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Prognostic Factors of Nintedanib-docetaxel in Patients with Previously Treated Non-small-cell Lung Cancer

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Abstract

Background: In advanced non-small-cell lung cancer (NSCLC), second-line treatment with nintedanib plus docetaxel improves survival compared with docetaxel, especially in patients with adenocarcinoma histology who progressed within 9 months after the start of first-line treatment. It is therefore necessary to identify new biomarkers/prognostic factors that select the patients who benefit from this type of treatment.

Patients and Methods: In this single-center retrospective study, we included patients treated NSCLC with nintedanib plus docetaxel in the second/third line and analyzed potential prognostic factors, many of them related to the inflammatory environment; PD-L1 expression levels, Lung Immune Prognostic Index (LIPI), derived neutrophil/lymphocytes ratio (dNLR), etc.

Results: Among 16 patients included in this analysis, the overall response rate was 12.5%, median progression-free survival was 2 months (95% CI, 1.22-2.78) and median overall survival was 6 months (95% CI, 2.11-9.89). LDH level is the only variable related to the disease control rate (70% in normal versus 0% in elevated LDH). The variables analyzed with prognostic significance were; no brain metastases (HR 0.33, 95% CI 0.14-0.78; p=0.011), less than 3 metastatic sites (HR 0.33, 95% CI 0.14-0.78; p=0.011), the non-use of antiangiogenic drugs in the first line (HR 0.53, 95% CI: 0.29-0.98; p=0.043), the absence of elevated LDH at the start of treatment (HR 0.55, 95% CI: 0.3-1; p=0.051) and the absence of liver metastases (HR 0.55, 95% CI: 0.29-1; p=0.05).

Conclusions: In NSCLC patients with less than three metastatic sites, no brain or liver metastases, normal LDH values and not previously treated with antiangiogenic drugs in the first line showed a better prognosis when treated with second/third line with nintedanib plus docetaxel.

Keywords: Biomarkers, Nintedanib, Lung Immune Prognostic Index (LIPI), Derived neutrophil to lymphocyte ratio (dNLR), Platelet-to-Lymphocyte Ratio (PLR), Lactate dehydrogenase (LDH), Non-small cell lung cancer (NSCLC)

Introduction

The leading cause of cancer death worldwide is lung cancer [1]. In 2020, a total of 19 million cancer patients were diagnosed, of which 11.4% were lung cancer, causing 18% of all cancer deaths [2]. In 2023 in Spain, 31.282 cases were estimated [3].

The emergence of programmed death pathway-1 (PD-1) inhibitors in the first-line treatment of advanced non-small cell

lung cancer (NSCLC) has revolutionized patient management, with a significant increase in progression-free survival (PFS) and overall survival (OS) of patients [4-8]. Nevertheless, the majority of patients experience progression within less than 8-10 months after the initiation of first line. About 70% of patients initially achieve clinical remission or disease stabilization with first-line platinum-containing therapy, nearly all have disease progression and need second-line therapy [9,10].

However, limited clinical data are available to help guide treatment decisions after immunotherapy (IO) failure, as the currently available options were originally approved in the post-chemotherapy setting before the widespread inclusion of IO in treatment algorithms [11-14]. Docetaxel, pemetrexed, docetaxel-nintedanib OR docetaxel-ramucirumab should be highlighted as options.

Nintedanib is an oral tyrosine kinase inhibitor (TKI) that targets the vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGRF) 1-3, and platelet-derived growth factor receptors α and β. Preclinical studies with nintedanib have shown sustained (>30 h) blockade of VEGFR2 *in vitro*, and delay or arrest of tumor growth in xenograft models of human solid tumors [15]. In phase 1/2 clinical trials, nintedanib showed a manageable safety profile and antitumor activity in patients with solid tumors, including NSCLC [16,17].

The LUME-Lung 1 trial (NCT00805194) showed that the combination of nintedanib plus docetaxel was an effective second-line therapy in patients with advanced lung adenocarcinoma [18]. Additionally, efficacy of nintedanib and docetaxel has also been observed in patients after first-line chemotherapy and second-line IO [19]. Therefore, it is one of the second-line treatment options in patients with advanced NSCLC [20,21]. In the Europe Union, nintedanib is approved in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic, or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy [22].

Programmed cell death ligand 1 (PD-L1) is to date the prognostic and predictive biomarker with the greatest potential for the selection of NSCLC patients treated with IT. Other parameters have shown their usefulness in trying to detect those patients who could benefit the most from IO [23]. Whether these same factors or others (such as the Lung Immune Prognostic Index (LIPI), derived neutrophil to lymphocyte ratio (dNLR), Platelet-to-Lymphocyte Ratio (PLR), etc...) could be useful in the context of treatment with nintedanib plus docetaxel in previously treated NSCLC patients is unknown. To date, there are no studies that analyze potential predictors of response in this context, especially after first-line treatment with IO or chemo-IO.

Here, we present a retrospective, real-world analysis of potential prognostic factors of nintedanib-docetaxel therapy in pre-treated patients with advanced NSCLC.

Patients and Methods

Study population

We retrospectively analyzed data from patients with advanced NSCLC treated with nintedanib plus docetaxel in the second/third line in the period between June 2016 and February 2023 in the Hospital Universitario de Torrejón (Madrid, Spain). Patients were included if they had given their consent to institutional review board-approved medical record review protocols at the institution and had advanced NSCLC previously treated and negative for genomic alterations in the epidermal growth factor receptor (*EGFR*), ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (*ROS1*) and anaplastic lymphoma kinase (*ALK*) genes.

The inclusion criteria were: 1) patients over 18 years of age; 2) a diagnosis of advanced NSCLC treated with nintedanib plus docetaxel in the second/third line; 3) Karnofsky performance status score ≥ 50 or ECOG performance status score <3 and outpatients at study entry; 4) patient's signed informed consent.

The exclusion criteria were those described as contraindication in the summary of product characteristics of docetaxel and nintedanib and patients with cognitive impairment or uncooperative.

Clinical outcomes

The overall response rate (ORR) and PFS were determined by radiologists using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS was defined as the time from the start of nintedanib-docetaxel to the date of disease progression or death. Patients who were alive without disease progression were censored on the date of their last disease assessment. OS was defined as the time from the start of treatment to death. Patients who were still alive at the time of data analysis were censored at the date of last contact.

Biomarkers assessment

EGFR mutation testing was done on fresh or paraffin-embedded tumor samples by Polymerase Chain Reaction (PCR) based direct sequencing. *ALK* status is determined by means of the Ventana *ALK* (D5F3) CDx immunohistochemical assay and *ROS1* rearrangement using break-apart fluorescence in situ hybridization (FISH).

PD-L1 expression was assessed in formalin-fixed tumor samples at a central laboratory with the use of a rabbit anti-human PD-L1 antibody (clone 28–8; Epitomics Inc, Burlingame, CA). Tumor samples were obtained by core-needle or excisional biopsy or from tissue resected at the time the metastatic disease was diagnosed. We used the

tumor proportion score (TPS). This score is the number of PD-L1 positive tumor cells, divided by all tumor cells, and then multiplied by 100. Predefined expression levels were defined by TPS ≥ 50%.

dNLR, LIPI, LDH and PLR analysis

Complete blood cell counts and lactate dehydrogenase (LDH) levels at baseline before nintedanib plus docetaxel treatment (within 5-7 days before the first treatment) were extracted from electronic medical records. dNLR was calculated by division of absolute neutrophil and lymphocyte counts measured in peripheral blood before start treatment. PLR was calculated by division of thrombocytes and lymphocytes accordingly.

LIPI was developed on the basis of dNLR greater than 3 and LDH greater than upper limit of normal (ULN), characterizing 3 groups (good, 0 factors; intermediate, 1 factor; poor, 2 factors). The LIPI analysis was also performed, dividing it into 2 categories (good-intermediate versus poor). The cutoff for dNLR was greater than 3 (according to the cutoff from the largest published study with immune checkpoints inhibitors (ICIs) in patients with cancer [24]), and the ULN for LDH was defined according to the limit of our center (423 UI/L).

Statistical analysis

The software IBPM SPSS statistics version 26 was used for statistical analyses. Frequency tables, chi-squared tests, and two-sided Fisher`s tests were carried out at first place to correlate categorical data. Survival analyses were performed using the Kaplan-Meier method and the log-rank test. All P-values are 2-sided and CIs are at the 95% level, with significance pre-defined to be at the 0.05 level. Association between prognostic factors and survival outcomes were modelled using Cox proportional hazards regression. The association between different variables was calculated by logistic regression.

The study was conducted in accordance with Occupational Safety and Health Administration's (OSHA's) standard rules.

Results

Patients and tumor characteristics

Sixteen patients were included. Patients and tumor characteristics are summarized in **Table 1**. All patients had adenocarcinoma histology (100%) and were former (43.8%) or current smokers (43.8%) with only a minority of never smokers (12.4%). Fourteen patients (81.3%) were Eastern Cooperative Oncology Group-Performance status (ECOG-PS) < 2 and 3 patients (18.7%) were 2. Liver was the most common metastatic site (43.8%), followed by central nervous system (31.2%) and bone (25%). All patients were *EGFR, ALK,* and *ROS-1* wild-type. PD-L1 was positive in 43.8% of patients, negative in 31.2% and unknown in 25%. dNLR ≥ 3 was obtained in 56.3%, PLR ≥ 200 in 50% and good, intermediate, and poor LIPI in 25%, 56%, and 19%, respectively. In 37.5% of the patients the LDH was greater than ULN. 43.8% of the patients had received immunotherapy ± chemotherapy in previous lines and 37.5% antiangiogenic plus chemotherapy. 50% of the patients received nintedanib plus docetaxel treatment in the second line and 50% in third or subsequent line.

Table 1. Patient and Tumor characteristics.

Characteristics	Population (n=16)
Age	Median 61 years
Gender	
Male	81.3% (13)
Female	18.7% (3)
Histology	
Adenocarcinoma	100% (16)
Non adenocarcinoma	0% (0)
Stage	
IIIB	18.7% (3)
IV	81.3% (13)
PD-L1 expression (%)	
Positive (≥1%)	43.8% (7)
Negative (0%)	31.2% (5)
Unknow	25% (4)
No. of metastatic sites	
≥3	31.3% (5)
<3	68.8% (11)
CNS metastasis	
Yes	31.2% (5)
No	68.8% (11)
Liver metastasis	
Yes	43.8% (7)
No	56.2% (9)
Bone metastasis	
Yes	25% (4)
No	75% (12)
Smoking history	
Nonsmoker	12.4% (2)
Former smoker	43.8% (7)
Current smoker	43.8% (7)
Pack-years	
<40	56.2% (9)
≥40	43.8% (7)

Antiangiogenic in previous line	
Yes	37.5% (6)
No	62.5% (10)
Immunotherapy in previous line	
Yes	43.8% (7)
No	56.2% (9)
Performance status	
0	12.5% (2)
1	68.8% (11)
2	18.7% (3)
Previous corticosteroids	
Yes	62.5% (10)
No	37.5% (6)
PFS in first line	
< 9 months	68.8% (11)
≥ 9 months	31.2% (5)
Treatment line	
Second	50% (8)
Third or subsequent	50% (8)

Abbreviations: CNS: Central Nervous System; PFS: Progression Free Survival

Survival outcomes

Median follow-up was 76 months. At the time of analysis, 15 patients (93.7%) had died and 1 (6.3%) were alive. Median OS was 6 months (95% CI, 2.11-9.89) and median PFS was 2 months (95% CI, 1.22-2.78).

The variables analyzed with an impact on PFS were; the absence of elevated LDH at the start of treatment (borderline significance) (HR 0.52, 95% CI: 0.26-1.04; p=0.065), the absence of brain metastases (HR 0.38, 95% CI: 0.19-0.76; p=0.007), less than 3 metastatic sites (HR 0.38, 95% CI: 0.19-0.76; p=0.007), and the absence of liver metastases (HR 0.55, 95% CI: 0.29-1; p=0.05).

The variables analyzed with an impact on OS were: no brain metastases (HR 0.33, 95% CI:0.14-0.78; p=0.011), <3 metastatic sites (HR 0.33, 95% CI: 0.14-0.78; p=0.011), the non-use of antiangiogenic drugs in the first line (HR 0.53, 95% CI: 0.29-0.98; p=0.043), the absence of elevated LDH at the start of treatment (HR 0.55, 95% CI: 0.3-1; p=0.051), the absence of liver metastases (HR 0.55, 95% CI: 0.29-1; p=0.05) and ECOG-PS (0-1 versus 2) (HR 0.41,95% CI:0.18-0.93, p=0.03) (**Figure 1**).

Multivariate analysis was not performed due to the small sample size.

No differences were observed in terms of OS and PFS according to dNRL, PLR, and PD-L1 expression. **Table 2** summarized the different variables analyzed.

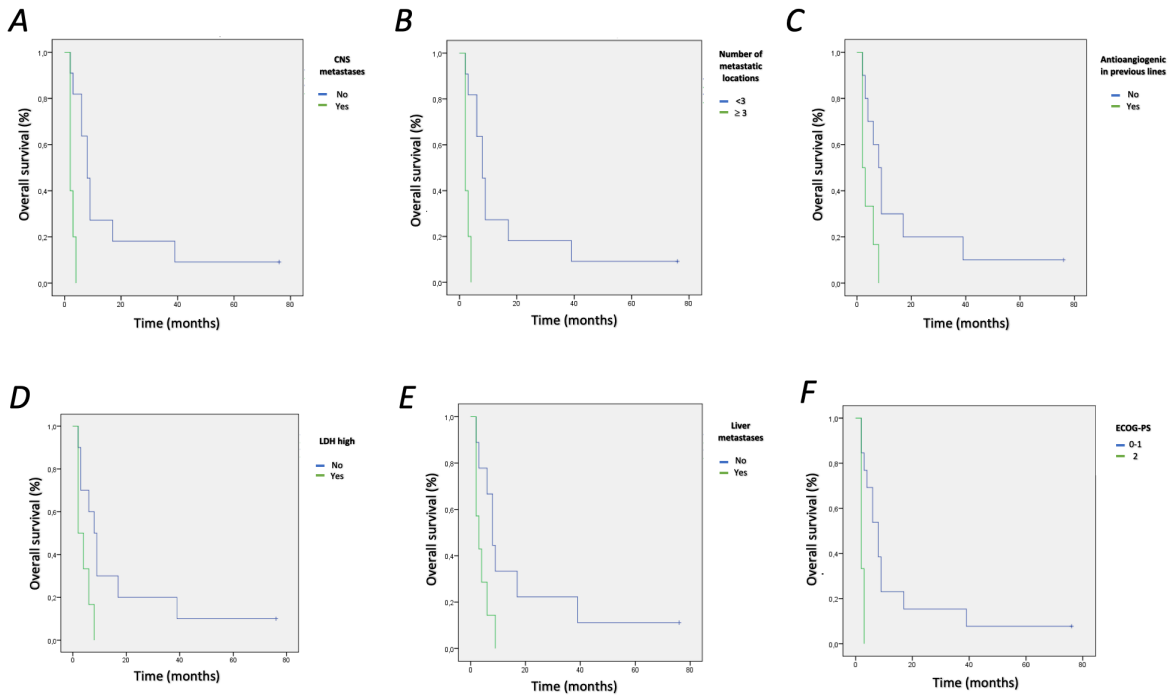

Figure 1. Overall survival based on different variables analyzed. (A), no brain metastases (HR 0.33, 95% CI: 0.14-0.78, p=0.011); **(B)** <3 metastatic sites (HR 0.33, 95% CI: 0.14-0.78, p=0.011); **(C)** the non-use of antiangiogenic drugs in the first line (HR 0.53, 95% CI: 0.29-0.98, p=0.043); **(D)** the absence of elevated LDH at the start of treatment (HR 0.55, 95% CI: 0.3-1, p=0.05); **(E)** the absence of liver metastases (HR 0.55, 95% CI: 0.29-1, p=0.05); and **(F)** the performance status (HR 0.41,95% CI:0.18-0.93, p=0.03).

Table 2. Univariate analysis.

Variables	PFS (months)	HR (95% CI)	p value	OS (months)	HR (95% CI)	p value
Age						
< 65 years	2.0	1.36 (0.76-2.45)	0.3	6.0	1.09 (0.66-1.81)	0.74
≥ 65 years	2.0			6.0		
PS						
0-1	3.0	0.53 (0.26-1.08)	0.08	8.0	0.41 (0.18-0.93)	**0.03**
2	1.0			2.0		
PD-L1						
Negative	2.0	0.71 (0.33-1.54)	0.39	6.0	0.75 (0.36-1.57)	0.44
Positive	4.0			8.0		
LDH						
< ULN	4.0	0.52 (0.26-1.04)	0.065	8.0	0.55 (0.3-0.99)	**0.05**
≥ ULN	2.0			2.0		
LIPI						
Good	4.0	0.47 (0.19-1.17)	0.1	8.0	0.49 (0.2-1.2)	0.12
Intermediate-Poor	2.0			3.5		
PLR						
< 200	3.0	0.72 (0.43-1.21)	0.22	8.0	0.8 (0.48-1.35)	0.41
≥ 200	1.0			3.0		
dNLR						
< 3	3.0	0.85 (0.5-1.42)	0.53	8.0	0.87 (0.52-1.47)	0.61
≥ 3	2.0			4.0		
CNS metastasis						
No	4.0	0.38 (0.19-0.76)	**0.007**	8.0	0.33 (0.14-0.78)	**0.011**
Yes	1.0			2.0		
Previous corticosteroids						
No	5.0	0.78 (0.45-1.35)	0.38	8.0	0.76 (0.45-1.3)	0.32
Yes	2.0			3.0		
BMI						
Normal	2.0	0.82 (0.48-1.4)	0.46	6.0	0.95 (0.57-1.6)	0.85
Abnormal	2.0			6.0		
Pack-years						
< 40	2.0	1.42 (0.81-2.49)	0.22	4.0	1.3 (0.77-2.18)	0.33
≥ 40	2.0			8.0		
Sex						
Male	3.0	0.29 (0.09-0.87)	**0.03**	8.0	0.52 (0.24-1.1)	0.09
Female	1.0			3.0		
No. of metastatic sites						
< 3	4.0	0.38 (0.19-0-76)	**0.007**	8.0	0.33 (0.14-0-78)	**0.011**
≥ 3	1.0			2.0		
Liver metastasis						
No	5.0	0.55 (0.29-1)	**0.05**	8.0	0.58 (0.33-1)	**0.05**
Yes	2.0			3.0		
Bone metastasis						
No	2.0	1.39 (0.73-2.64)	0.32	3.0	1.33 (0.7-2.5)	0.39
Yes	2.0			6.0		

Antiangiogenic in previous line **No** **Yes**	 3.0 2.0	0.6 (0.33-1.12)	0.11	 8.0 2.0	0.53 (0.29-0.98)	**0.04**
Immunotherapy in previous line **No** **Yes**	 2.0 4.0	1 (0.61-1.76)	0.9	 3.0 8.0	1.09 (0.65-1.82)	0.74
PFS in first line **< 9 months** **≥ 9 months**	 2.0 3.0	0.87 (0.5-1.5)	0.62	 6.0 8.0	1.06 (0.61-1.81)	0.84
Treatment line **Second** **Third or subsequent**	 2.0 1.0	0.69 (0.4-1.2)	0.17	 8.0 3.0	0.77 (0.46-1.29)	0.32

Abbreviations: OS: Overall Survival; PFS: Progression Free Survival; PS: Performance Status; LDH: Lactate Dehydrogenase; ULN: Upper Limit of Normal; LIPI: Lung Immune Prognostic Index; PLR: Platelet-to-Lymphocyte Ratio; dNLR: Derived Neutrophil to Lymphocyte Ratio; CNS: Central Nervous System; BMI: Body Mass Index

Response

The tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (ver.1.1) (RECIST 1.1) and clinical tumor response was assessed every 3 months. At the time of data cut-off response assessment to nintedanib-docetaxel treatment was available from all patients. ORR was 12.5%, stable disease (SD) 31.3%, and disease control rate (DCR = complete response + partial response + SD) 43.8%, whereas 9 patients (56.2%) were primary refractory. None of the variables studied (dNLR, PLR, LIPI, or PD-L1 expression) were correlated with the ORR.

LDH was the only variable related to the ORR and DCR; 40% and 70% in patients with normal LDH versus 0% in elevated LDH respectively (OR 8.21 [95% CI 2.35–23.19], p<0.01).

Discussion

In the phase III LUME – Lung-1 trial (NCT00805194), the combination of docetaxel and nintedanib increased the median OS of lung adenocarcinoma patients, who had relapsed within 9 months of first-line chemotherapy, from 7.9 months to 10.9 months (HR =0.75, 95% CI: 0.60- 0.92, P = 0. 0073) [18]. In the second cohort (all adenocarcinoma patients), the combination treatment also provided a survival benefit (median OS 12.6 months vs 10.3 months; HR = 0.83, CI:0.70-0.99, P = 0. 0359) [18].

In the real-world setting in patients treated with third-line docetaxel plus nintedanib after chemotherapy and IO, the median OS was 8.4 months [25]. The median OS in our series was 6.0 months (**Figure 1**), which could be explained by being a population with a worse prognosis (31% central nervous system (CNS) metastases, 44% liver metastases, 19% ECOG PS=2 and 70% with first-line PFS <9 months and 50% patients in third or subsequent line) (**Table 1**).

Identifying molecular biomarkers that can predict responses to angiogenesis inhibitors remains an important goal to optimize the clinical benefit of these agents [26]. Unfortunately, to date, there are no validated biomarkers that predict the response to bevacizumab, ramucirumab, or nintedanib [27].

There are numerous routine blood parameters studied as possible inflammatory biomarkers in cancer patients; elevated levels of circulating white blood cells, absolute neutrophil count, absolute platelet count, and LDH level. All associated with poor results in several cancer types [28-30].

In the subgroup analysis of the LUME-Lung-1 study (NCT00805194), patients with brain metastases and those who received first-line with bevacizumab, did not seem to benefit from the combination of nintedanib plus docetaxel. Our data is similar. Unfortunately, they do not analyze other variables how LDH, liver metastases, or inflammatory parameters. Although after reviewing the literature, we did not find similar results due to lack of studies, our results are consistent with other adverse prognostic factors related to NSCLC (elevated LDH levels and the presence of liver metastases) [31] (**Table 2**).

Multiple serum markers have been evaluated as possible poor prognostic factors in NSCLC. LDH is one of the most studied. Rotenberg et al. [32] determined the values for total LDH activity in serum and their isoenzymes at diagnosis in 273 patients with NSCLC and they concluded that total LDH in serum may be a direct indicator of clinical stage and high tumor burden in patients with NSCLC.

The presence of liver metastases in NSCLC is a proven adverse prognostic factor. The retrospective study analyzes the prognostic factors in lung cancer patients with M1b disease with the Surveillance Epidemiology and End-Results database (SEER). Among patients with multiple metastases, better outcomes were observed in adenocarcinoma patients (4 vs 3 months; OS and LCSS, p < 0.001) and small cell lung cancer patients (6 vs 4 months; OS, p = 0.017; LCSS, p = 0.023) without liver metastasis compared to those with liver metastasis [33].

Although some of our results are consistent with the literature, others are discordant, mainly those related to the inflammatory environment (dNRL, PD-L1, LIPI, PLR, etc.) [34-38].

Although all patients included in our study were EGFR, ALK, and ROS-1 wild-type, immunotherapy in patients with alterations in these genes has not proven to be an effective therapeutic strategy. There are no randomized clinical trials demonstrating the efficacy of nintedanib in these populations. In EGFR, ALK and ROS-1 wild-type advanced NSCLC, immunotherapy has not proven to be an effective therapeutic strategy [39-43]. Although there are no randomized clinical trials that demonstrate the efficacy of nintedanib in these populations, there are retrospective data. Highlight the study by Riudavets et al. [44], in which 19 patients with advanced EGFR-mutant NSCLC who had progressed to EGFR tyrosine kinase inhibitors and platinum-based chemotherapy receiving docetaxel and nintedanib at 14 Spanish institutions. With a median follow-up of 11.4 months (1-38), the median PFS was 6.1 months [95%CI, 4.9-7.3] and the median OS 10.1 months (95% CI 5.9-14.3). The ORR was 44.4% (23.7-66.8%) and the disease control rate (DCR) 72.2% (49.4-88.5%). In our study, all patients included were EGFR, ALK, and ROS-1 wild-type, so we cannot confirm the efficacy of nintedanib in the subgroup of EGFR-mutated NSCLC patients.

Different studies and meta-analyses have demonstrated the usefulness of these inflammatory factors in the context of IO treatment in advanced NSCLC [45-47]. The reason for not presenting similar results in our study could be due to the real lack of value in the context of antiangiogenic plus chemotherapy treatment or to the characteristics of our study, such as a small number of patients included, possible confounding factors such as infections intercurrent, cut-off point of dNLR and PLR, etc.

Another factor could be the lack of personalized medicine data. As reflected in Singh et al. [48] review, "the era of precision medicine is rapidly approaching, and the integration of personalized medicine, toxicology, toxicogenomics, and artificial intelligence can play a vital role in achieving its goals. These fields can help to optimize treatment outcomes and reduce the risk of adverse effects, by taking into account an individual's unique characteristics such as genetics, lifestyle, and environment".

Study limitations include the non-interventional, non-comparative retrospective design, the limited sample size, and the potential for selection bias. Another limitation is that RECIST analyses were done for every patient by the treating oncologist with no central independent radiologic review board. A prospective study including a larger cohort of patients would help to overcome the non-interventional, non-comparative retrospective design and limited sample size. Additionally, incorporating an independent radiologic review board would enhance the reliability of RECIST analyses and improve the robustness of the findings. Strengths include an evaluation of a real-world cohort that reflects real efficacy in unselected patients.

Conclusions

The absence of elevated LDH, CNS metastases, liver metastases, less than 3 metastatic sites, and the non-use of antiangiogenic drugs in first-line imply a better evolution of pretreated patients with advanced NSCLC receiving nintedanib-docetaxel. Although the study includes a relatively small sample size, these results generate interesting hypotheses that warrant prospective validation. The incorporation of toxicogenomics, artificial intelligence, or additional biomarkers, could help guide future research efforts and advance the understanding of prognostic factors in NSCLC treatment.

Authors Contributions

Conceptualization: Luis Cabezón-Gutiérrez

Methodology: Sara Custodio-Cabello, Vilma Pacheco-Barcia, and Luis Cabezón-Gutiérrez

Formal analysis and investigation: Sara Custodio-Cabello, Luis Cabezón-Gutiérrez, and Vilma Pacheco-Barcia.

Writing - original draft preparation: Luis Cabezón-Gutiérrez, Sara Custodio-Cabello, and Magda Palka-Kotlowska

Writing - review and editing: Luis Cabezón-Gutiérrez, Catalina Saez- Bertrand, and Vilma Pacheco-Barcia

Supervision: Luis Cabezón-Gutiérrez, Marta Blasco-Guerrero, and Magda Palka-Kotlowska

Conflicts of Interest

Luis Cabezón Gutiérrez declares the following conflicts of interest: Advisory role; Astra Zeneca, Roche, Eisai, and Brystol Myers Squibb. Speakers' bureau; Roche, Astra Zeneca, Brystol Myers Squibb, Merck Serono, Ipsen Pharma, Grunenthal, Kyowa Kirin, Pfizer, Roche, and Eisai.

Vilma Pacheco-Barcia declares the following conflicts of interest: Advisory role: Advanced accelerator applications, a Novartis company; Speakers' bureau: Merck, Eli Lilly, Eisai, Pierre Fabre. Congress attendance: Roche, Eli Lilly, Bristol-Myers Squibb, Merck, Amgen, Merck Sharp and Dhome, Nutricia; Grant support: FSEOM and Merck, Pfizer, Nutricia, LEO Pharma. Other: Bayer, Roche, Amgen, Esteve.

Sara Custodio-Cabello, Magda Palka-Kotlowska, Catalina Saez-Bernal and Marta Blasco-Guerrero, declare no conflict of interests.

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