CDx Biomarkers for Oncology Research & Development

Precision medicine is built on the premise of identifying patients who are most likely to respond to a therapy while avoiding serious adverse effects, thereby increasing the therapeutic index of a drug or biologic. Biomarkers, whether they are complex genomic signatures or single-gene mutations, can be critical for patient selection in therapeutic development.

Dr. Margaret Curnutte
Senior Director, In Vitro Diagnostics & Quality, Precision for Medicine

In this article, we discuss the development of companion diagnostics (CDx) for oncology therapeutics, providing considerations for evaluating both complex genomic signatures and single-gene biomarkers across all phases of oncology clinical trials.

Precision for Medicine is a global leader in CDx development, biospecimen sourcing, and CRO services to the life sciences industries. Precision's regulatory experts offer comprehensive CDx regulatory and evidence-development strategies, anticipating areas of regulatory risk and monitoring developments in a shifting policy landscape.

Background on oncology companion diagnostics

A biomarker is a characteristic that can be measured as an "indicator of normal or pathogenic biological processes or of responses to an exposure or intervention."[1] The Biomarkers, EndpointS, and other Tools (BEST) glossary defines 7 biomarker categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety.[2] In the context of oncology therapeutics, predictive biomarkers are used to identify individuals who are more likely to experience a favorable or unfavorable effect from exposure to a drug or biologic.[2]

Oncologic CDx are biomarker assays used to inform the management of patients by identifying treatment options that may be appropriate based on the unique drivers of their individual tumors. Approximately two-thirds of the breakthrough therapy designations granted by the US Food and Drug Administration (FDA) are accompanied by a CDx.[3] In oncology, CDx may be:

- Complex genomic signatures with a clinical cutoff, such as tumor mutational burden (TMB), microsatellite instability (MSI), or loss of heterozygosity (LOH)
- Single-gene biomarker assays based on mutations in known oncogenes or tumor suppressor genes, such as BRCA1/2, anaplastic large-cell lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR)

Over the past few years, the FDA has approved a number of CDx across cancer types, including immunohistochemistry-based assays such as PD-L1 immunohistochemistry (IHC) 22C3 pharmDx for identifying individuals with non-small cell lung cancer (NSCLC) who may be candidates for pembrolizumab (Keytruda®) and VENTANA ALK for identifying individuals with ALK-positive NSCLC who may be candidates for lorlatinib (Lorbrena®).[4] FoundationOne®CDx, a tissue-based genomic test has been approved as a CDx for more than 20 therapies, with the following recent indications:

- NSCLC: Identifying individuals with EGFR exon 19 deletions and exon 21 (L858R) alterations who may be candidates for EGFR inhibitors approved by the FDA[5]

- Solid tumors: Identifying individuals with MSI-high solid tumors who may be candidates for pembrolizumab[6]

- Melanoma: Identifying individuals with BRAF V600E and V600K who may be candidates for BRAF or MEK inhibitors, such as trametinib (Mekinist®), or BRAF/MEK inhibitor combinations approved by the FDA[4]

FoundationOne®Liquid CDx is a blood-based test with approved CDx indications in NSCLC and prostate, ovarian, and breast cancers.[4] In March 2022, Myriad Genetics received approval for BRACAnalysis CDx for identifying patients with germline BRCA-mutated, HER2-negative breast cancer who are eligible for olaparib (Lynparza®).[7]

Evaluating biomarkers for therapeutics that may require a CDx

If a biomarker is to be used for patient selection, it must be qualified. Qualification is a formal regulatory process that ensures the biomarker, and not the biomarker measurement method, can be relied on to have a specific application and interpretation within the stated context of use.[1] The CDx will also need to undergo analytical validation, which can involve establishing a cutoff and demonstrating that the assay accurately and reliably measures the biomarker.[8]

Transitioning a diagnostic from bench to bedside requires a disciplined strategy that balances product design considerations, regulatory requirements, and feasibility. Precision for Medicine integrates clinical development, biomarker assays, regulatory strategy, and commercialization capabilities within a single organization, giving us unique insight into what it takes to co-develop a targeted therapeutic and its CDx.

Potential biomarkers are often evaluated in prospective-retrospective studies in which biomarkers are retrospectively measured on archived specimens following the completion of prospective clinical trials.[9] Given that some biomarker assays can be costly, researchers may opt for random sampling designs where biomarker testing is only performed on a sub-sample of subjects selected on the basis of observed outcome or other variables. Group testing, which involves physically pooling specimens across subjects and performing biomarker testing on those pooled samples, is another approach for estimating the prognostic and predictive values of biomarkers.[6]

Biomarkers may also be measured prospectively and used for enrollment or patient stratification. At Precision for Medicine, we have supported more than 250 marketing clearances and approvals for in vitro diagnostic submissions and assisted with market access on more than 100 diagnostics and CDx. Below, we offer considerations for developing both complex genomic signature and single-gene biomarkers through clinical trial phases.

A). In Phase 1

Successful drug/biologic-diagnostic co-development depends on the strength of the biomarker hypothesis, which is based on a thorough molecular understanding of disease pathology and therapeutic mechanism of action.[7] Researchers may have multiple biomarker hypotheses which are tested through prototype assays in the early stages of clinical development to evaluate their predictive potential.

In phase 1, researchers can perform retrospective analyses of clinical data from all study subjects to look for signals that a biomarker may be predictive. However, given that the number of subjects is small and the primary endpoint may be safety, any signal will only be an early indicator. Depending on the biomarker, prevalence may be very low, so it is not uncommon to see few, if any, patients who are biomarker-positive. Thus, biomarker development in phase 1 will rely heavily on preclinical data.

B). In Phase 2

For complex genomic signatures with a clinical cutoff, a key challenge in phase 2 studies is how to determine a clinical cutoff when additional clinical outcome data are needed to support that cutoff. In the absence of sufficient outcome data, published literature, preclinical data, and risk to the patient can be used to establish a cutoff range. Applying machine learning and modeling to these data may be useful for both refining the genomic signature and defining an appropriate starting point for the clinical cutoff.[10]

Another consideration is the level of validation required for the biomarker and the associated clinical trial assay (CTA) at this stage, particularly if the true cutoff is still unknown. Therapeutics developers may consider splitting the study into cutoff establishment and cutoff validation cohorts, a method that has been accepted by the FDA. However, the feasibility of this approach will depend on disease prevalence. A robust limit of detection (LOD), limit of blank (LOB), or limit of quantification (LOQ) study may be useful for identifying a cutoff for enrollment. If multiple cutoffs will be examined in the study, developers may benefit from considering all-comers study design, as this allows for an unbiased analysis of potential cutoffs.

When designing phase 2 studies, developers should also understand the implications of prospective vs retrospective biomarker analysis. In prospective studies where patients are only enrolled if they are biomarker positive based on a pre-established clinical cutoff, analysis of other cutoffs may be limited based on patient selection. In retrospective studies, on the other hand, biomarker data can be bucketed and analyzed in many ways.

For single-gene biomarkers, the primary considerations in phase 2 are whether there is a clear, locked biomarker definition and whether it has been confirmed that the enrollment assay(s) can detect all aspects of that biomarker definition. Often phase 2 studies may utilize multiple laboratory-developed tests (LDTs) to enroll patients, as some centralized biomarker CTAs may be costly and are not regularly performed as part of routine care. It may also be more burdensome for sites to have to use tests that require a centralized lab rather than an LDT. A central laboratory assay, like those offered by Precision for Medicine, can reduce the risks associated with the need for a bridging study to the final CDx. If these enrollment assays differ from the final CDx, it is critical for sponsors to perform a gap analysis to thoroughly understand any differences between what is detected by the enrollment assay(s) and final CDx. If the enrollment assay(s) detects a variant that the final CDx does not, that variant cannot be included in the final biomarker definition.

Moreover, as a general rule, the biomarker definition can only include variants that are present in the clinical trial population, which can be challenging if the variant of interest is rare. The FDA has made exceptions to this rule, though, for tumor suppressor genes. The agency may allow tumor suppressor gene variants not seen in the clinical trial population to be included in a final biomarker definition as variants in such genes are known to alter the tumor suppression function.

C). In Phase 3

In a drug/biologic-diagnostic co-development model, phase 3 studies are used not only to demonstrate safety and efficacy of the therapeutic, but also to clinically validate the CDx assay. The CDx must be shown to discriminate between likely responders and non-responders and, as such, clinical sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are important metrics to consider.

For complex genomic signatures with a clinical cutoff, phase 2 data should inform the locked clinical cutoff. If sponsors choose to continue examining multiple cutoffs, those cutoffs must be validated and specified in the statistical analysis plan (SAP) prior to trial initiation.

Sponsors should avoid using multiple CTAs to enroll patients in phase 3 registrational studies due to varying quality and levels of validation. Ideally, the final CDx assay is used for enrollment, with only 1 testing laboratory to reduce possible site to site variation. While using multiple CTAs may help accelerate enrollment, this speed may come at a cost. If a different assay(s) is used to enroll patients, a bridging study to the final CDx will be required.[11]

Of note, for genomic signatures with a clinical cutoff, biomarker negative data are not needed as enrollment should be based on the cutoff.

For single-gene biomarkers, sponsors should use the final CDx assay for enrollment whenever possible and ensure a locked biomarker definition. Just as with genomic signatures with a clinical cutoff, any discordances between local assays and the final CDx would need to be explained if multiple CTAs are used.

With single-gene biomarkers, the need for biomarker-negative data will depend upon the assay used to enroll patients. If the final CDx is used to select the biomarker-positive population, biomarker negative data are not needed. If bridging from local assays, however, biomarker-negative data would be needed to establish concordance between the enrollment assay and the final CDx, specifically for negative percent agreement (NPA). High NPA is necessary for confirming that there would only have been screen failures if central testing had been conducted.

D). Conclusion

Increasingly, cancer treatment is dependent on biomarkers for insight into prognosis and treatment selection. Thus, biomarker discovery and development are critical for advancing oncology therapeutics. In some cases, CDx assays are developed in parallel with therapeutics based on known targets or mechanisms of action. In others, CDx are developed based on studies that failed to reach their primary endpoints, where retrospective analysis reveals correlations between biomarkers and therapies, as was the case with TMB and pembrolizumab. Precision for Medicine supports drug/biologic-diagnostic co-development programs through our Diagnostic Solutions team, offering scientific and regulatory strategy consulting, biospecimens, specialty lab services, and a full-service CRO for designing and executing all phases of oncology clinical trials.

With comprehensive genomic profiling platforms and multi-gene panels, valuable study specimens can provide reliable information on complex genomic signatures and single-gene mutations, supporting and accelerating CDx for oncology therapeutics. Continuous expansion of indications for marketed CDx fuels both personalized medicine and basic and clinical research related to drug/biologic response and mechanism of action.[12] Moreover, data from these investigations can be applied to other therapeutic areas, bringing us closer to realizing the full promise of precision medicine.

“Precision for Medicine supports drug/biologic-diagnostic co-development programs through our Diagnostic Solutions team, offering scientific and regulatory strategy consulting, biospecimens, specialty lab services, and a full-service CRO for designing and executing all phases of oncology clinical trials.”

Dr. Margaret Curnutte, Senior Director, In Vitro Diagnostics & Quality, Precision for Medicine

Dr. Maggie Curnutte is the Senior Director of Regulatory Affairs within Precision for Medicine's Translational and Regulatory Sciences Practice. Dr. Curnutte has over 9 years of research, regulatory policy, and US and major markets regulatory affairs experience focused on in vitro diagnostics (IVDs). She has extensive expertise in CDx development and clinical trial integration, IVD product development, next-generation sequencing (NGS) technologies, and translation of US regulatory strategy to major markets. Dr. Curnutte is skilled in developing analytical and clinical validation plans and leading regulatory submissions, including Pre-Submissions, investigational device exemptions (IDEs), study risk determinations (SRDs), and premarket approval applications (PMAs).

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