Clinical Trial Designs to Expedite Drug Development in Oncology

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Adaptive Designs

• Allows for planned design modifications
• Modifications based on data accrued in the trial up to the interim time
• Unblinded or blinded interim results
• Control probability of false positive rate for multiple options
• Control operational bias
• Assumes independent increments of information
Definition of Adaptive Design

A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (interim data) from subjects in the study.
Types of ADs

• Exploratory:
  – Less restrictive
  – Explore without adjusting for multiple looks, multiple adaptations to generate hypothesis to be tested

• Hypotheses Testing or Confirmatory:
  – Adequate and well controlled (A & WC) studies
  – Pre-planned, type I error rate (false positive rate) well controlled
  – Decision rules specified for each adaptation
Group Sequential and Bayesian Designs

Group Sequential Designs
• During the conduct of the study, data are analyzed and reviewed at periodic intervals
  – Correlated increments of information
• Using interim estimates of treatment effect
  – Decide whether to continue or stop the trial
  – If continuing, decide on any modifications to sampling scheme

Bayesian Designs
• In the Bayesian paradigm, the parameter measuring treatment effect is regarded as a random variable
• Bayesian inference is based on the posterior distribution (Bayes’ Rule – updated based on observed data)
Enrichment Designs

• Enrich the study population
• Enrichment by prognostic marker → Examples: high risk population (where events will occur in short time) third-line setting; triple negative metastatic breast cancer; specific histology – mantle cell lymphoma
• Enrichment by predictive marker → Examples: Herceptin for Her2+ breast cancer; Zelboraf for melanoma with BRAF mutation.
Adaptive Enrichment Design

All patients
Treatment A or B

Interim Analysis

Marker Negative:
Stop Accrual

Marker Positive:
Treatment A or B
Master Protocols

• One overarching protocol that includes one or more of the following:
  – Multiple diseases
  – Multiple treatments
  – Multiple molecular markers

• Other names:
  – Platform Trials
  – Umbrella Trials
  – Basket Trials
Characteristics of a Master Protocol

- One Protocol
- Central governance structure
- Central IRB
- Central DMC
- Central Independent review committee
- Central repository of data and specimens

- Study multiple drugs
  - Targeting more than one marker
  - More than one drug for one marker
- Study multiple markers
  - Overlapping expression of markers
- Leverage common control group(s)
- Flexibility to add/remove agents
Non-Comparative Studies

**Imatinib**
Considered as registration study with multiple cohorts of diseases with a common molecular biomarker (earlier approvals with proven efficacy and safety profile)

**NCI MATCH Trial**
Exploratory study; Not defined by histology, multiple molecular markers, multiple treatments

**Gleevec Tx**
- Dx1
- Dx2
- Dx3
- Dx4
- Dx5

**Screen**
- M1; Tx1
- M2; Tx2
- M3; Tx3
- M4; Tx4
- M5; Tx5

Tx = Treatment; Dx = Disease; M = Marker; P = Pathway
Exploratory Comparative Studies

**BATTLE 1**
Advanced NSCLC

- Screen
- M1, ..., M4
- Randomize
  - Tx1
  - Tx2
  - Tx3
  - Tx4

**ISPY 2**
Early Breast Cancer

- Screen
- HER2+
  - M1, ..., M8
  - C1
  - C1 + Tx1
  - C1 + Tx2
  - C1 + Tx3
- HER2-
  - M1, ..., M8
  - C2
  - C2 + Tx4
  - C2 + Tx5
  - C2 + Tx6

Bayesian Response-adaptive randomization in both studies
Phase 1/2 Expansion Cohort Studies

• Start with a dose escalation study in all solid tumors or hematological malignancies
• Amend protocol to start expansion cohorts in specific diseases, with different dosing regimens, single arm and randomized studies
• Central Governance

Things to consider:
• Pre-specified starting and stopping criteria and maximum sample size needed
• Patient protection – exposing patients to unknown safety risk
• Data tracking, Data dissemination, IRB involvement, etc.

Example: KEYNOTE 001 pembrolizumab study
Keynote-001: Phase I Trial of Patients with Advanced Solid Tumors (N=1255)

Fig. 1 Flowchart summarizing the KEYNOTE-001 treatment cohorts in solid tumors, melanoma, and NSCLC that have been reported to date. Abbreviations: IPI ipilimumab; NSCLC non-small cell lung cancer; PD-L1 programmed death receptor ligand 1; Q2W once every 2 weeks; Q3W once every 3 weeks.
Clinical Trial with Common Control

• Several treatments (T1, T2,...) compared to the same common control (C) in a given disease setting
• Compare each treatment with the control (T1 vs. C, T2 vs. C, etc.
• No comparison between treatments
• Equal randomization to treatments (1:1:1... randomization - C:T1:T2:....)
## Hypothetical Example to Illustrate Gain with Common Control

<table>
<thead>
<tr>
<th>To detect HR = 0.5 with respect to OS</th>
<th>Median ~ 6 months with C</th>
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<tr>
<td><strong>Two independent RCTs</strong>&lt;br&gt; (T1:C and T2:C)</td>
<td>176 events&lt;br&gt; 336 subjects</td>
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<tr>
<td><strong>Common Control Design</strong>&lt;br&gt; (T1:T2:C)</td>
<td>124 events (↓30%)&lt;br&gt; 216 subjects (↓36%)</td>
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Resources can be saved!

- 5 concurrent currently ongoing studies in advanced RCC
- In each of the 5 studies control arm is Sunitinib:
  - Checkmate 214: Ipi + Nivo → Nivo vs. Sunitinib
  - Keynote 426: Pembro + Axitinib vs. Sunitinib
  - Javelin Renal 001: Avelumab + Axitinib vs. Sunitinib
  - NCT02420821: Atezo + Bev vs. Sunitinib
  - NCT02811861: Lenvatinib + everolimus vs. Lenvatinib + pembro vs. Sunitinib
- Could have saved precious patient resource in one study with a common control!
Comparison of Dynamic Treatment Regimes

Example: US Intergroup study of R-CHOP vs. CHOP
A two-stage random assignment:
1\textsuperscript{st} stage: Induction R-CHOP vs. CHOP
2\textsuperscript{nd} stage: Maintenance R vs. Observation in patients who achieve CR/PR with induction treatment
Primary Endpoint: Failure-free survival (failure: relapse, non-protocol treatment or death)
A weighted Cox-regression analysis was conducted – to remove the bias from analyzing only a subset of patients randomized in the second stage.
Ref: Rituxan product label Study 7; Habberman et al JCO 2006
Comparison of Dynamic Treatment Regimes

- In practice patients are treated with sequential treatments
- The decision of the next treatment in sequence is specifically tailored to the patient
- Without re-randomization difficult to estimate treatment effect
- If the subsequent treatment is different from the first, then attribution of efficacy to a product is challenging
- Statistical methods for certain scenarios are available to determine the overall efficacy with a treatment regimen