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How MRD is accelerating effective use of biologic therapies

By **Personalis**
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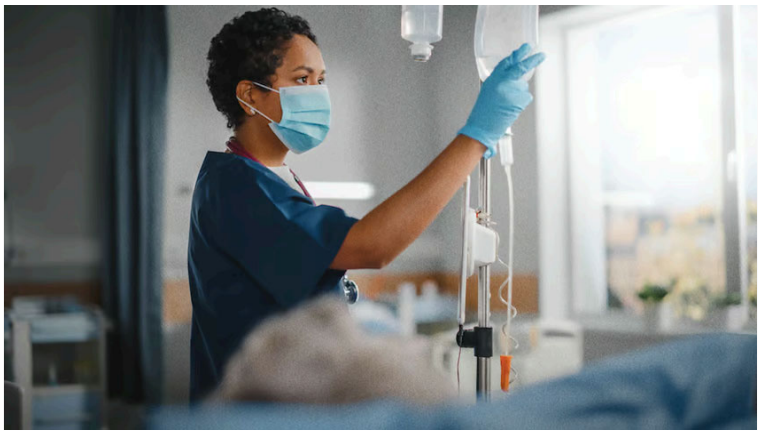

(Personalis)

Molecular residual disease (MRD) has grown in importance as an oncological biomarker[1]. The use of tumor-informed liquid biopsy has proven effective in early detection of circulating tumor-derived DNA (ctDNA) indicative of cancer recurrence. Standard-of-care radiological-based technologies, including CT, PET, and MRI scans, are limited in their ability to detect MRD due to the minimum tumor volume required[2]. First generation ctDNA technologies offered earlier detection than imaging, but lacked the sensitivity needed for robust post-diagnosis monitoring. Therefore, reliable, ultra-sensitive detection and quantification of MRD capable of guiding clinical decisions from the earliest stages has remained the goal.

To fill the gap, an industry-leading ctDNA technology has evolved to achieve a sensitivity in the range of 1-3 parts per million, representing a 10-100X increase over other available methods, while requiring only a single tube of blood and 1mm^3 of tumor tissue[3]. At this level of sensitivity, ctDNA holds great potential both in drug development[4] and as a clinical tool. When paired with next generation genomic sequencing, this breakthrough technology - NeXT Personal - enables early identification of cancer mutations to rapidly assess therapeutic effect and inform post-resection therapy. NeXT Personal enables detection and quantification of both MRD and clinically-relevant variants in a single platform.

And as described in this article, ctDNA biomarker efficacy in clinical trial design and translational research is growing, building a strong case for ctDNA analysis, where NeXT Personal is poised to make an impact in oncology.

Detecting ESR1 mutation resistance to aromatase inhibitors

Aromatase inhibitors are a class of drugs used in the treatment of breast cancer. Tumors can become resistant to aromatase inhibitors through mutations of Estrogen Receptor alpha (ESR1), which are frequent during disease progression on aromatase-based first-line therapy. French researchers investigated a new intervention among hormone receptor-positive metastatic breast cancer patients[5]. PADA-1 was the first trial to demonstrate that ESR1 mutations can be detected and targeted before disease progression. After detecting the mutations in cell-free DNA, the team initiated a therapeutic switch from an aromatase inhibitor plus palbociclib to Fulvestrant and palbociclib. This switch resulted in doubled progression-free survival in the phase III PADA-1 trial.

Interestingly, switching the therapy after disease progression resulted in a minor benefit. While Fulvestrant is unaffected by the ESR1 mutations, it did provide limited progression-free survival when used as a second-line therapy, highlighting the importance of detecting ESR1 mutations during first-line aromatase therapy and before disease progression. Moreover, the researchers concluded that monitoring the rise in resistance-associated mutations may create opportunities related to new therapeutic agents. To this point, ctDNA assessment using tumor-informed whole genome sequencing-based and fixed guideline-driven panels in a single assay provides unprecedented insights and facilitates longitudinal therapy response analysis, including variant tracking and proactive monitoring of resistance mechanisms[3].

Predicting clinical outcomes sooner with MRD

Neoantigens derived from tumor-specific mutations are promising immunotherapy targets that can be incorporated in personalized therapeutic cancer vaccines (PTCV) to boost T-cell activation. Findings were presented at the Society for Immunotherapy of Cancer 37th Annual Meeting[6] illustrating the correlation of disease status (using RECIST 1.1) with ctDNA levels relative to baseline.

Researchers treated patients with unresectable or metastatic hepatocellular carcinoma that were non-responsive to first-line tyrosine kinase inhibitor therapy, with PTCV. They observed a strong correlation between ctDNA quantification and tumor size over 2 years. Importantly, changes in ctDNA measured prior to MRI scans and RECIST 1.1. analysis were directly associated with objective clinical response such as overall survival, with no false-negatives reported. These results show that longitudinal high-sensitivity ctDNA monitoring[3] could help predict clinical outcome and guide real time clinical treatment decisions for personalized cancer therapy.

Ease of ctDNA sample handling and analysis, along with rapidly accessible MRD data offer significant advantages for fast and effective drug development. Excitingly, the value of longitudinal ctDNA measurement as a dynamic biomarker for treatment response prediction, understanding of emergent tumor variants and real time clinical treatment decision-making is supported by a growing body of evidence. Learn more about how partnerships between drug and diagnostic developers can enable a highly-personalized approach to cancer management in this upcoming Fierce Webinar (https://www.fiercebiotech.com/premium/webinar/highly-personalized-therapies-cancer-management).

References:

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Avidity's latest DMD data drop assuages safety concerns for RNA-based asset: analyst

By **Darren Incorvaia**
Mar 17, 2025 02:00pm

Duchenne muscular dystrophy (DMD) | Clinical Trial Results | Avidity Biosciences

After some earlier data sparked questions from analysts, Avidity Biosciences has released more data for its RNA-based Duchenne muscular dystrophy (DMD) candidate.

In a phase 1/2 trial, most adverse events after treatment with the antibody oligonucleotide conjugate, called delpacibart zotadirsen (del-zota), were mild to moderate, Avidity said in a March 17 release (https://aviditybiosciences.investorroom.com/2025-03-17-Avidity-Biosciences-Announces-Positive-Topline-Del-zota-Data-Demonstrating-Consistent,-Statistically-Significant-Improvements-in-Dystrophin,-Exon-Skipping-and-Creatine-Kinase-in-People-Living-with-Duchenne-Muscular-Dystrophy-Amenable-to-Exon-44).

Prior del-zota data prompted concern from analysts (https://www.fiercebiotech.com/biotech/analysts-dig-details-aviditys-dmd-win-revealing-nuances-strong-data) due to occurrences of anaphylaxis and an infusion-related reaction, which led to two patients dropping out of the trial.

Since those earlier discontinuations, no other patients have dropped out of the trial due to an adverse event, Avidity said in a March 17 presentation (https://aviditybiosciences.investorroom.com/events-and-presentations?item=77). The most common side effects for patients given del-zota were procedural pain and headache.

"Safety is clean," analysts from Evercore ISI wrote after the company's update March 17. "This update assuaged that potential concern" of anaphylaxis and infusion-related reactions.

The new data are from patients with DMD who received either 5 milligrams or 10 milligrams of del-zota per kilogram of body weight, with results consistent across doses. Past data released in August 2024 were limited to patients given 5 milligrams of the drug per kilogram of body weight.

Treatment with the antibody oligonucleotide conjugate increased dystrophin production by 25%, the San Diego biotech shared in August, which restored total dystrophin levels by 58%. The treatment also reduced creatine kinase, a marker of muscle damage, by as much as 80% from baseline.

The phase 1/2 trial (https://clinicaltrials.gov/study/NCT05670730), dubbed Explore44, wrapped up in November 2024 and studied the effect of del-zota in healthy volunteers and patients with DMD amenable to exon 44 skipping.

An open-label extension (https://clinicaltrials.gov/study/NCT06244082) of the trial is currently underway. The latest safety data came from 38 patients in the extended portion of the trial and 26 from the completed portion.

Evercore analysts found the reduction in creatine kinase, a key biomarker of DMD, "very intriguing," they wrote. "We hope this is a harbinger of functional benefit."

Avidity plans to present data on functional benefit in the fourth quarter of 2025, according to the release.

Further, the company plans to submit a biologics license application for del-zota at the end of the year. The asset has received rare pediatric disease and fast track designations from the FDA as well as an orphan drug designation from both the FDA and the European Medicines Agency, according to the release.

Because the 10-milligram results were similar to past 5-milligram results, Avidity has determined it will use dosing of 5 milligrams per kilogram of body weight every six weeks as it moves forward into future clinical trials.

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