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Tumor-Agnostic Drug Development

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OVERVIEW

Therapies designed to target cancers that harbor specific molecular signatures have reshaped the landscape of oncologic drug development, and advances in next generation sequencing have led to an increase in the identification of these alterations across tumor types. Tumor-agnostic trial designs, such as the “basket trial,” have been developed as an approach to study the efficacy of these treatments and increase patient access, especially for patients whose tumors carry these alterations infrequently. We review key aspects of these genomically enriched trial strategies and their impact on drug development and approval.

The growth in the availability of comprehensive, clinical-grade molecular profiling platforms has led to a rise in the number of predictive biomarkers that have been incorporated into therapeutic paradigms for various cancers. These advances in sequencing have likewise led to an increase in the identification of novel, putative genomic and genetic biomarkers of therapeutic efficacy. Drug development paradigms have had to adapt to a number of challenges in this era, including the decreasing frequencies of these alterations and their identification across multiple tumor histologies.[1,2] Select clinical trials have thus evolved to incorporate a strong focus on tumor-agnostic drug development, a strategy for enriching for novel targets regardless of tumor site of origin.

Tumor-agnostic patient inclusion on clinical trials is not a novel concept. The classic phase I dose escalation design that attempts to establish a recommended phase II dose is a histology-independent endeavor that only subsequently selects for specific cancers in later-phase testing.[3–5] The conceptual advance with tumor-agnostic drug development is that trial designs have co-opted this strategy by specifically enrolling molecularly enriched patients to establish efficacy data in phase I expansion cohorts and phase II studies.[6,7] In general, these studies fulfill the following features that are typical of a “basket trial”: (1) cancers are enriched for one or more molecular alterations, (2) these alterations have a reasonable likelihood of predicting response to a particular therapy based on preclinical functional and/or computational modeling, and (3) these alterations are found across a variety of cancers.[8,9]

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The first generation of basket trials was characterized by the exploration of a validated biomarker in one histology and the exploration of the predictive nature of that biomarker in other cancers. The VE-BASKET trial is an example of such an approach, leveraging the known efficacy of BRAF-directed therapy in *BRAF*^{V600E}-mutant melanomas.[10] In this phase II, multicenter, international trial, 122 patients with seven different *BRAF*^{V600E}-mutant nonmelanoma cancers, including gastrointestinal, thoracic, head and neck, thyroid, and hematologic malignancies, were treated with vemurafenib. Noteworthy activity was achieved in non–small cell lung cancer and Erdheim–Chester disease (overall response rates of 43% and 42% respectively), resulting in the U.S. Food and Drug Administration (FDA) granting breakthrough designation for the latter. Moreover, substantial activity was noted in patients with cancers such as pleomorphic xanthoastrocytoma; these patients would otherwise have had no access to targeted therapy in a prospective, histology-specific trial. Other basket trials have since been launched, such as a phase II trial of trastuzumab emtansine for patients with ERBB2-altered cancers. The reported activity of trastuzumab emtansine in *ERBB2*-mutant lung cancers has since resulted in the inclusion of this drug in the NCCN guidelines for non–small cell lung cancer.[11]

Subsequent trial designs have grown in complexity.[12] Select master protocols, often large, multicenter trials, are composed of several basket cohorts as opposed to investigating a single marker-drug pair.[13] Examples of ongoing trials are the National Cancer Institute MATCH trial, the ASCO TAPUR trial, and the MyPathway trial.[14–16] The three trials are different in terms of the goals, design, and funding. The NCI sponsored NCI-MATCH trial consists of 25 separate subprotocols, with plans to add more within the coming months, and was designed to evaluate whether patients whose tumors harbor specific gene mutations will benefit from targeted therapies regardless of histology. The trial is designed to screen approximately 3,000 patients and enroll approximately 1,000 onto the protocol. As of July 2017, 5,963 tumor samples from patients from more than 1,000 clinical sites across the United States had been screened using next-generation sequencing at one of four central gene-sequencing laboratories. The tumor samples included a wide range of cancer types including, but not limited to, colorectal, lung and prostate cancer, sarcomas, lymphomas, and myeloma.[14–17]

Different from the NCI-MATCH, which studies both investigational and commercially available drugs, the ASCO TAPUR trial is designed to collect information on the anti-tumor activity and toxicity of commercially available anti-cancer therapies. It has 16 discrete arms and 19 different drugs (both targeted therapy and immunotherapy). The ASCO TAPUR protocol expects that routine clinical trial costs will be covered by the patient's insurance plan. In addition, some pharmaceutical companies also agree to provide marketed, targeted drugs, and additional resources to support the trial. [18]

Results from the ongoing My Pathway trial, a pharmaceutical company sponsored phase IIA trial enrolling patients with advanced refractory solid tumors harboring molecular alterations in EGFR, ERBB2, BRAF, or the Hedgehog pathway, have recently been published. Two hundred fifty-one patients with 35 distinct tumor types were matched to one of six distinct matched therapy arms. The four FDA-approved targeted therapies evaluated in MyPathway included trastuzumab plus pertuzumab, vemurafenib, erlotinib, and vismodegib. These

aforementioned targeted approaches produced meaningful responses in patients with various tumor types with 23% of patients from 14 histologic groups that had objective responses.[19] The 37 patients with colorectal cancer treated with trastuzumab plus pertuzumab had an ORR of 38% (95% CI, 23%–55%) and a median DOR of 11 months, which compare favorably to regorafenib, panitumumab, and trifluridine and tipiracil, drugs which were recently approved in refractory colorectal cancer. Although the MyPathway study demonstrated meaningful responses in different tumor types, it had several notable limitations. Drug toxicities were not were not reported in this study's first publication, and detailed genomic information was not available for all patients who enrolled in the trial.

In many prior clinical trials, context-specific responses to therapy were observed, highlighting that the activity of targeted therapy can be conditioned by the tumor site of origin. Interestingly, two drug development programs have shown that the response to therapy can also largely be histology independent. In a program spanning five different clinical trials,[20–26] the immune checkpoint inhibitor was found to be active in microstatelite instability (MSI)-high and mismatch-repair deficient (dMMR) tumors across various histologies.[27–29] These aforementioned trials enrolled a total of 149 patients with either MSI-high or dMMR solid malignancies from 15 different tumor histologies finding an objective response rate of 39.6% (48 partial responses and 11 complete responses) leading to the first FDA approval of a tumor agnostic treatment regimen based off a biomarker.[30] Likewise, the TRK inhibitor, larotrectinib, was evaluated in TRK fusion–positive cancers in a program spanning three different clinical trials including adult, adolescent, and pediatric patients (NCT02122913,[31] NCT02637687,[32] and NCT02576431[33]). An overall response rate of 78% (95% CI, 64%–89%) was observed. This activity was tumor agnostic, age agnostic, and molecularly agnostic (did not differ by upstream fusion partner).[34,35] The FDA granted breakthrough designation for larotrectinib in TRK fusion–positive cancers in 2017.

The next generation of these trials will must build on the successes of these programs and evolve to address unmet needs.[35,36] As the multicenter SHIVA trial illustrated, both drug and target must undergo careful vetting prior to initiating a complex trial.[37] The SHIVA trial was a large histologically agnostic trial which screened 716 tumors and identified 293 patients with targetable genetic aberrations involving hormone receptors or the PI3K/AKT/mTOR or RAF/MEK pathways. A total of 195 patients were randomly assigned to treatment (99 to molecularly targeted therapy and 96 onto physician choice therapy). The study was designed with a primary endpoint of progression-free survival (PFS) comparing those on matched targeted therapy and those on physician choice systemic treatment. The study ultimately concluded that there was no benefit in PFS between the experimental group (2.3 months) versus the control arm (2.0 months; HR 0.88, 95% CI, 0.65–1.19, p = .41) finding no benefit to the use of molecularly targeted agents outside of the approved indication. The SHIVA trial has been subject to critique since publication. The trial was lacking in a strong biologic rationale supporting that the genomic biomarker/hormone receptors selected were true actionable drivers that were well matched to potential targeted therapy efficacy. Another noteworthy concern comes from the fact that some of targeted approaches used on protocol were nonselective inhibitors and, as such, call into question the precision of the approach.[8] It also exemplified the importance of utilizing rigorously vetted, and scientifically sound, companion diagnostic tests, to annotate truly actionable findings.[38] The SHIVA study results

and design serves as a valuable educational experience for future tumor agnostic trial designs.

Study designs must be flexible and allow a response to data that emerge after trial initiation and, by adopting a "platform trial" strategy, allow marker-drug pairs to exit and be replaced potentially with new drugs or combination therapies.[39] For example, the VE-BASKET trial was amended to administer the combination of cetuximab and vemurafenib in $BRAF^{V600E}$-mutant colorectal cancers after low single-agent vemurafenib activity was observed in these tumors.[40] Finally, trials must be willing to adopt a permissive enrollment strategy that allows the careful clinical credentialing of the vast array of genomic alterations identified by comprehensive sequencing, many of which cannot be explored in vitro/in vivo or computationally in a reasonable timeframe.

As we continue to make strides in redefining oncologic diagnoses by incorporating genome-driven information, the importance of new trial designs will continue to grow. Tumor-agnostic drug development programs have taught us that openness to novel strategies may increase our ability to find subpopulations of patients who are likely to benefit from a given therapeutic approach.

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PRACTICAL APPLICATIONS

- In the field of clinical research, the advent of tumor-agnostic trials represents an important step toward discovering biomarkers of response, establishing the effects of context, and elucidating mechanisms of treatment resistance across a variety of cancer types.
- A number of basket trials or master protocols are currently ongoing, including the NCI MATCH and the ASCO TAPUR trials, in addition to trials sponsored by industry.
- Tumor-agnostic drug development strategies have led and are likely to continue to lead to the integration of genomically informed therapies in the clinic.