



Clinical trial results: Ixazomib (MLN9708) in combination with carboplatin in pretreated women with advanced triple negative breast cancer (CARIXA)

Summary

EudraCT number	2016-001421-13
Trial protocol	AT
Global end of trial date	15 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 August 2021
First version publication date	12 August 2021

Trial information

Trial identification

Sponsor protocol code	AGMT_MBC-10 (X16087)
-----------------------	----------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993094
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.wolkersdorfer@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	11 January 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I: Determination of maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs)

Phase II: Overall response rate (ORR)

Protection of trial subjects:

Safety assessments were done on a regular basis. All patients having received at least one dose of the study medication have been followed for adverse events for 28 days after discontinuing study treatment or completion of study treatment. In general, concomitant medications and therapies necessary for supportive care and safety of the patient were allowed. Anti-emetic prophylaxis was mandatory, supportive therapy for diarrhoea was defined.

Background therapy:

In the AGMT_MBC-10 phase I trial a dose escalation of weekly carboplatin from AUC 1.5 to 2.5 for 3 of 4 weeks (according to a dose intensity per week from AUC 1.1 to 1.9) was tested. In phase II the maximum tolerated dose level determined in phase I was administered.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	16 February 2017
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	Austria: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	17
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between Feb-2017 and Jul-2020 31 patients were enrolled at 11 study sites in Austria. 9 patients were enrolled during phase I and further 22 patients during phase II.

Pre-assignment

Screening details:

Female patients with histologically confirmed metastatic or locally advanced (without curative loco-regional treatment options with curative intention) adenocarcinoma of the breast were screened for study participation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I

Arm description:

Accelerated dose-escalation phase: A single-patient cohort per dose level was enrolled, until one dose limiting toxicity (DLT), or 3 moderate toxicities were observed during cycle 1, or until dose level 4 was reached. At this dose level the cohort was expanded to three patients and dose escalation reverted to a conventional 3+3 escalation design.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib on days 1, 8, and 15 in combination with carboplatin on days 1, 8, and 15. Cycles were repeated every four weeks until progression, unacceptable toxicity or treatment discontinuation for any other reason.

Dose level 1: ixazomib 3 mg/ carboplatin AUC 1.5

Dose level 2: ixazomib 3 mg/ carboplatin AUC 2.0

Dose level 3: ixazomib 4 mg/ carboplatin AUC 2.0

Dose level 4: ixazomib 4 mg/ carboplatin AUC 2.5

After completion of phase I, all patients treated with a dose below the determined MTD were dose escalated at the discretion of the investigator.

Arm title	Phase II
------------------	----------

Arm description:

After establishing MTD in phase I, accrual continued to evaluate the efficacy and safety of the combination.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib on days 1, 8, and 15 in combination with carboplatin on days 1, 8, and 15. Cycles were repeated every four weeks until progression, unacceptable toxicity or treatment discontinuation for any

other reason.
Dose level: ixazomib 4 mg/ carboplatin AUC 2.5

Number of subjects in period 1	Phase I	Phase II
Started	9	22
Completed	9	17
Not completed	0	5
Physician decision	-	1
Patient's wish	-	3
Patient deceased	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	31	31	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age at study entry			
Units: years			
median	59		
full range (min-max)	33 to 79	-	
Gender categorical			
Only female patients were included per protocol			
Units: Subjects			
Female	31	31	
Male	0	0	

End points

End points reporting groups

Reporting group title	Phase I
Reporting group description:	
Accelerated dose-escalation phase: A single-patient cohort per dose level was enrolled, until one dose limiting toxicity (DLT), or 3 moderate toxicities were observed during cycle 1, or until dose level 4 was reached. At this dose level the cohort was expanded to three patients and dose escalation reverted to a conventional 3+3 escalation design.	
Reporting group title	Phase II
Reporting group description:	
After establishing MTD in phase I, accrual continued to evaluate the efficacy and safety of the combination.	

Primary: Maximum tolerated dose (MTD)

End point title	Maximum tolerated dose (MTD) ^{[1][2]}
End point description:	
Dose limiting toxicities (DLTs) were defined as inability to deliver the drug combination of ixazomib and carboplatin due to drug related toxicities as outlined below:	
<ul style="list-style-type: none">• grade 3 or 4 non-hematologic toxicity excluding alopecia, nausea, emesis, diarrhea• grade 3 or greater nausea and/or emesis despite the use of optimal anti-emetic prophylaxis• grade 3 or greater diarrhea that occurs despite maximal supportive therapy• grade 2 peripheral neuropathy with pain or polyneuropathy greater or equal grade 3• neutropenia grade 4 for more than 7 days• febrile neutropenia grade 3• thrombocytopenia grade 4• thrombocytopenia grade 3 with bleeding	
Moderate toxicities were defined as inability to deliver the drug combination of ixazomib and carboplatin due to drug related toxicity as outlined below:	
<ul style="list-style-type: none">• any grade 2 non-hematologic toxicity excluding alopecia• any grade 3 hematologic toxicity	
End point type	Primary
End point timeframe:	
Cycle 1 of subjects in phase I	

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: During dosing level 1 to 3 no patient developed a DLT or had more than 2 moderate toxicities. 6 further patients were enrolled into dosing level 4, no DLT occurred, no patient had more than 2 moderate toxicities during cycle 1. Dosing level 4 (ixazomib 4 mg, carboplatin AUC 2.5) was established as the MTD and was defined as starting dose for study phase II.

This non-randomised study was not designed for statistical comparisons by treatment arm.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is the primary endpoint of phase I of this study.

This non-randomised study was not designed for statistical comparisons by treatment arm.

End point values	Phase I			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
DLT or >2 moderate toxicities at dose level 1	0			
DLT or >2 moderate toxicities at dose level 2	0			

DLT or >2 moderate toxicities at dose level 3	0			
DLT or >2 moderate toxicities at dose level 4	0			
Dose level 1 (total)	1			
Dose level 2 (total)	1			
Dose level 3 (total)	1			
Dose level 4 (total)	6			

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR) ^{[3][4]}
-----------------	---

End point description:

ORR is estimated as the proportion of responders, defined as a patient whose best overall response is partial response (PR) or better during the treatment period. ORR is given as proportion.

End point type	Primary
----------------	---------

End point timeframe:

From inclusion to best response during treatment in phase II

Notes:

[3] - 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: Overall response rate was 20%.

This non-randomised study was not designed for statistical comparisons by treatment arm.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is the primary endpoint of phase II of this study.

This non-randomised study was not designed for statistical comparisons by treatment arm.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	20 ^[5]			
Units: Subjects				
Complete response (CR)	2			
Partial response (PR)	2			

Notes:

[5] - 2 patients were not evaluable according to protocol.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for adverse events for 28 days after discontinuing study treatment or completion of study treatment. Additional survival follow up was done until cut-off data point.

Adverse event reporting additional description:

Progression of disease (including death due to the underlying malignant disease) was not to be regarded as SAE.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.0
--------------------	------

Reporting groups

Reporting group title	Overall trial
-----------------------	---------------

Reporting group description:

All enrolled patients

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 31 (35.48%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events	0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 31 (87.10%)		
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			

Infusion related hypersensitivity reaction subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 5 4 / 31 (12.90%) 7 8 / 31 (25.81%) 15 12 / 31 (38.71%) 21		
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 3 3 / 31 (9.68%) 3 12 / 31 (38.71%) 16 3 / 31 (9.68%) 3		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 4		
Gastrointestinal disorders Abdominal pain upper			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	10 / 31 (32.26%)		
occurrences (all)	14		
Diarrhoea			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	20 / 31 (64.52%)		
occurrences (all)	33		
Vomiting			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Urinary tract infection			

subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		

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

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

Due to low recruitment study was withdrawn prematurely after inclusion of 31 patients.
--

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30400780>