Histology independent drug development – is this the future for cancer drugs?

Trial Design – Basket or Umbrella for Optimal Progress: Academic Perspective

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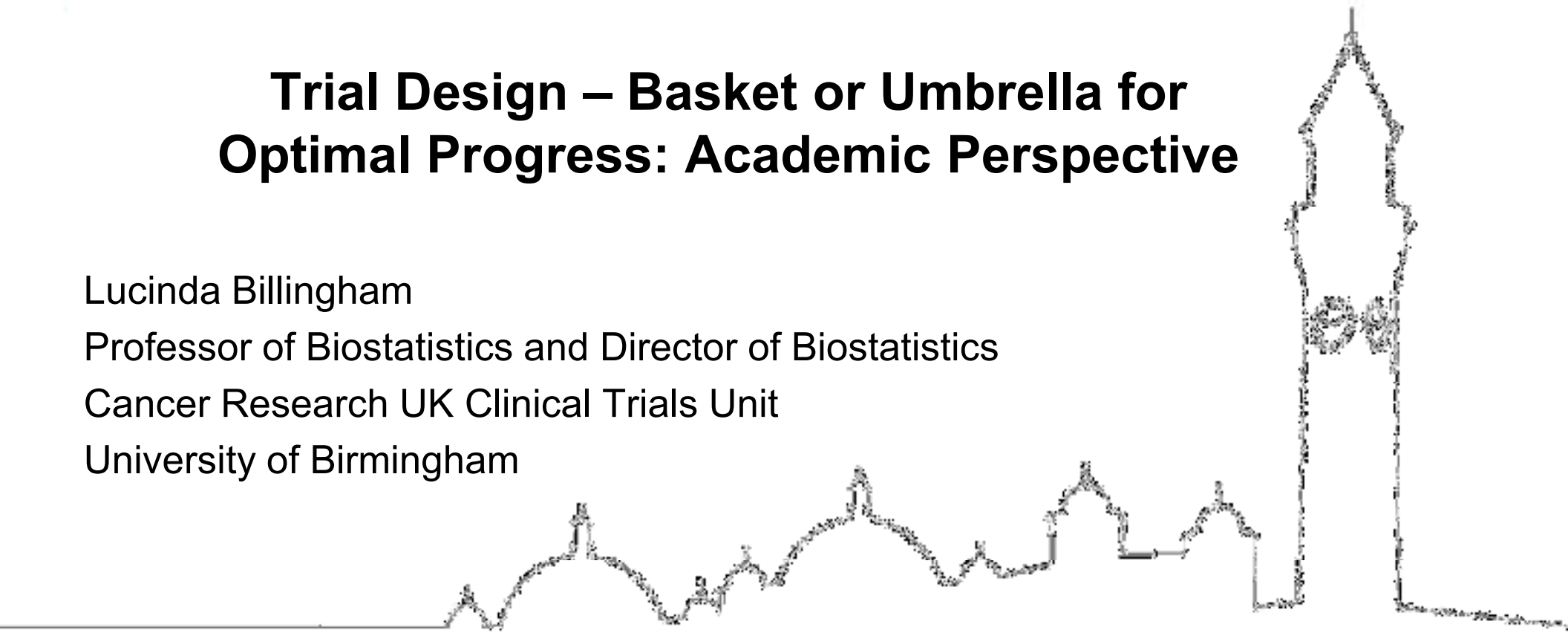

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Terminology: Complex Innovative Design (CID)

BJC British Journal of Cancer

www.nature.com/bjc

CONSENSUS STATEMENT

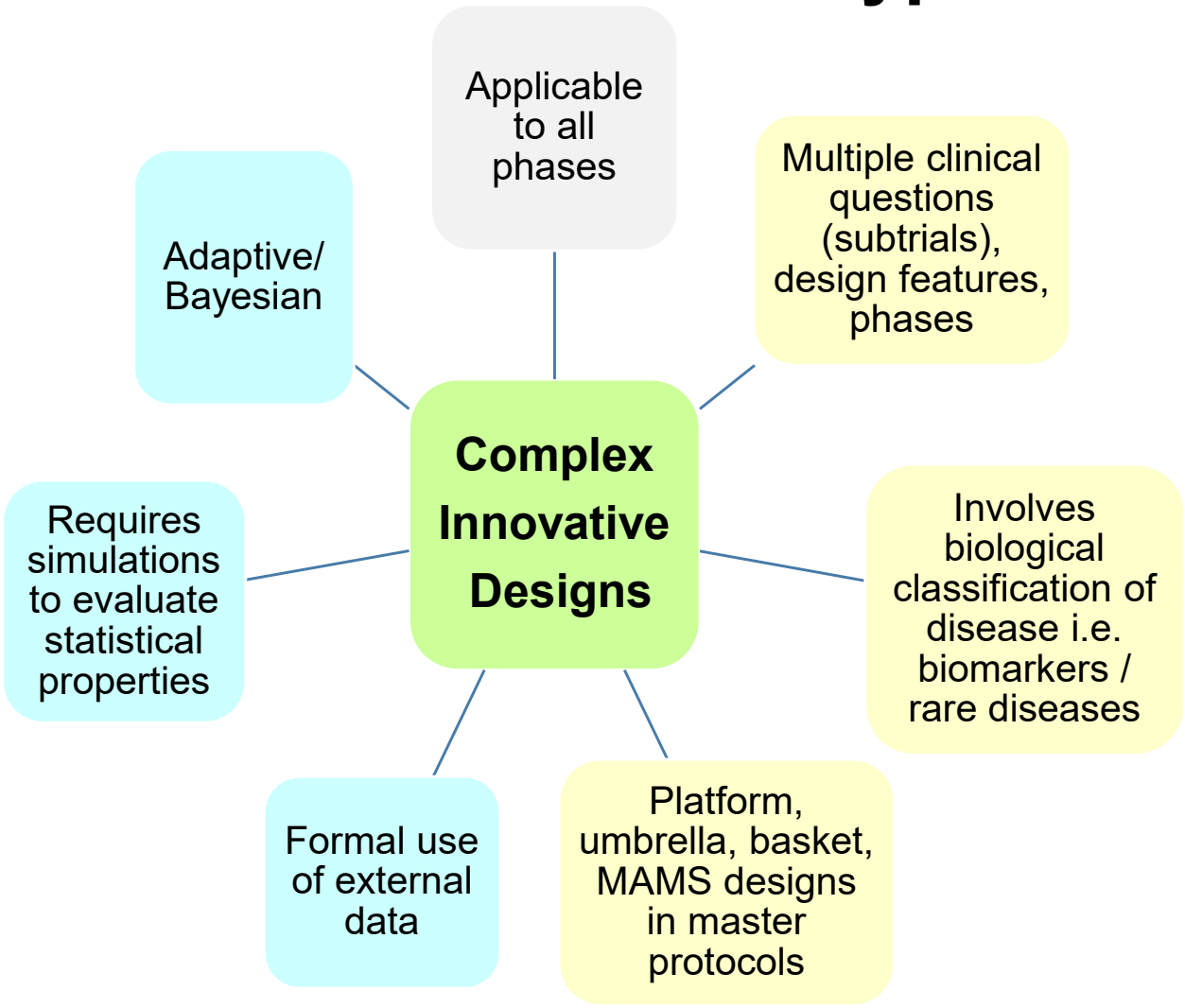
Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement

Sarah P. Blagden[1], Lucinda Billingham[2], Louise C. Brown[3], Sean W. Buckland[4], Alison M. Cooper[5], Stephanie Ellis[6], Wendy Fisher[7], Helen Hughes[8], Debbie A. Keatley[9], Francois M. Maignen[10], Alex Morozov[11], Will Navaie[6], Sarah Pearson[12], Abeer Shaaban[13], Kirsty Wydenbach[14], Pamela R. Kearns[2,15], on behalf of the Experimental Cancer Medicine Centres (ECMC) CID trials working group

The traditional cancer drug development pathway is increasingly being superseded by trials that address multiple clinical questions. These are collectively termed Complex Innovative Design (CID) trials. CID trials not only assess the safety and toxicity of novel anticancer medicines but also their efficacy in biomarker-selected patients, specific cancer cohorts or in combination with other agents. They can be adapted to include new cohorts and test additional agents within a single protocol. Whilst CID trials can speed up the traditional route to drug licencing, they can be challenging to design, conduct and interpret. The Experimental Cancer Medicine Centres (ECMC) network, funded by the National Institute for Health Research (NIHR), Cancer Research UK (CRUK) and the Health Boards of Wales, Northern Ireland and Scotland, formed a working group with relevant stakeholders from clinical trials units, the pharmaceutical industry, funding bodies, regulators and patients to identify the main challenges of CID trials. The working group generated ten consensus recommendations. These aim to improve the conduct, quality and acceptability of oncology CID trials in clinical research and, importantly, to expedite the process by which effective treatments can reach cancer patients.

British Journal of Cancer https://doi.org/10.1038/s41416-019-0653-9

Basket and Umbrella Trials: Types of CID



Basket Trials: Key Design for Histology-Independent Drug Evaluation

Multiple disease types with a common biological driver

Subtrials

Disease Type A
Disease Type B
Disease Type C
Disease Type D

Single drug X that targets the common biological driver

Generally non-randomised single arm designs

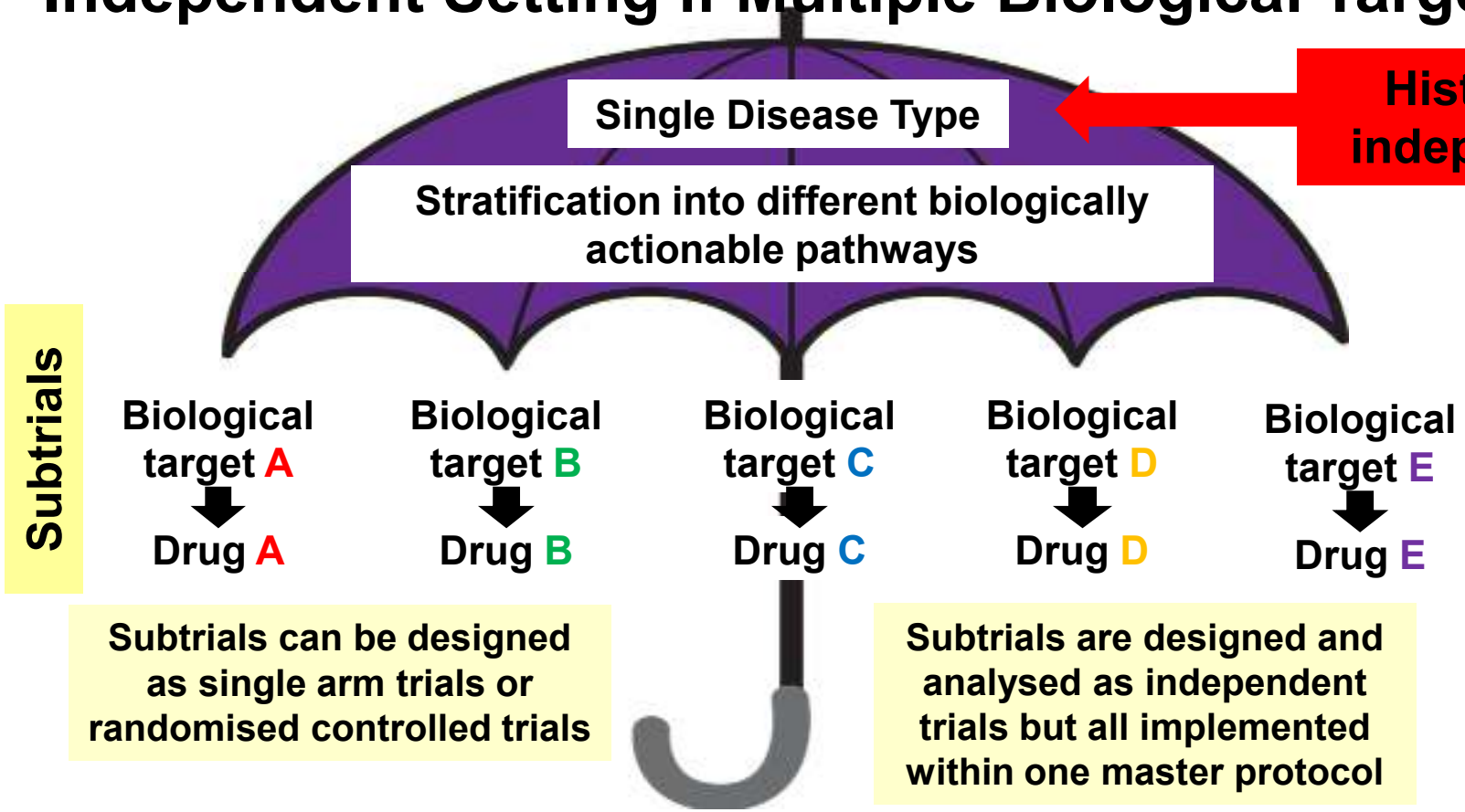
Often in advanced disease

Often aim to extend indications for drugs already proven beneficial

Platform trial: Parallel subtrials are dynamic rather than fixed; subtrials can exit at any time due to futility or completion; new subtrials can enter at any time

MASTER PROTOCOL

Umbrella Trials: Could be Applicable for Histology-Independent Setting if Multiple Biological Targets



Challenges of Planning Basket Trial Analysis

Independent analysis of each histology

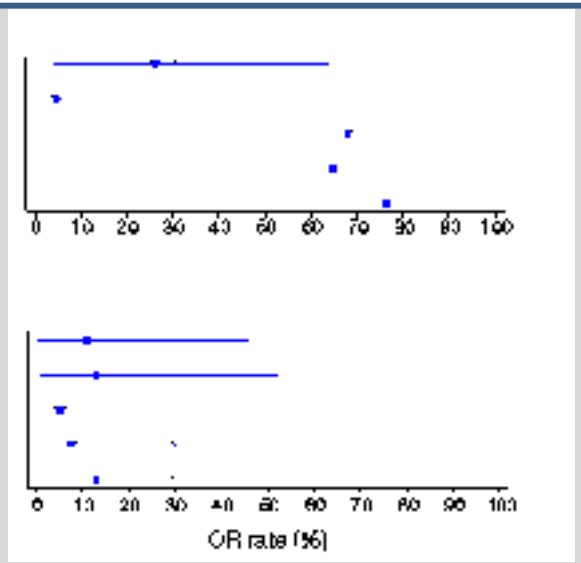
Inefficient if homogeneous

Assess homogeneity and pool or partially pool as appropriate

Hierarchical modelling: 'borrowing information' across different cohorts

Pooled (or stratified) analysis of whole trial

Inefficient if heterogeneous



Middleton et al; National Lung Matrix Trial; Nature 2020

DETERMINE – a collaborative effort

(aDvancing gEnomically maTchEd tReatMents IN rare cancErs)

The DETERMINE team is comprised of multiple experienced clinicians and researchers that will be working closely with CRUK and its various partner organisations

Key individuals

Dr Krebs
CI/Clinical lead

Dr Marshall
Paediatric lead

Prof Middleton
Translational lead

Prof Billingham
Stats lead

Dr Chaturvedi
Pathologist

Miss Gath & Mr Burchill
Patient representatives

Key organisations

Sponsor and Commercial

Trial delivery

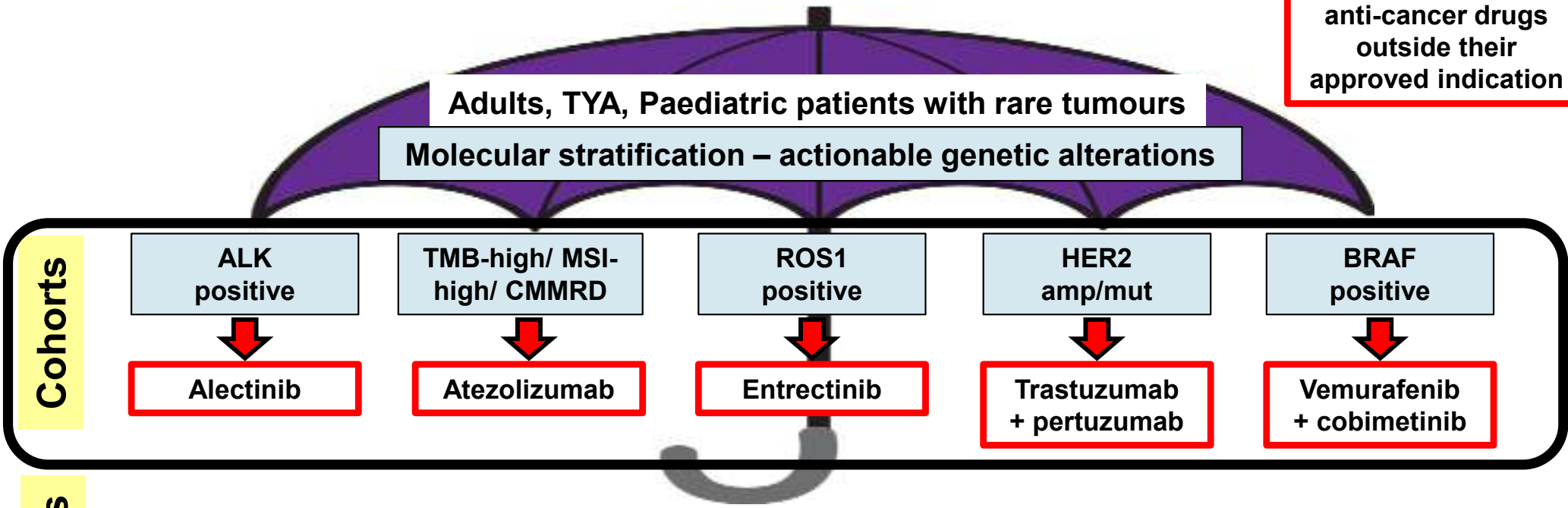
Clinical trial experience
Translational research (ctDNA, genomics)
Co-Investigators / Collaborators

Plus additional Pharma partners

CDF

DETERMINE: Umbrella-Basket Platform Trial

Licensed, targeted anti-cancer drugs outside their approved indication



Sub-Cohorts

Cancer types
Age groups
Genetic complexity

DETERMINE: Statistical Design for Whole Cohort in Each Treatment Arm : Single Arm Phase III

Statistics in Medicine

Research Article

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(wileyonlinelibrary.com) DOI: 10.1002/sim.7338

BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints

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DCB: durable clinical benefit – absence of disease progression for at least 24 weeks

- Co-primary outcomes: **OR / DCB**
- Level below which treatment is unacceptable = **10%**
- Level at which we want trial to have a high chance of correctly claiming that the treatment is acceptable = **30%**
- Prior: **Beta (0.1, 0.9)**
- Type I error rate = **0.1 (one-sided)**
- Final analysis at: **N=30**
- Interims at: **N=10,15,20,25**
- Beta-binomial conjugate analysis
- BOP2 design gives power **0.89**

DETERMINE: Decision-Making for Whole Cohorts at Interim and Final Analyses

BOP2 Design: Bayesian-adaptive approach

Guidelines for decision-making based on number of observed OR / DCB

Patients with rare tumours

Cohort X

(mutation X/drug X)

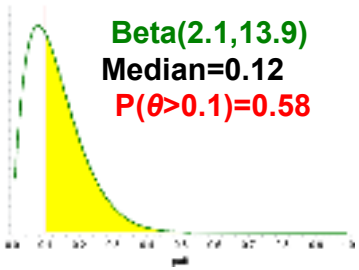
n=10	n=15	n=20	n=25	Final N=30
0	≤1	≤2	≤3	**≤5**
1+	2+	3+	4+	**6+**

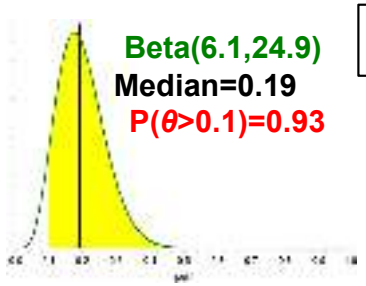
If single cohort then close cohort

If single cohort then GO or expand whole cohort

Keep recruiting into whole cohort

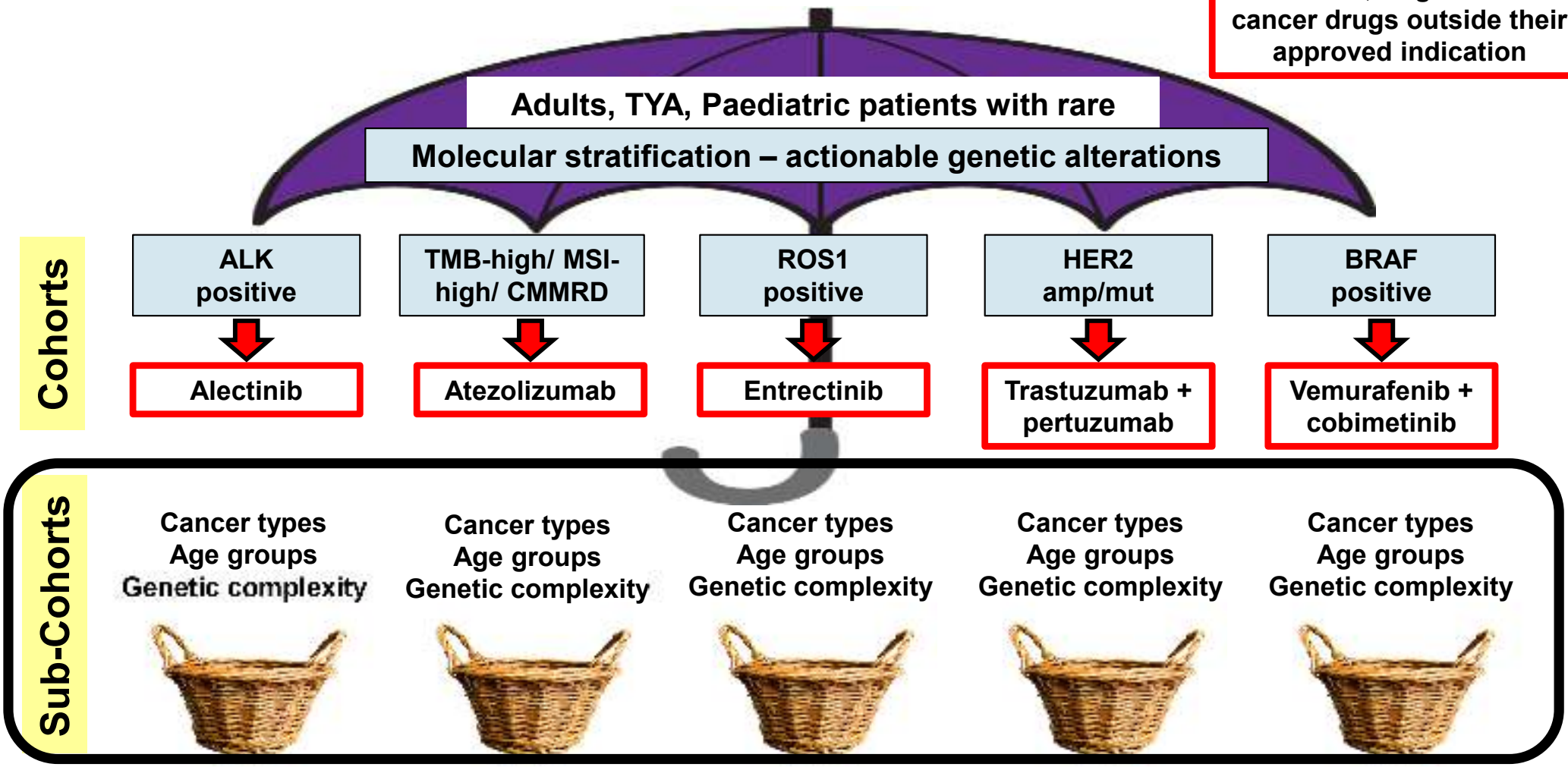
Cancer Drugs Fund (CDF)





DETERMINE: Umbrella-Basket Platform Trial

Licensed, targeted anti-cancer drugs outside their approved indication



DETERMINE: Decision-Making on Whole Cohorts and Sub-Cohorts at Interim and Final Analyses

BOP2 Design: Bayesian-adaptive approach

Guidelines for decision-making based on number of observed OR / DCB

Patients with rare tumours

Cohort X (mutation X/drug X)

Sub-cohorts: cancer types, age groups, genomic complexity

n=10	n=15	n=20	n=25	Final N=30
0	≤1	≤2	≤3	**≤5**
1+	2+	3+	4+	**6+**

If single cohort then close cohort

If >1 sub-cohort then consider continuation of sub-cohorts

If single cohort then GO or expand whole cohort

If >1 sub-cohort then consider expanding specific sub-cohorts

Keep recruiting into whole cohort

If >1 sub-cohort then consider sub-cohort heterogeneity

Cancer Drugs Fund (CDF)

Sub-cohort decisions:
Predicted Probability of Success (PPoS) = p (GO decision at N=30 | current data, prior)

Exploring Sub-Cohorts at Interim Analysis: Example

	Cohort X	Sub-Cohort X1	SubCohort X2
N	10	N/A	N/A
OR	1	N/A	N/A
Cohort Decision	GO	N/A	N/A
Sub-Cohort Decision		N/A	N/A
N	15	10	5
OR	4	0	4
Cohort Decision	GO		
PPoS		0.0025	0.9993
Sub-Cohort Decision		STOP	GO

*** Note: if design had used critical threshold > 10% then cohort X would have terminated at N=10, missing opportunity to discover benefit in X2**

Exploring Sub-Cohorts at Final Analysis: Example

	Cohort Y	Sub-Cohort Y1	Sub-Cohort Y2
N	30	20	10
OR	6	2	4
Cohort Decision	GO		
PPoS		0.035	0.972
Sub-Cohort Decision		STOP	GO

Keep recruiting?

Exploring Sub-Cohorts at Final Analysis: Example

	Cohort Z	Sub-Cohort Z1	Sub-Cohort Z2
N	30	20	10
OR	16	8	8
Cohort Decision	GO		
PPoS		1	1
Sub-Cohort Decision		GO	GO

Cancer Drugs Fund

Conclusions and Final Thoughts for Discussion

- Basket trial designs allow histology-independent evaluation of drugs (may also involve an umbrella trial design)
- Bayesian approaches will give greatest level of flexibility for adaptive designs and maximise the utility of the data
- Need to decide a priori on statistical analysis plan:
  - Pooled / stratified analysis of whole basket
  - Analysis of each sub-cohort within the basket – independent or borrowing information
  - Borrowing information may not always be straightforward
- Sub-cohort analysis in DETERMINE is difficult to plan
  - Unknown number, prevalence and recruitment rate for sub-cohorts
  - Decisions based on co-primary outcome measures