INNOVATIVE CLINICAL TRIAL DESIGNS IN THE ERA OF PRECISION ONCOLOGY

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Patients will be matched to the trials according to the molecular profiling of their disease as defined by the results of the tumour gene sequencing or other molecular technics.

Molecular aberrations in tumour are dictating sensitivity to targeted therapies.
MOLECULAR BIOLOGY TECHNICS (e.g. NGS,…) are the basis for new clinical trial designs
EXAMPLES OF CLINICAL TRIALS DESIGNS
Based on molecular biomarker assessment

Marker x Treatment Interaction Design

Register

Marker measurement: all patients

High

Low

A

B

A

B

Marker x Treatment Interaction Design for assessment of the Clinical Utility of Predictive Marker. The trial is the equivalent of 2 randomized treatment trials done in each marker status group. The design can assess whether the treatment effect depends on the marker status

Marker Strategy Design

Register

Marker measurement: all patients

Treat without reference to marker status

Treat according to marker status

Marker Strategy Design: This design assesses whether there is benefit to using a marker when choosing a treatment for a patient, compared to not using the marker (treating as is commonly done now, without considering predictive marker)

Hayes DF, et al., Trans Am Clin Climatol Assoc, 2015
PHASE I TRIALS

Advanced cancer patients treated with targeted agents matched with tumour molecular alteration have improved outcome in phase I trials.
EARLY METASTATIC BREAST CANCER SETTING
AURORA study design

- Newly diagnosed or first-line MBC patients
  - N=1300
  - Screening failures n=300

- Patients with ‘actionable’ mutation(s) (n=300)
- Downstream-targeted clinical trials

- Patients without ‘actionable’ mutation(s) (n=700)
- Standard of care

- Clinical outliers (exceptional responders and rapid progressors) to be subjected to WES

- Timeline
  - Entry in DCT
  - Cycle 1
  - Cycle 2
  - Cycle 3
  - Cycle x
  - Continue until disease progression
  - Disease progression

- Metastatic lesion
  - Biopsy – TGS and RNAseq

- Primary tumour
  - Archival – TGS and RNAseq

- Blood
  - TGS and RNAseq

- Plasma/serum
  - Collection every 6 months – up to 10 years

- Clinical outcome information
  - Collection every 6 months – up to 10 years

Zardavas D, British Journal of Cancer (2014) 111, 1881-1887 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License
MOLECULAR-DRIVEN CLINICAL TRIALS: PROS AND CONS

Pros
- New and selective therapeutic options for patients
- Better outcome

Cons
- Absence of agents in some detected driver targets
- No direct clinical implication or benefit in a large proportion of screened patients
- Difficulties to discriminate drivers from passengers targets
UMBRELLA TRIAL

- Different targeted agents investigated in parallel in the same tumour type and within independent cohorts of patients

- Defined by specific molecular aberrations that could predict sensitivity to the investigational agent under assessment
HISTOLOGY-BASED CLINICAL TRIAL DESIGN

To evaluate multiple molecular aberrations

Sleijfer S, et al., J Clin Oncol, 31(15); 2013:1834-1841. Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.
UMBRELLA TRIAL

Tumour type A (lung cancer)

Tumour molecular analysis

Biomarker 1
Drug 1

Biomarker 2
Drug 2

Biomarker 3
Drug 3

Biomarker 4
Drug 4

EXAMPLE OF UMBRELLA TRIAL (1): BATTLE TRIAL FOR NSCLC

Umbrella protocol

Core needle biopsy

Biomarker profile
- EGFR mutation/copy number
- KRAS/BRAF mutation
- VEGF/VEGFR-2 expression
- RXRs/Cyclin D1 expression and CCND1 copy number

Equal followed by adaptive randomization

Erlotinib
Vandetanib
Erlotinib + bexarotene
Sorafenib

EXAMPLE OF UMBRELLA TRIAL (2): LUNG-MAP PROTOCOLE

Herbst RS, et al., Clin Cancer Res, 2015, Apr1; 21(7): 1514-1524
UMBRELLA TRIAL: PROS AND CONS

Pros
- Less screening failure to enter clinical trial
- Possibly more patients will benefit from a targeted treatment

Cons
- Multiple arms
- More patients to be included
- Active and dynamic follow-up of the study is needed
BASKET TRIAL

Histology-independent trial design

Patients with cancers of different histologies enrolled in the clinical trial based on the presence of a specific molecular aberration
TRIAL DESIGN

Histology-independent, aberration-specific clinical trial design
BASKET TRIAL

- Tumour type A (lung cancer)
- Tumour type B (gastric cancer)
- Tumour type C (colon cancer)
- Tumour type D (breast cancer)

Tumour molecular analysis

- Biomarker 1
  - Drug 1
- Biomarker 2
  - Drug 2

EXAMPLE: NCI MPACT BASKET TRIAL

Tumour biopsy from all patients for sequencing

Mutation detected

Randomisation (clinical team is blinded)

Arm A
Assign treatment identified to target mutation

Arm B
Assign treatment NOT identified to target mutation

Mutation not detected

OR

Off study

Disease progression

CREATE EORTC TRIAL

- Six Cohorts of rare solid tumours and anaplastic large cell lymphoma
- ALK and/or MET alterations are considered to play a role of the carcinogenesis process of these tumours
PHASE II TRIAL 90101 "CREATE"

Activity of crizotinib in patients with clear cell sarcoma (CCSA) in EORTC

“CREATE” phase II trial assesses the safety and activity of ALK/MET inhibitor crizotinib in 6 different ALK- or MET-driven tumour types including CCSA

Full results of this trial are pending
BASKET TRIAL: PROS AND CONS

Pros

- Determining potential tumour efficacy of a single targeted agent in different cancer types with the same gene abnormality

Cons

- Risk of overlooking the impact of tumour histology type. In fact, different tumour responses by targeting the same mutation in several cancer types could be observed. (e.g. BRAF in melanoma versus BRAF in colorectal cancer: RR 50%-60% versus <5%)
The principle of this trial is based on modifying parameters (dose, sample size, drug, schedule ...) of a clinical trial evaluating a treatment in accord with observed outcomes in participants.
ADAPTIVE TRIAL DESIGN

Adaptive design

Adaptive trials offer a more flexible way to deal with drug performance over the course of a study. I-SPY 2 uses a design called Bayesian, in which patient allocation is shifted according to treatment response.

Colours represent different biomarker profiles

Outcome better than control

Outcome same as control

Subsequent recruitment favours profiles that benefit

Drug B shows no improvement over control for any biomarker

Discontinue drug B

Randomized recruitment to control arm continues

Modified recruitment creates potential for drug to reach endpoint faster, and informs phase III design.
A COMPARISON
Between the “Bayesian” and “Frequentist” approaches

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bayes</th>
<th>Frequentist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Differences</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main goal of inference</td>
<td>Predict outcomes of future trials and absolute risk for future patients</td>
<td>Estimate population average effects</td>
</tr>
<tr>
<td>Assumptions</td>
<td>Requires explicit specification of prior distributions of unknown population parameters. Incorporates a prior knowledge and clinical judgment formally. May be sensitive to specification of prior distributions</td>
<td>Does not require explicit specification of prior distributions of unknown population parameters. Incorporates a prior knowledge and clinical judgment informally</td>
</tr>
<tr>
<td>Interim monitoring</td>
<td>Only the data actually obtained are relevant for final conclusions (e.g., a credible interval or predictive probability). Whether or not a clinician examines accumulating evidence with the possibility of stopping the trial does not affect inference</td>
<td>Both the data actually obtained and the probabilities of data not obtained are relevant for final conclusions (e.g., a P value). Whether or not a clinician examines accumulating evidence with the possibility of stopping the trial does affect inference</td>
</tr>
<tr>
<td>Ease of use</td>
<td>Often computationally complex; careful modelling often requires simulation-based calculations</td>
<td>Often computationally simple, though careful modelling may require simulation-based calculations</td>
</tr>
<tr>
<td><strong>Similarities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptation</td>
<td>Can incorporate adaptive designs, multistage trials, early stopping, and adaptive randomisation</td>
<td></td>
</tr>
<tr>
<td>Role of statistical judgment</td>
<td>Options for data-driven analyses are available. Skill and substance-area knowledge of the data analyst are important in drawing correct conclusions</td>
<td></td>
</tr>
<tr>
<td>Compatibility</td>
<td>It is feasible to combine a Bayesian design with a frequentist analysis or a frequentist design with a Bayesian analysis</td>
<td></td>
</tr>
<tr>
<td>Prior knowledge</td>
<td>Both approaches rely on prior knowledge and clinical judgment (though they incorporate them in different fashions)</td>
<td></td>
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I-SPY2
Adaptive Randomisation of Veliparib–Carboplatin Treatment in Breast Cancer

ADAPTIVE TRIAL DESIGN: PROS AND CONS

Pros

- Faster evaluation of the drug
- Modification of drug, dosage and sample size during the trial according to the observed results

Cons

- Practical difficulties during the performance of the trial
- The clinicians are not familiar with the essential statistical part of this approach
- Active and dynamic follow-up of the trial is needed
N-OF-1 TRIALS

Recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between

Each involved patient serves as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives
EXAMPLE OF N-OF-1 TRIALS: STUDY FLOW DIAGRAM

Patient consent and evaluation for the study (N = 106)

Proceeding with MP (n = 86)
Not proceeding with MP (n = 20)
  Worsening condition (n = 6)
  Withdrew consent (n = 5)
  Lack of proof of progression (n = 3)
  Brain metastasis (n = 2)
  No malignant cells in the biopsy (n = 1)
  Unable to obtain tissue for analysis (n = 3)

Not treated following MP (n = 18)
  Worsening condition (n = 9)
  Withdrew consent (n = 4)
  Brain metastasis (n = 2)
  No malignant cells in the biopsy (n = 2)
  Needed to start treatment (n = 1)

Patients treated (n = 68)
  Treated according to MP (n = 66)
  Not treated according to MP (n = 2)

MP: molecular profiling

In 27% of patients, the molecular profiling approach resulted in a longer PFS on an MP-suggested regimen than on the regimen not based on molecular profiling on which the patient had just experienced progression.
N-OF-1 TRIALS: PROS AND CONS

Pros

- *In vivo* testing of agents in the same patient
- Eliminating the inter-individual genetic differences affecting drug metabolism

Cons

- The difference in outcome might be of multifactorial origin. As example, it could be due to difference in consecutive treatment sequence and change in the biology (sensitivity/resistance) of the disease
- Translation of the finding of these studies to future patients is difficult and unclear
WINDOW-OF-OPPORTUNITY TRIALS

- Assessing the administration of an investigational agent over a short period of time
- Most often in the pre-surgical setting, sometimes in metastatic
- No major efficacy endpoint
- *In vivo* biological effect(s) (pharmacodynamics) of an experimental agent
WINDOW-OF-OPPORTUNITY TRIALS

D-BEYOND trial design in early breast cancer

Baseline

Denosumab

Denosumab

Surgery

Tumour, normal breast tissue and blood samples

One week apart

Tumour, normal breast tissue and blood samples

NCT01864798
WINDOW-OF-OPPORTUNITY
TRIALS: PROS AND CONS

Pros

- *In vivo* evaluation of the mechanism of action of a drug or if the target is affected

Cons

- No direct clinical implication
- Short period treatment
CHALLENGES OF THE NEW CLINICAL TRIAL DESIGNS

- To show significant benefit in overall survival
- Rapidly evolving and not validated technics in use for tumour sequencing (NGS, circulating tumour cells, circulating tumour DNA...)
- High number of screened patients is needed
MORE EFFORTS ARE NEEDED ON:

- Networking between institutions to render molecular tumour board accessible to the majority of centres and consequently to clinical trials and new drugs.
- More collaboration between pharmaceutical companies due to the need of drugs (including off label drugs) with the different mechanisms of action to be used in precision medicine at the right time for the patient.
- Role of liquid biopsy in determining the biological heterogeneity and evolution of the tumour.
- Role of biomarkers and/or molecular imaging in determining mainly the negative predictive value of an evaluated drug.
Thank you!