End of Clinical Trial Report

CMML201: A phase 2 study of azacitidine in chronic myelomonocytic leukaemia (CMML)

1. Trial Summary

EudraCT	2008-006349-23
ISRCTN	ISRCTN21428905
Sponsor No.	HM08/8540
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	Debbie Sherratt, Senior Trial Manager, Clinical Trials Research Unit, University of Leeds, Leeds, LS2 9JT
CTA Approval	15/09/2009
Main REC Approval	28/04/2009
Final protocol version and date	Version 6.0, 15th April 2013
Phase of study	II
Investigational Medicinal Products (IMPs)	Azacitidine
Treatment Groups	All patients received Azacitidine
Target number of patients	30
Final number patients recruited	32, 30 treated with IMP
Report Date	25/03/2015

Signed:  Date: 18-MAY-2015

2. Trial Design

This trial is a two stage phase II, non randomised, single arm, multi-centre, prospective trial based on a Bryant and Day design (1), to assess the safety, tolerability and efficacy of azacitidine in patients with CMML. A randomisation versus a standard treatment group has not been included for this early phase II trial designed to make an initial assessment of safety, tolerability and efficacy. This trial is designed with safety and tolerability, and efficacy as joint primary endpoints.

All patients receive treatment with at least 6 courses of azacitidine. Responders may continue treatment until loss of response / disease progression.

A two stage design to incorporate a stopping rule after each stage to prevent recruitment continuing if the treatment is not felt to be acceptable at these times. The stopping rule to be applied after 12 patients have each received 6 courses of azacitidine. The trial would be stopped either if the safety and tolerability is unacceptably low (if 5 or more patients experience unacceptable toxicity) or the efficacy is unacceptably low (zero patients respond).

The primary efficacy objective of the study is to determine overall response rate after 6 courses of azacitidine. It is felt that if this success rate is below 5% the treatment would be rejected, and if this success rate is above 25% the treatment should be accepted. This is based on observed overall response rates of 1/9 patients (11%) and 2/10 (20%) in previous trials (2) and that it is felt that an overall response rate of 25% would be sufficient to develop a randomised phase III trial.

The primary safety and tolerability objective to determine the proportion of patients who suffer an unacceptable level of toxicity. It is felt that if less than 60% of patients do not suffer an unacceptable toxicity (more than 40% suffer toxicity) then the treatment would be rejected, and if at least 80% of patients do not suffer an unacceptable toxicity (less than 20% suffer some toxicity) then the treatment should be accepted. A maximum tolerated dose is often defined as the dose at or below the level which one-third of patients experience toxicity; and these figures correspond to this definition.

The significance level for both the efficacy and toxicity endpoints was chosen to be 15%. This is the bound of probability of recommending a treatment with either inadequate efficacy or unacceptable safety and tolerability. If the significance levels were chosen to be lower then the total number of patients who could be recruited into the study would be greater and it is felt that this may not be possible to achieve in a moderate time. With 85% power for both, the efficacy and toxicity endpoints, a total of 30 patients could be recruited into the study; with the stage I stopping rules assessed after the first 12 patients have available primary endpoint data.

Although the sample size and stopping rules are based on the two-stage approach, recruitment is continuous between the two stages for practical reasons. The DMEC can request to stop the study in accordance with the stopping rules or suspend recruitment if they deem it necessary while awaiting the results from stage I. The safety and tolerability endpoint will be reviewed on a continuous basis. To inform the decision of whether or not to suspend recruitment, overall response rates at day 28 of the third cycle will be presented to the DMEC as early indications of response.

3. Trial Objectives

Primary Objective

- To assess the safety and tolerability of azacitidine
- To assess the overall response rate

Secondary Exploratory Objectives

To assess response of disease to azacitidine, specifically:

- Incidence of CR/PR
- Haematological improvement
- Overall survival
- Progression-free survival
- Time to AML transformation of CMML
- Time to death or AML transformation of CMML
- Biological correlates

4. Population

Patients with newly diagnosed or previously treated CMML-1 or CMML-2 according to WHO criteria (2008) with the following characteristics were eligible for this study:

1. All **CMML-2** patients are eligible.
2. For patients classified as **CMML-1**, the following must be present:
   - Symptomatic bone marrow failure / myeloproliferation defined as any of the following:
     - Red cell transfusion dependence and pre-transfusion Hb <9.0
     - Symptomatic anaemia (Hb <11.5g/dl)
     - Thrombocytopenia <50 x 10^9/l
     - Symptomatic bleeding due to platelet functional defect or DIC/fibrinolysis
     - WCC > 50 x 10^9/l

   AND/OR

   - Düsseldorf Score intermediate or high (Appendix 4) for proliferative CMML-1 (i.e. WCC > 12 x 10^9/L)
   - IPSS Score of Int-2 or High Risk (Appendix 5) for non-proliferative CMML-1 (i.e. WCC <12 x 10^9/L)

   AND/OR

   - Systemic symptoms including weight loss with no alternative explanation (10% of baseline weight within previous 6 months)
   - Symptomatic splenomegaly
   - Symptomatic extramedullary involvement e.g. skin infiltration, serous effusions

3. Age ≥18 years
4. WHO performance status of ≤ 2 at study entry

5. Treatment

Patients were treated with 75mg/m^2 dose of azacitidine given on days 1-5 and 8&9 of a 28 day cycle by subcutaneous injection, with a 50% dose reduction for toxicity.

Batch numbers of the Azacitidine are:

13F0309, 11F0007, 10F0257, 10F0017, 09F0540

Patients received between 1 and 47 cycles of treatment (to Sept 14). Treatment was given until loss of response or progressive disease unless discontinued from treatment for other reasons such as toxicity.

One patient remains on trial treatment at the End of Trial Notification and has moved to compassionate use drug supplied free of charge by Celgene.

6. Participant Flow

Participants were recruited from 13 of 15 centres open to the trial:

St James University Hospital Leeds; Prof David Bowen

Castle Hill Hospital, Hull; Dr Chris Carter

St Bartholomews Hospital, London; Dr Jamie Cavenagh

The Royal Hallamshire Hospital, Sheffield; Dr Nick Morley

The Beatson Oncology Centre, Glasgow; Dr Mark Drummond

Freeman Hospital, Newcastle; Dr Gail Jones

University Hospital of Wales, Cardiff; Dr Jonathan Kell

Royal Bournemouth Hospital, Bournemouth; Dr Joseph Chacko

The Christie Hospital, Manchester; Dr Mike Dennis

Kent & Canterbury Hospital, Kent; Dr Chris Pocock

John Radcliffe Hospital, Oxford; Dr Paresh Vyas

Bradford Royal Infirmary, Bradford; Dr Sam Ackroyd

Worcestershire Royal Hospital, Worcester; Dr Juliet Mills

Bristol Haematology & Oncology Centre, Bristol; Dr Priyanka Mehta

Royal Free Hospital, London; Dr Panagiotis Kottaridis

Thirty two patients were registered to the trial in the nine months of the recruitment phase. Thirty went on to treatment. Two did not go on to treatment due worsening disease that did not meet the inclusion criteria at day 1 of treatment. All patients were followed up until death or until September 2014, the end date of the trial.

One patient withdrew consent at cycle 1. Thirty patients data were included in the analysis.

7. Statistical Methods

Overall Response Rate (ORR) was defined (by central review) as the sum of clinical remission, good response and minor response determined according to Wattel *et al.* (3) at day 28 of the sixth or last cycle of AZA

(whichever occurred first). These response criteria incorporate assessment of proliferative disease, including leukocytosis, extramedullary involvement and spleen size. Patients who received <1 cycle were not considered evaluable. OS, PFS, time to acute myelogenous leukemia (AML) transformation and death, and duration of response were based on available data on 21st January 2013.

The number and proportion of patients in response was summarised with the corresponding exact 95% confidence interval.

Overall survival was defined as the time from registration to the trial to death from any cause or last follow-up. Patients still alive at the time of analysis were treated as censored. Patients discontinuing protocol treatment or receiving non-protocol treatment were still followed for overall survival. Survival was summarised by a Kaplan-Meier survival curve and median survival time.

The causes of death in all patients were tabulated and the proportions of patients with each principal cause were calculated (with number of deaths as the denominator).

Time to AML transformation of CMML and time to death or AML transformation of CMML were calculated and summarised by Kaplan-Meier survival curves and median survival times.

Analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

8. Results

Consort flow diagram is given in figure 1. Fourteen patients stopped AZA between registration and the sixth or last course (whichever was the earliest) table 1 and 2; 24 had dose delays and/or modifications. Median number of cycles was seven. One patient had a grade 3/4 non-haematological adverse reaction (respiratory tract infection) during the first six cycles. No AZA-related deaths were reported during or beyond this time. Two patients (7%) discontinued AZA because of toxicity in the first six cycles (one after cycle 1 and one after cycle 6 of treatment). Overall non-haematological toxicity was manageable (predominantly Grade 1 or 2), and haematological toxicity was similar to or less than previous AZA studies.

ORR was 43% (95%CI (25.5, 62.6%). Responses are shown in table 3, the majority of response was in the minor response category. Twenty patients were red cell and/or platelet transfusion dependent at trial entry; six became transfusion independent during treatment (30%). Transfused units of red cells fell from a mean of 3 per patient (s.d. 3.6, n=29, 1 missing) during the first cycle to a mean of 1.1 (s.d. 1.6, n=20, 1 missing) by cycle 6. Median duration of response for those patients included in the ORR (n=13) was 7.5 months (range 2–32, 2 missing). Univariate landmark analysis of responders vs non-responders showed no difference in survival (log-rank test, P=0.7). Median survival was 16 months from registration (95% confidence interval (10, not reached)), figure 2. Time to AML transformation is summarised in figure 3 and time to AML transformation or death is summarised in figure 4.

A number of parameters were considered for their predictive value for response. These included mutation status, CMML-1 vs CMML-2, presence of cutaneous lesions, karyotypic abnormalities and methylation status. Small numbers in these groups precluded meaningful statistical analyses and no conclusions could be drawn.

Of eight patients in whom follow-up samples were available, seven had a reduction in DNA methylation levels after 6 months of treatment, and on average, the proportion of methylated CGs fell (from 53.1 to 50.9%, P=0.02, data not shown). Similar trends were observed when data for individual CGs were visualized as heat maps by hierarchical clustering. There was no relationship between the clinical response or TET2 mutations and the reduction in methylation.

Figure 1: CONSORT flow diagram

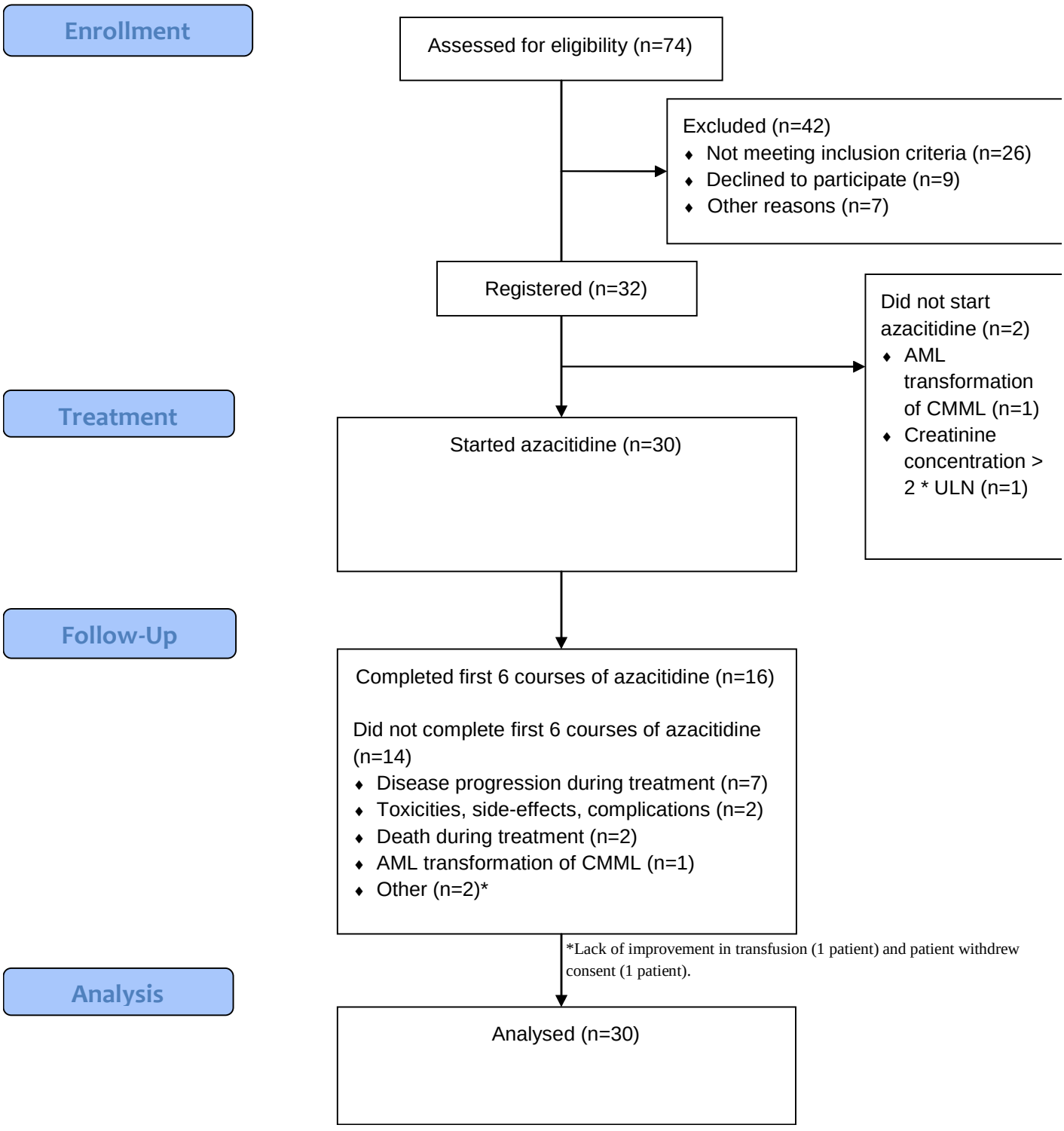

Figure 2: overall survival: Kaplan-Meier survival curve

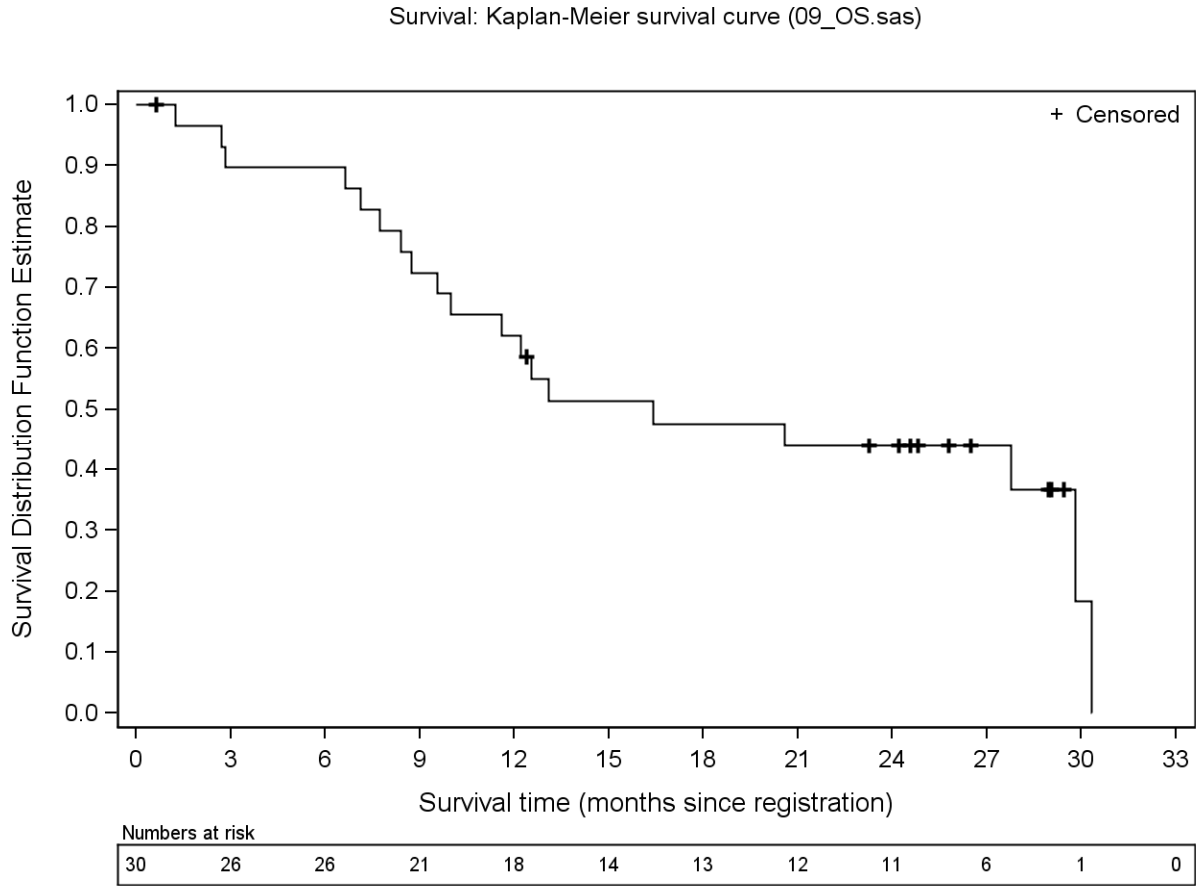

Figure 3: time to AML transformation of CMML: Kaplan-Meier survival curve

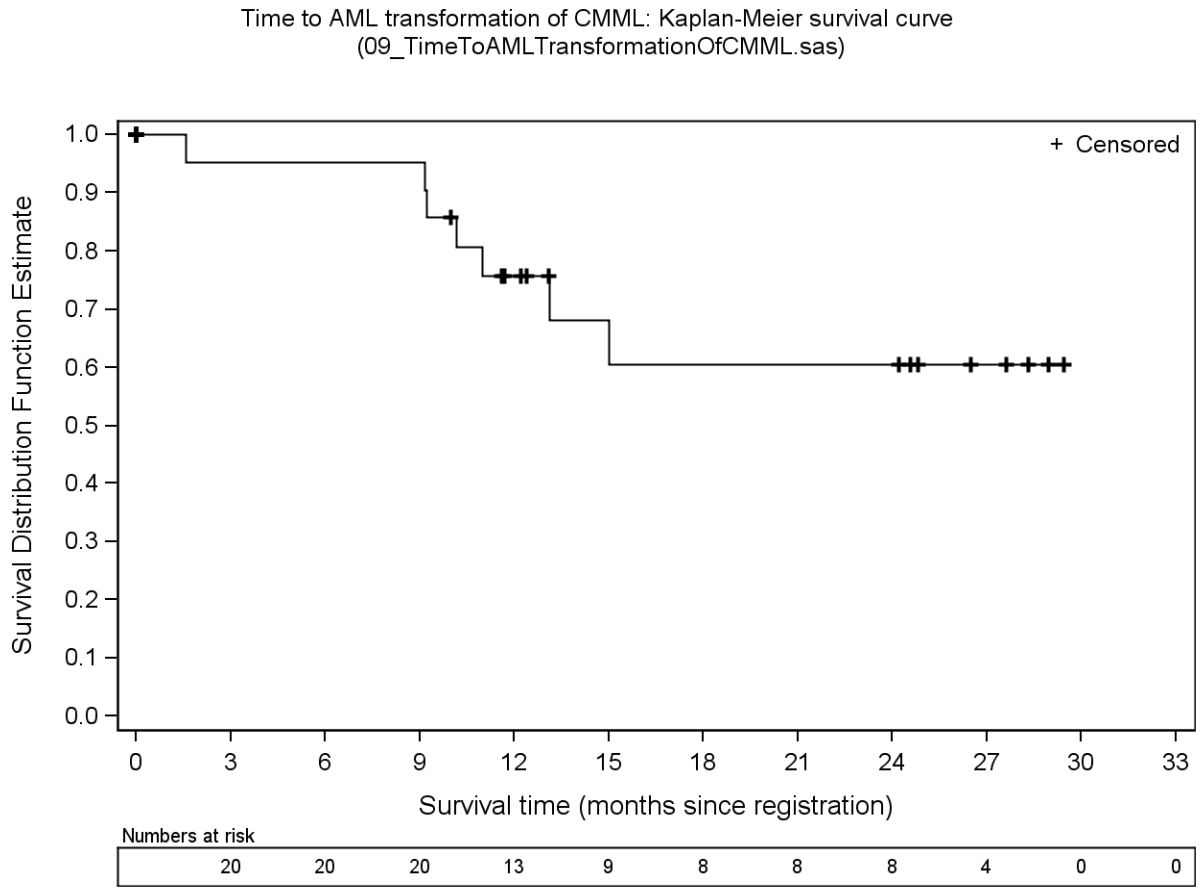

Figure 4: time to death or AML transformation of CMML: Kaplan-Meier survival curve

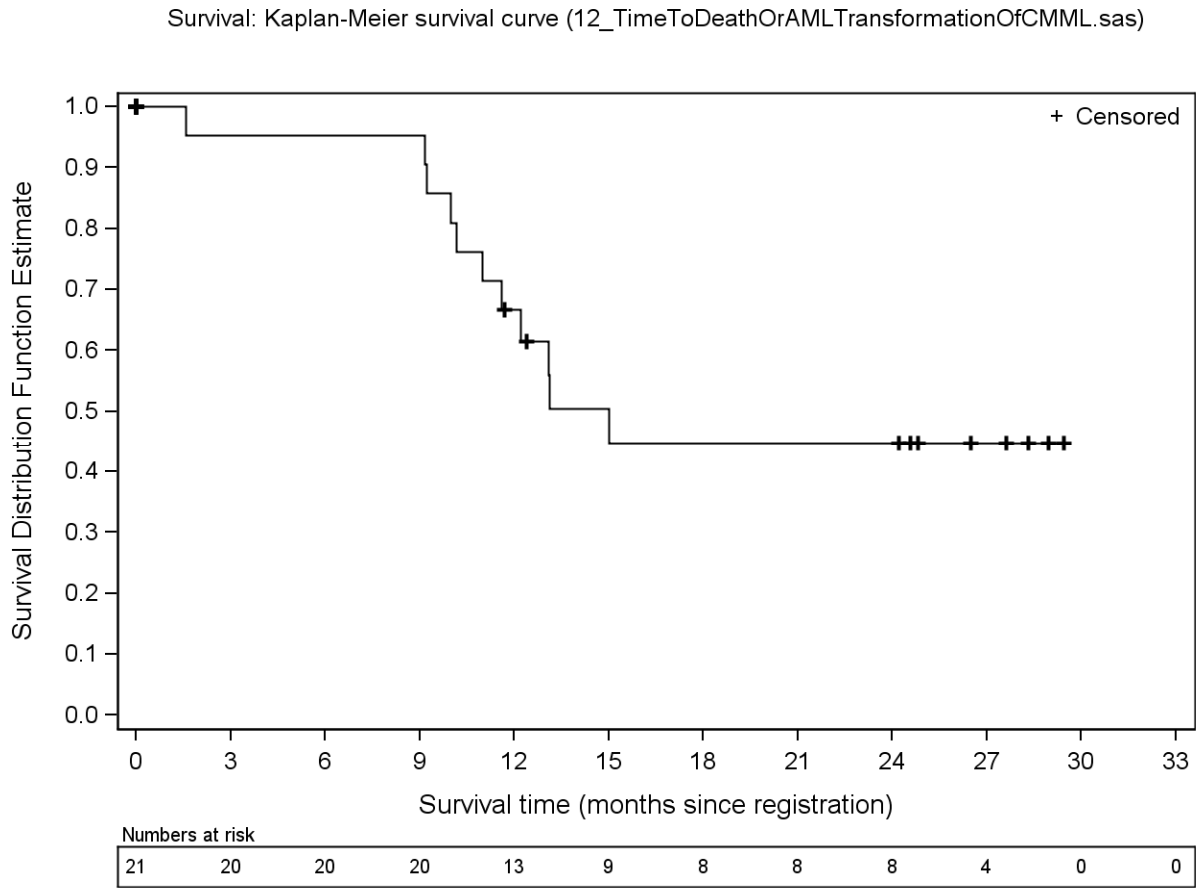

Table 1: number of cycles of treatment received, reasons for stopping treatment and dose delays/modifications *(05_ComplianceWithTreatment_.sas)*

	Total (n=30)
Number of cycles of treatment received	
1	4 (13.3%)
2	1 (3.3%)
3	2 (6.7%)
4	2 (6.7%)
5	0 (0.0%)
6	5 (16.7%)
Continuing treatment beyond course 6	16 (53.3%)
Reason for stopping azacitidine	
Toxicities, side-effects, complications	2 (6.7%)
Disease progression during treatment	7 (23.3%)
Death during treatment	2 (6.7%)
AML transformation of CMML	1 (3.3%)
Other*	2 (6.7%)
Continuing treatment beyond course 6	16 (53.3%)
Dose delays/modifications?	
Yes	24 (80.0%)
No	6 (20.0%)
Dose delays/modifications (excluding due to bank holidays and other logistical issues)?	
Yes	16 (53.3%)
No	14 (46.7%)

*Lack of improvement in transfusion (1 patient) and patient withdrew consent (1 patient).

Table 2: reasons for stopping treatment by number of cycles of treatment received *(05_ComplianceWithTreatment_.sas)*

	1 (n=4)	2 (n=1)	3 (n=2)	4 (n=2)	6 (n=5)	Continuing treatment beyond course 6 (n=16)	Total (n=30)
Reason for stopping azacitidine							
Toxicities, side-effects, complications	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	2 (6.7%)
Disease progression during treatment	0 (0.0%)	1 (100.0%)	2 (100.0%)	2 (100.0%)	2 (40.0%)	0 (0.0%)	7 (23.3%)
Death during treatment	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	2 (6.7%)
AML transformation of CMML	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Other	1 (25.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)**	0 (0.0%)	2 (6.7%)
Continuing treatment beyond course 6	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (100.0%)	16 (53.3%)

*Patient withdrew consent.

**Lack of improvement in transfusion.

Table 3: overall response rate (Wattel): response at day 28 of the 6th or last cycle of azacitidine (whichever was the earliest)

	Total (n=30)
Response using Wattel et al.	
Clinical remission	1 (3.3%)
Good Response	2 (6.7%)
Minor Response	10 (33.3%)
Stable Disease	2 (6.7%)
Progression	11 (36.7%)
Died before day 28 of the last cycle of azacitidine (1 cycle)*	1 (3.3%)*
Died before day 28 of the last cycle of azacitidine (2-6 cycle)	1 (3.3%)
Not evaluable (less than 1 cycle)	2 (6.7%)

*Patient received less than 1 cycle and died during treatment.

9. Conclusions

In this phase 2 study of AZA in CMML we have demonstrated good tolerability, but only modest response rates. The adverse event profile in our study compared very favourably with that described in MDS studies (Grade 3/4 anaemia, neutropenia and thrombocytopenia in 20, 30 and 33% as compared with 57, 91 and 85%, respectively, in the AZA001 trial). The lower incidence of neutropenia in particular may well relate to the frequent leukocytosis associated with CMML.

Definition of response in CMML is difficult because of the coexistence, often in the same patient, of both cytopenias and proliferative features. ORR rate in this study by the criteria of Wattel *et al.* was 43%. Most responses (10/13) were however minor by these criteria, predominantly a reduction in WCC by >50%. Although AZA clearly demonstrated cytoreductive ability, how clinically meaningful (or cost-effective) such responses are is debatable, as no improvement in marrow parameters were observed in this subgroup, and similar responses may have arguably been achieved by using alternative cytoreductive agents. Responses also appeared less durable than that in previous MDS studies with a median response duration of 7.5 months (as compared with 13.6 months in the AZA001 study). By IWG criteria, our ORR was 20%, with the incidence of CR/marrow CR 17% (as compared with 29% in the AZA001 study of all MDS subtypes). These results also compare less well with a phase 2 study of decitabine in CMML, which demonstrated a CR/marrow CR rate of 31% and ORR of 38%.Overall, a median of seven cycles of AZA were delivered, less than the nine cycles delivered in AZA001, but comparable to single-centre series. Our outcomes with AZA in this prospective, multi-centre setting are also inferior to those reported in retrospective series of CMML. A partial explanation for this may relate to the incorporation of higher numbers of poor-risk patients, as only CMML-2 or CMML-1 patients with symptomatic or significant marrow failure or myeloproliferative disease were included. A majority (57%) failed therapy or exhibited progressive disease: of 14 (47%) patients completing six or less cycles, 8 stopped due to disease progression or transformation to AML. More encouragingly, 15 of 16 patients who were classified as responding or as stable disease continued therapy beyond cycle 6. Of note are the four patients maintaining response and continuing therapy for 18 cycles or more.

Modest decreases in global levels of DNA methylation were observed although these did not correlate with clinical responses, as observed in other correlative studies of AZA and CG methylation.

In summary, despite AZA being licensed for non-proliferative CMML-2, our study demonstrated only modest response rates for a wider CMML population. Given these findings, we would caution against use of AZA as 'standard of care' in this relatively rare and difficult disorder, but would encourage further clinical trials given evidence of good efficacy in a small number of patients.

10. References

1. Bryant J, Day R. Incorporating Toxicity Considerations Into the Design of Two-Stage Phase II Clinical Trials. Biometrics 1995 Dec;51(4):1372-83.
2. Kaminskas E, Farrell A, Abraham S, Baird A, Hsieh L, Lee S, et al. Approval Summary: Azacitidine for Treatment of Myelodysplastic Syndrome Subtypes. Clinical Cancer Research 2005 May;11(10):3604-8
3. Wattel E, Guerci A, Hecquet B, Economopoulos T, Copplestone A, Mahe B, et al. A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Francais des Myelodysplasies and European CMML Group. Blood 1996 Oct 1;88(7):2480-7

11. Publications

MW Drummond, C Pocock, M Boissinot, J Mills, J Brown, P Cauchy, NCP Cross, S Hartley, J Kell, A Szubert, PN Cockerill, DT Bowen. A multi-centre phase 2 study of azacitidine in chronic myelomonocytic leukaemia. *Leukaemia* (2014) 28, 1570-1572; doi:10.1038/leu.0214.85