Matching Adjusted Indirect Comparison (MAIC) of Selpercatinib vs Cabozantinib in *RET* Mutation-positive Advanced Medullary Thyroid Cancer (MTC)

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Background

- The REarranged during Transfection (*RET*) proto-oncogene is involved in the pathogenesis of the majority of Medullary Thyroid Cancer (MTC) and is considered a therapeutic target. [1]
- Selpercatinib is a selective *RET* inhibitor that is approved in multiple countries for the treatment of RET-fusion positive and RET-mutant thyroid cancers. [2]
- LIBRETTO-001 is a single-arm phase 1/2 study of selpercatinib in patients with various solid tumours including *RET*-mutant MTC. [3]
- EXAM is a phase 3 study of cabozantinib versus placebo in patients with advanced MTC. [4]

Objective: To estimate comparative effectiveness, in terms of progression free and overall survival (PFS, OS) and objective response rate (ORR) using unanchored Matching Adjusted Indirect Comparison (MAIC) of single-arm LIBRETTO-001 (selpercatinib) and EXAM trials (cabozantinib vs placebo) in advanced/metastatic *RET*-mutant MTC.

Study Design/Methods

- Patient-level data from LIBRETTO-001 were weighted to match summary data from the cabozantinib arm of the EXAM trial.
- ORR and PFS were available for the RET-mutant cohort but only OS for the RET M918T subgroup in EXAM.
- MAIC was used to balance the cohorts on all available baseline covariates (age, weight, performance status, sex, smoking status, prior tyrosine kinase inhibitor therapy, and RET M918T mutation status). MAIC is a propensity score method and since it is a reweighting method, it does not allow extrapolation. Furthermore, MAIC assumes there are no unmeasured confounders.
- Hazard ratios (HR) for PFS and OS, odds ratios (OR) for ORR, and related 95% CIs were estimated.
- Multiple imputation marginalization (MIM) was performed as a sensitivity analysis for PFS and OS outcomes. MIM was conducted by fitting parametric survival models using data from LIBRETTO-001, followed by multiple imputation of all covariate data matched to EXAM trial, and by simulating time-to-event outcome data for each imputed data set. Finally marginal Cox models were fitted to each simulated data set together with reconstructed survival data from EXAM. [5]

Conclusions

- In weighted comparison, selpercatinib demonstrated an improvement in ORR, PFS and OS versus cabozantinib.
- MIM analysis demonstrates consistent results across different parametric specifications of the model.

Limitations:

- Fewer baseline characteristics were reported in the EXAM study and adjustment did not take those variables into consideration.
- A limited number of covariates were available for adjusting selpercatinib data. Hence, there is a risk of unmeasured confounding that could influence these findings. MAIC also assumes overlap between the covariate distributions in both studies. MIM made the same assumptions as MAIC regarding no unmeasured covariates but did not assume that the EXAM population was contained in the LIBRETTO-001 population.
- Additional uncertainty is due to EXAM OS data in RET M918T subgroup while MAIC used covariates, including proportion of RET M918T, from RET mutation-positive patients.
- These findings should be interpreted with caution considering the limitations of an unanchored population adjusted comparisons.

Results

Table 1: Baseline characteristics of patients with RET-mutant MTC from the LIBRETTO-001 and EXAM trials before and after weighting

Characteristic	Before weighting		After weighting
	LIBRETTO-001 Selpercatinib (N=295)	EXAM Cabozantinib (N=107)	LIBRETTO-001 Selpercatinib (N_{eff}=157)
Age (years [mean ± SD])	56.0 ±15.1	55.0 ± 15.2	55.0 ± 15.2
Weight (kg [mean ± SD])	73.1 ± 21.0	74.0 ± 21.0	74.0 ± 21.0
ECOG PS-0 (%)	37.6 %	61.7 %	61.7 %
Male (%)	61.0 %	68.2 %	68.2 %
Never smoker (%)	59.7 %	51.4 %	51.4 %
***RET* M918T mutant (%)**	62.7 %	74.6 %	74.6 %
Prior TKI therapy (%)	54.6 %	21.5 %	21.5 %

ECOG PS: Eastern Cooperative Oncology Group Performance Status; N_{eff}: effective sample size; SD: standard deviation; *RET*: REarranged during Transfection proto-oncogene; TKI, tyrosine kinase inhibitor.

Table 2: Comparison of PFS, OS, and ORR for selpercatinib (LIBRETTO-001) versus cabozantinib and versus placebo (both EXAM) in patients with RET-mutant MTC before and after propensity score weighting

Selpectatinib vs cabozantinib		Selpercatinib		Cabozantinib
		Unweighted	Weighted	
PFS	Median (95% CI)	NR (47.3-NR)	NR(53.1-NR)	13.6 (11.1-14.0)
	HR (95% CI)	0.12 (0.09-0.17)	0.08 (0.05-0.13)	Reference
OS	Median (95% CI)	NR (64.3-NR)	NR (NR-NR)	44.3 (31.1-NR)
	HR (95% CI)	0.38 (0.26-0.56)	0.20 (0.13-0.32)	Reference
ORR	Percent (95% CI)	80.0 (75.1-84.2)	82.9 (78.2-86.8)	31.7 (23.4-41.3)
	OR (95% CI)	8.6 (5.2-14.3)	10.5 (6.2-17.5)	Reference

PFS: Progression Free Survival, OS: Overall Survival, ORR: Objective Response Rate, HR: Hazard Ratio, CI: Confidence Interval, OR: Odds Ratio, NR: Not Reached.

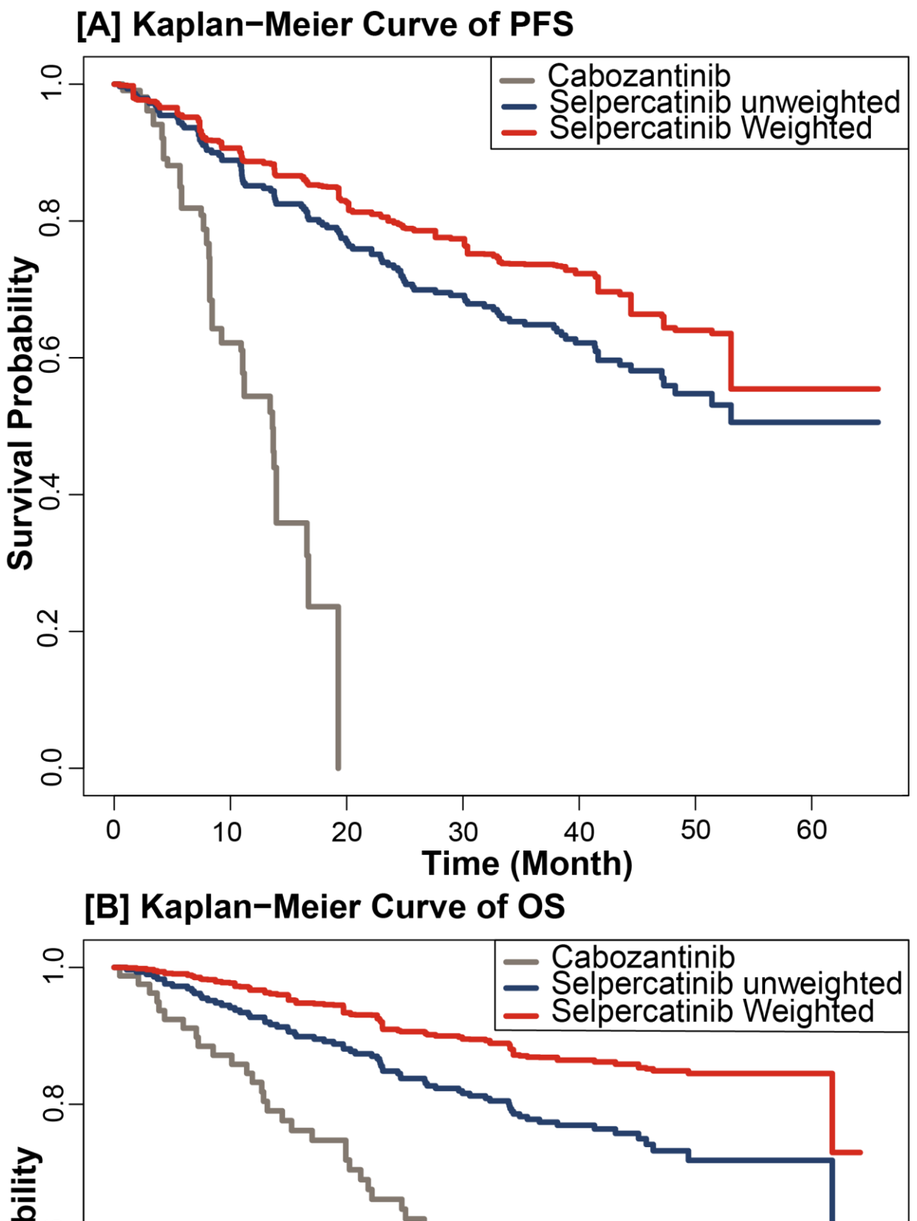

Figure 1: Kaplan-Meier curves of PFS [A] and OS [B] for patients with RET-mutant MTC who were treated with cabozantinib and selpercatinib before and after weighting from the EXAM and the LIBRETTO-001 trials.

PFS: Progression Free Survival, OS: Overall Survival.

Table 3: Multiple imputation marginalization sensitivity analysis for PFS and OS outcomes

Model	PFS, HR (95% CI)	OS, HR (95% CI)
Exponential	0.09 (0.06-0.13)	0.22 (0.14-0.33)
Weibull	0.08 (0.05-0.12)	0.23 (0.15-0.35)
Gompertz	0.10 (0.07-0.14)	0.23 (0.15-0.35)
Log-normal	0.09 (0.06-0.13)	0.23 (0.15-0.35)
Log-logistic	0.09 (0.06-0.13)	0.24 (0.16-0.37)
Gamma	0.09 (0.06-0.13)	0.26 (0.17-0.39)
Generalized gamma	0.09 (0.06-0.13)	0.25 (0.16-0.37)
Ensemble: AIC	0.09 (0.06-0.13)	0.23 (0.15-0.35)
Ensemble: BIC	0.08 (0.05-0.12)	0.23 (0.15-0.35)
Ensemble: mean (AIC,BIC weights)	0.08 (0.06-0.12)	0.24 (0.16-0.36)

PFS: Progression Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval.

References

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