Can Prior Indirect Treatment Comparisons (ITCs) Inform Health Technology Assessment (HTA) Strategy: A Case Study in Relapsed-Refractory Diffuse Large B Cell Lymphoma (RR-DLBCL)

Poster #HTA226

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Review of prior ITCs is currently not required by most HTAs. However, an increasing number of regulatory approvals are based on single-arm studies, and the use of un-anchored population-adjusted ITCs (PAICs) is increasing. We demonstrate that use of previously conducted ITCs may help with strategic HTA planning by informing the choice of comparator in pivotal trials and by estimating sufficient efficacy to achieve HTA success.

Background

Increasingly, therapies are approved for use based on single arm studies, and network meta-analysis based on relative treatment effects is not a feasible approach for comparison of all approved treatments in a given indication. Rather, a series of PAICs is likely to be the approach taken for estimating the relative efficacy of the set of treatments. We propose that previous PAICs could be used to plan for HTA and guide strategy such as choice of comparator and required efficacy in a pivotal trial.

Objective

To estimate the required relative efficacy of a hypothetical novel treatment "*Squirlitinib"* in RR-DLBCL patients who are ineligible for CAR-T therapy, as a function of chosen comparator. Further, to determine whether there is appreciable variation in efficacy depending on the population in which trials have been conducted.

Methods

Treatment network and precision adjustments

- Living-SLR database (LiveSLR® [1]) was used to gather published ITCs/PAICs in RR-DLBCL patients not eligible for CAR-Ts. The resulting network is shown in **Figure 1**.
- Published Hazard Ratios (HRs) were extracted and used to construct a network of direct and indirect treatment comparisons.
- In cases where both PAIC and ITC comparisons were available, the ITC comparison was used to avoid overrepresentation of particular trial populations.
- Confidence intervals (CIs) were adjusted to account for multiple comparisons.
    - Multiple PAICs were included against the same treatment arm. A Bonferroni-type correction was applied to account for multiple comparisons by analogy to a single trial with multiple treatment arms.

Addition of novel treatment and anticipated ranking

- Based on ongoing randomized-controlled trials (RCTs), we considered four potential RCTs of the hypothetical treatment *Squirlitinib* vs
    - bendamustine+rituximab (BR),
    - rituximab+gemcitabine+oxaliplatin (R-GemOx),
    - polatuzumab+bendamustine+rituximab (POLA-BR), and
    - tafasitamab+lenalidomide (TAFA-LEN).
- A Bayesian Network-Meta-Analysis tool was used to evaluate the HR required for *Squirlitinib* to achieve top NMA ranking versus all comparators (**Table 1, Figures 2-5**).
- In the trials of *Squirlitinib* vs comparators, we estimated the standard error by assuming proportional hazards and a trial with n=150 patients per arm.

Impact of differences in target population

- Previous PAIC adjustments may be informative when anticipating future PAIC adjustments
- If proportional hazards holds for prognostic or effect modifying differences in population characteristics when making PAIC adjustments, an assessment of the magnitude and direction of the previous adjustments may be informative when anticipating adjustments in future PAICs which include *Squirlitinib.*
- If adjustments to efficacy in a PAIC follow proportional hazards, we get an adjusted HR*:

$$\lambda^*_{active} = \left(\lambda_{comparator} e^{\beta_{pop}}\right) e^{\beta_{trt}}$$

$$HR^* = e^{\beta_{trt}+\beta_{pop}}$$

- The adjustment in a previous PAIC can thus be summarized by (**Table 2**)

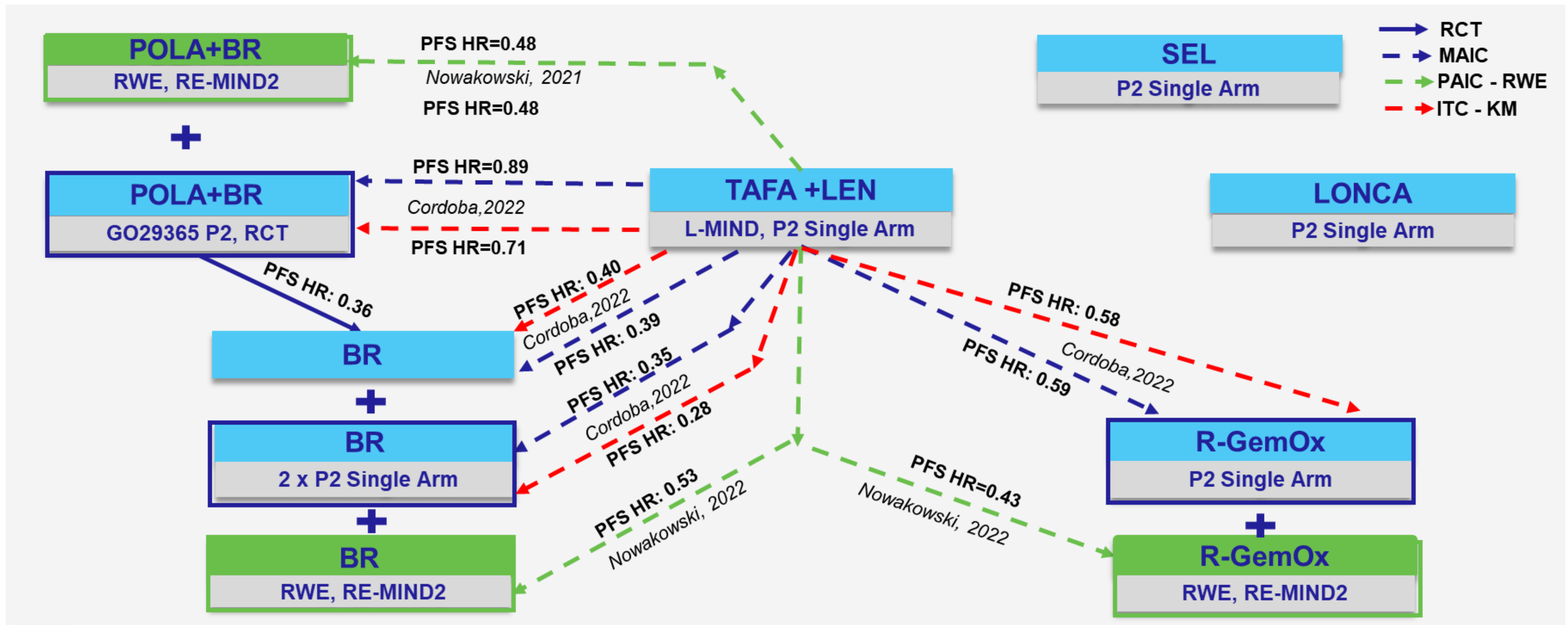
$$\frac{HR^*}{HR} = e^{\beta_{pop}}$$

- The anticipated PAIC HR for the novel treatment, assuming similar adjustment(s) to those made in previous PAICs is:

$$HR^*_{novel} = e^{\beta_{novel}+\beta_{pop}} = HR_{novel} \times \frac{HR^*}{HR}$$

Results

Figure 1. Network of direct and indirect comparisons in RR-DLBCL (CAR-T ineligible) with PFS endpoint.



Abbreviations: RCT is randomized controlled trial; MAIC is matching-adjusted indirect comparison; PAIC – RWE is population-adjusted indirect comparison using real-world evidence; ITC – KM is indirect treatment comparison using Kaplan-Meier curves; LONCA is Loncastuximab; SEL is Selinexor; PFS is progression-free survival. References [2-5]

Table 1. Relative efficacy required for Squirlitinib as a function of chosen comparator.

Hypothetical Trial	HR required for superiority	95% CI
Squirlitinib vs TAFA-LEN	0.75	(0.62, 0.90)
Squirlitinib vs POLA-BR	0.48	(0.40, 0.57)
Squirlitinib vs BR	0.26	(0.22, 0.32)
Squirlitinib vs R-GemOX	0.33	(0.27, 0.40)

Abbreviations: HR is hazard ratio; CI is confidence interval.

Figure 2. NMA results after addition of hypothetical Squirlitinib vs TAFA-LEN trial

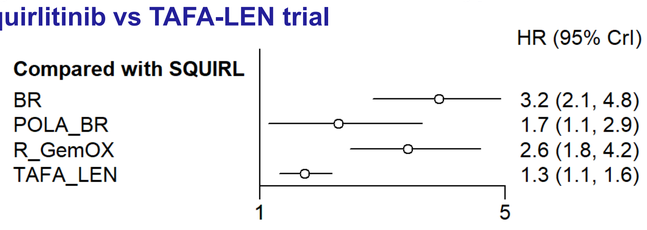


Figure 3. NMA results after addition of hypothetical Squirlitinib vs POLA-BR trial

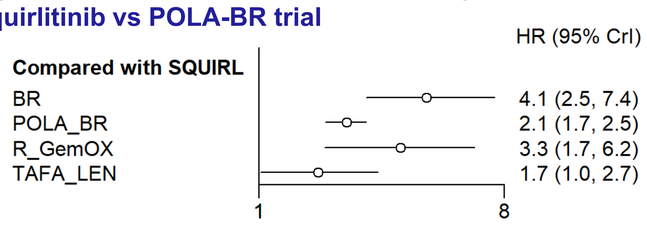


Figure 4. NMA results after addition of hypothetical Squirlitinib vs BR trial

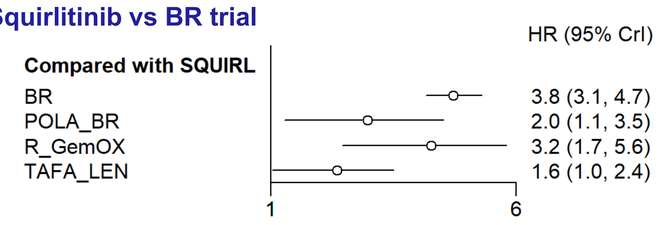
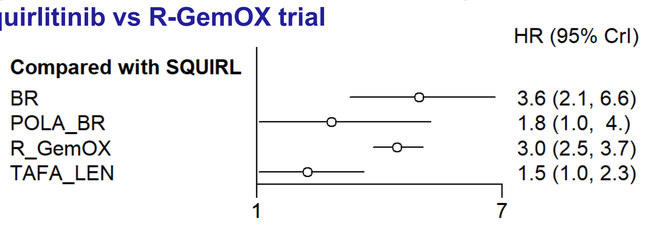


Figure 5. NMA results after addition of hypothetical Squirlitinib vs R-GemOX trial



- The hazard ratio required to achieve superiority varied as a function of comparators, from 0.75 for TAFA-LEN to 0.26 for BR (**Table 1**).
- TAFA-LEN had been previously the highest ranking treatment, followed closely by POLA-BR.
- If TAFA-LEN is chosen as the comparator for *Squirlitinib*, then a sufficient HR to demonstrate indirect superiority against POLA-BR is required (**Figure 2**), and vice-versa (**Figure 3**).
- If either BR or R-GemOX are chosen as the comparator, then a sufficient HR to demonstrate indirect superiority against both TAFA-LEN and POLA-BR is required (**Figures 4 and 5**).
- HR estimates used here assume similar populations among studies; results should be interpreted cautiously and should only be used for strategic planning of future HEOR analyses.

Table 2. PAIC adjustments made in previous studies.

Active Treatment	Comparator	HR	HR*	HR*/HR
TAFA-LEN	POLA-BR	0.71	0.89	1.25
TAFA-LEN	BR	0.40	0.39	0.98
TAFA-LEN	R-GemOX	0.58	0.59	1.02

Abbreviations: HR is hazard ratio; HR* is PAIC-adjusted HR.

- In the event that PAIC are required for comparison of *Squirlitinib* against other treatments, it is difficult to speculate how population adjustments may affect the HR.
- Past population adjustments for TAFA-LEN showed adjustments of up to 25 percent.
- The relative efficacy of *Squirlitinib* may need to be even stronger to demonstrate superiority if similar population adjustments are required in future.

Conclusions

- Utilization of previously conducted ITCs may help with strategic HTA planning to ensure appropriate comparator use in pivotal trials and investigational drug effectiveness is sufficient to achieve HTA success.
- Past PAIC adjustments may be useful in anticipating the effect of population adjustments on eventual comparisons.

References

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Disclosures

- All authors are employees of Cytel.

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