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Isavuconazole

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Isavuconazole

- Broad-spectrum, triazole antifungal
- Available in once-daily IV and oral formulations, without cyclodextrin
- Comparatively little interaction with CYP3A4
- Potent activity against *Candida* spp., *Aspergillus* spp., and the Mucorales *in vitro*, and in animal models against invasive candidiasis,[1] aspergillosis,[2] and mucormycosis[3]

[1]Lepak *et al* 2013 *Antimicrob Agents Chemother* 57:5642–8
[2]Lepak *et al* 2013 *Antimicrob Agents Chemother* 57:6284–9
[3]Luo *et al* 2014 *Antimicrob Agents Chemother* 58:2450–3

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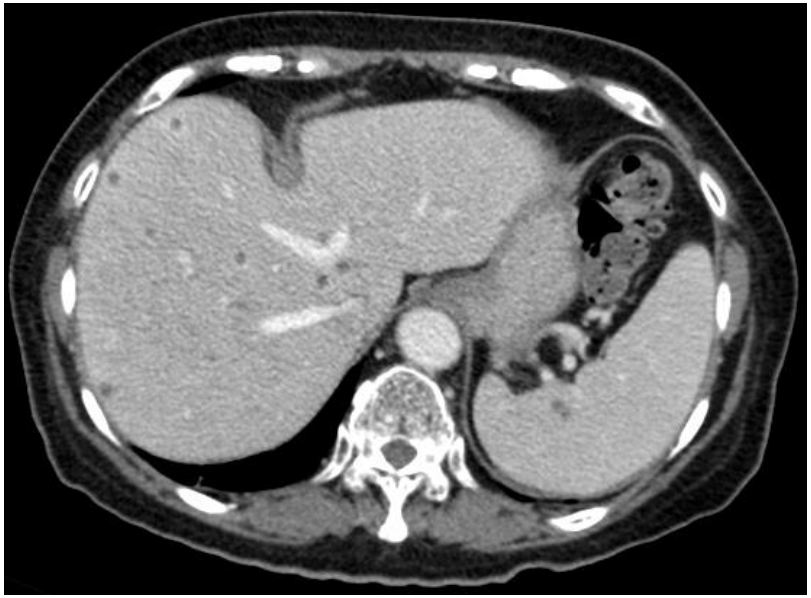
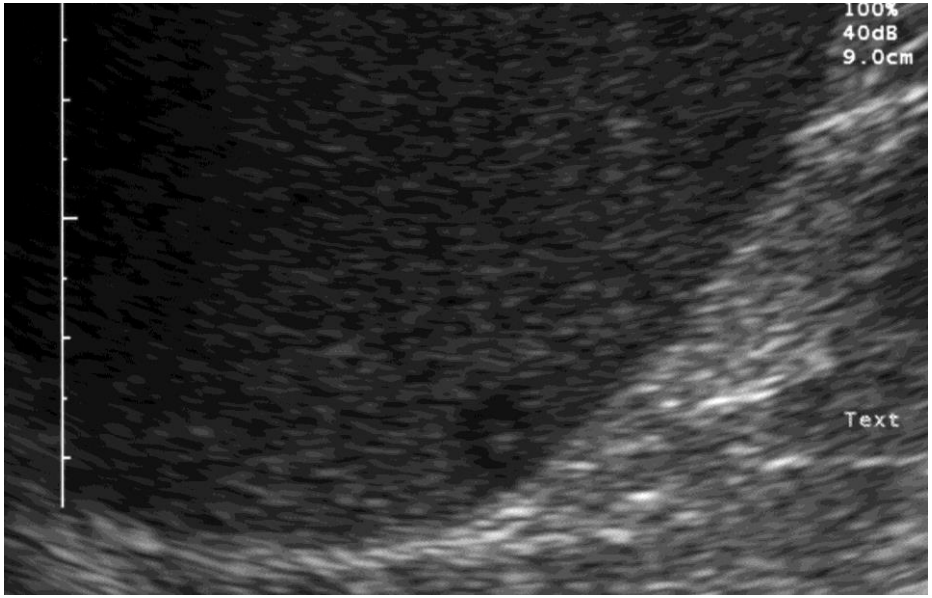
Isavuconazole – invasive candidiasis (IC)



Chronic disseminated candidiasis



Bull‘s eye lesion

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ACTIVE trial – isavuconazole vs. caspofungin for invasive candidiasis

- Indication
  - Candidemia or invasive candidiasis
- Study design
  - Randomized, placebo-controlled, multinational, non-inferiority study
  - iv isavuconazole vs. iv caspofungin for 10d, then switch to oral possible
  - Primary endpoint: Overall response at end of iv treatment
- Study population
  - 450 adult patients
- Primary endpoint
  - Overall response at end of iv treatment

Kullberg et al. ECCMID 2016 Abstract #1239

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ACTIVE trial – isavuconazole vs. caspofungin for invasive candidiasis

Parameter mITT	Isavuconazole (n=199)	Caspofungin (n=201)	Adjusted difference* % (95% CI)
Mean APACHE II score	14	14	
Baseline neutropenia, n (%)	24 (12.1)	24 (11.9%)	
Infecting pathogen, n (%)			
C. albicans	84 (42.2)	74 (36.8)	
C. tropicalis	41 (20.6)	38 (18.9)	
C. parapsilosis	26 (13.1)	27 (13.4)	
C. glabrata	22 (11.1)	21 (10.4)	
IV duration [days], mean (SD)	12.8 (7.6)	14 (8.7)	
Successful overall response, n (%)			
FU1	109 (54.8)	115 (57.2)	-2.7 (-12.2, 6.8)
All-cause mortality, n (%)			
Day 14	29 (14.6)	25 (12.4)	2.5 (-3.8, 8.9)
Day 56	61 (30.7)	60 (29.9)	1.4 (-7.1, 10)
Breakthrough fungal infections	5 (2.5)	15 (7.5)	
Safety	**(n=220)**	**(n=220)**	
Safety			
TEAEs	209 (95.0)	208 (94.5)	
Study-drug related TEAEs	78 (35.5)	71 (32.3)	

APACHE II, Acute Physiology and Chronic Health Evaluation II; TEAEs, Treatment-emergent adverse events

Non-inferiority criteria not fulfilled!

Kullberg et al. ECCMID 2016 Abstract #1239

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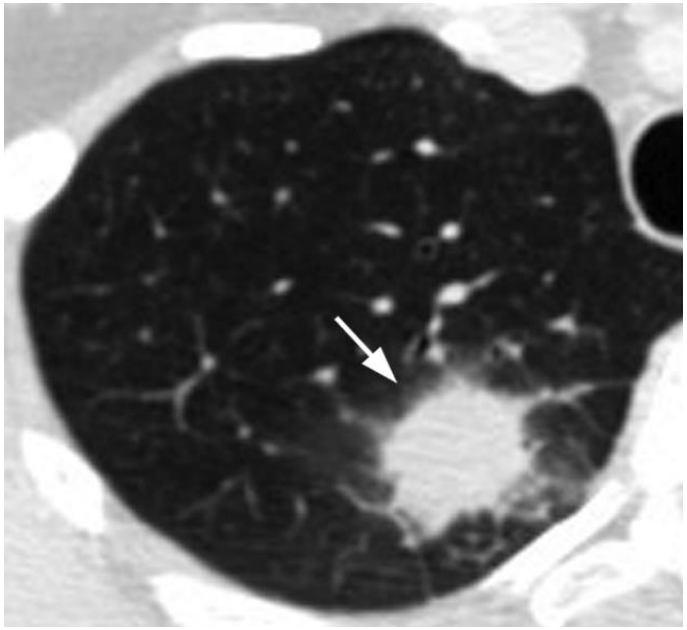
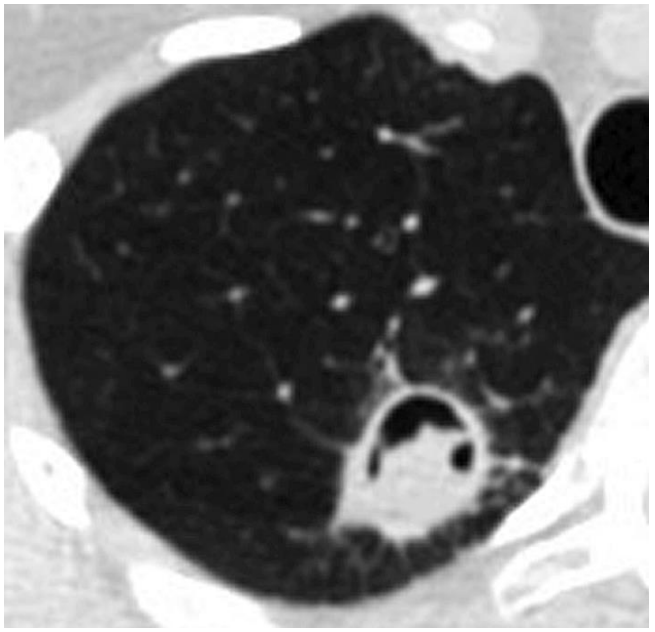
Isavuconazole – invasive aspergillosis (IA)



Nodular infiltrate with halo sign



Air crescent sign

Cornely, unpublished.

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SECURE trial - isavuconazole vs. voriconazole for IA

Isavuconazole

IV 200 mg TID (Days 1 & 2); IV or oral 200 mg QD (Day 3 onwards)

Randomisation 1:1

Treatment duration: 84 days
Efficacy & safety assessments:
Days 1, 2, 3, 7, 14, 28, **42**, 63 & **84**

Follow-up
28 days (±7) after EOT

Voriconazole

IV 6 mg/kg BID (Day 1); IV 4 mg/kg BID (Day 2); IV 4 mg/kg or oral 200 mg BID (Day 3 onwards)

Patients were stratiefied by geographical region, allogeneic HSCT and uncontrolled malignancy

Maertens et al. Lancet. 2016 Feb 20;387(10020):760-9..

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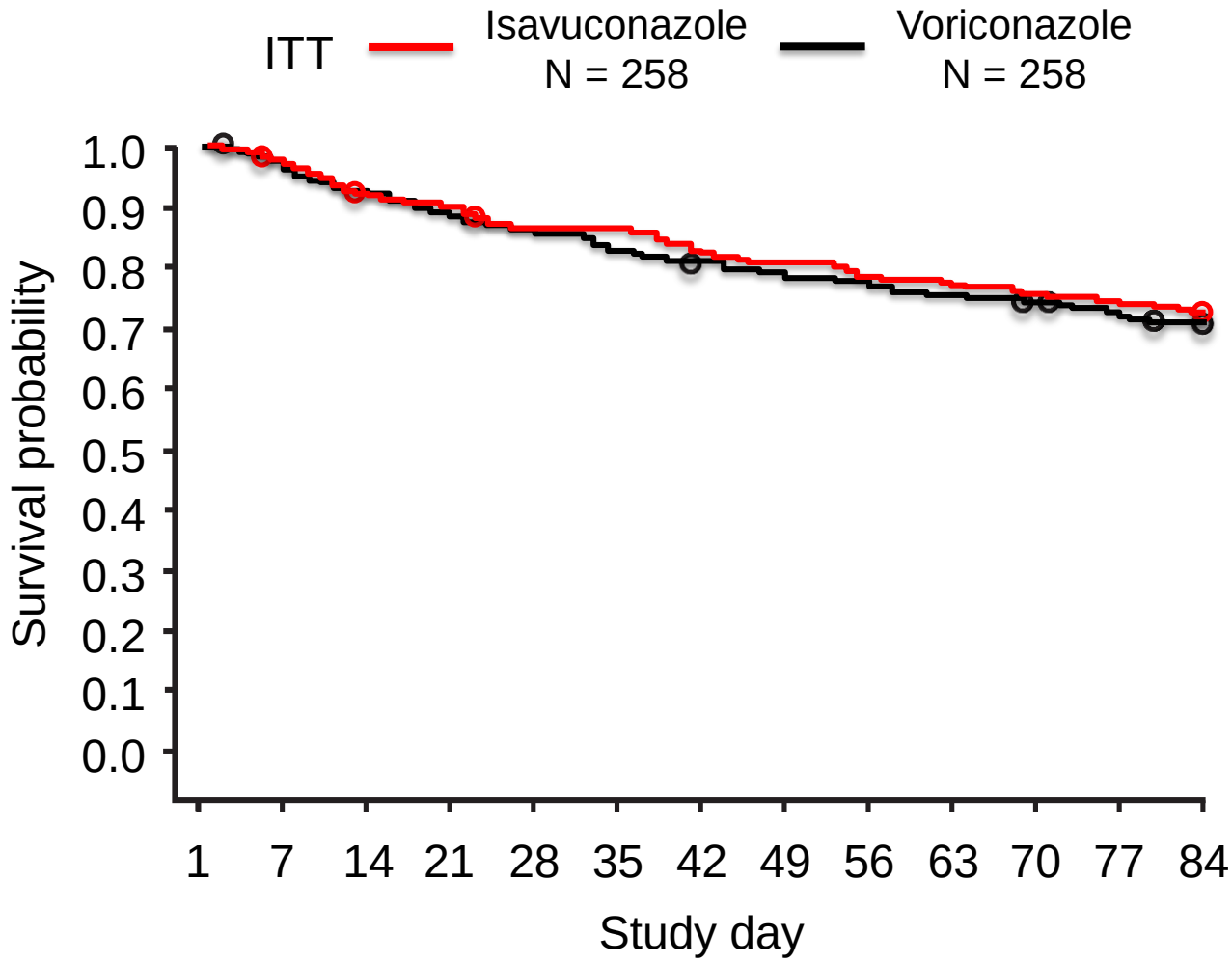
SECURE trial - isavuconazole vs. voriconazole for IA



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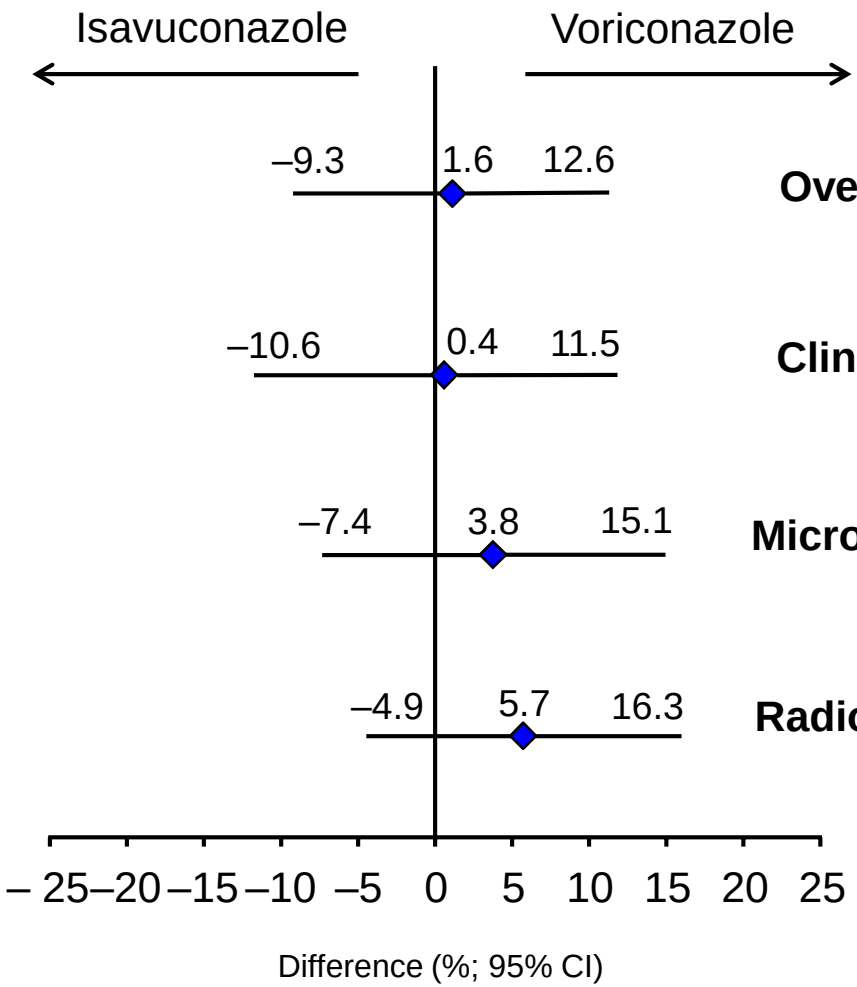
SECURE trial - isavuconazole vs. voriconazole for IA



	ISA	VRC
Overall response	50/143 (35%)	47/129 (36%)
Clinical response	85/137 (62%)	73/121 (60%)
Microbiol. response	54/143 (38%)	53/129 (41%)
Radiolog. response	41/141 (29%)	42/127 (33%)

Maertens et al. Lancet. 2016 Feb 20;387(10020):760-9.

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SECURE trial - isavuconazole vs. voriconazole for IA

Most frequent adverse events by organ system

System Organ Class	Isavuconazole N = 257	Voriconazole N = 259	p-value
Overall, n (%)	247 (96.1)	255 (98.5)	
Gastrointestinal disorders	174 (67.7%)	180 (69.5%)	
Infections and infestations	152 (59.1%)	158 (61.0%)	
General disorders & admin. site conditions	148 (57.6%)	144 (55.6%)	
Respiratory, thoracic & mediastinal disorders	143 (55.6%)	147 (56.8%)	
Metabolism and nutrition disorders	108 (42.0%)	121 (46.7%)	
Nervous system disorders	95 (37.0%)	89 (34.4%)	
Skin and subcutaneous tissue disorders	**86 (33.5%)**	**110 (42.5%)**	**0.037**
Investigations (abnormal laboratory tests)	85 (33.1%)	96 (37.1%)	
Blood and lymphatic system disorders	77 (30.0%)	82 (31.7%)	
Psychiatric disorders	70 (27.2%)	86 (33.2%)	
Eye disorders	**39 (15.2%)**	**69 (26.6%)**	**0.002**
Hepatobiliary disorders	**23 (8.9%)**	**42 (16.2%)**	**0.016**

Maertens et al. Lancet. 2016 Feb 20;387(10020):760-9.

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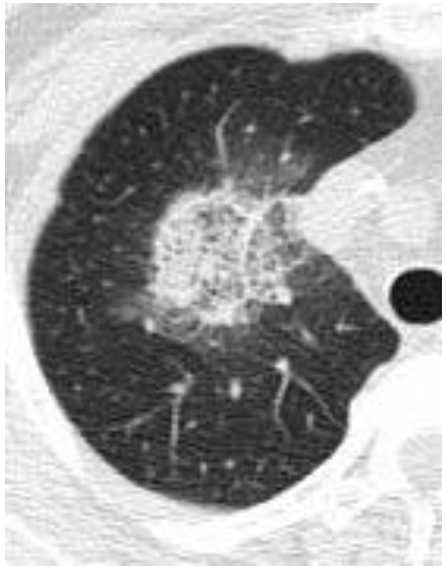
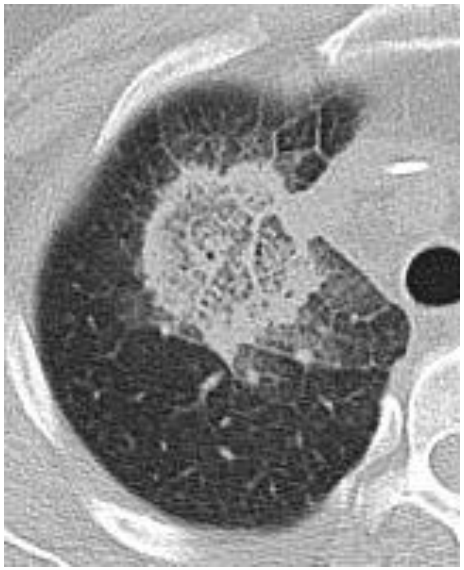
Isavuconazole – invasive mucormycosis (IM)



d1



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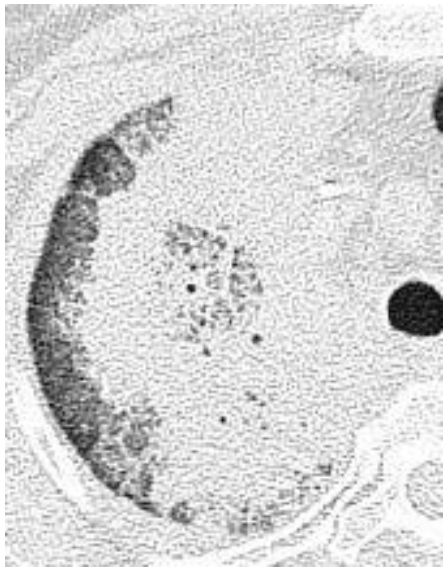

d15

Cornely OA. unpublished.

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VITAL study – isavuconazole for invasive mucormycosis (IM)

Table 1. Demographics and baseline characteristics by therapy status in patients with IM

Parameter, n (%)	Primary therapy (n=21)	Refractory (n=11)	Intolerant (n=5)	Total (n=37)
Baseline pathogen [DRC], n (%)				
Mucormycetes NOS	6 (28.6)	5 (45.5)	2 (40.0)	13 (35.1)
Mucor NOS	7 (33.3)	0	0	7 (18.9)
Rhizopus NOS	0	1 (9.1)	1 (20.0)	2 (5.4)
Rhizopus oryzae	4 (19.0)	3 (27.3)	0	7 (18.9)
Rhizomucor spp.	2 (9.5)	2 (18.2)	1 (20.0)	5 (13.5)
Lichtheimia (Absidia) corymbifera	2 (9.5)	0	0	2 (5.4)
Cunninghamella spp.	0	0	1 (20.0)	1 (2.7)
Disseminated disease[b]	8 (38.1)	2 (18.2)	1 (20.0)	11 (29.7)
IFD location				
LRTD only	1 (4.8)	5 (45.5)	4 (80.0)	10 (27.0)
LRTD plus other organs	8 (38.1)	3 (27.3)	1 (20.0)	12 (32.4)
Non-LRTD only	12 (57.1)	3 (27.3)	0	15 (40.5)
Total treatment duration [days], median (range)	102 (2–882)	33 (6–735)	85 (10–232)	84 (2–882)

Marty et al. Lancet Infect Dis. 2016 Jul;16(7):828-837.

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VITAL study – isavuconazole for invasive mucormycosis (IM)

Isavuconazol first line (VITAL-Study)

versus

Amphotericin B formulations (FungiScope™)

Marty et al. Lancet Infect Dis. 2016 Jul;16(7):828-837.

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VITAL study – isavuconazole for invasive mucormycosis (IM)

- **Indication**
  - Proven/probable IM
- **Study population**
  - 21 cases: Isavuconazole 1st line
  - 33 controls: Amphotericin B-based 1st line
- **Matching criteria**
  - Severe IM (CNS-involvement or dissemination)
  - Hematological malignancy
  - Surgical resection/debridement
- **Primary endpoint**
  - Overall mortality day 42

Marty et al. Lancet Infect Dis. 2016 Jul;16(7):828-837.

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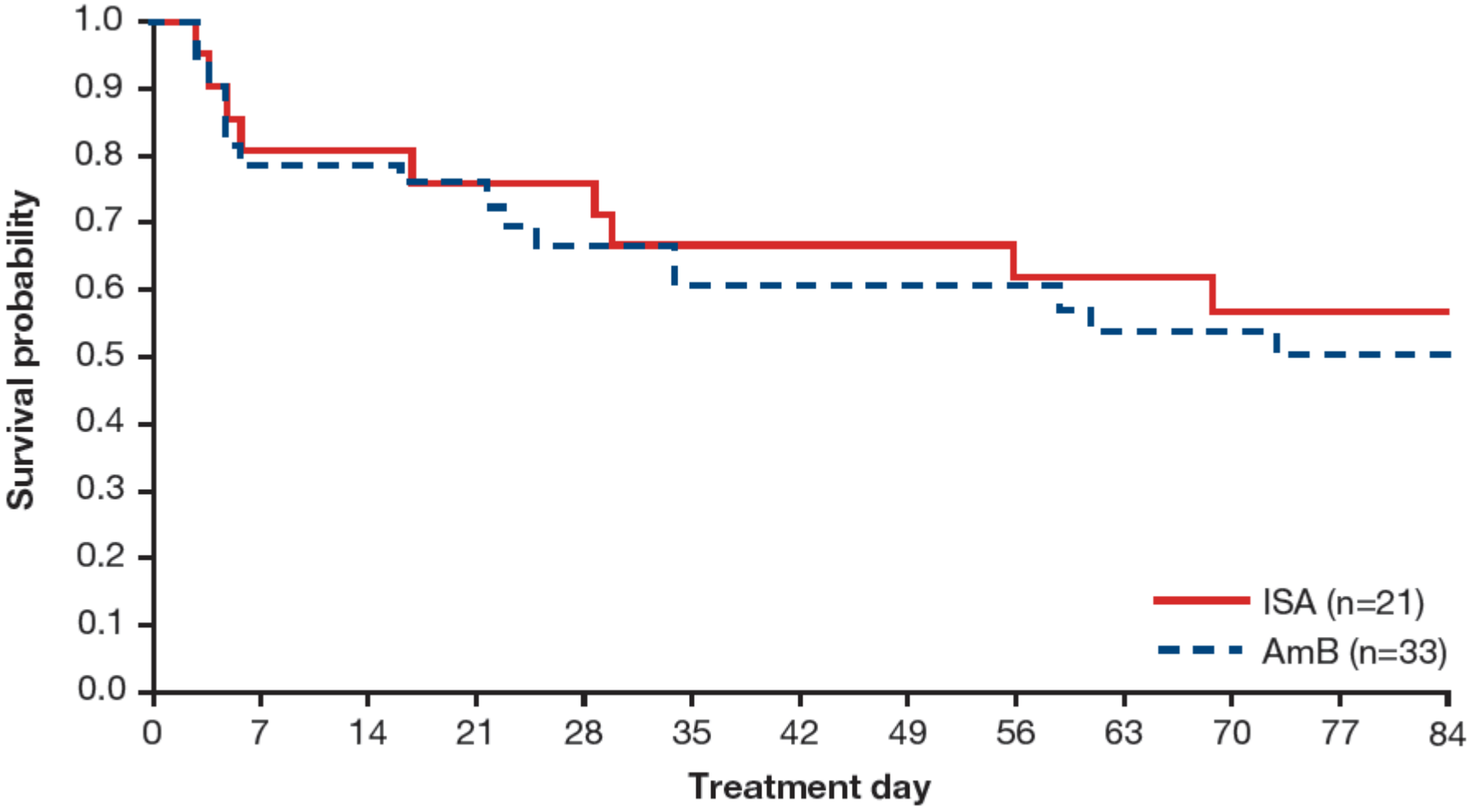
VITAL study – isavuconazole for invasive mucormycosis (IM)



No. of Subjects at Risk

ISA	21	17	17	16	16	14	14	14	14	13	12	12	12
AmB	33	26	26	25	22	20	20	20	18	16	16	14	14

Marty et al. Lancet Infect Dis. 2016 Jul;16(7):828-837.

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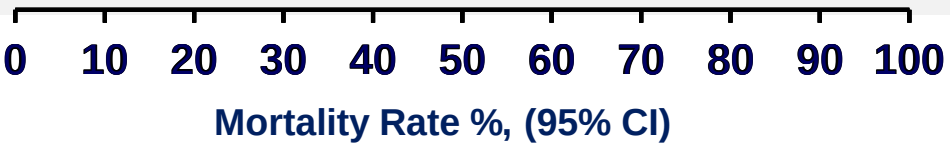
Mortality in treated and untreated patients with IM

Literature – Amphotericin B	n/N	Treated	Untreated	n/N
Roden	244/648			233/241
Skiada	58/152			21/22
FungiScope – Amphotericin B				
Day 42	41/107			29/29
Meta-Analysis – Amphotericin B				
All*	343/907			283/292
Study 0103 – Isavuconazole				
All Patients – Day 42	14/37			
Primary Therapy – Day 42	7/21			



*Roden MM et al. Clin Infect Dis 2005. Skiada A et al. Clin Microbiol Infect 2011. FungiScope

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VITAL study – isavuconazole for invasive mucormycosis (IM)

- Isavuconazole efficacy comparable to amphotericin B primary treatment of mucormycosis
- Survival through Day 84 similar between VITAL cases and Fungiscope controls
- Frequency of baseline immunosuppressant use and severe disease higher in VITAL cases than in Fungiscope controls, which may have impacted mortality
- 12 Fungiscope controls received posaconazole following amphotericin B, which may have affected mortality
- Registration in Europe: Indicated for treatment of mucormycosis, if amphotericin B-based formulations are not

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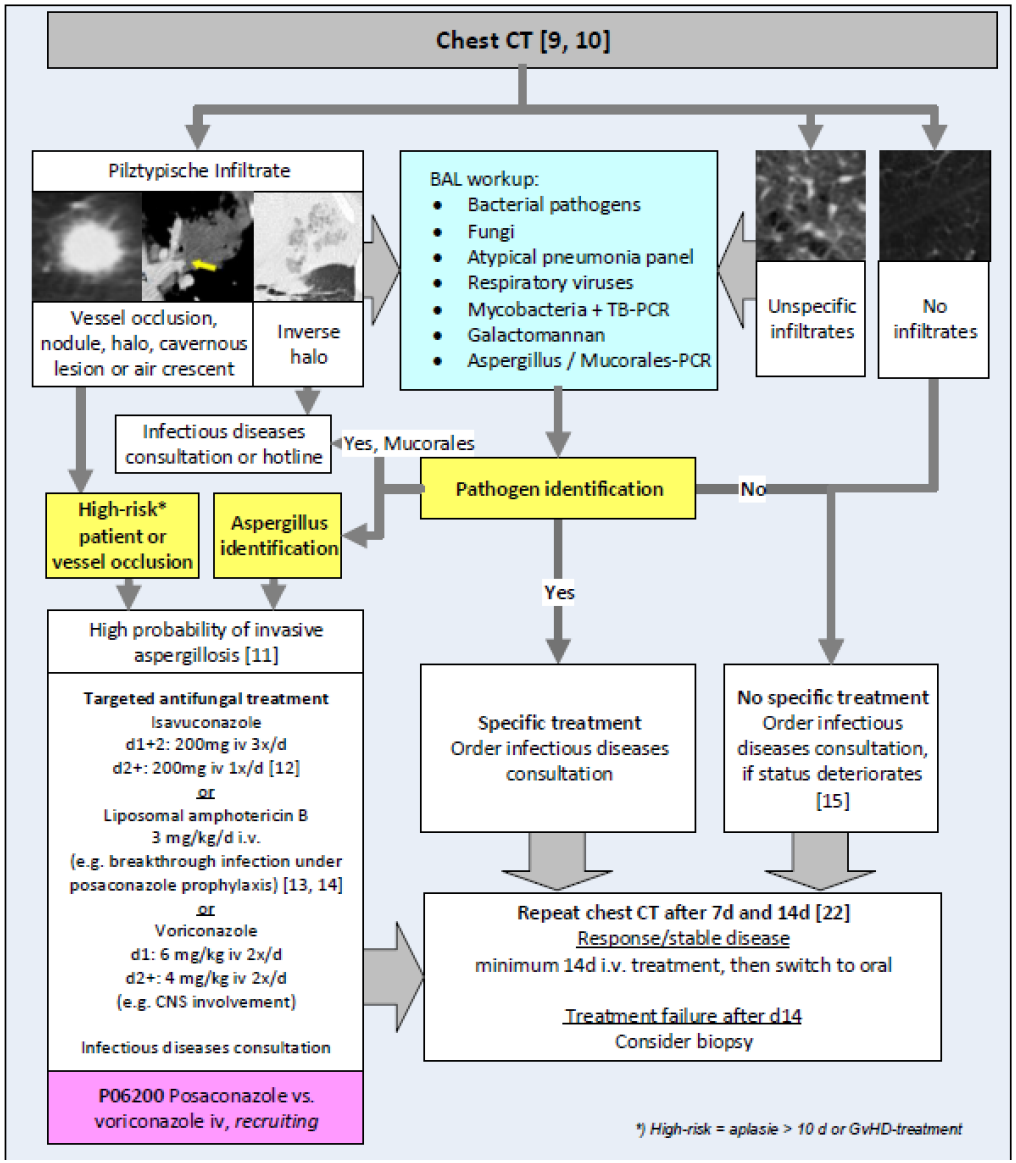
Cologne Conclusion



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ECIL-6 Guidelines: IA

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Tissot et al. Haematologica. 2017 Mar;102(3):433-444.

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Questions?