Methods for incorporating non-randomized evidence from single-arm trials into network meta-analyses: A case study in head and neck cancer

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Background

- Randomized controlled trials (RCTs) are the gold standard for determining the relative efficacy of healthcare interventions; however, individual RCTs often do not include all relevant interventions from a health technology assessment perspective. As such, decision makers often utilize indirect treatment comparisons (eg, network meta-analysis [NMA]) to estimate relative treatment effects between interventions not studied in a head-to-head fashion
- If RCTs from an evidence base form a connected network but the intervention of interest is only evaluated in a disconnected (eg, single-arm) study, it is of interest to explore alternative methods that allow for integration of the disconnected study into the existing network to enable comparisons across all interventions
- This study aimed to explore the application of such available methods, using a case study in recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). The case study compared the objective response rate (ORR) between pembrolizumab in combination with carboplatin and paclitaxel (the KEYNOTE-B10 regimen) from the phase 4, single-arm, KEYNOTE-B10 trial (NCT04489888) in R/M HNSCC[1] and other recommended first-line (1L) treatments from a connected network of RCTs

Methods

- A systematic literature review (search date: October 31, 2023) was conducted to identify RCTs evaluating interventions recommended for 1L treatment of R/M HNSCC. RCTs with patient eligibility criteria similar to those of KEYNOTE-B10 were included in this study
- Four different methods were leveraged to integrate aggregate-level data from the interim analysis of KEYNOTE-B10 into the NMA, while one additional method incorporated individual-patient-level data (IPD) (Table 1)

Table 1. Statistical methods to integrate a disconnected, single-arm trial into a network meta-analysis

Type of KEYNOTE-B10 data	Method	Details
Aggregate level	Aggregate-level matching (ALM)[2]	• ASD in baseline patient characteristics that act as prognostic factors and/or effect modifiers (eg, age, presence of metastatic disease, primary tumor location) were calculated between KEYNOTE-B10 and each RCT from the network. Covariates with an ASD <10% were considered 'balanced' between the 2 trials • The RCT with the lowest sum of ASDs and the highest number of balanced covariates was determined as the most similar RCT in the network to KEYNOTE-B10 • KEYNOTE-B10 was considered an additional treatment arm of the selected RCT
	Additive-component NMA (CNMA)[3]	• The NMA model was specified with a separate effect for each component monotherapy in the network • Assumed that the effect of a combination treatment is the sum of its component parts
	Random effects on baseline[4]	• An extension of conventional NMA to incorporate disconnected nodes into a network by modelling the overall reference treatment (eg, control) • The intervention with the most connections to the other nodes in the network was selected as the reference treatment • A random-effects model on reference treatment is fitted, as opposed to the reference treatment only being a nuisance parameter (ie, not of interest but necessary to estimate parameters of interest) in conventional NMA • Treatment effects relative to the reference treatment are then estimated for all non-referent treatments, including the disconnected single node
	Reference prediction[5]	• An extension of random effects on baseline • Instead of a strong assumption on the exchangeability of reference-treatment effect, only trials that include the reference treatment are used to estimate the reference-treatment effect, which in turn preserves randomization within trials • The choice of reference treatment becomes important
Individual patient level	Matching-adjusted indirect comparison (MAIC+NMA)[6,7]	• Similar concept to ALM in terms of matching an index study to a target trial. Instead of aggregate level data (as in ALM), individual patient-level data from KEYNOTE-B10 were used to match to aggregate-level data of the RCT that ALM identified as the most similar trial to KEYNOTE-B10 • Patients in KEYNOTE-B10 were then reweighted so that the average distributions of prognostic factors and/or effect modifiers in KEYNOTE-B10 match those of the selected RCT • KEYNOTE-B10 was then considered an additional treatment arm in the selected RCT

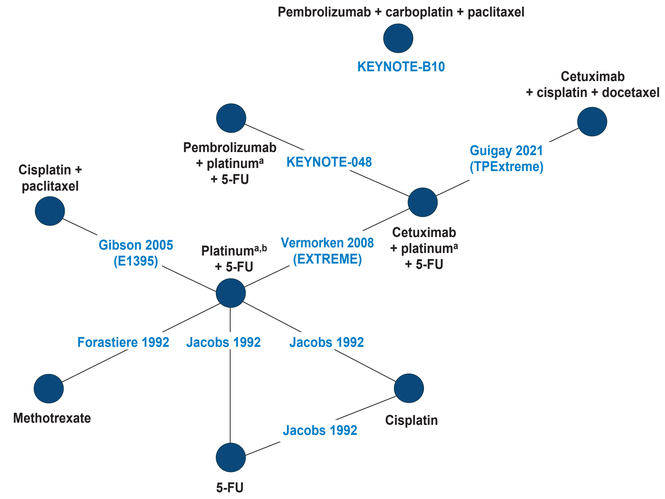
Notes: All NMAs were conducted in a Bayesian framework, except CNMA, which was conducted in a frequentist framework.

ALM, aggregate-level matching; ASD, absolute standardized difference; CNMA, additive component NMA; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomized controlled trial.

Results

- The systematic review identified 26 RCTs, of which 6 evaluated recommended interventions, formed a connected network, and matched the patient eligibility criteria of KEYNOTE-B10 (Figure 1)[8-13]
- KEYNOTE-048 was determined as the most similar trial in the network to KEYNOTE-B10
- Platinum + 5-FU was identified as the intervention with the most connections to the other nodes in the network and was selected as the reference treatment for all methods

Figure 1. Network of evidence for trials included in the analysis



[a]Type of platinum was unspecified if at least one trial with this treatment arm in the network had cisplatin or carboplatin as options at randomization.
[b]Forastiere 1992 had separate arms of cisplatin+5-FU and carboplatin+5-FU, which were pooled as platinum + 5-FU for the purpose of the network meta-analysis.

- The KEYNOTE-B10 regimen significantly improved ORR versus platinum + 5-FU, cisplatin + paclitaxel, cisplatin, 5-FU, and methotrexate, using the ALM, the CNMA, and the MAIC+NMA approaches (Table 2)
  - Although the point estimate of the odds ratios favored the KEYNOTE-B10 regimen versus pembrolizumab + platinum + 5-FU, cetuximab + platinum + 5-FU, and cetuximab + cisplatin + docetaxel using the ALM and the MAIC+NMA approaches, results were not statistically significant in either approach
- The random effects on baseline and reference prediction methods had more variable estimates with wider credible intervals (CrIs) that often did not capture the significant results from the other approaches

Table 2. Fixed effects NMA results of objective response for the KEYNOTE-B10 regimen vs. comparators

Model	Pembrolizumab + platinum[a] + 5-FU	Cetuximab + platinum[a] + 5-FU	Platinum[a,b] + 5-FU	Cisplatin + paclitaxel	Cetuximab + cisplatin + docetaxel	Cisplatin	5-FU	Methotrexate
Analysis incorporating aggregate-level data from KEYNOTE-B10								
ALM	1.35 (0.81, 2.22)	1.31 (0.79, 2.15)	**2.96 (1.53, 5.75)**	**3.59 (1.46, 8.92)**	1.28 (0.69, 2.35)	**6.84 (2.55, 18.90)**	**9.23 (3.31, 26.65)**	**9.76 (3.60, 28.09)**
CNMA	0.96 (0.71, 1.29)	0.94 (0.60, 1.48)	**2.14 (1.15, 4.01)**	**2.24 (1.29, 3.89)**	0.98 (0.70, 1.39)	**4.61 (1.74, 12.21)**	**6.50 (2.37, 17.82)**	**14.15 (5.32, 37.60)**
Random effects on baseline	0.94 (0.02, 32.86)	0.90 (0.02, 34.61)	2.08 (0.07, 52.25)	2.36 (0.04, 186.86)	0.87 (0.02, 35.73)	4.44 (0.07, 415.63)	5.98 (0.06, 390.14)	6.84 (0.10, 489.34)
Reference prediction	0.96 (0.21, 4.19)	0.92 (0.21, 3.90)	2.10 (0.49, 8.36)	2.53 (0.54, 11.42)	0.90 (0.20, 3.95)	4.84 (0.99, 23.03)	**6.50 (1.30, 31.88)**	**6.89 (1.40, 33.94)**
Analysis incorporating individual patient-level data from KEYNOTE-B10								
MAIC + NMA	1.49 (0.88, 2.52)	1.44 (0.85, 2.42)	**3.24 (1.64, 6.35)**	**3.91 (1.56, 9.71)**	1.41 (0.75, 2.62)	**7.35 (2.70, 20.23)**	**9.76 (3.46, 27.71)**	**10.27 (3.69, 28.82)**

[a]Type of platinum was unspecified if at least one trial with this treatment arm in the network had cisplatin or carboplatin as options at randomization.
[b]Forastiere 1992 had separate arms of cisplatin + 5-FU and carboplatin + 5-FU, which were pooled as platinum + 5-FU for the purpose of the NMA.

Notes: Each cell represents the estimated odds ratio (95% credible interval) of objective response for pembrolizumab + carboplatin + paclitaxel (the KEYNOTE-B10 regimen) versus the column-defining comparator intervention. All bolded values are statistically significant at the 0.05 significance level. For CNMA (conducted in a frequentist framework), 95% confidence intervals are presented.

ALM, aggregate-level matching; CNMA, additive component network meta-analysis; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis.

Discussion

- MAIC+NMA was the most reliable among the five evaluated approaches from both clinical and statistical standpoints
  - Adjusted (i.e., reweighted) KEYNOTE-B10 IPD were used, resulting in comparable populations for KEYNOTE-B10 and KEYNOTE-048 in terms of known prognostic factors and effect modifiers
  - Did not make heavy assumptions and was able to detect statistically significant results with reasonable accuracy
- MAIC+NMA is still limited to the reported aggregate-level data from the target trial (KEYNOTE-048), which makes it likely that some confounding variables remain unbalanced
- ALM and CNMA, although not as accurate or reliable as MAIC+NMA, could still be helpful in certain situations
  - ALM is a potentially viable method in the absence of IPD as its results closely aligned with those of MAIC+NMA due to the similar population and design of KEYNOTE-B10 with KEYNOTE-048
  - CNMA can be helpful when the population characteristics of the disconnected trial are considerably different than those of the RCTs included in the network
- Methods that incorporated aggregate-level data generally had more limitations and made stronger assumptions than MAIC+NMA
  - With ALM, some small differences in the distribution of known prognostic factors between KEYNOTE-B10 and KEYNOTE-048 remained unadjusted. There may have also been differences in terms of unknown prognostic factors
  - CNMA predicted the relative treatment effects based on the efficacy of the KEYNOTE-B10 regimen's individual components, i.e., did not use actual data from KEYNOTE-B10. It also assumed additive main effects since interactions could not be estimated for pembrolizumab or between platinum and taxanes
  - Random-effects on baseline and reference prediction made strong assumptions, leading to results with high variability and less precision that were subject to risk of bias

Conclusions

- Leveraging IPD in MAIC+NMA allowed for adjusting for baseline characteristics that act as prognostic factors and effect modifiers, yielding statistically significant results with precise estimates that were more reliable compared to other approaches
- MAIC+NMA results demonstrated superior/comparable efficacy of the KEYNOTE-B10 regimen versus interventions recommended for 1L treatment of R/M HNSCC
- Future research can complement the current analyses by incorporating the final analysis of KEYNOTE-B10, additionally including the OS and PFS outcomes

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Presented at ISPOR; Atlanta, GA, USA; May 5-8, 2024.