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Final results of the SENECA (SEcond line NintEdanib in non-small cell lung CAncer) trial

Enrica Capelletto[a,*], Maria Rita Migliorino[b], Alessandro Morabito[c], Rita Chiari[d], Francesco Grossi[e,f], Marcello Tiseo[g], Francesco Di Costanzo[h], Angelo Delmonte[i], Gianpiero Romano[j], Domenico Galetta[k], Vieri Scotti[l], Vanesa Gregorc[m], Salvatore Pisconti[n], Giovanni Luca Ceresoli[o], Alessandro Del Conte[p], Libero Ciuffreda[q], Ida Colantonio[r], Emilio Bria[s,t], Serena Ricciardi[b], Anna Manzo[c], Giulio Metro[d], Anna Maria Morelli[a], Rossana Critelli[a], Maria Vittoria Pacchiana[a], Ilaria Stura[u], Giuseppe Migliaretti[u], Silvia Novello[a]

[a] Department of Oncology, University of Turin, AOU San Luigi, Orbassano, Italy
[b] San Camillo Forlanini Hospital, UOSD Pneumologia Oncologica, Roma, Italy
[c] Thoracic Medical Oncology, Istituto Nazionale Tumori, "Fondazione G.Pascale" – IRCCS, Napoli Italy
[d] Santa Maria della Misericordia Hospital, Medical Oncology, Perugia Italy
[e] San Martino Hospital, Lung Cancer Unit, Genova Italy[1]
[f] Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano Italy[2]
[g] Department of Medicine and Surgery, University of Parma, Parma Italy
[h] AOU Careggi, Medical Oncology, Firenze Italy
[i] Istituto Scientifico Romagnolo Per Lo Studio E La Cura Dei Tumori (IRST) - IRCCS, Meldola Italy
[j] Vito Fazzi Hospital, UO Oncologia, Lecce Italy
[k] Clinical Cancer Center "Giovanni Paolo II", Thoracic Medical Oncology Unit, Bari Italy
[l] AOU Careggi, Radiation Oncology Unit - Oncology Department, Firenze Italy
[m] Department of Oncology, IRCCS San Raffaele, Milano Italy
[n] P.O.C.SS. Annunziata - S.G.Moscati, SC Oncologia Medica, Taranto Italy
[o] Humanitas Gavazzeni, Medical Oncology, Bergamo Italy
[p] Centro di Riferimento Oncologico (CRO) - IRCCS, Oncology Unit, Pordenone Italy
[q] A.O.U. Città della Salute e della Scienza di Torino - Presidio Molinette – SC Oncologia Medica I, Torino Italy
[r] S. Croce e Carle General Hospital, Medical Oncology, Cuneo Italy
[s] Department of Medicine, University of Verona, Oncology Unit,Verona Italy[1]
[t] Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma Italy[2]
[u] Department of Public Health and Paediatric Sciences, University of Turin Italy

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ABSTRACT

Objectives: Despite the scant docetaxel's tolerability, second-line association with nintedanib still represents a standard-of-care for non-squamous non-small cell lung cancer (nsNSCLC), giving to rapidly-progressing patients the greatest survival advantage. The SENECA trial is a phase IIb, open-label, study evaluating whether nintedanib/docetaxel can be equally effective and safe regardless docetaxel schedule.

Materials and Methods: Recurrent nsNSCLC patients were stratified into cohort 1 and 2, according to relapse-time (within or over 3 months) from end of first-line chemotherapy. They were treated with docetaxel (T1: 33 mg/mq on days 1 and 8 in a 21-days cycle; T2: 75 mg/mq q3wks) plus nintedanib, allowing maintenance in case of disease-control. Primary endpoint was progression-free survival (PFS) by investigator's assessment; secondary endpoints: overall survival (OS), safety and quality-of-life.

Results: Between January 2016-April 2018, 212 patients were evaluated: 30 resulted screening-failures, 12 were excluded for lack of compliance. According to investigator's choice, 85 patients received T1 docetaxel and 85 T2; 138 (81.2%) were stratified in C1, 32 (18.8%) in C2, with a median relapse-time of 0.54 and 9.29 months, respectively. Baseline characteristics were balanced between groups. After 35.5 months follow-up, no survival differences appear between cohorts and treatments; toxicity seems to be slightly higher in T2, especially for

* Corresponding author: Department of Oncology, University of Turin, Regione Gonzole 10, Orbassano (TO), Italy.
E-mail address: enrica.capelletto@gmail.com (E. Capelletto).
[1] actual affiliation in which the work was done.
[2] new affiliation.

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chemotherapy-related events. Perception of quality-of-life remains stable and docetaxel schedule doesn't modify patients' load.

Conclusion: The SENECA trial confirms efficacy of second-line nintedanib/docetaxel for nsNSCLC, regardless time of recurrence and docetaxel schedule; higher toxicities for q3wks docetaxel, without alterations in quality-of-life, have been described, underling the possibility, adopting the weekly schedule, to maintain efficacy with better tolerability.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1,2]. Over the past decade, significant improvements have been made in understanding cancer pathogenesis and many new drugs have been developed for the treatment of non-small cell lung cancer (NSCLC) without actionable oncogenic drivers. Immune checkpoint inhibitors have revolutionized lung cancer therapy in the first line setting [3–5] (alone or in combination with cytotoxic agents) regardless of histology and, in the second line, of PD-L1 expression, being these drugs a new standard of care for selected patients [6–9].

Despite this, the huge heterogeneity of lung cancer urgently requires other therapeutic options, especially for those patients with contra-indications to the use of immunotherapy or after its failure.

Angiogenesis is a central pathway for the development, growth and metastatization of NSCLC and a valid target for cancer drugs [10,11]. Vascular endothelial growth factor (VEGF) is the most potent proangiogenic agent that solid tumors can secrete in favour of their uncontrolled growth. Therapeutic approaches in the angiogenesis field include monoclonal antibodies and small molecules VEGF receptor tyrosine kinase inhibitors [12]. In this field, nintedanib is a modern, orally available, multi-target small-molecule with anti-angiogenic activity targeting the vascular endothelial growth factor receptors (VEGFR) 1–3, the platelet-derived growth factor receptor (PDGFR) α/β and the fibroblast growth factor receptors (FGFR) 1–3 [13].

Nintetanib plus docetaxel q3wks resulted more effective than docetaxel alone, as second line treatment option for non-oncogene addicted NSCLC patients after first-line platinum based chemotherapy. The randomized phase III, placebo-controlled, LUME-Lung1 trial [14] has showed, regardless of histology, a higher median PFS for the combination treatment versus placebo (3.4 vs 2.7 months, respectively; hazard ratio = 0.79; 95% confidence interval: 0.68–0.92; p = 0.0019). Median OS resulted greater for patients treated with nintedanib plus docetaxel in the subgroup with adenocarcinoma histology (12.6 vs 10.3 months, respectively; HR = 0.83; 95% CI: 0.70–0.99; p = 0.0359), while no differences have been described in the entire population (all the histologies). Incidence of treatment related Adverse Events (AEs) resulted numerically higher in the nintedanib containing arm. However, toxicity profile of the combination treatment was manageable, establishing the role of nintedanib plus docetaxel as a valid second-line treatment option for NSCLC patients [15].

Even though docetaxel is considered the reference second-line chemotherapy for advanced NSCLC, in the real-life, its toxicity can't be ignored. With the intent of reducing docetaxel toxicity, in the past decades alternative regimens, consisting of lower doses or different administration schedules, have been explored [16–18]. Weekly docetaxel repeatedly demonstrated a better safety profile than the standard three-weekly schedule, with a lower incidence of neutropenia in pre-treated patients [19].

Considering the higher tolerability of weekly docetaxel than docetaxel q3wks in the real-life, here we present the final results of the SEcond line NintEdanib in non-small cell lung CAncer (SENECA) trial (EudraCT Number: 2014-005016-42). SENECA is a phase IIb, open-label, multicenter study, aiming to evaluate whether treatment with nintedanib and docetaxel could be equally effective and safe as second-line treatment option in non-squamous NSCLC (nsNSCLC) patients, regardless the docetaxel schedule employed, The study aims to provide clinicians the required evidence in order to use weekly docetaxel instead of docetaxel q3wks, as previously assessed in the LUME-Lung1 trial, exploring the efficacy of the two association regimens and postulating a better safety profile for the weekly schedule.

2. Materials and methods

2.1. Study design and procedures

The study stratified patients by relapse-timing from the end of first-line chemotherapy, defining:

- Cohort C1 - within 3 months
- Cohort C2 - over 3 months.

According to investigator's choice (individually determined), patients were treated with oral nintedanib plus docetaxel 33 mg/mq by intravenous infusion on days 1 and 8 in a 21-days cycle (T1) or nintedanib plus docetaxel 75 mg/mq q3wks (T2), over a maximum of 6 chemotherapy cycles. Nintedanib dose (200 mg twice daily) had to be withheld on days of chemotherapy infusion. Patients who stopped docetaxel (before or at the completion of the sixth cycle) had the possibility to continue nintedanib as a maintenance treatment in case of disease control at the radiological assessments scheduled per protocol (at least four treatment courses of combination therapy were mandatory for statistical analysis). Mainteinance nintedanib was allowed until unacceptable toxicity, progressive disease or withdrawal of consent.

Docetaxel and nintedanib dose reductions were permitted according to label recommendations. Local investigator's assessment of tumor response has been performed at baseline and every six weeks after the beginning of treatment.

Differences between cohort and treatment were evaluated analyzing the Progression Free Survival (PFS) and Overall Survival (OS), using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20]. Safety analysis was performed coding adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [21]. Quality of life was assessed by using the Lung Cancer Symptom Score (LCSS) [22–24].

2.2. Patients

The study was performed in eighteen Italian oncologic centers: adult (≥18 years old) patients with histologically or cytologically confirmed stage IIIB/IV recurrent non-squamous NSCLC, who had received one previous chemotherapy regimen, were enrolled. Adjuvant, neo-adjuvant, or neo-adjuvant plus adjuvant therapy were allowed, if the last dose have been administered at least 12 months before study entry.

Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and at least one target lesion measurable according to RECIST version 1.1 [20]. Patients with active brain metastases, those who had received previous docetaxel or VEGFR inhibitors (with the exception of bevacizumab), with radiographic evidence of cavitary/necrotic tumors, centrally located, with invasion of major blood vessels, history of clinically significant hemoptysis or major thrombosis, were excluded from enrollment. Patients with known Epidermal Growth Factor Receptor (EGFR) activating mutations or Anaplastic Lymphoma Kinase (ALK) gene rearrangements were not

allowed to enter the study.

Prior to admission to the study, all patients provided a written informed consent. The study was done in full accordance with the Protocol and Declaration of Helsinki and totally respecting the good clinical practice and regulatory guidelines. The protocol was approved by independent ethics committees or institutional review boards at each center involved.

Patients have been enrolled between January 22th, 2016 and April 20th, 2018. Of the 212 patients screened, 170 have been enrolled according protocol design, considering the relapse timing from the end of first-line chemotherapy. Thirty patients were registered as screening failures (mainly for contraindication to nintedanib use and active brain metastases) and twelve were excluded because lost to follow-up or for lack of compliance to study procedures (Fig. 1). Characteristics of patients were well balanced between the two treatment groups (Table 1), with a similar duration of treatment (4 cycles for docetaxel [range 1–6] and 6 for nintedanib [range 1–27]).

2.3. Outcomes

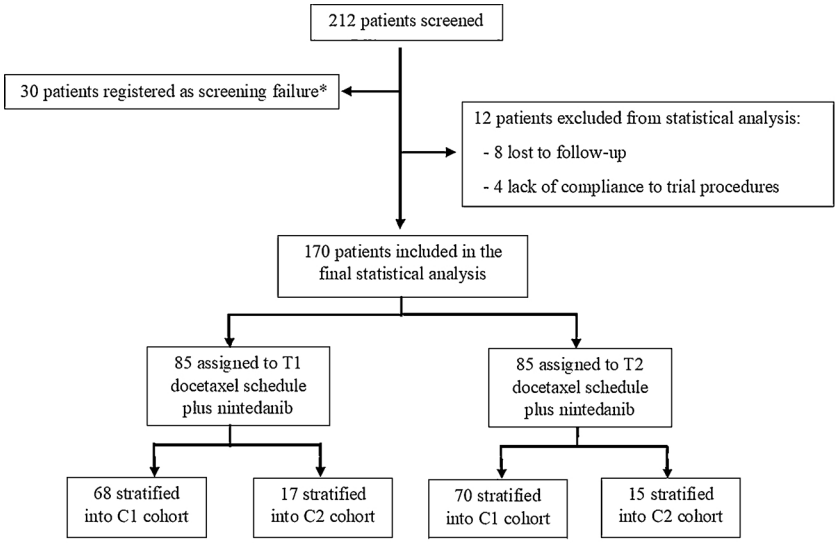
Objective of the SENECA trial was to optimize the combination treatment with docetaxel, exploring in a real-life population two different administration schedules (weekly and q3wks) in different cohorts of patients. The primary endpoint was the time from the start of treatment to progression or death (PFS), by investigator's assessment. According to RECIST 1.1 [20], overall survival (OS) time, disease response rate and safety were predefined as secondary endpoints.

The analysis of quality of life (QoL) has been based on the Lung Cancer Symptom Scale (LCSS). Because of the sample size, only the first twelve cycles of study treatment have been considered for QoL evaluation. The LCSS [22–24] is comprised of a nine-item questionnaire for the patient, and a six-item questionnaire for the health care professional; in our study we only used the patients scale. The patient-based LCSS includes three symptoms of a thoracic subset (cough, dyspnea and hemoptysis), three of a general subset (anorexia, fatigue and pain), and three summary items (symptom distress, interference with daily activities, and global QoL).

Table 1
Patients characteristics at study entry.

	T1 (N = 85)	T2 (N = 85)
Relapse timing		
C1	68 (80.0%)	70 (82.4%)
C2	17 (20.0%)	15 (17.6%)
Age (years)	64.2 (40–86)	62.8 (35–80)
Sex		
Men	53 (62.3%)	65 (76.5%)
Female	32 (37.7%)	20 (23.5%)
ECOG PS		
0	64 (75.3%)	59 (69.4%)
1	21 (24.7%)	26 (30.6%)
Smoking history		
Current	15 (17.6%)	24 (28.2%)
Former	58 (68.2%)	46 (54.2%)
Never	12 (14.2%)	15 (17.6%)
Histology		
Adenocarcinoma	85 (100%)	83 (97.6%)
Large cell carcinoma	0 (0%)	1 (1.2%)
Non-squamous NSCLC	0 (0%)	1 (1.2%)
Clinical stage at diagnosis*		
Stage < IIIb	18 (21.2%)	19 (22.3%)
Stage IIIb	3 (3.5%)	2 (2.3%)
Stage IV	64 (75.3%)	64 (75.3%)
Clinical stage at study entry*		
IIIB	2 (2.3%)	2 (2.3%)
IV	83 (97.7%)	83 (97.7%)
First line-bevacizumab	1 (1.2%)	3 (3.5%)
Main comorbidities		
Hypertension	27 (31.8%)	29 (34.1%)
Diabetes	11 (12.9%)	10 (11.7%)
COPD**	12 (14.2%)	8 (9.5%)
Pain	18 (21.2%)	9 (10.5%)
Other previous cancer	9 (10.5%)	6 (7.0%)
HCL§	8 (9.5%)	8 (9.5%)

* clinical stage according TNM 7th edition.
** Chronic obstructive pulmonary disease.
§ Hypercholesterolemia.



* 4 patients (13.3%): active brain metastases; 4 (13.3%): history of significant cardiovascular diseases; 4 (13.3%): not adequate histology and disease stage at study entry; 3 (10%): proteinuria = CTCAE grade 2; 3 (10%): ECOG PS > 1 at study entry; 3 (10%): serum creatinine = CTCAE grade 2; 2 (6.7%): radiographic evidence of cavitary or necrotic tumours; 2 (6.7%): history of haemoptysis or major thrombotic events; 2 (6.7%): withdrawal of consent; 1 (3.3%): serious infections requiring systemic antibiotic; 1 (3.3%): inheritated predisposition to bleeding or thrombosis; 1 (3.3%): platelets < 100.000/mL at study entry.

Fig. 1. Trial workflow.

2.4. Statistical analysis

2.4.1. Sample size

Using a Non-inferiority design, the sample size was estimated considering as primary endpoint the progression free survival between treatment groups (T1 and T2), and applying the Kieser and Hauschke method's [25]. Assuming an accrual time of 72 weeks and a follow-up time of 48 weeks and considering and hazard ratio = 1.250, with a non-inferiority bound $\delta_0 = 0.80$, to reach a power 1 - β equal to 80% with a two-sided type I error equal to 0.05, a total of 162 patients should have been enrolled. In order to consider 5% of possible losses at follow-up a total of 170 patients were recruited.

2.4.2. Statistical methods

In order to analyze the difference of Progression Free Survival (PFS) and Overall Survival (OS) between Cohort (C1 and C2) and Treatment (T1 and T2), Kaplan-Meier curves with relative Log Rank test have been made. Since a randomization was not performed, to adjust for the possible confounders a Cox proportional hazard models were carried out (proportional hazard assumption was checked using the Grambsh and Therneau test and diagnostic plots based on Schoenfeld residual). Results were showed in terms of Hazard Ratio (HR) and relative 95% Confidence Interval (95%CI).

Adverse events were compared by Cohort and Treatment using the Fisher's exact test. Differences of Quality of Life between Cohorts and Treatment, based on Lung Cancer Symptom Scale (LCSS) Score, were analyzed using non-parametric Mann Whitney test.

3. Results

Considering the relapse-timing from the end of first-line chemotherapy, 138 patients (81.2%) have counted in C1 and 32 (18.8%) in C2, with a median relapsing time of 0.54 and 9.29 months, respectively. Survival was slightly higher in cohort C2, without a statistical significance: median PFS was 5.13 months in C2 and 4.28 months in C1 (HR 0.752 [95% CI 0.473–1.194], p-value = 0.2383) (Fig. 2A); median OS was 9.53 months in C2 and 8.94 in C1 (HR 0.834 [95% CI 0.588–1.183], p-value = 0.7548) (Fig. 2B).

Considering that the majority of patients have been treated with platinum/pemetrexed in the first-line setting, using pemetrexed as maintenance after platinum induction, and that literature suggests to prolong maintenance until progression or unacceptable toxicity, it is likely that many patients began second line docetaxel/nintedanib at the time of relapse during maintenance treatment, being consequently classified into C1 cohort. This can partially explain the higher number of patients allocated into the C1 cohort than C2. In order to better describe survival outcomes of rapid and slow progressors, we have tried to optimize stratification reclassifying patients into two new cohorts, R1 and R2, considering a relapse time within 9 months from the start of first-line chemotherapy vs a longer one, respectively. One hundred-eighteen patients have been reclassified as rapid progressors (R1) and fifty-two as slow progressors (R2), with a median relapsing time of 4.69 months and 16.26 months, respectively. Also this way, the survival seems to be slightly higher in cohort R2, even though a statistically significant difference between the R1 and R2 cohorts has not been observed (median PFS equal to 5.15 months in R2 and 4.15 in R1, HR 1.458 [95% CI 0.980–2.171], p-value = 0.0707, and median OS equal to 9.51 months in R2 and 8.85 in R1, HR 1.225 [95% CI 0.832–1.803], p-value = 0.3061).

In the study, 85 patients (50.0%) have followed the T1 docetaxel schedule and 85 (50.0%) the T2; at the cut-off date (December 25th, 2018), after a median follow-up of 35.5 months, no significant

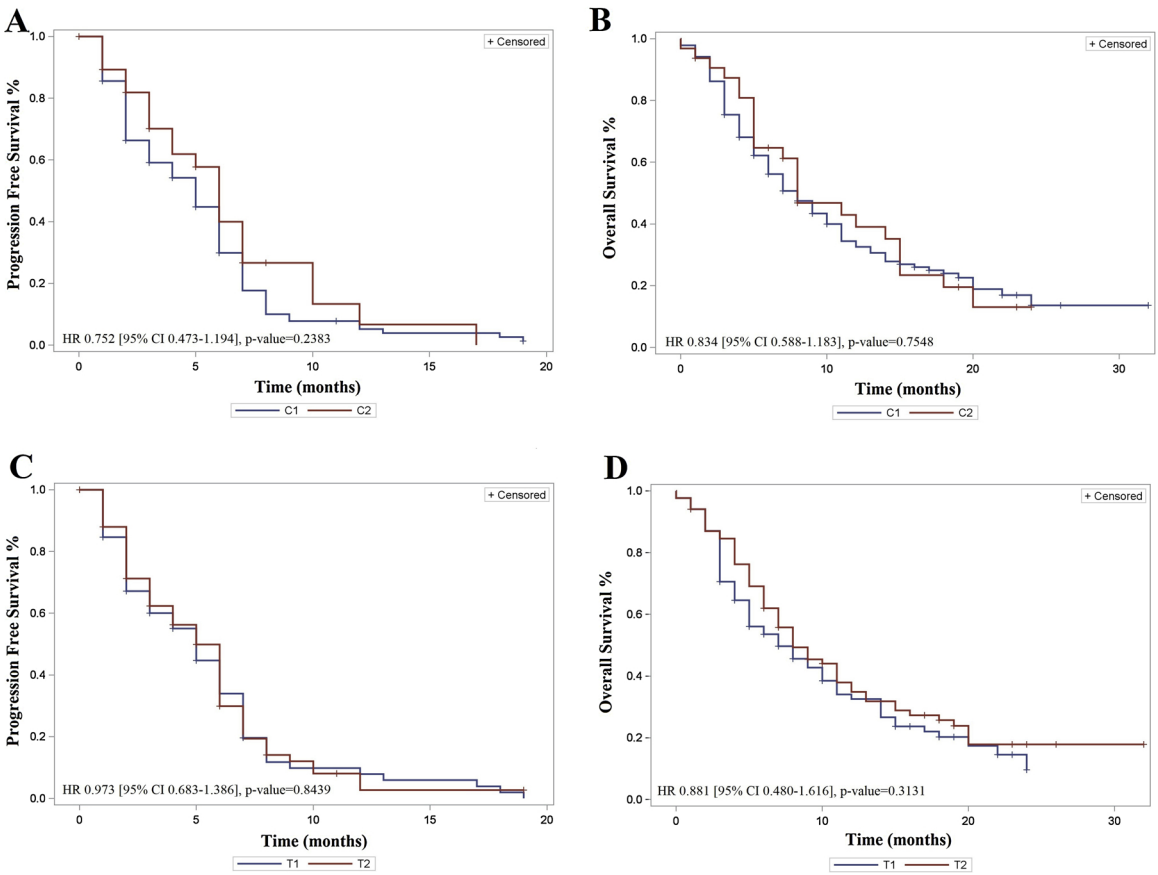


Fig. 2. Kaplan-Meier curves for progression free survival and overall survival according to relapse timing stratification cohorts (A and B, respectively) and docetaxel treatment groups (C and D, respectively).

differences appear between T1 and T2 in terms of PFS (4.79 vs 4.82 months, respectively; HR 0.973 [95% CI 0.683–1.386], p-value = 0.8439) (Fig. 2C). Median OS has been not significantly different between the two treatment groups (8.49 vs 9.62 months, respectively; HR 0.881 [95% CI 0.480–1.616], p-value = 0.3131) (Fig. 2D). Twenty patients have been considered censored at the last follow-up date, because of the early withdrawal from the study, without any progression date.

A specific analysis was finally conducted in order to highlight any differences between C1 and C2 within the same treatment. The results show no statistically significant differences for PFS (HR 1.22 [95% CI 0.853–1.733] and HR 0.899 [95% CI 0.573–1.411] for Treatment and Cohort respectively).

Defining the disease control rate as the percentage of patients with complete response, partial response and stable disease, no significant differences were observed between T1 and T2 (63.0% vs 72.7%, respectively, p-value = 0.4322).

3.1. Safety

Being the adverse events (AEs) observed during the study strictly related to treatment and having observed no difference between stratification cohorts in terms of toxicity, we will present safety results only according treatment groups (T1 and T2).

Incidence of any AEs grade [21] was numerically higher in T1 compared to T2 (731 vs 594 events, respectively), while grade ≥3 AEs resulted more common in T2 (77 vs 114 in T1 and T2, respectively). Main toxicities observed during the study were: fatigue (all grades, 71 of 731 [9.7%] vs 65 of 594 events [10.9%] in T1 and T2, respectively), diarrhea (75 of 731 [10.2%] vs 52 of 594 [8.7%] in T1 and T2, respectively), alanine aminotransferase elevation (51 of 731 [7.0%] vs 28 of 594 [4.7%] in T1 and T2, respectively), aspartate aminotransferase elevation (44 of 731 [6.0%] vs 17 of 594 [2.9%] in T1 and T2, respectively) and afebrile neutropenia (18 of 731 [2.5%] vs 62 of 594 [10.4%] in T1 and T2, respectively). An overview of the main AEs observed during the study is summarized in Table 2.

Comparative analysis of safety data suggests a trend of higher toxicities for the docetaxel q3wks combination schedule, especially for those adverse events strictly related to chemotherapy. A strong statistically significant difference in terms of afebrile neutropenia has been described: this toxicity was higher in T2 (p-value < 0.0001 for all grades afebrile neuropenia and for grades ≥3). A similar situation was evident for all grade oral mucositis, more common in T2 (p-value = 0.001). On the contrary, aspartate aminotransferase elevation, decrease of platelets and the onset of fever and paraesthesia during treatment resulted more common in the weekly docetaxel schedule (T1), together with a statistically significant difference between treatment groups (Table 2).

Considering the entire population enrolled in the study, docetaxel dose was reduced in 14.4% of patients, more frequently in T2 vs T1 (17 out 85 patients [20.0%] in T2 vs 12 out 85 [9.7%] in T1). Nintedanib reduction was needed in 22.3% of patients, 28.2% in T1 and 16.5% in T2, mainly for diarrhea. Thirty-one (18.2%) patients permanently discontinued study drugs (11 in T1 vs 20 in T2), mainly due to hypersensitivity reactions and pain.

Incidence of anti-angiogenic-specific adverse events has been low and consistent with literature data in both treatment groups. Gastrointestinal perforation has been extremely infrequent (only one case of sigma perforation has been observed in the q3wks docetaxel schedule). Bleeding (from respiratory tract or other sites) has resulted rare and of low grade. Only one case of grade 3 bleeding from a site different from airway has been described in the weekly docetaxel schedule. Study prevalence of any grade nintedanib-related hypertension was 3.5% (3 cases out 85 patients) and 9.4% (8 cases out 85 patients), in T1 and T2, respectively. The majority (9 of 11) of patients with drug-related hypertension had grade 1 or 2 events, while no patients had hypertension of grade 4 or 5. The proportion of patients with venous thrombosis has been extremely low and homogeneous in both treatment groups, 2.3% in T1 and 4.7% in T2. Arterial thromboembolism has been described only in the weekly docetaxel schedule (5 cases of any grade), while no case has been observed in the other treatment group. The different incidence of arterial thromboembolism has been the only statistically significant difference observed in the present study among the anti-angiogenic-specific adverse events, in favour of the q3wks docetaxel schedule. However, the small sample size and the low incidence of this event, make the data extremely inaccurate. Details of anti-angiogenic-specific adverse events are listed in Table 3.

3.2. Quality of life (QoL)

Similarly to toxicity analysis, we will present quality of life (QoL) results only according treatment groups (T1 and T2), since no

Table 2
Main AEs observed in the SENECA trial according to docetaxel schedule and CTCAE grade.

AEs	Any grades			Grade ≥ 3		
	T1 (N = 731)	T2 (N = 594)	*p-value*	T1 (N = 77)	T2 (N = 114)	*p-value*
Fatigue	71 (9.7%)	65 (10.9%)	0.46	5 (6.5%)	10 (11.87%)	0.56
Diarrhea	75 (10.2%)	52 (8.7%)	0.35	4 (5.2%)	5 (8.8%)	0.79
ALT elevation	51 (7.0%)	28 (4.7%)	0.08	10 (13.0%)	6 (5.3%)	0.05
Afebrile Neutropenia	18 (2.5%)	62 (10.4%)	< 0.0001	5 (6.5%)	51 (44.7%)	< 0.0001
AST elevation	44 (6.0%)	17 (2.9%)	0.006	5 (6.5%)	3 (2.6%)	0.19
Pain	41 (5.6%)	32 (5.4%)	0.86	5 (6.5%)	3 (2.6%)	0.19
Anemia	29 (4.0%)	19 (3.2%)	0.45	1 (1.3%)	0 (0%)	0.22
Nausea	25 (3.4%)	17 (2.9%)	0.56	3 (3.9%)	3 (2.6%)	0.62
Dyspnea	22 (3.0%)	25 (4.2%)	0.24	4 (5.2%)	4 (3.5%)	0.56
Fever	25 (3.4%)	10 (1.7%)	0.04	2 (2.6%)	0 (0%)	0.08
Cough	20 (2.7%)	13 (2.2%)	0.52	0 (0%)	0 (0%)	NE
Platelets decrease	12 (1.6%)	2 (0.3%)	0.02	0 (0%)	0 (0%)	NE
Skin Toxicity	15 (2.0%)	4 (0.7%)	0.70	0 (0%)	1 (0.9%)	0.40
Oral Mucositis	11 (1.5%)	26 (4.4%)	0.001	2 (2.6%)	1 (0.9%)	0.34
GGT elevation	16 (2.2%)	12 (2.0%)	0.83	5 (6.5%)	6 (5.3%)	0.72
Vomiting	13 (1.8%)	15 (2.5%)	0.34	0 (0%)	1 (0.9%)	0.40
Decreased leukocytes	9 (1.2%)	10 (1.7%)	0.49	0 (0%)	2 (1.7%)	0.24
Alopecia	6 (0.8%)	11 (1.8%)	0.09	1 (1.3%)	2 (1.7%)	0.80
Paraesthesia	18 (2.5%)	6 (1.0%)	0.04	0 (0%)	0 (0%)	NE
Nail Toxicity	19 (2.6%)	11 (1.8%)	0.36	0 (0%)	1 (0.9%)	0.40

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; NE: not evaluable.

Table 3
Anti-angiogenic-specific adverse events observed in the SENECA trial according to docetaxel schedule and CTCAE grade.

AEs	Any grades			Grade ≥ 3		
	T1 (N = 14)	T2 (N = 17)	*p-value*	T1 (N = 7)	T2 (N = 1)	*p-value*
Hypertension	3 (21.4%)	8 (47.0%)	0.06	2 (28.6%)	0 (0%)	0.08
Venous thrombosis	2 (14.3%)	4 (23.5%)	0.28	1 (14.3%)	1 (100%)	0.77
Arterial thrombosis	5 (35.7%)	0 (0%)	0.04	3 (42.8%)	0 (0%)	0.03
Respiratory bleeding	2 (14.3%)	4 (23.5%)	0.28	0 (0%)	0 (0%)	NE
Non respiratory bleeding	2 (14.3%)	0 (0%)	0.20	1 (14.3%)	0 (0%)	0.22
Gastrointestinal perforation	0 (0%)	1 (6.0%)	0.26	0 (0%)	0 (0%)	NE

differences have been observed between stratification cohorts.

The average of the total score of all nine items does not show any significant differences between T1 and T2 (p-value = 0.7142), and a certain homogeneity in the overall perception of the quality of life has been highlighted. The mean symptom score (T1 = 34.4; T2 = 34.8) represents a discrete symptom load or little interfering with health-related QoL (Fig. 3A).

We also evaluated the average symptom burden index perceived by patients using the mean of all six major symptoms and we have found a significant difference to T1 that reported a slight worsening of the symptoms associated with the disease compared to T2 (p-value = 0.0153), while there is no significant difference in the individual cycles. In this context there is a good patients' perception of symptoms, which improves particularly between cycle 2 and cycle 3 (Fig. 3B). The question related to "*how much the disease has affected its ability to perform normal activities*" (item 8) shows a significant difference in cycle 2 where T2 shows a marked worsening compared to T1 in maintaining the daily life (p-value = 0.0127) (Fig. 3C). In both samples the average score obtained highlights the perception of a greater influence of the disease in the patient's ability to perform their daily activities (T1 = 49.9; T2 = 53.1).

To the question "*how would you judge the quality of your life today*?" (item 9) we highlighted a significant difference to cycle 4 (p-value = 0.0232) and cycle 5 (p = 0.0258) between the two treatment groups, where patients allocated to T2 perceived a worsening in their QoL than the T1 treatment group (Fig. 3D).

4. Discussion

The SENECA trial was a real-world experience during which investigators had the possibility to optimize the use of nintedanib, after clear efficacy and safety demonstration as second line treatment option in association with docetaxel q3wks for recurrent non-squamous NSCLC in the LUME-Lung1 trial [14]. During the accrual period, no alternative therapeutic option was available to the use of the sole docetaxel for patients with adenocarcinoma already treated with platinum/pemetrexed chemotherapy in the front-line setting. The reports of the extraordinary efficacy of the immune checkpoint inhibitors for recurrent NSCLC were starting to emerge in 2015 from the results of randomized phase III trials comparing these drugs to docetaxel [6–8], but in Italy the first approval and reimbursement for immune checkpoint inhibitors in this setting was on April 2017, when 69.8% (148 patients out 212) was already enrolled in SENECA. In this historical context, the present study represented for Italian investigators an intriguing challenge in order to overcome their distrust toward docetaxel, its huge and well known toxicity (especially for the q3wks schedule), and to give patients

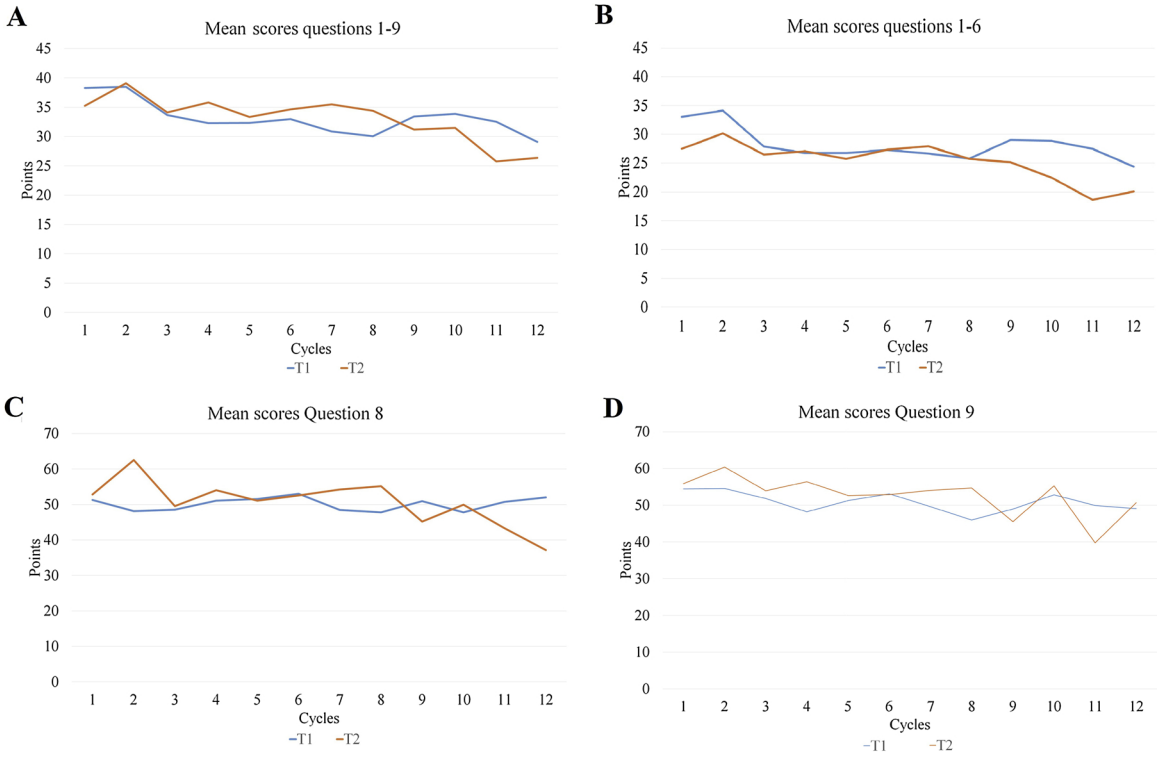


Fig. 3. Quality of life trend according the Lung Cancer Symptom Scale (LCSS) during the first 12 cycles of treatment. Data presented according to docetaxel treatment group (T1 and T2) and in relation to groups of items (A and B) or selected items (C and D) of the LCSS.

the possibility to improve survival adding to chemotherapy an anti-angiogenic compound.

In the SENECA trial, patients have been enrolled according to the relapse time from the end of first-line chemotherapy, leaving to investigators the individual choice of the preferred docetaxel schedule. Despite the biggest limitation of SENECA is strictly related to its statistical design (being this a non-randomized trial), fortunately a perfect balance between T1 and T2 has been reached, giving the possibility of a reliable statistical comparison. A similar median PFS and OS, without statistically significant difference, in both relapse-timing cohorts (C1 and C2) and treatment groups (T1 and T2), has been observed during the study. An analogous PFS and OS between the weekly docetaxel regimen and the classic q3wks schedule, has been described, without statistically significant differences, even without considering the pre-specified stratification cohorts, meaning that the association of docetaxel and nintedanib can be considered equally effective independently from the schedule of chemotherapy employed.

At the present time, these data seem outclassed from the availability in the clinical practice of many immune checkpoint inhibitors as standard treatment option for recurrent non-squamous NSCLC, but these are not discounted, as the efficacy of the weekly docetaxel schedule plus nintedanib had never been investigated before, and can be now considered as a valid alternative to the other regimens, giving to clinicians a new therapeutic opportunity after the publication of the LUME-Lung1 data. This would be even more interesting for those patients receiving immunotherapy combined with chemotherapy in the first-line setting or subsequently after failure of docetaxel/nintedanib. Angiogenesis and immunosuppression have been recently described as closely related processes, physiologically involved in non-pathological tissue repair. They can also be exploited in cancer, facilitating tumor development and progression [26]. Some angiogenic factors, such as VEGF, may have an immunosuppressive function, and anti-angiogenic drugs targeting VEGF can stimulate an immune response [27]. These preclinical data, even if still partially unclear, are really interesting and give clinicians the possibility to build a new hypothetical therapeutic algorithm which includes both anti angiogenic drugs and immunotherapy, variously combined. Because of the lack of data about optimal therapeutic algorithms for nsNSCLC patients and the evidence of a strong biologic rationale for using antiangiogenic drugs and immunotherapy variously combined, it could be of great interest in the next future to investigate if survival expectancy of SENECA patients could be positively influenced by previous immunotherapy, as well as evaluating the post-progression survival, exploring if third-line immunotherapy may be influenced from prior nintedanib use.

In this trial, patients that the investigators thought with the poorest prognosis did not experience the survival advantage expected. Data previously published had described a significantly prolonged survival for patients with recurrent adenocarcinoma who had progressed within 9 months from the start of first-line therapy, treated with nintedanib and docetaxel q3wks, compared to patients of the placebo containing arm, in contrast to what observed for late onset progressors (median OS 9.8 vs 6.3 months; HR 0.62 [95% CI 0.41–0.94], p = 0.0246 for early progressors) [14]. This left us to suppose a similar trend also in the present study, while, on the contrary, an opposite situation has been described, possibly due to independent prognostic factors for patients classified in C2 or R2 cohorts, or more likely due to the non-randomized study design.

Safety profile of the combination treatment resulted good and toxicities easily manageable in both treatment groups. The weekly access to the clinic for T1 patients can reasonably explain the higher number of any grade adverse events observed in this treatment group, with an over-report of adverse events in the T1 arm. Despite this, the SENECA trial has confirmed old literature data according to which the weekly docetaxel schedule can be a preferable treatment option for patients suitable for second-line docetaxel, even with the association to nintedanib, owing to some advantages in toxicities and no shorter survival than the standard regimen. Three randomized phase III trials comparing weekly versus three-weekly docetaxel as second line chemotherapy for advanced NSCLC have been published in the past [28–30]: survival did not statistically differ between the two treatment arms of all these trials, while grade 3–4 haematologic toxicity was significantly more common in the q3wks arm.

In our trial, a general trend of higher toxicity in the docetaxel q3wks schedule emerged for adverse events strictly related to chemotherapy, as confirmed by the higher incidence of afebrile neutropenia, fatigue and oral mucositis of any grade, and grade $\geq$ 3 diarrhea.

Even though in the clinical practice the weekly administration regimen implies that patients make repeated visits at the clinic, with a probable increase in costs and workload of health professionals, the timely management of low-grade toxicities, may result in a lower rate of adverse events requiring hospitalization or treatment discontinuation, with consequently higher overall effectiveness.

A low incidence of class effects associated with anti-angiogenic agents have been noted in both T1 and T2, confirming the safety of the association treatment independently to docetaxel schedule.

Data collected from patients during the study about quality of life (QoL) show that both T1 and T2 keep the perception of QoL stable and how the frequency of treatment does not modify the load for patients, being this not particularly burdensome. This data differs slightly from the literature that indicates that lung cancer is often associated with a greater symptom burden than other type of cancers [31,32]; this difference may be due to the fact that the LCSS evaluates in particular the physical and functional dimensions of the QoL and marginally those physical, social and spiritual ones that.

5. Conclusions

Despite the huge limitation to be a non-randomized trial, SENECA confirms the efficacy and safety of second-line nintedanib and docetaxel for recurrent non-squamous NSCLC patients regardless the docetaxel schedule employed, while few data can be presented according the efficacy of treatment (with the two different schedule) and the time of recurrence of the disease after failure of first-line chemotherapy. Considering the slightly higher toxicities observed in the three-weekly docetaxel treatment group, this study gives to clinicians the possibility to customize the association treatment with nintedanib on the basis of patients' characteristics, choosing to safely adopt the weekly schedule that now can be considered a valid second-line treatment option for non-squamous NSCLC patients. In conclusion, the addition of oral nintedanib to docetaxel infusion, as second-line treatment option for non-squamous NSCLC patients, does not modify safety profile of chemotherapy, leaving the investigators free to adopt the preferred docetaxel schedule according to the expected toxicities of standard chemotherapy.

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