Azacitidine with or without lenalidomide in higher risk myelodysplastic syndrome & low blast acute myeloid leukemia

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ALLG MDS4 SUPPLEMENTARY MATERIALS

Protocol Eligibility Criteria:

Inclusion criteria

All of the following criteria must be satisfied for enrolment in the study.

1. Disease diagnosis of either MDS or low marrow blast count AML or non-proliferative CMML as defined below:

A. MDS – as defined by WHO 2008 classification- See Appendix 1 (either primary or treatment related).

If RCUD or RARS, additional evidence of at least one clinically relevant cytopenia is required, to exclude low risk patients not requiring treatment:

• Transfusion dependent or symptomatic (Hb<100g/L) anaemia at least 3 months OR

• Clinically significant thrombocytopenia (either significant bleeding or platelet transfusion dependency) or thrombocytopenia with at least two counts ≤50x10^9/L at least one month apart OR

• Significant neutropenia with absolute neutrophil count (ANC) ≤1.0x10^9/L on at least two occasions 1 month apart or recurrent or severe infections requiring hospital admission

B. Low marrow blast count AML, fulfilling all the following criteria:

a. Bone marrow (BM) blast count 20-30% AND

b. Unequivocal morphologic or flow cytometric dysplastic changes on BM and/or peripheral blood (PB) AND

c. Absence of 'pure leukaemic' cytogenetics (ie t(8;21), t(15;17) or inv(16)) AND

d. Kinetically slow disease not requiring hydroxyurea or cytoreductive therapy in 4 weeks prior to enrolment AND

e. No previous history of high blast count process (PB blasts >30x10^9/L or BM blasts >80%)

C. Non-proliferative CMML

a. CMML as defined by WHO classification (See Appendix 1), with peripheral WBC <30x10^9/L

b. No hydroxyurea treatment in the 2 weeks prior to enrolment

2. Has provided written informed consent

3. Life expectancy at least 3 months

4. Available for follow-up for 2 years

5. Ability to comply with the contraceptive and other requirements of the Lenalidomide Risk Management Plan

6. Men and females of childbearing potential (FCBP)xxiii must use effective contraception during and up to 3 months after AZA treatment.

7. Adequate renal and hepatic function at Screening as defined by:

• Total bilirubin <1.5 x ULN (higher levels may be acceptable if attributed to active haemolysis or ineffective erythropoiesis)

• Alanine aminotransferase (ALT) ≤2 x ULN (higher levels may be acceptable if attributed to transfusion associated hepatic iron overload)

• Calculated creatinine clearance > 50ml/min

8. An Eastern Co-operative Oncology Group (ECOG) performance status score of 2 or less at Screening

9. Subjects must agree not to donate blood, semen or sperm while on study treatment and for 28 days after treatment discontinuation

10. Subjects must agree not to share their medication and return unused supplies

Exclusion criteria

Presence of any of the following criteria will exclude the subject from enrolment in the study.

1. Subjects aged less than 18 years at Screening
2. Women who are pregnant or lactating. FCBP must have a negative pregnancy test prior to start of study therapy.
3. Prior treatment with chemotherapy (including stem cell transplantation) for MDS or AML, and except for low dose cytarabine and hydroxyurea
4. Any prior treatment with a demethylating agent (including azacitidine or decitabine) or IMiD (including thalidomide or lenalidomide)
5. Prior diagnosis of cancer that was:

• more than 5 years prior to current diagnosis with subsequent evidence of disease recurrence orestimated clinical expectation of recurrence is greater than 10% within next 2 years

• within 5 years of current diagnosis with the exception of successfully treated basal cell or squamous cell skin carcinoma, carcinoma in situ of the cervix or localised cancer treated curatively with local therapy only

6. Known or suspected hypersensitivity to 5-azacitidine, mannitol or lenalidomide
7. Hepatic tumour or advanced liver disease
8. Significant cardiac or respiratory disease
9. Known active viral infection with human immunodeficiency virus (HIV) or viral hepatitis B
10. Severe active infection
11. Participation in other therapeutic studies in the last 30 days except for studies with a non-medical intervention. Documented evidence of receiving placebo will be required.
12. Has any other clinically important abnormalities as determined by the investigator that may interfere with his or her participation in or compliance with the study
13. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. This condition must be discussed with thepatient prior to signing consent and registration in the trial.

Protocol Treatment plan

Patients will be randomised after registration to the 5azacitidine alone arm (AZA) or 5azacitidine + lenalidomide (AZA+LEN) combination arm

Patients will be stratified by IPSS (low-int1 or int2-high), by centre and by disease diagnosis category (MDS, AML or CMML)

All treatment is intended to be given on an outpatient, day case basis.

AZA arm: AZA 75mg/m2/d subcutaneously for 7 days. The 7 doses will be given as an 'interrupted regimen' over 9 days (as 5-2-2 regimen – 5 days treatment from Monday to Friday, 2 days break from treatment

Saturday and Sunday then 2 days further treatment Monday and Tuesday). The cycle interval is intended to be every 28 days, but may be delayed for toxicity as per guidelines Treatment will continue until after completion of the current cycle at the timepoint 12 months from commencement of study treatment (C1D1).

AZA+LEN arm: The first 2 cycles will consist of AZA alone and will be administered exactly the same in both arms – so C1 and C2 AZA 75mg/m2/d subcutaneously for 7 days given as

an ‘interrupted regimen’ over 9 days (as 5-2-2 regimen – 5 days treatment from Monday to Friday, 2 days break from treatment Saturday and Sunday then 2 days further treatment Monday and Tuesday). The cycle interval is intended to be every 28 days, but may be delayed for toxicity as per guidelines (see section 11.4). From C3 onwards, AZA will be reduced to 5 days, and LEN commenced: AZA 75mg/m2/d subcutaneously for 5 consecutive days treatment from Monday to Friday and planned every 28 days but may be delayed for toxicity until completed 12 months treatment in total, and completion of the current cycle at that point, AND LEN (delay commencement of LEN until after first 2 cycles AZA completed to avoid early excess myelotoxicity; therefore commence LEN at C3D1 AZA) 10mg/d orally for 21 consecutive days commencing D1 of each cycle of AZA from C3 onwards until completion of the cycle at the time point 12 months from commencement of study treatment.

Body surface area (BSA) for calculation of AZA dose will be calculated at screening, and only amended if there is a change in body weight >10%.

In both arms, beyond this treatment phase of 12 months (plus the additional time taken to complete the current cycle at that point), ongoing treatment with AZA alone (PBS if patient meets eligibility criteria or alternatively provided by Celgene) should be continued or those deriving benefit until disease progression or unacceptable toxicity, per investigator discretion. This ongoing standard treatment is within the follow up phase, after the primary analysis.

Supplementary Table S1: All adverse events according to system

	AZA (n=79) Grade No.				LEN+AZA (n=80) Grade No.			
Adverse Event	≤ 2	3	4	5	≤ 2	3	4	5
Blood and lymphatic system disorders	55 (70)	19 (24)	5 (6)	0 (0)	57 (71)	17 (21)	6 (8)	0 (0)
Cardiac disorders	74 (94)	5 (6)	0 (0)	0 (0)	75 (94)	3 (4)	1 (1)	1 (1)
Ear and labyrinth disorders	79 (100)	0 (0)	0 (0)	0 (0)	80 (100)	0 (0)	0 (0)	0 (0)
Eye disorders	79 (100)	0 (0)	0 (0)	0 (0)	80 (100)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	66 (84)	11 (14)	2 (3)	0 (0)	70 (88)	8 (10)	2 (2)	0 (0)
General disorders and administration site conditions	72 (91)	6 (8)	1 (1)	0 (0)	73 (91)	6 (8)	0 (0)	1 (1)
Hepatobiliary disorders	78 (99)	0 (0)	0 (0)	1 (1)	79 (99)	1 (1)	0 (0)	0 (0)
Immune system disorders	79 (100)	0 (0)	0 (0)	0 (0)	79 (99)	1 (1)	0 (0)	0 (0)
Infections and infestations	58 (73)	19 (24)	1 (1)	1 (1)	50 (62)	20 (25)	8 (10)	2 (2)
Injury, poisoning and procedural complications	77 (97)	2 (3)	0 (0)	0 (0)	79 (99)	1 (1)	0 (0)	0 (0)
Investigations	38 (48)	18 (23)	23 (29)	0 (0)	37 (46)	17 (21)	26 (32)	0 (0)
Metabolism and nutrition disorders	72 (91)	6 (8)	1 (1)	0 (0)	68 (85)	11 (14)	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	78 (99)	1 (1)	0 (0)	0 (0)	77 (96)	3 (4)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	76 (96)	1 (1)	0 (0)	2 (3)	80 (100)	0 (0)	0 (0)	0 (0)
Nervous system disorders	76 (96)	2 (3)	0 (0)	1 (1)	73 (91)	7 (9)	0 (0)	0 (0)
Psychiatric disorders	77 (97)	2 (3)	0 (0)	0 (0)	78 (98)	2 (2)	0 (0)	0 (0)
Renal and urinary disorders	78 (99)	0 (0)	0 (0)	1 (1)	73 (91)	5 (6)	2 (2)	0 (0)
Reproductive system and breast disorders	79 (100)	0 (0)	0 (0)	0 (0)	79 (99)	1 (1)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	74 (94)	3 (4)	1 (1)	1 (1)	73 (91)	5 (6)	1 (1)	1 (1)
Skin and subcutaneous tissue disorders	75 (95)	4 (5)	0 (0)	0 (0)	71 (89)	9 (11)	0 (0)	0 (0)
Surgical and medical procedures	77 (97)	1 (1)	1 (1)	0 (0)	80 (100)	0 (0)	0 (0)	0 (0)
Vascular disorders	74 (94)	5 (6)	0 (0)	0 (0)	73 (91)	6 (8)	1 (1)	0 (0)
Maximum grade any adverse event	17 (22)	32 (41)	26 (33)	4 (5)	14 (18)	28 (35)	34 (43)	4 (5)

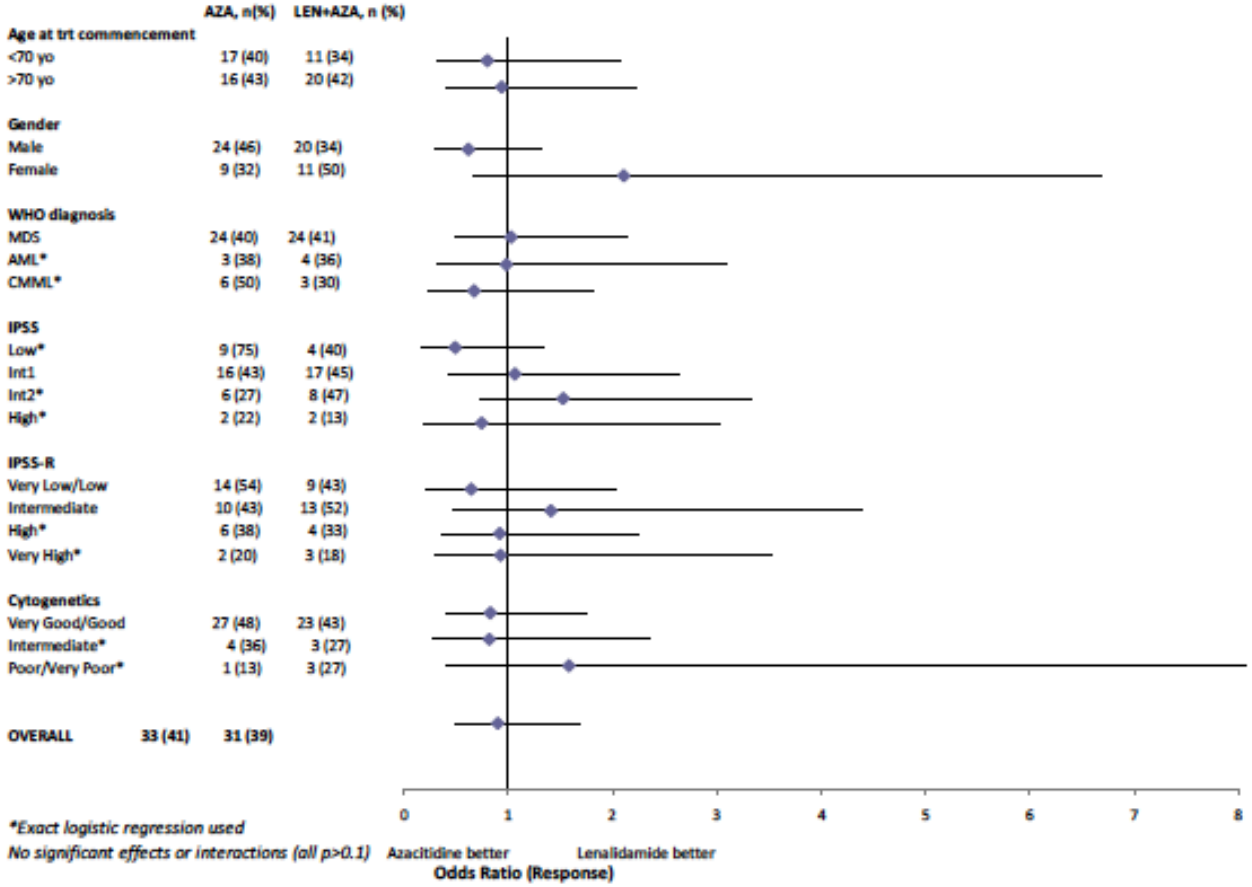
Supplementary Table S2: Cause of death by assigned treatment cohort

Cause	**AZA**	**LEN+AZA**	**Total**
Disease Progression	28	30	58
Protocol Treatment	0	1	1
Infection	7	10	17
Hemorrhage	3	2	5
Other	3	3	6
Unknown	0	3	3
Total	41	49	90

Supplementary Table S3: Treatment-Emergent Hematologic Toxicity (Grade 3 and above) by Assigned Treatment Cohort

	AZA		AZA+LEN	
	N	n (%)	N	N (%)
Emerging Hb<80g/L	70	32 (46%)	71	31 (44%)
Emerging neuts <1.0 x 10^9/L	50	34 (68%)	50	39 (78%)
Emerging plts <50 x 10^9/L	56	28 (50%)	52	33 (63%)

Supplementary Figure S1: **Subgroup analysis of treatment effect on disease response**



Supplementary Figure S2: Consort Flowchart