Clinical trial results:
Phase I/II trial of Carfilzomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma.

Summary

EudraCT number	2010-019462-92
Trial protocol	FR
Global end of trial date	20 February 2014

Results information

Result version number	v1 (current)
This version publication date	13 August 2022
First version publication date	13 August 2022

Trial information

Trial identification

Sponsor protocol code	BRD 10/3-D

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01279694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	5 allée de l'ile de Gloriette, Nantes, France, 44093
Public contact	Sponsor, CHU de Nantes, +33 253482835, Bp-prom-regl@chu-nantes.fr
Scientific contact	Sponsor, CHU de Nantes, +33 253482835, Bp-prom-regl@chu-nantes.fr

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	01 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The two primary objectives of this phase I/II study are to identify the most appropriate dose of Carfilzomib in combination with a standard MP treatment regimen (phase 1) and to evaluate the efficacy of Carfilzomib plus MP (CMP) in terms of response rate [(ORR), consisting of complete response (CR), very good partial response (VGPR), and partial response (PR) (phase 2)].

Protection of trial subjects:

Subjects should receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone (or trimethroprim/sulfamethoxazole if fluoroquinoles are contraindicated). In addition, subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis. Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator. Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically. Subjects may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed. Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines. Palliative radiation therapy is permitted if clinically indicated.
Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	06 October 2010
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	France: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	0
From 65 to 84 years	68
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

72 patients were included in 9 French centers. In phase I 6 patients are included at a dose of 20 mg/m² Carfilzomib, followed by another 6 patients at a dose of 27 mg/m², followed by another 6 patients at a dose of 36 mg/m², and finally another 6 at a dose of 45 mg/m². In phase II 45 patients were included at the 36 mg/m² dose.

Pre-assignment

Screening details:

Patients in elderly untreated patients with multiple myeloma.

Period 1

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

Arms

Arm title	One arm

Arm description:

Treatment comprises an initial phase consisting of nine 6-week cycles of Carfilzomib on Days 1, 2, 8, 9, 22, 23, 29, 30 (carfilzomib is administered at 20 mg/m² on Days 1 and 2 of the first cycle and 20, 27, 36 mg/m² or 45 mg/m² thereafter) followed by a 12 day rest period (42-day cycle), in combination with oral Melphalan 9 mg/m² and oral prednisone 60mg/m², both on days 1 to 4.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Days 1, 2, 8, 9, 22, 23, 29, 30 (carfilzomib is administered at 20 mg/m² on Days 1 and 2 of the first cycle and 20, 27, 36 mg/m² or 45 mg/m² depending on the cohort thereafter followed by a 12 day rest period (42-day cycle) during 9 cycles.

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

Dosage and administration details:

Melphalan 9 mg/m² days 1 to 4 durong 9 cycles

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

Dosage and administration details:

Prednisone 60 mg days 1 to 4 during 9 cycles

Number of subjects in period 1	One arm
Started	72
Completed	68
Not completed	4
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	essais global (overall period)

Reporting group description: -

Reporting group values	essais global (overall period)	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
From 65-84 years	36	36	
85 years and over	36	36	
Age continuous Units: years			
median	72		
full range (min-max)	66 to 86	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	36	36	

End points

End points reporting groups

Reporting group title	One arm

Reporting group description:

Treatment comprises an initial phase consisting of nine 6-week cycles of Carfilzomib on Days 1, 2, 8, 9, 22, 23, 29, 30 (carfilzomib is administered at 20 mg/m² on Days 1 and 2 of the first cycle and 20, 27, 36 mg/m² or 45 mg/m² thereafter) followed by a 12 day rest period (42-day cycle), in combination with oral Melphalan 9 mg/m² and oral prednisone 60mg/m², both on days 1 to 4.

Subject analysis set title	Analyse ORR
Subject analysis set type	Full analysis

Subject analysis set description:

50 patients were included in the analysis of the efficacy of MTD treatment evaluated at 36mg/m2: 6 patients in phase 1 and 44 patients in phase 2.

Primary: ORR

End point title	ORR[1]

End point description:

Après avoir effectué la première phase I de l'étude, comprenant 24 patients, dont 6 dans chaque cohorte de Carfilzomib de niveau de dosage différente. 1 DLT a été observée à la dose de 20 mg/m², 1 à la dose de 27 mg/m², 1 DLT à la dose de 36 mg/m² et 2 à la dose de 45 mg/m². Ainsi la dose de 36mg/m² a été considérée comme la dose maximale tolérée de Carfilzomib.

End point type	Primary

End point timeframe:

3 ans et demi

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: There is no comparison. I can't enter the data.

End point values	Analyse ORR			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: pourcentage				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

9 cycles

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	all patient

Reporting group description: -

Serious adverse events	all patient		
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 69 (72.46%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ureteric cancer metastatic			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Embolism venous				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shock				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
spinal haematoma				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Cataract operation				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary calculus removal				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chills				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

General physical health deterioration				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Hyperthermia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	3 / 69 (4.35%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory distress				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Affective disorder				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomania				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
fall				

subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haematoma				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory distress				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pulmonary oedema				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sudden death				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
cervical myelopathy				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
febril neutropenia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemolytic anaemia				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences causally related to treatment / all	11 / 11		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
VIth nerve paralysis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Odynophagia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
renal failure acute			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Influenza			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
lung infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Relapsing fever				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung cancer metastatic				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
dehydratation				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperuricaemia				
subjects affected / exposed	5 / 69 (7.25%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	all patient		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 69 (100.00%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	57 / 69 (82.61%)		
occurrences (all)	226		
Leukocytosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	35 / 69 (50.72%)		
occurrences (all)	116		
Lymphopenia			
subjects affected / exposed	51 / 69 (73.91%)		
occurrences (all)	392		
Neutropenia			
subjects affected / exposed	44 / 69 (63.77%)		
occurrences (all)	246		
Thrombocytopenia			
subjects affected / exposed	59 / 69 (85.51%)		
occurrences (all)	336		
Hepatobiliary disorders			
Alanine aminotransferase increased			

subjects affected / exposed	22 / 69 (31.88%)		
occurrences (all)	37		
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 69 (37.68%)		
occurrences (all)	44		
Blood alkaline phosphatase decreased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	18 / 69 (26.09%)		
occurrences (all)	25		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Cholecystitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
gamma glutamyl transferase increased			
subjects affected / exposed	28 / 69 (40.58%)		
occurrences (all)	58		
Hyperbilirubinaemia			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	22		
Transaminases increased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2010	Ajout d'un centre
16 June 2011	modification du nombre de patient De demander l'ajout de la cohorte 4 de 6 patients à 45mg/m² de Carfilzomib De mettre à jour le nombre et le nom des centres ayant acceptés de participer à l'étude.
17 April 2012	Ajout de 30 patients supplémentaires
02 August 2012	prolongation de l'étude

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25784682