A Bayesian Hierarchical Model for Indirect Comparison of Immuno-oncology Drugs

Ji Lin1, Zachary M. Thomas1, Jingyi Liu1, Myhilli Koneru1
1 Eli Lilly & Company, Indianapolis, IN, USA

ABSTRACT

The first PD-1 checkpoint inhibitor was approved in 2014, and subsequently the medical literature regarding cancer immunotherapy has rapidly expanded. This large amount of literature provides a unique opportunity to address many important clinical questions, e.g., whether antibodies targeting PD-1, the receptor located on T cells, have a different efficacy and/or safety profile from the antibodies targeting PD-L1, the ligand on tumor cells.

Understanding the ever-changing PD-1/PD-L1 landscape and optimizing treatment regimens is critical. However, there is only a limited focus on systematic statistical methodologies and analyses which provide a more formal quantitative characterization. We used a meta-analytic procedure to compare efficacy and safety data between PD-1 and PD-L1 checkpoint inhibitors across tumor types. The procedure uses a Bayesian hierarchical model to synthesize data from a large amount of studies, involving multiple mechanisms across a variety of types. While direct comparison of these mechanisms is difficult, if not impossible, our proposed method provides a quantitative approach to address the aforementioned and potentially other critical questions via indirect comparisons through the use of published literature data.

RESULTS

Figure 2. Graphical Representation of the Model

Methods

Model

A random effect term was included to estimate and adjust for the study-specific variability.

\[ r_i = \text{Binomial}(n_i, p_i) \]

\[ \logit(p_i) = \alpha + \delta_i + \epsilon_i \]

\[ \delta_i = \text{Normal}(0, \sigma^2) \]

\[ \epsilon_i = \text{Normal}(0, \omega^2) \]

\[ \text{observed Objective Response Rate (ORR) for Tumor Type } j \text{ and line of therapy } l \]

\[ p_{il} \text{ true event rate of the binomial distribution} \]

\[ g_{il} \text{ fixed-effects on indication-specific baseline (front-line here) log odds of ORR} \]

\[ x_{il} \text{ fixed-effects for line of therapy in contrast to front-line} \]

\[ j_{il} \text{ exchangeable random-effects model (by indication) for effect of PD-1 vs PD-L1} \]

\[ \text{Study-specific random study effect} \]

Analysis 1: PD-1 vs. PD-L1 Inhibitors in 2L NSCLC

Analysis 2: PD-1 vs. PD-L1 Inhibitors Across Tumor Types

Analysis 3: Class of PD-1/PD-L1 Inhibitors Across Tumor Type

Analysis 4: Safety and PFS across Tumor Types

CONCLUSIONS

• Given the characteristics of the available data, we proposed a Bayesian hierarchical model for indirect comparison of immunocompound drugs in the same class, that uses a random effect to absorb the study-specific variability, therefore reduces potential bias

• The analysis using the proposed model yield light on some important scientific hypotheses. There seems to be a strong class effect between the PD-1 and PD-L1 inhibitors. Treatment with PD-1 inhibitors resulted in slightly higher ORR, longer PFS and higher G1-3 AEs than PD-L1 inhibitors. The posterior probability of the class effect is significantly large due to the enormous sample size in the meta-analysis; however, the magnitude of the difference is small, thus is not considered clinically meaningful

• For future study design and practical purposes, the quantitative output from the proposed model could be incorporated. E.g.

- With the assumption of a class effect, we can make prediction on the clinical performance of any PD-L1/PD-L1 inhibitors

- If we acknowledge the difference, we can quantitatively adjust the assumptions on effect size in sample size evaluation

Moreover, the most valid comparison should be made by direct comparisons via well-designed randomized controlled trials or indirect comparisons via network meta-analysis. The performance of the proposed model will be further evaluated when more data become available.

References:


