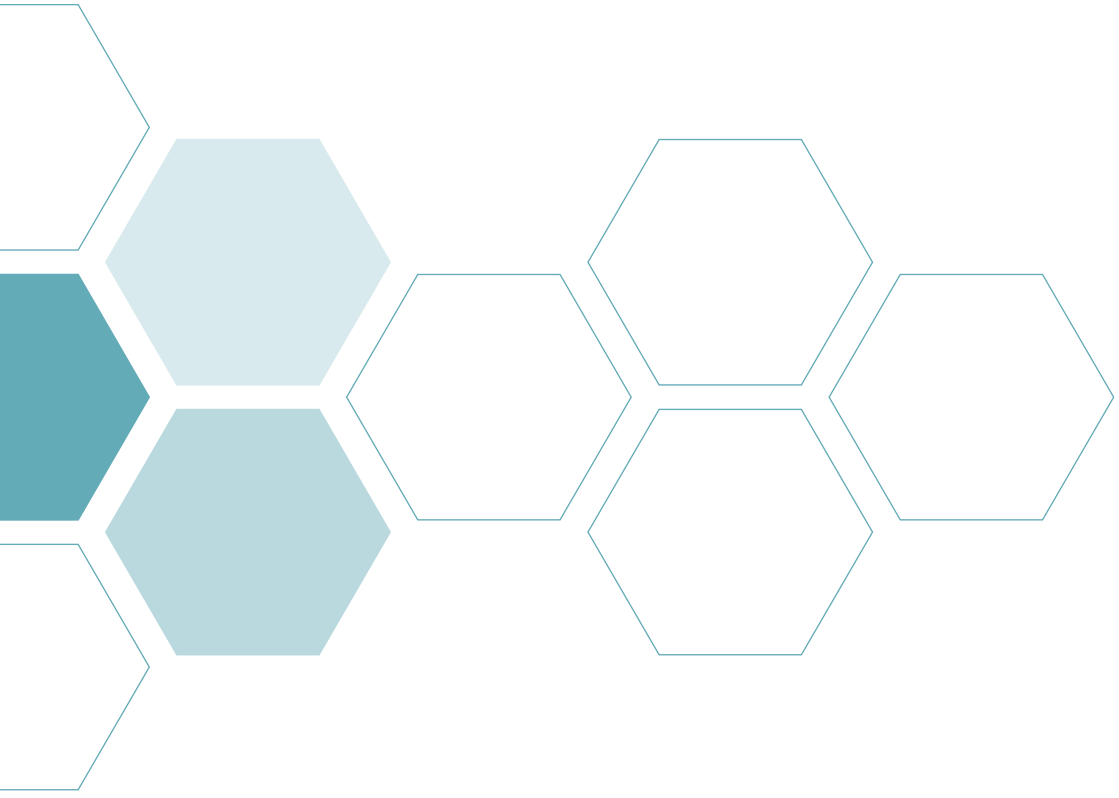
JOURNAL of MANAGED CARE MEDICINE

Vol. 26, No. 1, 2023

Educating Medical Directors of Employers, Health Plans and Provider Systems



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Treatment Updates in Alzheimer's Disease: Tailoring Management and Care Approaches to Improve Outcomes

Navigating the Changing Landscape in the Treatment and Management of Acute Myeloid Leukemia: Key Considerations in Managed Care Decision-Making

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JOURNAL OF MANAGED CARE MEDICINE

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ISSN: 1094-1525. The ***Journal of Managed Care Medicine*** is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: 15 Bridgehampton Place, Richmond, VA 23229; Tel (804) 387-7580. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 26, No. 1, 2023

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For adults with schizophrenia or bipolar I or II disorder,

There's a different way to treat agitation

IGALMI is the **first and only** sublingual film for the acute treatment of agitation[1]

INDICATION

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults.

Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension. Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death, including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia, or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions, Tolerance, and Tachyphylaxis: IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence, a withdrawal syndrome, tolerance, and/or tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

Discover the difference with IGALMI, a sublingual film formulation of dexmedetomidine[1]

TARGETS a key mediator of agitation[1-3]*

MUCOADHESIVE, so it cannot be spit out[1,3,4]

NONINVASIVE sublingual film[1]

ABSORPTION of dexmedetomidine into the bloodstream via the oral mucosa[1,3]

PATIENT-ADMINISTERED under the supervision of a healthcare provider[1]

NOT A CONTROLLED SUBSTANCE[1]

Learn more about the proven reductions in agitation at IGALMIhcp.com

*IGALMI reduces the release of norepinephrine, a key mediator among other neurotransmitters thought to be involved in agitation.[1-3]

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

Drugs That Prolong the QT Interval: Avoid use. Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use may cause enhanced CNS-depressant effects. Reduction in dosage of IGALMI or the concomitant medication should be considered.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment and Geriatric Patients (≥65 years old): A lower dose is recommended in patients with hepatic impairment and geriatric patients. See the full Prescribing Information for the recommended dosage depending on the agitation severity.

Please see the Brief Summary of the full Prescribing Information on the following pages.

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

bioxcel therapeutics®

References: 1. IGALMI. Package insert. BioXcel Therapeutics, Inc.; 2022. **2.** Miller CWT, Hodzic V, Weintraub E. Current understanding of the neurobiology of agitation. *West J Emerg Med.* 2020;21(4):841-848. doi:10.5811/westjem.2020.4.45779 **3.** Data on file. BXCL501-301 CSR (SERENITY I). BioXcel Therapeutics, Inc.; January 2021. **4.** Data on file. BXCL501-302 CSR (SERENITY II). BioXcel Therapeutics, Inc.; January 2021.

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

IGALMI™ (dexmedetomidine) sublingual film, for sublingual or buccal use. Rx Only. Brief Summary of Prescribing Information (PI) for IGALMI. See full PI.

Indication: IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

Important Recommendations Prior to Initiating IGALMI and During Therapy: IGALMI should be administered under the supervision of a healthcare provider. A healthcare provider should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope.

IGALMI is for sublingual or buccal administration. Do not chew or swallow IGALMI. Do not eat or drink for at least 15 minutes after sublingual administration, or at least one hour after buccal administration.

Recommended Dosage: The initial dose of IGALMI is based on agitation severity, with lower doses recommended in patients with hepatic impairment and geriatric patients. If agitation persists after the initial dose, up to two additional doses may be administered at least two hours apart, depending upon the patient population and agitation severity. Assess vital signs including orthostatic measurements prior to the administration of any subsequent doses. Due to risk of hypotension, additional half-doses are not recommended in patients with systolic blood pressure (SBP) less than 90 mmHg, diastolic blood pressure (DBP) less than 60 mmHg, heart rate (HR) less than 60 beats per minute, or postural decrease in SBP ≥ 20 mmHg or in DBP ≥ 10 mmHg.

The recommended dose in adults is 120 mcg for mild or moderate agitation and 180 mcg for severe agitation. Patients with mild or moderate hepatic impairment and mild to moderate agitation should receive 90 mcg. Patients with mild or moderate hepatic impairment and severe agitation should receive 120 mcg. Patients with severe hepatic impairment and mild to moderate agitation should receive 60 mcg. Patients with severe hepatic impairment and severe agitation should receive 90 mcg. Geriatric patients (patients ≥65 years old) with mild, moderate or severe agitation should receive 120 mcg. See Full Prescribing Information for recommendations on administering up to two additional doses and maximum recommended dosages.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies, 18%, 16%, and 9% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced orthostatic hypotension (defined as SBP decrease ≥ 20 mmHg or DBP decrease ≥ 10 mmHg after 1, 3, or 5 minutes of standing) at 2 hours post-dose. In those studies, 7%, 6%, and 1% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced HR ≤ 50 beats per minute within 2 hours of dosing. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension.

Reports of hypotension and bradycardia, including some resulting in fatalities, have been associated with the use of another dexmedetomidine product given intravenously (IGALMI is for sublingual or buccal use and is not approved for intravenous use). Clinically significant episodes of bradycardia and sinus arrest have been reported after administration of this other dexmedetomidine product to young, healthy adult volunteers with high vagal tone and when this product was given by rapid intravenous or bolus administration.

Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. In placebo-controlled clinical studies in adults with agitation associated with schizophrenia or bipolar I or II disorder, somnolence (including fatigue and sluggishness) was reported in 23% and 22% of patients treated with IGALMI 180 mcg and 120 mcg, respectively, compared to 6% of placebo-treated patients. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions: Symptoms of withdrawal have been observed after procedural sedation with another dexmedetomidine product administered intravenously. In this study, 12 (5%) adult patients who received intravenous dexmedetomidine up to 7 days (regardless of dose) experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing dexmedetomidine and 7 (3%) adult patients who received intravenous dexmedetomidine experienced at least 1 event related with withdrawal 24 to 48 hours after discontinuing dexmedetomidine. The most common withdrawal reactions were nausea, vomiting, and agitation. In these subjects, tachycardia and hypertension requiring intervention occurred at a frequency of <5% in the 48 hours following intravenous dexmedetomidine discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance and Tachyphylaxis: Use of another dexmedetomidine product administered intravenously beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of tolerance and tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS, Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IGALMI was evaluated in 507 adult patients with agitation associated with schizophrenia (N=255) or bipolar I or II disorder (N=252) in two randomized, placebo-controlled studies (Studies 1 and 2). In both studies, patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment. Patients were 18 to 71 years of age (mean age was 46 years old); 45% were female and 55% were male; 66% were Black, 31% were White, 2% were multiracial, and 1% were other.

In these studies, patients received an initial dose of IGALMI 180 mcg (N=252), IGALMI 120 mcg (N=255), or placebo (N=252). Patients who were hemodynamically stable (i.e., those with systolic blood pressure (SBP) > 90 mmHg, diastolic blood pressure (DBP) > 60 mmHg, and heart rate (HR) > 60 beats per minute) and without orthostatic hypotension (i.e., reduction in SBP < 20 mmHg or DBP < 10 mmHg upon standing) were eligible for an additional dose after 2 hours. An additional half dose (90 mcg, 60 mcg, or placebo) was given to 7.1% (18/252), 22.7% (58/255) and 44.0% (111/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively. After at least an additional 2 hours, an additional second half dose (total IGALMI dose of 360 mcg, total IGALMI dose of 240 mcg, or placebo, respectively) was given to 3.2% (8/252), 9.4% (24/255), and 21.0% (53/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively.

In these studies, one patient discontinued treatment due to an adverse reaction of oropharyngeal pain.

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were: somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

Adverse reactions that occurred in IGALMI-treated patients at a rate of at least 2% and at a higher rate than in placebo-treated patients in Studies 1 and 2 were as follows (adverse reaction is followed by percentage of patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Somnolence, includes the terms fatigue and sluggishness, (23%, 22%, 6%); Oral paresthesia or oral hypoesthesia (7%, 6%, 1%); Dizziness (6%, 4%, 1%); Hypotension (5%, 5%, 0%); Orthostatic hypotension (5%, 3%, <1%); Dry Mouth (4%, 7%, 1%); Nausea (3%, 2%, 2%); Bradycardia (2%, 2%, 0%); Abdominal discomfort, including dyspepsia, gastroesophageal reflux disease (2%, 0%, 1%).

Hypotension, Orthostatic Hypotension, and Bradycardia in Two Placebo-Controlled Studies: In clinical studies, patients were excluded if they were treated with alpha-1 noradrenergic blockers, benzodiazepines, antipsychotic drugs, or other hypnotics four hours prior to study drug administration; had a history of syncope or syncopal attacks; their SBP was less than 110 mmHg; their DBP was less than 70 mmHg; their HR was less than 55 beats per minute; or they had evidence of hypovolemia or orthostatic hypotension. In these studies, vital signs were monitored (at 30 minutes, 1-, 2-, 4-, 6-, and 8- hours post-dose), including orthostatic vital signs at 2-, 4-, and 8-hours post-dose. Maximum positional decreases in SBP and DBP after standing were observed at two hours post-dose. Maximal reductions on BP and HR were observed two hours post-dose.

The mean BP (in mmHg) and HR decrease (in bpm) across all patients from both studies at 2 hours post-dose were as follows for patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Mean SBP Decrease (15, 13, 1), Mean DBP Decrease (mmHg) (8, 7, <1), Mean Heart Rate Decrease (9, 7, 3). In the clinical studies: 13%, 8%, and <1% of patients in the single dose 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, experienced SBP ≤ 90 mmHg and a decrease ≥ 20 mmHg of SBP within 24 hours of dosing; 19%, 17%, and 2% of the patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a DBP ≤ 60 mmHg and a DBP decrease ≥ 10 mmHg within 24 hours of dosing; 4%, 3%, and 0% of patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute within 24 hours of dosing.

At 8 hours post-dose, 2% of patients in the IGALMI 180 mcg group experienced a SBP ≤ 90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 24 hours, none of the patients in the IGALMI 180 mcg group experienced a SBP ≤90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 8 hours post-dose, none of the patients in the IGALMI 180 mcg group had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute compared with one patient in the 120 mcg group (<1%) and none in the placebo group.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of another dexmedetomidine product given intravenously (IGALMI is not approved for intravenous use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Anemia; *Cardiac Disorders:* Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia; *Eye Disorders:* Photopsia, visual impairment; *Gastrointestinal Disorders:* Abdominal pain, diarrhea, nausea, vomiting; *General Disorders and Administration Site Conditions:* Chills, hyperpyrexia, pain, pyrexia, thirst; Hepatobiliary Disorders: Hepatic function abnormal, hyperbilirubinemia; Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram T wave inversion, gammaglutamyltransferase increased, electrocardiogram QT prolonged; *Metabolism and Nutrition Disorders:* Acidosis, hyperkalemia, hypoglycemia, hypovolemia, hypernatremia; *Nervous System Disorders:* Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder; *Psychiatric Disorders:* Agitation, confusional state, delirium, hallucination, illusion; *Renal and Urinary Disorders:* Oliguria, polyuria; *Respiratory, Thoracic and Mediastinal Disorders:* Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis; *Skin and Subcutaneous Tissue Disorders:* Hyperhidrosis, pruritus, rash, urticaria; *Surgical and Medical Procedures:* Light anesthesia;

Vascular Disorders: Blood pressure fluctuation, hemorrhage, hypertension, hypotension

DRUG INTERACTIONS

Drugs that Prolong the QT Interval: Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia. Avoid the use of IGALMI in combination with other drugs known to prolong the QT interval.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use of IGALMI with anesthetics, sedatives, hypnotics, or opioids is likely to lead to enhanced CNS depressant effects. Specific studies with another dexmedetomidine product given intravenously have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Due to possible enhanced CNS effects when given concomitantly with IGALMI, consider a reduction in dosage of IGALMI or the concomitant anesthetic, sedative, hypnotic, or opioid.

USE IN SPECIFIC POPULATIONS

Pregnancy, Risk Summary: There are no available data on IGALMI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal effects. Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects or miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

In animal reproductive studies fetal toxicity occurred in the presence of maternal toxicity with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 5 times the maximum recommended human dose [MRHD] of 360 mcg/day based on mg/m^2 body surface area. Adverse developmental effects, including early implantation loss and decreased viability of second generation offspring, occurred when pregnant rats were subcutaneously administered doses less than or equal to the MRHD based on mg/m^2 from late pregnancy through lactation and weaning *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data: *Animal Data*: Increased post-implantation losses and reduced live pups in the presence of maternal toxicity (decreased body weight) occurred in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine of 200 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (Gestation Day (GD) 5 to 16). No embryo-fetal toxicity was observed at 20 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2). No malformations were reported at any dose level.

No malformation or embryo-fetal toxicity were observed in a rabbit embryo-fetal developmental study in which pregnant dams were administered dexmedetomidine intravenously at doses up to 96 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring weights and grip strength were reported in a rat developmental toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at 8 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2) during late pregnancy through lactation and weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second generation offspring and an increase in early implantation loss along with delayed motor development occurred at 32 mcg/kg/day (equivalent to the MRHD of 360 mcg/day based on mg/m^2) when first generation offspring were mated. This study limited dosing to hard palate closure (GD 15-18) through weaning instead of standard dosing from implantation (GD 6-7) to weaning (PND 21).

Lactation, *Risk Summary*: Available published literature report the presence of dexmedetomidine in human milk following intravenous administration. There is no information regarding the effects of dexmedetomidine on the breastfed child or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IGALMI and any potential adverse effects on the breastfed child from IGALMI or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of IGALMI have not been established in pediatric patients.

Geriatric Use: Fifteen geriatric patients (≥ 65 years of age) were enrolled (no patients were 75 years of age and older) in the clinical studies for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder. Of the total number of IGALMI-treated patients in these clinical studies, 11/507 (2.2%) were 65 years of age and older. Dosage reduction of IGALMI is recommended in geriatric patients. A higher incidence of bradycardia and hypotension was observed in geriatric patients compared to younger adult patients after intravenous administration of another dexmedetomidine product. The pharmacokinetic profile of intravenous dexmedetomidine was not altered in geriatric subjects. Clinical studies of IGALMI did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in the effectiveness of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder compared to younger adult patients.

Hepatic Impairment: Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). Thus, a dosage reduction of IGALMI is recommended in patients with hepatic impairment compared to patients with normal hepatic function.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: IGALMI contains dexmedetomidine, which is not a controlled substance.

Dependence, Physical Dependence: Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. The dependence potential of dexmedetomidine has not been studied in humans. However, because studies in rodents and primates have demonstrated that intravenous dexmedetomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that dexmedetomidine may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance: Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). IGALMI has not been studied for longer than 24 hours after the first dose. There may be a risk for tolerance if IGALMI is administered in a manner other than indicated.

OVERDOSAGE: In a tolerability study of intravenous dexmedetomidine in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hour, the maximum blood concentration was approximately 13 times the upper boundary of the therapeutic range for the intravenous dexmedetomidine (IGALMI is not approved for intravenous use). The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second-degree heart block.

Five adult patients received an overdose of intravenous dexmedetomidine in intensive care unit sedation studies. Two patients who received a 2 mcg/kg loading dose (twice the recommended loading dose) over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading intravenous bolus dose of undiluted dexmedetomidine (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for overdosage management recommendations for IGALMI.

Distributed by: BioXcel Therapeutics, Inc., 555 Long Wharf Drive 12th Floor New Haven, CT 06511

US-IGA-2200049 November 2022

Treatment Updates in Alzheimer's Disease: Tailoring Management and Care Approaches to Improve Outcomes

Richard S. Isaacson, MD

This journal article is supported by an educational grant from Biogen

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

Alzheimer's disease (AD) is a devastating disease which develops over many decades before cognitive symptoms become apparent. Prevention rather than waiting until symptoms develop should be the goal. Cognitive enhancers and one agent that targets a component of the underlying pathology are available.

Key Points

- Biomarkers for AD are available to help improve diagnosis.
- Cholinesterase inhibitors and memantine are cognitive enhancers.
- Aducanumab is the first FDA-approved disease-modifying agent.
- Numerous other agents are on the horizon.
- The future is in finding better ways to prevent this devastating disease in those at risk.

ALZHEIMER'S DISEASE (AD) IS A SPECTRUM disease that develops over decades and affects about 40 million Americans. Preclinical disease has brain changes, including amyloid buildup and other nerve cell changes, already in progress, but significant clinical symptoms are not yet evident.[1] Mild cognitive impairment (MCI) is a stage marked by symptoms of memory, and/or other cognitive issues, which are greater than normal for a person's age and education, and which do not interfere with his or her independence.[2] People with MCI may or may not progress to Alzheimer's dementia. Alzheimer's dementia is the final stage of the disease in which symptoms such as memory loss, word-finding difficulties, and visual/spatial problems, are significant enough to impair a person's ability to function independently.[3]

Although people think of AD as a disease of old age, it is really a disease of middle age. The process of AD begins 20 to 30 years before the first memory loss symptom occurs. That leaves a long time to intervene. If someone already has dementia, that person has had AD for decades and effective treatment is not really possible if the brain cells have already died. Therefore, prevention is an important topic. The goal of preventive neurology is to identify people early in the process.

A combination of genetics, lifestyle, and environmental factors influence when AD begins and how it progresses. A rare type of familial Alzheimer's disease, called Early-Onset Alzheimer's Disease (EOAD), is caused by mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 genes. A person who inherits any of these mutations from a parent will surely develop Alzheimer's dementia before age 65 years. Genetic testing for the disease is common in families with a history of EOAD. The major genetic risk factor for the more common, sporadic form of the disease, or Late-Onset Alzheimer's disease (LOAD), is the

ε4 allele of the APOE gene. About 25 percent of the population carries the APOE variant which increases risk. Carrying this allele by itself does not mean a person has or will develop AD.

Initially, AD typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and hippocampus.[4] It later affects areas in the cerebral cortex responsible for language, reasoning, and social behavior. Beta-amyloid protein in several different molecular forms is thought to be involved in the pathologic process. One form, beta-amyloid 42, is thought to be especially toxic. It is formed from the breakdown of a larger protein, called amyloid precursor protein. In the Alzheimer's brain, abnormal levels of beta-amyloid clump together to form plaques that collect between neurons and disrupt cell function. Another pathologic aspect is neurofibrillary tangles caused by abnormal accumulation of tau protein that collect inside neurons. In AD, these tangles block the neuron's transport system, which harms the synaptic communication between neurons.

Clinical evaluation of a person with memory difficulties in everyday practice includes detailed clinical history, neuropsychological testing, B12 level, thyroid levels, blood panel, and liver function tests. Screening for neurosyphilis is not recommended unless there is high clinical suspicion. Genetic testing is controversial at this time but commercial testing for APOE ϵ4 allele and presenilin 1 and 2 is available.

Potential diagnostic biomarkers for AD include amyloid positron emission tomography (PET) scan, TAU PET scan, structural MRI, fluorodeoxyglucose (FDG)-PET, cerebrospinal fluid (CSF) and plasma beta-amyloid 42 to 40 ratio, CSF and plasma tau, and serum amyloid to tau ratio. Blood amyloid levels begin to increase decades before the onset of cognitive symptoms and may be a way to identify the disease earlier. A structural MRI that shows shrinkage of the hippocampus in a patient with progressive memory loss and a family history of AD is one of the least expensive ways to identify AD. Unfortunately, this approach has not caught on because it is not a definitive test.

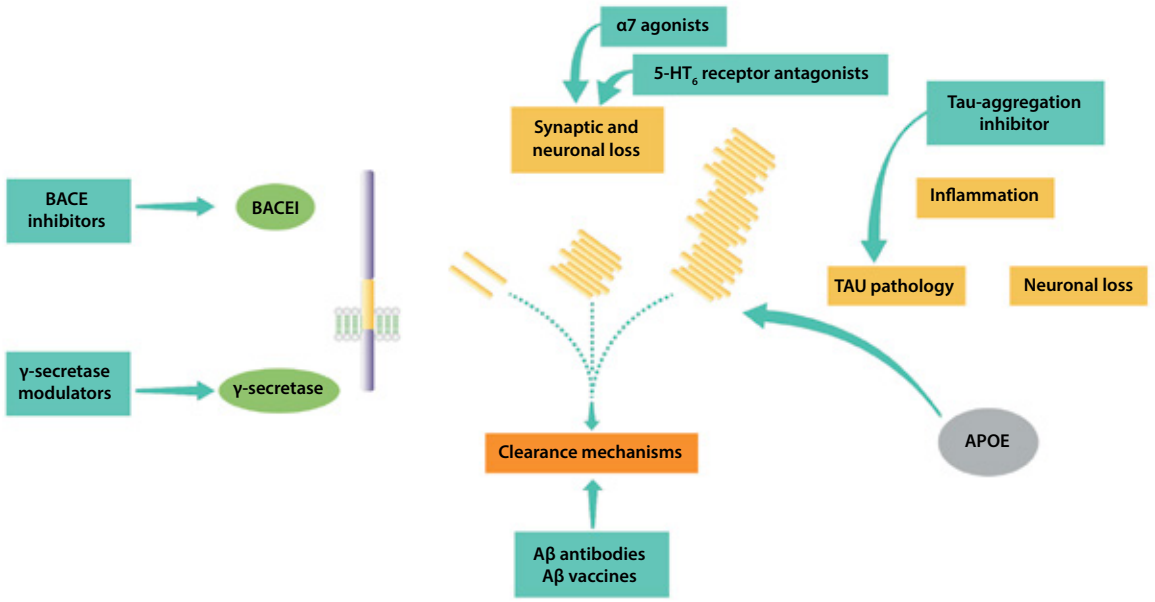
Amyloid PET using florbetapir (FDA-approved in 2012), flutemetamol (2013), and florbetaben (2014) estimate beta-amyloid (Aβ) plaques in cognitively impaired people. Amyloid PET is currently the only imaging modality recommended by the Alzheimer's Association and Alzheimer's and the Amyloid Imaging Task Force to support the diagnosis of AD.[5] Amyloid PET utilizes tracers that specifically bind to Aβ within amyloid plaques; a positive amyloid PET scan will show increased retention of tracer in regions of Aβ deposition within the brain.[6] Consequently, amyloid PET can strongly predict the presence of Aβ plaques in the brain and provide a means to directly assess relative brain amyloid pathology, thus, making it a useful tool to support the diagnosis of AD.[6,7] However, a positive amyloid PET scan does not definitively diagnose AD and these results must be combined with other clinical assessments, such as cognitive assessment, for an accurate diagnosis.

Previous research has shown that AD biomarkers from the brain can be detected in CSF 15 to 20 years before the onset of clinical symptoms.[8] Core AD CSF biomarkers, such as Aβ42 and phosphorylated tau (p-tau) and total tau (t-tau), can be measured to determine both the presence and severity of disease.[9] CSF Aβ42 and tau isoforms (p-tau and t-tau) have been shown to reach pathological levels during the early stages of AD and then remain stable during the disease course.[10] Amyloid and tau blood tests which don't have the risks of a spinal tap or the exposure of MRI or PET scan are part of the future of biomarkers for diagnosing AD.

Five medications are now FDA-approved for treating AD. Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine are considered cognitive enhancers which produce modest alleviation of symptoms (3 to 6 months delay in memory decline). These four agents had consistent effects in domains of cognition and global assessment but they do not prevent disease progression. They do provide modest cognitive and significant behavioral benefits which helps caregivers. Their role is in mild to moderate AD. Because of adverse events, patients need to begin with low doses of these agents and the dose should be increased slowly. It is recommended to start a cholinesterase inhibitor first and then add memantine. The combination of a cholinesterase inhibitor and memantine has been shown to delay nursing home placement by up to 18 months.

The newest therapy is controversial because of its cost, need for intravenous infusion, adverse events, and modest benefits. Aducanumab, an amyloid targeted monoclonal antibody, is considered a disease-modifying therapy for AD. Aducanumab is only for patients with MCI or in the mild dementia stage (the population in which treatment was initiated in the clinical trials). It is given as an every four-week intravenous infusion with a very slow dosing titration to prevent adverse events. Adverse events include hemosiderosis, microhemorrhage, brain edema, falling, headache, diarrhea, altered mental status, confusion, delirium,

Exhibit 1: Multiple Therapeutic Targets, Directed at AD Pathophysiology, are under Investigation



and disorientation. Amyloid-related imaging abnormalities (ARIA) which includes ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H) are the most serious. ARIA are white-matter lesions with or without evidence of brain edema obtained by neuroimaging which typically resolve. Their presence is not always associated with symptoms. These adverse events are primarily a function of being an APOE ε4 carrier and higher doses of anti-amyloid antibodies. Package labeling recommends a brain MRI be done prior to initiating treatment, prior to the seventh infusion, and prior to the twelfth infusion to monitor for ARIA. Some clinicians are doing additional MRIs, especially after dose increases. Medicare only covers this agent in context of a clinical trial which complicates the use of this agent. This agent does work in the right patient but the problem right now is identifying the right patient with precision.

Numerous other medications targeting various aspects of AD pathophysiology are under investigation (Exhibit 1). Recently, Phase III trial results for lecanemab, another anti-beta-amyloid monoclonal antibody, were published showing modest cognitive benefits but with similar adverse events to aducanumab.[11]

Prevention is really the key to managing AD in the future. There are both modifiable and non-modifiable risk factors for AD. Several RCTs have shown cognitive benefits from risk factor management in those at risk.[12-14] The ABCs of AD prevention are anthropometric, biomarker, and cognitive assessments to determine risk and then personalize treatment by targeting the individual's risk factors (Exhibit 2).[15] Alzheimer's Prevention Clinics at the New York-Presbyterian Weill Cornell Medicine Center use this ABC framework to apply evidence-based principles of clinical precision medicine to tailor individualized recommendations, follow patients longitudinally to continually refine the interventions, and evaluate N-of-1 effectiveness trials.[15] AD prevention programs primarily serve those with very early diagnosis and those with a family history. Modifiable risk factors are targeted with nonpharmacologic and pharmacologic therapies. Interventions may include nutrition, physical exercise, cognitive activities, music, stress reduction, social interaction, and sleep hygiene. Pharmacologic options may include various nutritional supplements (Exhibit 3). For example, in those with MCI and elevated homocysteine levels, supplementation with 0.8 mg folic acid, 0.5 mg B12, and 20 mg of B6 per day reduced the rate of brain atrophy by 53 percent and improved memory scores, category fluency, and episodic memory over two years compared to a control group.[16] A clinical trial of individualized multidomain interventions in people at risk for AD reduced AD and cardiovascular

Exhibit 2: ABCs of Alzheimer's Prevention Management[15]

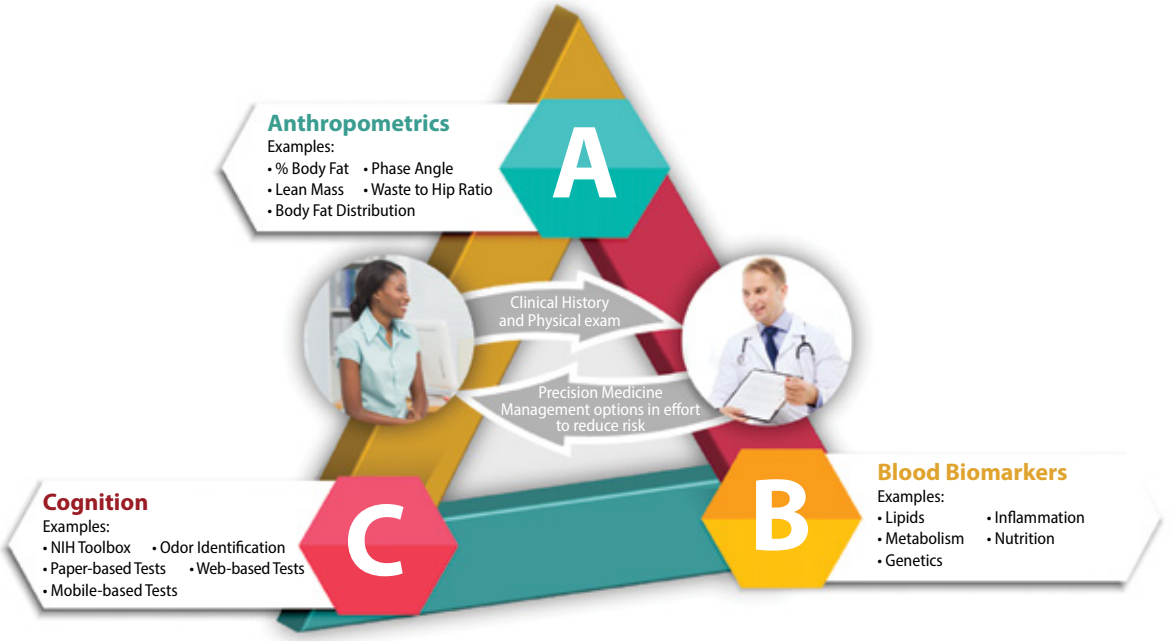


Exhibit 3: Pharmacologic Interventions

• Omega-3 fatty Acids – DHA > EPA ("Fish oil")
• Curcumin (Turmeric root)
• Folic Acid, B6, B12
• Vitamin D
• Caffeine/Coffee
• Dietary antioxidants
• Flavanols
• Medium chain triglycerides

disease risk scores and biomarkers and may improve cognition over 18 months.[17] This study did find that higher compliance with the prescribed interventions provided the most benefit. A first empirical trial in a clinical setting showed that individualized AD risk factor management may improve cognitive function related to AD pathology. From a practical clinical perspective, multi-domain individualized care may be applied for tens of millions of patients at risk for AD dementia. Further study in a large, multi-site, international cohort study, merits consideration.

Conclusion

Significant advances have been made in recent years in improving AD diagnosis. Biomarkers for AD are available to help support an accurate diagnosis. The currently available medications provide modest benefit but have the potential for significant adverse events. Aducanumab is the first FDA-approved disease-modifying agent but continues to be controversial. Numerous other agents targeting the underlying pathology of AD are on the horizon. In the near future, risk assessment and diagnosis will be driven by novel objective biomarkers. The future is finding a way to prevent this devastating disease.

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Navigating the Changing Landscape in the Treatment and Management of Acute Myeloid Leukemia: Key Considerations in Managed Care Decision Making

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This journal article is supported by educational grants from AbbVie; Bristol Myers Squibb; Jazz Pharmaceuticals

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Summary

There have been significant advances in the treatment of acute myeloid leukemia (AML) in the last decade. New targeted oral therapies are being used, in combination with chemotherapy in early disease, to treat relapsed/refractory disease, and in combination with older medications to manage older patients. The switch to outpatient oral therapies has presented some challenges.

Key Points

- Multiple new therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults.
- The unique toxicity profiles for many new medications, along with high acuity of AML patients, requires resources and excellent communication for optimal management in the community.
- There are opportunities for AML cost reductions if the new therapies are successful.

ACUTE MYELOID LEUKEMIA (AML) IS THE most common form of acute leukemia in adults. The American Cancer Society's estimated 20,050 new cases and 11,540 deaths for leukemia in the United States in 2022.[1] The median age at diagnosis is 65 years and five-year relative survival is 29.5 percent.

AML is molecularly very diverse. Various molecular mutations provide important prognostic and/or therapeutic information in AML including, best treatment strategies, transplant recommendations, and the significance of minimal residual disease (MRD) detection.[2] Advances in the molecular characterization have led to improved understanding of leukemogenesis and AML risk stratification, improved disease monitoring techniques, optimized therapeutic strategies, and the development of novel molecular-targeted therapeutics.[2]

Traditional treatment of AML focused on intensive induction of remission with daunorubicin and cytarabine followed by high-dose cytarabine or allogenic stem cell transplant. For those who were unable to undergo intensive treatment, symptomatic treatment with transfusions, treatment of infections, and hospice care were the only options. Modern non-intensive regimens are now numerous and are frequently used.

Improvements in non-intensive and intensive treatment and supportive care strategies over the past four decades have improved overall five-year survival rates in patients with AML. Rates were 9 percent, 15 percent, 22 percent, and 28 percent in the decades 1980 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2017, respectively.[3] Among those aged 70 years and older, the five-year survival rates were 1 percent, 2 percent, 3 percent, and 5 percent,

Exhibit 1: New Therapies Approved for AML 2017-2022

Year Approved	Drug	Class/Mechanism	Primary Indication
2017	Midostaurin (Rydapt®)	FT3L inhibitor	FT3L+, new AML
2017	Gemtuzumab Ozogamicin (Mylotarg®)	CD33 anti-body conjugate	CD33+, new AML
2017	Daunorubicin-cytarabine liposome (Vyxeos®)	Cytotoxic chemotherapy	New secondary AML
2017	Enasidenib (Idhifa®)	IDH2 inhibitor	IDH2+ rel/refr AML
2018	Venetoclax (Venclexta®)	BCL2 inhibitor	New, elderly AML (combined with azacitidine, decitabine, or cytarabine)
2018	Gilteritinib (Xospata®)	FT3L inhibitor	FT3L+ rel/refr AML
2018	Glasdegib (Daurismo®)	SMO inhibitor	New, elderly AML (combined with cytarabine)
2019	Ivosidenib (Tibsovo®)	IDH1 inhibitor	IDH1+ AML (new or rel/refr)
2020	Oral Azacitidine (Onureg®)	Hypomethylating agent	Maintenance in CR1
2020	Pemigatinib (Pemazyre®)	FGFR 1, 2 and 3 inhibitor	FGFR1 rearrangement rel/refr myeloid or lymphoid cancer
2022	Olutasidenib (Rezlidhia®)	IDH1 inhibitor	IDH1+ rel/refr AML

FLT3 = MS-like tyrosine kinase; rel/refr = relapsed/refractory; BCL = B-cell lymphoma/leukemia; IDH = isocitrate dehydrogenase; SMO = smoothened; FGFR = fibroblast growth factor receptor

respectively. The introduction of 11 new or improved agents since 2017 (Exhibit 1) hopefully will continue to improve outcomes in AML, particularly among older patients for whom there were few treatment options before 2017.

Six of the newer therapies target FMS-like tyrosine kinase 3 (FLT3) mutation, isocitrate dehydrogenase 1 or 2 (IDH1, IDH2) mutation, and fibroblast growth factor receptor (FGFR) 1, 2, or 3 rearrangements. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation. FLT3 ITD mutations occur in 25 to 30 percent of AML cases and result in poor prognosis and high rates of relapse after treatment; FLT3 TDK mutations occur in 5 to 10 percent of cases.[4,5] Gilteritinib is a next generation, more specific FLT3 inhibitor than previously available sorafenib and midostaurin and improves overall survival (OS). Enasidenib is an oral, selective inhibitor of mutant IDH2, and ivosidenib and olutasidenib target IDH1. Twenty to 30 percent of patients with AML have an IDH1 or IDH2 mutation.[6,7] Although IDH inhibitors demonstrate efficacy as monotherapy, recent trials have shown that they have higher response rates in combination with hypomethylating agents (HMAs).[7] Current trials of IDH inhibitors include combination with standard induction chemotherapy, as maintenance therapy, and in combination with venetoclax-based regimens. Pemigatinib is the newest targeted agent. It is an inhibitor of FGFR 1, 2 and 3 and is FDA approved for FGFR1 rearrangement relapsed or refractory myeloid or lymphoid cancer. A study in newly diagnosed AML is currently under way.

Venetoclax is an oral B cell lymphoma two (BCL2) inhibitor which selectively binds and inhibits BCL2, a pro-apoptotic protein, leading to the initiation of apoptosis in AML. In combination with hypomethylating agents it produces a very high rate of response (50% to 60%) and improves OS. Venetoclax plus azacitidine or decitabine is the National Comprehensive Cancer Network (NCCN) Guidelines preferred regimen for induction in those, who are over 60 years of age, who are not candidates for intensive remission induction chemotherapy.[8] Targeted therapy in those with IDH mutations is an option for induction but venetoclax containing regimens are Category 1 recommendations. Venetoclax is a highly myelosuppressive drug administered in the outpatient setting but infections are a significant risk.

Exhibit 2: Example Toxicities of Concern

Drug	Important Toxicities
Midostaurin	Nausea and vomiting Prolonged QT on electrocardiogram
Gilteritinib	Nausea and vomiting Prolonged QT on electrocardiogram Differentiation Syndrome
Enasidenib and Ivosidenib	Differentiation syndrome Prolonged QT on electrocardiogram Nausea and vomiting
Liposomal daunorubicin/cytarabine	Prolonged myelosuppression
Venetoclax	Severe myelosuppression
Oral Azacitidine	Nausea, Vomiting Neutropenia/thrombocytopenia

AML can develop after an antecedent myeloid malignancy [secondary AML (s-AML)], after leukemogenic therapy [therapy-related AML (t-AML)], or without an identifiable prodrome or known exposure (de novo AML).[9] A liposomal formulation of cytarabine and daunorubicin at a fixed five to one molar ratio was the first FDA-approved treatment specifically for patients with sAML or tAML. The approval was based on findings from a multicenter, randomized, open-label, Phase III study of this liposomal formulation versus standard cytarabine with anthracycline, in patients 60 to 75 years old with newly diagnosed sAML or tAML. In this study, there was a higher median OS with the liposomal formulation (9.56 versus 5.95 months, $p = 0.005$).[10]

Of the 11 new or improved agents since 2017, all but two are oral agents. Thus, there has been a major change in thinking in treating AML from primarily an inpatient chemotherapy/stem cell transplant focus to long-term outpatient oral-based therapies for many patients, particularly older patients. There are numerous challenges in this transition to outpatient care for a disease where many patients have high clinical acuity including distance from a primary treating center, patient transportation costs, education of community-based oncologists in management of AML, need for frequent visits to community oncologist to manage both therapy and adverse events, and resource strains (e.g., blood products to manage adverse events). Communication with tertiary specialists and accessibility of medical records between centers also contribute to the difficulty in managing oral therapies for those with AML. There are concerns that these challenges will affect overall efficacy of the regimens and negatively impact any potential cost savings when compared to the cost of stem cell transplants and chemotherapy regimen.

Another challenge is the unique toxicity profiles for many of the new medications used for AML (Exhibit 2). Community clinicians may not be aware of these and may assume that as many of these are oral agents, that they have minimal toxicity. One example is differentiation syndrome. It is caused by a large, rapid release of cytokines from leukemia cells as they die. Symptoms include unexplained fever, peripheral edema, hypotension, acute respiratory distress with interstitial pulmonary infiltrates, vascular capillary leak syndrome leading to acute renal failure, or pleuropericardial effusion. Differentiation syndrome occurs in about 20 percent of those who receive either ivosidenib or enasidenib.[11] Recognition and management of these toxicities requires education of community oncologists and emergency room personnel.

Another issue is the cost of these newer AML agents (Exhibit 3). In 2016 before targeted therapy became available, the mean total costs per patient with newly diagnosed AML were $386,077 in treated patients and $79,382 in untreated patients.[12] For treated patients, 60 percent of total costs ($231,867 per patient) were incurred during the initial health state, representing time without remission/relapse.

Exhibit 3: Costs of New Drugs are High

Drug	Average Wholesale Price
Midostaurin	$170.24 per 25 mg tablet
Gilteritinib	$300.00 per 40 mg tablet
Enasidenib	$1,029.79 per 100 mg tablet
Ivosidenib	$522.30 per 250 mg tablet
Venetoclax	$111.51 per 100 mg tablet
Glasdegib	$338.50 per 25 mg tablet
Oral Azacitidine	$1,650.14 per 200 mg tablet
Pemigatinib	$1,317 per 4.5 mg tablet

Mean monthly total healthcare costs were $21,055 and $4,854 among treated and untreated patients, respectively. Another study also showed substantial healthcare costs of treated elderly AML patients, particularly in the first year following diagnosis.[13]

Healthcare costs before targeted therapy were also substantial for patients whose disease relapsed. The mean total episode cost (from relapse date to death or end of study period) for all patients was $439,104 (with stem cell transplant $524,595 and without $263,310).[14] Inpatient visits accounted for the greatest cost component (mean $308,978) followed by intensive care unit stays (mean $221,537), non-clinician (e.g., lab tests) visits (mean $30,909), and outpatient pharmacy utilization (mean $24,640).

There are no published studies of pathway utilization and clinical and financial outcomes in AML treatment with the newer agents. Although no data on the overall costs of targeted therapy for AML have been published, the estimated costs for a patient over 60 years of age treated with targeted therapy are $250,000 per year. This translates to a $4.2 billion overall cost per year for cost of care of older AML patients (~17,000 cases per year).

Data on the overall costs of the newer therapies are needed. There is potential for costs savings compared to stem cell transplant and chemotherapy but there are barriers to these savings. Outpatient therapies are still complex, which could lead to a higher risk of adverse events and hospitalizations amongst patients cared for by less experienced clinicians. AML remains a disease with very limited curative potential, but this is changing. Extremely high drug prices make it mandatory to manage use appropriately such that any savings are not offset by increased hospitalization rates. Few strategies employ discontinuation of oral or maintenance therapies (fixed duration therapy) but this is a future option to identify those patients who would benefit from stopping therapy.

Conclusion

Multiple new therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults. The unique toxicity profiles for these new medications, along with high acuity of AML patients, will require resources and excellent communication for optimal management in the community. There is opportunity for AML cost reduction if the new therapies are successful. Future research should focus on patient financial burden of new oral AML medications and effects on outcomes.

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Innovative Approaches in the Management of Metastatic Breast Cancer: Managed Care Considerations on the Evolving Role of Targeted Therapy

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This journal article is supported by educational grants from Novartis Pharmaceuticals Corporation; Merck Sharp & Dohme LLC; AstraZeneca

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Summary

Therapies targeting selected genetic mutations and protein expression have dramatically changed the treatment of metastatic breast cancer. Three of these, PARP, PI3K, and CDK 4/6 inhibitors have all been shown to improve progression-free survival and, for some of the agents, overall survival.

Key Points

- For germline BRCA-mutated HER2 negative breast cancer, olaparib and talazoparib are therapeutic options.
- Germline BRCA testing should be considered in any patient meeting eligibility criteria for on label PARP inhibitor use.
- Alpelisib is the first FDA-approved PI3K inhibitor for hormone receptor positive HER2 negative PIK3CA-mutated metastatic breast cancer.
- Three CDK4/6 inhibitors are available for first-line treatment of hormone receptor positive HER2 negative metastatic breast cancer.
- Use of evidence-based guidelines and pathway-based care, patient assistance and education, and balanced cost sharing are keys to improving care for metastatic breast cancer while maximizing value.

THERE ARE AN ESTIMATED 168,000 PEOPLE in the United States (U.S.) living with metastatic breast cancer (mBC). The five-year survival rate for women with mBC is 29 percent and 22 percent for men.[1] It is estimated that 43,780 people (43,250 women and 530 men) will die from breast cancer this year. Treatment costs of mBC have been escalating with various new treatments becoming available; treatment costs are predicted to be $152 billion by 2030.[2]

DNA mutations are a precursor to the development of cancers including breast cancer. These mutations and damage are routine daily events and have endogenous (metabolic damage, replication errors) and exogenous (chemicals, ionizing radiation, ultraviolet light, viruses) causes. Cells must successfully repair DNA damage or they become old (senescence), die (apoptosis), or immortal (cancer).

Most changes to DNA are fixed by the body's repair system in a multistep process that starts with the detection of an abnormality in DNA structure. The abnormal DNA is removed and normal DNA is synthesized. Many mechanisms to maintain genomic stability are involved in DNA repair

including base excision repair, mismatch repair, nucleotide excision repair, single-strand annealing, homologous recombination, and nonhomologous end joining.

Breast cancer (BRCA) protein and poly ADP-ribose polymerase (PARP) are both involved in DNA repair. BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination and PARP is involved in base-excision repair. Cells with BRCA-gene mutations have nonfunctional homologous recombination but can repair DNA through base-excision repair but use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer. BRCA mutations can be germline (present in all cells) or somatic (present only in tumor cells).

PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in homologous repair deficient (HRD) cells such as from BRCA mutation. In cells with functional homologous recombination, the cell can still repair DNA when PARP inhibition is present. PARP inhibitors cause synthetic lethality in BRCA-mutated cells and two (olaparib, talazoparib) are currently approved for treating germline BRCA-mutated metastatic breast cancer.

The PARP inhibitors have been studied in germline BRCA mutated, human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer. In the trial that led to olaparib approval, oral olaparib twice a day was compared to standard of care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months versus 4.2 months; $p < 0.001$).[3] Overall survival (OS) was not statistically different. At 64 percent data maturity, median OS was 19.3 months with olaparib versus 17.1 months for chemotherapy.[4] The response rate was 59.9 percent in the olaparib group and 28.8 percent in the standard-therapy group. The rate of Grade 3 or higher adverse events was 36.6 percent in the olaparib group and 50.5 percent in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9 percent and 7.7 percent, respectively. Overall, olaparib monotherapy provided a median PFS survival advantage of 2.8 months and a 42 percent lower risk of disease progression or death compared with standard therapy.

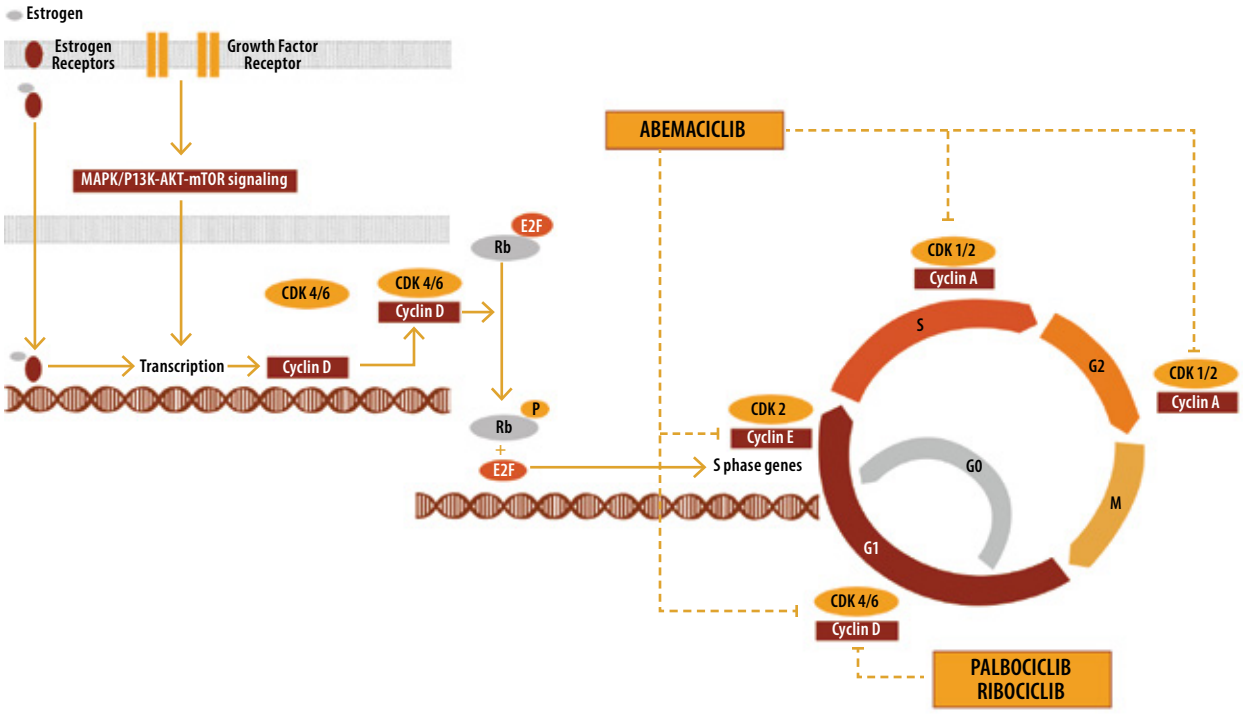
Talazoparib is the other PARP inhibitor approved for treating germline BRCA-mutated HER2 negative locally advanced or metastatic breast cancer. In the Phase III trial that led to FDA approval, subjects had no more than three prior lines of chemotherapy but had to have been treated with taxane and anthracycline previously. This trial compared oral talazoparib 1 mg once a day to standard of care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[5] The final median OS results were not statistically different (19.3 versus 19.5 months).[6] The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). Hematologic Grade 3 and 4 adverse events (primarily anemia) occurred in 55 percent of the patients who received talazoparib and in 38 percent of the patients who received standard therapy; nonhematologic Grade 3 adverse events occurred in 32 percent and 38 percent of the patients, respectively. Overall, like olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS.

BRCA-mutation testing in patients with mBC for treatment selection is not as straight forward as risk-stratified testing for prevention of BRCA-related cancers. In metastatic triple negative breast cancer about 14.6 percent of patients are found to have deleterious mutation, with 11.2 percent having BRCA1 or BRCA 2 mutations.[7] In Stage I to III unselected breast cancer patients, 10.7 percent had deleterious mutation, with 6.5 percent being BRCA1/2 mutation positive.[8] Positive family history for breast cancer suggestive of BRCA mutation enriches for positivity but will miss a portion of patients who could benefit from PARP inhibitors. Germline testing for BRCA mutation in HER2 negative mBC patients is a reasonable strategy because an effective therapy is available.

The cost of olaparib and talazoparib ranges from $15,000 to $20,000 per month which can be cost prohibitive for patients without prescription drug coverage. These agents still have significant toxicity which has to be communicated to patients but the toxicity is not much more than standard of care chemotherapy and these oral agents are much more convenient for patients. For now, PARP inhibitors should be used only in germline BRCA-mutated HER2 negative mBC patients as a line of therapy similar to chemotherapy. There is a need for more research to identify additional biomarkers for PARP inhibitor benefit to improve the cost/benefit ratio.

Mutations in the phosphatidylinositol 3-kinase (PI3K) gene are among the most frequent mutations in breast cancer; they occur in 40 percent of

Exhibit 1: CDK4/6 inhibitors in HR+ mBC[10]



hormone receptor (HR) positive breast cancer cases. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation, and the generation of tumors in in vitro and in vivo models. Alpelisib is an inhibitor of PI3K with inhibitory activity against PIK3CA and is the first in class agent approved by the FDA. Many more PI3K inhibitors are under investigation. In a cohort of patients with PIK3CA-mutated cancer, PFS was 11.0 months in the alpelisib-fulvestrant group, as compared with 5.7 months in the placebo-fulvestrant group ($p < 0.001$).[9] The most frequent adverse events of Grades 3 or 4 were hyperglycemia (36.6% in the alpelisib-fulvestrant group versus 0.7% in the placebo-fulvestrant group) and rash (9.9% versus 0.3%). Diarrhea of Grade 3 occurred in 6.7 percent of patients in the alpelisib-fulvestrant group, as compared with 0.3 percent of those in the placebo-fulvestrant group; no diarrhea of Grade 4 was reported. The percentages of patients who discontinued alpelisib and placebo owing to adverse events were 25.0 percent and 4.2 percent, respectively. To improve patient adherence with alpelisib, significant patient education on the adverse events and their management is required. Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR positive, HER2 negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Testing for PI3K mutations can be done with tumor-based (Foundation One CDX) or circulating tumor DNA (ctDNA, Guardant360) tests. Both are predictive of therapy response but ctDNA may be the better choice. The testing algorithm specifies if ctDNA is negative, the clinician should consider tissue testing. PI3K-mutation testing should be considered in all patients with HR positive HER2 negative mBC to guide therapy selection.

The cyclin-dependent kinase (CDK) 4/6 inhibitors have revolutionized treatment of HR positive HER2 negative mBC. These medicines interrupt the process through which breast cancer cells divide and multiply by inhibiting kinase activity, which phosphorylates the retinoblastoma protein pathway. By blocking this path, CDK 4/6 inhibitors are able to block cell-cycle progression in the middle of the G1 phase and prevent cancer cell progression (Exhibit 1).[10] A large number of patients are eligible for CDK 4/6 inhibitors because their mechanism of action does not depend on a mutation being present.

Palbociclib, ribociclib, and abemaciclib are the three FDA-approved CDK 4/6 inhibitors available in the U.S. Palbociclib was the first approved in

Exhibit 2: Comparing the CDK 4/6 Inhibitors

	Palbociclib	Ribociclib	Abemaciclib
Half-life	29 (+/-5) hours	32 hours	18.3 hours
Primary site of metabolism	Hepatic	Hepatic	Hepatic
Cell Cycle Arrest	G1 phase	G1 phase	G1, G2 phase
Targets	CDK4 and CDK6	CDK4 and CDK6	CDK1, CDK2, CDK4, CDK5, CDK6, CDK14, CDK16, CDK17, CDK18
Dosing	12mg once daily for 21 days followed by 7 days off	600mg once daily for 21 days	150mg twice daily continuously
Myelosuppression	++	++	+
GI toxicity	+	+	++
LFT abnormalities	-	+	+
Pneumonitis	+ (rare)	+ (rare)	+ (rare)

2015 and the other two in 2017. In 2021, abemaciclib was also approved in combination with endocrine therapy (tamoxifen or aromatase inhibitor) for the adjuvant treatment of adult patients with HR positive, HER2 negative, node-positive, early breast cancer at high-risk of recurrence and a Ki-67 score ≥ 20 percent as determined by an FDA-approved test. The Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent in resting cells (G0). The Ki-67 score is a marker of cellular proliferation and has been shown in early HR positive breast cancer to identify a subset of patients with high proliferation who derive greater benefit from adjuvant treatments.[11]

A meta-analysis of the clinical trials with these agents found that adding a CDK 4/6 inhibitor to hormone therapy is beneficial in terms of PFS, irrespective of the presence of visceral metastases, the number of metastatic sites, and the length of the treatment-free interval (TFI).[12] The addition of CDK4/6 inhibitors produces a significant OS improvement, both in aromatase inhibitor (AI)-sensitive and AI-resistant patients.[12] Real-world evidence on the efficacy and OS benefits of this class are now being published.[13]

The adverse event (AE) profiles of the three CDK 4/6 inhibitors are similar, but each medication has some unique AEs (Exhibit 2). The most common AEs reported with these agents are neutropenia, leukopenia, fatigue, nausea, infection, arthralgia, anemia, headache, and diarrhea. Aside from neutropenia and leukopenia, the majority of patients have Grade 1 or 2 AEs. Grade 3 or 4 neutropenia and leukopenia, which are very common with all CDK inhibitors but particularly with palbociclib and ribociclib, are managed with dose interruption and/or reduction. Complete blood count (CBC) should be monitored at baseline, every two weeks for the first two cycles of therapy, at the beginning of each subsequent four cycles, and as clinically necessary for bone marrow suppression. Ribociclib causes a higher incidence of liver function test abnormalities than the other agents and can cause QT interval prolongation. This agent should not be given in combination with other agents such as antiarrhythmics which also prolong the QT interval. Abemaciclib is associated with a significantly higher incidence of diarrhea compared with palbociclib and ribociclib; cases occur mostly during the first cycle and can be managed with antidiarrheal therapy. Abemaciclib is also associated with serum creatinine elevation and venous thromboembolic events (mostly mild), which have not been reported for the other two. The FDA has warned prescribers that rare but severe, life-threatening, or fatal interstitial lung disease (ILD) and pneumonitis can occur in patients treated with CDK 4/6 inhibitors. Therefore, patients should be monitored regularly for pulmonary symptoms indicative of ILD and/or pneumonitis.

All these newer targeted therapies are expensive requiring a holistic approach to maximize value-based care and patient adherence. Clinicians and managed care need to quickly integrate targeted

therapies into evidence and guideline concordant coverage policies to maximize value. A streamlined prior authorization process will help improve evidence-based care. If multiple options within a class of therapy with equal efficacy exist, formulary and step rules may help contain costs. All stakeholders including clinicians, manufacturers, government, pharmacy benefit managers and pharmacists need to work together to address overall therapy costs, rebates, product steering, and patient cost-sharing concerns affecting patient adherence, clinical outcomes, and overall value. Various stakeholders can work together with specialty pharmacy to develop patient management and drug dispensing processes to reduce medication waste.

Conclusion

For germline BRCA-mutated HER2 negative mBC, olaparib and talazoparib are therapeutic options. Germline BRCA testing should be considered in any patient meeting eligibility criteria for on-label PARP inhibitor use. Alpelisib is the first FDA-approved PI3K inhibitor for hormone receptor positive HER2 negative PIK3CA-mutated mBC. Three CDK4/6 inhibitors are available for first-line treatment of hormone receptor positive HER2 negative mBC. Use of evidence-based guidelines and pathway-based care, patient assistance and education, and balanced cost sharing are keys to improving care for mBC while maximizing value.

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Recent Advances in the Treatment and Management of Non-Small Cell Lung Cancer: Managed Care Perspectives for Improved Patient Outcomes

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This journal article is supported by educational grants from Novartis Pharmaceuticals Corporation; Amgen; Merck Sharp & Dohme LLC; AstraZeneca

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Summary

For those patients who have targetable tumor mutations, various targeted therapies are the first-line therapy of choice but immunotherapy alone, or in combination with chemotherapy, is the first-line choice for the majority of patients with Non-Small Cell Lung Cancer (NSCLC). Both immunotherapy and targeted therapies have improved outcomes for this disease in the advanced stage.

Key Points

- Selected genetic mutations and tumor histology drive therapeutic choices.
- Targeted therapy is first line for those with selected genetic mutations.
- Immunotherapy plus platinum-based chemotherapy doublets is standard for those without mutations.
- Anti-angiogenic therapy can enhance the impact of immunotherapy.
- Immunotherapy alone is a first-line option in selected patients.

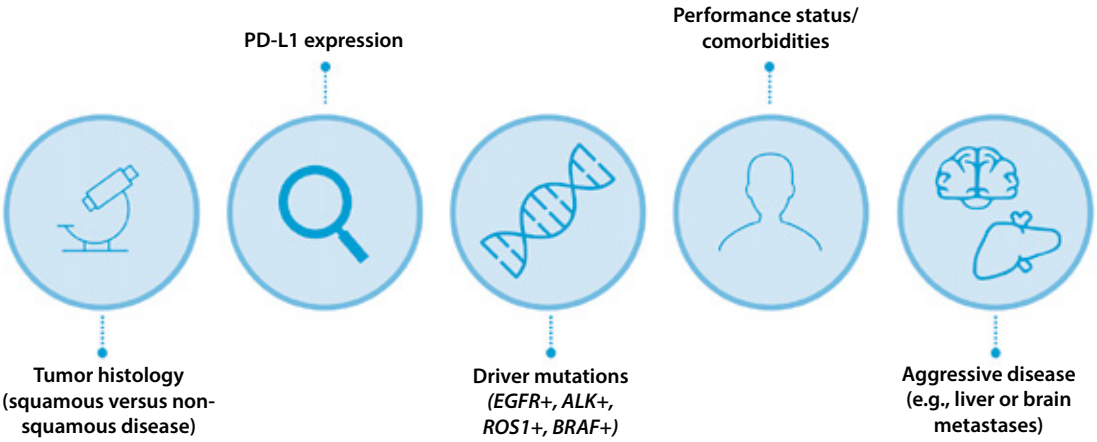
LUNG CANCER IS THE MOST COMMON CAUSE of cancer-related mortality in the United States and accounts for more deaths than breast, prostate, and colorectal cancers combined. The median age at diagnosis is 70 years and the major risk factor is smoking. Lung cancer is typically diagnosed at the later stages of the disease because lung cancer screening is not routinely practiced. Lung cancer is a very heterogeneous disease in terms of histology and molecularity; NSCLC the most common histological type.[1,2]

Treatment of advanced or metastatic NSCLC has evolved from chemotherapy in the 1980s and 90s to targeted therapy aimed at the various genetic mutation disease drivers and the addition of anti-angiogenics to chemotherapy in the 2000s. Checkpoint inhibition immunotherapy was introduced in 2015. Combinations of chemotherapy and anti-angiogenics with checkpoint inhibitors beginning in 2017 are the most recent advances.

The treatment of NSCLC results in a high economic burden. From 2010 to 2019, the total costs have been increasing, mainly driven by outpatient costs for systemic therapy, which might reflect the greater use of immunotherapy for advanced NSCLC since 2015. The total mean cost for NSCLC treatment was $250,942 per person per year.[3] Costs for inpatient services, other outpatient services, and pharmacy services remained stable but still accounted for the majority of the economic burden (60%). Further studies are required to assess the impact of innovative treatments on the disease management costs of advanced NSCLC.[3]

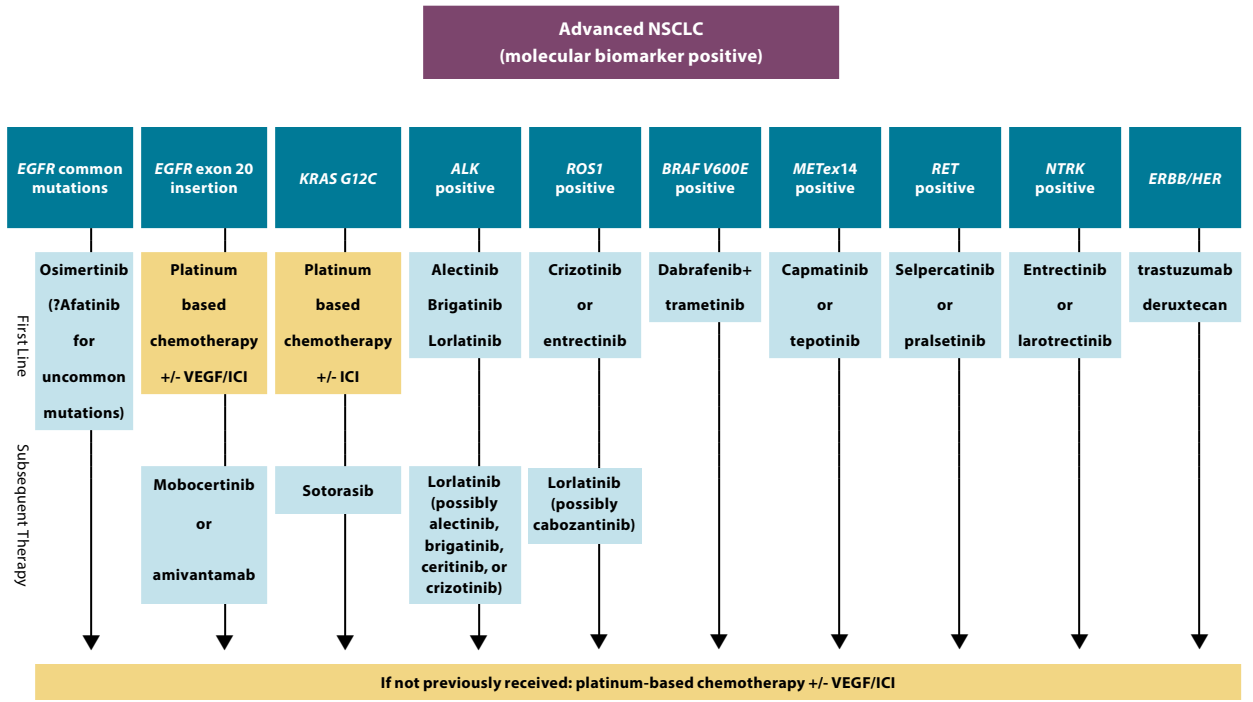
The major factors in selecting therapy are shown

Exhibit 1: How is a Regimen Chosen?



PD-L1 = programmed death ligand one

Exhibit 2: Approved Targeted Therapies for Molecular Biomarker-Positive NSCLC[5]



in Exhibit 1. Genomic testing is especially important because survival is as much as 12 months better in those with targetable mutations who receive appropriate targeted therapy compared with those who do not receive targeted therapy for a known mutation or have no targetable mutations.[4] Immunotherapy is relatively ineffective in those with actionable mutations and may pose a risk of worsened toxicity with targeted therapy if the patient is exposed to immunotherapy first. The National Comprehensive Cancer Network (NCCN) Guidelines recommend testing for EGFR, KRAS, BRAF, ERBB2 (HER2), and MET exon 14 skipping mutations; ALK, RET, and ROS1 rearrangements;

NTRK1/2/3 gene fusion; and programmed death-ligand 1 (PD-L1) expression in eligible patients with advanced or metastatic NSCLC.[5] Liquid biopsy (plasma) testing is an option if tissue is inadequate. Importantly, comprehensive genomic testing at the time of diagnosis in Stage IV NSCLC (non-squamous and selected squamous) is the standard of care and is not an option. Not identifying all actionable alterations is bad medicine. One real-world study of community oncology practices found that only 22 percent of those with advanced NSCLC were tested for the four main mutations and only 7 percent were tested for the seven for which targeted therapy was available at the time of the study.[6] This study also found underutilization of targeted therapies and immunotherapy being used first line in those with targeted mutations.

If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment, except in case of certain mutations where chemotherapy is first-line (Exhibit 2).[5] Approximately 30 percent of NSCLC cases are found to have an epidermal growth factor receptor (EGFR) mutation. Osimertinib is the tyrosine kinase inhibitor (TKI) of choice for common EGFR mutations (exon 19 and L858R).[5] Afatinib is approved for uncommon mutations (G719X, L816Q, S786I) and is an option for those. Two therapies have been approved (2021) for exon 20 insertion mutations (mobocertinib and amivantamab) after progression on platinum-based chemotherapy.

KRAS mutations occur in about 30 percent of NSCLC cases but an FDA-approved therapy is only available for KRAS G12V which occurs in about 6 percent of cases.[7] Sotorasib is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. This indication was FDA approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). In the Phase II study of sotorasib, an objective response was observed in 46 patients (37.1%) including in four (3.2%) who had a complete response and in 42 (33.9%) who had a partial response.[8] The median DOR was 11.1 months, median progression-free survival (PFS) 6.8 months, and median overall survival (OS) 12.5 months.

If the patient has no oncogenic driver, checkpoint inhibitor immunotherapy with or without chemotherapy is the treatment option, depending on the expression of PD-L1. PD-L1 expression testing should be performed on all initial biopsies and results typically take a few days. Ideally, final therapeutic decisions should not be made until full genomic information is available because initial immunotherapy followed by a tyrosine kinase inhibitor-targeted therapy exposes patients to undue risks. PD-L1 expression of 50 percent or higher is associated with favorable outcome with immunotherapy alone.

In patients who had greater than 50 percent expression of PD-L1 on their tumor and no targetable mutations, first-line immunotherapy for advanced NSCLC with pembrolizumab, atezolizumab, or cemiplimab improves OS and PFS.[9-11] Immunotherapy has also been studied in those with PD-L1 expression of 1 to 49 percent. Pembrolizumab monotherapy is an option in those with lower PD-L1 expression especially for a weakened patient but most clinicians prefer using immunotherapy in combination with chemotherapy because of a 20 to 25 percent better overall response rate compared to immunotherapy alone. Overall, monotherapy with immunotherapy is an acceptable standard for high PD-L1 expressors but may not be optimal for all high expressors (high tumor volume, heavy symptom burden). Low expressors or PD-L1 negative patients are best served with chemo-immunotherapy combinations.

There is a rationale for combining immunotherapy, chemotherapy, and anti-angiogenics (bevacizumab) in non-squamous NSCLC.[12-17] The critical role of angiogenesis in promoting tumor growth and metastasis and consequently blocking this pathway as a therapeutic strategy has demonstrated great clinical success for the treatment of cancer but it has also been discovered that bevacizumab has effects in reprogramming the tumor milieu from an immunosuppressive to an immune permissive microenvironment in human cancers.[12] Atezolizumab and pembrolizumab have been studied in these triple combinations and are recommended options in the NCCN Guidelines.[5] For example, the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS (8.3 versus 6.8 months) and OS (19.2 versus 14.7 months) among patients with metastatic nonsquamous NSCLC compared to bevacizumab/chemotherapy, regardless of PD-L1 expression and EGFR or ALK genetic alteration status.[18]

Overall, immunotherapy has revolutionized the treatment of advanced NSCLC and is part of the treatment regimen for the majority of patients with NSCLC. Both monotherapy as well as combinations with chemotherapy have changed outcomes. There are subsets of advanced NSCLC patients that may derive great benefit particularly in combination with bevacizumab. Although PD-L1 is an established (but not perfect) biomarker, other biomarkers are needed to help identify patients at the time of diagnosis who

will derive benefit from immunotherapy.

For those patients with advanced NSCLC who have no driver mutations and are ineligible for immunotherapy, chemotherapy is the standard of care. Chosen regimens will depend on whether the disease is squamous or nonsquamous.

Conclusion

Advanced NSCLC is an increasingly complex disease where histology, selected genetic mutations, and PD-L1 expression drive therapeutic choices. For patients with a targetable genetic mutation, targeted therapy should be used first. Platinum-based doublets in combination with immunotherapy is standard treatment for the majority of patients with advanced NSCLC without targetable mutations. Anti-angiogenic therapy appears to enhance the impact of immunotherapy and may be added to the regimen. Immunotherapy alone is a first-line option in selected patients.

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Clinical Management and Key Considerations to Target Optimal Treatment of Inflammatory Bowel Disease

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This journal article is supported by an educational grant from Bristol Myers Squibb

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Summary

Treatment of inflammatory bowel disease (IBD) during the early phase of the disease is important so as to avoid long-term damage from chronic inflammation. There are now multiple treatments available for moderate-to-severe IBD which when used appropriately should reduce the rate of complications.

Key Points

- Treat-to-target should be the management strategy for IBD.
- Several biologic agents are available for treating moderate-to-severe IBD.
- A new class was approved in mid-2022 for Crohn's disease.
- Tofacitinib and ozanimod are oral agents for induction and remission of moderate-to-severe ulcerative colitis.

THE INFLAMMATORY BOWEL DISEASES (IBD) represent a group of disorders of unknown cause that result in chronic intestinal inflammation, typically with a relapsing and remitting course. IBD includes Crohn's disease (CD), ulcerative colitis (UC), intermediate colitis, microscopic colitis (collagenous and lymphocytic), infectious colitis, ischemic colitis, radiation colitis, and drug-induced colitis. Indeterminate colitis which occurs in 10 to 15 percent of IBD cases has overlapping symptoms, histology, and pathology of both CD and UC. For the remainder of this article, IBD will only refer to CD and UC.

IBD affects a substantial proportion of the United States population. In 2016, one in 209 adults and one in 1,299 children aged 2 to 17 years were diagnosed with IBD.[1] Prevalence of IBD has been increasing compared with previously published 2009 data. Males and females are equally affected and the age of onset is usually 15 to 35 years, although IBD can develop at any age with 10 to 15 percent of new cases in adults 60 and over. Overall, IBD is a chronic, lifelong disease without medical cure.

Family history is the strongest risk factor for developing IBD. The rate of monozygotic twin concordance is 44 to 58 percent for CD and 6 to 18 percent for UC. The lifetime risk of developing IBD in first-degree relatives is 8.9 percent for offspring and 8.8 percent for siblings. Seventy-five to 80 percent of multiple affected families are concordant for disease type. Genome-wide searches have identified multiple genes that increase or decrease risk for IBD.

The pathogenesis of IBD is thought to be an interaction of genetic susceptibility, immune dysregulation, and environmental triggers. A defect in intestinal mucosal integrity appears to cause inappropriate and persistent immune activation against luminal antigens, leading to mucosal inflammation and damage. Environmental triggers include infection, nonsteroidal anti-inflammatories, smoking, diet, and early exposure to antibiotics.

The diagnosis of IBD is made utilizing clinical, laboratory, endoscopic, radiologic, and histologic features. Diagnosis of CD can be more difficult than

Exhibit 1: Potential Complications of IBD

Crohn's Disease	Ulcerative Colitis
• Anemia	• Anemia
• Bowel stenosis/perforation	• Bowel perforation
• Fistula formation	• Colorectal carcinoma
• Perianal disease	• Hemorrhage
• Calcium oxalate stones	• Toxic megacolon
• B12 malabsorption	• Malnutrition
• Colorectal carcinoma	
• Malnutrition	

UC. Gastrointestinal specific complaints of IBD include diarrhea, abdominal pain, rectal bleeding, and weight loss. Patients can also have extraintestinal manifestations. These are present in 10 percent of patients at presentation and up to 30 percent of patients over time. Extraintestinal manifestations of IBD include colitic arthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, episcleritis, iritis, uveitis, primary sclerosing cholangitis, autoimmune hepatitis, clotting disorders, and other autoimmune disorders.

Ulcerative colitis features are diffuse superficial mucosal disease, rectal involvement, contiguous inflammation, backwash ileitis (inflammation in the distal ileum thought to be due to backward movement of cecal contents), mucosal inflammation, loss of mucin, branching and foreshortening of glands, and crypt abscess. At diagnosis, 44 percent of patients have rectal only disease, 36 percent left side of colon disease, and 18 percent have pancolitis.[2]

Crohn's disease has transmural and segmental inflammation (skip lesions) usually affecting the small bowel and colon and may spare the rectum. The transmural inflammation leads to granuloma formation, submucosal fibrosis, muscular hypertrophy, and strictures. Forty percent of patients have ileocolitis, 25 percent colitis, 30 percent ileitis/jejunoileitis, and 5 percent gastroduodenitis at diagnosis.[2] On physical examination there may be peri-anal lesions, fistulae, and abdominal masses with CD. CD has three phenotypes – inflammatory, stenosing, and fistulizing. Because of the chronic inflammatory process, there are significant potential complications of both CD and UC (Exhibit 1).

Early diagnosis and treatment of UC and CD are important. Targeting the underlying immune process early in the disease can be disease-modifying which would prevent strictures and the need for surgery. Early disease is when there is major inflammation and there is a window of opportunity to intervene before structural damage is done.[3]

The goals of treatment are induced disease remission; maintain remission; maintain quality of life; prevent disease and therapy-related complications, hospitalizations, and surgery; and optimize timing of surgery. Disease location and severity may help dictate the necessary treatment modalities. Another factor in selecting therapy is risk for rapid progression in CD (Exhibit 2).[4] For

Exhibit 2: Risk Stratification to Identify Patients at Increased Risk for Rapid Progression of Crohn's Disease[4]

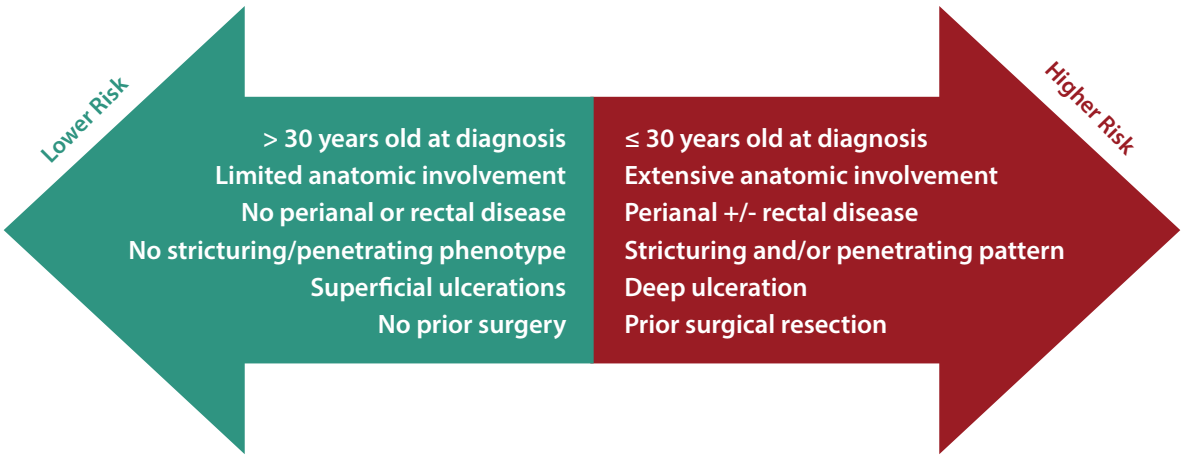

Exhibit 3: Advantages and Disadvantages of Biologics and Small Molecules for IBD

Class/Agent	Pros	Cons
Anti-TNF (Infliximab, adalimumab, certolizumab, golimumab)	60% to 90% initial response; ~ 50% continued response Several choices available for CD and/or UC Biosimilars for infliximab and adalimumab (2023) Effective when used with immunomodulators Self administered (except infliximab)	Systemic immunosuppression Tuberculosis/opportunistic infection warnings Need for viral hepatitis testing
Anti-Integrins/Anti-MAdCAM (Vedolizumab and Natalizumab – CD only)	Selective effect on gut-homing cells Favorable safety profile to date Equivalent efficacy to other mechanisms of action No PML cases in otherwise healthy patients with IBD	Intravenous administration Slower time to response ? Effect on non-gut manifestations
IL-12/23 Inhibitors (Ustekinumab)	Limited immune modulation Efficacy in anti-TNF failures Low rates of immunogenicity Self-administered	Systemic immunosuppression but less than anti-TNFs
IL 23 inhibitor (Risankizumab) Only for CD	Self administered Limited immune modulation Efficacy in anti-TNF failures Low rates of immunogenicity	Systemic immunosuppression but less than anti-TNFs
JAK Inhibitor (Tofacitinib and Upadacitinib) Only for UC	Oral agent Induction and maintenance efficacy Small molecule so no immunogenicity	Systemic immunosuppression Zoster (1.5% to 5%) Off-target effects; blood counts, HDL/LDL Black box warning for VTE Lab monitoring
S1P1 Modulator (ozanimod) Only for UC	Oral agent Induction and maintenance efficacy Small molecule so no immunogenicity	Systemic immunosuppression Need for EKG prior to initiation with certain patients not eligible for treatment (diabetes, cardiac conditions, etc.) Potential drug on drug interactions

CD = Crohn's disease; UC = ulcerative colitis; TNF = tumor necrosis factor; PML = Progressive multifocal leukoencephalopathy; IL = interleukin; JAK = Janus kinase; S1P = sphingosine-1-phosphate

those at elevated risk of rapid progression, early use and optimization of advanced therapies (small molecules and biologics) is recommended. Just reducing or elimination symptoms is not enough to avoid long-term complications; patients can have underlying ongoing inflammation and intestinal damage without symptoms.[5]

Treat-to-target in IBD is recommended by the American College of Gastroenterology guidelines and means achieving a disease remission using clearly defined and objective markers to prevent progressive bowel damage and complications.[6] The objective markers are serologic [C reactive protein (CRP) reduction], endoscopic (mucosal healing), and radiographic (computed tomography enterography improvement). A deep remission in CD is defined as Crohn's disease activity index score (CDEIS) < 150, no corticosteroids for eight weeks or more, no fistula, Crohn's disease endoscopic index of severity (CDEIS) < 4, and no deep ulcers. A biologic remission in CD is fecal calprotectin < 250 µg/g, CRP < 5 mg/L, and CDEIS < 4. A treat-to-target approach in CD results in higher rates of both deep and biologic remission.[7] Thus, treat-to-target is a management strategy that can lead to improvements in patient outcomes.

Corticosteroids, purine analogs, methotrexate, sulfasalazine, and mesalamine are all older treatment options for IBD. Azathioprine and

Exhibit 4: Contemporary Risk of Surgery in Patients With IBD[8]

Before 2000			
	1-year risk of surgery	**5- to 7-year risk of surgery**	**10-year risk of surgery**
Ulcerative colitis	4.8% (3.7 to 6.1)	9.5% (7.8 to 11.4)	16.2% (12.6 to 19.8)
Crohn's disease	23.6% (18.3 to 29.9)	35.7% (29.2 to 42.9)	46.5% (36.7 to 56.6)
After 2000			
	1-year risk of surgery	**5- to 7-year risk of surgery**	**10-year risk of surgery**
Ulcerative colitis	2.8% (2.0 to 3.9)	7.0% (5.7 to 8.6)	9.6% (6.3 to 14.2)
Crohn's disease	12.3% (10.8 to 14.0)	18.0% (15.4 to 21.0)	26.2% (23.4 to 29.4)

6-mercaptopurine are used in combination with TNF inhibitors to prevent anti-drug antibodies; these agents are no longer used alone for IBD. Sulfasalazine and mesalamine are used for mild disease. In mild disease, oral therapies and rectal therapies may be used in combination to induce remission. Once remission is achieved, the rectal therapies are stopped. Corticosteroids may be used to induce remission in mild disease but should be tapered off once remission is achieved.

For moderate-to-severe IBD, remission can be induced with corticosteroids, biologics, and small molecules. As in mild disease, corticosteroids should only be used for remission induction in moderate-to-severe IBD and never to maintain remission. Sixty to 80 percent of patients with IBD attain remission over a one- to three-month course. Corticosteroids cause numerous well known adverse events, especially with long-term use.

Most patients with moderate-to-severe disease will be treated with a biologic or a small molecule agent which are targeted therapy for IBD. Anti-tumor necrosis factor (TNF) agents will be used with or without an immune modulator (purine analogs, methotrexate). Exhibit 3 contains advantages and disadvantages of the biologic and small molecule agents. All of these are FDA-approved for remission induction and maintenance.

It is important that any therapy chosen for IBD is optimized before it is abandoned. IBD therapies do not work quickly. Three to four months is considered an adequate trial when treating UC and four to six months for CD for inflammation to calm down. Clinicians should be following a treat-to-target approach using objective measures to decide whether to switch therapy.

Some patients will require surgical intervention for their disease. Indications for surgery include perforation or uncontrollable hemorrhage, intractable or fulminant disease, suspicion or identification of cancer, growth retardation in children, systemic complications of the disease or medication, anorectal disease/fistula (CD), intra-abdominal abscess (CD), and intestinal obstruction due to stricture (CD). Typical surgical procedures in CD are stricturoplasty, resection of small intestinal segment, colectomy (partial or complete), and proctocolectomy. A proctocolectomy with ileostomy or restorative (ileoanal or J pouch) is most common in UC. Appropriately timed surgery can significantly improve quality of life in patients with IBD.

Historically, surgical intervention was required in two-thirds of CD patients and as many as one-third of UC patients. Patient-level risks of surgery have decreased significantly over time, with a five-year cumulative risk of surgery of 7.0 percent in UC and 18.0 percent in CD in contemporary cohorts (Exhibit 4).[8] This decrease is related to early diagnosis and/or better treatment including biologics which were first introduced for IBD in 2000.

Many more targeted therapies are under investigation for managing IBD. Mirikizumab (interleukin 23 inhibitor), guselkumab (interleukin 23 inhibitor already FDA-approved for psoriasis and psoriatic arthritis), and etrasimod (sphingosine-1-phosphate 1,4,5 agonist) are the three closest to market.

Conclusion

IBD is caused by chronic inflammation in the gut which can result in serious complications including colon cancer. Changing the course of IBD is possible with early diagnosis and intervention, treat-to-target, and tight control. Clinicians should set treatment goals to target not only symptom relief but more importantly disease remission based on markers of

inflammation and examination of the gastrointestinal tract. Numerous biologic and small molecule agents targeted at the underlying inflammatory process are now available and more are on the way.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Hereditary Angioedema: Managed Care Considerations for Improved Patient Outcomes

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This journal article is supported by educational grants from CSL Behring and BioCryst

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Summary

Hereditary angioedema (HAE) is a rare, potentially fatal disease which can also be very debilitating. Because of the impact of the swelling from an HAE attack, patients require on-demand medications for treatment of these attacks. In addition, many will also require short- or long-term prophylactic treatment.

Key Points

- Types I and II HAE result from a deficiency of C1-esterase inhibitor (C1-INH).
- HAE with normal C1-INH is associated with mutations that may also affect bradykinin production or signaling.
- Most treatments reduce bradykinin production or block the B2 receptor, which reduces vasodilation and swelling.
- HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, plus patient quality of life.
- Treatment of an orphan disease such as HAE improves and saves lives – and expenditures are in line with the incidence of this disease in the population served.

ANGIOEDEMA IS THE RESULT OF FLUID extravasation into deep dermis and subcutaneous tissues. Up to 25 percent of people in the United States (U.S.) will experience an episode of urticaria (hives) and/or angioedema during their lifetime.[1] About one million people seek care for urticaria and/or angioedema each year in the U.S., but overall mortality from angioedema is low (0.36 per million). Angioedema can be mediated by bradykinin or mast cell products such as histamine. Bradykinin-mediated angioedema results in a disproportionate number of deaths.[2]

Cases of angioedema may have similar symptoms but very different causes. Effective treatment relies on identifying the underlying cause, especially in life-threatening cases. Most cases result from mast cell product release typically from an allergic reaction. Exhibit 1 compares the two types of angioedema.

Hereditary angioedema (HAE) is a rare bradykinin-mediated condition characterized by the presence of angioedema without urticaria in the form of acute attacks that are sometimes preceded by prodromal symptoms.[3] It occurs in approximately one in 50,000 individuals worldwide. This angioedema can be quite severe, affecting the face, oropharynx (causing risk of asphyxiation), extremities, gastrointestinal system, and genitourinary tract. Depending on the location of swelling, HAE can be disabling or life-threatening. One-third of patients with HAE develop a prodromal non-itchy rash (erythema

Exhibit 1: Mast Cell-Mediated versus Bradykinin-Mediated

Mast Cell-Mediated Angioedema	Bradykinin-Mediated Angioedema
Allergic	Non-allergic
Related to mast-cell activation, often allergic • Commonly occurs with wheals • Skin and oropharyngeal symptoms predominant • Most common on face (lips and periorbital area) • Abdominal pain, GI symptoms uncommon • Swelling occurs rapidly and resolves in 24 to 36 hours	Not related to mast-cell activation • Swelling without wheals • Swelling occurs in subcutaneous and submucosal tissue • Face, hands, feet, genitalia, upper airway, GI tract • Recurrent abdominal pain common • May take time to peak and last for days
Typically responds to epinephrine, antihistamines and corticosteroids	Does not respond to epinephrine, antihistamines or corticosteroids
Usually not life threatening unless in the setting of anaphylaxis	Upper airway swelling can cause asphyxiation Rapid, appropriate treatment is essential to reduce suffocation risk

marginatum). HAE attacks increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Notably, they are unresponsive to treatment with antihistamines, corticosteroids, and epinephrine. Attacks typically occur unpredictably and vary in frequency. In most cases, a family history of HAE is identified. Similarly, HAE, angiotensin-converting enzyme (ACE) inhibitors also cause bradykinin-mediated angioedema.

Laryngeal attacks occur in 50 to 60 percent of patients and are the most common cause of death in those with HAE.[4] These attacks require acute medication and airway management. In one survey there was a 40 percent incidence of asphyxiation in untreated laryngeal attacks.[5] Common triggers for HAE attacks include emotional or physical stress, minor trauma, surgery, infections such as colds or influenza, ACE inhibitors, and changes in estrogen levels (oral contraceptives, hormone replacement therapy).[6] Unfortunately, many HAE episodes have no known trigger. Untreated patients can have attacks every one to two weeks.[7]

Symptoms of HAE typically begin in childhood and worsen during puberty. In 75 percent of cases there is a family history of HAE; HAE has an autosomal dominant inheritance pattern.[7] In the 25 percent of cases with no family history, de novo mutations cause HAE and these mutations subsequently follow an autosomal dominant inheritance pattern. There are no known ethnic or gender differences in HAE rates.

The majority of HAE cases are caused by complement (C1) esterase inhibitor (C1-INH) gene mutations which lead to deficiency in C1-INH. C1-INH inhibits all active enzymes of the bradykinin-forming cascade. With a C1-INH deficiency, bradykinin levels increase. Bradykinin causes endothelial cell leakage through vasodilatation and increased vascular permeability. Exhibit 2 outlines the three types of HAE.[8-10] Types I and II are bradykinin mediated and several features of normal C1-INH suggest it is also bradykinin mediated.[10] Type I is most common accounting for 85 percent of cases; Type II accounts for 15 percent.[7] There are no data regarding the incidence of HAE with normal C1-INH.[7]

Diagnosis requires suspicion of HAE in a patient with angioedema and no urticaria. It requires measurement of complement levels and C1-INH function and antigenic level and, if normal C1-INH, further genetic testing. Exhibit 3 compares laboratory results for several types of recurrent angioedema.[10,11] For those diagnosed with HAE, screening should be performed on all first-degree relatives.

The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization and disability, and prevent death and excessive pain. The three treatment strategies for HAE include on demand medication to resolve angioedema symptoms as quickly as possible during an attack, short-term prophylaxis to prevent an attack when the patient will be exposed to a known trigger, and long-term prophylaxis to decrease the frequency and severity of ongoing attacks.[10] All patients need on demand treatment and many will also need long-term prophylaxis. Short-term prophylaxis should be

Exhibit 2: Types of HAE[8-10]

	Type I	Type II	Normal C1-INH (Formerly "Type III")
Genes Affected	Serine esterase protease inhibitor G1 *(SERPING1)*	Serine esterase protease inhibitor G1 *(SERPING1)*	Coagulation factor XII (F12) Plasminogen (PLG) Angiopioetin-1 (ANGPT1) Kininogen-1 (KNG1) Myoferlin (MYO) Other unknown genes
Gene Products Affected	C1 esterase inhibitor (C1-INH)	C1 esterase inhibitor (C1-INH)	Coagulation factor XII Plasminogen Angiopioetin-1 Kininogen-1 Myoferlin HS3ST6 Other unknown gene products
Affect on Gene Product	C1-INH antigenic levels low C1-INH functional but insufficient amount leads to low function.	C1-INH antigenic levels normal C1-INH conformational changes result in dysfunctional protein, low function.	Mechanisms poorly understood though likely increased activation of contact system (F12, PLG), BK activity (KNG1), or increased susceptibility to vascular leak (ANGPT1, MYO).

prescribed for those with known triggers. Treatment for HAE must be individualized to provide optimal care and normalize health-related quality of life.

Plasma-derived (pd) and recombinant human (rh) C1-INH products are FDA-approved for on-demand treatment of HAE attacks. Both pdC1-INH and rhC1-INH products supplement existing levels of C1-INH in Type I and II HAE. In randomized, controlled trials, both agents significantly reduced the time to relief of symptoms compared with placebo.[12,13] The most common adverse events include headache and gastrointestinal symptoms, such as nausea, diarrhea, and vomiting. Plasma-derived C1-INH is approved for adult and pediatric patients and rhC1-INH is approved for adult and adolescent patients.

Ecallantide is a plasma kallikrein inhibitor FDA-approved for on-demand treatment of patients 12 years of age and older. In the clinical trial that led to FDA approval, the benefit of ecallantide was apparent within two hours after dosing and was maintained through 24 hours after dosing.[14] It is given as a subcutaneous injection but must be given by a healthcare professional because of the potential for anaphylaxis (3% to 4%). Common adverse events include gastrointestinal symptoms, headache, and injection site reactions.

Icatibant is a bradykinin B2 receptor antagonist FDA-approved for on-demand treatment for adults 18 years of age and older. Results of the FAST-3 Phase III trial found relief from symptoms was significantly faster with icatibant compared to placebo.[15] The most common adverse events are injection site reactions. Because this is self-administered subcutaneously and does not have the risk of anaphylaxis like ecallantide, it has become very commonly used. The location of treating acute HAE attacks has changed over the years. The majority of patients are now treating themselves at home rather than seeking care at an emergency room.[16]

Prophylactic treatments of HAE include pdC1-INH, lanadelumab, and berotralstat which can be given twice weekly by subcutaneous or intravenous delivery. The most common adverse events include headache and gastrointestinal symptoms, such as nausea, diarrhea, and vomiting. Both routes are approved for patients six years of age and older. Subcutaneous pdC1-INH reduces monthly HAE attacks by 95 percent compared to placebo.[17]

Exhibit 3: Laboratory Evaluation in Recurrent Angioedema[10,11]

	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE Type I	< 30%	< 30%	Low	Normal	Normal
HAE Type II	Normal	< 30%	Low	Normal	Normal
HAE with normal C1 inhibitor	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	< 30%	Normal/Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

Lanadelumab is a monoclonal antibody which binds plasma kallikrein and inhibits its proteolytic activity. It is given as a subcutaneous injection every two weeks with an option to move to every four weeks but response rates in the approval study were lower with every four weeks. In the Phase III clinical trial, administration reduced monthly attack rate by 87 percent compared to placebo.[18] Common adverse events include dizziness and injection site reactions and it is approved for patients 12 years of age and older.

Berotralstat is a once daily oral plasma kallikrein inhibitor approved for patients 12 years of age and older. Berotralstat demonstrated a significant reduction in attack rate (1.31 attacks per month; $p <$ .001) relative to placebo (2.35 attacks per month).[19] The most common adverse events are abdominal and back pain, vomiting, and diarrhea.

All patients should keep medication to treat two acute attacks at all times and treat attacks as quickly as possible, especially those involving the upper airway. Attacks should be treated with C1-INH, ecallantide, or icatibant.[10,11] Short-term prophylaxis is administered when a patient knows they will experience known or potential triggers. For long-term prophylaxis, first-line medications for HAE Types I and II, include IV or subcutaneous C1-INH, berotralstat, and lanadelumab. For normal C1-INH HAE, tranexamic acid or progestin-only medication can be considered for prophylaxis. First-line medications for acute and prophylactic treatment are also used in children even if they are not necessarily FDA approved for that age group. For women with HAE, avoidance of estrogen use is advised. C1-INH replacement is recommended in pregnant and lactating women.

Patients should have an action plan for acute attacks and short-term prophylaxis. Long-term prophylaxis treatment options should be discussed with every patient for potential inclusion in a management plan. The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient.[10] Physicians should help patients optimize their treatment plan, coordinate care, and provide education about HAE. Action plans should consider the patient's quality of life, symptoms, and tolerance of medications.

Because HAE is uncommon, most physicians have limited contact with HAE patients. Treating a patient with HAE requires more than management of symptoms. To individualize treatment, shared decision-making with the patient should consider symptom frequency and severity, response to medications, tolerability of medications, and various lifestyle factors such as work, school, and having family members at home to assist with medication administration.

Eight to 10 percent of the U.S. population has one of the 68,000 designated orphan diseases like HAE. This equates to 25 to 30 million individuals. Because so few people have a given disease, the cost of typical treatment for an orphan disease is expensive but treatment provides great benefits to affected individuals and families. The potential fiscal impact on managed care causes payers great concern due to perceived excess costs. These concerns result in barriers to treatment access including formulary exclusion, coinsurance, copayments, prior authorization, step therapy, and

Exhibit 4: Ongoing Therapy Studies

Therapy Type	Drug	Phase	Status	Description
Oral	KVD900	III	Ongoing	Oral plasma kallikrein inhibitor for on-demand treatment.
Oral	KVD824	II	Ongoing	Oral plasma kallikrein inhibitor for prophylaxis.
Oral	ATN-249	I	Complete	Oral plasma kallikrein inhibitor for prophylaxis.
Oral	PHA-121	II	Ongoing	Oral B2-receptor antagonist for on-demand or prophylactic treatment.
Monoclonal antibody	CSL312	III	Ongoing	Human monoclonal antibody against F12 for prophylaxis.
RNAi	IONIS-PKK	III	Ongoing	Antisense oligonucleotide reduces production of prekallikrein for prophylaxis.
RNAi	ALN-F12	N/A	-	RNA interference of FXII.
Gene	AAVrh.10hC1EI	I	Ongoing	Extrachromosomal copy of SERPING1 via adenovirus vector.
Gene	NTLA-2002	I	Ongoing	Gene editing to reduce prekallikrein production.

limits on quantity and resupply. In 2013, orphan disease medication expenditures were only 8.9 percent of total expenditures.[20] Additionally, orphan medication spending has been rising at a similar rate to all medication expenditures in the U.S. Overall, the costs of managing orphan diseases like HAE are in line with their incidence and are not increasing any faster than the costs for any other disease.

In one survey, the most important clinician-reported factors in selecting long-term prophylaxis for HAE, not associated with efficacy, was cost and insurance coverage.[16] The US Hereditary Angioedema Association Medical Advisory Board guidelines note that economic considerations should not be the determining factor in deciding the physician's recommendations for optimal management of HAE.[10]

HAE can be extremely debilitating and without effective treatment, patients with HAE have significant burden from their condition with an average of 20 days lost from work and/or school per year.[21] Those affected also experience decreased educational and work opportunities.[22] Importantly, on-demand therapy and long-term prophylaxis change the burden of illness significantly and have been shown to improve quality of life.[23,24]

There is still room for improvement in HAE treatment. Factors that will improve treatment are agents with increased efficacy and safety, reduced treatment burden, and improved accessibility. Innovations that may improve HAE patient outcomes include longer lasting prophylactic treatments, more targeted oral medications, additional monoclonal antibodies, RNA interference therapies, and gene therapies. Exhibit 4 shows some of the agents currently in clinical trials.

Conclusion

Type I and II HAE result from a deficiency of C1-INH; HAE with normal C1-INH is associated with mutations that may also affect bradykinin production or signaling. Most treatments reduce bradykinin production or block a bradykinin receptor, which reduces vasodilation and swelling. HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, plus patient quality of life. Treatment of an orphan disease such as HAE improves and saves lives – and expenditures are in line with the incidence of this disease in the population served.

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New Evidence in Excessive Daytime Sleepiness Management: Meeting the Challenge to Provide Treatment

Michael J. Thorpy, MD

This journal article is supported by an educational grant from Jazz Pharmaceuticals

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Summary

Two major causes of excessive daytime sleepiness (EDS) are obstructive sleep apnea syndrome (OSA) and central hypersomnias such as narcolepsy and idiopathic hypersomnia. For those with OSA, who still have residual EDS after effective positive airway pressure during sleep, alerting medications leads to improvement. For those with narcolepsy, several alerting medications are available but none are ideal. Many with narcolepsy may need more than one medication to manage all the consequences of narcolepsy.

Key Points

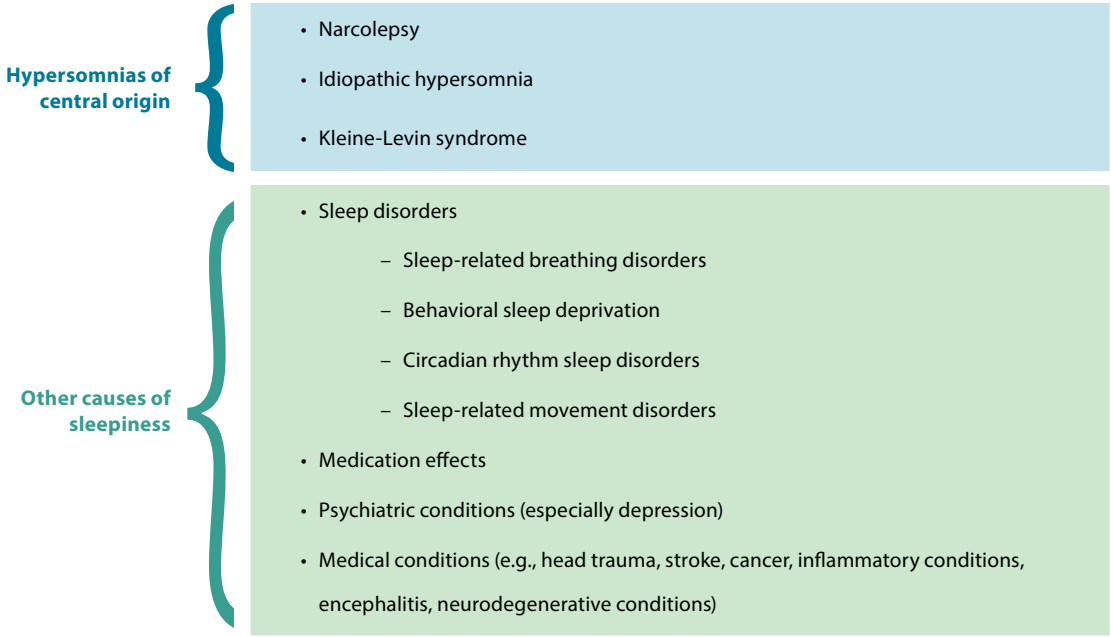
- OSA affects up to 10 percent of the population.
- Central hypersomnias affect approximately 1 in 2,000 people.
- Patients with EDS have higher healthcare costs and healthcare resource utilization (HCRU) than controls.
- Many alerting medications are now available and polypharmacy is the rule rather than exception in narcolepsy.

THE DIAGNOSIS AND MANAGEMENT OF excessive daytime sleepiness (EDS) has many issues currently and EDS is a prominent issue for managed care. Diagnosis can be difficult, there are numerous new medications which may be used inappropriately, and there are more new medications on the horizon. Clinicians may not know the best first-line choice of treatment depending on the cause of EDS. EDS is an inability to stay awake during the daytime and is a feature of many sleep disorders. It is not fatigue, a mental or muscular feeling of tiredness that does not result in a tendency to fall asleep, although many patients with EDS may also have fatigue. EDS is common. One population study found a prevalence of 20.5 percent using the Epworth Sleepiness Scale (ESS).[1] The rate of EDS is high in those with sleep deprivation and for a substantial number of people, EDS is behaviorally induced by insufficient sleep. Treatment as such is sleep education and good sleep hygiene.

There are several contributors to inadequate diagnosis and management of EDS. Clinicians view EDS as a common complaint not warranting special intervention, or for which there are no effective treatments. They may also think that sleepiness due to multiple disease states or lifestyle causes is too time-consuming and problematic to tease apart. Lastly, many clinicians assume the EDS will resolve on its own.

Exhibit 1 lists some common causes of excess sleepiness which must be considered when evaluating a patient with EDS. Assessment of EDS to identify the cause includes a thorough sleep, medical, and psychiatric history; appropriate sleep questionnaires such as ESS; psychiatric questionnaires for anxiety and depression; targeted clinical examination; and

Exhibit 1: Common Causes of Excessive Sleepiness



appropriate use of actigraphy to measure sleep duration and sleep-wake patterns. Actigraphy is a validated method of objectively measuring sleep parameters and average motor activity over a period of days to weeks using a noninvasive accelerometer commonly found in fitness watches such as Fitbit®. Polysomnography is used to assess for associated conditions such as sleep-related breathing disorders or other factors that might disrupt nighttime sleep. Multiple sleep latency testing (MSLT) is used to ascertain objective sleepiness and diagnose central disorders of hypersomnolence. The MSLT measures the mean speed with which the patient falls asleep during multiple daytime naps. Time from "lights out" to sleep onset on electroencephalogram is defined as sleep latency. Normal is greater than 10 minutes, however, in narcolepsy it is less than eight minutes. Lastly, the measurement of cerebrospinal fluid (CSF) hypocretin-1 concentration can be used to diagnosis narcolepsy.

The maintenance of wakefulness test (MWT) is used to assess alertness medication efficacy. It measures how long a patient can stay awake in a dark, quiet environment during the daytime. A sleep latency of 28 to 30 minutes suggests satisfactory daytime alertness. Psychiatric disorders rarely cause EDS but psychiatric disorders commonly occur in association with sleep disorders. Depression causes an excessive amount of time in bed due to fatigue and reduced motivation. Depression, anxiety, and psychosis commonly occur in narcolepsy.

Obstructive sleep apnea (OSA) is a common cause of EDS. OSA is the most prevalent and significant sleep-related breathing disorder characterized by recurrent episodes of upper airway obstruction that result in recurrent arousals and episodic oxyhemoglobin desaturations. It occurs in about 8 percent of men and 4 percent of women aged 45 and older.[2] OSA has significant clinical consequences beyond EDS including neurocognitive dysfunction, cardiovascular disease, metabolic dysfunction, and cor pulmonale. It also causes significant loss of productivity and reduced quality of life.[3] Although the primary treatment of OSA is positive airway pressure during sleep, a significant percentage of patients can have residual excessive daytime sleepiness (REDS) even when breathing and oxygenation parameters during sleep are normalized by successful OSA therapy. REDS is defined as score of 11 or more on the ESS. Three alerting medications (modafinil, armodafinil, and solriamfetol) improve subjective and objective daytime sleepiness in those with REDS (Exhibit 2).

Narcolepsy is a neurologic disorder characterized by EDS, rapid eye movement (REM)-related phenomena, and disturbed nocturnal sleep. EDS in narcolepsy includes continual background sleepiness, voluntary sleep episodes (naps), involuntary sleep episodes (sleep attacks), and wakeful sleepiness (automatic behavior, microsleeps). REM-related phenomena include cataplexy in about 60 percent, hypnagogic hallucinations in 67

Exhibit 2: Overview of FDA Approved Treatment Options for EDS in OSA

Drug (Approval Date)	Target	Efficacy	Observed TEAEs (≥ 5%)	
Modafinil (January 2004)	DRI	• Mean ESS ↓: 4.1	• Headache: 18% • Nervousness: 9% • Rhinitis: 6%	• Nausea: 5% • Dizziness: 5% • Anxiety: 5%
Armodafinil (June 2007)	DRI	• Mean ESS ↓: 5.5	• Headache: 18% • Insomnia: 7% • Nausea: 6%	• Anxiety: 5% • Dizziness: 5%
Solriamfetol (March 2019)	DNRI	• Mean ESS ↓: 4.7	• Headache: 10% • Nausea: 8% • Less Appetite: 8%	• Anxiety: 7% • Nasopharyngitis: 5%

Note: Methylphenidate and amphetamines, though often used, are not indicated for EDS and should be avoided due to the cardiovascular risks.

ESS = Epworth Sleepiness Scale; TEAEs = treatment emergent adverse effects; DRI = dopamine reuptake inhibitor; DNRI = dopamine norepinephrine reuptake inhibitor

percent, and sleep paralysis in 64 percent. There are two types of narcolepsy – type 1 and 2 – which are distinguished by low orexin levels and cataplexy in type 1 (Exhibit 3).[4]

Cataplexy the sudden and transient loss, or reduction of muscle tone, is pathognomonic for narcolepsy.[5] It can be triggered by laughter, elation, surprise, or anger but rarely can be spontaneous. It is typically partial or localized (~75%), usually short duration (seconds to minutes) and frequency varies widely (daily to yearly). Cataplexy can be socially disabling and isolating and it may lead to loss of balance, falls, and accidents.

The exact cause of narcolepsy is unknown but it is thought to be caused by a lack of orexin which regulates wakefulness. The lack of orexin is thought to be caused by the immune system mistakenly attacking the cells that produce it or the receptors that allow it to work.[6] Histamine function is also altered in narcolepsy type 1 with a marked increase in histaminergic neurons in the tubero-mamillary region.[7] Histamine agonists have recently become available for enhancing alertness in narcolepsy.

The median age of narcolepsy onset is 16 years and the prevalence is about 1 in 2,000 in the general United States population.[5] Narcolepsy is under-recognized and under-diagnosed with only approximately 50 percent of those affected being diagnosed.[8] Diagnosis is often very delayed and time to diagnosis is between eight and 15 years.[9] EDS and thus narcolepsy can often be overlooked in children. It can be a re-occurrence of daytime napping, extension of nocturnal sleep, or motor hyperactivity or restlessness. Cataplexy can be a complex movement disorder, dystonia, or altered gait. There can be facial hypotonia, bilateral ptosis, involuntary mouth opening, and tongue protrusion. With pediatric narcolepsy, there is typically rapid and substantial weight gain at symptom onset and precocious puberty can occur. Pediatric narcolepsy limits daily activities because of EDS and cataplexy leads to inferior performance in school and causes difficulty in social interactions.

Narcolepsy causes profound individual and socioeconomic burden. It impairs school and workplace performance, social interaction, and self-esteem.[10] Affected people have increased interpersonal difficulty, accidents and/or injury, depression, and anxiety. Patients also have significant challenges with medications for narcolepsy due to adverse events, costs, lack of efficacy, inconvenient dosing, and abuse potential.[11]

In contrast to narcolepsy, idiopathic hypersomnia (IH) is when a person has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months but no cataplexy and fewer than two sleep-onset REM periods (SOREMPs) on MSLT or no SOREMPs if the REM latency on the preceding nocturnal polysomnography was less than or equal to 15 minutes.[4] Orexin levels are lower with IH than normal controls and similar to narcolepsy type 2 but not as low as with narcolepsy

Exhibit 3: Narcolepsy Diagnosis Criteria[4]

Narcolepsy Type 1 (narcolepsy with cataplexy)
• Chronic EDS (daily for at least 3 months) and • Presence of one or both of the following: – Cataplexy + mean sleep latency ≤ 8 minutes and ≥ 2 SOREMPs on MSLT* – CSF hypocretin-1 level is either ≤ 110 pg/mL or < 1/3 of mean values
Narcolepsy Type 2 (narcolepsy without cataplexy)
• Chronic EDS (daily — at least 3 months) • Mean sleep latency ≤ 8 minutes and ≥ 2 SOREMPs on MSLT* • Cataplexy absent • CSF hypocretin-1 concentration not measured or CSF hypocretin-1 level is > 110 pg/mL or > 1/3 mean values • Hypersomnolence and/or MSLT findings not explained by other causes

SOREMP = sleep onset REM period; MSLT = mean sleep latency test; CSF = cerebrospinal fluid
*A SOREMP on the preceding night's polysomnogram may substitute for one of the SOREMPs on MSLT

type 1.[12] Exhibit 4 shows the overlap of narcolepsy types 1 and 2 and IH.

Patients with narcolepsy and IH have increased healthcare costs compared to those without. In one study, annual all-cause per-patient total costs were significantly greater ($p < 0.0001$) for patients with narcolepsy type 1 ($40,599), narcolepsy type 2 ($26,893), and IH ($18,067) compared with matched controls ($8,239; $8,924; $8,394, respectively).[13] Narcolepsy is associated with significant comorbidities. Associated sleep disorders include obstructive and central sleep apnea in 10 to 20 percent, periodic limb movements in 40 to 60 percent, REM sleep behavior disorder in 10 to 30 percent, and sleepwalking/sleeptalking/night terrors in approximately 20 percent.[14,15] Mild obesity is very common in conjunction with narcolepsy. Adult body mass index increases by about 15 percent on average. Depression occurs in about 30 percent and anxiety disorders in 25 percent.[16] Hypertension occurs in 41 percent of untreated patients and 58 percent on stimulants.[17]

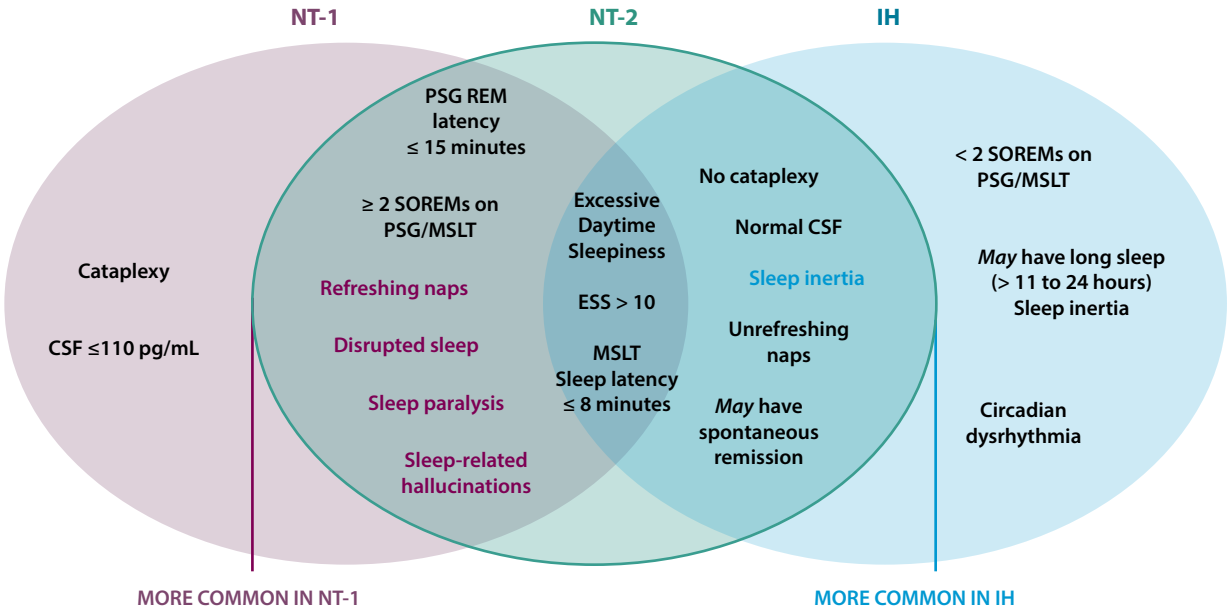
The goals of narcolepsy treatment are reduced daytime sleepiness, control REM associated features (cataplexy, nightmares and unpleasant frequent dreams, hallucinations, sleep paralysis), and improve disturbed nocturnal sleep. Other goals are to improve cognition, psychosocial and work functioning, improve safety of patient and public, and achieve the best medication risk to benefit ratio possible.

There are some behavioral treatments for narcolepsy. For EDS, those affected should increase daytime activity, schedule approximately two less than 20-minute naps per day, maintain a regular sleep-wake pattern with a goal of at least eight hours of nocturnal sleep. Those with narcolepsy should avoid sedentary or dangerous occupations and sedative medications. For cataplexy, patients can try to avoid emotional situations and should avoid dangerous activities. Rarely some medications can worsen cataplexy (e.g., prazosin).

The ideal narcolepsy medication eliminates cataplexy, returns alertness to a normal state, has a duration of effect on EDS and cataplexy of at least 16 hours, does not adversely affect nocturnal sleep, and improves ancillary symptoms of hypnagogic hallucinations, sleep paralysis, and abnormal dream phenomena. It should also allow for a normal sleep onset, sleep maintenance, and sleep offset with few if any adverse events. Lastly, it should not worsen common comorbidities such as mental disorders, OSA, cardiovascular, or metabolic disorders. Unfortunately, this ideal medication does not yet exist.

Oxybate is the most effective medication for cataplexy and the only medication that can treat all the symptoms of narcolepsy (Exhibit 5).[18] The two available oxybate products enhance activity of the gamma amino butyric acid (GABA) system in the central nervous system. Second-line for sleepiness with cataplexy is pitolisant. Modafinil, armodafinil, or solriamfetol are second-line for sleepiness alone. Pitolisant and solriamfetol are two of the newer

Exhibit 4: Narcolepsy Spectrum Disorder



NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; IH = idiopathic hypersomnia;
SOREMP = sleep onset REM period; PSG = polysomnography; MSLT = mean sleep latency test; CSF = cerebrospinal fluid; ESS = Epworth Sleepiness Scale

Exhibit 5: Medications for Narcolepsy

Drug	EDS	Cataplexy	Disturbed Nocturnal Sleep	Hypnagogic hallucinations Sleep paralysis Nightmares	Causes Insomnia
Oxybate	+++	+++	+++	++	
Pitolisant	+++	+++		+	+
Solriamfetol	+++				++
Modafinil/ Armodafinil	+++				++
Amphetamines/ Methylphenidate	+++	+			++
Antidepressants		+++		++	++

agents for narcolepsy. Pitolisant is a histamine-3 (H3) receptor antagonist/inverse agonist and solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI). Venlafaxine or atomoxetine are options for cataplexy not controlled by oxybate but are not FDA approved for this indication. Methylphenidate and amphetamines are third-line because of potential for abuse and adverse events.

In treating pediatric narcolepsy, oxybate is the only medication FDA approved for cataplexy in children aged seven years and older. The safety profile is similar to that in adults but it can be associated with weight loss. Methylphenidate and amphetamines are approved for narcolepsy in children and often used.

Modafinil is often used but in rare cases may produce Stevens-Johnson syndrome or rashes. Pitolisant and solriamfetol are not yet FDA approved for children but may be used off-label.

The treatment options currently available for narcolepsy are often unsatisfactory due to suboptimal efficacy, troublesome adverse events, development of drug tolerance, and inconvenience. An inadequate response to currently available medications is estimated to occur in 30 to 40 percent of patients. Patients who have failed other treatments have limited options for this debilitating condition. Most patients require polypharmacy for management and no single medication is effective in all patients.

Adverse events occur commonly in narcolepsy patients. Comorbidities, such as psychiatric disorders, can limit pharmacotherapy choices. There are little data on the best treatment strategy for the individual narcolepsy phenotypes. Orexin agonists are under investigation for narcolepsy. Early data from studies with these agents is promising. It is hoped that these agents will better target all facets of narcolepsy and be more ideal agents than the currently available therapies.

Before the introduction of lower-sodium oxybate, a combination of calcium, magnesium, potassium, and sodium oxybate, was the only FDA-approved medication for the treatment of IH in adults. EDS in IH was treated similarly to narcolepsy type 1 and 2. The American Academy of Sleep guidelines, which have not been updated since the approval of lower-sodium oxybate for this indication, recommend using modafinil first-line with the other alerting agents approved for narcolepsy, including high-sodium oxybate, as suggested conditional agents.[18]

Conclusion

Daytime sleepiness is a common symptom occurring in about 20 percent of people and for many behavioral-related insufficient sleep is the major cause. Sleep education is the key treatment for this cause of EDS. Central hypersomnias such as narcolepsy and idiopathic hypersomnia affect approximately 1 in 2,000 people and obstructive sleep apnea syndrome affects up to 10 percent of the population. Many alerting medications are now available and polypharmacy is the rule rather than exception in narcolepsy. Overall, narcolepsy remains a challenging disease for both diagnosis and treatment, with a significant unmet need for an ideal medication.

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Best Practices in the Management of Multiple Sclerosis: Optimizing Clinical and Economic Outcomes in an Evolving Treatment Paradigm

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This journal article is supported by an educational grant from Bristol Myers Squibb

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Summary

Multiple sclerosis (MS) is a major neurodegenerative disease with significant personal and financial costs. Effective treatment with disease-modifying therapies (DMTs) is available but treatment selection can be complicated. This process will become more complicated in the near future with numerous agents and cell-based therapies under investigation.

Key Points

- Improving outcomes in patients with MS requires that clinicians have to consider disease, medication, patient factors and patient preference when choosing a DMT.
- Modifiable risk factors for disease activity and progression should be addressed with health-maintenance and vascular risk-factor programs.
- Adherence to the therapeutic regimen with close monitoring and therapy adjustments for DMT efficacy and toxicity are other ways to improve patient outcomes.

MULTIPLE SCLEROSIS (MS) IS A LIFELONG, complex, heterogenous, neurodegenerative disease with significant personal and financial costs. The total economic burden for MS in 2019 was estimated at $85.4 billion per year of which $66.3 billion was direct medical expense.[1] Disease-modifying therapy represented 64 percent of those direct medical costs. Non-medical costs were $22.1 billion. Key drivers of the non-medical expense were lost earnings due to premature death (38%), presenteeism (28%), and absenteeism (26%). The projected prevalence of MS in 2039 is 1.1 million and the projected total annual economic impact is $105 billion.

The treatment of MS has evolved significantly over the past 20 years. There are now over 20 distinct disease-modifying therapies (DMT, including generics) which cover 10 different mechanisms of action. All are FDA approved for relapsing forms of MS, one is approved for primary-progressive disease (PPMS), and two for secondary-progressive (SPMS). These agents can be divided into injectables, orals, and monoclonal antibodies, plus the chemotherapy agent mitoxantrone (now rarely, if ever, used).

Exhibit 1 outlines the general principles of MS therapy. It is especially important to initiate treatment as soon as possible after diagnosis in order to prevent permanent damage and disability. It is also important that clinicians set expectations for therapies with patients who need to understand that the disease is not cured but slowed. In addition to considering many factors, treatment selection should use shared decision making with the patient to consider the benefits and risks of various therapies (Exhibit 2). When patients engage in shared decision making, they learn about their health and understand their health conditions, recognize that

Exhibit 1: General Principles for MS Therapy

- Treat as soon as possible.
  - Ideally clinically isolated syndrome (CIS) stage.
- Consider disease activity and prognostic (demographic, clinical, MRI) profile to select therapy.
  - If both are worrisome, efficacy becomes key.
- Follow patients closely.
- Do not be afraid to switch therapies for poor response.

decisions need to be made, are informed about the options, understand the pros and cons of different options, and have the information and tools needed to evaluate their options. They are more likely to follow through on their decisions (adherence).

Complexity of the therapeutic landscape dictates a multidisciplinary team to deliver comprehensive care where various team members address multiple issues. Comprehensive care leads to empowerment for patients, families, and the care team and improves communication with the care team, adherence to treatment, continuity of care, and patient quality of life. The comprehensive-care team may be able to identify breakthrough disease early and thus switch up therapy earlier than conventional care.

The current MS therapeutic approach is composed of health-maintenance and vascular risk-factor programs; treatment of clinical attacks and/or relapses; symptomatic therapy; and DMT. There is increasing evidence that health maintenance changes or improves central nervous system (CNS) reserve, function, and repair. Health maintenance can be considered a DMT for MS. Components involve achieving high-normal vitamin D levels and vitamin B12 greater than 400 pg/mL, regular aerobic exercise, weight loss if indicated, stopping smoking, limiting alcohol and salt, healthy diet, regular mental and social stimulation, good sleep hygiene, and stress management. Vascular risk-factor management involves monitoring and managing blood pressure, lipids, and hemoglobin A1C. In MS, the immune system attacks the protective myelin coating around nerves. All current DMTs aim to stop rogue immune cells from attacking the myelin. All FDA-approved therapies reduce annual relapse rate, accumulation of disability, and MRI evidence

Exhibit 2: Making Treatment Decisions

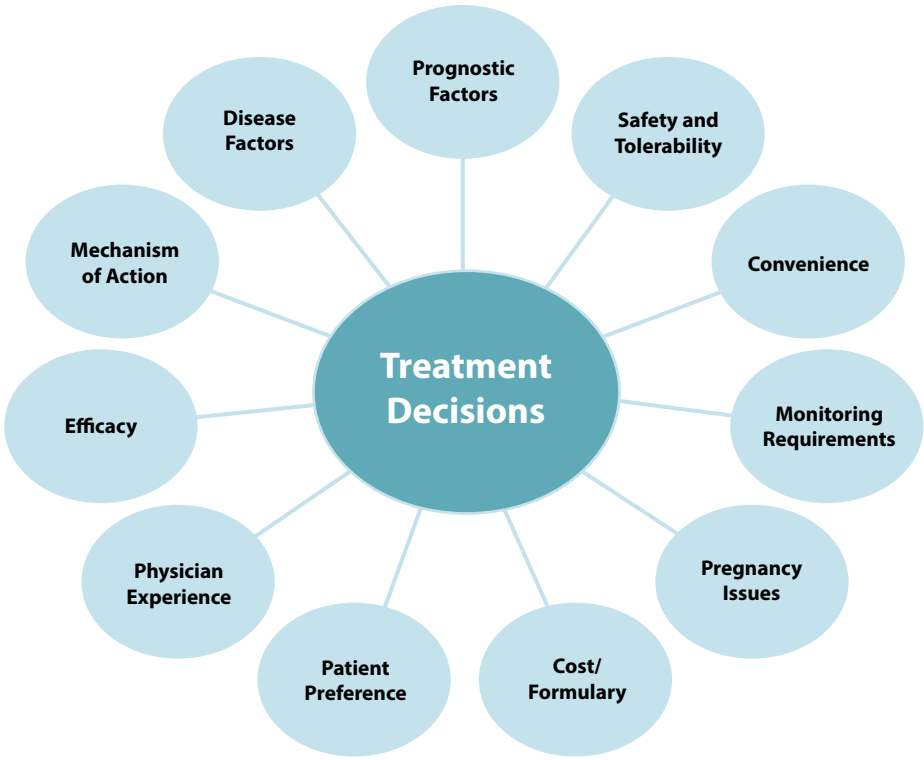
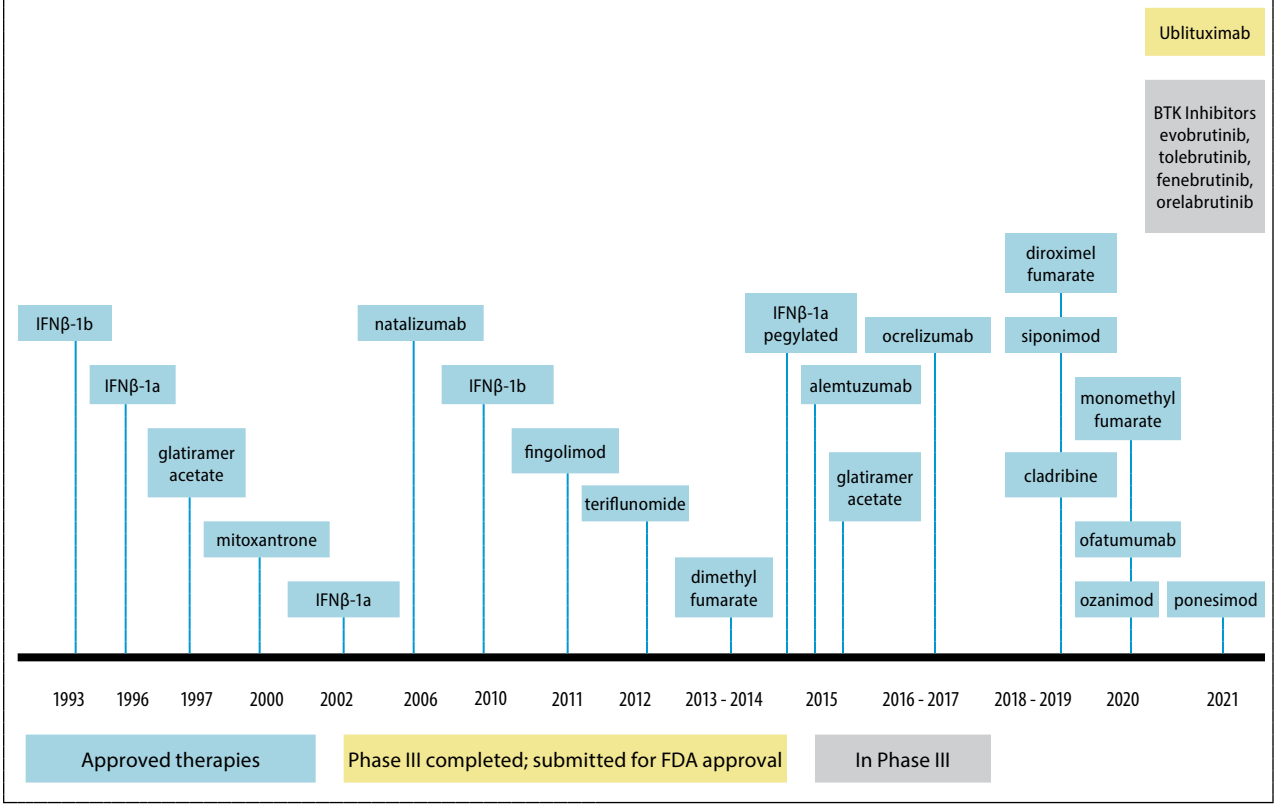


Exhibit 3: Disease Modifying Therapy for MS



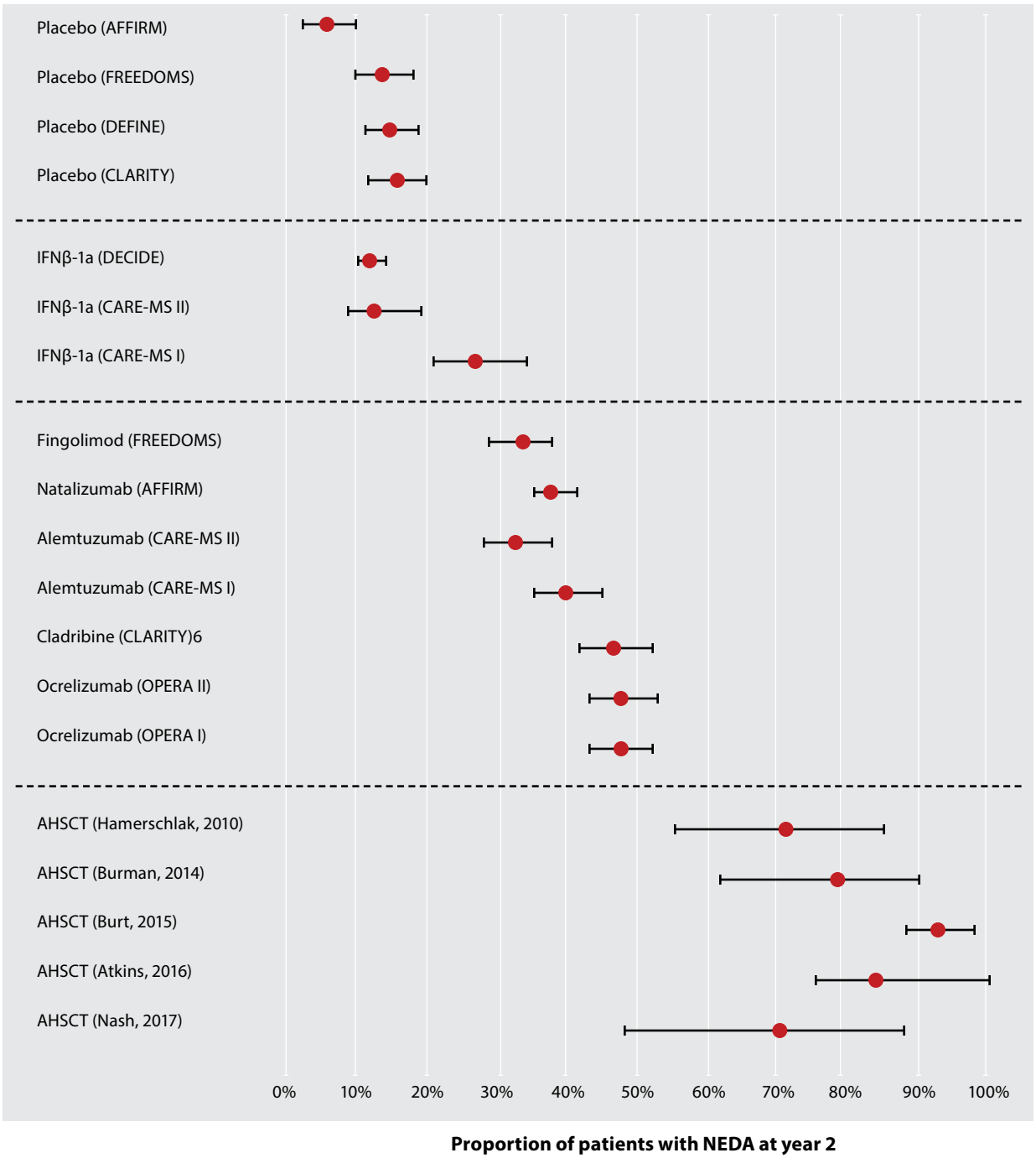
IFNβ = interferon beta

of disease but their potencies, safety, and tolerability vary (Exhibit 3). Natalizumab, ocrelizumab, ofatumumab, alemtuzumab, and cladribine are the most potent agents but also have the most safety risks. The older less potent agents such as interferons, glatiramer, and teriflunomide tend to be safer. There are no clear guidelines on which DMT to start first, or how best to sequence treatment, making patient preference extremely important. The agents are given as intravenous infusions, self-injections, or orally which can impact the convenience of a therapy. Patients with increased risk of worsening disability will benefit from more aggressive initial therapy with higher efficacy agents. Markers of risk include multiple relapses with short inter-relapse intervals, relapses with incomplete recovery, residual motor or cerebellar disability, older age at presentation, higher lesion burden on MRI, brainstem and spinal cord lesions, and African American ethnicity.[2]

The oral sphingosine-1-phosphate (S1P) receptor modulators are being more frequently used because of improved receptor targeting with the newer generation agents. There are now four of these – fingolimod, siponimod, ozanimod, and ponesimod. S1P receptor binding results in internalization and loss of signaling function necessary for activated lymphocytes to leave lymphoid tissue and enter circulation. Effector memory cells in tissues are not affected, thus preserving immune surveillance. S1P receptors in glial cells allow for potential effects in the central nervous system.[3] The newer generation agents are more selective than fingolimod and result in fewer off-target cardiovascular adverse events. All of the S1P receptor modulators reduce relapses and MRI activity better than interferon or teriflunomide. Availability for treatment in select individuals first line improves the potential for more effective early therapy leading to better long-term outcomes. As with all DMTs, selection requires a benefit-to-risk assessment based on the patient. Risk mitigation strategies, to deal with the potential for infections and sequencing to cell-depleting therapies such as alemtuzumab, have to be instituted.

MRI is used to monitor disease activity in the CNS and efficacy of DMT. For established MS, an MRI is recommended if no recent prior imaging is available (e.g., in cases of new patient referrals), postpartum to establish a new baseline, before

Exhibit 4: Efficacy of Autologous Hemopoietic Stem-cell Transplantation versus Disease-modifying Treatments[13]



NEDA = no evidence of disease activity

starting or switching a DMT, three to six months after switching a DMT (to establish a new baseline on therapy), every six months to two years during unchanged DMT to assess for subclinical disease, and in cases of unexpected clinical deterioration or to reassess the original diagnosis.[4] Enhancement of the MRI with gadolinium is helpful but not essential, because new T2-lesions can be identified on well-performed standardized MRI unless the T2-lesion burden was already high.

DMT failure in MS management is difficult to define. Most patients are not completely free of

disease activity during therapy and disease activity may occur shortly after DMT initiation and before the DMT is fully effective. Clinicians should consider treatment failure and switching DMT when patients experience one or more relapses or two or more unequivocally new MRI lesions or increased disability on neurologic examination over one year of therapy.[5]

Additional DMTs are on the horizon for MS treatment. Ublituximab, another B cell-depleting agent similar to ofatumumab and ocrelizumab, is an investigational agent for MS and the closest to market. It has been submitted to the FDA for approval. Among participants with relapsing MS, ublituximab resulted in lower annualized relapse rates and fewer brain lesions on MRIs than teriflunomide over a period of 96 weeks but did not result in a significantly lower risk of disability worsening.[6]

Bruton's tyrosine kinase (BTK) inhibitors are an emerging type of DMT for MS currently being tested in late-stage clinical trials for relapsing, primary, and secondary-progressive MS. BTK inhibitors are more selective than the existing DMTs which target B cells.[7] They could potentially reduce the chance and severity of adverse events compared to current DMTs. BTK inhibitors can cross the blood brain barrier which may make them more efficacious than other agents which only act peripherally. They may also be able to slow chronic progression which occurs independent from relapse activity or development of new central nervous system inflammatory lesions.[8] There are currently four BTK inhibitor treatments being investigated in Phase II and Phase III trials: tolebrutinib, evobrutinib, orelabrutinib, and fenebrutinib. The Phase II trials published so far have been positive.[9,10]

Various cell-based therapies are also under investigation for MS. Cell-based therapies, including immunoablation followed by autologous hematopoietic stem cell transplantation (aHSCT), mesenchymal stem cell transplantation, pharmacologic manipulation of endogenous stem cells to enhance their reparative capabilities, and transplantation of oligodendrocyte progenitor cells, have generated substantial interest as novel therapeutic strategies for immune modulation, neuroprotection, or repair of the damaged CNS.[11] Each approach has potential advantages but also safety concerns and unresolved questions. The goal of aHSCT is to reset the immune system and stop inflammation that contributes to MS. One trial of immunoablation and aHSCT for aggressive MS found 69.6 percent MS disease activity-free survival at three years after transplantation.[12] With up to 13 years of follow-up after the stem-cell transplant, no relapses occurred and no brain lesions were seen on 314 MRI sequential scans. The rate of brain atrophy decreased to that expected for healthy controls. One of 24 patients died of transplantation-related complications. Thirty-five percent of patients had a sustained improvement in their Expanded Disability Status Scale score. Exhibit 4 compares the effectiveness of this approach to placebo and several current DMTs in terms of no evidence of disease activity (NEDA).[13] Numerous studies are ongoing evaluating this treatment option in MS but it is not yet FDA approved. The National Medical Advisory committee of the National Multiple Sclerosis Society believes that aHSCT may be a useful treatment option for people with relapsing MS who demonstrate substantial breakthrough disease activity (i.e., new inflammatory CNS lesions and/or clinical relapses) despite treatment with high-efficacy DMT or have contraindications to high efficacy DMT.[14] The best candidates are likely people younger than 50 years of age with shorter durations of disease (< 10 years). The procedure should only be performed at centers with substantial experience and expertise. Ideally, recipients of the procedure should be entered into a single database, and further research is needed to establish ideal cell mobilization and immune-conditioning regimens.

Conclusion

Improving outcomes in patients with MS requires clinicians to have to consider disease, medication, patient factors and patient preference when choosing a DMT. Patients need to buy into the choice of therapy and understand the risk versus benefit of that choice. Modifiable risk factors for disease activity and progression should be addressed with health-maintenance and vascular risk-factor programs. Adherence to the therapeutic regimen and close monitoring and therapy adjustments for DMT efficacy and toxicity are other ways to improve patient outcomes.

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Evolving Considerations in the Management of HER2-Positive Advanced Breast Cancer: Individualized Treatments for Improved Clinical and Economic Outcomes

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This journal article is supported by educational grants from AstraZeneca; Seagen

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Summary

The treatment of human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (mBC) has evolved dramatically since the introduction of the first targeted therapy in 1998. There are now multiple agents which can be used to prolong survival in this incurable disease state.

Key Points

- Multiple lines of HER2+ targeting therapies are prolonging survival in those with HER2 mBC.
- Patients can now live for many years with HER2+ mBC potentially turning this into a chronic illness.
- One HER2 targeting antibody drug conjugate is now FDA approved for use in those with HER2-low disease.

IN GENERAL, BREAST CANCER CAN BE, broken down into three biologic subgroups which have a direct bearing on treatment choices – hormone receptor positive (HR+), human epidermal growth factor receptor 2 positive (HER2+), and triple-negative (not HR+ or HER2+). HER2+ disease can occur with or without hormone receptor expression. HER2+ disease accounts for 15 to 20 percent of all cases of mBC. The focus of this article is HER2+ advanced or metastatic breast cancer (HER2+ mBC).

In the 1980s when this subset of breast cancer was first identified, there were no treatment options except chemotherapy. HER2+ status was just a prognostic finding predicting a poor outcome. Treatment began to change dramatically in 1998 with the approval of the first HER2+ targeted therapy. Since then, multiple additional targeted therapies have been approved (Exhibit 1). Agents typically have been approved, first for the metastatic setting, and then for adjuvant or neoadjuvant use.

All of these new therapies are prolonging survival significantly beyond what can be achieved with chemotherapy alone; survival with HER2+ mBC is now better than that with hormone receptor positive disease.[1] The success in improving survival in HER2+ mBC, which is incurable, has come with a significant financial cost. This disease state is associated with years of chronic therapy and excess cost. A study using data from the IQVIA Real-World Data Adjudicated Claims Database (July 1, 2014 to July 31, 2019) found the mean annual total all-cause costs per patient with HER2+ mBC in years one, two and three were $320,892, $235,159, and $226,254, respectively (Exhibit 2).[2] The mean annual total breast cancer-related costs were $240,048,

Exhibit 1: Timeline of FDA Approvals for HER2+ Breast Cancer

1998	2007-08	2012	2013	2017	2019	2020	2022
Trastuzumab (metastatic)	Lapatinib (metastatic)	Pertuzumab (metastatic)	T-DM1 (metastatic)	Neratinib (adjuvant)	T-DM1 (adjuvant)	Tucatinib (metastatic)	Trastuzumab deruxtecan HER2-low
	Trastuzumab (adjuvant)		Pertuzumab (neoadjuvant)	Pertuzumab (adjuvant)	Trastuzumab deruxtecan (metastatic)	Neratinib (metastatic)	
						Margetuximab (metastatic)	

$175,631, and $165,506 in years one, two, and three, respectively. A major portion of breast cancer-related costs were associated with HER2 targeted treatments. A cost-saving measure would be to prevent patients with earlier stages of breast cancer from developing metastatic disease. Earlier use of targeted therapies to prevent recurrence in those at high risk is now part of the National Comprehensive Cancer Network (NCCN) Guidelines.[3]

The HER2 targeting agents include injectable monoclonal antibodies, antibody-drug conjugates, and oral small molecules (Exhibit 3). Use of these agents leads to death of cells by blocking growth signals or by introducing chemotherapy directly into the tumor cell (antibody-drug conjugates). HER2 targeting agents are continued throughout the disease process, even if progression occurs, to keep the brakes on cell growth.

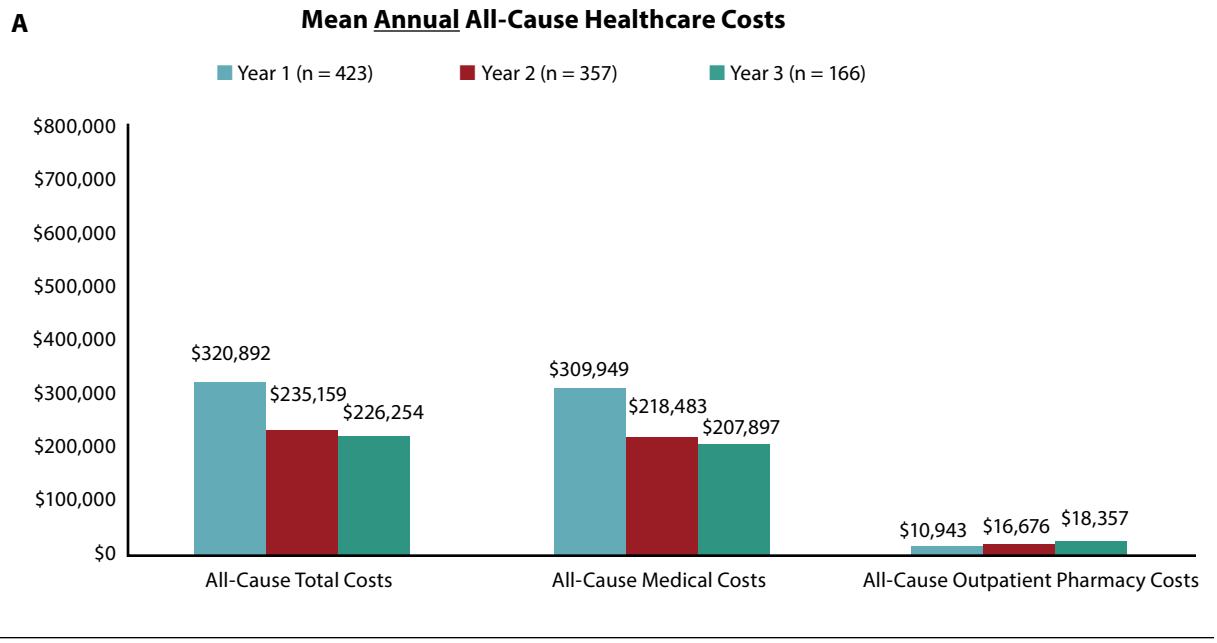
When trastuzumab was first introduced, it in combination with taxane chemotherapy quickly became the standard first-line treatment. The addition of pertuzumab to the backbone of trastuzumab and taxane chemotherapy was found to significantly improve survival over just placebo, trastuzumab, and a taxane. Median overall survival (OS) was 57.1 months in the pertuzumab group and 40.8 months in the placebo group (hazard ratio 0.69); eight-year landmark OS rates were 37 percent in the pertuzumab group and 23 percent in the placebo group.[4] This regimen is now the standard first-line treatment for HER2+ mBC.

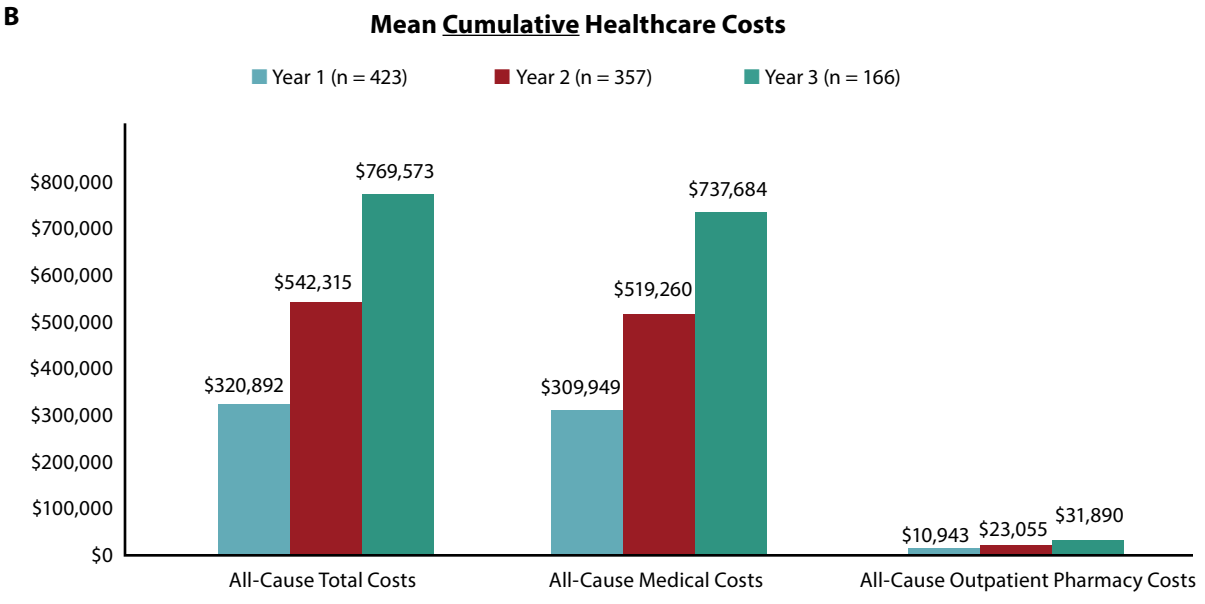
Once patients progress on the triple regimen of pertuzumab/trastuzumab/taxane, fam-trastuzumab deruxtecan is the NCCN preferred option unless the patient has central nervous system (CNS) disease (Exhibit 4).[3] Fam-trastuzumab deruxtecan is a HER2-directed antibody-drug conjugate. The antibody is a humanized anti-HER2 IgG1. The small molecule, deruxtecan, is a topoisomerase inhibitor attached to the antibody by a cleavable linker. Following binding to HER2 on tumor cells, fam-trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane permeable deruxtecan causes DNA damage and apoptotic cell death. For several years, the other antibody-drug conjugate ado-trastuzumab emtansine was the standard second-line therapy until the Destiny-Breast03 trial found that among patients with HER2-positive mBC previously treated with trastuzumab and a taxane, the risk of disease progression or death was lower among those who received trastuzumab deruxtecan than among those who received trastuzumab emtansine.[5]

Tyrosine kinase inhibitor small molecules are treatment options in the third-line (or second-line in the case of CNS disease). Tucatinib in combination with trastuzumab and capecitabine is preferred in the NCCN guideline with both system and CNS progression for third-line treatment.[3] Tucatinib is preferred over neratinib and lapatinib because of increased specificity for HER2 and thus lower rates of off target adverse events, particularly those related to HER1 (also known as epidermal growth factor receptor) effects (rash, diarrhea). It is also preferred because of demonstrated CNS activity; up to 50 percent of those with HER2+ mBC will develop brain metastases.

Another option is margetuximab in combination with chemotherapy. Margetuximab is an Fc-engineered monoclonal antibody with an improved binding to FcγRIIIA receptor, which leads to a greater antibody-dependent cellular cytotoxicity (ADCC) activation compared with trastuzumab.

Exhibit 2: Economic Burden of HER2 mBC Treatment[2]





In the Sophia trial, margetuximab was shown to slightly improve progression-free survival (PFS) compared with trastuzumab for the treatment of HER2+ mBC patients but provided no difference in median OS (21.6 versus 21.9 months).[6] The place for this therapy is currently third line and beyond but data are accumulating that it may be more effective in patients with a CD16A F allele, especially those who are homozygous (CD16A FF). In the Sophia trial, the median OS in those with CD16A FF was 23.6 months with margetuximab versus 19.2 months with trastuzumab ($p = 0.052$).[6] This allele testing is not currently being used for treatment selection but may be used in the future based on results of ongoing trials.

The most recent advance in HER2-related disease is the approval of fam-trastuzumab deruxtecan for HER2-low disease. The HER2-low category includes

Exhibit 3: HER2-Targeted Therapies

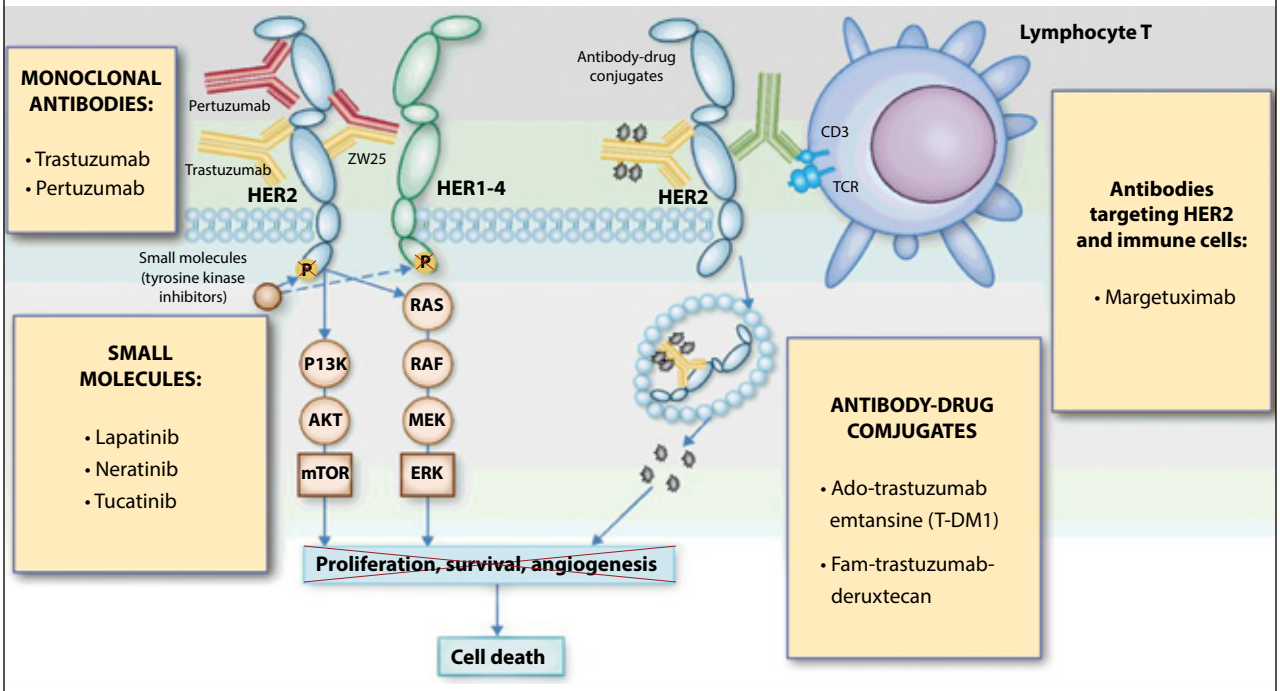
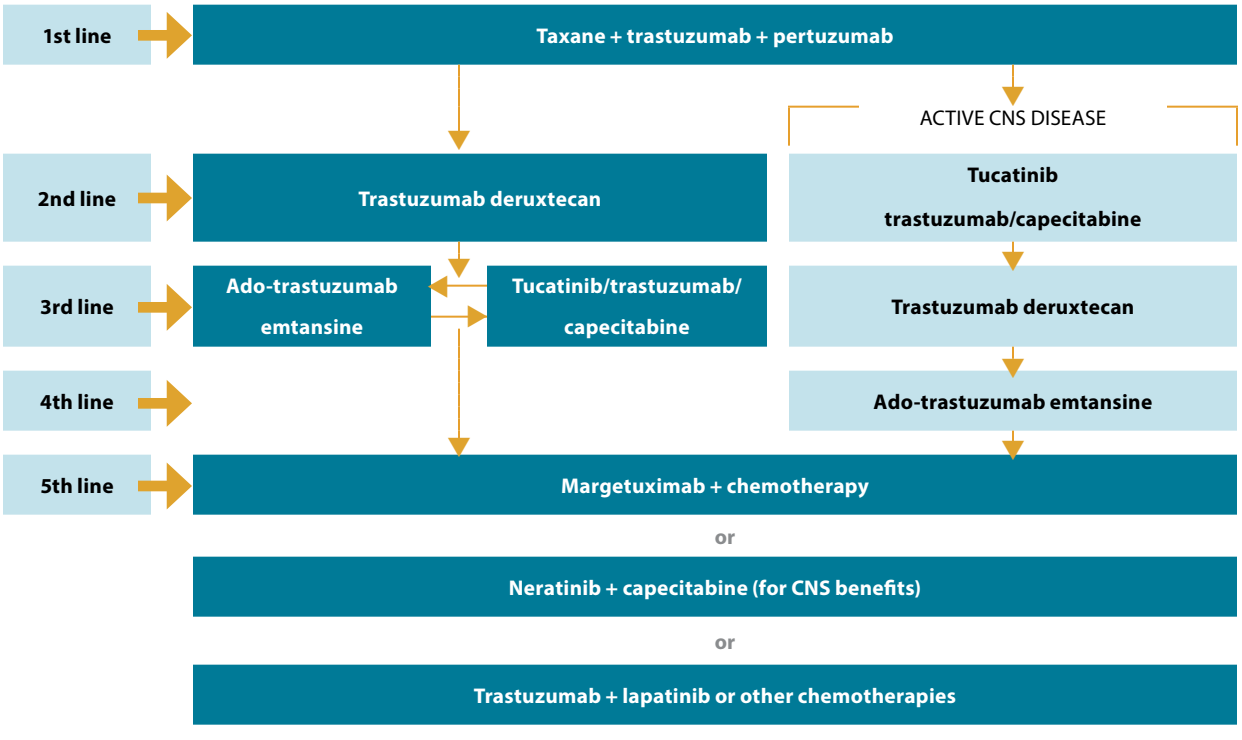


Exhibit 4: Approach to Therapy for HER2+ Metastatic Breast Cancer[3]



those who have borderline in situ hybridization scores of 1+ and 2+; HER2+ is defined as a score of 3+. Approximately 60 percent of people with HER2 negative breast cancer fall into this HER2-low category.[7,8] Low HER2 expression occurs in both hormone receptor positive and negative breast cancer and has previously not been actionable. In the DESTINY-Breast04 trial, patients with previously treated HER2-low mBC and who were treated with fam-trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy.[9] The median PFS was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice group (hazard ratio for disease progression or death, 0.51; $p < 0.001$), and OS was 23.9 months and 17.5 months, respectively (hazard ratio for death, 0.64; $p = 0.003$). The efficacy of fam-trastuzumab deruxtecan in HER2-low is thought to occur because of membrane permeability of the deruxtecan. The antibody conjugate delivers chemotherapy into HER2+ cells but some of the chemotherapy leaks back out of the cell and kills neighboring cells (bystander effect).

Conclusion

There are now multiple lines of HER2+ targeting therapies which are prolonging survival in those with HER2 mBC. Patients can live for many years with HER2+ mBC potentially turning this into a chronic illness. The latest innovation is use of a HER2 targeting antibody drug conjugate in those with HER2-low disease.

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Patient-Focused Treatment Decisions in the Management of Chronic Lymphocytic Leukemia

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This journal article is supported by educational grants from AstraZeneca; AbbVie; Pharmacyclics

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Summary

Chronic lymphocytic leukemia (CLL) is a common incurable malignancy in older adults. The treatment of CLL has evolved with the availability of oral agents which can control the disease for many years.

Key Points

- BTK inhibitors are highly effective therapies as single agents and in combination with anti-CD20 monoclonal antibodies.
- Second-generation BTK inhibitors appear to be equally effective as ibrutinib, with more favorable safety profiles.
- Venetoclax and an anti-CD20 monoclonal antibody are an excellent time-limited therapeutic approach.
- Optimal sequencing of BTK inhibitors and venetoclax is not clear, but either option is effective when used sequentially.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is the most common leukemia accounting for about 30 percent of adult leukemias and represents 1.1 percent of all cancers diagnosed annually in the United States (U.S.).[1] There are approximately 20,160 cases and 4,410 deaths annually in the U.S. About 180,000 are living with CLL in U.S. The five-year survival rate is 87.9 percent and the median age at diagnosis is 72 years.

CLL is a heterogeneous disease with a natural history ranging from an indolent clinical course in which patients do not require therapy for many years to an aggressive disease for which treatment is necessary soon after diagnosis. Those with CLL are treated when they have active disease which is defined as progressive marrow failure with worsening of anemia (hemoglobin < 10g/dL) and/or thrombocytopenia (platelets < 100), massive or progressive symptomatic splenomegaly or lymphadenopathy, progressive lymphocytosis with an increase of more than 50 percent over a two-month or lymphocyte doubling time of less than six months, symptomatic or functional extranodal involvement (e.g., skin, kidney, lung), or constitutional symptoms. Constitutional symptoms include significant fatigue, night sweats, weight loss, and fevers. Exhibit 1 shows some considerations before starting therapy.

In the initial workup, all patients will have, flow cytometry to confirm the CLL diagnosis, and laboratory tests that are informative for prognostic and/or therapy determination. These include interphase cytogenetics looking for various deletions [del(13q), del (17)(p13.1), and del(11)(q22.3)], immunoglobulin heavy chain variable (IGHV) and TP53 gene mutations, and β2-microglobulin. The

Exhibit 1: Considerations Prior to Initiating Therapy

Anemia or thrombocytopenia	• Exclude GI blood loss • Assess for AIHA/ITP
Symptomatic disease	• Assess for possible lymphoma transformation
Rapidly progressive disease	• Assess for possible lymphoma transformation

AIHA = autoimmune hemolytic anemia; GI = gastrointestinal; ITP = immune thrombocytopenic purpura

presence of del(17p) and del(11q) portend more aggressive disease. No CT scan is needed unless symptoms are present; a PET scan can be helpful if Richter's transformation is suspected. Bone marrow biopsy and aspirate are not necessary in the absence of cytopenias. In addition to these tests, age and functional status will also impact treatment selection.

First-line CLL treatment has shifted away from chemo-immunotherapy based approaches which combine chemotherapy and anti-CD20 agents to oral-targeted therapy because of survival advantages and fewer short- and long-term adverse events. B cell receptor signaling drives CLL cell survival thus the various targeted treatments alter this signaling. Treatment options include oral Bruton tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib, zanubrutinib), an oral B cell lymphoma 2 inhibitor (venetoclax), and injectable anti-CD20 monoclonal antibodies (e.g., obinutuzumab, rituximab). As shown in Exhibit 2, the National Comprehensive Cancer Network (NCCN) Guidelines recommend targeted therapy as first-line treatment for treatment naïve CLL.[2] BTK inhibitors are continued until disease progression and venetoclax is given as a time limited regimen.

Second-generation BTK inhibitors, acalabrutinib and zanubrutinib, are favored over ibrutinib because of an improved adverse event profile. In patients who are already taking ibrutinib with no intolerance, ibrutinib can be continued until disease progression. Zanubrutinib is a BTK inhibitor currently approved for mantle cell lymphoma but has completed Phase III testing for CLL and is listed as an option in the NCCN Guidelines. The one comparison trial of acalabrutinib versus ibrutinib (Elevate RR) found the two agents noninferior with a median progression-free survival (PFS) of 38.4 months in both arms.[3] All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; p = .02) and median overall survival (OS) was not reached in either arm.[3]

In patients with relapsed or refractory CLL or SLL, PFS was significantly longer among patients who received zanubrutinib than among those who received ibrutinib, and zanubrutinib was associated with fewer cardiac adverse events.[4] At 24 months, the investigator-assessed rates of PFS were 78.4 percent in the zanubrutinib group and 65.9 percent in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer PFS than those who received ibrutinib (hazard ratio for disease progression or death, 0.53; 95% CI, 0.31 to 0.88); PFS across other major subgroups consistently favored zanubrutinib. A BTK inhibitor is continued until disease progression and/or intolerance. BTK inhibitors do cause significant adverse events including atrial fibrillation, bleeding, and arthralgias. Recommendations for safety monitoring are shown in Exhibit 3.[2]

Exhibit 2: NCCN Recommended First Line Regimens for Treatment-Naïve CLL[2]

Type	Preferred First-Line	Selected Other options
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Zanubrutinib	Alemtuzumab ± rituximab Ibrutinib Obinutuzumab Ibrutinib + venetoclax (category 2B)
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (category 1) Venetoclax+ obinutuzumab (category 1) Zanubrutinib* (category 1)	Ibrutinib (category 1) FCR (fludarabine, cyclophosphamide, rituximab) – consider for IGHV-mutated CLL in patients aged less than 65 years without significant comorbidities.

*Zanubrutinib is not FDA approved for CLL but has been studied for this indication.

Exhibit 3: Summary of BTK Inhibitor Safety Monitoring Approaches[2]

- Monitor for and manage cardiac arrhythmias and treat appropriately.
- Don't give concomitantly with warfarin.
- For new-onset atrial fibrillation consider non-warfarin anticoagulation and monitor.
- Monitor blood pressure and manage hypertension with antihypertensives.
- Monitor patients for signs of bleeding.
- Monitor for infections and secondary malignancies.
- For arthralgia, rule out other causes, monitor, and use supportive care for lower-grade events.
  - ✓ Dose reduction once symptoms affect activities of daily living, dose holds for higher-grade arthralgia.
- Headaches commonly occur early in therapy with acalabrutinib and typically resolve in 1 to 2 months; manage with acetaminophen + caffeine
  - – Dose reductions/interruption are not required
- Monitor for neutropenia (particularly with zanubrutinib)

Exhibit 4: Choosing between a BTK inhibitor and Venetoclax[6]

BTK Inhibitor	Venetoclax
• Logistically very easy to start	• Cumbersome initiation/ramp-up
• Indefinite therapy	• Fixed duration
• Tumor lysis syndrome not of concern	• Risk for tumor lysis syndrome which requires prophylaxis monitoring
• More cardiac risk/hypertension	• Question if best choice for high-risk disease
• Some data favors for those with del(17p)/TP53 mutation	

Resistance to the current covalent BTK inhibitors occurs in many patients over the course of treatment. BTK C481 mutations are the dominant reasons for progressive CLL during treatment.[5] These mutations prevent covalent BTK inhibitors from effective target inhibition. Third-generation noncovalent BTK inhibitors such as pirtobrutinib and nemtabrutinib are currently under investigation for CLL and may be effective in those with resistance to covalent agents.

Venetoclax plus obinutuzumab is a fixed duration of treatment which may appeal to many patients. Venetoclax regimens are typically given for up to two years and then patients are observed for relapse and retreatment indications. Venetoclax-based approaches demonstrate high rates of undetectable minimal residual disease (uMRD). Optimal duration of therapy remains unclear but optimizing uMRD before stopping should be the goal. Exhibit 4 presents some considerations in choosing between the two approaches.[6]

Second-line therapy for CLL would be whichever class of therapy was not used in first-line treatment. For example, if BTK inhibitor was used first-line, then venetoclax plus an anti-CD20 monoclonal antibody would be instituted. For patients who have relapsed or refractory disease after a BTK inhibitor and venetoclax, phosphatidylinositol 3-kinase (PI3K) inhibitors (duvelisib, idelalisib ± rituximab) or chemo-immunotherapy are treatment options.

Future treatment of CLL is likely an initial combination of a BTK inhibitor and venetoclax, possibly with an anti-CD20 monoclonal antibody. Rationale for the combination are non-overlapping mechanisms of action, non-overlapping toxicity profile, and they act on CLL cells in different compartments.[7-9] Synergy has been shown in preclinical studies. One trial of ibrutinib plus venetoclax therapy for 24 cycles in previously untreated patients with CLL found durable remissions over a follow-up of more than three years, with activity seen across high-risk disease subgroups.[8] Numerous trials of BTK inhibitors, venetoclax, and anti-CD20 antibodies in various combinations are ongoing.

Conclusion

BTK inhibitors are highly effective therapies as single agents and in combination with anti-CD20 antibodies. Second-generation BTK inhibitors appear to be equally effective as ibrutinib, with more favorable safety profiles. Venetoclax plus anti-CD20 monoclonal antibody therapy is an excellent time-limited approach. Optimal sequencing of BTK inhibitors and venetoclax is not clear, but either option is effective when used sequentially. As data continue to emerge on the use of combinations, opportunities to treat CLL patients with a fixed duration of treatment rather than indefinite therapy may reduce the potential for long-term toxicities. Given the impressive efficacy of BTK inhibitors and venetoclax, appropriate management of toxicities are of critical importance, as these agents will remain a mainstay of therapy.

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Notes

CORPORATE PARTNERS

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