Clinical Study Report

Clinical Trial:	Phase II Study to Investigate the Treatment of Patients with NSCLC Stage IIIB and IV without the Option of Surgery with a Combination of Cisplatin, Docetaxel and Bevacizumab
Clinical Phase:	II
Protocol Number:	AGMT _NSCLC 1
EudraCT:	2008-000765-33
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Study initiation date (FPI)	10.06.2010
Study completion date (LPO)	06.12.2012

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1 Ethics

The study was conducted in accordance with GCP and all applicable local laws and the Declaration of Helsinki, including archiving of study documents.

The protocol was approved by local ethics committees and informed consent was obtained from all patients.

2 Investigators and Study Administration Structure

Coordinating Investigator: Univ.-Prof. Dr. Richard Greil

The list of investigators and participating sites can be found in Appendix 1.

3 Rational

Despite recent advances in the treatment of NSCLC overall survival within this patient population remains dismal and there is yet an unmet medical need for additional treatment options.

Angiogenesis has recently been identified to play a major role in cancer and the vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis in normal and malignant tissue. Bevacizumab, a humanized variant of a mouse monoclonal antibody directed against VEGF has shown clinical activity against a number of human cancers and offered some promising results in the treatment of NSCLC [1][2].

Although this data points in the correct direction, many questions remain unanswered, such as for example the fact that, despite the markedly greater difference in the response rate in favor of bevacizumab therapy, the chemo-immune therapy did not result in a survival benefit in women (ECOG 4599 Trial). Currently, documented survival benefits are only available for the ECOG 4599 Study, in which a dosage of 15 mg/kg bevacizumab was given in combination with chemotherapy with carboplatin and paclitaxel. In the AVAIL Study, this dosage of bevacizumab was not superior to the dosage of 7,5 mg/kg, but it was associated with a significant increase in the incidence of side effects. However, this study used a combination of cisplatin/gemcitabine as chemotherapy.

In terms of chemotherapeutic regimens, previous studies with chemotherapy alone have basically not shown any significant difference between the various combinations of cisplatin and a second cytostatic of the newer generation [3]. Nonetheless, this data cannot automatically be transferred to a situation with bevacizumab and it is necessary to furnish actual proof that the respective chemotherapy combinations are comparably effective. Meta-analyses show a significant survival difference in advanced stages between cisplatin combinations and therapies including carboplatin; in the biggest single study conducted so far, docetaxel proved to be superior to therapy with vinorelbine in such a combination [4]. Moreover, the interactions between chemotherapeutic agents and bevacizumab may differ. Indeed, the lowering of intratumoral interstitial pressure results in significantly improved permeabilization of the tumor for cytostatics. This effect does not automatically have to be identical for all chemotherapeutic agents or even for all dosages of bevacizumab. In fact, the differences between the three therapy arms in the AVAIL Study are considerably less than in the ECOG Study therefore the benefit with regard to response rate cannot automatically be assumed to also apply to the survival rate with the combination cisplatin/

gemcitabine. This is all the more true as there is significant uncoupling of response and survival in subpopulations in the ECOG 4599 Study. Moreover, the preceding study results with equivalence of various chemotherapy regimes have created a situation in which the side effects profile of the various regimes can be adapted to the patient's individual situation without any loss of effect. As a result, the total pool of treatable patients is significantly increased. Thus it is very important to show comparable response rates and overall therapy results also for other treatment regimes combined with bevacizumab in addition to the regime positive with regard to OS in the ECOG Study so far.

This clinical study therefore aims to investigate (i) to what extent a similar response rate to those achieved both in the ECOG 4599 and the AVAIL study can be achieved with treatment with cisplatin and docetaxel as a proven effective primary therapy combination combined with the lowest effective dose of bevacizumab, i.e. 7.5 mg/kg, and (ii) which profile of side effects can be achieved with this therapy regime. Altogether, a basis for the development of an alternative regime to the two therapy regimes so far is thus to be created.

4 Study Objectives

4.1 Primary Objective

The primary objective of this proof-of-concept study is to determine the objective response rate in patients with unresectable, stage IIIB and IV non-small cell lung carcinoma treated with the combination cisplatin, docetaxel and bevacizumab. This response rate will be compared to historical data from the ECOG4599 and AVAiL trials.

4.2 Secondary Objective

- Progression free survival, defined as the duration of time from first study treatment until progression or death from any cause as documented by the investigator.
- Overall survival, defined as the duration of time from first study treatment until death from any cause.
- Duration of response defined as timeframe from first response (CR or PR) until progression from best response.
- Overall toxicity according to NCI-CTC criteria.

5 Investigational Plan

This was a non-randomized, multicenter, open-label, single-arm Phase II study in patients with previously untreated inoperable NSCLC stages IIIB and IV.

It was planned to enroll a total number of 40 patients.

6 Overall Study Design

Eligible patients initially received 3 cycles of bevacizumab 7,5 mg/kg (Bev), cisplatin 75 mg/m^2 (C) and docetaxel 75 mg/m^2 (D). Patients with complete response (CR), partial response (PR) or stable disease (SD) received a further 3 cycles of treatment, which was followed by a final staging. In the case of radiological progressive disease (PD) at the specified staging times (or clinical at any time), or

as the result of clinical suspicion, participation in the study was terminated prematurely.

Patients having obtained CR, PR or SD after a full 6 cycles of therapy were eligible to receive maintenance treatment with bevacizumab monotherapy at 7,5 mg/kg until progression, withdrawal of patient consent or occurrence of unacceptable toxicity (Figure 1).

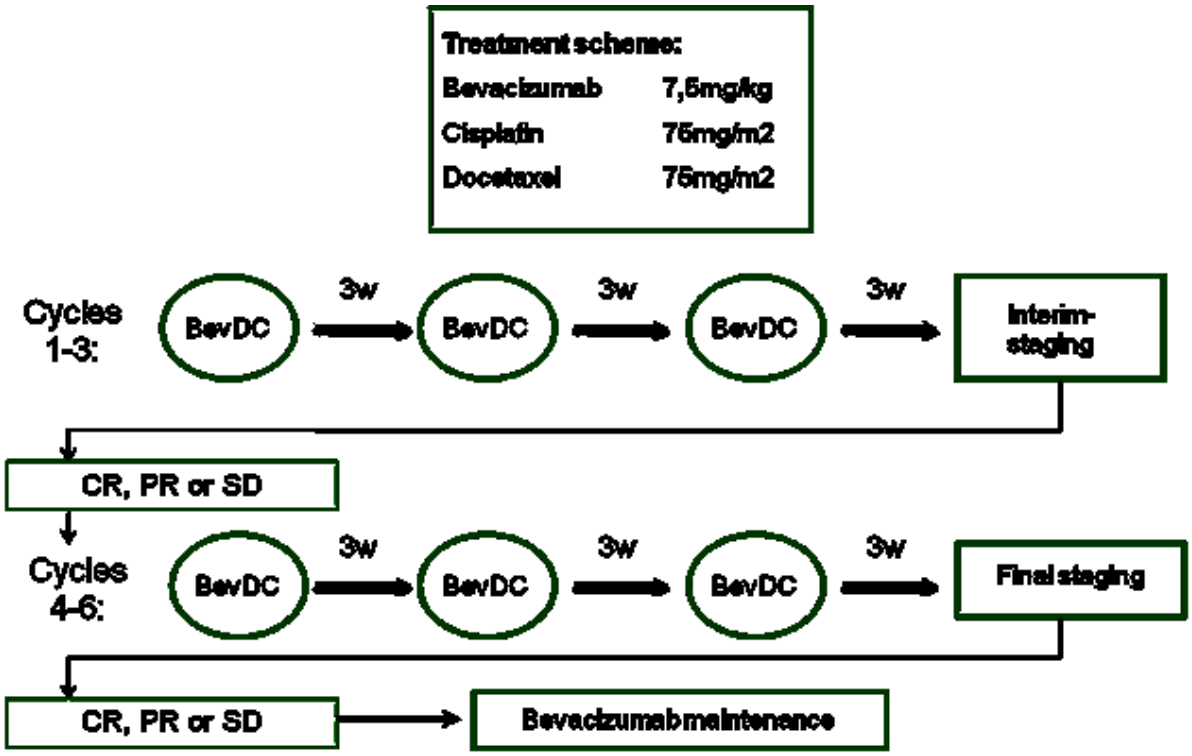

Figure 1: Study design

7 Early Termination of the Trial

Because of very slow recruitment the recruitment was set “on hold” in July 2012. Last Patient Last Visit (including safety evaluation) was 2012/12/06.

8 Study Population

In total 7 patients were enrolled. In Table 1 the characteristics of the enrolled patients is shown. Median age was 55 years at study entry. 4 patients were female, 3 were male. All enrolled patients showed NSCLC stage IV. The list of enrolled patients can be found in appendix 2.

Patient characteristics	
Median Age (range)	55 (41 – 64)
Female / Male	4 / 3
Stage IIIB / IV	0 / 7

Table 1: Patient characteristics (n=7)

9 Cumulative Doses

One patient terminated study treatment after the first induction treatment cycle. 2 patients received

3 cycles of induction therapy. 3 patients underwent 6 induction treatment cycles and 1 patient received 6 induction treatment cycles followed by 9 cycles of bevacizumab maintenance. Cumulative doses are shown in Table 2.

Patient	Number of Cycles	Cumulative doses Bevacizumab [mg] (days of exposition)		Cumulative doses Docetaxel [mg] (days of exposition)		Cumulative doses Cisplatin [mg] (days of exposition)	
101	6	2400	(107)	600	(85)	720	(107)
102	3	1680	(54)	420	(54)	420	(54)
9203	1	580,5	(1)	147,75	(1)	147,75	(1)
9304	6	3000	(106)	780	(106)	780	(106)
205	6 + 9	9675	(314)	761,25	(107)	761,25	(106)
106	3	1230	(43)	345	(43)	345	(43)
107	6	2500	(106)	760	(106)	760	(106)

Table 2: Cumulative doses of bevacizumab, cisplatin and docetaxel per patient

10 Efficacy Evaluation

According to the poor enrolment (7 patients enrolled, 40 patients planned) response rates cannot be evaluated. The defined sample size for interim analysis (20 patients) was not reached.

10.1 Overall Best Response

Overall best response was PR (3), SD (1), PD (2). One patient terminated study treatment without evaluation of response.

10.2 Study Termination

6 patients terminated study treatment because of disease progression, 3 of them after 6 induction cycles, 2 after 3 induction cycles. One patient could reach the maintenance phase and showed PD after 9 cycles of bevacizumab maintenance. One patient terminated study participation after the first treatment cycle due to an adverse event.

11 Safety Evaluation

11.1 Adverse Events

All reported adverse events are listed in Table 3. Grading was done using the CTCAE version 3.0.

75 adverse events were documented. 14 of them were in the opinion of the investigator at least possibly related to bevacizumab, 43 to docetaxel respectively, and were therefore classified as adverse reaction. 11 serious adverse events (SAE) were reported, 1 of them was considered possibly related to bevacizumab, 4 were considered at least possibly related to docetaxel, none was classified as SUSAR. The list of SAEs including a detailed description is attached (appendix 3).

						Relation to			
Patientnumber	Event Nr.	Event	Grade	Start	Stop	Bevacizumab	Cisplatin	Docetaxel	SAE
101	1	Adynamia	2	14.06.2010	17.06.2010	0	0	0	Yes
101	2	Anorexia	1	14.06.2010	17.08.2010	0	0	0	No
101	3	Fatigue	1	06.07.2010	08.07.2010	0	0	0	No
101	4	Elevated CRP	.	14.06.2010	09.01.2011	0	0	0	No
101	5	Nausea	2	09.07.2010	12.07.2010	2	4	4	No
101	6	Fatigue	2	09.07.2010	12.07.2010	2	4	4	No
101	7	Exanthema	1	13.07.2010	17.08.2010	0	0	0	No
101	8	Fever due to Avastin	1	15.06.2010	16.06.2010	4	0	0	No
101	9	COPD	2	18.08.2010	09.01.2011	0	0	0	No
101	10	Pain left femur	1	01.09.2010	20.09.2010	0	0	0	No
101	11	Dyspnoe due to Docetaxel	3	29.09.2010	29.09.2010	0	0	4	No
101	12	Fatigue	1	13.07.2010	09.01.2011	0	0	0	No
102	1	Seroma	3	02.09.2010	0	0	0	0	No
102	2	Wound dehiscence	2	02.09.2010	0	0	0	0	No
102	3	Nausea	1	13.09.2010	16.09.2010	0	2	2	Yes
102	4	Diarrhea	1	15.09.2010	15.09.2010	0	3	3	No
102	5	Pneumonia	3	19.10.2010	22.10.2010	0	0	0	Yes
102	6	Respiratory Infection	2	04.11.2010	15.11.2010	0	0	0	Yes
102	7	Hypokalemia	1	08.11.2010	11.11.2010	0	0	0	No
203	1	Abdominal pain /Colitis	3	12.11.2010	25.11.2010	2	1	1	Yes
203	2	Pneumothorax	2	u.k. 11.2010	17.11.2010	0	0	0	Yes
203	3	Neutropenia	4	16.11.2010	19.11.2010	1	3	3	No
203	4	Diarrhea	2	21.11.2010	25.11.2010	0	1	2	No
203	5	Diverticulosis	1	07.12.2010	0	5	5	5	No
304	1	Insomnia	2	21.02.2011	27.06.2011	0	0	0	No
304	2	Thoracic pain	2	21.02.2011	26.04.2011	0	0	0	No
304	3	Nose bleeding	1	10.03.2011	10.03.2011	0	0	0	No
304	4	Musculosceletal pain	1	01.03.2011	26.04.2011	2	0	2	No
304	5	Fatigue	1	23.02.2011	02.03.2011	0	2	2	No
304	6	Infection locally port	1	14.03.2011	04.04.2011	0	0	0	No
304	7	Hypertension	1	14.03.2011	27.07.2011	2	0	0	No
304	8	Fatigue	1	15.03.2011	22.03.2011	0	2	2	No
304	9	Alopecia	2	04.04.2011	0	0	1	4	No
304	10	Fatigue	1	05.04.2011	12.04.2011	0	2	2	No
304	11	Fatigue	2	27.04.2011	04.05.2011	0	2	2	No
304	12	Headache (not throughout the whole time - intermitted pain)	1	nk.05.2011	27.06.2011	1	1	1	No
304	13	Depressive mood	2	nk.05.2011	0	1	1	1	No
304	14	Fatigue	2	07.06.2011	14.06.2011	0	2	2	No
304	15	Sweating	2	nk.05.2011	.	1	1	1	No
304	17	Pneumothorax left	3	11.07.2011	19.07.2011	0	0	0	Yes

						Relation to			
Patientnumber	Event Nr.	Event	Grade	Start	Stop	Bevacizumab	Cisplatin	Docetaxel	SAE
205	1	Gastroenteritis	3	10.08.2011	16.08.2011	1	3	3	Yes
205	2	Soor stomatitis	2	10.08.2011	16.08.2011	1	3	3	No
205	3	Neutropenia	4	10.08.2011	23.08.2011	1	3	3	No
205	4	Thrombopenia	1	10.08.2011	23.08.2011	1	3	3	No
205	5	Leucocytopenia	4	10.08.2011	11.08.2011	1	3	3	No
205	6	Nausea	2	24.08.2011	31.08.2011	1	3	3	No
205	7	Weakness	1	24.08.2011	31.08.2011	1	3	3	No
205	8	Weakness	1	20.09.2011	04.10.2011	1	3	3	No
205	9	Loss of appetite	1	20.09.2011	04.10.2011	1	3	3	No
205	10	Diarrhea	1	20.09.2011	04.10.2011	1	3	3	No
205	11	Hoarseness	1	20.09.2011	04.10.2011	1	3	3	No
205	12	Soor stomatitis	1	20.09.2011	04.10.2011	0	3	3	No
205	13	Common cold	2	13.10.2011	27.10.2011	0	2	2	No
205	14	Hyperlacrimation	1	13.10.2011	23.01.2012	0	2	3	No
205	15	Skelasthenia	2	20.09.2011	30.11.2011	1	2	3	No
205	16	Onycholyse	2	27.10.2011	30.11.2011	1	3	3	No
205	17	Polyneuropathy	1	23.01.2012	0	3	3	3	No
205	18	Port-a-cath cauerne formation	2	07.12.2011	28.12.2011	5	5	5	No
205	19	Edema at port-a-cath canal	1	05.07.2012	0	5	5	5	No
106	1	Febrile infection	3	25.02.2012	05.03.2012	0	3	3	Yes
106	2	Chronic sinusitis	2	25.02.2012	05.03.2012	0	0	0	No
106	3	Headache	2	uk.03.2012	28.03.2012	0	0	0	No
106	4	Neutropenic fever	2	04.04.2012	10.04.2012	0	5	5	Yes
106	5	Hypertension	2	22.03.2012	28.03.2012	2	0	0	No
106	6	bone lesion	.	12.04.2012	23.04.2012	0	0	0	Yes
107	1	Diarrhea	1	uk.05.2012	uk.05.2012	1	4	4	No
107	2	Fatigue	1	15.06.2012	15.06.2012	2	2	2	No
107	4	Diarrhea	1	uk.06.2012	uk.06.2012	1	4	4	No
107	5	Hypertension	1	15.06.2012	15.06.2012	4	0	0	No
107	6	Alopecia	2	06.07.2012	0	0	2	4	No
107	8	Fatigue	1	16.08.2012	24.10.2012	2	2	2	No
107	9	Polyneuropathy legs	2	07.09.2012	0	0	4	4	No
107	10	Neutropenia	4	30.08.2012	06.09.2012	0	4	4	No
107	11	Increased CRP	1	16.08.2012	0	0	0	0	No
107	12	Cough	1	19.10.2012	25.10.2012	0	0	0	No

Table 3: List of all reported adverse events; Relation: 0=Unrelated; 1=Unlikely; 2=Possible; 3=Probable; 4= Definite; 5= Unknown

11.2 Grade 3/4 Adverse Events

Grade 3 and grade 4 AEs were summarized in Table 3. 11 adverse events grade 3 or 4 were documented. Most frequent was neutropenia grade 4 (3 times).

Adverse Event	Grade 3/4	Frequency
Neutropenia	4	3
Abdominal pain /Colitis	3	1
Dyspnoe due to Docetaxel	3	1
Febrile infection	3	1
Gastroenteritis	3	1
Leucocytopenia	4	1
Pneumonia	3	1
Pneumothorax left	3	1
Seroma	3	1

Table 4: Grade 3 and grade 4 adverse events

12 Literature

[1] Sandler, New Engl J Med (2006);355,2542

[2] Mannegold, LBA ASCO 7514, (2006)

[3] Schiller JH, et al. N Engl J Med (2002);346:92-8

[4] Fossella F, et al. J Clin Oncol. (2003);21(16):3016-24

APPENDIX 1: List of investigators

	Study site	Department	Principal Investigator	Site Initiation
01	Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	Universitätsklinik für Innere Medizin III	Prim. Univ.- Prof. Dr. Richard Greil	19.04.2010
02	Landeskrankenhaus-Universitätskliniken Innsbruck	Univ.-Klinik für Innere Medizin V, Hämatologie und Onkologie	Univ.- Prof. Dr. Wolfgang Hilbe	12.05.2010
03	Landeskrankenhaus Feldkirch	Interne E (Hämatologie und Onkologie)	OA Dr. Alois Lang	29.11.2010

APPENDIX 2: List of patients

Study Site	Patient number	Year of birth	Inclusion date	Status
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	101	10.06.2010	1968	Completed/ PD
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	102	06.09.2010	1946	Completed/ PD
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	106	13.02.2012	1956	Completed/ PD
Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	107	24.05.2012	1953	Completed/ PD
Landeskrankenhaus-Universitätskliniken Innsbruck	203	08.11.2010	1961	Withdrawal
Landeskrankenhaus-Universitätskliniken Innsbruck	205	02.08.2011	1950	Completed/ PD
Landeskrankenhaus Feldkirch	304	14.02.2011	1965	Completed/ PD

APPENDIX 3: List of serious adverse events (SAE)

Pat #	YoB	SAE #	Received	Event Term	Onset Date	Outcome Date	Outcome	SUSAR
101	1968	A100179	15.06.2010	Adynamia	14.06.2010	17.06.2010	Resolved	No
New in-patient hospitalization due to moderate adynamia on 14.06.2010. As planned the first cycle started on 15.06.2010. Patient left hospital on 17.06.2010 in good general condition.								
102	1946	A100204	15.09.2010	Nausea	14.09.2010	20.09.2010	Resolved	No
New in-patient hospitalization due to nausea on 14.09.2010. After treatment with antiemetics patient left hospital in good general condition on 20.09.2010.								

Pat #	YoB	SAE #	Received	Event Term	Onset Date	Outcome Date	Outcome	SUSAR
102	1946	A100231	10.11.2010	Respiratory Infection	05.11.2010	15.11.2010	Resolved	No
New in-patient hospitalization due to an respiratory infection on 05.11.2010. The patient thought that he had a pneumonia but this could be ecluded (x-ray, thorax). Due to safety reasons patient was hospitalised. After treatment with antibiotics patient´s condition improved. During this hospitalisation an interim staging was performed. Patient showed a progressive disease so the study treatment was discontinued. On 15.11.2010 patient left hospital in good general condition.								
102	1946	A100257	04.01.2011	Pneumonia	19.10.2010	22.10.2010	Resolved	No
New in-patient hospitalization due to Pneumonia on 19.10.2010. After treatment with antibiotics and O2 patient left hospital in good general condition on 22.10.2010.								
203	1961	A100234	14.11.2010	Pneumothorax	14.11.2010	25.11.2010	Resolved	No
The patient was admitted to the hospital due to abdominal pain on 14.11.2010. The patient was discharged 4 days ago, after the first cycle of CTX. Due to antiemetics (Novoban) the patient was constipated. After 2 days also pain started and worsened. On 14.11.2010 the patient collapsed and came into the emergency unit. In the abominal CT scan a pneumothorax on the right side was identified as a additional finding. The abdominal CT was without pathological finding. Due to the pneumothorax a Bülau drainage was placed. Under pain medication the symptoms meliorate. After treatment with antibiotics and G-CSF the patients symptoms released. Diarrhea occurred due to antibiotics, but no focus was found. On 25.11.2010 the patient was discharged in good general condition.								
203	1961	A100235	14.11.2010	Abdominal Pain	14.11.2010	17.11.2010	Resolved	No
The patient was admitted to the hospital on 14.11.2010 due to abdominal pain with constipation. Afterwards a CT scan of the abdomen was performed and as an incidental finding a pneumothorax was diagnosed and a Bülau drainage (15.11.2010) was inserted until 17.11.2010. The pneumothorax is resolved.								
304	1965	A100325	12.07.2011	Pneumothorax left	11.07.2011		Improved	No
For diagnostic reason patient got biopsy of lung metastasis. During this procedure a pneumothorax of left lung was caused. Thoracic drain acid analgetic infusion stabilized situation and improved breathing. Patient´s condition is stable and improved.								
205	1950	A100340	11.08.2011	Gastroenteritis	11.08.2011	16.08.2011	Resolved	No
Patient was admitted to hospital due to diarrhea, vomiting and reduced general condtion. Gastroenteritis was diagnosed. After treatment with antibiotics, antimycotics and antiemetics patients condition improved so that he could be discharged from hospital in good general condition on 16th of August 2011.								
106	1956	A100406	01.03.2012	Febrile Infection	25.02.2012	05.03.2012	Resolved	No
In patient hospitalization in Hospital Zell am See due to a febrile Infection (39,6°) on 25.02.2012. Under treatment with antibiotics and antipyretics the condition improved. An oral examination showed signs of a chronic sinusitis -> Treatment with nose drops (Nasonex, Fentrinol). Patient left hospital in good general condition on 05.03.2012. Start of 2nd cycle of study treatment was on 07.03.2012.								
106	1956	A100427	05.04.2012	Neutropenic Fever	04.04.2012	10.04.2012	Resolved	No
In-patient hospitalisation due to neutropenic fever (38,5°C) on 04.04.2012. Focus of infection is unclear. Treatment with antibiotics and G-CSF was initiated. Condition improved. Patient left hospital in good general condition on 10.04.2012.								
106	1956	A100431	17.04.2012	Bone lesions, left Femur-Fracture risk	12.04.2012	23.04.2012	Resolved	No
In-patient hospitalisation for the implantation of a hip endoprothesis (left side) on 15.04.2012. The recent CT on 12.04.2012 showed a new bone lesion in the left femur (3,2 x 2,2 cm). Due to the risk of a fracture an implantation of a hip endoprothesis was performed. Patient already discontinued from study treatment because of progressive disease on 13.04.2012. Hospitalisation from 15.04.2012-23.04.2012. Patient left hospital in good general condition. Start of futher therapy on 25.04.2012.								

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Landeskrankenhaus Salzburg Universitätsklinikum der Paracelsus Medizinischen Privatuniversität	107	24.05.2012	1953	Completed/ PD
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16.07.2014