19th Conference of the International Society of Geriatric Oncology

Integrative oncology – Leaving no one behind

#SDGACTION26996
UN Partnerships for Sustainable Development Goals (SDGs)
Composite/co-primary endpoints and challenges in statistics at EORTC

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COI Disclosures

Advisory role and/or speaker fees from Eisai, Roche, Eli Lilly
Choosing efficacy endpoints for older patients

Scientific progress depends on good research, and good research needs good statistics.

Asking the right question, designing the right trial, choosing the right statistical analysis, and sticking to the plan.

https://www.youtube.com/watch?v=Hz1fyhVOjr4
Efficacy ☐ clinical **benefit** provided by the treatment to the patient as demonstrated by a **clinically meaningful** and statistically **significant change in a pre-defined endpoint** observed in an adequate and well-controlled clinical trial.
Choosing efficacy endpoints for older patients

**Primary endpoints** in clinical trials must meet 3 criteria

- Clinically relevant
- Sensitive to treatment/strategy effect
- Measurable and interpretable
Choosing efficacy endpoints for older patients

**Secondary endpoints** could provide a more global view of the benefit of the treatment/strategy being tested:

- Some - like primary endpoints - are clinically relevant and may be taken into consideration i.e. for drug indications

- Some are “feel-good” endpoints (not likely to lead to a new indication or a change in practice but might provide reassurance about the primary endpoint along with new information about the disease)

- Some might be exploratory analyses, although they might demonstrate biologically plausible effects, they remain hypothesis-generating and will need to be confirmed by additional studies
## Common endpoints in oncology

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<tr>
<th>Endpoint</th>
<th>Definition</th>
<th>Advantage</th>
<th>Limitation</th>
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| Overall Survival       | Time from randomization until death from any cause                          | - Universally accepted measure of direct benefit  
- Easily and precisely measured                                                             | - Larger trial population and longer F-up to show statistical difference between groups  
- May be affected by crossover or subsequent therapies  
- Includes unrelated deaths                                                               |
| Progression-free survival | Time from randomization until disease progression or death                   | - Requires small sample size and shorter F-Up  
- Include measurement of stable disease  
- Not affected by crossover/subsequent therapies  
- Based on objective assessment                                                            | - Validation as a surrogate for survival can be difficult in some treatment settings  
- Not precisely measured (may be subject to bias)  
- Definition may vary among trials  
- Requires frequent assessments  
- Requires balanced timing of assessment among Rx arms                                     |
| Time to progression    | Time from randomization until disease progression; does not include deaths   | - Useless in settings in which toxicity is potentially as serious as disease progression       | - Does not adequately distinguish efficacy from other variables, such as toxicity             |
| Time to Treatment Failure | Time from randomization to treatment discontinuation for any reason (i.e. progression, toxicity, death) | - Useless in settings in which toxicity is potentially as serious as disease progression       | - Does not adequately distinguish efficacy from other variables, such as toxicity             |
## Common endpoints in oncology

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| **Event-free survival** | Time from randomization to progression, death, or discontinuation of treatment for any reason (e.g. toxicity, patient preference, or initiation, of a new treatment without documented progression) | Similar to PFS; may be useful in evaluation of highly toxic therapies | - Initiation of next therapy is subjective.  
- Generally not encouraged by regulatory agencies because it combines efficacy, toxicity, and patient withdrawal |
| **Quality Of Life** | Outcome self-reported by patients using wellness scales, presence of adverse effects and toxicity therapeutic | Patient perspective of direct clinical benefit. | - Reporting sometimes incomplete  
- Difficult to measure and identify clinically relevant cutoffs that determine whether therapy is worthwhile |
| **Toxicity**       | Rate of adverse effects                                                     | Definition of the benefit/risk balance of therapy                                                                 | - Difficulties in having accurate reports of adverse effects |


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<td>Maintenance of functional capacity: level at specified time point or time until deterioration compared with baseline</td>
<td>Evaluation of evolution of functioning and (in)dependence through validated instruments during course of disease/treatment/study</td>
<td>Main contributor to QoL in older cancer patients</td>
<td>No consensus on optimal measurement or clinically relevant cutoffs determining whether therapy is worthwhile</td>
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Choosing efficacy endpoints for older patients: some definitions

**Co-primary endpoints**: combination of $\geq$ two distinct primary endpoints

- Allows capturing more than efficacy alone

- Difficult statistical design because correlation between different endpoints is rarely known

- Might increase sample size
Choosing efficacy endpoints for older patients: some definitions

**Composite endpoint**: combination of different endpoints in one defined endpoint (“component endpoints”)

- Can take into account multiple dimensions in definition of treatment benefit, including efficacy and toxicity
- Increased statistical efficiency, decrease in sample-size requirements, shorter trial duration, and decreased cost.
- Allows separate reporting of different end points

But

☑ Individual components must be clinically meaningful and of similar relative importance
☑ Complex composite EP comprising many events with considerably heterogeneous severity imply difficulties with interpretation
☑ Difficult interpretation if there are divergent results for each component separately

Which are the most common endpoints in dedicated clinical trials?

Primary endpoints

![Graph showing the frequency of different endpoints in clinical trials between 2000-2004 and 2010-2014. The most common endpoints are OS, DSS, and tumor-centered endpoints.]

Le Saux O et al, Ann Oncol 2017
Evaluating the utility of composite end-points for older adults

Are the component endpoints of similar importance to patients?

Do the more / less important endpoints occur with similar frequency?

Can one be confident that the component endpoints share similar relative risk reductions?
  - Are the point estimates of the relative risk reductions similar, and are the confidence intervals narrow enough?

Despite a greater statistical efficiency, this approach can open the door to misdirection and statistical sleight of hand.
Useful composite endpoints in onco-geriatric research

- **Therapeutic success**
  efficacy, toxicity, and patient adherence to treatment

- **Overall Treatment Utility**
  - **Good OUT**: no progression and no major negative treatment effects
  - **Intermediate OUT**: either clinical deterioration but no negative treatment effect or a significant negative treatment effect but no clinical deterioration
  - **Poor OUT**: both clinical deterioration and a major negative treatment effect or death

*Ardizzoni A et al J Clin Oncol 2005; Seymour MT et al, Lancet 2011*
Primary end-point: **event-free survival**.

An event was either **disease progression, death, or functional decline** - defined as a decrease of at least 1 point from baseline values of ADL or IADL, deemed by the investigator as treatment-related and confirmed at the subsequent cycle.

N=160
Primary endpoint: **Time to treatment failure (TTF)**

TTF is defined as time from randomization to **discontinuation of treatment** for disease progression, severe treatment toxicity or death, whichever occurs first.
EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors


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In conclusion

Composite endpoints are being more and more used in onco-geriatric research

Major role for composite EPs which include impact on functional status

Beware of pitfalls:
✓ Must pre-specify outcomes to avoid to cherry pick other results that showed a benefit (*post hoc changes to the composite components should not be performed!*)

✓ When reporting benefit from a composite endpoint, need to evaluate whether there is a similar effect on all components of the composite; if not, the component of the composite primarily responsible for the result must be identified and relative importance compared to others explained