Combined Treatment of Sorafenib and pegylated interferon alpha 2b in stage IV metastatic melanoma: a prospective non-randomized, multicenter Phase II Study

Sponsor: Universitätsklinikum Schleswig-Holstein

Trial number: SoraPeg 2007

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FINAL REPORT

- Synopsis -

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Content

Aims

To evaluate the efficacy and safety of a combined treatment with Sorafenib (Nexavar®) and pegylated interferon-α-2b (PegIntron®) in patients with malignant melanoma in stage IV.

Study Design

Study design:	Open-label phase II single arm exploratory clinical trial
Name of IMP:	Pegylated Interferon α2b (PegIntron®) Sorafenib (Nexavar®)
Comparator:	none
Blinding:	none
Randomization:	none

Experimental Treatment

The investigational treatment will consist of:

- 3 µg PEG-IFNα2b/kg/week SC for 8 weeks (= 2 cycles)
- Sorafenib 2x400mg daily per os for 8 weeks (= 2 cycles)

Treatment duration: maximum of 12 cycles (48 weeks) or until development of disease progression or unacceptable toxicity.

Study Population

Male or female patients, ≥ 18 years old. Eligible patients are patients with stage IV (AJCC-2002) metastatic melanoma and measurable disease without prior systemic treatment of stage IV melanoma. Patients could be entered into the study if the following inclusion and exclusion criteria were fulfilled:

Inclusion Criteria

1. Histologically documented metastatic melanoma classified as stage IV (AJCC 2002) of cutaneous origin.
2. ≥ 18 years of age
3. ECOG performance status of 0 or 1
4. Patients should not have received any systemic treatment for stage IV disease (study = "first-line" treatment).

   Patients with progressive disease (PD) to stage IV under prior treatment with interferons as well as all patients who have already been treated with Sorafenib should not be included.

   The following are allowed:

   adjuvant interferon treatment (without progressive disease during treatment!) or vaccine therapy for resected stage I-III disease

   palliative surgery or radiotherapy for stage IV disease

   prior cytokine or chemotherapy treatment for local-regional disease by isolated limb perfusion or intralesional therapy
5. Life expectancy >6 months.
6. Patients must have measurable disease defined as ≥ 1 not pretreated unidimensional measurable lesion ≥ 20 mm (conventional techniques) or ≥ 10 mm by spiral CT/MRI.
7. Patients must have adequate hematological, renal and liver functions as defined by laboratory values below performed within 14 days prior to study inclusion:

- absolute neutrophil count (ANC) > 1.5 x 109/l
- platelet count > 100 x 109/l
- hemoglobin > 10 g/dl (> 6.2 mmol/l)
- serum creatinine ≤1.5 x upper limit of institutional values
- total serum bilirubin ≤1.5x upper limit of institutional values
- ALAT and ASAT ≤2.5x upper limit of institutional values (exception: liver metastases)

8. Patients should not suffer from frequent vomiting or medical conditions which could interfere with oral medication intake.
9. Negative pregnancy test of women of childbearing potential performed within 7 days prior to the start of treatment.
10. Women of childbearing potential must agree to use an effective method of contraception (Pearl-Index < 1, e.g. hormonal contraception including the combined oral contraceptive pill, the transdermal patch, and the contraceptive vaginal ring, intrauterine devices or sterilization) during treatment and for at least 6 months thereafter.
11. Men must agree to use an effective method of contraception during treatment and for at least 6 months thereafter.
12. Patients should understand the informed consent and will need to sign the consent.

Exclusion Criteria

1. Ocular or mucosal melanoma.
2. History or evidence of brain metastasis.
3. Patients with LDH values higher than 2x upper limit of institutional values.
4. Patients with thyroid dysfunctions not responsive to therapy.
5. Patients with uncontrolled diabetes mellitus.
6. Patients with prior or active autoimmune disease or autoimmune hepatitis.

7. Cardiac disease: congestive heart failure > class II NYHA, patients must not have unstable angina or new onset of angina or myocardial infarction within the past 6 months. Cardiac ventricular arrhythmias requiring antiarrhythmic therapy.
8. Uncontrolled hypertension defined as systolic blood pressure > 150 mm Hg or diastolic pressure > 90 mm Hg, despite optimal management.
9. Active clinically serious infections > CTCAE Grade 2.
10. Patients who are HIV positive or have AIDS.
11. Thrombotic or embolic events including transient ischemic attacks within the past 6 months.
12. Evidence or history of bleeding diathesis or coagulopathy.
13. Therapeutic anticoagulation with Vitamin K antagonists such as warfarin, or with heparins or heparinoids. Low dose warfarin is permitted if INR is < 1.5. Low dose aspirin is permitted.
14. Known or suspected allergy to Sorafenib or any ingredient of Sorafenib or PEG-IFN-α -2b or any ingredient of PEG-IFN-α -2b or to any interferon.
15. Previous cancer that is distinct in primary site or histology from melanoma except cervical cancer in situ, treated basal cell carcinoma, superficial bladder tumors or any cancer curatively treated 3 years prior to study entry.
16. Substance abuse, medical or psychological condition that may interfere with the patient's participation in the study.
17. Patients with medication requiring chronic systemic corticosteroids.
18. Patients with prior systemic anticancer treatment in the last 2 weeks.
19. Patients with severe liver disease or severe renal disease.
20. Patients with seizure disorders requiring anticonvulsant therapy.
21. Patients with any severe debilitating diseases.

Endpoints

Primary endpoint

To determine disease control rate (CR,PR,SD) after 8 weeks of treatment with pegylated interferon- α-2b (3 µg/kg body weight s.c. once a week) combined with Sorafenib 2x 400 mg (2 tablets orally, twice daily)

Secondary endpoint

Secondary outcome variables include the following:

- Best response within 12 months
- Progression free survival (PFS)
- Overall survival
- Evaluate possible surrogate markers in peripheral blood and tumor biopsies
- Safety and tolerability of the combined treatmentSide study parameters:
- Immunological responses induced by study treatment

- Correlation of immunological markers to treatment response

Assessments of efficacy

Patients are re-evaluated at regular intervals (every 8 weeks) for evidence of disease recurrence. Clinical and imaging studies are being evaluated according to RECIST criteria.

Assessments of safety

- Incidence of Adverse Events
- Incidence of abnormal laboratory test results

Follow-up

Detailed follow-up visits at week 1, 2 and 5; thereafter every 4 weeks until week 48. Staging examinations (re-evaluations) every 8 weeks until week 48 (after the completion of each cycle).

Dose adjustment

Possible dose decrease or temporary hold for patients experiencing adverse events or laboratory abnormalities. See protocol for details

Premature withdrawal

Patients with progressive disease according to RECIST criteria.

Patients who request to be withdrawn.

Patients who develop severe adverse events requiring treatment discontinuation.

Sample size calculation

To evaluate whether the disease control rate (CR,PR,SD) will increase from 30% (historical data) to 50% after at least 8 weeks: 50 evaluable patients should be included (alpha 5% and power 90%). The null hypothesis p<= 30% will be rejected if at least 21 disease controlled patients are observed after 8 weeks. In order to compensate for patient drop-outs 55 patients will be recruited.

Summary statistics will be provided on incidence and severity of adverse events as well as other safety measures. A Data Monitoring and Safety Board (DMSB) will be established. This board will evaluate the safety profile of the drug combination after 10 patients have received an 8 week treatment course.

Baseline characteristics

The following tabulated data show the demographic and clinical characteristics of the study population (ITT).

Table 1 Baseline characteristics I

		Patients
Number	total	55
Sex	male	29 (53%)
	female	26 (47%)
Age	median [years]	64
	(range)	(20-85)
Site of primary		
	Head/neck	6 (10.9 %)
	Trunc	24 (43.6 %)
	Upper limb	5 (9.1 %)
	Lower limb	13 (23.6 %)
	Unknown primary	5 (9.1 %)
	Other	2 (3,6 %)
Melanoma subtype		
	SSM	22 (40 %)
	NM	15 (27 %)
	LMM	2 (4 %)
	ALM	4 (7 %)
	Other/unknown	12 (21.8 %)
Tumor thickness (Breslow)		
	mean [mm] (SD)	3.2 (2.7)
	median [mm]	2.6
	(range)	(0.4-14)
Level of invasion		
	II	4 (7 %)
	III	12 (22 %)
	IV	24 (44 %)
	V	10 (18 %)
	unknown	5 (9 %)
Ulceration		
	no	29 (53 %)
	yes	21 (38 %)
	unknown	5 (9 %)

Table 2 Baseline characteristics II

		Patients
Number total		55
SLND	no	30 (55 %)
	yes	25 (45 %)
SLN pos	no	10 (18 %)
	yes	15 (27 %)
	not done	30 (55 %)
Adjuvant interferon	no	36 (65 %)
	yes	19 (35 %)
Locoregional (i.l., Perf.)	no	53 (96 %)
	yes	2 (4 %)
Vaccination	no	53 (96 %)
	yes	2 (4 %)
Radiotherapy	no	46 (84 %)
	yes	9 (16 %)
Chemotherapy	no	53 (96 %)
	yes	2 (4 %)

Table 3 Stage IV characteristics

		ITT Patients
Number	total	55
M stage		
	M1a	3 (6%)
	M1b	9 (16 %)
	M1c	43 (78 %)
Metastatic sites	1	5 (9 %)
	2	19 (35 %)
	3	18 (33 %)
	4	8 (15 %)
	5	3 (6 %)
	6	2 (4 %)
LDH elevated	yes	22 (40 %)
	no	33 (60 %)

Conduction of treatment

Forty one patients (75%) received at least 8 weeks of treatment; 9 patients withdrew prior to 8 weeks due to adverse events, 2 patients revoked consent, and 3 patients had overt PD prior to 8 weeks evaluation. Drug exposure and dose modifications are presented in the following Table.

Table 4 Treatment

		ITT Patients
Number	total	55
Cycles completed	0	8
	1	6
	2	23
	3	3
	4	7
	5	1
	6	3
	10	1
	12	3
Peg dose modifications		
	haem TOX	9
	non-haem TOX	22
	other reasons	7
	patient request	3
	any reason	34
PEG dose delay		
	heam TOX	7
	nonhaem TOX	13
	other reasons	7
	patient request	3
	any reason	30
Sorafenib dose modifications		
	dose reduction	24
	dose delay	28

A total number of 178 cycles in 55 patients resulted in an average of 3.2 cycles per patient (ITT), the median number of cycles performed was two.

Safety assesment

Adverse events

Adverse events (AEs) were graded in terms of severity according to The National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0.

Table 5 Adverse Events

	All Grades	Grade III	Grade IV
CONSTITUTIONAL SYMPTOMS	49	19	1
GASTROINTESTINAL	47	6	0
DERMATOLOGY/SKIN	41	14	0
BLOOD/BONE MARROW	40	23	3
PAIN	28	6	0
HEMORRHAGE/BLEEDING	15	1	2
METABOLIC/LABORATORY	14	5	1
NEUROLOGY	14	1	0
FLU-LIKE SYNDROME	11	5	0
PULMONARY/UPPER RESPIRATORY	10	1	1
MUSCULOSKELETAL/SOFT TISSUE	7	1	0
CARDIAC	6	3	0
INFECTION	6	2	0
HEPATORENAL SYNDROME	1	0	1
OTHER*	16	4	0

**including ALLERGY/IMMUNOLOGY, AUDITORY/EAR, ENDOCRINE, HEPATOBILIARY/PANCREAS, OCULAR/VISUAL, RENAL/GENITOURINARY, SECONDARY MALIGNANCY*

SEVERE Adverse Events

There were 32 independent serious adverse events occurring in 25 patients. Most of them were declared so due to uncomplicated hospitalization. Four of the serious adverse events were fatal, and one of these fatalities was possibly related to the study medication.

This was the case of a 49 year old female patient who developed thrombocytopenia (minimum 27/nl) and in addition a prothrombin-time (Quick) of <10% while on study medication. She was hospitalized with gingival bleeding and haematouria. She got comatose and CT scan revealed subdural bleeding. Despite immediate surgery she died two days after.

One other patient had a fatal gastral bleeding complication while being on study medication with normal platelets and coagulation tests. Gastric metastasis was known and a relation of the SAE to the study drug was rated unlikely.

The third fatal case was due to pneumonia without neutropenia, four days after start of treatment. It was rated unlikely to be study drug related.

The fourth fatility seven weeks after stop of study medication was most likely due to disease progression, though autopsy was not performed.

Fatal events during follow-up, which were clearly due to disease progression were not analyzed here as a safety issue according to protocol.

Table Overview SAEs

No	SAE	Death	Sora*	Peg*
2	fever (Temperatures up 40,8)and acut deterioration of general Health status		2	2
3	hospitalization due to worsening physical condition		2	2
6	hospitalize because of nausea, dehydratation and back pain		3	3
8	Death	Y	5	5
9	Hemoglobin of 6.0 g/dl		3	1
9	decrease in Hb, Grade 4		3	3
9	Constitutional Symptoms - Other (Specify, __) ECOG		1	1
9	decrease in Hb, Grade 4		1	1
9	decrease in Hb		2	2
10	reduction of general status		3	3
15	Thrombozytopenia -> Subdural bleeding	Y	2	3
16	Pain - Stomach		3	3
17	Fatigue (asthenia, lethargy, malaise)		3	3
17	Flatulence		3	3
18	pain		5	5
18	Hemorrhage, GI-Stomach Grade 3	Y	4	4
19	Pain - Stomach		3	3
20	Renal/Genitourinary - Other (Specify, __) bloody urinary		3	3
20	Pain - Muscle		3	3
21	Ascites with hepatorenal syndrome (renal shutdown) due to progression of disease		3	3
21	thrombocytopenia		2	3
21	fatigue		3	3
22	Cardiac Arrhythmia		3	2
22	Supraventricular and nodal arrhythmia - Atrial fibrillation		3	2
24	Hemorrhage/Bleeding - Other (Specify, __) Hypermenorrhoe		3	3
27	Severe thoracic pain, shortness of breath, severe fatigue, fever, Skin: Rash		2	2
27	Squamous cell carcinoma		4	4
29	insufficient woundhealing at left groin after Excision of metastases in June 2008		4	4
30	Supraventricular and nodal arrhythmia - Atrial fibrillation		4	2
31	Embolism		4	4
37	rash: hand foot skin reaction		1	4
43	Pneumonia	Y	4	4
46	GI and nasal bleeding		3	4
52	aneurysm truncus brachiocephalicus (brachiocephalic artery)		5	5
53	thrombocytopenia		2	2

*Causality: 1: definitive/most probable 2: probable 3:possible 4:improbable 5:no relation

Efficacy

The response data are presented in the following tables. Kaplan-Meier curves for median overall survival and median progression-free survival are presented in the, respective figures.

Table 5 Treatment Response

		ITT Patients	
Number	total	55	
8 week response			
	CR	0	
	PR	2	(3.6 %)
	SD	14	(25.5 %)
	PD	28	(50.9 %)
	NE	11	(20.0 %)
Best response			
	CR	0	
	PR	4	(7.3 %)
	SD	12	(21.8 %)
	PD	34	(61.8 %)
	NE	5	(9.1 %)
TCR 8 weeks		16	(29 %)

According to RECIST CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; NE: not evaluable

TABLE. Characteristics of responding patients.

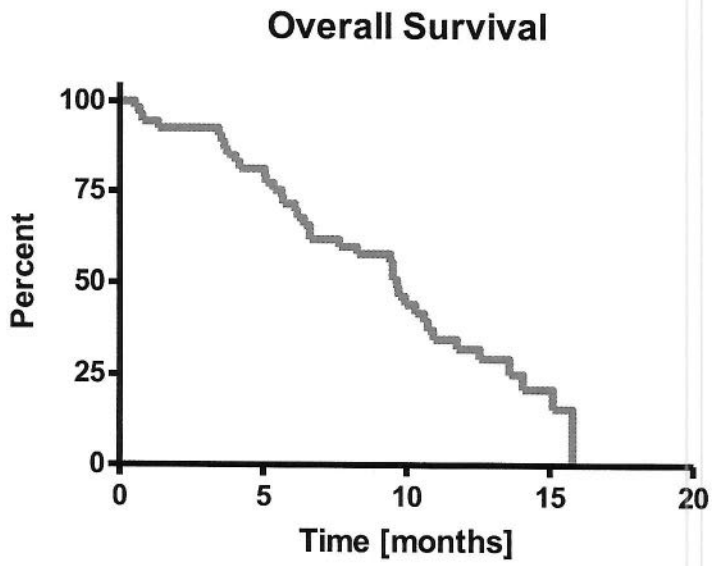
PtNo	Sex	Age	Primary	Metastatic sites	LDH	OR 8 wk	OR best	Cycles	PFS	OS
1	f	74	unknown	Skin, LN, bone	210	SD	SD	5	3,9	8,9
9	m	85	SSM, trunc, 1.8mm	Skin, LN, lung, liver	217	SD	SD	4	3,8	5,1
11	f	70	SSM, leg, 0.95mm	LN, lung	201	SD	SD	4	3,6	6,6
12	m	61	SSM, trunc, 8.1mm	LN, liver	277	SD	PR	12	11,5	11,6
26	f	20	unknown	LN, lung, bowel	223	SD	SD	2	6,7	9,4
29	f	70	Nevoid MM, trunc, 0.4mm	LN, liver	214	SD	SD	3	3,0	12,6
30	f	51	NM, trunc 5.5mm	LN, lung	158	SD	SD	10	8,8	15,8
31	m	42	NM, trunc, 2.8mm	lung, mesenterial, bone	236	SD	SD	5	10,5	15,8
33	m	51	Spindle cell MM, trunc, 3.3mm	LN, lung liver	370	SD	SD	5	4,1	11,8
36	f	46	SSM, skull, 4.4mm	LN, liver	330	SD	SD	12	13,3	13,5
37	m	29	NM, trunc, 5.3mm	lung, liver	219	SD	SD	7	5,7	12,8
39	m	44	NM, trunc, 0.4mm	Skin, liver	194	PR	PR	4	5,8	12,7
45	f	53	SSM, trunc, 1.1mm	LN	356	SD	PR	12	15,8	15,8
50	f	50	ALM, Leg, 1.2mm	lung, liver, adrenal, splenic	360	PR	PR	5	4,0	4,0
51	m	64	NM, trunc, 0.45mm	LN, lung, adrenal	236	SD	SD	6	8,5	8,5
54	m	73	NM, leg, 1.5mm	LN, lung	243	SD	SD	7	5,7	8,3

Overall Survival

Survival Analysis for OS_T

Number of Cases: 55 Censored: 17 (30,91%) Events: 38

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	9,36	,67	(8,05;	10,68)
Median:	9,67	,32	(9,04;	10,30)



In COX model:

---------- Variables in the Equation ----------

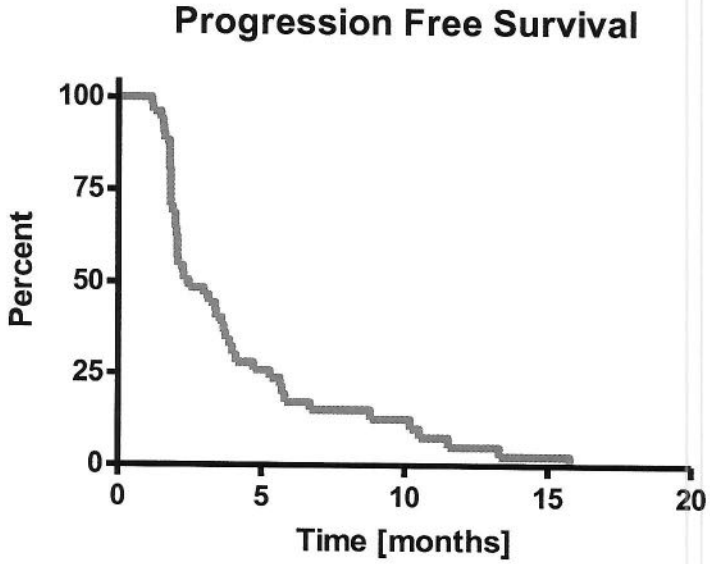
Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
LDH	,0103	,0021	25,0321	1	,0000	,3070	1,0104
N_METLOK	,3070	,1623	3,5789	1	,0585	,0804	1,3593
ALTER	,0226	,0125	3,2615	1	,0709	,0718	1,0229

Progression free survival

Survival Analysis for PFS_T

Number of Cases: 55 Censored: 7 (12,73%) Events: 48

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	4,19	,51	(3,18;	5,20)
Median:	2,47	,64	(1,22;	3,72)



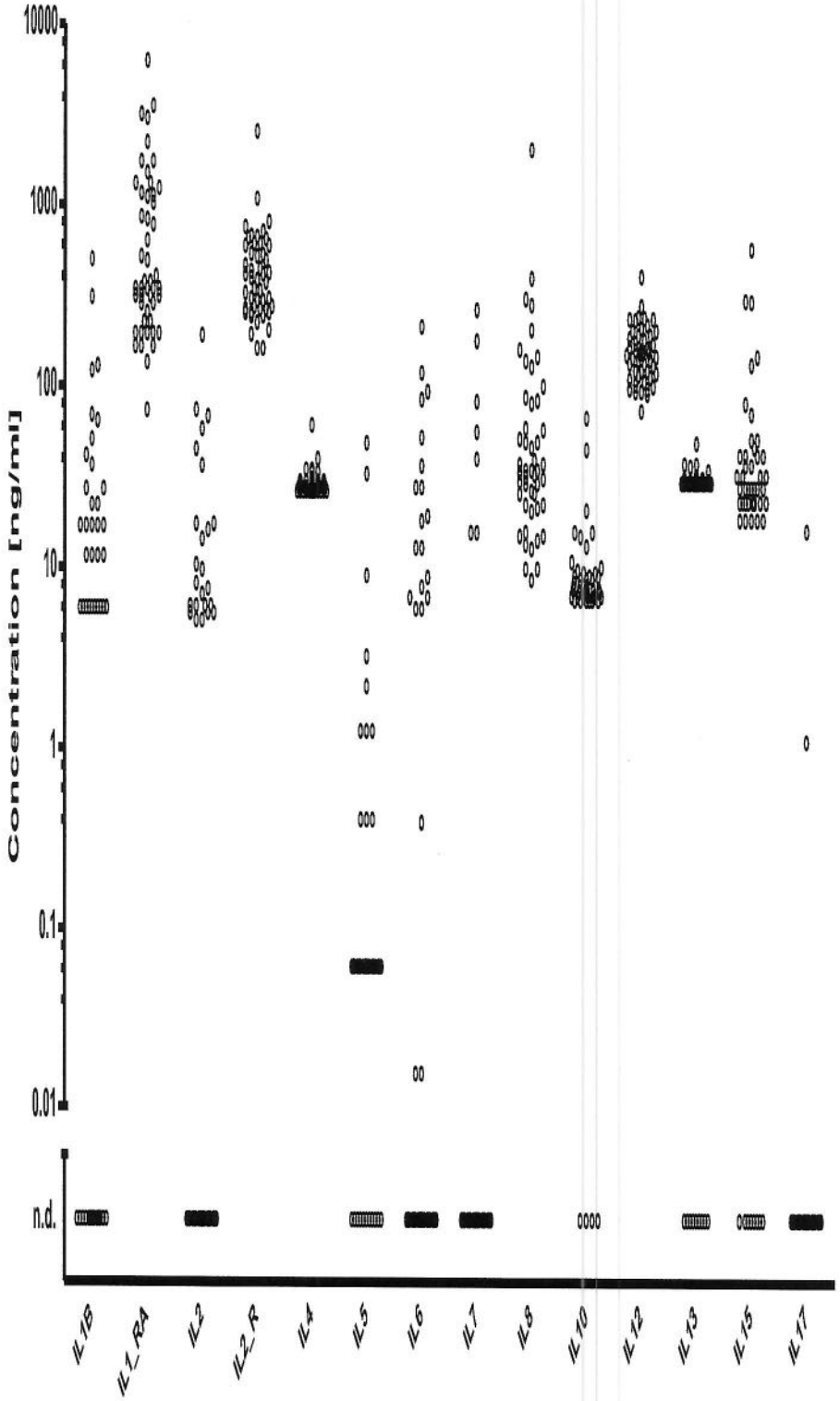
COX regression model

---------- Variables in the Equation ----------

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
LDH	,0043	,0021	4,3065	1	,0380	,0893	1,0043

Side Study

Parameter	valid value [n]	< low detection limit [n]	> high detection limit [n]
IL1B	34	14	0
IL1_RA	48	0	0
IL2	24	24	0
IL2_R	48	0	0
IL4	48	0	0
IL5	37	11	0
IL6	21	27	0
IL7	7	41	0
IL8	48	0	0
IL10	44	4	0
IL12	48	0	0
IL13	39	9	0
IL15	40	8	0
IL17	2	46	0
VEGF	43	5	0
TNFA	4	44	0
IFNA	47	1	0
IFNG	12	36	0
GM_CSF	31	17	0
MIP_1A	47	1	0
MIP_1B	48	0	0
IP10	48	0	0
MIG	43	5	0
EOTAX	48	0	0
RANTES	29	0	19
MCP_1	48	0	0
EGF	47	1	0
G_CSF	3	45	0
FGF_BAS	47	1	0
HGF	47	1	0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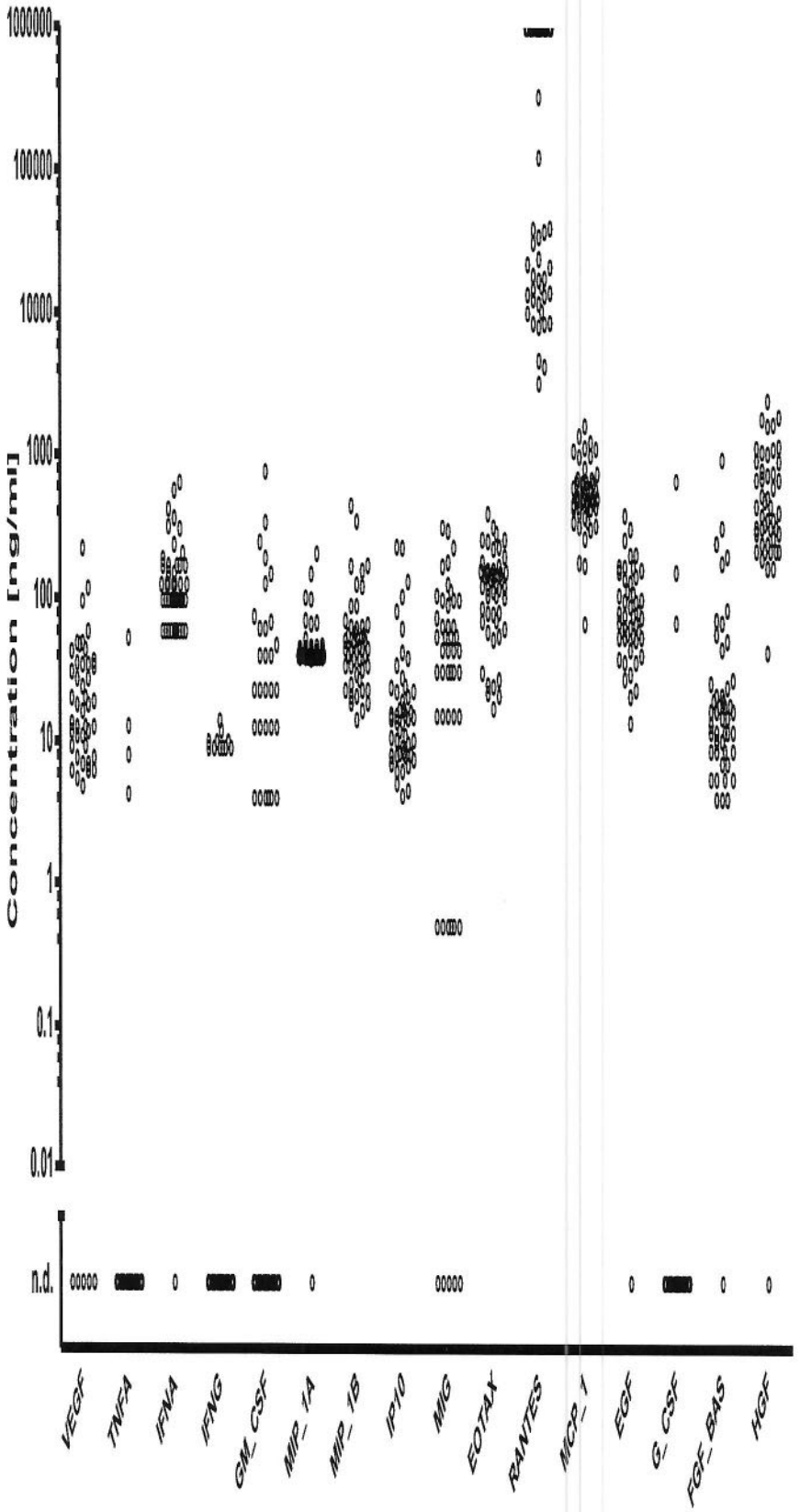
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