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NEWSLETTER

Clinician Update: Biomarker-Based Cancer Trials

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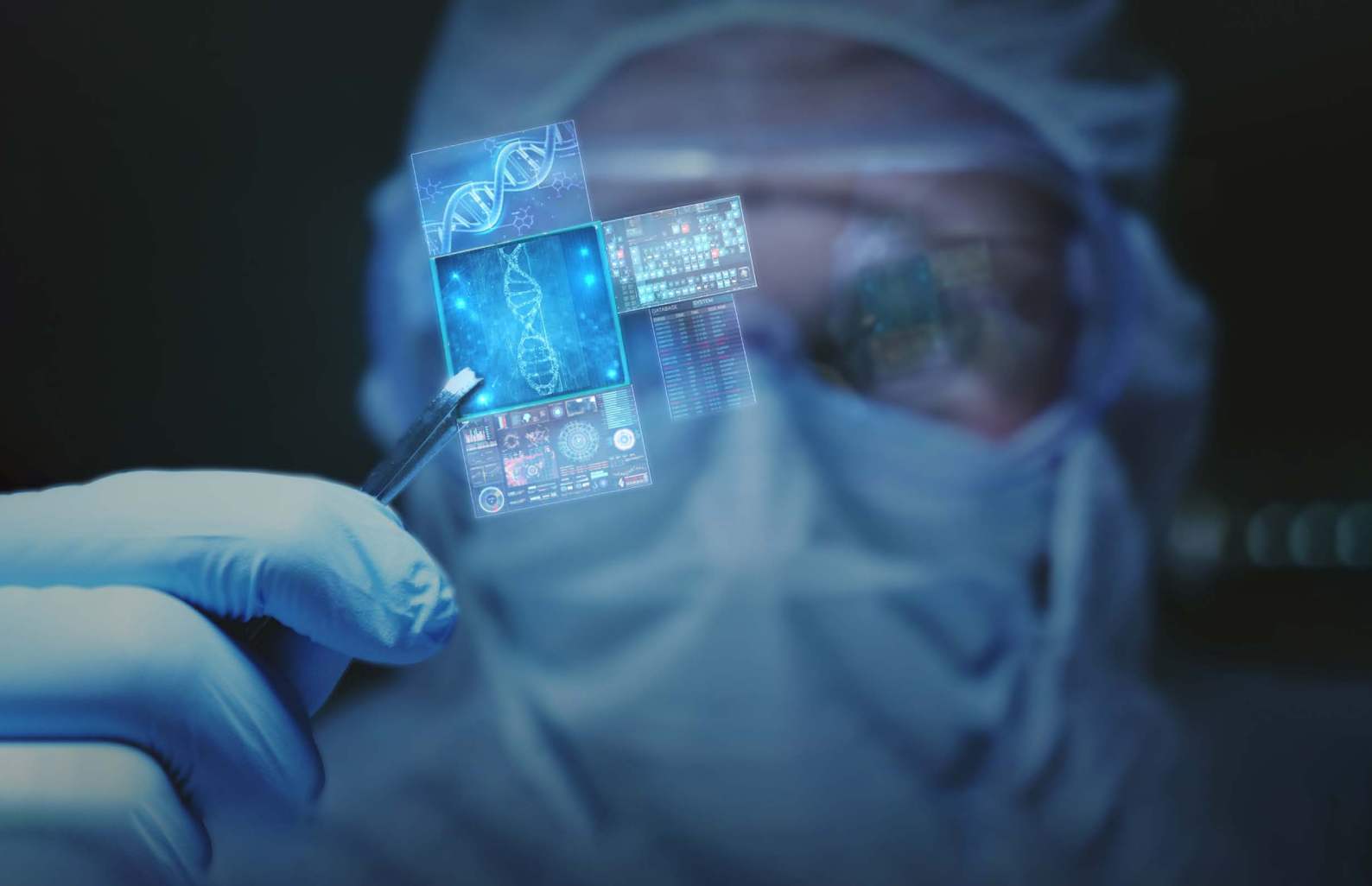


Cancer Biomarkers and the Evolution of Clinical Trials

As the number of actionable cancer biomarkers grows, the way investigators conduct clinical trials of new oncology agents will continue to change. Advances in next-generation sequencing and other technologies have produced an ever-expanding list of biomarkers—genes, proteins, and other substances—that increase cancer risk or worsen prognosis, and that are potential targets for new precision-medicine therapies.

Moreover, the growing understanding of cancer genomics has led to a change in how we think about many malignancies: That is, that the location of the tumor matters less than its molecular profile. (The title of one journal article about this paradigm shift sums it up nicely: "When Tissue is No Longer the Issue.") The number of so-called "tissue-agnostic" therapies is rapidly increasing, which is driving a dramatic change in how these medicines are developed and evaluated. Increasingly, traditional phase I, II, and III studies that evaluate the benefits and safety of one drug in a population of patients with the same or similar cancers are being supplanted by so-called master protocol studies. Surveys indicate that these novel approaches to designing clinical trials have become increasingly common, and the U.S. Food and Drug Administration has encouraged investigators to implement them.

Proponents say that master protocol designs have certain advantages over traditional clinical trials. They can streamline the regulatory process and expedite approval, for example, while lowering the cost of drug development. They're also useful for studying rare cancers with rare genetic mutations. Here are the three major forms of master protocol studies:

Basket trials
Instead of recruiting patients who all have the same type of cancer, a basket trial is tissue agnostic—that is, it involves patients with different types of malignancies that share a common biomarker or mutation, which is the target of the investigational drug or other therapy. (A basket trial may also be called a bucket trial.) There are currently about 30 investigational treatments under study in basket trials, while a number have already been reported.

Example: Patients with multiple forms of solid tumors that had NTRK fusions were treated with larotrectinib in the LOXO-TRK-14001, SCOUT, and NAVIGATE trials (17 cancer types; overall response rate, 75%); and entrectinib in the ALKA-372-001, STARTRK-1, and STARTRK-2 trials (10 cancer types; overall response rate, 57%).

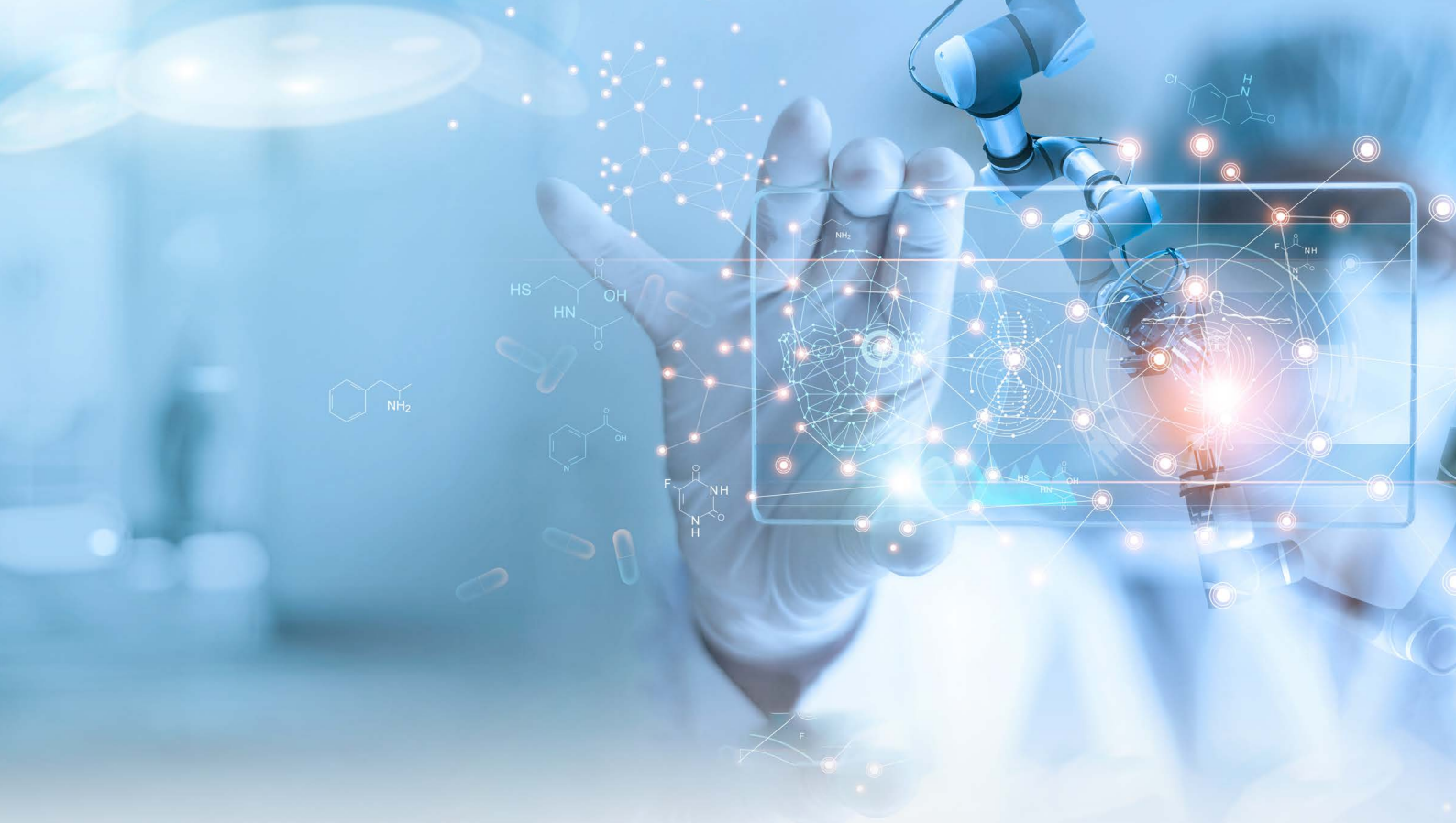
Umbrella trials
These trials include patients with one cancer type, but whose tumors have different biomarkers or mutations. Each tumor's unique genetic alteration is treated with a specific targeted therapy.

Example: The ongoing FOCUS4 Phase II/III randomized trial includes patients with advanced colorectal cancer that's positive for *PIK3CA, KRAS, NRAS, TP53,* and *BRAF* mutations.

Platform trials
While the definition of a platform trial differs across the literature, most agree that it's a hybrid of a basket trial and umbrella trial. What sets apart a platform trial is that it is conducted in an ongoing or perpetual manner, in which multiple drugs and/or multiple disease populations can be added to the trial as it proceeds.

Example: The TAPUR trial includes patients with *ALK, ROS1, MET, mTOR, TSC, HER2, BRCA, ATM, RET, VEGFR1/2/3, KIT, PDGFRβ,* and *BRAF* mutations, who are being treated with FDA-approved treatments known to target these actionable genetic alterations. In three cohorts, overall response has varied from 4% to 29%.

These gene-specific studies have limitations. For example, many tumors are driven by the interaction of multiple genetic alterations. And recruiting adequate numbers of patients with certain rare mutations can be a challenge. However, since these new-style trials can evaluate whether a targeted therapy is safe and effective faster and with fewer patients, they are undoubtedly here to stay. Massive Bio collaborates with several pharma partners that are conducting basket trials and other novel forms of clinical study. Contact us at (844) 627 7246 or support@massivebio.com to learn more and find out if your patients might be candidates for clinical trials.



Clinical Trial News

New Treatment for a New Designation

In September 2022, the U.S. Food and Drug Administration approved fam-trastuzumab-deruxtecan-nxki (*Enhertu*), an IV infusion for the treatment of patients with unresectable or metastatic HER2-low breast cancer. This newly defined designation represents a subset of HER2-negative breast cancer. (Some sources now prefer the term ERBB2-negative, denoting the gene that codes for epidermal growth factor receptor 2.) Previously, 80 to 85 percent of new breast cancer diagnoses were deemed to be HER2-negative, meaning that the tumors do not overexpress the HER2 protein, which promotes cancer growth and metastasis. Within this category, about 60 percent of patients who were previously classified as having the HER2-negative subtype have been reclassified as HER2-low, which describes a tumor with HER2 proteins on the cell surfaces, but too few to be considered as HER2-positive.

The approval of *Enhertu* is based on the results of DESTINY-Breast04, a randomized open-label trial that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. Patients were randomized in in a 2:1 ratio to receive trastuzumab deruxtecan or the physician's choice of chemotherapy. Among all patients, median progression-free survival was 9.9 months in the trastuzumab deruxtecan group and 5.1 months in the chemotherapy group (hazard ratio for disease progression or death, 0.50), and overall survival was 23.4 months and 16.8 months, respectively.

HER2-low patients have been treated with endocrine therapy or chemotherapy, but the addition of *Enhertu* adds a new option. In addition to being diagnosed with HER2-low breast cancer, eligibility for *Enhertu* requires that a patient has already received chemotherapy for metastatic

disease or the patient's cancer returned during, or within 6 months of completing, adjuvant chemotherapy.

Tissue-Agnostic Trial Suggests New Possible Roles for Pralsetinib

Pralsetinib (*Gavreto*) is a potent, selective inhibitor of RET receptor tyrosine kinase and is approved by the FDA for treatment of metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), as well as RET-mutant medullary and RET fusion-positive thyroid cancers. The RET gene plays a role in embryonic development of the nervous system and the kidneys, but fusions and mutations of this gene are known to be oncogenic. RET fusions occur in 1 to 2% of NSCLCs, approximately 20% of papillary thyroid cancers, and fewer than 1% of many other solid tumors, including ovarian, pancreatic, salivary, and colorectal cancers.

In phase I/II of the ARROW trial, the benefits and safety of pralsetinib were evaluated in patients with advanced RET-altered solid tumors. The trial included 29 patients with 12 different types of solid tumor (excluding NSLC and thyroid cancer) who had previously received or were not candidates for standard therapies. The study, published in *Nature Medicine*, had an overall response rate among 23 efficacy-evaluable patients was 57%, which occurred across all tumor types and RET fusion partners. Median duration of response, progression-free survival, and overall survival were 12 months, seven months and 14 months, respectively. However, several patients had particularly notable responses, including a man in his thirties with progressive pancreatic cancer who experienced treatment-limiting toxicity on capecitabine. The patient had a complete response with pralsetinib (100% decrease in the sum of lesion diameters), which continued for 33.1 months at the data cutoff.

Grade 3 or higher treatment-related adverse events included neutropenia (31%) and anemia (14%). The authors suggest that pralsetinib offers potential as a tissue-agnostic therapy for a variety of additional RET-positive solid tumor types.

For Your Patients: **Understanding Cancer Biomarkers**

The concept of a cancer biomarker can be difficult for a lay person to understand, especially one who has recently been diagnosed with cancer. The Cancer Support Community has a detailed, yet reader-friendly explanation of what biomarkers are, what their role is in making treatment decisions, and how biomarker testing is conducted, which your patients can find here. The Cancer Support Community, which calls itself the largest professionally led nonprofit network of cancer support worldwide, is dedicated to "ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community."