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Association of baseline absolute neutrophil counts and survival in patients with metastatic colorectal cancer treated with second-line antiangiogenic therapies: exploratory analyses of the RAISE trial and validation in an electronic medical record data set

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ABSTRACT

Background In the RAISE trial, ramucirumab+leucovorin/fluorouracil/irinotecan (FOLFIRI) improved the median overall survival (mOS) of patients with previously treated metastatic colorectal cancer versus patients treated with placebo+FOLFIRI but had a higher incidence of neutropaenia, leading to more chemotherapy dose modifications and discontinuations. Thus, we conducted an exploratory post-hoc analysis of RAISE and a retrospective, observational analysis of electronic medical record (EMR) data to determine and verify the association of neutropaenia, baseline absolute neutrophil count (ANC) and survival.

Methods The RAISE analysis used the study safety population (n=1057). IMS Health Oncology Database (IMS EMR) was the source for the real-world data set (n=617).

Results RAISE patients with treatment-emergent neutropaenia had improved mOS compared with those without (ramucirumab arm: 16.1 vs 10.7 months, HR=0.57, p<0.0001; placebo arm: 12.7 vs 10.7 months, HR=0.76, p=0.0065). RAISE patients with low ANC versus high baseline ANC also had longer mOS (ramucirumab arm: 15.2 vs 8.9 months, HR=0.49, p<0.0001; placebo arm: 13.2 vs 7.3 months, HR=0.50, p<0.0001). The results were similar for IMS EMR low versus high baseline ANC (bevacizumab+FOLFIRI patients: 14.9 vs 7.7 months, HR=0.59, p<0.0001; FOLFIRI alone: 14.6 vs 5.4 months, HR=0.37, p<0.0001). Patients in the RAISE trial with low baseline ANC were more likely to develop neutropaenia (OR: ramucirumab arm=2.62, p<0.0001; placebo arm=2.16, p=0.0003).

Conclusion Neutropaenia during treatment, and subsequent dose modifications or discontinuations, do not compromise treatment efficacy. Baseline ANC is a strong

Key questions

What is already known about this subject?

- Historically, the second-line treatment choice in patients with metastatic colorectal cancer (mCRC) has depended on the treatment administered as first-line therapy.
- However, ideally the decisions of which therapy to prescribe as second-line treatment and when to discontinue or change treatment, based on a lack of efficacy and/or high toxicity, would be informed from reliable predictive or prognostic biomarkers.
- Although therapy options for mCRC have increased, valuable predictive and prognostic markers of treatment efficacy remain largely unidentified.
- Neutropaenia has previously been characterised as a prognostic factor for cancer treatment efficacy.

What does this study add?

- An association between neutropaenia incidence and better overall survival was determined in patients with mCRC from the ramucirumab RAISE trial.
- Baseline absolute neutrophil count was confirmed as a prognostic marker for survival in previously treated patients with colorectal cancer in a post-hoc analysis of the RAISE trial and confirmed in a prespecified analysis using electronic medical record data.

Key questions

How might this impact on clinical practice?

- The treatment effect of ramucirumab in patients with neutropaenia with mCRC is unlikely to be compromised despite lower chemotherapy dose intensity.
- Furthermore, a simple neutrophil cell count at baseline is a strong prognostic factor for survival in the analysed populations.

prognostic factor for survival and is associated with treatment-emergent neutropaenia in the analysed population.

Trial registration number NCT01183780, Results.

INTRODUCTION

Although remarkable improvements have been achieved for the treatment of patients with metastatic colorectal cancer (mCRC) in the last decade, the 5-year survival rate is still only 11%.[1] Although chemotherapy remains the foundation of medical management of mCRC,[2] targeted therapies, such as those that inhibit the epidermal growth factor (EGFR) or vascular endothelial growth factor (VEGF) pathways, are a valuable addition to first-line and second-line options.[3] Ramucirumab is a recombinant human IgG1 monoclonal antibody receptor antagonist designed to block the ligand-binding site of VEGF receptor-2. Bevacizumab is a humanised monoclonal antibody that inhibits VEGF signalling by binding directly to circulating VEGF-A. Both of these therapies have been approved for use in specific populations of patients with mCRC.[4 5] Historically, the second-line treatment choice in patients with mCRC has depended on the treatment administered as first-line therapy.[6] However, ideally the decisions of which therapy to prescribe as second-line treatment and when to discontinue or change treatment, based on a lack of efficacy and/or high toxicity, would be informed from reliable predictive or prognostic biomarkers. Although therapy options for mCRC have increased, valuable predictive and prognostic markers of treatment efficacy remain largely unidentified. The National Comprehensive Cancer Network recommends screening for three particular mutations in patients with colorectal cancer (CRC)[7]: *RAS* mutations as predictive biomarkers of the ineffectiveness of anti-EGFR therapy[8 9]; *BRAF* mutations as an established prognostic indicator[10]; and the loss of normal mismatch repair (MMR) proteins and resulting microsatellite instability (MSI), which impart an MMR-deficient/MSI-high phenotype that is associated with improved outcomes and responsiveness to immunotherapy.[11]

Most patients with mCRC will not have curative options, and a balance between treatment efficacy and tolerability is an important component of treatment selection.[6] Systemic chemotherapies used for the treatment of mCRC have well-defined side effect profiles, including gastrointestinal toxicity, neurotoxicity and myelotoxicity.[12] Targeted therapies can contribute additional complications; for example, some of the most frequent adverse events (AEs) attributed to VEGF inhibitors include hypertension and proteinuria.[4 5 13 14] In several retrospective analyses of mCRC trials, the incidence of haematological toxicities, such as neutropaenia, thrombocytopaenia and anaemia, have been characterised as potential prognostic indicators of efficacy.[15 16] Therefore, special attention to treatment toxicity and AEs beyond patients' safety may be advantageous for determining subsequent regimens and establishing prognostic indicators.

In the RAISE study, ramucirumab+leucovorin/fluorouracil/irinotecan (FOLFIRI) improved the overall survival (OS) and progression-free survival of patients with previously treated mCRC compared with patients treated with placebo plus FOLFIRI.[14] However, some AEs were more frequent in the ramucirumab+FOLFIRI group, particularly neutropaenia (any grade): 58.8% in the ramucirumab arm vs 45.6% in the placebo arm.[14] This increase in neutropaenia led to more chemotherapy dose reductions, omissions, delays and discontinuations in the ramucirumab arm (47.8% vs 36.6%), which were associated with lower chemotherapy relative dose intensities (online supplementary table S1) and raised the concern for treatment efficacy in patients with neutropaenia. This led us to conduct a post-hoc, exploratory analysis of the RAISE patients' OS based on whether they had treatment-emergent neutropaenia,[17] followed by an analysis of the relationship between neutropaenia and baseline absolute neutrophil count (ANC). To validate these results, a real-world evidence, retrospective, observational study was subsequently conducted to determine the association between baseline ANC and OS with or without a VEGF inhibitor (ie, bevacizumab) plus FOLFIRI treatment in a second-line CRC population using electronic medical record (EMR) data.[18] The exploratory and confirmatory results from the CRC populations are reported.

PATIENTS AND METHODS

RAISE study design and patients

The study design and patient criteria for the RAISE study have been published previously.[14] Briefly, 1072 patients with mCRC with disease progression during or after first-line treatment with oxaliplatin, a fluoropyrimidine, and bevacizumab were randomised 1:1 to receive 8 mg/kg intravenous second-line ramucirumab in combination with FOLFIRI (ramucirumab arm) or placebo plus FOLFIRI (placebo arm) every 2 weeks (NCT01183780). A post-hoc, exploratory analysis of patients was conducted to determine the effect of neutropaenia on clinical outcomes. Patients from the safety population, who received at least one dose of study drug (n=1057), were grouped by those who developed any-grade neutropaenia after the initiation of study treatment (n=552/1057, 52.2% of the total RAISE patients) and those who did not (n=505/1057, 47.8% of the total RAISE patients). Neutropaenia was defined as ANC<1.5 x 10^9/L. Patients were stratified by low/high baseline ANC (≤5.6 or >5.6 Kcells/μL, the highest quartile).

Real-world evidence, patients and hypothesis testing

The IMS Health Oncology Database (IMS EMR), an integrated database of EMR from more than 600 000 de-identified patients with cancer who received care from approximately 550 providers in all 50 US states (with the southern region over-represented), was used as the data source for the real-world evidence, confirmatory study. Patients were included if they fulfilled the following criteria: ≥18 years old with CRC (International Classification of Diseases-9 code 153.x, 154.0 or 154.1); began second-line fluoropyrimidine and irinotecan (±bevacizumab) in 2007–2013 (index date), following first-line fluoropyrimidine and oxaliplatin (±any biologic); ≥1 ANC measure(s) in the 60 days prior to initiation of second-line therapy; and ≥1 health system interaction in the 3 months preceding their last interaction (important for best results using the OS proxy, which uses time of last interaction as an estimate of death date for patients).

For the IMS EMR analysis, the prespecified top quartile cut-off for baseline ANC was 5.5 x 10^9/L. Patients were stratified by second-line bevacizumab use (yes or no) and low/high baseline ANC (<5.5 or ≥5.5 x 10^9/L). Prespecified hypotheses included HRs for patients receiving bevacizumab by ANC level, HRs for patients not receiving bevacizumab by ANC level and the interaction between the groups. An overall study alpha of 0.05 was maintained using the Bonferroni-Holm procedure.[19]

Statistical analyses

For the RAISE retrospective analysis, patients with and without neutropaenia and patients with high and low baseline ANC were compared by treatment arm. ORs were calculated as odds of neutropaenia=yes in low ANC group/odds of neutropaenia=yes in high ANC group, with exact confidence limits and percentages based on the total number of patients in each ANC group. P values were based on Fisher's exact test. OS was analysed using the Kaplan-Meier (KM) method, a Cox proportional hazards model and a log-rank test. The significance level for interaction tests was p<0.1.

In the retrospective observational study, propensity scores adjusted for gender, age, disease stage, Eastern Cooperative Oncology Group performance status, baseline body mass index and duration of first-line treatments (<6 vs ≥6 months) were estimated using logistic regression. Propensity score matching (up to 1:3) was applied to adjust baseline difference between cohort pairs (bevacizumab/high ANC vs bevacizumab/low ANC, no bevacizumab/high ANC vs no bevacizumab/low ANC). KM analyses and Cox proportional hazards models were used to estimate the median OS and HR between cohorts. OS from the start of second-line therapy was approximated by time to the last health system interaction. The adjusted covariates in Cox models were as listed above in the propensity score model.

RESULTS

RAISE post-hoc, exploratory analyses

RAISE patient population

Patients with and without neutropaenia were compared by treatment arm; any-grade neutropaenia occurred in 58.8% (311/529) of ramucirumab patients (grade ≥3, 38.4%) vs 45.6% (241/528) of placebo patients (grade ≥3, 23.3%). The baseline demographics and disease characteristics of the RAISE patients with and without any-grade neutropaenia that developed after the initiation of study treatment are shown in table 1. Baseline characteristics were generally balanced between the arms, but the rates of neutropaenia for both ramucirumab and placebo patients were considerably different depending on certain baseline characteristics, including time to progression (<6 vs ≥6 months, ramucirumab: 46.4% vs 62.6%; placebo: 29.1% vs 50.9%), race (white vs Asian, ramucirumab: 53.5% vs 80.0%; placebo: 43.3% vs 59.2%) and gender (male vs female, ramucirumab: 54.2% vs 64.2%; placebo: 42.1% vs 51.2%). The median time to the first neutropaenic event in the ramucirumab arm was 2.6 weeks (range 0.9–41.7 weeks) for any-grade neutropaenia and 3.0 weeks (range 1.3–107.0 weeks) for grade ≥3 neutropaenia; in the placebo arm, it was 3.5 weeks (range 0.0–75.2 weeks) and 3.9 weeks (range 0.9–37.0 weeks), respectively. Among patients who had at least one neutropaenic event, 83% developed neutropaenia within 2 months of starting treatment.

OS by patient neutropaenia incidence

In both the ramucirumab and placebo arms, RAISE patients with treatment-emergent neutropaenia had longer median OS compared with patients who did not experience neutropaenia on study (figure 1). The median OS for patients with treatment-emergent neutropaenia compared with those without was 16.1 vs 10.7 months for ramucirumab (HR=0.57, 95% CI 0.46 to 0.70, p<0.0001) and 12.7 vs 10.7 months for placebo (HR=0.76, 95% CI 0.62 to 0.93, p=0.0065). In comparing treatment arms based on neutropaenia incidence, the HR of ramucirumab-treated versus placebo patients with any-grade neutropaenia was 0.79 (95% CI 0.64 to 0.96, p=0.02), whereas patients who did not experience a neutropaenic event had an HR of 1.05 (95% CI 0.86 to 1.28, p=0.646). The interaction between neutropaenia and treatment was significant (p=0.0546). Similar efficacy was detected in patients with grade ≥2 or ≥3 neutropaenia (median OS grade ≥2: ramucirumab=15.7 months, placebo=13.1 months; grade ≥3: ramucirumab=15.7 months, placebo=12.7 months).

Because neutropaenic events are likely to increase with time, it is possible that the longer survival of patients with neutropaenia is solely due to a survival bias—patients with very short survival are unlikely to develop neutropaenia. Therefore, an analysis was conducted in patients who survived for at least 2 months. A comparable efficacy trend was detected in these patients; the median OS for any-grade neutropaenia versus no neutropaenia within the first 2 months was 15.5 vs 12.9 months for ramucirumab (HR=0.75, 95% CI 0.61 to 0.93, p=0.0073) and 12.3 vs 12.0 months for

Table 1 Baseline demographics and disease characteristics of patients with and without any-grade neutropaenia (RAISE safety population)

	Ramucirumab+FOLFIRI			Placebo+FOLFIRI		
Factor, n	**With neutropaenia (n=311)**	**Without neutropaenia (n=218)**	**% Neutropaenic**	**With neutropaenia (n=241)**	**Without neutropaenia (n=287)**	**% Neutropaenic**
Geographical region						
Europe	121	112	51.9	95	137	40.9
North America	81	57	58.7	60	79	43.2
Other regions	109	49	69.0	86	71	54.8
Time to progression after first-line therapy						
<6 months	58	67	46.4	37	90	29.1
≥6 months	253	151	62.6	204	197	50.9
K-Ras status						
Mutant	156	110	58.6	110	149	42.5
Wild-type	155	108	58.9	131	138	48.7
Gender						
Male	155	131	54.2	135	186	42.1
Female	156	87	64.2	106	101	51.2
Age (years)						
<65	187	133	58.4	133	183	42.1
≥65	124	85	59.3	108	104	50.9
Race						
White	214	186	53.5	174	228	43.3
Asian	88	22	80.0	61	42	59.2
Other	7	10	41.2	6	12	33.3
Missing	2	0	100.0	0	5	0.0
ECOG PS						
0	160	100	61.5	119	137	46.5
1	149	116	56.2	121	149	44.8
2	1	0	100.0	0	1	0.0
3	0	0	0.0	1	0	100.0
Missing	1	2	33.3	0	0	0.0
Number of metastatic sites						
1	95	76	55.6	68	87	43.9
2	130	73	64.0	86	106	44.8
≥3	86	69	55.5	87	94	48.1
Liver-only metastasis						
No	265	171	60.8	204	231	46.9
Yes	46	47	49.5	37	56	39.8
Site of primary tumour						
Colon	209	141	59.7	169	183	48.0
Colorectal	3	1	75.0	3	4	42.9
Rectum	99	76	56.6	69	100	40.8
Carcinoembryonic antigen						
<200 µg/L	232	152	60.4	180	208	46.4
≥200 µg/L	61	46	57.0	46	58	44.2
Missing	18	20	47.4	15	21	41.7
Baseline ANC ($\times 10^9$/L)						
Median (range)	3.8 (1–26)	4.7 (1–15)	–	3.9 (1–13)	4.6 (2–29)	–

ANC, absolute neutrophil count; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, leucovorin/fluorouracil/irinotecan.

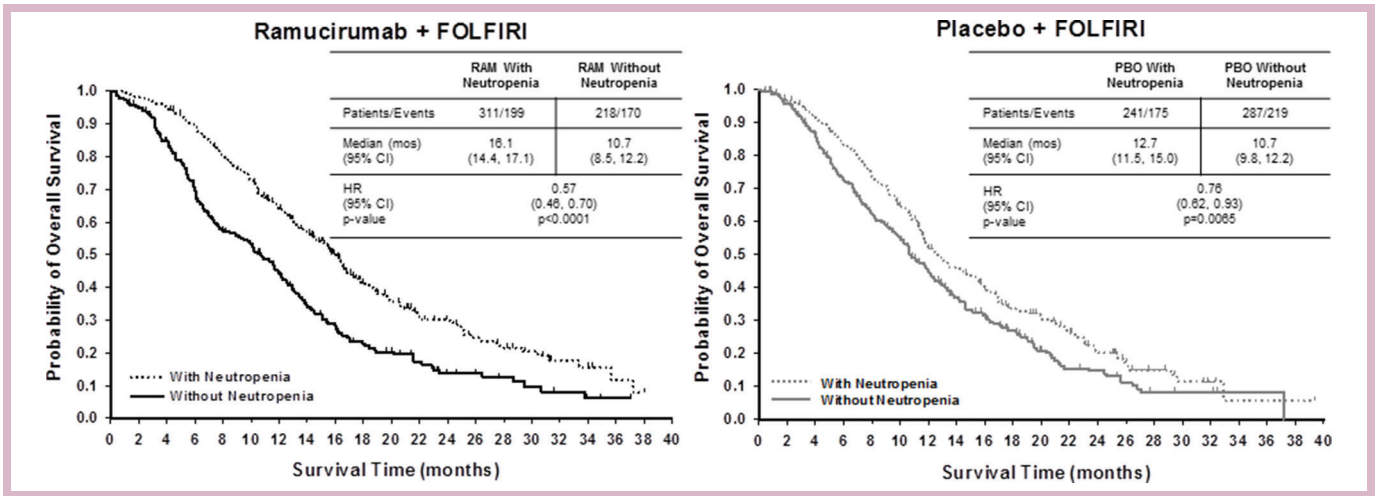

Figure 1 Patients with treatment-emergent neutropaenia had improved overall survival in RAISE trial. FOLFIRI, leucovorin/fluorouracil/irinotecan; PBO, placebo; RAM, ramucirumab.

placebo (HR=0.88, 95% CI 0.72 to 1.09, p=0.2326). A treatment arm comparison between ramucirumab and placebo demonstrated that patients with any-grade neutropaenia within the first 2 months had an HR of 0.79 (95% CI 0.63 to 0.99, p=0.0401); patients with no neutropaenia within the first 2 months had an HR of 0.93 (95% CI 0.77 to 1.13, p=0.4531). These analyses suggest that survival bias is not the sole cause of the relationship between neutropaenia and survival.

OS and neutropaenia association with patient baseline ANC

OS was analysed in RAISE patients from both the ramucirumab and placebo arms by low/high baseline ANC (≤5.6 or >5.6 x 10^9/L). Patients taking ramucirumab with low ANC had a median OS of 15.2 months, whereas patients taking ramucirumab with high ANC had a median OS of 8.9 months (HR=0.49, 95% CI 0.39 to 0.61, p<0.0001). Placebo patients showed a similar trend, with a median OS of 13.2 months with low ANC and a median OS of 7.3 months with high ANC (HR=0.50, 95% CI 0.40to 0.63, p<0.0001) (figure 2). There was little evidence for an interaction effect between the treatment and ANC group (p=0.8827); the HR for ramucirumab and low ANC versus placebo and low ANC was 0.84 (95% CI 0.71 to 0.99, p=0.0382), and the HR for ramucirumab and high ANC versus placebo and high ANC was 0.88 (95% CI 0.67 to 1.15, p=0.3425).

Baseline ANC was additionally analysed to determine whether there was an association with treatment-emergent neutropaenia in the RAISE patients. Ramucirumab patients with low baseline ANC had a 64.7% chance of developing neutropaenia, whereas ramucirumab patients with high baseline ANC had a 41.2% chance (OR=2.62, 95% CI 1.75 to 3.92, p<0.0001). Placebo patients demonstrated a similar trend; patients with low baseline ANC had a 50.3% chance of developing neutropaenia, and those

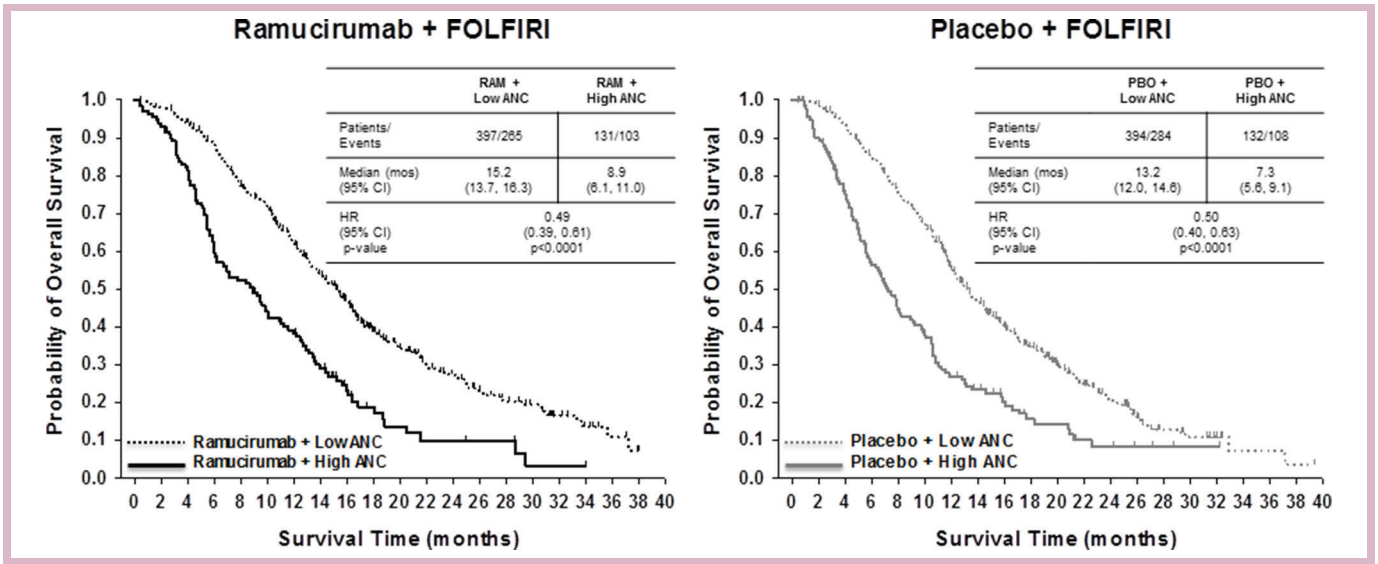

Figure 2 Patients with low baseline ANC had improved overall survival in RAISE trial. ANC, absolute neutrophil count; FOLFIRI, leucovorin/fluorouracil/irinotecan; PBO, placebo; RAM, ramucirumab.

with high baseline ANC had a 31.8% chance (OR=2.16, 95% CI 1.43 to 3.28, p=0.0003). Overall, RAISE patients with low baseline ANC had a higher likelihood of having neutropaenia and better outcomes.

Validation of ANC effects in a retrospective, observational study with real-world data

IMS EMR patient population

Data from patients with CRC initiating second-line therapy from 2007 to 2013 were obtained from the IMS EMR. A total of 617 patients met the entry criteria for this study and could be matched by propensity scores (online supplementary table S2).

Baseline demographics and use of biologics in the real-world population of CRC patients at the start of second-line treatment with FOLFIRI with or without bevacizumab are listed in table 2. Patients had a median age of 59 years (range 20–82 years) and were mostly Caucasian (67%) and male (57%). Most of the patients also had stage IV CRC at diagnosis (74%). Bevacizumab treatment in first-line and second-line therapy was the predominant biologic regimen (48%); 14% were given bevacizumab only in first-line treatment, 23% were given bevacizumab only in second-line treatment, and 14% did not receive bevacizumab in either first-line or second-line therapy.

OS by patient baseline ANC

OS was assessed in individual patients by low/high (<5.5 or ≥5.5 x 10^9/L) baseline ANC values (online supplementary figure S1). Low baseline ANC with or without bevacizumab resulted in a longer median OS versus high baseline ANC. With bevacizumab, the median OS was 14.9 months for patients with low baseline ANC vs 7.7 months for those with high baseline ANC (HR=0.59, 95% CI 0.47 to 0.74, p<0.0001); without bevacizumab, the median OS was 14.6 months for patients with low baseline ANC vs 5.4 months for those with high baseline ANC (HR=0.37, 95% CI 0.25 to 0.53, p<0.0001) (figure 3). There was also a modest interaction effect between bevacizumab treatment and baseline ANC (p=0.012), indicating greater bevacizumab benefit in the high baseline ANC group.

Table 2 Real-world demographics and baseline characteristics at start of second-line treatment

Demographics and characteristics		Patients with FOLFIRI with or without bevacizumab (n=617)
Gender, male, % of patients		57
Age, years		
Median [min, max]		59 [20, 82]
Race (of 63% with known race), % of patients		
Caucasian		67
African–American		26
Hispanic		2
Asian		1
Other		4
Disease stage at diagnosis (of 67% with known stage), % of patients		
Stage IV		74
ECOG PS at index (of 66% with known ECOG PS), % of patients		
0/1		63
Baseline ANC, median [min, max]		4.1 [1, 21]
Tumour location, % of patients		
Colon		83
Rectum		17
Biologic treatment, % of patients		
First-line	Second-line	
Bevacizumab	Bevacizumab	48
No biologic	Bevacizumab	23
Bevacizumab	No biologic	14
Cetuximab	Bevacizumab	1
Cetuximab	No biologic	<1
No biologic	No biologic	14
Time between first-line and second-line treatment, % of patients		
<6 months		37
BMI<20, % of patients		8

ANC, absolute neutrophil count; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, leucovorin/fluorouracil/irinotecan; max, maximum; min, minimum.

DISCUSSION

The RAISE trial reported a higher incidence of neutropaenia following ramucirumab+FOLFIRI treatment in patients with mCRC, but patients still demonstrated significantly improved survival.[14] In the current post-hoc analysis of the RAISE trial, any-grade neutropaenia was associated with improved OS versus no neutropaenia, regardless of treatment arm. Furthermore, the likelihood of having treatment-emergent neutropaenia was higher in patients with low baseline ANC, and the survival difference was higher in the low versus high baseline ANC comparison than in the neutropaenia versus no neutropaenia comparison. Because baseline ANC is also earlier temporally, this suggests that baseline ANC is the better prognostic marker of patient outcomes, although it does not exclude the possibility that treatment-emergent neutropaenia has additional independent prognostic value. In addition, the stronger association between baseline ANC and survival suggests that neutropaenia is not itself beneficial, but rather is associated with survival because of the poorer prognosis of high baseline ANC patients and the lower likelihood that those patients experience large enough decreases in neutrophil count during treatment to become neutropaenic.

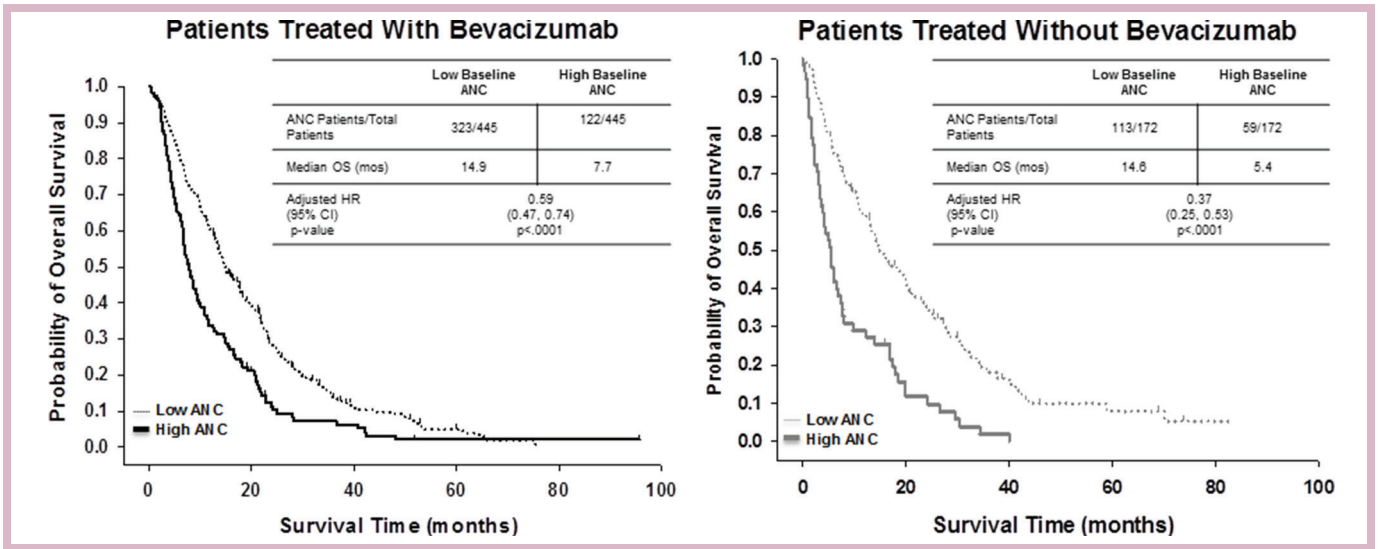

Figure 3 IMS EMR patients with low baseline ANC had improved overall survival. ANC, absolute neutrophil count; EMR, electronic medical record.

Neutropaenia, neutrophil counts and neutrophil-to-lymphocyte ratio have previously been characterised as prognostic markers for survival in CRC.[15 16 20 21] The rationale for why neutrophil levels are associated with survival is unclear. Generally, inflammation is known to drive tumourigenesis, and neutrophils are active contributors to the tumour inflammatory milieu.[22] Although neutropaenia has previously been described as a surrogate marker for antitumour cytotoxicity of chemotherapy,[16] the complete biological mechanism(s) remains uncertain. Neutrophils have been linked to promoting angiogenesis,[23–25] driving tumour growth,[21 26] activating the stress response and accelerating metastatic disease progression.[24] Inflammation has also been associated with p53 mutations,[27] which have been suggested to increase resistance to both 5-fluorouracil and irinotecan.[28 29] More work in this area would be valuable, perhaps considering associations between comorbidities and the baseline factors associated with differences in neutrophil levels such as race, gender and time to progression.

In this study, we saw a weak, apparent, predictive effect in the EMR analysis, indicating greater benefit for bevacizumab (vs no bevacizumab)-treated patients in the high baseline ANC group. By contrast, the RAISE study showed less evidence for a predictive effect, and the significant result in the neutropaenia group trended towards more benefit of ramucirumab versus placebo (corresponding to the low baseline ANC group). Other studies have also suggested associations between either neutropaenia or baseline ANC and cancer treatment effectiveness, including neutropaenia that occurred early in the course of treatment as a positive predictive factor for TAS-102 efficacy in CRC[30] and a baseline ANC>6.0 Kcells/μL as a negative prognostic factor for patient survival, yet a positive predictive factor for bevacizumab efficacy.[31] Further study will be necessary to confirm these results and to determine whether differences may be drug-specific or relate to differences between treatment-emergent neutropaenia and baseline ANC.

There are several limitations to the current analyses. For the post-hoc analysis of RAISE patients, the results should be interpreted with caution due to the non-randomised nature of the subgroup analysis. With regard to the treatment arm comparisons in particular, defining subgroups based on a postrandomisation factor confounds the very definition of such subgroups with treatment effect. The clinical implications of the neutropaenia data alone are also limited because neutropaenia only occurs postinitiation of therapy. Furthermore, longer time on therapy implied increased probability of developing neutropaenia, potentially confounding the analyses by associating longer survival with neutropaenia; however, as previously mentioned, most of the neutropaenic events (83%) occurred within the first 2 months of treatment, and OS results similar to those in the entire study by neutropaenic status were detected early, in patients who survived at least 2 months and had or did not have neutropaenia during that period. For the analysis of real-world evidence, EMR data can prove useful for testing exploratory hypotheses generated in clinical trials, but significant data were missing, likely not at random, and key fields such as line of therapy were derived. Treatment choices are not random in the real world and may bias comparisons between groups. Additionally, the observational results presented here are specific to the population studied (US community-based EMR, weighted towards the south) and may not be generalisable. In the EMR analysis, the time to last interaction was used as a proxy for survival time and therefore understates OS. Moreover, high baseline ANC was defined based on a prespecified cut-point and may not have optimised understanding of patient differences. Lastly, all of our patients in both studies

received FOLFIRI, and it is not clear if the current results are generalisable to patients receiving other therapies.

CONCLUSION

Study populations from the RAISE clinical trial and from the IMS EMR database demonstrated a significant relationship between baseline ANC and survival. Treatment-emergent neutropaenia appears to occur most commonly in a population with lower baseline ANC, yet does not lead to poorer outcomes. Overall, a simple neutrophil cell count at baseline is suggested to be strong prognostic factor for survival in the analysed population.

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