

# Myelodysplastic Syndromes with del(5q)

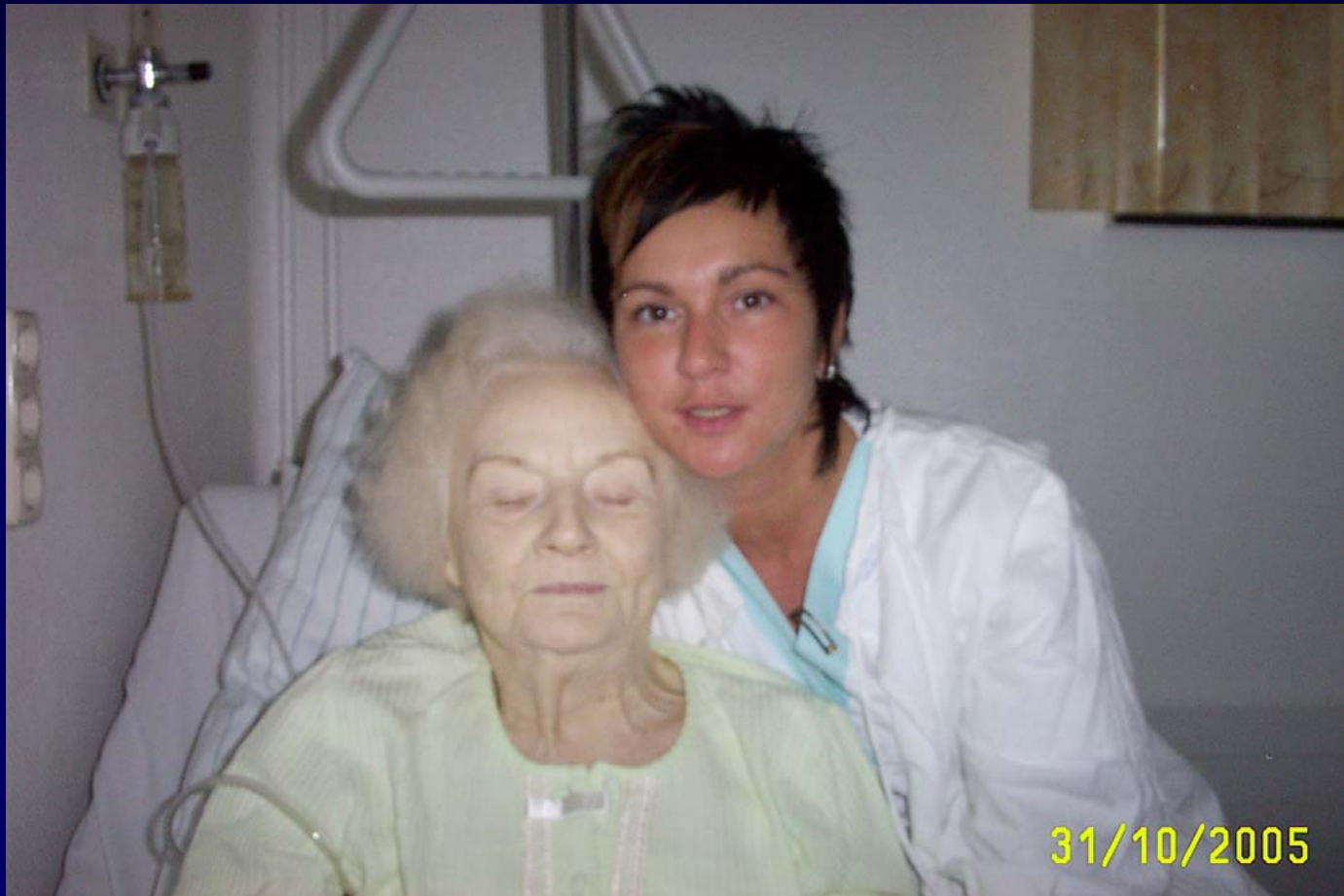
Aristoteles Giagounidis, MD, PhD

St Johannes Hospital  
Duisburg, Germany

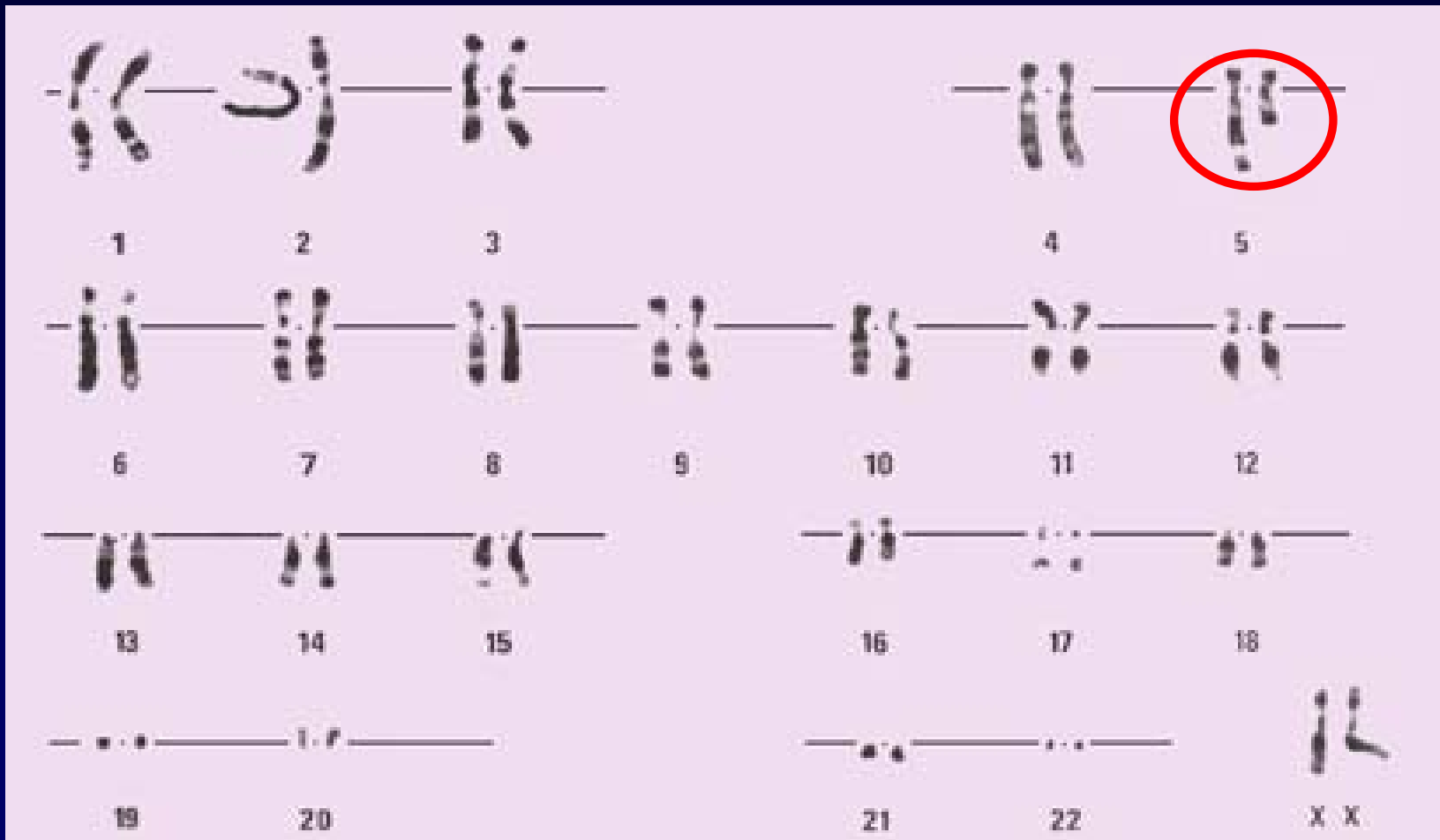


5q<sub>minus</sub>

# MDS increases morbidity and mortality

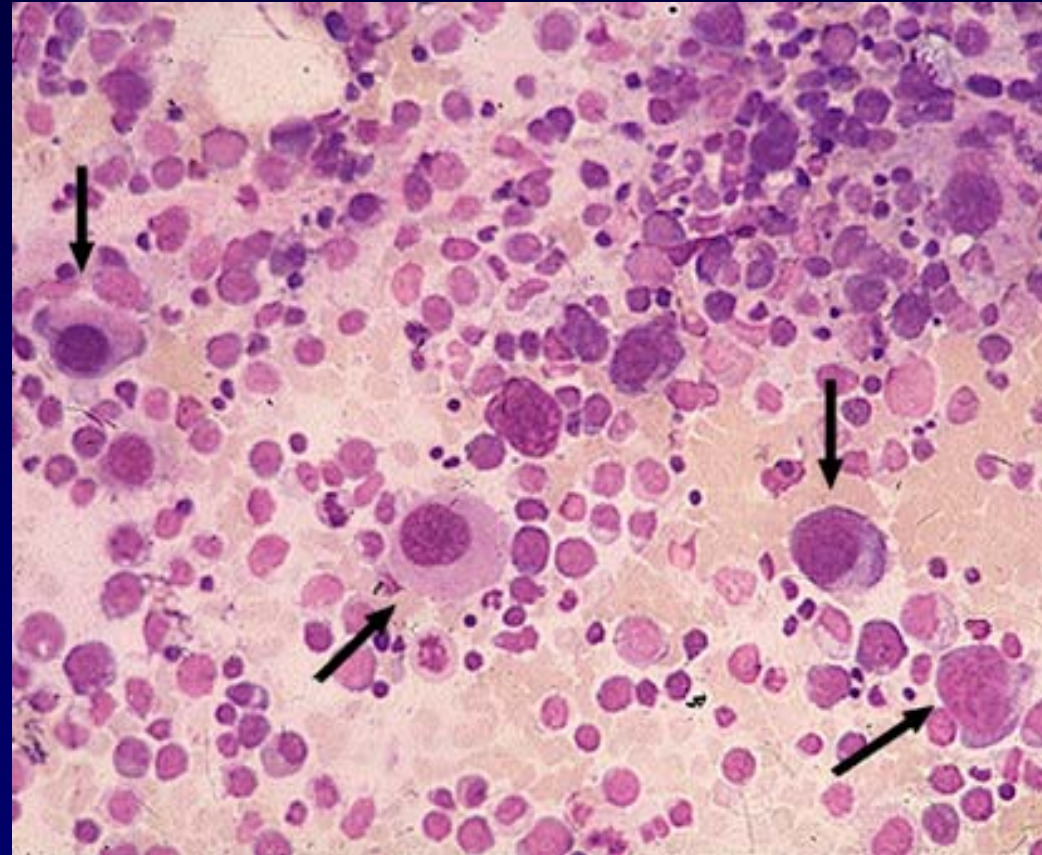


# Del(5q) karyotype

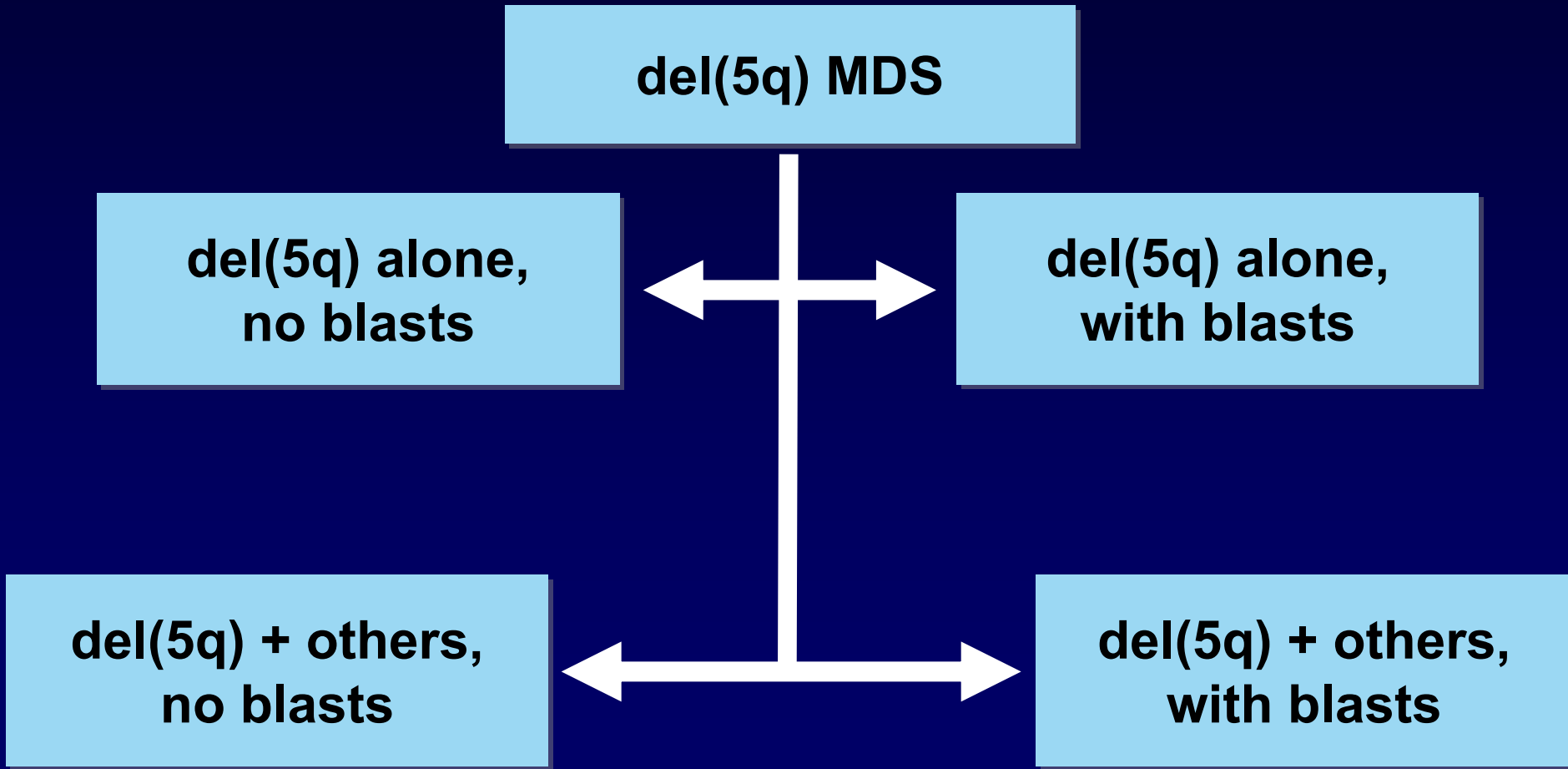


# The 5q-Syndrome

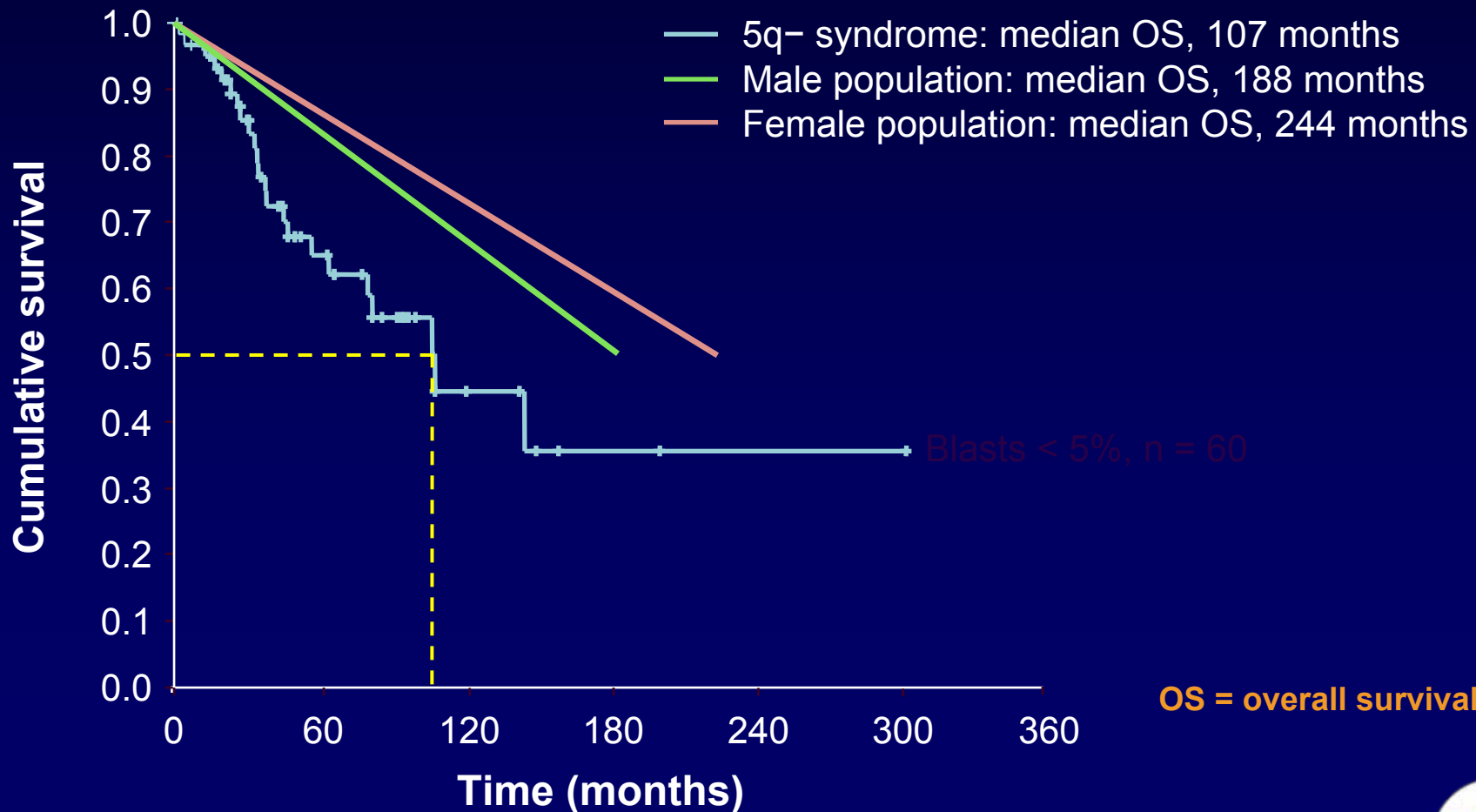
- **Affects predominantly women**
- **Mononuclear, spheronuclear megakaryocytes**
- **Macrocytic anemia**
- **Thrombocytosis**
- **Mild leukopenia**
- **Low probability of AML transformation**



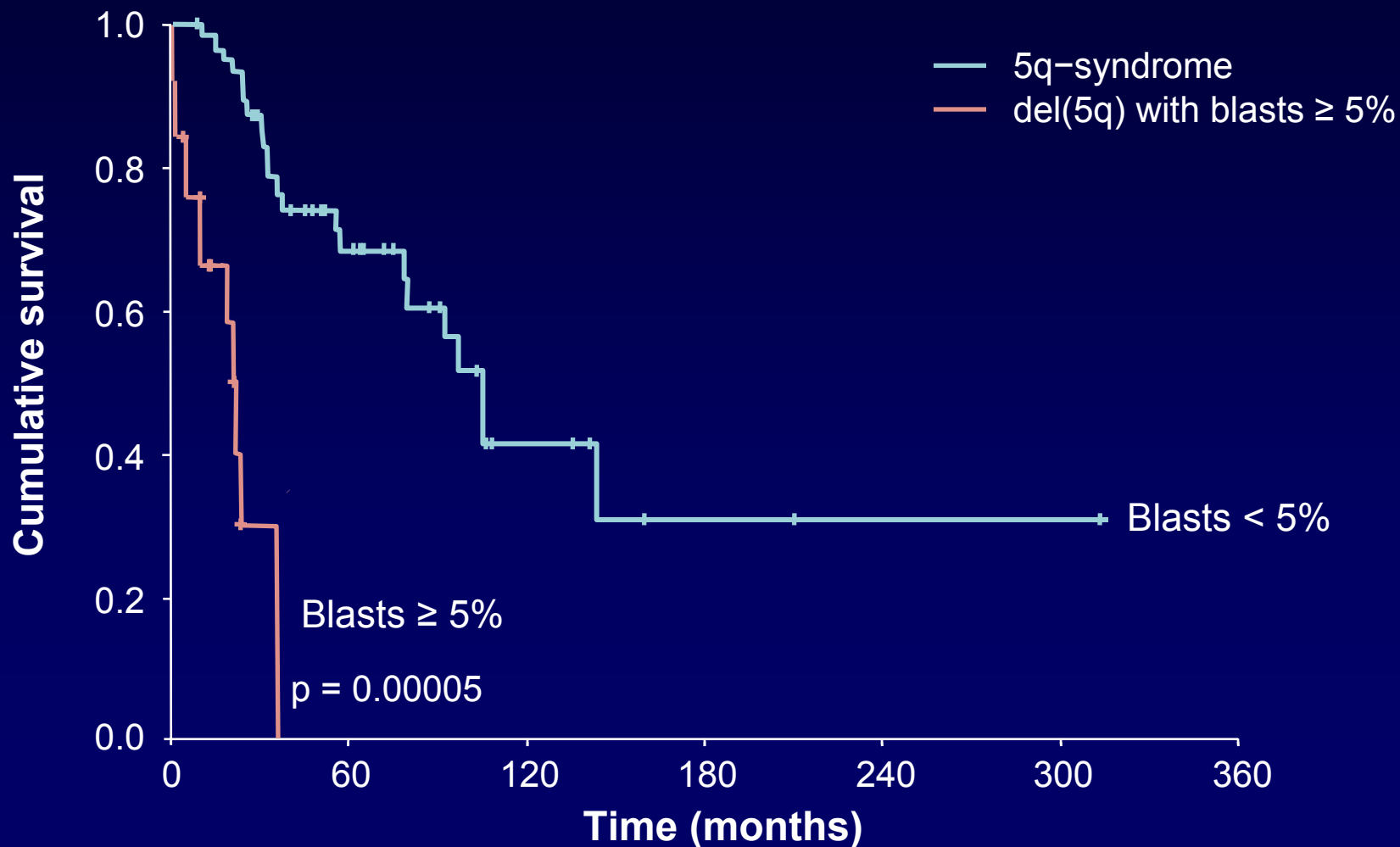
# del(5q) MDS is a Heterogeneous Disease



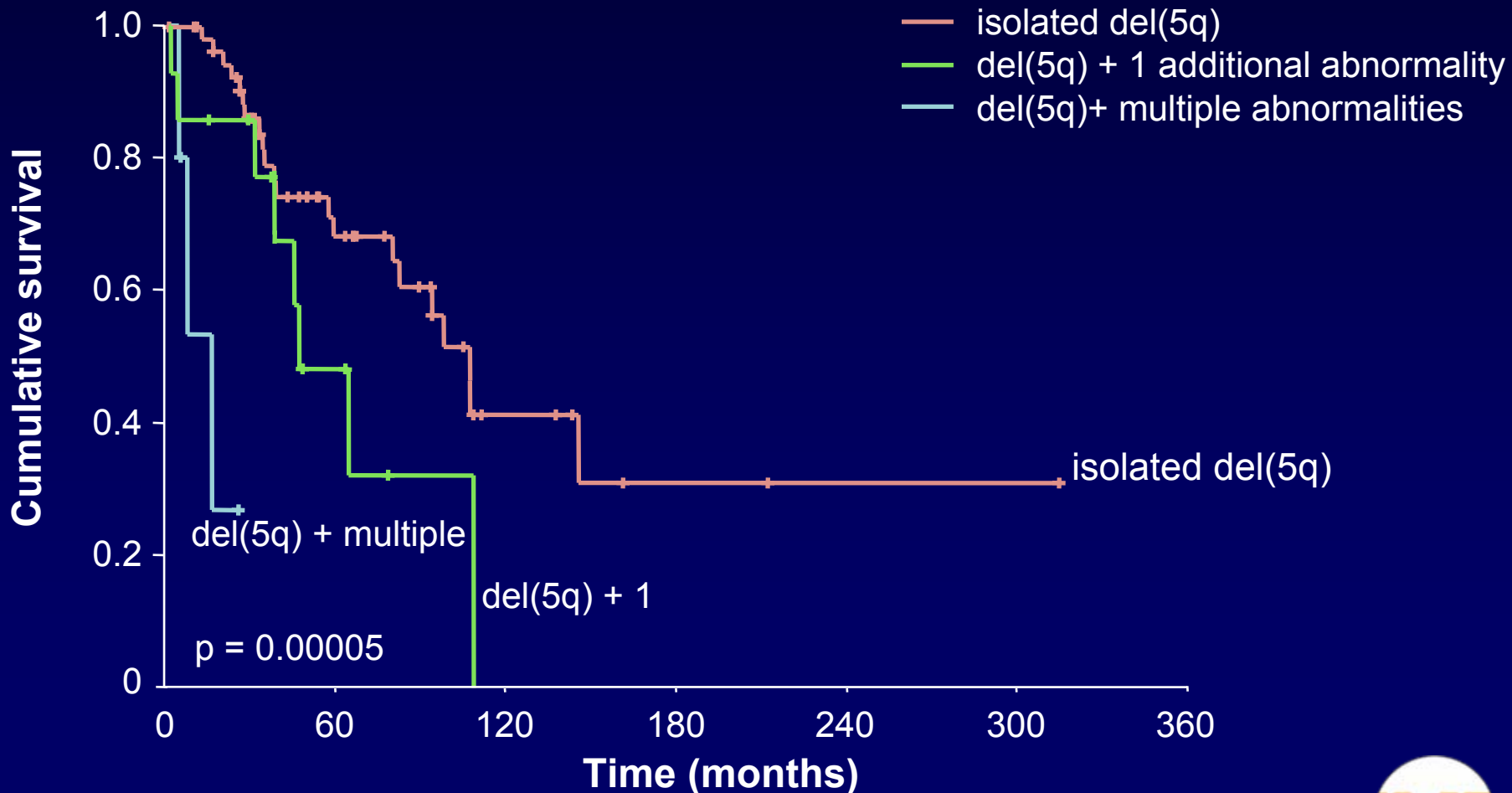
# del(5q) MDS: Differences in Median OS Between Genders



# Prognostic Impact of Medullary Blast Count in del(5q) MDS

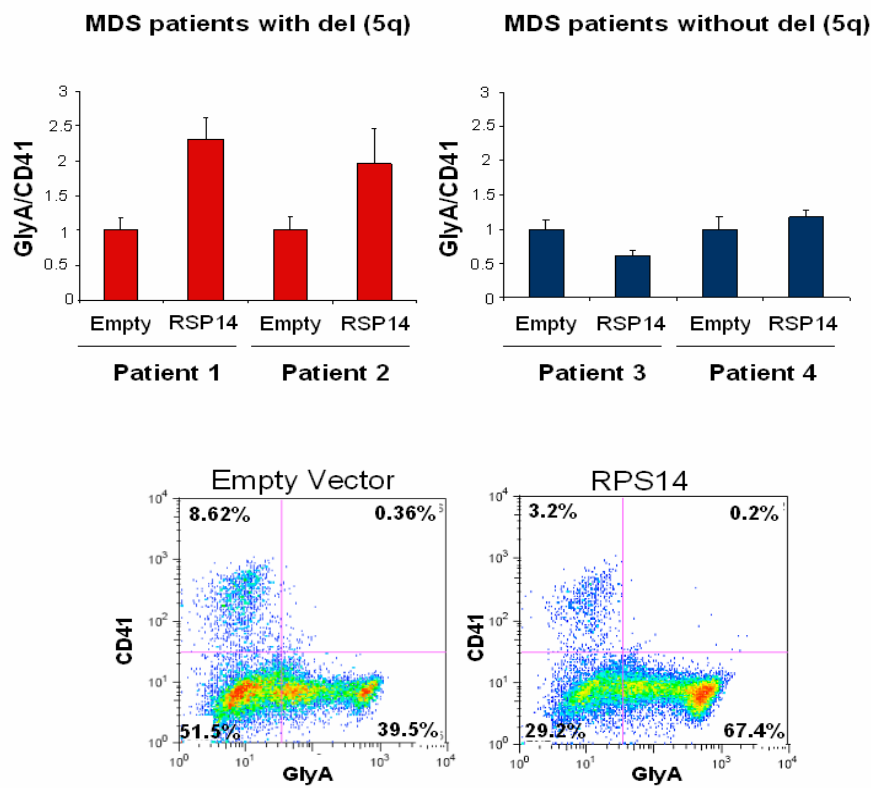


# Prognostic Impact of Additional Chromosomal Aberrations on Survival in del(5q) MDS



# Identification of Critical Deleted Gene in del(5q)

## Rescue of erythropoiesis with RPS14 overexpression



# Treatment Options in del(5q) MDS

## Therapy

## Goal

**Supportive therapy**

**Rise in hemoglobin,  
Prevention of hemo-  
siderosis/infections**

**All-*trans*-retinoic acid**

**Differentiation**

**Low-dose cytarabine therapy**

**Suppression of clone**

**IMiDs™**

**Eradication of clone?**

**Allogeneic stem cell  
transplantation**

**Eradication of clone**

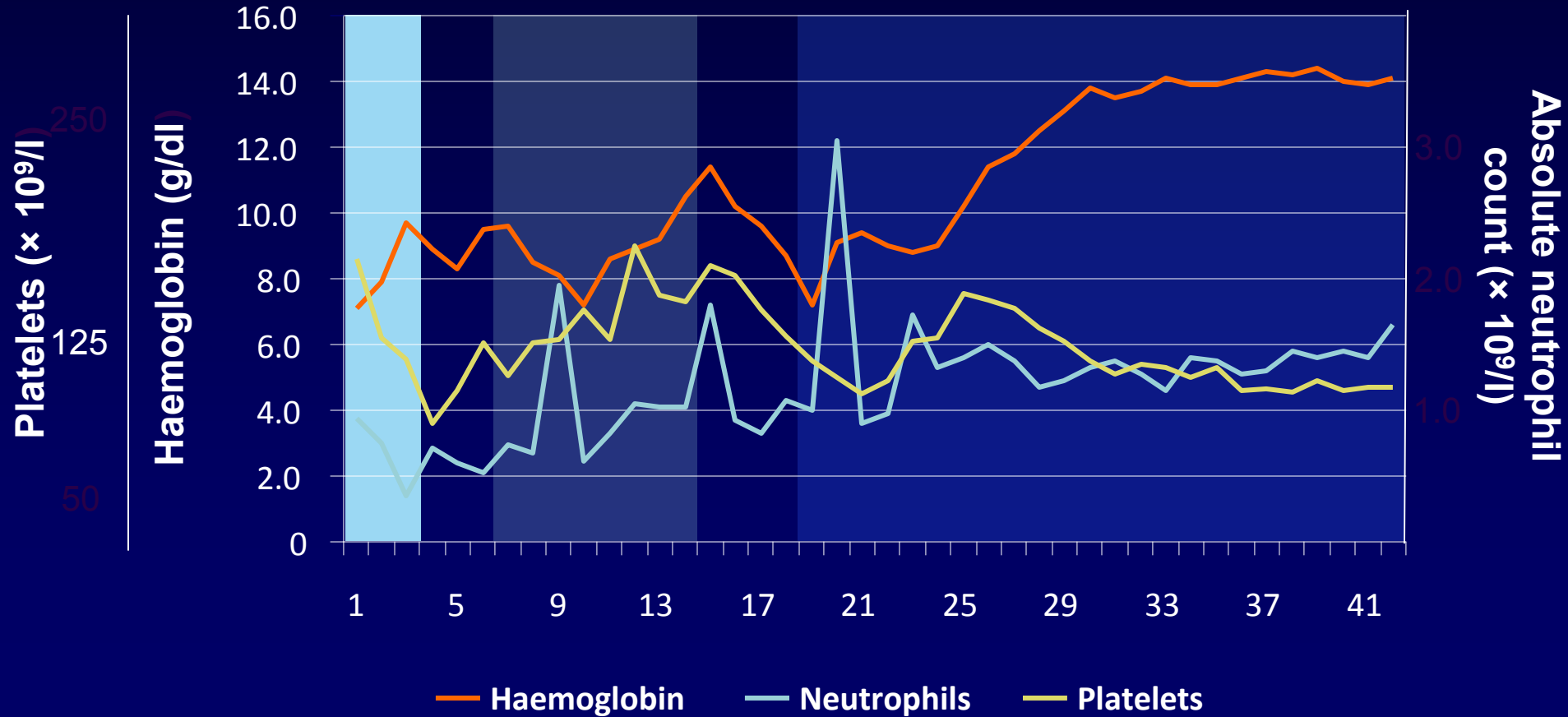
# Lenalidomide (Revlimid™)



# Case presentation 1: 79-year-old female

- **Oct. 2006: anaemia (general practitioner)**
  - exertional dyspnoea; otherwise well
- **Feb. 2007: received first blood transfusion**
- **Aug. 2007: diagnosis of 5q- syndrome**
- **Aug. 2007: start lenalidomide 5 mg/day PO**
  - grade 4 neutropenia after 6 weeks – interruption of lenalidomide

# Patient 1: Complete Blood Count Plot



# MDS-003: Lenalidomide in del(5q) MDS

## Erythroid response (intent-to-treat)

Response	Dose		Total, n (%) [95% CI] (n = 148)
	10 mg/day (n = 102)	10 mg/day x 21 days (n = 46)	
<b>Erythroid response</b>			
TI, n (%)	71 (70)	28 (61)	99 (67) [59–74]
Minor,* n (%)	8 (8)	5 (11)	13 (9) [5–15]
TI + minor,* n (%)	79 (77)	33 (72)	112 (76) [68–82]
<b>Time to response</b>			
Median, weeks	4.7	4.3	4.6
Range	1–34	1–49	1–49

\*Minor response denotes a  $\geq 50\%$  decrease in number of transfusions.

TI = transfusion independence.

# MDS-003: Transfusion-independence Rate by Cytogenetic Pattern

<b>Complexity*</b>	<b>n (N = 147)<sup>#</sup></b>	<b>Transfusion- independent patients, n (%)</b>
<b>Isolated del(5q)</b>	<b>110</b>	<b>79 (72)</b>
<b>del(5q) + 1 additional abnormality</b>	<b>25</b>	<b>12 (48)</b>
<b>Complex karyotype (≥ 3 abnormalities)</b>	<b>12</b>	<b>8 (67)</b>

\*p > 0.05 for all.

<sup>#</sup>Excluding 1 patient whose cytogenetic characteristics were defined by FISH only.

TI = transfusion independence.



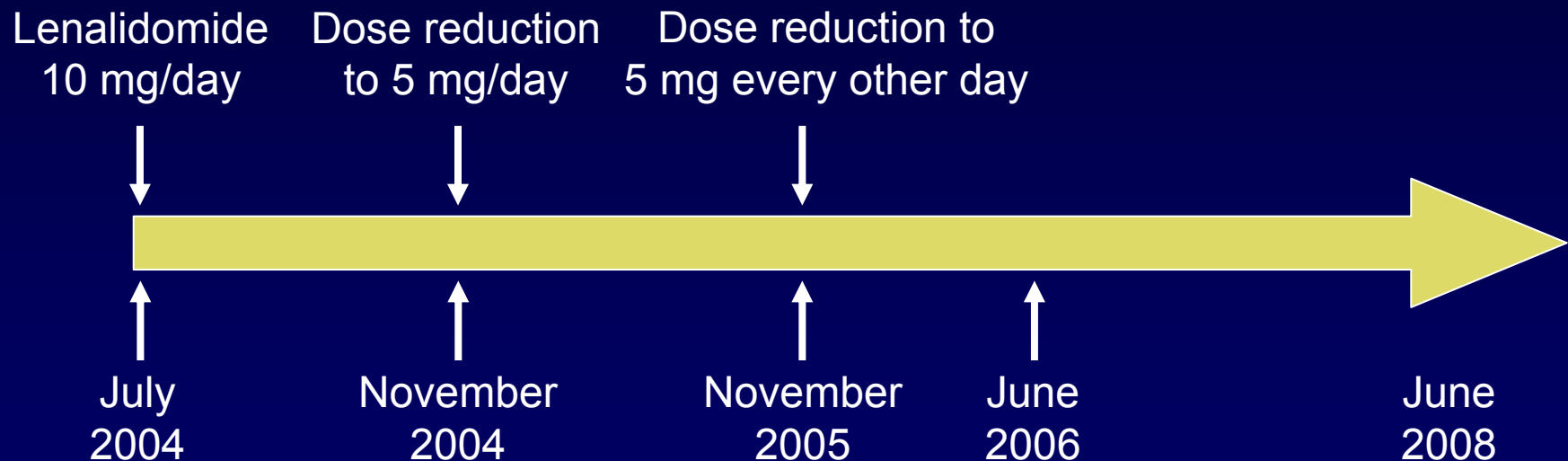
## Case presentation 2: 76-year-old female

- Admitted to hospital in Jan. 2004
- Hb: 8.9 g/dl
- Platelet count:  $278 \times 10^9$  cells/l  
(normal range:  $150\text{--}350 \times 10^9$ /l)
- White blood cell count:  $4.3 \times 10^9$  cells/l  
(normal range:  $4\text{--}10 \times 10^9$  cells/l)
- Absolute neutrophil count:  $2.6 \times 10^9$  cells/l  
(normal range:  $1.8\text{--}7 \times 10^9$  cells/l)
- Mean corpuscular volume: 92 fl  
(normal range: 80–95 fl)

# Patient 2: Cytogenetics

- Bone marrow aspirate
- Medium-sized dysplastic megakaryocytes with round to oval nuclei
- Megaloblastoid erythroid cells, few signs of other dysplasias
- White blood cells were essentially normal
- Blast count = 3%
- Cytogenetics revealed a complex karyotype:  
46, XX, der(1)t(1;2)p13;?),  
der(2)t(1;2)(p13;q31)del(2)(p23),  
**del(5)(q15q31)[19]/46, XX [1]**

# Patient 2: treatment



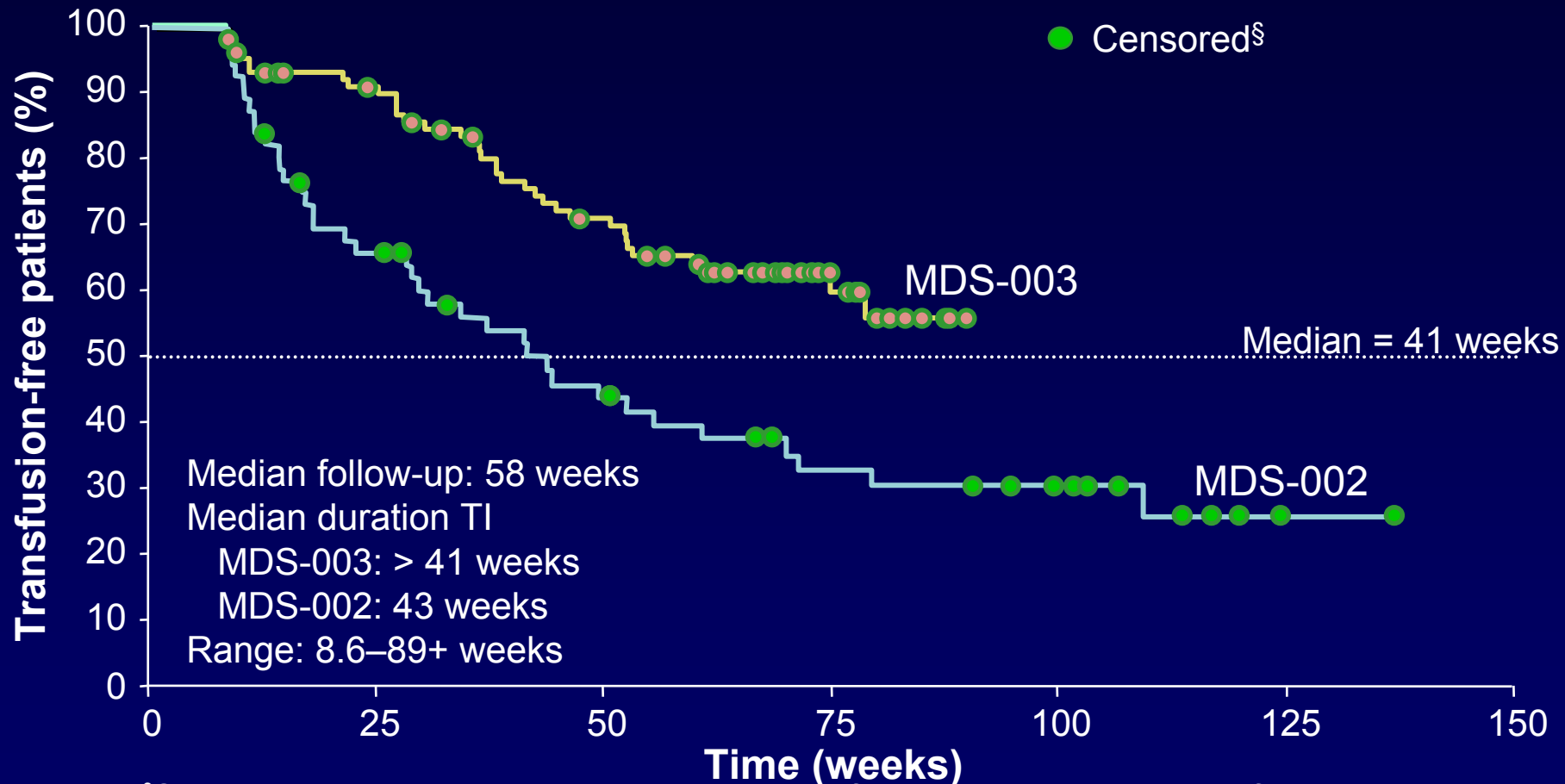
**No evidence of cytogenetic abnormalities  
in any of the follow-up analyses**

# MDS-002: Erythroid Response to Lenalidomide in non-del(5q) MDS at 24 weeks

## Intent-to-treat population

	MDS-002 non-del(5q) (N = 214)
<b>Erythroid response, n (%)</b>	
<b>Transfusion independent</b>	<b>56 (26)</b>
<b>Minor (&gt; 50% ↓)</b>	<b>37 (17)</b>
<b>Transfusion-independent + minor</b>	<b>93 (43)</b>
<b>Median duration of transfusion independence, weeks</b>	<b>41</b>
<b>Median increase in Hb, g/dl (range)</b>	<b>3.2 (1.0–9.8)</b>
<b>Median time to response, weeks (range)</b>	<b>4.8 (1–39)</b>

# MDS-002 and MDS-003: duration of transfusion independence



<sup>§</sup>Symbols are censored patients who remain transfusion independent at time of data cut-off or at time of study discontinuation.

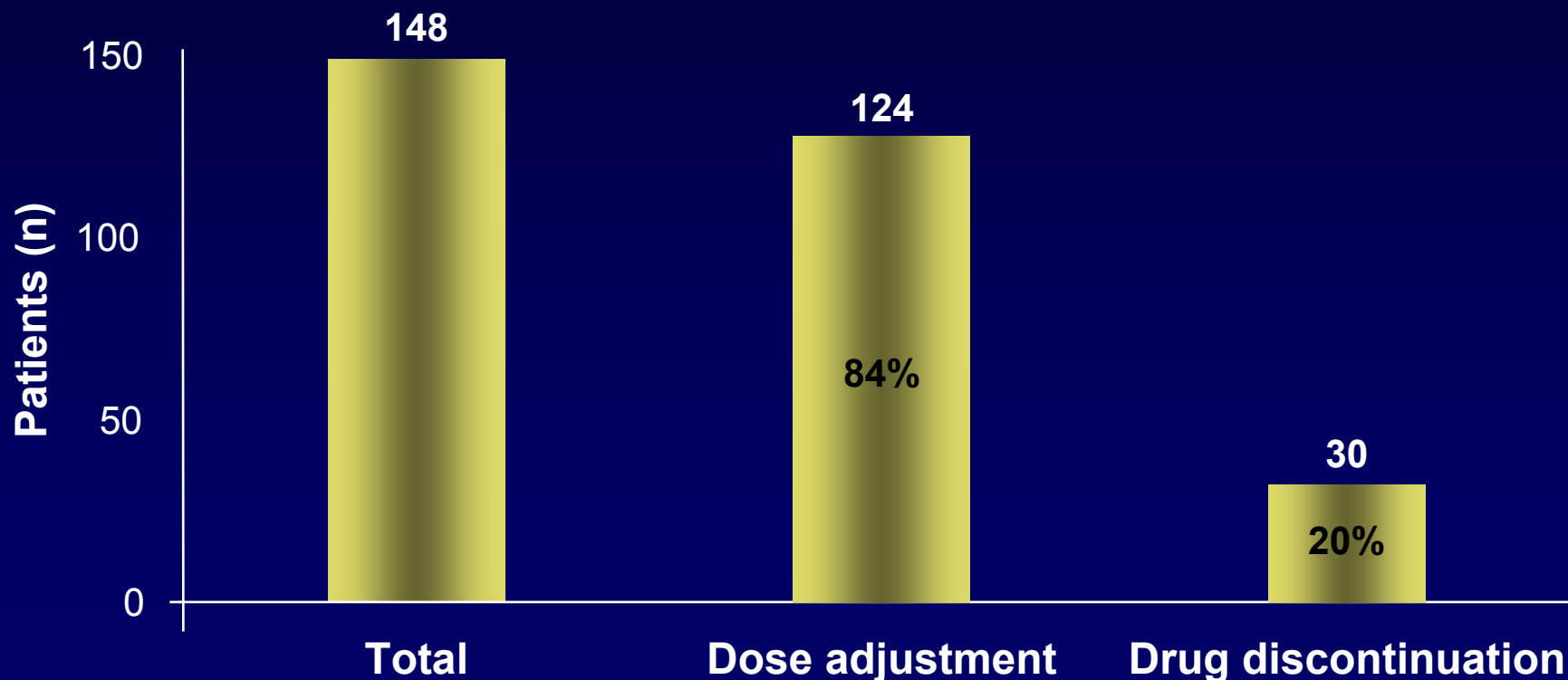
# MDS-002 and MDS-003: Most Common Treatment-related Adverse Events

Adverse events $\geq$ grade 3	MDS-002 non-del(5q), %	MDS-003 del(5q), %
<b>Thrombocytopenia</b>	<b>20</b>	<b>44</b>
<b>Neutropenia</b>	<b>25</b>	<b>55</b>
<b>Pruritus</b>	<b>1</b>	<b>3</b>
<b>Rash</b>	<b>4</b>	<b>6</b>
<b>Diarrhoea</b>	<b>1</b>	<b>3</b>
<b>Fatigue</b>	<b>4</b>	<b>3</b>
	MDS-002, n	MDS-003, n
<b>Deaths on study</b>	<b>21</b>	<b>11</b>
<b>Possibly drug-related</b>	<b>2</b>	<b>3*</b>

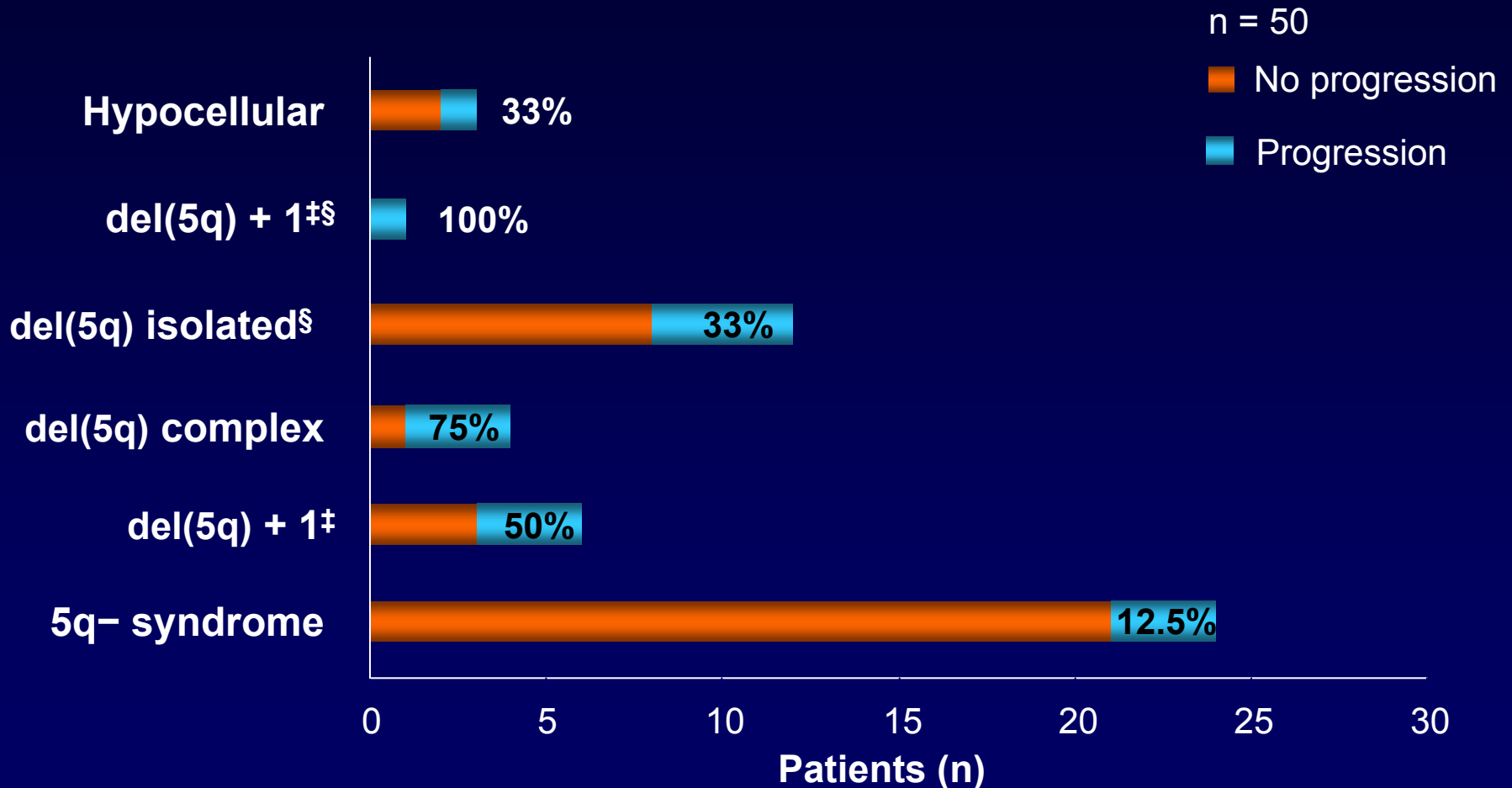
\*Neutropenic infection.

# MDS-003: Implication of Adverse Events

## Lenalidomide dose adjustment and discontinuation



# Lenalidomide does not induce AML transformation in del(5q) MDS



#1 additional chromosomal abnormality to del(5q).

§Patients with blasts > 5%.

# Conclusions

- **del(5q) is the most common cytogenetic abnormality found in MDS**
- **del(5q) MDS is not a uniform disease**
- **Lenalidomide offers effective treatment in patients with Low- or Int-1-risk MDS**
  - **yields high rate of erythroid and cytogenetic responses with prolonged duration of transfusion independence**
  - **restores haematopoiesis in a considerable number of patients, especially those with del(5q) MDS**