OPEN

Markers of Systemic Inflammation in Neuroendocrine Tumors

A Pooled Analysis of the RADIANT-3 and RADIANT-4 Studies

David L. Chan, PhD, MBBS,† James C. Yao, MD,‡ Carlo Carnaghi, MD,§ Roberto Buzzoni, MD,|| Fabian Herbst, MD,¶ Antonia Ridolfi, MSc,# Jonathan Strosberg, MD,** Matthew H. Kulke, MD,†† Marianne Pavel, MD,‡‡ and Simron Singh, MD**

Objective: The aim of the study was to assess the impact of systemic markers of inflammation on the outcomes in patients with neuroendocrine tumors (NETs) treated with everolimus or placebo (as measured by baseline neutrophil-to-lymphocyte ratio [NLR] and lymphocyte-to-monocyte ratio [LMR]).

Methods: Patient data (gastrointestinal, pancreatic, and lung NETs) from 2 large phase 3 studies, RADIANT-3 (n = 410) and RADIANT-4 (n = 302), were pooled and analyzed. The primary end point was centrally assessed progression-free survival (PFS) as estimated by the Kaplan-Meier method.

Results: In the pooled population, elevated LMR (median PFS, 11.1 months; 95% confidence interval, 9.3–13.7; hazard ratio, 0.69; $P < 0.001$) and reduced NLR (median PFS, 10.8 months; 95% confidence interval, 9.2–11.7; hazard ratio, 0.75; $P = 0.0060$) correlated with longer PFS among all patients. These markers were also found to be prognostic in the everolimus- and placebo-treated subgroups.

Conclusions: Data from this study suggest that LMR and NLR are robust prognostic markers for NETs and could potentially be used to identify patients who may receive or are receiving the most benefit from targeted therapies. As both are derived from a complete blood count, they can be routinely used in clinical practice, providing valuable information to clinicians and patients alike.

Key Words: neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, RADIANT-3, RADIANT-4

(*Pancreas* 2021;50: 130–137)

Neuroendocrine tumors (NETs) constitute a heterogeneous group of tumors with distinct biological behaviors based on the site of tumor origin and the extent of tumor proliferation.[1] Neuroendocrine tumors have previously been regarded as a rare condition; however, in the recent years, increased incidence rates have been observed.[2] Moreover, many NETs remain dormant for long periods, and patients with NETs often remain undiagnosed.[3,4]

Understanding the complex tumor biology of NETs and inflammatory markers associated with NETs could aid in the development of an individually tailored treatment approach and improve the outcomes.[5] Over time, researchers have proposed several biomarkers to predict the clinical outcomes from NETs; however, only a few can consistently predict prognosis and help optimize treatment selection.[6,7]

The neutrophil-to-lymphocyte ratio (NLR, the ratio between the absolute neutrophil count and the absolute lymphocyte count) and the lymphocyte-to-monocyte ratio (LMR, the ratio between the absolute lymphocyte count and the absolute monocyte count) are blood-based markers of systemic inflammation whose prognostic significance has been determined in many cancers.[8–10] Elevated preoperative NLR and lower LMR (both reflective of higher baseline systemic inflammation) were significantly associated with a shorter overall survival in several malignancies.[9–13] The exact cutoff selected for NLR and LMR varies between studies; values such as predefined values (3 or 5), median, or statistically selected values (to maximize the difference between subgroups) have been investigated.

Several studies have evaluated the prognostic value of NLR in NETs.[14] However, the effectiveness of this biomarker to predict survival of the patients was not consistent, and the value of NLR as a prognostic factor in NETs remains uncertain. An exploratory analysis from the CLARINET study demonstrated no significant association between NLR and progression-free survival (PFS) in patients with advanced intestinal and pancreatic NETs.[15]

From the *Sunnybrook Health Sciences Centre, Toronto, Canada; †Faculty of Medicine and Health, Northern Clinical School, University of Sydney, Sydney, Australia; ‡Division of Cancer Medicine, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; §Oncology and Hematology Unit, Humanitas Istituito Clinico Catanese, Catania; ||Medical Oncology Department, San Carlo Specialist Clinic, Paderno Dugnano, Italy; ¶Oncology, Novartis Pharma AG, Basel, Switzerland; #Oncology, Novartis Pharma S.A.S., Rueil-Malmaison, France; **Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL; ††Section of Hematology and Oncology, Boston University and Boston Medical Cancer Center, Boston, MA; and ‡‡Department of Medicine 1, Endocrinology, Friedrich Alexander University Erlangen, Erlangen, Germany.

Received for publication April 22, 2020; accepted December 21, 2020.

Address correspondence to: David L. Chan, PhD, MBBS, Level 1, Acute Services Bldg, Royal North Shore Hospital, St Leonards, NSW 2065, Australia (e-mail: david.chan@sydney.edu.au).

D.L.C. reports personal fees and nonfinancial support from Novartis and Ipsen and grants from Merck KGaA, outside the submitted work. J.C.Y. reports personal fees from Novartis, Ipsen, Mallinckrodt, Tarveda, Crinetics, Hutchison Medi, Chiasma, Exelixis, and Nektar, outside the submitted work. F.H. was an employee of Novartis (during the time of this research). A.R. is an employee of Novartis. J.S. reports personal fees from Ipsen, Lexicon, and Novartis, outside the submitted work. M.P. reports honoraria for presentations/advisory boards from Ipsen, Pfizer, Lexicon, and Novartis and research support from former institutions—Charité, Ipsen, and Novartis. S.S. reports others from Novartis during the conduct of the study and personal fees from Novartis and Ipsen, outside the submitted work. The other authors declare no conflict of interest.

This investigator-initiated study was sponsored by Novartis Pharmaceuticals Corporation.

Trial Registration: ClinicalTrials.gov identifiers, NCT01524783 and NCT00510068.

D.L.C., J.C.Y., C.C., R.B., J.S., M.H.K., M.P., and S.S. were involved in patient recruitment in the RADIANT program. D.L.C. contributed toward the study conception, study design, and data analysis. A.R. performed the statistical analysis. All authors contributed toward data interpretation and drafting and critically revising the paper, provided final approval to the version to be published, and agree to remain accountable for all aspects of the work.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

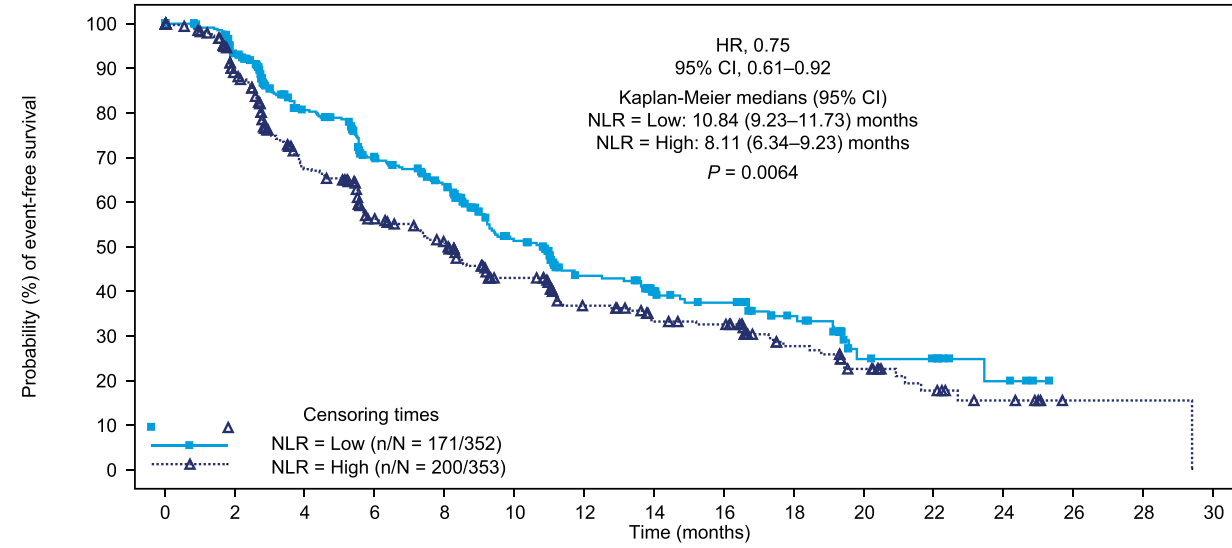
DOI: 10.1097/MPA.0000000000001745

To test NLR and LMR in a large prospectively treated and monitored population, we pooled data from 2 large phase 3 studies, RADIANT-3 (n = 410, pancreatic NETs) and RADIANT-4 (n = 302, gastrointestinal [GI] or lung NETs). Our goal was to assess the impact of systemic inflammation (as measured by baseline NLR and LMR) on PFS, both in the active everolimus-treated cohort and in the placebo control cohort to potentially allow for an easily accessible and useful biomarker in NETs.

MATERIALS AND METHODS

Study Design

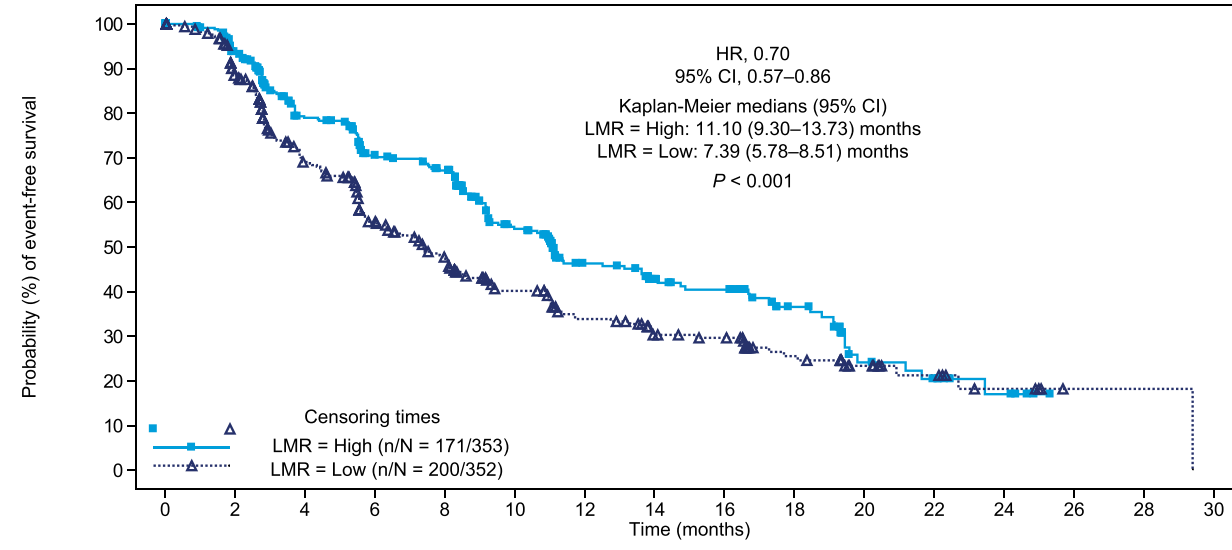
Data were pooled from 2 phase 3, international, multicenter, randomized, double-blind, placebo-controlled studies, RADIANT-3 (NCT00510068) and RADIANT-4 (NCT01524783), that evaluated the use of everolimus in patients with advanced NETs. Study



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
NLR = Low	352	311	236	190	165	110	74	57	46	30	11	9	4	0	0	0
NLR = High	353	285	197	149	128	91	67	54	51	30	19	11	6	1	1	0

A



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
LMR = Low	353	310	233	192	177	119	79	63	53	33	14	10	5	0	0	0
LMR = High	352	286	200	147	116	82	62	48	44	27	16	10	5	1	1	0

B

FIGURE 1. Kaplan-Meier plots of PFS (central review) in the pooled population by baseline (A) NLR (low vs high) and (B) LMR (high vs low). An unstratified Cox model was used to calculate the HR and associated 95% CI as well as the *P* value. n, total number of events included in the analysis; N, total number of patients included in the analysis; CI, confidence interval; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

protocols were approved by the institutional review board or ethics committee at each participating center. These studies were conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and all applicable local regulations. All patients provided written informed consent. An independent data monitoring committee provided an ongoing oversight on safety and study conduct.[16,17]

In the RADIANT-3 study, patients with advanced-, low-, or intermediate-grade pancreatic NETs were randomized to either everolimus 10 mg/d oral (n = 207) or matching placebo (n = 203), both in conjunction with the best supportive care.[16] In the RADIANT-4 study, patients with advanced-, low-, or intermediate-grade nonfunctioning GI or lung NETs were randomized to either everolimus 10 mg/d oral (n = 205) or matching placebo (n = 97), both in conjunction with the best supportive care.[17]

In both studies, an initial everolimus dose reduction to 5 mg/d and a subsequent reduction to 5 mg every other day or treatment interruption were allowed for patients who were unable to tolerate or manage the adverse events (AEs) that were suspected to be related to the study drug. Treatment was continued until

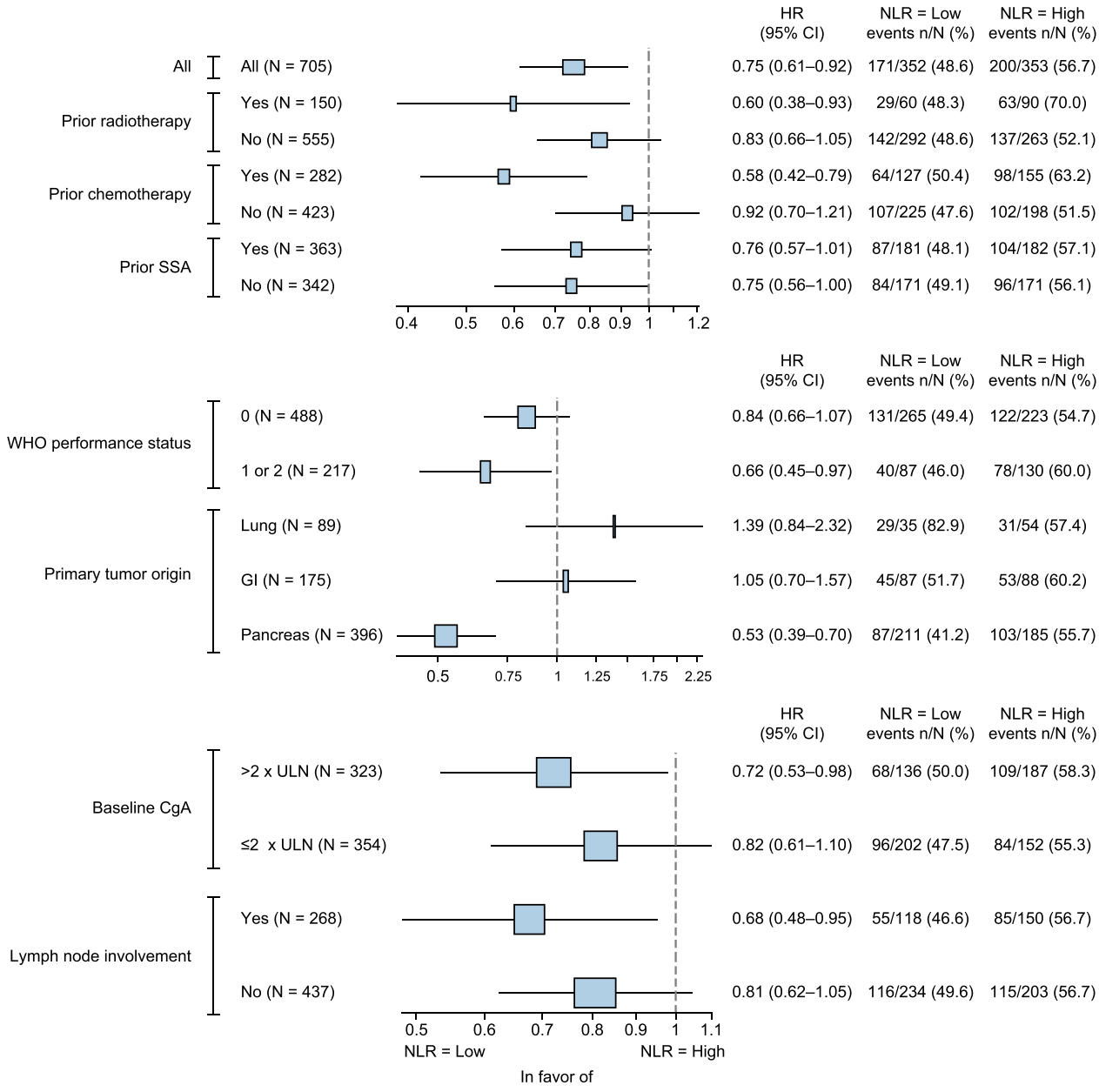


FIGURE 2. Forest plot of HR (NLR low vs high) with 95% CI for PFS (central review) in the pooled population. High NLR is defined as 2.523316 or greater (median value for the pooled population). An unstratified Cox model was used to calculate the HR and associated 95% CI. Prior SSA, tumor origin, and WHO performance status are as reported in the item response theory system. In the primary tumor origin category, appendix, cecum, colon, duodenum, jejunum, ileum, rectum, and stomach are grouped as GI category. Data for lung and GI are from RADIANT-4 and pancreas from RADIANT-3. Lymph node is any lymph node/lymphatic system involvement. CgA, chromogranin A; n, total number of events included in the analysis; N, total number of patients included in the analysis; SSA, somatostatin analog; ULN, upper limit of normal; WHO, World Health Organization.

disease progression, initiation of a new cancer therapy, development of an intolerable AE, or withdrawal of consent.[16,17]

Assessments

The primary end point for this analysis was the centrally assessed PFS, defined as the time from randomization to documented radiological disease progression as per the modified Response Evaluation Criteria In Solid Tumors (mRECIST) Version 1.0 or death due to any cause. The full analysis set consisted of all patients who were randomized. Patients in the full analysis set who had valid baseline laboratory values were considered for the efficacy analyses. The secondary end point of this study was safety. Safety assessments consisted of monitoring and recording of all AEs, vital signs, physical examinations, and clinical laboratory evaluations in the RADIANT-3 and RADIANT-4 studies. Adverse events in this pooled analysis were coded using Version 17.1 of the Medical Dictionary for Regulatory Activities and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Statistical Analyses

Patients treated with everolimus or placebo were dichotomized based on their baseline median values for high versus low NLR (cutoff, ≥2.58 vs <2.58, respectively) and high versus low LMR (≥3.76 vs <3.76, respectively). Neutrophil-to-lymphocyte ratio and LMR were calculated using data obtained from the complete blood count. The association between systemic inflammatory markers (NLR and LMR) and PFS was established using the Kaplan-Meier method. Hazard ratios (HRs) and their corresponding confidence intervals (CIs) were calculated using an unstratified Cox regression model. For subgroups, forest plots were used to display HRs and 95% CIs. Safety sets from RADIANT-3 and RADIANT-4 were considered in reporting the AEs.

RESULTS

Patients

Of the total 712 patients pooled from the RADIANT-3 (n = 410) and RADIANT-4 (n = 302) studies, 705 patients (everolimus, 407; placebo, 298) with valid baseline laboratory values were considered for the pooled population analysis. The most common primary sites of disease in these 705 patients were the pancreas (n = 410), GI tract (n = 168), and lungs (n = 90).

Inflammatory Markers—PFS By Baseline NLR and LMR Groups

In the pooled population, patients with a higher NLR had a shorter median PFS (mPFS) versus patients with a lower NLR (8.1 months vs 10.8 months, respectively; HR, 0.75; 95% CI, 0.61–0.92; $P = 0.0064$) and patients with a lower LMR had a shorter mPFS versus patients with a higher LMR (7.4 months vs 11.1 months, respectively; HR, 0.70; 95% CI, 0.57–0.86; $P < 0.001$; Figs. 1, 2).

Similar results were observed in both the everolimus and placebo population subgroups when considered separately. In the everolimus population, a shorter mPFS was observed in patients

TABLE 1. Median PFS (95% CI) in the NLR (Low and High) Subgroups of the Pooled Population

	Low NLR (n = 352)		High NLR (n = 353)	
Subgroup Variable	**n/N**	**Median PFS (95% CI), mo**	**n/N**	**Median PFS (95% CI), mo**
Any prior therapy				
Yes	169/348	10.9 (9.2–11.7)	194/342	8.1 (6.3–9.2)
No	2/4	9.2 (1.9–NE)	6/11	5.8 (1.9–16.6)
Prior therapy				
Prior radiotherapy	29/60	8.6 (5.7–19.8)	63/90	5.5 (3.6–8.3)
No prior radiotherapy	142/292	11.0 (9.3–13.6)	137/263	9.2 (7.4–11.2)
Prior chemotherapy	64/127	10.8 (8.3–11.7)	98/155	5.6 (4.6–7.9)
No prior chemotherapy	107/225	10.9 (9.2–13.6)	102/198	11.0 (8.1–13.9)
Prior SSA	87/181	11.1 (9.0–12.5)	104/182	8.3 (5.6–11.0)
No prior SSA	84/171	10.6 (8.5–14.1)	96/171	7.5 (5.7–9.2)
WHO performance status				
0	131/265	10.8 (9.2–13.7)	122/223	9.2 (7.6–11.2)
1/2	40/87	11.0 (5.7–11.4)	78/130	5.6 (4.5–7.9)
Primary tumor origin				
Lung	29/35	7.4 (5.6–9.2)	31/54	7.1 (3.8–13.3)
GI*	45/87	9.4 (7.9–16.7)	53/88	11.0 (7.4–16.6)
Pancreas	87/211	13.6 (10.3–18.1)	103/185	7.6 (5.6–8.5)
Baseline CgA				
≤2× ULN	96/202	11.1 (9.0–13.7)	84/152	9.2 (5.8–11.2)
>2× ULN	68/136	10.0 (8.2–11.2)	109/187	7.4 (5.1–8.6)
Lymph node/lymphatic system involvement				
Yes	55/118	10.3 (8.6–19.8)	85/150	7.9 (5.5–9.2)
No	116/234	10.9 (9.2–12.5)	115/203	8.3 (6.3–11.0)

*Primary tumor origin: appendix, cecum, colon, duodenum, jejunum, ileum, rectum, and stomach are grouped as GI category.

CgA indicates chromogranin A; n, total number of events included in the analysis; N, total number of patients included in the analysis; NE, not evaluable; SSA, somatostatin analog; ULN, upper limit of normal; WHO, World Health Organization.

with a higher NLR versus those with a lower NLR (11.0 months vs 14.1 months, respectively; HR, 0.64; 95% CI, 0.48–0.85; $P = 0.0019$; see Supplemental Table 1, http://links.lww.com/MPA/A849, which shows the mPFS [95% CI] in the NLR [low and high] subgroups of the everolimus population) and in patients with a lower LMR versus those with a higher LMR (9.5 months vs 14.8 months, respectively; HR, 0.64; 95% CI, 0.48–0.85; $P = 0.0018$; see Supplemental Table 2, http://links.lww.com/MPA/A849, which shows the mPFS [95% CI] in the LMR [low and high] subgroups of the everolimus population, and see Supplemental Fig. 1, http://links.lww.com/MPA/A849, which shows the Kaplan-Meier plots of PFS [central review] in the everolimus population by baseline [A] NLR [low vs high] and [B] LMR [high vs low]). In the placebo population, a nonsignificantly shorter mPFS was observed in patients with a higher NLR versus those with a lower NLR (5.1 months vs 5.6 months, respectively; HR, 0.90; 95% CI, 0.67–1.22; $P = 0.5050$) and in patients with a lower LMR versus those with a higher LMR (5.1 months vs 8.2 months, respectively; HR, 0.75; 95% CI, 0.56–1.01; $P = 0.0620$; see Supplemental Fig. 2, http://links.lww.com/MPA/A849, which shows the Kaplan-Meier plots of PFS [central review] in the placebo population by baseline [A] NLR [low vs high] and [B] LMR [high vs low]).

Inflammatory Markers—PFS By Primary Tumor Origin

In the pooled population, in patients with primary pancreatic NETs, a lower baseline NLR was significantly associated with prolonged PFS versus a higher baseline NLR (13.6 months vs 7.6 months, respectively; HR, 0.53; 95% CI, 0.39–0.70). A higher baseline LMR was also associated with a prolonged PFS versus a lower baseline LMR (12.5 months vs 6.3 months, respectively; HR, 0.50; 95% CI, 0.38–0.67; Tables 1, 2; Fig. 2; see Supplemental Fig. 3, http://links.lww.com/MPA/A849, which shows the forest plot of HR [LMR high vs low] with 95% CI for PFS based on central review in the pooled population). However, these patterns were not observed in GI NETs, where both lower NLR and higher LMR were associated with a nonsignificantly shorter PFS compared with higher NLR and lower LMR (Tables 1, 2; Fig. 2; see Supplemental Fig. 3, http://links.lww.com/MPA/A849, which shows the forest plot of HR [LMR high vs low] with 95% CI for PFS based on central review in the pooled population).

The benefit of everolimus in prolonging the PFS compared with placebo was preserved in both the high NLR (HR, 0.59; 95% CI, 0.44–0.78) and low NLR (HR, 0.39; 95% CI, 0.29–0.53) subgroups (see Supplemental Fig. 4, http://links.lww.com/MPA/A849, which shows the forest plot of HR [NLR high] with 95% CI for PFS in everolimus versus placebo population [by subgroup], and Supplemental Fig. 5, http://links.lww.com/MPA/A849, which shows the forest plot of HR [NLR low] with 95% CI for PFS in the everolimus versus placebo populations [by subgroup]). Similarly, everolimus prolonged the PFS in both the high LMR (HR, 0.45; 95% CI, 0.33–0.60) and low LMR (HR, 0.51; 95% CI, 0.39–0.68) subgroups (see Supplemental Fig. 6, http://links.lww.com/MPA/A849, which shows the forest plot of HR [LMR high] with 95% CI for PFS in the everolimus versus placebo populations [by subgroup], and Supplemental Fig. 7, http://links.lww.com/MPA/A849, which shows the forest

TABLE 2. Median PFS (95% CI) in the LMR (Low and High) Subgroups of the Pooled Population

	Low LMR, N = 352		High LMR, N = 353	
Subgroup Variable	**n/N**	**Median PFS (95% CI), mo**	**n/N**	**Median PFS (95% CI), mo**
Any prior therapy				
Yes	194/343	7.4 (6.0–8.5)	169/347	11.1 (9.3–13.7)
No	6/9	4.5 (1.9–16.6)	2/6	9.2 (1.9–NE)
Prior therapy				
Prior radiotherapy	68/98	5.5 (3.6–7.1)	24/52	8.8 (7.9–19.8)
No prior radiotherapy	132/254	8.1 (7.2–11.0)	147/301	11.2 (9.3–13.9)
Prior chemotherapy	98/155	5.7 (4.6–7.3)	64/127	11.0 (9.0–14.1)
No prior chemotherapy	102/197	9.2 (7.4–12.7)	107/226	11.2 (9.2–16.7)
Prior SSA	110/187	7.4 (5.6–9.2)	81/176	11.2 (9.5–14.9)
No prior SSA	90/165	7.2 (5.7–9.4)	90/177	10.8 (8.5–14.8)
WHO performance status				
0	129/225	8.1 (6.4–9.5)	124/263	13.1 (9.9–17.3)
1/2	71/127	6.1 (5.4–8.1)	47/90	9.2 (5.6–11.2)
Primary tumor origin				
Lung	37/60	7.4 (5.5–11.0)	23/29	7.6 (3.7–9.2)
GI*	50/89	10.9 (7.4–16.6)	48/86	9.3 (7.5–16.7)
Pancreas	99/181	6.3 (5.5–8.1)	91/215	12.5 (10.8–18.8)
Baseline CgA				
≤2× ULN	89/157	7.6 (5.7–10.9)	91/197	11.4 (9.2–16.7)
>2× ULN	102/179	6.7 (5.1–8.1)	75/144	10.8 (9.2–13.6)
Lymph node/lymphatic system involvement				
Yes	88/152	6.8 (5.5–8.5)	52/116	14.1 (9.2–19.8)
No	112/200	8.1 (6.1–9.5)	119/237	11.1 (9.2–13.1)

*Primary tumor origin: appendix, caecum, colon, duodenum, jejunum, ileum, rectum, and stomach are grouped as GI category.

CgA indicates chromogranin A; LMR, lymphocyte-to-monocyte ratio; n, total number of events included in the analysis; N, total number of patients included in the analysis; NE, not evaluable; SSA, somatostatin analog; ULN, upper limit of normal; WHO, World Health Organization.

plot of HR [LMR low] with 95% CI for PFS in the everolimus versus placebo populations [by subgroup]). Associations between inflammatory markers and PFS by central review are shown in Supplemental Figure 8 (http://links.lww.com/MPA/A849), which shows the forest plot of HR (NLR low vs high) with 95% CI for PFS (central review) in the everolimus population, Supplemental Figure 9 (http://links.lww.com/MPA/A849), which shows the forest plot of HR (LMR high vs low) with 95% CI for PFS (central review) in the everolimus population, Supplemental Figure 10 (http://links.lww.com/MPA/A849), which shows the forest plot of HR (LMR high vs low) with 95% CI for PFS (central review) in the placebo population, and Supplemental Figure 11 (http://links.lww.com/MPA/A849), which shows the forest plot of HR (NLR low vs high) with 95% CI for PFS (central review) in the placebo population.

Safety

The safety findings for everolimus versus placebo in this pooled analysis were consistent with the safety findings reported in the individual RADIANT-3 and RADIANT-4 studies (Table 3).[16,17]

DISCUSSION

This exploratory analysis of systemic markers of inflammation (NLR and LMR) in a pooled population of patients with NETs from the RADIANT-3 and RADIANT-4 studies showed a statistically significant association between the baseline inflammation status (as determined by NLR and LMR) and patient outcomes. The study demonstrated that low NLR and high LMR are associated with improved PFS compared with high NLR and low LMR, respectively, in the pooled population. Our study showed that the benefit of everolimus was preserved in patients regardless of their baseline inflammation status.

Similar findings were observed among the everolimus-treated and placebo-treated populations. With respect to the primary site, the association between NLR, LMR, and PFS was observed predominantly in pancreatic NETs. No significant trends were noted in the GI or lung NET population.

Growing evidence shows an association of systemic inflammation with poor survival outcomes in many cancers.[5,18–22] Among the several biomarkers/prognostic scores (performance status, white blood cell/C-reactive protein, lactate dehydrogenase, Ki-67 index, and platelet count) that have been proposed, only a few (Ki-67, chromogranin A) are regularly used in predicting treatment outcomes.[6] Neutrophil-to-lymphocyte ratio and LMR, derived from neutrophils and lymphocytes, are cost-effective and readily available markers of inflammation for the prognosis of different types of cancers.[23,24]

More recently, the prognostic significance of NLR has been tested in many cancers, including advanced renal cell

TABLE 3. Safety Outcomes in Patients With High NLR Versus Low NLR (Regardless of the Study Drug)

	Pooled Population				Everolimus Population				Placebo Population			
	NLR (High), n (%) N = 351		NLR (Low), n (%) N = 351		NLR (High), n (%) N = 202		NLR (Low), n (%) N = 201		NLR (High), n (%) N = 150		NLR (Low), n (%) N = 149	
Preferred Term	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Diarrhea	156 (44.4)	28 (8.0)	144 (41.0)	15 (4.3)	95 (47.0)	18 (8.9)	87 (43.3)	13 (6.5)	61 (40.7)	10 (6.7)	57 (38.3)	2 (1.3)
Stomatitis	154 (43.9)	20 (5.7)	171 (48.7)	9 (2.6)	107 (53.0)	17 (8.4)	114 (56.7)	9 (4.5)	47 (31.3)	2 (1.3)	57 (38.3)	1 (0.7)
Fatigue	141 (40.2)	18 (5.1)	140 (39.9)	12 (3.4)	86 (42.6)	9 (4.5)	80 (39.8)	10 (5.0)	57 (38.0)	9 (6.0)	58 (38.9)	2 (1.3)
Nausea	116 (33.0)	13 (3.7)	120 (34.2)	6 (1.7)	65 (32.2)	8 (4.0)	58 (28.9)	3 (1.5)	53 (35.3)	5 (3.3)	60 (40.3)	3 (2.0)
Rash	113 (32.2)	3 (0.9)	153 (43.6)	1 (0.3)	66 (32.7)	1 (0.5)	101 (50.2)	1 (0.5)	46 (30.7)	2 (1.3)	53 (35.6)	0
Edema peripheral	111 (31.6)	7 (2.0)	97 (27.6)	5 (1.4)	80 (39.6)	5 (2.5)	74 (36.8)	4 (2.0)	30 (20.0)	2 (1.3)	24 (16.1)	1 (0.7)
Decreased appetite	104 (29.6)	10 (2.8)	96 (27.4)	8 (2.3)	61 (30.2)	4 (2.0)	51 (25.4)	1 (0.5)	45 (30.0)	6 (4.0)	43 (28.9)	7 (4.7)
Pyrexia	102 (29.1)	7 (2.0)	82 (23.4)	1 (0.3)	61 (30.2)	5 (2.5)	55 (27.4)	1 (0.5)	41 (27.3)	2 (1.3)	27 (18.1)	0
Weight decreased	96 (27.4)	6 (1.7)	81 (23.1)	2 (0.6)	61 (30.2)	4 (2.0)	45 (22.4)	0	36 (24.0)	2 (1.3)	35 (23.5)	2 (1.3)
Abdominal pain	90 (25.6)	23 (6.6)	94 (26.8)	21 (6.0)	42 (20.8)	9 (4.5)	48 (23.9)	8 (4.0)	46 (30.7)	14 (9.3)	48 (32.2)	13 (8.7)
Cough	89 (25.4)	0	85 (24.2)	1 (0.3)	54 (26.7)	0	54 (26.9)	1 (0.5)	36 (24.0)	0	30 (20.1)	0
Vomiting	87 (24.8)	12 (3.4)	89 (25.4)	9 (2.6)	45 (22.3)	4 (2.0)	47 (23.4)	5 (2.5)	43 (28.7)	8 (5.3)	41 (27.5)	4 (2.7)
Asthenia	75 (21.4)	17 (4.8)	73 (20.8)	10 (2.8)	42 (20.8)	8 (4.0)	44 (21.9)	3 (1.5)	33 (22.0)	9 (6.0)	29 (19.5)	7 (4.7)
Dyspnea	72 (20.5)	10 (2.8)	52 (14.8)	5 (1.4)	45 (22.3)	7 (3.5)	30 (14.9)	3 (1.5)	26 (17.3)	3 (2.0)	23 (15.4)	2 (1.3)
Anemia	72 (20.5)	23 (6.6)	68 (19.4)	20 (5.7)	47 (23.3)	15 (7.4)	44 (21.9)	13 (6.5)	24 (16.0)	7 (4.7)	25 (16.8)	8 (5.4)
Headache	65 (18.5)	3 (0.9)	93 (26.5)	4 (1.1)	34 (16.8)	0	54 (26.9)	2 (1.0)	32 (21.3)	2 (1.3)	38 (25.5)	3 (2.0)
Back pain	60 (17.1)	5 (1.4)	59 (16.8)	6 (1.7)	37 (18.3)	2 (1.0)	27 (13.4)	3 (1.5)	24 (16.0)	3 (2.0)	31 (20.8)	3 (2.0)
Dysgeusia	57 (16.2)	1 (0.3)	65 (18.5)	1 (0.3)	35 (17.3)	1 (0.5)	40 (19.9)	0	22 (14.7)	0	25 (16.8)	1 (0.7)
Pruritus	54 (15.4)	0	80 (22.8)	0	28 (13.9)	0	45 (22.4)	0	26 (17.3)	0	35 (23.5)	0
Constipation	54 (15.4)	0	59 (16.8)	0	25 (12.4)	0	27 (13.4)	0	29 (19.3)	0	32 (21.5)	0
Epistaxis	52 (14.8)	1 (0.3)	52 (14.8)	0	36 (17.8)	1 (0.5)	35 (17.4)	0	16 (10.7)	0	17 (11.4)	0
Hyperglycemia	50 (14.2)	21 (6.0)	71 (20.2)	25 (7.1)	24 (11.9)	11 (5.4)	40 (19.9)	15 (7.5)	24 (16.0)	9 (6.0)	33 (22.1)	11 (7.4)

n, total number of events included in the analysis; N, total number of patients included in the analysis; NLR, neutrophil-to-lymphocyte ratio.

carcinoma,[25] advanced esophageal cancer,[26] and small cell lung cancer,[27] wherein NLR was demonstrated to be a reliable marker in predicting the survival outcomes.[12] Several small studies have also demonstrated the prognostic significance of NLR in patients with NETs.[28] Salman et al[29] regarded NLR as an easy-to-measure laboratory parameter and suggested that an increased NLR could be used as a prognostic marker to identify patients with NETs with poor survival outcomes. However, there have been limited data on NETs to date.

Several studies have identified LMR as a key prognostic marker and showed associations between preoperative LMR and survival outcomes in several cancers, including hepatocellular carcinoma, colorectal cancer, gastric cancer, non–small cell lung cancer, and pancreatic adenocarcinoma.[12,28,30]

The etiology of inflammation is not yet completely known; however, it has been observed that both lymphocytes and neutrophils play a vital role in the process of inflammation.[31–33] Although the role of monocytes is less clear, tumor-associated macrophages derived from this cell population are thought to play a key role in the pathogenesis of tumor growth and metastasis.[34]

There are some intriguing future avenues of research regarding the interaction between systemic markers of inflammation and immunotherapy. In a retrospective study conducted in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors, both an early decline in NLR (from baseline to week 6) and low NLR at week 6 predicted better survival outcomes.[35] Another study showed an association between NLR and outcomes in melanoma patients treated with ipilimumab but not in those treated with BRAF inhibitors.[36] The critical interplay between inflammation, host response, and immunotherapy efficacy gives rise to potential future therapeutic strategies—for example, combining immunotherapy with targeted therapies in patients with elevated markers of systemic inflammation in an attempt to offset the poor prognosis associated with inflammation.

The safety findings in this pooled analysis were consistent with those observed in the individual RADIANT-3 and RADIANT-4 studies.[16,17] No new safety signals were highlighted in this study, with patients reporting mainly grade 1 or 2 AEs.

This study used one of the largest consecutive cohorts of patients with NETs to study systemic markers of inflammation albeit using a retrospective study design. The data were, however, collected prospectively in accordance with the maximum number of participants and a very low dropout rate.

To our knowledge, this study is the first and largest of its kind to evaluate the prognostic role of LMR and NLR in patients with NETs. Given the randomized, double-blind, placebo-controlled, phase 3 data and the large number of patients assessed, our findings are a valuable contribution to the understanding of NET biology. Our findings establish the potential applicability of NLR and LMR as prognostic markers of clinical benefit in patients with NET during targeted therapy, immunotherapy, or treatment with other novel therapies. These observations require future prospective biomarker validation.

This pooled analysis of 2 large, randomized, phase 3 studies revealed the prognostic role of NLR and LMR, markers of systemic inflammation, in patients with NETs of GI or pancreatic origin. These data suggest that markers of systemic inflammation could potentially be used as prognostic factors to identify patients who may receive or are receiving the most benefit from targeted therapies. Further validated prospective studies are warranted.

ACKNOWLEDGMENT

The authors thank patients, their families, and their caregivers, as well as the investigators and research nurses. The authors also thank Charu Pundir and Anuradha Bandaru of Novartis Healthcare Pvt. Ltd for medical writing and editorial support.

REFERENCES

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–1342.
2. Leoncini E, Boffetta P, Shafir M, et al. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine*. 2017;58:368–379.
3. Pinchot SN, Holen K, Sippel RS, et al. Carcinoid tumors. *Oncologist*. 2008;13:1255–1269.
4. Metz DC, Choi J, Strosberg J, et al. A rationale for multidisciplinary care in treating neuroendocrine tumours. *Curr Opin Endocrinol Diabetes Obes*. 2012;19:306–313.
5. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15:e493–e503.
6. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24:152–160.
7. Chan DL, Clarke SJ, Diakos CI, et al. Prognostic and predictive biomarkers in neuroendocrine tumours. *Crit Rev Oncol Hematol*. 2017;113:268–282.
8. Imtiaz F, Shafique K, Mirza SS, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med*. 2012;5:2.
9. Huang C, Cao LL, Zheng CH, et al. The preoperative blood lymphocyte-to-monocyte ratio acts as a superior prognostic factor and predicts tumor metastasis in gastric neuroendocrine neoplasms after surgery. *Ann Oncol*. 2017;28(suppl 3):iii48.abstract P-123.
10. Zhou B, Zhan C, Wu J, et al. Prognostic significance of preoperative neutrophil-to-lymphocyte ratio in surgically resectable pancreatic neuroendocrine tumors. *Med Sci Monit*. 2017;23:5574–5588.
11. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106:dju124.
12. Chan JC, Chan DL, Diakos CI, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. *Ann Surg*. 2017;265:539–546.
13. Zhou Y, Li D, Lin Y, et al. Pretreatment hematologic markers as prognostic predictors of gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *Onco Targets Ther*. 2018;11:2489–2496.
14. Krasnick BA, Davidson JT, Panni RZ, et al. Prognostic value of neutrophil-to-lymphocyte ratio (NLR) in intestinal neuroendocrine tumors: an analysis of the U.S. Neuroendocrine Tumor Study Group. *J Clin Oncol*. 2018;36(suppl 4):abstract 649.
15. Grenader T, Ruszniewski P, Pavel M, et al. Prognostic value of neutrophil/lymphocyte ratio in intestinal and pancreatic neuroendocrine tumors: exploratory analysis of data from the CLARINET trial of lanreotide depot/autogel. *Eur J Cancer*. 2015;51(suppl 3):S443.abstract 2331.
16. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514–523.
17. Yao JC, Fazio N, Singh S, et al; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387:968–977.
18. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860–867.
19. Asher V, Lee J, Innamaa A, et al. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. *Clin Transl Oncol*. 2011;13:499–503.

20. Pichler M, Hutterer GC, Stoeckigt C, et al. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. *Br J Cancer*. 2013;108: 901–907.
21. Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. *Int J Cancer*. 2014;134:2403–2413.
22. Pan QX, Su ZJ, Zhang JH, et al. A comparison of the prognostic value of preoperative inflammation-based scores and TNM stage in patients with gastric cancer. *Onco Targets Ther*. 2015;8:1375–1385.
23. Torun S, Tunc BD, Suvak B, et al. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. *Clin Res Hepatol Gastroenterol*. 2012;36: 491–497.
24. Ahsen A, Ulu MS, Yuksel S, et al. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. *Inflammation*. 2013;36:1357–1362.
25. Keizman D, Ish-Shalom M, Huang P, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. *Eur J Cancer*. 2012;48:202–208.
26. Yoo EJ, Park JC, Kim EH, et al. Prognostic value of neutrophil-to-lymphocyte ratio in patients treated with concurrent chemoradiotherapy for locally advanced oesophageal cancer. *Dig Liver Dis*. 2014;46:846–853.
27. Kang MH, Go SI, Song HN, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. *Br J Cancer*. 2014;111:452–460.
28. Gaitanidis A, Patel D, Nilubol N, et al. Markers of systemic inflammatory response are prognostic factors in patients with pancreatic neuroendocrine tumors (PNETs): a prospective analysis. *Ann Surg Oncol*. 2018;25: 122–130.
29. Salman T, Kazaz SN, Varol U, et al. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for patients with neuroendocrine tumors: an Izmir Oncology Group study. *Chemotherapy*. 2016;61:281–286.
30. Lu A, Li H, Zheng Y, et al. Prognostic significance of neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio, and platelet to lymphocyte ratio in patients with nasopharyngeal carcinoma. *Biomed Res Int*. 2017;2017:3047802.
31. Basso S, Zecca M, Merli P, et al. T cell therapy for nasopharyngeal carcinoma. *J Cancer*. 2011;2:341–346.
32. Tecchio C, Scapini P, Pizzolo G, et al. On the cytokines produced by human neutrophils in tumors. *Semin Cancer Biol*. 2013;23:159–170.
33. Duong CP, Yong CS, Kershaw MH, et al. Cancer immunotherapy utilizing gene-modified T cells: from the bench to the clinic. *Mol Immunol*. 2015;67: 46–57.
34. Galdiero MR, Bonavita E, Barajon I, et al. Tumor associated macrophages and neutrophils in cancer. *Immunobiology*. 2013;218:1402–1410.
35. Lalani AA, Xie W, Martini DJ, et al. Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immunother Cancer*. 2018;6:5.
36. Cassidy MR, Wolchok RE, Zheng J, et al. Neutrophil to lymphocyte ratio is associated with outcome during ipilimumab treatment. *EBioMedicine*. 2017;18:56–61.