Poster #: MSR77

# Bayesian Hierarchical Model-based Network Meta-analysis to Overcome Survival Extrapolation Challenges Caused by Immature Data. Application in Previously Treated Metastatic Non-small Cell Lung Cancer (NSCLC) PD-L1 >1%

B. Heeg,[1] A. Verhoek,[1] G. Tremblay,[2] H. Chu,[3] S. Roychoudhury,[3] J. Cappelleri,[3] M. Soltanifar,[2] O. Harari,[2]
[1]Cytel, Rotterdam, Netherlands; [2] Cytel, Canada; [3]Pfizer Inc, Groton, CT, US;

## Background & Objective

- At health technology assessment (HTA), overall survival trial data are often immature. Several immunotherapies have shown negligible disease-related event risks with sufficient follow-up.[1] Extrapolation methods, like mixture cure models, cannot accurately estimate cure based on immature trial data alone. This might lead to clinical, implausible extrapolations informing HTA decision-making.
- Bayesian hierarchical (BH) network meta-analysis (NMA) allows for defining a common parameter distribution for same-class treatments. Information can then be borrowed from treatments with longer follow-up to inform parameters of same-class therapies examined in trials in the network with shorter follow-up.
- The aim was to inform long-term survival of therapies by BH-NMA.[2]

## Methods

- A network of four trials in previously treated metastatic non-small cell lung cancer with PD-L1 >1% compared nivolumab, pembrolizumab and atezolizumab (twice) individually with docetaxel.[3-6] Follow-up for the two atezolizumab trials was shorter than those for the pembrolizumab and nivolumab trials (Figure 1).
- The BH-NMA approach was applied to a Weibull mixture cure (WMC) NMA and compared with a standard WMC NMA approach. A fixed-effects standard WMC NMA model was defined with study-specific shape, scale and cure parameters, and corresponding treatment coefficients. Non-informative priors were assumed. The BH-WMC NMA was identical, except class effects were defined on the cure parameter for docetaxel over the studies and on the cure treatment effect parameter of the immunotherapies. Impact of study-specific variance τ’ over the cure class parameter for docetaxel and immunotherapy class cure treatment effect σ’ was assessed. These parameters defined how common the docetaxel cure rates were by study and how common the treatment effect was over the different immunotherapies. The fit-statistic, cure rates and mean survival were compared.

## Conclusions

- BH-NMA is a means to overcome selected immature trial data in the evidence network, which has important consequences in predicted mean life years and, therefore, potentially HTA decisions.
- Base-case selection of the variances (τ’ and σ’) in BH-NMA requires similar standard parametric extrapolations from clinical opinion on clinical plausibility of the extrapolations.
- BH-NMA can easily be extended to the standard parametric approach to mixture, spline and fractional polynomial NMAs.
- The BH-WMC NMA approach requires an evidence network with same-class therapies with at least some mature data.

## Key Results

### Base-case WMC NMA

- This was the best-fitting model in terms of leave one out information criterion (LOOIC; Table 1).
- The atezolizumab trials were relative immature and, consequently, the standard WMC NMA approach predicted similar cure rates for placebo and atezolizumab (~3%) and higher cure rates for pembrolizumab (7%) and nivolumab (~18%).
- Mean survival (Figure 2) and incremental mean survival (Table 1) of docetaxel and atezolizumab were very similar and not significantly different. Nivolumab and pembrolizumab showed a significant survival benefit compared to docetaxel.

### BH-NMA

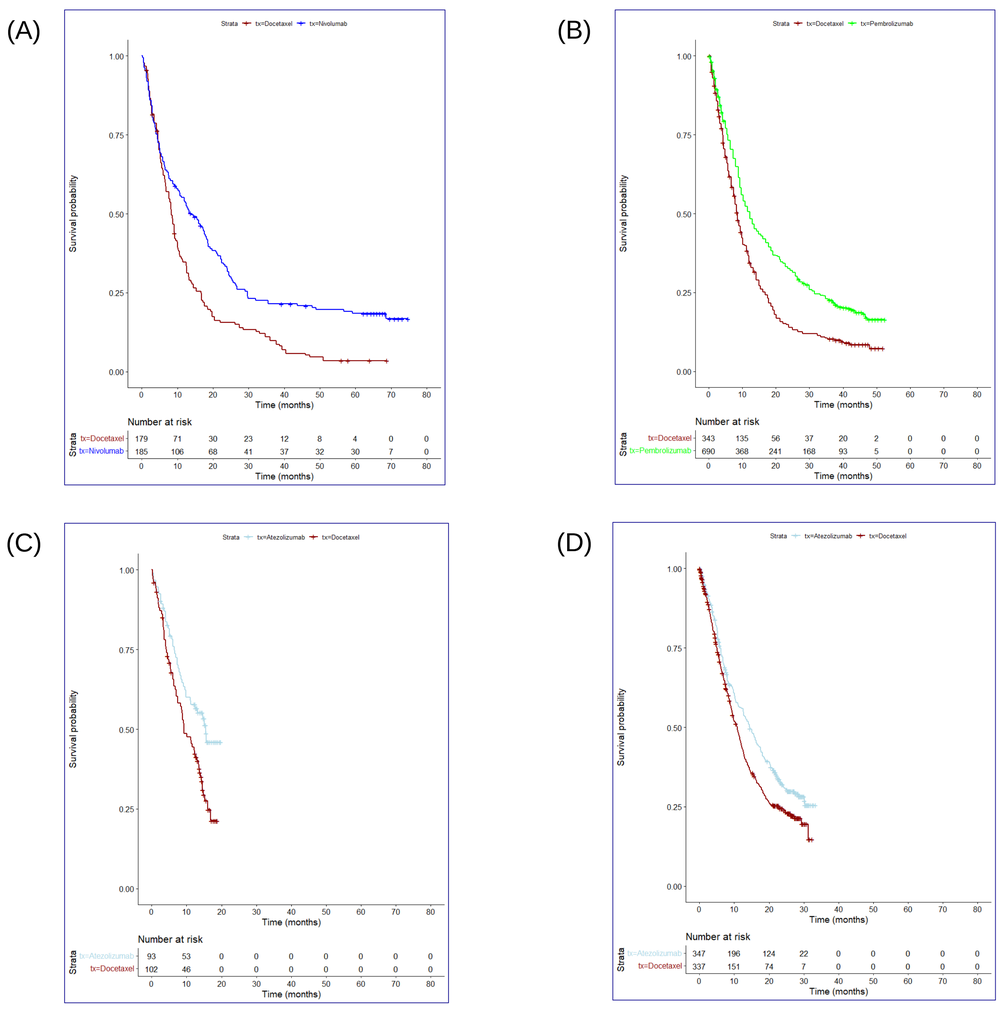
- Assuming little variance (σ’ = 0.1) over immunotherapies class treatment effect on cure resulted in very similar cure rates and survival predictions for the immunotherapies, including atezolizumab, which were significantly different from docetaxel (Figure 2 and Table 1).
- Assuming large variance (σ’ = 10) resulted in different cure rates and overall survival predictions by immunotherapy that were much more in line with the base-case WMC NMA (Figure 2 and Table 1).
- The docetaxel fit improved with larger τ’, which allowed more variation over predicted docetaxel cure rates by study. (Please note, the focus was clinical, plausible extrapolations and not best fit).

### Table 1. Overview of LOOIC cure rates and mean predicted life expectancy by model (with 95% credible intervals)

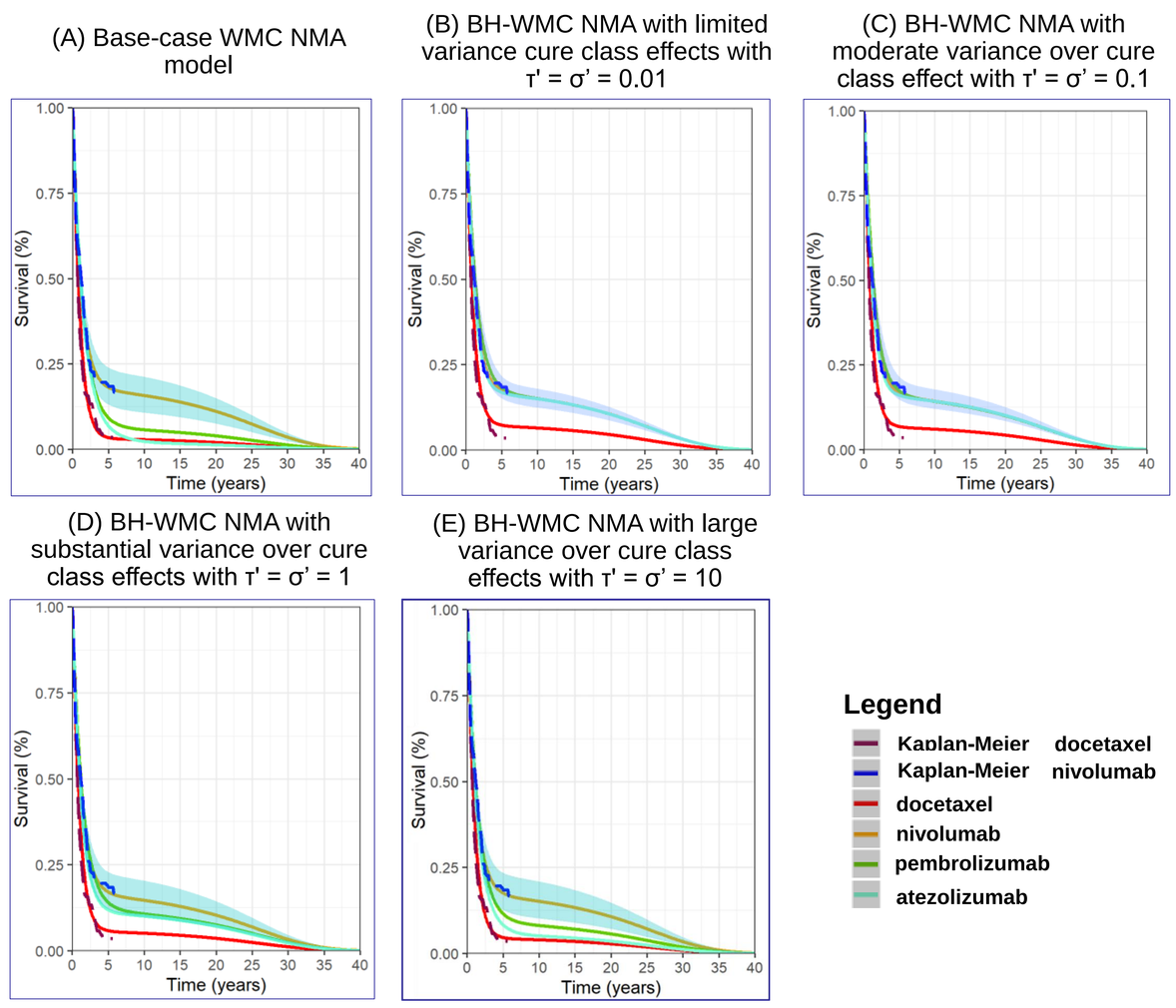
| Model | | LOOIC | Docetaxel | Nivolumab* | Pembrolizumab | Atezolizumab |
|---|---|---|---|---|---|---|
| **Cure rates** | | | | | | |
| Base-case NMAs | | 13462 | 0.03 [0.00; 0.06] | 0.18 [0.11; 0.24] | 0.07 [0.02; 0.15] | 0.03 [0.00; 0.10] |
| Bayesian hierarchical model NMAs | τ’ = σ’ = 0.01 | 13465 | 0.07 [0.05; 0.10] | 0.17 [0.14; 0.20] | 0.16 [0.14; 0.20] | 0.17 [0.14; 0.20] |
| | τ’ = σ’ = 0.10 | 13465 | 0.07 [0.04; 0.10] | 0.17 [0.13; 0.21] | 0.16 [0.13; 0.20] | 0.17 [0.13; 0.21] |
| | τ’ = σ’ = 1.00 | 13464 | 0.06 [0.03; 0.09] | 0.17 [0.11; 0.23] | 0.12 [0.05; 0.20] | 0.12 [0.03; 0.23] |
| | τ’ = σ’ = 10.0 | 13463 | 0.05 [0.02; 0.09] | 0.17 [0.11; 0.24] | 0.09 [0.03; 0.18] | 0.07 [0.00; 0.21] |
| **Incremental mean survival compared to docetaxel** | | | | | | |
| Base case | | | - | 3.16 [1.68; 4.74] | 1.07 [0.41; 2.41] | 0.42 [-0.59; 1.72] |
| Bayesian hierarchical model NMAs | τ’ = σ’ = 0.01 | | - | 2.19 [1.17; 3.24] | 2.37 [1.42; 3.34] | 2.16 [1.21; 3.13] |
| | τ’ = σ’ = 0.10 | | - | 2.37 [1.20; 3.17] | 2.48 [1.44; 3.17] | 2.31 [1.23; 3.12] |
| | τ’ = σ’ = 1.00 | | - | 2.41 [1.05; 3.99] | 1.67 [0.67; 3.01] | 1.33 [-0.05; 3.71] |
| | τ’ = σ’ = 10.0 | | - | 2.78 [1.25; 4.37] | 1.34 [0.50; 2.76] | 0.66 [-0.44; 3.43] |

Where τ’ is variance over docetaxel cure rates by trial and σ’ is variance over treatment effect of individual immunotherapies (atezolizumab, pembrolizumab and nivolumab) on cure rate
*Reference trial; Abbreviations: LOOIC, leave one out information criterion; NMA, network meta-analysis

### Figure 1. Kaplan-Meier curve in evidence network of overall survival for the trial comparing docetaxel with nivolumab (A), pembrolizumab (B), and atezolizumab (C) and (D)




### Figure 2. Standard (A) and BH-WMC NMAs (B–E) predicted survival for docetaxel, nivolumab, pembrolizumab, and atezolizumab with corresponding uncertainty for therapy with the longest predicted survival




## References

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Presented at ISPOR Europe | Vienna, Austria | November 6–9, 2022