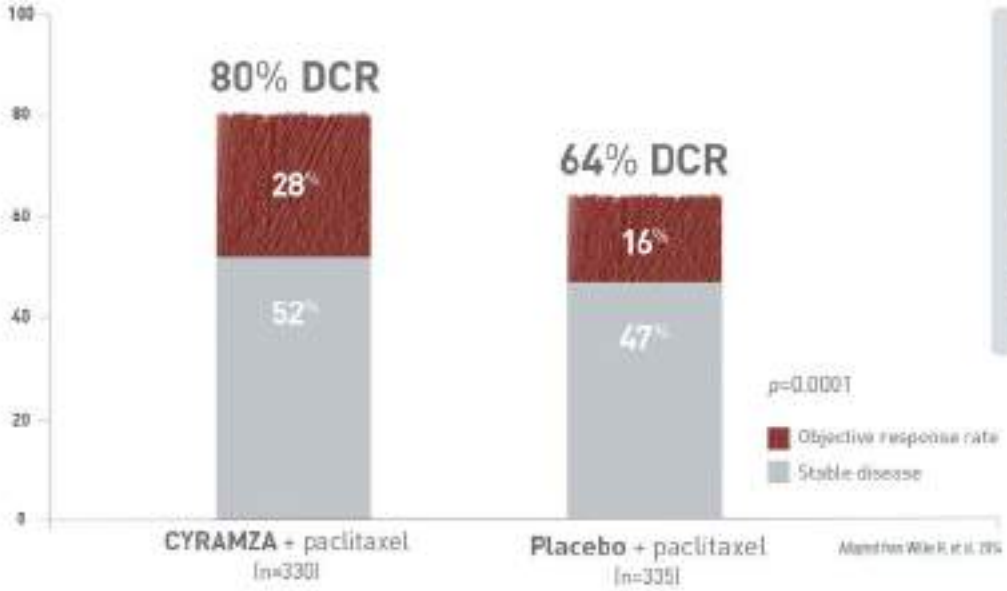
My time has never been more valuable

RAINBOW Study: Control of the Disease[1]



8 out of 10 patients on CYRAMZA + paclitaxel achieved disease control.

STUDY DESIGN

Combination | Monotherapy

RAINBOW Study: Control of the Disease[1]

RAINBOW Study Design[1]

Multicentre, randomized, double-blind trial of 665 locally advanced or metastatic gastric or GEJ adenocarcinoma patients (ECOG PS 0/1) previously treated with fluoropyrimidine- and platinum-containing chemotherapy who progressed ≤6 months of the last dose.* Patients were randomized 1:1 to CYRAMZA 8 mg/kg every 2 weeks + paclitaxel 80 mg/m2 (n=330) or placebo + paclitaxel 80 mg/m2 (n=335).† Primary endpoint was OS; secondary endpoints were PFS, ORR and QoL.

* 15% of patients randomized in the study received prior platinum/fluoropyrimidine combination therapy without anthracycline; 75% received platinum/fluoropyrimidine combination therapy with anthracycline; 8.3% of patients received prior HER2/neu-targeted therapy.[1]

† Stratification criteria were geographic region, time to progression on 1st-line therapy (≤6 months vs. >6 months), and disease measurability (measurable vs. non-measurable disease).[1]

‡ 1 cycle=28 days.

GEJ=gastroesophageal junction; ECOG=Eastern Cooperative Oncology Group; PS=performance status; OS=overall survival; PFS=progression-free survival; ORR=objective response rate; QoL=quality of life.

CYRAMZA + paclitaxel (n=330)

Placebo + paclitaxel (n=335)

Combination | Monotherapy

My time has never been more valuable

RAINBOW Study: Control of the Disease[1]

80% DCR

8 out 10

Reference:

1. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.

CYRAMZA + paclitaxel

Placebo + paclitaxel

Combination | Monotherapy

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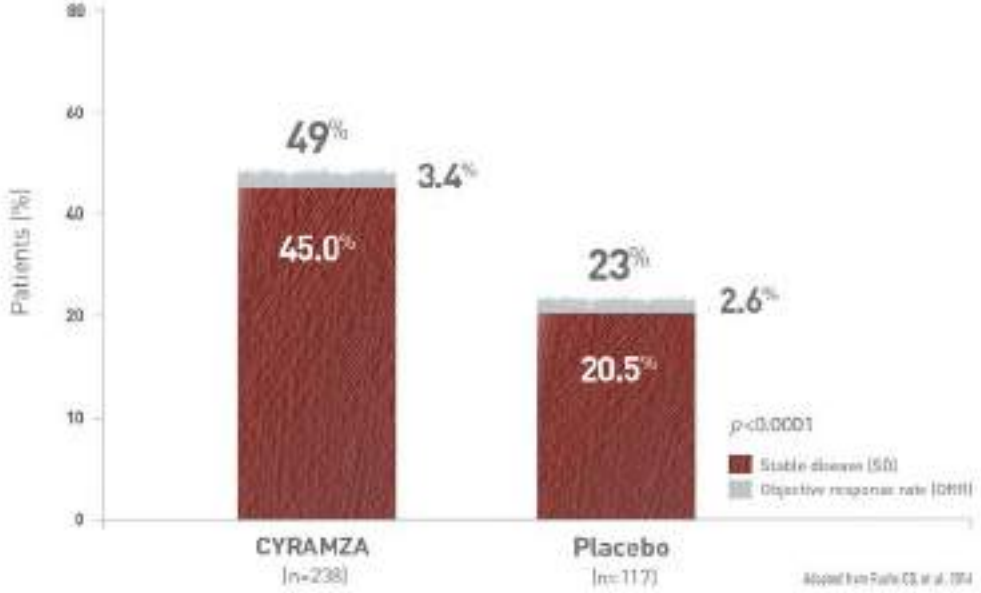
REGARD Study: Control of the Disease[1]



More than double

the Disease Control Rate in patients receiving CYRAMZA

STUDY DESIGN

REGARD Study: Control of the Disease[1]

REGARD Study Design[1]

Multinational, randomized, double-blind, placebo-controlled study in 355 patients (ECOG PS 0-1) with locally recurrent and unresectable or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- or fluoropyrimidine-containing chemotherapy. Disease progression must have occurred ≤4 months from the last dose 1st-line chemotherapy or ≤6 months from the last dose of adjuvant therapy. Patients were randomized 2:1* to CYRAMZA 8 mg/kg every 2 weeks (n=238) + BSC or placebo every 2 weeks + BSC (n=117).[1] The primary endpoint was overall survival.[1]

* Stratification criteria: geographic region, location of the primary tumour and weight loss (≥10% vs. <10%).
† 1 cycle=14 days.
BSC=best supportive care; GEJ=gastroesophageal junction; ECOG=Eastern Cooperative Oncology Group; PS=performance status.

CYRAMZA

Placebo

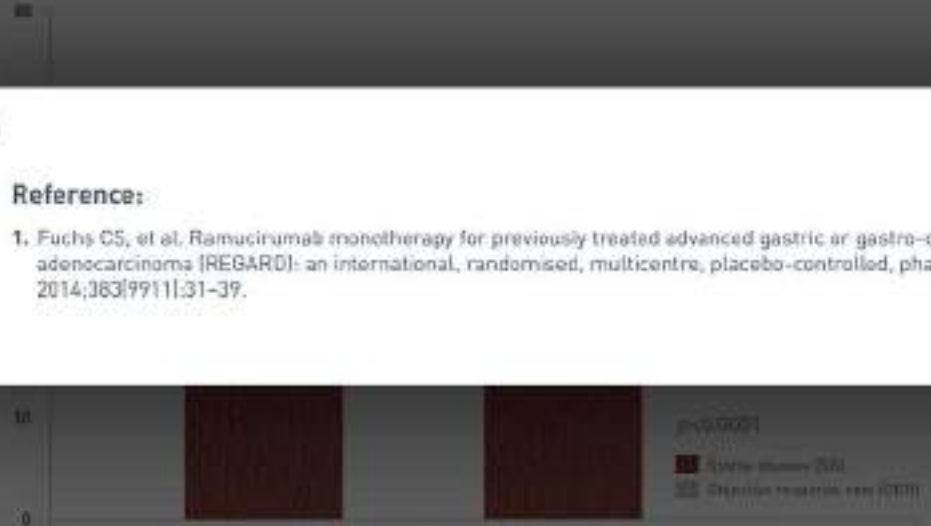
My time has never been more valuable

REGARD Study: Control of the Disease[1]

More than

Reference:

1. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383(9911):31–39.



My time has never been more valuable

RAINBOW Study: Progression-free Survival[1]

6-month PFS rate

36%

$p<0.0001$

CYRAMZA + paclitaxel

Placebo + paclitaxel

Adapted from Wilke H, et al. 2014

Number at risk

CYRAMZA + paclitaxel	330	259	188	104	70	43	28	15	11	7	3	1	–
Placebo + paclitaxel	335	214	124	50	34	21	12	8	5	3	3	3	–

*CYRAMZA + paclitaxel vs. placebo + paclitaxel; HR=0.64 (0.54, 0.76); p<0.0001
HR=hazard ratio; PFS=progression-free survival

STUDY DESIGN

Combination | Monotherapy

RAINBOW Study: Progression-free Survival[1]

4.4 MONTHS

4-month PFS rate

Time from randomization (months)

Reference:

1. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.

My time has never been more valuable

REGARD Study: Progression-free Survival[1]

PFS rate: 12 weeks

40.1%

STUDY DESIGN

Combination | Monotherapy

My time has never been more valuable

REGARD Study: Progression-free Survival[1]

Reference:

1. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383(9911):31–39.

My time has never been more valuable

RAINBOW Study: Significant Improvement in Overall Survival[1]

40%

of patients on CYRAMZA + paclitaxel **survived 1 year or longer** after start of 2nd-line treatment

Number at risk

CYRAMZA + paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	4	1	0
Placebo + paclitaxel	335	294	241	180	143	109	81	44	47	30	22	13	5	2	0

HR=hazard ratio; OS=overall survival.

Combination | Monotherapy

STUDY DESIGN

My time has never been more valuable

RAINBOW Study: Significant Improvement in Overall Survival[1]

9.6 MONTHS

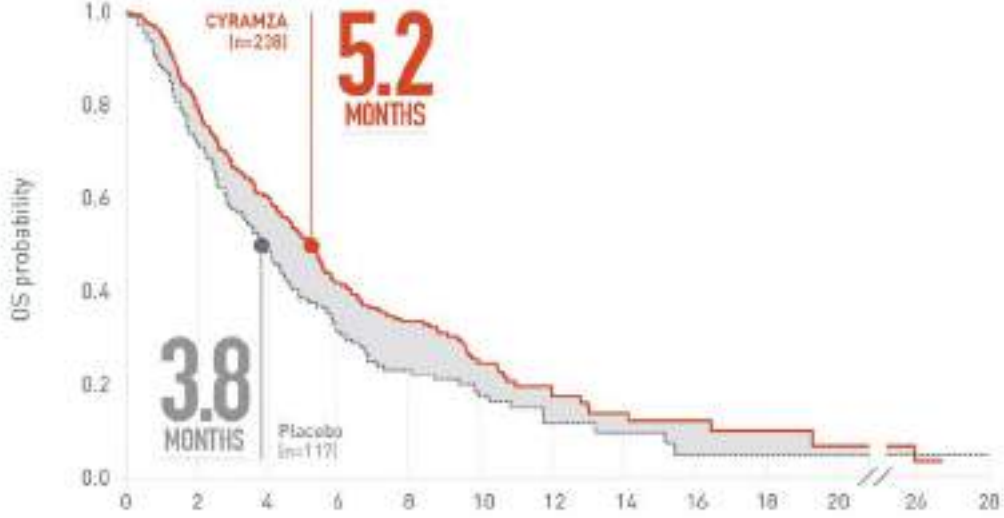
40%

Reference:

1. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.

My time has never been more valuable

REGARD Study: Overall Survival[1]



Number at risk

CYRAMZA	238	154	92	49	17	7	3	0	0
Placebo	117	66	34	20	7	4	2	1	0

37%
relative increase in **median OS***

HR (95% CI)=0.776 (0.603, 0.998); p=0.047

CYRAMZA
Placebo

Combination | Monotherapy

STUDY DESIGN

My time has never been more valuable

REGARD Study: Overall Survival[1]

5.2
MONTHS

37%

Reference:

1. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383(9911):31–39.

RAINBOW Study: Consistent Efficacy Across Age Groups

<65 Years

9.3 months **CYRAMZA** + paclitaxel (n=204) VS. **7.1 months** **Placebo** + paclitaxel (n=212)

≥65 Years

10.7 months **CYRAMZA** + paclitaxel (n=126) VS. **8.7 months** **Placebo** + paclitaxel (n=123)

STUDY DESIGN

RAINBOW Study: Consistent Efficacy Across Age Groups

<65 years

9.3 CYRAMZA + paclitaxel (n=284) VS. 7.1 Placebo + paclitaxel (n=212)

months months

Reference:

1. Muro K, et al. Age does not influence efficacy of ramucirumab in advanced gastric cancer: subgroup analyses of REGARD and RAINBOW. *J Gastroenterol Hepatol* 2018;33(4):814–824.

My time has never been more valuable

RAINBOW Study: Survival Benefit Maintained in Patients with Ascites

Presence of Ascites is a Poor Prognostic Factor in Gastric Cancer Patients, with Potentially Critical Complications[1]

Exploratory Analyses from RAINBOW Trial[*1]

CYRAMZA Prolonged Overall Survival in Patients with Ascites[1]

HR* (95% CI) 0.86 (0.64, 1.16)

CYRAMZA + paclitaxel

Placebo + paclitaxel

Safety profile was similar in patients with and without ascites:[1]

No increase in TEAEs of special interest (thromboembolic events, GI perforation)

STUDY DESIGN

CI=confidence interval; GI=gastrointestinal; HR=hazard ratio; ET=intent-to-treat; TEAE=treatment-emergent adverse event(s).

Adapted from Mera R, et al. 2019

*Stratified analysis.

My time has never been more valuable

RAINBOW Study: Survival Benefit Maintained in Patients with Ascites

Presence of Ascites is a Poor Prognostic Factor in Gastric Cancer Patients, with Potentially Critical Complications[1]

Exploratory Analyses from RAINBOW Trial[1]

CYRAMZA Prolonged Overall Survival in Patients with Ascites[1]

Safety profile was

Reference:

1. Muro K, et al. Is ramucirumab and paclitaxel therapy beneficial for second-line treatment of metastatic gastric or junctional adenocarcinoma for patients with ascites? Analysis of RAINBOW phase 3 trial data. *Cancer Manag Res* 2019;11:2261–2267.

5.2 MONTHS

Time from randomization (months)

STUDY DESIGN

My time has never been more valuable

Survival Benefit Seen with CYRAMZA Regardless of Prior Trastuzumab Use

OS, PFS and ORR Subgroup Analysis by Prior Trastuzumab Therapy, Unstratified Analysis – RAINBOW[1*]

Endpoint	Prior use of trastuzumab	CYRAMZA + paclitaxel (n=330)		Placebo + paclitaxel (n=335)		
		n	Median	n	Median	HR
OS	Yes	20	11.4	19	7.0	0.679
	No	310	9.6	316	7.4	0.835
PFS	Yes	20	4.2	19	2.7	0.399
	No	310	4.4	316	2.9	0.657
		n	Incidence of events	n	Incidence of events	
ORR[†]	Yes	20	45%	19	10.5%	–
	No	310	26.8%	316	16.5%	–
DCR[‡]	Yes	20	80%	19	57.9%	–
	No	310	80%	316	63.9%	–

Consistent efficacy was observed regardless of HER status

– HER2+ patients receiving CYRAMZA 2nd-Line appear to respond well – and for longer[2]

Prior use of trastuzumab
No prior use of trastuzumab

* HER2 IHC or FISH testing was not mandatory in the RAINBOW protocol, so there is no information on the actual HER2 status in this patient population.
† Complete response + partial response
‡ Complete response + partial response + stable disease
CI=confidence interval; CEA=disease control rate; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

STUDY DESIGN

Survival Benefit Seen with CYRAMZA Regardless of Prior Trastuzumab Use

OS, PFS and ORR Subgroup Analysis by Prior Trastuzumab Therapy, Unstratified Analysis – RAINBOW[1]

Endpoint	Prior use of trastuzumab	CYRAMZA + paclitaxel (n=330)		Placebo + paclitaxel (n=326)		
	No	310	24.8%	316	16.5%	–
ORR[c]	Yes	20	80%	19	57.9%	–
	No	310	80%	316	63.9%	–

Consistent efficacy was observed regardless

Prior use of trastuzumab
No prior use of trastuzumab

References:

1. European Medicines Agency. CHMP assessment report; CYRAMZA. September 25, 2014.
2. Tehfe M, et al. Ramucirumab in HER-2-positive gastroesophageal adenocarcinoma: an argument for overcoming trastuzumab resistance. *Future Oncol* 2018;14(3):223–228.

My time has never been more valuable

Efficacy in patients receiving CYRAMZA + paclitaxel vs. placebo + paclitaxel in the RAINBOW study[1]

Efficacy parameter	CYRAMZA + paclitaxel	Placebo + paclitaxel	HR *p*-value	Delta
Response rate	28%	16%	*p*=0.0001	+12%
Disease control rate	80%	64%	*p*<0.0001	+16%
PFS (median, months)	4.40	2.66	HR=0.635 *p*<0.0001	+1.5 months
PFS rate at 6 months PFS rate at 9 months	36% 22%	17% 10%	N/A N/A	+19% +10%
OS (median, months)	9.63	7.36	HR=0.807 *p*=0.0169	+2.3 months
OS rate at 6 months OS rate at 12 months	72% 40%	57% 30%	N/A N/A	+15% +10%

STUDY DESIGN

Combination | Monotherapy

My time has never been more valuable

Efficacy in patients receiving CYRAMZA + paclitaxel vs. placebo + paclitaxel in the RAINBOW study[1]

Efficacy parameter	CYRAMZA + paclitaxel	Placebo + paclitaxel	HR p-value	Delta
OS (median, months)	9.63	7.36	HR=0.807 p=0.0169	+2.3 months
OS rate at 6 months	72%	57%	N/A	+15%
OS rate at 12 months	40%	30%	N/A	+10%

Combination | Monotherapy

Reference:

1. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.

My time has never been more valuable

Efficacy in patients receiving CYRAMZA vs. placebo in the REGARD study [1]

Efficacy parameter	CYRAMZA + BSC	Placebo + BSC	HR *p*-value	Delta
Objective response rate	3%	3%	*p*=0.76	0%
Disease control rate	49%	23%	*p*<0.0001	+26%
PFS (median, months)	2.1	1.3	HR=0.483 *p*<0.0001	+0.8 months
OS (median, months)	5.2	3.8	HR=0.776 *p*=0.047	+1.4 months

STUDY DESIGN

BSC=best supportive care; IR=hazard ratio; OS=overall survival; PFS=progression-free survival

Combination Monotherapy

My time has never been more valuable

Efficacy in patients receiving CYRAMZA vs. placebo in the REGARD study [1]

Efficacy parameter	CYRAMZA + BSC	Placebo + BSC	HR p-value	Delta

Reference:

1. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383(9911):31–39.

My time has never been more valuable

CYRAMZA Efficacy in a Multi-Institutional Real-World Setting Is Similar to RAINBOW

25 Italian Oncology Centres: Observational, Retrospective Study in Metastatic Gastric Cancer Patients Who Received CYRAMZA for Compassionate Use (RAMoss)[1]

Outcome	RAINBOW[2] (CYRAMZA paclitaxel)	RAINBOW[2] (Western subgroup)	RAMoss[1] (CYRAMZA paclitaxel)
Median OS (months)	9.6	8.6	8.3
Median PFS (months)	4.4	4.2	4.5
ORR (%)	28	26.8	20.2
DCR (%)	80	76.8	59.4

Survival benefit in real-world setting is consistent with the RAINBOW study in a clinical setting.[1,3]

My time has never been more valuable

CYRAMZA Efficacy in a Multi-Institutional Real-World Setting Is Similar to RAINBOW

25 Italian Oncology Centres: Observational, Retrospective Study in Metastatic

References:

1. Di Bartolomeo M, et al. Ramucirumab as second-line therapy in metastatic gastric cancer: real-world data from the RAMoss study. *Targeted Oncol* 2018;ePub. https://doi.org/10.1007/s11523-018-0562-5.
2. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.
3. Shitara K, et al. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. *Gastric Cancer* 2016;19:927–938.