Multizentrische randomisierte Phase II Studie zur Therapie des okal fortgeschrittenen oder metastasierten NSCLC (Stadium IIIB/IV) mit Cisplatin/Docetaxel oder Oxaliplatin/Docetaxel
EudraCT Nummer 2008-002197-35
Code 417

Synopsis Results Report

Report-ID: S417

1. Name of Sponsor/Company
Krankenhaus Nordwest GmbH, Steinbacher Hohl 2-26, 60488 Frankfurt/M

2. Name of Finished Product
Eloxatin 5mg/ml, Zul.-Nr.: 63264.00.00
Taxotere 20 mg, Zul.-Nr.: EU/1/95/002/001
Taxotere 80 mg, Zul.-Nr.: EU/1/95/002/002
Cisplatin-Lösung Ribosepharm, Zul.-Nr.: 3001928.02.00

3. Name of Active Substance
Oxaliplatin
Cisplatin
Docetaxel

4. Individual Study Table: Referring to Part of the Dossier
Not applicable

5. Title of Study
Multizentrische randomisierte Phase II Studie zur Therapie des lokal fortgeschrittenen oder metastasierten NSCLC (Stadium IIIB/IV) mit Cisplatin/Docetaxel oder Oxaliplatin/Docetaxe
(Prospective Phase II Study with either Cisplatin/Docetaxel or Oxaliplatin/Docetaxel in patients with advanced or metastatic non-small cell lung cancer

Version 1 -14.04.2008 – for first submission, never in use.
Version 2 -24.07.2008 (Amendment only regarding inclusion/exclusion criteria as requested by regulatory authorities during submission process) – first and only used version.
There were no further protocol amendments and no amendment/ modification regarding the treatment protocol. There was no interruption or delay of study conduct, and no early termination of the study.

6. Investigators (principal investigators, alphabetical)
7. Study centre(s)

Prof. Dr. Elke Jäger (LKP)
Dr. Akin Atmaca
Krankenhaus Nordwest
Klinik für Onkologie
Steinbacher Hohl 2-26
60488 Frankfurt am Main

Prof. Dr. Helga Bernhard
Klinikum Darmstadt
Med. Klinik V
Grafenstr. 9
64283 Darmstadt

Dr. Patrick Brück
Klinikum Offenbach
Ambulantes Onkologisches Zentrum
Starkenburgring 66
63069 Offenbach

Prof. Dr. Karel Caca
Klinikum Ludwigsburg
Med. Klinik I
Posilipostr. 4
71640 Ludwigsburg

Prof. Dr. H. Guenter Derigs
Städtisches Klinikum Frankfurt Höchst
Hämatolgie und Internistische Onkologie
Gotenstr. 6-8
65929 Frankfurt am Main

Gerrit Dingeldein
Onkologisches Studienzentrum
Eschollbrücker Str. 26
64285 Darmstadt

Dr. Andreas Jakob
Onkologische Schwerpunktpraxis
Offenburg
Hauptstr. 42
77652 Offenburg

Prof. Dr. Michael Koenigsmann
MediProjekt
Dres.med.Gaede/Ehlers/Rodewig
Marienstr. 90
30171 Hannover

Prof. Dr. Frank Kullmann
Klinikum Weiden
Med. Klinik I
Söllnerstr. 16
92637 Weiden

Prof. Dr. Thomas Neuhaus
St. Vincenz-Krankenhaus Limburg
Abteilung Hämatologie und internistische Onkologie
Auf dem Schafsberg
65549 Limburg

PD Dr. Gernot Seipelt
Onkologische Schwerpunktpraxis
Kronberger Str. 38
65812 Bad Soden

Dr. Bernd Sulzbach
Gemeinschaftspraxis
Wilhelmsplatz 11
63065 Offenbach

Prof. Dr. Florian Weissinger
Ev. Krankenhaus Bielefeld gGmbH
Innere Medizin: Onkologie/Hämatologie u. Palliativemedizin
Schildescher Str. 99
33611 Bielefeld

8. Publication (reference)
Manuscript published 02/2013 in British Journal of Cancer
Br J Cancer. 2013 Feb 5;108(2):265-70. doi: 10.1038/bjc.2012.555. Epub 2013 Jan 17

9. Studied period (years): date of first enrolment, date of last completed
2008-2011

10. Phase of development
Phase II

11. Objectives

Primary
Response Rate
Secondary
Toxicity
Quality of Life
Time to treatment failure (TTF)
Progression-free survival
Overall Survival

12. Methodology

Patients with histological or cytological confirmed, previously untreated, advanced or metastatic non-small cell lung cancer were eligible. Patients were stratified by centre and performance status and were randomly assigned to either cisplatin/docetaxel (arm A) or oxaliplatin/docetaxel (arm B).

Patients were seen for clinical visits at baseline/screening and during treatment period for safety assessment and therapy application until disease progression or discontinuation of trial therapy for other reasons. Patients were assessed for adverse events by non-directive questioning at each visit during the study. Adverse events also were detected when they were volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Adverse events were documented according to the CTC AE version 3. Additionally, relationship of an adverse event to the investigational agent was determined by the Investigator. Radiological tumor assessment (CT, MRI) and evaluation of quality of life (via questionnaires EORTC-QLQ-C30 and EORTC QLQ-LC13) was performed at baseline and then every 8 weeks until progression of the disease. Post-study follow-up was completed after 6 months for survival and tumor assessment.

13. Number of patients (planned and analysed)

Planned: 88 patients in total (44 pts. per arm)

Analysed: 86 patients evaluable for efficacy analysis (43 pts in arm A and 45 pts in arm B), 87 patients were evaluable for safety analysis

14. Diagnosis and main criteria for inclusion

- Patients with histologically confirmed stage IIIB or IV (UICCC 6) NSCLC
- Measurable target lesion
- no brain metastases
- no previous cytostatic therapy in metastatic setting
- patients (male and female) older than 18 years
- ECOG 0, 1 or 2
- Leucocytes > 3000/µl
- Thrombocytes >100000/µl
- Creatinine serum level < 1,25 x ULN or Creatinine clearance > 45 ml/min
- signed informed consent

15. Test product, dose and mode of administration, batch number

Patients in the arm A received cisplatin 75 mg/m^2 as a 2-h infusion and docetaxel 75 mg/m^2 as a 1-h infusion every 3 weeks. Patients in the experimental arm B received oxaliplatin 85 mg/m^2 as a 1-h infusion and docetaxel 50 mg/m^2 as a 1-h infusion every 2 weeks.

Batch numbers Oxaliplatin/Eloxatin:

50 mg	**100 mg**
D8A215	D8A201
D8C516	D8A446
D8C280	D8A684
D9A150	D8C226
D9A820	D8D137
D9C196	D9A139
	D9A140
	D9A292
	D9A872
	D9C185
	D0A201

Not applicable for other substances (not provided, generics with marketing authorization)

16. Duration of treatment

Treatment in arm A was continued up to six cycles and in arm B up to 8 cycles or until disease progression, unacceptable toxicity, patient's refusal or physician's decision.

17. Reference therapy, dose and mode of administration, batch number

Not applicable

18. Criteria for evaluation: Efficacy, Safety

For the assessment of toxicity, patients were interviewed using a standardized set of questions and were evaluated by physical examination and laboratory tests, including complete blood count, blood chemistry, and urine analysis, every week. Toxic effects were graded according to NCI-CTC version 3.0. Responses were classified according to RECIST version 1.0. Computed tomography or magnetic resonance imaging scans of target areas were performed before the start of the treatment and were repeated every 8 weeks in both arms. Patients who discontinued the study were evaluated every 2 months. Time to progression (TTP) was measured from the date of random assignment until disease progression. Overall survival (OS) was measured from the date of random assignment until death of any cause.

19. Statistical methods

The primary end point was response rate according to RECIST 1.0 (Fisher's exact test). Secondary end points were toxicity (P for trend test), TTP (log-rank test), and OS (logrank test). Survival data were calculated using the Kaplan–Meier method on the intent-to-treat (ITT) population, which was predefined as all randomly assigned patients with NSCLC (efficacy population). The safety analysis included all patients who received chemotherapy (safety population). According to Simons optimal two-stage design for clinical trials, calculated sample size with the assumption of a lower response rate of 30% and a difference of 15% was 81. Expecting a drop-off at a rate of 10%, we decided to enrol 88 patients in total.

20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

Results:

A total of 88 patients (median age: 65 (39–86) years; stage IV: 93%) were randomly assigned. Response rate (complete and partial response) was 47% (95% CI: 33–61%) in the cisplatin/docetaxel arm and 28% (95% CI: 17–43%) in the oxaliplatin/docetaxel arm (P=0.118). There was no significant difference in time to progression (6.3 vs 4.9 months, P=0.111) and median overall survival (11.6 vs 7.0 months, P=0.102) with cisplatin/docetaxel vs oxaliplatin/docetaxel, although slight trends favouring cisplatin were seen. Oxaliplatin/docetaxel was associated with significantly less (any grade) renal toxicity (56% vs 11%), any grade fatigue (81% vs 59%), complete alopecia (76% vs 27%), any grade leukopenia (84% vs 61%) and grade 3/4 leukopenia (44% vs 14%) and neutropenia (56% vs 27%).

The primary endpoint (improvement of response rate) was not met.

Oxaliplatin/docetaxel has activity in metastatic non-small cell lung cancer, but it seems to be inferior to cisplatin/docetaxel.

Table 1: Response rate

	Cis/Doc (n=43)		Ox/Doc (n=43)	
	No.	%	No.	%
CR	1	2	1	2
PR	19	44	11	26
RR*	**20**	**47**	**12**	**28**
SD	12	30	15	35
PD	3	7	11	26
NE	8	19	5	12

CR: complete response, PR: partial response, RR: response rate, SD: stable disease, PD: progressive disease, NE: not evaluable

Cis/Doc: 95% CI (confidence interval): 0.3251 to 0.6109. Ox/Doc: 95% CI: 0.1663 to 0.4281; *p-value=0.1178

Table 2: Main toxicities according to the National Cancer Institute Common Toxicity Criteria version 3 (treatment-related toxicities)

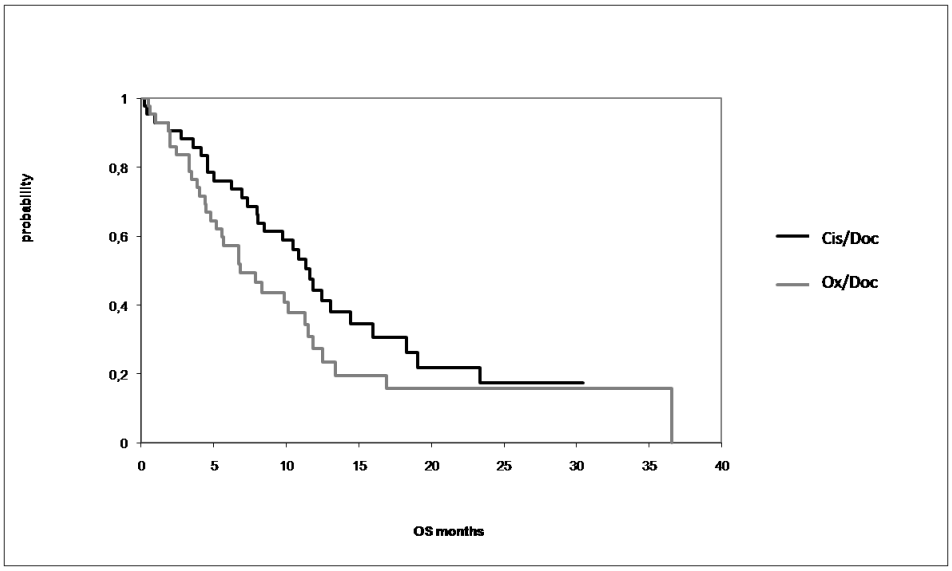
	all grade					**grade 3/ 4**				
	Cis/Doc (n=43)		Ox/Doc (n=44)		p-value	Cis/Doc (n=43)		Ox/Doc (n=44)		p-value
	No.	%	No.	%		No.	%	No.	%	
Hematologic										
anaemia	33	76,7	30	68,2	ns	1	2,3	5	11,4	ns
leukopenia	**36**	**83,7**	**27**	**61,4**	**0.0300**	**19**	**44,2**	**6**	**13,6**	**0.0020**
neutropenia	31	72,1	26	59,1	ns	**24**	**55,8**	**12**	**27,3**	**0.0091**
thrombocytopenia	14	32,6	7	15,9	ns	4	9,3	0	0	0.0554
Gastrointestinal										
nausea	39	90,7	38	86,3	ns	10	23,6	10	22,7	ns
vomitting	25	58,1	22	50	ns	6	14	2	4,5	ns
diarrhea	28	65,1	25	56,8	ns	8	18,6	4	9,1	ns
constipation	12	27,9	8	18,2	ns	0	0	0	0	ns
stomatitis	24	55,8	17	38,6	ns	4	9,3	1	2,3	ns
Hepatic										
AST/ALT	7	16,3	15	34,1	ns	1	2,3	2	4,5	ns
ALP	7	16,3	9	20,5	ns	0	0	1	2,3	ns
Neurologic										
neuro-sensory	23	53,5	27	61,4	ns	1	2,3	2	4,5	ns
Other										
alopecia	38	88,4	31	70,5	ns	**33**	**76,4**	**12**	**27,3**	**>0.0001**
fatigue	**35**	**81,4**	**26**	**59,1**	**0.0344**	9	20,1	9	20,5	ns
creatinine	**24**	**55,8**	**5**	**11,4**	**>0.0001**	1	2,3	1	2,3	ns
weight loss	18	41,9	12	27,3	ns	1	2,3	0	0	ns
infection	18	41,9	13	29,5	ns	11	25,6	4	9,1	0.0507
fever	10	23,6	8	18,2	ns	0	0	0	0	ns

Abbreviations: Cis/Doc, cisplatin/docetaxel; Ox/Doc, oxaliplatin/docetaxel; AST/ALT, aspartate aminotransferase/alanine aminotransferase; ALP, alkaline phosphatase; NS, not significant. Bold numbers indicate statistically significant differences.

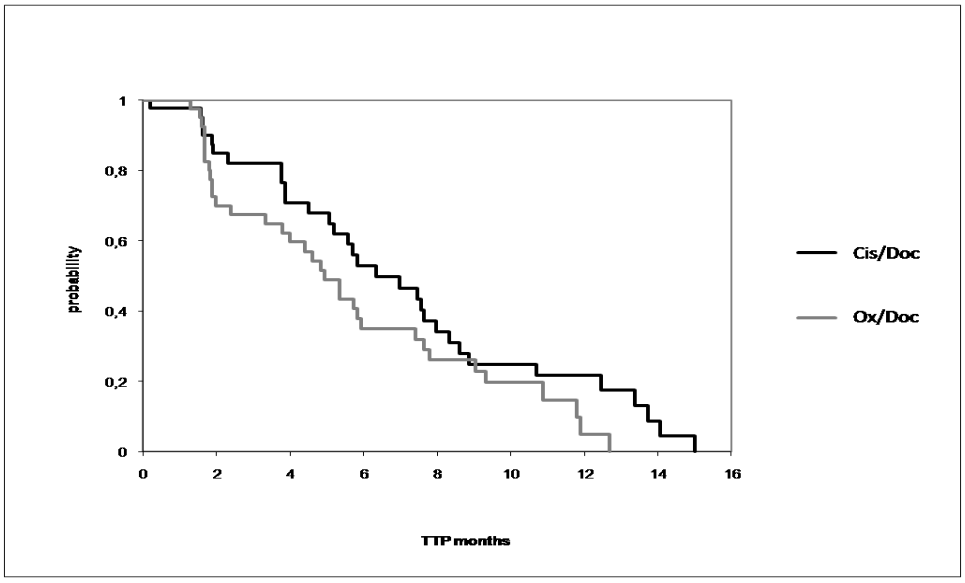
Figure 1: Survival analysis

Kaplan-Meier curves for (A) overall survival (OS) and (B) time-to-progression (TTP), assessed in the entire population. Median OS was 11.6 vs. 7.0 months and median TTP 6.3 vs. 4.9 months with cisplatin/docetaxel vs. oxaliplatin/docetaxel, respectively.

A



B



Conclusion:

This study showed that the oxaliplatin/docetaxel combination has activity in the first-line treatment of metastatic non-small lung cancer but it seems to be inferior to cisplatin/docetaxel. The extent of activity observed in this trial does not justify further evaluation in a phase III setting. The study also showed that some reduction of toxicity was observed, mainly with respect to nephrotoxicity and leukopenia/neutropenia, as expected.

In conclusion, oxaliplatin/docetaxel is an active first-line regime for patients with metastatic NSCLC. Nevertheless, therapy with oxaliplatin should be applied only to patients who do not qualify for therapy with cisplatin.

21. Date of report

08.02.2019 (revised 25.02.2019)