ASCO Updates 2014: GI Cancers

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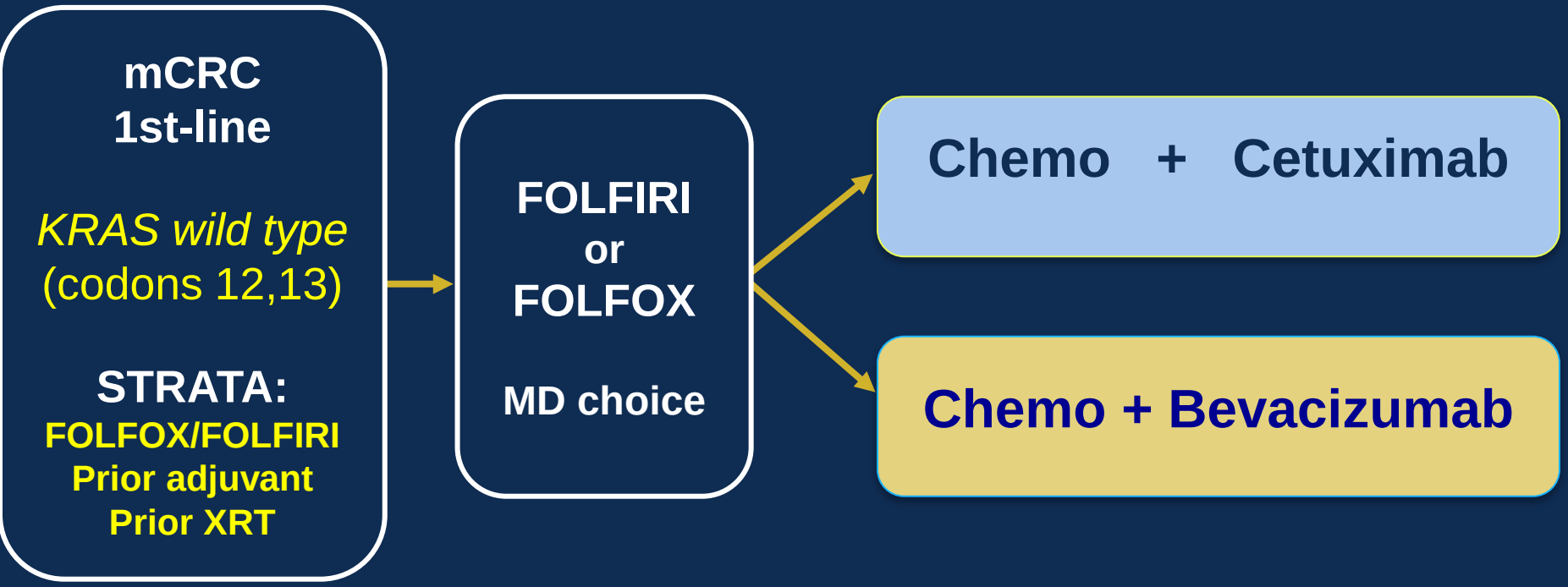
Disclosures

- Advisory Role
  - Genentech, Roche, Pfizer, Sanofi, Regeneron, BMS, Amgen, Novartis, Tracon, Threshold, Lilly, GSK, Incyte
- Research Funding
  - Genentech, Roche, Pfizer, Sanofi, Regeneron, BMS, Amgen, Novartis, Tracon, Threshold, GSK, Incyte
- No Stock, Leadership, Speakers Bureaus
- All conflicts managed by DUMC

CALGB/SWOG 80405: Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients w/ KRAS *wild type* untreated metastatic adenocarcinoma of the colon or rectum

A Venook, D Niedzwiecki, HJ Lenz,
F Innocenti, M Mahoney, B O'Neil,
J Shaw, B Polite, H Hochster,
R Goldberg, R Mayer, R Schilsky,
M Bertagnolli, C Blanke
for the ALLIANCE and SWOG

CALGB/SWOG 80405: FINAL DESIGN

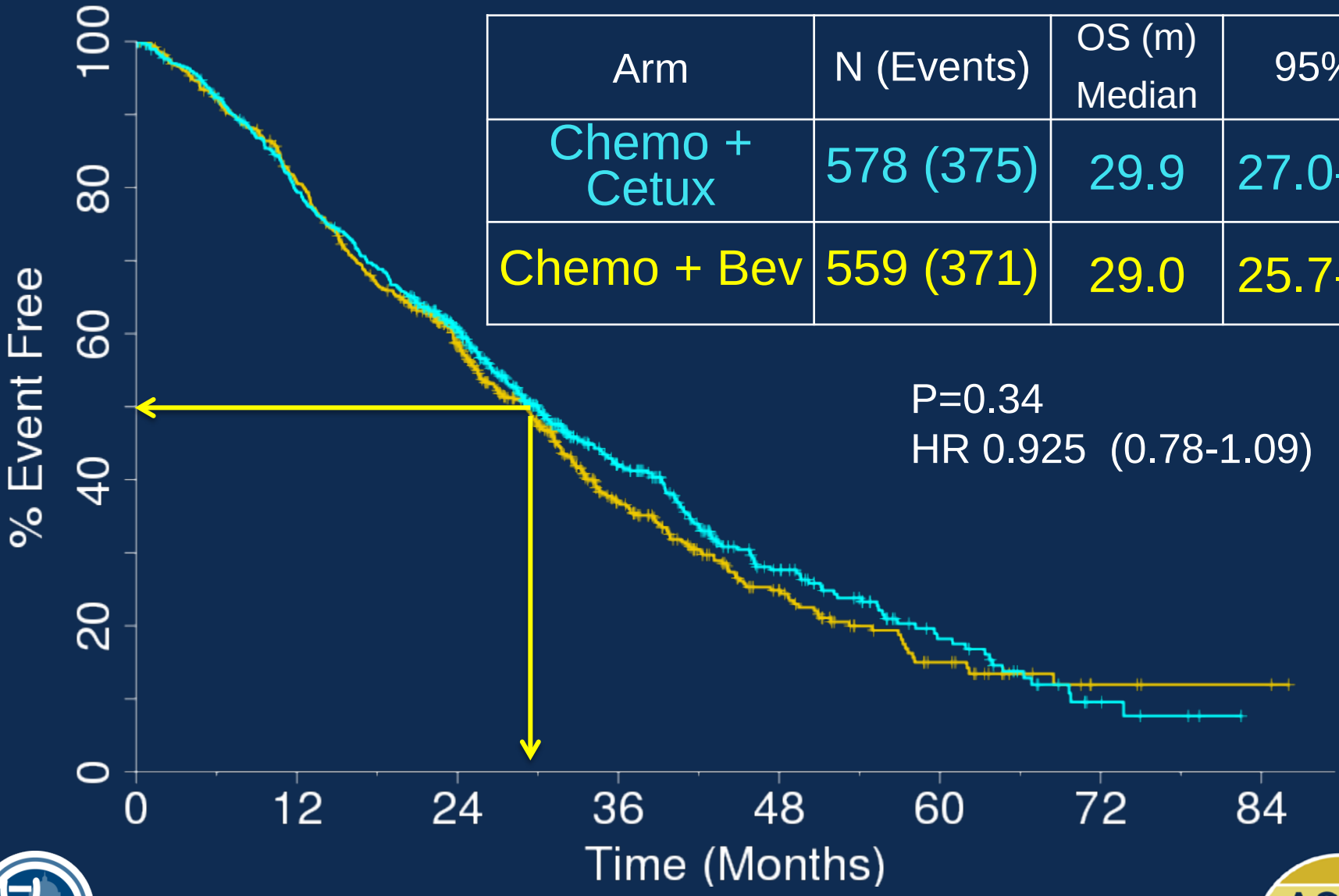


N = 1140

1˚ Endpoint: Overall Survival

CALGB/SWOG 80405: Overall Survival

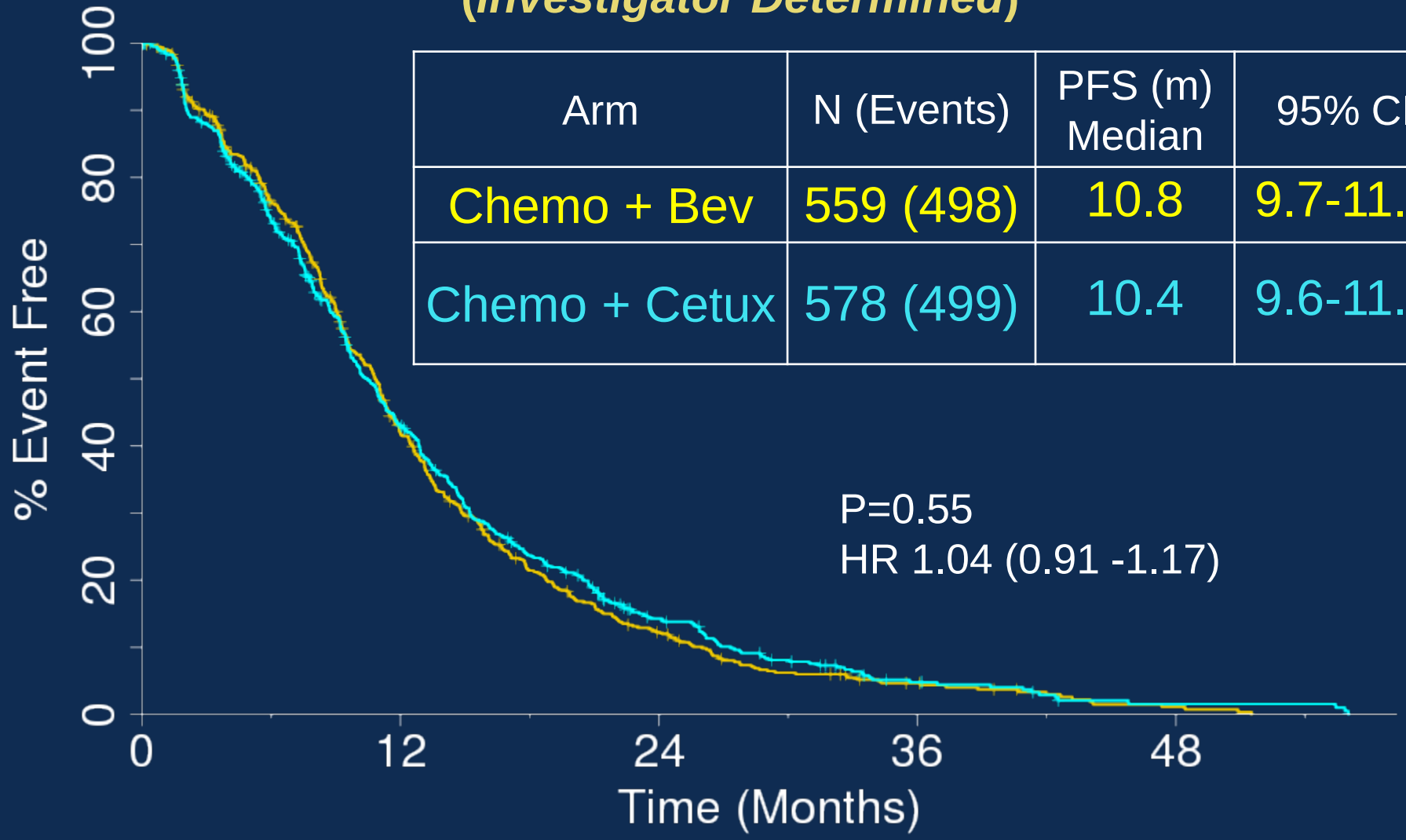
Arm	N (Events)	OS (m) Median	95% CI
Chemo + Cetux	578 (375)	29.9	27.0-32.9
Chemo + Bev	559 (371)	29.0	25.7-31.2



P=0.34
HR 0.925 (0.78-1.09)

CALGB/SWOG 80405: Progression-Free Survival
(*Investigator Determined*)

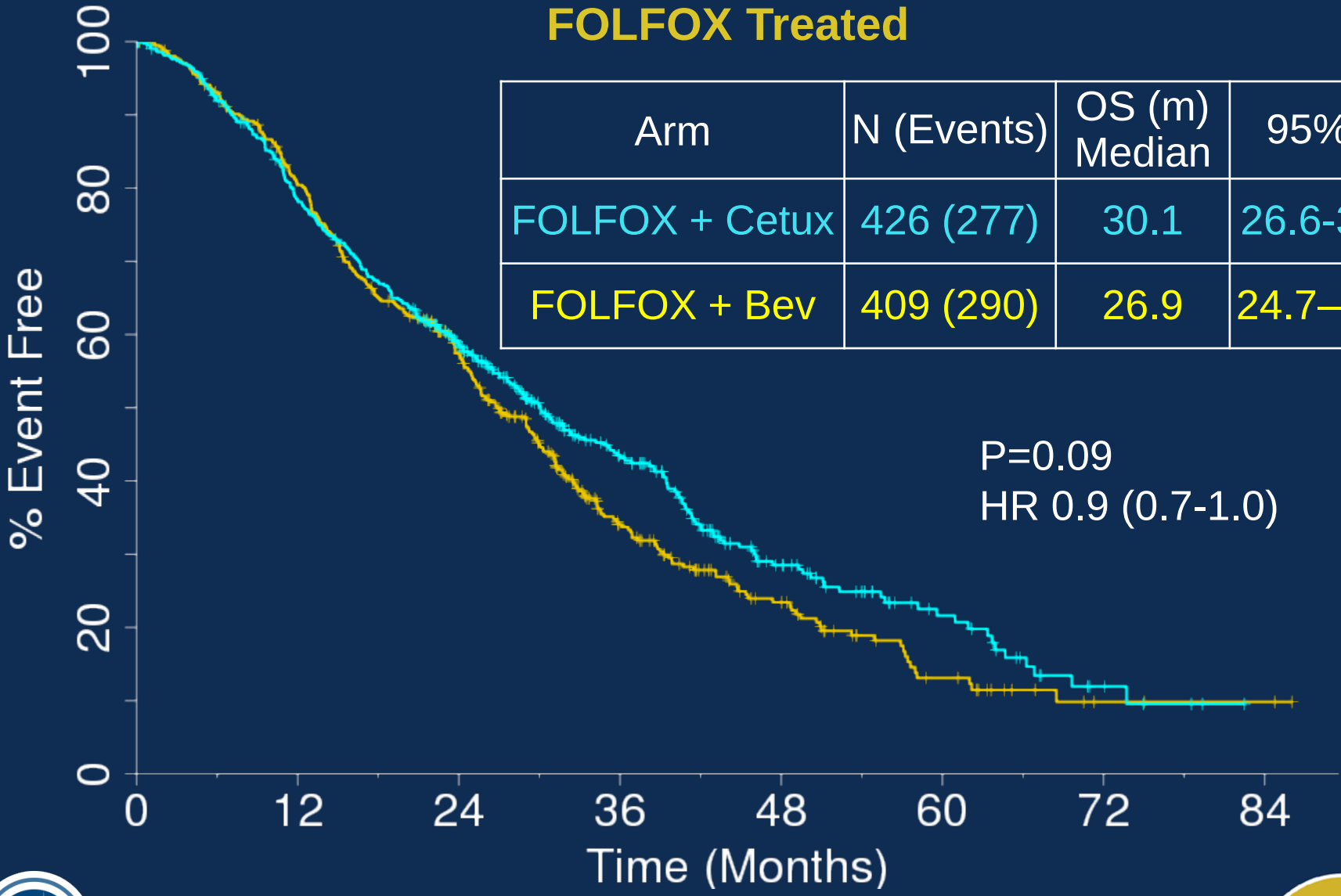
Arm	N (Events)	PFS (m) Median	95% CI
Chemo + Bev	559 (498)	10.8	9.7-11.4
Chemo + Cetux	578 (499)	10.4	9.6-11.3



CALGB/SWOG 80405: Overall Survival

FOLFOX Treated

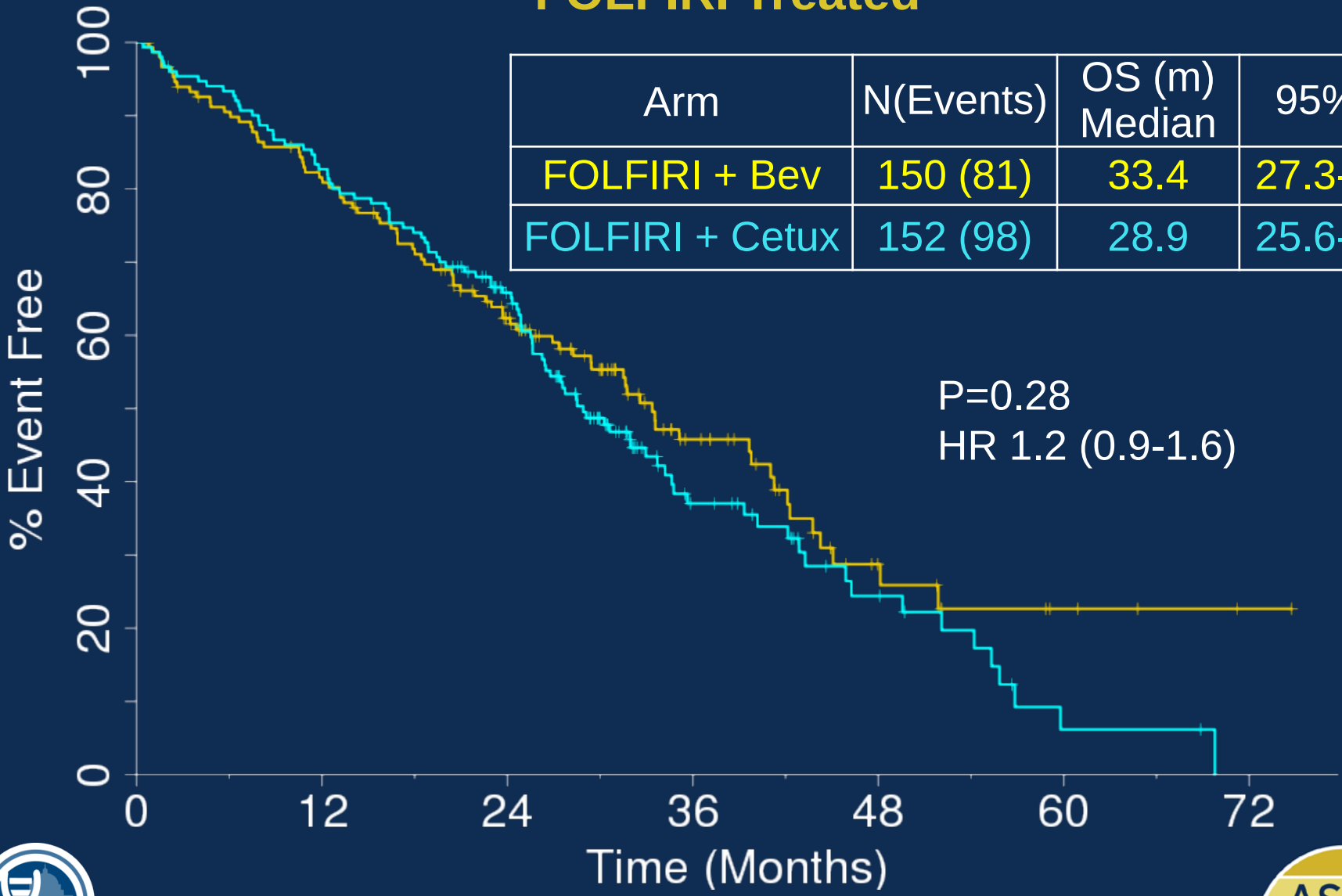
Arm	N (Events)	OS (m) Median	95% CI
FOLFOX + Cetux	426 (277)	30.1	26.6-34.8
FOLFOX + Bev	409 (290)	26.9	24.7–30.0



P=0.09
HR 0.9 (0.7-1.0)

CALGB/SWOG 80405: Overall Survival
FOLFIRI Treated

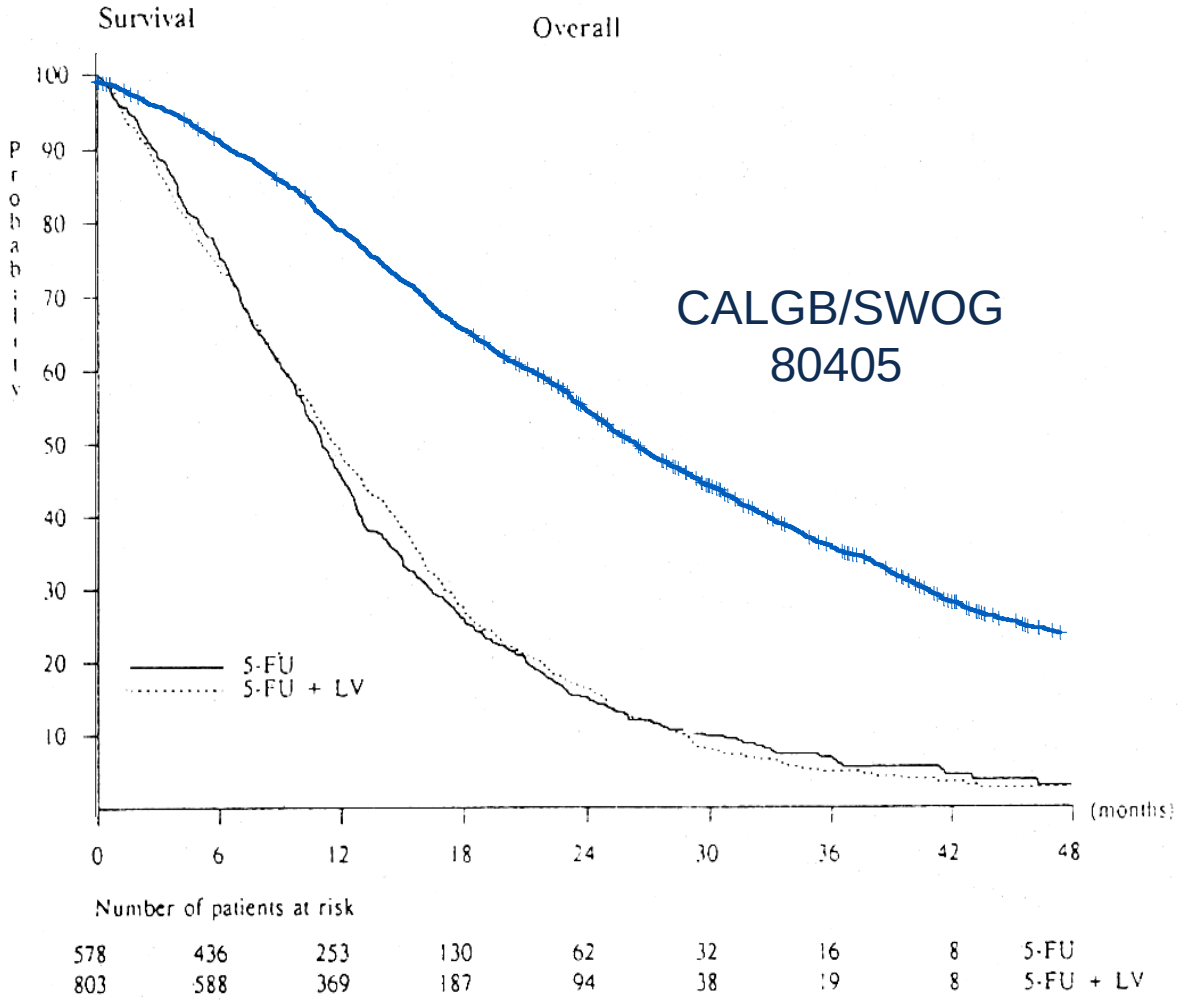
Arm	N(Events)	OS (m) Median	95% CI
FOLFIRI + Bev	150 (81)	33.4	27.3-41.3
FOLFIRI + Cetux	152 (98)	28.9	25.6-34.2



P=0.28
HR 1.2 (0.9-1.6)

Colorectal Cancer: 20 Years Later

meta-analysis 1992 80405 results



CALGB/SWOG
80405

Fig 2. Overall survival.

J Clin Oncol, 1992

Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab

F. Ciardiello, H.-J. Lenz, C.-H. Köhne, V. Heinemann, S. Tejpar, I. Melezínek, F. Beier, C. Stroh,

Eric Van Cutsem*

*University Hospitals Leuven and KU Leuven, Leuven, Belgium

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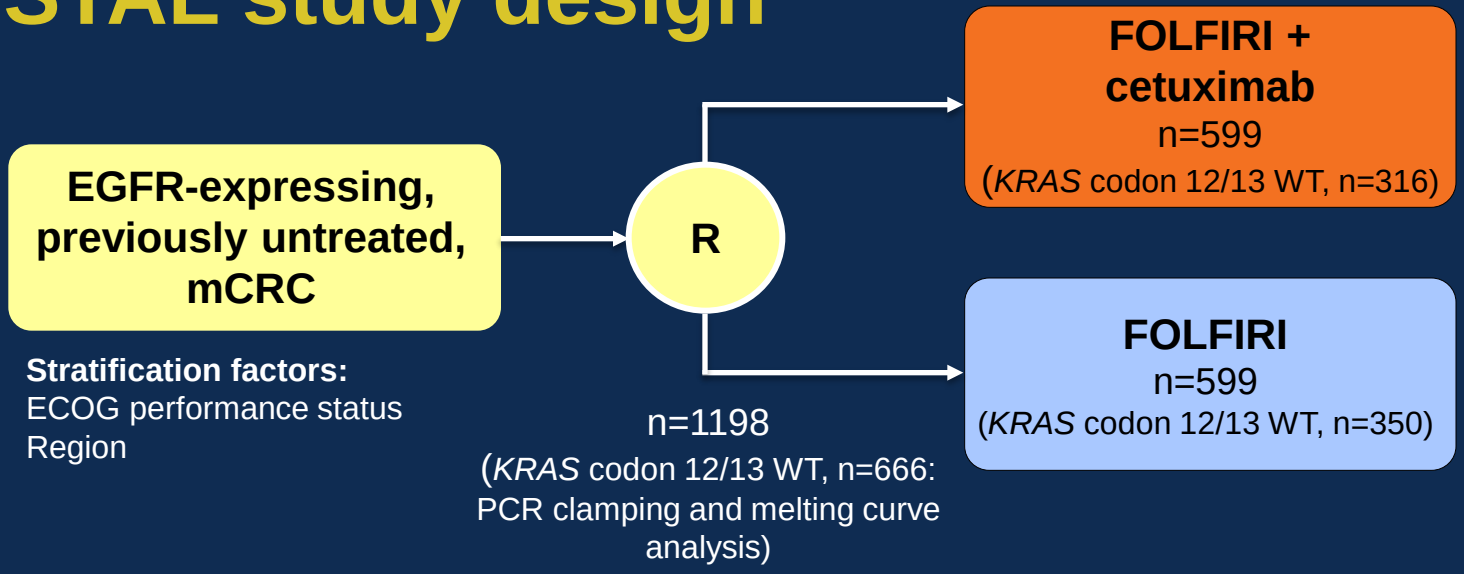
CRYSTAL study design



	FOLFIRI (q2w)	Cetuximab
Irinotecan	180 mg/m^2, day 1	400 mg/m^2 initial dose then
LV	200 mg/m^2*, day 1	250 mg/m^2 weekly
5-FU	400 mg/m^2 bolus, then	
	2400 mg/m^2 infusion over 46 h	

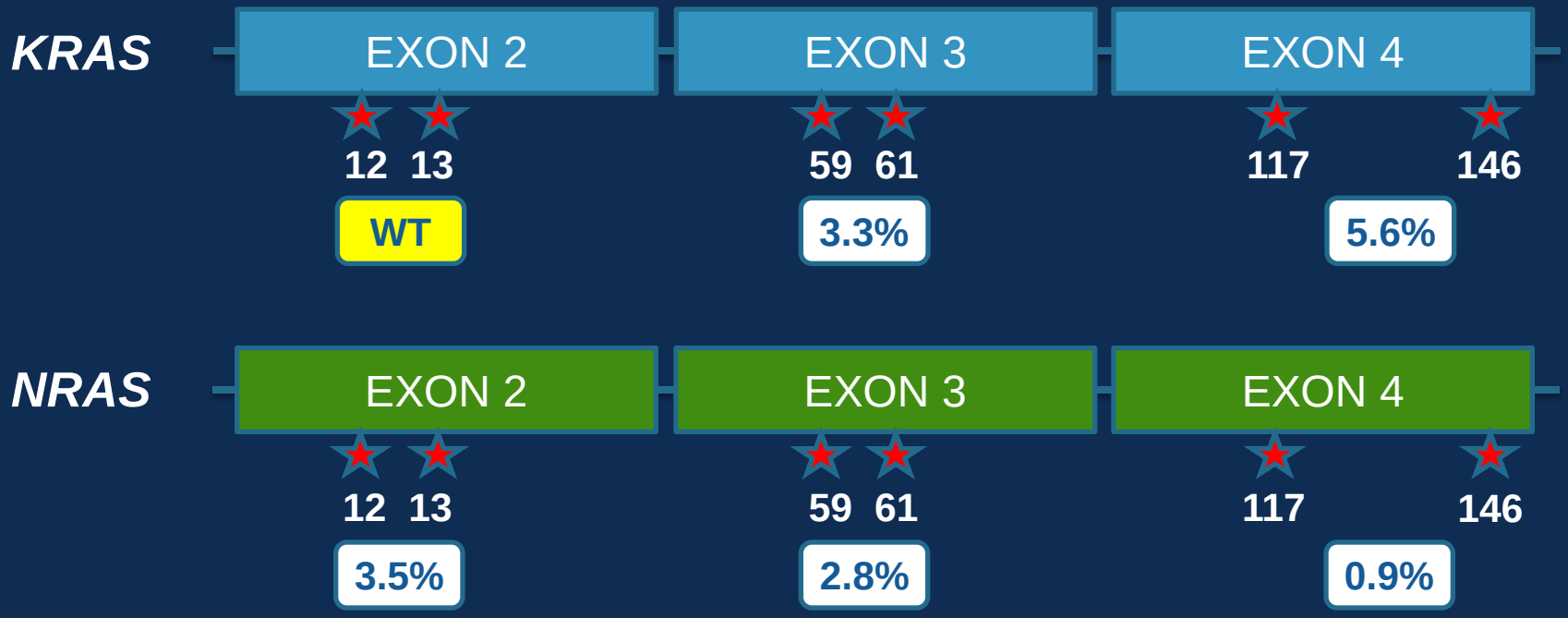
Treatment until disease progression, unacceptable toxicity, withdrawal of consent

*L-form; 400 mg/m^2, racemic. 5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin; PCR, polymerase chain reaction; R, randomization; WT, wild-type

Van Cutsem E, et al. N Engl J Med 2009;360:1408-17
Van Cutsem E, et al. J Clin Oncol 2011;29:2011-9

Other *RAS* mutations: CRYSTAL

430/666 patients with *KRAS* codon 12/13 wild-type tumors evaluable for tumor *RAS* status
Other *RAS* mutations: 63/430 (14.7%) patients



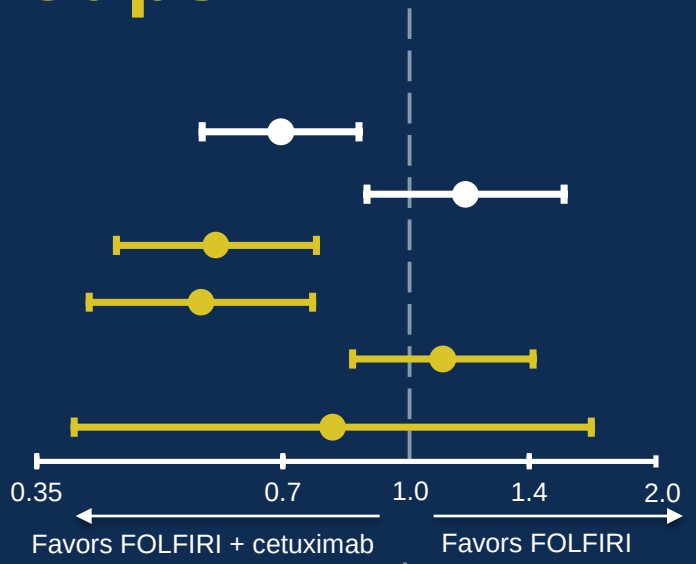
Percentages relate to fraction of *RAS* evaluable patients with mutations in particular exons

In 5 tumors with *KRAS* mutations, an *NRAS* mutation also detected (low prevalence, 0.1%–<5%, in 4/5 samples)
In 1 tumor, 2 *NRAS* mutations detected (1 with low prevalence)

Efficacy: *RAS* subgroups

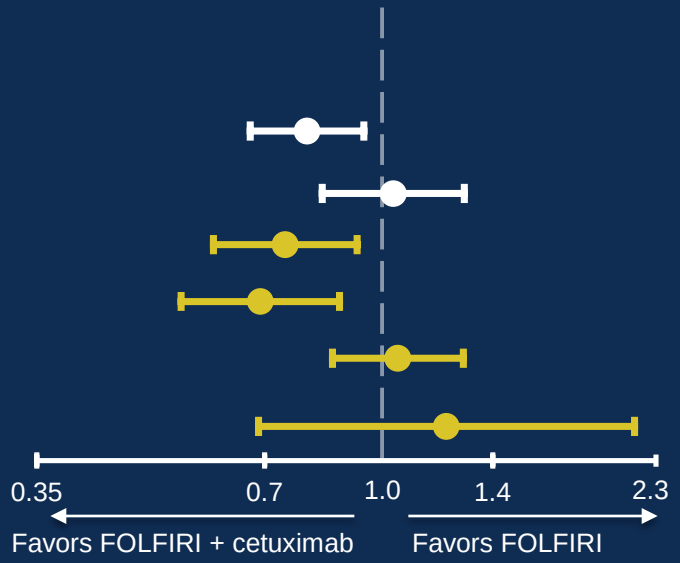
PFS

Subgroup	n	HR (95% CI)
***KRAS* codon 12/13 WT**	666	0.70 (0.56–0.87)
***KRAS* codon 12/13 MT**	397	1.17 (0.89–1.54)
RAS* evaluable	430	0.58 (0.44–0.77)
***RAS* WT**	367	0.56 (0.41–0.76)
Any *RAS* MT†	460	1.10 (0.85–1.42)
Other *RAS* MT*	63	0.81 (0.39–1.67)



OS

Subgroup	n	HR (95% CI)
***KRAS* codon 12/13 WT**	666	0.80 (0.67–0.95)
***KRAS* codon 12/13 MT**	397	1.04 (0.83–1.28)
RAS* evaluable	430	0.75 (0.60–0.93)
***RAS* WT**	367	0.69 (0.54–0.88)
Any *RAS* MT†	460	1.05 (0.86–1.28)
Other *RAS* MT*	63	1.22 (0.69–2.16)



**KRAS* codon 12/13 WT; †*KRAS* codon 12/13 or other *RAS* MT, mutant; WT, wild-type

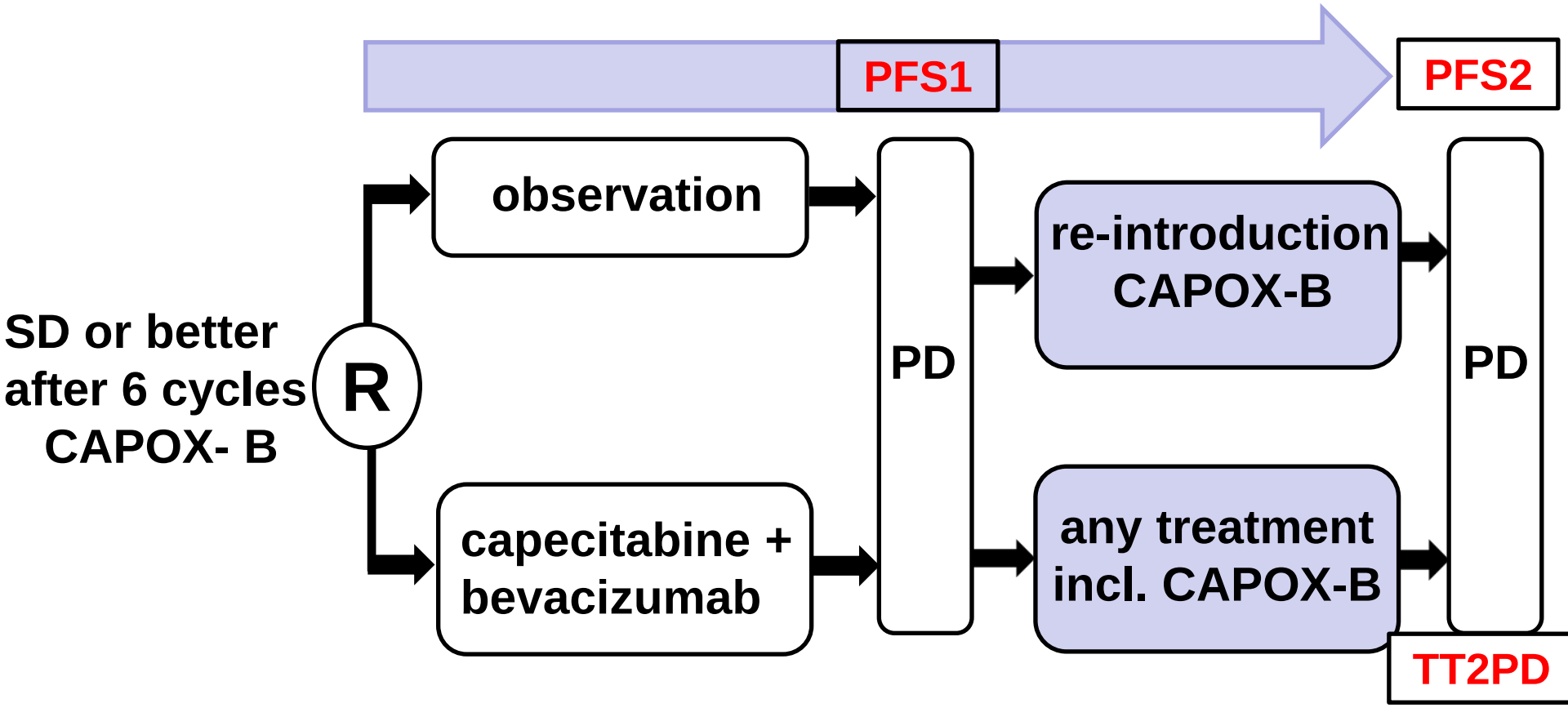
Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer

Final results and subgroup analyses of the phase 3 CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG)

ASCO June 2nd 2014, Chicago

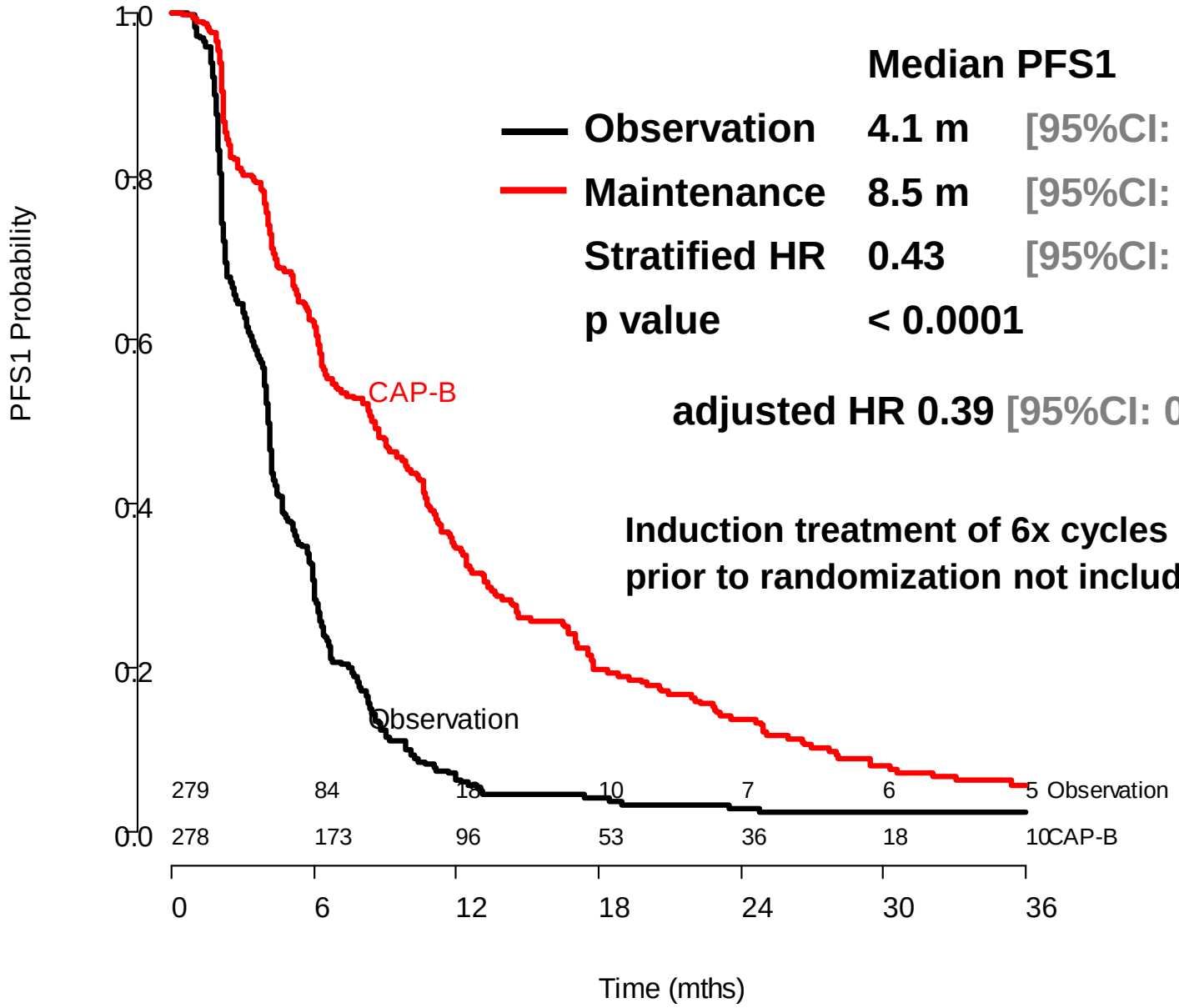
Miriam Koopman, L Simkens, A May, A ten Tije, G Creemers, O Loosveld, F de Jongh, F Erdkamp, Z Erjavec, A van der Torren, J van der Hoeven, P Nieboer, J Braun, R Jansen, J Haasjes, A Cats, J Wals, V Derleyn, A Honkoop, L Mol, H van Tinteren, C Punt

Study design



- Stratification factors: prior adjuvant therapy, serum LDH, response to induction treatment, WHO PS, institution
- Primary endpoint: PFS2
- PFS2 is considered to be equal to PFS1 for patients in whom CAPOX- B is not reintroduced after PFS1 for any reason

PFS1

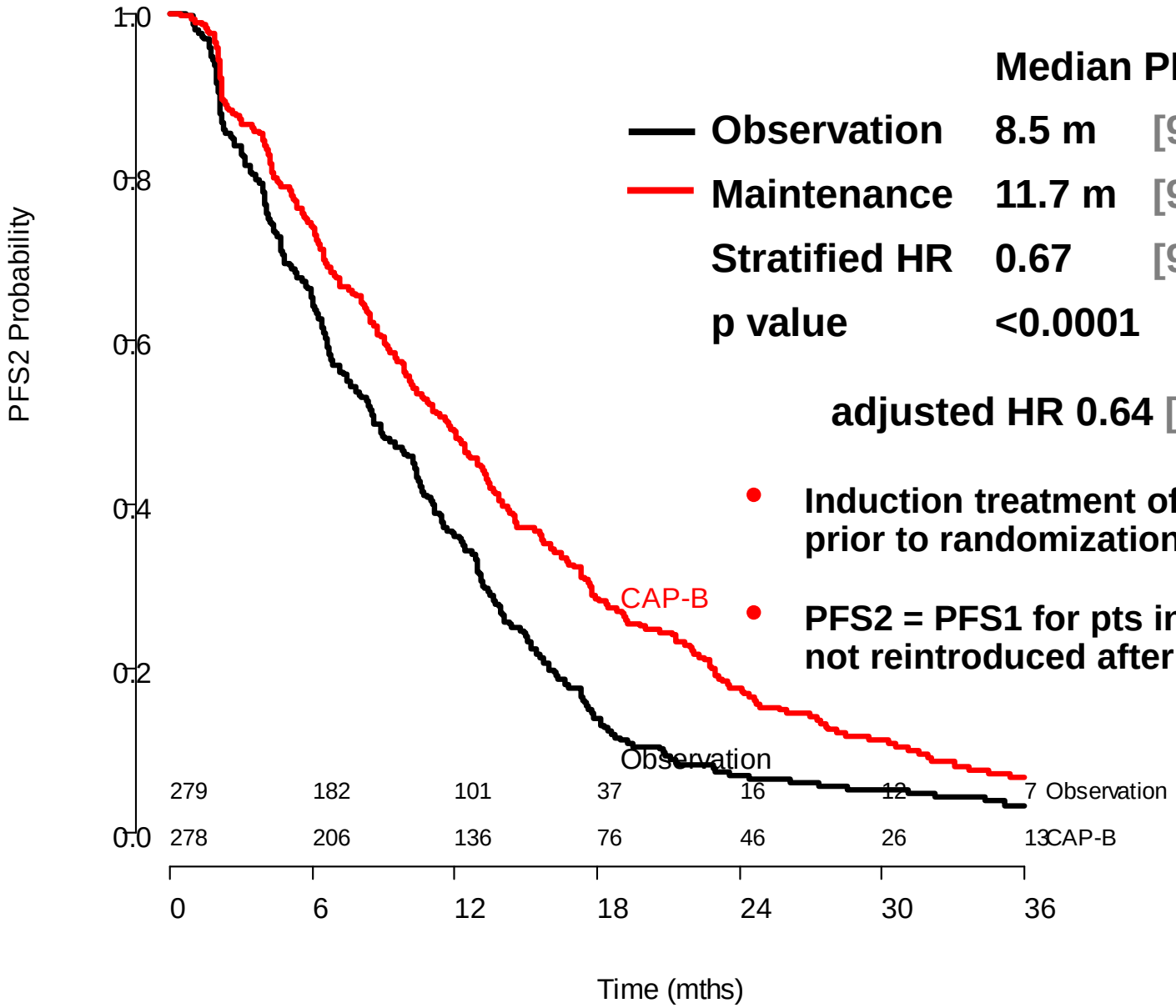


	Median PFS1	
Observation	4.1 m	[95%CI: 3.9-4.2]
Maintenance	8.5 m	[95%CI: 6.5-10.3]
Stratified HR	0.43	[95%CI: 0.36-0.52]
p value	< 0.0001	

adjusted HR 0.39 [95%CI: 0.33-0.48]

Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)

Primary endpoint PFS2

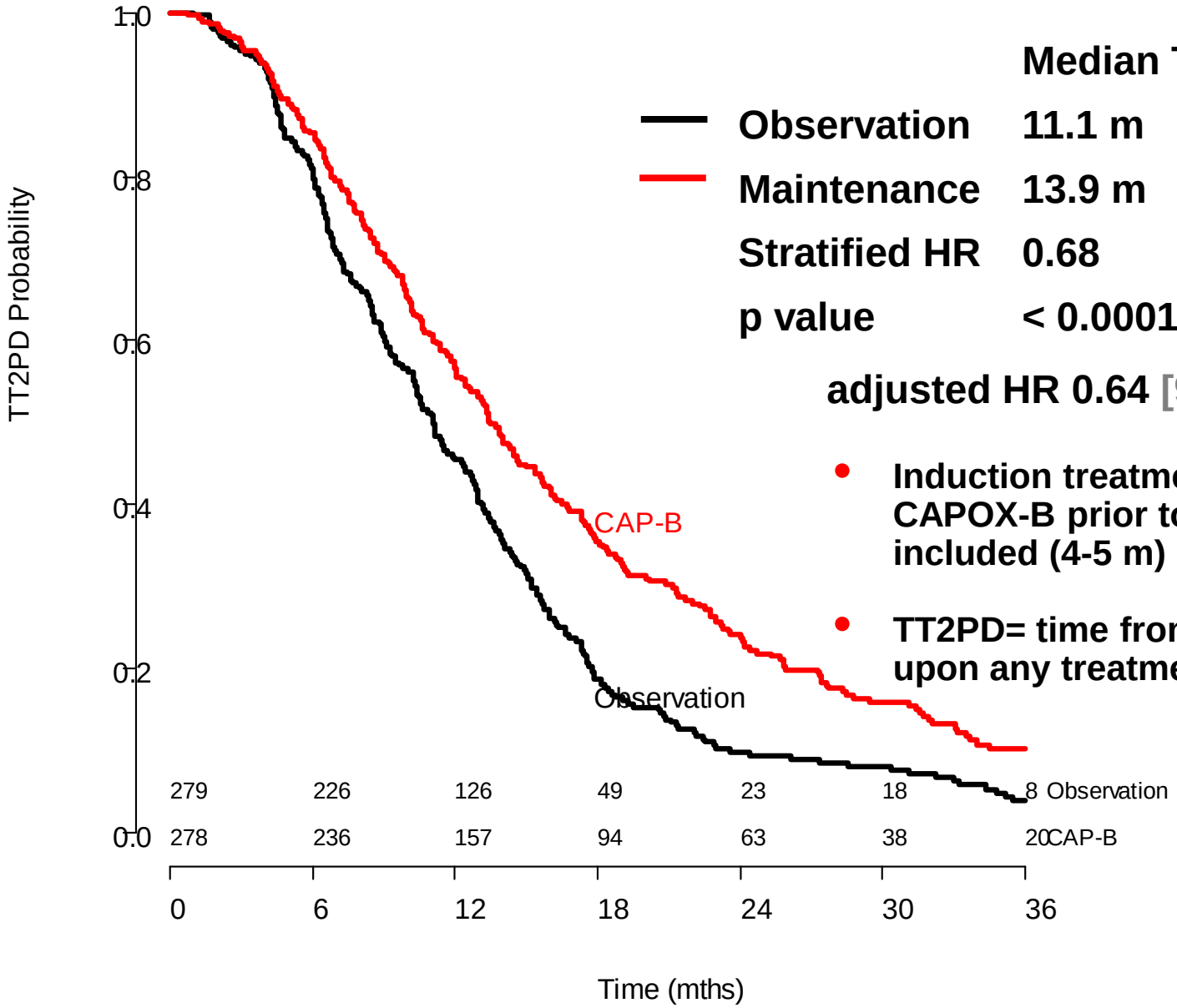


	Median PFS2	
Observation	8.5 m	[95%CI: 7.4-10.4]
Maintenance	11.7 m	[95%CI: 10.1-13.3]
Stratified HR	0.67	[95%CI: 0.56-0.81]
p value	<0.0001	

adjusted HR 0.64 [95%CI: 0.53-0.76]

- **Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)**
- **PFS2 = PFS1 for pts in whom CAPOX- B is not reintroduced after PFS1 for any reason**

TT2PD

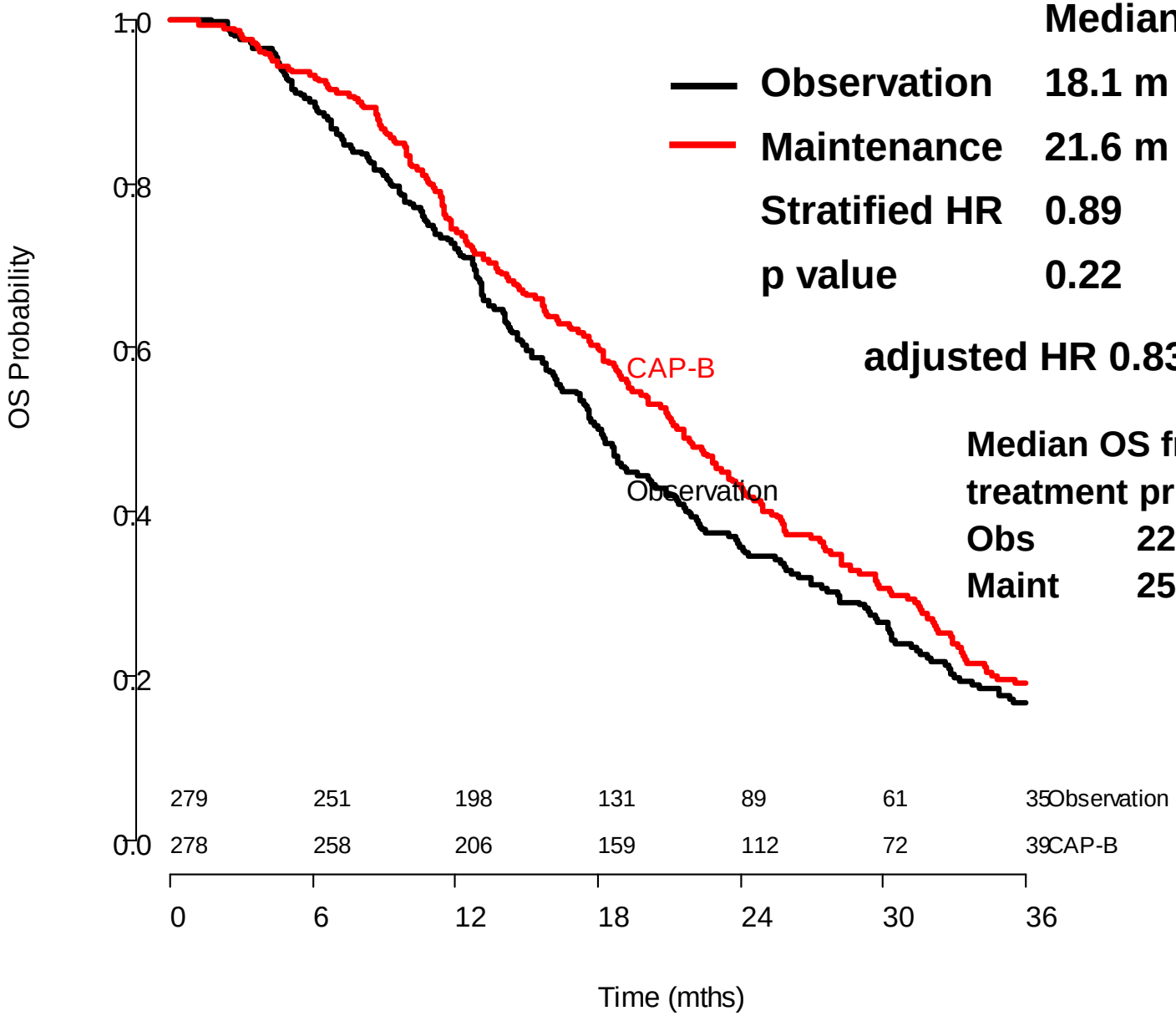


	Median TT2PD	
Observation	11.1 m	[95%CI:10.3-12.6]
Maintenance	13.9 m	[95%CI: 12.3-15.6]
Stratified HR	0.68	[95%CI: 0.57-0.82]
p value	< 0.0001	

adjusted HR 0.64 [95%CI: 0.53-0.77]

- **Induction treatment of 6x cycles CAPOX-B prior to randomization not included (4-5 m)**
- **TT2PD= time from randomization to PD upon any treatment given after PFS1**

Overall Survival



	Median OS	
Observation	18.1 m	[95%CI: 16.3-20.2]
Maintenance	21.6 m	[95%CI: 19.4-23.8]
Stratified HR	0.89	[95%CI: 0.73-1.07]
p value	0.22	

adjusted HR 0.83 [95%CI: 0.68-1.01]

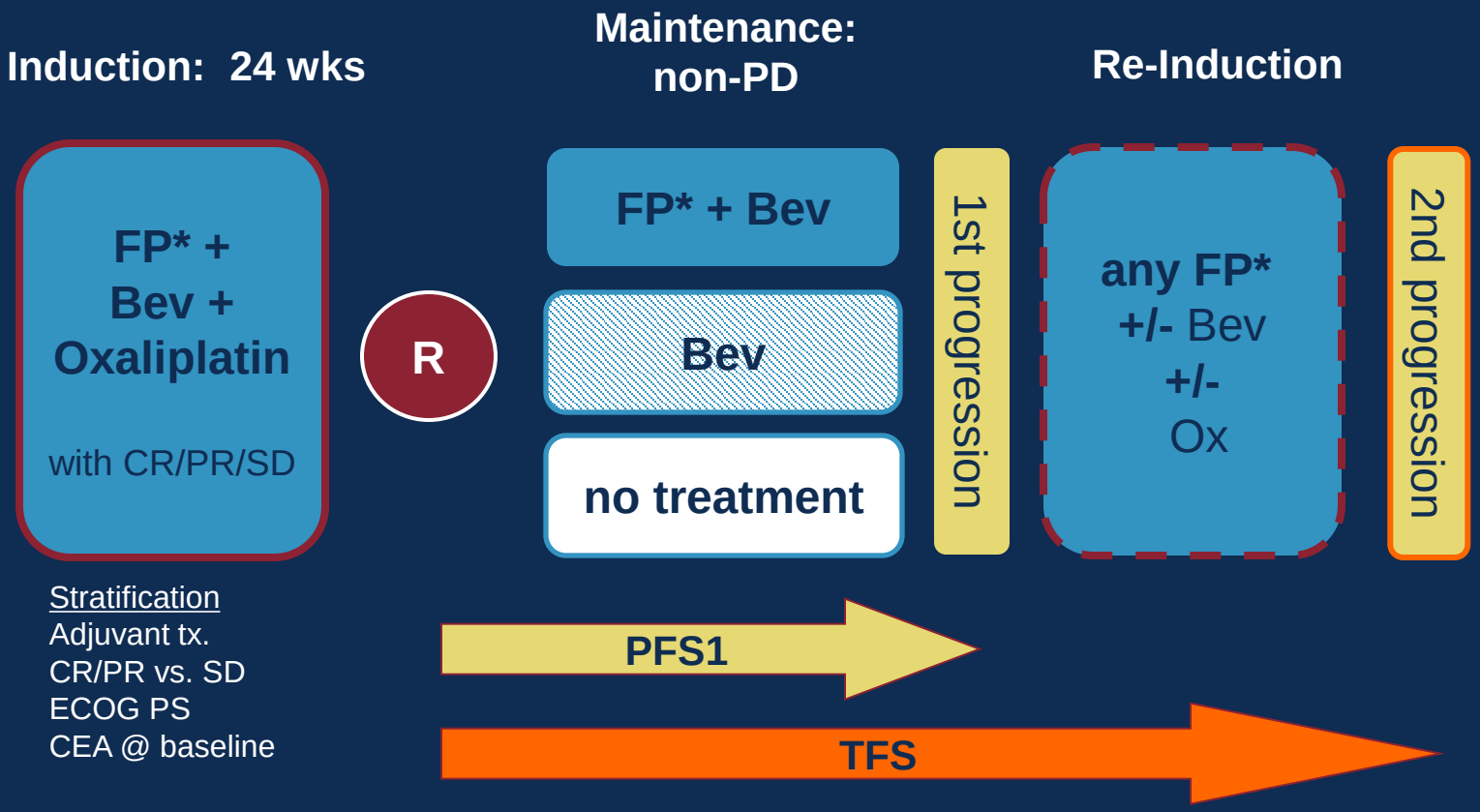
Median OS from start induction treatment prior to randomization

Obs	22.4 m [95% CI 20.8-24.9]
Maint	25.9 m [95% CI 23.7-28.4]

Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A non-inferiority phase III trial: AIO 0207

D. Arnold, U. Graeven, C. Lerchenmueller, B. Killing,
R. Depenbusch, C.-C. Steffens, S. Al-Batran, T. Lange,
G. Dietrich, J. Stoehlmacher, A. Tannapfel,
H.-J. Schmoll, A. Reinacher-Schick, S. Hegewisch-Becker
on behalf of the AIO CRC Study Group

AIO 0207: Treatment algorithms

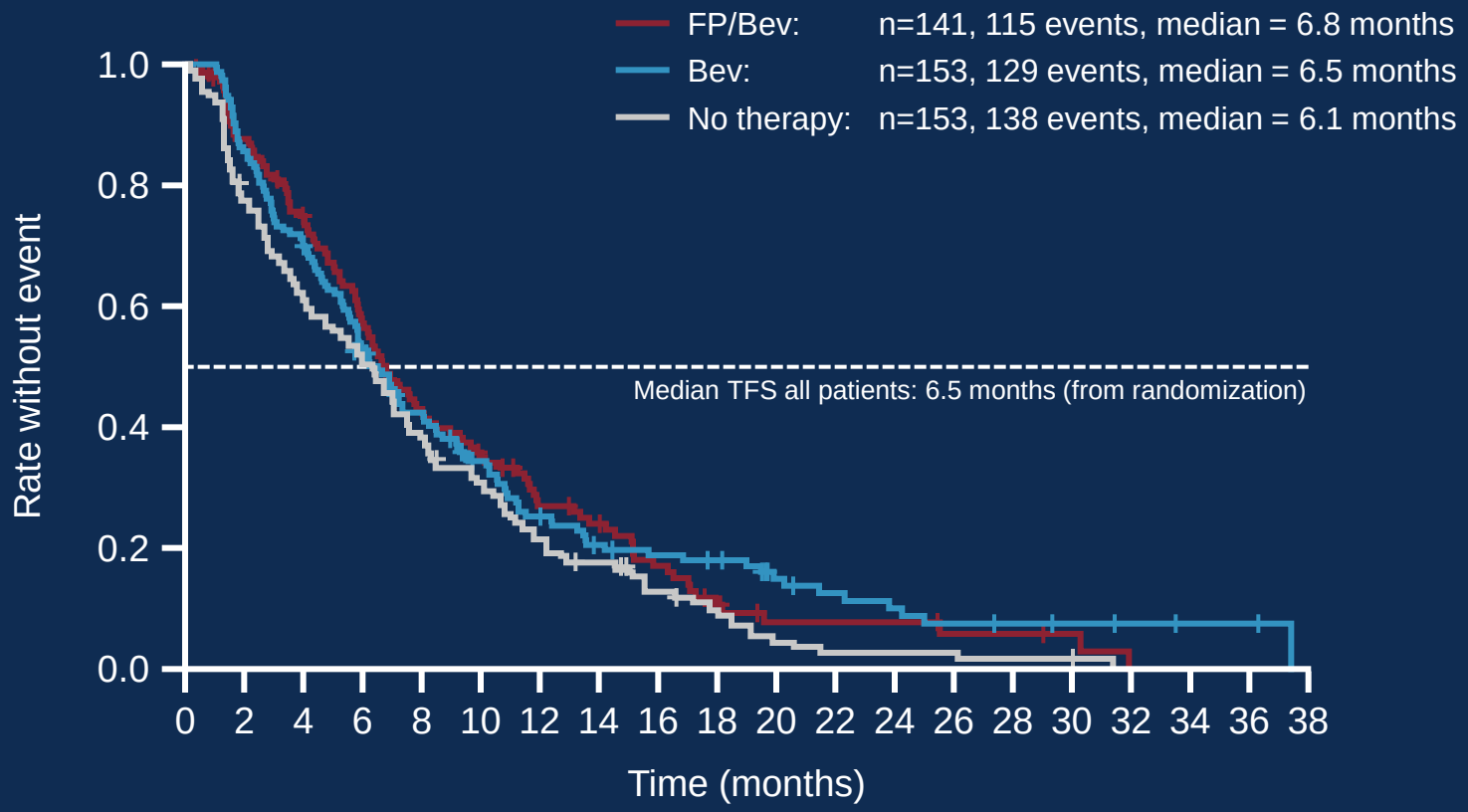


*FP= any fluoropyrimidine in a standard protocol (e.g. mFOLFOX6, FOLFOX4, Cape/Ox, LV5FU2; Cape 2x1000)

Bev used in standard doses (5mg/kg q 2 wks or 7.5mg/kg q 3wks arm A; 7.5 mg/kg 3q 3 wks arm B)

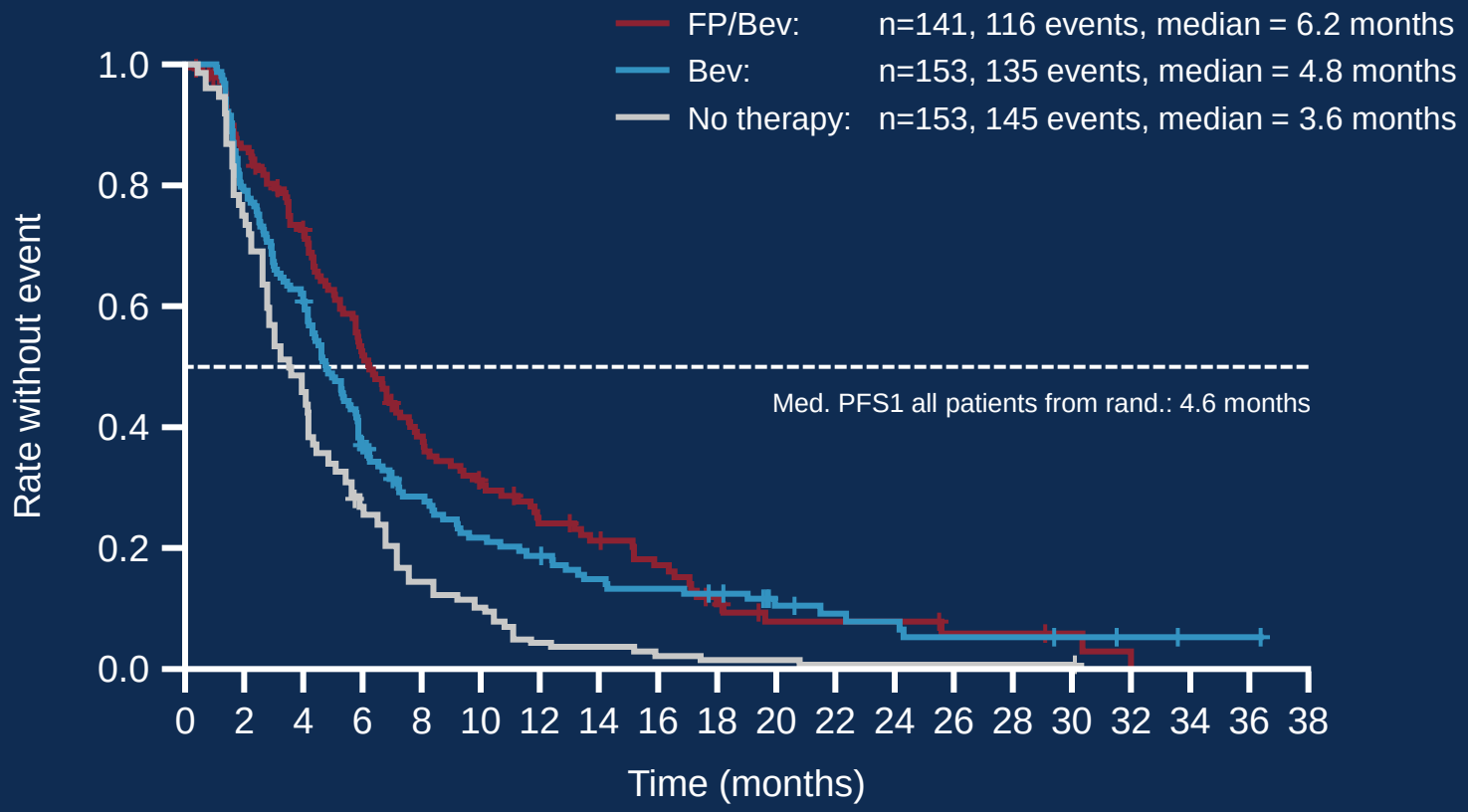
TFS= Time to failure of strategy (randomziation to 2nd progression, or new treatment/no treatment at re-induction)

TFS: All arms



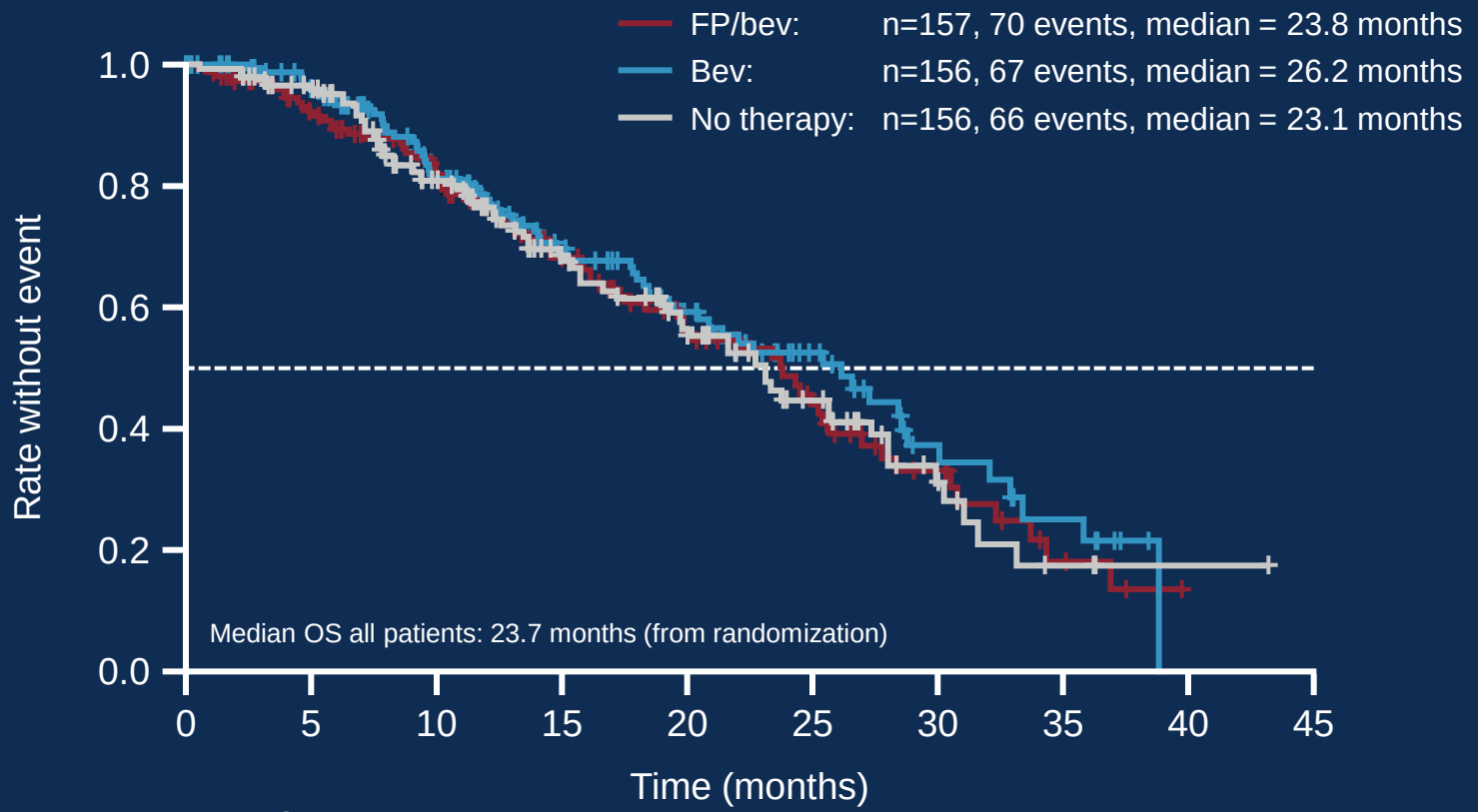
Log rank test: p=0.099

PFS1 from start of maintenance



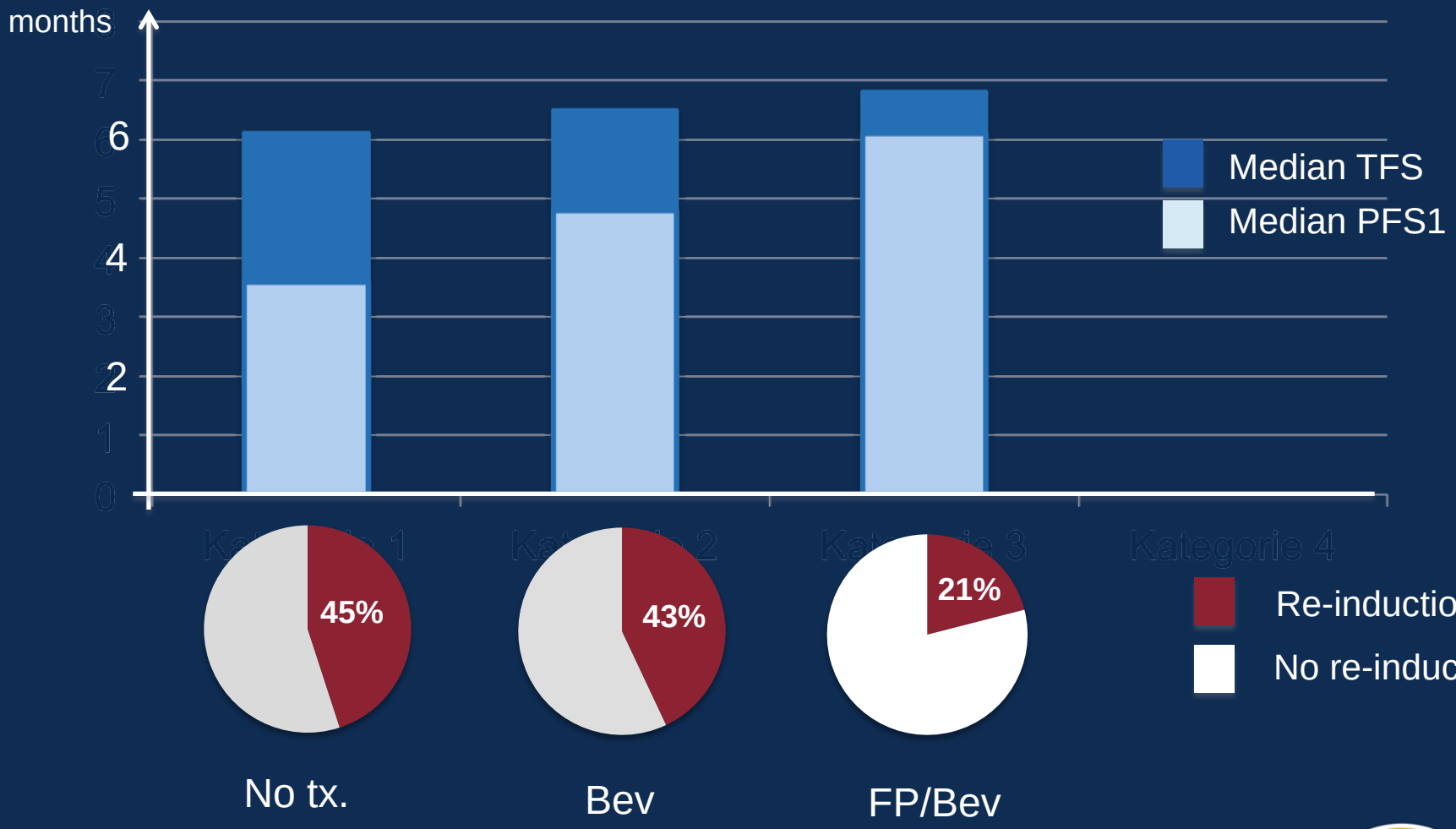
B vs A: HR=1.21; 95% CI: 0.95-1.56; log rank p=0.13
C vs A: HR=2.06; 95% CI: 1.60-2.66; log rank p<0.001
C vs B: HR=1.57; 95% CI: 1.24-1.99; log rank p<0.001
Log rank test: p<0.0001

OS from start of maintenance



N=473
Interim analysis: 203 events
Log rank p=0.70

Re-induction rates and PFS1/TFS



A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC)

Hurwitz H,[1] Uppal N,[2] Wagner SA,[3] Bendell JC,[4] Beck JT,[5] Wade S,[6] Nemunaitis JJ,[7] Stella PJ,[8] Pipas JM,[9] Wainberg ZA,[10] Manges R,[11] Garrett WM,[12] Hunter DS,[12] Clark J,[12] Leopold L,[12] Levy RS,[12] and Sandor V,[12] on behalf of the RECAP investigators

[1]Duke University Medical Center, Durham, NC, [2]NYU Langone Arena Oncology, Lake Success, NY; [3]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [4]Sarah Cannon Research Institute, Nashville, TN; [5]Highlands Oncology Group, Fayetteville, AR; [6]Virginia Cancer Institute, Richmond, VA; [7]Mary Crowley Medical Research Center, Dallas TX; [8]St. Joseph Mercy Health System - Alexander Cancer Care Center, Ann Arbor, MI; [9]Dartmouth Hitchcock Medical Center - Section of Hematology and Oncology, Lebanon, NH; [10]UCLA Division of Hematology-Oncology, Los Angeles, CA; [11]Investigative Clinical Research of Indiana, LLC; [12]Incyte Corporation, Wilmington, DE

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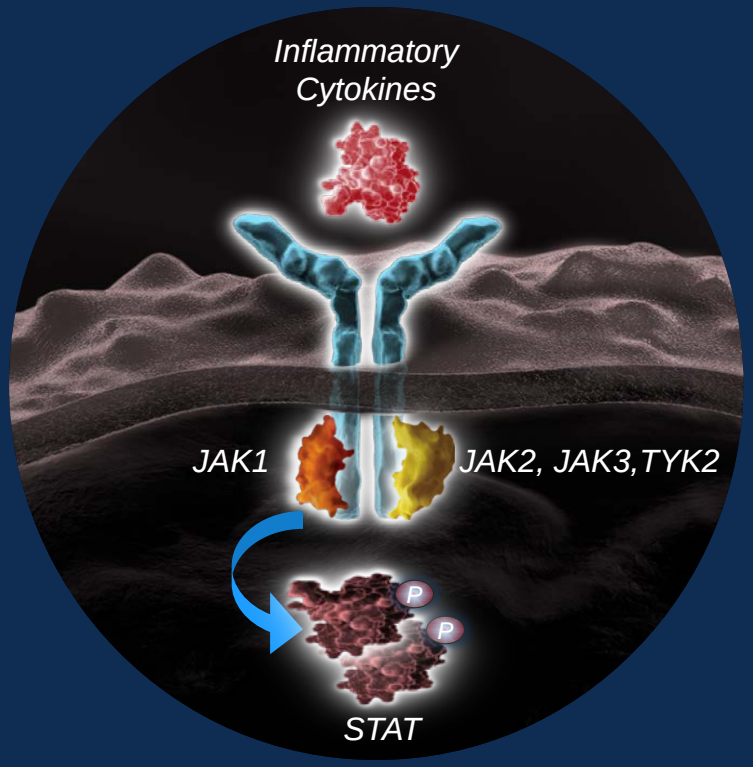
JAK-STAT Signaling Inhibition as a Novel Approach to Cancer Therapy

- Janus kinases (JAKs)
  - family of kinases that includes JAK1, JAK2, JAK3, and TYK2
  - mediate cytokine signaling by activating STAT transcription factors
- Ruxolitinib
  - inhibitor of JAK1 and JAK2
  - blocks signaling mediated by many proinflammatory cytokines
  - reduced levels of inflammatory cytokines and improved symptoms and overall survival in clinical studies of patients with myelofibrosis[1-3]
  - Active in preclinical models of pancreatic cancer



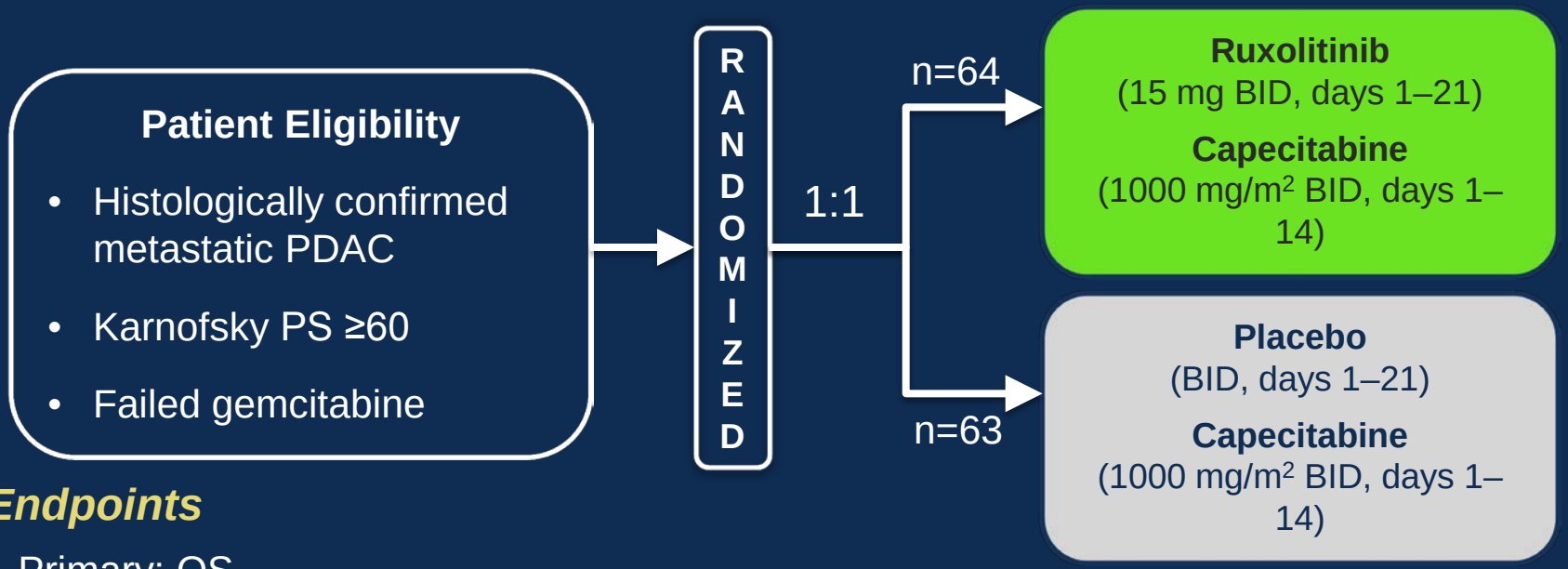
1) Verstovsek S, et al. *N Engl J Med* 2012;366:799-807; 2) Harrison C, et al. *N Engl J Med* 2012;366:787-98; 3) Cervantes F, et al. *Blood* 2013;122:4047-53.

Inflammation and Overall Survival in mPC: CALGB80303

	p-value*	< Median		> Median		< Median vs > Median	
		Median Survival	95% CI	Median Survival	95% CI	Hazard ratio	95% CI
Ang2	<.0001	9.6	(7.7, 10.4)	4.6	(3.3, 5.8)	2.4	(1.7, 3.3)
CRP	<.0001	9.7	(8.1, 10.6)	3.8	(2.9, 4.8)	2.3	(1.6, 3.1)
IGFBP-1	<.0001	9.2	(7.3, 9.9)	4.3	(3.1, 5.7)	1.7	(1.2, 2.4)
TSP-2	<.0001	9.0	(6.8, 9.7)	4.6	(3.3, 5.6)	1.6	(1.1, 2.1)
VCAM-1	0.0002	9.0	(6.7, 9.7)	4.8	(3.6, 5.9)	1.6	(1.2, 2.3)
ICAM-1	<.0001	8.4	(6.1, 9.7)	4.8	(3.5, 6.8)	1.4	(1.01,1.90)
IL-8	<.0001	8.7	(6.1, 9.7)	5.0	(3.5, 6.9)	1.3	(0.98, 1.86)
PAI1-act	0.0004	8.1	(6.7, 9.2)	4.8	(3.4, 5.9)	1.3	(0.94, 1.77)
IGF-1	0.0012	4.2	(3.3, 5.6)	9.0	(6.8, 9.7)	0.65	(0.47, 0.89)

Nixon AB, et al. *Clin Cancer Res* 2013;19:6957-66.

Study Design



Endpoints

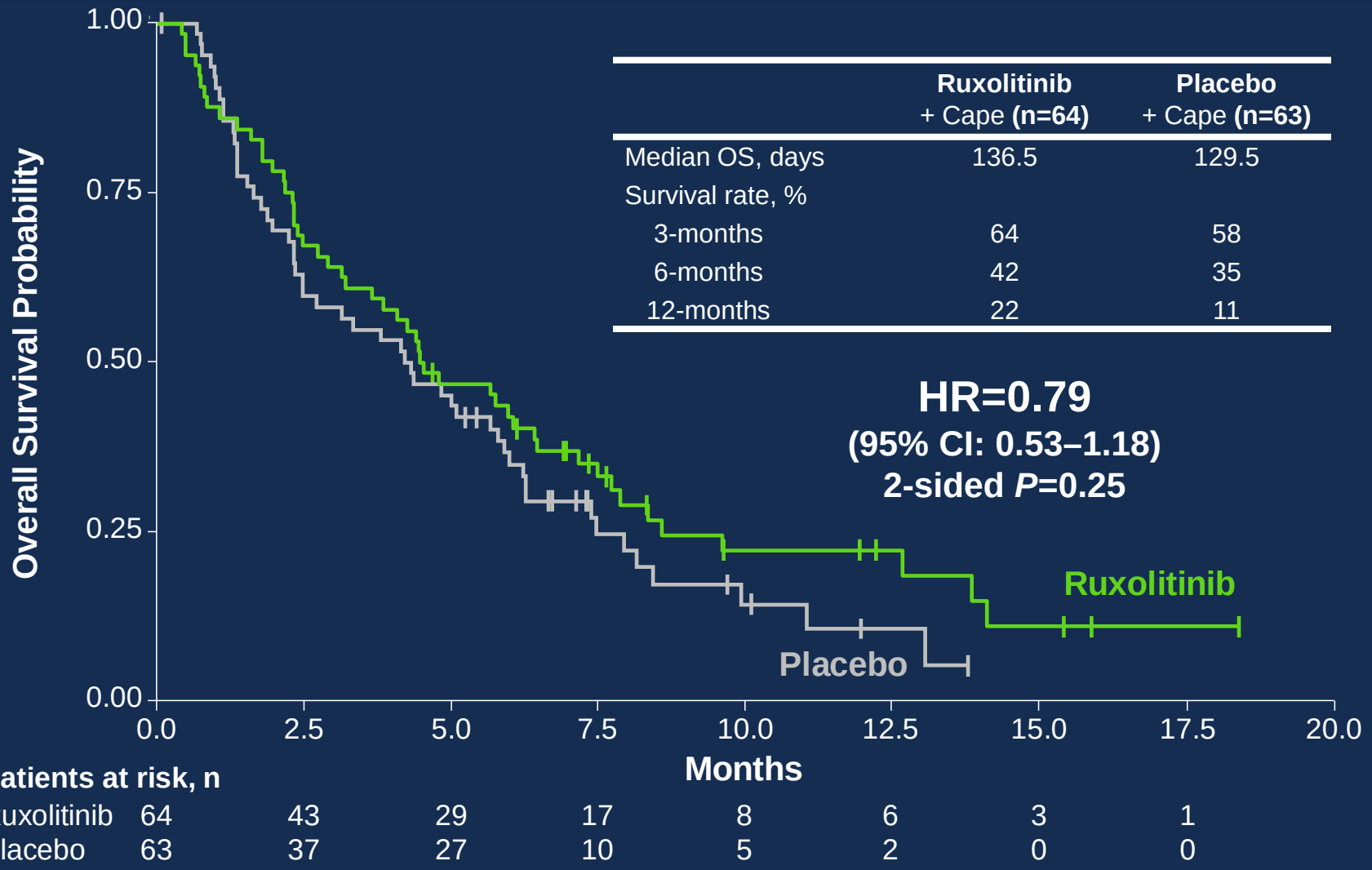
- Primary: OS
- Secondary: Clinical benefit response (composite of pain, Karnofsky PS, analgesic use, body weight),[1] ORR (RECIST), confirmed response (4 weeks), PFS, QoL, safety

Analysis Plan

- 2-sided $\alpha = 0.2$; $\beta < 0.2$
- Prospectively defined subgroup analyses, including CRP, albumin, and performance status, were conducted to explore an inflammation hypothesis
- Additional prespecified subgroup analyses based on patient demographics and standard prognostic criteria in pancreatic cancer were performed to test for treatment heterogeneity

1) Burris HA, et al. *J Clin Oncol* 1997;15:2403-13.

Overall Survival (ITT)



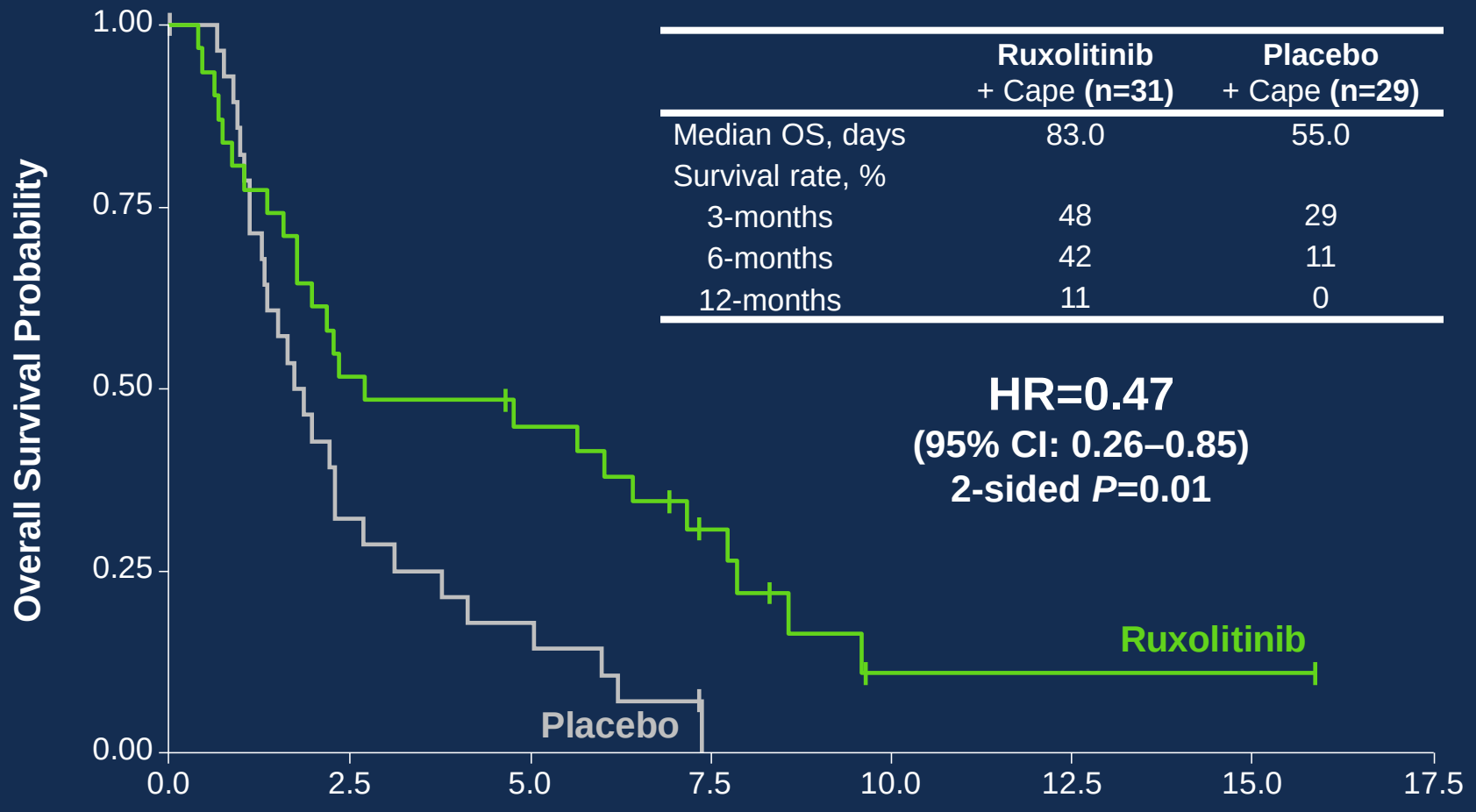
	Ruxolitinib + Cape (n=64)	Placebo + Cape (n=63)
Median OS, days	136.5	129.5
Survival rate, %		
3-months	64	58
6-months	42	35
12-months	22	11

Patients at risk, n

Ruxolitinib	64	43	29	17	8	6	3	1
Placebo	63	37	27	10	5	2	0	0

HR, hazard ratio; ITT, intent-to-treat.

Overall Survival in Patients with CRP > 13 mg/L



	Ruxolitinib + Cape (n=31)	Placebo + Cape (n=29)
Median OS, days	83.0	55.0
Survival rate, %		
3-months	48	29
6-months	42	11
12-months	11	0

HR=0.47
(95% CI: 0.26–0.85)
2-sided *P*=0.01

Patients at risk, n							
Ruxolitinib	31	16	13	7	1	1	1
Placebo	29	9	5	0	0	0	0

Modified Glasgow Prognostic Score (mGPS)

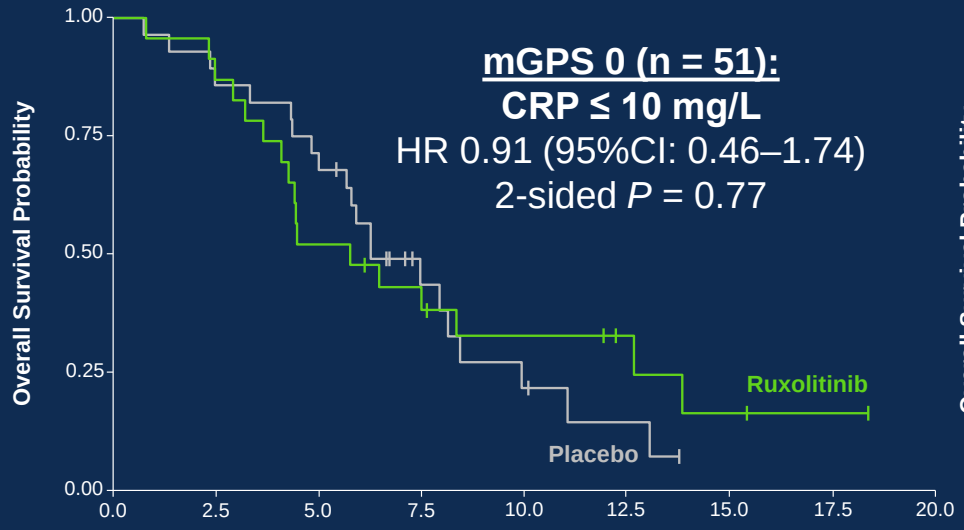
- Well characterized clinical measure of inflammation in cancer[1]
- Combines CRP and serum albumin using generally established cutoff values for clinically significant results

CRP or albumin value	mGPS
CRP ≤ 10 mg/L	0
CRP > 10 mg/L and albumin ≥ 35 g/L	1
CRP > 10 mg/L and albumin < 35 g/L	2

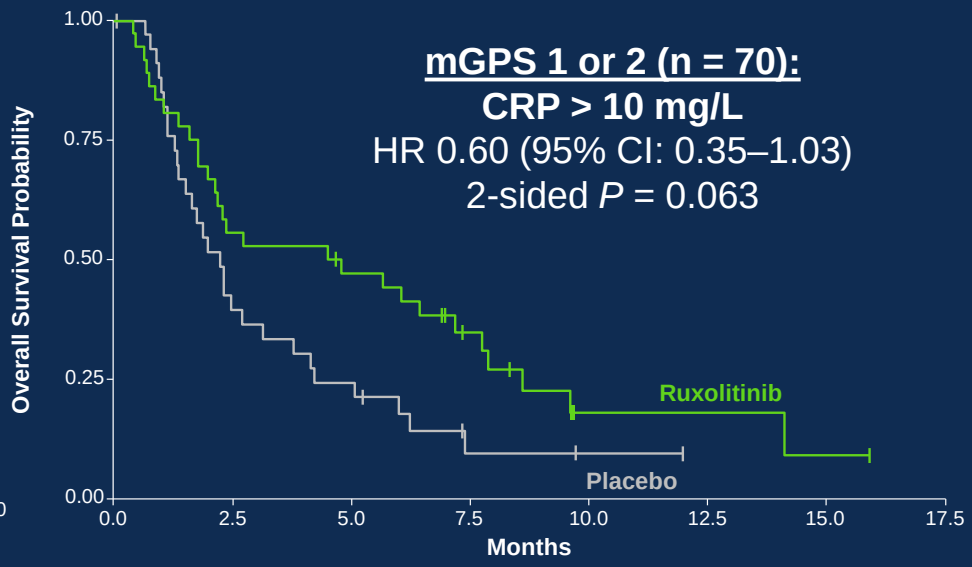
- > 50 clinical studies across multiple tumor types in over 25,000 patients support the independent prognostic value of mGPS[2]

1) McMillan DC, et al. *Int J Colorectal Dis* 2007;22:881-6; 2) McMillan DC. *Cancer Treat Rev* 2013;39:534-40.

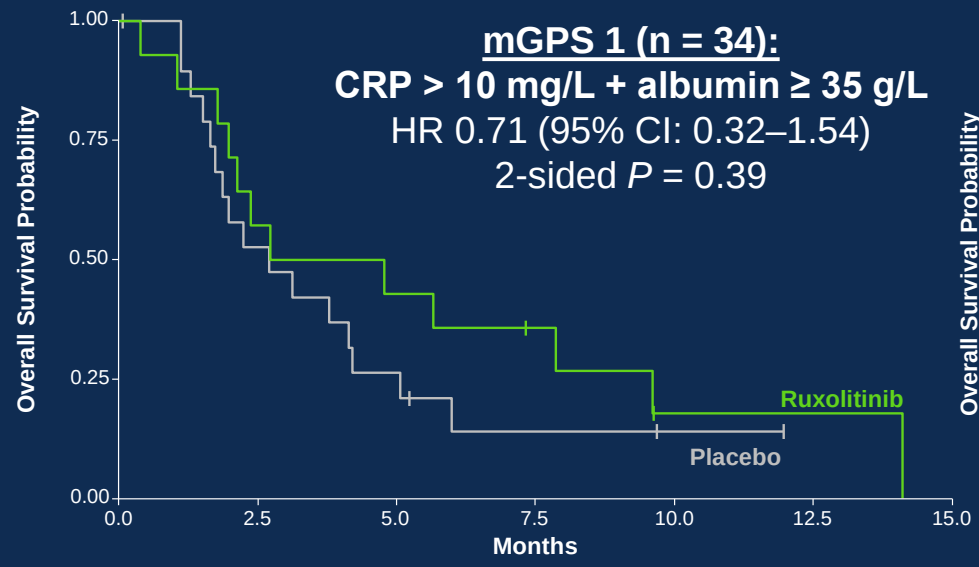
Overall Survival by mGPS



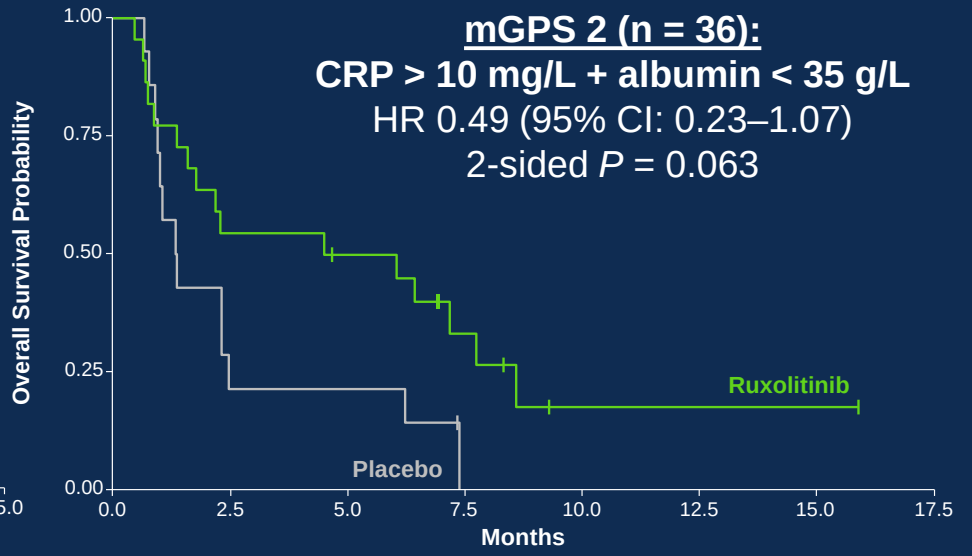
mGPS 0 (n = 51):
CRP ≤ 10 mg/L
HR 0.91 (95%CI: 0.46–1.74)
2-sided *P* = 0.77



mGPS 1 or 2 (n = 70):
CRP > 10 mg/L
HR 0.60 (95% CI: 0.35–1.03)
2-sided *P* = 0.063



mGPS 1 (n = 34):
CRP > 10 mg/L + albumin ≥ 35 g/L
HR 0.71 (95% CI: 0.32–1.54)
2-sided *P* = 0.39

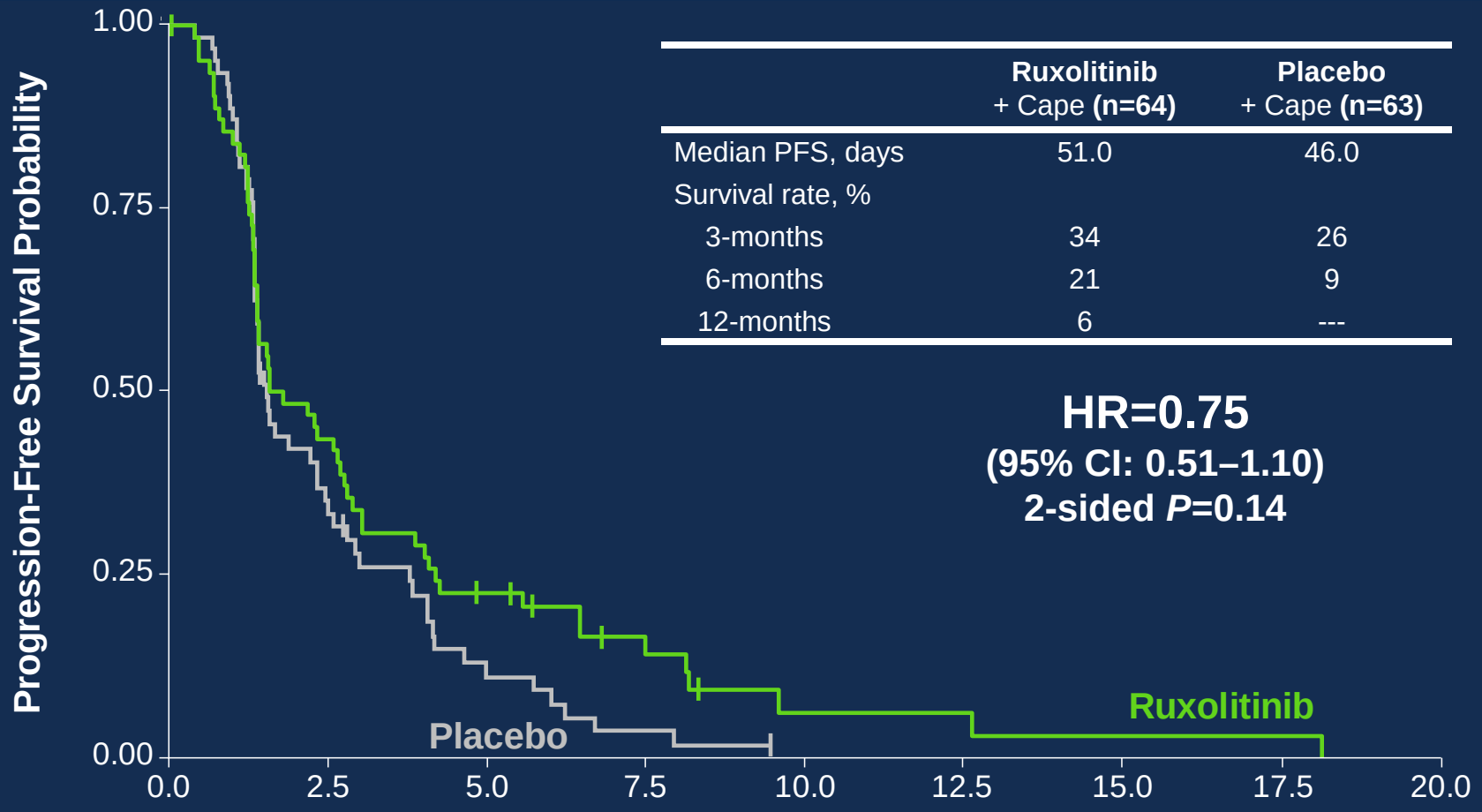


mGPS 2 (n = 36):
CRP > 10 mg/L + albumin < 35 g/L
HR 0.49 (95% CI: 0.23–1.07)
2-sided *P* = 0.063

Progression-Free Survival (ITT)

	Ruxolitinib + Cape (n=64)	Placebo + Cape (n=63)
Median PFS, days	51.0	46.0
Survival rate, %		
3-months	34	26
6-months	21	9
12-months	6	---

HR=0.75
(95% CI: 0.51–1.10)
2-sided *P*=0.14

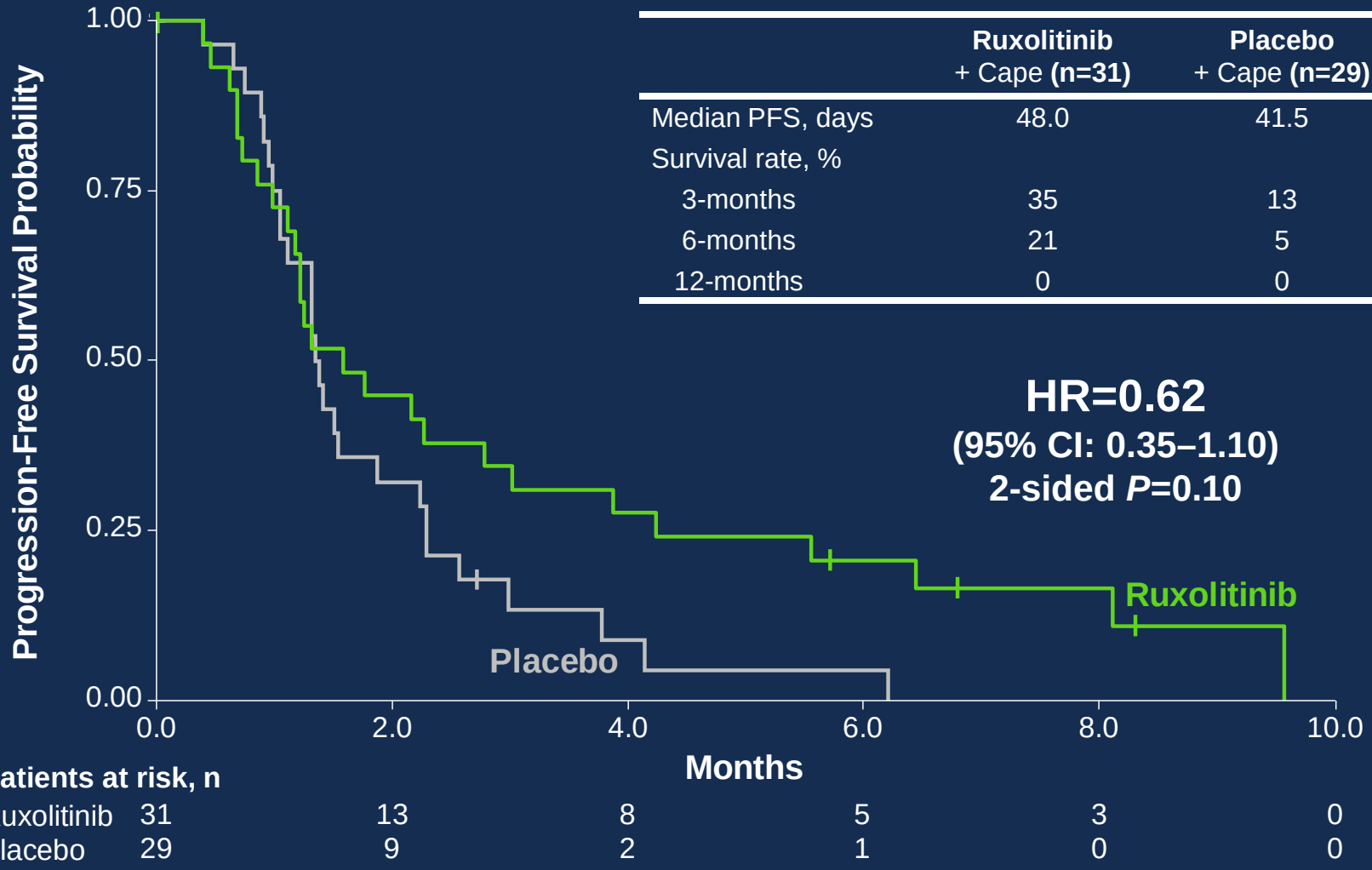


Patients at risk, n

Ruxolitinib	64	27	13	6	2	2	1	1
Placebo	63	19	6	2	0	0	0	0

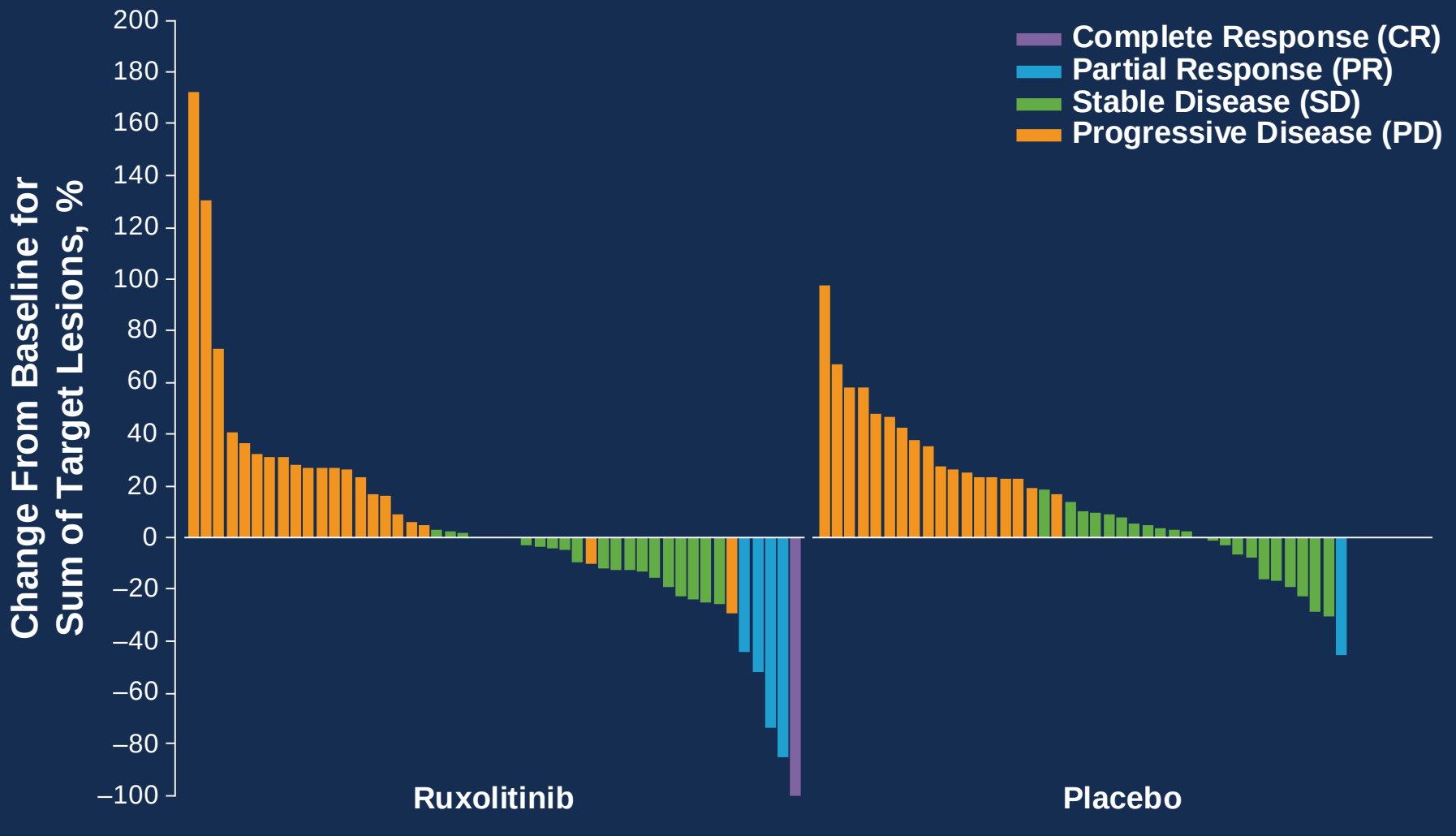
Progression-Free Survival in Patients with CRP > 13 mg/L

	Ruxolitinib + Cape (n=31)	Placebo + Cape (n=29)
Median PFS, days	48.0	41.5
Survival rate, %		
3-months	35	13
6-months	21	5
12-months	0	0



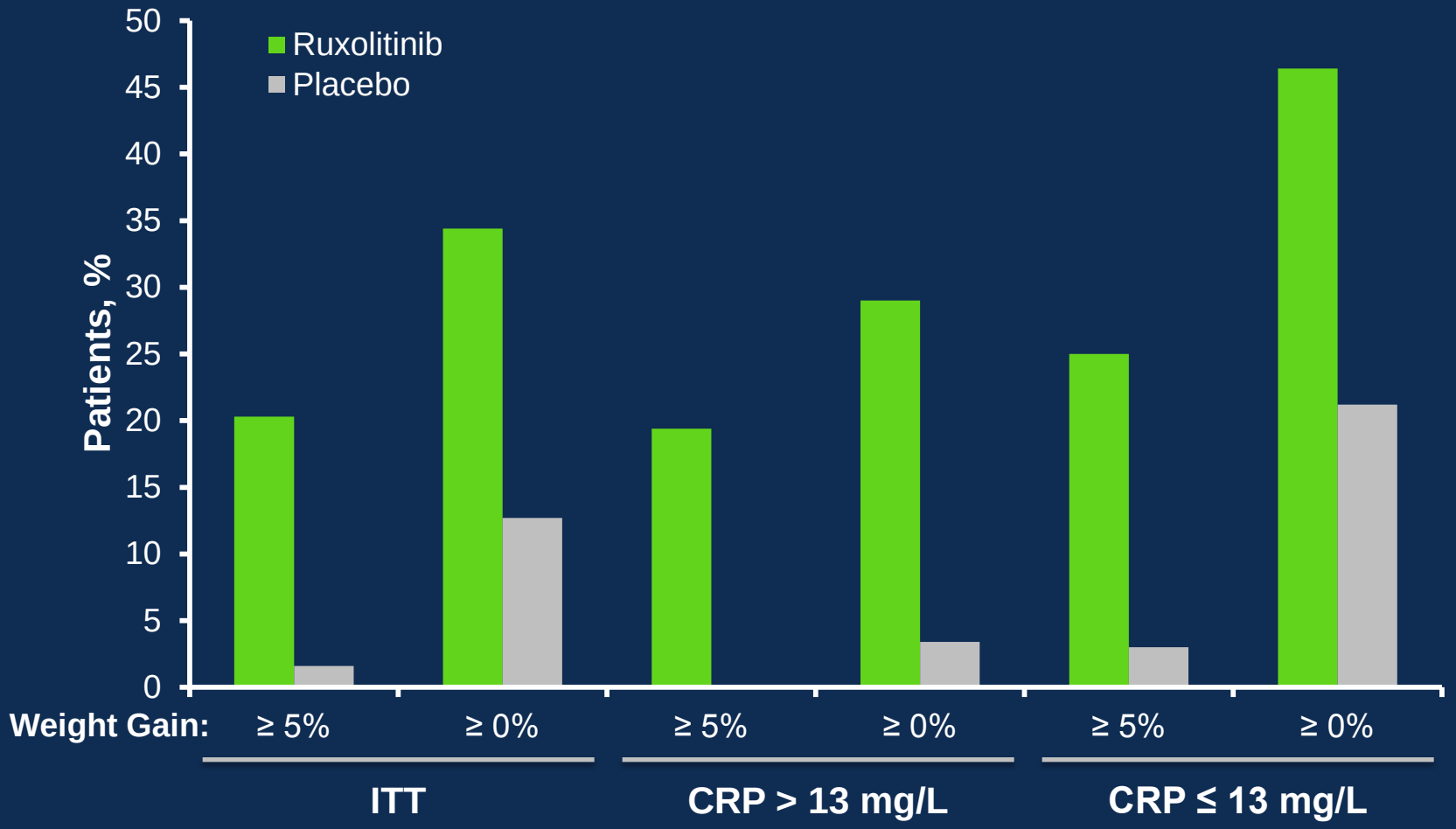
- PFS in patients with CRP ≤ 13 mg/L: 0.82 (95% CI: 0.47–1.41); *P*=0.47

Change From Baseline in Target Lesions* (ITT)



*Investigator assessed.

Proportion of Patients with Weight Gain



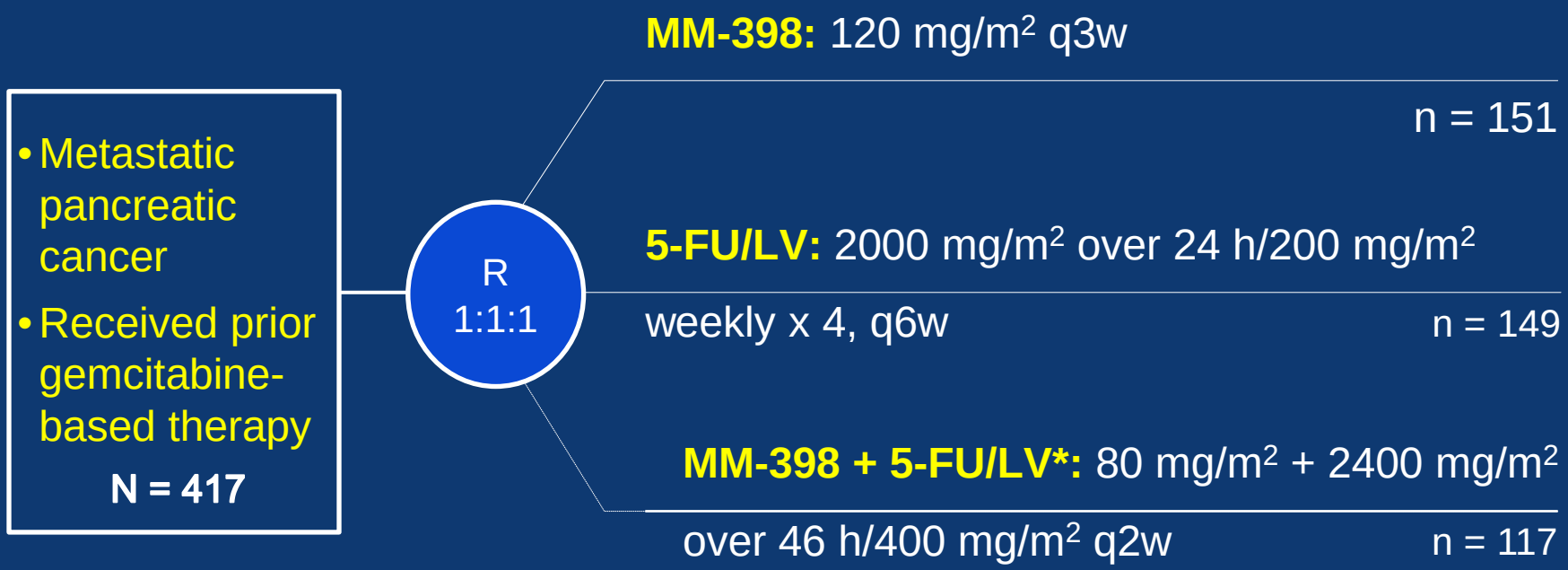
A patient qualified as a responder if they had 2 consecutive weight assessments displaying a ≥0% or ≥5% increase in weight from baseline without worsening of edema or ascites when compared to baseline.

NAPOLI-1: Randomized Phase 3 Study of MM-398 (nal-IRI), With or Without 5-Fluorouracil and Leucovorin versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer Progressed on or following Gemcitabine-Based Therapy

Daniel Von Hoff,[1] Chung-Pin Li,[2] Andrea Wang-Gillam,[3] György Bodoky,[4] Andrew Dean,[5] Gayle Jameson,[1] Teresa Macarulla,[6] Kyung-Hun Lee,[7] David Cunningham,[8] Jean Frédéric Blanc,[9] Richard Hubner,[10] Chang-Fang Chiu,[11] Gilberto Schwartsmann,[12] Jens Siveke,[13] Fadi Braiteh,[14] Victor Moyo,[15] Bruce Belanger,[15] Navreet Dhindsa,[15] Eliel Bayever,[15] Li-Tzong Chen[16]

[1]TGen, Scottsdale Healthcare, Scottsdale, AZ, USA; [2]Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan; [3]Washington University, St. Louis, MO, USA; [4]St László Teaching Hospital, Budapest, Hungary; [5]St John of God Hospital, Subiaco, Western Australia, Australia; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Seoul National University Hospital, Seoul, South Korea; [8]The Royal Marsden Hospital, London, UK; [9]Hôpital Saint-André, Bordeaux, France; [10]The Christie NHS Foundation Trust, Manchester, UK; [11]China Medical University Hospital, Taichung, Taiwan; [12]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [13]Klinikum rechts der Isar der TU München, Munich, Germany; [14]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [15]Merrimack Pharmaceuticals Inc., Cambridge, MA, USA; [16]National Institute of Cancer Research, Tainan, Taiwan

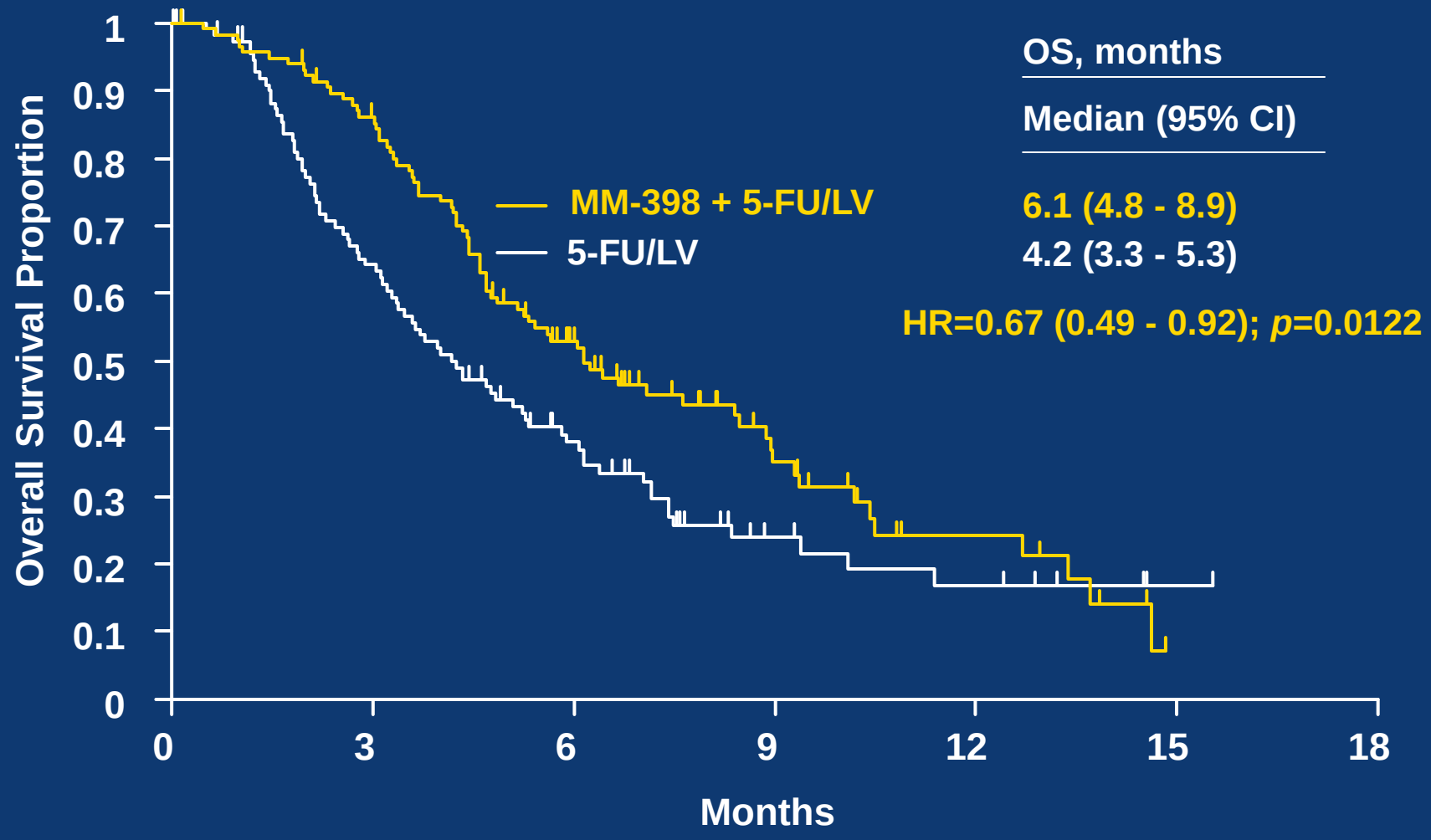
NAPOLI-1 Study Design



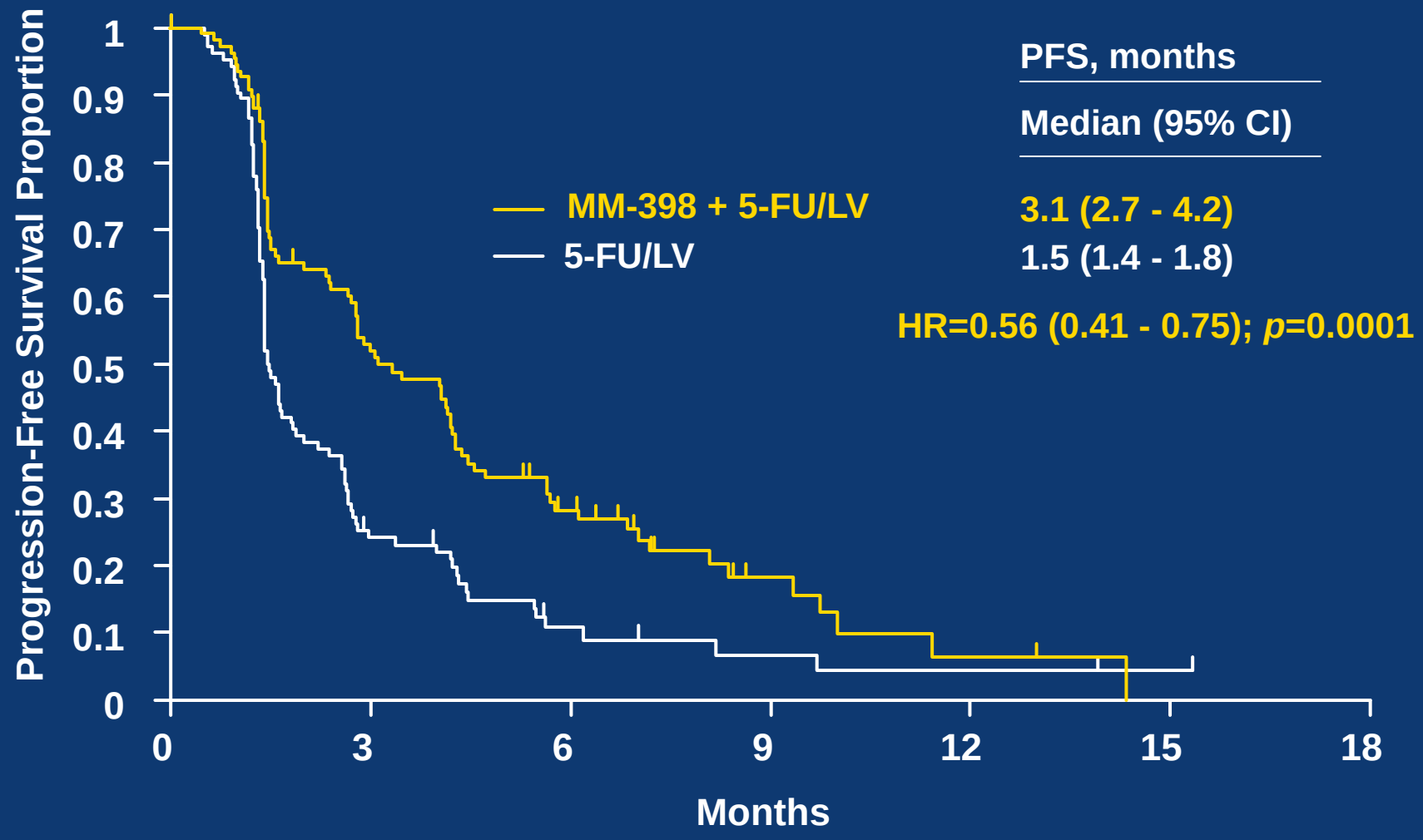
- Primary endpoint: Overall survival
- Secondary endpoints: PFS, ORR, CA19-9 response, and safety
- Stratification factors: Albumin, KPS, and ethnicity

* Study was amended to add the MM-398 + 5-FU/LV arm once safety data on the combination became available; 63 patients already had been enrolled in the original 2-arm study at the time of amendment.

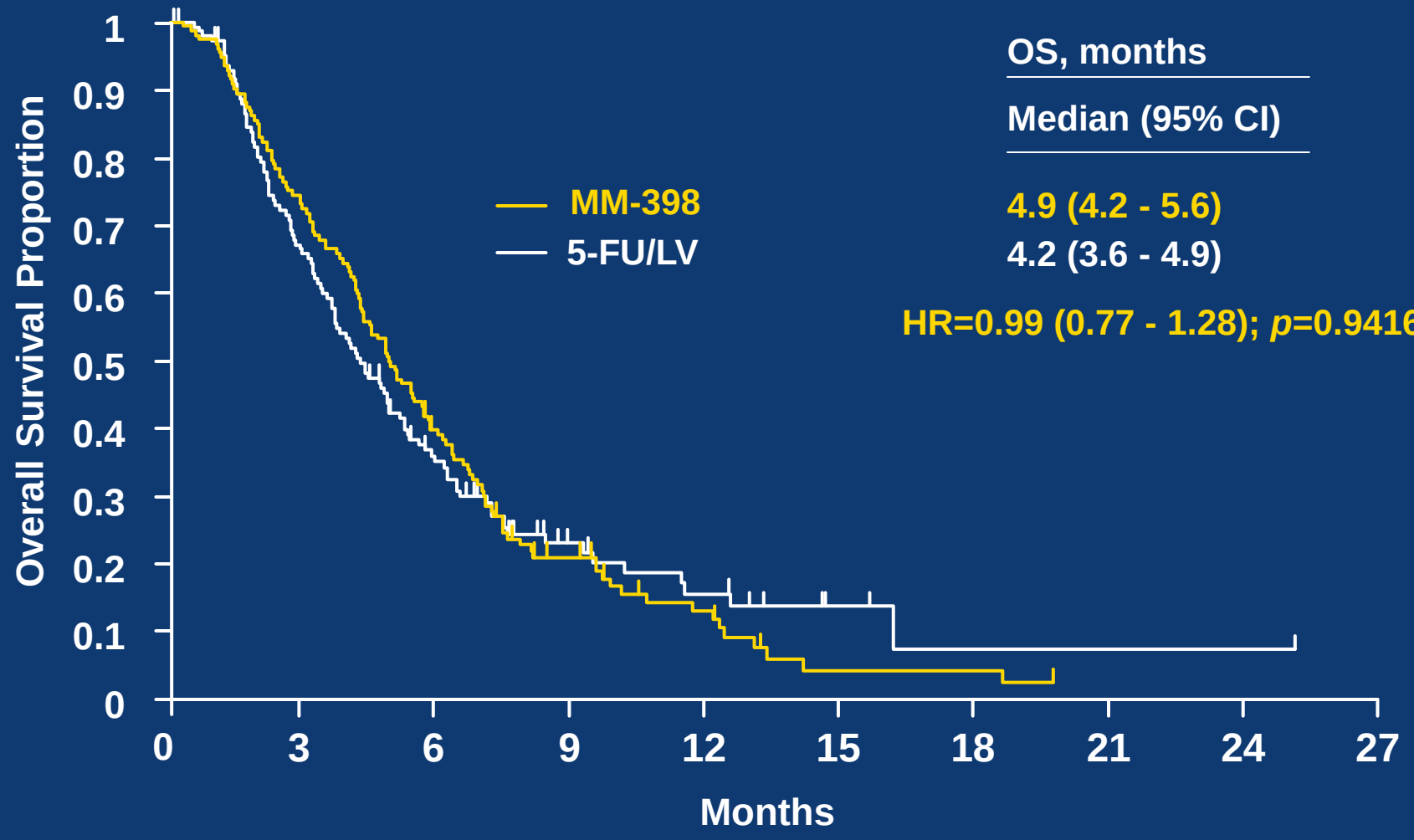
OS: MM-398 + 5-FU/LV



PFS: MM-398 + 5-FU/LV

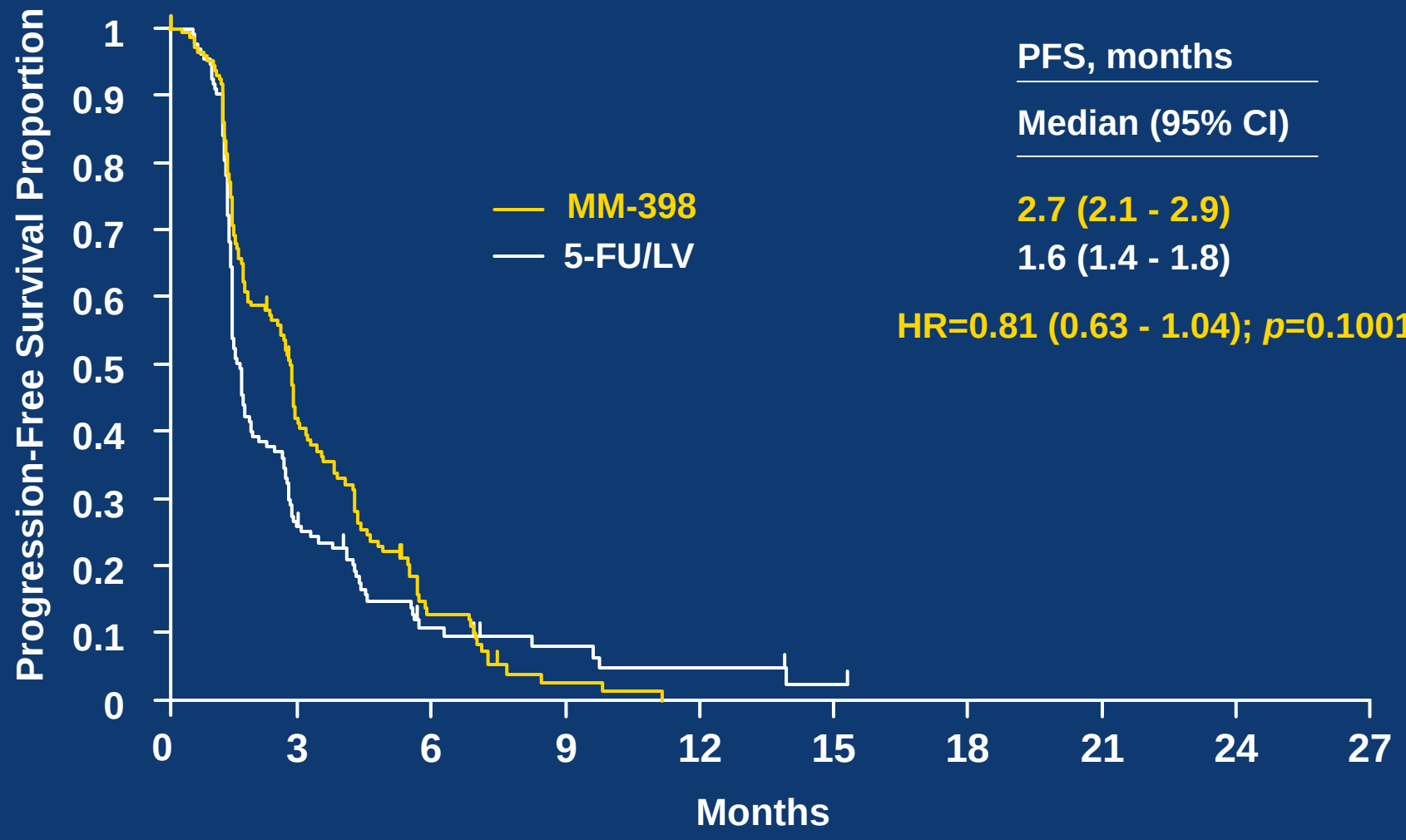


OS: MM-398 Monotherapy



Von Hoff et al. ESMO GI 2014.

PFS: MM-398 Monotherapy



Abstract #4003

Phase III study of Apatinib in metastatic gastric cancer:

A randomized, double-blind, placebo-controlled trial

Shukui Qin*, Jin Li*, Jianming Xu, Jianping Xiong, Changping Wu, Yuxian Bai, Wei Liu, Jiandong Tong, Yunpeng Liu, Ruihua Xu, Zhehai Wang, Qiong Wang, Xuenong Ouyang, Yan Yang, Yi Ba, Jun Liang, Xiaoyan Lin, Deyun Luo, Rongsheng Zheng, Kaichun Wu, Guoping Sun, Liwei Wang, Leizhen Zheng, Hong Guo, Jingbo Wu, Nong Xu, Jianwei Yang, Honggang Zhang, Ying Cheng, Ningju Wang, Lei Chen, Zhining Fan, Hao Yu

*__Co- PI__ (*clinicalTrials.gov : NCT01512745*)

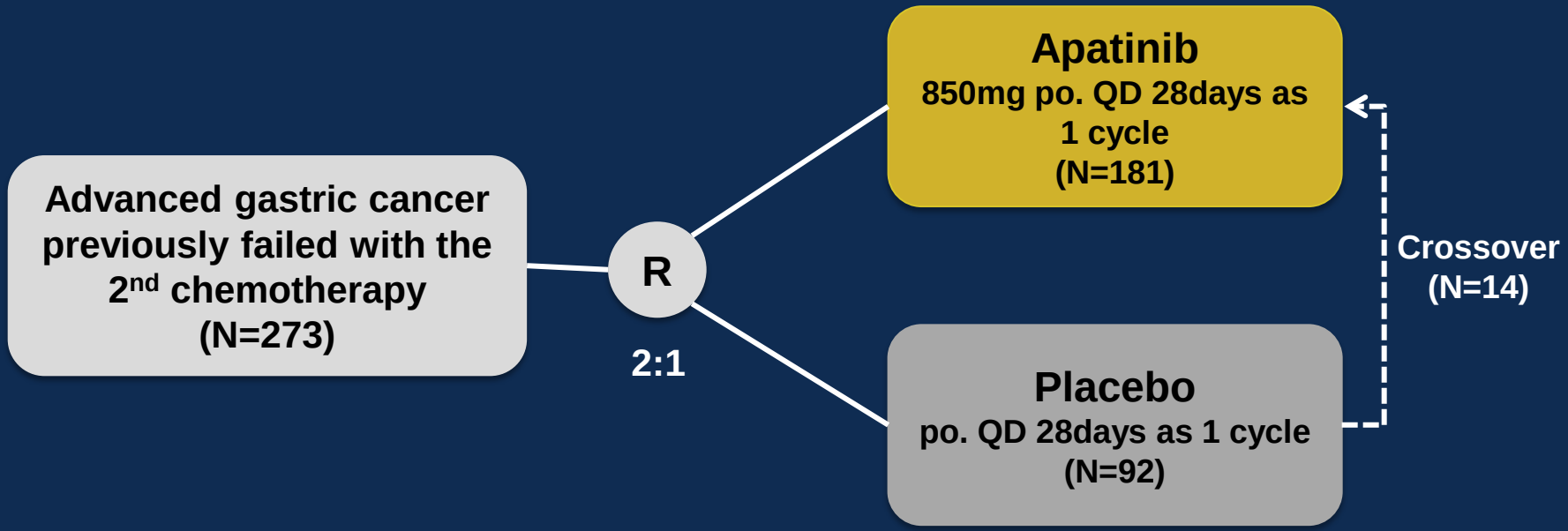
Shukui Qin*, PLA Cancer Center, Bayi Hospital, Nanjing, China

Jin Li*, Fudan University Shanghai Cancer Center, Shanghai, China

ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

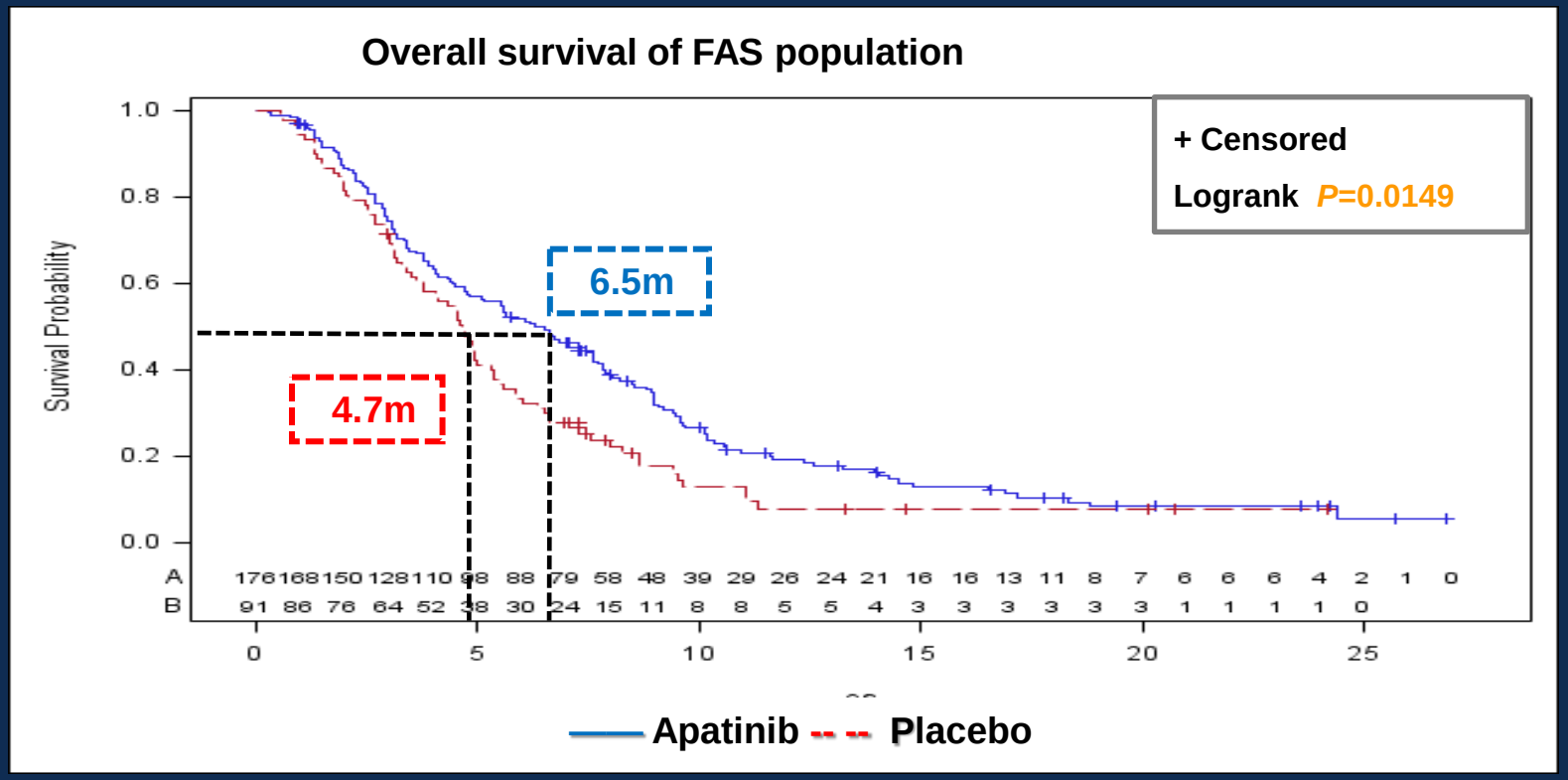
Phase III Study design

- Design: multicenter, randomized, double-blind, placebo-controlled clinical trial



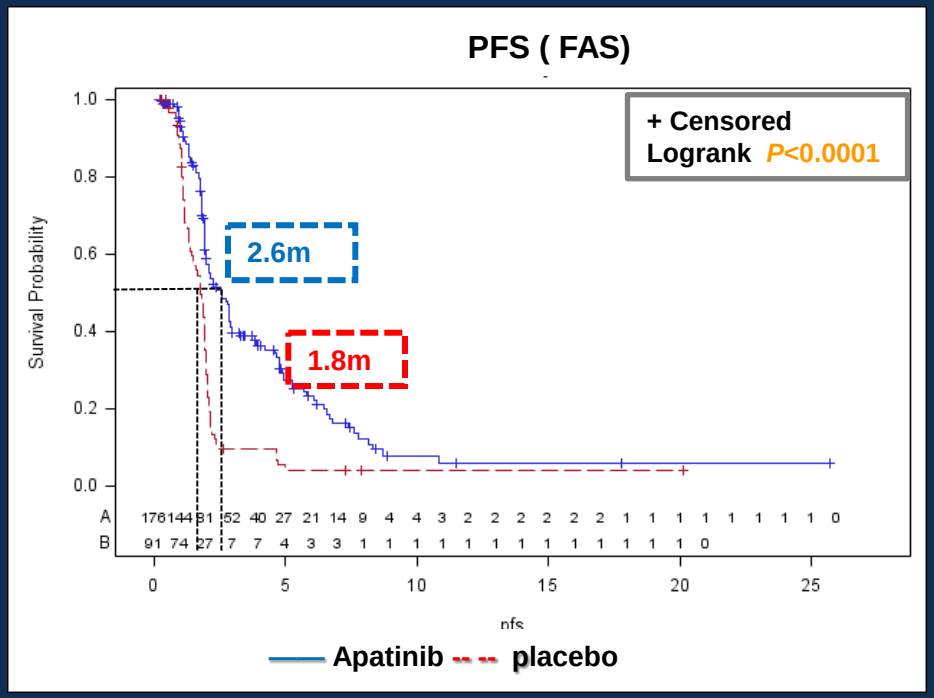
- 1 treatment cycle = 28 days
- Stratification factor: the number of metastatic sites (≤ 2 *vs.* >2)

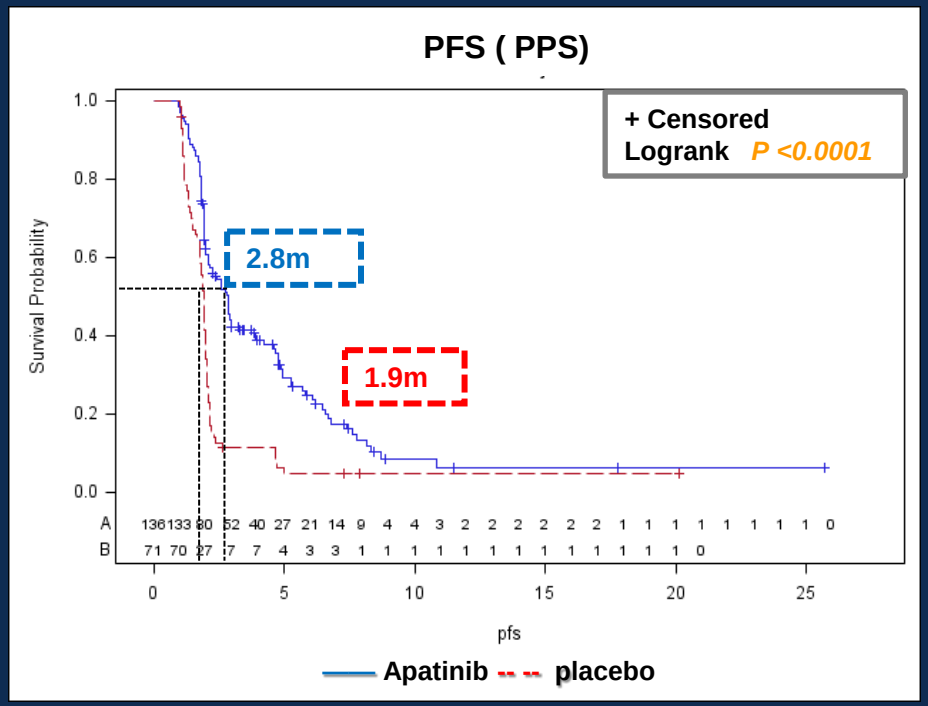
Primary end point – OS (FAS population)



Group	n	mOS (95% CI), months	*P* value	HR(95%CI)
Apatinib	176	6.5(4.8-7.6)	*0.0149*	0.709 (0.537-0.937)
Placebo	91	4.7(3.6-5.4)		

Secondary end point – PFS (FAS and PPS)





Group	n	mPFS (95% CI), months	*P* value	HR (95%CI)
Apatinib	176	2.6(2.0-2.9)	<0.0001	0.444 (0.331-0.595)
Placebo	91	1.8(1.4-1.9)		

Group	n	mPFS (95% CI), months	*P* value	HR (95%CI)
Apatinib	136	2.8(2.1-3.3)	<0.0001	0.455 (0.332-0.624)
Placebo	71	1.9(1.1-1.7)		

Ramucirumab combined with FOLFOX as front-line therapy for advanced adenocarcinoma of esophagus, gastroesophageal junction, or stomach: Randomized, double-blind, multicenter phase 2 trial

Harry H. Yoon[1], Johanna C. Bendell[2], Fadi S. Braiteh[3], Irfan Firdaus[4], Philip A. Philip[5], Allen L. Cohn[6], Nancy Lewis[7], Daniel M. Anderson[8], Edward Arrowsmith[9], Jonathan D. Schwartz[10], Yihuan Xu[11], Minori Koshiji[12], Steven R. Alberts[1], Zev A. Wainberg[13]

[1]Mayo Clinic, Rochester, MN; [2]Sarah Cannon Research Institute, Tennessee Oncology Nashville, TN; [3]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [4]Sarah Cannon Research Institute/Oncology Hematology Care, Inc, Cincinnati, OH; [5]Barbara Ann Karmanos Cancer Institute/Wayne State University, Detroit, MI; [6]Rocky Mountain Cancer Center/US Oncology, Denver, CO; [7]Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA; [8]Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, MN; [9]Sarah Cannon Research Institute/Tennessee Oncology, Chattanooga, TN; [10]ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Branchburg, NJ; [11]ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Bridgewater, NJ; [12]ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Kobe, Japan; [13]David Geffen School of Medicine at UCLA, Los Angeles, CA

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

Study Design

I4T-MC-JVBT (NCT01246960)

Previously untreated

- Esophagus
- GEJ
- Stomach

R

Double blinded 1:1

RAM
8 mg/kg on Day 1
+ mFOLFOX6 on Day 1

placebo
8 mg/kg on Day 1
+ mFOLFOX6 on Day 1

Cycle length = 14 days

Disease assessment every 8 weeks until PD or toxicity.[a]

Discontinuation of ≥ 1 agents, while continuing others, was specifically permitted.

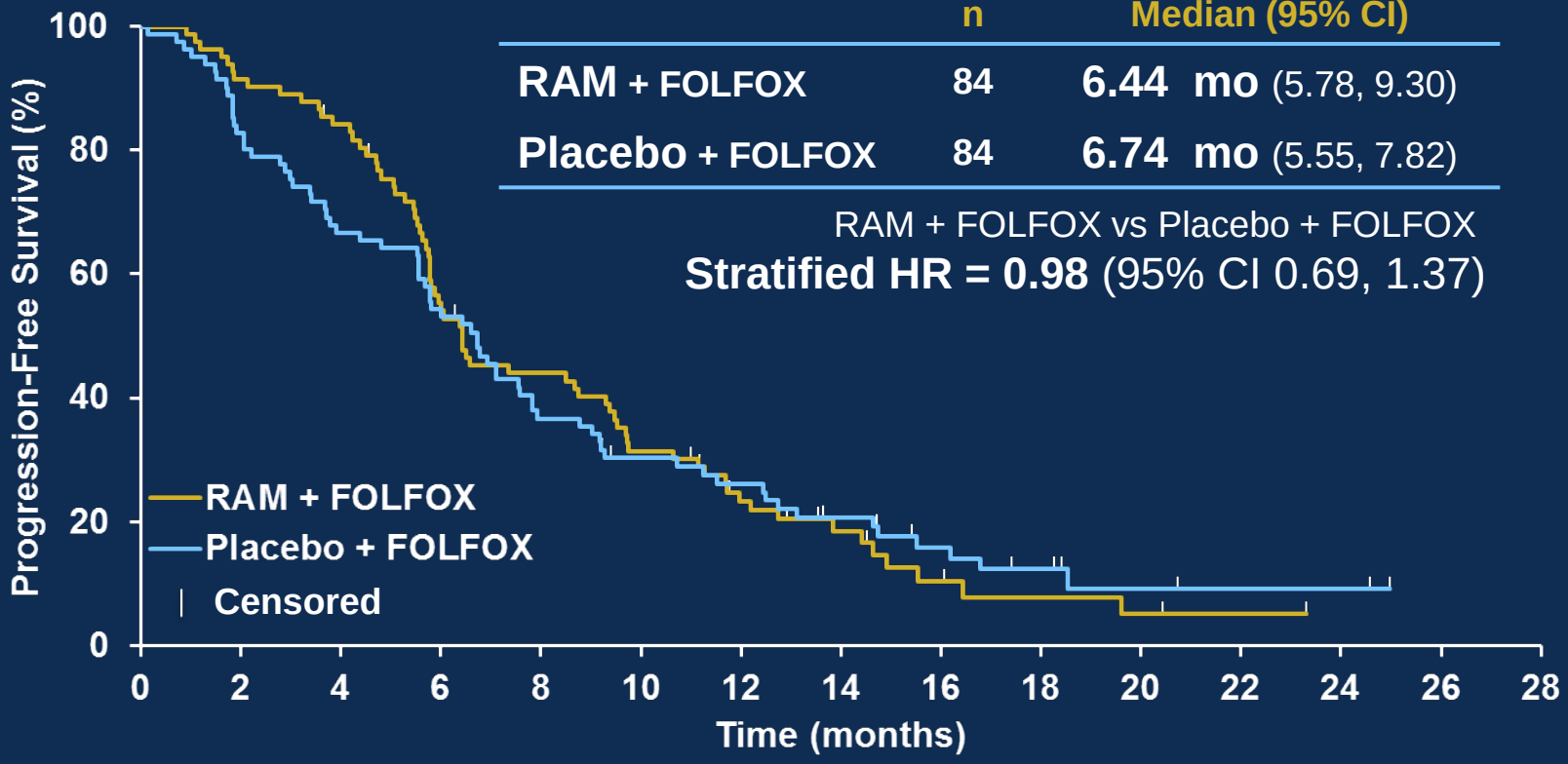
Stratification factors

- Metastatic *vs* locally advanced unresectable
- Esophagus/GEJ *vs* gastric

[a] Treatment continued until progressive disease (PD), unacceptable toxicity, patient or investigator decision.
mFOLFOX6 = 5-FU 400 mg/m2 bolus, leucovorin 400 mg/m^2, oxaliplatin 85 mg/m^2, then 5-FU continuous infusion 2,400 mg/m^2 (for 46-48 hr)

Primary Endpoint

Progression-free survival in ITT population



	n	Median (95% CI)
RAM + FOLFOX	84	**6.44 mo** (5.78, 9.30)
Placebo + FOLFOX	84	**6.74 mo** (5.55, 7.82)

RAM + FOLFOX vs Placebo + FOLFOX

Stratified HR = 0.98 (95% CI 0.69, 1.37)

No. at risk					
RAM + FOLFOX	84	44	16	3	0
Placebo + FOLFOX	84	44	19	6	2

Overall Survival: HR 1.08 (95% CI 0.73, 1.58), stratified; median 11.7 *vs* 11.5 mo

Conclusions
CRC

- 80405:
  - In Ras WT – Anti-VEGF vs Anti-EGFR overall similar activity.
- AIO/CAIRO4:
  - Maintenance helpful. FU/Cap +Bev
- Extended Ras
  - Crystal and Prime, 181, PEAK, FIRE3 (not shown), etc
  - c/w Exon 2 (codon 12/13).
  - Not labeled, important caveats (small subset, technical issues, eg tumor content/clonal frequency)
  - In 2014, probably best practices.

Conclusions
Pancreatic Cancer

- RECAP
  - Jak inhibition interesting/promising.
- MM398
  - Liposomal Irinotecan: Modest activity, significant toxicity. Role TBD.

Conclusions
Gastric Cancer

- Ramucirumab
  - 1st line with FOLFOX not active, but caveats
  - 2nd line still intact: with paclitaxel (RAINBOW), monotherapy (REGARD)
- Apatinib
  - OS benefit. Toxicity c/w VEGF MKI. Role ex-China TBD.

Bench to bedside to bench … and back