

CLINICAL STUDY REPORT

Clinical Trial: Phase I/II Trial of Lenalidomide in Combination with Vorinostat and Dexamethasone as Therapy in Relapsed or Refractory Patients with Peripheral T-Cell Non-Hodgkin's Lymphoma (PTCL)

Clinical Phase: I/II

Protocol Number: AGMT_PTCL 1

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Coordinating Investigator: OA Dr. Georg Hopfinger
Universitätsklinik für Innere Medizin III
Universitätsklinikum der PMU
Salzburger Landeskliniken
Müllner Hauptstraße 48, 5020 Salzburg
Tel.: 0662/4482-2879
e-mail: g.hopfinger@salk.at

Sponsor: AGMT gemeinnützige GmbH
Prim. Univ.-Prof. Dr. Richard Greil
Universitätsklinik für Innere Medizin III
Universitätsklinikum der PMU
Salzburger Landeskliniken
Müllner Hauptstraße 48, 5020 Salzburg

Sponsor Contact: Dr. Daniela Wolkersdorfer
Tel.: 0664 1422504
e-mail: d.wolkersdorfer@agmt.at

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Clinical Trials Lead Manager, AGMT:
Dr. Daniela Wolkersdorfer

18.03.2013
date, signature

Head of AGMT:
Prim. Univ.-Prof. Dr. Richard Greil

20. Feb. 2013
date, signature

Coordinating Investigator:
OA Dr. Georg Hopfinger

20.2.2013
date, signature

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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 ADMINISTRATIVE STRUCTURE

Coordinating Investigator: OA. Dr. Georg Hopfinger

List of investigators is attached (appendix 1).

3. INTRODUCTION

Peripheral T-cell lymphomas (PTCL) constitute less than 15% of all non-Hodgkin lymphomas (NHL) in adults of the Western hemisphere and often present at advanced stage at the time of diagnosis; most nodal PTCL have an aggressive clinical course requiring prompt treatment.

Especially in primary refractory or relapsed patients outcome is dismal. Therefore, improvement in clinical outcome in PTCL remains mandatory. Investigational drugs with a new mode of action remain a reasonable way in improving outcome.

The aim of this study is to evaluate the potential of a Lenalidomide plus Vorinostat and Dexamethasone combination therapy as an effective and safe therapeutic regimen, in the treatment of relapsed or refractory PTCL following failure of prior regimens.

4. STUDY OBJECTIVES

The primary objective of this study is to determine the maximum tolerated dose (MTD) of a Lenalidomide, Vorinostat, and Dexamethasone combination regimen in terms of occurrence of dose-limiting toxicities (DLT) at any dose level.

Secondary objective are

- To determine the remission rate of a combination therapy with Lenalidomide, Vorinostat, and Dexamethasone in a treatment refractory or relapsed population, defined as the percentage of patients achieving a complete response (CR) or partial response (PR) throughout treatment with the combination regimen.
- To determine the median progression-free survival times following treatment with a Lenalidomide, Vorinostat, and Dexamethasone combination regimen, in terms of duration of time from treatment start until progression or death from any cause.
- To determine the median overall survival time following treatment with a Lenalidomide, Vorinostat, and Dexamethasone combination regimen, in terms of duration of time from treatment start until death from any cause.
- To determine the safety of this regimen in terms of occurrence of any adverse and serious adverse events under treatment.

5. INVESTIGATIONAL PLAN

This is a non-randomized, multicenter, open-label, single-arm Phase I/II study in patients with previously treated peripheral T-cell Non-Hodgkin's lymphoma. Eligible patients may have received no more than 2 lines of previous treatment. Patients with primary refractory PTCL after one previous treatment for PTCL may also be included. Following a 3+3 cohort design Lenalidomide and Vorinostat doses will be escalated in groups of 3 patients until the identification of the Maximum Tolerated Dose (MTD), defined as the next lower dose level than the dose level, where at least 2 Dose-Limiting Toxicities (DLT) occur.

Eligible patients will receive Lenalidomide, Vorinostat and Dexamethasone for up to 6 cycles. Patients who show progression will stop medication and are treated on the decision of the treating physician. Safety assessments will be conducted in 4-weekly intervals; efficacy assessments will be conducted at 8 weekly intervals, at completion of every second treatment cycle.

Study medication for each cohort will be given in six treatment cycles, each of 28 days duration. Lenalidomide and Vorinostat are administered at the predetermined dose on days 1 through 21 of each 4-week cycle. Dexamethasone is administered on days 1, 8 and 15 of each 28-day treatment cycle.

Cohort	Lenalidomide	Vorinostat	Dexamethasone
-I	5mg d1-21 q28d	400mg d1-21 q28d	40mg d1,8,15 q28d
I	10mg d1-21 q28d	400mg d1-21 q28d	40mg d1,8,15 q28d
II	15mg d1-21 q28d	400mg d1-21 q28d	40mg d1,8,15 q28d
III	20mg d1-21 q28d	400mg d1-21 q28d	40mg d1,8,15 q28d
IV	25mg d1-21 q28d	400mg d1-21 q28d	40mg d1,8,15 q28d

Table 1: Cohorts of the AGMT_PTCL 1 trial

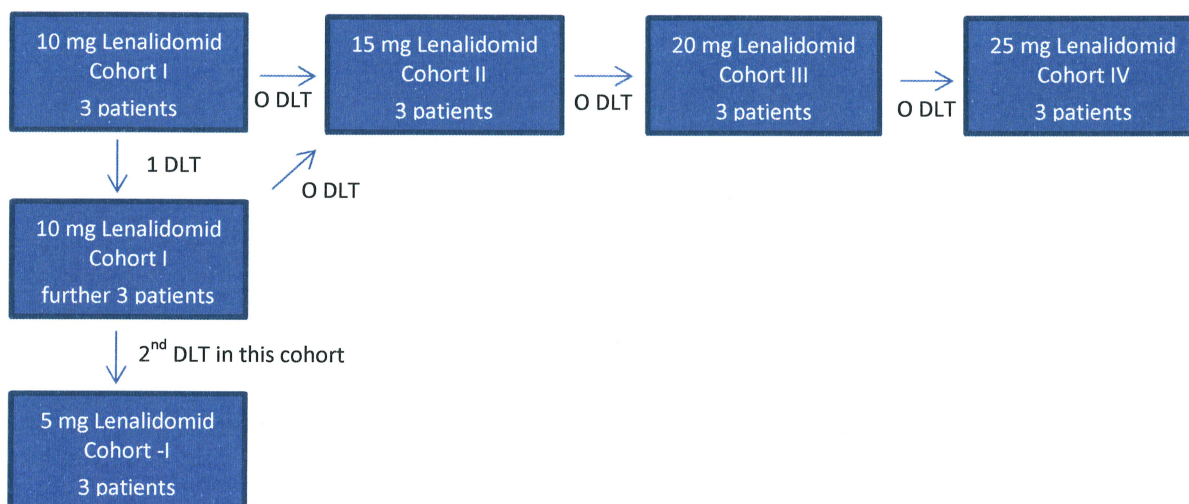


Figure 1: Treatment schedule

Patients will be enrolled in cohorts of 3 subjects each following a 3+3 study design. In the absence of dose-limiting toxicities (DLT) within the first cycle of treatment the following 3 patients will be enrolled into the next cohort. In case 1 DLT occurs at a certain dose level, an additional group of 3 patients will be treated at the same dose level. In all a total of 12 patients will be recruited into 4 cohorts until identification of a Maximum Tolerated Dose (MTD).

If within the first 6 patients enrolled in cohort I 2 DLTs occur, all remaining patients will be enrolled in cohort –I (5mg Lenalidomide).

Patients who discontinue study treatment during cycle 1 because of other reasons than dose limiting toxicities will be replaced.

Upon definition of the MTD any remaining patients up to a total sample size of 20 will be enrolled to receive study treatment at the predetermined MTD.

6. EFFICACY EVALUATION

Between December 2009 and May 2012 a total of 9 patients entered the trial.

Histology of these patients was as follows:

- PTCL, NOS (Peripheral T-cell Lymphoma, unspecified): 3
- AILT (Angioimmunoblastic T-cell Lymphoma: 5
- Anaplastic large-cell Lymphoma, ALK-: 1

Median age was 71 years, 2 female and 7 male patients were included in the trial.

All patients had relapsed after at least one therapy. Median time from first diagnosis to study entry was 226 days.

Number of cycles and cumulative dosages of Lenalidomide, Vorinostat and Dexamethasone (DMS) are summarized in table 2.

Patient	Cohort	DLT	Number of cycles	Cum. dose Lenalidomide (mg)	Cum. dose Vorinostat (mg)	Cum. dose DMS (mg)
1	10 mg	no	4	840	33.600	480
2	10 mg	no	6	1.260	50.400	720
3	10 mg	na	< 1	20	800	40
4	10 mg	yes	6	1.140	50.400	720
5	10 mg	yes	1	120	4.800	80
6	5 mg	no	6	555	37.200	600
7	5 mg	na	< 1	25	1.900	120
8	5 mg	no	2	210	16.800	240
9	5 mg	no	2	160	12.800	200

Table 2: Cumulative doses of lenalidomide, vorinostat and dexamethasone per patient

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

Median Progression free survival was 66 days. Median overall survival was 112 days (see figure 2).

At the end of the study two patients were still alive (follow up of these patients was 66 and 309 days, respectively).

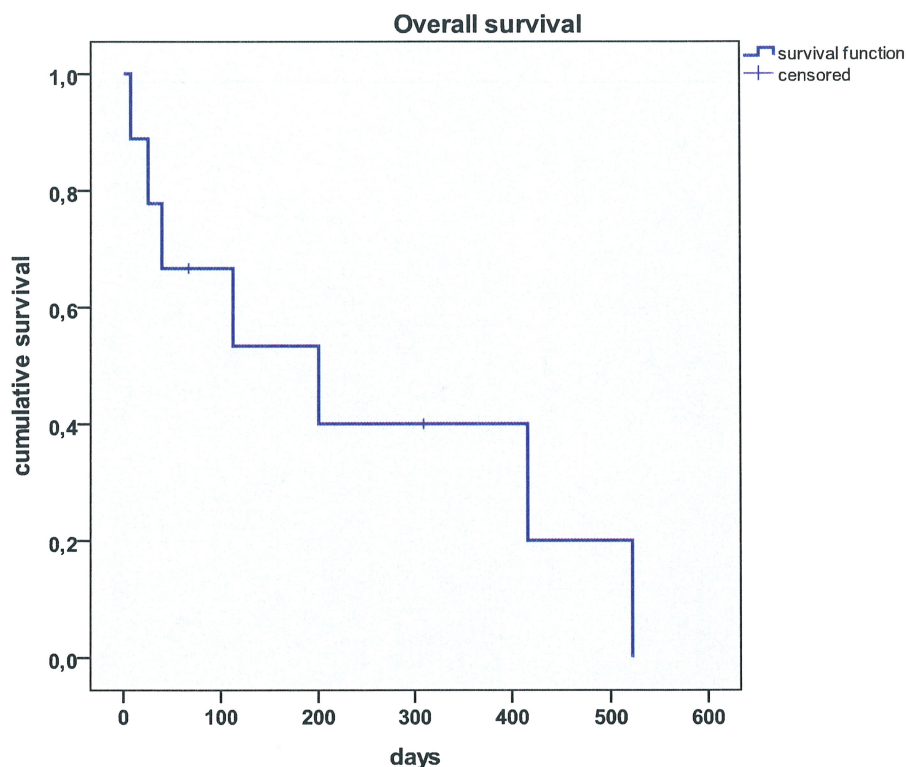


Figure 2: Kaplan-Meier curve: overall survival (2 patients were still alive)

Out of 5 patients, treated in cohort 1 with 10 mg lenalidomide, 2 patients experienced DLTs (thrombocytopenia grade 3, insult grade 4). 1 patient was excluded for the evaluation of the MTD, because cycle 1 was not completed for reasons other than DLT.

4 patients were treated in cohort -1 with 5 mg lenalidomide. 1 patient was excluded for the evaluation of the MTD, because cycle 1 was not completed for reasons other than DLT. The 3 remaining patients completed cycle 1 without DLT and therefore 5mg Lenalidomide (cohort -I) was defined as maximum tolerated dose.

The trial was closed prematurely after phase I. Phase II of the trial was not continued due to slow recruitment.

7. SAFETY EVALUATION

All reported adverse events are summarized in table 2. Toxicity grading was done using the CTCAE version 3.0.

Hematological toxicities grade 3/4 were thrombocytopenia grade 3, neutropenia grade 4, neutropenia grade 3, leucopenia grade 3 and anemia grade 3 in one patient each. Infectious toxicities grade 3/4 were fungal infection grade 3, erysipiel grade 3, pneumonia grade 3, pneumonia grade 4 and generalized herpes zoster grade 3. Additionally one patient experienced renal infarction (grade 3) and one patient had an insult (grade 4).

12 SAEs were reported. 5 of these were considered related to study treatment and 2 were classified as SUSARs. The list of SAEs including a precise description is attached (appendix 2).

Pat	Event Nr.	Event	Grade	Start	Stopp	Relation to			SAE
						Lenalidomide	Vorinostat	DMS	
1	1	Erysipel right leg	3	05.02.10	08.02.10	2	1	2	yes
1	2	Unspec. lymphadenitis	3	06.03.10	11.03.10	0	0	0	yes
1	3	Infect with fever	2	03.2010	03.2010	2	1	1	no
1	4	Fungal infection	3	03.2010	12.04.10	2	1	2	no
1	5	Appetite loss	2	03.2010	11.04.10	0	0	0	no
1	6	Exanthema	2	03.2010	11.04.10	0	0	0	no
1	7	Cramp	1	03.2010	04.2010	0	0	1	no
1	8	Seeing disorder	1	03.2010	04.2010	0	0	0	no
2	1	Pharyngitis	1	17.10.10	27.10.10	0	0	0	no
2	2	Neutropenia	4	13.01.11	17.01.11	4	3	0	no
3	1	Thrombocytopenia	3	25.01.11	02.2011	3	0	0	no
3	2	Thrombocytopenie	3	22.02.11	03.2011	3	0	0	yes
3	3	Renal infarction	3	04.05.11	09.05.11	4	0	0	yes
3	4	Neutropenia	2	09.03.11	03.2011	4	0	0	no
3	5	Cough and cold	1	06.2011	. 6.2011	2	1	1	no
4	1	Fever	na	08.07.11	08.07.11	5	5	5	no
4	2	Increased CRP	na	08.07.11	31.07.11	5	5	5	no
4	3	Insult	4	18.07.11	21.07.11	3	3	3	yes
4	4	Pneumonia	4	21.07.11	31.07.11	2	2	2	yes
4	5	Death	5	31.07.11	31.07.11	0	0	0	yes
5	1	Constipation	1	27.11.11	19.12.11	2	2	1	no
5	2	Increased glucose (343mg/dl)	3	06.12.11	19.12.11	0	0	0	no
5	3	Thrombocytopenia (52G/l)	2	09.01.12	24.01.12	0	2	0	no
5	4	Increased creatine (2,06mg/dl)	2	31.01.12	20.02.12	1	2	1	no
5	5	Increased temperature (37,7°C)	NA	02.2012	02.2012	5	5	5	no
5	6	Bleeding haemorrhoids	NA	.02.2012	.02.2012	5	5	5	no
5	7	Infection (Mouth blisters)	NA	24.02.12	19.03.12	2	2	1	no
5	8	Cough and cold with increased temp. (37,7°C)	NA	19.12.11	27.12.11	2	2	1	no
5	9	Pneumonia	NA	25.03.12	31.03.12	2	2	1	yes
5	10	Eczema soles of the feet	NA	26.04.12	14.05.12	1	1	1	no
6	1	Fatigue	1	01.06.12	22.06.12	na	2	2	no
6	2	Swelling retro auricular left and right	1	01.06.12	22.06.12	1	1	1	no
6	3	Generalized Herpes zoster	3	01.07.12	16.07.12	2	2	2	yes
6	4	Potassium deficiency	1	27.05.12	01.06.12	1	2	1	no
7	1	FUO	1	18.11.10	18.11.10	1	1	1	yes
7	2	Meningeosis	NA	22.11.10	25.12.10	1	1	1	Yes
7	3	Pneumonia	3	18.11.10	25.12.10	1	1	1	yes
8	1	Diarrhea	2	14.12.11	15.12.11	1	2	1	no
8	2	Hyperuricemia	1	15.12.11	17.12.11	2	2	1	no
8	3	Electrolyte decompensation	3	15.12.11	19.12.11	2	2	1	no
8	4	Tachycardia atrial fibrillation	2	16.12.11	17.12.11	1	1	1	no
8	5	Hypernatremia	4	17.12.11	19.12.11	2	2	1	no
8	6	Nausea	2	14.12.11	19.12.11	2	2	1	no
8	7	Hypercalcemia	2	17.12.11	18.12.11	1	1	1	no
8	8	Pain whole body	2	16.12.11	19.12.11	0	0	0	no
8	9	Hypophosphatemia	4	17.12.11	18.12.11	2	2	1	no
8	10	Disease Progression	5	19.12.11	19.12.11	0	0	0	yes
9	1	Stomatitis	1	03.05.12	16.05.12	5	5	5	no
9	2	Fatigue	2	01.05.12	16.05.12	3	3	0	no
9	3	loss of appetite	1	01.05.12	14.06.12	3	3	0	no
9	4	reduced general condition	2	12.05.12	14.05.12	3	3	0	no
9	5	edema lower legs	1	14.06.12	ongoing	3	3	2	no
9	6	weight loss	1	30.05.12	20.06.12	3	3	0	no
9	7	tainting of food	2	16.05.12	21.06.12	3	3	0	no
9	8	tainting of food	1	21.06.12	ongoing	3	3	0	no

Table 2: Adverse events (AE) listing

Relation: 0=unrelated, 1=unlikely, 2=possible, 3=probable, 4=definite, 5=unknown

8. APPENDIX 1: List of investigators

Site#	Site	Department	Principal Investigator
01	Hanusch KH Wien	3. Medizinische Abteilung	Dr. Thomas Nösslinger
02	AKh Linz	Department für Innere Medizin 3	Doz. Dr. Michael Fridrik
03	Universitätsklinikum der PMU Salzburg	Univ. Klinik für Innere Medizin III	Prof. Dr. Richard Greil
04	Universitätsklinik Innsbruck	Innere Medizin IV, Hämatonkologie	OA Dr. Wolfgang Willenbacher
05	KH Elisabethinen Linz	1. Interne Abteilung	OA Dr. Michael Girschikofsky
06	Universitätsklinik Graz	Abteilung für Hämatologie	Prof. Dr. Werner Linkesch

9. APPENDIX 2: List of serious adverse events (SAE)

(S)AE Reconciliation List

Cut-off date: 13.02.2013

IMPs: Lenalidomide (Revlimid®)

Vorinostat (Zolinza®)

AGMT_PTCL-1

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100130	01/01		08.02.2010	SAE	No		05.02.2010	Resolved	08.02.2010	Not related

Event Term	Description	Medra Codierung
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Erysipel ped. dext.

Patient was admitted with erysipiel right leg, DVT was excluded by ultrasound, antibiotal treatment was started and erysipiel disappeared.

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100140	01/01		08.03.2010	SAE	No		06.03.2010	Resolved	11.03.2010	Not related

Event Term	Description	Medra Codierung
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Unspec. Lymphadenitis

Patient was re-admitted for new enlargement of cervical lymph nodes (LN); a CT scan showed 16x23mm LN, PD is suspected, however LN appear reactive; a CT thoracic and abdominal scan is pending.
Follow Up: Patient was hospitalized on 06.03.2010, because of swelling cervical left. Patient was treated with antibiotics. Performance status got better and on 11.03.2010 cycle 4 was started (3 days delay). Patient was released on 13.03.2010 in good general condition.

AGMT_PTCL-1

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100237	07/01		02.12.2010	SAE	No		18.11.2010	Persisting	25.12.2010	Not related
Event Term		Description								

Pneumonia
Patient started with study medication on 16.11.2010 and was hospitalized according to recommendation of sponsor. Fever up to 39°C on 18.11.2012. Since 19.11.2010 no fever, X-ray proved pneumonic infiltration, antibiotics given. Due to paralysis of upper lip and missing eyelid closure CT head, MR head was done. The results were normal. Cerebrospinal fluidpuncture on 19.11.2010 finally proved Meningeosis lymphomatosa. Further therapy with Celyx, Bortezomib and Depocyte planned. Patient died on 25.12.2010 due to underlying malignant disease.

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100245	07/01		02.12.2010	SAE	No		23.11.2010	Persisting	25.12.2010	Not related
Event Term		Description								

Meningeosis lymphomatosa
Patient was hospitalized due to study start which accured on 13.11.2010. Fever (serious) paralysis of facialis, CT and MR head done. The results were normal. Cerebrospinal fluid purdue on 19.11.2010 proved meningeosis lymphomatosa. Study medication was permanently discontinued on 23.11.2010. Patient died om 25.12.2010 due to underlying malignant disease.

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100274	01/03		23.02.2011	SAE	No		22.02.2011	Resolved	10.03.2012	Related
Event Term		Description								

Thrombocytopenia
Revimid treatment was paused due to onset of Thrombocytopenia (28 G/L).

AGMT_PTCL-1

►	SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
	A100297	01/03		09.05.2011	SAE	Yes	11.05.2011	05.05.2011	Resolved with sequelae	09.05.2011	Related

Event Term	Description	Medra Codierung
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Renal Infarction
In CT-Scan performed after 4 cycles of treatment within the PTCL-1 trial renal infarction right side was suspected. In special CT-Scan this suspicion was confirmed on 5th May 2011. The patient had no clinical signs (no pain, normal sediment of urine) of renal infarction nor positive lab values. The event was charged as medically significant by the physician.

►	SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
	A100328	03/01		01.08.2011	SAE	Yes	19.07.2011	18.07.2011	Resolved	21.07.2011	Related

Event Term	Description	Medra Codierung
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Insult
Inpatient hospitalisation because of insult on 18.07.2011. Symptoms were problems in seeing and walking and the loss of short term memory. Aspirin, Plavix and Lovenox 40mg were administered and patient's status became better on 21.07.2011. New neurologic deficits appeared, but after all symptoms vanished the patient left hospital due to his own wish.

►	SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
	A100331	03/01		04.08.2011	SAE	No		21.07.2011	Fatal	31.07.2011	Related

Event Term	Description	Medra Codierung
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Pneumonia
Inpatient hospitalisation. Pneumonia was detected by thorax x-ray on 21.07.2011. Patient died of disease progression on 31.07.2011.

AGMT_PTCL-1

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100338	03/01		03.08.2011	SAE	No		31.07.2011	Fatal	31.07.2011	Not related
Event Term		Description								
Disease progression		Medra Codierung								

In-patient hospitalisation because of insult on 18.07.2011. Patient left hospital on 21.07.2011 on his own wish, but returned on the same day (21.07.2011) and had to stay in hospital because of pneumonia. Prolonged hospitalisation because of pneumonia. Although antibiotics were administered the general state worsened. Patient died on 31.07.2011 because of disease progression.

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100380	07/02		21.12.2011	SAE	No		19.12.2011	Fatal	19.12.2011	Not related
Event Term		Description								
Disease progression		Medra Codierung								

Tumor infiltration hypophysis, RCA closed due to tumor infiltration.

SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
A100417	06/01		29.03.2012	SAE	No		25.03.2012	Resolved	31.03.2012	Not related
Event Term		Description								
Infection		Medra Codierung								

Patient was admitted to hospital due to fever and cough, thorax x-ray showed signs of bronchitis, but no infiltrates. CRP is still high on 27.03.2012. Patient was treated with unasyn and bronchopulmonal infection resolved finally on 31.03.2012 and patient could leave hospital.

AGMT_PTCL-1

▶	SAE Nr	PatNr	Externe ID	Received	SAETyp	SUSAR	SUSAR Date	Onset Date	Outcome	Outc. Date	Relation
	A100465	06/02		16.07.2012	SAE	No		01.07.2012	Resolved	16.07.2012	Related
	Event Term										
	Herpes zoster										
	Description										
	Medra Codierung										

Patient was admitted to hospital due to hyponatremia. The other electrolytes were also decreased (hypokalemia, chlorid decreased). Furthermore amylase and lipase were increased and patient complains about stomach pain, nausea and vomiting and constipation since 4 days. On 16.07.2012 in Follow up report SAE term was changed from hyponatremia to generalized herpes zoster. Additionally to the symptoms of herpes zoster an exanthema of the skin was observed on 06.07.2012. After the diagnosis of herpes zoster a therapy with Zovirax iv was started and the symptoms got better. The exanthema was diagnosed as a bacterial secondary infection and was treated with Maxipime. On 16.07.2012 patient could leave hospital in good condition.