GANNET53: AN UPCOMING CLINICAL TRIAL TARGETING STABILISED MUTANT p53 PROTEIN TO COMBAT PLATINUM-RESISTANT OVARIAN CANCER

N. Concin[1], E.I. Braicu[2], S. Mahner[3], C. Marth[4], U. Moll[5], E. Pujade-Lauraine[6], I. Ray-Coquard[7], J. Sehouli[8], I. Vergote[9], R. Zeillinger[10]

on behalf of the whole GANNET53 consortium (18 partners)

[1]Department of Obstetrics and Gynaecology, Innsbruck Medical University, Austria; [2]Department of Gynaecology, Campus Virchow Clinic, Charité Medical University Berlin, Germany; [3]German Gynaecological Oncology Trial Group (G-AGO), Wiesbaden, Germany; [4]Austrian Gynaecological Oncology Trial Group (A-AGO), Innsbruck, Austria; [5]Goettingen Centre for Molecular Biosciences, Georg-August-Universitaet Goettingen, Germany; [6]Department of Adult Medical Oncology, Centre Anticancereux Leon Berard, Lyon, France; [7]Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du Sein (GINECO), Paris, France; [8]North-Eastern German Society of Gynaecological Oncology (NOGGO), Berlin, Germany; [9]Gynaecological Oncology, Katholieke Universiteit Leuven, Leuven, Belgium; [10]Molecular Oncology Group, Medical University Vienna, Austria

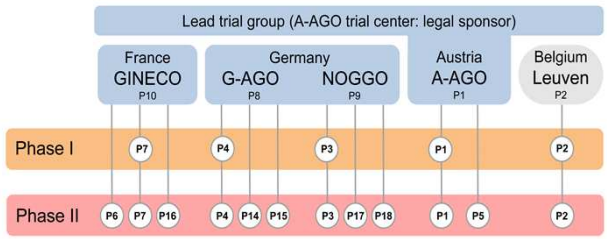
Abstract

Background:
There is a pressing need for more effective, innovative treatment strategies to improve survival in platinum-resistant (Pt-R) epithelial ovarian cancer (EOC) patients. The GANNET53 clinical trial has recently been positively evaluated for funding by the European Union (Seventh Framework Programm) and started in October 2013. The acronym GANNET53 stands for Ganetespib in metastatic, p53 mutant, platinum-resistant ovarian cancer.

Aims:
The GANNET53 clinical trial aims to substantially improve survival in Pt-R ovarian cancer patients by applying a highly innovative concept that has grown from solid basic research findings made by a member of the GANNET53 consortium. With the present abstract the GANNET53 consortium aims to provide information on this upcoming clinical trial.

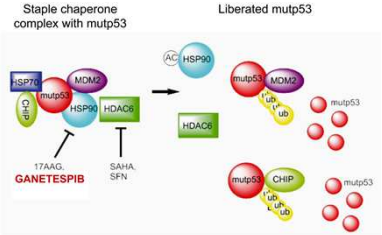
Methods:
This is a drug strategy targeting a central driver of tumour aggressiveness and metastatic ability, namely mutant p53 (mutp53), via an innovative new Hsp90 (heat shock protein 90) inhibition mechanism. The clinically most advanced second-generation Hsp90 inhibitor will be used, Ganetespib, and applied in a stratified treatment approach in Type II ovarian cancer patients. The first part (Phase I) of the GANNET53 trial will test the safety of Ganetespib in a new combination with Paclitaxel weekly in Pt-R Type II EOC patients. The second part (randomised two-arm open-label Phase II) will examine the efficacy of Ganetespib in combination with Paclitaxel weekly versus Paclitaxel weekly alone in EOC patients with Pt-R Type II tumours. We have established a highly efficient consortium featuring powerful clinical capacities, compelling knowledge in clinical trail performance, research excellence, and management competence to guarantee fast bench-to bedside translation of a highly innovative basic research finding.

Recruitment concept in the GANNET53 trial



Recruitment strategy: The GANNET53 trial is a Europe-wide multi-centre clinical trial, involving national trial groups to safeguard sufficient enrolment of patients with this deadly disease.
The GANNET53 trial will be open nation-wide in **Austria, Germany** and **France** via the respective national trial groups and at the high-volume University Centre **Leuven in Belgium** (P).

Scientific Principle of the GANNET53 trial



Destabilisation of mutant p53 protein (mutp53) by inhibition of the Hsp90 chaperone causes subsequent degradation by MDM2 or CHIP E3 ligases (Li et al, Cell Death & Diff 18:1904-13, 2011; Li et al, Mol Cancer Res 9:577–88, 2011):

Stable complex formation with Hsp90 causes aberrant stabilisation of mutp53 in cancer cells. Mdm2 and CHIP, which in principle are capable of degrading mutp53, are unable to degrade mutp53 as long as it is protected by the complex ('caging'). Stabilised mutp53 exerts oncogenic gain-of-function (GOF). Acute depletion of mutp53 in tumour cells is strongly cytotoxic in all tested mutp53 solid cancer cell types tested (ovarian, breast, colon, prostate). Small molecule inhibitors of the Hsp90 ATPase [such as the highly potent second generation Hsp90i Ganetespib, or the weaker first generation 17AAG + SAHA (causes Hsp90 inhibition via HDAC6 inhibition, an obligate positive regulator of the Hsp90 ATPase)] acutely deplete mutp53, which is strongly cytotoxic in mutp53 harboring tumour cells.

18 European partners in the GANNET53 project:

Participant no.	Participant organisation name	Short- name	Country
1 (Coordinator)	Medizinische Universitaet Innsbruck	IMU	Austria
2	Katholieke Universiteit Leuven	KUL	Belgium
3	Charité - Universitaetsmedizin Berlin	Charité	Germany
4	Universitaetsklinikum Hamburg-Eppendorf	UKE	Germany
5	Medizinische Universitaet Wien	MUW	Austria
6	Assistance Publique - Hôpitaux de Paris	AP-HP	France
7	Centre Anticancereux Léon Bérard	CLB	France
8	AGO Research GmbH	G-AGO	Germany
9	Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie	NOGGO	Germany
10	ARCAGY-GINECO	GINECO	France
11	Universitaetsmedizin Goettingen	UMG-GOE	Germany
12	OncoLab Diagnostics GmbH	OncoLab	Austria
13	xailabs GmbH	xailab	Germany
14	Klinik Essen-Mitte, Evang. Huyssens-Stiftung/ Knappschaft gemeinnutzige GmbH	KEM	Germany
15	Technische Universitaet Dresden,University Hospital Carl Gustav Carus Dresden	TUD	Germany
16	Centre de lutte contre le cancer, Francois Baclesse, Caen	CFB	France
17	Ernst-Moritz-Arndt-Universität Greifswald	EMAUG	Germany
18	Otto-von-Guericke-Universität Magdeburg	OVGU	Germany

Ganetespib

The test drug used in the GANNET53 trial, Ganetespib, is a highly potent, 2nd generation Hsp90 inhibitor (synthetic small molecule) developed by Synta Pharmaceuticals Corp. (Lexington, MA, USA). *In vitro*, Ganetespib leads to degradation of oncogenic client proteins and is a potent inducer of cell death in many cancer cell lines that depend on high levels of the respective client. Of central importance, mutant p53 has recently been shown to be a Hsp90 client. *In vivo*, it inhibits the growth of human tumour cell lines in mouse xenograft models. Ganetespib is in advanced clinical development and currently being studied in **26 unrelated clinical trials.**

Phase I Dose Escalation/De-Escalation Study

SYNOPSIS: An estimated number of 9-15 Pt-R Type II EOC patients will take part in the dose escalation/de-escalation study with a traditional 3+3 design. There will be no intra-patient dose escalation. The first 3 patients will be treated with a starting dose of 100 mg/m2 Ganetespib and the standard dose of Paclitaxel weekly (80 mg/m2, fixed dose). If this dose does not cause significant adverse effects in the first cohort during cycle 1 (weeks 1-4), Ganetespib will be escalated to 150 mg/m2, as a second cohort takes part in the study. If the dose of 150 mg/m2 does not cause significant adverse effects, it will be used in the GANNET53 Phase II trial. In the unexpected case of significant side effects at 150 mg/m2, a dose reduction of Ganetespib to 125 mg/m2 is permitted. Each patient will receive a total of 2 cycles of experimental therapy. The observation period will last from the first day of cycle 1 to the last day of cycle 2. At the dose level going to be used in Phase II an additional cohort of 3 patients will be included.
Study Type: Interventional; Study Design: Single group assignment; open label;

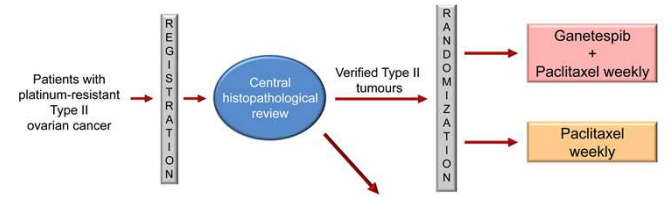
Primary endpoints: Safety
Secondary endpoints: Quality of life

Arm	Assigned Intervention
Experimental	Paclitaxel 80 mg/m² and Ganetespib will be given once weekly for 3 weeks out of 4 weeks (Days 1, 8, 15 of each 4-week cycle). Agents will be administered as a separate 1-hour infusion. The sequence of administration will be Paclitaxel followed by Ganetespib.

Randomized, Two Arm Phase II Study

SYNOPSIS: Eligible patients will undergo **central histopathological review** of archival ovarian cancer tissue at primary diagnosis to ensure Type II designation of tumours. **200 patients** with verified Type II Pt-R EOC will be randomised in a 1:1 ratio (**100 patients per arm**) to receive either Ganetespib and Paclitaxel weekly or Paclitaxel weekly alone. The Ganetespib dose used depends on results of Phase I. For Paclitaxel weekly the standard dose of 80 mg/m2 is applied. Patient will receive the respective therapy until disease progression. **All patients included** will be **analysed for p53 mutational status** from archival ovarian cancer tissues at primary diagnosis. This analysis will be performed during ongoing Phase II
Study Type: Interventional; Study Design: Randomised, parallel assignment, open label

Primary endpoints: PFS and PFS at 6 months
Secondary endpoints: Objective response rate (ORR), OS, Quality of life, Safety
Experimental endpoints: Molecular efficacy



Arms	Assigned Interventions
Active Comparator: 1	*Drug*: Paclitaxel: 80 mg/m2, given iv once weekly for 3 out of 4 weeks (Days 1, 8, 15 of each 4-week cycle), until progression
Experimental: 2	*Drug*: Ganetespib, dose will depend on Phase I results, given iv once weekly for 3 out of 4 weeks (Days 1, 8, 15 of each 28 days cycle); *Drug:* Paclitaxel, 80mg/m2, given iv once weekly for 3 out of 4 weeks (Days 1, 8, 15 of each 4-week cycle), until progression. The sequence of administration will be Paclitaxel followed by Ganetespib.