Confidential

EE2012 ISRCTN Registry Upload

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

Tuesday 3rd November, 2026

Coordinating Sponsor: University of Birmingham

Sponsor Protocol No: RG 11-152

ISRCTN Ref No: ISRCTN 92192408

Date R1 Opened: 20th December 2013

CAS CODE: SA3008

Eudract No: 2012-002107-17

Date R2 Opened: 21st March 2014

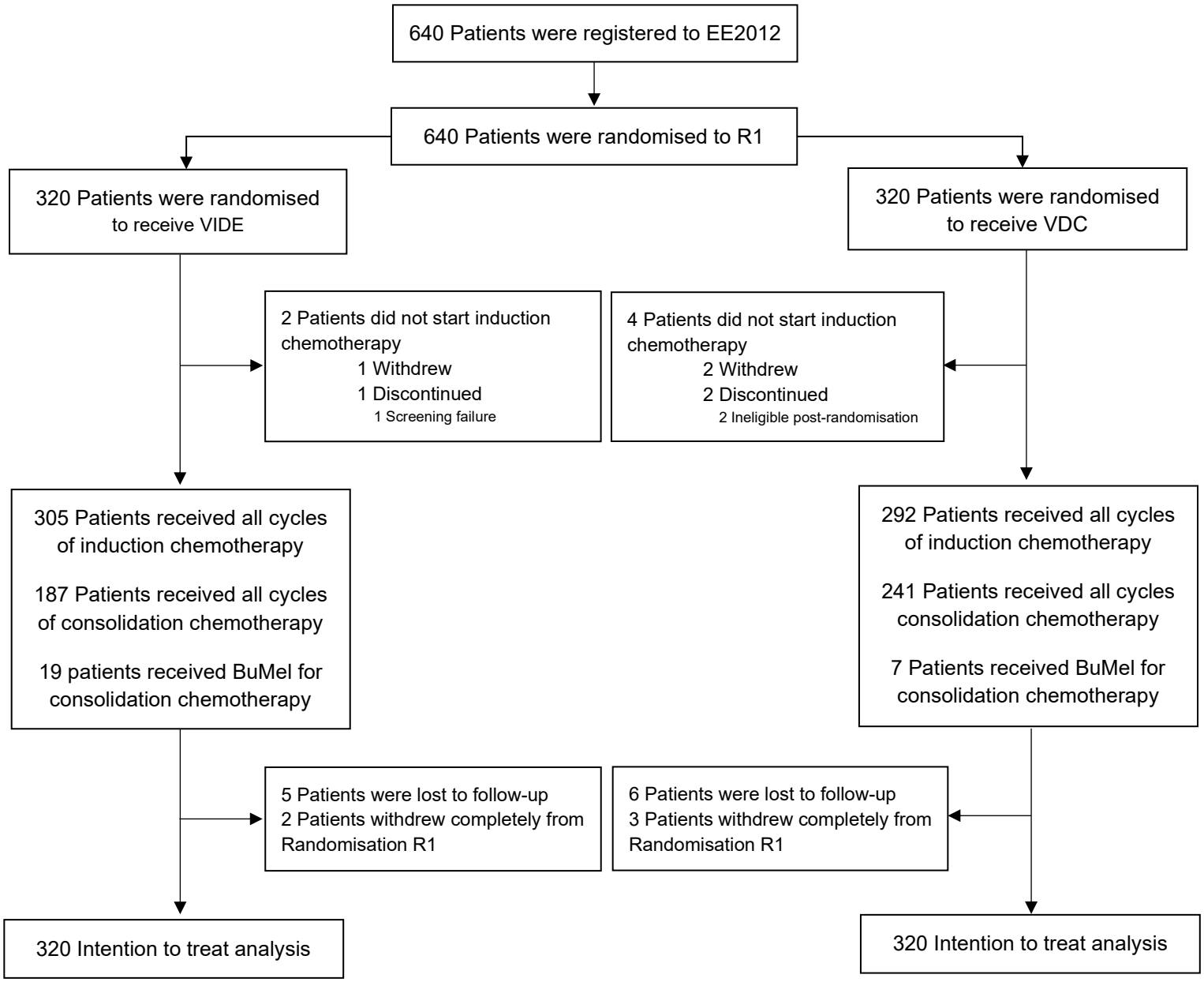
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640 Patients were registered to EE2012
640 Patients were randomised to R1
320 Patients were randomised to receive VIDE
320 Patients were randomised to receive VDC
2 Patients did not start induction chemotherapy
1 Withdrew
1 Discontinued
1 Screening failure
4 Patients did not start induction chemotherapy
2 Withdrew
2 Discontinued
2 Ineligible post-randomisation
305 Patients received all cycles of induction chemotherapy
187 Patients received all cycles of consolidation chemotherapy
19 patients received BuMel for consolidation chemotherapy
292 Patients received all cycles of induction chemotherapy
241 Patients received all cycles consolidation chemotherapy
7 Patients received BuMel for consolidation chemotherapy
5 Patients were lost to follow-up
2 Patients withdrew completely from Randomisation R1
6 Patients were lost to follow-up
3 Patients withdrew completely from Randomisation R1
320 Intention to treat analysis
320 Intention to treat analysis

Clinical trial results:
International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

Summary

EudraCT number	2012-002107-17
Trial protocol	GB ES HU CZ NL IE DK BE
Global end of trial date	05 November 2025

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Appendix: R1 non-serious AEs and R2 randomisation (EE2012 EudraCT Appendix - v1.0 30Oct2026.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_11-152

Additional study identifiers

ISRCTN number	ISRCTN92192408
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Cancer Research UK Clinical Trials Unit (CRCTU), Birmingham, United Kingdom, B15 2TT
Public contact	Jennifer Anderton, University of Birmingham, +44 01214159877, ee2012@trials.bham.co.uk
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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 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2024
Global end of trial reached?	Yes
Global end of trial date	05 November 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. The objective of the induction/consolidation chemotherapy randomisation (R1) is to compare: VIDE strategy with VDC/IE strategy as first line treatment in all patients with Ewing Sarcoma Family of Tumours (ESFT), with respect to clinical outcome and toxicity
2. The objective of the zoledronic acid randomisation (R2) is to determine whether the addition of zoledronic acid to the consolidation chemotherapy assigned at R1 is associated with improved clinical outcome in patients in the EE2012 trial.
3. The objective of the biological studies associated with this trial is to identify informative prognostic biomarkers for assessment of disease status and response at diagnosis and throughout the disease course. Whether they are predictive of response to therapy and may be used to improve stratification of patients and whether they might predict those patients that may not tolerate a particular therapy will be explored.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. A risk assessment was done prior to the trial commencing. Due to the known risk of osteonecrosis of the jaw from zoledronic acid treatment, patients with a history of dental surgery (extraction or jaw surgery) in the 6 months preceding the start of zoledronic acid treatment, or planned dental surgery within the treatment period or within 6 months after the end of treatment were excluded from entering the randomisation, as were patients with a history of jaw fracture, Ewings tumour of the maxilla or of the mandible. Patients were also required to have dental examinations prior to treatment with zoledronic acid and six-monthly during treatment with zoledronic acid and for a follow-up period of five years after the end of treatment. Invasive dental procedures were to be avoided while on treatment if possible. If osteonecrosis of the jaw or ear develops during treatment, the protocol stated that zoledronic acid should be discontinued and not recommenced. Due to the known risks of veno-occlusive disease of the liver from treatment with Busulfan, blood chemistry was monitored prior to treatment. Due to the risk of blood/bone marrow suppression from Melphalan, blood counts were checked monitored prior to treatment and treatment only given on adequate recovery. There was a known risk of Amenorrhoea and Azoospermia from Busulfan treatment, for which the protocol mandated fertility preservation should be considered before treatment. Busulfan/Melphalan treatment had a risk of causing ineffective radiotherapy treatment to particular sites of the body, therefore the protocol included contraindications to when Busulfan/Melphalan treatment should be used in this regard.

Background therapy:

In addition to the investigational medicinal products, the protocol recommended G-CSF support and Peripheral blood stem cell (PBSC) mobilisation and harvesting for some patients, which was to be done as per local institutional guidelines. For patients receiving zoledronic acid, oral calcium and vitamin D were recommended in accordance with local practice, and paracetamol in the case of flu like symptoms. In addition, patients may have had local control of their disease by radiotherapy and/or surgery, which was done as per usual local practice.

Evidence for comparator:

The EURO-E.W.I.N.G. 99 trial employed VIDE induction chemotherapy (6 cycles of vincristine, ifosfamide, doxorubicin and etoposide given approximately every 3 weeks prior to local control), followed by risk adapted randomised treatment of either vincristine, actinomycin D and ifosfamide or cyclophosphamide (VAI/VAC) as consolidation chemotherapy or high-dose busulfan/melphalan. The other widely used treatment regimen for ESFT, employed mainly in the USA, is that from the Children’s Oncology Group (COG) AEWS0031 trial. In this study, patients with localised ESFT received alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide (VDC/IE) as induction chemotherapy, and alternating cycles of ifosfamide-etoposide and vincristine-cyclophosphamide (IE/VC)

as consolidation chemotherapy. There was an upfront randomisation to compare 3-weekly cycles of this treatment (standard arm) with 2-weekly cycles (experimental arm). At a median of 3 years, there was significantly superior EFS of 76% in the compressed 2-weekly VDC/IE/VC, compared to 65% in the standard arm (p=0.028), and also improved overall survival (p=0.026). This compressed induction regimen has now become the standard in the USA. Therefore, an upfront randomisation in EE2012 (R1) was necessary to compare the VIDE and VDC/IE regimens for efficacy and toxicity.
Additionally, bisphosphonates are effective inhibitors of bone resorption and have been widely used for the treatment of osteoporosis, osteogenesis imperfecta, systemic osteolytic bone disease or local bone loss, but also for the treatment of bone metastases in patients with breast cancer, multiple myeloma and prostate cancer. Nitrogen-containing bisphosphonates (N-BPs) are potent at inhibiting bone resorption and in vitro and in vivo data have proven the anti-tumour activity against ESFT cells. Therefore, the addition of zoledronic acid or not to the consolidation treatment allocated at R1 was tested in R2.

Actual start date of recruitment	20 December 2013
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	Switzerland: 1
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 148
Country: Number of subjects enrolled	United Kingdom: 242
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czechia: 20
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 195
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Ireland: 4
Worldwide total number of subjects	640
EEA total number of subjects	397

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)	189
Adolescents (12-17 years)	216
Adults (18-64 years)	235
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

640 patients entered the trial at randomisation 1 (R1) at 96 hospitals within 13 countries (England, Rep. of Ireland, Wales, Scotland, Northern Ireland, Switzerland, Denmark, Netherlands, France, Spain, Belgium, Czech Rep., Hungary). The trial opened on 20th December 2013 and closed to R1 on 3rd May 2019. 272 R1 patients then went on to enter R2.

Pre-assignment

Screening details:

All assessments relating to patient eligibility were performed as standard practice.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	VIDE

Arm description:

VIDE induction chemotherapy followed by VAI, VAC or BuMel consolidation treatment.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For VIDE/VAI/VAC: 1.5 mg/m2/cycle.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

VIDE: 9 g/m2/cycle
VAI: 6g/m2/cycle

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Solution for injection

Dosage and administration details:

VIDE: 60 mg/m2/cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Solution for injection

Dosage and administration details: VIDE: 450 mg/m2/cycle.	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: VAC: 1500mg/m2/cycle.	
Investigational medicinal product name	Actinomycin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: VAI/VAC: 1.5 mg/m2/cycle.	
Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Solution for infusion
Dosage and administration details: A total of 16 doses. Adults: 0.8mg/kg. body weight (BW). Children and adolescents:<9kg: 1mg/kg. BW. 9 - <16kg: 1.2mg/kg. BW. 16 - 23kg: 1.1mg/kg. BW. >23 - 34kg: = 0.95mg/kg. BW. >34kg: 0.8mg/kg. BW.	
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 140mg/m² IV infusion over 30 min.	
Arm title	VDC/IE
Arm description: VDC/IE induction chemotherapy followed by IE/VC or VAI/BuMel consolidation.	
Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: VDC/VC: 2 mg/m2/cycle.	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: VDC: 75 mg/m2/cycle.	

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Solution for infusion
Dosage and administration details: VDC/VC: 1200 mg/m2/cycle.	
Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Injection
Dosage and administration details: IE: 9 g/m2/cycle	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Solution for injection
Dosage and administration details: IE: 500 mg/m2/cycle.	
Investigational medicinal product name	Busulfan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: A total of 16 doses. Adults: 0.8mg/kg. body weight (BW). Children and adolescents:<9kg: 1mg/kg. BW. 9 - <16kg: 1.2mg/kg. BW. 16 - 23kg: 1.1mg/kg. BW. >23 - 34kg: = 0.95mg/kg. BW. >34kg: 0.8mg/kg. BW.	
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 140mg/m² IV infusion over 30 min.	

Number of subjects in period 1	VIDE	VDC/IE
Started	320	320
Completed	313	311
Not completed	7	9
Consent withdrawn by subject	2	3
Lost to follow-up	5	6

Baseline characteristics

Reporting groups	
Reporting group title	VIDE
Reporting group description:	
VIDE induction chemotherapy followed by VAI, VAC or BuMel consolidation treatment.	
Reporting group title	VDC/IE
Reporting group description:	
VDC/IE induction chemotherapy followed by IE/VC or VAI/BuMel consolidation.	

Reporting group values	VIDE	VDC/IE	Total
Number of subjects	320	320	640
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	89	100	189
Adolescents (12-17 years)	114	102	216
Adults (18-64 years)	117	118	235
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	15	15	
full range (min-max)	2 to 48	2 to 49	-
Gender categorical Units: Subjects			
Female	134	134	268
Male	186	186	372
R1 tumour volume Units: Subjects			
<200ml	180	179	359
>=200ml	140	141	281
Country of recruitment Units: Subjects			
UK	122	120	242
Other	101	102	203
France	97	98	195
R1 disease type			
The trial was still collecting data when the R1 results were published. Minor data clarifications occurred after the publication with more follow-up which has resulted in minimal differences between EudraCT and the paper for the R1 data.			
Units: Subjects			
No metastasis or involvement of regional lymph nod	234	237	471
Lung or pleural metastasis only	52	52	104

Other metastasis	34	31	65
Age at R1 randomisation Units: Subjects			
Under 14	132	133	265
14 and over	188	187	375
Site of primary tumour			
The trial was still collecting data when the R1 results were published. Minor data clarifications occurred after the publication with more follow-up which has resulted in minimal differences between EudraCT and the paper for the R1 data.			
Units: Subjects			
Pelvis	78	69	147
Abdomen	14	15	29
Spine	24	31	55
Chest	65	56	121
Head and neck	15	22	37
Upper extremity	25	20	45
Lower extremity	97	107	204
Unknown origin	1	0	1
Missing	1	0	1

End points

End points reporting groups

Reporting group title	VIDE
Reporting group description:	
VIDE induction chemotherapy followed by VAI, VAC or BuMel consolidation treatment.	
Reporting group title	VDC/IE
Reporting group description:	
VDC/IE induction chemotherapy followed by IE/VC or VAI/BuMel consolidation.	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised patients in the R1 randomisation.	
Subject analysis set title	Post-induction chemotherapy surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All R1 randomised patients who received post-induction chemotherapy surgery, defined as the main surgery occurring after induction chemotherapy was initiated.	

Primary: Event-free survival

End point title	Event-free survival
End point description:	
Event-free survival (EFS) is defined as the time from randomisation to first event, where an event is: • progression without complete remission or • recurrence (following complete remission) or • diagnosis of second malignancy or • death. Patients who have not had an event will be censored at their last follow-up data. Patients lost to follow-up without an event will be censored at the data of their last consultation. The trial was still collecting data when the R1 results were published. Minor data clarifications and additional follow-up occurred after the publication, which has resulted in minimal differences between EudraCT and the paper for the R1 data.	
End point type	Primary
End point timeframe:	
From R1 randomisation until the first event or at least 2-years follow-up, assessed in years	

End point values	VIDE	VDC/IE	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	320	320	640	
Units: Patients	320	320	640	

Statistical analyses

Statistical analysis title	R1 randomisation EFS
Statistical analysis description:	
VIDE vs VDC/IE for the R1 randomisation. A hazard ratio of less than 1 is in favour of VDC/IE.	
Comparison groups	VDC/IE v VIDE

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.028 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.92

Notes:

[1] - No direction of superiority was specified. Both treatment arms were standard of care in different countries, and therefore the aim was to show one arm was superior over the other.
[2] - The R1 primary outcome was designed using a Bayesian approach. The posterior probability for the adjusted Cox model from a normal-normal conjugate analysis that VDC/IE is better than VIDE (i.e., Pr (true HR < 1 | data)) is 100%.

Primary: Event-free survival at 3-years

End point title	Event-free survival at 3-years[3]

End point description:

Event-free survival at 3-years.
The trial was still collecting data when the R1 results were published. Minor data clarifications and additional follow-up occurred after the publication, which has resulted in minimal differences between EudraCT and the paper for the R1 data.

End point type	Primary

End point timeframe:

3-years

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: The statistical analysis for the primary outcome has been described in another endpoint.

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	320		
Units: %				
number (confidence interval 95%)	60 (55 to 66)	68 (63 to 73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) is defined as the time from randomisation to death, irrespective of the cause. Surviving patients will be censored at their last follow-up date.
The trial was still collecting data when the R1 results were published. Minor data clarifications and additional follow-up occurred after the publication, which has resulted in minimal differences between EudraCT and the paper for the R1 data.

End point type	Secondary

End point timeframe:

From the R2 randomisation until death or at least 2-years follow-up.

End point values	VIDE	VDC/IE	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	320	320	640	
Units: Patients	320	320	640	

Statistical analyses

Statistical analysis title	R1 randomisation OS

Statistical analysis description:

VIDE vs VDC/IE for the R1 randomisation. A hazard ratio of less than 1 is in favour of VDC/IE.

Comparison groups	VIDE v VDC/IE
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.004 [5]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.84

Notes:

[4] - No direction of superiority was specified. Both treatment arms were standard of care in different countries, and therefore the aim was to show one arm was superior over the other.

[5] - This R1 secondary outcome utilised a Bayesian approach. The posterior probability for the adjusted Cox model from a normal-normal conjugate analysis that VDC/IE is better than VIDE (i.e., Pr(true HR < 1 | data)) is 100%.

Secondary: Lung and/or pleural metastases and other metastasis (number of patients)

End point title	Lung and/or pleural metastases and other metastasis (number of patients)

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint considers the number of patients with each type of metastasis.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Recorded at four time points (except bone marrow) – at the baseline, after course 2 or 3 (depending on

the treatment arm) (assessment 1; A1), prior to local control of primary tumour (assessment 2; A2) and at the end of treatment (EoT).

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	320		
Units: Patients				
Patients with lung metastases at baseline	54	60		
Lung metastases not quantified at baseline	11	6		
Patients with lung metastases at A1	35	34		
Patients with lung metastases at A2	28	41		
Patients with lung metastases at EoT	34	26		
Patients with bone marrow metastases at baseline	10	10		
Patients with bone marrow metastases at EoT	7	2		
Patients with bone metastases at baseline	24	21		
Bone metastases not quantified at baseline	2	3		
Patients with bone metastases at A1	24	20		
Patients with bone metastases at A2	24	18		
Patients with bone metastases at EoT	18	13		
Patients with other metastases at baseline	8	9		
Other metastases not quantified at baseline	1	1		
Patients with other metastases at A1	5	8		
Patients with other metastases at A2	2	8		
Patients with other metastases at EoT	6	3		
Patients with brain metastases at baseline	1	0		
Brain metastases not quantified at baseline	0	0		
Patients with brain metastases at A1	1	0		
Patients with brain metastases at A2	1	0		
Patients with brain metastases at EoT	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control

End point title	Histological response of the primary tumour to induction chemotherapy if surgery is performed as local control

End point description:

Histological response is defined as patients with good histological response are defined as follows:

o No viable tumour cells (Salzer-Kuntschik [SK]: grade 1)
o 1% - <5% viable tumour cells (SK: grade 2)
o ≥5% - <10% viable tumour cells (SK: grade 3)
Patients with poor histological response are defined as follows:
o ≥10% - <50% viable tumour cells (SK: grade 4)
o ≥50% viable tumour cells (SK: grade 5+6)
Patients who did not have surgery will be excluded from the analysis.
The trial was still collecting data when the R1 results were published. Minor data clarifications and additional follow-up occurred after the publication, which have resulted in minimal differences between EudraCT and the paper for the R1 data. In addition, it was decided that there was a more appropriate way to categorise patients with post-chemotherapy surgery since the R1 publication, and therefore the total number of patients in this analysis set differs with EudraCT.

End point type	Secondary

End point timeframe:

At the time of surgery following induction chemotherapy

End point values	VIDE	VDC/IE	Post-induction chemotherapy surgery	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	211	213	424	
Units: Patients				
Good histological response; SK grade 1	61	94	155	
Good histological response; SK grade 2	24	28	52	
Good histological response; SK grade 3	22	26	48	
Poor histological response; SK grade 4	54	38	92	
Poor histological response; SK grade 5 and 6	44	22	66	
Missing evaluation	6	5	11	

Statistical analyses

Statistical analysis title	R1 randomisation histological response

Statistical analysis description:

VIDE vs VDC/IE for the R1 randomisation. A risk ratio of greater than 1 is in favour of VDC/IE.

Comparison groups	VIDE v VDC/IE
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Risk ratio (RR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.59

Notes:

[6] - No direction of superiority was specified. Both treatment arms were standard of care in different countries, and therefore the aim was to show one arm was superior over the other.
Surgery was a post randomisation event that was not controlled for, and therefore this analysis should be considered exploratory when using it to compare the R1 treatment arms, due to the uncontrolled confounders.

Secondary: Achievement of local control at the end of treatment

End point title	Achievement of local control at the end of treatment

End point description:

The definition of local control is either:
o complete surgical resection following induction chemotherapy
o or no measurable disease, assessed by end of treatment MRI scan
o or no change in measurable residual tumour over a six month period from the end of treatment, assessed by MRI scan at the end of treatment and six months after the end of treatment

Note: This outcome was not well defined and has therefore been reported descriptively.

End point type	Secondary

End point timeframe:

At the point of surgery, an end of treatment (EoT), and for patients with residual disease a six month period from the end of treatment (6 mo EoT)

End point values	VIDE	VDC/IE	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	320	320	640	
Units: Patients				
Achievement of local control at surgery: Yes	168	165	333	
Achievement of local control at surgery: No	58	60	118	
Achievement of local control at surgery: Missing	94	95	189	
Achievement of local control at EoT: Yes	182	193	375	
Achievement of local control at EoT: No	69	63	132	
Achievement of local control at EoT: Missing	69	64	133	
Achievement of local control at 6 mo EoT: Yes	79	73	152	
Achievement of local control at 6 mo EoT: No	10	11	21	
Achievement of local control at 6 mo EoT: Missing	231	236	467	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 3-years

End point title	Overall survival at 3-years

End point description:

Overall survival at 3-years.
The trial was still collecting data when the R1 results were published. Minor data clarifications and additional follow-up occurred after the publication, which has resulted in minimal differences between EudraCT and the paper for the R1 data.

End point type	Secondary

End point timeframe:

3-years

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	320		
Units: Percentage				
number (confidence interval 95%)	75 (70 to 79)	82 (77 to 85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lung and/or pleural metastases count at baseline

End point title	Lung and/or pleural metastases count at baseline

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of lung/pleural metastases at baseline.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Baseline

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	60		
Units: Count				
median (inter-quartile range (Q1-Q3))	4 (2 to 11)	3 (2 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lung and/or pleural metastases count at assessment 1

End point title	Lung and/or pleural metastases count at assessment 1

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate;

measured in mm). This endpoint describes the number of lung/pleural metastases at assessment 1. Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 1 (after course 2 or 3 depending on the treatment arm)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Count				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	2 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lung and/or pleural metastases count at assessment 2

End point title	Lung and/or pleural metastases count at assessment 2

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of lung/pleural metastases at assessment 2. Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 2 (prior to local control of primary tumour)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	41		
Units: Count				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lung and/or pleural metastases count at end of treatment

End point title	Lung and/or pleural metastases count at end of treatment

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of lung/pleural metastases at the end of treatment.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

End of treatment

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	26		
Units: Count				
median (inter-quartile range (Q1-Q3))	2 (1 to 6)	2 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone metastases count at baseline

End point title	Bone metastases count at baseline

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of bone metastases at baseline.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Baseline

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	21		
Units: Count				
median (inter-quartile range (Q1-Q3))	4 (2 to 8)	5 (2 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone metastases count at assessment 1

End point title	Bone metastases count at assessment 1

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of bone metastases at assessment 1.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 1 (after course 2 or 3 depending on the treatment arm)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	20		
Units: Count				
median (inter-quartile range (Q1-Q3))	3 (2 to 8)	4 (1 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone metastases count at assessment 2

End point title	Bone metastases count at assessment 2

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of bone metastases at assessment 2.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 2 (prior to local control of primary tumour)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	18		
Units: Count				
median (inter-quartile range (Q1-Q3))	4 (2 to 7)	6 (2 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bone metastases count at end of treatment

End point title	Bone metastases count at end of treatment

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of bone metastases at the end of treatment.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

End of treatment

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	13		
Units: Count				
median (inter-quartile range (Q1-Q3))	2 (1 to 5)	4 (2 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other metastases count at baseline

End point title	Other metastases count at baseline

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of other metastases at baseline.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Baseline

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Count				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	1 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other metastases count at assessment 1

End point title	Other metastases count at assessment 1

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of other metastases at assessment 1.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 1 (after course 2 or 3 depending on the treatment arm)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Count				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	2 (1 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other metastases count at assessment 2

End point title	Other metastases count at assessment 2

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of other metastases at assessment 2.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due

to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 2 (prior to local control of primary tumour)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	8		
Units: Count				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	2 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other metastases count at end of treatment

End point title	Other metastases count at end of treatment

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of other metastases at the end of treatment. Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

End of treatment

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: Count				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	2 (2 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain metastases count at baseline

End point title	Brain metastases count at baseline

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of brain metastases at baseline.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Baseline

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[7]		
Units: Count				
median (inter-quartile range (Q1-Q3))	5 (5 to 5)	(to)		

Notes:

[7] - No patients had brain metastases at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Brain metastases count at assessment 1

End point title	Brain metastases count at assessment 1

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of brain metastases at assessment 1.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 1 (after course 2 or 3 depending on the treatment arm)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[8]		
Units: Count				
median (inter-quartile range (Q1-Q3))	5 (5 to 5)	(to)		

Notes:

[8] - No patients had brain metastases at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Brain metastases count at assessment 2

End point title	Brain metastases count at assessment 2

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of brain metastases at assessment 2.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 2 (prior to local control of primary tumour)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[9]		
Units: Count				
median (inter-quartile range (Q1-Q3))	5 (5 to 5)	(to)		

Notes:

[9] - No patients had brain metastases at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Brain metastases count at end of treatment

End point title	Brain metastases count at end of treatment

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the number of brain metastases at the end of treatment.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

End of treatment

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	0[10]		
Units: Count				
median (inter-quartile range (Q1-Q3))	1 (1 to 1)	(to)		

Notes:

[10] - No patients had brain metastases at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter of the largest node (or group if not separate) at baseline

End point title	Diameter of the largest node (or group if not separate) at baseline

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the diameter of the largest node (or group if not separate; measured in mm) at baseline.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Baseline

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	22		
Units: mm				
median (inter-quartile range (Q1-Q3))	15 (10 to 21)	14 (10 to 20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter of the largest node (or group if not separate) at assessment 1

End point title	Diameter of the largest node (or group if not separate) at assessment 1

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the diameter of the largest node (or group if not separate; measured in mm) at assessment 1.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 1 (after course 2 or 3 depending on the treatment arm)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	3		
Units: mm				
median (inter-quartile range (Q1-Q3))	10 (7 to 24)	13 (4 to 35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter of the largest node (or group if not separate) at assessment 2

End point title	Diameter of the largest node (or group if not separate) at assessment 2

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate; measured in mm). This endpoint describes the diameter of the largest node (or group if not separate; measured in mm) at assessment 2.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

Assessment 2 (prior to local control of primary tumour)

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: mm				
median (inter-quartile range (Q1-Q3))	8 (7 to 10)	6 (2 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter of the largest node (or group if not separate) at end of treatment

End point title	Diameter of the largest node (or group if not separate) at end of treatment

End point description:

Tumour and metastatic response is defined as the volume of the primary tumour, the number of lung and/or pleural and other metastases, the diameter of the largest node (or group if not separate;

measured in mm). This endpoint describes the diameter of the largest node (or group if not separate; measured in mm) at the end of treatment.
Note: tumour volume has not been analysed due to unreliable data as a result of different practices for collecting this information across sites. In addition, this outcome has not been analysed statistically due to the small sample sizes and unreliable reporting.

End point type	Secondary

End point timeframe:

End of treatment

End point values	VIDE	VDC/IE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: mm				
median (inter-quartile range (Q1-Q3))	24 (12 to 32)	18 (13 to 23)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse reactions experienced during treatment were collected on treatment forms.

Serious adverse events (SAEs) were collected from the date of protocol defined treatment until 30 days after the administration of the last treatment on SAE forms.

Adverse event reporting additional description:

Certain SARs were considered expected (unless life threatening or proved fatal), and these were reported using 4 broad categories on expected SAR forms.

Certain SAEs did not require reporting - hospitalisations for protocol treatment, elective procedures, and treatment for progression. Progression and death was also captured elsewhere.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	VIDE

Reporting group description:

This contains the expected Serious Adverse Reactions (expected SARs) and Serious Adverse Events (SAEs) reported in patients randomised (R1) to receive VIDE.
Unlike the expected SARs and SAEs, the Adverse Events recorded on treatment forms were collected separately for the induction and consolidation phases, and so only those collected during induction are shown here (the Adverse Events experienced during consolidation have been included in the appendix). Of note, the SAE information may differ from what was presented in the R1 publication (PMID: 36522207) for the following reasons: At the time of the publication patients were still being followed up for R2, and in the paper only selected grade 3-5 SAEs were reported whereas all SAEs are reported here. Also for non-serious adverse events (reported here as grade 3-5), the threshold for reporting in the publication was 10%, and the decision on which to include was based on their clinical significance whereas all are shown here

Reporting group title	VDC/IE

Reporting group description:

This contains the expected Serious Adverse Reactions (expected SARs) and Serious Adverse Events (SAEs) reported in patients randomised (R1) to receive VDC/IE.
Unlike the expected SARs and SAEs, the Adverse Events recorded on treatment forms were collected separately for the induction and consolidation phases, and so only those collected during induction are shown here (the Adverse Events experienced during consolidation have been included in the appendix). Of note, the SAE information may differ from what was presented in the R1 publication (PMID: 36522207) for the following reasons: At the time of the publication patients were still being followed up for R2, and in the paper only selected grade 3-5 SAEs were reported whereas all SAEs are reported here. Also for non-serious adverse events (reported here as grade 3-5), the threshold for reporting in the publication was 10%, and the decision on which to include was based on their clinical significance whereas all are shown here

Serious adverse events	VIDE	VDC/IE	
Total subjects affected by serious adverse events			
subjects affected / exposed	235 / 318 (73.90%)	228 / 316 (72.15%)	
number of deaths (all causes)	117	82	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Leukemia secondary to oncology chemotherapy			
subjects affected / exposed	0 / 318 (0.00%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	4 / 318 (1.26%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pneumoperitoneum and anastomotic perforation			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Slow healing of scar			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 318 (0.00%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 318 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 318 (0.31%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death NOS			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Asthenia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Premature menopause			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal hemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 318 (0.31%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sore throat			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adult respiratory distress syndrome			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory syndrome			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haematological toxicity (e.g. haemoglobin, WBC, granulocytes, platelets) (expected SAR)	Additional description: This is a broad category of event terms as very common Serious Adverse Reactions (SARs), which were a known to be expected reactions to the treatments, were grouped together for collection on expected SAR forms.		

subjects affected / exposed	46 / 318 (14.47%)	38 / 316 (12.03%)	
occurrences causally related to treatment / all	115 / 116	95 / 95	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increased			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell decreased			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	3 / 318 (0.94%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic cardiac thrombus secondary to picc			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	2 / 318 (0.63%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increase in cardiac size			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	6 / 318 (1.89%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	4 / 318 (1.26%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	6 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal reaction			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic pain leg (left)			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 318 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia / fever / febrile neutropenia (expected SAR)	Additional description: This is a broad category of event terms as very common Serious Adverse Reactions (SARs), which were a known to be expected reactions to the treatments, were grouped together for collection on expected SAR forms.		
subjects affected / exposed	207 / 318 (65.09%)	193 / 316 (61.08%)	
occurrences causally related to treatment / all	749 / 760	593 / 599	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 318 (1.26%)	6 / 316 (1.90%)	
occurrences causally related to treatment / all	4 / 4	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia and anemia			

subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gut toxicity (e.g. mucositis/stomatitis, nausea, vomiting, diarrhoea) (expected SAR)	Additional description: This is a broad category of event terms as very common Serious Adverse Reactions (SARs), which were a known to be expected reactions to the treatments, were grouped together for collection on expected SAR forms		
subjects affected / exposed	53 / 318 (16.67%)	46 / 316 (14.56%)	
occurrences causally related to treatment / all	88 / 89	75 / 75	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhlitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 318 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralityc ileus			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alanine aminotransferase			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin atrophy			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter scar inflamation			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	1 / 318 (0.31%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal calculi			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection (expected SAR)	Additional description: This is a broad category of event terms as very common Serious Adverse Reactions (SARs), which were a known to be expected reactions to the treatments, were grouped together for collection on expected SAR forms.		

subjects affected / exposed	50 / 318 (15.72%)	50 / 316 (15.82%)	
occurrences causally related to treatment / all	68 / 71	64 / 65	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Joint infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 318 (0.31%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	7 / 318 (2.20%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin infection			
subjects affected / exposed	1 / 318 (0.31%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 318 (0.63%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	0 / 318 (0.00%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected right prothesis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection sepsis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoniae			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 318 (0.31%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	2 / 318 (0.63%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VIDE	VDC/IE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	315 / 318 (99.06%)	313 / 316 (99.05%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 318 (5.35%)	19 / 316 (6.01%)	
occurrences (all)	33	31	
Lymphocyte count decreased			
subjects affected / exposed	81 / 318 (25.47%)	77 / 316 (24.37%)	
occurrences (all)	269	369	
Neutrophil count decreased			
subjects affected / exposed	179 / 318 (56.29%)	175 / 316 (55.38%)	
occurrences (all)	627	728	
Platelet count decreased			
subjects affected / exposed	222 / 318 (69.81%)	179 / 316 (56.65%)	
occurrences (all)	774	530	
White blood cell decreased			

subjects affected / exposed	141 / 318 (44.34%)	121 / 316 (38.29%)	
occurrences (all)	571	601	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	207 / 318 (65.09%)	197 / 316 (62.34%)	
occurrences (all)	586	661	
Febrile neutropenia			
subjects affected / exposed	235 / 318 (73.90%)	185 / 316 (58.54%)	
occurrences (all)	689	476	
Gastrointestinal disorders			
Mucositis oral			
subjects affected / exposed	88 / 318 (27.67%)	111 / 316 (35.13%)	
occurrences (all)	173	171	
Nausea			
subjects affected / exposed	17 / 318 (5.35%)	10 / 316 (3.16%)	
occurrences (all)	21	19	
Vomiting			
subjects affected / exposed	26 / 318 (8.18%)	22 / 316 (6.96%)	
occurrences (all)	45	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	Substantial Amendment 1 (SA01) -Protocol v2.0 – removal of R2loc and P2pulm randomisations, addition of central pathology review, changes to R2, change to Arm A treatment, & other minor changes.
23 January 2015	Substantial Amendment 02 (SA02) - Protocol v3.0 – change to Arm A treatment, changes in terminology of sponsorship, changes to pharmacovigilance, & other minor changes.
04 March 2016	Substantial Amendment 04 (SA04) - Protocol v4.0 - addition biological studies, addition of metastatic patients, & other minor changes.
02 June 2017	Substantial Amendment 05 (SA05) - Protocol v5.0 - Change of consolidation treatment for patients with poor risk localised disease to 1 cycle VAI plus BuMel, & other minor changes.

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.

Patients with widely metastatic disease were included only from September, 2016 (and due to a competing study not entered at all from France).
The number of patients recruited to R2 was lower than planned due to R1 closure.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36522207

http://www.ncbi.nlm.nih.gov/pubmed/41832299

http://www.ncbi.nlm.nih.gov/pubmed/31952545

Confidential

EE2012 EudraCT Appendix

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

Friday 30th October, 2026

Coordinating Sponsor: University of Birmingham

Sponsor Protocol No: RG 11-152

CAS CODE: SA3008

ISRCTN Ref No: ISRCTN 92192408

Eudract No: 2012-002107-17

Date R1 Opened: 20th December 2013

Date R2 Opened: 21st March 2014

CANCER RESEARCH UK | UNIVERSITY OF BIRMINGHAM | Cancer Research UK Clinical Trials Unit

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Appendix 1: R1 Randomisation - Consolidation chemotherapy treatment non-serious adverse events

The following adverse event tables for the R1 randomisation are slightly different to what was presented in the R1 publication for the following reasons:
- The R1 publication was reported whilst the EE2012 was still following up the R2 randomised patients, and therefore the data collection and validation was ongoing at that time.
- The threshold for reporting adverse events in the R1 publication was 10% and the minimum requirement for EudraCT is 5%.
- Some adverse events were not deemed clinically relevant given how commonly they occur on these standard of care chemotherapy regimens. Therefore, they were either excluded from the R1 publication reporting (e.g., white blood cell count decreased) or they were summarised using the overall CTCAE categories rather than the individual toxicity types (e.g., gastrointestinal disorders rather than individual mucositis oral).
- Some adverse events were deemed clinically relevant for reporting, despite the number of affected patients (e.g., encephalopathy) and were therefore included in the R1 publication but not the EudraCT tables, although they are reported elsewhere in the CSR.

Table 0.1: R1 Randomisation: Grade 3-5 adverse events experienced by at least 5% of patients on the trial by CTCAE category and toxicity for patients allocated to VIDE receiving consolidation. Used for Eudract submission

Category	CTCAE Toxicity	Affected	Exposed	Occurrences	% Affected
Blood and lymphatic system disorders	Anemia	84	271	177	31
	Febrile neutropenia	75	271	124	28
Gastrointestinal disorders	Mucositis oral	17	271	19	6
Investigations	Lymphocyte count decreased	78	271	346	29
	Neutrophil count decreased	135	271	550	50
	Platelet count decreased	143	271	530	53
	White blood cell decreased	106	271	450	39
Metabolism and nutrition disorders	Hypophosphatemia	16	271	28	6

Table 0.2: R1 Randomisation: Grade 3-5 adverse events experienced by at least 5% of patients on the trial by CTCAE category and toxicity for patients allocated to VDC receiving consolidation. Used for Eudract submission

Category	**CTCAE Toxicity**	**Affected**	**Exposed**	**Occurrences**	**% Affected**
Blood and lymphatic system disorders	Anemia	113	269	192	42
	Febrile neutropenia	74	269	103	28
Gastrointestinal disorders	Mucositis oral	8	269	8	3
Investigations	Lymphocyte count decreased	71	269	233	26
	Neutrophil count decreased	138	269	342	51
	Platelet count decreased	140	269	278	52
	White blood cell decreased	102	269	293	38
Metabolism and nutrition disorders	Hypophosphatemia	5	269	9	2

Appendix 2: R2 Randomisation - Subject disposition

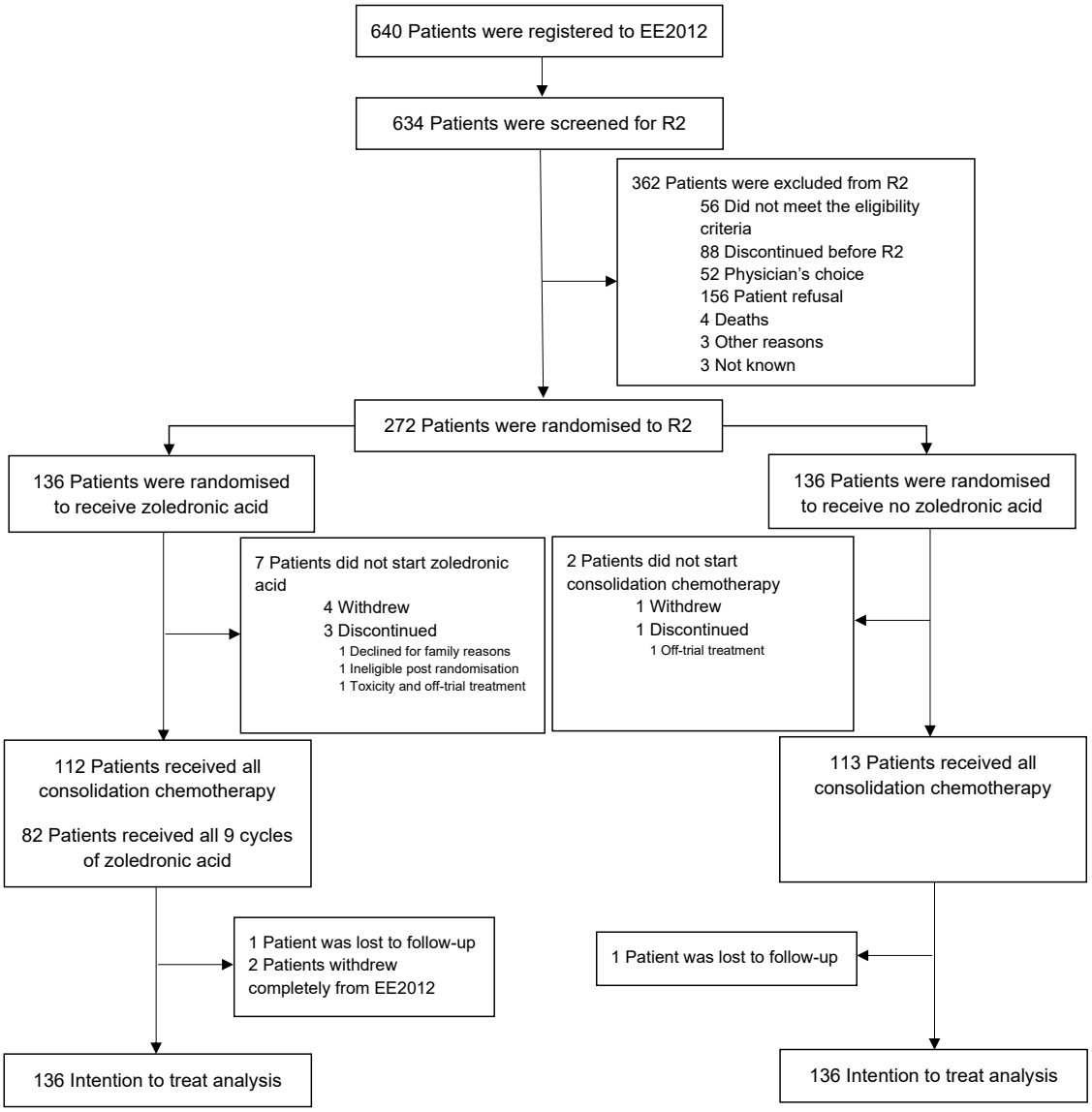
Period 1 for R2 randomisation: Randomised-controlled and not blinded

Arm 1 (experimental): 9 cycles of zoledronic acid following the first cycle of consolidation chemotherapy (as described for R1). Given at 28 day intervals (+/- 3 days). All patients less than 18 years old received 0.05 mg/kg (maximum dose 4 mg). Patients 18 years or older received 4mg.

Arm 2 (experimental): No zoledronic acid (i.e., just consolidation chemotherapy as described for R1).

Number of subjects in Period 1 for the R2 randomisation: The following flow diagram details the number of subjects in period 1 for the R2 randomisation.

Figure 0.1: R2 Randomisation: CONSORT flow diagram



Appendix 3: R2 Randomisation - Baseline characteristics

Patients were stratified for the R2 randomisation using their R1 randomisation (VIDE; VDC) ,age (<14; $\geq$ 14), sex (male; female) R2 disease status (good risk localised disease; poor risk localised disease; lung or pleural metastases; other metastases) and country (UK; other; France). The table below details the minimisation factors by treatment arm and overall.

Table 0.3: R2 Randomisation: Minimisation factors

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
R1 Treatment (N (%))			
VIDE	67 (49)	67 (49)	134 (49)
VDC	69 (51)	69 (51)	138 (51)
Total	136 (100)	136 (100)	272 (100)
Age at R1 randomisation (years) (N (%))			
Under 14	55 (40)	55 (40)	110 (40)
14 and over	81 (60)	81 (60)	162 (60)
Total	136 (100)	136 (100)	272 (100)
Sex (N (%))			
Male	79 (58)	80 (59)	159 (58)
Female	57 (42)	56 (41)	113 (42)
Total	136 (100)	136 (100)	272 (100)
R2 Disease Status (N (%))			
Localised Disease or regional lymph node involvement only at diagnosis and good risk after induction	57 (42)	59 (43)	116 (43)
Localised Disease or regional lymph node involvement only at diagnosis and poor risk after induction	29 (21)	32 (24)	61 (22)
Lung or pleural metastases at diagnosis	26 (19)	26 (19)	52 (19)
Other metastases at diagnosis	24 (18)	19 (14)	43 (16)
Total	136 (100)	136 (100)	272 (100)
Country (N (%))			
UK	46 (34)	47 (35)	93 (34)
Other	62 (46)	61 (45)	123 (45)
France	28 (21)	28 (21)	56 (21)
Total	136 (100)	136 (100)	272 (100)

Additional baseline characteristics are further described in the following tables

Table 0.4: R2 Randomisation: Other R1 minimisation factors

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
R1 disease type (N (%))			
No metastasis or involvement of regional lymph nodes only	86 (63)	91 (67)	177 (65)
Lung or pleural metastasis only	26 (19)	26 (19)	52 (19)
Other metastasis	24 (18)	19 (14)	43 (16)
Total	136 (100)	136 (100)	272 (100)
R1 Tumour Volume (N (%))			
less than 200ml	67 (49)	79 (58)	146 (54)
more or equal to 200ml	69 (51)	57 (42)	126 (46)
Total	136 (100)	136 (100)	272 (100)

Table 0.5: R2 Randomisation: Age and development

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
Age			
N	136	136	272
Median	15	15	15
Min	2	4	2
Max	49	49	49
Age categorisations for EudraCT (N (%))			
2-11 years	40 (29)	38 (28)	78 (29)
12-17 years	40 (29)	54 (40)	94 (35)
18-64 years	56 (41)	44 (32)	100 (37)
Total	136 (100)	136 (100)	272 (100)
Pubertal status (N (%))			
Prepubertal	40 (29)	36 (26)	76 (28)
Intrapubertal	23 (17)	26 (19)	49 (18)
Postpubertal	68 (50)	68 (50)	136 (50)
Not Applicable	0 (0)	1 (1)	1 (0)
Not Known	5 (4)	5 (4)	10 (4)
Total	136 (100)	136 (100)	272 (100)

Table 0.6: R2 Randomisation: Primary tumour site details

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
Type of involvement (N (%))			
Osseous lesion with or without soft tissue component...	112 (82)	118 (87)	230 (85)
Extra-osseous lesion (no bone involvement)	24 (18)	18 (13)	42 (15)
Total	136 (100)	136 (100)	272 (100)
Site of primary tumour: body part (N (%))			
Pelvis	24 (18)	36 (26)	60 (22)
Abdomen	6 (4)	2 (1)	8 (3)
Spine	10 (7)	11 (8)	21 (8)
Chest	23 (17)	31 (23)	54 (20)
Head and neck	2 (1)	3 (2)	5 (2)
Upper extremity	13 (10)	12 (9)	25 (9)
Lower extremity	58 (43)	40 (29)	98 (36)
Unknown origin	0 (0)	1 (1)	1 (0)
Total	136 (100)	136 (100)	272 (100)
Site of primary tumour: bone or soft tissue (N (%))			
Bone	103 (76)	109 (80)	212 (78)
Soft tissue	33 (24)	27 (20)	60 (22)
Total	136 (100)	136 (100)	272 (100)

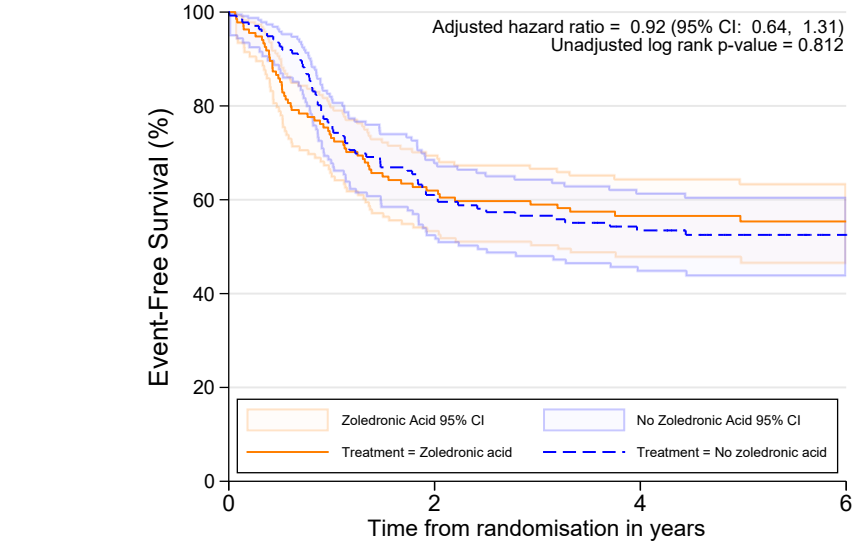
Appendix 4: R2 Randomisation - Primary endpoint

Event-Free Survival (EFS)

Subject analysis set: Intention-to-treat (all randomised patients in the R2 randomisation)
Outcome definition: EFS is defined as the time from randomisation to first event, where an event is progression without completed remission, recurrence (following complete remission), diagnosis of second malignancy or death. Patients who have not had an event will be censored at their last follow-up data. Patients lost to follow-up without an event will be censored at the data of their last consultation.
End point timeframe: From the R2 randomisation until an event or at least 2-years follow-up
Number of subjects analysed: 272 (136 in each arm)
Units: Time measured in years
Analysis description: The design was frequentist and aimed to show the superiority of adding zoledronic acid to consolidation chemotherapy

The p-value from the log-rank test of the unadjusted cox model is 0.812. The hazard ratio and 95% confidence interval from adjusted cox model is 0.92 (0.64, 1.31), with a p-value of 0.632. This model has been adjusted for the stratification variables: country, age, sex, R2 disease status and R1 treatment allocation. However, the R1 treatment allocation means the proportional hazards assumption of the model has been violated. Therefore, the stratified-Cox model approach has been utilised, estimating a baseline hazard for each category of the R1 treatment allocation. The results demonstrate that there is not enough evidence of a difference between zoledronic acid and no zoledronic acid.
3-year EFS overall is 0.58 (95% CI: 0.49, 0.66)
3-year EFS for zoledronic is 0.59 (95% CI: 0.50, 0.67)
3-year EFS for no zoledronic is 0.57 (95% CI: 0.48, 0.64)
5-year EFS overall is 0.54 (95% CI: 0.45, 0.62)
5-year EFS for zoledronic is 0.55 (95% CI: 0.46, 0.63)
5-year EFS for no zoledronic is 0.53 (95% CI: 0.44, 0.61)
The Kaplan-Meier for EFS from the R2 randomisation is given below.

Figure 0.2: R2 Randomisation: Event-free Survival Kaplan-Meier



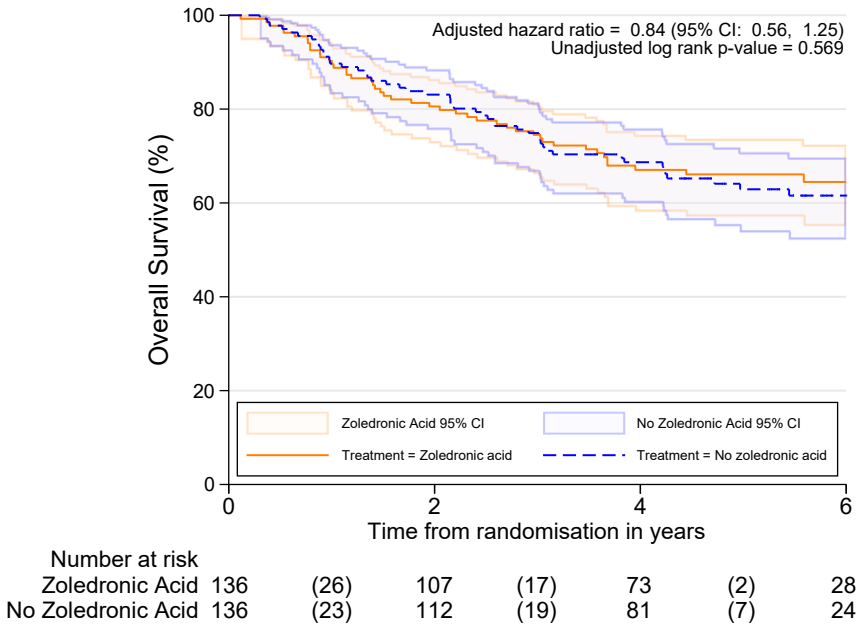
Appendix 5: R2 Randomisation - Secondary endpoint 1

Overall Survival (OS)

Subject analysis set: Intention-to-treat (all randomised patients in the R2 randomisation)
Outcome definition: OS is defined as the time from randomisation to death, irrespective of the cause. Surviving patients will be censored at their last follow-up date.
End point timeframe: From the R2 randomisation until an event or at least 2-years follow-up
Number of subjects analysed: 272 (136 in each arm)
Units: Time measured in years
Analysis description: The design was frequentist and aimed to show the superiority of adding zoledronic acid to consolidation chemotherapy

The p-value from the log-rank test of the unadjusted cox model is 0.569. The hazard ratio and 95% confidence interval from adjusted cox model is 0.84 (0.56, 1.25), with a p-value of 0.386. This model has been adjusted for the stratification variables: country, age, sex, R2 disease status and R1 treatment allocation. These results demonstrate that although there is slight benefit with zoledronic acid compared to no zoledronic acid, although this evidence is not statistically significant.
3-year EFS overall is 0.75 (95% CI: 0.66, 0.81)
3-year OS for zoledronic is 0.75 (95% CI: 0.66, 0.81)
3-year OS for no zoledronic is 0.75 (95% CI: 0.67, 0.81)
5-year EFS overall is 0.64 (95% CI: 0.55, 0.72)
5-year OS for zoledronic is 0.66 (95% CI: 0.57, 0.74)
5-year OS for no zoledronic is 0.63 (95% CI: 0.54, 0.71)
The Kaplan-Meier for OS from the R2 randomisation is given below.

Figure 0.3: R2 Randomisation: Overall Survival Kaplan-Meier



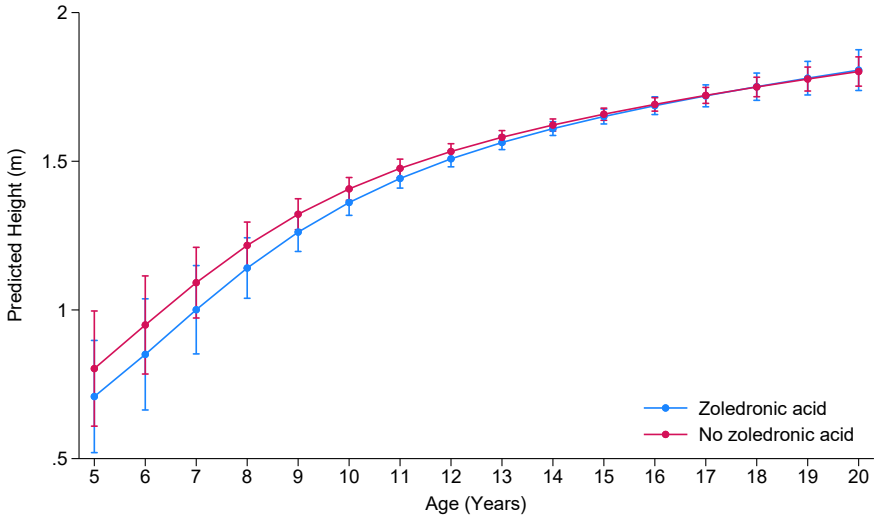
Appendix 6: R2 Randomisation - Secondary endpoint 2

Growth parameters and jaw/ear osteonecrosis

Subject analysis set: All patients <18 trial entry randomised to R2 Outcome definition: Growth parameters will be assessed using patient's height measured at baseline, treatment and throughout follow up for all patients who enter the second randomisation and who are less than 18 years of age at entry.
Whether the patient was diagnosed with jaw and ear osteonecrosis will be recorded at the end of or during treatment for all patients who were randomised to R2.
End point timeframe: From the R2 randomisation (i.e., baseline), through treatment and follow-up, with at least 2-years follow-up
Number of subjects analysed: 172 (80 in the zoledronic acid arm; 92 in the no zoledronic acid arm)
Units: Height measured in cm
Analysis description: Equivalence, with the aim to show the additional of zoledronic acid would not affect patients' height. This was analysed using a 3-parameters Gompertz model.
Additional information: For the primary analysis, only height measurements at baseline and whilst on treatment have been considered, due to the extent of missingness of follow-up heights. A sensitivity analysis using follow-up heights does not change the conclusions.

Another growth curve model was generated using a mixed effects non-linear model, adjusting for treatment and sex. There was no significant difference between treatment arms for height over age, with all parameters having a p-value of greater than 0.2. Alternatively, the sex parameter in the model was significant for the growth rate parameter, which can likely be explained by the growth rate differences between males and females generally, but neither of the other parameters were significant. The coefficients for each variable for the three parameters are as follows:
R2 treatment coefficient for the asymptote parameter = 0.02 (95% CI: -0.03 to 0.06, p = 0.485)
Sex coefficient for the asymptote parameter = -1.19 (95% CI: -2.86 to 0.47, p = 0.161)
R2 treatment coefficient for the growth rate parameter = -0.01 (95% CI: -0.01 to 0.00, p = 0.200)
Sex coefficient for the growth rate parameter = 0.36 (95% CI: 0.19 to 0.52, p = 0.000)
R2 treatment coefficient for the inflection parameter = -0.65 (95% CI: -1.72 to 0.41, p = 0.228)
Sex coefficient for the inflection parameter = 1.72 (95% CI: -7.32 to 10.75, p = 0.710)
The resulting growth curve is given in the figure below.

Figure 0.4: R2 Randomisation: Growth curve by treatment adjusting for sex



When considering the growth curve model during treatment and follow-up, the same conclusions remain (i.e., no significant differences between the treatment arms for the three parameters).

In addition to growth parameters, jaw osteonecrosis and osteonecrosis of the ear was of interest for the R2 randomisation, and in particular for patients randomised to zoledronic acid. All patients are included here. The table below describes the jaw osteonecrosis experienced by R2 randomised patients, by treatment arm and overall. Only one patient on the no zoledronic acid arm experienced jaw osteonecrosis.

Table 0.7: R2 Randomisation: Jaw osteonecrosis

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
Did the patient have osteonecrosis of the jaw? (N (%))			
No	135 (99)	128 (94)	263 (97)
Yes	0 (0)	1 (1)	1 (0)
Not Applicable	1 (1)	3 (2)	4 (1)
Not Known	0 (0)	4 (3)	4 (1)
Total	136 (100)	136 (100)	272 (100)

The table below describes osteonecrosis of the ear experienced by R2 randomised patients, by treatment arm and overall. Only one patient on the zoledronic acid arm experienced osteonecrosis of the ear.

Table 0.8: R2 Randomisation: Ear osteonecrosis

R2 Treatment	**Zoledronic acid (136)**	**No zoledronic acid (136)**	**Overall (272)**
Did the patient have osteonecrosis of the ear? (N (%))			
No	122 (90)	117 (86)	239 (88)
Yes	1 (1)	0 (0)	1 (0)
Not Applicable	1 (1)	2 (1)	3 (1)
Not Known	12 (9)	17 (12)	29 (11)
Total	136 (100)	136 (100)	272 (100)

Appendix 7: R2 Randomisation - Serious adverse events

The following serious adverse event tables for the R2 randomisation differ from what was presented in the R2 publication for the following reason:
- The R2 publication reported all grade 3-5 SAEs whereas the EudraCT tables include all adverse events, regardless of grade.

Table 0.9: Expected SAE details, capturing relatedness and fatality for EudraCT upload for R2 randomised zoledronic acid treatment

Category	Toxicity	Affected	Exposed	Occurrences	Fatal	Related	Related & Fatal	% Affected
Blood and lymphatic system disorders	Febrile neutropenia	33	136	62	0	62	0	24
Gastrointestinal disorders	e.g. mucositis stomatitis, nausea, vomiting, diarrhoea	8	136	9	0	9	0	6
Infections and infestations	Infections	12	136	13	0	13	0	9
Investigations	e.g. haemoglobin, WBC, granulocytes, platelets	9	136	18	0	18	0	7

Table 0.10: Non-expected SAE details, capturing relatedness and fatality for EudraCT upload for R2 randomised zoledronic acid treatment

Category	Toxicity	Affected	Exposed	Occurrences	Fatal	Related	Related & Fatal	% Affected
General disorders and administration site conditions	Fever	1	136	1	0	0	0	1
	Pain	1	136	1	0	0	0	1
Infections and infestations	Lung infection	1	136	1	1	1	1	1
	Sepsis	1	136	1	0	1	0	1
Metabolism and nutrition disorders	Hypocalcemia	1	136	1	0	1	0	1
	Hypophosphatemia	1	136	2	0	2	0	1
Musculoskeletal and connective tissue disorders	Pain	1	136	1	0	0	0	1
Nervous system disorders	Headache	1	136	1	0	1	0	1
Renal and urinary disorders	Hematuria	1	136	1	0	1	0	1
Reproductive system and breast disorders	Premature menopause	1	136	1	0	1	0	1
	Vaginal hemorrhage	1	136	1	0	0	0	1
Vascular disorders	Thromboembolic event	1	136	1	0	0	0	1

Table 0.11: Expected SAE details, capturing relatedness and fatality for EudraCT upload for R2 randomised no zoledronic acid treatment

Category	Toxicity	Affected	Exposed	Occurrences	Fatal	Related	Related & Fatal	% Affected
Blood and lymphatic system disorders	Febrile neutropenia	35	134	59	0	58	0	26
Infections and infestations	Infections	8	134	10	0	10	0	6
Investigations	e.g. haemoglobin, WBC, granulocytes, platelets	7	134	17	0	17	0	5

Table 0.12: Non-expected SAE details, capturing relatedness and fatality for EudraCT upload for R2 randomised no zoledronic acid treatment

Category	Toxicity	Affected	Exposed	Occurrences	Fatal	Related	Related & Fatal	% Affected
Blood and lymphatic system disorders	Febrile neutropenia	1	134	1	0	1	0	1
General disorders and administration site conditions	asthenia	1	134	1	0	1	0	1
Infections and infestations	Catheter related infection	1	134	1	0	0	0	1
	Sepsis	1	134	1	0	1	0	1
	Skin infection	1	134	1	0	0	0	1
Injury, poisoning and procedural complications	Wound dehiscence	1	134	1	0	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukemia secondary to oncology chemotherapy	2	134	2	0	2	0	1
Psychiatric disorders	Suicide attempt	1	134	1	0	0	0	1
Renal and urinary disorders	Renal colic	1	134	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	134	1	0	0	0	1
Vascular disorders	Thromboembolic event	1	134	1	0	0	0	1

Appendix 8: R2 Randomisation - Non-serious adverse events

The following adverse event tables for the R2 randomisation are slightly different to what was presented in the R2 publication for the following reasons:
- The R2 publication included clinically relevant adverse events as well as those that met the 5% threshold (e.g., hypocalcaemia), whereas the EudraCT table only includes the adverse events that meet this threshold. The clinically relevant adverse events are included in the main body of the report.
- The threshold for adverse events in the R2 publication was 5% overall, whereas for the EudraCT table it's 5% in either arm. As a result, vomiting is included in the table below but not the R2 publication.
- The R2 publication summarised the CTCAE categories that occurred in more than 5% of patients, whereas the EudraCT tables focus on specific adverse events occurring in more than 5% of patients.

Table 0.13: R2 Randomisation: Grade 3-5 adverse events experienced by at least 5% of patients on the trial by CTCAE category and toxicity for patients allocated to zoledronic acid receiving consolidation. Used for Eudract submission

Category	CTCAE Toxicity	Affected	Exposed	Occurrences	% Affected
Blood and lymphatic system disorders	Anemia	41	136	83	30
	Febrile neutropenia	36	136	51	26
Gastrointestinal disorders	Vomiting	7	136	11	5
Investigations	Lymphocyte count decreased	30	136	128	22
	Neutrophil count decreased	59	136	188	43
	Platelet count decreased	58	136	159	43
	White blood cell decreased	41	136	163	30
Metabolism and nutrition disorders	Hypophosphatemia	14	136	24	10

Table 0.14: R2 Randomisation: Grade 3-5 adverse events experienced by at least 5% of patients on the trial by CTCAE category and toxicity for patients allocated to no zoledronic acid receiving consolidation. Used for Eudract submission

Category	**CTCAE Toxicity**	**Affected**	**Exposed**	**Occurrences**	**% Affected**
Blood and lymphatic system disorders	Anemia	43	134	85	32
	Febrile neutropenia	37	134	59	28
Gastrointestinal disorders	Vomiting	2	134	3	1
Investigations	Lymphocyte count decreased	31	134	133	23
	Neutrophil count decreased	70	134	232	52
	Platelet count decreased	68	134	189	51
	White blood cell decreased	45	134	174	34
Metabolism and nutrition disorders	Hypophosphatemia	5	134	13	4