Editorial Commentary

Dynamic change of CD8$^+$ T cell: immunotherapy fate tell?

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In recent years, immune checkpoint blockade (ICB) has emerged as a new way to treat patients with non-small cell lung cancer (NSCLC). Two programmed cell death-1 (PD-1) inhibitors and one programmed death-ligand 1 (PD-L1) inhibitor are now approved for metastatic NSCLC when a treatable oncogenic driver mutation can be excluded and the tumor has an immunohistochemical tumor proportional score (TPS) of PD-L1 ≥50% (1). In addition, combinations of ICB in combination with chemotherapy and/or CTLA-4 inhibitors are approved for metastatic NSCLC regardless of PD-L1 expression (2). Because there have been no head-to-head clinical trials comparing ICB monotherapy with combination strategies, clinicians can use clinical and laboratory findings to decide whether to start monotherapy or combination therapy or to switch to chemo-immunotherapy after starting ICB alone. Early prognostic and predictive factors are of paramount importance for this important therapeutic decision. In addition to tumor mutational burden and performance status, the need to take oral glucocorticoids or an elevated C-reactive protein (CRP) level at baseline may also be criteria for the therapeutic decision (3). However, all these factors are not evaluated prospectively and independently.

Nowadays, scientific research focuses on the anti-tumor T-cell response, which is believed to be a necessary prerequisite for ICB-mediated restoration of anti-tumor T-cell activity (4,5). Indeed, a dynamic change in peripheral blood CD8$^+$ T cells could be an early surrogate for ICB activity and detectable much earlier than radiological response according to RECIST criteria (6). In this approach, blood is drawn before initiation and during ICB treatment. The difference from baseline is expressed as Δ and describes an increase or decrease in CD8$^+$ T-cell activity measured by flow cytometry or mRNA expression.

A recent article published in this journal entitled "*Immune profile analysis of peripheral blood and tumors of lung cancer patients treated with immune checkpoint inhibitors*" illustrates the research activities in this challenging field (7).

The aim of the research led by Ichiki and colleagues was to analyze the relationship between immune-related molecular expression in peripheral blood mononuclear cells (PBMCs) and lung cancer tissues and the effects of immune-checkpoint inhibitor (ICI) monotherapy. The study prospectively examined changes in the expression of immune-related molecules in PBMCs at baseline and after 4–8 weeks of ICB treatment, as well as major histocompatibility complex (MHC) class I, PD-L1, CD8, and CD103 expression in lung cancer tissue before ICI administration. The goal was to determine whether changes in immune-related molecular expression could be used as biomarkers to predict the efficacy of ICI therapy and inform treatment decisions.

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Table 1 Dynamic change of $CD8^+$ T cells in peripheral blood during therapy with ICB

Study	Year	N	Dynamic change measured (after start of ICB), week	Improved outcome Δ $CD8^+$	Measurements	Kind of ICB
Kim (11)	2019	79	1	Increase	$CD8^+PD1^+Ki67^+$	Pembrolizumab/nivolumab
Maniar (12)	2023	23	3–6	Increase	$CD8^+CCR7^-TCF^+$	PD-1 inhibitor
Brueckl (8)	2021	45	3	Increase	$CD8^+$ mRNA	Pembrolizumab
Kamphorst (9)	2017	29	3–6	Increase	$CD8^+PD1^+Ki67^+$	Pembrolizumab, nivolumab, atezolizumab
Ichiki (7)	2022	21	4–8	Increase	$CD8^+CD39^+CD103^+$	Pembrolizumab, nivolumab, atezolizumab, durvalumab
Fehlings (4)	2019	14	NR	Increase	$CD8^+$ 2B4 CD57, CD161, TIGIT, CD23	Atezolizumab
Ottonello (13)	2020	54	2–4	Decrease	$CD8^+PD1^+Eomes^+$	Nivolumab
				Decrease	$CD8^+CD39^+$	
Kim (10)	2021	94	3	Decrease	$CD8^+PD1^+$	PD-1 inhibitor
Sheng (14)	2021	12	6	Decrease	$CD8^+PD1^+$	Atezolizumab
Yan (15)	2022	276	12	Decrease	$CD8^+$	Atezolizumab, nivolumab, camrelizumab, sintilimab

ICB, immune checkpoint blockade; Δ, dynamic change of $CD8^+$ from baseline; NR, not reported; PD-1, programmed cell death-1.

In the study, researchers conducted univariate and multivariate analyses to identify factors associated with progression-free survival (PFS). One of the significant factors identified in these analyses was the change in $CD103^+$ $CD39^+$ $CD8^+$ cells after dosing. The researchers found that this change correlated closely with clinical response to ICI therapy, with patients who had greater changes more likely to have a better outcome. In addition to the univariate analyses, two independent factors were identified in these analyses: the change in $CD103^+$ $CD39^+$ $CD8^+$ cells after administration and the Brinkman index, a composite measure assessing immune system activity, taking into account T-cell counts and natural killer cell activity.

This work adds to the rapidly growing information that specific $CD8^+$ T cells are expressed shortly after induction of ICB and can be measured in peripheral blood (4,7-15). While $CD39^+$ $CD103^+$ cells have already been detected on tumor-reactive T cells in tumor infiltrates and the presence of these T cells has been associated with response to ICB, other forms of $CD8^+$ T cells in peripheral blood may show resistance to ICB therapy (10,13,14,16,17).

In particular, $CD8^+$ $PD1^+$ T cells are considered a hallmark of exhausted T cells (5). While Ichiki *et al.* did not find such a correlation with PFS in their work, there are other studies showing a dynamic change with a decrease in $CD8^+$ $PD1^+$ T cells after one or two ICB cycles that is predictive of a better outcome (7,10,13-15) (for an overview of recent data on Δ $CD8^+$ T cell subtypes, see *Table 1*). Different ICB (PD-1 versus PD-L1 based immune-checkpoint inhibitors), a wide range of time points chosen for peripheral blood sampling during ICB (7 d to 12 weeks), and small case numbers might have contributed to conflicting results between different studies. Although $CD8^+$ T cells are an essential prerequisite for the effect of ICB on tumor cells and dynamic change can be readily measured on peripheral blood cells, much more needs to be done to gain deeper insight into these complex mechanisms and establish robust predictive markers for early response.

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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