

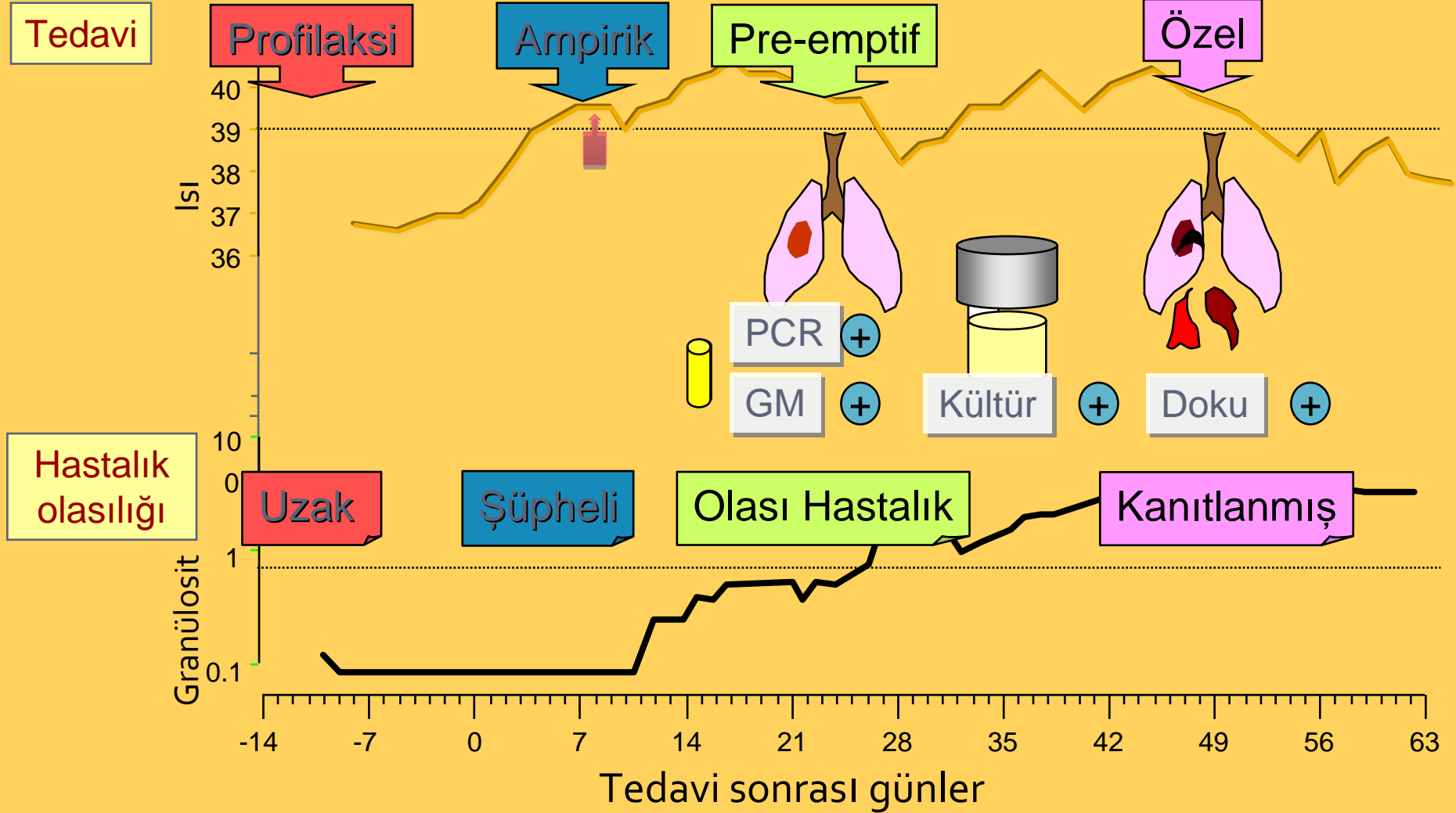
ECIL-3 Kılavuzu

Antifungal Profilaksi

Hamdi Akan

Ankara Tıp Fakültesi Hematoloji Bilim Dalı

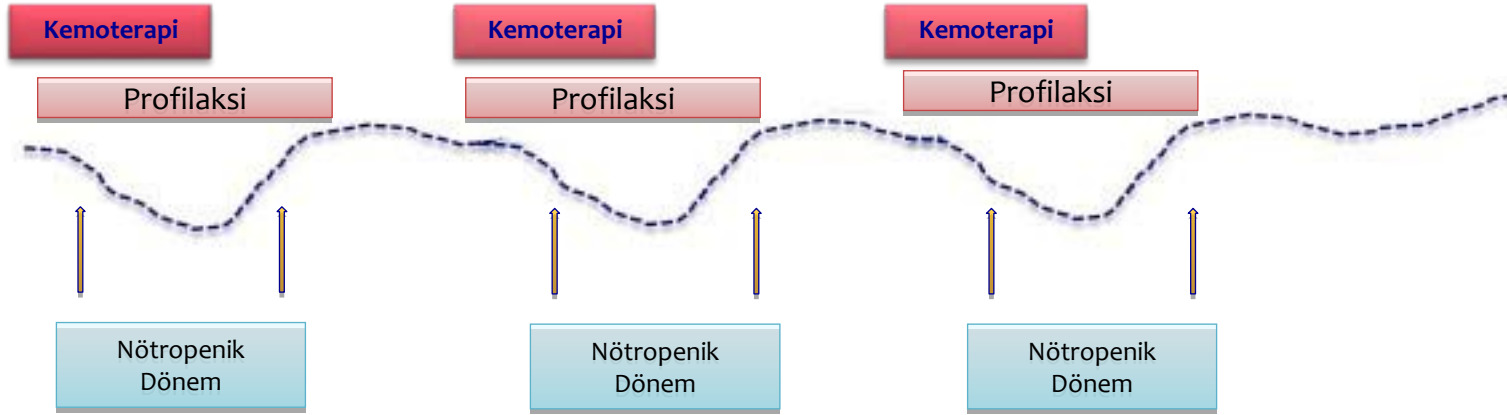
TEDAVİ YAKLAŞIMLARI



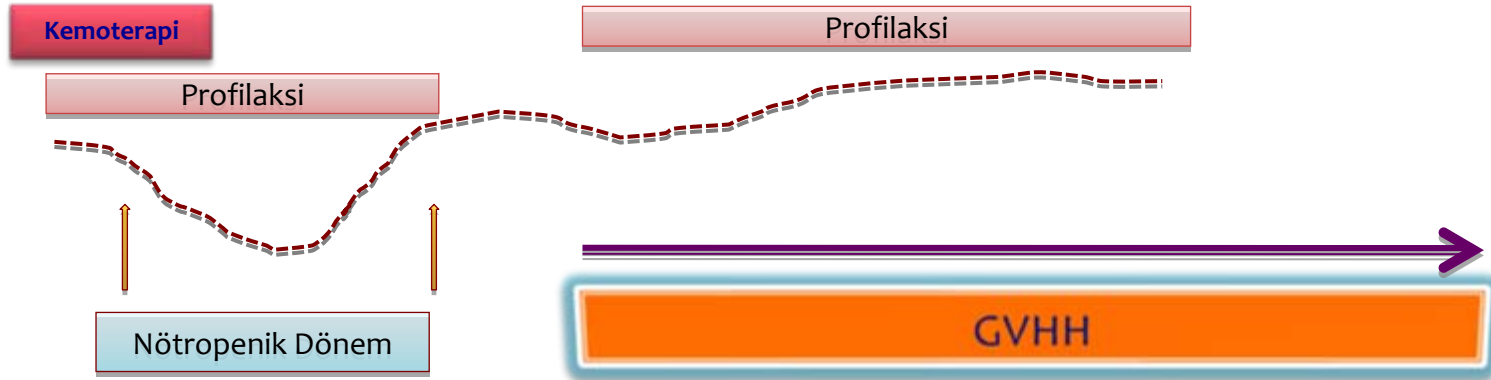
3 önemli grup var

- İndüksiyon alan AML
- Erken fazda (nötropenik) allojeneik kök hücre nakli
- GVHH olan allojeneik kök hücre nakli

AKUT LÖSEMİ - MDS



Allojeneik KÖK HÜCRE NAKLI



Profilaksi için Kılavuz

	ECIL II 2008	IDSA 2008	BSH 2008
Allojeneik KHN			
Fluconazole	A I		
Itraconazole	B I ^{1,2}	B I	A I
Posaconazole	A I ³	A I	A I
Micafungin	C I		
Polyene	C I ³		B II
Akut lösemi indüksiyon		AML & MDS	
Fluconazole	C I		
Itraconazole	C I ^{1,2}	B I	A I
Posaconazole	A I ³	A I	A I
Polyene	C I		B II
	1. İlaç etkileşimi/intolerans 2. Serum kons. izle		

Fluconazole (AI) vs. posaconazole (AI) in Allogeneic HSCT

Proposals within the group

- 1. To separate the neutropenic from the non-neutropenic (GvHD) phase
- 2. To add a footnote
 - Fluconazole AI only
 - during the neutropenic phase of allogeneic HSCT and
 - when combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of invasive mould infections

Primary prophylaxis with voriconazole in allogeneic hematopoietic stem cell transplant recipients : *Two trials analyzed*

1- Wingard J et al. ASH 2007 Oral Session

Results of a Randomized, Double-Blind Trial of Fluconazole (FLU) vs. Voriconazole (VORI) for the Prevention of Invasive Fungal Infections (IFI) in 600 Allogeneic Blood and Marrow Transplant (BMT) Patients

2 – Marks D et al. ICAAC 2009, San Francisco, M-1249a

Voriconazole (VOR) versus itraconazole (ITR) for primary prophylaxis of invasive fungal infections in allogeneic HSCT recipients

Voriconazole vs Itraconazole for Primary Prophylaxis of Invasive Fungal Infection (IFI) in Allogeneic Hematopoietic Cell Transplant (HCT) Recipients

D. I. MARKS¹, C. KIBBLER², A. PAGLIUCA³, P. RIBAUD⁴, C. SOLANO⁵, C. P. HEUSSEL⁶, G. COOK⁷, A. GLASMACHER⁸, H. SCHLAMM⁹, M. KANTECKI⁹, Improvit Study Group;

¹UH Bristol, Bristol, United Kingdom, ²Royal Free H, London, United Kingdom, ³King's Coll H, London, United Kingdom, ⁴H Saint-Louis, Paris, France, ⁵H Clínic, Valencia, Spain, ⁶Radiology, Thoraxklinik at Univ H, Heidelberg, Germany, ⁷St James' Univ H, Leeds, United Kingdom, ⁸Univ klinikum Bonn, Bonn, Germany, ⁹Pfizer Inc, New York, NY.

Prospective, Open-Label, Multicenter Study

- 489 patients \geq 12 years of age undergoing allogeneic HCT (myeloablative or reduced intensity)
- Randomized to primary IFI prophylaxis, stratified by conditioning regimen and donor type

Voriconazole (N=234)

- IV loading dose: 6 mg/kg BID
- PO maintenance dose: 200 mg BID for patients >40 kg and 100 mg BID for those <40 kg

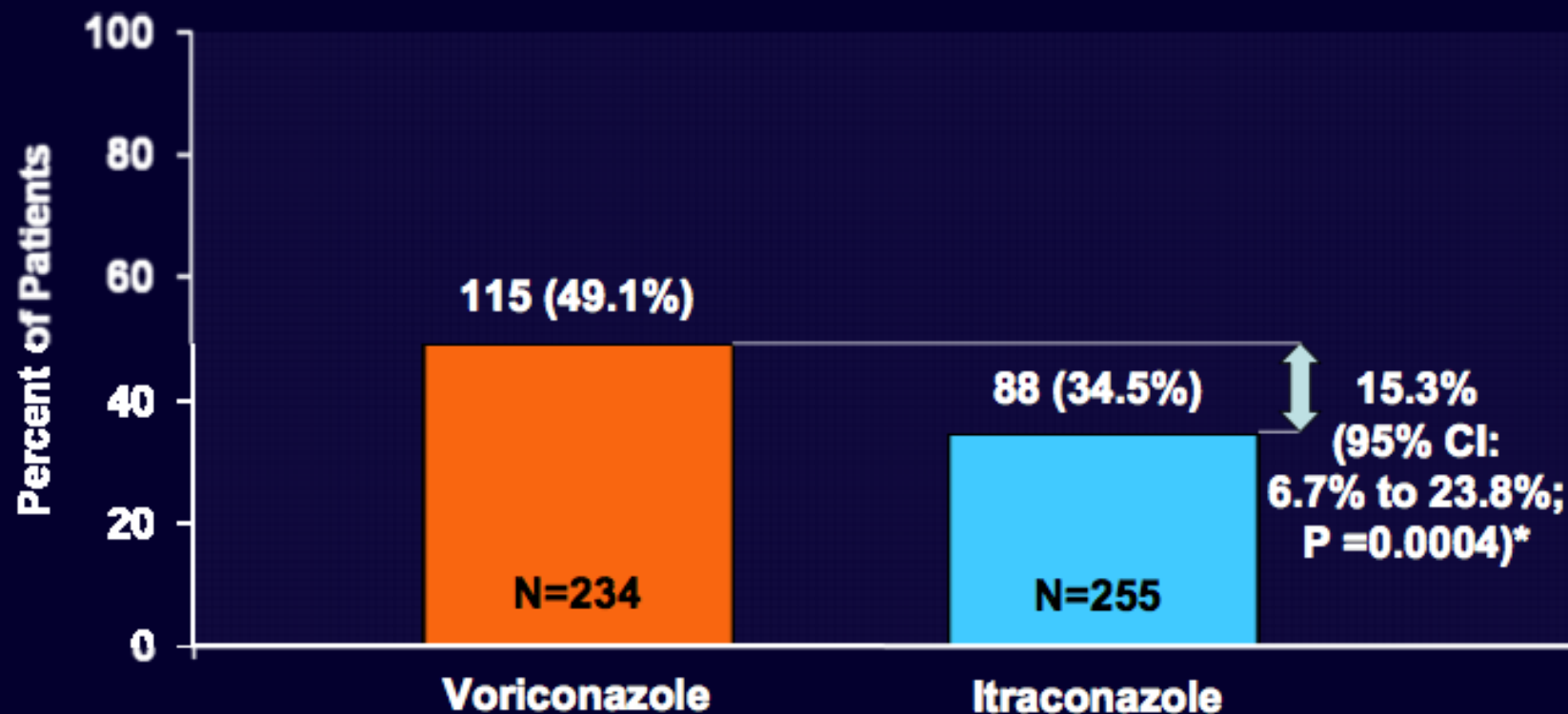
Itraconazole (N=255)

- IV loading dose: 200 mg BID
- PO maintenance dose: 200 mg BID (Itraconazole capsules for total of ≤ 14 days only, ≤ 5 day periods suggested)

- Duration: at least 100 and up to 180 days
- Empirical therapy with non-study antifungal agent was permitted if signs of possible IFI developed

Participating countries: UK, Spain, France, Canada, Czech Republic, Portugal, Switzerland, Egypt, Greece, Russia, Turkey, Jordan

Success of Antifungal Prophylaxis at Day 180 (Primary Endpoint)



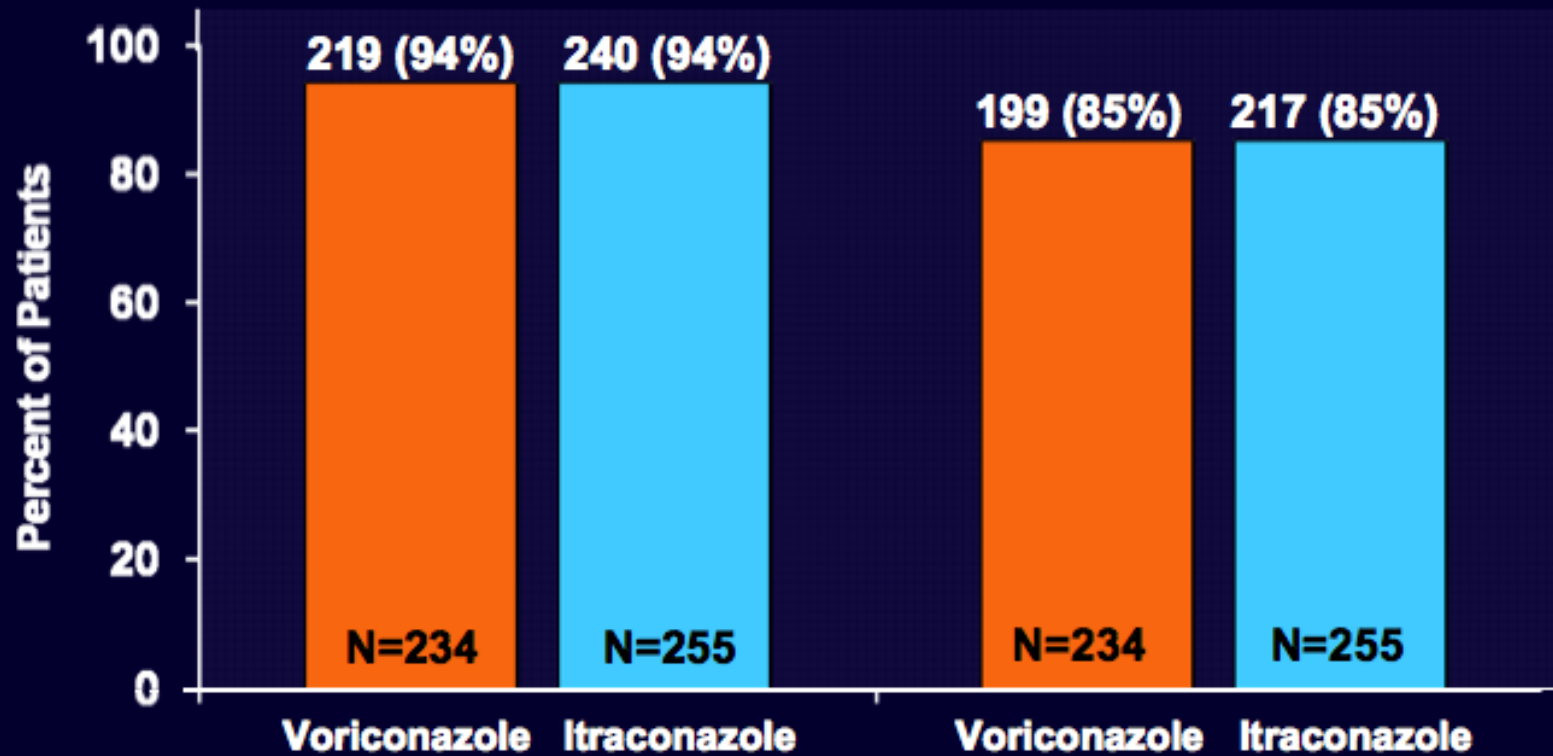
Voriconazole met criteria for non-inferiority and superiority

* Difference in proportions (Voriconazole – Itraconazole) adjusted for conditioning regimen (myeloablative vs. non-myeloablative) and relatedness of donor (matched related donor vs. mismatched/unrelated donor)

Survival

Day 100

Day 180



Voriconazole (VOR) versus itraconazole (ITR) for primary prophylaxis of invasive fungal infections in allogeneic HSCT recipients
Marks et al. ICAAC 2009, San Francisco, M-1249a

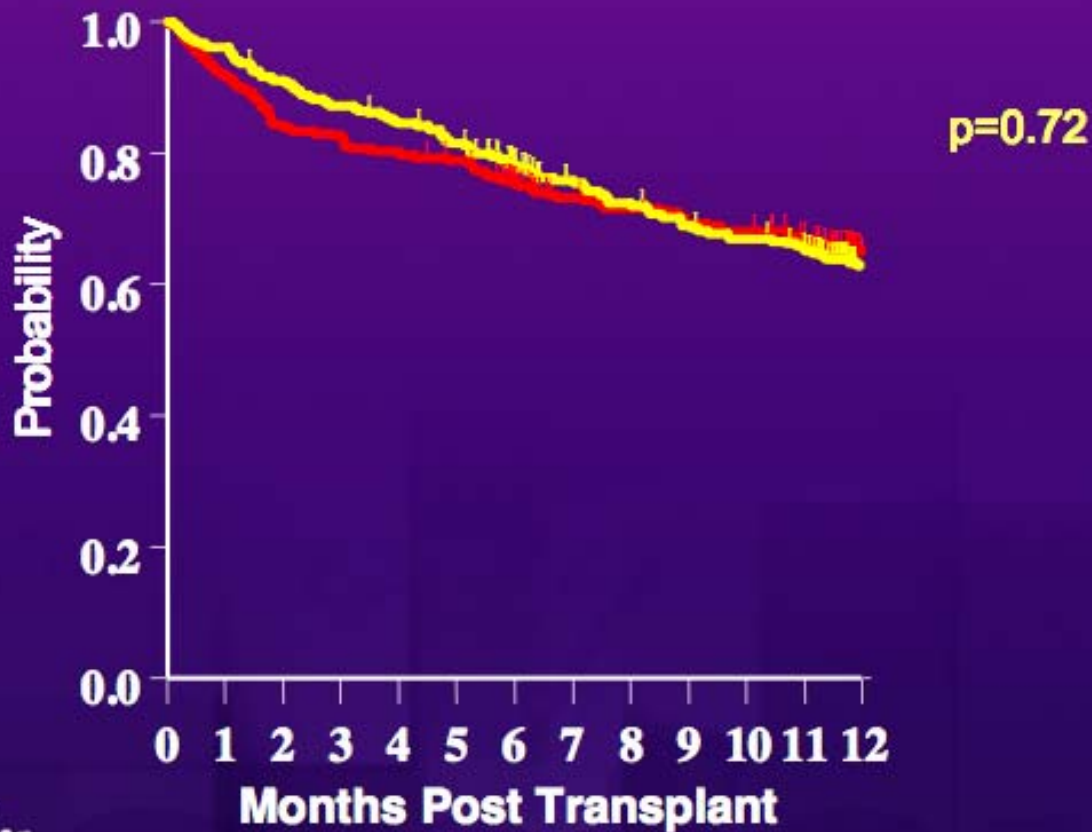
- **Prospective, open-label, multicenter study**
- **Patients ≥ 12 y of age; 234 VOR and 255 ITR**
- **From day 0 till at least day + 100 and up to day +180**
- **Primary composite endpoint: patient surviving without proven or probable IFI at day +180 or discontinuing prophylaxis for >14 days (= success of prophylaxis or SoP)**
- **SoP at day +100: VOR 55% vs. ITR 41% (p=0.0007)**
- **SoP at day +180: VOR 49% vs. ITR 35% (p=0.0004)**
- **IFI incidence: VOR 1.3% and ITR 2%**
- **Survival at day +180: 85% both arms**
- **Sufficient days of prophylaxis: VOR 54% vs. ITR 40% (p=0.0014)**
- **No patient developed IFI while on VOR vs. 3 patients while on ITR**

Patient Characteristics

	FLU N=295	VORI N=305
Age (median)	43 years	43 years
% 18 years or above	92%	91%
Disease		
AML	101 (34%)	133 (44%)
ALL	64 (22%)	58 (19%)
CML	60 (20%)	43 (14%)
MDS	49 (17%)	49 (16%)
NHL	21 (7%)	22 (7%)
Disease risk status = good	263 (89%)	283 (93%)
Donor source = related	169 (57%)	168 (55%)

Fungal-free Survival

— Fluconazole (N=295) 75% at 180 Days
— Voriconazole (N=305) 78% at 180 Days



Microbiologically Documented Proven/Probable Fungal Infections Through Day 180

Fungal Genus	FLU	VORI
• Aspergillus*	16*	7*
• Candida	3	3
• Zygomycetes	3	2
• Other	1	1
Totals**	23**	13**

* $p = 0.05$

** $p = 0.11$

Antifungal prophylaxis in allogeneic SCT

Proposed changes only

Neutropenia w/o GvHD	
Fluconazole* 400 mg/d	AI
Posaconazole	No data
Voriconazole 200 mg bid	Provisional AI
GvHD > grade I	
Fluconazole 400 mg/d	CI
Posaconazole 200 mg tid	AI
Voriconazole 200 mg bid	Provisional AI

* combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

Unsolved Questions and New Areas of Research

Secondary antifungal prophylaxis has not been studied in a well-designed prospective, randomized clinical trial.



1st
European
Conference on
Infection in
Leukemia

Does Secondary Prophylaxis Reduce the Incidence of Breakthrough IFI?

Population	Dose	Result	Ref
Allogeneic	Various	Relapse rate 33% univariate risk factor analysis	Offner 1998
Autologous	?	?	?
AML w/o SCT	Various	Relapse rate 16% multivariate risk factor analysis	Cornely 2003

In allogeneic SCT secondary prophylaxis to reduce BT-IFI	C III
In autologous SCT secondary prophylaxis to reduce BT-IFI	C III
In AML w/o SCT secondary prophylaxis to reduce BT-IFI	C III