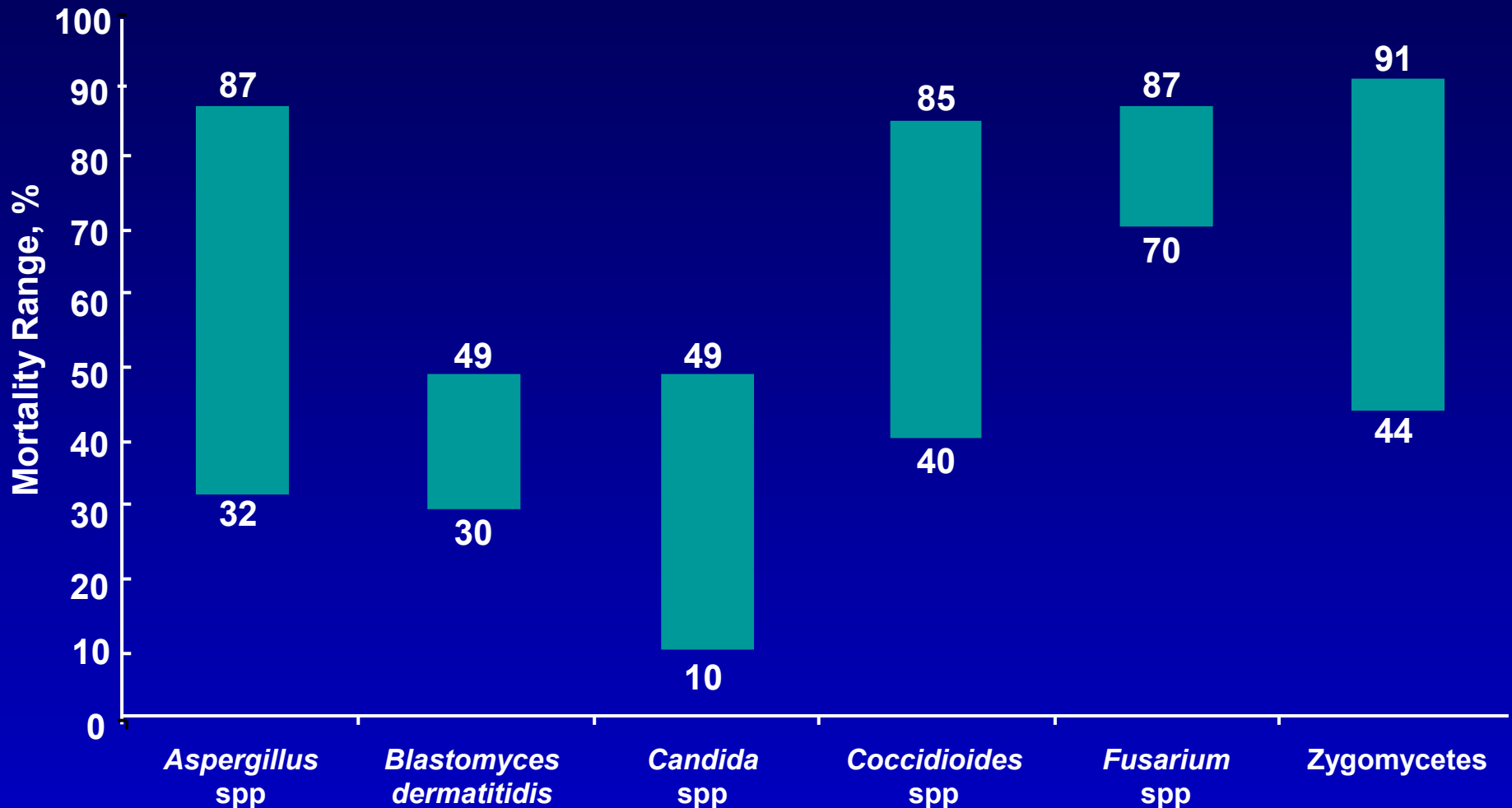# Why Not Use Antifungal Prophylaxis?

1. Low incidence of IFIs but still high mortality
2. Risk for antifungal resistance
3. IFIs can be managed empirically
4. Cost of prophylaxis is high
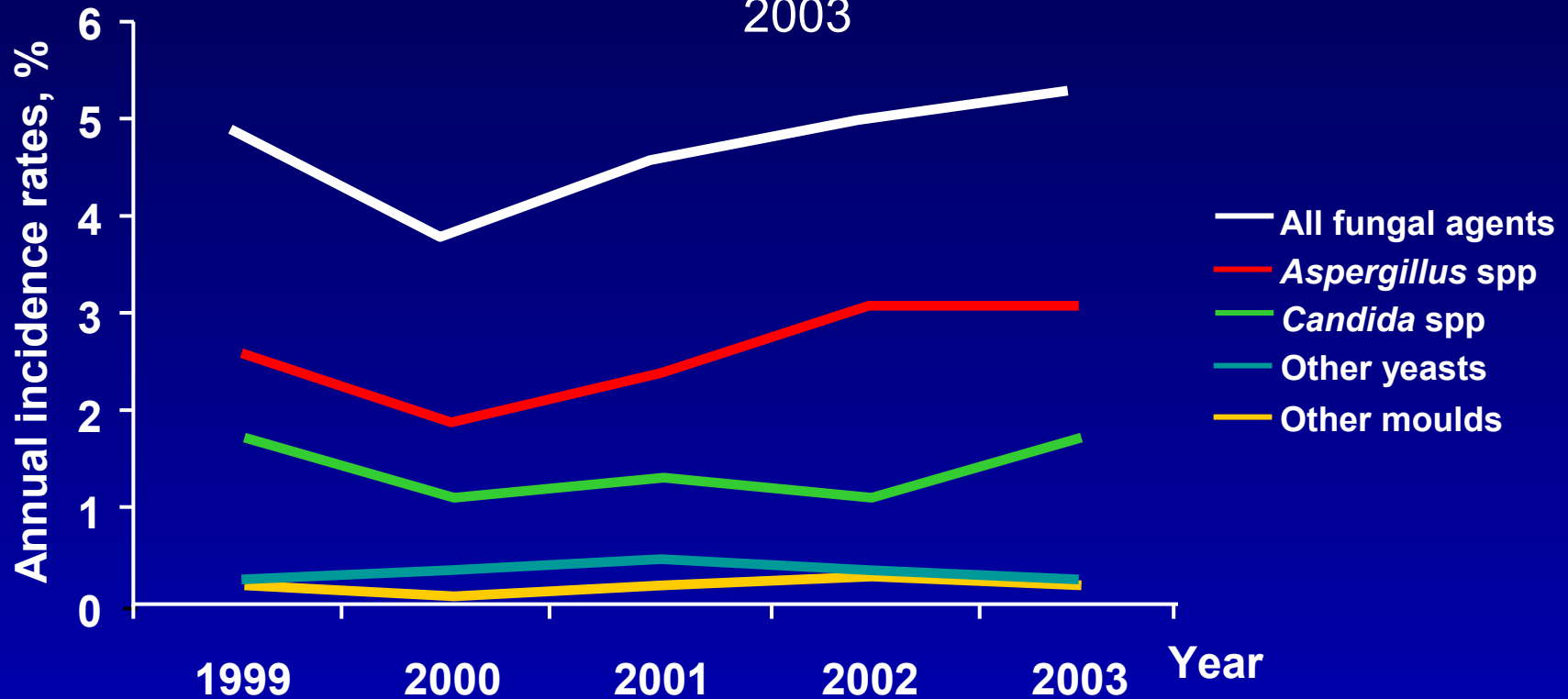5. Prophylaxis may unnecessarily expose patient to drug

IFIs Are a Substantial Source of Mortality in Patients at High-risk

Mortality Range, %

Species	Range
Aspergillus spp	32–87
Blastomyces dermatitidis	30–49
Candida spp	10–49
Coccidioides spp	40–85
Fusarium spp	70–87
Zygomycetes	44–91

Cornely O et al. *Infection*. 2008;36:296.

The incidence of IFIs is increasing

Annual incidence rates for IFIs in patients with hematologic malignancies from 18 centers in Italy between 1999 and 2003
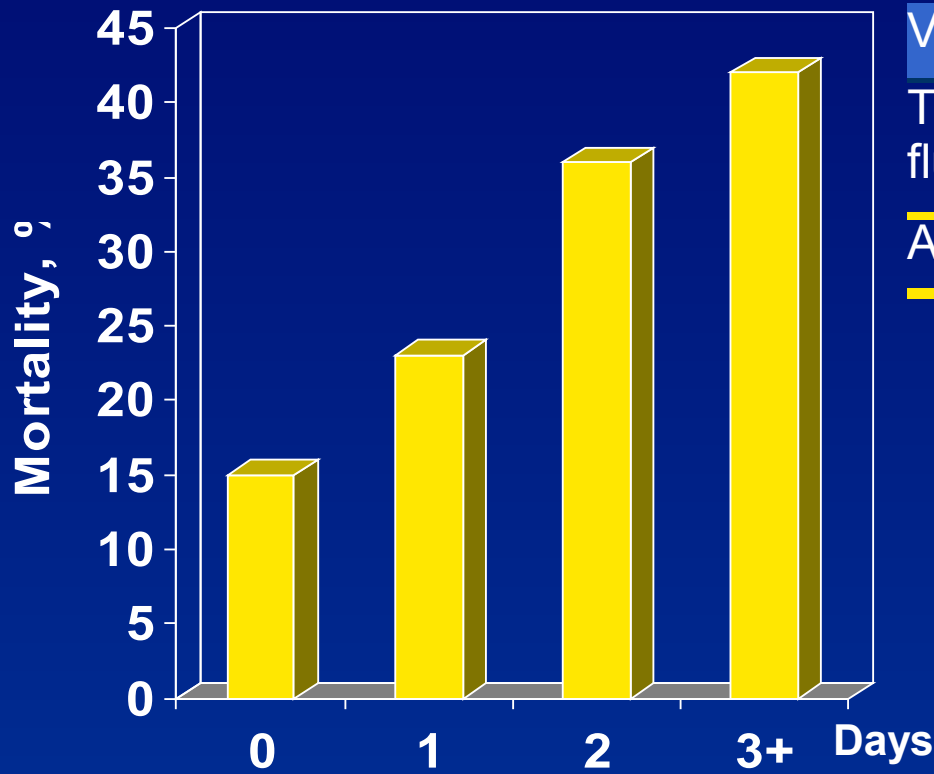

- **All fungal agents**
- **Aspergillus spp**
- **Candida spp**
- **Other yeasts**
- **Other moulds**

- *Aspergillus* **spp :** Aspergillosis was responsible for 62% of all IFI-related deaths in patients with hematologic malignancies
- *Candida* **spp :** Bloodstream infection caused by C glabrata, which is resistant to fluconazole, have significantly increased from 1989-1999 (P = .05)

Pagano L et al. *Haematologica*. 2006;91:1068
Herbrecht R et al. *N Engl J Med.* 2007;347:408

Early Intervention is Important

Up to 70% patients do not receive antifungals within 24 hours + blood

Mortality, %

Days: 0, 1, 2, 3+

Mortality vs. number of days to initiate fluconazole after culture done

Multivariate model independent risk factors for hospital mortality

Variable	Odds Ratio	*P* Value
Time to start fluconazole	1.50	0.014
APACHE II	1.13	<0.001

Garey KW et al. *Clin Infect Dis*. 2006;43:25.

Success Rates with Empiric Therapy

Treatment	Patients, n	Overall Success Rate, %	Resolution of Baseline Infections, %
Conventional AmB	344	49.4	72.7
vs			
L-AmB[1]	343	50.1	81.8
Voriconazole	415	26.0	46.2
vs			
L-AmB[2]	422	30.6	66.7
Caspofungin	556	33.9	51.9
vs			
L-AmB[3]	539	33.7	25.9

1. Walsh TJ et al. *N Engl J Med*. 1999;340:764.
2. Walsh TJ et al. *N Engl J Med*. 2002;346:225.
3. Walsh TJ et al. *N Engl J Med*. 2004;351:1391.

IFI Cost Estimation

Societal Perspective

- **Initial Hospitalizations**

	GVHD	AML
GHS	5 079 €	6 189 €
(Extension of hospitalization) EXH	10 713 €	3 571 €
STF (LAF Room)	0 €	3 961 €
Total	15 792 €	13 721 €

- **Mean cost of antifungal treatment**

	GVHD	AML
	46 056 €	35 967 €

- **Other Hospitalizations**

	GVHD	AML
	5 567 €	1 345 €

Total cost	GVHD	AML
	67 415 €	51 033 €

IFI Incidence and Unit Costs

- **IFI incidence :**
  - Posaconazole : 4.5%
  - Itraconazole : 11%
- **IFI cost :** 51 033 € €
- **Prophylaxis cost (TTC)** :
  - Posaconazole   93 € x 29 days
  - Itraconazole   22 € x 25 days
  - Fluconazole   18 € x 25 days

Mean Cost (€) per patient

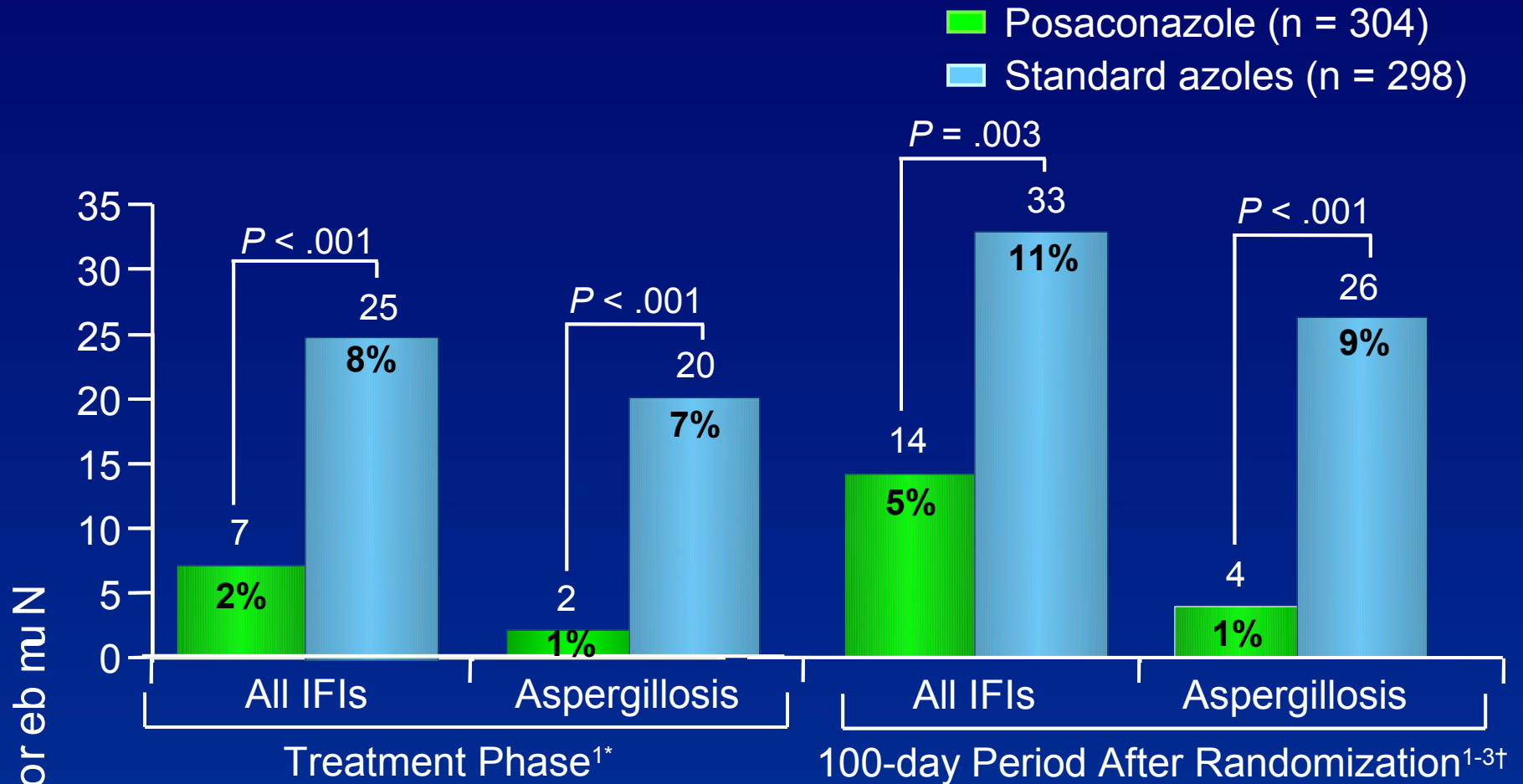| Strategy	Posaconazole	Itra/Fluco
Prophylaxis	2 697 €	469 €
IFI	2 526 €	5 614 €
Total	5 223 €	6 083 €
Difference	- 859 €	

The Posaconazole strategy is better than the Itra/Fluco strategy in regards to French society and Sickness Fund perspectives

At-risk Populations Have Been Identified as Candidates for Prophylaxis

Patient Population	Major Risk Factors for IFI
AML/MDS and neutropenia	• Prolonged, profound neutropenia • Multiple cycles of neutropenia • Mucositis • Leukemia-related immunodeficiency
Allogeneic HSCT recipients ↓ GVHD	• Neutropenia • Immunosuppression to prevent or treat GVHD • HLA-mismatched transplants • Other infectious agents
	• Lymphopenia caused by immunosuppressive therapy • GVHD-related skin and mucosal damage

Jantunen E et al. *Transpl Infect Dis*. 2008;10:156.
Martino R et al. *BJH*. 2002;116:475.

Posaconazole Prophylaxis in Neutropenic Patients
Results – Proven/Probable IFI

Legend: Posaconazole (n = 304), Standard azoles (n = 298)

Treatment Phase[1*]:
- All IFIs: Posaconazole 7 (2%), Standard azoles 25 (8%), P < .001
- Aspergillosis: Posaconazole 2 (1%), Standard azoles 20 (7%), P < .001

100-day Period After Randomization[1-3†]:
- All IFIs: Posaconazole 14 (5%), Standard azoles 33 (11%), P = .003
- Aspergillosis: Posaconazole 4 (1%), Standard azoles 26 (9%), P < .001

Y-axis: Number of IFIs

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.

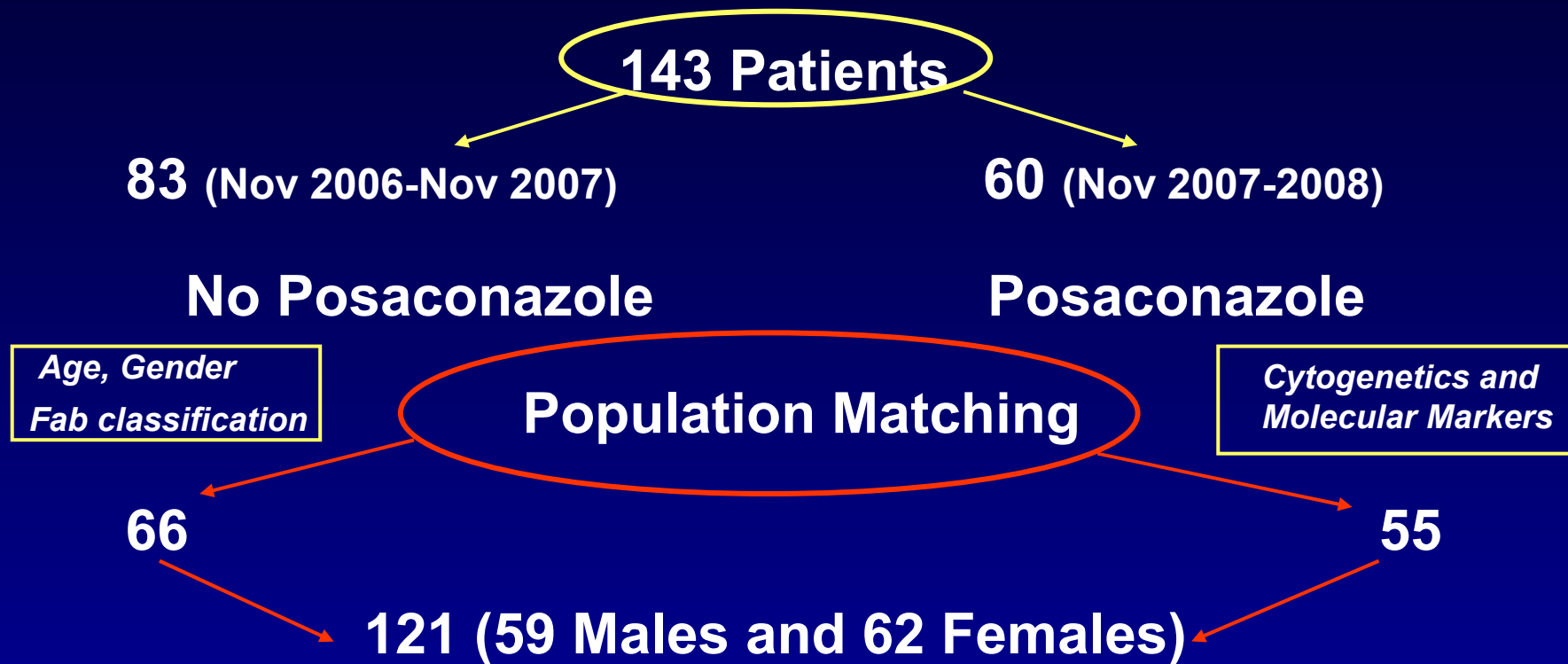# Posaconazole Prophylaxis in Neutropenic Patients
Results – Death From Any Cause

*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.

General Characteristics

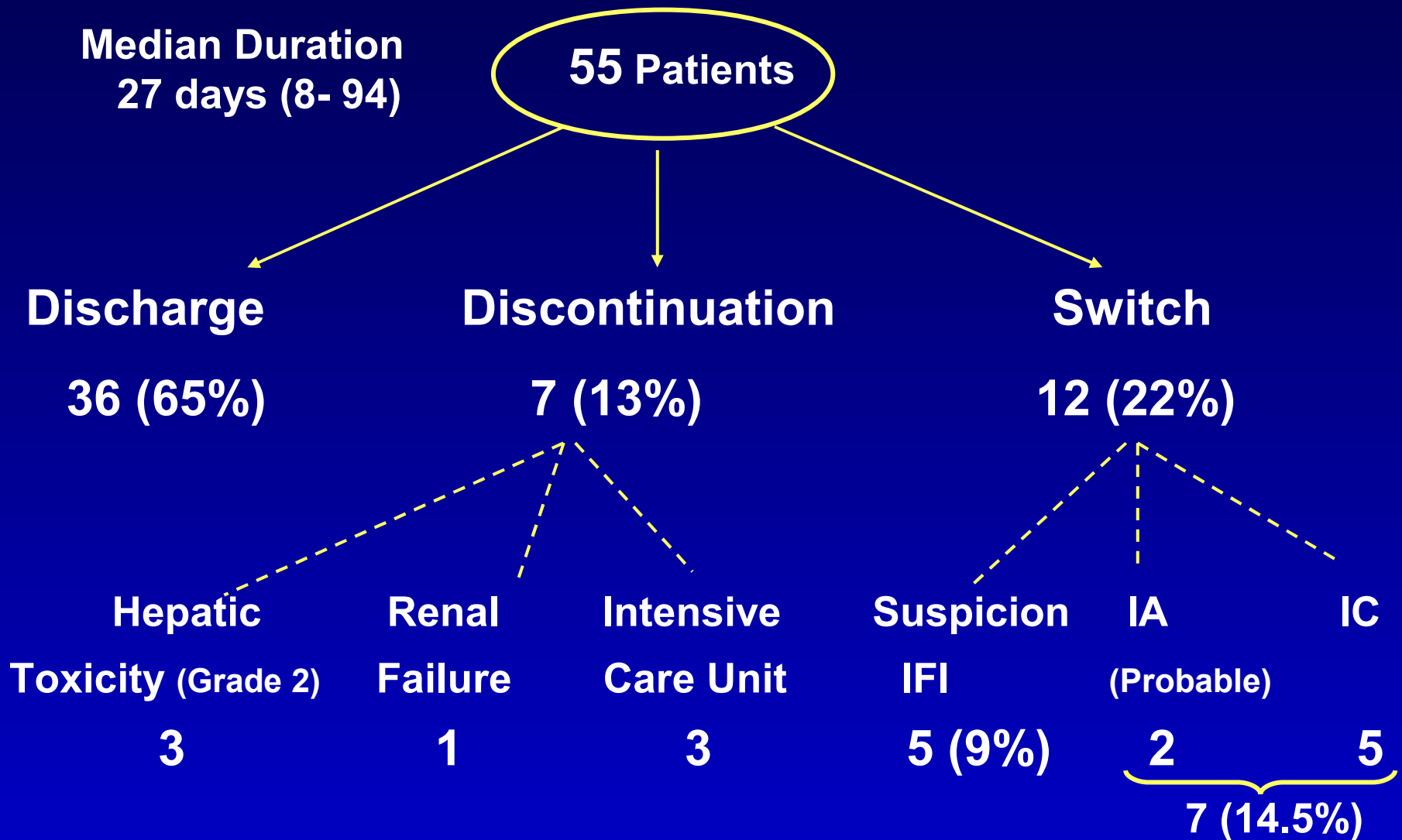## Total Population

Control / NOXAFIL

143 Patients

83 (Nov 2006-Nov 2007)   **60** (Nov 2007-2008)

No Posaconazole   **Posaconazole**

Age, Gender Fab classification   **Population Matching**   *Cytogenetics and Molecular Markers*

66   **55**

121 (59 Males and 62 Females)

- **Median Age** : 54.9 years (18.4 – 77)

- **AML Type** : 91 AML de novo and 30 Secondary AML

- **FAB 0 to 7** : 3, 19, 26, 18, 7, 23, 1, 3 (20 unclassified)

- **Cytogenetics** : Good / Intermediate / Poor : 18/43/58 (2 non evaluated)

- **Prognosis** : Good (n=29) [(Favorable + Interm 1 (Flt3 ITD, CEBPA, NMP1)], Poor (n=75) (Interm 2+ Defavorable), ND (n=17)

- **Presence of Molecular Marker** : 79 / No Marker : 28 (Not Done : 14)

Characteristics of the Total Population

- **Chemotherapy : ALFA 9801 and 9803 (n=50), ALFA 9802 and 0702 (n=36), APL (n=17), EORTC (n=6), CBF (n=5), Others (n=7)**

- **Diagnosis - Hospitalization :** 0 day (-41 – +7)

- **Laminar Air Flow Rooms :** 92 patients (76%)

- **Response after Induction :**

- CR : 100
(83%)
- Failures : 19
(16%)
- Death during
Induction : 2 (1%)

- **Median Duration of Aplasia :** 28 days (7 – 91)

- **Median of Hospitalization :** 37days (22 – 101)

	Population Control	Patients NOXAFIL	p
Number of Patients	66	55	
Median Age (Range)	53 (19.3 – 77)	53.4 (18.4 – 73)	NS
Sex M / F	36 / 30	23 / 32	NS
Diagnosis-Hosp (days)	1 (-36 – +6)	0 (-41 – +7)	NS
Laminar Air Flow Y/N/NA	51 / 13 / 2	46 / 9 / 0	NS
AML de Novo / II	52 / 14	39 / 16	NS
FAB 0/1/2/3/4/5/6/7/ND	3/1/1/14/11/2/15/1/3/ 6	0/8/12/7/5/8/0/0/0/14	NS
Prognosis (Good/Poor/ND)	13 / 44 / 9	16 / 31 / 8	NS
Cytogenetics (Good/Inter/Poor/ND)	8 / 20 / 36 / 2	10 / 23 / 22 / 0	NS
Molecular Markers (Normal/Mut/ND)	15 / 44 / 7	13 / 35 / 7	NS
ALFA 801&9803/0702&9802 APL/EORTC/CBF/NoP/Other	34 / 14 / 10 / 6 / 0 / 1 / 1	16 / 22 / 7 / 0 / 5 / 4 / 1	S
Response to Induction CR/ Failure / Death	54 / 10 / 2	46 / 9 / 0	NS
Median Duration Aplasia (days)	28 (9 – 52)	29 (7 – 91)	NS
Median Duration H (days)	37 (22 – 57)	38 (25 – 101)	NS

Incidence of IA during induction

Among the 121 patients : 10 patients with 4 Possible or 6 Probable IA (8.2%)
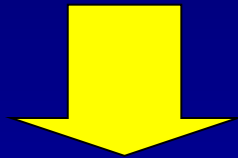
In Control Cohort (n=66)
- 4 Possible IA (6%)
- 4 Probable IA (6%)
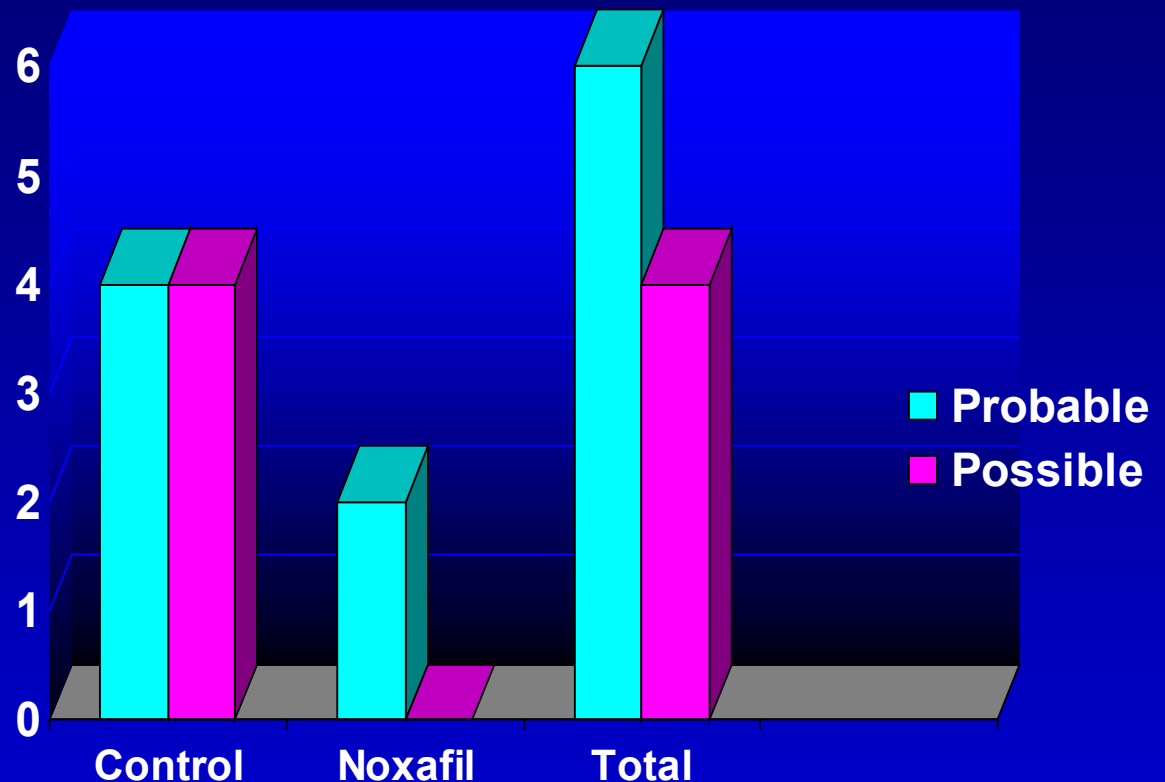Possible + Probable IA (12%)

In Noxafil Cohort (n=55)
- 2 Probable IA (3.6%)

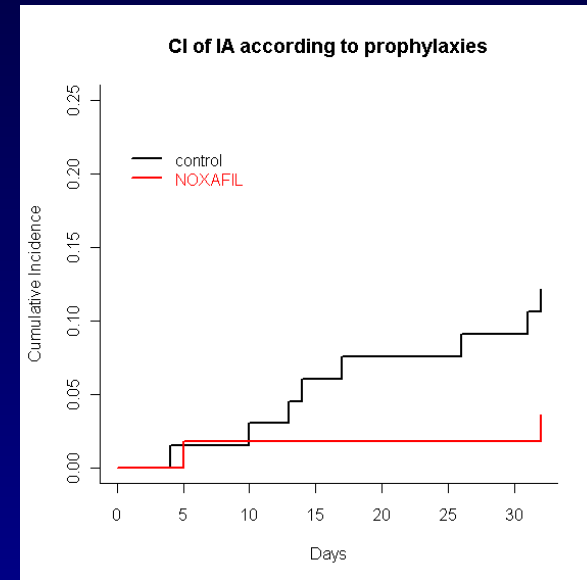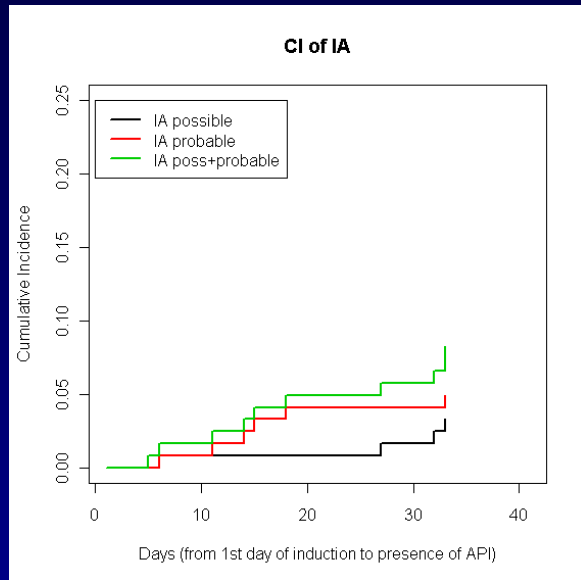2 times less IA in patients
on NOXAFIL :

Odd RATIO
0.276 [IC 95% 0.027 – 1.47]
(p=0.11)

Variables		% IA	Odd-ratio (IC 95%)	p-value
Age	≤ 55 years	4.9%	OR = 2.53 [0.54 – 15.96]	p = 0.2
	> 55 years	11.67%		
Diag – Hospit	Before Hospit	8%	OR = 1.06 [0.24 – 5.41]	p = 1
	In Hospit and >	8.45%		
LAF	Yes	7.2%	OR = 2.01 [0.31 – 9.88]	p = 0.39
	No	13.6%		
AML	De Novo	9.9%	OR = 0.31 [0.007 – 2.46]	p = 0.44
	II	3.3%		
NOXAFIL	No	12.1%	OR = 0.276 [0.068 – 1.47]	p = 0.11
	Yes	5.5%		
Cytogenetics	Good+Inter	3.3%	OR = 4.66 [0.875 – 47.06)	p = 0.05
	Poor	13.8%		
Prognosis	Good	10.3%	OR = 0.5 [0.4 – 9.8]	p = 1
	Poor	16%		
Response to Therapy	CR	6%	OR = 3.63 [0.68 – 17.3]	p = 0.07
	Failure+Death	19%		
Duration of Aplasia	≤ 28 days	6.55%	OR = 1.57 [0.35 – 8.03]	p = 0.53
	> 28 days	10%		

Cumulative Incidence of IA

Cumulative Incidence of IA during Induction

Median of CI of IA : 15 days [4 – 32]
At Day 32 :
CI of IA : 8.26% (+/-2.5%)
    CI of possible IA : 3.3% (+/-1.8%)
    CI of probable IA : 4.96% (+/-2.2%)

CI of the IA at day 32 in :
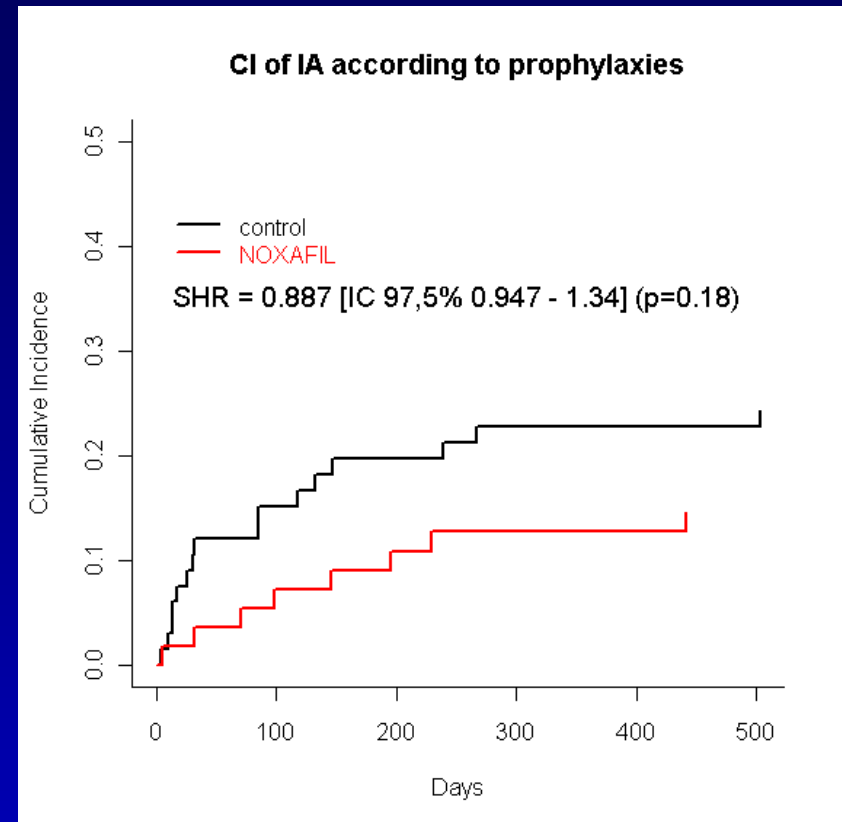 - **Control Group** : 12.1% (+/- 4.3%)
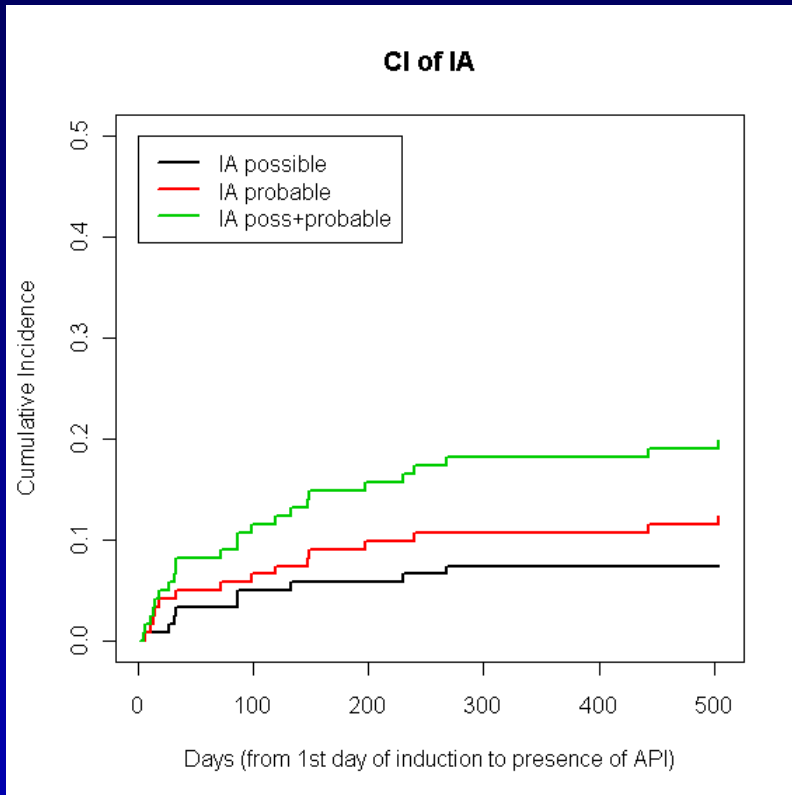 - **NOXAFIL Group** : 3.6% (+/-3.1%)

Univariate Analysis : No significant impact of Gender, Interval, Type of AML, LAF, Duration of Aplasia, Cytogenetics, Prognosis.
=> Influence of NOXAFIL (SHR =1.1 [97% IC 0.99 – 1.22] and p=0.08) and the impact of the age was significant (SHR=0.995 [97%IC 0.992 – 0.999] (p=0.0083)

Multivariate Analysis

	SHR	CI 97.5%	p value
Age	0.998	0.994 - 1.00	p=0.05*
Diagnosis-Hospit	1.000	0.993 - 1.01	p=0.93
LAF	0.964	0.821 - 1.13	p=0.63
AML de Novo/II	1.084	1.004 - 1.17	p=0.04*
NOXAFIL	1.056	0.967 - 1.15	p=0.22
Prognosis	1.031	0.938 - 1.13	p=0.52
Response to Ttt	0.995	0.858 - 1.15	p=0.95
Duration Aplasia	0.997	0.992 - 1.00	p=0.28

Cumulative Incidence of IA over Time

General Characteristics

Population with and without IA

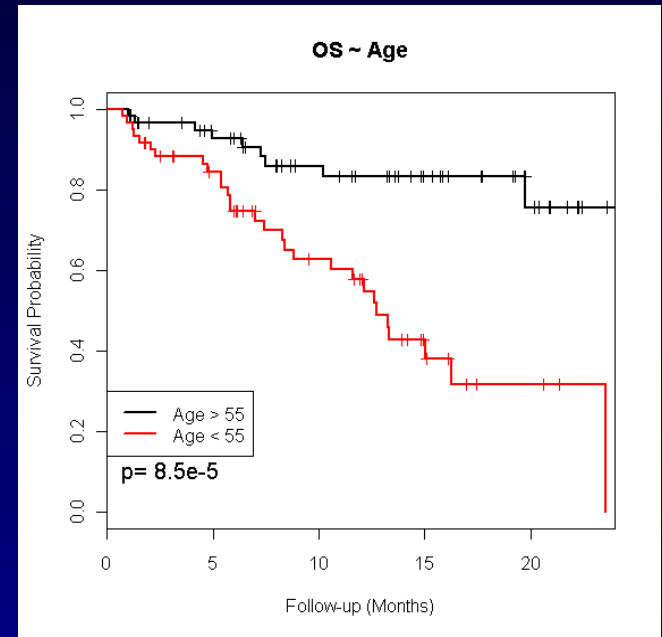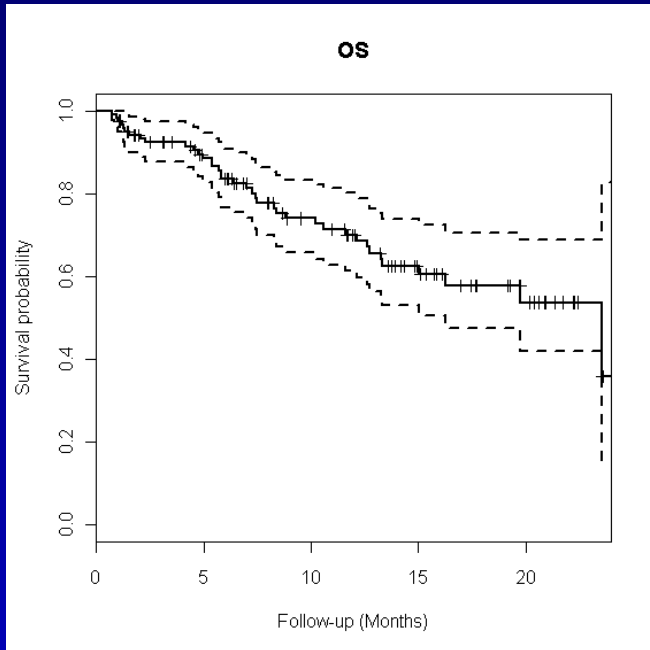| Variables		Without IA	Possible IA	Probable IA	p
Age		54.6 (18.45 – 72.9)	59.8 (52.2 – 68.3)	66.4 (47.9 – 77)	p = 0.03
Gender	M/F	53/58	3/1	3/3	p = 0.61
Diag-Hospit		0 (-41 – +7)	2 (-7 – +2)	0 (-26 – +3)	p = 0.73
LAF	Yes/No	90/19	3/1	4/2	p = 0.65
AML	De Novo/II	82/29	4/0	5/1	p = 0.55
NOXAFIL	No /Yes	58/53	4/0	4/2	p = 0.15
FAB	0/1/2/3/4/5/6/7/ND	2/15/25/17/7/22/1/3/18	0/2/1/1/0/0/0/0/0	1/2/0/0/0/1/0/0/1	p = 0.38
Cytogenetics	Good/Inter/Poor	17/42/50	1/0/3	0/1/5	p = 0.22
Molecular Markers	Normal/Mutated	75/25	1/1	2/2	p = 0.59
Prognosis	Good/Poor	28/70	1/1	0/4	p = 0.38
Protocols	ALFA 9801/9803	345	0	1	p = 0.62
	ALFA 0702/9802	43	3	4	
	APL/CBF/EORTC	16/5/6	1/0/0	0/0/0	
	No Prot/Other	4/2	0/0	1/0	
Response to treatment	CR/Failure/Death	94/16/1	2/2/0	4/1/1	p = 0.09
Duration Aplasia		28 (7 – 91)	33 (25 – 52)	28 (21 – 42)	p = 0.4
Duration Hospit		37 (22 – 101)	49 (40 – 55)	37 (29 – 55)	p = 0.09

Multivariate Analysis (IA vs No IA)

Variables	p-value
Age	p = 0.24
Gender	p = 0.91
Diag – Hospit	p = 0.94
LAF	p = 0.30
AML (De Novo/II)	p = 0.379
NOXAFIL	p = 0.45
Cytognetics	p = 0.53
Prognosis	p = 0.89
Response to Therapy	p = 0.93
Duration of Aplasia	p = 0.70

Overall Survival

- Median Follow-up was 8.6 months (0.72 – 26.7)

The median Survival was 23.6 months

- **Among the total population :** 39 patients died [29 in control cohort (mortality of 44%) and 10 in the NOXAFIL cohort (mortality of 18.8%)]
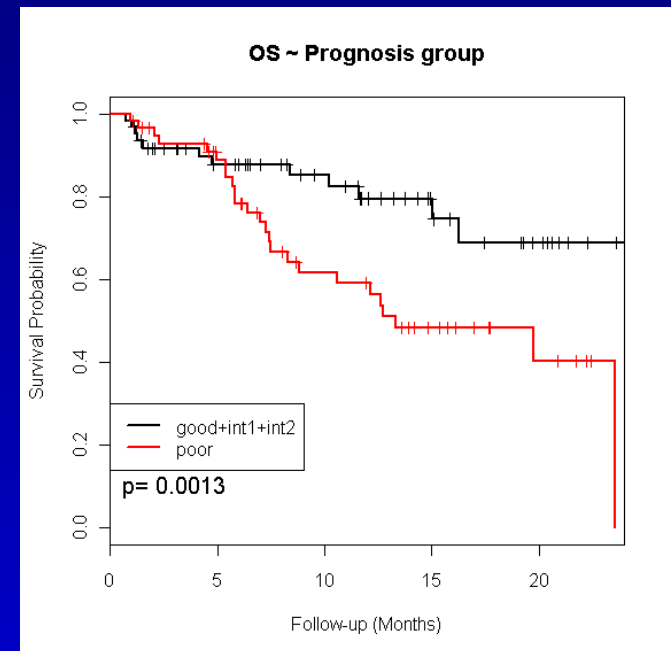

OS ~ Age
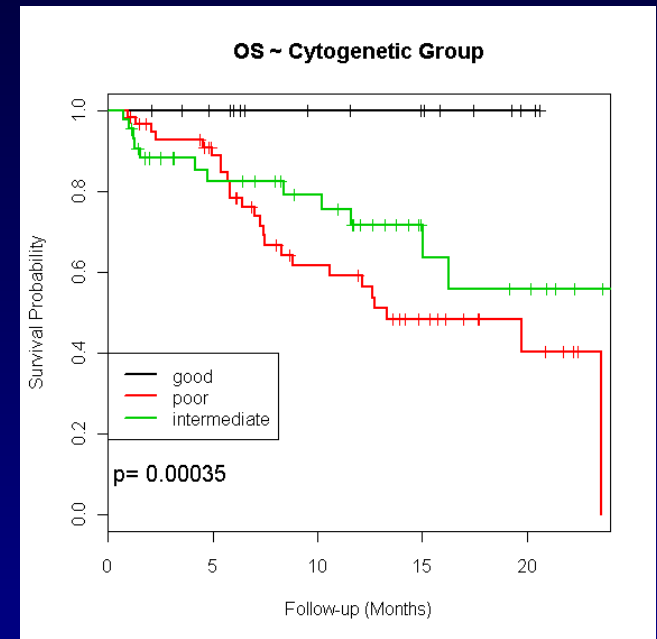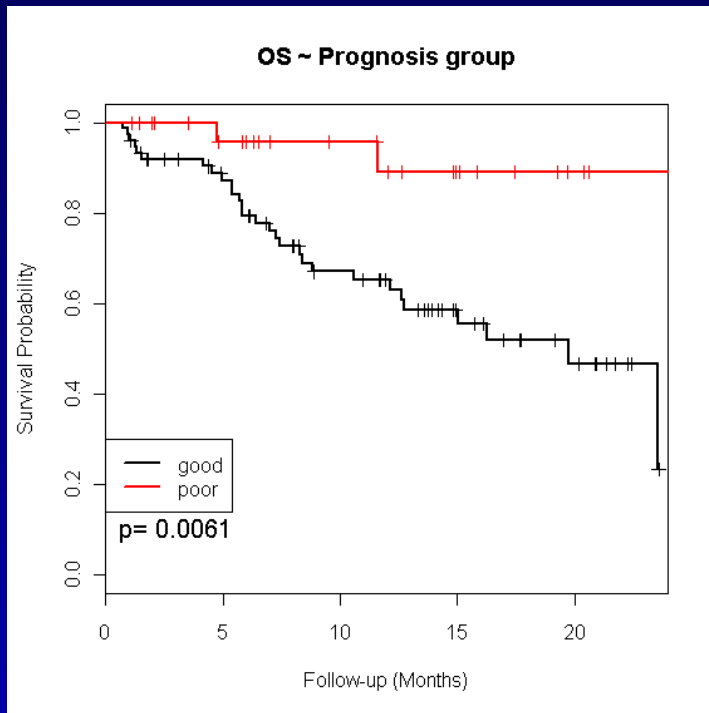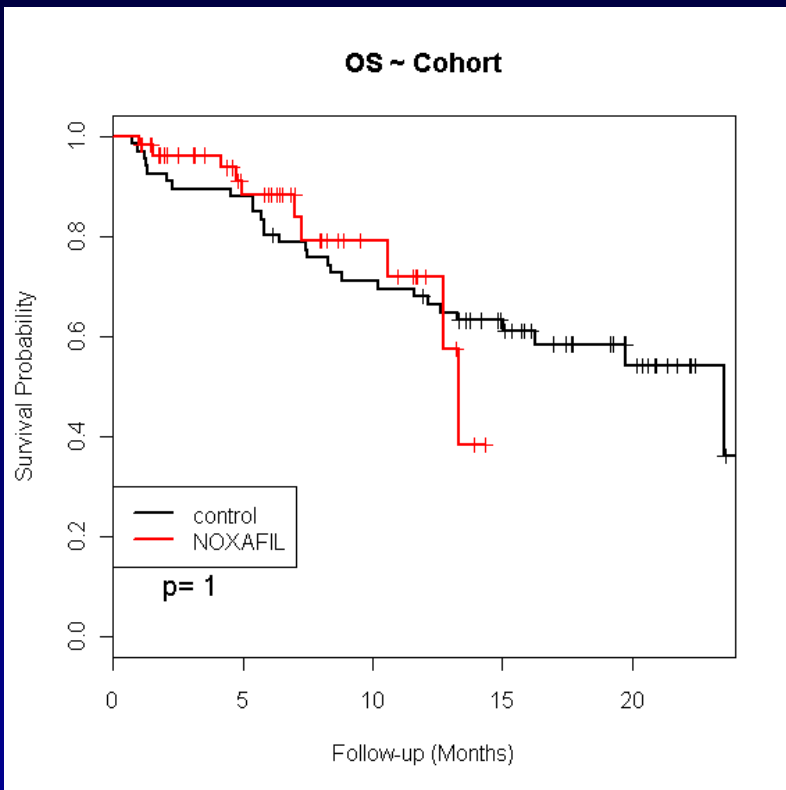
p= 8.5e-5

Significant Influence of Age and Response to Ttt

OS

OS ~ Treatment response

p= 8.6e-10

D100	6 m	9 m	1 Year	18 m	2 Years
92.3%	83.5%	74%	70%	58%	35.8%
(87.6-97.3)	(76.7-91)	(65.7-83.3)	(61-80)	(47.4-70.6)	(15.5- 83)

Overall Survival

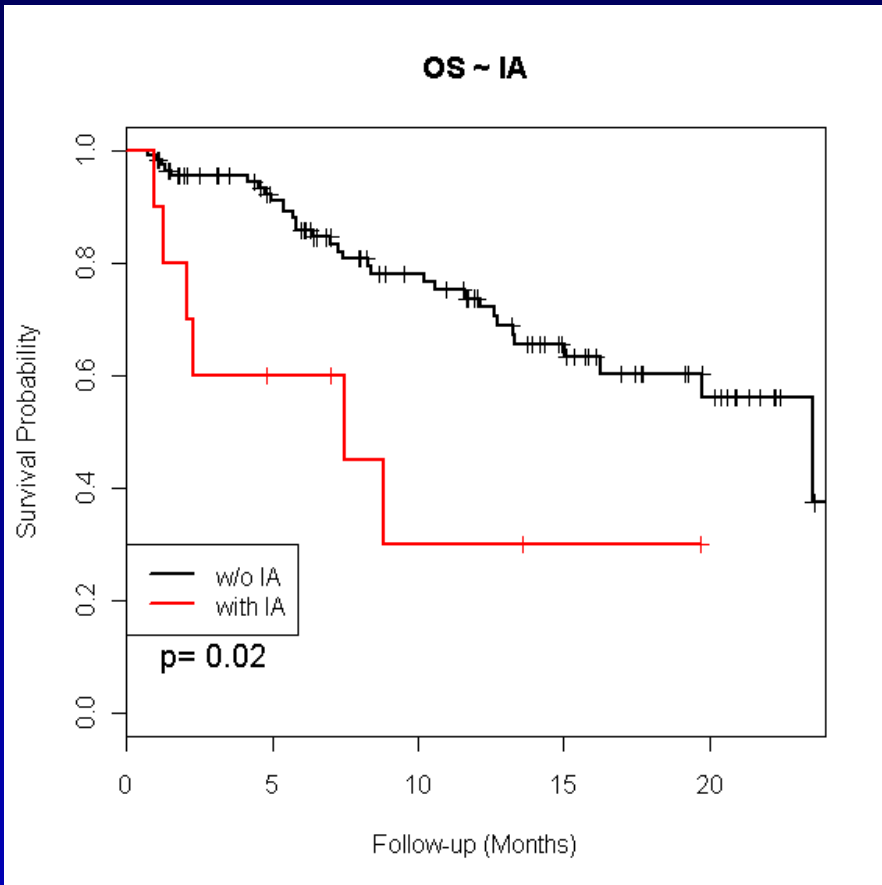## Cytogenetics and Molecular Markers and other parameters

OS ~ Prognosis group
p= 0.0061

OS ~ Cytogenetic Group
p= 0.00035

OS ~ Prognosis group
p= 0.0013

No significant influence of :
Gender, type of AML, LAF, Interval Diag-Hospit, Duration of Aplasia

OS ~ Cohort (control / NOXAFIL, p= 1)

OS ~ Cohort at D100 (control / NOXAFIL, p= 0.0029)

Zoom on the 100 first days : HR= 0.103 [CI 95% 0.02 – 0.5] (p= 0.00029)

	D100	IA	Death	Causes of Death
NOXAFIL	17	None	2	Failure (2)
Control	7	4 (1 Possible/3 Probable)	4 (IA)	IA in CR (1), Failure+IA (1), Failure (2)
			3 (Without IA)	Failure (2), Cardiac Toxicity (1)

Survival according to the Presence of IA

Survival of IA Population (n=19)

- **Significant influence of :**
- Age (p= 0.011)
- Cytogenetics (p=0.041)
- Response to Treatment (p= 0.035)
- A trend of kind of protocol (p=0.067)

- **No significant influence** of NOXAFIL

Multivariate Analysis (OS)

	HR	CI 95%	p-value
Possible IA	0.956	0.1931 - 4.73	0.96000
Probable IA	1.335	0.3477 - 5.13	0.67000
Age	**1.051**	**1.0124 - 1.09**	**0.00930**
Gender	0.806	0.3400 - 1.91	0.63000
AML de Novo/II	1.145	0.4610 - 2.84	0.77000
NOXAFIL	1.594	0.6337 - 4.01	0.32000
LAF	0.788	0.2860 - 2.17	0.64000
Cytogenetics	**2.375**	**0.8918 - 6.32**	**0.08300**
Prognosis	0.434	0.0835 - 2.26	0.32000
Response to Ttt	**5.345**	**2.2435 - 12.74**	**0.00015**
Duration of Aplasia	0.997	0.9448 - 1.05	0.91000

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