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

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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 disclosures provides a unique opportunity to assess 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 may 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 between molecules across indications. Whilst direct comparison of these molecules is difficult, if not impossible, our proposed method provides a quantitative approach to address the aforementioned and potentially other critical scientific questions via indirect comparison through efficient use of publically available data.

INTRODUCTION

Motivating Question

The PD-1/PD-L1 treatment axis is characterized by:

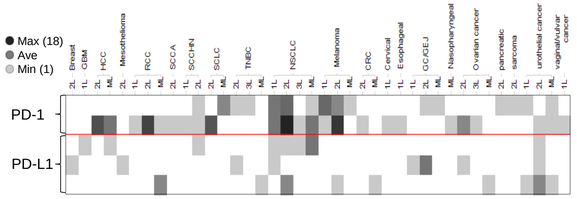
1. the same pathway with 2 counterpart binding-sites
2. a large number of similar molecules in development
3. broad range of indications being explored, and
4. Similar, yet different, efficacy and safety results between studies, most with single arm design

Question: Do PD-1 and PD-L1 inhibitors deliver different clinical outcome?

Population, Endpoints and Meta-statistics

- The model was applied to public data collected through ASCO 2017
  - 2 PD-1 and 3 PD-L1 antibodies as monotherapy
  - 21 solid tumor types
  - Line of therapies: 1L, 2L, 3L and multiple lines (ML)
  - Unratified by PD-L1 status
- Overall response rate (ORR), PFS and rate of Grade 3/4 adverse events are collected for:
  - 143 clinical trials / cohorts
  - Total 15,294 patients
  - A maximum of 18 studies / cohorts for a single indication

Figure 1. Number of Data Points by Drug by Indication



Literature Review

- Direct comparison in randomized studies is most valid[1] for between treatment comparison
- Without proper adjustment, the treatment effect between drugs estimated by indirect comparison is subject to bias. Adjusted indirect comparison[2,3,4] and network meta-analysis for indirect treatment comparisons[5,6] were proposed when two treatments were not compared directly in a randomized trial, but each compared directly to other treatment in common or through a network of a set of treatments interlinked
- However, there was lack of method for proper adjustment when most data points were generated from single arm studies for which none of the above methods is applicable

METHODS

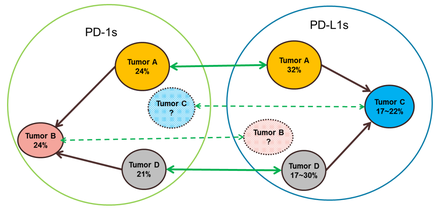
Model

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

$$r_{ij} \sim Binomial(n_{ij}, p_{ij})$$
$$logit(p_{ij}) = \gamma_i + \alpha_j + \beta_i \cdot I_{ij}(PD1) + \epsilon_{ij}$$
$$\beta_i \sim Normal(\mu, \tau^2)$$
$$\epsilon_{ij} \sim Normal(0, \sigma^2)$$

r_{ij}: observed Objective Response Rate (ORR) for Tumor Type i and Line of therapy j
p_{ij}: true event rate of the binomial distribution
γ_i: Fixed-effects on indication-specific baseline (front-line here) log odds of ORR
α_j: Fixed-effects for line of therapy in contrast to front-line
β_i: Exchangeable random-effects model (by indication) for effect of PD-1 vs. PD-L1
ϵ_{ij}: Study specific random study effect

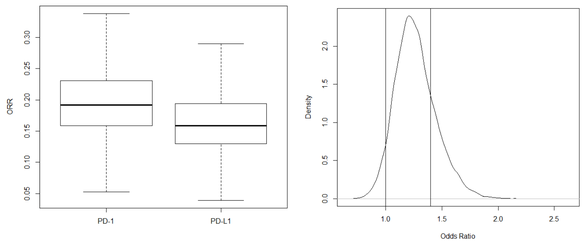
Figure 2. Graphical Representation of the Model



RESULTS

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

Figure 3. Posterior of ORR and its Odds Ratio PD-1 vs PD-L1

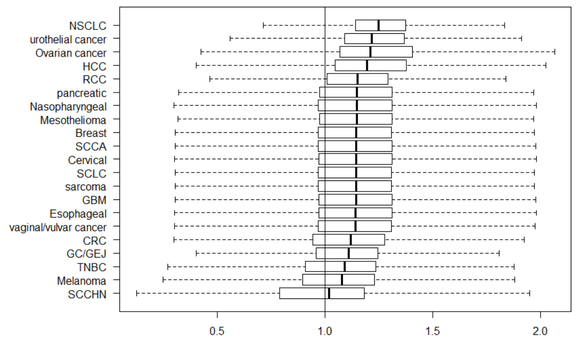


- The ORR of PD-1 inhibitors is higher than that of PD-L1 inhibitors, with statistical significance
  - ORR (95% CI) of PD-1: 19.8% (10.6%, 32.1%) vs. PD-L1: 16.5% (8.5, 27.8%)
  - Odds ratio = 1.27, 95% CI=(0.96, 1.70)
  - Pr(OR > 1)=95.0%
- However, the probability that the effect size, in terms of ORR difference, could be considered clinically meaningful is low
  - $Pr(ORR_{PD\text{-}1} - ORR_{PD\text{-}L1} \geq 5\%) = 19.0\%$ (corresponding to odds ratio=1.42)

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

- The ORR of PD-1 inhibitors are consistently higher than PD-L1 inhibitors across tumor types
- The posteriors of each tumor type are spread wide, thus there is no clinically meaningful difference between PD-1 and PD-L1 inhibitors in ORR. The overall treatment effect (posterior distribution of β_i's) has
  - Odds ratio = 1.23, 95% CI=(0.17, 9.48)
  - Pr(OR > 1)=58.6%

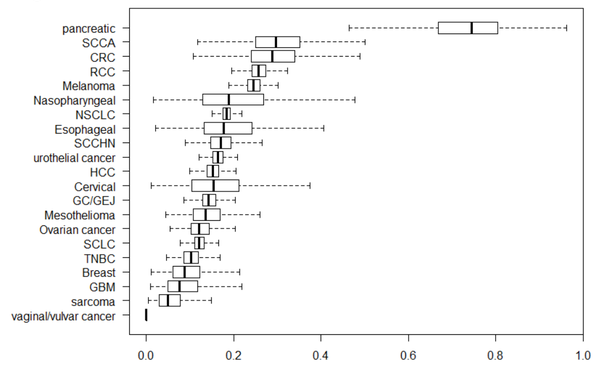
Figure 4. Posterior of Odds Ratio PD-1 vs PD-L1 Across Tumors



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

- Incorporating the class effect of PD-1/PD-L1 inhibitors, inference can be made to the ORR of each tumor type. E.g. for 2L NSCLC
  - Among all PD-(L)1 inhibitors, mean ORR = 18%
  - Less than 2.5% probability that any PD-(L)1 inhibitor has a ORR worse than 15%

Figure 5. Posterior of ORR of Class of PD-1/PD-L1 Across Tumors



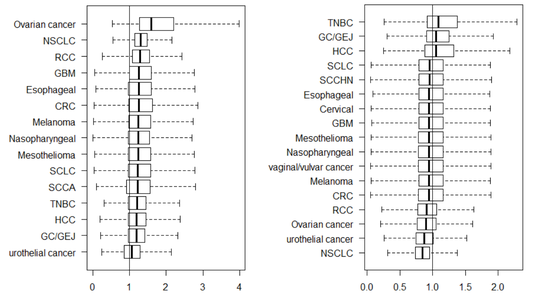
Analysis 4: Safety and PFS across Tumor Types

- The rate of Gr 3/4 AE is higher in PD-1 than PD-L1 inhibitors across tumor types in general, but neither statistically significant (Pr(OR>1)=80.0%) nor clinically meaningful (Pr(OR>1.42)=20.8%)
- The mPFS is longer in PD-1 than PD-L1 inhibitors across tumor types in general, but neither statistically significant (Pr(HR<1)=66.2%) nor clinically meaningful (Pr(HR<0.7)=13.5%). For this comparison, the following model was used

$$\log(\lambda_{ij}) \sim Normal(\mu_{ij}, \sigma_{ij}^2)$$
$$\mu_{ij} = \gamma_i + \alpha_j + \beta_i \cdot I_{ij}(PD1) + \epsilon_{ij}$$
$$\beta_i \sim Normal(\mu, \tau^2)$$
$$\epsilon_{ij} \sim Normal(0, \sigma^2)$$

λ_{ij}: hazard rate for Tumor Type i and Line j, based on an exponential model of the PFS

Figure 6. Gr 3/4 AE Rate Odds Ratio (left) and PFS HR (right)



CONCLUSIONS

- Given the characteristics of the available data, we proposed a Bayesian hierarchical model for indirect comparison of immuno-oncology drugs in the same class, that uses a random effect to absorb the study specific variability, therefore reduces potential bias
- The analyses using the proposed method shed 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 Gr3/4 AE rate than PD-L1 inhibitors. The posterior probability of the difference is statistically significant 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 planning 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-1/PD-L1 inhibitors
  - If we acknowledge the difference, we can quantitatively adjust the assumptions on effect size in sample size calculation
- Nevertheless, the most valid comparison should be made by direct comparisons via well designed randomized controlled studies or indirect comparisons via network meta-analysis. The performance of the proposed method will be further evaluated when more data become available

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