Systemic Markers of Inflammation in Neuroendocrine Tumors (NETs) & Outcomes With Everolimus: A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 & RADIANT-4 Trials

CLICK TO GO BACK TO KIOSK MENU

David Chan[1,2], James C Yao[3], Carlo Carnaghi[4], Roberto Buzzoni[5], Fabian Herbst[6], Antonia Ridolfi[7], Jonathan Strosberg[8], Matthew H Kulke[9], Marianne Pavel[10], Simron Singh[2]

[1]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Oncology Unit Ospedale di Bolzano, Bolzano, Italy; [5]Clinica San Carlo Paderno Dugnano; Milano, Italy; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharma S.A.S., Rueil-Malmaison, France; [8]Moffitt Cancer Center, Tampa, Florida, USA; [9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [10]University of Erlangen-Nuremberg, Erlangen, Germany

Introduction

- Neuroendocrine tumors (NETs) are extremely heterogeneous tumors with distinct biological behaviors based on the site of tumor origin and the rate of tumor proliferation.[1]
- Tumor-promoting inflammation is a hallmark of cancer and may contribute to shorter survival in cancer patients. Understanding the complexity of tumor biology and associated inflammatory markers may help to improve patient survival.[2]
- Several biomarkers have been proposed for patients with NETs, however, only a few are consistently used to predict prognosis and optimize treatment selection.[3]
- Neutrophil-to-lymphocyte (NLR) and lymphocyte-to-monocyte (LMR) ratios are markers of systemic inflammation, and are associated with prognosis in a variety of cancers.[4-6]
  - An elevated NLR and lower LMR (both reflective of higher baseline systemic inflammation) were correlated with a shorter overall survival in a variety of malignancies.[4,5,7,8]
  - However, there is mixed data to date in patients with NETs.
  - An exploratory analysis from CLARINET reported no significant association between NLR and progression-free survival (PFS) in patients with advanced intestinal and pancreatic NETs (panNET).[9]
- The objective of this pooled analysis was to assess the impact of baseline NLR and LMR on efficacy and safety related outcomes among patients with NETs.

Methods

Study Design and Patient Population

- RADIANT-3 and RADIANT-4 were international, multicenter, randomized, double-blind, placebo-controlled phase 3 studies.
  - In the RADIANT-3 trial, patients with advanced, low-, or intermediate grade panNET were randomized either to everolimus 10 mg/day (N = 207) or placebo (N = 203).
  - In the RADIANT-4 trial, patients with advanced, low-, or intermediate grade gastrointestinal (GI) or lung NETs were randomized either to everolimus 10 mg/day (N = 205) or placebo (N = 97).
  - In both studies, treatment was continued until disease progression, initiation of a new cancer therapy, development of an intolerable adverse event (AE), or withdrawal of consent.

Assessments

- PFS (defined as the time from the date of randomization to the date of first documented radiological progression or death due to any cause) was reported as per the central radiology review.
- 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.
- AEs were coded using the Medical Dictionary for Regulatory Activities version 17.1 for both the studies. AEs were graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).
- NLR/LMR at baseline were calculated and then dichotomized (high/low) based on median values.

Statistical Analysis

- The median PFS (95% CI) was estimated using the Kaplan-Meier methods. Hazard ratios (HRs) and confidence intervals (CIs) were calculated using unstratified Cox regression model.
- Forest plots are used to display HR by subgroups.
- The Full Analysis Set (FAS) consists of all patients who were randomized. Patients in the FAS who had valid laboratory values at baseline were used for the efficacy analyses presented.
- Patients were stratified based on their high and low baseline NLR and LMR. High NLR is defined as ≥ 2.577381 (median value for everolimus patients); high LMR is defined as ≥ 3.758621 (median value for everolimus patients).

Results

Progression-Free Survival

- In the pooled analysis, the median PFS in the everolimus arm was consistent with the median PFSs of individual RADIANT-3 and RADIANT-4 trials.
  - A total of 712 (RADIANT-3, n = 410; RADIANT-4, n = 302) patients were pooled from RADIANT-3 and RADIANT-4 studies. Patients with valid baseline laboratory values were considered (N = 705 overall; N = 407 everolimus).
    - The pooled median PFS (95% CI) with everolimus was 11.37 months (11.01–13.93); 13.67 months (11.17–18.79) in RADIANT-3, and 11.01 months (9.23–13.31) in RADIANT-4 trials.

Systemic Markers of Inflammation in Neuroendocrine Tumors (NETs) & Outcomes With Everolimus: A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 & RADIANT-4 Trials

David Chan[1,2], James C Yao[3], Carlo Carnaghi[4], Roberto Buzzoni[5], Fabian Herbst[6], Antonia Ridolfi[7], Jonathan Strosberg[8], Matthew H Kulke[9], Marianne Pavel[10], Simron Singh[2]

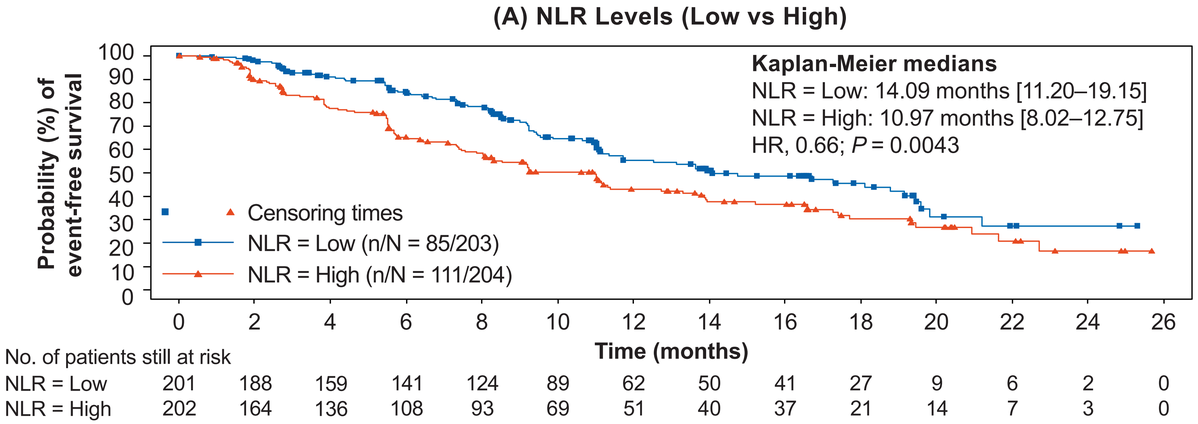
[1]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Oncology Unit Ospedale di Bolzano, Bolzano, Italy; [5]Clinica San Carlo Paderno Dugnano; Milano, Italy; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharma S.A.S., Rueil-Malmaison, France; [8]Moffitt Cancer Center, Tampa, Florida, USA; [9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [10]University of Erlangen-Nuremberg, Erlangen, Germany

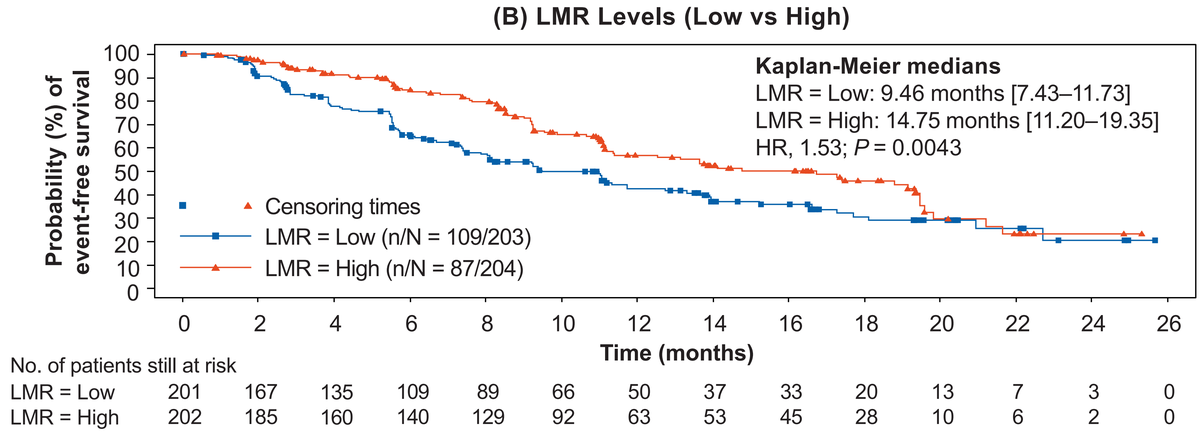
Results (Contd.)

Inflammatory Markers Response at Baseline by NLR and LMR Groups

- Everolimus-treated patients with high NLR had shorter PFS than patients with low NLR; median PFS (95% CI: 11.0 months [8.0–12.7] vs 14.1 months [11.2–19.2]; HR, 0.66, P = 0.0043; **Figure 1A** and **Figure 2)**.
- Everolimus-treated patients with low LMR had shorter PFS than patients with high LMR; median PFS (95% CI: 9.5 months [7.4–11.7]); HR, 1.53, P = 0.0043 vs 14.8 months [11.2–19.4]; **Figure 1B** and **Figure 3**).
- In the overall population, patients with high NLR had shorter PFS than patients with low NLR; median PFS (8.1 months [6.3 months – 9.2 months]) vs 10.8 months [9.2 months – 11.7 months], HR 0.75, P = 0.0060).
- In the overall population, patients with low LMR had shorter PFS than patients with high LMR; median PFS (7.4 months [5.8 months – 8.5 months] vs 11.1 months [9.3 months – 13.7 months]), HR 1.46, P < 0.001).

Figure 1. Kaplan-Meier Plots of PFS (Central Review) in Everolimus-Treated Patients by Baseline (A) NLR and (B) LMR Levels (Low vs High)





LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

Inflammatory Markers Response by Primary Tumor Origin

- In patients with primary GI NETs, low NLR (16.7 months vs 11.2 months) and high LMR (16.7 months vs 11.1 months) were associated with prolonged PFS vs patients with high NLR and low LMR.
- In patients with primary panNET, low NLR (19.2 months vs 8.3 months) and high LMR (18.8 months vs 9.4 months) were associated with prolonged PFS vs patients with high NLR and low LMR.
  - In the lung subgroup there was no trend observed, possibly due to the small number of patients in the group.
- The benefit of everolimus was preserved in patients regardless of baseline inflammation status.
- The impact of systemic inflammation on treatment outcomes appeared consistent across the subgroups in patients treated with everolimus.

Systemic Markers of Inflammation in Neuroendocrine Tumors (NETs) & Outcomes With Everolimus: A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 & RADIANT-4 Trials

David Chan[1,2], James C Yao[3], Carlo Carnaghi[4], Roberto Buzzoni[5], Fabian Herbst[6], Antonia Ridolfi[7], Jonathan Strosberg[8], Matthew H Kulke[9], Marianne Pavel[10], Simron Singh[2]

[1]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Oncology Unit Ospedale di Bolzano, Bolzano, Italy; [5]Clinica San Carlo Paderno Dugnano; Milano, Italy; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharma S.A.S., Rueil-Malmaison, France; [8]Moffitt Cancer Center, Tampa, Florida, USA; [9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [10]University of Erlangen-Nuremberg, Erlangen, Germany

Results (Contd.)

Figure 2. Forest Plot of Hazard Ratio (NLR High vs Low) With 95% CI for PFS in Everolimus-Treated Patients

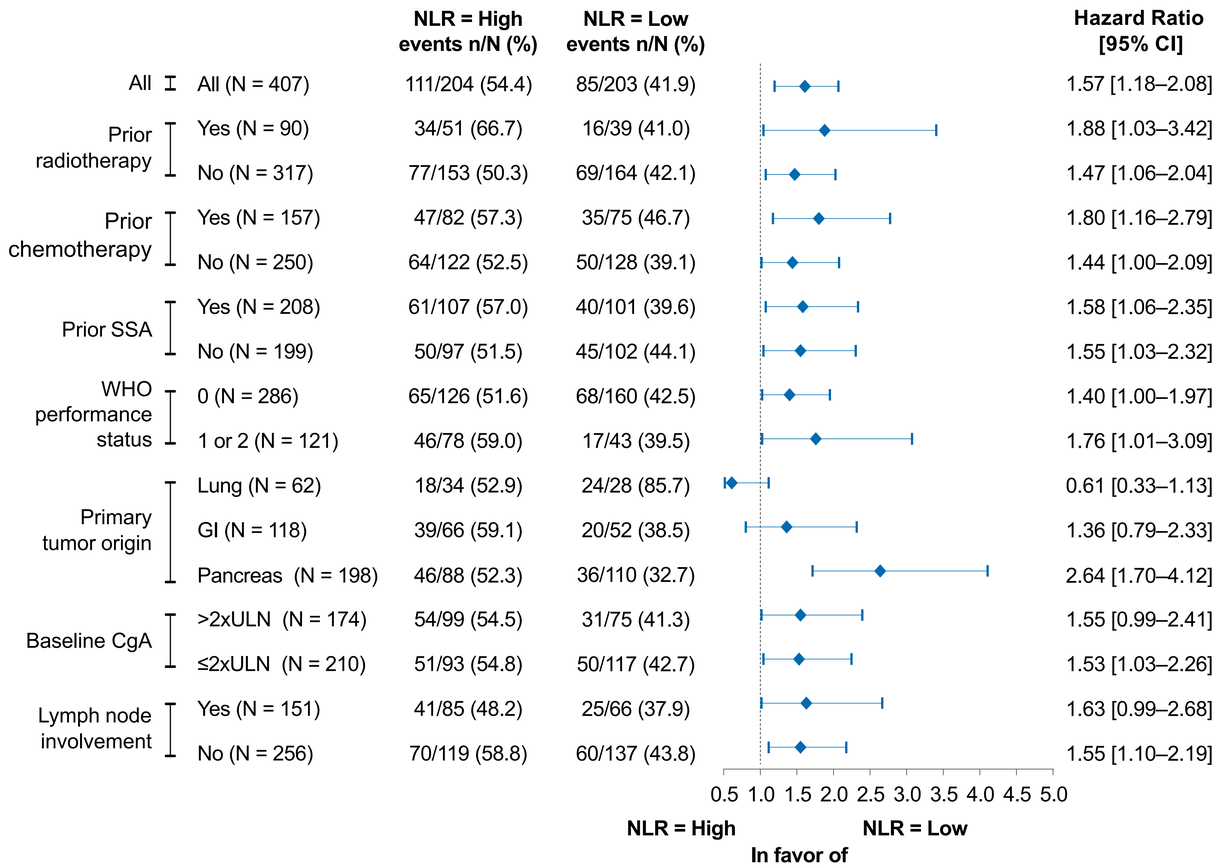
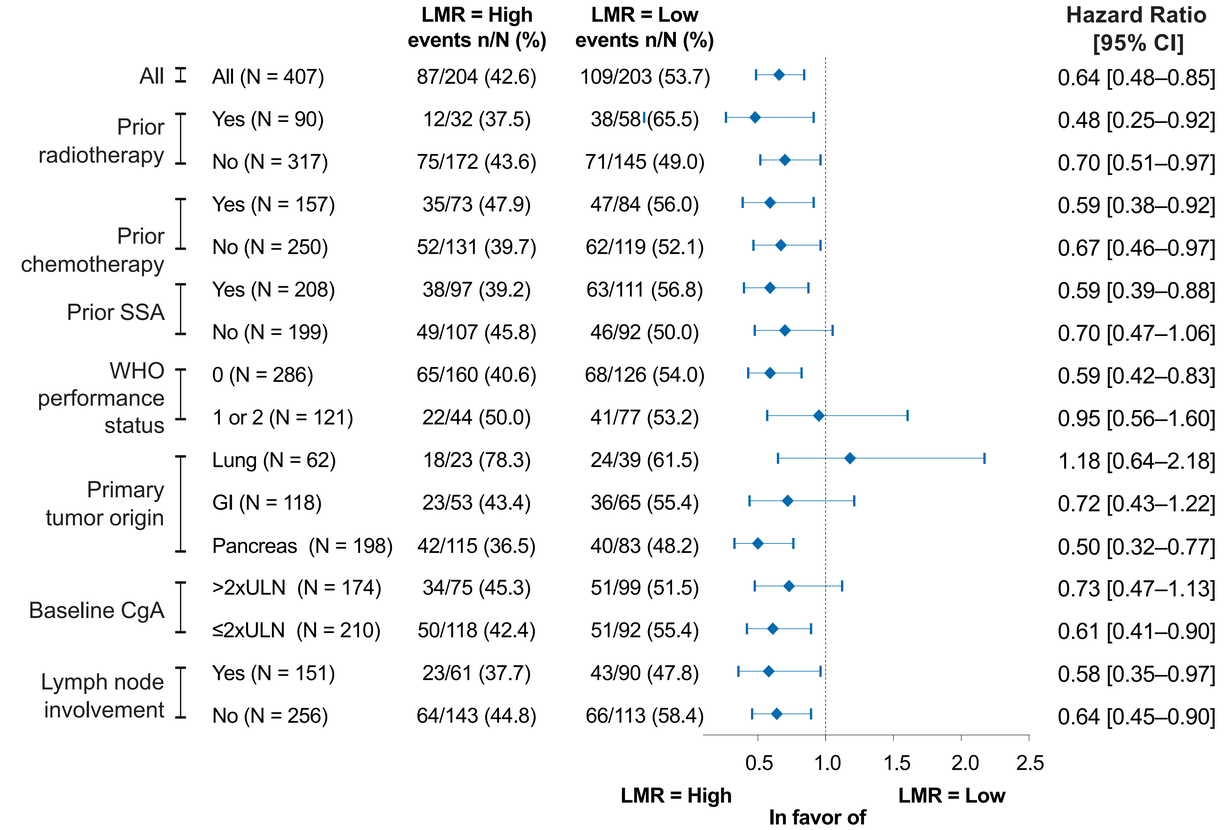


Figure 3. Forest Plot of Hazard Ratio (LMR High vs Low) With 95% CI for PFS in Everolimus-Treated Patients



Prior SSA, tumor origin, WHO performance status are as reported in IRT system; In primary tumor origin category: Appendix, cecum, colon, duodenum, jejunum, ileum, rectum and stomach are grouped as GI category; Lymph node is any lymph node/lymphatic system involvement. CgA, chromogranin; CI, confidence interval; GI, gastrointestinal; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; SSA, somatostatin analog; ULN, upper limit of normal; WHO, world health organization.

Systemic Markers of Inflammation in Neuroendocrine Tumors (NETs) & Outcomes With Everolimus: A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 & RADIANT-4 Trials

David Chan[1,2], James C Yao[3], Carlo Carnaghi[4], Roberto Buzzoni[5], Fabian Herbst[6], Antonia Ridolfi[7], Jonathan Strosberg[8], Matthew H Kulke[9], Marianne Pavel[10], Simron Singh[2]

[1]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Oncology Unit Ospedale di Bolzano, Bolzano, Italy; [5]Clinica San Carlo Paderno Dugnano; Milano, Italy; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharma S.A.S., Rueil-Malmaison, France; [8]Moffitt Cancer Center, Tampa, Florida, USA; [9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [10]University of Erlangen-Nuremberg, Erlangen, Germany

Results (Contd.)

Safety

- The safety of everolimus vs placebo in this pooled analysis were consistent with the safety of individual RADIANT-3 and RADIANT-4 studies. No new safety signals were highlighted with patients reporting mainly grade 1 or 2 AEs (regardless of study drug) such as diarrhea, stomatitis, fatigue, nausea, and rash; **Table 1 and Table 2**).

Table 1. Safety outcomes in high NLR vs low NLR (pooled-overall, everolimus and placebo populations; incidence >20%)

	Overall Population				Everolimus Population				Placebo Population			
	NLR (High) N = 351		NLR (Low) N = 351		NLR (High) N = 202		NLR (Low) N = 201		NLR (High) N = 202		NLR (Low) N = 201	
Preferred Term	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)
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
Oedema 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)	NA	NA	NA	NA	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	90 (25.6)	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)
Dyspnoea	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)
Anaemia	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)

Table 2. Safety outcomes in high LMR vs low LMR (pooled-overall, everolimus and placebo populations; incidence >20%)

	Overall Population				Everolimus Population				Placebo Population			
	LMR (High) N = 351		LMR (Low) N = 351		LMR (High) N = 202		LMR (Low) N = 201		LMR (High) N = 202		LMR (Low) N = 201	
Preferred Term	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)
Stomatitis	166 (47.3)	9 (2.6)	159 (45.3)	20 (5.7)	114 (56.4)	11 (5.4)	107 (53.2)	15 (7.5)	53 (35.3)	53 (35.3)	51 (34.2)	3 (2.0)
Fatigue	147 (41.9)	13 (3.7)	134 (38.2)	17 (4.8)	81 (40.1)	8 (4.0)	85 (42.3)	11 (5.5)	64 (42.7)	64 (42.7)	51 (34.2)	6 (4.0)
Rash	141 (40.2)	1 (0.3)	125 (35.6)	3 (0.9)	92 (45.5)	0	75 (37.3)	2 (1.0)	52 (34.7)	52 (34.7)	47 (31.5)	1 (0.7)
Diarrhea	133 (37.9)	18 (5.1)	167 (47.6)	25 (7.1)	80 (39.6)	16 (7.9)	102 (50.7)	15 (7.5)	54 (36.0)	54 (36.0)	64 (43.0)	10 (6.7)
Nausea	115 (32.8)	8 (2.3)	121 (34.5)	11 (3.1)	53 (26.2)	5 (2.5)	70 (34.8)	6 (3.0)	58 (38.7)	58 (38.7)	55 (36.9)	5 (3.4)
Oedema peripheral	101 (28.8)	6 (1.7)	107 (30.5)	6 (1.7)	75 (37.1)	4 (2.0)	79 (39.3)	5 (2.5)	27 (18.0)	2 (1.3)	27 (18.1)	1 (0.7)
Abdominal pain	99 (28.2)	21 (6.0)	85 (24.2)	23 (6.6)	47 (23.3)	11 (5.4)	43 (21.4)	6 (3.0)	50 (33.3)	50 (33.3)	44 (29.5)	17 (11.4)
Pyrexia	97 (27.6)	2 (0.6)	87 (24.8)	6 (1.7)	62 (30.7)	1 (0.5)	54 (26.9)	5 (2.5)	35 (23.3)	0	33 (22.1)	2 (1.3)
Decreased appetite	96 (27.4)	10 (2.8)	104 (29.6)	8 (2.3)	48 (23.8)	1 (0.5)	64 (31.8)	4 (2.0)	48 (32.0)	48 (32.0)	40 (26.8)	4 (2.7)
Headache	96 (27.4)	3 (0.9)	62 (17.7)	4 (1.1)	58 (28.7)	1 (0.5)	30 (14.9)	1 (0.5)	38 (25.3)	38 (25.3)	32 (21.5)	3 (2.0)
Vomiting	89 (25.4)	9 (2.6)	87 (24.8)	12 (3.4)	44 (21.8)	5 (2.5)	48 (23.9)	4 (2.0)	42 (28.0)	42 (28.0)	42 (28.2)	8 (5.4)
Weight decreased	87 (24.8)	2 (0.6)	90 (25.6)	6 (1.7)	47 (23.3)	0	59 (29.4)	4 (2.0)	39 (26.0)	39 (26.0)	32 (21.5)	3 (2.0)
Cough	81 (23.1)	0	93 (26.5)	1 (0.3)	52 (25.7)	0	56 (27.9)	1 (0.5)	30 (20.0)	0	36 (24.2)	0
Pruritus	79 (22.5)	0	55 (15.7)	0	43 (21.3)	0	30 (14.9)	0	36 (24.0)	36 (24.0)	25 (16.8)	0
Hyperglycaemia	72 (20.5)	29 (8.3)	49 (14.0)	17 (4.8)	43 (21.3)	18 (8.9)	21 (10.4)	8 (4.0)	31 (20.7)	13 (8.7)	26 (17.4)	7 (4.7)
Anaemia	72 (20.5)	25 (7.1)	68 (19.4)	18 (5.1)	47 (23.3)	16 (7.9)	44 (21.9)	12 (6.0)	26 (17.3)	9 (6.0)	23 (15.4)	6 (4.0)

Systemic Markers of Inflammation in Neuroendocrine Tumors (NETs) & Outcomes With Everolimus: A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 & RADIANT-4 Trials

David Chan[1,2], James C Yao[3], Carlo Carnaghi[4], Roberto Buzzoni[5], Fabian Herbst[6], Antonia Ridolfi[7], Jonathan Strosberg[8], Matthew H Kulke[9], Marianne Pavel[10], Simron Singh[2]

[1]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Oncology Unit Ospedale di Bolzano, Bolzano, Italy; [5]Clinica San Carlo Paderno Dugnano; Milano, Italy; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharma S.A.S., Rueil-Malmaison, France; [8]Moffitt Cancer Center, Tampa, Florida, USA; [9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [10]University of Erlangen-Nuremberg, Erlangen, Germany

Conclusions

- **Low baseline NLR and high LMR correlate with improved PFS outcomes among pooled everolimus patients including patients with NETs of GI or pancreatic origin. These effects remain consistent among patients in the pooled overall population.**
  - **No such association was observed among patients with lung NETs. However, this subgroup analysis should be interpreted with caution due to lower number of patients.**
- **Safety events did not differ significantly across the high vs low subgroups of NLR and LMR.**
- **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.**
- **These findings and their role should be further validated with prospective biomarker studies.**

References

1. Hallet J, et al. *Cancer* 2015; 121:589–97.
2. Diakos CI, et al. *Lancet Oncol* 2014; 15:493–503.
3. Sorbye H, et al. *Ann Oncol* 2013; 24:152–160.
4. Huang C, et al. *Ann Oncol* 2017; 28:mdx261.122–mdx261.122.
5. Zhou B, et al. *Med Sci Monit* 2017; 23:5574–88.
6. Imtiaz F, et al. *Int Arch Med* 2012; 5:2.
7. Templeton AJ, et al. *J Natl Cancer Inst* 2014; 106.
8. Chan JC, et al. *Ann Surg* 2017; 265:539–46.
9. Grenader T, et al. Poster presented at ECC 2015, Vienna, Austria, Sept 25–29, 2015.

Disclosures

DC reports personal fee and non-financial support from Novartis, outside the submitted work. JCY reports grants from NCI, during the conduct of this study. JS reports personal fee from Novartis. MP reports grants and personal fee from Novartis and Ipsen, and personal fee from Pfizer, and Lexicon. SS reports honoraria and travel funding from Ipsen, Pfizer and Novartis, and research funding from EMD Serono and Novartis. MHK, CC, and RB has nothing to disclose. FH and AR are employees of Novartis.

Presented at NANETS Annual Multidisciplinary NET Disease Symposium, Seattle, Washington; 4-6 October 2018

Efficacy analysis was previously presented at 15th Annual ENETS Conference, Barcelona, Spain; 7-9 March 2018

Acknowledgments

The study was sponsored by Novartis Pharmaceuticals Corporation. We thank the patients, caregivers and investigators for their participation in the study; we also thank the worldwide network of research nurses, trial coordinators, and operations staff for their contributions. In addition, we would like to thank Charu Pundir of Novartis Healthcare Pvt Ltd for the medical editorial assistance with this poster.

Text: Q57de2
To: 8NOVA (86682) US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe and Russia
+46737494608 Sweden, Europe

Visit the web at:
http://novartis.medicalcongressposters.com/Default.aspx?doc=57de2

Scan this QR code

Corresponding author:
dlhchan1@gmail.com