Nové směry v terapii anemie MDS

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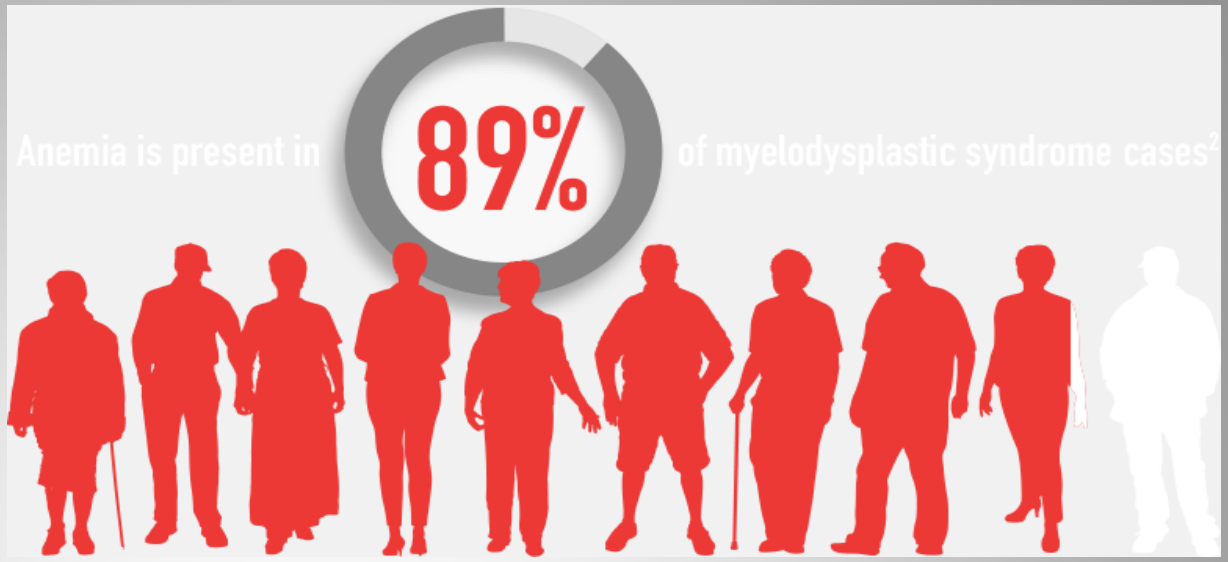
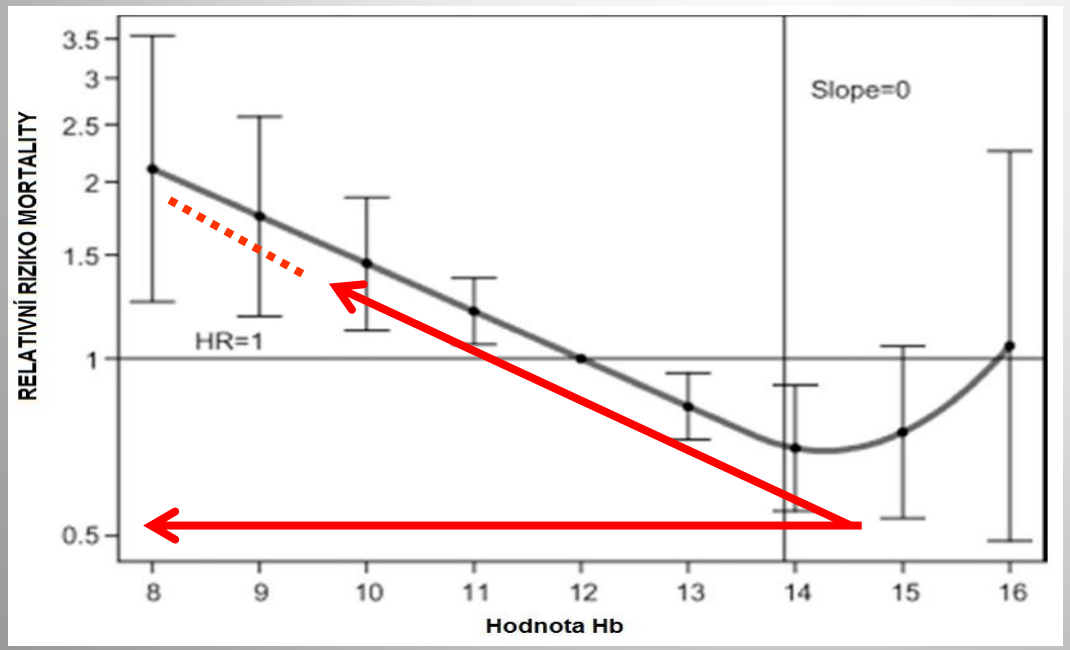
Anemie u MDS



Vztah mezi Hb a mortalitou



60% transfuzní závoslost

Goodnough 2015

Anemie u nízce rizikových MDS nemocných vztah k mortalitě

➢ ***Monserrat Arnan Sangerman et al. Impact of Red Blood Cell Transfusion Burden Status in Patients with Lower-Risk MDS, abstract No 3031***

474 lower-risk (R-IPSS risk very low, low a intered.)

Median OS:

NTD (8 years; 95% CI 6.6-9.5),

LTB (6.2 years; 95% CI 4.2-8.1)

HTB (3.1 years; 95% CI 2.4-3.8) (p<0.001)

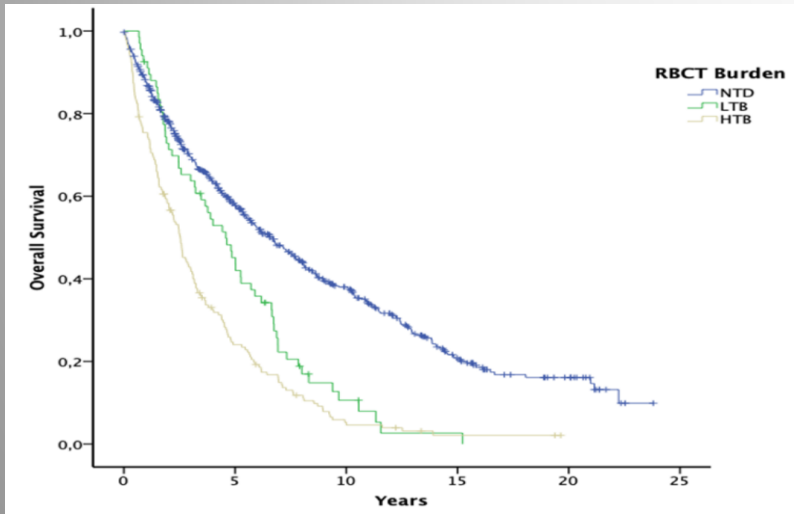
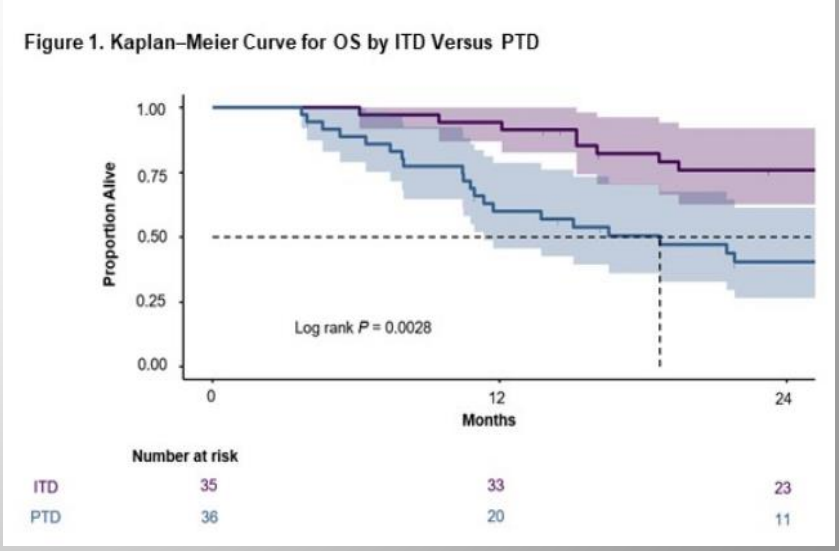


Figure 1. Kaplan-Meier for OS according to RBCT burden status categories.

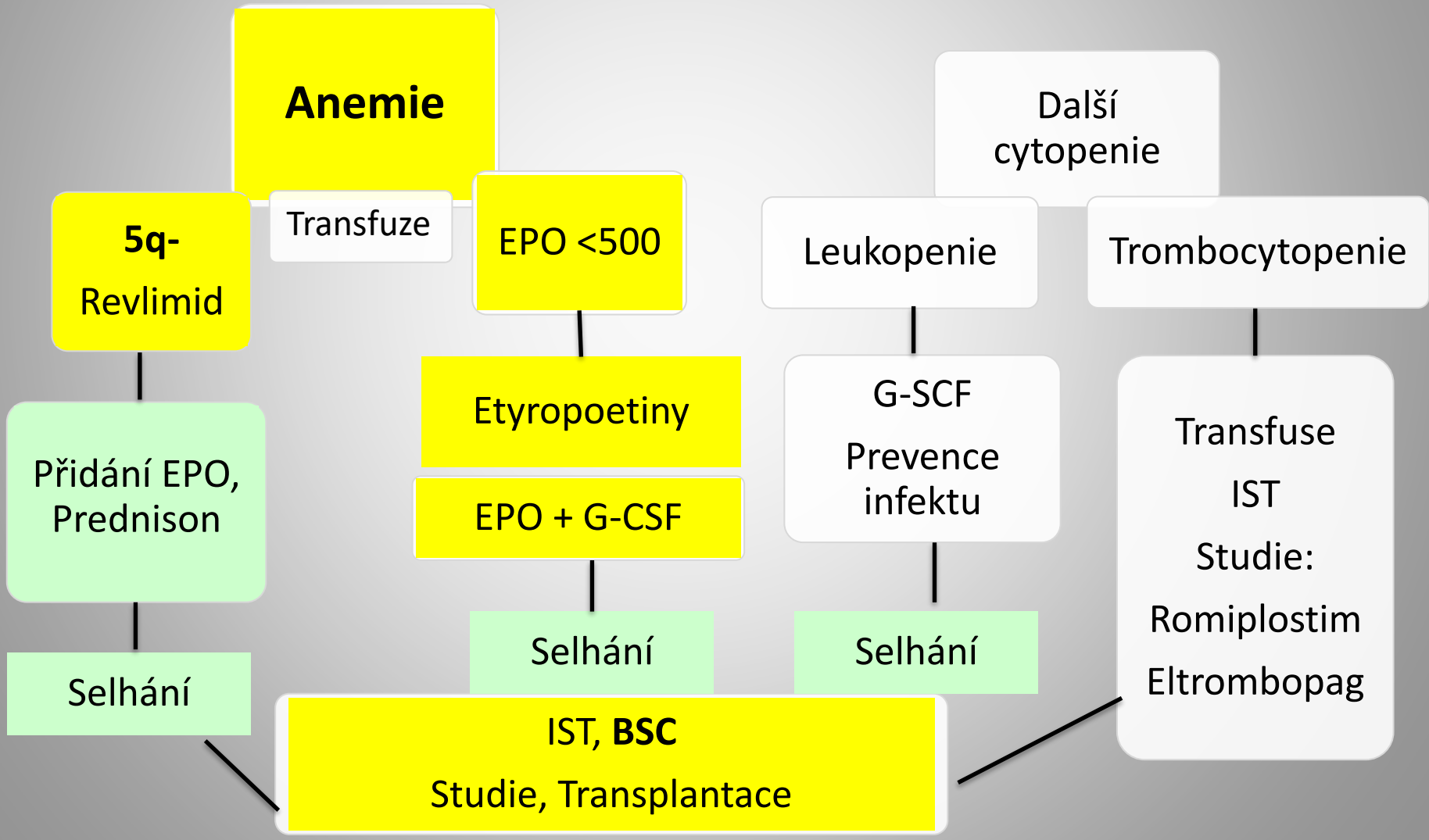
➢ ***Rena Buckstein et al. Persistent Red Blood Cell (RBC) Transfusion Is Associated with Increased Mortality Risk in Transfusion-Dependent (TD) Patients with MDS with Ring Sideroblasts (RS+), abstract No 3012***

191 MDS Low risk - RS+ TRF dependentních

Median OS : 18.7 months TRF dep. X **48.7 months TRF indep.**



Algoritmus terapie MDS s nižším rizikem



Novinky v terapii anemie

Kombinace Len + EPO
Kombinace Len + EPO + Prednison
Luspatercept (REBLOZYL)
Imetelstat
Roxadustat (FG-4592)
Perorální HMA: Azacitidine (ONUREG)
ASTX727(cedazuridine/decitabine)

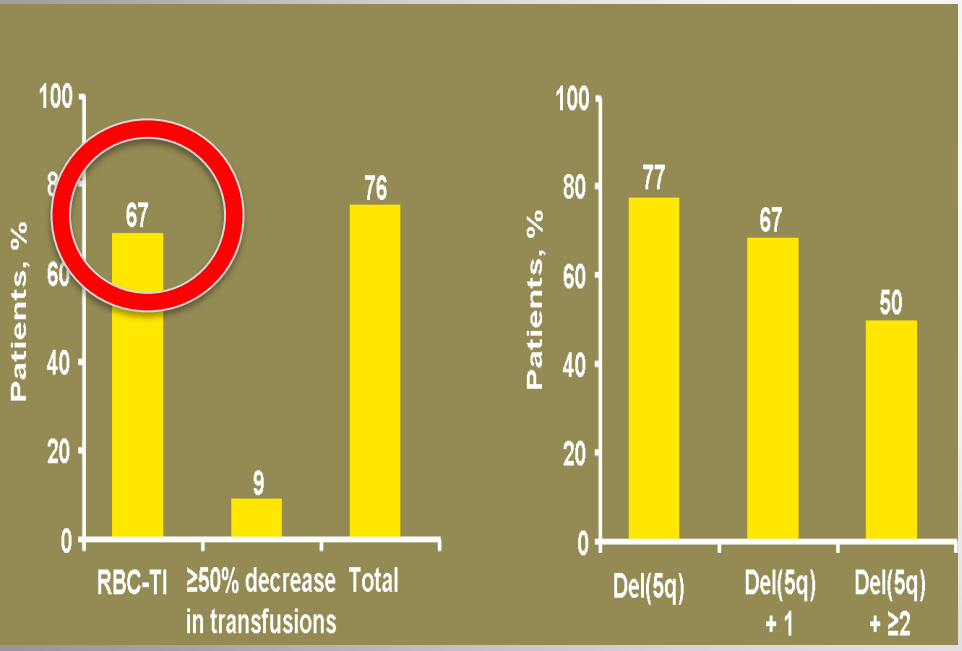
Imunomodulační terapie - Lenalidomid

MDS-003: lenalidomid pro del(5q) MDS

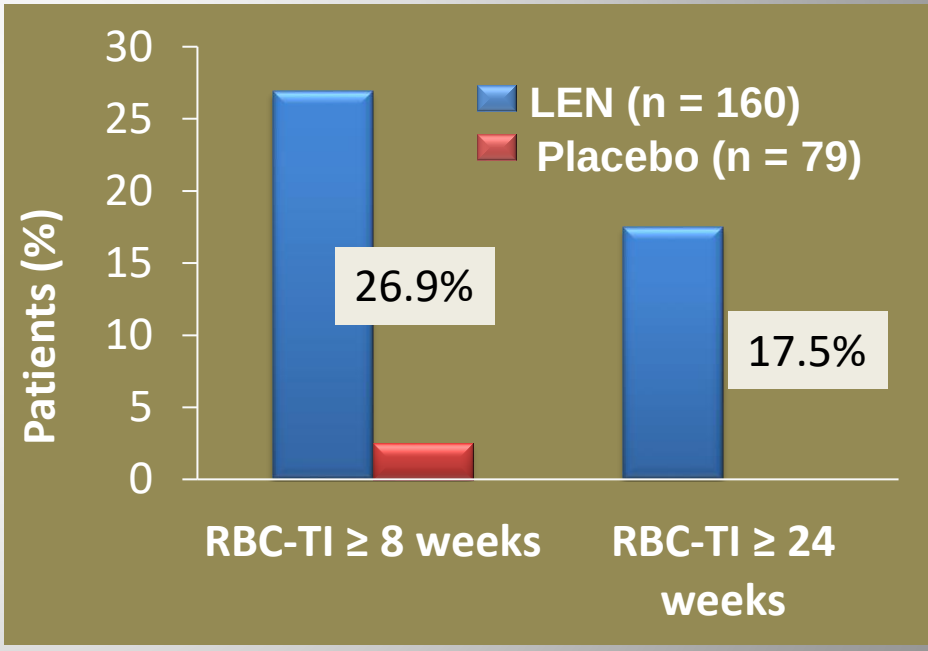
MDS-005: lenalidomide pro non 5q- MDS

N=148, lenalidomide 10 mg/day for 21/28-day

Odpověd:erytroc | **Odpověd:cytogen**



Odpověd: RBC-TI



List A, et al. N Engl J Med 2006, Santini et al, Leukemia 2016

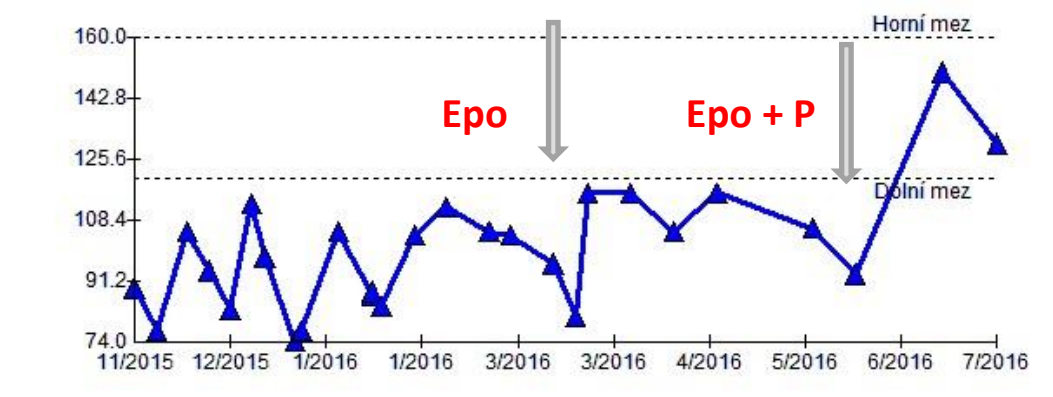
Kombinace lenalidomid + EPO + prednison u refrekterních či relabujících MDS s nízkým rizikem léčených lenalidomidem pro chronickou transfuzní závilost

➢ *Jonasova A et al. Leuk Res. 2018 Mar 27;69:12-17*

Charakteristiky	Počty
Počet	**51**
Věk median	72
Sex F/M	36/15
WHO 2008:	
5q- syndrom	26
RCMD	16
RARS-T	2
RAEB-1	7

	Odpověd TI
Skupina 5q-	**80%**

Primárně refrakterní	Relabující
8 (16%)	**8 (30%)**
Odpovědi	
4 (50%)	**5 (62%)**



➢ *Alan F. List et al. Len + Epoetin in Lower Risk Non-Deletion 5q [Del(5q)] MDS: Phase III Study, ASH 2019, abstract No 841*

Odpovědi (major ery response):
Len + Epo : 38,9% , Len : 15,6%

Luspatercept

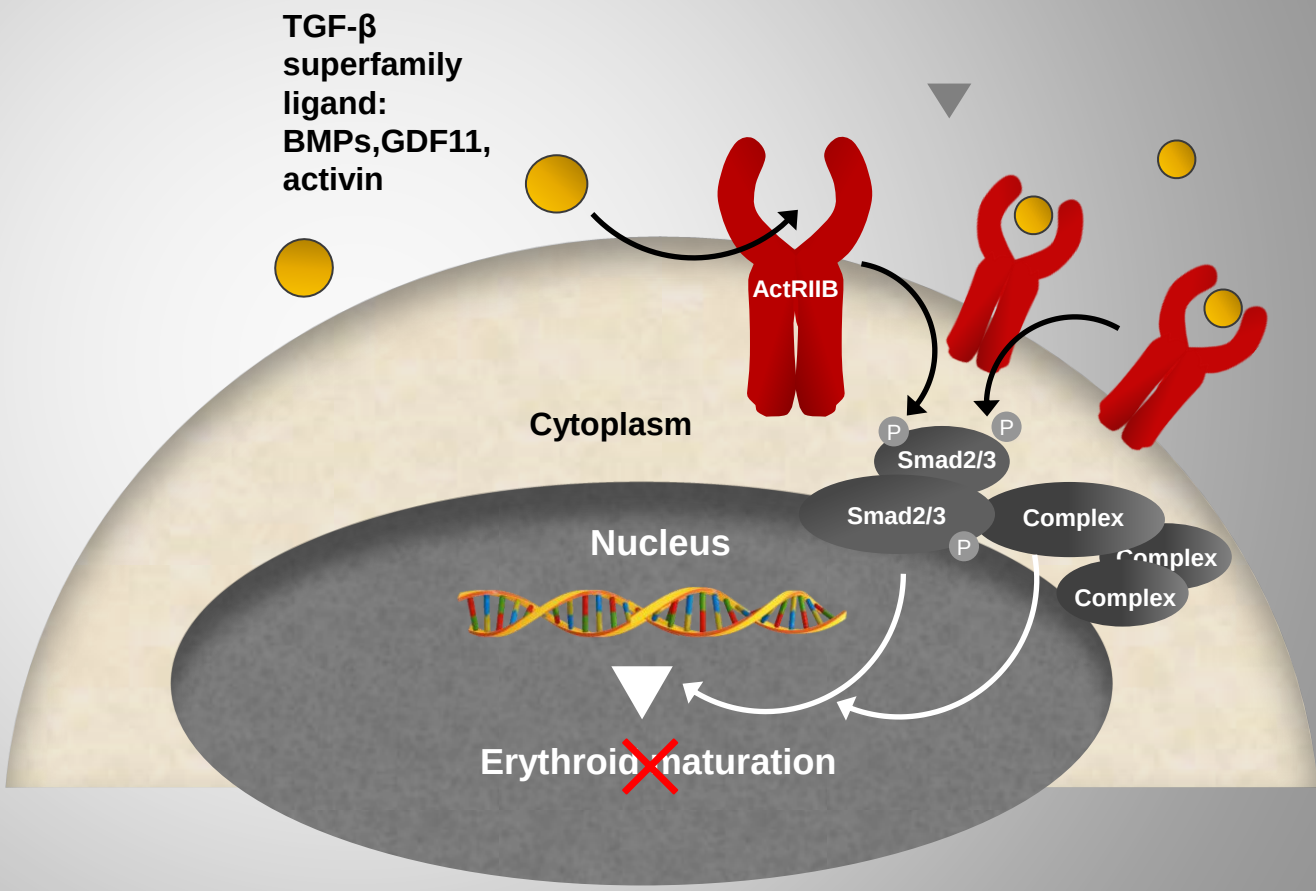
Ineffectivní Erythropoesa: Negativní vliv ”TGF-β superfamily"
Aberantní SMAD2/3 Signalizace

TGF-β superfamily skrze aberantní aktivaci Smad2/3 signální dráhy ovlivňuje erytroidní maturaci v pozdních fázích erytropoesy[1]

TGF-β superfamily ligandy se vážou na ActRIIB spouštějí Smad2/3 signální dráhu[1-3]

Dochází k fosforilaci Smad2/3 k jejich aktivaci a tvorbě Smad complexú[3,4]

Smad komplexy se dostávají do jádra kde modifikuj/blokují transkripci genů důležitých v pozdní fázi erytropoesy



1. Attie et al. *Am J Hematol* 2014;89:766–70; 2. Cappellini et al. *Blood Rev* 2018;32:300–11; 3. Blank et al. *Blood* 2015;125:3542–50; 4. Hata, Chen *Cold Spring Harb Perspect Biol* 2016;8:a022061; 5. Blank, Karlsson. *Leukemia*. 2011;25:1379–88; 6. Suragani et al. *Blood* 2014;123:3864–72; 7. Suragani et al. *Nat Med* 2014;20:408–14.

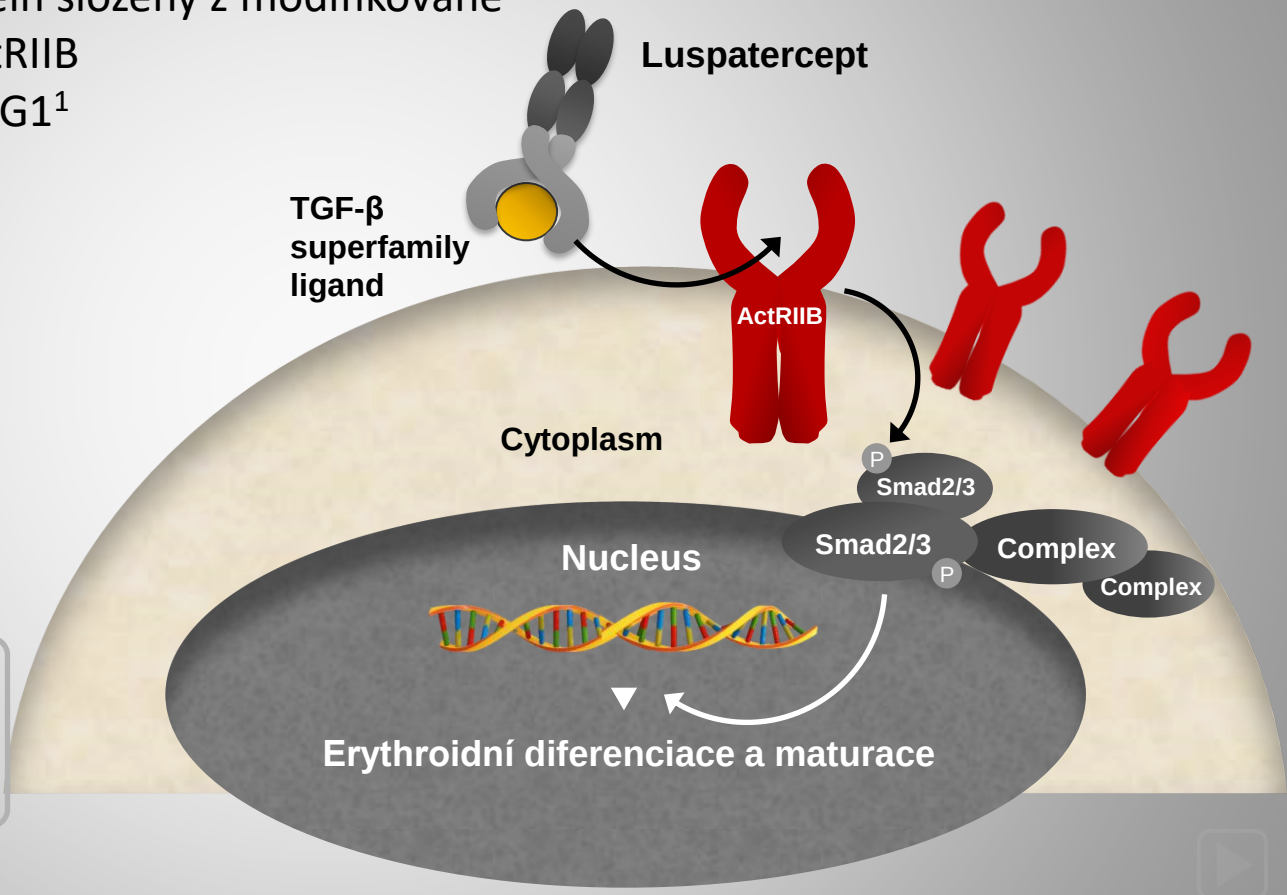
Luspatercept - mechanismus učinku (inhibice SMAD2/3 signální dráhy)

- Luspatercept – stimuluje diferenciaci a zrání červené řady
- Recombinantní fusní protein složený z modifikované extracelulární domény ActRIIB a Fc domény humáního IgG1[1]

Luspatercept váže ligandy TGF-beta[2-4]…

… inhibuje tak Smad2/3 signální dráhu[2]

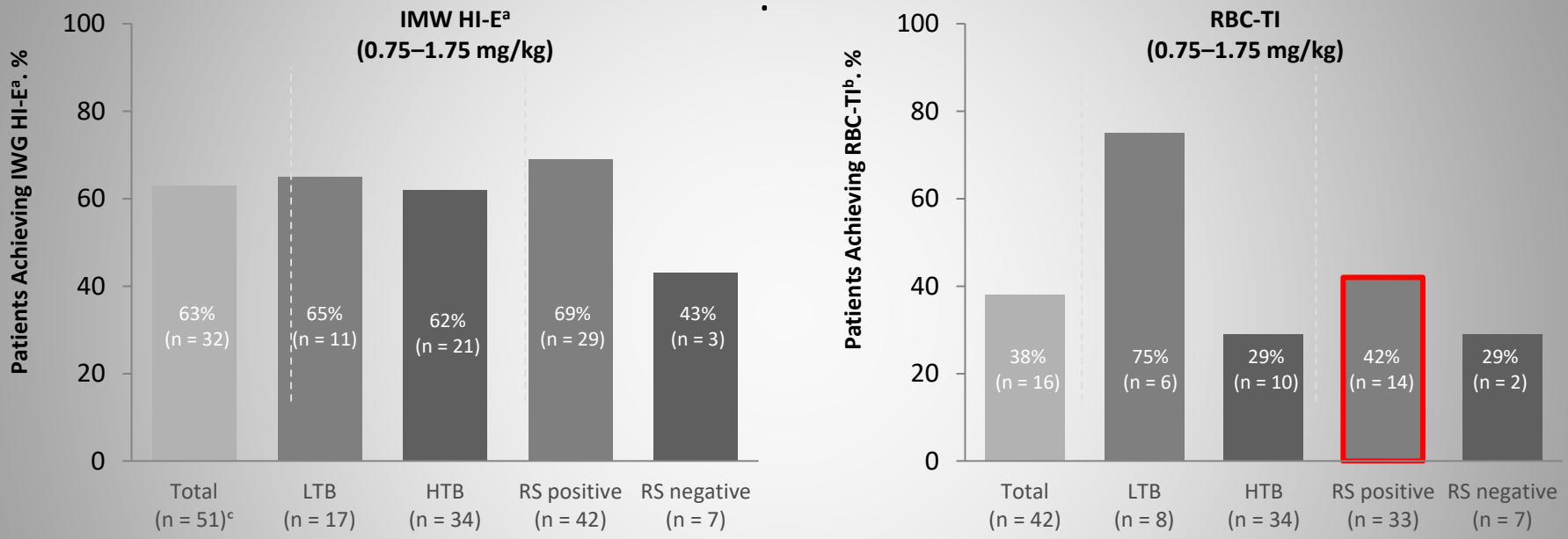
Inhibice Smad2/3 signaální dráhy
Stimuluje diferenciaci a maturaci v pozdních fázích erythropoesy[3]



1. Attie et al. *Am J Hematol* 2014;89:766–70. 2. Suragani et al. *Nat Med* 2014;20:408–14. 3. Suragani et al. *Blood* 2014;123:3864–72. 4. Cappellini et al. *Blood* 2018;132:163.

Luspatercept for the Treatment of Anaemia in Patients with Lower-Risk Myelodysplastic Syndromes **(PACE-MDS):** A Multicentre, Open-Label Phase 2 Dose-Finding Study with Long-Term Extension Study

Platzbecker U et al. , Lancet Oncology 2017, Oct



- Treatment-related grade 3 AEs: myalgia (2%), increased blast cell count (2%), and general physical health deterioration (2%)
- No grade 4 AEs , no treatment-related deaths
- 2 (3%) patients discontinued treatment due to AEs

[a] Defined as ≥ 1.5 g/dL Hb increase over 8 weeks (LTB) or ≥ 4 U RBC reduction over 8 weeks (HTB).

LTB < 4TU/8 týdnů, HTB > 4 TU/8 týdnů

Luspatercept

PACE-MDS – Fáze 2

Platzbecker U et al. , Lancet Oncology 2017, Oct

.

Subgroup n (%)	IWG HI-E Response Rate	RBC-TI Response Rate
EPO < 200 U/L	**16 of 25 (64)**	**10 of 18 (56)**
EPO 200–500 U/L	4 of 11 (36)	3 of 9 (33)
EPO > 500 U/L	4 of 13 (31)	1 of 13 (8)
Prior ESA	**16 of 35 (46)**	**10 of 29 (35)**
ESA naïve	8 of 14 (57)	4 of 11 (36)

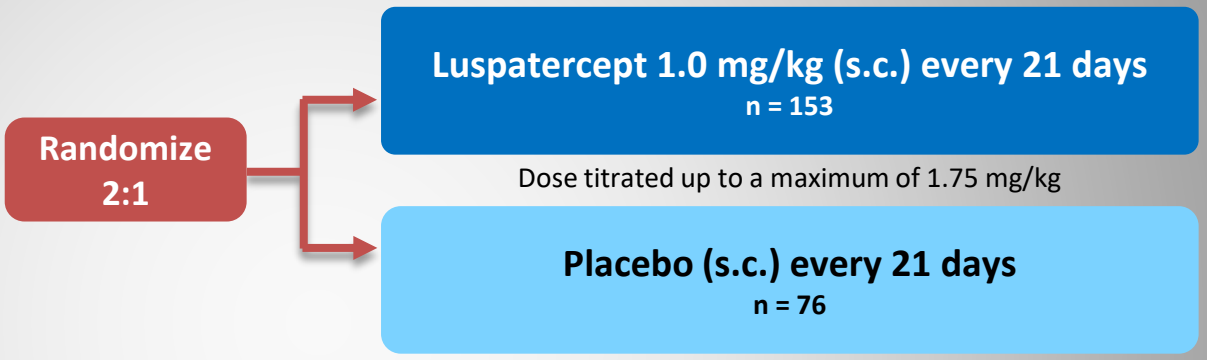
Guillermo Garcia-Manero et al. Hematologic Improvement–Neutrophil and –Platelet in the MEDALIST
ASH 2019 abstract No 4243 **- Odpovědi : 5/8 (62.5%) HI-P, 3/15 (20%) HI-N**

The **MEDALIST** Trial: Results of a **Phase 3**, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated **Anemia With Ring Sideroblasts** (RS) Who Require Red Blood Cell (RBC) Transfusions

Pierre Fenaux et al. N.Eng.J Med. 2020 Jan 9;382(2):140-151

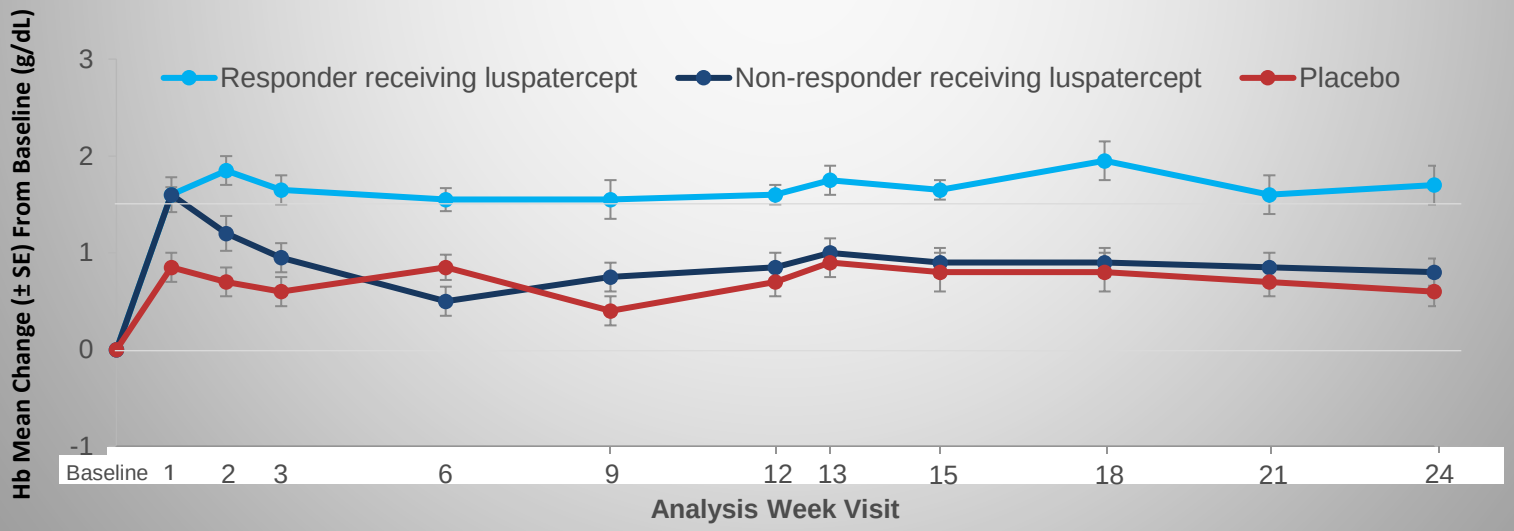
Patient Population

- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with *SF3B1* mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks



RBC-TI ≥ 12 Weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

	Luspatercept (n = 153)	Placebo (n = 76)
Achieved HI-E[a] (weeks 1–24), n (%)	**81 (52.9)**	**9 (11.8)**
Reduction of ≥ 4 RBC units/8 weeks (baseline transfusion burden ≥ 4 units/8 weeks)	52/107 (48.6)	8/56 (14.3)
Hb increase of ≥ 1.5 g/dL (baseline transfusion burden < 4 units/8 weeks)	29/46 (63.0)	1/20 (5.0)
95% CI	44.72–61.05	5.56–21.29
P value[b]	< 0.0001	
Achieved HI-E[a] (weeks 1–48), n (%)	**90 (58.8)**	**13 (17.1)**
Reduction of ≥ 4 RBC units/8 weeks (baseline RBC transfusion burden ≥ 4 units/8 weeks)	58/107 (54.2)	12/56 (21.4)
Hb increase of ≥ 1.5 g/dL (baseline RBC transfusion burden < 4 units/8 weeks)	32/46 (69.6)	1/20 (5.0)
95% CI	50.59–66.71	9.43–27.47
P value[b]	< 0.0001	

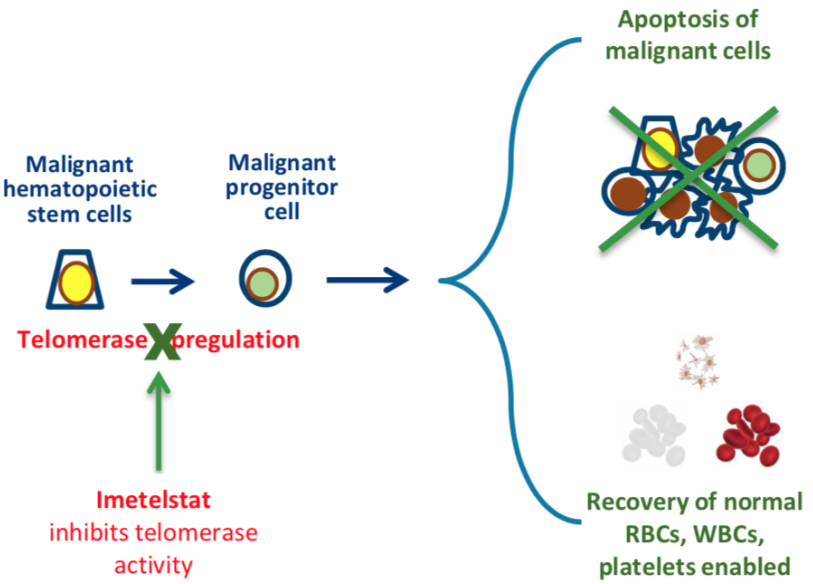


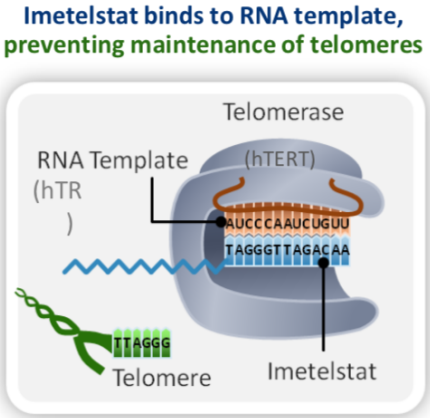
Guillermo Garcia-Manero et al. Hematologic Improvement–Neutrophil and –Platelet in the MEDALIST
ASH 2019 abstract No 4243 **- Odpovědi : 5/8 (62.5%) HI-P, 3/15 (20%) HI-N**

Imetelstat

Inhibitor telomerázové aktivity

MDS - významně kratší teloméry ve srovnání se zdravou populace
- vyšší aktivitu telomeráz



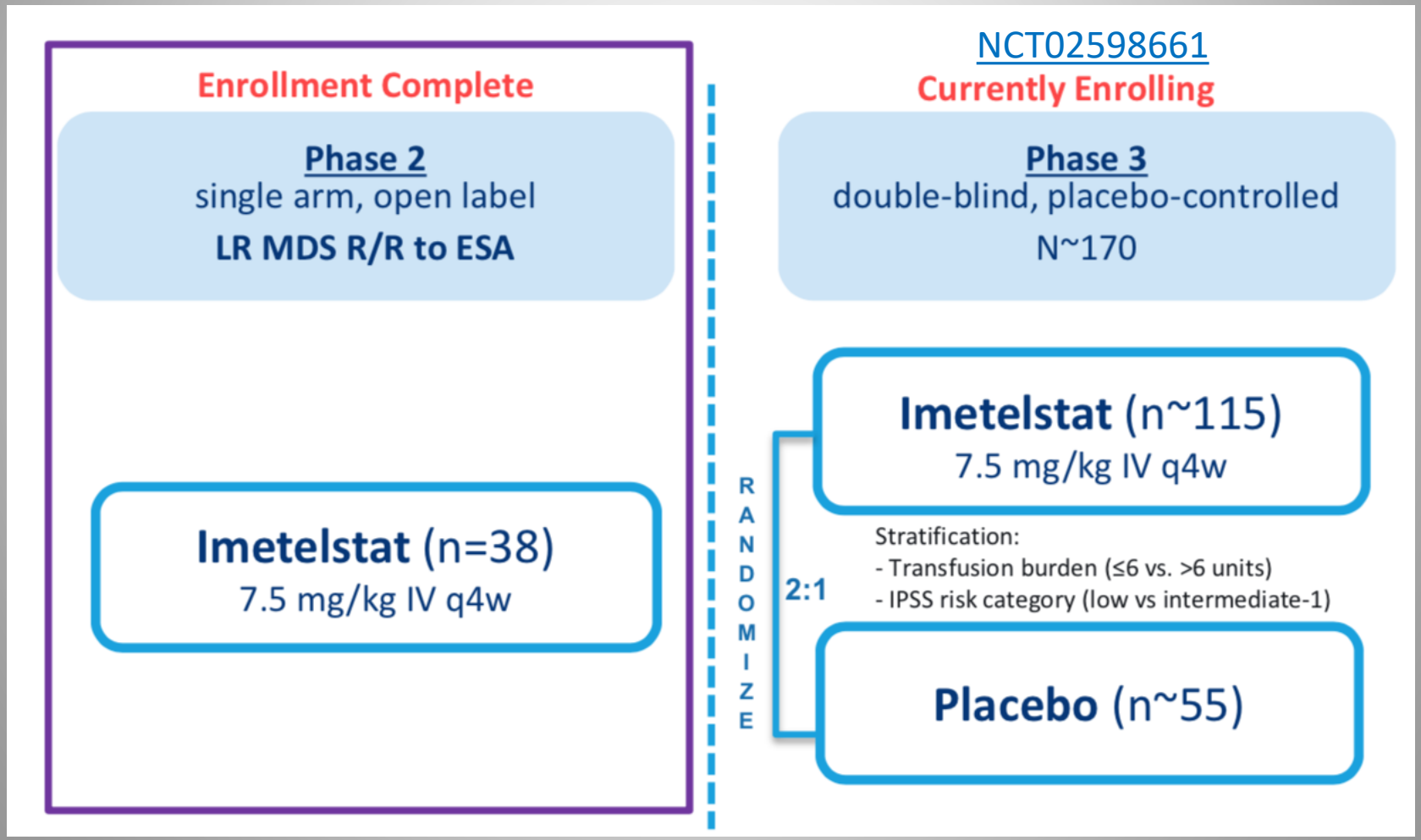


Mechanism of Action

- **Potent competitive inhibitor of telomerase activity**
- **Structure:** Proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Disease-modifying potential: selective killing** of malignant stem and progenitor cells enabling normal blood cell production

TREATMENT WITH IMETELSTAT PROVIDES DURABLE TRANSFUSION INDEPENDENCE (TI) IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESAs)

Uwe Platzbecker, EHA 2020



Odpovědi faze II

Platzbecker et al. EHA 2020

Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	**11 (29)**

Parameters	N = 38
HI-E per IWG 2006, n (%)	**26 (68)**
≥1.5 g/dL increase in Hb lasting ≥ 8 weeks[a], n (%)	13 (34)
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68)
Duration of HI-E, weeks, median (95% CI)[b]	**92.7 (37.1, 149.4)**
Major and Minor Response per IWG 2018	
Major response: 16-week TI, n (%)	**14 (37)**
Minor response: ≥ 50% transfusion reduction/16 weeks, n (%)	21 (55)

Potential Disease-Modifying Activity with Imetelstat Treatment: Reduction of Malignant Clones Associated with Treatment Response

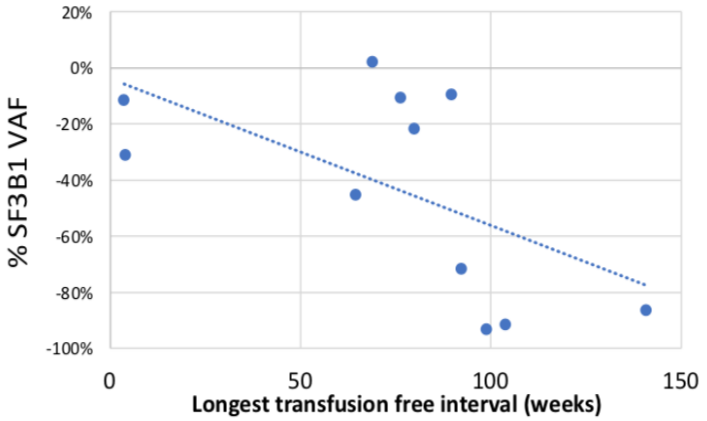
11 patients had SF3B1 mutations detected at baseline and had paired post-treatment mutation data available:

A. 10/11 had reduction (ranging 10-93%) in SF3B1 variant allele frequency (VAF)

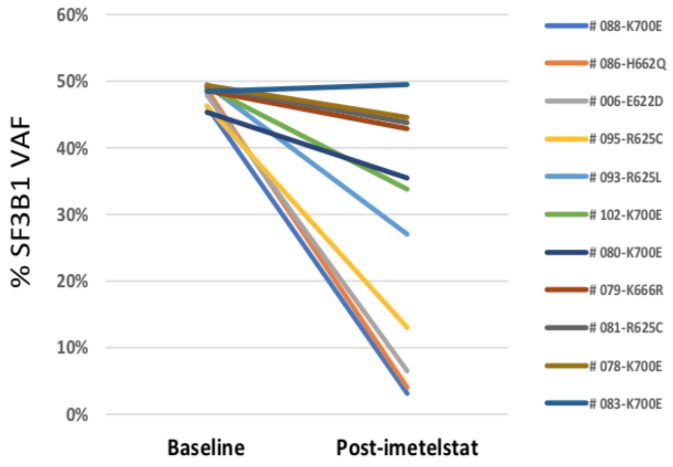
B. The greater reduction of SF3B1 VAF, the longer TI duration patients maintained

C. Significant correlation between greater reduction of SF3B1 VAF and shorter onset time to achieve the longest TI interval (Pearson correlation coefficient r=0.646, p=0.032)

B. Reduction of SF3B1 VAF vs the longest TI duration



A. Reduction of SF3B1 VAF with Imetelstat treatment



C. Reduction of SF3B1 VAF vs time to the longest TI

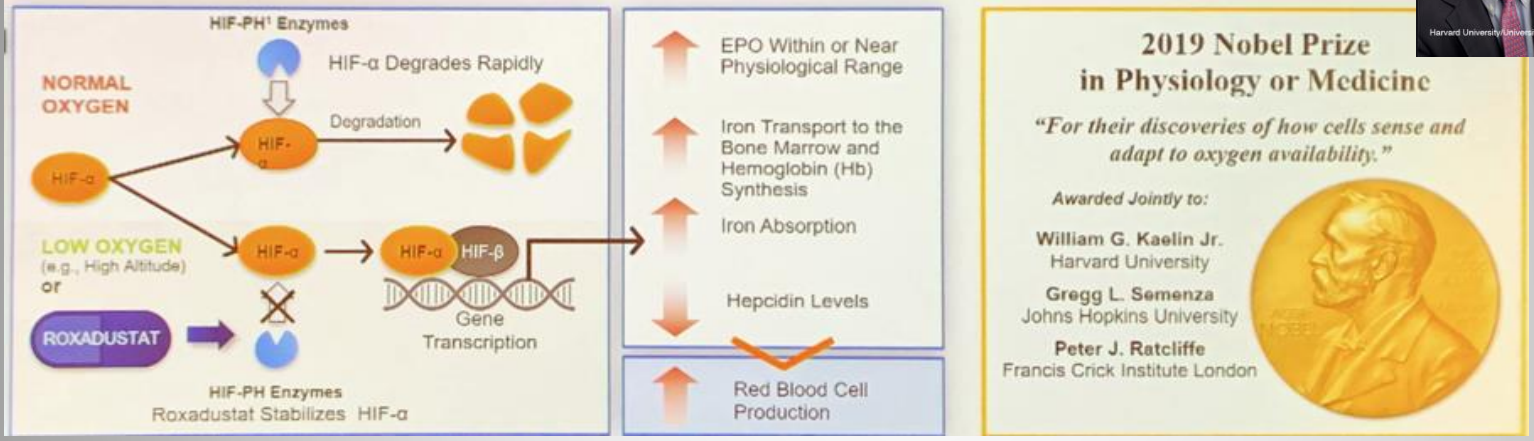
Patient ID	The longest TI interval (weeks)	Time to the longest TI interval start (weeks)	% SF3B1 VAF reduction
200088*	98.9	6.6	-93.3%
200086*	104	4.3	-91.8%
200006	140.9	9.9	-86.4%
200095	92.4	5.4	-71.9%
200093*	64.6	40.7	-45.5%
200102*	4	32.9	-31.2%
200080	79.9	44.1	-21.9%
200079	3.6	20.7	-11.6%
200081*	76.3	12.1	-10.9%
200078*	89.7	23.1	-9.8%
200083*	68.9	37.1	2.0%

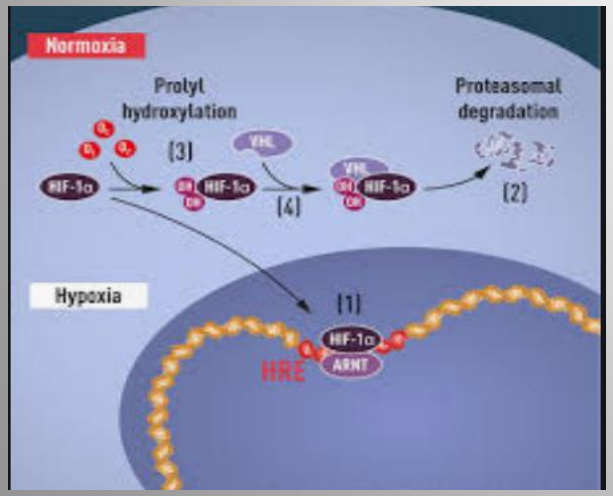
*Remain on treatment as of 4 Feb 2020

Roxadustat (FG-4592)

Roxadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor

- 2019 Nobel Prize winning science is the foundation of roxadustat
- Increases Hb by mimicking body's natural response to low oxygen
- Studied for treatment of anemia in Stage 3 to 5 CKD patients, dialysis and non-dialysis
- Approved in China: (dialysis 12/2018, non-dialysis 8/2019) and Japan: (dialysis 9/2019)





Roxadustat - **orální** HIF prolyl hydroxylase inhibitor →

ke stabilizaci a aktivaci HIF →

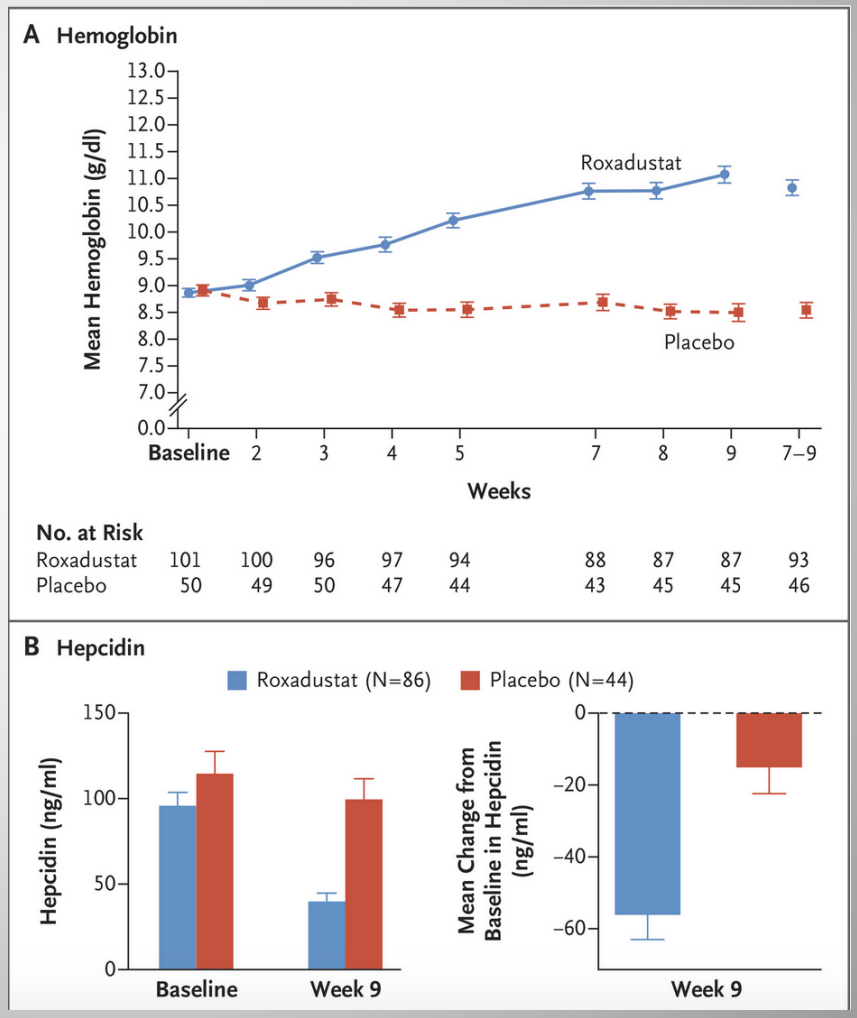
↑ syntese EPO, ↑ citlivosti a produkci EPO receptorů, inhibice hepcidinu →

↑ resorpci Fe

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N Engl J Med. 2019 Sep 12;381(11):1001-1010 Nan Chen et al.

Randomizovaná studie faze 3
2:1 (Roxadustat : Placebo)
154 nemocných s chronickým renálním selháním



Roxadustat (FG4592; ASP1517; AZD9941) in the Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (LR-MDS) and Low Red Blood Cell (RBC) Transfusion Burden (LTB)

David H. Henry et al. , ASH 2019, abstract No 843

Otevřená studie faze 2:

No = 24 epo refrakterní -TRF dependentní - nízce rizikoví MDS

Odpovědi: 38% TI, > 58% redukce TRF

Dávka 2,5 mg největší aktivita

Nízká toxicita, dobrá tolerabilita

V současnosti probíhá náběr studie faze 3

(*NCT03263091*)

Hypometylační látky

Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of CALGB. Silverman LR, et al. J Clin Oncol. 2002

➤ **A Phase III, Randomized, Placebo-Controlled Trial of CC-486** in Patients with Red Blood Cell Transfusion-Dependent Anemia and Thrombocytopenia Due to IPSS Lower-Risk MDS. *Guillermo Garcia-Manero, Valeria Santini, Antonio Almeida, Uwe Platzbecker, Anna Jonasova et al.(EHA 2020)*

216 Nízce rizikových TRF dep nemocných s PLT < $75x10^9$

TI: 31%

HI-E 43%

HI-PLT 24%

➤ **Fáze 1-2 "Study of Low Dose ASTX727 (ASTX727 LD) in Lower Risk MDS"**

NCT03502668 – probíhající studie

Testování bezpečnosti a účinosti malých dávkek perorálního decitabinu s citidin deaminasovým inhibitorem cedazuridinem

(tento inhibuje degradaci decitabinu v GIT)

Budoucností terapie anemie budou velmi pravděpodobně kombinace výše uvedených preparátů

DĚKUJI ZA POZORNOST