

**Prophylaxis
vs.
Treatment**

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Disclosure:

- **Consultant/Research:** Basilea, Pfizer, Schering-Plough, Astellas, Gilead, Aicuris
- **Speaker's bureau:** Astellas, Gilead, Merck/MSD-Schering-Plough (New Merck), Astellas, and Pfizer

Presentation will focus on:

- Invasive Aspergillosis (some *Candida* Data):
 - Treatment options
 - Prophylaxis
- Focus on morbidity and mortality

Therapeutic Options

Anything really new?

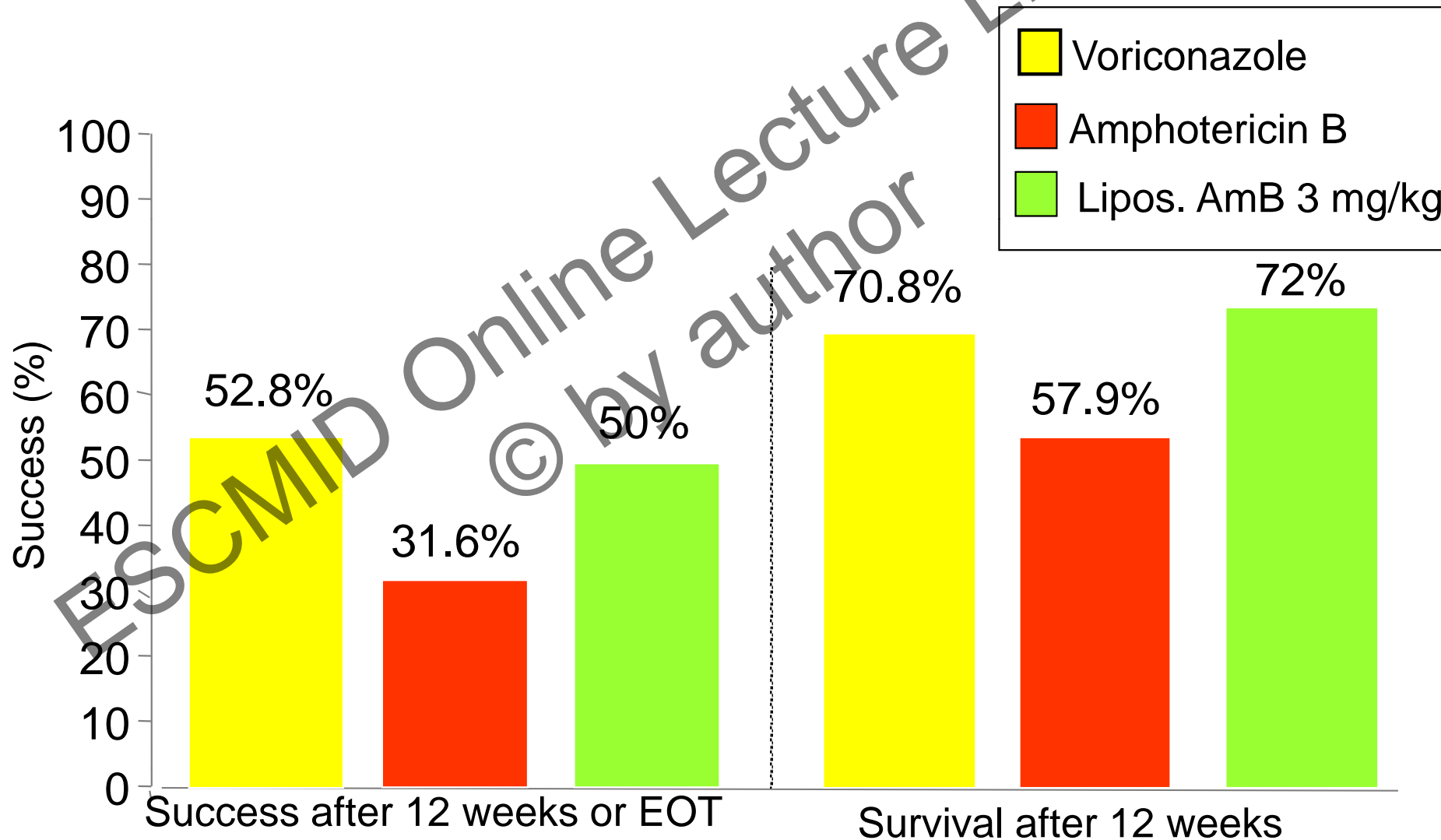
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Patients at risk of invasive aspergillosis

- Acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) during remission induction chemotherapy;
 - Prolonged and profound neutropenia, i.e. >10 consecutive days with neutrophil cell counts $<500/\mu\text{L}$, is the single most important risk factor
- Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT)
- Recipients of solid organ transplants;
- Those with other conditions of severe and prolonged immunosuppression.

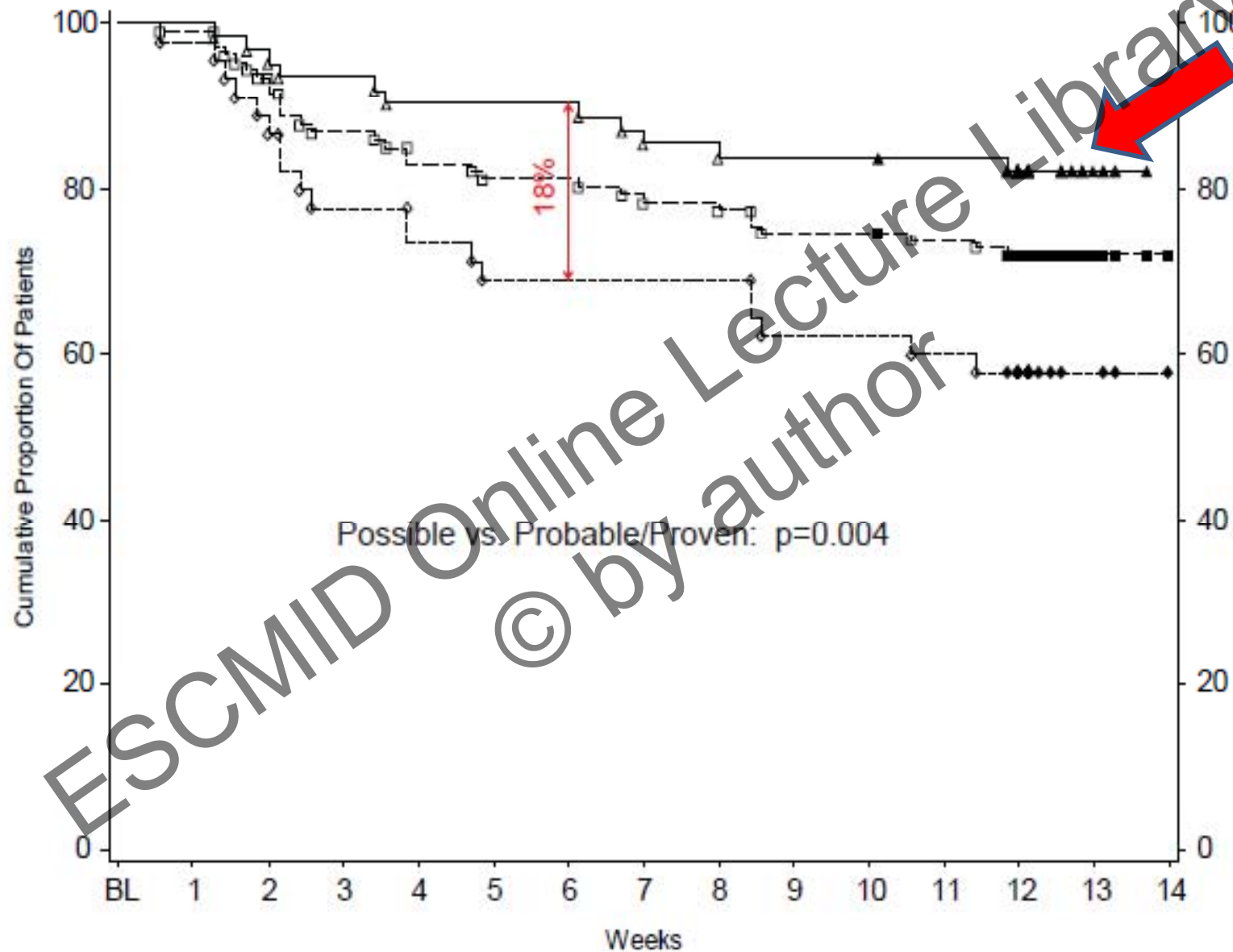


Invasive Aspergillosis: Results in Primary Therapy Trials



Ambiload Trial : Survival

Kaplan-Meier-Analysis



△	Possible (n=):	62	62	59	58	56	56	56	53	52	52	52	51	34	15	10
◇	Probable/Proven (n=):	45	44	39	35	33	31	31	31	31	28	28	27	19	6	3
□	Overall (n=):	107	106	98	93	89	87	87	84	83	80	80	78	53	21	13

Results Primary Treatment Caspofungin: Successful Therapy in Neutropenia

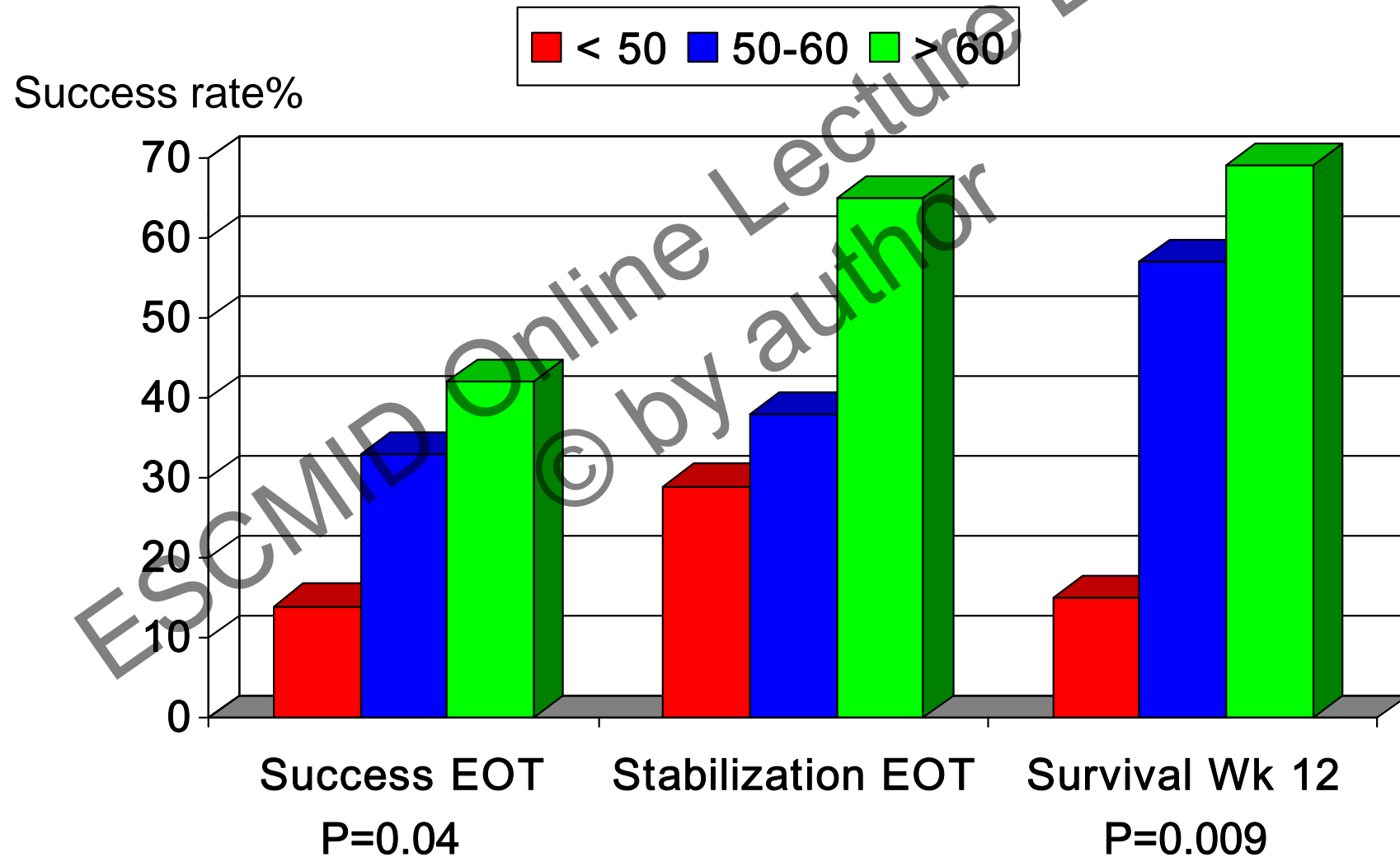
Response assessment in the MITT analysis (N = 61)

Standard response assessment according to DRC

At end of treatment

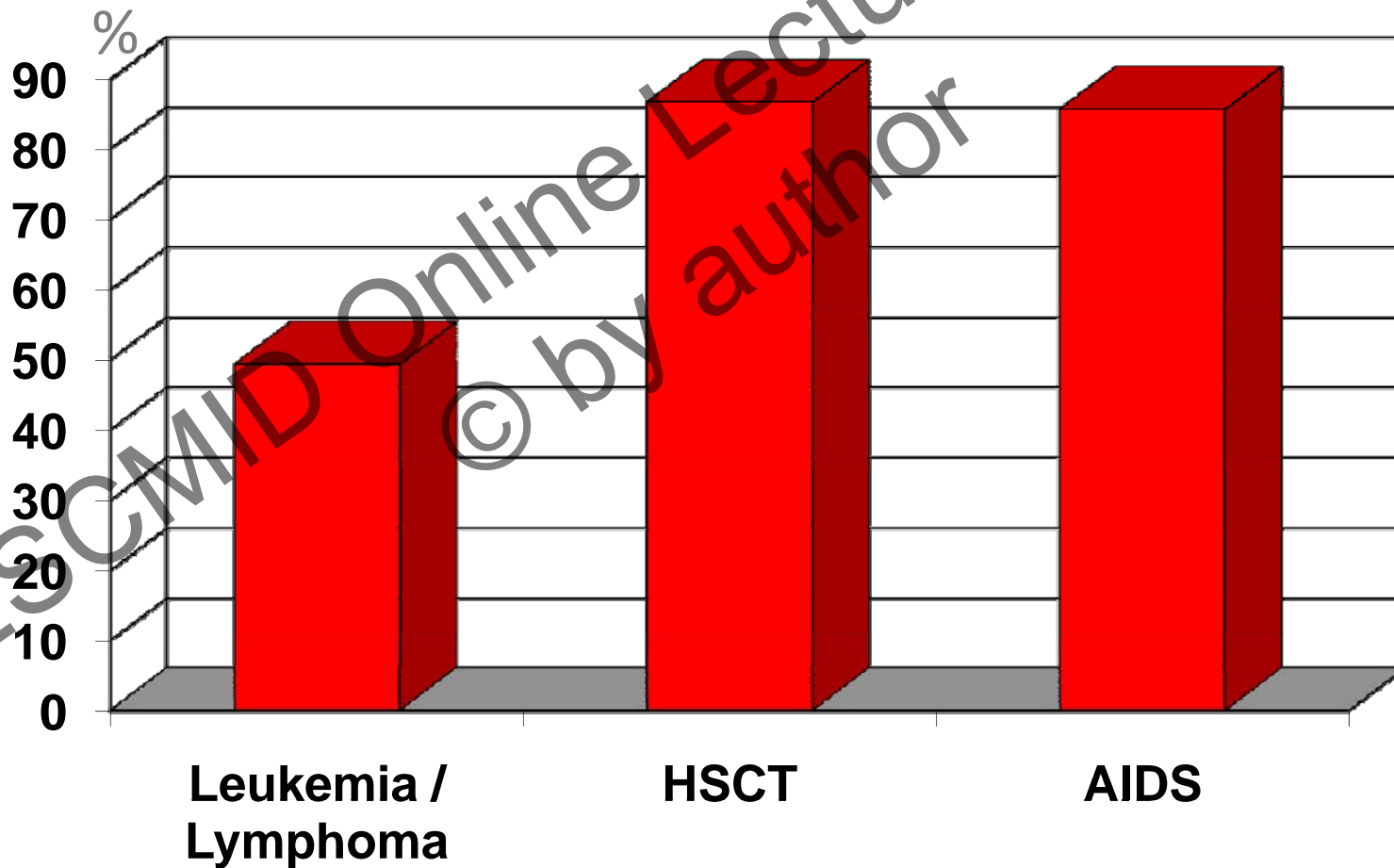
Success	Complete response	1	2%
	Partial response	19	31%
Failure	Stable disease	9	15%
	Progression of disease	31	51%
	Not done	1	2%

Results by Karnofsky score



Case Fatality Rate in Aspergillosis:

Underlying Disease

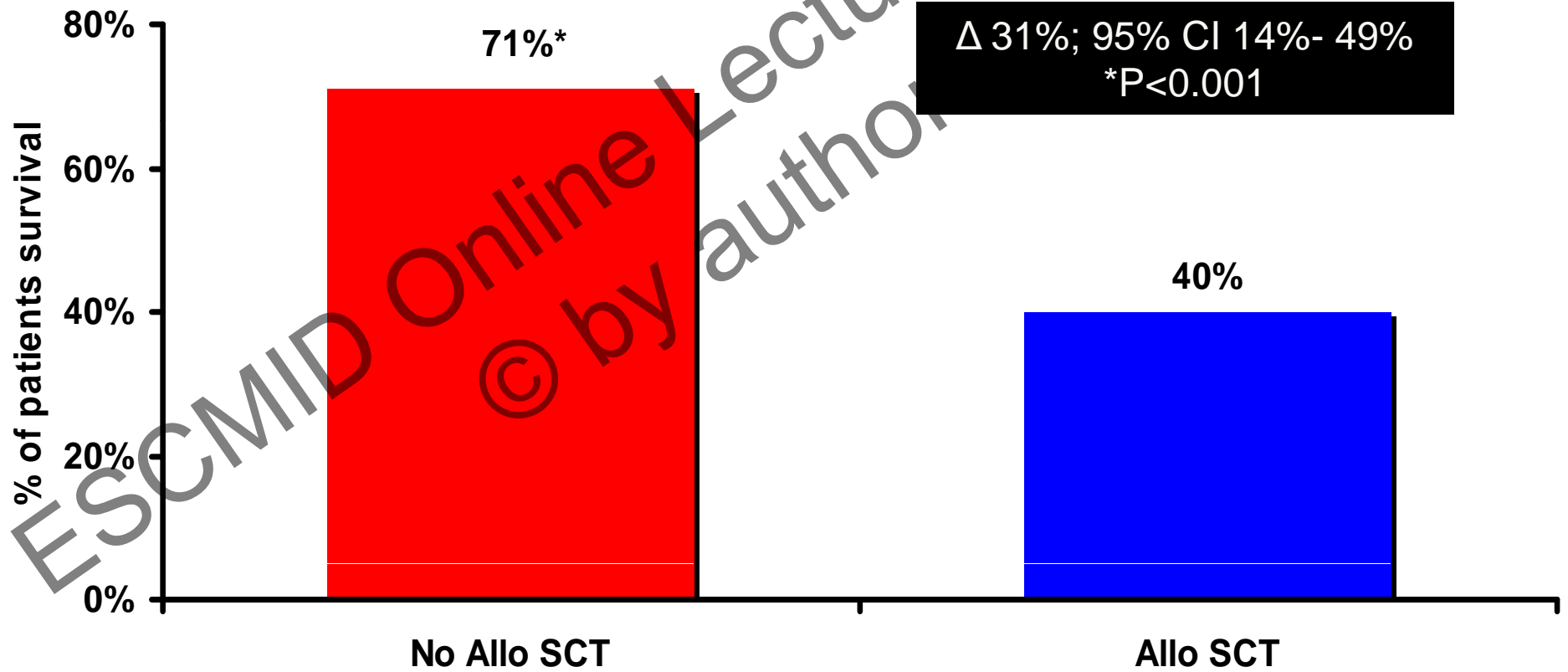


First Line Invasive Aspergillosis Trials

Allogeneic HSCT Patients

	Herbrecht et al, NEJM 2002	Herbrecht et al, NEJM 2002	Cornely et al. CID 2007
	Voriconazole N=37	cAmB N=30	L-AmB-3mg N=17
Disease Definition Proven/probable IA	Modified criteria Halo/air crescent sign only allowed	Modified criteria Halo/air crescent sign only allowed	Modified criteria Halo/air crescent sign only allowed
Favorable response	32%	13%	47%
Complete response Defined as resolution:	> 90% all lesions and symptoms	> 90% all lesions and symptoms	All lesions and symptoms as Herbrecht
Partial response	Clinical improvement and resolution 50% lesions	Clinical improvement and resolution 50% lesions	„Softer“ radiologic endpoints (Denning, CID 2007) halo sign disappear, lesions decrease size

AmBiLoad: Survival at 12 Weeks



Allogeneic HSCT, Invasive Aspergillosis

Caspofungin 1st Line Therapy

Success (Complete or Partial Response) at EOT and D.84 - MITT Analysis

Time Point	Favorable Response Rate	95 % CI
EOT	10 / 24 (42%)	22 – 63%
Day 84	7 / 23 (30%)	13 – 53%

Survival at Day 84 - MITT Analysis

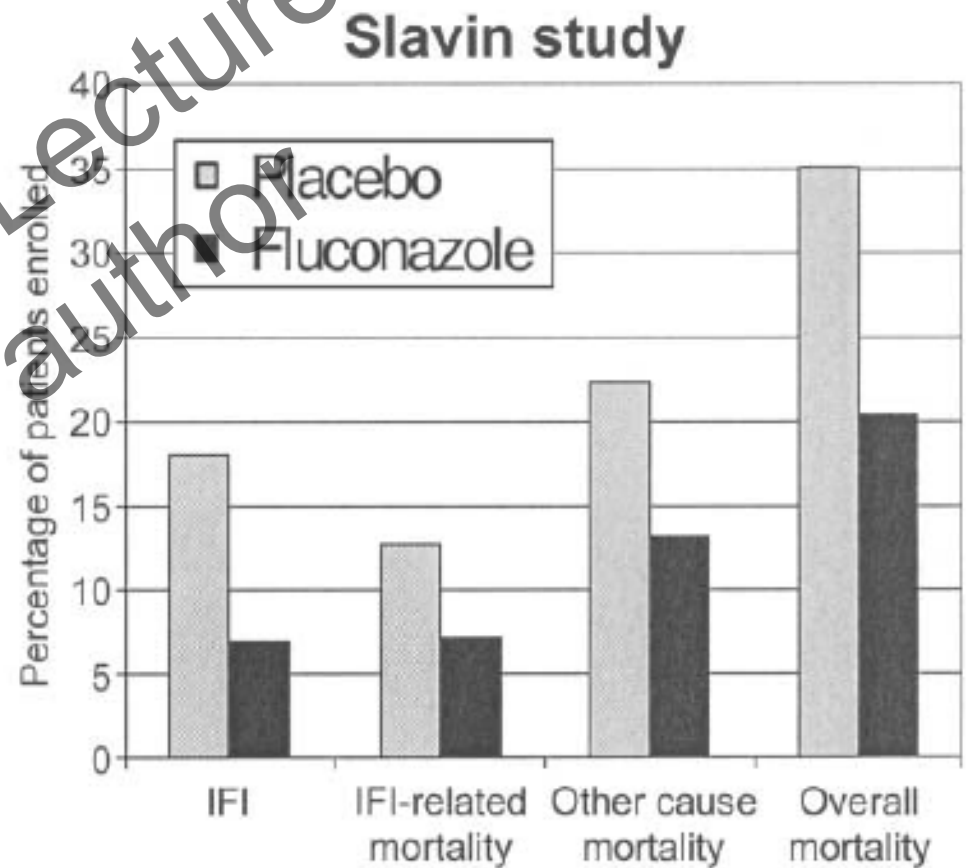
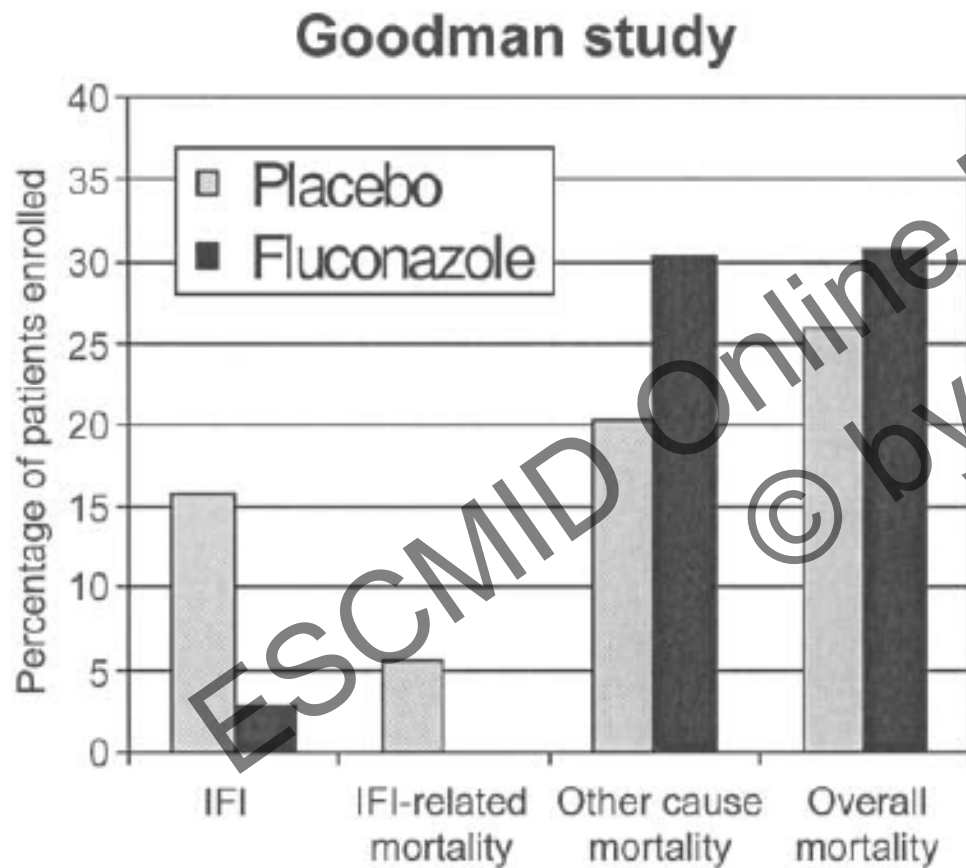
	MITT (N=24)
Alive	11 (46%)
Death	12 (50%)
Main Cause of Death (according to DRC)	
IA	5
Haemorrhage with IA	1
Underlying Disease with IA	3
IA + Concomitant Infection	1
Other	2
Unknown (Lost to Follow Up)	1 (4%)

Prophylaxis

An Alternative?

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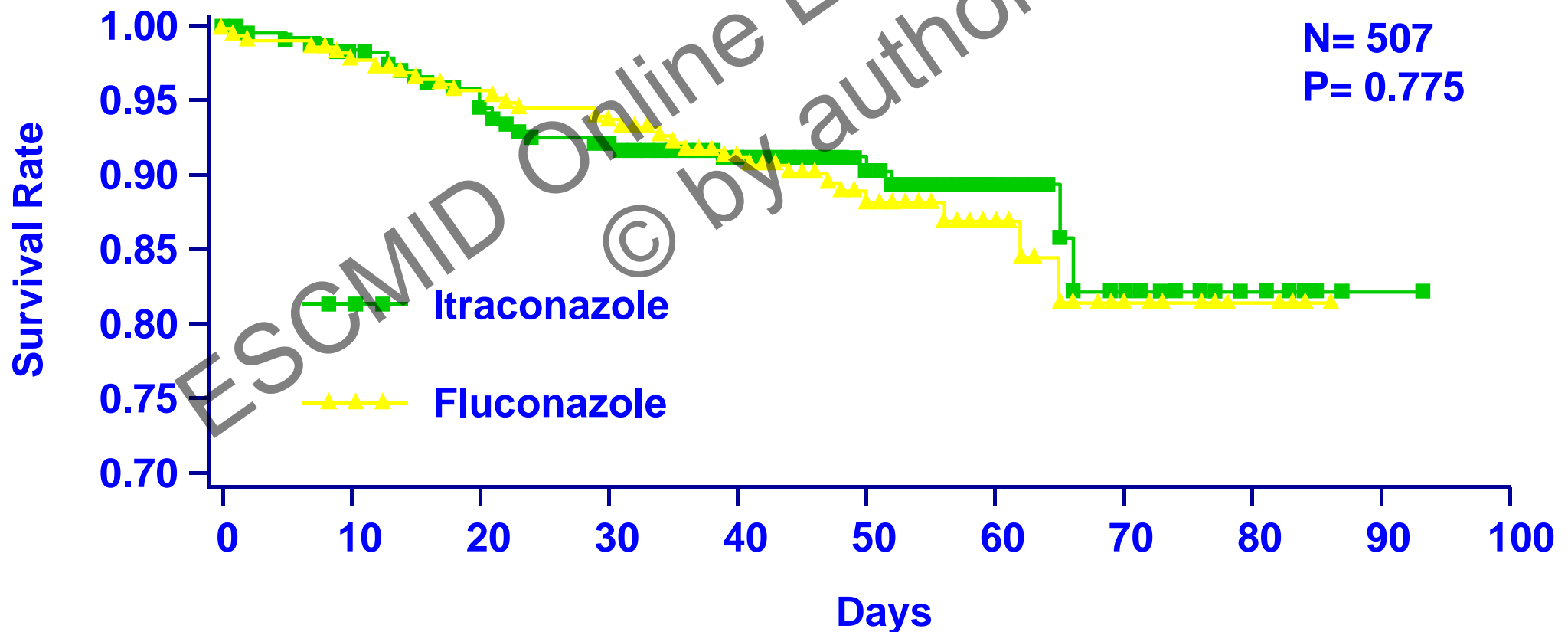
Pivotal Results in HSCT



An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia

Axel Glasmacher^{1*}, Oliver Cornely², Andrew J. Ullmann³, Ulrich Wedding⁴, Heinrich Bodenstein⁵, Hannes Wandt⁶, Christian Boewer⁷, Rita Pasold⁸, Hans-Heinrich Wolf⁹, Mathias Hänel¹⁰, Gottfried Dölken¹¹, Christian Junghanss¹², Reinhard Andreesen¹³ and Hartmut Bertz¹⁴

Time to Death – Intent-To-Treat Population



Proven/Probable Invasive Fungal Infections

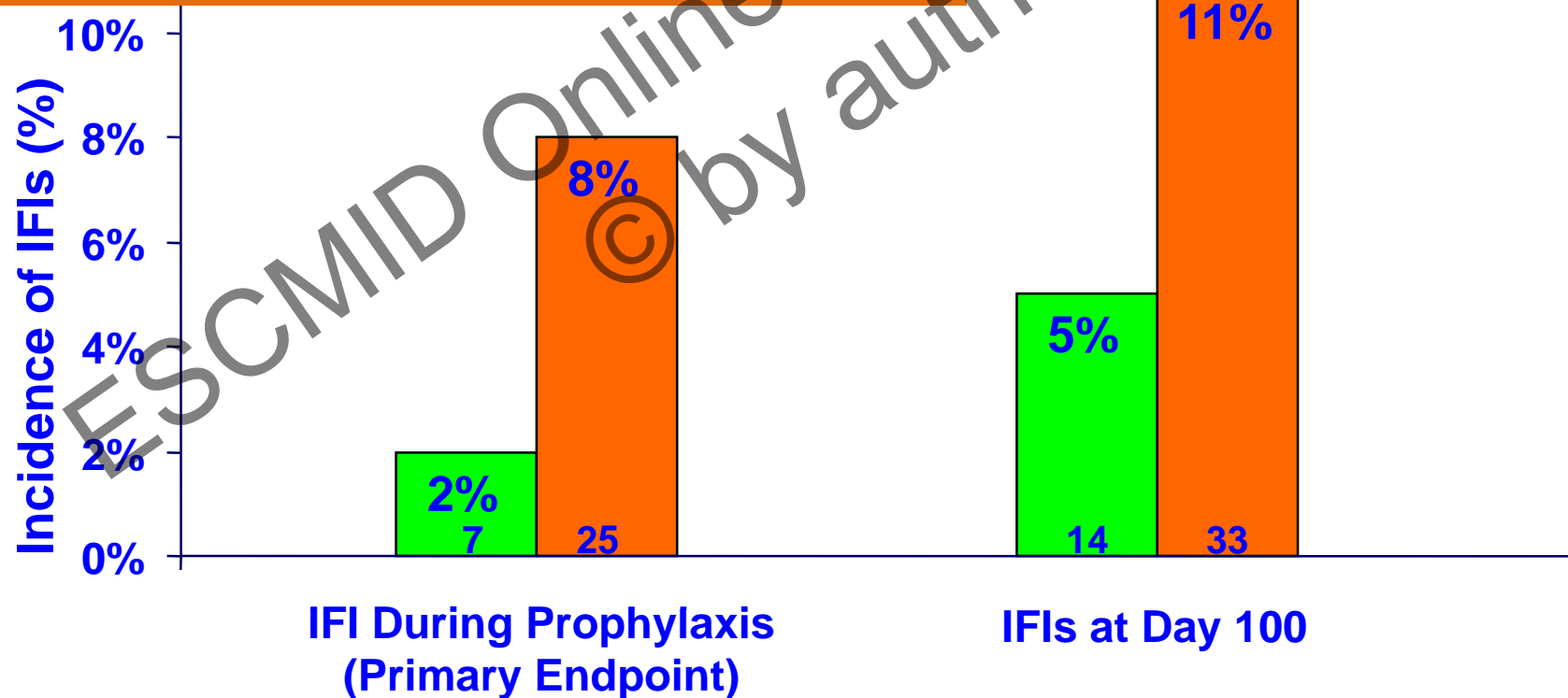
...and Candida:

POSA	3 cases
FLUC	3 cases
ITRA	0 cases

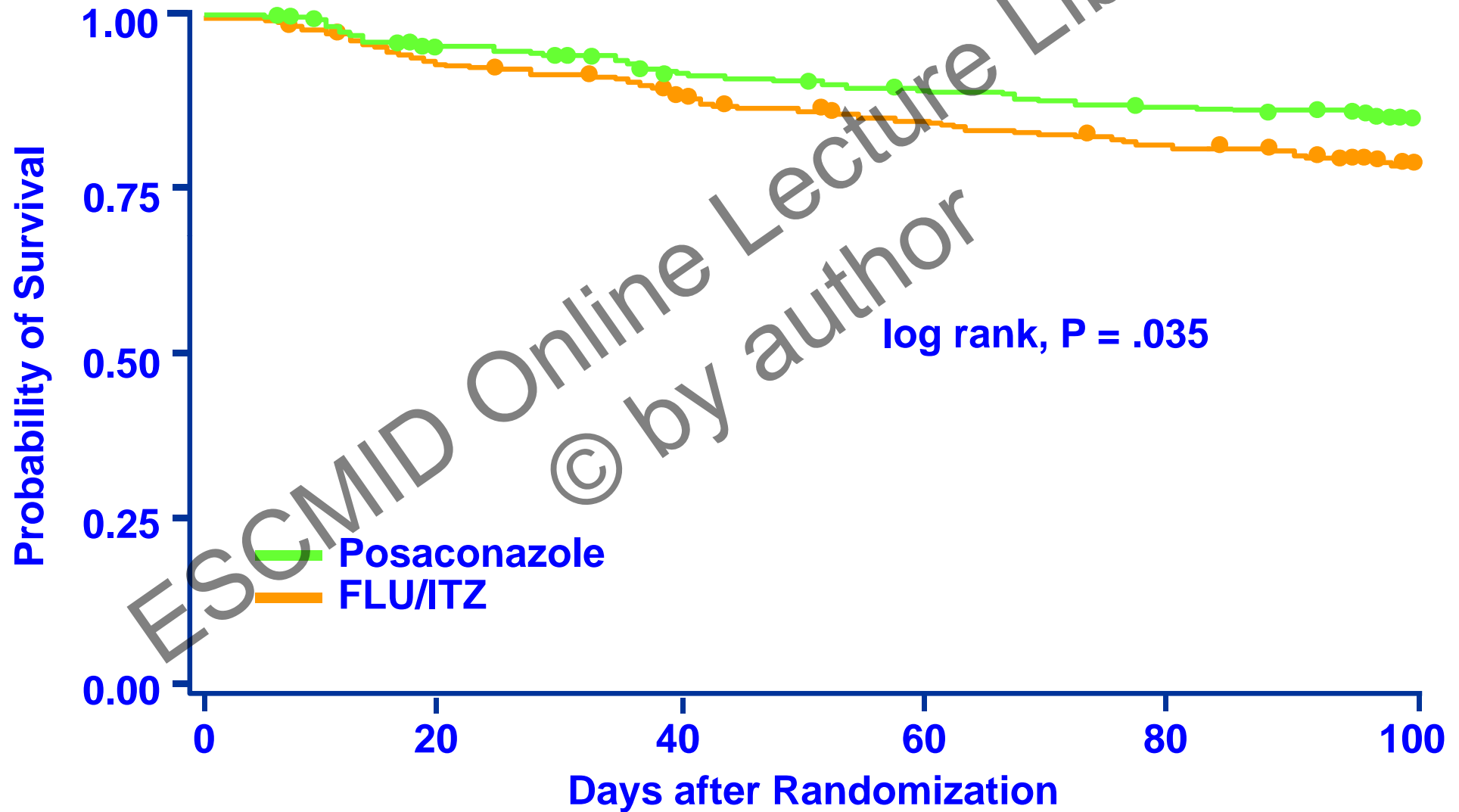
■ Posaconazole

■ FLU/ITZ

$P = .0031$



Overall Mortality – Time to Death



Number Needed to Treat

Real Numbers

Neutropenia^a

Incidence rates, %

Clinical outcome	Posaconazole (200 mg TID)	Fluconazole (400 mg QD) or itra- conazole (200 mg BID)	Relative risk reduction ^c	Absolute risk reduction ^d	NNT ^e
Invasive fungal infection	2.3	8.4	0.73	0.061	16
Invasive aspergillosis	0.7	6.7	0.9	0.061	17
Death due to fungal infection	1.6	5.4	0.69	0.037	27
Death due to any cause	14.5	21.5	0.33	0.07	14

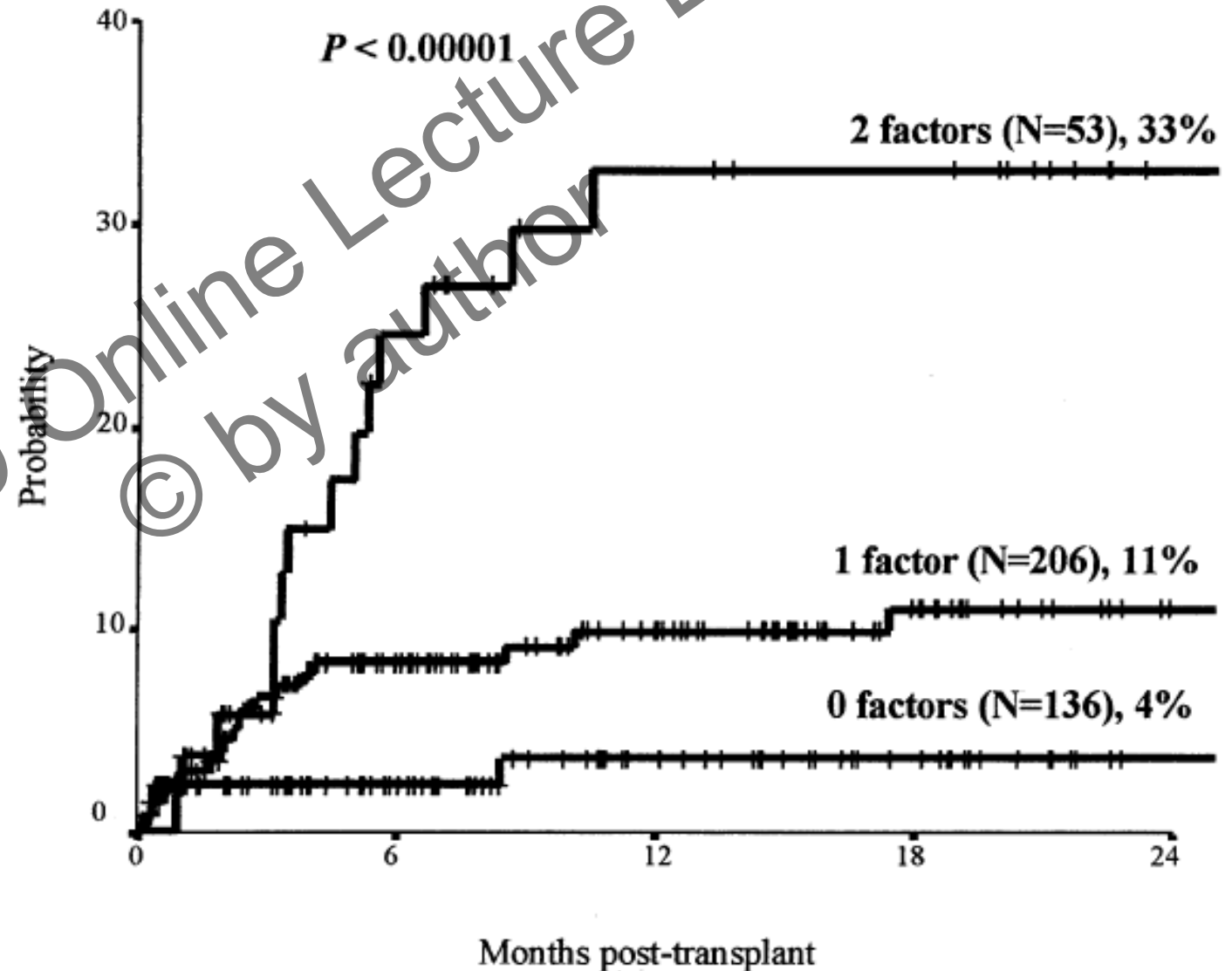
Invasive Fungal Infections in allogeneic HSCT

Risk Factors in Relation to Incidence

Overall incidence rate of IFI in 395 allogeneic HSCT: 14%

Risk Factors:

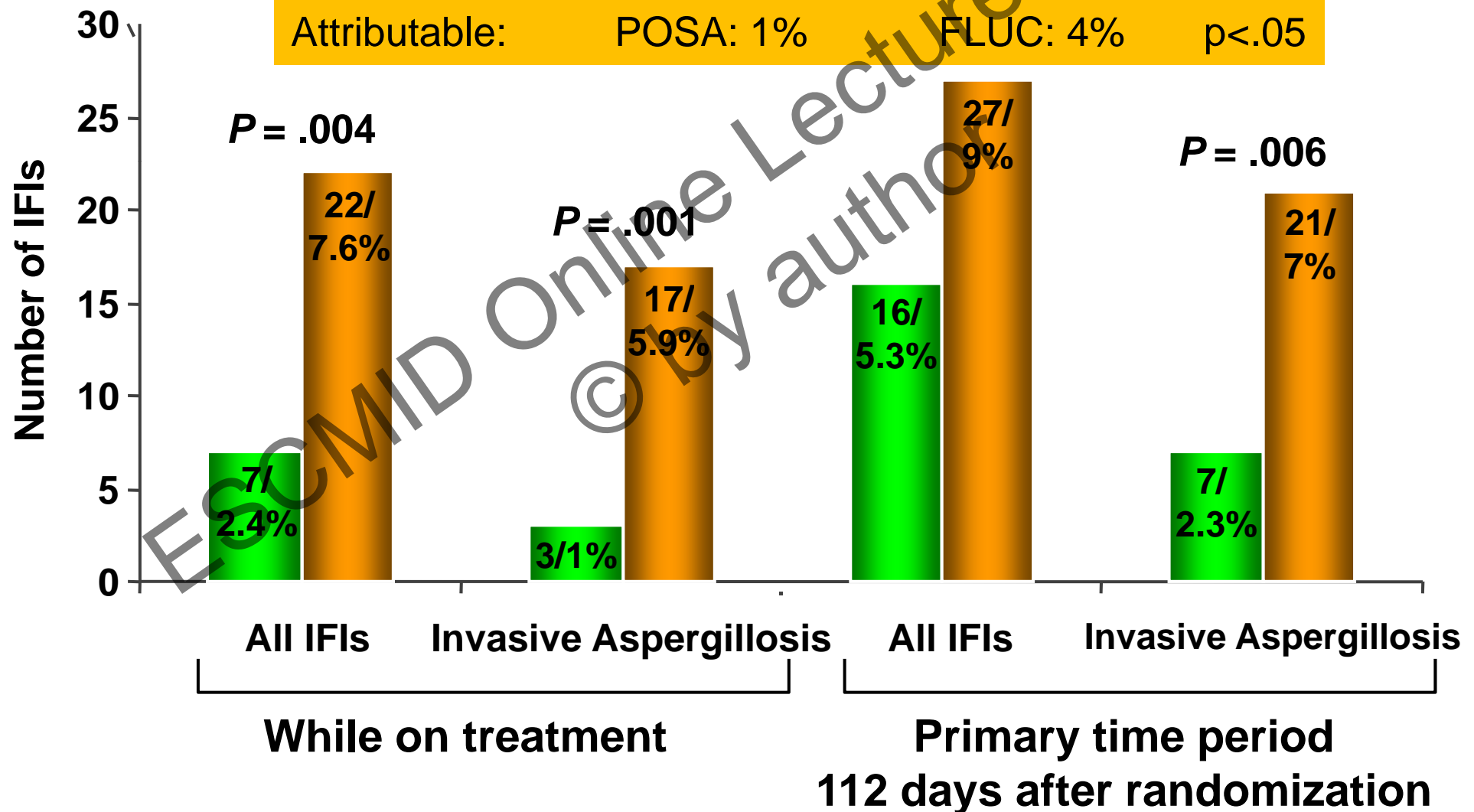
- Steroid prophylaxis
- Moderate-to-severe GVHD



Posaconazole Prophylaxis Study Incidence of Proven/Probable IFIs

Mortality:

Overall:	POSA: 25%	FLUC: 28%	n.s.
Attributable:	POSA: 1%	FLUC: 4%	p<.05



Posaconazole Prophylaxis Study Incidence of Yeasts

Proven/
Probable IFI, n

Posaconazole
n = 301

Fluconazole
n = 299

Candida

4

4

Candida NOS

1

0

C. krusei

1

1

C. albicans

0

1

C. glabrata

2

1

C. parapsilosis

0

1

Trichosporon

1

0

beigelii

Number Needed to Treat

	GvHD				
	Incidence rates				NNT
Allocated treatment	Posaconazole 200mg TID (Pp)	Fluconazole 400mg QD (Pf)	Relative risk reduction (Pf-Pp)/Pf	Absolute risk reduction (Pf-Pp)	1/(Pf-Pp)
Invasive fungal infection	5.3%	9%	0.41	0.037	(27)*
Invasive aspergillosis	2.3%	7%	0.67	0.047	21
Death from fungal infection	1%	4%	0.75	0.03	33
Death from any cause	19%	20%	0.05	0.01	(100)*

Fluconazole 400 QD vs Voriconazole 200 BID

Prevention of IFI in Allogeneic HSCT

N=600	FLU N=295	VORI N=305	p
Proven + probable + presumptive IFI 6 months at 12 months	10.6% 13.1%	6.6% 11.6%	p=0.11 p=0.50
First 180 days: <i>Aspergillus</i> spp. <i>Candida</i> spp. Zygomycetes (& multiple) Other	17 3 3 2	9 3 1 1	p=0.09
Fungal-free survival at 6 months	76%	78%	NS
12 months	65%	63%	NS
Event-free and overall survival at 6 and 12 mo			NS



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Summary

- Focus on the “unmet medical need”
- Treatment success of IFD differs by
 - Species
 - Host factors
- If response or survival data are clinical unsatisfactory, prophylaxis might be an option in:
 - AML/MDS patients during neutropenia
 - Allogeneic HSCT with GVHD
 - in various ICU settings unclear data
- Focus in prophylaxis (=targeted prophylaxis)
 - High risk population
 - Keep NNT low
 - Safety/tolerability/feasibility of agent utilized
- Other alternatives?



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