



Tissue-Agnostic Therapeutics & Biomarkers in Oncology

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Currently, there is a need for novel cancer therapies. This is due not only to the prevalence and biological complexity of this class of diseases but also to the intractability of many types of cancer. Cancer is the second leading cause of death in the United States, preceded only by heart disease. Estimates suggest that almost 40% of Americans will be diagnosed with cancer at some point in their lives. Despite many years and billions of dollars invested in cancer therapies, many types of cancer remain incurable.

The need for innovative oncology therapies has spurred new and ongoing research both from academic institutions and private industry partners. Some research has been supported, in part, by the Cancer Moonshot Initiative and 21st Century Cures Act, which authorized \$1.8 billion in funding a 7-year period through 2023. As a result, 2017 saw approvals for key revolutionary cancer therapies, including the first approved chimeric antigen receptor T-cell (CAR T-cell) therapies. We discuss these more in our blog posts on [CAR T design](#) and [CAR T regulatory considerations](#).

Another impressive step forward has been in the area of oncology biomarkers, leading to the first approved tissue-agnostic (i.e., non-tissue specific) cancer treatments.

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What are Cancer Biomarkers?

Cancer biomarkers are specific tumor responses or molecules that signal the presence of cancer. Biomarkers can be proteins, genes or gene mutations, molecular modifications, or microenvironmental changes. Generally, biomarkers are disease specific. For example, breast cancer biomarkers allow sub-typing based on hormone receptor status (e.g., estrogen-receptor positive, HER2-positive, and triple negative). In lung cancer, various mutations such as EGFR, ALK, ROS-1, and BRAF are biomarkers used to subtype non-small cell lung cancer (NSCLC).

Why are Biomarkers Important?

The ability to break cancers into subtypes tells us that not all cancers are the same, even if they are in the same anatomical location. For example, HER2-positive breast cancer demonstrates key molecular differences from triple negative breast cancer and will respond differently to treatment.



Cancer diversity indicates that the best approach to treatment is through a personalized medicine approach. Biomarkers can potentially tell clinicians if a treatment is likely to succeed based on the molecular identity of the tumor. As a result, modern medical treatments are attempting to determine treatments based on a patient's unique genetic and biomarker fingerprint.

Personalized Therapies: A Paradigm Shift to Tissue-Agnostic Treatment

The standard approach to personalized cancer treatment targets tumors based on their location in the body, using biomarkers to sub-divide those cancers. However, in May 2017, the US Food and Drug Administration (FDA) turned the concept of "cancer treatment" on its head with the accelerated approval of Merck's pembrolizumab (Keytruda).

Keytruda is a programmed death receptor-1 (PD-1) inhibitor that affects the immune system ([immunotherapy](#)). In tumor cells, PD-1 inhibitors can help the host immune system make tumor cells more susceptible to treatments, such as chemotherapy. Previously, Keytruda had been approved for metastatic melanoma, NSCLC with high PD-L1 expression, head and neck cancers, and classical Hodgkin Lymphoma. In May of 2017, however, the FDA added approval of pembrolizumab for microsatellite instability-high or mismatch repair deficient cancer.

This approval was revolutionary not because of the mechanism of action. Instead, the indication itself was the exciting part of the approval — the FDA approved Keytruda for the treatment for any unresectable or metastatic solid tumor with microsatellite instability-high or mismatch repair deficient biomarkers. In essence, the FDA approved **the biomarker** as the indication rather than approving the drug for a particular tumor type. For the first time ever, as long as a tumor has the biomarker, it doesn't matter where it is in the body; Keytruda may be considered to treat it.

Because this compound has therapeutic capabilities across a broad number of tumor types, the drug has been termed "**tissue-agnostic**." As such, it also embodies a revolutionary paradigm shift in cancer drug development and personalized cancer treatment.

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Since the approval of Keytruda, the FDA has added additional drugs to their tissue-agnostic arsenal with the approvals of Vitrakvi (larotrectinib) in December 2018 and Rozlytrek (entrectinib) in August 2019. These drugs are indicated for the treatment of solid tumors with neurotrophic receptor tyrosine kinase gene fusion in adults and pediatrics (Vitrakvi) and in adults and adolescents (Rozlytrek).

Ongoing Support for Tissue-Agnostic Cancer Treatments

With a strong focus on personalized medicine and approvals in 2017, 2018, and 2019, it seems that the age of tissue-agnostic cancer drugs is only just beginning. Indeed, US Governmental and Regulatory Agencies are taking steps to streamline development and improve chances for success, such as:

NCI'S MATCH AND ASCO'S TAPUR

The National Cancer Institute (NCI) and American Society of Clinical Oncology (ASCO) are sponsoring first-of-their kind, tissue-agnostic clinical trials in collaboration with industry partners: NCI's MATCH program and ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) Study. Each study is enrolling patients based on their genetic biomarkers, **not tumor type**, in an attempt to determine if anticancer drugs can successfully treat cancers based on biomarkers. Patients began enrolling in MATCH in 2015 and TAPUR in 2016, so it is likely that over the next several years, more approvals for biomarker-specific indications will emerge.

FDA'S ONCOLOGY CENTER OF EXCELLENCE AND PUBLIC WORKSHOPS

The FDA Oncology Center of Excellence was created in January 2017 and combines the experience of regulatory scientists and reviewers with backgrounds in drugs, biologics, and devices. In just a year, the Center has successfully sped revolutionary approvals for two CAR T therapies, tissue-agnostic Keytruda, and next-generation sequencing tumor profiling, among others.



Communication from the FDA suggests that the Agency intends to continue to support tissue-agnostic cancer drugs. The FDA held a public workshop on May 9, 2018, titled “Tissue-Agnostic Therapies in Oncology: Regulatory Considerations for Orphan Drug Designation,” to allow discussion of orphan drug products with tissue-agnostic capabilities. The Agency also recently published a Guidance on Genomic Sampling to explore biomarkers in clinical trials. In addition, in October 2018, the FDA finalized their guidance [“Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease”](#).

STIPULATIONS IN PDUFA VI

It is also interesting to note that PDUFA VI, the most recently passed Prescription Drug User Fee Act (approved in 2017 for the fiscal years 2018 to 2022), provides the FDA with new authority to require a pediatric investigation into an adult cancer drug as long as that drug is directed at a molecular target that is relevant to a pediatric cancer. This is likely a product of predicted future approval of other tissue-agnostic compounds. Because of these regulations, sponsors of biomarker-based treatments should hold discussions with the FDA early in development to determine if pediatric clinical trials will be required for efficacy, safety, and/or exposure.

Conclusions

With cancer continuing to be a significant public health concern, the pioneering approvals of tissue-agnostic cancer treatments, starting in 2017, provide hope that even more tissue-agnostic approvals in oncology will be forthcoming. This is an exciting time for targeted therapies and oncology as a whole, but these advancements also highlight important questions for researchers and regulatory authorities alike.

As industry, academia, government agencies, and their partners navigate the nuances and pitfalls of this burgeoning field, support from regulators appears to be strong. In the near future, it is likely that the FDA will continue to evaluate acceptable biomarkers and surrogate endpoints, explore uncertainties around tissue-agnostic orphan drug products, and bolster its support for dynamic tissue-agnostic clinical trials, such as MATCH or TAPUR trials, in order to foster even more groundbreaking advances in cancer medicine.

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