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Randomized phase 3 ANGEL study of rivoceranib (apatinib) + best supportive care (BSC) vs placebo + BSC in patients with advanced/metastatic gastric cancer who failed ≥2 prior chemotherapy regimens

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Disclosures – Professor Min-Hee Ryu

Disclosures relevant to this presentation

- None

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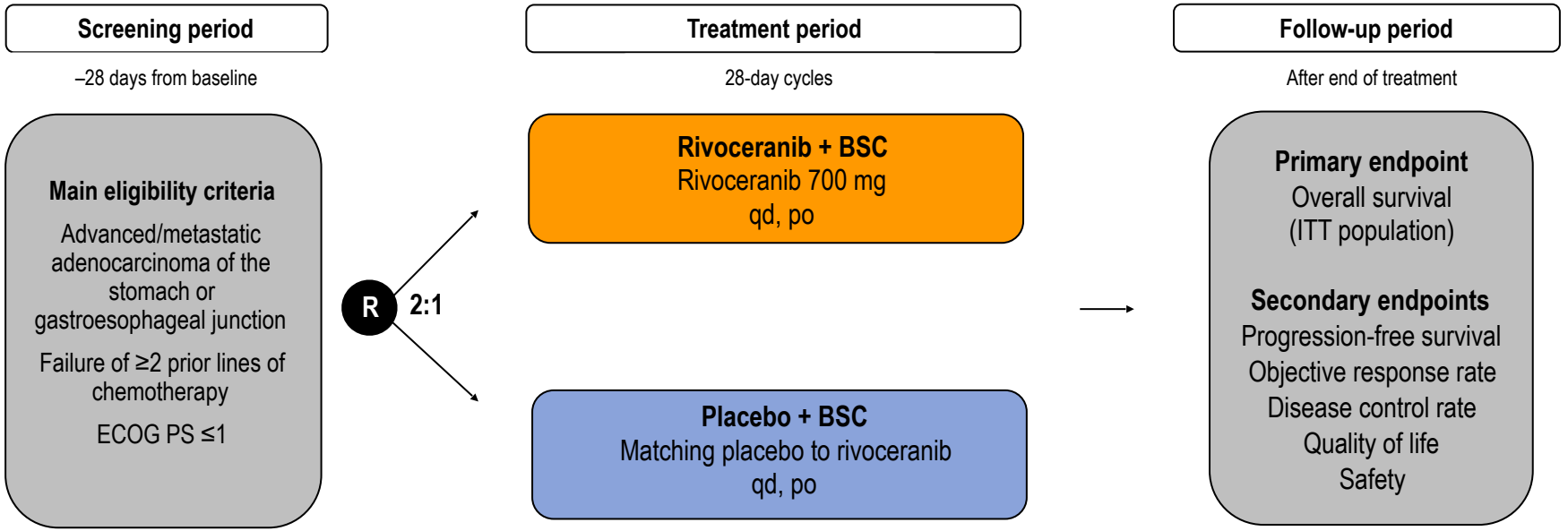
Background

- Rivoceranib (also known as apatinib and YN968D1) is an orally administered, highly selective tyrosine kinase inhibitor of VEGFR-2 with demonstrated efficacy and approval as ≥3rd-line treatment for advanced gastric cancer in China[1]
- Phase I/II trials in Korean and US patients established the recommended dose of rivoceranib and demonstrated promising efficacy in patients with gastric cancer outside of China[2,3]
- However, rivoceranib had not previously been evaluated in a global randomized placebo-controlled study
- The ANGEL study (Clinical trial registration: NCT03042611) was a multinational, placebo-controlled, phase 3 study of rivoceranib in patients with advanced gastric cancer in Asia Pacific, North America, and Europe

1. Li J, et al. J Clin Oncol 2016;34:1448–54
2. Kang YK, et al. Ann Oncol 2015;27:114–35
3. Sharma S, et al. J Clin Oncol 2015;33(suppl: abstr 2525)

ANGEL: a global, randomized, phase 3 study



Patients stratified by

- Geographic region (Asia vs North America/Europe)
- Disease measurability
- Prior ramucirumab use
- Line of therapy (3rd or ≥4th)

Treatment given until disease progression, intolerable toxicity or withdrawal of consent

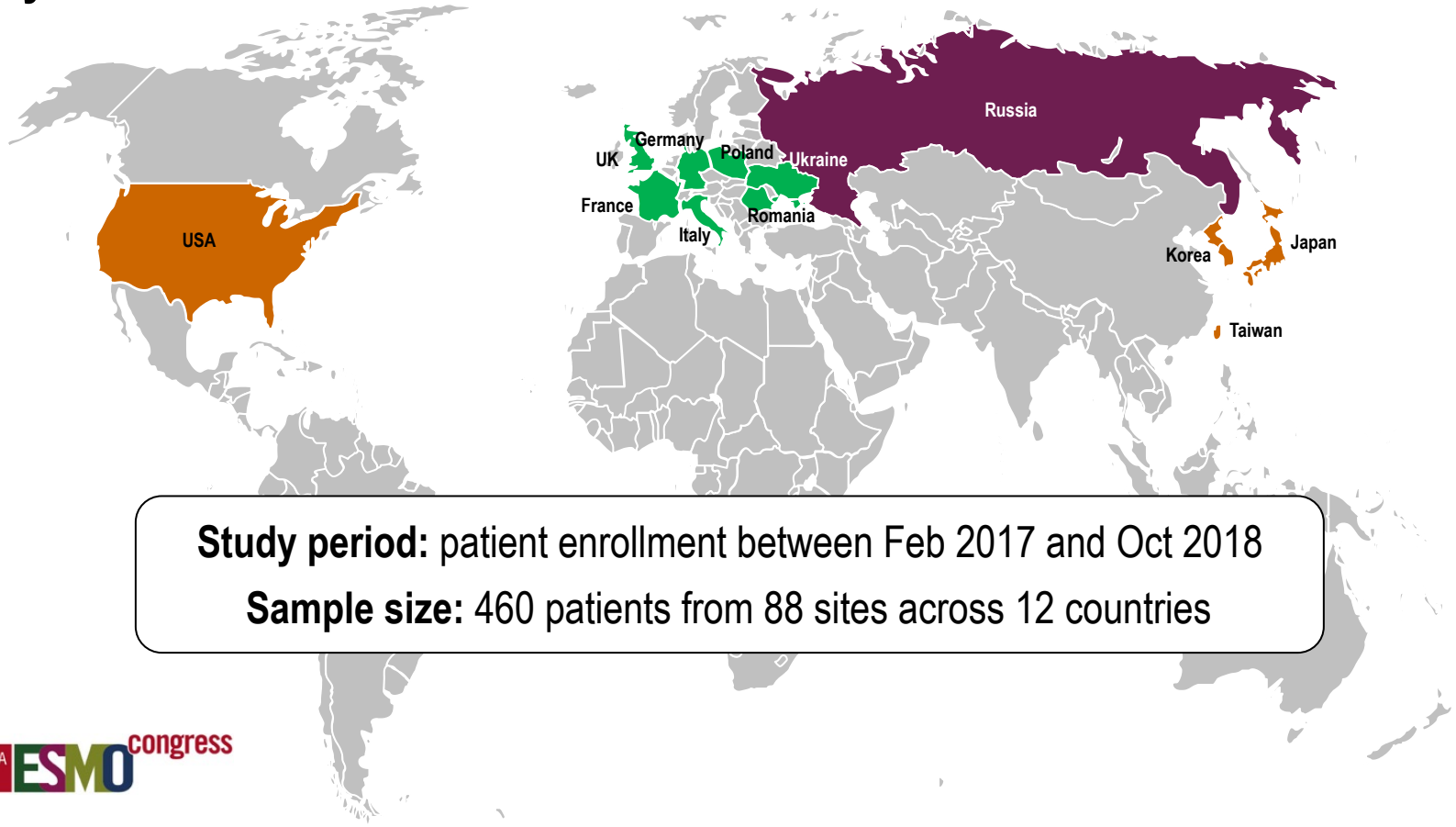
Patients allowed to continue treatment after PD (at investigators' discretion)

Tumor evaluation by CT/MRI q2 cycles (RECIST 1.1)

Study statistics and conduct

- **Primary endpoint:** OS in ITT population
- **Assumptions:** median OS 6.5 months vs 4.7 months for rivoceranib vs placebo (HR=0.72)
- **Required number of events and patients:** 325 death events and 459 patients for 80% power with a two-sided alpha of 0.05
- **Interim analysis:** safety and futility analysis planned and conducted after approx. 163 death events; recommendation by IDMC was made to continue without modification
- **Final analysis:** done with database lock on 30 May 2019 with 369 events

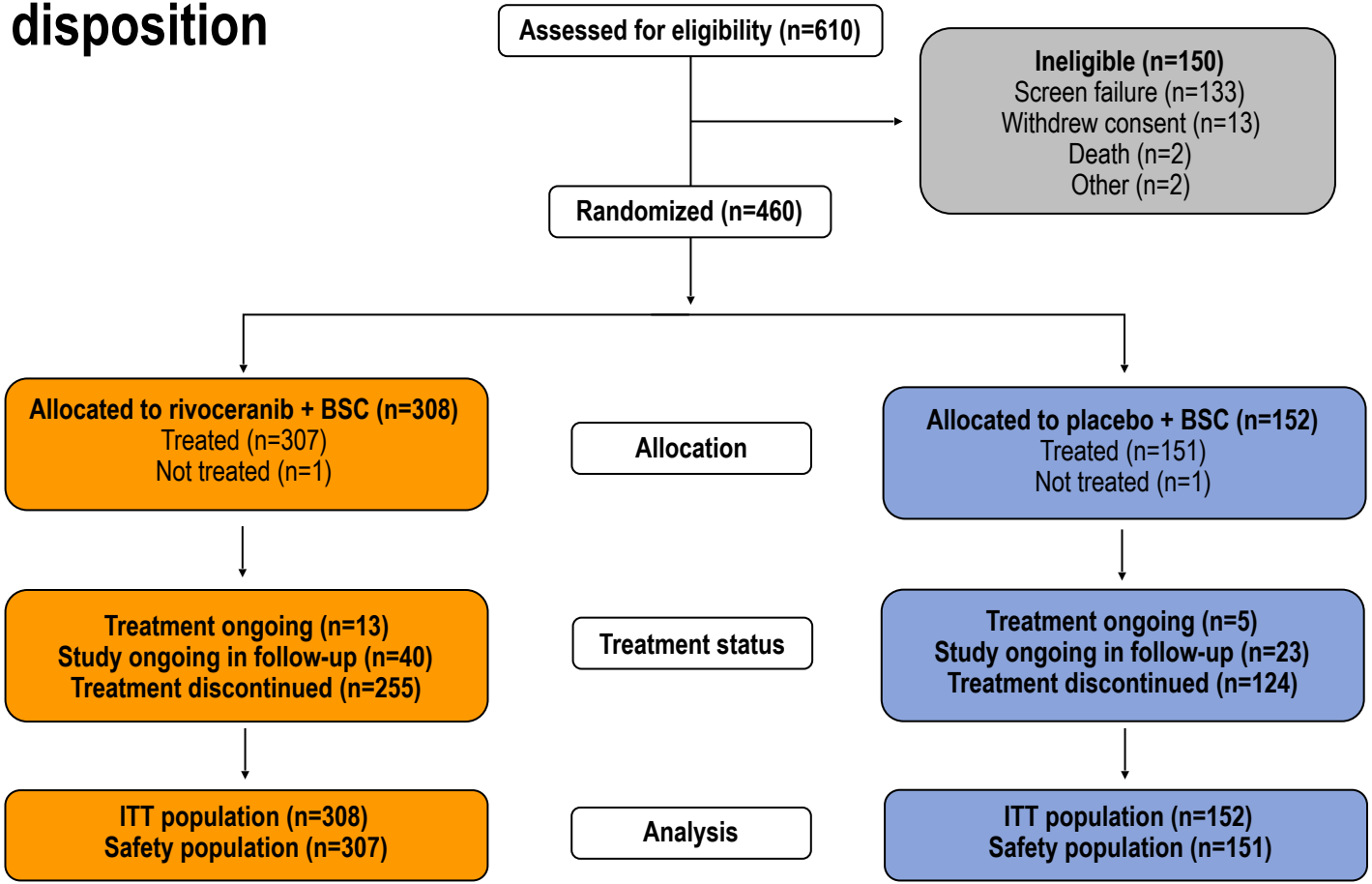
Study enrollment



Study period: patient enrollment between Feb 2017 and Oct 2018

Sample size: 460 patients from 88 sites across 12 countries

Patient disposition

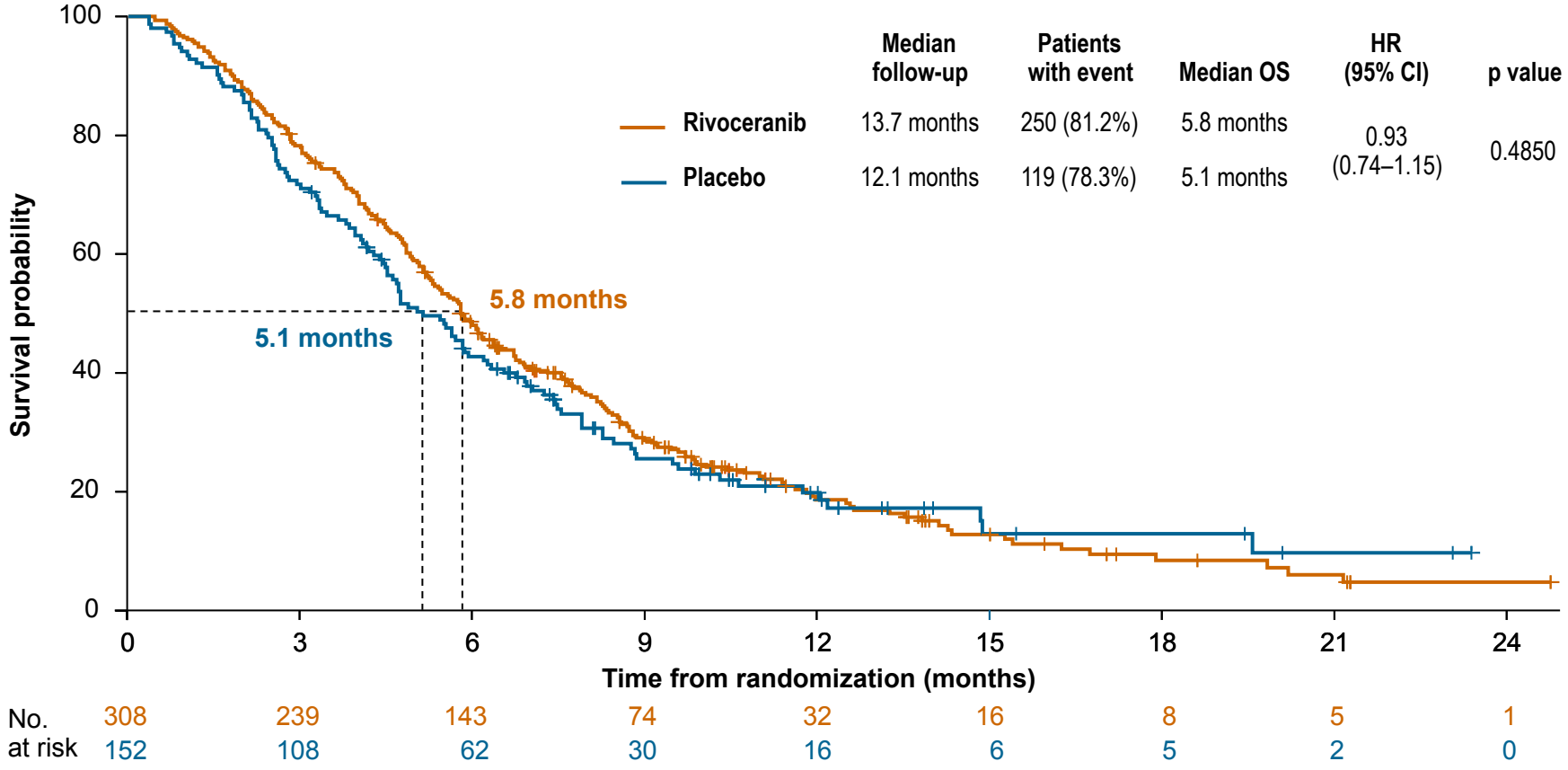


Baseline characteristics (ITT population)

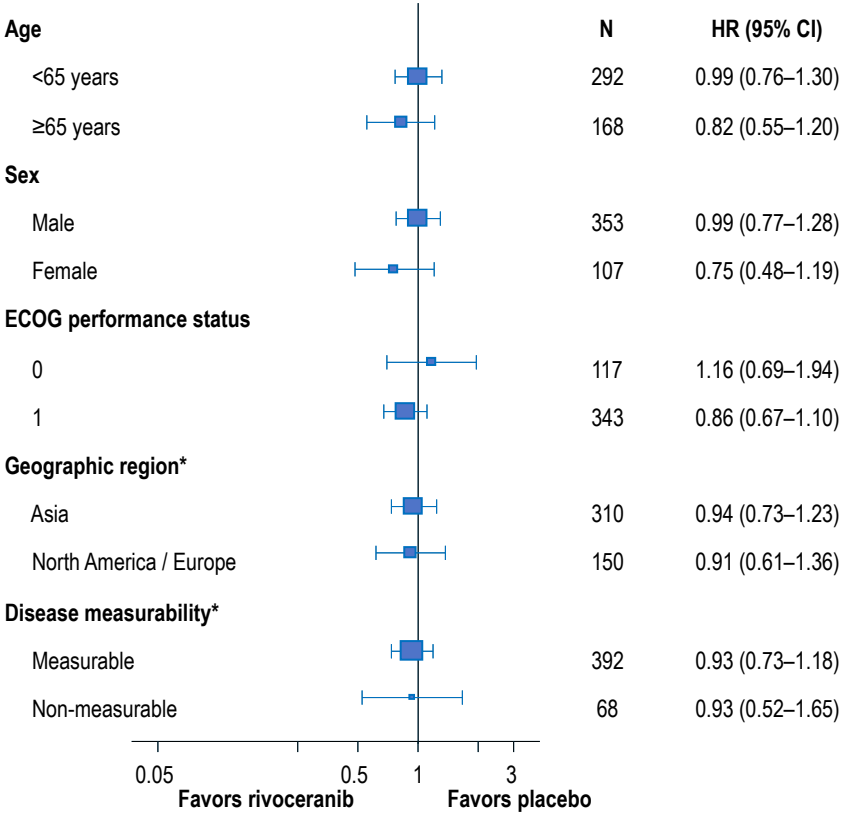
Stratification factors

Characteristic	Rivoceranib + BSC (n=308)	Placebo + BSC (n=152)	Total (n=460)
Median age, years (range)	60.0 (21.0–91.0)	61.0 (27.0–82.0)	60.0 (21.0–91.0)
Male, n (%)	241 (78.3)	112 (73.7)	353 (76.7)
Geographic region, n (%) Asia Pacific North America/Europe	 207 (67.2) 101 (32.8)	 103 (67.8) 49 (32.2)	 310 (67.4) 150 (32.6)
Disease measurability, n (%) Measurable Non-measurable	 262 (85.1) 46 (14.9)	 130 (85.5) 22 (14.5)	 392 (85.2) 68 (14.8)
Line of therapy, n (%) 3rd line / ≥4th line	186 (60.4) / 122 (39.6)	89 (58.6) / 63 (41.5)	275 (59.7) / 185 (40.2)
Prior ramucirumab treatment, n (%)	102 (33.1)	49 (32.2)	151 (32.8)
ECOG performance status, n (%) 0 / 1	82 (26.6) / 226 (73.4)	35 (23.0) / 117 (77.0)	117 (25.4) / 343 (74.6)
Primary tumor site, n (%) Gastric / gastroesophageal junction	274 (89.0) / 34 (11.0)	129 (84.9) / 23 (15.1)	403 (87.6) / 57 (12.4)
Previous gastrectomy, n (%)	148 (48.1)	78 (51.3)	226 (49.1)
No. of organs with metastases, n (%) <2 / ≥2	113 (36.7) / 195 (63.3)	59 (38.8) / 93 (61.2)	172 (37.4) / 288 (62.6)
Liver metastasis, n (%)	134 (43.5)	68 (44.7)	202 (43.9)

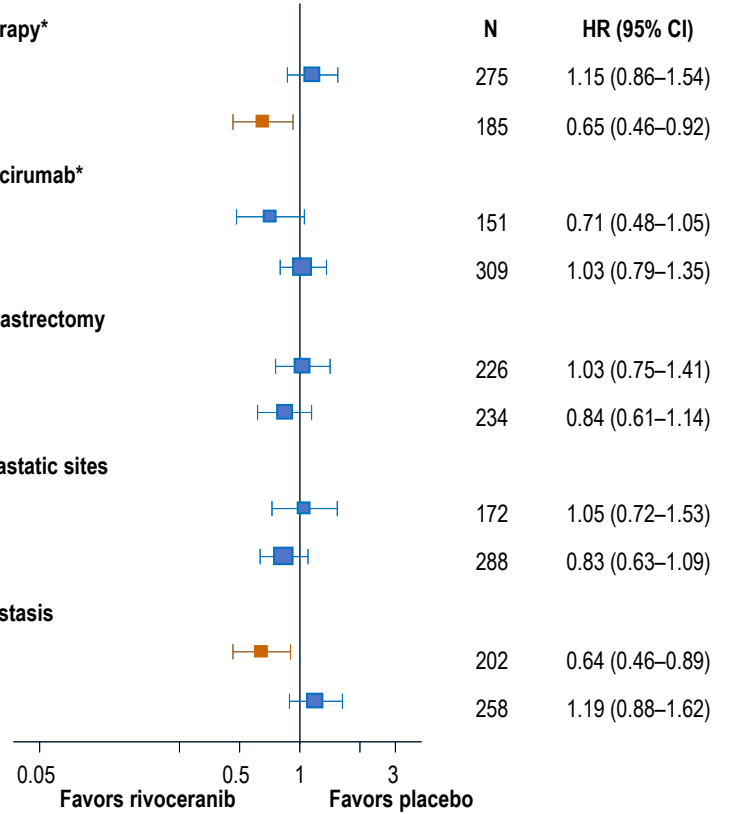
Overall survival



Overall survival – subgroup analysis



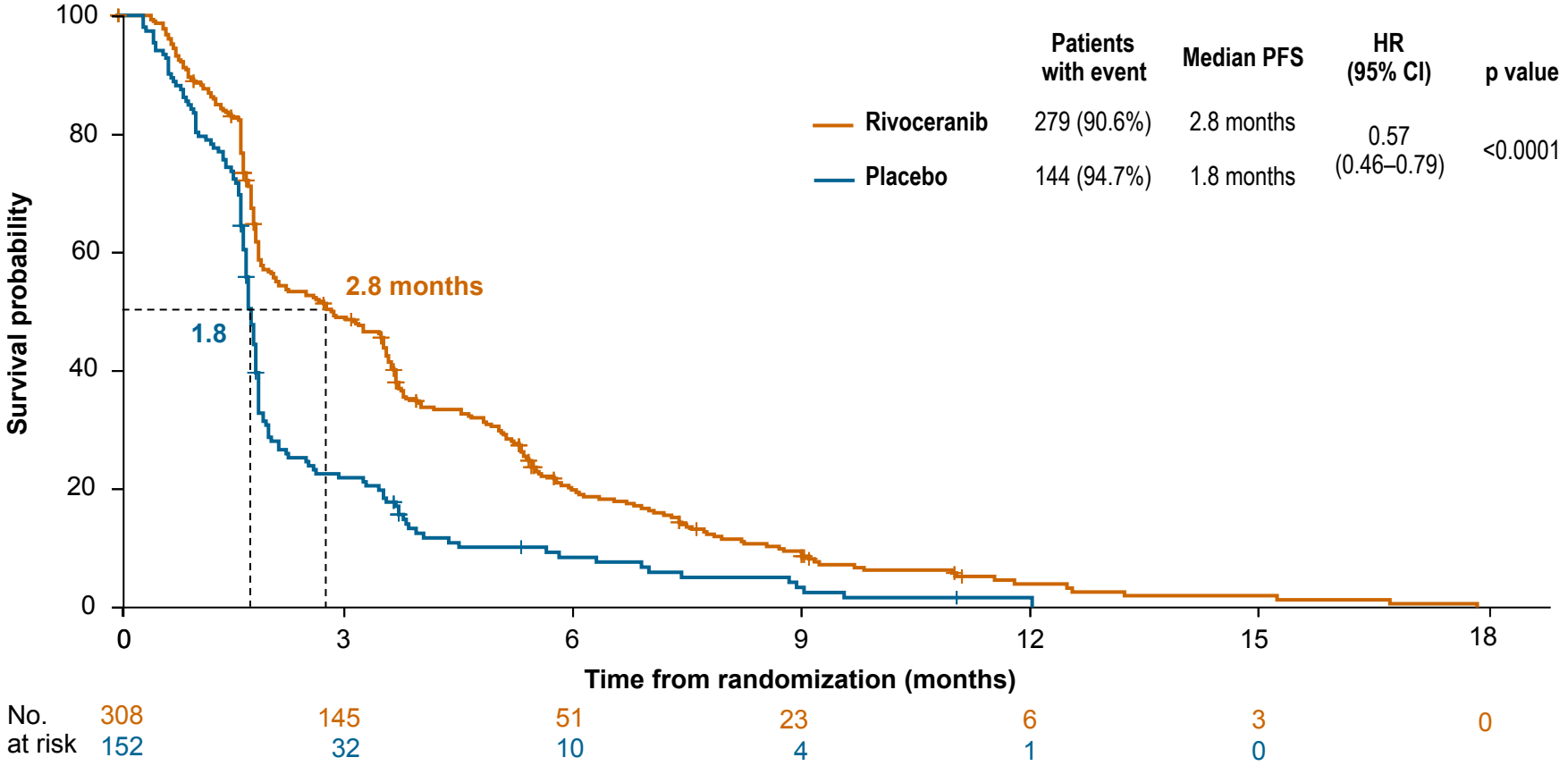
	N	HR (95% CI)
Age		
<65 years	292	0.99 (0.76–1.30)
≥65 years	168	0.82 (0.55–1.20)
Sex		
Male	353	0.99 (0.77–1.28)
Female	107	0.75 (0.48–1.19)
ECOG performance status		
0	117	1.16 (0.69–1.94)
1	343	0.86 (0.67–1.10)
Geographic region*		
Asia	310	0.94 (0.73–1.23)
North America / Europe	150	0.91 (0.61–1.36)
Disease measurability*		
Measurable	392	0.93 (0.73–1.18)
Non-measurable	68	0.93 (0.52–1.65)



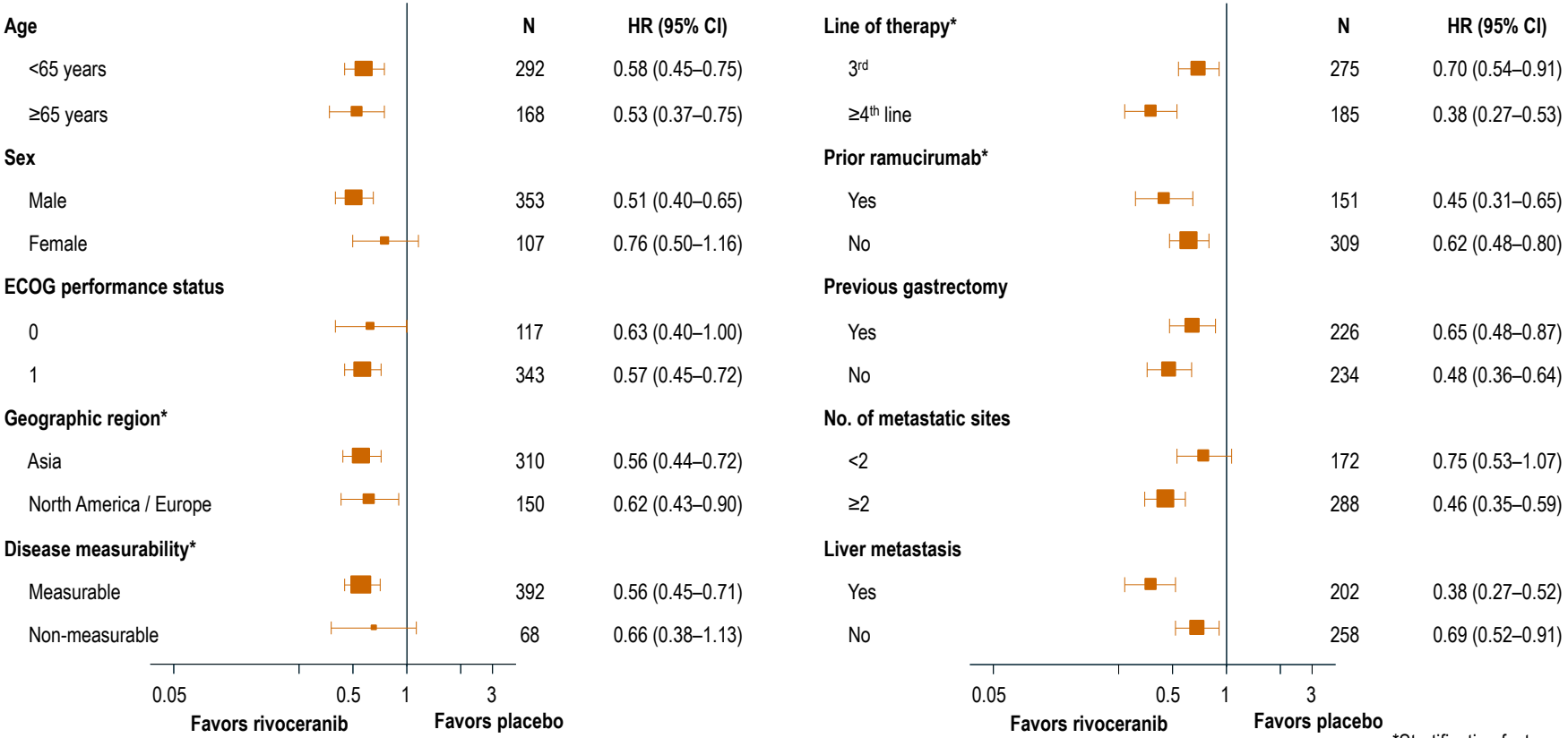
	N	HR (95% CI)
Line of therapy*		
3rd	275	1.15 (0.86–1.54)
≥4th line	185	0.65 (0.46–0.92)
Prior ramucirumab*		
Yes	151	0.71 (0.48–1.05)
No	309	1.03 (0.79–1.35)
Previous gastrectomy		
Yes	226	1.03 (0.75–1.41)
No	234	0.84 (0.61–1.14)
No. of metastatic sites		
<2	172	1.05 (0.72–1.53)
≥2	288	0.83 (0.63–1.09)
Liver metastasis		
Yes	202	0.64 (0.46–0.89)
No	258	1.19 (0.88–1.62)

*Stratification factors

Progression-free survival (central review)



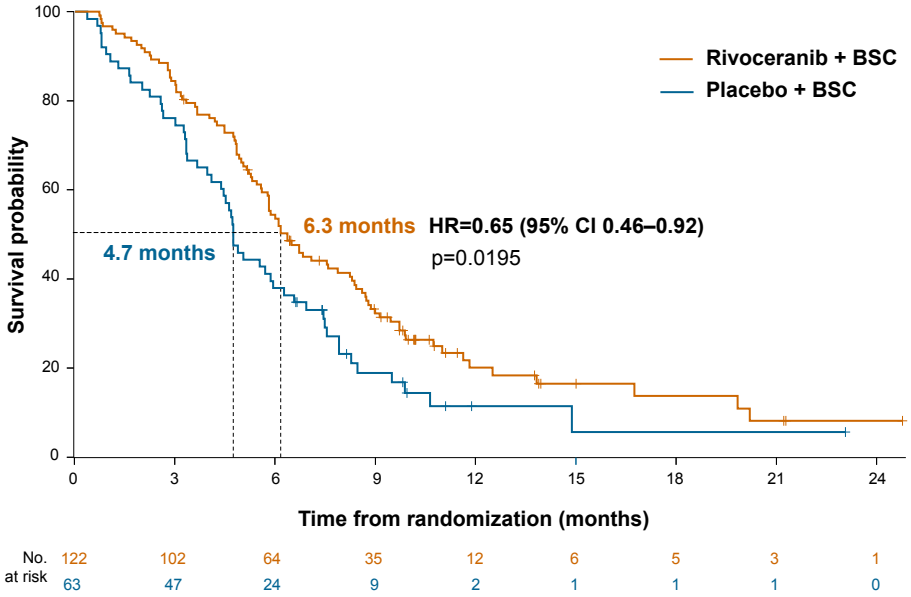
Progression-free survival – subgroup analysis



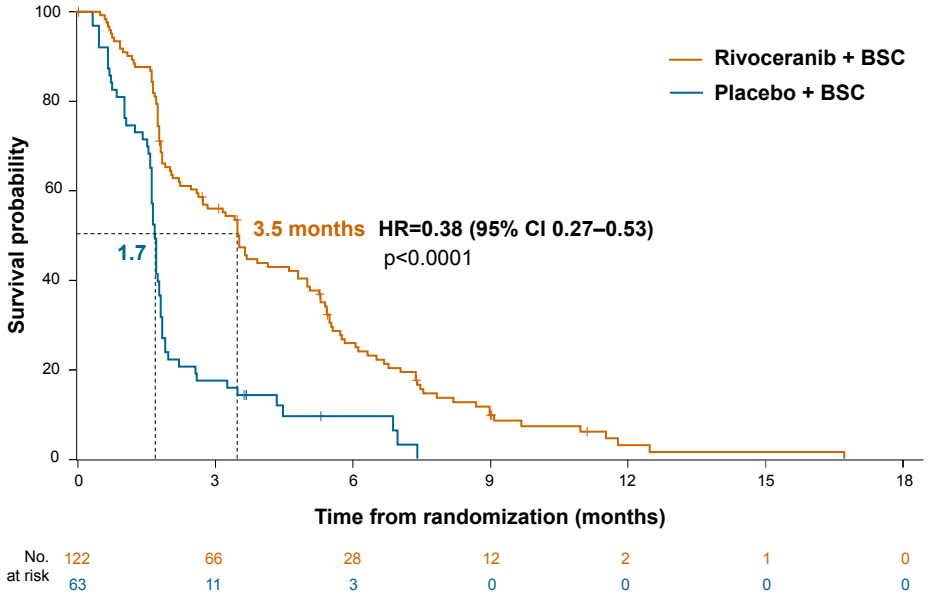
*Stratification factors

Overall survival and PFS in ≥4th-line patients

Overall survival



Progression-free survival



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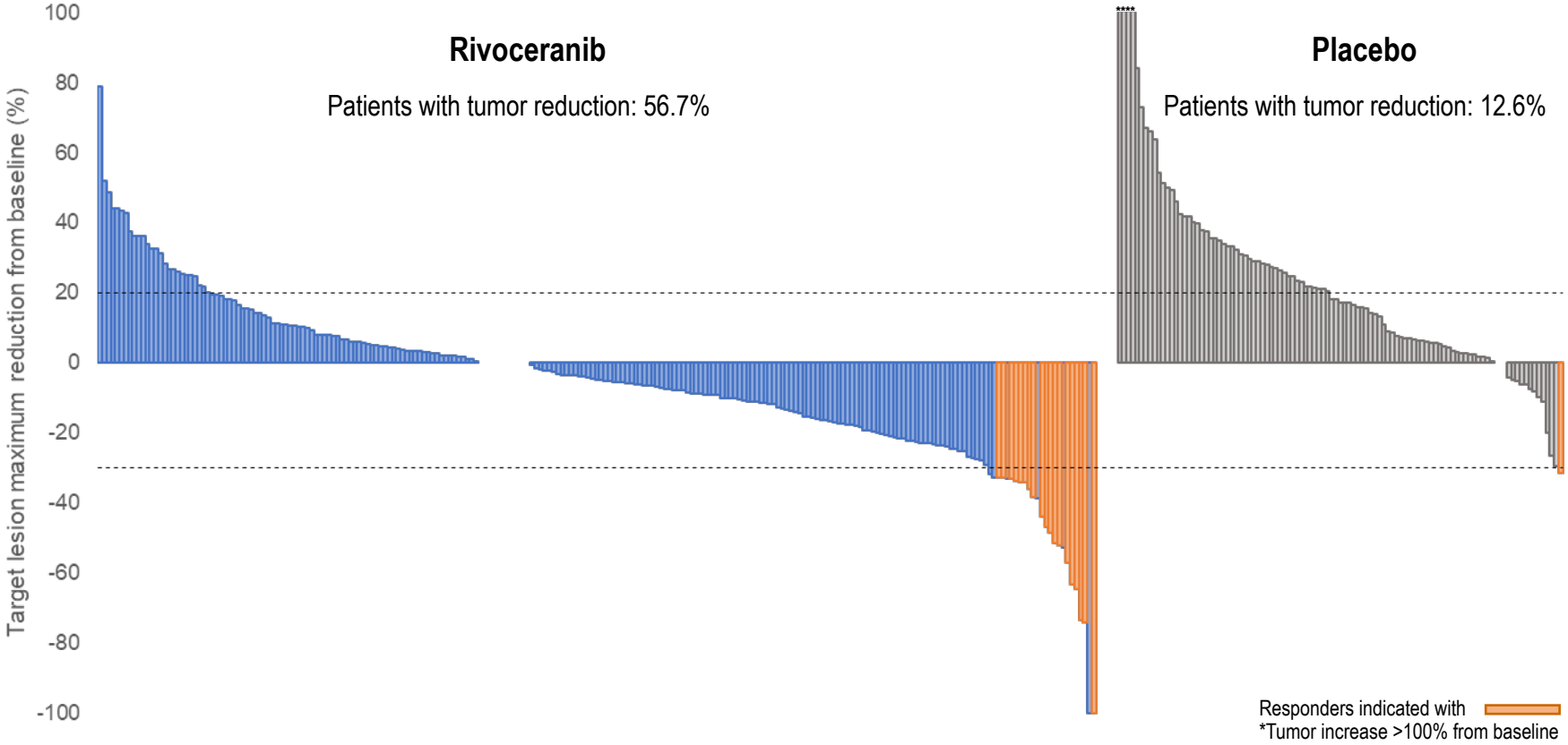
Objective response / disease control (measurable disease)

Response, n (%)	Rivoceranib + BSC (n=262)	Placebo + BSC (n=130)
Objective response rate	**18 (6.9)**	**0**
(95% CI)	(3.8–9.9)	(0–0)
p-value	0.002	
Best overall response		
Complete response	2 (0.8)	0
Partial response	16 (6.1)	0
Stable disease	93 (35.5)	17 (13.1)
Progressive disease	98 (37.4)	81 (62.3)
Not evaluable	18 (6.9)	6 (4.6)
Missing	30 (11.5)	20 (15.4)
Disease control rate	**111 (42.4)**	**17 (13.1)**
(95% CI)	(36.4–48.4)	(7.3–18.9)
p-value	<0.0001	

Waterfall plot (central review of measurable patients)



TEAEs occurring in ≥20% of rivoceranib patients

Adverse event, n (%)	Rivoceranib + BSC (n=307)		Placebo + BSC (n=151)	
	All grades	Grade ≥3	All grades	Grade ≥3
TEAEs	306 (99.7)		144 (95.4)	
Serious TEAEs	146 (47.6)		66 (43.7)	
TEAEs leading to discontinuation	71 (23.1)		25 (16.6)	
TEAEs leading to death	21 (6.8)		11 (7.3)	
AEs of special interest				
Hypertension	105 (34.2)	55 (17.9)	5 (3.3)	0
Proteinuria	90 (29.3)	23 (7.5)	11 (7.3)	0
Hand-foot skin reaction	81 (26.4)	9 (2.9)	6 (4.0)	0
Other AEs				
Decreased appetite	130 (42.3)	22 (7.2)	48 (31.8)	7 (4.6)
Diarrhea	90 (29.3)	10 (3.3)	20 (13.3)	0
Asthenia	87 (28.3)	26 (8.5)	35 (23.2)	15 (9.9)
Abdominal pain	85 (27.7)	22 (7.2)	31 (20.5)	7 (4.6)
Nausea	71 (23.1)	5 (1.6)	34 (22.5)	0
Stomatitis	69 (22.5)	11 (3.6)	5 (3.3)	0
Weight decreased	68 (22.2)	6 (2.0)	12 (8.0)	0
Anemia	64 (20.9)	30 (9.8)	41 (27.2)	24 (15.9)

Summary and conclusions

- Primary endpoint was not met
  - OS in the overall group was not different for rivoceranib vs placebo (median 5.8 vs 5.1 months; HR=0.93; 95% CI 0.74–1.15; p=0.4850)
- Secondary endpoints were significantly better for rivoceranib vs placebo
  - PFS: median 2.8 vs 1.8 months (HR=0.57; 95% CI 0.46–0.79; p<0.0001)
  - ORR: 6.9% vs 0% (p=0.0020)
  - DCR: 42.4% vs 13.1% (p<0.0001)
- In ≥4th-line patients, both OS (median 6.4 vs 4.7 months; HR=0.65; 95% CI 0.46–0.92; p=0.0195) and PFS (median 3.5 vs 1.7 months; HR=0.38; 95% CI 0.27–0.53; p<0.0001) were significantly better for rivoceranib vs placebo
- Treatment was generally well tolerated
- These findings suggest that rivoceranib has a benefit with a favorable safety profile in gastric cancer

Acknowledgements

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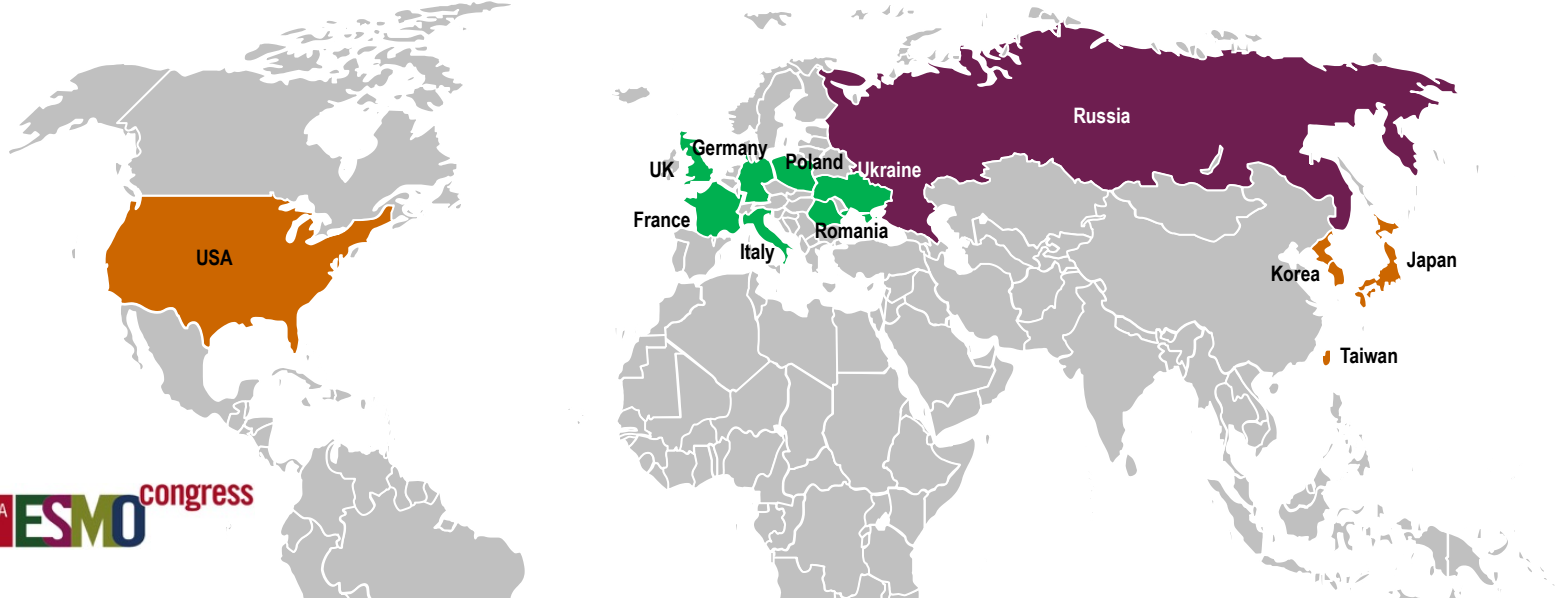

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