Four mold active in a row

VORICONAZOLE

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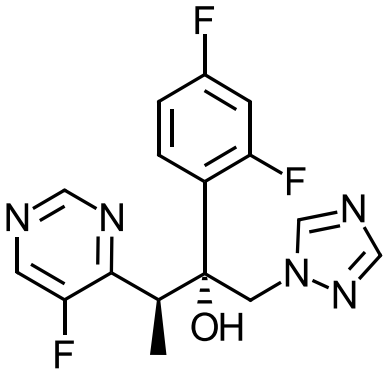
Astellas, Basilea, Gilead Science, MSD, Pfizer, Scynexis

A well known molecule



- Small, lipophilic molecule
- Excellent tissular diffusion
- Broad spectrum of activity
- Known therapeutic window
- Pioneer in the survival improvement of invasive aspergillosis
- « AI » in any guideline since more than 10 y for primary therapy of invasive aspergillosis

Main PK properties of triazoles

	ITRA	VORI	POSA	ISAVU
Formulation	PO	PO, IV	PO, IV	PO, IV
Volume of distribution (L/kg)	10.7	4.6	6.5	4.4-7.7
Half-life (h)	24-30	6-24	16-35	56-104
Protein binding	99%	58%	99%	99%
Metabolism	95% (CYP3A4)	95% (CYP3A4, 2C9,2C19)	14% (UGT)	95% (CYP3A4, 3A5)
CYP inhibition	CYP3A4, 2C9	CYP3A4, 2C19, 2C9	CYP3A4	CYP3A4
CNS penetration	poor	good	poor	poor
Probability of drug interactions	High	High	Moderate	Moderate

Lass-Flörl C, Drugs 2011; Flaci DR, Inf Drug Resist 2013

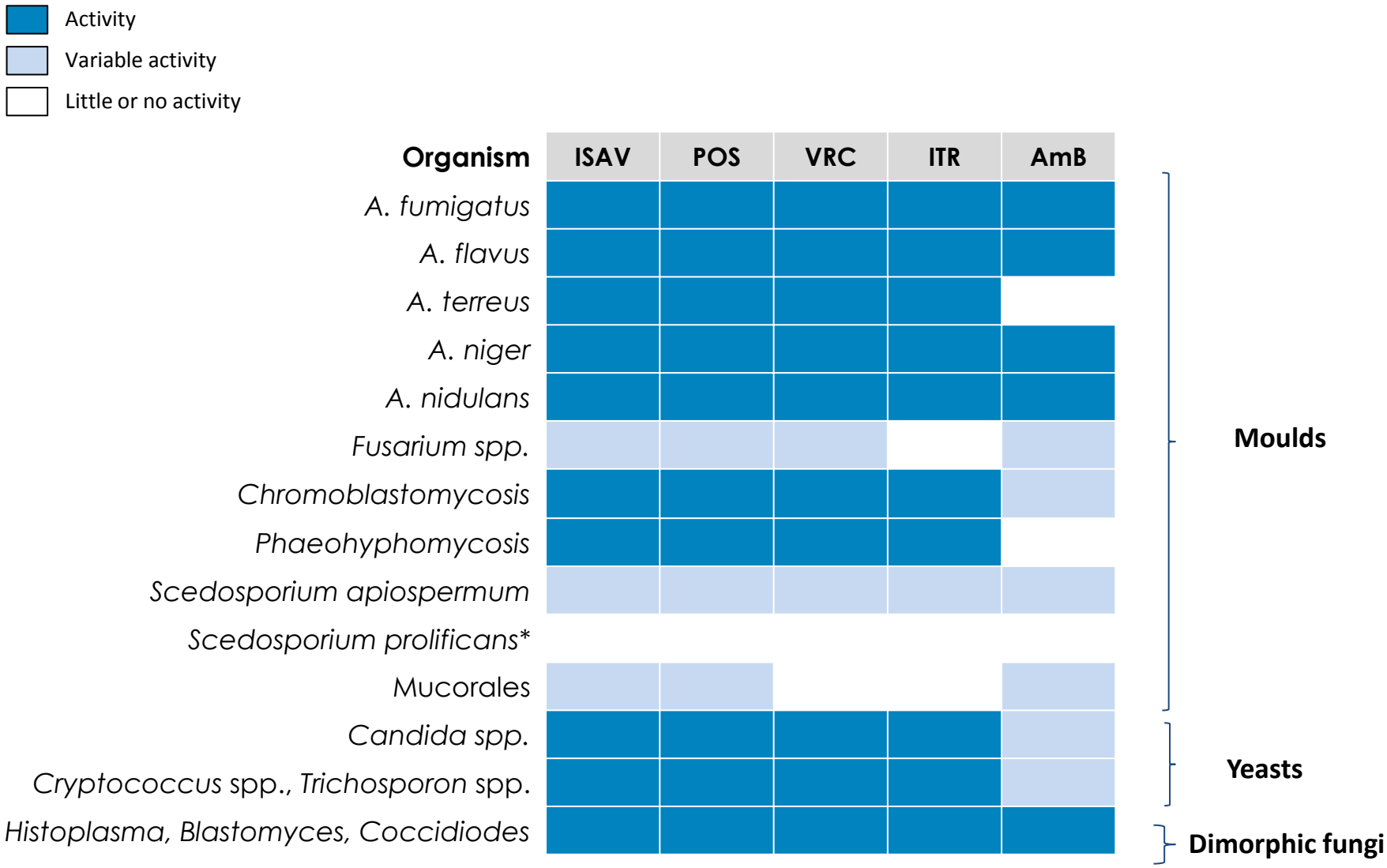
Drug interactions

	ITRA	VORI	POSA	ISAVU
Ciclosporine	++	+++	++	+/-
Sirolimus	++	++++	++	++
Tacrolimus	++	+++	++	++
MMF				++
Vinca alkaloids	++	++	++	?
Midazolam	++	++	++	++
Simvastatin	++++	++++	+++	
Rifampicin	↓↓ itra	↓↓↓ vori	↓posa	↓↓ isa*
Phenytoin	++	+++	+++	+++
	↓↓ itra	↓↓ vori	↓posa	↓ isa
Omeprazole	↓↓ itra	↑vori	↓posa	

** Twonsend, Clin Pharmacol Drug Del, 2017*

Inspired form C Lass-Flörl, Drugs 2011

Overview of spectrum of activity



Lomentospora prolificans

FDA Advisory Committee Briefing Document 2015

Mucorales in the hematology ward

SEIFEM data:

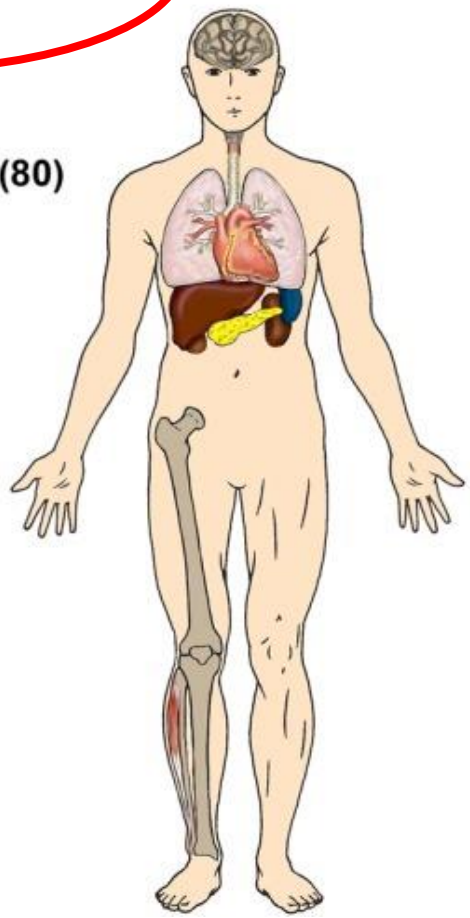
- *Pagano et al, 2006*: 14 / 11,802 hematology patients
- *Pagano et al, 2007*: 1/121 IFI developed in 3228 HSCT recipients

Prophylactic studies in allogeneic HSCT:

- *Wingard et al. 2010*: 3/600
- *Marks et al. 2011*: 0/534

Tissue and fluid concentrations of voriconazole

(expressed as multiple of blood or plasma)



Brain Abscess 1.0-2.3 x **(243)**

Cerebrospinal Fluid
0.2-1.0 x **(83)**

*Lung Tissue
0.3-3.2 x **(80)**

*Myocardium 0.4-4.6 x **(80)**

Epithelial Lining Fluid
2-1.1 x **(58, 142)**

*Liver 1.1-7.4 x **(80)**

Pleura
0.7-1.0 x **(153, 154)**

Bone 5 x **(208)**

*Spleen 0.4-3.5 x **(80)**

Synovium 0.25 x **(208)**

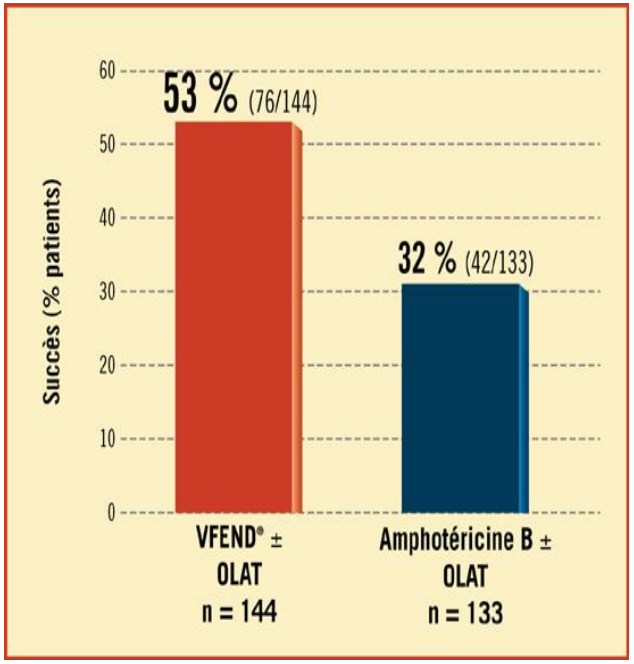
*Kidney 0.6-2.7 x **(80)**

Felton et al. Clin Microb Rev 2014

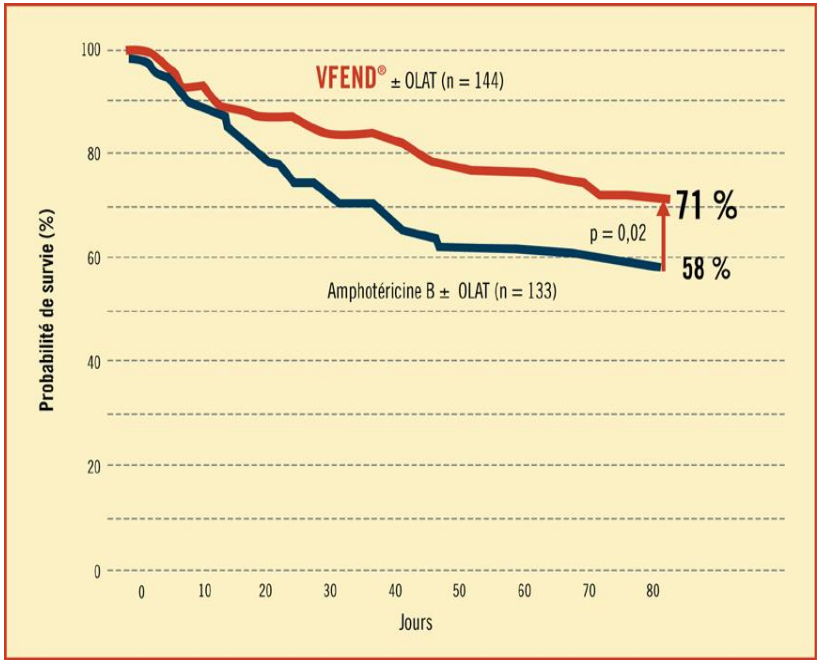
Clinical efficacy of voriconazole in 1st line therapy of invasive aspergillosis

Voriconazole vs Amphotericin B *(MITT)*

Overall success at week 12*



Survival at week 12



*Complete and partial responses

Herbrecht R et al. N Engl J Med 2002

Voriconazole in combination

A double-blind, randomized study of vori+placebo *vs.* vori+anidulafungin for primary treatment of IA

KA Marr et al. Ann Intern Med 2015

First line, proven or probable aspergillosis

Voriconazole: 6 mg/kg IV x2/j at d1, then 4 mg/kg IV x 2/d
Anidulafungin: 200 mg IV d1, then 100mg/d

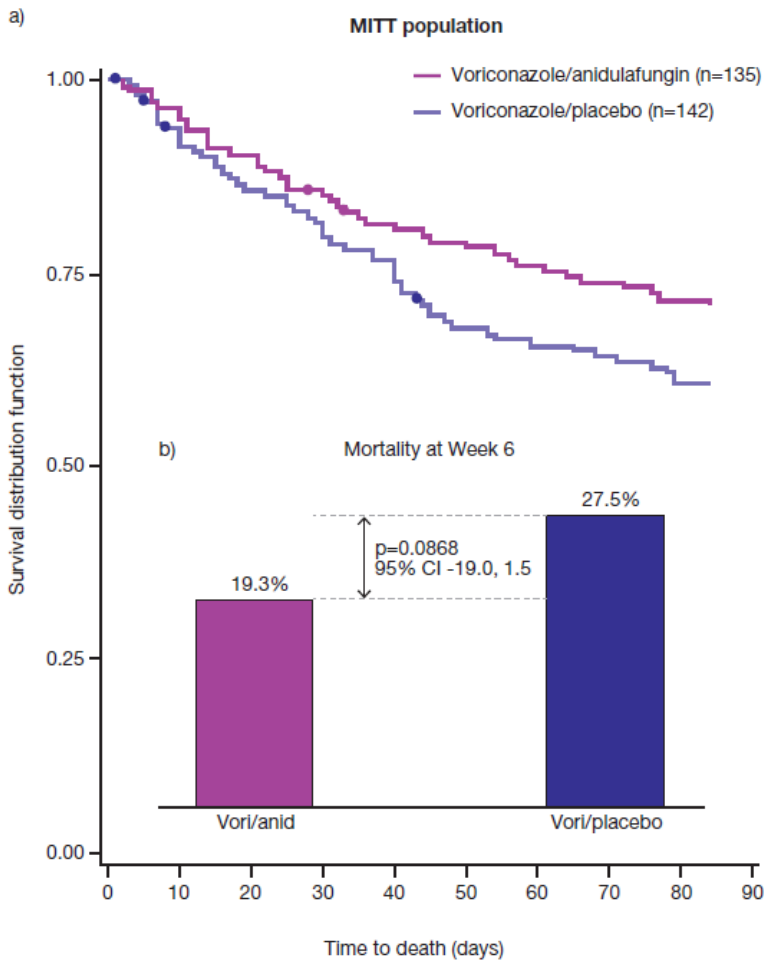
For 2 to 4 weeks

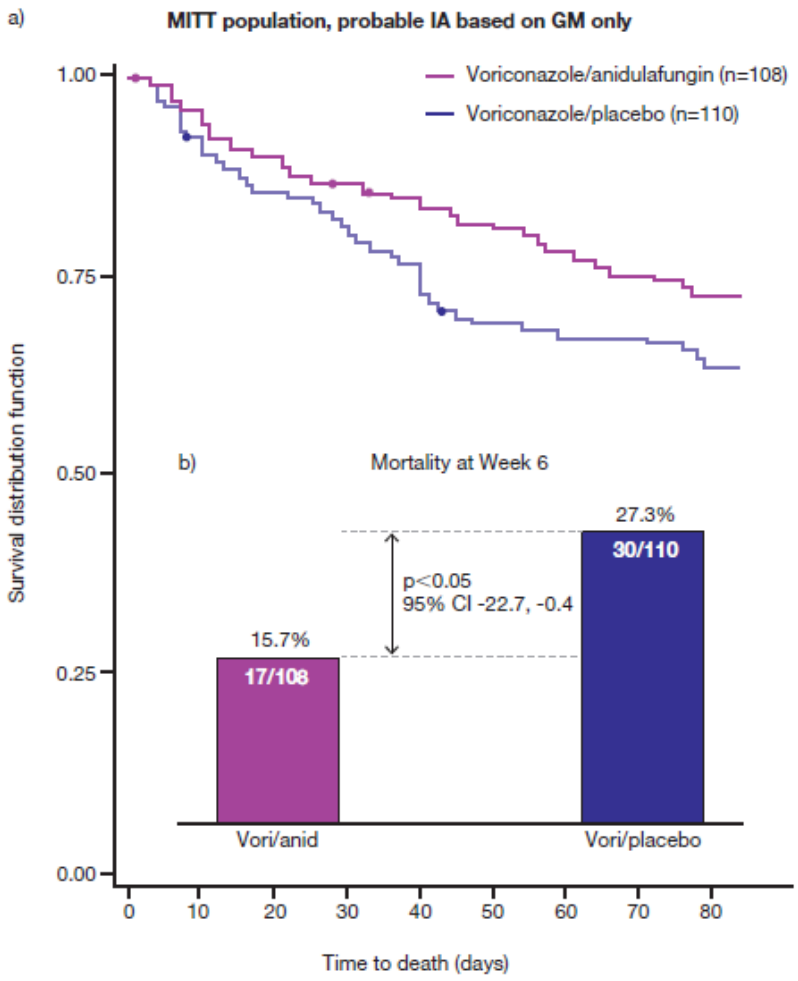
Possibility of switch to oral vori from d14

Total duration of study treatment: 6 weeks

Primary objective: overall survival at 6 weeks

Voriconazole+placebo vs. voriconazole+anidulafungin for primary treatment of IA



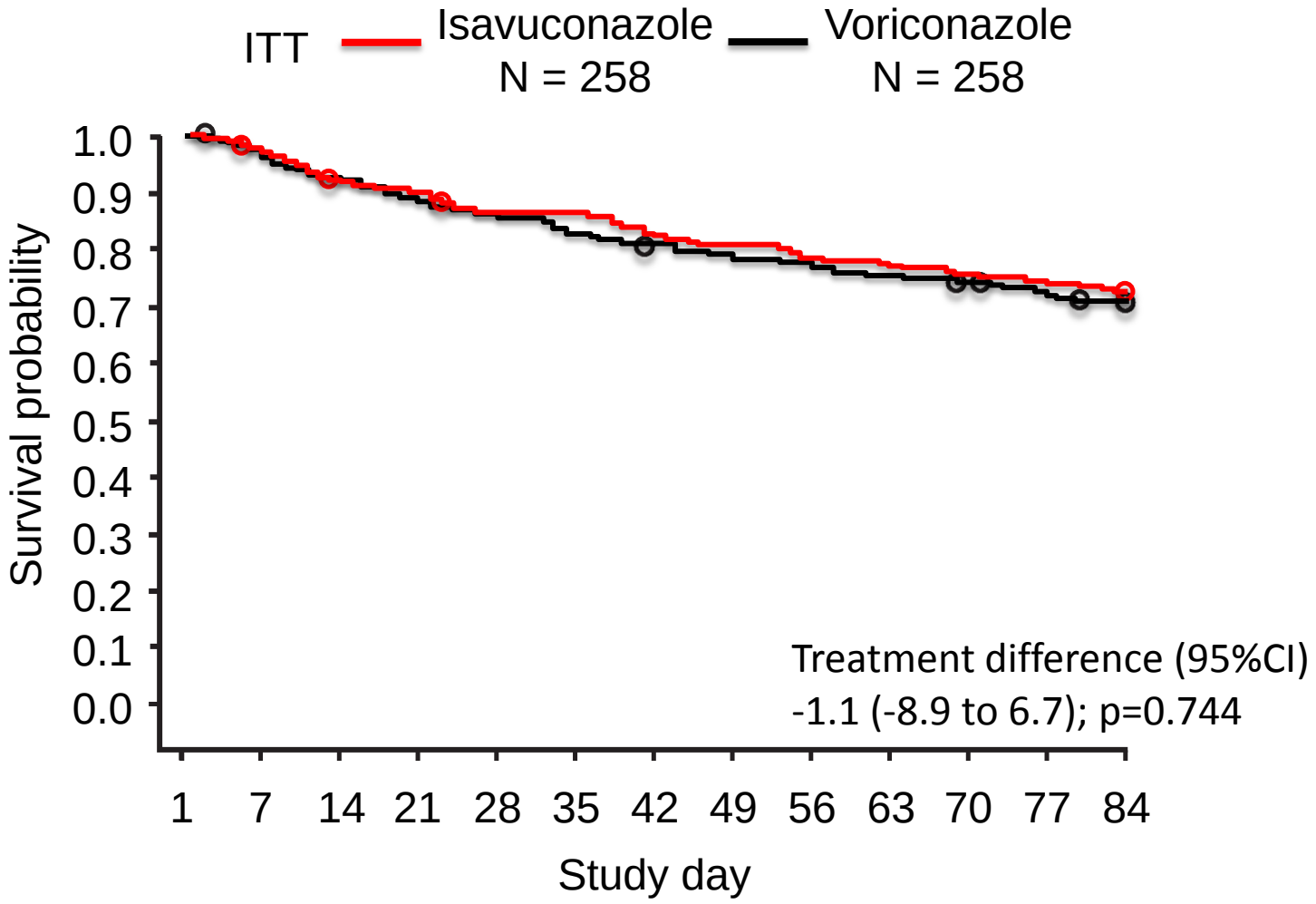


KA Marr et al. Ann Intern Med 2015

Isavuconazole vs. Voriconazole in 1st line IA

SECURE study

Kaplan–Meier analysis of all-cause mortality



Maertens J et al. Lancet 2016

Most frequent AEs (≥10%*) by System Organ Class (SECURE)

System Organ Class (%)	Isavuconazole (N=257)	Voriconazole (N=259)
Patients with any AE	96.1	98.5
Gastrointestinal disorders	67.7	69.5
Infections and infestations	59.1	61.0
General disorders and administration site conditions	57.6	55.6
Respiratory, thoracic and mediastinal disorders	55.6	56.8
Metabolism and nutrition disorders	42.0	46.7
Nervous system disorders	37.0	34.4
Skin and subcutaneous tissue disorders	33.5#	42.5
Investigations	33.1	37.1
Blood and lymphatic system disorders	30.0	31.7
Psychiatric disorders	27.2	33.2
Musculoskeletal and connective tissue disorders	26.8	29.7
Vascular disorders	26.1	29.7
Renal and urinary disorders	21.4	22.4
Cardiac disorders	16.7	22.0
Eye disorders	15.2#	26.6
Injury, poisoning and procedural complications	12.8	15.1
Hepatobiliary disorders	8.9#	16.2
Neoplasms benign, malignant and unspecified	7.4	12.0

*sorted in descending order in isavuconazole column; #p<0.05

Maertens ECCMID 2014

Treatment-emergent adverse events

SECURE study

Patients with Treatment-emergent Adverse Events (TEAEs)	Isavuconazole N=257 %	Voriconazole N=259 %	p-value
Patients with any TEAE	96.1	98.5	NS
Study drug-related TEAEs	42.4	59.8	<0.05
Serious TEAEs	52.1	57.5	NS
Study drug-related serious TEAEs	10.9	11.2	NS
Permanent drug discontinuation due to TEAEs	14.4	22.8	<0.05
Permanent drug discontinuation due to drug-related TEAEs	8.2	13.5	NS
Death	31.5	33.6	NS

Maertens ECCMID 2014

CLINICAL AND EPIDEMIOLOGICAL STUDY

The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis

S. Schwartz · A. Reisman · P. F. Troke

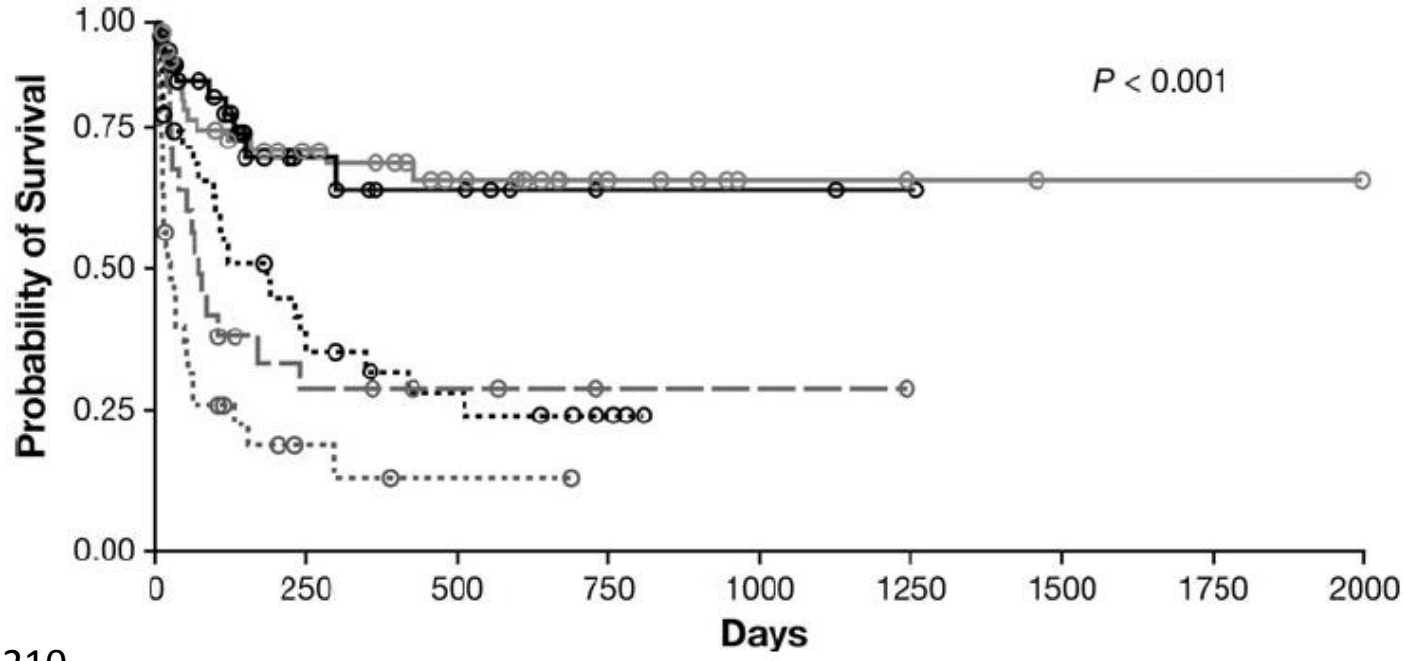


Fig. 1 Kaplan–Meier curves of survival by underlying condition: *grey dotted line* haematopoietic stem cell transplant; *black dotted line* haematologic malignancy; *grey dashed line* solid organ transplant; *black line* chronic immune suppression; *grey line* other; *circles* censored patients

*Infection, 2011:*39:201–210

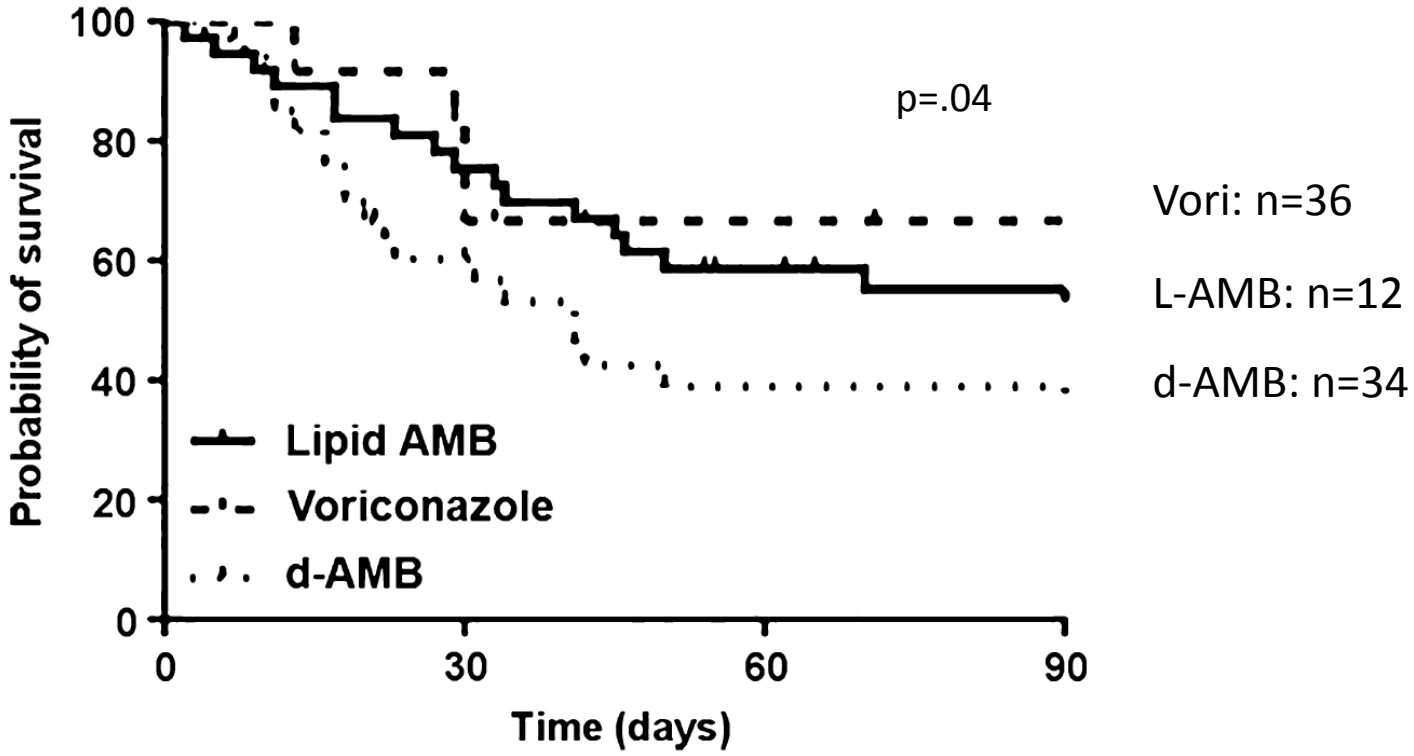
No change over time in the guidelines for 1st line treatment of invasive aspergillosis for voriconazole

Guidelines		Voriconazole	Isavuconazole
IDSA	Walsh et al. 2008	AI	-
	Patterson et al 2016	Strong recommendation High-quality evidence	Strong recommendation Moderate-quality evidence
ECIL	Maertens et al. 2008	AI	-
	Maertens et al. 2010	AI	-
	Tissot et al. 2017	AI	AI (better tolerated)

Improvement in the outcome of invasive fusariosis in the last decade

Nucci et al, Clin Microbiol Infect. Oct. 2013

Survival rate at 90 days in 83 patients with invasive fusariosis (2001-2011) treated with amphotéricine B deoxycholate (d-AMB), a lipid formulation of ampho (lipid AMB) or voriconazole



Scedosporium infections

ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis

M Arendrup et al, CMI

Fusarium, Scedosporium, Acremonium, Scopulariopsis, Purpureocillium and Paecilomyces

Therapy should include voriconazole and surgical debridement where possible or posaconazole as salvage treatment. **Voriconazole represents the first-line treatment of infections due to members of the genus Scedosporium**

For Acremonium spp., Scopulariopsis spp., Purpureocillium spp. and Paecilomyces spp. the optimal antifungal treatment has not been established. Management usually consists of surgery and antifungal treatment, depending on the clinical presentation.

M Arendrup et al. CMI 2014, CMI, 20 (Suppl. 3), 27–46

Voriconazole primary prophylaxis in allogeneic stem cell transplantation

Wingard et al. Blood 2010: **Vori vs. Fluco** (n=600)

No difference for IFD, fungal-free survival (FFS), and overall survival.

In pts with AML: fewer IFD (8.5% vs. 21%; *P* .04) and improved FFS

Marks et al. BJH 2011: **Vori vs. Itra** (n=489)

Better "success" (combining FFS at d180 and tolerance of the study drug up to d100) in the vori group, mainly due to a better tolerance and duration of study drug with vori

Update: ECIL 5, 2013

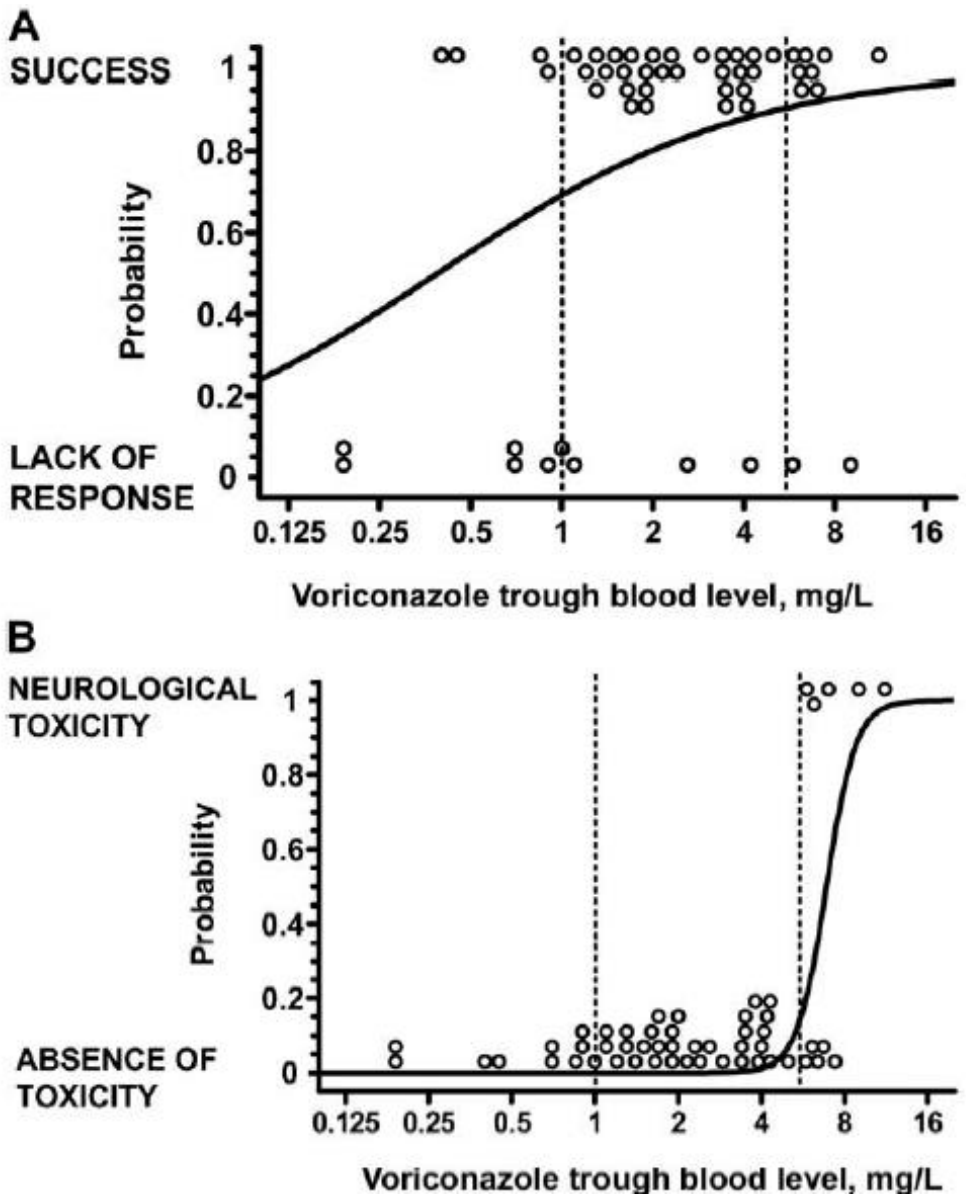
Recommendations for allogeneic HSCT recipients (2013)

Antifungal prophylaxis*	Pre-engraftment Low risk for moulds	Pre-engraftment High risk for moulds	GvHD
Fluconazole	A-I	A-III - against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole OS/Tablet	B-II	B-II	A-I
Micafungin	B-I	C-I	C-II
Caspofungin /anidulafungin	No data	No data	No data
Liposomal Amphotericin B	C-II	C-II	C-II
Aerosolized amphotericin B plus fluconazole	C-III	B-II	No data

*For doses & need for Therapeutic Drug Monitoring: please refer to slides 21 and 22

Relationship between voriconazole trough blood levels, efficacy and toxicity

A Pascual et al. CID 2008



Voriconazole concentration-efficacy relationship

- ***Prospective*** **studies have reported trough concentrations of ≥ 1.5-2 mg/L are associated with near maximal clinical response in treatment of IFI [1-6]**

- **Post-hoc analysis of Phase II/III clinical trials:[4]**
  - Vori C_{avg} /MIC target > 2, or vori plasma 2-5 mg/L
  - Response rate: 74%

Recommendation: voriconazole prophylaxis and treatment target: > 1-2 mg/L **(AII);**

higher troughs (> 2) are recommended for severe infections or when there are concern of treating fungi with elevated MICs

1. Pascual A,et al. Clin Infect Dis 2012; 55: 381–390.
2. Pascual A, et al. Clin Infect Dis 2008; 46: 201–211.
3. Park WB et al. Clin Infect Dis 2012; 55: 1080–1087.
4. Troke PF, et al. Antimicrob Agents Chemother 2011; 55: 4782–47
5. Trifilio S et al. Bone Marrow Transplant 2007; 40: 451–456.
6. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799

Voriconazole concentration-toxicity relationship

Recommendation: voriconazole safety target: < 5.0-6.0 mg/L (AII);

Patients without symptoms of clinical toxicity may not require dose reductions, however the risk versus benefit must be weighed for each patient

Maintenance of exposures near this threshold may be needed for severe infections (e.g., CNS infection) or when treating fungi with elevated MICs

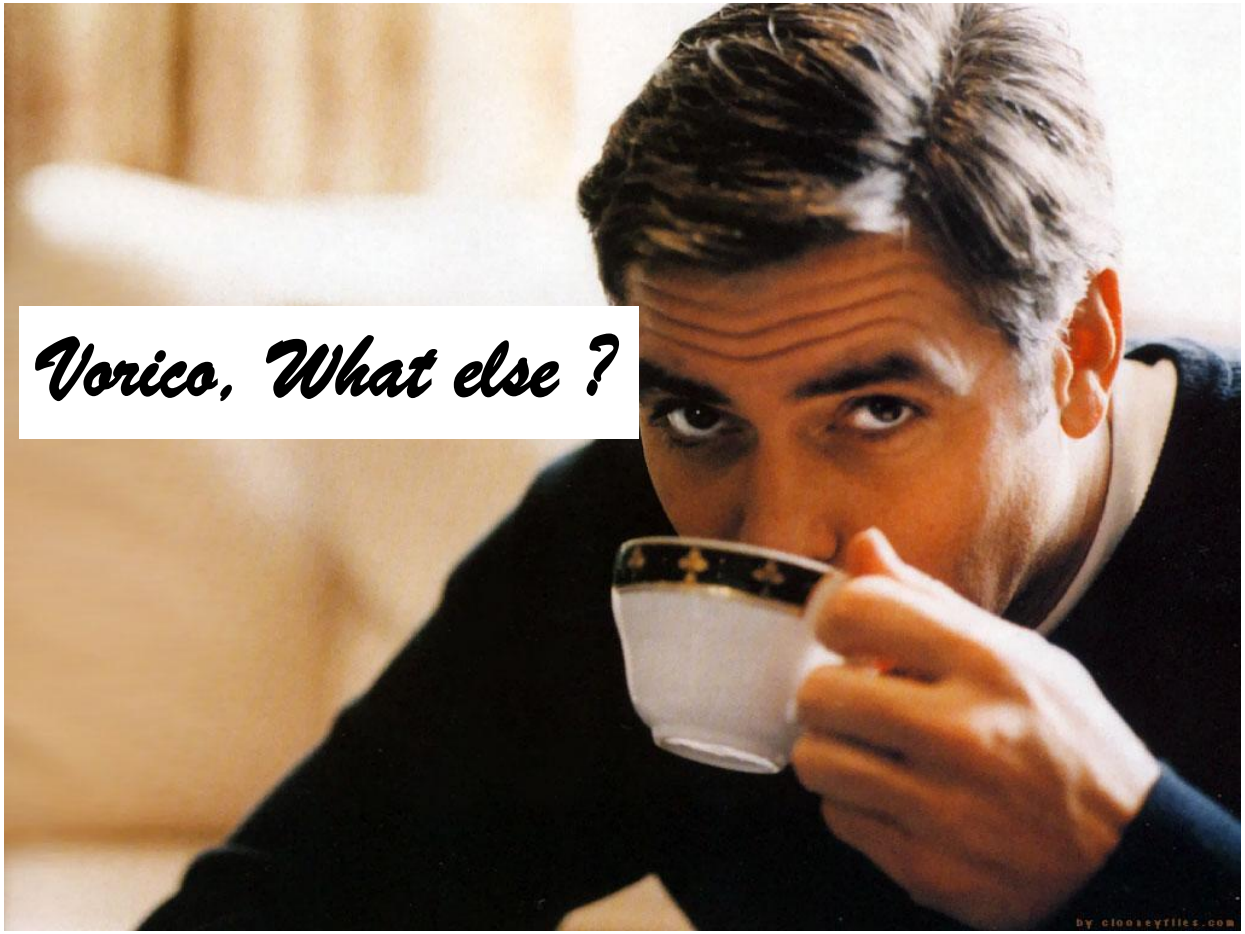
Lower trough < 4 mg/L in Japanese patients may be associated with lower hepatotoxicity risk (CYP2C19 genotype/higher exposures)

Conclusion

Voriconazole is:

- a gold standard for primary therapy of IA
- a main therapy for fusariosis and scedosporium infections
- an effective prophylaxis of IFD at the different phases of allogeneic HSCT

Its development allowed major progress in the design of antifungal trials



Thank you for your attention