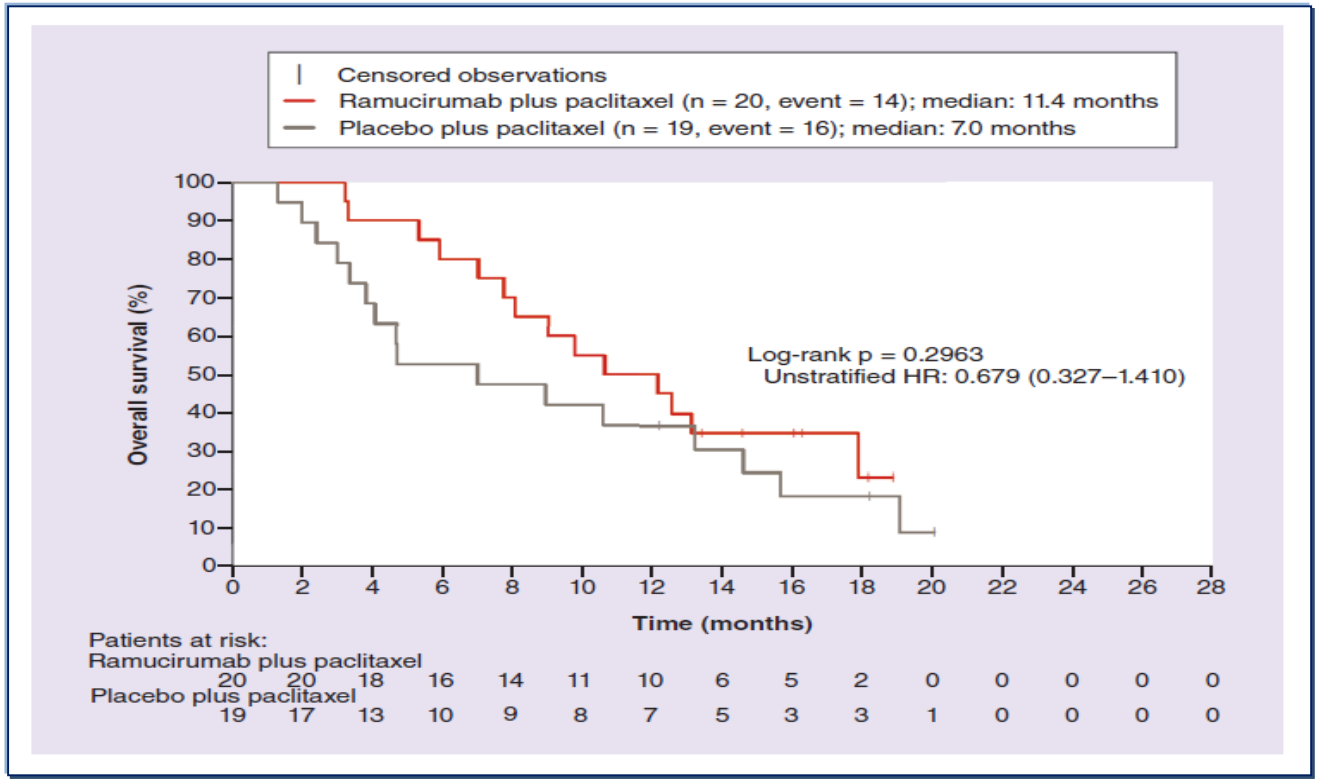
The clinical relevance of Ramucirumab data
Subgroup analysis of RAINBOW trials

RAMUCIRUMAB OS BENEFIT: SUBGROUP ANALYSES



Wilke H, Lancet Oncol 2014





De Vita F & Muro K, Future Oncol 2019

Metastatic setting treatment
Sequential treatment improves outcome beyond 2nd line CT

Efficacy outcome: OS,PFS and ORR

A

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Kang 2012	-0.2083	0.3007	33	21	15.3%	0.81 [0.45, 1.46]
Li 2013a	-0.8819	0.2823	46	24	16.3%	0.41 [0.24, 0.72]
Li 2013b	-0.9943	0.2652	47	24	17.3%	0.37 [0.22, 0.62]
Li 2016	-0.3439	0.1423	176	91	25.1%	0.71 [0.54, 0.94]
Ohtsu 2013	-0.1054	0.1282	229	114	26.0%	0.90 [0.70, 1.16]
Total (95% CI)			531	274	100.0%	0.63 [0.46, 0.87]

Heterogeneity: Tau² = 0.09; Chi² = 13.31, df = 4 (P = 0.010); I² = 70%
Test for overall effect: Z = 2.77 (P = 0.006)

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours TLT Favours BSC

B

Study or Subgroup	log[Hazard Ratio]	SE	Third-line treatment Total	Best supportive care Total	Weight	Hazard Ratio IV, Random, 95% CI
Kang 2012	-0.2083	0.3007	33	21	16.1%	0.81 [0.45, 1.46]
Li 2013a	-0.8819	0.2788	46	24	17.2%	0.41 [0.24, 0.72]
Li 2013b	-0.9943	0.2652	47	24	18.0%	0.37 [0.22, 0.62]
Li 2016	-0.3439	0.1422	176	91	25.0%	0.71 [0.54, 0.94]
Ohtsu 2013	-0.0202	0.1644	145	72	23.7%	0.98 [0.71, 1.35]
Total (95% CI)			447	232	100.0%	0.63 [0.45, 0.90]

Heterogeneity: Tau² = 0.11; Chi² = 13.76, df = 4 (P = 0.008); I² = 71%
Test for overall effect: Z = 2.54 (P = 0.01)

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours TLT Favours BSC

D

Study or Subgroup	log[Hazard Ratio]	SE	Third-line treatment Total	Best supportive care Total	Weight	Hazard Ratio IV, Random, 95% CI
Li 2013a	-1.575	0.3099	46	24	22.2%	0.21 [0.11, 0.38]
Li 2013b	-1.7148	0.3245	47	24	21.4%	0.18 [0.10, 0.34]
Li 2016	-0.8119	0.1494	176	91	32.2%	0.44 [0.33, 0.60]
Pavlakis 2015	-1.1394	0.2763	56	29	24.2%	0.32 [0.19, 0.55]
Total (95% CI)			325	168	100.0%	0.29 [0.18, 0.45]

Heterogeneity: Tau² = 0.14; Chi² = 9.64, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 5.47 (P < 0.00001)

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours TLT Favours BSC

E

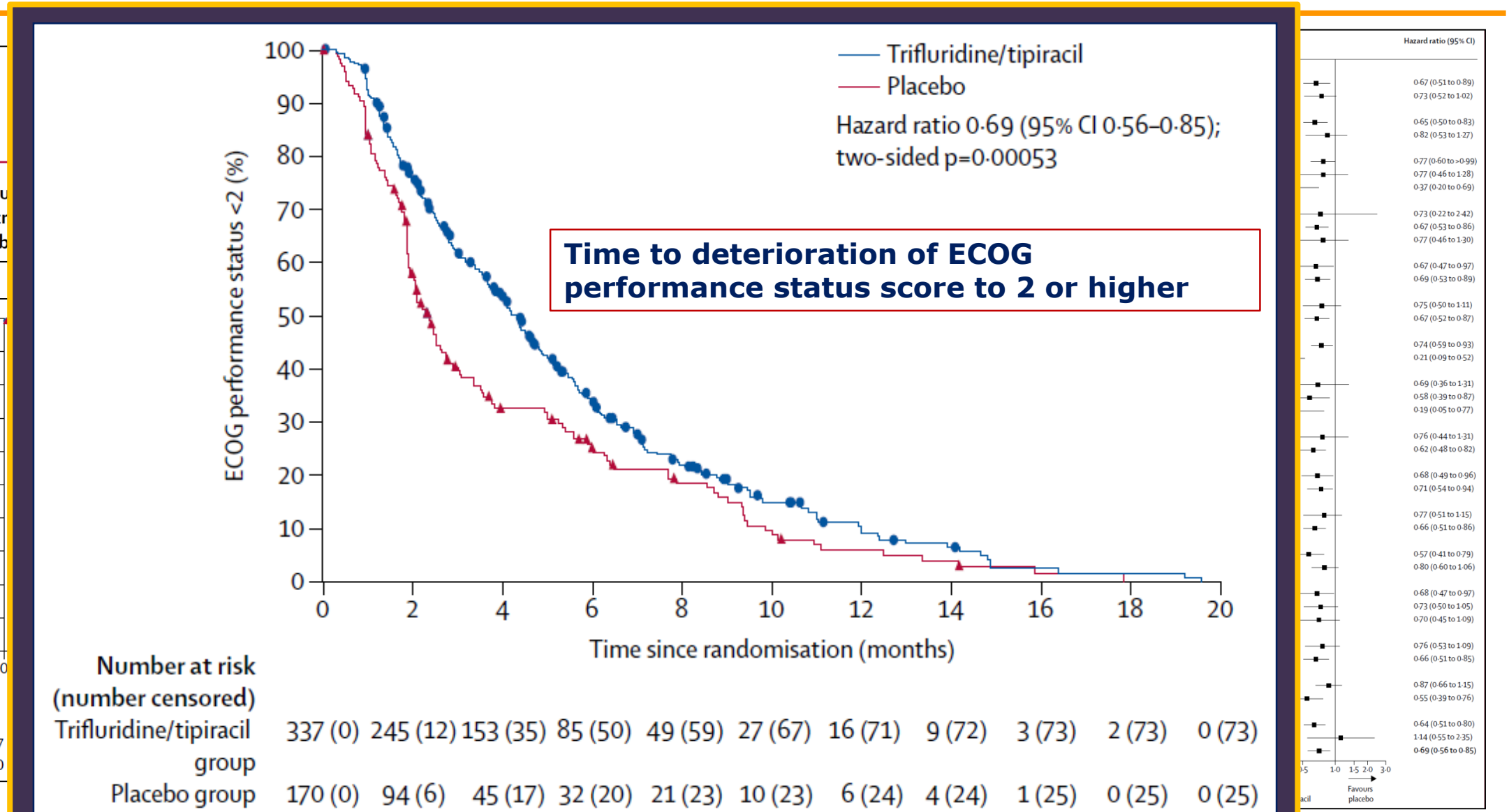
Study or Subgroup	Third-line treatment Events	Total	Best supportive care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Li 2013a	6	46	0	24	34.4%	6.91 [0.41, 117.79]
Li 2013b	3	47	0	24	32.4%	3.65 [0.20, 67.83]
Li 2016	5	176	0	91	33.2%	5.72 [0.32, 102.27]
Total (95% CI)		269		139	100.0%	5.28 [1.00, 27.83]
Total events	14		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours BSC Favous TLT

Chan W, Crit Rev Oncol Hematol 2017

Sequential treatment improves outcome beyond 2nd line CT
Evidence from TAGS trial

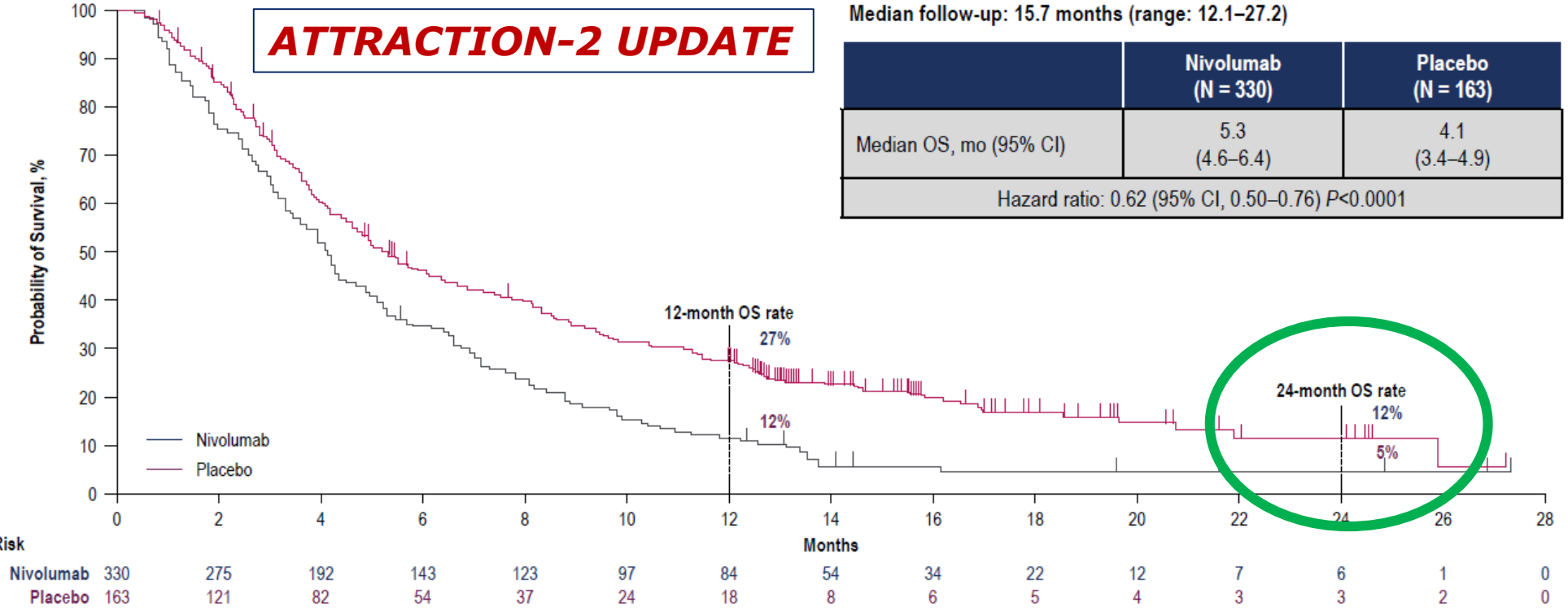


Shitara K, Lancet Oncol 2018

Anti-PD-1 therapy is superior to BSC in CT refractory GC pts
ATTRACTION-2 & KEYNOTE-059

ATTRACTION-02 (Nivolumab) **KEYNOTE-059 (Pembrolizumab)**

ATTRACTION-2 UPDATE



Median follow-up: 15.7 months (range: 12.1–27.2)

	Nivolumab (N = 330)	Placebo (N = 163)
Median OS, mo (95% CI)	5.3 (4.6–6.4)	4.1 (3.4–4.9)
Hazard ratio: 0.62 (95% CI, 0.50–0.76) *P*<0.0001		

Kang Y-K, et al. ASCO-GI, 2017

Fuchs CS, et al. ASCO, 2017
Wainberg ZA, et al. ESMO, 2017

How to select pts for later line treatments?

Median OS was similar for pts receiving CT or PD-1 inhibitors

	TAGS	*ATTRACTION-02*	*KEYNOTE-059*
Med OS (mo)	**5.7**	**5.3**	**5.6**

Clinical features

- ***safety profile***
- ***tumor chemosensitivity***
- ***response to early-line treatment***

Biological features

How to select pts for later line treatments?
Safety profile

TOXICITY	TAGS	ATTRACTION-2	KEYNOTE-059
Anemia	45%/19%		
Neutropenia	53%/34%		
Anorexia	34%/9%		
Diarrhea	23%/3%		
Interstitial lung ds		2%/1%	0.8%
Hypothyroidism		<1%/<1%	0.4%

Arkenau HT, ESMO 2018; Kang YK, Lancet 2017; Kang YK, ESMO 2018

How to select pts for later line treatments?
Tumor chemosensitivity

VOLUME 22 · NUMBER 12 · JUNE 15 2004
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Multivariate Prognostic Factor Analysis in Locally Advanced and Metastatic Esophago-Gastric Cancer—Pooled Analysis From Three Multicenter, Randomized, Controlled Trials Using Individual Patient Data

Ian Chau, Andy R. Norman, David Cunningham, Justin S. Waters, Jacqui Oates, and Paul J. Ross

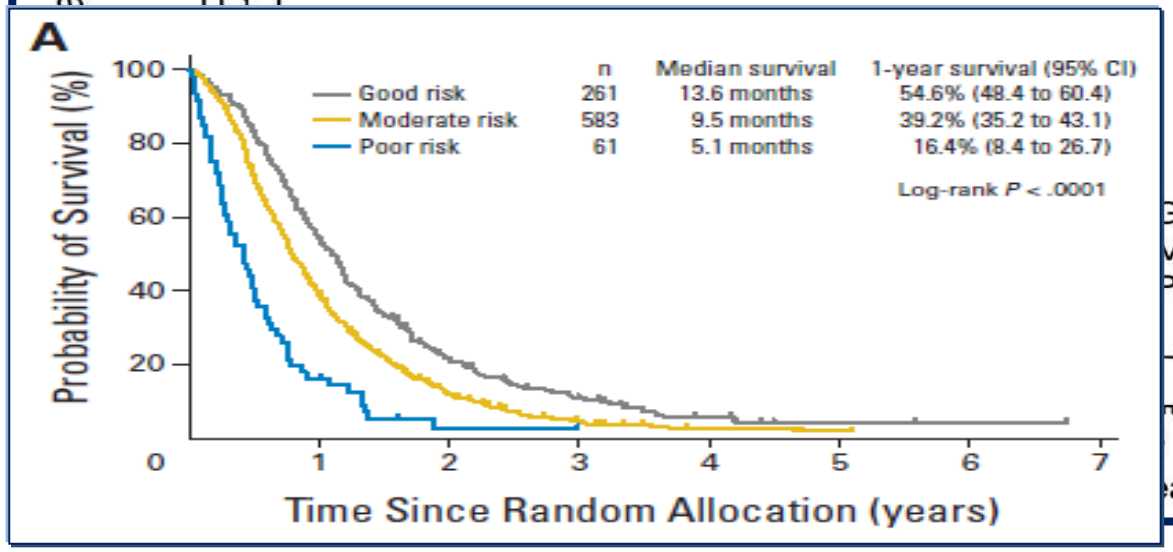
VOLUME 27 · NUMBER 19 · JULY 1 2009
JOURNAL OF CLINICAL ONCOLOGY

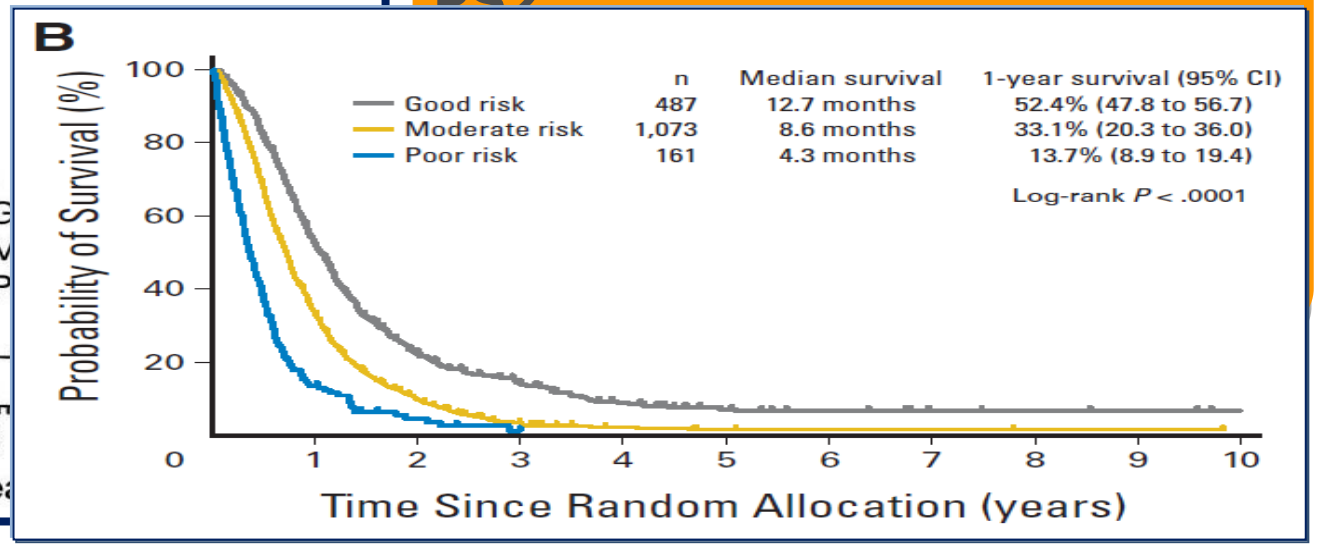
Validation of the Royal Marsden Hospital Prognostic Index in Advanced Esophagogastric Cancer Using Individual Patient Data From the REAL 2 Study

index

ear survival (95% CI)
3.5% (41.9 to 54.7%)
5.7% (22.5 to 29.7%)
% (5.6 to 18.4%)

PS2





Chau I, JCO 2004; Chau I, JCO 2009

How to select pts for later line treatments?
Response to early-line treatment

Table 3. Univariate and multivariate analyses

	Univariate analysis						Multivariate analysis					
	PFS in third-line			OS in third-line			PFS in third-line			OS in third-line		
Variable	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Intensity of treatment												
Doublet/triplet vs. single agent-CT	0.70	0.56–0.89	.004	0.73	0.57–0.93	.012	0.69	0.54–0.88	.003	0.72	0.57–0.93	.010
PFS in first-line												
≥6.9 months vs. <6.9 months	0.70	0.56–0.89	.003	0.65	0.51–0.82	<.0001	0.74	0.58–0.95	.017	0.71	0.55–0.92	.008
PFS in second-line												
≥3.5 months vs. <3.5 months	0.64	0.51–0.81	<.0001	0.57	0.44–0.73	<.0001	0.64	0.50–0.82	<.0001	0.59	0.46–0.77	<.0001
Age												
≥70 years vs. <70 years	0.83	0.64–1.07	.149	0.82	0.63–1.06	.126	—	—	—	—	—	—

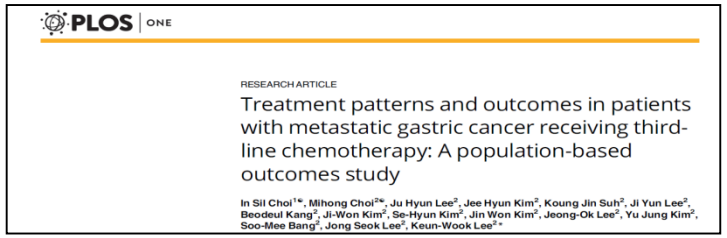

The Oncologist

Gastrointestinal Cancer

Outcomes of Advanced Gastric Cancer Patients Treated with at Least Three Lines of Systemic Chemotherapy

Valentina Fanotto,[a] Mario Uccello,[b] Irene Pecora,[c] Lorenza Rimassa,[d] Francesco Leone,[e] Gerardo Rosati,[f] Daniele Santini,[g] Riccardo Giampieri,[h] Samantha Di Donato,[i] Gianluca Tomasello,[j] Nicola Silvestris,[k] Filippo Pietrantonio,[l] Francesca Battaglin,[m] Antonio Avallone,[n] Mario Scartozzi,[o] Eufemia Stefania Lutrino,[p] Davide Melisi,[q] Lorenzo Antonuzzo,[r] Antonio Pellegrino,[s] Laura Ferrari,[a] Roberto Bordonaro,[b] Caterina Vivaldi,[c] Lorenzo Gerratana,[a] Silvia Bozzarelli,[d] Roberto Filippi,[e] Domenico Bilancia,[f] Marco Russano,[g] Giuseppe Aprile[g,t]

868 pts with mGC
300 treated with a third-line CT


PLOS ONE

RESEARCH ARTICLE

Treatment patterns and outcomes in patients with metastatic gastric cancer receiving third-line chemotherapy: A population-based outcomes study

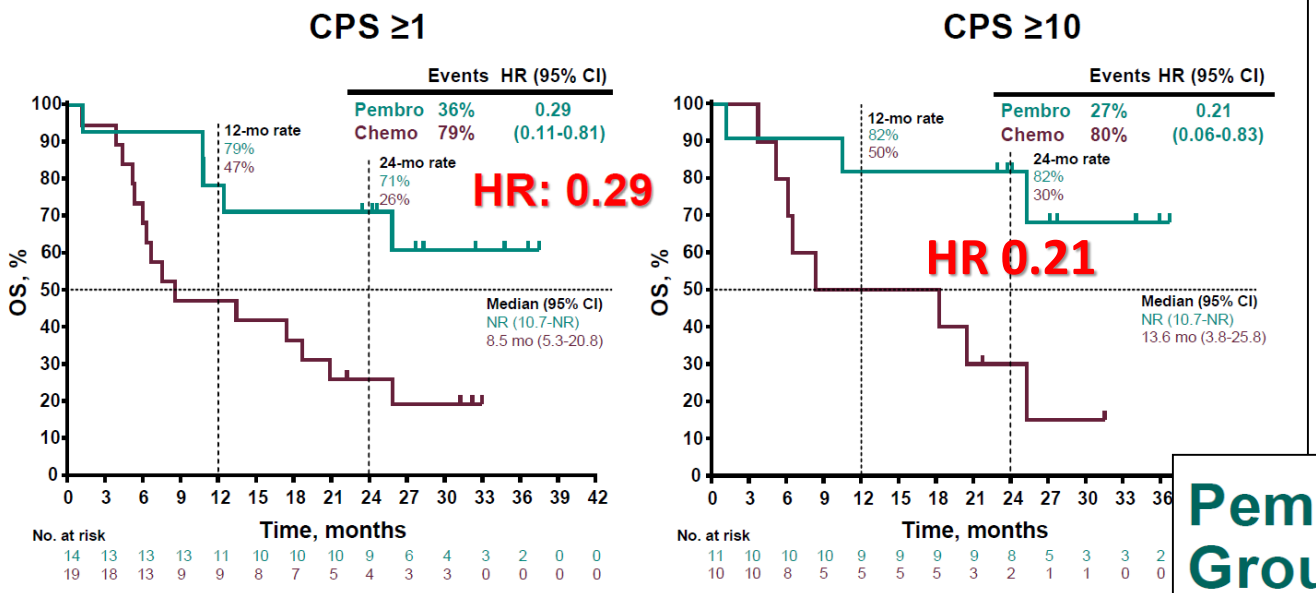
In Sil Choi[1*], Mihong Choi[2*], Ju Hyun Lee[2], Jee Hyun Kim[2], Koung Jin Suh[2], Ji Yun Lee[2], Beodeul Kang[2], Ji-Won Kim[2], Se-Hyun Kim[2], Jin Won Kim[2], Jeong-Ok Lee[2], Yu Jung Kim[2], Soo-Mee Bang[2], Jong Seok Lee[2], Keun-Wook Lee[2,3]

1871 pts with mGC
229 treated with a third-line CT

		Univariable analysis			Multivariable analysis	
	N	Overall survival (months; median)	*p*	Hazard ratio	95% confidence interval	*p*
Sex			0.676			0.873
Male	159	4.3	-	1.00	-	-
Female	70	4.6	-	0.98	0.73–1.31	-
Age (year)			0.875			
< 70	206	4.3	-	1.00	-	-
≥ 70	23	4.5	-	1.07	0.67–1.71	-
Duration from first-line to third-line chemotherapy			< 0.001			< 0.001
< 9.5 months (median)	111	3.3	-	1.00	-	-
≥ 9.5 months (median)	118	5.3	-	0.53	0.40–0.70	-
Chemotherapy regimens			0.985			0.961
FOLFOX	33	4.3	-	1.00	-	-
Taxane-based therapy	67	4.6	-	1.04	0.67–1.62	0.863
Irinotecan-based therapy	98	4.2	-	0.98	0.65–1.47	0.909
Others	31	4.7	-	0.92	0.55–1.55	0.762

Biological features: a key question for immunotherapy
Data from KEYNOTE-062

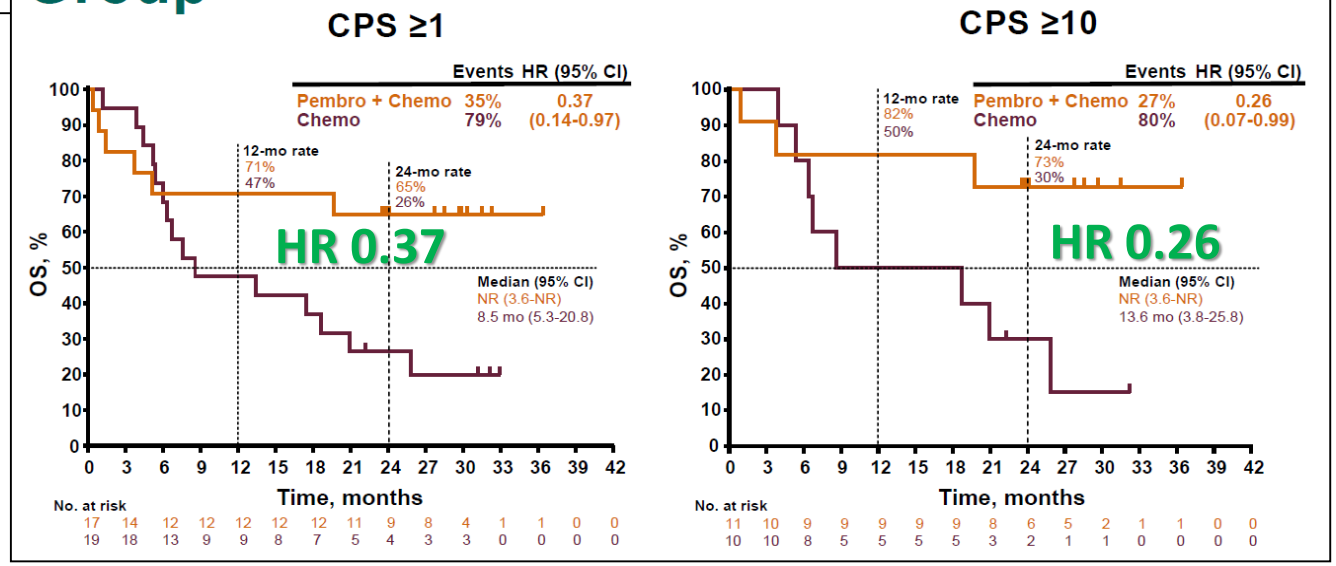
Pembro vs Chemo: OS in MSI-H Group



Pembro vs CT: OS	HR
NON-MSI	
CPS≥1	**0.94**
CPS≥10	**0.76**
MSI-H	
CPS≥1	**0.29**
CPS≥10	**0.21**

Pembro vs CT: OS	HR
ALL POPULATION	
CPS≥1	**0.91**
CPS≥10	**0.69**
MSI-H	
CPS≥1	**0.29**
CPS≥10	**0.21**

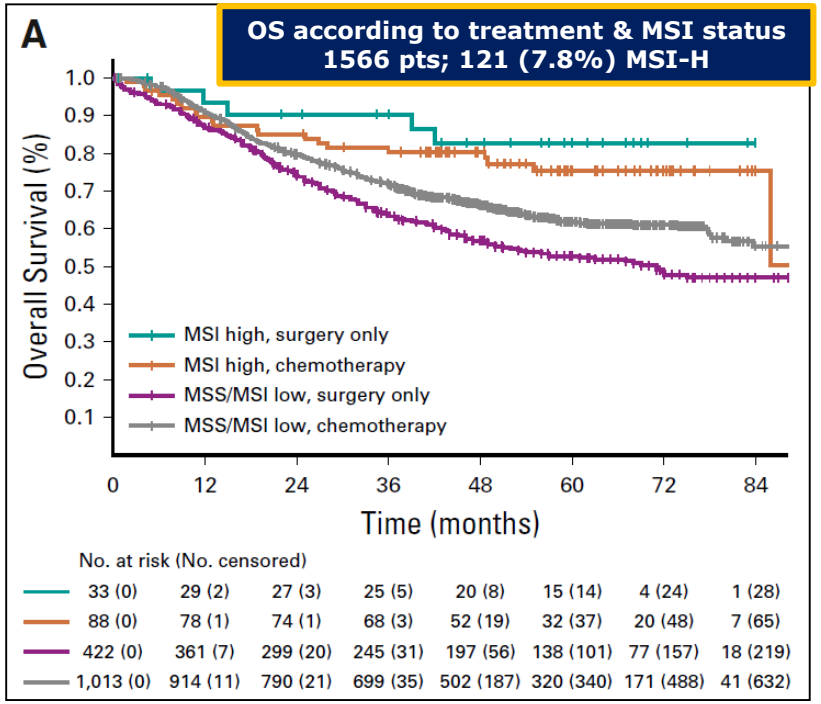
Pembro + Chemo vs Chemo: OS in MSI-H Group



Shitara K, et al. ESMO 2019

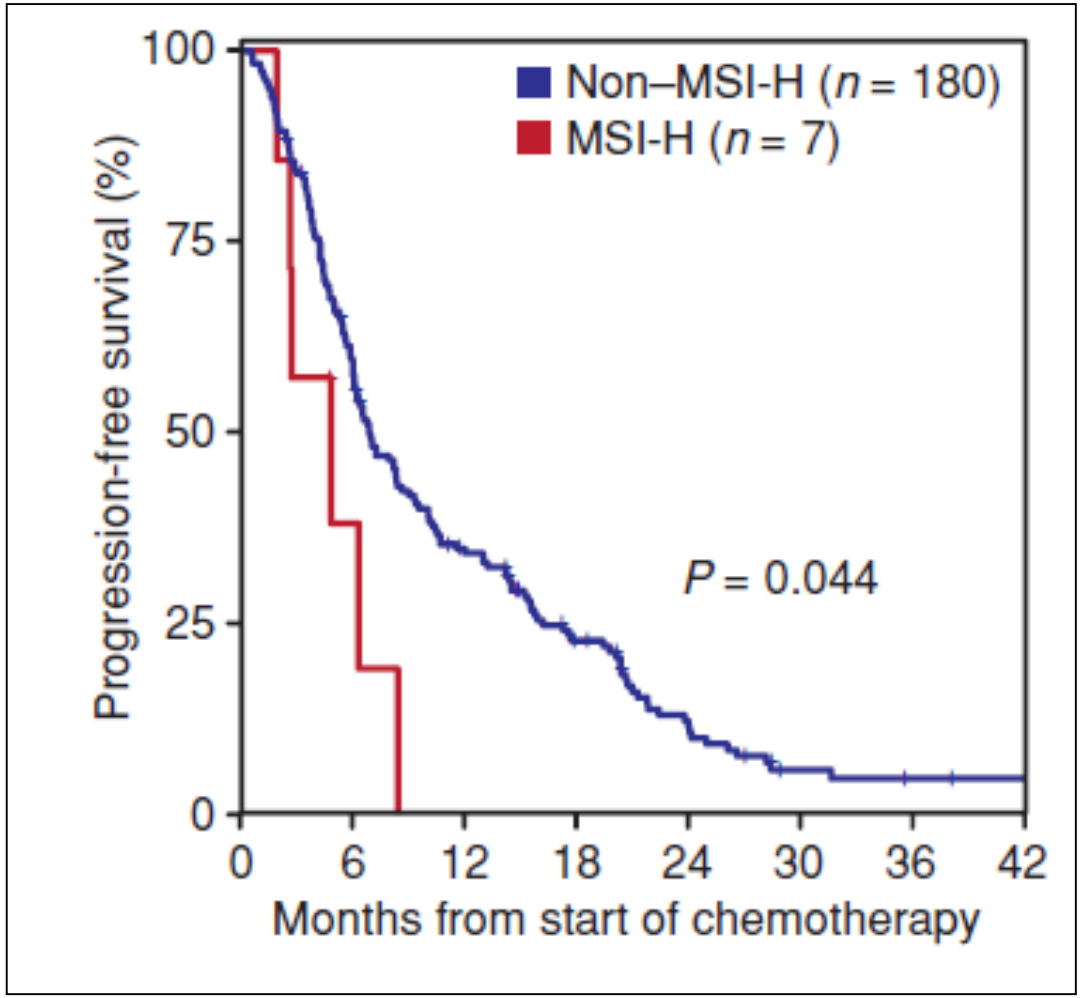
How to select pts for later line treatments?
Biological features: for MSI-H tumors CT may not be effective

OS according to treatment & MSI status
1566 pts; 121 (7.8%) MSI-H



Treatment Comparison by MSI Status and Survival Type	MAGIC + CLASSIC + ITACA-S + ARTIST No. of Events	5-Year Survival, % (95% CI)	HR (95% CI)	P*
OS				
MSS/MSI low: CT + surgery *v* surgery only	368 *v* 198	62.0 (58.9 to 65.3) *v* 52.8 (48.0 to 58.0)	0.75 (0.60 to 0.94)	.180
MSI high: CT + surgery *v* surgery only	21 *v* 5	75.4 (66.4 to 85.6) *v* 82.8 (70.1 to 97.8)	1.50 (0.55 to 4.12)	

PFS on first-line platinum-based therapy for pts with MSI-H vs. non–MSI-H tumors



Pietrantonio F, JCO 2019; Janjigian YY, Cancer Discovery 2018

Gastric cancer immune environment

EBV
- EBV-CIMP
- *PIK3CA* mutation
- *PD-L1/2* overexpression

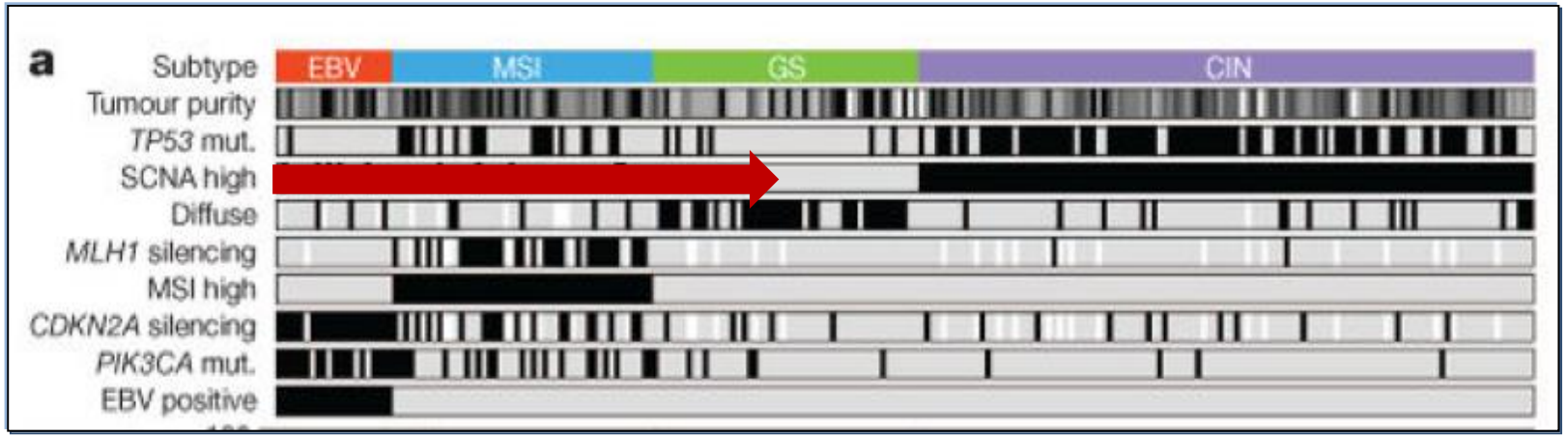
Rare in metastatic patients
PD-L1:
tumour ++ TILs +++
High IFNγ signature

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing

Rare in metastatic patients
PD-L1:
tumour ++ TILs ++
High IFNγ signature

CIN
- *ERBB2* amplification
- *VEGFA* amplification
- *TP53* mutation

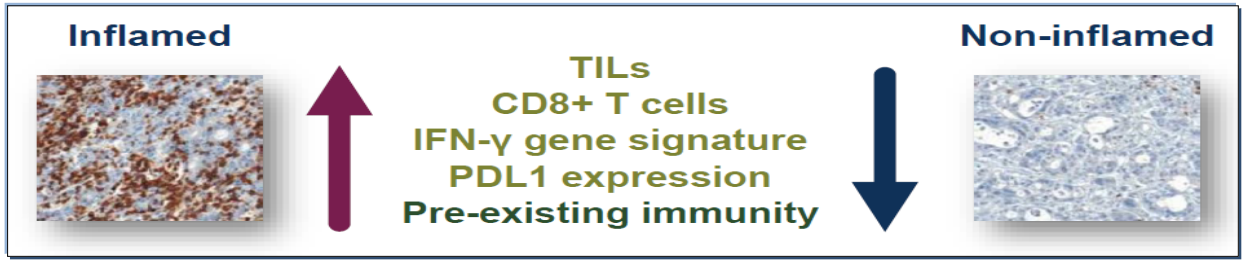
Copy number changes:
Low immune score
Low IFNγ signature



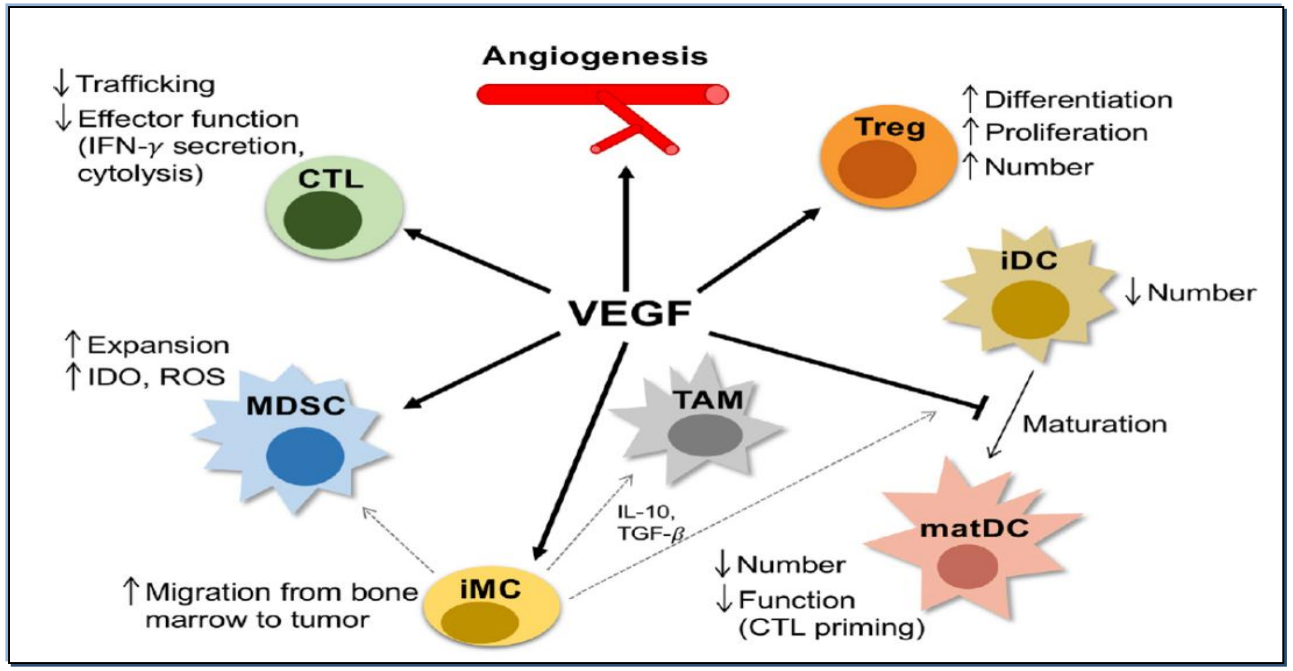
Copy number alterations associated with low immune gene expression

Amplification associated with immune ignorance: VEGFA, ERB-B2

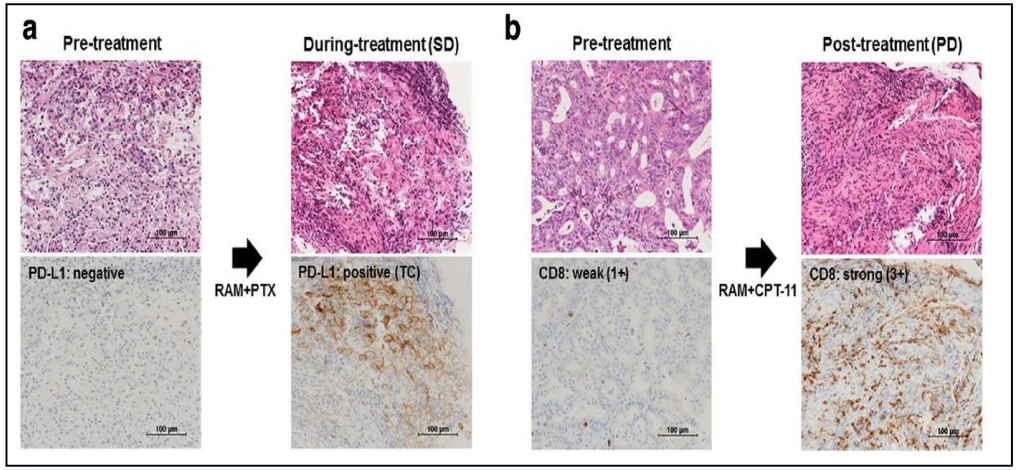
Can we turn cold tumors into hot tumors?
Anti-PD1 and anti-angiogenic inhibitors

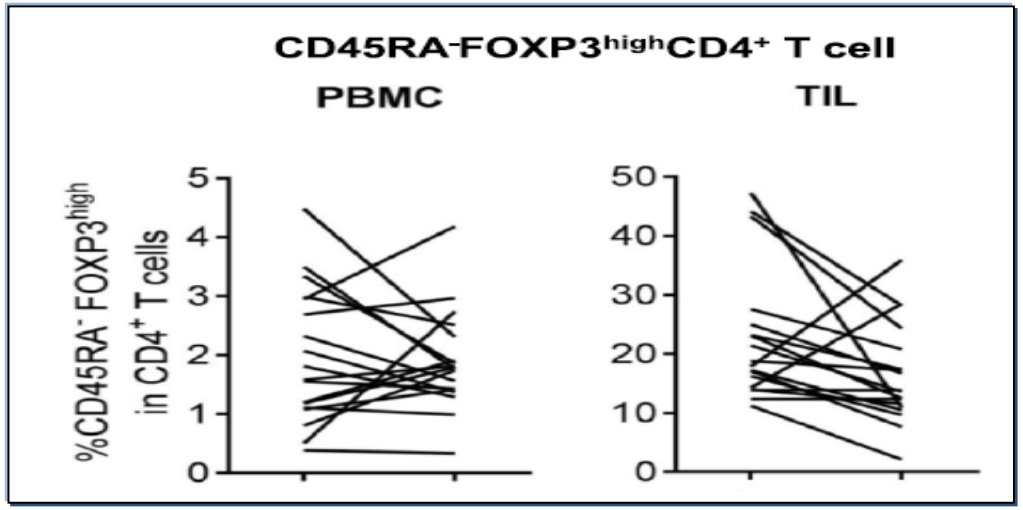


The role of VEGFA in immune suppression



Ramucirumab induces CD8+ T-cell infiltration and decreases Treg cells

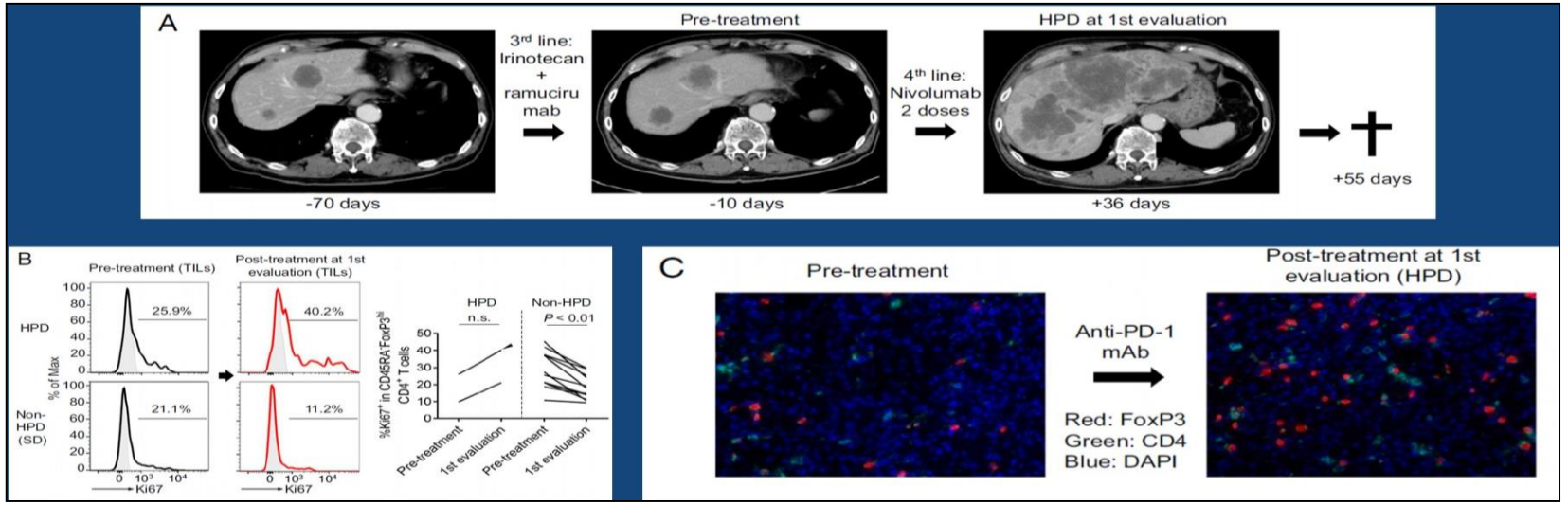


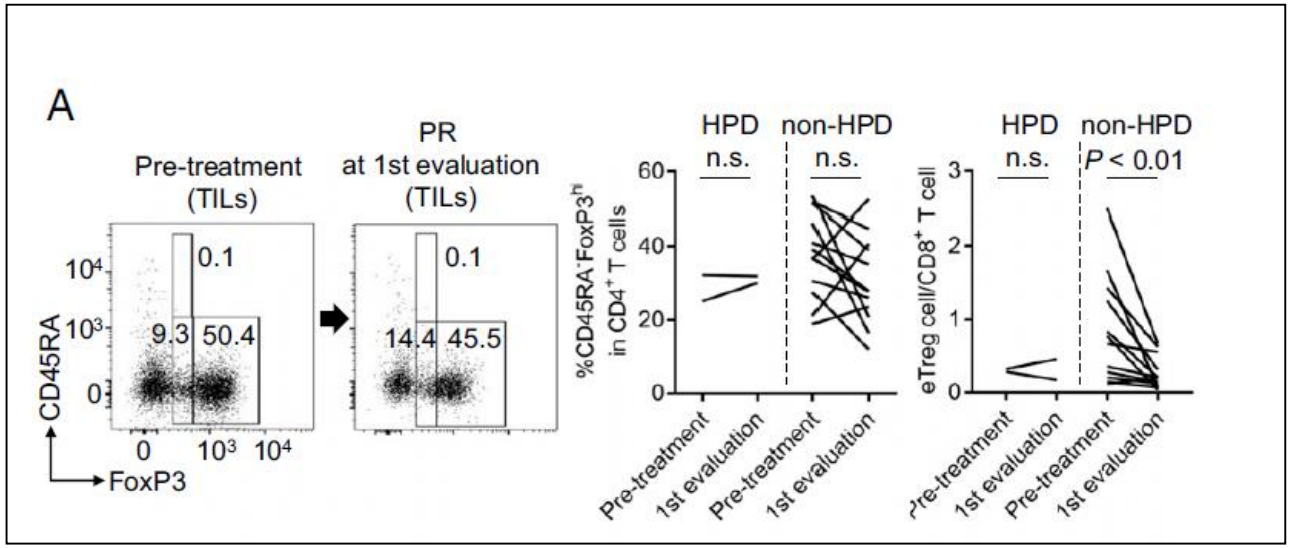


Datta M, ASCO 2019; Tada T, J Immunother Cancer 2018

Can we turn cold tumors into hot tumors?
Anti-PD1 and anti-angiogenic inhibitors

PD-1 blockade may facilitate the proliferation of highly suppressive PD-1+ eTreg cells in HPDs





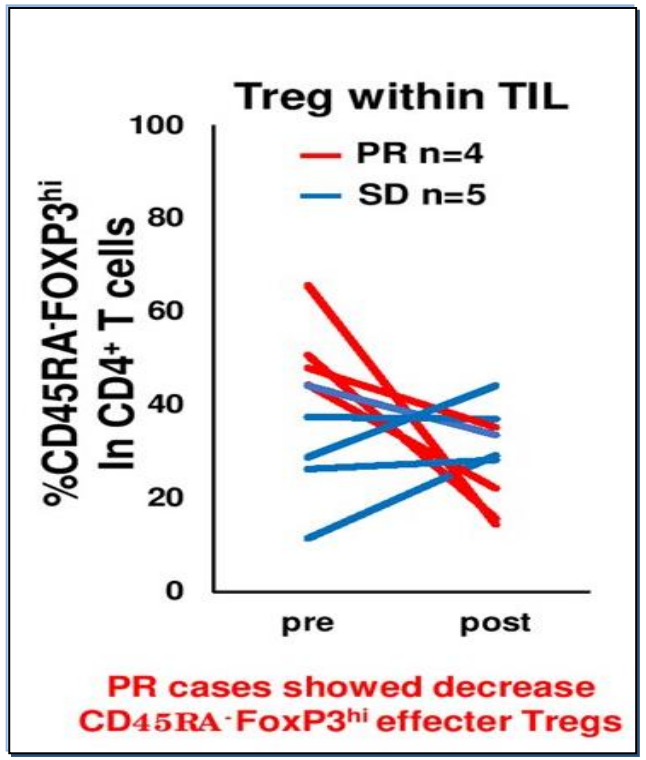
Kamada T, PNAS 2019

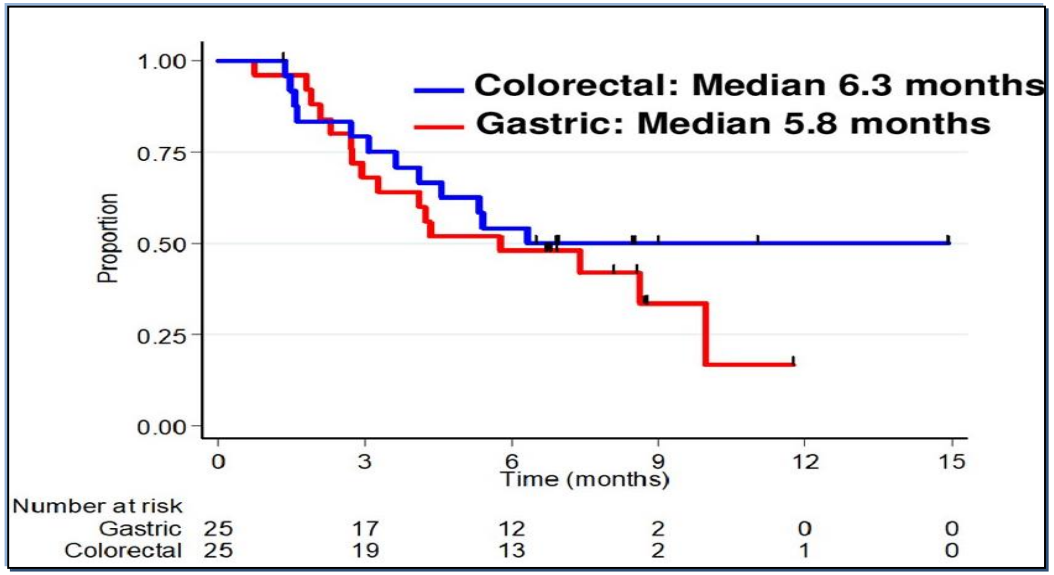
Can we turn cold tumors into hot tumors?
Anti-PD1 and anti-angiogenic inhibitors

Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): an open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603)

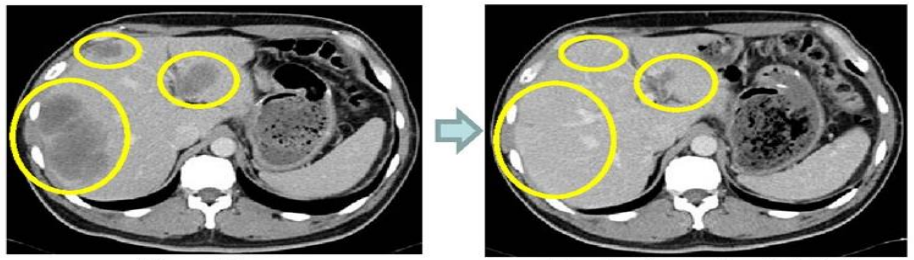
Shota Fukuoka[1], Hiroki Hara[2], Naoki Takahashi[2], Takashi Kojima[1], Akihito Kawazoe[1], Masako Asayama[2], Takako Yoshii[2], Daisuke Kotani[1], Hitomi Tamura[3] Yuichi Mikamoto[3], Ayako Sugama[3], Masashi Wakabayashi[3], Shogo Nomura[3], Yosuke Togashi[4], Hiroyoshi Nishikawa[4], Kohei Shitara[1]
1) Department of Gastroenterology, National Cancer Center Hospital East, Kashiwa, Japan 2) Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan
3) Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan 4) Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan
Contact e-mail: shfukuok@east.ncc.go.jp

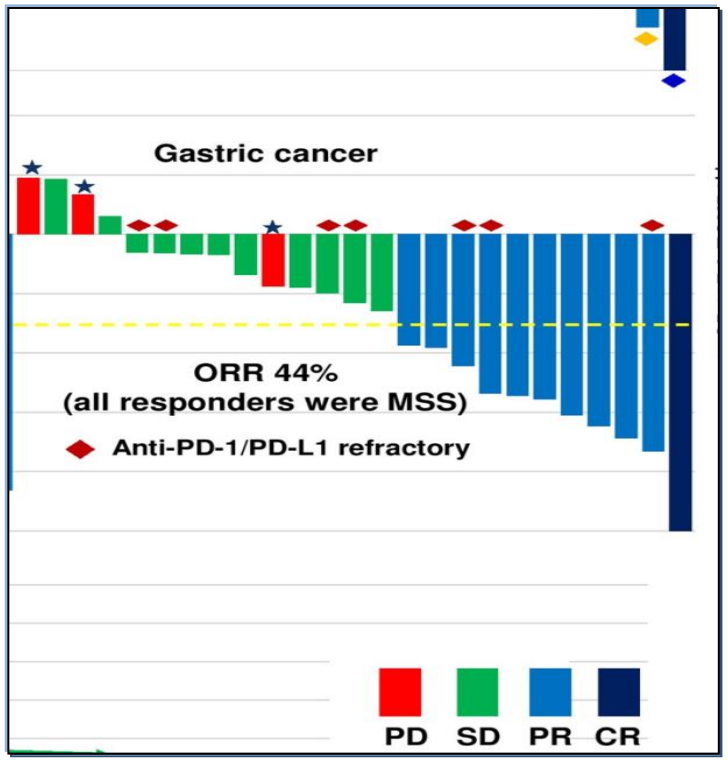
Abstract No. 2522





- 45-year-old male with HER2-negative metastatic gastric cancer
- Disease progression after S1+oxaliplatin, paclitaxel+ramucirumab
- MSS, PD-L1 CPS 1, EBV negative





Fukuoka S, ASCO 2019

Can we turn cold tumors into hot tumors?
Anti-PD1 and anti-HER2 inhibitors

Janjigian_KN375_ASCO-GI_2019

Pembrolizumab/Trastuzumab/Chemotherapy

Janjigian_KN375_ASCO-GI_2019

KEYNOTE-811
Global Randomized Double-Blind Phase III Trial
Pembrolizumab/Trastuzumab/Chemotherapy vs. Placebo/Trastuzumab/Chemotherapy
NCT03615326

1st line Stage IV Gastric/GEJ Cancer

HER2 IHC 3+ or IHC 2+/FISH>2.0

Central confirmation required prior to Rx

RECIST measurable disease

N=692

Pembrolizumab
Trastuzumab/Chemotherapy
N=346

Placebo
Trastuzumab/Chemotherapy
N=346

Stratification: PD-L1 status, Region (Asia vs. US vs. ROW), and chemotherapy regimen
Cisplatin + 5-FU or CapeOx or SOX

Primary enpoint: Dual endpoint PFS and OS
Secondary enpoint: ORR, Biomarker analysis

PI Janjigian

Memorial Sloan Kettering Cancer Center

Janjigian YY, ASCO 2019

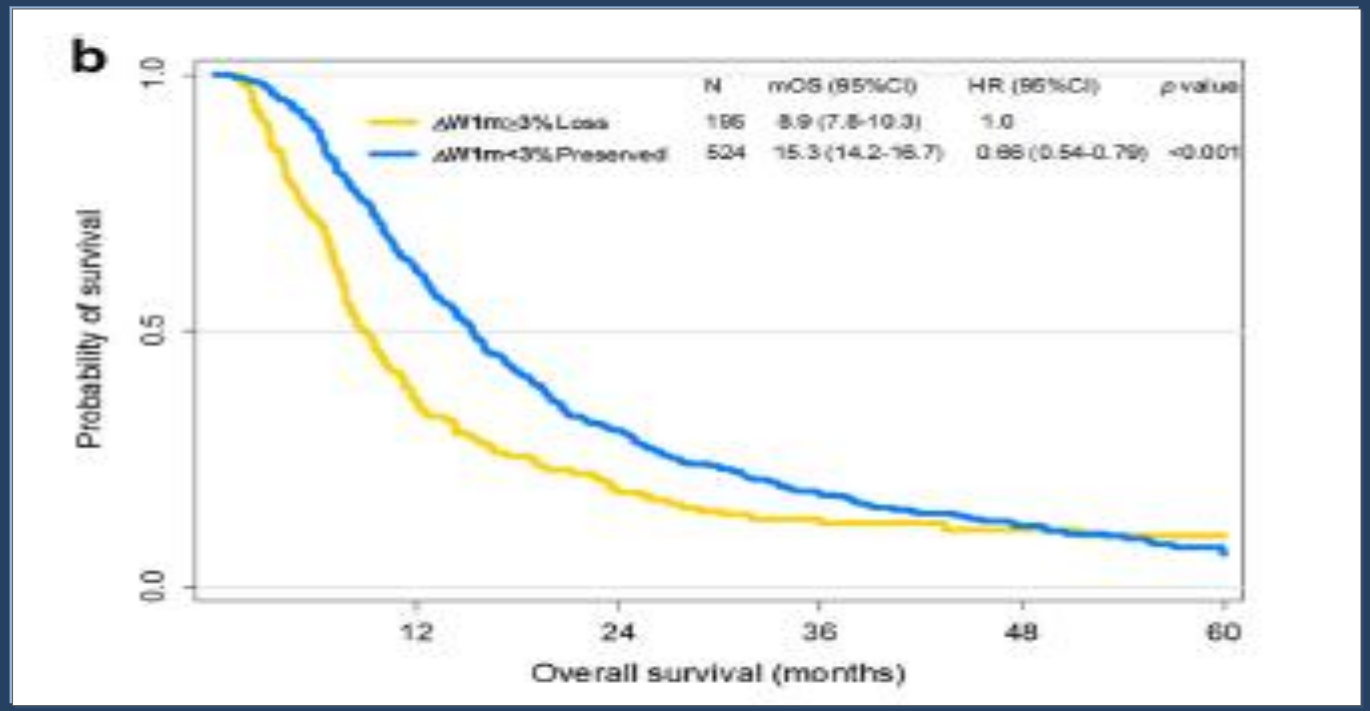
Metastatic setting treatment
Sequential treatment improves outcome

SIGNIFICANCE OF NUTRITIONAL STATUS IN PTS RECEIVING CT FOR MGC

Gastric Cancer (2016) 19:597–606
DOI 10.1007/s10120-015-0481-4

ORIGINAL ARTICLE

Weight loss at the first month of palliative chemotherapy predicts survival outcomes in patients with advanced gastric cancer



Chan YO, Gastric Cancer 2016

I line

regimen

BS
C
FOLFI
DC
EC
X
EO
C+S
Trastuzumab +X/F
TAX/RA
Ramucirum
Docetax
Irinoteca

II LINE

III linea

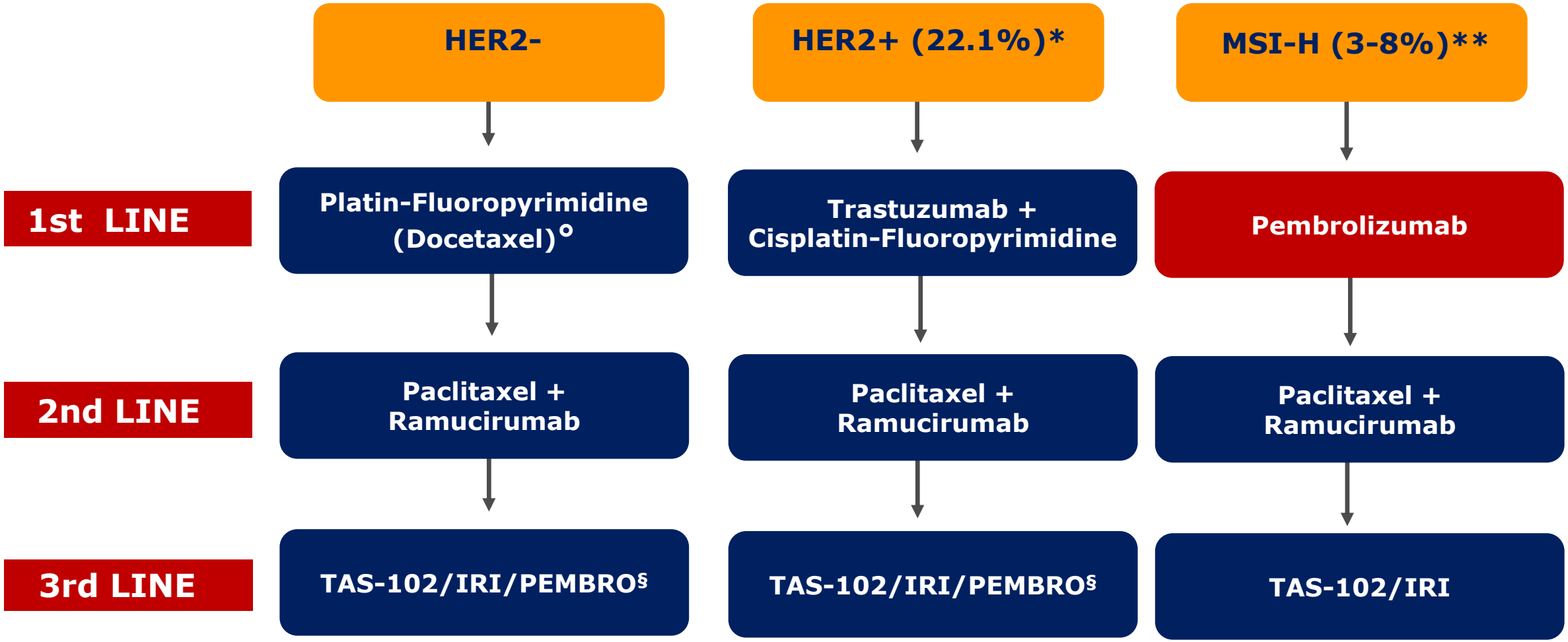
TAS-102/NIVO

30

median os (months)

mod. from Salati M, ESMO Open 2017

Biomarker-driven therapy for mGC PS 0/1 pts
A new perspective



**ToGA data*
***MSKCC data; KEYNOTE-062 data*

°Triplet if high tumor burden, locally advanced unresectable disease & oligometastatic disease

§PD-L1 ≥CPS10

“A Journey of a Thousand Miles Begins with a Single Step”

Lau Tzu, 6th century BC

Thank you for your attention