RANDOMIZED OPEN-LABELED ACADEMIC TRIAL COMPARING 'G-CSF PRIOR AZA' WITH STANDARD AZA THERAPY IN HIGH RISK MDS PATIENTS.

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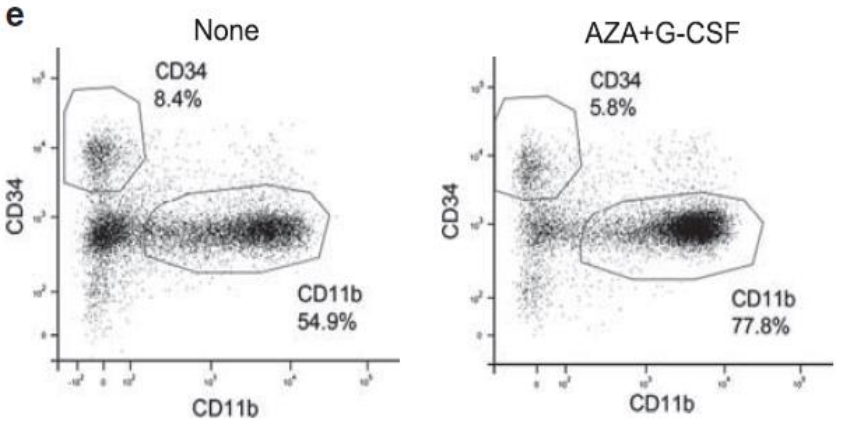
- G-CSF is representing a cytokine that stimulates myelopoiesis from earliest cells to late granulocyte precursors.

- The addition of G-CSF-prior-HMA induces myeloid differentiation and inhibits stem cell programs.

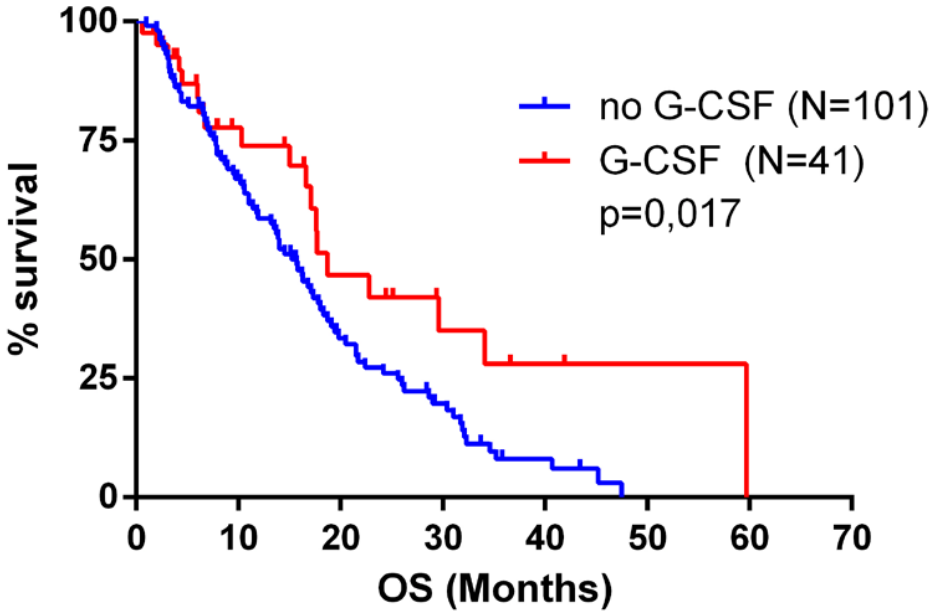
  Hu et al. Decitabine maintains hematopoietic precursor self-renewal by preventing repression of stem cell genes by a differentiation-inducing stimulus. Molecular Cancer Therapeutics 2010.

- Our work showed that preincubation of primary MDS cells with G-CSF promotes AZA-induced myeloid differentiation *in vitro*.



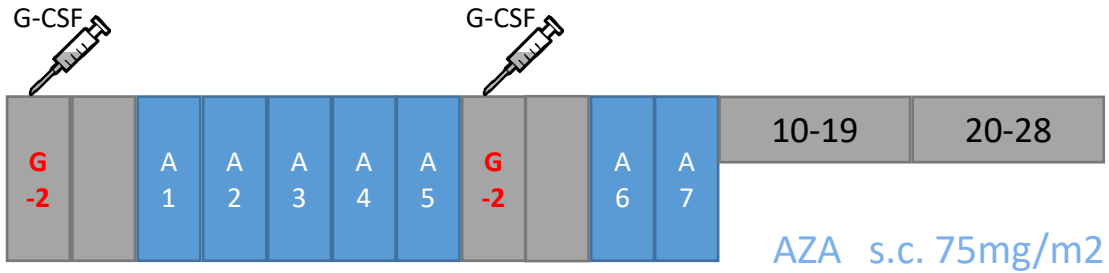
Curik N, et al. 5-azacitidine in aggressive myelodysplastic syndromes regulates chromatin structure at PU.1 gene and cell differentiation capacity. Leukemia. 2012

Based on the Prague General Hospital registry of the AZA therapy involving 142 HR-MDS patients: the **AZA-treated patients with higher G-CSF consumption** had significantly reduced occurrence of Grade 4 neutropenias and longer OS.



STUDY POPULATION AND DESIGN

- Single center, open-label, randomized academic trial for newly diagnosed patients with high-risk MDS, AML with less then 30% blasts and CMML II not eligible for hematopoietic stem cell transplantation or intensive chemotherapy.
- We compare **standard AZA (arm A) v.s.** novel AZA-based therapy combination with **G-CSF prior AZA (arm GA).**



AZA s.c. 75mg/m2 (5-2-2)

G-CSF s.c. 48MU (day -2 & day 6 of AZA)

STUDY END POINTS

PRIMARY:

Prolong OS

Prolong time-to-AML transformation and time-to-progression

Increase ORR: CR, PR, HI

SECONDARY:

Evaluate effect of NGS-based mutations btw GA & A arms

PATIENTS

- Currently GA study enrolls 80 HR-MDS subjects.
- The **Interim analysis at 3.5 years** includes **62 HR-MDS** patients of similar age & sex distribution.
- G-CSF was allowed in both arms in case of febrile neutropenia or Gr4 neutropenia. Therefore, we **monitored number of G-CSF injections** in relation to clinical outcomes in A vs GA arm.

	A	GA
PATIENTS, N	27	35
AGE, median (range)	73 (65 - 85)	73 (65 - 86)
Male/ Female, N	16/11	20/15
IPSS-R		
- intermediate & high	18	20
- very high	9	15
CYTOGENETIC SCORE		
- poor	5	14
DIAGNOSIS (WHO 2016)		
- MDS/AML (up to 30% Mb)	8	7
- EB 2	16	18
- EB 1	0	7
- MDS-MLD or MDS-RS-MLD	2	2
- CMML	1	1
Secondary MDS	2	9

ANC 10^9/l, median (range)	1.39 (0,1-15)		1.01 (0,1-15)	
Blast cells in BM %, median	9,6		17	
G-CSF arms	**No G-CSF**	**some G-CSF**	**2x G-CSF per AZA cycle**	**>2 inj. G-CSF per AZA cycle**
G-CSF inj. per AZA cycle, avg (range)	0	2 (1-5)	2	4,6 (2,5-9)
Number of Pts, n	19	8	13	22
AZA Cycles, median (range)	**3 (1-16)**	**6 (3 -16)**	**5 (2 - 30)**	**7 (1-23)**
Overal Survival Mo median (range)	**4 (1- 22)**	**10 (3 - 25)**	**14 (3 - 37)**	**11 (2 - 40)**
Responses (Patients, TTR)	6 pts (4,2 mo)	6 pts (4,8 mo)	8 pts (4,12 mo)	16 pts (4,5 mo)

THERAPY RESPONSE

	A	GA
Response Rate	11 (41%)	25 (71%)
- CR	6 (22%)	17 (48%)
- PR	3 (11%)	5 (14%)
- SD HI	2 (7%)	3 (8%)
Progression	9 (33%)	4 (11%)
No response	5 (25%)	6 (17%)
Patients (total)	27	35

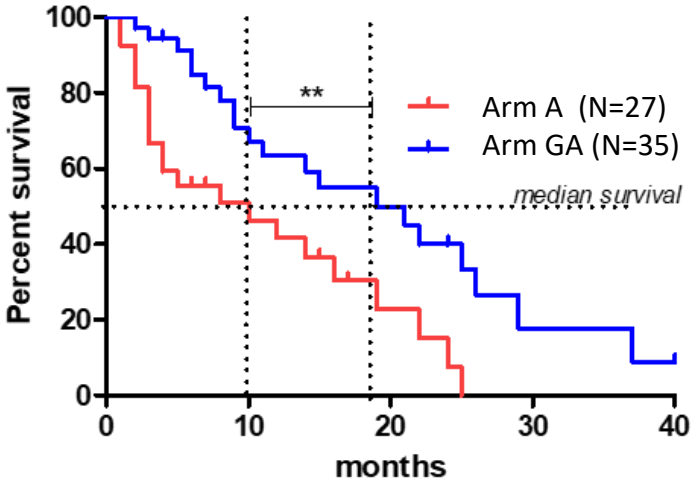
The joint model suggested the **estimated odds for the GA-mediated response was 4-times higher** compared to AZA arm (**p=0.0045**).

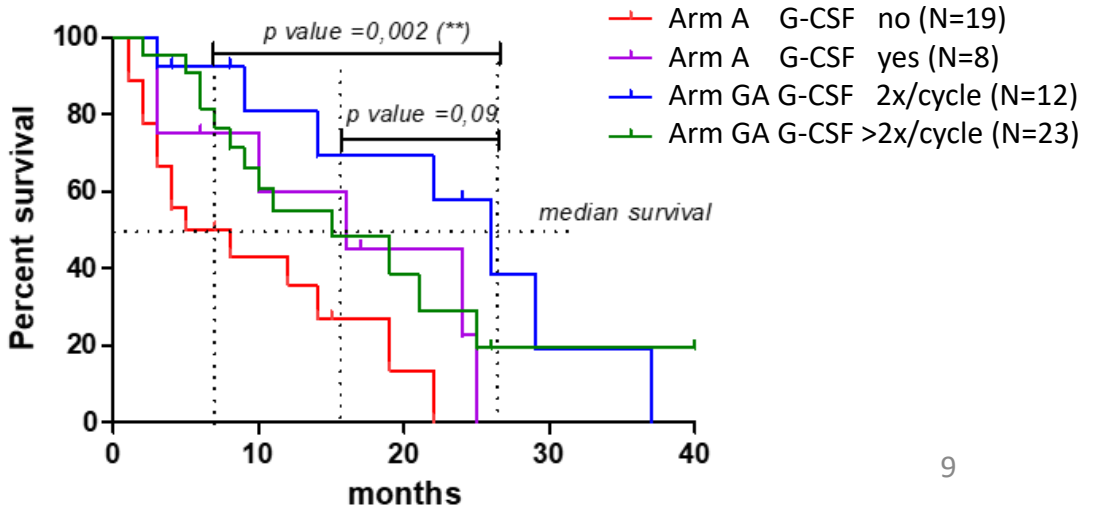
Significant interaction exists between the treatment outcome (AZA/GA) and the dosage of G-CSF (p=0.00211).

PATIENT SURVIVAL

- Survival analysis indicates 8 months benefit of GA arm compared to A arm (p=0.0044).
- According to the number of G-CSF applications, addition of G-CSF in A arm improves OS. Excessive G-CSF administration in GA arm does not further improve OS.

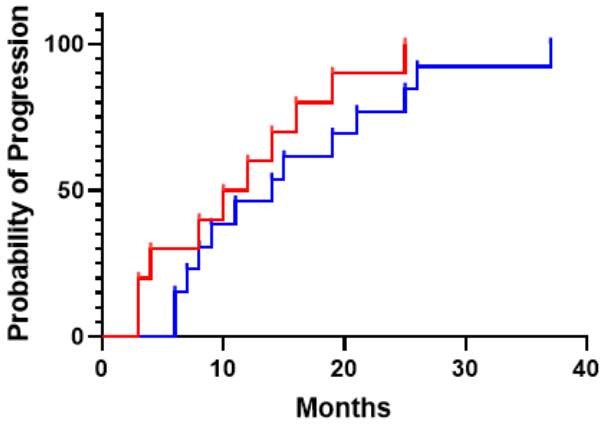
Overall survival comparison in GA vs A arm (left) and according to G-CSF load (right)

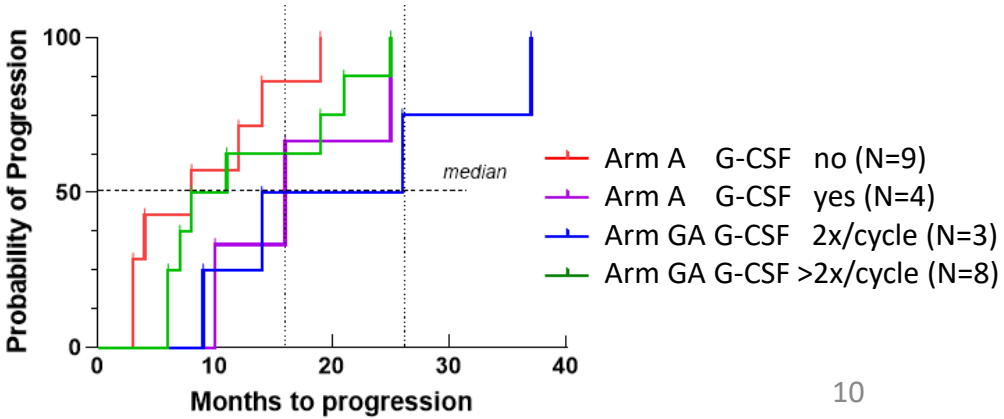




PROGRESSION

- GA and A arms have comparable progression to AML.
- Progression to AML is likely not a function of a number of G-CSF applications. However, a trend to progression is rather inverse to # G-CSF applications.





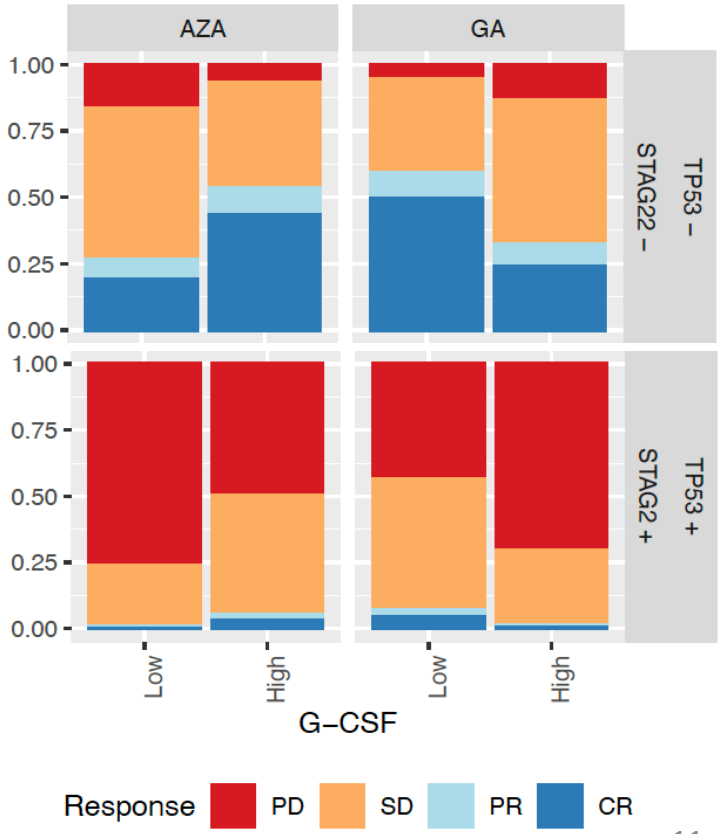
MUTATIONS

- significant effects of mutated genes to worsen therapy's response:

TP53 (p=0.00151)

and/or

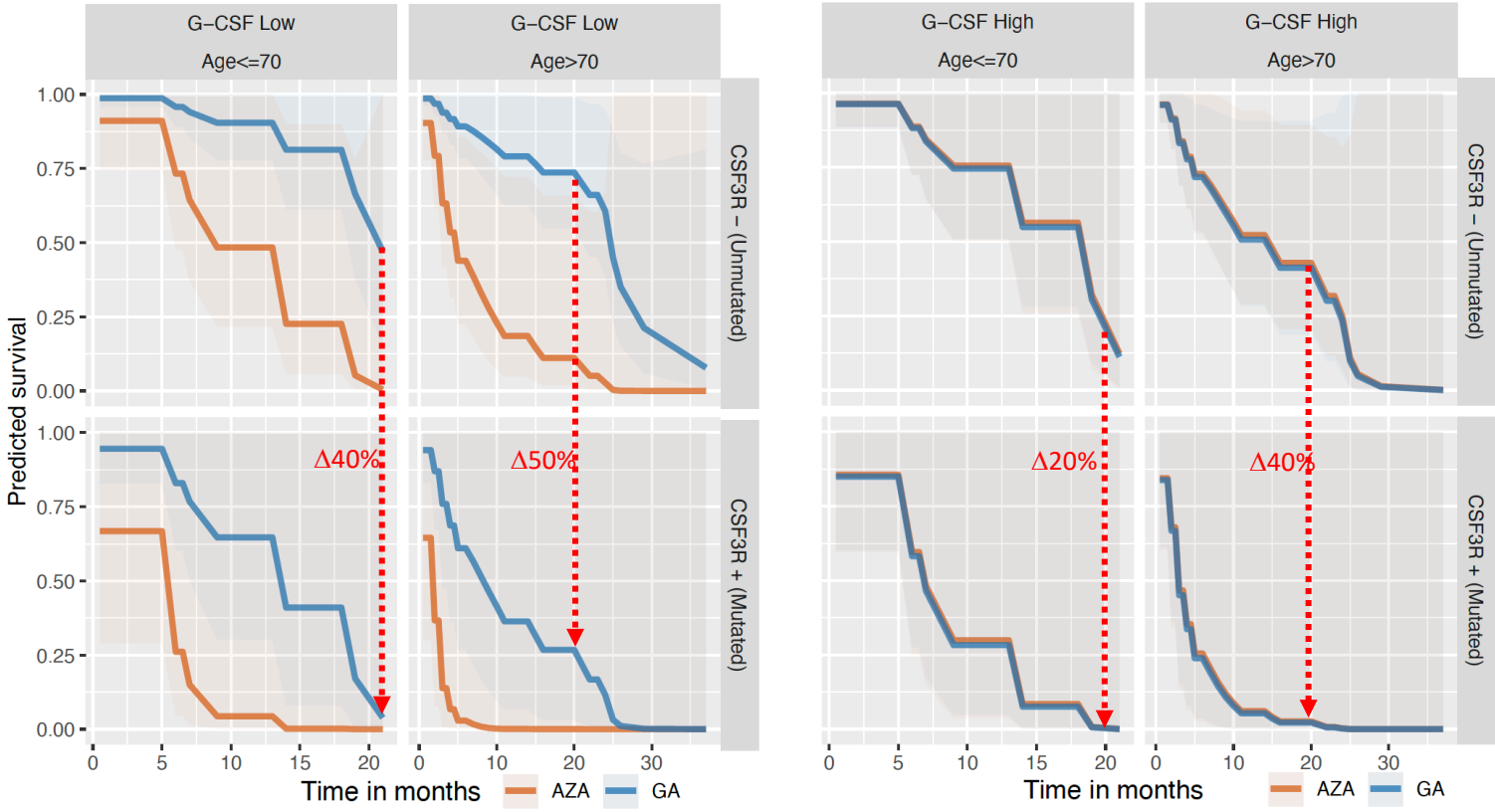
STAG2 (p=0.01006)



The joint model represents the response (Progressive Disease (PD) / Stabilized Disease (SD) / Partial Remission (PR) / Complete Remission (CR)) to the treatment.

MUTATIONS IN CSF3R PRECLUDE LOWER OS

Significant effect on the overall survival caused by the **CSF3R** variants (4 PTS) (p= 0.02874) representing higher risk of death and, hence, shorter OS



CONCLUSIONS

- **Interim analysis at 3.5 years** involving 62 HR-MDS subjects with similar age & sex distributions suggests **beneficial effect of G-CSF-prior-AZA** compared to AZA monotherapy (without increasing toxicity compared to standard AZA).
- GA patient has **4-times** higher chance to gain response compared to AZA monotherapy.
- GA and A arms have **comparable progression to AML.**
- **GA therapy arm yields longer surviving,** however, patients with high G-CSF applications have a significantly higher risk of death compared to the patients from the **low G-CSF in GA arm**.
- Variants in **TP53, STAG2**, and **CSFR3** have a negative impact on GA-based response and, hence, shorten overall survival.

ACKNOWLEDGEMENTS

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