Problématique statistique des essais baskets et umbrella

Stefan Michiels, PhD
Head of Oncostat team, CESP, INSERM U1018,
Chef de Service de Biostatistique et d'Epidémiologie,
Gustave Roussy, Université Paris-Sacla, Villejuif, France
stefan.michiels@gustaveroussy.fr

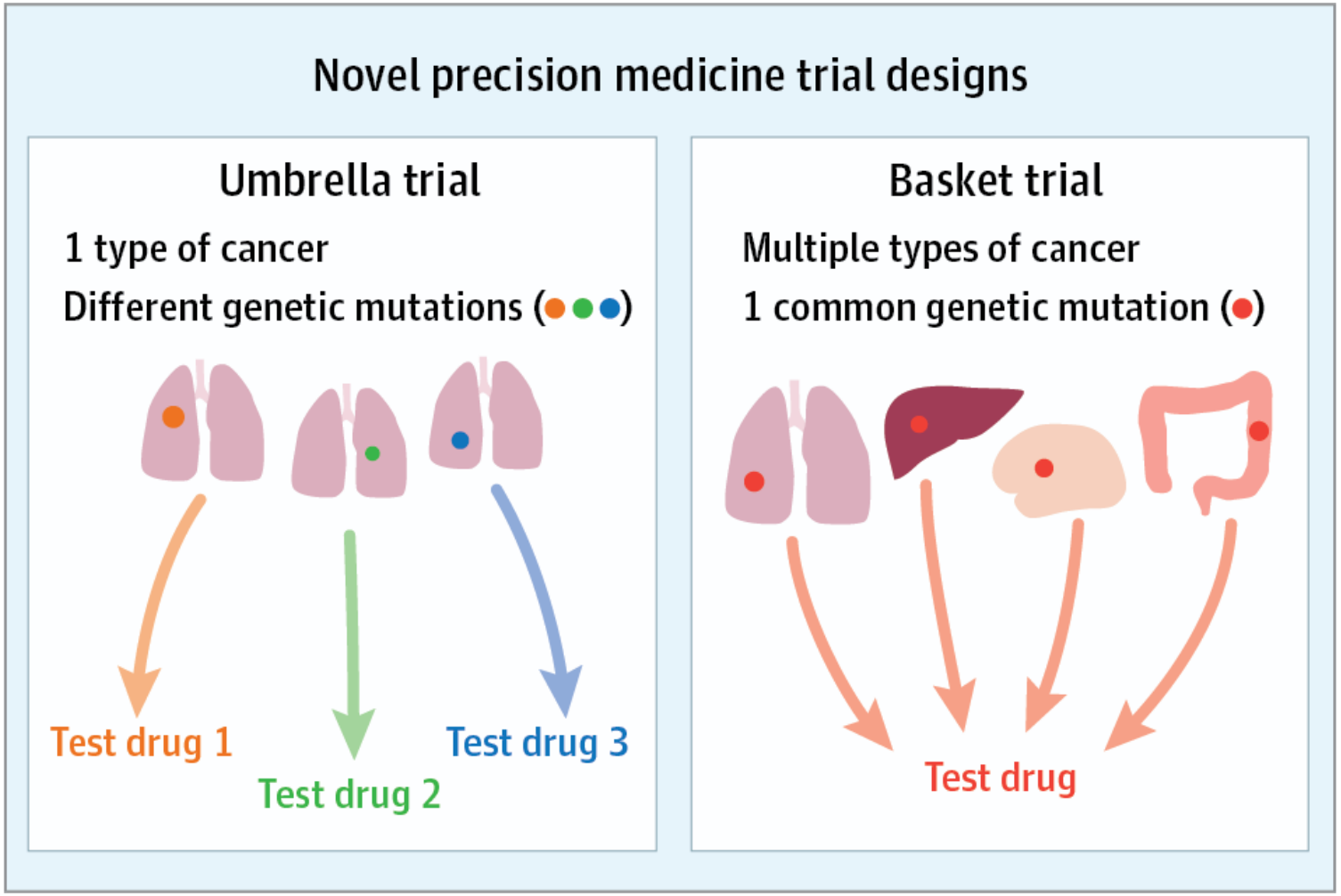
>10 years ago: types of biomarker-based trials

Table 2. Trial designs using biomarkers.

Trial phase	Treatment	Biomarker type	Validated biomarker	Trial design	Examples
	Standard	Prognostic	No	Retrospective series	MammaPrint™ in early breast cancer Oncotype DX® in early breast cancer
	Standard	Predictive	No	Retrospective analyses of randomized trials	Oncotype DX in early breast cancer (SWOG-8814) *KRAS* mutations in advanced colorectal cancer (CRYSTAL) *EGFR* mutations in non-small-cell lung cancer (IPASS)
III	Standard	Prognostic	No	Clinical utility	MINDACT in early breast cancer TAILORx in early breast cancer
III	Standard	Predictive	No	Randomize-all Interaction Biomarker strategy	MARVEL in non-small-cell lung cancer P53 in advanced breast cancer ERCC1 in non-small-cell lung cancer
II	Experimental	Predictive	Yes	Targeted Bayesian	Herceptin in advanced breast cancer BATTLE in non-small-cell lung cancer I-SPY 2 in advanced breast cancer
III	Experimental	Predictive	Yes	Targeted	PETACC-8 in advanced colorectal cancer TOGA in advanced gastric cancer
II	Experimental	Predictive	No	Adaptive parallel Tandem two-step TTP ratio	Dovitinib in HER2-negative advanced breast cancer Saracatinib in pancreatic cancer Molecular profiling in various tumor types
III	Experimental	Predictive	No	Enrichment Prospective subset	IPASS in non-small-cell lung cancer SATURN in non-small-cell lung cancer

TTP: Time to progression.

Buyse, Michiels et al, Expert Rev Mol Diag 2011



West Jama Oncol 2017

Today's Glossary

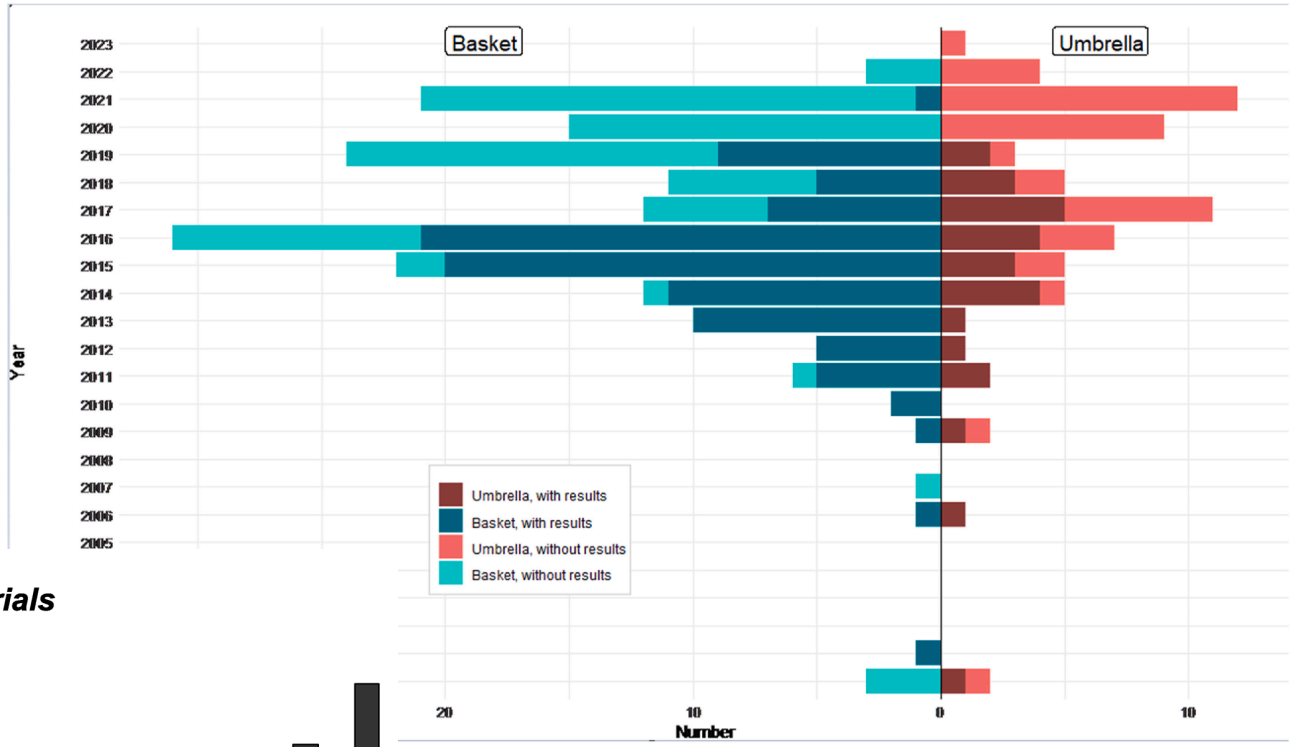
Master protocol : Single overarching design in which parallel multiple clinical "trials" with different hypotheses are performed

Basket trial : Biomarker-based (randomised or not) clinical trial that includes multiple histologies investigating a therapeutic intervention, such as a drug or a drug combination targeting a specific molecular aberration across different cancer types.

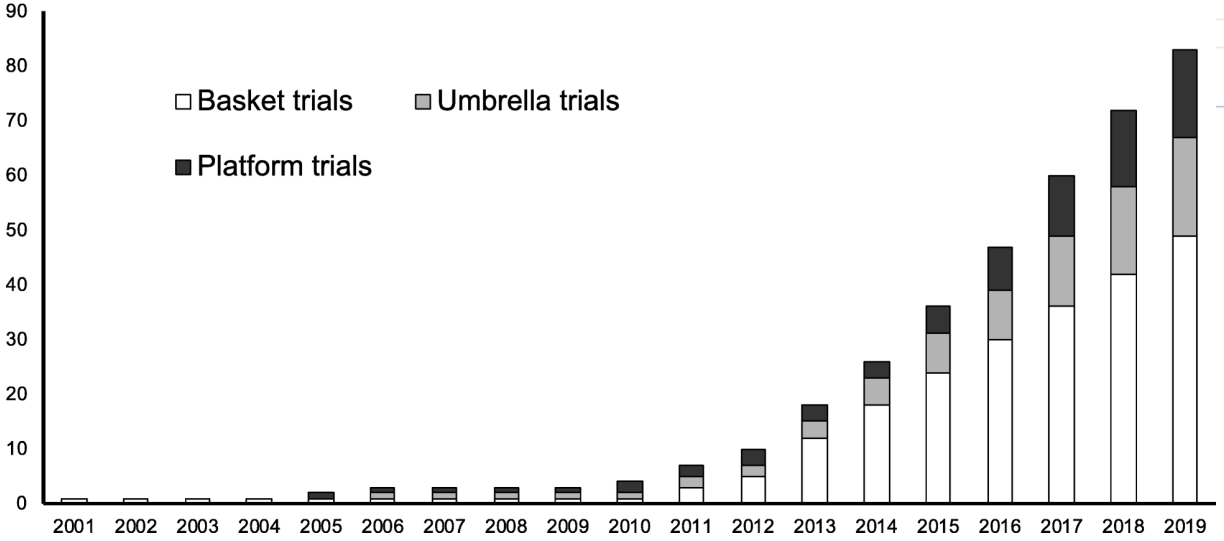
Umbrella Trial : Biomarker-based (randomised or not) clinical trial that is histology-specific investigating different therapeutic interventions, such as different drugs or drug combinations, matched to different molecular aberrations in a single cancer type.

Platform trials : allow flexible addition of new treatment arms or patient subgroups, often multi-arm multistage trials. Can be "perpetual"!

ESMO Precision Medicine Glossary Ann Onc 2018; Park et al Trials 2019



Number of Master Protocols over Time:
Basket Trials, Umbrella Trials, and Platform Trials

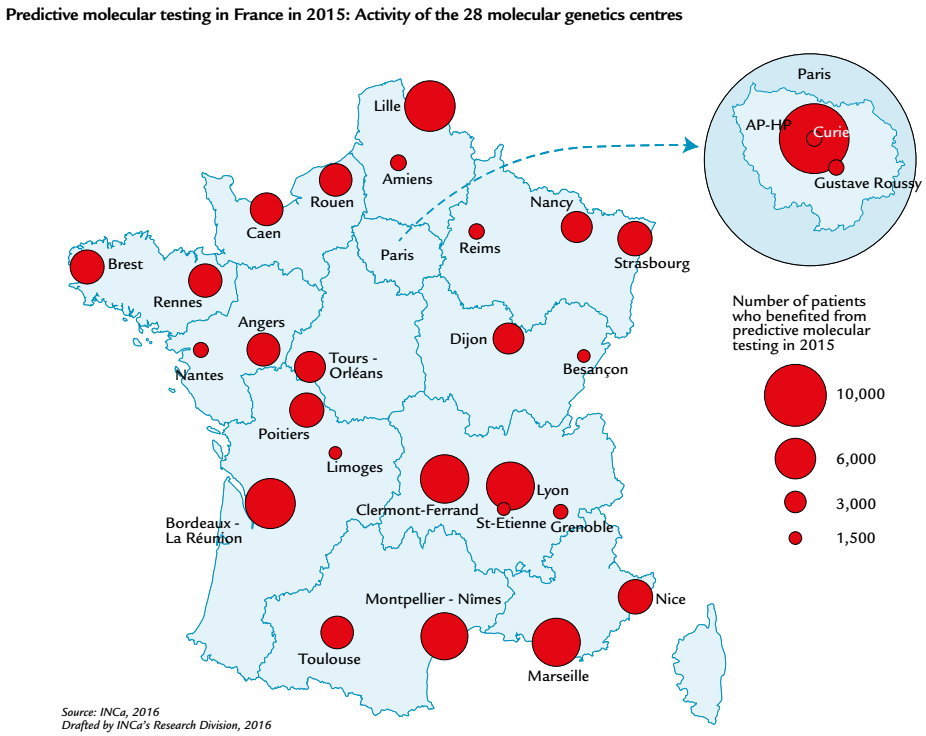


Park et al Trials 2019;
Haslam et al EJC 2023

A basket trial in France: Acsé

- AcSé crizo (launched in 2013) : a multi-basket phase II trial of crizotinib across cancer types, using molecular screening platforms labeled by the national cancer institute (INCa)

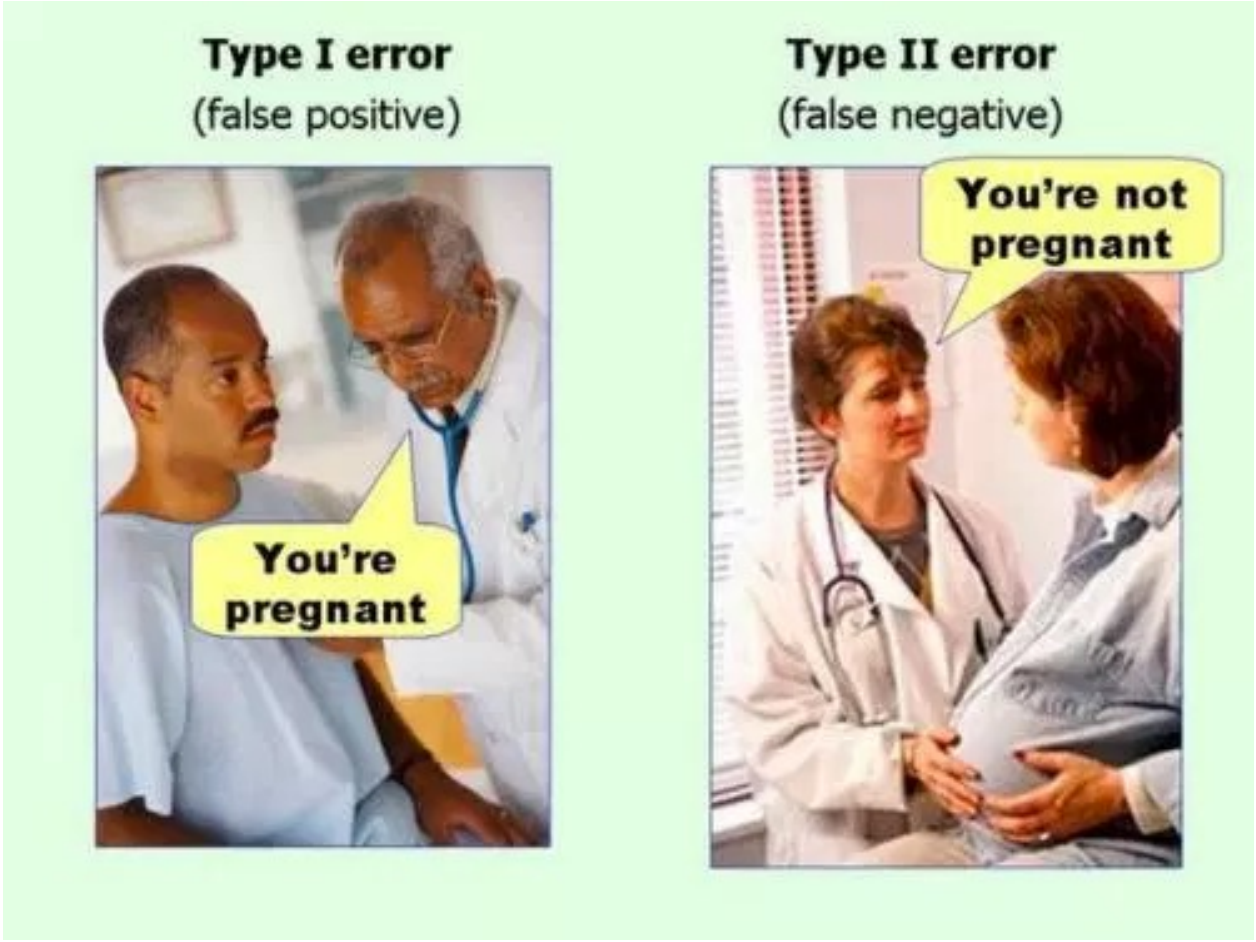
Clinical trial information: NCT02034981



- Analysis can be performed in a frequentist or in a bayesian fashion
- Baskets can be treated independently or information can be shared across baskets

Berry Clin Trials 2013, Cunanan Stat Med 2017; Hobbs Stat med 2018; Chu Clin Trials 2018; Nan SMMR 2022; Zheng Biostatistics 2022

Remember the statistician's nightmare



- Type I and II errors for treatments
- Type I and II errors for biomarkers

Ellis, *http://www.effectsizefaq.com*

Use of basket trials in oncology

Number of studies (up to early 2022)	180
Number of study participants, median (IQR)	94 (47, 242)
Phase, n (%)	
I	18 (10.0)
I/II	30 (16.7)
II	131 (72.8)
Not indicated	1 (0.6)
Randomisation, n (%)	
Randomised	5 (2.8)
Non-randomised with multiple groups	59 (32.8)
Single arm	115 (63.9)
Not indicated	1 (0.6)

- Most of the times: single-arm trials with response rate as endpoint

Haslam et al EJC 2023

FDA's « tentative » surrogate endpoints

Surrogate endpoint	Type of approval appropriate for
Durable objective overall response rate (ORR)	Accelerated/Traditional
Progression free survivial (PFS)	Accelerated/Traditional
Disease-free survival (DFS)	Accelerated/Traditional
Event-free survival (EFS)	Accelerated/Traditional
Pathological complete response (pCR)	Accelerated

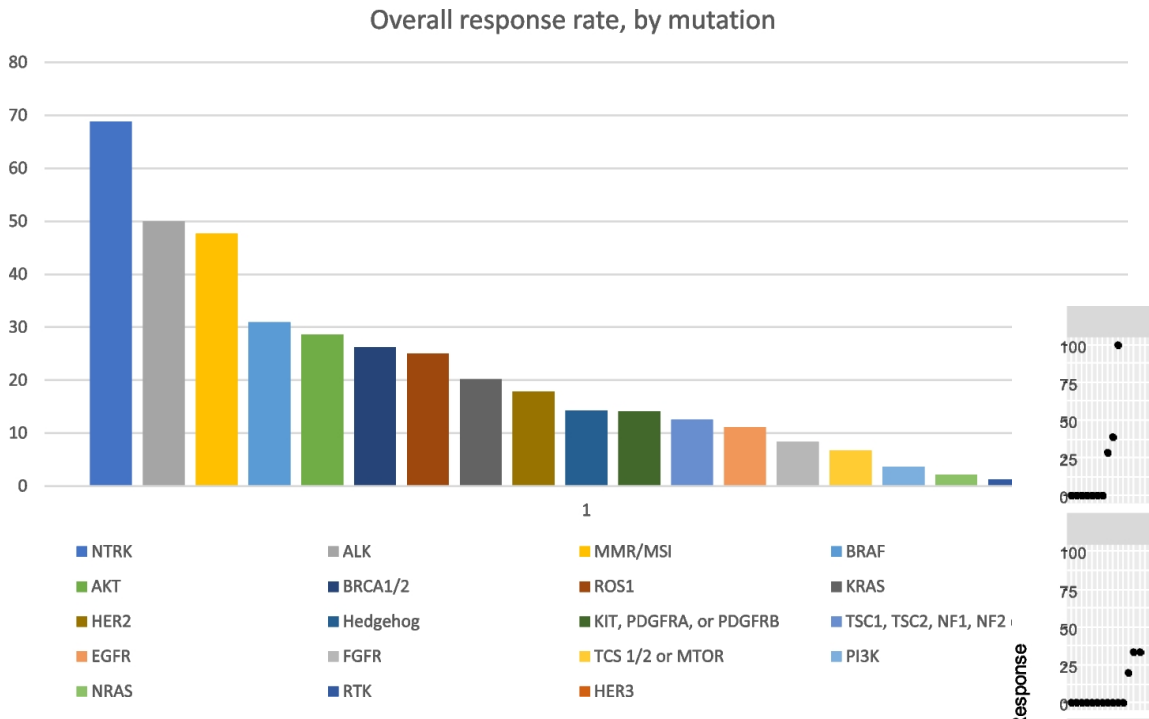
- Response rates (ORR or pCR) not validated as surrogate endpoint

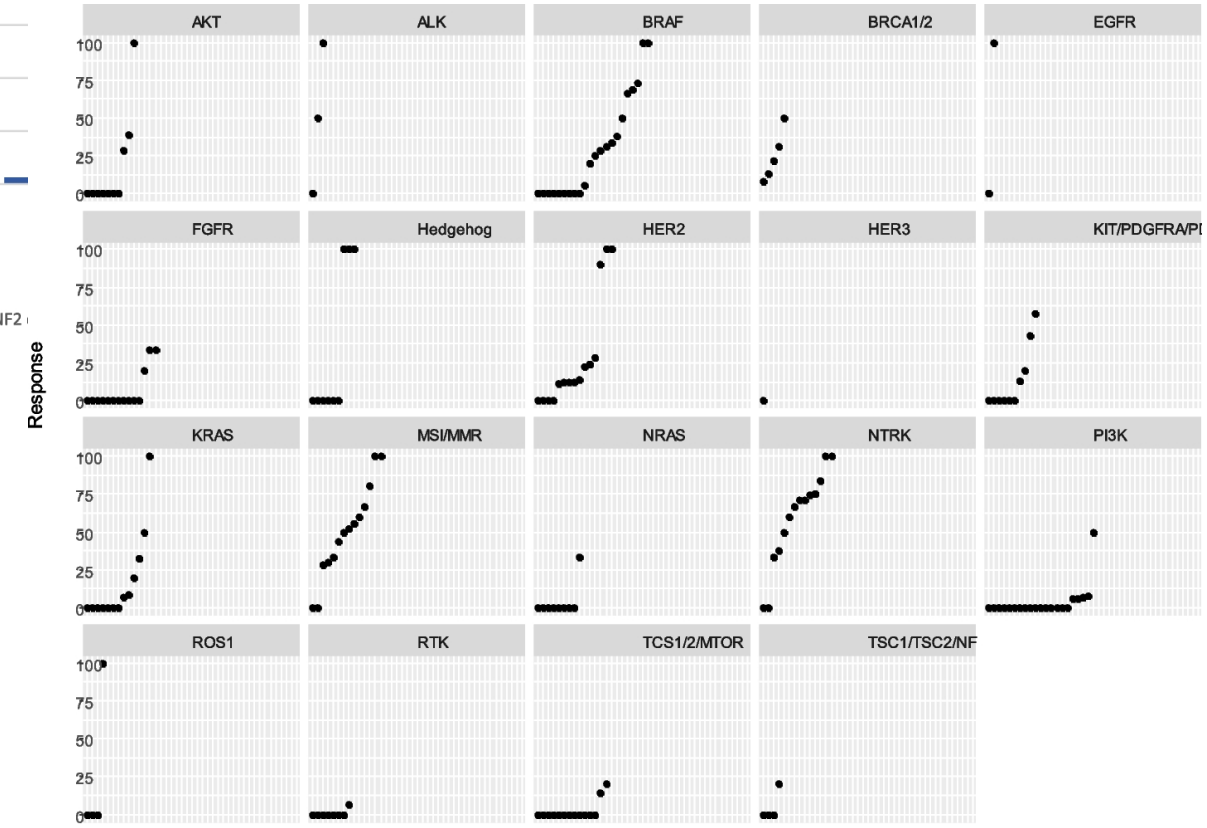
- Single-arm phase-II trials with response rates poorly control for the "true" false positive rate if the of null response rate is misspecified (Baey Eur J Cancer 2011)

- Risk-benefit approach for use of surrogate as primary endpoint in conditional approval?
- Improved postapproval monitoring mechanisms

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Basket trials





- Prognostic effect of biomarker varies or treatment effect varies across histologies?

Haslam BMC Cancer 2023

Basket trials

- Several design propositions for randomised basket trials, even with Bayesian borrowing (Ouma J R Stat Soc Ser C Appl Stat 2022), or a frequentist method for time-event and interim analyses (He SMMR 2022)

- Sharing across substudies requires a preplanned biological and clinical rationale

- Assessment of the benefit/risk in pooled target populations can be complicated by differences in design or in efficacy/safety signals between the substudies (Collignon C Clin Pharmacol Ther 2020)

- Distinguish exploratory basket trials from confirmatory basket trials
  -Basket design with bayesian False Discovery Rate control (Zabor Clin Trials 2022)

  -In a master basket protocol intented for successive submissions → master protocol family wise error rate may be required (quite similar to subgroup analyses)

Use of umbrella trials in oncology

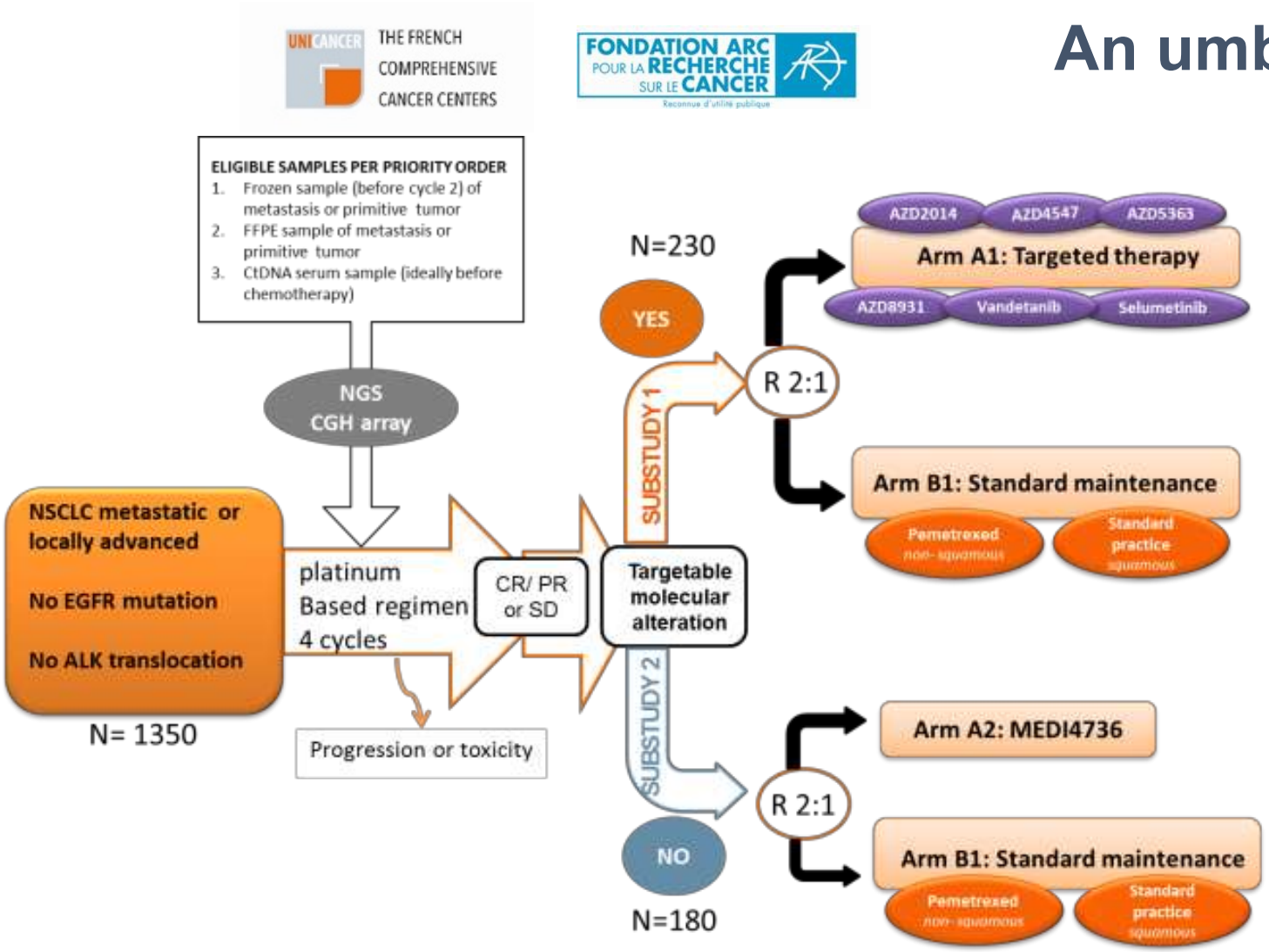
Number of studies (up to 2021)	38
Trial phase	
Early phase (I, II)	23 (60.5)
Late phase (III-IV)	3 (7.9)
Seamless (I/II, II/III, III/IV)	10 (26.3)
Unclear	2 (5.3)
Disease setting	
Oncology	35 (92.1)
Primary endpoint	
time-to-event	9 (23.7)
Binary	18 (47.4)
(others including combinations)	9 (23.7)
Treatment allocation	
Randomized	12 (31.6)
Non-randomized	14 (36.8)
Both (randomized and non-randomized)	7 (18.4)
Unclear	5 (13.2)

Ouma Front Med 2022

Number of studies (up to early 2022)	73
Number of arms	5 (3, 8)
Number of study participants, median (IQR)	240 (82, 411)
Phase, n (%)	
I	4 (5.5)
I/II	16 (21.9)
II	40 (54.8)
II/III	4 (5.5)
III	2 (2.7)
Not indicated	7 (9.6)
Randomisation, n (%)	
Randomised	15 (20.5)
Non-randomised with multiple groups	31 (42.5)
Single arm	16 (21.9)
Observational	9 (12.3)
Not indicated	2 (2.7)

Haslam et al EJC 2023

An umbrella trial in France : SAFIR02 trial



Open-label, multicentric phase II

Barlesi Clin Cancer Res. 2022

Risk: Heterogeneity of treatment effects

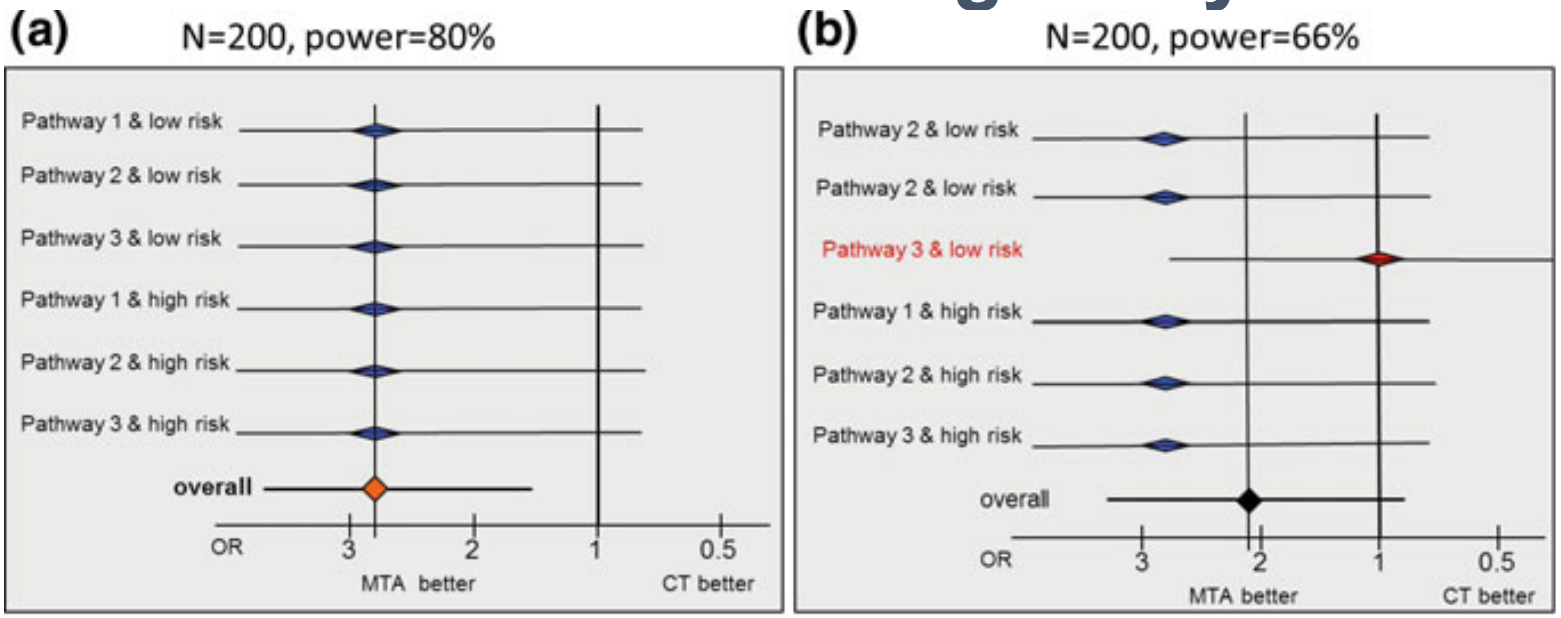


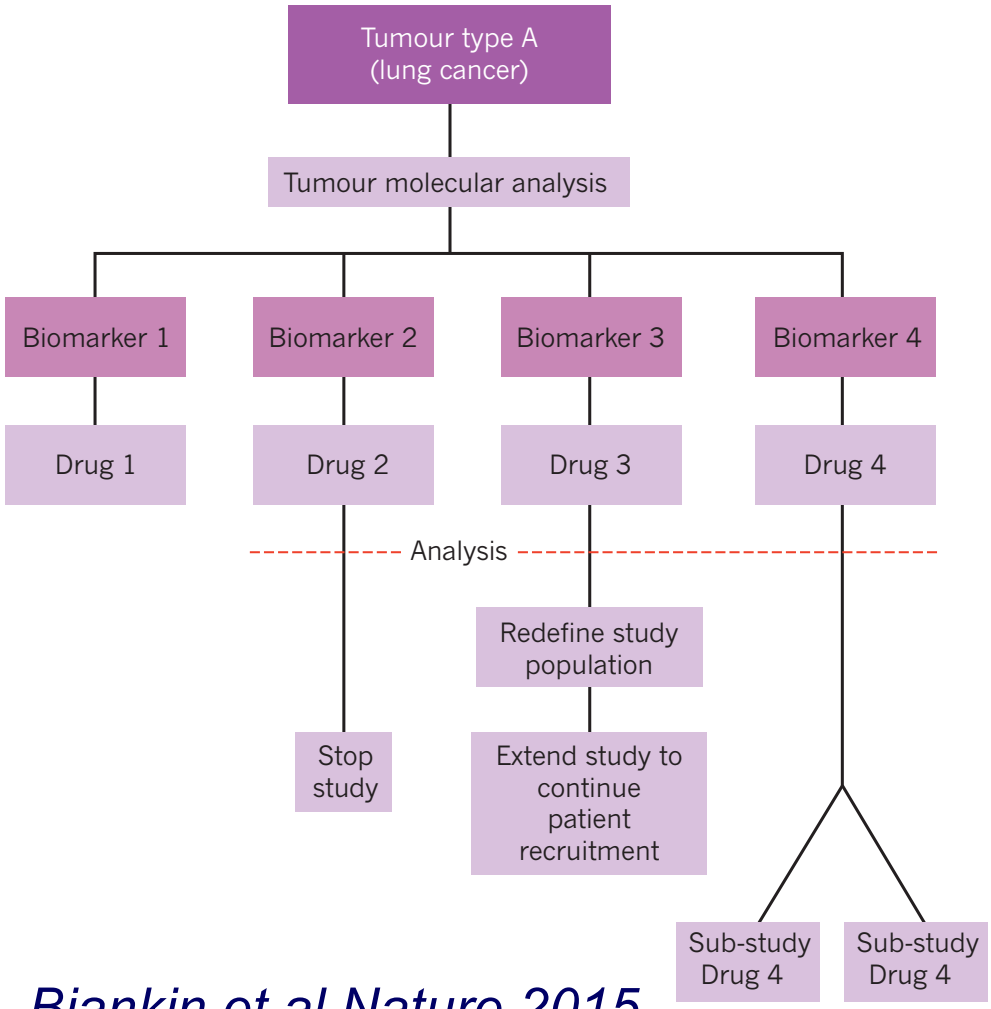
Fig. 3 Impact of heterogeneity in the treatment effect related to the algorithm assuming balanced prevalence for the six different strata and the same follow-up for all patients censored at the cut-off date. High and low risk denote the risk group; Pathway 1, 2, 3 correspond to the grouping of the different targets; MTA stands for molecularly targeted agent; CT stands for control treatment; *N* is the total sample size; OR stands for odds ratio; Point estimates and 95% confidence intervals (horizontal lines) are provided. *Panel A* Homogeneous benefit of the targeted treatment selected based on molecular alterations in all strata (OR = 2.67); *Panel B* benefit of the targeted treatment selected based on molecular alterations in all but one stratum

Paoletti, Michiels, Frontiers of Biostatistical Methods and Applications in Clinical Oncology, 2017

SAFIR02 targeted substudy characteristics

- Equal randomization 2:1
- Molecular treatment algorithm (function of targetable alterations)
- Add/remove targeted therapies and/or biomarkers
- Targeted substudy will test an 'average' treatment effect (powered to detect an effect on progression-free survival of HR=0.66 at two-sided α=0.05 with 205 events) under the assumption of not too strong treatment heterogeneity across targeted strata
- A frailty model may be useful for the statistical analysis in the case of heterogeneous treatment effects *(Beisel et al Biom J 2017)*

Adaptive umbrella platform trial



Biankin et al Nature 2015

- Add trial arms (agents) and biomarkers to an ongoing trial
- Early stopping for futility and/or efficacy of treatments
- Gain efficiency trough screening of multiple biomarkers and interim analyses
- Reduce ”white space” between set-up of small independent trials

Umbrella trials

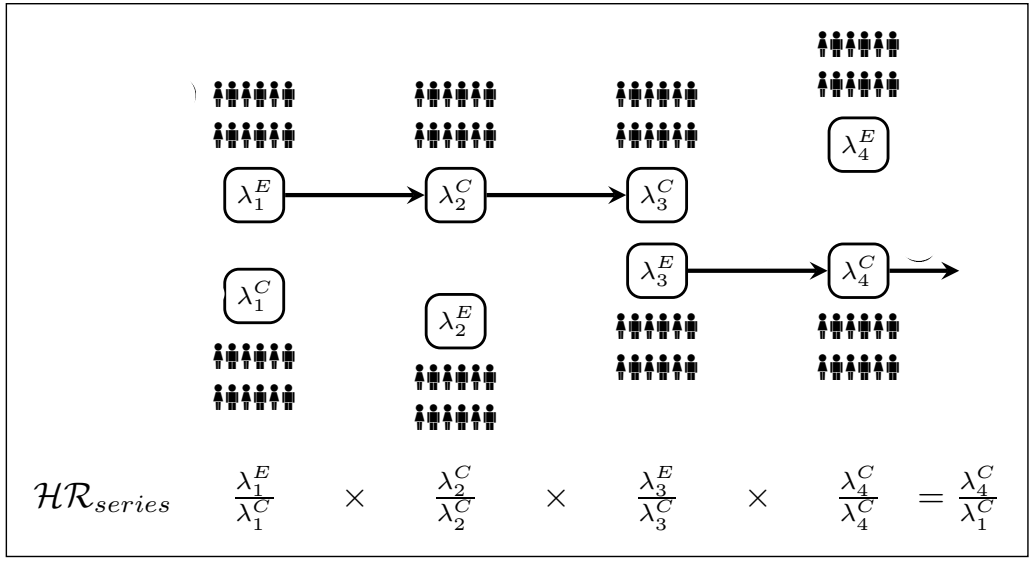
- Borrowing is possible
  - But, <> basket trials, can be seen as unfavourable (different hypotheses in different subtrials, Lee Cancer J 2019)
  - limited methodology around borrowing techniques tailored to the umbrella context (Ouma Front Med 2022)
  - Borrowing across subgroups most straightforward

- Sharing a control arm would not require Type I error adjustement (Collignon C Clin Pharmacol Ther 2020)
  - But if by chance the control group underperforms, inflation of Type I error can occur
  - Use of non-concurrent controls is debated → specific adjustment techniques (Marschner Clin Trials 2022; Roig BMC Med Res Meth 2022; Saville Clin Trials 2022)

Relaxed signifance levels for randomized trials in rare cancers?

Long-term horizon (15y)

Illustration of one repetition of a series of four consecutive two-arm RCTs



① The hazard rate λ_1^C of the control treatment of the first trial characterizes the severity of the underlying disease as perceived at the beginning of the research horizon.

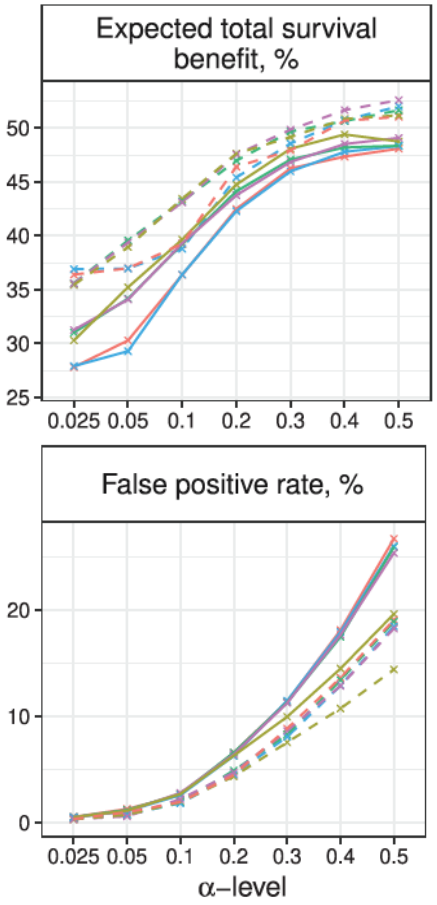
Bayar A SMMR 2022; Bayar A Stat Med 2016

Relaxed signifance levels for randomized trials in rare cancers?

Long-term horizon (15y)

- Historical distribution of treatment effects
- Performing a series of small randomized trials with relaxed α-levels leads, on average, to **larger survival benefits over a long horizon compared with larger trials with a 2.5% one-sided α-level for a moderate increase in risk**
- The recommendation is only valid when considering a series of trials run over a relatively long research horizon and when the supply of new treatments is large

- Performing multi-arm multi-stage trials with relaxed α-level can further increase the expected survival benefit on the long run



Bayar A SMMR 2022; Bayar A Stat Med 2016

Conclusion

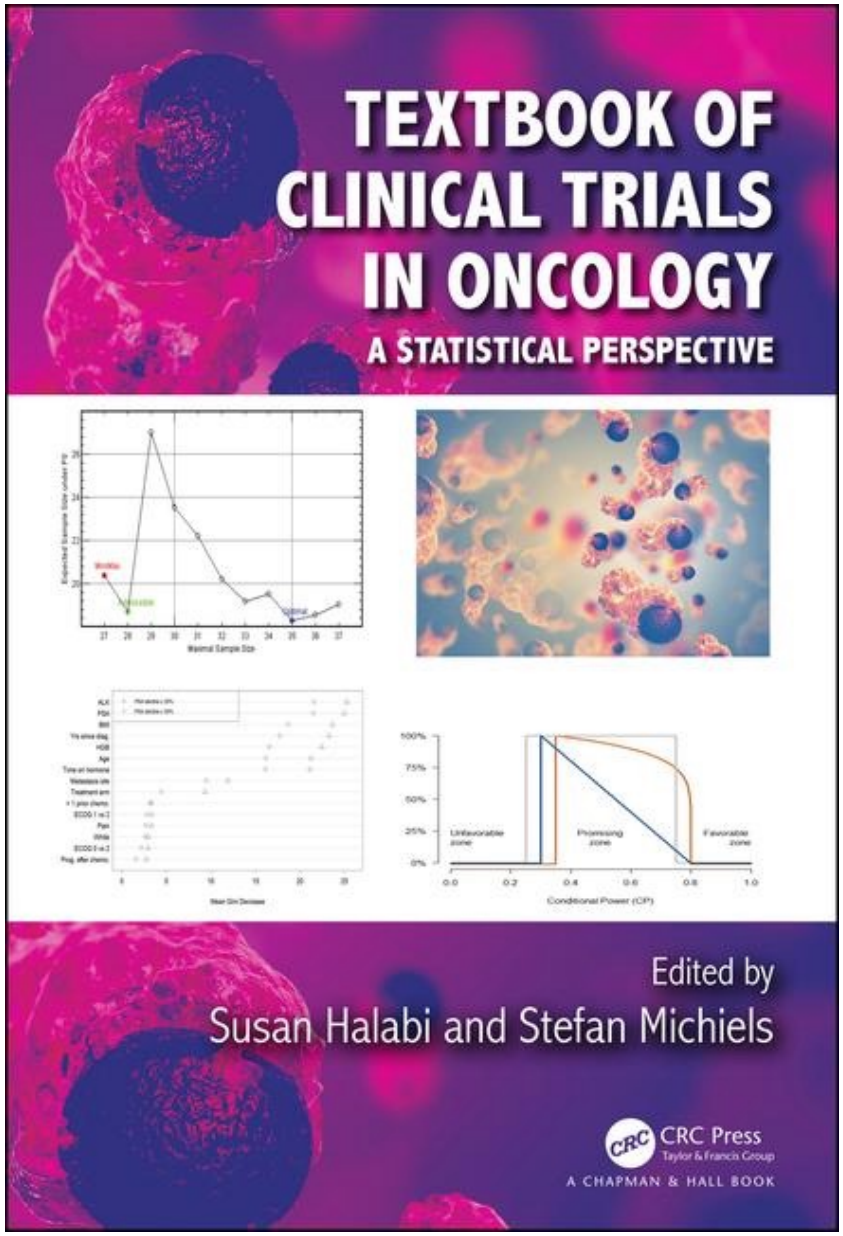
- Trials with treatments and biomarkers: Type I and II errors for both treatments and biomarkers

- Added value of randomization
  - Use of external control is currently limited to ultrarare tumours, well known natural disease, solid endpoint and a large expected treatment effect

- Learning trials vs confirmatory platform trials

- To adjust or not in confirmatory trials : for biomarker subgroups yes but for different treatments not (Stallard Ann Onc 2019)

- Umbrella-type multi-arm multi-treatment platform trials



More on clinical trials designs in oncology

Thank you for your attention !

https://www.crcpress.com/9781138083776