Clinical trial results:
A phase 1b/2 open-label, dose-escalating study of safety and efficacy of disulfiram, copper and vinorelbine in advanced solid tumors and advanced breast cancer

Summary

EudraCT number	2019-001972-12
Trial protocol	DK
Global end of trial date	19 June 2023

Results information

Result version number	v1 (current)
This version publication date	24 May 2024
First version publication date	24 May 2024

Trial information

Trial identification

Sponsor protocol code	AA1817

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Oncology, Herlev & Gentofte Hospital
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2023
Global end of trial reached?	Yes
Global end of trial date	19 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b: To assess the safety and tolerability of increasing doses of disulfiram in combination with copper and vinorelbine and to determine the dose-limiting toxicities (DLTs) and/or the Recommended Phase 2 Dose (RP2D) to patients with advanced and/or refractory solid malignancies.
Phase 2: To determine the efficacy of treatment with disulfiram, copper and vinorelbine in patients with advanced or metastatic HER2-negative breast cancer by assessing the clinical benefit rate (CBR=CR+PR+SD≥18 weeks) per RECIST 1.1.

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment. Dose escalation i phase 1b part was with 3+3 design and sponsor/investigators review of safety data at each cohort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was open for recruitment of patients from Jan 2020 to October 2023. All patients are recruited at a single site: Copenhagen University Hospital - Herlev and Gentofte in Denmark. Phase 2 part not opened.

Pre-assignment

Screening details:

For Phase1b part, eligible patients were ≥ 18 years with advanced solid tumors with PDand/or intolerable adverse effects with established therapy, ECOG PS 0-1, adequate organ and hematologic function. Phase 2 part should have included women wiht Her2 negative breast cancer after max 2 lines of treatment for advanced disease.

Period 1

Period 1 title	Phase 1b (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose Level 1

Arm description:

Disulfiram (200 mg) orally daily plus Copper 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks.

Dose level 1 tested initially with 3 patients and reevaluated with 6 patients after Dose level 2 revealed DLT.

Arm type	Experimental
Investigational medicinal product name	Disulfiram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg daily

Investigational medicinal product name	Copper
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg daily

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m2 day 1 and 8 every 3 weeks

Arm title	Dose Level 2

Arm description:

Disulfiram 400 mg orally daily plus Cu 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	Disulfiram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg daily

Investigational medicinal product name	Copper
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg daily

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m2 day 1 and 8 every 3 weeks

Arm title	Dose Level 3

Arm description:

Disulfiram 400 mg orally from day 1 to day 7. Disulfiram 200 mg from day 8 to day 14. Daily copper 2 mg orally from day 1 to day 14 in combination with disulfiram. Vinorelbine 30 mg/m2 IV day 4 and day 11. Dosing schedule will be repeated every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Disulfiram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg orally from day 1 to day 7 and 200 mg from day 8 to day 14. Dosing schedule will be repeated every 3 weeks.

Investigational medicinal product name	Copper
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg daily from day 1 to day 14 in combination. Dosing schedule will be repeated every 3 weeks

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vinorelbine 30 mg/m2 IV day 4 and day 11. Dosing schedule will be repeated every 3 weeks

Number of subjects in period 1	Dose Level 1	Dose Level 2	Dose Level 3
Started	9	4	3
Completed	8	3	3
Not completed	1	1	0
Adverse event, non-fatal	-	1	-
Patient wish to stop treatment	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Dose Level 1
Reporting group description:	
Disulfiram (200 mg) orally daily plus Copper 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks. Dose level 1 tested initially with 3 patients and reevaluated with 6 patients after Dose level 2 revealed DLT.	

Reporting group title	Dose Level 2
Reporting group description:	
Disulfiram 400 mg orally daily plus Cu 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks.	

Reporting group title	Dose Level 3
Reporting group description:	
Disulfiram 400 mg orally from day 1 to day 7. Disulfiram 200 mg from day 8 to day 14. Daily copper 2 mg orally from day 1 to day 14 in combination with disulfiram. Vinorelbine 30 mg/m2 IV day 4 and day 11. Dosing schedule will be repeated every 3 weeks	

Reporting group values	Dose Level 1	Dose Level 2	Dose Level 3
Number of subjects	9	4	3
Age categorical Units: Subjects			
Adults (18-64 years)	3	2	0
From 65-84 years	6	2	3
Age continuous Units: years			
median	68	66.5	73
full range (min-max)	54 to 74	58 to 77	69 to 75
Gender categorical Units: Subjects			
Female	5	0	1
Male	4	4	2
ECOG Performance status Units: Subjects			
PS 0	6	3	1
PS 1	3	1	2
Cancer Units: Subjects			
Pancreatic cancer	4	0	0
Uveal melanoma	2	0	2
Cholangiocarcinoma	1	0	0
Prostate cancer	1	3	0
Colon cancer	1	0	1
Rectal cancer	0	1	0

Reporting group values	Total		
Number of subjects	16		

Age categorical Units: Subjects			
Adults (18-64 years)	5		
From 65-84 years	11		
Age continuous Units: years median full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	6		
Male	10		
ECOG Performance status Units: Subjects			
PS 0	10		
PS 1	6		
Cancer Units: Subjects			
Pancreatic cancer	4		
Uveal melanoma	4		
Cholangiocarcinoma	1		
Prostate cancer	4		
Colon cancer	2		
Rectal cancer	1		

End points

End points reporting groups

Reporting group title	Dose Level 1

Reporting group description:

Disulfiram (200 mg) orally daily plus Copper 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks.

Dose level 1 tested initially with 3 patients and reevaluated with 6 patients after Dose level 2 revealed DLT.

Reporting group title	Dose Level 2

Reporting group description:

Disulfiram 400 mg orally daily plus Cu 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks.

Reporting group title	Dose Level 3

Reporting group description:

Disulfiram 400 mg orally from day 1 to day 7. Disulfiram 200 mg from day 8 to day 14. Daily copper 2 mg orally from day 1 to day 14 in combination with disulfiram. Vinorelbine 30 mg/m2 IV day 4 and day 11. Dosing schedule will be repeated every 3 weeks

Primary: Dose limiting toxicities

End point title	Dose limiting toxicities[1]

End point description:

End point type	Primary

End point timeframe:

From start to end of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive endpoint - statistical analyses N/A

End point values	Dose Level 1	Dose Level 2	Dose Level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	4	3	
Units: subjects				
Fatigue grade 3	1	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
from start of study treatment until 28 days after last treatment	
Adverse event reporting additional description:	
For non-serious AE section, only AEs with causal relationship to treatment (AR) are listed (numbers includes subjects/occurences reported as SARs as well).	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI-CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	Dose Level 1
Reporting group description:	
Disulfiram (200 mg) orally daily plus Copper 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1 and 8 every 3 weeks. Dose level 1 tested initially with 3 patients and reevaluated with 6 patients after Dose level 2 revealed DLT.	
Reporting group title	Dose Level 2
Reporting group description:	
Disulfiram 400 mg orally daily plus Cu 2 mg p.o. daily in combination with vinorelbine 30 mg/m2 day 1and 8 every 3 weeks.	
Reporting group title	Dose Level 3
Reporting group description:	
Disulfiram 400 mg orally from day 1 to day 7. Disulfiram 200 mg from day 8 to day 14. Daily copper 2 mg orally from day 1 to day 14 in combination with disulfiram. Vinorelbine 30 mg/m2 IV day 4 and day 11. Dosing schedule will be repeated every 3 weeks	

Serious adverse events	Dose Level 1	Dose Level 2	Dose Level 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	0 / 3 (0.00%)
number of deaths (all causes)	9	4	1
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Dose Level 1	Dose Level 2	Dose Level 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	4 / 4 (100.00%)	3 / 3 (100.00%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	3
White blood cell count decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	5
Platelet count decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Paresthesia			
subjects affected / exposed	3 / 9 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	3
Balance disorder	Additional description: includes verbatims impaired balance/balance difficulties, tendency to fall		
subjects affected / exposed	2 / 9 (22.22%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	3
Memory impairment	Additional description: Impaired short-term memory		
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Concentration impairment			
subjects affected / exposed	3 / 9 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Dizziness			
subjects affected / exposed	4 / 9 (44.44%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	5	0	2
Headache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 9 (66.67%)	3 / 4 (75.00%)	3 / 3 (100.00%)
occurrences (all)	9	5	3
Heavy Legs			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 9 (66.67%)	3 / 4 (75.00%)	2 / 3 (66.67%)
occurrences (all)	10	9	2
Nausea			
subjects affected / exposed	4 / 9 (44.44%)	2 / 4 (50.00%)	1 / 3 (33.33%)
occurrences (all)	10	3	3
Vomiting			
subjects affected / exposed	3 / 9 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Mucositis oral			
subjects affected / exposed	2 / 9 (22.22%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Dry mouth			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sore throat			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
nail changes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Alopecia			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations Fungal infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 2	0 / 3 (0.00%) 0
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 5	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2022	Based on observations of a high incidence of fatigue and constipation among the patients in the initial dose escalation part, an amendment for optimization of the therapy was done. Dose level 3, a treatment schedule with staggered dosing of disulfiram/copper and vinorelbine as well as a drug holiday in the third week of each 3-week cycle was introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

After phase 1b, trial was terminated with recommended dose found. As per risk/benefit assessment it was not feasible to continue treatment combination for metastatic breast cancer patients in a phase 2 trial. Efficacy of treatment was not assessed.

Notes: