References

1. Dahl O, Dale JE, Brydøy M. Rationale for combination of radiation therapy and immune checkpoint blockers to improve cancer treatment. *Acta Oncol.* 2019;58:9-20.
2. Jang H, Lee H-S, Ramos D, Park IK, Kang CH, Burt VM, et al. Transcriptome-based molecular subtyping of non-small cell lung cancer may predict response to immune checkpoint inhibitors. *J Thorac Cardiovasc Surg.* 2020;159:1598-610.e3.

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Commentary: Breaking down non-small cell lung cancer tumor microenvironment heterogeneity and predicting response to immune checkpoint inhibitors

Joshua Boys, MD, and Mark Onaitis, MD

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CENTRAL MESSAGE

The study in the current issue sheds new light on how the microenvironment of tumors may predict response to immune modulators.

Immune checkpoint inhibitors have brought new hope for improving survival in patients with non-small cell lung cancer (NSCLC). However, determinants of response to immune checkpoint therapy are unclear. Studies have shown a correlation of PDL-1 expression and response to checkpoint inhibitors,^{1,2} but many of us have seen patients respond to checkpoint inhibitors when their expression levels were not significant and vice versa, indicating that responses to checkpoint inhibitors are not always as simple as expression levels. In the current study, Jang and colleagues³ address the complexity of lung cancer microenvironments by using transcriptome-based molecular subtyping of NSCLC to predict response to immune checkpoint inhibitors. They used NSCLC mRNA transcriptomes in conjunction with tumor and immune cell function microenvironments to assess treatment response to anti-PD-1 therapy in 87 adenocarcinomas and 101 squamous cell carcinomas. Using mRNA transcriptomes for both adenocarcinoma and squamous cell carcinoma as the base subtypes, they additionally analyzed tumor and immune cell functional activity to classify the tumor

microenvironment as “good” or “bad” for response to therapy. They then used previously published mRNA data from a Barcelona cohort of 35 patients with NSCLC treated with anti-PD-1 therapy to perform forward and backward modeling for response to treatment.⁴ In both the forward and backward models they found a high concordance with treatment response in the “good” subtype for both adenocarcinoma and squamous cell carcinoma.

Although it is limited by small sample size and does not consider the gold standard of PD1 or PD-L1 protein expression by immunohistochemistry nor tumor mutation burden, this is an interesting study in that it identifies subgroups of patients that seem to benefit from immune checkpoint therapy. The authors should be congratulated for trying to measure the complexity of tumor microenvironment and how it potentially affects response to anti-PD-1 therapy. More and more often, tumors are sequenced for evaluation of therapeutic targets. This sort of analysis may allow combination of genetic targets and immune checkpoint inhibitors.

Over the next years, the role of immune modulators in various stages of lung cancer will be studied. It will be important for surgeons to take an active part in these studies. The recent PACIFIC trial (Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable

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non-small cell lung cancer) using durvalumab in patients with unresectable stage III disease demonstrates increased disease-free survival to 17.2 months compared with 5.6 months against placebo and improved overall survival.⁵ The survival in the treated group is similar to that of stage III patients undergoing trimodality therapy including surgical resection. Such results should lead all of us to actively take part in induction immunotherapy trials for locally advanced lung cancer such as the new Alliance CHIO3 Trial: Chemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B Non-Small Cell Lung Cancer. Understanding the role of immunotherapy in addition to surgery for these patients is paramount.

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Commentary: TiME may actually tell good from bad

Sanjeet Patel, MD, PhD,^a and Anthony W. Kim, MD^b

In its scope and impact, the translational work pursued jointly between the investigators at the Baylor College of Medicine and Seoul National University led by Drs Burt and Kim, respectively, and presented in this issue of the *Journal* by Jang and colleagues,¹ is quite impressive. With the onslaught of information pertaining to the efficacy of checkpoint inhibition well upon us, it is clear that the knowledge regarding the interaction between the programmed death (PD-1) receptor and the programmed death ligand (PD-L1) is evolving, rapidly and voluminously. The lung cancer community has come to understand that at a rudimentary level, the T-cell PD-1 receptor and the tumor cell PD-L1 interaction facilitates the evasion of the native immune system by these tumor cells. It is therefore also understood that inhibition of the PD-1/PD-L1 interaction

Sanjeet Patel, MD, PhD (left), and Anthony W. Kim, MD (right)

CENTRAL MESSAGE

Identifying “Good TiME” biomarkers enhances the understanding of additional mechanisms associated with successful checkpoint inhibition that may enhance anti-PD-1/PD-L1 therapy in the future.

is integral to the immunogenic destruc-

tion of malignant cells. As ideal as this distilled interpretation is, tumors, like humans, have evolved to the extent that a simple explanation such as the aforementioned is representative of only a single facet of a more complex relationship. As Jang and colleagues¹ rationalize for the basis of their study, differential responses to anti-PD1 and anti-PD-L1 therapy occur and are based on a variety of factors.

In their collaborative effort, Jang and colleagues¹ describe in fantastic detail how messenger RNA

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