Workshop 310

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Approaches to addressing challenges in cost-effectiveness analysis of tumor agnostic drugs

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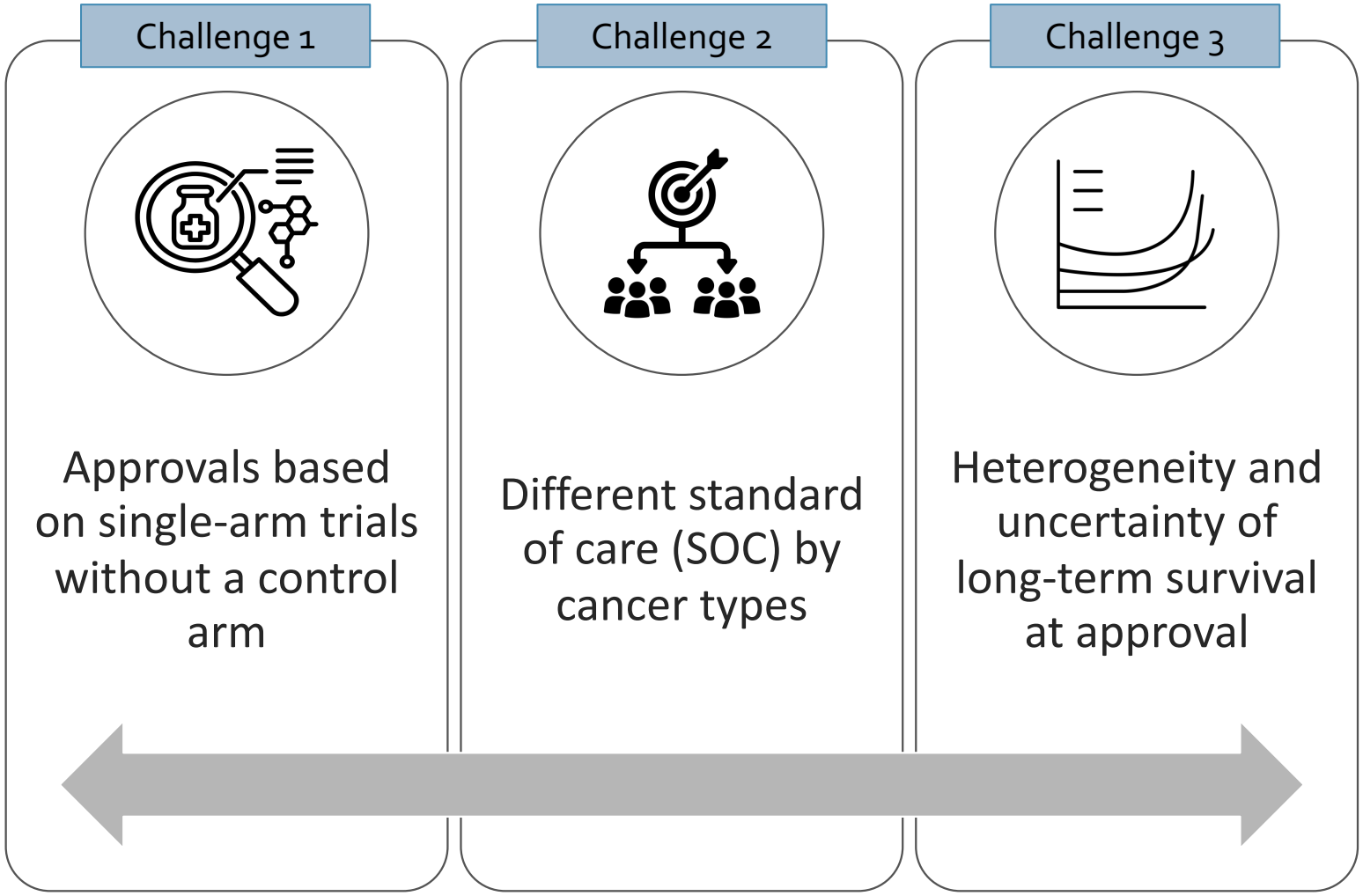
Disclosures

This research was conducted as part of my PhD dissertation at UW and prior to my tenure at Curta.

I declare no financial interests or affiliations related to the content discussed in this presentation.

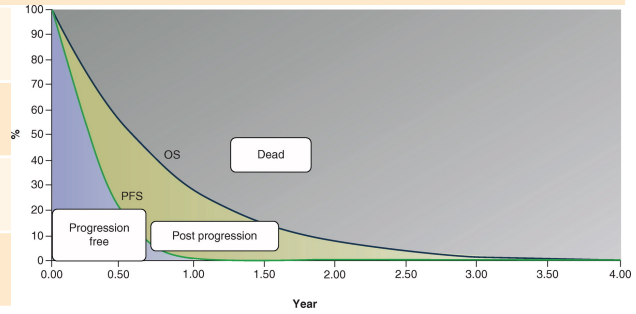
Challenges of conducting CEA of tumor agnostic drugs



Case study – pembrolizumab

- Indication: Pembrolizumab in previously-treated unresectable or metastatic, microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) solid tumors
- The US FDA approval based on single-arm trials:
  - May 2017, accelerated approval based on five trials.
  - March 2023, full approval based on KEYNOTE 146, 158, and 051.
- CEA model overview

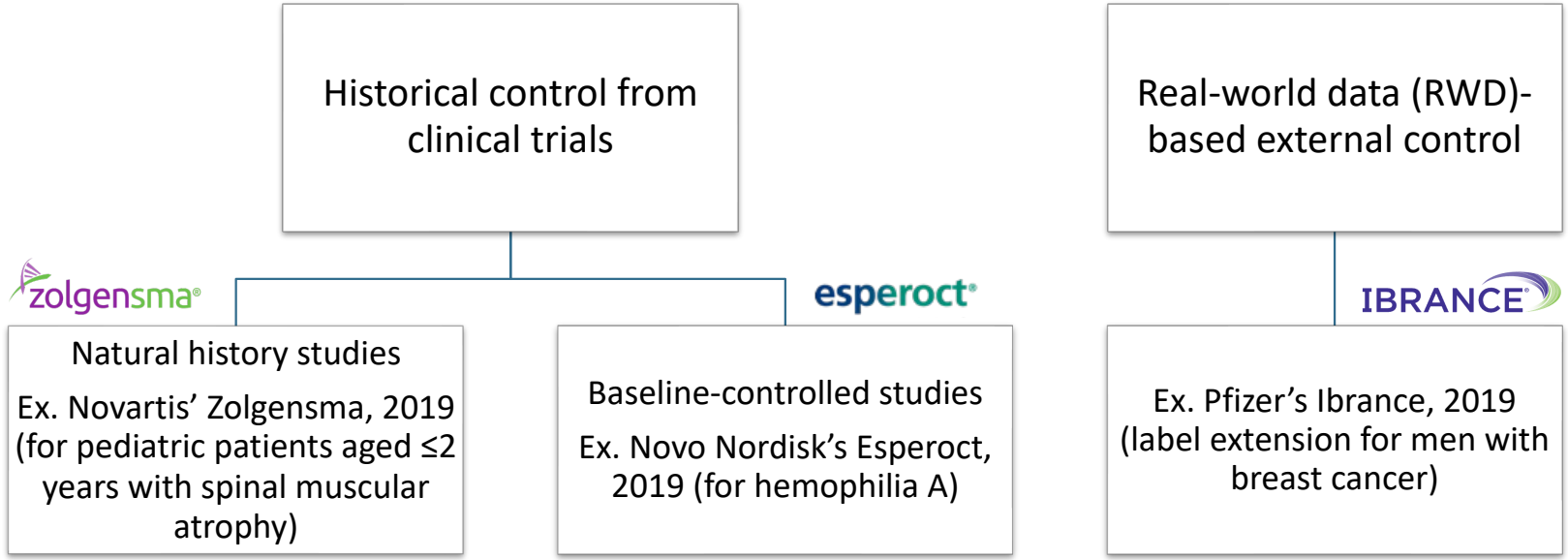
Cancer Types	Colorectal, endometrial, gastric, cholangiocarcinoma, small intestine, ovarian, pancreatic, and brain
Structure	Partitioned Survival Model
Intervention	Pembrolizumab
Comparators	SOC chemotherapies
Cycle Length	1 month
Time Horizon	Lifetime
Perspective	US Payer



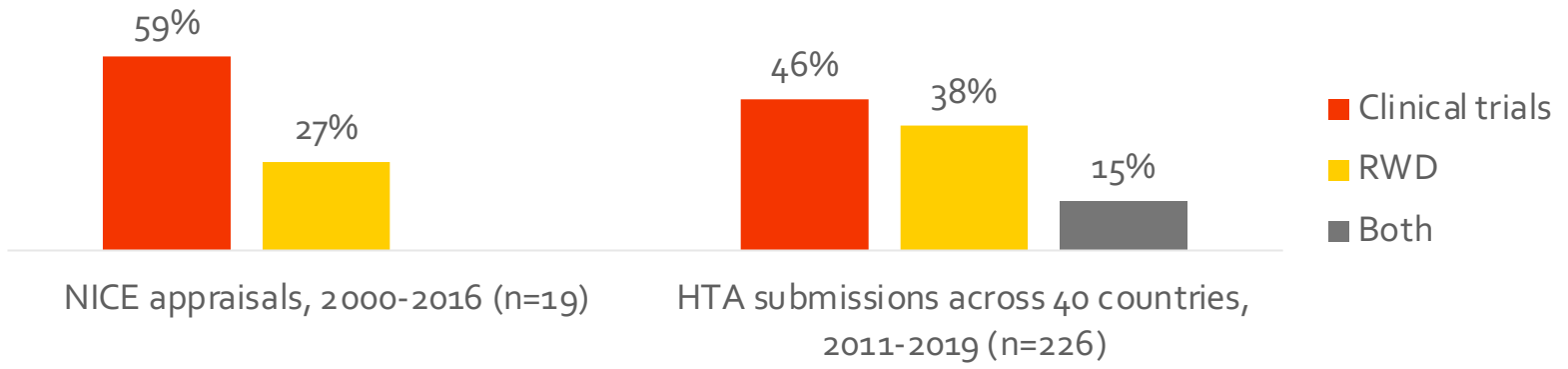
Chen Y, Martin P, Inoue LY, Basu A, Carlson JJ. Tackling Challenges in Assessing the Economic Value of Tumor-Agnostic Therapies: A Cost-Effectiveness Analysis of Pembrolizumab as a Case Study. Value in Health. 2024 Mar 26. Now available from: https://authors.elsevier.com/a/1iwrN3vkP0CS7e

Challenge 1 - Lack of Comparative Data

Construct synthetic or external control arm



Trend of using external control arms in SAT-based HTA submissions



HTA, health technology assessment; RWD, real-world data; SAT, single-arm trial

Source: Anderson M et al, J Clin Epidemiol 2019; Patel D et al, Value in Health 2021; Jahanshahi M et al, Therapeutic Innovation & Regulatory Science 2021; FDA press release.

Considerations for external control arms

Disease characteristics

- Rare disease or rare indication
- High unmet need
- Objective measure as a primary endpoint

External data sources

- Large well-conducted RCT(s) or high-quality prospective cohort studies

Assessment of bias

- Similarity of external control population to the clinical trial population
- Feasibility of capturing endpoints and prognostic variables

Synthetic control methods

- Appropriate disease-dependent cohort selection for the research question
- Propensity score methods
- Further statistical adjustment in instances of heterogeneity

Relevance and reliability

- Similar designs and processes as possible for historical trials
- Relevant time periods considering evolving SoC and outcome definitions

RCT, randomized control arm; SoC, standard of care

Seeger JD, Davis KJ, Iannacone MR, et al. Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. Pharmacoepidemiology and Drug Safety. 2020 Nov;29(11):1382-92.

Thorlund K, Dron L, Park JJ, et al. Synthetic and external controls in clinical trials–a primer for researchers. Clinical epidemiology. 2020 May 8:457-67.

Challenge 1 - Lack of Comparative Data

Case example: RWD-based external control

- Data source: TriNetX® electronic health record databases
- Cancer types: CRC, endometrial, gastric, CCA, small intestine, ovarian, pancreatic, and brain

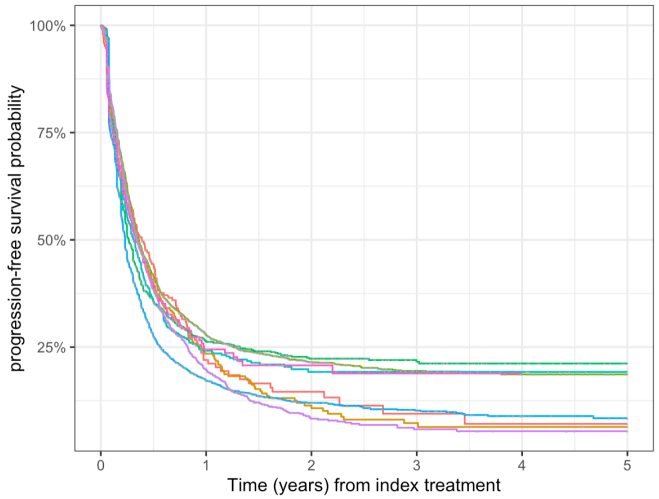
Eligibility criteria aligned with trial protocol	Patient Count
Include patients with primary diagnosis of eight cancers and having metastasis after index diagnosis	CRC: 49;462 non-CRC: 93,944
Include patients with their first metastasis on or after the initial diagnosis date	CRC: 35,537 non-CRC: 81,066
Require ≥1 prior SOC systemic therapy and ≥2 lines of therapies in total after the metastasis date	CRC: 5,495 non-CRC: 10,232
Exclude patients on chemotherapies at the index line of therapy and whose 1L treatment initiated after 90 days following their index metastasis date	CRC: 3,262 non-CRC: 6,930
Exclude patients with prior anti–PD-1, –PD-L1, or –PD-L2 therapy	CRC: 3,237 non-CRC: 6,847
Exclude patients aged <18 years and with certain comorbidities at initial cancer diagnosis	CRC: 3,104 non-CRC: 6,163

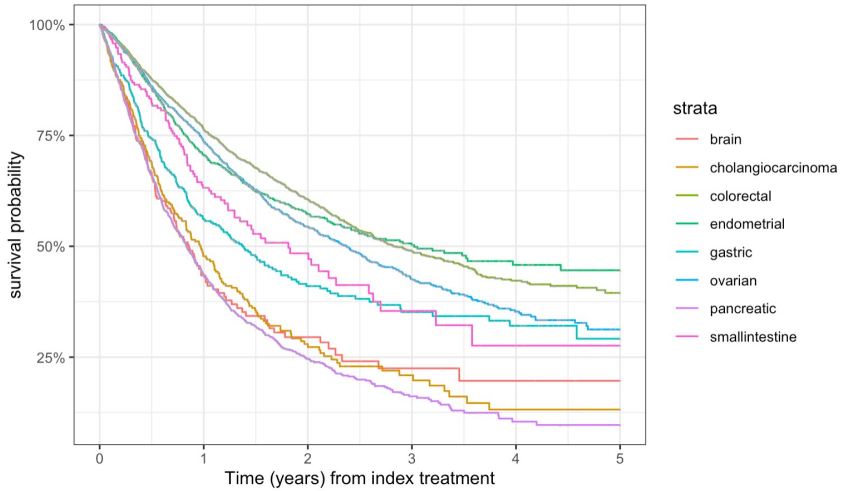
CCA, cholangiocarcinoma; CRC, colorectal cancer; RWD, real-world data; SOC, standard of care
The data period extended from January 1, 2010 to March 31, 2019 for CRC and to November 31, 2019, for non-CRC.

Challenge 1 - Lack of Comparative Data

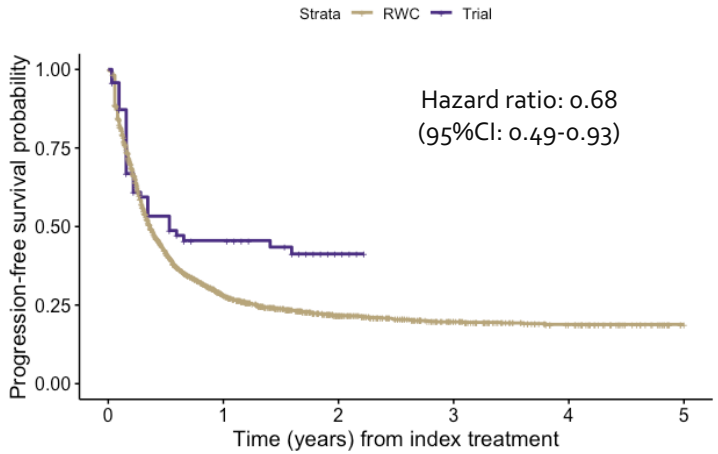
Case example: RWD-based external control

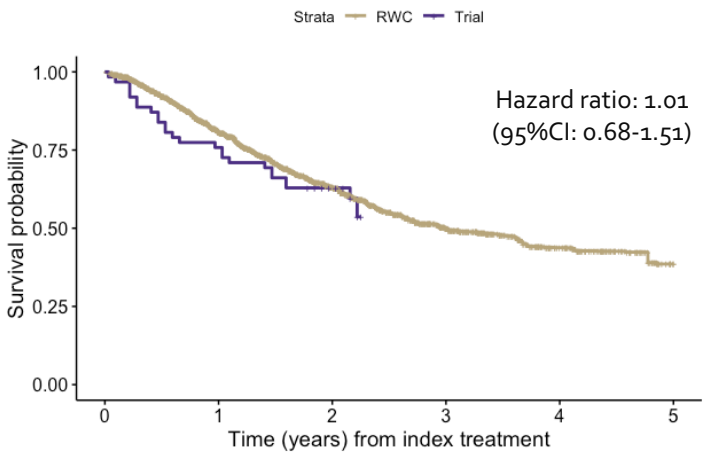
Survival curves of real-world standard of care comparators by tumor types





Weighted survival curves of colorectal cancer





RWC, real-world control; CI, confidence interval.

Time to progression: the period from the index treatment date to either the discontinuation date, the day before the next line of therapy, or the date of death, whichever occurred first.

Challenge 2 – Different SOC by tumor types

1. How to model different comparator arms by cancer types?

- Define SOC based on clinical guidelines relevant to each cancer type
- Calculate total drug costs for SOC:
  - $\sum_{j=1}^{m}\sum_{i=1}^{n} monthly\ drug\ cost_i \times \%\ pts\ receiving\ drug_i \times \%\ pts\ on\ treatment_{ij}$
  - i: chemotherapy drug in the comparator line; j: number of cycle; n: total number of chemotherapy drugs; m: total number of cycles
  - % patients on treatment over time estimated from TriNetx® databases
- Lifetime Drug Acquisition and Administration Costs (2022 USD)

Tumor type	Pembrolizumab	Chemotherapy
Colorectal	$173,866	$15,373
Endometrial	$196,893	$9,111
Gastric	$66,782	$8,024
Cholangiocarcinoma	$84,955	$9,761
Pancreatic	$46,282	$9,706
Small Intestine	$232,639	$12,862
Ovarian	$48,114	$12,503
Brain	$27,537	$16,826

SOC, standard of care.

Challenge 2 – Different SOC by tumor types

2. Report tumor-specific ICERs along with an aggregated ICER value where possible

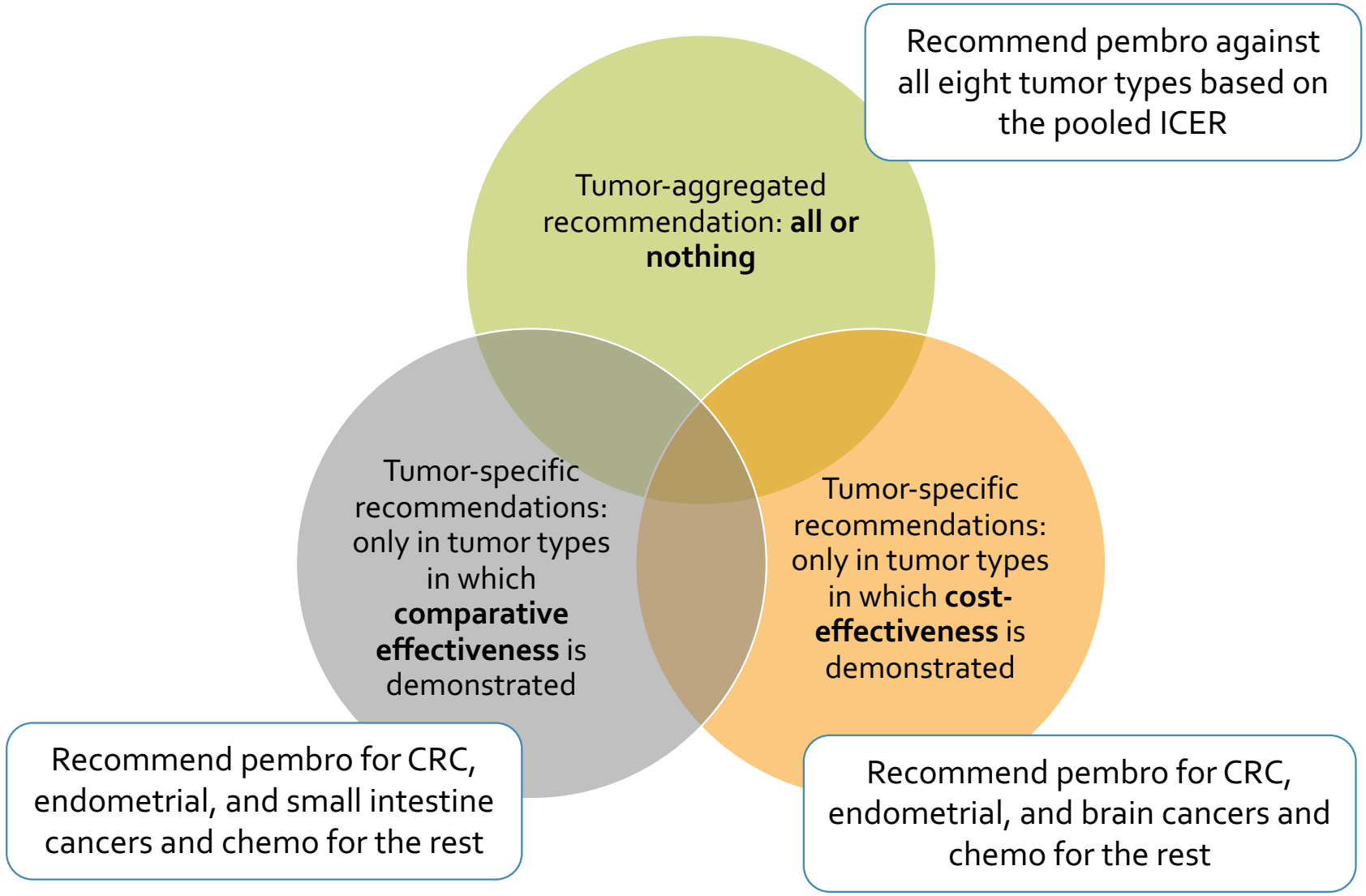
Base-case incremental cost-effectiveness ratios varied substantially across tumor types

Tumor type	ΔCosts	ΔQALYs	ΔLYs	Incremental Cost per QALY Gained
Colorectal	$77,965	0.64	0.64	$122,000
Endometrial	$527,813	3.79	5.47	$139,000
Gastric	$40,145	-2.03	-2.58	Less effective, more costly
Cholangiocarcinoma	$119,408	-0.06	-0.06	Less effective, more costly
Pancreatic	-$130,956	-1.12	-1.43	$117,000
Small Intestine	$509,713	1.73	2.48	$294,000
Ovarian	$95,839	-0.18	-0.23	Less effective, more costly
Brain	-$170,770	-0.83	-1.46	$205,000
Aggregated Cohort	**$54,656**	**-0.04**	**-0.09**	**Less effective, more costly**

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; LY, life years.

Challenge 2 – Different SOC by tumor types

3. Implication for payer's coverage decisions: partial stratification for a few cancer types where the greatest benefit is demonstrated



CRC, colorectal; ICER, incremental cost-effectiveness ratio; Pembro, pembrolizumab.

Challenge 3 – Heterogeneity in long-term survival

1. Use of Bayesian hierarchical models to improve precision in survival estimates through borrowing of information across tumor types

Summary of posterior distributions for median PFS by tumor types

Random-effects Model:

$$\log(y_j) \sim Normal(\theta_j, \sigma_j^2)$$
$$\theta_j \sim Normal(\phi, \tau^2)$$

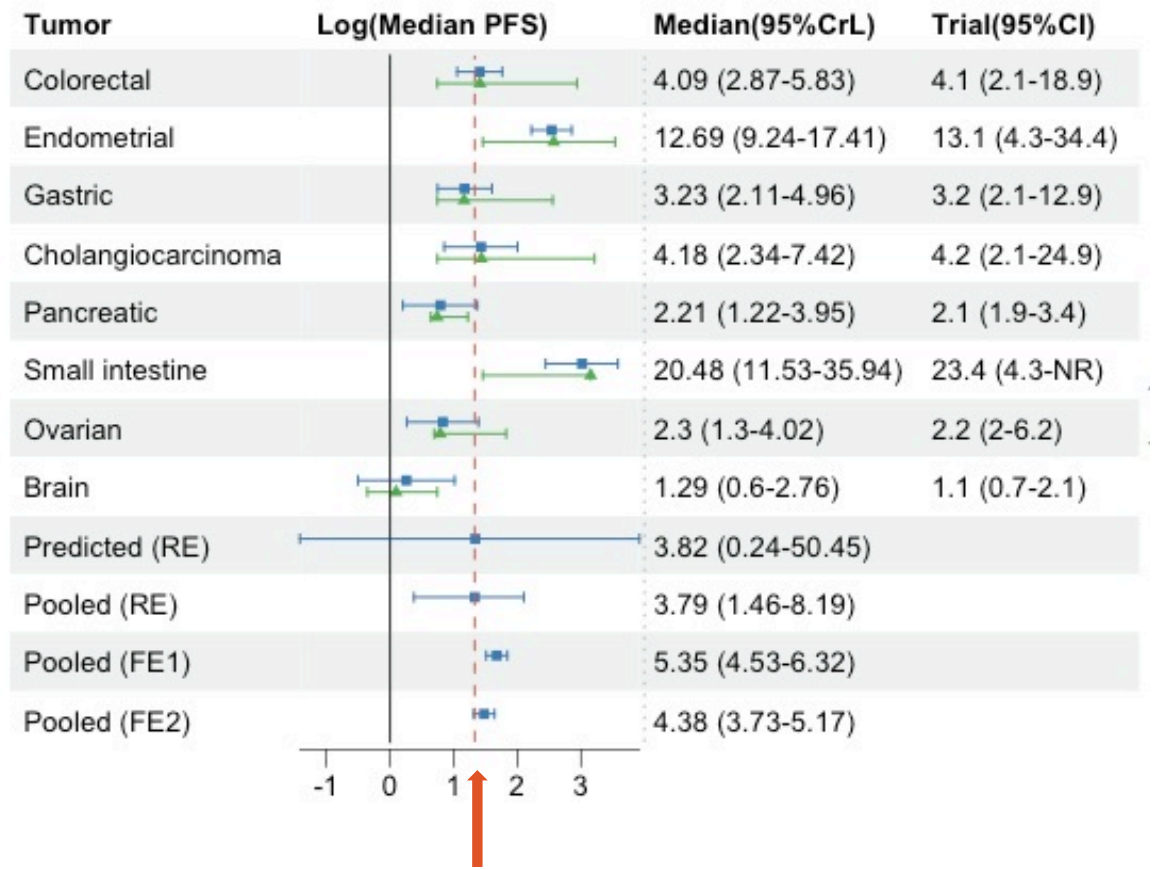
Prior distributions:

$$\phi \sim Normal(0, 2)$$
$$\tau \sim Uniform(0, 5)$$

Legend

Model

Trial



The red dashed line represents the mean effect size from the RE model: 3.79 (1.46-8.19).
The posterior between-tumor standard deviation from the RE model is 3.23 (1.87-10.12).

PFS, progression-free survival; RE, random-effects model; FE1, fixed-effect model with single mean effect; FE2, fixed-effects model with varying mean effects; CrI, credible interval; CI, confidence interval; NR, not reached.

Chen Y, Carlson JJ, Montano-Campos F, Basu A, Inoue LY. Tumor-Specific Decisions Using Tumor-Agnostic Evidence from Basket Trials: A Bayesian Hierarchical Approach. medRxiv. 2023:2023-09.

Challenge 3 – Uncertainty of long-term survival

2. Sensitivity analysis: fit different models to extrapolate long-term effectiveness for SOC and re-evaluate once longer-term data are available

- **Standard parametric models** (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma models)
  - Complex shapes not captured by standard hazard functions
- **Flexible parametric models** (such as restricted cubic spline models)
  - Not generate turning points beyond the period of observed trial data
- **Fractional polynomials**
  - The lack of restrictions on extrapolation leading to implausible predictions
- **Piecewise models**
  - Sensitive to the choice of cut-off points
- **Mixture cure models**
  - Difficult to estimate a cure fraction reliably based on short term data

"Models for survival extrapolation should be parsimonious but not too parsimonious" (CADTH Methods and Guidelines, 2023)

Latimer NR, Adler AI. Extrapolation beyond the end of trials to estimate long term survival and cost effectiveness. BMJ medicine. 2022;1(1).
Coyle D, Haines A, Lee K. Extrapolating clinical evidence within economic evaluations. Canadian Journal of Health Technologies. 2023 May 15;3(5).

Thank You

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Challenge 1

Lack of Comparative Data

- Historical controls from clinical trials
- RWD-based external controls

Challenge 2

Different SOC by Tumor Type

- Model different comparator arms by tumor types
- Report tumor-specific ICER along with an aggregated ICER
- Partial stratification

Challenge 3

Heterogeneity and Uncertainty of Long-Term Survival

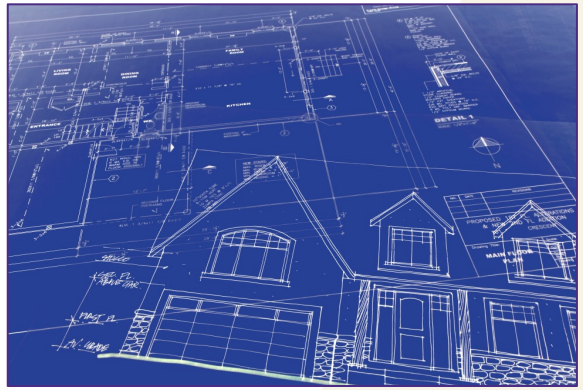
- Use of Bayesian hierarchical models to improve precision
- Sensitivity analysis on extrapolation methods

ICER, incremental cost-effectiveness ratio; RWD, real-world data; SOC, standard of care.

Take-aways!

Hazards of accelerated approval

Challenges to HTA



Methods development

Promising methods

- Bayesian hierarchical modeling with priors
- Indirect treatment comparisons
- Synthetic (external) control arms using RWE
- Extrapolation of survival estimates

[1]PMID: 27041795

Thank you!

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