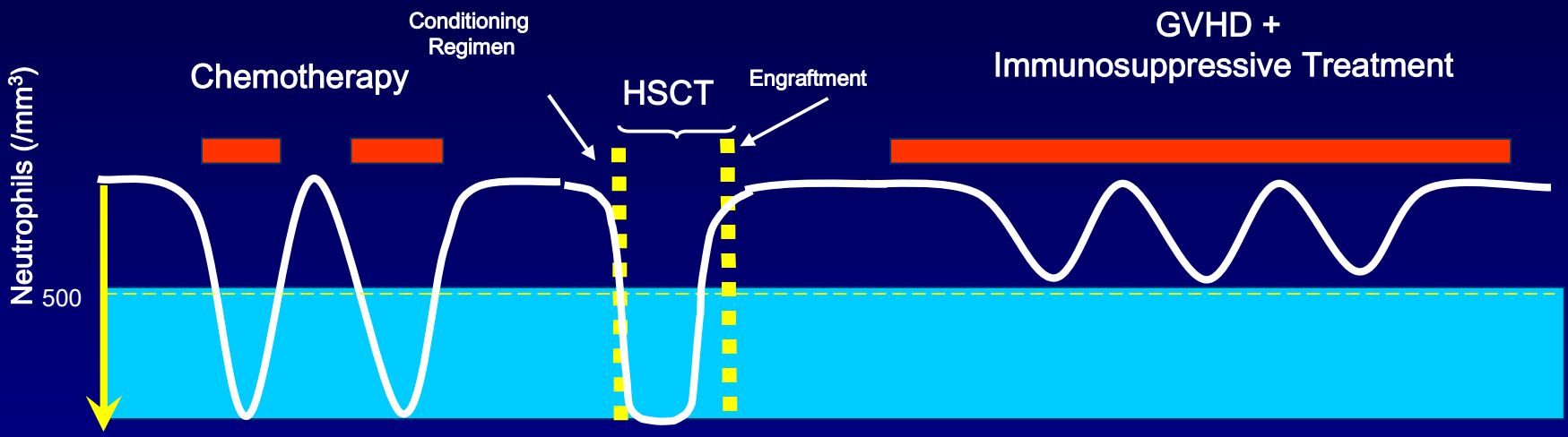
Therapy of Hematologic Malignancies
Period at high risk of IFI



Cutaneous and mucositis :
- Direct inoculation (Central catheter)
- ingestion or translocation (alimentation, intestinal flora)

- Inhalation, Fungal colonisation of GI tractus, mucositis

High Incidence of IFI in HSCT recipients :

- **35 %** in case of acute GVHD (grades III-IV)
- **39 %** in case of chronic GVHD chronique (*)

* Increase incidence because of RIC, PBSC and Cord blood cell using

Jantunen E *et al*,. Bone Marrow Transplant 1997;19 : 801-8

1st Case : The Story of de Mrs H

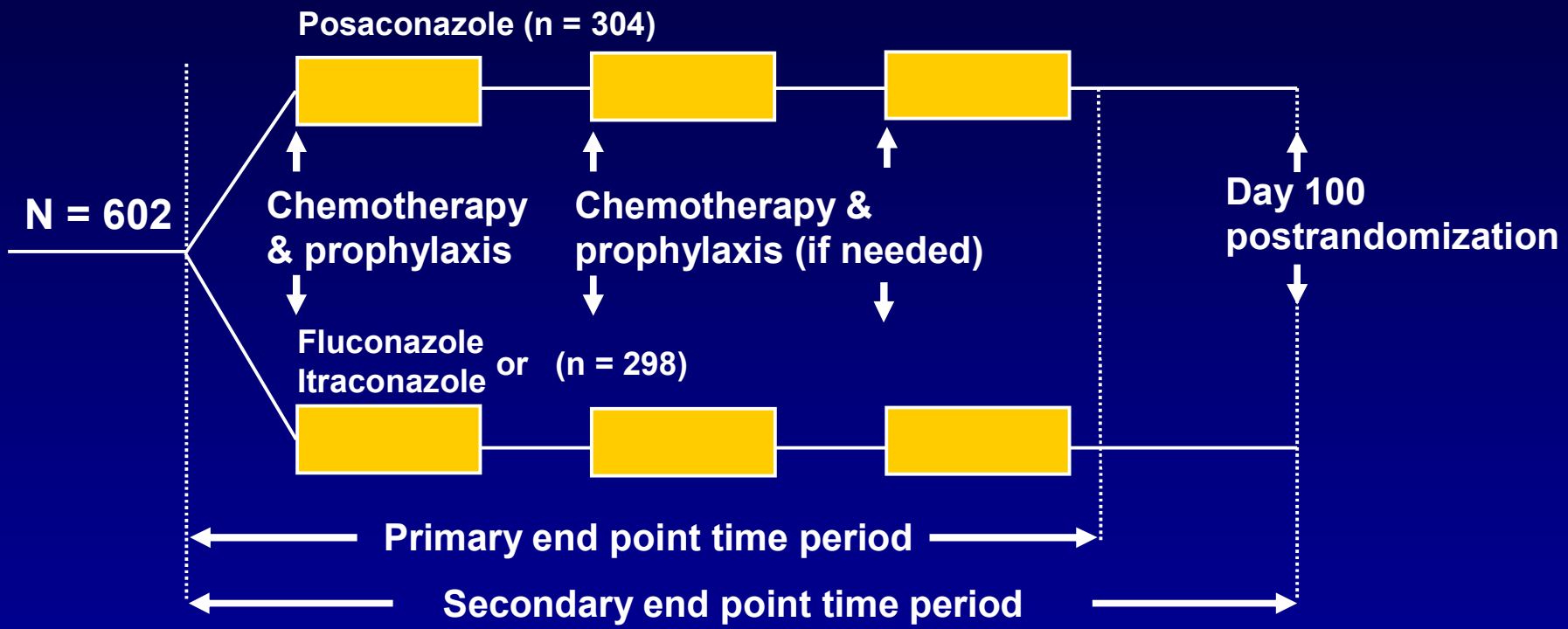
- Female, 35 years
- **AML 1** : Diagnosis in october 2006
- During **Induction Therapy**

  - We precribed Posaconazole PO 200 mg TID

  - She achieved a complete remission (CR1)

Posaconazole Prophylaxis in Neutropenic Patients

Study Overview



Treatment phase (on-treatment period): From randomization up to 7 days after last dose (primary end point time period).

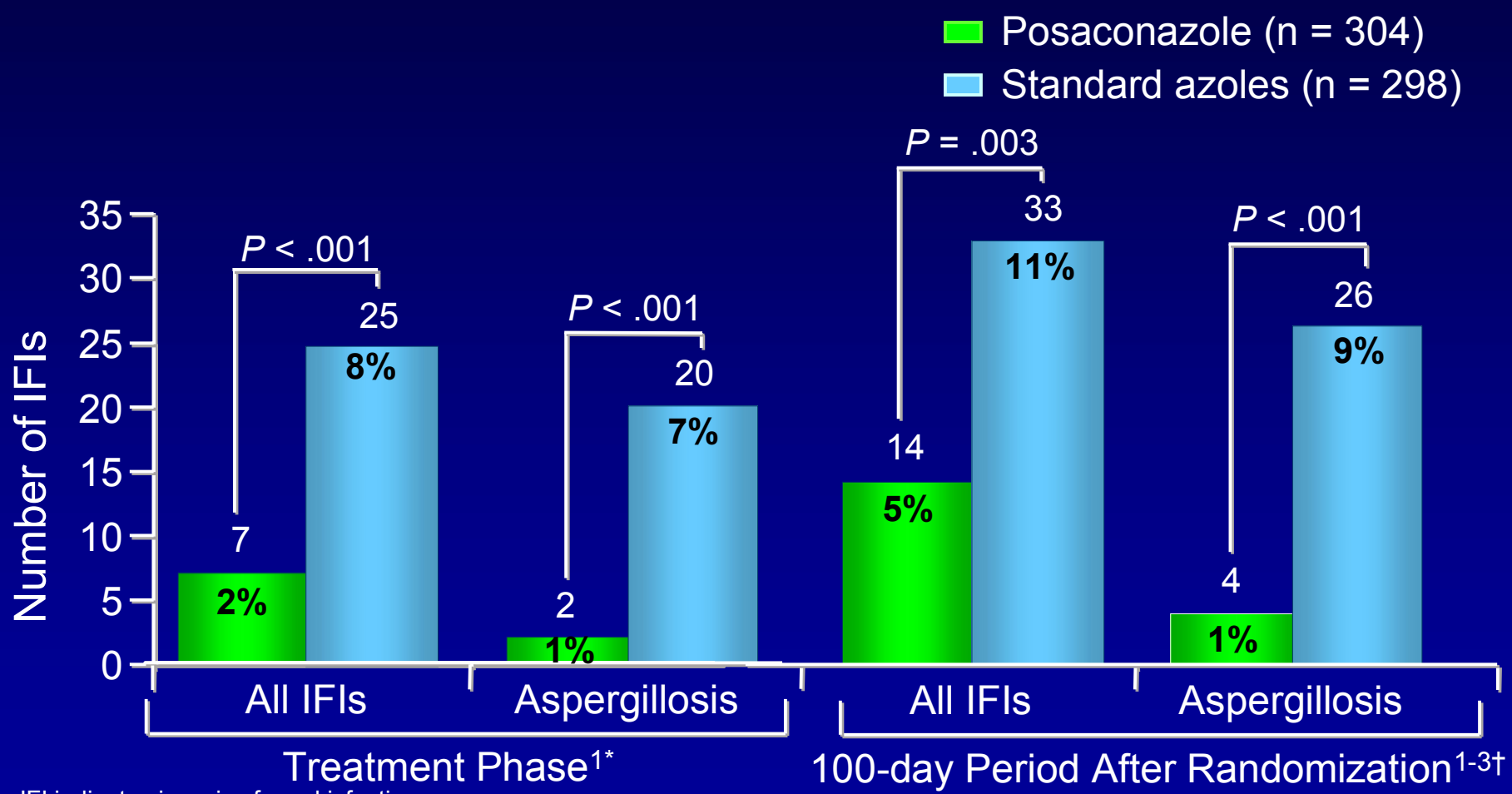
100-day period after randomization (fixed time period): 100 days after randomization (secondary end point time period).

Cornely OA et al. *N Engl J Med*. 2007;356:348-359.

Additional information available in Study Report P01899, p 3,4. SPRI, Kenilworth, NJ, USA; November 2005.

Posaconazole Prophylaxis in Neutropenic Patients

Results – Proven/Probable IFI



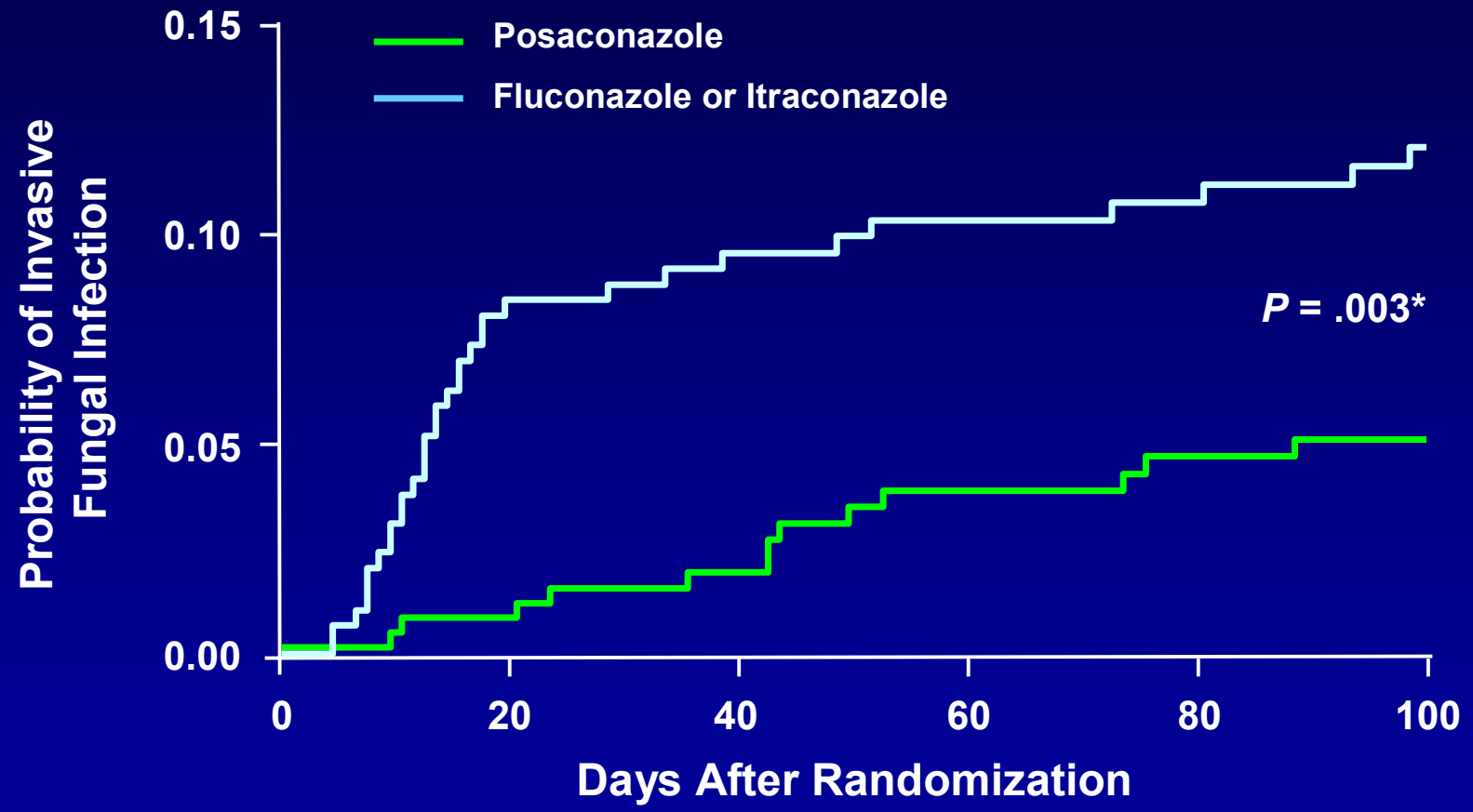
IFI indicates invasive fungal infection.

1. Noxafil [summary of product characteristics]. Brussels, Belgium; SP Europe; 2006.
2. Cornely OA et al. *N Engl J Med*. 2007;356:348-359.
3. Study report P01899, p 106,108,109. SPRI, Kenilworth, NJ, USA; November 2005.

*On-treatment period.
†Fixed-time period.

Posaconazole Prophylaxis in Neutropenic Patients

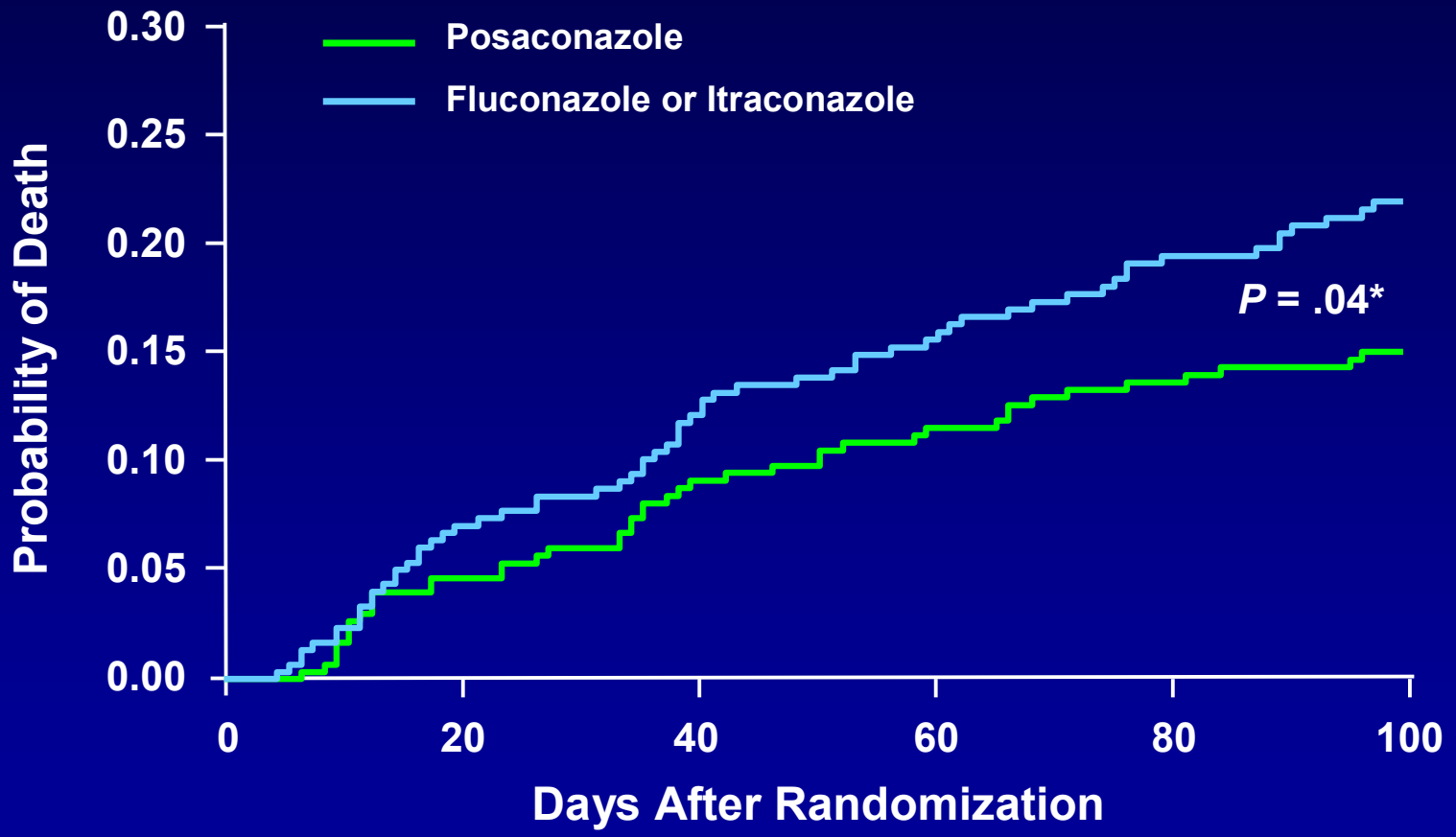
Results – Time to Invasive Fungal Infection



*Estimated using log-rank statistics.
Censoring time is the minimum of the last contact date and day 100.
Cornely OA et al. *N Engl J Med*. 2007;356:348-359.

Posaconazole Prophylaxis in Neutropenic Patients

Results – Death From Any Cause



*Estimated using log-rank statistics.
Censoring time is the minimum of the last contact date and day 100.
Cornely OA et al. *N Engl J Med*. 2007;356:348-359.

Prophylaxis in Neutropenic Patients
Serious Treatment-related AEs*

Event	Patients, n (%)			
		Standard Azoles		
	POS (n = 304)	FLU/ITZ (n = 298)	FLU (n = 240)	ITZ (n = 58)
Event possibly or probably related to treatment				
Total	19 (6)	6 (2)	4 (2)	2 (3)
Bilirubinemia	5 (2)	3 (1)	2 (1)	1 (2)
Increased hepatic enzymes	3 (1)	1 (<1)	1 (<1)	0
Increased alanine aminotransferase	1 (<1)	1 (<1)	0	1 (2)
Hepatic failure	1 (<1)	0	0	0
Hepatitis	1 (<1)	0	0	0
Hepatocellular damage	1 (<1)	0	0	0
Jaundice	1 (<1)	0	0	0
Diarrhea	1 (<1)	0	0	0
Atrial fibrillation	1 (<1)	0	0	0
Syncope	2 (1)	0	0	0
Decreased ejection fraction	1 (<1)	0	0	0
QT or QTc prolongation†	1 (<1)	0	0	0
Torsades de pointes	1 (<1)	0	0	0
Diplopia	0	1 (<1)	1 (<1)	0

* Events are listed for the period from randomization until 30 days after the last dose of the study drug had been administered. Numbers for subentries may not sum to the total numbers because patients could have more than 1 event.

†QTc denotes the QT interval corrected for heart rate. Prolongation was defined as a period of more than 450 msec for men and more than 470 msec for women.

Cornely OA et al. *N Engl J Med*. 2007;356:348-359.

The Story of de Mrs H

- **In January 2007** : She underwent an **Allogeneic HSCT** from an HLA Identical Unrelated Donor (10/10) after a myeloablative conditioning regimen combining Cyclophosphamide 120 mg/kg and TBI at 12Gy
- She received a gut decontamination and an antiviral prophylaxis from D-9 to D100

Do you prescribe an **Antifungal Prophylaxis?**

1) No Prophylaxis

2) Yes :

- Fluconazole PO
- Voriconazole PO
- Ambisome IV
- Caspofungine IV
- Posaconazole PO

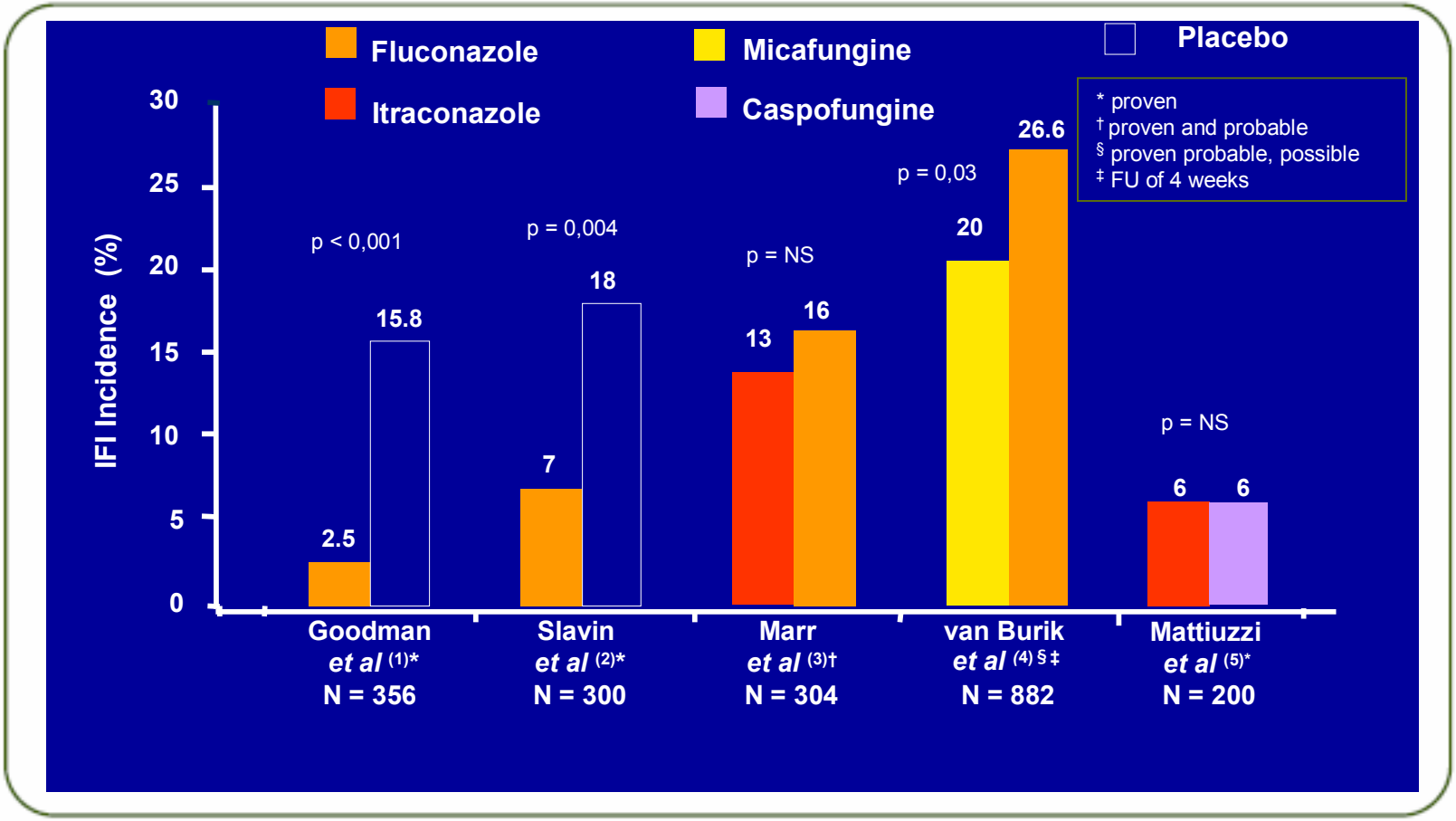
The story of de Mrs H

- We decided to give :

  Fluconazole PO 400 mg qd

Antifungal Prophylaxis

Hematologic Malignancies and Allogeneic HSCT



1. *Goodman JL et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med. 1992;326:845-51.*
2. *Slavin MA et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation-a prospective, randomized, double-blind study. J Infect Dis. 1995;171:1545-52.*
3. *Marr KA et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood. 2004;103:1527-33.*
4. *van Burik JA et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004; 39: 1407-16.*
5. *Mattiuzzi GN et al. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. Antimicrob Agents Chemother. 2006; 50:143-47.*

The story of de Mrs H

- She well engrafted without any immediate complication and she discharged on D28 with:
  - Neoral® PO (3 mg/kg/day)
  - Fluconazole PO 400mg qd
  - Oracilline, Valaciclovir and Bactrim®
- ***At Day 36 she developped an acute GVHD of Grade III*** that we treated with Methylprednisolone (2 mg/kg/day) with maintenance of Neoral

Antifungal Prophylaxis

- Do you maintain Fluconazole ?
- Do you switch ? For which molecule ?

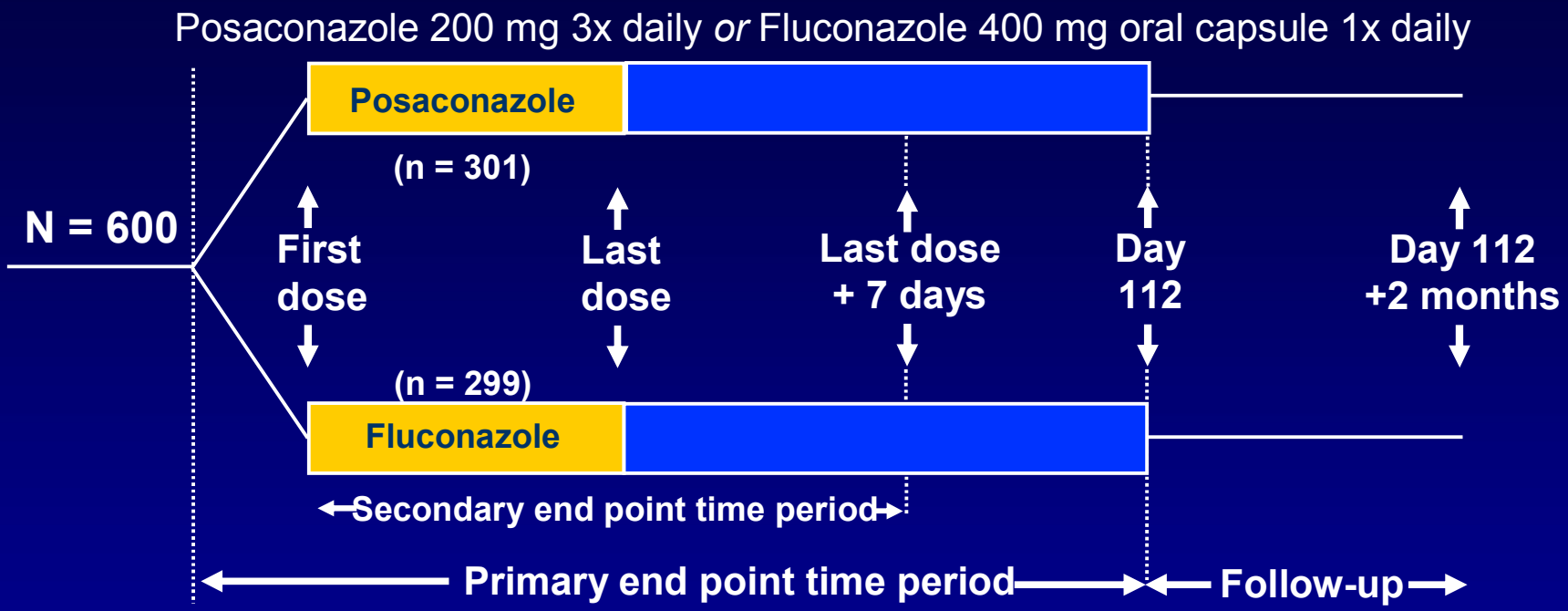
The story of de Mrs H

We decided to switch to :

Posaconazole PO 200mg TID

The evolution of the patient was good without any complications and any breakthrough fungal infections.

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD (Double-blind, randomized trial)



- **Fixed treatment period (fixed-time period) :** study period, 112 days
- **Exposure period (on-treatment period) :** time from first study drug dose to 7 days after last dose

Principal Objective : Determine efficacy of posaconazole versus fluconazole in preventing proven or probable IFI from randomization to 112 days after first dose

Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD

Characteristics	Posaconazole (n = 301)	Fluconazole (n = 299)
Acute graft-versus-host disease grade		
I	3 (1)	1 (<1)
II	135 (45)	136 (45)
III	52 (17)	54 (18)
IV	12 (4)	6 (2)
Chronic graft-versus-host disease		
Limited	2 (1)	1 (<1)
Extensive	96 (32)	99 (33)

Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD

	Posaconazole (n = 301)	Fluconazole (n = 299)
Aspergillus antigen, n (%)		
Positive (≥0.5 baseline)	21 (7)	30 (10)
Negative	259 (86)	243 (81)
Missing	21 (7)	26 (9)
Immunosuppressive agents, n (%)		
1	64 (21)	48 (16)
2	151 (50)	168 (56)
≥3	85 (28)	82 (27)
None	1 (<1)	1 (<1)
Prior antifungal therapy duration		
Mean ± SD	26.4 ± 39	35.3 ± 82
Median (range)	16 (0-254)	19 (0-1002)

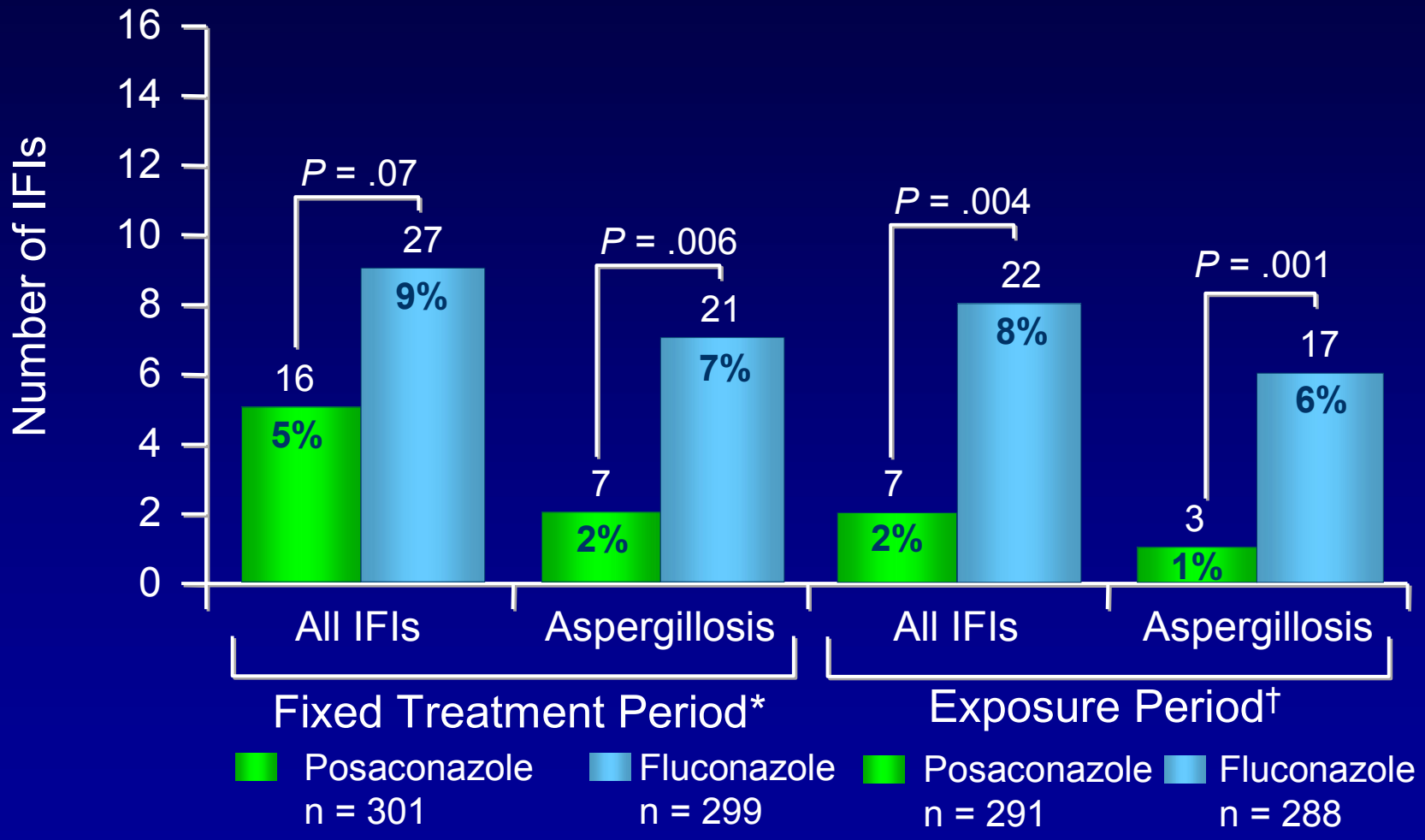
Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD

	Posaconazole (n = 301)	Fluconazole (n = 299)
Duration of prophylaxis, days		
Mean ± SD	80 ± 43	77 ± 43
Median (range)	111 (1-138)	108 (1-130)

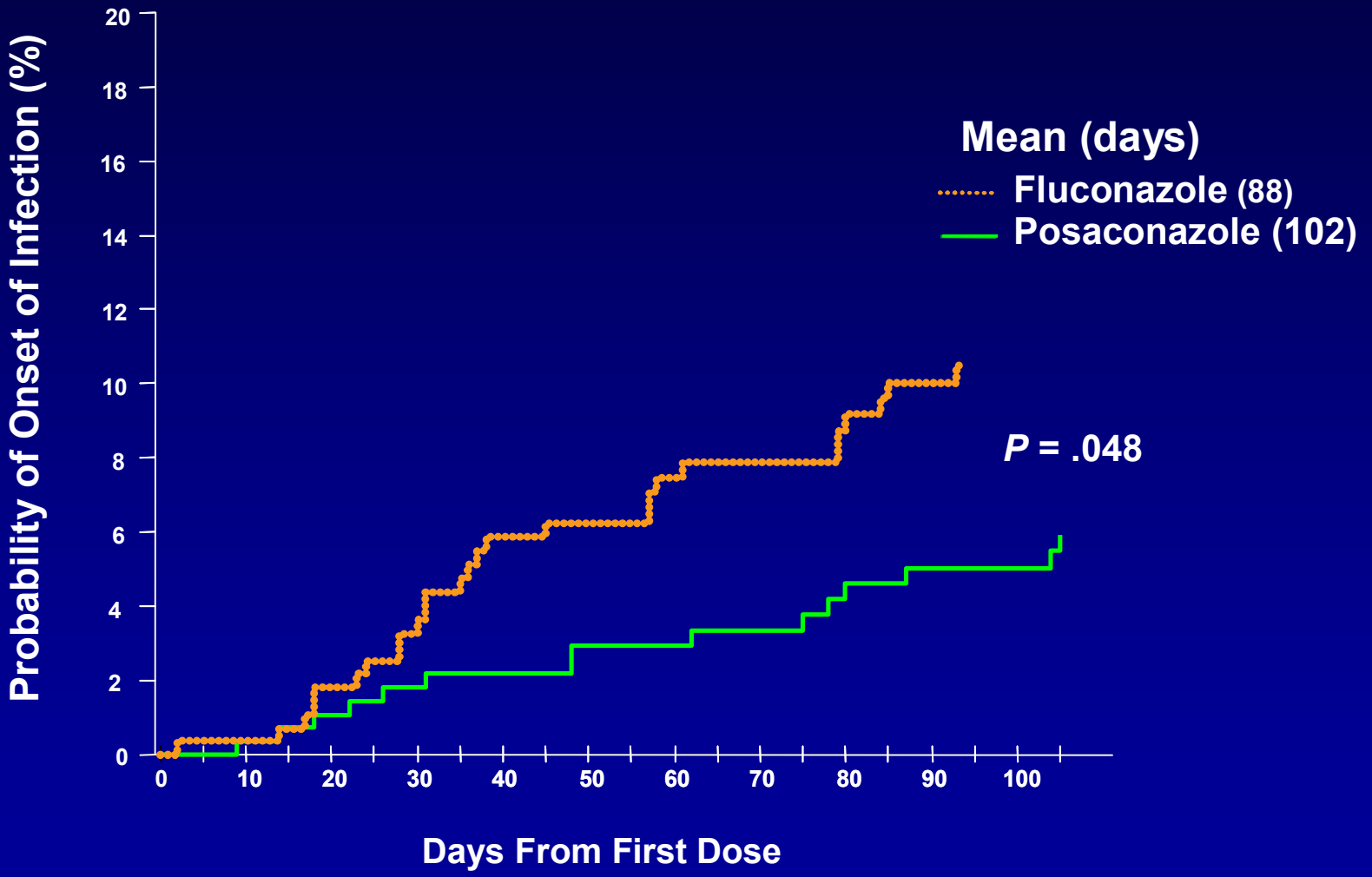
Ullmann AJ et al. *N Engl J Med*. 2007;356:335-34

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD



Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347.

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD



*

Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Posaconazole Prophylaxis in Allogeneic HSCT Recipients With GVHD

Cause of death (Investigator assessment), n (%)	Posaconazole n = 301	Fluconazole n = 299
Total deaths	76 (25)	84 (28)
Adverse event	39 (13)†	37 (12)
Complications related to invasive fungal infection	4 (1)‡	12 (4)†
Progression of underlying disease/graft-versus-host disease	31 (10)	33 (11)
Other	2 (1)	2 (1)

No significant difference in time to death (*P* = .847) between groups

†P = .01 by Chi-square test.
‡*P* = .046 by log-rank test.

Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Prophylaxis in Allogeneic HSCT Recipients With GVHD

Body System/Preferred Term	Patients, n (%)	
	Posaconazole (n = 301)	Fluconazole (n = 299)
Subjects reporting any AE	107 (36)	115 (38)
Body as a whole – General disorders		
Anorexia	3 (1)	7 (2)
Dizziness	4 (1)	5 (2)
Drug level altered	5 (2)	2 (1)
Fatigue	4 (1)	6 (2)
Headache	3 (1)	8 (3)
Weakness	3 (1)	5 (2)
Cardiovascular disorders, general		
Hypertension	2 (1)	5 (2)
Central and peripheral nervous system disorders		
Tremor	4 (1)	6 (2)
Disorders of the eye		
Vision blurred	3 (1)	5 (2)

Supplementary Appendix to: Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

Prophylaxis in Allogeneic HSCT With GVHD

Body System/Preferred Term	Patients, n (%)	
	Posaconazole (n = 301)	Fluconazole (n = 299)
Gastrointestinal system disorders		
Abdominal pain	4 (1)	7 (2)
Constipation	1 (<1)	5 (2)
Diarrhea	8 (3)	12 (4)
Dyspepsia	3 (1)	6 (2)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Liver and biliary system disorders		
Bilirubinemia	8 (3)	5 (2)
GGT increased	9 (3)	7 (2)
Hepatic enzymes increased	8 (3)	7 (2)
Aspartate aminotransferase increased	8 (3)	3 (1)
Alanine aminotransferase increased	9 (3)	4 (1)

Supplementary Appendix to: Ullmann AJ et al. *N Engl J Med*. 2007;356:335-347

ECIL

UPDATE ECIL-2 2007

Antifungal prophylaxis in leukemia patients

- Allogeneic hematopoietic stem cell transplantation
  - Fluconazole 400 mg qd iv/oral: AI[2]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Micafungin 50 mg qd iv: CI
  - Polyene[4] iv: CI
- Induction chemotherapy of acute leukemia
  - Fluconazole 50-400 mg qd iv/oral: CI[2]
  - Itraconazole oral solution 2.5 mg/kg bid: CI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Candins iv: insufficient data
  - Polyene[4] iv: CI

1st European Conference on Infection in Leukemia

1 may be limited by drug interactions and/or patient tolerability
2 azoles should not be used empirically in case of prior azole prophylaxis
3 it is recommended to monitor serum drug concentrations
4 includes low doses of conventional amphotericin B and lipid formulations. The ECIL recommendation for aerosolized amphotericin B is DI

IDSA

Table 2. *(Continued.)*

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Cutaneous aspergillosis	...[f]	Similar to invasive pulmonary aspergillosis	Surgical resection is indicated where feasible
Aspergillus peritonitis	...[f]	Similar to invasive pulmonary aspergillosis	...
Empirical and preemptive antifungal therapy	For empirical antifungal therapy, L-AMB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), itraconazole (200 mg every day IV or 200 mg BIDI, voriconazole (6 mg/kg IV every 12h for 1 day, followed by 3 mg/kg IV every 12 h; oral dosage is 200 mg every 12 hl	...	Preemptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result)
Prophylaxis a aspergillosi	[redacted]	[redacted]	of posaconazole laxis demonstrated in high-risk patients with patients with and neutropenic ts with AML and MDSI
Aspergilloma[g]	No therapy or surgical resection	Itraconazole or voriconazole; similar to invasive pulmonary aspergillosis	The role of medical therapy in treatment of aspergilloma is uncertain; penetration into preexisting cavities may be minimal for AMB but is excellent for itraconazole
Chronic cavitary pulmonary aspergillosis[g]	Itraconazole or voriconazole	Similar to invasive pulmonary aspergillosis	Innate immune defects demonstrated in most of these patients; long-term therapy may be needed; surgical resection may lead to significant complications; antal responses to
Allergic bronc aspergillosi	[redacted]	[redacted]	steroids are a cornone of therapy; nazole has a demonstrable corticosteroid-sparing effect
Allergic aspergillus sinusitis	None or itraconazole	Few data on other agents	...

1st case: Conclusion

- In acute myelogenous leukemia patients with neutropenia due to chemotherapy, posaconazole was
  - Significantly better than pooled standard azoles for prophylaxis for *Candida* and *Aspergillus* infections
  - Associated with a decrease in all cause mortality at day 100
- In hematopoietic stem cell transplant recipients with graft versus host disease, posaconazole was
  - Significantly better than fluconazole for prophylaxis for *Candida* and *Aspergillus* infections during the exposure period*
  - Associated with a reduction in invasive fungal infection-related mortality
- Posaconazole has a safety profile comparable to fluconazole

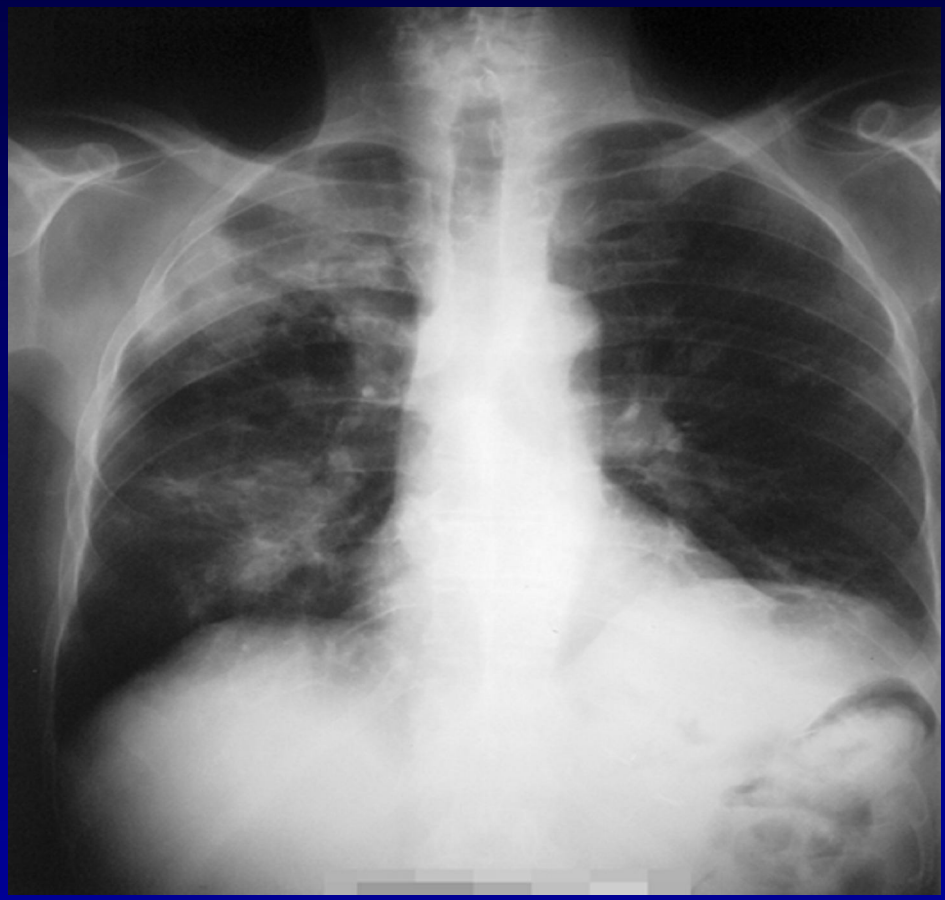
*On-treatment period.

2nd Case: The story of de Mrs B

- The similar story in the beginning but patient maintained fluconazole when she developed GVHD
- At D 70 : she developed a **Fever, a productive cough**, **a chest pain** and she was hospilalized.

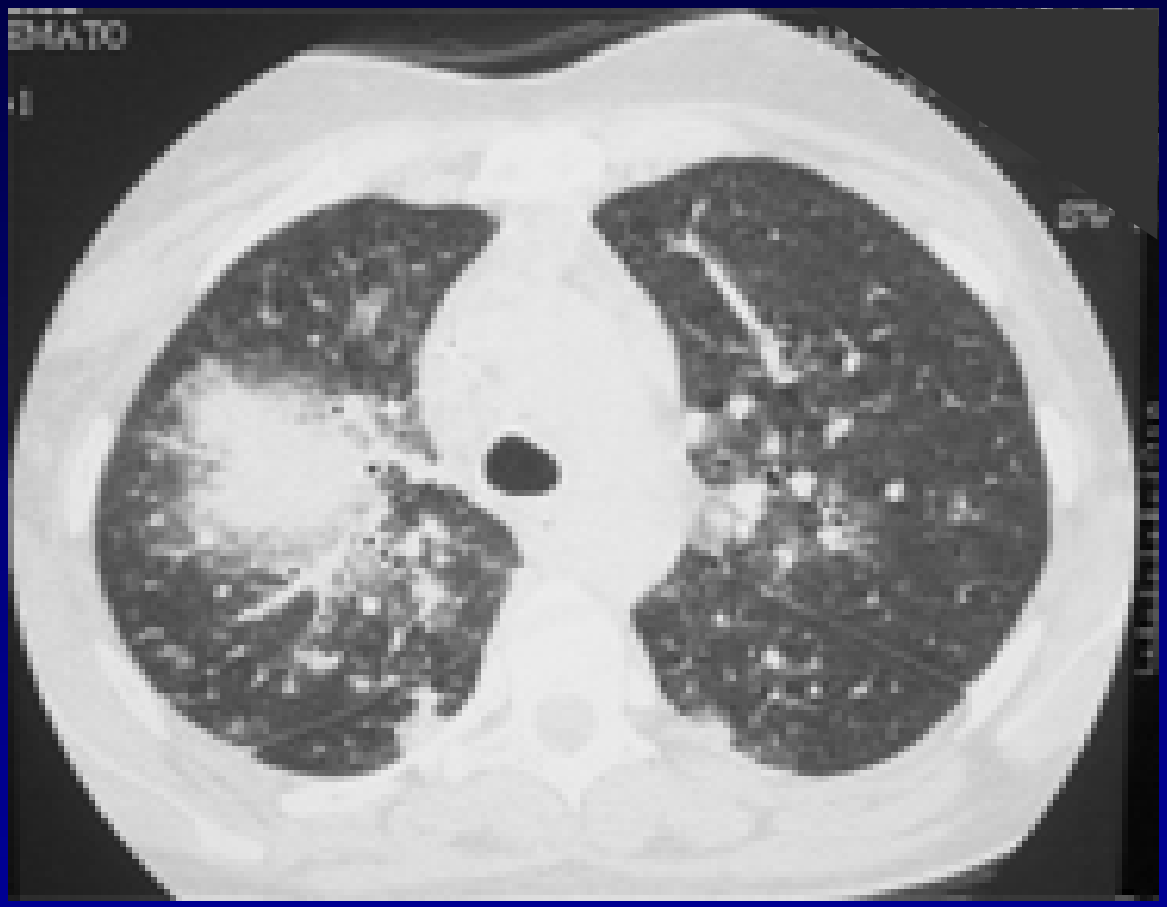
The leucocyte count *showed 11800/mm³ (10600 Neutro)*
GM Antigenemia *was positive at a level of 2.9*
The Fibrinogen level *was 11.7 g/L*

The story of de Mrs B



Chest Xray

The story of de Mrs B



Scanner

It is a probable Invasive pulmonary Aspergillosis according to the EORTC criteria

What do you do ?

- Complementary exams ?
- Specific Treatment ?

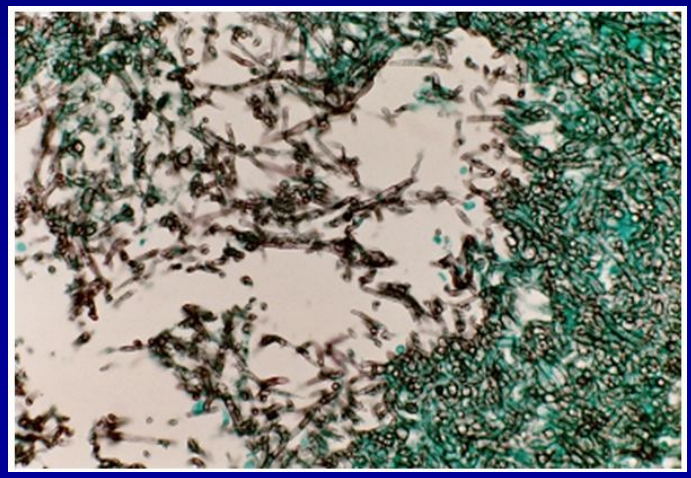
The story of de Mrs B

We do :

A Bronchoalveolar Lavage which showed :

- Mycellar filaments at the direct exam and culture showed an Aspergillus Fumigatus

- BAL : Ag+



Diagnosis of Proven **Pulmonary Apergillosis**

Choice of **Antifungal Treatment**

- Voriconazole IV then *PO* ?
- Voriconazole *PO* ?
- Caspofungine *IV* ?
- Ambisome *IV* ?
- Posaconazole *PO* ?
- Amphotericine *B* ?
- Combinations ?

The story of de Mrs B

- It is a proven IFI (IPA)
- We decided to give :

Ambisome IV

Treatment of First Line
International Recommendations

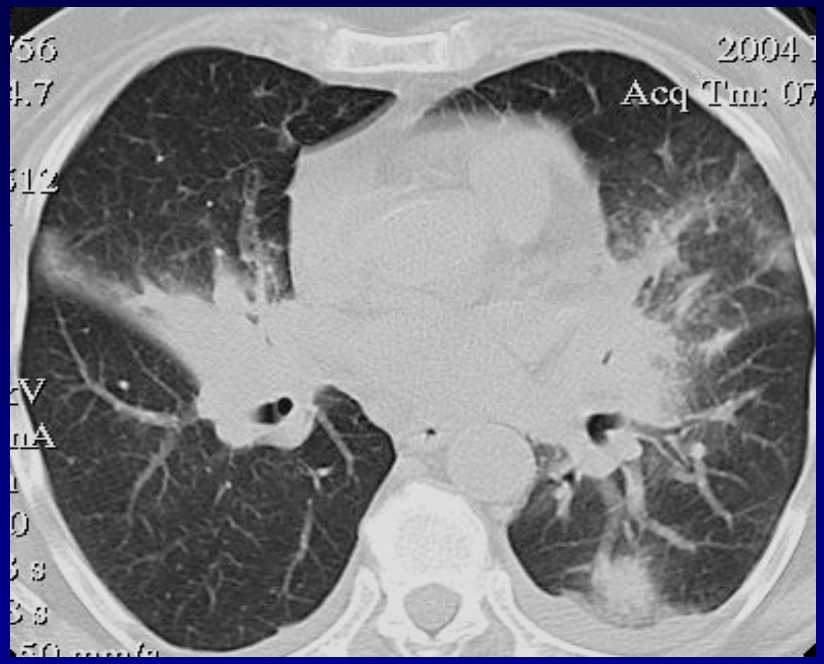
ECIL 2007

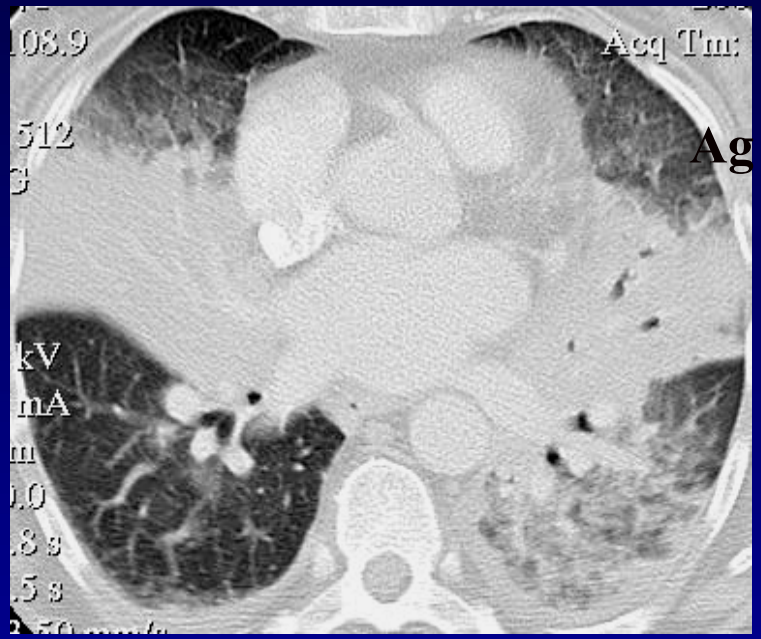
- Voriconazole : AI
- Ambisome : BI
- Combinations : not recommended

IDSA 2008

- Voriconazole : AI
- Ambisome : AI
- Combinations : not recommended

The story of de Mrs B





Evolution of the Scanner over time on Ambisome IV

What do you do in front of IFI worsening?

- A new monotherapy :
  - Caspofungine IV?
  - Voriconazole IV ?
  - Posaconazole PO ?
  - Other monotherapies ?

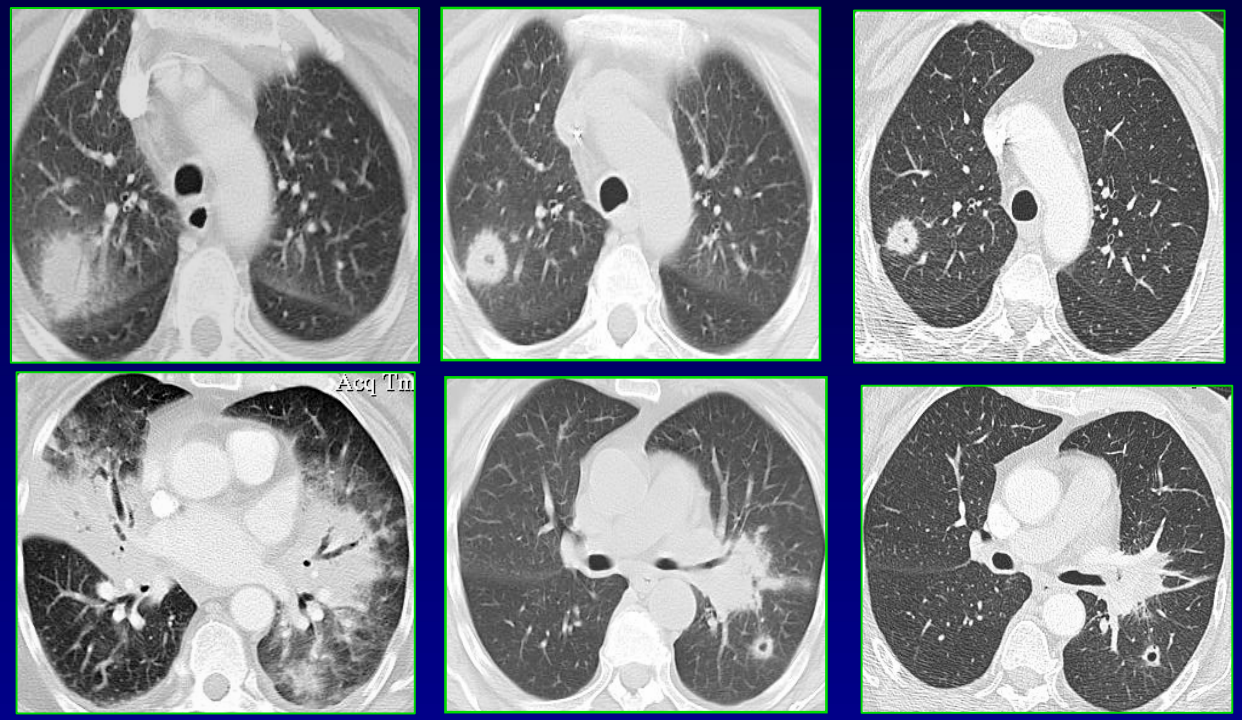
- A combination of antifungal molecules ?

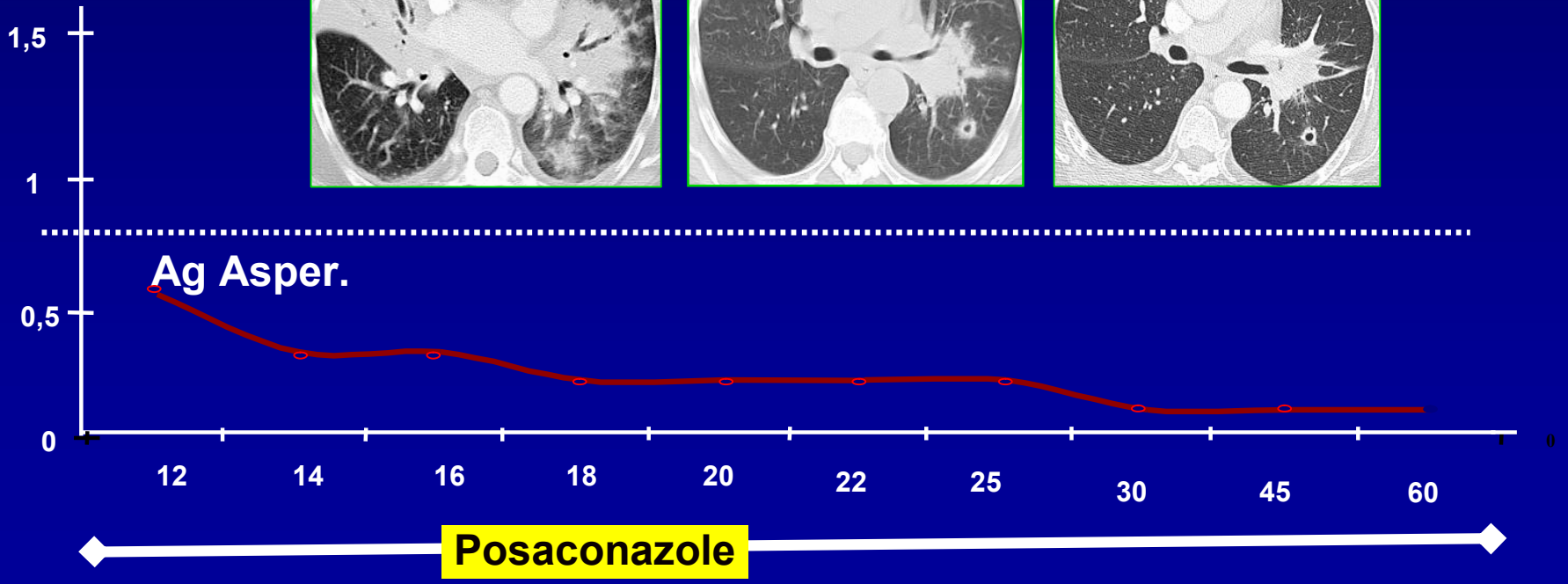
The story of de Mrs B

We decided to give

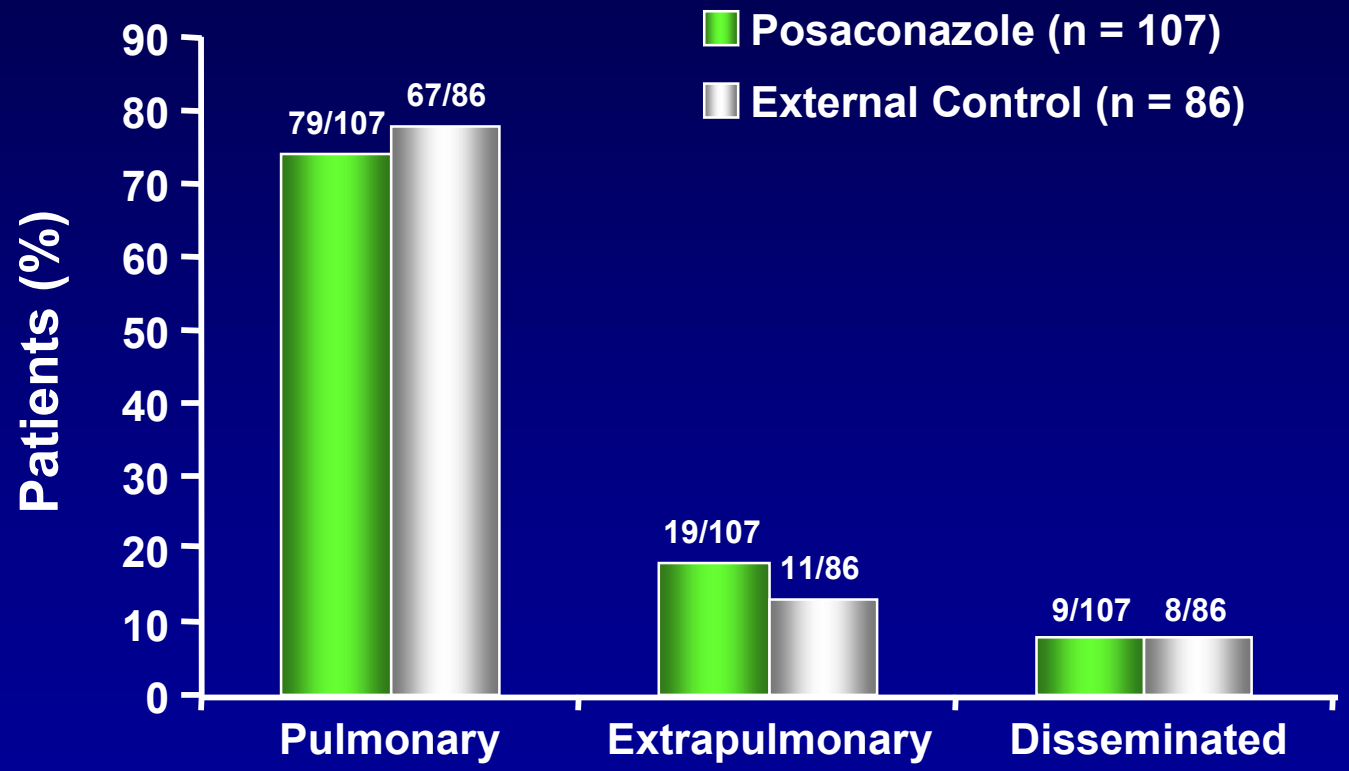
Posaconazole PO 400 mg X 2 / day

The story of de Mrs B



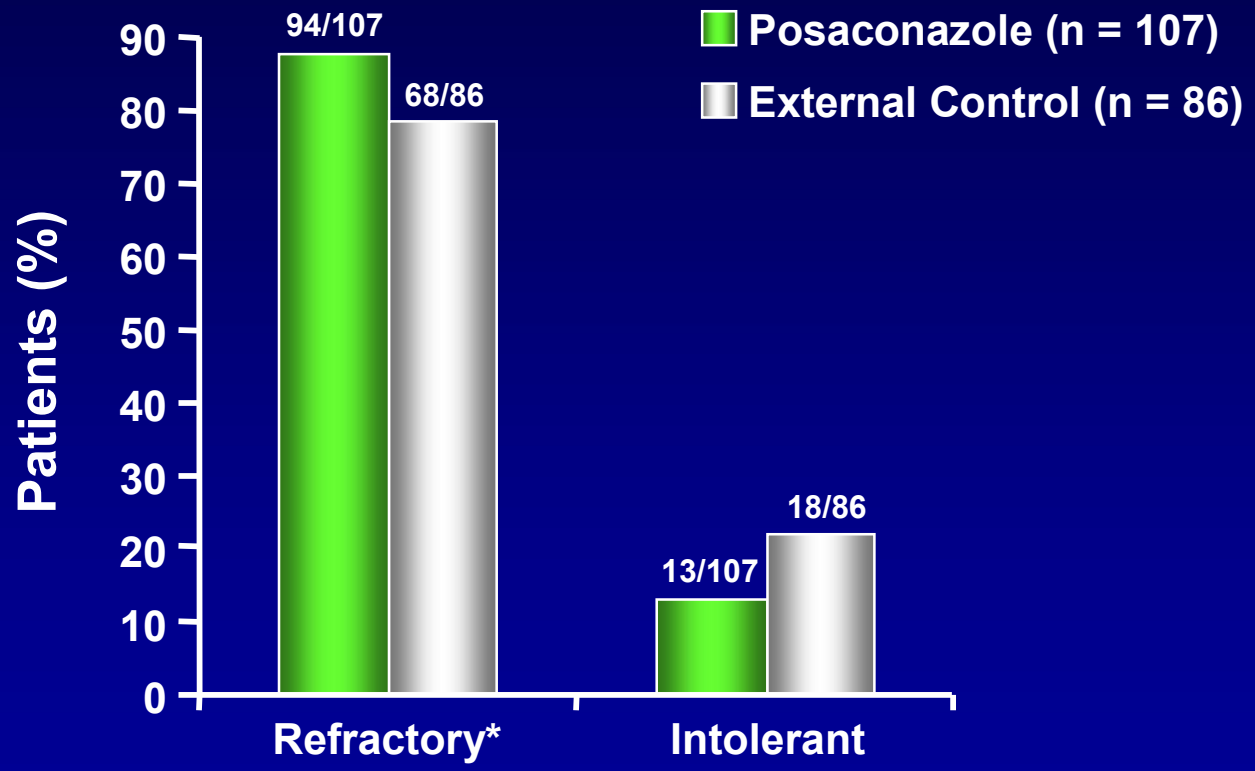


Posaconazole Treatment of Refractory Invasive Fungal Infections



Walsh T et al. *Clin Infect Dis*. 2007;44:2-12

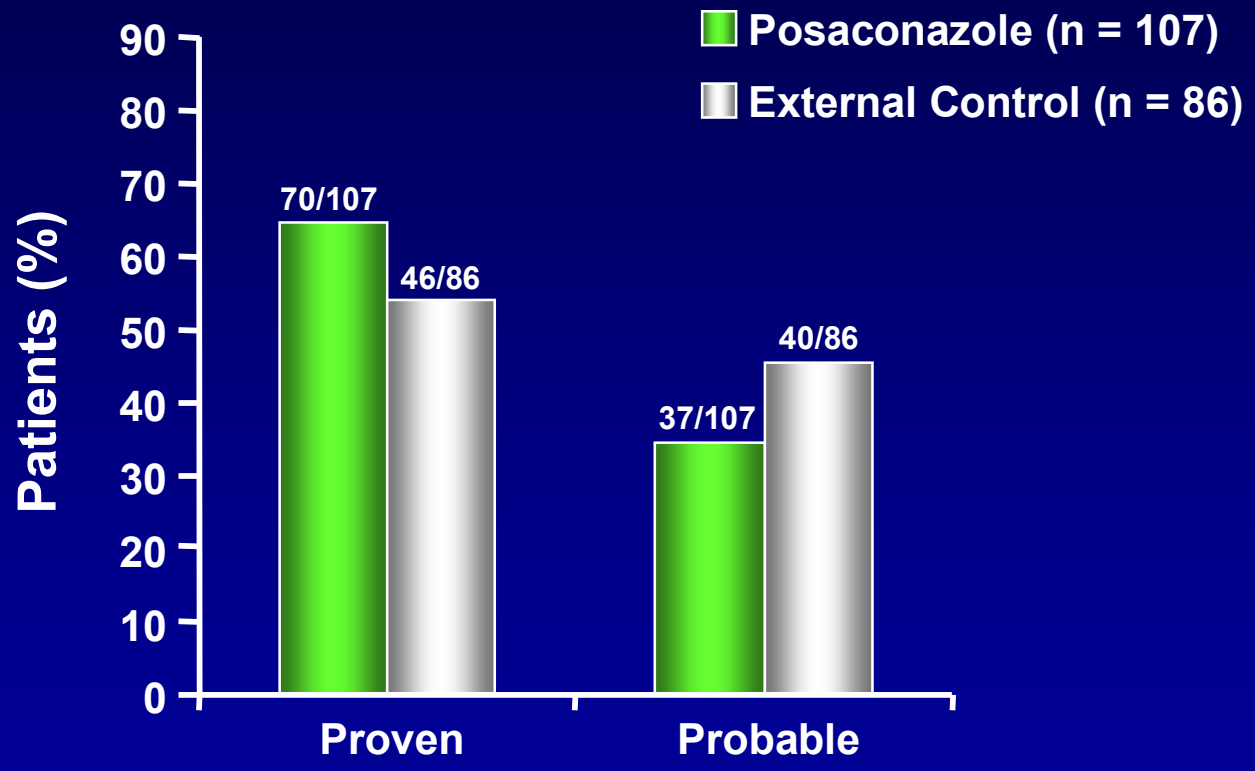
Posaconazole Treatment of Refractory Invasive Fungal Infections



*Includes subjects who were both refractory and intolerant.

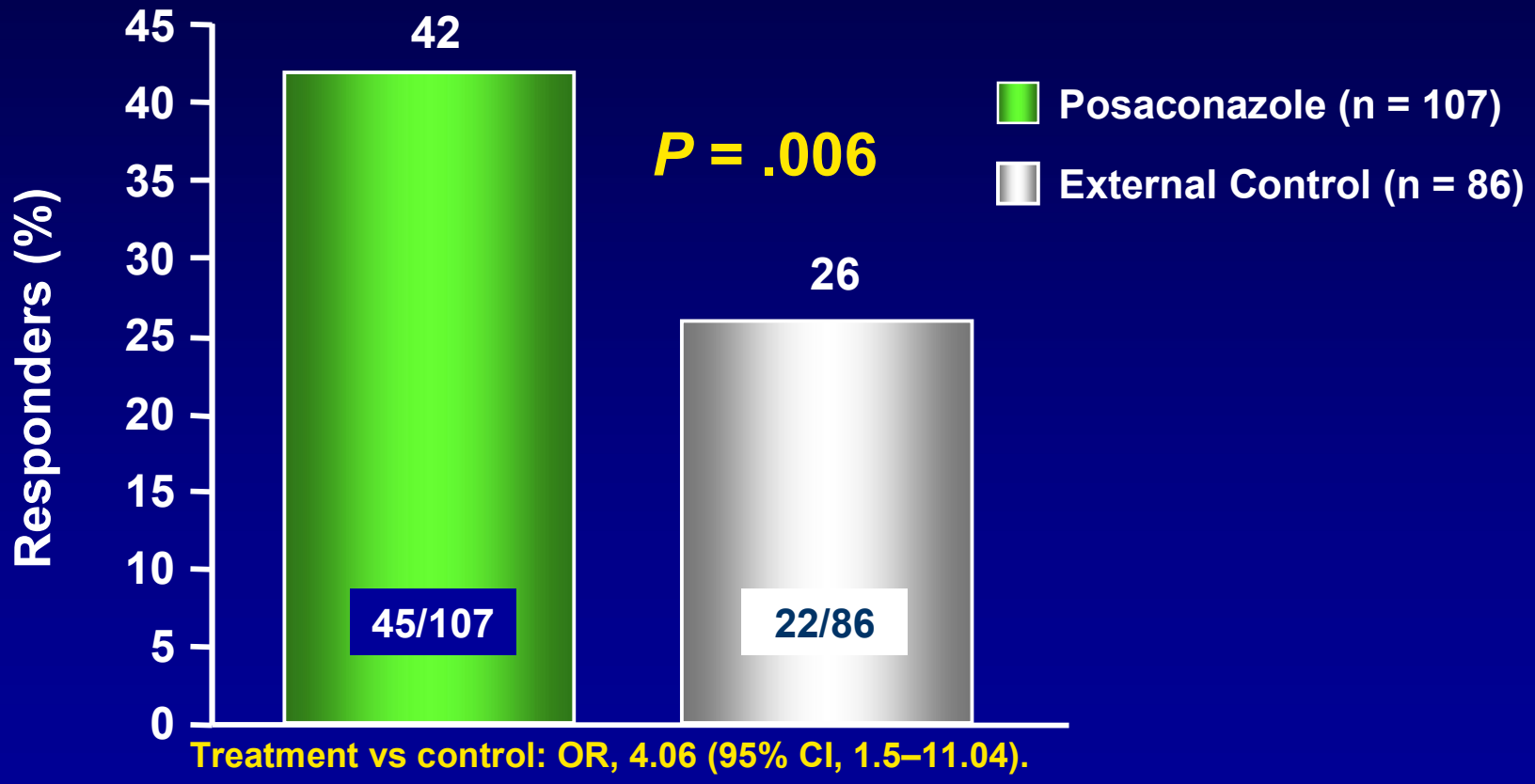
Walsh T et al. *Clin Infect Dis*. 2007;44:2-12

Posaconazole Treatment of Refractory Invasive Fungal Infections



Study report P02952, p 87. SPRI, Kenilworth, NJ, USA; March 2004

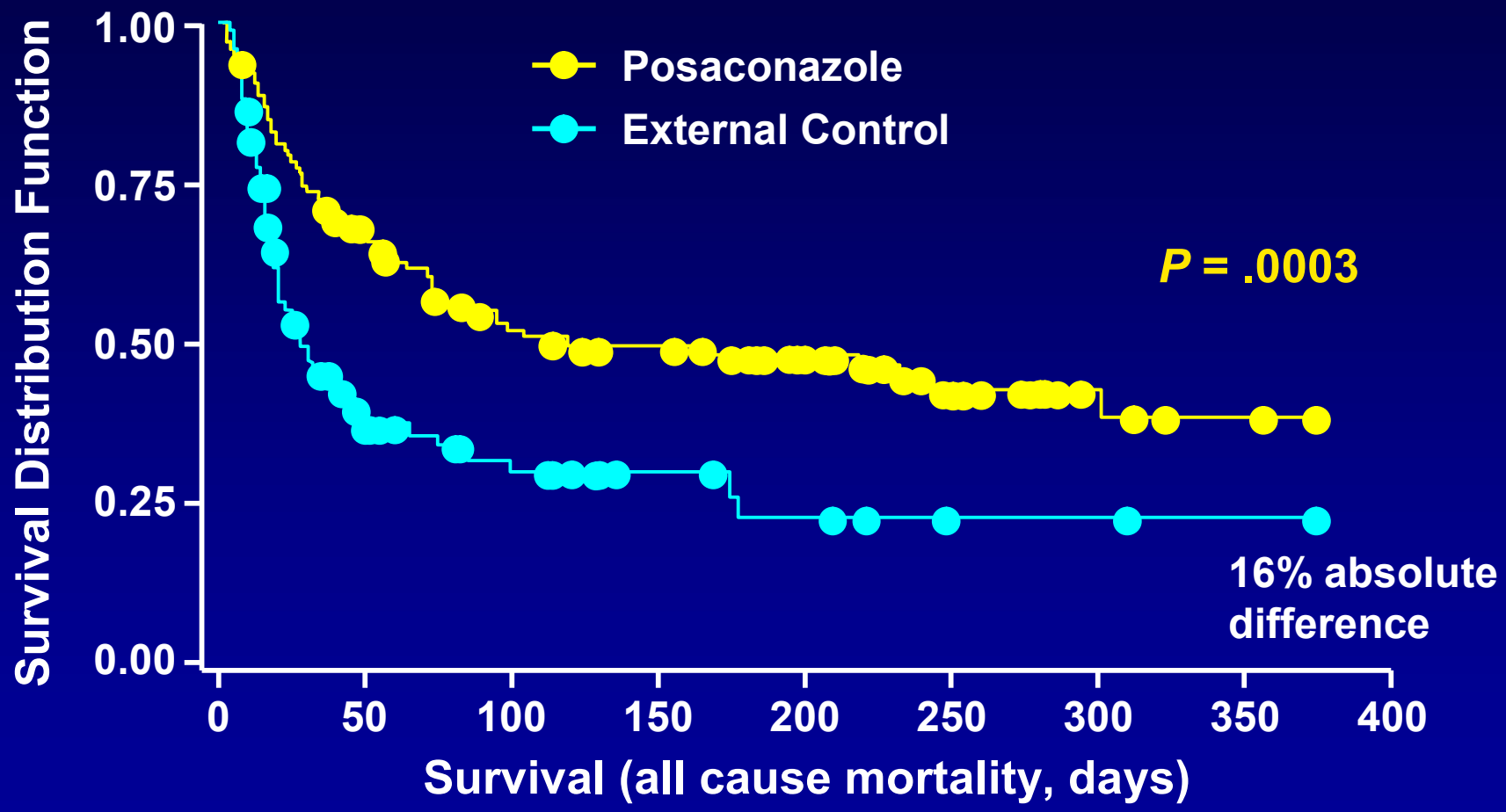
PosaconazoPosaconazole Treatment of Refractory Invasive Fungal Infections



*Primary efficacy analysis (logistic regression).

Walsh T et al. *Clin Infect Dis*. 2007;44:2-12

Posaconazole Treatment of Refractory Invasive Fungal Infections



Walsh T et al. *Clin Infect Dis*. 2007;44:2-12

Posaconazole Treatment of Refractory Invasive Fungal Infections

Clinical evidence demonstrates posaconazole is an effective option for invasive aspergillosis refractory to amphotericin B or itraconazole or in patients intolerant of these agents

Response, n/total (%)	Posaconazole	External Control
Overall response	45/107 (42)	22/86 (26)*
All *Aspergillus* spp†	34/76 (45)	19/74 (26)
A fumigatus	12/29 (41)	12/34 (35)
A flavus	10/19 (53)	3/16 (19)
A terreus	4/14 (29)	2/13 (15)
A niger	3/5 (60)	2/7 (29)

Posaconazole therapy conferred a survival benefit

**P* = .006.
†Mycologically confirmed *Aspergillus* species including other less known or unknown species

Walsh T et al. *Clin Infect Dis*. 2007;44:2-12

Posaconazole for Zygomycosis

- Posaconazole resulted in a 60% success rate in patients with zygomycosis
  - Additional 21% of patients had stable disease
- Successful outcomes were observed in patients regardless of
  - Infection site
  - Predisposing condition
  - Enrollment reason
  - Primary pathogen
- Posaconazole may offer an alternative oral treatment to amphotericin B for zygomycosis

van Burik J-A et al. *Clin Infect Dis*. 2006;42:e61-e65.