Prediction of clinical response to checkpoint blockade immunotherapy is improved with ensembling

Mostapha Benhenda

RESEARCH

Prediction of clinical response to checkpoint blockade immunotherapy is improved with ensembling

Mostapha Benhenda

Full list of author information is available at the end of the article

Abstract

Predicting clinical response to checkpoint blockade immunotherapy is a major challenge in oncology. In the case of melanoma, we show how prediction is improved with the use of averaging, a simple ensembling method in machine learning. We report +3.7 percent improvement of the best response predictor (from AUC=0.81 to AUC=0.84), on a clinical dataset of 70 patients.

Keywords: Cancer; Melanoma; Immunotherapy; Immune Checkpoint Inhibitors; RNA-seq; Precision Medicine; Ensembling

1 Introduction

Immunotherapies are promising ways to address cancer. They provide long-term benefit, with fewer side-effects. They work by leveraging the immune system against cancer cells. However, they don't work all the time. In order to elect patients and overcome cancer resistance, it's important to predict and understand clinical response.

Among immunotherapies, immune checkpoint blockade inhibitors (ICB) are an important class. And among cancers, melanoma is a common and widely studied case of solid tumor. Therefore, clinical response to ICB treatment of melanoma is the focus of this paper.

There are many predictors of ICB response (for a recent survey, see [1]) in the case of melanoma, most of them relying on bulk RNA-seq from the tumor. Two of them, IMPRES [2] and TIDE [3], have simultaneously been published in August 2018 [4], each reporting state-of-the-art performance. Since then, these two predictors have not been beaten in any more recent benchmark.

In this paper, we compare IMPRES, TIDE, and the average of the two. Ensembling methods are classical in machine learning (see [5] for a survey), and averaging is a simple case. Ensembling methods have not been applied to the prediction of clinical response to ICB yet, and that is the originality of this paper.

2 Data

The dataset comprises 70 melanoma patients in total: 42 patients treated with ICB anti-CTLA4 ipilimumab (Yervoy by Bristol-Myers Squibb) [6], and 28 patients treated with ICB anti-PD1 pembrolizumab (Keytruda by Merck Sharp & Dohme) or nivolumab (Opdivo by Bristol-Myers Squibb) [7].

For computing TIDE scores, we use the TIDE web application (`http://tide.dfci.harvard.edu/` [Accessed: April, 30 2019]). For IMPRES scores and data labels, we use IMPRES results [2, Supplementary Table 9], except that we relabeled "long-survival" as "responder". The rationale for this modification [8] is that some patients who get pseudo-progression might be classified as non-responder by RECIST [9], but they will still benefit from immunotherapy.

3 IMPRES

Immuno-predictive score (IMPRES) is a predictor of ICB response in melanoma, which encompasses 15 pairwise transcriptomics relations between 28 immune checkpoint genes. IMPRES was discovered by comparing RNA-seq data from neuroblastoma (another type of cancer) patients having spontaneous regression, with those having progressing disease.

4 TIDE

TIDE is a gene signature measuring Tumor Immune Dysfunction and Exclusion. Immune dysfunction is measured by looking at correlations between cytotoxic T lymphocyte (CTL) level, patient survival, and gene expression.

Immune exclusion is measured by looking at the expression profiles of cell types known to restrict T cell infiltration in tumors, namely cancer-associated fibroblasts, myeloid-derived suppressor cells and the M2 subtype of tumor-associated macrophages.

TIDE is a combination of both immune dysfunction and exclusion signatures.

5 Average predictor IMPRES+TIDE

We compute the z-scores of IMPRES and TIDE, respectively, which gives new scores with average zero and variance 1. This normalizes scores. Then we perform their arithmetic mean, which gives the averaged (ensembled) predictor IMPRES+TIDE. See the table in the supplementary material for details.

6 Result

	AUC ROC
IMPRES	0.76
TIDE	0.81
Avg. IMPRES+TIDE	0.84

We find that the average predictor IMPRES+TIDE brings $+3.7\%$ AUC-ROC improvement to the best predictor, TIDE (AUC-ROC is the Area Under the Receiver Operating Characteristic Curve). This happens despite that IMPRES has 6% lower AUC-ROC than TIDE.

7 Further directions

Using a larger dataset is the first direction of further study. The IMPRES paper [2] reported 297 samples, but the potential is much larger, given the recent growth of clinical trials in immuno-therapy [10], and of ICB use in the clinic.

Using a larger ensemble of predictors is another direction. There are at least 50 ICB outcome predictors in total [11, p.991], which use tumor bulk RNA-seq as input. In particular, we did not include the recent [11] predictor in our benchmark, despite that it reports state-of-the-art performance, because of the lack of response by [11] authors to issues we raised on Github [12].

More complex ensemble methods can be used: bagging, boosting, and so on [5].

Finally, benchmarking and ensembling predictors of response to combination therapies should be done.

8 Conclusion

We showed how averaging can improve the prediction of the clinical response to Immune Checkpoint Blockade. This opens new research directions in this area.

Availability of data and material

Data is available at: `https://github.com/mostafachatillon/immunotherapy-response-prediction`

Competing interests

The author declares that he has no competing interests.

Funding

This study was self-funded by the author.

References

1. Keenan, T.E., Burke, K.P., Van Allen, E.M.: Genomic correlates of response to immune checkpoint blockade. Nature medicine, 1 (2019)
2. Auslander, N., Zhang, G., Lee, J.S., Frederick, D.T., Miao, B., Moll, T., Tian, T., Wei, Z., Madan, S., Sullivan, R.J., *et al.*: Robust prediction of response to immune checkpoint blockade therapy in metastatic melanoma. Nature medicine **24**(10), 1545 (2018)
3. Jiang, P., Gu, S., Pan, D., Fu, J., Sahu, A., Hu, X., Li, Z., Traugh, N., Bu, X., Li, B., et al.: Signatures of t cell dysfunction and exclusion predict cancer immunotherapy response. Nature medicine, 1 (2018)
4. Killock, D.: Signatures impres and might turn the tide in predicting responses. Nature Reviews Clinical Oncology **15**(11), 654 (2018)
5. Dietterich, T.G.: Ensemble methods in machine learning. In: International Workshop on Multiple Classifier Systems, pp. 1–15 (2000). Springer
6. Van Allen, E.M., Miao, D., Schilling, B., Shukla, S.A., Blank, C., Zimmer, L., Sucker, A., Hillen, U., Foppen, M.H.G., Goldinger, S.M., *et al.*: Genomic correlates of response to ctla-4 blockade in metastatic melanoma. Science **350**(6257), 207–211 (2015)

7. Hugo, W., Zaretsky, J.M., Sun, L., Song, C., Moreno, B.H., Hu-Lieskovan, S., Berent-Maoz, B., Pang, J., Chmielowski, B., Cherry, G., *et al.*: Genomic and transcriptomic features of response to anti-pd-1 therapy in metastatic melanoma. Cell **165**(1), 35–44 (2016)
8. Jiang, P. Email communication (2019-04-30)
9. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., *et al.*: New response evaluation criteria in solid tumours: revised recist guideline (version 1.1). European journal of cancer **45**(2), 228–247 (2009)
10. Kaiser, J.: Too much of a good thing? Science **359**(6382), 1346–1347 (2018)
11. Jerby-Arnon, L., Shah, P., Cuoco, M.S., Rodman, C., Su, M.-J., Melms, J.C., Leeson, R., Kanodia, A., Mei, S., Lin, J.-R., *et al.*: A cancer cell program promotes t cell exclusion and resistance to checkpoint blockade. Cell **175**(4), 984–997 (2018)
12. Benhenda, M.: Github Issues - livnatje/ImmuneResistance. `https://github.com/livnatje/ImmuneResistance/issues` [Accessed: May, 5 2019] (2019)