EDISON

Oncology ABCs (part 4)

Blood cancers (AML) – notable innovations

Edison themes

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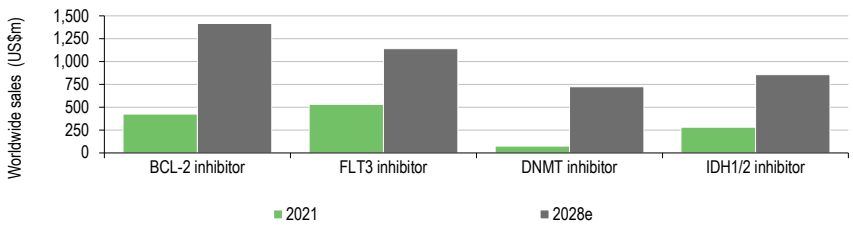
Acute myeloid leukemia (AML) is a highly heterogenous blood cancer that has a diverse array of underlying causes. Owing to this, intensive chemotherapy has historically been the default approach, which has serious limitations resulting from toxicities. To address this serious unmet medical need, drug developers continue to pursue a myriad of innovative approaches to treat AML, including bispecific antibodies, cell therapies and cancer vaccines. There are several innovative therapies in development that we believe may show promise.

New drugs improve survival, but need remains

The relatively recent approvals of new classes of targeted therapies have evolved the treatment landscape for AML; BCL-2, FLT3 and ID-H1/2 inhibitors have had an important impact on patient survival, and their use is now commonplace in AML treatment. Accordingly, worldwide sales of these classes of drugs are estimated to grow considerably over the coming years (Exhibit 1), with the total AML treatment market growing at a c 32% CAGR from 2022 to 2028 to US$10.1bn (EvaluatePharma). This highlights the opportunity for novel therapies in the space. Despite this success, however, the diverse nature of AML biology means large portions of AML patients are left underserved.

Exhibit 1: Forecasted global AML drug sales



Source: Edison Investment Research. Note: Forecasts are attributable to consensus estimates compiled by EvaluatePharma.

AML complexity continues to drive innovation

The development pipeline for AML continues to be an innovative space, driven by the heterogeneity of the disease and the limited success of certain treatment modalities commonly used in other oncology indications, for example checkpoint inhibitors. The heterogeneity of AML is such that recently approved drugs, like BCL2s, FLT3s and IDH-1/2 inhibitors are not suitable or effective for many AML patients, leaving the room for other innovative approaches. Therefore, a range of different approaches are in development for the treatment of AML, including cutting-edge therapies like bispecific antibodies, CAR T-cell therapies, epigenetic drugs and cancer vaccines. Furthermore, the identification of at-risk patient populations and the need for effective maintenance therapies to combat relapse have led to a more holistic view of AML therapy, beyond first-line intensive chemotherapy.

Series recap

We expect the most robust science will remain the underpinning of biotech success and drive long-term growth. Despite the tightening financial market, oncology developments will continue to blaze new trails in driving advancements, and oncology therapies are anticipated to remain front and center of healthcare. Read our first note in this series here.

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Companies mentioned in this report (Edison clients in bold)

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Actinium Pharma (ATNM: NYSE AMERICAN)
Argenx (ARGX: NASDAQ)
Astellas Pharma (ALPMY: OTC)
Bristol Myers Squibb (BMS: NYSE)
Cellectis (ALCLS: NASDAQGM)
Century Therapeutics (IPSC: NASDAQ)
Daiichi Sankyo (4568:TYO)
Gilead Sciences (GILD: NASDAQ)
GSK (GSK.L:LSE)
GT Biopharma (GTBP: NASDAQ)
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Imago Biosciences
ImmunoGen (IMGN: NASDAQ)
Johnson & Johnson (JNJ: NYSE)
Lava Therapeutics (LVTX: NASDAQ)
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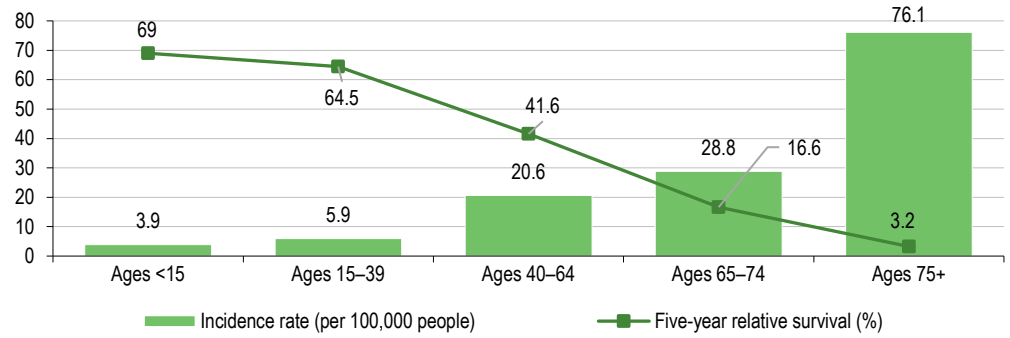
AML is a highly diverse disease

AML is an aggressive type of blood and bone marrow cancer that affects a patient's white blood cells. While the disease is among the most common leukemia in adults, AML is still a relatively rare cancer, with an estimated 60,650 new cases expected to be diagnosed in the United States in 2022. The five-year relative survival rate for AML (based on data from SEER 17 2012–2018) is 30.5%; however, survival varies significantly by age group (Exhibit 2). AML is rare in individuals under 40 years of age and most diagnoses are made in patients over the age of 60. In addition, five-year overall survival drops dramatically in elderly patients, as these individuals are commonly ineligible for chemotherapy and/or have difficult comorbidities. Accordingly, c 80% of newly diagnosed AML patients in the United States are over the age of 65 and therefore highly likely to be ineligible for chemotherapy.

Exhibit 2: AML US incidence and survival by age



Source: Edison Investment Research, SEER AML database

The AML subtype classification will also dictate the treatment options available to patients. The identification of several important cancer survival and proliferation mechanisms has led to the development of targeted therapies, which have changed the AML treatment landscape. For example, FLT3 (FMS-like tyrosine kinase 3), IDH-1 and -2 (isocitrate dehydrogenase 1 and 2) and BCL-2 (B-cell lymphoma 2) are relatively common target proteins in AML and their respective inhibitors now form an important part of treatment regimens. In addition, the approval of azacitidine (a modern chemotherapeutic agent) as an AML maintenance therapy has had a positive impact on patient relapse rates. However, these newly approved therapies are only indicated in portions of the AML population (see Exhibit 3), such as those who possess the relevant mutations (FLT3, IDH-1/2) or who are eligible to receive the remaining treatments (eg patients over 75 for venetoclax, patients who achieve a complete response but are not able to complete curative therapy for azacitidine). This means these drugs are ineffective or unsuitable in many patients. In addition, the development of resistance, occurrence of relapse and patient fitness further drives the need for new drugs to treat AML.

Other targets are the focus of much drug development effort, and this area is large enough to be the subject of its own review; however, we will discuss alternative approaches in this report. The treatment options available for AML patients are therefore highly influenced by age and AML subtype and, particularly in chemo-unfit patients (elderly) and those with few targetable mutations, there is a distinct unmet medical need.

Current standards of care are evolving

Historically, for newly diagnosed chemo-fit AML patients, the standard of care consists of a 3+7 chemotherapy regimen (three days of anthracyclines followed by seven days of cytarabine) to induce remission followed by one to two rounds of consolidation therapy (commonly high-dose cytarabine) to produce a complete response (CR). Eligible patients will then receive an allogenic stem cell transplant (or maintenance therapy, if ineligible) to reduce the risk of relapse. It is estimated that the 3+7 regimen has a 54% CR rate in AML patients. Combinations of the 3+7 regime and other drugs, which target patient-specific mutations, are an area of considerable research.

We note that the 3+7 regimen treatment is only available to those fit for chemo, which often excludes many elderly patients (the majority of AML cases, Exhibit 2) and, given the aggressive nature of AML, chemotherapy resistance and relapse following remission is common. The relatively recent approval of modern drugs allows clinicians to complement or replace the 3+7 standard of care regimen according to patient suitability. A selection of these is presented in Exhibit 3. Despite these advancements, however, average survival rates for AML patients remain low.

Exhibit 3: Selected modern approved therapies in AML

Drug class	Approved examples (company)	Indication	Notes
BCL-2 inhibitors	■ Venetoclax (AbbVie)	Newly diagnosed adult AML patients over 75 years or with comorbidities (induction chemotherapy unfit) in combination with azacitidine, decitabine or low-dose cytarabine	Venetoclax was granted FDA accelerated approval in 2018 based on data from non-randomized, open-label trials: Study M14-358 (NCT02203773) and Study M14-387 (NCT02287233). Full FDA approval was granted in Oct 2020 based on data from two Phase III trials: VIALE-A and VIALE-C. VIALE-A demonstrated a median OS of 14.7 months (versus 9.6 months for placebo), a CR rate of 37% (versus 18% for placebo) and a median duration of CR of 18.0 (vs 13.4 months for placebo) in the venetoclax plus azacitidine arm.
FLT3 inhibitors	■ Gilteritinib (Astellas) ■ quizartinib (Daiichi Sankyo) ■ midostaurin (Novartis)	Relapsed or refractory AML with an FLT3 mutation (gilteritinib); newly diagnosed FLT3-mutated AML (quizartinib, midostaurin)	Gilteritinib and midostaurin are currently approved in the United States, quizartinib was granted FDA priority review in Oct 2022 based on data from the Phase III QuANTUM-First trial (NCT02668653), in which quizartinib (in combination with induction chemotherapy) significantly improved median OS versus placebo (31.9 months vs 15.1 months). FLT3 mutations are estimated to be present in c 30% of AML cases. Note: the gilteritinib label contains a black box warning for potentially life-threatening differentiation syndrome.
IDH inhibitors	■ Enasidenib (BMS) ■ ivosidenib (Les Laboratoires Servier)	r/r AML with an IDH-2 mutation (enasidenib); newly diagnosed chemo unfit and r/r AML with IDH-1 mutation (ivosidenib)	Both enasidenib and ivosidenib labels contain a black box warning for potentially life-threatening differentiation syndrome. IDH-1 or IDH-2 mutations are estimated to be present in c 8% and 12% of AML cases, respectively (total c 20%).
Hypomethylating agents	■ Azacitidine (BMS)	Adult AML patients who achieve CR after chemotherapy and are not able to complete intensive curative therapy	Oral azacitidine (Onureg) was approved by the FDA in Jan 2020 based on data from the pivotal Phase III Quazar AML-001 trial (NCT01757535). Primary endpoint analysis showed treatment with Onureg produced a statistically significant and clinically meaningful improvement in OS compared to placebo (24.7 months vs 14.8 months).

Source: Edison Investment Research, clinicaltrials.gov, company websites. Note: BCL-2 = B-cell lymphoma-2, FLT-3 = FMS-like tyrosine kinase-3, IDH = isocitrate dehydrogenase, DNMT = DNA methyltransferase, OS = overall survival, r/r = relapsed or refractory, CR = complete remission.

The AML treatment market size in 2021 was estimated at US$1.5bn (EvaluatePharma) and is expected to grow at c 32% CAGR to reach US$10.1bn in 2028 (EvaluatePharma). This growth is expected to be driven by the increased uptake of the recently approved therapies (venetoclax, gilteritinib, ivosidenib and azacitidine), but also by the anticipated approval of a variety of new treatments over this time. Hence, we expect the AML market in future will be fragmented and the major opportunity for drug developers will lie in treatment regimens that target large portions of the AML population. We therefore believe that the AML development pipeline will become an increasingly innovative space, to which smaller biotechnology companies will be significant contributors.

The proving ground for innovation

The distinct unmet medical need in AML, driven in large part by the heterogenous nature of the disease, has led to a diverse pipeline of treatment options under development. The lack of success that common oncology interventions, such as immune checkpoint inhibitors (ICIs), have met with has forced drug developers to think outside the box and, hence, the AML development pipeline contains a myriad of innovative approaches relative to solid tumor indications. Sticking to our thesis that smaller, more specialized and nimbler biotechnology companies may have an advantage in discovering innovative AML treatments, we believe there is an opportunity for significant future M&A and licensing activity, provided breakthroughs prove meaningful. Below we highlight approaches in the AML pipeline that we see as particularly interesting and differentiated and present examples of companies pioneering these approaches.

Targeting DNA information relay with epigenetic modulators

Epigenetics refers to a group of processes that regulate access to DNA in the cell, therefore facilitating DNA transcription, repair and replication. Dysregulation of epigenetic processes is a common driver in AML progression and therefore drugs that modulate epigenetic activity have received a lot of development attention; in fact, several approved drugs combat AML through their effect on epigenetic processes (azacitidine/decitabine, IDH inhibitors). Following the success of these and their potential to target large numbers of AML patients, the next generation of epigenetic drugs are now in development.

For example, Oryzon Genomics' LSD1 inhibitor iadademstat has displayed promising results (in combination with azacitidine) in the Phase II ALICE study in newly diagnosed elderly/unfit patients, which met its primary endpoints of safety and tolerability with no major non-hematological or organ related toxicities in June 2022. Notably, iadademstat also displayed an encouraging efficacy profile, achieving an objective response rate (ORR) of 81% and median overall survival (mOS) of 11.1 months, significantly higher than previously reported values for azacitidine monotherapy (ORR: c 30%; mOS: c 7–8 months), although we note that comparison between trials must be undertaken with caution. Short treatment times to response (TTR) are important for older AML patients as, due to the aggressive nature of chemotherapy treatment, many patients are unable to complete the minimum recommended four cycles of hypomethylating agent (HMA) monotherapy treatment. Oryzon reported a rapid TTR, with 19 of 22 ORR patients (86%) responding after two 28-day cycles of treatment, a clinically significant result, in our view.

LSD1 is a gene expression regulator, the inhibition of which reduces the expression of certain proteins important for cancer proliferation and survival. Dysregulation of LSD1 has been shown to play a key role in the development of a variety of cancers, including AML, and is considered an important therapeutic target across multiple indications in oncology. In recognition of this, Merck recently announced that it would acquire the LSD1 focused biotech Imago BioSciences for US$1.35bn (US$36.00 per share in cash), news that saw Imago's stock price jump by c 100%. The deal is expected to close in Q123.

Need to maintain remission

An emerging space in AML treatment paradigms is that of maintenance therapy, which involves the complete eradication of residual cancerous cells from the body to prevent relapse. An important concept in AML maintenance therapy is measurable residual disease (MRD), which refers to the presence of cancerous cells at levels conventional testing methods cannot detect but more sensitive modern methods can. Therefore, a patient may be classified as in complete remission while still being MRD positive. Importantly, as a prognostic biomarker, MRD status is recognized as an important relapse risk factor in AML, and MRD negativity is associated with superior long-term

survival. As such, the inclusion of more sensitive testing methods to identify MRD in CR patients in become is becoming more common in practice.

Maintenance therapies are designed to combat MRD after remission, as the safety and toxicity of continuing certain chemotherapy regimens is unsatisfactory (venetoclax + azacitidine, 3+7 regimens). Currently, oral azacitidine (Onureg, Bristol Myers Squibb) monotherapy is the only approved AML maintenance therapy. We note that azacitidine is considered a chemotherapy but possesses a safer profile, making it suitable for longer-term use. As the number of AML patients in complete remission is likely to increase in future, as new, effective therapies are approved and patients survive longer, the need for safe and effective AML maintenance therapies that do not affect patient quality of life will represent a considerable area of unmet medical need, in our opinion. Of the AML maintenance therapies in development, many use an immunotherapy approach by priming the body's immune system to recognize residual circulating AML cells. Two noteworthy examples of novel immunotherapies in development as potential AML maintenance therapies are:

- **DCP-001:** an allogenic, cell-based AML relapse vaccine being developed by Mendus. DCP-001 cells are derived from the proprietary DCOne platform and express multiple common tumor-associated antigens. DCP-001 is administered during remission with the aim of priming the immune system to control residual disease, thereby preventing or delaying recurrence. Recently reported data from the ADVANCE II Phase II trial (NCT03697707) of DCP-001 in AML maintenance demonstrated significant extensions in patient survival.
- **Galinpepimut-S (GPS)**: currently in development by Sellas Life Sciences Group. GSP is comprised of four peptides that prime the immune system to recognize the Wilms tumor 1 (WT1) antigen, which is highly expressed in the majority of AML cases. Sellas is currently conducting the Phase III REGAL trial (NCT04229979) after two Phase II trials showed substantial survival improvements for patients receiving GPS over the best standard of care.

Antibodies: Not just ICIs

Owing largely, in our view, to the limited success of ICIs, a wide variety of antibody-based therapeutics are in development for the treatment of AML. The antibody drug conjugate gemtuzumab ozogamicin (GO) was reapproved (after being withdrawn due to toxicity concerns) for the treatment of CD33-positive, newly diagnosed and relapsed or refractory (r/r) AML in 2017, and the drug is commonly used as an addition to chemotherapy in many patients. A selection of different monoclonal antibodies (mAbs), targeting many proteins, are currently under development for the treatment of AML. These include, but are not limited to magrolimab (Gilead Sciences, CD47 targeting mAb), Keytruda (Merck, anti-PD1 mAb), sarclisa (Sanofi, CD38-targeting mAb) and IMGN632 (ImmunoGen, CD123-targeting mAb). However, development is not only focused on mAbs but also other less well-established but highly innovative antibody-based approaches, such as antibody conjugates and bi- and tri-specific antibodies (Exhibit 4), which may offer differentiated approaches to AML treatment.

Exhibit 4: Antibody-based therapeutics in development for the treatment of AML

Therapy	Company	Status	Description	Notes
Iomab-B	Actinium Pharmaceuticals	Phase III	CD-45 targeting mAb conjugated to a radioactive iodine isotope (^{131}I)	Iomab-B is being investigated in the pivotal Phase III SIERRA trial (NCT02665065) as an induction and conditioning agent in r/r AML patients (+55 years) before bone marrow transplant. The trial completed patient enrollment in the third quarter of 2021. Phase II clinical trial results showed Iomab-B produced CR in 100% of patients. Estimates one-year OS rate was 41% in total patient population (n=58)
LAVA-051	Lava Therapeutics	Phase I/IIa	Vγ9 Vδ2 T-cell activating and CD1d binding bispecific antibody	Phase I/IIa trial (NCT04887259) assessing the safety and tolerability of LAVA-051 in r/r AML patients is currently recruiting. Vγ9 Vδ2 T cells are a subset of immune cells that may play an important role in tumor killing and also have an immunostimulatory effect. CD1d antigens are estimated to be overexpressed in 24% of adult AML patients.
GTB-3550/ GTB-3650	GT Biopharma	Phase I	Trispecific antibody targeting CD16, CD33 and IL-15.	GBT-3550 is based on GT Biopharma's proprietary modified bispecific antibody, natural killer T-cell engager technology (TriKE). Trispecific format of GT3550 is designed to cause antibody dependent cellular cytotoxicity (anti-CD16), specifically target AML cells (anti-CD33), and mediate an anti-cancer immune response (IL-15 promoting). A Phase I trial (NCT03214666) in AML showed 57% of patients treated with GTB-3550 had significant reduction in cancer cell burden. Development of GTB-3550 was halted to focus on the next-generation TriKE product, GTB-3650.

Source: Edison Investment Research, clinicaltrials.gov, company websites

We note that the wide-ranging success of monoclonal antibodies in other oncology indications has made antibody-based therapeutics a competitive space in AML drug development.. Therefore, we believe that licensing and M&A activity in this field will be a dynamic space in the near future.

Cell therapies

Among the more modern technologies in the AML development pipeline are cell therapies, which use genetically modified immune cells (derived either from a patient or donor) to target and destroy tumors. Blood malignancies have been an area where cell therapies have previously had success (compared to solid tumors) and currently a handful of treatments are approved for the treatment of liquid tumors. Of these, Novartis' Kymriah (an anti-CD19 CAR-T cell therapy) is probably the most well-known after becoming the first ever FDA approved CAR-T therapy in 2017, for the treatment of B-cell precursor acute lymphoblastic leukemia. Following the Kymriah approval, interest in developing new cell therapies increased; however, in AML (unlike other blood-borne malignancies), limited progress has been made. This is largely thought to be due to the numerous immune-evasion mechanisms present in AML.

Despite the limited success to date, drug developers are still progressing innovative cell therapies for the treatment of AML. As an example, we highlight Cellectis, which is developing UCART123, an allogenic ('off-the-shelf') CD123 targeting cell therapy, which the company believes may become a universal treatment for AML. CD123 is widely overexpressed throughout immune cell development in AML, making it an interesting target for AML drug developers. Cellectis is currently recruiting for a first-in-human, open-label, dose-escalation/expansion, Phase I study (AMELI-01, NCT03190278), investigating the use of UCART123 in r/r AML patients (expected n=65).

We note that while cell therapy technology has evolved considerably in the last decade, issues with safety, manufacturing complexity and treatment cost remain. Breakthroughs in any of these areas will represent a significant advancement for the industry, in our view, and could serve as a catalyst to further cell therapy therapeutic product development.

AML assets can make attractive targets

In our view, the potential commercial opportunities in AML are considerable, with the distinct unmet medical needs present in the field and limited success of other established treatment modalities creating a competitive development landscape. The degree of expertise needed to develop specialized drugs, such as those classes highlighted above, is often concentrated in smaller biotechnology companies, in our view. Accordingly, there have been notable examples of M&A activity targeting companies with AML assets in development since 2018.

In August 2021, Pfizer announced the proposed acquisition of Trillium Therapeutics for US$2.26bn (118% premium to Trillium's 60-day weighted average share price). The acquisition brought Trillium's two SIRPα-Fc fusion proteins (including TTI-662, which was in various early-stage combination trials for the treatment of AML) into Pfizer's development pipeline. Furthermore, Gilead Sciences announced the acquisition of Forty Seven for US$4.9bn in March 2020, largely due to company's work developing magrolimab (an anti-CD47 antibody) in myelodysplastic syndrome, diffuse large B-cell lymphoma and AML. Magrolimab is currently in a Phase III trial for the treatment of AML (NCT04778397) and is expected to report top-line results mid-2025. We believe these examples support our hypothesis that smaller, highly specialized biotechnology companies with AML assets in development can be attractive targets for M&A activity and will continue to be so as the treatment landscape and new technologies evolve.

The licensing of AML assets by large pharmaceutical companies over recent years has also been a reasonably active area. However, the majority of licensing deals have been struck between smaller entities. Nevertheless, there have been a handful of deals in which large pharmaceutical companies have licensed developmental AML assets for considerable amounts (a selection is shown in Exhibit 5). We believe these deals further demonstrate the variety of treatments in development (cell therapies, bispecific and new monoclonal antibodies are represented) and broad interest from the pharmaceutical industry in novel approaches to AML therapy.

Exhibit 5: Recent AML licensing deals

Deal date	Company	Product	Status on deal date	Deal partner	Description	Potential total deal value, US$m (upfront payment, US$m)
16/10/2022	Gilead Sciences	MGD024	Phase I	MacroGenics	MGD024 is a CD123 x CD3 bispecific antibody.	1,760 (60)
10/01/2022	Bristol Myers Squibb	CNTY-104	Preclinical	Century Therapeutics	Research collaboration and license agreement to develop and commercialize up to four cell therapy programs for hematologic malignancies and solid tumors	3,150 (100)
04/09/2020	AbbVie	Lemzoparlimab	Phase II	I-Mab Biopharma	A Lemzoparlimab is an anti-CD47 monoclonal antibody	1,940 (200)
03/12/2018	Johnson & Johnson	ARGX-110 (cusatuzumab)	Phase II	Argenx	ARGX-110 is a CD70 targeting antibody. CD70 is an immune checkpoint implicated in many cancers.	1,800 (300)

Source: Edison Investment Research, company websites

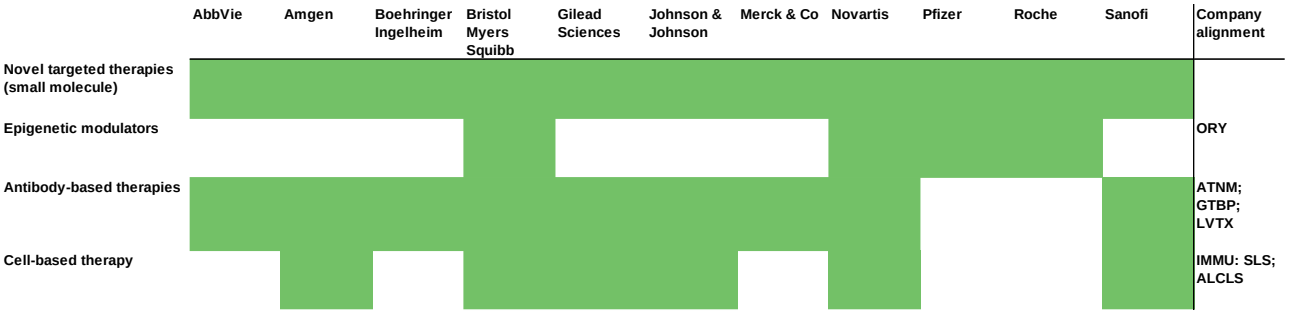
Conclusion: Pipeline ripe with opportunity

AML treatment is still highly reliant on intensive chemotherapy, meaning large numbers of the AML patient population are left under-served by such treatment regimens (c 80% of new AML patients are aged over 65 and are highly unlikely to be fit for chemotherapy). Recent approvals of new drugs have had a considerable impact on patient survival for those with the actionable mutations (30% FLT3, c 20% IDH-1/2) or those eligible for venetoclax or azacitidine. However, distinct unmet medical needs remain in the field. We view the AML development pipeline as an increasingly innovative area, which is, in our opinion, likely to see considerable investment and M&A/licensing activity in the coming years. The range of therapeutic approaches in development is due to the complicated nature of AML and, as such, a wide variety of advanced treatment modalities are under investigation for the treatment of AML.

We therefore believe that this indication will become the proving ground for new classes of oncology drugs, including novel targeted therapies, new antibody technologies (bi/tri-specifics, conjugates), epigenetic modulators and cell and maintenance therapies. M&A and licensing activity in recent years demonstrates there is significant interest in the development of AML treatments and considerable opportunities for smaller biotech companies that can address the unmet needs present in the field. Hence, as therapeutic approaches continue to evolve, we believe that

M&A/licensing activity will continue, as large pharmaceutical companies look to capitalize on the innovation often present in specialized biotechnology companies. To highlight the potential for M&A/licensing, Exhibit 6 displays a selection of pharmaceutical companies with AML assets in clinical development split by the therapeutic areas discussed in this report. AML assets in clinical development are highlighted in green, categorized using the technology described above, for each of the selected pharmaceutical companies. We believe this represents clear interest by large pharmaceutical companies in developing these types of therapeutic technology, which could result in further M&A/licensing activity in future. The company alignment column in Exhibit 6 shows the overlap between the selected pharma companies and the development-stage companies mentioned in this report. We note that any future potential deals covering these technologies in AML may come from other pharma and/or biotech companies not shown below.

Exhibit 6: Interest in AML by large pharma



Source: Edison Investment Research, Company websites Note: ORY = Oryzon Genomics, ATNM = Actinium Pharma, GTBP = GT Biopharma, LVTX = Lava Therapeutics, IMMU = Mendus, SLS = Sellas Life Sciences Group, ALCLS = Cellectis.

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