

**Clinical trial results:****A phase III study of lenalidomide maintenance after debulking therapy in patients with advanced cutaneous T-cell lymphoma.****Summary**

EudraCT number	2009-011020-65
Trial protocol	DE FR AT FI DK ES GB NL BE
Global end of trial date	02 September 2013

**Results information**

Result version number	v1 (current)
This version publication date	10 August 2016
First version publication date	10 August 2016

**Trial information****Trial identification**

Sponsor protocol code	EORTC 21081
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01098656
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	08 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 September 2013
Global end of trial reached?	Yes
Global end of trial date	02 September 2013
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

The overall objective is to determine if maintenance treatment with lenalidomide prolongs response after debulking in patients with advanced stage cutaneous T-cell lymphoma (CTCL) who have not been previously treated with intravenous chemotherapy except the chemotherapy received in the preceding debulking stage. Patients will be randomized to either receive the maintenance therapy or not, and these two study arms will be compared in terms of the difference in progression free survival (PFS).

Despite early closure and as the study population is a very rare disease, it was decided by the study coordinator and the team to have the final analysis for the trial addressing:

- information related to randomization failures
- baseline information
- treatment information
- descriptive information on primary endpoint: progression-free survival
- toxicity

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

No background therapy

Evidence for comparator:

No active comparator

Actual start date of recruitment	20 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Belgium: 1

Worldwide total number of subjects	30
EEA total number of subjects	29

Notes:

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**Subjects enrolled per age group**

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	13
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

- Advanced stage mycosis fungoides (stage IIB-IV), or Sézary Syndrome.
- Prior debulking therapy with either mono-chemotherapy, Poly-chemotherapy/combination chemo and radiotherapy or radiotherapy alone (e.g. Total Skin Electron Beam body radiation [TSEB]) (according to local institutional guidelines) resulting in complete or partial response

### Pre-assignment period milestones

Number of subjects started	30
Number of subjects completed	21

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	progressive disease: 7
Reason: Number of subjects	other: 2

### 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
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<b>Arm title</b>	Lenalidomide
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Arm description:

Maintenance Lenalidomide: Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal. The maximum duration of treatment, calculated in calendar days from the first dose of drug, is 560 days. After that time, the patient will be considered to have completed protocol treatment.

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

Dosage and administration details:

Lenalidomide capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Initial Dose

The starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings as described in the section on "Dose Modification", in the protocol. For patients allocated to the lenalidomide arm, the first treatment dose must be given within 7 days of randomization.

<b>Arm title</b>	Observation
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Arm description: -

Arm type	No intervention
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<b>Number of subjects in period 1<sup>[1]</sup></b>	Lenalidomide	Observation
Started	9	12
Started allocated treatment	8	12
Completed	0	1
Not completed	9	11
Consent withdrawn by subject	1	-
Treatment not started	1	-
Lost to follow-up	-	1
Adverse event, non-fatal	1	-
Progression	5	9
other	1	1

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 30 patients were registered but only 21 patients were randomized. Reasons of non-randomization are given in the pre-assignment period. All results are presented on randomized patients.

## Baseline characteristics

### Reporting groups

Reporting group title	Lenalidomide
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Reporting group description:

Maintenance Lenalidomide: Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal. The maximum duration of treatment, calculated in calendar days from the first dose of drug, is 560 days. After that time, the patient will be considered to have completed protocol treatment.

Reporting group title	Observation
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Reporting group description: -

Reporting group values	Lenalidomide	Observation	Total
Number of subjects	9	12	21
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	6	11
From 65-84 years	3	6	9
85 years and over	1	0	1
Age continuous			
Units: years			
median	64	64	
full range (min-max)	38 to 87	53 to 74	-
Gender categorical			
Gender: Male or Female			
Units: Subjects			
Female	5	8	13
Male	4	4	8
Was the patient diagnosed with advanced stage mycosis fungoides (stage IIB-IV), or Sézary syndrome			
Stratification factor for the randomization			
Units: Subjects			
Mycosis fungoides	8	10	18
Sézary syndrome	1	2	3
Overall Response to primary debulking therapy			
Stratification factor for the randomization			
Units: Subjects			
CCR	2	3	5
PR	7	9	16
Performance Status			
WHO performance status			

Units: Subjects			
0 (Zero)	7	9	16
1 (One)	2	2	4
2 (Two)	0	1	1
Primary debulking			
Primary debulking therapy before entry into the trial according to the recommended debulking regimens specified by protocol			
Units: Subjects			
Gemcitabine	5	10	15
Liposomal doxorubicin	3	2	5
Gemcitabine-liposomal doxorubicin switch (or vice	1	0	1

## End points

### End points reporting groups

Reporting group title	Lenalidomide
Reporting group description: Maintenance Lenalidomide: Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal. The maximum duration of treatment, calculated in calendar days from the first dose of drug, is 560 days. After that time, the patient will be considered to have completed protocol treatment.	
Reporting group title	Observation
Reporting group description: -	

### Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description: Progression free survival will be measured from the date of randomization to either the date that progressive disease was objectively documented or, in the absence of progressive disease, death. If progression has not been observed and the patient is still alive, the patient will be censored at the date of the last examination.	
End point type	Primary
End point timeframe: From randomization till end of study	

End point values	Lenalidomide	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: months				
median (confidence interval 95%)	5.3 (1.9 to 22.5)	2 (0.9 to 7.8)		

<b>Attachments (see zip file)</b>	PFS/PFS-21081.jpg
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### Statistical analyses

<b>Statistical analysis title</b>	PFS comparison in intent to treat population
Statistical analysis description: Hazard ratio was estimated from Cox-Regression	
Comparison groups	Lenalidomide v Observation

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.49

Notes:

[1] - Given the circumstances of the study which was closed early with only less than 20% of the originally foreseen number of patients accrued, p-value for progression free survival (PFS) comparison should be interpreted carefully was not reported.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF to be submitted at pre-specified timepoint: at pre-treatment workup, before each cycle (Lenaledomide arm) or every 8 weeks (observation), and 4 weeks after end of last treatment / observation visit

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (1% of AEs are reported as "other" and are not reported as not available from the list of SOC).

AEs are evaluated using CTC v4, SAEs using MedDra. Non-SAEs has not been collected specifically, therefore all AEs (any grade) will be reported in non-SAE section.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Observation
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Reporting group description:

Safety population: all patients who started allocated treatment

Reporting group title	Lenaledomide
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Reporting group description:

Safety population: all patients who started allocated treatment

Serious adverse events	Observation	Lenaledomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: From pharmacovigilance database		
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Observation	Lenaledomide	
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 12 (50.00%)	7 / 8 (87.50%)	
Investigations			
Weight gain alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	Additional description: From clinical database. All adverse events (any grade).
Weight loss alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	Additional description: From clinical database. All adverse events (any grade).
Cardiac disorders			
Sinus bradycardia alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	Additional description: From clinical database. All adverse events (any grade).
Nervous system disorders			
Headache alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	Additional description: From clinical database. All adverse events (any grade).
Other toxicity alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 7	Additional description: From clinical database. All adverse events (any grade).
Paresthesia alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	Additional description: From clinical database. All adverse events (any grade).
General disorders and administration site conditions			
Edema limbs alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 4	Additional description: From clinical database. All adverse events (any grade).
Fatigue			Additional description: From clinical database. All adverse events (any grade).

alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	4 / 8 (50.00%) 19	
Immune system disorders			
Allergic reaction	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	
Gastrointestinal disorders			
Constipation	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 1	
Diarrhea	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 13	
Nausea	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 2	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	
Erythema multiforme	Additional description: From clinical database. All adverse events (any grade).		
alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 8 (25.00%) 7	

Periorbital edema alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	
Pruritus alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	2 / 12 (16.67%) 3	4 / 8 (50.00%) 6	
Urticaria alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	
Psychiatric disorders Depression alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	0 / 12 (0.00%) 0	1 / 8 (12.50%) 3	
Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	
Infections and infestations Upper respiratory infection alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	Additional description: From clinical database. All adverse events (any grade).		
	1 / 12 (8.33%) 1	2 / 8 (25.00%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2011	<ul style="list-style-type: none"><li>- To rephrase the debulking regimens criteria and allow sites to follow debulking regimens as per local institutional policies</li><li>- To extend the registration period (post de-bulking) up to 2 weeks</li><li>- To add the possibility of biobanking biological material samples for use in future research</li><li>- To clarify the TR sections</li><li>- To add pregnancy as withdrawal criteria</li><li>- Some administrative changes</li></ul> Other documents submitted together with the amendment to the protocol: <ul style="list-style-type: none"><li>- the updated version of the IMP's labels used in this trial to include the address of the sponsor, EORTC.</li><li>- the updated version of the Investigator's brochure of Lenalidomide version 14 dated 17 December 2010 .together with the Line Listing (from 16-Jul-2010 to 15-Oct-2010) and the Updated Benefit Risk Assessment and</li></ul>
11 May 2011	<p>Due to a shortage of drug, the protocol has been updated so the patients can receive Gemcitabine as an alternative.</p> <p>Although, it may not been available in Belgium. So, as a temporary as a temporary measure until the quality and supply issues of Caelyx are resolved, Belgium may use all drugs of the liposomal doxorubicin class, as per locally applicable policy at participating centres.</p>

04 October 2012	<p>Rationale for the amendment and its classification:</p> <ul style="list-style-type: none"> <li>• The company supplying the study drug gave information about an update of the Pregnancy Prevention Program (PPP), leading to changes of the pregnancy tests frequencies/methods to be implemented in the protocol and PIS/IC. The Program leads also to the implementation of new note to file to be signed by</li> <li>• the Principal Investigator (PI) and reminders that the patient needs to be aware of pregnancy risks before each drug dispensing. As more information will be given in the PIS/IC, the reference to a separate brochure for the partner mentioned in the protocol will be removed.</li> <li>• Addition of monetary support for the trial</li> <li>• Addition of central technical facilities</li> <li>• Addition of subcontractors</li> </ul> <p>The timelines of SAE pregnancy reporting are updated from 24h to immediate, as per request of the company.  This amendment also includes clarification of the debulking regimens allowed in order to add flexibility in order to match more real clinical practice.  Therefore, stratification factors will be modified, as well as the title of the protocol.  The amendment also includes:</p> <ul style="list-style-type: none"> <li>- clarification on the CT-scan and disease assessment frequency</li> <li>- harmonization of the SAE reporting for second primary malignancies</li> <li>- removal of the "Caelyx" trade name in order to permit use of other liposomal doxorubicin agent as Caelyx is encountering a shortage</li> <li>- simplification of the eligibility criteria for registration (unnecessary redundant tests at both registration and randomization are removed)</li> <li>- removal of "2 week" timelines of the registration period</li> <li>- clarification of retention period for study documentation, monitoring of drug compliance at participating sites etc.as per Swissmedic request</li> <li>- Clarification of AE reporting timelines in chapter 6</li> <li>- correction of late toxicity definition</li> <li>- change of the drug packaging from bottles to b</li> </ul>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 April 2013	The EORTC has been informed by the marketing authorization holder/ the company supplying the study drug (Celgene), Lenalidomide/ Revlimid that it withdraws the financial support for the study. As a consequence financial support to any new patients enrolled after the date of withdrawal cannot be secured. A review of feasibility of the studies for all partners needs to be assessed prior to taking further decisions on the continuation of the study.	-

Notes:

## Limitations and caveats

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

Less than 20% of the originally foreseen number of patients were accrued, therefore results should be interpreted carefully

Notes: