APTITUDE HEALTH


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**Introduction**

On September 14, 2019, at the conclusion of the 2019 Society of Hematologic Oncology (SOHO) annual meeting, Aptitude Health brought together a group of experts in leukemia, to attend the closed-session Emerging Paradigms in Care Series (EPICS) expert panel meeting. This group included experts in chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML), who discussed the state-of-the-art, recent developments, and future directions in leukemia.

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*Acute Lymphoblastic Leukemia*

Genetic analysis continues to reveal an expanding number of subtypes of ALL. The optimal therapeutic approaches have yet to be determined for most of these subtypes, but a frequent characteristic of most subtypes is abnormal activation of a signaling pathway, which may indicate a role for a corresponding inhibitor. Two therapeutic modalities that have come to play a major role in ALL therapy are monoclonal antibodies and chimeric antigen receptor (CAR) T cells. Key targets and antibodies in ALL include CD19 (blinatumomab), CD20 (rituximab), and CD22 (inotuzumab ozogamicin). Currently, tisagenlecleucel, which targets CD19, is the only CAR T-cell therapy approved in ALL, which is indicated for patients ≤25 years of age and whose disease is refractory or in second or later relapse; however, early-phase data have also demonstrated activity in adult patients. Finally, the development of next-generation sequencing–based assays for assessment of measurable/minimal residual disease (MRD) allows for greater sensitivity, although there will be a learning curve in the migration from the current systems for MRD testing, which are based on flow cytometry.

*Acute Myeloid Leukemia*

The recent approvals of new agents in AML have established genetic subsets of this disease. These subsets include patients with *FLT3* mutations, for which midostaurin and gilteritinib have been approved, and other FLT3 inhibitors are in development. Mutations in isocitrate dehydrogenase (IDH) genes *IDH1* and *IDH2* have been addressed with the approvals of ivosidenib and enasidenib, respectively. Other recent approvals involve targeted agents that are not restricted by molecular characteristics, including the Hedgehog signaling inhibitor glasdegib and the BCL-2 inhibitor venetoclax. In particular, venetoclax-based combinations have become a new standard for elderly patients and in patients who are not candidates for intensive chemotherapy. Trials are ongoing to evaluate novel combinations of FLT3, IDH1/2, and BCL-2 inhibitors, as well as hypomethylating agents. Given the challenge in carrying out trials in rare genotypes with small patient cohorts, expert opinion is that another approach would be to focus on agents that are active across multiple genotypes (eg, BCL-2 inhibitors); for the patient subgroups that don't respond, further molecular characterization can be pursued.

# ALL: Genetic Subsets

### Overview and Highlights

Dr. Mullighan described the expanding number of subtypes of acute lymphoblastic leukemia (ALL). Genomic analyses have so far identified over 20 different subtypes, and this information has the potential for improved prognosis and matched therapies. A key challenging subtype, Ph-like ALL, can be grouped based on signaling pathways, such as JAK, and ABL, with ruxolitinib or dasatinib, respectively, being investigated. Other kinase fusions, such as *FGFR1*, *NTRK3*, and *FLT3* might be targeted with respective TKIs for these molecules. Other ALL genetic subsets highlighted by Dr. Mullighan included:

- *DUX4* rearrangements, which correspond with a favorable outcome in both pediatric and adult patients
- *MEF2D* rearrangements, which result in the dysregulation of *HDAC9* and are sensitive to histone deacetylase inhibitors

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- *ZNF384* rearrangements, which lead to high *FLT3* expression, with anecdotal responses to sunitinib
- Hypodiploid ALL, which is highly sensitive to BCL-2 inhibition
- *IKZF1* (Ikaros) alterations, which may respond to rexinoids or FAK inhibitors

Key points or questions raised by the expert panel during the discussion included:

- Although several disease subtypes have emerged in ALL, even in just the past year, one of the experts expressed concern that some subtypes are extremely rare, and it is difficult to obtain targeted agents for biology-based therapies
    - Expert opinion is that the low number of patients in some subgroups will make it impossible to conduct focused clinical trials
    - It was suggested by one of the experts to focus instead on therapies that cut across genotypes, such as BCL-2 inhibitors; subtypes that do not respond to these therapies can then be identified, with an indication of support in NCCN guidelines for targeted therapy
    - On the other hand, another of the experts mentioned that even for agents that may be active in multiple subtypes, such as venetoclax, resistance still occurs
- One of the experts mentioned that most genetic research in ALL has been done in the setting of newly diagnosed disease, but molecular characterization is needed in the setting of poor responses to therapy

# ALL: Role of Monoclonal Antibodies

**Overview and Highlights**

Dr. Jabbour discussed the establishment of monoclonal antibodies in the treatment of patients with ALL. In patients with newly diagnosed, CD20-positive, pre-B ALL, the addition of rituximab to chemotherapy significantly improved event-free survival in a phase 3 French study. In patients with measurable/minimal residual disease (MRD)-positive ALL in first or second CR, targeting CD19 with blinatumomab has received approval; blinatumomab is also approved as a single agent in patients with relapsed/refractory disease. A third antigen, CD22, is also an established therapeutic target, with approval of single-agent inotuzumab ozogamicin in patients with relapsed/refractory ALL. Antibody-based combinations are being explored, with reduced-dose chemotherapy plus inotuzumab ozogamicin and blinatumomab yielded a median OS of 14 months; by comparison, a historical comparison showed a median OS of 6 months with inotuzumab ozogamicin alone. The combination of reduced-dose chemotherapy and monoclonal antibodies is being explored as first-line therapy.

Key points or questions raised by the expert panel during the discussion included:

- While blinatumomab and inotuzumab ozogamicin are both approved as single agents in patients with relapsed/refractory ALL, expert opinion (from MD Anderson) is that going beyond the label to combine with chemotherapy provides superior outcome
    - However, some experts noted that using monoclonal antibodies in combination with chemotherapy has so far not encountered challenges in reimbursement
- Regarding upfront regimens for patients with ALL that include blinatumomab, one of the experts raised the concern that upon progression, CD19 expression may be low due to blinatumomab-driven antigen escape. However, it was mentioned that the vast majority of patients retained CD19 expression after blinatumomab, so that CD19-targeted CAR T cells could still be an option at relapse

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- The role of SCT following blinatumomab was debated by the experts
    - One of the experts stated that long-term outcomes from the BLAST study suggest that SCT will still be required following blinatumomab in MRD-positive patients
    - However, in the TOWER trial, patients in first salvage who achieved MRD negativity after blinatumomab did not receive additional benefit from subsequent SCT
- For extramedullary leukemia, one of the experts argued that blinatumomab is not particularly effective; however, it was noted that with hyperCVAD + inotuzumab ozogamicin, extramedullary disease is no longer an issue
- There was support for the use of blinatumomab or inotuzumab ozogamicin as a bridge to CAR T-cell therapy

# ALL: Role of CAR T Cells

**Overview and Highlights**

Dr. Shah discussed the development of chimeric antigen receptor (CAR) T cells in patients with ALL. Currently, tisagenlecleucel is approved for patients with ALL who are ≤25 years of age and whose disease is refractory or in second or later relapse. This approval was based on the phase 2 ELIANA trial, with updated results showing an ORR of 82%, and a 24-month relapse-free survival rate of 62%. Another CAR T-cell construct, KTE-X19, has been investigated in adult patients with relapsed/refractory ALL in the ZUMA-3 trial; at the recommend phase 2 dose, the CR/CRi rate in 19 patients was 84%. Given the recent implementation of this therapeutic modality, there remain challenges to resolve. The most well-known of these is the toxicity associated with CAR T-cell therapy, particularly cytokine release syndrome and neurotoxicity. Furthermore the relative positioning of CAR T cells and stem-cell transplant, including whether or not CAR T cells can replace stem-cell transplant, remains an open question.

Key points or questions raised by the expert panel during the discussion included:

- One of the experts pointed out that the response rates for CAR T-cell studies are not typically calculated on the basis of the ITT population—that is, patients who are enrolled but cannot receive therapy are not included in the denominator. The concern is that this may overestimate the success rate of CAR T cells
- An argument in favor of monoclonal antibody-based therapy over CAR T cells was made due to the cost, toxicity, and technical complexity of the latter; however, it was pointed out that just as off-the-shelf systemic regimens took time to optimize, CAR T cells are still in the first generation clinically, and new technologies, such as dual antigen-targeted CARs and controllable CAR T cells may truly be able to provide greater benefit (eg, replacing SCT)

# ALL: Measurable/Minimal Residual Disease

**Overview and Highlights**

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Dr. Logan presented an overview of the evolving topic of MRD assessment in patients with ALL. First, MRD is not a binary entity, but exists on a spectrum. Furthermore, current flow cytometry-based methods to assess MRD vary from laboratory to laboratory, with different antibody panels used and with results potentially biased by operator interpretation. A recent advance in MRD assessment was achieved with the approval in September 2018 of a next-generation sequencing (NGS)-based MRD assay for patients with ALL or multiple myeloma. Compared with flow cytometry, NGS-based assessment of MRD has multiple advantages, including increased sensitivity ($10^{-6}$ versus $10^{-4}$ with flow cytometry), as well as the capability of using fresh or frozen samples. As with other areas of ALL therapy, several questions remain, including the interpretation of MRD results in the context of normal versus high-risk genotypes, when and how often to assess MRD, and how changes in a patient's MRD levels should be translated into a change in management.

Key points or questions raised by the expert panel during the discussion included:

- Expert opinion is that NGS, with a sensitivity of $10^{-6}$, should replace flow cytometry, with a sensitivity of $10^{-4}$, for MRD assessment in ALL
- Experts with experience using the FDA-approved NGS platform for MRD assessment have not experienced any difficulty with reimbursement
- When low-level MRD positivity (eg, $10^{-5}$) is detected by NGS, experts who use NGS testing typically follow up with imaging, particularly checking for extramedullary disease

## AML: Patient Subsets (including ELN classification, prognostic groups, unfit elderly)

### Overview and Highlights

Dr. Ravandi discussed the evolution of patient subgroups in AML. Cytogenetics were the initial approach to designate subgroups, but more recently, mutations in certain genes, along with matched therapies, have defined therapeutically actionable subtypes. For example, the *FLT3*-ITD abnormality confers sensitivity to FLT3 inhibitors, and also influences risk stratification. In the 2017 European LeukemiaNet classification, the allelic burden of *FLT3*-ITD, together with *NPM1* status, determines if a patient has favorable-, intermediate- or adverse-risk disease. The assessment of MRD can also be used as a prognostic tool for relapse, with a European study demonstrating additive prognostic value with the combination of NGS-based and flow cytometry-based assessment of MRD in patients with AML.

Key points or questions raised by the expert panel during the discussion included:

- Expert opinion is that the assessment of mutation burden in AML will become more complex; currently this is only done for *FLT3*, which is still an unsettled area, but the identification of additional mutations will further add to the complexity
- For an elderly patient with a *FLT3-ITD* mutation, the experts would generally be comfortable recommending venetoclax/HMA with a FLT3 inhibitor, assuming availability
    - One of the experts would still recommend 7+3 plus midostaurin if the patient was fit
    - It was also mentioned by one of the experts that patients with a *FLT3* mutation tend to benefit less with a BCL-2 inhibitor, so they would recommend azacitidine/sorafenib

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- In a newly diagnosed, elderly patient with an *IDH2* mutation, one of the experts would recommend venetoclax/HMA, reserving the IDH2 inhibitor for relapse, since the response rate does not appear to diminish in later lines of therapy
- For a 68-year-old patient with AML and MDS-related changes, expert recommendation would be CPX-351 followed by SCT. This is based on data that patients who respond to CPX-351 and proceed to SCT do well; there are less data with venetoclax/azacitidine
- Regarding the use of gemtuzumab ozogamicin, expert opinion is that this would be best suited to patients with CBF-AML; for patients with intermediate-risk disease, the expert argument against using this agent is that SCT is a key part of therapy, and the use of gemtuzumab ozogamicin would increase the risk of VOD

# AML: Targeting FLT3

**Overview and Highlights**

Dr. Stone reviewed the development of targeted agents for patients with *FLT3* mutation-positive AML. The landmark trial for this subset of patients is the phase 3 RATIFY trial, in which patients with newly diagnosed AML and *FLT3* mutations received standard chemotherapy with either placebo or the multikinase inhibitor midostaurin. This study demonstrated superior OS with the addition of midostaurin, establishing targeted therapy in AML. Next-generation FLT3 inhibitors with greater specificity, such as gilteritinib, quizartinib, and crenolanib, are currently in phase 3 trials in patients with newly diagnosed, *FLT3* mutation-positive AML. In patients with relapsed/refractory AML and *FLT3* mutations, gilteritinib has received approval, based on the phase 3 ADMIRAL trial. Most of the patients on this trial had not previously received a *FLT3* inhibitor, however, and the optimal approach to *FLT3* inhibition in patients who received midostaurin in the first-line setting remains to be determined.

Key points or questions raised by the expert panel during the discussion included:

- In newly diagnosed patients with a *FLT3* mutation, given the choice between gilteritinib and midostaurin, the experts would choose gilteritinib if available, given the positive experience using gilteritinib in the second-line setting
    - For older patients, experts would use gilteritinib with HMAs
    - Regarding the concern over losing a second-line option if gilteritinib is used upfront, one of the experts pointed out that this used to be the argument against using ATRA and arsenic trioxide upfront in patients with APL, but the goal should be to use the best regimens upfront to prevent relapse
- The experts were impressed with the activity of the combination of quizartinib and azacitidine in relapsed patients. Based on these results, expert opinion is that gilteritinib should also be used in a combination regimen, rather than as a single agent
- For a patient who relapsed 1 year after completing therapy with a *FLT3* mutation, one of the experts stated that single-agent gilteritinib is a consideration because of the indication, but since patients with *FLT3* mutation-positive disease are responsive to chemotherapy, their recommendation would be intensive chemotherapy if the goal was to bring the patient to SCT

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- In the setting of resistance to midostaurin, the experts thought that next-generation FLT3 inhibitors (eg, gilteritinib or quizartinib) might temporarily overcome resistance, but even these agents will be susceptible to other resistance pathways
    - One of the experts mentioned *KRAS, BCR-ABL*, and F691L as resistance mutations/mechanisms, which may provide the opportunity for other targeted agents and/or research to overcome specific resistance mechanisms

# AML: New Therapeutic Targets

**Overview and Highlights**

Dr. Fathi discussed the development of new targeted therapies, with a focus on inhibitors of isocitrate dehydrogenase (IDH) and Hedgehog pathway signaling. For patients with relapsed/refractory AML, the IDH2 inhibitor enasidenib and the IDH1 inhibitor ivosidenib were approved for patients with the respective *IDH* mutation. Furthermore, ivosidenib as a single agent has been approved as first-line therapy for elderly patients who are not eligible for standard induction chemotherapy. Phase 3 trials are ongoing to evaluate the combination of IDH inhibitors with chemotherapy in patients with newly diagnosed AML. The approval of the Hedgehog signaling inhibitor glasdegib was based on the phase 2 BRIGHT AML 1003 trial, which randomized patients to low-dose cytarabine (LDAC) with glasdegib or LDAC alone, with an OS benefit demonstrated with the addition of glasdegib to LDAC. Finally, targeting of cell-surface antigens with monoclonal antibodies, such as CD47 and CD70, is also being explored in patients with AML.

Key points or questions raised by the expert panel during the discussion included:

- For an elderly patient with newly diagnosed AML and an *IDH1* mutation, expert recommendation would be a venetoclax/HMA combination, even though there is an indication for ivosidenib in this setting (similar to the *IDH2* mutation scenario described previously). This is because the response rates with ivosidenib do not appear to diminish in subsequent lines of therapy, so it would not be necessary to use ivosidenib immediately
- Other than IDH-DS, one of the experts mentioned severe fatigue as a notable adverse event with IDH inhibitors
- For a young patient who relapses with an *IDH* mutation, the experts had varying approaches to management
    - FLAG-IDA or MEC followed by SCT
    - FLAG-IDA with an IDH inhibitor followed by SCT
    - Decitabine with an IDH inhibitor

# AML: Targeting BCL-2

**Overview and Highlights**

Dr. Daver discussed current and future directions for BCL-2 inhibition in AML. The BCL-2 inhibitor venetoclax has been approved in combination with azacitidine, decitabine, or LDAC in elderly patients and patients for whom intensive chemotherapy is not appropriate. Potential future combinations with venetoclax

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are being explored, such as combinations with FLT3 inhibitors and IDH inhibitors. Combinations with chemotherapy are also under investigation; in a phase 1b trial of venetoclax plus FLAG-IDA in patients with relapsed/refractory AML, a CR/CRi was achieved by 11 of 15 patients (73%), of whom 4 patients were primary non-responders. Finally, approaches to overcome resistance to BCL-2 inhibition are being explored, including inhibitors of MCL1 or FLT3, or inhibition of MDM2 to reactivate p53 function.

Key points or questions raised by the expert panel during the discussion included:

- With regards to other venetoclax-based combinations, expert opinion is that doublets, such as venetoclax/gilteritinib, are highly active. However, considerable myelosuppression has been observed, and the experts have been pursuing an approach where venetoclax is held after 21 days, with gilteritinib continued, to allow the bone marrow to recover
- With the establishment of venetoclax-based regimens in AML, expert opinion is that the next logical step is to add targeted agents, for example, adding a FLT3 inhibitor to venetoclax/HMA combination in patients with a *FLT3* mutation
- A major challenge remains for patients with AML who are MRD-positive and otherwise candidates for SCT

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