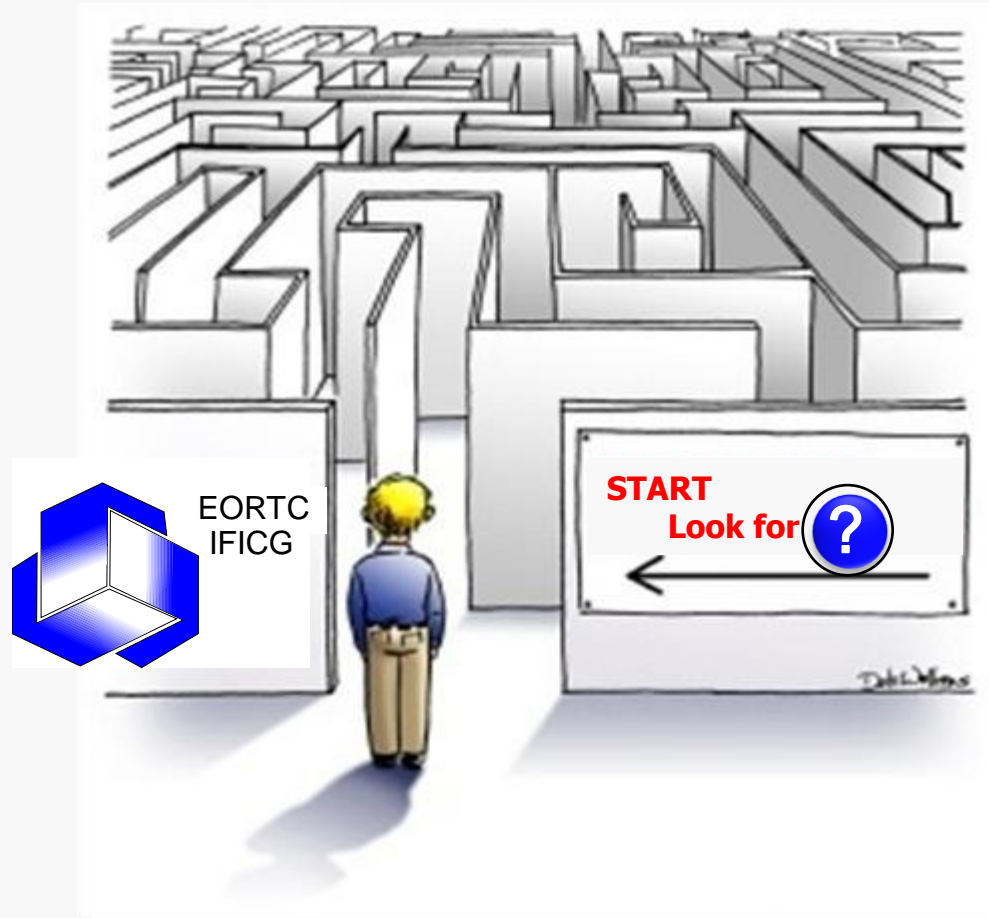
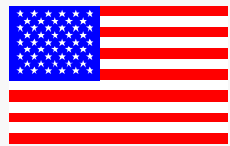


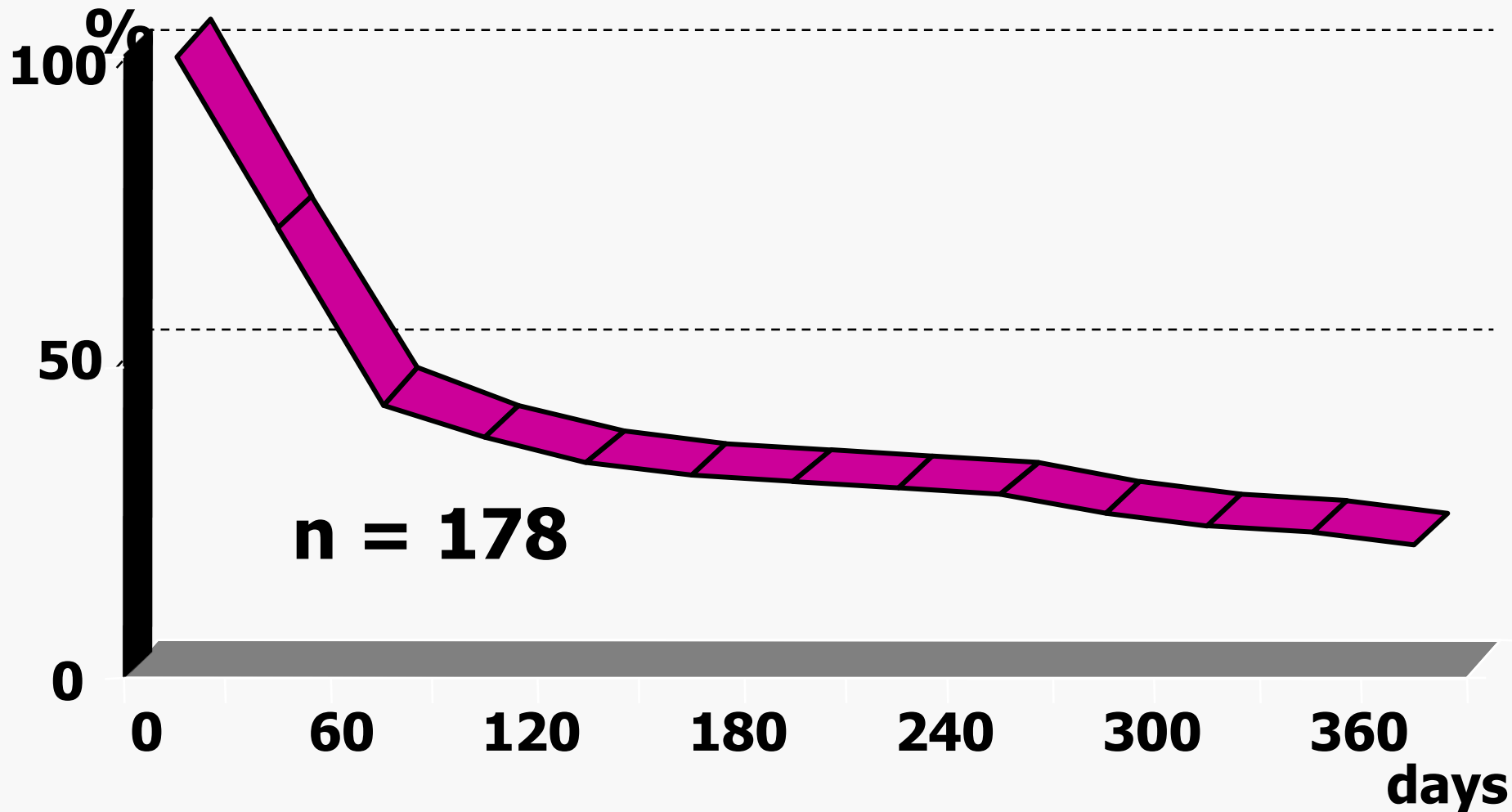
HOW TO DEFINE RESPONSE IN ANTIFUNGAL CLINICAL TRIALS?



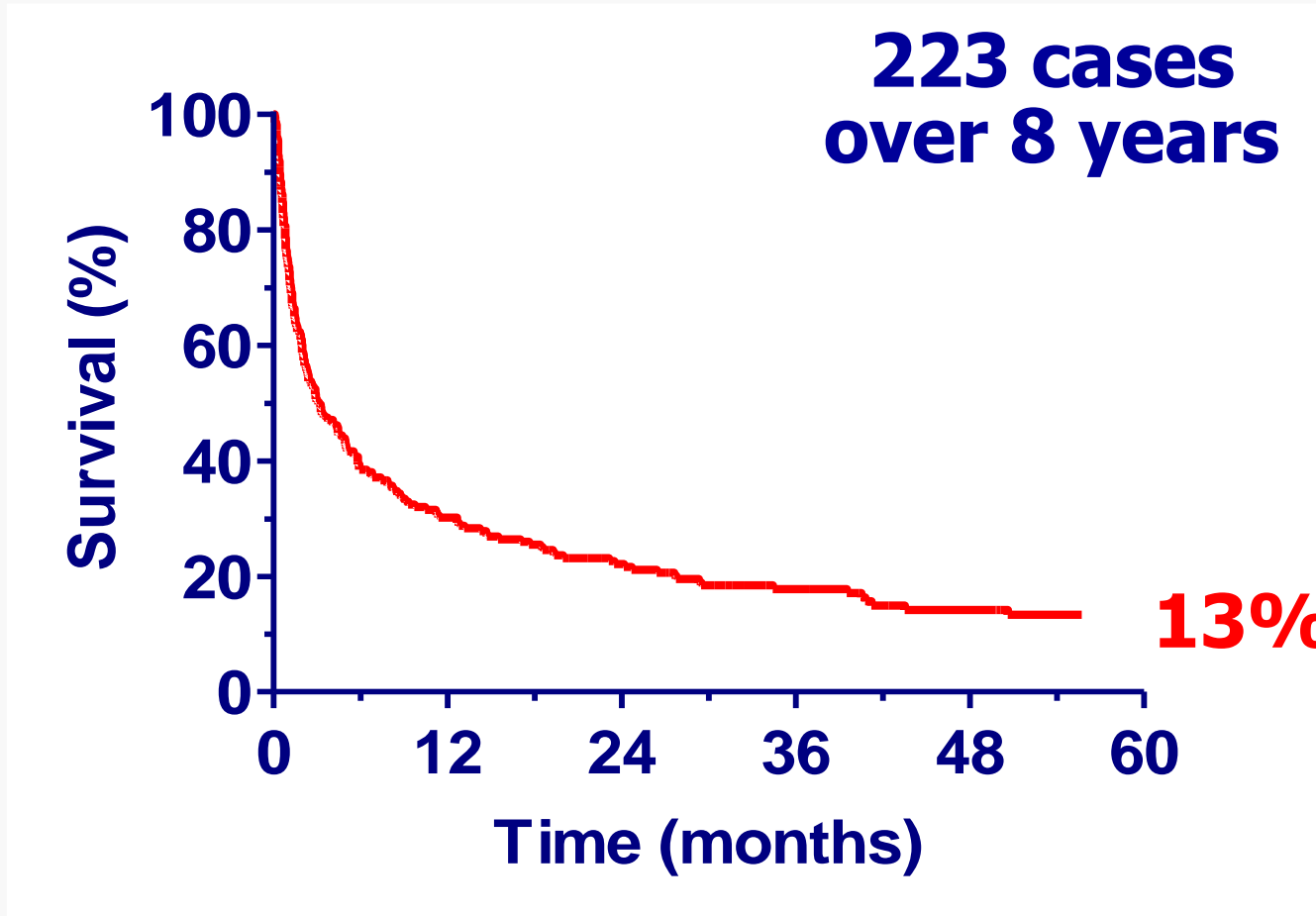


MORTALITY ASSOCIATED WITH INVASIVE ASPERGILLOSIS

Lin et al. Clin Infect Dis 2001;32:358



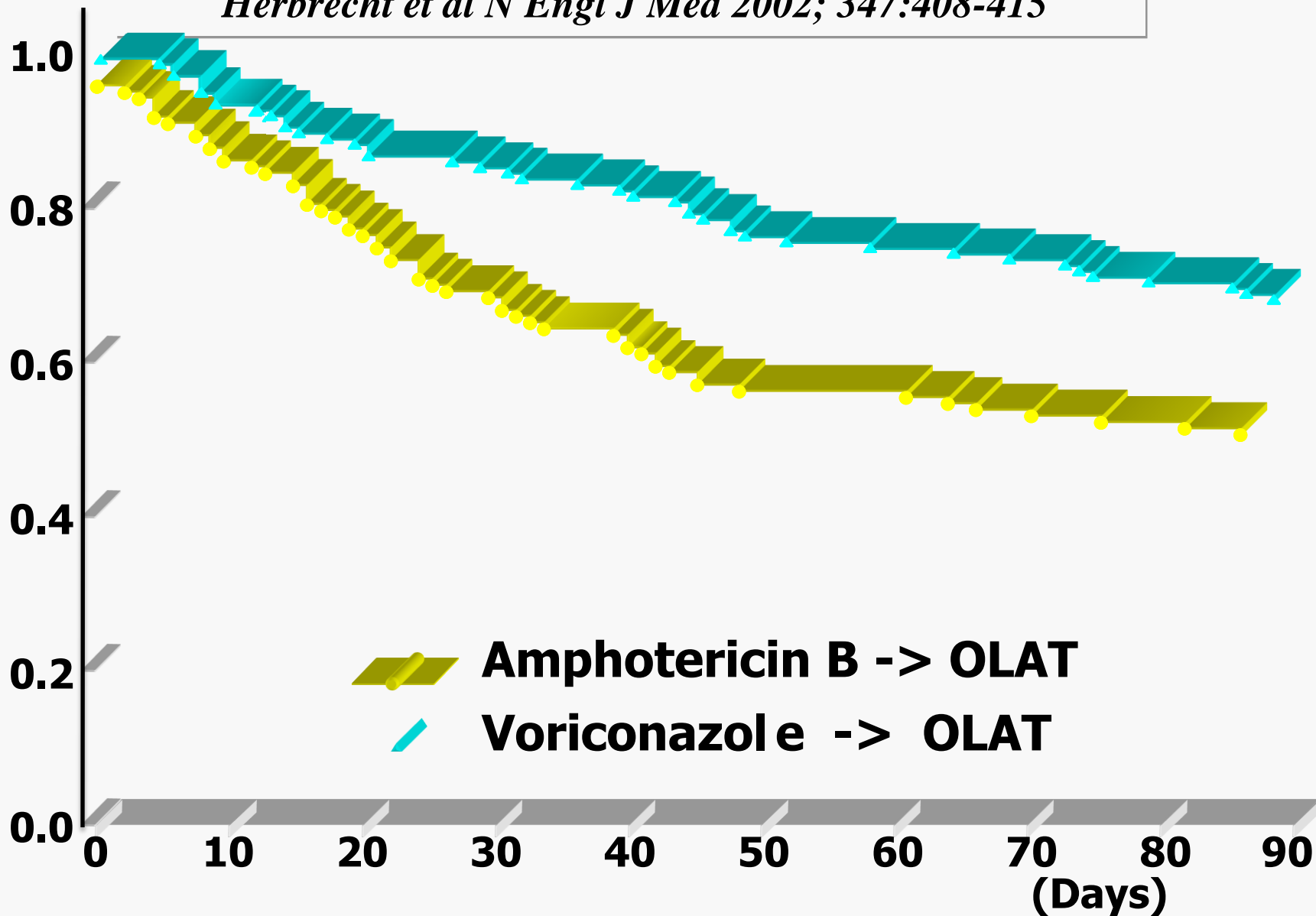
ASPERGILLOSIS: A SEVERE DISEASE IN SEVERELY ILL PATIENTS





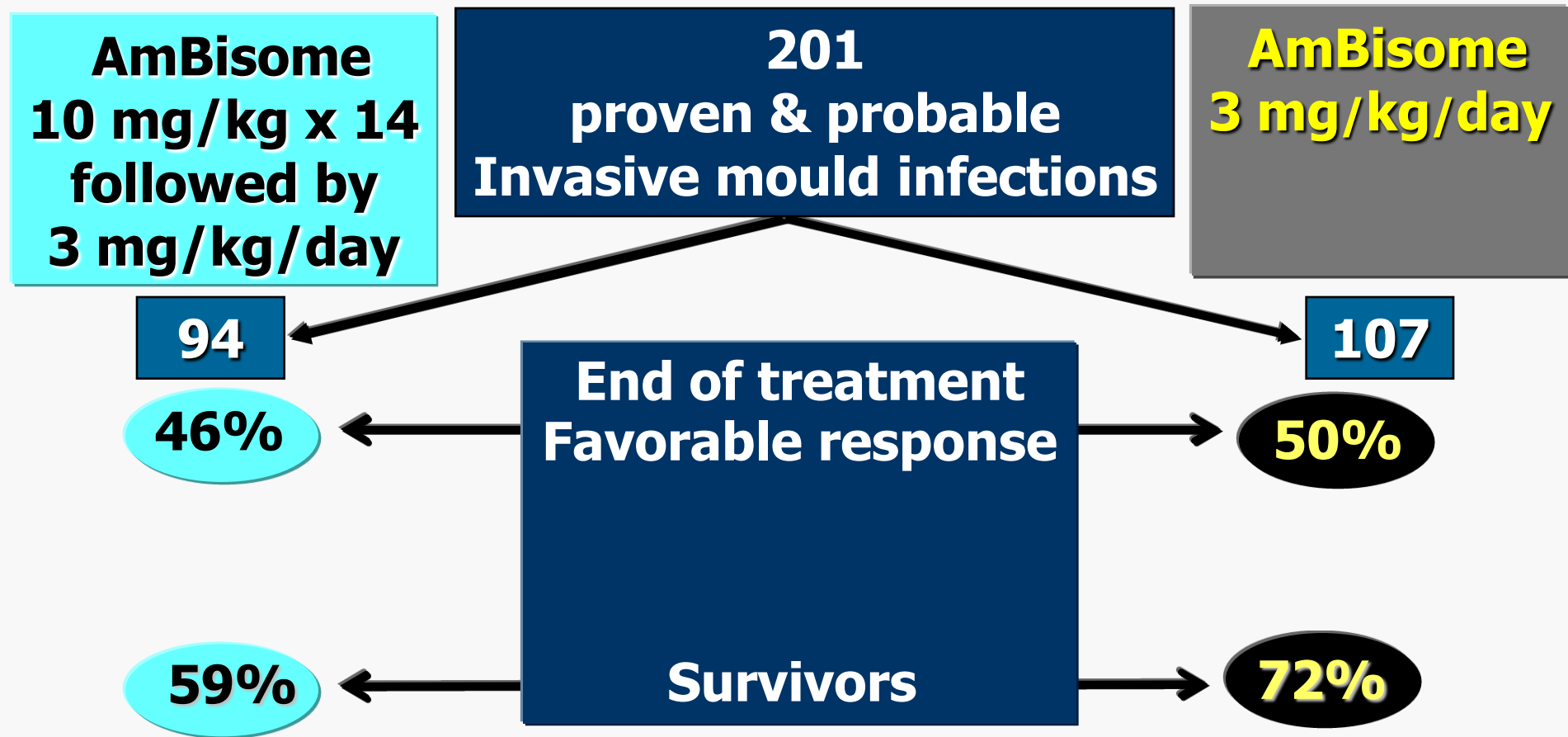
VORICONAZOLE VERSUS AMFOTERICIN B IN INVASIVE ASPERGILLOSIS: SURVIVAL

Herbrecht et al N Engl J Med 2002; 347:408-415



HIGH VERSUS STANDARD DOSE AMBISOME FOR INVASIVE MOULD INFECTIONS

Cornely et al. Clin Infect Dis 2007; 44:1289-1297



DATA??



THE CLINICAL TRIAL AS GUIDANCE FOR DAILY PRACTICE



DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Clinical trials

Statistics

DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Clinical trials

Statistics

WEAK SPOTS

DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Clinical trials

Statistics

WEAK SPOTS

TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN

DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Clinical trials

Statistics

WEAK SPOTS

CLINICIAN

STATISTICIAN

TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN

DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Statistics

CLINICIAN

STATISTICIAN

CHANGING ROLE OF THE STATISTICIAN



STATISTICIAN

CHANGING ROLE OF STATISTICIAN

**No!!! You got it wrong!
It is not 'superior' or
'inferior'
It is "Not non-inferior"**



CLINICIAN



STATISTICIAN

CONFLICT OF SCIENCE AND CLINICAL CARE



CLINICAL TRIAL AS PROOF OF THE PRINCIPLE



DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical trials

WEAK SPOTS

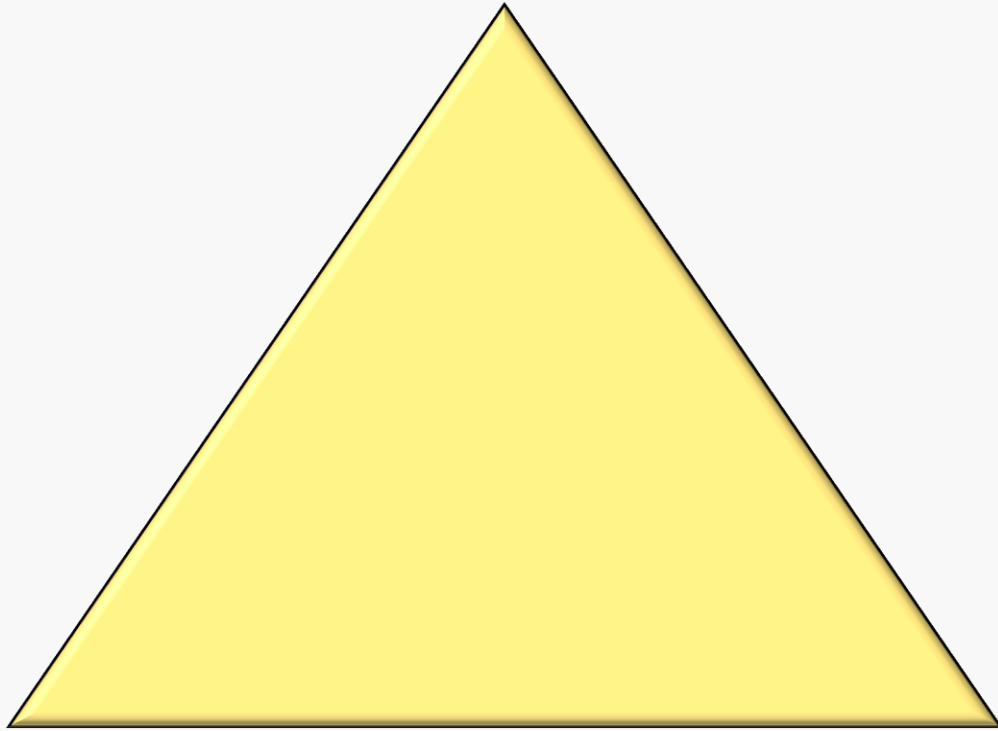
TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN

**PREREQUISITES TO INTERPRETE
CLINICAL TRIAL DATA**

TRIAL POPULATION



CRITERIA FOR OUTCOME

STUDY DESIGN

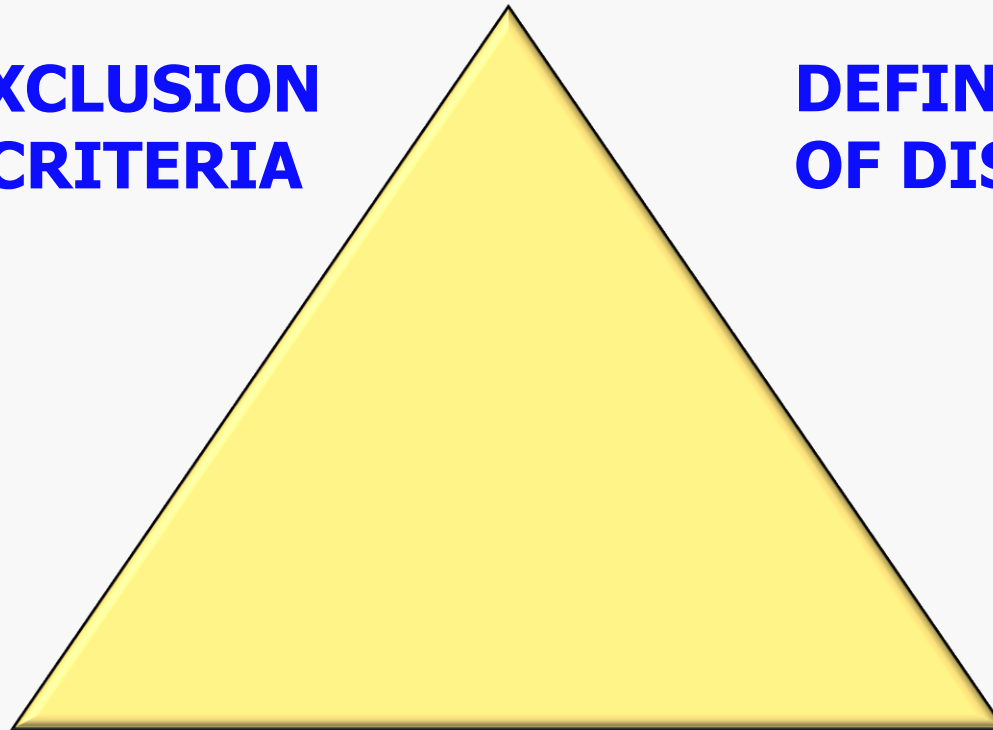


PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

**IN- /EXCLUSION
CRITERIA**

**DEFINITION
OF DISEASE**



CRITERIA FOR OUTCOME

STUDY DESIGN

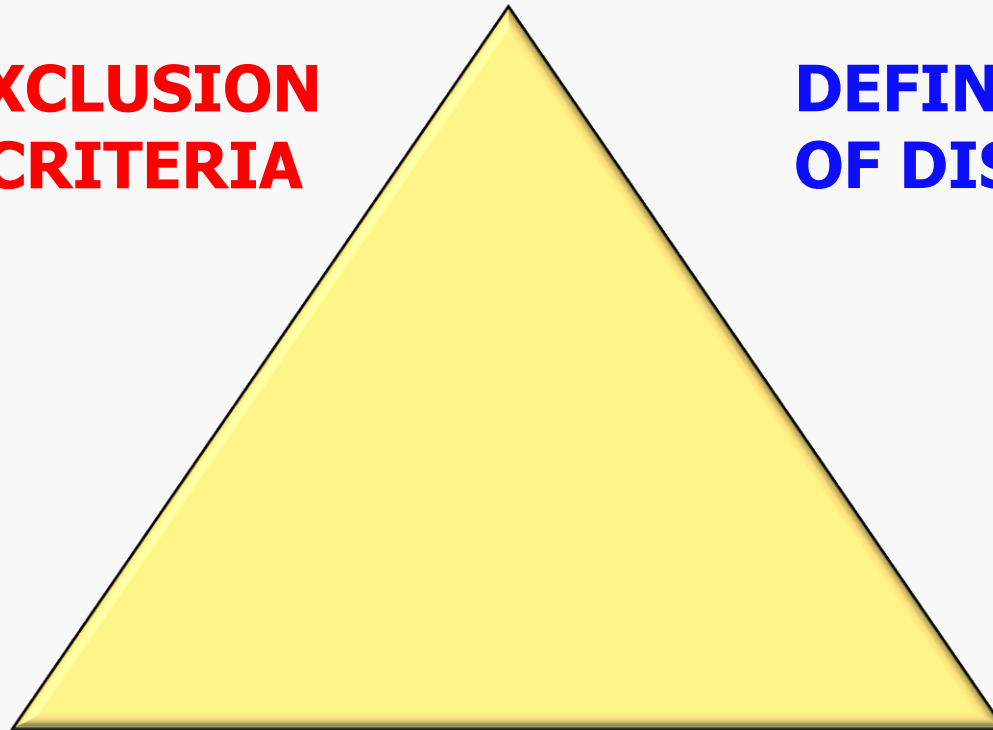


PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

**IN- /EXCLUSION
CRITERIA**

**DEFINITION
OF DISEASE**



CRITERIA FOR OUTCOME

STUDY DESIGN



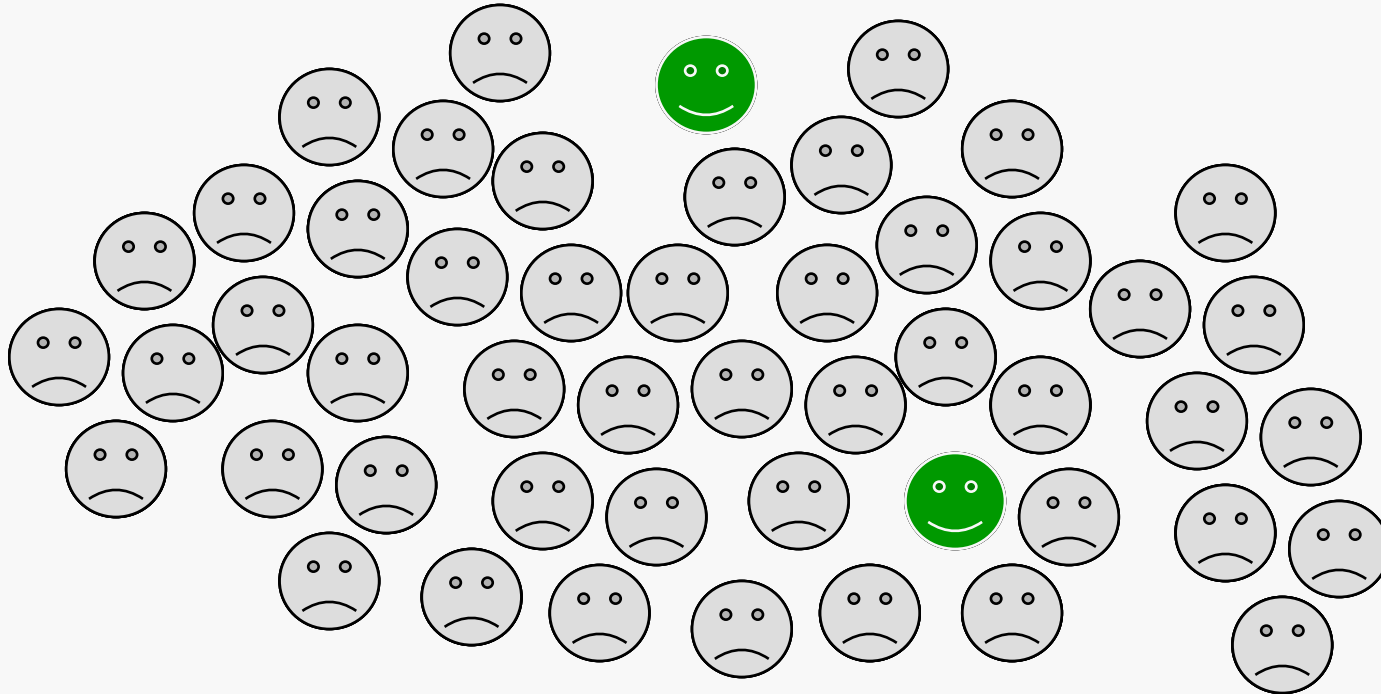
POTENTIAL IMPACT IN/EXCLUSION CRITERIA ON A TRIAL POPULATION



DIAGNOSIS OF A FUNGUS

Invasive fungus

4% in trials !!



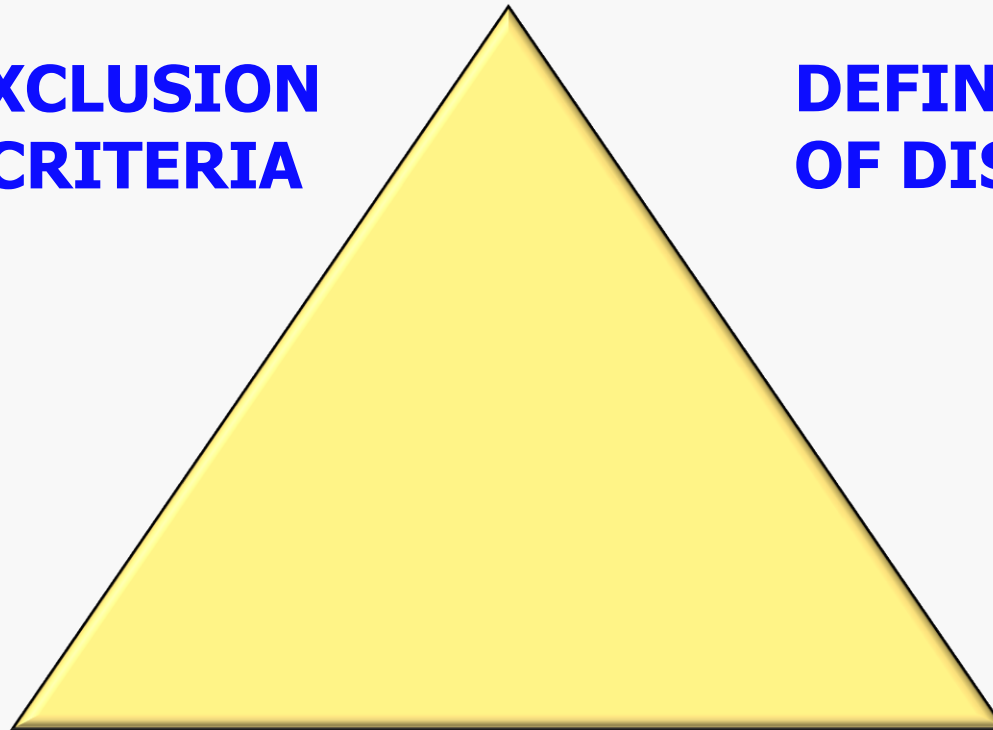
REPRESENTATIVE !?

PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

**IN- /EXCLUSION
CRITERIA**

**DEFINITION
OF DISEASE**



CRITERIA FOR OUTCOME

STUDY DESIGN

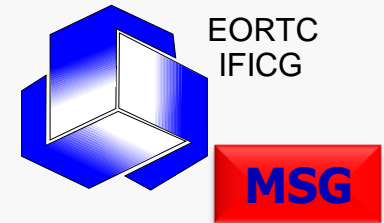


PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

**IN- /EXCLUSION
CRITERIA**

**DEFINITION
OF DISEASE**



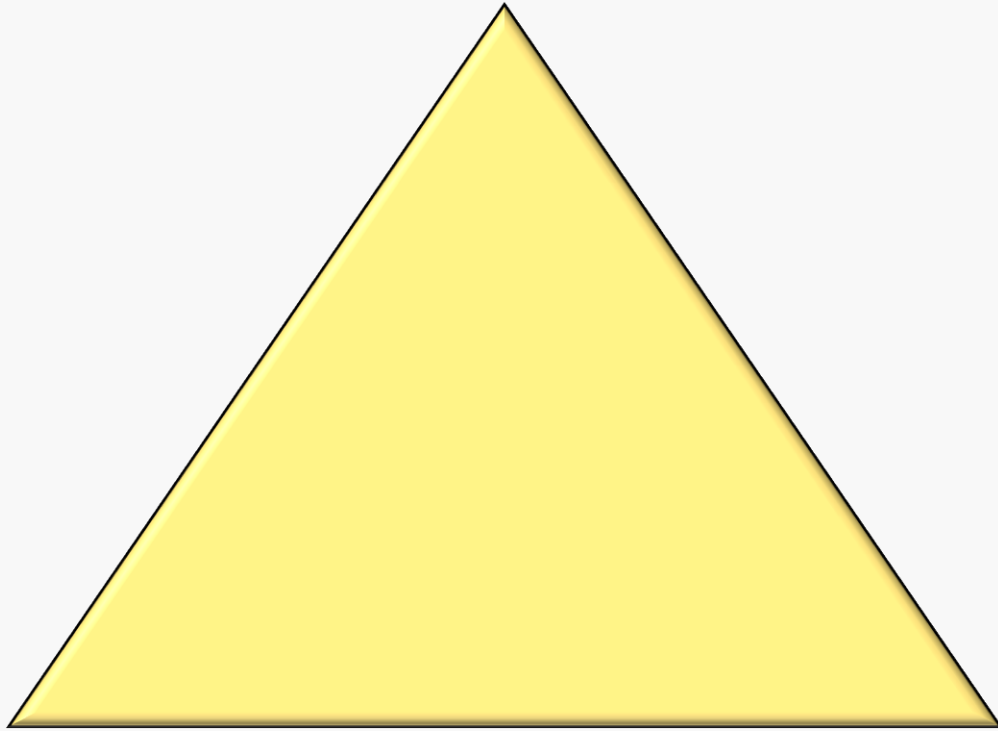
CRITERIA FOR OUTCOME

STUDY DESIGN



**PREREQUISITES TO INTERPRETE
CLINICAL TRIAL DATA**

TRIAL POPULATION



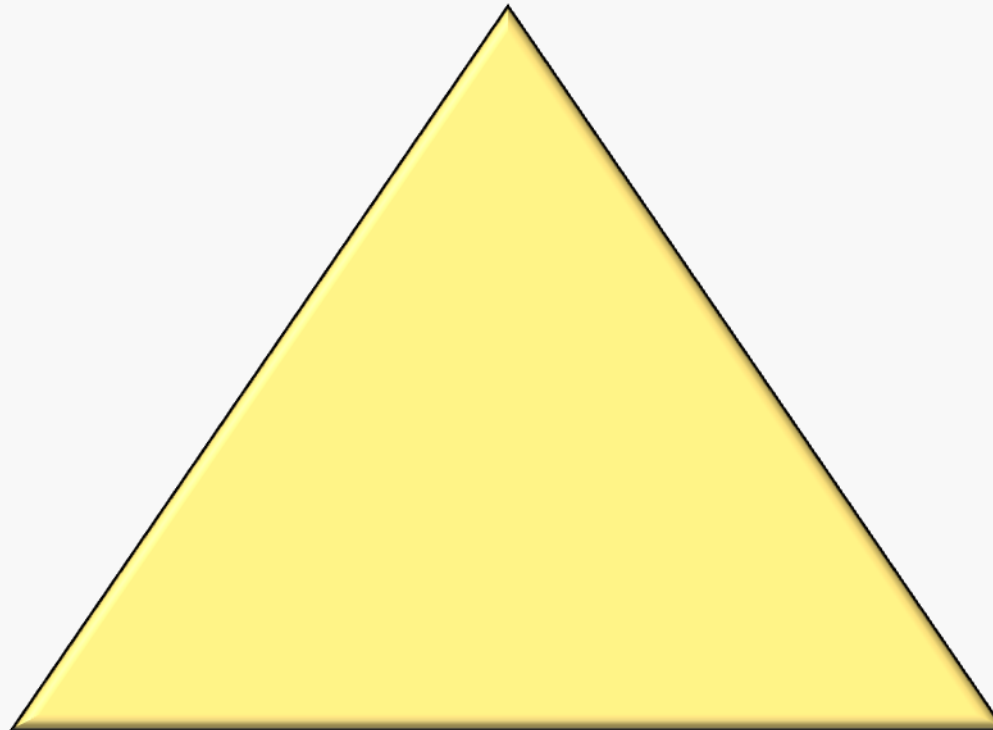
CRITERIA FOR OUTCOME

STUDY DESIGN



PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

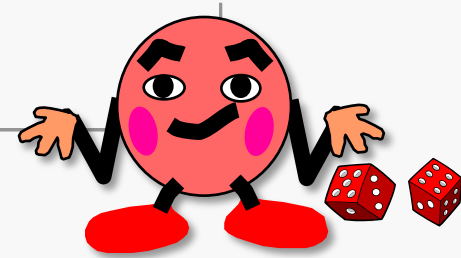


CRITERIA FOR OUTCOME

STUDY DESIGN



SUCCESS - FAILURE



PATIENT

keep alive

DOCTOR



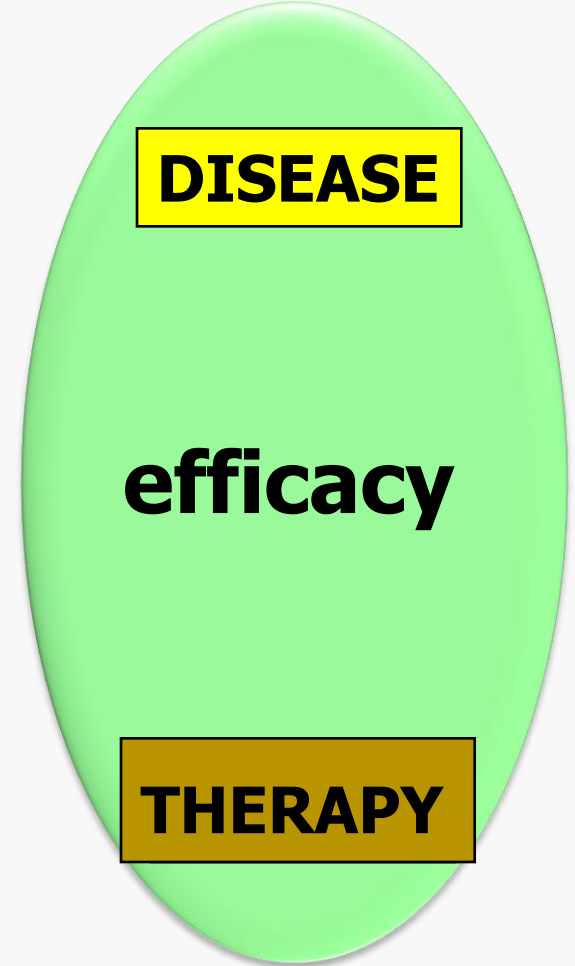
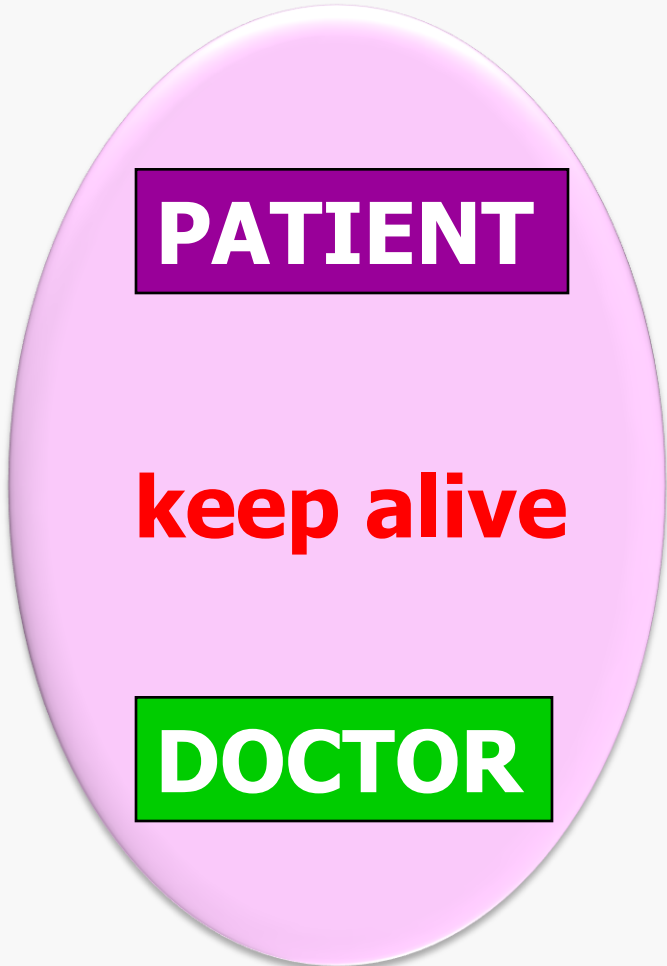
DISEASE

efficacy

THERAPY

JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL ----- *versus* ----- DRUG TRIAL



PARAMETERS FOR JUDGEMENT

STRATEGIC TRIAL ----- *versus* ----- **DRUG TRIAL**

-survival

-costs

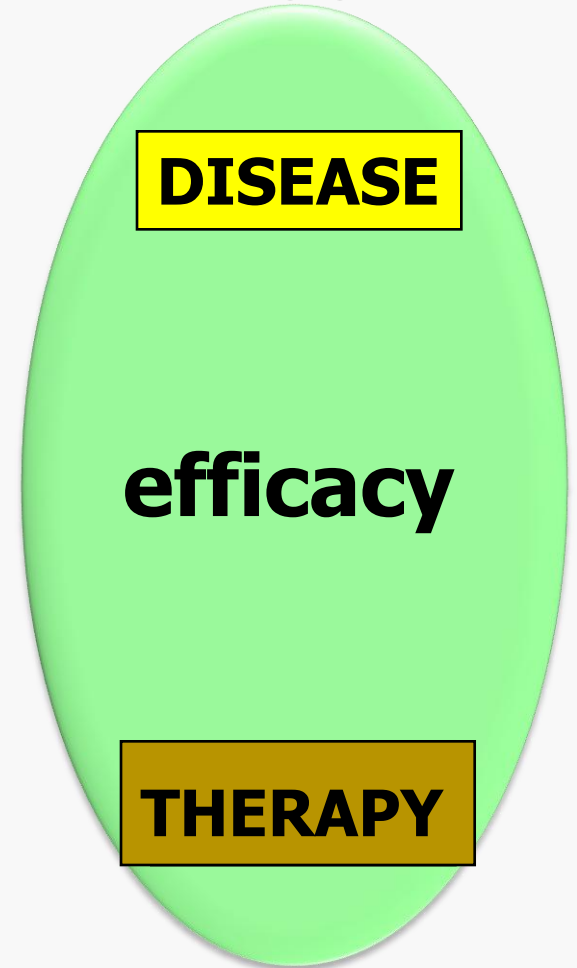
-quality of life

-regression

**-toxicity,
tolerance**

JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL ----- *versus* ----- DRUG TRIAL



RESPONSE CLINICAL TRIALS

Segal et al. Clin Infect Dis 2008;47: in press

- **SUCCESSFUL**



- ✓ **Complete response**



- ✓ **Partial response**



- **FAILURE**



- ✓ **Stable**



- ✓ **Progression**



- ✓ **Death**

- **NON-EVALUABLE**



- ✓ **Indeterminate (conflicting data)**



RESPONSE CLINICAL TRIALS

Segal et al. Clin Infect Dis 2008;47: in press

- **SUCCESSFUL**



- ✓ **Complete response**



- ✓ **Partial response**



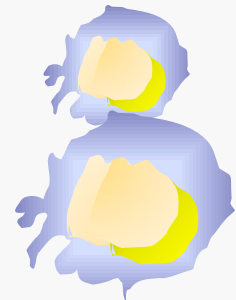
- **FAILURE**



- ✓ **Stable**

- ✓ **Progression**

- ✓ **Death**



- **NON-EVALUABLE**



- ✓ **Indeterminate
(conflicting data)**



TRIAL PARAMETERS FOR SUCCESS

- *defervescence**
- *normalization related signs & symptoms**
- *fungus-related mortality (autopsy)**
- *eradication/prevention of organism**
(few positive cultures - surrogates)
- *completion of therapy course**
- *overall survival**
(at EOT, day 10, 30, 60, 90, 120??)

JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL ----- *versus* ----- DRUG TRIAL

PATIENT

keep alive

DOCTOR

TRIAL PARAMETERS FOR SUCCESS

- *defervescence**
- *normalization related signs & symptoms**
- *fungus-related mortality**
- *eradication/prevention of organism**

- *completion of therapy course**
- *overall survival**
(at EOT, day 10, 30, 60, 90, 120??)

CLINICIAN'S APPRECIATION OF SUCCESS

***defervescence**

***normalization related signs & symptoms**

*** survival**

CLINICIAN'S APPRECIATION OF SUCCESS

*defervescence

***MORBIDITY**

*fungus-related mortality

*eradication/prevention of organism

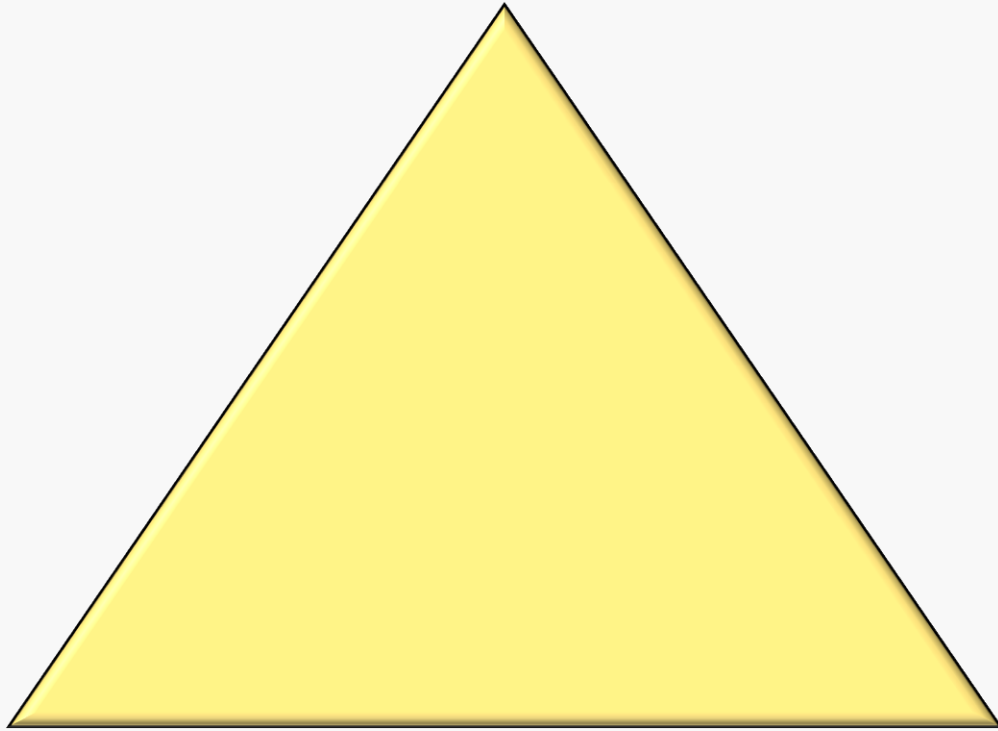
*completion of therapy course

***MORTALITY**

(at EOT, day 10, 30, 60, 90, 120??)

**PREREQUISITES TO INTERPRETE
CLINICAL TRIAL DATA**

TRIAL POPULATION



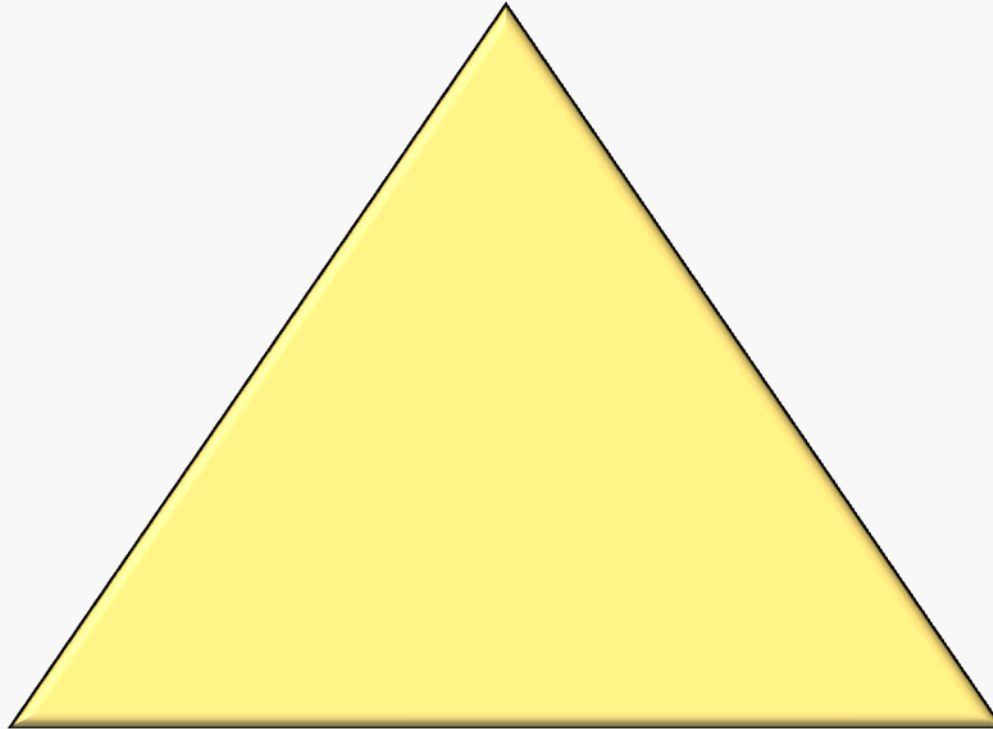
CRITERIA FOR OUTCOME

STUDY DESIGN



PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION



CRITERIA FOR OUTCOME

STUDY DESIGN



MAIN MOTIVATION FOR TRIALS

**effectiveness / safety of
a strategy**

community

ORGANISMS -- CLINICAL SYNDROMES

**effectiveness / safety of
a new drug
(vs established one)**

industry

STRATEGIC TRIAL as a DRUG-EFFICACY TRIAL



POSACONAZOLE vs AZOLES AS PROPHYLAXIS IN MYELOID MALIGNANCIES

Cornely et al. N Engl J Med 2007; 356:348-359

Randomized; AML, MDS 12 weeks

AZOLES
400 mg/day iv/po
n = 298

POSACONAZOLE
200 mg/day tid
n = 304

INVASIVE FUNGUS

8%

2%

ASPERGILLOSIS

7%

1%

FATAL FUNGUS

5%

2%

OVERALL MORTALITY

22%

16%

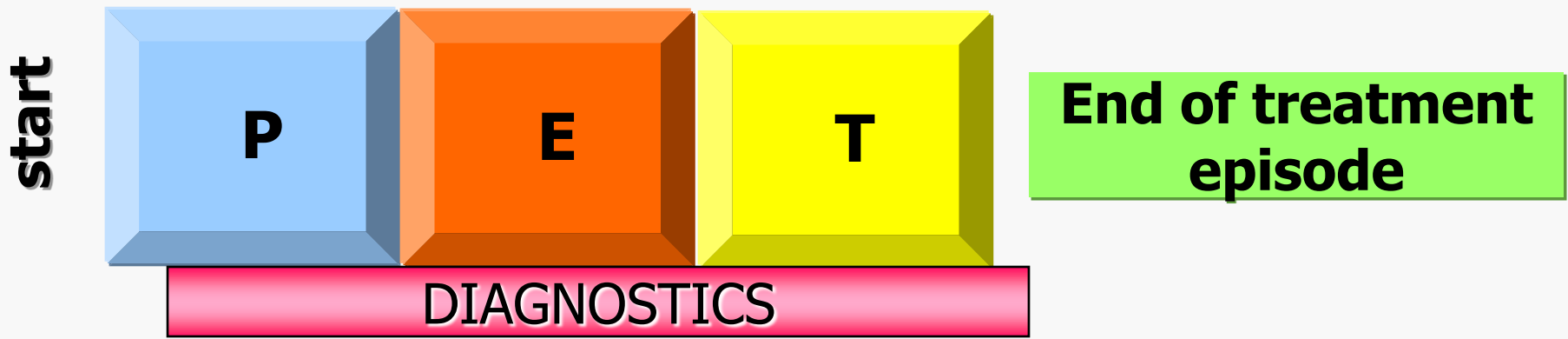
SERIOUS ADVERSE EVENTS

2%

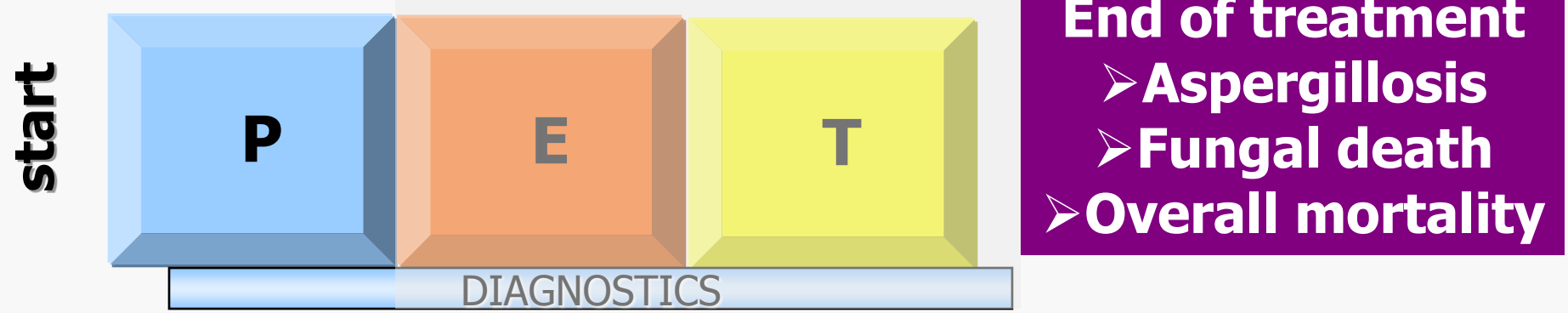
6%

PUTATIVE ANTIFUNGAL STRATEGY

PROPHYLAXIS EMPIRICAL (PRE-EMPTIVE) THERAPY



ULLMANN – CORNELY REPORTS



DEATH AS A PARAMETER OF OUTCOME

DEATH AND SURVIVAL DEPEND ON

- TREATMENT UNDERLYING DISEASE
- TREATMENT OF COMPLICATIONS

INCLUDING INFECTIONS

SURVIVAL OF **INFECTIONS** DEPENDS ON

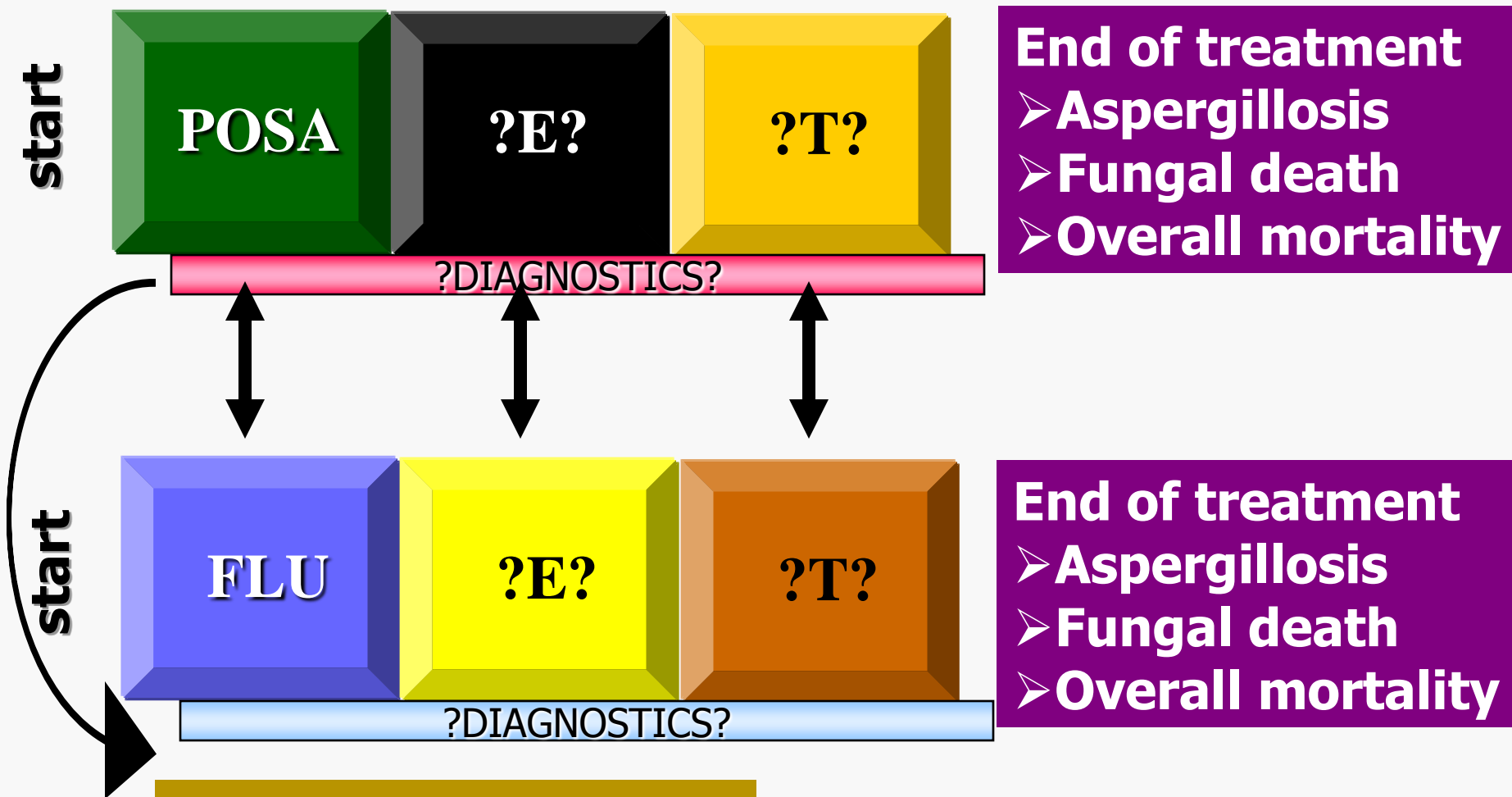
- EARLY DIAGNOSIS
- TIMELY INTERVENTION
- SELECTION OF ADEQUATE ANTI-INFECTIVES

**DEATH AND SURVIVAL ARE 'ENDPOINTS' OF
A COMPLETE STRATEGY DURING THE RISK EPISODE**

POSA CONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES (2)

Cornely et al - Ullmann et al. N Engl J Med 2007

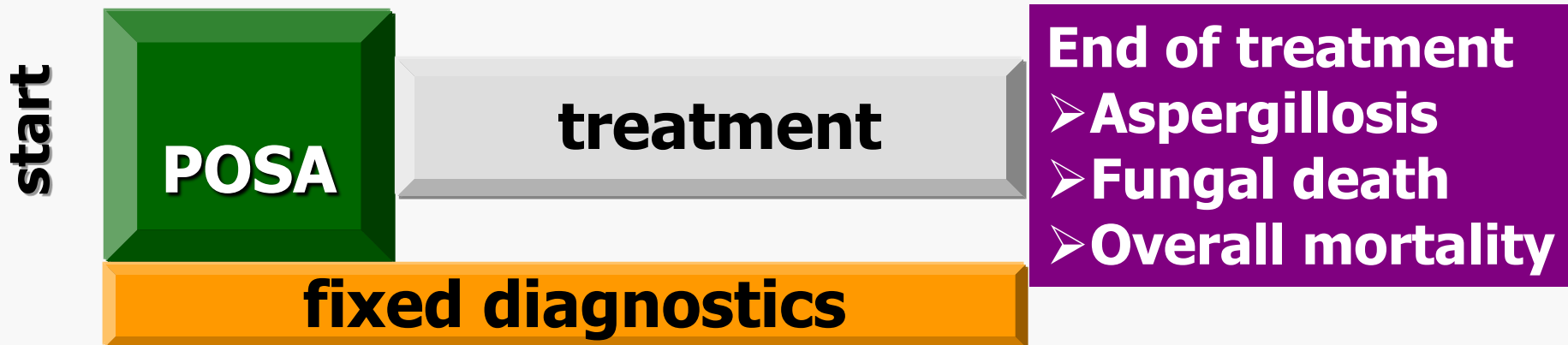
ULLMANN – CORNELY STUDIES



POSACONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES (3)

Cornely et al - Ullmann et al. N Engl J Med 2007

ULLMANN – CORNELY AS DRUG STUDIES





POSA CONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES (4)

Cornely et al - Ullmann et al. N Engl J Med 2007

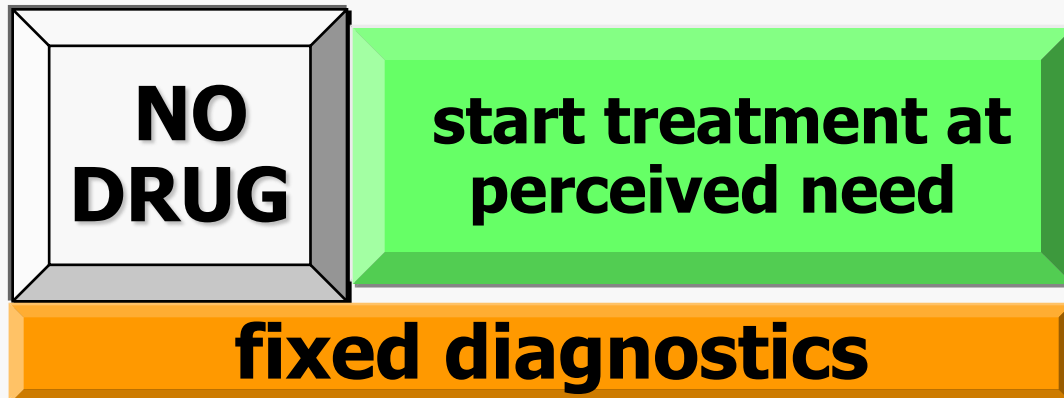
ULLMANN – CORNELY AS STRATEGIC STUDIES

start



- End of treatment
- Aspergillosis
 - Fungal death
 - Overall mortality

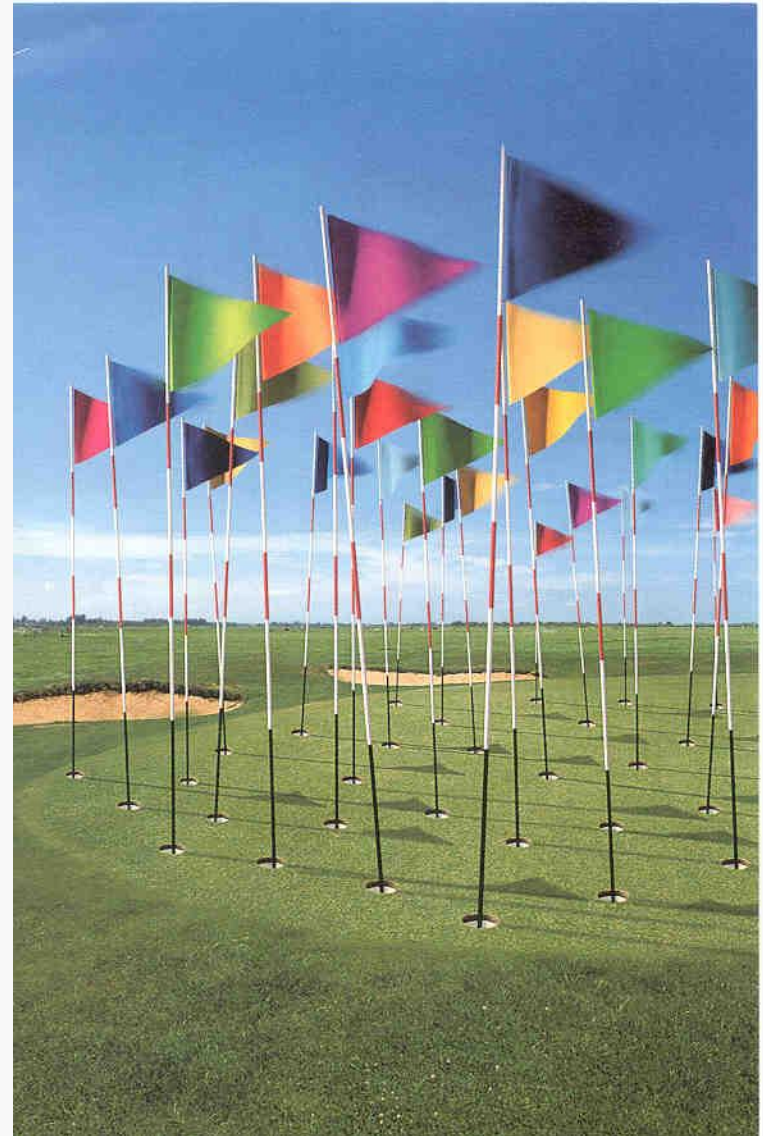
start



- End of treatment
- Aspergillosis
 - Fungal death
 - Overall mortality

STRATEGIC TRIAL as a DRUG-EFFICACY TRIAL

Use of empirical and prophylactic trials to assess drug efficacy



PROPHYLAXIS

EMPIRICAL

THERAPY

**POSA
CONAZOLE**

**CASPO
FUNGIN
-
LIPOSOMAL
AMPHO B**

**VORI-
CONAZOLE**

WHAT?

The best choice is always the most effective agent against a given pathogen

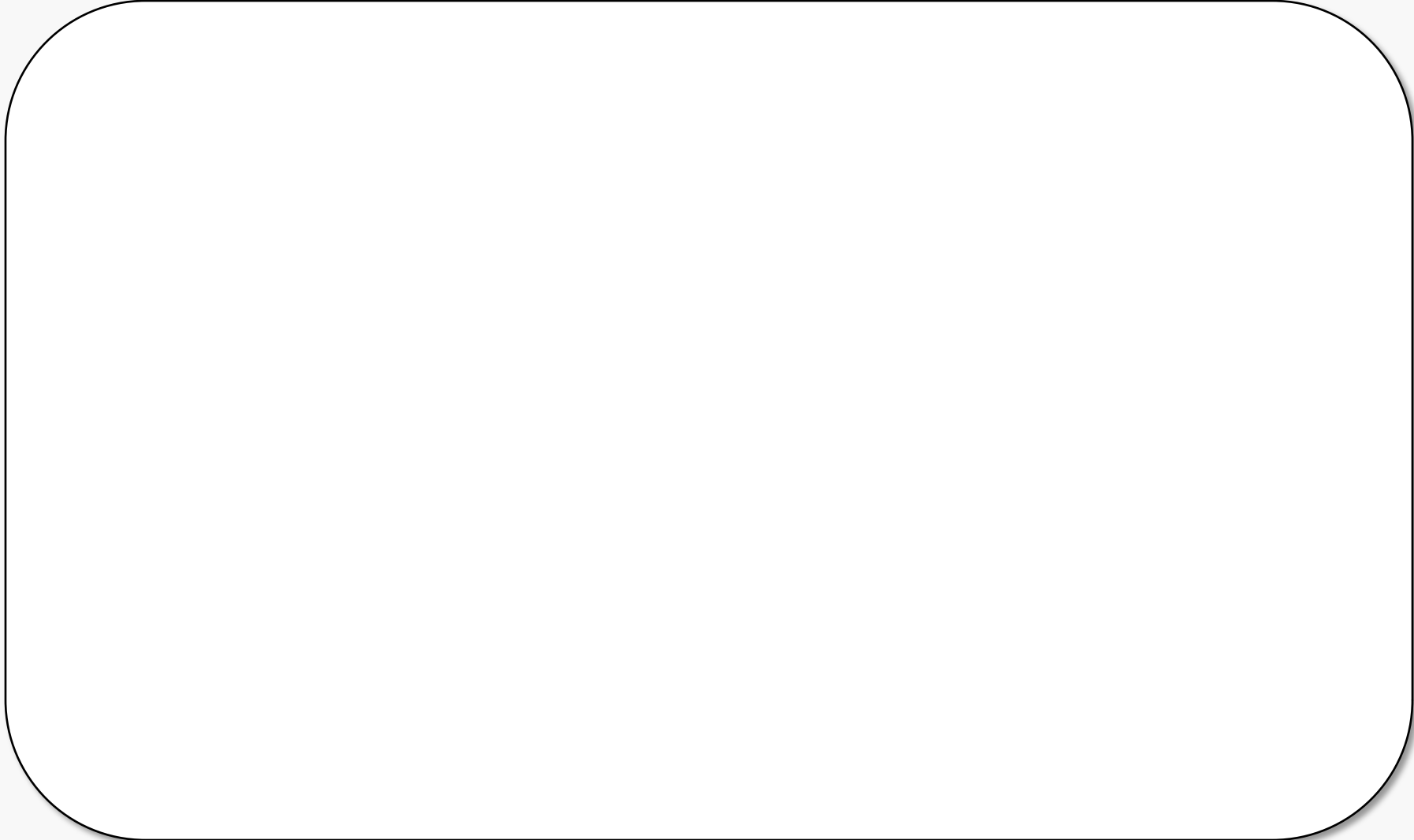
-independent of strategy

(prophylaxis, empirical, etc)

-selection may be influenced by inconveniences

(formulation, tolerance, interactions, price)

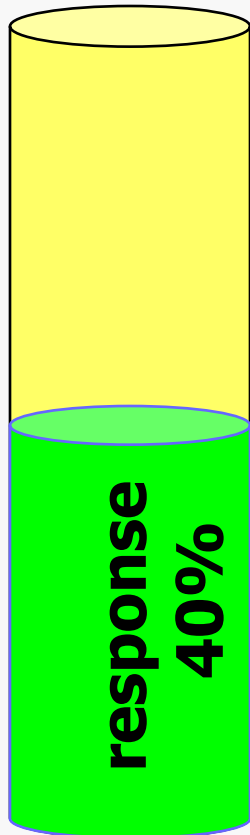
POSACONAZOLE RESULTS FIRST LINE TREATMENT ASPERGILLOSIS



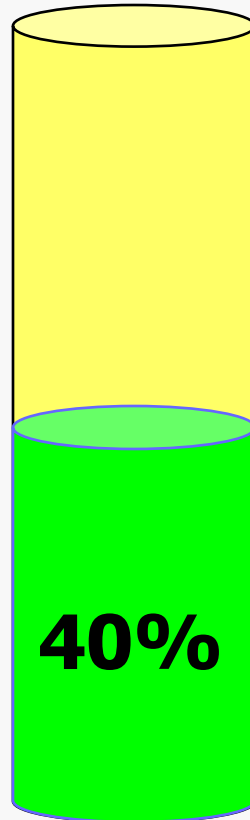
SALVAGE FOR INVASIVE ASPERGILLOSIS

Refractory / intolerant amphotericin B

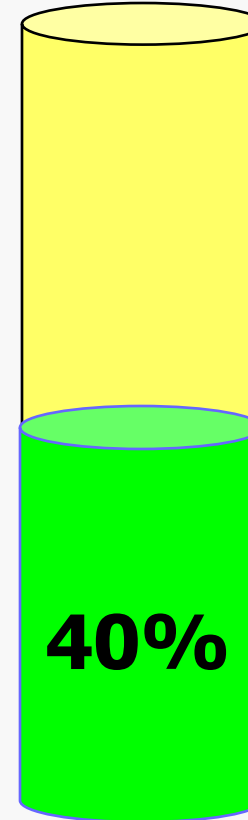
posaconazole
n=107



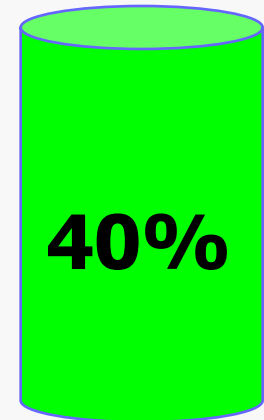
ampho B
lipid complex




caspofungin
n=146



'totocidafun'
n=xxx



KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- **entry criteria**
 - **course of underlying disease**
 - **concurrent medication**
 - **carry-over effect previous antifungals**
- 

KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- **entry criteria**
- **course of underlying disease**
- **concurrent medication**
- **carry-over effect previous antifungals**

WEAK SPOTS OF SALVAGE TRIALS IN INVASIVE FUNGAL DISEASE

“REFRACTORY TO OR INTOLERANT OF...”

MIXED POPULATION WITH:

- **Subjective entry criteria**
- **Less sick patients with oral compounds**
- **Carry-over effect of previous antifungals**

CASES FOR RESCUE?

**INTOLERANT:
OBJECTIVELY VERIFIABLE ORGAN TOXICITY**

SUBJECTIVE INTOLERABILITY

**REFRACTORY :
NO RESPONSE, STABLE
PROGRESSION**



FAILURES?

creatinine
increase

renal
failure

toxicity

potassium
levels

**INTOLERANT:
OBJECTIVELY VERIFIABLE ORGANICITY**

SUBJECTIVE INTOLERABILITY

a single
shiver

hyperpyrexia

intolerance

**REFRACTORY :
NO RESPONSE, STABLE
PROGRESSION**



CASES FOR RESCUE?

**INTOLERANT:
OBJECTIVELY VERIFIABLE ORGAN TOXICITY**

SUBJECTIVE INTOLERABILITY

**REFRACTORY :
NO RESPONSE, STABLE
PROGRESSION**



CASES FOR RESCUE?

**INTOLERANT:
OBJECTIVELY VERIFIABLE ORGAN TOXICITY**

SUBJECTIVE INTOLERABILITY

**3 days
stable**

**life-threatening
progression**

**REFRACTORY :
NO RESPONSE, STABLE
PROGRESSION**

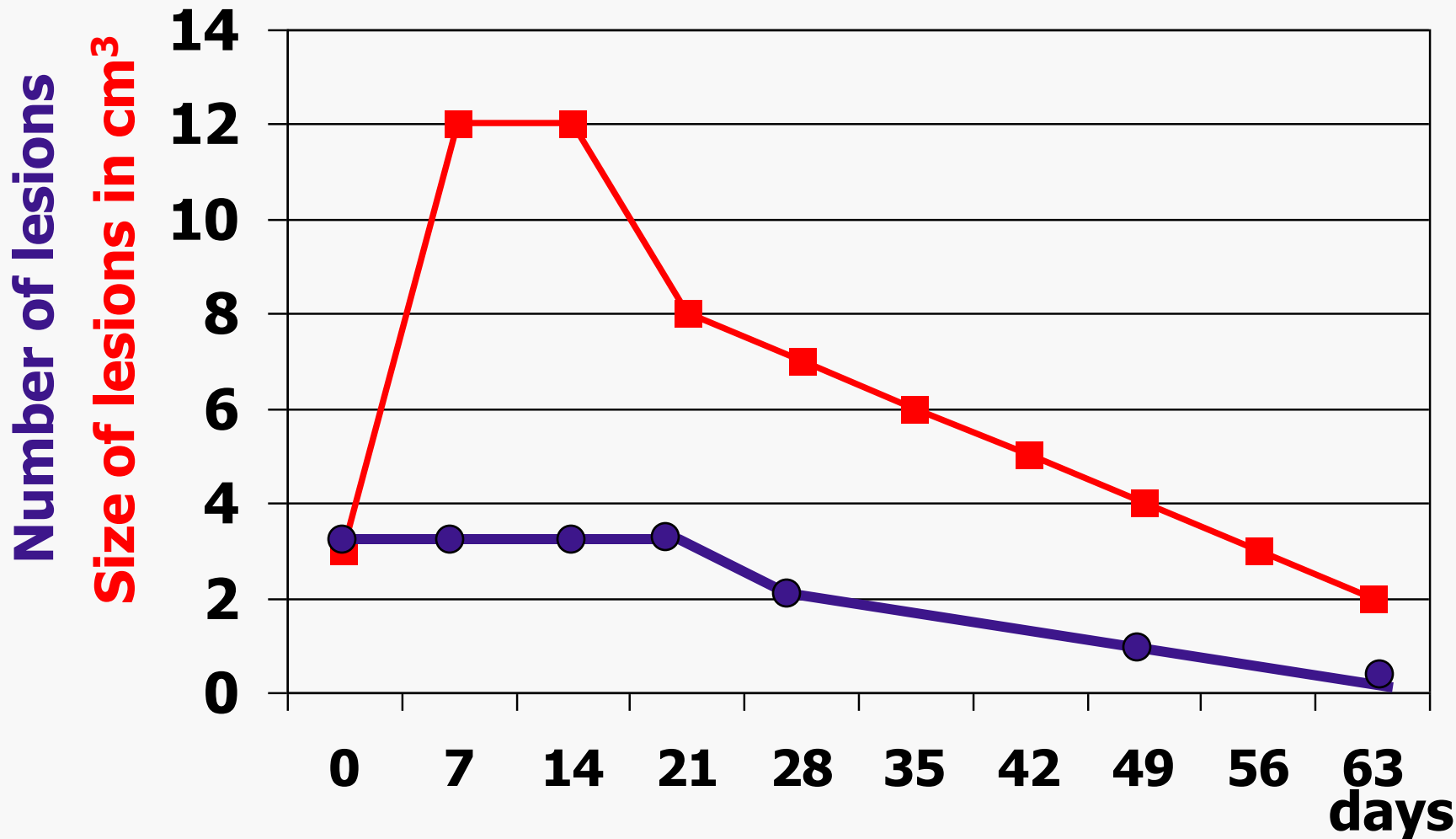
**treatment
refractory**

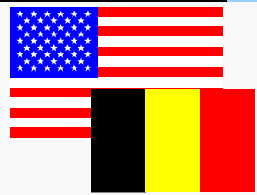




EVOLUTION OF CT-LESIONS DUE TO PULMONARY ASPERGILLOSIS

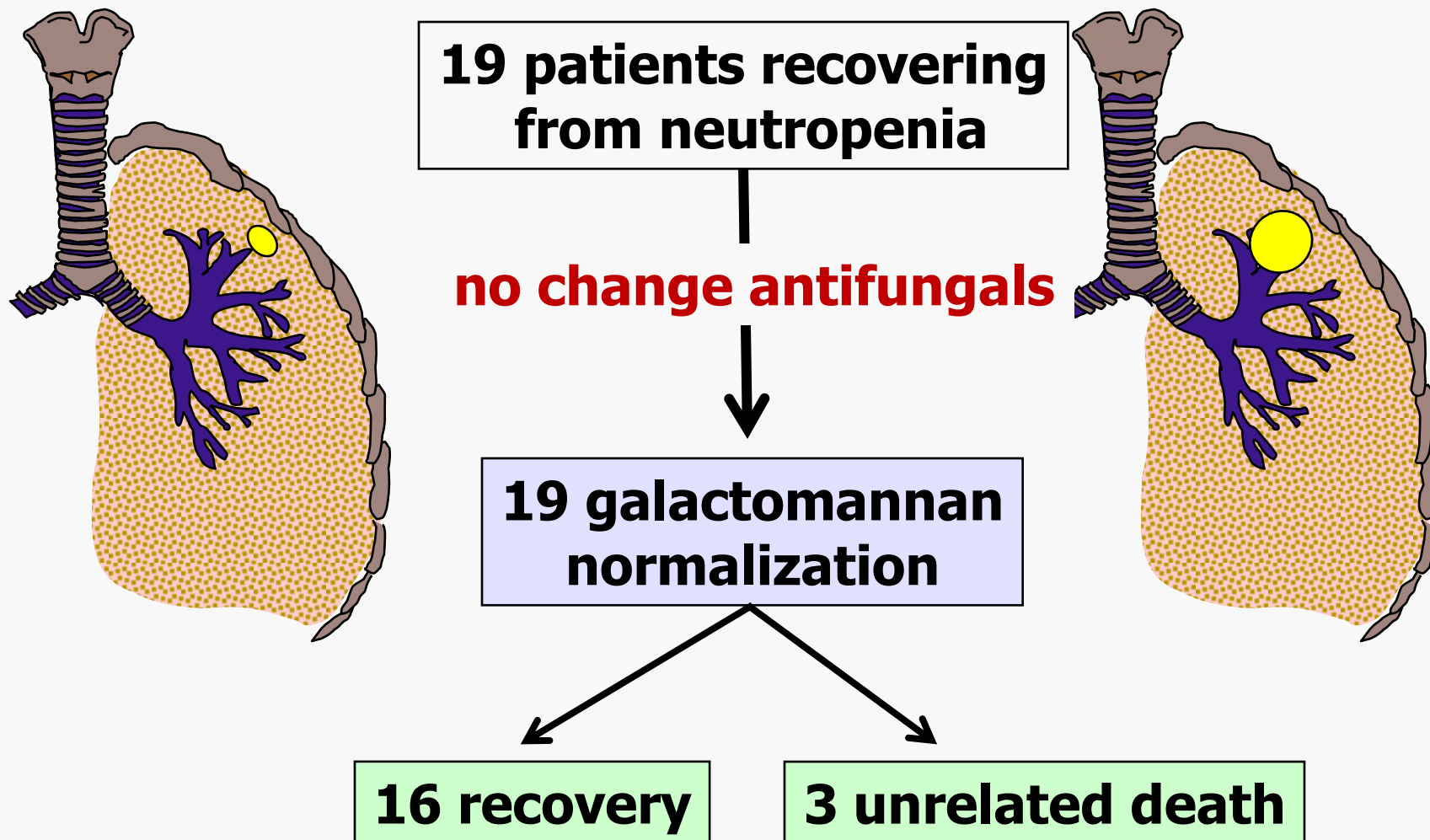
Brodoefel et al. Am J Radiol 2006; 187:404-413.

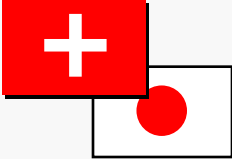




LUNG LESIONS vs GALACTOMANNAN AS PARAMETERS FOR INVASIVE ASPERGILLOSIS

Micelli et al. Cancer 2007; 110:112-120



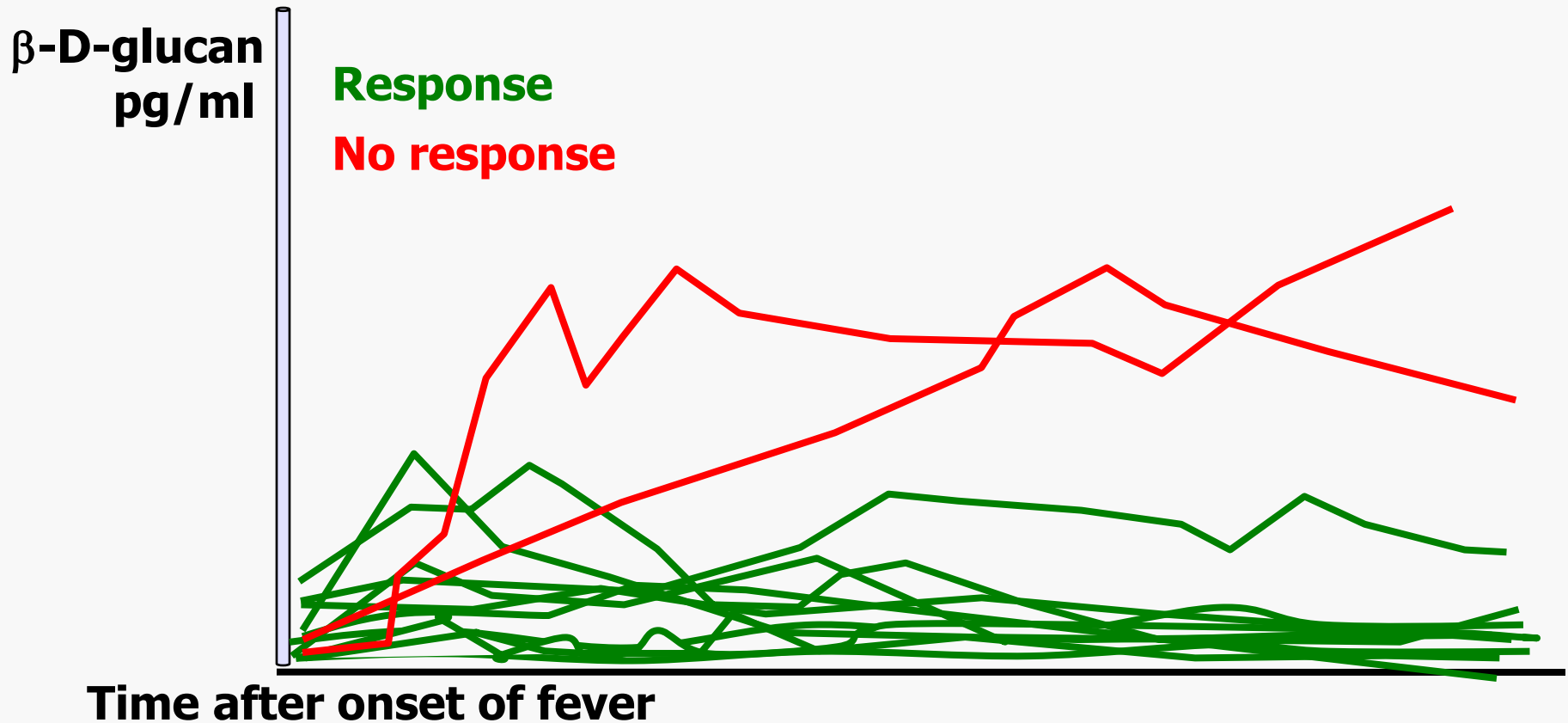


COURSE OF β -D-GLUCAN TO MONITOR THERAPY OF INVASIVE FUNGAL INFECTIONS

Senn et al. Clin Infect Dis 2008;46:878-885

95 patients treated for acute leukemia

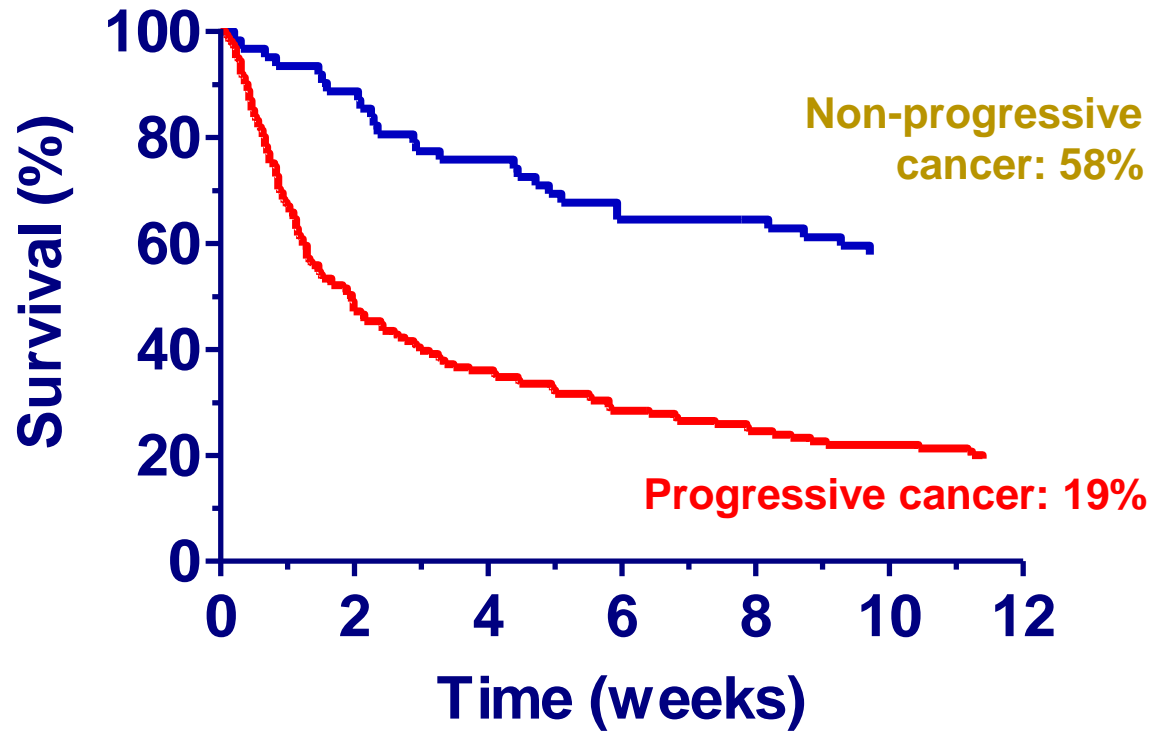
190 neutropenic episodes



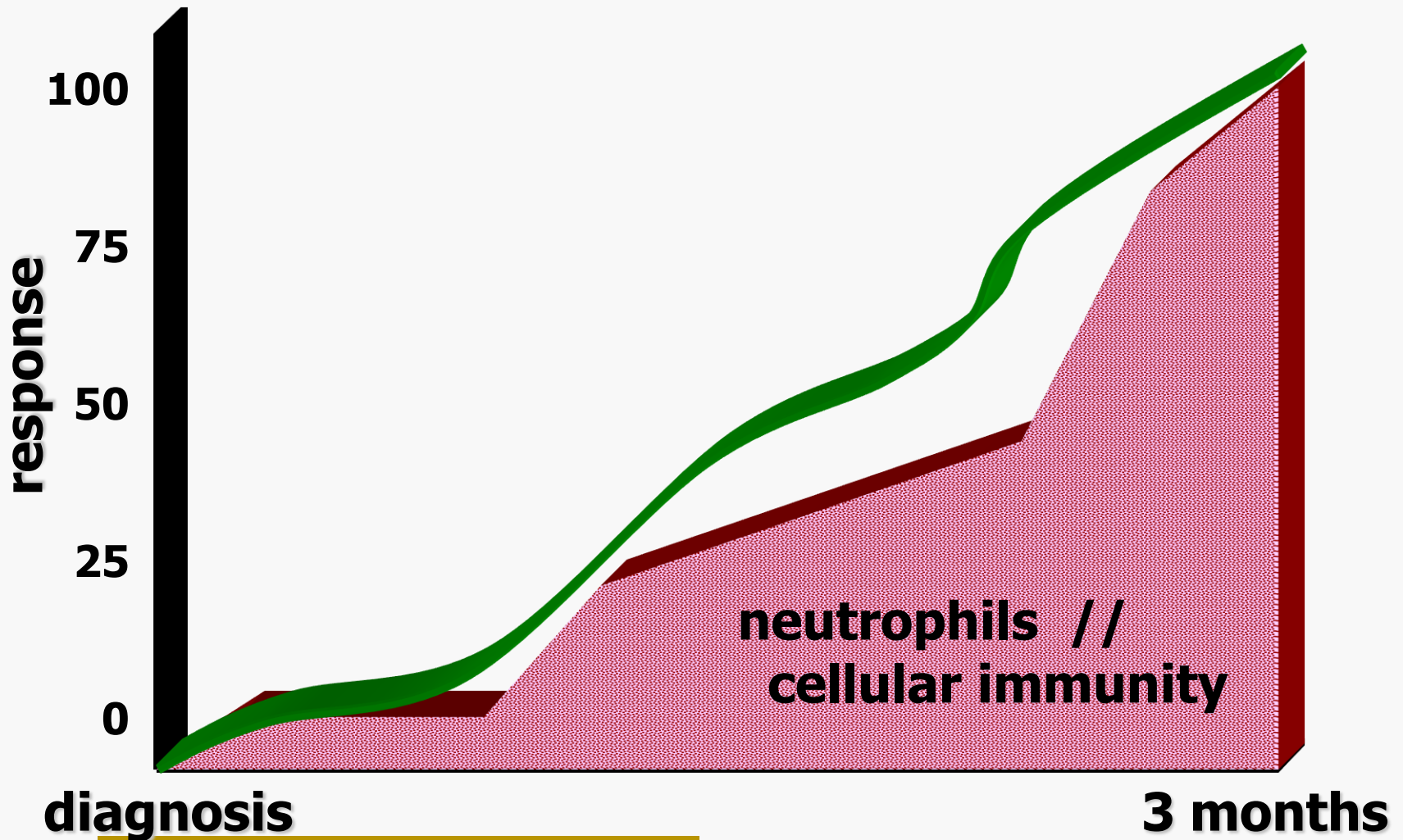
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- **entry criteria**
- **course of underlying disease**
- **concurrent medication**
- **carry-over effect previous antifungals**

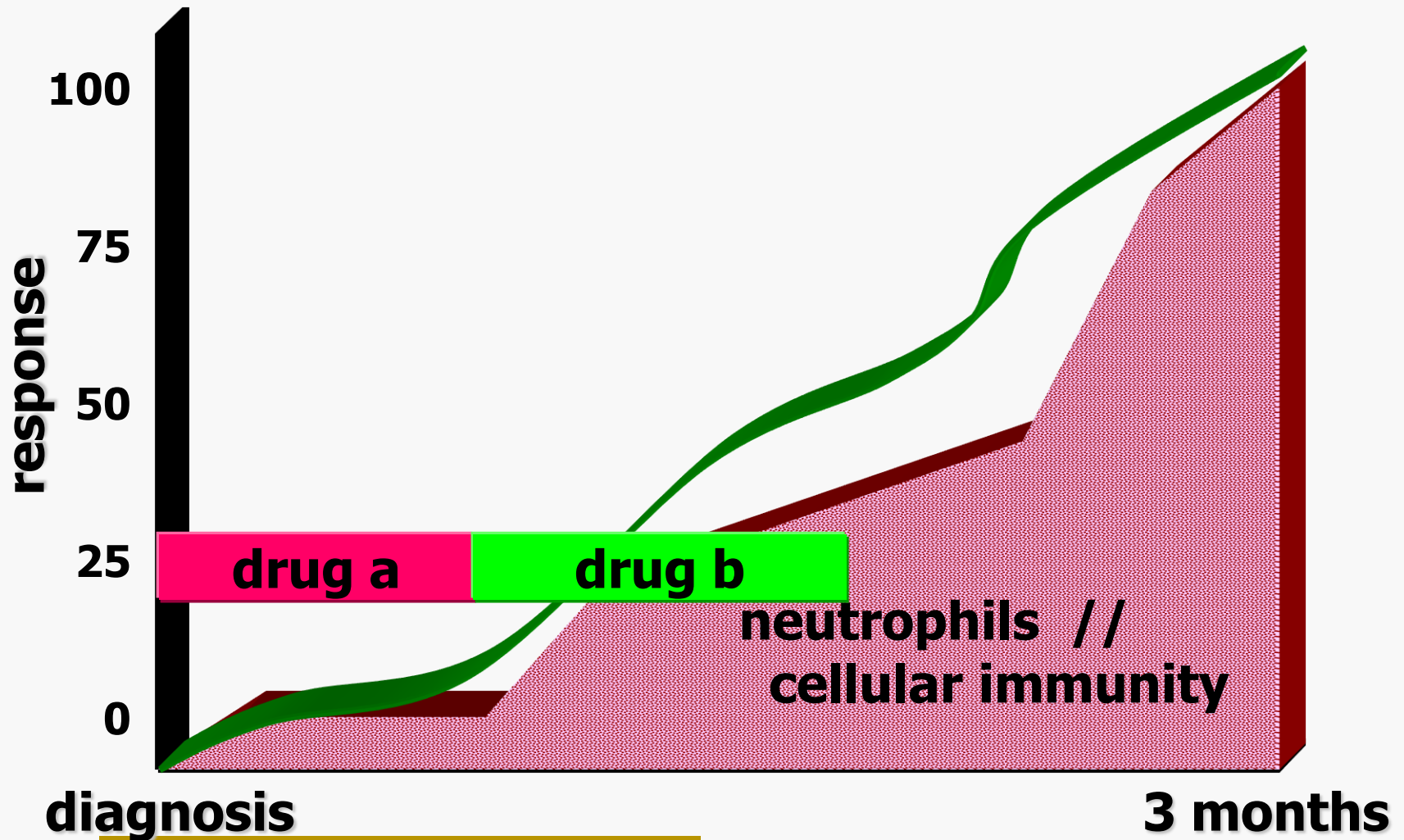
MULTIVARIATE ANALYSIS PROGNOSIS FACTORS IN 223 PATIENTS



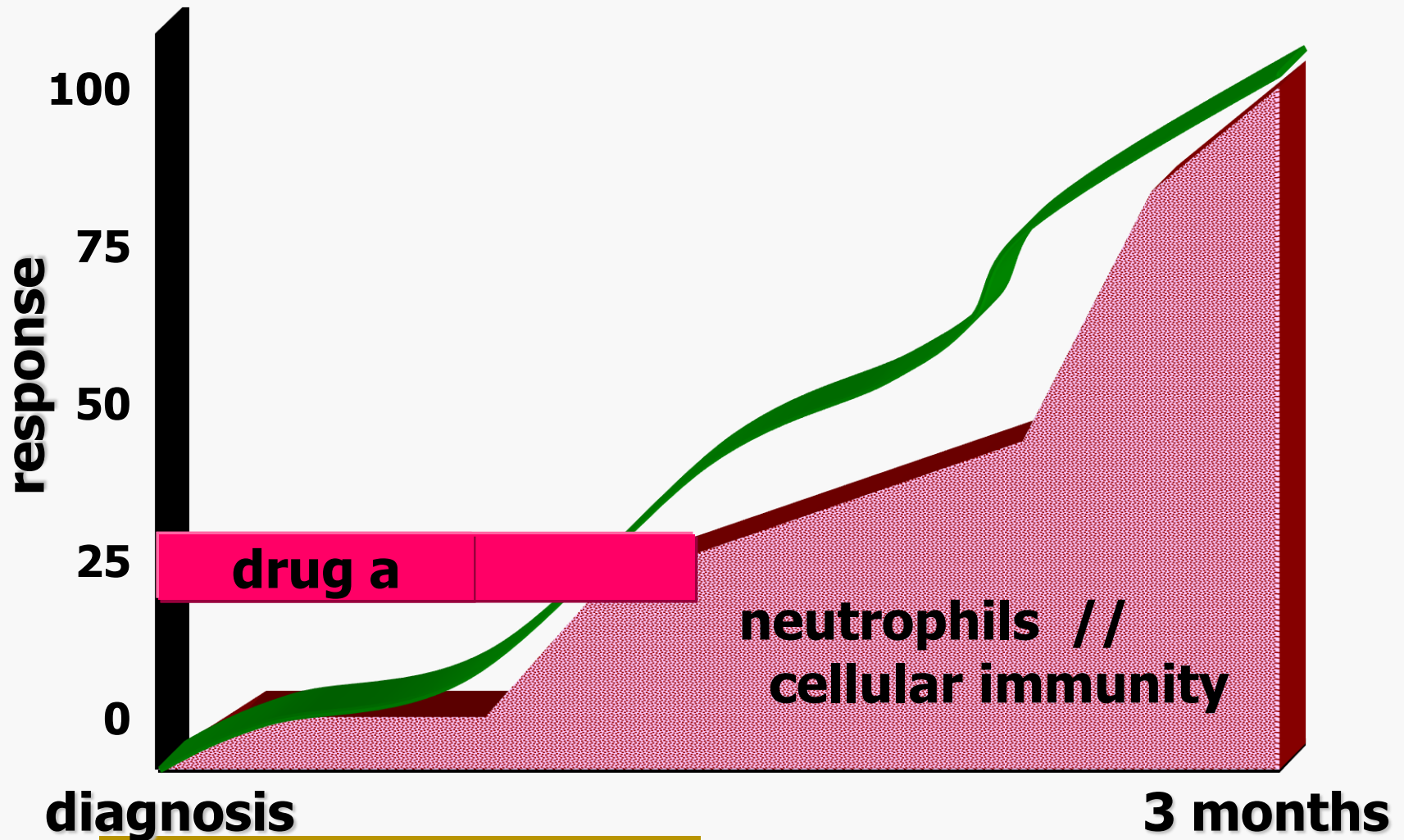
CONSIDERATIONS ON THE EXPLORATION OF COMBINATION THERAPY



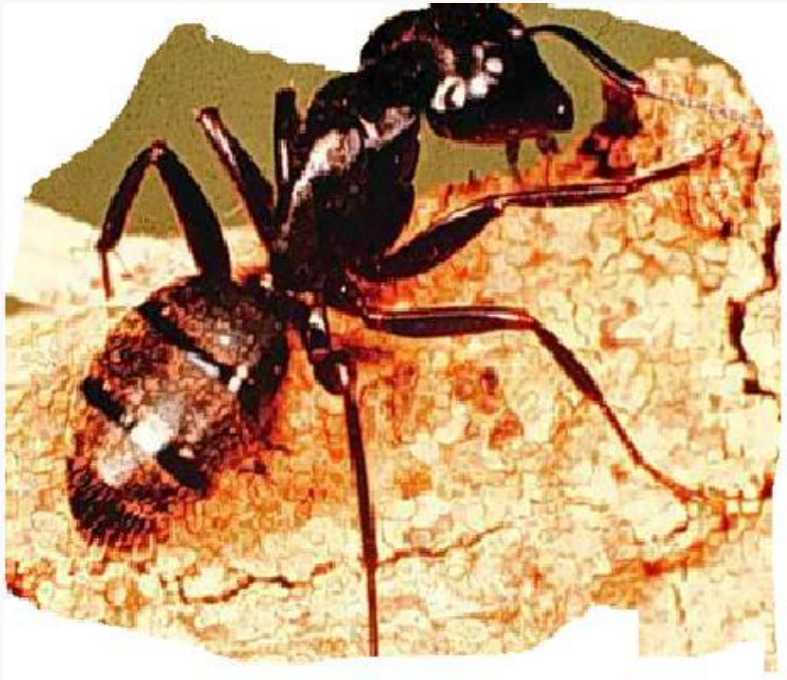
CONSIDERATIONS ON THE EVALUATION OF A GIVEN DRUG



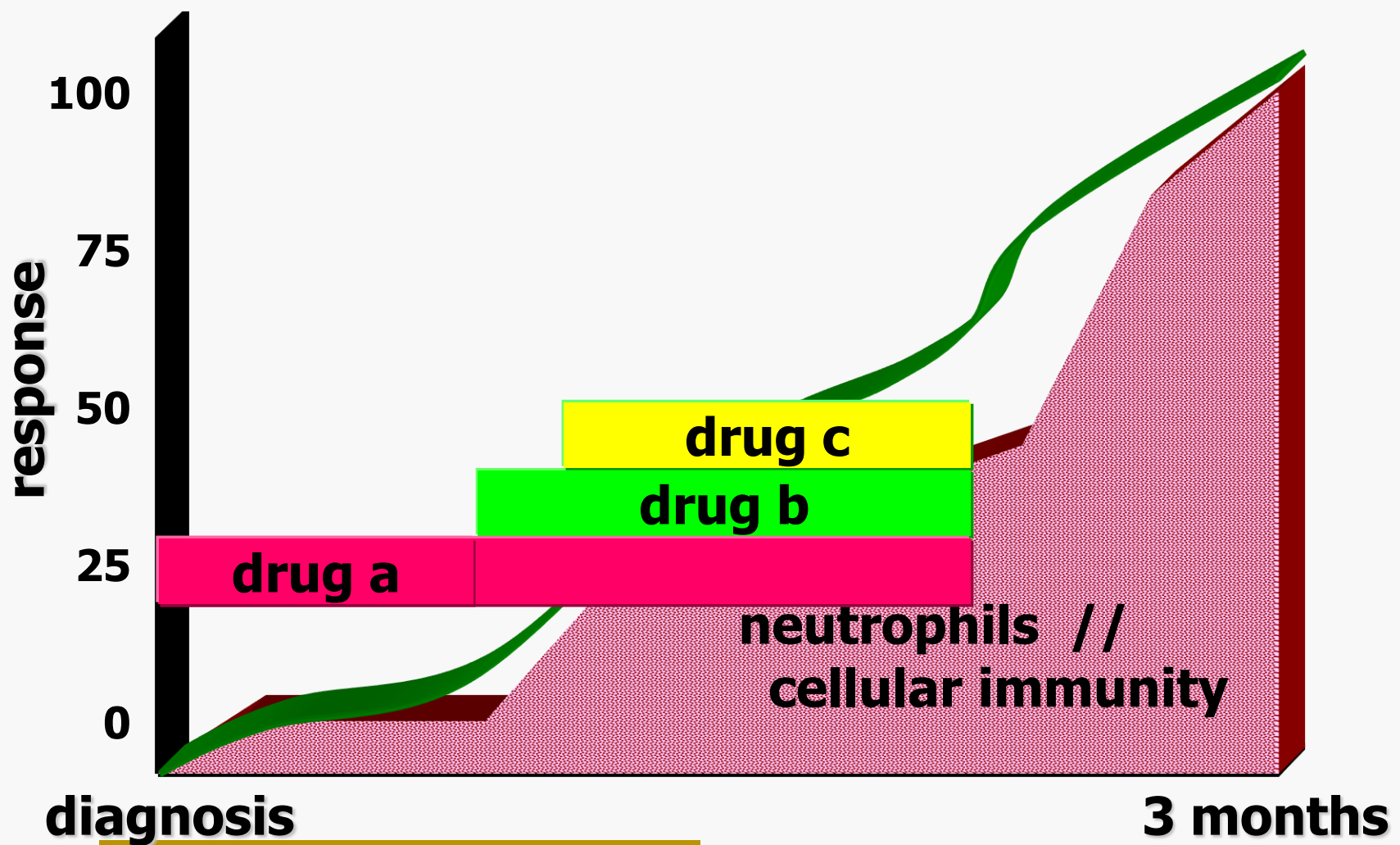
CONSIDERATIONS ON THE EVALUATION OF A GIVEN DRUG



CORDYCEPS UNITARIUS



MORE MONEY THAN SENSE?

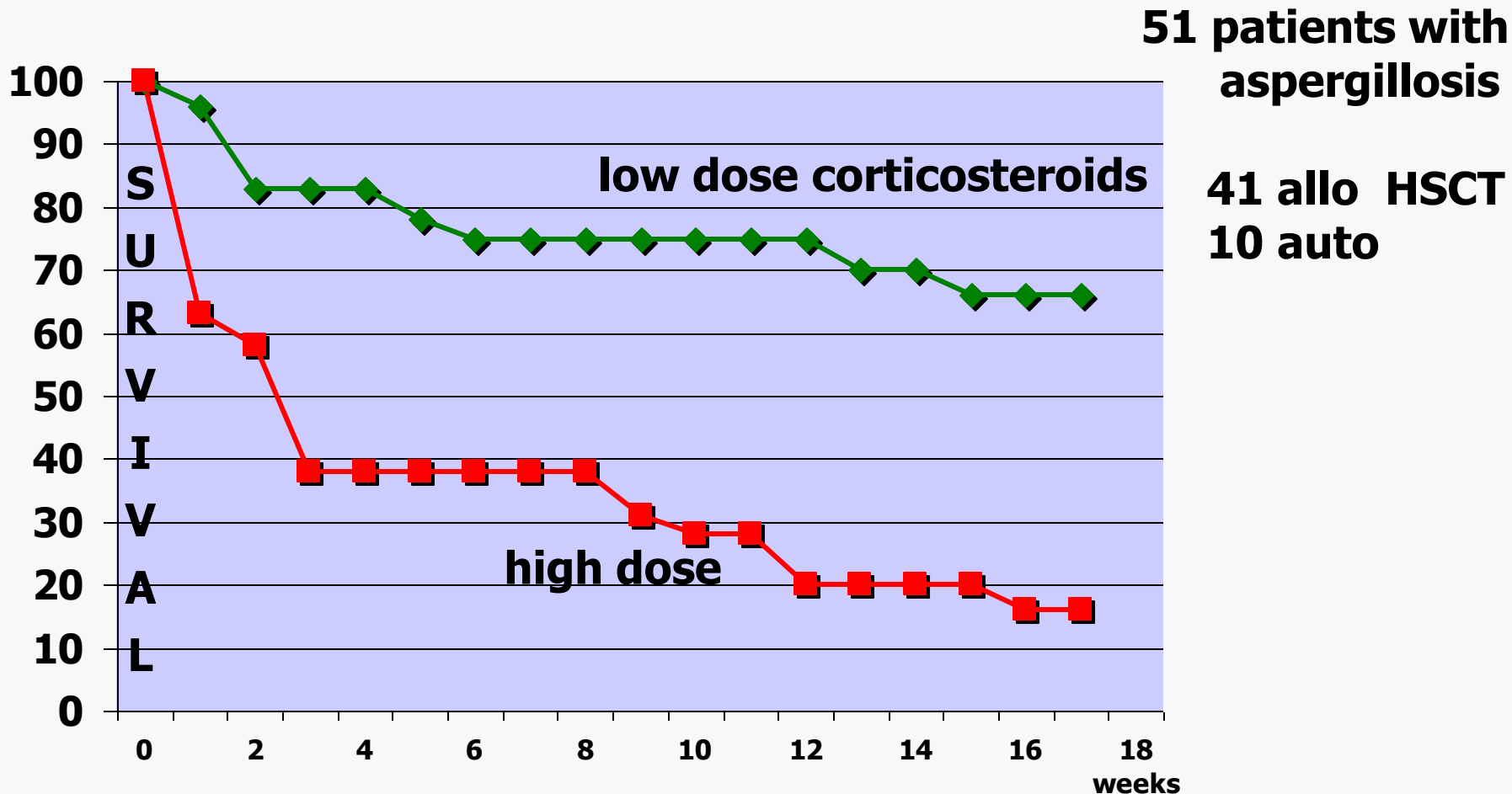


KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- **entry criteria**
- **course of underlying disease**
- **concurrent medication**
- **carry-over effect previous antifungals**

CORTICOSTEROIDS AND SURVIVAL OF ASPERGILLOSIS IN HSCT

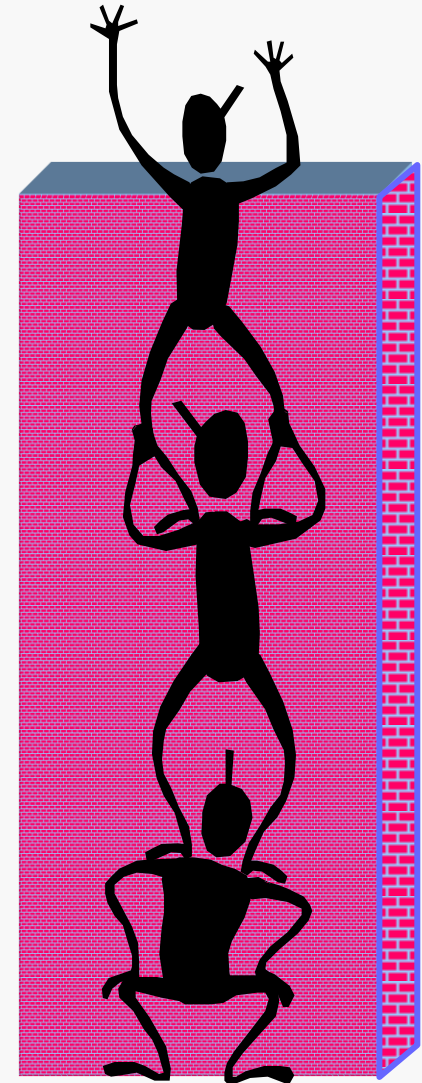
Cordonnier et al. Clin Infect Dis 2006;42:955-963



KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- **entry criteria**
- **course of underlying disease**
- **concurrent medication**
- **carry-over effect previous antifungals**

THE TRUE MERITS OF A SALVAGE THERAPY



SALVAGE.....

**A salvage study is, as per definition,
a strategy study
and **NOT** suited for
assessment of drug efficacy**

FATE OF MANY A CLINICAL TRIAL



LIFE IS FULL OF DIFFICULT CHOICES

