# BiomarkerLIVE

## Application of Biomarkers in Clinical Trials

The field of oncology is increasingly adopting a precision medicine approach in which biomarkers are used to guide care management.[1] A biomarker is defined by the U.S. Food and Drug Administration (FDA) as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions."[2] Biomarkers can be categorized according to their specific use, such as those that are diagnostic, prognostic, or predictive, among others. This white paper will focus primarily on the application of predictive biomarkers in clinical trials.

A predictive biomarker identifies individuals who are at an increased likelihood of experiencing a favorable or unfavorable effect from a medical intervention or environmental exposure.[2] A randomized clinical trial is generally required to establish that a biomarker is predictive. In contrast, a prognostic biomarker provides prognostic information regardless of therapy by determining the likelihood of a specific clinical event, such as disease progression, and is often identified from observational data. In some cases, a biomarker can be both predictive and prognostic.

Biomarkers have become a critical component of disease assessment and treatment decision-making. As of mid-2021, there were at least 45 oncology drugs approved by the FDA that were developed with a biomarker.[3] The use of these agents requires the biomarker to be present, as determined by an approved companion diagnostic. There are also three anticancer agents approved for patients with cancers with a genetic aberration—rather than a specific cancer type or subtype—as of April 2021.[4] This includes larotrectinib and entrectinib for tumors with *NTRK* fusions, and pembrolizumab for tumors that have high microsatellite instability (MSI-H), DNA mismatch repair deficiency (dMMR), or high tumor mutational burden.[5-8]

### THE ROLE OF BIOMARKERS IN CLINICAL TRIALS

The molecular testing of tumors is important, because such testing has the potential to identify an actionable genomic alteration, even among patients with tumors that currently have few approved targeted therapy options.[9] One example is molecular profiling (such as with next-generation sequencing) that identifies an *NTRK* fusion, thus making the patient a candidate for larotrectinib or entrectinib. Molecular testing can also result in expanding or refining the treatment plan. In one study, 96 percent of patients with rare cancers had at least one genomic alteration, with 35 percent resulting in genomically-guided therapy, diagnostic modification, or germline genetic testing.[10] Evaluating patients for biomarkers may expand treatment options—not only for existing FDA-approved options, but also for inclusion in a clinical trial.

Clinical trials are a critical component of oncology. They offer patients an option for novel treatment approaches, and they give researchers important information about the feasibility and efficacy of using new therapeutic targets in specific patient populations. Patients with a cancer that harbors a genetic alteration for which no approved therapy exists may qualify for a clinical trial, as by April 2021 there are more than 2,600 ongoing oncology trials that include a biomarker component.[11]

Patients who have undergone biomarker testing as part of their general cancer care are more likely to be matched to a clinical trial.[12] This is especially true if patients undergo extensive molecular profiling that includes RNA sequencing and immunotherapy biomarkers such as PD-L1 tumor expression.[13] For example, in a study of 500 samples from patients with diverse tumor types, extensive biomarker testing demonstrated that 76.8 percent of patients had the potential to be matched with at least one relevant clinical trial.[13] Furthermore, patients enrolled in

genotype-matched trials are more likely to experience a response to treatment compared to non-genotype matched trials.[14]

Despite the benefits of molecular testing and enrollment in clinical trials, accrual rates to trials with a biomarker component are low. For example, a retrospective chart review conducted between 2012 and 2014 found that 41 percent of the 971 patients referred to phase 1 trials had received prior molecular profiling.[12] The number of these patients who were then enrolled into a genotype-matched clinical trial was low, at 11 percent. In another study, 15 percent of 1,640 patients with advanced solid tumors who underwent molecular testing were enrolled in a clinical trial, of which 5 percent were genotype-matched.[14]

Racial and ethnic disparities in clinical trial enrollment remain a critical issue that likely extends to clinical trials including a biomarker component.[15,16] It is important that the population of clinical trials is representative of the population that is affected by the disease being studied, and this is no different for trials that include biomarkers. Clinicians should ensure that they are ordering biomarker testing for all patients, including members of racial/ethnic minority groups.

Broad molecular profiling of patients is important not only to potentially expand treatment options and guide management decisions, but also to increase the likelihood that patients are eligible for and can be enrolled in clinical trials.

## LANDSCAPE OF CLINICAL TRIALS

The gold-standard interventional trial design includes the randomization of patients into an experimental treatment arm and a control arm. However, this traditional design is not necessarily ideal for trials that include a biomarker component or for evaluating rare cancer types or populations.[17] When the traditional two-arm trial design is used, trials that include a biomarker component frequently require either multiple trials or subgroups, which can be tedious and costly. Therefore, novel trial designs have been developed that aim to improve the efficiency of the logistics required to conduct trials involving biomarkers, thus shortening such trials. There are three main categories of these novel designs for trials with biomarker components: biomarker-driven, randomize-all, master protocol, and adaptive designs.

### Biomarker-Driven Trials

Biomarker-driven trials include biomarker-matched subgroups.[17] In an enrichment design, only patients who are positive for the biomarker of interest are included in the trial. This design is more commonly used in later-phase clinical trials, when the clinical utility of the predictive biomarker may be more established. Because the enrichment design only includes patients who are most likely to benefit from

the experimental treatment, the advantage of this design is that it increases the power of detecting treatment efficacy, thereby reducing the sample size that is needed.

One example of a biomarker-driven, enrichment design is the phase 3 ToGA trial, in which patients with gastric or gastroesophageal junction (GEJ) cancers with an overexpression of HER2 were enrolled.[18] The trial demonstrated that trastuzumab plus chemotherapy increased the response rate and prolonged progression-free survival (PFS) and overall survival (OS) of patients, compared to chemotherapy alone. This combination has become the standard of care for patients with gastric or GEJ tumors with HER2 overexpression.

### Randomize-All Designed Trials

In a randomize-all designed trial, patients are enrolled whether they test positive for a given biomarker or not, but they are stratified according to their biomarker status.[17] This design allows for more research questions than an enrichment designed trial does. Patients can either be randomly assigned to a therapeutic strategy and their outcomes stratified by biomarker status (such as in the EORTC10994/BIG 1-00 trial), or they can be assigned to a treatment strategy based on their biomarker status (such as in the MINDACT trial).[17,19,20] In the EORTC10994/BIG 1-00 trial, patients with breast cancer were randomly assigned to neoadjuvant chemotherapy with a taxane or non-taxane.[19] The outcomes were then stratified by *TP53* status, which demonstrated that although the presence of a *TP53* mutation was prognostic for OS, it was not predictive for response to taxanes.

In the phase 3 MINDACT trial, patients with early-stage breast cancer underwent the MammaPrint 70-gene signature test to determine their genetic risk.[20] Patients were assigned to treatment based on the results of their genetic and clinical risk; those with low clinical and genomic risk did not receive chemotherapy, whereas patients with high clinical and genomic risk did. In cases of discordant risk, patients were assigned to chemotherapy based on either their clinical or genomic risk. The study demonstrated that approximately 46 percent of patients with early-stage breast cancer at high clinical risk may not need chemotherapy, thus sparing them from its associated adverse effects.

A disadvantage of the randomize-all design is that a large number of patients have to be screened if the biomarker of interest is rare. To address this issue, alternative trial designs have been developed.

### Master Protocol Trials

Master protocol trials include multiple sub-studies that share key designs and operational specifications.[17] The advantage of this design is improved screening and patient accrual,

which is perhaps why the number of master protocol trials is rapidly increasing.[17,21] There are several types of master protocol trials, including umbrella and basket trials.

Umbrella trials include multiple biomarker-matched subgroups with different targeted therapies.[17] Importantly, all patients have the *same* cancer type or histology. Each sub-study is formed from a different biomarker, and the investigational agent is targeted to that specific biomarker.[22] A new sub-study can be added under the same master protocol if a new biomarker is discovered or a new therapy that targets a specific biomarker is developed. Similarly, a sub-study can be closed or terminated without affecting the other sub-studies if the treatment is shown to be futile or harmful.

One example of an umbrella trial is the phase 2/3 SWOG Lung-MAP trial of patients with metastatic squamous cell carcinoma (SCC), which included nine sub-studies of either unmatched populations or those with alterations in *PI3KCA*, cell cycle genes, *FGFR*, *MET*, or homologous recombination repair genes.[23] Some sub-studies were closed at their interim analysis due to futility or discontinued development of the treatment, but one sub-study showed a response to its investigational agent (i.e., talazoparib for homologous repair deficiency).

Basket trials include multiple biomarker-matched subgroups with different cancer types and/or histologies, but a single targeted therapy.[17] Each basket or subgroup is considered a cancer or histologic type with the goal of identifying an effective therapy for a single predictive biomarker that occurs across multiple cancer types or histologies.[22] The sub-studies can have the same or a different design.

One example of a study with basket trial design (as well as umbrella trial features) is the phase 2 NCI-MATCH study.[24] Patients with any advanced, refractory solid tumor, lymphoma, or multiple myeloma were enrolled and evaluated using high-throughput NGS and immunohistochemistry. Patients with actionable mutations were assigned to one of the initial ten subgroups, and each subgroup tested a different experimental agent. There were some cases in which the same drug was evaluated in two different subgroups for two different mutations. Another example is the phase 2 VE-BASKET trial, in which patients with BRAF V600–mutated nonmelanoma cancers were assigned to one of seven subgroups and treated with vemurafenib.[25] The results from this trial led to the FDA approval of vemurafenib for the treatment of Erdheim-Chester disease.[26]

## Adaptive Design Trials

Adaptive designed trials have a protocol that can be modified according to prespecified rules as the trial progresses.[22] These rules may include dosing changes, adding or removing treatment arms, combining phases, changing the proportion of patients in the treatment arms, or reassessing the sample size. The advantage of this design is that it may improve efficiency by potentially leading to smaller trials and shortening drug development time.

One example of an adaptive design is the phase 2 BATTLE program, which included the BATTLE-1 and BATTLE-2 trials.[27] In BATTLE-1, patients with previously treated non-small cell lung cancer (NSCLC) were equally assigned to one of five biomarker groups and treated with different targeted agents. The disease control rate (DCR) was continuously monitored in each subgroup, and patients were adaptively randomized into different subgroups based on the updated DCR estimate for their specific biomarker profile.

Another example of an adaptive design is the phase 2 MATRIX trial, which assigned patients with NSCLC to 18 different molecular cohorts to test eight therapies.[28] New cohorts with different biomarker-drug combinations can be added in such trials, and patients who are biomarker-negative may be treated in a cohort if sufficient evidence exists that suggests they may benefit from the therapy.

## CONCLUSION

The number of clinical trials with a biomarker component is increasing in the field of oncology, highlighting the importance of comprehensive biomarker testing for all patients with cancer. Clinical trials give patients with genomic alterations the opportunity to access treatment options beyond those currently approved by the FDA. Multiple trial designs have been developed and are in use that aim to improve the efficiency of incorporating biomarker components into clinical trials. Patients who have undergone broad molecular profiling are more likely to match and be enrolled in a biomarker-driven trial.

Therefore, one important aspect to consider when determining whether to conduct biomarker testing on a patient is the role the test results may play in potentially making that patient eligible for future clinical trials. For patients who have already undergone biomarker testing, clinicians should use their results to search for potential matches with relevant clinical trials. Clinicians should never forget to give each potentially eligible patient they treat—regardless of background—the opportunity to participate in clinical trials.

## REFERENCES

1. Antoniou M, Jorngensen AL, Kolamunnage-Dona R. Biomarker-guided adaptive trial designs in phase II and phase III: a methodological review. *PLoS ONE*. 2016;11(2):e0149803.

2. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring, MD: Food and Drug Administration (US). Co-published by National Institutes of Health (US), Bethesda, MD. Created: January 28, 2016; Updated: January 25, 2021.

3. U.S. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). April 27, 2021. Available at: *https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools*. Last accessed May 27, 2021.

4. Jorgensen JT. A paradigm shift in biomarker guided oncology drug development. *Ann Transl Med*. 2019;7(7):148.

5. U.S. Food and Drug Administration. FDA approves an oncology drug that targets a key genetic driver of cancer, rather than a specific type of tumor. Press Release. November 26, 2018. Available at: *https://www.fda.gov/news-events/press-announcements/fda-approves-third-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor*. Last accessed April 21, 2021.

6. U.S. Food and Drug Administration. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. Press Release. August 15, 2019. Available at: *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc*. Last accessed April 21, 2021.

7. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Press Release. May 23, 2017. Available at: *https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-locally-recurrent-unresectable-or-metastatic-triple*. Last accessed April 21, 2021.

8. U.S. Food and Drug Administration. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. Press Release. June 16, 2020. Available at: *https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors*. Last accessed May 27, 2021.

9. Fernandez-Rozadilla C, Simoes AR, Lleonart ME, Carnero A, Carracedo A. Tumor profiling at the service of cancer therapy. *Front Oncol*. 2021;10:595613.

10. Hirshfield KM, Tolkunov D, Zhong H, et al. Clinical actionability of comprehensive genomic profiling for management of rare or refractory cancers. *Oncologist*. 2016;21(11):1315–1325.

11. ClinicalTrials.gov search. Search terms: "cancer" and "biomarker" for recruiting, not yet recruiting, active not recruiting, enrolling by invitation, interventional, phase 1, 2, or 3 clinical trials. Available at: *https://clinicaltrials.gov/ct2/results?*

12. Tan T, Rheaume M, Wang L, et al. Referrals to a phase I clinic and trial enrollment in the molecular screening era. *Oncologist*. 2019;24:e518–e525.

13. Beaubier N, Bontrager M, Heuther R, et al. Integrated genomic profiling expands clinical options for patients with cancer. *Nat Biotech*. 2019;37:1351–1360.

14. Stockley TL, Oza AM, Berman HK, et al. Molecular profiling of advanced solid tumors and patient outcomes with genotype-matched clinical trials: the Princess Margaret IMPACT/COMPACT trial. *Genome Med*. 2016;8:109.

15. Ajewole VB, Akindele O, Abajue U, et al. Cancer disparities and black American representation in clinical trials leading to the approval of oral chemotherapy drugs in the United States between 2009 and 2019. *JCO Oncol Pract*. 2021;17:e623-e628.

16. Khandwala P, Desai D, Das DG, et al. Racial disparities in cancer clinical trials. *J Clin Oncol*. 2020;38 (suppl; abstr 97).

17. Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev*. 2019;73:20–30.

18. Bang Y-J, Cutsem EV, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376:688-697.

19. Bonnefoi H, Piccart M, Bogaerts J, et al. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1-00): a randomised phase 3 trial. *Lancet Oncol*. 2011;12:527-539.

20. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729.

21. Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials*. 2019;20:572.

22. Le-Rademacher J, Dahlberg S, Lee JJ, Adjei AA, Mandrekar SJ. Biomarker clinical trials in lung cancer: design, logistics, challenges, and practical considerations. *J Thorac Oncol*. 2018;13(11):1625–1637.

23. Redman MW, Papadimitrakopoulou VA, Minichiello K, et al. Biomarker-driven therapies for previously treated squamous non-small-cell lung cancer (Lung-MAP SWOG S1400): a biomarker-driven master protocol. *Lancet Oncol*. 2020;21(12):1589-1601.

24. Flaherty KT, Gray R, Chen A, et al. The Molecular Analysis for Therapy Choice (NCI-MATCH) trial: lessons for genomic trial design. *JNCI J Natl Cancer Inst*. 2020;112(10):djz245.

25. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373(8):726-736.

26. Park JJH, Hsu G, Siden EG, Thorlund K, Mills EJ. An overview of precision oncology basket and umbrella trials for clinicians. *CA Cancer J Clin*. 2020;70:125–137.

27. Liu S, Lee JJ. An overview of the design and conduct of the BATTLE trials. *Chin Clin Oncol*. 2015;4(3):33.

28. Middleton G, Crack LR, Popat S, et al. The National Lung Matrix Trial: translating the biology of stratification in advanced non-small-cell lung cancer. *Ann Oncol*. 2015;26:2464-2469.