RAINBOW: A Global, Phase III, Randomized, Double-Blind Study of Ramucirumab Plus Paclitaxel Versus Placebo Plus Paclitaxel in the Treatment of Advanced Gastric and Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First-Line Platinum- and Fluoropyrimidine-Containing Combination Therapy: An Age Group Analysis

Abstract 11

Muro K, Bodoky G, Cesas A, Chao Y, Clingan P, Hironaka S, Komatsu Y, Kurteva GP, Lipatov ON, Nishina T, Oh SC, Ohtsu A, Shimada Y, Sugimoto N, Van Cutsem E, Carlesi R, Chandrawansa K, Wilke H

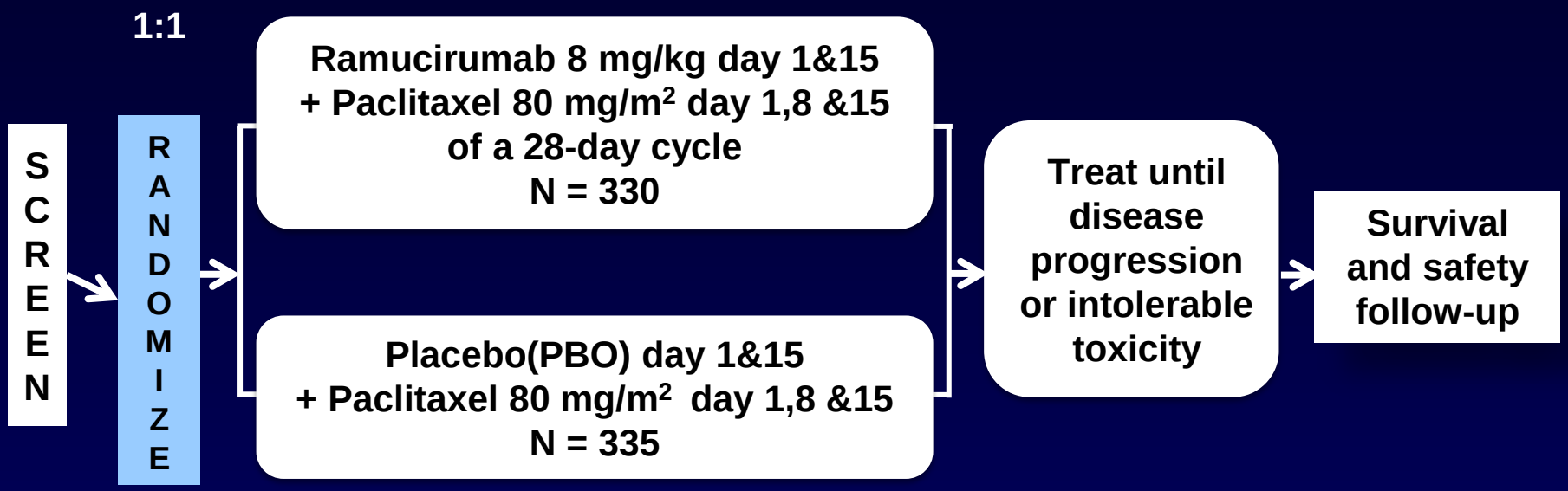
Background

- Ramucirumab (RAM) is a human immunoglobulin GI (IgG1) monoclonal antibody vascular endothelial growth factor (VEGF) receptor 2 antagonist recently approved by the US FDA for use as a single agent or in combination with paclitaxel in second-line metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma
- In the pivotal RAINBOW trial,[1] 665 patients with gastric/GEJ adenocarcinoma were randomized to receive paclitaxel +/- ramucirumab as second-line treatment after disease progression on platinum and fluoropyrimidine- based chemotherapy. Ramucirumab added to paclicaxel significantly improved overall survival, progression-free survival, and objective response rate in the overall population
  - Median OS: 9.6 months vs 7.4 months (HR = 0.807; *P* = .0169)
  - Median PFS: 4.4 months vs 2.9 months (HR = 0.635; *P*<.0001)
  - ORR: 27.9% vs 16.1% (odds ratio = 2.14; *P* = .0001)
- Here we report the efficacy and safety results by age subgroup (<65 vs ≥65 years) in the RAINBOW trial

1. Wilke H, et al. *Lancet Oncol.* 2014;15(11):1224-1235.

Muro K, et al. *J Clin Oncol.* 2015;33 (suppl 3): Abstract 11.

RAINBOW: Study Design



- Important inclusion criteria:
  - Metastatic or loc. adv. 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

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RAINBOW: Patient Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed gastric / GEJ adenocarcinoma
- Disease progression during first-line therapy or ≤4 months after last dose of first-line therapy with any platinum/fluoropyrimidine doublet with or without an anthracycline
- ECOG PS score 0-1
- Adequate hepatic, hematologic, coagulation, and renal function

Key Exclusion Criteria

- No prior treatment with an antiangiogenic agents
- GI perforation and/or fistulae within 6 months prior to randomization
- Significant GI bleeding within 3 months prior
- Venous thromboembolic event within 3 months, or arterial thromboembolic event within 6 months prior to randomization

ECOG PS, Eastern Cooperative Oncology Group performance statuS

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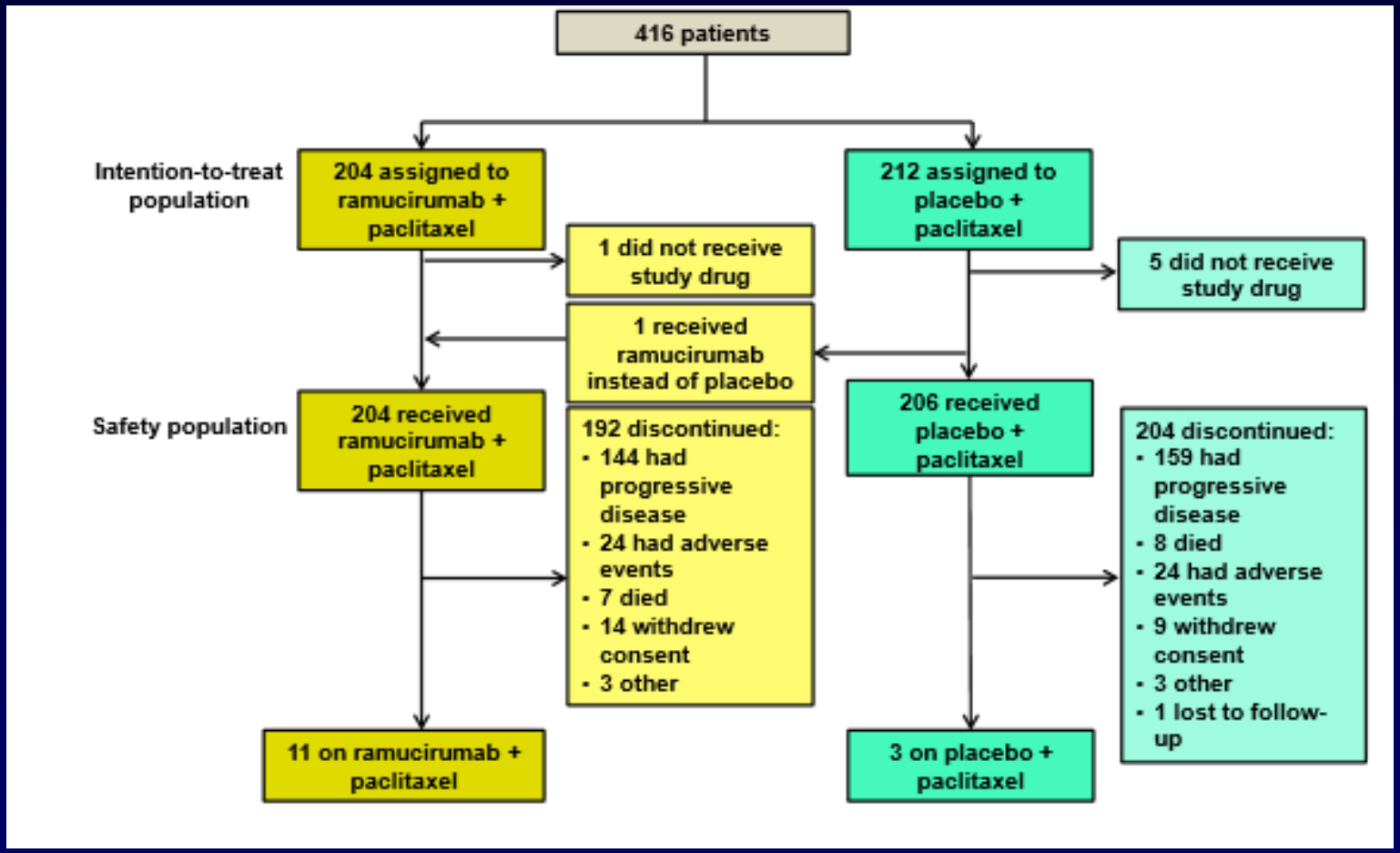
Patient Disposition by Age Group
Patients <65 Years



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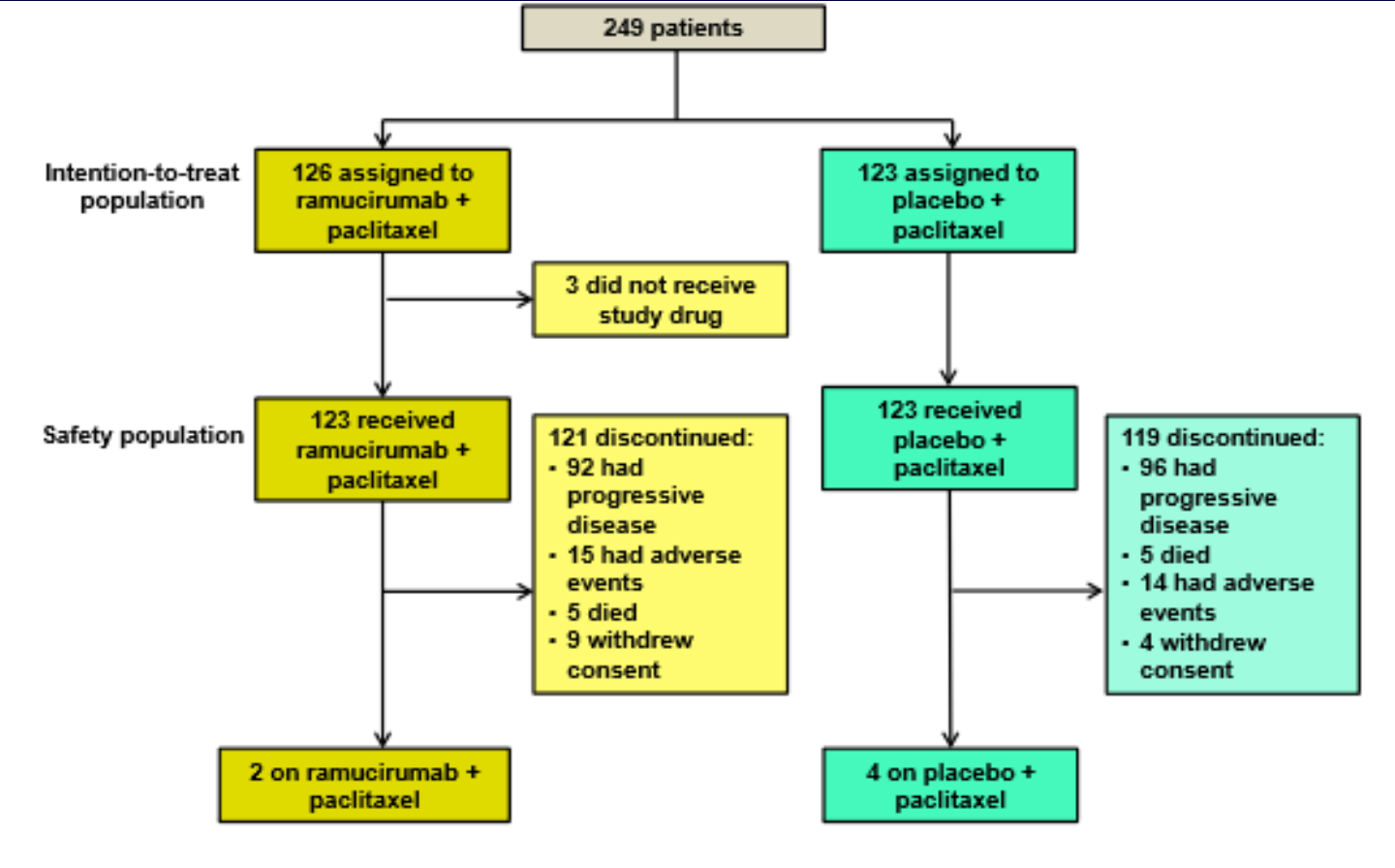
Patient Disposition by Age Group Patients ≥65 Years



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Baseline Patient Characteristics (1)

	Age <65 Years		Age ≥65 Years	
	RAM (N = 204)	PBO (N = 212)	RAM (N = 126)	PBO (N = 123)
Mean Age, years (SD)	54 (8.8)	53 (8.8)	70 (4.0)	71 (3.8)
Male, n (%)	141 (69)	144 (68)	88 (70)	99 (80)
Race, n (%)				
Caucasian	127 (62)	127 (60)	81 (64)	72 (58)
Asian	68 (33)	73 (34)	42 (33)	48 (39)
Black	4 (2.0)	4 (1.9)	2 (1.6)	2 (1.6)
Other	5 (2.5)	8 (3.8)	1 (0.8)	1 (0.8)
ECOG PS, n (%)				
0	73 (36)	95 (45)	44 (35)	49 (40)
1	131 (64)	117 (55)	82 (65)	74 (60)

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Baseline Patient Characteristics (2)

	Age <65 years		Age ≥65 years	
	RAM (N = 204)	PBO (N = 212)	RAM (N = 126)	PBO (N = 123)
Measureable disease, n (%)	153 (75)	162 (76)	103 (82)	103 (84)
Location of primary tumor, n (%)				
Gastric	157 (77)	168 (79)	107 (85)	96 (78)
Gastroesophageal junction	47 (23)	44 (21)	19 (15)	27 (22)
Histological subtype, n (%)				
Intestinal	80 (39)	77 (36)	65 (52)	58 (47)
Diffuse	80 (39)	89 (42)	35 (28)	44 (36)
Mixed/unknown	44 (22)	46 (22)	26 (21)	21 (17)
0	73 (36)	95 (45)	44 (35)	49 (40)
1	131 (64)	117 (55)	82 (65)	74 (60)
Metastases >2 sites	73 (36)	62 (29)	48 (38)	41 (33)
TTP on first-line <6 months, n (%)	148 (72)	132 (62)	60 (48)	68 (55)

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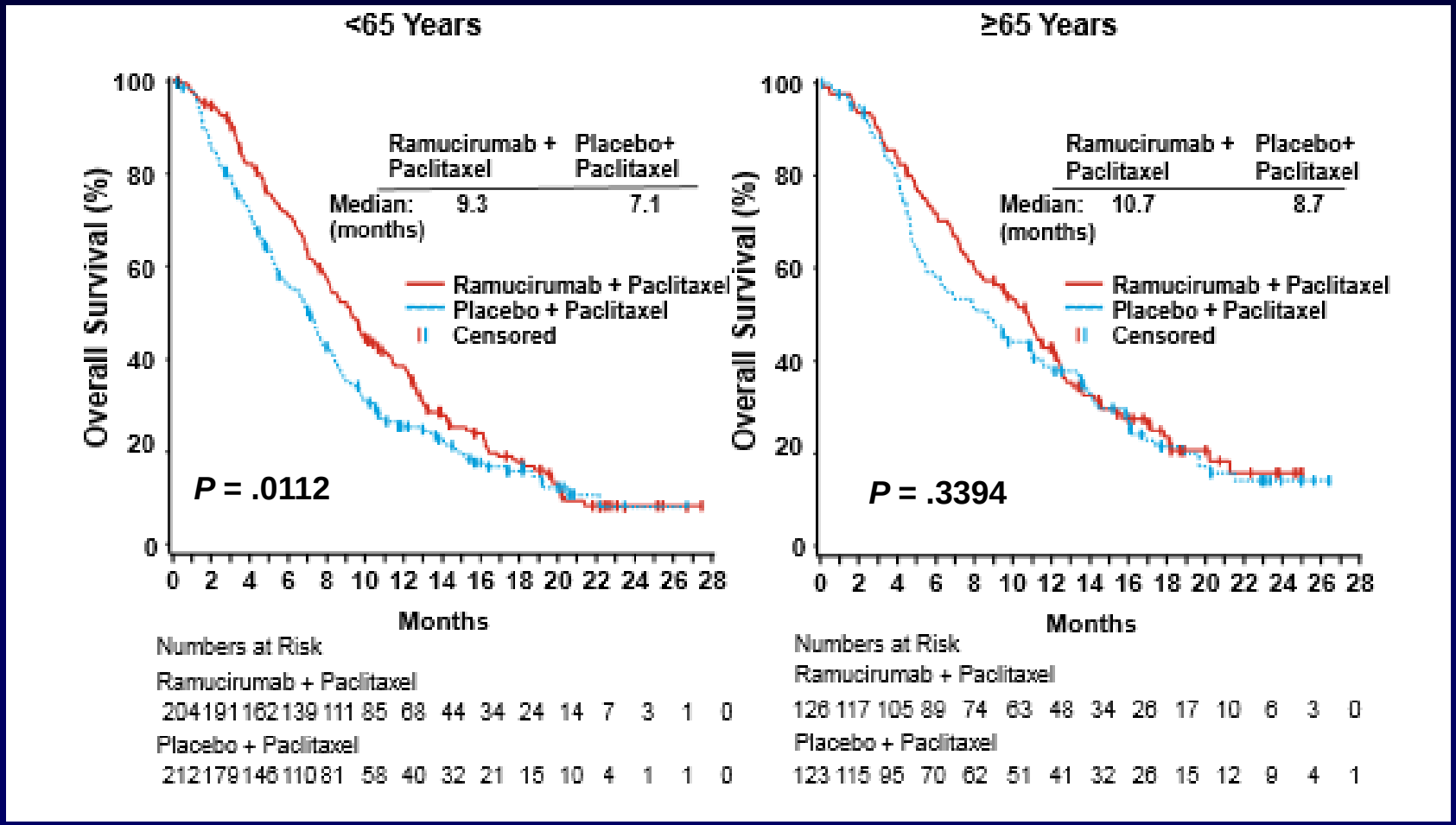
Kaplan-Meier Estimates of Overall Survival



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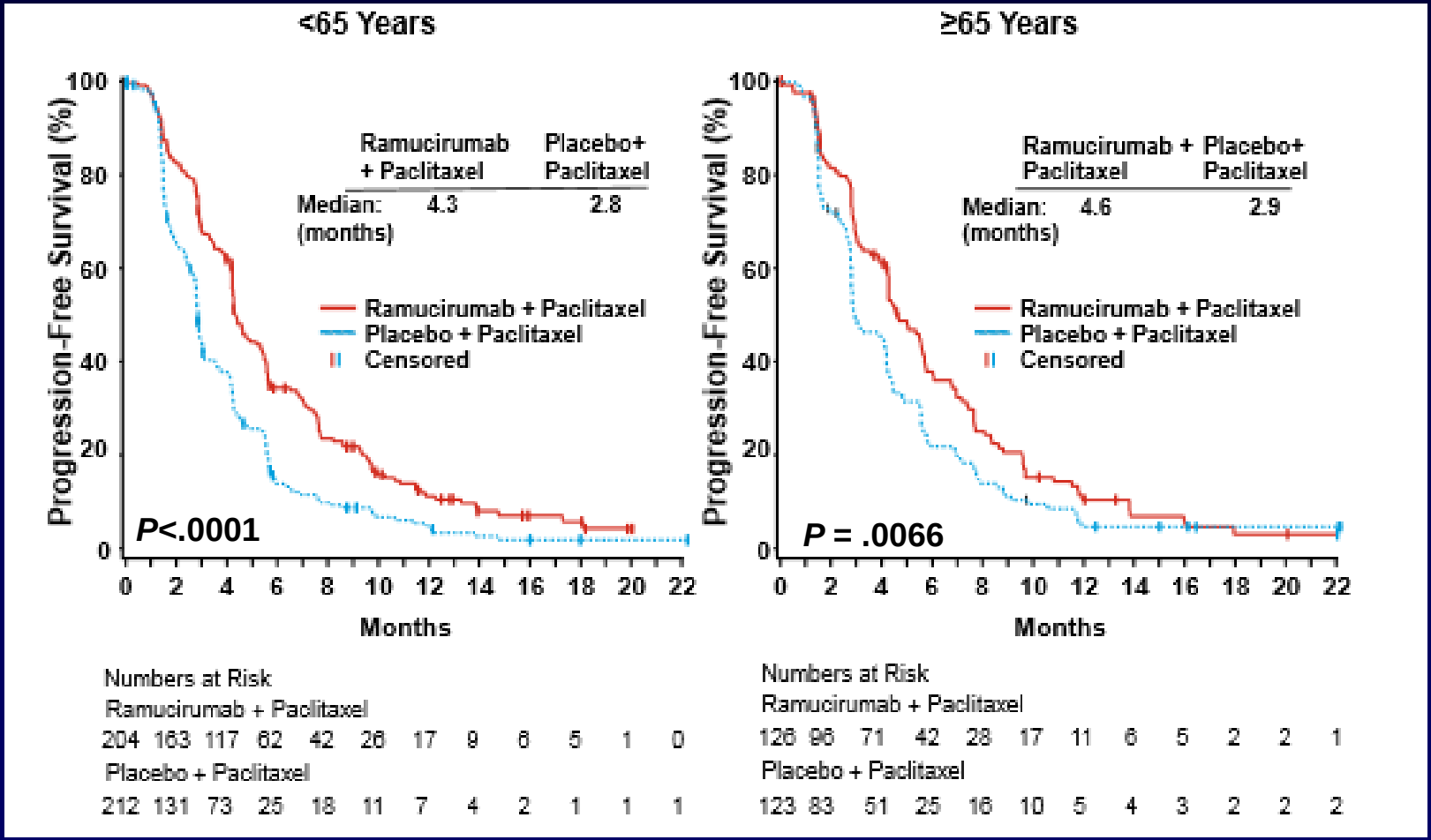
Kaplan-Meier Estimates of Progression-Free Survival



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Response and Duration of Therapy

	Age <65 Years		Age ≥65 Years	
	RAM (N = 204)	PBO (N = 206)	RAM (N = 123)	PBO (N = 123)
Objective response rate	28.4	14.2	27.0	19.5
Duration of therapy, weeks, mean (SD)	23.4 (18.4)	16.2 (13.4)	23.8 (19.1)	18.6 (16.5)
Total # 28-day cycles received, mean (SD)	5.7 (4.2)	4.1 (3.2)	5.8 (4.5)	4.6 (3.9)

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Non-Hematologic Treatment-Emergent Adverse Events (≥20% of Patients)

	Age <65				Age ≥65			
	RAM (N = 204)		PBO (N = 206)		RAM (N = 123)		PBO (N = 123)	
%	Any grade	Grade ≥3	Any Grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.0	79.4	97.1	64.1	99.2	85.4	99.2	60.2
Alopecia	29.4	0	36.9	0	38.2	0	41.5	0.8
Neuropathy	47.1	8.3	32.0	2.4	43.9	8.1	43.1	8.1
Decreased appetite	37.3	2.5	29.6	4.4	44.7	4.1	35.8	3.3
Fatigue	54.9	9.8	42.2	5.3	60.2	15.4	46.3	5.7
Diarrhea	34.8	3.9	20.9	1.5	28.5	3.3	26.8	1.6
Epistaxis	30.4	0.0	5.8	0.0	30.0	0.0	8.9	0.0
Stomatits	16.7	1.0	4.9	0.5	24.4	0.0	11.4	0.8
Nausea	34.8	1.5	34.0	2.9	35.8	2.4	30.9	1.6
Vomiting	28.9	2.9	25.7	5.3	23.6	3.3	12.2	0.8
Peripheral edema	22.5	2.0	12.1	0.5	29.3	0.8	16.3	0.8
Abdominal pain	39.7	7.4	32.5	3.9	30.1	4.1	25.2	2.4
Pyrexia	20.1	1.5	10.2	0.5	14.6	0.0	13.0	0.0

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Hematologic Treatment-Emergent Adverse Events (≥10% of Patients)

	Age <65				Age ≥65			
	RAM (N = 204)		PBO (N = 206)		RAM (N = 123)		PBO (N = 123)	
%	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	4.95	35.8	24.3	16.0	62.6	48.8	42.3	23.6
Febrile neutropenia	2.0	2.0	2.9	2.9	4.9	4.9	1.6	1.6
Leukopenia	31.9	14.7	17.0	6.3	37.4	22.0	27.6	7.3
Anemia	30.4	9.3	36.9	10.7	39.8	8.9	33.3	9.8
Thrombocytopenia	12.3	1.5	5.8	2.9	14.6	1.6	6.5	0.0

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

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AEs of Special Interest

	Age <65				Age ≥65			
	RAM (N = 204)		PBO (N = 206)		RAM (N = 123)		PBO (N = 123)	
%	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	64.7	24.5	35.9	10.2	63.4	26.0	39.8	11.4
Bleeding/hemorrhage	41.2	3.9	17.5	3.4	43.1	4.9	18.7	0.8
Proteinuria	18.1	2.0	5.8	0	14.6	0	6.5	0
Hypertension	23.5	12.3	5.8	1.9	27.6	18.7	5.7	4.1
GI hemorrhage	9.8	3.4	6.8	1.9	10.6	4.1	4.9	0.8
Infusion-related reaction	6.9	0.5	3.9	0	4.1	0.8	3.3	0
Venous thromboembolic	4.4	2.9	3.9	1.9	3.3	1.6	8.1	5.7
Cardiac failure	1.5	0.5	1.5	1.0	4.1	0.8	0.8	0
Arteriothromboembolic	2.9	1.5	1.0	1.0	0	0	2.4	0.8
GI perforation	1.0	1.0	0	0	1.6	1.6	0.8	0

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Conclusions

- Patient characteristics were generally well-balanced between the treatment arms in both age groups
- There were more patients with intestinal type tumors and with time progression on first-line therapy >6 months in the ≥65 year group
- Ramucirumab plus paclitaxel conferred similar improvements over placebo plus paclitaxel for OS, PFS, and ORR in both age groups
- Drug exposure for ramucirumab plus paclitaxel and placebo plus paclitaxel was similar in both age groups
- Higher percentages of patients in the ramucirumab plus paclitaxel arm discontinued treatment due to adverse events and had dose modifications
  - Dose modifications of paclitaxel occurred more frequently in patients aged ≥65 years
- Toxicity profiles were similar in both age groups, although a relatively higher incidence of grade ≥3 neutropenia and of grade >3 leukopenia was seen in patients aged ≥65 years

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