Ospedale S. Cuore Don Calabria

La terapia sistemica nel Carcinoma Gastrico avanzato: le domande

Massimo Cirillo

Verona 1 Aprile 2016

REGATTA: a phase 3 randomized trial: Gastrectomy plus Chemotherapy versus Chemotherapy in advanced gastric cancer

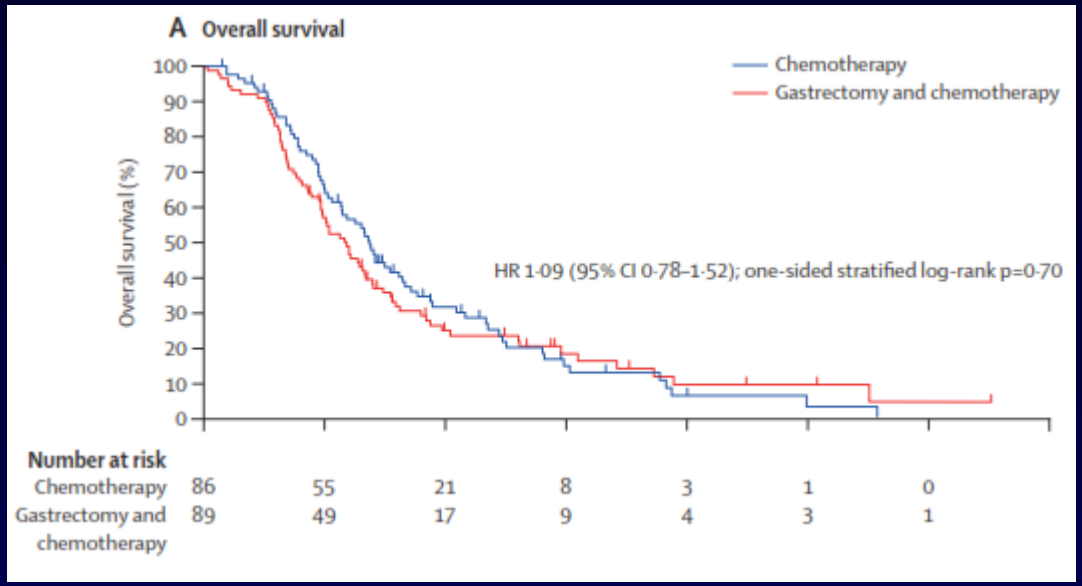
Patients aged 25-75 ys
HER-2 negative,
with a single non curable factor confined to liver, peritoneum, para-aortic lymph-node
No ascites or obstruction
(N = 175)

Chemotherapy alone (S1 + CDDP)
(randomized n = 86;
analysis n = 74)

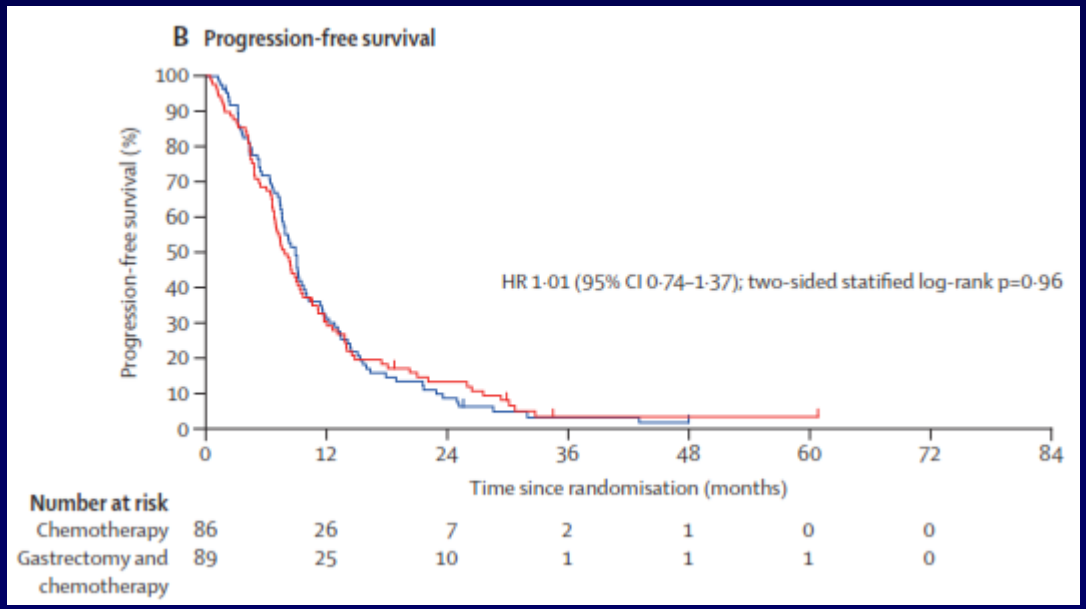
D1 gastrectomy followed by Chemotherapy (randomized n = 89;
analysis = 76)

- Primary endpoint: OS
- Secondary endpoints: PFS, Safety

Fujitani K . et al. Lancet Oncol 2016



2 ys OS 31.7% vs 25%
mOS 16.6 vs 14.3 mos



2 ys PFS 8.4% vs 13%

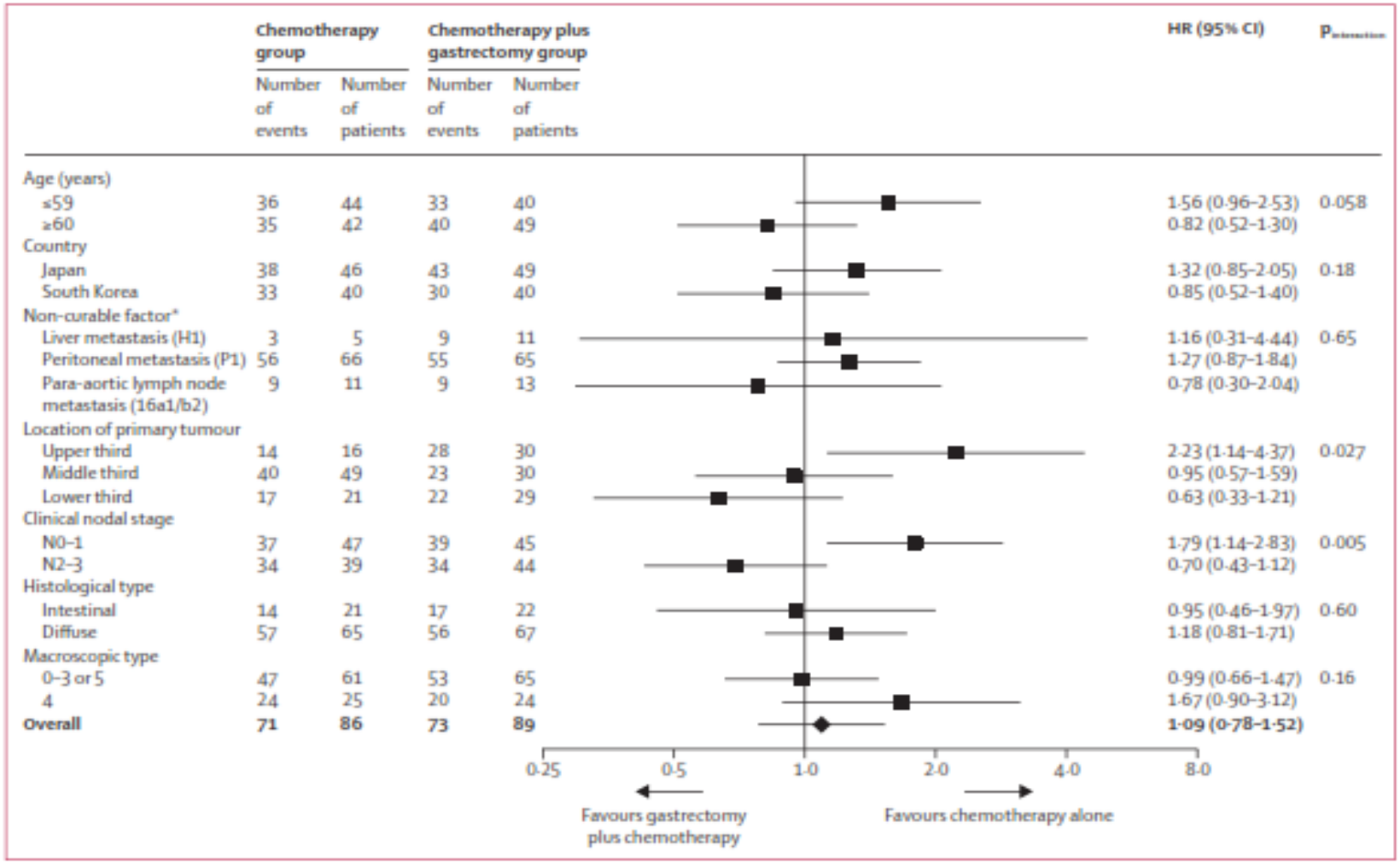


***Figure 3*: Subgroup analyses**

HRs for death in the patients assigned to gastrectomy plus chemotherapy are shown with 95% CIs. HR=hazard ratio. *Data missing for four patients in the chemotherapy alone group.

Chirurgia svantaggiosa nei tumori prossimali dove diminuisce la compliance alla CT

Nella malattia metastatica alla diagnosi esiste un consenso sulla opportunità di gastrectomia come prima scelta terapeutica ?

Gastrectomia

Chemioterapia

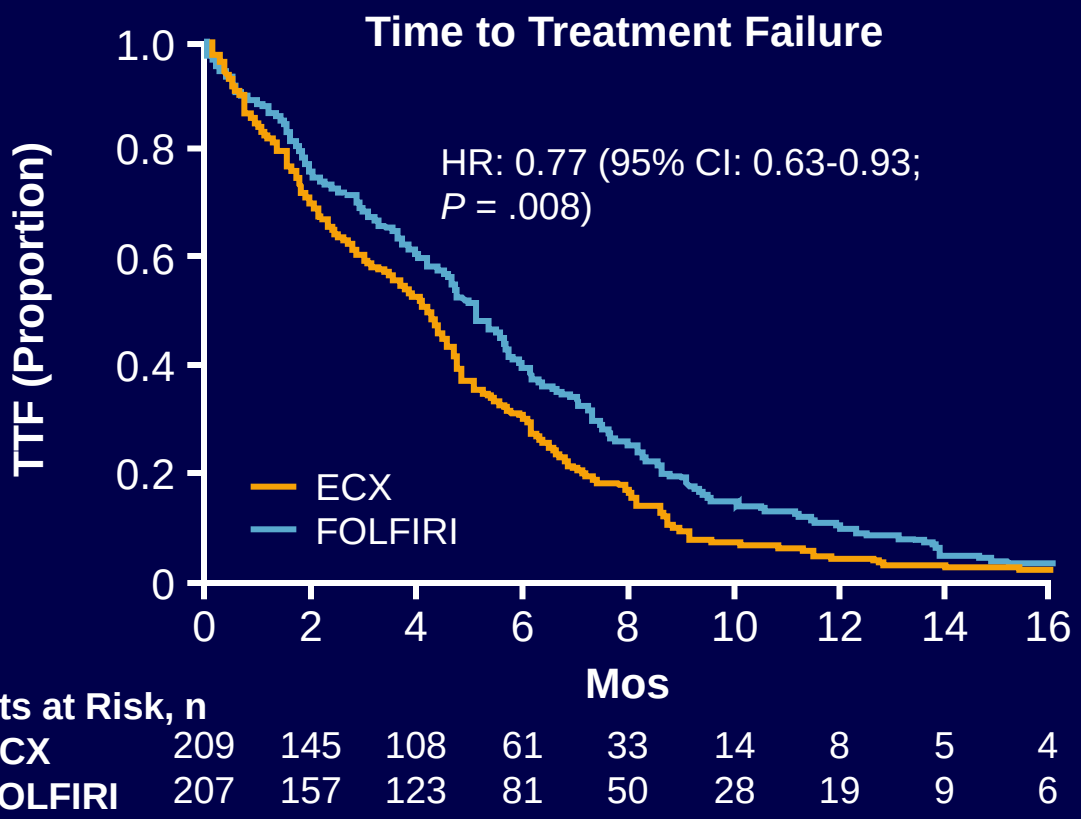
Chemioterapia

NCCN guidelines: First-line Therapy Reccomendations (v. 3:2015)

- Preferred regimens*
  - Fluoropyrimidine + cisplatin (category 1) or oxaliplatin (2A)
  - DCF (category 1)
  - ECF (category 1)
  - Fluorouracil + irinotecan (category 1)
- HER2-positive disease
  - Trastuzumab + cisplatin/ fluoropyrimidine (category 1)
  - Trastuzumab + other agents† (2B)
- Other regimens
  - Paclitaxel + cis- or carboplatin (category 2A)
  - Docetaxel with cisplatin (category 2A)
  - Docetaxel + irinotecan (category 2B)
  - Fluoropyrimidine
  - Docetaxel
  - Paclitaxel

*2-drug regimens preferred due to lower toxicity, reserving triplet therapy for younger, medically fit pts.
†Trastuzumab should not be combined with anthracyclines.

Tripletta con Epirubicina ?
FOLFIRI vs ECX



- N = 416
  - 1/3 GEJ, 2/3 gastric
- ORR: 39% vs 38%
- Median PFS:
  5.3 vs 5.8 mos
- Median OS:
  9.5 vs 9.7 mos
- TTF, toxicity favored first-line FOLFIRI over ECX

Guimbaud R, et al. J Clin Oncol. 2014;32:3520-3526

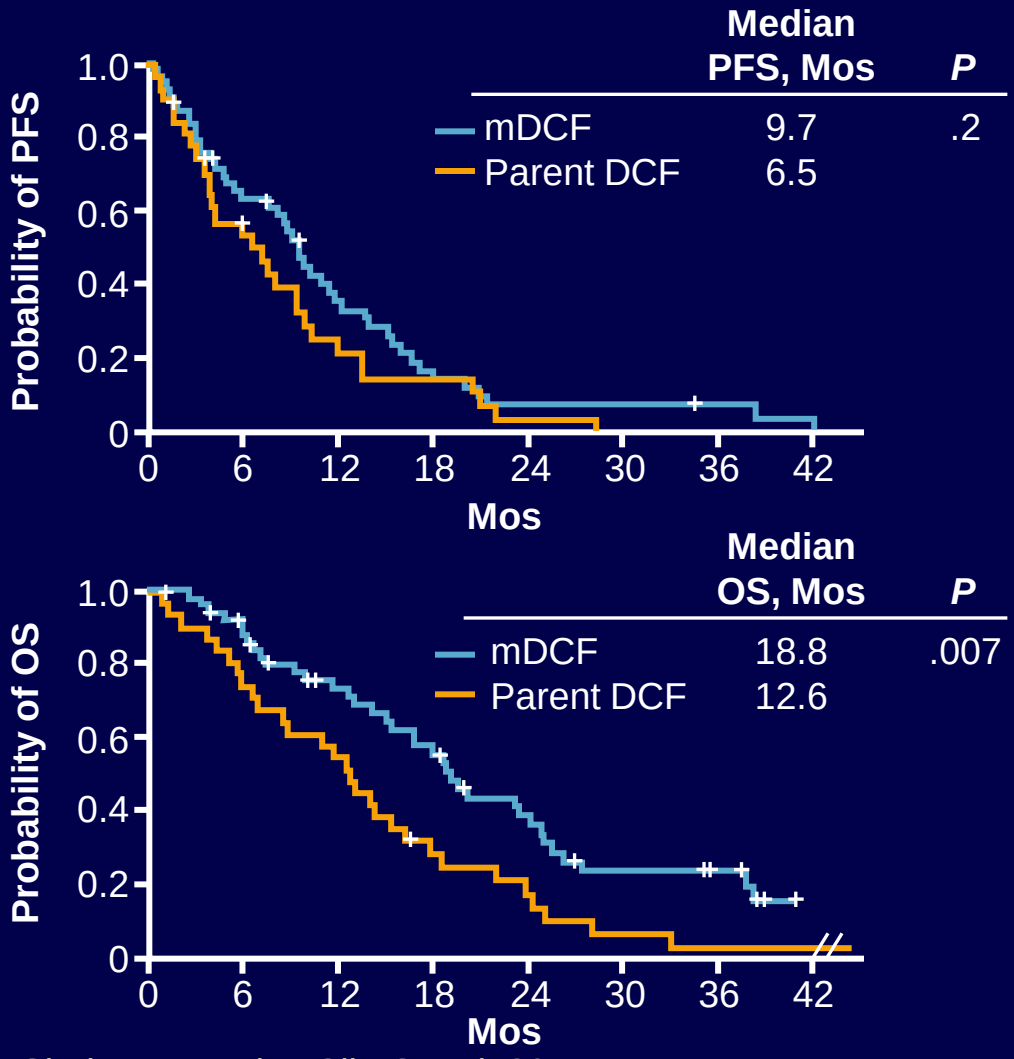
DCF vs CF in Advanced Gastric Cancer (TAX-325): Efficacy (457 pts)

Parameter	DCF (n = 221)*	CF (n = 224)*	*P* Value
Median age, yrs	55	55	--
Metastatic disease, %	96	97	--
ORR, %	37	25	.01
Median TTP, mos	5.6	3.7	≤ .001
Median OS, mos	9.2	8.6	.02

*Full analysis population (treated pts).

Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997.

Parent DCF vs Modified DCF in Metastatic Gastric Cancer: Efficacy



Parameter	mDCF (n = 54)	Parent DCF (n = 31)
Median cycles, n (range)	5.7 (3.4-6.8)	4.0 (2.5-6.3)
6-mo PFS, %	63	53
6-mo TTF, %	56	51
1-yr OS, %	63	55
2-yr OS, %	30	12
ORR (CR + PR), %	49	33

Shah MA, et al. J Clin Oncol. 2015

Malattia avanzata: quale regime di chemioterapia ?

	3-Drug Regimens				2-Drug Regimens			
	Oxali: EOX or EOF[1]	Cape: ECX or 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.

NCCN guidelines: Second-line Therapy Recommendations (v.3.2015)

- Depends on prior therapy and PS
- Preferred regimens (all category 1)
  - Ramucirumab + paclitaxel
  - Docetaxel
  - Paclitaxel
  - Irinotecan
  - Ramucirumab
- Other regimens
  - Irinotecan and cisplatin (category 2A)
  - Irinotecan and fluoropyrimidine (category 2B)
  - Docetaxel and irinotecan (category 2B)
- Alternative regimens (category 2B)
  - Mitomycin and irinotecan
  - Mitomycin and fluorouracil

NCCN Guidelines: gastric cancer. v.3.2015.

OPEN ACCESS Freely available online

PLOS ONE

Chemotherapy or Targeted Therapy as Second-Line Treatment of Advanced Gastric Cancer. A Systematic Review and Meta-Analysis of Published Studies

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Table 2. Overall Survival in overall population and based on type of studies.

Type of study	Trial	Year	N° of Patients		HR (95% CI)
			Experim. Arm	Control Arm	
Positive studies	Thuss-P. PC et al.	2011	21	19	0.48 (0.25–0.92)
	Kang JH et al.	2012	133	69	0.66 (0.48–0.89)
	Fuchs CS et al.	2014	238	117	0.78 (0.60–1.00)
	Ford HER et al.	2014	84	84	0.67 (0.49–0.92)
	Subtotal		*476*	*289*	*0.73 (0.61–0.86)*
Negative studies	Ohtsu A et al.	2013	439	217	0.90 (0.75–1.08)
TOTAL			**915**	**506**	**0.82 (0.79–0.85)**

Chemotherapy (231 pts) HR 0.73 (0.58-0.96)
Target therapy (677 pts) HR 0.78 (0.60-1.0)

HR 0.82 (0.79-0.85)

Table 3. Overall Survival by type of therapy in patients with ECOG performance status of 0.

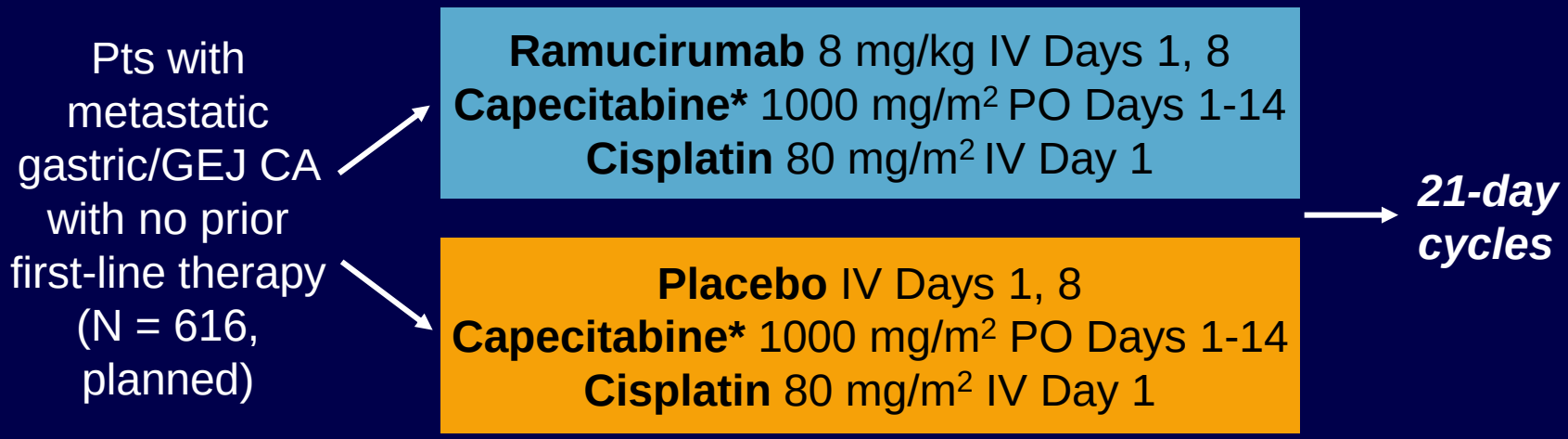
Type of therapy	Trial	Year	N° of Patients		HR (95% CI)
			Experim. Arm	Control Arm	
Chemotherapy	Kang JH et al.	2012	72	36	0.59 (0.38–0.90)
	Ford HER et al.	2014	22	19	0.48 (0.24–0.95)
	Subtotal		*94*	*55*	*0.57 (0.36–0.91)*
mTOR inhibitor	Ohtsu A et al.	2013	144	70	1.14 (0.81–1.61)
VEGFR inhibitor	Fuchs CS et al.	2014	67	31	1.07 (0.64–1.81)
TOTAL			**305**	**156**	**0.88 (0.61–1.28)**

Table 4. Overall Survival by type of therapy in patients with ECOG performance status of 1 or more.

Type of therapy	Trial	Year	N° of Patients		HR (95% CI)
			Experim. Arm	Control Arm	
Chemotherapy	Kang JH et al.	2012	61	33	0.72 (0.46–1.13)
	Ford HER et al. PS = 1	2014	45	50	0.80 (0.53–1.21)
	Ford HER et al. PS = 2	2014	13	12	0.81 (0.36–1.82)
	Subtotal		*119*	*95*	*0.80 (0.34–1.89)*
mTOR inhibitor	Ohtsu A et al. PS = 1	2013	269	120	0.86 (0.58–1.08)
	Ohtsu A et al. PS = 2	2013	25	27	1.43 (0.82–2.48)
	Subtotal		*294*	*147*	*0.92 (0.70–1.23)*
VEGFR inhibitor	Fuchs CS et al.	2014	171	86	0.68 (0.51–0.91)
TOTAL			**584**	**328**	**0.79 (0.64–0.98)**

RAINFALL: Capecitabine/5-FU + Cisplatin ± Ramucirumab in Metastatic Gastric CA

- Randomized, double-blind, phase III trial



*Pts unable to take capecitabine receive 5-FU 800 mg/m^2/day Days 1-5.

- Primary endpoint: PFS
- Secondary endpoints: OS, PFS2, ORR, DCR, TTP, DoR, QoL, PK

ClinicalTrials.gov. NCT02314117.

Targeting EGFR pathway

Targeting HER 2: TRASTUZUMAB

TOGA trial: incremento significativo in OS, PFS, OR

Targeting EGFR:

CETUXIMAB (**EXPAND trial**): incremento n.s. in PFS, OS e OR sovrapponibili

PANITUMUMAB (**REAL 3 trial**): decremento significativo in OS e PFS

Doppia inibizione: LAPATINIB

TRIO 013-LOGiC trial: incremento n.s. significativo in OS, vantaggio in PFS, OR
Vantaggio significativo in OS nei pz asiatici ed età < 60 anni

TyTAN trial (II linea): incremento n.s. in OS e PFS, vantaggio in OR
Vantaggio in OS nei pz cinesi ed HER2 +++

Targeting VEGF

AVAGAST: CDDP + Capecitabine ± BEVACIZUMAB

incremento n.s. in OS, incremento significativo in PFS, OR
incremento significativo in OS nei pz non asiatici con alto VEGF-A e bassa NLP1

REGARD (RAMUCIRUMAB vs BSC)
RAINBOW (Paclitaxel ± RAMUCIRUMAB)

Vantaggio significativo in OS, PFS, (OR in RAINBOW)

FOLFOX ± RAMUCIRUMAB

168 pz trattati in 1 linea
No vantaggi in PFS e OS
circa 45% carcinoma esofageo

APATINIB (Doppia inibizione: TKI + VEGF2)

incremento significativo in OS e PFS
267 pz asiatici con 35% > 2 linee di CT

Randomized phase II vs. III results with chemo +/- rilotumumab

	Phase II in MET+ (retrosp) Iveson, Lancet Oncol 2014		Phase III in MET+ (prosp) Asco 2015	
	ECX	ECX + rilo	ECX	ECX + rilo
N° pts	39	82	305	304
ORR	21%	39%	39.2%	30%
mPFS, mos	4.2	5.7	5.7	5.7
mOS, mos	8.9	10.6	11.5	9.6

Other anti-MET therapies

- METGastric, a phase III study of mFOLFOX6 ± onartuzumab (anti-MET Ab) in 562 MET IHC+ Pts, is also negative:
  - mOS 11.3 vs. 11.0 mos (HR 0.82, p=0.244) overall
  - mOS 9.7 vs. 11.0 mos (HR 0.64, p=0.062) in MET 2/3+

Shah, J Clin Oncol 2015;33:4012 [abstr]

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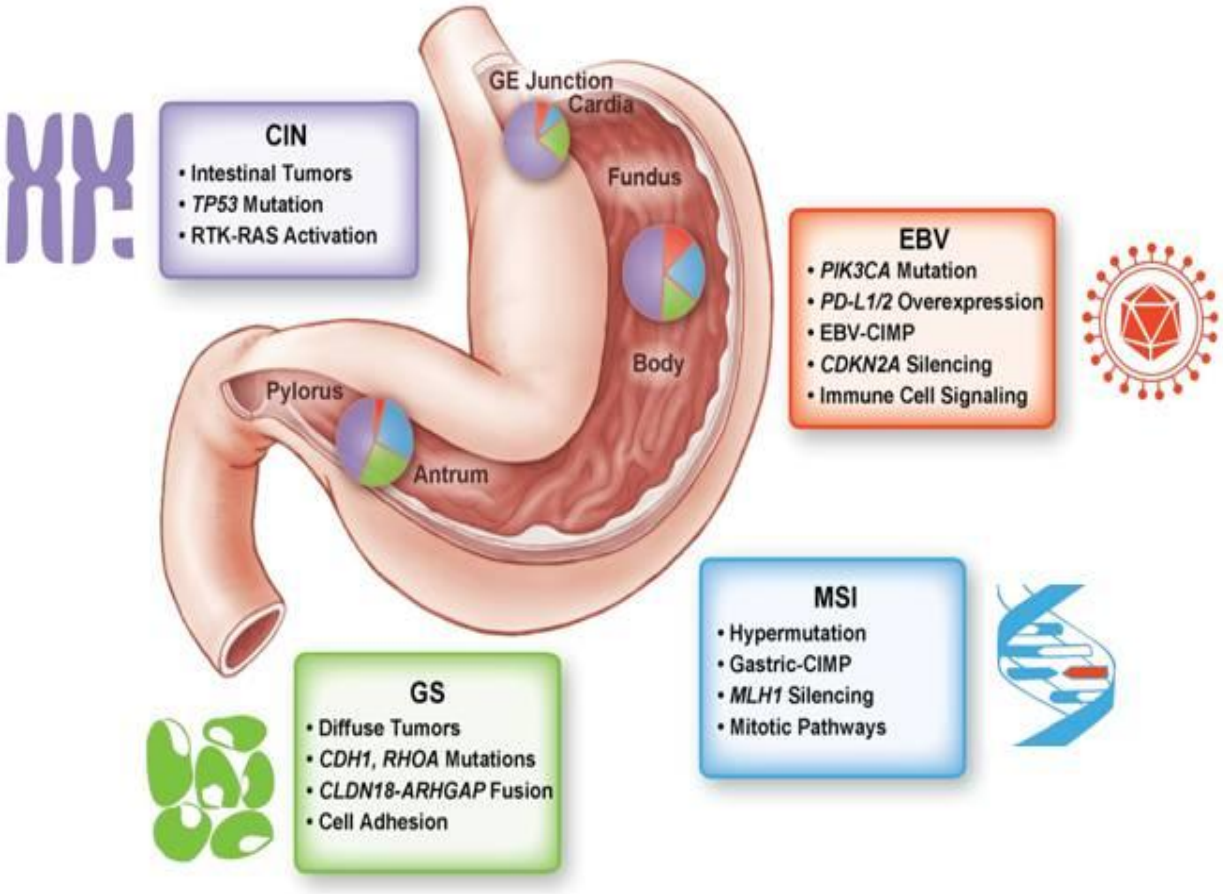
The study on AMG337, a MET inhibitors under clinical development in MET-amplified gastric cancer, was recently stopped due to toxicity

What about tivantinib?

Molecular Subtypes of GC and Key Features



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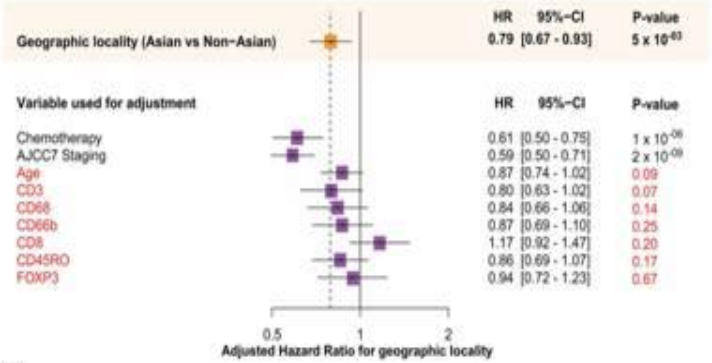
Possiamo spiegare i risultati deludenti solo sulla base della eterogeneità delle casistiche o anche sulla base della mancanza di adeguati fattori predittivi di risposta ?

Difference between Asian and non-Asian GC

Signatures of tumour immunity distinguish Asian and non-Asian gastric adenocarcinomas

LinS, Tan P. et al: Gut: on line :2014

A



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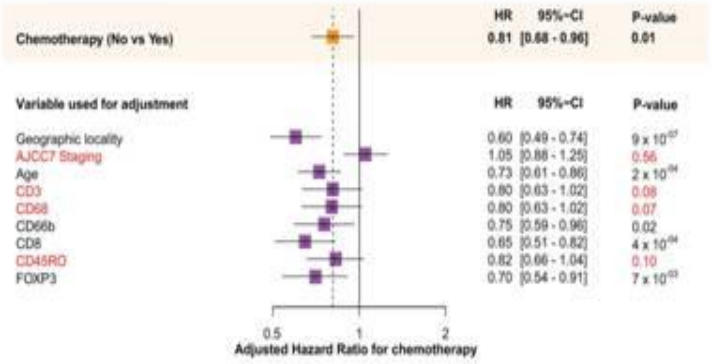


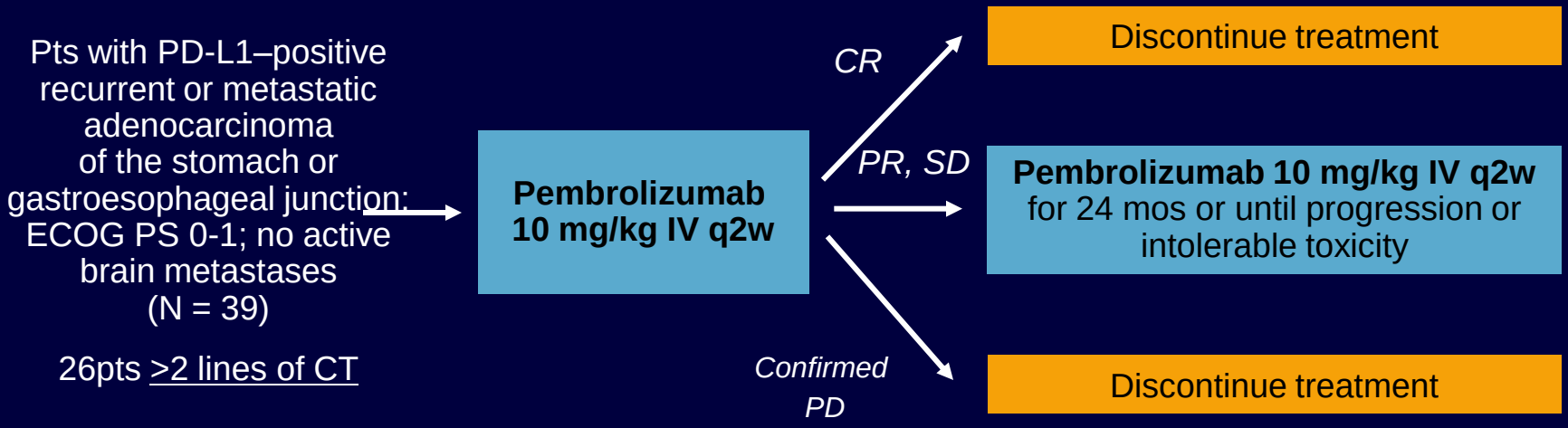
- Nine GC expression cohorts involving 1016 patients (890 Asians and 126 non-Asians)
  Cardiac cancer and diffuse type in non Asia
- somatic gene mutation and gene amplification rates in major cancer oncogenes such as KRAS, HER2 and FGFR2 appear to be similar in Asian and non-Asian GCs
- Non-Asian gastric cancers were associated with enrichment of tumour infiltrating T-cells as well as T-cell gene expression signatures, including CTLA-4 signaling.

  Non-Asian:
  high expression of T-cell marker (CD3, CD66b, CD8)
  Low expression of T-regulatory cell marker FOXP3

(Conclusion)
Tumor immunity differences may contribute to geographical differences in clinical outcome and design of future trials particularly in immuno-oncology.

KEYNOTE-012: Pembrolizumab in Gastric Cancer Cohort

- Multicenter, multicohort open-label phase Ib trial



- Endpoints: association of clinical response with PD-L1 expression
  - Assessment of response every 8 wks by RECIST v1.1
  - Assessment of PD-L1 expression by IHC

Bang YJ, et al. ASCO 2015. Abstract 4001.

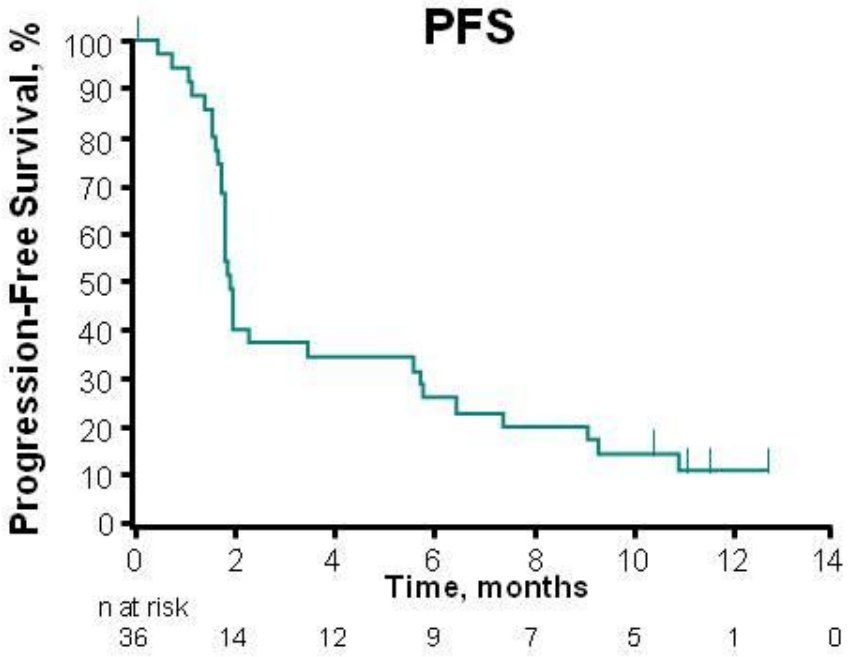
Pembrolizumab in Gastric Cancer Cohort (KEYNOTE-012): Responses

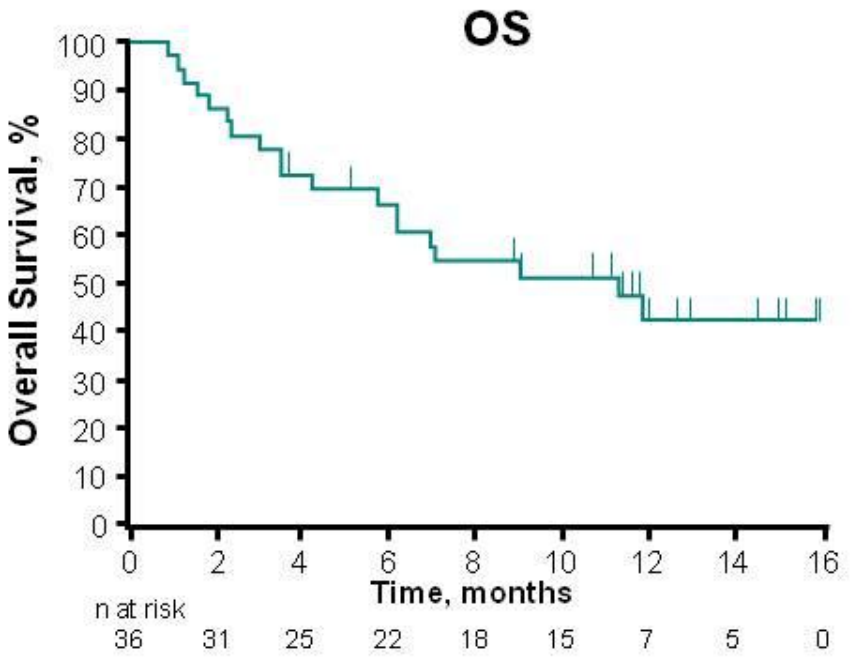
- Pembrolizumab therapy associated with PR in 13 of 39 pts by investigator review and 8 of 36 pts by central review
  - 53% of pts had decrease in lesion size
  - Median time to response: 8 wks
  - 4 of 8 responses ongoing at time of data cutoff
  - Median response duration: 40 wks (range: 20+ to 48+)

Outcomes		
Response	**Investigator Review (n = 39)**	**Central Review (n = 36)**
ORR, % (95% CI)	33 (19-50)	22 (10-39)
Best response, n (%)		
▪ CR	0	0
▪ PR	13 (33)	8 (22)
▪ SD	3 (8)	5 (14)
▪ PD	23 (59)	19 (53)
▪ No assessment	0	1 (3)
▪ Not determined	0	3 (8)

Bang YJ, et al. ASCO 2015. Abstract 4001.

Kaplan-Meier Estimates of Survival





- 6-month PFS rate: 26%
- Median PFS: 1.9 months (95% CI, 1.8-3.5)

- 6-month OS rate: 66%
- Median OS: 11.4 months (95% CI, 5.7-NR)

Analysis cut-off date: March 23, 2015.

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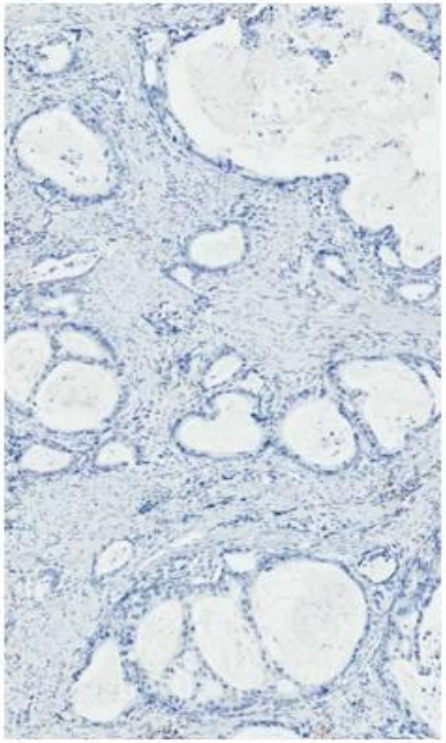
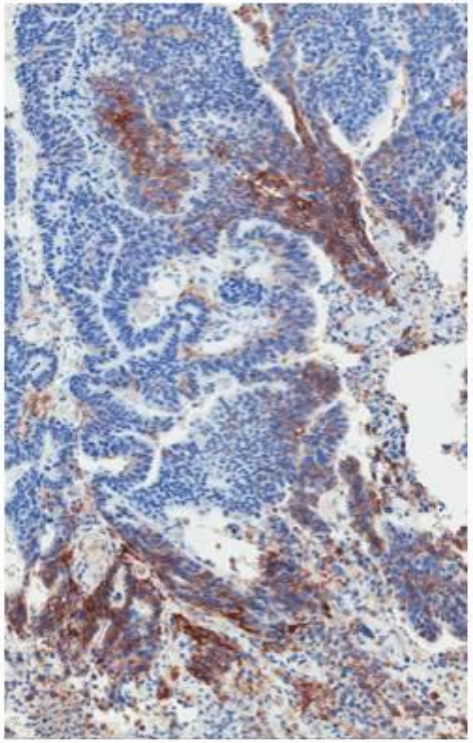
51% OR

Presented By Geoffrey Ku at 2015 ASCO Annual Meeting

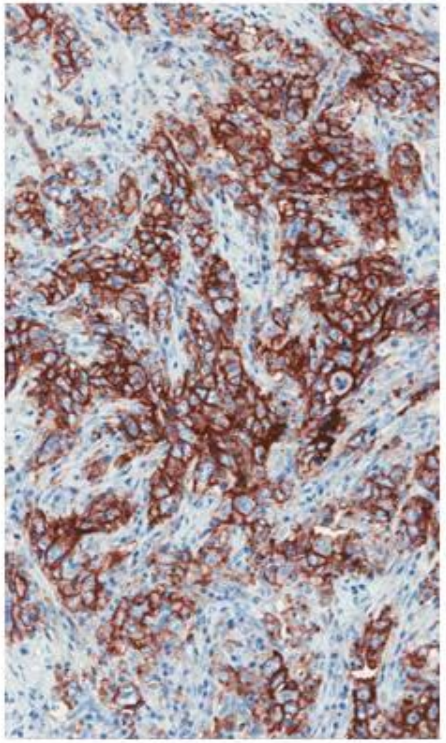
Gastric Cancer Staining Using Dako Assay



PD-L1 Negative



PD-L1 Positive



PD-L1 Positive

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PD-L1 IHC as biomarker?

- Multiple technical factors:
  - Choice of Ab / cut-off
  - Tumor heterogeneity spatially and temporally
  - Stability of PD-L1 protein in cell block/slides

Presented By Yung-Jue Bang at 2015 ASCO Annual Meeting

Immune Checkpoint Inhibitors in Adv. Gastric CA: Ongoing Clinical Trials

Checkpoint	Agent	Trial Details	NCT Number
CTLA-4	Ipilimumab	Ph II maintenance ipi	NCT01585987
PD-1	Pembrolizumab	KEYNOTE-061: Ph III 2nd-line pembro vs paclitaxel	NCT02370498
	Pembrolizumab	KEYNOTE-062: Ph III first-line pembro monotherapy	NCT02494583
	Pembrolizumab	KEYNOTE-059: Ph II pembro vs pembro+ cis/5-FU	NCT02335411
PD-L1	Avelumab	Ph III avelumab vs continuation of first-line chemo	NCT02625610
	Avelumab	Ph III avelumab vs chemo, 3rd-line	NCT02625623
Combo	Tremelimumab + durvalumab	Ph Ib/II tremelimumab + durvalumab vs treme vs durvalumab	NCT02340975
	Nivolumab + ipilimumab	Ph I/II nivolumab vs nivo/ipi	NCT01928394

Phase III LOGiC: CapeOx ± Lapatinib in HER2+ Advanced Gastric Cancer

Stratified by prior neo/adjuvant therapy, region (Asia vs North America vs rest of the world)

Pts with HER2-amplified locally advanced, unresectable, or metastatic gastric, esophageal, or GEJ cancer (N = 545)

CapeOx* + **Lapatinib** 1250 mg QD
21-day cycles

CapeOx* + Placebo

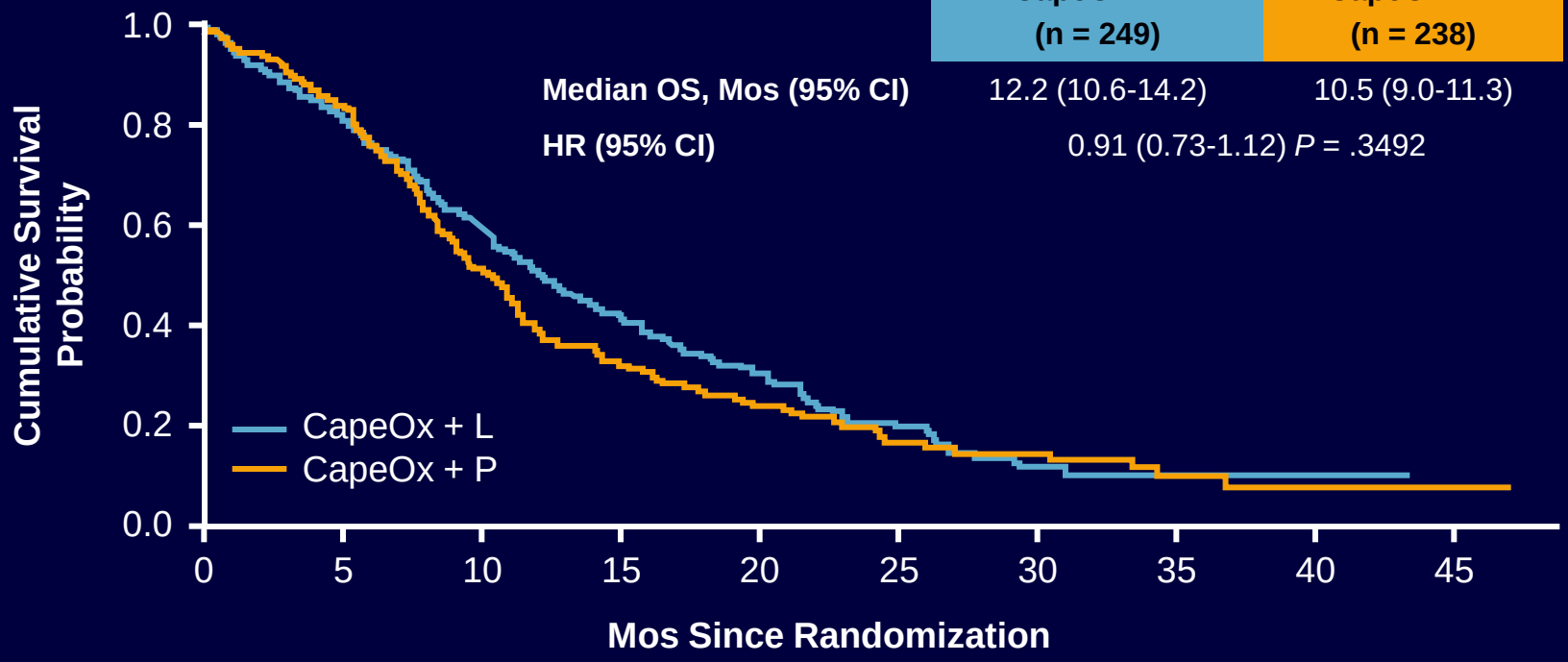
*Day 1: oxaliplatin 130 mg/m^2, Days 2-14: capecitabine 850 mg/m^2 BID.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DoR, CBR, safety/toxicity, QoL, molecular and pharmacogenetics analyses

Hecht J, et al. J Clin Oncol. 2015

CapeOx ± Lapatinib in HER2+ Advanced Gastric Cancer (LOGiC): OS

	CapeOx + L (n = 249)	CapeOx + P (n = 238)
Median OS, Mos (95% CI)	12.2 (10.6-14.2)	10.5 (9.0-11.3)
HR (95% CI)	0.91 (0.73-1.12) *P* = .3492	



Pts at Risk, n

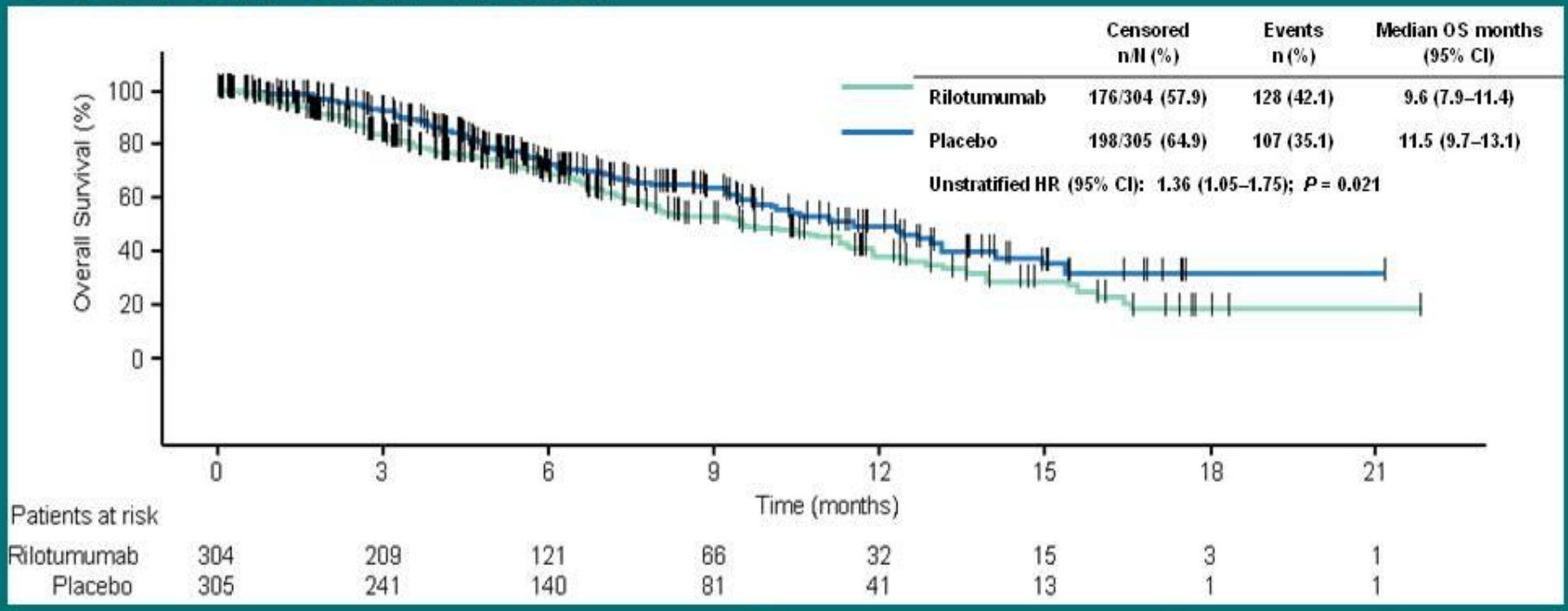
CapeOx + L	249	199	133	83	47	24	9	3	3	
CapeOx + P	238	189	106	53	34	17	11	7	2	2

ITT analysis HR: 0.91

Hecht J, et al. J Clin Oncol. 2015

Slide credit: clinicaloptions.com

Overall Survival



- More deaths in the rilotumumab arm, primarily due to disease progression

	Rilotumumab (n=304)	Placebo (n=305)
Events, n (%)	128 (42.1)	107 (35.1)
• Due to disease progression	103 (33.9)	87 (28.5)
• Not due to disease progression	25 (8.2)	20 (6.6)

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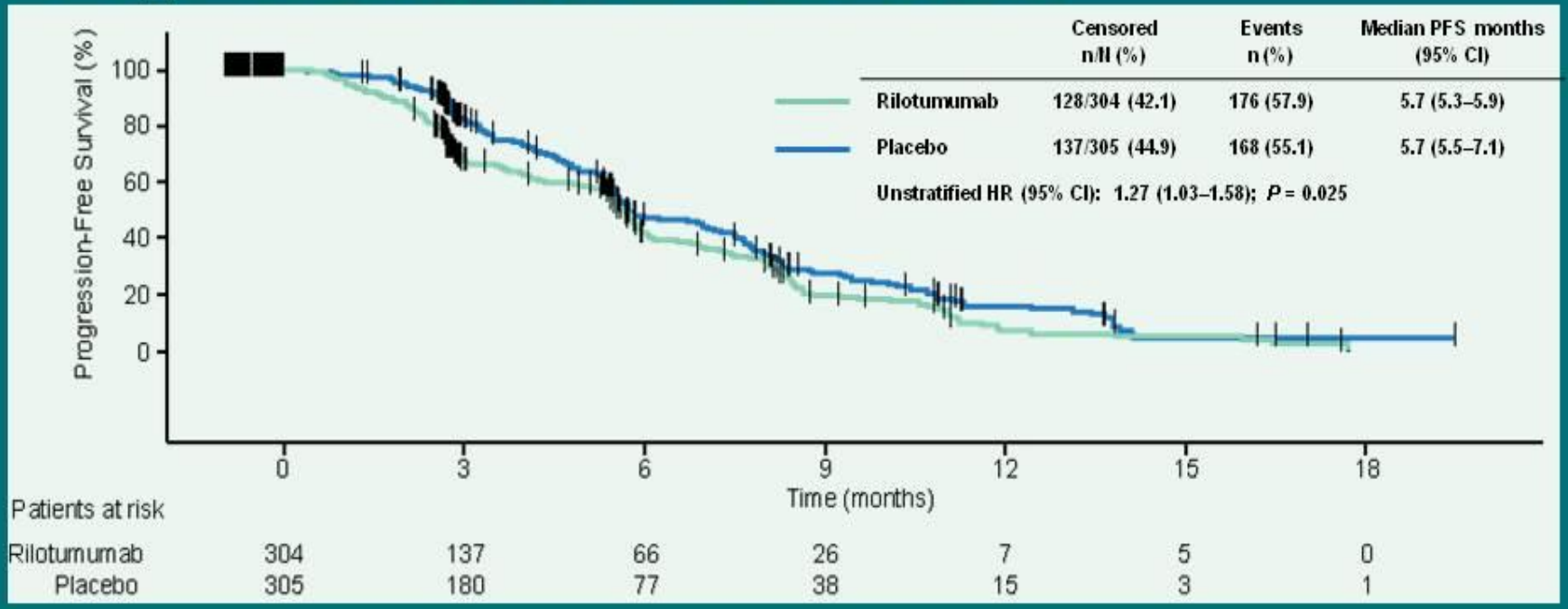
cMET expression (based on percentage of cells with ≥ 1+ MET staining) did not correlate with poorer prognosis or better outcome with Rilotumab

Progression-Free Survival



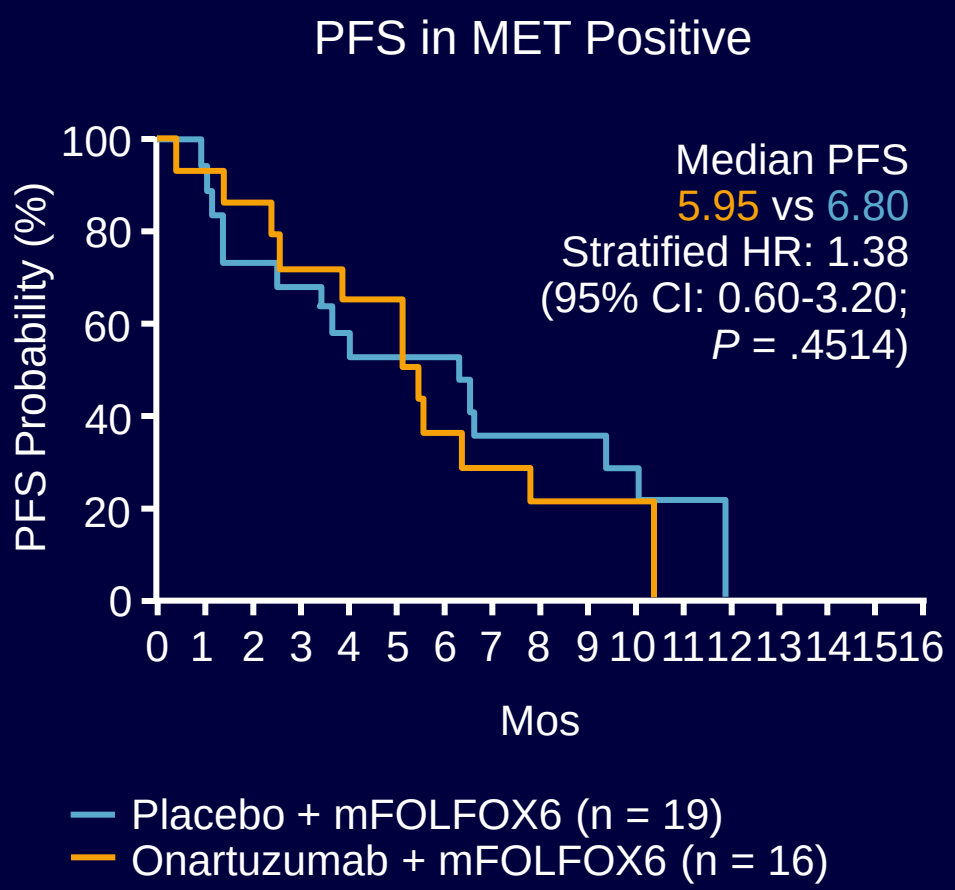
	Rilotumumab (n=304)	Placebo (n=305)
Events, n (%)	176 (57.9)	168 (55.1)
• Due to disease progression	112 (36.8)	118 (38.7)
• Death	64 (21.1)	50 (16.4)

Response Rate

	Rilotumumab + ECX, n (%) (n=263)		Placebo + ECX, n (%) (n=265)		All Patients (N=528)
Complete response	5 (1.9)	30.0%	8 (3.0)	39.2%	13 (2.5)
Partial response	74 (28.1)		96 (36.2)		170 (32.2)
Stable disease	63 (24.0)		68 (25.7)		131 (24.8)
Progressive disease	41 (15.6)		34 (12.8)		75 (14.2)
Non-CR/Non-PD	1 (0.4)		0 (0)		1 (0.2)
Inevaluable	8 (3.0)		8 (3.0)		16 (3.0)
Data not available at cutoff	71 (27.0)		51 (19.2)		122 (23.1)

- **An objective response rate of 30.0% was observed with rilotumumab vs 39.2% with placebo (*P*=0.03)**
- **A disease control rate of 54.0% was observed with rilotumumab vs 64.9% with placebo (*P*=0.01)**

METGASTRIC: FOLFOX ± Onartuzumab in Metastatic Gastroesophageal Cancer

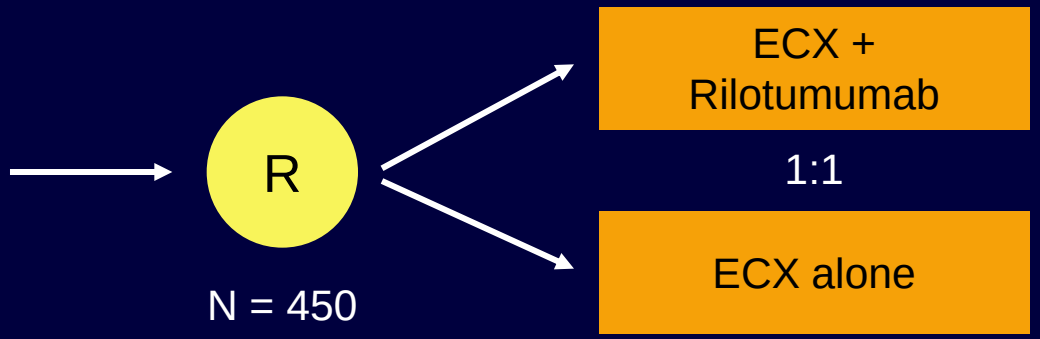


- No significant PFS improvement with onartuzumab (in both ITT and MET positive)[15]
- No difference in median OS with onartuzumab in ITT (10.61 vs 11.27 mos) or MET-positive (8.51 vs 8.48 mos) populations
- Asian pts had longer PFS and OS regardless of treatment arm, consistent with previously described trends in gastric cancer[16]

cMET Antibodies in Gastric Cancer: Phase III Trials

RILOMET-1[1]

Locally advanced or metastatic gastric and AEG Cancer, MET-positive by immunohistochemistry (IHC) HER2 negative

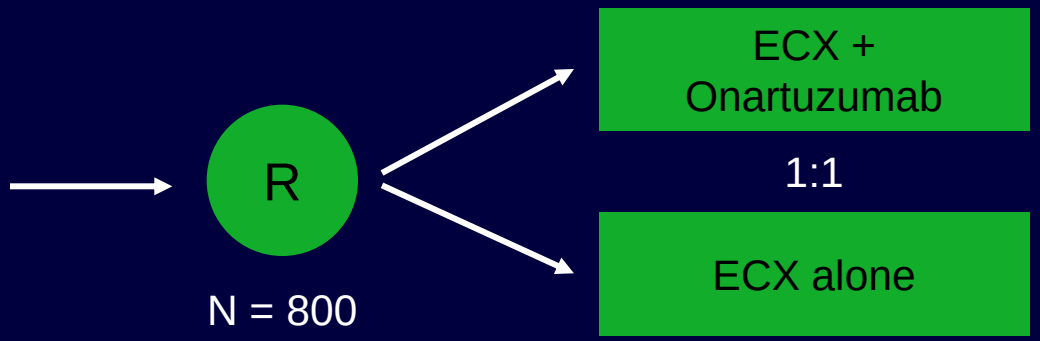


Primary endpoint: OS

Nessun vantaggio in OS e PFS

MetGastric[2]

Locally advanced or metastatic gastric and AEG Cancer, MET-positive by immunohistochemistry (IHC) HER2 negative



- Primary endpoint: OS in the Met IHC 2+/3+ pt subgroup

1. ClinicalTrials.gov. NCT01697072. 2. ClinicalTrials.gov. NCT01662869.

Phase III TAX325 Study: Docetaxel/ Cisplatin/5-FU vs Cisplatin/5-FU

Pts with advanced gastric cancer and no previous palliative chemotherapy (N = 457)

DCF
Docetaxel 75 mg/m^2 IV over 1 hr on Day 1 +
Cisplatin 75 mg/m^2 IV over 1-3 hrs on Day 1 +
5-FU 750 mg/m^2/day by CIV over 5 days
q3w
(n = 227)

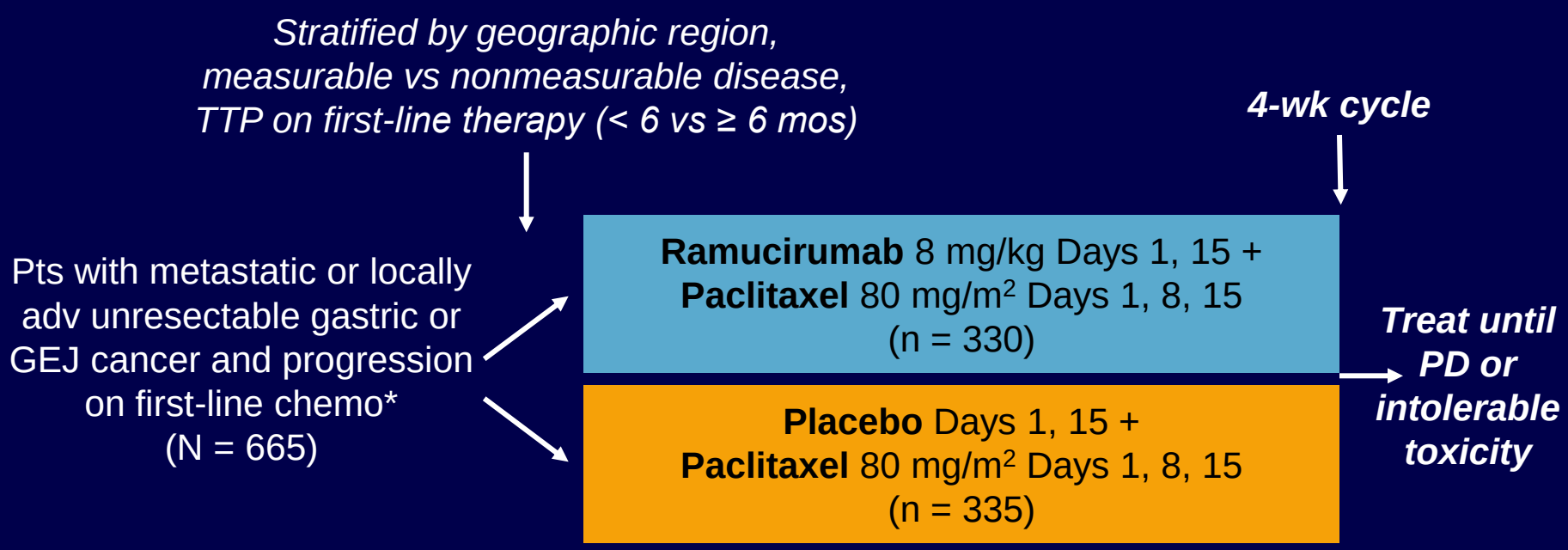
CF
Cisplatin 100 mg/m^2 IV over 1-3 hrs on Day 1 +
5-FU 1000 mg/m^2/day by CIV over 5 days
q4w
(n = 230)

- Primary endpoint: TTP from 4 → 6 mos
- Secondary endpoints: OS, RR, safety, QoL, clinical benefit

Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997.

RAINBOW: Second-line Paclitaxel ± Ramucirumab in Advanced Gastric Cancer

- Randomized, double-blind phase III trial

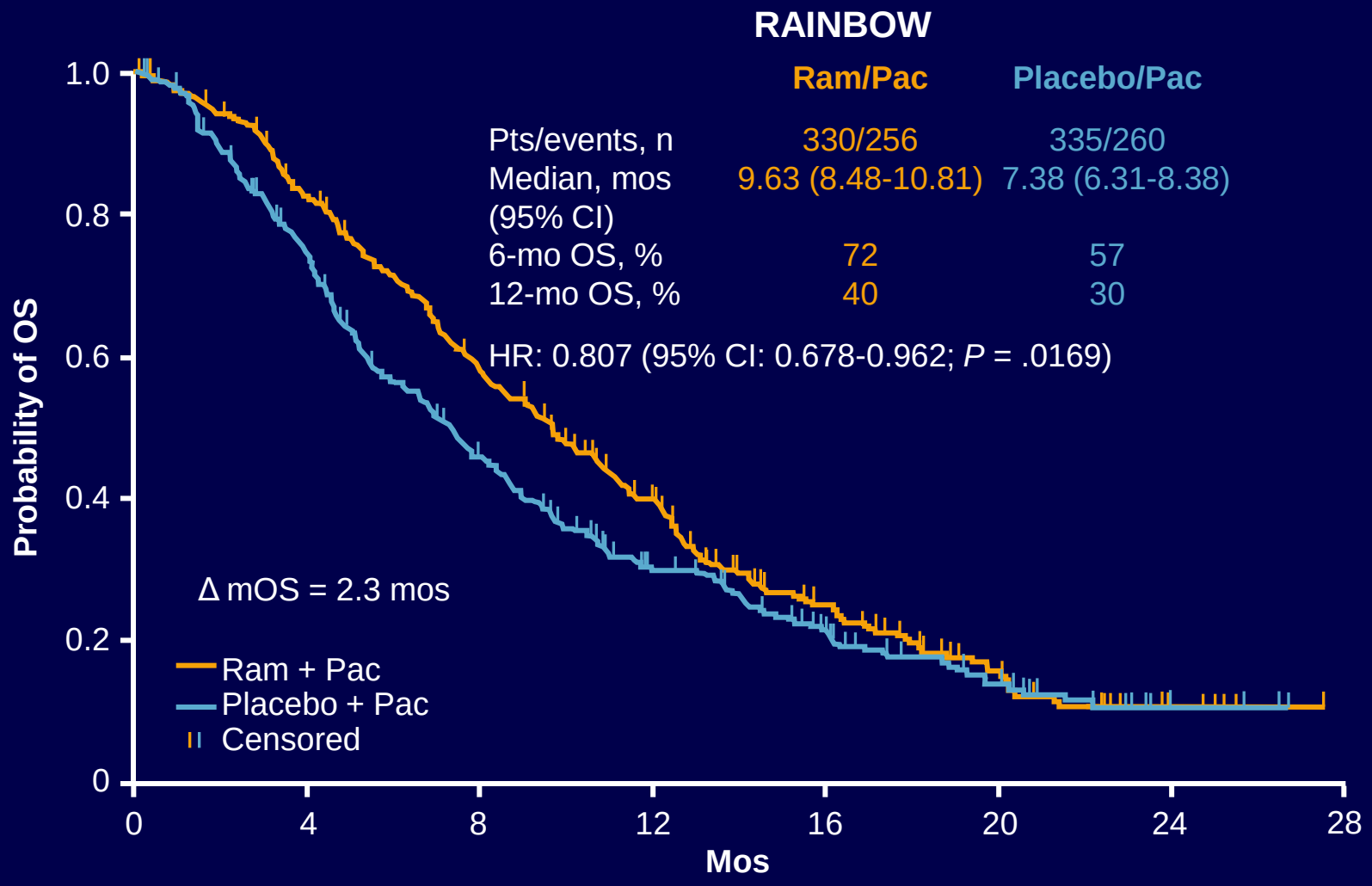


*Platinum agent plus fluoropyrimidine ± anthracycline.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, TTP

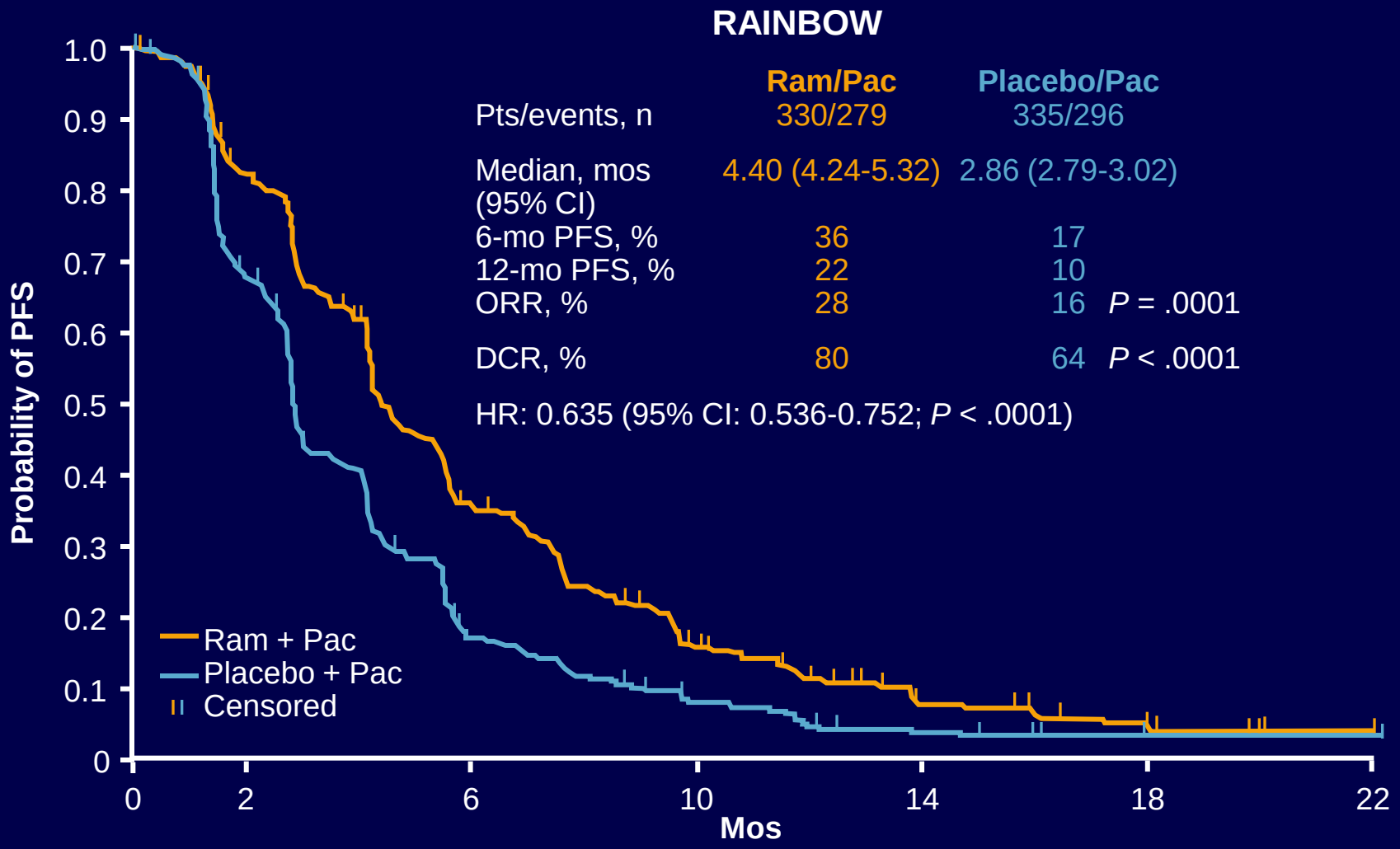
Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.

2nd-Line Ramucirumab in Advanced Gastric Cancer (RAINBOW): OS



Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.

Second-line Ramucirumab in Adv Gastric Cancer (RAINBOW): PFS, Responses



Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.

Gastric Adenocarcinoma: 4 Genomic Subsets

- Genomically unstable (50%)
  - Intestinal, present in most GEJ tumors
  - High rate of *p53* mutation, amplification of RTKs
- MSI-high (22%): High rate of microsatellite instability, gene mutation, and promoter hypermethylation
- Genomically stable (20%)
  - Associated with diffuse histology, *CHD-1* and *RHOA* mutation
- High Epstein-Barr virus burden (9%)
  - High rate of *PIK3CA* mutation, *PD-L1* and *PD-L2* amplification, strong IL-12 signaling indicating an immune presence

The Cancer Genome Atlas Research Network. Nature. 2014;513:202-209. Slide credit: clinicaloptions.com

Current and recent randomized studies in gastric and gastroesophageal junction cancer

Table 1 | Current and recent phase III studies in gastric and gastroesophageal junction cancer

Agent	Clinical trial	Randomization	*n*	NCT identifier
MET pathway inhibitors				
Onartuzumab	METGASTRIC	FOLFOX with or without onartuzumab	800	NCT01662869
Rilotumumab	RILOMET	ECX with or without rilotumumab	450	NCT01697072
HER2 inhibitors				
Pertuzumab	JACOB	XP–T with or without pertuzumab	780	NCT01774786
Trastuzumab	HELOISE	XP–T (standard) vs XP–T (high dose)	400	NCT01450696
TDM-1	GATSBY	TDM-1 versus taxane*	412	NCT01641939
EGFR inhibitors				
Panitumumab	REAL-3	EOX with or without panitumumab	574	NCT00824785
Cetuximab	EXPAND	XP with or without cetuximab	904	NCT00678535
Angiogenesis inhibitors				
Ramucirumab	REGARD	Ramucirumab versus BSC*	355	NCT00917384
Ramucirumab	RAINBOW	Paclitaxel with or without ramucirumab*	665	NCT01170663
Regorafenib	INTEGRATE	Regorafenib versus BSC*	150	ACTRN12612000239864

*Second-line. Abbreviations: BSC, best supportive care; ECX, epirubicin, cisplatin and capecitabine; EOX, epirubicin, oxaliplatin and capecitabine; T, trastuzumab; vs, versus; XP, cisplatin and capecitabine.

Parent DCF vs Modified DCF in Metastatic Gastric Cancer

- Randomized, multicenter phase II trial

Pts with previously untreated metastatic or GEJ adenocarcinoma (N = 90)

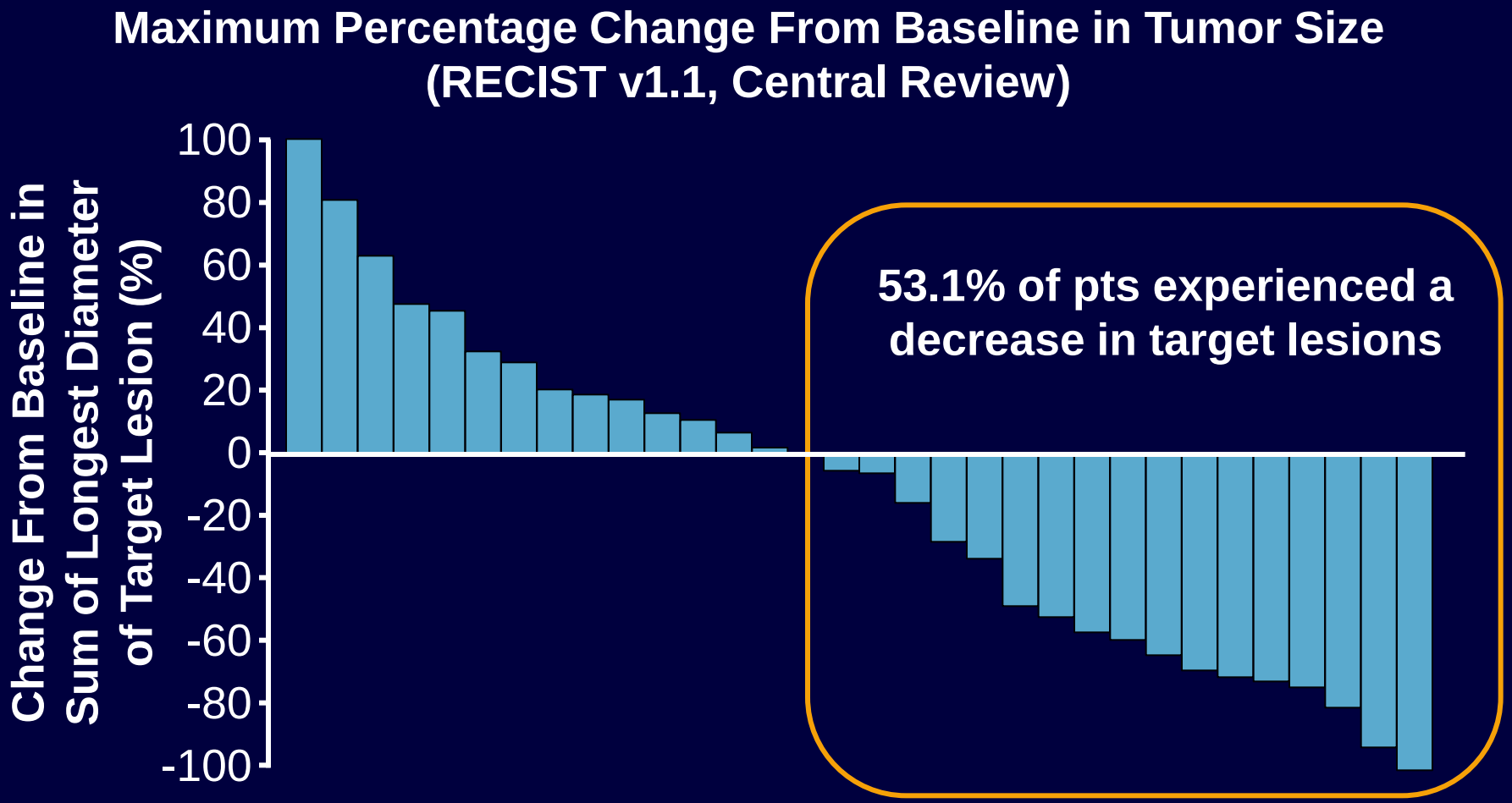
Modified DCF
Docetaxel 40 mg/m^2 IV on Day 1 +
Cisplatin 40 mg/m^2 IV on Day 2 or 3 +
5-FU 1000 mg/m^2/day IVCI X 2 days q2w
(n = 57)

Parent DCF
Docetaxel 75 mg/m^2 IV over 1 hr on Day 1 +
Cisplatin 75 mg/m^2 IV over 1-3 hrs on Day 1 +
5-FU 750 mg/m^2/day by IVCI over 5 days with GCSF q3w
(n = 33)

- Primary endpoint: safety and 6-mo PFS
- Secondary endpoints: response, median PFS, OS, 1- and 2-yr survival

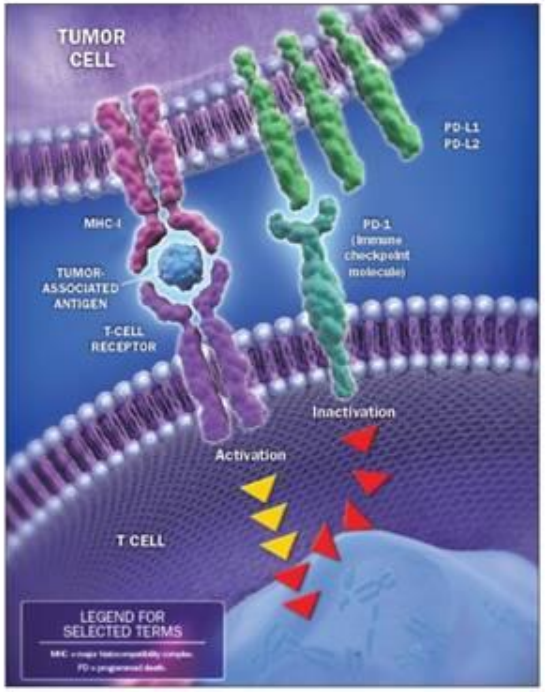
Shah MA, et al. J Clin Oncol. 2015

Pembrolizumab in Gastric Cancer Cohort (KEYNOTE-012): Change in Tumor Size



Bang YJ, et al. ASCO 2015. Abstract 4001.

PD-1 Pathway and Immune Surveillance



- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells[1]
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function[1]
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth[2]
- The anti-PD-1 antibody pembrolizumab has demonstrated clinical activity in multiple tumor types[3-9] and is approved in several countries for advanced melanoma

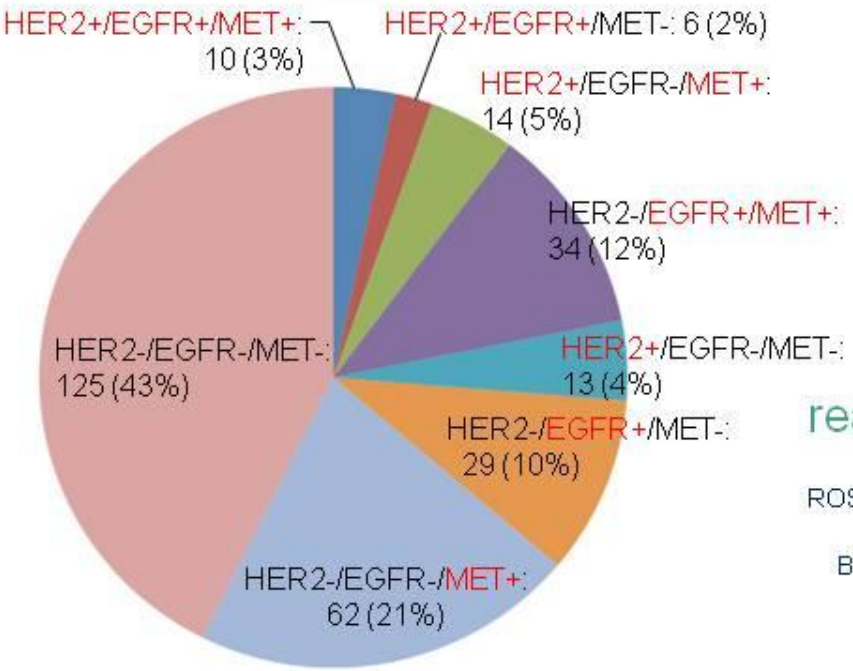
1. Keir ME et al. *Annu Rev Immunol.* 2008;26:677-704. 2. Pardoll DM. *Nat Rev Cancer.* 2012;12:252-64. 3. Ribas A et al. *J Clin Oncol.* 2014;32(suppl 5):abstr LBA9000. 4. Rizvi N et al. *J Clin Oncol.* 2014;32(suppl 5): abstr 8007. 5. Garon EB et al. *J Clin Oncol.* 2014;32(suppl 5):abstr 8020. 6. Seiwert TY et al. *J Clin Oncol.* 2014;32(suppl 5):abstr 6011. 7. Plimack E et al. Abstr. LBA23. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain. 8. Moskowitz CH et al. *Blood.* 2014;124(21):abstr 290. 9. Nanda R et al. Abstract 1349 (S1-09) presented at SABCS 2014, Dec 9-13, San Antonio, TX.

ASCO Annual '15 Meeting

Towards the Goal of Personalized Medicine in Gastric Cancer — Time to Move Beyond HER2 Inhibition.

Part I: Targeting Receptor Tyrosine Kinase Gene Amplification

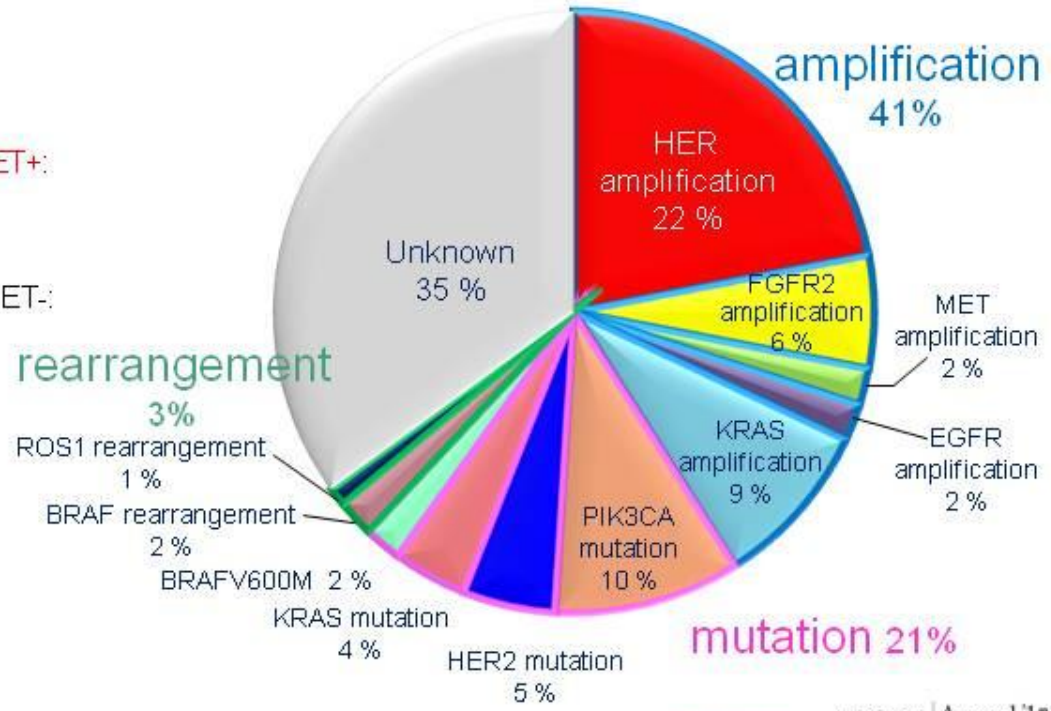
Fuse N, Ochiai A, et al.: Gastric Cancer 2015
Published online: 15 February 2015



Expression status of HER2, EGFR, and c-MET in unresectable advanced gastric cancers

Proportion of potential driver mutations identified in gastric carcinoma

Lee J, Ou SH. Discov Med, 2013, 16:7-14.



PRESENTED AT: ASCO Annual '15 Meeting