WHAT TO CONSIDER WHEN DESIGNING A TRIAL

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DISCLOSURES

Ulrich Keilholz has reported Research support from Pfizer, MerckSerono and Innate. Speaker honoraria from Amgen, Astra Zeneca, BMS, Merck Serono, Merck/MSD, Pfizer, Glycotope and Novartis.

Dirk Arnold has reported Company leadership role, employment relationship or ownership interest: Eli Lilly

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Susen Burock has reported no conflicts of interest

Emiliano Calvo has reported no conflicts of interest

Urania Dafni has reported no conflicts of interest

Nadia Harbeck has reported to be the Scientific Director of the West German Study Group

Eric Raymond has reported to have conducted trials and acted as consultant for Eli Lilly, Ipsen, Novartis and Pfizer

Piotr Rutkowski has reported no conflict of interest related to the current presentation. However he has received honoraria from Novartis, Roche, GSK, MSD, BMS, Pfizer, Bayer and Amgen and has served as a member of Advisory Board for Novartis, Roche, Amgen, Bayer, MSD and BMS.

Marcel Verheij has reported to be currently conducting research sponsored by AstraZeneca, Roche and Elekta

WHAT TO CONSIDER WHEN DESIGNING A TRIAL

Key Points:

Define a clear research question

Define the appropriate endpoint(s)

Define the right trial design

Calculate the sample size

Determine feasibility

WHAT TO CONSIDER WHEN DESIGNING A TRIAL

Research question

- The clinical trial must have a primary research question clearly stated in advance. This has to be formulated in a hypothesis – which is the basis for the quantitative calculations
- This question should be relevant for patients and public (health care) needs
- Biostatistical input is needed to confirm or withdraw hypotheses and to perform sample size calculation
- Further important issues should be developed as secondary research questions
- The research questions should be based on relevant existing evidence (strong preclinical data and understanding of the biology of the disease)
- The incorporation of an accompanying translational research programme is highly desirable

WHAT TO CONSIDER WHEN DESIGNING A TRIAL

What is the goal of a trial?

Phase I – define safety/toxicity profile, activity signal, proof of principle and recommended dose for further clinical evaluation

Phase II – show that treatment has activity in a defined patient population

Phase III – to demonstrate treatment efficacy:

- Significant improvement in delaying progression (progression-free survival) or of survival over existing standard
- Significant improvement in delaying progression (progression-free survival) or of survival over placebo/observation (if no standard exists)
- Reduced toxicity, improved quality of life, unless survival or progression-free survival is greatly prolonged cost-effectiveness

Phase IV – to follow up drug safety and activity in usually large unselected patient population cohorts after approval or implementation of treatment in routine practice

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Appropriate endpoint(s)

- Endpoints shall be measurable using reliable scales and metrics
- The primary endpoint must be appropriate to answer the research question, the primary objective of the study, usually supported by secondary endpoints
- The primary and secondary endpoints should be relevant to patients and public in qualitative as well as quantitative aspects
- Measurement of endpoints should be feasible and reflecting clinical practice (frequency of measurements and follow-up duration)
- Consider possibilities of in- or out-of-trial cross-over

WHAT TO CONSIDER WHEN DESIGNING A TRIAL

Trial design

- There is no one-fits-all approach, the clinical trial design must be appropriate to answer the specific research question
- Carefully choose your comparator (if applicable) in order to clearly answer the research questions
- Carefully consider the possibility of placebo as a comparator in single agent as well as in multi-agent trials. In case of single agent trials, single agent placebo needs to be justified, often cross-over to active drug in case of disease progression is implemented
- Blinding is desirable but not always possible (e.g. if supportive measures significantly differ between treatments or drug/placebo administration is a high burden for patients in control group)

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Sample size calculation

Sample size is depending on various factors like:

- Endpoint chosen
- Magnitude of the expected differences between treatment groups
- Research question (e.g. equivalence or superior)
- Statistical quality parameters (alpha and beta error)
- Clinical relevance of effect size
- Standard deviation (if a continuous variable)
- Sample size in each group (if comparing groups)

WHAT TO CONSIDER WHEN DESIGNING A TRIAL

Feasibility (I)

Is the patient population existing in a sufficiently large number to conduct a trial?

- Will it be feasible to recruit enough patients in a reasonable timeframe so that the research question is still relevant?
- Should the trial be conducted as a mono-centre or multi-centre trial?
- Should the trial be conducted as a national or a international trial?
- Is the experimental treatment feasible in all sites and countries?

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Feasibility (II)

Is the comparator (e.g. Gold-Standard) accepted in all sites and countries?

- Is the budget available sufficient to perform the trial, follow up, and evaluation?
- Are there competing trials in the same patient population?
- Are all relevant medical specialties involved?
- Is feasibility of a translational research programme and biobanking ensured?
- Is involvement of patient representatives feasible?

Thank you!