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BRINGING CLINICAL TRIALS TO LIFE

Oncology Basket Clinical Trials
Six Key Considerations

Highlights:

- In basket trials, cancers with differing histologies are pooled and the common element is a singular genetic mutation or protein alteration. The tumors of interest are grouped in baskets for the analysis.
- The basket trial tests a drug that targets a common biologic process. Because of the different tumors involved, the recruiting physicians may represent many different areas of specialization.
- In 2017, the FDA approved the first cancer treatment, pembrolizumab, for any solid tumor with a specific biomarker, regardless of where the cancer started – a landmark accomplishment.

Clinical trials of new cancer treatments have historically focused on a disease type by tumor location: breast cancer, brain tumor, colon cancer, and so on. With advances in medical oncology and genomic characterization of tumors, we are now able to test new therapies that target a single biomarker in multiple tumor types by conducting "basket trials." The biomarker may be a protein or a DNA alteration.

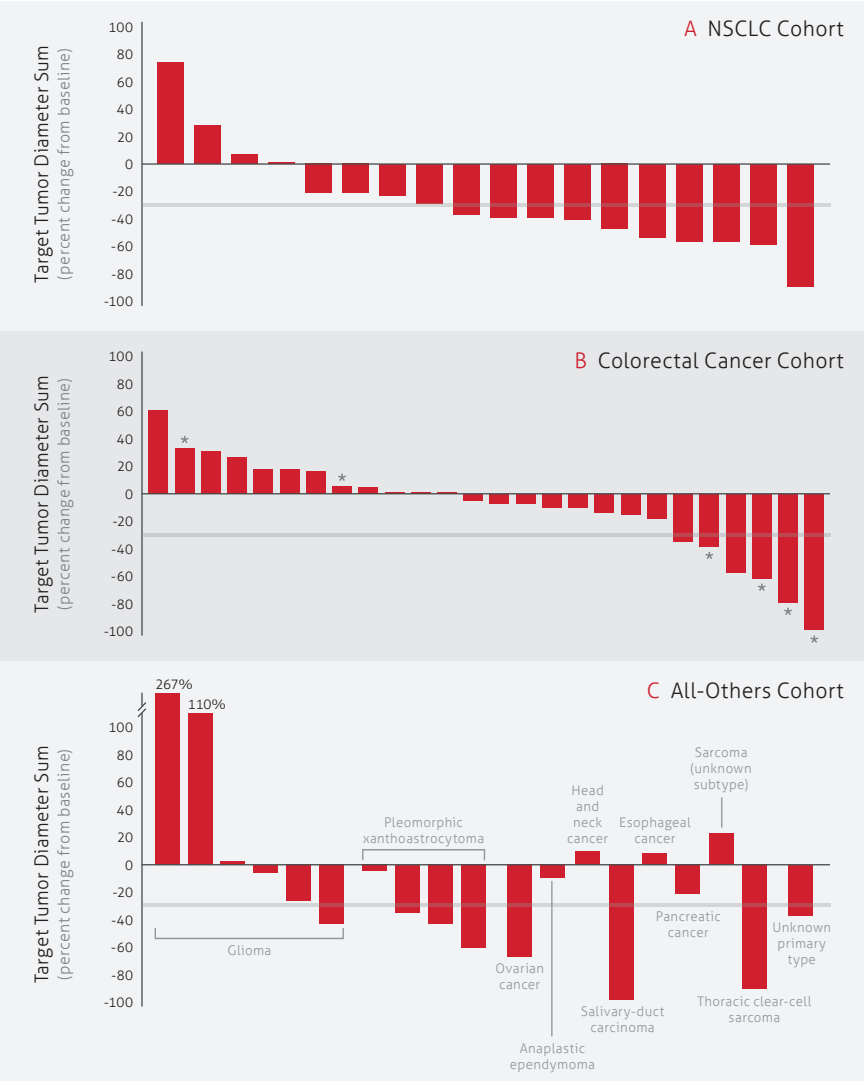
While Phase I clinical trials have always been unique with novel therapies, a basket trial goes a step further. Patients entering Phase I basket trials possess a specific biologic marker in their tumor tissue. The patient and provider who seek out these clinical trials are very informed of the changing clinical trial landscape.

As we continue to make progress in oncology, it's crucial to be aware of the complexity of designing and conducting a basket trial. We've identified several key points to consider with your CRO before conducting a basket trial.

1 What is the clinical significance of the marker on prognosis?

A marker associated with a poor prognosis can significantly impact the disease process for that individual. The potential trial participants with the associated abnormality will be highly motivated to find an active agent that can impact tumor growth. When a potential agent is to be tested against a poor prognosis marker, there will be a natural selection of the most ill patients with that disease. In contrast, a marker may indicate a better prognosis, such as slower tumor growth, less risk of recurrence, and less risk of metastasis. Subjects may be less aware of the presence of the marker and less motivated for a clinical trial. Furthermore, the clinical significance of effective therapies may be more difficult to recognize with the slower growing disease.

Efficacy by basket: individual patients with positive results to treatment share the same mutation



2 How valid are the results or how well tested is the biomarker?

We want to understand the biomarker and the methodology used to test for it. Immunohistochemistry is the most commonly used for protein expression. It can be qualitative or quantitative, and results can vary based on several factors, including reagent, processing time, and/or antibodies. Genomic expression is more precise but, although the availability of testing is on the rise, it still has some limitations in availability and experience. It is important to fully explore the frequency of the biomarker in the population targeted and consider options for expanding the pool of potential subjects

if the expression is lower than anticipated. It is important to consider that there may be subjects tested for the biomarker of interest and they need to be notified about the availability of your clinical trial. There may be opportunities to enhance access to potential clinical trial participants through social media outlets, rare-tumor networks, and strategic partnerships.

3 Identify site challenges to a particular biomarker.
For example, mutations of a particular gene may be expressed in very different types, such as central nervous system tumor and a gastrointestinal tumor – and these are cared for by different oncology specialties. Sites selected for basket trials ideally include multiple medical specialists that can collaborate on one clinical trial. If a biomarker is a prerequisite for entry into a basket trial study, there can be challenges, such as getting results back in time, obtaining a two-stage consent form, or coordinating with a central lab. There can be individual challenges with a complex clinical trial screening process in subjects with a life-threatening disease.

4 Identify subjects for a basket trial using creative tactics.
Patient who screen positively for a rare mutation or cancer type are often found in a limited pool of advanced-stage cancer patients. Understanding how a clinical trial can affect patients with a chronic illness, and how the therapy will impact their lives, will facilitate recruitment. Engaging with community networks, support societies and advocacy groups, and reaching out through social media are effective strategies for recruiting patients for basket trials.

Other creative tactics may be:

- Accommodating the various practice patterns of differing teams of specialists.
- Assembling a committed team by training personnel and familiarizing them with the biomarker impact on the disease.
- Coordinating with partners, such as mutational analysis companies.

The need for outreach also applies to the health care community's responsibility to keep the public informed about their options. Finding and qualifying for a basket trial requires patients to take a few steps beyond a typical phase 1 trial, including being tested for a biomarker and locating a study. Facilitating this process lessens the chances of leaving patients behind.

5 Consider liquid biopsy as an alternative or adjunct to tumor biopsy.
In order to identify the presence of specific mutations by tumor biopsy, it is critical to obtain tumor tissue, and the timing may impact trial participation. Given that only a small section of the tumor is taken in a biopsy, there is a risk that the sample tissue doesn't reflect all of the variations within a tumor. Furthermore, there can be limited viability of tumor tissue in a biopsy sample which limits the tests that can be done.

Liquid biopsy is an attractive alternative. Blood acts as a reservoir for all metastatic sites in the body, so it may provide a more complete profile of disparate clonal populations. Patients benefit from the relative ease of taking a simple blood test compared to tissue biopsy. The validity of liquid biopsy is under review. It can be included to complement tumor biopsy or be used on its own as a diagnostic and monitoring tool.

6 Prepare to respond to shifting outcomes.

From study proposal to defining patients by baskets to analysis of study results, a lot of things can change. Therefore, a basket trial study should contain adaptive rules for expanding a study or even dropping a basket. Considering baskets individually as well as collectively provides insights that may impact the study and its patients.

- If biomarker prevalence in disease types is low, then accrual to a basket may lag and delay the study overall.
- Presumptions may have been made about biomarker distribution based on one tumor type and it may not apply to all tumor types for which there is a basket.
- Patients with prior biomarker positivity may need new biopsies rather than relying on archival results.
- Consider that the standard of care differs for each basket, which impacts the prior therapy exposure and ongoing therapy needs.
- The selection of a subset of a particular tumor type by biomarker can prevent a comparison to known historical controls.

The study may need to be adapted during the clinical trial. Should the treatment show efficacy in a particular tumor type early on, a cohort that was not intended to be expanded may do so. This can mean bringing on new sites and investigators or the contrast may occur.

Having demonstrated the ability to effectively test therapies targeting a single biomarker in multiple tumor types, basket trials present exciting new options for oncologists and for their patients.

Julia A. Lawrence, DO, is the Head Oncologist and Senior Medical Director with Synteract.

About Synteract

Synteract is an innovative, full-service CRO supporting biopharma companies across all phases of drug development to help bring new medicines to market. Synteract has conducted 4,000 studies on six continents and in more than 60 countries, working with more than 26,000 investigative sites and 750,000 patients. It has contributed to more than 240 product approvals. Synteract offers a notable depth of expertise in oncology, general medicine, dermatology, and neuroscience indications, as well as rare and orphan, pediatric, and immunotherapy studies.

Contact us. If you're interested in learning more or would like to schedule a meeting with one of our oncology experts, please email ContactUs@Synteract.com.