Universitätsklinikum Würzburg

How do I treat Invasive Fungal Infections? Aspergillosis

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Disclosure:

1. Employment or Leadership Position

None

2. Advisory Role

Basilea, Boehringer Ingelheim, Pfizer, MSD, Astellas, Gilead, Aicuris

3. Stock Ownership

None

4. Honoraria

Astellas, Basilea, Gilead, MSD, Astellas, and Pfizer

5. Financing of Scientific Research

Astellas, Gilead, MSD, Astellas, Pfizer, and BioCryst

6. Expert Testimony

Astellas

7. Other Financial Relationships

None

Difficulty in Diagnosis of Aspergillosis

- Possible disease
  - *Host factors + Radiology*
- Proven and Probable disease
  - *Mycologic Criteria*
    - Culture
    - Histolo
    - Sc BAL Galactomannan
- Treat h systemic antifungals unless alternative etiology is identified

De Pauw, et al., 2008.

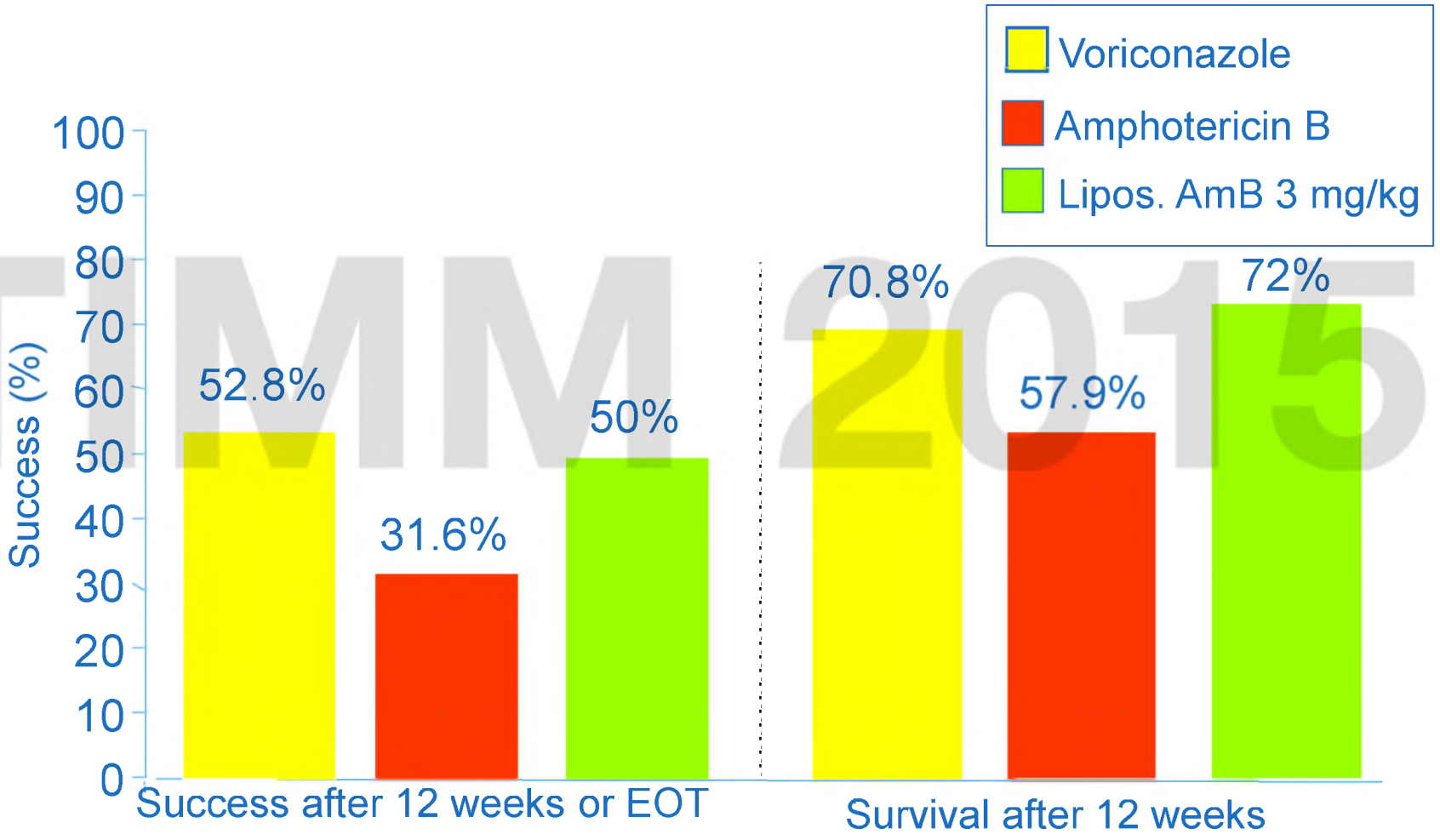
Essential to Treat Patients with Possible Disease

- Report of autopsy data from 1,017 patients with hematologic malignancies[1]
  - *31% found to have IFD at autopsy*
  - *75% not diagnosed prior to death*
- Autopsy of 38 allogeneic stem cell patients[2]
  - *10 died with IFD*
    - 4 proven/ probable before death
    - 6 deep mycoses were missed
      - 3 with invasive aspergillosis

1. Chamilos, et al. 2006. 2.Sinko, et al. 2008.

What are our options for therapy?

Invasive Aspergillosis: Results in Primary Therapy Trials



Herbrecht et al. N Engl J Med 2002; Cornely OA, .et al. Clin Infect Dis 2007

What are our new options for therapy?

What are our new options for therapy?
Combination?

A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis

Kieren A. Marr,[1] Haran Schlamm,[2] Scott T. Rottinghaus,[2] Shyla Jagannatha,[2] Eric J. Bow,[3] John R. Wingard,[4] Peter Pappas,[5] Raoul Herbrecht,[6] Thomas J. Walsh,[7] Johan Maertens[8] and the Mycoses Study Group

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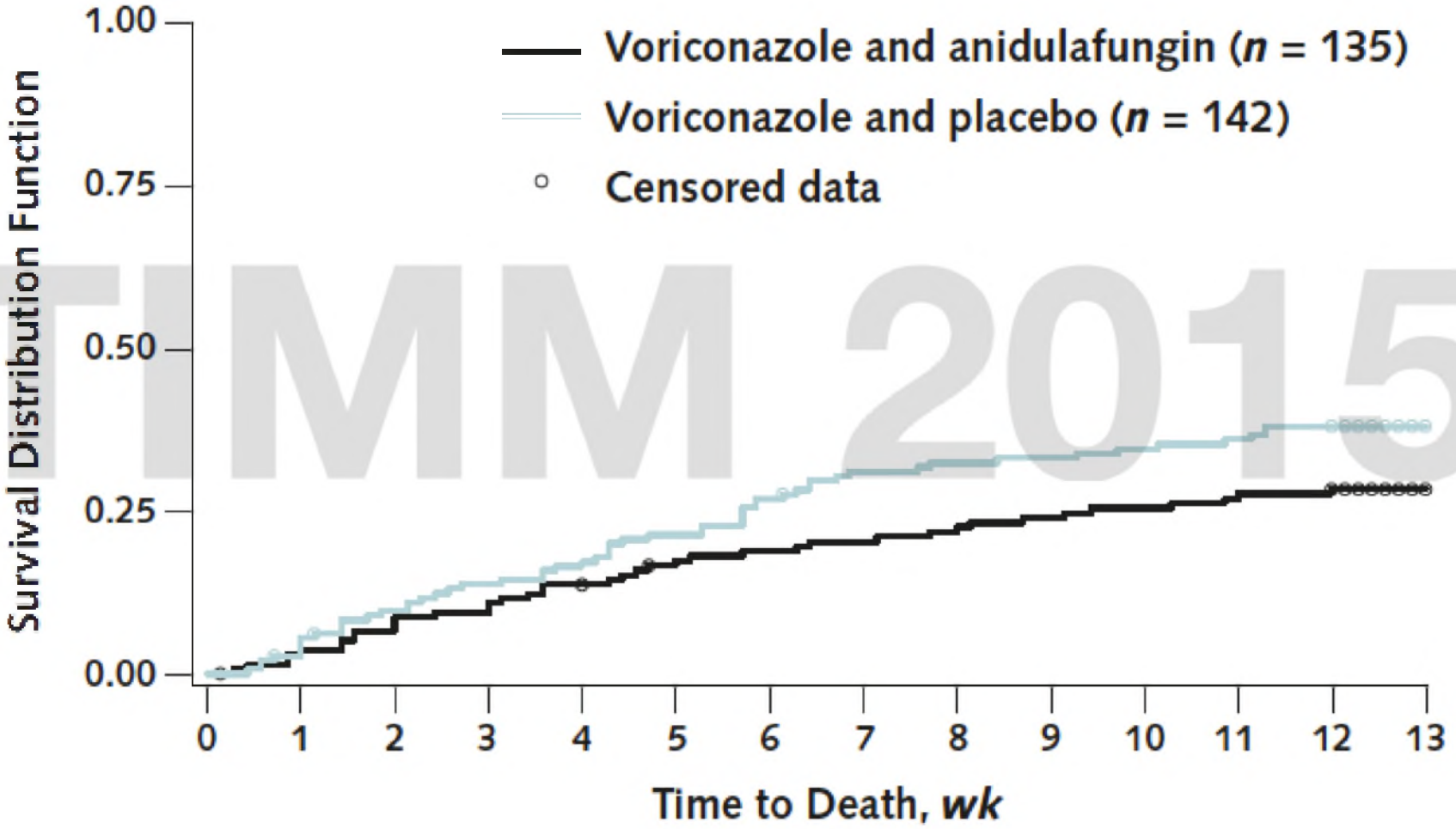
LB 2812

- The primary endpoint was overall survival at 6 weeks in patients with proven or probable IA confirmed by day 7 (modified intent-to-treat population, MITT).
- MITT population:
  - *142 (vori) 135 (combo)*

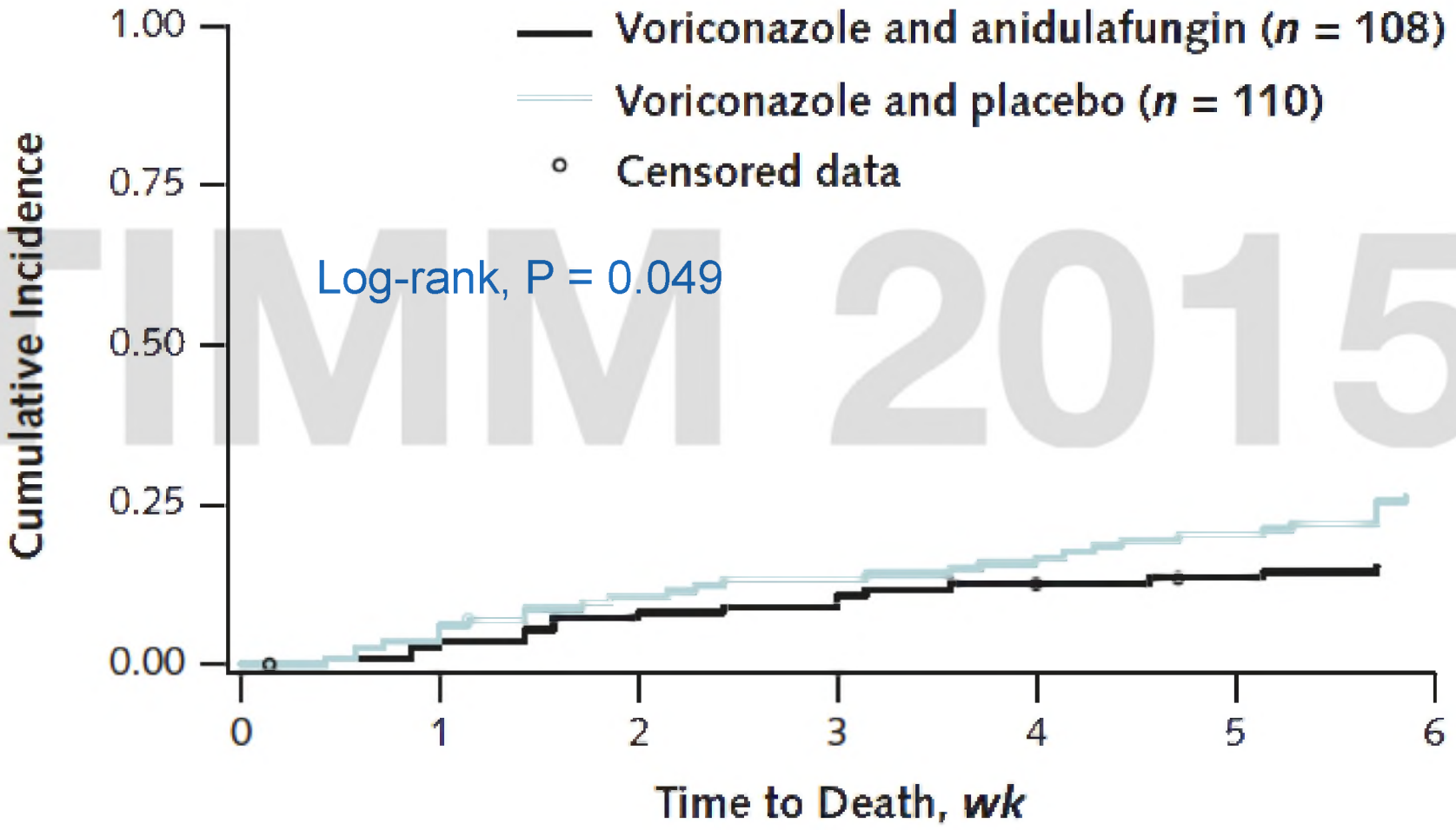
Variable	Voriconazole monotherapy	Combination therapy
Underlying diseases, non-HSCT	97	86
Acute leukaemia	2 (2)	1 (1)
Acute lymphoblastic leukaemia	19 (20)	12 (14)
Acute myeloid leukaemia	43 (44)	47 (55)
Aplastic anaemia	1 (1)	1 (1)
Chronic lymphocytic leukaemia	8 (8)	5 (6)
Chronic myeloid leukaemia	1 (1)	0
Lymphoma	13 (13)	12 (14)
Multiple myeloma	3 (3)	2 (2)
Myelodysplastic syndrome	7 (7)	2 (2)
Myeloproliferative syndrome	0	2 (2)
Non haematological	0	2 (2)
Neutropenic,[3] n (%)	86 (61)	77 (57)

Marr K et al ECCMID 2012, AIM 2015

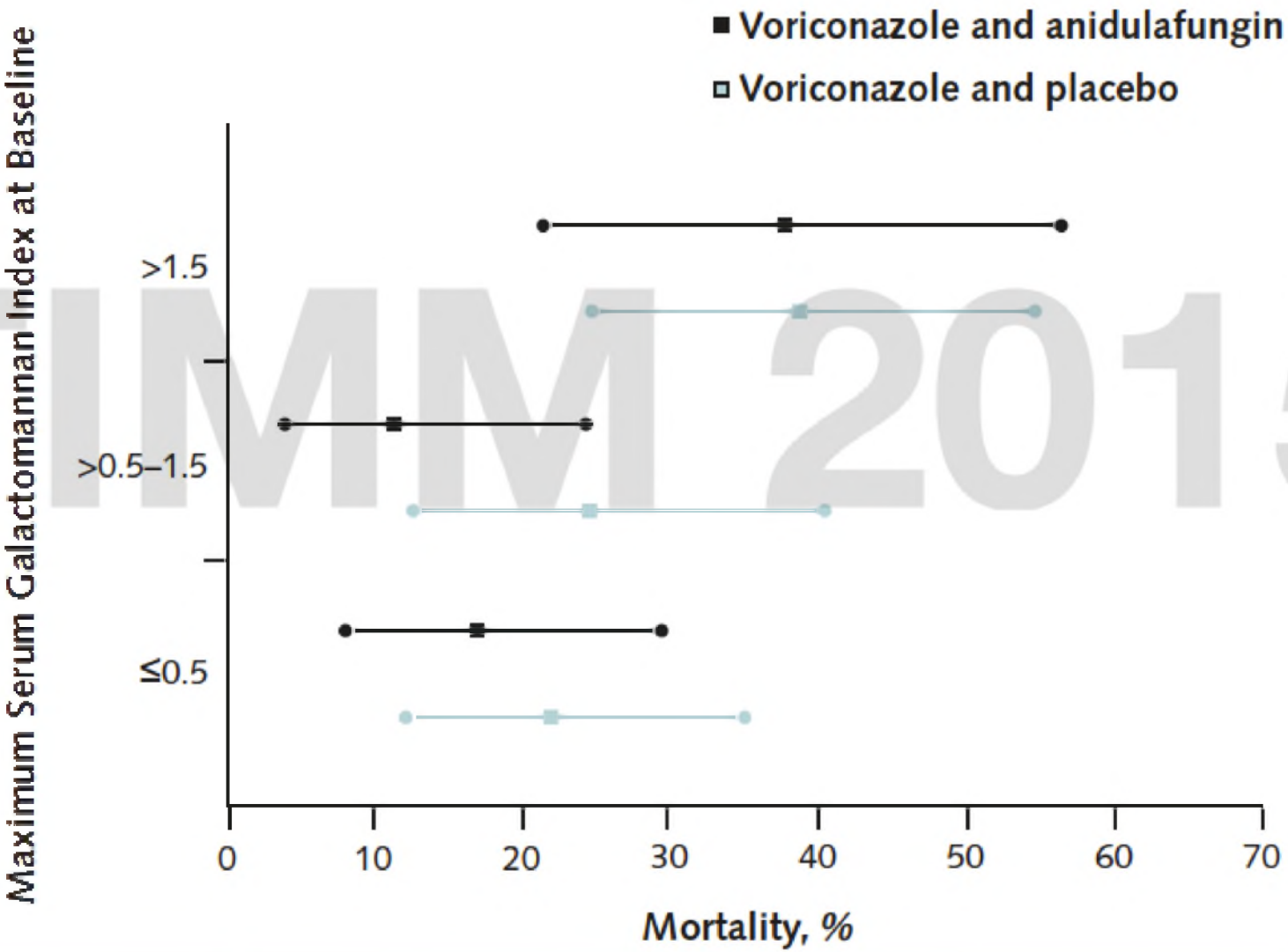
Combo-Trial: Cumulative incidence of death in the modified intention-to-treat population



Combo-Trial: Cumulative incidence of death in the mITT population with probable invasive aspergillosis based on radiographic abnormalities and positive galactomannan antigen



Combo-Trial: 6-week mortality rate by range of maximum serum galactomannan index values at baseline



Guidelines?

Add ons?

G-CSF: Invasive fungal infections for prevention and treatment of infectious complications in patients with acute myelogenous leukemia

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)
Invasive fungal infection	Study population		RR 1.4 (0.9 to 2.19)	929 (4 studies)
	62 per 1000	87 per 1000 (56 to 136)		
	Moderate			
	53 per 1000	74 per 1000 (48 to 116)		

Granulocytes Transfusion:
Primary Outcome Success Stratified by Infection

	Total N (% Success)	Granulocytes N (% Success)	Control N (% Success)	P-Value
MITT				
Overall	97 (42%)	48 (42%)	49 (43%)	>0.99
Bacterial Infection	51 (33%)	26 (35%)	25 (32%)	>0.99
Bacteremia Only	25 (24%)	14 (29%)	11 (18%)	0.66
Tissue Bacterial Infection	26 (42%)	12 (42%)	14 (43%)	>0.99
Fungal Infection	46 (52%)	22 (50%)	24 (54%)	>0.99
Fungemia Only	11 (64%)	3 (33%)	8 (75%)	0.49
Tissue Fungal Infection	35 (49%)	19 (53%)	16 (44%)	0.74
High Risk with Invasive Mold Infection	22 (55%)	13 (54%)	9 (56%)	>0.99
Low Risk with Invasive Mold Infection	9 (44%)	4 (50%)	5 (40%)	>0.99
High Risk with other Infection	41 (27%)	17 (29%)	24 (25%)	>0.99
Low Risk with other Infection	25 (56%)	14 (43%)	11 (73%)	0.23
Mold Pulmonary/Chest	23 (57%)	13 (46%)	10 (70%)	0.40
Mold ExtraPulmonary	10 (40%)	4 (75%)	6 (17%)	0.19

Summary

- Treatment Guidelines, stressing the two main agents for first line therapy of invasive pulmonary aspergillosis
  - *Voriconazole and liposomal Amphotericin B*
- Besides targeted treatment, pre-emptive and prophylaxis seem to be valid options besides empiric therapy
- But, mortality remains high
- Improved new agents / old concepts?
  - *Combination therapy seems to be better than monotherapy if only GMI is positive (caveat: study was not powered for this statement)*
  - *Isavuconazole appears to have less toxicity compared to voriconazole*


VIRTVTIBVS
MAIORVM
VT SIT OMNIBVS DOCVMENTO P P D
Obrigado!