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.

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Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Nov 19, 2019; accepted for publication Nov 20, 2019; available ahead of print Jan 22, 2020.

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J Thorac Cardiovasc Surg 2020;159:1613-4

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.11.095>

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is integral to the immunogenic destruction 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

sequencing can identify the existence or absence of tumor microenvironments permissive for checkpoint therapy. They provide a transcriptional signature that serves to delineate an “immunologically hot” from an “immunologically cold” tumor immune microenvironment (TiME). Through the rigor of their transcriptome-based molecular subtyping, followed by additional validation, Jang and colleagues¹ have identified a set of markers that are associated with a favorable response to anti-PD-1/P-L1 therapy for lung adenocarcinomas and squamous carcinomas. This well-performed study highlights an inherent advantage of messenger RNA sequencing, in which a particular gene’s influence is amplified in the cell’s transcriptome and thus is less susceptible to signal dropout than is sequencing single-copy genomes for variants. Although the interpretation of hundreds of genes is less tangible than a handful of driver mutations at the genome level, messenger RNA sequencing can provide signatures that, as a panel, are clinically useful and mimic the strength behind the use of polygenic risk scores from genome-wide studies.

The greater significance of the work by Jang and colleagues¹ is that their granular approach for uncovering

potential mechanisms of PD-1/PD-L1 resistance may facilitate an enhanced understanding of successful checkpoint inhibition. The “Good TiME” and “Bad TiME” gene signatures highlight active contributions from multiple cell types, and thus this is an early step in the process of better characterizing novel therapeutic potentials within the tumor microenvironment. The findings of active B-cell-derived gene activity outside T-cell-derived PD-1/PD-L1 pathways provides a translational foundation for a future of multimodal immunologic therapy impervious to single-agent resistance. The work of these joint investigators opens up the possibility that intervening at multiple derivative levels of checkpoint inhibition may be associated with enhancing the efficacy of anti-PD-1/PD-L1 therapy, which would truly signal good times. In the end, the accumulation of more time to pursue more data on transcriptome-driven subtyping may actually inform all of us of better TiMEs to come.

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Commentary: The checkpoint before checkpoint inhibitors

William A. Blessing, PhD, and
Yolonda L. Colson, MD, PhD

Until recently, few therapeutic options existed for patients with unresectable non-small cell lung cancer (NSCLC)—particularly if targetable mutations within the tumor were not present, as is common in squamous cell lung cancer. Results from several recent clinical trials

Yolonda L. Colson, MD, PhD

CENTRAL MESSAGE

Transcriptomic profiling of NSCLC may aid in screening and identifying patients with immunologically active tumor microenvironments that could benefit from immunologic checkpoint inhibition.

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Nov 25, 2019; accepted for publication Nov 25, 2019; available ahead of print Feb 4, 2020.

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J Thorac Cardiovasc Surg 2020;159:1614-5

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.11.096>