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Prognostic significance of neutrophil/lymphocyte ratio in patients undergoing treatment with nivolumab for recurrent Non-Small Cell Lung Cancer.

B.L. Rapoport [1,2], D.A. Vorobiof [3], L. Langenhoven [3], J.M. Hall [5], R.I. Van Eeden [1], T. Smit [1], S.W. Chan [6], M.C. Botha [7], J.I. Raats [5,8] M. De Necker [9], H. Duvenhage [10]

[1] The Medical Oncology Centre of Rosebank, Johannesburg, ZA, [2] Department of Immunology, Faculty of Health Sciences, University of Pretoria, ZA, [3] Belong, Belong, Bnei Atarot, IL, [4] Tygerberg Hospital, Cape Town, ZA, [5] Vincent Pallotti Hospital, Cape Town, ZA, [6] Medical Oncology, Sandton Oncology, Sandton, ZA

[7] GVI Oncology-Outeniqua Oncology, George, ZA, [8] Christiaan Barnard Memorial Hospital, Cape Town, ZA, [9] TCD Outcomes Research, Pretoria, ZA, [10] Bristol-Myers Squibb (Pty) Ltd, Woodmead, ZA

Background

Non Small Cell Lung Cancer

- Lung cancer is the leading cause of cancer death with only 17.4% 5-year survival[1].
- In 2015, an estimated number of 221,200 new cases were diagnosed and 158,040 deaths occurred[2].
- Approximately 85% of lung cancers can be classified as non-small cell lung cancer (NSCLC), divided into two major groups by histology: squamous and non-squamous.
- Half of patients have already distant metastatic disease at diagnosis with a 5-year survival rate of less than 5%.
- The use of chemotherapy has produced objective responses and small improvement in survival for patients with metastatic disease[3].
- For patients who have relapsed after platinum-based chemotherapy, second-line therapy can be considered.
- A meta-analysis of five trials assessing the efficacy and safety of chemotherapy reported a survival of approximately 26 weeks. Additionally, chemotherapy was associated with severe toxicity[4-5].
- Prior to the availability of checkpoint inhibitors the treatment of progressive metastatic NSCLC represented a considerable unmet medical need.
- Nivolumab is a fully human IgG4 monoclonal antibody that binds to and blocks the activation of PD-1 by its ligand.
- Nivolumab was initially approved in March 2015 for advanced squamous NSCLC based on improvement of overall survival (OS) in an open-label, multicenter, randomized phase III trial (CheckMate 017) (overall survival nivolumab 9.2 vs docetaxel 6 months)[6].
- Approval of nivolumab for advanced non-squamous NSCLC was issued in October 2015, based on demonstration of improvement in OS in an international, multicenter, open-label phase III clinical trial (CheckMate 057) (nivolumab 12.2 months vs docetaxel 9.4 months)[7].

NLR:

- The neutrophil–lymphocyte ratio (NLR), a measure of the proportion of systemic neutrophils and lymphocytes, has been proposed as an indicator of cancer-related inflammation, and has been shown to have prognostic relevance across a large variety of tumour types. [8]
- The NLR was defined as the quotient of baseline absolute peripheral neutrophil count (cells/mm^3) by absolute peripheral baseline lymphocyte count (cells/mm^3). [8]

Methods

- A retrospective, multi-center, non-interventional analysis was performed on data collected from the nivolumab expanded access programme in South Africa (SA-EAP).
- The study investigated clinical outcomes and toxicity associated with nivolumab in patients with relapsed metastatic NSCLC.
- Each patient signed informed consent and institutional ethics approval was obtained from the Human Sciences Research Council (HSRC) of South Africa.

Patient Population

Inclusion Criteria

- The patient had histologically- or cytologically-documented locally advanced squamous or non-squamous NSCLC.
- Patients progressed on or after treatment with a minimum of 1 prior systemic treatment for stage IIIB or stage IV disease following multimodal therapy.
- Aged ≥ 18 years of age.
- ECOG performance status of ≤ 2.
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue had resolved to Grade 1(NCI CTCAE v4.0) or baseline.
- Patients signed informed consent.

Exclusion Criteria

- Active, known or suspected autoimmune disease, HIV, Hepatitis B or C.
- Symptomatic brain metastases.
- Received other concurrent systemic anti-cancer treatments for NSCLC.
- Life expectancy of less than 6 weeks.
- The patient had previously participated in, or is eligible for an accessible, nivolumab clinical study.
- The patient had received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2, anti CT137 or any other antibody and other T-cell co-stimulation or checkpoint pathways.
- The patient had a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of administration of nivolumab.
- The patient had any known active chronic liver disease.
- The patient had previous malignancies unless a complete remission was achieved at least 3 years prior to administration of nivolumab.
- The patient had a known medical condition (e.g. a condition associated with diarrhea or acute diverticulitis).
- The patient had not recovered from major surgery.
- The patient had a history of severe hypersensitivity reactions to other monoclonal antibodies.

Statistical Analysis

- The collected data was statistically analyzed using descriptive statistics, with medians and ranges of continuous variables and frequencies and percentages for categorical variables.
- Progression free survival (PFS) and overall survival (OS) was estimated using the Kaplan-Meier method, with 95% CIs reported. PFS and OS were analyzed using time from nivolumab initiation date and date of most recent visit or date of progression/death, whichever occurred first.
- NLR cut-off value of ≥ 5 was calculated using the receiving operating characteristic (ROC) curves.

Results

- The median age of 65 (46-86 years).
- The median number of nivolumab treatment cycles was 10 (1-36 cycles).

Table 1. Patient Characteristics.

Patient Characteristics (n=56)	
Gender	
Male	32 (57%)
Female	24 (43%)
Race	
Black	2 (4%)
Coloured	7 (12%)
Indian	2 (4%)
White	45 (80%)
Smoking Status	
Current	13 (23%)
Former	29 (52%)
Never	15 (25%)
ECOG	
0	6 (11%)
1	44 (79%)
2	6 (11%)
Metastatic sites	
Brain	
Yes	6 (11%)
No	50 (89%)
Lung	
Yes	44 (79%)
No	12 (21%)
Liver	
Yes	3 (5%)
No	53 (95%)
Bone	
Yes	16 (29%)
No	40 (71%)
Skin	
Yes	2 (4%)
No	54 (96%)
Lymph nodes	
Yes	40 (71%)
No	16 (29%)
Other	
Yes	10 (18%)
No	46 (82%)

Table 2. Response.

Responses		
Response	Number of Responses	Percentage (95% CI)
CR	2	4% (0-8%)
PR	11	20% (9-30%)
SD	18	32% (20-44%)
PD	22	39% (26-52%)
NE	3	5% (0-11%)

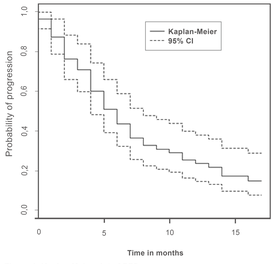


Figure 1: Kaplan-Meier plot of PFS.

Table 3. Progression Free Survival.

Progression Free Survival	
Median PFS	6 months (4-8 months)
One year PFS	25% (14-36%) N [% (95% CI)]

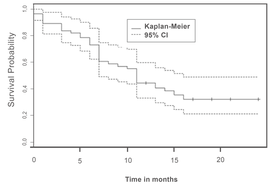


Figure 2: Kaplan-Meier plot of OS.

Table 4. Overall Survival.

Overall Survival	
Median overall survival	11 months (7-16 months)
Survival Rates of 1 year	45% (32-58%) N [% (95% CI)]
Survival Rates of 2 years	32% (20-45%) N [% (95% CI)]

Toxicities

Table 5. Toxicities.

Toxicities						
Toxicity	n	Grade				
		1	2	3	4	5
Respiratory						
Pulmonary Embolism	3			1	1	1
Pneumonitis	6	1	1	2	1	1
Endocrine						
Addison's	1		1			
Hyperthyroid	2	1	1			
Hypophysitis	2		1	1		
Neuromuscular						
Arthralgia	2	2				
Skin						
Erythema Multiform	1		1			
Rash	7	7				
Vitiligo	2	1	1			
Ocular						
Xerostomia	3	3				
Sjögren's Syndrome	1		1			
Renal						
Increased Creatinine	1	1				
Nephritis	1		1			
Hepatic						
Increased Liver Enzymes	6	2	2	2		
Gastro-Intestinal						
Colitis	13	6	6		1	
Other						
Mucositis	1	1				
Fatigue	9	6	3			
Autoimmune Thrombocytopenia	1				1	
Posterior Reversible Encephalopathy Syndrome (PRES)	1		2			

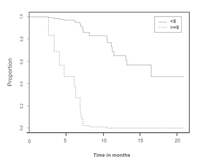
NLR

- Pre-treatment NLR was tested for association with the same outcomes using landmark survival analyses and time dependent Cox regression models.
- NLR was categorized as NLR < 5 or NRL ≥ 5.
- Univariate analysis tested the association of NLR to Progression Free Survival and Overall Survival.

Association of NLR on Overall Survival

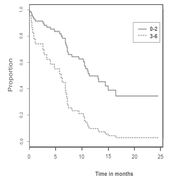
- Median OS NLR ≥ 5 consistently at 3, 5 and 9 weeks= 4.72 months
- Median OS NLR < 5 consistently at 3, 5 and 9 weeks = 16.5 months
- Logrank = 23.92 (p=000008)
- Hazard Ratio 0.3489 (95% CI 0.1705-0.7137) P= 0.00393

Univariate analysis



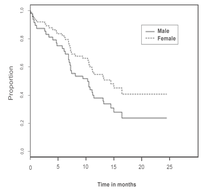
Median OS
NLR <5 = 14.5 months vs. **NLR** ≥5 = 7.02 months
Logrank test = 9.04,p=0.002635

Figure 3: NLR <5 and NLR >=5: Kaplan-Meier plot of overall survival (OS).



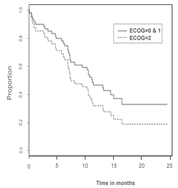
Median OS
Metastatic Sites 0 to 2 = 11.4 months vs. 3 to 6 = 6.1 months.
Logrank test = 6.33, p=0.01185

Figure 4: Metastatic sites 0-2 vs. 3-6 Kaplan-Meier plot of overall survival (OS).



Median OS
Male 10.3 months vs. Female 14.5 months
Logrank test = 1.86, p=0.1726

Figure 5: Male vs. Female Kaplan-Meier plot of overall survival (OS).



Median OS
ECOG 0-1 = 11.21 months vs. ECOG 2 = 7.44 months
Logrank test = 0.73, p=0.3943

Figure 6: ECOG 0-1 vs. ECOG 2 Kaplan-Meier plot of overall survival (OS).

Multivariate Cox-Regression Analysis

Table 6. Multivariate Cox-Regression Analysis.

Variable	Hazard Ratio	p-Value
Baseline NLR (<5 = 0; ≥5 = 1)	**2,3209**	**0,0447**
Gender	0,7162	0,3776
ECOG (0&1= 0; 2 = 1)	1,7101	0,2847
Number of Metastatic Sites (0-2 = 0; 3-6 = 1)	2,3183	0,1338

On Cox proportional hazard model NLR at baseline was the only variable associated with improvement in OS.

Conclusions

- Our study found that in pretreated patients with recurrent metastatic NSCLC, the efficacy and tolerability of nivolumab at 3mg/kg aligned with the data in numerous published studies. The patient populations, outcomes and toxicities were similar.
- Elevated NLR is associated with a poor outcome in patients with recurrent metastatic NSCLC treated with nivolumab.

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Corresponding author: brapoport@rosebankoncology.co.za