An open-label trial to assess the safety of regorafenib in Turkish patients with metastatic colorectal cancer (mCRC) that progressed on standard therapy (REGARD)

Faysal Dane[1], Kirhan Ozgurdal[2], Şuayib Yalçın[3], Mustafa Benekli[4], N. Faruk Aykan[5], Idris Yucel[6], Metin Özkan[7], Turkkan Evrensel[8], Alper Sevinç[9], Hasan Şenol Coskun[10], Ulus Ali Sanli[11], Ismail Oguz Kara[12]

[1]Marmara University Medical Faculty, Istanbul, Turkey; [2]Bayer HealthCare, Istanbul, Turkey; [3]Hacettepe University Medical Faculty, Ankara, Turkey; [4]Gazi University Medical Faculty, Ankara, Turkey; [5]Istanbul University, Institute of Oncology, Istanbul, Turkey; [6]Ondokuz Mayis University Medical Faculty, Samsun, Turkey; [7]Erciyes University Medical Faculty, Kayseri, Turkey; [8]Uludag University Medical Faculty, Bursa, Turkey; [9]Gaziantep University Medical Faculty, Gaziantep, Turkey; [10]Akdeniz University Medical Faculty, Antalya, Turkey; [11]Ege University Medical Faculty, İzmir, Turkey; [12]Cukurova University Medical Faculty, Adana, Turkey

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BACKGROUND

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in the regulation of oncogenesis, tumor angiogenesis, and the tumor microenvironment[1]
- In the randomized, double-blind, international CORRECT phase III trial, regorafenib significantly improved overall survival (OS) and progression-free survival (PFS) versus placebo in patients with mCRC refractory to available standard therapies[2]
  - OS, hazard ratio (HR) 0.77 (95% CI 0.64–0.94); one-sided P=0.0052[2]
  - Most frequently reported grade 3 or higher AEs included hand–foot skin reaction (HFSR), fatigue, diarrhea, and hypertension[2]
- The phase III CONCUR trial confirmed the OS benefit for regorafenib in Asian patients[3]
  - OS, HR 0.55 (95% CI 0.40–0.77); one-sided P=0.00016[3]
  - The adverse events reported in CONCUR are consistent with the known safety profile of regorafenib in other clinical trials[2,3]
- Here we present interim results from REGARD, an open-label trial of regorafenib in Turkish patients with pretreated mCRC

OBJECTIVE

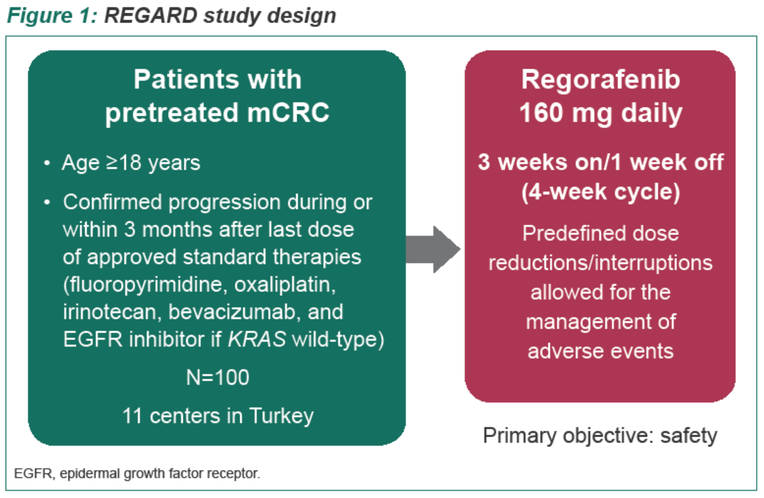
- To characterize the safety profile and estimate PFS of regorafenib in Turkish patients with mCRC whose disease has progressed on standard therapies

METHODS

REGARD study design

- REGARD (NCT01853319) is an ongoing open-label trial (Figure 1)
- Patients were treated until disease progression, unacceptable toxicity, patient/investigator decision to stop, or death

Figure 1: REGARD study design



EGFR, epidermal growth factor receptor.

RESULTS

Patient flow and baseline characteristics

- Patients were enrolled between July 2013 and July 2014
  - The data cut-off for the present analysis was 24 September 2014
- A total of 100 patients have received regorafenib treatment; 3 patients were receiving treatment as of June 5, 2015 (Figure 2)
- Baseline patient and tumor characteristics are shown in Table 1

Treatment duration

- The median treatment duration was 11.0 weeks and the mean (standard deviation) duration was 15.7 (± 14.2) weeks (Table 2)
- Patients received a median of 3 cycles (range 1–15) of regorafenib

Safety

- Almost all patients (96%) had at least one treatment-emergent AE, of which 79% were considered related to regorafenib by the study investigator (Table 3)
- Serious AEs occurred in 35% of patients; 15% were drug-related

*Figure 2: Patient disposition**

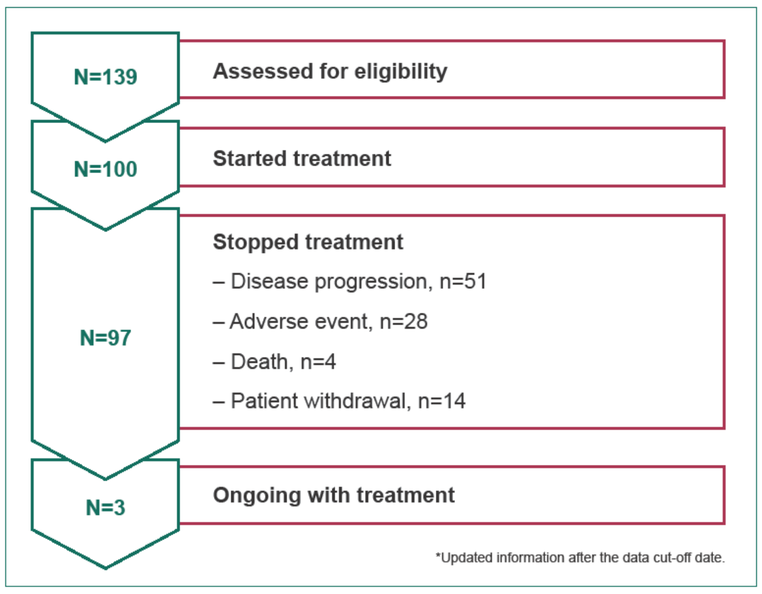


Table 1: Baseline characteristics

		Patients (N=100)
Sex, n	Male	58
	Female	42
Age	Median years (range)	56.5 (31–78)
	≥65 years, n	22
ECOG score, n	0	54
	1	46
Time from initial diagnosis	Median weeks (range)	146.1 (32.1–600.4)
	<18 months, n	11
	≥18 months, n	89
Time from diagnosis of metastatic disease	Median weeks (range)	127.6 (29.9–600.4)
	<18 months, n	17
	≥18 months, n	83
Primary site of disease, n	Colon	55
	Rectum	24
	Colon and rectum	21
KRAS status, n	Wild-type	43
	Mutant	53
	Unknown	4
BRAF status, n	Wild-type	6
	Mutant	0
	Unknown	94
Brain metastases, n	No	77
	Yes	2
	Unknown	21
Liver metastases, n	No	22
	Yes	78

ECOG, Eastern Cooperative Oncology Group.

Table 2: Treatment exposure

		Patients (N=100)
Overall duration of treatment*	Mean ± SD weeks	15.7 ± 14.2
	Median weeks (range)	11.0 (0.6–59.3)
	>18 weeks, n	29
Number of cycles	Mean ± SD	4.1 ± 3.5
	Median (range)	3 (1–15)
	≥5, n	29
Patients with treatment modifications, n	Any	71
	Dose reduction†	33
	Dose re-escalation‡	7
	Treatment interruption/delay	63

*Includes treatment interruptions/delay and drug holidays.
†Lowest recommended dose 80 mg/day.
‡Permitted at the discretion of the treating physician, up to a maximum 160 mg/day.
SD, standard deviation

- AEs led to treatment modifications in 69% of patients and drug discontinuation in 27% of patients. Drug-related AEs led to treatment modifications in 55% of patients and drug discontinuation in 17% of patients
- The most common AEs are listed in Table 4

Table 3: Overview of adverse events

Adverse events, n		Patients (N=100)	
		Treatment-emergent*	Drug-related
Any		96	79
Worst grade†	1	6	9
	2	15	18
	3	55	42
	4	10	6
	5 (death)	10	4
Serious		35	15
Leading to treatment modification§		69	55
Leading to permanent discontinuation		27	17

*Treatment-emergent adverse events include any event arising or worsening after the start of study drug administration until 30 days after the last study medication, regardless of relationship to study drug.
†Overall, treatment-emergent adverse events may have occurred at a worse grade than drug-related adverse events, resulting in more low-grade drug-related than treatment-emergent adverse events.
§Dose reduction or treatment interruption.

*Table 4: Treatment-emergent adverse events occurring at any grade in ≥10 patients**

	Patients (N=100)		
	Any grade‡	Grade 3‡	Grade ≥4‡
Blood bilirubin increased	25	13	1
Decreased appetite	21	7	1
Fatigue	20	8	1
Hypertension	20	7	0
Hypophosphatemia	19	15	0
Palmar-plantar erythrodysesthesia syndrome	19	4	0
Weight decreased	19	0	0
Aspartate aminotransferase increased	17	8	0
Diarrhea	17	3	0
Anemia	14	3	0
Dysphonia	13	0	0
Blood alkaline phosphatase increased	12	6	0
Alanine aminotransferase increased	12	5	0
Hypothyroidism	12	1	0
Lipase increase	10	4	3
Skin reaction	10	4	0
Asthenia	10	2	0

*Treatment-emergent adverse events include any event arising or worsening after the start of study drug administration until 30 days after the last study medication, regardless of relationship to study drug.
†Terms based on Medical Dictionary for Regulatory Activities (MedDRA) v17.0 and Preferred Term.
‡Graded according to National Cancer Institute Common Terminology Criteria for AEs v4.

CONCLUSIONS

- REGARD is the first study assessing regorafenib in a large number of Turkish patients with mCRC who progressed on standard therapy
- The safety profile of regorafenib in this population is consistent with that seen in other phase III trials in this indication[2,3]
- The majority of AEs could be managed with dose modifications

References

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