Appendix A. Novel AML Therapies: Indications And Clinical Implications

Generic	Brand	Drug class	Indication	Clinical implication
Liposomal-encapsulated combination of daunorubicin and cytarabine (Jazz Pharmaceuticals, 2019)	Vyxeos	<ul style="list-style-type: none"> Cytotoxic chemotherapy Cytarabine: antimetabolite interfering with DNA replication Daunorubicin: topoisomerase II inhibitor 	Newly diagnosed t-AML or AML-MRC	New option, but caution for risk of improper interchange with daunorubicin or cytarabine alone
Glasdegib (Pfizer Oncology, 2019)	Daurismo	Hedgehog inhibitor	In combination with low-dose cytarabine, for the treatment of newly diagnosed AML in adult patients age ≥ 75 or who have comorbidities that preclude use of intensive induction chemotherapy	Elderly patients ineligible for intensive chemotherapy
Venetoclax (AbbVie Inc. and Genentech USA, Inc., 2019)	Venclexta	BCL2 inhibitor	In combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults who are ≥ 75 or who have comorbidities that preclude use of intensive induction chemotherapy	Elderly patients ineligible for intensive chemotherapy
Gemtuzumab ozogamicin (Pfizer Oncology, 2019b)	Mylotarg	Antibody-drug conjugate: recombinant humanized IgG4 κ antibody conjugated to calicheamicin derivative targeting CD33	Newly diagnosed CD33-positive AML in adults, OR relapsed/refractory CD33-positive AML in adults and in pediatric patients age ≥ 2	Return to market of agent due to lower dose, which showed improved efficacy and safety
Midostaurin (Novartis Pharmaceuticals Corporation, 2019)	Rydapt	FLT3 inhibitor	Newly diagnosed AML with an <i>FLT3</i> mutation ^a in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	Newly diagnosed <i>FLT3</i> -positive AML; midostaurin is not indicated as a single-agent induction therapy
Gilteritinib (Astellas Pharma US, Inc., 2019)	Xospata	FLT3 inhibitor	Adult patients with relapsed/refractory AML with an <i>FLT3</i> mutation ^a	Relapsed or refractory <i>FLT3</i> -mutated AML
Enasidenib (Celgene Corporation, 2019)	Idhyfa	IDH2 inhibitor	Adult patients with relapsed/refractory AML with an <i>IDH2</i> mutation ^a	Relapsed or refractory <i>IDH2</i> -mutated AML
Ivosidenib (Agiros Pharmaceuticals, Inc., 2019)	Tibsovo	IGH1 inhibitor	Newly diagnosed AML with a susceptible <i>IDH1</i> mutation ^a in patients who are ≥ 75 or who have comorbidities that preclude the use of intensive induction chemotherapy	<i>IDH1</i> mutation, which occurs in 6%-10% if AML with a negative prognosis

Note. AML = acute myeloid leukemia; AML-MRC = AML with myelodysplasia-related changes; t-AML = therapy-related AML.

^aAs detected by an FDA-approved test.

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Appendix B. Novel AML Therapies: Dosing

Agent	Dose	How supplied	Treatment considerations
Liposomal-encapsulated combination of daunorubicin and cytarabine (Jazz Pharmaceuticals, 2019)	<ul style="list-style-type: none"> • <u>First induction</u>: daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on days 1, 3, and 5 • <u>Second induction if needed</u>: daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on days 1 and 3 • <u>First consolidation</u>: daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on days 1 and 3 • <u>Second consolidation</u>: daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome on days 1 and 3 	Single-dose vial containing 44 mg daunorubicin and 100 mg cytarabine	<ul style="list-style-type: none"> • Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient • Second induction can be started 2 to 5 weeks after first induction in patients not achieving a response • Assess cardiac function, CBC, and liver and renal function before each consolidation cycle • Do not start consolidation until ANC recovers to > 0.5 Gi/L and platelet count recovers to > 50 Gi/L in the absence of unacceptable toxicity • Administer the first consolidation cycle 5 to 8 weeks after the start of last induction • Administer the second consolidation cycle 5 to 8 weeks after the start of the first consolidation cycle in patients who do not show disease progression or unacceptable toxicity
Glasdegib (Pfizer Oncology, 2019a)	<ul style="list-style-type: none"> • 100 mg orally once daily on days 1 to 28 in combination with: <ul style="list-style-type: none"> » Cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle in the absence of unacceptable toxicity or loss of disease control • For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response 	100-mg tablets, do not split or crush	ECG monitoring, diligent medication reconciliation
Venetoclax (AbbVie Inc. and Genentech USA, Inc., 2019)	<ul style="list-style-type: none"> • Follow ramp-up schedule: <ul style="list-style-type: none"> » Day 1: 100 mg » Day 2: 200 mg » Day 3: 400 mg » ≥ Day 4 with azacitidine or decitabine: 400 mg » ≥ Day 4 with cytarabine: 600 mg • Once daily with a meal and water; do not chew, crush, or break tablets 	10-mg, 50-mg, 100-mg tablets	Based upon CBC and CMP prior to initiation, monitor for tumor lysis syndrome
<p>Note. ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = echocardiogram; FDA = U.S. Food & Drug Administration; ULN = upper limit of normal.</p>			

Appendix B. Novel AML Therapies: Dosing (cont.)

Agent	Dose	How supplied	Treatment considerations
Gemtuzumab ozogamicin (Pfizer Oncology, 2019b)	<p>Newly diagnosed de novo AML (combination):</p> <ul style="list-style-type: none"> • Induction: 3 mg/m² on days 1, 4, and 7 in combination with daunorubicin/cytarabine • Consolidation: 3 mg/m² on day 1 in combination with daunorubicin/cytarabine <p>Newly diagnosed AML (single-agent):</p> <ul style="list-style-type: none"> • Induction: 6 mg/m² on day 1 and 3 mg/m² on day 8 • Consolidation: up to 8 continuous courses 2 mg/m² on day 1 of every 4 weeks <p>Relapsed/refractory AML (single agent):</p> <ul style="list-style-type: none"> • 3 mg/m² on days 1, 4, and 7 	4.5 mg as a lyophilized cake or powder in a single-dose vial for reconstitution and dilution	<ul style="list-style-type: none"> • Premedicate to reduce infusion reactions, delay or discontinue for prolonged thrombocytopenia and/or neutropenia • Delay for bilirubin > 2 × ULN, AST or ALT 2.5 × ULN • Omit dose if delayed more than 2 days from scheduled dose
Midostaurin (Novartis Pharmaceuticals Corporation, 2019)	<ul style="list-style-type: none"> • 50 mg orally twice daily with food • Administer prophylactic antiemetic 	25-mg capsules	Ensure ANC > 1,000/L, platelets > 50,000/L, and hemoglobin > 8 g/dL prior to initiation
Gilteritinib (Astellas Pharma US, Inc., 2019)	120 mg (4 tablets) orally once daily	40-mg tablets to allow for dose adjustment	Assess CBC, chemistry including creatinine phosphokinase, and ECG for QT interval per FDA guidance
Enasidenib (Celgene Corporation, 2019)	100 mg once daily until disease progression or unacceptable toxicity	50- or 100-mg tablets	Assess for IDH differentiation syndrome
Ivosidenib (Agiros Pharmaceuticals, Inc., 2019)	<ul style="list-style-type: none"> • 500 mg orally once daily with or without food until disease progression or unacceptable toxicity • Avoid a high-fat meal 	250-mg tablets	Ensure electrolytes are within normal limits prior to initiation, monitor for differentiation syndrome, noninfective leukocytosis, and QT prolongation
<p><i>Note.</i> ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = echocardiogram; FDA = U.S. Food & Drug Administration; ULN = upper limit of normal.</p>			

Appendix C. Novel AML Therapies: Adverse Events and Drug-Drug Interactions

Generic	Key adverse events	High-alert concerns	Treatment parameters	Known drug-drug interactions
Liposomal-encapsulated combination of daunorubicin and cytarabine (Jazz Pharmaceuticals, 2019)	Hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%)	Hemorrhage, cardiotoxicity (daunorubicin), copper overload, hypersensitivity, embryo-fetal toxicity, extravasation emergency (daunorubicin)	<ul style="list-style-type: none"> • Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient • Second induction can be started 2 to 5 weeks after first induction in patients not achieving a response • Assess cardiac function, CBC, and liver and renal function before each consolidation cycle • Do not start consolidation until ANC recovers to > 0.5 Gi/L and the platelet count recovers to > 50 Gi/L in the absence of unacceptable toxicity • Administer the first consolidation cycle 5 to 8 weeks after the start of last induction • Administer the second consolidation cycle 5 to 8 weeks after the start of the first consolidation cycle in patients who do not show disease progression or unacceptable toxicity 	Other chemotherapeutic agents, agents which may contribute to high-alert concerns
Glasdegib (Pfizer Oncology, 2019a)	≥ 20%: anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash	<ul style="list-style-type: none"> • Avoid concomitant CYP3A4 inducers, attempt change of therapy with CYP3A4 inhibitors and/or QTc-prolonging agents • Embryo-fetal death or severe birth defects when administered to a pregnant woman • Pregnancy testing in females of reproductive potential prior to initiation of glasdegib • Advise females of reproductive potential to use effective contraception during treatment and for at least 30 days after the last dose • Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment and for at least 30 days after the last dose to avoid potential drug exposure 	<ul style="list-style-type: none"> • ECG monitoring • Diligent medication reconciliation 	Other QTc-prolonging agents, strong CYP3A4 inhibitors, strong CYP3A4 inducers

Note. ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = echocardiogram; FDA = U.S. Food & Drug Administration; SOS = sinusoidal obstruction syndrome; ULN = upper limit of normal; VOD = veno-occlusive disease.

Appendix C. Novel AML Therapies: Adverse Events And Drug-Drug Interactions (cont.)

Generic	Key adverse events	High-alert concerns	Treatment parameters	Known drug-drug interactions
Venetoclax (AbbVie Inc. and Genentech USA, Inc., 2019)	In combination with azacitidine or decitabine or low-dose cytarabine: nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension	<ul style="list-style-type: none"> Hepatic impairment: reduce initial dose by 50% Premedicate with antihyperuricemia agent and ensure adequate hydration 	Based upon CBC and CMP prior to initiation, monitor for tumor lysis syndrome	<ul style="list-style-type: none"> Strong or moderate CYP3A4 or P-glycoprotein inhibitors: adjust venetoclax dosing AVOID coadministration with strong CYP3A4 inducers Separate dose by AT LEAST 6 hours when given with a P-glycoprotein substrate
Gemtuzumab ozogamicin (Pfizer Oncology, 2019b)	<ul style="list-style-type: none"> Infusion-related reactions: premedicate with corticosteroid, acetaminophen and diphenhydramine and then monitor 1 hour post-infusion Hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis 	<ul style="list-style-type: none"> Black box warning: hepatotoxicity, including severe or fatal hepatic VOD, also known as SOS, has been reported in association with the use of gemtuzumab ozogamicin as a single agent, and as part of a combination chemotherapy regimen Monitor frequently for signs and symptoms of VOD after treatment 	<ul style="list-style-type: none"> Premedicate to reduce infusion reactions Delay or discontinue for prolonged thrombocytopenia and/or neutropenia Delay for bilirubin $> 2 \times$ ULN, AST or ALT $2.5 \times$ ULN Omit dose if delayed more than 2 days from scheduled dose 	Other hepatotoxic agents
Midostaurin (Novartis Pharmaceuticals Corporation, 2019)	Febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, and upper respiratory tract infection	<ul style="list-style-type: none"> Embryo-fetal toxicity Interstitial lung disease 	Ensure ANC $> 1,000/L$, platelets $> 50,000/L$, and hemoglobin > 8 g/dL prior to initiation	<ul style="list-style-type: none"> Avoid concomitant use with CYP3A3 inducers Consider alternative agents with strong CYP3A4 inhibitors
<p><i>Note.</i> ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = echocardiogram; FDA = U.S. Food & Drug Administration; SOS = sinusoidal obstruction syndrome; ULN = upper limit of normal; VOD = veno-occlusive disease.</p>				

Appendix C. Novel AML Therapies: Adverse Events And Drug-Drug Interactions (cont.)

Generic	Key adverse events	High-alert concerns	Treatment parameters	Known drug-drug interactions
Gilteritinib (Astellas Pharma US, Inc., 2019)	≥ 20%: increased transaminase, myalgia/arthralgia, fatigue/malaise, fever, mucositis, edema, rash, noninfectious diarrhea, dyspnea, nausea, cough, constipation, eye disorders, headache, dizziness, hypotension, vomiting, and renal impairment	<ul style="list-style-type: none"> Black box warning: risk of IDH differentiation syndrome, which may be life-threatening or fatal if not treated Posterior reversible encephalopathy syndrome Prolonged QT interval: interrupt and reduce gilteritinib dosage in patients who have a QTcF > 500 ms Correct hypokalemia or hypomagnesemia prior to and during gilteritinib administration Pancreatitis Embryo-fetal toxicity 	Assess CBC, chemistry including creatinine phosphokinase, and ECG for QT interval per FDA guidance	<ul style="list-style-type: none"> Combined P-glycoprotein and strong CYP3A4 inducers: avoid use Strong CYP3A4 inducers: consider alternative agents or monitor closely
Enasidenib (Celgene Corporation, 2019)	≥ 20% nausea, vomiting, diarrhea, elevated bilirubin, and decreased appetite	Embryo-fetal toxicity	Assess CBC and chemistry for leukocytosis and signs of tumor lysis syndrome	Potential for increase or decrease of oral contraceptive levels, significance currently unknown
Ivosidenib (Agiros Pharmaceuticals, Inc., 2019)	Fatigue, arthralgia, leukocytosis, diarrhea, edema, nausea, dyspnea, mucositis, electrocardiogram QT prolonged, rash, cough, decreased appetite, myalgia, constipation, and pyrexia	QT prolongation, CYP3A4 interactions with inducers, substrates, or inhibitors	<ul style="list-style-type: none"> Ensure electrolytes are within normal limits prior to initiation, Monitor for IDH differentiation syndrome, noninfective leukocytosis, and QT prolongation 	<ul style="list-style-type: none"> Strong or moderate CYP3A4 inhibitors: reduce ivosidenib dose with strong CYP3A4 inhibitors Avoid QTc-prolonging drugs, sensitive CYP3A4 substrates, and strong CYP3A4 inducers
<p><i>Note.</i> ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = echocardiogram; FDA = U.S. Food & Drug Administration; SOS = sinusoidal obstruction syndrome; ULN = upper limit of normal; VOD = veno-occlusive disease.</p>				

Disclosure

Dr. Nix has served on the speakers bureau for Cohrus BioSciences and advisory boards for Bristol-Myers Squibb, Genentech, Puma, Sandoz, and Teva. Ms. Price has served as a consultant for Agios and on an advisory board for Daiichi Sankyo.

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