Master Protocols, Basket Trials, and Umbrella Trials: Overviews, Features, Challenges, and Examples

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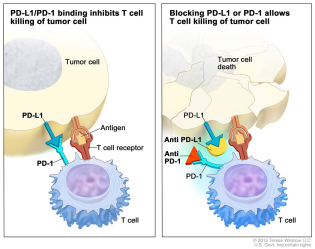
Background

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

Groundbreaking FDA Approval: June 2017

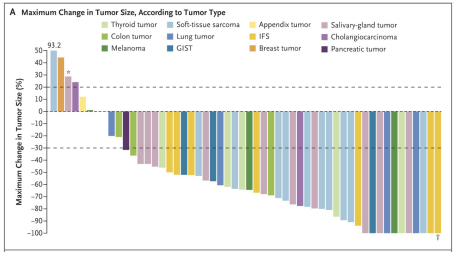
- Pembrolizumab (immunotherapy)
- Unresectable metastatic solid tumors with microsatellite instability (MSI-H) or mismatch-repair deficient (dMMR) status
- Approval based on biomarkers rather than location: FDA first!



www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm

Another Groundbreaking Approval: November 2018

- Larotrectinib
- Advanced solid tumors with NTRK gene fusions
- 55 children and adults with 17 different cancer types from 3 different trials
- High tumor response rate (75%) and durable responses



Drilon et al. NEJM 2018; 378:731-739.

Issue: Traditional Approach to Cancer Trials

- Narrow focus to one cancer type (e.g., stage III colon cancer)
- Pose a treatment-related question (e.g., longer survival than standard Rx)
- Design a trial to enroll enough patients to answer the question
- Maybe: collect biomarker data and analyze retrospectively, discover relationship years later

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But now, cancer "type" is a moving target!

Solution: Biomarker-Driven Trial Designs

New ways of treating cancer $\rightarrow$ New trial designs!

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New ways of treating cancer $\rightarrow$ New trial designs!

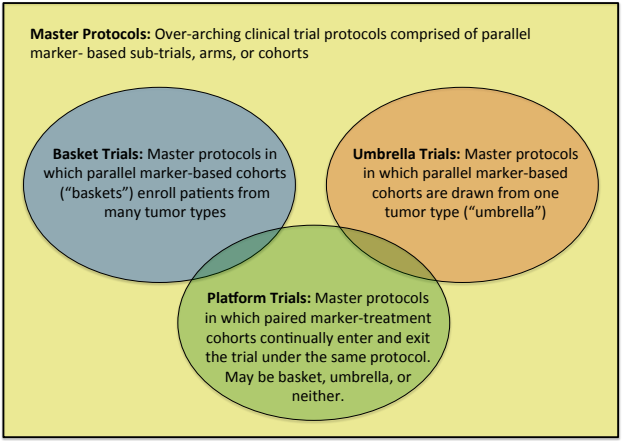
Molecular features may matter as much as (or more than) tumor location

Basket and Umbrella Trials: Terminology

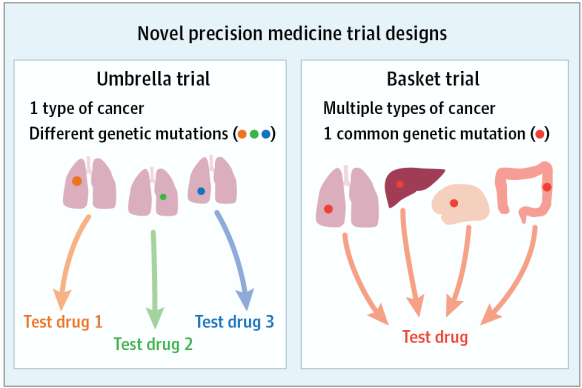
- Not straightforward...
- Early literature: terms like "basket trial" and "umbrella trial" used inconsistently
- Basket trials: differing perspectives on what constitutes the "basket"
- More recently, publications attempting to standardize terminology[1],[2]

[1] Renfro and Sargent, Ann Oncol 2017; 28: 34-43
[2] Woodcock and LaVange, NEJM 2017; 377: 62-70.

Proposed Definitions and Venn Diagram of Master Protocols



Basket vs. Umbrella

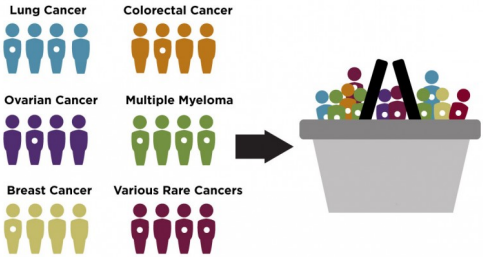


http://jamanetwork.com/journals/jamaoncology/fullarticle/2591161

Basket Trials

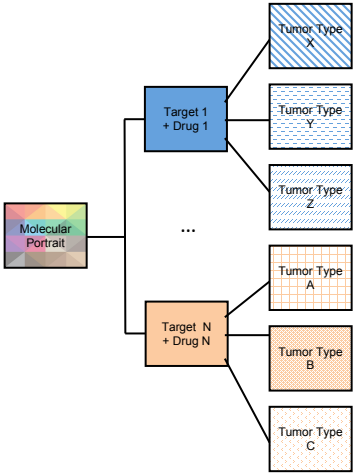
Basket Trial: Definition

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

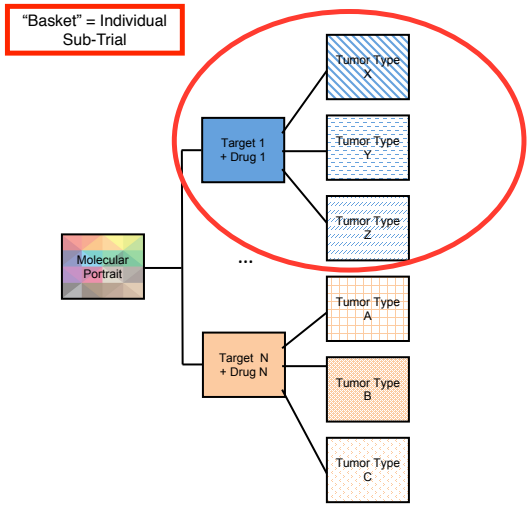


https://www.mskcc.org/blog/clinical-trial-shows-promise-basket-studies-drugs

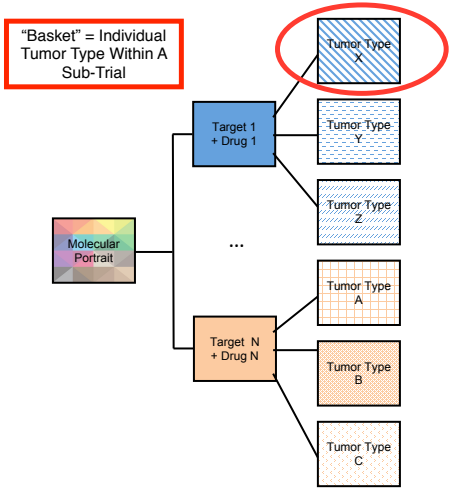
Basket Trial: General Schema



One Definition of "Basket"



Alternative Definition of "Basket"



Basket Trial: Defining Features

- Sub-Study Design
  - Usually single-arm phase II, single stage or two-stage with futility rules
- Sub-Study Objective
  - Identify a large, unambiguous signal of activity that seems specific to the basket's molecular feature (rather than tumor type)
- Sub-Study Characteristics
  - Master protocol governs shared screening and operations, sub-study protocols (baskets) added or removed over time
  - Useful for testing many preliminary target-treatment hypotheses in parallel
  - Small: usually only 20-30 (initial) patients per "basket"
  - "Success" may lead to expansion cohorts or larger confirmatory studies

Basket Trial: Advantages

- Operational efficiencies compared to conducting many individual small 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 Trial: Disadvantages

- Prognostic heterogeneity inevitable across tumor types, even within same marker basket
- Don't know distribution of cancer types that will enroll up front
- Challenging to define historical controls across diseases
  - For this reason, time-to-event endpoints usually not primary (though often relevant)
  - Tumor response primary endpoints far more common
  - Still, "overall response" defined differently for solid tumors vs. leukemia
- Practical challenges with screening or too-rare baskets may arise

NCI-COG Pediatric MATCH[1]

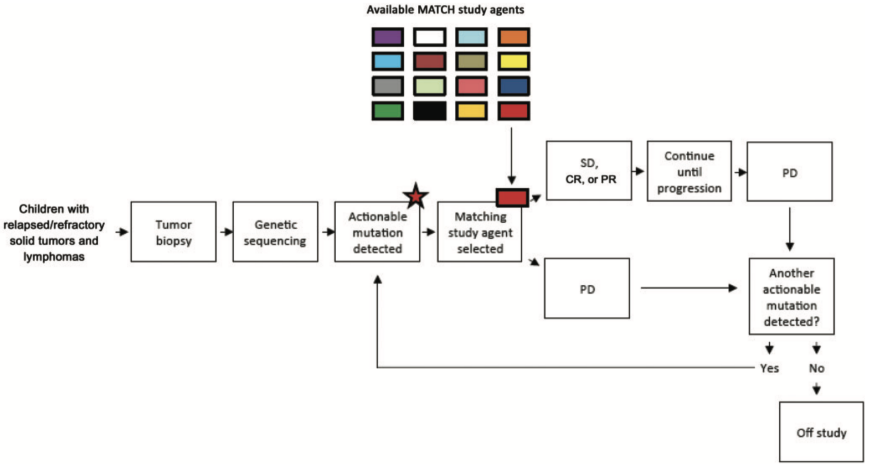
- Hypothesis: By identifying genetic changes affecting pathways of interest in refractory and recurrent pediatric cancers, we will be able to deliver targeted anticancer therapy that produces a clinically meaningful objective response rate.

CHILDREN'S ONCOLOGY GROUP

NIH NATIONAL CANCER INSTITUTE

[1] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match

NCI-COG Pediatric MATCH: Schema



NCI-COG Pediatric MATCH: Statistical Design

- 1,000 patients to be screened
- 10 therapeutic sub-studies open (at least 3 more planned)
- Cohort design:
  - $n = 20$, single arm, single stage
  - Primary endpoint: Objective Response Rate (ORR)
  - 90% power to detect increase in ORR from 5% to 25%
    - 5% "historical control" rate: $\rightarrow$ just want to see *any* signal of activity!
  - Type I error rate: 10%
  - 3+ responses with same histology $\rightarrow$ histology-specific cohort expansion ($n_2 = 10$)

NCI-COG Pediatric MATCH: Selection of Study Agents

- Prior evidence of clinical activity in **some** cancer type (adults or children)
- Previous pediatric experience **not** required

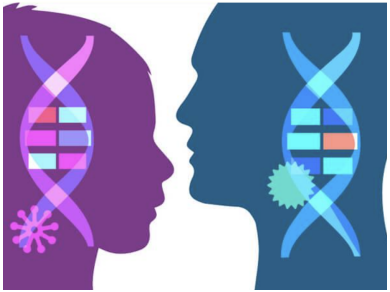
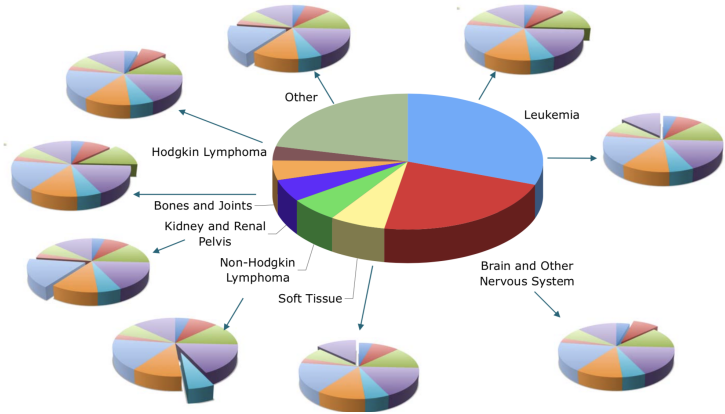


Image: NCI

Challenge: Thankfully, Pediatric Cancer is Rare



Pediatric MATCH: Active Sub-Protocols

Agent Class	Agent	Protocol ID
TRK inhibitor	Larotrectinib	APEC1621-A
FGFR inhibitor	Erdafitinib	APEC1621-B
EZH2 inhibitor	Tazemetostat	APEC1621-C
PI3K/mTOR inhibitor	LY3023414	APEC1621-D
MEK inhibitor	Selumetinib	APEC1621-E
ALK inhibitor	Ensartinib	APEC1621-F
BRAF inhibitor	Vemurafenib	APEC1621-G
PARP inhibitor	Olaparib	APEC1621-H
CDK4/6 inhibitor	Palbociclib	APEC1621-I
ERK1/2 inhibitor	Ulixertinib	APEC1621-J

Update: ASCO 2019[1]

- NCI-Pediatric MATCH opened in July 2017
- More than 420 patients enrolled, 357 patients screened through 2018
- Desired match rate: 10%
  - Actual match rate: 24%!
  - Screening to targeted therapy receipt rate: 10%

....Cohort-specific results forthcoming....

[1] https://www.cancer.gov/news-events/cancer-currents-blog/2019/pediatric-match-targetable-genetic-changes

Other Basket Trials

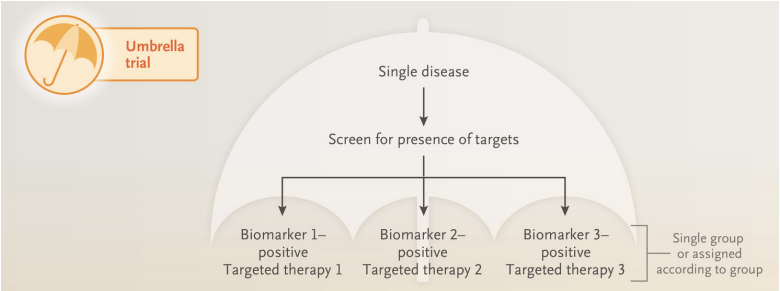
- NCI MATCH (adult version) [1]
- Signature (Novartis) [2]
- AcSe[3]
- CREATE[4]

[1] https://ecog-acrin.org/nci-match-eay131
[2] Kang et al. Clin Pharmacol Ther 2015; 98:124-126
[3] https://clinicaltrials.gov/ct2/show/NCT02304809
[4] http://www.eortc.org/sites/default/files/90101.pdf

Umbrella Trials

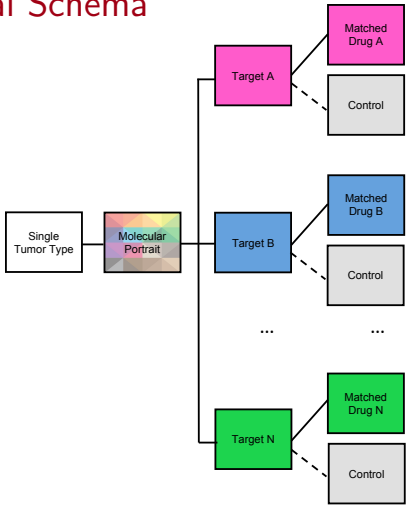
Umbrella Trial: Definition

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



Woodcock and LaVange. NEJM 2017;377:62-70.

Umbrella Trial: General Schema



Umbrella Trial: 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: Defining Features

- Sub-Study Design
  - Often randomized (targeted vs standard) with futility stopping and/or graduation to confirmatory trial
- Sub-Study Objective
  - Identify a large, unambiguous signal of activity that is likely driven by molecular features
- Sub-Study Characteristics
  - Master protocol governs shared screening and operations, sub-studies added or removed over time
  - Useful for testing several promising target-treatment hypotheses within one disease type
  - Larger: 10s to 100s of patients per sub-trial

Umbrella Trial: Advantages

- 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
- Results generally easier to interpret
- Positive result $\rightarrow$ patient population or "label" easier to define

Umbrella Trial: Disadvantages

- Often larger size, particularly when sub-trials are randomized
- Therefore longer duration
- More difficult to fully enroll rare marker sub-trials when limited to a single tumor type
- Susceptible to changes in the "treatment landscape" during the trial
  - E.g., introduction of a new standard of care (may change control arm)

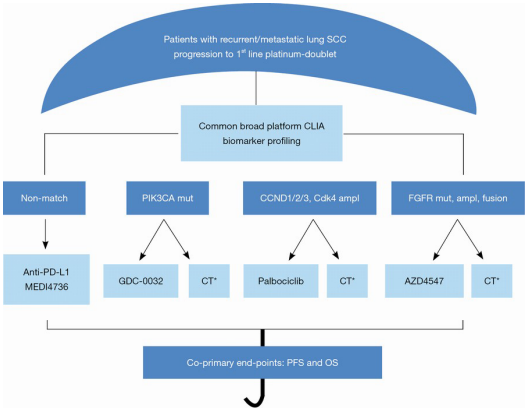
Example: Lung-MAP (SWOG S1400)

- 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

Lung-MAP Schema (Original)



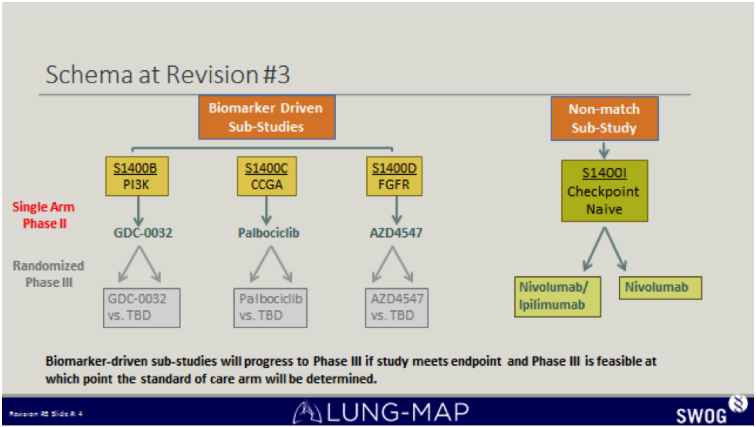
Ferrarotto et al. (2015). *Chin Clin Oncol* 4(3).

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:
  - Control arm dropped in phase II $\rightarrow$ single arm only
  - Non-match arm: single vs. combo immunotherapy
- 2017-2019:
  - First few cohort results published (negative)
  - More cohorts added (PARP inhibitor; VEGF + PD-L1 inhibitors) and others forthcoming
  - Now open to all NSCLC histologies

http://www.lung-map.org

Lung-MAP Revised Schema



Other Umbrella Trials

- ALCHEMIST[1]
- FOCUS4[2]

[1] Gerber et al. ALCHEMIST, Clin Pharmacol Ther 2015; 97: 447-450.
[2] Kaplan R et al. J Clin Oncol 2013; 36: 4562-4570.

Practical Considerations in Basket and Umbrella Trials

- New collaboration paradigm
- Logistics far beyond a single trial
- Trials must adapt to external changes over years, decades
- Reality often messy!

Global Statistical Issues (Hot Topics and Open Research Questions!)

- Cohort, treatment, and marker selection
  - Balancing meaningful effect size vs. feasible sample size
  - Whether/how to study marker "negative" patients
  - Classification of patients with multiple markers or genetic mutations
- Modeling and hypothesis testing
  - Can we borrow statistical information across sub-trials or tumor types?
  - Multiple testing and controlling type I error: when do we need to worry?

The Multiple Testing Question

- Basket, umbrella: multiple hypotheses being tested across marker groups, tumor types, drugs
- When to adjust tests for multiplicity?
- In general, adjust when multiple hypotheses lead to multiple opportunities to inform a single claim of effectiveness for a drug
  - Umbrella trial: usually one test per marker sub-trial with distinct treatment (no adjustment)
  - Basket trial: usually one test per overall marker “”basket” (across tumor types) with a distinct treatment (no adjustment)
  - But do adjust if testing *within* each tumor type of a basket!

Stallard, Todd, Parashar, Kimani, Renfro. On the need to adjust for multiplicity in confirmatory clinical trials with master protocols. Annals of Oncology 30(4): 506-509, 2019

Conclusions

- Biomarker-based designs $\rightarrow$ the path forward in precision medicine
- Will increase in popularity as traditional trials become less feasible and "success stories" accumulate
- Continued need for design solutions to address practical and statistical challenges, e.g., rare molecular subtypes

Thank you!

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