PRECISION ONCOLOGY NEWS

Study Shows Value of Routine MRD Analysis Using Foresight's PhasED-Seq in Lymphoma Patients

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This article has been updated to reflect the correct percentages of DLBCL patients who are cured and who relapse.

NEW ORLEANS – An analysis presented at the American Society of Hematology's annual meeting supports the routine analysis of minimal residual disease in patients with diffuse large B-cell lymphomas using Foresight Diagnostics' PhasED-Seq circulating tumor DNA test as a surrogate endpoint in future studies.

Mark Roschewski, clinical director of the National Cancer Institute's Lymphoid Malignancies Branch, presented a pooled analysis from five clinical trials and reported that patients' MRD levels during and at the end of therapy as determined by PhasED-Seq were associated with progression-free survival and had high prognostic value compared to conventional response criteria using PET and CT scans. The news comes as Foresight is preparing to launch a lab-developed test based on the PhasED-Seq platform in 2023.

Roschewski's team pooled data generated by PhasED-seq MRD from prospective clinical trials evaluating chemotherapy combined with AstraZeneca's Calquence (acalabrutinib), Bristol Myers Squibb's Revlimid (lenalidomide), Roche's Gazyva (obinutuzumab) and Polivy (polatuzumab), and MorphoSys/Incyte's Monjuvi (tafasitamab). The study also drew on a large repository of tumor tissue collected by the Leukemia and Lymphoma Society. Investigators analyzed tumor or plasma and peripheral blood mononuclear cells before, during, and at the end of therapy.

Median ctDNA levels decreased in both progressors and non-progressors after one cycle of therapy, Roschewski said. "But after two or three cycles, [ctDNA levels] were commonly undetectable in non-progressing patients, but remained detectable in most patients who ultimately progressed," he said. "This pattern continued, but was even more pronounced as 16 of 17 patients that ultimately progressed still had measurable residual disease by PhasED-Seq, while most patients who are currently progression-free had undetectable ctDNA."

The clinical sensitivity of the PhasED-Seq test was 94 percent for detecting future progression events with lead times as long as 30 months. On the other hand, 69 out of 70 patients who were MRD-negative at the end of therapy remained progression-free after a median follow-up of 17 months.

"The prognostic significance of achieving undetectable ctDNA appeared to increase throughout therapy," said Roschewski. "Achieving undetectable ctDNA after any of the first three cycles of therapy was indeed prognostic for predicting progression or death … but it was the persistence of detectable DNA at the end of therapy that was the most prognostic and that identified patients with a markedly worse prognosis compared to those without detectable ctDNA."

PhasED-Seq, developed by Stanford University researchers Max Diehn and Ash Alizadeh, harnesses the co-location of two or more mutations in ctDNA to reduce sequencing errors and increase sensitivity of MRD measurements. Foresight has been working to integrate PhasED-Seq MRD testing in DLBCL as part of the standard of care for identifying patients who have not fully responded to therapy.

The data presented at this meeting, the investigators said, demonstrated the analytic sensitivity of PhasED-Seq to detect ctDNA at very low levels. Among patients who experienced eventual disease progression or died, 35 percent had ctDNA at the end of therapy at levels near or below 1 in 10,000 by PhasED-Seq. "These cases at least suggest that assays that are less sensitive would have considered them to be undetectable," said Roschewski.

He concluded that end-of-therapy MRD status measured via PhasED-Seq could enhance current response criteria and holds promise as a surrogate clinical trial endpoint. To that end, he said, "clinical trials for large-cell lymphoma, in my opinion, should prospectively collect plasma at baseline during therapy and at the end of therapy for analysis of MRD."

Roschewski added that because the trials included in the pooled analysis are ongoing, some patients who have not yet progressed may still do so. "We have to follow these patients for a long time to truly call them a non-progressor," he explained. "At least in patients at our institution, we do have serial samples, and one of the plans is to follow them over time and see if you can get some patterns."

"In terms of our commercialization strategy, we've been focused on generating the evidence required to support adoption of this test clinically," said Foresight Cofounder and CEO Jake Chabon. "The data that [Roschewski] showed clearly demonstrated that using a single end-of-therapy time point, a single blood draw following the completion of curative intent chemotherapy in those patients, our test could very robustly identify which patients are cured and which patients will later experience a disease relapse. That's a major unmet clinical need right now."

Chabon noted that while the standard of care for assessing response following therapy in DLBCL is PET and CT imaging, many patients that will later relapse have no disease visible in scans. In contrast, Roschewski presented data at the meeting showing that PhasED-Seq MRD could identify which patients in complete remission according to imaging tests still have disease and which patients are likely cured with a sensitivity above 95 percent.

"That would give patients real peace of mind following the completion of therapy to know there is a 95 percent chance or greater that they are cured," said Chabon. "Whereas right now, in the clinical setting, it's more like a 60 to 70 percent chance they're cured and a 30 to 40 percent chance their disease may come back."

Although, in theory, earlier detection could have value for guiding cancer treatment, Alizadeh, who serves as Foresight's chief medical adviser, said, "there is no direct evidence to show that treating MRD in the absence of radiographic evidence of disease improves outcomes." That means that patients who test MRD-positive without such radiographic evidence may not receive treatment, but at least their doctors can make a case for them to be closely monitored for signs of recurrence through imaging. "But … when patients have bona fide evidence of disease a few months afterwards, instead of neglecting the patients, you've caught a patient at the lowest disease burden," Alizadeh said.

On the industry side, Foresight wants to incorporate its PhasED-Seq platform into drug development. "It could enable faster drug development if this test were to be adopted or accepted by the FDA for use as an early endpoint [in therapy trials]," Chabon said.

Foresight has a number of studies underway, continuing to evaluate PhasED-Seq MRD in DLBCL and also in solid tumors. Meanwhile, it has established a centralized laboratory in Colorado for the PhasED-

Seq test. Although initially Foresight will market PhasED-Seq as a lab-developed test, Chabon said that because the platform has the same workflow for every patient, it is amenable to other formats via partnerships with international laboratories or development as a kit.

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