

Experts Discuss Personalized ctDNA Assays to Predict Immunotherapy Response



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Despite the broad success of immunotherapy across different solid tumor and hematologic malignancies, reliable biomarkers of response to immune checkpoint blockade have eluded investigators, creating an unmet medical need in the oncology space.

The recently reported prospective phase 2 INSPIRE study (NCT02644369) aimed to address this need by examining circulating tumor DNA (ctDNA) in 5 distinct cohorts of patients with advanced solid tumors using bespoke assays.

In a recent *Between the Lines* discussion, George Ansstas, MD, reviewed key findings from the trial with Firas B. Badin, MD, with a focus on the benefit of this study and the personalization of therapy selection.

Regarding the results of this strategy for predicting therapy response, Ansstas, who is an associate professor of

medicine at Washington University School of Medicine in St Louis, Missouri, said, “It’s the best biomarker we currently have to predict [which patients have a] durable response and longevity.”

“Personalized’ is important to highlight here. There are many different assays that simply look at [ctDNA], or fragments of cancer cells in the blood,” Badin, who is a medical oncologist with the Baptist Health Medical Group in Lexington, Kentucky, explained. “Here we are using a personalized assay by using tissue as well as patient’s blood. That really guides our approach to reliably evaluate response [and may] correlate with survival.”

INSPIRE Design and Results

In total, 106 patients with metastatic or advanced solid tumors were enrolled in the study, with 94 (89%) having sufficient tumor tissue for exome sequencing

TABLE 1. Outcomes by ctDNA Levels at Baseline in the INSPIRE Trial

Outcome	Correlation with baseline ctDNA (95% CI)	Significance
OS	aHR, 0.49 (0.29-0.83)	Significant for lower-than-median ctDNA at baseline
PFS	aHR, 0.54 (0.34-0.85)	Significant for lower-than-median ctDNA at baseline
CBR	OR, 3.24 (1.19-8.8)	Significant for lower-than-median ctDNA at baseline
ORR	OR, 2.57 (0.82-8.08)	Nonsignificant for lower-than-median ctDNA at baseline

aHR, adjusted hazard ratio; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

TABLE 2. Outcomes by ctDNA Levels at Cycle 3 in the INSPIRE Trial

Outcome	Correlation with ctDNA levels at cycle 3 (95% CI)	Significance
OS	aHR, 0.36 (0.18-0.71)	Significant for decrease from baseline
PFS	aHR, 0.33 (0.19-0.58)	Significant for decrease from baseline

aHR, adjusted hazard ratio; ctDNA, circulating tumor DNA; OR, odds ratio; OS, overall survival; PFS, progression-free survival.

analysis. The 5 parallel cohorts included patients with head and neck squamous cell carcinoma (HNSCC; n = 16), triple-negative breast cancer (TNBC; n = 18), high-grade serous ovarian cancer (HGSOC; n = 18), melanoma (n = 12), and mixed solid tumors (n = 30).

Patients were treated with the anti-PD-1 agent pembrolizumab (Keytruda), and whole-exome sequencing was performed on tumor tissue biopsies obtained within 4 weeks of treatment initiation (n = 71) or on archival tissue (n = 23). Each patient had up to 16 clonal somatic mutations selected for personalized ctDNA assay design. In total, testing was performed across more than 300 serial plasma samples obtained from baseline assessment up to every 3 cycles of treatment.

“What the study did is capture circulating tumor DNA levels at baseline as well as every 3 weeks [for] up to 6 months, and then they looked at outcomes, [such as] response rate, progression-free survival [PFS], and overall survival [OS],” Badin said.

The investigators identified a clear correlation between ctDNA levels at different time points throughout the study and PFS and OS outcomes. For example, baseline ctDNA levels above the median were significantly associated with a reduction in OS and PFS. Similarly, increasing ctDNA levels that increased from baseline were associated with poor response to pembrolizumab (see **Tables 1 and 2**).

Notably, total ctDNA clearance, which is defined as undetectable ctDNA for at least 1 on-treatment time point, was significantly associated with improved outcomes. In the 12 patients who

experienced ctDNA clearance, prolonged objective responses and a 100% OS rate at a median of 25.4 months (range, 10.8-29.5) were noted in the trial.

“Circulating tumor DNA might really trump our conventional methods, whether it’s imaging or serology,” Badin explained. “I think we’ve seen clearly that circulating tumor DNA may decrease regardless of what you’re seeing on imaging, whether it’s progression or any kind of response to stable disease, and you’re going to end up having a better outcome.”

Using ctDNA to Determine Pseudoprogression

Both Badin and Ansstas agreed that personalized ctDNA analysis throughout treatment with immunotherapy offered several advantages, with pseudoprogression emerging as one of the key discussion points.

“If patients did not decrease their [ctDNA] very early—by 6 weeks—98% of the time, they are not going to respond to pembrolizumab,” Badin said. “I love the clear-cut, rapid, and persistent decline of circulating tumor DNA versus the step-wise steep responses [seen on] imaging. Also, with the pseudoprogression phenomenon, [sometimes] you don’t know if it’s true progression. But if you have the aid of circulating tumor DNA showing decline, that is reassuring [based on] how rapid and clean it is versus fluctuation when it comes to serology or radiology.”

Ansstas agreed with this and added that pseudoprogression presents a key challenge in the clinic. “Pseudoprogression is very demanding intellectually, especially those who deal with immunotherapy.

Many times, you see that progression on the scan and don’t know the significance... If the [ctDNA] is going downwards or we are seeing a clearance, that would [help us decide to] continue on the treatment and not change the course.”

Questions Answered

Regarding utility of these data in real-world practice, Ansstas reflected on the key takeaways of these data.

“Patients with cleared circulating tumor DNA [had] no relapses in a follow-up of almost 3 years,” Ansstas noted. “The data makes you feel like this biomarker can have a lot of value in this practice and can give you a lot of assurance in our decision making.”

Badin added that these early results are strong and are likely to inform the future of oncology care. “Some say this is not yet prime time for [ctDNA]. But to me, this is really the future of oncology. We’re taking our oncology clinic to a whole new level beyond conventional methods, beyond imaging, beyond radiology, and beyond serology. Now we have a way of evaluating at 6 weeks whether or not the patients are going to draw benefit from the current treatment and also predict their survival [outcomes]. We can use this new method to help clarify confusing clinical findings, [such as pseudoprogression].”

Moving forward, Ansstas said this strategy will be incorporated into his practice more as time goes on. “I am starting to use this more and more. I’ve been an adopter of this in the past 6 months or so, but I use it more frequently now to try to help myself in the clinic and answer these questions that were raised,” Ansstas concluded. ■

REFERENCE

Lee JH, Long GV, Menzies AM, et al. Association between circulating tumor DNA and pseudoprogression in patients with metastatic melanoma treated with anti-programmed cell death 1 antibodies. *JAMA Oncol*. 2018;4(5):717-721. doi:10.1001/jamaoncol.2017.5332

EDITOR’S NOTE: Interview modified for readability.