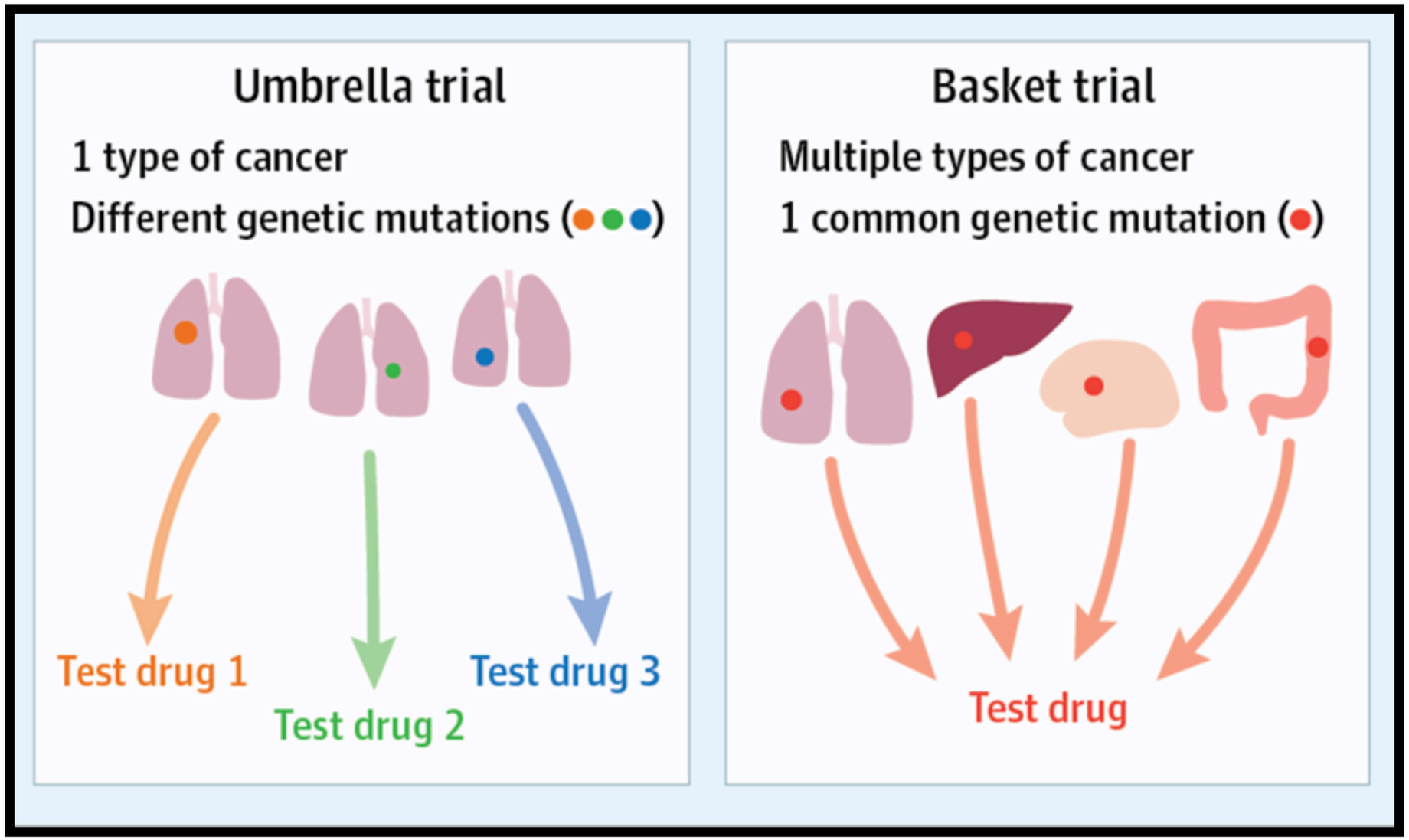
Multi-arm multi-stage designs for early phase oncology trials

Dominic Magirr
Cambridge Cancer Genomics

Plan

- Review of master protocol trials in early phase oncology.
- Choice of primary endpoint.
- Circulating tumour DNA.

Master protocol trials



West H. Novel Precision Medicine Trial Designs: Umbrellas and Baskets. *JAMA Oncol.* 2017;3(3):423. doi:10.1001/jamaoncol.2016.5299

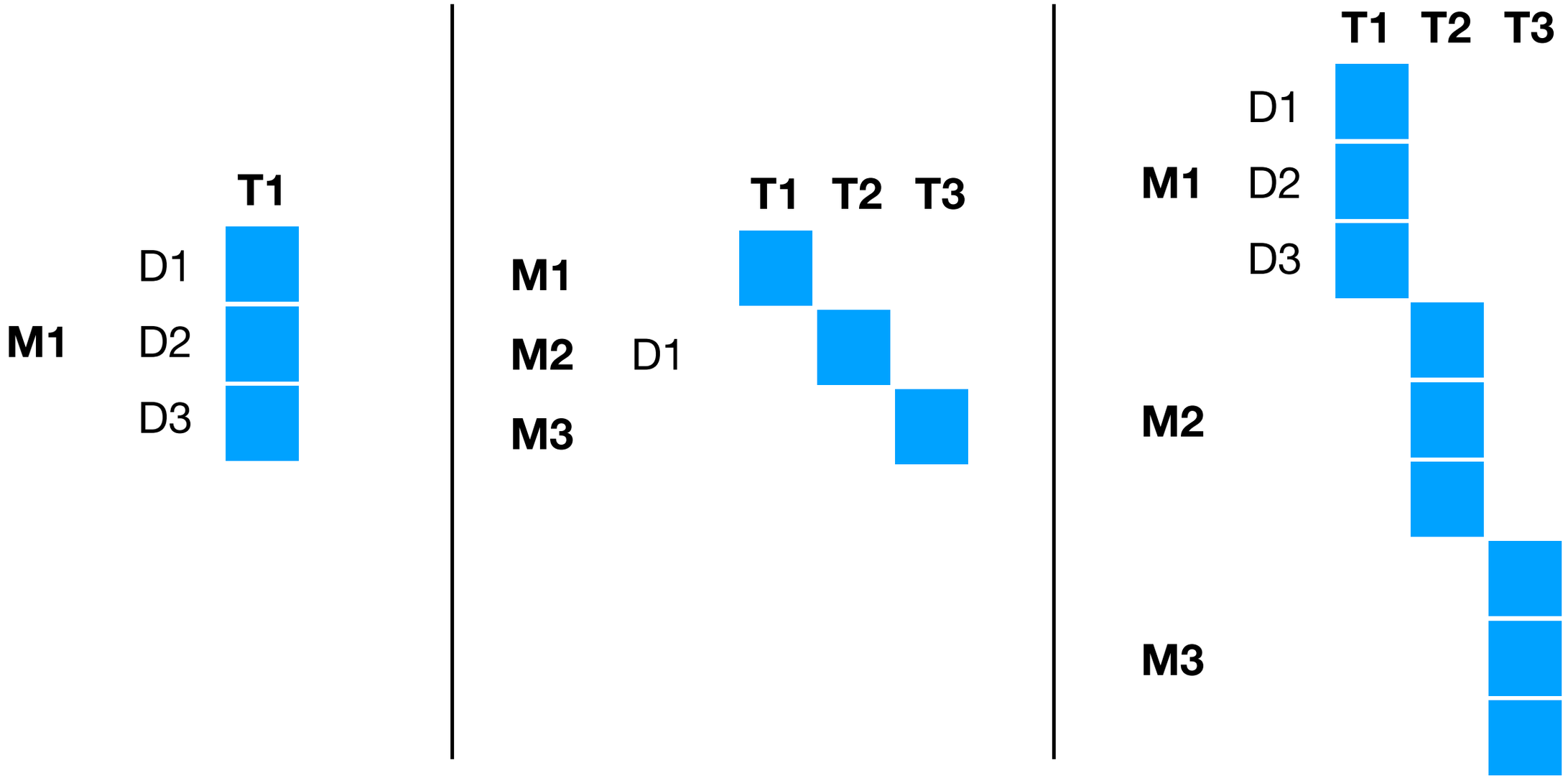
Current landscape

Janiaud, Perrine, Stylianos Serghiou, and John PA Ioannidis. "New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology." *Cancer treatment reviews* (2018).

- Systematic review of master protocol trial designs.
- 30 “basket” and 27 “umbrella” trials.
- Most (65%) labelled phase 2 trials.
- Time period 2006 — 2018, but most trials started after 2015.
- Classification difficult due to overlap and mislabelling.

Refined classification

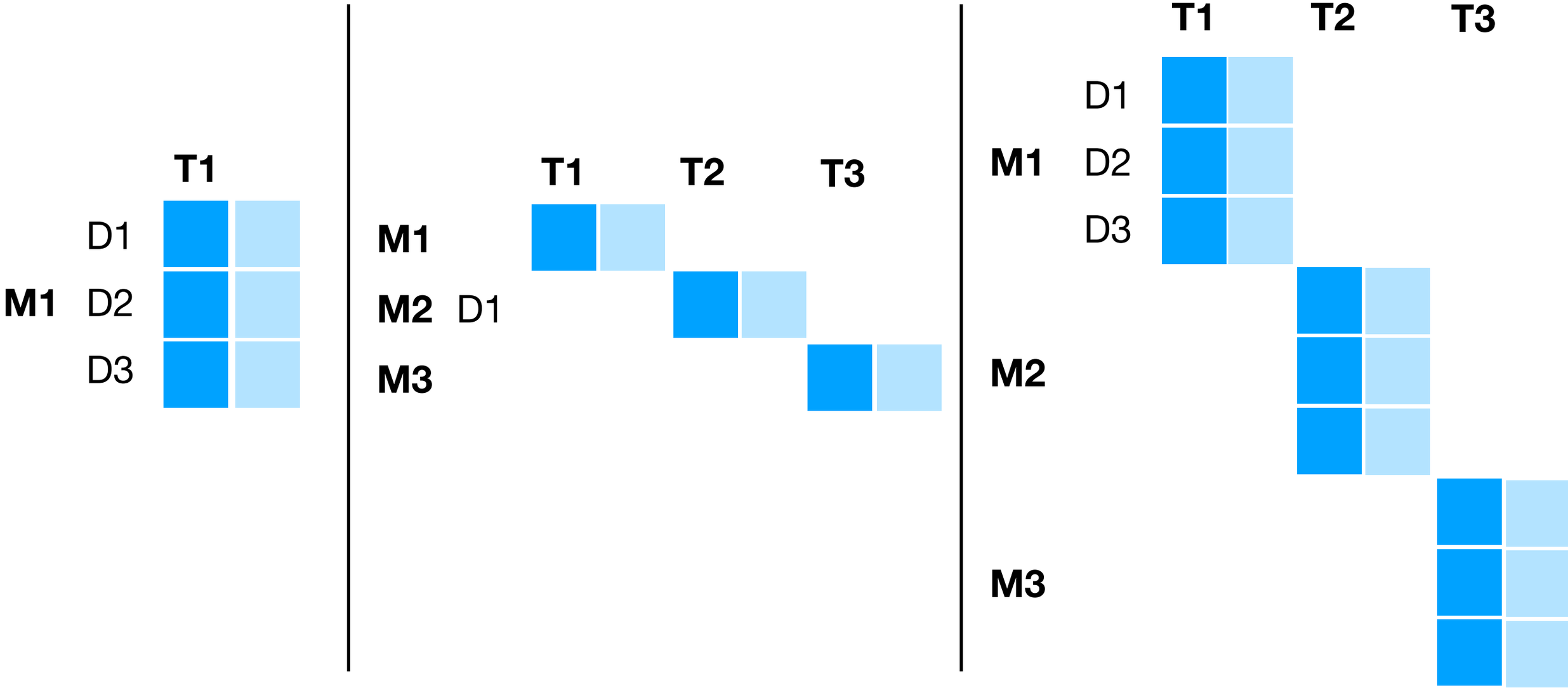
N Stallard, S Todd, D Parashar, P K Kimani, L A Renfro, On the need to adjust for multiplicity in confirmatory clinical trials with master protocols, *Annals of Oncology*, https://doi.org/10.1093/annonc/mdz038



M = mutation; D = disease; **T** = treatment

Refined classification

N Stallard, S Todd, D Parashar, P K Kimani, L A Renfro, On the need to adjust for multiplicity in confirmatory clinical trials with master protocols, *Annals of Oncology*, https://doi.org/10.1093/annonc/mdz038



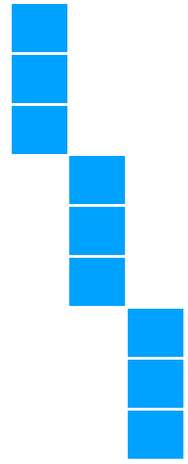
M = mutation; D = disease; **T** = treatment

Current landscape

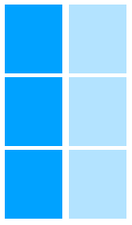
- Categories from Stallard et al. (2019)
- Data from Janiaud et al. (2018)

19

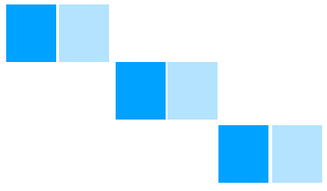
9



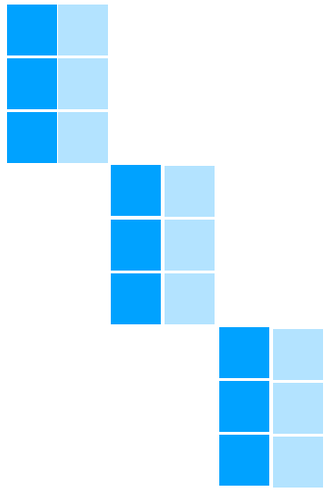
6



0



9



2

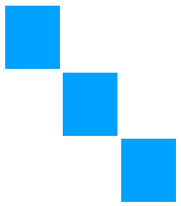
Current landscape

Industry sponsored

9

- 8 Response rate
- 1 Toxicity

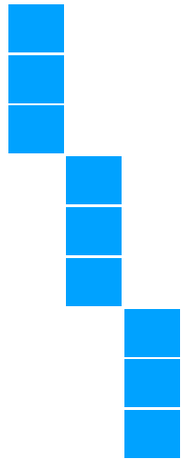
- 6 monotherapy
- 3 combination



2

- 2 Response rate

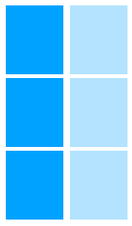
- 2 combination



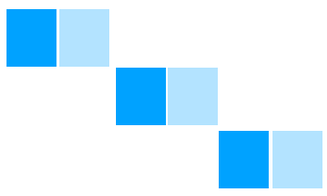
1

- 1 Disease control rate

- 1 monotherapy



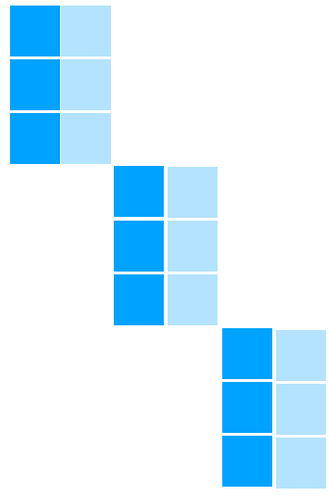
0



2

- 2 Response rate

- 2 combination



0

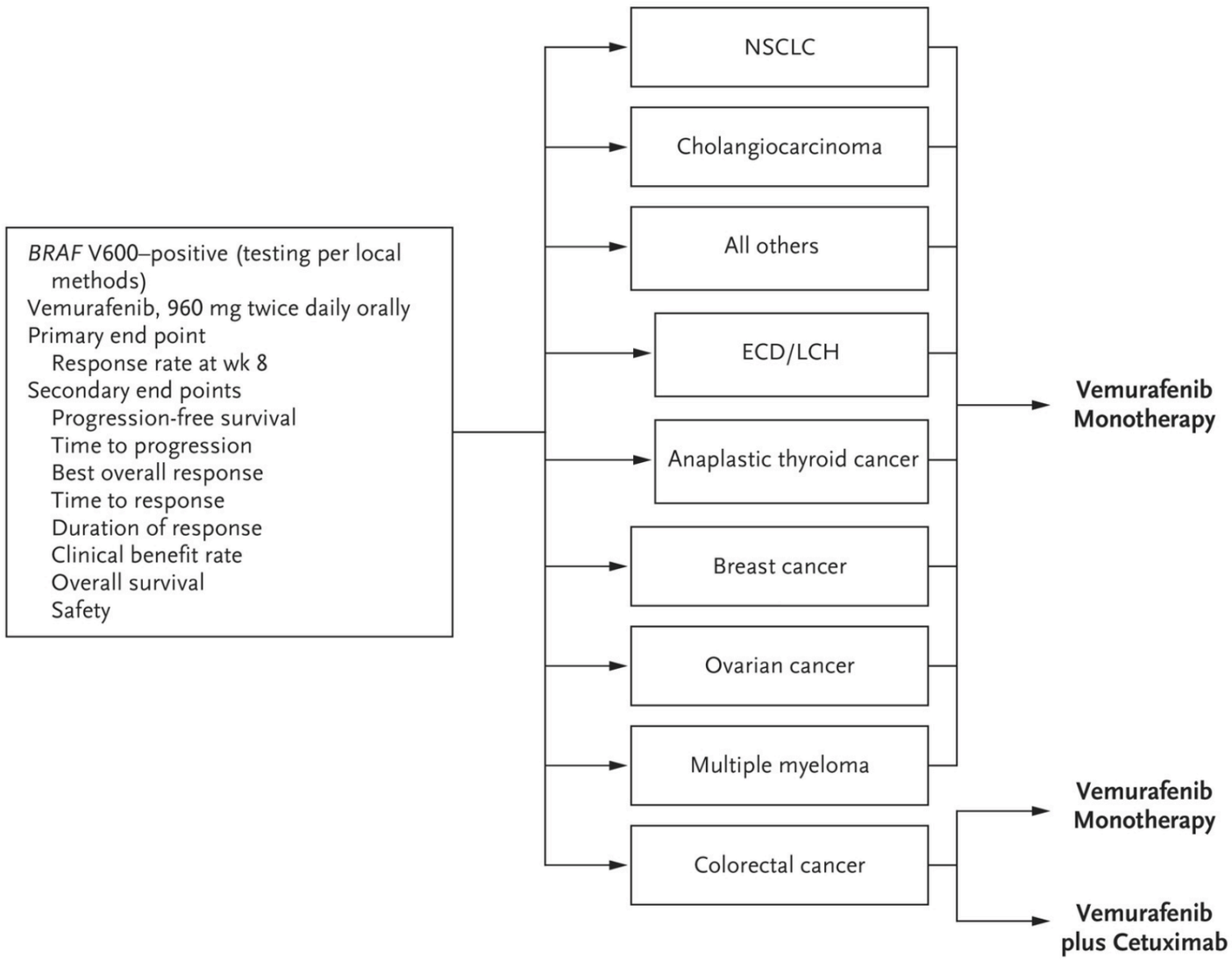
$N \approx 5 - 30$

$N \approx 30 - 100$

$N \approx 5 - 30$

Example

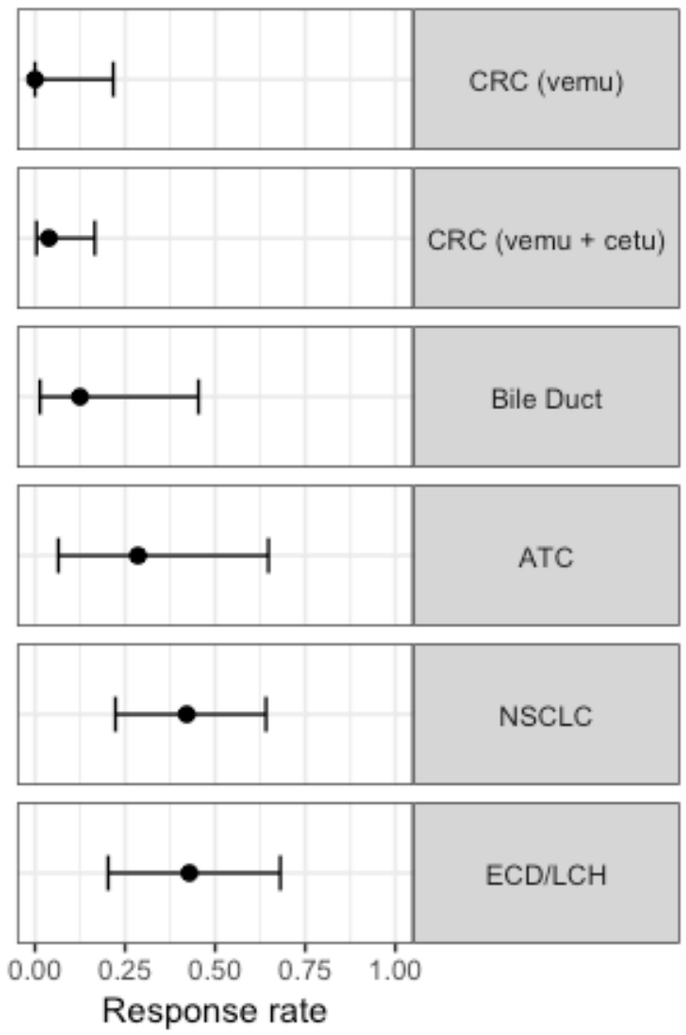
Hyman, David M., et al. "Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations." *New England Journal of Medicine* 373.8 (2015): 726-736.



- Each tumour-specific cohort used a Simon's 2-stage design. Stop early for futility.
- Final cohort sizes between 5 and 27.

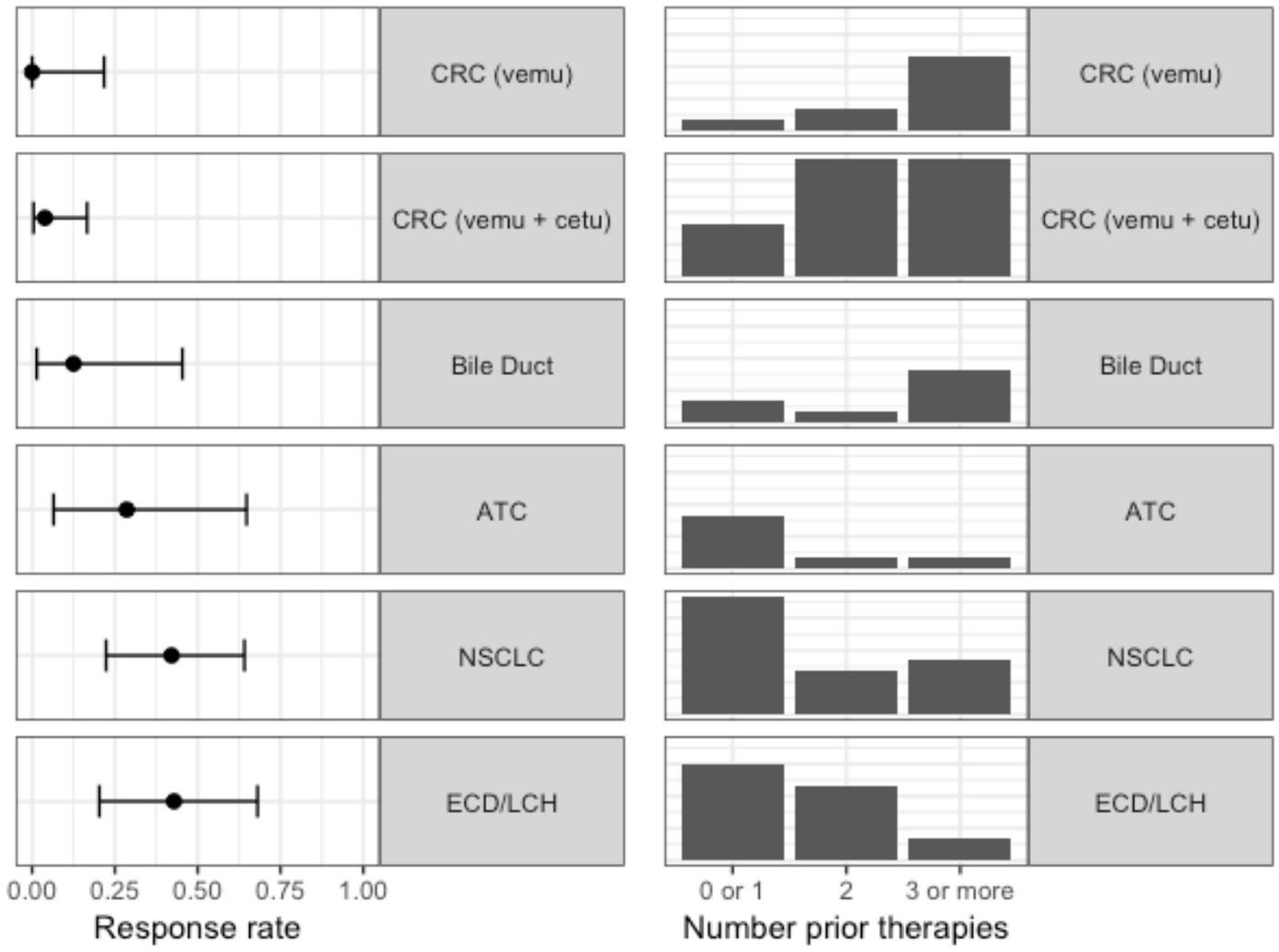
Statistical challenges

Hobbs, B. P., et al. "Statistical challenges posed by uncontrolled master protocols: sensitivity analysis of the vemurafenib study." *Annals of Oncology* 29.12 (2018): 2296-2301.



Statistical challenges

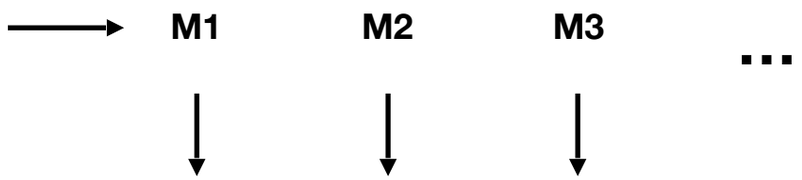
Hobbs, B. P., et al. "Statistical challenges posed by uncontrolled master protocols: sensitivity analysis of the vemurafenib study." *Annals of Oncology* 29.12 (2018): 2296-2301.



A more complex design

Slosberg, Eric D., et al. "Signature program: a platform of basket trials." *Oncotarget* 9.30 (2018): 21383.

Research physician identifies actionable genetic alteration in cancer patient.



Agent[a]	Buparlisib (BKM120)	Dovitinib (TKI258)	Binimetinib (MEK162)	Encorafenib (LGX818)	BGJ398	Ceritinib (LDK378)	Ribociclib (LEE011)
Cohorts	· Colorectal[b]	· GIST	· NSCLC (adeno)[b]	· Thyroid	· Breast	· Colorectal	· NSCLC (adeno)
	· Sarcoma[b]	· Colorectal	· Ovarian		· Colorectal	· NSCLC	· HNSCC
	· Ovarian[b]	· Ovarian	· Uterine		· HNSCC	(adeno)	· Sarcoma
	· Cervical	· Adenoid	· Appendix		· NSCLC	· Sarcoma	· Uterine
	· HNSCC	cystic	· Small intestine		(adeno)		· NSCLC
	· Anal	· HNSCC	· Sarcoma		· Ovarian		(squamous)
	· Gallbladder	· NSCLC	· Thyroid				· Breast (triple negative)
	· Bladder	(adeno)	· Unknown primary				
	· Gallbladder	· Thymus	· Breast				· Mesothelioma
	duct		· Bladder				· Pancreatic
	· GE junction		· GE junction				· Bladder

	Buparlisib (BKM120)	Dovitinib (TKI258)	Binimetinib (MEK162)	Encorafenib (LGX818)	Sonidegib (LDE225)	BGJ398	Ceritinib (LDK378)	Ribociclib (LEE011)
Dosed patients, n	146	80	110	12	10	82[a]	47	106
Clinical benefit, n (%)	22 (15.1)	11 (13.8)	25 (22.7)	3 (25.0)	0	12 (14.6)	9 (19.1)	19 (17.9)

- Analyse as individual cohorts, or pool data with same treatment?
- A compromise was used for futility monitoring: hierarchical model (Berry et al. 2013).
- Final report pooled the cohorts.

Single arm or randomised?

	$\hat{p}_E - p_C^*$	$\hat{p}_E - \hat{p}_C$
Var	$\frac{p(1-p)}{N}$	$\frac{4p(1-p)}{N}$
Bias	$p_C^* - p_C$	0
Var + Bias²	$\frac{p(1-p)}{N} + (p_C^* - p_C)^2$	$\frac{4p(1-p)}{N}$

More thorough analysis in Taylor et al. (2006).

Response rate or PFS?

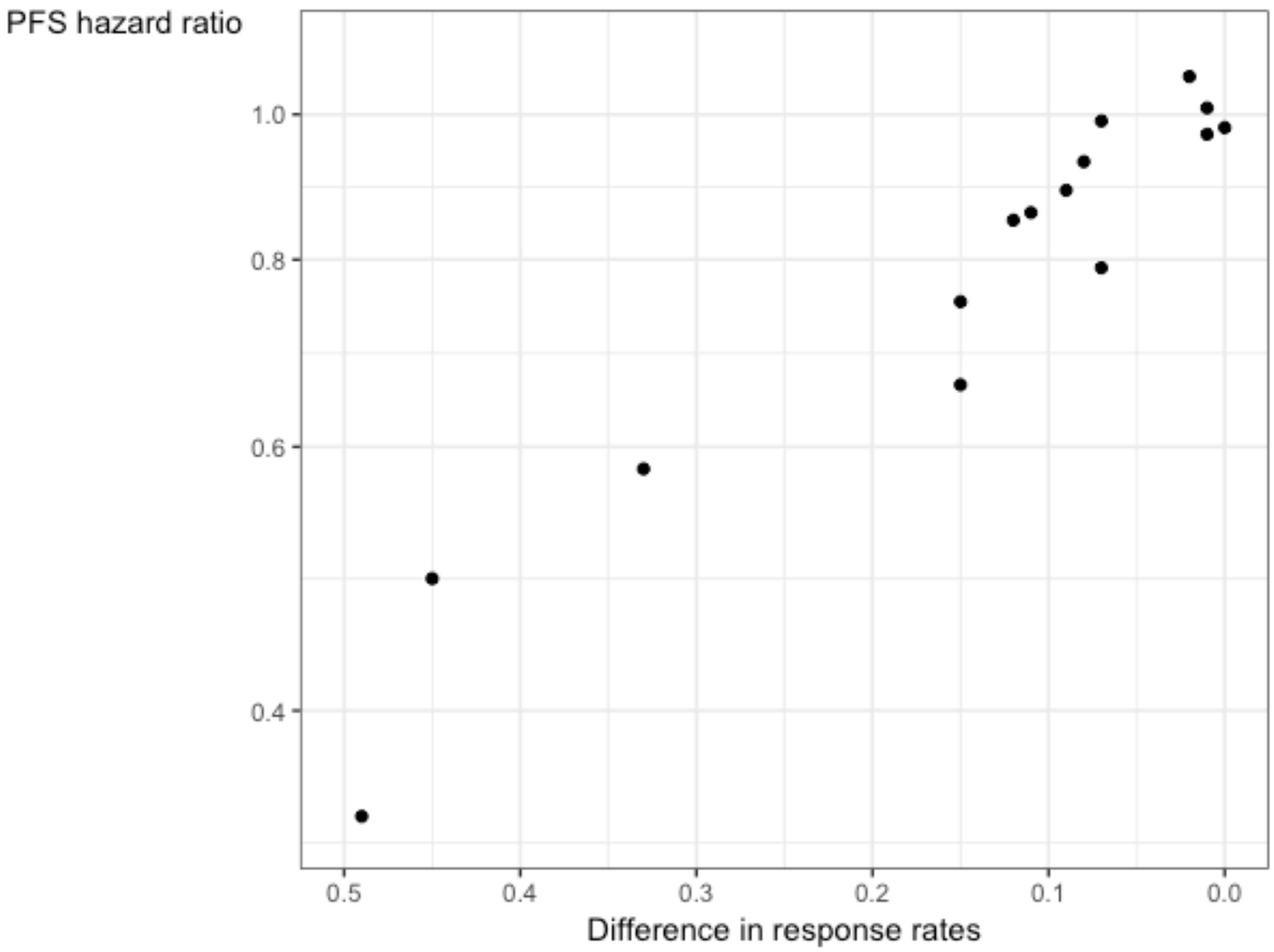
	$\hat{p}_E - p_C^*$	$\hat{p}_E - \hat{p}_C$	$\hat{\theta}_{PFS}$
Var	$\frac{p(1-p)}{N}$	$\frac{4p(1-p)}{N}$	$\frac{4}{Nm}$
Bias	$p_C^* - p_C$	0	0
Var + Bias²	$\frac{p(1-p)}{N} + (p_C^* - p_C)^2$	$\frac{4p(1-p)}{N}$	$\frac{4}{Nm}$

Response rate or PFS?

	$\hat{p}_E - p_C^*$	$\hat{p}_E - \hat{p}_C$	$\hat{\theta}_{PFS}$
Var	$\frac{p(1-p)}{N}$	$\frac{4p(1-p)}{N}$	$\frac{4}{Nm}$
Bias	$p_C^* - p_C$	0	0
Var + Bias²	$\frac{p(1-p)}{N} + (p_C^* - p_C)^2$	$\frac{4p(1-p)}{N}$	$\frac{4}{Nm}$

Measuring different things on different scales.

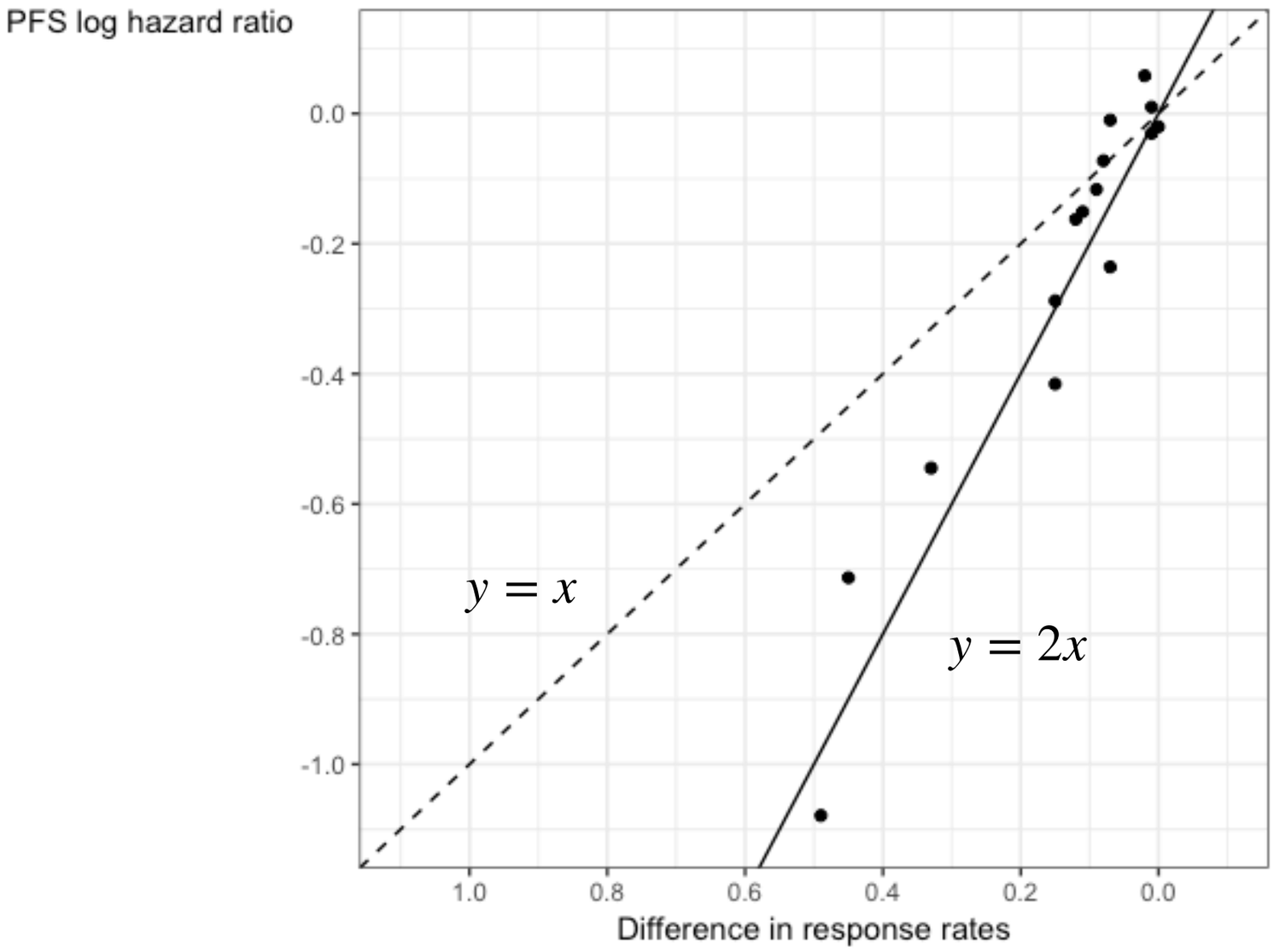
Advanced lung cancer data



14 large RCTs submitted to FDA from 2003 to 2013

Blumenthal, Gideon M., et al. "Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses." *Journal of Clinical Oncology* 33.9 (2015): 1008.

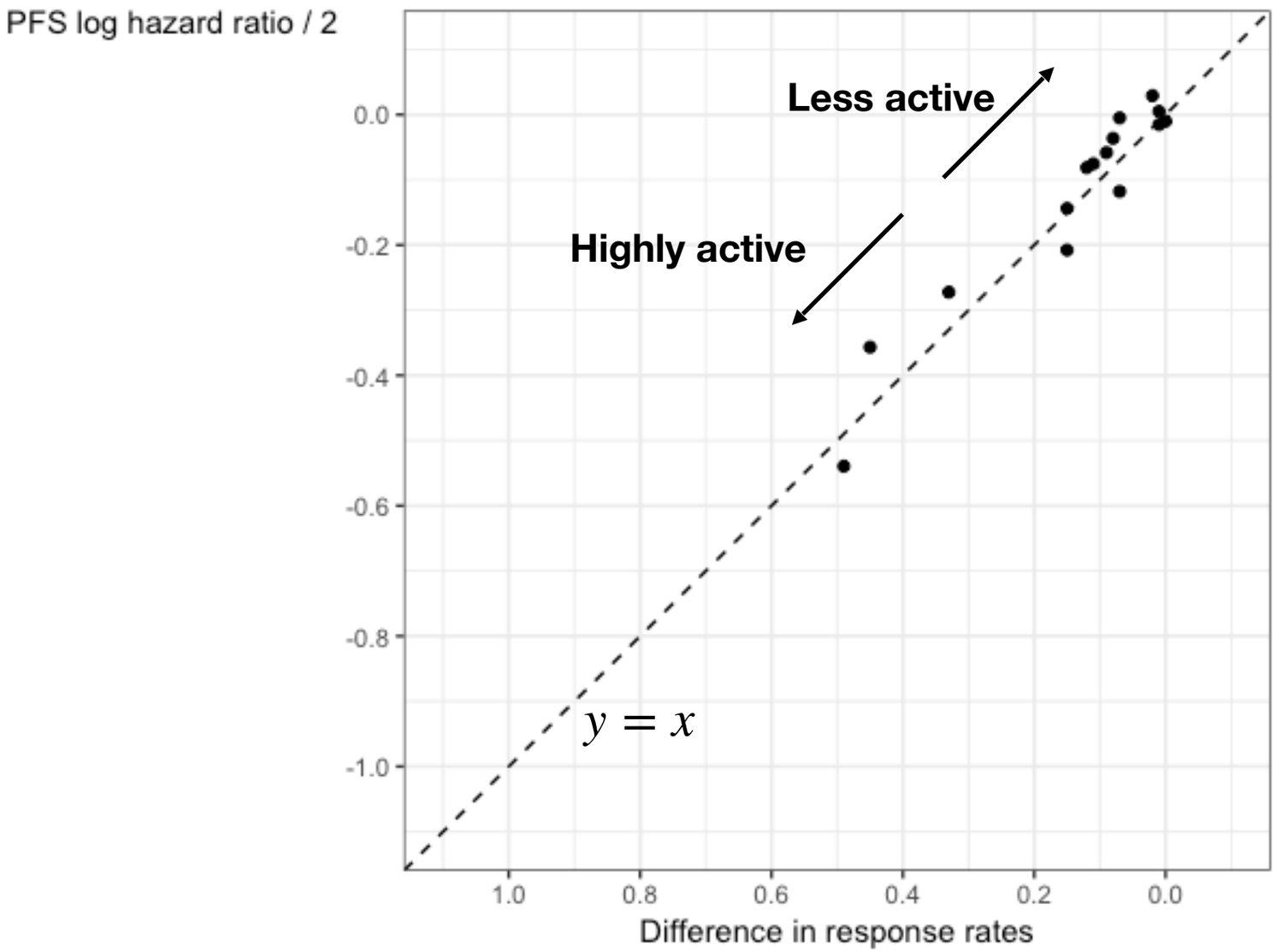
Advanced lung cancer data



14 large RCTs submitted to FDA from 2003 to 2013

Blumenthal, Gideon M., et al. "Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses." *Journal of Clinical Oncology* 33.9 (2015): 1008.

Advanced lung cancer data



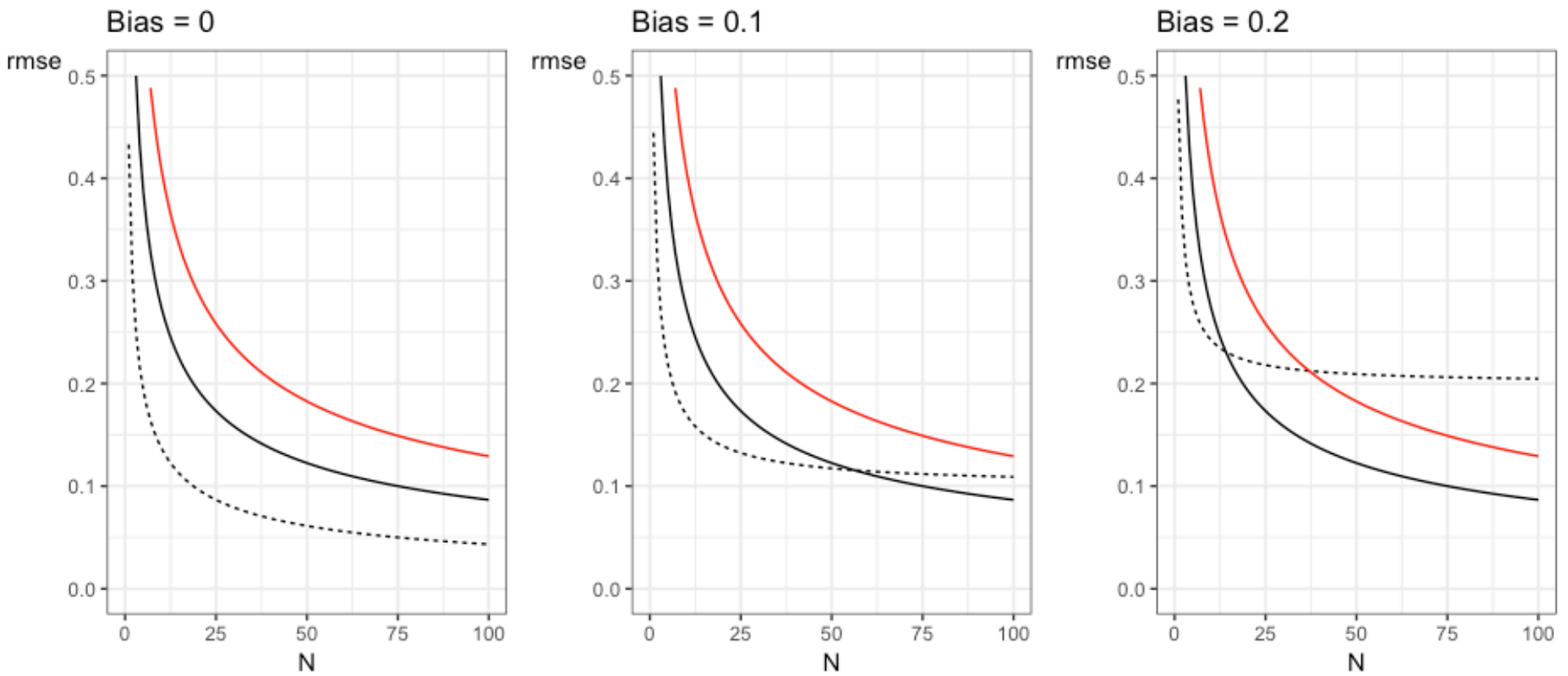
14 large RCTs submitted to FDA from 2003 to 2013

Blumenthal, Gideon M., et al. "Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses." *Journal of Clinical Oncology* 33.9 (2015): 1008.

Response rate or PFS?

	$\hat{p}_E - p_C^*$	$\hat{p}_E - \hat{p}_C$	$\frac{1}{2}\ \hat{\theta}_{PFS}$
Var	$\frac{p(1-p)}{N}$	$\frac{4p(1-p)}{N}$	$\frac{1}{4}\ \frac{4}{Nm}$
Bias	$p_C^* - p_C$	0	0
Var + Bias²	$\frac{p(1-p)}{N} + (p_C^* - p_C)^2$	$\frac{4p(1-p)}{N}$	$\frac{1}{4}\ \frac{4}{Nm}$

Compare precision



$p = 0.2$

$m = 0.6$

endpoint

Difference in response rates

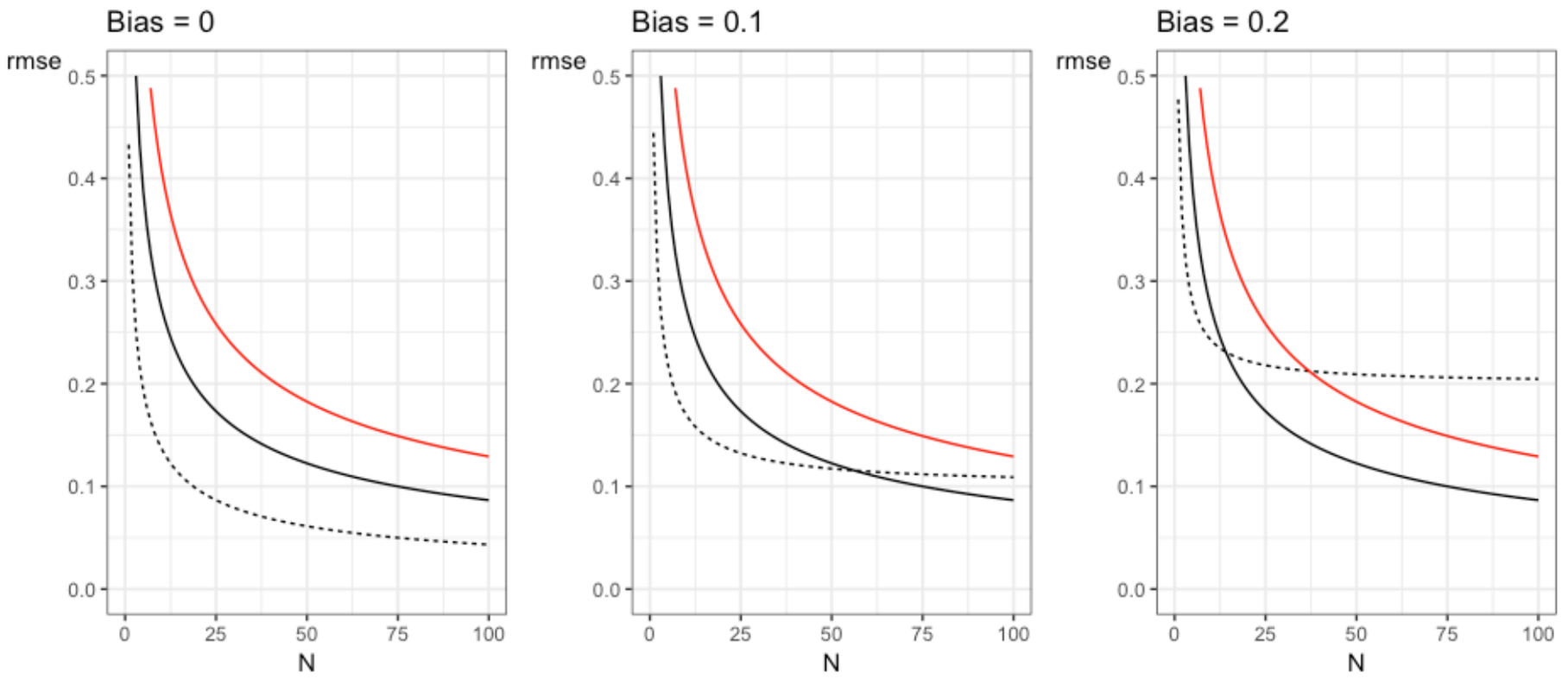
PFS log hazard ratio / 2

design

Randomized

Single arm

Compare precision



$p = 0.2$

$m = 0.6$

endpoint

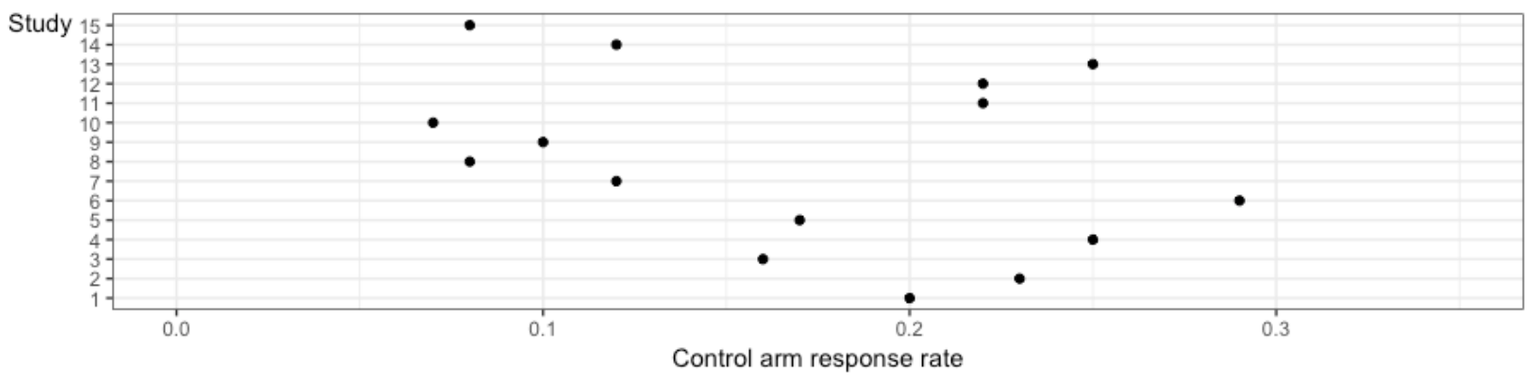
Difference in response rates

PFS log hazard ratio / 2

design

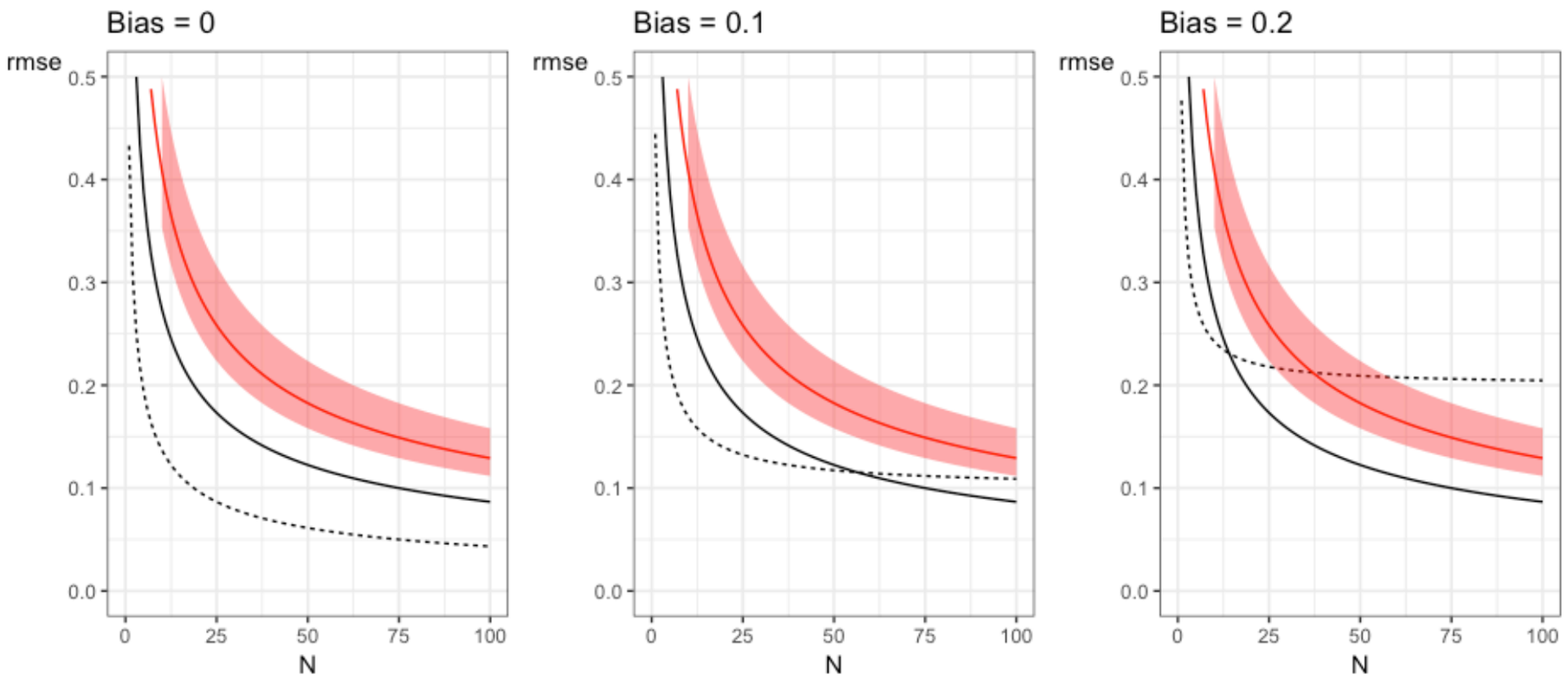
Randomized

Single arm



Blumenthal (2015) data set

Compare precision



$p = 0.2$

$m = 0.6(0.4, 0.8)$

endpoint

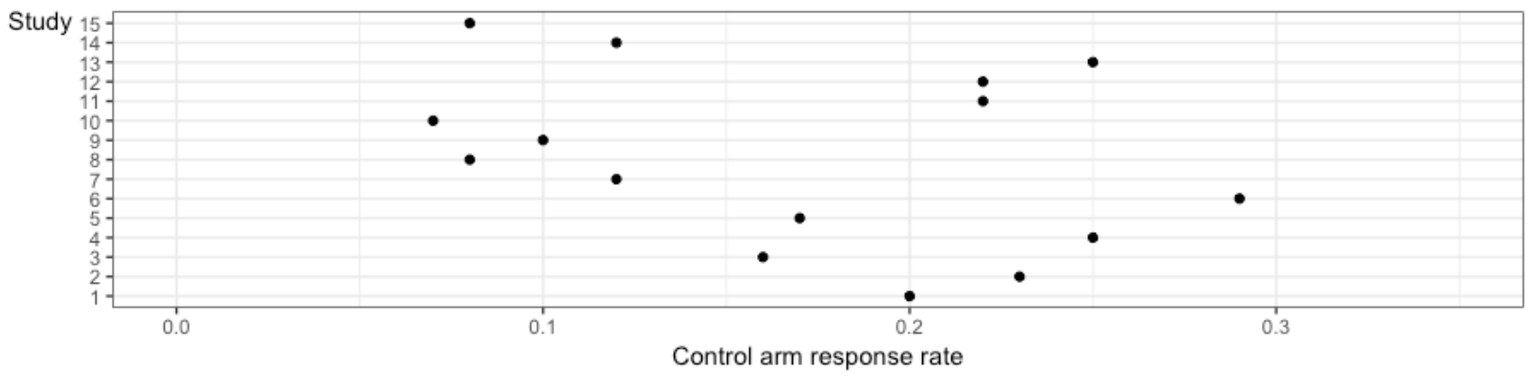
Difference in response rates

PFS log hazard ratio / 2

design

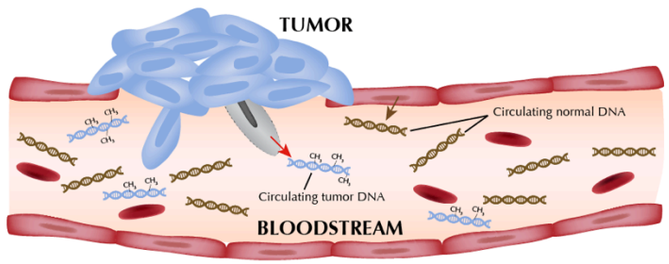
Randomized

Single arm



Blumenthal (2015) data set

Circulating tumour DNA



BLOOD PLASMA
OR SERUM SAMPLE

Analysis pipeline

Reference Genome

ACGCGATTCAGGTTACCACGCGTAGCGCATTACACAGATTAG

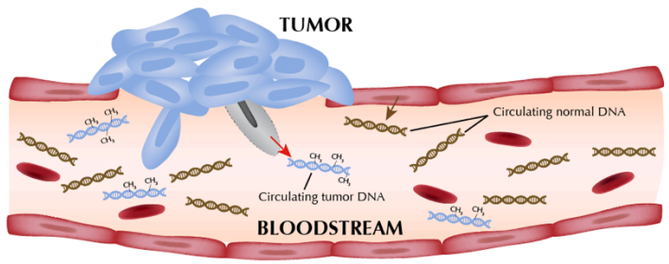
Aligned Sequenced Reads

```
ACGCGATTCAGGTTACCACG
  GCGATTCAGGTTACCACGCG
    GATTCAGGTTACCACGCGTA
      TTCAGGTTACCACGCGTAGC
        CAGGTTACCACGCGTAGCGC
          GGTTACCACGCGTAGCGCAT
            TTACCACGCGTAGCGCATTA
              ACCACGCGTAGCGCATTACA
                CACGCGTAGCGCATTACACA
                  CGCGTAGCGCATTACACAGA
                    CGTAGCGCATTACACAGATT
                      TAGCGCATTACACAGATTAG
```

https://uofuhealth.utah.edu/huntsman/labs/varley/research/detecting-circulating.php

Mutation	Depth of read	Number of mutant reads	Variant-allele frequency	Call
BRCA1 S689R	1000	0	0%	✗
EGFR L858R	6000	4	0.07%	✗
⋮				
PIK3CA R38C	4500	150	3%	✓
TP53 R282W	5500	110	2%	✓
⋮				

Circulating tumour DNA



BLOOD PLASMA
OR SERUM SAMPLE

Analysis pipeline

Reference Genome

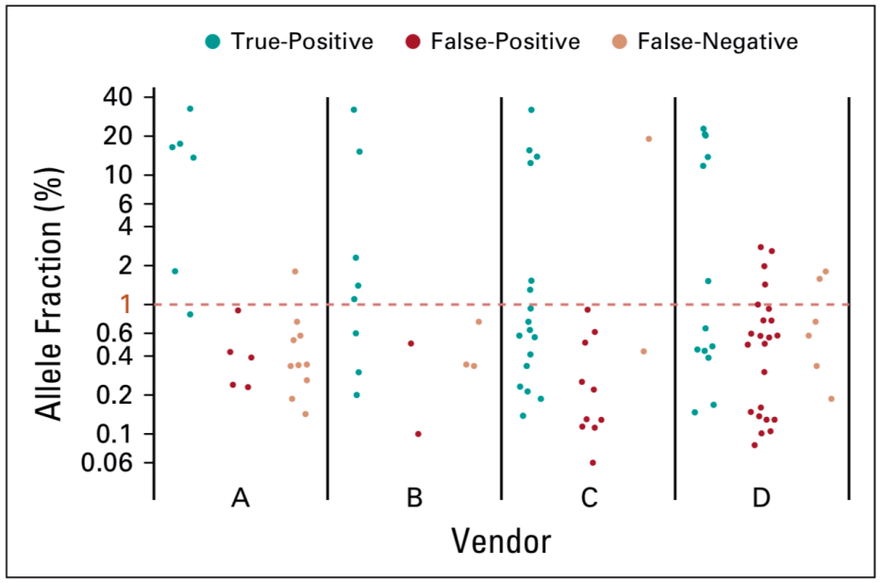
```
ACGCGATTCAGGTTACCACGCGTAGCGCATTACACAGATTAG
```

Aligned Sequenced Reads

```
ACGCGATTCAGGTTACCACG
  GCGATTCAGGTTACCACGCG
    GATTCAGGTTACCACGCGTA
      TTCAGGTTACCACGCGTAGC
        CAGGTTACCACGCGTAGCGC
          GGTTACCACGCGTAGCGCAT
            TTACCACGCGTAGCGCATTA
              ACCACGCGTAGCGCATTACA
                CACGCGTAGCGCATTACACA
                  CGCGTAGCGCATTACACAGA
                    CGTAGCGCATTACACAGATT
                      TAGCGCATTACACAGATTAG
```

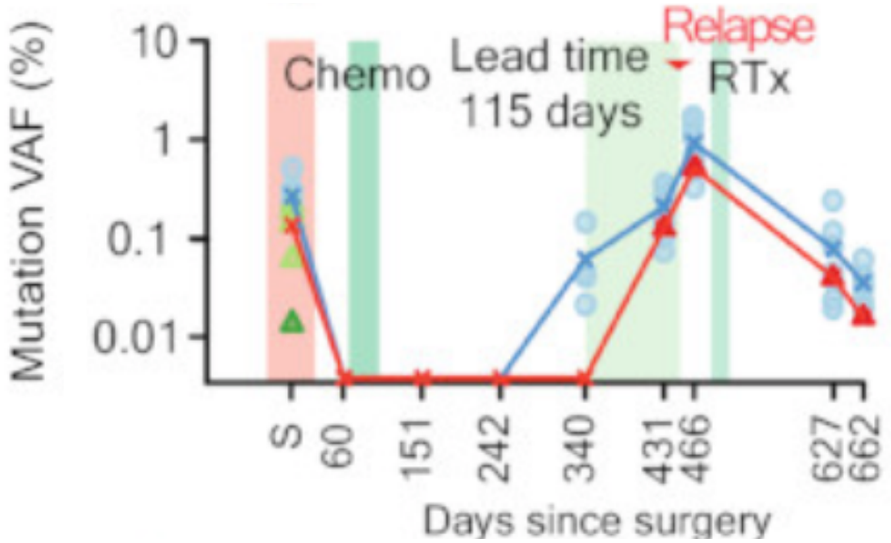
https://uofuhealth.utah.edu/huntsman/labs/varley/research/detecting-circulating.php

Mutation	Depth of read	Number of mutant reads	Variant-allele frequency	Call
BRCA1 S689R	1000	0	0%	✗
EGFR L858R	6000	4	0.07%	✗
⋮				
PIK3CA R38C	4500	150	3%	✓
TP53 R282W	5500	110	2%	✓
⋮				

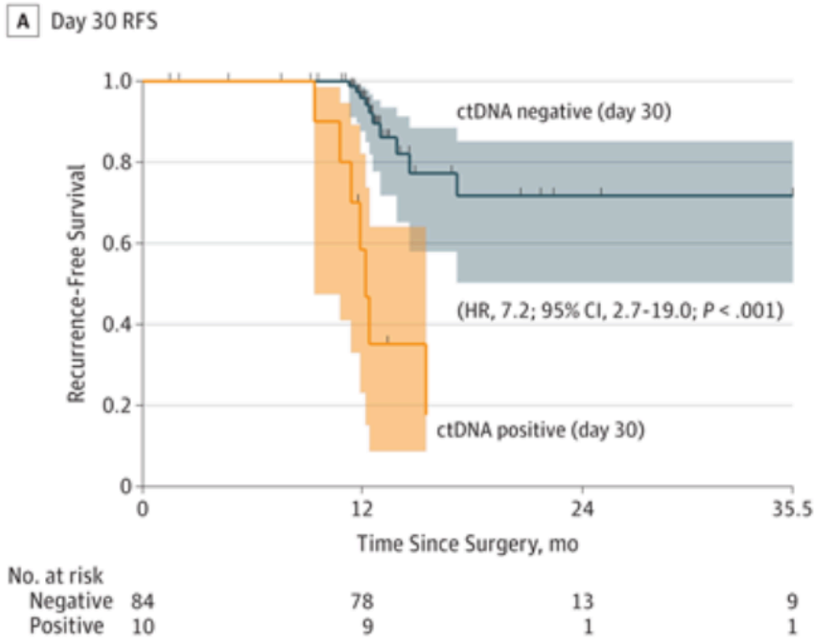


Stetson, Daniel, et al. "Orthogonal comparison of four plasma NGS tests with tumor suggests technical factors are a major source of assay discordance." *JCO Precision Oncology* 3 (2019): 1-9.

Monitoring ctDNA to detect relapse in early-stage cancer



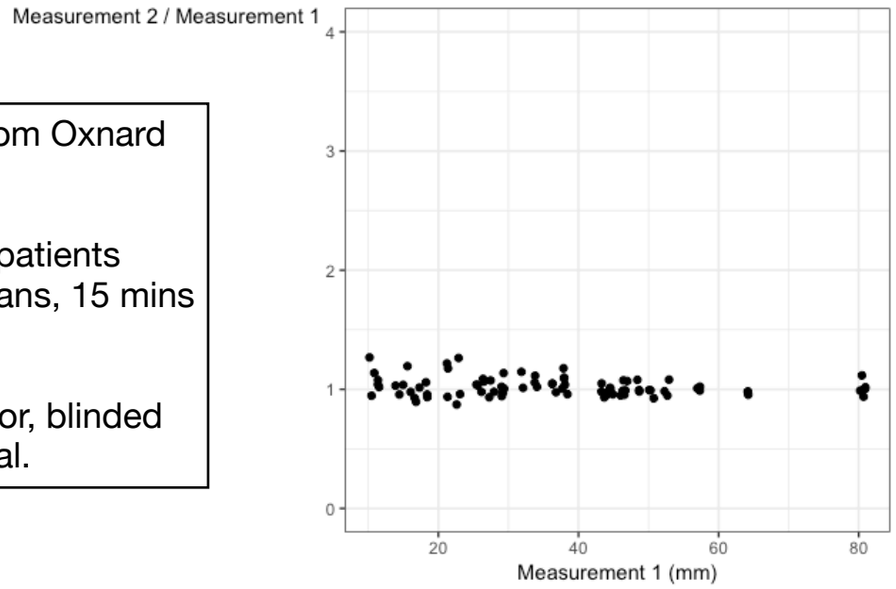
Abbosh, Christopher, et al. "Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution." *Nature* 545.7655 (2017): 446.

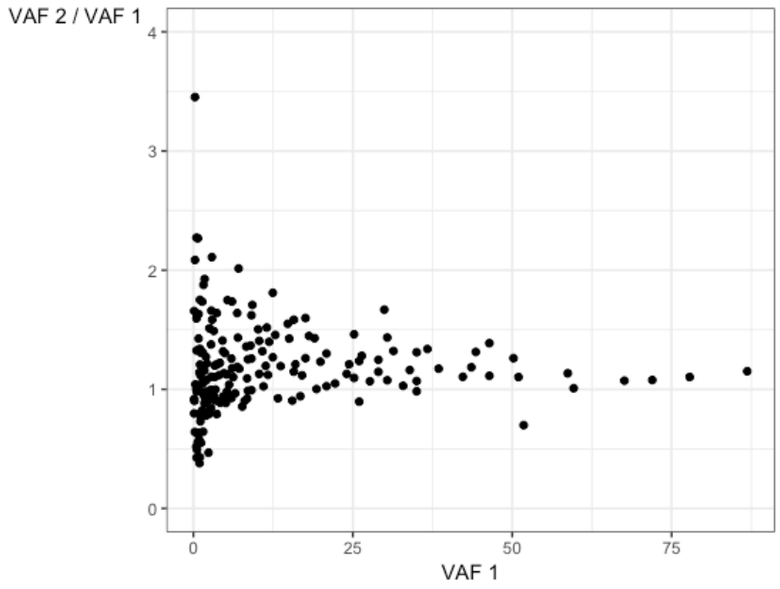


Reinert, Thomas, et al. "Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer." *JAMA oncology* (2019).

VAF as an endpoint?

- Data taken from Oxnard et al. (2011).
- Lung cancer patients have 2 CT scans, 15 mins apart.
- Same assessor, blinded to time interval.

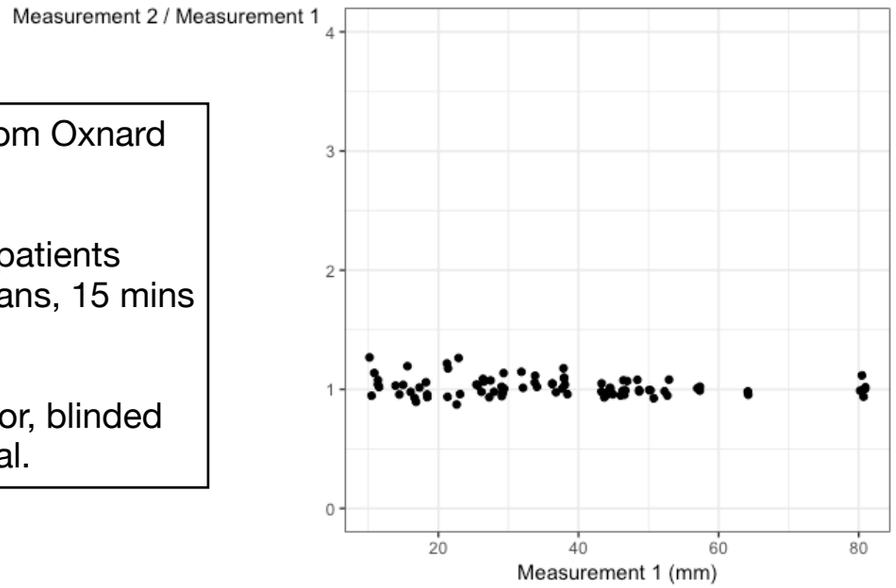


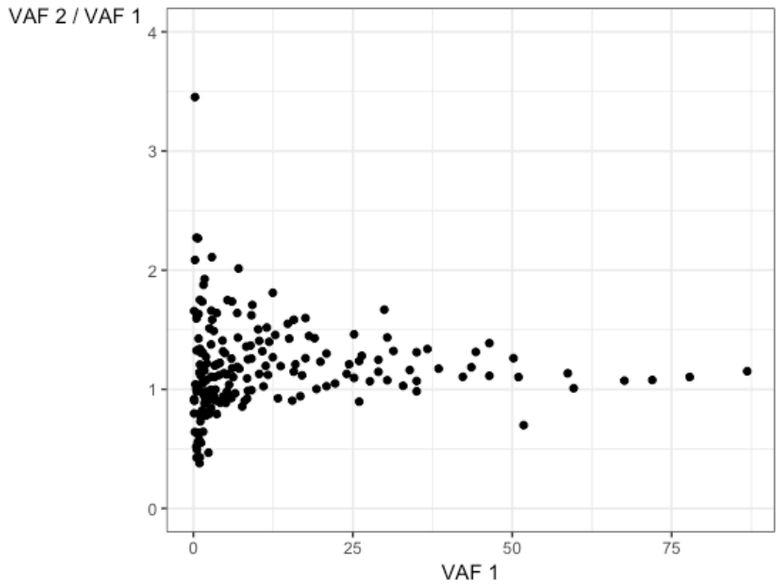


- Data taken from Odegaard et al. (2018).
- 2 blood samples are taken and sent to independent labs to measure VAF.
- Dots correspond to individual variants from 222 samples.

VAF as an endpoint?

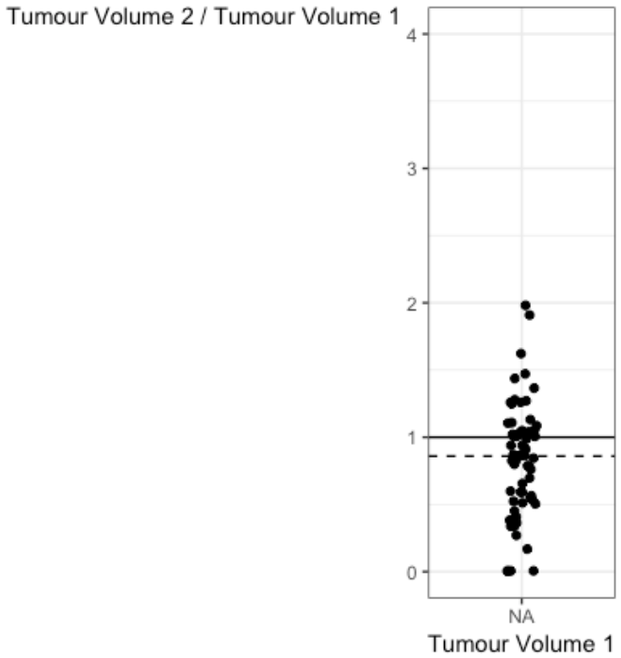
- Data taken from Oxnard et al. (2011).
- Lung cancer patients have 2 CT scans, 15 mins apart.
- Same assessor, blinded to time interval.

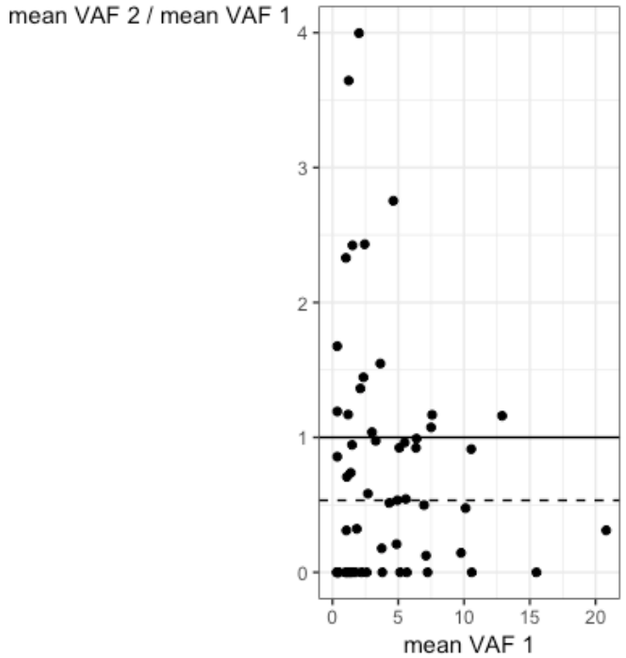




- Data taken from Odegaard et al. (2018).
- 2 blood samples are taken and sent to independent labs to measure VAF.
- Dots correspond to individual variants from 222 samples.

- Data taken from Raja et al. (2018).
- 64 advanced lung cancer patients treated with immunotherapy drug.
- Baseline and post-treatment tumour volume.





- Data taken from Raja et al. (2018).
- 64 advanced lung cancer patients treated with immunotherapy drug.
- Baseline and 6-week blood samples.

Summary

- Master protocol trials in early phase oncology are an efficient way to test multiple hypotheses.
- Regardless of overall structure, most use single-arm cohorts and measure response rate.
- We are making assumption of big effect sizes on response rate scale, relative to progression-free survival time. Even so, for cohort sizes 50 to 100, a 2-arm comparison would give more precision. Many other considerations:
  - Adverse event comparisons.
  - Predictive/prognostic biomarker.
  - Combination therapy.
  - Time to observe overall survival data.
  - Dose finding.
  - Recruitment.
  - Futility stopping.
- Variant-allele frequency (VAF) in circulating tumour DNA is a very promising new endpoint. In particular, for detecting relapse in early-stage cancer following surgery. However, false positives and false negatives are a concern. Further standardisation and better understanding of limitations is required.
- For measuring activity in later stage disease, the measurement error of VAF is high but effect sizes could be large enough to overcome this. We need more validation studies (including longitudinal data) and research into analysis methods.

References

West H. Novel Precision Medicine Trial Designs: Umbrellas and Baskets. JAMA Oncol. 2017;3(3):423. doi:10.1001/jamaoncol.2016.5299

Janiaud, Perrine, Stylianos Serghiou, and John PA Ioannidis. "New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology." Cancer treatment reviews (2018).

N Stallard, S Todd, D Parashar, P K Kimani, L A Renfro, On the need to adjust for multiplicity in confirmatory clinical trials with master protocols, Annals of Oncology, https://doi.org/10.1093/annonc/mdz038

Hyman, David M., et al. "Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations." New England Journal of Medicine 373.8 (2015): 726-736.

Hobbs, B. P., et al. "Statistical challenges posed by uncontrolled master protocols: sensitivity analysis of the vemurafenib study." Annals of Oncology 29.12 (2018): 2296-2301.

Berry, Scott M., et al. "Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase II oncology clinical trials." Clinical Trials 10.5 (2013): 720-734.

Taylor, Jeremy MG, Thomas M. Braun, and Zhiguo Li. "Comparing an experimental agent to a standard agent: relative merits of a one-arm or randomized two-arm phase II design." Clinical Trials 3.4 (2006): 335-348.

Blumenthal, Gideon M., et al. "Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses." Journal of Clinical Oncology 33.9 (2015): 1008.

Abbosh, Christopher, et al. "Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution." Nature 545.7655 (2017): 446.

Stetson, Daniel, et al. "Orthogonal comparison of four plasma NGS tests with tumor suggests technical factors are a major source of assay discordance." *JCO Precision Oncology* 3 (2019): 1-9.

Oxnard, Geoffrey R., et al. "Variability of lung tumor measurements on repeat computed tomography scans taken within 15 minutes." Journal of Clinical Oncology 29.23 (2011): 3114.

Odegaard, Justin I., et al. "Validation of a plasma-based comprehensive cancer genotyping assay utilizing orthogonal tissue-and plasma-based methodologies." Clinical Cancer Research 24.15 (2018): 3539-3549

Raja, Rajiv, et al. "Early reduction in ctDNA predicts survival in patients with lung and bladder cancer treated with durvalumab." Clinical Cancer Research 24.24 (2018): 6212-6222.