What is new in Myelodysplastic Syndrome in 2021?

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Overview

- Overview
- Case Presentations
- Novel therapies for low-risk and high risk MDS.
- Future Directions
- Conclusion

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Overview

- Myelodysplastic is a heterogenous disease with varied outcome.
- Characterized by ineffective hematopoiesis, cytopenia and risk of progression to AML.
- The annual age-adjusted incidence in the US is 4/100,000 person: incidence rises with age.

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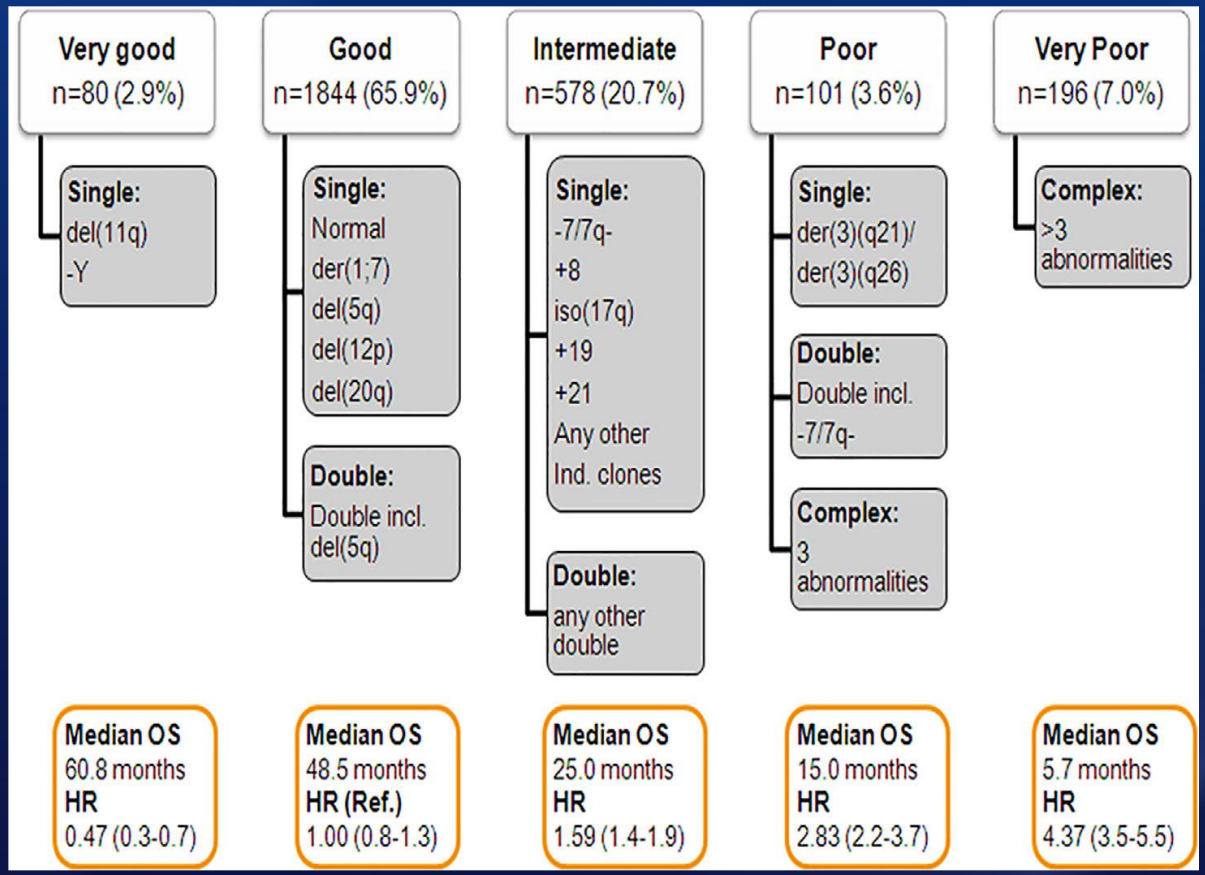
CG Classification



Garcia Manero et al. *AJH* 2021
Schanz J et al. *JCO* 2012

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MDS Risk Assessment Tools

Metric	Score
Blast	
<5%	0
5-10%	0.5
11-20%	1.5
21-30%	2
CG	
Good	0
Intermediate	0.5
Poor	2
Cytopenia (Hb <10 g/dl, PLT <100, ANC <1.5/uL	
0-1	0
2-3	0.5
Risk Group	
Low	0
INT-1	0.5-1
INT-2	1.5-2
High	≥ 2.5

IPSS

Metric	Score
Blast	
≤ 2%	0
> 2- <5%	0.5
5-10%	1.5
> 10%	2
CG	
Very Good	0
Good	0.5
Intermediate	2
Poor	3
Very Poor	4
Cytopenia	
Hb 8 - <10 g/dl	1
Hb < 8 g/dl	1.5
ANC <0.8/uL	0.5
Plt 50-100/ uL	0.5
Plt <50/ uL	1
Risk Group	
Very Low	≤ 1.5
Low	1.5-3
INT-1	3.5-4.5
INT-2	5-6
High	>6

IPSS-R

Metric	Score
WHO classification	
RA, RARS, del 5q	0
RCMD, RCUD-RS	1
RAEB-1	2
RAEB-2	3
CG	
Good	0
Intermediate	1
Poor	2
Transfusion Requirement	
Yes	1
Risk Group	
Very Low	0
Low	1
Intermediate	2
High	3-4
Very High	5-6

WPSS

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Incorporation of Molecular Data for Risk Stratification in Treated Patients

- Observational study= 508 pts.
- Mutational data was incorporated in IPSS-R
- Six mutations (> 5%)= *TET2* (18%), *ASXL1* (14%), *SF3B1* (14%), *STAG2* (9%) and *DNMT3A* (8%).
- *ASXL1,RUNX1*, *TP53* , *EZH2*, *SRSF2* and *NPM1*= associated with inferior outcome.
- *SF3B1*= associated with improved OS.

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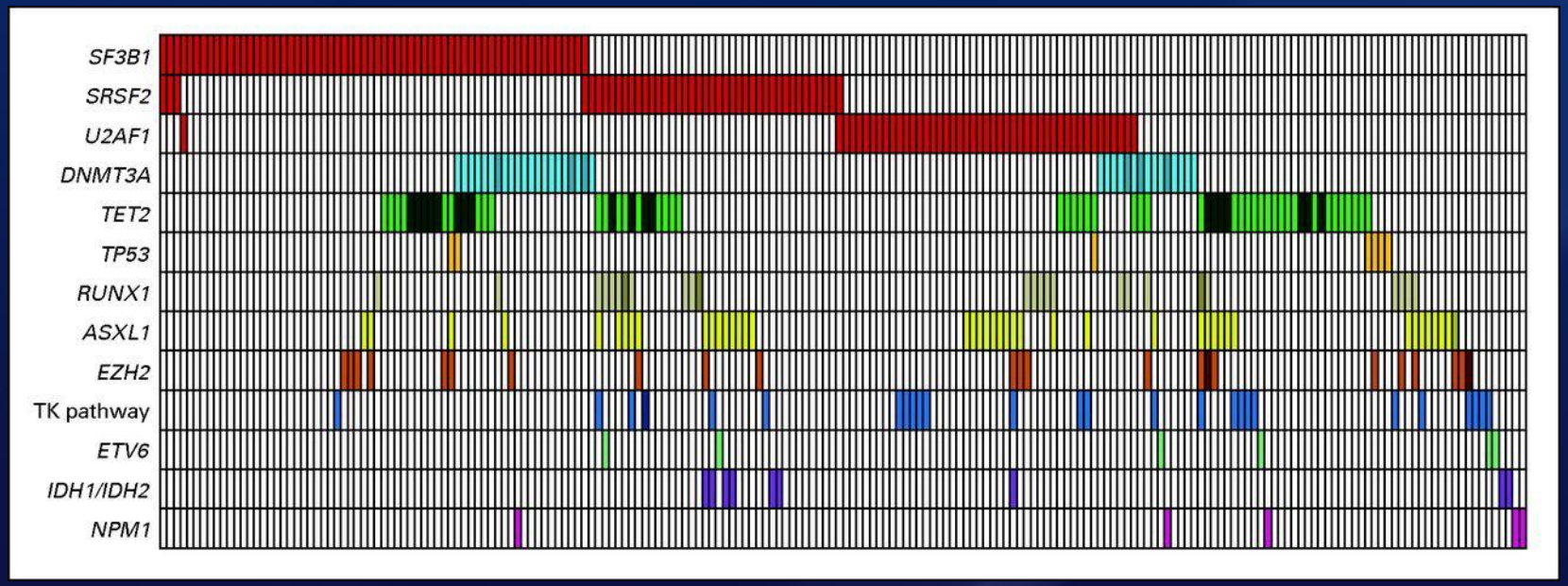
A Nazha et al. *Leukemia* 2016

Impact of mutations in Low risk MDS

- Mol. data was incorporated in 288 low/Int-1 risk MDS pts.
- Mutations of *EZH2*, *RUNX1*, *TP53*, and *ASXL1* were associated with shorter OS independent of the risk category.



Bejar et al. *JCO* 2012

Low and Intermediate Risk MDS

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Case Presentation

- 61 yrs old lady with transfusion dependent anemia. CBC revealed: Hb 7.0 g/dl, WBC 4.7, ANC 2.6, Plt 325. EPO > 200. BM biopsy revealed erythroid hyperplasia with ring sideroblast (>15%). No ↑ in blast. CG = Trisomy 8 [15/20]. NGS= *DNMT3A* & *SF3B1.* IPSS-R= low risk. How would you treat?

- Lenalidomide
- Luspatercept
- Azacitidine or decitabine

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Original Article

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

Pierre Fenaux, M.D., Ph.D., Uwe Platzbecker, M.D., Ghulam J. Mufti, F.R.C.P., Guillermo Garcia-Manero, M.D., Rena Buckstein, M.D., Valeria Santini, M.D., María Díez-Campelo, M.D., Ph.D., Carlo Finelli, M.D., Mario Cazzola, M.D., Osman Ilhan, M.D., Mikkael A. Sekeres, M.D., José F. Falantes, M.D., Beatriz Arrizabalaga, M.D., Flavia Salvi, M.D., Valentina Giai, M.D., Ph.D., Paresh Vyas, B.Ch., B.M., David Bowen, M.D., Dominik Selleslag, M.D., Amy E. DeZern, M.D., Joseph G. Jurcic, M.D., Ulrich Germing, M.D., Katharina S. Götze, M.D., Bruno Quesnel, M.D., Ph.D., Odile Beyne-Rauzy, M.D., Thomas Cluzeau, M.D., Maria-Teresa Voso, M.D., Dominiek Mazure, M.D., Edo Vellenga, M.D., Ph.D., Peter L. Greenberg, M.D., Eva Hellström-Lindberg, M.D., Amer M. Zeidan, M.B., B.S., M.H.S., Lionel Adès, M.D., Amit Verma, M.D., Michael R. Savona, M.D., Abderrahmane Laadem, M.D., Aziz Benzohra, M.D., Jennie Zhang, M.S., Anita Rampersad, B.A., Diana R. Dunshee, Ph.D., Peter G. Linde, M.D., Matthew L. Sherman, M.D., Rami S. Komrokji, M.D., and Alan F. List, M.D.

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Study Overview

- Luspatercept is a fusion protein aimed at binding TGF-β family members and reducing SMAD2 and SMAD3 signaling in patients with RARS.
- In a RCT involving transfusion-dependent lower-risk MDS, transfusion independence for ≥ 8 weeks: 38% vs. 13%.

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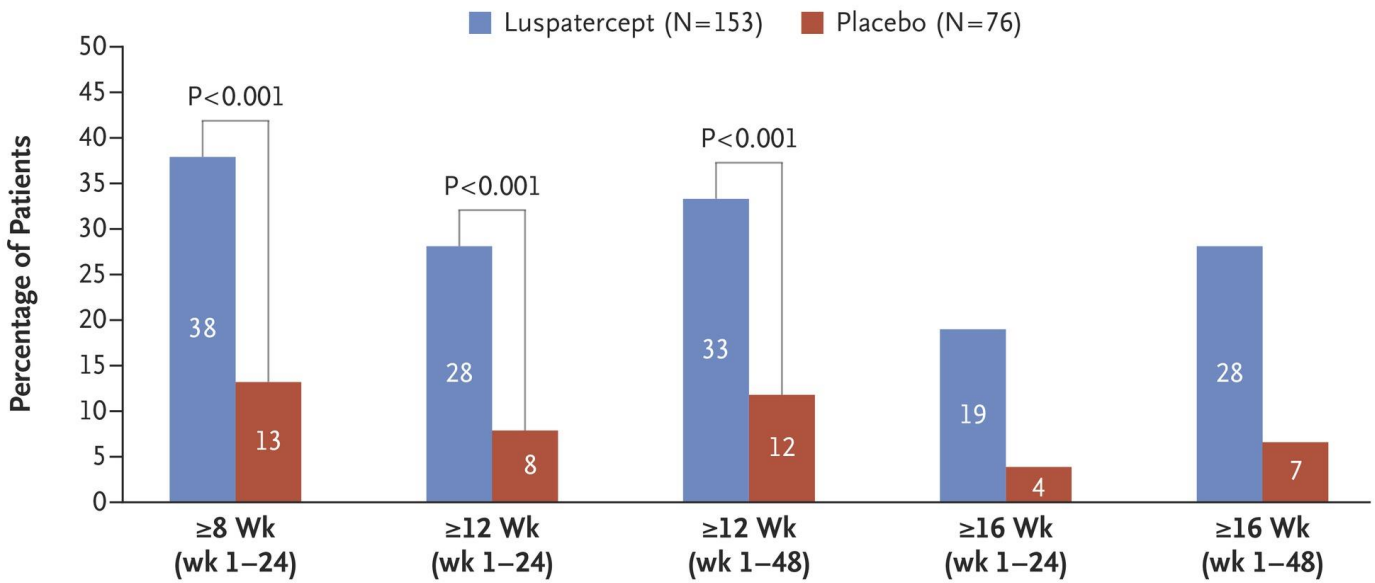
Transfusion independence



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux P et al. *NEJM* 2020

HMA for Low risk MDS

- A randomized phase II trial was conducted comparing a 3-day schedule of AZA vs. Decitabine
- ORR= 49% vs 70%, p 0.03
- CG response= 61% vs 25%, p= 0.02
- TI= 32% vs. 16%
- OS= NR, EFS = 18 mo
- No early deaths or significant G3 AE's.

Jabbour E et al. Blood 2017

Recommendations of Low risk MDS

- ESA for symptomatic anemia
- Luspatercept for MDS-RS
- Lenalidomide for 5q
  - Also shown activity in non-5q & MDS/MPN; RS-T
- Low dose HMA
- Participation in Clinical Trial

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Intermediate & High risk MDS

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Case Presentation

- 70 yrs old lady with long standing history of T-LGL and low risk MDS was on observation, noted to have worsening leukopenia (ANC < 500) and thrombocytopenia (49k). BM biopsy was repeated showed MDS with 9% blast. CG were normal. NGS showed *ASXL1* and *GATA2* mutations. IPSS-R high risk
- Azacitidine or Decitabine alone
- HMA followed by alloHCT
- Enrolment in clinical trial

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HMA in High Risk MDS

- Azacitidine and Decitabine are approved agents for treating patients with MDS.
- Only AZA showed OS benefit in phase III RCT.
- Recently, ASTX727 [oral decitabine and cedazuridine] was approved.

Kantarjian et al. *Cancer* 2006
Fenaux et al. *Lancet Oncology* 2009
Garcia-Manero et al. *Blood* 2020

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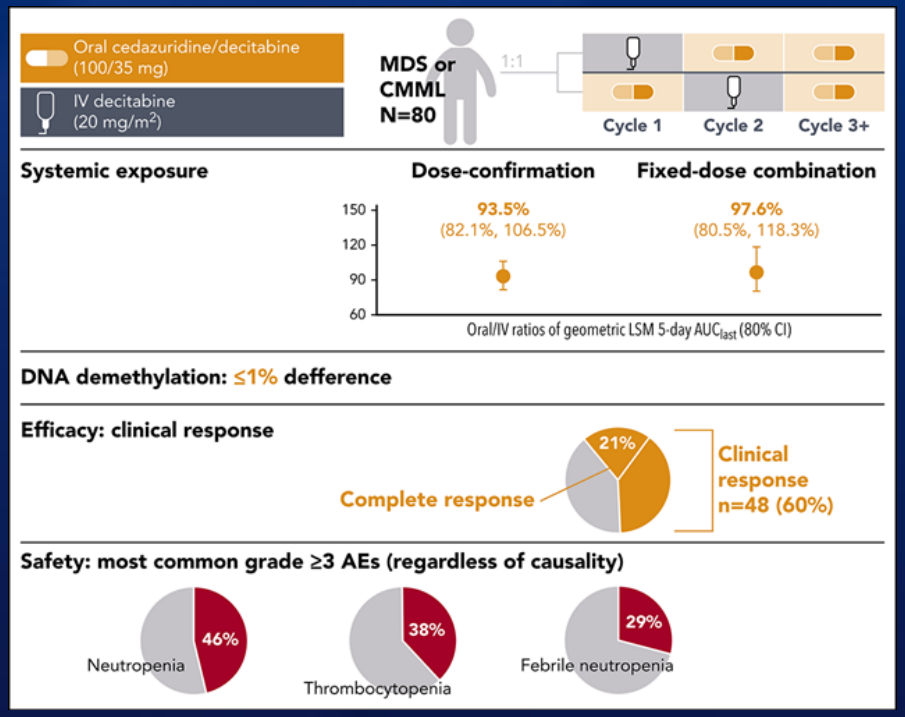
Oral Cedazuridine/Decitabine for MDS and CMML

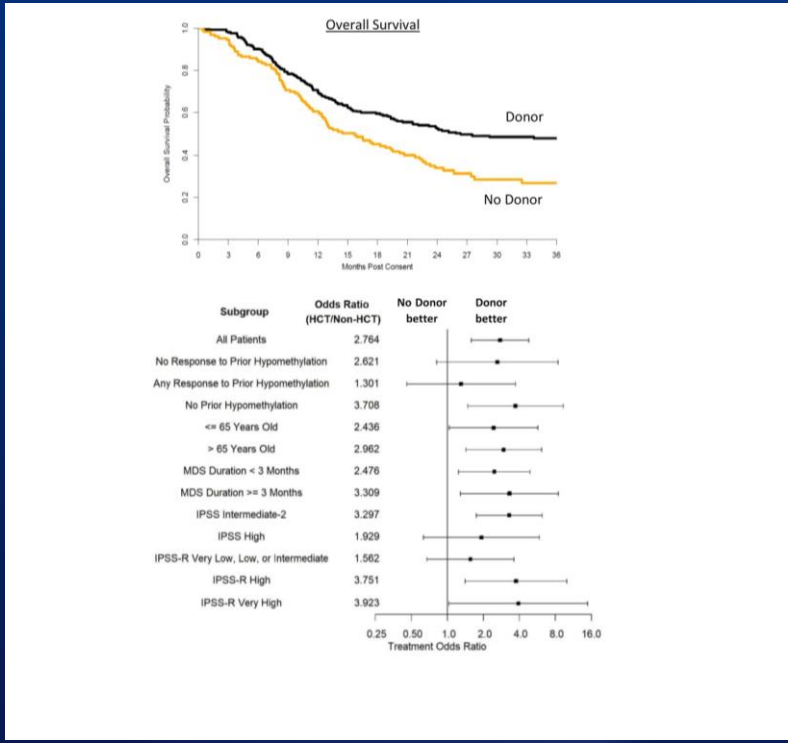


- Phase II study was conducted, comparing oral vs. IV formulation in Int1/2 and high risk MDS.
- PD, safety and efficacy data was comparable.

Garcia-Manero et al. *Blood* 2020

RIC AlloHCT vs HMA vs BSC in Age 50-75

- BMT-CTN 1102 was conducted to evaluate benefit of alloHCT in elderly high risk MDS.
- OS at 3 yrs= 47.9% vs. 26.6% in Donor vs No Donor arm
- LFS at 3 yrs= 35.8% vs 20.6% in Donor vs No Donor arm.



Nakamura &Cutler et al. ASH abstract 2020

Case Presentation

- 63 yrs old gentleman on work up of macrocytic anemia, underwent BM biopsy that revealed MDS-RAEB-2. CG showed complex monosomal karyotype. NGS= TP53 mutation. Best treatment option:

- HMA alone
- HMA followed by alloHCT
- AML like therapy
- Enrollment in clinical trial

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High-risk MDS with Monosomal Karyotype

- Response to HMA are sub-optimal and short lived. (median OS 15 mo)

- Conventional AML-like therapies are inferior to HMA

Sekeres et al. J Clin Oncol. 2017

Novel Therapy Combinations in High-Risk MDS

Study	Phase	No of Pts	ORR (CR)	OS	Current Status
AZA + Ven[1]	Phase Ib	57	77% (37%)	NR	Phase III study ongoing (NCT04401748)
AZA + APR-246[2] (*TP53* mutated)	Phase II	55	71% (46%)	10.8 mo	Phase III study didn't reach primary end point of CR rate
AZA + Pevonedistat vs AZA[3]	Phase II	58 vs 62	71% (52%) vs 60% (38%)	23.9 vs 19.1 mo	Phase III study didn't reach primary end point of EFS
AZA + Magrolimab[4]	Phase Ib	35	92% (50%)	NR	Phase III (ENHANCE) study ongoing (NCT04313881)
AZA + MBG453[5]	Phase Ib	1	58% (26%)	NA	Phase II randomized (STIMULUS) study ongoing

[1]Wei et al. *ASH abstract* 2019
[2] Sallman et al. *ASH abstract* 2019
[3] Swords et al. *Blood* 2018
[4] Sallman et al. *ASH abstract* 2019
[5] Borate et al. *ASH abstract* 2019

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Venetoclax plus AZA for high-risk MDS

- Phase Ib study in treatment naïve HR-MDS (≥Int 2).
- CMML, t-MDS or candidate for intensive therapy were excluded.
- Venetoclax dose= 100, 200, 400 (14/28 days)
- ORR 77%= CR 42%, mCR 35%
- Median DOR= 14.8 mo (OS= NR)
- G3 AE's= FN (46%), ↓ANC (51%), ↓Plt (30%)

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Garcia et al. ASH abstract 2020

Magrolimab plus AZA in high risk MDS

- Magrolimab= anti-CD47 (macrophage targeting immunotherapy)
- Int/high risk MDS (n= 39)
- AZA dose was standard.
- Magrolimab (1-30 mg/kg QW, Q2W C3+)
- ORR= 91% (CR 42%, mCR 24%, PR 3%)
- Median DOR= NR
- 100% alive at 6 mo
- AE's= ↓Hb(38%), ↓ fatigue (21%), ↓ ANC (19%), ↓Plt (18%)

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Sallman et al. ASCO 2020

MBG453 plus HMA in high risk MDS

- MBG453 (anti-TIM-3): immune check point
- Treatment naïve high & very high MDS
- Dec + MBG435 (n=17): ORR= 41% (5 CR, 4 mCR, 2 HI)
- AZA + MBG435 (n= 10): ORR 70% (6 mCR, 1 PR)
- G ≥3 AE= ↑ALT, arthritis, hepatitis, hypothyroidism, rash.

Brunner et al. SOHO 2020

Recommendations for Int & High risk MDS

- HMA alone
- Enrollment in clinical trial for HMA plus novel combination
- AlloHCT in eligible patients.

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Future Directions

- Incorporation of molecular alterations in prognostic model.
- Better understanding on pathogenesis of HMA failure

- Incorporation single cell analysis.

- Predictive biomarkers for response assessment.
- Targeted therapy for MDS

- IDH, FLT3, NPM1, p53, SF3B1

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Questions/Comments