Phase II results of GANNET53: A European multicenter phase I/randomized II trial of the Hsp90 inhibitor Ganetespib (G) combined with weekly Paclitaxel (P) in women with high-grade serous, high-grade endometrioid, or undifferentiated, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer

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BACKGROUND

Stabilized mutant p53 protein (mutp53) is a novel target in ovarian cancer. Mutp53 proteins depend on folding support by the Hsp90 chaperone. Hsp90 blockade induces degradation of mutp53, resulting in anti-tumor cytotoxicity and increased sensitivity to chemotherapeutics. The GANNET53 trial (EUDRACT 2013-003868-31, European Union Seventh Framework Programme Project funded with 6 Mio € over 5.5 years) tests the combination of Ganetespib (G) with Paclitaxel (P) in platinum-resistant epithelial ovarian cancer (PROC) patients.

PATIENTS & METHODS

Patients were randomized in a 2:1 manner to receive weekly P (80 mg/m²) + G (150 mg/m²) or weekly P alone. Treatment was given i.v. on days 1, 8, 15 in a 28 day cycle until disease progression. Primary endpoint was PFS and PFS at 6 months, secondary endpoints were OS, ORR, PFS2, safety, PRO and PK.

Main inclusion criteria:

- Platinum-resistant epithelial ovarian cancer (PROC)
- ≤ 4 prior chemotherapy lines
- high-grade serous, high-grade endometrioid or undifferenciated histology
- disease measurable according to RECIST 1.1 or assessable according to GCIG CA-125 criteria.

STUDY DESIGN

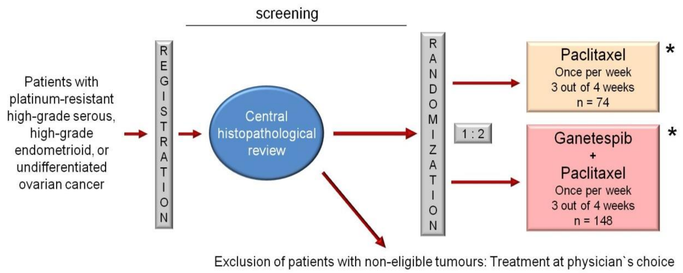


Figure 1. Randomised, open-label Phase II GANNET53 trial

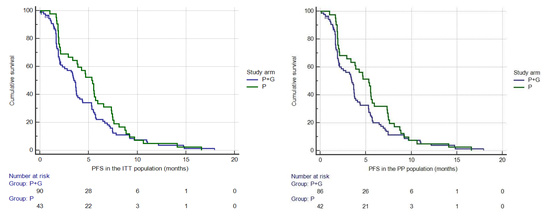
RESULTS

A total of 133 patients were enrolled. Median follow-up was 10.0 months in the ITT population. The study was prematurely closed due to unsecured drug supply with G (initially planned 222 patients).

Table 1. Baseline characteristics of the patients in the ITT population

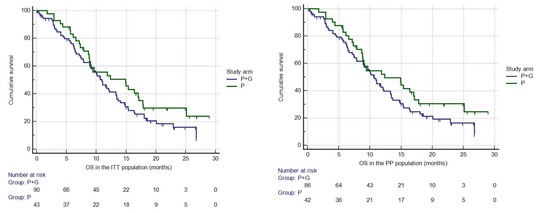
	Paclitaxel +Ganetespib (n=90)	Paclitaxel (n=43)	p-value
Median age at enrolment (range)	61.4 (40.7-79.9)	62.1 (46.1-81.7)	0.70
Median time between first diagnosis and enrolment, years (range)	2.5 (0.8-18.3)	2.3 (0.8-5.3)	0.47
ECOG performance status	0: 50 (55.6%) 1: 40 (44.4 %)	0: 21 (48.8%) 1: 22 (51.2%)	0.58
Median CA-125 at screening (range)	421 (8-39505)	246 (5-7370)	0.07
Number of prior debulking surgeries (DS) per patient	0 prior DS: 6 (6.7%) 1 prior DS: 72 (80%) 2 prior DS: 6 (6.7%) Unclear: 6 (6.7%)	0 prior DS: 3 (7%) 1 prior DS: 33 (76.7%) 2 prior DS: 4 (9.3%) Unclear: 3 (7%)	0.89
Residual tumour in mm after debulking at primary diagnosis	0 : 63 >0: 14	0: 26 >0: 11	0.22
Central histopathology review result	High-grade serous: 88 (97.8 %) High-grade endometrioid: 1 (1.1%) Undifferentiated: 1 (1.1%)	High-grade serous: 41 (95.3%) High-grade endometrioid: 1(2.3%) Undifferentiated: 1 (2.3%)	0.39
FIGO stage at diagnosis	I: 5 (5.6%) II : 3 (3.3%) III: 50 (55.6%) IV: 32 (35.6%)	I: 0 II: 0 III : 32 (74.4%) IV: 11 (25.6%)	0.12
BRCA1/2 mutation status (germline or somatic) at enrolment	Mutation is present: 16 (17.8%) No mutation present: 40 (44.4%) Unknown: 34 (37.8%)	Mutation is present: 3 (7.0%) No mutation present: 21 (48.8%) Unknown: 19 (44.2%)	0.26
Median therapy-free interval prior to enrolment, months (range)	1.7 (0.6-18.0)	1.9 (0.6-19.1)	0.47
Median platinum-free interval prior to enrolment, months (range)	6.2 (1.0-29.3)	5.7 (0.9-27.7)	0.48
Median number of total prior treatment lines[1] per patient (range)	2 (1-5)	2 (1-4)	0.12
Total number of prior treatment lines in platinum resistance	0: 56 (62.2%) 1: 26 (28.9%) 2: 8 (8.9%)	0: 31 (72.1%) 1: 9 (20.9%) 2: 3 (7.0%)	0.56
Method of Response evaluation	RECIST: 78 (86.7%) GCIG CA-125 criteria: 12 (13.3%)	RECIST: 33 (76.7%) GCIG CA-125 : 10 (23.3%)	0.21
Presence of ascites at screening	yes: 13 (14.4%) no: 77 (85.6%)	yes: 9 (20.9%) no: 34 (79.1%)	0.45

Figure 2. Progression-free survival (PFS) in ITT and PP population



	ITT population		PP population	
	Paclitaxel+Ganetespib (n=90)	Paclitaxel (n=43)	Paclitaxel+Ganetespib (n=86)	Paclitaxel (n=42)
Estimated median PFS (95%CI)	3.49 (3.09-3.88)	5.33 (4.01-6.65)	3.45 (2.68-4.23)	5.33 (4.02-6.64)
Log Rank (Mantel-Cox)	0.16		0.136	
HR (95%CI)	1.30 (0.90 - 1.90)		1.33 (0.91 - 1.94)	

Figure 3. Overall-survival (OS) in ITT and PP population



	ITT population		PP population	
	Paclitaxel+Ganetespib (n=90)	Paclitaxel (n=43)	Paclitaxel+Ganetespib (n=86)	Paclitaxel (n=42)
Estimated median OS (95%CI)	10.95 (9.19-12.71)	14.90 (7.59-22.22)	10.66 (8.69-12.62)	12.34 (5.27-19.40)
Log Rank (Mantel-Cox)	0.13		0.14	
HR (95%CI)	1.40 (0.90 - 2.17)		1.40 (0.90 - 2.19)	

Cumulative PFS rate at 6 months in the ITT population was 22% (95%CI: 14%-31%) in the P+G arm and 33% (95%CI: 20%-48%) in the P arm. **Median PFS II** in the ITT was 8.49 months in the P+G arm and 11.25 in the P arm (HR 1.31, 95%CI 0.87-1.97; p=0.2).

Table 3. Objective response rate

	ITT population		PP population	
	Paclitaxel+Ganetespib (n=90)	Paclitaxel (n=43)	Paclitaxel + Ganetespib (n=86)	Paclitaxel (n=42)
Objective response rate (complete +partial response)	23 (25.6%)	17 (39.5%)	22 (25.6%)	16 (38.1%)
p (Mantel-Haenszel test)	0.110		0.155	

Treatment-related grade 1-2 AEs

The most frequent **treatment-related grade 1-2 AEs** in the P+G arm were typical transient (1-2 days) diarrhea (79% of patients), anemia (46%), nausea (41%), and peripheral neuropathy (36%), and in the P arm anemia (51%), peripheral neuropathy (47%), nausea (40%) and diarrhea (26%).

Table 2. Treatment-related AEs of grade 3-5 in > 1 patient in the Paclitaxel + Ganetespib and in the Paclitaxel arm

Paclitaxel+Ganetespib Grade 3-5 events in > 1 patient	Number of patients (n=90)	Number of events
Neutrophil count decreased	11 (**12.2%**)	16
Diarrhoea	10 (**11.1%**)	15
Anemia	7 (**7.8%**)	7
Asthenia	3 (3.3%)	3
Fatigue	2 (2.2%)	2
Febrile neutropenia	2 (2.2%)	2
Lymphocyte count decreased	2 (2.2%)	2
Nausea	2 (2.2%)	2
Small intestinal perforation	2 (2.2%)	2
Vomiting	2 (2.2%)	2
White blood cell decreased	2 (2.2%)	2

Paclitaxel Grade 3-5 events in > 1 patient	Number of Patients (n =43)	Number of events
Neutrophil count decreased	4 (**9.3%**)	7
Diarrhoea	2 (**4.7%**)	2
Anemia	4 (**9.3%**)	4
White blood cell decreased	3 (7.0%)	3
Alanine aminotransferase increased	2 (4.6%)	2

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CONCLUSION

The addition of Ganetespib to weekly Paclitaxel did not improve survival in platinum-resistant epithelial ovarian cancer patients.