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Trial **2012-000750-66**, ECOG 3A06

Randomized Phase III Trial of Lenalidomide versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Clinical Trial Results:

This trial was sponsored by Cancer Trials Ireland in Europe however was led and sponsored by NCI in the US. Due to differences in the reporting of specific data fields in the US and EU, certain details required for validation of trial results in EudraCT are not available to us.

We are therefore uploading and posting a summary attachment (download from ClinicalTrials.gov) together with a PDF download from EudraCT of (partial) results of the trial.

Results on CT.gov can be accessed at this link: Study Details | NCT01169337 | Lenalidomide or Observation in Treating Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma | ClinicalTrials.gov

They correspond to what is uploaded onto EudraCT.

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Clinical trial results:
Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Summary

EudraCT number	2012-000750-66
Trial protocol	IE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	CTRIAL 12-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01169337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, Dublin, Ireland, D02 H903
Public contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, info@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, info@cancertrials.ie

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	Interim
Date of interim/final analysis	03 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of Phase II part of this trial was to study the risk of grade 3 adverse events that effect vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic adverse events among patients receiving lenalidomide as treatment for high-risk asymptomatic, smoldering multiple myeloma.
The main objective of Phase III was to compare progression free survival where failure is defined as death or the development of symptomatic myeloma indicating treatment between patients receiving lenalidomide versus observation alone in high-risk asymptomatic, smoldering multiple myeloma.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The trial was also conducted in accordance with ethical principles founded in the Declaration of Helsinki.
The study wad approved by HPRA and Cork Clinical Research Ethics Committee. Written informed consent was required for participation.

Background therapy:

N/A

Evidence for comparator:

The primary objective of Phase III was to compare patients receiving lenalidomide (Arm A) versus observation alone (Arm B) in high-risk asymptomatic, smoldering multiple myeloma.

Actual start date of recruitment	24 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Puerto Rico
Worldwide total number of subjects	3
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0

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

Subject disposition

Recruitment

Recruitment details:

Between January 2011 and January 2013, 44 patients were enrolled in the phase II safety run in portion of the study and were treated with lenalidomide as a single agent. Between February 2013 and July 2017, 182 patients were randomly assigned between the two treatment arms in the phase III portion of the study

Pre-assignment

Screening details:

Patients with Smoldering Multiple Myeloma who have the highest risk of progression to symptomatic Multiple Myeloma. The patients must fulfill all of the inclusion criteria and none of the exclusion criteria.

Period 1

Period 1 title	Overall Study (Phase II/III) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Lenalidomide; Phase II)

Arm description:

Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25mg by mouth days 1-21 every 4 weeks (28 days).

Arm title	Arm A (Lenalidomide; Phase III)

Arm description:

Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 2mg by mouth days 1-21 every 4 weeks (28 days)

Arm title	Arm B (Observation; Phase III)

Arm description:

Patients undergo observation until progression to symptomatic myeloma.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Started	44	90	92
Completed	0	0	86
Not completed	44	90	6
Other complicating disease	1	1	-
Changed hospital	-	1	-
Never started treatment	-	2	-
Consent withdrawn by subject	11	11	6
Physician decision	1	5	-
Reason not reported	1	-	-
Adverse event, non-fatal	12	18	-
Death	2	-	-
Alternative therapy	-	2	-
Continuing lenalidomide	9	43	-
Lack of efficacy	5	7	-
Noncompliance	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Lenalidomide; Phase II)
Reporting group description:	
Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	
Reporting group title	Arm A (Lenalidomide; Phase III)
Reporting group description:	
Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	
Reporting group title	Arm B (Observation; Phase III)
Reporting group description:	
Patients undergo observation until progression to symptomatic myeloma.	

Reporting group values	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Number of subjects	44	90	92
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)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	62	63	64
full range (min-max)	36 to 83	31 to 82	33 to 96
Gender categorical Units: Subjects			
Female	24	48	46
Male	20	42	46
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	4
Not Hispanic or Latino	43	81	81
Unknown or Not Reported	1	7	7
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	6	12	19
White	37	72	68
More than one race	0	0	0
Unknown or Not Reported	1	5	4

Reporting group values	Total		
Number of subjects	226		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	118		
Male	108		
Ethnicity Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	205		
Unknown or Not Reported	15		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	37		
White	177		
More than one race	0		
Unknown or Not Reported	10		

End points

End points reporting groups

Reporting group title	Arm A (Lenalidomide; Phase II)
Reporting group description:	
Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	
Reporting group title	Arm A (Lenalidomide; Phase III)
Reporting group description:	
Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	
Reporting group title	Arm B (Observation; Phase III)
Reporting group description:	
Patients undergo observation until progression to symptomatic myeloma.	

Primary: Proportion of patients with grade 3 adverse events that effect vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic adverse events (Phase II Primary Endpoint)

End point title	Proportion of patients with grade 3 adverse events that effect vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic adverse events (Phase II Primary Endpoint)[1][2]
End point description:	
The first 36 patients in the phase II part as planned in the study design.	
End point type	Primary
End point timeframe:	
Assessed every 4 weeks while on treatment up to 24 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis has been reported on the primary end point (2-year Progression-free Survival (PFS) Rate) for the Phase III portion of the trial.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This End point relates only to the Phase II portion of the clinical trial. As planned in the study design, this includes the first 36 patients in the phase II part.

End point values	Arm A (Lenalidomide; Phase II)			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Proportion of Participants				
number (confidence interval 90%)	0.056 (0.010 to 0.165)			

Statistical analyses

No statistical analyses for this end point

Primary: 2-year Progression-free Survival (PFS) Rate (Phase III Primary Endpoint)

End point title	2-year Progression-free Survival (PFS) Rate (Phase III Primary Endpoint)[3]

End point description:

PFS is defined as time from randomization to progression or death, whichever occurs first. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 2-year PFS rate.

Any of the following:

Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression".

Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression".

Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%).

Any of the following felt related to the underlying clonal plasma cell proliferative disorder:
Hypercalcemia (> 11 mg/dL)
Decrease in hemoglobin of ≥ 2 gms/dL
Serum creatinine level ≥ 2mg/dL
Development of myeloma bone lesions or soft tissue plasmacytoma

End point type	Primary

End point timeframe:

Assessed every 3 months for 2 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As planned in the study design, this end point relates only to the Phase III portion of the trial.

End point values	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Proportion of participants				
number (confidence interval 90%)	0.93 (0.88 to 0.99)	0.76 (0.66 to 0.87)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A (Lenalidomide; Phase III) v Arm B (Observation; Phase III)
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Logrank
Parameter estimate	stratified 1-sided log-rank test

Confidence interval	
sides	1-sided

Secondary: Proportion of Participants With Response (Phase II Secondary Endpoint)

End point title	Proportion of Participants With Response (Phase II Secondary Endpoint)[4]

End point description:

Response is defined as complete response (CR), very good partial response (VGPR) or partial response (PR).

CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hours

PR:

≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours
If followed by free light chain (FLC) only, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels
If unmeasurable disease by serum M-protein, urine M-protein, and serum FLC at baseline, a ≥50% reduction in plasma cells provided baseline bone marrow percentage was ≥ 30%
If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas

End point type	Secondary

End point timeframe:

Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As planned in the study design, this end point relates only to the Phase II portion of the trial.

End point values	Arm A (Lenalidomide; Phase II)			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Proportion of participants				
number (confidence interval 95%)	0.477 (0.325 to 0.633)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with Response (Phase III Secondary Endpoint)

End point title	Proportion of Participants with Response (Phase III Secondary Endpoint)[5]

End point description:

Response is defined as complete response (CR), very good partial response (VGPR) or partial response (PR).

CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hours

PR:

≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours
If followed by free light chain (FLC) only, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels
If unmeasurable disease by serum M-protein, urine M-protein, and serum FLC at baseline, a ≥50% reduction in plasma cells provided baseline bone marrow percentage was ≥ 30%
If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas

End point type	Secondary

End point timeframe:

Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As planned in the study design, this end point relates only to the Phase III portion of the trial.

End point values	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	86		
Units: Proportion of particpants				
number (confidence interval 95%)	0.50 (0.391 to 0.608)	0 (0 to 0.042)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year Progression-free Survival (PFS) Rate (Phase III Secondary Endpoint)

End point title	1-year Progression-free Survival (PFS) Rate (Phase III Secondary Endpoint)

End point description:

PFS is defined as time from randomization to progression or death, whichever occurs first. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 1-year PFS rate.

Any of the following:

Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression"
Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression"
Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%)
Any of the following felt related to the underlying clonal plasma cell proliferative disorder:

Hypercalcemia (> 11 mg/dL)
Decrease in hemoglobin of ≥ 2 gms/dL
Serum creatinine level ≥ 2mg/dL

Development of myeloma bone lesions or soft tissue plasmacytoma

End point type	Secondary

End point timeframe:

Assessed every 3 months for one year

End point values	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Proportion of participants				
number (confidence interval 95%)	0.98 (0.95 to 1.00)	0.89 (0.82 to 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year Progression-free Rate (Phase III Secondary Endpoint)

End point title	2-year Progression-free Rate (Phase III Secondary Endpoint)[6]

End point description:

TTP is defined as the time from randomization to progression. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 2-year progression-free rate.

Any of the following:

Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression"
Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression"
Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%)
Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder:

Hypercalcemia (> 11 mg/dL)
Decrease in hemoglobin of ≥ 2 gms/dL
Serum creatinine level ≥ 2mg/dL
Development of myeloma bone lesions or soft tissue plasmacytoma

End point type	Secondary

End point timeframe:

Assessed every 3 months for 2 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As planned in the study design, this end point relates only to the Phase III portion of the trial.

End point values	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Proportion of participants				
number (confidence interval 95%)	94.3 (85.4 to 97.9)	75.8 (63.6 to 84.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year Overall Survival (OS) Rate (Phase III Secondary Endpoint)

End point title	2-year Overall Survival (OS) Rate (Phase III Secondary Endpoint)[7]

End point description:

Overall survival is defined as the time from randomization to death or date last known alive among all randomized patients in the phase III part of the study. Kaplan-Meier method was used to estimate the 2-year OS rate.

End point type	Secondary

End point timeframe:

Assessed every 3 months for 2 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As planned in the study design, this end point relates only to the Phase III portion of the trial.

End point values	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Proportion of participants				
number (confidence interval 95%)	0.98 (0.95 to 1.00)	1.00 (1.00 to 1.00)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every 4 weeks while on treatment and for 30 days after the end of treatment, up to 10 years

Adverse event reporting additional description:

Serious adverse events are defined as treatment-related adverse events of grade 3 or higher. Other adverse events are treatment-related adverse events not included in serious adverse events.
Only patients who started protocol therapy are included in the analysis of AEs. All registered patients are included in the analysis of all-cause mortality.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm A (Lenalidomide; Phase II)

Reporting group description:

Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Reporting group title	Arm A (Lenalidomide; Phase III)

Reporting group description:

Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Reporting group title	Arm B (Observation; Phase III)

Reporting group description:

Patients undergo observation until progression to symptomatic myeloma.

Serious adverse events	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Total subjects affected by serious adverse events			
subjects affected / exposed	/	/	/
number of deaths (all causes)			
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Treatment related secondary malignancy			
subjects affected / exposed	0 / 44 (0.00%)	2 / 88 (2.27%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 0	/	/
deaths causally related to treatment / all	0 / 0	/	/
Thromboembolic event			
subjects affected / exposed	2 / 44 (4.55%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 44 (11.36%)	5 / 88 (5.68%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 44 (0.00%)	3 / 88 (3.41%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Insomnia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Investigations			
Creatinine increased			

subjects affected / exposed	0 / 44 (0.00%)	0 / 88 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	/
deaths causally related to treatment / all	0 / 0	0 / 0	/
Lymphocyte count decreased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	7 / 44 (15.91%)	12 / 88 (13.64%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	/	/	/
deaths causally related to treatment / all	/	/	/
Platelet count decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Weight loss			
subjects affected / exposed	1 / 44 (2.27%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
White blood cell count decreased			
subjects affected / exposed	1 / 44 (2.27%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Dizziness			

subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 44 (4.55%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 88 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	/
deaths causally related to treatment / all	0 / 0	0 / 0	/
Peripheral motor neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	2 / 88 (2.27%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Syncope			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 88 (2.27%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Blood and lymphatic disorders-Other			

subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)	3 / 88 (3.41%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	/	/	/
deaths causally related to treatment / all	/	/	/
Vomiting			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Gastrointestinal disorder-Other			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Erythroderma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Pruritus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	2 / 44 (4.55%)	2 / 88 (2.27%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 44 (0.00%)	0 / 88 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	/
deaths causally related to treatment / all	0 / 0	0 / 0	/
Chronic kidney disease			
subjects affected / exposed	0 / 44 (0.00%)	0 / 88 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	/
deaths causally related to treatment / all	0 / 0	0 / 0	/
Renal and urinary disorders-Other			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Myalgia			

subjects affected / exposed	0 / 44 (0.00%)	2 / 88 (2.27%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Sepsis			
subjects affected / exposed	2 / 44 (4.55%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 44 (2.27%)	1 / 88 (1.14%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	/	0 / 0
deaths causally related to treatment / all	/	/	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 44 (4.55%)	0 / 88 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	/	0 / 0	0 / 0
deaths causally related to treatment / all	/	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 88 (0.00%)	2 / 86 (2.33%)
occurrences causally related to treatment / all	0 / 0	/	0 / 0
deaths causally related to treatment / all	0 / 0	/	0 / 0

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

Non-serious adverse events	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Total subjects affected by non-serious adverse events subjects affected / exposed	/	/	/
Investigations Lymphocyte count decreased subjects affected / exposed	3 / 44 (6.82%)	4 / 88 (4.55%)	2 / 86 (2.33%)
occurrences (all)			
Neutrophil count decreased subjects affected / exposed	5 / 44 (11.36%)	8 / 88 (9.09%)	1 / 86 (1.16%)
occurrences (all)			
Platelet count decreased subjects affected / exposed	5 / 44 (11.36%)	5 / 88 (5.68%)	1 / 86 (1.16%)
occurrences (all)			
White blood cell count decreased subjects affected / exposed	6 / 44 (13.64%)	9 / 88 (10.23%)	2 / 86 (2.33%)
occurrences (all)			
Blood and lymphatic system disorders Anaemia subjects affected / exposed	6 / 44 (13.64%)	5 / 88 (5.68%)	2 / 86 (2.33%)
occurrences (all)			
General disorders and administration site conditions Fatigue subjects affected / exposed	4 / 44 (9.09%)	9 / 88 (10.23%)	2 / 86 (2.33%)
occurrences (all)			
Gastrointestinal disorders Constipation subjects affected / exposed	2 / 44 (4.55%)	7 / 88 (7.95%)	1 / 86 (1.16%)
occurrences (all)			
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed	4 / 44 (9.09%)	1 / 88 (1.14%)	1 / 86 (1.16%)
occurrences (all)			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2018	The first version of the protocol approved in Ireland was Addendum #7. The protocol was amended multiple times during the period of time the trial was open in Ireland. Approval for Protocol Addendum #13 dated 31May2018 was obtained on 17-sep-2018. This was the final version of the Protocol approved in Ireland.

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.

No limitations or caveats to note.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31652094

Active, not recruiting

Lenalidomide or Observation in Treating Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma

ClinicalTrials.gov ID NCT01169337

Sponsor National Cancer Institute (NCI)

Information provided by National Cancer Institute (NCI) (Responsible Party)

Last Update Posted 2025-09-10

Results Posted Tab

Results Overview

Conditions

Light Chain Deposition Disease | Smoldering Multiple Myeloma

Intervention/Treatment

- Other: Clinical Observation
- Drug: Lenalidomide
- Other: Quality-of-Life Assessment

Other Study ID Numbers

- NCI-2011-02057
- NCI-2011-02057 (Registry Identifier) (REGISTRY: CTRP (Clinical Trial Reporting Program))

Show 7 more study numbers

Study Design

Allocation: Randomized

Interventional Model: Parallel Assignment

Masking: None (Open Label)

Primary Purpose: Treatment

Results Point of Contact

Name/Title: Study Statistician
Organization: ECOG-ACRIN Biostatistics Center
Phone: 617-632-3012
Email: eatrials@jimmy.harvard.edu

Enrollment (Actual)

226

Study Type

Interventional

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates

First Submitted

2010-07-23

First Posted (Estimated)

2010-07-26

Results Reporting Dates

Results First Submitted

2021-03-12

Results First Posted

2021-05-18

Study Record Updates

Last Update Posted
2025-09-10

Last Verified
2025-09

Participant Flow

Recruitment Details

Between January 2011 and January 2013, 44 patients were enrolled in the phase II safety run in portion of the study and were treated with lenalidomide as a single agent. Between February 2013 and July 2017, 182 patients were randomly assigned between the two treatment arms in the phase III portion of the study.

Pre-assignment Details

[Not Specified]

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.

Period Title: **Overall Study**

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Started	44	90	92
Received Treatment/Observation	44	88	86
Completed	0	0	86
Not Completed	44	90	6
Reason Not Completed			
Lack of Efficacy	5	7	0
Adverse Event	12	18	0
Death	2	0	0
Withdrawal by Subject	11	11	6
Noncompliance	2	0	0
Other complicating disease	1	1	0
Physician Decision	1	5	0

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Alternative therapy	0	2	0
Changed hospital	0	1	0
Never started treatment	0	2	0
Reason not reported	1	0	0
Continuing lenalidomide	9	43	0

Baseline Characteristics

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Overall Number of Baseline Participants	44	90	92
Baseline Analysis Population Description	All registered patients in phase II portion and randomized patients in phase III portion		

Expand all / Collapse all

Age, Continuous

Median (Full Range) | Unit of measure: years

Number Analyzed	44 participants	90 participants	92 participants
	62 (36 to 83)	63 (31 to 82)	64 (33 to 96)

Sex: Female, Male

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	44 participants	90 participants	92 participants
Female	24 54.5%	48 53.3%	46 50.0%
Male	20 45.5%	42 46.7%	46 50.0%

Ethnicity (NIH/OMB)

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	44 participants	90 participants	92 participants
Hispanic or Latino	0 0.0%	2 2.2%	4 4.3%
Not Hispanic or Latino	43 97.7%	81 90.0%	81 88.0%
Unknown or Not Reported	1 2.3%	7 7.8%	7 7.6%

Race (NIH/OMB)

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	44 participants	90 participants	92 participants
American Indian or Alaska Native	0 0.0%	0 0.0%	0 0.0%
Asian	0 0.0%	1 1.1%	1 1.1%
Native Hawaiian or Other Pacific Islander	0 0.0%	0 0.0%	0 0.0%
Black or African American	6 13.6%	12 13.3%	19 20.7%
White	37 84.1%	72 80.0%	68 73.9%
More than one race	0 0.0%	0 0.0%	0 0.0%

Unknown or Not Reported	1 2.3%	5 5.6%	4 4.3%

Outcome Measures

Expand all / Collapse all

1. Proportion of Patients With Grade 3 Adverse Events That Effect Vital Organ Function or Any Grade 4 or Higher Non-hematologic Adverse Events (Phase II Primary Endpoint)

Type: Primary | Time Frame: Assessed every 4 weeks while on treatment up to 24 weeks

Description	Proportion of patients with grade 3 adverse events that effect vital organ function (such as cardiac, hepatic or thromboembolic) or any grade 4 or higher non-hematologic adverse events
Time Frame	Assessed every 4 weeks while on treatment up to 24 weeks
Analysis Population Description	The first 36 patients in the phase II part as planned in the study design

Arm/Group Title	Arm A (Lenalidomide; Phase II)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.
Overall Number of Participants Analyzed	36
Measure Type: Number (90% Confidence Interval) | Unit of Measure: proportion of participants	0.056 (0.010 to 0.165)

2. 2-year Progression-free Survival (PFS) Rate (Phase III Primary Endpoint)

Type: Primary | Time Frame: Assessed every 3 months for 2 years

Description	PFS is defined as time from randomization to progression or death, whichever occurs first. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 2-year PFS rate. 1. Any of the following: ◦ Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression" ◦ Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression" ◦ Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%) 2. Any of the following felt related to the underlying clonal plasma cell proliferative disorder: ◦ Hypercalcemia (> 11 mg/dL)

	◦ Decrease in hemoglobin of ≥ 2 gms/dL ◦ Serum creatinine level ≥ 2mg/dL ◦ Development of myeloma bone lesions or soft tissue plasmacytoma	
Time Frame	Assessed every 3 months for 2 years	
Analysis Population Description	All randomized patients	
Arm/Group Title	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation until progression to symptomatic myeloma.
Overall Number of Participants Analyzed	90	92
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.93 (0.88 to 0.99)	0.76 (0.66 to 0.87)

Statistical Analysis 1
Statistical Analysis Overview

Comparison Group Selection	Arm A (Lenalidomide; Phase III), Arm B (Observation; Phase III)
Comments	[Not Specified]
Type of Statistical Test	Superiority
Comments	[Not Specified]

Statistical Test of Hypothesis

P-Value	0.0005
Comments	[Not Specified]
Method	Log Rank
Comments	stratified 1-sided log-rank test

3. Proportion of Participants With Response (Phase II Secondary Endpoint)

Type: Secondary | Time Frame: Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10

Description	Response is defined as complete response (CR), very good partial response (VGPR) or partial response (PR). CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hours PR: • ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours

	• If followed by free light chain (FLC) only, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels • If unmeasurable disease by serum M-protein, urine M-protein, and serum FLC at baseline, a ≥50% reduction in plasma cells provided baseline bone marrow percentage was ≥ 30% • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas
Time Frame	Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10
Analysis Population Description	All registered patients in the phase II part
Arm/Group Title	Arm A (Lenalidomide; Phase II)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.
Overall Number of Participants Analyzed	44
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.477 (0.325 to 0.633)

4. Proportion of Participants With Response (Phase III Secondary Endpoint)

Type: Secondary | Time Frame: Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10

Description	Response is defined as complete response (CR), very good partial response (VGPR) or partial response (PR). CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hours PR: • ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If followed by free light chain (FLC) only, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels • If unmeasurable disease by serum M-protein, urine M-protein, and serum FLC at baseline, a ≥50% reduction in plasma cells provided baseline bone marrow percentage was ≥ 30% • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas
Time Frame	Assessed every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, then annually for years 6-10
Analysis Population Description	Among randomized patients who received treatment or observation

Arm/Group Title	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation until progression to symptomatic myeloma.
Overall Number of Participants Analyzed	88	86
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.50 (0.391 to 0.608)	0 (0 to 0.042)

5. 1-year Progression-free Survival (PFS) Rate (Phase III Secondary Endpoint)

Type: Secondary | Time Frame: Assessed every 3 months for one year

Description	PFS is defined as time from randomization to progression or death, whichever occurs first. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 1-year PFS rate. 1. Any of the following: ◦ Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression" ◦ Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression" ◦ Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%) 2. Any of the following felt related to the underlying clonal plasma cell proliferative disorder:

	◦ Hypercalcemia (> 11 mg/dL) ◦ Decrease in hemoglobin of ≥ 2 gms/dL ◦ Serum creatinine level ≥ 2mg/dL ◦ Development of myeloma bone lesions or soft tissue plasmacytoma	
Time Frame	Assessed every 3 months for one year	
Analysis Population Description	All randomized patients	
Arm/Group Title	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation until progression to symptomatic myeloma.
Overall Number of Participants Analyzed	90	92
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.98 (0.95 to 1.00)	0.89 (0.82 to 0.96)

6. 2-year Progression-free Rate (Phase III Secondary Endpoint)

Type: Secondary | Time Frame: Assessed every 3 months for 2 years

Description	TTP is defined as the time from randomization to progression. Patients are considered to have progression if both of the following criteria are met. Kaplan-Meier method was used to estimate 2-year progression-free rate.

	1. Any of the following: ◦ Increase in serum M-protein to ≥ 25% above the lowest response level with an absolute increase of at least 0.5g/dl to qualify as "progression" ◦ Increase in urine M-protein to ≥ 25% above the lowest response level for 24-hour excretion with an absolute increase of at least 200mg/24 hours of urine M-protein to qualify as "progression" ◦ Increase in bone marrow plasma cell percentage to ≥ 25% from lowest response value (the absolute % increase must be ≥ 10%) 2. Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder: ◦ Hypercalcemia (> 11 mg/dL) ◦ Decrease in hemoglobin of ≥ 2 gms/dL ◦ Serum creatinine level ≥ 2mg/dL ◦ Development of myeloma bone lesions or soft tissue plasmacytoma
Time Frame	Assessed every 3 months for 2 years
Analysis Population Description	All randomized patients in the phase III part of the study

Arm/Group Title	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation until progression to symptomatic myeloma.
Overall Number of Participants Analyzed	90	92
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	94.3 (85.4 to 97.9)	75.8 (63.6 to 84.4)

7. 2-year Overall Survival (OS) Rate (Phase III Secondary Endpoint)

Type: Secondary | Time Frame: Assessed every 3 months for 2 years

Description	Overall survival is defined as the time from randomization to death or date last known alive among all randomized patients in the phase III part of the study. Kaplan-Meier method was used to estimate the 2-year OS rate.
Time Frame	Assessed every 3 months for 2 years
Analysis Population Description	All randomized patients in the phase III part of the study

Arm/Group Title	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase III)
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation until progression to symptomatic myeloma.
Overall Number of Participants Analyzed	90	92
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.98 (0.95 to 1.00)	1.00 (1.00 to 1.00)

Adverse Events

Time Frame
Assessed every 4 weeks while on treatment and for 30 days after the end of treatment, up to 10 years

Adverse Event Reporting Description
Serious adverse events are defined as treatment-related adverse events of grade 3 or higher. Other adverse events are treatment-related adverse events not included in serious adverse events. Only patients who started protocol therapy are included in the analysis of adverse events. All registered patients are included in the analysis of all-cause mortality.

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.

Expand

All-Cause Mortality

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	7/44 (15.91%)	2/90 (2.22%)	4/92 (4.35%)

Serious Adverse Events

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	23/44 (52.27%)	40/88 (45.45%)	8/86 (9.30%)
Blood and lymphatic system disorders			
Febrile neutropenia †1	0/44 (0.00%)	2/88 (2.27%)	0/86 (0.00%)
Blood and lymphatic disorders - Other †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Myocardial infarction †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Ear and labyrinth disorders			
Hearing impaired †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Vertigo †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Gastrointestinal disorders			
Constipation †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Diarrhea †1	1/44 (2.27%)	3/88 (3.41%)	1/86 (1.16%)
Vomiting †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Gastrointestinal disorders - Other †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
General disorders			
Fatigue †1	5/44 (11.36%)	5/88 (5.68%)	0/86 (0.00%)

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Cholecystitis †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Immune system disorders			
Allergic reaction †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Infections and infestations			
Lung infection †1	1/44 (2.27%)	1/88 (1.14%)	0/86 (0.00%)
Sepsis †1	2/44 (4.55%)	0/88 (0.00%)	0/86 (0.00%)
Skin infection †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Investigations			
Creatinine increased †1	0/44 (0.00%)	0/88 (0.00%)	1/86 (1.16%)
Lymphocyte count decreased †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Neutrophil count decreased †1	7/44 (15.91%)	12/88 (13.64%)	1/86 (1.16%)

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Platelet count decreased †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Weight loss †1	1/44 (2.27%)	1/88 (1.14%)	0/86 (0.00%)
White blood cell decreased †1	1/44 (2.27%)	1/88 (1.14%)	0/86 (0.00%)
Metabolism and nutrition disorders			
Dehydration †1	1/44 (2.27%)	1/88 (1.14%)	0/86 (0.00%)
Hypokalemia †1	2/44 (4.55%)	0/88 (0.00%)	0/86 (0.00%)
Hyponatremia †1	0/44 (0.00%)	0/88 (0.00%)	2/86 (2.33%)
Musculoskeletal and connective tissue disorders			
Back pain †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Myalgia †1	0/44 (0.00%)	2/88 (2.27%)	0/86 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Treatment related secondary	0/44 (0.00%)	2/88 (2.27%)	0/86 (0.00%)

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
malignancy †1			
Nervous system disorders			
Ataxia †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Dizziness †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Headache †1	2/44 (4.55%)	0/88 (0.00%)	0/86 (0.00%)
Paresthesia †1	0/44 (0.00%)	0/88 (0.00%)	1/86 (1.16%)
Peripheral motor neuropathy †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Peripheral sensory neuropathy †1	1/44 (2.27%)	2/88 (2.27%)	0/86 (0.00%)
Syncope †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Nervous system disorders - Other †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Psychiatric disorders			
Confusion †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Insomnia †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Renal and urinary disorders			
Acute kidney injury †1	0/44 (0.00%)	0/88 (0.00%)	1/86 (1.16%)
Chronic kidney disease †1	0/44 (0.00%)	0/88 (0.00%)	1/86 (1.16%)
Renal and urinary disorders - Other †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Dyspnea †1	0/44 (0.00%)	3/88 (3.41%)	0/86 (0.00%)
Skin and subcutaneous tissue disorders			
Erythroderma †1	0/44 (0.00%)	1/88 (1.14%)	0/86 (0.00%)
Pruritus †1	1/44 (2.27%)	0/88 (0.00%)	0/86 (0.00%)
Rash maculo-papular †1	2/44 (4.55%)	2/88 (2.27%)	0/86 (0.00%)
Vascular disorders			

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Hypertension †1	0/44 (0.00%)	1/88 (1.14%)	2/86 (2.33%)
Thromboembolic event †1	2/44 (4.55%)	1/88 (1.14%)	0/86 (0.00%)

† Indicates events were collected by systematic assessment

1 Term from vocabulary, CTCAE 4.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	14/44 (31.82%)	20/88 (22.73%)	5/86 (5.81%)
Blood and lymphatic system disorders			
Anemia †1	6/44 (13.64%)	5/88 (5.68%)	2/86 (2.33%)
Gastrointestinal disorders			

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
Arm/Group Description	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients receive lenalidomide PO QD on days 1-21. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Patients undergo observation un progression to symptomatic myeloma.
Constipation †1	2/44 (4.55%)	7/88 (7.95%)	1/86 (1.16%)
General disorders			
Fatigue †1	4/44 (9.09%)	9/88 (10.23%)	2/86 (2.33%)
Investigations			
Lymphocyte count decreased †1	3/44 (6.82%)	4/88 (4.55%)	2/86 (2.33%)
Neutrophil count decreased †1	5/44 (11.36%)	8/88 (9.09%)	1/86 (1.16%)
Platelet count decreased †1	5/44 (11.36%)	5/88 (5.68%)	1/86 (1.16%)
White blood cell decreased †1	6/44 (13.64%)	9/88 (10.23%)	2/86 (2.33%)
Skin and subcutaneous tissue disorders			
Rash maculo-papular †1	4/44 (9.09%)	1/88 (1.14%)	1/86 (1.16%)

† Indicates events were collected by systematic assessment

Arm/Group Title	Arm A (Lenalidomide; Phase II)	Arm A (Lenalidomide; Phase III)	Arm B (Observation; Phase II
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Limitations and Caveats

[Not Specified]

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor

National Cancer Institute (NCI)

Investigators

- Principal Investigator: Sagar Lonial, ECOG-ACRIN Cancer Research Group

Publications

From PubMed

These publications come from PubMed, a public database of scientific and medical articles. This list is automatically created by ClinicalTrials.gov Identifier (NCT Number), and these articles may or may not be about the study.

- Lonial S, Jacobus S, Fonseca R, Weiss M, Kumar S, Orlowski RZ, Kaufman JL, Yacoub AM, Buadi FK, O'Brien T, Matous JV, Anderson DM, Emmons RV, Mahindra A, Wagner LI, Dhodapkar MV, Rajkumar SV. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. J Clin Oncol. 2020 Apr 10;38(11):1126-1137. doi: 10.1200/JCO.19.01740. Epub 2019 Oct 25. (https://pubmed.ncbi.nlm.nih.gov/31652094)

More Information

Record History

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed