Ergebnisbericht

A prospective phase II, randomized multi-center trial of a biomodulatory treatment with metronomic low-dose treosulfan, pioglitazone and clarithromycin versus nivolumab in patients with squamous cell lung cancer and non-squamous cell lung cancer, respectively, after platin failure

ModuLung

Sponsor Name and Address:	University Hospital Regensburg Represented by Prof. A. Reichle (LKP) Franz-Josef-Strauß-Allee 11 93053 Regensburg, Germany
Investigational Medicinal Products:	Treosulfan (Ovastat®) Pioglitazone (Actos®) Clarithromycin Nivolumab (Opdivo®)
Indication	Non-small cell lung cancers (NSCLCs)
EudraCT-No	2014-004095-31
NCT-No	NCT02852083
Start of Trial	April 2016
End of Trial	March 2019
Version	1.0, November 11, 2020
Written by	Prof. Albrecht Reichle, Dr. Daniel Heudobler

Signature Page

Professor Albrecht Reichle,
Coordinating Investigator

signature

08/02/2021
date

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Trial Statistician

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04-Feb-2021
date

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1 Name of Sponsor/Company

Universitätsklinikum Regensburg
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Franz-Josef-Strauß-Allee 11
93053 Regensburg

2 Name of Finished Product	3 Name of Active Ingredient
Ovastat®	Treosulfan
Actos®	Pioglitazon
Clarithromycin	Clarithromycin
Opdivo®	Nivolumab

4 Individual Study Table

Not applicable

5 Title of Study

A prospective phase II, randomized multi-center trial of a biomodulatory treatment with metronomic low-dose treosulfan, pioglitazone and clarithromycin versus nivolumab in patients with squamous cell lung cancer and non-squamous cell lung cancer, respectively, after platin failure

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8 Publication (reference)

- Xx
- xx
- Xx
- Final analysis (version 3.0, of April 06, 2020)
- Statistical Report (Version 1.0 of August 03, 2020

9 Study period

First patient in: 05. April 2016, **Last patient out**: 18. March 2019

The first patient was enrolled on April 5, 2016. On March 21, 2019, the study trial was prematurely terminated due to the recent availability of new therapeutic options for patients with squamous and non-squamous cell lung cancer (Appendix 22.8 “Early Termination”).

10 Phase of development

Phase II

11 Objectives

According to the study protocol, the primary objective is to assess the efficacy of a biomodulatory therapy with treosulfan, pioglitazone and clarithromycin compared to nivolumab in NSCLC (squamous and non-squamous cell lung cancer) as measured by progression-free survival (PFS).

Secondary objectives are:

- To evaluate the efficacy of the combined biomodulatory treatment with treosulfan, pioglitazone and clarithromycin compared to nivolumab, measured by
  - Overall survival (OS)
  - Duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)
- To evaluate the safety and tolerability of the treatment with treosulfan, pioglitazone and clarithromycin compared to nivolumab
- To evaluate universal response parameters (cellular secretome analytics in serum) for modulation of hallmarks of cancer (inflammation, angiogenesis and immune response)
- To evaluate and compare patient reported outcome (PROs) of lung cancer symptoms, patient functioning and health-related quality of life (HRQoL) between treatment arms, using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module
- To evaluate the relationship between tumor tissue PPARy expression and efficacy
- To assess change in predictive and prognostic exploratory biomarkers in archival and/or fresh tumor tissue and blood (serum)
- Tumor tissue taken at diagnosis or relapse: routine moleculatgenetic biomarkers (EGFR, K-RAS, ALK) and tissue microarray for PPARgamma expression
- Serum: secretome analytics to monitor functions of tumor-associated cellular compartments. Serum probes are taken at the beginning of each cycle.

12 Methodology

The ModuLung trial is a national, multicentre, prospective, open-label, randomized phase II trial in patients with histologically confirmed stage IIIB/IV lung cancer (NSCLC) who failed first-line platinum-based chemotherapy. Patients were randomly assigned on a 1:1 ratio to the biomodulatory or control group, treated with nivolumab. Patients randomized to the biomodulatory group received an all-oral therapy consisting of treosulfan 250 mg twice daily, pioglitazone 45 mg once daily, clarithromycin 250 mg twice daily, until disease progression or unacceptable toxicity.

This study is a phase II, national, multicentre, open-label, randomized and controlled study, evaluating the efficacy and safety of combined modularized treatment of treosulfan, pioglitazone and clarithromycin in patients with locally advanced or metastatic NSCLC, who have progressed during or following a platinum-containing regime.
According to study protocol it was planned to treat 86 patients with platin refractory NSCLC either with metronic low-dose treosulfan, pioglitazone and clarithromycin (**experimental arm**) or with nivolumab (**control arm**). Due to low recruitment rate the study was stopped 21.03.2019 after 40 randomized patient before the planned sample size of 86 has been reached.

Initially (according to study protocol version 3.0, 10.06.2015) was planned to treat 86 patients with platin refractory NSCLC either with metronomic low-dose treosulfan, pioglitazone and clarithromycin (experimental arm) or with docetaxel or docetaxel plus nintedanib (control arm). With amendment 1 (protocol version 6.0, 28.09.2015) treatment in the control arm was changed to nivolumab or docetaxel plus nintedanib in patients with squamous cell lung cancer and non-squamous cell lung cancer, respectively. No patient was included before amendment 1. With amendment 2 (protocol version 7.0, 08.06.2016) treatment in the control arm was finally changed to nivolumab monotherapy for both, patients with cell lung cancer and non-squamous cell lung cancer.

Patients

Eligible patients were patients with histologically or cytologically confirmed locally advanced, unresectable or metastatic NSCLC who had experienced disease progression during or following treatment with a platinum-containing regimen. Patients had to have an ECOG performance status of 0 or 1. Patients with EGFR mutation or ALK rearrangement were eligible if they had progressed during or after standard targeted therapy. Patients with known active or untreated central nervous system (CNS) metastases were excluded.

The institutional review boards and ethic committees of all participating centers approved the protocol (ethics committee of the University of Regensburg approval No.: 15-112-0124).

Randomisation

After a screening period of maximum 30 days, each eligible patient was stratified by histology (squamous cell carcinoma versus adenocarcinoma) and randomized 1:1 to receive either the biomodulatory treatment with treosulfan, pioglitazone and clarithromycin (experimental arm, Arm A) or nivolumab (control arm, Arm B).

- Arm A (experimental arm) – combined biomodulatory treatment:
  The biomodulatory treatment is an all-oral therapy consisting of treosulfan 250 mg twice daily, pioglitazone 45 mg once daily, clarithromycin 250 mg twice daily until progression (patients that showed radiographic progression were allowed to be considered for continued study treatment at the discretion of the investigator as long as evidence of clinical benefit was observed) or unacceptable toxicity.
- Arm B (control arm) – checkpoint blockade:
  Nivolumab, at a dose of 3 mg per kilogram of body weight every 2 weeks until disease progression per RECIST v1.1 or unacceptable toxicity.
  Or pulsed chemotherapy (before amendment 2):
  - Squamous cell carcinoma:
    Docetaxel 75 3g/m² intravenously on day 1 of each 21-day cycle until progression or unacceptable toxicity, for a maximum of 6 cycles until disease progression per RECIST v1.1 or unacceptable toxicity.
  - Non-squamous cell carcinoma:
    Docetaxel 75 mg/m² intravenously on day 1 plus twice daily nintedanib 200 mg p.o. on day 2 to 21 of each 21-day cycle until disease progression or unacceptable toxicity, for a maximum of 6 cycles.

No crossover was allowed between the both arms.

13 Number of patients (planned and analysed)

Planned: 86 patients, **Randomized:** 40 patients, **Treated and analyzed:** 37 patients
(Appendix 22.4 CONSORT-Flowchart)

The first patient was enrolled on April 5, 2016. On March 21, 2019, the study trial was prematurely terminated due to the recent availability of new therapeutic options for patients with squamous and non-squamous cell lung cancer (Appendix 22.8 “Early Termination”).
Since September 17, 2018 no patient received study medication anymore. Until the end of the study, 40 patients were enrolled, randomized in a 1:1 ration in either Arm A (20 patients) or Arm B (20 patients) and stratified according to histology results: squamous cell carcinoma (12 patients) and adenocarcinoma (28 patients). 37 patients (20 patients in Arm A and 17 patients in Arm B) received study medication regularly and are counted as patients treated with study medication.

All 37 patients (20 patients in the experimental Arm - Arm A and 17 patients in the control Arm - Arm B), who were treated with study medication terminated study treatment due to different reasons (multiple reasons for the termination of study treatment for one patient: progression and death due to tumour):

- Progression of the underlying disease (30)
- (Serious) adverse event (5)
  - with causality to study medication (5)
- Death (3), thereof
  - due to Tumour (1)
  - due to Adverse Event (2)
-

14 Diagnosis an main criteria for inclusion

We enrolled patients ≥ 18 years who met the following main criteria:
• Signed Informed Consent Form
• Ability to comply with protocol
• Age ≥ 18 years
• Measurable disease, as defined by RECIST v1.1
• ECOG performance status of 0 or 1
• Life expectancy ≥ 12 weeks
• Histologically or cytologically confirmed locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the Union Internationale Contre le Cancer/American Joint Committee on Cancer [UICC/AJCC] staging system);
• Disease progression during or following treatment with a prior platinumProtocol ModuLung Version 7.0 _ 2016-06-08 8 containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinumbased adjuvant/neoadjuvant regimen
• No more than 2 cytotoxic chemotherapy regimens
• Patients that have progressed during or after treatment with EGFR TKI in firstline, or are intolerant to treatment with erlotinib, gefitinib, or another EGFR TKI may be included.
• Patients that have progressed during or after , or intolerant to treatment with crizotinib or another ALK inhibitor
• The last dose of prior systemic anti-cancer therapy must have been administered ≥ 21 days prior to randomization (≥ 14 days for vinorelbine or other vinca alkaloids or gemcitabine.)
•

• Adequate hematologic and end organ function, defined by the following (max 14 days prior study treatment): ANC ≥ 1500 cells/µL (without granulocyte colonystimulating factor support within 2 weeks of sampling), WBC counts > 2,500/µL and < 15,000/µL, Lymphocyte count ≥ 500/µL, Platelet count ≥ 100,000/µL (without transfusion within 2 weeks of sampling), Hemoglobin ≥ 9.0 g/dL. Transfusion or erythropoietic treatment is allowed.
• Liver function tests meeting one of the following criteria: AST or ALT ≤ 2.5 × ULN, with normal alkaline phosphatase or AST and ALT ≤ 1.5 × ULN in conjunction with alkaline phosphatase > 2.5 × ULN; Serum bilirubin ≤ 1.0 × ULN. Patients with known Gilbert's disease must have serum bilirubin level ≤ 3 × ULN.
• INR and aPTT ≤ 1.5 × ULN, without anticoagulantia. Patients receiving therapeutic anticoagulation must be on a stable dose for at least 1 week prior to randomization.

15 Test product, close and mode of administration, batch number

Patients who were randomly assigned to the experimental arm received an combined biomodulatory treatment:

The biomodulatory treatment is an all-oral therapy consisting of **treosulfan** 250 mg twice daily, **pioglitazone** 45 mg once daily, **clarithromycin** 250 mg twice daily until progression (patients that showed radiographic progression were allowed to be considered for continued study treatment at the discretion of the investigator as long as evidence of clinical benefit was observed) or unacceptable toxicity.

16 Duration of treatment

See above/below (15, 17)

17 Reference substance

Patients who were randomly assigned to the control arm (checkpoint blockade) received **Nivolumab,** at a dose of 3 mg per kilogram of body weight every 2 weeks until disease progression per RECIST v1.1 or unacceptable toxicity.

18 Criteria for evaluation (Efficacy and Safety)

The ModuLung trial addresses the medical need for low-toxic therapies in frequently comorbid patients with relapsed or refractory non-small cell lung cancer (NSCLC). We evaluated safety and efficacy of a biomodulatory approach in patients undergoing second or further line of treatment.
The primary endpoint of the study was progression-free survival (PFS) defined as time from the date of first administration of study therapy to progression or death from any cause, whichever came first. Progression was defined as progressive disease according to RECIST criteria 1.1 (Eisenhauer et al., 2009). Clinical secondary endpoints were overall survival (OS), duration of response, safety, health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13).

19 Statistical methods

The study was designed to detect a change of median PFS from 3 months to 4.5 months. Using a phase II screening design as proposed by Lawrence and colleagues (Lawrence et al., 2005), a power of 0.8 and an alpha of 0.20 (one-sided), 69 events (progression or death) were needed to show superiority of the experimental arm. To observe 69 events, 80 evaluable patients were required (40 per group). To account for an estimated drop-out rate of 5%, 86 patients were to be randomized.
The intention-to-treat population (Full analysis set) was used for all efficacy analyses. Patients' demographics and baseline characteristics were summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum values) for continuous parameters and frequencies and percentages for categorical data. PFS and OS were estimated using the Kaplan-Meier method and compared between groups by the Log-Rank test. Hazard Ratio (HR) comparing the two groups and their 95% Confidence Intervals (CIs) were estimated from a Cox proportional hazards model. Safety analyses included incidence of SAEs. All statistical tests were 2-sided with a 5% Type I error except for the primary endpoint for which a 20% type I error was used as per trial design.
All data were analyzed using the statistical analysis software SAS®.

20 Summary – conclusions

Between April 2016 and Juni 2018, 40 patients from seven sites in Germany were randomly assigned to the bio-modulatory treatment (n=20) or to nivolumab (n=20). The sponsor terminated the trial early because of the approval of anti-PD-1 in the first-line treatment of NSCLC. The control arm of the ModuLung trial became inappropriate. As there is no consensus on a standard control arm treatment following these changes, no amendment could prevent the termination of the trial.
Patients' characteristics are summarized in Table 2 (Appendix 22.2). The CONSORT diagram (Figure 1, Appendix 22.4) illustrates the repartition of the patients within the two study arms. Three patients were excluded due to withdrawal of consent, protocol violation and SAE before receiving treatment. Therefore, the safety set comprises altogether 37 patients.
The scheduled stratification according tumor histology led to a well-balanced distribution of squamous and non-squamous cell carcinomas among the study arms. Even if patients' characteristics were predominantly balanced, the biomodulatory arm only, included three patients with controlled cerebral metastases, and the mean duration of metastatic disease was shorter in the biomodulatory arm, 10.1 months versus 13.3 months, respectively. Within each study group similar proportions of patients were treated in second- to forth-line.
Thirteen patients of the biomodulation arm (65%) received nivolumab/atezolizumab following progression to biomodulatory therapy, whereas few patients in the nivolumab arm were treated with further chemotherapy cycles in case of further progression (Table 2, Appendix 22.2).

Efficacy Results

The efficacy of the study treatment was measured by various parameters:

- In the analysis of progression-free survival 37 patients reached progression or death (100.0% and 100.0%). The median progression-free survival time was 1.4 months (confidence interval [1.2, 2.0]) in arm A and 1.6 months (95%-confidence interval [1.4, 6.2]) in arm B. P-value was 0.0483, hazard ratio 1.908.
- In the analysis of overall survival 26 patients reached death (65.0% and 76.5%), the median survival time was 9.4 months (95%-confidence interval [6.0, 33.0]) in arm A and 6.9 months (95%-confidence interval [4.6, 24.0]) in arm B. P-value was 0.4368, hazard ratio 0.733.

- In the analysis of objective response rate 1 patient (5.0%) (95%-confidence interval [0.1, 24.9]) in arm A and 2 patients (11.5%) (95%-confidence interval [1.5, 36.4]) in arm B were responders. P-value was 0.5843, odds ratio 0.395 (95%-confidence interval [0.033, 4.781]). Disease control (CR-SD) was reached for 2 patients (10.0%) (95%-confidence interval [1.2, 31.7]) in arm A and 6 patients (35.3%) (95%-confidence interval [14.2, 61.7]) in arm B. P-value was 0.1090, odds ratio 0.204 (95%-confidence interval [0.035, 1.193]).
- In the analysis of duration of response (only patients with CR/PR as best response were included) 3 of 3 patients reached progression (100.0% and 100.0%). The median duration of response time was 4.2 months (confidence interval [-, -]) in arm A and 14.3 months (confidence interval [4.6, 24.0]) in arm B. P-value was 0.1573, HR could not calculated due to 100% events and only 3 patients in analysis.

After a median follow-up of 8.25 months, there was a significant difference in PFS (Figure 2, Appendix 22.5). between the study arms. The median PFS time was 1.4 months in the biomodulatory arm and 1.6 months in the control arm B (HR, 1.908; 95% CI, 0.962 to 3.788; p= 0.0483). Best response was one partial response (5%) and one stable disease (5%) in the biomodulatory arm, two partial responses (11.8%), and four stable diseases (23.5%) in the nivolumab arm; with an objective response rate of 5% versus 11,8%, p=0.584. As PFS was the primary endpoint, this is a negative study showing significant inferior PFS for the biomodulatory treatment arm compared with nivolumab. There was, however, no difference in the secondary endpoint median OS (HR, 0.733; 95% CI, 0.334 to 1.610; p= 0.4368) as shown in Figure 3 (Appendix 22.6).

Safety Results

After a median follow-up of 8.25 months, the mean treatment duration was 2.6 months (standard deviation [SD], 3.2 months) overall, in the biomodulatory arm 2.0 months (SD, 2.4 months), in the nivolumab arm 3.4 months (SD, 3.8 months), respectively.

In the pooled safety analysis, treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were reported in fewer patients treated with biomodulatory therapy than in patients treated with nivolumab. 15 patients (75.0%) in the biomodulatory arm and 14 patients (82.4%) in the nivolumab arm had at least one TEAE of any grade. Study medication-related TEAEs of any grade were observed in nine patients (45%) treated with biomodulation and in seven patients (41.2%) treated with nivolumab. Typical treatment-related select TEAEs in the biomodulation arm were peripheral edema, likely due to pioglitazone treatment, N=3 (15%). Six nivolumab-treated patients had first onset of treatment-related typical AEs in GI, hepatic, renal, nervous system or pulmonary categories. There were two study medication-related TEAEs by maximum NCI-CTCAE grade 3-5 in the biomodulatory arm (10%), and five (29%) in the nivolumab arm.

The cumulative TESAEs, NCI-CTCAE grade 3 to 5, are presented in Table 3. No patient in the biomodulatory arm and one patient (5.9%) in nivolumab arm had at least one TESAE related to study medication. During biomodulation, NCI-CTCAE grade 3 to 5 toxicities leading to treatment discontinuation occurred less frequently in 5% versus 29%, respectively. TESAEs in most categories resolved but led to death in the nivolumab arm in N=3 cases (17.6%).

In the nivolumab arm, (scheduled) dose reductions were performed in 3.5% of the cycles, in the biomodulatory arm in 18% of the cycles for treosulfan and pioglitazone, respectively, and in 16% for clarithromycin. Responders in the biomodulatory arm had received dose reductions. Thus, there seems to be no negative impact of dose reduction on outcome.

Results

In this multi-centre study 40 patients were randomized, of which 37 (92.5%) were treated with study medication. 37 patients are included in the safety set, 37 patients in the full analysis set.
The study was planned with 86 patients to be randomized and 69 events (progression/death) needed for the primary endpoint PFS. As only 40 patients were randomized and 37 patients treated, the results have to be interpreted with caution.
The aim of the study was to show, that the experimental arm A with biomodulatory treatment (treosulfan, pioglitazone, clarithromycin) was superior to the control arm B with nivolumab or docetaxel plus nintedanib. This goal could not shown, instead there is a significant superiority for the control arm B.
The study had to be closed pre-maturely due to the approval of immune checkpoint inhibitors (ICi) in first-line treatment. Thirty-seven patients, available for analysis, were treated in second to forth-line. PFS was significantly inferior for biomodulation (N= 20) versus nivolumab (N= 17) with a median PFS (95% confidence interval): 1.4 (1.2-2.0) months versus 1.6 (1.4-6.2), respectively; with a hazard ratio (95% confidence interval) of 1.908 [0.962; 3.788]; p= 0.0483. Objective response rate was 11.8% with nivolumab versus 5% with biomodulation, median follow-up 8.25 months. OS, the secondary endpoint, was comparable in both treatment arms; biomodulation with a median OS (95% confidence interval) of 9.4 (6.0-33.0) months versus nivolumab 6.9 (4.6-24.0), respectively; hazard ratio (97.7% confidence interval) of 0.733 [0.334; 1.610]; p= 0.4368. Sixty-five percent of patients in the biomodulation arm received rescue therapy with checkpoint inhibitors. The frequency of grade 3 to 5 treatment-emergent adverse events was 47% with nivolumab and 40% with biomodulation.

Conclusions
Subsequent to the ostensibly negative result for biomodulatory therapy concerning the primary endpoint PFS, the beneficial median OS based on successful consecutive checkpoint inhibitor therapy, gives rise to the hypothesis that the well-tolerable biomodulatory therapy may prime tumor tissues for efficacious checkpoint inhibitor therapy, even in very advanced treatment lines where poor response to ICi might be expected, increasing with therapy line.

21 Date of Report

11. November 2020

22 Appendix

APPENDIX

22.1 Table 1: Study populations

	A: Biomodulatory therapy (N=20)		B: Checkpoint blockade/pulsed chemotherapy (N=17)		Overall	
	N	%	N	%	N	%
Randomized patients	20	100.0	20	100.0	40	100.0
Safety set (SAF)	20	100.0	17	85.0	37	92.5
Full analysis set (FAS)	20	100.0	17	85.0	37	92.5

22.2 Table 2: Baseline characteristics of the patients

Full analysis set, N=37

Characteristics	Biomodulation, N=20		Nivolumab, N=17	
Age, years				
Mean (SD)	65.4 (±7.4)		61.2 (±7.1)	
Range	56 - 81		50 - 70	
Gender, N (%)				
Female	4	20%	4	24%
Male	16	80%	13	76%
Ethnicity				
Caucasian	20	100%	16	94.1%
African	0	0%	1	5.9%
ECOG Performance Status, N (%)				
0	12	60%	10	58.8%
1	8	40%	7	41.2%
Duration of disease, in months				
Mean (SD)	16.6 (± 18.6)		20.5 (± 20.1)	
Duration of metastatic disease, in months				
Mean (SD)	10.1 (±7.6)		13.3 (±13.2)	
Histology, N (%)				
Squamous cell carcinoma	6	30%	5	29%
Adenocarcinoma	14	70%	12	71%
Grading according to WHO:				
G2	0	0%	1	5.9%
G3	4	20%	5	29.4%
G3-4	12	60%	8	47.1%

GX	4	20%	3	17.6%
EGFR or ALK alteration, N (%)				
***EGFR* wild type**	11	55%	12	70.6%
EGFR	1	5%	0	0%
ALK	0	0%	1	5.9%
unknown	8	40%	4	23.5%
Stage, N (%)				
IIIB	1	5%	0	0%
IVA	5	25%	5	29.4%
IVB	14	70%	12	70.6%
Location of metastatic sites				
Brain (controlled)	3	15%	0	0%
Lung, pleura	13	65%	10	58.8%
Liver	3	15%	3	17.6%
Bone	5	25%	6	35.3%
Adrenal gland	2	10%	2	11.8%
Kidney	0	0%	1	5.9%
Other	13	65%	11	64.7%
Number of metastatic sites				
1	8	40%	7	41.2%
2	8	40%	5	29.4%
3	2	10%	4	23.5%
4	1	5%	1	5.9%
5	1	5%	0	0%
Previous treatment, N (%)				
Platinum-based chemotherapy	20	100%	17	100%
Radiotherapy	9	45%	12	70.6%
Number of lines of chemotherapy, N (%)				
1	13	65%	10	59%
2	6	30%	6	35%
3	1	5%	1	6%
Consecutive therapies				
Checkpoint inhibitor	12	60%	4	24%
Chemotherapy	5	25%	6	35%
No further tumor-directed therapy	3	15%	7	41%

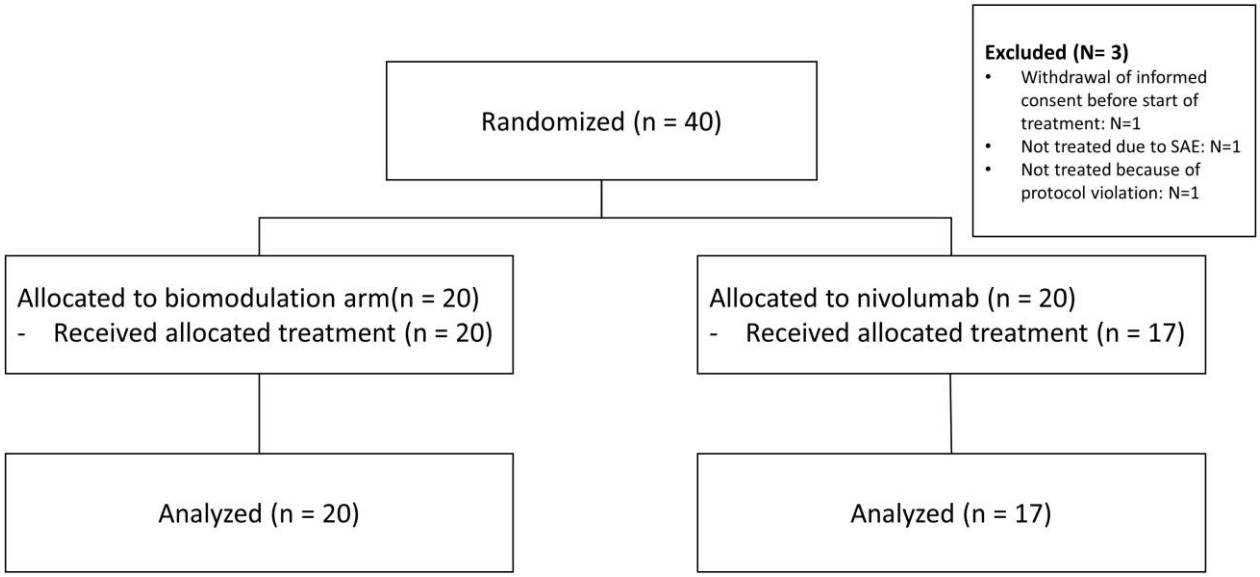
22.3 Table 3: Treatment-emergent serious adverse events (TESAEs)

Treatment-emergent serious adverse events (TESAEs) by maximum NCI-CTCAE grade 3-5 (Population: Safety set, N=37)

System, organ according NCI-CTCAE		Biomodulatory therapy N=20		Checkpoint blockade N=17	
		N	%	N	%
Cardiac disorders	Cardiac failure	-	-	1	5.9
	Pericardial effusion	-	-	1	5.9
Gastrointestinal disorders	Autoimmune colitis	-	-	1	5.9
Infection, Infestation	Peridontitis	-	-	1	5.9
	Pneumonia	-	-	3	17.6
Injury, poisoning, procedural complications	Femur facture	-	-	1	5.9
	Thoracic vertebra fructure	1	5.0	-	-
Nervous system disorders	Cerebral hemorrhage	-	-	1	5.9
Renal and urinary disease	Renal failure	-	-	1	5.9
	Hyronephrosis	-	-	1	5.9
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	5.0	-	-
Skin and subcutaneous tissue disorders	Skin ulcer	1	5.0	-	-

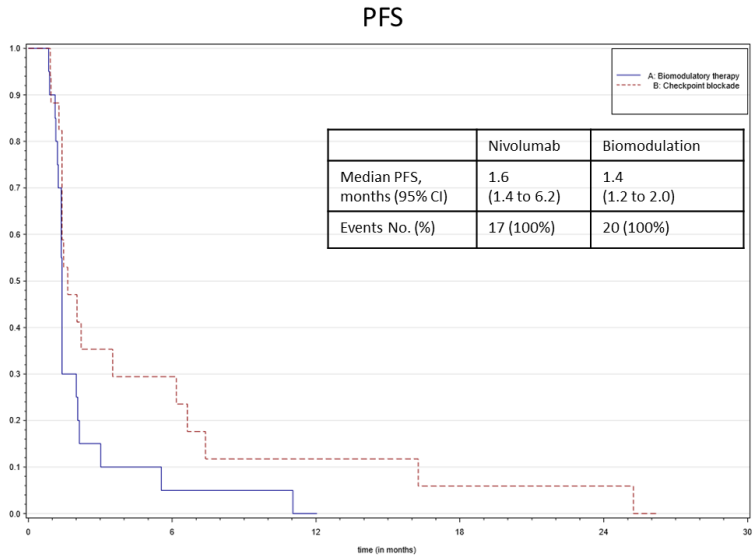
22.4 CONSORT Flowchart

Figure 1



22.5 Kaplan-Meier Representation of the PFS

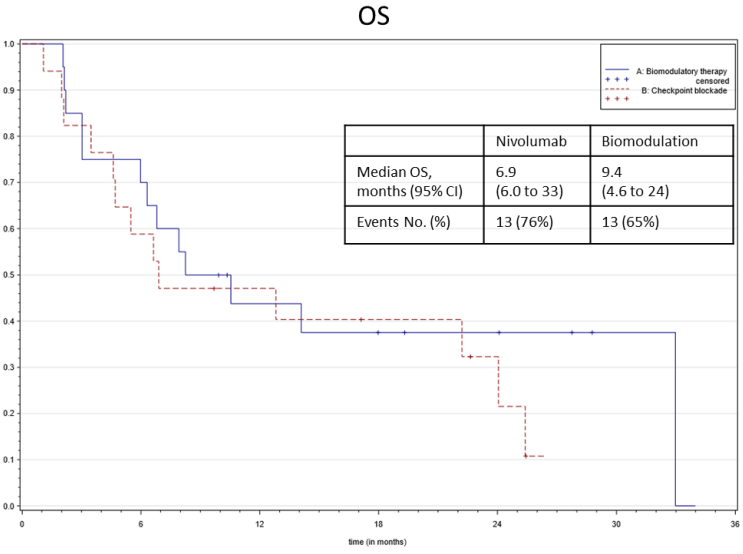
Figure 2



	Nivolumab	Biomodulation
Median PFS, months (95% CI)	1.6 (1.4 to 6.2)	1.4 (1.2 to 2.0)
Events No. (%)	17 (100%)	20 (100%)

22.6 Kaplan- Meier Representation of the OS

Figure 3



	Nivolumab	Biomodulation
Median OS, months (95% CI)	6.9 (6.0 to 33)	9.4 (4.6 to 24)
Events No. (%)	13 (76%)	13 (65%)

22.7 Substantial Amendments

The study was initially designed for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), who have a progression of the disease during or following a platinum-containing regimen. The standard arm treatment was then chosen to consist of docetaxel or docetaxel plus nintedanib.

In **July 2015,** the monoclonal antibody nivolumab was approved in Europe as a standard therapy for second-line treatments of patients with squamous cell lung cancer. Therefore, the standard arm treatment was adapted as follows: patients with squamous cell lung cancer receive nivolumab and patients with non-squamous cell lung cancer receive docetaxel plus nintedanib as a standard arm treatment (**amended Protocol Version 6.0**, dated September 28, 2015; the **Amendment 1** received authorization on October 26, 2015).

Furthermore, in **April 2016,** the monoclonal antibody nivolumab was approved in Europe as a standard therapy for second-line treatments of patients with non-squamous cell lung cancer. Therefore, the standard arm treatment was adapted for patients with non-squamous cell lung cancer. Both, patients with squamous cell and patients with non-squamous cell carcinoma receive nivolumab in the standard arm (amended **Protocol Version 7.0**, dated June 8, 2016; the **Amendment 2** received authorization on July 18, 2016).

22.8 Early termination

On **March 21, 2019**, the study trial was **prematurely terminated** due to the recent availability of new therapeutic options for patients with squamous and non-squamous cell lung cancer. Checkpoint-inhibitors were approved for first-line therapy, which made the recruitment of patients for second-line treatment within the ModuLung study very difficult. This limitation in patients' recruitment could not be resolved.