Abstr. # 8584

A phase I/II trial of very low to low-dose continuous azacitidine in combination with standard doses of lenalidomide and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma

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BACKGROUND

- **Azacitidine (AZA) may overcome drug resistance of relapsed or refractory multiple myeloma (RRMM).**
- **Continuous administration should maximize epigenetic effects and safety.**
- **In myeloid neoplasias, plasma CDA activity inversely correlates with aza nucleoside benefit[1].**

METHODS

Lenalidomide (len) 25mg (10mg if GFR 30-59 ml/min) d1-21 every 28d and dexamethasone (dex) 40mg weekly (len-dex) were combined with escalating doses of AZA from 30mg/m² SC weekly to 50mg/m² SC twice a week. Dose limiting toxicity (DLT) was assessed during cycle 1. IMWG uniform response criteria (partial response, PR) and adapted EBMT criteria (minor response, MR) were used[2].

Plasma activity of the AZA inactivating enzyme cytidine deaminase (CDA) was measured by HPLC at Zymo Research Corp., CA at the following time-points:

- **Screening (before treatment)**
- **Weekly during first 28 day cycle**
- **Monthly cycle 2-6**

RESULTS

Table 1. Patient baseline characteristics

Age, median (range)	62(39-88)
Gender F:M	22:18
Median prior regimens, # (range)	4 (1-10)
LEN refractory, N (%)	32 (80)
PI (BTZ +/- CFZ) refractory, N (%)	32 (80)
LEN and PI refractory, N (%)	28 (70)
High-risk CG (del17p, t[14;any other than 11], N (%)	10 (25)

Figure 1. Best responses

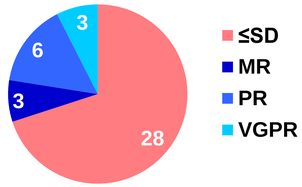

Table 2. Severe adverse events possibly related to study drug(s)

	G3 N (%)	G4 N (%)	G 3 or 4 N (%)
Neutropenia	9* (22.5)	4 (10)	13 (32.5)
Thrombocytopenia	4 (10)	1 (2.5)	5 (13)
Fatigue	3 (7.5)	-	3 (7.5)
Infection	2 (5)	-	2 (5)
Anemia	1 (2.5)	1 (2.5)	2 (5)
Pleural effusion	-	1 (2.5)	1 (2.5)
Fever	1 (2.5)	-	1 (2.5)
Atrial fibrillation	1 (2.5)	-	1 (2.5)

*: One G3 neutropenia episode was with fever and constituted the only DLT seen, in DL 4 (AZA 40mg/m² SC twice a week).

Figure 2. Plasma cytidine deaminase (CDA) activity at screening (A) and throughout study (B) inversely correlates with response

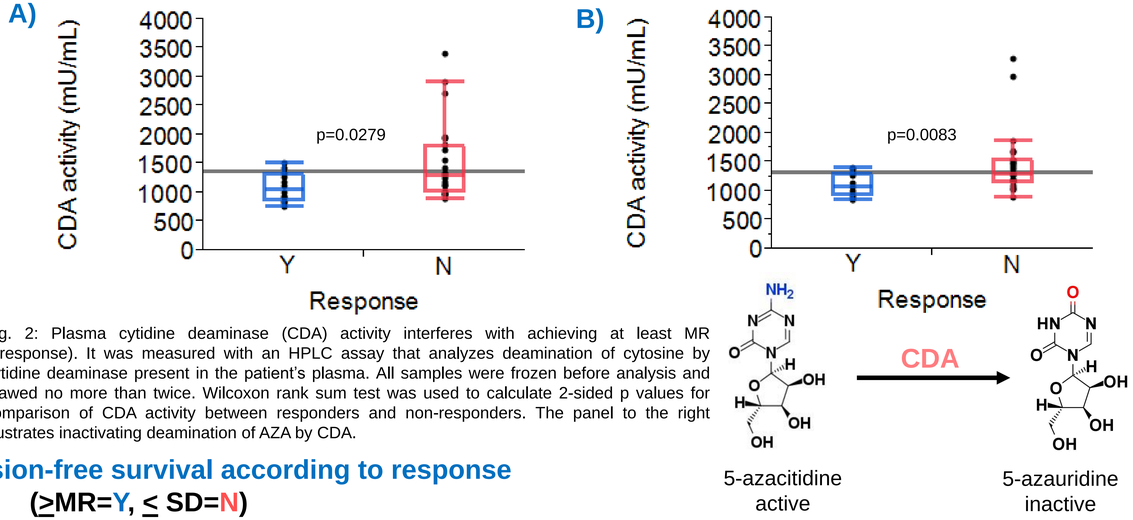

Fig. 2: Plasma cytidine deaminase (CDA) activity interferes with achieving at least MR (=response). It was measured with an HPLC assay that analyzes deamination of cytosine by cytidine deaminase present in the patient's plasma. All samples were frozen before analysis and thawed no more than twice. Wilcoxon rank sum test was used to calculate 2-sided p values for comparison of CDA activity between responders and non-responders. The panel to the right illustrates inactivating deamination of AZA by CDA.

Figure 3. Progression-free survival according to response (≥MR=Y, ≤ SD=N)

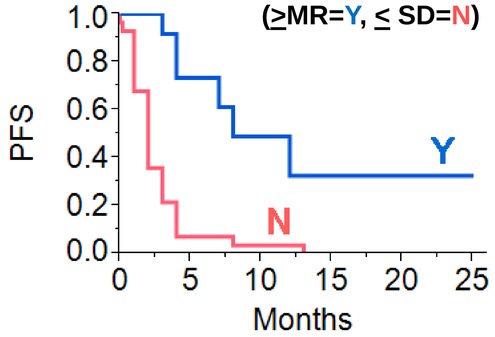

Fig. 3: Time to progression or death from study entry. Two responding patients continued AZA injections with lenalidomide and dexamethasone or prednisone after study exit for convenience or dose reduction below study minimum. Their time to progression, not to study exit is shown. Five patients remain on study and one was censored because of decision to enroll in allo SCT study after 25 months.

CONCLUSIONS

- **AZA was well tolerated up to target 50mg/m2 SC twice a week in combination with len-dex .**
- **Inverse correlation of CDA activity with response suggests AZA contributed to benefit and supports development of the HPLC assay to select patients for aza nucleoside treatment and guide development of CDA inhibitors.**

References

1) *Mahfouz et al Clin Can Res 19:938-48, 2013*

2) *Rajkumar et al. Blood 117: 4691-4695, 2011*