Clinical trial results:
Phase II single-arm “window-of-opportunity” study of a combination of obinutuzumab (GA-101) and venetoclax (ABT-199) in relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Summary

EudraCT number	2016-001760-10
Trial protocol	AT
Global end of trial date	19 October 2021

Results information

Result version number	v1 (current)
This version publication date	19 October 2022
First version publication date	19 October 2022

Trial information

Trial identification

Sponsor protocol code	AGMT_NHL-15B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02987400
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/21, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, +43 6626404412, d.wolkersdofer@agmt.at
Scientific contact	Richard Greil, AGMT, +43 5725525801, r.greil@salk.at

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	03 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Objective response rate (complete or partial responses; best response) defined by PET/CT scan and bone marrow examination (Lugano Criteria 2014) after 3 cycles.

Protection of trial subjects:

Safety measurements were assessed at screening, every 3 weeks during and at the end of treatment, and at final visit. All (serious) adverse events occurring during study treatment were collected from signing the informed consent form until 28 days after last study treatment.
Recommendations for administration of first and subsequent infusions of Obinutuzumab including premedication and supportive care were given. Guidelines and recommendations for dosage delays and modifications were defined. In general, concomitant medications and therapies necessary for supportive care and safety of the patient were allowed. Antiviral prophylaxis and PJP prophylaxis were recommended at the physician´s discretion. Monitoring and treatment for Hepatitis B reactivation was discussed in the protocol.

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	12
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 04-Jan-2017 and 10-Jun-2020 22 patients were enrolled at five sites in Austria.

Pre-assignment

Screening details:

One patient received study treatment but was withdrawn from study during the first treatment cycle because inclusion criterion "diagnosis" was not met according to the result of the reference pathology. This patient was replaced and was not included in primary endpoint analysis.

Period 1

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

Arms

Arm title	Overall study

Arm description:

Combination treatment is repeated for up to 3 cycles. The first response assessment (including PET-CT) is performed after the first cycle of obinutuzumab-venetoclax and patients with at least stable disease (SD) or better are given another 2 cycles of therapy and have assessment after a total of 3 cycles. Patients with complete or partial remission (CR, PR) after 3 cycles of therapy go on to transplant or receive 9 further cycles of the combination therapy (if transplant ineligible). Patients with progressive disease at any time-point or stable disease after 3 cycles are taken off study.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Given IV at a dose of 1000 mg on days 1, 8, 15 in cycle 1 and on day 1 of each following cycle. One cycle is 21 days.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Given (prior to Obinutuzumab) at a dose of 800 mg daily p.o. starting from d1, cycle 1. One cycle is 21 days.

Number of subjects in period 1	Overall study
Started	22
Response assessment after cycle 3	12
Transplant or start of further 9 cycles	5

Completed	3
Not completed	19
Not eligible according to reference pathology	1
Stable disease after cylce 3	1
Progressive disease	16
Patient lost	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	10	10	
Age continuous Units: years			
arithmetic mean	63.9		
full range (min-max)	47 to 79	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	10	10	

End points

End points reporting groups

Reporting group title	Overall study

Reporting group description:

Combination treatment is repeated for up to 3 cycles. The first response assessment (including PET-CT) is performed after the first cycle of obinutuzumab-venetoclax and patients with at least stable disease (SD) or better are given another 2 cycles of therapy and have assessment after a total of 3 cycles. Patients with complete or partial remission (CR, PR) after 3 cycles of therapy go on to transplant or receive 9 further cycles of the combination therapy (if transplant ineligible). Patients with progressive disease at any time-point or stable disease after 3 cycles are taken off study.

Primary: Response rate

End point title	Response rate[1]

End point description:

Objective response rate (complete or partial responses) defined by PET/CT scan and bone marrow examination (Lugano Criteria 2014) after 3 cycles

End point type	Primary

End point timeframe:

After 3 cycles of combination therapy

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: No statistical analysis is provided as this is an one armed, open label, non-comperative study.
Overall response rate after 3 cycles of therapy is 5/21 (23.8%).

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	21[2]			
Units: Subjects				
Complete response	4			
Partial remission	1			
Stable disease	1			
Progressive disease	6			
NA	9			

Notes:

[2] - One patient was excluded because inclusion criterion DLBCL was not met acc. to reference pathology.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion of patient until final visit (28 days after completion or discontinuation of study treatment).

Adverse event reporting additional description:

Abnormal laboratory value was not assessed as AE unless that value led to discontinuation or delay in treatment, dose modification, therapeutic intervention. Progression of disease was not to be regarded as SAE. Relation to IMPs obinutuzumab and/or venetoclax is given. Deaths during FU are not part of this analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All enrolled patients received the IMP and were included in the safety analysis.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 22 (22.73%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hyponatraemic seizure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic infarction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 22 (86.36%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Surgical and medical procedures			

Tooth extraction subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 7		
General physical health deterioration subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Pyrexia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Epistaxis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Stridor subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Upper respiratory tract congestion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	4		
Platelet count decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Troponin T increased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cardiac disorders			

Supraventricular extrasystoles subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 2 1 / 22 (4.55%) 4 3 / 22 (13.64%) 4		
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		

Diarrhoea subjects affected / exposed occurrences (all) Gastrointestinal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 5 1 / 22 (4.55%) 1 10 / 22 (45.45%) 10 1 / 22 (4.55%) 1		
Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4 1 / 22 (4.55%) 1 3 / 22 (13.64%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Campylobacter infection subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		

Candida infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported