FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE



CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
23-24 ottobre 2026

NATIONAL MDS GUIDELINES: AN UPDATE

MARCHETTI Monia

AOU AL Azienda Ospedaliero-Universitaria di ALESSANDRIA
UPO UNIVERSITÀ DEL PIEMONTE ORIENTALE

Disclosures of Monia Marchetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS					ϒ	ϒ	
ROCHE						ϒ	
BMS						ϒ	
BEIGENE						ϒ	
MENARINI						ϒ	
ASTRA ZENECA						ϒ	
MSD					ϒ		
OTSUKA					ϒ		
GSK							ϒ

bjh guidelines

British Society for Haematology guidelines for the management of adult myelodysplastic syndromes

Sally B. Killick,[1] Wendy Ingram,[2] Dominic Culligan,[3] Helen Enright,[4] Jonathan Kell,[2] Elspeth M. Payne,[5] Pramila Krishnamurthy,[6] Austin Kulasekararaj,[6] Manoj Raghavan,[7] Simon J. Stanworth,[8] Simone Green,[9] Ghulam Mufti,[6] Lynn Quek,[6] Catherine Cargo,[10] Gail L. Jones,[11] Juliet Mills,[12] Alex Sternberg,[13] Daniel H. Wiseman[14] and David Bowen[10]

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025 Myelodysplastic Syndromes

VIA MEDICA

GUIDELINES/EXPERT CONSENSUS

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Treatment recommendations of Polish Adult Leukemia Group (PALG) for management of myelodysplastic syndromes (MDS) and other MDS-related conditions in Poland

Krzysztof Mądry[1*], Bożena Katarzyna Budziszewska[2], Karol Lis[1], Joanna Drozd-Sokołowska[1],

GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: leukemia-6. Myelodysplastic syndromes (MDS)

Yasushi Miyazaki[1]



ADOPTED RECOMMENDATIONS

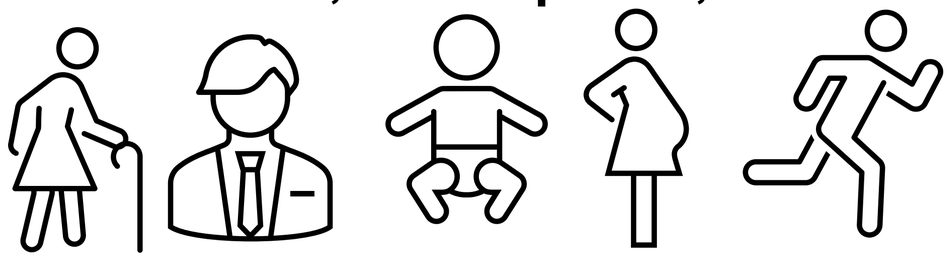
RACCOMANDAZIONI ADOTTATE dalle LINEEGUIDA BCSH 2021

- I pazienti con MDS e citopenie sintomatiche dovrebbero ricevere terapia di supporto
- Le trasfusioni di emazie concentrate dovrebbero essere somministrate per migliorare l'anemia sintomatica
- Le strategie trasfusionali, incluse le soglie di emoglobina, dovrebbero considerare i fattori clinici, inclusi quelli paziente-specifici
- Nei pazienti che ricevono emotrasfusioni con regolarità, andrebbero garantiti il match per Rh, k o antigeni addizionali
- I pazienti a rischio basso/intermedio (IPSS basso o int-1 o IPSS-R molto basso, basso, intermedio = score inferiore a 3.5) e che presentano anemia sintomatica o hemoglobina inferiore a 10 g/dl dovrebbero essere considerati per un tentativo terapeutico con ESA se presentano una intermedia/elevata probabilità di risposta in base allo score nordico
- Al fine di massimizzare i benefici degli ESA, il trattamento dovrebbe essere iniziato non appena appropriato e prima che il paziente sviluppi trasfusione-dipendenza
- I pazienti dovrebbero proseguire il tentativo terapeutico con ESA per un massimo di 24 settimane (inclusivo di 8 settimane iniziali, 8 settimane ad alte dosi, e, se necessario, 8 settimane di combinazione con G-CSF) prima di definire la refrattarietà al trattamento
- I pazienti che ottengono una risposta parziale o completa agli ESA dovrebbero proseguire il trattamento a lungo termine alla dose minima efficace a mantenere la risposta o finchè la risposta non venga persa
- I valori di emoglobina nei pazienti in trattamento con ESA non dovrebbero superare i 12 g/dl
- Tutti i pazienti a rischio basso/intermedio dovrebbero ricevere chelazione marziale dopo aver ricevuto 20 unità di emazie concentrate o quando la ferritinemia risulta superiore a 1000 mcg/l (1-B)
- La chelazione marziale è inoltre raccomandata nei pazienti candidati al trapianto di cell staminali emopoietiche, se la finestra temporale è compatibile
- Il deferasirox è il farmaco di scelta per operare la chelazione marziale nei pazienti con MDS sulla base dei dati di safety e compliance (on label in Italia in 1^ linea?)
- La chelazione marziale dovrebbe essere interrotta alla riduzione della ferritinemia sotto i 500 mcg/l (sotto i 1000 mcg/l per la desferoxamina)
- I pazienti anziani fit e senza un cariotipo sfavorevole dovrebbero ricevere chemioterapia intensiva con regimi AML-like oppure terapia demetilante. I pazienti devono tuttavia essere informati della durata inferiore della sopravvivenza mediana riportata dagli studi di real-life rispetto allo studio pivotal (12.4 vs 18.9 mesi)
- La terapia demetilante preferita in prima linea è l'azacitidina 75 mg/m2 al giorno per 7 giorni consecutivi oppure con pause di 2 giorni week-end (5-2-2) e dovrebbe essere proseguita finchè viene mantenuta la risposta
- La decisione di interrompere la terapia con azacitidina nei pazienti che non ottengono la risposta dopo 6 cicli ma hanno una malattia stabile è a

Grading of Recommendations, Assessment, Development, and Evaluation

PICO

Population



Host

Disease

TD MDS-RS

Prior therapies

ESA refract or inelegible

Intervention

Luspatercept

Comparator

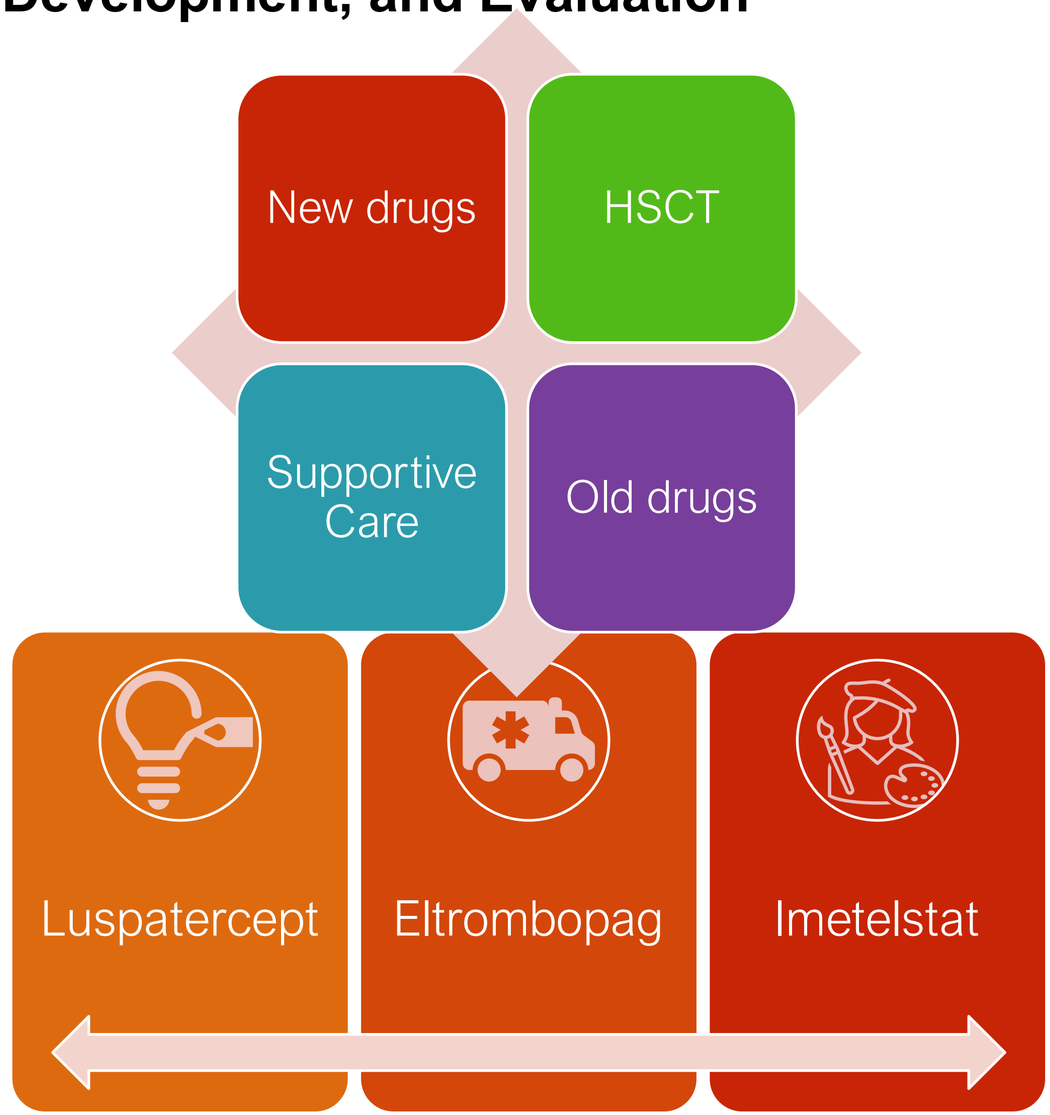
Transfusions

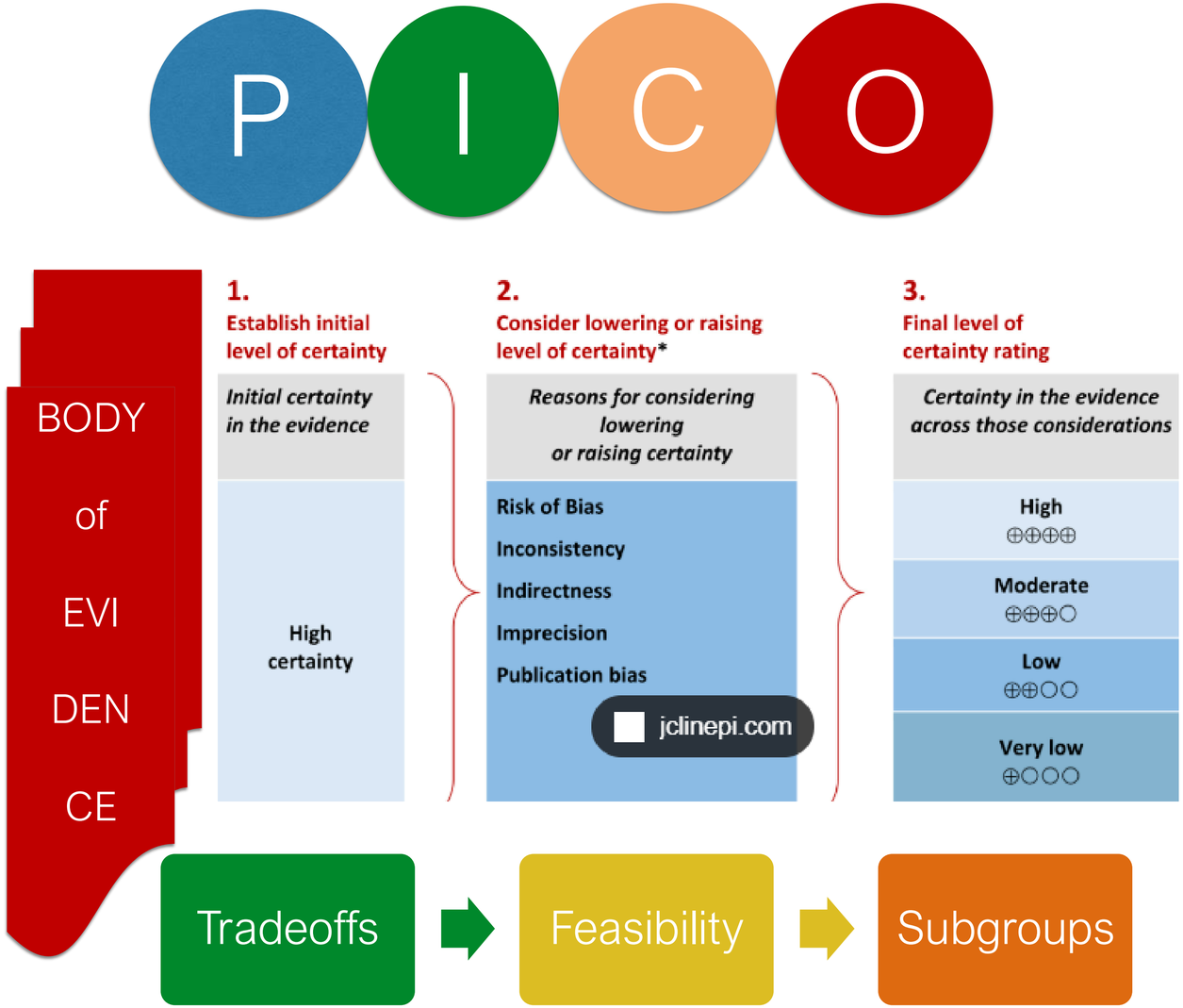
Outcome

Transf-Indep

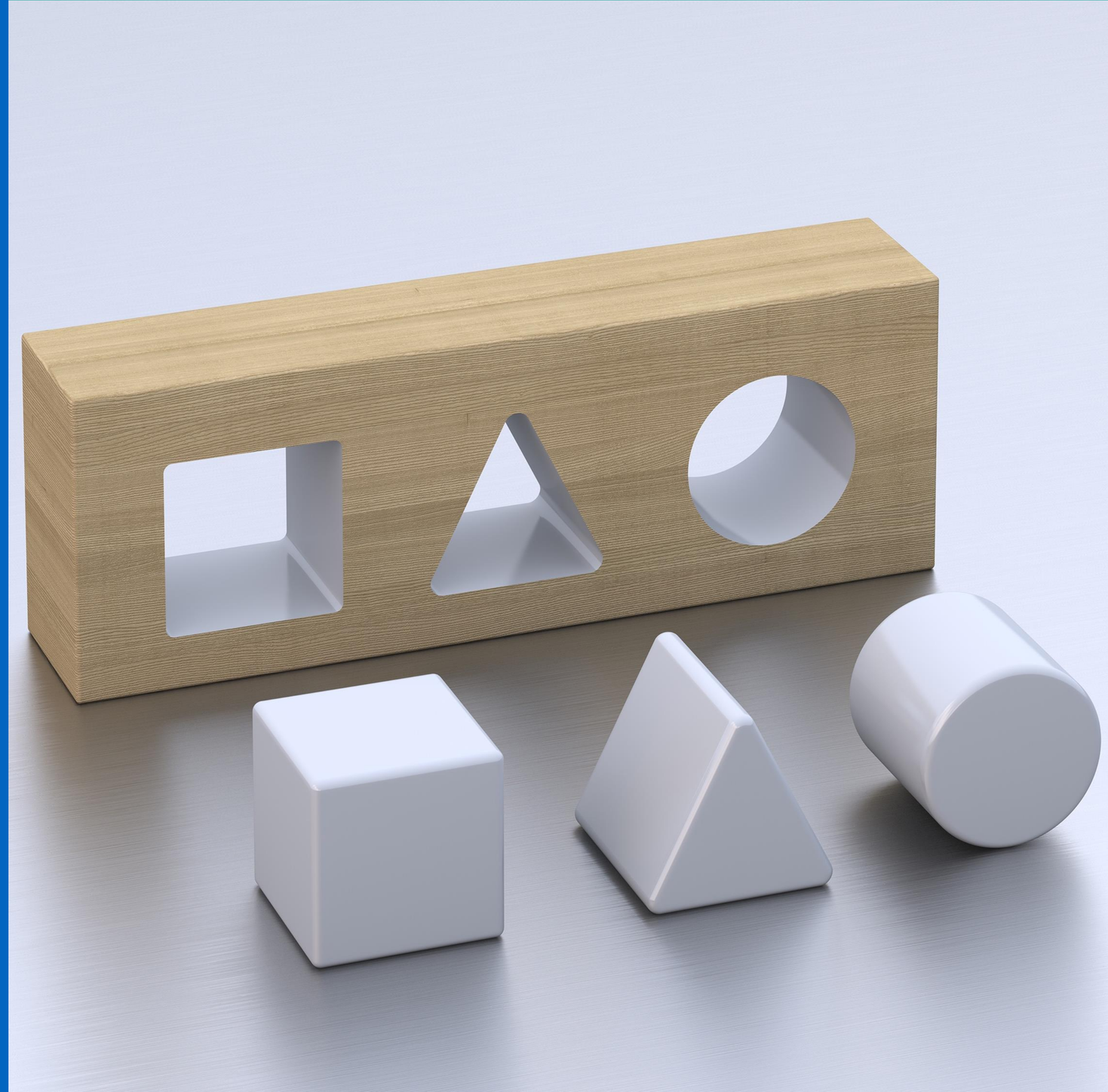
QoL

Grading of Recommendations, Assessment, Development, and Evaluation

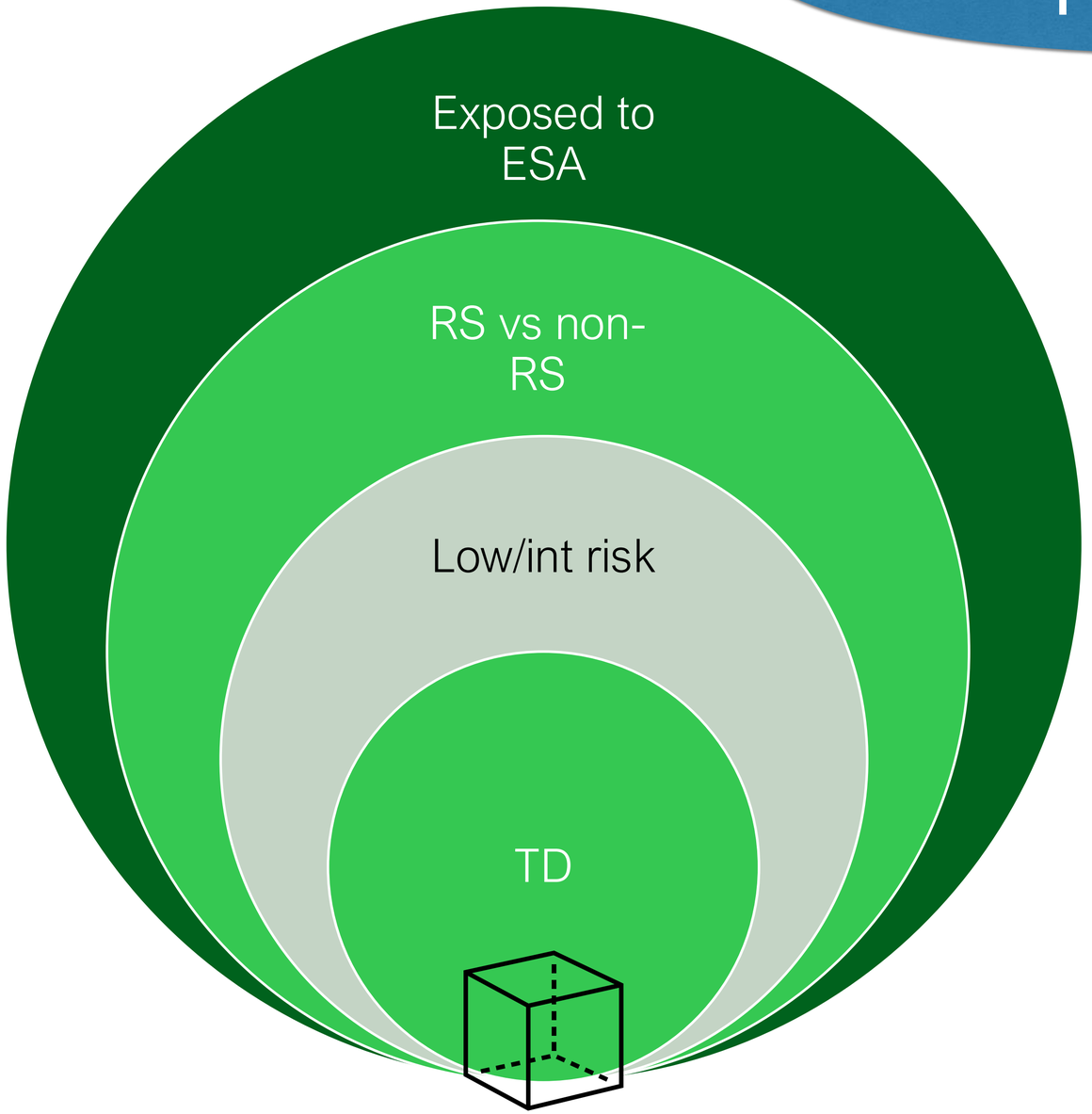


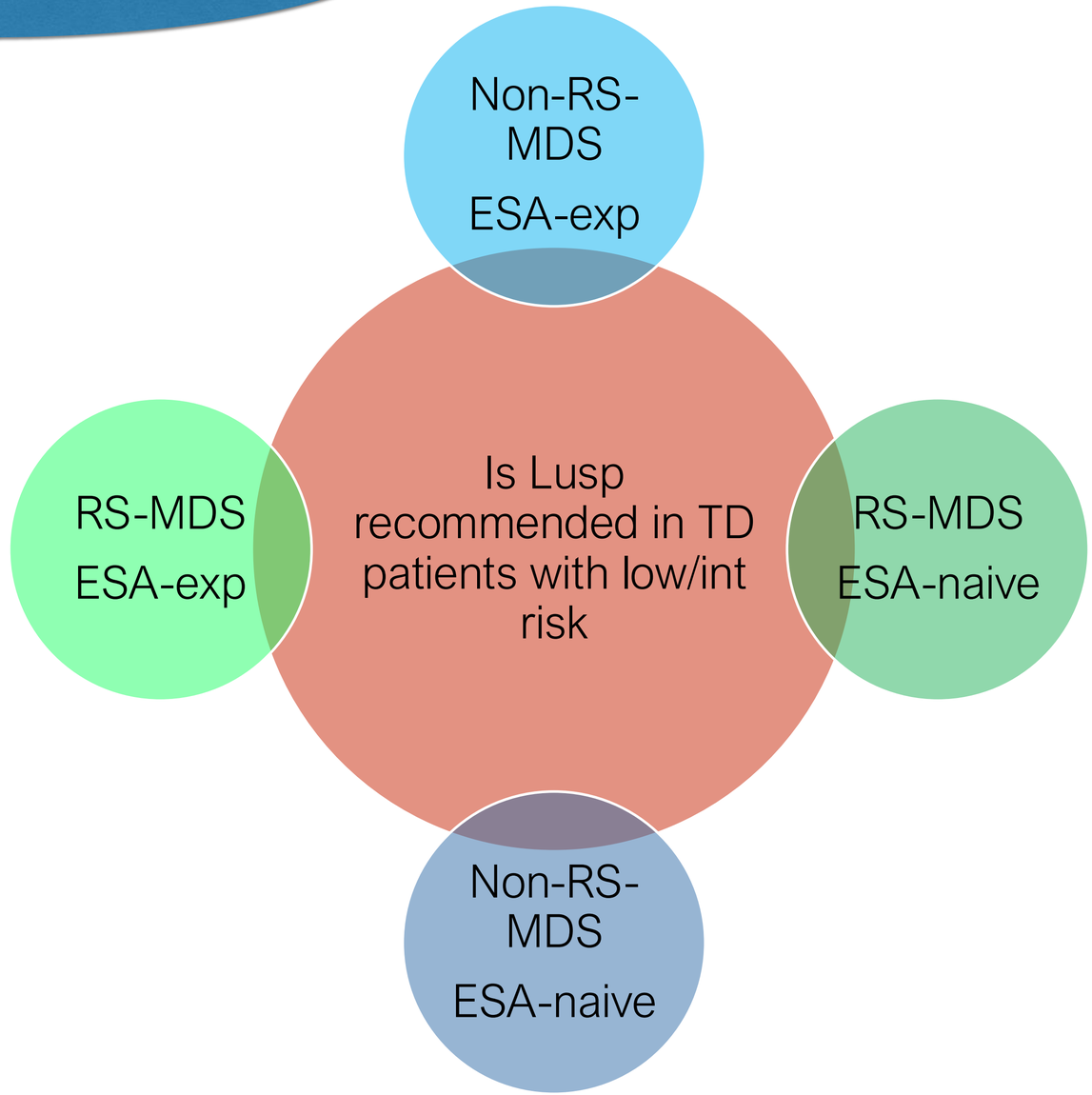


PICO



Population


Exposed to ESA
RS vs non-RS
Low/int risk
TD


Non-RS-MDS
ESA-exp
RS-MDS
ESA-exp
Is Lusp recommended in TD patients with low/int risk
RS-MDS
ESA-naive
Non-RS-MDS
ESA-naive

POPULATION LEGEND

Does this PICO population EXCLUDES:

- **intermediate risk patients with a blast count >5 % (not eligible to COMMANDS trial)?**
- **SF3B1-wt?**
- **5q-?**
- **TP53 mut?**

Does eligibility to ESA = sEpo below 200 based on epoetin-alpha label?

Is Transfusion Dependence to be assessed in 16 wks observation period (MDS Response Criteria 2023) = 2 or more packed red blood cell units in a 8 week time frame?

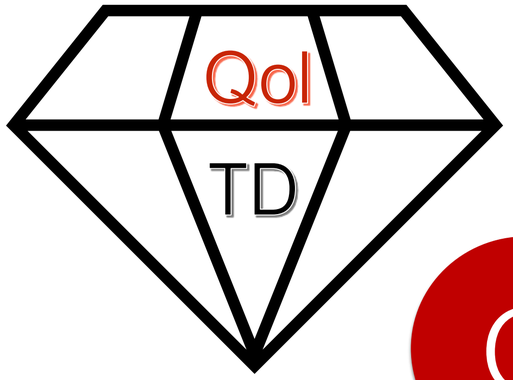
Is Transfusion Independence lasting for at least 12 weeks?

Innovative (or invasive) treatment



I





O

C



Best Available (or standard) Therapy

Improved survival and enhanced quality of life through anaemia correction in lower risk myelodysplastic syndromes: meaningful insights from an EUMDS Registry study

| The focus of a study by Hege Kristin Gravdahl Garelius and The main outcomes of their study were the evaluation of

- 2448 pts low/int1 IPSS mdn fup 3.9 yrs
- ESAs OS 44·9 months [95% CI 40·2–50·5] vs 34·8 months [28·6–39·2]
- the absence of RBCT correlated to markedly better HRQoL, regardless of ESA exposure.
- Gravdahl Garelius HK, Bagguley T, Taylor A, et al. Survival and quality of life in patients with lower risk myelodysplastic syndromes exposed to erythropoiesis-stimulating agents: an observational cohort study. *Lancet Haematol* 2025; **12:** e128–37.

Received: 19 January 2022 | Revised: 30 September 2022 | Accepted: 16 November 2022
DOI: 10.1002/cam4.5487

RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

Raising the standards of patient-centered outcomes research in myelodysplastic syndromes: Clinical utility and validation of the subscales of the QUALMS from the MDS-RIGHT project

Fabio Efficace[1] | Karin Koinig[2] | Francesco Cottone[1] | David Bowen[3] |

ELSEVIER

Blood 138 (2021) 64–67

63rd ASH Annual Meeting Abstracts

ORAL ABSTRACTS

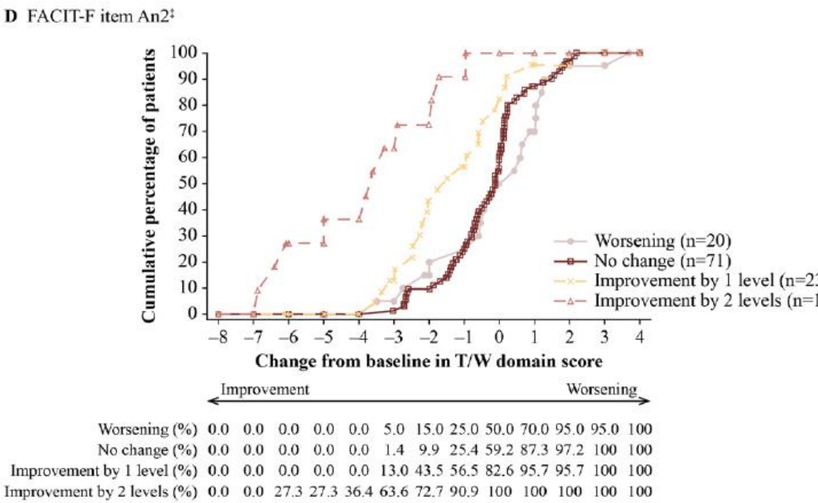
637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

The EQ-5D-5L Predicts Treatment Outcomes and Provides Added Value to the R-IPSS in Patients with MDS, CMML or AML Treated within the Austrian Azacitidine Registry - a Prospective Cohort Study By the AGMT Study Group

Lisa Pleyer[1,2,3], Sonja Heibl[4,2], Christoph Tinchon[5,2], Sonja Vallet[6,2], Branka Petricevic[2,7], Michael Leisch[8,2,3],

BMJ Open Identifying thresholds for meaningful improvements in NTDT-PRO scores to support conclusions about treatment benefit in clinical studies of patients wit non-transfusion-dependent beta-thalassaemia: analysis of pooled da from a phase 2, double-blind, placebo-controlled, randomised trial

Ali T Taher [1], Khaled M Musallam[2,3] Vip Viprakasit[4] Antonis Kattamis[5] Jennifer Lord-Bessen[6] Aylin Yucel[6] Shien Guo[7] Christopher G Pelligra [8] Alan L Shields[9] Jeevan K Shetty[10] Mrudula B Glassberg[11] Luciana Moro Bu Maria Domenica Cappellini[12]



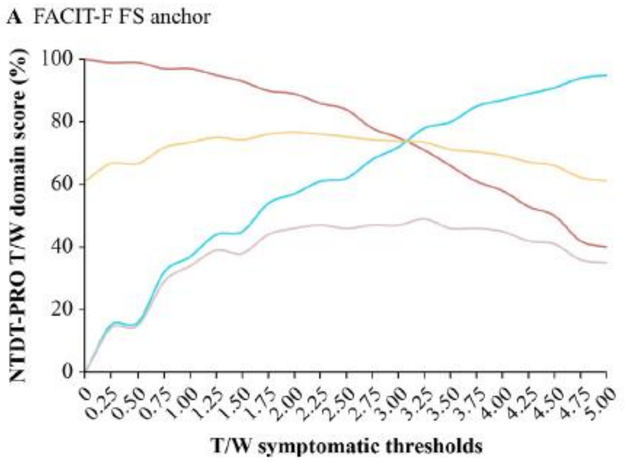
bjh research paper

Development of a core outcome set for myelodysplastic syndromes – a Delphi study from the EUMDS Registry Group

U. Rochau *et al.*

Table 4. Definitions of the MDS core outcomes.

Health-related quality of life	General definition: Quality of life is described 'as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features o their environment'[61]
Treatment-related mortality	Any unexpected cause of death, which cannot be contributed to the disease itself, but can be explained by one of the applied MDS therapeutic interventions. This may include early death after induction or septicaemia due to prolonged cytopenia after drug therapy. The actual cause of death should be specified if possible. Those deaths which can be explained by other conditions (e.g., stroke, heart attack, other malignancies, suicide, etc.) should be excluded
Overall survival	The length of time from the first MDS diagnosis until death, irrespective of the cause
Performance status	General definition: 'The performance status describes the status of symptoms and functions with respect t ambulatory status and need for care'[38]
Safety	General definition: Safety can include assessment of the 'adverse events, laboratory evaluations, vital signs'[60], physical examinations, etc.
Haematological improvement	Definition according to the MDS IWG response criteria until the ongoing improvements become available



OUTCOME LEGEND

ANEMIA RESPONSE (IWG response criteria): important but NOT critical outcome

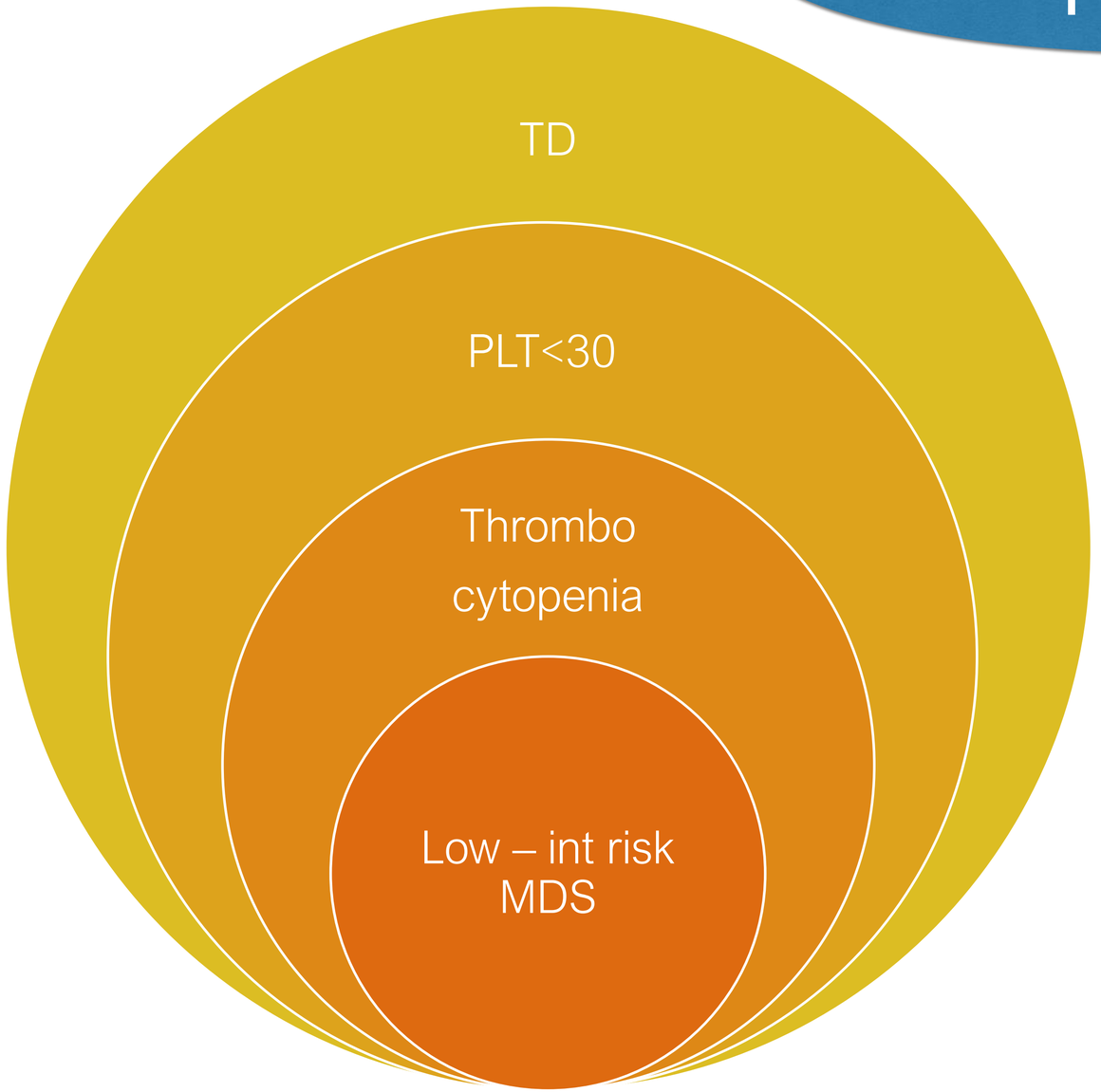
TRANSFUSIONAL BURDEN: inaccurate outcome therefore neither critical nor important

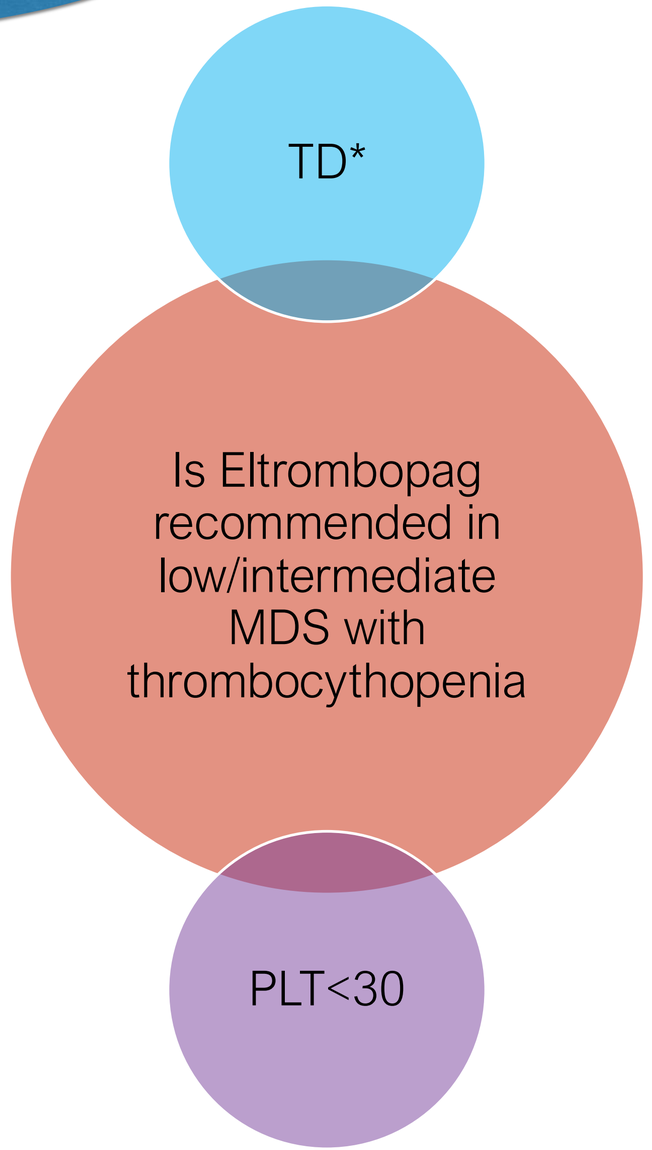
INTERVENTION & COMPARATOR LEGEND

LUSPATERCEPT treatment is DISCONTINUED if IWG disease progression or HEMOGLOBIN decline > 1.5-2 g/dl or insufficient DECLINE of TRANSFUSION BURDEN (-2 U/8 wk vs baseline) [COMMANDS criteria]

ESA treatment is DISCONTINUED Criteria for discontinuation reported for ESA and luspatercept (COMMANDS trial) include : a) Disease Progression IMWG criteria 12; b) hemoglobin decline by more than 1.5-2 g/dl; c) lack of clinical benefit ontotransfusion burden (=reduction by more than 2 units in 8 weeks vs baseline

Population


TD
PLT<30
Thrombo
cytopenia
Low – int risk
MDS

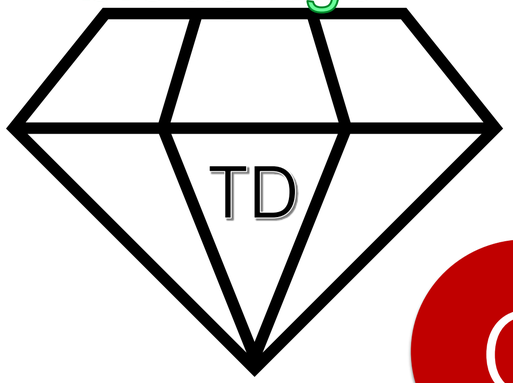

TD*
Is Eltrombopag
recommended in
low/intermediate
MDS with
thrombocythopenia
PLT<30

Innovative (or invasive) treatment





Clinically relevant major bleedings



O

C

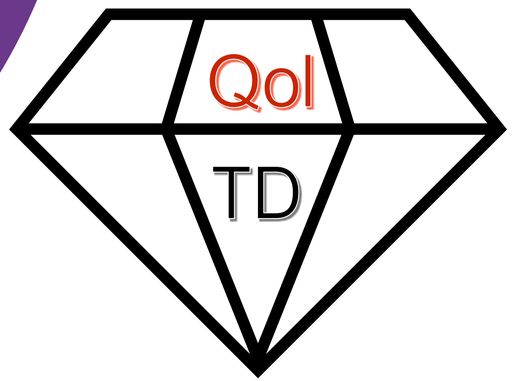


Best Available (or standard) Therapy

Population

ESA refractory
or not eligible

Low – int risk MDS

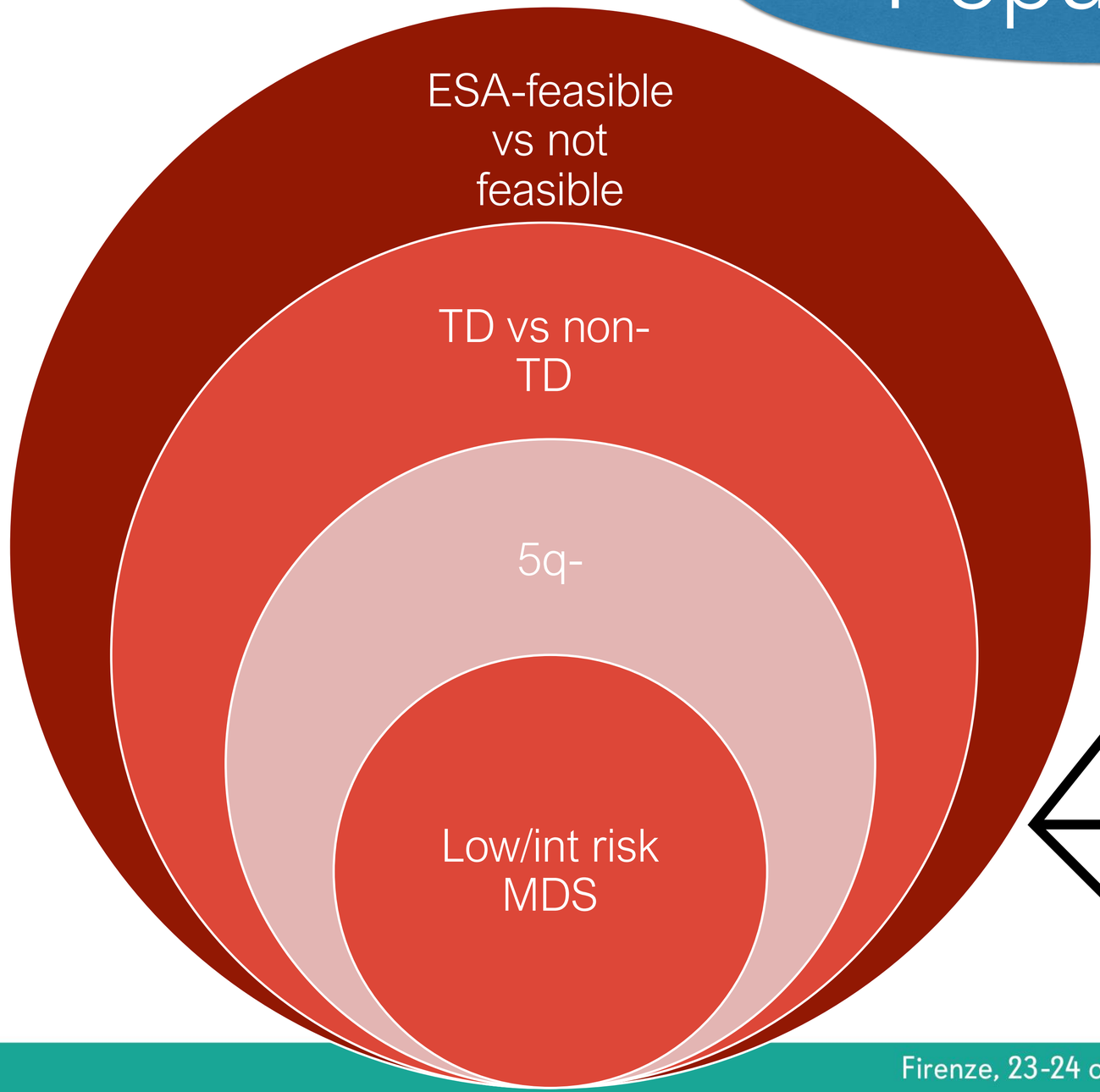


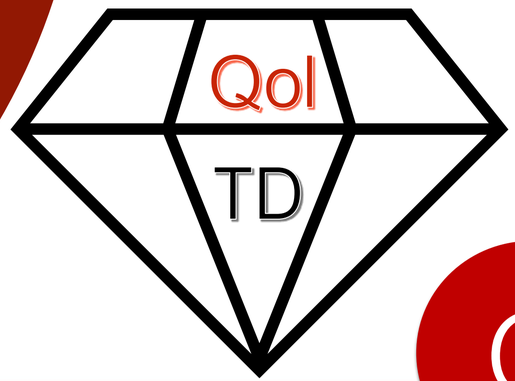
ESA
refractory

Is IMETELSTAT
recommended in
low/intermediate risk
MDS

ESA
inelegible

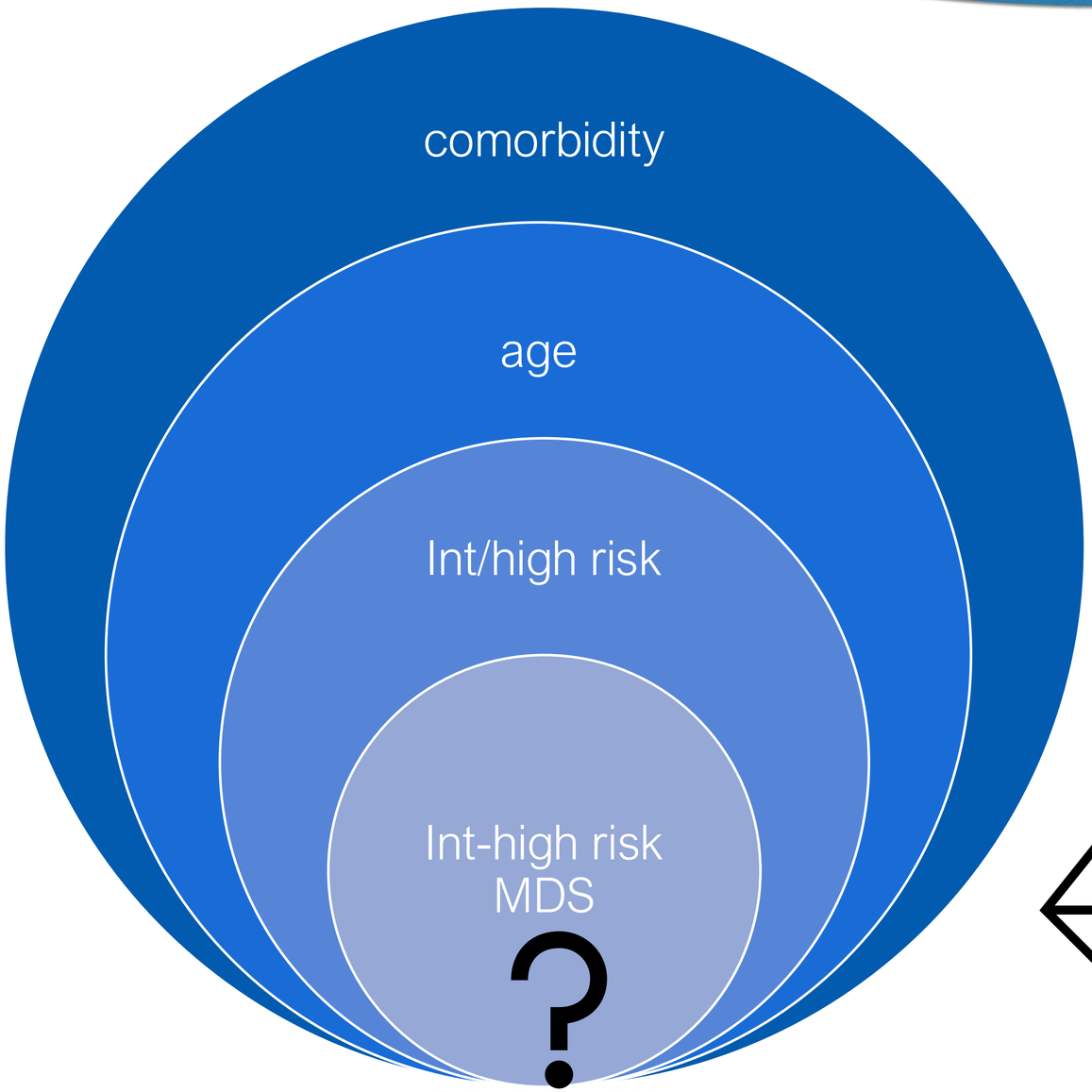
Population

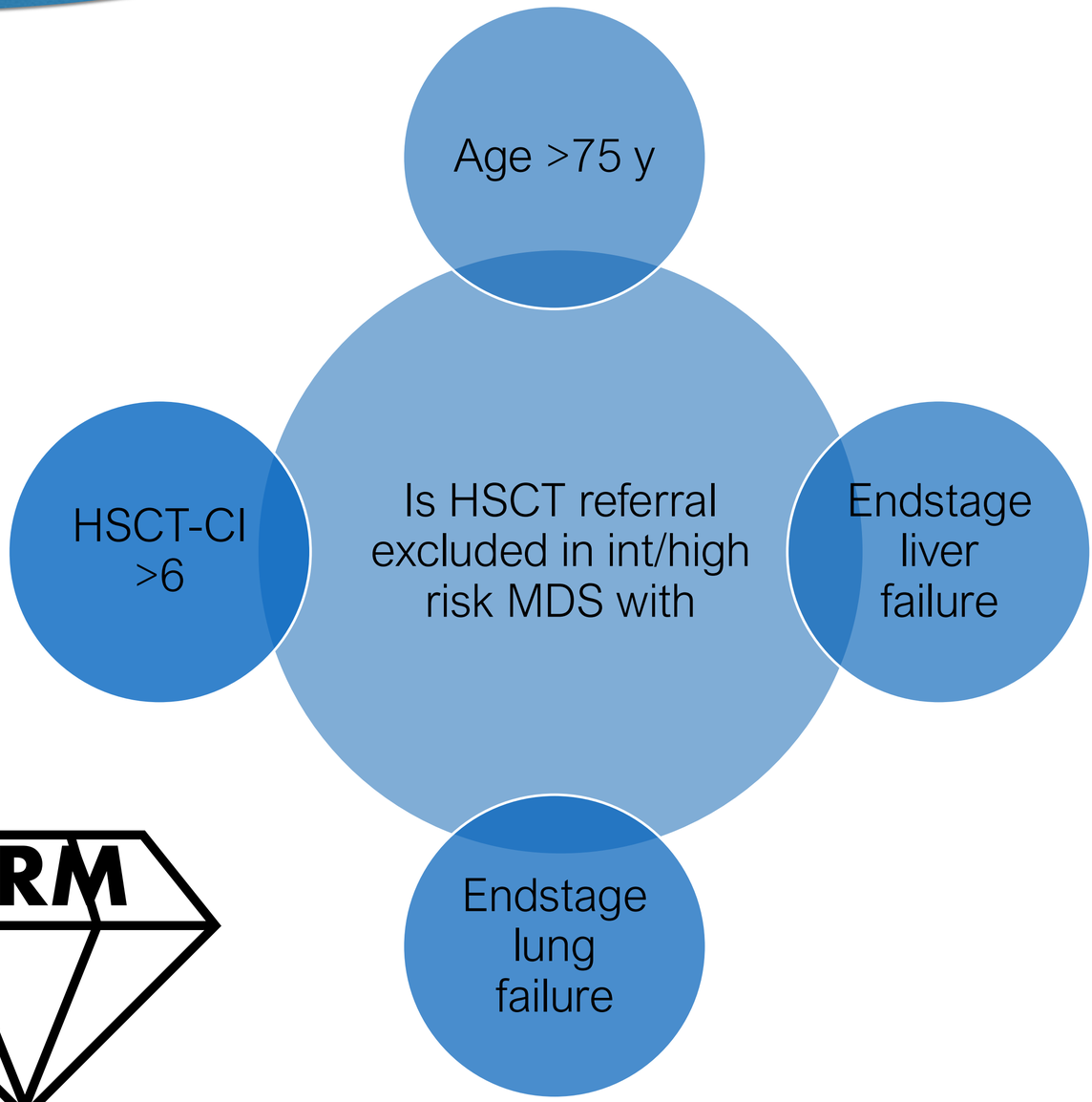

ESA-feasible vs not feasible
TD vs non-TD
5q-
Low/int risk MDS


QoL
TD

TD & ESA refractory
Non-TD & ESA naive
Is LENALIDOMIDE recommended in low/in risk MDS with 5q-
Non-TD & ESA refractory
TD & ESA naiive

Population





NRM

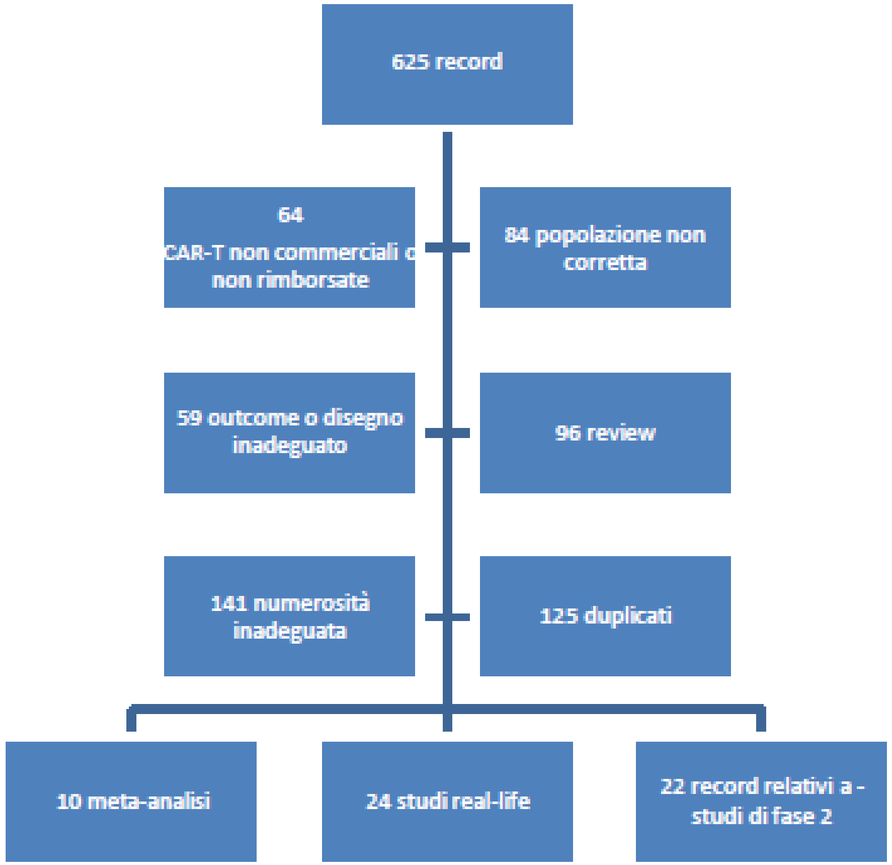
EVIDENCE & DECISION



2a- Is the CPG robust = SYSTEMATIC?



PRISMA Diagram PICO 1.1.A e 1.1.B



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BODY of EVIDENCE



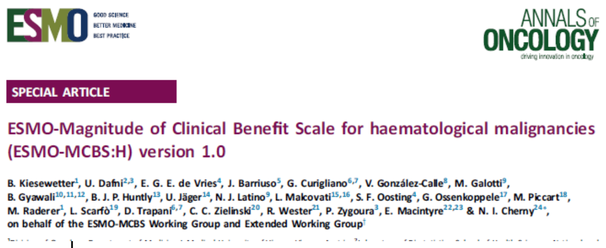
1. CRITICAL Outcomes
2. Relative EFFECT size
3. INDIRECT evidence

Summary of findings – PICO 1A

OUTCOME	END POINT	STUDY (N pts, design)	PTCY (& IS)	COMPARATOR	RELATIVE EFFECT	QUALITY
aGVHD	Gr 2-4 d100	Ayala 2023 (matched pair retrospective analysis 100 vs 100)[1]	57%	CysA-based 23%	P<0.001	MODERATE
	Gr 2-4 Gr 3-4	Greco 2021 [48 pts]	25% 9%			LOW
	Gr 3-4 d100	Holtan 2022 ASH (randomized study BMT CTN - 128 matched related donors)[2]	&Tac+MMF 6.3%	Tac/MMF 14.7%	P=0.001	NA
	Gr 2-4 Gr 3-4 d100	Iqbal 2023[3] [8 vs 28]	&Sirolimus 17.2% 7%	MTX+Tac 34.5% 11.5%	Ns But shorter time to IS discontinuation (138 vs 232 days, p<0.001)	VERY LOW (indirectness: most MUD)
	Gr 2-4 Gr 3-4	Kwon 2019 (#57 vs 50 pts, retrospective)[4]	22.6% 8.8%	CysA+MTX 52.2% 24.4%	P=0.0015 (p=0.006 at MV analys) P=0.016	LOW
	Gr 2-4 Gr 3-4	Lazzari 2022 [77 pts, siroliums]	18% 6%			LOW
	Gr 2-4 d180 Gr 3-4	Mehta 2022 (140 vs 271)	44% 8%	37% 11%	ns	LOW
	Gr 2-4 Gr 3-4	Mehta 2022 bis [242 vs 144; MUD & MSD]	&Tac 38% 8%	Tac/MMF 67% 10%	HR 2.1 (1.6-2.8) Ns Lower rate of grade 1-2 GI and skin	LOW (mixed MRD & MUD)

Outcome-specific Body of Evidence

MINIMAL IMPORTANT DIFFERENCE of OUTCOMES



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies (ESMO-MCBS:H) version 1.0

B. Kiesewetter[1], U. Dafni[2,3], E. G. E. de Vries[4], J. Barriuso[5], G. Curigliano[6,7], V. González-Calle[8], M. Galotti[9], B. Gyawali[10,11,12], B. J. P. Huntly[13], U. Jäger[14], N. J. Latino[5], L. Malcovati[15,16], S. F. Oosting[4], G. Ossenkoppele[17], M. Piccart[18], M. Raderer[1], L. Scarfò[19], D. Trapani[6,7], C. C. Zielinski[20], R. Wester[21], P. Zygoura[3], E. Macintyre[22,23] & N. I. Cherny[24]*, on behalf of the ESMO-MCBS Working Group and Extended Working Group

	GVHD ORR	GRFS	REL	NRM
TRIVIAL	<5%	<5%	<3%	<3%
SMALL	5-10%	5-10%	3-5%	3-5%
MOD	10-20%	10-15%	5-10%	5-10%
LARGE	>20%	>15%	>10%	>10%

Quanto sono sostanziali gli effetti DESIDERABILI attesi?

- Irrilevanti
- Piccoli
- Moderati
- Grandi
- Variano
- Non so

EVIDENCE-to-DECISION

DESIRABLE OUTCOMES

Size of effect & certainty of the evidence

UNDESIRABLE OUTCOMES

Size of effect & certainty of the evidence

BALANCE

Discussion on desirable vs undesirable

OTHER OUTCOMES

Costs, equity, acceptability, applicability

SUBGROUPS

Specific issues

Raccomandazione forte contro l'intervento	Raccomandazione condizionata contro l'intervento	Raccomandazione condizionata di non differenza fra l'intervento e il confronto	Raccomandazione condizionata a favore dell'intervento	Raccomandazione forte a favore dell'intervento
○	○	○	○	●

Explicit grading

Cost-Effectiveness of Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation for Older Patients With High-Risk Myelodysplastic Syndrome: Analysis of BMT CTN 1102

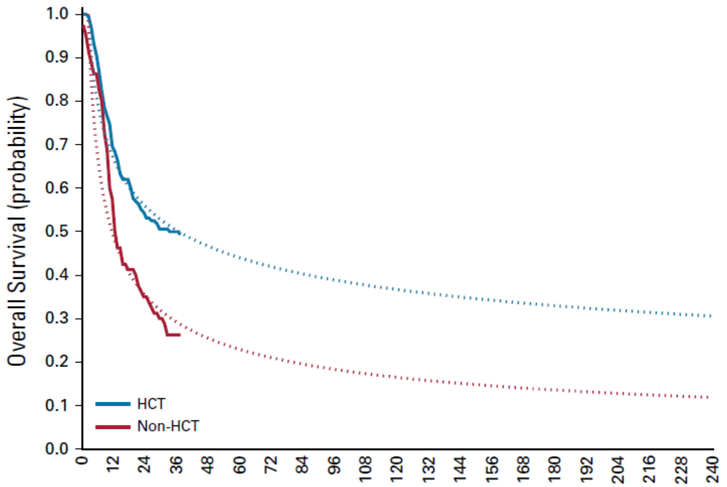
Wael Saber, MD, MS[1]; Aasthaa Bansal, PhD[2,3]; Lily Li, MPA[2]; Bart L. Scott, MD[2]; Lindsey R. Sangaralingham, MPH[4,5];

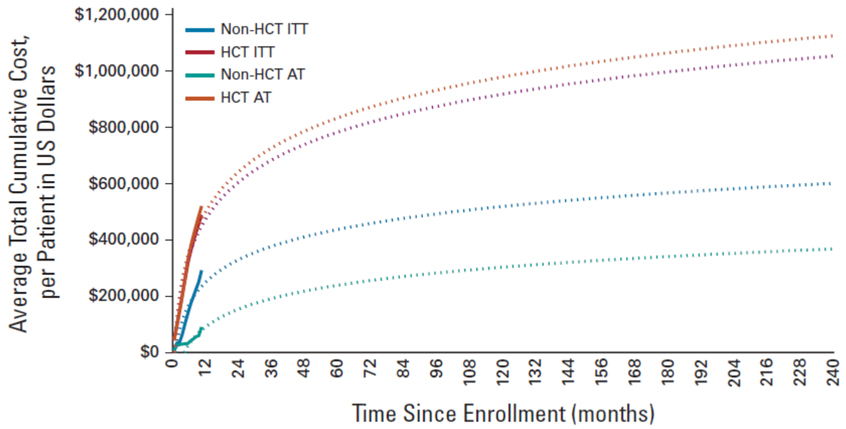
A Input ranges for persons <65 years

One-Way Sensitivity Analysis Input Range	LYs	QALYs	Costs
HCT	7.32 to 8.58	3.02 to 6.53	$1,029,024 to $1,076,578
Non-HCT	3.69 to 5.27	3.03 to 4.20	$586,138 to $614,979

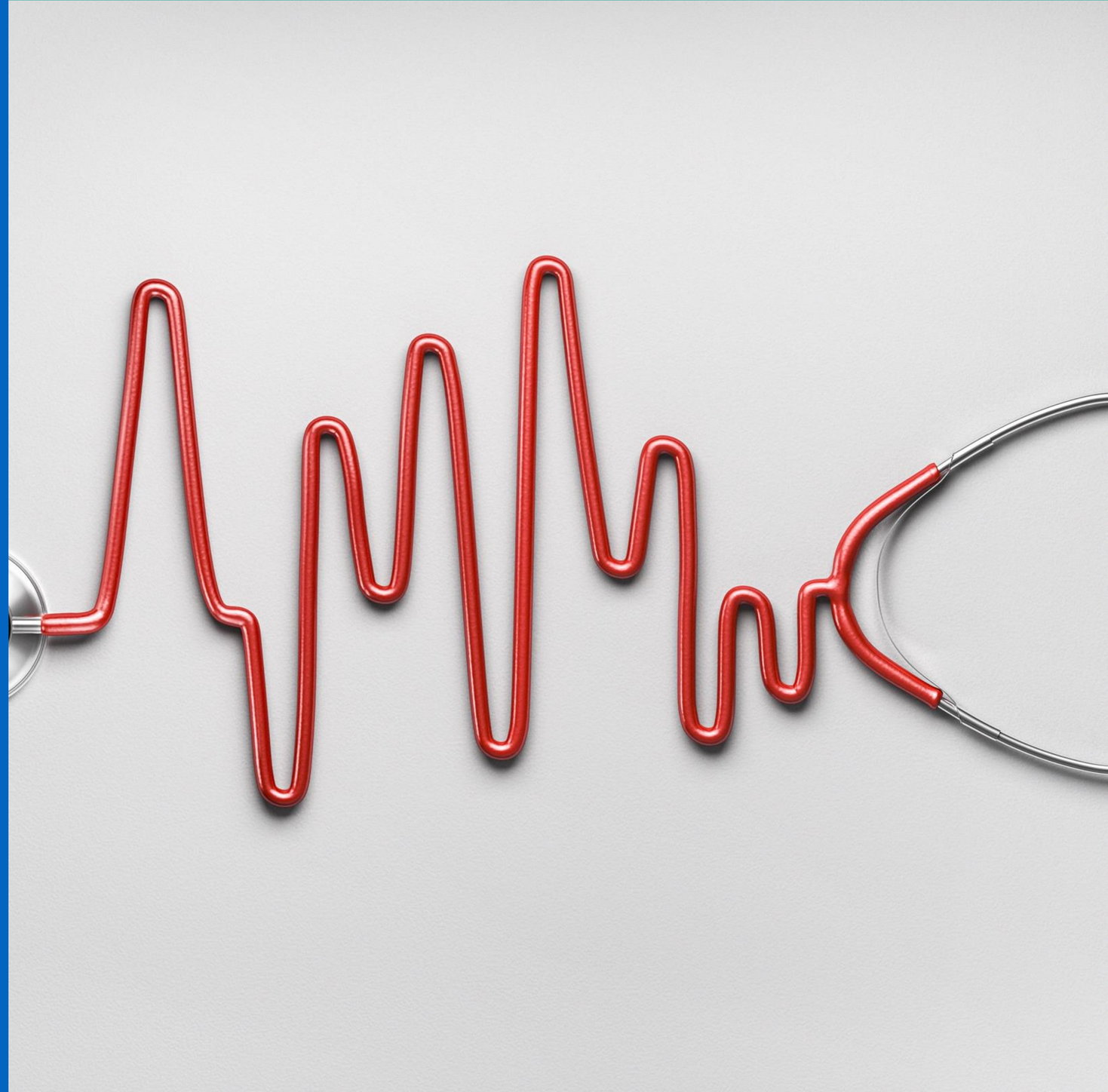
B Input ranges for persons ≥65 years

One-Way Sensitivity Analysis Input Range	LYs	QALYs	Costs
HCT	7.49 to 8.73	5.98 to 6.99	$775,195 to $817,220
Non-HCT	3.51 to 5.12	2.95 to 4.31	$547,141 to $578,847





LUSPATERCEPT



LUSPATERCEPT

PICO 1.1.a = RS ESA-refractory or inelegible

The BODY of EVIDENCE included:

4 meta-analyses devoted to Luspatercept (I) in MDS and including over a1000 patients from trials and real-world studies (11 studies)

1 RCT (MEDALIST) devoted to the target population MDS-RS

2 Italian RW studies (Lanino et al)

A moderate-quality body of evidence (>10 studies included 1 RCT and 2 meta-analyses) consistently reported a clinically relevant amelioration of transfusion-independent portion of patients (NNT 3) assigned to LUSPA vs placebo (or SOC): 31.4% (vs 7.9%) patients achieved persistent TI longer than 16 wks.

Similar TI rates were reported in the MEDALIST trial and in the real world practice, which further confirms the robustness of the results.

However, no clinically meaningful amelioration of patients PRO was reported by the MEDALIST randomized trial in the first 24 wks.

Effect size

- MODERATE desirable vs TRIVIAL undesirable

Feasibility & costs

- Reimbursed AIC … missing Italian HTA

Subgroups

The expected response (TI rate) in patients with a high transfusion burden (>6 U/8 wks) or a high IPSS-M is not clinically meaningful (e.g. 6% vs 3% TI in MEDALIST trial). In particular, the chance of achieving TI is severely reduced in those patients receiving 8 or more units/8wks at baseline (Lanino et al).

CRITICAL OUTCOMES

1 RCT 2:1 vs placebo MEDALIST 229 MDS-RS	TI 38%	TI 13%	+25% NNT = 3.2

= Meta-analysis =RW

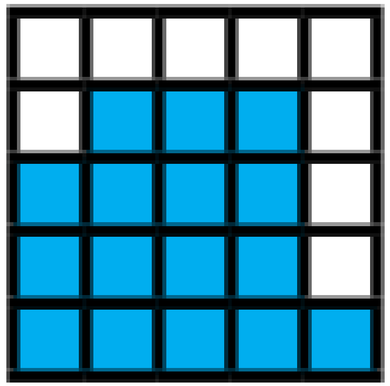
1 RCT 2:1 vs placebo MEDALIST 229 MDS-RS	Impact of TD worsen in 12% & ameliorates in 39%	Impact of TD worsens in 22% & improves in 22% **ns**

		LUSPA	CONTROL	DELTA
Adverse Effects	1 meta-analysis (Calvalcante)	ge mild 11%, fatigue 8.8%, heart 8.9%, neurol 6.8%, bone pain 3.8%	NA	NA
	1 RCT Platzbecker 2023	Diarrhea 25.8/100 PY Dizziness 19.2/100 PY Bronchitis 10.7/100 PY Vertigo 5.8/100 PY Influenza 5.3/100 PY	Diarrhea 18.4/100PY Dizziness 8.9/100PY Bronchitis 2.2/100 PY Vertigo 0 Influenza 0	Diarrhea +7.2/100 PY Dizziness + 10.3/10 PY Bronchitis +8.5(100 PY
Discontinuation for toxicity	1 meta-analysis (Htut)	6%	4% ESA or placebo	NA
Transformation to AML	1 RCT MEDALIST Platzbecker 2023 Fenaux 2022	2.6% Median 61.7 mo after random HR-MDS or AML 13/153 (8.5%) In 401 observation years	3.9% Median 32.7 mo after randomization HR-MDS or AML 5/76 (6.6%) in 191 patient years	Ns
Mortality	1 meta-analysis (Htut)	3.9%	6.3% ESA or placebo	RR 0.65 (p=0.24)

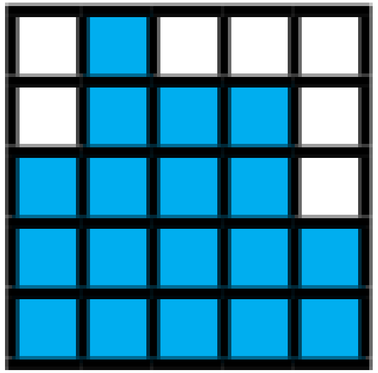
EVIDENCE BLOCKS FOR TREATMENT OF SYMPTOMATIC ANEMIA

MDS-*SF3B1* (low blasts): No del(5q) ± other cytogenetic abnormalities with RS ≥15% (or RS ≥5% w

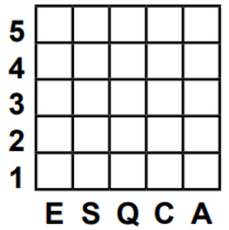
IMETELSTAT



EPOETIN ALPHA



NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Quality of Evidence

MDS-*SF3B1* (low blasts): No del(5q) ± other cytogenetic abnormalities with RS ≥15%

Primary treatment	
Preferred regimen	
Luspatercept-aamt	
Other recommended regimens	
Imetelstat	
Epoetin alfa	
Darbepoetin alfa	

ELTROMBOPAG



BODY of EVIDENCE

The BODY of EVIDENCE included:

- 5 meta-analyses including 6-10 placebo-controlled RCTs devoted to low-intermediate risk MDS and comparing TPOm (eltrombopag or romiplostim) to placebo.
- 1 RCT specifically adherent to PICO 2 (EQOL-MDS trial, Oliva 2023 JCO)
- Moderate-quality consistent evidence did NOT report a significant effect onto platelet transfusion rate and reported a mild effect onto the number of transfused platelet units (Aziz 2025), and bleedings (Dodillet, Meng, Azharuddin). The quality of the evidence has been downgraded to MODERATE despite meta-analyses and RCTs being high-quality because of indirectness (romiplostim based trials, combo therapies…)
- No adverse effects of TPOm therapy was reported by a LOW quality body of evidence (pieces of very low and low quality of evidence despite from RTCs)

Effect size

- Insufficient amelioration of desirable critical outcomes

Feasibility & costs

- Off-label (approved for ITP and AA)

Eltrombopag (1)

OUTCOME = Platelet transfusion incidence	**Aziz 2025 Meta-analysis 10 RCT (908 patients)**		**RR 0.67 (95% CI, 0.54-0.86; I^2 = 10%). Eltrombopag (RR: 0.74; 95% CI, 0.45-1.21)**	**MOD**
	Wang 2022 meta-analysis of 8 RCTs (908 pts) double-blind RCTs		RR 0.83 (95% CI 0.60–1.15) Transfused PLT units RR 0.68 (0.53-0.84)	
	Azharuddin 2021 metanalysis 8 RCTs		RR 0.98, 95% CI 0.67 to 1.43	
	Meng 2020 meta-analysis 8 RTCs		ns	
	Dodillet 2017 Cochrane Meta-analysis 6 trial 746 pts		Romiplostim reduced the exposure-adjusted platelet transfusion rate vs placebo (RR 0·69; 95% CI: 0·53-0·88). RR 0.83, 95% CI 0.66 to 1.05, N = 4 trials, 358 patients	
	Oliva 2023 placebo-ctr RCT 112 vs 57 pts low-int1 MDS	50—300 mg 54.3% vs 35.3% Mdn duration of TI 32 wks Transfusion incidence rate ? 16.3/100 PW (95% CI, 15.4 to 17.2) vs 16.9/100 pt weeks (15.5-18.4)	P=0.24 P=0.49	LOW

Eltrombopag (2)

OUTCOME Clinically Relevant Bleeding	Aziz 2025 Meta-analysis 10 RCT (908 patients)	RR 0.73, 95% CI, 0.47-1.12 grade 3-5 bleedings Eltrombopag R 0.77 (0.47-1.27)	MOD
	Azharuddin 2021 meta-analysis 8 RCTs (930 pts)	Eltrombopag (RR 0.37, 95% CI 0.20 to 0.69)	
	Meng 2020 meta-analysis 8 RCTs (1047 pts)	RR: 0.36; 95% CI, 0.36–0.92 Eltrombopag 0.6 (95% CI: 0.37–0.96, P = 0.03)	
	Dodillet 2017 Cochrane Meta-analysis 6 trial 746 pts	RR 0.84 (0.57-1.24) exposure-adjusted bleeding rate ROMIPLOSTIM vs placebo (RR 0·92; 95% CI: 0·86-0·99)	
	Oliva 2023 RCT	Bleedings grade 2-5 Incidence Rate Ratio 0.54 (0.38-0.75) Bleeding grade 3-4 incidence rate ratio INCREASED in Eltrombopag-exposed pts (p 0.002).	MOD

Eltrombopag (3)

All bleeding events rate	Dodillet 2017 Cochrane		RR 0.92, 95% CI 0.86 to 0.99 NNT 18	MOD
	Oliva 2023 RCT		Grade 1-2 bleedings = ns	
Quality of Life	Oliva 2017 LH		Ns QOL-E improved proportionally to PLT counts	VERY LOW
	Mittleman 2018 LH (ASPIRE trial)		EQ5D ns (exepct wk 5) FACIT-F ns	
ORR response	Aziz 2025 meta-analysis 10 RCTs 908 patients		RR 1.09 (95% CI, 0.73-1.64)	
	Meng 2020 metanalysis 8 RCTs		RR: 0.65; 95% CI, 0.47–0.9 Eltrombopag 0.58 (95% CI: 0.41–0.83, P = 0.003)	MOD
	Oliva 2023 Placebo-controlled RTC	PLT response at wk 25 = 42.3% (vs 11%) thrombocytopenia relapse-free survival at 60 months 63.6% (95% CI, 46.0 to 81.2)	OR 5.9 (2.3-14.9)	

Eltrombopag (4)

Overall Survival	Aziz 2025 meta-analysis 10 RTCs		RR 0.88, 95% CI, 0.63-1.23	
	Meng 2020		ns	
	Oliva 2023 Placebo-controlled RTC		ns	
Mortality	Aziz 2025 meta-analysis 10 RTCs		RR 1.03, 95% CI, 0.90-1.18	LOW
	Azharuddin 2021 metanalysis 8 RCTs		RR 1.02, 95% CI 0.82 to 1.27	LOW
	Dodillet 2017 Cochrane		RR 0.97, 95% confidence interval (CI) 0.73 to 1.27	LOW
Adverse Events	Dodillet 2017 Cochrane		RR 1.01, 95% CI 0.96 to 1.07, N = 5 trials, 390 patients,	MOD
	Oliva 2023 Placebo-controlled RCT		ns	MOD
Grade 3-4 nonhematologic AE	Oliva 2023 Placebo-controlled RCT	2.5/100PY 19 pts discontinued for AE (vs none in placebo)	Higher in eltrombopag arm p=0.002	MOD
SAE	Dodiellte 2017 Cochrane		RR 0.89, 95% CI 0.54 to 1.46, N = 4 trials, 356 patients	VERY LOW

Five-year cumulative LFS, PFS, combined outcome-free survival (CFS), and OS in the eltrombopag arm were 65.0% (95% CI, 51.7 to 78.3), 61.4% (95% CI, 45.3 to 77.5), 54.0% (95% CI, 39.3 to 68.7), and 77.3% (95% CI, 64.4 to 90.2),respectively, compared with 44.9% (95% CI, 4.3 to 85.5), 44.6%(95%CI, 5.8 to 83.4), 34.5%(95% CI, 2.4 to 66.6), and 58.1% (95% CI, 9.7 to 100.0) in the placebo arm, and did not reach statistical significance. Additional results are available in the Data Supplement ([Figs S4 and S5]).

IMETELSTAT



IMETELSTAT

BODY of EVIDENCE

- 1 RCT (IMerge): low-int MDS (IPSS), ESA-relapsed or ESA-refractory or ESA-inelegible. Randomization 2:1 (118 :60) to imetelstat 7.5 mg/Kg q4w vs placebo. Primary endpoint 8-wk TI. Median fup 19.5 mo in imetelstat arm
- Risk of Bias (RoB2) of IMerge Trial = low
- 3 phase 2 trials
- 1 meta-analysis pooled the results from 4 trials (abstract at ASCO)

Effect size

MODERATE improvement of both the CRITICAL outcomes versus trivial undesirable outcomes

Feasibility & costs

- Approved EMA
- Fahim 2024 reported a North American HTA including a network meta-analysis comparing Imetelstat vs Luspatercept RR of TI 0.85 (0.35, 2.25) and an estimated median quality-adjusted survival of 2.84 QALYs in RS-MDS with either of the two drugs at a substantially higher cost for patients managed with Imetelstat. The incremental cost per life year saved or QLAY saved was higher than 1 million dollars for imetelstat. The long-term value for money at current pricing was judged to be LOW in either 5q- and not-5q- subgroups

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Outcome	Body of Evidence	Imetelstat	RBC transfusions	Relative Effect
Transfusion Independence Rate	Samardali 2025 meta-analysis of 4 trials	0.52 (95% CI: 0.45, 0.58) 24-week RBC-TI rate 0.26 (95% CI: 0.20, 0.33) Median duration of TI = 123 d		
	Platzbecker 2024 LH (Imerge RCT)	40% [95% CI 30·9–49·3] 45% RS 32% not RS Sustained TI in 83% of responders Low transfusion-buden (4-6 U/8 wk) 45% High transfusion burden >=6 U/8 wk) 34% Prior luspatercept 30% (vs 50%) Prior lenalidomide 38% (vs 42%)	15% [7·1–26·6]) 19% RS 9% not RS Sustained TI in 56% of responders 21% 7%	rate difference 25% [9·9 to 36·9]; p=0·0008 rate diff RS 26% rate diff not RS 23% Rate diff 24% (signif) Rate diff 27% (signif)

RBC-TI ≥ 8 wks during Wks 1-24

		Imetelstat	RBC-transf
QOL	ImERGE TRIAL	FACIT-F (clin meaningful amelior = + 3 points) 50% Responders 70% vs 20-40% non responders (Sekeres 2024) Median time to first sustained fatigue improvement 28 wks (vs 65) Higher FACIT-F amelioration rate in TI responders	40%
	IMerge trial (Sekeres 2024) EQ-5D-5L	0.75	0.69

IMETELSTAT

HI-E IWG 2006	Sarmardali 2025 meta-analysis 4 trials	0.64 (95% CI: 0.57, 0.71) major HIE response rate 0.30 (95% CI: 0.23, 0.38) minor HI-E response rate 0.46 (95% CI: 0.38, 0.54)		
	IMerge trial	60% Transf indep 34% Hb increase > 1.5	50% 10%	Ns +24%
HI-E IWG 2018	IMerge trial	Low transfusion burden 33% High transfusion burden Major response 31% Minor response 44%	22% 0% 10%	ns
Treatment-emergent grade 3-4 AE	IMerge trial	91% 11/91 discontinuation for treatment-related AE	47%	ARR + 44%
Grade 3-4 neutropenia	Sarmardali 2025 meta-analysis 4 trials	0.67 (95% CI: 0.60, 0.73)		
	IMerge trial	68%	3%	ARR +65%
Grade 3-4 thrombocytopenia	Sarmardali 2025 meta-analysis 4 trials	0.59 (95% CI: 0.53, 0.66)		
	Imerge trial	62%	8%	ARR +54%

CONCLUSIONS

ADAPTATION and REPURPOSING

- ADOLOPT of GRADE-based guidelines
- Differences vs other-EB system guidelines (e.g. NCCN)

TREATMENT TAILORING

- Genomic/molecular features
- TD & burden

CRITICAL APPRAISAL of EV

- Critical outcomes = decisional impact
- Size of effect (beyond p value) = clinical relevance
- Consistency of the BODY of evidence
- PRO

TRANSPARENCY

- Experts opinion or RCT results are NOT the whole story

HURDLES

- AIC
- Missing HTA data

grazie

