Iron chelation and targeted therapy in MDS: Shifting the treatment paradigm

The 2nd Regional Symposium on Myelodysplastic Syndromes

Thursday 5 March
Tel Aviv, Israel

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Iron chelation and targeted therapy in MDS: Shifting the treatment paradigm

Time	Session	Speaker
13:30–13:45	Welcome and Introductions *Faculty discussion:* **Are current therapies doing enough to meet the needs of patients with Myelodysplastic Syndromes?**	Moshe Mittelman
13:45–14:00	**Rethinking treatment selection for patients with low-risk Myelodysplastic Syndromes**	Emanuele Angelucci
14:00–14:15	**Moving towards a targeted approach for patients with Myelodysplastic Syndromes**	Uwe Platzbecker
14:15–14:30	Q&A *Faculty discussion:* **Paving the way for novel therapeutic opportunities in Myelodysplastic Syndromes treatment** Meeting close	Moderator: Moshe Mittelman

Welcome & introductions

Moshe Mittelman

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Myelodysplastic Syndromes (MDS)

- **A heterogeneous group of malignancies**
- **Bone marrow stem cell disease**
- **Peripheral blood cytopenias**
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- **Risk of leukemic evolution**

1. Arber DA, et al. *Blood.* 2016;127:2391–2405; 2. Mittelman M. *Is J Med Sci.* 1990; 26:468–78; 3. Mittelman M. *Acta Haematol.* 1993;90:53–57; 4. de Swart L, et al. *Br J Haematol.* 2015;170:372–383.

Faculty

Emanuele Angelucci

Hematology and Hematopoietic Stem Cell Transplantation Center at the IRCCS San Martino University Hospital in Genoa, Italy

Uwe Platzbecker

Medical Clinic I, Hematology and Cellular Therapy at the University Hospital in Leipzig, Germany

Are current therapies doing enough to meet the needs of patients with MDS?

Panel discussion

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Are current therapies doing enough to meet the needs of patients with MDS? Questions (I)

What are the problems with current MDS treatments?

MDS, myelodysplastic syndromes.

Are current therapies doing enough to meet the needs of patients with MDS? Questions (II)

Do complications occur more in transfusion-dependent MDS patients?

- **Due to iron overload?**

MDS, myelodysplastic syndromes.

Question for the audience

Are you satisfied with the current treatment landscape for patients with MDS?

Please raise your hand for YES

Rethinking treatment selection for patients with lower-risk Myelodysplastic Syndromes

Emanuele Angelucci

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Disclosures

Honoraria from Novartis and Celgene, involvement in local advisory boards for Jazz Pharmaceuticals, Bluebird Bio, and Roche, and participation in DMC for Celgene and Vertex Pharmaceuticals Incorporated, and CRISPR Therapeutics.

DMC, data monitoring committee.

Treatment objectives – classical view

Correct diagnosis is KEY to the choice of treatment strategy

Lower risk IPSS

- Improve blood cytopenias
- Improve quality of life

Higher risk IPSS

- Delay disease progression
- Prolong survival

IPSS, International Prognostic Scoring System.
Information provided by the speaker.

Treatment objectives – new view

Correct diagnosis is KEY to the choice of treatment strategy

Lower risk IPSS

- Improve blood cytopenias
- Improve quality of life
- **Improve survival**

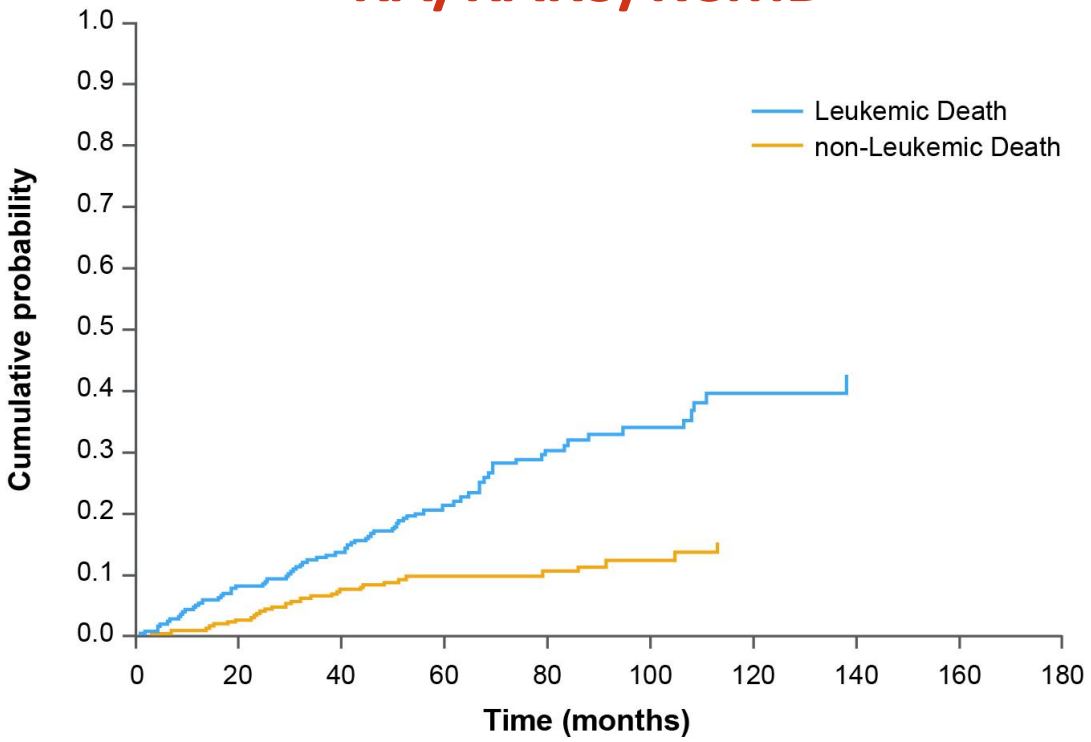
Higher risk IPSS

- Delay disease progression
- Prolong survival

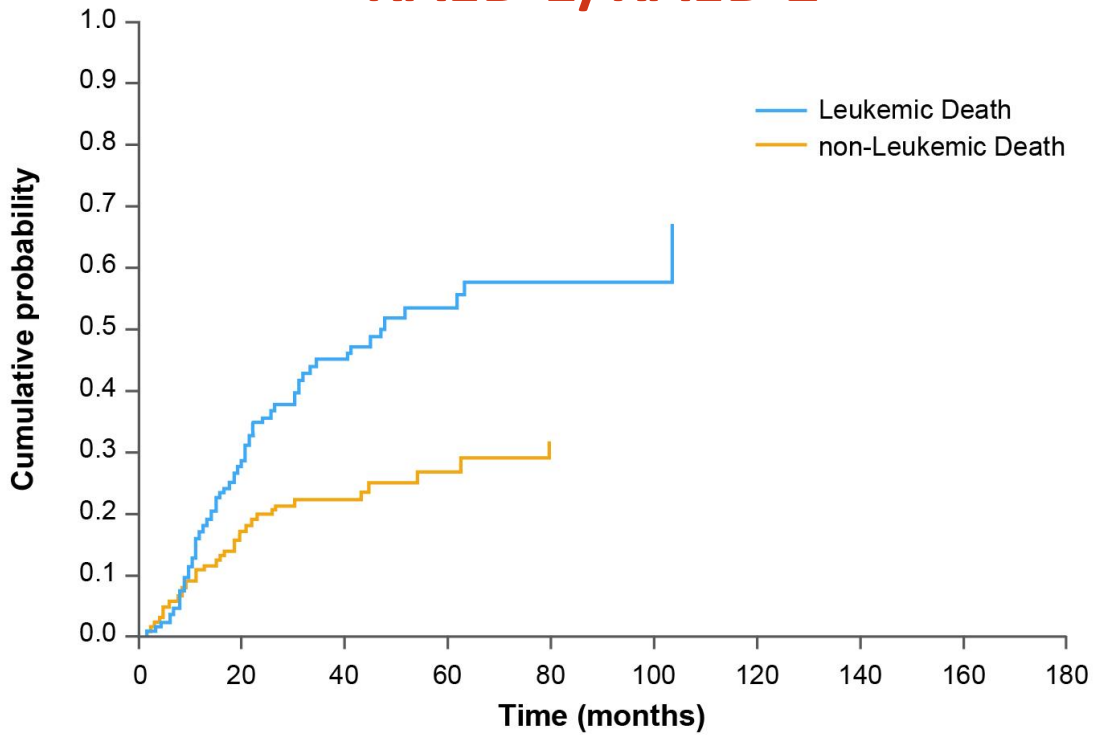
IPSS, International Prognostic Scoring System.
Information provided by the speaker.

Competitive risk of death in MDS subgroups

RA/RARS/RCMD



RAEB-1/RAEB-2



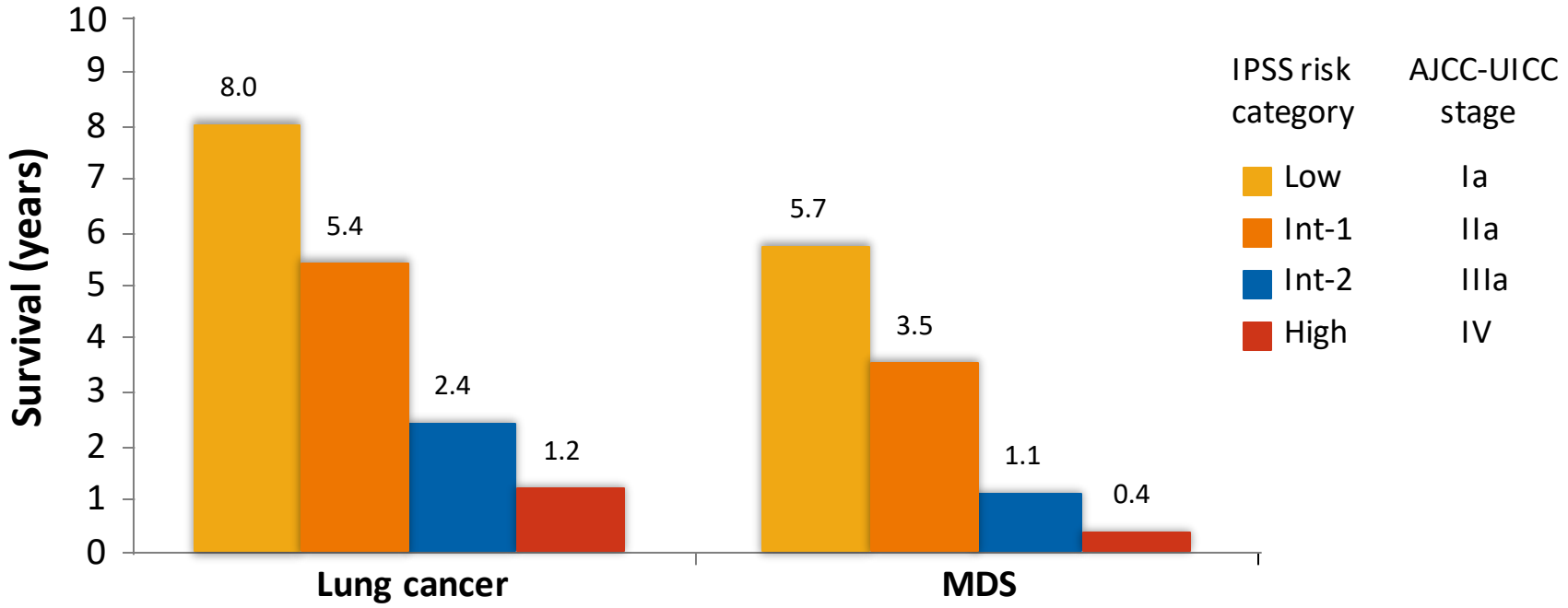
Adapted from Giovanni Della Porta & Malcovati. 2009

MDS, Myelodysplastic syndromes; RA, refractory anaemia; RAEB, RA with excess blasts; RARS, RA with ringsideroblasts; RCMD, refractory cytopenia with multi-lineage dysplasia.
Giovanni Della Porta M, Malcovati, L. *Haematologica*. 2009;94:602–606.

haematologica the hematology journal

Reduced survival is an inherent feature of MDS, even for low-risk subgroups

Life expectancy is shorter for US patients with MDS than for those with lung cancer[a,b,1,2]



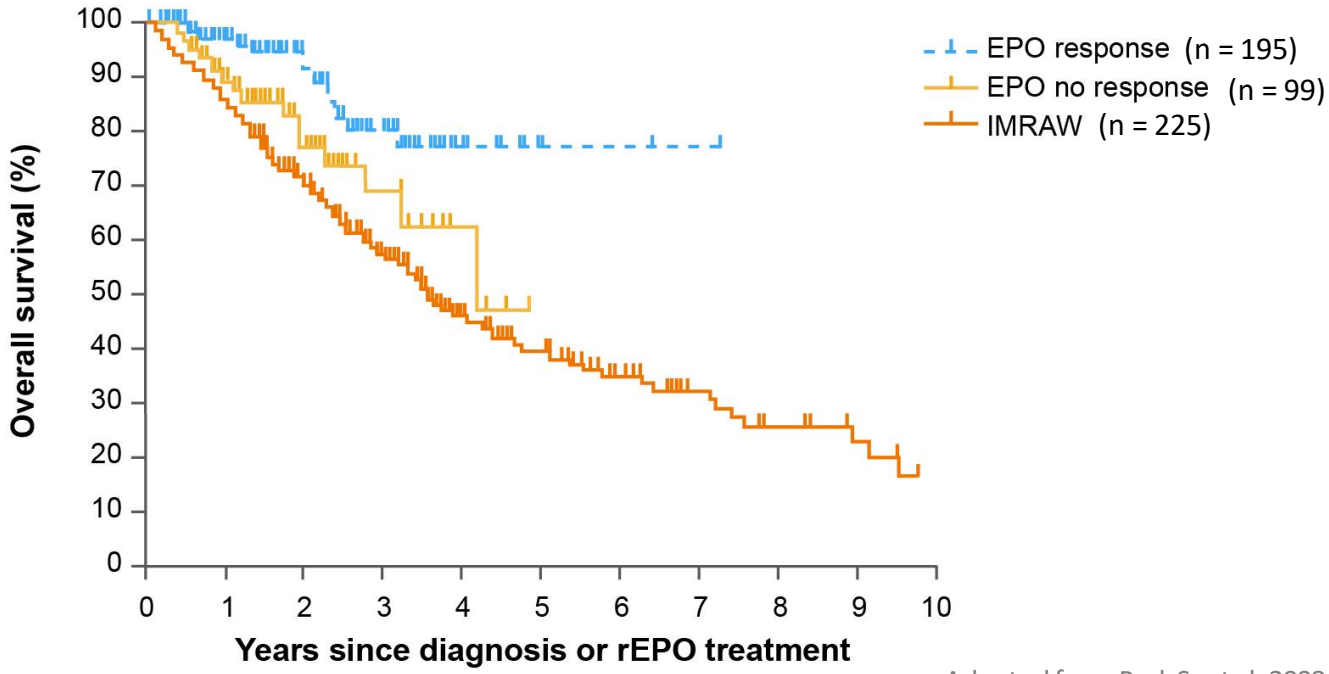
[a] Adjusted for age (lung cancer, median 66 years of age; MDS, median 69 years of age) and risk/stage.[1,2]
[b] All histological subtypes.[1,2]

AJJC-UICC, American Joint Committee on Cancer Union for International Cancer Control; IPSS, International Prognostic Scoring Sys tem; MDS, Myelodysplastic syndromes; US, United States.

1. Greenberg P, et al. *Blood*. 1997;89:2079–2088; 2. Adebonojo SA, et al. *Chest*. 115:1507–1513.

Predictive factors of response and survival in MDS treated with erythropoietin and G-CSF: the GFM experience

Overall survival between IMRAW (untreated) and French-EPO (rEPO-treated) cohorts*



Adapted from Park S, et al. 2008

*P<0.001 between IMRAW and rEPO responders; P=0.17 between IMRAW and rEPO no-nresponders.
EPO, erythropoietin; rEPO, recombinant EPO; GFM, Groupe Francophone des Myélodysplasies; IMRAW, International MDS Risk Analysis Workshop; INT1, intermediate-1.
Figure and legend Copyright © 2020 American Society of Hematology.
Park S, et al. *Blood*. 2008;111:574–582.

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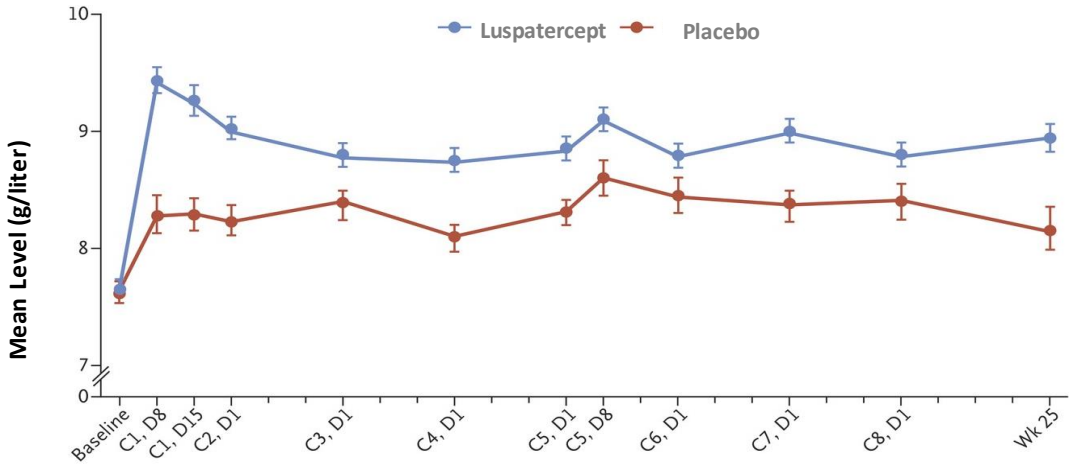
Luspatercept in Patients with Lower-Risk MDS

Changes in mean hemoglobin levels over time

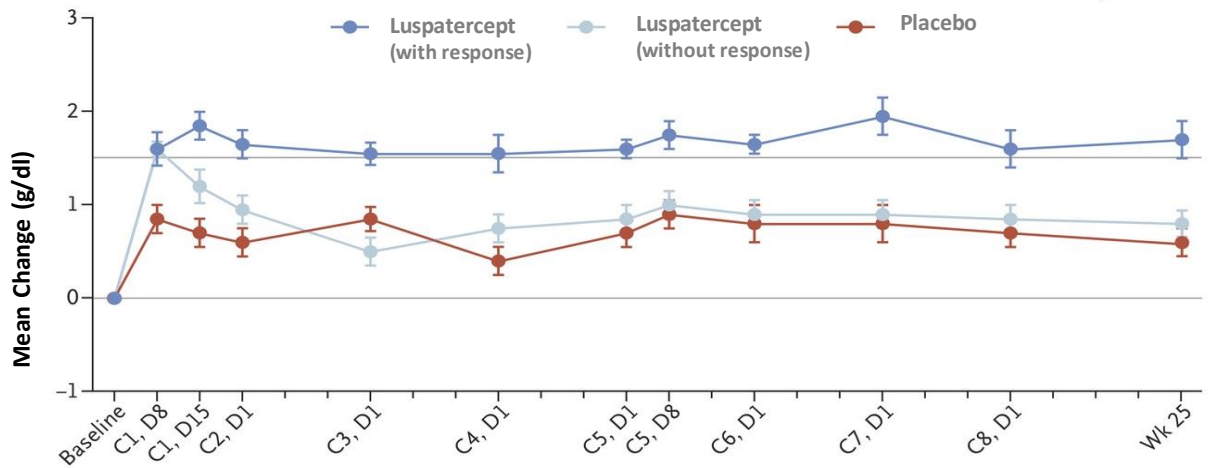
Changes in Mean Observed Hemoglobin Levels over time



No. of Patients												
Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32

Adapted from Fenaux P, et al. 2020

Change from Baseline in Hemoglobin Level



No. of Patients												
Luspatercept (with response)	-	24	36	55	53	52	50	42	47	50	42	45
Luspatercept (without response)	-	33	51	61	52	60	53	34	45	56	48	35
Placebo	-	32	36	41	47	40	52	29	44	47	44	32

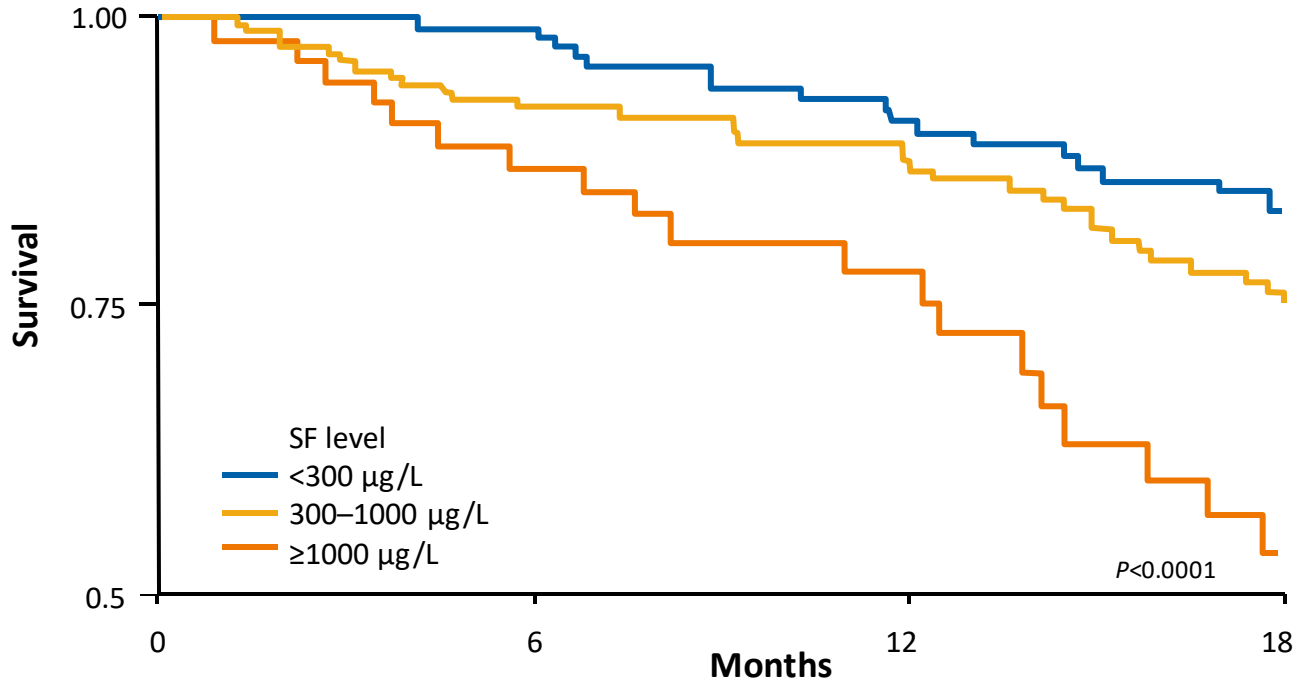
Luspatercept* reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts….

*Luspatercept is not yet licensed for MDS indications in any country.
MDS, myelodysplastic syndromes.
Fenaux P, et al. *N Engl J Med*. 2020;382:140–151.

The NEW ENGLAND JOURNAL of MEDICINE

Impact of increasing serum ferritin levels on overall survival of patients from the Leukemia Net Prospective Registry

OS of transfusion-dependent patients by baseline SF status (n=1000) (Kaplan-Meier survival estimates)

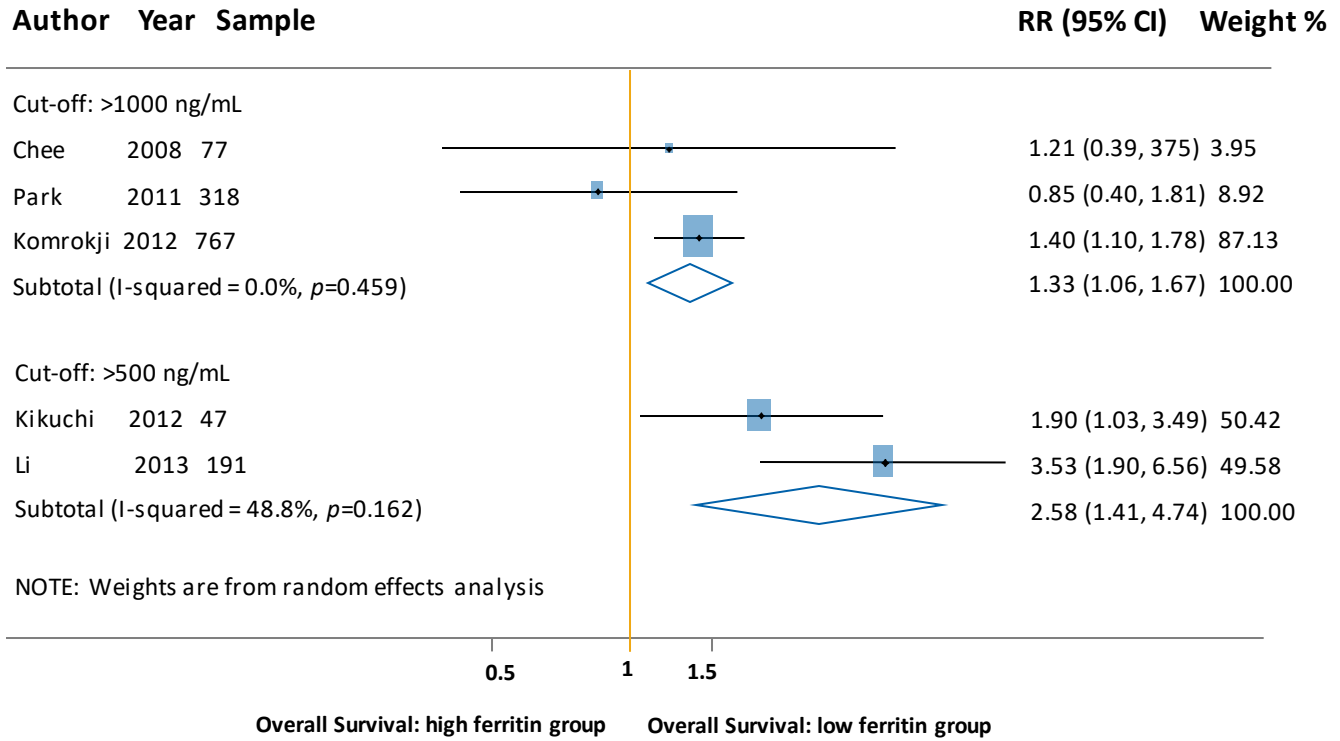


Adapted from de Swart L, et al. 2018

OS, overall survival; SF, serum ferritin.
de Swart L, et al. *Blood*. 2011;118:abst 2775.

Role of serum ferritin level on overall survival in patients with MDS: Results of a meta-analysis of observational studies

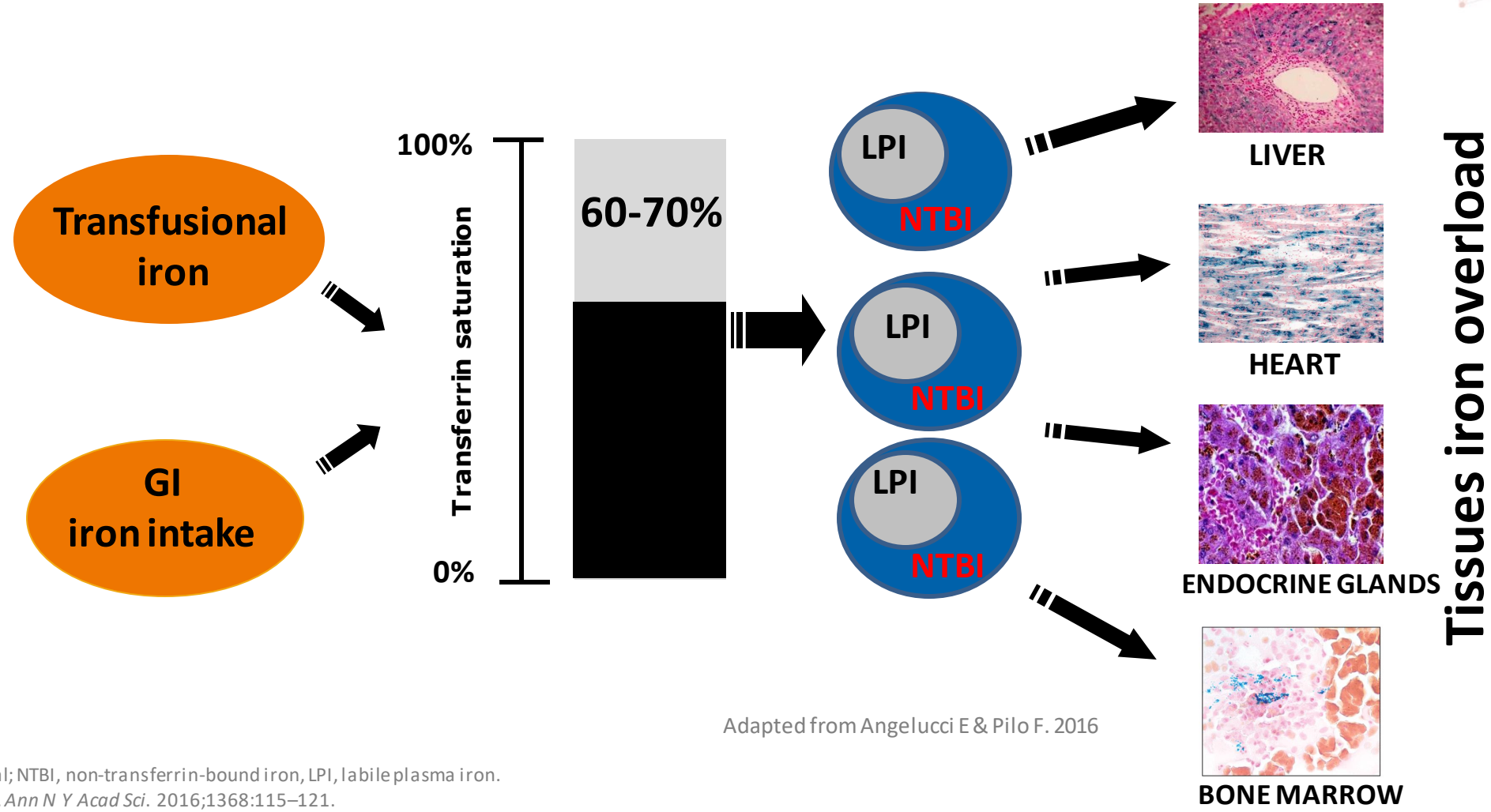
Forest plot of the subgroup analyses of the association of OS and SF according to SF≥1000 ng/mL and SF≥500 ng/mL cut-offs



Adapted from Pileggi C, et al. 2017

MDS, Myelodysplastic syndromes; OS, overall survival; RR, relative risk; SF, serum ferritin.
Pileggi C, et al. *PLOS ONE.* 2017;12:e0179016.

Development of tissue iron overload and tissue damage



Adapted from Angelucci E & Pilo F. 2016

GI, gastrointestinal; NTBI, non-transferrin-bound iron, LPI, labile plasma iron.
Angelucci E, Pilo F. *Ann N Y Acad Sci*. 2016;1368:115–121.

Iron tissue toxicity

ΣTissue Reactive Iron x Genetics x Environmental Factors x Time

"Iron toxicity depends on many factors in addition to the level of iron per se"

- There is a different relation (iron and damage) for different tissues
- Tissue toxicity sums (Σ) over time (ΔTime)
- It will likely never be possible to accurately predict toxicity from individual component factors

Not only the magnitude of iron overload is important, but the duration of exposure to toxic iron is important

GI, gastrointestinal; NTBI, non-transferrin-bound iron; LPI, labile plasma iron.

1. Coates TD. *Free Radic Biol Med.* 2014;72:23–40; 2. Angelucci E, et al. *Am J Hematol.* 2017;92:411–413.

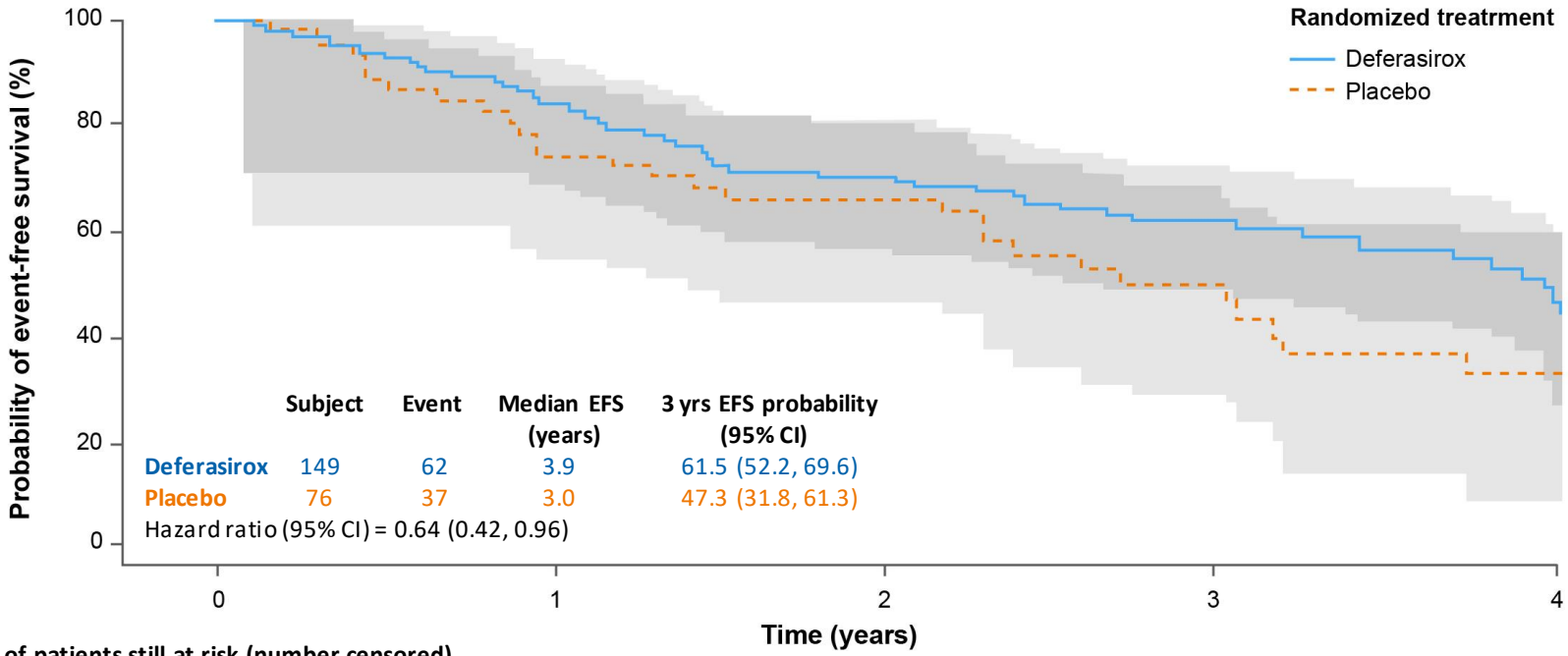
Studies demonstrating a survival benefit of chelation therapy presented limitations

Study	N	Design	Survival	Non-chelated patients	Chelated patients	*P* value
Leitch 2008	36	Retrospective	Median overall OS	40 months	Not reached	0.003
			4-year survival	43%	64%	0.003
Rose 2010	97	Prospective follow-up	Median OS from diagnosis	53 months	124 months	<0.0003
			Median OS with adequate vs weak chelation	NA	124 vs 85 months	<0.001
Neukirchen 2012	188	Matched pair analysis	Median OS	49 months	75 months	0.002
Neukirchen 2012	417	Retrospective, registry	Median time to death in transfusion-dependent patients	30 months	67 months	NR
Komrokji 2011	97	Retrospective	Median OS	34 months	59 months	0.013
Delforge 2012	186	Retrospective	Median OS in Low/Int-1	37 months	126 months	<0.001
Zeidan 2012	4226	Retrospective, registry	Median survival	47 weeks	110 weeks	0.003
			HR for 27–52 weeks on DFX	1	0.77	NR
			HR for ≥53 weeks on DFX	1	0.34	NR
de Witte 2012	1000	Prospective, registry	Adjusted HR	1	0.51 (0.19–1.32)	NS
Delforge 2014	127	Retrospective follow-up	Median OS	3.1 years	10.2 years	<0.001
Remacha 2015	263	Retrospective	Median OS	153 months	Not reached	<0.001
Langemeijer 2016	195/573	Registry	Adjusted HR	1.3 (0.95–1.7)	1	0.01
Lyons 2017	599	Prospective, registry	Median OS from diagnosis	47.8 months	All 86.3 months ICT >6 months: 98.7 months	<0.0001
Leitch 2018	239	Prospective, registry	Median OS from transfusion dependence	2.1 years	5.2 years	<0.0001

DFX, deferasirox; HR, hazard ratio; ICT, iron chelation therapy; Int-1, intermediate 1; OS, overall survival.

Platzbecker U, Fenaux P. Myelodysplastic Syndromes: Diagnosis - Prognosis – Therapy [eBook]. Springer, Cham. 2018. Iron Chelation [cited February 2020]: 105–111.

The TELESTO prospective, randomized, placebo-controlled trial: Kaplan Meier plot for EFS



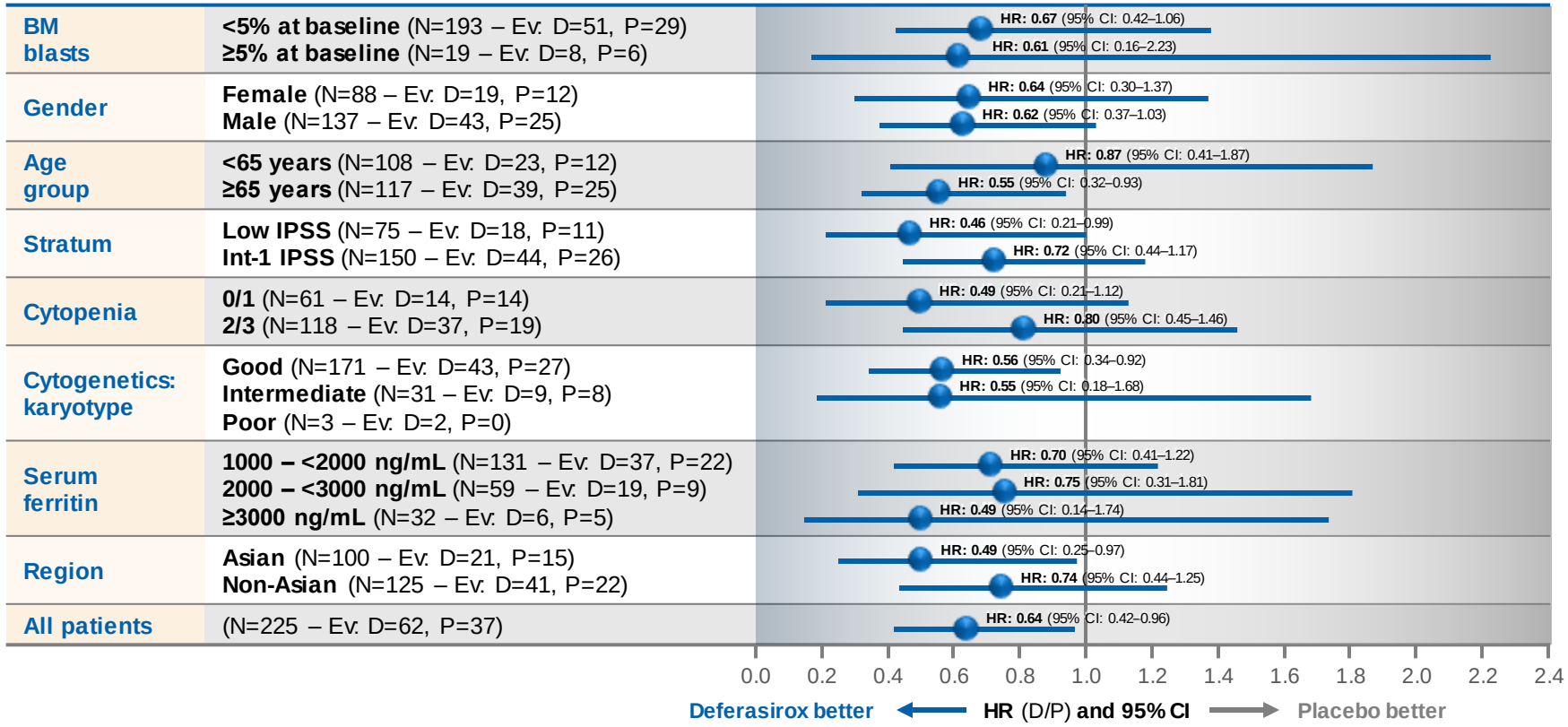
No. of patients still at risk (number censored)					
Deferasirox	149	104(25)	82(5)	61(11)	23(27)
Placebo	76	43(8)	27(8)	15(5)	8(10)
No. of patients still at risk (number censored)					
Deferasirox	148	90	65	41	16
Placebo	76	38	20	7	1

Data beyond 4 years are not shown, as few patients were followed at later timepoints. A stratified Cox regression model was used to provide estimates of the hazard ratio and associated Wald 95% confidence intervals. Median EFS and survival probability estimates were obtained by Kaplan-Meier methodology. Number of patients censored refers to the previous time interval.

CI, confidence interval; EFS, event-free survival.
Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

Adapted from Angelucci E, et al. 2020

The TELESTO prospective, randomized, placebo-controlled trial: Forest plot for EFS



BM, bone marrow; CI, confidence interval; D, deferasirox; Ev, event; EFS, Event-free survival; HR, hazard ratio; Int-1, Intermediate-1; IPSS, International Prognostic Scoring System P, placebo.

Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

Adapted from Angelucci E, et al. 2020

The TELESTO prospective, randomized, placebo-controlled trial: EFS events

EFS events that occurred first as confirmed by the EAC (adjudication rate 44%)

Parameter	Patients with events†		
	Deferasirox (N=149) n (%)	Placebo (N=76) n (%)	All patients (N=225) n (%)
Non-fatal events confirmed by EAC*	14 (9.4)	12 (15.8)	26 (11.6)
Progression to AML	10 (6.7)	6 (7.9)	16 (7.1)
Hospitalization for CHF	1 (0.7)	3 (3.9)	4 (1.8)
Liver cirrhosis	0	0	0
Liver function impairment	1 (0.7)	1 (1.3)	2 (0.9)
Worsening of cardiac function	2 (1.3)	2 (2.6)	4 (1.8)
Deaths during treatment	48 (32.2)	25 (32.9)	73 (32.4)

*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included.
†A patient with multiple occurrences of the same event is counted only once in the component category

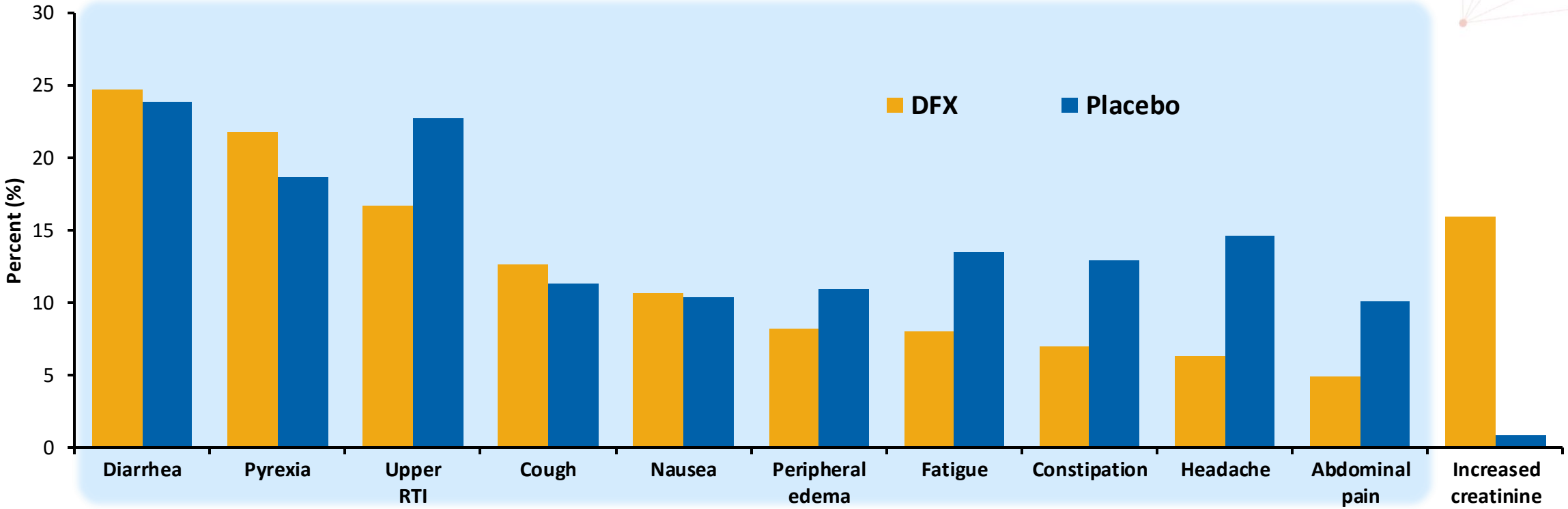
Adapted from Angelucci E, et al. 2020

TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS

AML, acute myeloid leukemia; CHF, congestive heart failure; EAC, endpoint adjudication committee; EFS, event-free survival.
Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

The TELESTO prospective, randomized, placebo-controlled trial: Exposure-adjusted AEs (>10% either arm)

All AEs, n
(Incidence rate per 100 subject treatment years)



IR = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in subject treatment years (STY) is counted up to the first event (or EOT for subjects without an event)

Adapted from Angelucci E, et al. 2020

AEs, adverse events; DFX, deferasirox; EOT, end of therapy.
Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

The TELESTO prospective, randomized, placebo-controlled trial: Exposure-adjusted AEs (>10% either arm)

All AEs, n
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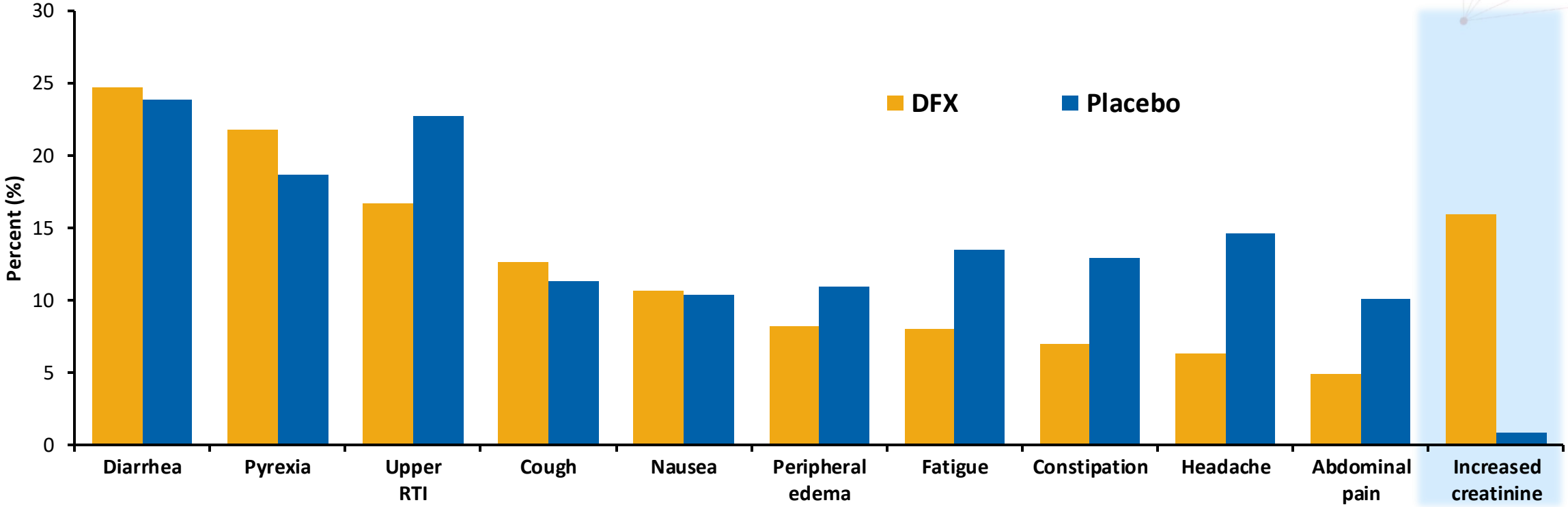


IR = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in subject treatment years (STY) is counted up to the first event (or EOT for subjects without an event)

Adapted from Angelucci E, et al. 2020

AEs, adverse events; DFX, deferasirox; EOT, end of therapy.
Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

Several retrospective, registry and finally a prospective, randomized clinical trial (TELESTO) consistently demonstrated clinical benefit of iron chelation therapy in transfusion-dependent MDS

MDS, Myelodysplastic syndromes.

Chelation indication and guidelines

On the assumptions that development of tissue damage requires:

- **Iron burden accumulation and**
- **Long life expectancy**

Usual indication to iron chelation required:

- **Transfusion dependency**
- **Bulky iron accumulation (serum ferritin / number of transfusions / LIC)**
- **Lower IPSS risk category**

IPSS, International Prognostic Scoring System; LIC, liver iron content.
Information provided by the speaker.

Rethinking treatment selection for patients with lower-risk MDS

BULKY DISEASE → **Changing the paradigm** → **TOXIC DISEASE**

- **Iron toxicity depends on many factors in addition to the level of iron per se**
- **Iron toxicity may not only depend on the degree of tissue iron accumulation but may also be related to chronic exposure to NTBI/LPI ⇒ ROS**
- **Not only the magnitude of iron overload is important, but also the duration of exposure to toxic iron**
- **With modern disease-modifying treatment MDS patients' survival is extended over the classical IPSS life expectancy**
- **TELESTO trial demonstrated a clinical benefit after two years of chelation therapy**

IPSS, International Prognostic Scoring System; LPI, labile plasma iron; MDS, myelodysplastic syndromes; NTBI, non-transferrin bound iron; ROS, reactive oxygen species.
Information provided by the speaker.

Rethinking treatment selection for patients with lower-risk MDS

- **Considering early chelation**
- **NTBI/LPI ideal chelation targets (not yet available) but transferrin saturation today reasonable surrogate**
- **Consider real life expectancy and additional risk in MDS patients**

LPI, labile plasma iron; MDS, Myelodysplastic syndromes; NTBI, non-transferrin bound iron.
Opinions of the speaker.

A Multicenter, Italian Trial of Early Iron Chelation Therapy with Low Dose Deferasirox (Exjade®) in Patients with Low/Intermediate-1 Risk MDS at the Beginning of Transfusional Story

Emanuele Angelucci, MD, Mario Capasso, PhD, Matteo Giovanni Della Porta, MD Gian Luca Forni, Domenico Girelli, M.D., PhD, Esther Natalie Oliva, MD, Federica Pilo, MD, Marino Clavio, MD, Marta Riva, MD, Annamaria Pelizzari, MD, Pasquale Niscola, MD, PhD, Daniela Cilloni, MD, PhD, Gianni Binotto, MD, Elena Crisà, MD and Valeria Santini

BACKGROUND

Most MDS patients require regular packed red blood cells (RBC) transfusions and finally most become transfusion dependent. One of the unavoidable consequences of transfusion therapy is iron overload which has been found to be deleterious for different categories of patients including MDS patients.

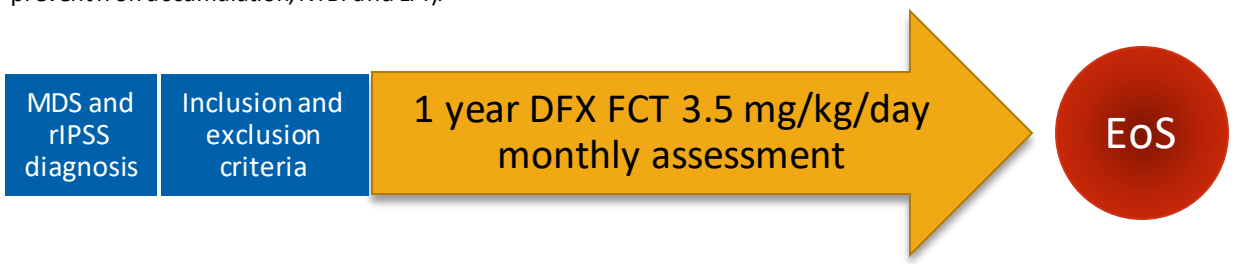
So far tissue and organ damage have been directly and strictly connected to the amount of tissue iron deposition (i.e. a "bulky" disease). All the studies performed in the last years have linked survival to markers of iron accumulation (mainly indirect markers) such as serum ferritin.

Recent data support the notion that iron disease is not only a "bulky" disease exclusively secondary to iron accumulation but rather it is a toxic disease in which tissue damage is due to toxic iron forms (Non-Transferrin-Bound-Iron, NTBI, and Labile Plasma Iron, LPI). These tissue reactive iron species are present in plasma since early phase of transfusion therapy or even before . NTBI and LPI emerge in the serum only once iron binding capacity is saturated in a rate over 60-70%

Notably these iron fractions are chelatable and can be removed from circulation by a chelator.

The scientific rationale for this study (ClinicalTrials.gov: NCT03920657; CICL670AIT17T) is the notion that iron-induced tissue damage is not only a process of progressive organs bulking through high-volumes iron deposition, but also a reactive iron species related "toxic" damage. Therefore, a timely early initiation of iron chelation may be of benefit before overt iron overload is seen.

Our hypothesis is that early and low dose Deferasirox film coated tablets (DFX-FCT) is well tolerated and is able to prevent iron accumulation, NTBI and LPI).



DFX, deferasirox; EOS, end of study; FCT, film coated tablets; MDS, myelodysplastic syndrome; rIPSS, Revised International Prognostic Scoring System

Angelucci E, et al. *Blood*. 2019;134:abst 4256.

STUDY DESIGN AND METHODS

INCLUSION CRITERIA

- Patients must be affected by Myelodysplastic Syndrome (MDS)
- aged ≥ 18 years
- very low, low and intermediate revised IPSS stage
- limited history of transfusions (5-20 RBC units)
- chelation naïve
- Additional inclusion criteria are serum ferritin levels >350 ng/mL and transferrin saturation >60%.

In a recruitment period of 1 years, 60 patients from 10 Italian centers will be included in the study. DFX-FCT will be administered at the fixed dose of 3.5 mg/kg/day for the entire study year.

PRIMARY EFFICACY OBJECTIVE AND END POINT:

evaluate impact on of iron burden in one-year treatment in early phase of transfusion requirement by low dose DFX-FCT acting as prevention of iron accumulation as demonstrated by hepatic iron concentration determined by liver MRI (end of study versus baseline).

SECONDARY OBJECTIVES AND ENDPOINTS:

1. Definition of iron overload and oxidative stress in MDS at beginning of transfusion history
2. demonstrating presence and quantitative changes of toxic serum iron forms and oxidative stress under low dose DFX-FCT therapy by regular NTBI, LPI and serum Malonildialdehyde (MDA) monitoring.
3. Verify if regular suppression of the "free iron forms" prevent tissue iron accumulation by absolute change in hepatic iron concentration end of study versus baseline
4. Evaluate the overall safety of low DFX-FCT dose in patients with lower risk MDS at the beginning of their transfusion history
5. hemopoietic response

CONCLUSIONS

This prospective multicenter study has been designed to investigate the clinical benefit and safety of early chelation therapy with DFX-FCT in patients with MDS at the beginning of their transfusion history to verify the possibility to continually suppress tissue NTBI, LPI and Oxidative stress thus preventing iron accumulation and tissue damage.

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Thank you for your very kind attention

Moving towards a targeted approach for patients with Myelodysplastic Syndromes

Uwe Platzbecker

D·MDS
Deutsche MDS-Studiengruppe

EMSCO
MYELODYSPLASTIC SYNDROMES

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Disclosures

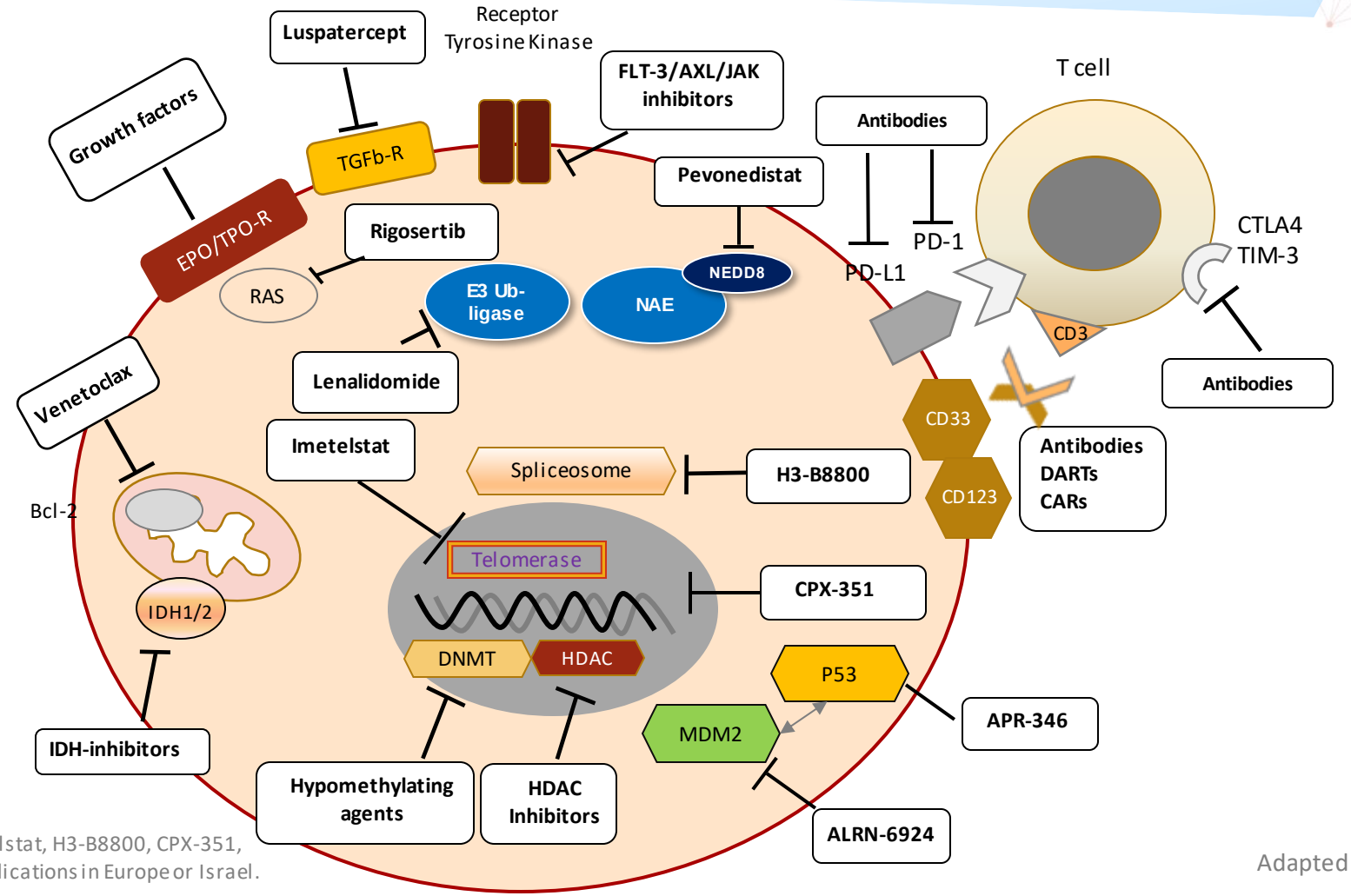
Research support:

- Amgen
- Celgene Corporation
- Janssen Biotech
- Merck
- Novartis

Consultant

- Celgene
- Celgene Corporation
- Novartis

No drug will be useful for all types of MDS, but different pathways may be possible targets



Luspatercept, pevonedistat, venetoclax, rigosertib, imetelstat, H3-B8800, CPX-351, APR-346 and ALRN-6924 are not yet licensed for MDS indications in Europe or Israel.
Platzbecker U. *Blood.* 2019;133:1096–1107.

Adapted from Platzbecker U. 2019

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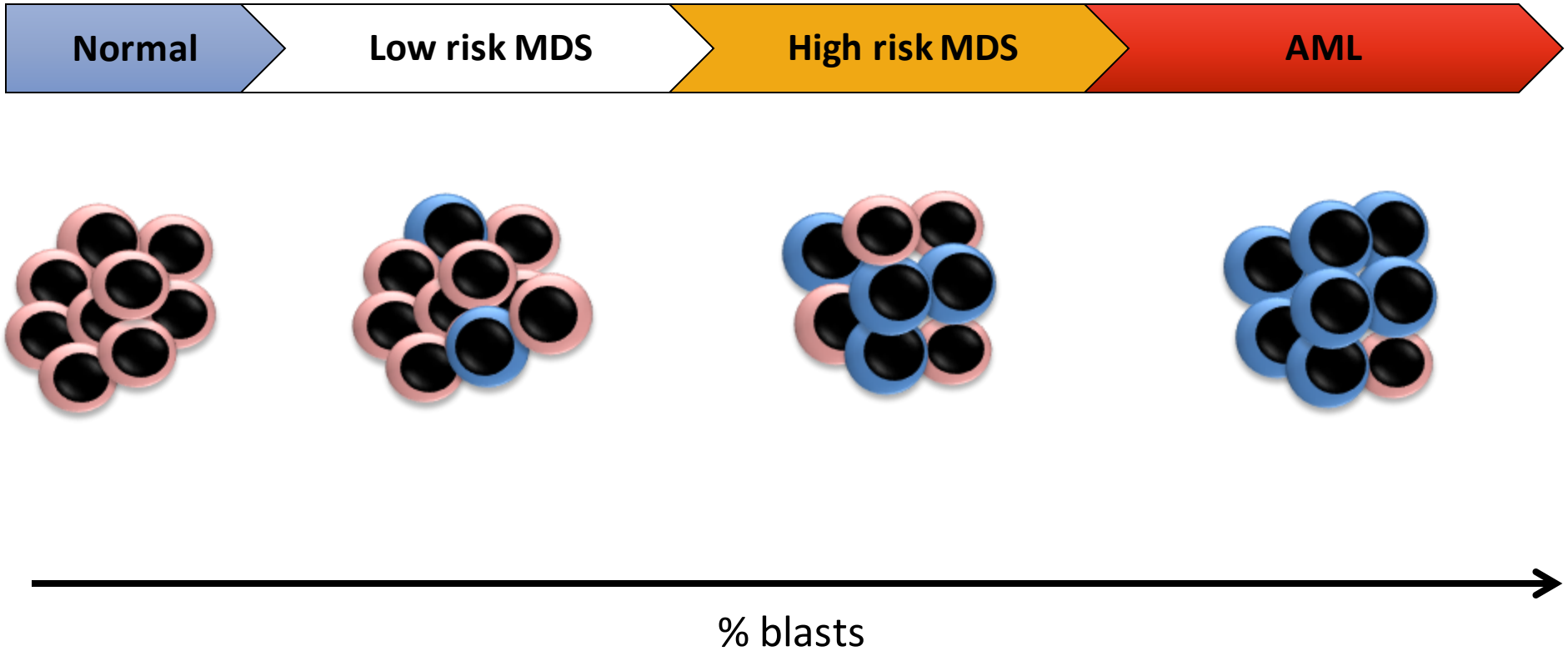
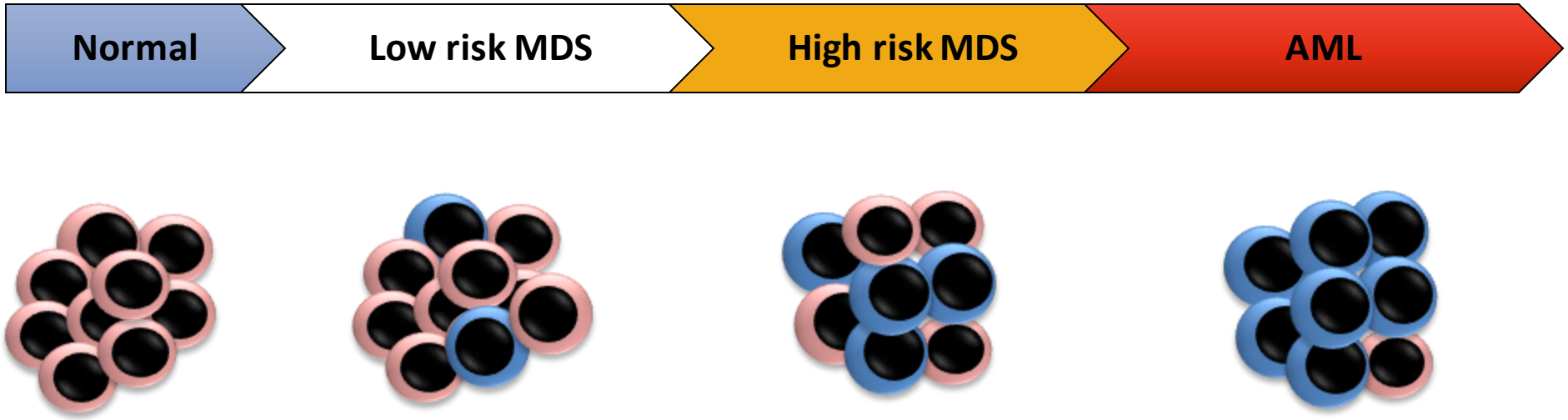
Bcl-2, B-cell lymphoma 2; CAR, Chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DART, dual-affinity re-targeting antibody; DNMT, DNA methyltransferase; EPO, erythropoietin; FLT-3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; JAK, janus kinase; MDM2, murine double minute 2; NAE, NEDD8-activating enzyme; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TGF b-R, transforming growth factor beta receptor; TIM-3, T-cell immunoglobulin and mucin domain-3; TPO, thrombopoietin.

Classification MDS/AML: Quantitative



AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

Classification MDS/AML: Quantitative

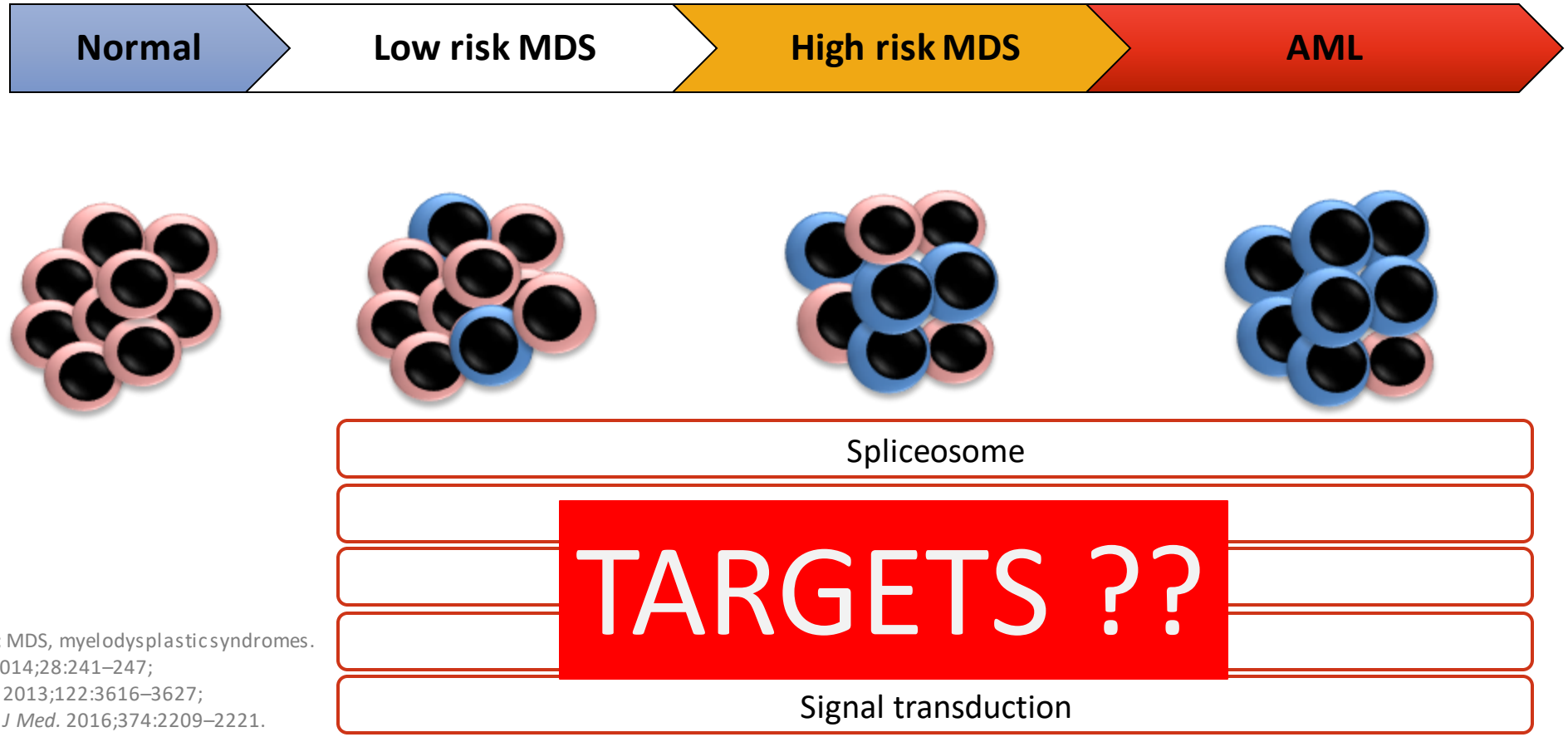


- Spliceosome
- Histone modification
- DNA methylation
- Transcription factors
- Signal transduction

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

Haferlach T, et al. *Leukemia*. 2014;28:241–247;
Papaemmanuil E, et al. *Blood*. 2013;122:3616–3627;
Papaemmanuil E, et al. *N Engl J Med*. 2016;374:2209–2221.

Classification MDS/AML: Quantitative



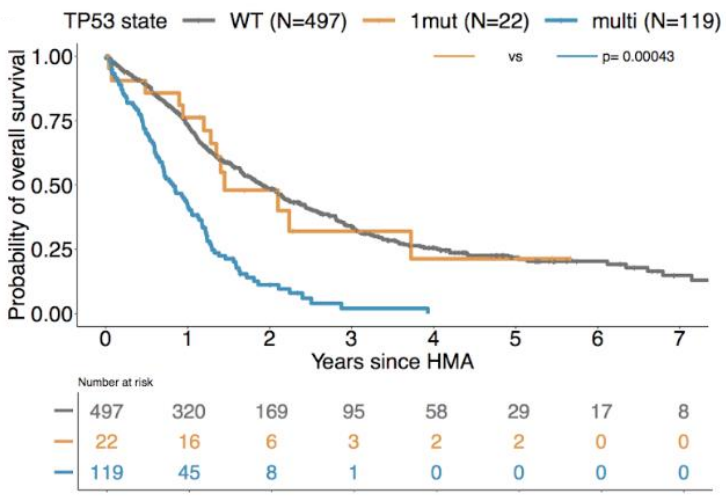
AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

Haferlach T, et al. *Leukemia*. 2014;28:241–247;
Papaemmanuil E, et al. *Blood*. 2013;122:3616–3627;
Papaemmanuil E, et al. *N Engl J Med*. 2016;374:2209–2221.

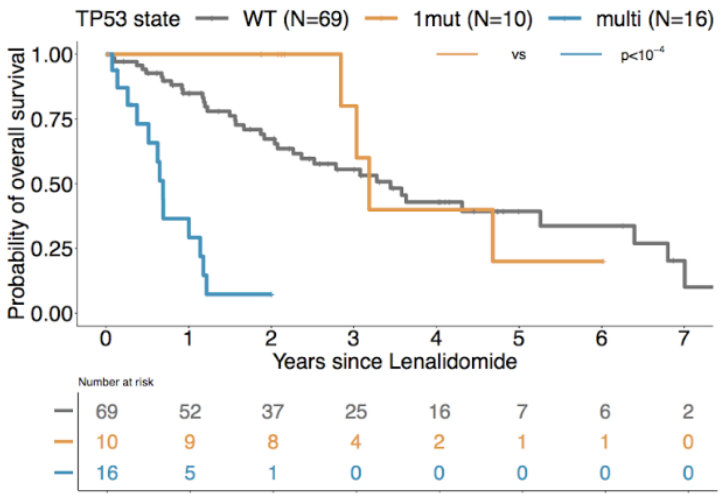
Implication of allelic states for treatment response

mTP53 ≠ mTP53

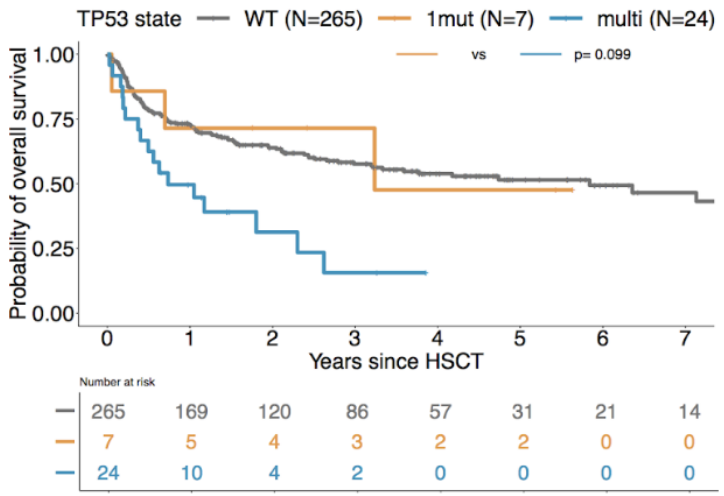
Hypomethylating agents



Lenalidomide



HSCT



Bernard E, et al. 2019

Consideration of TP53 allelic state in correlative studies of treatment response

HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; TP53, tumor protein p53; WT, wild type.
Bernard E, et al. Presented at ASH 2019. Abstr #675.

Targeting TP53

- **Drugs having p53 independent activity:**
  - **Anti-Bcl2 drug Venetoclax**
  - **Vosaroxin**
- **Drugs competing for p53 binding to MDM2:**
  - **Nutlin-3 (Roche)**
  - **HDM 201 (Novartis)**
  - **DS-3032 (Daiichi)**
- **10-day regimen of Decitabine**
- **“Reconforming” mutated p53 : APR 246**

Venetoclax, vosaroxin, APR-346, nutlin-3, HDM 201 and DS-3032 are not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe.
TP53, tumor protein p53; MDM2, murine double minute 2.
Information provided by the speaker.

APR-246 combined with AZA in TP53-mutated MDS and AML

Phase 2 study by the Groupe Francophone des Myélodysplasies (GFM)

Response in the 44 patients enrolled before June 2019

Intention to treat	n=44		
Time of evaluation	Best response	After C3	After C6
ORR	55%	51%	51%
CR	39%	25%	39%
mCR/MLFS	7%	12%	7%
PR	0%	7%	0%
SD with HI	9%	7%	5%

Evaluable patients*	n=35		
Time of evaluation	Best response	After C3	After C6
ORR	66%	64%	64%
CR	49%	31%	49%
mCR/MLFS	9%	15%	9%
PR	0%	9%	0%
SD with HI	9%	9%	6%

*ie patients who received at least 3 cycles and had a marrow evaluation after 3 cycles

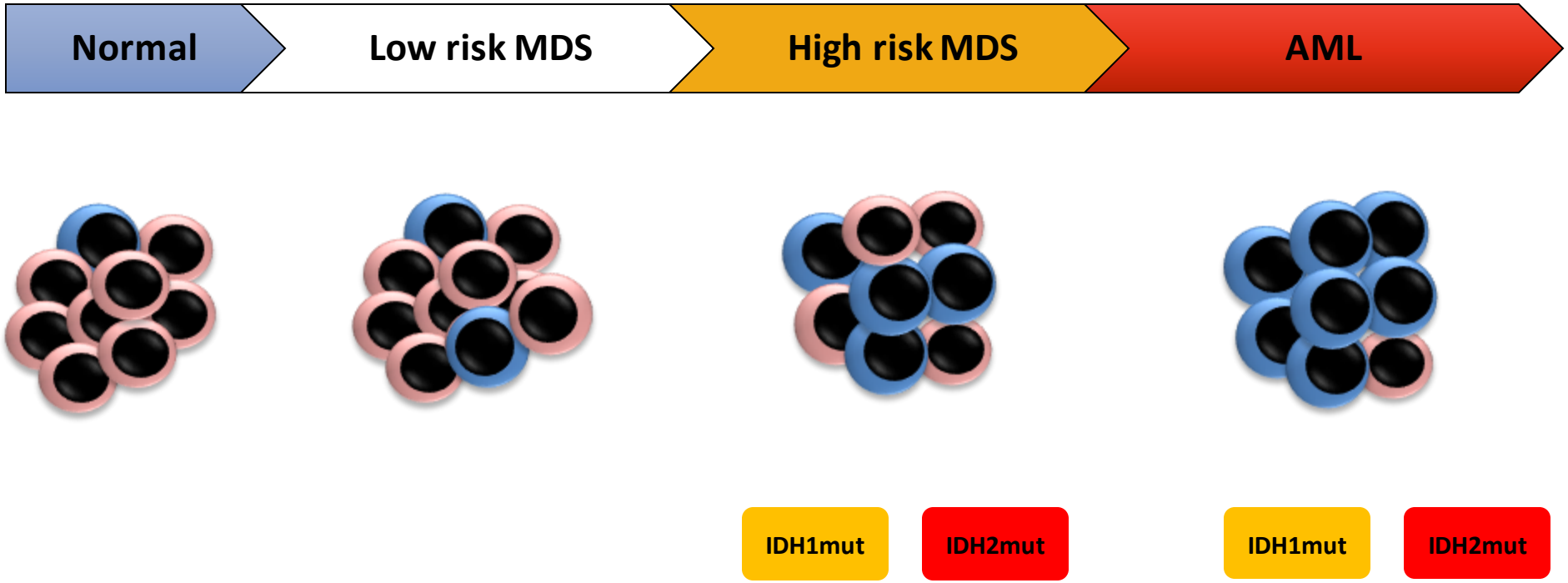
3 patients underwent allogeneic SCT, one of them had started maintenance treatment post transplant

APR-346 is not yet licensed for MDS indications in Europe or Israel.

AML, acute myeloid lymphoma; AZA, azacitidine; CR, complete response; HI, hematologic improvement; mCR, marrow complete response; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; SCT, stem cell transplant; SD, stable disease; TP53, tumor protein p53.

Cluzeau T, et al. Presentation at ASH 2019. Abstr #677.

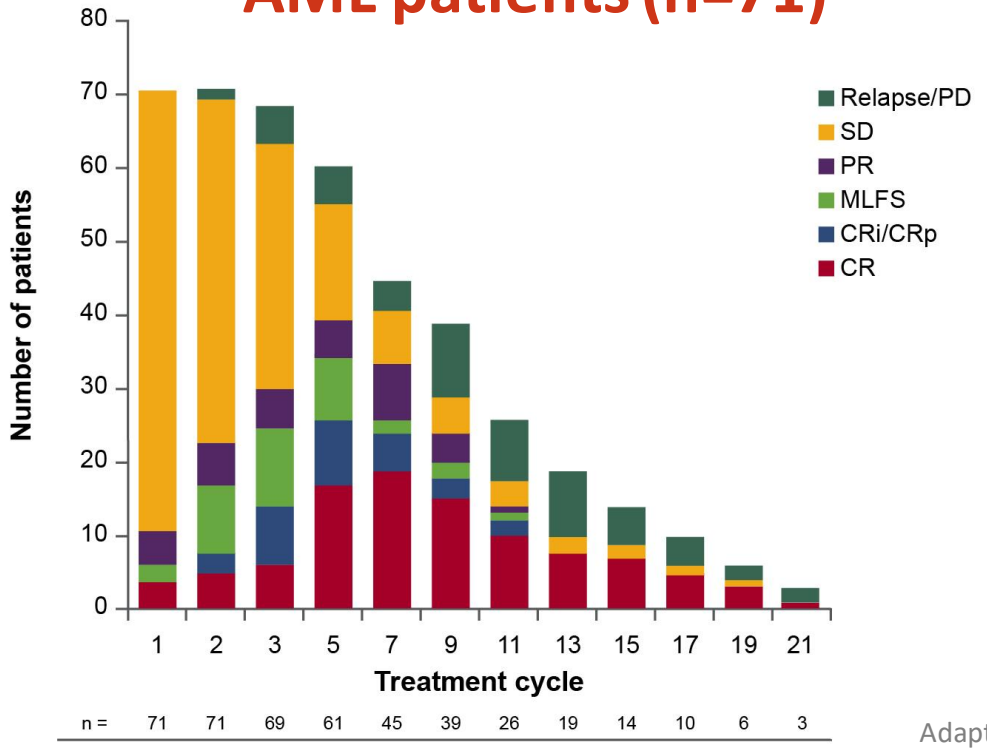
IDH-Mutations



AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndromes.
Stein EM, et al. *Blood*. 2017;130:722–731; DiNardo CD, et al. *N Engl J Med.* 2018:378:2386–2398.

Enasidenib - IDH2 inhibitor

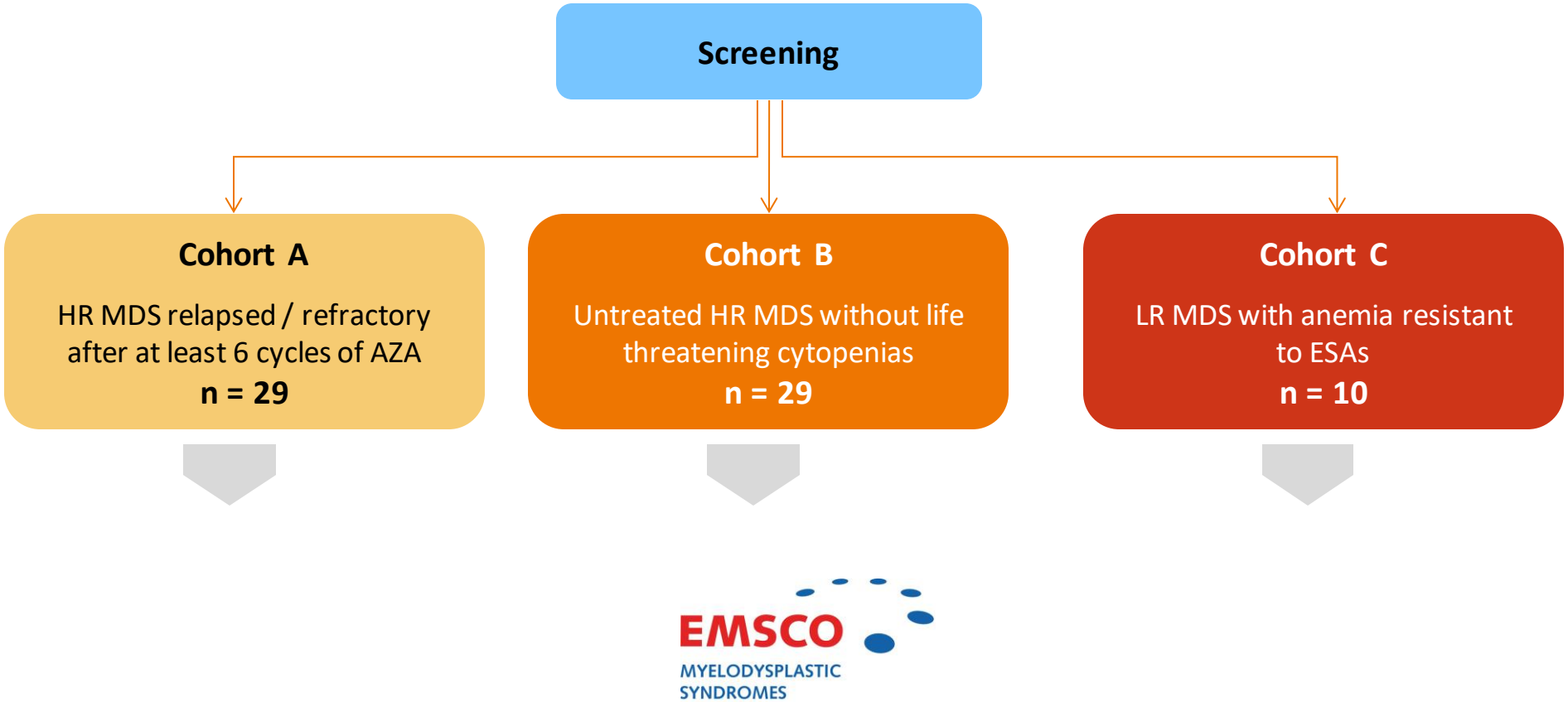
Evolution of response during Enasidenib treatment or responding AML patients (n=71)



Adapted from Stein EM, et al. 2017

Enasidenib is not yet licensed for MDS indications in Europe or Israel.
AML, acute myeloid leukemia; CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.
Stein EM, et al. *Blood*. 2017;130:722–731.

IDEAL – trial design



EMSCO
MYELODYSPLASTIC SYNDROMES

AZA, azacitidine; ESA, erythropoietin stimulating agent; HR, high risk; LR, low risk; MDS, myelodysplastic syndromes.
Information provided by the speaker.

Phase 2: Enasidenib + AZA in mIDH2-positive newly diagnosed AML

Efficacy	ENA + AZA (n=68)		AZA (n=33)
ORR, n (%)	**48 (71)**	*P*=0.0064	**14 (42)**
CR	36 (53)	*P*=0.0001	4 (12)
CRi/CRp	7 (10)		4 (12)
PR	3 (4)		4 (12)
MLFS	2 (3)		2 (6)
Median time to first response, months (range)	1.9 (1–9)		2.0 (1–6)
Median DOR, months (95% CI)	24.1 (11–NR)		12.1 (3–15)

Median OS in the ENA + AZA group was 22.0 months, and in the AZA Only group was 22.3 months

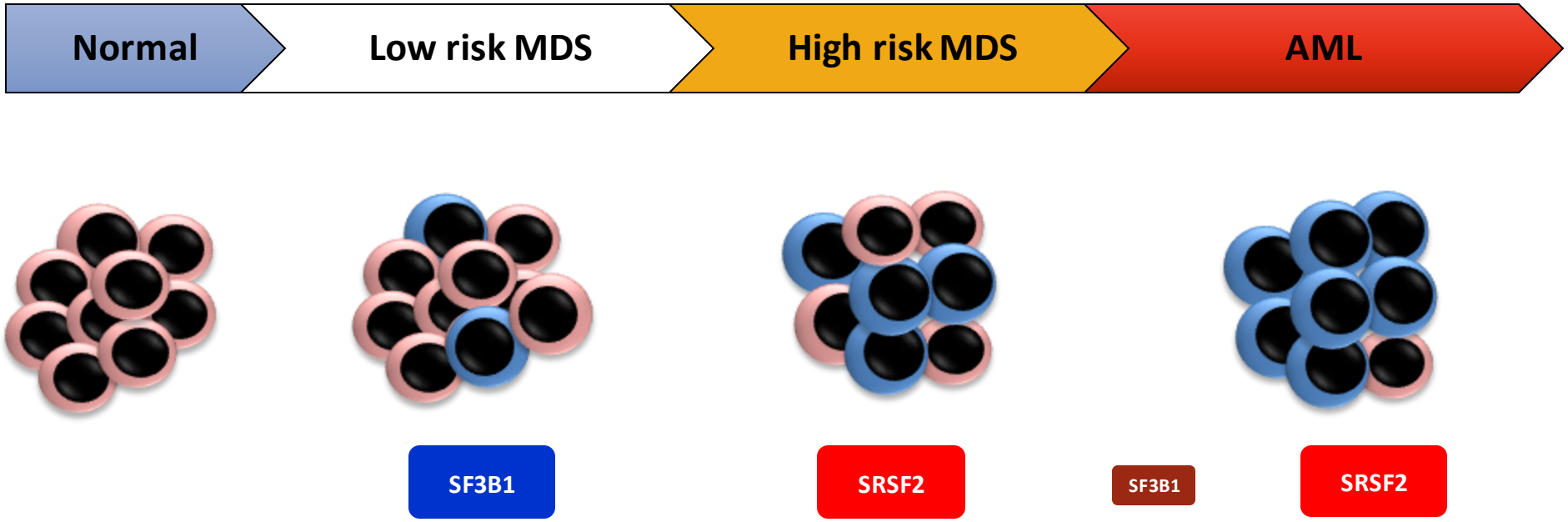
- (HR 0.99 [95% CI: 0.52–1.87], *P*=0.9686)

Enasidenib is not yet licensed for MDS indications in Europe or Israel.

AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DOR, duration of response; ENA, enasidenib; mIDH, mutant isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial response.

Di Nardo CD, et al. Presented at ASH 2019. Abstr #643.

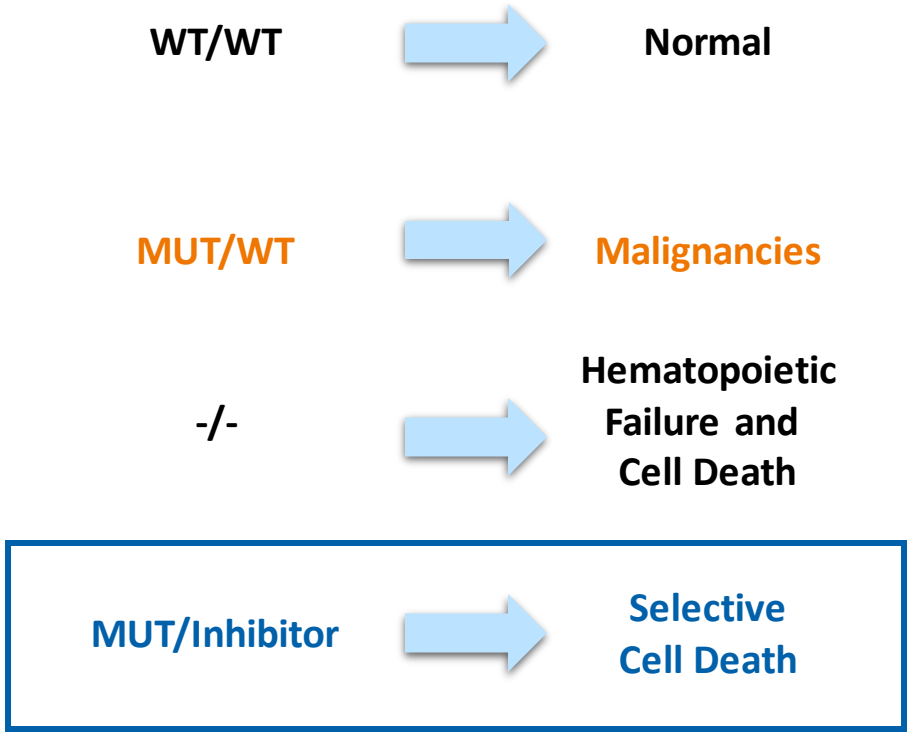
Molecular targets



AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2.
Information provided by the speaker.

“Spliceosomal sickness”

SF3B1-SRSF2-U2AF1



MUT, mutant; WT, wild type; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2; U2AF1, U2 small nuclear RNA auxiliary factor 1.
Seiler M, et al. *Nat Med.* 2018;24:497–504.

Based on Seiler M, et al. 2018

“Spliceosomal sickness”

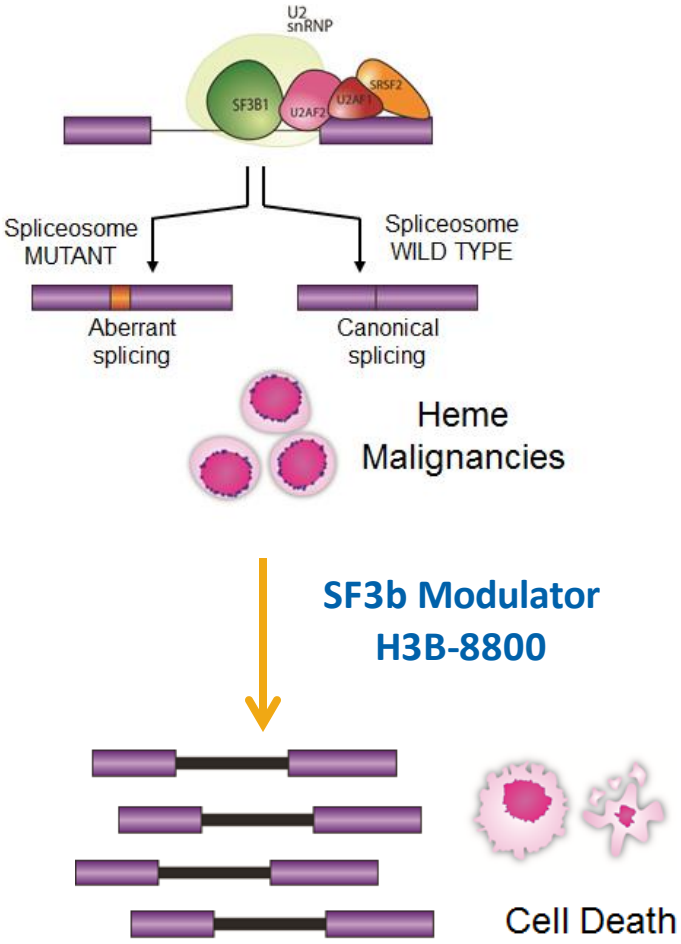
SF3B1-SRSF2-U2AF1

WT/WT → **Normal**

MUT/WT → **Malignancies**

-/- → **Hematopoietic Failure and Cell Death**

MUT/Inhibitor → **Selective Cell Death**



H3B-8800 is not yet licensed for MDS indications in Europe or Israel.
MUT, mutant; WT, wild type; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2; U2AF1, U2 small nuclear RNA auxiliary factor 1.
Seiler M, et al. *Nat Med.* 2018;24:497–504.

Based on Seiler M, et al. 2018

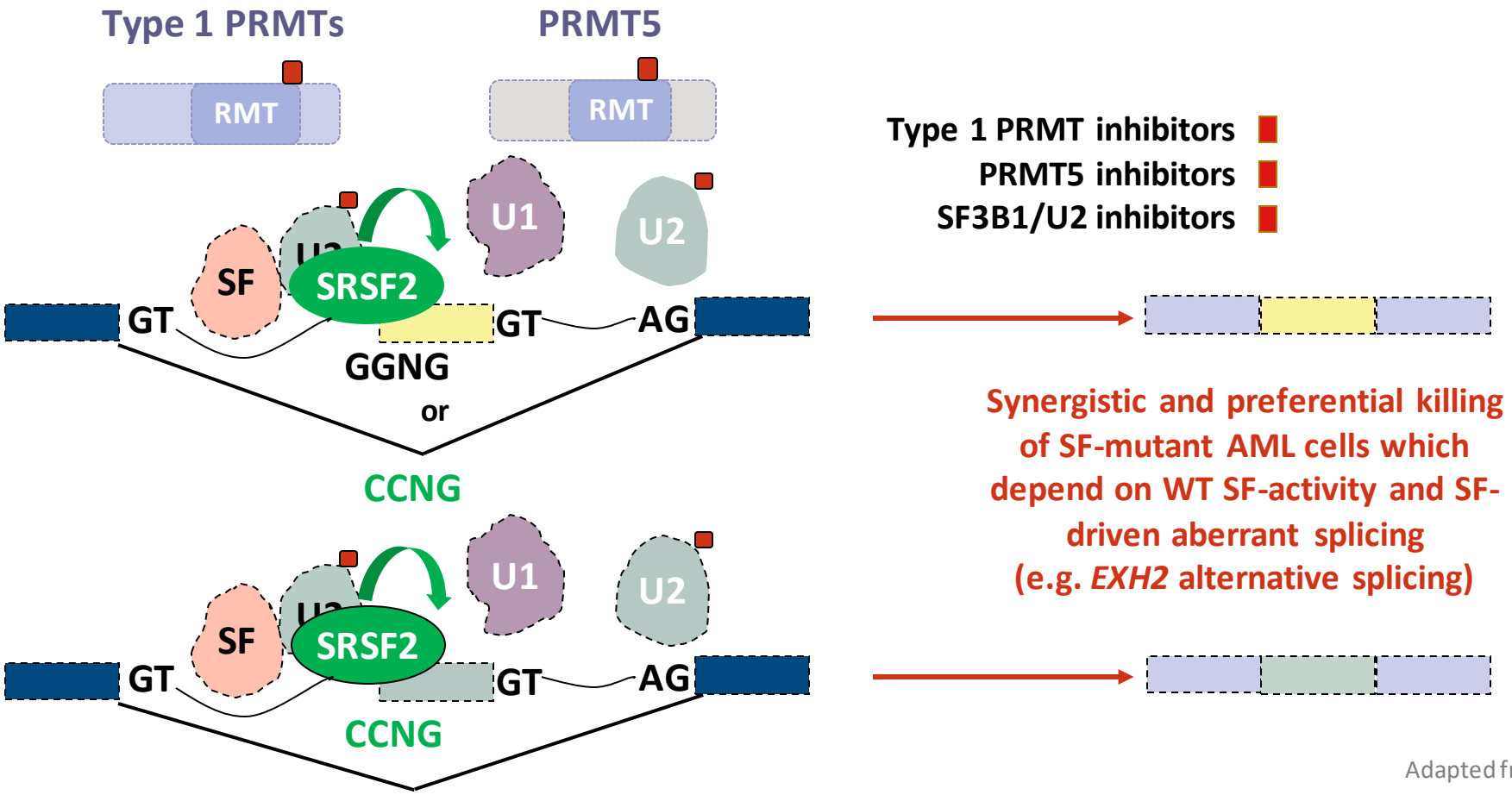
Results of a clinical trial of H3B-8800, a splicing modulator, in patients with MDS, AML or CMML

Open-label, first-in-human, Phase I, dose escalation (3 + 3) study (NCT02841540)

Outcome measure, n (%)	N=84
Complete response*	0
Partial response*	0
Bone marrow response	1[†] (1.2)
RBC transfusion dependence* at baseline	**n=61**
RBC transfusion independence ≥8 weeks	13[‡] (21.3)
RBC transfusion independence ≥8 weeks	13[‡] (21.3)

H3B-8800 is not yet licensed for MDS indications in Europe or Israel.
*International Working Group criteria; [†]One patient with CMML. Began in Cycle 1 and persisted through Cycle 13; [‡]Ten patients with MDS/CMML and 3 patients with AML. Up to 28 weeks.
AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes.
Steensma DP, et al. Presented at ASH 2019. Abstr #673.

Inhibition of Type 1 PRMTs and/or PRMT5

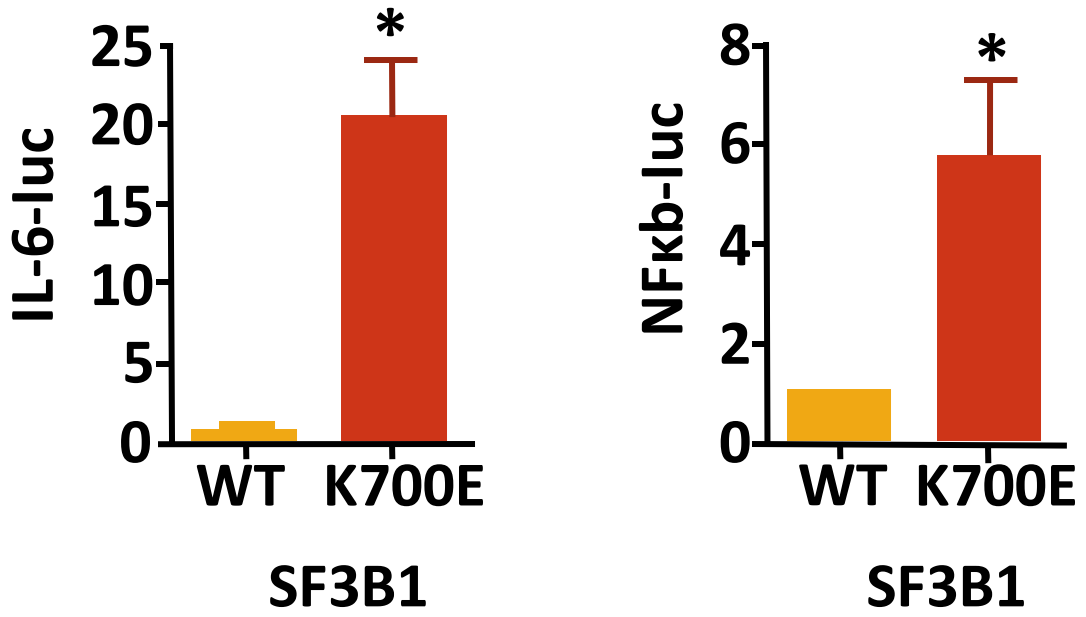


Synergistic and preferential killing of SF-mutant AML cells which depend on WT SF-activity and SF-driven aberrant splicing (e.g. *EXH2* alternative splicing)

Adapted from Fong JY, et al. 2019

AML, acute myeloid leukemia; EXH2, enhancer of zeste homolog 2; PRMT, protein arginine N-methyltransferase; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2 WT, wild type.
Fong JY, et al. *Cancer Cell.* 2019;36:194–209.

Spliceosome gene mutations found in MDS patients enhance inflammatory signalling in macrophages

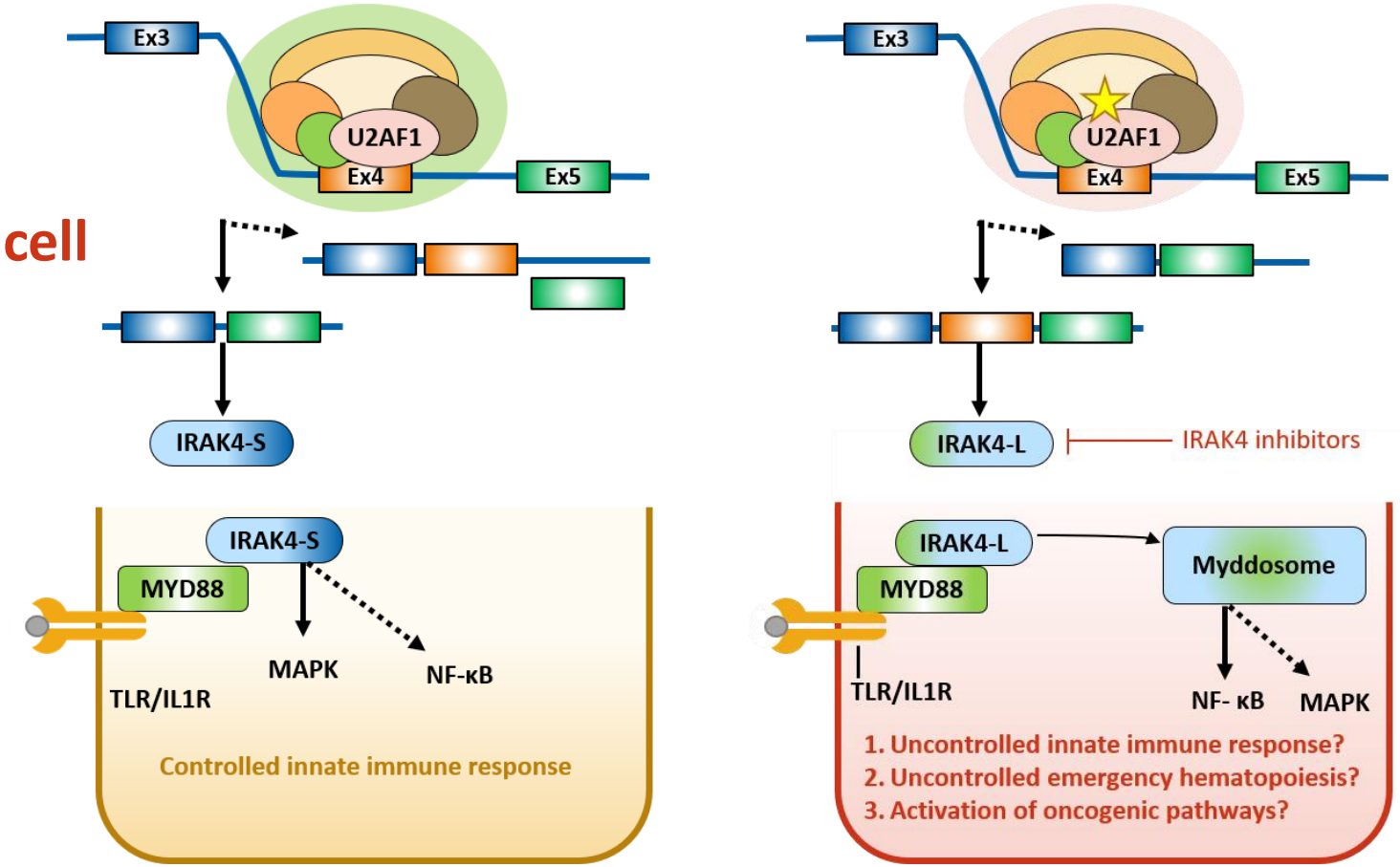


Adapted from Pollyea DA, et al. 2019

IL-5-luc, interleukin-6 luciferase reporter construct; MDS, myelodysplastic syndrome; NFκb-luc, NFκB-dependent luciferase reporter construct; SF3B1, splicing factor 3b subunit 1; WT, wild type.
Pollyea DA, et al. *Haematologica.* 2019;104:e391.

“Spliceosomal inflammation”

Normal haematopoietic cell



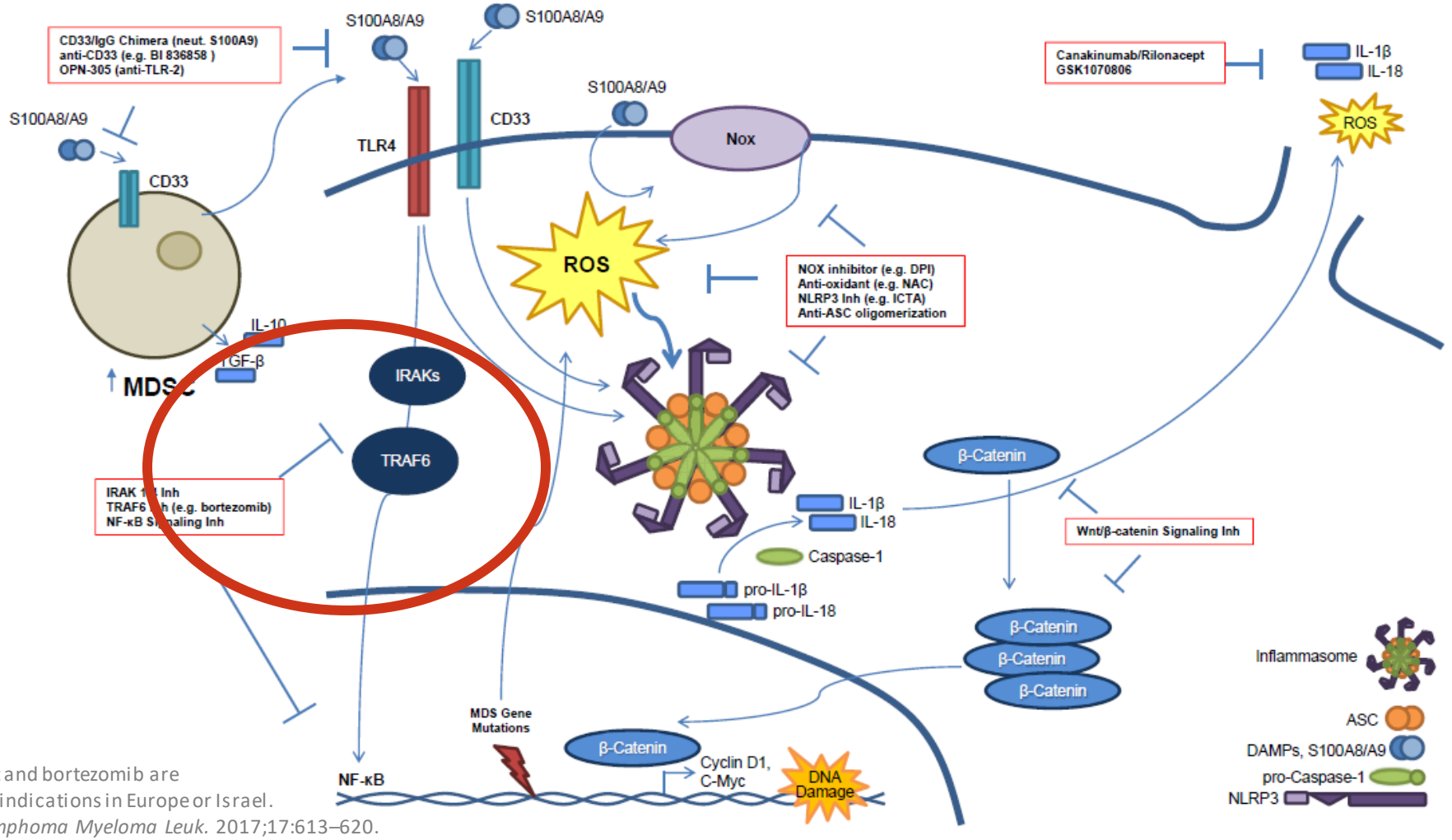
Malignant hematopoietic cell

Adapted from Guillamot M. 2019

IRAK, interleukin-1 receptor-associated kinase 4; MAPK, mitogen-activated protein kinase; TLR/IL1R, toll-like receptor/interleukin-1 receptor; U2AF1, U2 small nuclear RNA auxiliary factor 1.

Guillamot M, Aifantis I. *Nat. Cell Biol*. 2019;21:536–537.

Targeting the "Inflammasome"



Canakinumab, rilonacept and bortezomib are not yet licensed for MDS indications in Europe or Israel.

Sallman DA, et al. *Clin Lymphoma Myeloma Leuk.* 2017;17:613–620.

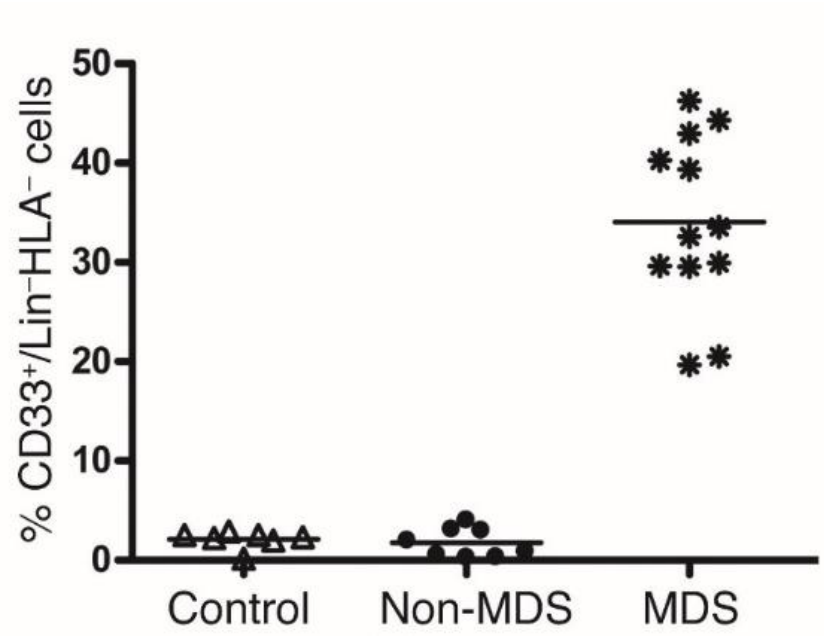
Sallman DA, et al. 2017

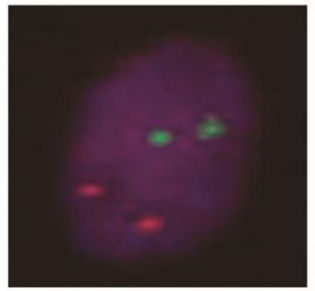
NOVARTIS

ASC, associated speck-like protein containing a caspase-recruitment domain; DAMPs, damage-associated molecular patterns; IL, interleukin; IRAKs, IL-1 receptor-associated kinases; Inh, inhibitor; neut., neutrophil; NOX, dihydronicotinamide-adenine dinucleotide phosphate oxidase; TGF-b, transforming growth factor-b; TLR, Toll-like receptor; TRAF6, tumor necrosis factor receptor-associated factor 6.

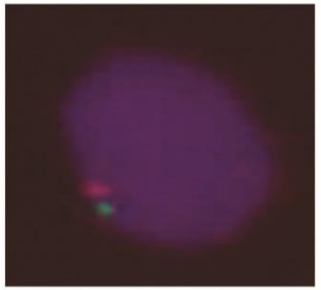
Inflammation driving ineffective hematopoiesis

Myeloid-derived suppressor cells

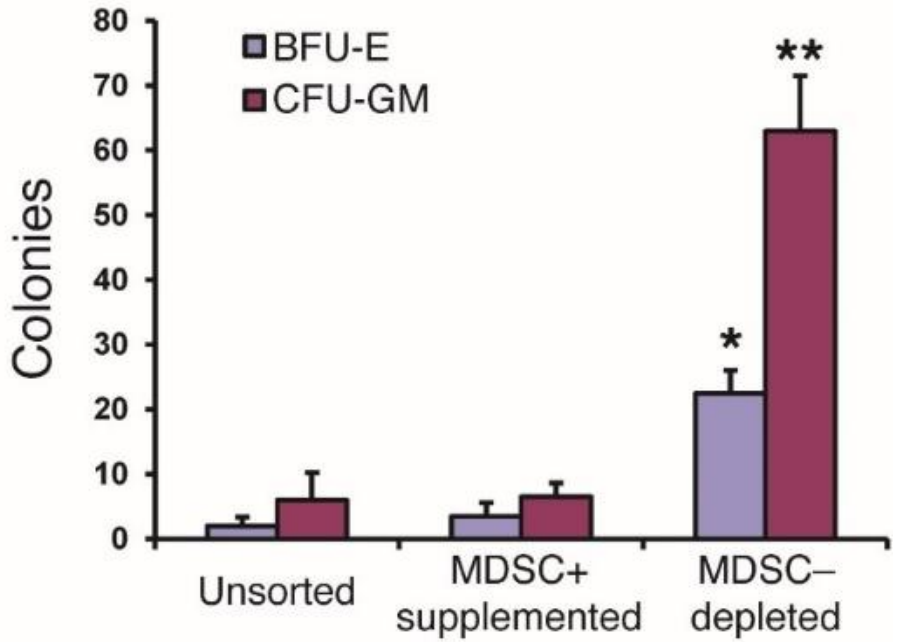




MDS-MDSC



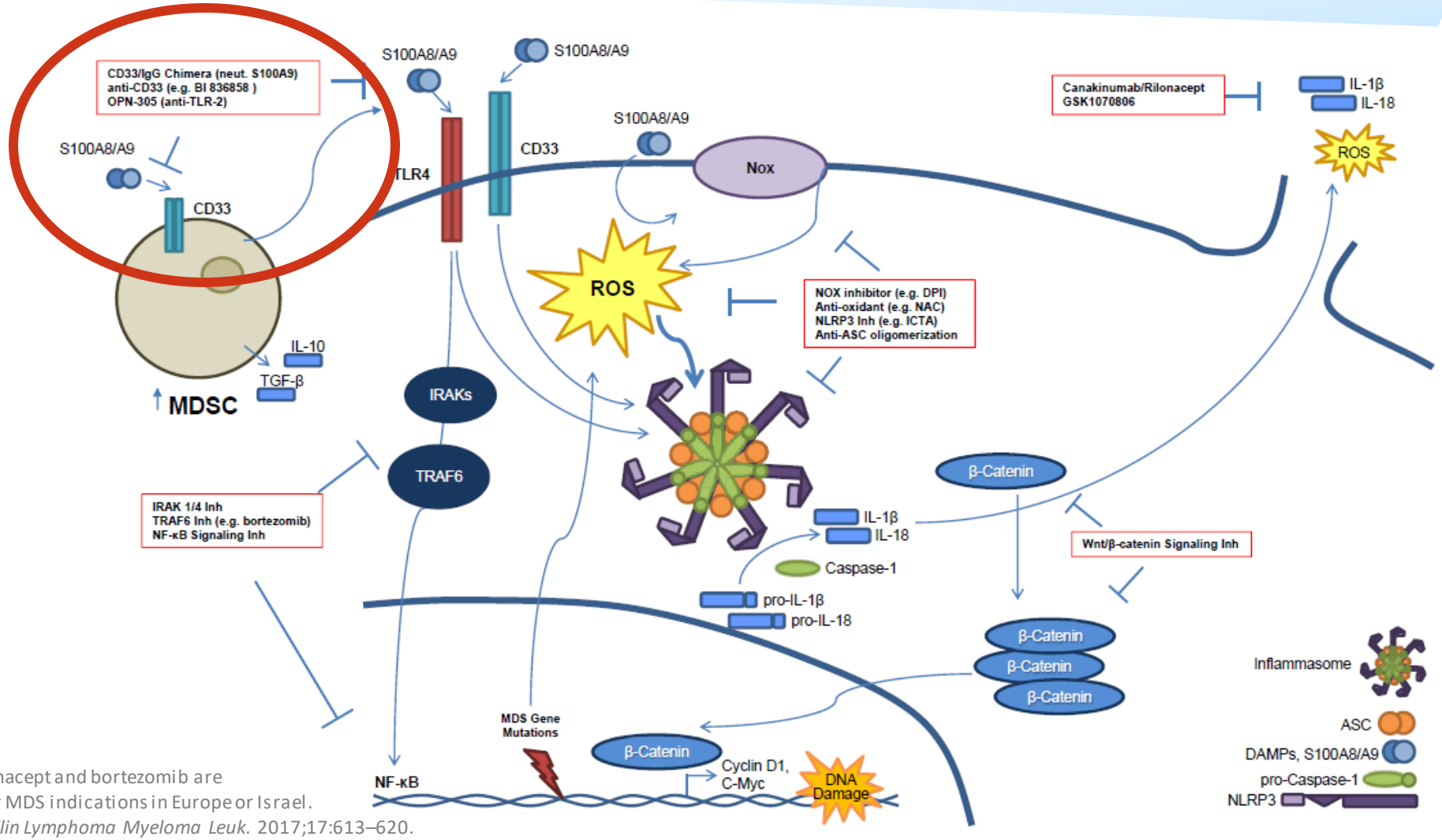
MDS



Images from: Chen X, et al. 2013

Images provided by speaker.
BFU-E, burst-forming unit–erythroid; CFU-GM, colony-forming unit–granulocyte-macrophage; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; MDSC, myeloid-derived suppressor cells.
Chen X, et al. *J Clin Invest.* 2013;123:4595–4611.

Targeting the "Inflammasome"



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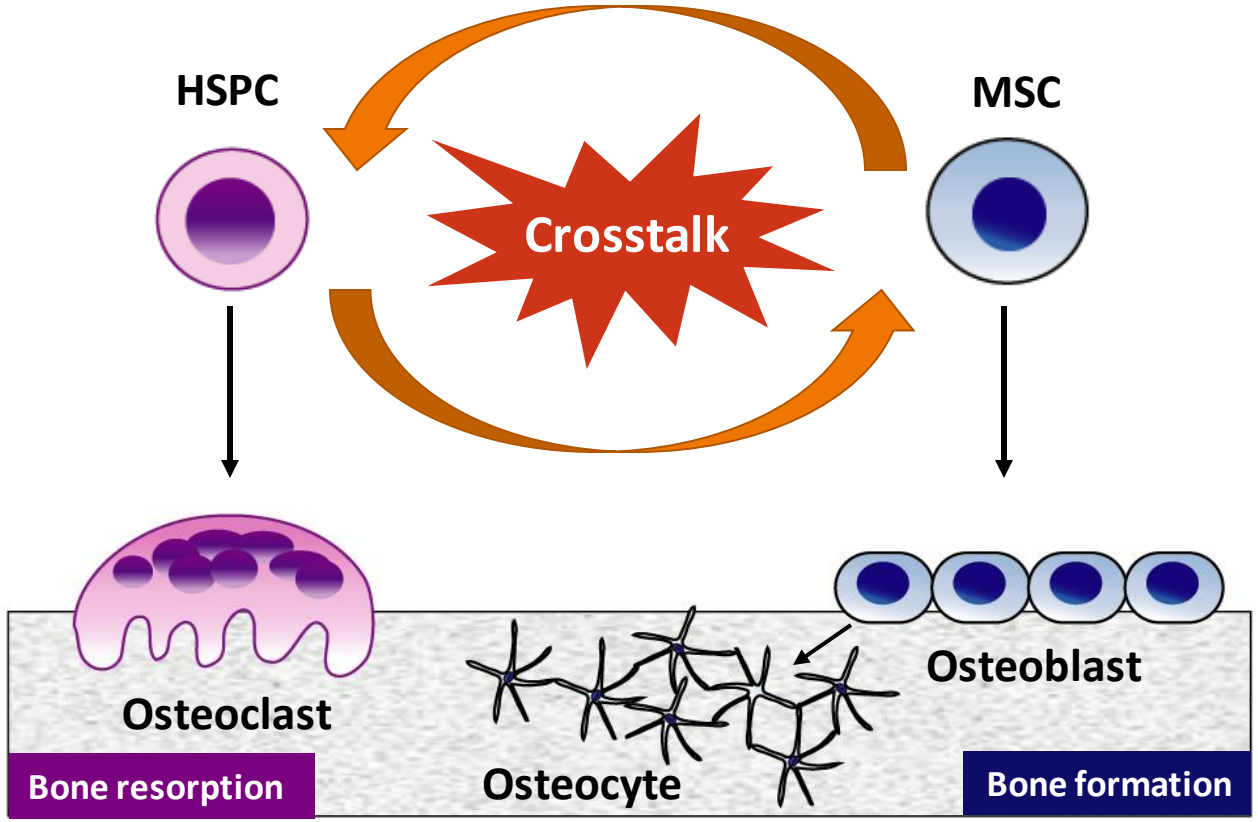
The osteo-hematopoietic niche in MDS



Adapted from Bulycheva E, et al. 2015

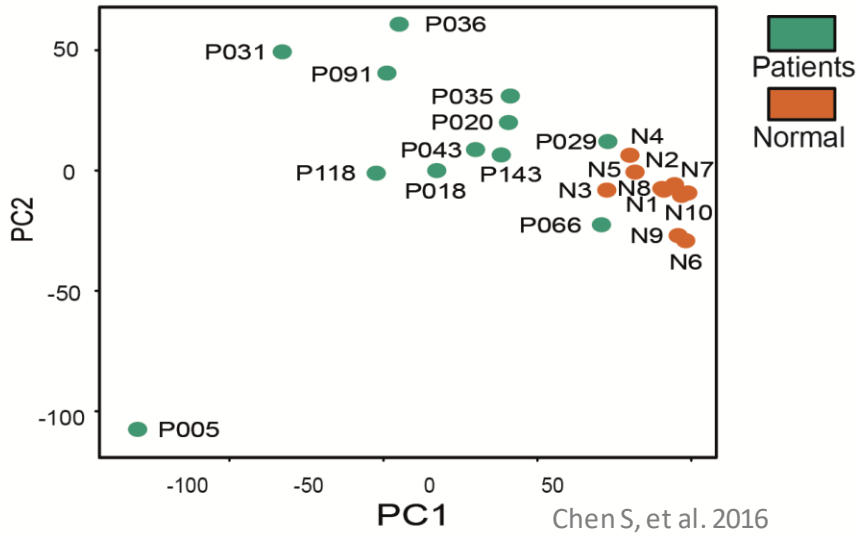
HSPC, hematopoietic stem and progenitor cells; MDS, myelodysplastic syndrome; MSC, mesenchymal stem cell.

Bulycheva E, et al. *Leukemia.* 2015;29:259–268.

Transcriptional network analysis of mesenchymal elements in low-risk MDS

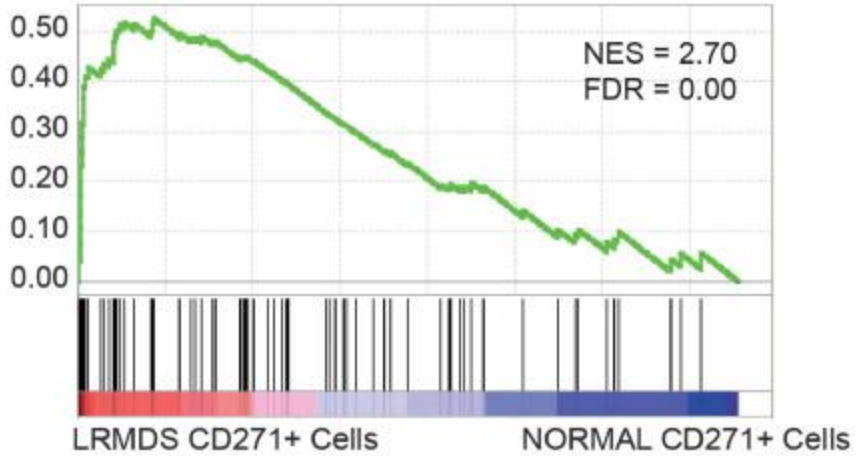
- Common, distinct molecular signature separating these cells molecularly from non-diseased stroma
- Activation of inflammatory programs
- Tissue-context dependent (lost in culture)

PCA on the transcriptomes of normal and LR-MDS mesenchymal cells



Chen S, et al. 2016

Example of GSEA plot revealing inflammatory response in the mesenchymal cells from LR-MDS

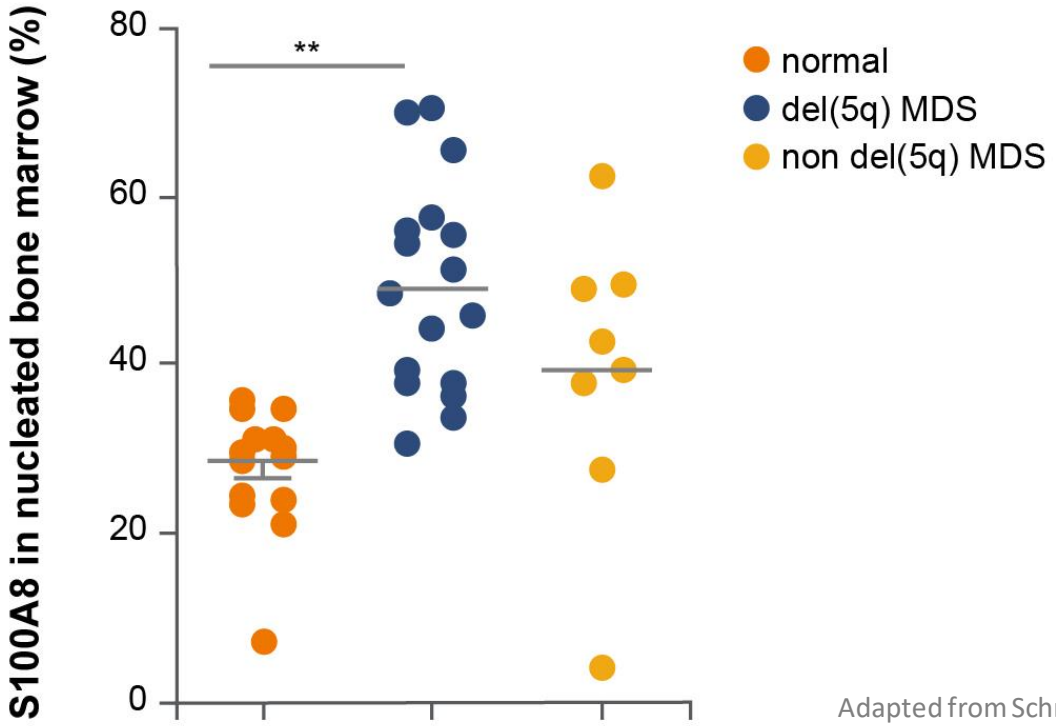


Chen S, et al. 2016

LR-MDS, low-risk myelodysplastic syndromes; FDR, false discovery rate; GSEA, gene set enrichment analysis; NES, normalized enrichment score; PCA, principal component analysis.
Chen S, et al. *Leukemia*. 2016;30:1938–1942.

Inflammation driving ineffective hematopoiesis: S100A

S100A8/S100A9 is induced during inflammatory processes including MDS

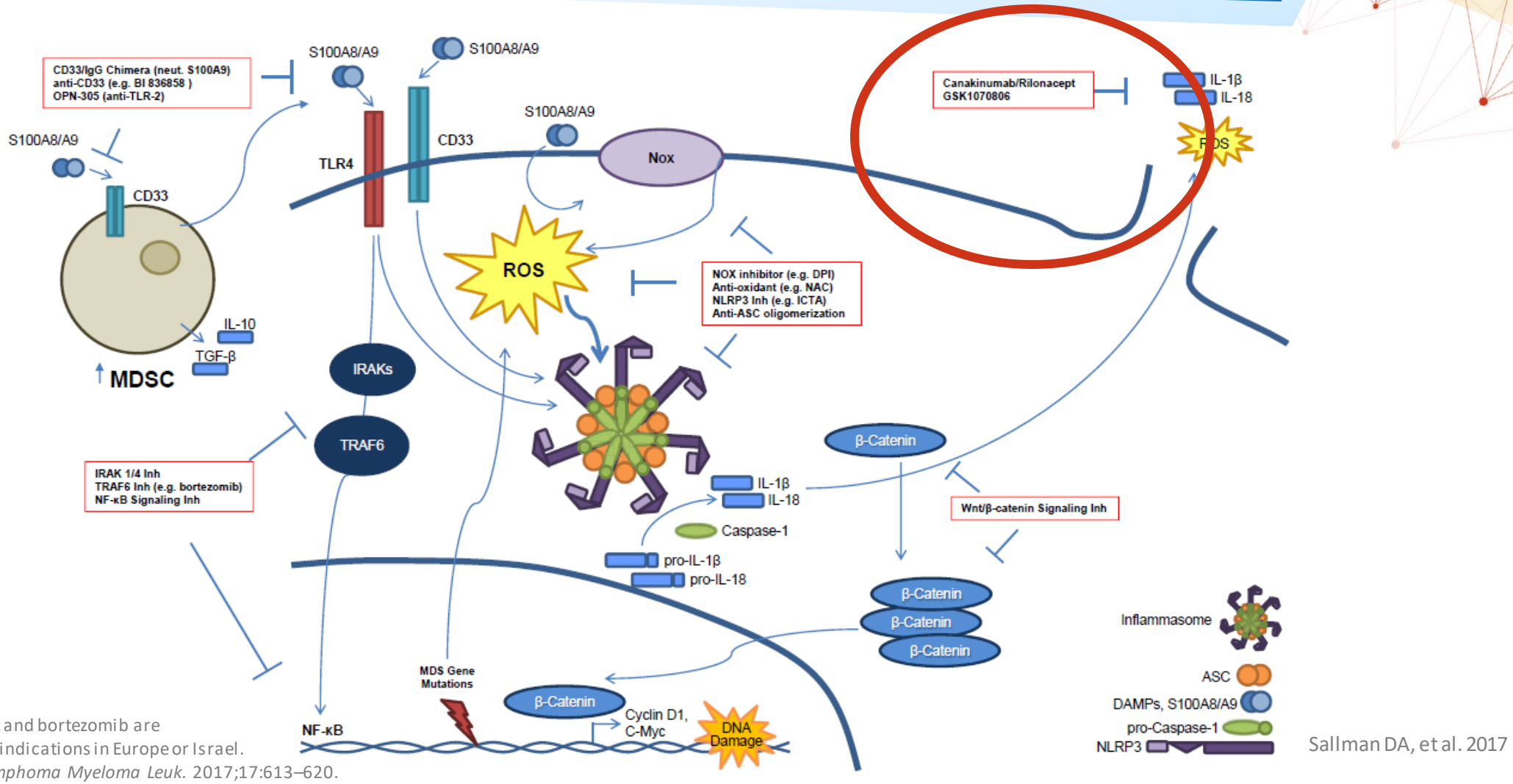


Adapted from Schneider RK, et al. 2016

MDS, myelodysplastic syndromes.

Schneider RK, et al. *Nat Med*. 2016;22:288–297.

Targeting the "Inflammasome"



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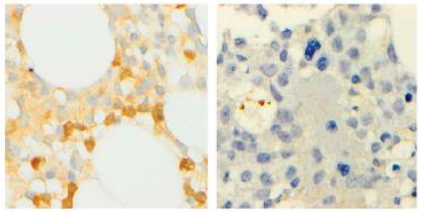
Immune checkpoint in MDS

Immunohistochemical analysis of PDL-1 and PD-1 membranous expression in CD34+ cell biopsy samples from MDS, CMML and AML patients

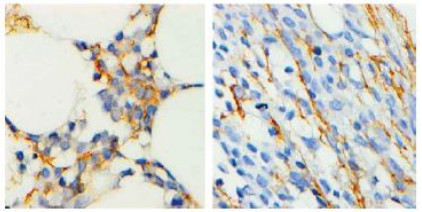
Bone marrow PD-L1

blast + blast -



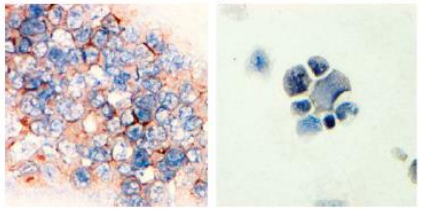
Bone marrow PD-1

blast + blast -, stroma +



Cytospin PD-L1

blast + blast -



Cytospin PD-1

blast + partial blast -

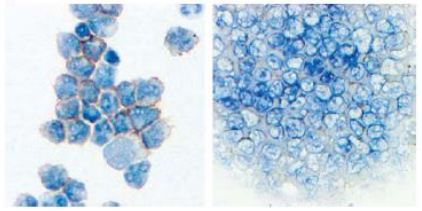


Image credit: Yang H, et al. 2014

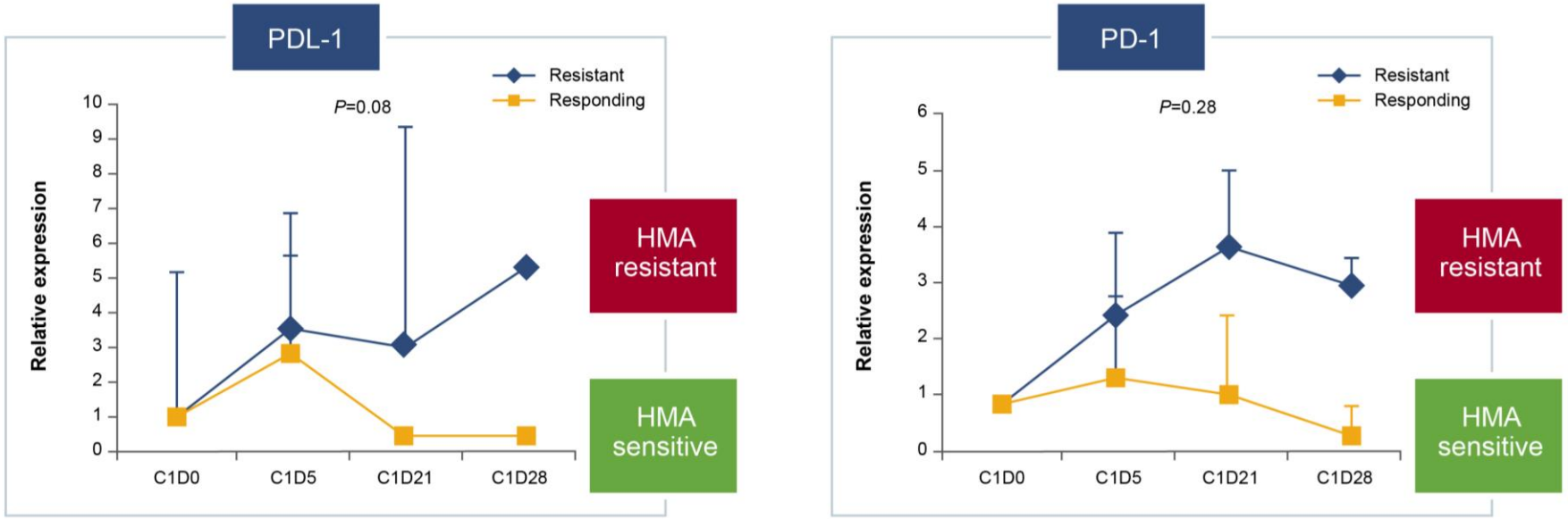
AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic sydromes; PD-1, programmed cell death protein 1; PDL, programmed cell death ligand.
Yang, H. et al. *Leukemia*. 2014;28:1280–1288.

Checkpoint modulation in HMA failure

Phase II trial of vorinostat + azacitidine

- A trend toward increased expression of PDL-1 and PD-1 in HMA resistant patients compared with HMA sensitive patients

Induction of PD-L1 and PD-1 expression in patients treated with vorinostat + azacitidine (NCT00948064)



Vorinostat is not yet licensed for MDS indications in Europe or Israel.
C, course; D, days on therapy; HMA, hypomethylating agent; PD-1, programmed cell death protein 1 ; PDL, programmed cell death ligand 1.
Yang H, et al. *Leukemia*. 2014;28:1280–1288.

Adapted from Yang H, et al. 2014

Nivolumab or ipilimumab in combination with azacitidine

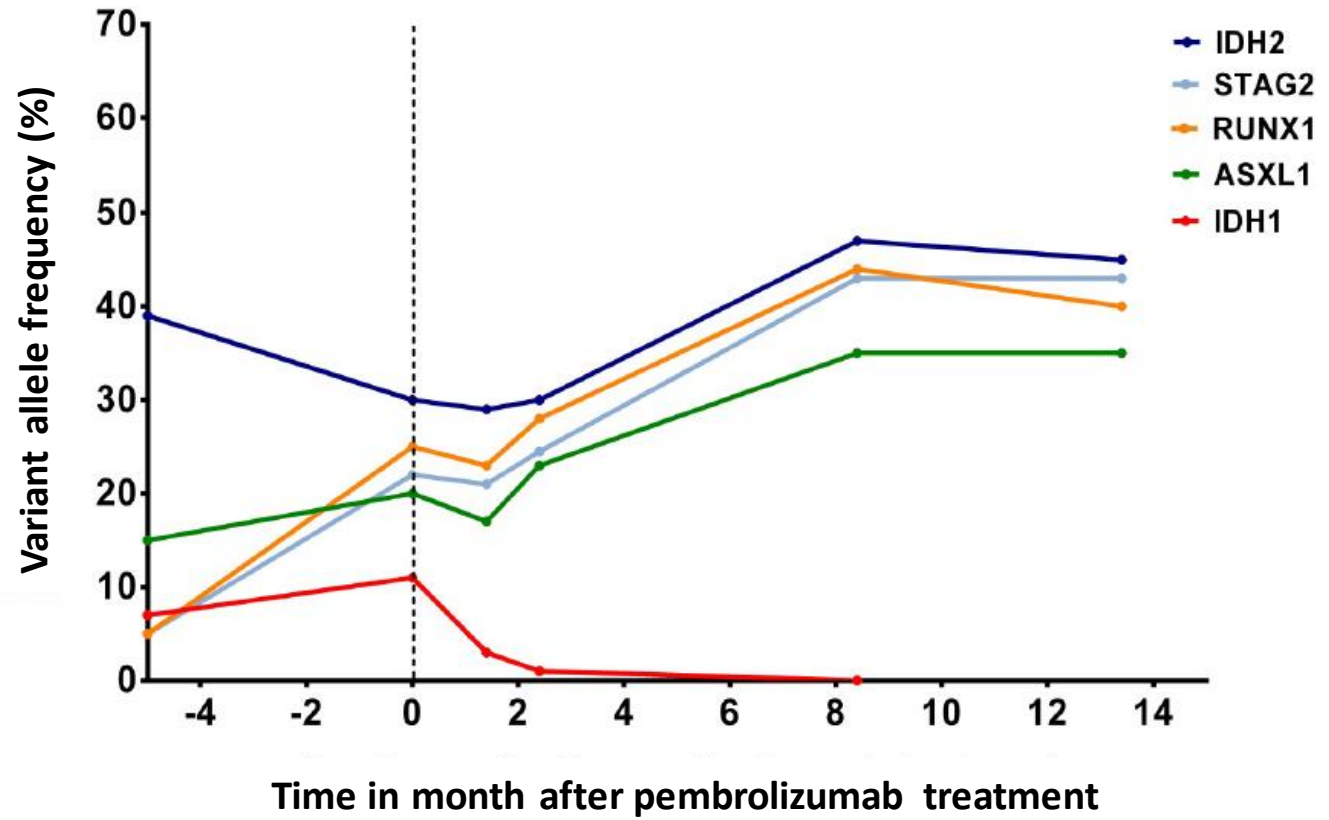
	Frontline		HMA failure	
	Nivo + AZA N=20	Ipi + AZA N=21	Nivo N=15	Ipi N=20
Response				
ORR	14 (70)	13 (62)	0 (0)	6 (30)
CR	8 (**40**)	3 (**14**)	0 (**0**)	0 (**0**)
mCR + HI	2 (10)	0 (0)	0 (0)	1 (5)
mCR	3 (15)	7 (33)	0 (0)	3 (15)
HI	1 (5)	3 (14)	0 (0)	3 (15)
SD	0 (0)	1 (5)	0 (0)	0 (0)
NR	5 (25)	5 (24)	15 (100)	13 (65)

Garcia-Manero, et al. 2018

Nivolumab and ipilimumab are not yet licensed for MDS indications in Europe or Israel.
AZA, azacitidine; CR, complete response; HI, hematologic improvement; HMA, hypomethylating agent; Ipi, ipilimumab; mCR, marrow complete response; Nivo, nivolumab; NR, no response; ORR, overall response rate; SD, stable disease.
Garcia-Manero et al. Presented at ASH 2018. Abstr #465.

Pembrolizumab in sAML molecular course

EB-1……sAML……



Kubasch AS, et al. 2018

ASXL1, additional sex combs like 1; EB-1, excess blasts-1; IDH, isocitrate dehydrogenase; RUNX1, runt-related transcription factor 1; sAML, secondary acute myeloid leukemia; STAG2, stromal antigen 2.
Kubasch AS, et al. *Blood Advances*. 2018;2:1187–1190.

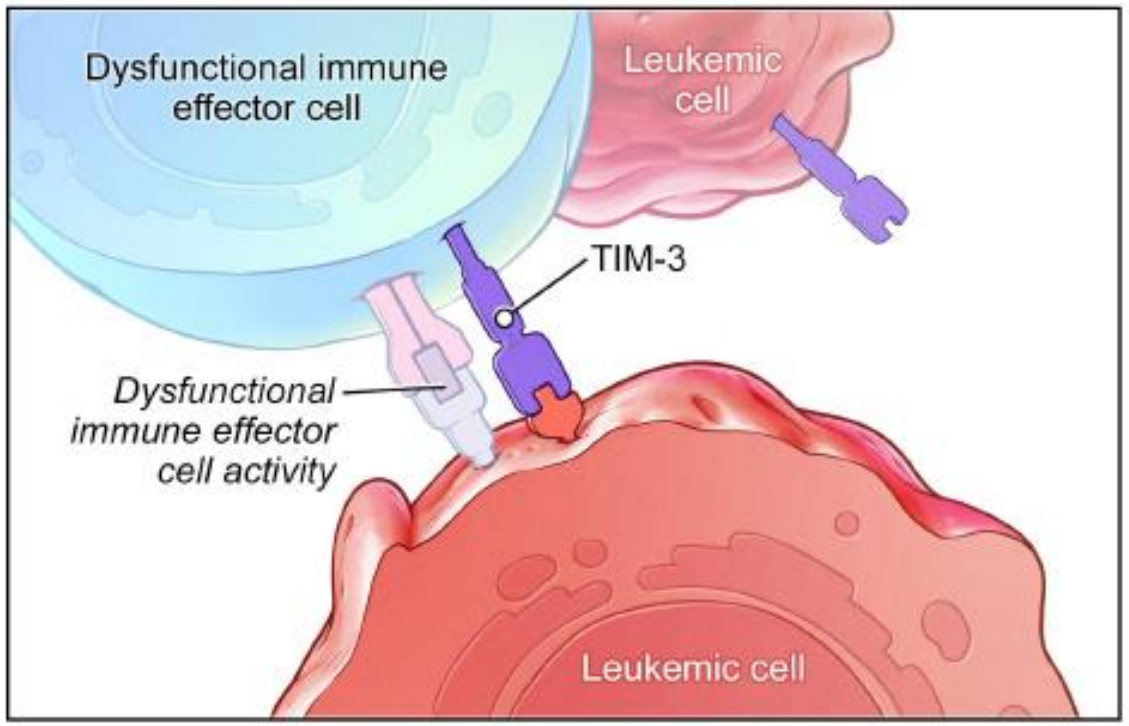
TIM-3 role in immune response against cancer

Upon interaction with their ligands TIM-3 acts as a co-inhibitory receptor inhibiting the activity of different immune cell subtypes:[1,2]

- Activated IFN-γ-producing T-cells
- FoxP3+ Treg cells
- Macrophages
- Dendritic cells

TIM-3 is expressed by leukemic stem cells[2–4]

- TIM-3 expression is seen to correlate with the severity of MDS and progression to AML
- TIM 3 activation is involved in LSC self renewal and activation, as well as immune escape in AML

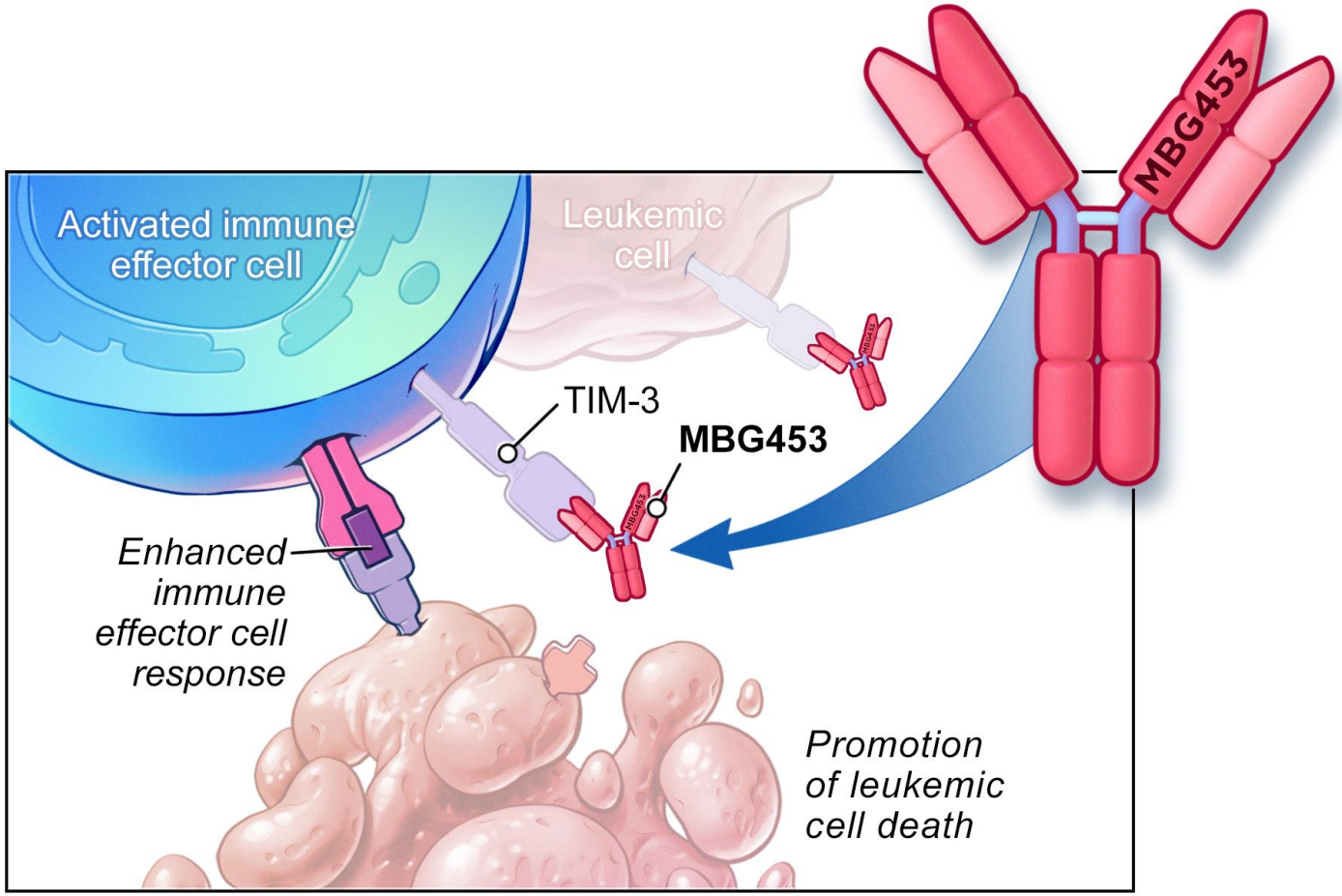


Borate U, et al. 2019

AML, acute myeloid leukemia; IFN, interferon; LSC, leukemic stem cell; MDS, myelodysplastic syndromes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; Treg, regulatory T-cells.

1. Das M, et al. *Immunological Reviews.* 2017;276:97–111; 2 Kikushige Y, et al. *Cell Stem Cell.* 2015;17:341–352; 3. Asayama T, et al. *Oncotarget.* 2017;8:88904–88917;
4. Gonçalves Silva I, et al. *EBioMedicine.* 2017;22:44–57.

MBG453 + decitabine in Phase Ib study for patients with HR-MDS and AML



Borate U, et al. 2019

MBG453 is not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe.
AML, acute myeloid leukemia; HR-MDS, high-risk myelodysplastic syndromes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3.
Borate U, et al. Presented at ASH 2019. Abstr #570.

MBG453 + decitabine in Phase Ib study for patients with HR-MDS and AML

MBG453 + decitabine exhibits promising efficacy, with responses occurring at a median of 2.1 months

	HR-MDS (n=19)
Evaluable patients, n	19
Response, n (%)	
CR	5 (26.3)
mCR	4 (21.1)
with HI	3 (15.8)
SD	9 (47.4)
with HI	2 (10.5)
PD	1 (5.3)
Unknown	0 (0.0)
ORR (CR, mCR, HI), n (%) [95% CI]	**11 (57.9)** [33.5–79.7]

	Newly diagnosed unfit AML (n=22)	R/R AML (n=28)
Evaluable patients, n	17	25
Response, n (%)		
CR	3 (17.6)	0 (0.0)
CRi	2 (11.8)	6 (24.0)
PR	2 (11.8)	0 (0.0)
TF	8 (47.1)	13 (52.0)
No response*	2 (11.8)	3 (12.0)
Unknown	0 (0.0)	3 (12.0)
ORR (CR, CRi, PR), n (%) [95% CI]	**7 (41.2)** [18.4 67.1]	**6 (24.0)** [9.4–45.1]

*Patients who are ongoing with "No response" as best overall response as of data cut-off date.

MBG453 is not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe.
CR, complete response; CRi, AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; HI, hematologic improvement; HR-MDS, high-risk myelodysplastic syndromes; mCR, marrow complete response; ORR, overall response rate; PD, progressive disease; SD, stable disease; TF, treatment failure.
Borate U, et al. Presented at ASH 2019. Abstr #570.

Thank you for your very kind attention

Paving the way for novel therapeutic opportunities in MDS treatment

Panel discussion

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Paving the way for novel therapeutic opportunities in MDS treatment: Questions (I)

How do you see the future of MDS treatment?

MDS, myelodysplastic syndromes.

Paving the way for novel therapeutic opportunities in MDS treatment: Questions (II)

Which emerging therapies could have the biggest impact?

MDS, myelodysplastic syndromes.

Paving the way for novel therapeutic opportunities in MDS treatment: Questions (III)

How can mutation profiling benefit diagnosis and prognosis determination?

Paving the way for novel therapeutic opportunities in MDS treatment: Questions (IV)

What is the role for combination strategies in MDS?

MDS, myelodysplastic syndromes.

Question for the audience

Are you optimistic that emerging treatments will provide a better future for patients with MDS?

Please raise your hand for YES

Closing Remarks

Moshe Mittelman

THANK YOU!

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