POSITION PAPER

CATALYST ONCOLOGY

Shaping the Future of Hematologic Oncology:
Clinical Innovation and Trial Execution Strategies

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Hematologic malignancies, commonly referred to as blood cancers, represent some of the most complex and aggressive diseases in oncology. These cancers originate in the bone marrow and lymphatic system, disrupting normal blood cell production and immune function. With over 1.34 million new cases globally in 2022 and significant mortality despite therapeutic advances, the need for specialized expertise in trial design and execution is critical.

Blood cancer types and treatments

Blood cancers comprise five main types that encompass diverse subtypes, each with unique biology and clinical behavior.

Leukemia

- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia (AML)
- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)

Lymphoma

- Hodgkin lymphoma
- Non-Hodgkin lymphoma:
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Burkitt lymphoma

Multiple myeloma

- Plasma cell myeloma

Myelodysplastic syndromes (MDS)

- Refractory anemia
- Refractory cytopenia
- MDS with excess blasts

Myeloproliferative neoplasms (MPNs)

- Polycythemia vera
- Essential thrombocythemia
- Primary myelofibrosis

Treatment depends on the specific type and stage at time of diagnosis and often involves a combination of strategies. Common approaches include chemotherapy to kill or inhibit cancer cell growth, targeted therapies that block key cellular pathways and immunotherapies such as monoclonal antibodies and checkpoint inhibitors. Stem cell transplantation—either autologous or allogeneic—is frequently used after high-dose chemotherapy, while CAR-T cell therapy employs genetically engineered T-cells to attack cancer cells. Radiation therapy is typically reserved for localized disease or pre-transplant conditioning. Supportive care, including blood transfusions, antibiotics, steroids and symptom management, is essential throughout treatment. Treatment plans often combine these strategies. For example:

- **Acute leukemia**: Intensive chemotherapy followed by possible stem cell transplant.
- **Lymphoma**: Chemo-immunotherapy (e.g., CHOP + rituximab) with or without radiation.
- **Multiple myeloma**: Targeted drugs (proteasome inhibitors, immunomodulators) plus autologous stem cell transplant.

An added complexity is that hematologic malignancies are not static, and they can evolve over time. Two key mechanisms that drive this transformation are:

Clonal evolution - Under treatment pressure, cancer cells accumulate new mutations, creating resistant subclones. This can lead to disease progression e.g., chronic leukemia evolving to an acute form and explains why relapse often looks different from the original disease.

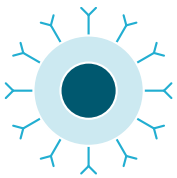
Lineage switch - Rare but clinically significant, this occurs when a leukemia changes its cell lineage—for example, B-ALL transforming into AML. Often seen after targeted therapies like CAR-T, lineage switch

complicates treatment because the new leukemia type may require a completely different regimen and is linked to poor prognosis.

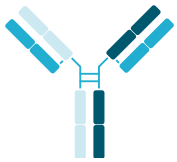
Understanding these dynamics is critical for trial design, biomarker strategies and next-generation therapies. As precision medicine advances, anticipating disease evolution will be key to improving outcomes.

Advances in treatment – beyond chemotherapy

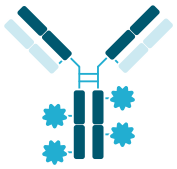
There are a number of key emerging therapies that are reshaping treatment paradigms. These therapies aim to reduce the reliance on traditional chemotherapy, improve durable responses and minimize toxicity.



- **CAR-T cell therapy** has transformed treatment for hematologic cancers, delivering deep and durable responses in relapsed/refractory settings and moving earlier in the treatment course. Emerging innovations include dual-target CAR-T and combination strategies with checkpoint inhibitors or cytokine therapy to overcome T-cell exhaustion and antigen escape.



- **Bispecific antibodies (bsAbs)** are emerging as a major therapeutic class, enabling immune cell engagement for tumor destruction. Agents like blinatumomab have shown high minimal residual disease negativity in ALL, and newer bsAbs are achieving response rates of 60% in multiple myeloma. Examples include Anti-CD20/CD3 for lymphomas and Anti-BCMA/CD3 for multiple myeloma.



- **Antibody-drug conjugates (ADCs)** and next-generation immunotherapies are increasingly integrated into hematologic oncology pipelines, complementing traditional chemotherapy and stem cell transplant approaches. Examples include Polatuzumab vedotin (anti-CD79b) for diffuse large B-cell lymphoma and Belantamab mafodotin (anti-BCMA) for multiple myeloma.

Navigating operational and scientific challenges

Running clinical trials in hematologic malignancies involves unique operational challenges that go beyond those seen in solid tumor studies. Here are the key complexities:

Rapid disease progression and urgent enrollment

- Many blood cancers (e.g., acute leukemias) progress quickly and require immediate treatment, leaving very short windows for screening and enrollment—sometimes ≤2 weeks.
- Sponsors must enable fast site activation, expedited regulatory approvals and flexible logistics to avoid losing eligible patients.

Complex response criteria and endpoints

- Trials often require specialized assessments like minimal residual disease (MRD), bone marrow biopsies and hematologic toxicity grading.
- Multiple guideline frameworks (Cheson Lugano, IMWG) demand custom site and CRA training and centralized review to ensure consistency.

High logistical complexity

- Advanced therapies (CAR-T, bispecific antibodies stem cell transplants) involve chain-of-identity compliance, cryopreservation and global shipping of patient cells.
- Coordinating vendors for cell processing and drug supply adds layers of complexity.

Intensive safety monitoring

- Hematologic oncology trials have high AE/SAE rates due to immunosuppression, infections and cytokine release syndrome.
- Requires real-time data capture, specialized toxicity grading (CTCAE) and rapid intervention protocols to treat life threatening symptoms.

Global recruitment for rare subtypes

- Diseases like mantle cell lymphoma or myelofibrosis are rare, requiring broad geographic reach and partnerships with academic centers and patient advocacy groups.
- Enrollment is further complicated by stringent biomarker-driven eligibility in precision medicine trials.

Frequent protocol amendments

- Adaptive designs and evolving standards of care lead to multiple amendments, increasing regulatory and operational burden.
- Each amendment can delay timelines and require retraining across sites.

Operational excellence in practice

Catalyst Oncology brings deep therapeutic insight and operational excellence, having supported numerous hematological cancer trials to date. Catalyst has demonstrated success in overcoming these challenges, including delivering:

- **Global Phase 3 AML trial**: Managed both Phase 2 and Phase 3 programs, achieving preliminary EMA approval and meeting aggressive FPI timelines.
- **Cell therapy programs**: Delivered complex logistics for autologous and allogeneic CAR-T trials, ensuring chain-of-identity compliance.
- **Rescue of high-risk studies**: Transitioned technology platforms mid-study and delivered regulatory-ready data under compressed timelines.

Lessons learned and best practices

Through our experience managing hematological cancer studies, we've developed a deep understanding of the critical success factors needed to operationalize these trials effectively.

- Speed and adaptability are critical for trials in rapidly progressing diseases.
- Data-driven site selection and early engagement with academic centers improve enrollment in rare subtypes.
- Customized CRA training on disease-specific endpoints ensures protocol fidelity and high-quality data.
- Integrated vendor and logistics management are essential for cell therapy programs and complex drug modalities.

Accelerating breakthroughs in hematologic oncology

Hematological cancer trials are among the most complex in oncology, demanding specialized expertise, global coordination and unwavering commitment to quality. Catalyst has repeatedly demonstrated success in this space. With experience with over 200 sites across 18 countries, Catalyst offers biotech sponsors a global infrastructure and a seasoned team capable of executing even the most challenging hematological cancer studies.

Ready to accelerate your hematologic oncology program?

Let's talk about how Catalyst Oncology can help you navigate complexity, optimize trial execution and bring transformative therapies to patients faster. Contact us now.

Louise Scott, PhD, Senior Director Oncology Drug Development. Lou leverages more than 25 years of scientific/clinical research experience primarily focused on oncology. She started her industry experience working as a cell biologist with a PhD in molecular medicine and an undergraduate degree in Biochemistry. Lou completed a post-doctoral position at The Christie (Paterson Cancer Research Centre), Manchester UK investigating the mechanisms of metastasis in Prostate Cancer before moving over to Clinical Research. She has worked across several roles within Clinical Operations. Prior to joining Catalyst, Lou was Director of Clinical Services for Aptus Clinical, an oncology focused UK-based CRO, where she headed up the Clinical Operations and Biometrics departments.