Use of Multi-Level Network Meta Regression (ML-NMR) model in RET Mutation-Positive Medullary Thyroid Cancer (MTC)

Manoj Khanal[1], Min-Hua Jen[1], Michael David Sonksen[1], Tarun Puri[1], Jacek Kiesel[1], Urpo Kiiskinen[1]

[1]Eli Lilly and Company, Indianapolis, USA

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OBJECTIVE

Applied ML-NMR to perform indirect comparisons across clinical trials, explicitly adjusting for differences in study populations, including key prognostic and effect-modifying variables. By leveraging individual patient-level covariate data where available:

- This approach improves the validity and interpretability of the comparisons, reducing bias from population heterogeneity.
- It addresses the industry's growing need for practical examples of advanced methods like ML-NMR to support robust and credible evidence synthesis in HTA submissions and payer decision-making.

CONCLUSION

- This case study demonstrates the feasibility of using ML-NMR for comparing time to event outcomes across studies, and shows consistency with the direct evidence from the LIBRETTO Phase 3 findings.
- Selpercatinib is more efficacious than cabozantinib, vandetanib, and placebo for MTC
- ML-NMR combines IPD and AgD to provide population-adjusted estimates in specific target populations for decision making
- With only three studies in the network, there is computational burden as running the model takes long time (for example, 8+ hours for 300K samples)

SCENARIO

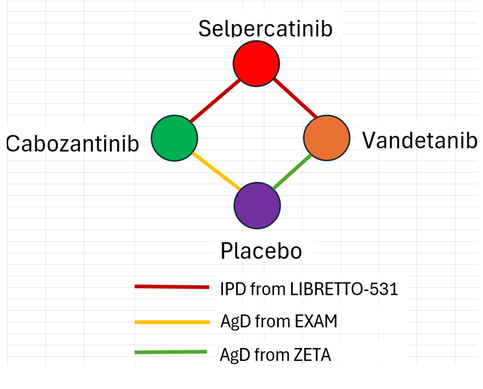


Figure 1: Network diagram of randomized controlled trials

Study	Patient ID	time*	CNSR*	treat	endpoint	M918T	Age	Sex	ECOG
LIBRETTO-531	LIBRETTOID 1	8	1	Cabozantinib	PFS	RET M918T mutation positive	50	M	0
LIBRETTO-531	LIBRETTOID 2	5	1	Selpercatinib	PFS	RET M918T mutation positive	55	F	>=1
LIBRETTO-531	LIBRETTOID 3	3	0	Cabozantinib	PFS	non M918T RET mutation positive	60	M	0
LIBRETTO-531	LIBRETTOID 4	2	1	Selpercatinib	PFS	non M918T RET mutation positive	75	F	>=1
EXAM	EXAMID 1	6	1	Cabozantinib	PFS	RET M918T mutation positive	X	X	X
EXAM	EXAMID 2	12	1	Cabozantinib	PFS	RET M918T mutation positive	X	X	X
EXAM	EXAMID 3	17	1	Cabozantinib	PFS	RET M918T mutation positive	X	X	X
EXAM	EXAMID 4	5	0	Placebo	PFS	RET M918T mutation positive	X	X	X
EXAM	EXAMID 5	9	0	Placebo	PFS	non M918T RET mutation positive	X	X	X
EXAM	EXAMID 6	11	0	Placebo	PFS	non M918T RET mutation positive	X	X	X
EXAM	EXAMID 7	29	0	Placebo	PFS	non M918T RET mutation positive	X	X	X
ZETA	ZETAID 1	4	1	Vandetanib	PFS	X	X	X	X
ZETA	ZETAID 2	2	1	Vandetanib	PFS	X	X	X	X
ZETA	ZETAID 3	22	1	Vandetanib	PFS	X	X	X	X
ZETA	ZETAID 4	12	0	Placebo	PFS	X	X	X	X
ZETA	ZETAID 5	19	0	Placebo	PFS	X	X	X	X
ZETA	ZETAID 6	7	0	Placebo	PFS	X	X	X	X
ZETA	ZETAID 7	9	0	Placebo	PFS	X	X	X	X

*: Digitized data for EXAM and ZETA
X: Data not available

Table 1: Example of IPD as fake data

Treatment	RET M918T mutation positive (%)	Age#	SexM (%)	ECOG 0 (%)	Study
Vandetabnib	0.498	50.7	0.58	0.67	ZETA
Placebo	0.432	53.4	0.56	0.58	ZETA
Cabozantinib	XX	55	0.68	0.56	EXAM
Placebo	XX	55	0.63	0.51	EXAM

#: Mean age for ZETA and median for EXAM
XX: Data already available as IPD

Table 2: Example of AgD (actual numbers used in the analysis)

- The trial design in LIBRETTO-531 [1] contained 2 randomized arms: Selpercatinib and physician's choice of either Cabozantinib or Vandetanib
- Individual patient level data (IPD) from LIBRETTO-531 were used
- Main published evidence for Cabozantinib and Vandetanib comes from 2 randomized controlled trials, EXAM [2,3] and ZETA [4] respectively
- Published Kaplan Meier curves from EXAM and ZETA were digitized to obtain observed time and censoring indicator as IPD
- Covariate information from EXAM and ZETA used aggregate data (AgD)

BACKGROUND

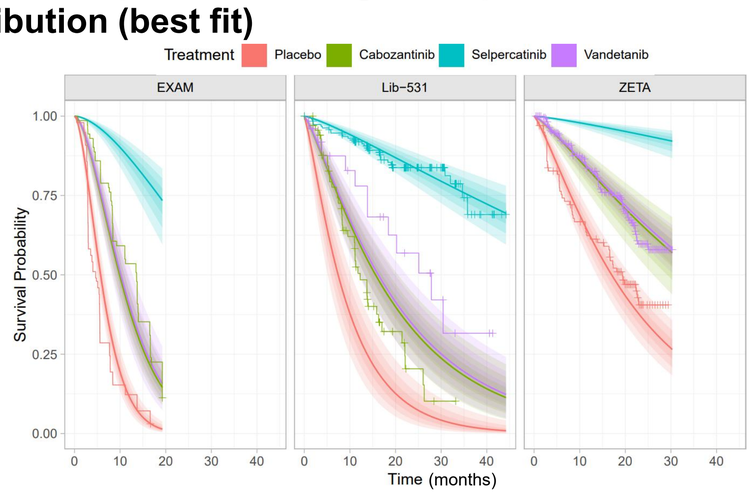
- Most common indirect comparison includes Network Meta-Analysis (NMA) and Matched Adjusted Indirect Comparison (MAIC) with some limitations
- Standard NMA only uses aggregate data (for example, hazard ratio and 95% CI for time to event outcome) and the covariate characteristics of the various trials are assumed to be from the same distribution of patients which is a very strong assumption that may or may not hold
- MAIC is currently the widely used method for population adjustment, however it is limited to the pairwise indirect comparison scenario with one study having IPD and another study with AgD
- MAIC cannot be extended to incorporate larger network of studies across multiple treatments
- ML-NMR extends beyond MAIC and NMA in way that it uses IPD from the trials that have it, and covariate information from all the trials
- Not many publications where ML-NMR is applied for time to event outcome [5]. This will be one of the very few applications in time to event outcome

Benefits of using ML-NMR

- Can handle larger network as compared to MAIC
- Produces population-adjusted estimates in specific target populations for decision making

RESULTS

Figure 2: Population-average PFS probabilities based on the Weibull distribution (best fit)



- Figure 2 shows the population-average PFS probability that are estimated for each target population separated by each panel. For each target population Selpercatinib is more efficacious than cabozantinib, vandetanib, and placebo.

METHODS

ML-NMR handles survival outcome by integrating individual-level likelihoods from both arms over covariate distributions from AgD [6]. R package **multinma** [7,8]. It assumes that all key effect modifiers are measured, study effects are exchangeable after covariate adjustment, covariate relationships are correctly specified, and sufficient overlap exists between IPD and AgD covariate distributions.

Individual level likelihood

- Use full covariate and survival data to compute likelihoods directly
- Likelihood function is $L^{\text{Con}}_{ijk|\boldsymbol{x}}(\boldsymbol{\xi}; t_{ijk}, c_{ijk}, \boldsymbol{x}_{ijk}) = S_{jk}(t_{ijk}|\boldsymbol{x}_{ijk}) h_{jk}(t_{ijk}|\boldsymbol{x}_{ijk})^{c_{ijk}}$,

where $t_{\{ijk\}}$, $c_{\{ijk\}}$, $x_{\{ijk\}}$ are the observed time, event indicator and covariates respectively for individual i in study j receiving treatment k. The survival and hazard functions are denoted by S and h that depend on the specific parametric model chosen

Aggregate level likelihood

- Only summary covariate distributions are available; individual event/censoring times for comparator studies are reconstructed from Kaplan-Meier curves
- Marginal likelihood is computed by integrating over the joint covariate distribution $f(.)$

$$L^{\text{Mar}}_{ijk}(\xi; t_{ijk}, c_{ijk}) = \int_{\mathfrak{X}} L^{\text{Con}}_{ijk|\boldsymbol{x}}(\xi; t_{ijk}, c_{ijk}, \boldsymbol{x}) f_{jk}(\boldsymbol{x})\, d\boldsymbol{x} = \int_{\mathfrak{X}} S_{jk}(t_{ijk}|\boldsymbol{x}) h_{jk}(t_{ijk}|\boldsymbol{x})^{c_{ijk}} f_{jk}(\boldsymbol{x})\, d\boldsymbol{x}.$$

- The integral is evaluated using quasi-Monte Carlo integration over $\tilde{N}$ integration points

$$L^{\text{Mar}}_{ijk}(\boldsymbol{\xi}; t_{ijk}, c_{ijk}) \approx \tilde{N}^{-1} \sum_{\tilde{\boldsymbol{x}}} S_{jk}(t_{ijk}|\tilde{\boldsymbol{x}}) h_{jk}(t_{ijk}|\tilde{\boldsymbol{x}})^{c_{ijk}}$$

Data used in the analysis

- Outcome: Progression-free survival (PFS)
- LIBRETTO-531: IPD was used
- EXAM: Digitized IPD for RET M918T mutation positive (Figure 1C in [2]) and non-M918T RET mutation positive (Figure 1E in [2]). Covariates as AgD (Table 1 in [3])
- ZETA: Digitized IPD for ITT population (Figure 2A in [4]) as RET M918T mutation positive subgroup was not available. Covariates as AgD (Table 1 in [4]). Proportion of M918T mutation positive (Figure 2C in [4])
- List of covariates: Age, M918T(RET M918T mutation positive; non M918T RET mutation positive), Sex (Male; Female) and ECOG (0; >=1)

Table 3: Summary of fit

Model	DIC
weibull	2921.27
gompertz	2941.76
exponential	2973.39

Table 3 provides the summary of fit based on fixed effects model. Weibull distribution results in smallest deviance information criterion (DIC)

Table 4: Summary of hazard ratio (HR) and 95% credible interval (CI) based on Weibull distribution

Comparison	HR	Lower 95% CI	Upper 95% CI
Selpercatinib vs. Cabozantinib	0.14	0.08	0.23
Selpercatinib vs Vandetanib	0.15	0.09	0.25
Selpercatinib vs Placebo	0.06	0.03	0.09

CHALLENGES IN APPLIED SETTING

- Trade-offs between model performance and computation speed
  - Higher number of integration points means better fit but much slower speed
- Algorithms can be slow even with small networks
  - Experienced 8+ hours for 300K samples in a 3-study network
- High memory usage
- Slow not only for model fitting but also for predicting population-average estimates

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