ALMAC
Partnering to Advance Human Health

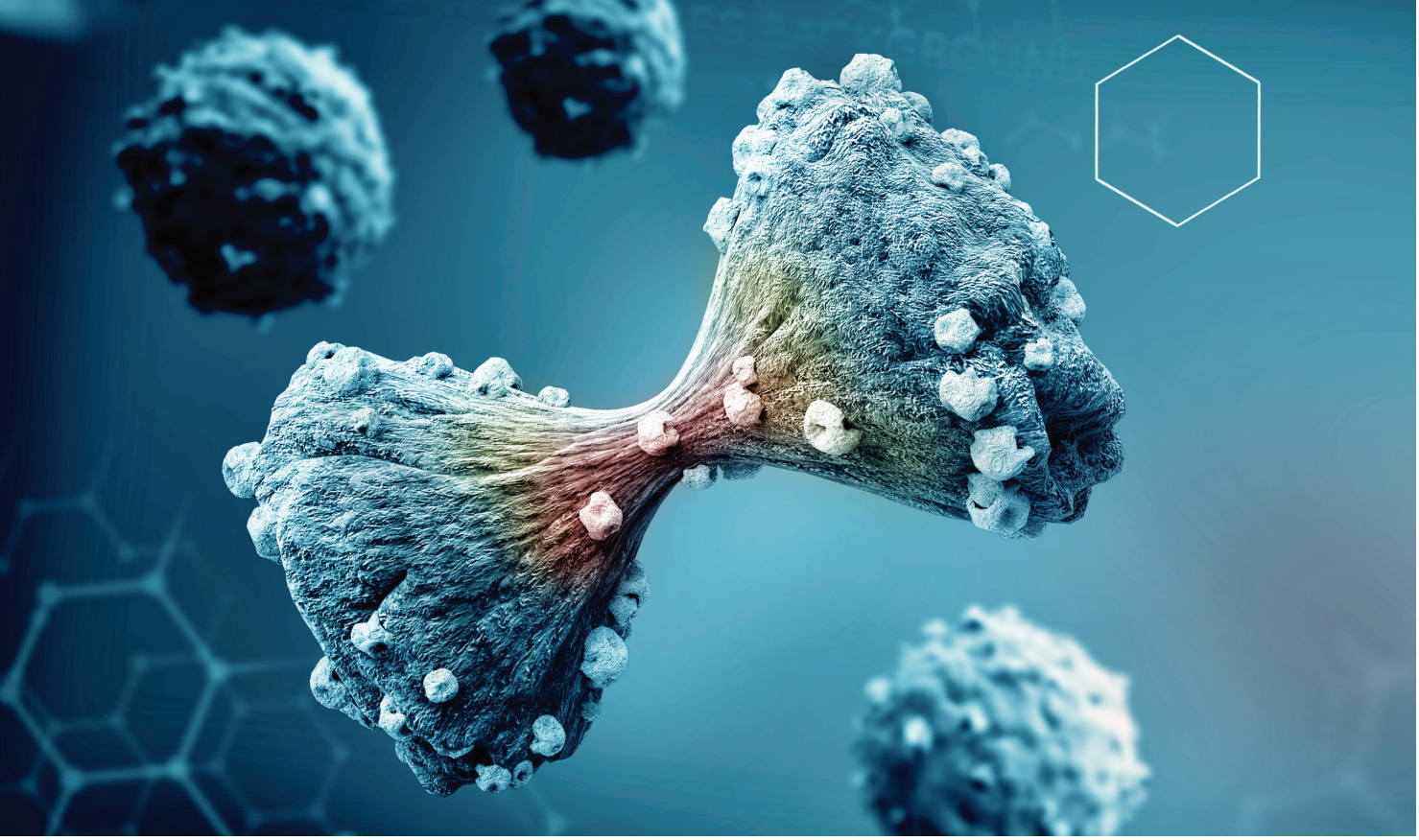
PANCREATIC CANCER ACTION NETWORK®

Berry Consultants
Statistical Innovation

Case study

Accelerating Outcomes with a Pancreatic Cancer Adaptive Platform

Mastering the master protocol through collaboration and IRT expertise



Prevalence of Pancreatic Cancer

Pancreatic cancer is a top cause of cancer death in the United States, where the incidence and death rates are on the rise. Each year, more than 60,000 Americans are diagnosed with pancreatic cancer and the five-year survival rate is as low as 10 percent.[1] Unfortunately, there is a shortage of effective treatments for Pancreatic cancer. Identifying effective treatments has posed to be a challenge, as the failure rate in Phase 3 PDAC clinical trials is over 95%.[2,3] Since these clinical trial results have been disappointing, many pharmaceutical sponsors have been rethinking their investment in the therapeutic area, which is a potentially devastating situation for patients.

PanCan's Precision Promise:

Pancreatic Cancer Action Network® (PanCan®)[4] is an organization dedicated to fighting pancreatic cancer in a comprehensive way. In response to the negative clinical trials results, PanCan has launched Precision Promise℠,[5] which is a Platform Trial (Master Protocol) aimed at identifying effective and ineffective treatments quicker than traditional clinical trials. Traditional clinical trials are usually focused on evaluating one investigational treatment within a single disease subtype, whereas Precision Promise is a Platform Adaptive Trial[6], which is a perpetual trial that evaluates multiple treatments in various subtypes of Pancreatic cancer. *(See Table 1 for feature comparison of traditional clinical trials vs. platform adaptive trials).*

The goal of this Complex Innovative Design is to improve patient outcomes at an accelerated pace while de-risking entry into the space for pharmaceutical sponsors. PanCan takes on the role of the Sponsor within Precision Promise and allows investigational treatments to be included from various pharmaceutical companies. With PanCan taking on the Sponsor role, this offsets the effort and costs that would be required by pharmaceutical companies to launch traditional clinical trials of their own. Since PanCan is a patient advocacy organization, they serve as a neutral party, allowing pharmaceutical companies to allow their investigational treatments to be studied alongside of others, while maintaining their confidentiality.

Collaboration is Key:

Since this Platform Adaptive Trial is perpetual, it takes a lot of planning, and collaboration to be successful. In their Precision Promise Platform Adaptive Trial, PanCan brings together leading experts, stakeholders, researchers, clinicians, and industry / pancreatic cancer thought leaders. There are multiple parties that partnered with PanCan to make this vision a reality, for instance:

- Covance by Labcorp to manage the trial as the Contract Research Organization (CRO).
- Berry Consultants, world experts in the Bayesian approach to design and execute the Bayesian Response-Adaptive Randomization algorithm.
- Almac Clinical Technologies to design, implement and maintain the Interactive Response Technology (IRT) system.

This Case Study will outline the complexities involved with implementing this Complex Innovative Design, and how through effective collaboration, the IRT was set up for success. This Case will additionally feature insights from an interview with Regina Deck, Vice President, Clinical Trial Operations at PanCan.

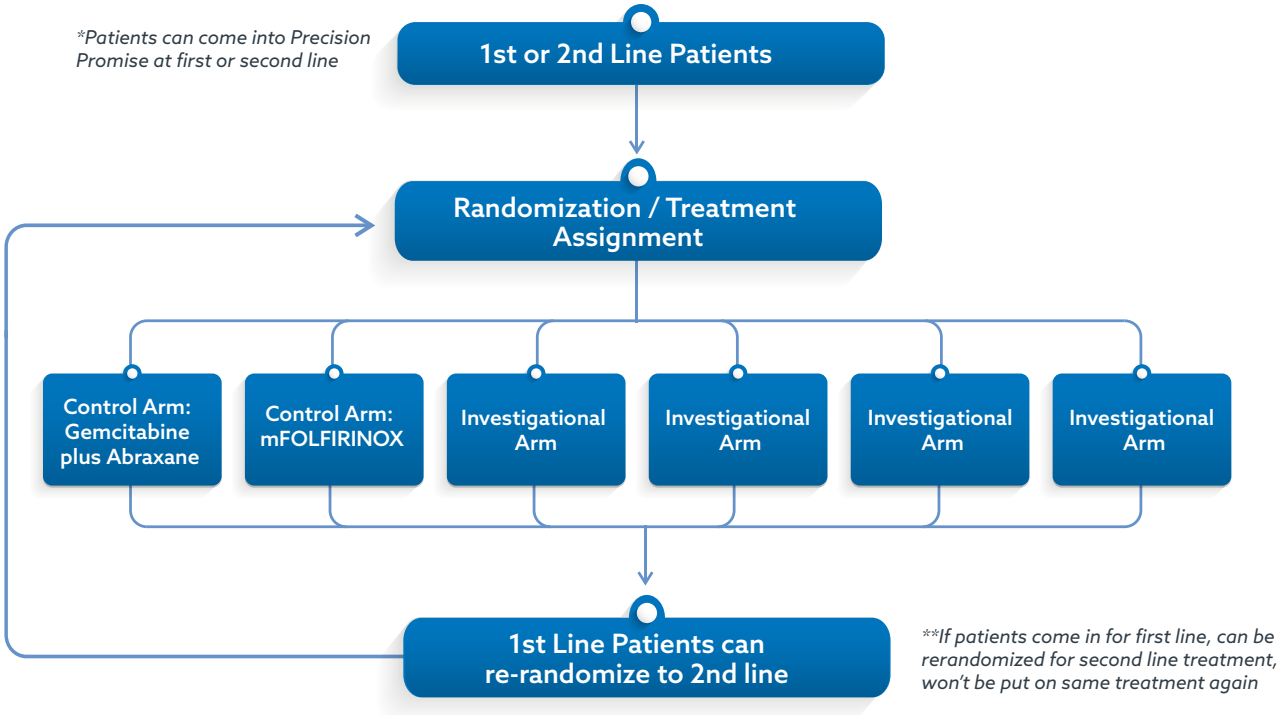
The Challenge:
Make the Complex Vision a Reality

Precision Promise has characteristics that make it rather Complex in the clinical trial world.

1. It is a Platform Trial:

As mentioned above, rather than studying a single treatment in a single patient population, this trial evaluates multiple treatments in multiple patient populations called subtypes. It perpetually allows ineffective investigational treatments to be dropped and new investigational treatments to be introduced throughout the trial within the subtypes. Many of the treatments that will eventually be evaluated are unknown when the trial starts. The trial begins with two main subtypes, first line and second line disease. Additional subtypes may be introduced if treatment(s) enter the trial that target specific biomarker(s). Since there is no prescribed end to the trial, the IRT system had to be built to support it well into the future, even though it was challenging to predict what may be needed. How many unknown treatments to include in the IRT? How many unknown subtypes to include? (See Figure 1 for an illustration of the trial design).

Precision Promise: Breaking Down the Design



Supportive care and testing for all patients

2. Precision Promise uses a Bayesian Response-Adaptive algorithm for Randomization.

For Bayesian Response-Adaptive Randomization (BRAR), treatment assignment probabilities are updated continuously based on accumulating patient response data. Regina explains that this methodology allows PanCan to "learn as we go". For instance, if a treatment is performing well for a subtype, the randomization probabilities can be adjusted in favor of that treatment for that subtype. This allows the trial to accumulate patients into the trial faster on treatments that have the best potential, and to identify effective and ineffective treatments quicker.

The BRAR algorithm is designed and executed by Berry Consultants (world experts in the Bayesian approach), who provide updated treatment assignment probabilities to the IRT. Thus, data integrations between the Berry Consultants and the IRT were required for automatic utilization of the updated treatment assignment probabilities for randomization for each subtype.

3. The Master Protocol required the IRT to consider various scenarios for treatment eligibility.

Many treatments in the trial will be combination therapies. There are standard of care treatments that patients typically receive, referred to as their backbone of therapy. Regina explains that "every investigational treatment that is coming into Precision Promise will be in combination with the backbones." When patients enroll in Precision Promise, they may be naïve to any treatments (first line subtype). Otherwise, patients may have previously received a backbone therapy, or an investigational treatment in another clinical trial (second line subtype). Additionally, patients who are randomized as first line can be re-randomized as second line if they discontinued their initially assigned treatment for toxicity or intolerability. Second line patients who are being randomized or re-randomized are not eligible to be assigned to their first line treatment or backbone. Therefore, the IRT and Randomization algorithm was required to prevent assignment to any previous treatment. To account for the possible previous treatment combinations, Regina conveyed that "the number was mindboggling".

4. New treatments opened are staggered across sites.

Each time a new Treatment is introduced within this study, a site must obtain Institutional Review Boards (IRB) approval before opening it. Thus, it is possible for each site to differ in the set of treatments that are opened. The Randomization algorithm and IRT was required to account for preventing randomization to any Treatments at sites without IRB approval.

The Almac Solution:
Partnership, Collaboration, and Seamless Operations

To ensure that the Almac's IXRS IRT system for the trial would be built to accommodate the design complexity, the Almac team facilitated regular collaborations across the key stakeholders. Almac set up weekly meetings between its own team (comprised of system designers, developers, testers, biostatisticians, and project managers) and representatives of PanCan, Covance by Labcorp, and Berry Consultants. Almac brought discipline and structure to the collaboration, with establishing roles, responsibilities, and decision-making authority across the groups.

During the requirements-gathering phase of the IRT, it was important for the group to determine what was realistic to include in the IRT in the short, mid, and long term. What would be necessary in the initial build vs what would make sense to address in future amendments? It is not realistic to account for an infinite number of scenarios; therefore, it is important to determine the amount that would be reasonable and still sufficient. For instance, the number of possible previous treatment combinations to "was mindboggling." Through discussion and evaluation on which scenarios would be most likely through least likely, the team determined that the set of possible scenarios could be narrowed from several thousands to 792 permutations.

When asked if she anticipated all the complexities to consider, Regina explained the value of working with the experienced Almac team, "We anticipated perhaps 75 percent of the difficulty, but there was another 25 percent or so that arose that we hadn't thought to consider. We're not coders or system builders. Almac knew what questions to ask and what issues to discuss."

Almac's biostatisticians and system developers worked especially closely with Berry Consultants to ensure that IRT was programmed to accept and implement the changing randomization probabilities in a controlled manner. The IRT receives the data transfer from the Berry Consultants, and the system automatically updates the randomization probabilities. When new a treatment enters the trial, the IRT has smart logic to know which sites are eligible for which treatment sets based on their IRB approval.

Early Success:
Seamless Introduction of Investigational Treatments

At the time of writing this Case Study, the Precision Promise Trial is still in its early days, where Regina describes success as "having a platform and the infrastructure built to support the addition of more investigational treatments." Rapid onboarding new treatments into the study is a leading indicator for the long-term goal of improving patient outcomes. Specifically, with respect to the IRT, Regina reports that the system's acceptance of new treatments has been seamless: "Everything gets approved, we go live, and BOOM, now we have this next treatment in."

Almac is honored to play a role in Precision Promise, which is such an important study for the Pancreatic Cancer patient community. The PanCan mission inspired Almac to establish an in-house Adaptive Design Center of Excellence, which is team of experts from cross-functional areas (such as Biostatistics, Software Development, Testing, Project Management, IXRS Design, Data Integrations, Quality Assurance, and Medication Management) who is committed to making Complex Innovative Designs operationally feasible and ensure their success across all phases of the study. This team is focused on ensuring optimal maintenance for Precision Promise, and continuously evaluate best practices for all types of complex innovative designs (adaptive designs, Master Protocols, Platform, Umbrella, Basket, etc.).

Reflecting on Almac's role in helping PanCan prepare to launch the trial, Regina added, "I have nothing but positive things to say. The Almac team has been phenomenal. They coordinated all the meetings and ensured we stayed on track with the project. They've also been very patient and kind in explaining technical details to us. They have been great partners."

This Case Study has illustrated how early and frequent collaboration amongst key players drives the successful implementation of the IRT for Complex Innovative Designs. Remember, it is impossible and unrealistic to account for infinite amount of adaptations. In planning the appropriate amount of adaptations for initial IRT, the following should be considered: What parameters are needed initially? What parameters are not needed? What parameters are not needed initially but may be needed in the future? What are the initial, mid, and long-term goals? The objective of the initial planning is to design the IRT to be able to seamlessly get to the next phase. Collaboration is essential in getting the answers that will drive these decisions, as proven with the experience of implementing Precision Promise.

Table 1. Feature Comparison of Traditional Clinical Trials vs. Platform Adaptive Trials

Feature	Traditional Clinical Trial	Adaptive Platform Trial
Treatment Inclusion	Single Investigational Treatments	Multiple Investigational Treatments
Population Inclusion	Single Patient Population	Multiple Patient Populations
Duration	Fixed Duration	Long-term / Perpetual
Treatment Characteristics	Pre-specified / Fixed	Pre-specified + Unknown (Adaptive)
Ineffective Treatment(s)	Stop Entire Trial	Drop Ineffective Treatment(s) / Trial Continues
Randomization Approach	Fixed Randomization Methodology	Adaptive / Flexible Randomization
Treatment Ratio	Fixed Ratio	Updates to Randomization Ratio(s) or Probabilities
Sponsor Involvement	Single Sponsor / Agency / Institution	Single or Multiple Sponsors / Agencies / Institutions

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