

Aspergillus guidelines

To a consensus of ECIL and ESCMID/ECMM

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Isavuconazole in invasive aspergillosis

- Large double-blinded RCT comparing
 - Isavuconazole (2x200 mg iv on day 1 and 2, then 200 mg/d either iv or oral)
 - Voriconazole (2x6 mg/kg iv on day 1, then 2x400 mg/d iv on day 2 then 200 mg/d iv or oral)
 - Fixed dose and TDM allowed locally (double-blind)
- 527 patients randomized
 - 516 received at least one dose of study drug (ITT)
 - 272 patients in mITT population (ISA: 143 ; VRC:129)
 - All with probable or proven mold infections (85% were aspergillosis)
 - 85% of the patients had an hematological malignancy or HSCT
- Primary endpoint: non-inferiority for day 42 all-causes mortality in the ITT population



Isavuconazole in invasive aspergillosis

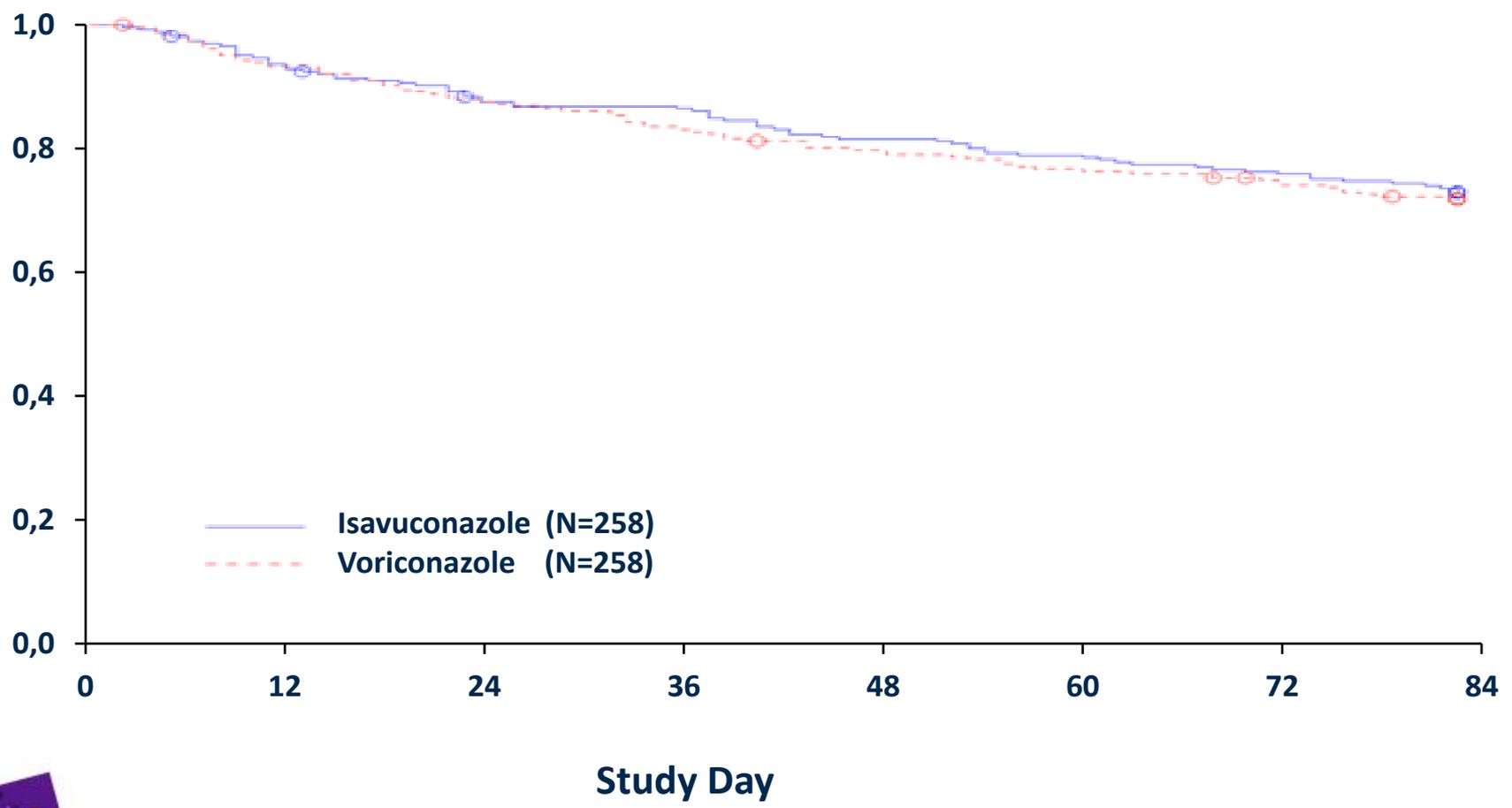
- All cause mortality at day 42 (ITT population)
 - ISA : 18.6%
 - VCR : 20.2% } Primary objective of non-inferiority was achieved
- Similar response rates
- Similar all-cause mortality at day 84 in mITT population
 - ISA : 30.1%
 - VCR : 37.2%
- More drug-related events for voriconazole
 - ISA : 42.4%
 - VCR : 59.8%



Isavuconazole in invasive aspergillosis

Survival Probability

ITT



(Maertens et al., ECCMID, 2014)

All AEs by system organ class (SOC) >5%

System Organ Class, %	Isavuconazole N = 257	Voriconazole N = 259
Gastrointestinal Disorders	67.7	69.5
Infections and Infestations	59.1	61.0
General Disorders and Admin. 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
Immune System Disorders	7.8	9.7
Neoplasms Benign, Malignant and Unspecified	7.4	12.0
Ear and Labyrinth Disorders	5.4	5.0

(Maertens et al., ECCMID, 2014)

Invasive aspergillosis: First-line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Isavuconazole	A I	provisional
Ambisome	B I	dose 3 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	
ABCD	C I	
Combination voriconazole + anidulafungin	C I	
Other combinations	C III	

~~AGAINST THE USE~~

Amphotericin B deoxycholate **A I-against**

In the absence of data in 1st line, posaconazole has not been graded



Bias resulting from including isavuconazole in the guidelines

- Integration of isavuconazole data was not initially planned but has been approved by you yesterday
- Risk of reduction of the strength of the guidelines by weakness in the methodology
 - Addition of one study without checking for other potential abstracts or publications for other drugs or strategies in the treatment of aspergillosis
 - Aspergillus recommendations are updated but not candidiasis and mucormycosis



Bias resulting from including isavuconazole in the guidelines

- Proposal:
 - The subgroup will search for new data since September 2013 for *Candida*, *Aspergillus* and Mucorales infections
 - Already identified :
 - full paper for high-dose liposomal amphotericin B in mucormycosis
 - abstracts with pooled data from anidulafungin trials in *Candida* infections (*Candida krusei* and neutropenic patients)
 - All new data will be analyzed and all fungal treatment recommendations will be updated
 - A meeting of the subgroup is expected during TIMM to have a face to face discussion rather than phone conferences
 - We need your comments and expect your approval

