



Case #2

Low-Risk Myelodysplastic Syndromes

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Treatment Options in MDS

Risk stratification according to IPSS



**Low risk
intermediate 1**

**Intermediate 2
high risk**

International Risk Score

	Points				
	0	0.5	1	1.5	2.0
BM blasts (%)	0-4	5-10	-	11-20	21-29
Number of cytopenias ¹	0-1	2-3	-	-	-
Cytogenetic category ²	low	int	high	-	-

Risk groups	Score
low	0
intermediate I	0.5 - 1
intermediate II	1.5 - 2
high	≥ 2.5

¹ Platelets < 100.000/μl, Hemoglobin < 10 g/dl, Neutrophils < 1.800/μl

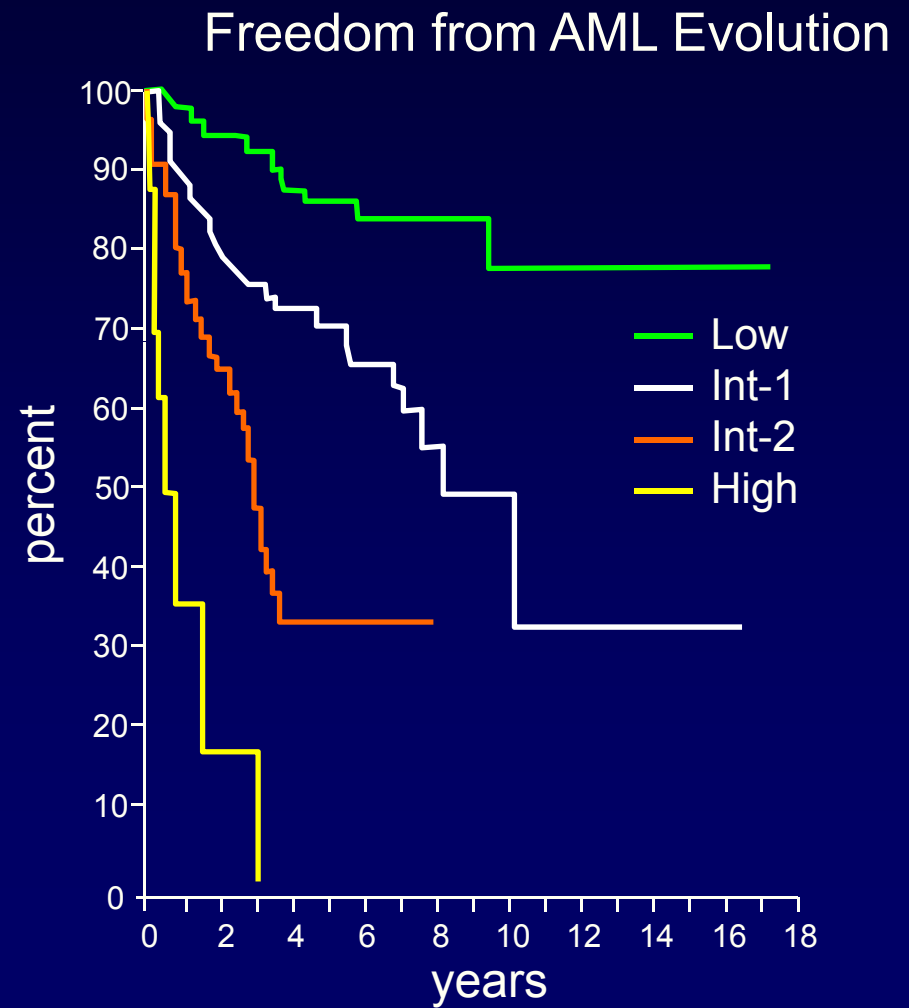
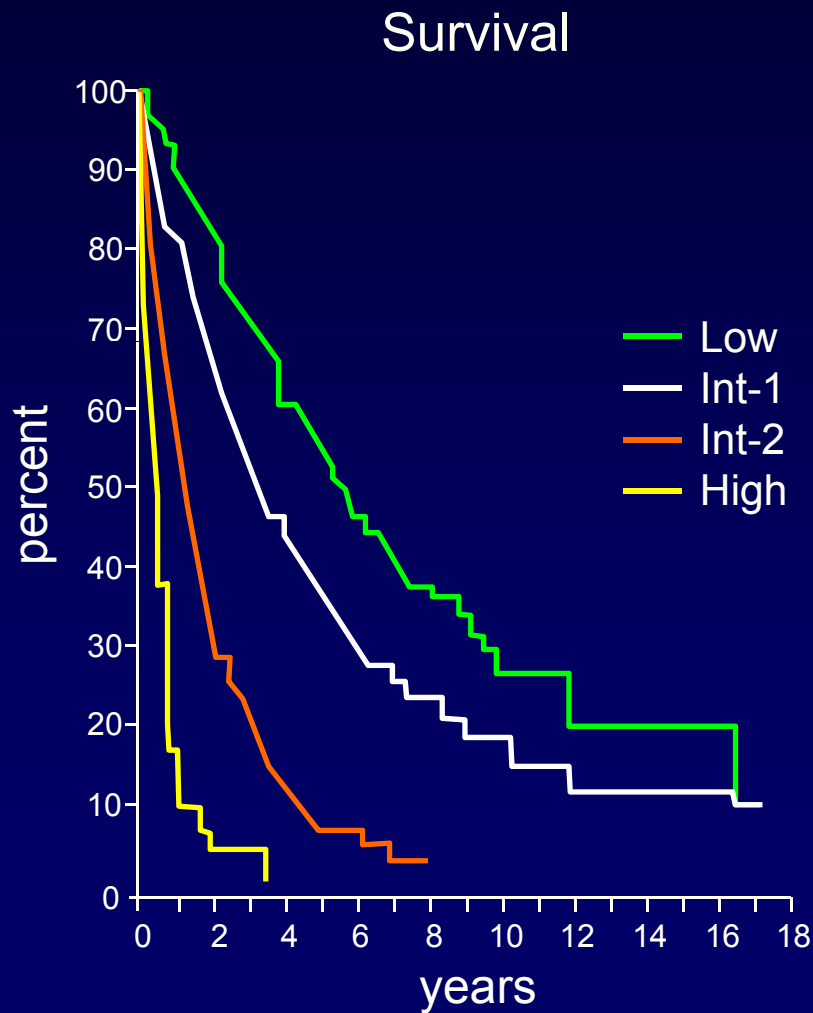
² low = normal, 5q-, 20q-, -Y

intermediate = other anomalies

high = complex (≥ 3 abnormalities), chromosome 7 anomalies

Greenberg P, et al. *Blood*.1997;89(6):2079-2088.

International MDS Risk Classification



Del(5q) MDS is a Heterogeneous Disease

del(5q) MDS

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graph TD; A[del(5q) MDS] --> B[del(5q) alone no blasts]; A --> C[del(5q) alone with blasts]; A --> D[del(5q) + others no blasts]; A --> E[del(5q) + others with blasts];
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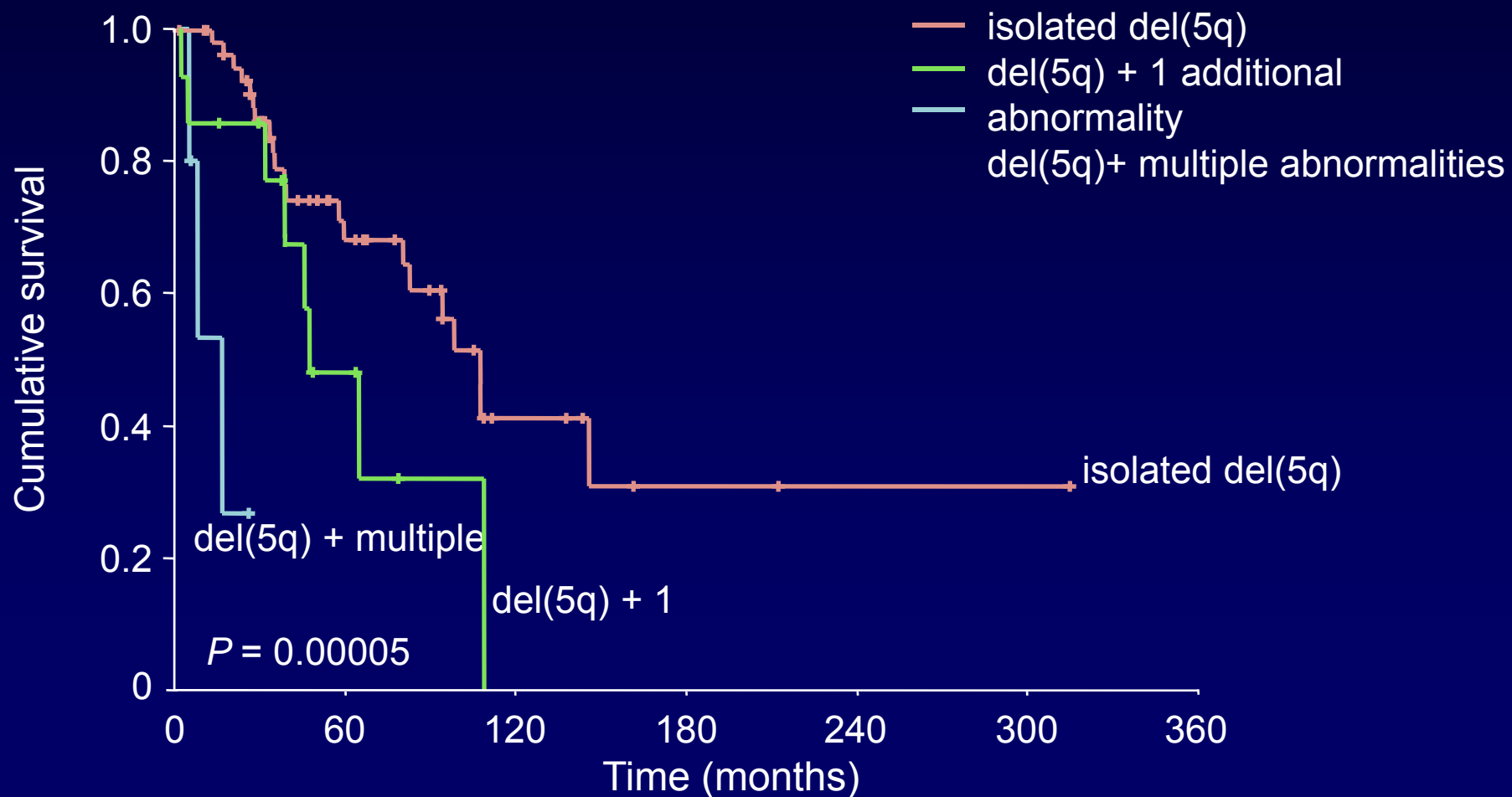
del(5q) alone
no blasts

del(5q) alone
with blasts

del(5q) + others
no blasts

del(5q) + others
with blasts

Prognostic Impact of Additional Chromosomal Aberrations on Survival in del(5q) MDS

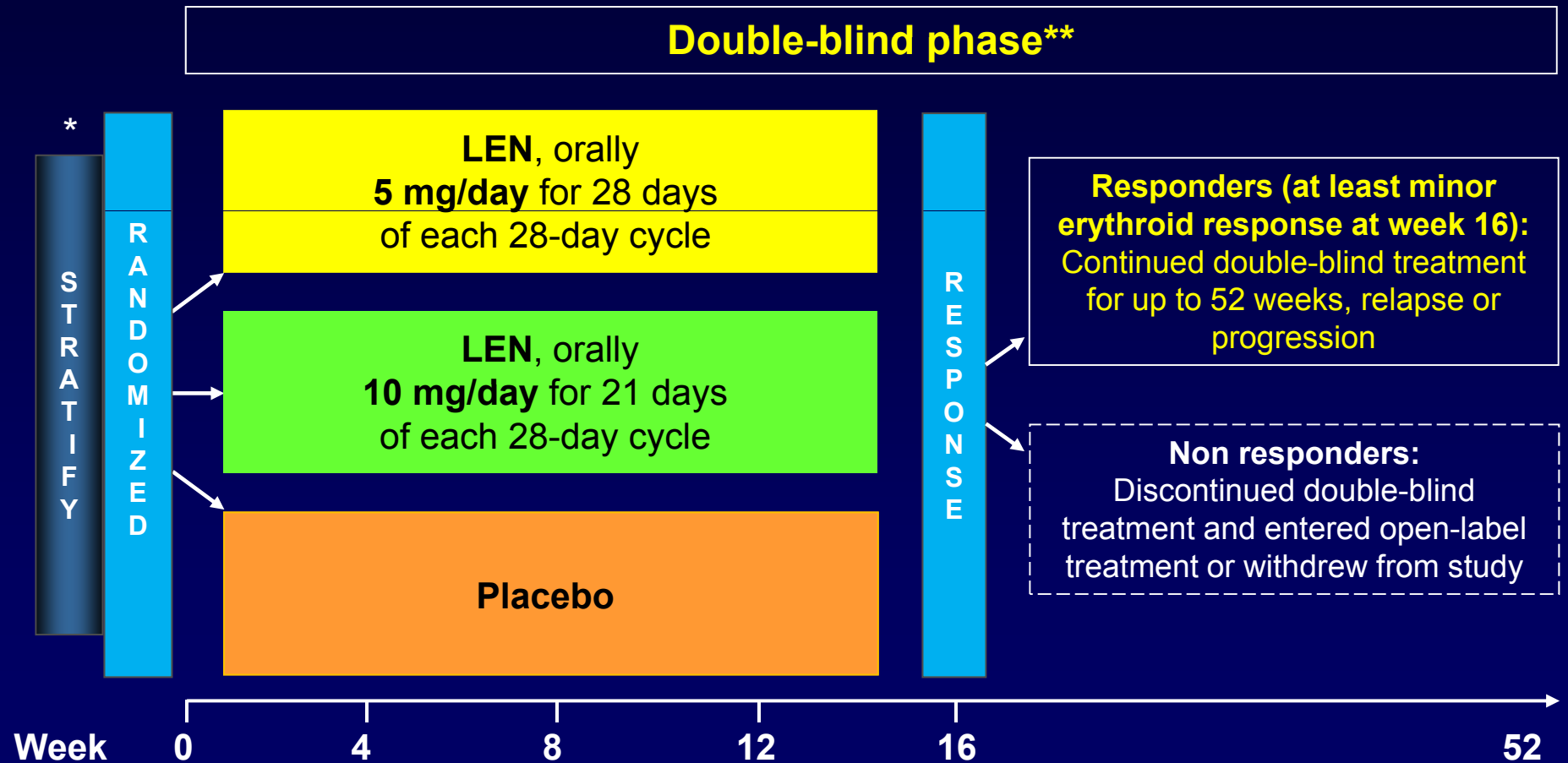


Treatment of del(5q) Disease (<5% blasts)

- **Watch and wait**
- **Transfusion therapy with iron chelation**
- **Erythropoietin**
- **Lenalidomide**
 - **High erythroid response rate**
 - **Consistent cytogenetic response rate**
 - **Manageable side effects**
 - **In Europe, concerns about cytogenetic progression**

MDS-004: Study Design

Planned enrollment
(N = 205)



*Patients stratified by IPSS score and cytogenetic complexity prior to randomization.

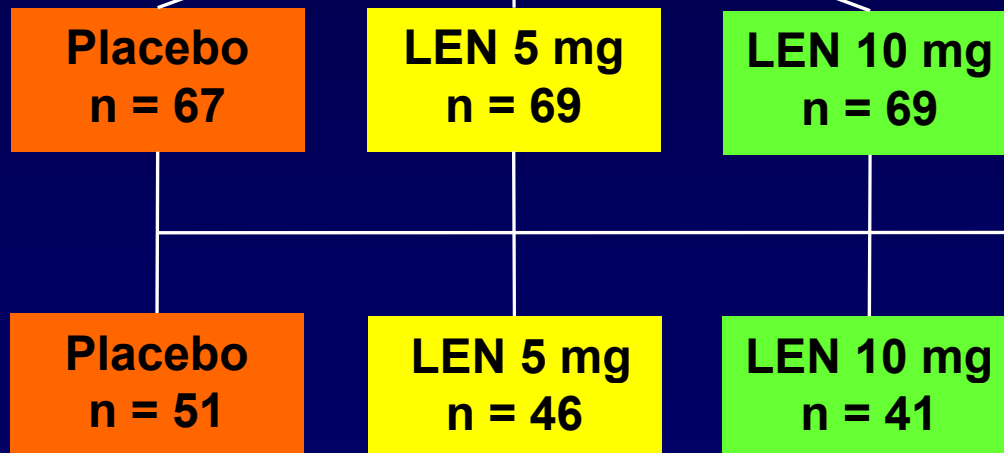
**Bone marrow assessments were performed at baseline, 12 weeks, and every 24 weeks thereafter.

MDS-004: Study Populations (Double-Blind Phase)

IPSS low- to int-1-risk MDS with
an associated del 5q(31)
cytogenetic abnormality
N = 205 randomized

ITT population (N = 205)
all randomized patients

Safety population (N = 205)
patients who received ≥ 1 dose

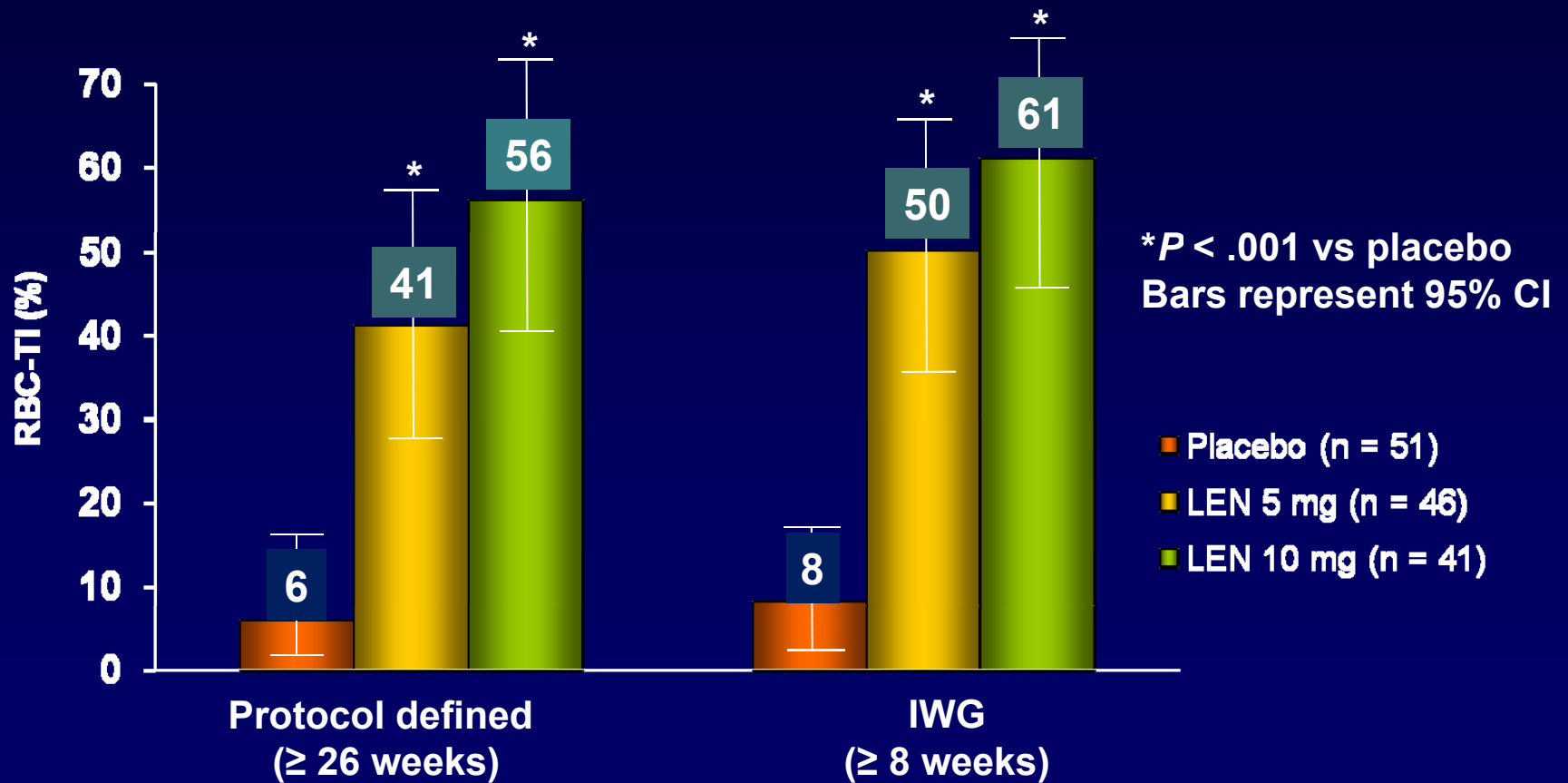


Reasons for exclusion (n = 67)

- inadequate BM sample (58%)
- Int-2/High IPSS score (16%)
- insufficient IPSS info (22%)
- no del(5q) at central review (3%)

mITT population (N = 138)
centrally-confirmed MDS who
received ≥ 1 dose

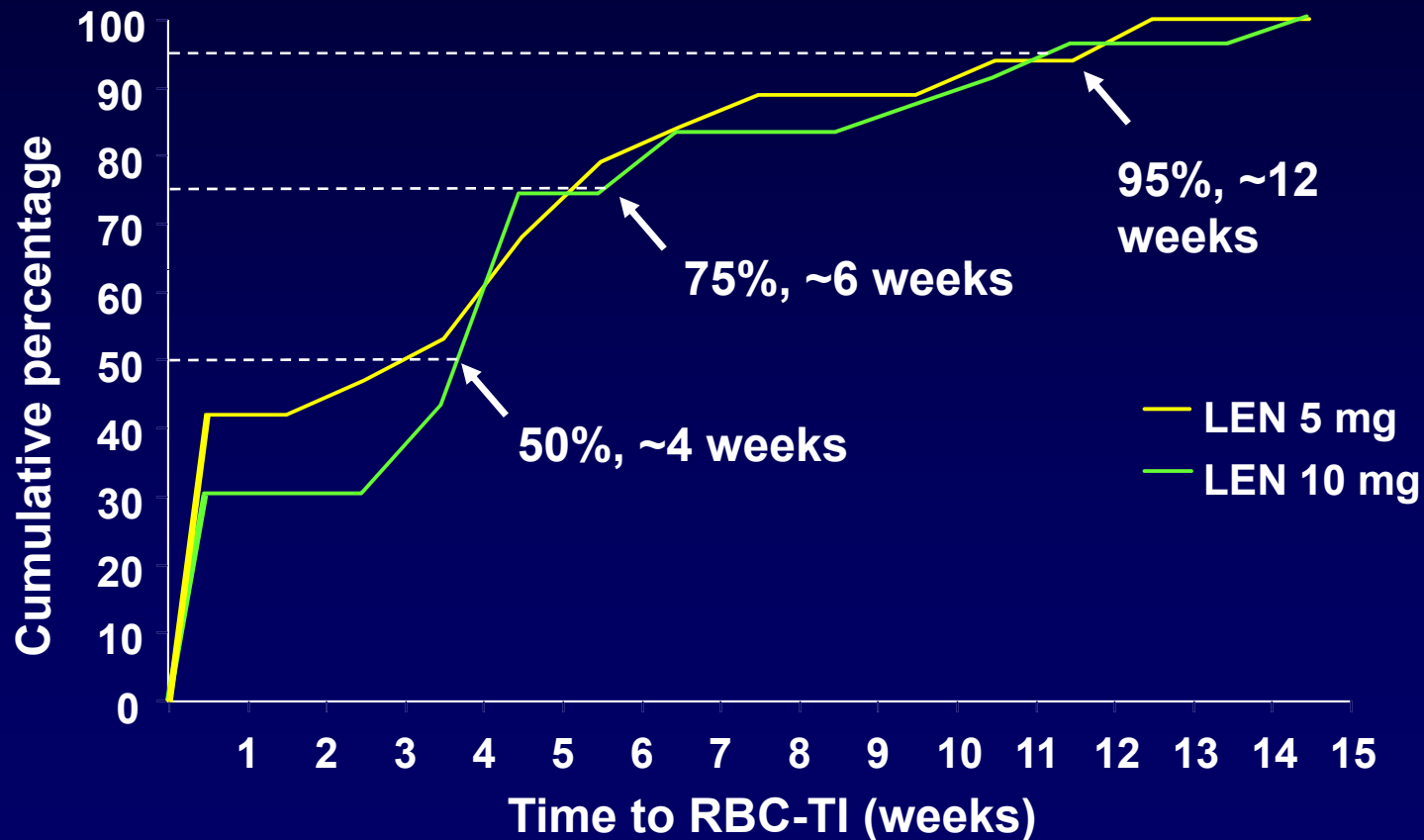
MDS-004: RBC-TI (mITT Population)



RBC-TI, red blood cell transfusion independent

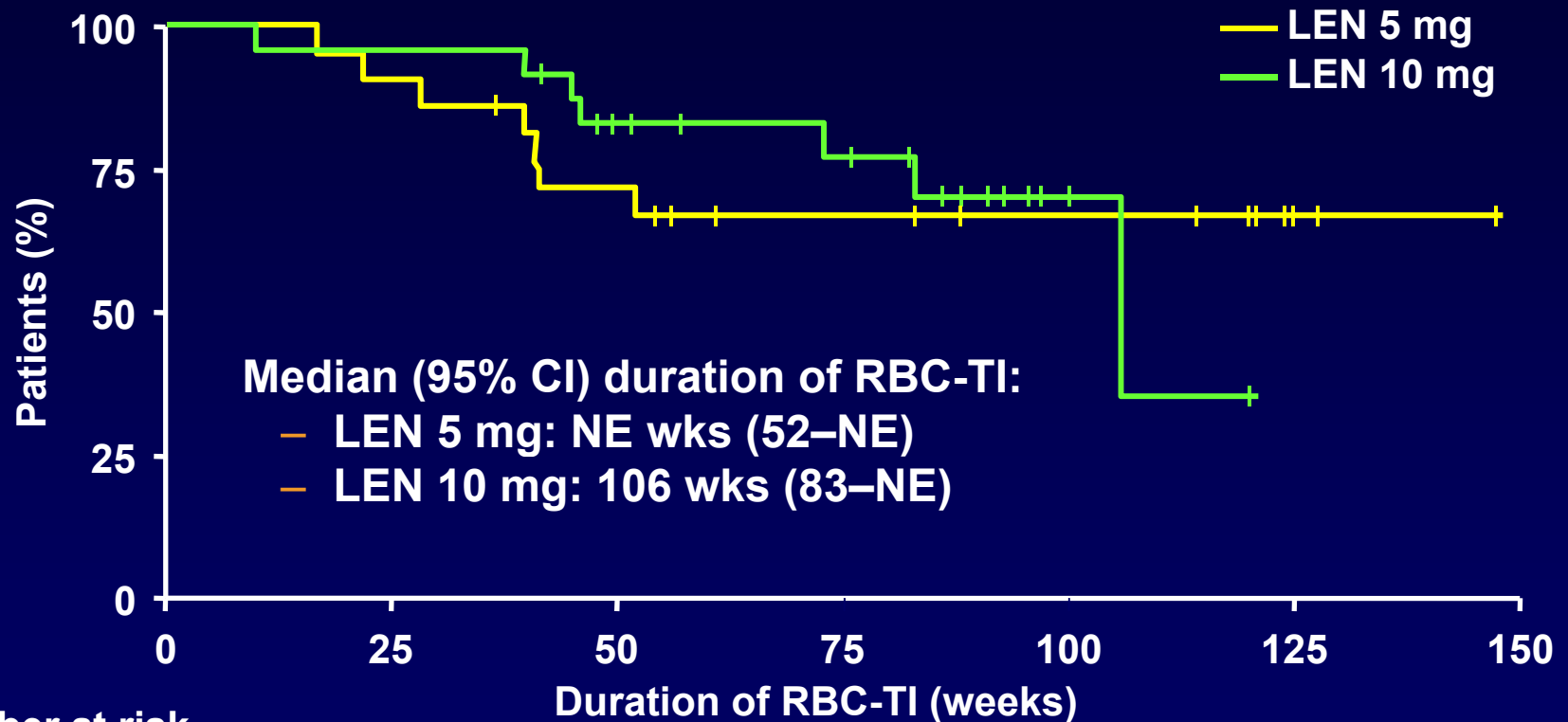
Fenaux P, et al. *Blood*. 2009;114: Abstract 944.

MDS-004: Time to RBC-TI ≥ 26 Weeks in LEN groups (mITT Population)



Initial RBC-TI achieved at median of 1 cycle (4 weeks) of LEN (5 mg: 3.3 weeks; 10 mg: 4.3 weeks) for patients with RBC-TI ≥ 26 weeks

MDS-004: Duration of RBC-TI ≥ 26 Weeks in LEN Groups (mITT Population)



Number at risk		Duration of RBC-TI (weeks)						
	0	25	50	75	100	125	150	
LEN 5 mg	23	20	15	10	8	2	0	
LEN 10 mg	25	23	17	13	2	0	0	

MDS-004: Cytogenetic Response (mITT Population)

Cytogenetic response, %	Placebo (n = 51)	LEN 5 mg (n = 46)	LEN 10 mg (n = 41)
Complete response (CCyR)	0	10.9*	24.4**
Partial response (PCyR)	0	6.5	17.1
CCyR + PCyR	0	17.4**	41.5**

* $P = .01$ vs placebo

** $P < .001$ vs placebo

- Assessed by standard cytogenetics and FISH.
- CR defined as absence of chromosome 5q31 abnormality
- PR defined as reduction of abnormality by $> 50\%$.

MDS-004: Most Common Grade 3 or 4 Adverse Events (Safety Population)

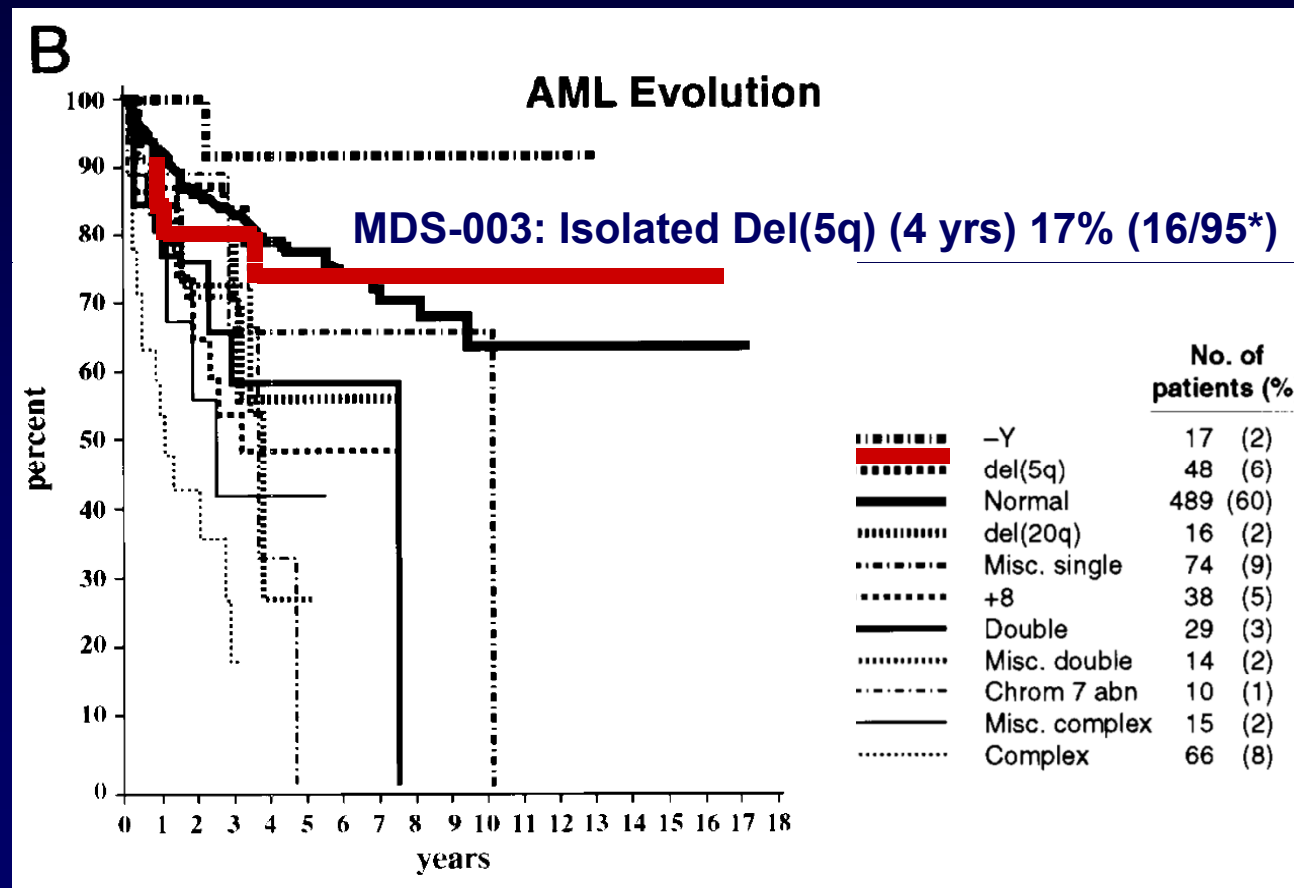
Grade 3 or 4 adverse events (≥5% of patients in any group)	Placebo (n = 67)	LEN 5 mg (n = 69)	LEN 10 mg (n = 69)
Patients with ≥ 1 event, n (%)	29 (43)	62 (90)	65 (94)
Neutropenia	10 (15)	51 (74)	52 (75)
Thrombocytopenia	1 (2)	23 (33)	28 (41)
Leukopenia	0 (0)	9 (13)	6 (9)
Anemia	6 (9)	4 (6)	2 (3)
Deep vein thrombosis	1 (2)	1 (1)	4 (6)
Adverse events leading to, n (%)			
Discontinuation	3 (5)	11 (16)	6 (9)
Dose reduction	0 (0)	36 (52)	40 (58)
Dose interruption	4 (6)	19 (28)	28 (41)

MDS-004: AML Progression (ITT Population)

- Data cut-off 26 June 2008
- **2-year crude cumulative incidence in LEN-treated patients: 7.7%**

Treatment arm	Pts n	Event % (n)	Censored % (n)
LEN 10 mg	69	7 (5)	93 (64)
LEN 5 mg	69	10 (7)	90 (62)
Placebo	67	9 (6)	91 (61)

Risk of AML According to International Prognostic Scoring System (IPSS) and Isolated del(5q)



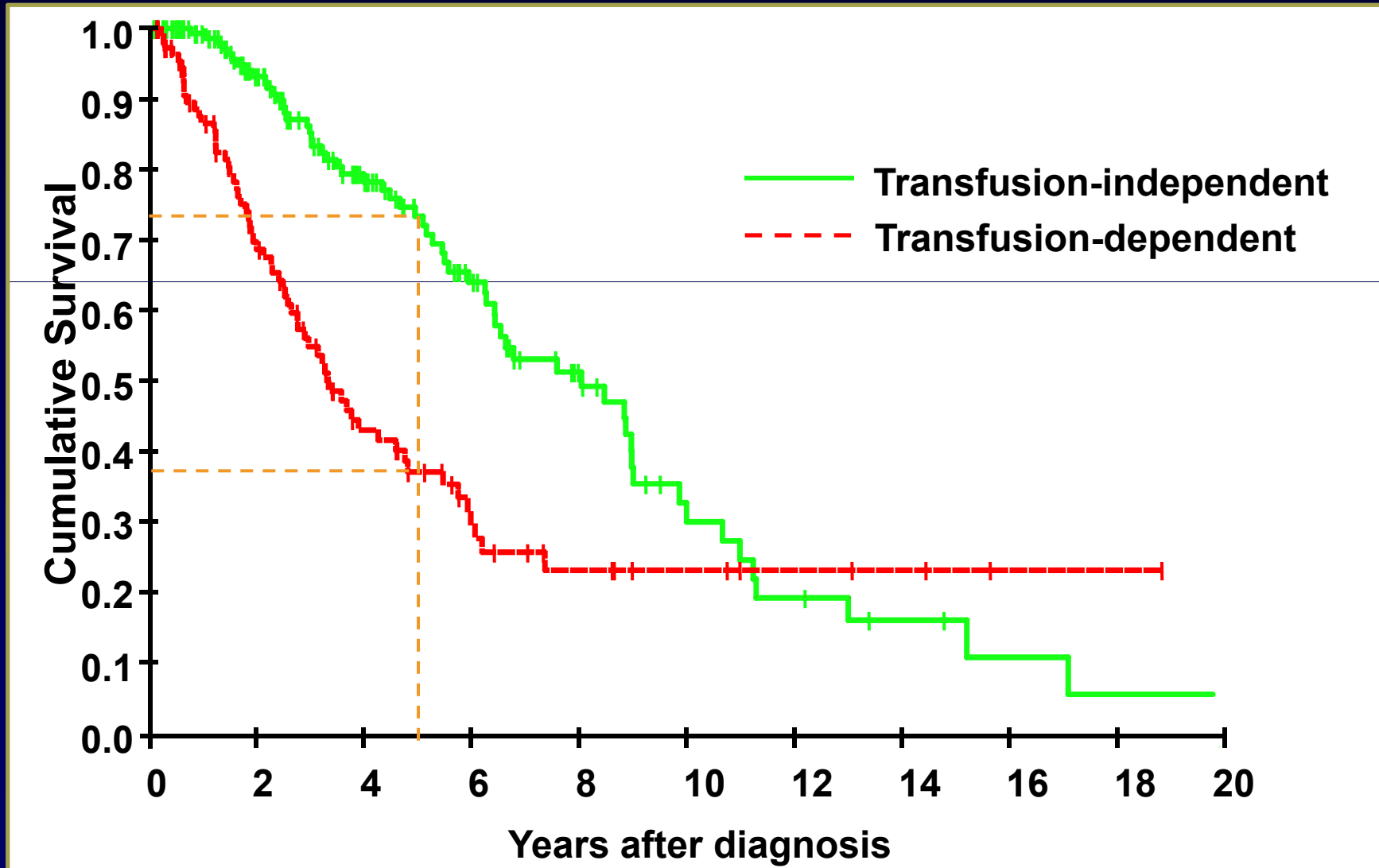
*MDS-003: centrally reviewed population with isolated del(5q)

Additional Registry Analyses

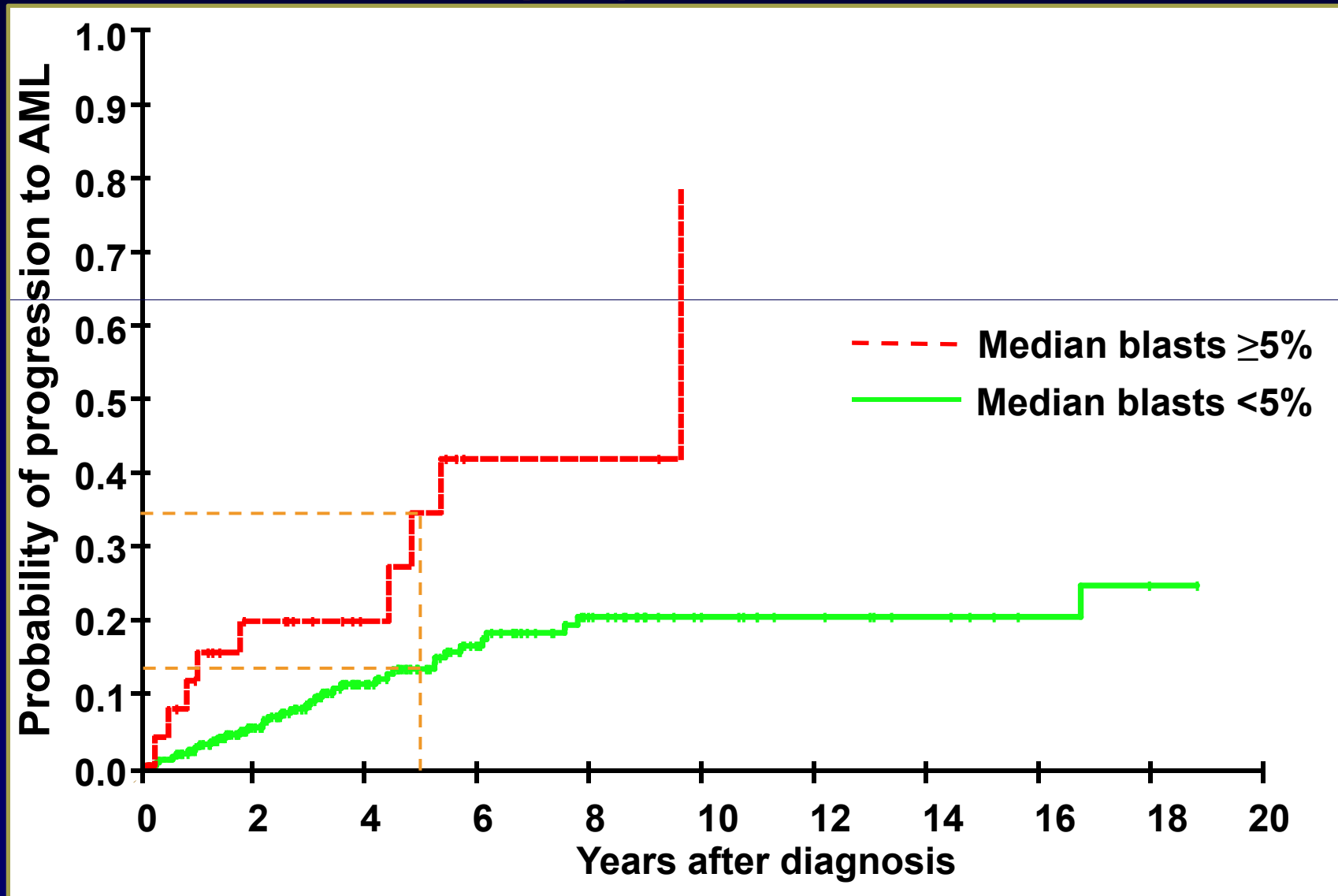
- **Merger of international registries**
- **Germany, Austria, Spain, Czech Republic, USA / Australia**
- **All untreated del(5q) patients**
- **No lenalidomide exposure**
- **AML transformation rate uniformly at about 25%**

- **GFM data regarding named-patient program and comparison with untreated del(5q) patients**
- **Lenalidomide treatment without effect on progression to AML**
- **Survival of lenalidomide-treated patients improved**

Overall Survival for Untreated Low/Int-1 Del(5q) Patients

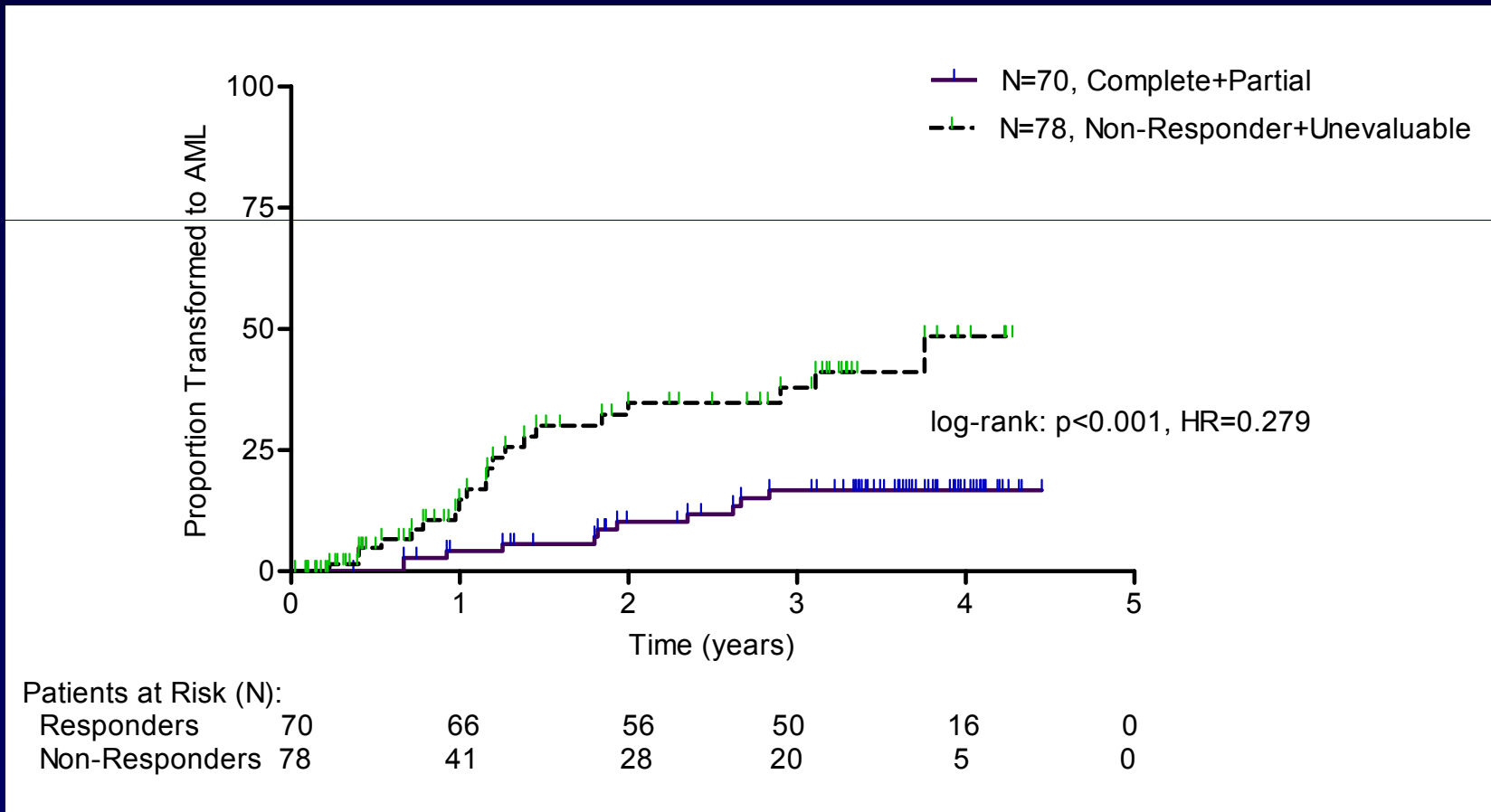


AML Evolution for Untreated Low/Int-1 Del(5q) Patients



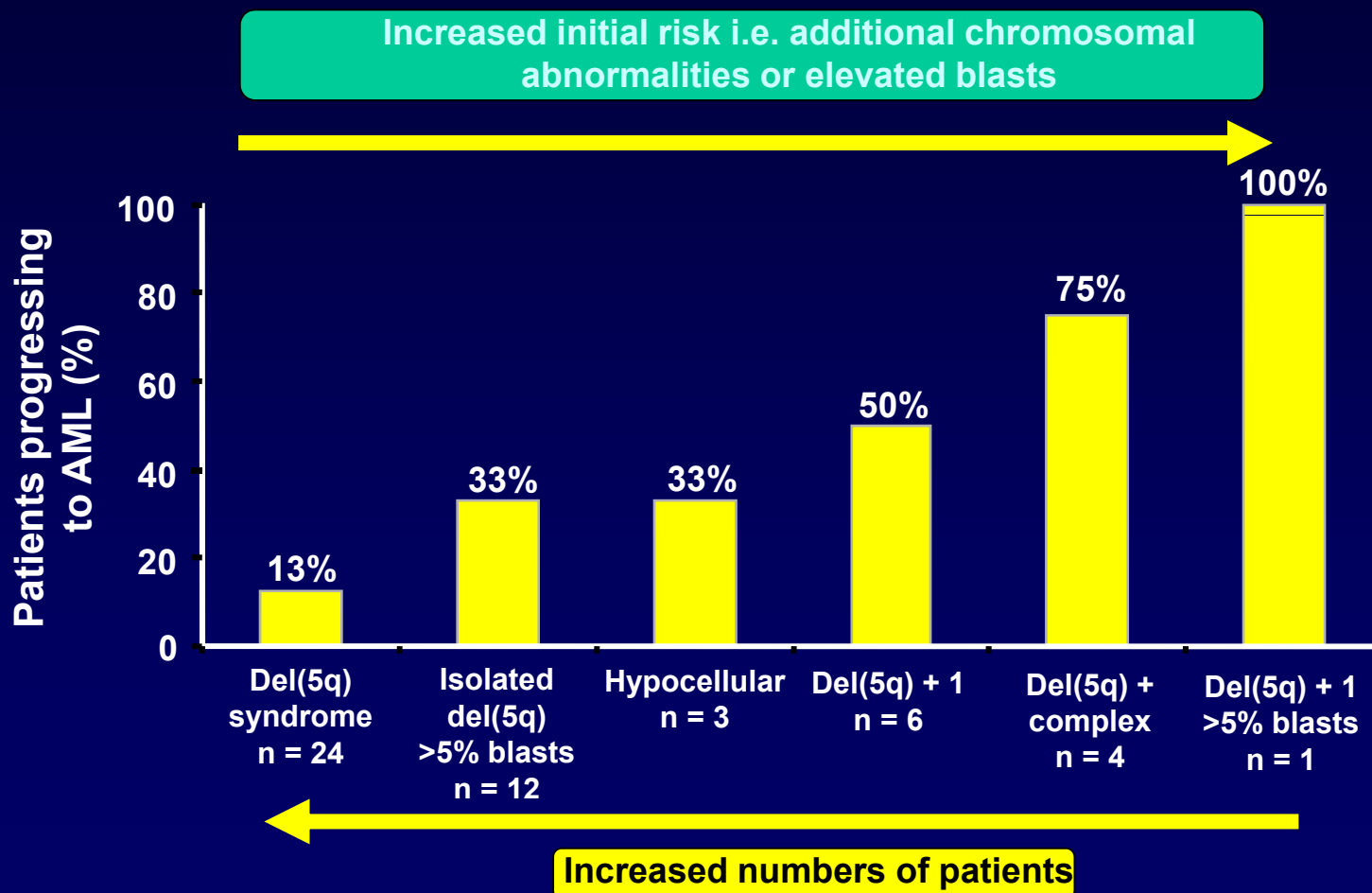
Germing U, et al. *Blood*. 2009;114: Abstract 945.

AML Transformation According to Cytogenetic Response



'Real world' Clinical Experience with Lenalidomide: AML Progression Rates

Experience at a single institute (n = 50)



ORIGINAL ARTICLE

Persistent Malignant Stem Cells in del(5q) Myelodysplasia in Remission

Ramin Tehrani, M.D., Ph.D., Petter S. Woll, Ph.D., Kristina Anderson, M.D., Ph.D.,
Natalija Buza-Vidas, Ph.D., Takuo Mizukami, Ph.D., Adam J. Mead, M.D., Ph.D.,
Ingbritt Åstrand-Grundström, B.Sc., Bodil Strömbeck, M.Sc., Andrea Horvat, M.Sc.,
Helen Ferry, Ph.D., Rakesh Singh Dhanda, Ph.D., Robert Hast, M.D., Ph.D.,
Tobias Rydén, Ph.D., Paresh Vyas, M.D., Gudrun Göhring, M.D.,
Brigitte Schlegelberger, M.D., Ph.D., Bertil Johansson, M.D., Ph.D.,
Eva Hellström-Lindberg, M.D., Ph.D., Alan List, M.D., Ph.D.,
Lars Nilsson, M.D., Ph.D., and Sten Eirik W. Jacobsen, M.D., Ph.D.

MDS-LE-MON-5-Study (Germany)

Design:

- Phase II, single-arm, multi-center
- **100 Patients:** transfusion-dependent IPSS low/Int-1, isolated del (5q)-MDS; no previous lenalidomide
- Primary endpoint: **safety of enalidomide**
- **10 mg lenalidomide, d1-21, q28d**
- Study ends on March 2014

Treatment Algorithm with Lenalidomide in del(5q) Disease

del(5q) MDS

Stratify for risk factors

Start lenalidomide treatment

Complete cytogenetic responder

44%

6 monthly bone marrow

No cytogenetic response / relapse

Watch for: Cytogenetic evolution, loss of CHR

Salvage treatment: azacitidine, allo-Tpx, investigational therapies

Conclusions

- **Del (5q) MDS is a heterogenous disease**
- **Transfusion-dependent patients and those with elevated blast count have an elevated risk of AML progression**
- **Lenalidomide displays high efficacy in transfusion-dependent Low-/Int-1-risk MDS**
- **Clinical trials show some efficacy in higher-risk isolated del (5q) MDS**