AMM Européenne

NOXAFIL®
posaconazole

Disponible depuis le 26/01/2006

NOXAFIL® est indiqué dans le traitement des infections fongiques invasives réfractaires suivantes chez l'adulte :

- **Aspergillose invasive chez les patients réfractaires à l'AmB ou à l'itraconazole ou intolérants à ces médicaments**
- **Fusariose chez les patients réfractaires ou intolérants à l'Am B**
- **Chromoblastomycose et mycétome chez les patients réfractaires ou intolérants à l'itraconazole**
- **Coccidioïdomycose chez les patients réfractaire à l'AmB, à l'itraconazole ou au fluconazole ou intolérants à ces médicaments.**

Posaconazole: Mécanisme d'Action

- **Mécanisme commun à celui de la classe des azolés**
- **Inhibition sélective de l'α-déméthylase du système cytochrome P450 (CYP51A), impliqué dans la biosynthèse de l'ergostérol**
- **Les liaisons hydrophobes à la 14-déméthylase assurent une stabilité de fixation ce qui explique l'efficacité de NOXAFIL sur les souches ayant développé une résistance aux autres azolés**

Inhibition In Vivo *du Cytochrome P450 Potentiel Comparé aux Autres Azolés*

Molécule	CYP3A4		CYP2C8/9		CYP2C19	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Posaconazole	√					
Fluconazole	√		√			
Itraconazole	√	√	√			
Ketoconazole	√	√	√			
Voriconazole	√	√		√		√

Wexler D et al. *Eur J Pharm Sci*. 2004;21:645-653.
Cupp MJ et al. *Am Fam Phys.* 1998;57:107-116.
Drug interactions. *Med Letter*. 2003;45(W1158B):46-48.
Sporanox IV [summary of product characteristics]. Bucks, UK; Janssen-Cilag Ltd; 2005.
Nizoral tablets [summary of product characteristics]. Bucks, UK; Janssen-Cilag Ltd; 2001.
Hyland R et al. *Drug Metab Dispos.* 2003;31:540-547.
VFEND [summary of product characteristics]. Kent, UK; Pfizer Ltd; 2005.

Activité du Posaconazole
IFI Description des études

- Posaconazole
  - Traitement de dernier recours
  - prouvé, probable,
  - réfractaire ou intolérant
  - 330 patients inclus
  - 12 mois de traitement

- Contrôle Externe
  - Traitement disponible à la même période
  - prouvé, probable
  - réfractaire ou intolérant
  - 279 patients inclus
  - 12 mois de traitement

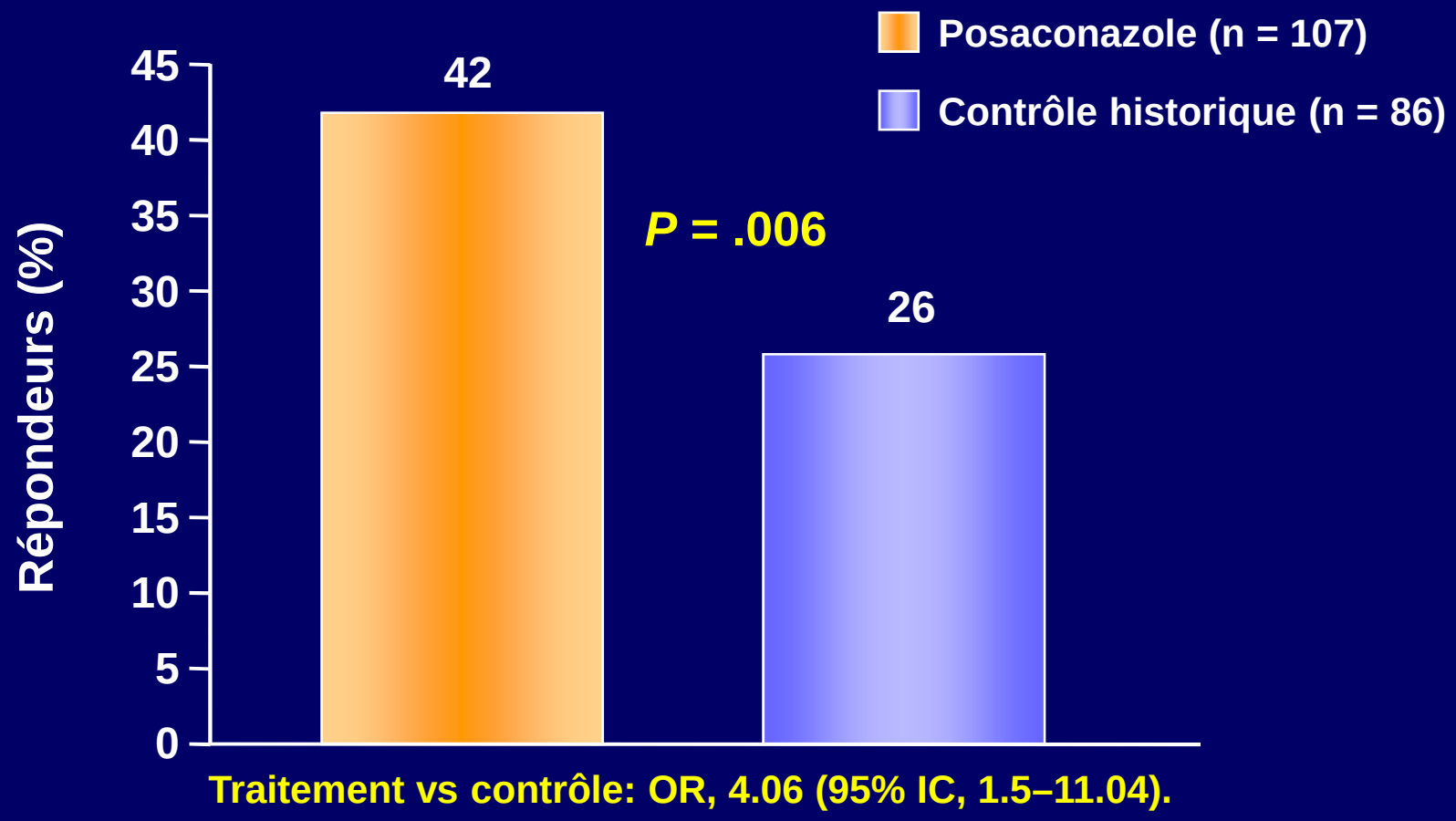
Comité Externe d'Experts

- **15 spécialistes en infections fongiques et 2 radiologues**
- **En aveugle, évaluation simultanée de l'éligibilité et des résultats à la fin du traitement**

IFI indique infection fongique invasive.

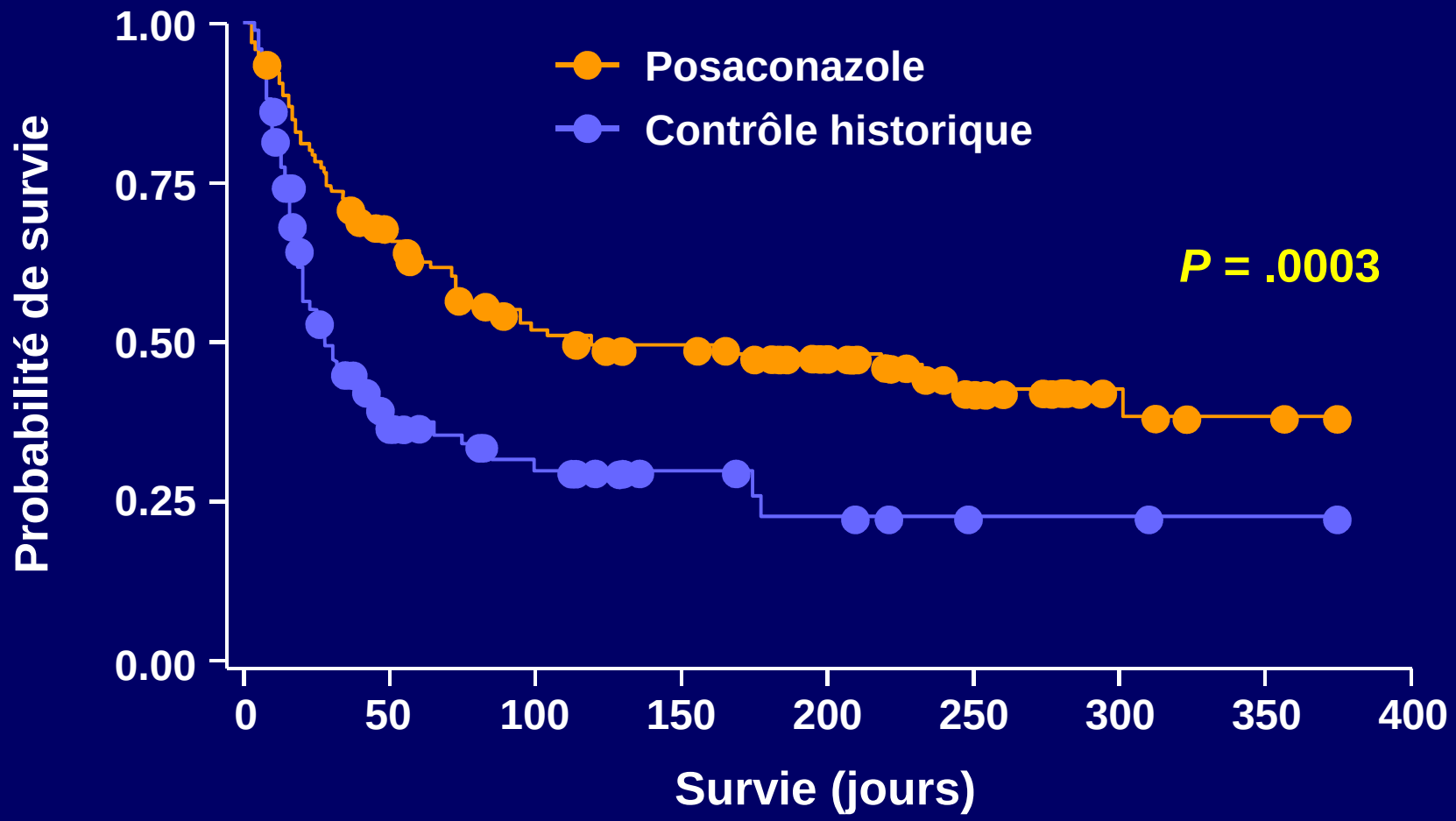
Raad I et al. ICAAC 2004. Abstract M-669.

Réponse globale à la fin du traitement
*Sous-population ITTM** Aspergillus



*Analyse du critère principal d'efficacité (régression logistique).
ITTM indique un intent-to-treat modifié; OR, odds ratio; IC, intervalle de confiance.
Walsh et al. ASH 2003. Abstract 682; Raad et al. ICAAC 2004. Abstract M-669

Analyse de survie de Kaplan-Meier
Aspergillus



Raad I et al. ICAAC 2004. Abstract M-669.

Infections réfractaires
Aspergillus

- **Puissante activité *in vivo* et *in vitro* du posaconazole confirmée**
- 42% **de succès dans le groupe** posaconazole **vs** 26% **de succès dans le groupe** contrôle (p = .006)
  - **actif contre les souches d' *Aspergillus* résistantes à l'amphotéricine B**
- **Posaconazole améliore** la survie

Raad I et al. ICAAC 2004. Abstract M-669.
Walsh TJ et al. ASH 2003. *Blood.* 2003;102:11:195a. Abstract 682.

Activité Posaconazole - Fusarium

- **Puissante activité *in vitro* et *in vivo* du posaconazole confirmée**
- **Taux de succès:** 46% (11/24)
  - **18 réfractaires/intolérants**
  - **6 infections prouvées mais pas réfractaires/intolérantes**
- **Infections réfractaires/intolérantes :** 39% (7/18)
  - **9 patients présentaient une infection disséminée**
  - **14 réfractaires, 4 intolérants**
  - **Traitement précédent par l'amphotéricine B**

Raad I et al. ICAAC 2004. Abstract M-669.

Tolérance posaconazole - Résumé

- **Large expérience**
  - **>2200 patients traités**
  - **>1000 patients traités par ≥800 mg par jour**
- **Profil de tolérance:**
  - **Les effets secondaires gastro-intestinaux ont été les plus fréquemment observés**
  - **Les anomalies visuelles ont été rares**
  - **L'augmentation des enzymes hépatiques a été minime, même pendant l'exposition maximale**
  - **Faible potentiel d'allongement du QTc**

Data on file. SPRI, Kenilworth, NJ.

Posaconazole - Résumé

- **Suspension orale**
- **Dose recommandée de 400 mg 2 x jour**
- **Large spectre d'activité contre une variété de levures et de champignons filamenteux**
- **Profil de tolérance similaire au fluconazole**
- **Chez les patients avec *Aspergillus*, posaconazole a une activité supérieure à celle du contrôle historique (p = .006) avec une amélioration de la survie statistiquement significative (p < 0.001)**
- **Efficacité confirmée sur les infections rares (ex.: Zygomycoses et fusarioses)**
- **Pas d'ajustement de posologie en cas d'insuffisance rénale.**

Posaconazole vs Fluconazole for Prophylaxis of Invasive Fungal Infections in Allogeneic Hematopoietic Stem Cell Transplant Recipients With Graft-Versus-Host Disease

Ullmann AJ et al. ICAAC 2005. Abstr. 2111.

Current Prophylaxis Options

- **Fluconazole approved for prophylaxis in patients undergoing HSCT in the US[1]**
  - **Fluconazole does not have activity against moulds including *Aspergillus*[2]**
- **Itraconazole approved for prevention of fungal infection during prolonged neutropenia when standard therapy is considered inappropriate in the EU[3]**
  - **Itraconazole associated with poor tolerability and erratic bioavailability[4]**
- **Micafungin approved for prophylaxis in patients undergoing HSCT in the US[5]**
  - **Micafungin did not demonstrate significant benefit over fluconazole in reducing infections due to *Aspergillus*/other moulds[6]**

HSCT indicates hematopoietic stem cell transplantation.

[1]Diflucan [prescribing information]. New York, NY: Pfizer Inc; 2004.
[2]Gallagher JC et al. *Exp Rev Anti-infect Ther*. 2004;2:253-268.
[3]Sporanox™ IV [prescribing information]. Bucks, United Kingdom: Janssen-Cilag Ltd; 2004.
[4]Marr KA et al. *Blood*. 2004;103:1527-1533
[5]Mycamine [prescribing information]. Deerfield, Ill: Astellas Pharma; 2005.
[6]van Burik J et al. *Clin Infect Dis.* 2004;39:1407-1416.

Purpose and Objective of Posaconazole Prophylaxis Study

Purpose

- Determine safety, tolerability, and efficacy of posaconazole as prophylaxis for IFI in high-risk HSCT recipients with grade II-IV acute GVHD or extensive chronic GVHD receiving intensive immunosuppressive therapy

Primary objective

- Determine efficacy of posaconazole vs fluconazole in preventing IFIs

GVHD indicates graft-versus-host-disease; HSCT, hematopoietic stem cell transplant; IFI, invasive fungal infection.

Posaconazole Prophylaxis Study
Methods

Study design	Inclusion/ exclusion	Treatment & duration	DRC adjudication	Clinical end points

Selected inclusion criteria

- Male or female HSCT recipients ≥13 years of age
- Acute or chronic extensive GVHD
- Treatment with intensive immunosuppressive therapy
  - High-dose corticosteroids
  - Antithymocyte globulin
  - Steroid-sparing regimen comprising a combination of ≥2 immunosuppressive agents or modalities

DRC indicates Data Review Committee; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant.

Posaconazole Prophylaxis Study
Methods

Study design	Inclusion/ exclusion	Treatment & duration	DRC adjudication	Clinical end points

Treatment

- Double-blind, double-dummy study
- Posaconazole 200 mg oral suspension 3 times daily
- Fluconazole 400 mg capsule once daily

Duration

- Up to 112 days therapy or until
  - Breakthrough IFI
  - Adverse event requiring discontinuation
  - Death due to underlying disease or GVHD
- 2-month follow-up

DRC indicates Data Review Committee; GVHD, graft-versus-host disease; IFI, invasive fungal infection.

Posaconazole Prophylaxis Study
Methods

Study design	Inclusion/ exclusion	Treatment & duration	DRC adjudication	Clinical end points

- **Primary endpoint**
  - Incidence of DRC-adjudicated proven or probable IFI during primary time period for ITT population
- **Secondary endpoints include**
  - Incidence of proven or probable
    - Aspergillosis during the primary time period
    - Breakthrough IFIs while on treatment
    - Breakthrough aspergillosis while on treatment
  - Mortality (overall and IFI-attributable)

DRC indicates Data Review Committee; IFI, invasive fungal infection.

Posaconazole Prophylaxis Study
Patient Disposition and Treatment Duration

	Posaconazole	Fluconazole
ITT population, n	301	299
All-treated subjects, n	291	288
Mean treatment duration, days (SD)	80.3 (42.9)	77.2 (42.7)
Median treatment duration, days (range)	111 (1–138)	108 (1–130)

ITT population: all randomized subjects

All-treated subjects: ITT subset who received ≥ 1 dose

ITT indicates intent-to-treat.

Posaconazole Prophylaxis Study
Incidence of Filamentous Fungi

Proven/Probable IFI, n	Posaconazole n = 301	Fluconazole n = 299
Aspergillus		
Aspergillus NOS	5	11 (9)
A. fumigatus	2	5 (4)
A. flavus	0	3
A. niger	0	1
A. terreus	0	1
Mould NOS	2 (1)	1
Rhizomucor spp.	0	1 (1)
Scedosporium prolificans	1 (1)	0
Pseudallescheria boydii	1 (1)	0

Numbers in parentheses indicate proven/probable IFIs while on study drug.
IFI indicates invasive fungal infection; NOS, not otherwise specified.

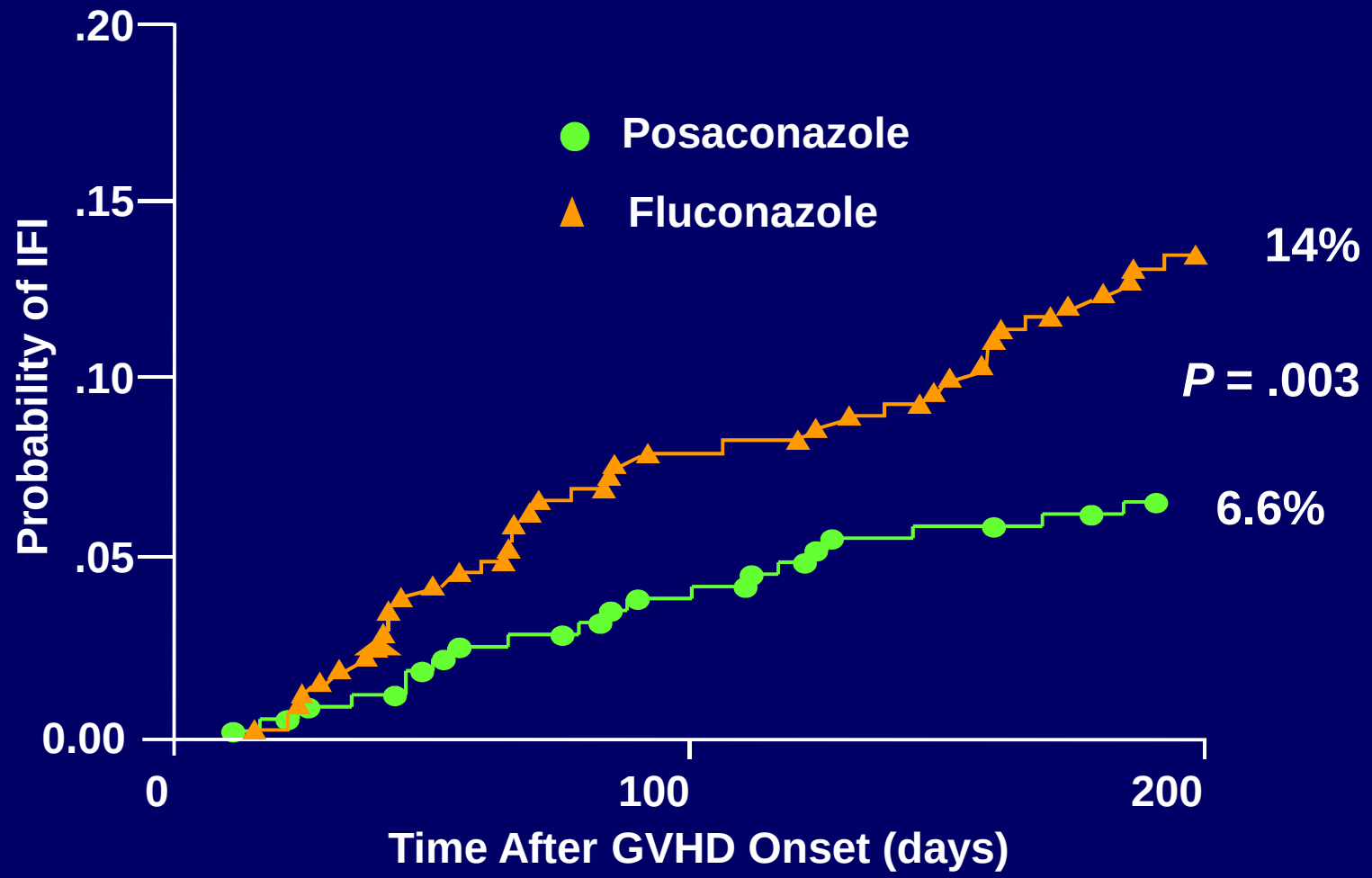
Posaconazole Prophylaxis Study
Incidence of Yeasts

Proven/Probable IFI, n	Posaconazole n = 301	Fluconazole n = 299
Candida		
Candida NOS	1	0
C. krusei	1	1 (1)
C. albicans	0	1 (1)
C. glabrata	2 (1)	1 (1)
C. parapsilosis	0	1
Trichosporon beigelii	1 (1)	0

Numbers in parentheses indicate proven/probable IFIs while on study drug.
IFI indicates invasive fungal infection; NOS, not otherwise specified.

Probability of IFI After GVHD Onset

All 62 Cases (Any Time)



Non–Kaplan-Meier cumulative incidence.
GVHD indicates graft-versus-host disease; IFI, invasive fungal infection.

Posaconazole Prophylaxis Study
All-Cause Mortality—Primary Time Period

Cause of Death [Investigator assessment], n (%)	Posaconazole n = 301	Fluconazole n = 299
Total Deaths	**79 (25)**	**84 (28)**
Adverse event	39 (13)	37 (12)
Complications related to IFI*	**2 (1)***	**11 (4)***
Progression of underlying disease/GVHD	31 (10)	33 (11)
Other	2 (1)	2 (1)

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

*p=0.041 by Chi-square test

b1

Posaconazole Prophylaxis Study
Safety and Tolerability Results

Adverse events, n (%)	Posaconazole n = 301	Fluconazole n = 299
Discontinuations due to events (occurring in ≥4%)	103 (34)	114 (38)
Nausea	13 (4)	9 (3)
Vomiting	10 (3)	12 (4)
Serious events* (occurring in ≥2%)	40 (13)	29 (10)
Elevated gamma-GT	5 (2)	3 (1)
Elevated hepatic enzymes	6 (2)	1 (<1)
Events* (occurring in ≥4%)	107 (36)	115 (38)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Diarrhea	8 (3)	12 (4)

One posaconazole treated patient experienced cyclosporine toxicity leading to death, considered possibly related to study treatment

*Treatment-related

Diapositive 22

b1 SP: Discontinuations here do not match overall disconituations in 316 subject disposition (Slide 20). Please advise.

Please advise whether you perfer slide 27 or 28. Slide 28 has the D/Cs due to AEs only if they were treatment related.

bkamp; 03/10/2005

Posaconazole Prophylaxis Study Overall Summary

- **First randomized trial demonstrating efficacy of antifungal prophylaxis in HSCT patients with severe GVHD**
- **Primary time period**
  - **POS superior to FLU in preventing breakthrough invasive aspergillosis**
  - **POS as effective as FLU in preventing IFIs overall**
- **While on treatment**
  - **POS superior to FLU in preventing breakthrough aspergillosis and IFIs overall**
- **POS decreased mortality due to IFIs vs FLU**
- **POS and FLU were similarly well tolerated**

FLU indicates fluconazole; IFI, invasive fungal infection; POS, posaconazole.

Posaconazole vs Standard Azoles as Antifungal Prophylaxis in Neutropenic Patients With Acute Myelogenous Leukemia or Myelodysplastic Syndrome: Impact on Mortality

OA Cornely, MD[1], J Maertens, MD[2], DJ Winston, MD[3], J Perfect, MD[4], D Helfgott, MD[5], AJ Ullmann, MD[6], and D Angulo-Gonzalez, MD[7]

[1]University of Cologne, Cologne, Germany; [2]University Hospital Gasthuisberg, Leuven, Belgium; [3]University of California, Los Angeles, CA, United States; [4]Duke University Hospital, Durham, NC, United States; [5]Cornell University Medical Center, New York, NY, United States; [6]Johannes Gutenberg University, Mainz, Germany; and [7]Schering-Plough Research Institute, Kenilworth, NJ, United States

Randomized, Open-label, Active-controlled, Multicenter Study

- **Population**
  - **Newly diagnosed or 1st relapse AML or MDS patients requiring intensive chemotherapy**
  - **Anticipated neutropenia (ANC ≤500 cells/mm^3) for ≥7 days**

- **Study Drugs (all oral suspension/solution)**
  - **POS 200 mg 3x daily**

    versus
  - **Standard azole**
    - **FLU 400 mg 1x daily or**
    - **ITZ 200 mg 2 x daily**

Designated by site prior to study initiation

- **Treatment was initiated with each cycle of chemotherapy for a maximum duration of 84 days**

Prespecified Study Endpoints

- **Primary Endpoint**
  - **Incidence of proven or probable IFI during the treatment phase (DRC-determined)**
- **Other Endpoints**
  - **Overall and IFI-related mortality at d100 after randomization**
  - **Incidence of IFIs from randomization to d100**
  - **Incidence of IFIs caused by *Aspergillus* spp during the treatment phase**

Blinded DRC adjudicated all IFIs as proven, probable, or possible according to EORTC/MSG consensus criteria

Demographic Characteristics

Characteristic	POS (n = 304)	FLU/ITZ (n = 298)*
Age, median, y (range)	53 (13–82)	53 (13–81)
Caucasian, n (%)	220 (72)	231 (78)
Male, n (%)	158 (52)	160 (54)
Primary diagnosis, n (%)		
AML New diagnosis	213 (70)	222 (74)
AML 1st relapse	42 (14)	38 (13)
MDS	49 (16)	38 (13)
Neutropenia severity, n (%)		
Baseline ANC ≤ 500 cells/mm^3	192 (63)	189 (63)
Nadir ** ANC < 500 cells/mm^3	298 (98)	290 (97)
Nadir ** ANC ≤ 100 cells/mm^3	264 (87)	261 (88)

*FLU, n = 240; ITZ, n = 58. ** During Treatment.

Patient Characteristics During Treatment Phase

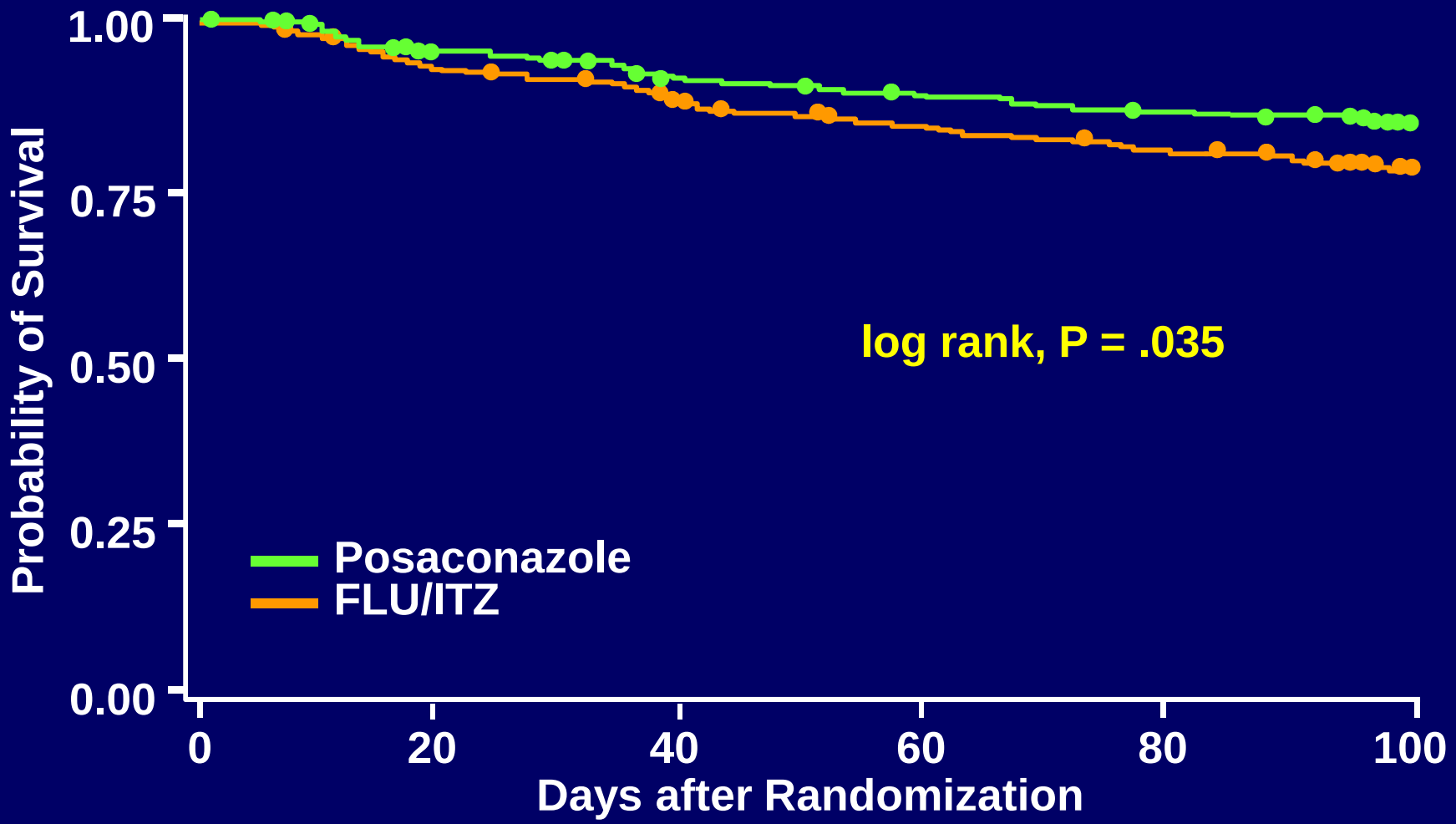
Characteristic	POS (n = 304)	FLU/ITZ (n = 298)
Duration of neutropenia, total days, n (%)		
0–7	21 (7)	21 (7)
>7–21	141 (46)	143 (48)
>21	142 (47)	134 (45)
Mean (SD)	25 (17.1)	23 (13.1)
Total chemotherapy cycles, n (%)		
1	174 (57)	182 (61)
2	96 (32)	89 (30)
≥3	34 (11)	27 (9)

All-Cause Mortality Comparison

n (%)	POS (n = 304)	FLU/ITZ (n = 298)	*P* value, chi²
Deaths total	**49 (16)**	**67 (22)**	**.048**
IFI*	**5 (2)**	**16 (5)**	**.012**
AML/MDS*	**24 (8)**	**21 (7)**	
Intercurrent illness*	**20 (7)**	**30 (10)**	
Deaths after randomization until d100	**44 (14)**	**64 (21)**	**.025**

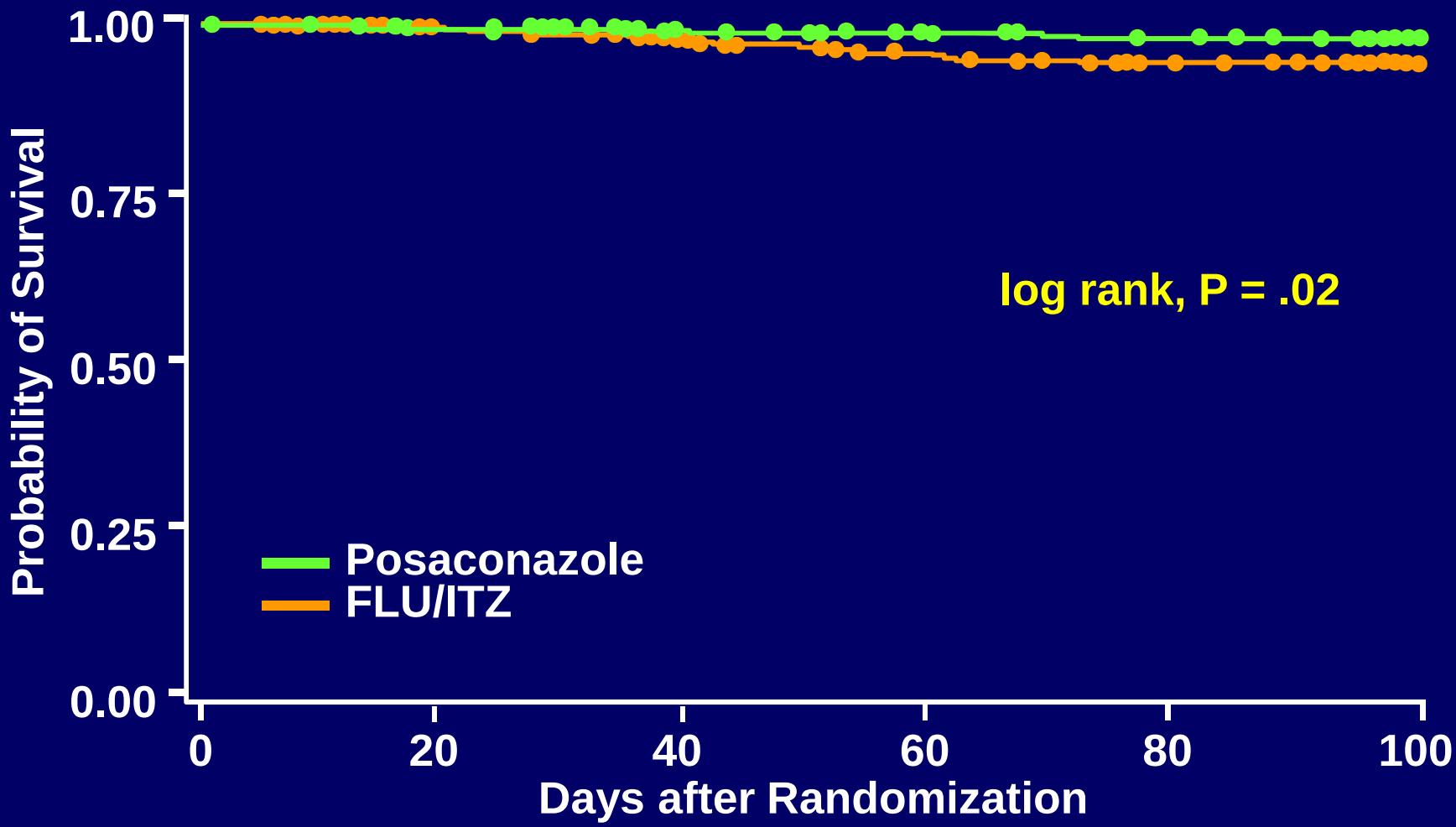
*attributable cause assessed by the investigator

Overall Mortality – Time to Death



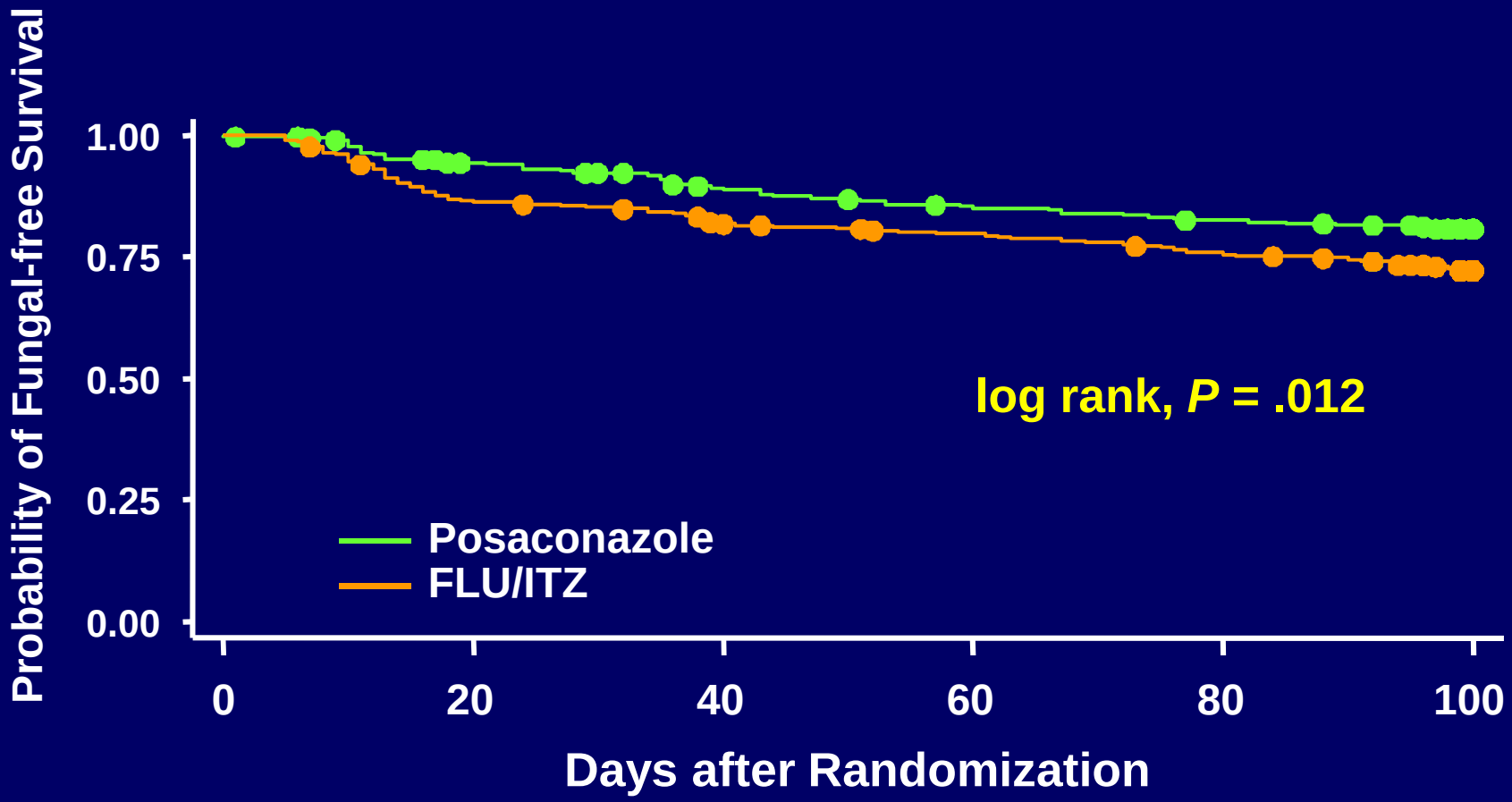
Censoring time is last contact or day 100.

IFI-Related Mortality – Time to Death



Censoring time is last contact or day 100.

Fungal-Free Survival



Incidence of Proven or Probable IFIs During Treatment and 100 Days Post-Randomization

n (%)	POS n = 304	FLU/ITZ n = 298	*P* value
IFIs during treatment phase	7 (2)	25 (8)	.0009
Aspergillosis during treatment phase	2 (1)	20 (7)	.0001
IFIs at day 100	14 (5)	33 (11)	.0031

Details of Proven and Probable IFIs During Treatment

Invasive Fungal Infection, n (%)	POS (n = 304)	FLU/ITZ (n = 298)
All	7 (2)	25 (8) FLU = 19/240 ITZ = 6/58
Aspergillosis	2 (1)	20 (7) FLU = 15/240 ITZ = 5/58
Other	*Candida* = 3 Mould NOS = 1 *Pneumocystis carinii* = 1	*Candida* = 2 *Pseudallescheria boydii* = 1 *Rhizopus* = 1 *Pneumocystis carinii* = 1

NOS indicates not otherwise specified.

Conclusions

In AML/MDS patients undergoing myelosuppressive chemotherapy

- **Posaconazole compared to FLU/ITZ in prophylaxis was associated with significant benefits in**
  - **overall survival**
  - **IFI-related survival, and**
  - **fungal free survival**
- **Posaconazole was superior to FLU/ITZ for prevention of proven and probable IFIs (ASH 2005)**
- **Posaconazole demonstrated a safety and tolerability profile comparable to that of the standard azoles group with FLU/ITZ**

---> 2 nouvelles indications pour NOXAFIL

AMM pour prophylaxie des IFI chez :

- patients LAM ou MDS recevant une chimiothérapie induisant une neutropénie prolongée

- receveurs de greffe de CSH sous traitement immunosuppresseur à haute dose pour GVHD

Posologie 600 mg/jour (200 mg x 3)

Projets: posaco IV (phase II vs vorico en 2007)

posaco vs L-AmB dans zygomycoses

Posaconazole et Zygomycoses

JAH van Burik et al CID 2006, 42, 61-5

Etude rétrospective 2001-4 91 pts

Usage compassionnel pour traitement de sauvetage

Zygomycose prouvée 69, probable 22

Patient : - réfractaire au traitement antérieur 81
- intolérant 10

800 mg/j

Evaluation après 12 semaines

60% succès (RC 14%+ RP 46%)

21% maladie stable

17% échec, 2% inclassables

38% DC jusqu'à 1 mois de suivi post traitement
(la moitié imputés à la zygomycose)

Succès Posaco à 12 semaines

Pathogène	Nb patients	% succès
Rhizopus sp	25	52
Mucor sp	17	77
Rhizomucor sp	7	29
Cunninghamella sp	8	75
Abdsidia sp	2	2/2

Conclusion : posaco = bonne alternative pour le moins

A évaluer vs AmB en 1ère ligne