



AGO STUDIENGRUPPE OVARIALKARZINOM

AGO-Austria

**Phase-III Studie:  
HECTOR  
Topotecan plus Carboplatin**

**(Paclitaxel plus Carboplatin oder Gemcitabin plus Carboplatin)**

**-Intergroup Study of NOGGO und Studiengruppe Ovar  
(NOGGO-R9, AGO Ovar 2.12)  
-AGO-Austria, GEICO**

**RATIONALE:**

**NOGGO-Phase-I/II-Study**

**Könsgen et al Cancer Chemother Pharmacol. 2008  
Aug; 62(3): 393-400. Epub, 2006**

This clinical trial was a prospective multi-institutional phase I/II study of the North-Eastern German Society of Gynaecologic Oncology (NOGGO) study group ovarian cancer. Patients were enrolled at seven German institutions (six hospitals and one outpatient facility). The Department of Gynaecology and Obstetrics of the Charité University Hospital, Berlin, was the coordinating centre. The study was performed in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. Protocol approval was gained from the institutional review board or the local ethics committee of each participating institution. An independent monitoring institute was responsible for data control.

## Topo/Carbo NOGGO- Phase-I/II-Study Könsgen et al, 2006

- The primary objective of the study was to determine the toxicity profile, MTD and dose-limiting toxicity of the carboplatin/ topotecan combination. The remission rate (RR), overall survival and progression-free survival (PFS) were defined as secondary endpoints.
- Patients were stratified according to the platinum-free interval, defined as the period between completion of first-line chemotherapy with carboplatin and paclitaxel and time of recurrence (6 to 12 months versus >12 months), to identify potential differences in tolerability between both cohorts



## Topo/Carbo Phase-I/II-Study Könsgen et al, 2006

### Inclusion criteria

- Women  $\geq 18$  years of age with platinum-sensitive recurrent ovarian cancer, fallopian tube carcinoma or primary peritoneal cancer, relapsed at least six months after completion of primary standard therapy with surgery and first-line combination therapy with platinum and paclitaxel were eligible for study enrolment. Patients were required to have measurable or assessable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , normal hematological, liver and renal function with laboratory parameters within the normal range, including a glomerular filtration rate  $\geq 60$  ml/min, serum creatinine levels  $\leq 1.5$  mg/dl and an adequate bone marrow function (absolute neutrophil count [ANC]  $\geq 1.5 \times 10^9/l$  and platelets  $\geq 100 \times 10^9/l$ ). Patients suffering from a secondary malignancy or serious concomitant systemic disorders or psychiatric disease were excluded from the study, as were subjects receiving other cytotoxic, immunological, hormonal or targeted therapy. All patients provided written informed consent.

## NOGGO-Phase-I/II-Study


### Treatment plan

- Patients received six cycles of topotecan 1.0 mg/m<sup>2</sup> on days 1 to 3 plus carboplatin equating an area under the curve (AUC) of 5 on day 3 after infusion of topotecan, repeated every 21 days. Both study drugs were infused over 30 min in 250 ml of 0.9% saline solution.
- A 5-HT<sub>3</sub>-antagonist was given intravenously 15 min prior to each courses of chemotherapy.
- Two dose-levels were defined:
  - 1) - dose level 0: Topotecan 1.00 mg/m<sup>2</sup>/d1-3 + Carboplatin AUC5/d3, q21d
  - 2) - dose level -1: Topotecan 0.75 mg/m<sup>2</sup>/d1-3 + Carboplatin AUC5/d3, q21d




## Topo/Carbo Phase-I/II-Study

- In the phase I of this study, nine patients in each stratum (treatment-free interval 6-12 months and >12 months) were planned to receive treatment according to dose level 0. In case of no dose-limiting toxicity during the first four cycles of treatment, further nine patients in each stratum were planned to be included in the study to receive treatment according to dose level 0. Dose reduction to dose level -1 was required in case of occurrence of a dose-limiting toxicity during the first four cycles of treatment. Treatment for all patients in this stratum was continued in dose level -1. Further dose-escalation was not allowed.
- No primary prophylactic use of granulocyte colony-stimulating factor (G-CSF) was allowed. Darbepoetin alfa (2.25 µg/kg weekly or 6.75 µg/kg three-weekly) was applied in case of anaemia with hemoglobin concentrations ≤11.0 g/d.
- It was at the investigator's discretion to continue treatment until disease progression




**Multicentric, prospective  
phase-I/II-study**

	alle	6-12 Mo,	> 12 Mo,
n	26	13	13
Age	61,5	60	63
FIGO, n (%):			
I/II	5 (19,2)	1 (7,7)	4 (30,8)
III/IV	21 (80,8)	12 (92,3)	9 (69,2)
Ascites, n (%):			
no	15 (57,7)	7 (53,8)	8 (61,5)
yes	11 (42,3)	6 (46,2)	5 (38,5)



**Multicentric, prospective  
phase-I/II-study**

	all	6-12 mo,	> 12 mo,
Median number of cycle	6	6	6
n			
dose level 0:	16	13	3
dose level -1:	10	0	10
Median dosis			
Topotecan (mg/m <sup>2</sup> )	1,0	1,0	0,75
Carboplatin	AUC 5	AUC 5	AUC 5
DLTs: Dose level 0	3	2	1
Leukopenia			



## Multicentric, prospective phase-I/II-study

**Dose level 0:**

Topotecan	1,0 mg/m <sup>2</sup>	d1-3	
Carboplatin	AUC 5	d3	q21d

**Dose level -1:**


Topotecan	0,75 mg/m <sup>2</sup>	d1-3	
Carboplatin	AUC 5	d3	q21d

2 cohorts:

A:	6-12 months	
B:	>12 months	

DLT: Thrombocytopenia and Leukopenia

*Könsgen et al, Cancer Chem Phar, 2007*



## Multicentric, prospective phase-I/II-study toxicity

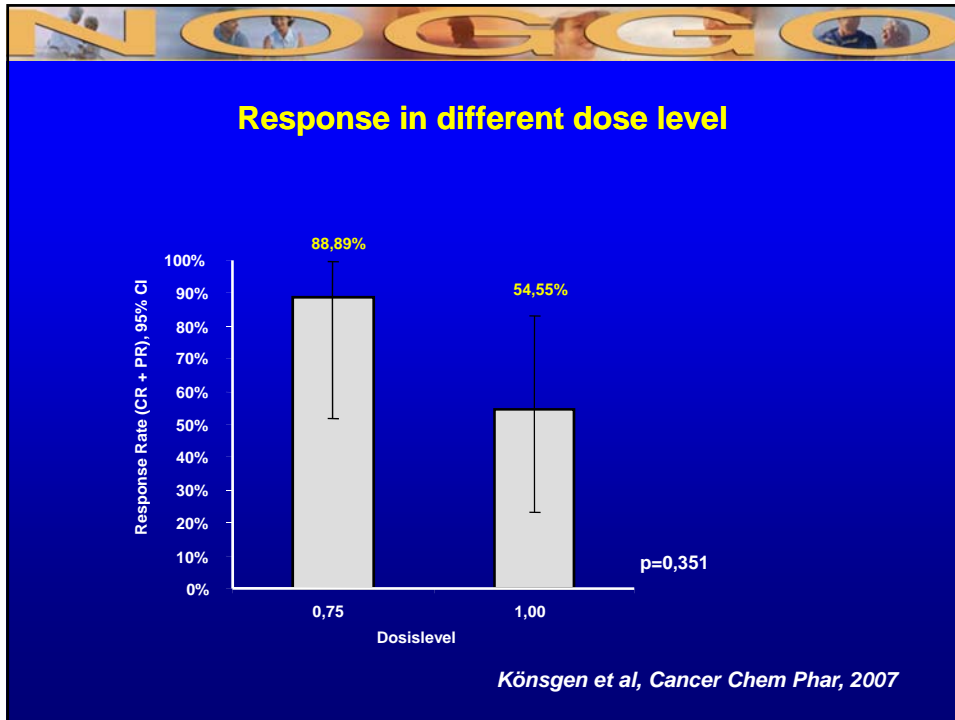
**hematological toxicities (grade 3/4)**

	6-12 Mo,	>12 Mo,	
Anemia	2	1	Patients
Leukopenia	10	5	
Neutropenia	7	8	
Thrombocytopenia	4	4	
Neutrop, fever	3	0	

**Non-hematologic toxicity( grade 3/4)**

	6-12 Mo,	>12 Mo,	
PNP	0	0	Patients
Diarrhea	0	4	
Nausea	2	2	
Emesis	3	2	

Könsgen et al, ASCO 2006, Abstr, 5089




- 
- Multicentric, prospective phase-I/II-study**
- Combination of Topotecan and Carboplatin is feasible and shows promising activity,
  - Tolerability is independent from platinum-free.
  - Recommended dose for phase-III trial:
 

– Topotecan	0,75 mg/m <sup>2</sup>	d 1-3	
– Carboplatin	AUC 5	d 3	q21d
- Könsgen et al, ASCO 2006, Abstr, 5089

## Multizentrische, prospektive Phase-I/II-Studie Könsgen et al, 2006

- In summary, the present data demonstrate that a combination therapy with topotecan and carboplatin is a tolerable and an effective chemotherapy regimen. Therefore this combination warrants further investigation in platinum-sensitive recurrent ovarian cancer. Based on these encouraging data we now have designed a randomized phase III trial comparing topotecan 0.75 mg/m<sup>2</sup> plus carboplatin AUC 5 to the current standard of care. In this concept patients will receive carboplatin (AUC 5) plus paclitaxel (175mg/m<sup>2</sup>/q21d) or carboplatin (AUC 5) plus gemcitabine (1000mg/m<sup>2</sup>d1,d8/q21d according to the individual patient's preference in order to more accurately reflect clinical reality (*HECTOR*-trial). Progression-free survival is defined as primary objective; and quality of life, response rate and overall survival are secondary objectives.



**HECTOR Phase-III-Studie**

AGO STUDIENGRUPPE OVARIALKARZINOM

GRUPO ESPAÑOL DE INVESTIGACION EN CÁNCER DE OVARIO

**AGO-AUSTRIA**

**R**  
**A**  
**N**  
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**A**  
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**I**  
**O**  
**N**

**experimental arm**

Topotecan	0,75 mg/m <sup>2</sup>	d 1-3	
Carboplatin	AUC 5	d 3	q21d

**control arm**

Paclitaxel	175 mg/m <sup>2</sup>		
Carboplatin	AUC 5		q21d

**or**

Gemcitabine	1000 mg/m <sup>2</sup>	d 1+8	
Carboplatin	AUC 4		q21d

\*Carboplatin +  
peg. lip. doxorubicin  
Is amended for  
the control arm boc



# HECTOR

## Design

- Prospective, randomized multicentric phase III-trial

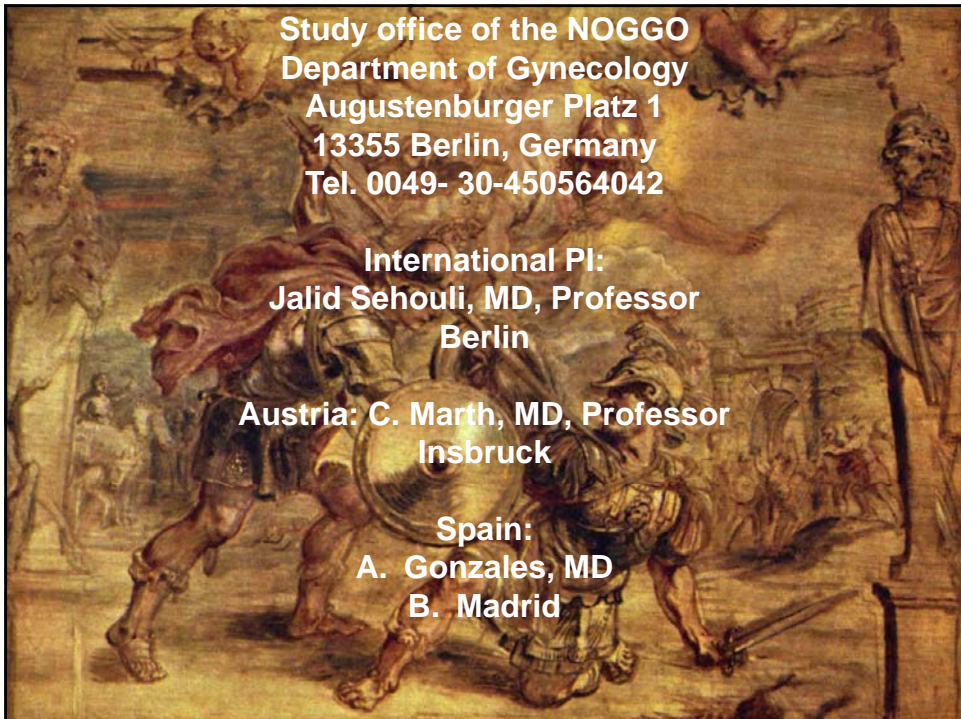
## Patients

- 550 patients

## Objectives

Primary PFS

Secondary: OS, ORR, Toxicity, QoL



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### Hector - Rekrutierungsverlauf

Stand vom 16.09.2009: 488 Patientinnen

