Analysis of Angiogenesis Biomarkers for Ramucirumab (RAM) Efficacy in Patients with Metastatic Colorectal Cancer (mCRC) from RAISE, a Global, Randomized, Double-blind, Phase 3 Study

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BACKGROUND

- Colorectal carcinoma (CRC) is the third leading cause of cancer and cancer deaths worldwide[1,2]
- Metastatic colorectal carcinoma (mCRC) develops in approximately half of patients diagnosed with this disease[3]
- The poor prognosis of mCRC drives ongoing efforts to find treatments that improve patients' outcomes[4]
- Antiangiogenic treatments are proven to improve mCRC patients' outcomes; however, there are currently no predictive biomarkers to guide patient selection for therapies targeting angiogenesis
- Ramucirumab (RAM) is a human IgG1 monoclonal antibody that specifically binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor (VEGFR)-2 with high affinity, preventing binding of agonist ligands VEGF-A, VEGF-C, and VEGF-D, as well as VEGFR-2 activation[5]
- The RAISE trial (NCT01183780) demonstrated a statistically significant survival benefit for patients treated with RAM+FOLFIRI vs. placebo+FOLFIRI with median overall survival (OS) of 13.3 months for the RAM group vs. 11.7 months for the placebo group (hazard ratio [HR] 0.844; 95% confidence interval [CI] 0.730-0.976; log-rank p=.0219)[6]
- An extensive RAISE biomarker program assessed the association of multiple candidate biomarkers with RAM efficacy outcomes

METHODS

- The RAISE trial[6] enrolled mCRC patients with:
  - Known *KRAS* exon 2 mutation status (mutant or wild type)
  - Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
  - Disease progression during or within 6 months of last dose of first-line combination therapy with bevacizumab, oxaliplatin, and fluoropyrimidine for metastatic disease
- Patients were randomized 1:1 to receive either 8 mg/kg RAM or placebo as a 60-minute intravenous infusion, followed by the FOLFIRI regimen[6]
- Plasma and tumor tissue collection were mandatory
- Analyses were performed to assess correlations of baseline individual marker levels with clinical outcomes
- Plasma samples were collected from whole blood prior to cycle 1; VEGF-C, VEGF-D, soluble VEGFR-1 (sVEGFR-1), sVEGFR-2, and sVEGFR-3 were assessed by exploratory, individual, proprietary Eli Lilly and Company–developed dual-monoclonal sandwich immunoassays (Version 1 for each)
  - VEGF-A was not assessed because blood samples were collected in heparin tubes, and it has been determined that heparin interferes with bioanalytical assay for VEGF-A, such that reliable results cannot be obtained
- Archived tumor samples were submitted to a central laboratory for VEGFR-2 immunohistochemistry assay[7]
- An adaptive analysis design[8] was used in which the population was randomly and prospectively split (after initial randomization) into a marker exploratory (ME) set and a marker confirmatory (MC) set in 1:2 ratio
- This allowed broad exploration of markers in the ME set and prespecification for any noteworthy findings to be confirmed independently in the MC set
- Stratification was applied to balance the ME and MC sets according to treatment assignment and the 3 study stratification factors: geographic region, *KRAS* exon 2 mutation status, and time to disease progression on first-line treatment
- Kaplan-Meier estimates and 95% CIs were used to analyze OS and progression-free survival (PFS); Cox regression analyses were performed for each marker with stratification factors adjusted
- A subpopulation treatment effect pattern plot (STEPP) was used to evaluate the relationship of each marker's levels with efficacy outcomes[9]; in generating STEPP, treatment effect was assessed in subsets of patients who had similar biomarker levels, with subsets together spanning the full range of that marker's values (sliding window approach)

RESULTS

Table 1. Summary of Biomarker Levels

Marker	Total
sVEGFR-1	
N	889
Median (pg/mL)	258
Interquartile range (pg/mL)	203-523
sVEGFR-2	
N	880
Median (pg/mL)	21,162
Interquartile range (pg/mL)	17,791-24,483
sVEGFR-3	
N	889
Median (pg/mL)	95,057
Interquartile range (pg/mL)	76,208-120,223
VEGF-C	
N	885
Median (pg/mL)	81,150
Interquartile range (pg/mL)	68,380-102,010
VEGF-D	
N	884
Median (pg/mL)	135
Interquartile range (pg/mL)	91-208
VEGFR-2 (IHC H-Score) neoplastic vessels	
N	869
Median (pg/mL)	50
Interquartile range (pg/mL)	15-92

Table 2. Baseline Patient Characteristics by VEGF-D Levels (ME+MC Population)

	VEGF-D High ≥115 pg/mL		VEGF-D Low <115 pg/mL	
	RAM+ FOLFIRI (n=270) n (%)	Placebo+ FOLFIRI (n=266) n (%)	RAM+ FOLFIRI (n=176) n (%)	Placebo+ FOLFIRI (n=172) n (%)
Age group				
≥65 years	111 (41)	109 (41)	64 (36)	70 (41)
≥70 years	59 (22)	53 (20)	31 (18)	42 (24)
Gender				
Male	137 (51)	162 (61)	100 (57)	110 (64)
Female	133 (49)	104 (39)	76 (43)	62 (36)
Geographic region				
Japan/ East Asia	67 (25)	61 (23)	33 (19)	28 (16)
Rest of world	203 (75)	205 (77)	143 (81)	144 (84)
Race				
Black	8 (3)	9 (3)	6 (3)	5 (3)
Other	72 (27)	70 (26)	38 (22)	30 (17)
White	189 (70)	185 (70)	132 (75)	134 (78)
Missing	1 (0.4)	2 (1)	---	3 (2)
ECOG PS				
0	143 (53)	126 (47)	88 (50)	93 (54)
1	127 (47)	140 (53)	87 (49)	79 (46)
Missing	---	---	1 (1)	---
Time to progress after first line				
<6 months	63 (23)	71 (27)	43 (24)	36 (21)
≥6 months	207 (77)	195 (73)	133 (76)	136 (79)
KRAS status				
Mutant	137 (51)	119 (45)	89 (51)	86 (50)
Wild type	133 (49)	147 (55)	87 (49)	86 (50)

- At the initial plasma ME subset analyses (RAM, n=153; placebo, n=146), VEGF-D showed a strong signal associating higher levels with greater OS and PFS improvement in the RAM arm
- To test the relationship of VEGF-D levels with efficacy outcomes seen in the dataset from the ME patients, a VEGF-D level of 115 pg/mL was prespecified (based on multiple analyses from the ME set) as the cutoff value for high and low subgroup analysis of the independent MC population and the full translational research (TR) population (ME+MC populations)
- Results from the MC population independently confirmed the ability of the prespecified cutoff from the ME dataset to predict RAM efficacy (interaction p-values .0107 and .0013 for OS and PFS, respectively)
- The ME+MC analyses (Table 3 and Figures 1-4) show the VEGF-D relationship in the overall TR population

Table 3. OS and PFS Results from ME+MC Population by VEGF-D Levels

	High VEGF-D (≥115 pg/mL)		Low VEGF-D (<115 pg/mL)	
	RAM+ FOLFIRI (n=270)	Placebo+ FOLFIRI (n=266)	RAM+ FOLFIRI (n=176)	Placebo+ FOLFIRI (n=172)
Median OS, months (95% CI)	13.9 (12.5-15.6)	11.5 (10.1-12.4)	12.6 (10.7-14.0)	13.1 (11.8-17.0)
HR (95% CI)	0.73 (0.60-0.89)		1.32 (1.02-1.70)	
p-value (likelihood ratio)	.0022		.0344	
Interaction p-value	.0005			
Median PFS, months (95% CI)	6.0 (5.6-7.0)	4.2 (4.1-4.5)	5.4 (4.2-5.8)	5.6 (5.3-6.9)
HR (95% CI)	0.62 (0.52-0.74)		1.16 (0.93-1.45)	
p-value (likelihood ratio)	<.0001		.1930	
Interaction p-value	<.0001			

Figure 1. OS by Treatment Arm with Stratification Factors as Covariates, High VEGF-D Expression Levels (≥115 pg/mL), TR Population

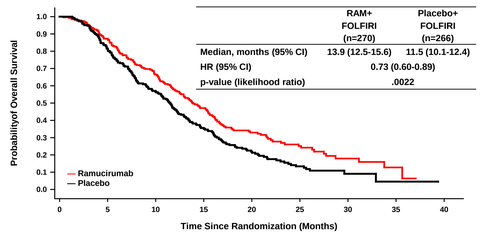


Figure 2. OS by Treatment Arm with Stratification Factors as Covariates, Low VEGF-D Expression Levels (<115 pg/mL), TR Population

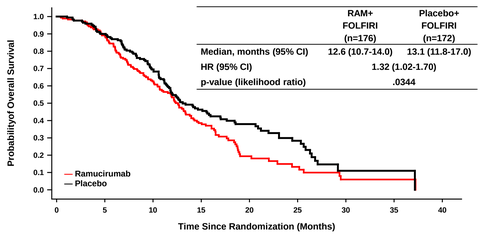


Figure 3. PFS by Treatment Arm with Stratification Factors as Covariates, High VEGF-D Expression Levels (≥115 pg/mL), TR Population

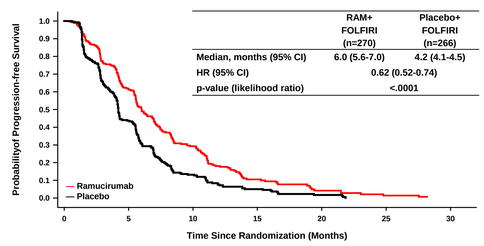
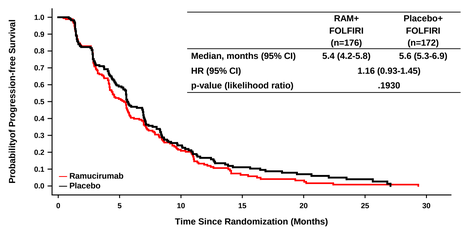


Figure 4. PFS by Treatment Arm with Stratification Factors as Covariates, Low VEGF-D Expression Levels (<115 pg/mL), TR Population



- STEPP figures were created to examine the VEGF-D predictive relationship more granularly
- The STEPP figures show point estimates for the treatment HR across a range of VEGF-D levels
- For both OS and PFS, a consistent relationship was observed between HR and VEGF-D values (Figures 5 and 6, respectively)
- The STEPP figures also demonstrate that the 115 pg/mL cutoff identified, based on results from the ME dataset, is well suited to data from the full TR population

Figure 5. VEGF-D OS STEPP, TR Population

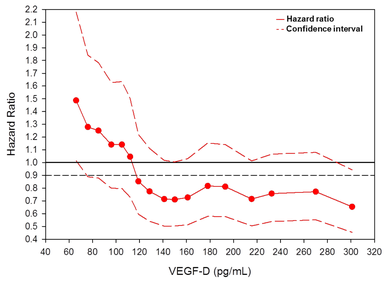


Figure 6. VEGF-D PFS STEPP, TR Population

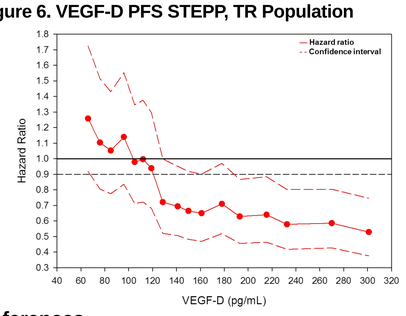


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Table 4. TEAEs by VEGF-D Cutoff Point (115 pg/mL): Grade ≥3 3% or Higher in Either Treatment Arm

	Grade ≥3			
	RAM+FOLFIRI		Placebo+FOLFIRI	
	VEGF-D Low (n=176) n (%)	VEGF-D High (n=271) n (%)	VEGF-D Low (n=172) n (%)	VEGF-D High (n=265) n (%)
Any TEAE	133 (76)	219 (81)	110 (64)	160 (60)
Diarrhea	18 (10)	33 (12)	21 (12)	22 (8)
Neutropenia	56 (32)	115 (42)	36 (21)	73 (28)
Fatigue	15 (9)	33 (12)	17 (10)	15 (6)
Nausea	5 (3)	6 (2)	3 (2)	9 (3)
Decreased appetite	3 (2)	9 (3)	3 (2)	2 (1)
Stomatitis	10 (6)	8 (3)	5 (3)	6 (2)
Vomiting	5 (3)	8 (3)	3 (2)	9 (3)
Hypertension	22 (13)	28 (10)	8 (5)	4 (2)
Abdominal pain	7 (4)	9 (3)	7 (4)	8 (3)
Thrombocytopenia	4 (2)	9 (3)	0	3 (1)
Anemia	2 (1)	6 (2)	6 (4)	10 (4)
Adverse events of special interest				
Hypertension	23 (13)	29 (11)	8 (5)	4 (2)
VTEs	10 (6)	10 (4)	4 (2)	3 (1)
Proteinuria	6 (3)	8 (3)	0	1 (<1)
Bleeding/hemorrhage event	3 (2)	9 (3)	4 (2)	3 (1)
GI perforation	3 (2)	5 (2)	0	3 (1)
Congestive heart failure	3 (2)	0	0	1 (<1)
GI hemorrhage	2 (1)	7(3)	2 (1)	2 (1)
Infusion-related reaction	2 (1)	2 (1)	2 (1)	0
Renal failure	1 (1)	4 (2)	3 (2)	2 (1)
Arterial thromboembolic events	0	3 (1)	1 (1)	4 (2)

Abbreviations: GI, gastrointestinal; TEAE, treatment-emergent adverse event; VTEs, venous thromboembolic events

CONCLUSIONS

- Among the candidate angiogenic biomarkers analyzed, only VEGF-D showed a strong signal as a predictive biomarker
- In mCRC patients, the relationship observed between higher baseline plasma VEGF-D levels and greater efficacy was consistent for both OS and PFS
- For the 60% of patients with higher VEGF-D, the median OS benefit with RAM was 2.4 months; for the remaining 40% of patients with lower VEGF-D, the difference in median OS was 15 days, favoring placebo
- Higher levels of VEGF-D seem to be a predictive biomarker for RAM efficacy on OS and PFS in mCRC
- Findings were obtained with an assay developed and validated for exploratory research purposes only
- Development and validation of an assay appropriate for clinical decision making are currently underway; if successful, this assay will be used to confirm the relationship observed in the RAISE samples

Disclosures

This is an encore of an poster presented at the European Society for Medical Oncology (ESMO) Congress; Madrid, Spain; September 8-12, 2017.

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