Challenges of patient recruitment for invasive aspergillosis trials

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Challenges

Inclusion of a maximum number of patients for a minimum length of time

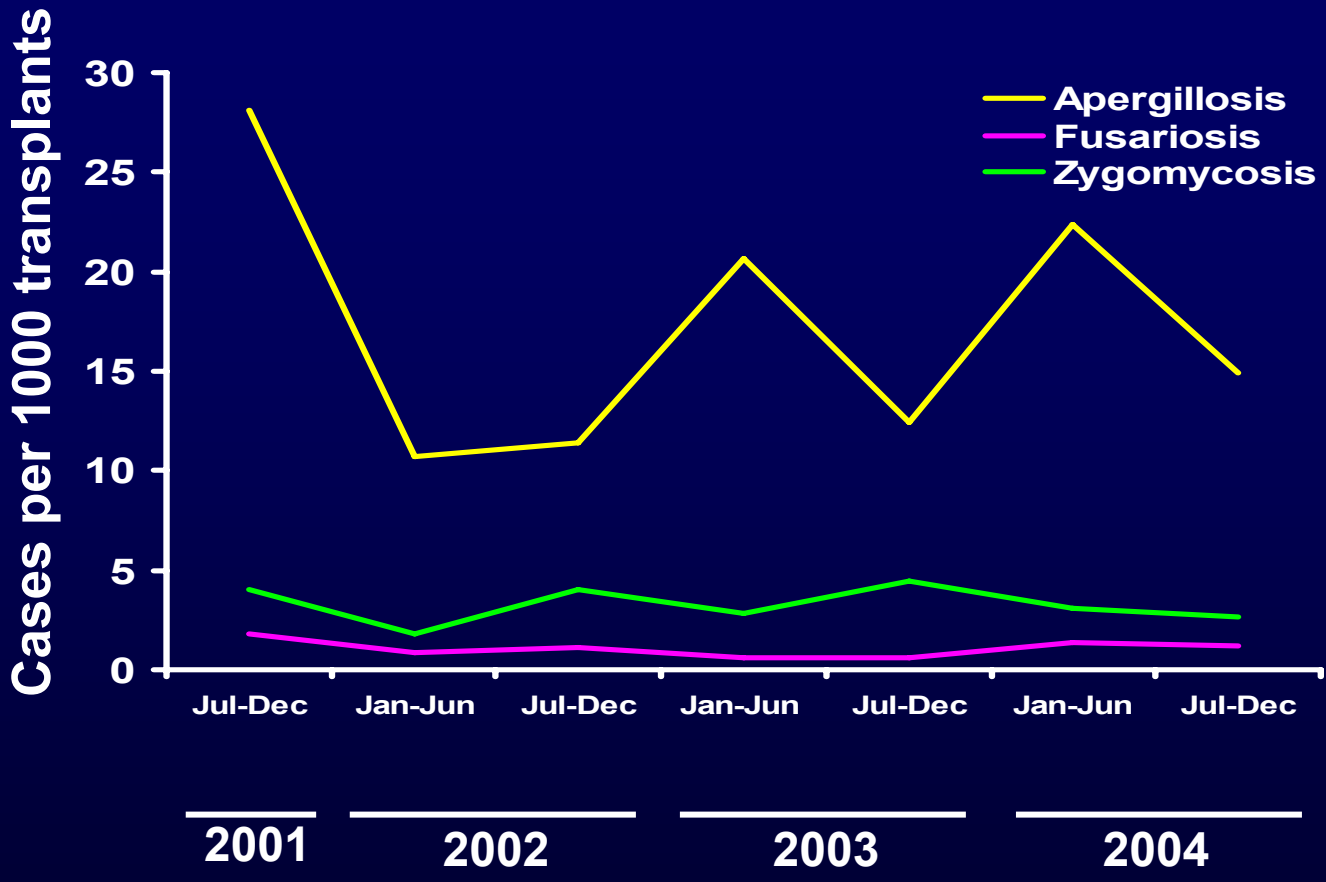
The final objective of an IA trial being to improve the prognosis of patients with invasive aspergillosis (IA)

Need a “good” drug and a “good” strategy

Problems…

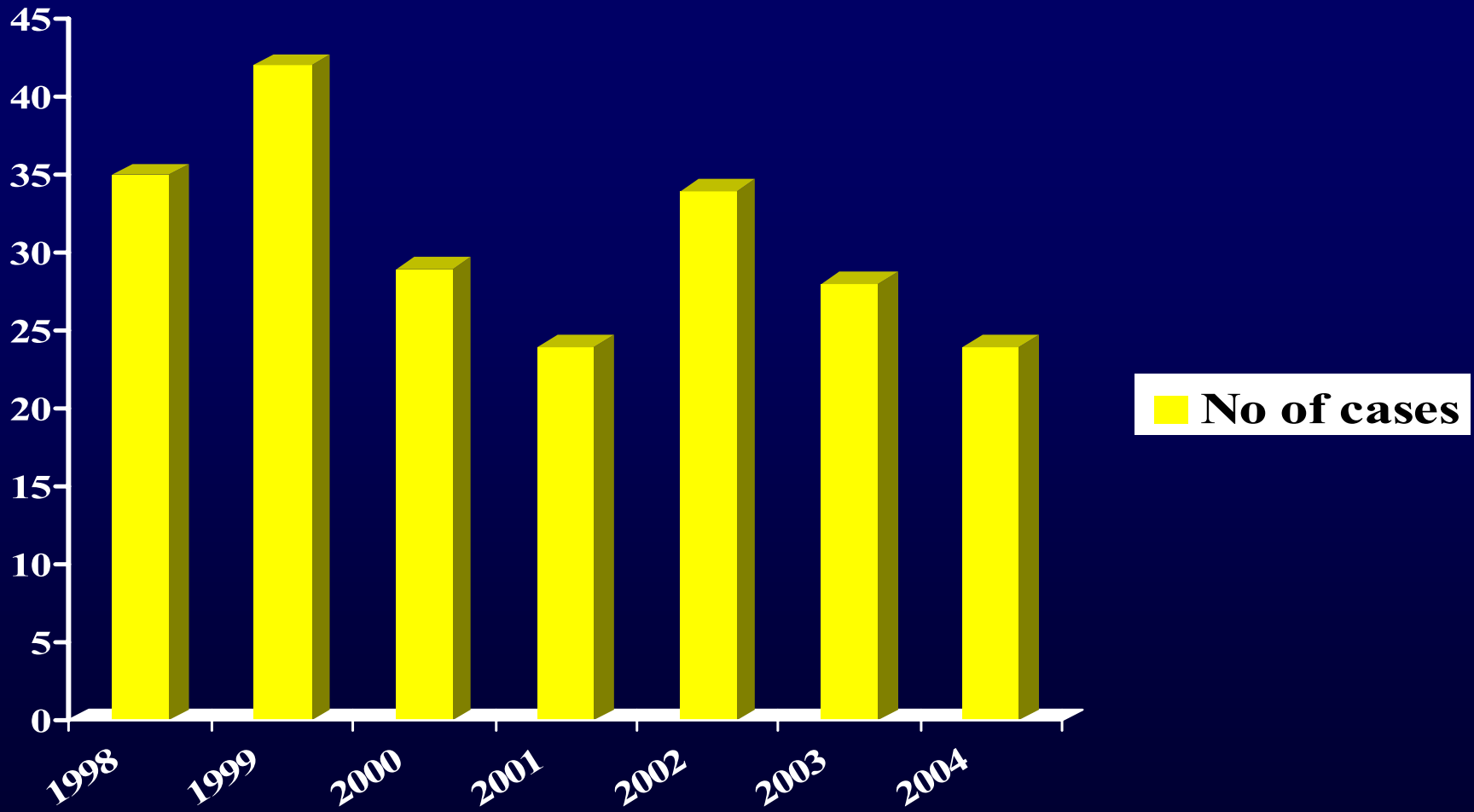
TRANSNET IFI Incidence

July 2001-Dec 2004



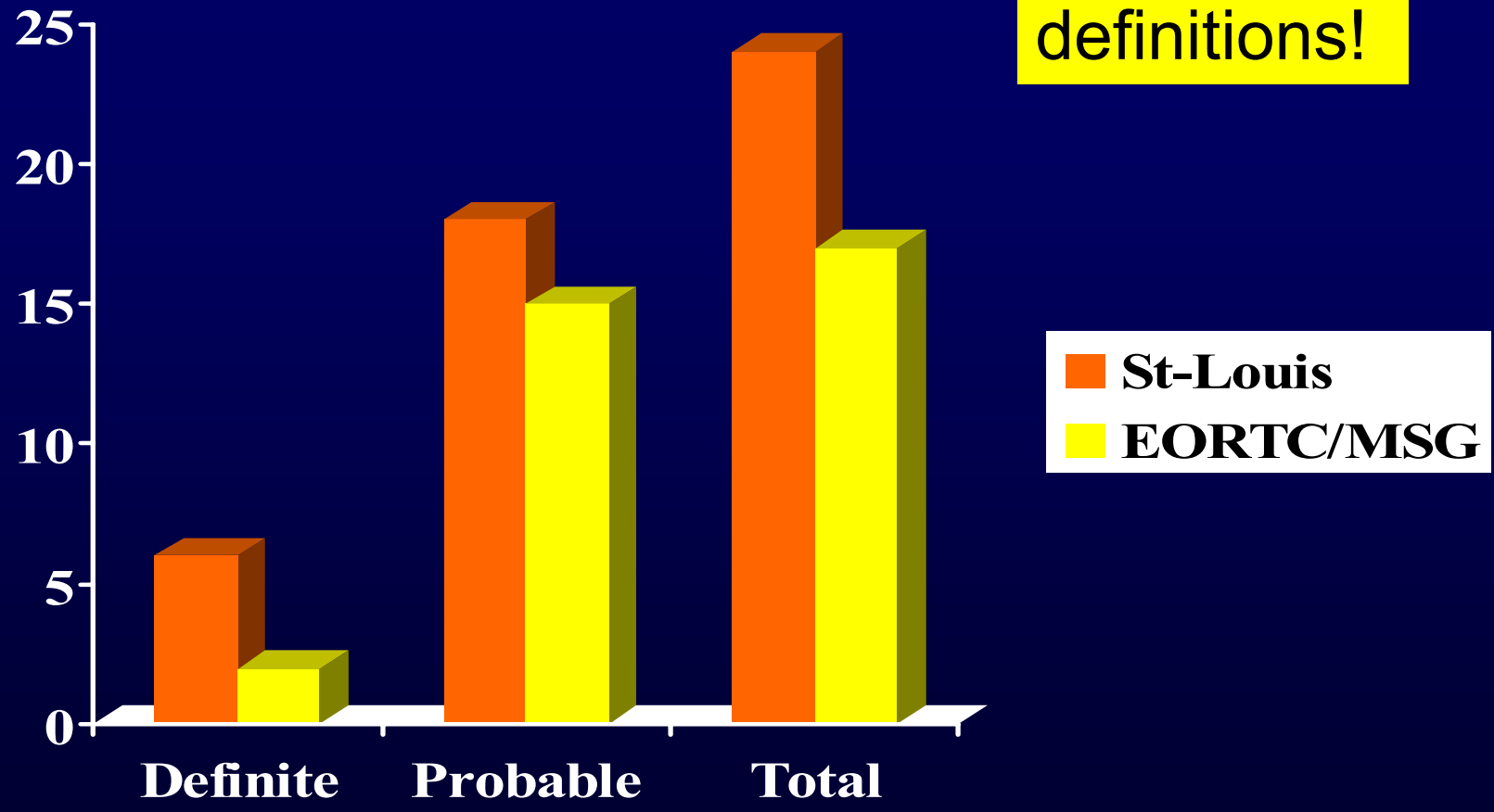
Park et al ICAAC 2004. Additional unpublished data added.

Invasive aspergillosis at Saint-Louis Hospital 1998-2004

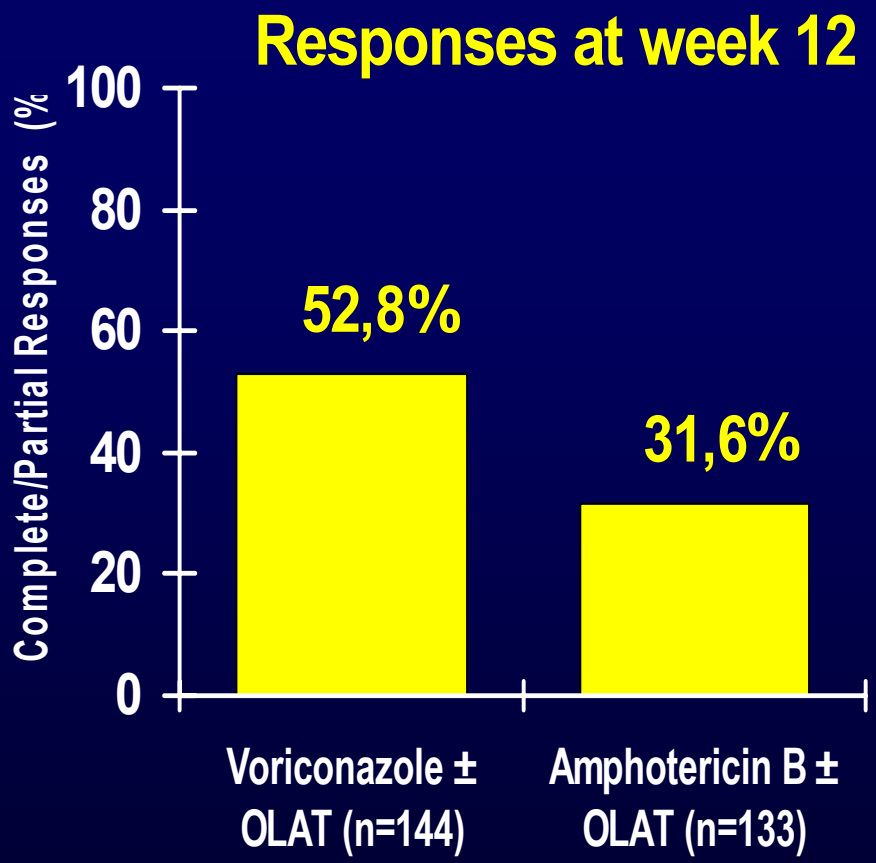


Number of IA cases according to definition criteria (St-Louis versus EORTC/MSG) 2004

Problem of definitions!



Voriconazole in Invasive Aspergillosis: Global Comparative Study



- Largest randomized trial of invasive aspergillosis
- Study conducted July ’97-Oct ’01
- Utilized “modified” EORTC/MSG criteria (published Nov ’01)

Note: OLAT=other licensed antifungal therapy

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

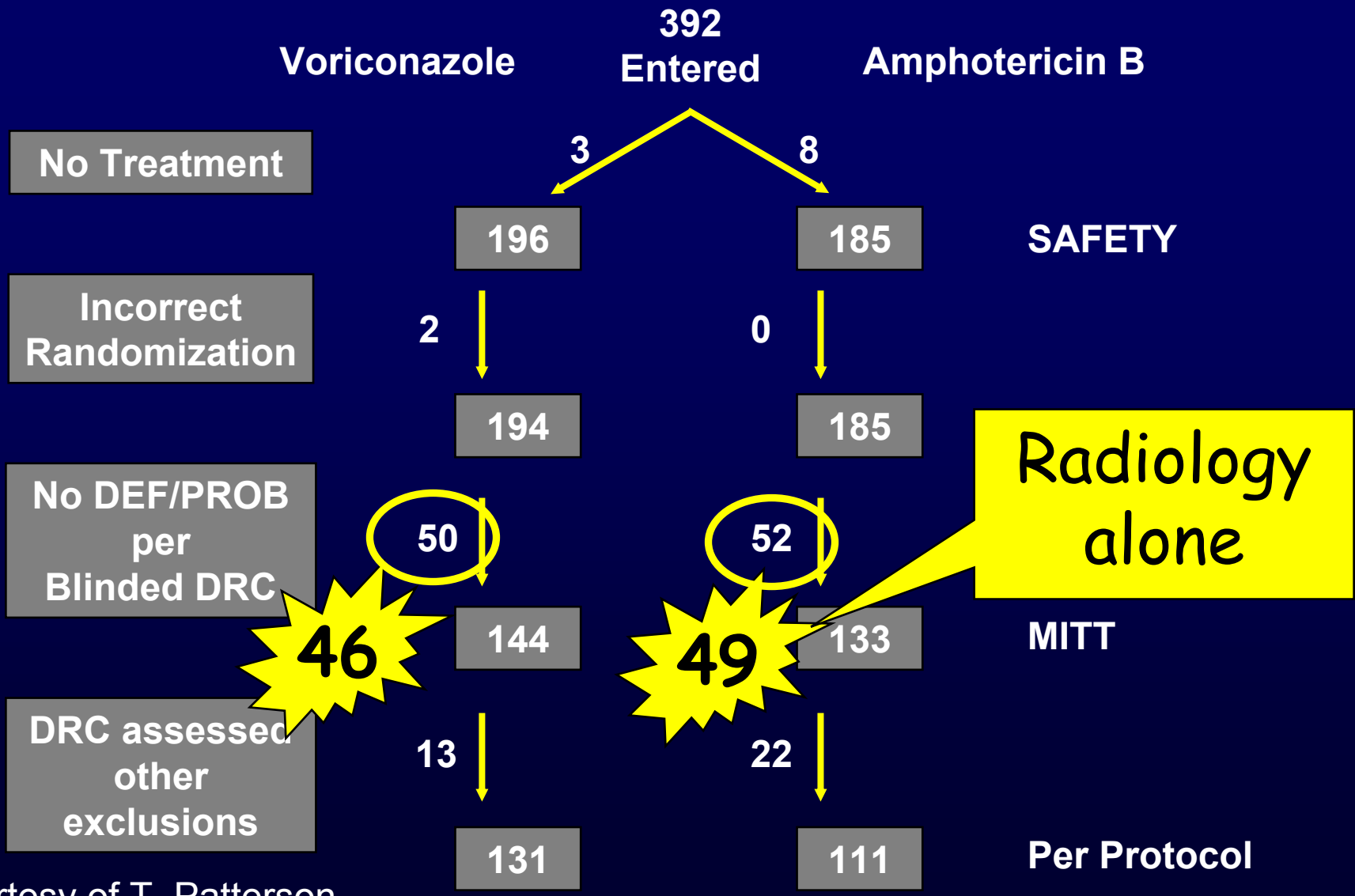
Courtesy of T. Patterson

Global Comparative Aspergillosis Study (307/602)

EORTC/ MSG and 307/602 criteria: main differences

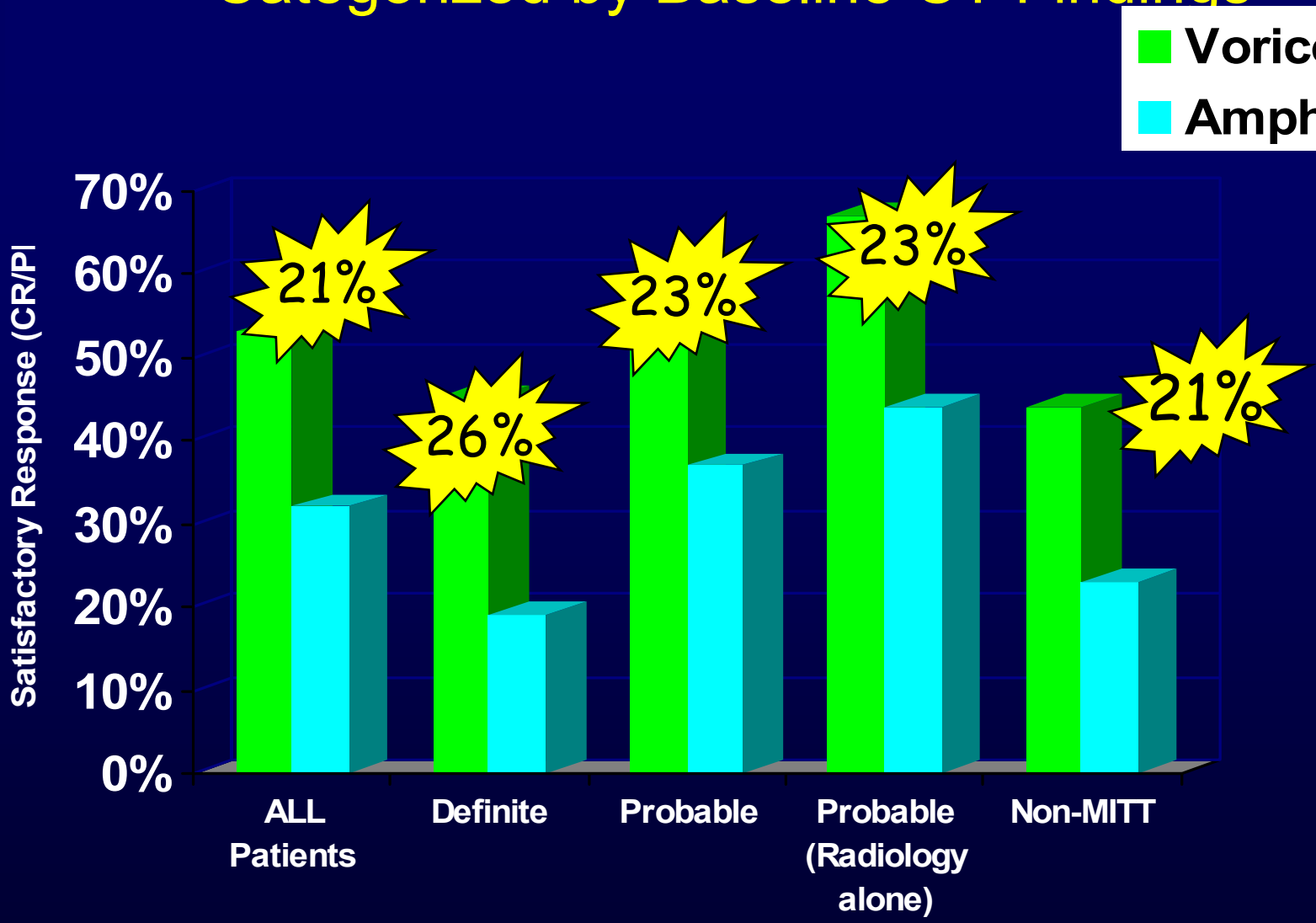
Diagnostic Criteria	MSG/EORTC	307/602
Histopath wo culture	Definite	Probable
Positive BAL culture		
(allo BMT or neutropenia)	Probable	Definite
(other immunosuppresssed)	Probable	Probable
Positive sputum culture		
(allo BMT or neutropenia)	Probable	Probable
(other immunosuppressed)	Probable	Not criteria
Antigenemia (blood or BAL)	Probable	Not criteria
A halo/air crescent sign on CT (allo BMT or neutropenia ONLY)	Possible	Probable

Global Comparative Aspergillosis Study (307/602)
Patient Disposition



Courtesy of T. Patterson

Patients with Satisfactory Treatment Response Categorized by Baseline CT Findings



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

Courtesy of T. Patterson

Consensus Definitions: *Aspergillus* & Filamentous Fungi

- Consideration for modification of criteria to include "possible" cases of invasive moulds to meet study case criteria:
  - Not majority of cases
  - Results biologically plausible and consistent with microbiologically defined cases

T. Patterson ICAAC 2005

de Pauw & Patterson *Clin Infect Dis* 2005;41:S377-80

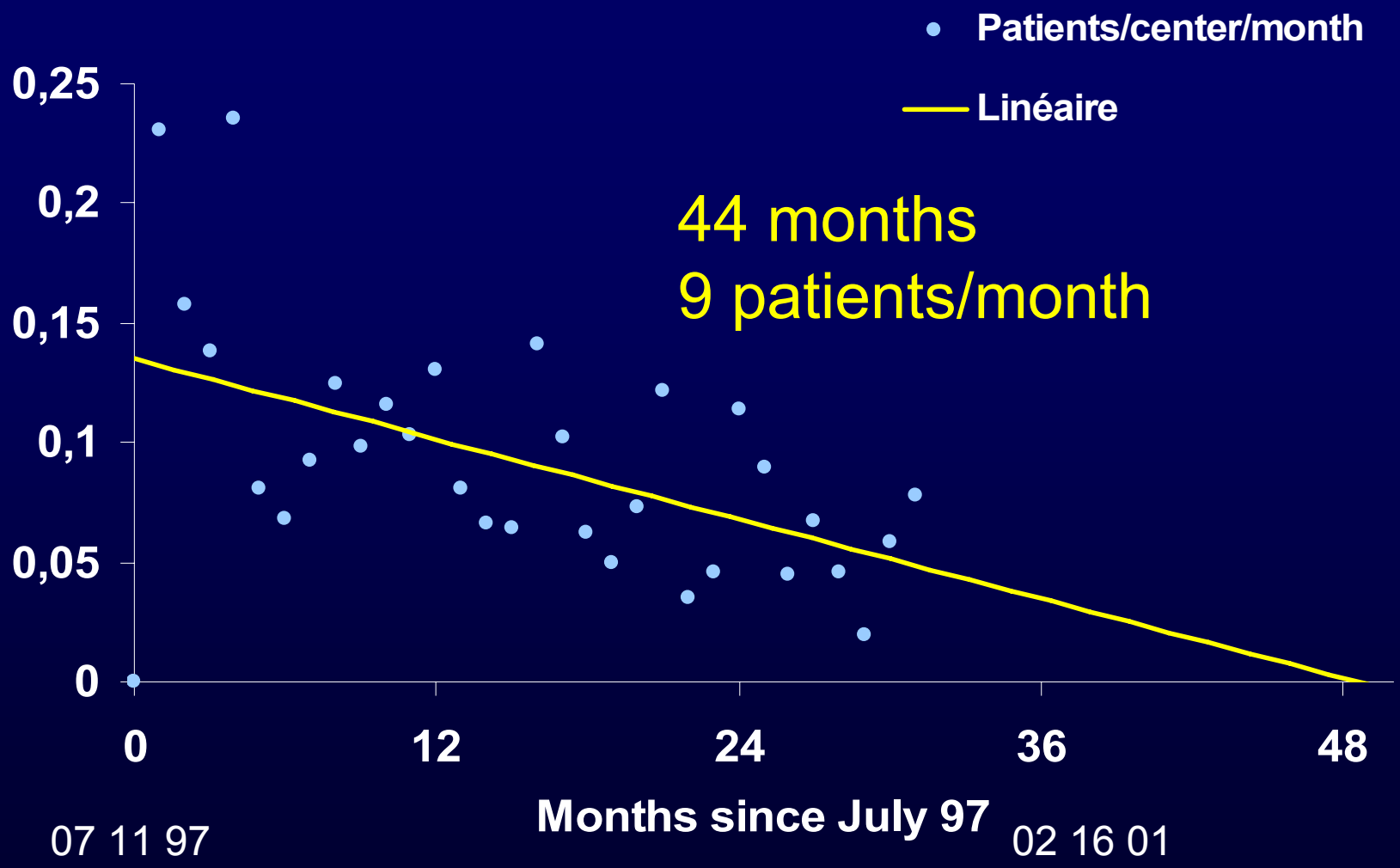
Global Comparative Aspergillosis Study (307/602) Recruitment Statistics

	Approved Centers	Active Centers	Patients Enrolled
Study 602			
United States	50	29	112
Canada	18	8	19
Mexico, Argentina, Brazil	11	4	4
India	1		
Study 307			
Germany	24	17	126
France	16	10	65
Belgium	8	5	27
UK, Hungary, Italy, Netherlands, Slovakia, Spain, Sweden, Switzerland	55	15	26
Australia	6	2	6
Israel	3	2	3
Total	199	95 48%	392

Choose motivated teams!

Courtesy of H. Schlamm

Global Comparative Aspergillosis Study (307/602)
Study 307 - Monthly Recruitment Rates



Courtesy of H. Schlamm

AmBiLoad Trial: Enrollment

Sites

- 72 sites in EU and Australia
- 46 sites enrolled patients (64%)

Enrollment period [April 03-October 04]	Total	AmBi-3mg	AmBi-10mg
Total* enrolled	339	172	167
	8 to 14 qualified patients/month!		
Proven/Probable IFI [MITT]:	201	107	94

*** Possible IFI enroll conditionally; may continue in study if Proven or Probable IFI confirmed within 4 working days after study entry**

Courtesy of M. Bresnik

AmBiLoad Trial : Final IFI Diagnosis Day 0 to Day 4 Upgrade [ITT]

N (%)	AmBi-3mg N=115	AmBi-10mg N=111
Possible → Probable	22 (19)	14 (13)
Possible → Proven	1 (1)	1 (1)
Probable → Proven	0	0
Total: Possible → Proven/Probable	38/226 (17)	

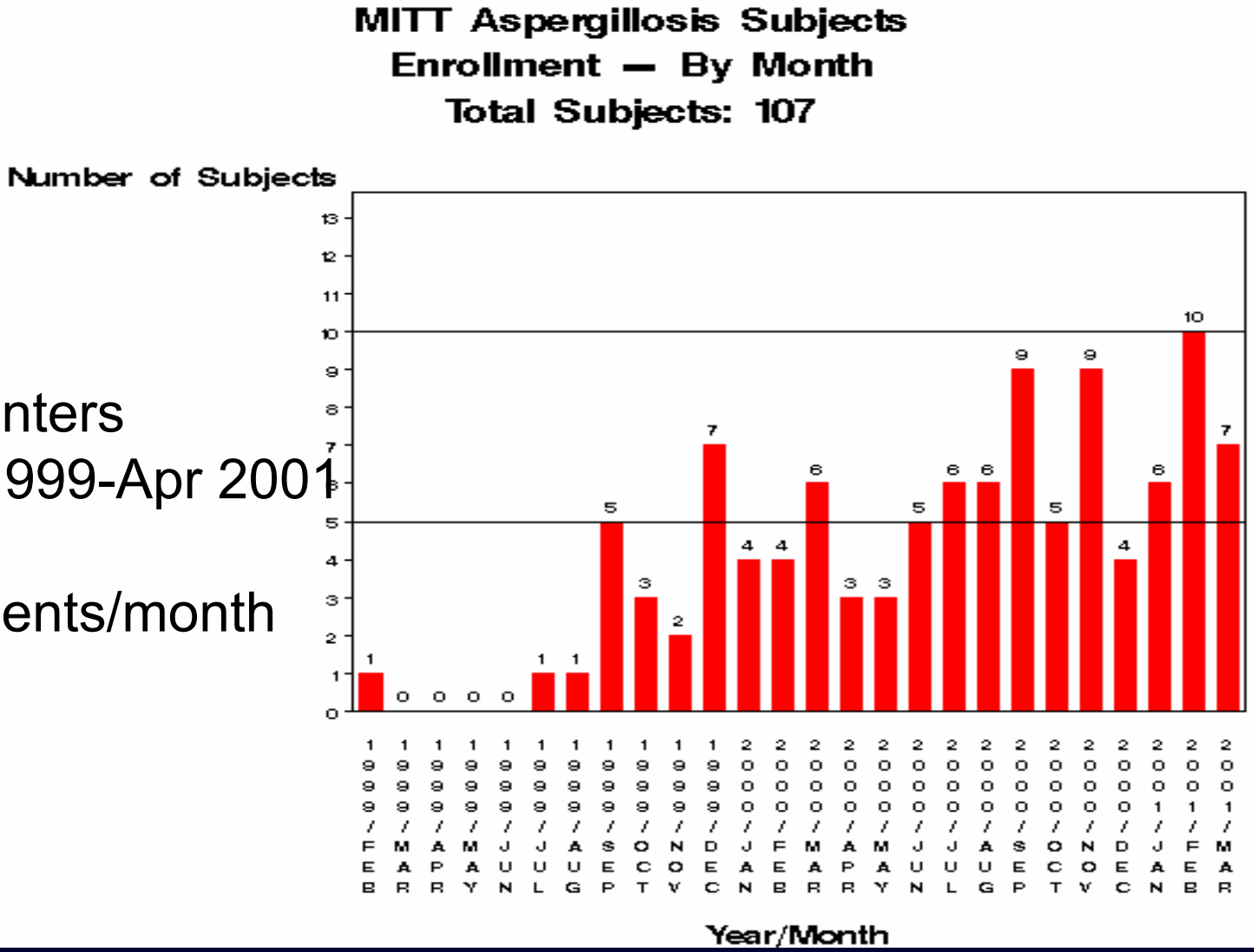
Possible IFI → begin randomized study drug Rx
Proven/probable IFI must be confirmed by day 4 in order to continue in the trial [ITT population]

Courtesy of M. Bresnik

Enrollment of Aspergillosis Into Posaconazole Salvage Therapy Program

79 centers
Fev 1999-Apr 2001

4 patients/month



Courtesy of C. Hardalo

Enrollment of Aspergillosis Into Caspofungin Salvage Therapy Program

Protocol 019 (monotherapy)
May 98-June 2003
75 centers (44% enrolled patients)
Total number enrolled: 127
Recruitment rate: 2.27 patients/month

Protocol 037 (combination therapy)
February 2003-June 2004
32 centers (56% enrolled patients)
Total number enrolled: 53
Recruitment rate: 2.94 patients/months

Courtesy of N. Kartsonis and E. Dohin

Limiting factors to patient recruitment (1)

Epidemiology of IA

Definition of IA

Center capacity

Methodological constraints

Limiting factors to patient recruitment (2)

Competing IA trials
- Treatment of disease
- “Preemptive” protocols

Concomitant non IA trials

Patient willingness to consent

Cost/Regulatory authorities requirement ?

Ways to improve patient recruitment for IA trials

- Better diagnostic tools
  - Many invasive aspergillosis remain undiagnosed antemortem (Chamilos, ICAAC 2005, M-720)
- Lessons from screen failures analysis
- Creative endpoints" . E. Anaissie, ICAAC 2005: M-715
  - Time to response/progression
  - Surrogate endpoints
    - Decreased duration of studies+++
    - Fewer patients needed+