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POSTER# HTA71

The Prevalence of Fractional-Polynomial Network Meta-Analyses in Supporting Reimbursement Recommendations by Canada's Drug Agency

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BACKGROUND

- The assessment of proportional hazards is critical in determining the most appropriate methods for indirect treatment comparisons (ITCs) when using time-to-event data
- Where time-varying hazard ratios are observed and proportionality is violated, the implementation of time-varying methods, specifically parametric survival or fractional-polynomial network meta-analyses (fpNMAs) methods, are recommended for EU Joint Clinical Assessment (JCA) submissions[1]
  - The recommendation for time-varying methods to support clinical efficacy may extend beyond the European landscape to other regulatory bodies
- fpNMA methods address non-proportionality by using a multidimensional treatment effect approach to generate survival estimates that aim to closely align to trial data
  - This method explores a wide range of multivariate distributions (i.e. P_1 and P_2 values of -2, -1, -0.5, 0, 0.5, 1, 2 and 3) where all treatment arms in the network are assumed to follow the same polynomial function distribution[2]
  - First and second order fractional-polynomial (fp) models allow for changes in the direction of hazard ratios over time, permitting a flexible fit of observed survival data

OBJECTIVES

- As regulatory reviews often critique the lack of attention to proportional hazard violations, this review aims to understand the use of fpNMA across Canada's Drug Agency (CDA-AMC) submissions and their critiques by the pan-Canadian Oncology Drug Review Expert Review Committee (pERC)
- The goal of this exercise is to identify reporting practices for fpNMA model characteristics and interpretations presented in submissions

METHODS

- A pragmatic review was conducted by three researchers using fp related search terms (e.g. "fractional polynomial", "fp + fractional", "fp + polynomial") to identify CDA-AMC submissions using fpNMA methods with no time-constraint
- Relevant information was extracted from the "Summary of pERC deliberations" and "Overall clinical benefit" sections of the Final Recommendations documentation as well as clinical efficacy sections of the Final Clinical Guidance Report
- Figure 1 describes the extraction criteria, including:
  - Intervention, therapeutic area, target population, and approval date
  - Model parameters including polynomial order, follow-up time points, and model effects type
  - Criterion to determine the best polynomial model fit alongside the assessment of model convergence
  - Choice of base case and/or sensitivity analyses
  - The availability of comparator evidence and distribution of patient baseline characteristics
  - Reimbursement decision by the pERC and notable limitations of the supporting evidence

RESULTS

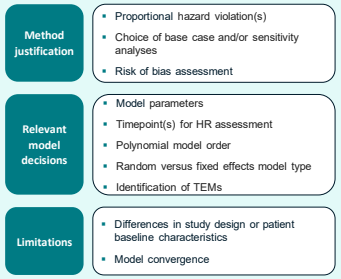
- Twenty submissions were identified, 10 of which reported using fpNMA as base case and/or sensitivity analyses to support evidence generation for comparative efficacy

Table 1. Submission details

Intervention	Target patient population	Submission date	Outcomes	Recommendation type
Pembrolizumab monotherapy; pembrolizumab + platinum + 5-FU chemotherapy	Metastatic or unresectable recurrent HNSCC as monotherapy for patients whose tumors have PD-L1 expression CPS ≥ 1 (or in combination with platinum and 5-FU chemotherapy regardless of PD-L1 expression level)	May 1, 2020	OS and PFS	Reimburse with clinical criteria and/or conditions
Niraparib	Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	February 7, 2020	PFS	Reimburse with clinical criteria and/or conditions
Atezolizumab, with and without bevacizumab, + carboplatin + paclitaxel	Metastatic eGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on targeted therapies	November 18, 2019	OS and PFS	Do not reimburse
Pembrolizumab + axitinib	Advanced RCC patients	August 2, 2019	OS and PFS	Reimburse with clinical criteria and/or conditions
Pembrolizumab	Stage III melanoma patients following resection	December 13, 2018	RFS and OS	Reimburse with clinical criteria and/or conditions
Dabrafenib + trametinib	Patients with melanoma with a *BRAF* V600 mutation and involvement of lymph node(s), following complete resection	September 21, 2018	RFS and OS	Reimburse with clinical criteria and/or conditions
Lenvatinib	Patients with advanced or metastatic, clear cell RCC following one prior VEGF-targeted therapy	June 8, 2018	RFS and OS	Do not reimburse
Atezolizumab	Patients with locally advanced or metastatic NSCLC and who have disease progression on or after cytotoxic chemotherapy	December 15, 2017	OS and PFS	Reimburse with clinical criteria and/or conditions
Olaratumab	Patients with advanced STS not amenable to curative treatment with radiotherapy or surgery and for whom treatment with an anthracycline-containing regimen is appropriate	October 26, 2017	OS and PFS	Reimburse with clinical criteria and/or conditions
Dabrafenib + trametinib	Patients with advanced NSCLC with a *BRAF* V600 mutation and who have been previously treated with chemotherapy	March 31, 2017	OS and PFS	Do not reimburse

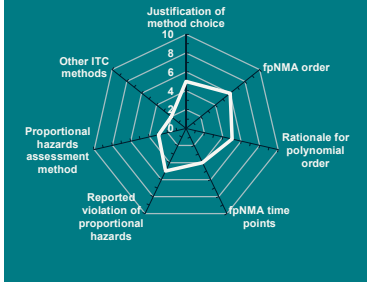
Key: ALK, anaplastic lymphoma kinase; CPS, combined positive score; eGFR, estimated glomerular filtration rate; FU, fluorouracil; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, relapse-free survival; STS, soft tissue sarcoma; VEGF, vascular endothelial growth factor.

Figure 1. Key extraction steps from CDA-AMC submission



Key: HR, hazard ratio; TEMs, treatment effect modifiers.

Figure 2. ITC methodology transparency



Key: fpNMA, fractional polynomial network meta-analysis; NMA, network meta-analyses; PH, proportional hazards.

Submission details

- All submissions using fpNMA were found in oncology indications, majority of which were targeting patients in advanced or metastatic stage of disease (Table 1). Three of the submissions identified were in non-small cell lung cancer
  - The prevalence of this method across oncology submissions may indicate a higher incidence of proportional hazard violations due to differences in long-term efficacy between interventions
  - Treatment effect modifiers and/or prognostic factors may impact proportionality between treatment arms due to lack of maturity in survival data available in oncology trials
- As is expected by the nature of oncology submissions, overall survival was the most commonly analyzed outcome. Submissions also investigated progression-free survival or relapse-free survival
- The submission dates ranged from March 31, 2017 to May 1, 2020. Notably, no submissions have been published in the last five years, suggesting that recent submissions may be using alternative time-varying methods

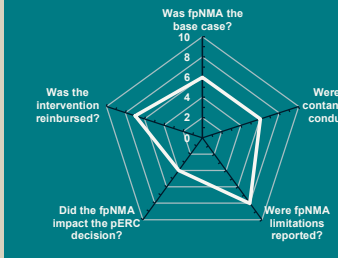
fpNMA method-related details

- Figure 2 highlights the lack of standardization across reporting of fpNMA results in CDA-AMC submissions, regardless of the reimbursement decision
- There was little consistency in the reporting of model parameterizations such as methods used to determine best fit, polynomial order and fpNMA time points. Diagnostic summaries were not reported in the submissions, meaning the convergence of fpNMA models had to be assumed
- Five submissions reported violation of proportional hazards, which merits the use of time-varying methods. However, only three of those submissions reported the details on the assessment of proportionality. Only one submission mentioned the use of any additional time-varying methods (i.e. parametric NMA)
- While six submissions reported the order of best fitting fp models for each outcome, only five justified their order choice
- Time points were only reported by four submissions. Due to the complexity of the fpNMA method, the choice of time point may be influential to model results

Reimbursement decision

- The CDA-AMC recommended that 70% of the submissions were reimbursed with clinical criteria and/or conditions that varied across indications (Figure 3)
- The reimbursement decision did not seem to depend on the use of fpNMA, likely due to the limitations posed by the small sizes and heterogeneity between trials in the comparator evidence base
- Four of the seven reimbursed submissions used fpNMA as base case, while the other three included fpNMA in sensitivity analyses
- Time-constant network meta-analyses (NMAs) results were presented alongside the fpNMA results for five submissions, which likely supported successful reimbursement decisions due to the prevalence and interpretability of the method in oncology submissions
- Limitations associated with fpNMA were reported by eight studies; however, our review did not find that those reimbursement decisions were directly linked to the use of fpNMA

Figure 3. Summary of reimbursement submission details



Key: fpNMA, fractional polynomial network meta-analysis; NMA, network meta-analyses; pERC, pan-Canadian Oncology Drug Review Expert Review Committee; PH, proportional hazards.

CONCLUSIONS

- There was large variability in how fpNMA results were leveraged to support submissions. Some submissions also presented time-constant NMA results to support evidence of comparative efficacy
- Many submissions reported second-order fp as the best fitting model; however, little justification was provided to support the choice of model order
- The reimbursement decision did not always cite fpNMA methods as a key limitation, though pERC committee feedback noted issues of clinical heterogeneity, small sample sizes, lack of comparator data, and immature survival data, which restricted the validity and interpretability of the results
- As the search strategy did not identify any submissions which included fpNMA methods since 2020, researchers may be interested in exploring a similar review for alternative time-varying methods to explore emerging trends in CDA submissions

REFERENCES

1. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons; HTA CG. 2024.
2. Sauerbrei W et al. Biometrical J. 2007; 49(3):453-473.

An electronic version of the poster can be viewed by scanning the QR code.