


Machine learning predicted fast progression after initiation of immune checkpoint inhibitors in advanced non-small cell lung cancer

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BACKGROUND

Immune checkpoint inhibitors (ICIs), with or without chemotherapy, are now standard first-line therapy for advanced non-small cell lung cancer (NSCLC) without a driver mutation.¹ A phenomenon of rapid tumour progression following ICIs has been reported in several clinical studies with differing criteria and no agreed definition.² Gandara *et al* proposed clinically applicable criteria for fast progression (FP) to define this phenomenon.³ The incidence of FP was approximately 10% in the OAK randomised trial and a French retrospective cohort study.^{3,4}

A MODEL TO PREDICT FP AFTER ICIS

In this issue, Zhou and colleagues evaluated 21 pretreatment, blood-based variables in seven different machine learning models as predictors of FP among participants treated with atezolizumab in four trials of atezolizumab for advanced NSCLC.⁵ Their proposed final model included four, readily available variables: C reactive protein, neutrophil count, lactate dehydrogenase and alanine transaminase.

STRENGTHS AND LIMITATIONS

The key strengths of this study were the use of multiple, state-of-the-art, machine learning approaches to develop a simple, parsimonious model based on a few routinely collected variables from the OAK trial⁶ and validation of the model using data from other trials.^{7–9} Five issues that affect the clinical applicability of this model are discussed below.

First, the study population used to train the model is no longer frequent in routine clinical practice. The model was trained using participants' progressing after

treatment with cytotoxic chemotherapy.⁶ The model was validated using data from the BIRCH⁷ and FIR⁹ trials, in which approximately 20% of participants were treatment naïve. However, separate results for this subgroup were not reported, so the applicability of the results to treatment-naïve patients remains unclear.

Second, FP is not a phenomenon that occurs only after treatment with atezolizumab. Nine per cent of participants randomly assigned docetaxel in the OAK trial subsequently met criteria for FP.³ It would be helpful to see how the model proposed by Zhou *et al* performs in patients treated with chemotherapy alone or with other ICIs.⁵

Third, as expected, the model's observed performance in the development cohort was better than it was in the validation cohorts. For example, the AUC (area under the receiver operating characteristic curve) statistics of the proposed model in the development cohort versus the validation cohorts were 0.908 versus 0.666 and 0.776. Further evaluation of the proposed model in other data sets is needed to determine its true utility.

Fourth, selecting variables for inclusion in the proposed model was data driven rather than based on specific biological or mechanistic principles. For example, in the OAK and POPLAR trials, elevated pretreatment lactate dehydrogenase was associated with worse overall survival regardless of whether treatment was with atezolizumab or docetaxel.¹⁰ Elucidation of the pathophysiology of this proposed phenomenon would help identify candidate variables that are more specific to the proposed mechanisms of rapid tumour progression.

Fifth, for the model to be clinically useful, we need effective, alternative management strategies for those predicted to have FP. It remains unclear whether those who developed FP after starting single-agent ICI in these trials would have done better if they had been treated with chemotherapy or chemotherapy plus ICI.

IMPLICATIONS

This work by Zhou and colleagues highlights three important considerations for investigators hoping to develop a machine learning model for clinical implementation. First, the problem that the model addresses must be clinically relevant. Second, the model needs to accurately identify those with the problem within the population of interest. Finally, viable interventions are needed to mitigate the problem. Below, we highlight an excellent example illustrating these considerations in developing a machine learning model for routine clinical practice.

Investigators from The University of California, San Francisco and Duke University noted that 10%–20% of outpatients undergoing radiation therapy or chemoradiation required acute care (an admission or unscheduled visit). They developed a machine learning model using gradient-boosted trees to predict a patient's likelihood of requiring acute care based on pretreatment variables captured in the electronic health record.¹¹ They then demonstrated in a randomised trial that those identified by the model to be at 10% or greater risk of requiring acute care, required significantly lower rates of acute care when randomly assigned to evaluations scheduled two times a week versus one time a week (12% vs 22%, respectively).¹²

CONCLUDING REMARKS

Hence, for the proposed model to address the problem of FP, we first need to validate the model in newly diagnosed advanced NSCLC treated with ICIs, with or without chemotherapy. Second, we need to identify the potential treatments that can delay FP. Finally, we can perform a biomarker enrichment design trial where those predicted to be at high risk of developing FP by the model are randomised to receive either the standard treatment plus potential treatment to delay FP or the standard treatment alone. The proposed model and treatment strategy will be deemed clinically useful if the incidence of FP in the intervention group is lower than in the control group.

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REFERENCES

- Singh N, Temin S, Baker S Jr, *et al.* Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline. *J Clin Oncol* 2022;40:3323–43.
- Borcoman E, Nandikolla A, Long G, *et al.* Patterns of Response and Progression to Immunotherapy. *Am Soc Clin Oncol Educ Book* 2018;38:169–78.
- Gandara D, Reck M, Moro-Sibilot D, *et al.* Fast progression in non-small cell lung cancer: results from the randomized phase III OAK study evaluating second-line atezolizumab versus docetaxel. *J Immunother Cancer* 2021;9:e001882.
- Ferrara R, Mezquita L, Texier M, *et al.* Comparison of Fast-Progression, Hyperprogressive Disease, and Early Deaths in Advanced Non-Small-Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or Chemotherapy. *JCO Precis Oncol* 2020;4:829–40.
- Zhou J-G, Yang J, Wang H, *et al.* Machine learning based on blood test biomarkers predicts fast progression in advanced NSCLC patients treated with Immunotherapy. *Bmjnc* 2024;3:e000128.
- Rittmeyer A, Barlesi F, Waterkamp D, *et al.* Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–65.
- Peters S, Gettinger S, Johnson ML, *et al.* Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). *J Clin Oncol* 2017;35:2781–9.
- Fehrenbacher L, Spira A, Ballinger M, *et al.* Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46.
- Spigel DR, Chaft JE, Gettinger S, *et al.* FIR: Efficacy, Safety, and Biomarker Analysis of a Phase II Open-Label Study of Atezolizumab in PD-L1-Selected Patients With NSCLC. *J Thorac Oncol* 2018;13:1733–42.
- Tjokrowidjaja A, Lord SJ, John T, *et al.* Pre- and on-treatment lactate dehydrogenase as a prognostic and predictive biomarker in advanced non-small cell lung cancer. *Cancer* 2022;128:1574–83.
- Hong JC, Niedzwiecki D, Palta M, *et al.* Predicting Emergency Visits and Hospital Admissions During Radiation and Chemoradiation: an Internally Validated Pretreatment Machine Learning Algorithm. *JCO Clin Cancer Inform* 2018;2:1–11.
- Hong JC, Eclow NCW, Dalal NH, *et al.* System for High-Intensity Evaluation During Radiation Therapy (SHIELD-RT): a Prospective Randomized Study of Machine Learning-Directed Clinical Evaluations During Radiation and Chemoradiation. *J Clin Oncol* 2020;38:3652–61.