Biased borrowing or borrowing bias? Leveraging Bayesian borrowing and quantitative bias analysis for robust comparative effectiveness insights

PSI 2025 | June 11

Grace Hsu | grace.hsu@syneoshealth.com

Agenda

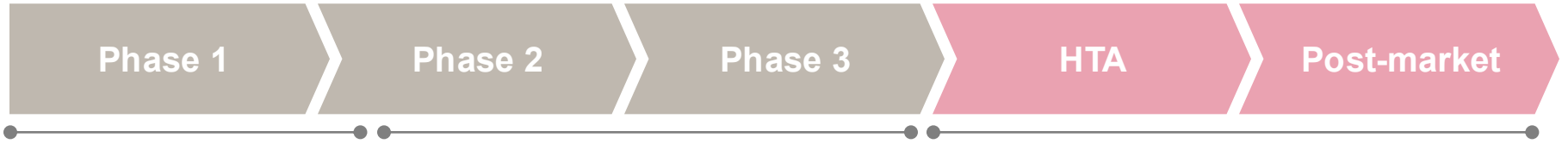
01 | Bayesian borrowing and QBA

02 | Takeaways

03 | Case study

Bayesian Borrowing and QBA

Use of “external data” in drug development



Internal decision-making

- Efficacy signal finding
- Dose selection

Accelerated approvals

- Establishing natural history of disease
- Isolation of treatment effect
- Supportive comparative efficacy

Reimbursement

Clinical guidelines

- Comparative effectiveness

What is Bayesian Borrowing?

Statistical framework that **integrates "external data"**, e.g. historical trial data or RWD, with clinical trial data.

Uses Bayesian principles to update prior information into a posterior distribution that can **combine evidence from multiple sources simultaneously**.

Case Study - A Bayesian borrowing study in MSI-H mCRC

Background

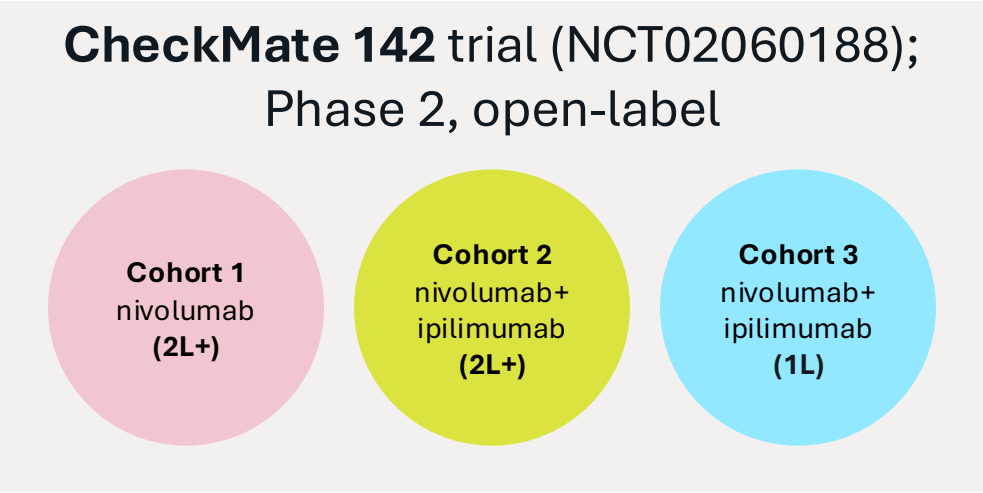
- **Sponsor**: Bristol Myers Squibb
- **Disease**: Microsatellite instability-high metastatic colorectal cancer (**MSI-H mCRC**)
- **Drug of interest**: **2L+** nivolumab (**nivo**) monotherapy **vs**. **2L+** nivolumab + ipilimumab (**nivo+ipi**) combination therapy
- **Goal**: comparative effectiveness of nivo and nivo+ipi as a 2L+ therapy in MSI-H mCRC

Endpoints - OS, PFS

Abbreviations: PFS – progression free survival; mCRC - metastatic colorectal cancer

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

Case Study - A Bayesian borrowing study in MSI-H mCRC

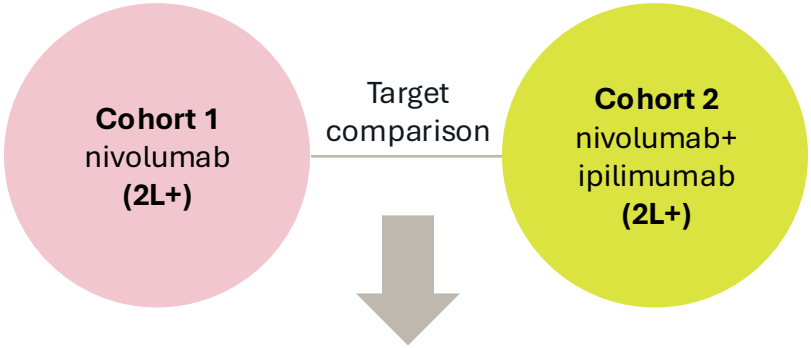


- **Non-randomised** study
- **Some methods**:
  - Pre-processing step to adjust for key confounders
  - Parametric (Weibull and piece-wise exponential) proportional hazards models

Abbreviations: PFS – progression free survival; mCRC - metastatic colorectal cancer

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

Setup – Bayesian borrowing



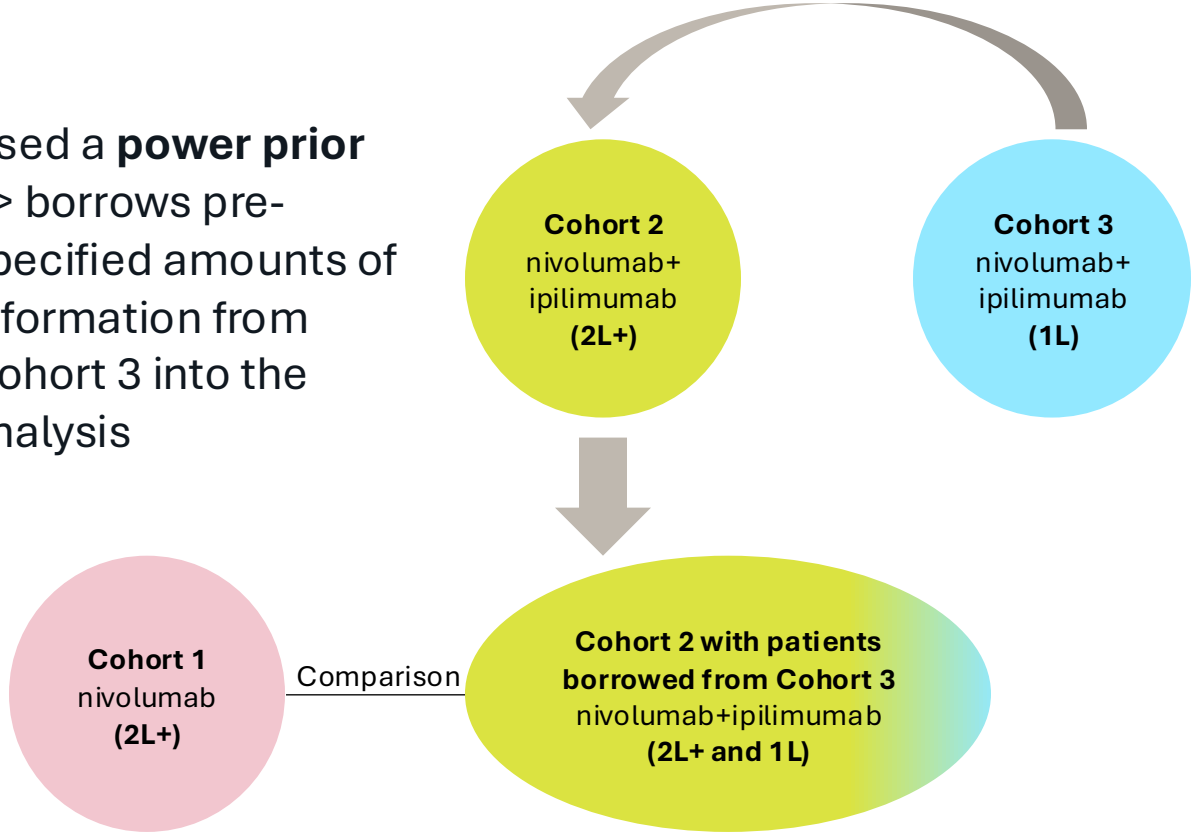
Possibly under-powered

Results are
not statistically significant or
only **weakly** significant

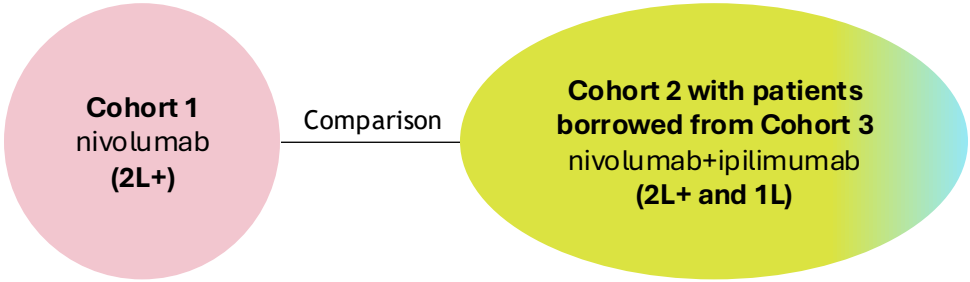
Setup – Bayesian borrowing

”Borrow” patients from another source to **increase the power** of the target comparison

Used a **power prior** => borrows pre-specified amounts of information from Cohort 3 into the analysis



Potential criticisms?



1L patients may be expected to have **better survival** vs **2L+** patients

How **robust** are the effect estimates given this expected bias?

Quantitative bias analysis (QBA)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence

"**Sources of bias should be clearly identified at the design stage** [...] It is particularly important to identify potentially important **unmeasured confounders**. [...] The analytical methods to address potential confounding should be **pre-specified** in the protocol or analysis plan.

QBA is a set of methods to estimate how data limitations/bias affect study conclusions and validity, endorsed by NICE, HAS, CDA-AMC, FDA, etc.

- Can estimate **quantitatively (not control)** the direction, magnitude, and uncertainty associated with systematic errors that influence measures of associations. (Lash et al 2016; Lash et al 2014)

- Assesses the impact of **missing data**, **residual confounding, and more** on results from any study, especially non-randomised studies

EMA: "Missing data can lead to bias and confounding [...] consider **sensitivity analyses to missing data assumptions** made in the main analysis to **understand their impact on the results**"

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products
Guidance for Industry

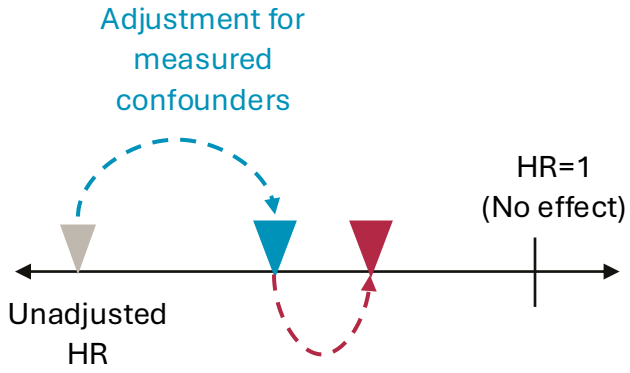
CDA-AMC: "QBAs have several benefits, including identifying systemic error and providing ranges of potential impacts of bias on study results, reducing undue confidence in results and conclusions."

NICE real-world evidence framework

Lash, Timothy L., et al. "Good practices for quantitative bias analysis." *International journal of epidemiology* 43.6 (2014): 1969-1985.
Lash, Timothy L., et al. "Quantitative bias analysis in regulatory settings." *American journal of public health* 106.7 (2016): 1227-1230.

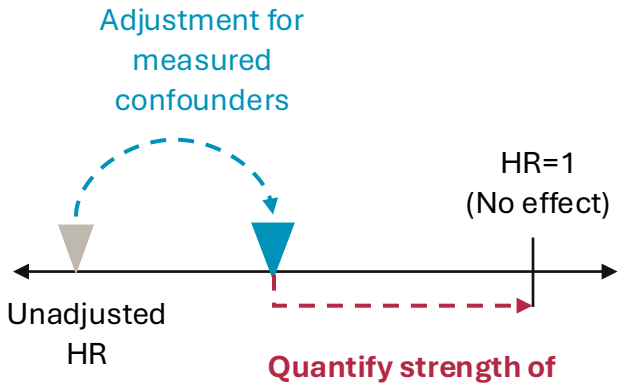
A couple concepts for addressing bias

External adjustment



External adjustment for known unmeasured confounders

Tipping point analysis

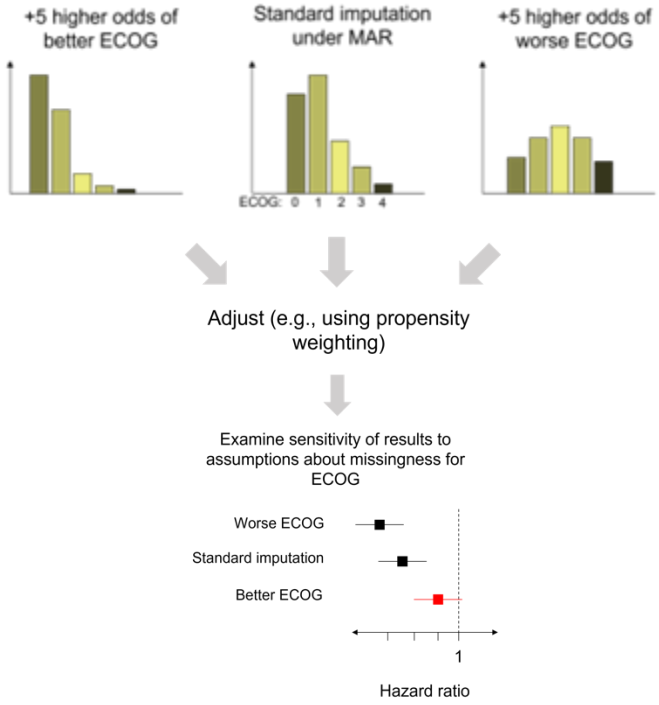


Quantify strength of confounding required to **tip** HR or upper CI to 1 and interpret plausibility

A **series of tipping point-based QBA** were conducted to **assess the robustness** of the study findings by quantifying the impact of multiple sources of bias.

Handling missing values under different assumptions
δ-adjustment for MNAR

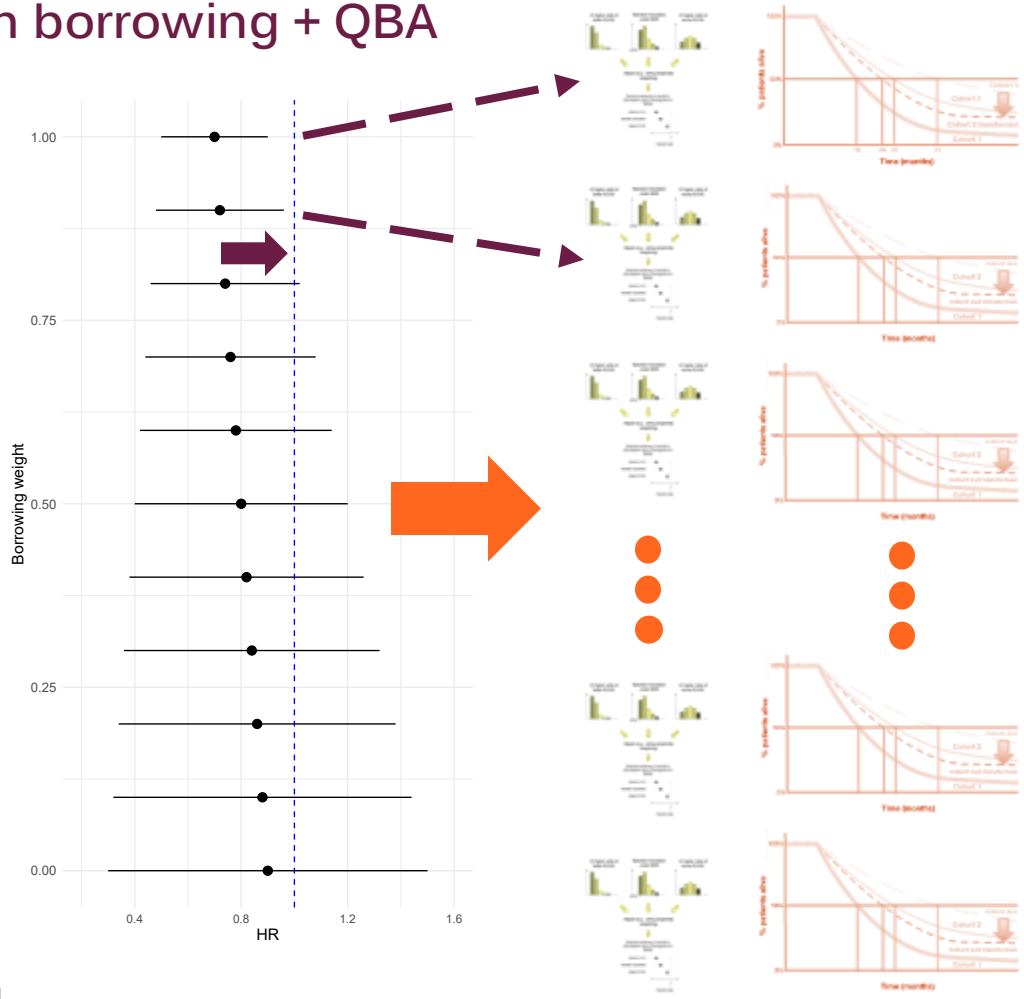
Apply a shift value to predictions to **simulate better- or worse-than-expected** (given observed data) imputations in one treatment group



1. **Imputation of missing values using different settings**
2. **Adjustment for each setting**
3. **Compare conclusions**

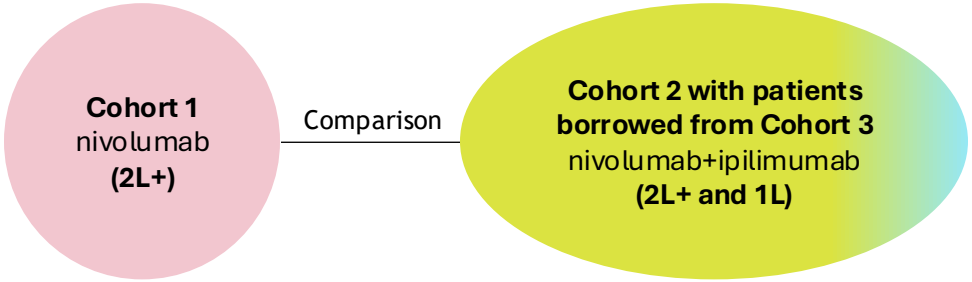
Abbreviations: MNAR – missing not at random

Bayesian borrowing + QBA



Each borrowing weight leads to a separate QBA to be interpreted

Potential criticisms in addition to differences in target cohorts?



1L patients may be expected to have **better survival** vs **2L+** patients

How **robust** are the effect estimates given this expected bias?

Quantitative bias analysis (QBA) executed

1. QBA for patients with **uncertain MSI-H status -** Local

2. QBA for **unmeasured confounding**

3. QBA for **missing data**

4. QBA for **target cohort differences due to Bayesian borrowing**

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

Case Study Results

Overall Survival (OS) - Bayesian Borrowing using power priors

- HRs and upper 95% credible interval (CI) below 1 **for all weights**
- Relative cohort sizes affect sensitivity of HRs and CIs to borrowing weight
- After pre-processing:
  - Cohort 1 = 55
  - Cohort 2 = 119
  - Cohort 3 = 35

Power Prior Borrowing Weight[1]	% reduction in CI width
0	0
0.25	2.4
0.5	3.9
0.75	5.4
1	5.8

1. 0 - no pooling, 1 - Cohort 3 fully pooled into Cohort 2

Table . OS estimates from the Weibull model

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

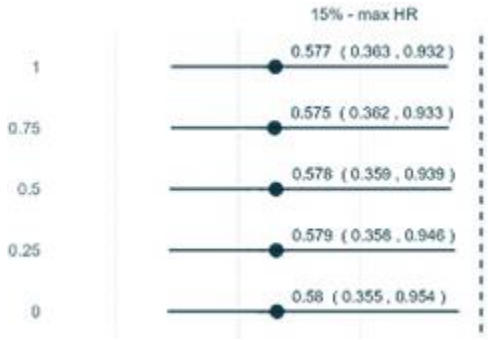
QBA for patients with only a local test or a false positive local test - OS

- After **randomly removing 15% and 25%** of such patients:
  - Re-run entire analysis repeatedly
  - Consider the **worst-case scenario** = subset with the **worst** possible HR estimates

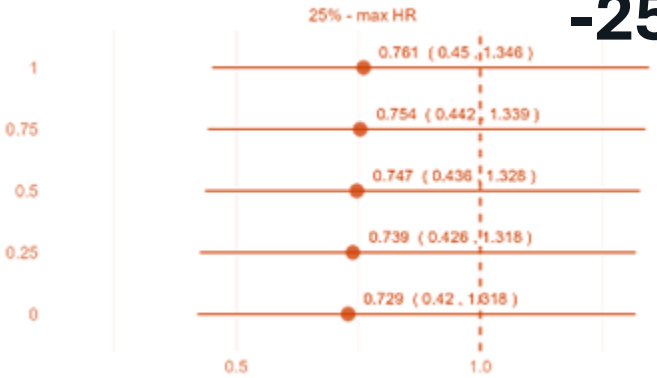
- Very wide CIs suggest perceived lack of robustness is owing to poor balance between cohorts
  => small cohort sizes/events/power

Worst-case scenarios

-15%



-25%



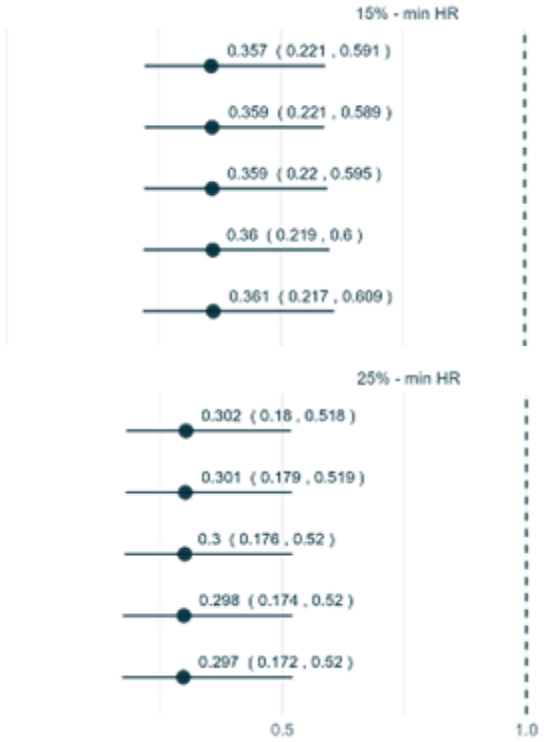
Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

QBA for patients with only a local test or a false positive local test - OS

- Now consider the **best-case scenario** = subset with the **best** possible HR estimates

For OS, the study results are quite robust against patients with only a local test or a false positive local test under all borrowing scenarios.

Best-case scenarios

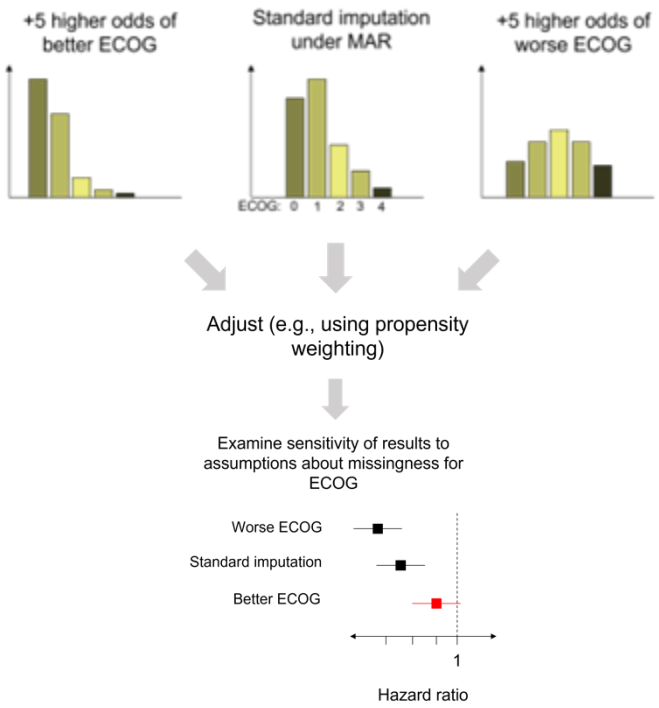


-15%

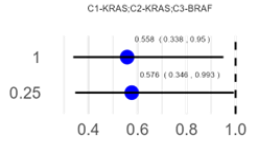
-25%

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

QBA for missing data – BRAF/KRAS mutation - OS



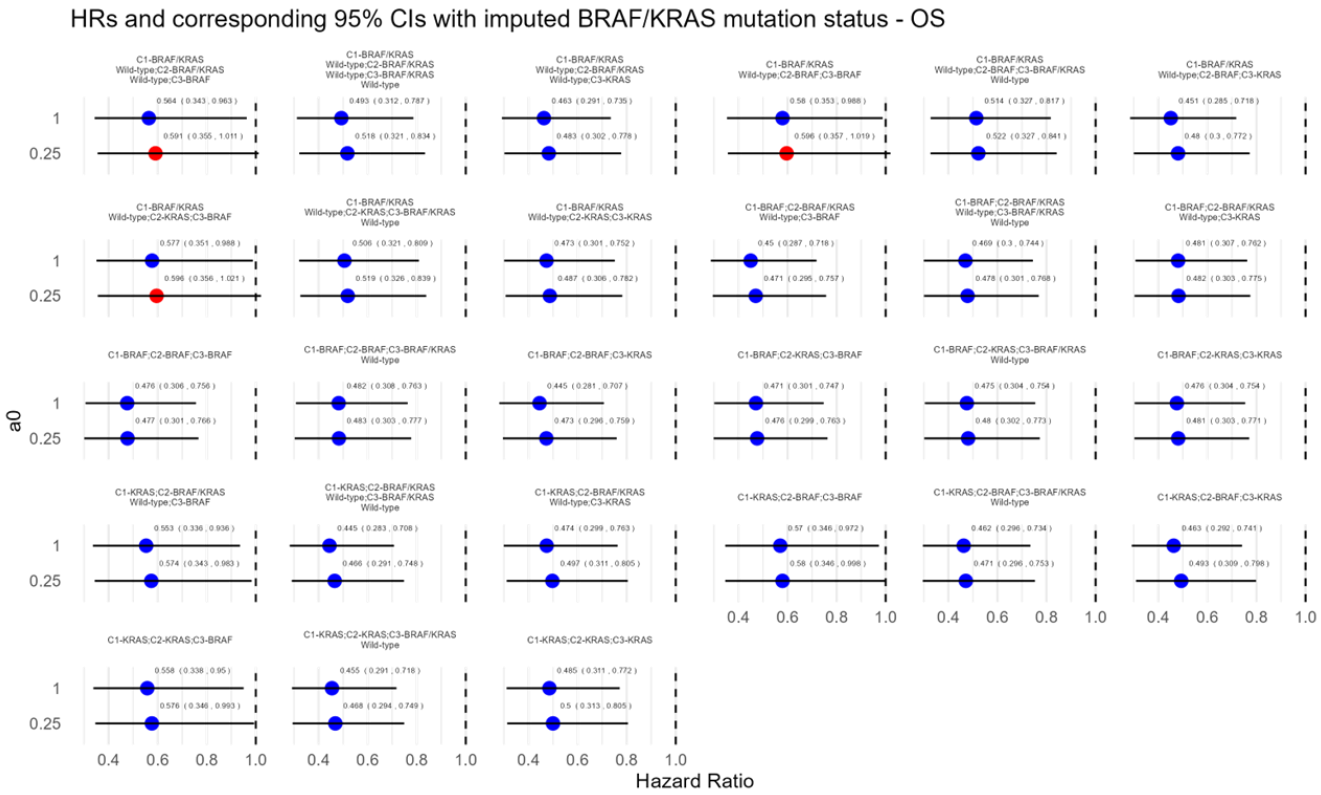
- KRAS/BRAF mutation status, **key confounders**, were assessed to ses whether study conclusions hold under all plausible missingness assumptions.
- Missingness in 3 cohorts across multiple variables => **computational** + **communication** challenge



- Plots will show 25% vs full borrowing for each plausible distribution of missing mutation status

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

QBA for missing data – BRAF/KRAS mutation - OS



The study results for OS are very robust against missing BRAF/KRAF mutation status, particularly as the amount of borrowing increases.

- All HR point estimates of OS are < 1 across all scenarios
- **Borrowing or not makes a difference in robustness** against missing BRAF/KRAS

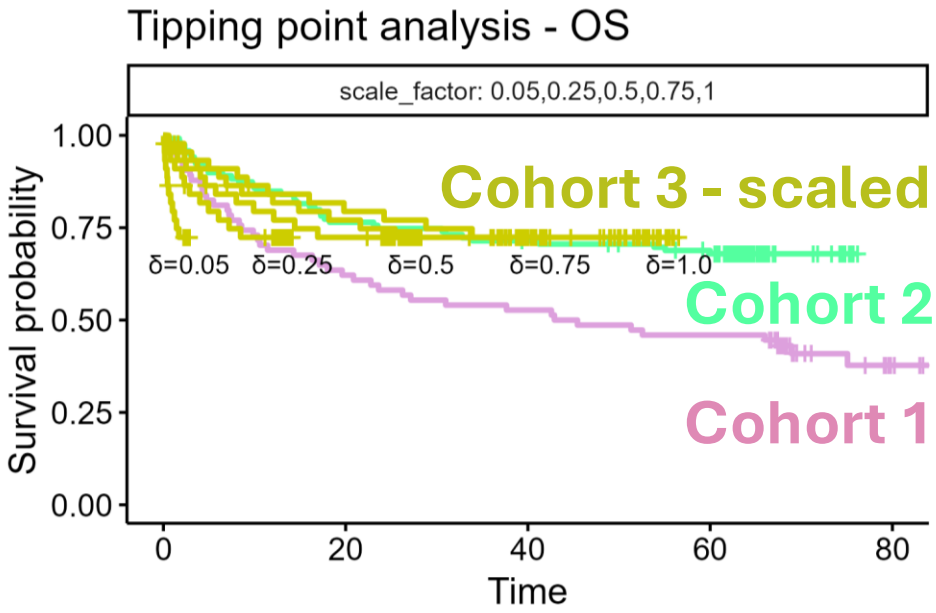
Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

QBA for target cohort differences due to Bayesian borrowing

Concern: Cohort 3 patients may have **inflated survival** vs Cohort 2

Solution: **scaled down** the OS and PFS time of cohort 3 by a **scaling factor** between 0 and 1.

- **0 =** time of cohort 3 patients to death or progression becomes immediate at 0
- **1 =** original study data of Cohort 3 for OS and PFS.

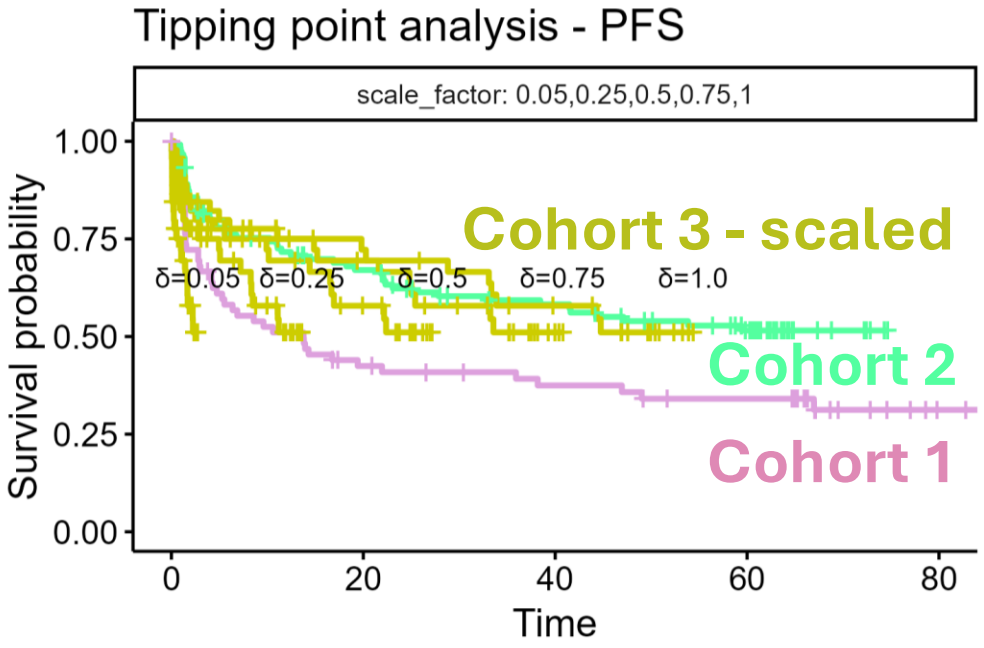


Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

QBA for target cohort differences due to Bayesian borrowing

- **HR point estimates: No tipping points** where conclusions were reversed were identified for OS and PFS

- **HR upper CIs:** Tipping point where conclusions were reversed for **only** PFS scenarios that were most likely **implausible**,
  - i.e. patients had progression times reduced by **over 90%**



Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

Conclusions

- Estimates have low sensitivity to the amount of borrowing, most likely owing to a combination of factors, chiefly cohort sizes after pre-processing

- **QBA shows that study conclusions are largely either very robust or generally robust for OS and PFS against all the sources of bias assessed**
  - *i.e.,* uncertainty in MSI-H status, unmeasured confounding, missing data, target cohort differences due to Bayesian borrowing
  - In some cases, **borrowing was beneficial for reducing the number of cases where statistical significance may be lost**
  - The exception being PFS, with greater uncertainty for the QBA regarding MSI-H status due to the insufficient number of patients

- Additional borrowing into the nivo+ipi and nivo arms is expected to yield improvements in the estimates' precision

Dixon, M., et al. "CO135 Comparative Analysis of Nivolumab and Nivolumab Plus Ipilimumab in MSI-H Metastatic Colorectal Cancer: A Bayesian Borrowing and Quantitative Bias Approach." *Value in Health* 27.12 (2024): S40.

Takeaways

QBA can answer a wide range of questions

Assessing missing values?	Imputation methods and **tipping point analyses**
Underpowered studies or insufficient sample sizes?	Bayesian borrowing and **tipping point analyses** for a range of borrowing weights
Assess impact of errors in lab tests needed for patient eligibility on comparative effect estimates?	Generate the range of potential effect estimates when accounting for test properties for a **tipping point analyses**
Quantify strength of hypothetical confounding required to change conclusions?	The E-value-based **tipping point analyses**
Concerns regarding differences in RWD and trial patients?	Transform patient cohort outcomes and conduct **tipping point analyses**

QBA can answer a wide range of questions

Bayesian borrowing challenges: **Computational** burden, **interpretation** and **communication** amongst technical and non-technical audiences can all be challenging

Well-designed QBA empowers researchers and decision-makers to **interpret results from analyses that use imperfect data in a nuanced manner whilst maintaining scientific integrity**

Thank you!