Early Stage Cancer Therapies and Surrogate Endpoints

Agenda:

- 7:30-7:55 – Expert remarks (Bick, Thorlund, Machado, Bourgoin)
- 7:55-8:55 – Facilitated discussion and workshop collaboration
- 8:55-9:00 – Closing remarks and reflections / next steps from Bob Bick

Challenge Question:

How do we ensure patient and clinician access to early-stage cancer treatments that rely on surrogate outcomes?

Early Stage Cancer Therapies and Surrogate Endpoints

Kristian Thorlund
McMaster University
Hamilton, ON

Oct 18, 2022

Fun Fact!

An oncology drug is more likely to get approved

if the trial does NOT include Overall Survival

Pinto et al. ViH 2022; 23(3):319–327.
Davies et al. BMJ 2017; 359:j4530.

Sparse validation in early cancers

- Two reviews of 23 systematic reviews: NSCLC and Breast cancer
- Only 3 trials concentrated on ‘early stage’ cancer
- All reported on correlations as measure of surrogacy
- None reviewed QoL

Research Paper

Evaluating the evidence behind the surrogate measures included in the FDA’s table of surrogate endpoints as supporting approval of cancer drugs

Bishal Gyawali[a,b,*], Spencer P. Hey[a,c], Aaron S. Kesselheim[a,c]

[a] Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, US
[b] Department of Oncology, Department of Public Health Sciences and Division of Cancer Care and Epidemiology, Queen’s University, Kingston, Canada
[c] Harvard Center for Bioethics, Harvard Medical School, Boston, MA, US

OPEN ACCESS

The Relationship Between Short-Term Surrogate Endpoint Indicators and mPFS and mOS in Clinical Trials of Malignant Tumors: A Case Study of Approved Molecular Targeted Drugs for Non-Small-Cell Lung Cancer in China

*Mingjun Rui[1,2], Zijing Wang[1,2], Zhengyang Fei[1,2], Yao Wu[1,2], Yingcheng Wang[1,2], Lei Sun[1], Ye Shang[1,2] and Hongchao Li[1,2]**

[1]School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, China, [2]Center for Pharmacoeconomics and Outcomes Research, China Pharmaceutical University, Nanjing, China

‘A correlate does not a surrogate make’[1]

*‘the surrogate must be a **correlate** of the true clinical outcome and **fully capture the net effect of treatment** on the clinical outcome.’*[2]

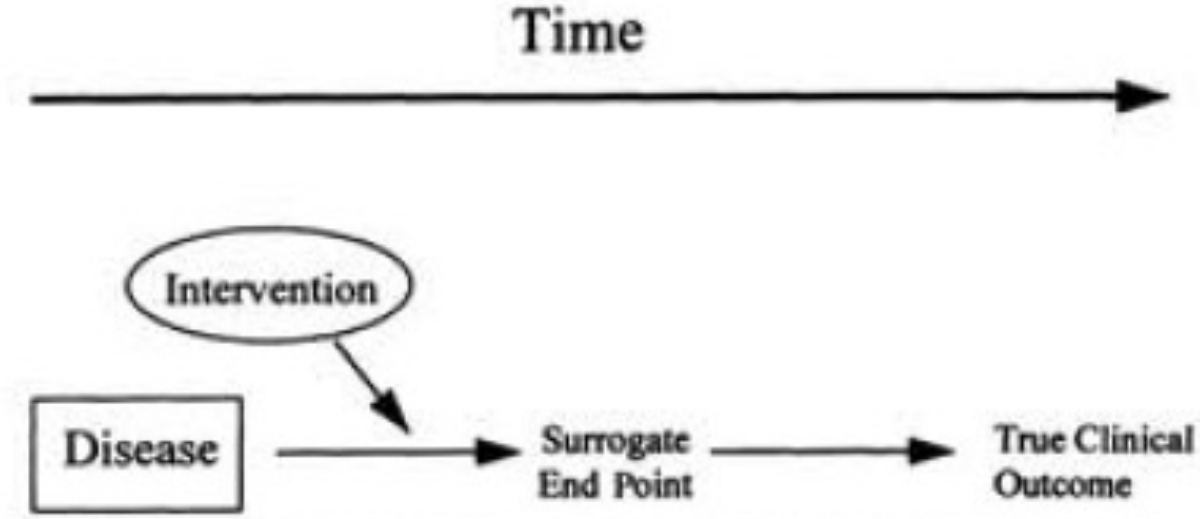
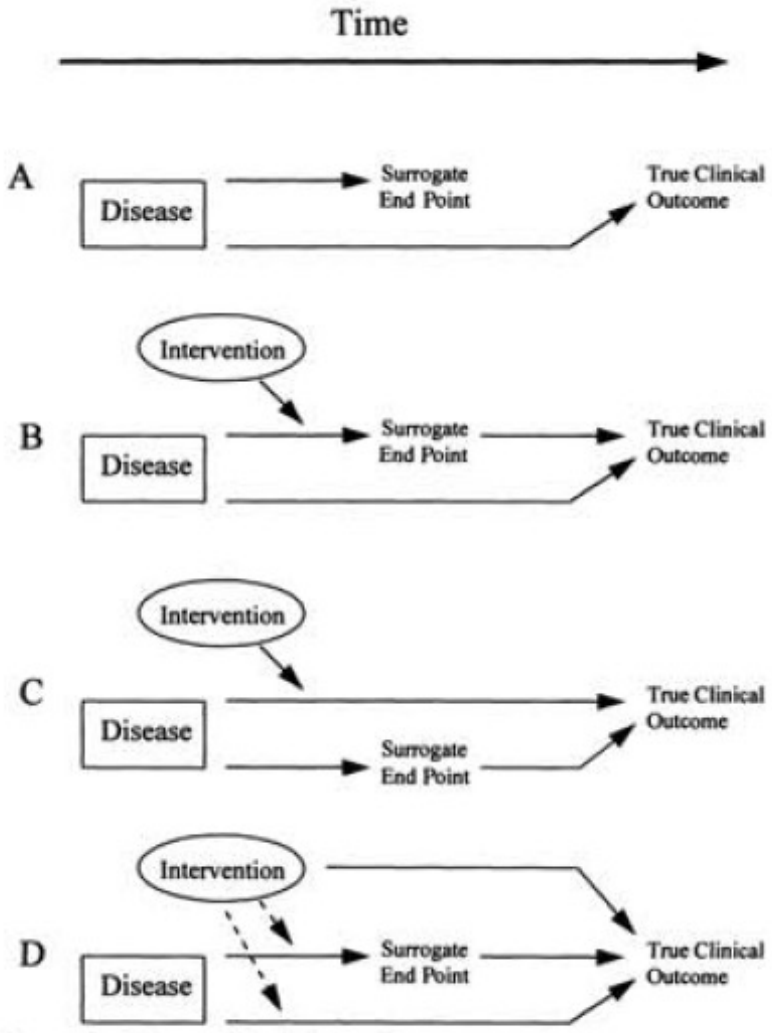


Figure 2. The setting that provides the greatest potential for the surrogate end point to be valid.

[1]*Fleming & DeMets. Ann Int Med 1996. Surrogate Endpoints in Clinical trials. Are we being Misled?*
[2] *Prentice RL. Stat Med 1989. Surrogate Endpoints in Clinical trials. Definition and Operational Criteria*

What is NOT a good surrogate?



Not involving same pathological process that results in outcome

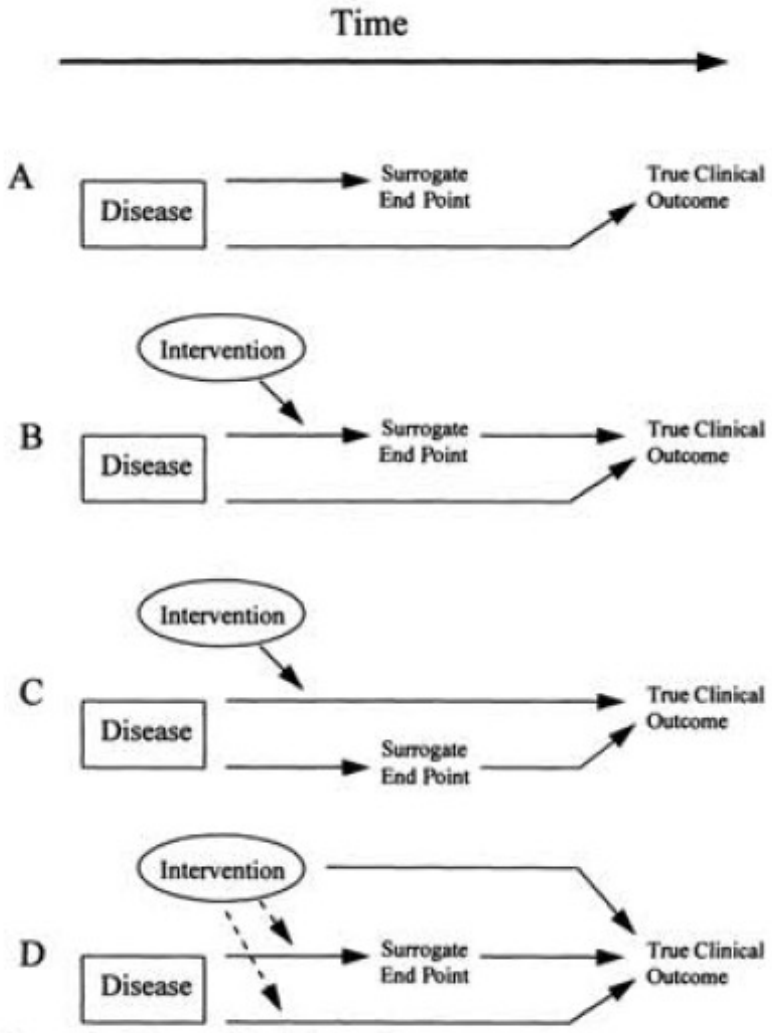
Intervention only affects pathways of the surrogate outcome

Intervention affects pathways independent of the surrogate outcome

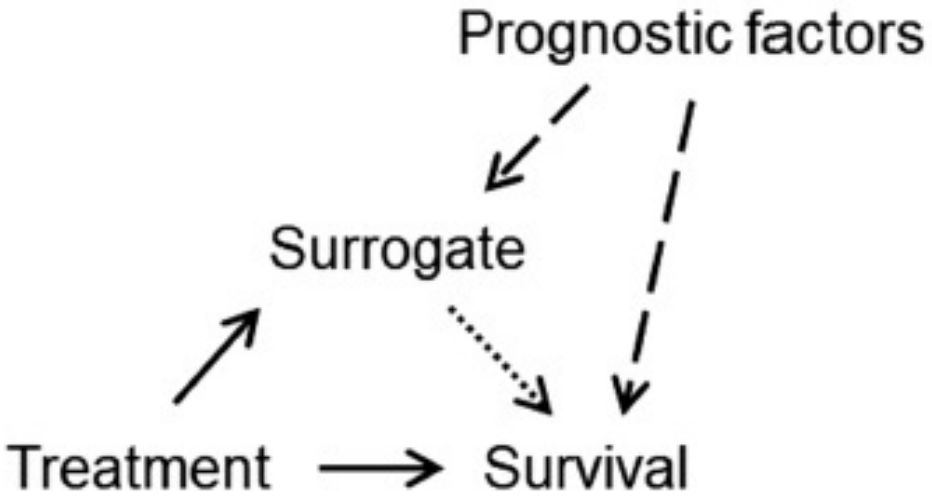
Intervention effect through intended pathways offset by under-recognized mechanisms

Fleming & DeMets. Ann Int Med 1996. Surrogate Endpoints in Clinical trials. Are we being Misled?

What is NOT a good surrogate?



Fleming & DeMets. Ann Int Med 1996.



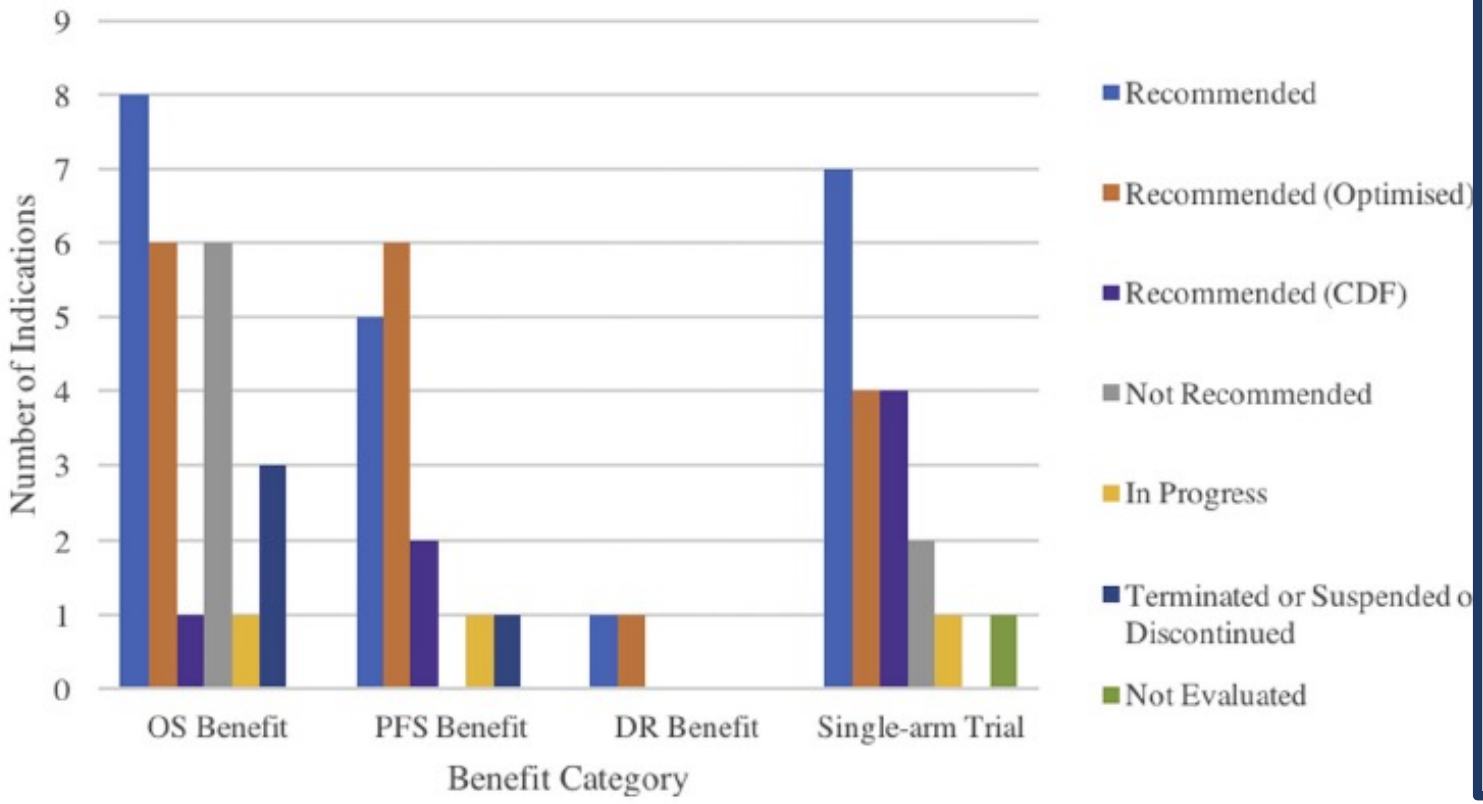
Presence of prognostic factors (known or unknown) correlated both with surrogate and survival

Buyse M et al. The Oncologist 2022. Surrogacy beyond prognosis:…

How would and should HTAs deal?

Health Policy Analysis

**Association Between the Use of Surrogate Measures in Pivotal Tr
Health Technology Assessment Decisions: A Retrospective Analys
NICE and CADTH Reviews of Cancer Drugs**



25 OS-based recommendations

- 15 positive with NICE
- 14 (2) positive with CADTH

14 PFS-based recommendations

- 12 positive with NICE
- 9 (2) positive with CADTH

2 DR-based recommendations

- 2 positive with NICE
- 1 (0) positive with CADTH

** Numbers in parentheses represent recommendations without requirement for improved cost-effectiveness*

How would and should HTAs deal?

CADTH

Classic EBM, Risk of Bias, GRADE
Surrogate is ‘indirect evidence’ in GRADE
Using Prentice criteria, few surrogate would survive downgrading
Pembrolizumab for the Adjv. Tx for RCC at high risk of recurrence DFS was the surrogate outcome. (2022)

NICE

Can be heavy on stats methods
Has endorsed several novel RWD approaches lately
Realistically, most surrogate outcomes still won’t make it
Atezolizumab for the resected Stage I-IIIa NSCLC DFS was the surrogate outcome. (2022)

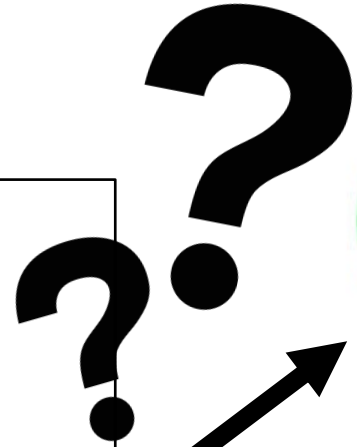
Bad habits to shed, new ones to adopt

Correlation Studies (only)

Classic EBM & 1:1 RCTs

Aggregate Data Meta-analyses

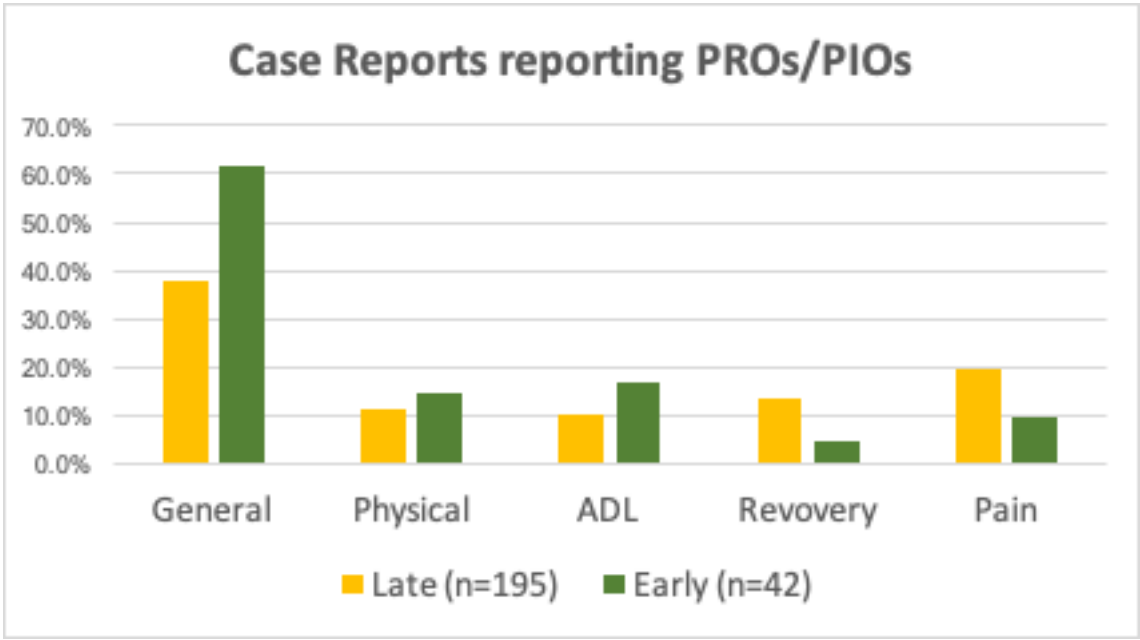
Proactive RWD studies
QoL/PROs/PIOs
Adaptive trials
Surrogacy ‘prognosis’
Surrogacy comparative bias
Quantitative Bias Analysis
Causal Inference
Mixture-cure models

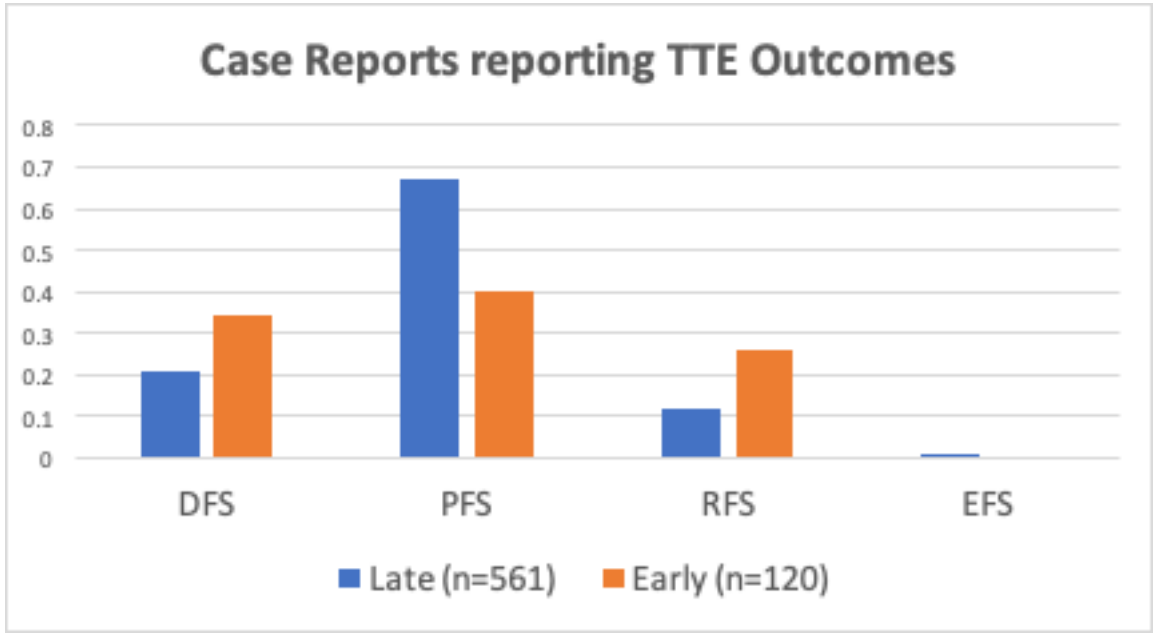


RWD = Real World Data;
QoL = Quality of Life;
PRO = Patient Reported Outcome
PIO = Patient Important Outcome

What might RWD studies look like?

1,000 randomly selected published oncology case reports from 2016-2021 in Lung, Breast, Colorectal, Pancreatic, Bladder and Hematological Cancers

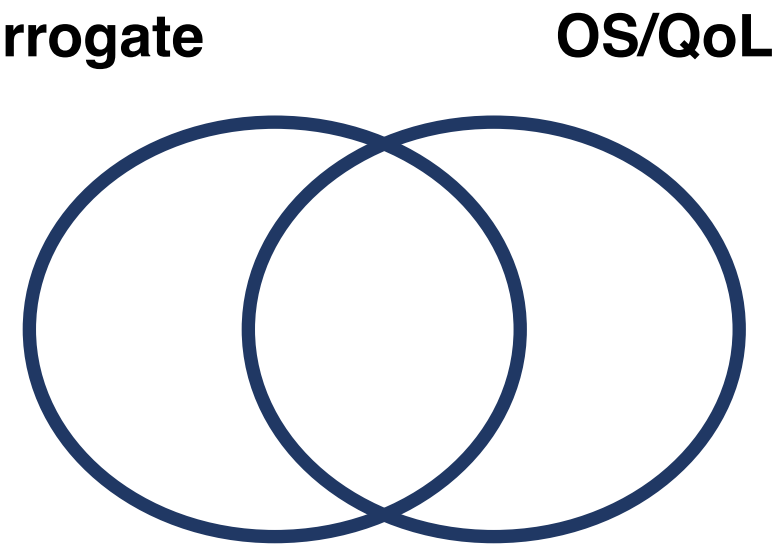




OpenCase
Powered by BioSpark AI Technologies

(pre-launch Oct 2022) www.opencase.ai

Beyond correlation – prognostic accuracy and bias

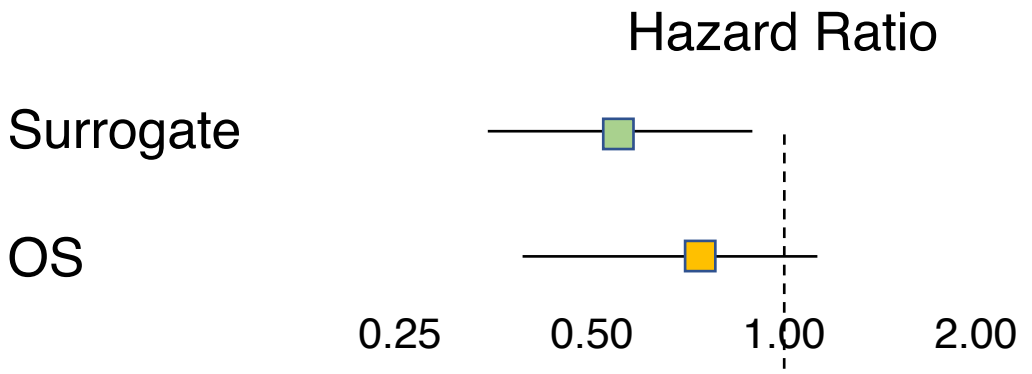


ImmunoTx

Predictions	Surrogate+	Surrogate-
OS/QoL+	85%	10%
OS/QoL-	15%	90%

SOC

Predictions	Surrogate+	Surrogate-
OS/QoL+	95%	20%
OS/QoL-	5%	80%

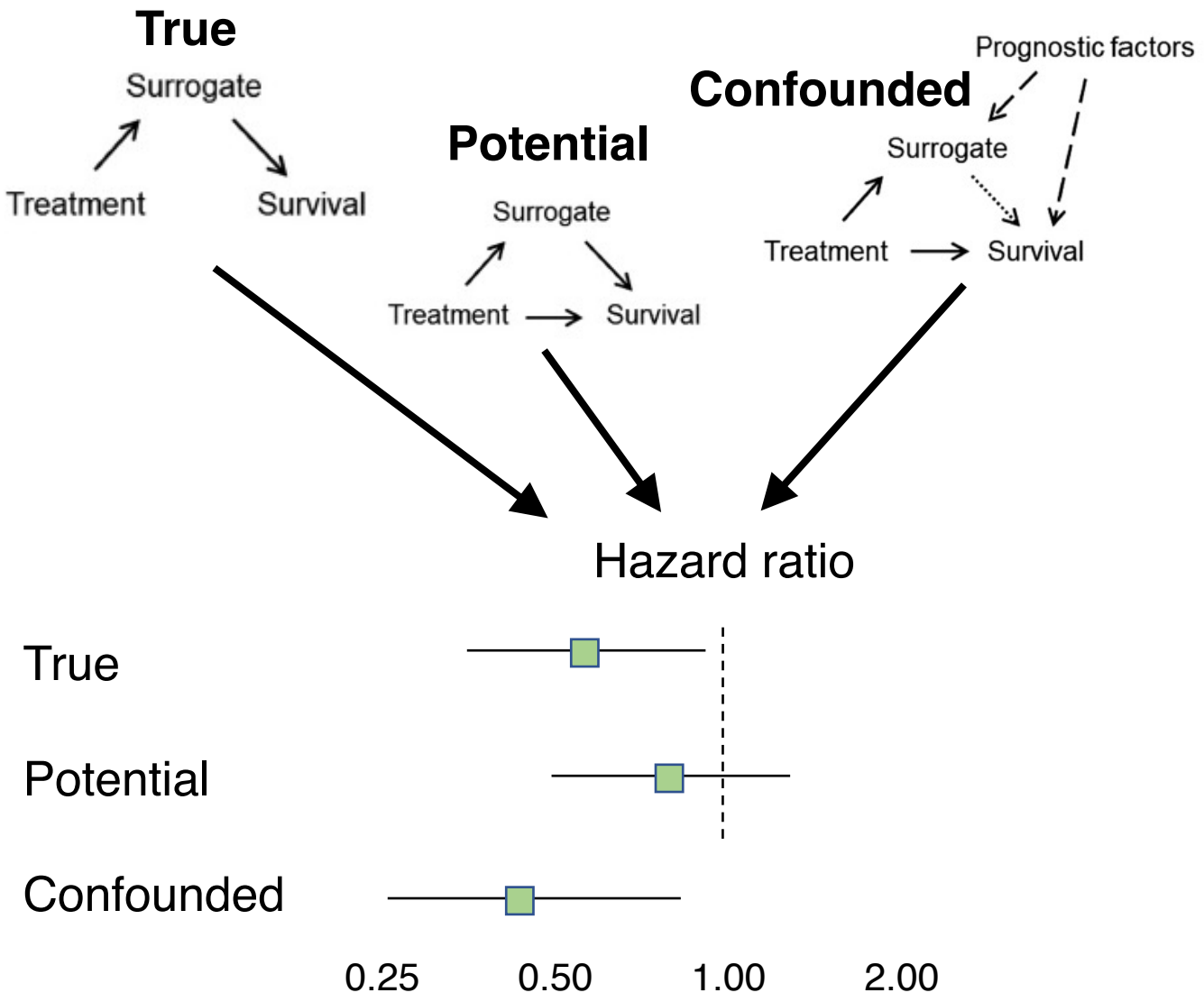


Quantitative Bias Analysis

Unmeasured confounding in nonrandomized studies: quantitative bias analysis in health technology assessment

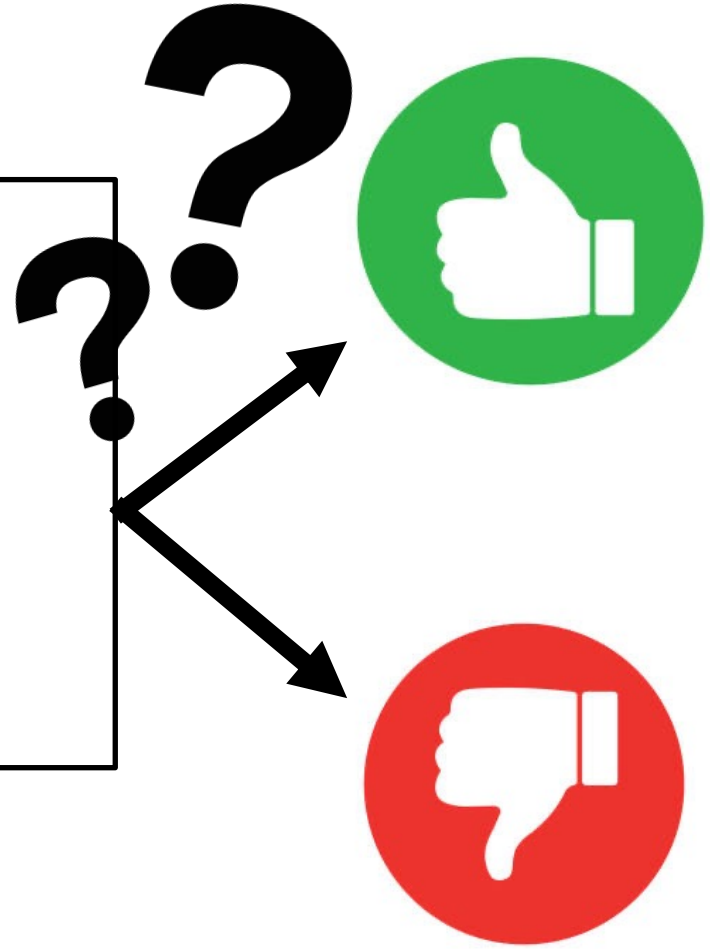
Thomas P Leahy[1], Seamus Kent[2], Cormac Sammon[1], Rolf HH Groenwold[3], Richard Grieve[4], Sreeram Ramagopalan*[,5] & Manuel Gomes[6]

Quantitative bias analysis (QBA) is a broad collection of approaches for modeling the magnitude and direction of systematic errors (bias) in the data that cannot otherwise be adjusted for



Time to discuss…

For Discussion



Lisa Machado

Executive Director, Canadian CML Network and Executive Producer, healthing.ca

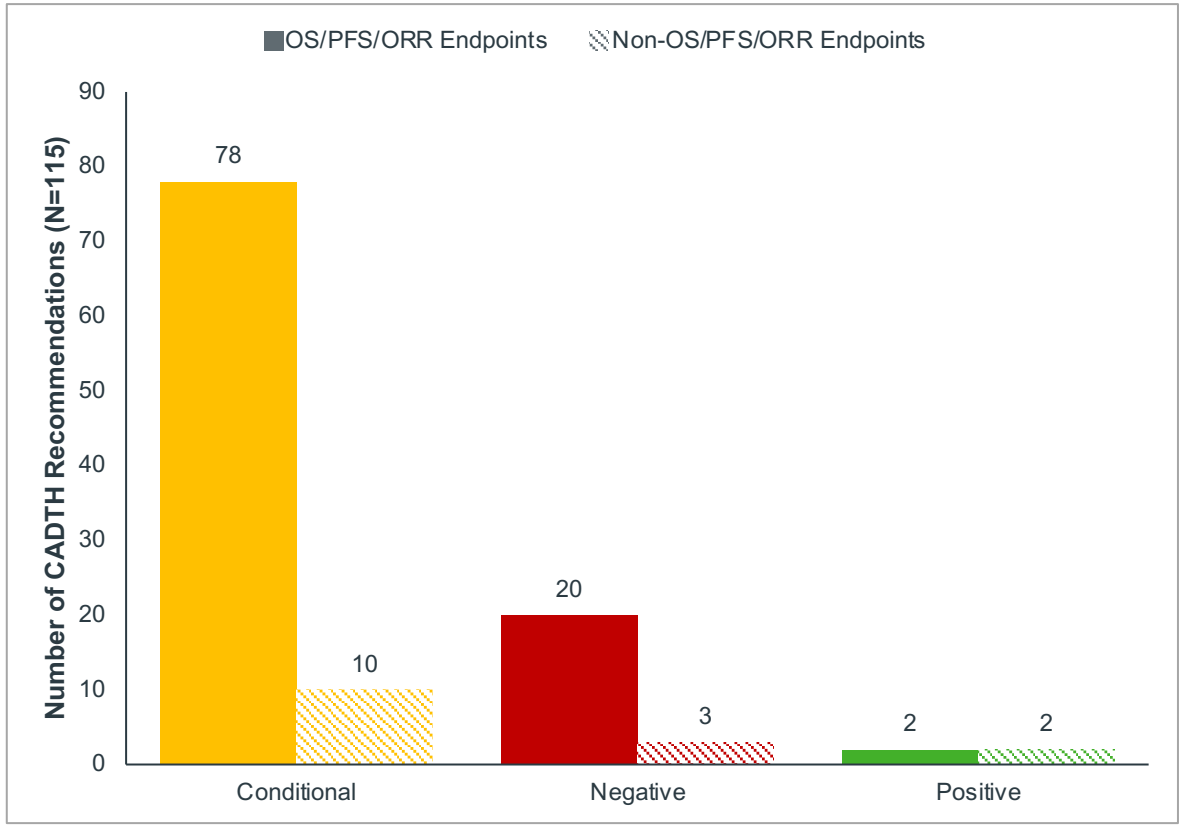
"Early-Stage Cancer Therapies: How Can Canadian Evaluators and Funders Adapt to Review Treatments with Surrogate Endpoints?"

October 18, 2022

Tara Bourgoin, Sr. Consultant
IQVIA Real World Solutions

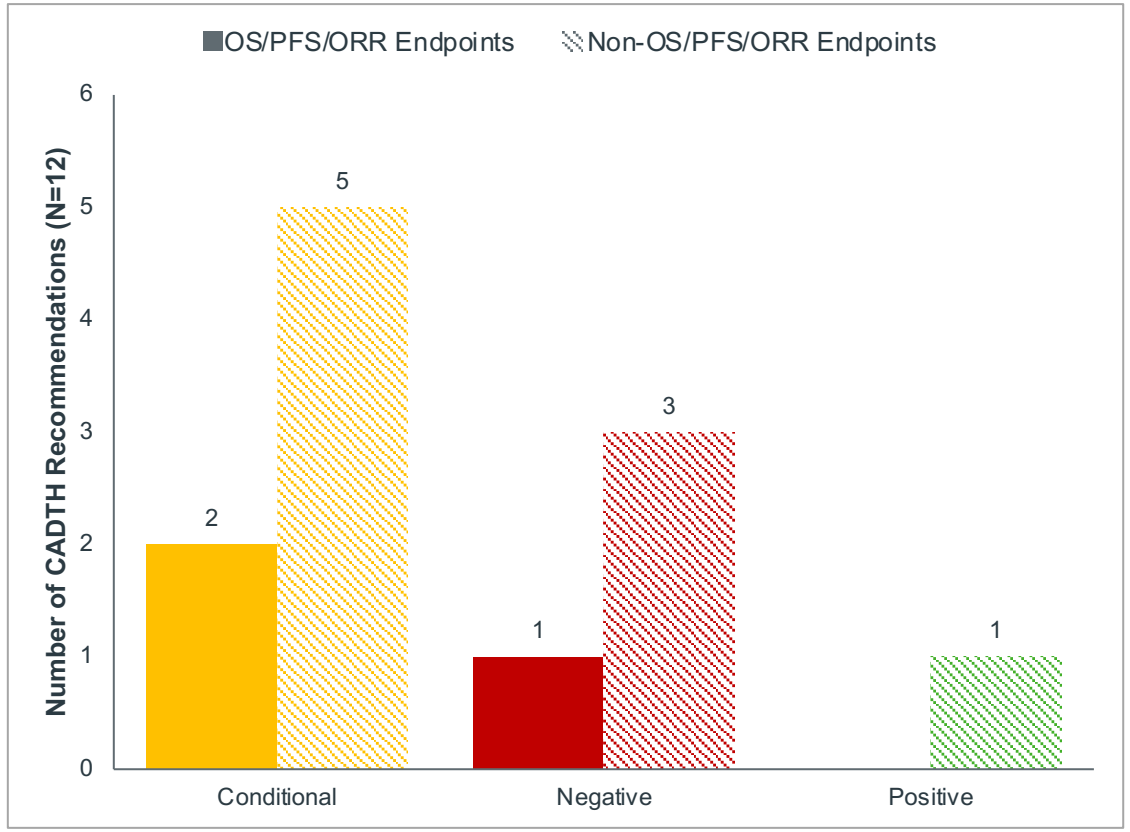
Evaluation of CADTH recommendations demonstrates a proportionally higher use of non-traditional endpoints for early-stage cancers

Recommendations – All oncology indications and disease stages



115 CADTH recommendations from Jan 2017 – Dec 2021 were evaluated and included **all indications and disease stages**. Recommendations assessed did not include the following: Resubmissions, submissions with 2nd pCPA attempt, non-manufacturer submissions, or those for gene therapies or biosimilars.

Recommendations – Early-stage solid tumours



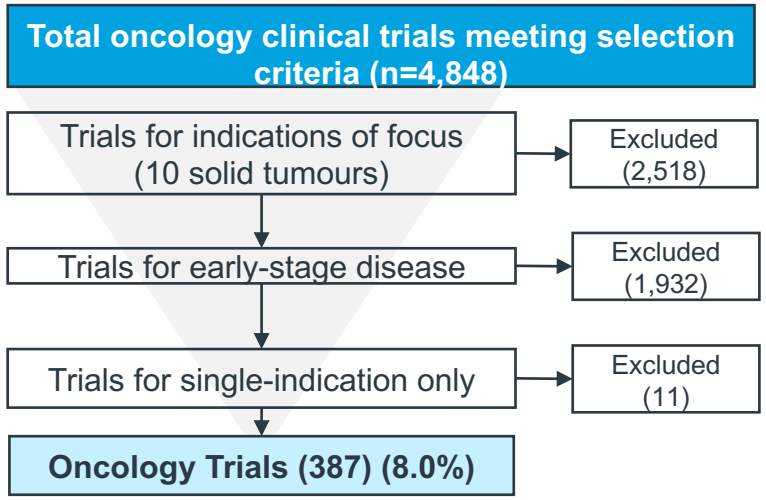
12 CADTH recommendations from Jan 2017 – Mar 2021 were evaluated and included **only solid tumours in early-stage disease**. Recommendations assessed did not include the following: Resubmissions, submissions with 2nd pCPA attempt, non-manufacturer submissions, or those for gene therapies or biosimilars.

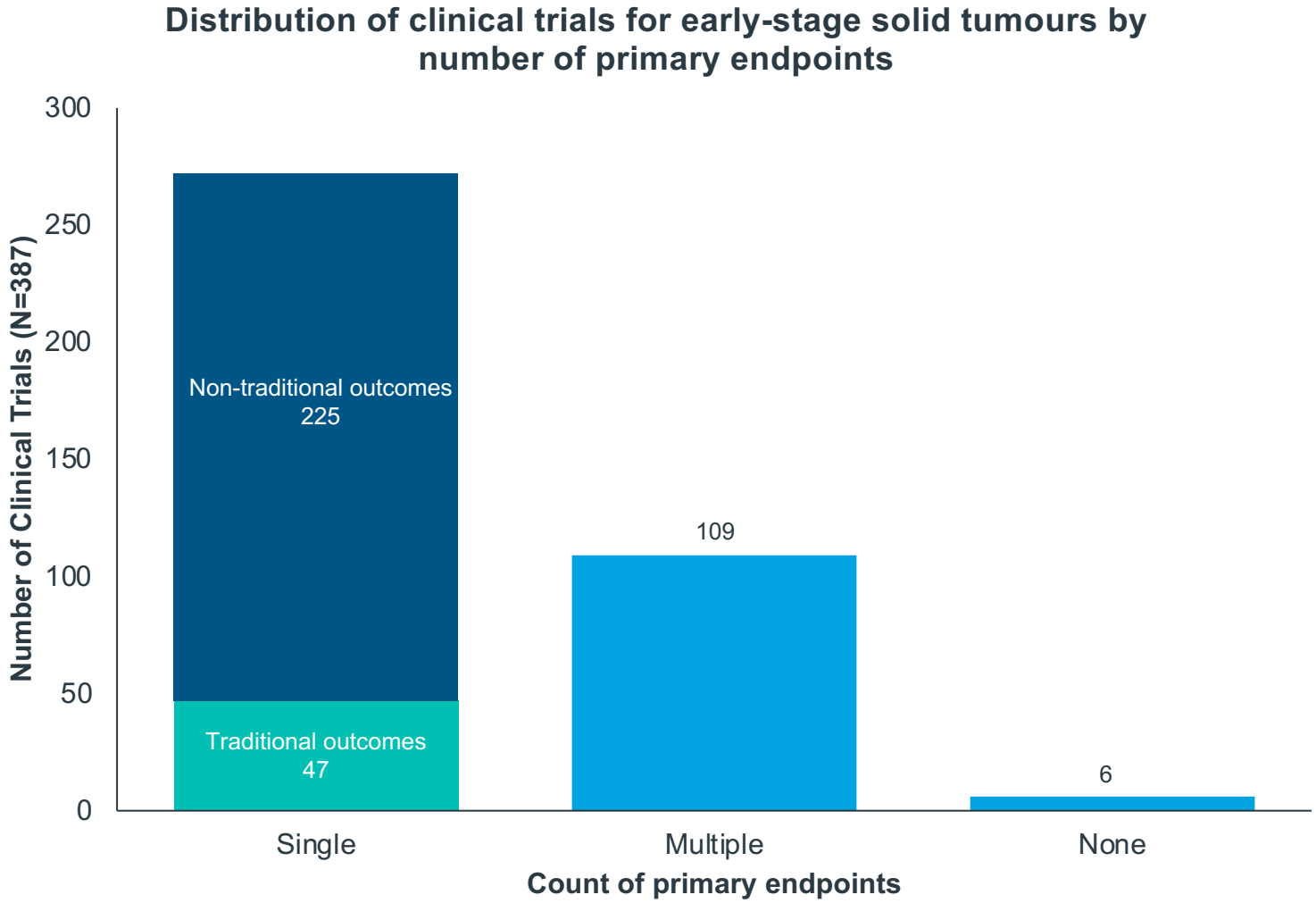
Source: IQVIA's Market Access Metrics database
Analysis conducted by IQVIA, and sponsored by AstraZeneca

An independent study of clinical trials in early-stage disease for solid tumours was conducted to estimate the potential impact of non-traditional endpoints on future HTA

Selection Criteria

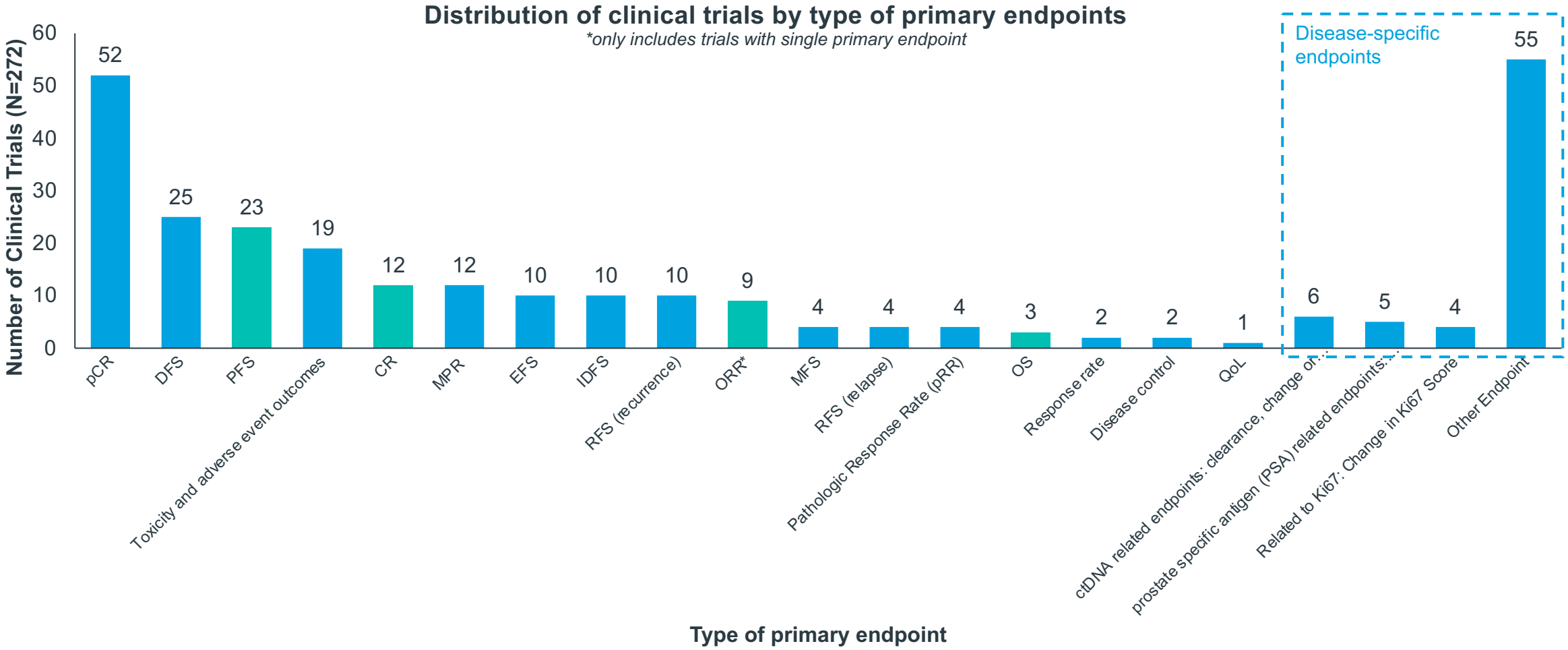
Trial type: Interventional clinical trials
Trial timing: Start date of Jan 2017 - Mar 2022
Sponsor: Industry
Study Phase: Phase 2 and 3
Status: not withdrawn, suspended or completed
Top 10 tumor types: Lung, Breast, Prostate, Melanoma, Ovarian, Colorectal, Pancreatic, Esophageal, Gastric, Bladder (single indication)
Disease stage: Early stage, non metastatic, non invasive, localized, Stage I-III





Source: clinicaltrials.gov
Analysis conducted by IQVIA, and sponsored by AstraZeneca

~82% of clinical trials in early-stage disease with a single primary endpoint include non-traditional outcomes; type of frequency of outcome is varied



Abbreviations: CR; complete response; DFS, Disease free survival; EFS, event free survival; IDFS, Invasive disease free survival; MFS, Metastasis free survival; MPR, major pathological response; ORR, overall response rate; OS, overall survival; pCR, Pathologic complete response; PFS, progression free survival; QoL, quality of life; RFS (recurrence free survival); RFS (relapse free survival)
**Includes eight clinical trials for lung cancer and one for melanoma*

Source: clinicaltrials.gov
Analysis conducted by IQVIA, and sponsored by AstraZeneca