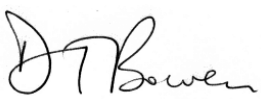
End of Clinical Trial Report

AML Len5: A pilot safety / tolerability study of Lenalidomide administered as monotherapy and in combination with standard chemotherapy for Acute Myeloid Leukaemia / high risk Myelodysplastic Syndrome with structural abnormalities of chromosome 5

1. Trial Summary

EudraCT	2008-004891-28
ISRCTN	ISRCTN58492795
Sponsor No.	HM08/8451
Sponsor	Leeds Teaching Hospitals NHs Trust (Non-commercial sponsor), R&D Department, 34 Hyde Terrace, Leeds, LS2 9NL
Chief Investigator	Prof David Bowen, Honorary Professor of Myeloid Leukaemia Studies and Consultant Haematologist, St James's Institute of Oncology, Bexley Wing, Beckett Street, Leeds, LS9 7TF
Trial Contact	Suzanne Hartley, Head of Trial Management, Clinical Trials Research Unit, University of Leeds, Leeds, LS2 9JT
CTA Approval	16/12/2008
Main REC Approval	23/09/2008
Protocol version and date	Version 4.0; 06 July 2010
Full Title	AML Len5: A pilot safety / tolerability study of Lenalidomide administered as monotherapy and in combination with standard chemotherapy for Acute Myeloid Leukaemia / high-risk Myelodysplastic Syndrome with structural abnormalities of chromosome 5 (Len5)
Phase of study	II
Investigational Medicinal Products (IMPs)	Lenalidomide (Revlimid®); Daunorubicin; Etoposide; Cytarabine
Treatment Groups	Revlimid® is used as monotherapy, or in combination with ADE chemotherapy (Daunorubicin; Etoposide; Cytarabine).
Target number of patients	39
Final number patients recruited	14



Signed electronically by Prof David Bowen on 06th May 2014

2. Trial Design

Patients with high risk myelodysplasia (HR-MDS) and acute myeloid leukaemia (AML) with chromosomal changes involving deletion of the long arm of chromosome 5 (del 5q), especially with a complex karyotype, rarely have a durable response to combination chemotherapy. In the subgroup with monosomal karyotype there are no long term survivors. Recent experience indicates that the incidence of del5q in AML is 20–30%, with only 20–25% of patients achieving complete remission (CR). Additionally, therapy has significant toxicity, with induction death rates 20% even in younger patients. This lack of efficacy provides the clinical rationale for combination/sequential therapy with Lenalidomide and combination chemotherapy. Dose dependent haematological toxicity is the major safety concern with such a combination protocol. Therefore we conducted a phase 2 study to assess safety, tolerability and efficacy of lenalidomide monotherapy, followed by lenalidomide with intensive chemotherapy in patients with primary/relapsed/refractory high-risk MDS or AML with abnormalities of chromosome 5.

Figure 1 and Figure 2 (Appendix 1) display the AML Len5 flow diagrams.

Patients with ≥5% blasts at entry who achieve complete remission were scheduled to receive at least two courses of the combination of lenalidomide plus intensive intravenous chemotherapy. Complete remission may have been achieved with monotherapy but two combination courses were scheduled to be administered as consolidation. Patients with <5% blasts at entry were scheduled to receive only monotherapy with lenalidomide, except if progression to ≥5% blasts was documented on study.

Following remission induction and consolidation, patients with a donor and considered suitable for allogeneic stem cell transplantation were scheduled to be recommended to proceed to allografting. Patients unfit for or ineligible for allogeneic stem cell transplant were scheduled to be offered maintenance therapy with lenalidomide for a maximum of 12 months following the end of chemotherapy.

An early death rate of more than 30%, or less than 40% of patients recovering their platelets and surviving by 42 days after the combination chemotherapy, will be classed as unacceptable safety and tolerability. This is based on observed early death rates of 5-26% in previous trials. These values are absolute cut-offs and we do not specify upper and lower acceptable values, i.e. we will consider this treatment safe and acceptable only if the early death rate is not above 30% and the platelet recovery proportion (with patient surviving) is not below 40%.

If the treatment is found to be safe and acceptable the complete remission rate will be assessed, and this has been used to determine the sample size for the study, and will be used to decide whether or not to proceed to a phase III trial. The maximum unacceptable complete remission rate has been set as 40%, and the minimum acceptable complete remission rate as 60%. This is based on observed complete remission rates of approximately 40% in previous Medical Research Council AML trials and that it was felt that a clinically relevant improvement would be to 60%. In the case that the true complete remission rate lies between these two values, the decision to proceed to a phase III trial will be based on the observed complete remission rate and the overall toxicity. We have therefore based the sample size on a three outcome design proposed by Sargent et al, which incorporates the possibility that the phase II trial will be inconclusive based on the observed complete remission rate. We must define the following parameters: α – the probability that we will definitely proceeded to phase III when in fact the complete remission rate is ≤0.40; β – the probability that we will definitely not proceeded to phase III when in fact the complete remission rate is ≥0.60; η – the minimum probability that we will correctly not proceeded to phase III when the complete remission rate is ≤0.40; and π – the minimum probability that we will correctly proceeded to phase III when the complete remission rate is ≥0.60. Setting α=0.05 (type I error), β=0.20 (type II error), η=0.80 and π=0.70, 39 patients are required.

If, after 39 patients have been recruited, we see 19 or fewer complete remissions we will conclude not to continue to phase III, however a larger phase II or phase II/III trial may be warranted. If we see 22 or more complete remissions we will conclude to proceed to a phase III. However if we see 20 or 21 complete remissions, we will state that the efficacy endpoint is inconclusive and base our decision to move to phase III on the observed complete remission rate and overall toxicity.

A number of stopping rules were put in place to ensure the trial is stopped as early as possible in the case of unacceptable safety and tolerability from lenalidomide therapy alone or in combination.

3. Trial Objectives

Primary Objective

To assess safety, tolerability and efficacy of the combination of oral Lenalidomide administered as a single agent and simultaneously with induction chemotherapy using Cytosine Arabinoside, Daunorubicin +/- Etoposide (ADE) for patients with AML/MDS and chromosome 5 cytogenetic abnormalities.

Secondary Exploratory Objectives

To look at response rates, recovery of neutrophils and platelets, blood product usage, length of time spent in hospital, time on antibiotics, the proportion of patients proceeding to allograft/DLI/maintenance therapy, survival, relapse-free survival, AML transformation of MDS and haematological improvement in patients with MDS.

4. Population

Patients with the following characteristics were eligible for the study:

Inclusion Criteria

1) Patients diagnosed with primary/relapsed/refractory AML (as defined by WHO) or high risk MDS (defined as IPSS INT-2/High) with chromosome 5 cytogenetic abnormalities
2) Aged at least 18 years old
3) Considered suitable for intensive chemotherapy
4) The subject is capable of understanding and complying with protocol requirements
5) The subject signs a written, informed consent form prior to the initiation of any study procedures
6) Females of child bearing potential must have a negative pregnancy test 14 days prior to start of lenalidomide treatment and agree to participate and follow the Celgene approved process for Lenalidomide risk management and pregnancy prevention
7) Males must participate and follow the Celgene approved process for Lenalidomide risk management and pregnancy prevention

Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1) Use of prior investigational agents within 4 weeks prior to consent
2) The subject has received lenalidomide in a previous clinical study or as a therapeutic agent
3) The subject has a history or clinical manifestations of HIV, Hepatitis B or Hepatitis C
4) The subject has a history of hypersensitivity or allergies to lactose
5) If female, the subject is pregnant or lactating
6) The subject has another active malignancy
7) The subject has other severe concurrent disease or mental illness
8) Eastern Cooperative Oncology Group (ECOG) performance status greater than 2 (Appendix 2)
9) Myocardial dysfunction (as defined by left ventricular ejection fraction <50%)
10) Creatinine clearance (Cockroft-Gault) <60 mls / min
11) ALT/AST >3 x ULN

5. Treatment

All subjects received an initial cycle of lenalidomide monotherapy 10mg daily on days 1-21 of a 28-day cycle. Subjects who presented with High Risk-MDS (<5% blasts) and had no blast excess at day 28 and who also achieved haematopoietic recovery, received further 28 day cycles of lenalidomide monotherapy 10mg daily on days 1-21.

After receiving 3 cycles of Lenalidomide monotherapy, subjects in remission were considered for allogeneic stem cell transplant. If transplant was not an option then subjects would continue with maintenance Lenalidomide consisting of 10mg daily on days 1-21 of a 28 day cycle for up to 12 cycles.

Subjects who presented with High Risk-MDS or AML (≥5% blasts) who at day 28 had achieved a Partial response (PR) could receive a second cycle of lenalidomide monotherapy. If Complete Response (CR) or no response then subjects progressed to combination chemotherapy with Lenalidomide administered at 10 mg once daily for 10 days concurrently with ADE (10+3+5) induction therapy which comprises: Cytarabine 100 mg/m2 twice daily by intravenous push for 10 days, Daunorubicin 50mg/m2 days 1, 3, and 5 by intravenous infusion and Etoposide 100 g/m2 daily days 1-5 by intravenous infusion. If CR/PR then consolidation was with a further course of combined lenalidomide and ADE (8+3+5), followed by a course of combined lenalidomide and high dose Cytarabine1.5 g/m2 twice daily by intravenous infusion on days 1, 3 and 5 (6 doses).

Following this subjects in remission were considered for allogeneic stem cell transplant or lenalidomide maintenance consisting of 10mg daily on days 1-21 of a 28 day cycle for up to 12 cycles.

6. Participant Flow

See Appendix 2 for the trial CONSORT diagram.

A total of 15 patients were considered for entry into the trial. One patient screened for potential enrolment into AML Len5 did not undergo registration (inclusion criteria not met). 14 patients were registered into the trial and received at least one dose of Lenalidomide monotherapy; following on from this:

- Nine went on to receive combination therapy: 2 subsequently received a transplant and seven discontinued treatment.
- One went on to receive 12 cycles of lenalidomide maintenance and continued to receive lenalidomide maintenance off-trial. Trial follow-up continued on this subject for 2 years completion of protocol lenalidomide maintenance.
- Four discontinued monotherapy.

No patients withdrew consent to the trial. All 14 subjects were included in the analysis.

7. Criteria for Evaluation

Primary Endpoints:

Early death rate Platelet recovery (>100x10^9/l) and survival 42 days from last dose of the first course of the combination chemotherapy Complete remission rate

The primary endpoint is safety and tolerability of the combination therapy, assessed by early death rate and the proportion of patients recovering their platelets and surviving 42 days post combination chemotherapy. If the treatment is found to be safe and tolerable, for BOTH of these endpoints, then the short term efficacy in terms of complete remission rate as a third primary endpoint will be considered, and we will use this to determine whether or not to proceed to a phase III trial.

Early death is defined as within 30 days of starting combination chemotherapy.

Complete remission rate is defined as complete remission rate (CR/CRi) at day 21 post the last cycle of Lenalidomide plus intensive chemotherapy and will be determined according to the protocol definition

Secondary Endpoints:

The secondary endpoints were: response rates for each cycle; neutrophil and platelet recovery (time to recovery and proportion recovering by 42 days for each cycle); blood product usage (number of blood/platelet transfusions); days in hospital; days on antibiotics; toxicity (adverse and serious adverse events); proportion of patients proceeding to allograft/DLI/maintenance therapy; survival; relapse-free survival; AML transformation of MDS; haematological improvement for each cycle in patients with MDS.

8. Statistical Methods

The cut-off date for final analysis was 11th January 2011. All data entered onto the database up to this time point were incorporated in the final analysis.

Survival, relapse-free survival and AML transformation of MDS were based on available data on 14th July 2011 and updated based on available data on 21st January 2013.

Long-term follow-up data on the one subject who remained in follow-up were updated based on data received up to 30th May 2013 (this corresponds to 2 years post completion of protocol maintenance treatment).

Unless otherwise stated, all summaries and analyses regarding the efficacy of the monotherapy were carried out using the monotherapy population. This population included all patients who received any of the study monotherapy, regardless of whether they were eligible and/or remained in the study, prematurely discontinued the treatment or did not comply with the regimen.

All summaries and analyses regarding the efficacy of the combination therapy were carried out using the combination therapy population. This population included all patients who received any of the study combination therapy, regardless of whether they were eligible and/or remained in the study, prematurely discontinued the treatment or did not comply with the regimen.

9. Results

9.1 Enrolment

Fourteen patients were recruited between August 2009 and May 2010: 4 at St James Hospital, Leeds (28.5%); 3 at Nottingham City Hospital (21.4%); 3 at Western General Hospital (21.4%); 2 at The Christie Hospital (14.2%); 1 at Aberdeen Royal Infirmary (7%) and 1 at St Bart's Hospital (7%).

9.2 Treatment

All 14 patients had been given some protocol treatment (four monotherapy; seven monotherapy and combination therapy; one monotherapy and lenalidomide maintenance; and two monotherapy, combination therapy and transplant). Neither of the transplant patients received transplant between initial diagnosis and entry into the trial. Both transplants were from an unrelated donor. The median time to starting protocol treatment was one day.

One patient received protocol lenalidomide maintenance – 12 cycles – and continued lenalidomide maintenance off-trial. This subject remains in complete cytogenetic remission and continues to receive lenalidomide therapy off-trial.

Two patients did not start the recommended number of cycles of protocol treatment and 12 had dose delays/modifications.

9.3 Effectiveness

Primary endpoint

Early death rate and platelet recovery (>100x10^9/l) and survival 42 days from last dose of the first course of the combination chemotherapy

Early death and platelet recovery and survival were assessed for the combination therapy population. The stopping rule is ≥5 early deaths (in the first 10 patients) or ≥8 not recovering platelets and surviving.

Nine patients received combination therapy so the primary endpoint data are in the table for these patients. One further patient only received a single dose of ADE but did not receive the lenalidomide as the patient was nil by mouth. The Data Monitoring and Ethics Committee (DMEC) recommended that this patient should not be considered as receiving combination therapy and should not count towards the stopping rule.

There were no early deaths (in the first nine patients) and seven patients not recovering platelets and surviving. Therefore it is clear that the stopping rule would have been activated (i.e. if the trial design was to be followed, the trial should have been stopped) if 10 patients received combination therapy and the 10th patient did not recover their platelets and survive.

Complete remission:

If the treatment was found to be safe and tolerable at stage IV (i.e. the results from the early death rate and platelet recovery and survival endpoints were deemed acceptable), then at final analysis the short term efficacy in terms of complete remission (CR/CR with incomplete haematopoietic recovery) rate would have been considered as a third primary endpoint, and this would have been used to determine whether or not to proceed to a further trial.

However, response was assessed for the nine patients in the combination therapy population. Responses were as follows:

- Complete remission (n=2)
- Complete remission with incomplete haematopoietic recovery (n=1)
- Partial response (n=1)
- No response (n=3)
- Progressive disease (n=1)
- Not evaluable – no bone marrow sample (n=1)

Three patients (33%) were therefore in complete remission (CR/CR with incomplete haematopoietic recovery) (95% CI [7, 70]).

Other secondary endpoints:

Blood product utilisation was in keeping with the recognised requirements for such patients undergoing intensive chemotherapy. During the first cycle of combination chemotherapy, patients received a median of 10 units of blood (range4–24) and 10 units of platelets (range2–29). Intravenous antibiotic usage was for a median duration of 21 days (range13–44).The median duration of hospital in-patient stay was 32 nights (range16–44).

9.4 Toxicity and Serious Adverse Events

Adverse events were frequent in this challenging cohort of patients. In total 9 SAEs were reported during combination therapy, 6 of which were suspected to be related to the therapy and included neutropenic

sepsis or thrombocytopenia. All patients experienced the anticipated haematological toxicity. Other notable toxicities included grade 3 ALT rise (22%) and venous thromboembolism (11%).

10. Conclusions

More than 20% of patients recruited with ≥5% blasts had a treatment-related death on lenalidomide monotherapy which was deemed a potentially excessive induction treatment death rate. As a result of this, recruitment was temporarily halted. A revised protocol to remove the monotherapy run-in phase for patients with ≥5% blasts at trial entry was developed.

Whilst recruitment was halted, the Trial Management Group requested the DMEC to recommend whether or not the trial should re-open to recruitment based on the data available for those patients on combination therapy. The DMEC recommended a further protocol amendment then to recommence recruitment. The recommended further protocol amendment was as follows:

- Define platelet recovery as 80-100*10^9/l rather than 100*10^9/l;
- New stopping rule: at least 50% of patients achieving CR must recover their platelets; and
- Collect further platelet recovery data on each cycle);

Following interaction between the DMEC and the TMG, a decision was taken to permanently halt recruitment rather than amend the protocol. This was because it was anticipated that recruitment, already substantially slower than was anticipated, would have slowed again due to de-motivation during the continued temporary halt which would have been required to amend the protocol.

In conclusion, lenalidomide monotherapy at a dose of 10mg daily is ineffective as induction therapy in HR-MDS/AML patients with increased marrow blasts. When lenalidomide is combined with ADE chemotherapy there is predictable and manageable toxicity, which is not clearly greater than with combination chemotherapy alone. Efficacy is limited in this particularly adverse patient cohort. Currently very few of these patients, even after allogeneic transplant, achieve long-term disease free survival such that innovative combination strategies are urgently required.

11. References

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2. Burnett AK, Milligan D, Goldstone A, Prentice A, McMullin M-F, Dennis M, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. Brisith Journal of Haematology 2009;145:318-32.
3. Wheatley K, Brookes CL, Howman AJ, Goldstone A, Milligan D, Prentice A, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. British Journal of Haematology 2009;145:598-605.

12. Publications

M Dennis, D Culligan, D Karamitros, P Vyas, P Johnson, NH Russell, J Cavenagh, A Szubert, S Hartley, J Brown and D Bowen. Lenalidomide monotherapy and in combination with cytarabine, daunorubicin and etoposide for high-risk Myelodysplasia and Acute Myeloid Leukemia with chromosome 5 abnormalities. Leukemia Research Reports. Volume 2, Issue 2, 2013, Pages 70–74

Appendix 1. Study Flow Diagram

Figure 1: High-risk MDS with <5% blasts and chromosome 5 abnormality

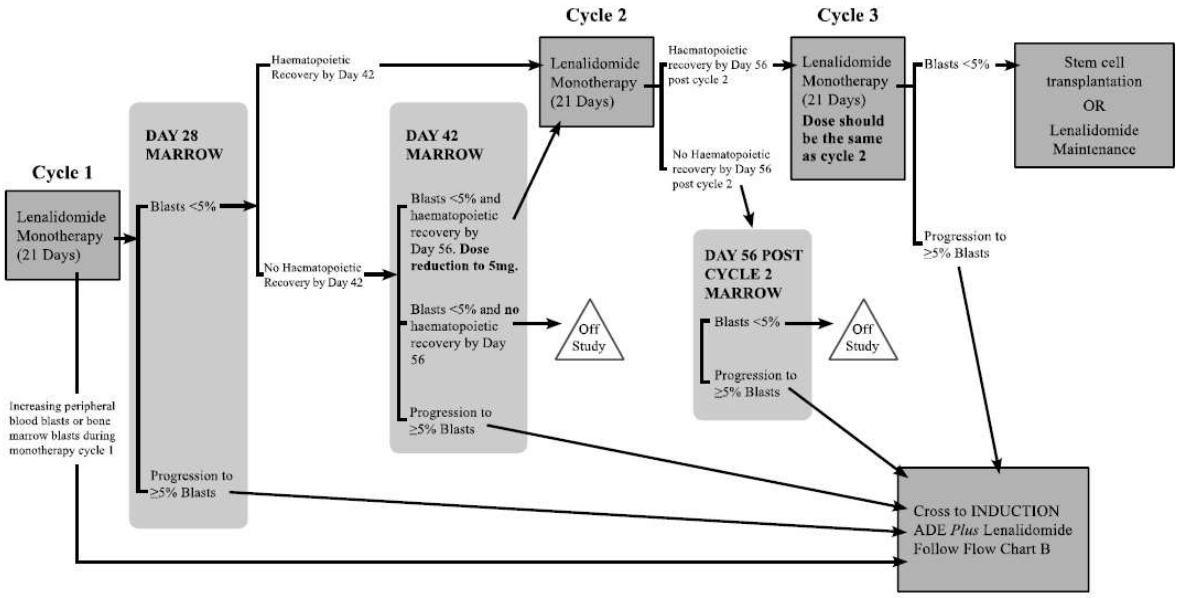
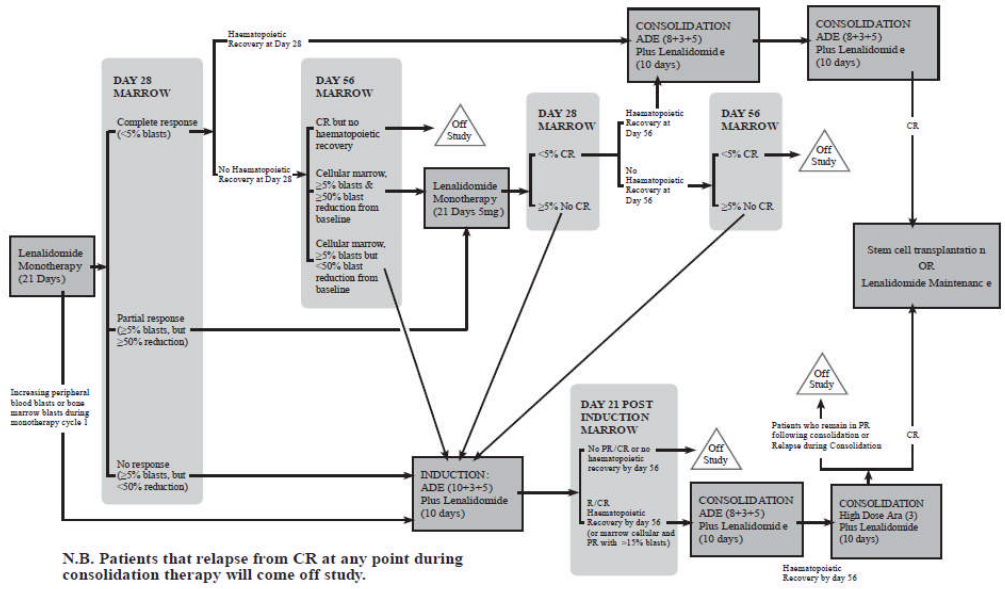
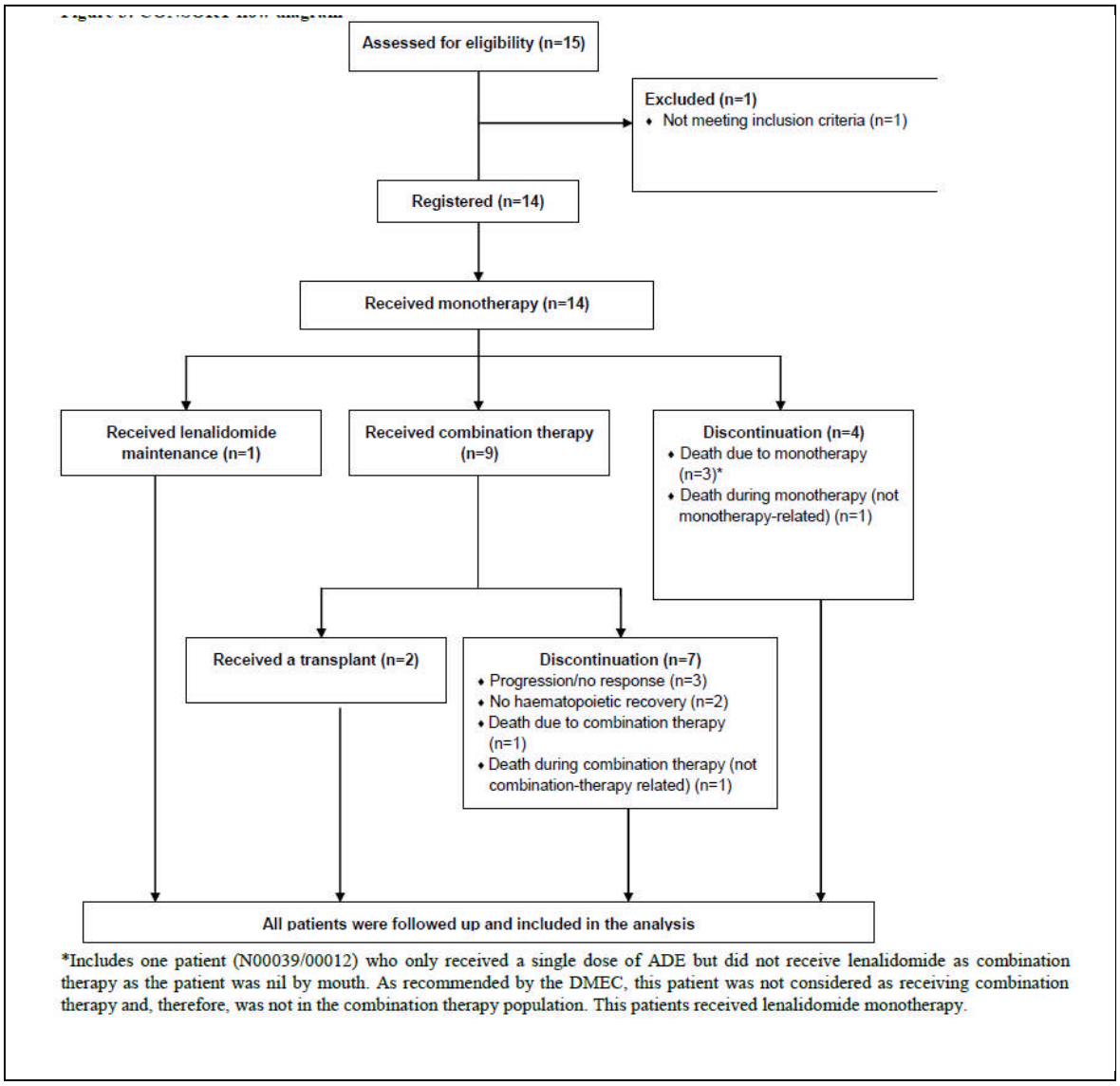


Figure 2: High-risk MDS with ≥ 5% blasts or AML with chromosome 5 abnormality



Appendix 2: CONSORT Diagram



*Includes one patient (N00039/00012) who only received a single dose of ADE but did not receive lenalidomide as combination therapy as the patient was nil by mouth. As recommended by the DMEC, this patient was not considered as receiving combination therapy and, therefore, was not in the combination therapy population. This patients received lenalidomide monotherapy.