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Current and Future Treatment of Gastric and Gastro-Esophageal Cancer

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Disclosures

Consulting Agreements	Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology, Merck, Taiho Oncology Inc
Data and Safety Monitoring Board	Exelixis Inc, Silagen

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The role of anti-VEGF Therapy

- Bevacizumab:
  - No OS benefit for addition of bevacizumab to Capecitabine/cisplatin in first-line setting
- Apatinib
  - Phase III refractory trial shows median OS significantly longer vs. placebo in Chinese patients
- Ramucirumab
  - 2 phase III refractory trials show improved activity over placebo as a single agent and with paclitaxel

1. Ohtsu A, et al. J Clin Oncol. 2011;29:3968-3976.
2. Qin S, et al. ASCO 2014. Abstract 4003.
3. Fuchs CS, et al. Lancet. 2014;383:31-39
4. Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.

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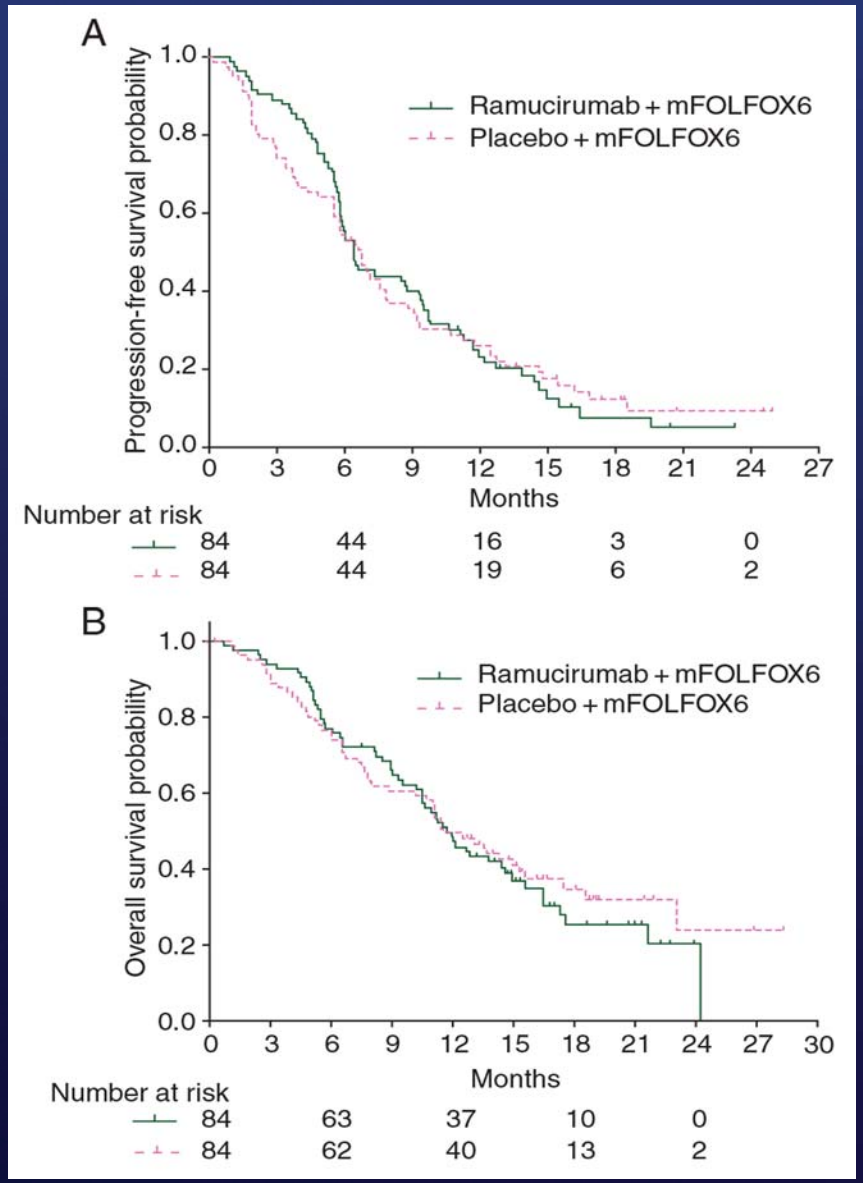
Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastro-esophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II: Efficacy Results.



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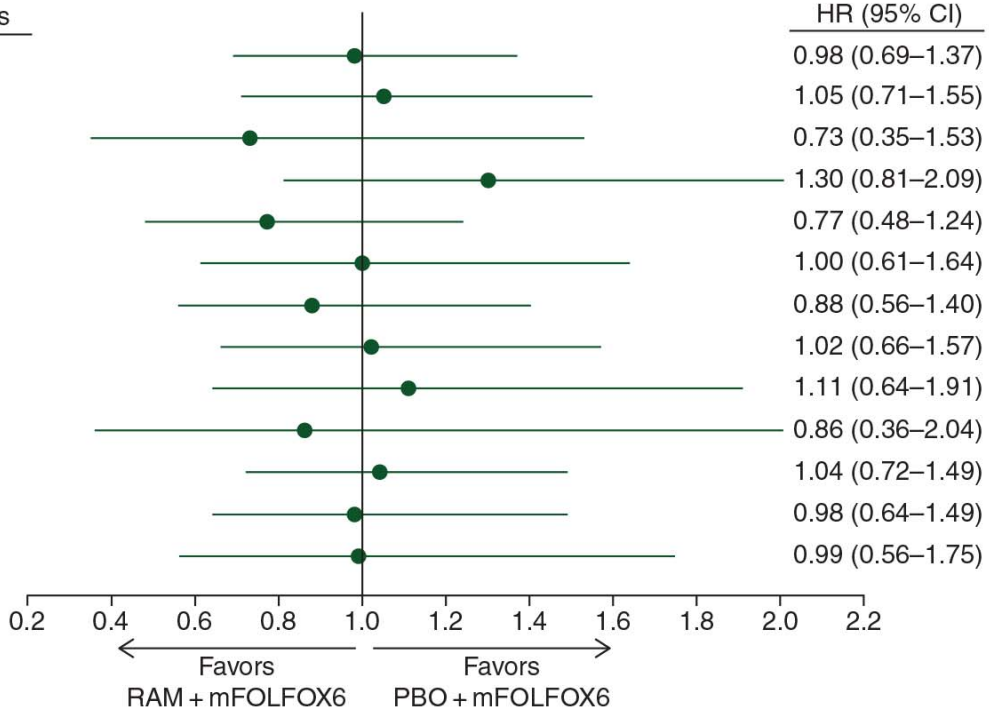
H. H. Yoon et al. Ann Oncol 2016;annonc.mdw423

Annals of Oncology

FOLFOX +/- Ramucirumab: Forest plot for subgroup analysis of progression-free survival (PFS) in the ITT population with and without censoring for premature treatment discontinuation

A

		RAM + mFOLFOX6	PBO + mFOLFOX6	HR (95% CI)
		N/Events	*N*/Events	
Overall	RAM vs PBO	84/70	84/69	0.98 (0.69–1.37)
Tumor location (pre-specified catagorization 1)	Esophagus/GEJ	65/54	64/53	1.05 (0.71–1.55)
	Gastric	19/16	20/16	0.73 (0.35–1.53)
Tumor location (pre-specified catagorization 2)	Esophagus	39/35	41/35	1.30 (0.81–2.09)
	Gastric/GEJ	45/35	43/34	0.77 (0.48–1.24)
ECOG performance status	0	40/31	43/33	1.00 (0.61–1.64)
	1	43/38	41/36	0.88 (0.56–1.40)
Age (years)	<65	42/38	56/47	1.02 (0.66–1.57)
	≥65	42/32	28/22	1.11 (0.64–1.91)
Prior surgery with curative intent	Yes	12/9	14/14	0.86 (0.36–2.04)
	No	72/61	70/55	1.04 (0.72–1.49)
Weight loss in 3 months prior to study entry	<10%	54/43	54/44	0.98 (0.64–1.49)
	≥10%	26/24	29/24	0.99 (0.56–1.75)

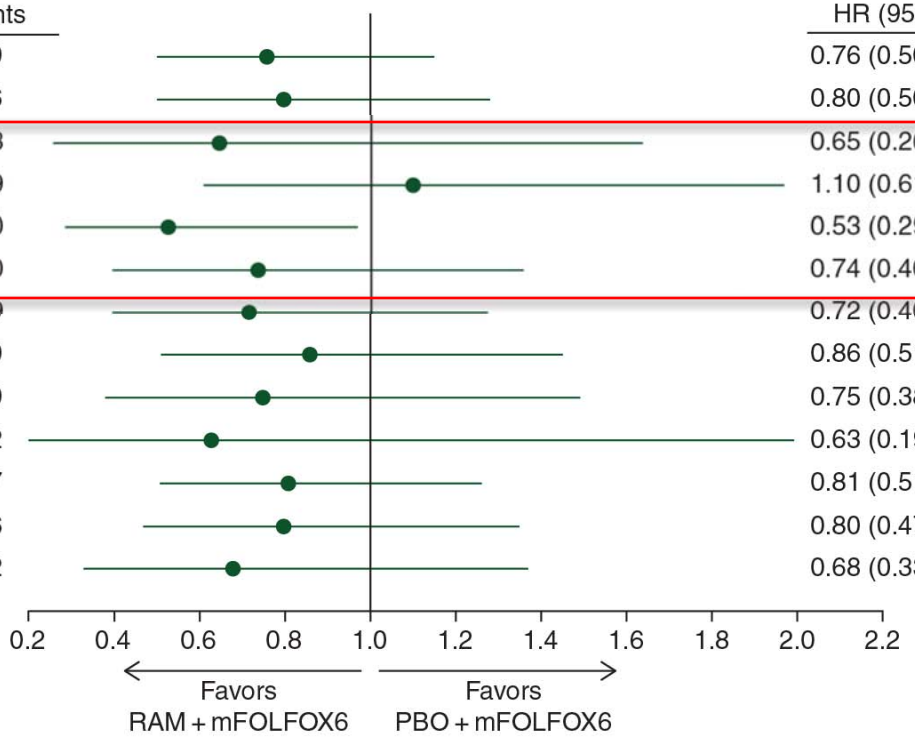


H. H. Yoon et al. Ann Oncol 2016;annonc.mdw423

FOLFOX +/- Ramucirumab: Forest plot for subgroup analysis of progression-free survival (PFS) in the ITT population with and without censoring for premature treatment discontinuation

B

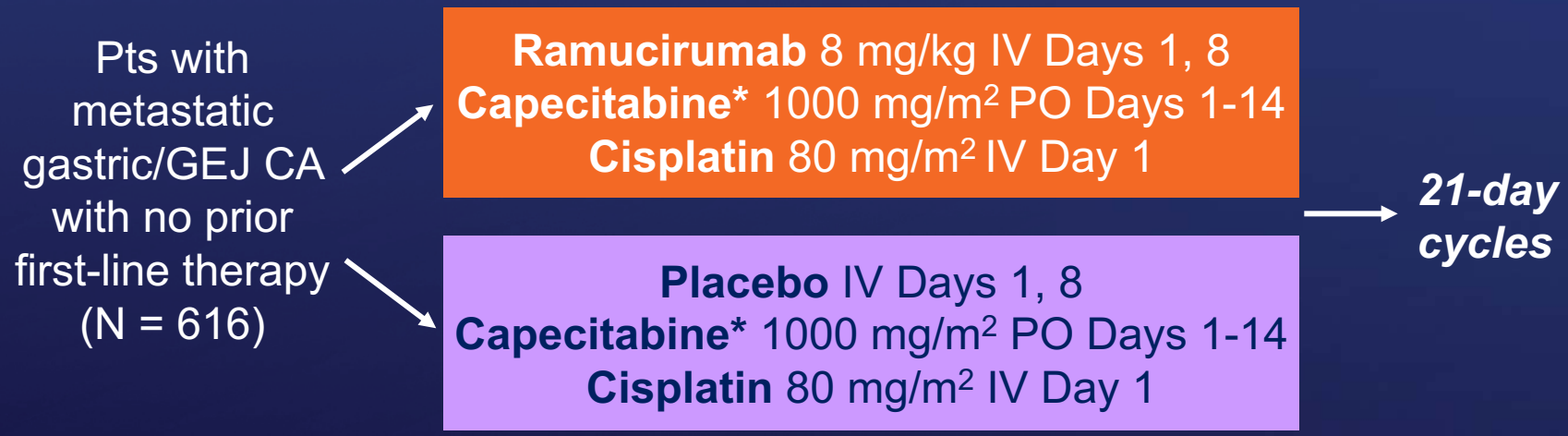
		RAM + mFOLFOX6 *N*/Events	PBO + mFOLFOX6 *N*/Events	HR (95% CI)
Overall	RAM vs PBO	84/37	84/59	0.76 (0.50–1.15)
Tumor location (pre-specified catagorization 1)	Esophagus/GEJ	65/30	64/46	0.80 (0.50–1.28)
	Gastric	19/7	20/13	0.65 (0.26–1.64)
Tumor location (pre-specified catagorization 2)	Esophagus	39/20	41/29	1.10 (0.61–1.97)
	Gastric/GEJ	45/17	43/30	0.53 (0.29–0.97)
ECOG performance status	0	40/16	43/30	0.74 (0.40–1.36)
	1	43/20	41/29	0.72 (0.40–1.27)
Age (years)	<65	42/22	56/40	0.86 (0.51–1.45)
	≥65	42/15	28/19	0.75 (0.38–1.49)
Prior surgery with curative intent	Yes	12/4	14/12	0.63 (0.19–2.03)
	No	72/33	70/47	0.81 (0.51–1.26)
Weight loss in 3 months prior to study entry	<10%	54/23	54/36	0.80 (0.47–1.35)
	≥10%	26/12	29/22	0.68 (0.33–1.37)



H. H. Yoon et al. Ann Oncol 2016;annonc.mdw423

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

- Randomized, double-blind, phase III trial

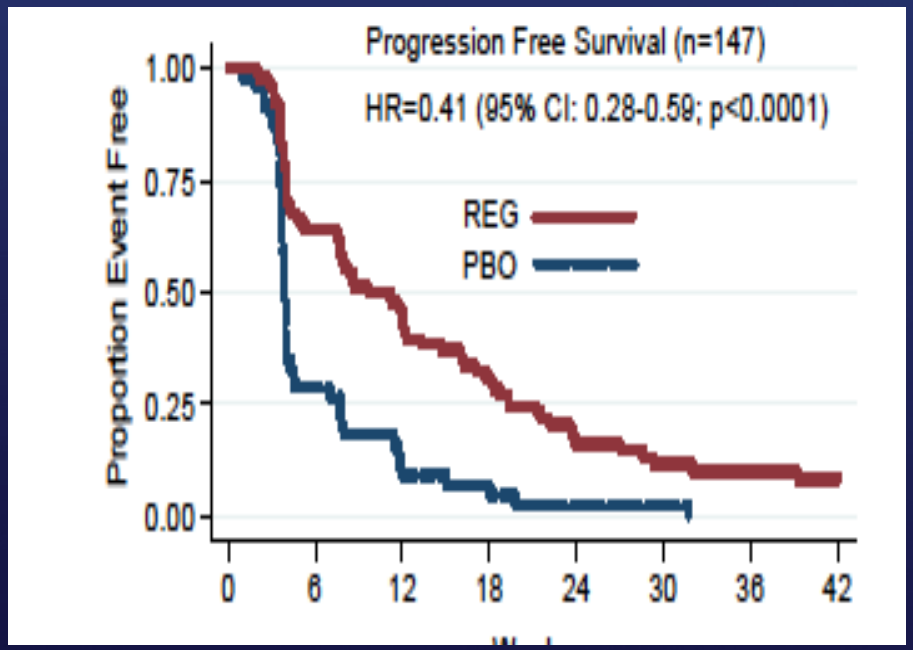


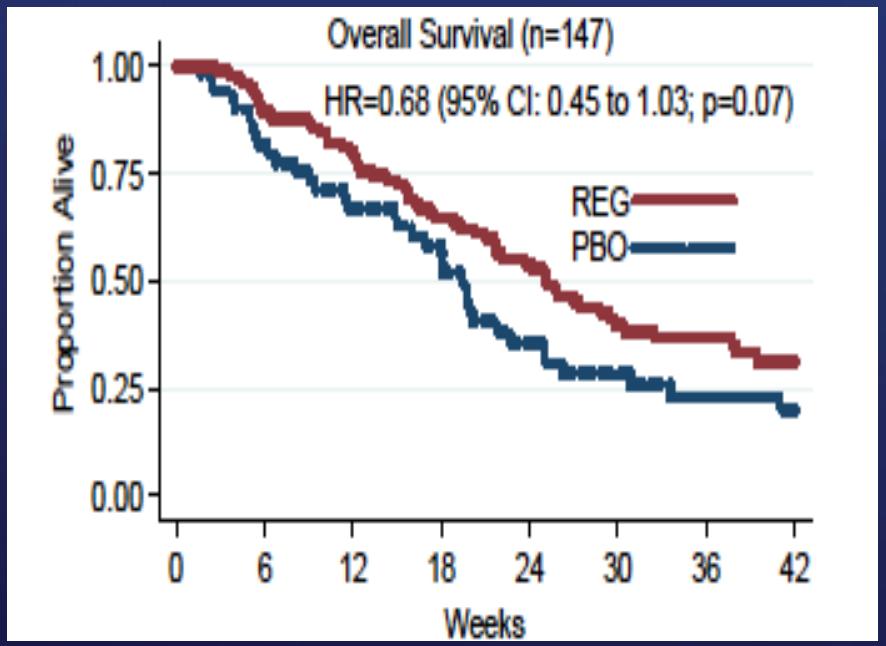
*Pts unable to take capecitabine receive 5-FU 800 mg/m^2/day Days 1-5.

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

ClinicalTrials.gov. NCT02314117.

INTEGRATE: A Randomised Phase II Double-Blind Placebo-Controlled Study of Regorafenib in Refractory Advanced Oesophago-Gastric Cancer





Pavlakis N. J Clin Oncol. 2016 Aug 10;34(23):2728-35

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A Randomised Phase III Double-Blind Placebo-Controlled Study of regorafenib in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)

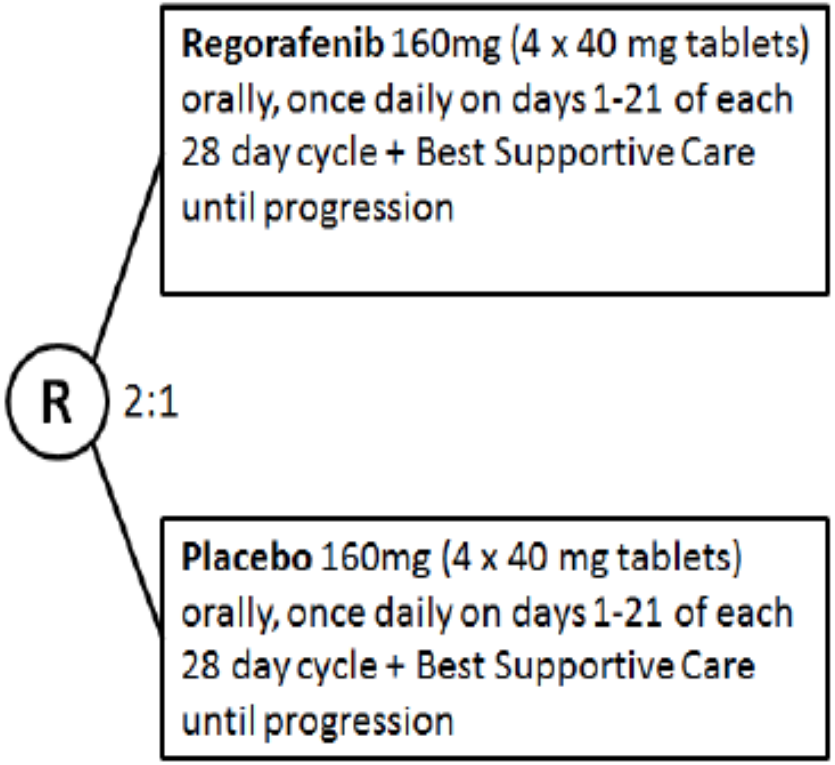
1.2. SCHEMA

Eligibility

- Metastatic or locally recurrent gastro-oesophageal cancer
- Adenocarcinoma or undifferentiated carcinoma
- Failed or intolerant to 2 lines of prior anti-cancer therapy

Stratification

- Location of tumour (GOJ vs gastric)
- Geographic region (Asia vs Rest of World)
- Prior VEGF inhibitors



Endpoints

Overall survival (Primary)
Progression free survival (PFS)
Objective tumour response rate (RR)
Quality of life (QoL)
Safety
Biomarkers
Pharmacokinetics (PK)

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Immunotherapy in GE cancers

KEYNOTE-012: Pembrolizumab in Gastric Cancer Cohort

	Central review*		Investigator review	
	Asia (n=17)	Rest of the world (n=19)	Asia (n=19)	Rest of the world (n=20)
Objective response (%, 95% CI†)	4 (24%, 7–50)	4 (21%, 6–46)	7 (37%, 16–62)	6 (30%, 12–54)
Best overall response				
Complete response‡	0	0	0	0
Partial response‡	4 (24%)	4 (21%)	7 (37%)	6 (30%)
Stable disease	3 (18%)	2 (11%)	2 (11%)	1 (5%)
Progressive disease	7 (41%)	12 (63%)	10 (53%)	13 (65%)
No assessment§	0	1 (5%)	0	0
Not determined¶	3 (18%)	0	0	0
Time to response (weeks)	8 (7–8)	8 (8–12)	8 (7–16)	8 (8–16)
Duration of response (weeks)	40 (32–NR)	NR (22–NR)	40 (30–NR)	42 (40–NR)
Median progression-free survival (95% CI; months)	1·9 (1·8–5·7)	1·8 (1·6–5·8)	1·9 (1·4–10·6)	1·8 (1·6–7·1)
Median overall survival (95% CI; months)	11·4 (3·1–NR)	NR (3·5–NR)	11·4 (3·1–NR)	NR (3·5–NR)

Data are n (%) or median (IQR) unless otherwise specified. Responses were assessed in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. Only confirmed responses are included. NR=not reached. *Three patients were not included in the central review because the central reviewer deemed their tumours not to be measurable. †95% CIs calculated based on the Clopper-Pearson exact method. ‡All responses were confirmed. §Patient with centrally evaluable disease at baseline who discontinued therapy because of clinical progression before the first scan. ¶Patients with centrally evaluable disease at baseline for whom best overall response could not be determined.

Table 3: Efficacy outcomes in evaluable patients

	Overall responses
Mononuclear inflammatory cell density score	
0	0/1 (0%)
1	2/8 (25%)
2	2/17 (12%)
3	4/9 (44%)
4	0/0
Total	8/35 (23%)
Tumour proportion score	
0	7/29 (24%)
1–49	0/3 (0%)
50–100	1/3 (33%)
Total	8/35 (23%)

Data are number of overall responses/number of patients (%). PD-L1 expression was calculated with the clinical trial assay. All tumours were PD-L1 positive in the prototype assay. No complete responses were achieved.

Table 4: Responses by PD-L1 expression

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Muro K et al. Lancet Oncol 2016; 17: 717–26

KEYNOTE 012: Relationship Between PD-L1 Expression And Clinical Outcomes In Patients With Advanced Gastric Cancer Treated With The Anti-PD-1 Monoclonal Antibody Pembrolizumab

- Reassessment of PD-L1 expression found that it only matters if expressed on immune cells but not as much on tumor cells (the criteria for allowance on study was expression on immune cells and/or tumor cells).
- Repeat testing in 35 patients suggested they were PD-L1 negative although they seem to respond to pembrolizumab.
- A recent genomic analysis suggested that 2 groups of gastric cancer patients exist that are either in the setting of MSI or EBV. This may explain some, but not all of the observed activity, adding to the uncertainty of how to optimally select patients for pembrolizumab in gastric cancer.

Muro K et al. Lancet Oncol 2016; 17: 717–26

The Cancer Genome Atlas Research Network. Nature. 2014;513:202-209.

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.

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ONO-4538-12: Phase 3, randomized, double-blind clinical trial evaluating the efficacy and safety of nivolumab in patients with refractory gastric cancer

- ONO-4538-12 is a multicenter, double-blind, randomized, placebo-controlled, Phase 3 clinical trial conducted in Japan, Korea and Taiwan
- Patients with unresectable advanced or recurrent gastric cancer, including gastro-esophageal junction cancer, refractory to, or intolerant of, standard therapy were included.
  - Patients were not selected based on PD-L1 expression
- Nivolumumab @ 3 mg/kg or placebo was administered every two weeks
- The primary endpoint was overall survival
  - **The study met its primary endpoint of overall survival (OS)**

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Targeting Cancer Stem Cells in the Treatment of Gastric Cancer

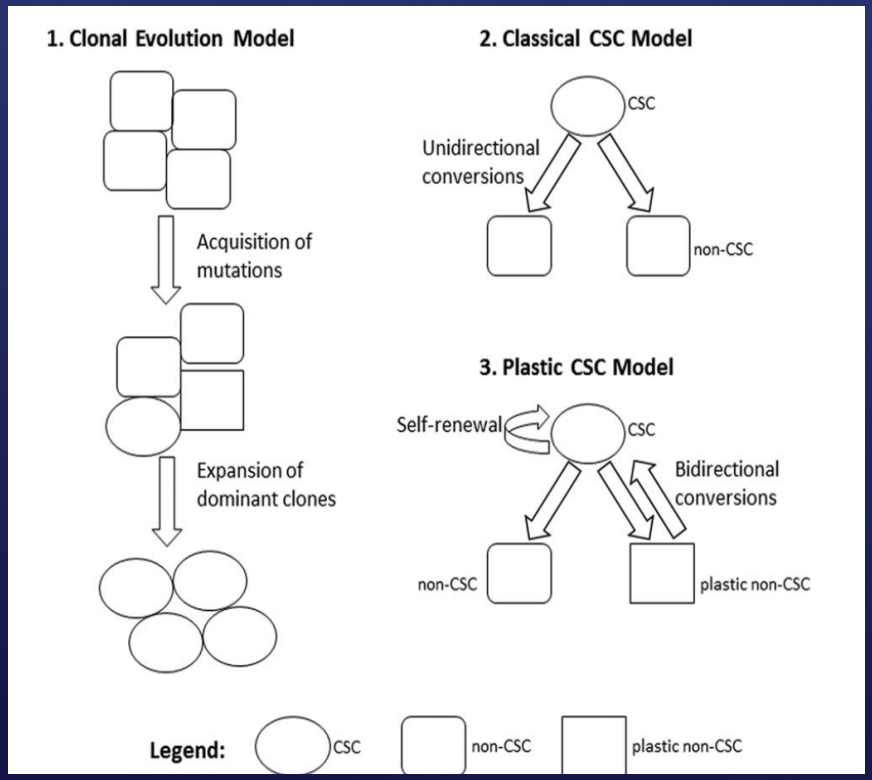
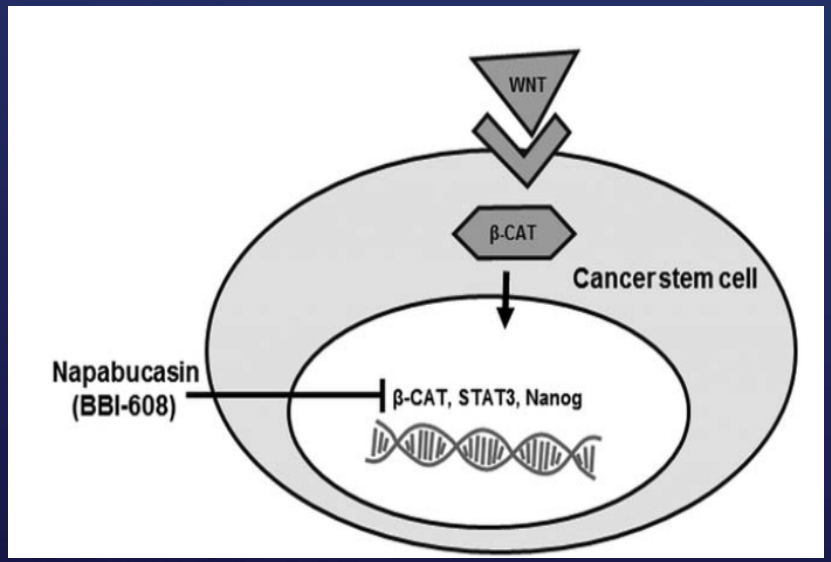


Figure 1: Primary models of cancer stem cells (CSCs) and tumor heterogeneity

Figure 2: Inhibiting the signal transducer and activator of transcription 3 (STAT3) signaling pathway with napabucasin



Bekaii-Saab T et al; *Cancer* 2017. In Press

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BBI608-201: A Phase 1b/2 study of BBI608 combined with paclitaxel in advanced gastric and gastroesophageal junction adenocarcinoma — Select AEs

Adverse event (N = 46)	Grade 3
Diarrhea	6.5%
Nausea	2.2%
Vomiting	8.7%
Abdominal pain	2.2%
Decrease in WBC count	2.2%

Becerra C et al. ASCO 2015; abst 4069

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BBI 608-201: Efficacy results

	All patients (n = 46)	Prior taxane (n = 19)	No taxane (n = 16)
Objective response rate	15%	11%	31%
Disease control rate	54%	68%	75%
Median PFS	13.0 wks	12.6 wks	20.6 wks
Median OS	31.6 wks	33.1 wks	39.3 wks

Evaluable patients who received 1 prior line of therapy without a taxane (n = 6): ORR = 50%; DCR = 83%

Becerra C et al. ASCO 2015; abst 4069

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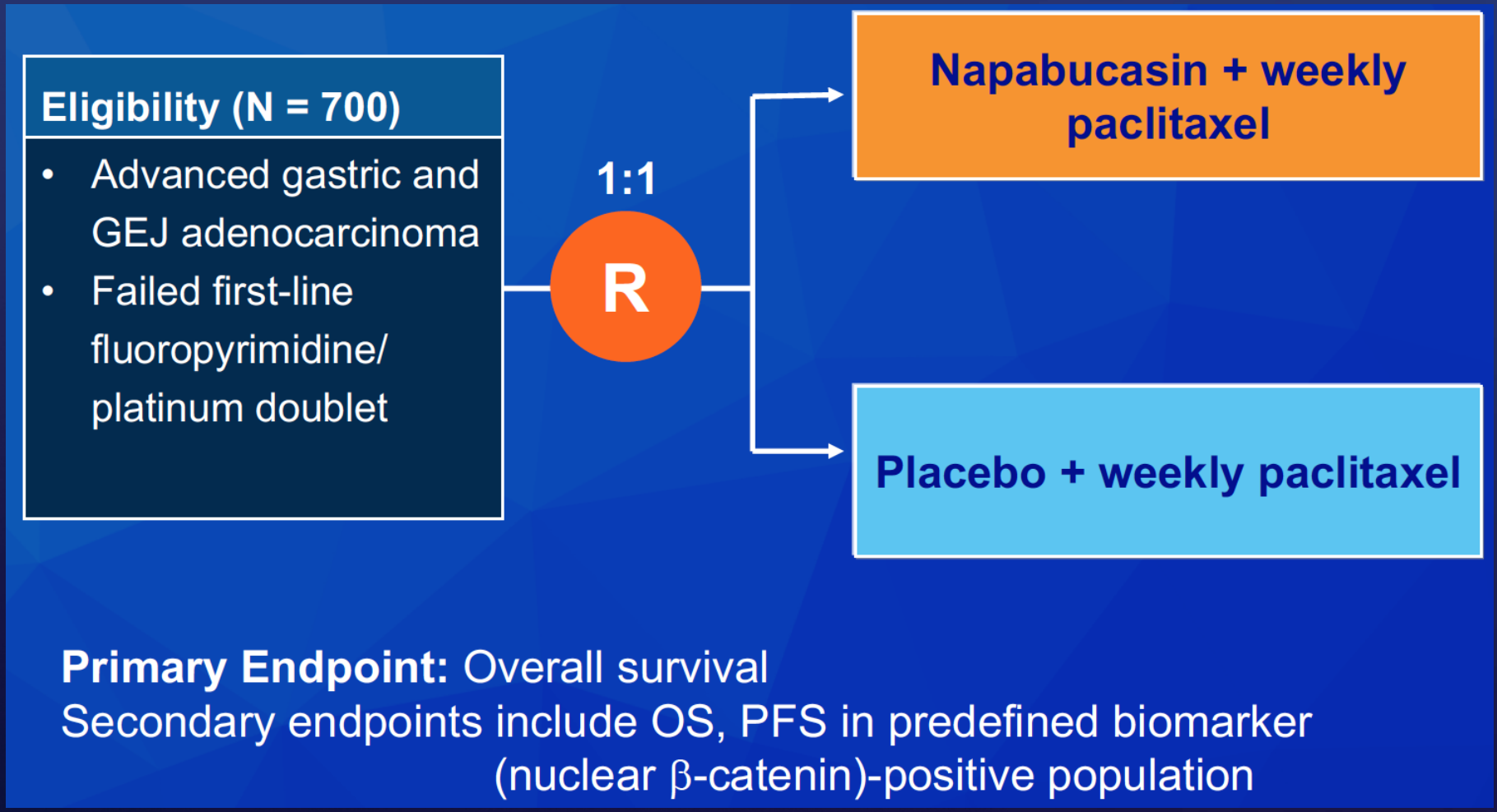
BRIGHTER: A Phase III Study of Napabucasin (BBI608) with Weekly Paclitaxel in Pretreated Advanced Gastric and GEJ Adenocarcinoma



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Shah MA et al. *Proc ASCO* 2016; abst TPS4144

Targeted Therapies In Advanced Gastro-esophageal Cancer

Pathway	Agent	Clinical Trial	Randomization	Patients
[illegible]	Ona[illegible]umab	METGASTRIC	FOLFOX +/- onartuzumab	800
	Rilotu[illegible]umab	RILOMET	ECX +/- rilotumumab	450
HER2	Pertuzumab	JACOB	XP-T +/- pertuzumab	780
	Tra[illegible]umab	ToGA	XP-+/- trastuzumab	349
	Trastuzumab	HELOISE	XP-T (standard) vs. XP-T (high dose)	400
	T[illegible]M1	GATSBY	T-DM1 vs taxane (2nd line)	412
	La[illegible]nib	TyTAN	Paclitaxel +/- lapatinib (2nd line)	261
[illegible]	Pan[illegible]umab	REAL-3	EOX +/- panitumumab	574
	Ce[illegible]nab	EXPAND	XP +/- cetuximab	904
Angiogenesis	Beva[illegible]umab	AVAGAST	XP +/- bevacizumab	774
	Ran[illegible]umab	REGARD	Ramucirumab vs. BSC (2nd line)	355
	Ran[illegible]umab	RAINBOW	Paclitaxel +/- Ramucirumab (2nd line)	665
	Ramucirumab	RAINFALL	Cape/5FU + Cis +/- Ram (1st line)	616
	Regorafenib	INTEGRATE II	Regorafenib vs Placebo (2nd line)	350
CSC	Napabucasin	BRIGHTER	Paclitaxel +/-BBI608 (2nd line)	700
[illegible]OR	Eve[illegible]mus	GRANITE	Everolimus vs. Placebo (2nd line)	656
Chemotherapy	TAS-102		TAS-102 vs. Placebo (2nd line)	500

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Questions & Discussion

