Clinical Trial Design for Mould-active Agents: Time to Break the Mold

Aspergillosis in Neutropenic Patients

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Lecture Outline

- PET/CT: Show & Tell
- A Patient with Aspergillosis
- Immunity confounds assessment
- Aspergillus Galactomannan
  - For diagnosis
  - For outcome assessment

FDG-PET Scan For Diagnosing Infection

176 episodes, 153 patients

Various Sites:

- Respiratory (106): Pneumonia (99); Sinusitis (7)
- Vascular (21): Septic phlebitis (13); Implanted CVL (8)
- Discitis/ osteomyelitis/septic arthritis: (21) Cellulitis (6)
- Periodontal abscess (10)
- Gastrointestinal (9): colitis (8), abscess (3) esophagitis (1)

Different Pathogens:

Bacteria 41, fungi 15 (IA), *P. carinii: 2,* viruses 2, mycob 2

Regardless of Immune Status:

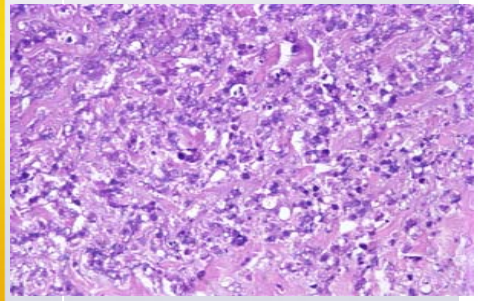
Effective in severe immunosuppression: 37, (20%)

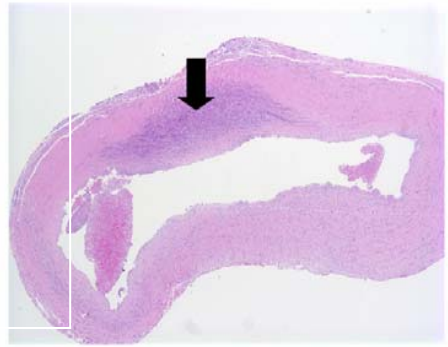
Clinically contributory in 84 patients (55%)

20 silent infections detected on PET for Ca staging

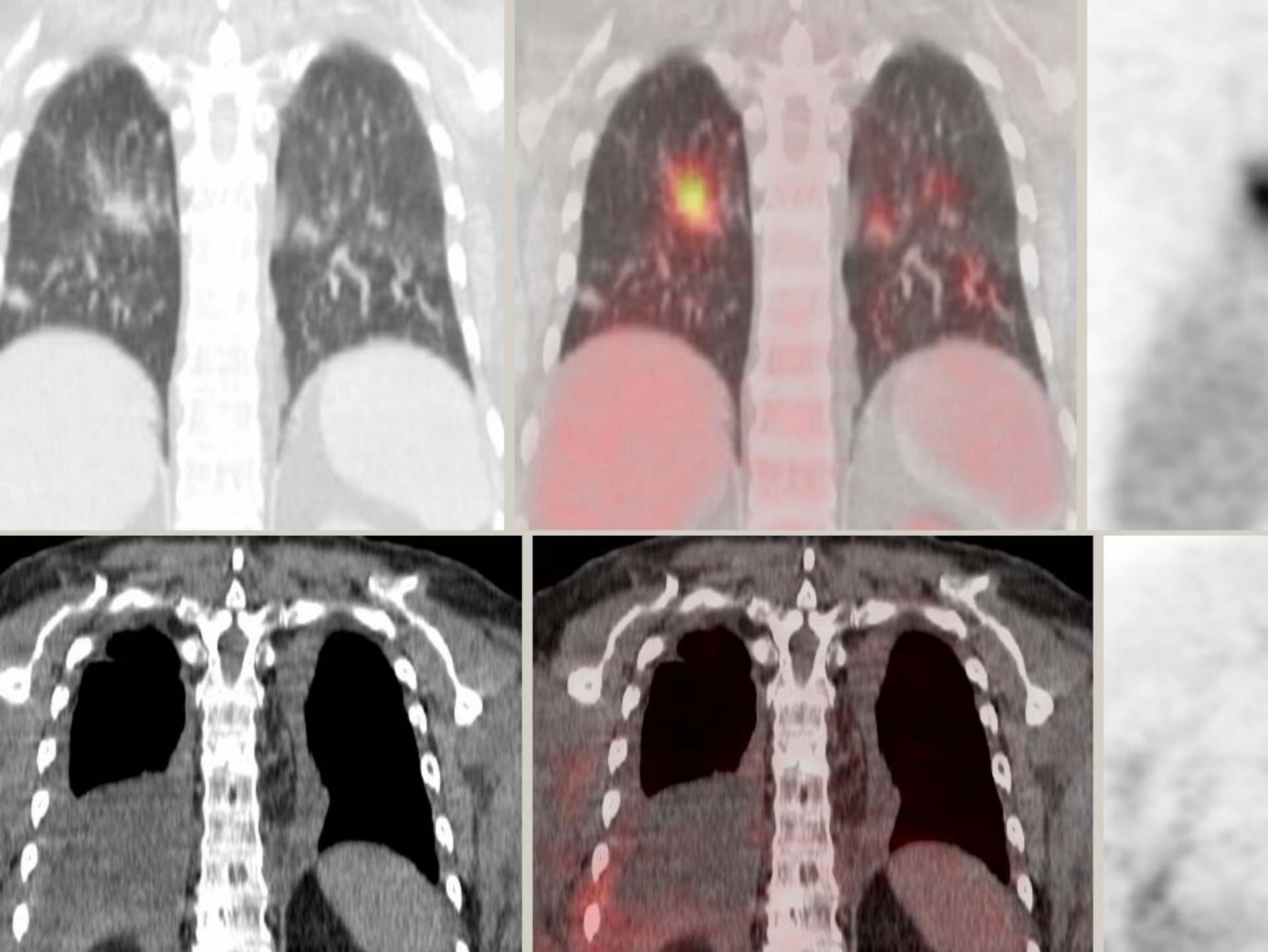
Mahfouz et al . J Clin Oncol 2004

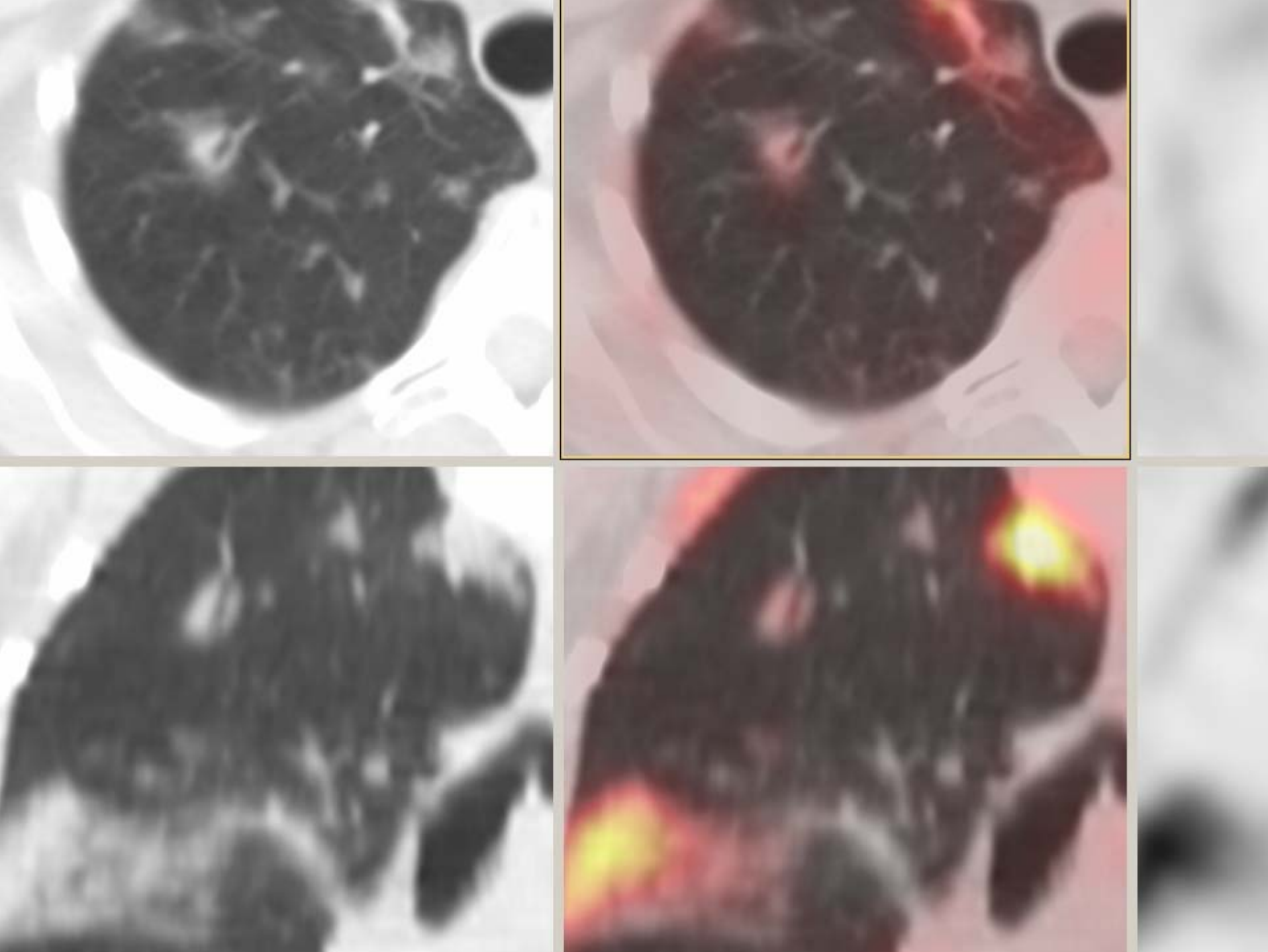
Septic Thrombophlebitis

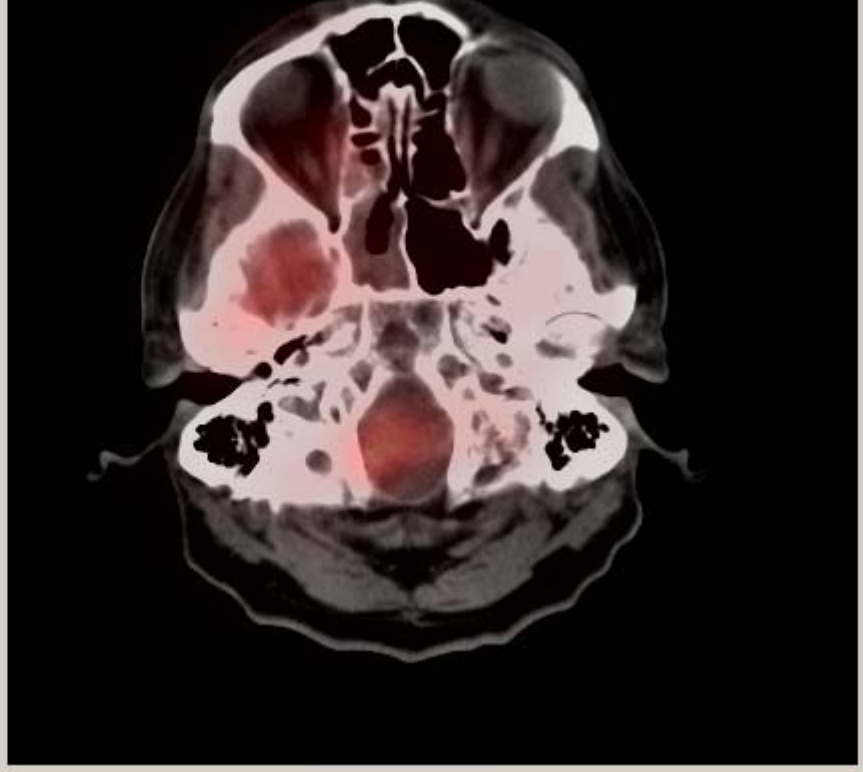


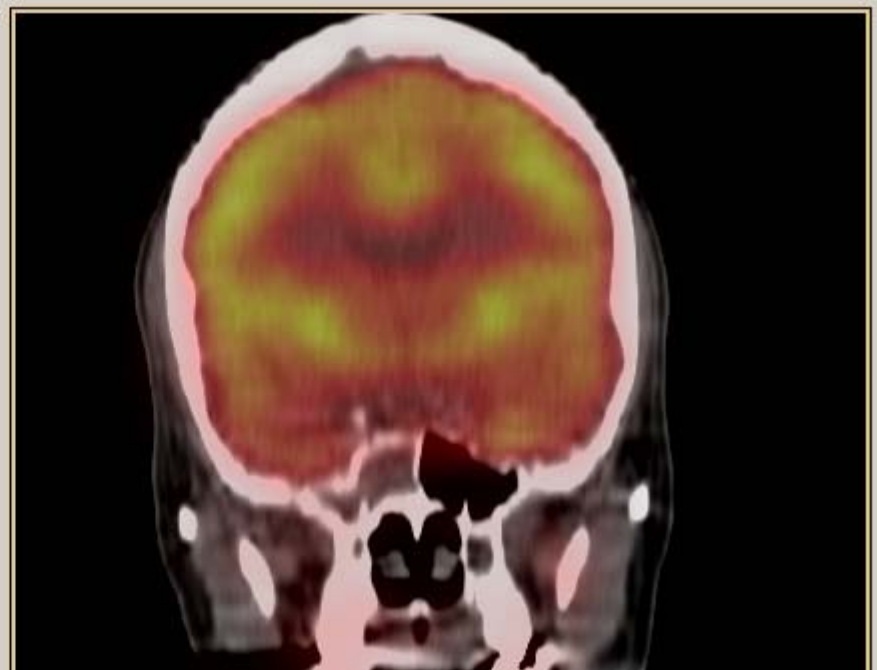


Miceli M, J Clin Oncol 22 (8) ; 1529-1531; 2004
Miceli M, Nucl Med Comm (8); 813-818, 2004
Miceli M, J Clin Oncol 22; 1949; 2004

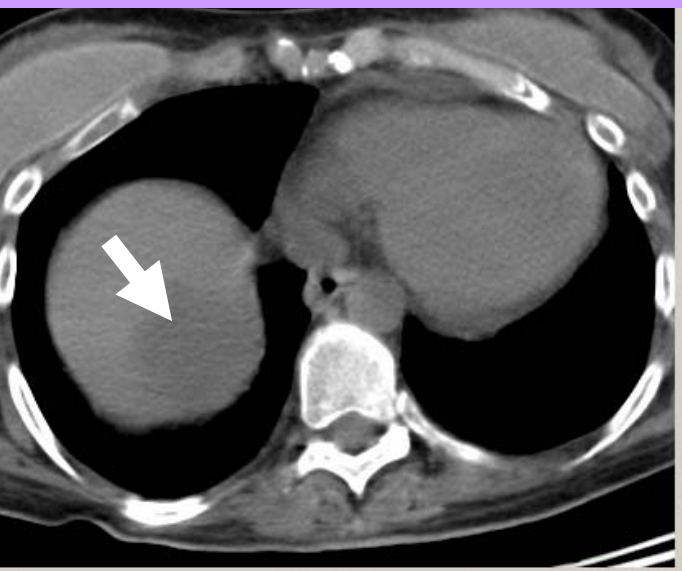


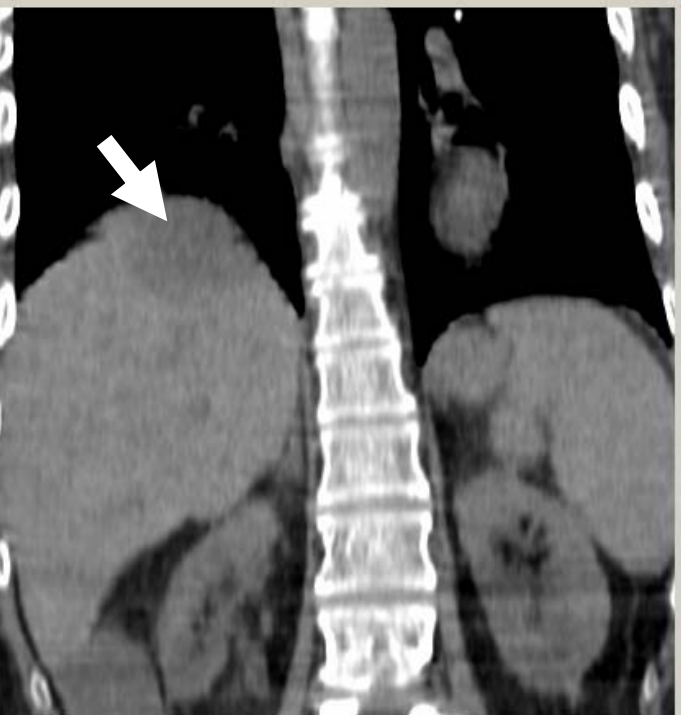


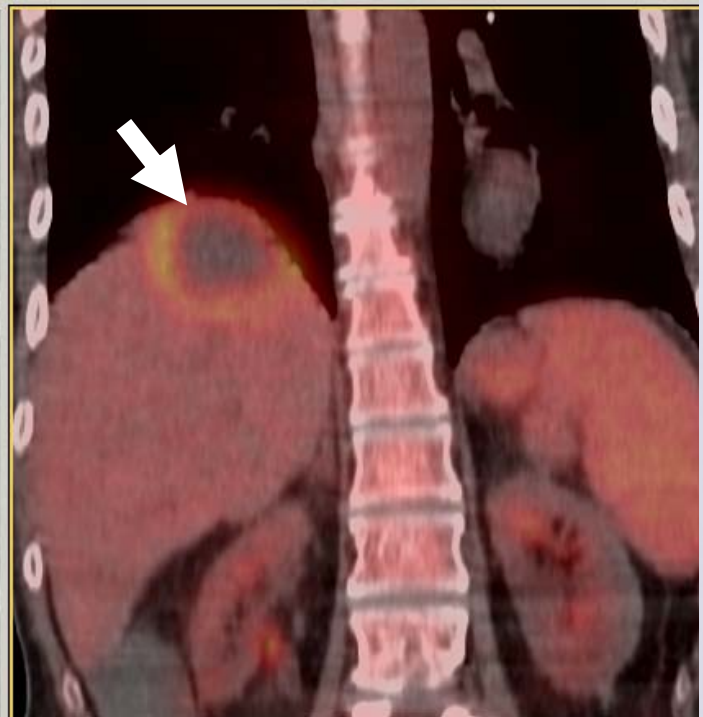





FUO. Non-neutropenic. Normal LFTs.

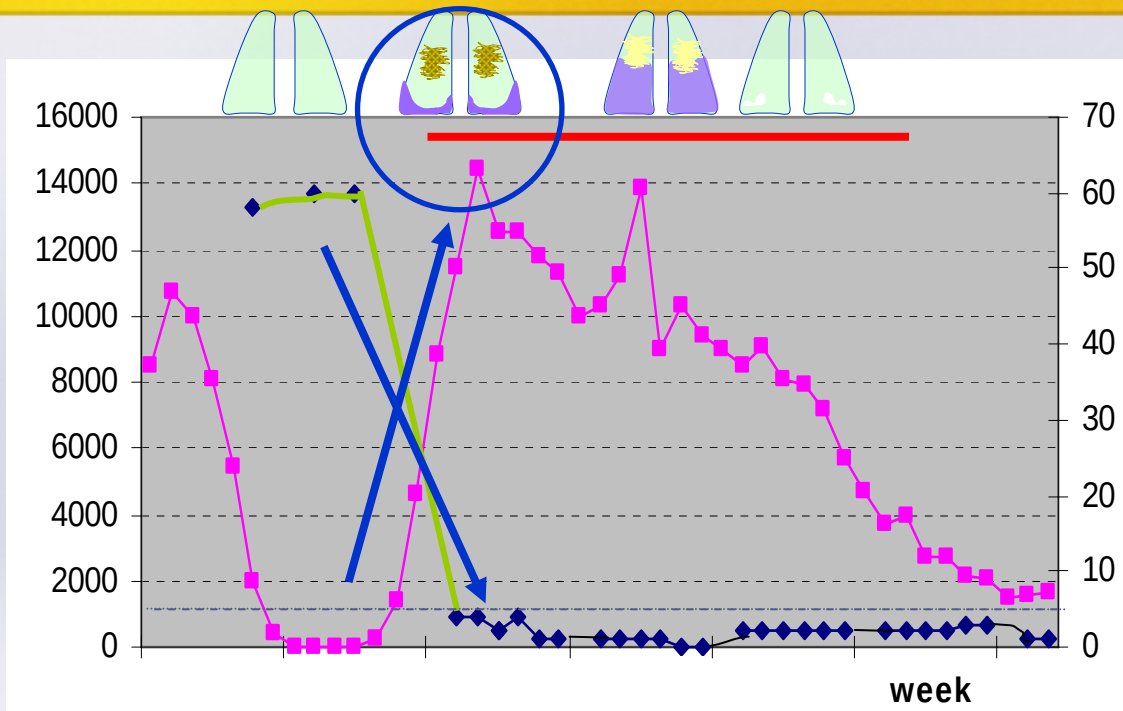






A Patient with Aspergillosis

68 y.o male, MYELOMA
8/29/05:
Auto-Tx; fluco prophylaxis
9/2: ANC <100.
Fever, CT chest (-)
9/7: (+) GMI (x3 up to 6.0)
9/9: ANC>1000
Sputum (+) *A. fumigatus*
Ambisome
9/10: GMI (-)
9/11: ↑SOB, O2↓ → ICUCT: bil infilt, nodules



Management: Methylprednisone 1 mg/kg BID (9/11-13), Ambisome

Outcome: CR; CT (-); repeatedly (-) GMI; Alive and well 28 mo. later

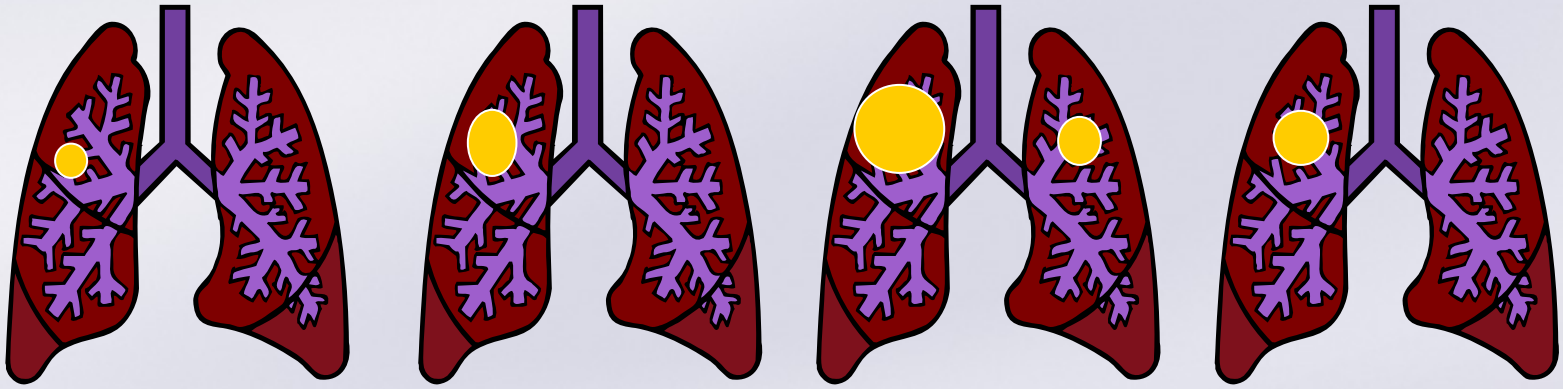
Immune Reconstitution and Inflammatory Syndrome (IRIS)

The restored ability to mount an inflammatory response against the antigens of an existing opportunistic infection

TB Abscess as part of IRIS In HIV (+) patient

It Gets Worse Before it Gets Better
IRIS in Aspergillosis

25 Neutropenic patients with tissue-proven IPA



4X↑Volume

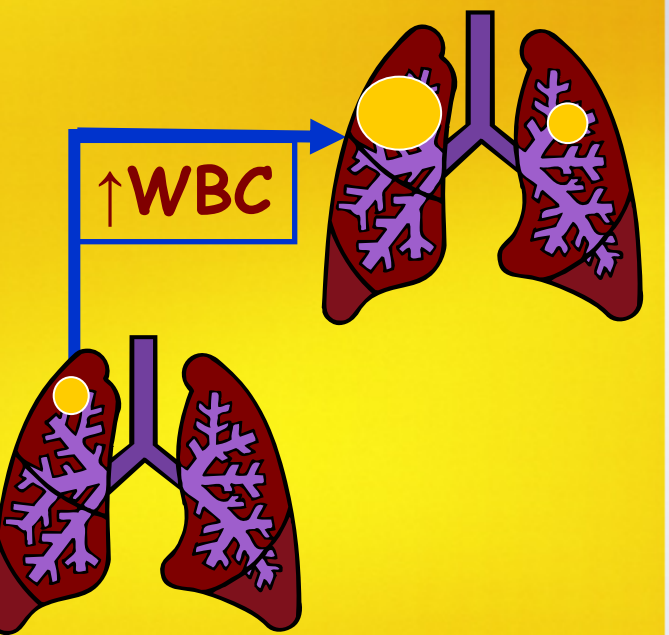
Day			14
Cm^3			34
PMN med	0	0	930	normal

Refractory

84% resolved

Caillot J Clin Oncol 2001

Immunity Confounds Outcome: P-IRIS



P-IRIS in Aspergillosis

- 19 Hem. ca. (04-06), neutropenia
- ≥ 2 consecutive (+) GM (OD ≥ 0.5)
- Aspergillosis (EORTC/MSG)

- Clinical/radiologic deterioration with
  - Neutrophil recovery and
  - Microbiologic response: normal GMI
- Complete response, survival at 3 mo
  - Same antifungal therapy
  - Addition of steroids in 2 pts.
- Implications:

Serial GM testing to guide management

Miceli et al., Cancer 2007

Assessing Aspergillosis Response: Difficult

	CR	PR	S[illegible]le Dz	Failure	Ind[illegible]*
Clinical: attributable signs & symptoms	Gor	Imp	or t	Worse s&s or	Can't tell
Radiological: attributable abnormalities				Worse radiological or	Can't tell
Mycological: eradication			ated	(+) histology or culture	Can't tell

Need Sensitive and Specific Marker for Outcome

- Unable to assess response: inadequate diagnostic evaluation, conflicting clinical, radiologic or mycologic data (P-IRIS) or presence of other factors such as other infection, GvHD, etc..

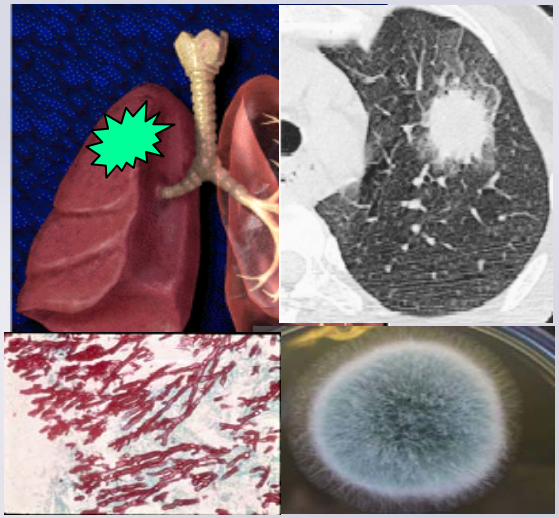
Diagnosing Aspergillosis: even more Difficult with Serious Impact on Clinical Trials

Subira rte , 2001

Galactomannan Index Improves Diagnosis (I)

GMI vs. Clinical/Radiologic Diagnosis

Clinical Diagnosis



BEFORE: 31/48 **(65%)**

-25 — -8 — -1

~1 wk before

AFTER:
12/48 **(25%)**

SIMULTANEOUS:
5 /48 **(10%)**

Cancer 2001;91:311-8.

GMI Improves Diagnosis (II)

Cut off	0.5	0.6	0.7	0.8	0.9	1.0	1.5	2 x 0.5
Sensitivity	97.4	92.1	92.1	86.8	84.2	81.6	76.3	92.1
Specificity	90.5	93.0	94.5	95.5	96.5	96.5	97.5	97.5
PPV	66.1	71.4	78.6	78.6	82	81.6	85.3	87.5
NPV	99.4	98.4	97.5	97.5	97	96.5	95.6	98.5

Serum GMI and Outcome

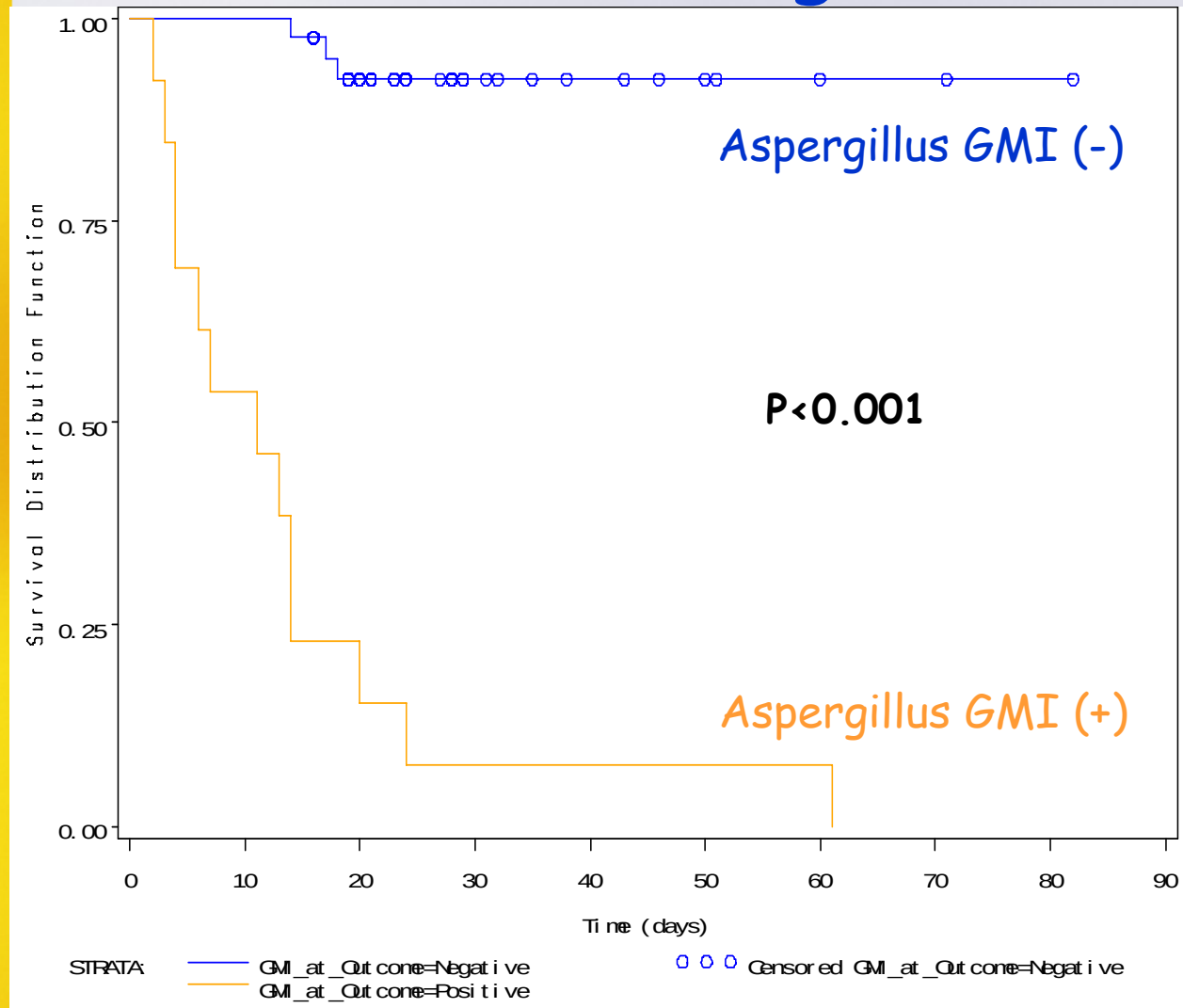
A Very Strong Correlation

Serum Aspergillus Galactomannan

- Improves Outcome Assessment of IA
- Qualifies as a Surrogate Endpoint

GMI Predicts Outcome and Survival

Survival of 56 pts with Hem. Ca and IA according to GMI



Woods, G et al. Cancer 2007

Serum GMI, a "Validated" Surrogate Endpoint Using Stringiest Criteria (I)

Biological Plausibility	
In causal chain of disease, in proximity to clinical endpoint	✓
Outcome Prediction	
Captures net effect of intervention on clinical outcome	✓
Consistently sensitive to effects of the intervention	✓
Predicts clinical outcome: changes in mechanistically compatible direction, rate, temporal sequence	✓
Experimental: Quantitative and qualitative concordance between GMI and survival, histopathology and microbiology. Effects present in different species and sizes (rat, mouse, guinea pig, rabbit, dog)	✓
Clinical trials: Strong concordance with outcome (KCC)	✓
Validated in trials for a specific disease and population	✓

Anaissie E, Clin Infect Dis May 07

Serum GMI, a "Validated" Surrogate Endpoint Using Stringiest Criteria (II)

Good Test Attributes	
Standardized, quantifiable, reproducible, non-invasive	✓
Short latency to observation of effects	✓
Generic: Tracks all therapies equally (all classes) *	✓
Representative of disease burden	✓
Dichotomous and quantitative	✓
Valid for all species/ infection sites	✓

Anaissie E, Clin Infect D is 2007

*** Paradoxical effect with echinocandins: not so paradoxical after all**

Miceli M, Anaissie E, Clin Infect. Dis 2007

Validating Surrogates

Correlation

Concordance

= concordant

= discordant

John H. Powers, MD

Lead Medical Officer

Antimicrobial Drug Development and Resistance Initiatives

www.FDA.gov

	Surrogate success	Surrogate failure
Clinical success	A	B
Clinical failure	C	D

Kappa coefficient of correlation

$0 \leq k \leq 0.4$ = marginal (or no) agreement

$0.4 \leq k < 0.75$ = good agreement

$k \geq 0.75$ = excellent agreement

Kraemer HC Stat Med 2002:21:2109-29

Validating Surrogates

Correlation

Concordance

Lit Review

<u>Serum GMI</u> vs. Aspergillosis

Literature review: 1994-2007

257 Pts: KCC 0.86

Woods G et al, Cancer 2007

Miceli M, et al Clin Inf Dis march 2008

Validating Surrogates

Correlation

Concordance

Hem. Cancer

Aspergillosis

≥ 2 cons. (+) GM

Serial Testing

Arkansas Experience

Kappa Correlation Coefficient (KCC) GMI and Survival

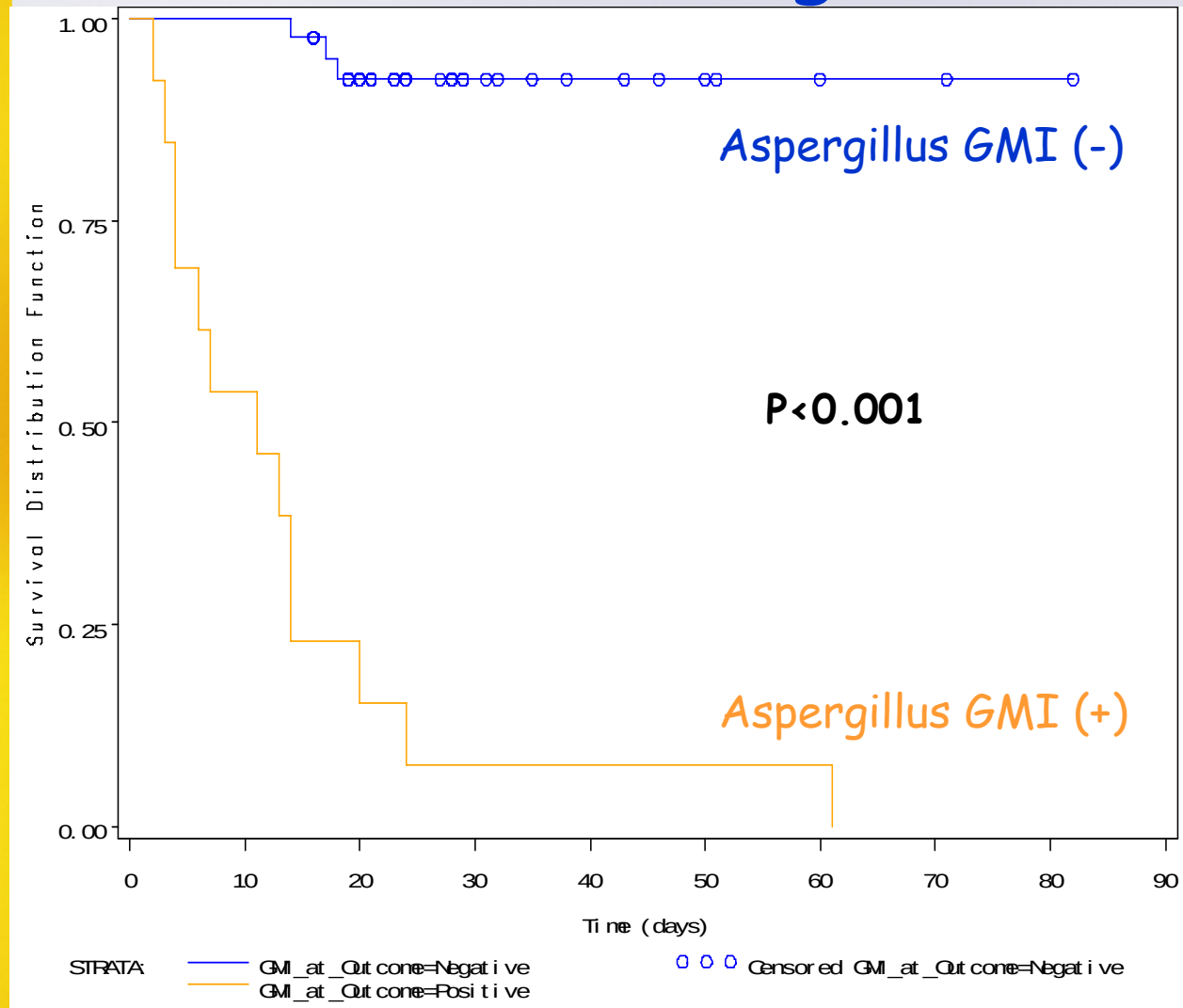
- 56 pts: Auto-Tx (21), allo (3),other (32)
- KCC GMI & Survival:

	KCC (95% CI)	*P* value
Overall	.8609 (.7093-1.000)	<.0001
Neutropenic	.8271 (.6407-1.000)	<.0001
Non-neutropenic	1.0	.0083

Woods G, et al. Cancer 2007

GMI Predicts Outcome incl. Survival

Survival of 56 pts with Hem. Ca and IA according to GMI



Woods, G et al. Cancer 2007

Validating Surrogates

Correlation

Concordance

Literature

Proven/Probable IA

Sequential testing

- (within 1 wk of outcome)

KCC between GMI and Survival Literature (27 pub):

- 257pts; Hem. Ca. auto-Tx, allo-Tx, oth.
- 3 outcomes:
  - Survival (survival/death)
  - Global (survival/death incl. autopsy)
  - Autopsy (autopsy findings only)

Outcome	KCC (95% CI)	*P* value
Survival	.8737 (.8140-.9333)	<.0001
Global	.9123 (.8617-.9629)	<.0001
Autopsy	.8498 (.5608-1.000)	<.0001

KCC for all outcomes comparable across age groups (peds and adults) and treatment modalities including allo-HSCT.

Miceli M et al., Clin Inf Dis March 2008

"Limitations" of GMI:
False (+) & (-) vs. diagnostics
-rarely available
-non-specific
-unvalidated
-transient

Exceptions:

Pip-Tazo,amox-clav

Mould prophylaxis

- Test Performance: always compare to Gold Standard

For Aspergillosis: Autopsy

False (+) :1.3%

False (-): 2.6%

Maertens J. JCM 199 Rovira M Transpl. 2004

Maertens J CID 2005 Verweij PE. Infect 1997

Maertens J. Blood 2001 Ulusakarya A Hem J 2000

Kawazu M JCM 2004 Salonen Scand.J ID 2000

Moragues MD Rev Iberoam Micol 2003

Breaking the Mold
Surrogate Endpoints & Novel Strategies

- The Diagnosis & Management of IA is Difficult
- Serum Aspergillus Galactomannan: excellent surrogate marker for diagnosis and surrogate endpoint for outcome assessment
- Implications for patient care & novel trial strategies
- **Now is the time to break the mold** of conventional clinical trials for Aspergillus-active agents

Anaissie E. Clin Infect Dis, May 07