Basket Trials: Features, Examples, and Challenges

Lindsay A. Renfro, Ph.D.
Associate Professor of Research
Division of Biostatistics
University of Southern California

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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

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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
Big Picture

New ways of treating cancer → New trial designs!
Biomarker-Based Designs

- **Many types:** Enriched or targeted designs, interaction or marker-stratified designs, adaptive enrichment designs, etc.
- **Special class of biomarker designs:** “Master protocols”
  - Basket trials, umbrella trials, platform trials$^{1,2}$
- **Goals:**
  - Personalized medicine
  - Increased efficiency in drug development when target-drug combinations exist

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$^{1}$Renfro and Sargent, Ann Oncol 2017; 28: 34-43
$^{2}$Woodcock and LaVange, NEJM 2017; 377: 62-70.
Biomarker-Based Designs

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Basket and Umbrella Trials: Terminology

- Not straightforward...
- Early literature: terms like “basket trial” and “umbrella trial” used inconsistently
- “Basket trial”: some disagreement about what is the “basket”
- More recently, terms becoming somewhat standardized\(^1\),\(^2\)

\(^1\)Renfro and Sargent, Ann Oncol 2017; 28: 34-43
Proposed Definitions

- **Master Protocol**: An over-arching protocol or trial mechanism comprised of several parallel sub-trials differing by molecular features or other objectives
  - **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")
  - **Platform Trial**: A master protocol where sub-trials may be added or removed in an operationally seamless way
**A Venn Diagram of Master Protocols**

**Master Protocols**: Over-arching clinical trial protocols comprised of parallel marker-based sub-trials, arms, or cohorts

**Basket Trials**: Master protocols in which parallel marker-based cohorts ("baskets") enroll patients from many tumor types

**Umbrella Trials**: Master protocols in which parallel marker-based cohorts are drawn from one tumor type ("umbrella")

**Platform Trials**: Master protocols in which paired marker-treatment cohorts continually enter and exit the trial under the same protocol. May be basket, umbrella, or neither.
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

http://jamanetwork.com/journals/jamaoncology/fullarticle/2591161
Basket vs. Umbrella

**Umbrella**
Test the impact of different drugs on different mutations in a single type of cancer

- BATTLE
- I-SPY 2
- Lung-MAP
- FOCUS4

**Basket**
Test the effect of one or more drugs on one or more single mutations in a variety of cancer types

- NCI MATCH
- NCI MPACT

Basket Trials
Basket Trial: Definition

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

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 A**
- **Tumor Type B**
- **Tumor Type C**
Definition of “Basket”

“Basket” = Individual Sub-Trial

- Tumor Type X
- Tumor Type Y
- Tumor Type Z
- Tumor Type A
- Tumor Type B
- Tumor Type C

- Target 1 + Drug 1
- Target N + Drug N

Molecular Portrait
Alternative Definition of “Basket”

“Basket” = Individual Tumor Type Within A Sub-Trial

Target 1 + Drug 1

Tumor Type Y

Target N + Drug N

Tumor Type A

Tumor Type B

Molecular Portrait

Tumor Type C

Tumor Type X

Tumor Type Z

Tumor Type Y
Basket Trials: Defining Features

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

- Operational efficiencies compared to designing and conducting individual targeted trials without shared infrastructure
- Relatively small sample size per sub-study
- Increased “hit rate” by enrolling patients with rare molecular features across tumor types
- Array of novel therapeutics offered to a broader 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, time-to-event endpoints (though often relevant) usually not primary
- Practical challenges with screening may arise
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%)
Background and Terminology

Basket Trials
Umbrella Trials

Considerations and Conclusions

Definition and Features
Advantages
Disadvantages
Example

NCI Match Schema

![Diagram showing the NCI Match Schema flowchart](image)

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

ECOG-ACRIN
NIH
NATIONAL CANCER INSTITUTE

03/17/2016 14
NCI Match Update / Challenges

- Opened in 2015, initial cohort results in 2017, 2018\(^1\)
  - Screening registration rapid: 6,000 patient cap 2 years early
  - 18% of screened patients “matched”; 69% of those enrolled to sub study
  - Low enrollment of “common” subtypes; will need to screen tens of thousands more
  - Relaxed screening process (to include more laboratories)
  - 18 cohorts open; some expanding to enroll 70 patients
  - Results for 4 cohorts announced to date

NCI Match Results to Date

- November 2017: First cohort\(^1\)
  - **Arm Z1D**: Nivolumab in MMR-d cancers: 24% ORR (+)

- June 2018: 3 more cohorts at ASCO\(^2\)
  - **Arm I**: Taselisib in PIK3CA-mutated cancers: (−) for ORR, but prolonged stable disease
  - **Arm Q**: T-DM1 in HER2 over-expressing cancers: (−) for ORR, but prolonged stable disease
  - **Arm W**: AZD4547 in FGFR-mutated cancers: 20% ORR (+)

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\(^1\)[https://jitc.biomedcentral.com/track/pdf/10.1186/s40425-017-0297-3]

Other Basket Trials

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

¹https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match
³https://clinicaltrials.gov/ct2/show/NCT02304809
⁴http://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")

Basket and Umbrella Trials

Umbrella Trial: General Schema

- Single Tumor Type
- Molecular Portrait
- Target A
  - Matched Drug A
  - Control
- Target B
  - Matched Drug B
  - Control
- Target N
  - Matched Drug N
  - Control

...
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 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

Definition and Features

Advantages

Disadvantages

Example

Lung-MAP Schema (Original)

Lung-MAP Updates / Challenges

- One cohort (c-MET) closed early for toxicity; reopened 2018
- March 2015: FDA approved nivolumab in same patient population
  - Control arm (docetaxel) no longer the standard of care
- Lung-MAP re-opened with modifications: ¹
  - Control arm dropped in phase II → single arm only
  - Non-match arm: single vs. combo immunotherapy
- July 2018: 1,700+ patients screened, 1325 assigned, 600 registered to sub-studies
- Several sub-studies closed and reported, more added
- Late 2018: Sub-study for PD-1/PD-L1-resistant patients, opening to all histologies

¹http://www.lung-map.org
Lung-MAP Revised Schema

Schema at Revision #3

Biomarker Driven Sub-Studies

- S1400B PI3K
  - Single Arm Phase II: GDC-0032
  - Randomized Phase III: GDC-0032 vs. TBD

- S1400C CCGA
  - Single Arm Phase II: Palbociclib
  - Randomized Phase III: Palbociclib vs. TBD

- S1400D FGFR
  - Single Arm Phase II: AZD4547
  - Randomized Phase III: AZD4547 vs. TBD

Non-match Sub-Study

- 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.

LUNGMAP

SWOG
Other Umbrella Trials

▶ ALCHEMIST\textsuperscript{1}
▶ FOCUS4\textsuperscript{2}

\textsuperscript{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

- **Statistical Issues:**
  - Effect size vs. sample size
  - Whether to include an all-marker-negative subgroup
  - Classification of patients with multiple markers or genetic mutations
  - How to maintain feasibility without compromising objectives
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!

Slides or questions: Irenfro@usc.edu