INTERPRETATION OF CLINICAL TRIALS

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DISCLOSURES

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CLINICAL TRIALS: THE 5 PHASES AND THEIR ACTORS

The clinical investigators and the statisticians

Design  Conduct  Analysis  Reporting  Interpretation

The patients and an army of people
DESIGN

1. METHODOLOGY
2. ORIGINALITY
3. RELEVANCE
4. FEASIBILITY

TRUE DATA
NEW DATA
RELEVANT DATA
TRIAL FEASIBLE
INTERPRETATION

SO WHAT?
INTERPRETATION

1. How true?
2. How generalizable?
3. How relevant?
How true?

INTERNAL VALIDITY

+ INTERNAL and EXTERNAL CONSISTENCY

+ BIOLOGICAL AND CLINICAL PLAUSIBILITY
EXTERNAL VALIDITY

- Pt characteristics
- Therapeutic regimen
- Compliance
- Comparator arm
Clinical relevance vs statistical significance
1. Size of benefit?
2. Which endpoints? OS PFS RFS RR QOL
3. How were these expressed? Median, HR, % at....
4. Under which condition
5. How generalizable? → external validity
6. Which toxicity?

(Which cost?)
CLINICAL BENEFIT

EFFICACY
- Setting
  - curative vs palliative
  - prognosis within palliative
- Endpoint
  - type
  - ways to summarize the efficacy endpoint
- Size
  - delta

TOXICITY

CONVENIENCE
A “model” of Kaplan–Meier figure showing the four OS-related parameters.

1. HR (Cox model)
2. Gain in median OS (a↔b)
3. Absolute increase in OS (c↔d) at 2–3 years
4. Proportional increase in OS (ce/de) at 2–3 years

Reprinted from Clinical Cancer Research, © 2015, 21(5), 1036-1043, Alberto F. Sobrero, et al., Raising the Bar for Antineoplastic Agents: How to Choose Threshold Values for Superiority Trials in Advanced Solid Tumors, with permission from AACR.
THE FOUR WAYS TO ASSESS OS BENEFIT

OS BENEFIT

- Small benefit for many
  - HR and gain in MST

- Large benefit for few
  - Absolute and proportional gain in long term OS (2–3 years)

HR, hazard ratio; MST, median survival time; OS, overall survival.
INCREASE IN MEDIAN PFS / OS FOR DIFFERENT HR AS A FUNCTION OF THE SEVERITY OF PROGNOSIS

<table>
<thead>
<tr>
<th>MST / PFS in control (months)</th>
<th>Increase in median values (months) as a function of HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 0.9</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>12</td>
<td>1.4</td>
</tr>
<tr>
<td>24</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Clinically worthless | Unrealistic

HR, hazard ratio; OS, overall survival; MST, median survival time; PFS, progression-free survival
CLINICAL BENEFIT

EFFICACY

TOXICITY

♦ Toxic deaths
♦ Hospitalization rate
♦ Impact on QOL
♦ % grade 3-4 of symptomatic toxicity
♦ Need for growth factors

CONVENIENCE
INTERPRETATION

SO WHAT?

1. SUPERSTARS
2. INCREMENTALISTS
3. TRADE-OFFS
4. OUTCASTS
INTERPRETATION OF NEW DATA

Are these data true?
- Internal validity
- Internal consistency
- Plausibility
- External consistency

Are they relevant?
- External validity
- Clinical benefit

Are they practice-changing?
- ‘Relevant enough’
INTERPRETATION OF NEW DATA

Are these data true?
- Internal validity  
  stat. design, randomization endpoint, ITT
- Internal consistency  
  concordance among RR, PFS, OS
- Plausibility  
  philosophical issue
- External consistency  
  results in other trials

Are they relevant?
- External validity  
  pt charact, schedule, compliance, comparator
- Clinical benefit  
  efficacy, toxicity, convenience

Are they practice-changing?
- ‘Relevant enough’  
  clinical benefit, clinical value
CONCLUSIONS

Never be dogmatic
Consider internal validity
Consider external validity
Consider all aspects of efficacy
Consider the entire story, when available
Thank you!