Pioglitazone and clarithromycin combined with metronomic low-dose chemotherapy versus nivolumab in patients with advanced non–small-cell lung cancer treated in 2nd-line and beyond: Outcomes from a randomized phase II trial (ModuLung)

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BACKGROUND

Despite improvements in the first-line treatment of patients with advanced Non-Small Cell Lung Cancer (NSCLC), nearly all patients experience disease progression. Until recently, patients with previously untreated NSCLC with no driver mutation were treated with first-line chemotherapy, mainly platinum-based. Second-line treatment consisted of a different line of chemotherapy with single-agent docetaxel as the main option. The advent of inhibitors of the programmed cell death protein 1 (PD-1) or its ligand (PD-L1) in NSCLC has improved patients' outcomes and changed the therapeutic landscape. Anti-PD-1 were first shown to be superior to docetaxel as second-line treatment. This was followed by results of first-line anti-PD-1 combined with chemotherapy showing superiority to chemotherapy alone in the first-line treatment of these patients. Just when the ModuLung trial was initiated, nivolumab became a standard second-line option in both squamous and non-squamous NSCLC in Germany. However, anti-PD-1 in first line were not yet standard treatment.

Our group has shown that a combination of therapies modulating tumour angiogenesis, inflammation and immune response can result in a significant survival benefit in patients with various advanced malignancies. **This approach, called biomodulation, aims to induce communicative reprogramming of dysregulated cellular and intercellular homeostasis (anakoinosis)**. In the trial reported here, biomodulation consisted of a combination of pioglitazone, clarithromycin and low-dose treosulfan.

METHODS

The ModuLung trial (EUDRACT 2014-004095-31, NCT02852083) is a national, multicentre, prospective, open-label, randomised phase II trial in advanced NSCLC who failed first-line platinum-based chemotherapy. Patients were randomly assigned on a 1:1 ratio to the experimental or to the control group (Figure 1).

The intention-to-treat population was used for all efficacy analyses.

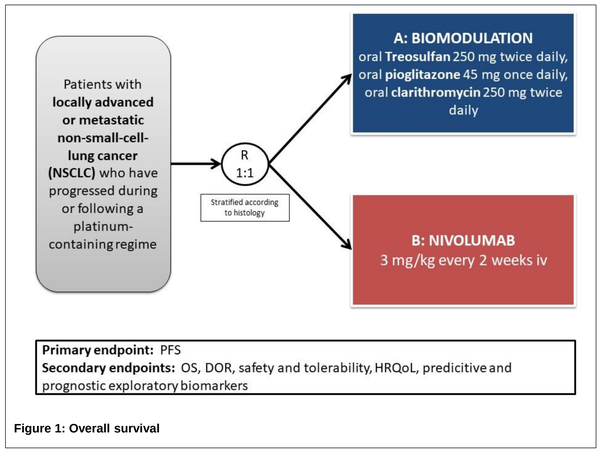

Figure 1: Overall survival

RESULTS – Pat. characteristics

Between April 2016 and June 2018, 40 patients from 9 sites in Germany were randomly assigned to the bio-modulatory treatment (n=20) or to nivolumab (n=20). The trial was terminated 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 second-line treatment following these changes, no amendment could prevent the termination of the trial.

The data cut-off for the primary efficacy analysis (PFS) was 3th April 2019 with a median duration of observation of 6.9 months (range: 1.1-33).

The main efficacy results are presented in the Table 2 and show no statistically significant difference between groups. Kaplan-Meier-Plots for PFS and OS are shown in Figure 2+3. The two-year survival rate achieved in the biomodulatory arm was 10% (95% CI, 1.2 to 31.7) and 5.9% (95% CI, 0.1 to 28.7) in the nivolumab arm. 75% and 53% of the patients proceeded to a further line of therapy, respectively.

Characteristics	A: Biomodulation N=20		B: 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%)
ECOG Performance Status, N (%)				
0	11	(55%)	10	(59%)
1	8	(40%)	6	(35%)
Unknown	1	(5%)	1	(6%)
Time from first diagnosis to randomisation, in months				
Mean (SD)	16.5 (18.7)		20.5 (20.1)	
Range	12 – 91		13 - 81	
Histology, N (%)				
Squamous cell carcinoma	6	(30%)	5	(29%)
Adenocarcinoma	14	(70%)	12	(71%)
PD-L1-Status				
	tbd		tbd	
EGFR or ALK alteration, N (%)				
EGFR-wt	10	(50%)	11	(65%)
ALK translocation	0	(0%)	1	(6%)
Unknown	10		5	(29%)
Stage, N (%)				
IIIB	1	(5%)	0	(0%)
IV	19	(95%)	17	(%)
Previous treatment, N (%)				
Platinum-based chemotherapy	20	(100%)	17	(100%)
Radiotherapy	9	(45%)	11	(65%)
Number of lines of chemotherapy, N (%)				
1	13	(65%)	10	(59%)
2	6	(13%)	6	(35%)
3	1	(5%)	1	(6%)

Table 1: Baseline Characteristics; tbd = to be determined

Central testing for PD-L1-Status, mutational profiling as well as biomarker analysis is still ongoing.

RESULTS - Efficacy

	A: Biomodulation (n=20)	B: Nivolumab (n=17)	HR & 95% CI or p-value
	35% > 2nd-line	41% > 2nd-line	
PFS, median in months	**1.6**	**2.1**	HR=1.17; 95% CI, 0.59-2.34
OS, median in months	**8.2**	**6.9**	HR=0.86; 95% CI, 0.38-1.96
ORR, n (%)	**2 (10%)**	**0 (0%)**	P=0.49

Table 2: Efficacy

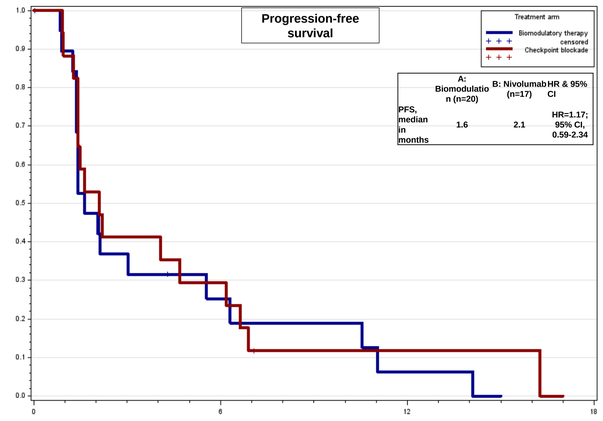

Figure 2: Progression-free survival

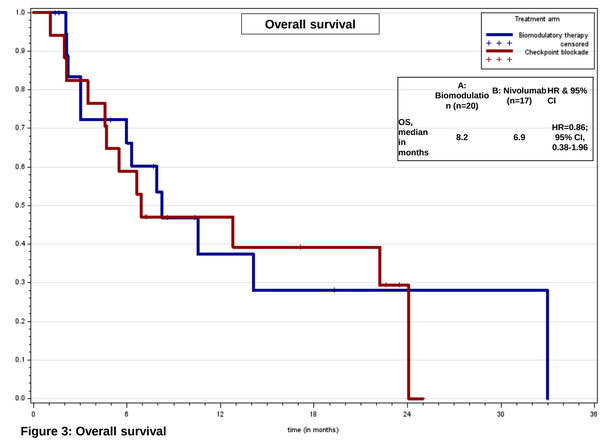

Figure 3: Overall survival

RESULTS - Safety

All (serious) adverse events are presented in Table 3+4. In the Nivolumab-arm two grade 5 events occurred (pneumonia + cardiac failure) which were evaluated to be not related to the study intervention.

Category	A: Biomodulation, N=20		B: Nivolumab, N=17	
	N	%	N	%
At least one AE	12	60.0	10	58.8
At least one AE with max. NCI-CTCAE grade 3-5	5	25.0	6	35.3
At least one AE with max. NCI-CTCAE grade 5	-	-	2	11.8

Table 3: Adverse events ; Population: Safety set, N=37

Term	A: Biomodulation, N=20		B: Nivolumab, N=17	
	N	%	N	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	10.0	2	11.8
CARDIAC DISORDERS	-	-	1	5.9
GASTROINTESTINAL DISORDERS	-	-	1	5.9
GENERAL DISORDERS	-	-	3	17.6
INFECTIONS	1	5.0	2	11.8
INJURY	1	5.0	1	5.9
LABORATORY INVESTIGATIONS	-	-	1	5.9
PSYCHIATRIC DISORDERS	1	5.0	-	-
RENAL AND URINARY DISORDERS	-	-	1	5.9

Table 4: Adverse events with maximum NCI-CTCAE grade 3-5; Population: Safety set, N=37

CONCLUSIONS

- Combination of clarithromycin, pioglitazone and metronomic chemotherapy **is active in the >=2nd line treatment of NSCLC and warrants further investigations**.
- The biomodulatory **treatment was very well tolerated.**
- **Novel treatment approaches are urgently needed** for patients who previously received platinum-based chemotherapy for advanced squamous and non-squamous NSCLC

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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