

Where to go with AZA in MDS ?

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Where are we now ?

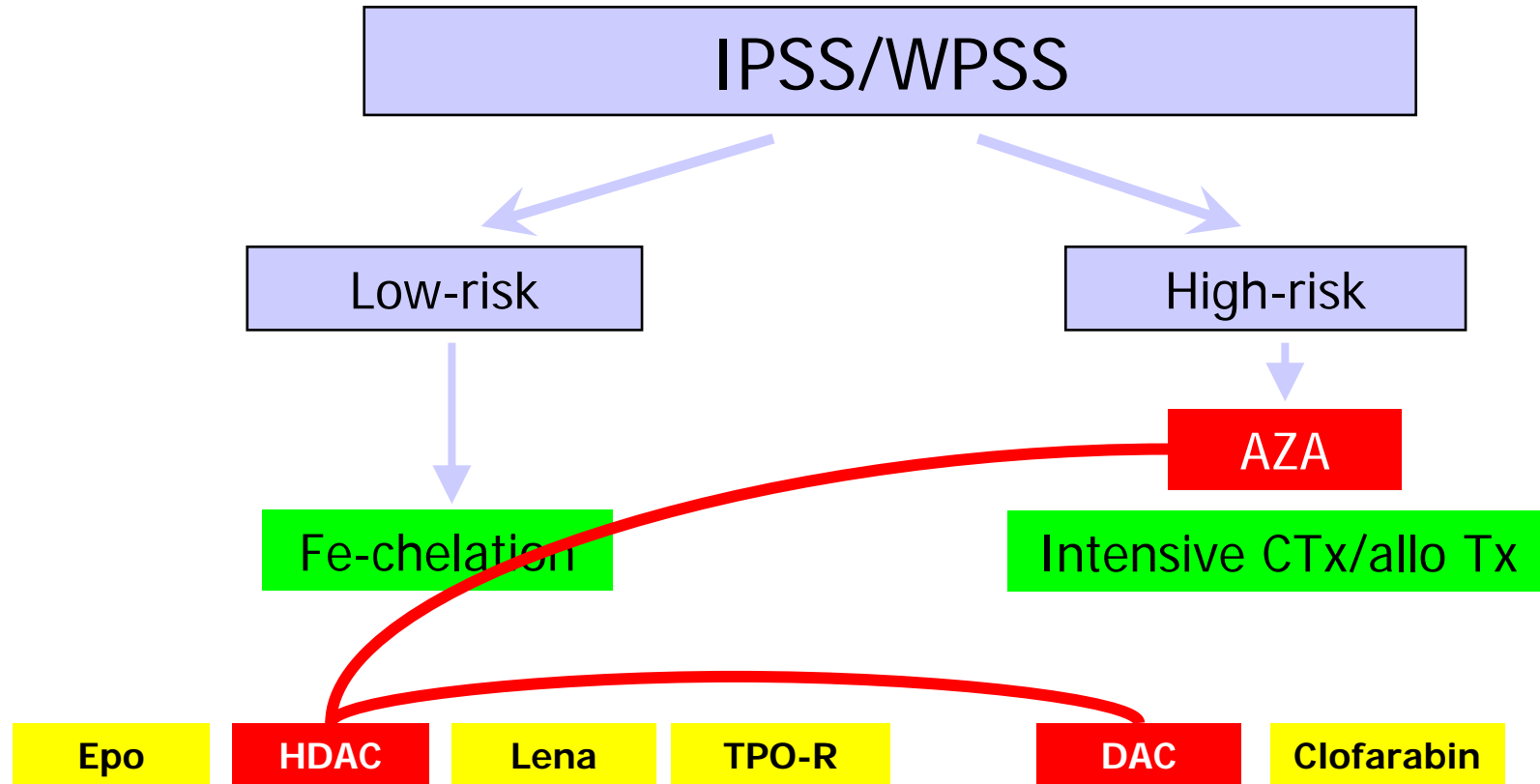
Score	0	1	2
ECOG	0-1	2	
PB blasts	NO	YES	
RBC units	< 4 U/8 W	4 U/8 W	
Karyotype	Good	Intermediate	Poor
Total score	0	1-3	4-5
APSS group	Low	Intermediate	High
Median OS, months	Not reached	15	6

Who to combine with ?

Prerequisite:

- active as single agent
- safe
- pathophysiology

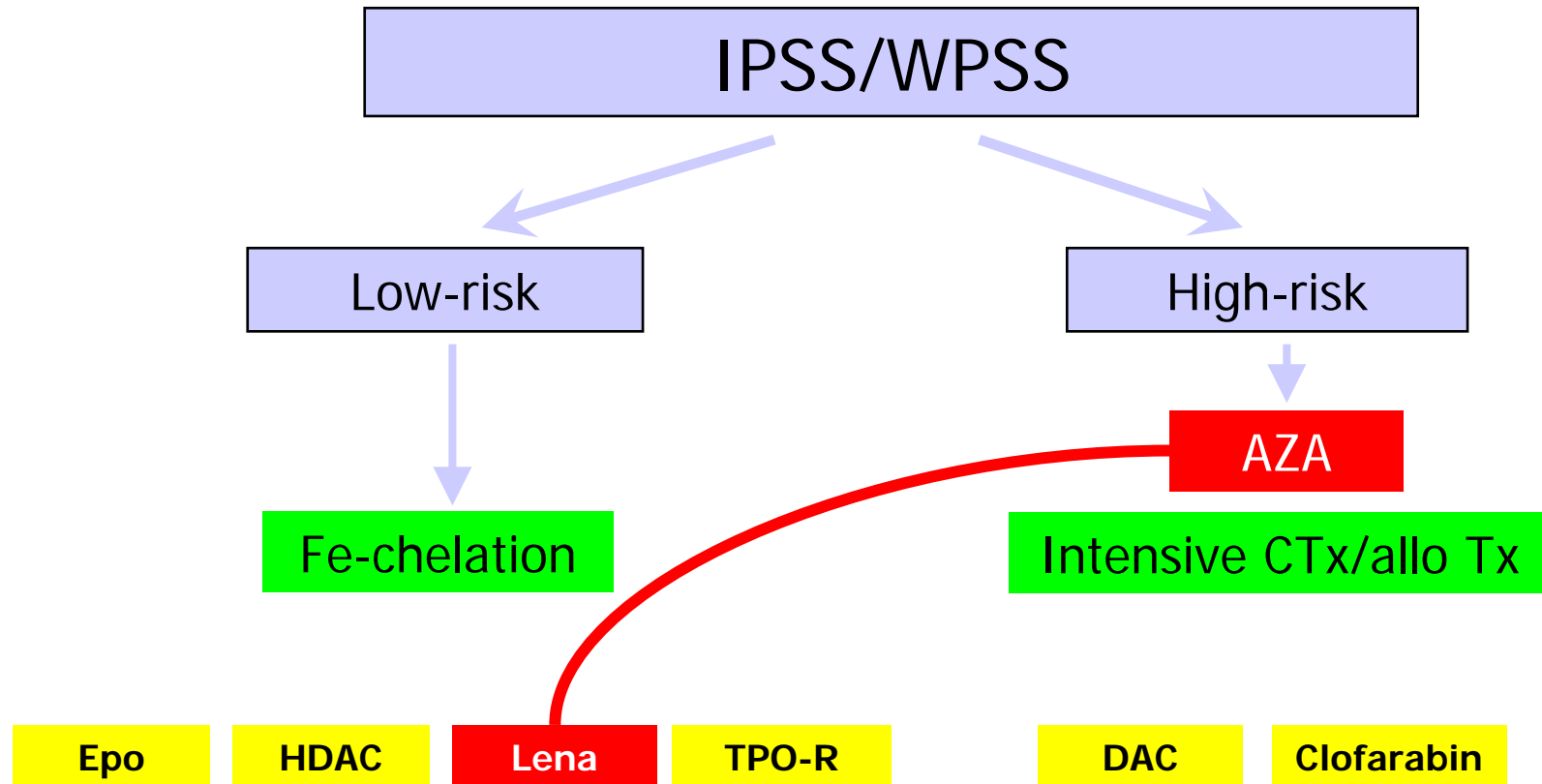
Therapeutic options in MDS



Combinations with DMTI

Disease	n	Kombination	CR	ORR	study
MDS + AML	27	Aza + MS-275	7	44	Gore 06
MDS + AML	53	Aza + VPA + ATRA	22	42	Soriano 07
MDS + AML	37	Aza + MGD0103	11	52	Garcia-Manero 07
MDS + AML	136	Aza +/- Entinostat	7	42	Prebet 10
MDS + AML	23	Aza + Vorinostat	45	82	Silverman 07
MDS + AML	17	Aza + Vorinostat	17	51	Garcia-Manero 10
MDS + AML	54	DAC + VPA	19	22	Garcia-Manero 08
MDS + AML	25	DAC + VPA	16	44	Blum 07
MDS + AML	60	DAC + Vorinostat	18	25	Kirschbaum 08
MDS + AML	27	DAC + Vorinostat	4	16	Yee 07

Therapeutic options in MDS



Phase I: AZA + Len in MDS

- **ORR 67%** (44% CR)
- „Go-forward“ schedule:
AZA 75 mg/m² SC. d1-5 and Lenalidomid 10 mg PO d1-21

Kohorte	AZA Dose	Rev Dose	IPSS Categories	Grade 3/4 non-heme toxicities	Maximum Response
1	75 mg/m ² SC days 1-5	5 mg PO days 1-14	1 Int-1 2 Int-2	1	2 CR 1 progression
2	75 mg/m ² SC days 1-5	5 mg PO days 1-21	2 Int-2 1 High	2	1 CR, 1 PR, 1 HI
3	75 mg/m ² SC days 1-5	10 mg PO days 1-21	1 Int-2 2 High	0	2 CR, 1 stable disease
4	50 mg/m ² SC days 1-5, 8-12	5 mg PO days 1-14	1 Int-1 2 Int-2	2	2 CR, 1 stable disease
5	50 mg/m ² SC days 1-5, 8-12	5 mg PO days 1-21	2 Int-2 1 High	2	1 HI 1 stable disease 1 progression
6	50 mg/m ² SC days 1-5, 8-12	10 mg PO days 1-21	1 Int-1 1 Int-2 1 High	2	1 HI 2 BM CR

What is the target population ?



WPSS

Variable	0	1	2	3
WHO	RA, RARS, del5q-	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
RBC	no	yes	-	-

* Karyotype: good: normal, -Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities, chr 7 anomalies); and intermediate: other abnormalities.

Score	WPSS group	Median OS (mon) Italian cohort	Median OS (mon) German cohort
0	Very low	103	141
1	Low	72	66
2	Intermediate	40	48
3-4	High	21	26
5-6	Very high	12	9

LR MDS

IPSS vs WPSS

IPSS	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	< 5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

WPSS	0	1	2	3
WHO	RA, RARS, del5q-	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
RBC	no	yes	-	-

RAEB-1/2 - RBCs + neutrop+/-thrombopenia + normal karyotype