Metastatic Gastroesophageal Cancers: Current and Emerging Treatment Options

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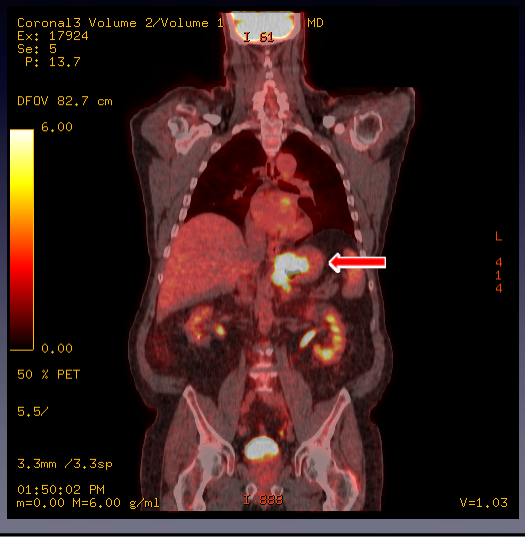
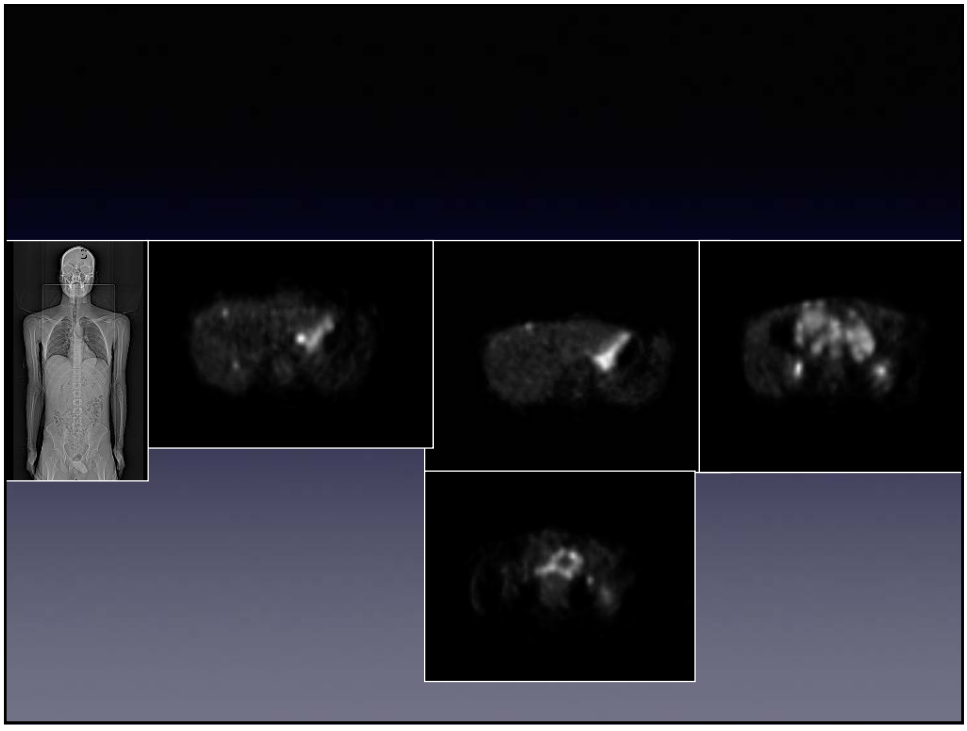
Newly-diagnosed gastric cancer



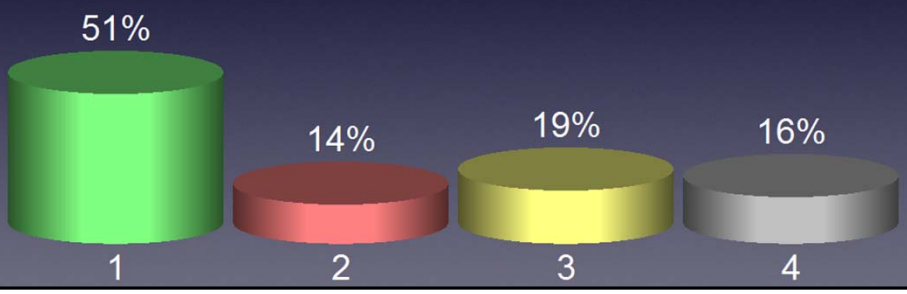
Audience Polling Results

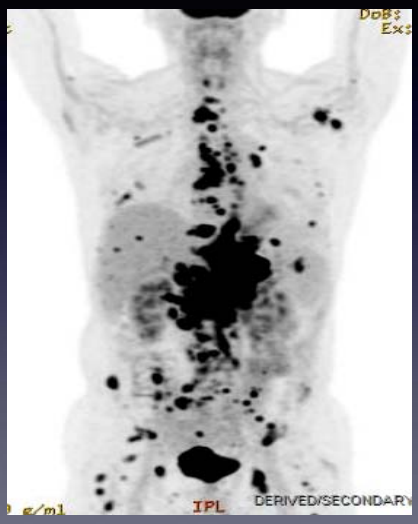


Audience Polling Results

This patient has a HER2 positive GAC. You will add transtuzumab to which of the following combinations?

1. Fluropyridimine plus a platinum compound
2. ECF or ECF modification
3. DCF or DCF medication
4. Irinotecan-based therapy

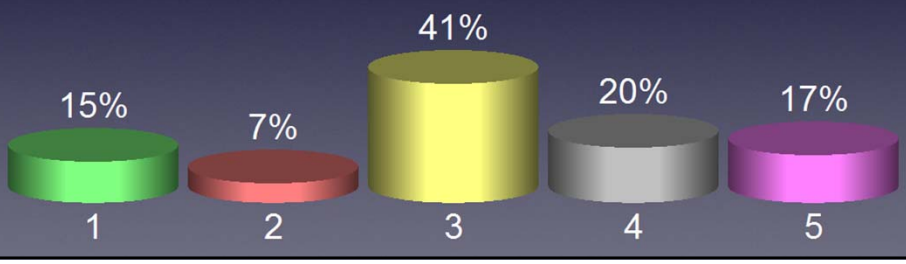




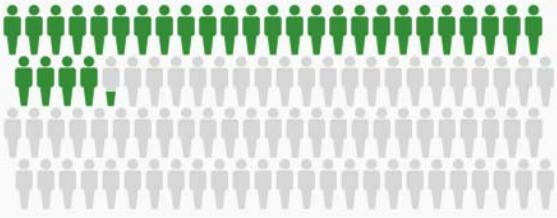
Audience Polling Results

This patient has a HER2 negative GAC. You will start him on which of the following?

1. Cisplatin + 5 FU
2. ECF or medication
3. Oxaliplatin + Fluropyrimidine
4. FOLFIRI
5. Add ramucirumab to any of the above



Gastric Adenocarcinoma (GAC)



Percent Surviving 5 Years

29.3%

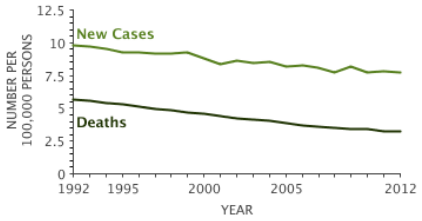
Based on data from SEER 18 2005–2011. Gray figures represent those who have died from stomach cancer. Green figures represent those who have survived 5 years or more.

SEER Cancer Statistics Factsheets: Stomach Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/stomach.html

GAC

› At a Glance

Estimated New Cases in 2015	24,590
% of All New Cancer Cases	1.5%
Estimated Deaths in 2015	10,720
% of All Cancer Deaths	1.8%



Percent Surviving 5 Years

29.3%

2005–2011

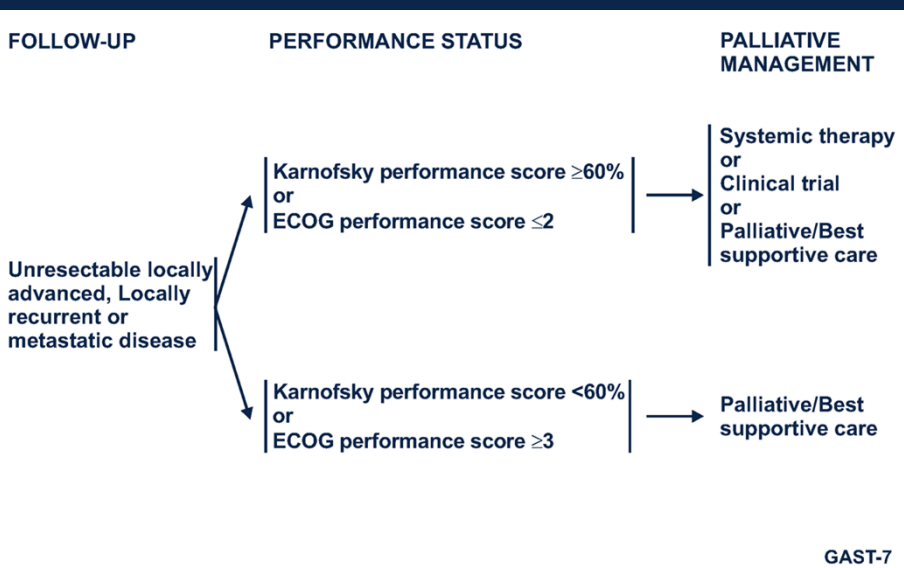
SEER Cancer Statistics Factsheets: Stomach Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/stomach.html

Metastatic GAC

Median Survival for all comers: 9-10 months

Most patients are very Symptomatic and nutritionally deficient

2-year survival = 30 %
3-year survival = 20 %
5-year survival = <3 %



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Gastric Cancer

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of Overexpression of HER2-neu in Gastric Cancer

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended. The following criteria used in the ToGA trial are recommended:

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TABLE 3

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Immunohistochemical Criteria for Scoring HER2-neu Expression in Gastric and Esophagogastric Carcinoma*,#

	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2-neu Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

#The NCCN Guidelines panel recommends that cases showing less than 3+ overexpression of HER2-neu by immunohistochemistry should be additionally examined by FISH or other in situ hybridization methods. Cases with 3+ overexpression by IHC or FISH positive (HER2:CEP17 ratio ≥2) are considered positive.

*Reprinted and adapted from The Lancet, 376(9742), Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. pages 687-697, 2010, with permission from Elsevier.

GAST-B 3 of 4

Trastuzumab FDA Update

Table 13

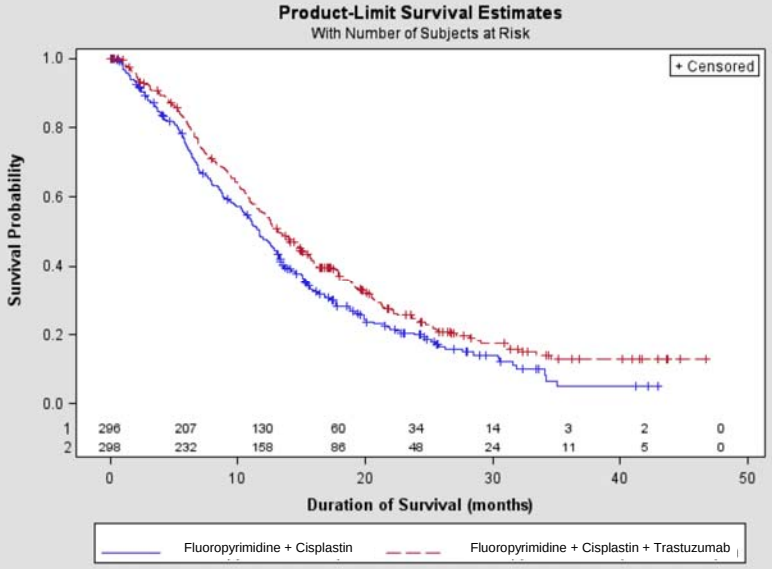
Study 7: Overall Survival in ITT Population

	FC Arm N=296		FC + H Arm N=298
Definitive (Second Interim) Overall Survival			
No. Deaths (%)	184 (62.2%)		167 (56.0%)
Median	11.0		13.5
95% CI (mos.)	(9.4, 12.5)		(11.7, 15.7)
Hazard Ratio		0.73	
95% CI		(0.60, 0.91)	
p-value*, two-sided		0.0038	
Updated Overall Survival			
No. Deaths (%)	227 (76.7%)		221 (74.2%)
Median	11.7		13.1
95% CI (mos.)	(10.3, 13.0)		(11.9, 15.1)
Hazard Ratio		0.80	
95% CI		(0.67, 0.97)	

* Comparing with the nominal significance level of 0.0193.

Trastuzumab Prescribing information.

Updated Trastuzumab Survival Benefit



Trastuzumab Prescribing Information.

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Gastric Cancer

PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.**
- **Trastuzumab should be added to chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.**
- **Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.**

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PRINCIPLES OF SYSTEMIC THERAPY

- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.
- Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.
- Perioperative chemotherapy, or postoperative chemotherapy plus chemoradiation is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection. (See Principles of Surgery [GAST-C])
- Induction chemotherapy may be appropriate as clinically indicated.
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

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Gastric Cancer

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Metastatic or Locally Advanced Cancer
(where local therapy is not indicated)

First-Line Therapy

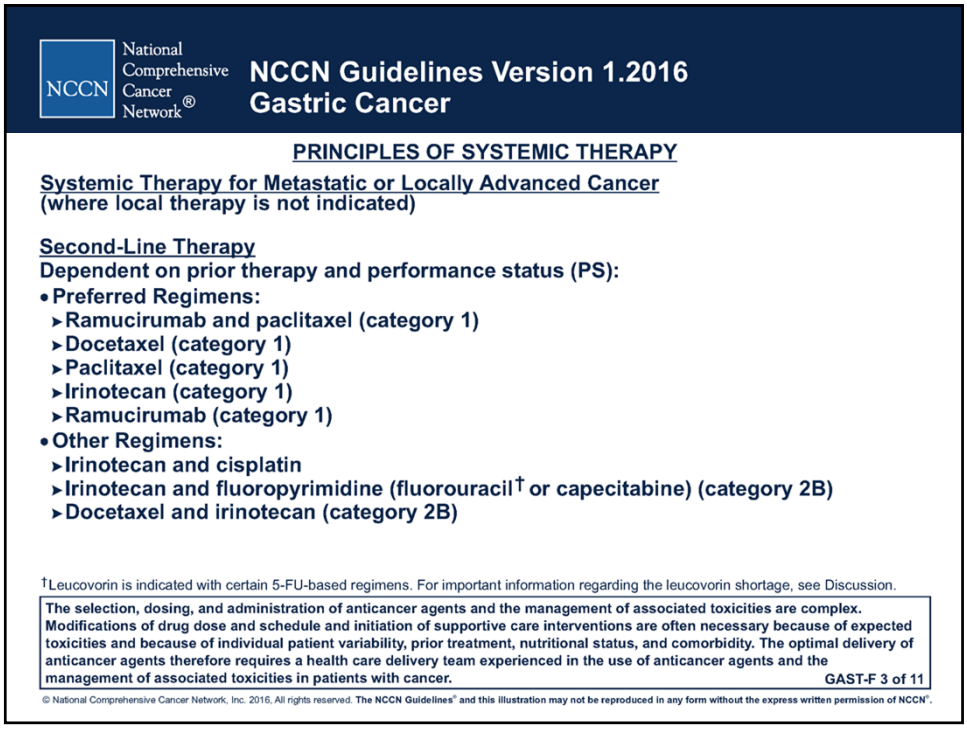
Two-drug cytotoxic regimens are preferred because of lower toxicity.
Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- **Preferred Regimens:**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin (category 1)**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin**

†Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, see Discussion.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

- **Other Regimens:**
  - **Paclitaxel with cisplatin or carboplatin**
  - **Docetaxel with cisplatin**
  - **Fluoropyrimidine (fluorouracil† or capecitabine)**
  - **Docetaxel**
  - **Paclitaxel**
  - **Fluorouracil† and irinotecan (category 1)**
  - **DCF modifications**
    - **Docetaxel, cisplatin, and fluorouracil**
    - **Docetaxel, oxaliplatin, and fluorouracil†**
    - **Docetaxel, carboplatin, and fluorouracil (category 2B)**
  - **ECF (epirubicin, cisplatin, and fluorouracil) (category 1)**
  - **ECF modifications (category 1)**
    - **Epirubicin, oxaliplatin, and fluorouracil**
    - **Epirubicin, cisplatin, and capecitabine**
    - **Epirubicin, oxaliplatin, and capecitabine**



Metastatic GAC

Only the following drugs have been approved:

Docetaxel in first line

Trastuzumab in the first line with other cytotoxics

Ramucirumab (alone or with paclitaxel) in second line

Metastatic GAC

Drugs that are grand fathered in and still useful:

Fluoropyrimidines Any line

Platinum compounds First line

Irinotecan in second or third line

Metastatic GAC

Agents that are not recommended:

Epirubicin Any line

Mitomycin Any line

Metastatic GAC

Standard of care recommendations:

Add trastuzumab to 2-drug cytotoxic combo for Her2 positive GAC patients in the front line

Otherwise

Platinum plus fluoropyrimidine in the first line

Paclitaxel/ramucirumab in the second line and

Irinotecan plus/minus fluoropyrimidine in the third line

Metastatic GAC

Some general principles when treating these patients:

Two drugs are better than one (Spirits trial)

Three drugs are not necessarily better than two

Do not use ramucirumab alone (not effective)

If possible, always consider paclitaxel/ramucirumab

Do not recommend taxane in the first line

Do not recommend epirubicin at all

No benefit for anthracycline

- Peri-operative chemotherapy:

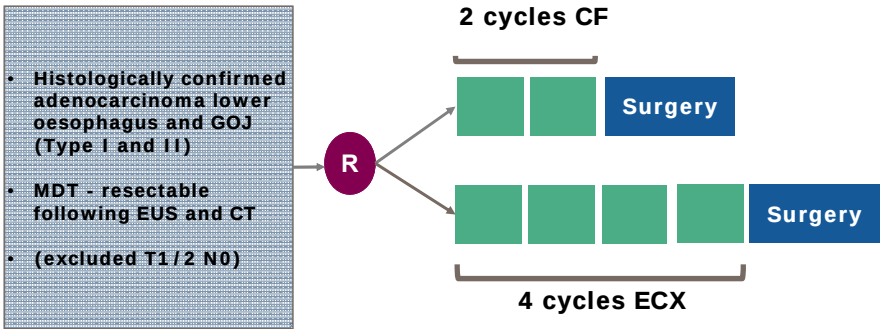
Study	No. of Pts	Treatment	Surgery-only	Peri-op chemo
MAGIC[1]	503	ECF	5-yr 23%	5-yr 36%
FNCLCC/FFCD[2]	224	5-FU/Cis	5-yr 24%	5-yr 38%

- Adjuvant chemoradiation:[3]
  - CALGB 80801 study: 5-FU/LV + chemoRT vs. ECF + chemoRT

1. Cunningham, NEJM 2006;355:11
2. Ychou, J Clin Oncol 2011;29:1715
3. Fuchs, J Clin Oncol 2011;29:4003 [abstr]

Presented By Geoffrey Ku at 2015 ASCO Annual Meeting

OEO5 Trial Design



- CF: Two 3-weekly cycles of cisplatin (80mg/m² D1) and 5FU (1g/m² D 1-4)
- ECX: Four 3-weekly cycles of epirubicin (50mg/m² D1), cisplatin (60mg/m² D1) and capecitabine (1250mg/m² daily)

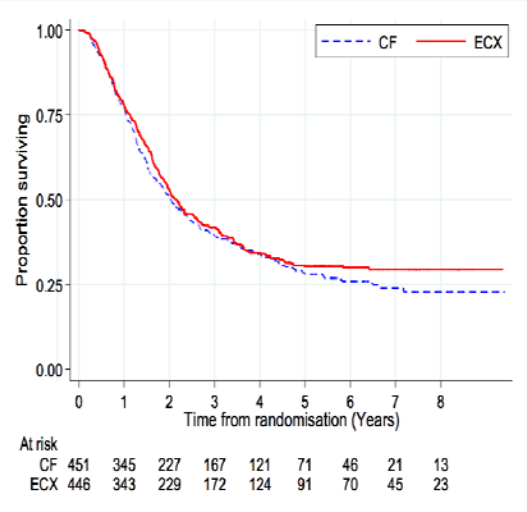
Cunningham D, et al. J Clin Oncol 2014;32 (15_suppl):Abstract 4014.

Baseline Characteristics

897 patients, Jan 2005 – Oct 2011 72 UK centers		CF (N=451)		ECX (N=446)	
		n	%	n	%
Age (years)	Median (Range)	62 (27 – 81)		62 (33 – 80)	
Sex	Male	412	91%	398	89%
WHO PS	0	311	69%	292	65%
	1	140	31%	154	35%
Stage (TNM6)	T1 N1	3	1%	5	1%
	T2 N1	49	11%	41	9%
	T3 N0	97	22%	99	22%
	T3 N1	287	64%	289	65%
	T4 N0	3	1%	1	<1%
	T4 N1	12	3%	11	2%
Laparoscopy	Yes	216	48%	213	48%
PET	Yes	271	60%	270	61%

Cunningham D, et al. J Clin Oncol 2014;32 (15_suppl):Abstract 4014.

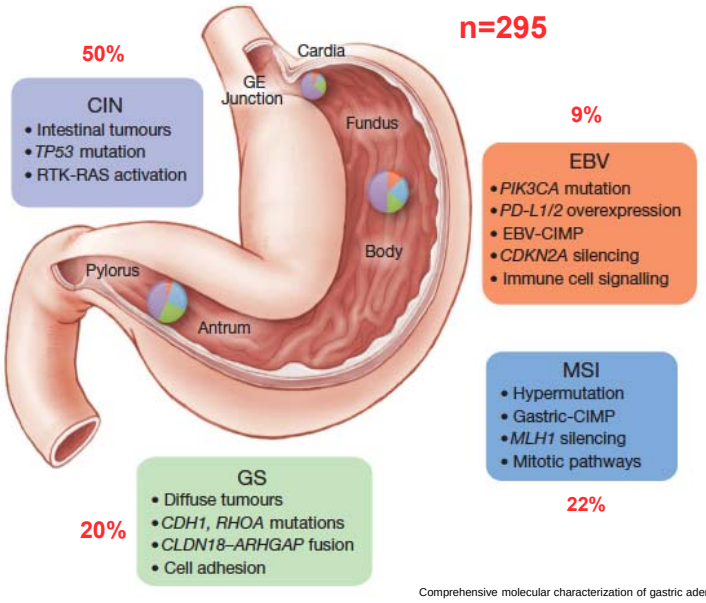
Overall Survival



Median survival (95% CI)	
CF	2.02 (1.80, 2.38)
ECX	2.15 (1.93, 2.53)
HR	0.92 (0.79, 1.08)
P-value	0.8582
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)

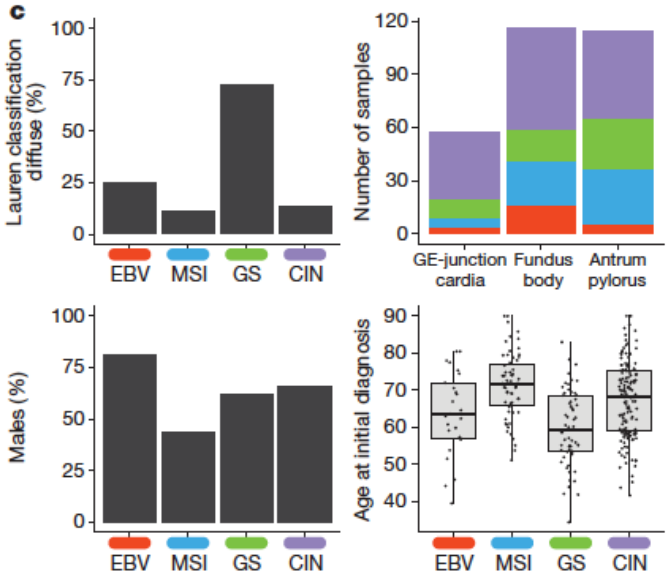
Cunningham D, et al. J Clin Oncol 2014;32 (15_suppl):Abstract 4014.

Key Features of Gastric Cancer Subtypes



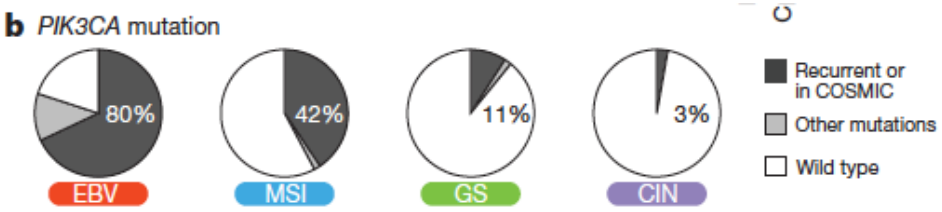
Comprehensive molecular characterization of gastric adenocarcinoma. The Cancer Genome Atlas (TCGA) project. Nature 2014 ;513(7517):202-9.

Differences in Clinical and Histological Characteristics Among Subtypes



Comprehensive molecular characterization of gastric adenocarcinoma. The Cancer Genome Atlas (TCGA) project. Nature 2014 ;513(7517):202-9.

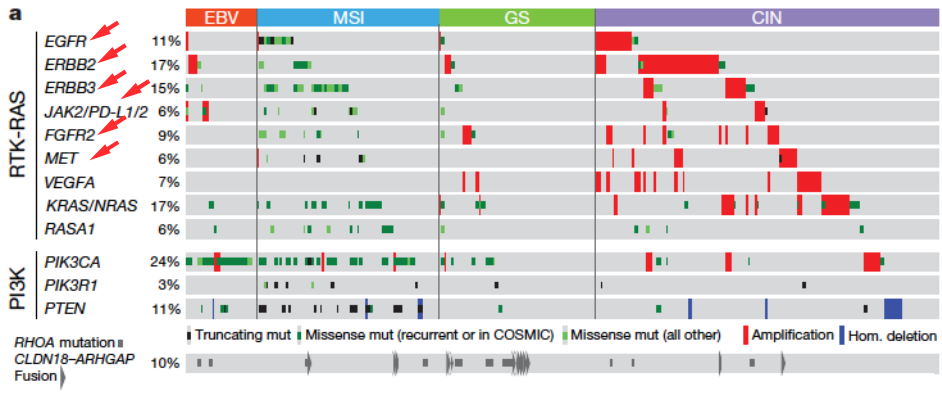
Molecular Characteristics of EBV-positive Gastric Cancers



The proportion of tumors harboring *PIK3CA* mutation in the molecular subtypes with mutations at sites noted recurrently in this data set or in the COSMIC database marked separately.

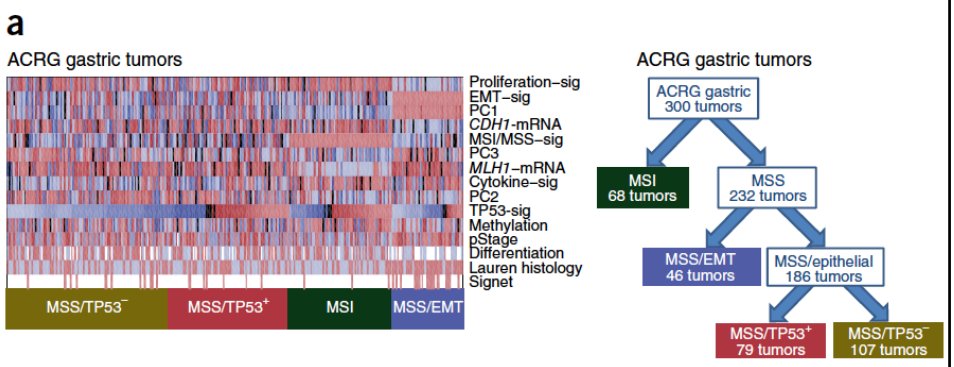
Comprehensive molecular characterization of gastric adenocarcinoma. The Cancer Genome Atlas (TCGA) project. Nature 2014 ;513(7517):202-9.

Red=Amplifications and Green=Mutations



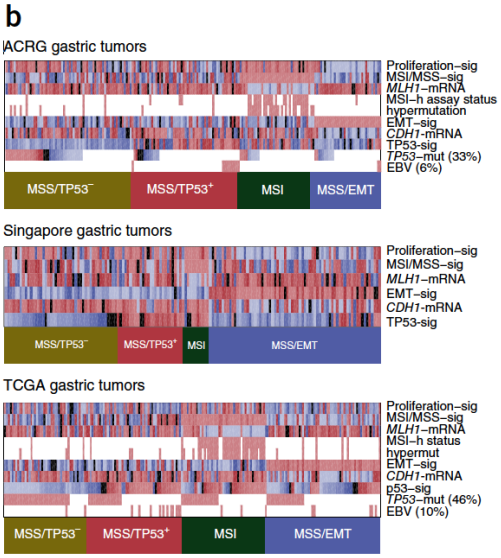
Comprehensive molecular characterization of gastric adenocarcinoma. The Cancer Genome Atlas (TCGA) project. Nature 2014 ;513(7517):202-9.

Molecular Analysis of Gastric Cancer



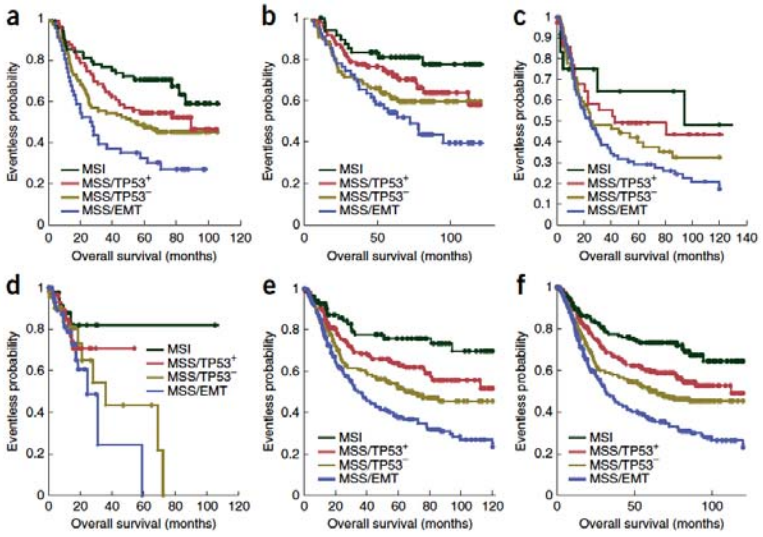
Cristescu, R., et al. Nature Medicine. 2015; 21: 449-456.

Molecular Analysis of Gastric Cancer



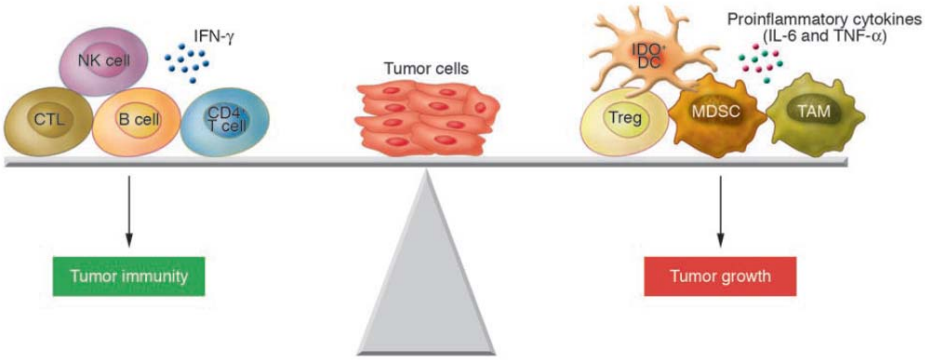
Cristescu, R., et al. Nature Medicine. 2015; 21: 449-456.

Molecular Subtype and Survival Association

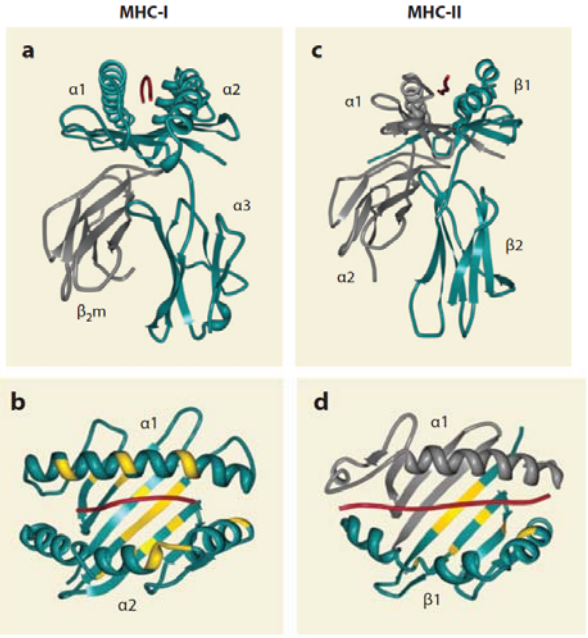


Cristescu, R., et al. Nature Medicine. 2015; 21: 449-456.

Immune System and Gastroesophageal Adenocarcinoma



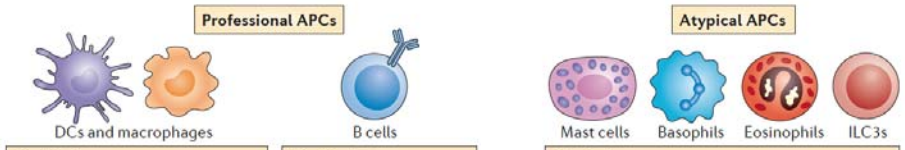
Bhardwaj, N. *J Clin Invest.* 2007;117(5):1130-1136



Three dimensional structures of MHC-I and MHC-II molecules with peptide ligands.

Blum, JS, et al. Annu Rev Immunol. 2013; 31: 443 -473

Cells that have MHC-Class II molecules

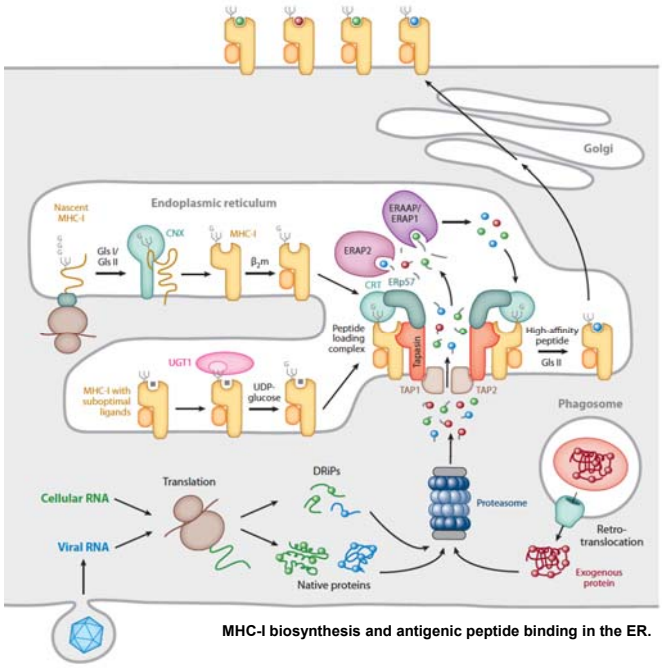


Key features
- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

Key features
- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

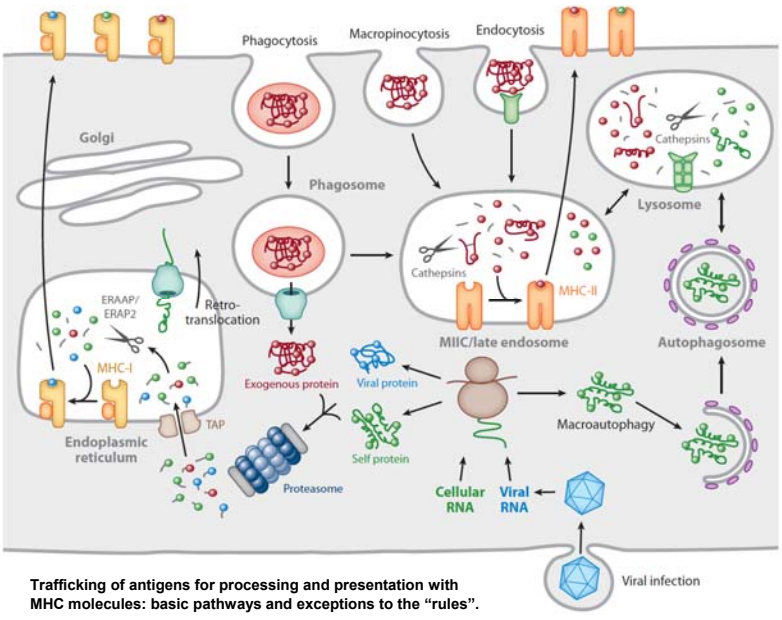
Key features
- Inducible expression of MHC class II molecules
- Antigen-presenting functions limited to specific immune environments (especially type 2 immune settings)
- Lack of compelling evidence that they can activate naive $CD4^+$ T cells in an antigen-specific manner

Nature Rev Imm November 2014



MHC-I biosynthesis and antigenic peptide binding in the ER.

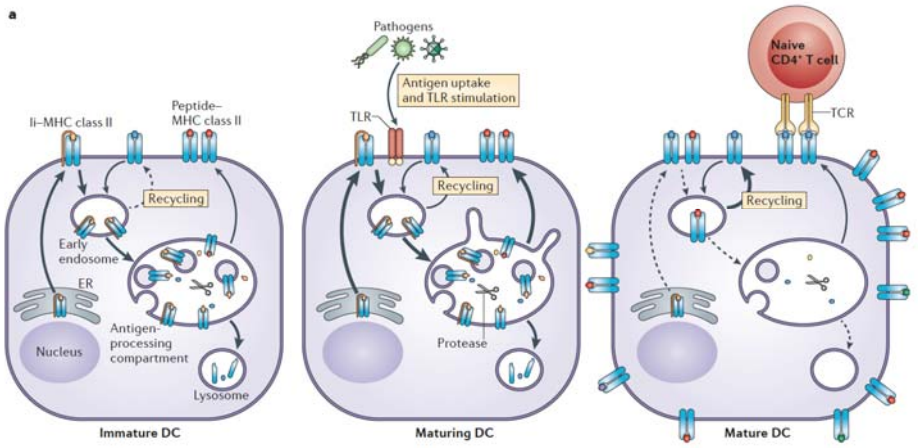
Blum, JS, et al. Annu Rev Immunol. 2013; 31: 443 -473



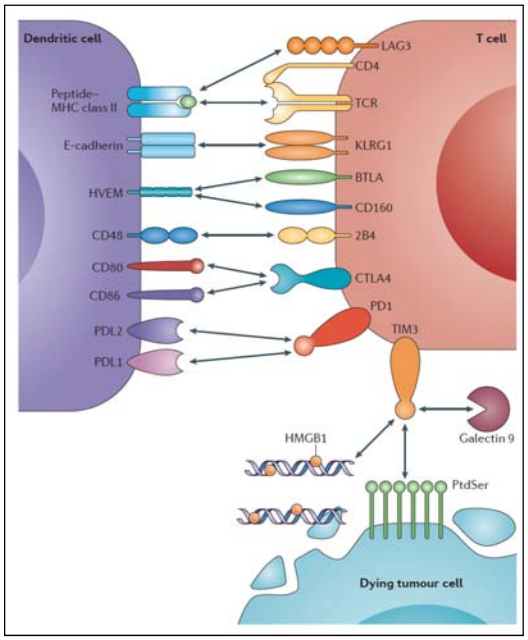
Trafficking of antigens for processing and presentation with MHC molecules: basic pathways and exceptions to the "rules".

Blum, JS, et al. Annu Rev Immunol. 2013; 31: 443 -473

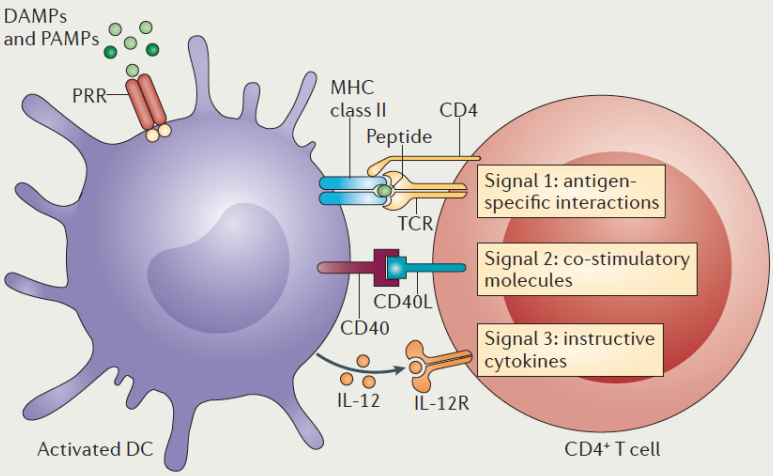
MHC Class II Molecules: Antigen Uptake and Processing



Roche and Futura. Nature Rev Immunology. 2015; 15: 203-216.



Nature Rev Imm January 2015



Nature Rev Imm November 2014

MADRID 2014 ESMO congress

A Phase 1b Study of Pembrolizumab (Pembro; MK-3475) in Patients With Advanced Gastric Cancer

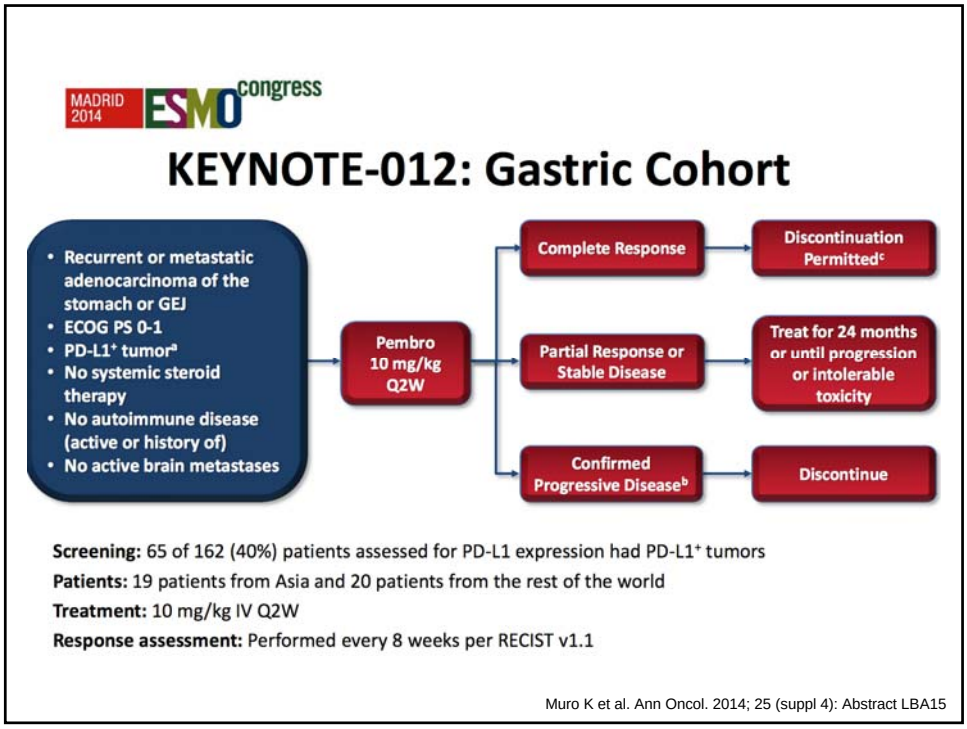
Kei Muro,[1] Yung-Jue Bang,[2] Veena Shankaran,[3] Ravit Geva,[4] Daniel Catenacci,[5] Shilpa Gupta,[6] Joseph Paul Eder,[7] Raanan Berger,[8] Edward J. Gonzalez,[9] Jennifer Pulini,[9] Archana Ray,[9] Marisa Dolled-Filhart,[9] Kenneth Emancipator,[9] Kumudu Pathiraja,[9] Xinxin Shu,[9] Minori Koshiji,[9] Jonathan Cheng,[9] Hyun Cheol Chung[10]

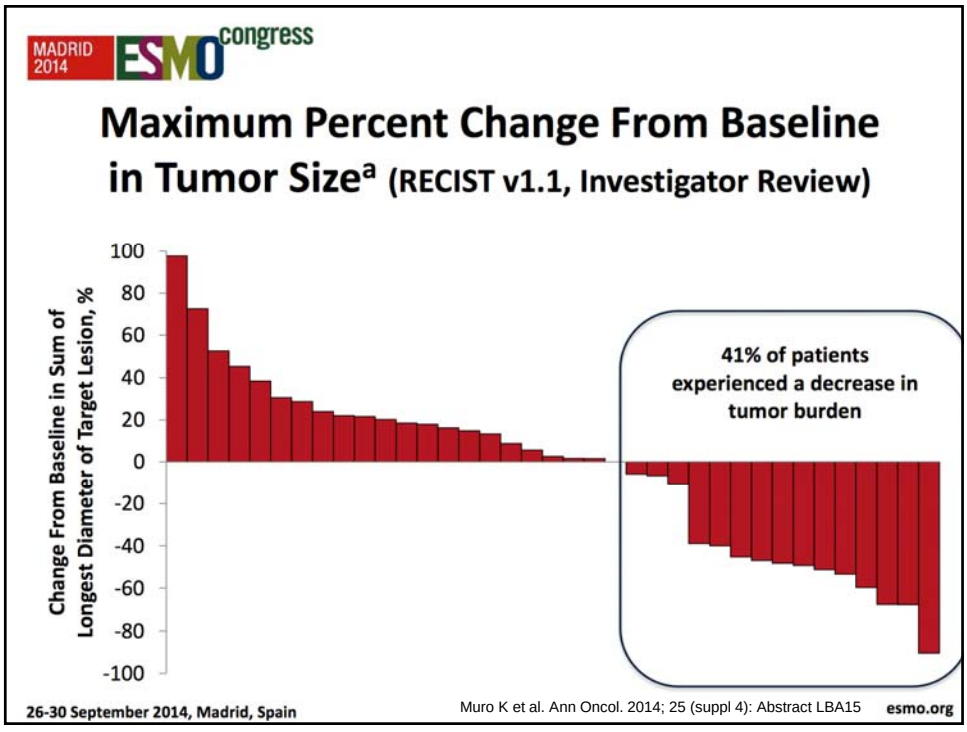
[1]Aichi Cancer Center Hospital, Nagoya, Japan; [2]Seoul National University Hospital, Seoul, South Korea; [3]University of Washington, Seattle, WA, USA; [4]Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; [5]University of Chicago, Chicago, IL, USA; [6]H.Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [7]Yale University, New Haven, CT, USA; [8]Sheba Medical Center, Tel Hashomer, Israel; [9]Merck & Co, Inc, Whitehouse Station, NJ, USA; [10]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

26-30 September 2014, Madrid, Spain

esmo.org

Muro K et al. Ann Oncol. 2014; 25 (suppl 4): Abstract





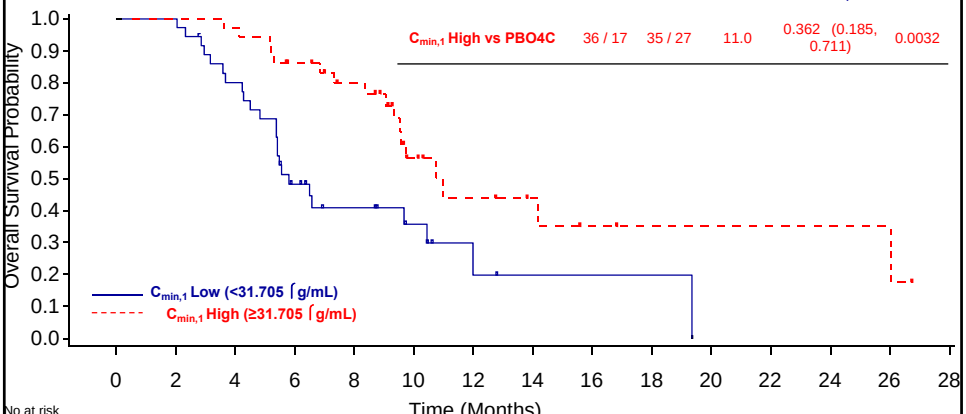
Current Trials for Esophagogastric Cancer

Anti-CTLA-4 or Anti-PD-1 or -PD-L1	Perioperative	1L	2L	3L + Refractory to Standard
Ipilimumab (BMS) Anti-CTLA-4		Combo w/ Nivo?	NCT01585987 Ph II Ipi vs SOC	
Nivolumab (ONO/BMS) Anti-PD-1	Adjuvant **Ph III**	**Ph III** CTX +/- Nivo **Ph Ib** Nivo Combo	ONO-4538-24 Ph III Nivo vs PTX or DTX	ONO-4538-07 Ph II Nivo
Pembrolizumab (MSD) Anti-PD-1		KEYNOTE-062 Ph III Pembro vs Pembro, Cis, 5-FU vs Cis, 5-FU	KEYNOTE-181 Ph III Pembro vs SOC KEYNOTE-061 Ph III Pembro vs PTX	KEYNOTE-180 Ph II KEYNOTE-059 Ph III
Durvalumab (AZ) Anti-PD-L1	Adjuvant **Ph II**	NCT02520453 Ph II Durva vs placebo	NCT02340975 Ph Ib / II Durva vs Tremel vs Combo	NCT02340975 Ph Ib / II Durva + Treme
Atezolizumab (Roche) Anti-PD-L1	Perioperative Ph II FOLFOX / FLOT +/- Atezo			
Avelumab (Merck Serono/Pfizer) Anti-PD-L1		JAVELIN GASTRIC 100 **Ph III** Maintenance after FOLFOX		NCT01772004 **(Ph I) / III** Ave JAVELIN GASTRIC 300

Moehler, et al. Discussant Presented at: ASCO GI. 2016 (abstr 06 and 07).

ASCOGI2015

Efficacy Parameter	RAM N/ #events	PBO4C N/ #events	Median (months)	Hazard Ratio[a] (95% CI)	P-value
REGARD Overall survival					
PBO4C			6.2		
$C_{min,1}$ Low vs PBO4C	36 / 24	35 / 27	5.8	0.891 (0.496, 1.602)	0.7008
$C_{min,1}$ High vs PBO4C	36 / 17	35 / 27	11.0	0.362 (0.185, 0.711)	0.0032



No at risk															
$C_{min,1}$ Low	36	36	28	15	10	6	2	1	1	1	0	0	0	0	0
$C_{min,1}$ High	36	36	35	29	24	12	7	5	3	2	2	2	2	2	0

Abbreviations: $C_{min,1}$ = minimum concentration following the first dose; CI = confidence interval; N = total number of patients; OS =overall survival; PBO4C = patients in placebo arm who had at least 4 cycles of treatment; Low/High = RAM-treated patients with $C_{min,1}$ < or ≥31.705 µg/mL (median), respectively.

[a]Adjusted for peritoneal metastasis, ECOG PS, and location of primary tumour.

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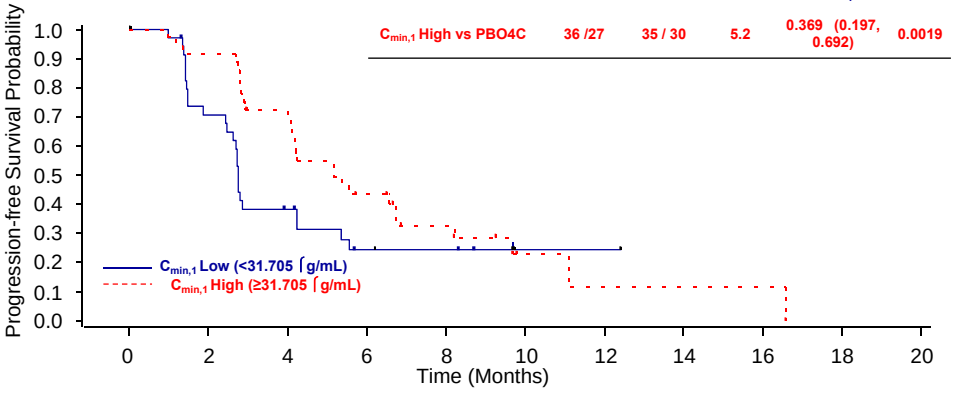
ASCOGI2015

Efficacy Parameter	RAM N/#events	PBO4C N/ #events	Median (months)	Hazard Ratio[a] (95% CI)	P-value
REGARD Progression-free Survival					
PBO4C			2.8		
$C_{min,1}$ Low vs PBO4C	36 / 25	35 / 30	2.8	0.701 (0.399, 1.232)	0.2168
$C_{min,1}$ High vs PBO4C	36 /27	35 / 30	5.2	0.369 (0.197, 0.692)	0.0019



No at risk

$C_{min,1}$ Low	36	24	12	6	5	1	1	0	0	0
$C_{min,1}$ High	36	33	25	14	8	2	1	1	1	0

Abbreviations: $C_{min,1}$ = minimum concentration following the first dose; CI = confidence interval; N = total number of patients; PFS = progression-free survival; PBO4C = patients in placebo arm who had at least 4 cycles of treatment; Low/High = RAM-treated patients with $C_{min,1}$ < or ≥31.705 µg/mL (median), respectively.

[a]Adjusted for peritoneal metastasis, ECOG PS, and location of primary tumour.

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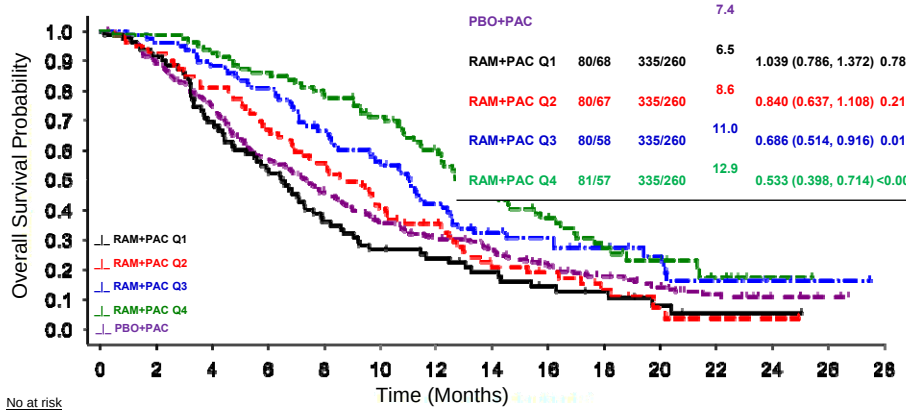
RAINBOW Multivariate Cox Regression and Kaplan-Meier Analysis of OS by $C_{min,1}$ Quartile

ASCOGI2015

Efficacy Parameter	RAM+PAC N/#events	PBO+PAC N/#events	Median (months)	Hazard Ratio[a] (95% CI)	P-value
RAINBOW Overall Survival					
PBO+PAC			7.4		
RAM+PAC Q1	80/68	335/260	6.5	1.039 (0.786, 1.372)	0.7891
RAM+PAC Q2	80/67	335/260	8.6	0.840 (0.637, 1.108)	0.2168
RAM+PAC Q3	80/58	335/260	11.0	0.686 (0.514, 0.916)	0.0107
RAM+PAC Q4	81/57	335/260	12.9	0.533 (0.398, 0.714)	<0.0001



No at risk

RAM+PAC Q1	80	73	54	40	27	20	17	12	8	6	3	1	1	0	0
RAM+PAC Q2	80	74	64	53	44	32	25	12	10	6	2	1	1	0	0
RAM+PAC Q3	80	76	70	63	51	41	30	21	18	13	9	6	3	1	0
RAM+PAC Q4	81	80	74	69	62	54	43	33	24	16	10	5	1	0	0
PBO+PAC	335	294	241	180	143	109	81	64	45	30	22	13	5	2	0

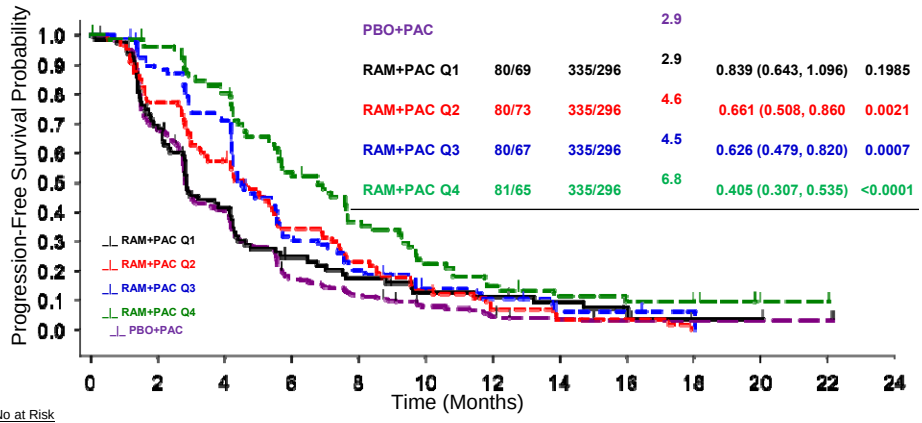
[a]Adjusted for Eastern Cooperative Oncology Group performance status, weight loss, number of metastatic sites, presence of ascites, tumor differentiation, prior gastrectomy, and region

Taberno J et al. J Clin Oncol. 2015;33(Suppl 3); Abstract 121

RAINBOW Multivariate Cox Regression and Kaplan-Meier Analysis of PFS by $C_{min,1}$ Quartile

ASCOGI2015

Efficacy Parameter	RAM+PAC N/#events	PBO+PAC N/#events	Median (months)	Hazard Ratio[a] (95% CI)	P-value
RAINBOW Progression-free Survival					
PBO+PAC			2.9		
RAM+PAC Q1	80/69	335/296	2.9	0.839 (0.643, 1.096)	0.1985
RAM+PAC Q2	80/73	335/296	4.6	0.661 (0.508, 0.860	0.0021
RAM+PAC Q3	80/67	335/296	4.5	0.626 (0.479, 0.820)	0.0007
RAM+PAC Q4	81/65	335/296	6.8	0.405 (0.307, 0.535)	<0.0001



No at Risk													
RAM+PAC Q1	80	53	30	17	12	8	7	5	2	1	1	0	0
RAM+PAC Q2	80	59	43	25	17	10	4	2	2	0	0	0	0
RAM+PAC Q3	80	67	53	22	14	8	6	2	2	1	0	0	0
RAM+PAC Q4	81	75	61	39	26	16	10	6	5	5	2	1	0
PBO+PAC	335	214	124	50	34	21	12	8	5	3	3	3	0

aAdjusted for sex, weight loss, number of metastatic sites, and liver metastasis.

Taberno J et al. J Clin Oncol. 2015;33(Suppl 3); Abstract 121

Metastatic GAC

Disappointments

mTOR inhibitors

EGFR inhibitors

c-MET inhibitors

Lapatinib and T-DM1 (Her2 positive pts)

Metastatic GAC

Promising leads

FGFR2 inhibitors

BET-bromodomain inhibitors

Coached (activated) T-cell therapy

Peptide Vaccine therapy