InterActive Clinical Scenarios

Refining the Management of Advanced Gastric Cancer

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Case: Background

- 40-year-old man presents with upper abdominal pain and unexplained weight loss of 6 pounds over 2 months
- Medical history of chronic gastritis, no history of familial cancer
- Esophagogastroduodenoscopy results reveal 4 ulcerated masses (6 cm) arising in the gastric cardia and extending into the gastric body in the lesser curvature of the stomach
- Biopsy results show poorly *Helicobacter pylori*–negative, HER2-negative poorly differentiated intestinal-type adenocarcinoma
- Computed tomography (CT) results show an enhanced mass in the lesser curvature of the stomach, lymphadenopathy along the gastrohepatic ligament, and multiple liver metastases up to 3 cm in size
- Laboratory: Hgb 11g/dL, AST and ALT 1.5 x ULN, bilirubin and renal function tests normal; CEA and CA 72-4 4x ULN
- ECOG PS 1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; PS, performance status; ULN, upper limits of normal

What would you recommend for first-line therapy for this young patient with metastatic HER2-negative gastric cancer?

1. Three drug docetaxel-based chemotherapy regimen (eg, DCF, DCX, DOF, DOX)
2. Three drug anthracycline-based regimen (eg, ECF, ECX, EOF, EOX)
3. Two drug chemotherapy regimen (eg, FOLFOX, cisplatin/5FU, cisplatin/capecitabine)
4. Clinical trial of targeted agent

Gastric Cancer Overview

- Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related deaths worldwide[1,2]
- Despite an overall decrease in gastric cancer, there is a growing incidence of gastroesophageal junction (GEJ) tumors[2-4]
- Metastatic gastric cancer has a poor prognosis
  - 2-year survival rate of around 20%[1,4-5]
  - Median survival: <1 year[6]
  - Overall survival (OS) improvement, 1975-77, 1984-86, 1999-2006
    16% » 18% » 27%

1. Kamangar F, et al. *J Clin Oncol.* 2006;24(14):2137-2150. 2. American Cancer Society. *Global Cancer Facts & Figures 2nd Edition.* Atlanta: American Cancer Society; 2011. 3. Garcia M, Jemal A, Ward EM, Center MM, Hao Y, Siegel RL, Thun MJ. *Global Cancer Facts & Figures 2007.* Atlanta, GA: American Cancer Society, 2007. 4. Kusano C, et al. *J Gastroenterol Hepatol*. 2008;23(11):1662-1665. 5. Cunningham SC, et al. *J Gastrointest Surg.* 2005;9(5):718-725. 6. Wagner AD, et al. *Cochrane Database Syst Rev.* 2010;(3):CD004064.

Metastatic Gastric Cancer

- 30% to 40% of patients present with stage IV disease due to the absence of effective screening
- No role for surgery given metastatic disease, unless primary tumor is bleeding or obstructing
- Systemic chemotherapy is the mainstay of therapy
- Median OS 10 months

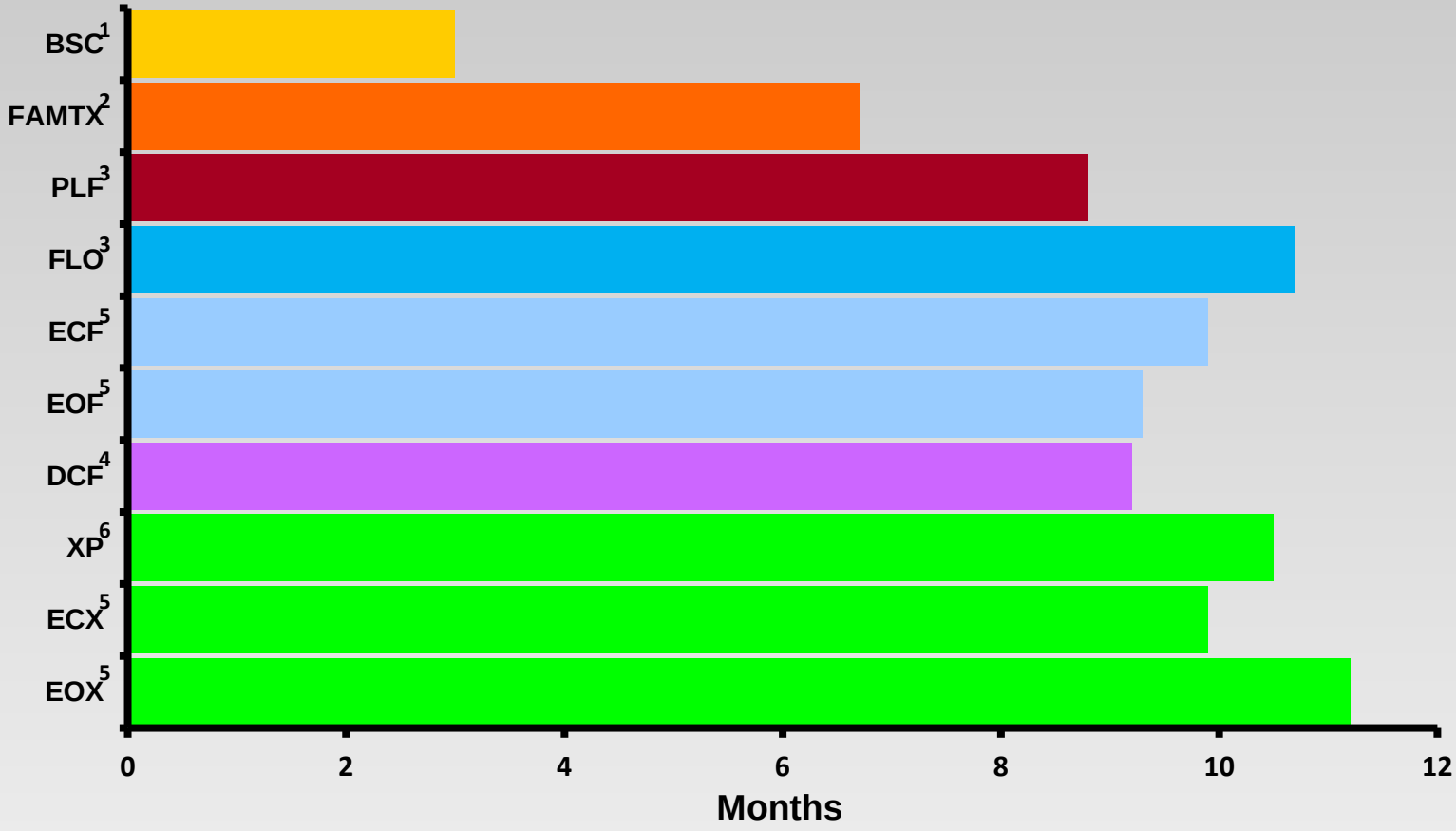
Chemotherapy Regimens for Metastatic Disease

- CIV 5FU + cisplatin[1-4]
  - 4-5 day to 6-week 5FU infusion
  - Response rate (RR) 20% to 40%
  - Median survival 7-10 months
- Adding a third drug
  - Epirubicin (ECF)[5,6]: RR 40% to 45%, median survival 9 months
  - Docetaxel (DCF)[7,8]: RR 37%, median survival 9 months
  - ~10% increment in RR
  - ~1-month increment in survival
- Capecitabine = 5FU, oxaliplatin = cisplatin

CIV, continuous intravenous infusion

1. Vanhoefer U, et al. *J Clin Oncol*. 2000;18(14):2648-2657. 2. Lacave AJ, et al. *Ann Oncol.* 1991;2(10):751-754. 3. Rougier P, et al. *Eur J Cancer.* 1994;30:1263-1269. 4. Lim DH, et al. *BMC Cancer.* 2010;10:583. 5. Cunnigham D, et al. *N Engl J Med.* 2008;358(1):36-46. 6. Webb A, et al. *J Clin Oncol.* 1997;15(1):261-267. 7. Van Cutsem E, et al. *J Clin Oncol.* 2006;24(31):4991-4997. 8. Roth AD, et al. *J Clin Oncol.* 2007;25(22):3217-3223.

Patient Outcome After First-Line Chemotherapy



1. Murad AM, et al. *Cancer*. 1993;72(1):37-41. 2. Vanhoefer U, et al. *J Clin Oncol*. 2000;18(14):2648-2657.
3. Al-Batran SE, et al. *J Clin Oncol.* 2008;26(9):1435-1442. 4. Van Cutsem E, et al. *J Clin Oncol.* 2006;24(31):4991-4997.
5. Cunnigham D, et al. *N Engl J Med.* 2008;358(1):36-46. 6. Kang YK, et al. *Ann Oncol*. 2009;20(4):666-673.

Patient Selection for Chemotherapy

- Assess age, functional status, comorbidities
- Combination chemotherapy preferred over single agents
  - Monotherapy with 5FU, capecitabine, taxanes in elderly patients, patients with poor PS
- Three-drug regimens
  - High functional status, younger patients without comorbidities
  - Willingness to tolerate side effects
  - Access to frequent follow up and toxicity assessment

Case: Patient Treatment and Monitoring

- Patient initiated on epirubicin/oxaliplatin/capecitabine (EOX), which he tolerated relatively well
- Initial response included disease stabilization and clinical improvement
- Results from CT evaluation after 6th cycle of chemotherapy show progression of liver metastases
  - AST and ALT 2 x ULN, bilirubin normal, CEA and CA 72-4 6x ULN
  - PS 1

Which of the following therapies would your recommend?

1. Single-agent chemotherapy
2. Reintroduction of an oxaliplatin-containing regimen (eg, FOLFOX)
3. Other combination chemotherapy (eg, FOLFIRI, docetaxel/cisplatin, docetaxel/irinotecan)
4. Paclitaxel + ramucirumab
5. Ramucirumab as a single agent

Second-Line Chemotherapy for Gastric Cancer

- Cougar Trial-02 (UK)[1]
  - 168 patients with gastric and GEJ cancer
  - **BSC vs docetaxel** 75 mg/m^2 every 3 weeks
  - OS improved from 3.6 months ➔ 5.2 months (HR 0.67, *P* = .01)
  - Responses in 7% of patients
- Kang[2]
  - 202 patients with gastric cancer
  - **Docetaxel** 60 mg/m^2 every 3 weeks or **irinotecan** 150 mg/m^2 every 2 weeks vs **BSC**
  - OS improved from 3.8 months ➔ 5.3 months (HR 0.657, *P* = .007)
  - RR 10% irinotecan, 17% for docetaxel

BSC, best supportive care; HR, hazard ratio; RR, response rate

1. Ford H, et al. *J Clin Oncol.* 2013;31(suppl 4): Abstract LBA4. 2. Kang JH, et al. *J Clin Oncol.* 2012;30(13):1513-1518.

Second-Line Chemotherapy: Paclitaxel vs Irinotecan

AGC refractory to prior FP confirmed by imaging

Age 20-75 years, PS 0-2, No history of irinotecan (CPT-11) or taxane

Weekly Paclitaxel (wPTX)

80 mg/m² d1, 8, 15 q4w

Irinotecan (IRI)

150 mg/m² d1, 15 q4w

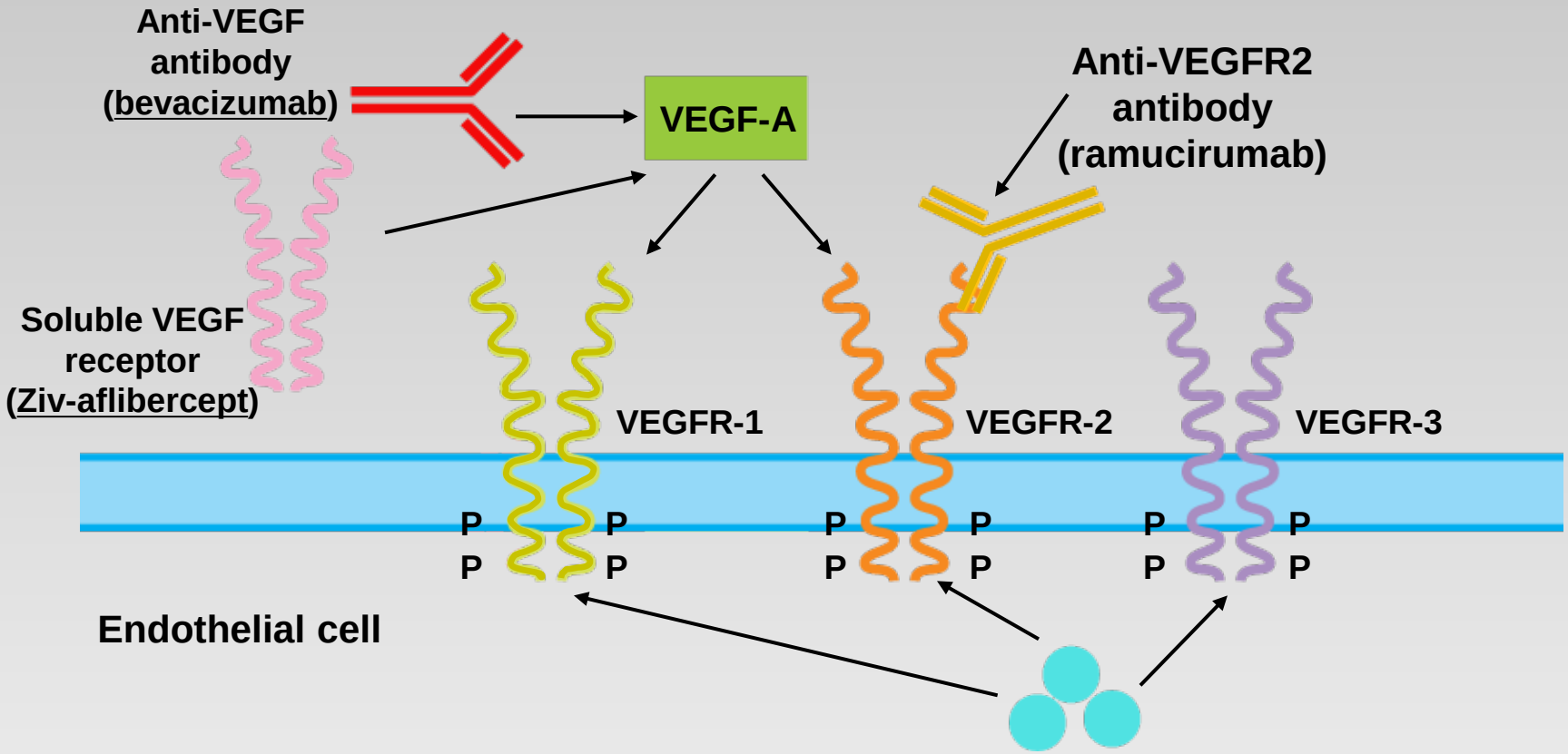
	n	Median	HR (95% CI)	*P*
wPTX	108	9.5 m	1.13 (0.86-1.49)	.38
IRI	111	8.4 m		

Log-rank test

AGC, advanced gastric cancer; FP, fluoropyrimidine plus platinum

Hironaka S, et al. *J Clin Oncol.* 2013;31(35): 4438-4444.

Agents Targeting the VEGF Pathway



VEGFR, VEGF receptor

Bevacizumab for Gastric Cancer

- AVAGAST: Cape-Cisplatin + / - **Bevacizumab**
  - Negative trial failed to meet primary endpoint of improved OS
  - Improvements in RR and PFS
  - Trend toward improved OS in patients treated in the United States and South America

Ohtsu A, et al. *J Clin Oncol.* 2011;29(30):3968-3976.

Next Generation VEGF Inhibitors

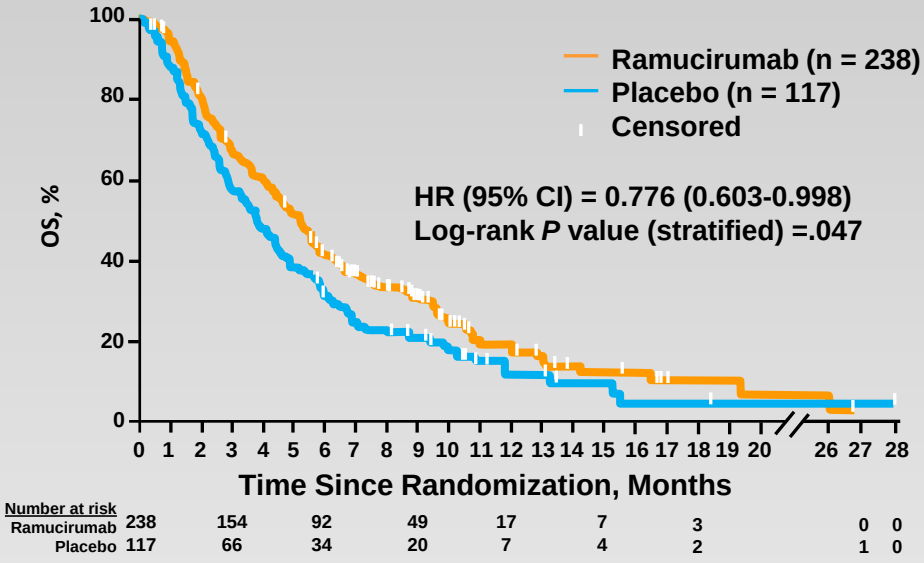
- Apatinib[1]
  - Small-molecule multitargeted TKI with activity against VEGFR
  - 144 patients, placebo vs apatinib 850 mg/d or 425 mg BID
  - OS 2.5 months, 4.83 months, 4.27 months
  - RR 10%
- Ramucirumab, REGARD Trial[2]
  - Humanized antibody blocking VEGFR2
  - 355 patients post 5FU or platinum-based chemotherapy
  - BSC vs ramucirumab 8 mg/kg IV every 2 weeks

TKI, tyrosine kinase inhibitor

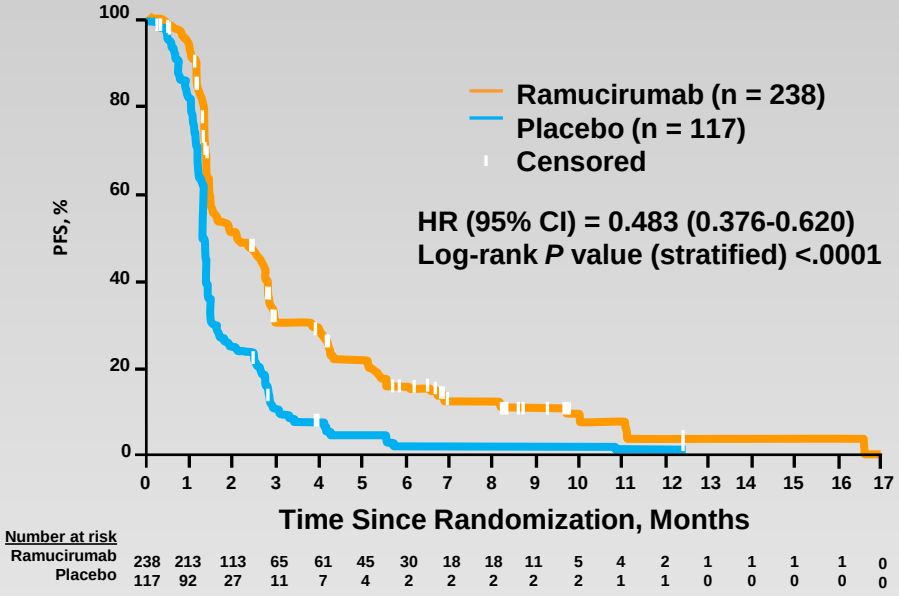
1. Li J, et al. *J Clin Oncol*. 2013;31(26):3219-3225. 2. Fuchs CS, et al. *Lancet*. 2014;383(9911):31-39.

REGARD Trial: Results

OS



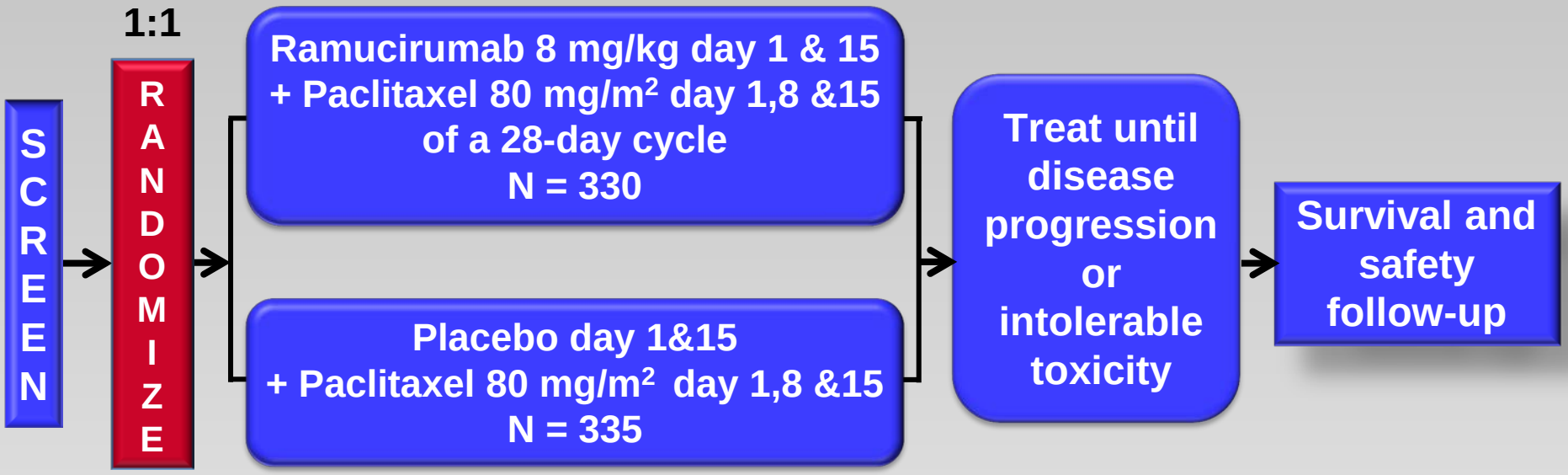
PFS



- Disease control rate improved from 23% to 49%
- Very low toxicity—8% grade ≥3 hypertension

Fuchs CS, et al. *Lancet*. 2014;383(9911):31-39.

RAINBOW: Phase III Study Design



- Important inclusion criteria:
  - Metastatic or locally advanced unresectable gastric or GEJ* adenocarcinoma
  - Progression after first-line platinum/fluoropyrimidine-based chemotherapy
- Stratification factors:
  - Geographic region
  - Measurable vs nonmeasurable disease,
  - Time to progression on first-line therapy (<6 months vs ≥6 months)

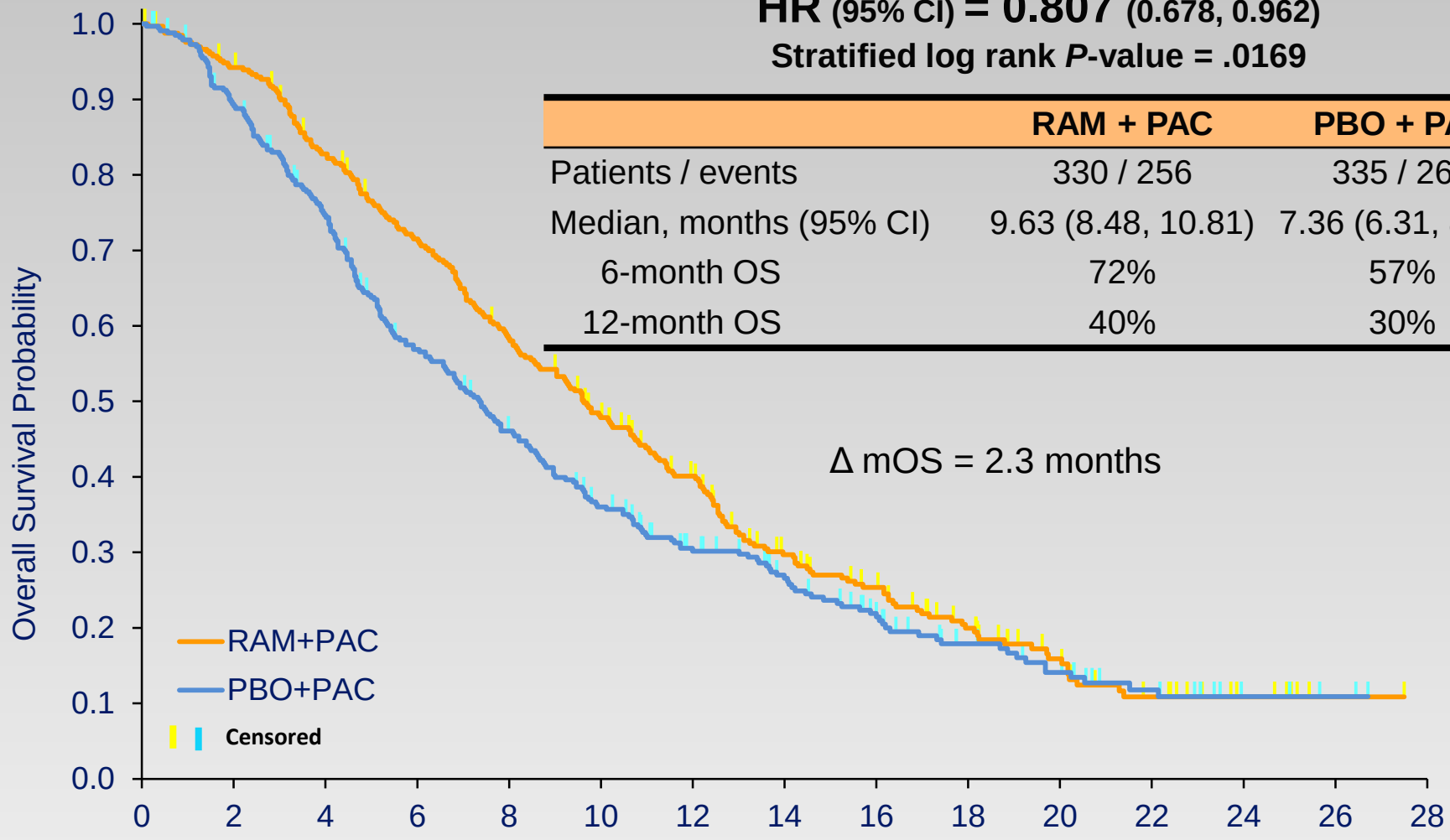
***Gastric and GEJ will be summarized under the term GC**

Wilke H, et al. *J Clin Oncol.* 2014;32(suppl 3): Abstract LBA7.

RAINBOW: Overall Survival

HR (95% CI) = 0.807 (0.678, 0.962)
Stratified log rank *P*-value = .0169

	RAM + PAC	PBO + PAC
Patients / events	330 / 256	335 / 260
Median, months (95% CI)	9.63 (8.48, 10.81)	7.36 (6.31, 8.38)
6-month OS	72%	57%
12-month OS	40%	30%

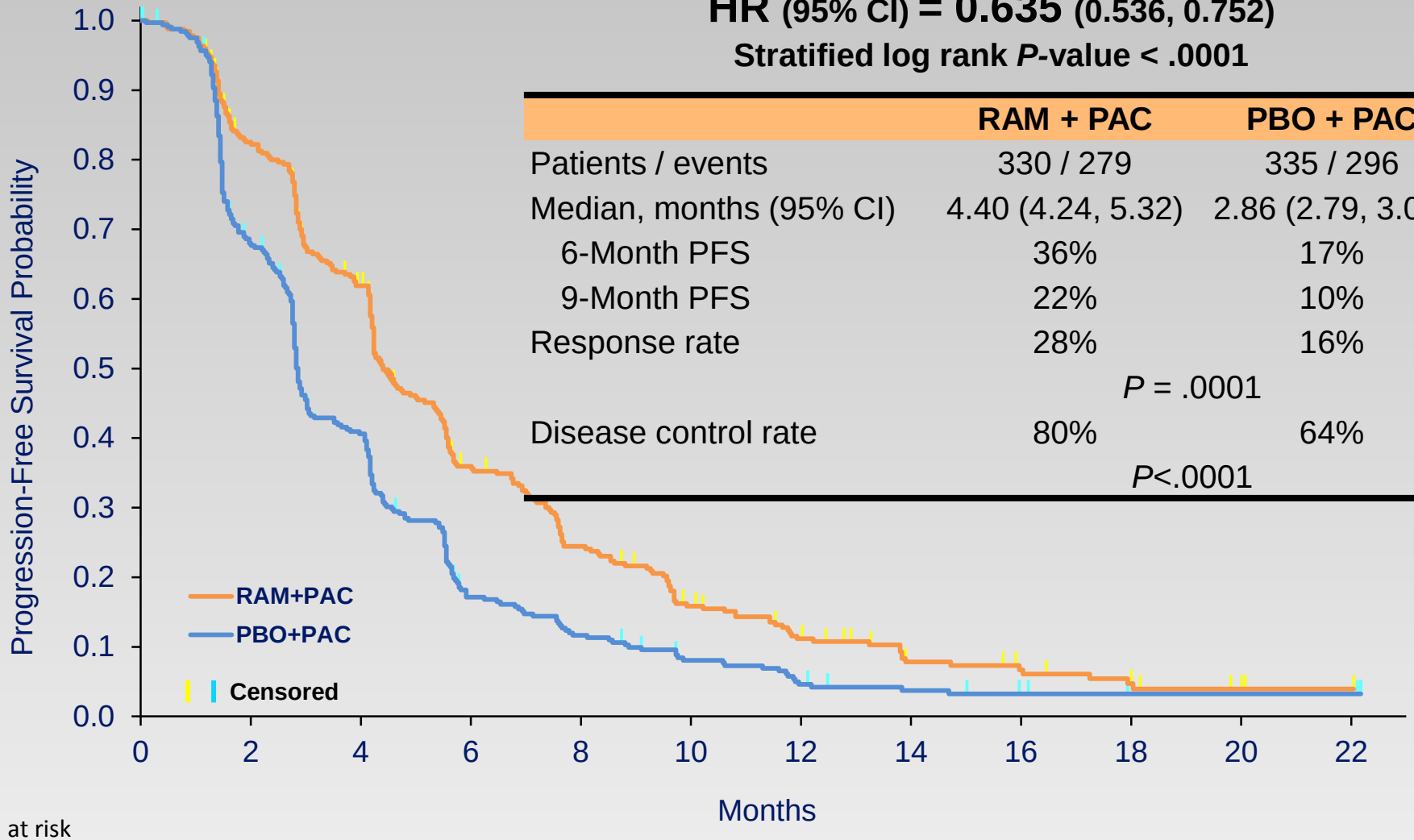


No. at risk

RAM + PAC	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
PBO + PAC	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

Wilke H, et al. *J Clin Oncol.* 2014;32(suppl 3): Abstract LBA7.

RAINBOW: PFS & Response Rates



HR (95% CI) = 0.635 (0.536, 0.752)

Stratified log rank *P*-value < .0001

	RAM + PAC	PBO + PAC
Patients / events	330 / 279	335 / 296
Median, months (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)
6-Month PFS	36%	17%
9-Month PFS	22%	10%
Response rate	28%	16%
	P = .0001	
Disease control rate	80%	64%
	P<.0001	

No. at risk

RAM + PAC	330	259	188	104	70	43	28	15	11	7	3	1
PBO + PAC	335	214	124	50	34	21	12	8	5	3	3	3

Wilke H, et al. *J Clin Oncol.* 2014;32(suppl 3): Abstract LBA7.

How Might Our Treatment Differ if This Patient Had Been HER2-Positive?

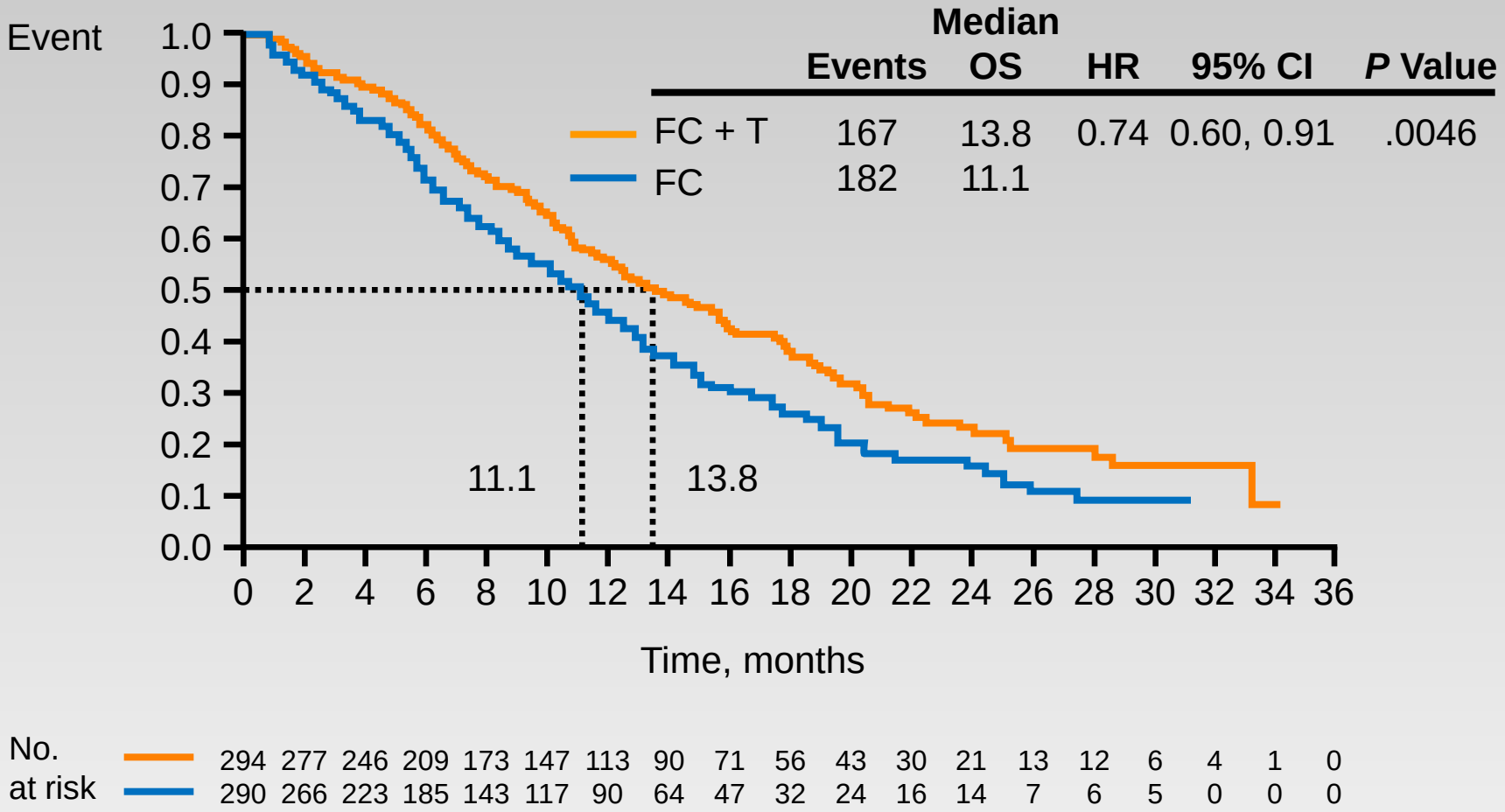
Expression of HER2 in Gastric Cancer

Incidence of HER2 Expression by IHC or FISH[1-6]		
All gastric cancer tumors	—	13% to 23%
Histology	Intestinal	16% to 34%
	Diffuse	6% to 7%
	Mixed	20%
	Unknown	14%
Primary tumor location	GEJ	25% to 34%
	Gastric	9% to 20%

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry

Bang YJ, et al. *Lancet.* 2010;376(9742):687-697. Gravalos C, et al. *Ann Oncol*. 2008;19(9):1523-1529. Yano T, et al. *J Clin Oncol*. 2004;22(14S): Abstract 4053. Gravolos C, et al. Presented at: 2007 Gastrointestinal Cancer Symposium; January 19-21, 2007: Orlando, Florida. Abstract 89. Lordick F, et al. *Eur J Cancer Suppl.* 2007;5(4): Abstract 3541.

Results of the Phase III ToGA Trial



T, trastuzumab

Bang Y, et al. *Lancet.* 2010;6736(10):61121-61132.

Second-Line Treatment in HER2-Positive Gastric Cancer

- No standard therapy for second-line HER2+ gastric cancer previously treated with trastuzumab
  - Lapatinib (EGFR and HER2 inhibitor)
    - Demonstrated activity but did not statistically improve OS compared with paclitaxel[1]
  - Pertuzumab (HER2 inhibitor): Clinical trials ongoing
  - Pertuzumab plus trastuzumab
    - Approved for metastatic breast cancer; phase II trial in gastric demonstrated activity[2]
  - Trastuzumab emtansine (T-DM1): Clinical trials ongoing

1. Satoh T, et al. *J Clin Oncol.* 2014;32(19):2039-2049. 2. Baselga J, et al. *J Clin Oncol.* 2010;28(7):1138-1144.

Patient Case Continued: Response to Therapy

- Patient received paclitaxel + ramucirumab, which he tolerated well
- Prior to the third cycle of therapy, the patient is diagnosed with grade 3 hypertension (blood pressure 180/100 mm Hg)

Patient Case Continued: Response to Therapy

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- Prior to the third cycle of therapy, the patient is diagnosed with grade 3 hypertension (blood pressure 180/100 mm Hg)

What would you do?

1. Continue paclitaxel + ramucirumab and give antihypertensive medication
2. Hold paclitaxel + ramucirumab until blood pressure is controlled
3. Continue paclitaxel, but hold ramucirumab until blood pressure is controlled
4. Continue treatment with ramucirumab in reduced dose
5. Discontinue ramucirumab permanently and continue paclitaxel alone

RAINBOW: Adverse Events of Special Interest

Category of Event†	RAM + PAC (n = 327)		PBO + PAC (n = 329)	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Bleeding/hemorrhage	41.9	4.3	17.9	2.4
Epistaxis	30.6	0	7.0	0
Hypertension	25.1	14.7	5.8	2.7
Proteinuria	16.8	1.2	6.1	0
GI hemorrhage	10.1	3.7	6.1	1.5
Renal failure	6.7	1.8	4.3	0.9
Infusion-related reaction	5.8	0.6	3.6	0
Venous thromboembolic	4.0	2.4	5.5	3.3
Cardiac failure	2.4	0.6	1.2	0.6
Arteriothromboembolic	1.8	0.9	1.5	0.9
GI perforation	1.2	1.2	0.3	0

†Each AESI category is composed of consolidated synonymous MeDRA preferred terms

Wilke H, et al. *J Clin Oncol.* 2014;32(suppl 3): Abstract LBA7.

Managing Adverse Events Associated With Angiogenesis Inhibitors

- Hypertension
  - Important to evaluate patients' risk of developing hypertension prior to the start of therapy (eg, current medications, salt intake)
  - Preventive strategies best, including changes in diet and regular blood pressure monitoring
  - Use antihypertensives to manage hypertension, but avoid diuretics if possible
  - Dose reductions or treatment discontinuation should be used as needed if hypertension does not resolve
- Proteinuria
  - Evaluate baseline proteinuria
  - Test frequently (every 3 weeks to 4 weeks) using qualitative means such as dipstick test
    - Use quantitative measure if levels increase
  - Discontinue therapy if grade 2+ proteinuria develops

Shord SS, et al. *Am J Health Syst Pharm*. 2009;66(11):999-1013. Saif MW. *J Support Oncol.* 2009:7(6):245-251.

Managing Adverse Events Associated With Angiogenesis Inhibitors (cont)

- Thrombotic events (TEs)
  - Prophylactic aspirin may be used for high-risk patients when there are no contraindications
  - With grade 3 or higher venous TEs, hold angiogenesis inhibitors while initiating anticoagulants, and resume when patient is stable
  - Therapy should be discontinued if any arterial TEs develop
- Bleeding, wound healing
  - Discontinue angiogenesis inhibition 6 weeks to 8 weeks prior to elective surgeries; wait 4 weeks after surgery to reinstate
  - Avoid anticoagulants when possible (in absence of TEs)

Shord SS, et al. *Am J Health Syst Pharm*. 2009;66(11):999-1013. Saif MW. *J Support Oncol.* 2009:7(6):245-251.

prIME POINTS™

Second-Line Treatment of Gastric Cancer

- Though first-line treatment for gastric cancer has improved, patients will eventually relapse
- Targeted therapy represents an alternative to toxic chemotherapy combinations
- The anti-VEGFR antibody ramucirumab improves OS in patients who have progressed on first-line treatment
- Adverse events for ramucirumab are manageable with monitoring and dose reduction
- Several molecular pathways are being investigated for potential future therapies