

# Management of Confirmed Aspergillosis



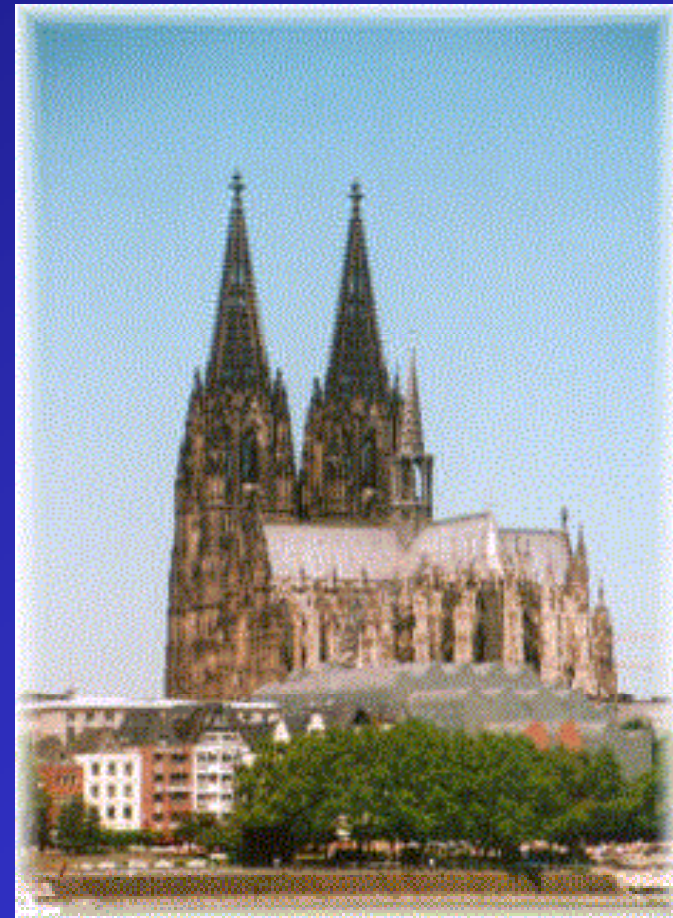
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University of Cologne



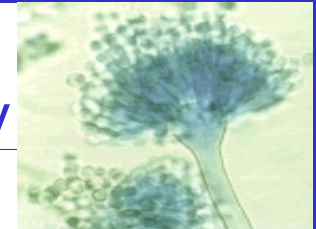
## VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

RAOUL HERBRECHT, M.D., DAVID W. DENNING, F.R.C.P., THOMAS F. PATTERSON, M.D., JOHN E. BENNETT, M.D.,  
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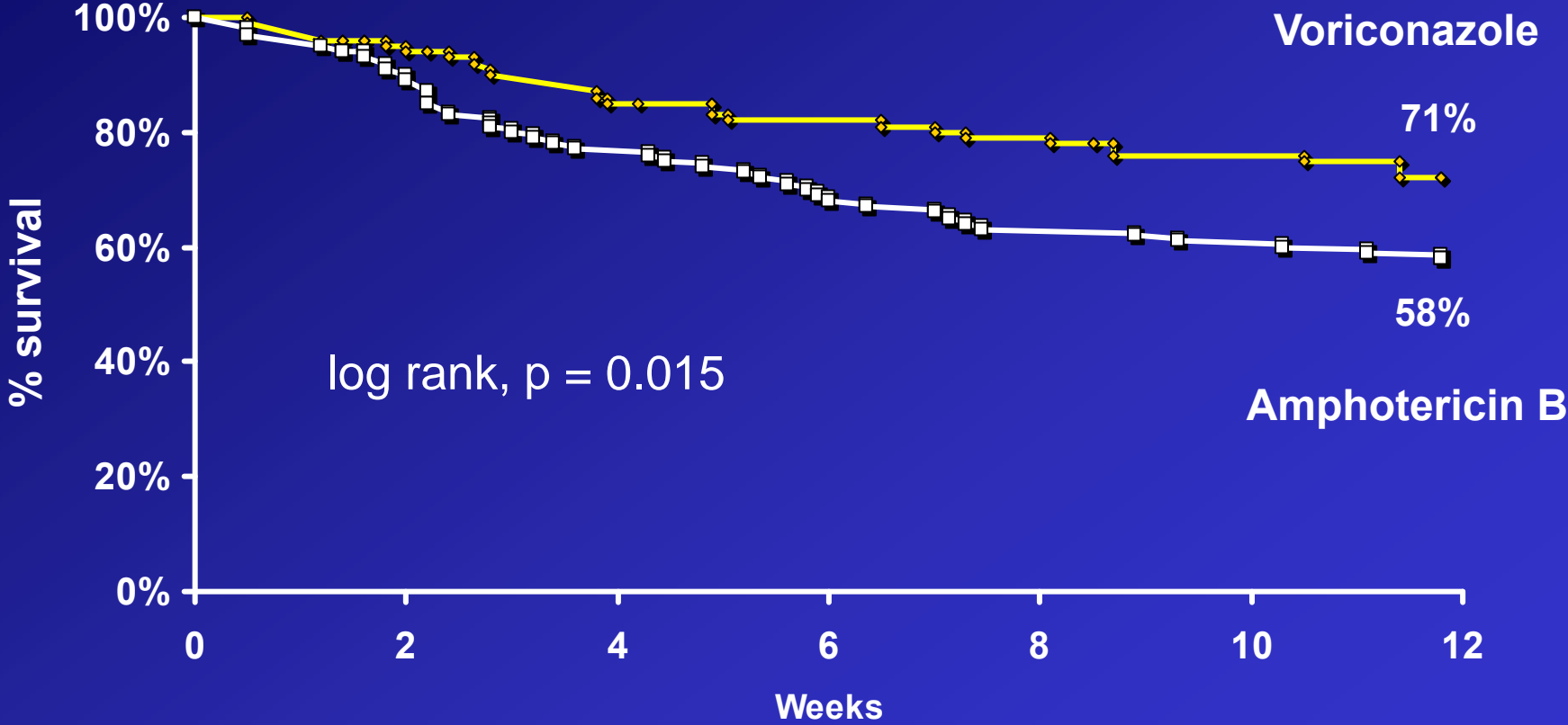


# Successful Response Rate

	Voriconazole n = 144	c-AmB n = 133
<b>Week 12</b> (95% CI 10 - 33%)	<b>76 (53%)</b>	<b>42 (32%)</b>

- **Voriconazole is superior to amphotericin B deoxycholate.**

# Overall Survival



Number of patients at risk

	0	2	4	6	8	10	12
Voriconazole	144	131	125	117	111	107	102
c-AmB	133	117	99	87	84	80	77

# What do European Guidelines Propose?

EJC SUPPLEMENTS 5 (2007) 49–59



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## Treatment of invasive *Candida* and invasive *Aspergillus* infections in adult haematological patients ☆

Raoul Herbrecht<sup>a,\*</sup>, Ursula Flückiger<sup>b</sup>, Bertrand Gachot<sup>c</sup>, Patricia Ribaud<sup>d</sup>,  
Anne Thiebaut<sup>e</sup>, Catherine Cordonnier<sup>f</sup>

# ECIL-1

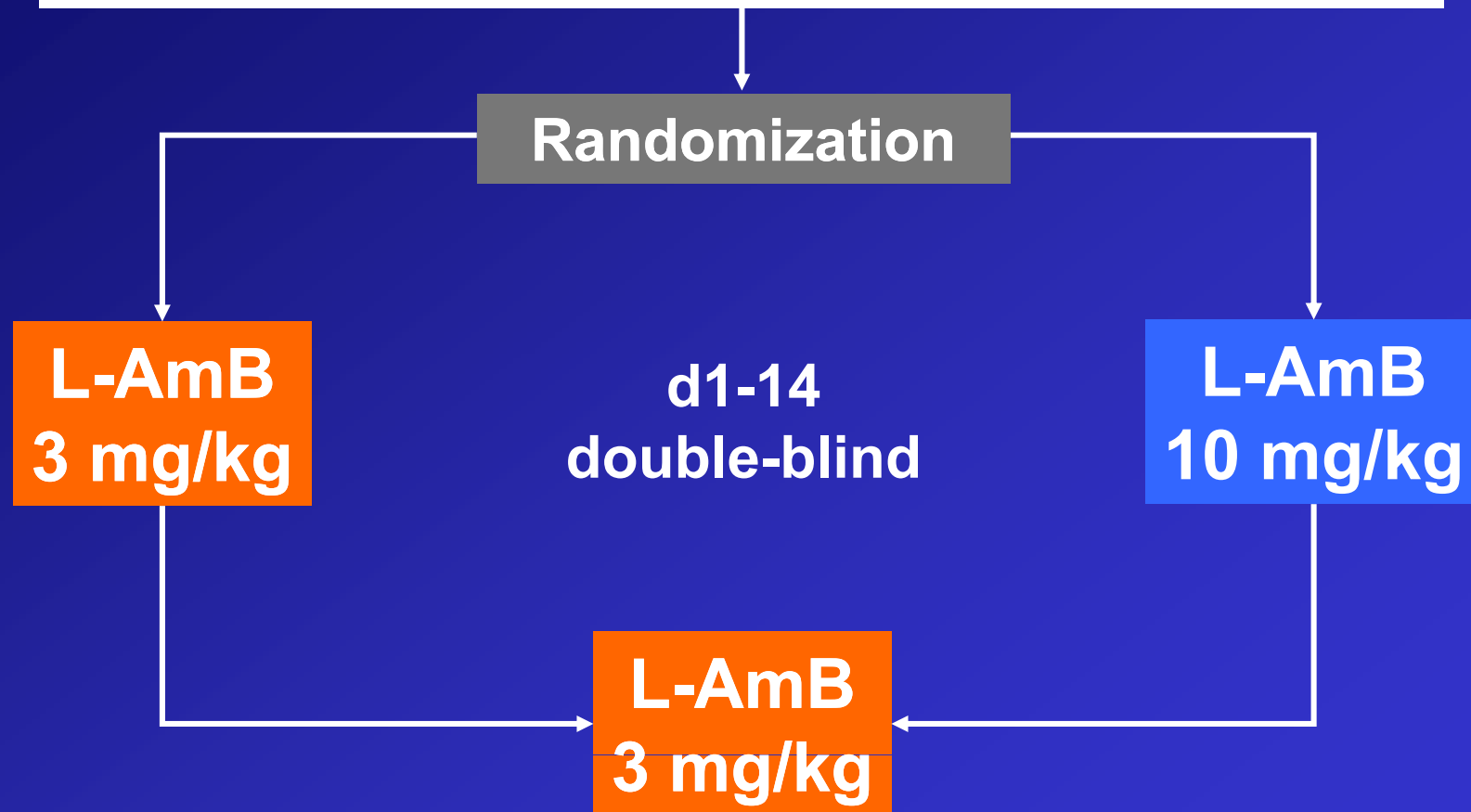
<b>Products</b>	<b>Rating</b>
<b>Voriconazole</b>	<b>A I</b>
<b>Amphotericin B deoxycholate</b>	<b>D I</b>
<b>Liposomal amphotericin B</b>	<b>B I</b>
<b>Amphotericin B lipid complex</b>	<b>B II</b>
<b>Amphotericin B colloidal dispersion</b>	<b>D I</b>
<b>Caspofungin</b>	<b>C III</b>
<b>Itraconazole</b>	<b>C III</b>
<b>Combination therapy</b>	<b>D III</b>

# Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High-Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

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# AmBiLoad – Trial Design

## Invasive Filamentous Fungal Infection

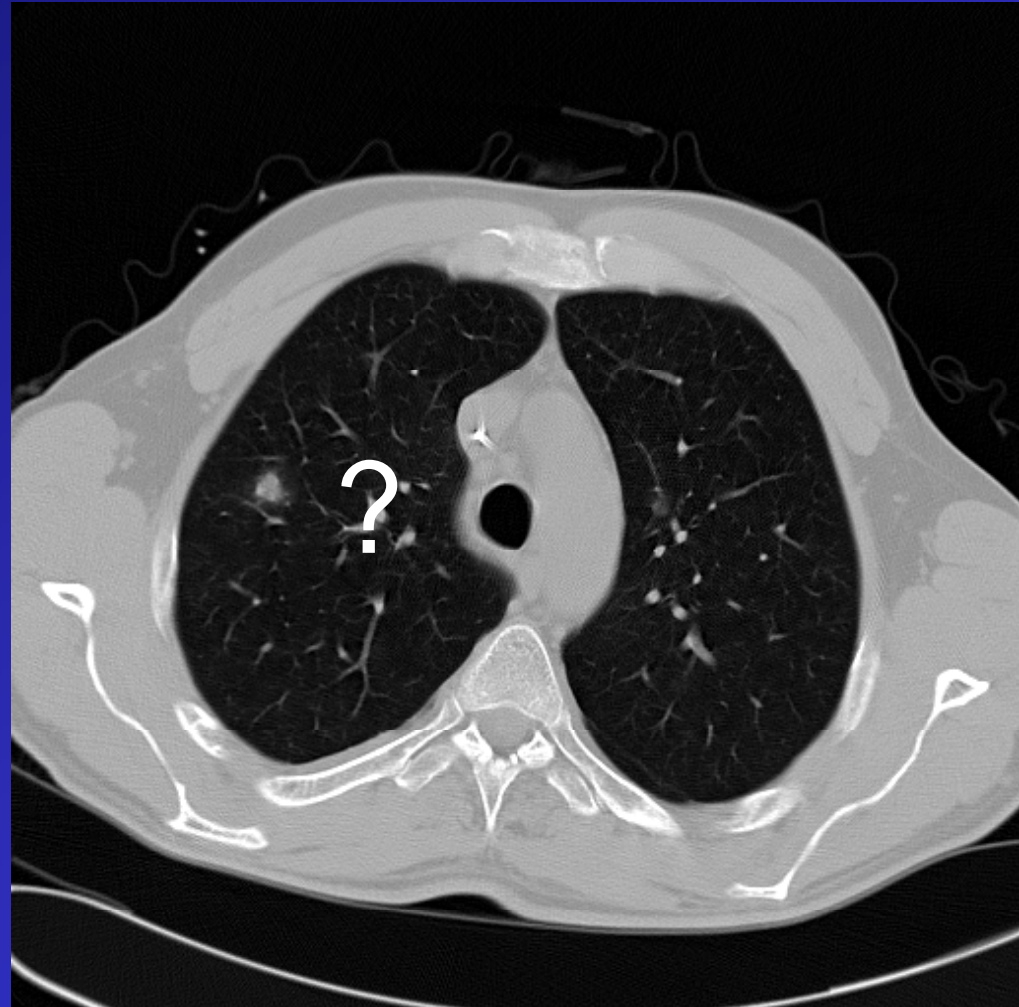
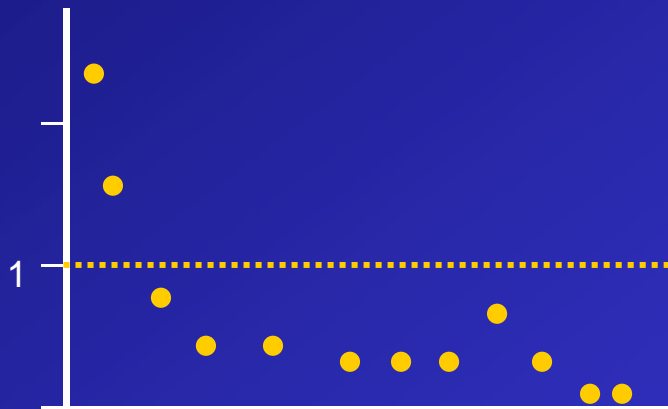




# Patient 1001 - probable

ALL  
Steroids  
Neutropenia  
Fever >72h

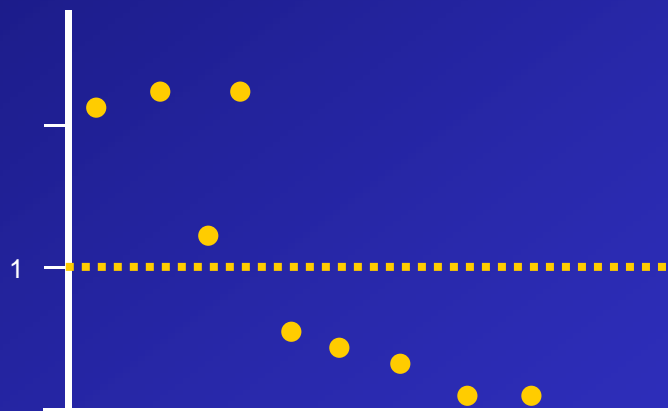
Galactomannan



# Probable Invasive Aspergillosis

AML  
Neutropenia  
Fever >72h  
Cough  
Dyspnea  
Pleuritis

Galactomannan



# Baseline Characteristics

	AmBi-3mg N=107	AmBi-10mg N=94
Age (mean, yrs) [range]	50.9 [15-76]	50.4 [2-78]
Sex: M/F (%)	57/43	67/33
Hematological Malignancies <sup>1</sup>	99 (93)	87 (93)
Controlled	36/99 (36)	26/85 (31)
Uncontrolled <sup>2</sup>	63/99 (64)	59/85 (69)
Allo-SCT	17 (16)	18 (19)
Auto-SCT	1 (1)	4 (4)
Solid Organ Transplant	1 (1)	0
HIV	2 (2)	2 (2)
Neutropenia at baseline	76 (71)	71 (76)

# Overall Response at EOT

<b>N (%)</b>	<b>L-AmB 3mg N=107</b>	<b>L-AmB 10mg N=94</b>
<b>Favorable</b>	<b>53 (50)</b>	<b>43 (46)</b>
<b>CR</b>	<b>1 (1)</b>	<b>2 (2)</b>
<b>PR</b>	<b>52 (49)</b>	<b>41 (44)</b>
<b>Unfavorable</b>		
<b>Stable</b>	<b>8 (7)</b>	<b>5 (5)</b>
<b>Failure</b>	<b>36 (34)</b>	<b>36 (38)</b>
<b>Not evaluable</b>	<b>10 (9)</b>	<b>10 (11)</b>

# Conclusions

- **In a highly immunocompromised population**
  - 93% hematological malignancies
  - 42% neutropenia persisting at EOT
  
- 1. L-AmB 3mg/kg as 1st line treatment for aspergillosis resulted in a**
  - 50% success rate
  - 72% 12 week survival rate
  
- 2. L-AmB 10 mg/kg**
  - did not improve response or survival
  - was associated with higher rates of toxicity

# What do US Guidelines Propose?

IDSA GUIDELINES

## Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

**Thomas J. Walsh,<sup>1,a</sup> Elias J. Anaissie,<sup>2</sup> David W. Denning,<sup>13</sup> Raoul Herbrecht,<sup>14</sup> Dimitrios P. Kontoyiannis,<sup>3</sup> Kieren A. Marr,<sup>5</sup> Vicki A. Morrison,<sup>6,7</sup> Brahm H Segal,<sup>8</sup> William J. Steinbach,<sup>9</sup> David A. Stevens,<sup>10,11</sup> Jo-Anne van Burik,<sup>7</sup> John R. Wingard,<sup>12</sup> and Thomas F. Patterson<sup>4,a</sup>**

<sup>1</sup>Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland; <sup>2</sup>University of Arkansas for Medical Sciences, Little Rock;

<sup>3</sup>The University of Texas M. D. Anderson Cancer Center, Houston, and <sup>4</sup>The University of Texas Health Science Center at San Antonio, San Antonio; <sup>5</sup>Oregon Health and Sciences University, Portland; <sup>6</sup>Veterans Affairs Medical Center and <sup>7</sup>University of Minnesota, Minneapolis, Minnesota; <sup>8</sup>Roswell Park Cancer Institute, Buffalo, New York; <sup>9</sup>Duke University Medical Center, Durham, North Carolina; <sup>10</sup>Santa Clara Valley Medical Center, San Jose, and <sup>11</sup>Stanford University, Palo Alto, California; <sup>12</sup>University of Florida, College of Medicine, Gainesville, Florida;

<sup>13</sup>University of Manchester, Manchester, United Kingdom; and <sup>14</sup>University Hospital of Strasbourg, Strasbourg, France

**Walsh T, et al. Clinical Infectious Diseases 2008; 46:327–60.**

# IDSA Guidelines 2000→2008: Primary Therapy of Invasive Aspergillosis

IDSA Guidelines 2000		
<p><b>Amphotericin B</b> <b>Liposomal amphotericin B</b></p>	<p><b>Amphotericin B has been the standard of treatment in invasive aspergillosis, particularly for life-threatening and severe infections. In well-characterized patients, the overall response rate has been 37% (range, 14%–83%)</b></p> <p><b>The lipid based formulations are indicated for patients with invasive aspergillosis who develop nephrotoxicity while receiving amphotericin</b></p>	<p><b>Rating</b> <b>AII<sup>1</sup></b></p>
IDSA Guidelines 2008		
<p><b>Voriconazole</b></p>	<p><b>Preferred therapy-Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients</b></p>	<p><b>Rating</b> <b>AI<sup>2,3</sup></b></p>
<p><b>Liposomal amphotericin B</b></p>	<p><b>Alternative-A randomized trial comparing two dosages of liposomal amphotericin B showed similar efficacy in both arms, suggesting that liposomal therapy could be considered as alternative primary therapy in some patients</b></p>	<p><b>AI<sup>2,3</sup></b></p>

<sup>1</sup>Stevens D, et al. *Clinical Infectious Diseases* 2000;30:696–709

<sup>2</sup>Patterson W, et al. *IDSA IA guidelines 2007, ICAAC 2007*

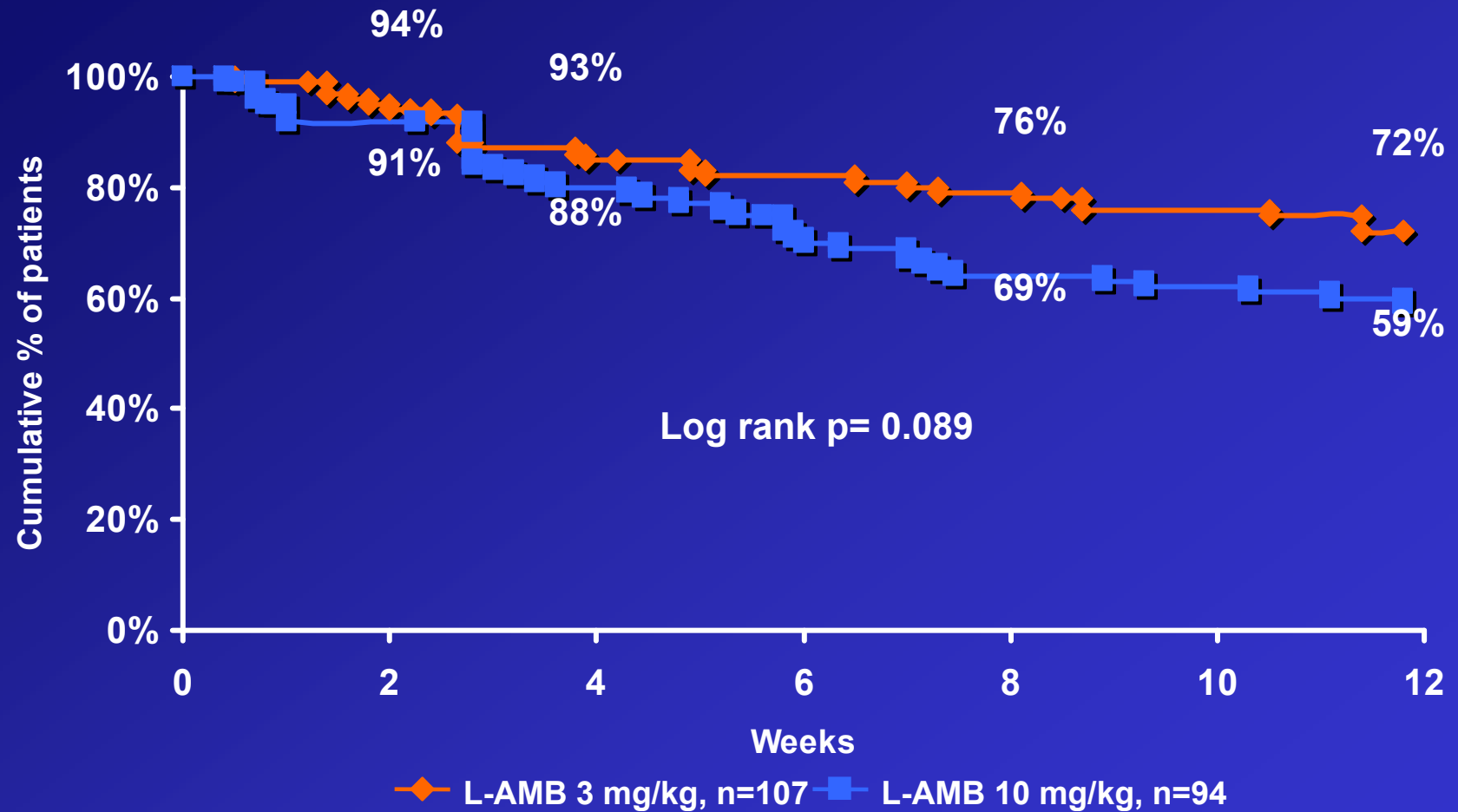
<sup>3</sup>Walsh T, et al. *Clinical Infectious Diseases* 2008; 46:327–60.

# **Survival and Sub-group Analyses from the AmBiLoad Trial**

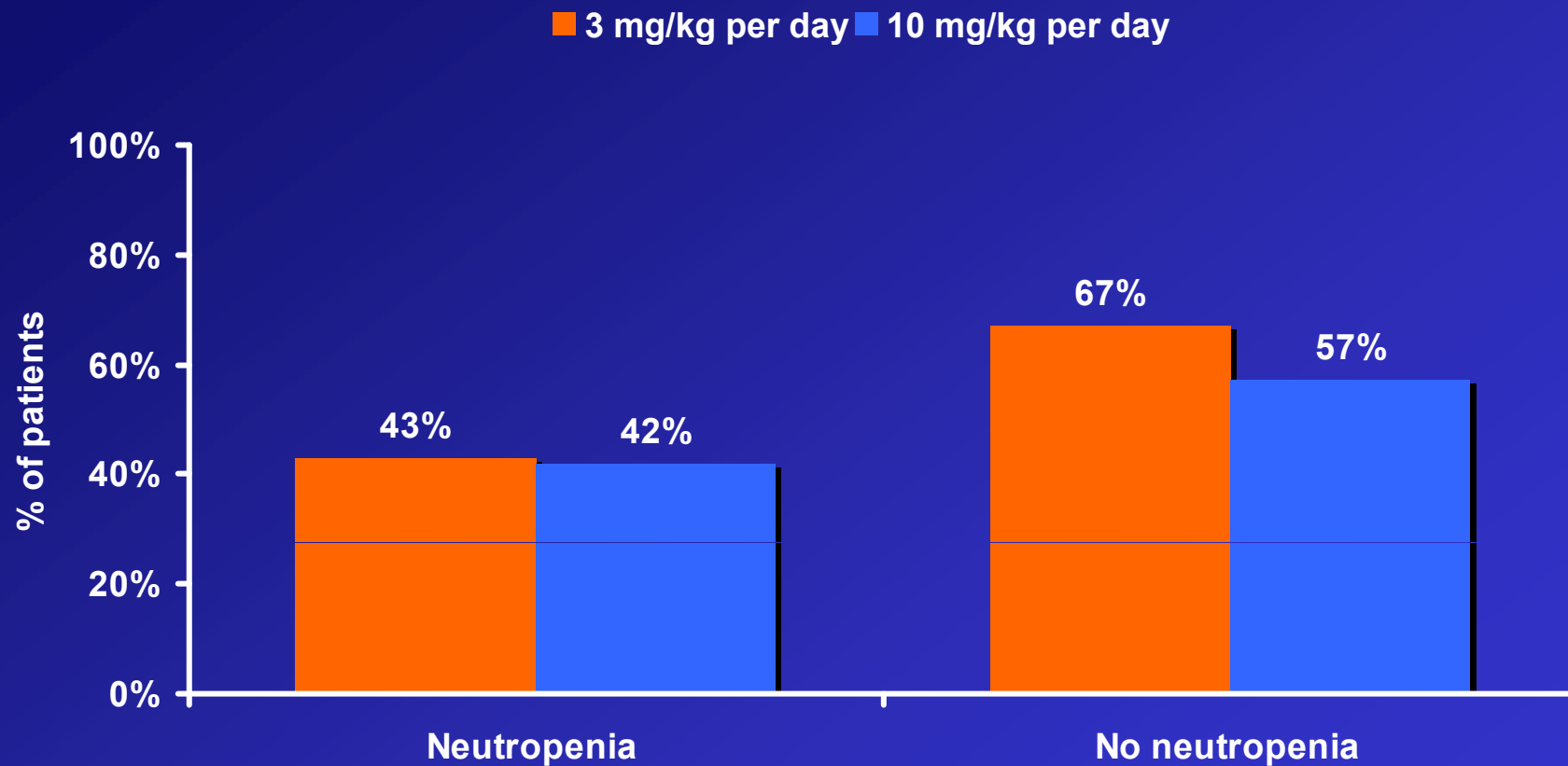
**New Insights**



# Survival Was Similar in Both Treatment Groups



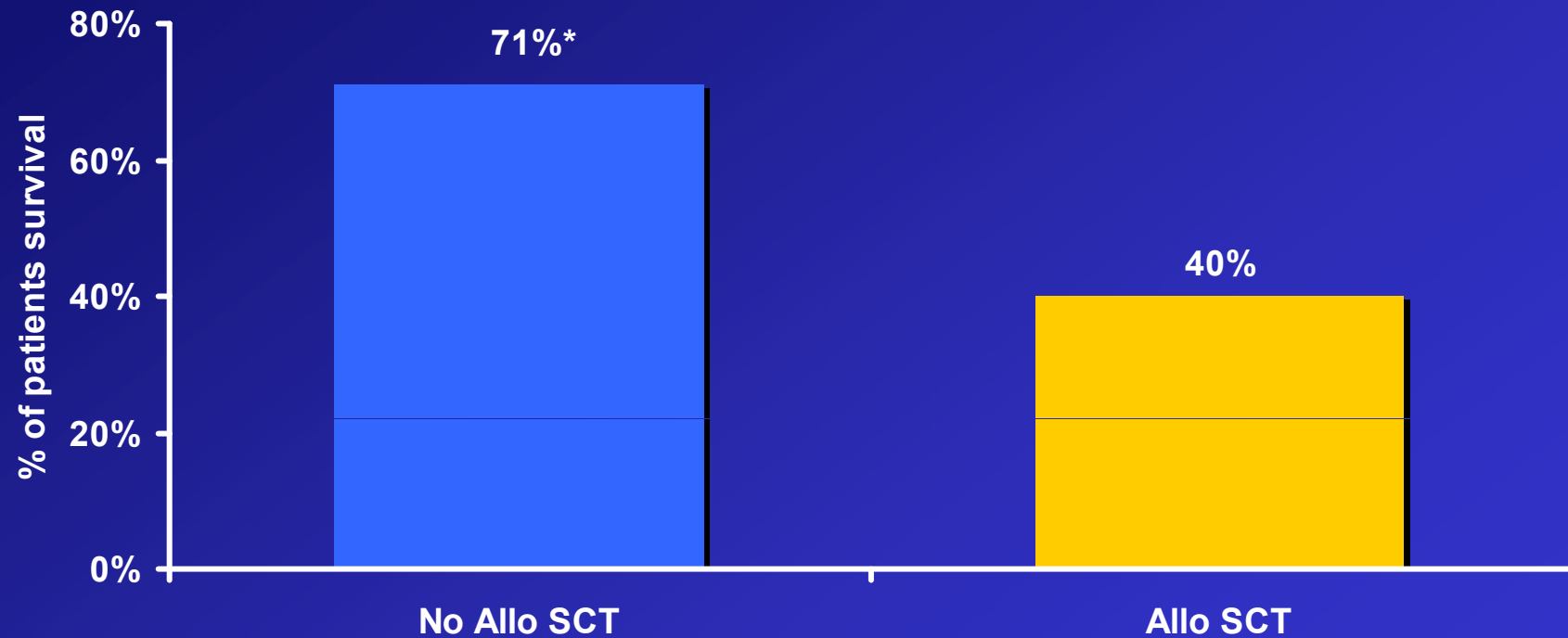
# Favorable Overall Response with L-AMB by Baseline Neutropenia Status



Cornely O, et al. Poster P122. 2nd Advances Against Aspergillosis, Athens, Greece, Feb 2006.

# **Stepwise Logistic Regression Analysis 12 Week Survival**

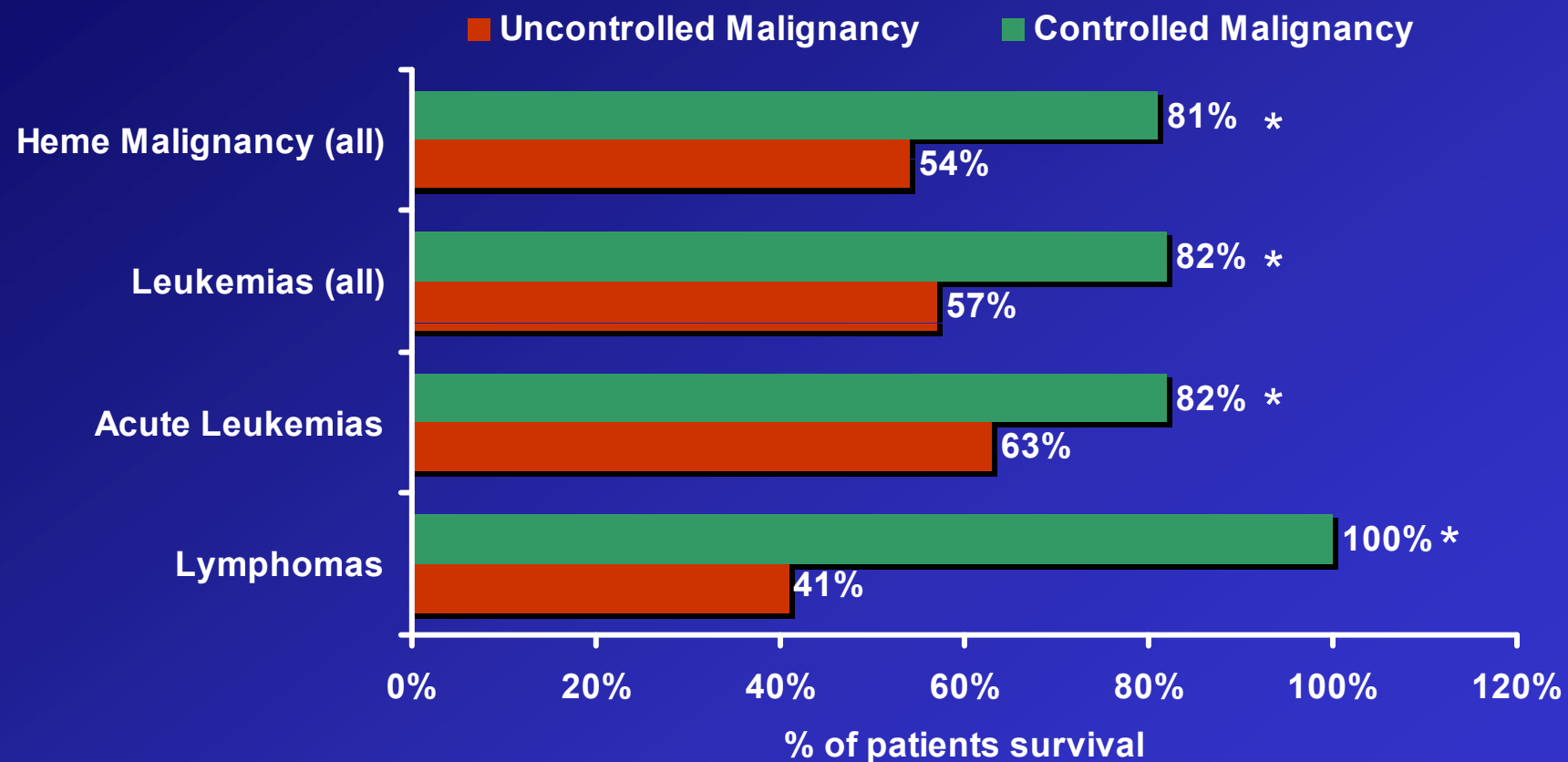
# Patients with Allo SCT Had a Lower Survival at 12 Weeks



\*P<0.001

Cornely O, et al. Poster P122. 2nd Advances Against Aspergillosis, Athens, Greece, Feb 2006.

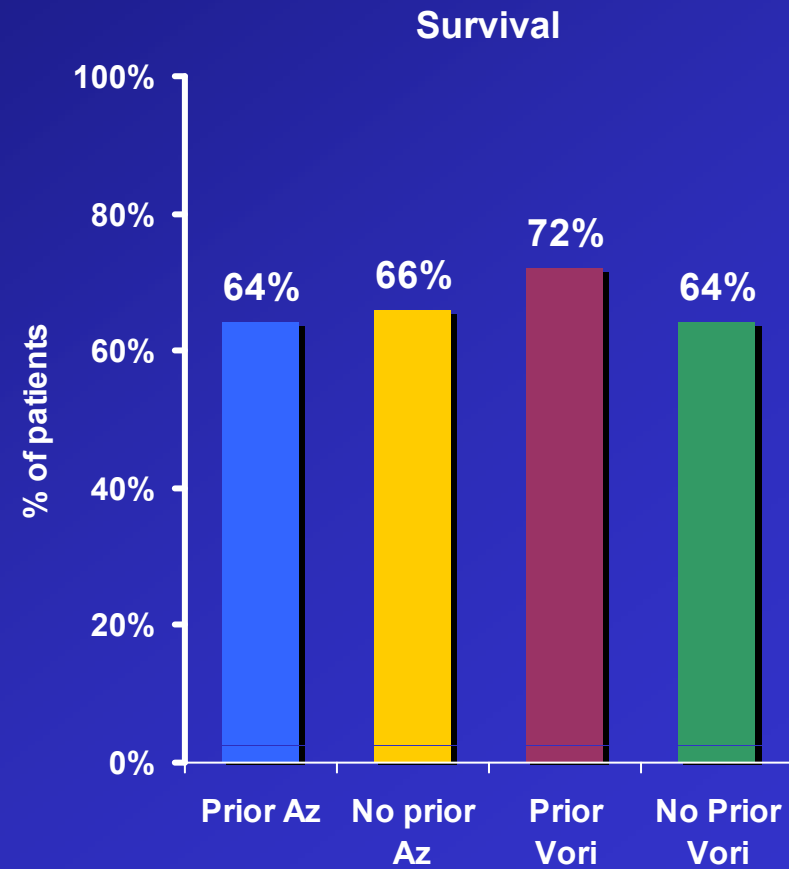
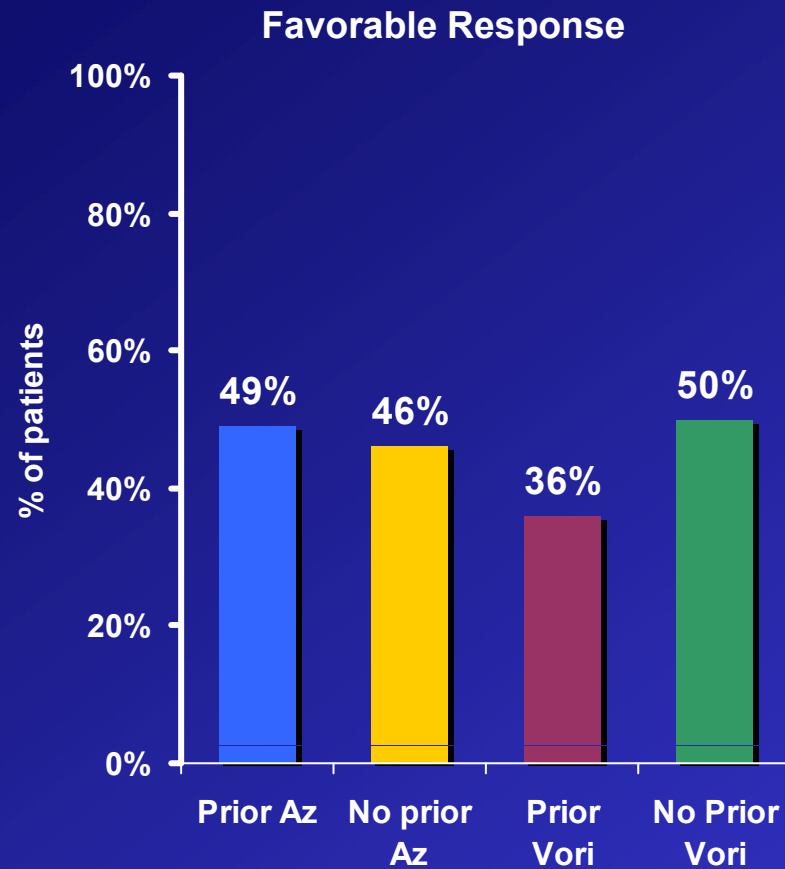
# Patients with Uncontrolled Malignancy Had a Lower Survival with L-AmB at 12 Weeks



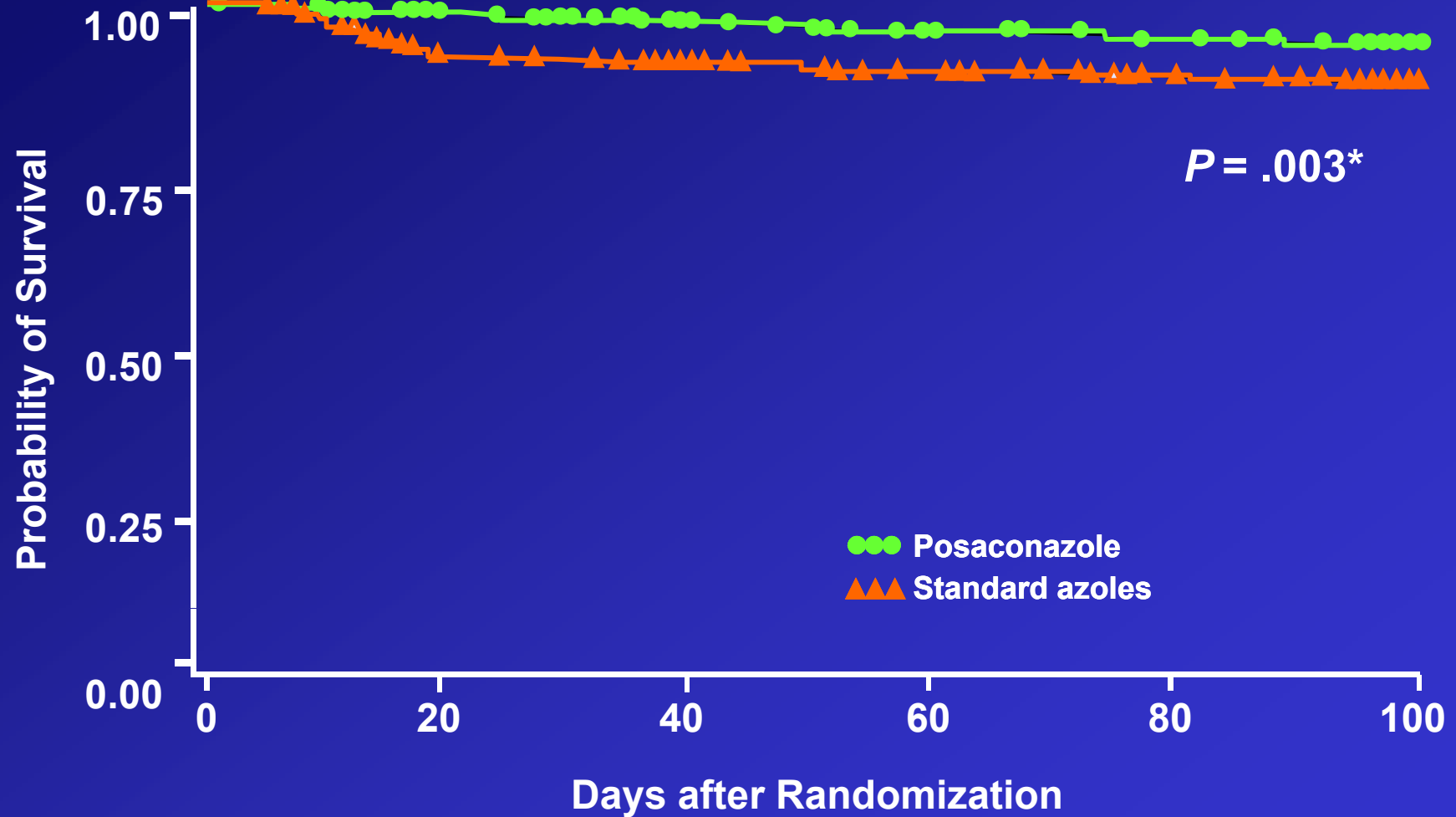
\* P < 0.05

# **Does Prior Antifungal Therapy Affect Outcomes with Liposomal Amphotericin B Therapy?**

# Response and Survival with L-AMB Was Not Affected by Prior Azole or Voriconazole Use



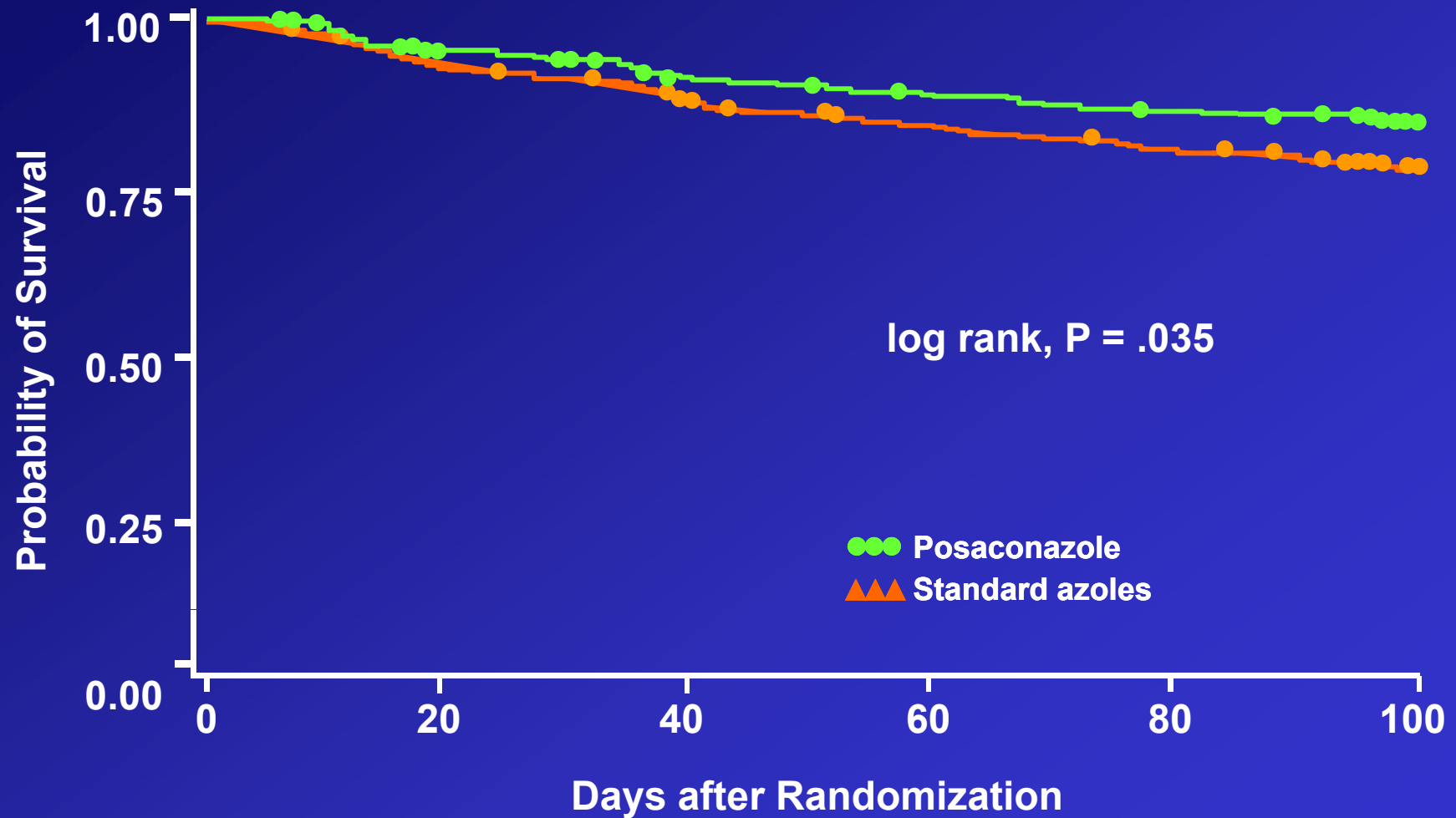
# Overall Mortality – Time to Death



Censoring time is last contact or day 100.



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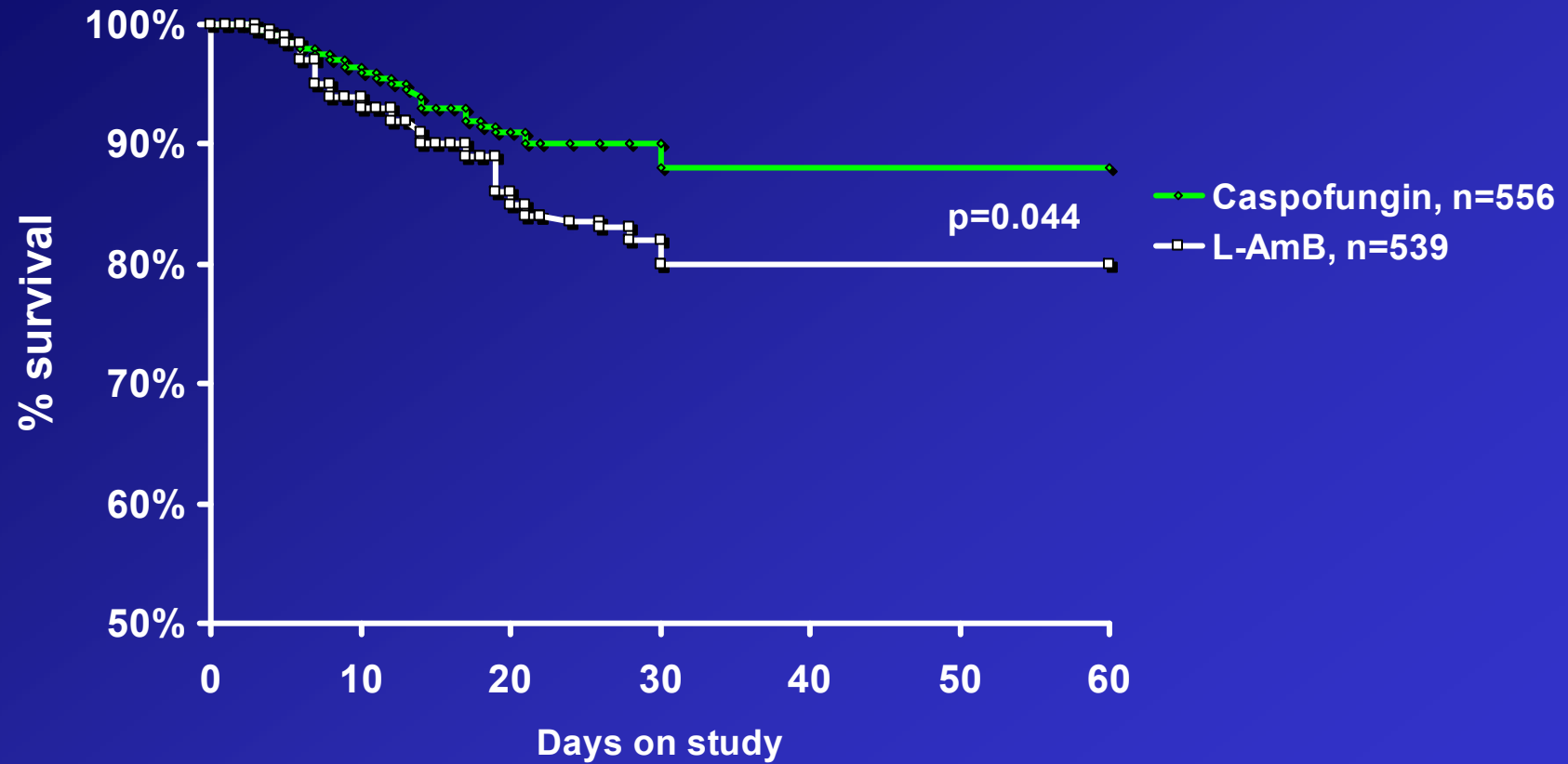
SEPTEMBER 30, 2004

VOL. 351 NO. 14

Caspofungin versus Liposomal Amphotericin B  
for Empirical Antifungal Therapy in Patients  
with Persistent Fever and Neutropenia

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Lindsey R. Baden, M.D., Anna Dmoszynska, M.D., Ph.D., Oliver A. Cornely, M.D., Michael R. Bourque, M.S.,  
Robert J. Lupinacci, M.S., Carole A. Sable, M.D., and Ben E. dePauw, M.D., Ph.D.

# Survival until Day 7 post EOT (MITT)



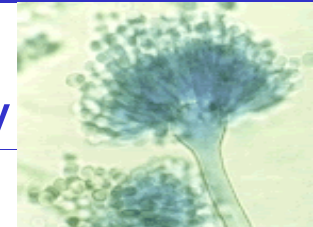
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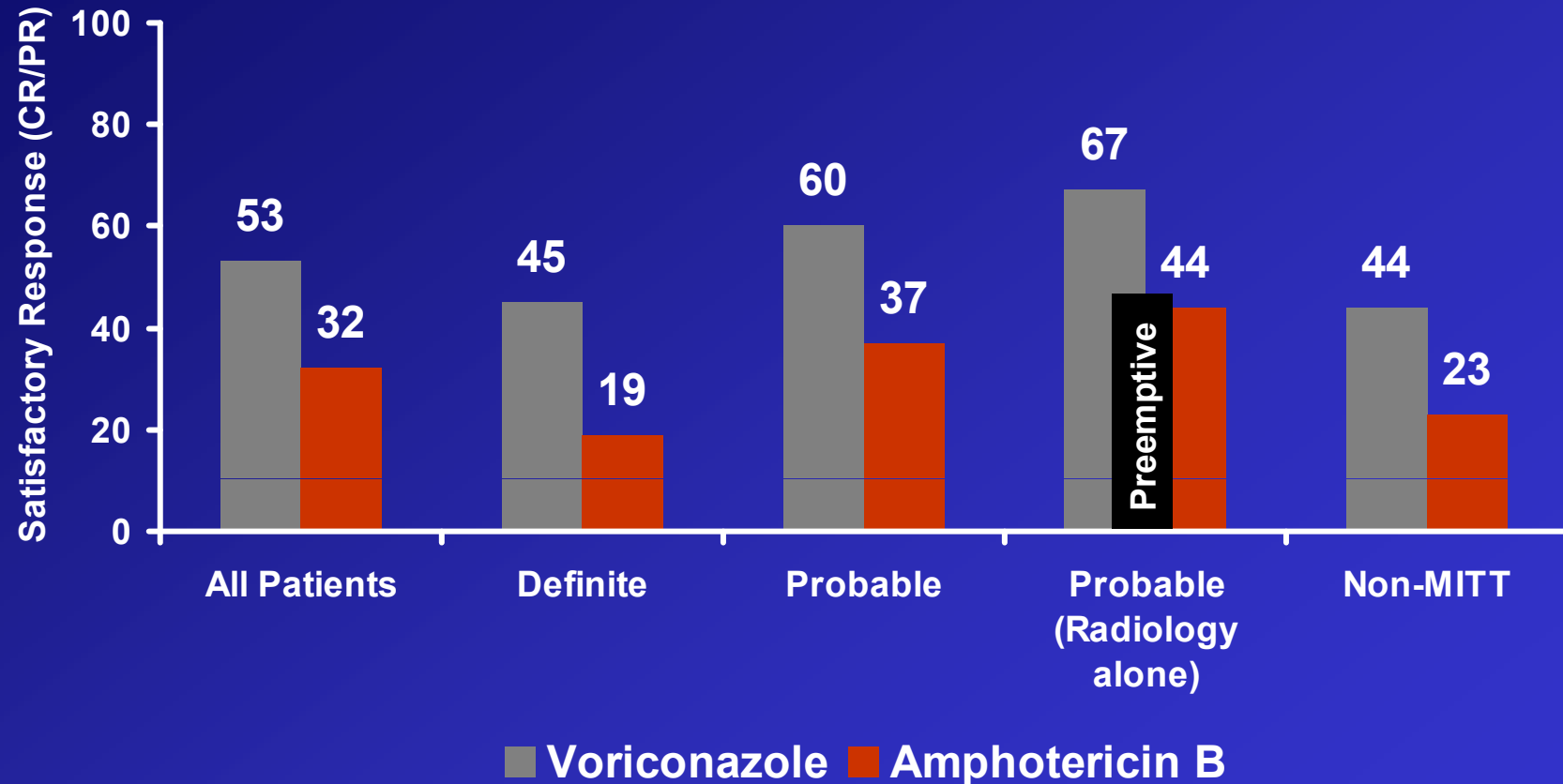


and  
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## Patients with Satisfactory Treatment Response Categorized by Baseline CT Findings (adapted from Tom Patterson)

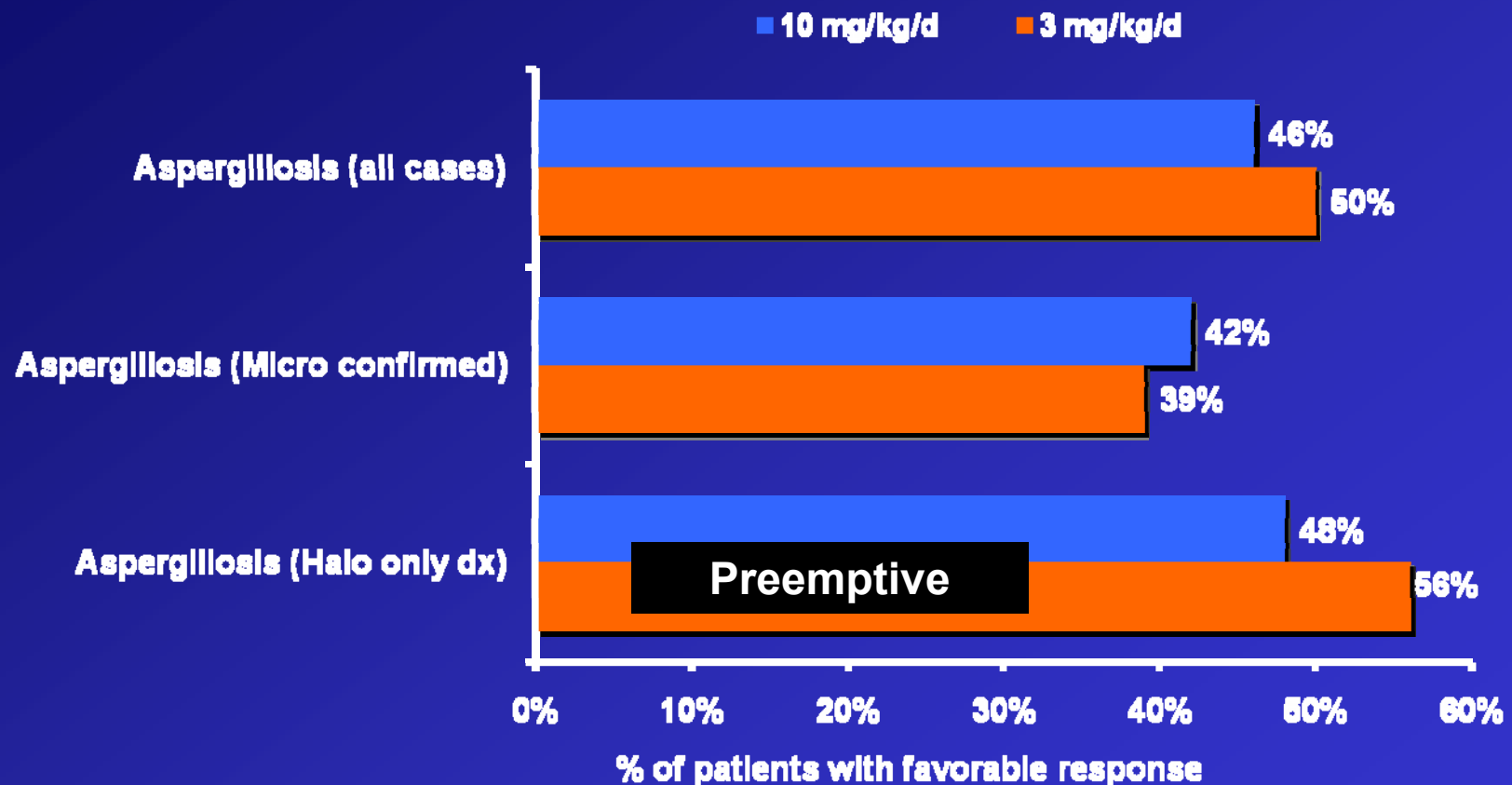


Herbrecht R et al. NEJM 2002;347:408-15;  
Patterson TF et al, Clin Infect Dis 2005;41:1448-52;  
Greene R et al. ECCMID 2003

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# Favorable Overall Response: No Significant Differences between Treatment Groups



No differences are statistically significant

Cornely O. et al. *Blood* 2005; 106:900a, Abstract 3222.

## Caspofungin for IA in Hematological Patients (EORTC)

- **Multicenter, open, phase II**
- **First-line therapy**
- **Probable and proven invasive aspergillosis**
- **First study to apply strict EORTC/MSG diagnostic criteria**
- **Response rate (%) in the 30s.**



# Conclusions

- **Voriconazole and liposomal amphotericin B both are AI recommended for 1st line treatment of IA.**
- **Diagnostic options are still very limited, making overtreatment clinical practice.**
  - **Early treatment yields the highest rates in response and survival.**
- **The clinical field moves away from treating proven/probable IA.**