Table 1: Criteria for dose-limiting toxicities (DLTs)

	Adverse Event	Grade	Comment	DLT (yes/no)
NON-HEMATOLOGIC	any (with exceptions)	4	significant, clinically relevant	Yes with the exceptions of 1. alopecia 2. nausea and 3. vomiting without optimal prophylactic measures
	alopecia	4		no
	nausea	4		no
	vomiting	4	occurred despite optimal prophylactic measures (e.g., antiemesis, loperamide)	yes
		4	no optimal prophylactic measures applied	no
	diarrhoea	4	occurred despite optimal prophylactic measures (e.g., loperamide)	yes
		4	no optimal prophylactic measures applied	no
	fatigue	4		yes
		1, 2, 3		no
	any	3, 4	Not improving to baseline or grade ≤ 1 within 21 days of last treatment dose and despite adequate supportive care/toxicity management	yes
	elevation of serum bilirubin	4		yes
	elevation of AST, ALT, or ALP		> 10 x ULN	yes
			> 5-10 x ULN and not improving to ≤ 5 x ULN (grade ≤ 2) by day 7	yes
			> 5-10 x ULN which improved to ≤ 5 x ULN (grade ≤ 2) by day 7	no
	any AEs		Related to disease progression or considered to be clearly not study drug-related	no
HEMATHOLOGIC	thrombocytopenia	4		yes
	thrombocytopenia	3	if not recovered to ≤ 2 by day 7 of AE onset	yes
		3	if recovered to ≤ 2 by day 7 of AE onset	no
	neutropenia	4	If lasting ≥ 7 days	yes
		4	If lasting less than 7 days	no
	febrile neutropenia	any grade		yes
OTHER	any toxicities		Which is treatment-related and prompt a dose reduction of Ganetespib during DLT observation time*	yes
	Laboratory toxicity	3, 4	Considered as clinically insignificant by the PI or related to an underlying condition	no
	any death		Which is considered possibly related to the study drug (determined by the PI)	yes
			Which is considered not related to the study drug (determined by the PI)	no
	any AEs		Related to disease progression or considered to be clearly not study drug-related	no
	any dose hold during DLT observation time*			no

* DLT observation time: D1 of cycle 1 to D28 of cycle 2

Table 2. Baseline characteristics of patients included into the Phase I GANNET53 trial

	Cohort 1 (100 mg/m2) 4 patients included	**Cohort 2 + 3 (150 mg/m2) 6 patients included**	**Total of 10 patients included**
Median age (range), years	58 (43-62)	60.5 (52-70)	59 (43-70)
Median time between first diagnosis and enrolment (range), years	2.35 (1.35-5.95)	1.93 (0.9-3.58)	1.93 (0.9-5.95)
ECOG performance status	1 (n=4)	0 (n=5) 1 (n=1)	0 (n=5) 1 (n=5)
Median CA125 at screening (range), U/ml	504.25 (401-2677)	1366.75 (224-4914)	791.25 (224-4914)
Number of previous surgeries for ovarian cancer	0 (n=1) 1 (n=1) 3 (n=2)	1 (n=3) 2 (n=2) 3 (n=1)	0 (n=1) 1 (n=4) 2 (n=2) 3 (n=3)
Residual tumour after the latest surgery prior to enrolment, mm	No surgery (n=1) 0 (n=3)	0 (n=2) 3 (n=1) 5 (n=1) 20 (n=2)	No surgery (n=1) 0 (n=5) 3 (n=1) 5 (n=1) 20 (n=2)
High-grade histology	endometrioid (n=1) serous (n=3)	serous (n=6)	endometrioid (n=1) serous (n=9)
Median time to prior chemotherapy (range), months	1.63 (1.47-1.83)	4.03 (1.13-6.73)	2 (1.13-6.73)
Number of total previous chemotherapy lines	2 (n=1) 3 (n=1) 4 (n=2)	1 (n=2) 2 (n=1) 3 (n=2) 4 (n=1)	1 (n=2) 2 (n=2) 3 (n=3) 4 (n=3)
Number of previous chemotherapy lines in platinum-resistance	0 (n=3) 1 (n=1)	0 (n=3) 1 (n=1) 2 (n=2)	0 (n=6) 1 (n=2) 2 (n=2)
Method of Tumour response evaluation	measurable disease by RECIST (n=3) one fast clinical progression (replaced)	measurable disease by RECSIT (n=4) Assessable by GCIG CA125 criteria (n=2)	measurable disease by RECIST (n=7) Assessable by GCIG CA125 criteria (n=2)

n: referrers to the number of patients

Table 3. Summary of grade 1/2 adverse events (AEs) occurring in >1 patient and all grade ≥3 AEs

Grade 1/2 AEs			**Grade 3/4 AEs**		
Reported Term	**Number of patients affected and relatedness* to Ganetespib (n=10)**	**Total number of events (n)**	**Reported Term**	**Number of patients affected and relatedness* to Ganetespib (n=10)**	**Total number of events (n)**
Diarrhoea	6, related **6**	56	Diarrhoea	3, related **3**	5
QT corrected interval prolonged	6, related **4****	11	Neutropenia	2, related **2**	2
Nausea	6, related **3**	6	Anemia	3, related **1**	3
Headache[1]	5, related **3**	7	Asthenia	1, related **1**	1
Fatigue	3, related **3**	3	Acute cardiac insufficiency stage IV	1, related **1**	1
Anemia	3, related **3**	3	Gastroduodenal haemorrhage & Haemorrhagic shock from an ulcer duodeni	1, related **1**	1
Dyspnoea	3, related **3**	3	Syncope	1, related **1**	1
Anorexia	3, related **2**	3	Pain	1, related 0	1
Peripheral neuropathy	2, related **2**	2	Vomiting	1, related 0	1
Oedema peripheral	2, related **2**	2	Polyneuropathy	1, related 0	1
Weight loss	2, related **2**	2	Subileus[4]	2, related 0	2
Abdominal pain[2]	5, related **1**	5	Placement of Tenckhoff catheter	1, related 0	1
Dysgeusia	2, related **1**	2	Ascites	2, related 0	4
Alopecia	2, related **1**	2			
Pain[3]	3, related 0	4			
Asthenia	2, related 0	2			
Pruritus	2, related 0	2			
Subileus[4]	2, related 0	2			
Constipation	2, related 0	5			

[1]Includes: Migraine; [2]Includes: Abdominal cramping, Abdominal pain with vomiting; [3]Includes: Pain in extremity (lower), Pain leg; [4]Includes: Small bowel subobstruction, Obstruction

* relatedness as evaluated by local PI; AEs categorized as related to study treatment included possibly, probably or definitely related

** for QT prolongation central reviewed of all data were performed by the Sponsor and relatedness as evaluated by Sponsor is given; AEs categorized as related to study treatment included possibly, probably or definitely related

Table 4. Serious adverse reactions (SARs)

Reported Term	**Grade**	**Ganetespib dose (mg/m^2)**	**Relatedness to Ganetespib evaluated by Investigator/Sponsor**	**Outcome**
Gastroduodenal haemorrhage & Haemorrhagic shock from an ulcer duodeni	5 (SUSAR*)	150	unlikely related / possibly related	Fatal
Acute cardiac insufficiency stage IV[1]	4 (SUSAR*)	150	probably related / possibly related	Recovered with sequelae
Diarrhoea	2	100	definitely related / definitely related	Complete recovery
Dyspnoea	2	150	possibly related / possibly related	Complete recovery
Abdominal pain with vomiting	2	150	possibly related/ possibly related	Complete recovery

[1] Cardiac insufficiency NYHA stage II-III; loss of systolic LV-function; atrial fibrillation

* Two exclusive SUSARS reported in this Phase I trial

Table 5. Treatment exposure and clinical activity

	Patient no	No. of started cycles	Duration of treatment (months)	PFS (months)	Best overall response (Best OR)	Evaluation of the Best OR by	End of treatment (EOT) reason
100 mg/m2	1	2	1.4	1.6	Progressive disease	RECIST	progression of disease
	2	2	1.6	1.8	Progressive disease	RECIST	progression of disease
	3	1	one dose only	0.5	Progressive disease	*immediate clinical progression*	progression of disease
	4	2	1.6	1.7	Progressive disease	RECIST	progression of disease
150 mg/m2	5	3	2.3	2.8	Stable disease	GCIC CA125	SAE (SUSAR)
	6	10	9.2	9.3	Stable disease	RECIST	progression of disease
	7	6	5.3	7.9	Partial response*	RECIST	investigator and patient decision
	8	2	1.6	5.0	Stable disease	RECIST	SAE
	9	3	1.8	4.4	Stable disease	RECIST	SAE (SUSAR)
	10	11	10.1	10.3	Partial response	GCIC CA125	progression of disease

*confirmed response

Table 6. Baseline characteristics of the patients in the ITT population

	Ganetespib/Paclitaxel (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 (U/ml) 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
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
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 (TFI) prior to enrolment, months (range)	1.7 (0.6-18.0)	1.9 (0.6-19.1)	0.47
Median time between last platinum-based treatment and study 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
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: 12 (13.3%)	RECIST: 33 (76.7%) GCIG CA-125: 10 (23.3%)	0.21

Abbreviations: ITT, intention to treat; N=total number of subjects in each arm; ECOG, Eastern Cooperative Oncology Group; CA-125, carcinoma antigen-125; DS, debulking surgery; BRCA, breast cancer gene; RECIST, response evaluation criteria in solid tumours; GCIG, gynaecological cancer intergroup

[1] Includes pure chemotherapy and combinations of chemotherapy (with targeted, endocrine, and palliative radiotherapy)

Table 7. Treatment exposure of patients in the Per-Protocol population

	Ganetespib/Paclitaxel (N=86)	**Paclitaxel (N=42)**	***p-value***
started cycles per patient, median (range)	3 (1-16)	5 (1-18)	0.02
completed cycles[1], median (range)	2 (0-12)	4 (0-18)	0.002 <0.01
optimal cycles[2], median (range)	2 (0-11)	4 (0-18)	0.003 <0.01
patients with at least one dose reduction[3] **median dose reductions (range)**	22/86 (25.6%) 1 (1-2)	6/42 (14.3%) 1 (1-1)	0.15 0.64
patients with at least one dose delay[3] **median dose delays (range)**	15/86 (17.4%) 1 (1-3)	5/42 (11.9%) 1 (1-2)	0.42 0.67
patients with least one skipped dose[3] **median skipped doses (range)**	40/86 (46.5%) 1.5 (1-8)	15/42 (35.7%) 1 (1-7)	0.25 0.90

abbreviations: N=total number of subjects in each arm.

[1] completed cycles defined as cycles with study drug administration on all days, i.e. days 1, 8, and 15 (independent of dose reductions)

[2] optimal cycles defined as cycles without dose reductions, without dose delay and with study drug administration on all days, i.e. days 1, 8, and 15

[3]applies to at least one study drug

Table 8. Progression-free (PFS), PFS rate at 6 months and Overall survival (OS) in the ITT and PP populations

	ITT population			**PP population**		
	Ganetespib/ Paclitaxel N=90	Paclitaxel N=43	*p-value** HR (95%CI)	Ganetespib/ Paclitaxel N=86	Paclitaxel N=42	*p-value** HR (95%CI)
PFS						
Median PFS in months (95%CI)	3.5 (3.1-3.9)	5.3 (4.0-6.7)	0.16 1.3 (0.90 - 1.90)	3.5 (2.7-4.2)	5.3 (4.0-6.6)	0.14 1.3 (0.91 - 1.94)
PFS rate at 6 months (95%CI)	22% (14-31)	33% (20-48)		20% (13-28)	32% (19-45)	
OS						
Median OS in months (95%CI)	11.0 (9.2-12.7)	14.9 (7.6-22.2)	0.13 1.4 (0.90 - 2.17)	10.7 (8.7-12.6)	12.3 (5.3-19.4)	0.14 1.4 (0.9 – 2.19)

abbreviations: ITT, intention to treat; PP, per protocol; G/P; N=total number of subjects in each arm; CI, confidence interval; PFS, progression free survival; HR, hazard ratio; OS, overall survival.

*Log Rank

Table 9. Objective Response Rates, Disease Control Rates and Clinical Benefit Rates in the ITT and PP populations

	ITT population			**PP population**		
	Ganetespib/ Paclitaxel	Paclitaxel	*p-value**	Ganetespib/ Paclitaxel	Paclitaxel	*p-value**
Best ORR	N=90	N=43		N=86	N=42	
CR	2 (2.2%)	3 (7.0%)		2 (2.3%)	2 (4.8%)	
PR	21 (23.3%)	14 (32.6%)		20 (23.3%)	14 (33.3%)	
ORR[1]	23 (25.6%)	17 (39.5%)	0.101	22 (25.6%)	16 (38.1%)	0.165
DCR[2]	53 (58.9%)	29 (67.4%)	0.373	51 (59.3%)	28 (66.7%)	0.384
CBR+ve[3]	16 (17.8%)	16(37.2%)	0.017	16 (18.6%)	15 (35.7%)	0.036
Confirmed best ORR[4]	13 (14.4%)	12 (27.9%)	0.052	12 (14%)	12 (28.6%)	0.042

Abbreviations: ITT, intention to treat; PP, per protocol; N=total number of subjects in each arm; CR, complete response; PR, partial response; SD, stable disease; ORR objective response rate; DCR, disease control rate; PD progressive disease; n.e., not evaluable; CBR, clinical benefit rate

[1]ORR was calculated as CR+PR.

[2]DCR was calculated as CR+PR+SD.

[3]CBR was considered +ve (positive) if the time between the first beneficial response (CR, PR or SD) and the first confirmed progression of a patient was more than or equal to 4 months.

[4]ORR could be confirmed for only 48 patients in the ITT population and 47 patients in the PP population, which was used for the computation of Confirmed best ORR.

*p-value was calculated using z-test.

Table 10. Summary of all treatment-related Adverse Events (AEs) in the safety population. Data are shown for grade 1-2 AEs occurring in >=10 % of patients, and for all grade 3-5 AEs in > 1 patient.

	Ganetespib/Paclitaxel (N=86)		**Paclitaxel (N=43)**	
Grade 1-2 Adverse Events (in >= 10% of patients)	**n (%)**		**n (%)**	
Diarrhoea	71 (78.9%)		11 (25.6%)	
Anaemia	41	45.6	22	51.6
Nausea	37	41.1	17	39.5
Alopecia	35	38.9	13	30.2
Peripheral neuropathy	32	35.6	20	46.5
Vomiting	23	25.6	4	9.3
Fatigue	21	23.3	7	16.3
Abdominal pain	19	21.1	5	11.6
Neutrophil count decreased	18	20.0	7	16.3
Asthenia	13	14.4	10	23.3
Constipation	11	12.2	5	11.6
Electrocardiogram QT corrected interval prolonged	11	12.2	-	-
Insomnia	11	12.2	-	-
White blood cell decreased	11	12.2	3	7.0
Anorexia	10	11.1	3	7.0
Headache	9	10.0	2	4.7
Dysgeusia			5	11.6
Dyspnoea			5	11.6
Grades 3-5 Adverse Events (complete list)				
Neutrophil count decreased	11	12.2	4	9.3
Diarrhoea	10	11.1	2	4.7
Anaemia	7	7.8	4	9.3
Asthenia	3	3.3	-	-
Fatigue	2	2.2	-	-
Febrile neutropenia	2	2.2	-	-
Lymphocyte count decreased	2	2.2	1	2.3
Nausea	2	2.2	-	-
Small intestinal obstruction/perforation	2	2.2	-	-
Vomiting	2	2.2	-	-
White blood cell decreased	2	2.2	3	7.0
Alanine aminotransferase increased	-	-	2	4.7

abbreviations: AE, adverse event; N=total number of subjects in each arm; n=number of patients in the respective row category.

Table 11. Treatment-Emergent Serious Adverse Events (SAEs) by System Organ Class and Lowest Level Term (all causalities) in safety population

System Organ Class (SOC) **Lowest Level Term (LLT)**	**G/P arm** **(N=86)**	**P arm** **(N=43)**
	n (%)	**n (%)**
Number of patients with at least one SAE	34 (39.5)	10 (23.3)
Blood and lymphatic system disorders		
Anaemia	1 (1.2)	0
Febrile neutropenia	1 (1.2)	0
Hypovolemia	1 (1.2)	0
Gastrointestinal disorders		
Abdominal distension	1 (1.2)	0
Abdominal pain	3 (3.5)	1 (2.3)
Anal haemorrhage	0	1 (2.3)
Diarrhoe[a]	3 (3.5)	0
Esophagitis	1 (1.2)	0
Ileus	2 (2.3)	1 (2.3)
Rectal ulcer	1 (1.2)	0
Small intestinal obstruction	8 (9.3)	1 (2.3)
Small intestinal perforation	2 (2.3)	0
Subileus	1 (1.2)	0
Subobstruction colon	1 (1.2)	0
Vomiting	1 (1.2)	2 (4.7)
General disorders and administration site conditions		
Fever	1 (1.2)	1 (2.3)
General physical health deterioration	2 (2.3)	1 (2.3)
Infusion site extravasation	0	1 (2.3)
Sudden death NOS	1 (1.2)	0
Hepatobiliary disorders		
Haemobilia	1 (1.2)	0
Hepatic failure	1 (1.2)	0
Icterus	1 (1.2)	0
Infections and Infestations		
Sepsis	6 (7.0)	0
Urinary tract infection	5 (5.8)	1 (2.3)
Erysipelas[c]	0	3 (7.0)
Catheter related infection	1 (1.2)	0
Urethral infection	1 (1.2)	0
Infection NOS	0	1 (2.3)
Injury, poisoning and procedural complications		
Rupture of renal pelvis	1 (1.2)	0
Vascular access complication	0	1 (2.3)
Metabolism and nutrition disorders		
Anorexia	1 (1.2)	0
Hyperpotassaemia	1 (1.2)	0
Hypokalaemia	1 (1.2)	0
Nervous system disorders		
Visual acuity reduced	1 (1.2)	0
Renal and urinary disorders		
Acute kidney injury	1 (1.2)	0
Cystitis	1 (1.2)	0
Kidney insufficiency	1 (1.2)	0
Renal disorders NEC[d]	1 (1.2)	0
Urinary tract obstruction	0	2 (4.7)
Respiratory, thoracic and mediastinal disorders		

Dyspnea	1 (1.2)	0
Pleural effusion	1 (1.2)	0
Respiratory failure	1 (1.2)	0
Vascular disorders		
Deep vein thrombosis	0	1 (2.3)
Thromboembolic events	1 (1.2)	0

Abbreviations: SAE, serious adverse event; SOC, system organ class; LLT, lowest level term; G/P, Ganetespib+Paclitaxel treatment arm; P, Paclitaxel only treatment arm; N=total number of subjects in each arm; n=number of patients in the respective row category; NOS, not otherwise specified; NEC, not elsewhere classified.

CTCAE criteria v4.03 applied

a Including one report with Reported Term “Diarrhoea and Vomiting” and one report with “Diarrhoea and Nausea”

b Including one report with Reported Term “Occlusive syndrome”

c Including one report with Reported Term “Left thigh erysipelas”

d Reported Term: “Renal ectasy left”

Table 12. Treatment-Emergent Serious Adverse Reactions (SARs) by System Organ Class and Lowest Level Term (Treatment-Related) in safety population

System Organ Class (SOC) **Lowest Level Term (LLT)**	**G/P arm** **(N=86)**	**P arm** **(N=43)**
	n (%)	**n (%)**
Number of patients with at least one SAR	14 (16.3)	3 (7.0)
Blood and lymphatic system disorders		
Febrile neutropenia	1 (1.2)	0
Gastrointestinal disorders		
Abdominal distension	1 (1.2)	0
Anal haemorrhage	0	1 (2.3)
Diarrhoe[a]	2 (2.3)	0
Esophagitis	1 (1.2)	0
Rectal ulcer	1 (1.2)	0
Small intestinal obstruction	1 (1.2)	0
Small intestinal perforation	2 (2.3)	0
General disorders and administration site conditions		
Fever	0	1 (2.3)
Hepatobiliary disorders		
Icterus	1 (1.2)	0
Infections and Infestations		
Sepsis	2 (2.3)	0
Erysipelas[b]	0	2 (4.7)
Catheter related infection	1 (1.2)	0
Infection NOS	0	1 (2.3)
Nervous system disorders		
Visual acuity reduced	1 (1.2)	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	1 (1.2)	0

Abbreviations: SAR, serious adverse reaction; SOC, system organ class; LLT, lowest level term; G/P, Ganetespib+Paclitaxel treatment arm; P, Paclitaxel only treatment arm; N=total number of subjects in each arm; n=number of patients in the respective row category; NOS, not otherwise specified.

[a] Including one report with Reported Term “Diarrhoea and Vomiting” and one report with “Diarrhoea and Nausea”

[b] Including one report with Reported Term “Left thigh erysipelas”

Table 13. Biomaterial collected at various timepoints.

	screening	C1D1	C4D1	C7D1	C10D1	C13D1	C16D1	C19D1	C22D1	EOT
No of Patients (n)	131	118	92	62	34	14	3	1	1	71
Serum (n)		118	92	62	34	14	3	1	1	58
Plasma (n)		117	92	62	33	14	3	1	1	64
Cell pellets (n)		113								45
EDTA (n)		104								42
CTC (n)		97								30
FFPE (n)	113									
Biopsy fresh frozen (n)	9									

Figure 1: Actual course of the GANNET53 phase I dose escalation/de-escalation trial. Boxes depict patient cohorts and provide information on the number on patients (4 in cohort 1, and 3 in cohorts 2 and 3, respectively) and the dose level of ganetespib (100mg/m^2 in cohort 1, and 150mg/m^2 in cohorts 2 and 3, respectively). The actual course of the trial took place as expected with one dose escalation step and without necessity for dose de-escalation due to lack of dose-limiting toxicities (DLTs) in the DLT observation time frame of cycles 1 and 2.

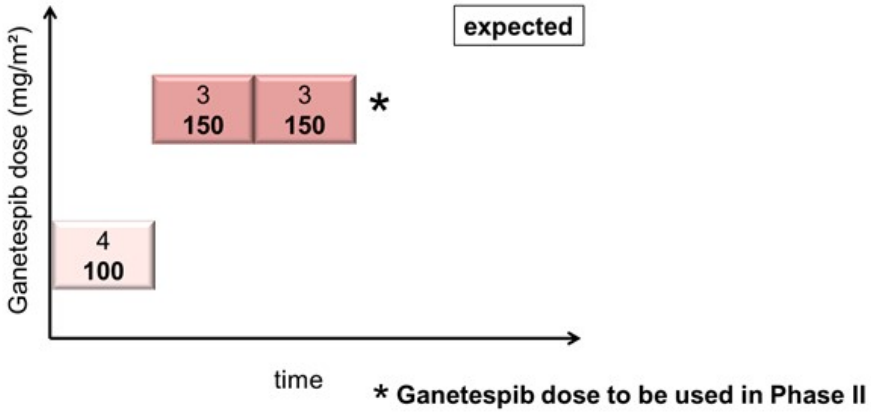


Figure 2: Kaplan-Meier plot of progression-free survival (PFS) in the GANNET53 Phase I trial. All 10 patients included experienced disease progress.

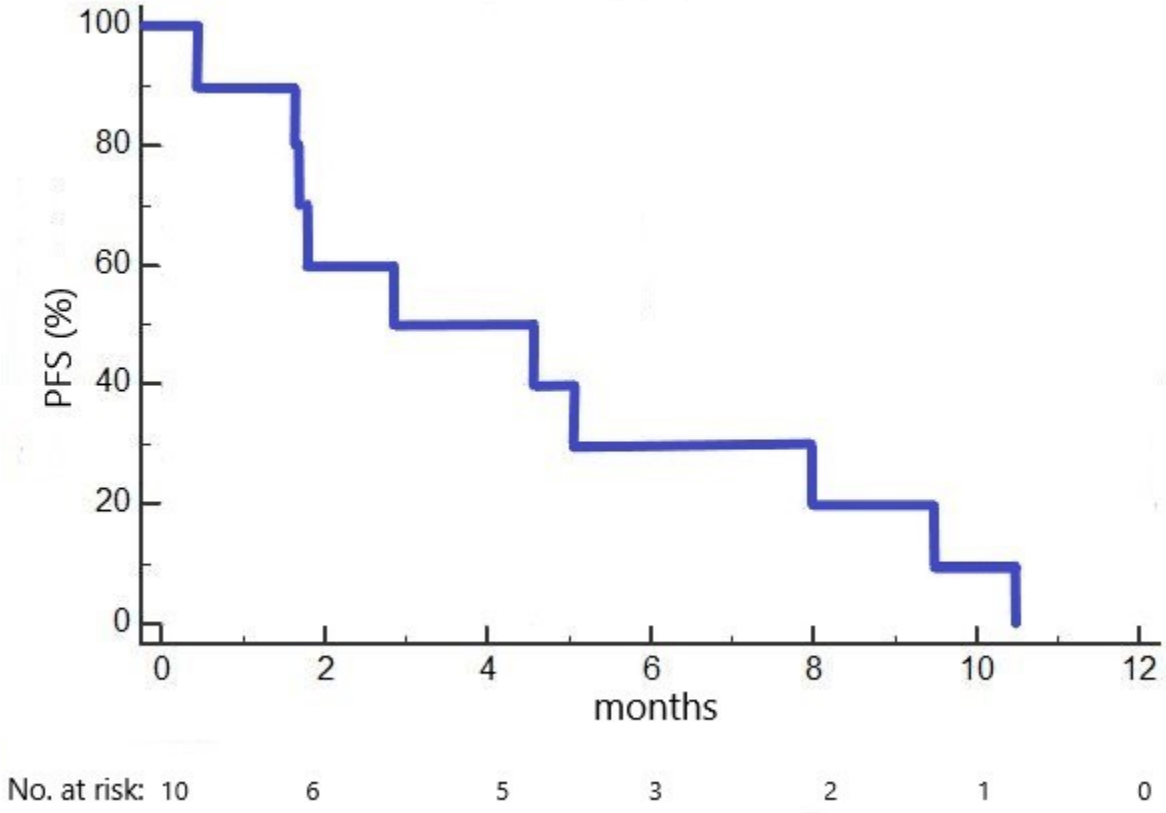


Figure 3. CONSORT diagram showing patient disposition.

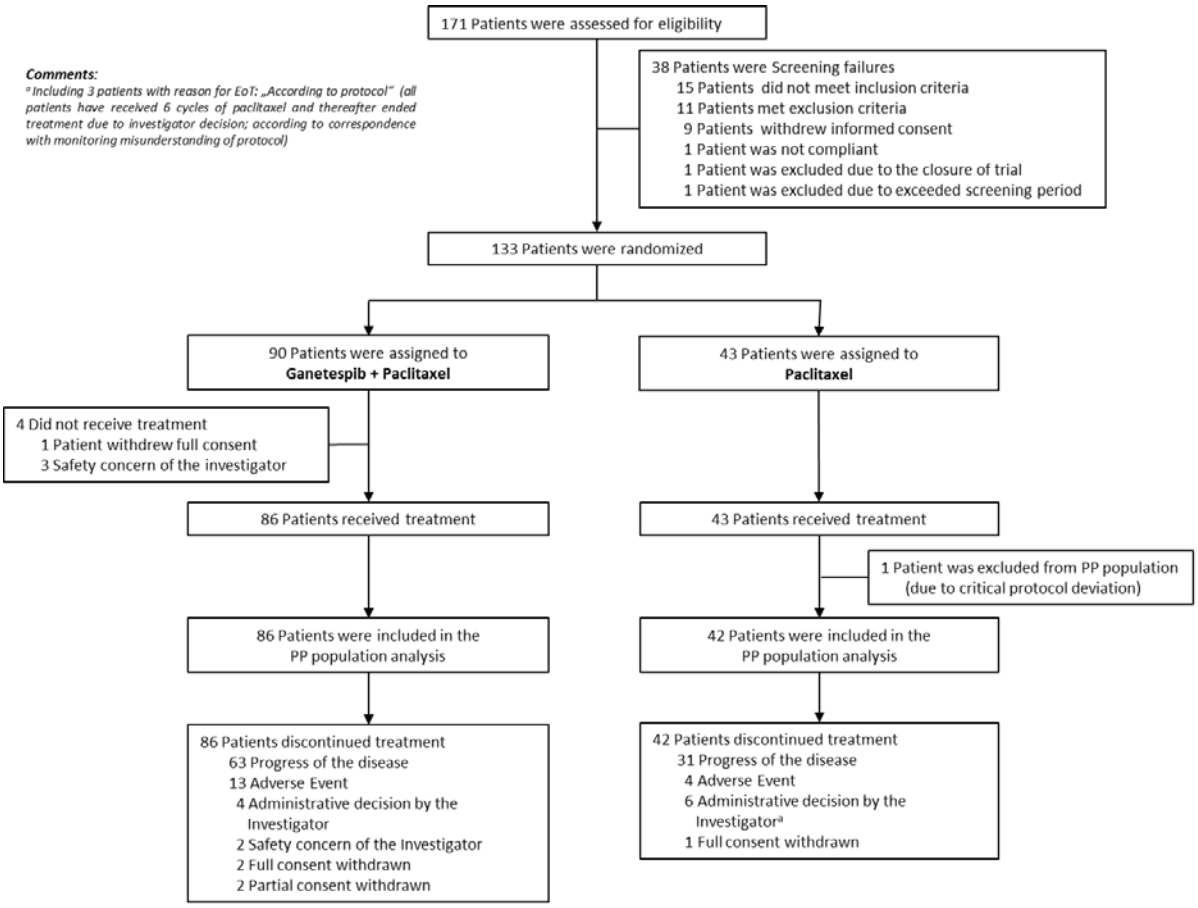
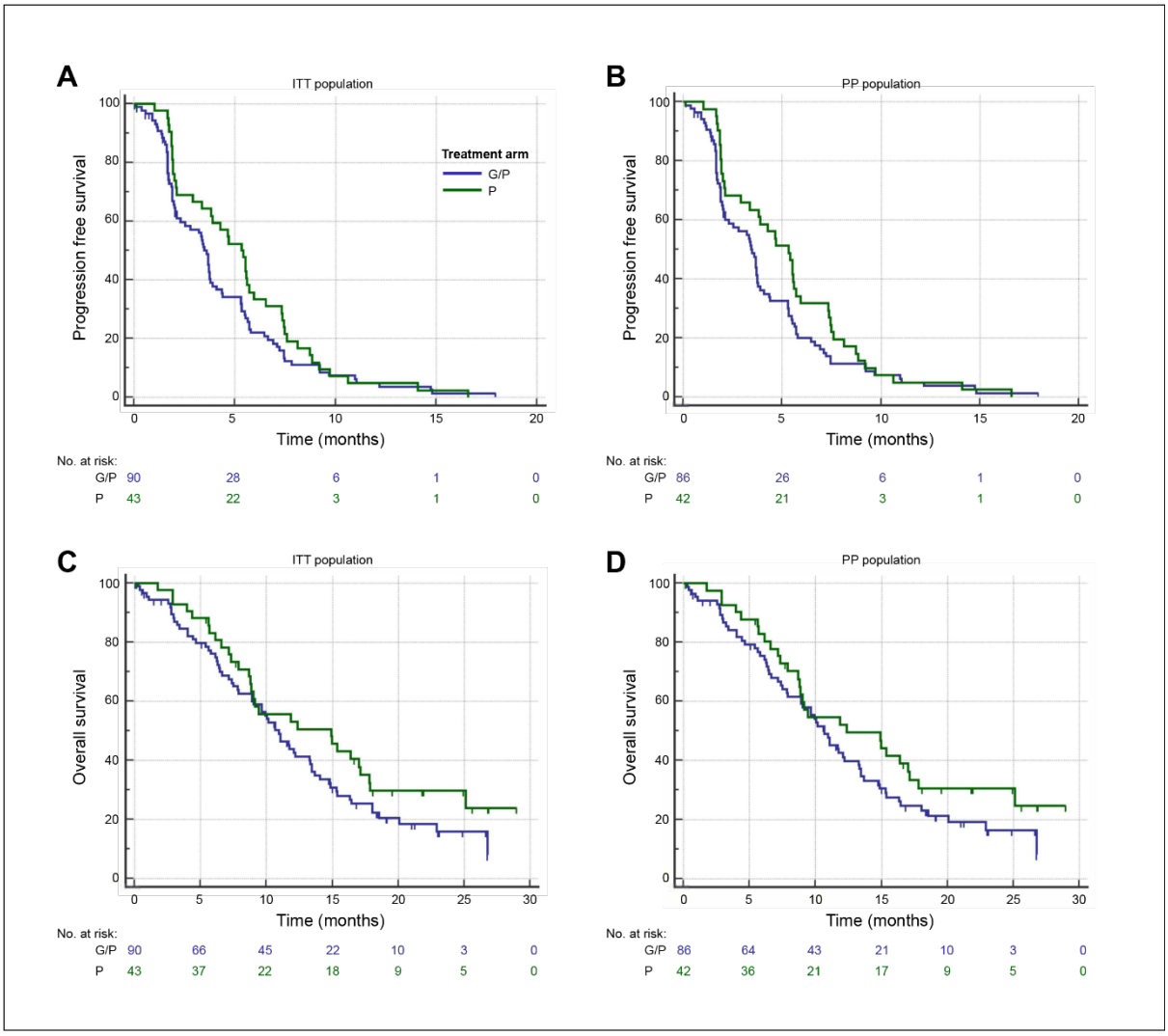


Figure 4. Kaplan-Meier estimates of progression free survival in the ITT (A) and PP population (B) and of overall survival in ITT population (C) and PP population (D).Ganetespib/Paclitaxel (G/P; blue line) is the experimental treatment and Paclitaxel (P; green line) is the standard treatment (control arm).



Abbreviations: ITT, intention to treat; PP, per protocol.

Figure 5: Final enrolment per centre in the EUDARIO trial (into the 3 different study-arms A “orange”, B “grey” and C “yellow”).