



@ Cancer Research UK Clinical Trials Unit
CRCTU

Introduction to Basket, Umbrella and Platform Designs

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Cancer Research UK Clinical Trials Unit**

NIHR Statistics Group:
Early Phase Clinical Trials Meeting
Birmingham, February 28th 2019

**UNIVERSITY OF
BIRMINGHAM**

Methodology for Stratified Medicine

More **stratified** than **precision or personalised**:
sub-classification of patient according to tumour
molecular profile to maximise chance of potential
treatment benefit for the individual patient

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
2018, VOL. 28, NO. 2, 217–228
<https://doi.org/10.1080/10543406.2017.1372778>



Definitions and statistical properties of **master protocols** for
personalized medicine in oncology

Lindsay A. Renfro and Sumithra J. Mandrekar

Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

Umbrella

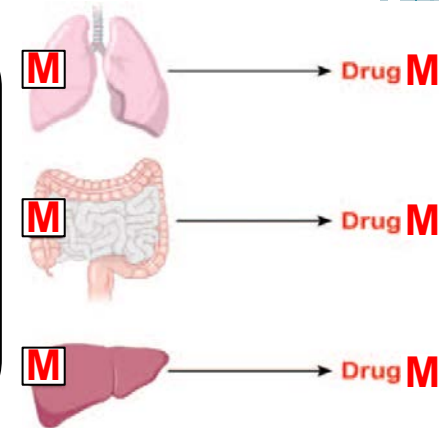
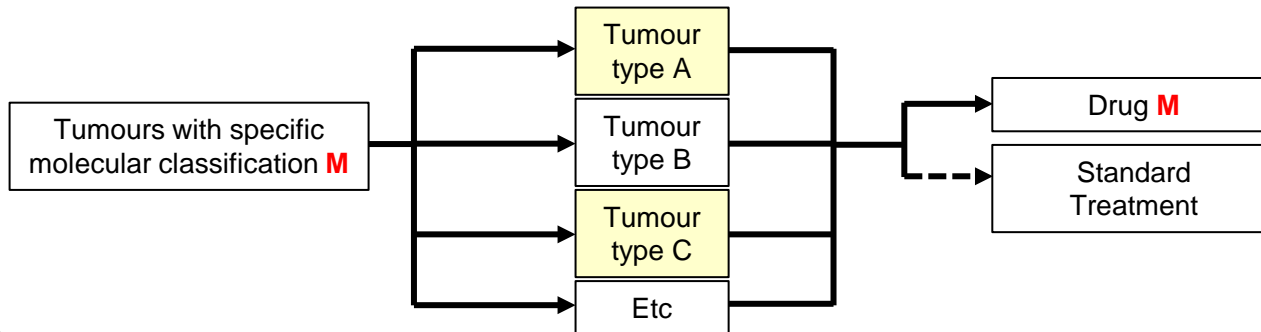
Basket

Platform

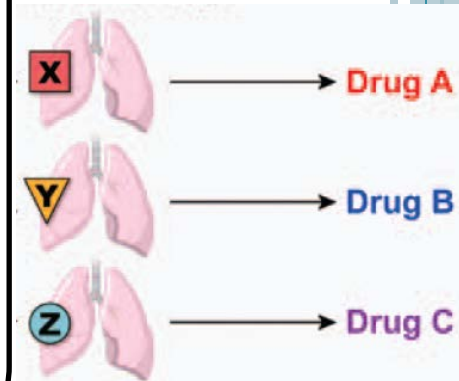
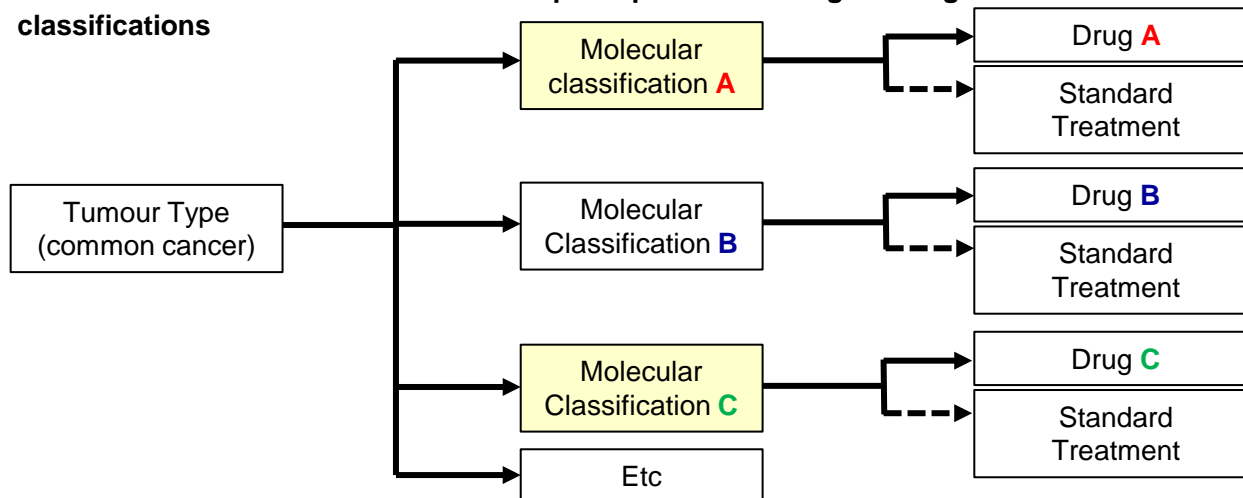
‘Any top-level or overarching clinical trial protocol
that comprises several parallel biomarker-based or
genomically-based sub-trials or cohorts

Basket, Umbrella and Platform Trials

Basket trial to evaluate experimental drug in tumours with specific molecular classification

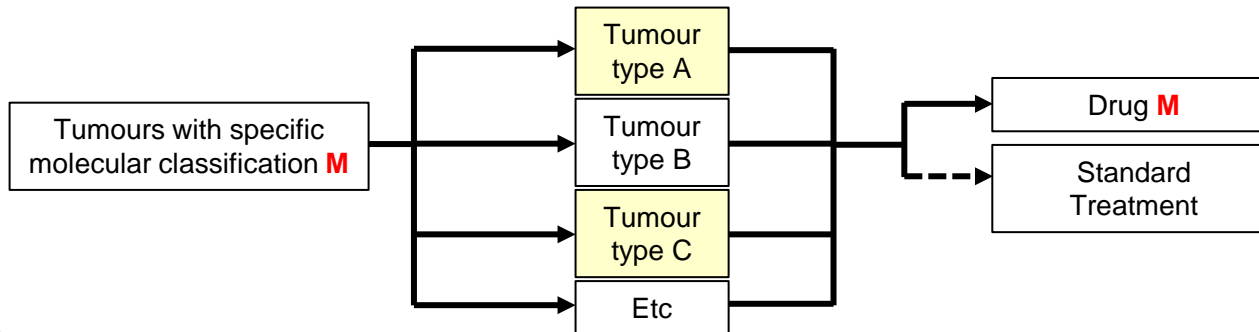


Umbrella trial to evaluate multiple experimental drugs in range of molecular classifications



Basket, Umbrella and Platform Trials

Basket trial to evaluate experimental drug in tumours with specific molecular classification



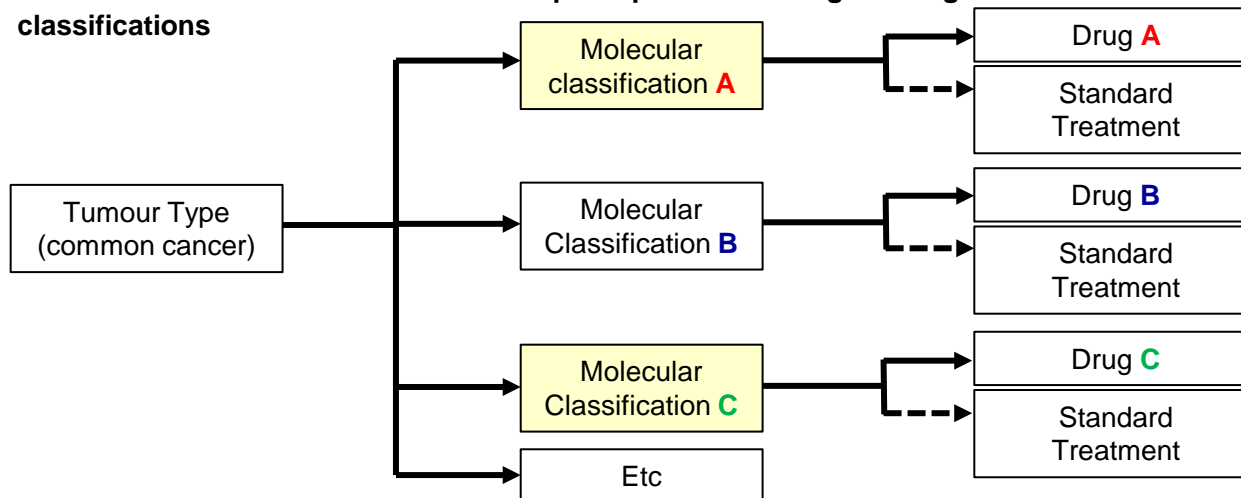
Platform trial

Parallel cohorts are dynamic rather than fixed

Subtrials can exit at any time due to futility or completion

New subtrials can enter at any time – new molecular classifications and/or drugs

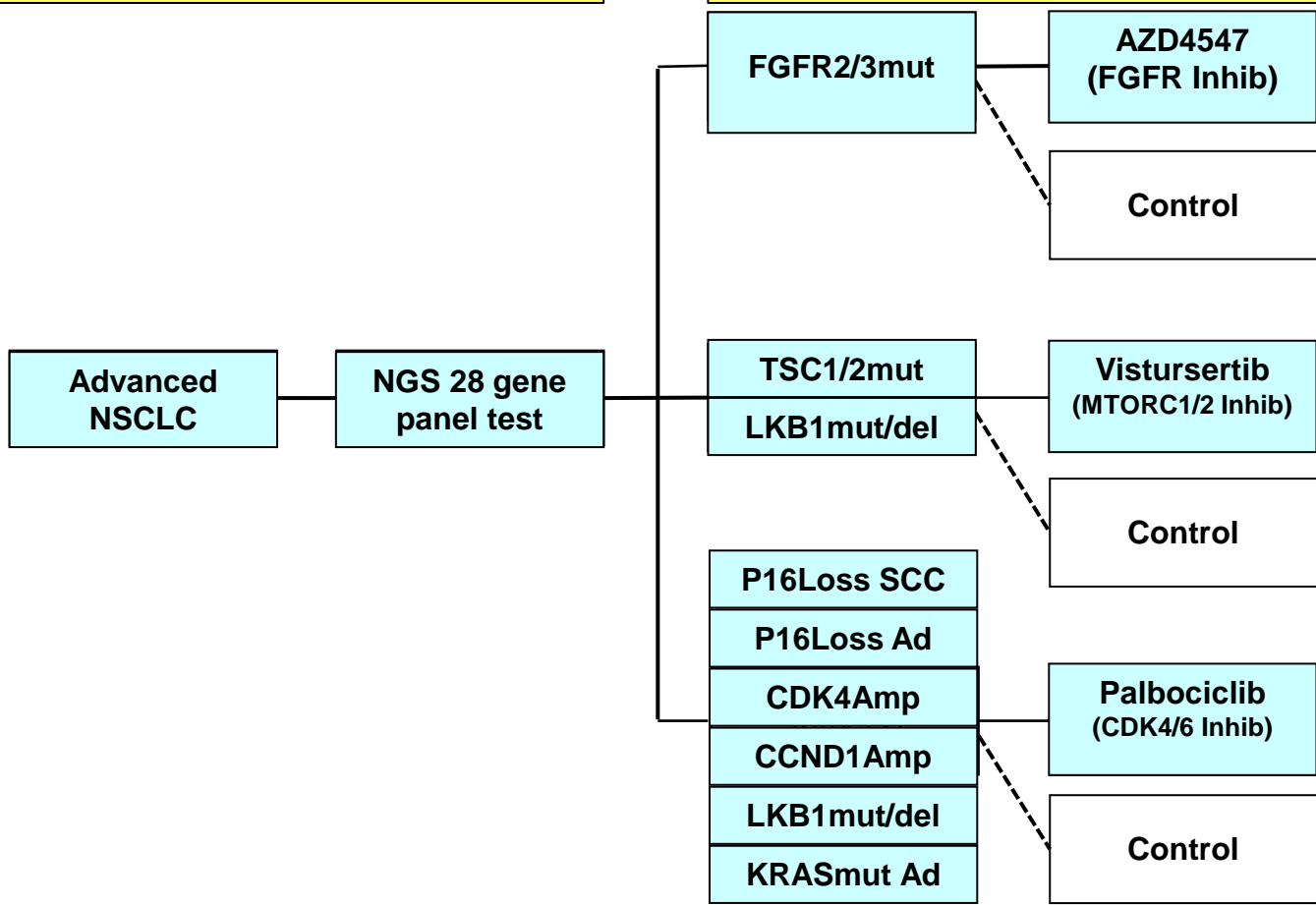
Umbrella trial to evaluate multiple experimental drugs in range of molecular classifications



National Lung Matrix Trial: An Example of an Early Phase Umbrella/Basket Trial

**Stratified Medicine
Programme 2**

**National Lung
Matrix Trial**

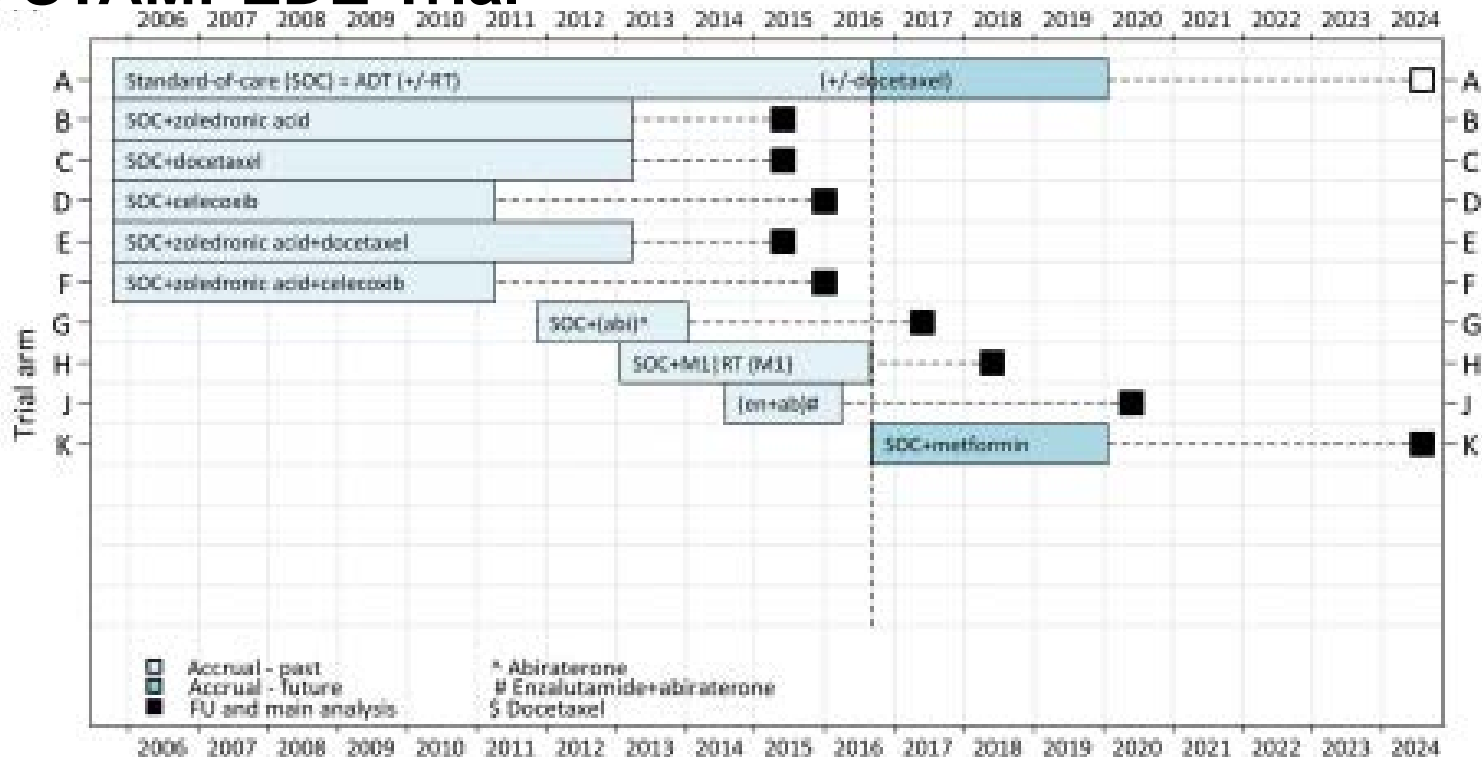


Etc → 21 drug-biomarker cohorts

Testing many treatments within a single protocol over 10 years at MRC CTU at UCL: Multi-arm, multi stage platform, umbrella and basket protocols

Mahesh KB Parmar, Matthew R Sydes, Fay H Cafferty, Babak Choodari-Oskoei, Ruth E Langley, Louise Brown, Patrick PJ Phillips, Melissa R Spears, Sam Rowley, Richard Kaplan, Nicholas D James, Timothy Maughan, Nicholas Paton, and Patrick J Royston

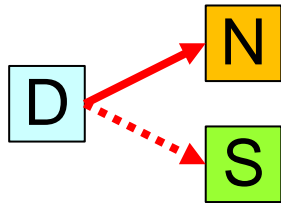
STAMPEDE Trial



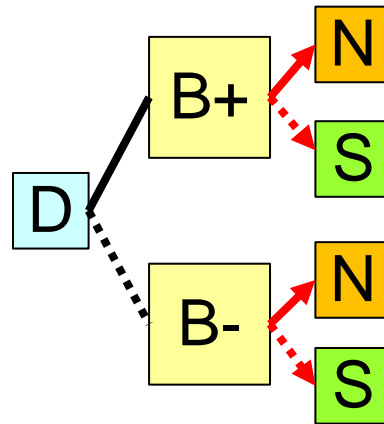
Categorising Trial Designs

- **Diseases:** single or multiple diseases
- **Biomarkers** - population stratified by:
 - No biomarkers
 - Single biomarker
 - Multiple biomarkers
 - Include biomarker negative
- **Experimental treatments:**
 - Single or multiple
 - Comparison multiple against each other
 - Comparison against control
 - Parallel evaluations
- **Other aspects:** phase, adaptive, platform

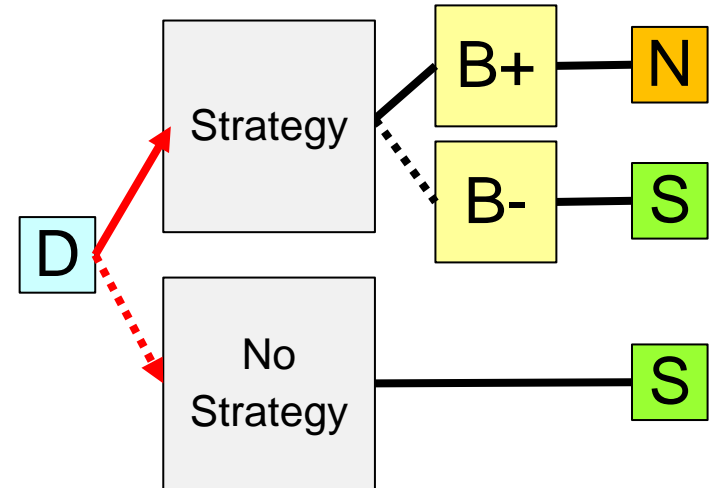
Design Terminology in The Old Days



**Randomised
Controlled Trial
(RCT)**

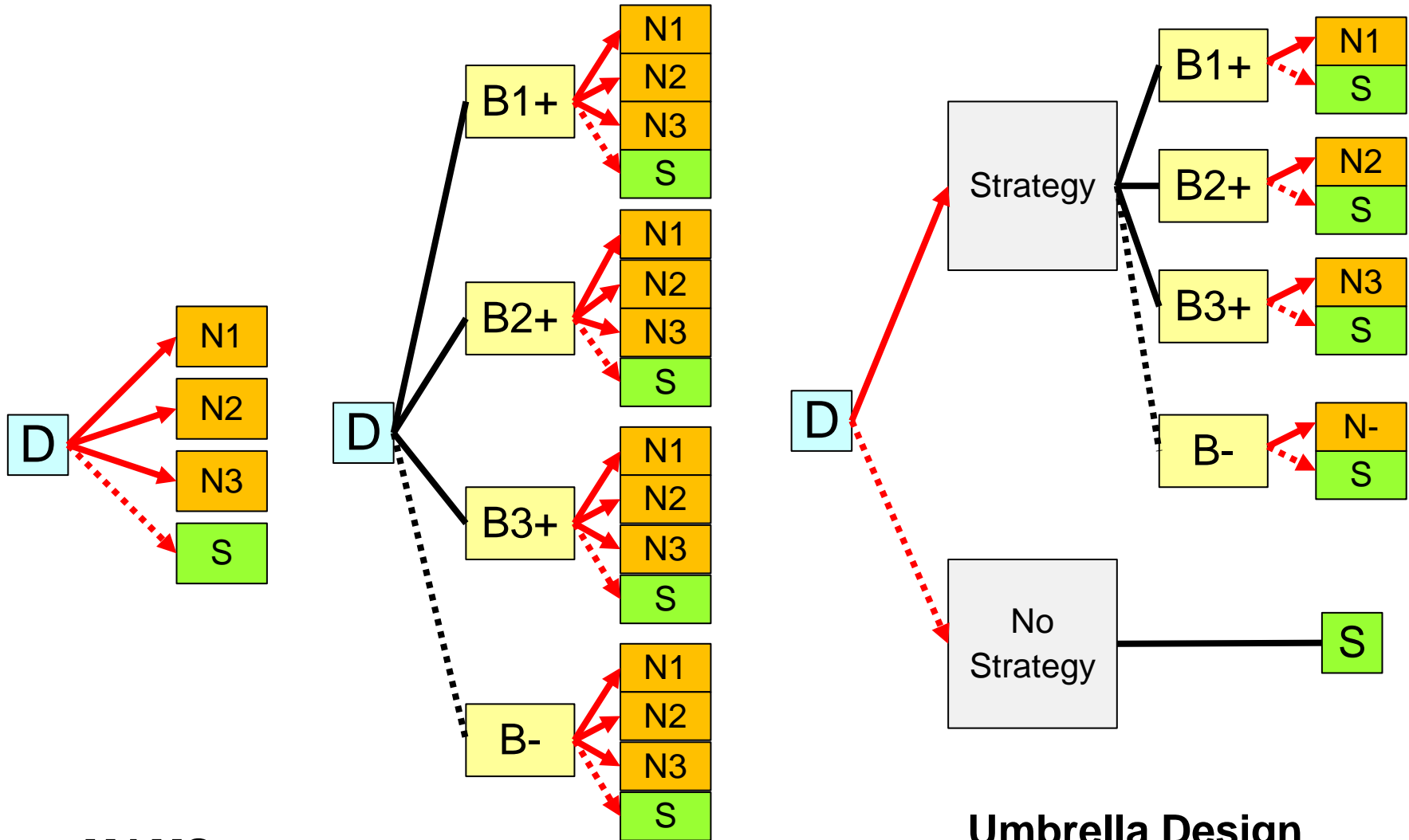


**Biomarker
Stratified Design**
(enrichment /
biomarker-treatment
interaction)



**Biomarker
Strategy
Design**

Extensions For Multiple Treatments & Biomarkers



MAMS

**Biomarker Stratified
MAMS Design
(e.g. BATTLE)**

**Umbrella Design
(e.g. National Lung
Matrix, FOCUS4)
BIRMINGHAM**



Example: The BATTLE Trial

Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination
Kim ES et al Cancer Discovery 2011; Zhou et al Clinical Trials 2008

Population: Non-Small Cell Lung Cancer (pre-treated)

Core needle biopsy of tumour

Biomarker measurement

- EGFR mutation / copy number
- KRAS/BRAF mutation
- VEGF/VEGFR-2 expression
- RXRs/Cyclin D1 expression and CCND1 copy number
- None

Equal RANDOMISATION followed by ADAPTIVE RANDOMISATION

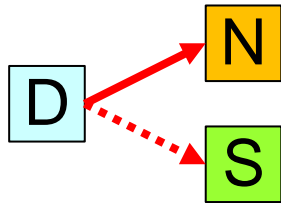
Erlotinib

Vandetanib

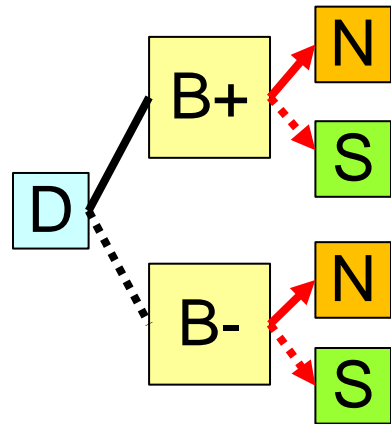
Erlotinib +
Bexarotene

Sorafenib

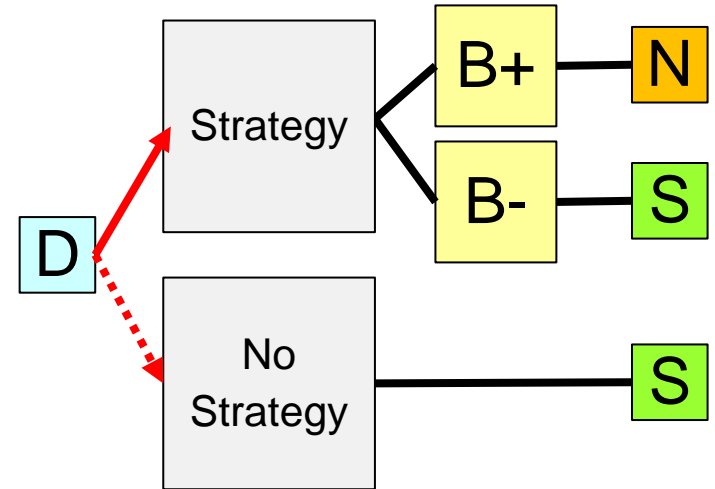
Design Terminology in The Old Days



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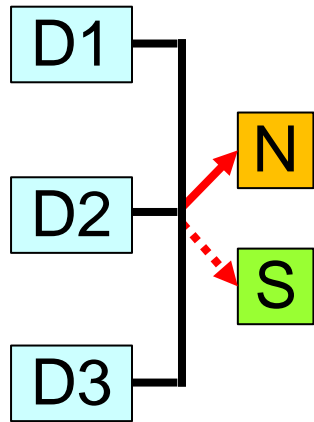


**Biomarker
Stratified Design**
(enrichment /
biomarker-treatment
interaction)

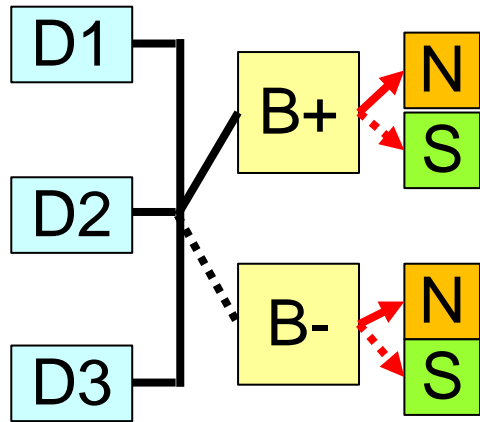


**Biomarker
Strategy
Design**

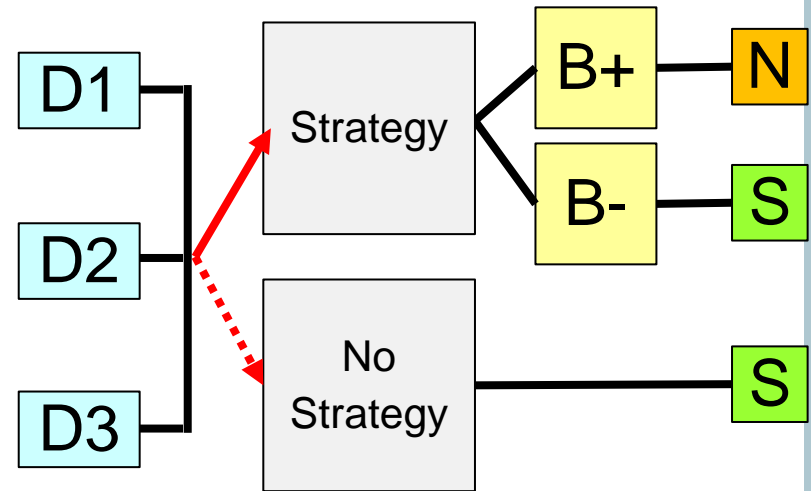
Extensions for Multiple Diseases



**Stratified RCT
across a basket
of diseases**



**Biomarker
Stratified Design
across basket of
diseases**



**Biomarker
Strategy Design
across basket of
diseases**

Results: combined vs individual vs hierarchical

NCI-MATCH: umbrella trial in basket of tumours

Advanced solid tumours and lymphoma (breast, colon, lung prostate) and aiming for 25% rare (e.g. eye, ureter, pituitary gland)

Arm / Target	Drugs(s)	Arm / Target	Drug(s)
A EGFR mut	Afatinib	R BRAF nonV600	Trametinib
B HER2 mut	Afatinib	S1 NF1 mut	Trametinib
C1 MET amp	Crizotinib*	S2 GNAQ/GNA11	Trametinib
C2 MET ex 14 sk	Crizotinib*	T SMO/PTCH1	Vismodegib
E EGFR T790M	AZD9291	U NF2 loss	Defactinib
F ALK transloc	Crizotinib	V cKIT mut	Sunitinib
G ROS1 transloc	Crizotinib	W FGFR1/2/3	AZD 4547*
H BRAF V600	Dabrafenib+trametinib	X DDR2 mut	Dasatinib
I PIK3CA mut	Taselisib	Y AKT1 mut	AZD 5363*
N PTEN mut	GSK2636771	Z1A NRAS mut	Binimetinib*
P PTEN loss	GSK2636771	Z1B CCND1,2,3 amp	Palbociclib*
Q HER 2 amp	Ado-trastuzumab emtansine	Z1D dMMR	Nivolumab*

*Pending approval

Everyone wants to do them!

Everyone is learning on the job!

- MRC Hubs Workshop
- Cancer Drug Development Forum
- NCRI Cancer Conference
- CRUK Honest Forum
- Consensus paper on 'Complex Innovative Designs'
- MRC Clinical Trials Unit, London