



A prospective, randomized, double-blind, phase III study of rivoceranib (apatinib) + best supportive care (BSC) vs placebo + BSC in patients with advanced/metastatic gastric cancer who failed ≥ 2 prior chemotherapy regimens: the ANGEL study

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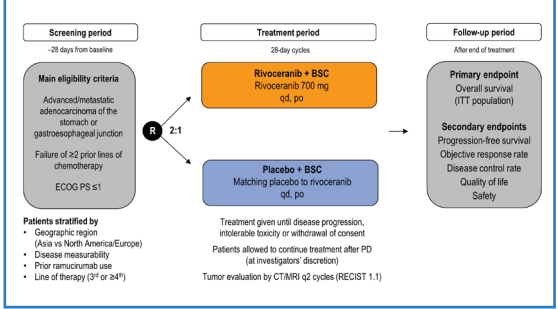
Background

- 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 $\geq 3^{\text{rd}}$ -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.

Methods

- Main eligibility criteria were as follows: patients with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction for whom at least 2 prior lines of standard chemotherapy had failed, ECOG performance status ≤ 1 , and disease progression <6 months after last chemotherapy treatment.
- A total of 460 patients were randomized in a 2:1 ratio to receive continuous 28-day cycles of rivoceranib 700 mg or a matched placebo daily with BSC until disease progression, intolerable toxicity or withdrawal of consent.
- Stratification factors included geographic region (Asia vs. North America/Europe), disease measurability, prior ramucirumab treatment, and treatment therapy line (3^{rd} or $\geq 4^{\text{th}}$).
- The primary endpoint was overall survival (OS) in the intent-to-treat population.
- Secondary endpoints were progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), quality of life, and safety.
- OS was analyzed in the ITT population after approximately 325 events occurred using a stratified log-rank test at the two-sided alpha=0.05 level of significance.

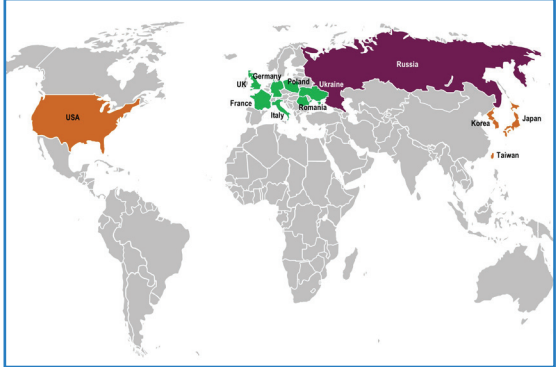
Figure 1. ANGEL: a global, randomized, phase 3 study



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.

Figure 2. Study enrollment



- Study period:** patient enrollment between Feb 2017 and Oct 2018.
- Sample size:** 460 patients from 88 sites across 12 countries.

Figure 3. Patient disposition

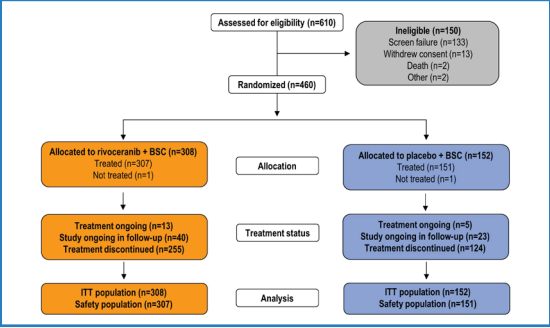


Table 1. Baseline characteristics (ITT population)

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	207 (67.2)	103 (67.8)	310 (67.4)
North America/Europe	101 (32.8)	49 (32.2)	150 (32.6)
Disease measurability, n (%)			
Measurable	262 (85.1)	130 (85.5)	392 (85.2)
Non-measurable	46 (14.9)	22 (14.5)	68 (14.8)
Line of therapy, n (%)			
3 rd line/ $\geq 4^{\text{th}}$ 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)

Figure 4. Overall survival

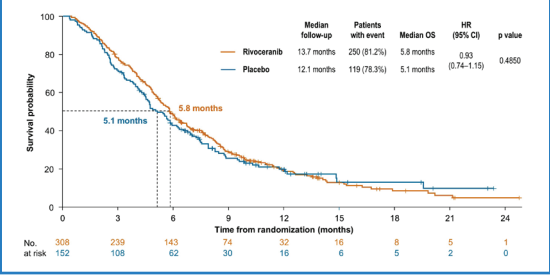


Figure 5. Overall survival – subgroup analysis

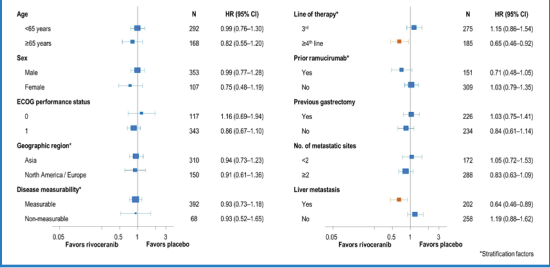


Figure 6. Progression-free survival (central review)

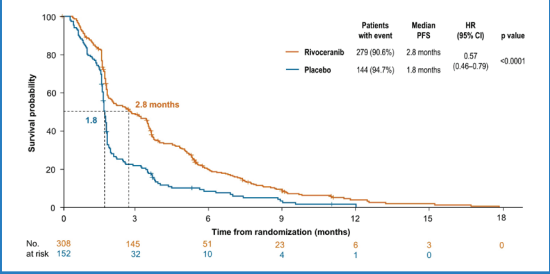


Figure 7. Progression-free survival – subgroup analysis

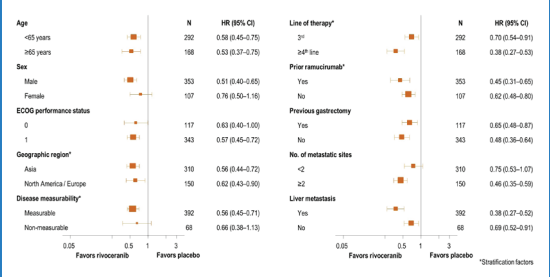


Figure 8. Overall survival and PFS in $\geq 4^{\text{th}}$ -line patients

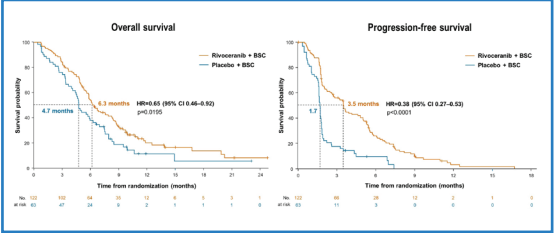


Table 2. Objective response/disease control (measurable disease)

Response, n (%)	Rivoceranib + BSC (n=262)	Placebo + BSC (n=130)
Objective response rate (95% CI)	18 (6.9) (3.8–9.9)	0 (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 (95% CI)	111 (42.4) (36.4–48.4)	17 (13.1) (7.3–18.9)
p-value	<0.0001	

Figure 9. Waterfall plot (central review of measurable patients)

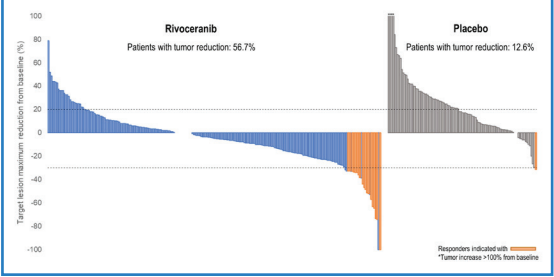


Table 3. TEAEs occurring in $\geq 20\%$ of rivoceranib patients

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 $\geq 4^{\text{th}}$ -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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