Basket and Umbrella Trials: Definitions, Statistical Properties, and Examples

Lindsay A. Renfro, Ph.D.
Associate Professor of Biostatistics
Mayo Clinic

10th CDDF Alpine Conference
Innsbruck, Austria
26 February 2018
Background

- New treatment paradigm in oncology
  - Organ-specific cancers $\rightarrow$ molecularly-defined sub-cancers
  - Cytotoxic $\rightarrow$ cytostatic drugs

- Targeted therapy
  - Hypothesized to “hit” a molecular target
  - Interrupts cancer cell growth and division along 1+ cellular “pathways”

- Immunotherapy
  - Unleashes patient’s own immune system against disease
Recent FDA (USA) Approvals

- **EGFR inhibitors** (e.g., cetuximab, panitumumab):
  - KRAS-WT metastatic colorectal cancer
- **Trastuzumab**:
  - HER-2 positive metastatic breast cancer
- **Vemurafenib**:
  - BRAF-V600E-mutant melanoma
- **Erlotinib** / **crizotinib**:
  - EGFR-mutated / ALK-mutated lung cancer

---

Groundbreaking FDA Approval in June 2017

- Pembrolizumab (immunotherapy)\(^1\)
- Unresectable metastatic solid tumors with microsatellite instability (MSI-H) or mismatch-repair deficient (dMMR) status
- Approval based on biomarkers rather than location: FDA first!

\(^1\)www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm
Clinical Trials

“...the weakest links in the chain of knowledge for determining therapeutic advances...”

“It is ironic that we take the same clinical trial approach to evaluate all manner of potentially amazing transformative experimental therapies and yet we don’t experiment with the design of the clinical trial itself.”

–Don Berry, MD Anderson¹

New ways of treating cancer → require new trial designs!

“Biomarker-based” designs

- **Interaction designs**: Enroll marker + and −, randomized to targeted vs. non-targeted therapy
- **Enrichment designs**: Enroll marker + only (randomized or not)
- **Adaptive enrichment designs**: Adapt enrollment during trial from full population to patients who seem to benefit
- **Marker strategy designs**: Randomize to treatment *strategy*: based on biomarker vs. not based on biomarker (e.g., physician’s choice)
Biomarker-Based Designs, Continued

▶ “Master protocols”
  ▶ Basket trials, umbrella trials, platform trials, etc.
▶ Goals:
  ▶ Personalized medicine
  ▶ Increased efficiency in drug development when target-drug combinations exist
Biomarker-Based Designs, Continued

▶ “Master protocols”
  ▶ Basket trials, umbrella trials, platform trials, etc.
▶ Goals:
  ▶ Personalized medicine
  ▶ Increased efficiency in drug development when target-drug combinations exist
Basket and Umbrella Trials: Terminology

- Not straightforward...
- Early literature: terms like “basket trial” and “umbrella trial” used inconsistently
- More recently, terms becoming somewhat standardized\(^1\)

Proposed Definitions

- **Master Protocol**: An over-arching protocol or trial mechanism comprised of several parallel sub-trials differing by molecular features
  - **Basket Trial**: A master protocol where each sub-trial enrolls multiple tumor types (“the basket”)
  - **Umbrella Trial**: A master protocol where all patients (and all sub-trials) share a common tumor type (“the umbrella”)
Basket vs. Umbrella

**Novel precision medicine trial designs**

**Umbrella trial**
- 1 type of cancer
- Different genetic mutations (●●●)
- Test drug 1
- Test drug 2
- Test drug 3

**Basket trial**
- Multiple types of cancer
- 1 common genetic mutation (●)
- Test drug

---

Basket vs. Umbrella

**Background**

- **Terminology**
- **Basket Trials**
- **Umbrella Trials**

**Considerations and Conclusions**

Basket Trials
Basket Trial: Definition

- **Basket Trial**: A master protocol where each sub-trial enrolls multiple tumor types ("the basket")

---

1. https://www.mskcc.org/blog/clinical-trial-shows-promise-basket-studies-drugs
Basket Trial: General Schema

- **Target 1 + Drug 1**
- **Target N + Drug N**
- **Molecular Portrait**
- **Tumor Type X**
- **Tumor Type Y**
- **Tumor Type Z**
- **Tumor Type A**
- **Tumor Type B**
- **Tumor Type C**

Background and Terminology

Basket Trials

Umbrella Trials

Considerations and Conclusions

Definition and Features

Advantages

Disadvantages

Examples
Basket Trials: Defining Features

- Usually early phase, single-arm sub-studies
- Design: often single stage or Simon two-stage with futility stopping
- Preliminary target-treatment hypotheses
- Objective: identify large, unambiguous signals of activity based on molecular features (rather than tumor type)
  - “Success” within a sub-study may lead to larger confirmatory study
- Usually 20-30 patients per “basket” or molecular sub-study
Basket Trials: Advantages

- Relatively small sample size
- Increased “hit rate” by enrolling patients with rare molecular features **across** tumor types
- Offer an array of novel therapeutic agents to a broad group of patients who may benefit
Basket Trials: Disadvantages

- Prognostic heterogeneity across tumor types
- Single arm sub-studies generally require a tumor response rate endpoint (with a high bar)
- Challenging to define historical controls across diseases
  - For this reason, PFS endpoint (though often relevant) usually not primary and is challenging to assess
- Multiple testing (though separate studies face the same issue)
Example: NCI Match

- NCI Molecular Analysis for Therapeutic Choice (NCI-MATCH)
- Second-and-later line treatment of advanced solid tumors and lymphoma
- 30 planned (initially 10) histology-independent marker-based cohorts, 17+ therapies
- 6,000+ patients (initially 3,000) centrally screened by NGS → 35-70 eligible patients per cohort
NCI Match Cohort Design

- Most cohorts: 35 eligible → 31 evaluable patients
- Endpoint: overall response rate (ORR) by RECIST v1.1
- 90% power to detect ORR improvement 5% → 25% with <2% type I error
- Observed (empirical) ORR of 16% → success
- Strong efficacy within a tumor type → separate phase II or III study
- Patients who progress may be re-screened for another cohort
- Key secondary endpoint: progression-free survival (PFS)
- Target: 25% rare cancers (actual: 60%)
NCI Match Schema

Genetic sequencing
PTEN IHC

Actionable mutation detected

Study agent

Stable disease, complete or partial response (CR+PR)¹

Continue on study agent until progression

Progressive disease (PD)²

Check for additional actionable mutations²

PD

Repeat biopsy and sequencing

No additional actionable mutations, or withdraw consent

No

Yes

3 Year Follow Up

¹CR, PR, SD, and PD as defined by RECIST
²Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH
NCI Match Update / Challenges

- Opened to enrollment in 2015
- Published 2017 updates
  - Screening registration rapid: 6,000 patient cap 2 years early
  - “Common” subtypes rarer than expected; will need to screen tens of thousands to fill 31-patient cohorts
  - Relaxed screening process (to use outside laboratories); currently enrolling
  - 18% of screened patients were eligible for one of the sub-trials
  - 8 out of 30 cohorts reached accrual goal of 35 patients; some now expanding to enroll 70 patients
  - Most cohorts still trying to reach 35 patients

Other Basket Trials

- Pediatric NCI-Match ¹
- Signature (Novartis) ²
- AcSe³
- CREATE⁴

¹ https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match
³ https://clinicaltrials.gov/ct2/show/NCT02304809
⁴ http://www.eortc.org/sites/default/files/90101.pdf
Umbrella Trials
Umbrella Trial: Definition

- Umbrella Trial: A master protocol where all patients (and all sub-trials) share a common tumor type (“the umbrella”)

Background and Terminology
Basket Trials
Umbrella Trials
Considerations and Conclusions

Umbrella Trials: Defining Features

▶ Mid-to-late phase sub-studies
▶ Design: often randomized with futility stopping or “graduation” to phase III
▶ Better understood target-treatment hypotheses
▶ Objective remains identification of large effects (within a single tumor type)
  ▶ ...to keep trial size feasible, particularly for rare molecular cohorts
▶ Sub-studies generally larger than those of basket trials
Umbrella Trial: General Schema
Umbrella Trials: Advantages

- Relatively improved prognostic homogeneity (all patients from same tumor group)
  - Any observed benefit may be more readily attributed to the marker
  - Particularly true when randomization against a control treatment occurs
  - Even more true when marker-negative patients concurrently randomized to same treatments
    - Treatment-by-marker interaction may be computed
Umbrella Trials: Disadvantages

- Larger size, particularly when sub-trials are randomized
- Longer duration
- Difficulty enrolling rare molecular subtypes of a single tumor type
- Susceptibility to changes in the “treatment landscape” during the trial
  - E.g., introduction of a new standard of care (may change control arm)
Example: Lung-MAP

- **Lung-MAP (SWOG S1400)**
- Patients with previously-treated advanced squamous cell lung cancer
- Initially 3 parallel randomized phase II/III sub-trials for targeted therapy vs. SOC (docetaxel)
- Goal: 500-1,000 patients screened per year
- Contains 4th cohort: non-match study for patients not eligible for target cohorts
Lung-MAP Design

- Phase II endpoint: PFS
  - 68-124 patients per sub-study
- Phase III endpoint: overall survival (OS) with phase II patients contributing
  - 272-336 patients per sub-study
- No cross-cohort comparisons
- Initially, non-match patients randomized to anti-PD-L1 immunotherapy vs. SOC
Background and Terminology
Basket Trials
Umbrella Trials
Considerations and Conclusions

Lung-MAP Schema (Original)

Lung-MAP Updates / Challenges

- One initial cohort (c-MET-positive) closed early for toxicity
- March 2015: FDA approved nivolumab in same patient population
  - Control arm (docetaxel) no longer the standard of care
- Lung-MAP re-opened with modifications: 
  - Control arm dropped in phase II → single arm experimental therapy only 
  - New objectives in non-match arm (single vs. combo immunotherapy)
- Oct 2017: 1,400 patients registered
- Nov 2017: Non-match sub-study for PD-1/PD-L1-resistant patients

Basket and Umbrella Trials

Considerations and Conclusions

Definition and Features
Advantages
Disadvantages
Examples

Lung-MAP Revised Schema

Schema at Revision #3

**Biomarker Driven Sub-Studies**

- **$\text{S1400B}$ PI3K**
  - GDC-0032
  - Randomized Phase III
  - GDC-0032 vs. TBD

- **$\text{S1400C}$ CCGA**
  - Palbociclib
  - Randomized Phase III
  - Palbociclib vs. TBD

- **$\text{S1400D}$ FGFR**
  - AZD4547
  - Randomized Phase III
  - AZD4547 vs. TBD

**Non-match Sub-Study**

- **$\text{S1400I}$ Checkpoint Naive**
  - Nivolumab/Ipilimumab
  - Nivolumab

Biomarker-driven sub-studies will progress to Phase III if study meets endpoint and Phase III is feasible at which point the standard of care arm will be determined.
Other Umbrella Trials

- ALCHEMIST\(^1\)
- FOCUS4\(^2\)

\(^1\)Gerber et al. ALCHEMIST, Clin Pharmacol Ther 2015; 97: 447-450.
Basket and Umbrella Trials: Practical and Statistical Issues

- **Practical Issues:**
  - New collaboration paradigm
  - Logistics far beyond a single trial
  - Trials must adapt to external changes over years, decades
  - Unforeseen screening challenges may affect feasibility

- **Statistical Issues:**
  - Effect size vs. sample size
  - Whether to include an all-marker-negative subgroup
  - Classification of patients with multiple markers or genetic mutations
Conclusions

- Basket and umbrella trials → potential solution to challenges of precision medicine
- Expected increase in popularity as larger, traditional trials become less feasible
- Need for improved statistical methodology to address design challenges, e.g., rare molecular subtypes
References / Resources

Thank you!

renfro.lindsay@mayo.edu