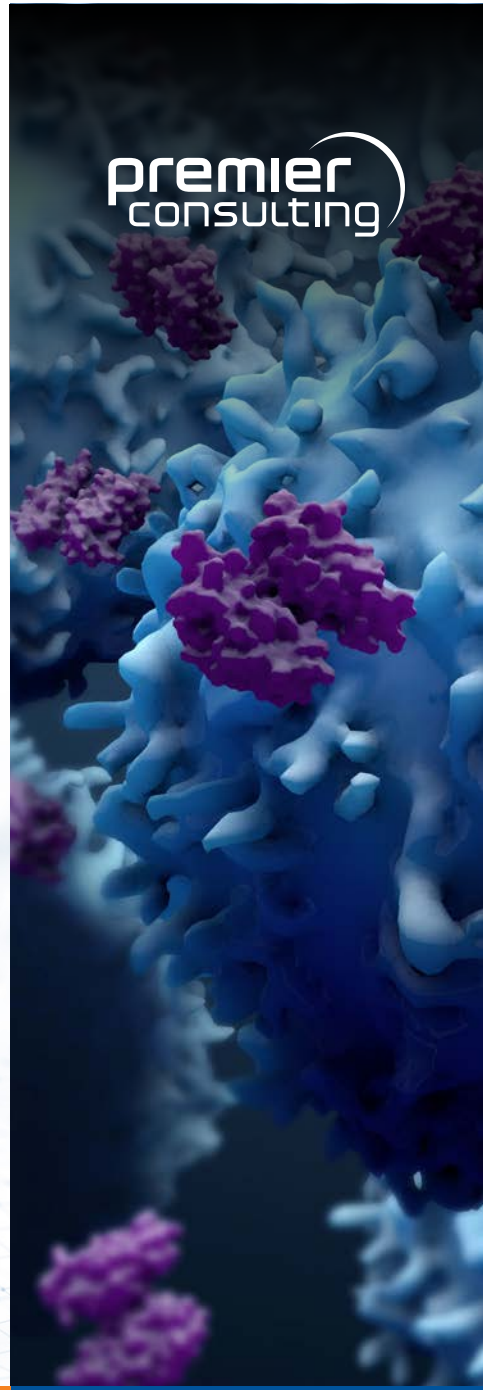
Premier Consulting Insight 200

Multidisciplinary Team Accelerates Immuno-Oncology Approval



Background

Acute myeloid leukemia (AML) is a life-threatening cancer which develops in the bone marrow, often quickly spreading into the blood and sometimes other parts of the body. Estimates show that nearly 20,000 new cases will be diagnosed in 2020. Based on the surveillance, epidemiology, and end results (SEER) data from 2010 to 2016, the 5-year relative survival rate for patients diagnosed with AML is 28.7 percent.

An emerging immuno-oncology company sought to bring better treatment to AML patients through its targeted monoclonal antibody therapy.

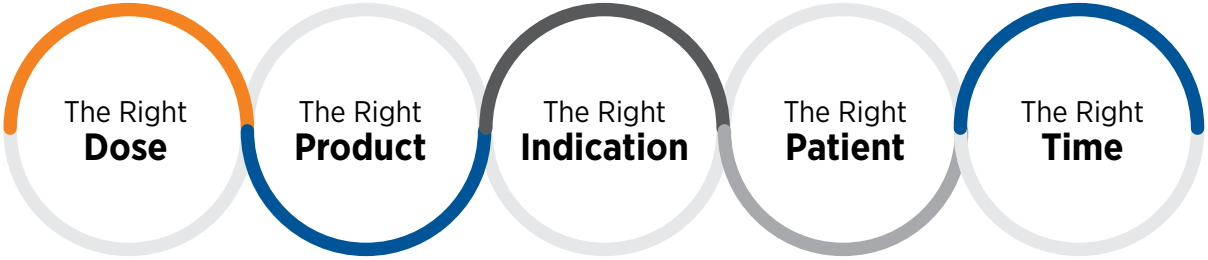
Challenge

Based on the available product data, the sponsor believed the program would be eligible for accelerated approval by the U.S. Food and Drug Administration (FDA). Before moving forward with a biologics license application (BLA), the company sought a collaborative partner to review the proposed strategy, validate key assumptions, and identify development and regulatory risks. In particular, this partner would:

- Review the available product data for development and marketing suitability in the United States
- Review the regulatory acceptability of the implemented and planned chemistry, manufacturing, and controls (CMC); nonclinical; clinical pharmacology; and clinical programs
- Review all product data with an eye toward the intended BLA filing
- Offer regulatory insights and recommend strategies for successful accelerated approval

What's needed to get it right?

Therapies like this molecularly targeted monoclonal antibodies are aimed at personalized treatment and require a patient-centered approach to development. Critical to success was finding a partner with deep expertise in oncology programs and accelerated approval pathways and with multidisciplinary experts able to evaluate fully the proposed strategy, while keeping in mind the Five Rs:



Solution

Based on our targeted therapeutic and regulatory expertise and our multidisciplinary teams, the sponsor selected Premier Consulting to partner on the program. Using a patient-centered drug development (PCDD) approach, Premier Consulting identified several components critical to the investigation:

- Identifying the target patient population
- Defining the current standard of care (SOC)
- Selecting endpoints – surrogate vs. survival
- Carrying out appropriate study design – Single arm vs. comparator; monotherapy vs. combination therapy vs. combination therapy
- Conducting an appropriate benefit/risk assessment
- Mapping the manufacturing timeline of clinical trial material

Key findings

The Premier Consulting in-house experts reviewed individually and then as a whole the regulatory, CMC, nonclinical, clinical pharmacology, and clinical aspects of the program to produce a due diligence report with an integrated strategy and a program assessment.

Regulatory

Regulatory strategists reviewed past regulatory strategies to identify "lessons learned" from similar AML programs. In addition, Premier Consulting evaluated expedited programs options based on the FDA guidance titled Expedited Programs for Serious Conditions – Drugs and Biologics. This guidance canvasses Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review programs. All four expedited programs represent efforts to address an unmet medical need in the treatment of a serious condition.

Sufficient data was available to support a Fast Track Designation. However, for a product to be eligible for Breakthrough Therapy Designation, preliminary clinical evidence must demonstrate a substantial improvement over available therapy with a sufficient number of patients. This requirement for a "sufficient number of patients" had not been met at the time of Premier's due diligence.

CMC

CMC experts evaluated key base parameters likely to impact product development, adversely or positively:

- Extended product characterization
- Assay sufficiency
- Comparability between clinical lots
- Appropriate development
- Master cell bank and working cell bank stock materials
- Recovery options in case of cell line failure
- Production (and master) cell line clonality

Premier Consulting developed key summaries for each area and laid out a timeline of what could be accomplished in the following six to eight months.

Nonclinical

The Premier Consulting nonclinical evaluation focused on determining whether the available nonclinical data supported accelerated approval via expedited programs and a BLA submission within the following year. Premier discovered sufficient data in a human xenograft model of AML to be considered reasonably supportive of a Fast Track Designation by the FDA.

Overall, the nonclinical package was comprehensive with respect to the stage of development for an antibody for treating cancer, and it was in alignment with relevant FDA and ICH guidances (ICH S6(R1) and S9). Premier identified two outstanding studies that would likely be necessary for BLA submission: an embryo-fetal toxicity study and a likely three-month toxicity study.

The due diligence report provided both a 360-degree interdisciplinary review and efficient strategies for an accelerated BLA submission. For the sponsor, this report provided a way to anticipate and reduce development and regulatory risk while controlling expenses.

Clinical Pharmacology

Premier Consulting's clinical pharmacology assessment focused on key pharmacokinetic (PK) and pharmacodynamic (PD) data to address optimal dosing for the patient:

- Mechanism of action
- Bioanalytical method validation
- Antigen sink
- Exposure-response relations
- Dosage regimen
- Immunogenicity
- PK/PD parameters in patients
- QT prolongation

Premier Research provided specific PK/PD areas and studies to efficiently collect data during the development program.

Clinical

The PCDD approach coupled with Premier Consulting's extensive regulatory experience and insight brought to light several critical trial elements needed for the sponsor's clinical program:

- Treating the newly diagnosed and relapsed or refractory patients as different intended patient populations
- Enrolling appropriate patients by identifying robust inclusion/exclusion criteria, regardless of age: The FDA advocates defining patients that are "unfit" for intensive chemotherapy and excluding only those who would not benefit from any type of treatment.
- Selecting the SOC rather than comparing against historical control patient populations: The FDA suggests that sponsors confirm with clinicians that the control arm is acceptable and reviews the SOC for safety when clinical protocols are submitted to the IND.
- Achieving optimal dose: Due to the limited efficacy signal in a few patients, the sponsor considered a dose increase. Premier noted that the benefit/risk would need to be reassessed for accelerated approval.

Benefit to Sponsor and Patient

The due diligence report provided both a 360-degree interdisciplinary review and efficient strategies for an accelerated BLA submission. For the sponsor, this report provided a way to anticipate and reduce development and regulatory risk while controlling expenses. Specifically, the sponsor appreciated several key deliverables:

- A CMC plan that was mapped out by rate-limiting development steps and tasks that were prioritized for a rapid ramp-up phase for commercial product manufacture
- Nonclinical findings that were supportive of a Fast Track Designation
- Key clinical pharmacology, clinical, and regulatory strategies that optimized Phase 2 and Phase 3 study design and increased the likelihood of demonstrating patient efficacy in the clinical setting

These contributions were instrumental in setting the sponsor's development program on the right path to bring better treatment to AML patients. This path ultimately led to its acquisition by a leading biopharmaceutical company that intends to use the program as the anchor for its immuno-oncology efforts.

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Takeaway

Every development program must be customized based on real-world patient experience and optimized to enhance patient outcomes and boost commercial success. Premier Consulting has the breadth and depth of interdisciplinary expertise to partner with product sponsors and achieve success, while de-risking patient and program failures through the PCDD approach. Thus, the right development planning leads to the right program execution, and the right product gets into the right patient's hands.

Project Description

An emerging immuno-oncology company sought to bring better treatment to AML patients through targeted monoclonal antibody therapy. The Premier Consulting experts were chosen to review and define the FDA accelerated approval strategy for a BLA license.

Therapeutic Area

Oncology

Geographic Scope

United States

Outcome

The due diligence report provided both a 360-degree interdisciplinary review and efficient strategies for an accelerated BLA submission.

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