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Building a Phase 1 Cancer Research Program: Lessons Learned and Progress Made

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The advent of the Ochsner Precision Cancer Therapies Program (PCTP), a multidisciplinary partnership between Ochsner Cancer Institute (OCI) and the Translational Genomics Research Institute (TGen) of Phoenix, AZ, offers the Gulf South region access to the latest in early-phase cancer therapeutics, research, and advanced diagnostics. The program fills a healthcare delivery void by offering the only phase 1 clinical trials center dedicated to cancer between Houston, TX and Birmingham, AL.

EARLY-PHASE TRIALS

Experimental therapeutics (early drug development) programs have been in place in major academic centers for approximately 4 decades. In the early 1980s, only a handful of cancer drug development programs were located at the largest centers, all sponsored by the National Cancer Institute (NCI). But as the number of major cancer centers in the United States grew and cancer drug development became more interesting to industry, the number of experimental therapeutics programs increased.

Traditionally, early-phase clinical trials have been clinical havens of last resort for patients whose cancers had progressed on all known therapies. These traditional phase 1 trials focused exclusively on dose optimization and toxicities and were broadly aimed across cancer types in the hope of achieving a response or signal. In these early studies, no real effort was made to pair patients with best therapies, and not surprisingly, few patients responded to these experimental approaches. Response rates in older phase 1 trials ranged from 5%-7%.[1]

Early-phase cancer trials have evolved significantly during the last decade. By using next-generation precision medicine techniques based on molecular profiling and genomic analysis to match a patient's underlying biology (driving mutations, protein expression, gene amplifications, gene deletions, and epigenetic changes) to the most appropriate therapy, improved outcomes are achieved. Most current phase 1 trials actually function largely as phase 2 studies in that efficacy is an endpoint, and they are often combined as phase 1/2. Today, response rates closer to 20% with a disease control rate >30% are routinely observed for otherwise treatment-refractory patients. In an article published in 2017 in the *Journal of the National Comprehensive Cancer Network*, Razelle Kurzrock, a national leader in early-phase research, and her colleagues point out that many precision medicine therapies that pair specific drugs with patients whose tumors harbor very specific mutations can expect response rates of 70%-80%, and in the case of BCR/ABL translocations, response rates to targeted therapies approach 100%.[2]

CHALLENGES OF PHASE 1 RESEARCH

But improved outcomes come at a premium. The regulatory requirements to run phase 1 trials, the efforts to identify patients with the perfect needle-in-the-haystack mutation that matches an investigational targeted agent, the complexity of the studies, and the intense clinical monitoring required all make conducting early-phase trials difficult and expensive.

In addition, many other factors contribute to the complexity and challenges of early-phase trials compared to phase 3 studies:

- Unknowns: Early-phase trials, by their nature, are replete with unknowns. The proper drug dosage may not be defined, and toxicity profiles may be unknown or poorly understood.
- Intense monitoring and demanding protocols for investigators and patients: Early-phase trials require much more intense patient monitoring than later-phase studies. For example, some protocols require multiple electrocardiograms during treatment, challenging pharmacokinetic measurements such as hourly laboratory draws, inpatient hospital stays for 24 hours, baseline and follow-up tumor biopsies, multiple ancillary consults (ophthalmology, cardiology, pulmonary, etc), arduous imaging schedules, daily or very frequent patient follow-up (particularly at the study start), weekly visits, and multiple other time-consuming functions.
- Massive amounts of behind-the-scenes work: A large amount of regulatory paperwork is required to document early-phase studies, and intense training for investigators and study staff is also necessary. Frequent conference calls, in-person meetings, and out-of-town study-related conferences are critical. All of these tasks are time-consuming and require a great deal of resources and funding.
- Extensive and challenging enrollment (inclusion/exclusion) criteria: Often hundreds of patients must be screened to identify one eligible patient.
- Limited enrollment: The industry sponsor criteria may allow a site such as Ochsner to enroll only 2-3 patients. Therefore, the enormous amount of effort required to launch an early-phase study is not reflected in high enrollment numbers.

MEETING THE CHALLENGES

These challenges can best be met when a specifically assigned team of professionals work together in a highly integrated system. The ingredients necessary for a specialized program dedicated to effectively running multiple early-phase cancer studies include the following:

- Medical expertise
- Nursing expertise
- Regulatory affairs expertise (knowledge of federal, state, local, and organization requirements and guidelines)
- Specimen processing experience
- Dedicated experimental pharmacy
- Dedicated physical facilities
- Aligned administrative support and buy-in from senior executives
- Special equipment for specimen processing and laboratories
- Access to high-level interventional radiology (for biopsy specimen acquisition) and other specialty teams (such as specialized medical and surgical services)
- Financial team to handle budgets and contracts with an accelerated turnaround time
- Legal infrastructure with experts who understand the limits of intellectual property and have experience with research contracts
- Vast and deep networks of contacts, referring physicians, and industry partners

In building our own early cancer trials program, we identified these essential elements and put significant staff resources in place. Dedicated staff resources include a physician medical director and deputies, all with protected time to devote to the program; a highly engaged PhD administrative director with ample experience in the laboratory and in leadership; a full-time nurse supervisor with phase 1 trial experience from a leading cancer center; a scheduler/concierge to help with patient navigation; phase 1 research nurses; a phase 1 regulatory coordinator; a phase 1 data coordinator; a patient screener who focuses on identifying eligible patients from the medical record and other sources; and a laboratory technician. In addition, we are recruiting a research pharmacist and a dedicated Medicare coverage analyst/budget officer for the program. The general oncology research staff also helps staff the phase 1 unit and provides disease-specific expertise.

In terms of physical space (Figures 1-4), a dedicated laboratory allows for processing and shipping samples. A suite of offices off the main entrance atrium lobby of the Benson Cancer Center serves as the face or front door of the PCTP for patients, sponsors, and visitors. This area includes a welcoming reception area, a flexible space in which patients can meet with research nurses or sponsors and monitors can meet with research staff, and office space for the medical director. Currently, clinic visits are conducted in the third floor hematology and oncology clinic.

Expansion of the Benson Cancer Center is currently being planned, and a new large space for the PCTP will include offices, examination rooms, a laboratory, and a dedicated infusion center in one contiguous area—all devoted to early-phase trials.

In addition to the staff and space resources required to run an early-phase cancer research program, an immense amount of work is necessary to convince sponsors to bring their best new agents to a program. Often, small startup pharmaceutical companies may have only 1 or 2 experimental agents and may plan to open small, early-phase trials at only 1 or 2 sites. The success and continued existence of these companies may rest on the ability of the clinical sites to appropriately administer a trial and successfully recruit eligible patients. Most companies in this position can understandably be biased toward awarding their studies to large comprehensive cancer centers with programs that have been established for decades.

Figure 1. River view from the infusion department.

OPPORTUNITIES AND PARTNERSHIPS

Yet new, smaller programs like our PCTP can offer advantages. For example, large centers may not have the opportunity or interest to offer highly customizable and personal experiences to a small company. Large centers tend to be backlogged with competing studies, making even the most provocative studies from a small company a lower priority. Our center has made a great effort to distinguish itself by offering quick startup times for sponsors. Today, we can usually start a study in less than 45 days, an extremely swift startup time in the industry. This

Figure 2. Lobby within the infusion area.

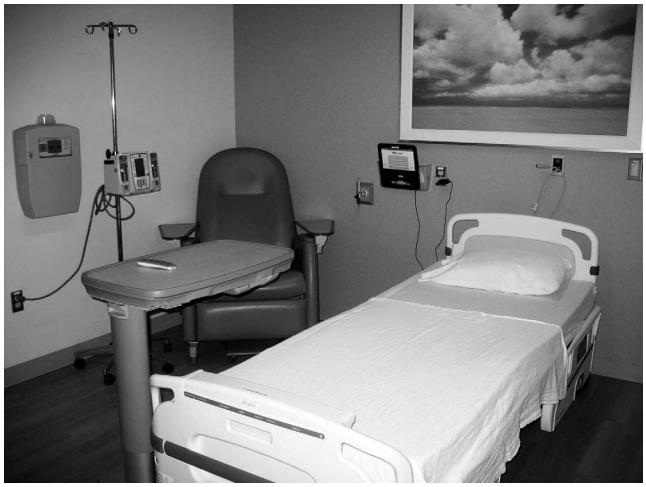

Figure 3. Private infusion room.

Figure 4. Precision Cancer Therapies Program laboratory.

achievement requires alignments and streamlined cooperation from multiple individuals and departments, including the regulatory team, physicians, the director, the Office of Grants Management and Finance, the Office of Human Research Protection and Institutional Review Board, and many others. By offering such service, we can often provide advantages compared to larger centers and attract more studies for our patients.

Ochsner's unique partnership with TGen has strengthened our program, allowing us to develop relationships with basic science investigators and companies that otherwise may have taken years to foster. Ochsner's position and reputation as a regional leader in cancer research has also given us leverage. OCI was formed in 1982 with 3 goals: (1) to obtain accreditation under the American College of Surgeons, (2) to establish a tumor registry, and (3) to coordinate the cancer clinical trials program that at the time principally involved the NCI Community Clinical Oncology Program (now replaced by the NCI Community Oncology Research Program [NCORP]) trials.[3] OCI is an active leader in the region and enrolls heavily in NCORP trials, but industry trials have played a much bigger role in the cancer center during the past few years, and investigator-initiated trials have increased as well.

TGen is a nonprofit biomedical research organization under the leadership of Dr Daniel Von Hoff, who serves as physician-in-chief. Dr Von Hoff is one of the world's most experienced early-phase clinical investigators and has led more than 500 phase 1 trials. TGen collaborates widely with the oncology community to increase cancer survival rates through research-enabled medicine and early-phase clinical trials. Dr Von Hoff works directly with his corollary at Ochsner, Dr Marc Matrana, medical director of the PCTP, to engage sponsors, select appropriate studies for our patient population, and deliver satisfactorily to our partners.

CONCLUSION

Obviously, building a phase 1 cancer program from the ground up requires a serious and prolonged financial commitment from the entire health system and an enormous amount of resources. The benefits of such a program will be limited initially, and the full impact may not be realized for many years. Even when the program is at full maturity, the benefits may not be entirely tangible on a spreadsheet. The greatest rewards of an early-phase research program are the direct benefits the research brings to patients—both now and in the future. The choice to develop and sustain a dedicated early-phase program, as Ochsner has chosen to do with the PCTP, is a choice for quality over quantity and a choice to provide tailored, individualized service to our patients. The PCTP further positions OCI as the region's leader in clinical research.

As Ochsner celebrates its 75th anniversary in 2017, the PCTP continues our legacy of innovative and collaborative cancer care. To learn more or view a list of current trials, visit www.ochsner.org/earlyphase.

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