

White Paper

ACUTE MYELOID LEUKEMIA

New approaches to solving complex clinical development challenges

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EXECUTIVE SUMMARY

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. The incidence rate is rising each year. Key factors include the aging of the population and the fact that AML can be linked to chemotherapy for other cancers.

The conventional treatment approach for a younger patient with newly diagnosed AML is induction chemotherapy followed by consolidation or intensification treatment. For older patients, there is no standard of care. There is also currently no standard of care for relapsed AML. Younger patients can re-attempt induction chemotherapy regimens or go into a clinical trial. Due to high unmet patient needs, multiple forms of novel therapy are currently in clinical trials.

In patients diagnosed with AML, molecular biomarkers are used for prognosis and, as a companion diagnostic for approved targeted therapies, to predict drug response. Well-known chromosomal abnormalities may be identified in approximately 50% of all AML patients. FLT3 alterations were first identified as the most common oncogenic driver as well as a strong poor prognostic factor for long-term survival in AML. These have since been the leading drug target in this indication.

Leveraging the IQVIA CORE™ (Figure 1), IQVIA applies a unique combination of data, machine learning and domain expertise to produce more predictable results and to offer innovation to the AML community. This approach has four elements: domain expertise, transformative technology, unparalleled data and advanced analytics.

CORE-enabled clinical development brings real-world and commercial data insights into the clinical development and planning process for novel drugs targeting AML, facilitating identification of potential alternative paths to shorten timelines, decrease costs and maximize asset value.

Authored by an IQVIA team with expertise across translational medicine, clinical trials and data science, this paper provides a comprehensive review of AML disease pathology and biomarkers, and highlights how the CORE-enabled approach can support the successful delivery of trials in this indication.

Due to high unmet patient needs, multiple forms of novel AML therapy are currently in clinical trials.

SECTION 1 – MEDICAL OVERVIEW

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow and/or other tissues. AML develops as the consequence of a series of genetic changes in a hematopoietic precursor cell. The leukemic cells proliferate in the marrow and interfere with production of normal blood cells, causing weakness, infection, bleeding and other symptoms and complications. In general, AML is rapidly lethal unless treated with intensive chemotherapy and/or targeted therapies together with supportive care. A disease overview is included in Figure 2.

While recurrent acquired genetic abnormalities have been found in leukemia blasts, the direct causes of AML are unknown for most patients.¹

DISEASE CLASSIFICATION

The World Health Organization (WHO) classification has established a blast cutoff of 20% to distinguish AML from myelodysplastic syndrome (MDS), except for

Figure 1: The IQVIA CORE™ powers clinical development

Domain Expertise



Institutional knowledge and domain expertise across diseases, geographies and scientific methods

Transformative Technology



Leading technologies to provide real-time access to operations-critical information



Unparalleled Data



One of the world's largest curated healthcare data sources with innovative privacy protections

Advanced Analytics



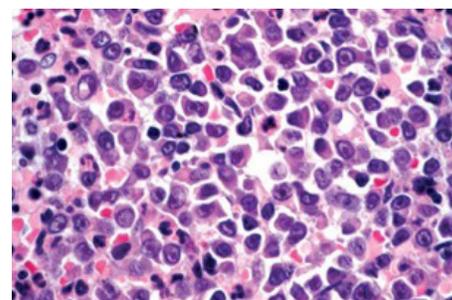
Faster, more precise decision-making powered by data science, designed exclusively for healthcare

Figure 2: Acute Myeloid Leukemia Disease Overview



AML DESCRIPTION

- Myeloid precursor cells have a **lower ability to differentiate**, and this results in **accumulation of immature cells**²
- Defined by the presence of **≥20% myeloblasts** in peripheral blood and bone marrow²
- **~4.2 per 100,000** new cases in the U.S. each year (orphan disease status)³
- Median age at diagnosis: **68 years old**³
- Estimated **21,380 new cases** in 2017⁴



BURDEN OF ILLNESS

- Estimated **10,590 deaths** in 2017, making up **1.8%** of all cancer deaths, despite making up **1.3%** of all new cancer cases^{2,3}
- 5-year overall survival rate for AML is **26.9%**²
- **FLT3+ AML** is the most common high-risk AML subtype (approximately 30% of the cases)⁵
 - » The estimated **5-year overall survival** of FLT3+ AML is **15%**, which is much lower than that for FLT3- AML patients (56%)²
 - » The **5-year relapse rate** for FLT3+ AML is about **50% higher** than FLT3- AML (64% vs. 44%)²

certain genetic abnormalities that are characteristic or pathognomonic for AML, which require < 20% blasts in the marrow or peripheral blood, i.e., t(8;21), inv(16), t(15;17).¹ WHO classification also recognizes a variety of categories that reflect the clinical and biologic heterogeneity of the disease, including AML with certain genetic abnormalities, AML with MDS-related changes, AML related to previous chemotherapy or radiation, and AML not otherwise specified.⁶

In 2008, the WHO revised the diagnostic and response criteria for AML to include additional recurrent genetic abnormalities created by reciprocal translocations/inversions, and a new provisional category for some of the molecular markers that have been found to have a prognostic impact.⁶

Patients with recurrent cytogenetic aberrations (~45%) may be grouped into favorable-, intermediate-, and poor-risk categories.¹ For example, the European Leukemia Net (ELN) classification incorporates NPM1 and CEBPA mutations and FLT3 internal tandem duplication (ITD) in an integrated cytogenetic-molecular classification that separates AML patients into four genetic groups: favorable, intermediate I, intermediate II, and adverse.^{7,8} Mutations in the Fms-related tyrosine kinase 3 gene (FLT3), which encodes a member of the class III receptor tyrosine kinase family, often lead to aberrant tyrosine kinase activation and rapid blast proliferation. FLT3-ITD mutations occur in 25% to 35% of AML patients, and are linked to increased risk of relapse and mortality.⁹ Among patients with FLT3-ITD, median overall survival (OS) from time of diagnosis ranged from six to 12 months.¹⁰

EPIDEMIOLOGY

AML is the most common acute leukemia in adults. Median age of AML at diagnosis is approximately 68 years, and incidence increases as age advances, from 1.3 per 100 000 population in patients less than 65 years old, to 12.2 cases per 100 000 population in those over 65 years. Incidence is slightly more frequent in male than females.^{11,12}

Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly, who account for most new cases, remains poor. AML is a highly lethal disease where survival is age-dependent and survival rates are extremely poor for the elderly: up to 70% of patients 65 years or older will die of their disease within one year of diagnosis.¹³ Limited progress has been made towards new therapies.

Limited progress has been made towards new AML therapies.

Five-year survival has consistently increased each decade from the 1970s. In patients younger than 60 years old, five-year survival has increased from 3% (pre-1970s) to 38% (2000-2009), with a concurrent increase in median survival from 2.7 months (pre-1970s) to 22.8 months (2000-2009). Patients over 60 years old have also seen improvements in their survival but at a more moderate pace.¹⁴

Incidence rate is rising each year because of the aging of the population, and as more people are treated successfully for other cancers, with a subset of survivors developing therapy-related myeloid neoplasms.¹⁵

AML incidence is forecast to increase in the next 10 years, based on industry data. The adjusted diagnosed incidence of cases of AML may increase from 103,000 cases in 2018 to 114,811 in 2028, with a potential growth rate of 1.09% during the forecast period (Figure 3).

CURRENT TREATMENT APPROACHES

Figure 4 provides an overview of AML treatment guidelines. The conventional approach for a patient with newly diagnosed AML is induction chemotherapy followed by consolidation or intensification treatment.

Figure 3: Projected AML incidence from 2018 to 2028 (numbers of new diagnosed cases)

YEAR	U.S.	UK	JAPAN	WORLDWIDE
2018	19,520	3,072	2,397	103,000
2019	19,581	3,076	2,391	105,842
2020	19,736	3,091	2,385	106,905
2021	19,889	3,106	2,378	107,949
2022	20,042	3,120	2,370	108,976
2023	20,194	3,134	2,362	109,988
2024	20,344	3,147	2,353	110,985
2025	20,493	3,160	2,344	111,965
2026	20,640	3,173	2,335	112,929
2027	20,785	3,185	2,325	113,878
2028	20,927	3,196	2,315	114,811
GROWTH RATE	0.70%	0.40%	-0.35%	1.09%

Note: Projections account for the increase in population size over time
 Source: Clarivate Analytics Incidence and Prevalence Database, extracted May 2018

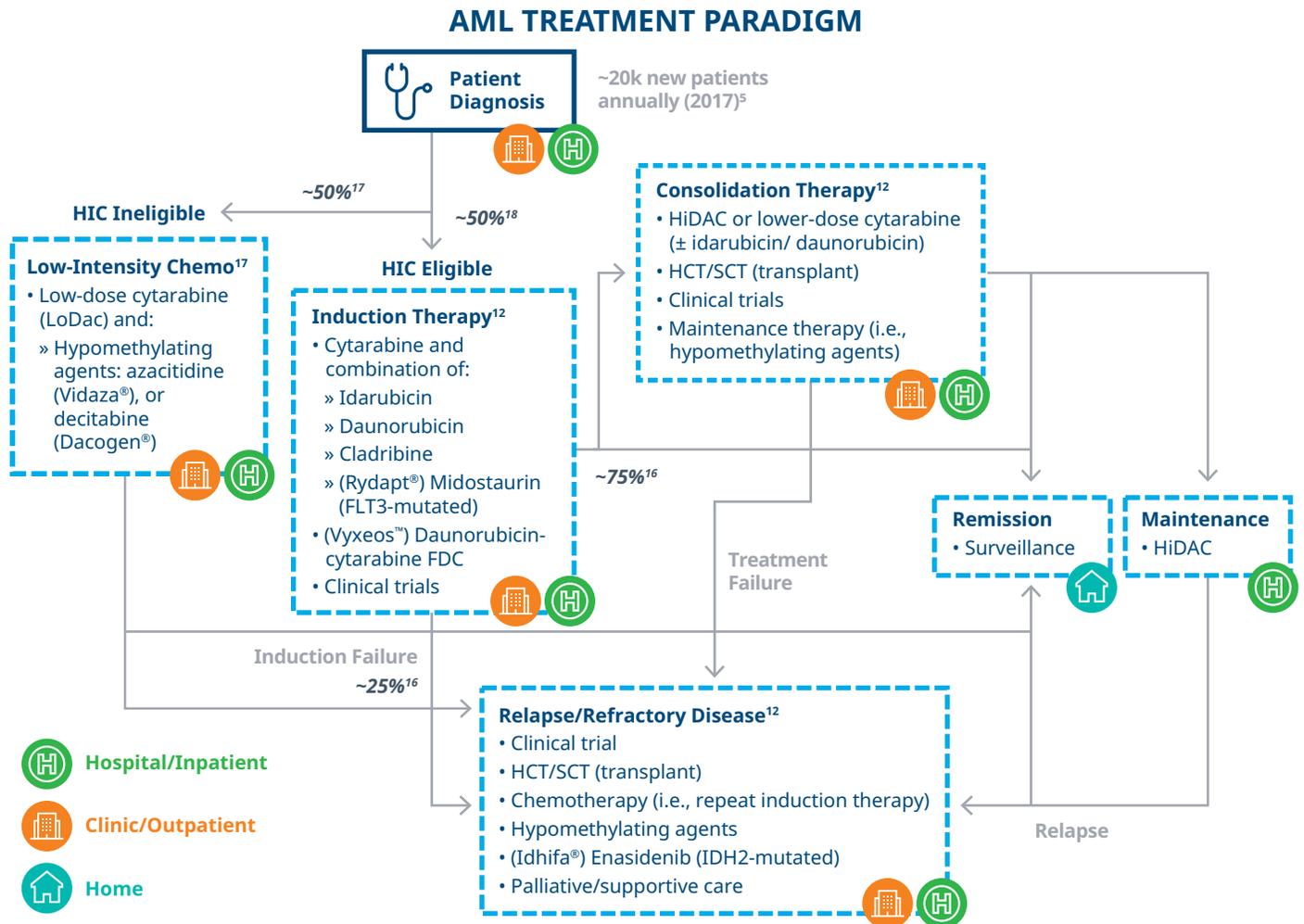
The goal in remission-induction chemotherapy is to reduce the number of leukemic cells in the blood, bone marrow and extramedullary sites to undetectable levels and to restore normal hematopoiesis. Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent, more intensive treatments during consolidation to achieve durable disease control. However, at the time of remission, lower levels of leukemic cells are likely to persist and can lead to disease relapse if additional treatment with high-dose chemotherapy and/or allogeneic hematopoietic stem cell transplantation (allo-HSCT) is not administered. Patients who do not receive post-remission therapy may relapse, usually within six to nine months.

The response to treatment and overall survival of patients with AML is heterogeneous. Most improvements in recent years have been in the treatment of patients with acute

promyelocytic leukemia (APL), which serves as a paradigm for understanding how the biology of the disease can inform treatment. Using all-trans retinoic acid (ATRA) based induction regimens followed by consolidation with regimens containing either ATRA with anthracyclines, or cytarabine with anthracyclines, more than 80% of patients with APL can be cured of their disease.¹⁹

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Figure 4: Overview of AML treatment guidelines, 2017



Recommendations for induction chemotherapy in patients with AML consider age 60 years as a therapeutic divergence point. This is based on the higher prevalence of unfavorable cytogenetics and antecedent myelodysplasia, along with a higher incidence of multidrug resistance in patients older than 60 years, and an increased frequency of concomitant medical conditions that affect the patient’s ability to tolerate intensive treatment.²⁰

The basic treatment for patients younger than age 60 years – remission induction with “7+3” chemotherapy with

cytarabine and an anthracycline – has changed little in the past four decades. Complete response (CR) rates for patients who are 50 years or younger have consistently been in the range of 60% to 70% in most large cooperative group trials of infusional cytarabine and anthracycline.

A large randomized Phase III Eastern Cooperative Oncology Group (ECOG) study reported a significant increase in CR rate (71% vs. 57%) and median OS (24 vs. 16 months) using daunorubicin 90 mg/m² daily for three days (n = 327) versus 45 mg/m² daily for three days (n = 330) in patients with previously untreated AML younger than

60 years.²⁰ Patients between 50 and 60 years of age with FLT3-ITD or nucleophosmin (NPM1) also benefitted from high-dose daunorubicin.²² Later it was established that a dose of 60 mg/m² daunorubicin is as effective as 90 mg/m² and has a lower toxicity.²²

Emerging data have demonstrated improved survival for patients with newly diagnosed FLT3-positive AML when midostaurin (Rydapt®) is added to standard chemotherapy as part of frontline treatment. This led to its breakthrough designation and approval by the FDA in 2017. In the CALGB 10603 (RATIFY) alliance trial, patients aged 18 to 60 years, with newly diagnosed FLT3-positive AML (internal tandem duplication, ITD or second tyrosine kinase domain, TKD) were randomized (n = 717) to receive standard cytarabine and daunorubicin therapy with placebo or midostaurin (50 mg, twice daily on days eight to 22). Patients who received midostaurin with standard induction and consolidation therapy experienced significant improvement in OS compared with those on the placebo arm.²⁴

Emerging data have demonstrated improved survival for patients with newly diagnosed FLT3-positive AML when midostaurin (Rydapt®) is added to standard chemotherapy as part of frontline treatment.

High-dose cytarabine-based (HiDAC) regimens have also been successful in achieving high CR rates, but it remains to be fully determined whether this approach yields better results than standard-dose cytarabine without worsening toxicity.

Consolidation therapy generally consists of additional rounds of chemotherapy with HiDAC, 7+3, or another

chemotherapy regimen. The goal of consolidation therapy is to prevent relapse. Ideally most patients will proceed to a bone marrow transplant.

Patients with unfavorable karyotypes, with antecedent hematologic disease or treatment-related AML are considered poor-risk. Although all patients with AML are best managed within the context of an appropriate clinical trial, it is particularly important that this poor-risk group of patients should be entered into a clinical trial (incorporating either chemotherapy or novel agents), if available, given that only 40% to 50% of these patients experience a CR with standard induction therapy. In addition, human leukocyte antigen (HLA) testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity conditioning and allogeneic hematopoietic cell transplantation (HCT) from a matched sibling or an alternative donor, which constitutes the best option for long-term disease control. An allogeneic HCT may be effective in 25% to 30% of patients with induction failure.²⁵

Patients who are unfit to tolerate aggressive chemotherapy generally receive low intensity chemotherapy with hypomethylating agents or low dose cytarabine as induction therapy. There are two hypomethylating agents, Vidaza® and Dacogen®, both approved for MDS. While not approved for AML, they are both compendia-listed and are commonly used in the unfit population in the U.S. and are approved for AML in Europe. In clinical studies, Vidaza® has shown a significant survival benefit in elderly AML patients. Dacogen® has shown a trend toward improved survival.

NOVEL THERAPIES IN DEVELOPMENT

Combined cytarabine and anthracycline (7+3) remains the best available induction therapy for fit patients, although it can be improved with an additional agent.

Unfit patients currently are treated with lower intensity chemo regimens that produce much lower CR rates than 7+3. A viable strategy to improve these CR rates is to combine the lower

intensity regimens with novel agents. The goal is to improve CR rates with minimal or acceptable increases in toxicity.

There is currently no standard of care for relapsed AML. Patients can re-attempt induction chemotherapy regimens or go into a clinical trial. Drug development in this area is quite active.

Multiple forms of novel therapy are currently in clinical trials. A summary is provided in Table 1. These novel therapies include improved chemotherapeutic agents, targeted molecular inhibitors, cell cycle regulators, pro-apoptotic agents, epigenetic modifiers and metabolic

therapies. Immunotherapies are also being evaluated in the form of vaccines; naked, conjugated and bispecific monoclonal antibodies; cell-based therapy; and immune checkpoint inhibitors.²⁶

FLT3-ITD, the most common gene mutation, leads to uncontrolled hematopoietic proliferation and poor clinical outcomes. Multiple drugs targeting FLT3 are being developed for patients with FLT3 mutations.

Newly approved in November 2018, Xospata® (gilteritinib) is the first drug approved by the FDA for use alone in treating adults with AML and an FLT3 mutation

Table 1: Summary of novel therapies in clinical development

<p>PROTEIN KINASE INHIBITORS</p>	<ul style="list-style-type: none"> • FLT3 inhibitors (quizartinib, gilteritinib, crenolanib, MEN1703) • KIT inhibitors • PI3K/AKT/mTOR inhibitors • Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CHK1, WEE1 and MPS1 inhibitors • SRC and HCK inhibitors 	<p>THERAPIES TARGETING ONCOGENIC PROTEINS</p>	<ul style="list-style-type: none"> • Fusion transcripts targeting • EVI1 targeting • NPM1 targeting • Hedgehog inhibitors (glasdegib)
<p>EPIGENETIC MODULATORS</p>	<ul style="list-style-type: none"> • DNA methyltransferase inhibitors (SGI-110/guadecitabine) • Histone deacetylase (HDAC) inhibitors • IDH1 and IDH2 inhibitors • DOT 1L inhibitors • BET-bromodomain inhibitors 	<p>ANTIBODIES AND IMMUNOTHERAPIES</p>	<ul style="list-style-type: none"> • Monoclonal antibodies against CD33, CD123, CD44, CD47, CD38, CLEC 12A • Immunoconjugates (GO, SGN33A) • Bispecific T-cell engagers (BiTEs) and dual affinity re-targeting molecules (DARTs) • Chimeric antigen-receptor (CAR) T-cells or genetically engineered T-cell receptor (TCR) T-cells • Immune checkpoint inhibitors (PD-1, PD-L1, CTLA-4) • antiKIR antibody (lirilumab) • Humanized defucosylated monoclonal IgG1 antibody (MEN1112) • Vaccines (WT1)
<p>CHEMOTHERAPEUTIC AGENTS</p>	<ul style="list-style-type: none"> • CPX-351 • Vosaroxin • Nucleoside Analogs 	<p>THERAPIES TARGETING AML ENVIRONMENT</p>	<ul style="list-style-type: none"> • CXCR4 and CXCL12 antagonists (plerixaflor) • Anti-angiogenic therapies
<p>MITOCHONDRIAL INHIBITORS</p>	<ul style="list-style-type: none"> • Bcl-2, Bcl-xL and Mcl-1 inhibitors • Caseinolytic protease inhibitors 		

who have relapsed or who don't respond to initial treatment.²⁷ Approval was based on results from the ADMIRAL trial and included an expanded indication for a companion diagnostic – the FLT3 mutation assay from Invivoscribe Technologies, now approved for use with Xospata® as well as Rydapt®.

Another rapidly developing therapeutic area is that of epigenetic modulators. Guadecitabine (SGI-110) is a second-generation DNA methyltransferase inhibitor, currently in Phase III development. Isocitrate dehydrogenase (IDH) enzymes mutations have been reported in approximately 30% of *de novo* AML.²⁸ FDA has approved enasidenib (Idhifa®) as a treatment for patients with relapsed or refractory IDH2-mutated acute myeloid leukemia based on findings of a Phase I/II study.²⁹ A safety study of AG-120 or AG-221 in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH1 and/or IDH2 mutation is ongoing. Other IDH inhibitors (AG120 -Ivosidenib, BAY1436032, FT-2102) are undergoing Phase I testing.

CPX-351 is a liposomal formulation of cytarabine and daunorubicin designed to deliver synergistic drug ratios to leukemia cells. Based on a recent Phase III trial, it was recently approved by FDA for first-line therapy for patients with therapy-related AML and AML with myelodysplasia-related changes.³⁰

Venclexta® (venetoclax/ABT-199), a highly selective oral inhibitor of the anti-apoptotic protein BCL2 approved for treatment resistant 17p-deleted chronic lymphocytic leukemia, recently received accelerated approval by FDA for treatment of newly diagnosed AML in subjects above 75 years old in combination with hypomethylating agents or low-dose cytarabine.³¹ High response rates and a safety profile were observed in a Phase II study of this combination, and is being further evaluated.

Targeted immunotherapeutic modalities are currently under evaluation. A variety of therapeutic antibodies directed against AML antigenic targets (CD33, CD123,

CLEC12A) served as the main focus for monoclonal antibody studies. Gemtuzumab ozogamicin (GO), a CD33 directed antibody linked to the antibiotic cytotoxin calicheamicin, was approved by FDA in 2000 but withdrawn from the U.S. market in 2010 due to an increased rate of fatal adverse events. There are conflicting data about the use of GO for older patients with AML. Three Phase III randomized trials evaluated the efficacy and safety of adding the anti-CD33 antibody-drug conjugate GO to induction therapy with daunorubicin and cytarabine in older patients with previously untreated AML.

Other anti-CD33 antibodies include lintuzumab and SGN-CD33A. CSL362 is an anti-CD123 antibody found to be safe and well tolerated as maintenance therapy in a Phase I study of AML patients with CR and high risk of relapse.

A Phase I study is currently ongoing to test MEN1112, a novel humanized defucosylated monoclonal IgG1 antibody in relapsed/refractory AML. Bispecific T-cell engagers (BiTE) or dual affinity re-targeting molecules (DART) as well as engineered chimeric antigen receptor (CAR) T cells targeting the CD33 and CD123 antigens are currently in early clinical trials.³²

Several studies have looked at vaccination with different leukemia-associated antigens including WT1, PR1, proteinase 3 and RHAMM, with the goal of establishing an immunological response capable of eradicating malignant cells. These studies have generally demonstrated safety and immune correlates but no clinical efficacy.

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In addition to AML clonal characteristics, the bone marrow microenvironment has also shown to affect therapeutic efficacy in patients with AML. Overexpression of CXCR4, a chemokine receptor, has been correlated with poor survival and its inhibition is the focus of several studies.

SECTION 2 – BIOMARKER CONSIDERATIONS

Molecular biomarkers are used to predict patient prognosis and to predict drug response as a companion diagnostic for approved targeted therapies in patients diagnosed with AML. Well-known chromosomal abnormalities may be identified in approximately 50% of all AML patients.³¹ These prognostic cytogenetic biomarkers may be linked to specific alterations in genes known to be associated with oncogenic development and may reflect patient disease lineage and characteristics. Similar to other hematological oncology indications, AML is a heterogeneous disease and multiple studies have proposed classifications or subgroups defined by genomic analysis. However, the disease remains a complex combination of multiple lineages, generally with a very poor prognosis and numerous genetic alterations and potentially useful biomarkers for clinical research.

BIOMARKERS IN PROGNOSIS

A relatively large number of molecular biomarkers or genetic alterations including karyotypes, chromosomal translocations, inversions and deletions, and gene mutations have been described to be prognostic in AML in the NCCN and European LeukemiaNet AML guidelines.²⁶ A number of the cytogenetic results including, inv(16), t(16;16), t(8;21) and t(15;17), normal cytogenetics and t(9;11) and complex cytogenetics, deletion 5q, 7q, 11q23-non t(9;11), inv(3), t(3;3), t(6;9) and t(9;22) are recommended to determine a favorable, intermediate or poor patient risk status, respectively.¹ Specific genetic abnormalities or combinations of genetic profiles, including NPM1, CEBPA, KIT, FLT3, TP53, RNX1 and

ASXL1 mutations, are also recommended for patient risk assessment.²⁶ Molecular test results may be influenced by cut-off values, choice of probes or other reagents as well as test methods. The test setting in primary or secondary AML or stage of disease may also impact the value and the use of the results. As in other hematological oncology indications, the availability of molecular prognostic tests such as these do not guarantee that the results will actually be used and impact patients, given the complexity of the biomarkers and test results. Attempts to consolidate molecular and clinical information into a single prognostic index have been pursued but not implemented.³⁴ Alternatively, approaches that take advantage of technical advances, such as the development of next-generation sequencing, have been used to identify novel risk profiles³⁵ that may be more feasible and accurate.

BIOMARKERS IN DRUG RESPONSE

FLT3 alterations were first identified as the most common oncogenic driver as well as a strong poor prognostic factor for long-term in AML and have since been the leading drug target in the indication. The 2017 approval of midostaurin (Rydapt®) for patients with FLT3 mutations along with Invivoscribe's genetic test brought FLT3 testing to the forefront in patient testing and care. Upfront testing for FLT3 ITD (internal tandem duplications) and TKD (tyrosine kinase domain) mutations is recommended for all AML patients. However, test rates may be less than 60% at community sites but could be improved by better access to multi-gene panel tests.^{36,37}

Strategies to most effectively target these patients, including approaches to address acquired resistance, continue to be developed, and may require further evolution of the tests including detection of the ITD versus TKD mutations and allelic burden. A small number of AML patients that are BCR-ABL positive have been identified and may be effectively treated with current therapies.³⁸

Additional AML oncogenes targeted in current clinical research that may result in new companion diagnostics include IDH1, IDH2, KIT and CD33.⁹ Finally, studies

have also identified a number of genetic alterations, including RUNX1, NPM1 and DNMT3A mutations, which may be predictive of survival following standard of care treatments and could be incorporated into patient testing protocols in the future.³⁹

THE FUTURE OF BIOMARKERS IN AML

The AML biomarker landscape will surely continue to change but has already firmly established the importance of molecular testing for prognosis and drug response. The significance of further molecular classification has yet to be determined. Knowledge of sites and investigators conducting prognostic and targeted molecular or genomic testing will be crucial for studies directed at

subpopulations defined by these biomarkers. Experience with these populations will also be important for a better understanding of clinical unmet need for relevant clinical research and improved patient care.

SECTION 3 – CLINICAL DEVELOPMENT FOR AML

The AML clinical trial space is highly competitive and complex, requiring a high degree of specificity given the heterogeneity of this indication and the current increase in the number of oncology clinical trials. Looking specifically at the FLT3 mutated patients, the challenge is that only approximately 30% of the overall AML patient population is eligible.

IQVIA's use of data and analytics brings real-world and commercial insights into the clinical development and planning process, facilitating identification of potential alternative paths which shorten timelines, decrease costs and maximize asset value.

Figure 5 provides a comparison of the conventional, experience-driven approach vs. the evidence-driven approach. In the experience-driven approach, sites are selected using the traditional site selection methodology, based on prior experience with investigators. In contrast, the evidence-driven approach uses a data-driven site selection strategy that leverages multiple healthcare data sources to identify the target patient population and the physicians who treat these patients.

NOVEL APPROACH TO FINDING PATIENTS

IQVIA's new approach allows sponsors to specifically target the patient population relevant to their protocol. In the U.S., this is achieved through analysis of medical claims, prescription and physician reference data to identify physicians who both treat AML patients and run FLT3 genetic testing. Identification of sites and investigators with AML patients tested for FLT3 is illustrated in Figure 6.

CLINICAL TRIAL BENCHMARKS

When planning for the development of a novel compound, a critical aspect to consider is the expected recruitment rate as this drives the trials and the overall clinical development plan lengths.

Key clinical trial benchmarks (per Citeline database extract, May 2018) are:

- Phase III median recruitment rate is around 0.18-0.20 patient per site per month and does not appear to vary by patient population
- Duration of enrollment is higher in the "untreated" population (43 months) vs. the relapsed/refractory population (28 months)
- Recruitment durations below 24 months are infrequent
- Phase III studies targeting "untreated AML patients" have larger sample size and experience slightly longer overall enrollment durations than studies targeting "not-untreated" AML

Figure 5: Comparison of traditional approach vs. novel approach to enrollment

Experience-driven approach



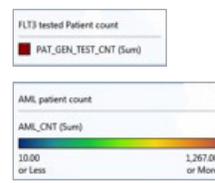
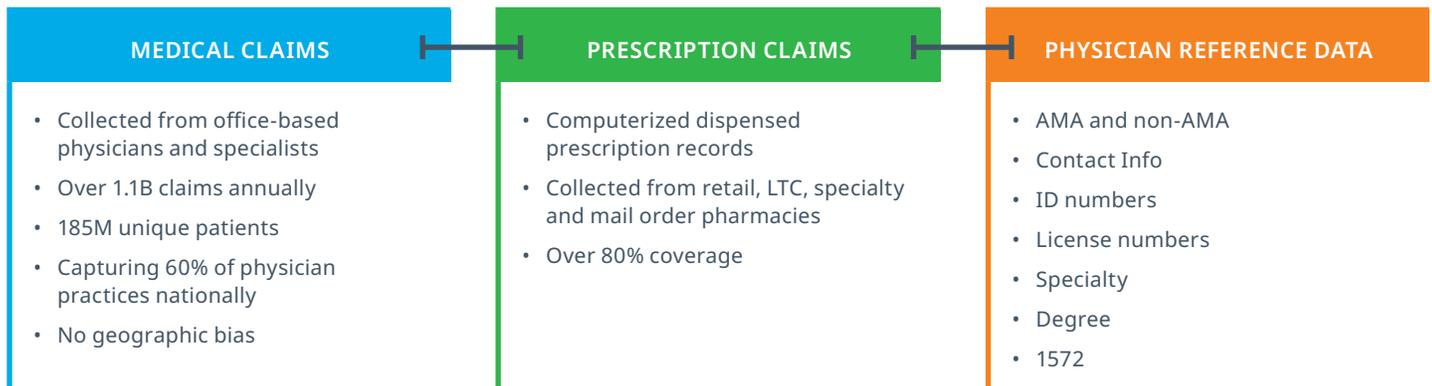
- Long timeframe to treatment
- Some non-enrolling sites
- Frequent screen failures

Evidence-driven approach



- Short timeframe to treatment
- Limited non-enrolling sites
- Zero screen failures

Figure 6: Linking data sources to identify AML patients tested for FLT3 mutation in the U.S.



Sites with >10 Relapsed AML patients and FLT3 genetic testing count

(Red bars, height of bars represents patient count)

An additional challenge of a trial targeting the FLT3 mutation is that it might target either FLT3 naïve or FLT3 pre-treated patients. In the U.S., IQVIA's unique ability to cross link physicians' reference data with medical claims and prescription data enables us to identify physicians who treat AML patients and run FLT3 genetic testing with Rydapt® prescription. Investigators with high AML patient and FLT3 testing numbers with comparatively low Rydapt® prescription numbers would be targeted as potential investigators to recruit naïve patients.

ENHANCED SITE STRATEGIES FOR GLOBAL TRIALS

Similarly, CORE-enabled approaches to development have enabled identification of potential AML patients in several other countries including the UK, France and Germany (Figure 7).

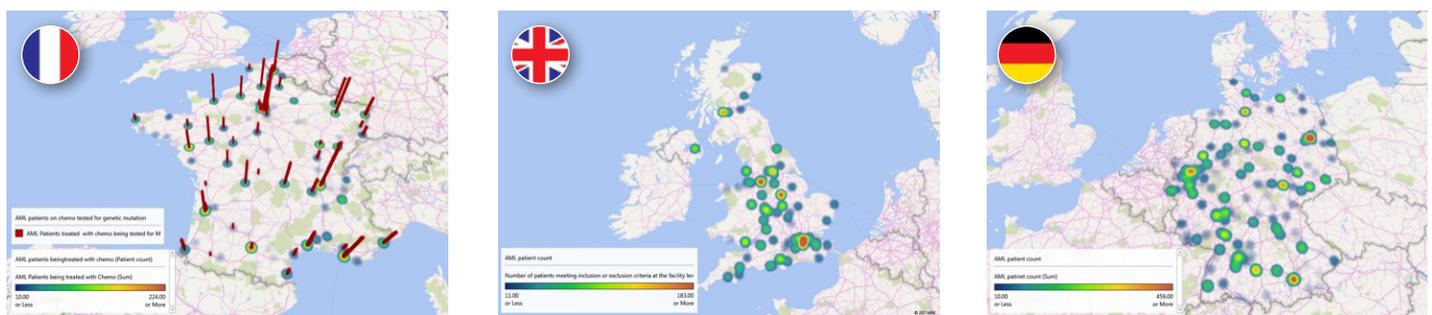
Better targeting of sites with eligible patients creates efficiencies in site recruitment. Insights from global data enhance site selection strategy and support site identification and enrollment strategies. This is done through a multi-step approach:

- Identify high potential sites based on patient potential (i.e. volume of treated patients). The data used to

drive this analysis will vary by country and include medical claims, prescriptions, hospital drug sales and consumption data.

- In the U.S., real-world medical claims data can be used to validate target sites and provide context for site-specific enrollment strategies by explaining available patient volume at the site, as well as treatment dynamics for this patient population. Outside of the U.S., IQVIA's new approach can also determine patient potential at the site level, but in most cases patient potential is based on a proxy of prescription drug use.
- The potential sites identified with use of data and analytics can then be matched with site quality metrics, which include past study performance, protocol compliance, recruitment results and project experience so that the most suitable sites are then included in the study.
- Based on these metrics, physicians can also be contacted to make referrals for the surrounding investigator sites. This approach further accelerates enrollment to meet the study objectives.

Figure 7: IQVIA analyzed medical claims data (France & Germany) and/or drug consumption (UK) to identify site-level patient volume



Sites with >10 AML patients that perform genetic mutation testing count

Sites with >10 AML patients

Sites with >10 AML patients

(Red bars, height of bars represents patient count)

CONCLUSIONS

Drug development in AML is very active given the forecast increase in incidence and the unmet medical need. The AML clinical trial space is also highly competitive and requires a high degree of specificity given the complexities associated with this indication and the current increase in the number of oncology clinical trials. IQVIA's use of data and analytics may significantly facilitate the clinical development plans of new drugs in this indication with an evidence-driven approach to plan trial strategies.

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