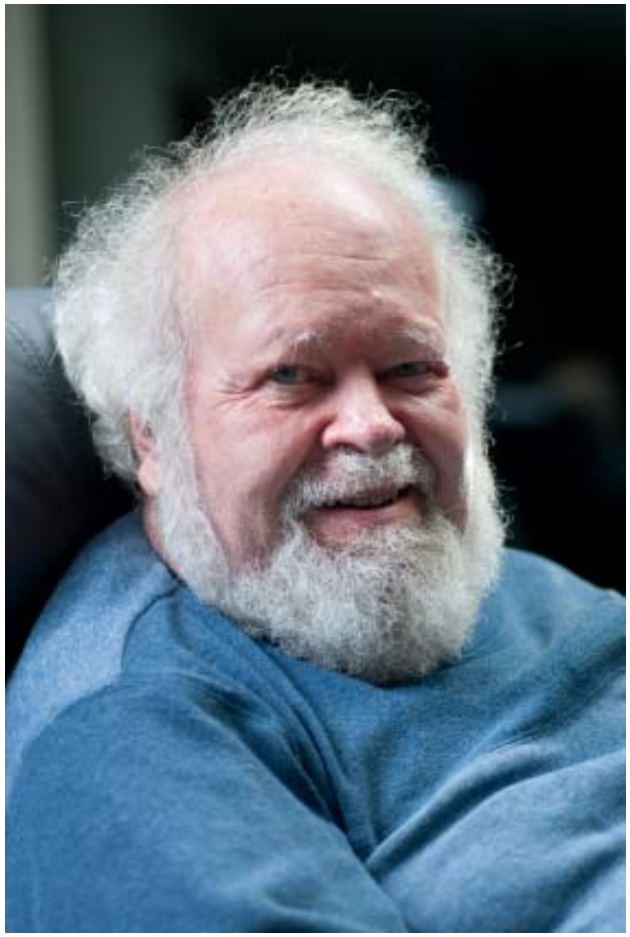
MDS 2013 – Standards und Perspektiven

U. Platzbecker
Medizinische Klinik und Poliklinik I
Universitätsklinikum „Carl Gustav Carus“ Dresden

Der mögliche MDS-Patient

Variable	
Hb	Ek-Pflicht
ANC	1.5
PLT	96
EPO	280
KMP:	5% Blasten
Zytog.:	46 XY



IPSS = 1

Variable	Score				
	0	0,5	1,0	1,5	2,0
KM Blasten (%)	< 5	5–10		11–20	21–30
Karyotyp	Good	Intermediate	Poor		
Zytopenien	0/1	2/3			

Score	IPSS-Gruppe	Medianes Überleben (Jahre)	
0	Low	5,7	Low R
0,5–1,0	Int-1	3,5	Low R
1,5–2,0	Int-2	1,2	High R
≥ 2,5	High	0,4	High R

Greenberg et al. Blood 1997

IPSS-R = 5

Variable	IPSS-R-Score						
	0	0,5	1,0	1,5	2,0	3,0	4,0
Zytogenetik†	Very good		Good		Intermediate	Poor	Very poor
KM-Blasten (%)	≤ 2		> 2 – < 5		5 – 10	> 10	
Hämoglobin (g/dL)	≥ 10		8 – <10	< 8	–		
Thrombozyten (x10⁹/L)	≥ 100	50 – < 100	< 50	–	–		
ANC (x10⁹/L)	≥ 0,8	< 0,8					

* IPSS-R-Risikogruppen: Very low ≤ 1,5; Low 1,5 – 3; Intermediate 3 – 4,5; **High 4,5 – 6**; Very high > 6

† Very good = -Y, del(11q); Good = normal, del(5q), del(12p), del(20q), doppelt einschließlich del(5q); Int. = del(7q), +8, +19, i(17q), andere einzelne oder doppelte unabhängige Klone; Poor = -7, inv(3)/t(3q)/del(3q), komplex (3 Aberrationen); Very poor = komplex (>3 Aberrationen).

ANC = absolute Neutrophilenzahl; KM = Knochenmark.

Greenberg et al. Blood 2012

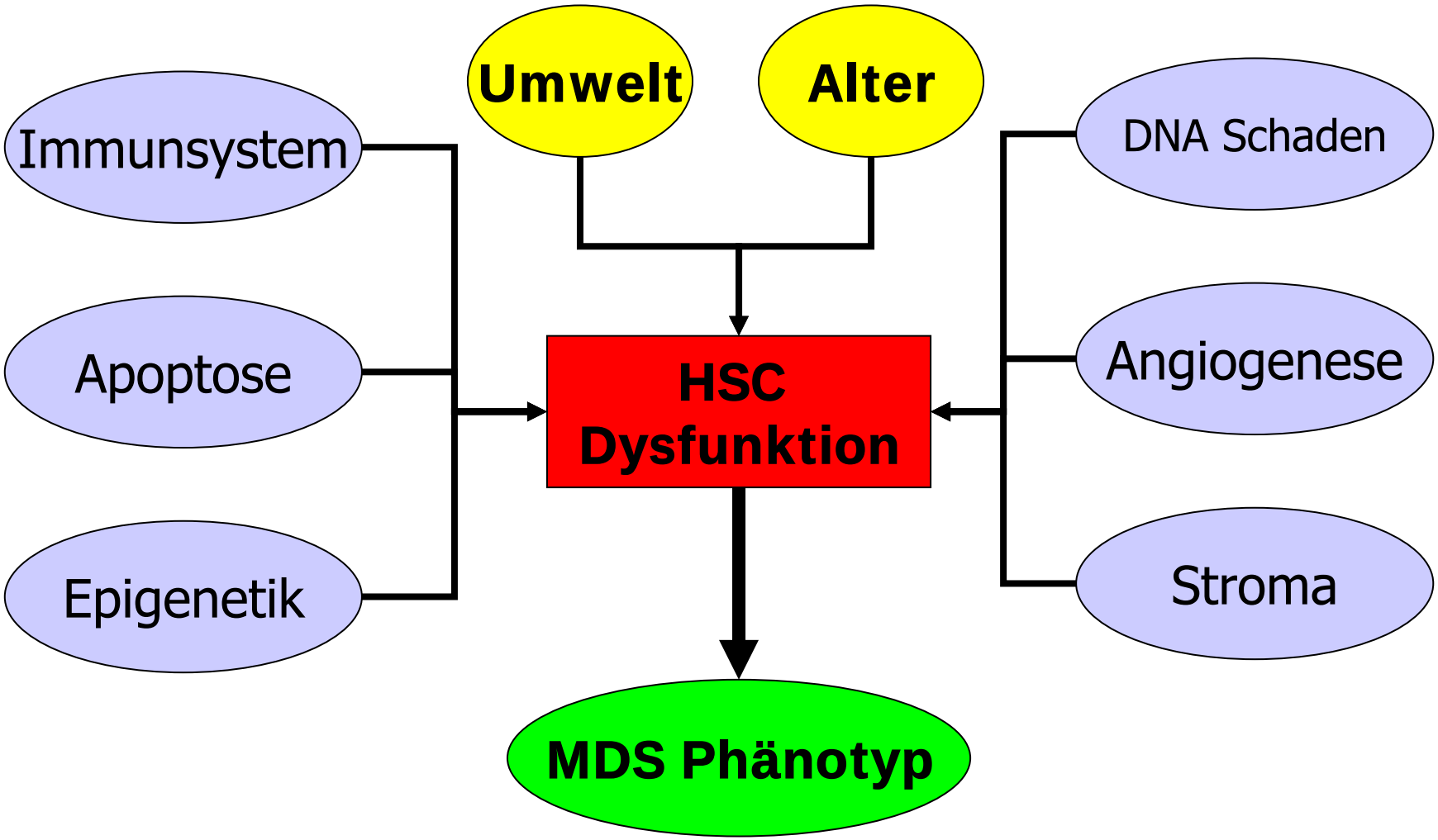
IPSS-R-Score

	Anzahl Patienten	Very Low	Low	Inter-mediate	High	Very High
Patienten (%)	7012	19 %	38 %	20 %	13 %	10 %
Überleben		**8,8**	**5,3**	**3,0**	**1,6**	**0,8**

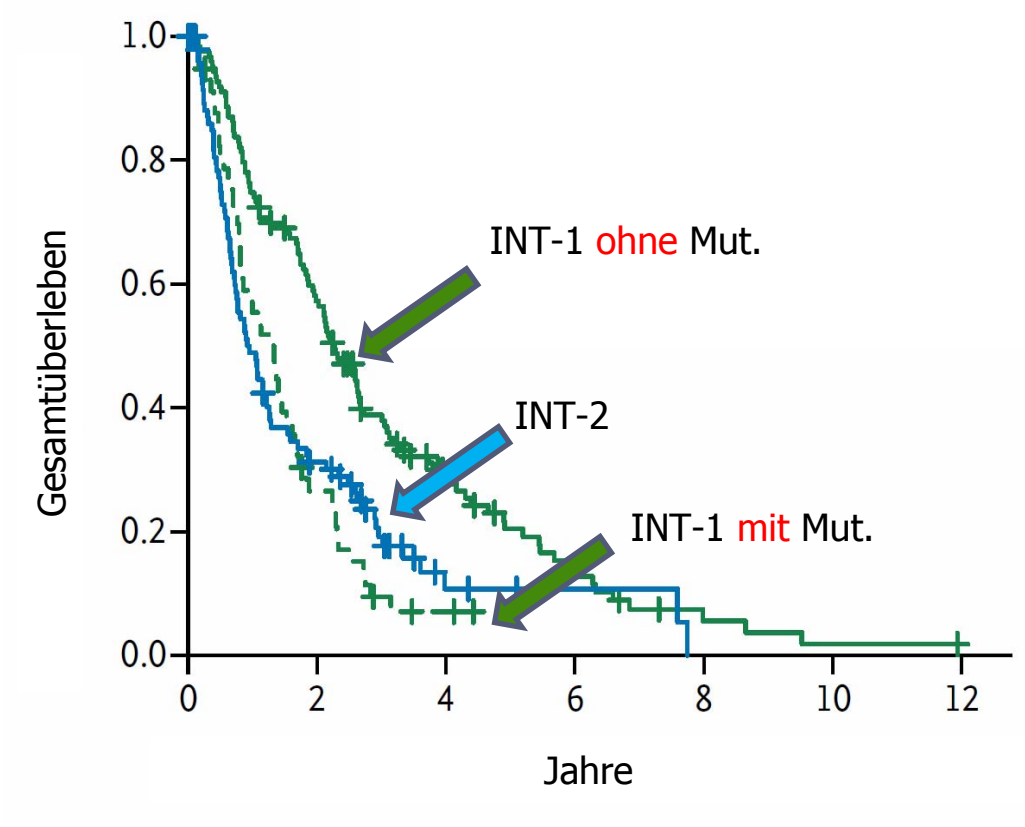
Mit 4% Blasten wären es 3 Jahre...

Greenberg et al. Blood 2012

Gibt es das „MDS bcr-abl“ ?

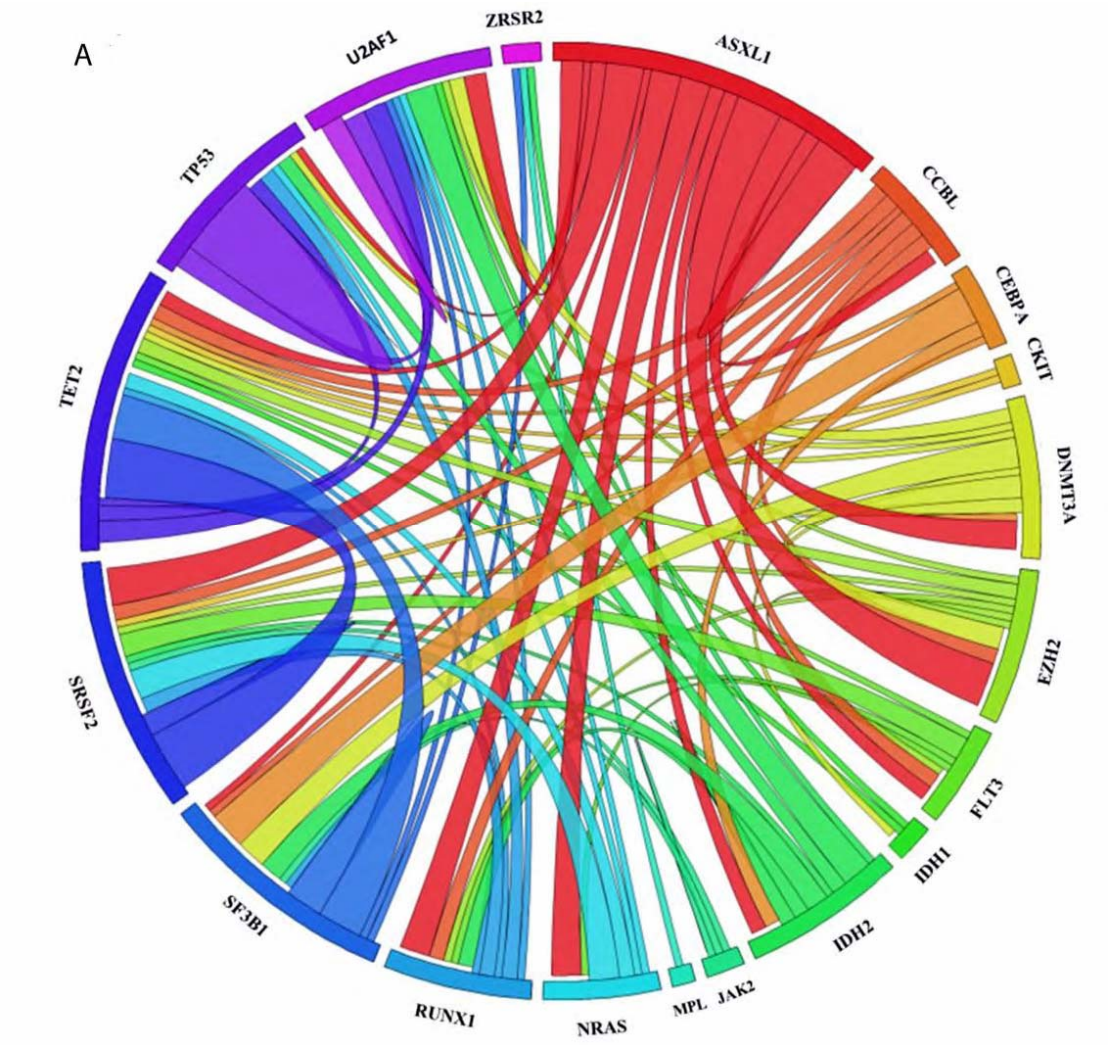


Mutationen von EZH2, p53, ASXL1, RUNX1



Bejar et al. NEJM 2011

Mutationen bei MDS



Mian et al. Haematologica 2013

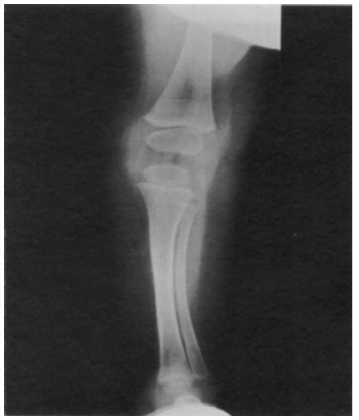
Schinzel-Giedion-Syndrom

Malformations in Sibs

A. Schinzel and A. Giedion

Division of Medical Genetics (A. Schinzel) and Division of Pediatric Radiology (A. Giedion), Department of Pediatrics, University of Zürich

American Journal of Medical Genetics 1:361–375 (1978)



BRIEF COMMUNICATIONS

nature genetics

De novo mutations of *SETBP1* cause Schinzel-Giedion syndrome

Alexander Hoischen[1,14], Bregje W M van Bon[1,14], Christian Gilissen[1,14], Peer Arts[1], Bart van Lier[1], Marloes Steehouwer[1], Petra de Vries[1], Rick de Reuver[1], Nienke Wieskamp[1], Geert Mortier[2], Koen Devriendt[3], Marta Z Amorim[4], Nicole Revencu[5], Alexa Kidd[6], Mafalda Barbosa[7], Anne Turner[8], Janine Smith[9], Christina Oley[10], Alex Henderson[11], Ian M Hayes[12], Elizabeth M Thompson[13], Han G Brunner[1], Bert B A de Vries[1] & Joris A Veltman[1]

Schinzel-Giedion syndrome is characterized by severe mental retardation, distinctive facial features and multiple congenital malformations; most affected individuals die before the age of ten. We sequenced the exomes of four affected individuals (cases) and found heterozygous *de novo* variants in *SETBP1* in all four. We also identified *SETBP1* mutations in eight additional cases using Sanger sequencing. All mutations clustered to a highly conserved 11-bp exonic region, suggesting a dominant-negative or gain-of-function effect.

We sequenced the exomes (37 Mb of genomic sequence, targeting ~18,000 genes) of four unrelated individuals with Schinzel-Giedion syndrome to a mean coverage of 43-fold (**Supplementary Table 1**, **Supplementary Figs. 1** and **2**). The exomes of all four individuals were enriched using the SureSelect human exome kit (Agilent) and were subsequently sequenced using one quarter of a SOLiD sequencing slide (Life Technologies). A total of 2.7–3.0 gigabases of mappable sequence data were generated per individual, with 65–72% of bases mapping to the targeted exome (**Supplementary Table 1**). On average, 85% of the exome was covered at least tenfold, and 21,800 genetic variants were identified per individual, including 5,351 nonsynonymous changes. A number of prioritization steps were applied to reduce this number and to identify the potentially pathogenic mutations, similar to the methods used in previous studies[4,5] (**Supplementary Table 2**). A comparison with the NCBI dbSNP build 130 as well as with recently released SNP data from other groups and in-house SNP data (see **Supplementary Note**) showed that >95% of all variants investigated here were previously reported SNPs and cannot explain a genetically dominant disease. We focused on the 12 genes for which all four individuals studied carried variants and found that only two genes showed variants at different genomic positions, strengthening the likelihood that these variants are causative and not simply unidentified SNPs. One of these two candidate genes, *CTBP2*, was excluded

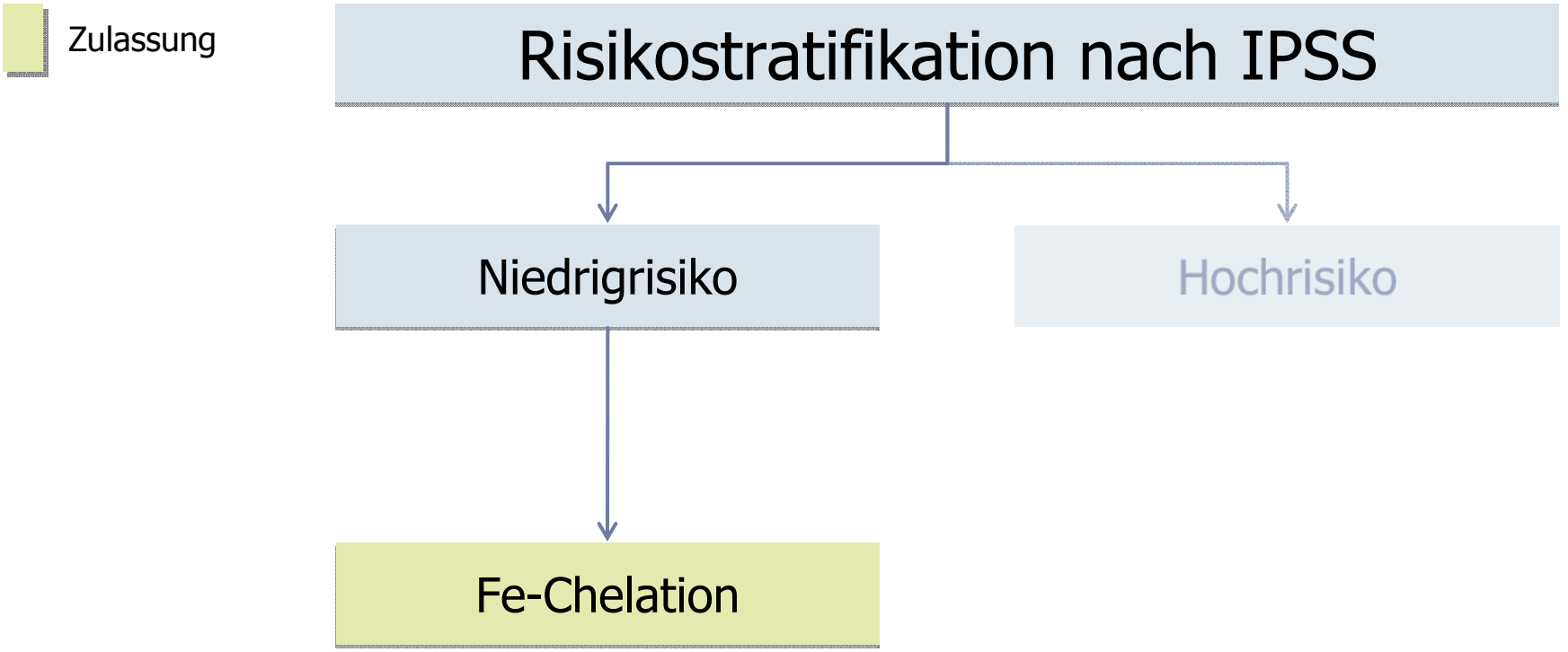
2 Somatic Mutations in Schinzel-Giedion Syndrome Gene *SETBP1* Determine Progression in Myeloid Malignancies

Program: Oral and Poster Abstracts
Type: Oral
Session: Plenary Scientific Session

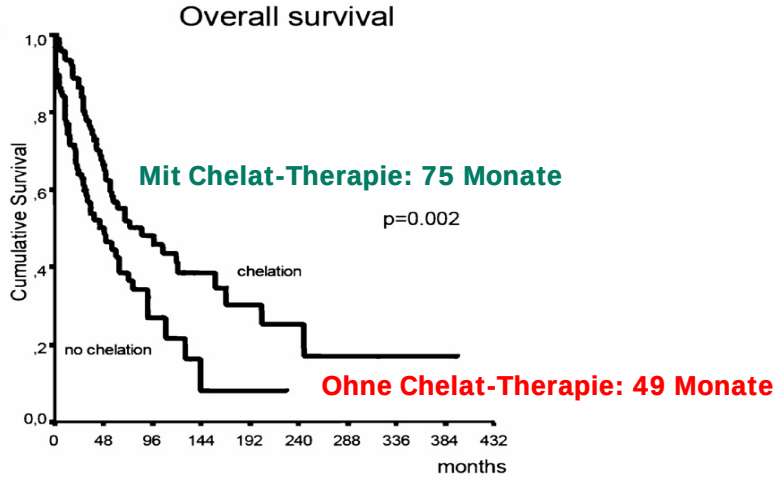
Sunday, December 9, 2012: 2:25 PM
Hall B5, Level 1, Building B (Georgia World Congress Center)

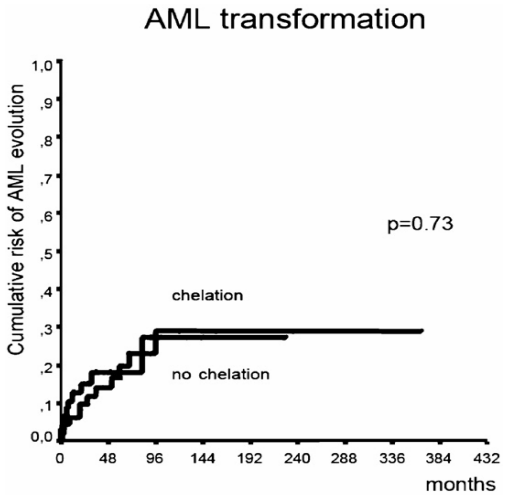
Hideki Makishima, MD, PhD[1], *Kenichi Yoshida, MD*[2*], *Nhu Nguyen, PhD*[3*], *Masashi Sanada, MD*[2*], *Yusuke Okuno, MD, PhD*[2*], *Kwok Peng Ng, PhD*[4], *Bartlomiej P Przychodzen*[5*], *Kristbjorn O Gudmundsson, PhD*[3*], *Bandana A Vishwakarma, PhD*[3*], *Andres Jerez, MD*[6*], *Ines Gomez-Segui, MD*[7*], *Mariko Takahashi, MD*[8*], *Yuichi Shiraishi, PhD*[2*], *Yasunobu Nagata, MD*[2*], *Kathryn M Guinta*[9*], *Hiraku Mori, MD, PhD*[10*], *Mikkael A. Sekeres, MD, MS*[1], *Kenichi Chiba, BA*[11*], *Hideki Muramatsu, MD, PhD*[12*], *Hirotoshi Sakaguchi, MD*[12*], *Ronald Paquette, MD, PhD*[13*], *Michael A McDevitt, MD, PhD*[14], *Seiji Kojima*[15*], *Yogen Saunthararajah, MD*[4], *Satoru Miyano, PhD*[2*], *Lee-Yung Shih, MD, PhD*[16], *Yang Du, PhD*[3*], *Seishi Ogawa, MD, PhD*[2] *and Jaroslaw P. Maciejewski, MD, PhD*[1]

Aktuelle Optionen bei MDS

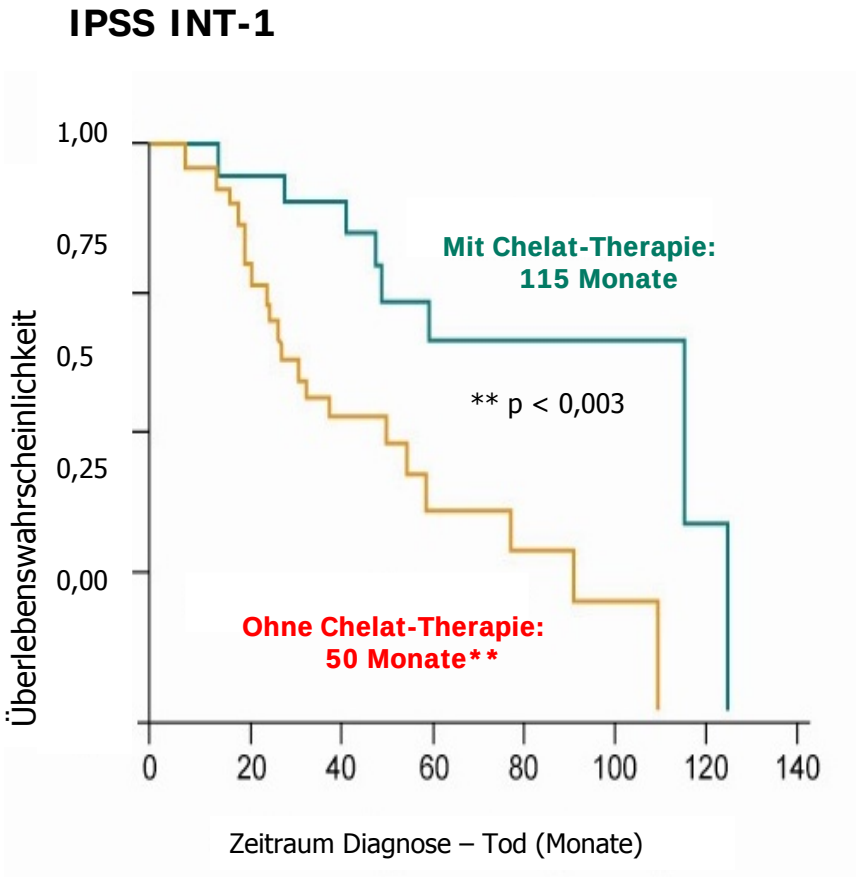


Eisenchelation assoziiert mit besserem Gesamtüberleben?



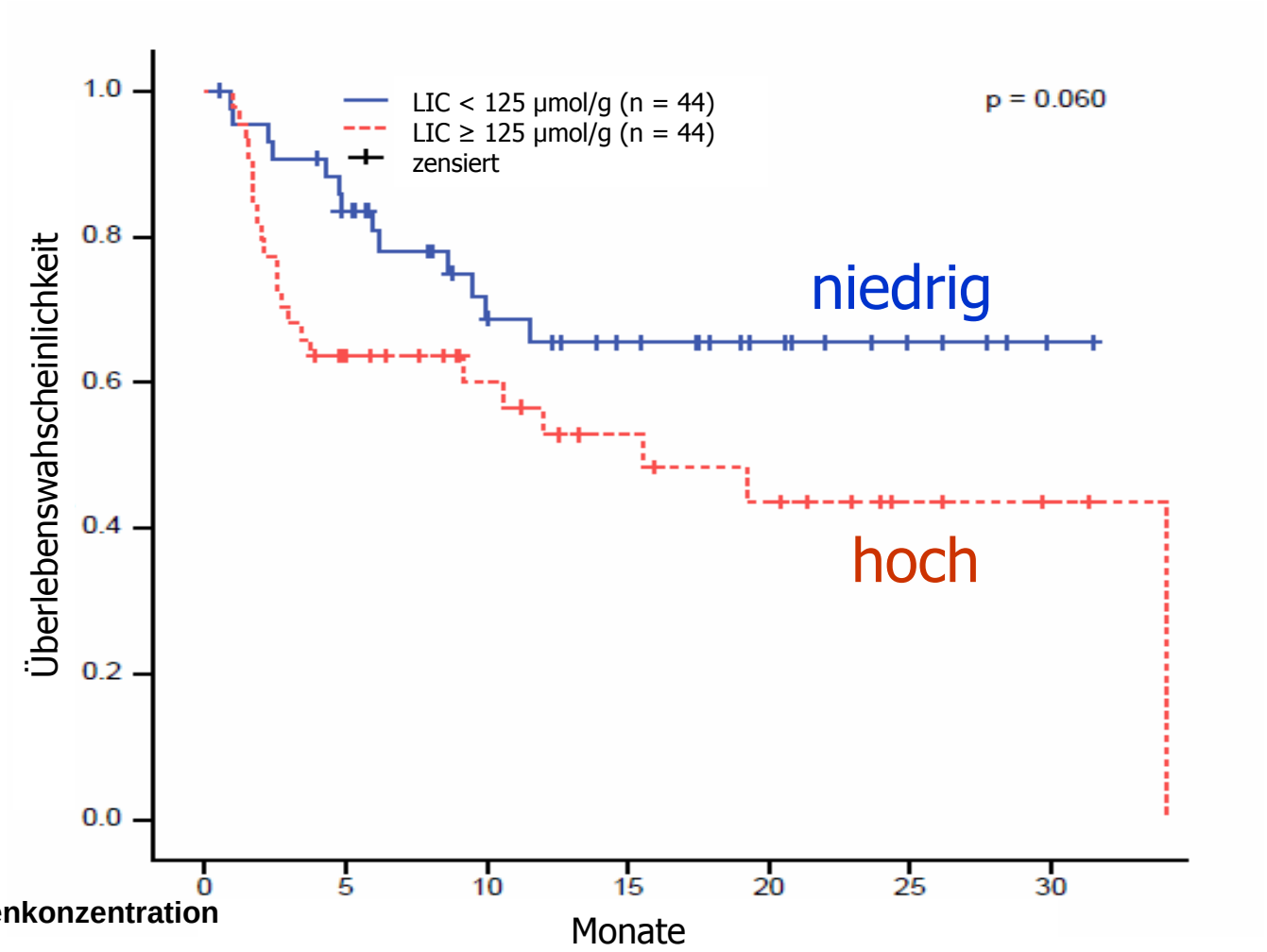


Neukirchen et al. Leuk Res 2012



Rose et al. Leuk Res 2010

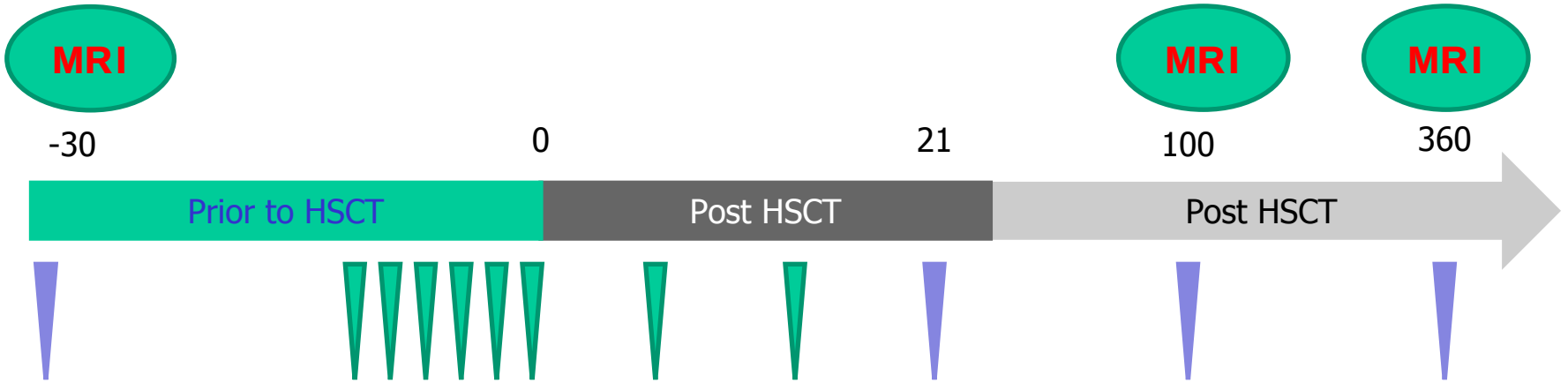
Hepatische Eisenüberladung im Kontext der allogenen SZT



LIC = Lebereisenkonzentration

Wermke et al. Clin Cancer Research 2012

ALLogeneic **I**ron in**VE**stigators observational Trial

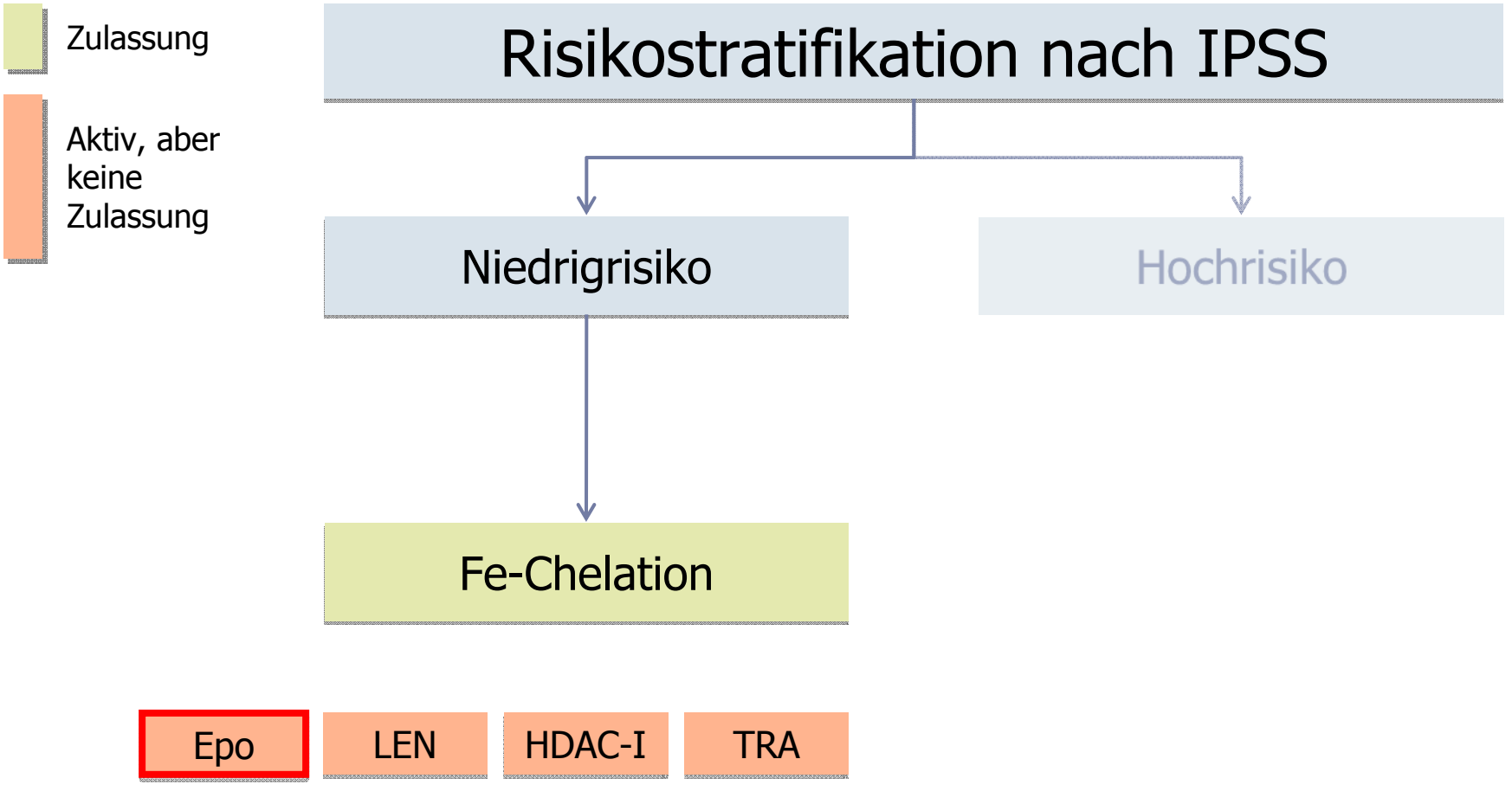


- LPI, eLPI, DCI, Hepcidin
- Immune modulation

- LPI, eLPI, DCI, Hepcidin

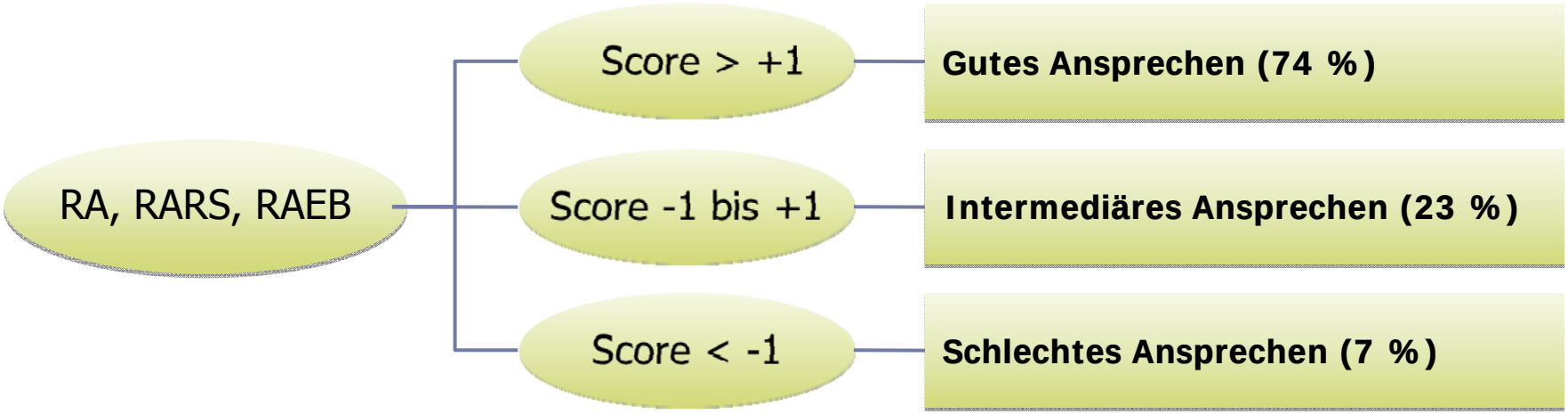
Wermke & Platzbecker

Aktuelle Optionen bei MDS



Epo = Erythropoetin; LEN = Lenalidomid; HDAC-I = Histon-Deacetylase-Inhibitor; TRA = Thrombopoetinrezeptor-Agonisten

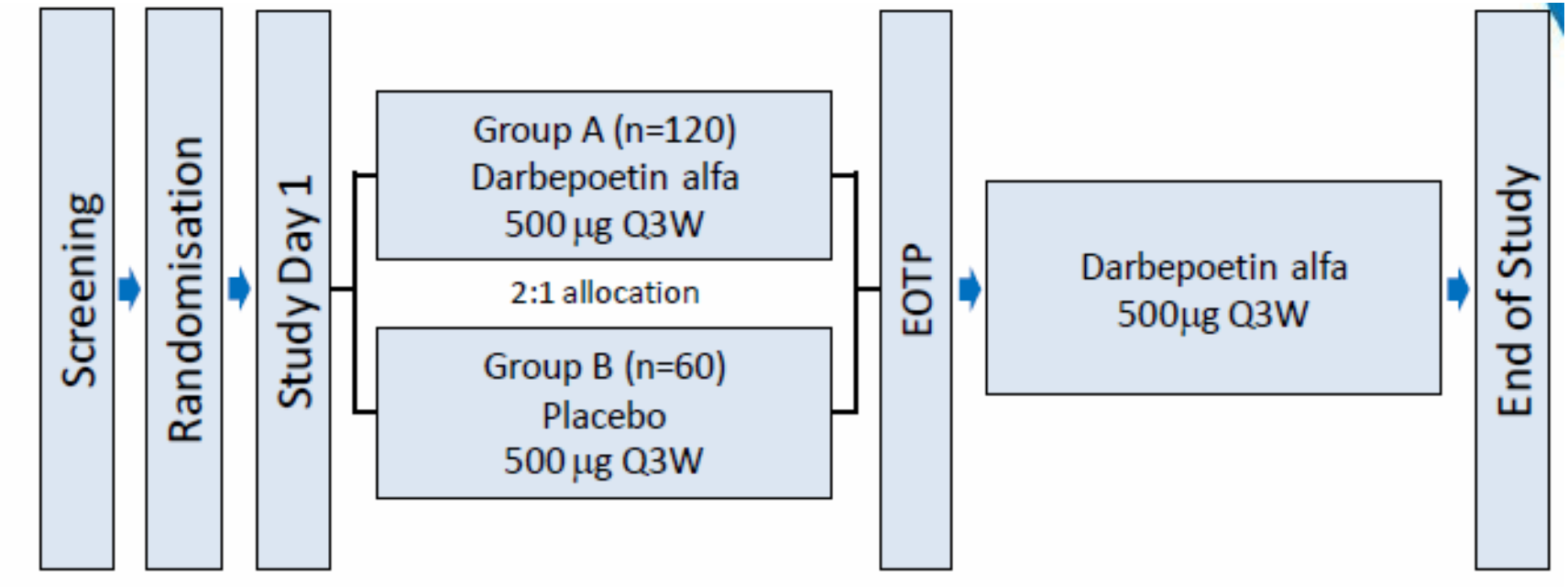
Prädiktion Ansprechen Epo



Therapieansprechen: Score		
S-EPO (U/l)	< 100	+2
	100–500	+1
	> 500	-3
Transfusionen (EKs/Monat)	< 2	+2
	≥ 2	-2

Hellstrom-Lindberg E et al. Br J Haematol 1997; 99: 344–351

ARCADE Studie LR-MDS

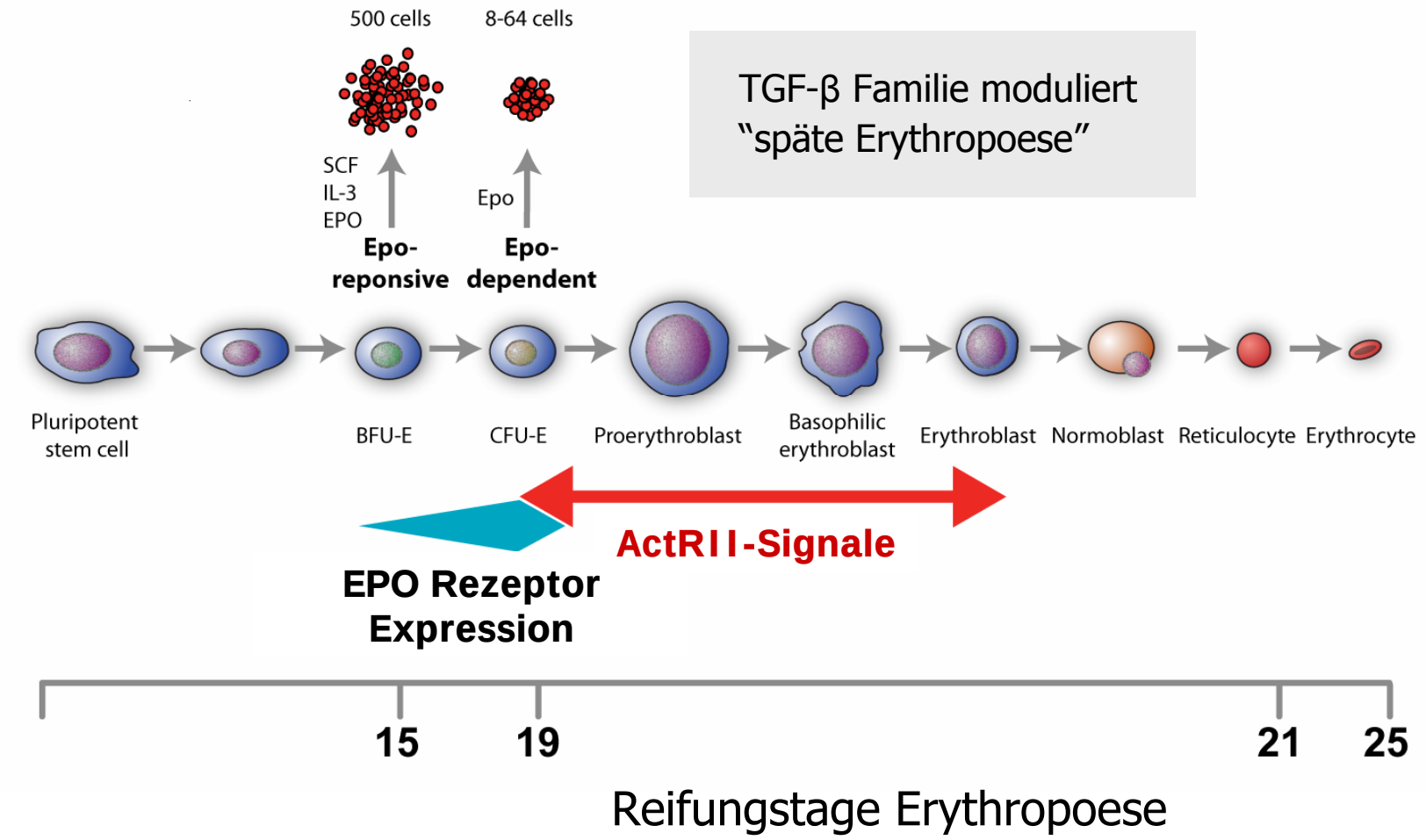


	Double-blind treatment period (24 weeks)	Active treatment period (48 weeks)
G-CSF	No[1]	Yes
Dose escalation	No	Yes, on or after week 31
Response modifiers	No	Yes

[1] Except for neutropenia with fever and/or infection

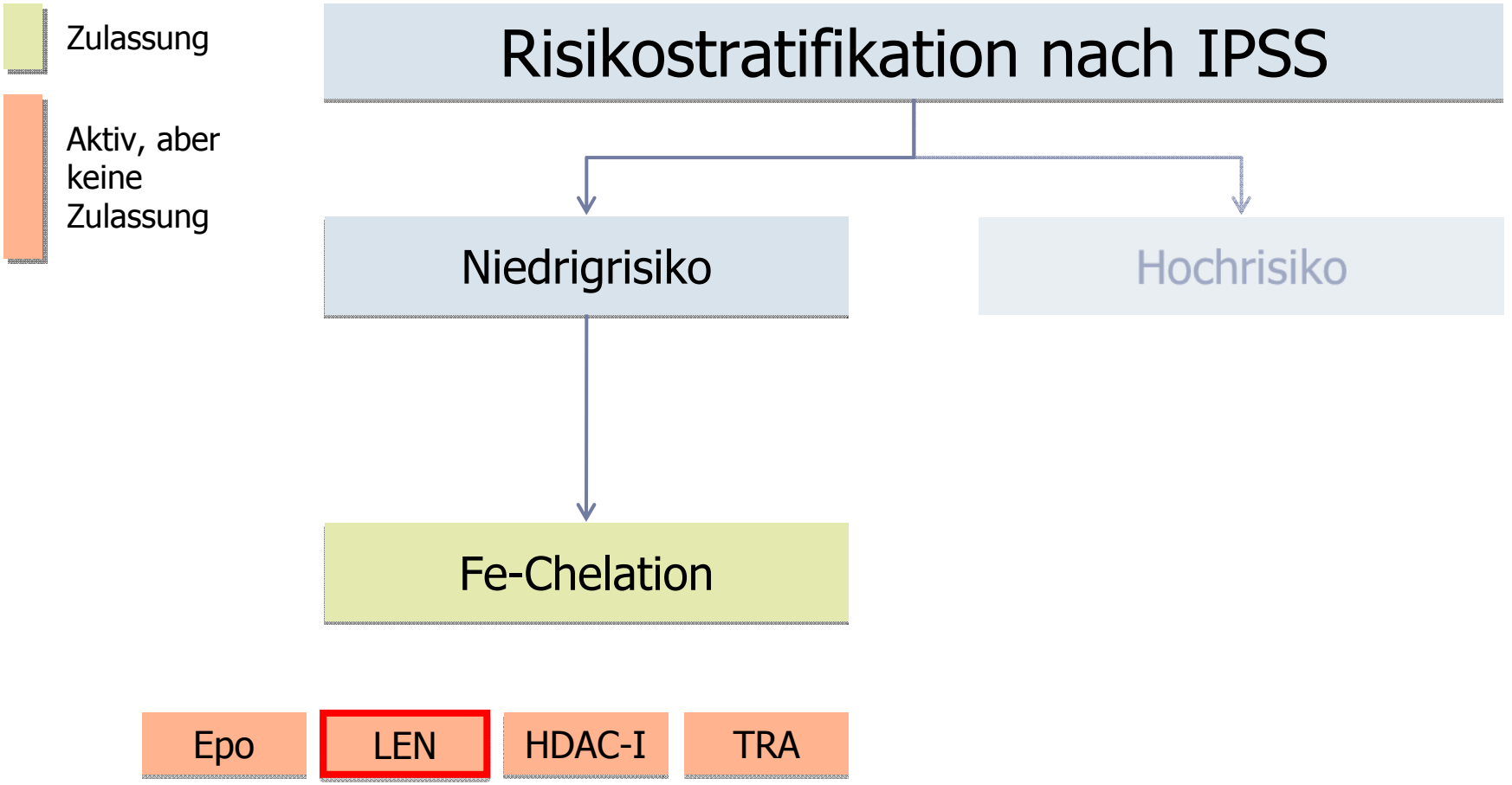
Amgen

PACE-MDS-Studie



Suragani et al. ASH 2011

Aktuelle Optionen bei MDS



Epo = Erythropoetin; LEN = Lenalidomid; HDAC-I = Histon-Deacetylase-Inhibitor; TRA = Thrombopoetinrezeptor-Agonisten

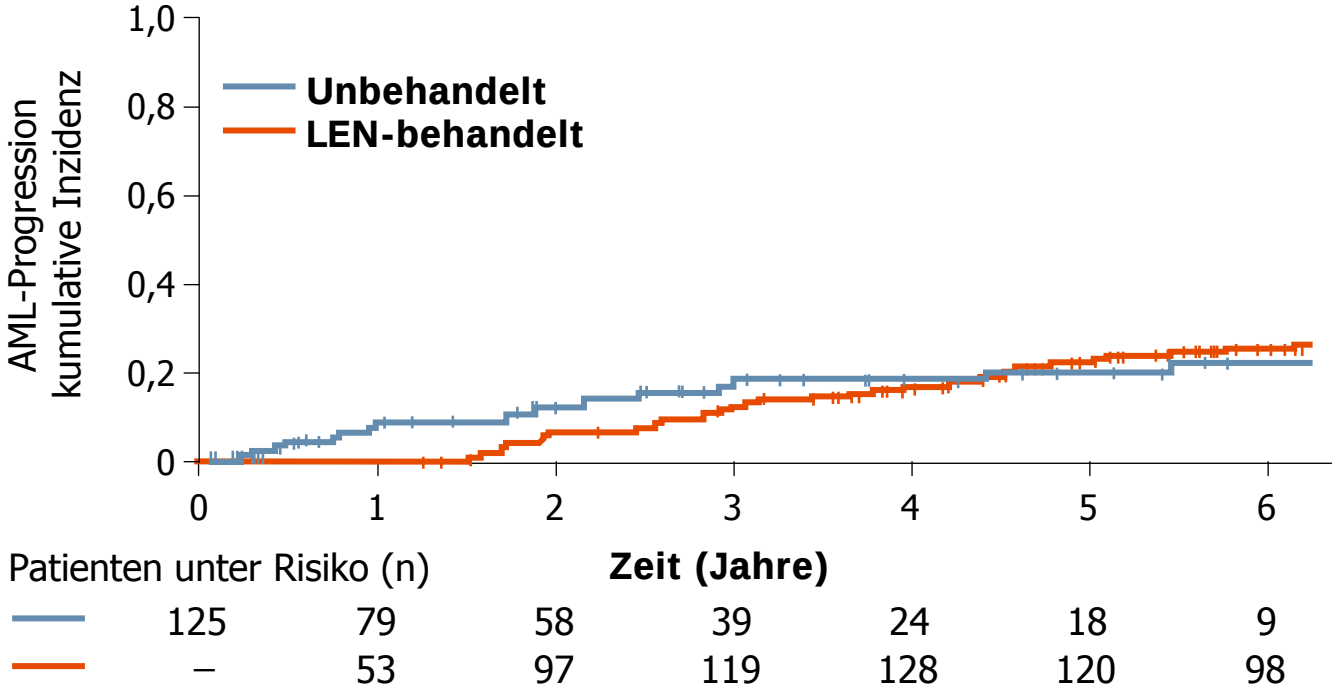
MDS 005 Studie

- IPSS LOW/INT-1 und NON-del5q
- EPO refr. oder keine Ansprechen
- Mind. 4 Eks/8 Wochen

LEMON5-Studie

- IPSS LOW/INT-1 und del5q
- <5% Blasten
- Rekrutierung beendet

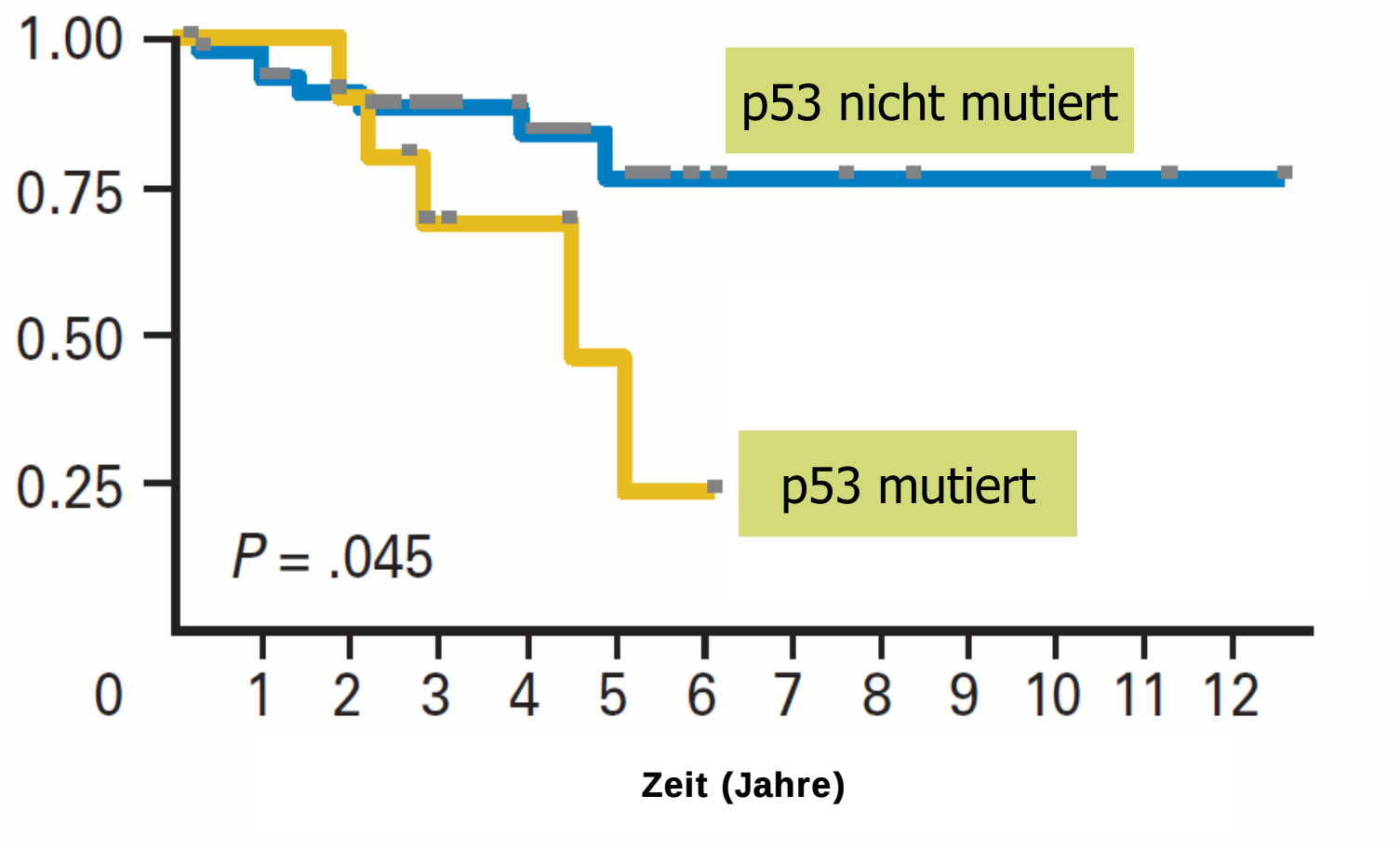
AML-Progression bei Niedrigrisiko-MDS mit del(5q) im Vergleich



	LEN-behandelt	Unbehandelt
Kumulative 2-Jahres-Inzidenz	7 %	12 %
Kumulative 5-Jahres-Inzidenz	23 %	20 %
Mediane Zeit bis zur AML-Progression	nicht erreicht	nicht erreicht

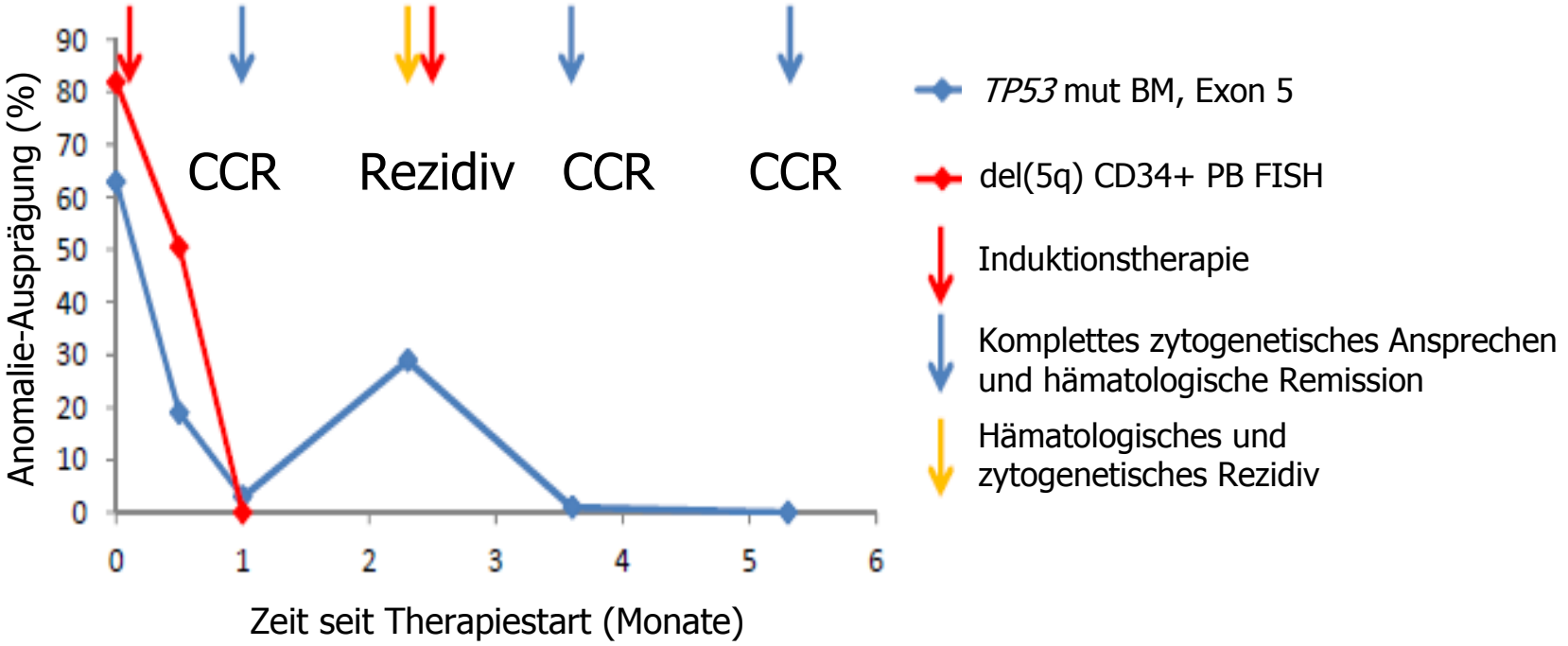
Kündgen et al. Leukemia 2013

AML-Übergang bei MDS del(5q)



Jädersten M et al. JCO 2011

AZA+LEN Phase-I-Studie
bei HR-MDS mit del(5q)

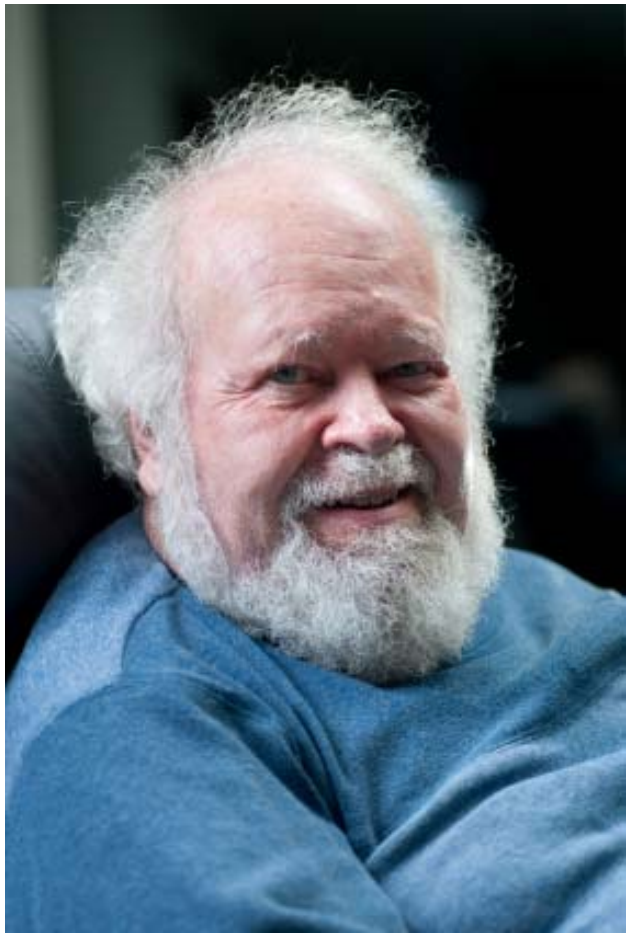


HR-MDS = Hochrisiko-MDS

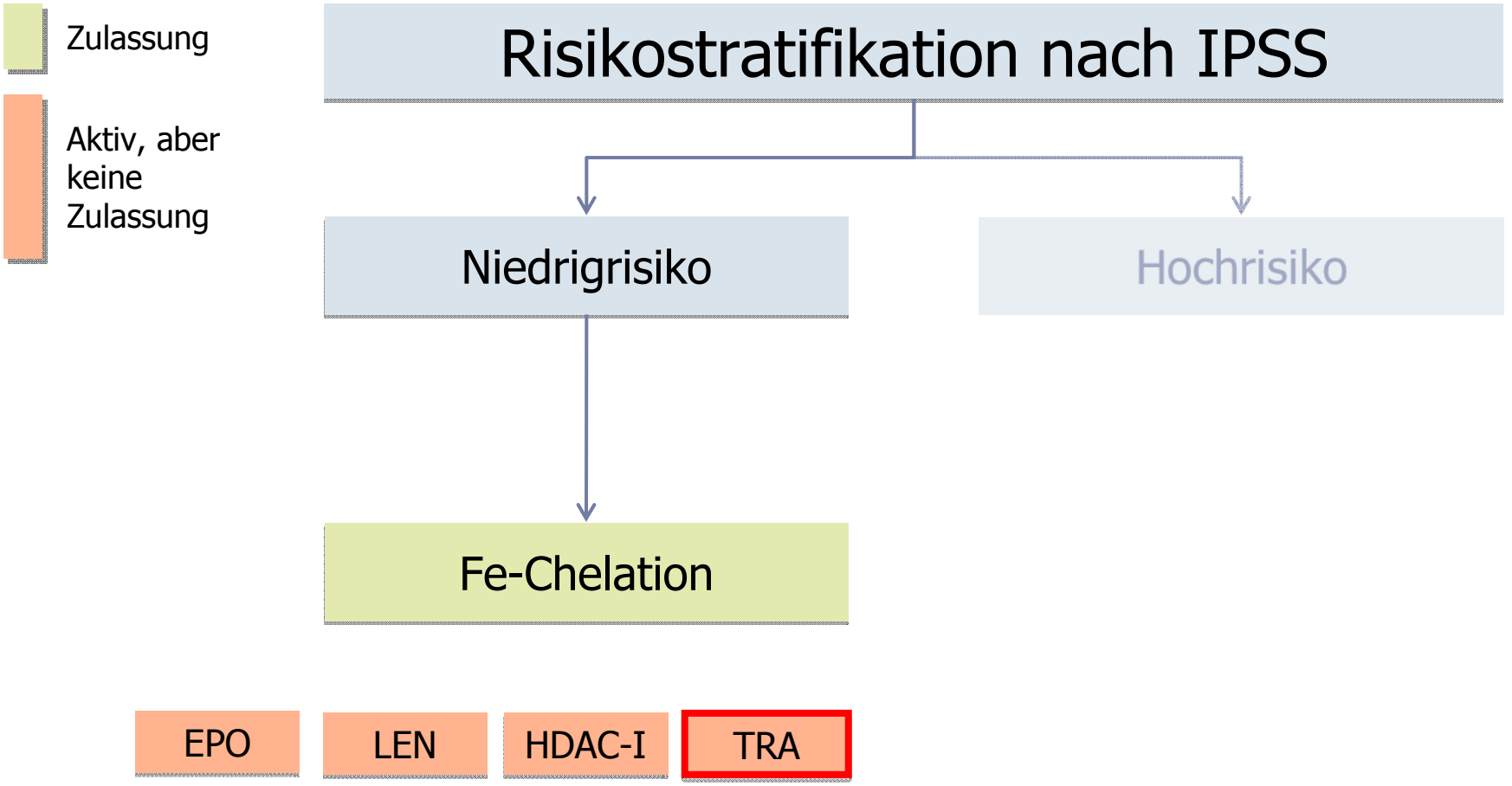
Platzbecker et al. Leukemia 2013

Der mögliche MDS-Patient

Variable	
Hb	Ek-Pflicht
ANC	0.8
PLT	12
EPO	>500
KMP:	5% Blasten
Zytog.:	46 XY



Aktuelle Optionen bei MDS



Epo = Erythropoetin; LEN = Lenalidomid; HDAC-I = Histon-Deacetylase-Inhibitor; TRA = Thrombopoetinrezeptor-Agonisten

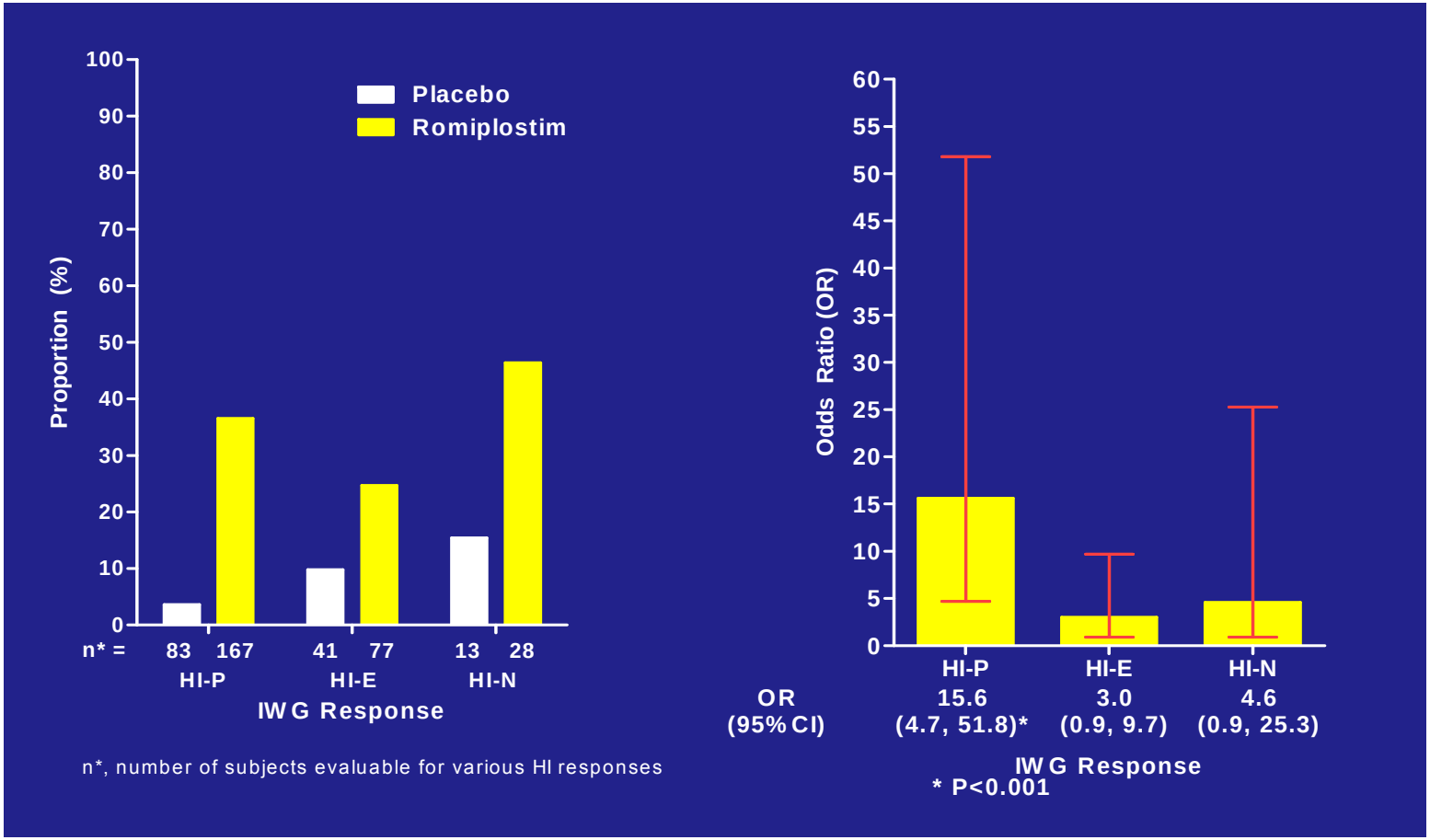
Romiplostim bei Niedrig-Risiko MDS

	Romiplostim	Placebo	Total	HR, 95% CI
AML	10/168 (6.0%)	2/82 (2.4%)	12/250 (4.8%)	2.54, 0.6-11.5
- RAEB-1/-2	6/25 (24%)	2/9 (22%)	8/34 (24%)	1.06, 0.21-5.49
- Non-RAEB	4/143 (2.8%)	0/73 (0%)	4/216 (1.9%)	NA

	Romiplostim	Placebo	HR	95% CI
Deaths	17.9% (30)	20.7% (17)	0.86	0.47, 1.56
AML	6.0% (10)	4.9% (4)	1.20	0.38, 3.84
AML-free survival	19.6% (33)	23.2% (19)	0.85	0.48, 1.50

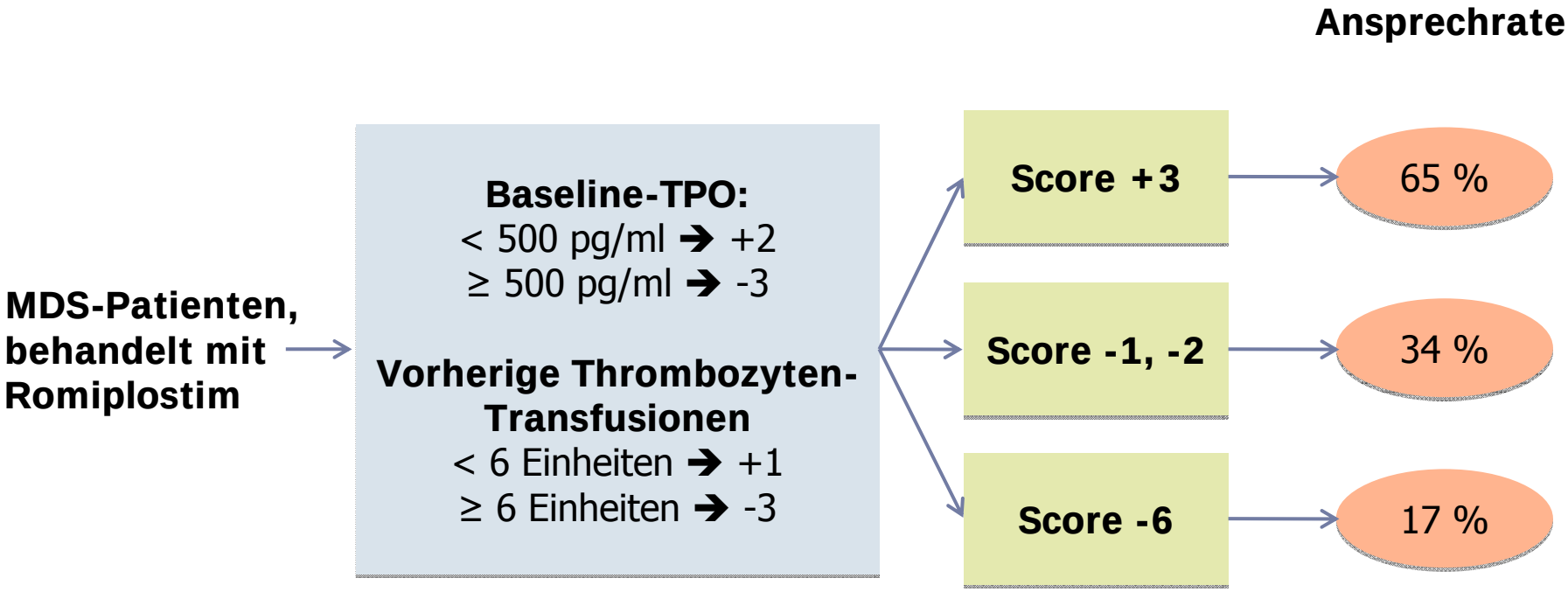
Kantarjian et al. ASH 2012

Romiplostim bei Niedrig-Risiko MDS



Kantarjian et al. ASH 2012

Romiplostim bei Niedrig-Risiko-MDS



TPO = Thrombopoeitin

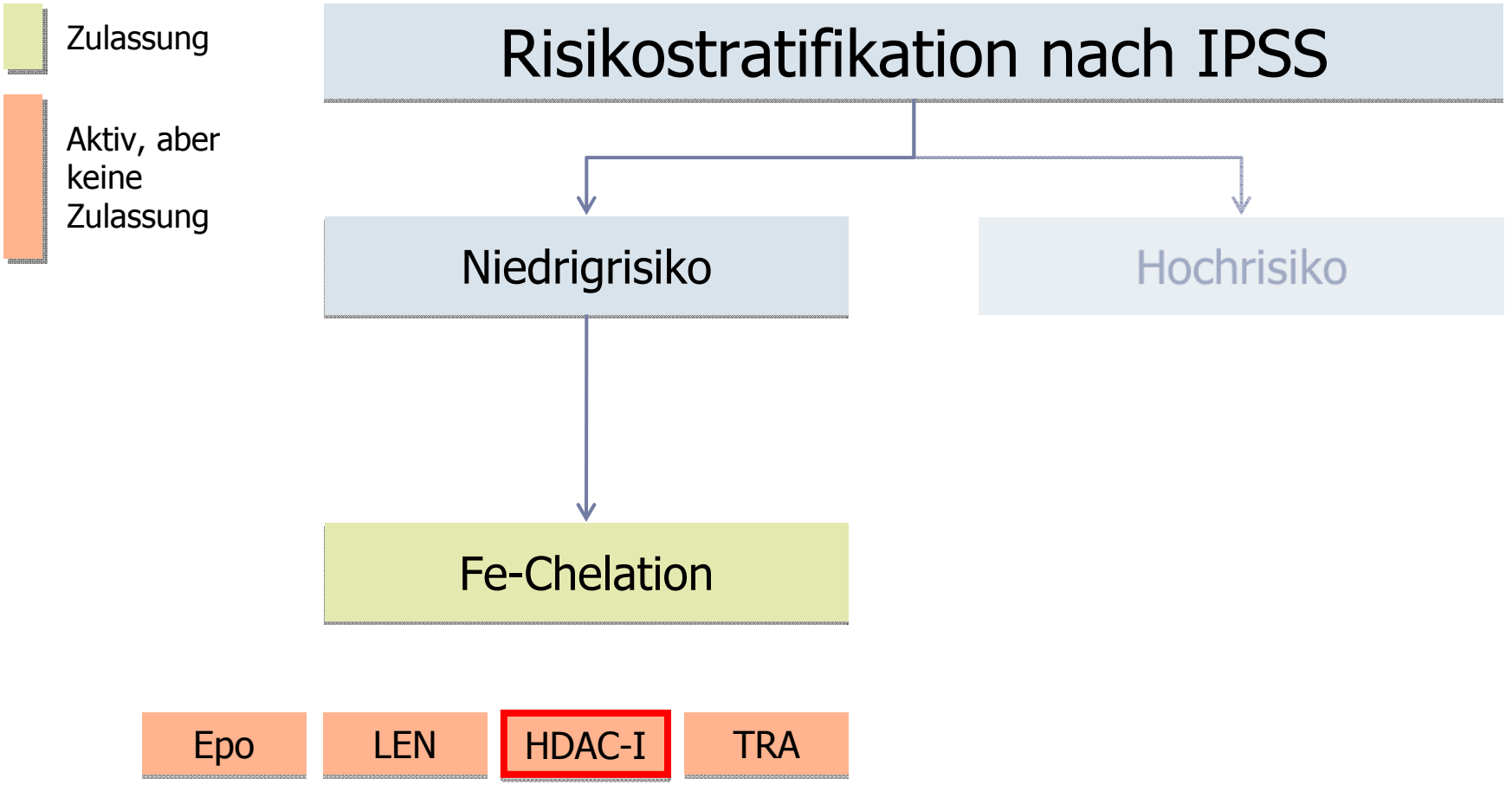
Sekeres & Platzbecker ASH 2012

Eltrombopag

- Phase II, >10% Blasten, PLT<30
- 2:1 Randomisierung
- Endpunkt: Überleben

GSK

Aktuelle Optionen bei MDS



Epo = Erythropoetin; LEN = Lenalidomid; HDAC-I = Histon-Deacetylase-Inhibitor; TRA = Thrombopoetinrezeptor-Agonisten

GEPARD Studie

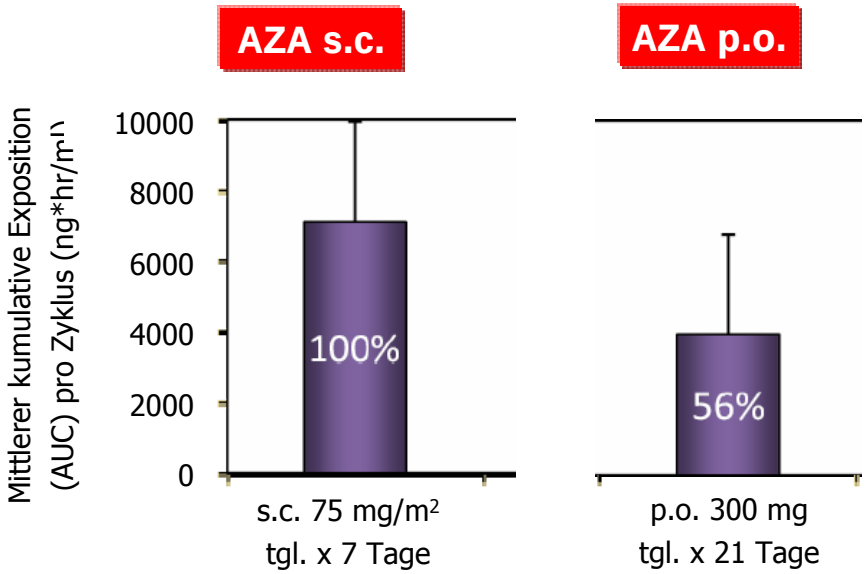
- Phase II, IPSS LOW/INT-1
- Ek-abhängig
- Panobinostat +/- EPO
- Kein Ansprechen - Toxizität

Platzbecker et al. EHA 2012

Novartis

Orales Azacitidin

Extrapolierte kumulative AZA-Exposition pro Zyklus

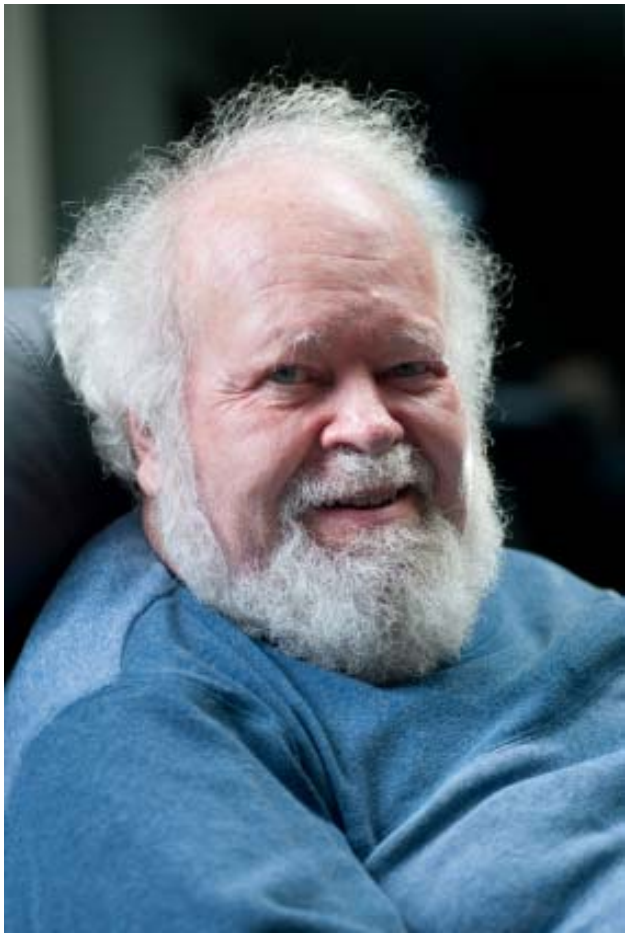


- 300 mg p.o. Tag 1–21 führt zu anhaltender Hypomethylierung
- **Studie: IPSS INT-1 mit PLT <50**

Laille et al. MDS 2011, Edinburgh, UK

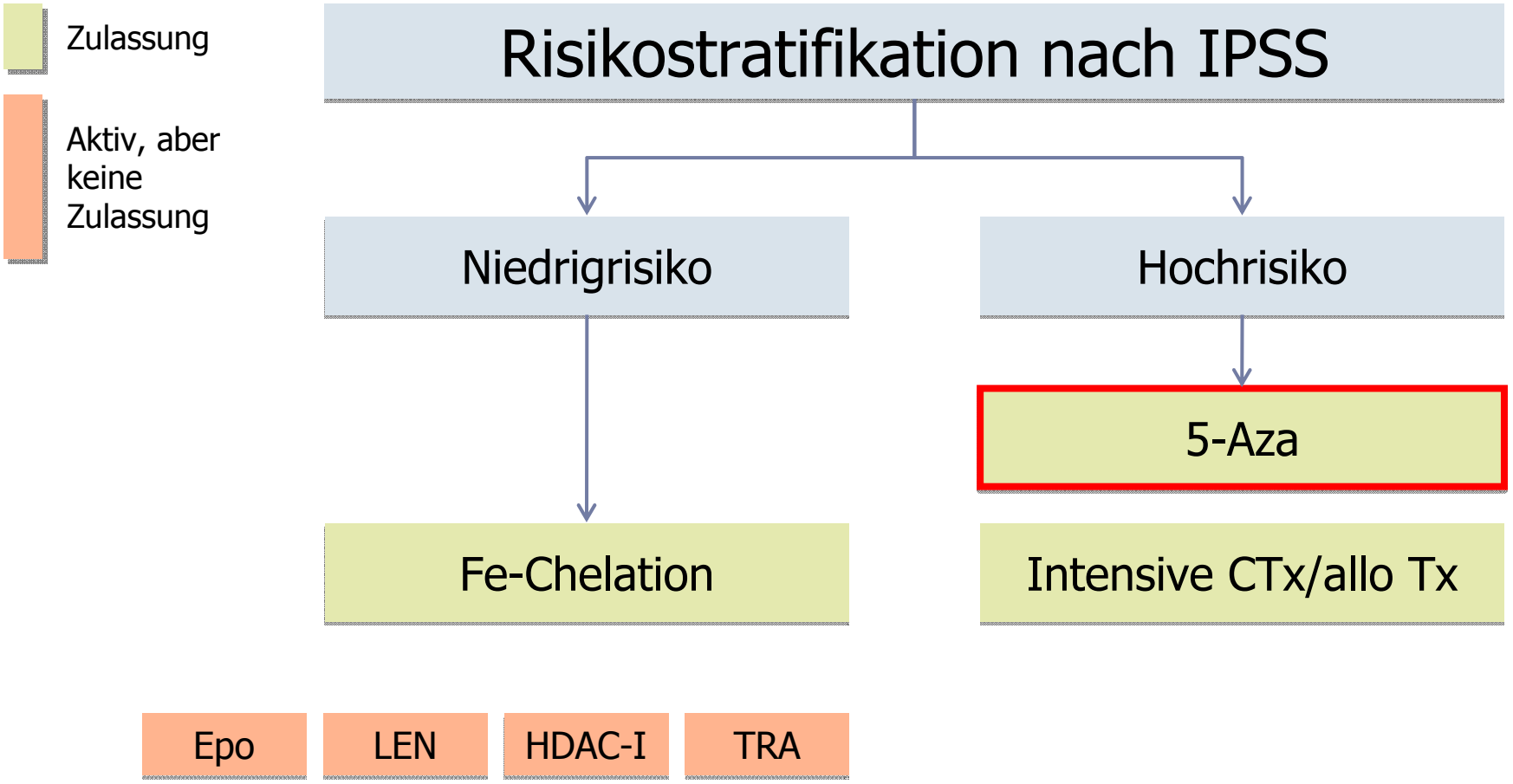
Der mögliche MDS-Patient

Variable	
Hb	Ek-Pflicht
ANC	1.5
PLT	96
EPO	280
KMP:	5% Blasten
Zytog.:	46 XY



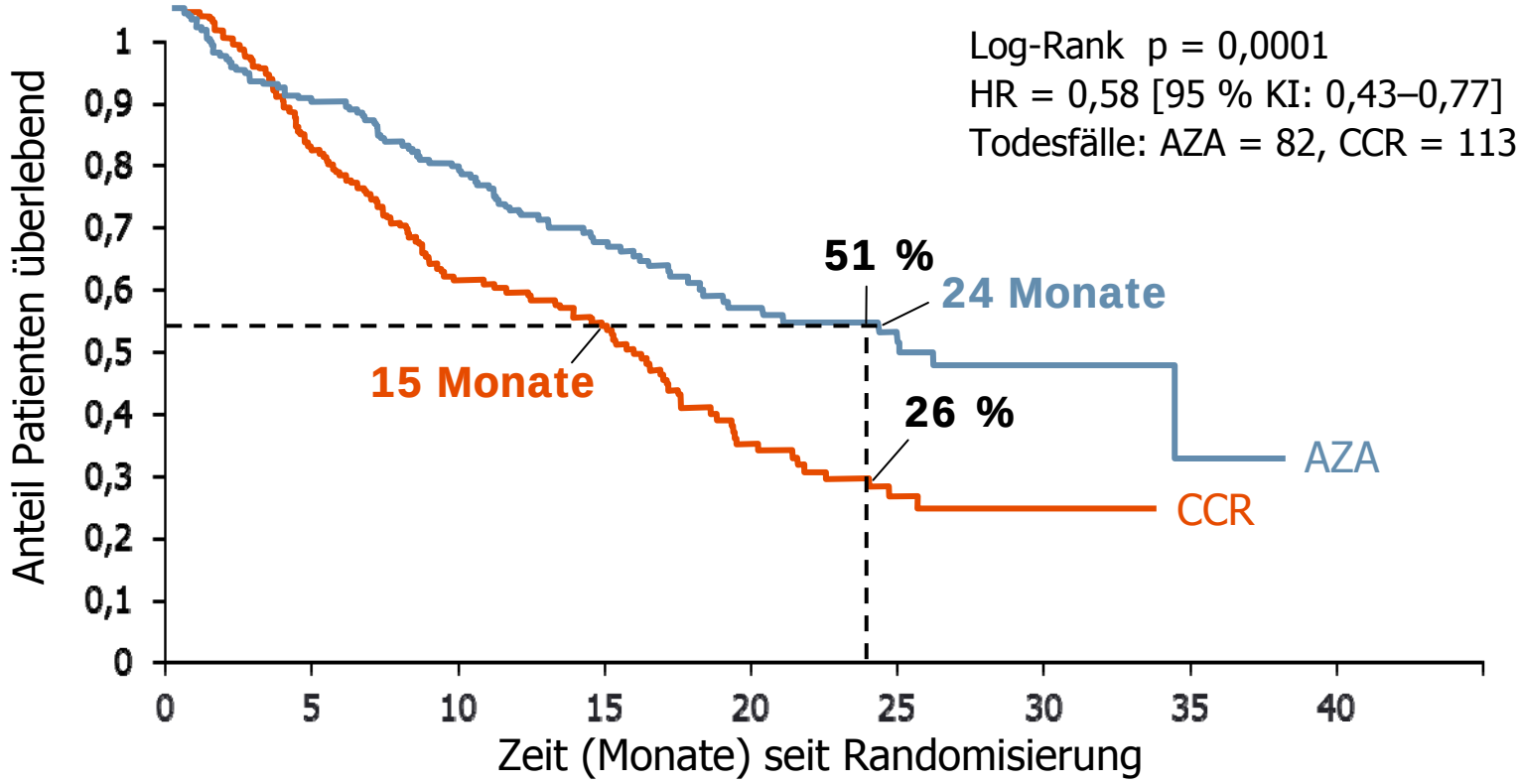
Variable	
Hb	Ek-Pflicht
ANC	0.9
PLT	23
EPO	560
KMP:	15% Blasten
Zytog.:	46 XY

Aktuelle Optionen bei MDS



Epo = Erythropoetin; LEN = Lenalidomid; HDAC-I = Histon-Deacetylase-Inhibitor; TRA = Thrombopoetinrezeptor-Agonisten
5-Aza = Azacitidin; CTx = Chemotherapie; Tx = Transplantation

AZA-001 – Gesamtüberleben Azacitidin vs. konventionelle Therapie



CCR = Conventional Care Regime

Fenaux P et al. Lancet Oncol 2009; 10: 223–232

Prognostische Faktoren mit Aza

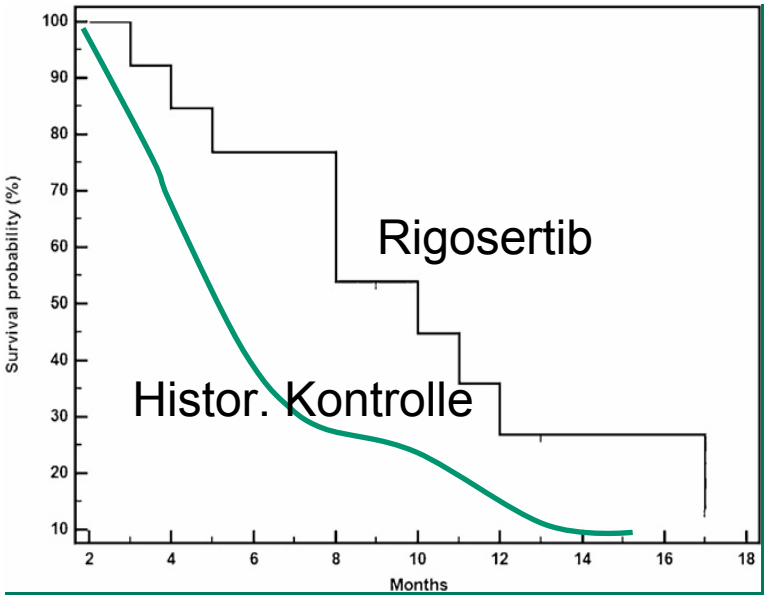
Score	0	1	2
ECOG	0–1	2	
Zirkulierende Blasten	NEIN	JA	
EKs	< 4 U/8 Wochen	4 U/8 Wochen	
IPSS-Zytogenetik	günstig	intermediär	schlecht

Gesamtscore	0	1–3	4–5
APSS-Gruppe	niedrig	intermediär	hoch
Medianes OS, Monate	nicht erreicht	15 Monate	6 Monate

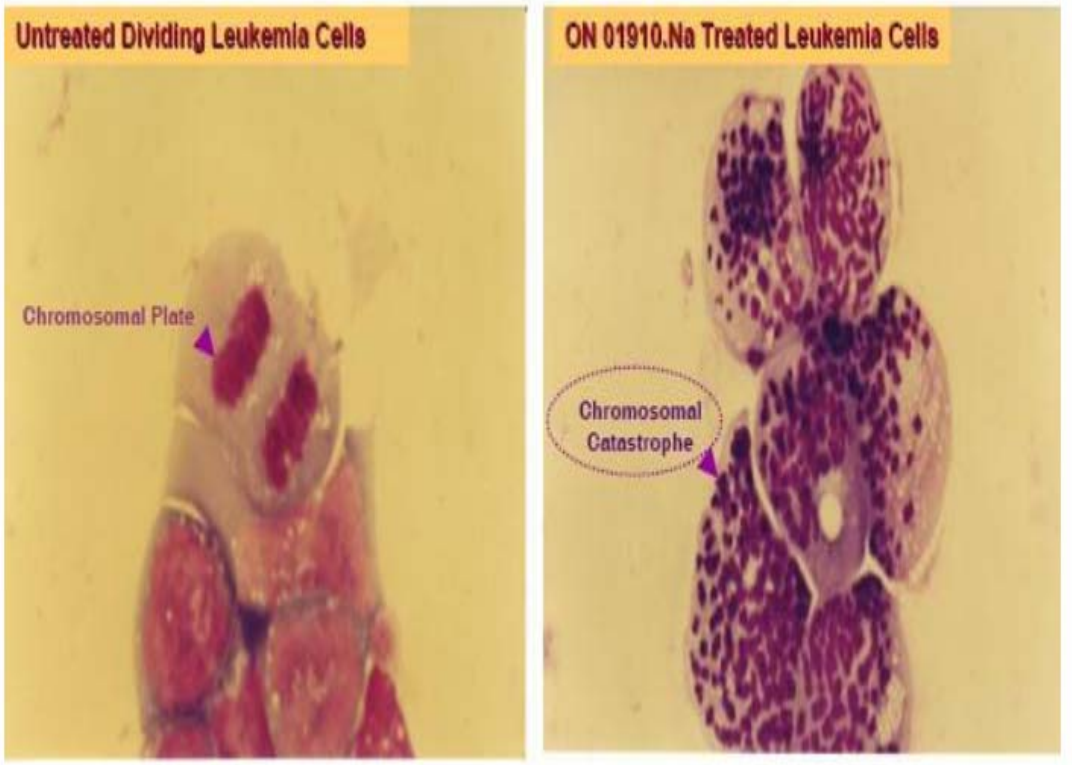
ECOG = ECOG Performance Status
EK = Erythrozytenkonzentrat
IPSS = International Prognostic Scoring System
APSS = Azacitidine Prognostic Scoring System
OS = Gesamtüberleben (Overall Survival)

Itzykson R et al. Blood 2011; 117: 403–411

Rigosertib bei AZA Versagen



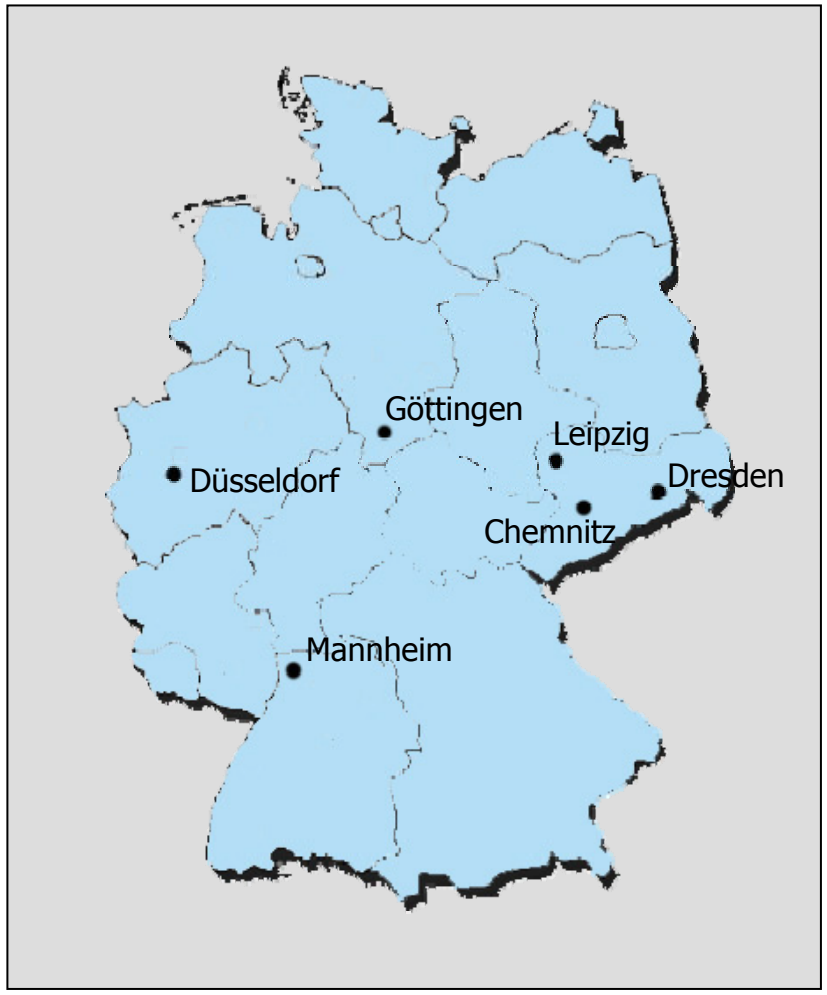
N=13, 4x mCR, 8x SD
Keine hämat. Verbesserung



2:1 Randomisierung, Phase 3

Seetharam et al. ASH 2012, Leukemia Res 2012

Temsirolimus bei MDS (TEMDS)



- **Temsirolimus 25mg i.v. 4-12 Monate**
- **n=40**
- **multizentrisch**

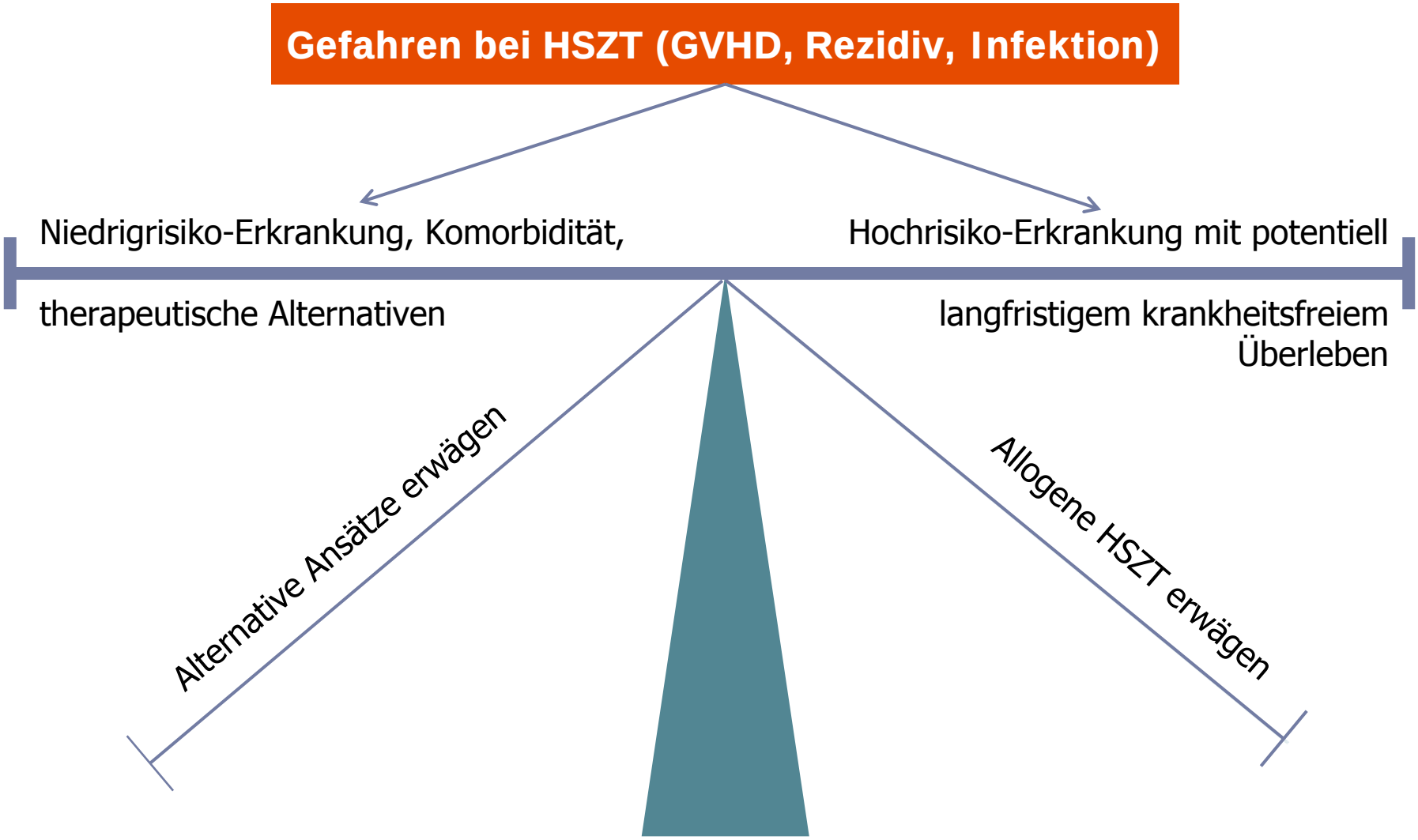
Platzbecker / Wermke

Phase I “ROMDS-Studie”

-Ziel: MTD/ DLT von Romidepsin + Azacitidin (Vidaza®)

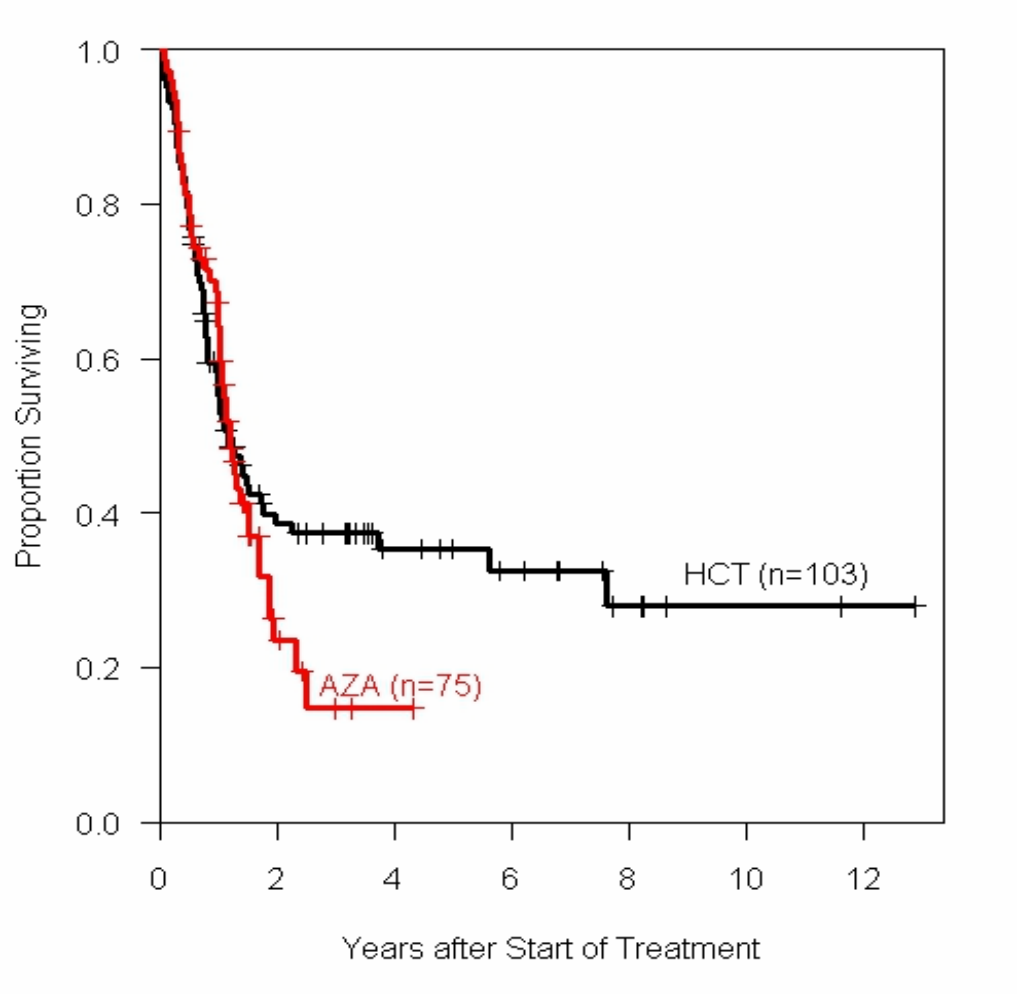
- monozentrisch

Pro und Cons der allogenen HSZT



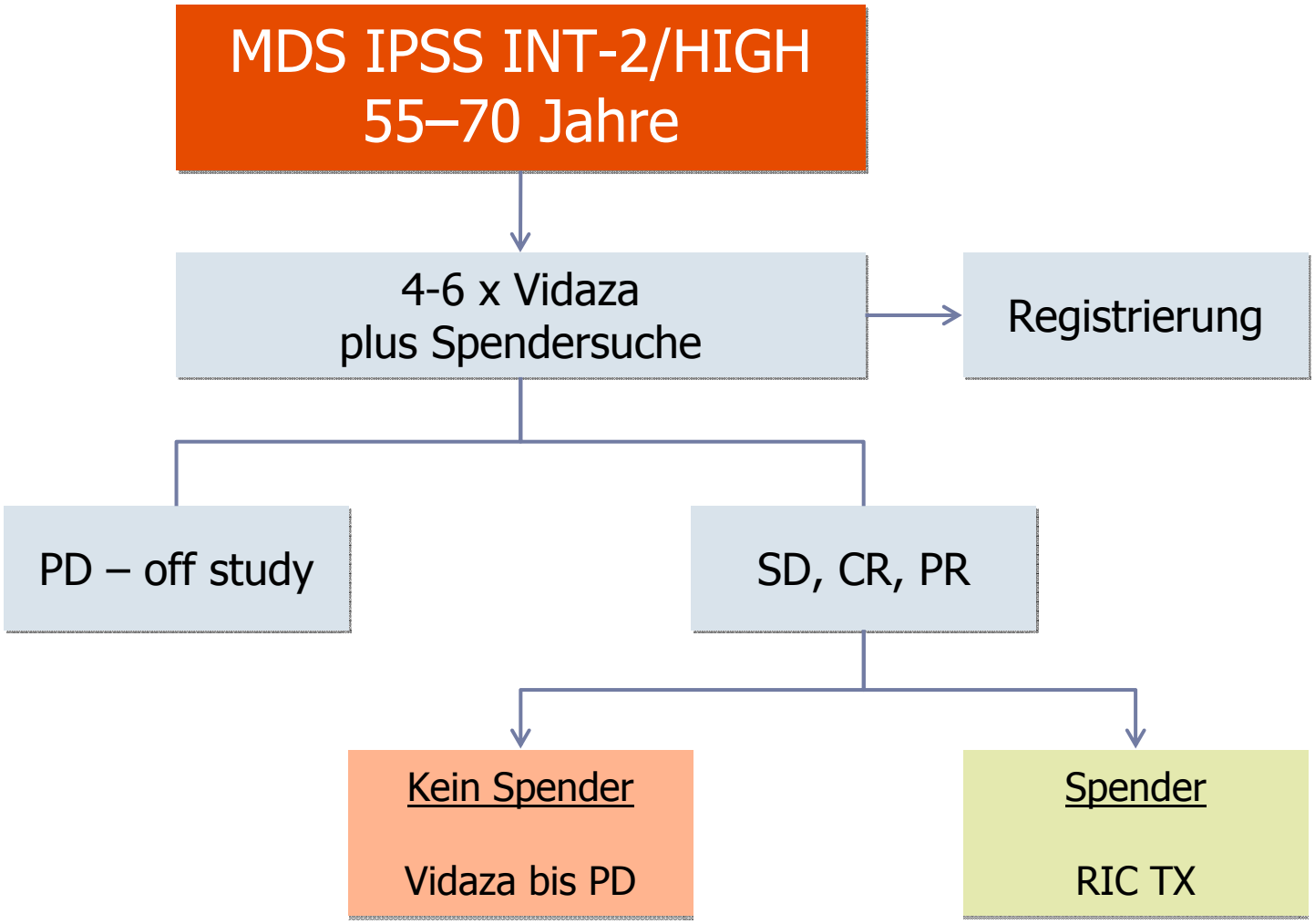
HSZT = hämatopoetische Stammzelltransplantation
GVHD = Graft-verus-host disease

Allogene HSZT vs AZA bei MDS 60-70 Jahre



Platzbecker et al BBMT 2012

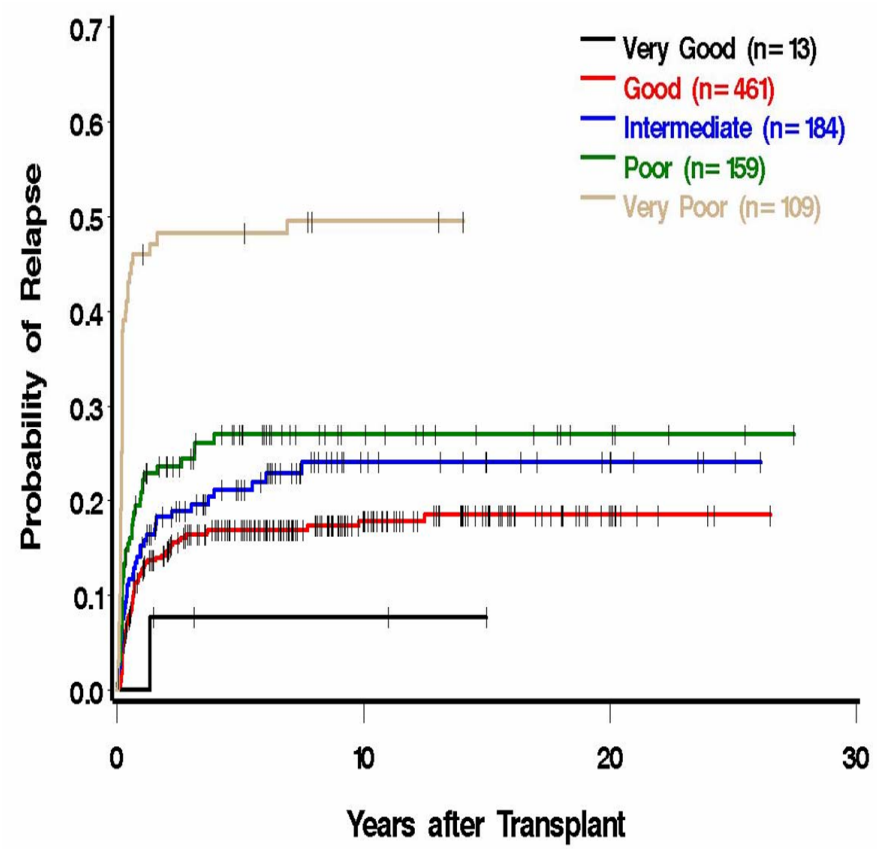
Deutsche VidazaAllo-Studie

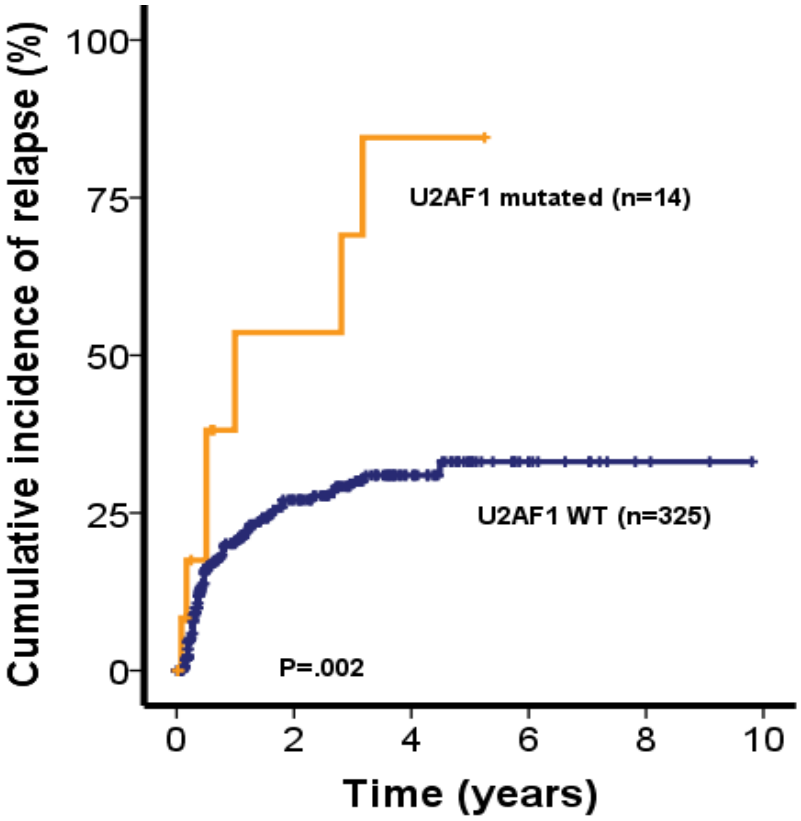


RIC TX = allogene Stammzelltransplantation
mit reduzierter Konditionierungsintensität

PI: Kröger/ Co-PI: Platzbecker

Kann die allogene SZT ungünstige Prognosemerkmale eliminieren ?

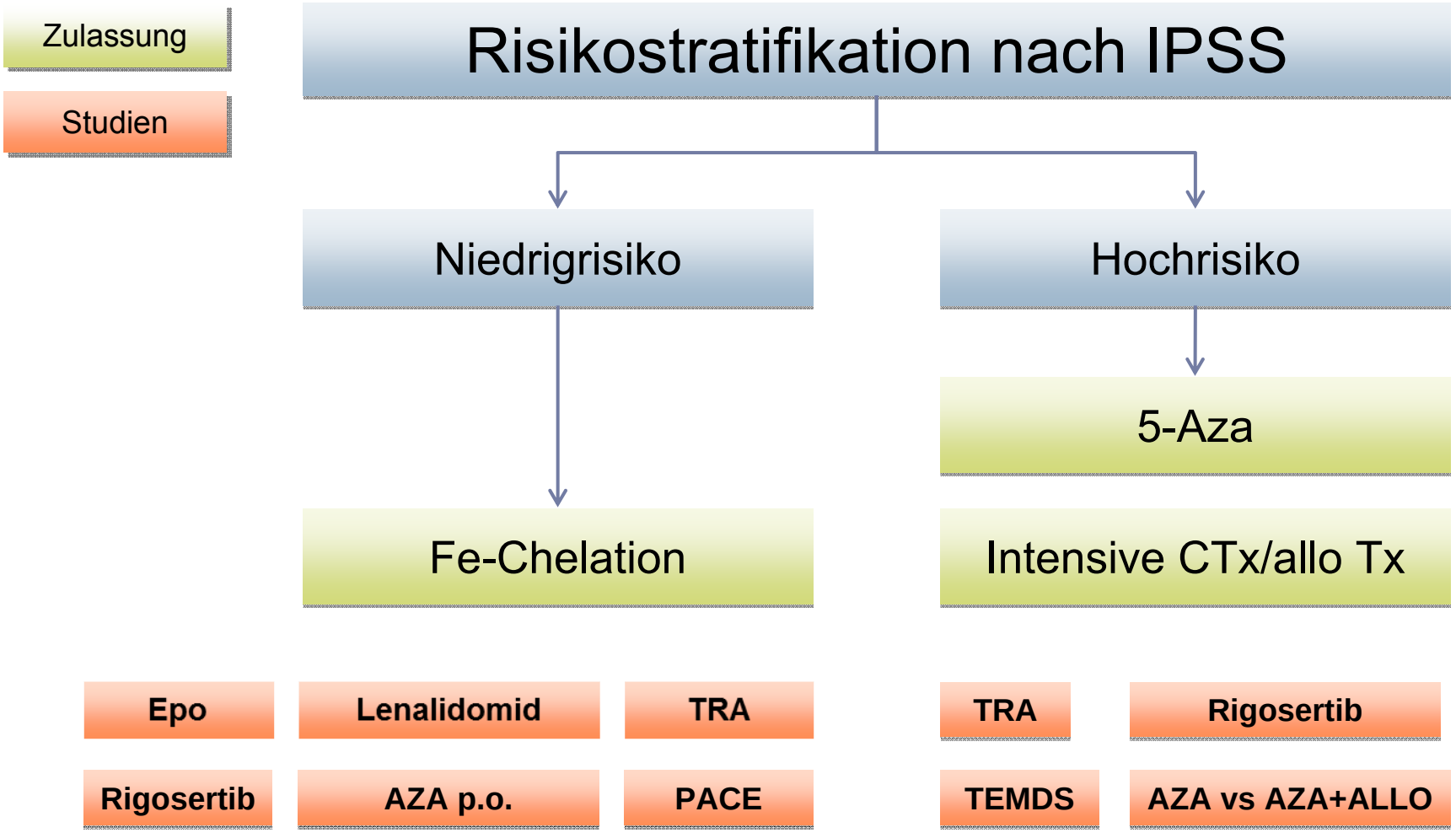




Deeg et al. Blood 2012

Thol et al. ASH 2012

Aktuelle Optionen bei MDS

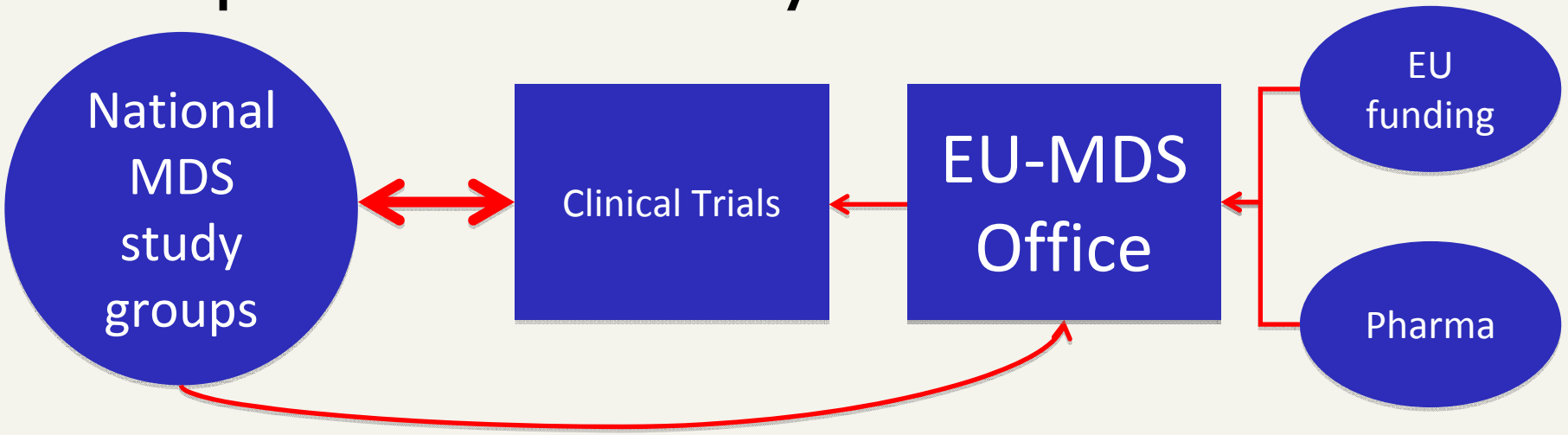


CTx = Chemotherapie; Tx = Transplantation; Epo = Erythropoetin; TRA = Thrombopoetinrezeptor-Agonisten

EMSCO
MYELODYSPLASTIC SYNDROMES

GMIHO
INNOVATION IN HEMATOLOGY AND MEDICAL ONCOLOGY

European MDS Study Coordination Office



ELN European LeukemiaNet

Zusammenfassung

- Sehr heterogene Erkrankung
- IPSS Standard
- „Molekulare Dämmerung“

- Therapeutisches Problem speziell Niedrigrisiko-MDS
- Pat. in klinische Studien einschließen