Indirect Treatment Comparison of Larotrectinib vs. Entrectinib in NTRK-fusion Solid Tumours: *Demonstration of a Novel Bayesian Hierarchical Modelling Approach for Basket Trials*

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Disclosures

- AS was an employee at Cytel at the time of his contributions to this work. He is currently employed by AstraZeneca.

- Opinions expressed are our own and do not necessarily reflect the views of Inka Health, AstraZeneca, Cytel, or the Centre for Reviews and Dissemination at the University of York

Background

- Evaluating new drugs targeting rare cancer mutations/biomarkers can be extremely challenging due to difficulties recruiting enough patients
- Increased use of basket trial designs in recent years which recruit patients with many different tumour types / histologies who are positive for a mutation/biomarker targeted by the experimental treatment[1, 2]
- These basket trials are typically phase I/II, lack a concurrent control arm, focus on response endpoints, and have limited sample sizes both overall and within each tumour histology
- The need for estimates of comparative effectiveness vs. standard-of-care to evaluate the cost-effectiveness of these new treatments for health technology assessment (HTA) has been highlighted--for both specific histologies and for tumour-agnostic consideration[3, 4, 5, 6]

Objective

- Our goal is to demonstrate an indirect treatment comparison (ITC) method for basket trials which:
  - Compensates for potential confounding due to differences in histology composition between trials
  - Allows for partial pooling of information across histologies to improve precision/power where sample sizes are severely limited
  - Is implementable using aggregate data that is likely to be available from publications
  - Can be used to estimate tumour-specific relative treatment effects
- We apply a Bayesian hierarchical modelling (BHM) approach which builds on earlier work in basket trial settings[7, 8, 9, 10, 11]
- We apply our approach to an ITC of two treatments--larotrectinib and entrectinib--studied in basket trial settings for NTRK-fusion positive solid tumours

Modelling Assumptions

- Our model relies on several key assumptions:

  (a) Histologies are exchangeable (variability in prognosis across histologies can be modelled as random effects),

  (b) The distribution of prognostic factors within each histology is similar between basket trials, and,

  (c) There is overlap in included histologies between the two trials

- Our proposed approach relaxes the assumption of constant relative treatment effects in our earlier work[7, 8] and, additionally, allows for estimation of histology-specific relative treatment effects

Model Setup

- We model the number of responders, r_{jk}, out of n_{jk} patients, for each basket trial $j \in \{0, 1\}$ and histology $k \in \{1, ..., K\}$ as follows:

$$
\begin{aligned}
r_{jk} &\sim \text{Binomial}(n_{jk}, p_{jk}) \\
\text{logit}(p_{jk}) &= \mu + \beta_k + (d + \delta_k) \cdot 1\{j = 1\} \\
\beta_k &\sim \text{N}(0, \sigma^2) \\
\delta_k &\sim \text{N}(0, \tau^2)
\end{aligned}
$$

- where μ is an intercept term, β_k is a histology-specific intercept random effect with variance σ^2, δ_k is a histology-specific random effect for the relative treatment effect with variance τ^2, and d is the pooled relative treatment effect.
- We use weakly informative priors for all parameters

Application to an ITC of Larotrectinib vs. Entrectinib

- We focus on an objective response rate (ORR) endpoint
- We apply the method to estimate pooled and histology-specific relative treatment effects (log odds ratios of response) for larotrectinib vs. entrectinib in adult patients with NTRK fusion-positive solid tumours
- We also report estimated response rates by histology for each treatment--including estimates for histologies that are only available for one of the two treatments
- Posteriors are estimated via Markov chain Monte Carlo (MCMC) in Stan[12] with convergence assessed via trace plots.

Data (1 / 2)

- We use published aggregate data for entrectinib from the pooled phase-I ALKA-372-001 and STARTRK-1, and phase-II STARTRK-2 studies in adults with NTRK fusion-positive solid tumours[14].
- For larotrectinib we use published aggregate data for the pooled phase-I LOXO-TRK-14001 study in adults, phase-I/II SCOUT study in pediatric patients, and phase-II NAVIGATE study in pediatric and adult patients with NTRK-fusion-positive solid tumours[13].
- We attempt to remove all pediatric larotrectinib patients using supplemental data from Hong et al.[13] (a total of 51 pediatric patients were removed of whom 47 were responders)

Data (2 / 2) -- Responders and Observed Objective Response Rate (%)

Tumour Type	Larotrectinib	Entrectinib
Sarcoma	17 / 23 (74%)	15 / 26 (58%)
Thyroid	17 / 22 (77%)	7 / 13 (54%)
Salivary	18 / 20 (90%)	20 / 24 (83%)
Lung	9 / 12 (75%)	14 / 22 (64%)
Colorectal	4 / 8 (50%)	2 / 10 (20%)
Melanoma	3 / 6 (50%)	0 / 0 (–)
Breast	3 / 4 (75%)	5 / 7 (71%)
Pancreatic	1 / 2 (50%)	3 / 4 (75%)
Cholangiocarcinoma	1 / 2 (50%)	1 / 1 (100%)
Unknown Primary	1 / 1 (100%)	1 / 3 (33%)
Appendix	0 / 1 (0%)	0 / 0 (–)
Hepatocellular	0 / 1 (0%)	0 / 0 (–)
Neuroendocrine Tumours	0 / 0 (–)	2 / 5 (40%)
Gynecologic	0 / 0 (–)	1 / 2 (50%)
Head and Neck	0 / 0 (–)	2 / 2 (100%)
Adenocarcinoma of Upper GI Tract	0 / 0 (–)	1 / 1 (100%)
Neuroblastoma	0 / 0 (–)	0 / 1 (0%)
Pooled	74 / 102 (73%)	74 / 121 (61%)

- Note that there are 102 larotrectinib patients split across 12 histologies
- There are 121 entrectinib patients split across 14 histologies
- Many histologies contain only a few patients and only 9 / 17 histologies are present for both treatments

Pooled Treatment Effect Estimates

- We compare estimates of the proposed BHM vs. a simple pooling approach which ignores potential heterogeneity in response across histologies

Model	Median OR [95% CrI]	Prob. Superiority
Simple Pooling	1.665 [0.963, 2.908]	0.966
Proposed BHM	1.669 [0.819, 3.195]	0.928

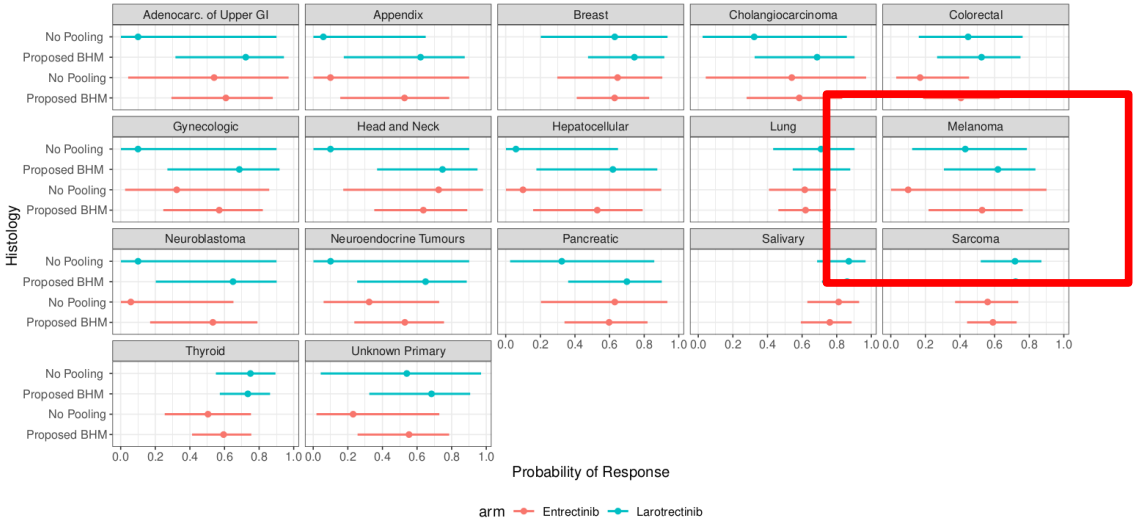
- The median odds ratios (OR) are similar under both models, however the 95% credible intervals (CrI) are wider under the BHM than the simple pooling approach, reflecting more uncertainty/restrained borrowing based on observed cross-histology heterogeneity
- Posterior probability of superiority for larotrectinib is high under both models, however 95% CrIs include an OR of 1

Histology-Specific Treatment Effect Estimates

Histology	Median OR [95% CrI]	Prob. Superiority
Adenocarcinoma of Upper GI Tract	1.695 [0.463, 5.116]	0.849
Appendix	1.567 [0.353, 4.014]	0.800
Breast	1.716 [0.598, 4.736]	0.873
Cholangiocarcinoma	1.623 [0.458, 4.243]	0.830
Colorectal	1.657 [0.593, 4.056]	0.862
Gynecologic	1.692 [0.470, 5.155]	0.850
Head and Neck	1.693 [0.472, 5.150]	0.850
Hepatocellular	1.569 [0.348, 4.001]	0.799
Lung	1.743 [0.729, 4.227]	0.906
Melanoma	1.565 [0.465, 3.776]	0.814
Neuroblastoma	1.696 [0.472, 5.142]	0.850
Neuroendocrine Tumours	1.693 [0.463, 5.091]	0.850
Pancreatic	1.619 [0.454, 4.199]	0.829
Salivary	1.913 [0.845, 5.362]	0.942
Sarcoma	1.799 [0.838, 4.005]	0.937
Thyroid	1.888 [0.866, 4.649]	0.946
Unknown Primary	1.774 [0.596, 5.829]	0.881

- Posterior probability of superiority for larotrectinib is greater than 79% for all included tumour types, however, 95\% CrIs still include OR of 1

Estimated Objective Response Rates (Median and 95% CrI)



Limitations

- This method relies on several strong assumptions, key among them that:
  - the random effects parameterizations are considered to be an acceptable approximation for capturing cross-histology heterogeneity
  - there are no major remaining imbalances in baseline characteristics beyond histology that are likely to confound the treatment effect estimates
- Due to the severe data limitations encountered in basket trial settings, we argue that choice of ITC method should be viewed through the lens of determining an appropriate trade-off between precision and risk of bias

Conclusions

- We demonstrate how a BHM ITC approach can be applied in practice to two drugs for NTRK-fusion positive solid tumours evaluated in single-arm basket trial settings
- We argue that this BHM ITC approach is better-suited to basket trial settings than many established population-adjusted indirect comparison methods such as those outlined by the NICE Decision Support Unit[15] (see also Mackay & Springford[16] for a discussion of the advantages of Bayesian approaches for HEOR/HTA decision-making for rare diseases)
- This approach can also be generalized to a comparison vs. an external control arm constructed using real-world data
- Manuscript preprint will be available very shortly--stay tuned!

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Thank You!

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