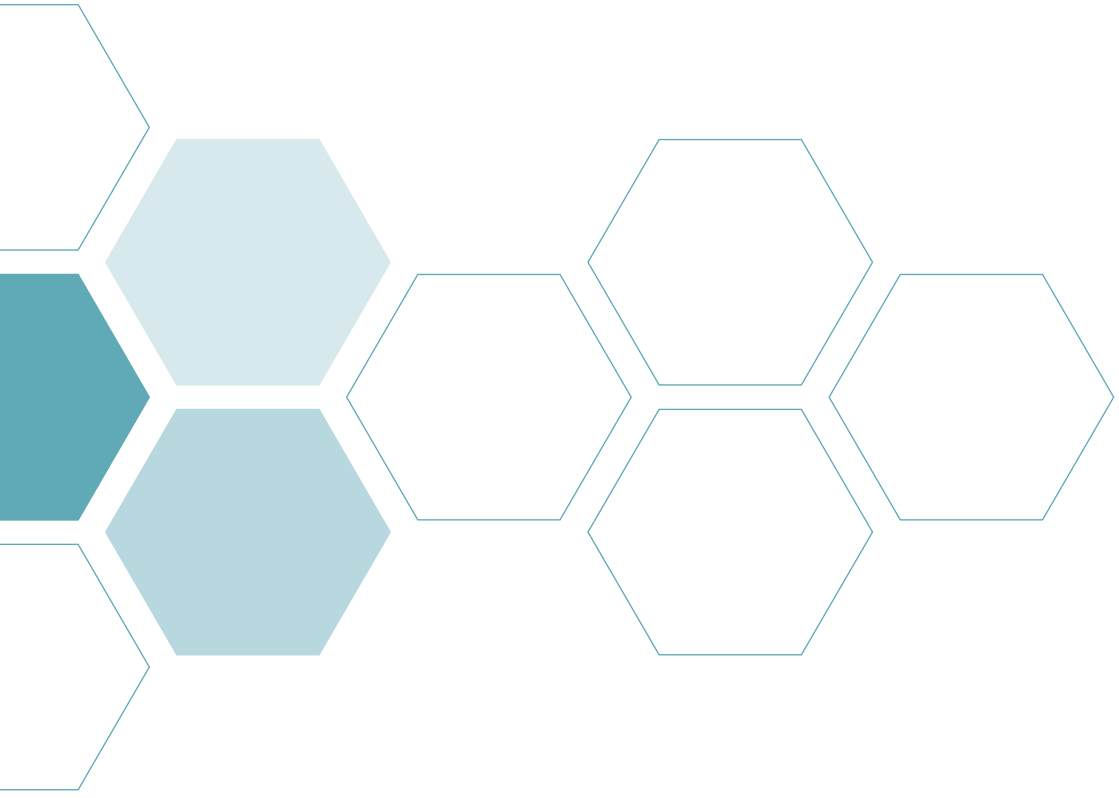
Vol. 27, No. 3, 2024

JOURNAL of MANAGED CARE MEDICINE

Educating Medical Directors of Employers, Health Plans and Provider Systems



FEATURED ARTICLES INCLUDE:

New Horizons in the Treatment and Management of Advanced Non-Small Cell Lung Cancer

New Horizons in the Treatment and Management of Alzheimer's Disease: Managed Care Considerations on Role of New and Emerging Therapies

Incorporating Biosimilars into the Clinical Landscape: Expert Insights for Managed Care Considerations

Editorial Review Board

JMCM

JOURNAL OF MANAGED CARE MEDICINE

4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
Thomas Morrow, MD

PUBLISHER
Jeremy Williams

ADVERTISING REPRESENTATIVE
Maria Sercia
American Medical Communications, Inc.
msercia@americanmedicalcomm.com
(267) 614-6809

JOURNAL MANAGEMENT
Douglas Murphy Communications
Richmond, Virginia
grant.murphy@douglasmurphy.com
(804) 387-7580

GRAPHIC DESIGN
Douglas Murphy Communications

Custom Article Reprints
High quality reprints of individual articles are available in print and electronic formats.
Contact Jeremy Williams,
jwilliams@namcp.org,
(804) 527-1905 for reprints.

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. 27, No. 3, 2024

TABLE OF CONTENTS

New Horizons in the Treatment and Management of Advanced Non-Small Cell Lung Cancer
Gary M. Owens, MD 4

New Horizons in the Treatment and Management of Alzheimer's Disease: Managed Care Considerations on Role of New and Emerging Therapies
Richard S. Isaacson, MD 9

Incorporating Biosimilars into the Clinical Landscape: Expert Insights for Managed Care Considerations
Allan Gibofsky, MD, JD, MACR, FACP, FCLM. 14

Informed Managed Care Decision-Making in the Management of Acute Myeloid Leukemia: Optimizing Clinical and Economic Outcomes in an Evolving Paradigm
Amir T. Fathi, MD. 19

Integrating Novel Approaches to Psoriasis Management: Closing the Gap with Innovative Treatment Strategies
April W. Armstrong, MD, MPH 24

Keeping Pace with Rapid Advancements in the Treatment and Management of Multiple Myeloma
Ravi Vij, MD, MBA 28

New Horizons in the Treatment and Management of Endometrial Cancer: Leveraging Immunotherapy for Improved Clinical and Economic Outcomes
Dario R. Roque, MD 32

Targeting New Strategies in Narcolepsy and Idiopathic Hypersomnia: Novel Approaches to Diagnosis and Treatment
Anne Marie Morse, DO, FAASM. 37

Informed Managed Care Decision-Making in the Management of Hereditary Angioedema: Optimizing Clinical and Economic Outcomes in an Evolving Paradigm
Marc A. Riedl, MD, MS 42

Implementing New Data and Evolving Standards in HER2-Positive Advanced Breast Cancer: Applying the Latest Evidence to Improve Outcomes
Gary M. Owens, MD 47

New Horizons in the Treatment and Management of Advanced Non-Small Cell Lung Cancer

Gary M. Owens, MD

This journal article is supported by educational grants from Merck Sharp & Dohme LLC; AstraZeneca; Daiichi Sankyo; Janssen Biotech, Inc.; Regeneron Pharmaceuticals

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

Summary

The management of advanced non-small cell lung cancer (NSCLC) has changed dramatically with the introduction of targeted therapy for specific genetic mutations which drive this cancer and immunotherapy which helps the body's natural defense work in conjunction with chemotherapy.

Key Points

- Targeted therapy is first-line for those with advanced disease and actionable genetic mutations.
- Immunotherapy plus platinum-based chemotherapy doublets is standard for those without mutations.
- Newer targets such as Trop2 are the future of treatment.

LUNG CANCER IS THE SECOND MOST common cancer in both men and women (Exhibit 1).[1] Around 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women. Lung cancer deaths have begun to decline in both men and women, reflecting a decrease in smoking, but are still the leading cause of cancer deaths. The most common type of lung cancer is non-small cell lung cancer (NSCLC).

In 2020, lung cancer was the third most costly cancer.[2] With NSCLC, costs are driven primarily by outpatient visits and medication costs, especially for checkpoint inhibitor immunotherapy and targeted agents.[3] Although costly to treat, society is benefiting from the increased costs. In one study, population-level mortality in the United States from NSCLC fell sharply from 2013 to 2016, and survival after diagnosis improved, which was likely driven by targeted therapies.[4] Despite improvements in survival, there may be patient financial consequences because of significant out-of-pocket expenses. Financial toxicity is the detrimental effect of the excess financial strain caused by the diagnosis of cancer on the well-being of patients and has become an important consideration in cancer care (Exhibit 2).[5]

Molecular testing is central to selection of effective therapeutic options in NSCLC because targeted therapies have consistently demonstrated significantly improved outcomes for patients with NSCLC. Methods for screening NSCLC patients for driver mutations and other abnormalities continue to evolve. There is no single standard platform for testing but features that make a platform clinically useful are fast turnaround times (two weeks or less), cost efficiencies, the ability to perform on clinically

Exhibit 1: Lung Cancer is Second Most Common Cancer in Men and Women[1]

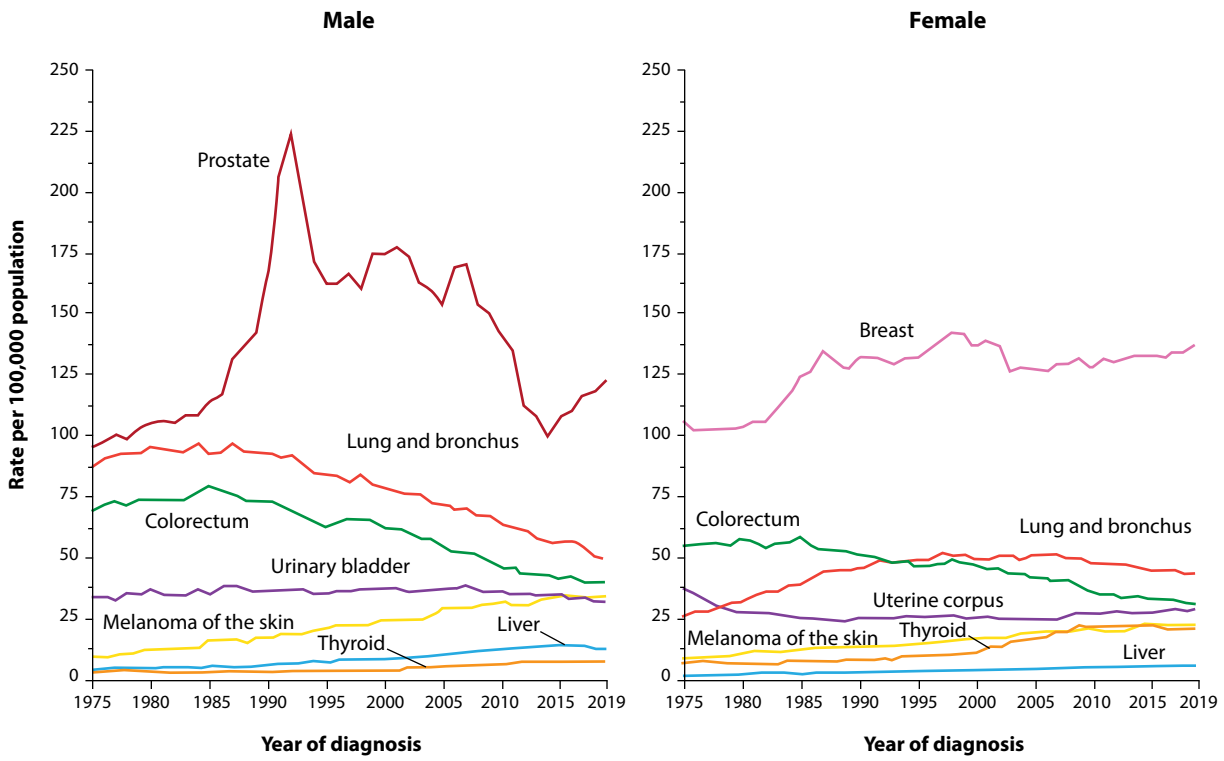
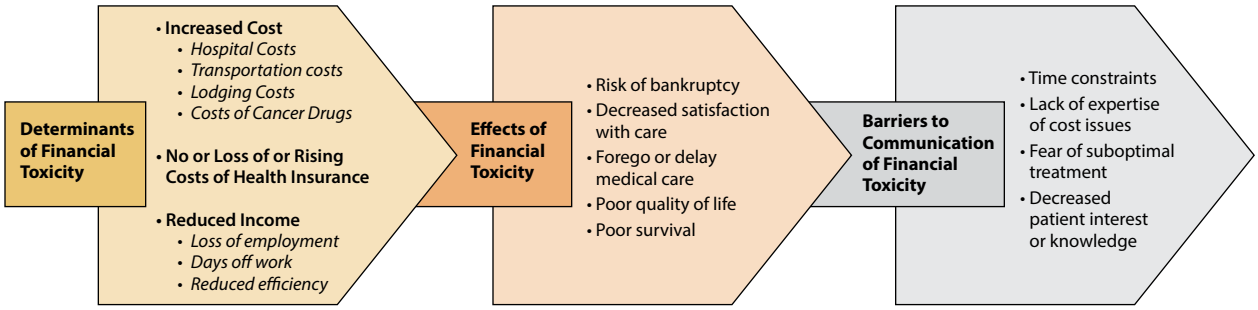


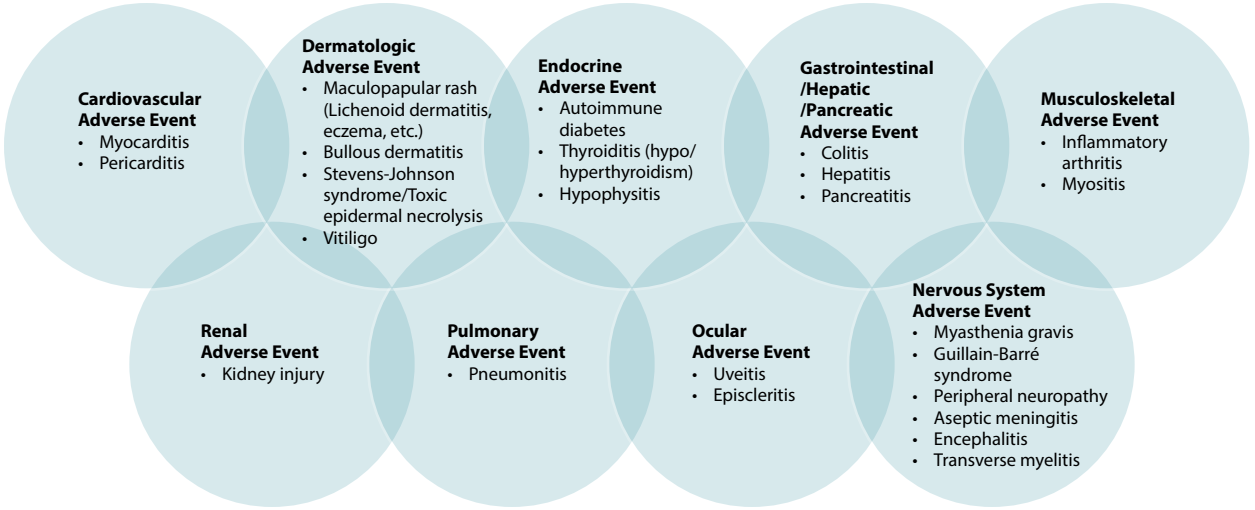
Exhibit 2: Financial Toxicity of Cancer[5]



available samples, and semi-automation eliminating reliance upon a single operator.[6] In NSCLC, the most common mutations are KRAS (29%) and EGFR (19%).[6] These driver mutations create pathways for targeted therapy.

Driver mutations, for which a specific inhibitor is available, are one key factor in initial treatment selection for advanced NSCLC. Other key factors are the presence of an elevated level of programmed cell death ligand 1 (PD-L1) expression; the extent of disease, including the number and sites of metastases; squamous versus nonsquamous histology; performance status, comorbidities, and brain or liver metastases.[7]

Exhibit 3: Immune-Related Adverse Events with PD1/PDL-1 Checkpoint Inhibitors[11]



If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment, except in the case of certain mutations where chemotherapy is first-line.[7] If the patient has no targetable mutations, checkpoint inhibitor immunotherapy with or without chemotherapy and/or bevacizumab is the treatment option, depending on the expression of PD-L1, a biomarker of immunotherapy efficacy in NSCLC.

Immune checkpoint inhibitors targeting programmed death one (PD-1) or PD-L1 have become a routine part of the clinical approach for management of NSCLC. Patients with PD-L1 expression of 50 percent or more are offered either monotherapy with a checkpoint inhibitor or a platinum-doublet chemotherapy plus a checkpoint inhibitor. For patients with PD-L1 expression of less than 50 percent, the combination of a platinum-doublet chemotherapy and a checkpoint inhibitor is standard. For those receiving chemotherapy, choice is influenced by tumor histology.

Checkpoint inhibitor immunotherapy improves overall survival (OS) in NSCLC. In the Keynote 189 study with pembrolizumab, five-year OS was improved by the addition of immunotherapy to chemotherapy (19.4% versus 11.3%).[8,9] Cemiplimab also improved median OS in the EMPOWER Lung 3 trial (22 versus 13 months).[10] These agents also improve progression-free survival (PFS) and overall response rates. Because these agents take the brakes off the immune system, they produce a wide range of immune-mediated adverse events which must be monitored and managed to avoid significant consequences (Exhibit 3).[11]

Newer data on selected driver mutations (HER2, EGFR Exon20, and TROP2) are impacting treatment selection in selected patients. Human epidermal growth factor two (HER2) is a member of the human epidermal growth factor receptor, along with HER1 (also known as EGFR), HER3, and HER4. HER2 expression occurs in about 3 percent of NSCLC cases.[12] After the use of HER2-directed therapies in patients with breast cancer was studied, strategies targeting HER2 were studied in other tumor types, including NSCLC. Three principal forms of HER2 alterations are found in NSCLC—gene mutation, gene amplification and protein overexpression.[13] HER2 activation triggers the phosphorylation of tyrosine kinase residues and activates downstream tumorigenic signaling pathways.

Fam-trastuzumab deruxtecan (T-Dxd) is an antibody drug conjugate (ADC) composed of the anti-HER2 monoclonal antibody trastuzumab, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor, deruxtecan. In 2022, the FDA gave accelerated approval to T-Dxd for adults with previously treated, unresectable or metastatic NSCLC. The Phase II trial used for accelerated approval evaluating two doses (5.4 and 6.4 mg/kg) of T-Dxd, confirmed the overall response rate was 49.0 percent and 56.0 percent and median duration

of response was 16.8 months and not estimable, respectively.[14] Median treatment duration was 7.7 months (range, 0.7 – 20.8) with 5.4 mg/kg and 8.3 months (range, 0.7 – 20.3) with 6.4 mg/kg. The 5.4 mg/kg dose was better tolerated with fewer Grade 3 or higher drug-related treatment-emergent adverse events and is the recommended dose.

Classical activating mutations (exon 19 deletions and the L858R point mutation in exon 20) comprise 90 percent of EGFR mutations and are well defined as strong predictors for good clinical response to EGFR tyrosine kinase inhibitors.[15] EGFR exon 20 insertion mutation occurs in about 2 percent of NSCLC cases and is more commonly found in people who never smoked and in Asian persons.[12] Rarer mutations including point mutations, deletions, insertions, and duplications occur within exons 18 to 25 of the EGFR gene in NSCLC and are associated with poor responses to EGFR inhibitors. Because of poor response to EGFR inhibitors, chemotherapy has been the preferred first-line treatment for advanced NSCLC patients harboring EGFR exon 20 insertion mutations. Since 2021, amivantamab, a bispecific EGFR and MET receptor antibody, has been available to target the exon 20 insertion mutation. It is approved now for both first-line treatment in combination with standard chemotherapy and as monotherapy for second-line treatment for patients with progression during or after first-line chemotherapy. In combination with carboplatin and pemetrexed, amivantamab improved PFS compared to chemotherapy alone (11.4 versus 6.7 months). OS data from this trial have not yet been reported.[16]

A new area of treatment in some cancers is targeting trophoblast cell surface antigen (Trop2), a transmembrane glycoprotein calcium signal transducer. Trop2 mediates cell migration and anchorage-independent growth and is associated with poor overall and disease-free survival in several types of solid tumors.[17] In lung cancer, Trop2 overexpression has been observed in up to 64 percent of adenocarcinomas and 75 percent of squamous cell carcinomas.[18] Trop2 overexpression is associated with reduced survival and a potential role in resistance to chemotherapy in NSCLC. Sacituzumab govitecan, FDA-approved for other cancers, and datopotamab deruxtecan, an investigational ADC, has shown promising activity signals in NSCLC.[19] Additional larger trials are ongoing with these two agents with datopotamab deruxtecan appearing to be the closest to market.

Combination therapy with chemotherapy, immunotherapy, and Trop2 targeting agents are likely to be the future of treating some types of NSCLC. Such combinations can be very expensive which is worrisome for managed care. Payers have seen projections that estimate the cost of combination therapy with personalized approaches in the range of $250,000 to over $1 million per year. Payers view this cost as representative of cancer care cost and often use the term "unsustainable". Payers are not the only ones involved as their employer customers are now demanding action on escalating costs as well.

Current value assessments for novel therapies may need revision. Payers need to better define and understand the key aspects and attributes of personalized therapies that should be considered in any assessment of their value. Payers need to address evidence gaps in existing value frameworks given the unique properties of patient outcomes with personalized therapies. A better characterization of the benefit of personalized treatment will allow a more thorough assessment of its benefits and provide a template for the design of management programs and roadmaps for healthcare insurers to optimize coverage for patients with NSCLC.

One of the evidence gaps to address is alternate stakeholder perspective. There needs to be more research emphasis on the societal perspective when considering treatment value. Cost-effectiveness analyses should include both quality of life year (QALY) and no QALY adjustment so that absolute mortality reductions can be easily reported for decision-makers. Addressing outcomes that "matter" to patients is another gap which can help decision-makers compare drugs within the same disease state.[20] Hope is one outcome which matters to patients. The Professional Society for Health Economics and Outcomes Research (ISPOR) Special Task Force identifies the value of hope as an area needing more research to quantify. A cancer patient facing a terminal diagnosis may be willing to risk taking a more novel therapy if his or her chances include the possibility of durable response and even functional cure. For a cancer patient, any innovation that can extend life (even at the same or worse quality of life) may give a patient a chance to live long enough for a new treatment to develop, and even cure.

Lastly, payers may need to leverage patient-reported outcomes, real-world evidence, and other tools to expand the knowledge base and continuously improve patient outcomes from personalized approaches. From such analyses, payers and providers together must develop careful patient selection to ensure treatments are provided only to those patients most likely to benefit.

Conclusion

The treatment of advanced NSCLC continues to evolve. For most patients, the combination of checkpoint immunotherapy and chemotherapy is the treatment of choice. For those with selected driver mutations, targeted therapy is the initial therapy choice. Additional agents targeting other mutations are on the horizon.

Gary M. Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17-48.
2. National Cancer Institute. Cancer Trends Progress Report. Financial Burden of Cancer Care. Available at progressreport.cancer.gov/after/economic burden. Accessed 7/1/2024.
3. Nesline MK, Knight T, Colman S, Patel K. Economic burden of checkpoint inhibitor immunotherapy for the treatment of non-small cell lung cancer in U.S. clinical practice. *Clin Ther.* 2020;42(9):1682-98.e7.
4. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med.* 2020;383(7):640-9.
5. Desai A, Gyawali B. Financial toxicity of cancer treatment: Moving the discussion from acknowledgement of the problem to identifying solutions. *EClinicalMedicine.* 2020;20:100269.
6. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present, and future. *World J Clin Oncol.* 2021;12(4):217-37.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 7.2024. Available at nccn.org. Accessed 7/1/2024.
8. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378:2078-92.
9. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the Phase III KEYNOTE-189 study. *J Clin Oncol.* 2023;41:1992-8.
10. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: A randomized, controlled, double-blind Phase III trial. *Nat Med.* 2022;28:2374-80.
11. Okiyama N, Tanaka R. Immune-related adverse events in various organs caused by immune checkpoint inhibitors. *Allergol Int.* 2022;71(2):169-78.
12. Friedlaender A, Perol M, Banna GL, et al. Oncogenic alterations in advanced NSCLC: A molecular super-highway. *Biomark Res.* 2024;12(1):24.
13. Li BT, Ross DS, Aisner DL, et al. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. *J Thorac Oncol.* 2016;11(3):414-9.
14. Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small-cell lung cancer: Primary results from the randomized, Phase II DESTINY-Lung02 trial. *J Clin Oncol.* 2023;41(31):4852-63.
15. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol.* 2020;61:167-79.
16. Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. *N Engl J Med.* 2023;389(22):2039-51.
17. Li Z, Jiang X, Zhang W. TROP2 overexpression promotes proliferation and invasion of lung adenocarcinoma cells. *Biochem Biophys Res Commun.* 2016;470(1):197-204.
18. Wang X, Long M, Dong K, et al. Chemotherapy agents-induced immunoresistance in lung cancer cells could be reversed by trop-2 inhibition in vitro and in vivo by interaction with MAPK signaling pathway. *Cancer Biol Ther.* 2013;14(12):1123-32.
19. Parisi C, Mahjoubi L, Gazzah A, Barlesi F. TROP-2 directed antibody-drug conjugates (ADCs): The revolution of smart drug delivery in advanced non-small cell lung cancer (NSCLC). *Cancer Treat Rev.* 2023;118:102572.
20. Kaufman HL, Atkins MB, Subedi P, et al. The promise of immuno-oncology: Implications for defining the value of cancer treatment. *J Immunother Cancer.* 2019;7(1):129.

New Horizons in the Treatment and Management of Alzheimer's Disease: Managed Care Considerations on Role of New and Emerging Therapies

Richard S. Isaacson, MD

This journal article is supported by an educational grant from Eisai

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 in the brain over many decades before the first symptoms of memory loss begin. Prevention and identifying the disease early are important goals. Agents which target a component of the underlying pathology are now available and are appropriate for selected patients.

Key Points

- AD is a middle-age disease that needs to be identified as early as possible.
- Precision medicine is the future of AD.
- FDA-approved anti-amyloid agents are now available and another is on the horizon.
- Prevention interventions are showing positive benefits.

ALZHEIMER'S DISEASE (AD) IS A SPECTRUM of disease that develops over decades and affects about 40 million Americans. In 2024, health and long-term care costs for people living with Alzheimer's and other dementias are projected to reach $360 billion, and this does not include the cost of unpaid caregiving.[1] As our society continues to age, the significant financial and social impact of this disease is a major reason to focus on prevention. Even a modest improvement in disease rates and care costs can have a significant impact.

A change in mindset needs to occur with clinicians. AD is a disease of middle age rather than one of old age. The process of AD begins 20 to 30 years before the first memory loss symptom occurs. For patients who are diagnosed at 85, their disease process began between 55 and 65 years of age. That leaves a long time to intervene. If someone already has dementia, that person has had AD for decades and effective treatment is not possible if brain cells are already dead. Therefore, prevention is an important topic. The goal of preventive neurology is to identify people early in the process.

Initially, AD typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and hippocampus.[2] It later affects areas in the cerebral cortex responsible for language, reasoning, and social behavior. Beta-amyloid protein in several different molecular forms including beta-amyloid 40 and 42 is a pathologic protein. One form, beta-amyloid 42, is thought to be especially toxic and the ratio of 42 to 40 is especially important. Beta-amyloid 42 is formed from the breakdown of a larger protein, called amyloid precursor protein. Two out of three people with demonstrated amyloid in their brain will go on to develop AD. In the Alzheimer's brain, abnormal levels of beta-amyloid clump together to form plaques that collect between neurons and disrupt cell function. Blood amyloid levels begin to increase decades before the onset of cognitive symptoms and may be a way to identify the disease earlier.

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. There are several forms of tau but p-Tau217 has been shown to be a good predictor of future cognitive decline and brain atrophy.[3]

Diagnosis of AD earlier in the disease process is getting easier. Typical clinical evaluation of a person with memory difficulties in everyday practice includes detailed clinical history, family 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. Although not common, reversible causes of cognitive decline, like low B12, are occasionally found. Genetic testing in suspected AD is still controversial but commercial testing for APOE ϵ4 allele and presenilin 1 and 2 are available. Early-Onset Alzheimer's Disease (EOAD), which is rare, is caused by mutations in the amyloid precursor protein genes, presenilin 1 or presenilin 2. 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. Because of the new anti-amyloid medications, more genetic testing is being done to identify those at a higher risk of developing AD.

The use of biomarkers for diagnosis is becoming more common. 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. In the future, some or all these biomarkers will be used to monitor risk of AD over time such as the use of cholesterol levels for cardiovascular risk. 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. This approach is good but not perfect because it is not specific enough.

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.[4] 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.[5] 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.[5,6] 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.

Another future biomarker is neurofilament light (Nfl) which is a sensitive but not specific marker of neurodegeneration. Nfl is released by damaged or dying neurons and reflects axonal degeneration and injury of longer myelinated axons. Higher levels are associated with faster disease progression and atrophy. It is currently being investigated as a measure of intensity of ongoing neurodegeneration.

Amyloid and tau blood tests which do not have the risks of a spinal tap or the exposure of MRI or PET scan, are less expensive, and are part of the future of biomarkers for diagnosing AD. The AD diagnostic criteria are being updated to include blood-based biomarkers. These biomarkers can be used for diagnosis in symptomatic patients, risk stratify those without symptoms, and to measure effectiveness of risk reduction intervention and medications.

Aducanumab and lecanemab are the two currently approved anti-amyloid agents. Donanemab is an investigational agent which as of May 2024 had not yet been approved by the FDA. Anti-amyloid therapy is still controversial because of its cost, need for intravenous infusion, adverse events, and modest average benefits. However, in the right patient, at the right dose, and for the right duration, the anti-amyloid medications can be very effective.

It is important to note that patients who are being considered for these medications must have demonstrated amyloid pathology in their brains. Many of the early studies of anti-amyloid medications were done before the availability of good biomarkers for amyloid and did not produce significant results. Later examination of these studies found that about 40 percent of study subjects never had amyloid.

Aducanumab, the first amyloid-targeted monoclonal antibody, was FDA approved for early AD [mild cognitive impairment (MCI) due to AD or mild AD dementia] in 2021 but is being discontinued in 2024 by the manufacturer.[7] This is not a safety decision and is likely due to the approval of lecanemab and low use of aducanumab.

Lecanemab, another anti-beta-amyloid monoclonal antibody, was approved by the FDA in July 2023 based on Phase III trial results for mild AD. This agent slowed the rate of cognitive decline by 27 percent in the Phase III, 18-month study in early AD.[8] The incidence of adverse events was 21.3 percent for those who received lecanemab and 9.3 percent for those who received a placebo.

Adverse events, which are common to the anti-amyloid agents, include hemosiderosis, microhemorrhage, brain edema, falling, headache, diarrhea, altered mental status, confusion, delirium, 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 and their presence is not always associated with symptoms. The ARIA adverse events are primarily a function of being an APOE ϵ4 carrier and higher doses of anti-amyloid antibodies. APOE ϵ4 homozygotes are at the highest risk. The package labeling for lecanemab recommends a baseline MRI and MRIs prior to the fifth, seventh, and 14th infusions. Some clinicians are doing additional MRIs, especially after dose increases. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms.

The effects of lecanemab on amyloid and tau levels have also been studied in those with early AD and preclinical amyloid accumulation. Another ongoing trial is a prevention study pairing lecanemab with an anti-tau antibody E2814 in people with familial AD mutations.

Medicare now covers anti-amyloid agents when a beneficiary is diagnosed with mild cognitive impairment or AD dementia with documented evidence of beta-amyloid plaque in the brain and has a physician participating in a registry with an appropriate clinical team and follow-up care. The initial decision by Medicare to limit coverage to patients in a clinical trial led to low use of aducanumab.

Anti-amyloid therapies agents really should be used as prevention in people at risk for AD but are only FDA approved for early AD. They have not been shown to be effective for moderate or severe AD and should not be used in these types of patients. In those with early AD with demonstrated amyloid, patients have a slowing of cognitive decline but never an

Exhibit 1: Anti-amyloid Medications

DRUG	ADUCANUMAB: APPROVED	LECANEMAB: APPROVED	DONANEMAB: PENDING APPROVAL
Binding	Fibrils > oligomers	Protofibrils 75 – 300 kDa	Fibrils, no oligomers
Inclusion	+ Amyloid PET	+ Amyloid PET	+ Amyloid PET and + tau PET
MMSE	24 – 30	22 – 30	20 – 28
Number of patients	Phase III: 3,285 pts half to the drug, half on placebo 3, 6, 10mg doses.	Phase III: 1,800 pts, half to the drug half on placebo.	Phase II: 257 pts; 130+/group; 93/ completed trial.
Length	18 months	18 months	18 months
Dosing	10mg/kg q m, 1mg to 10mg titrated over 8 m	10mg/kg biweekly, no titration	700mg q m for 3m, then 1,400mg q m.
Plaque Reduction	44 CL↓ in 26 wks, 50% plaque-, 57 CL↓ in 18 m	70% plaque-, 59 CL↓ in 18 m	40% plaque-, 68 CL↓ in 6 m; 70% plaque-, 85 CL↓ in 18 m
Clinical Outcome	0.4 versus placebo on 18-pt CDR-SB, 10mg dose	0.45 versus placebo on 18-pt CDR-SB	3 pts versus placebo, iADRS; no change on 18 pt CDR-SB
ARIA H	34% 10mg dose	17%	31%
ARIA E	35% 10mg dose	13%	27%
ARIA E/ H	41% 10mg dose	21%	40%

ARIA = Amyloid Related Imaging Abnormalities; ARIA H = Amyloid Related Imaging Abnormalities hemorrhage;
ARIA E = Amyloid Related Imaging Abnormalities edema; MMSE = Mini-mental state examination; CL = Centiloid units to measure plaque;
CDR-SB = Clinical dementia rating scale - sum of boxes 18-point scale of cognitive ability, higher score more impairment.
iADRS = integrated Alzheimer's Disease Rating Scale is a 144-point scale of cognitive ability, lower score more impairment
PET = Positron Emission Tomography:

improvement in cognition. Remember also that 27 percent reduction in cognitive decline is the average. There is nuance when giving these medications to maximize benefit while minimizing adverse events and figuring which patient will have the most benefit is critical. There are also logistical and financial challenges to using these medications.

It is important that APOE ϵ4 allele state be evaluated before giving anti-amyloid medication. Patients with a variant are much more likely to have brain adverse events, so a slower titration should be done in these patients. Additionally, those with allele variants tend to have a better response to anti-amyloid therapy.

Donanemab is another anti-amyloid monoclonal antibody under investigation. In a trial in subjects with early AD and meeting criteria on amyloid and tau PET scans, there was significantly slowed clinical progression and functional decline at 18 months.[9] Forty-seven percent of those who received donanemab, compared to 29 percent who received a placebo, showed no signs of cognitive decline after one year of treatment. The treatment group showed a slowing of clinical decline by 22.3 percent compared to the placebo. The incidence of serious adverse events was 17.4 percent for those who received donanemab and 15.8 percent for those who received a placebo; additionally, three donanemab-related deaths occurred during the trial.

An ongoing trial is evaluating donanemab in cognitively normal subjects at high risk for AD based on elevated plasma pTau217 and runs through September 2027. Another trial in those with mild dementia and a positive amyloid PET scan is a Phase III head-to-head comparison trial with donanemab and aducanumab. Topline results from this trial showed a significantly higher number of subjects reached amyloid clearance and amyloid plaque reductions with donanemab compared to aducanumab at six months.[10] Final results of this trial have not yet been published. In March 2024, the FDA delayed approval of donanemab and plans to hold an advisory panel meeting to evaluate the safety and efficacy of donanemab in June 2024.[11] Exhibit 1 presents comparative data on the three anti-amyloid agents. It is important to note that these data are not from head-to-head trials.

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] Alzheimer's Prevention clinics use anthropometric, biomarker, and cognitive assessments (ABC) to determine risk and then personalize treatment by targeting the individual's risk factors. These clinics 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.

In these prevention programs, modifiable risk factors are targeted with nonpharmacologic and pharmacologic therapies. Interventions may target vision, hearing, nutrition, exercise, cognitive activities, music, stress reduction, social interaction, sleep hygiene, and cardiovascular risk (BP, lipids, tobacco, glucose). Each of these have been shown to be effective in selected patients but not every intervention is appropriate for all patients. Potential nutritional interventions are shown in Exhibit 2. For example, in those with MCI and elevated

Exhibit 2: Example Preventive Nutritional Interventions

Dietary Patterns	Single / Multi-nutrients
Mediterranean-style	Omega-3 fatty acids (DHA > EPA "Fish oil")
Low saturated fat/high glycemic index diet	Curcumin (Turmeric root)
Ketogenic	Folic Acid, B6, B12
Caloric restriction	Vitamin D
DASH (Dietary Approaches to Stop Hypertension)	Caffeine/Coffee
MIND (mediterranean/dash)	Dietary antioxidants
FINGER (fbhi.se/the-finger-model)	Flavanols
	Medium chain triglycerides

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] But this intervention would not be recommended for everyone since there is no evidence of effectiveness.

Most interventions have been evaluated separately but evidence is now accumulating for multidomain interventions. A clinical trial of individualized multidomain interventions in people at risk for AD in a clinical setting showed that individualized AD risk factor management may improve cognitive function related to AD pathology.[17] Secondary analyses showed reductions in calculated Alzheimer's and cardiovascular disease risk scores and possible influence on age-related cognitive decline. This study did find that higher compliance with the prescribed interventions (> 60% of recommended interventions) provided the most benefit in those who already have some memory impairment. 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.

Data are now coming from AD prevention programs showing benefits of biomarker reductions. An example is one 55-year-old male with MCI and APOE ε4 variant who after an individualized prevention program for three years and aducanumab for 18 months no longer has amyloid in the brain and less tau in blood. On cognitive testing, he now meets criteria for pre-clinical AD. He still has some memory issues but these are not as significant as before. How long he will have this effectiveness is not known.

For people not near an AD prevention program, an option is to participate in an ongoing NIH study that uses the principles of prevention discussed here (retainyourbrain.com). Additionally, people can be referred to brainmind.org/alz for a master class on AD.

Conclusion

Significant advances have been made in recent years in improving AD diagnosis. Biomarkers for AD are available to help support an accurate diagnosis. Soon, risk assessment and diagnosis will be driven by blood-based biomarkers. The future is finding a way to prevent this devastating disease.

Richard S. Isaacson, MD serves as Director of the Center for Brain Health and Director of the Alzheimer's Prevention Clinic at Florida Atlantic University's Charles E. Schmidt College of Medicine in Boca Raton, FL.

References

1. Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. *Alzheimer's Dement*. 2024;20(5).
2. National Institute of Aging. What Happens to the Brain in Alzheimer's Disease? Available at nia.nih.gov/health/what-happens-brain-alzheimers-disease. Accessed 5/18/2024.
3. Mattsson-Carlgren N, Salvadó G, Ashton NJ, et al. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. *JAMA Neurol*. 2023;80(4):360-9.
4. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *Lancet Neurol*. 2017;16(8):661-76.
5. Villemagne VL, Doré V, Burnham SC, et al. Imaging tau and amyloid-β proteinopathies in Alzheimer disease and other conditions. *Nat Rev Neurol*. 2018;14(4):225-36.
6. Alzheimer's Association. Amyloid Imaging Task Force. Available at alz.org/research/for_researchers/partnerships/amyloid-imaging-task-force. Accessed 5/18/2024.
7. Alzheimer's Association. Aducanumab to Be Discontinued as an Alzheimer's Treatment. Available at alz.org/alzheimers-dementia/treatments/aducanumab. Accessed 5/18/2024.
8. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21.
9. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: The Trailblazer-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-27.
10. Salloway S, Lee E, Papka M, et al. TRAILBLAZER-ALZ 4: Topline study results directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease. *BJPsych Open*. 2023;9(Suppl 1):S67.
11. Lilly statement on FDA Advisory Committee meeting on donanemab for early symptomatic Alzheimer's disease. Eli Lilly. May 7, 2024. Available at investor.lilly.com/news-releases/news-release-details/lilly-statement-fda-advisory-committee-meeting-donanemab-early. Accessed May 18, 2024.
12. Ngandu T, Lehtisalo J, Solomon A, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomized controlled trial. *Lancet*. 2015;385(9984):2255-63.
13. Smith PJ, Mabe SM, Sherwood A, et al. Metabolic and neurocognitive changes following lifestyle modification: Examination of biomarkers from the ENLIGHTEN randomized clinical trial. *J Alzheimer's Dis*. 2020;77(4):1793-803.
14. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, et al. Effect of intensive vs standard blood pressure control on probable dementia: A randomized clinical trial. *JAMA*. 2019;321(6):553-61.
15. Isaacson RS, Ganzer CA, Hristov H, et al. The clinical practice of risk reduction for Alzheimer's disease: A precision medicine approach. *Alzheimer's Dement*. 2018;14(12):1663-73.
16. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. *PLoS One*. 2010;5(9):e12244.
17. Isaacson RS, Hristov H, Saif N, et al. Individualized clinical management of patients at risk for Alzheimer's dementia. *Alzheimer's Dement*. 2019;15(12):1588-1602.

Incorporating Biosimilars into the Clinical Landscape: Expert Insights for Managed Care Considerations

Allan Gibofsky, MD, JD, MACR, FACP, FCLM

This journal article is supported by educational grants from Boehringer Ingelheim; Coherus BioSciences

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

Summary

Biosimilars have been gaining acceptance but their use still lags in some therapeutic areas. Provider and patient education can help advance their use to achieve the original goals of cost savings and access expansion.

Key Points

- Biosimilars under extensive comparative analytical studies against a reference product must demonstrate similar efficacy and safety.
- Biosimilars in inflammatory diseases are comparable in efficacy and safety to reference products in biologic-naïve patients and data supports switching from reference to biosimilar.
- Clinicians need to address patient concerns about biosimilars through communication, shared decision-making, and patient education.

A BIOSIMILAR IS HIGHLY SIMILAR TO AN already FDA-approved reference biologic with no clinically meaningful differences from the reference product in safety, purity, or potency.[1] Biologics are not generics. Exhibit 1 illustrates the primary differences.[2]

Biologics are manufactured using living systems such as microorganisms, plant cells, or animal cells and are composed of large complex molecules which can be difficult to manufacture. Biological products contain inherent variation and can change over time with manufacturing changes.[2] Inherent variation exists within lots and between different lots of a given biologic. This variation applies to both reference biologics and biosimilars.

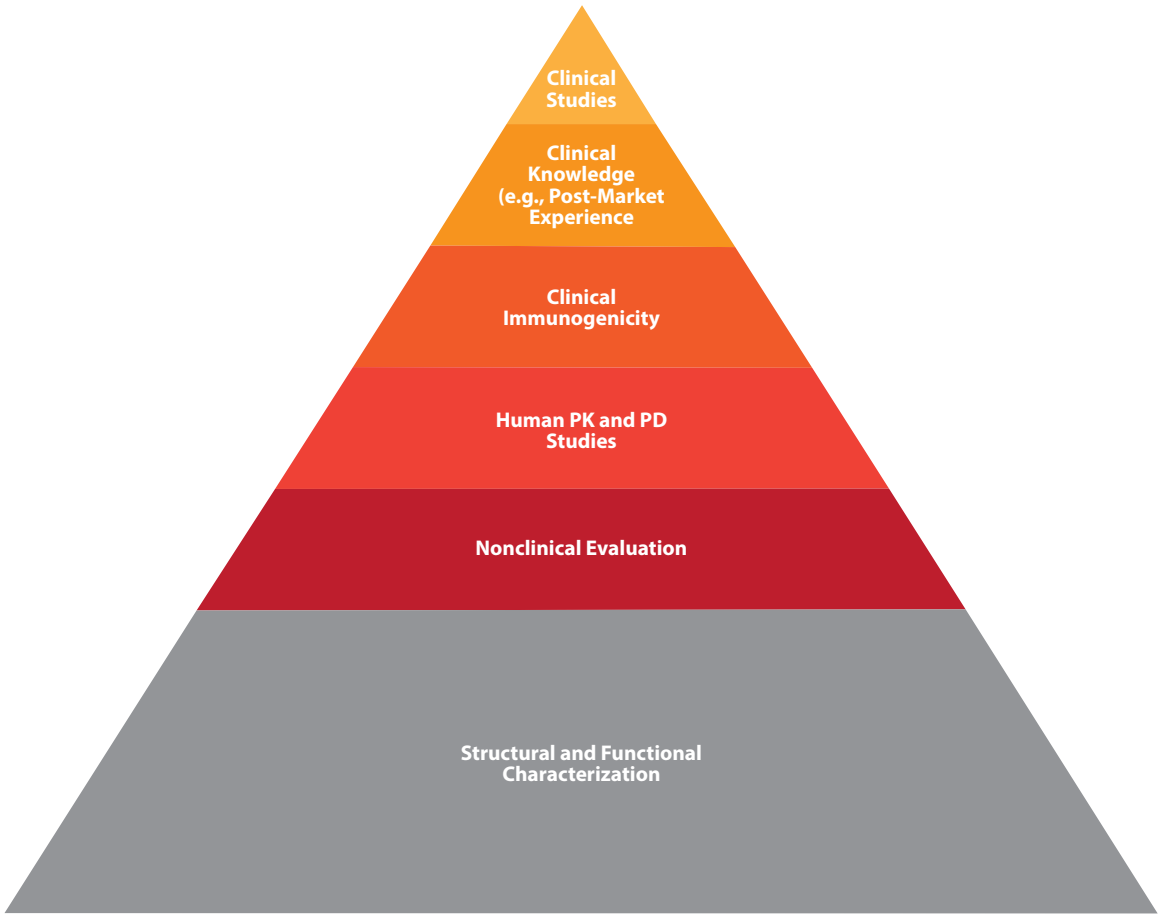
The Biologics Price Competition and Innovation Act (BPCIA) was enacted in 2010 and established an abbreviated pathway to FDA approval for biosimilars under section 351(k) of the Public Health Service Act.[3] Exhibit 2 shows types of evaluations used in demonstrating biosimilarity.[3] Extensive comparative analytical studies first show the biosimilar to be highly similar to reference product. Minor differences in clinically inactive components are acceptable. Similar efficacy and safety, compared to reference product are demonstrated with pharmacokinetic, pharmacodynamic, and immunogenicity studies and small double-blind, parallel-group, active comparator clinical trial(s). Data for a biosimilar from a clinical trial for one indication may be used to support approval for additional indications for which the reference product is already licensed. There is no need to demonstrate efficacy of the biosimilar in all indications.[3]

Biosimilars were developed because of the expense of biologic products. They are intended to generate

Exhibit 1: Generics versus Biosimilars[2]

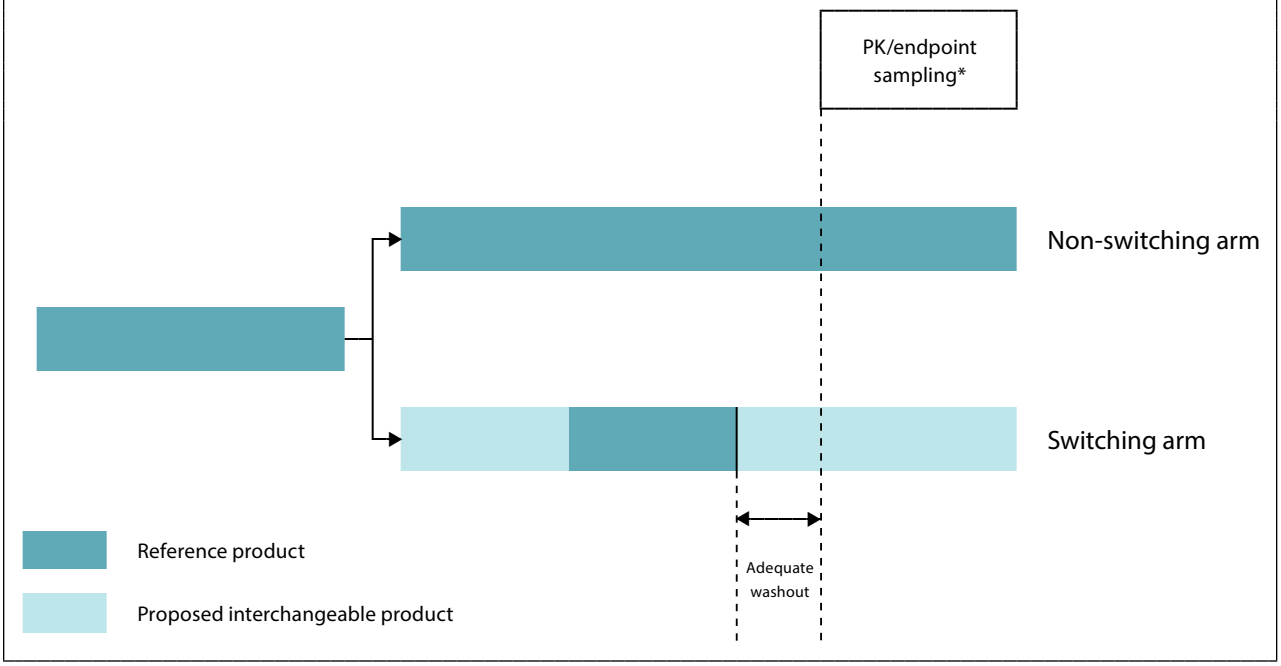
Generics	Biosimilars
Typically manufactured through chemical synthesis.	Typically manufactured from living sources.
Generally small, simple molecules.	Generally large molecules with complex structures.
~ 2 years to develop.	~ 5 to 9 years to develop.
Identical active ingredient between lots (i.e., no variation).	Inherent variability (i.e., small variations in protein molecules) from lot to lot.
Must demonstrate active ingredient is the same as in the reference listed drug.	Must demonstrate is highly similar to the reference product with only minor differences in inactive ingredients.
Must demonstrate bioequivalence to the reference listed drug.	Must demonstrate no clinically meaningful differences from the reference product.

Exhibit 2: Demonstrating Biosimilarity[3]



PK = pharmacokinetic, PD = pharmacodynamic

Exhibit 3: Study Design Comparing Proposed Interchangeable Biosimilar to Reference Product[8]



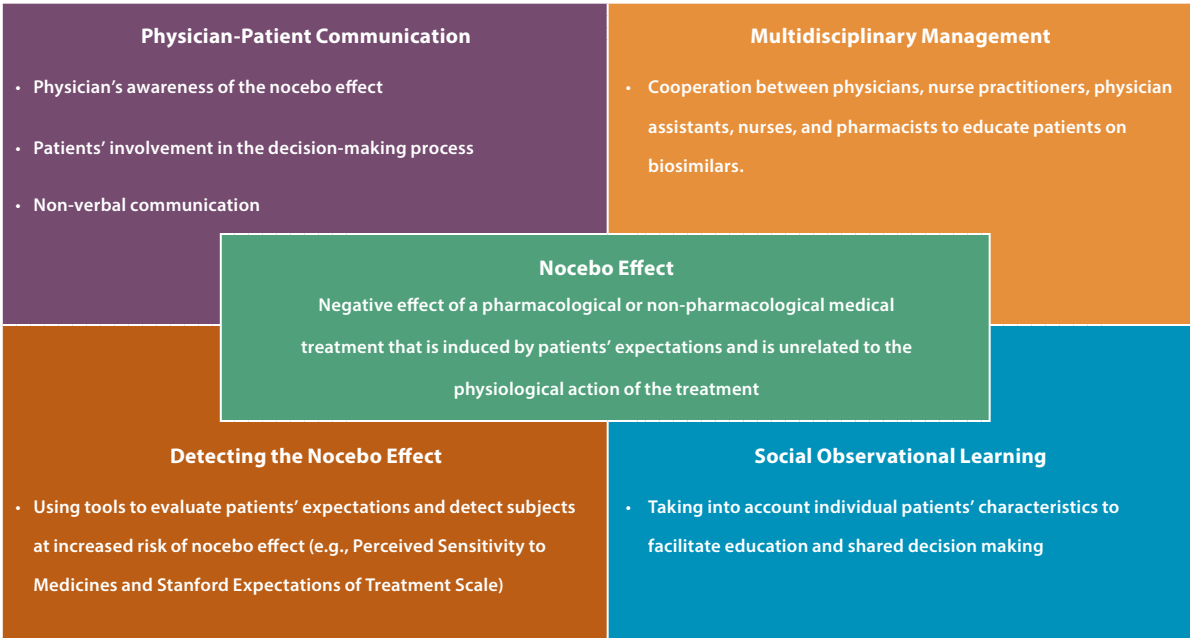
*Appropriate pharmacokinetic (PK) parameters and other endpoints (e.g., pharmacodynamic) also collected and analyzed in previous switch intervals.

product and price competition, increase treatment access, and ideally lower healthcare costs. The FDA currently approves over 50 biosimilar products.[4] Not all FDA-approved biosimilars are available on the market due to factors including ongoing patent litigation, exclusivity protections that delay market entry, and individual company decisions regarding product marketing.

Industry analysts expect biosimilars to reduce drug expenditure in the United States (U.S.) by $133 billion by 2025.[5] Since the first biosimilar was introduced in 2015, biosimilar use has grown overall. However, adoption has been slow in certain therapeutic areas. Two of these are rheumatology and gastroenterology. In a survey of board-certified rheumatologists in the U.S., 73 percent would initiate a biosimilar treatment for a biologic-naïve patient, but only 35 percent would switch to a biosimilar for a patient doing well on reference product.[6]Among clinicians caring for patients with inflammatory bowel disease, only 24 percent were comfortable in decision-making about biosimilars.[7] In addition to a lack of comfort with biosimilars, it can be hard for a clinician to be familiar with all available biosimilars for a given reference product. For example, in rheumatology, there are four biosimilars for infliximab, three for rituximab, two for etanercept, and 10 for adalimumab.

Another significant barrier to widespread use of biosimilars is the issue of interchangeability. Interchangeability is a regulatory designation specific to the U.S., which allows pharmacists to substitute a reference product with its biosimilar without requiring the prescribing clinician's approval or notifying them after dispensing—subject to state law. Demonstrating interchangeability of a biosimilar with a reference product requires that the manufacturer must show that the proposed interchangeable product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient in all the reference product's licensed conditions of use (i.e., all FDA-approved indications).[8] Data for each indication is gained from prospective, and controlled switching studies. In these studies, there is a lead-in period of treatment with the reference product followed by randomized two-arm periods (switching arm versus non-switching arm, Exhibit 3).[8] At least three switches, with each switch crossing over to alternative product, are performed. The primary endpoint of the studies is analysis of geometric mean ratios of pharmacokinetic parameters between a switching and non-switching arm following a final switch. Secondary endpoints are safety, immunogenicity, and efficacy measures. As an example, adalimumab-adbm is interchangeable with adalimumab reference product (Humira®).

Exhibit 4: Strategies to Minimize the Nocebo Effect[19]



Numerous studies have been published examining the use of reference products and biosimilars in the treatment of inflammatory bowel disease.[9-15] Data from these trials support similar efficacy in treatment-naïve patients. Additionally, there is growing evidence to support the safety and efficacy of switching to a biosimilar for patients in remission. Lastly, there are accumulating data for reverse switching, multiple switching, and cross-switching among biosimilars. Knowledge of these studies can help clinicians become more comfortable with the use of biosimilars.

Uptake of biosimilars for immune-mediated inflammatory diseases in rheumatology and gastroenterology in the U.S., has been limited for numerous reasons. Prescriber lack of knowledge and comfort has already been discussed. There has been a relatively slow regulatory process bringing biosimilars to market, patent litigation, and preemptive competition by bio-originator (reference product) companies have also limited use. Pharmacy benefit managers have also given bio-originators preferred formulary status. There has been no systematic effort to educate prescribers and patients who are concerned about biosimilar safety and efficacy. Lastly, there has been little economic incentive for healthcare providers to prescribe a lower cost biosimilar and for patients to use a lower cost biosimilar. Physicians generally disapprove of non-medical switching in stable patients—many believe that non-medical switching leads to office management issues, poorer patient mental health, decreased efficacy, and worsened patient safety.[16]

Patients also have worries about efficacy and safety of biosimilars.[17] Good patient-physician relationships will improve patients' acceptance of biosimilars and limit the risk of inappropriate negative bias and the nocebo effect. The nocebo effect is defined as a negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations that is unrelated to the physiological action of the treatment.[18] The nocebo effect lowers patients' quality of life and negatively affects treatment adherence rates in biosimilar-treated patients and may negatively impact the cost-savings of biosimilars. Healthcare providers need to be aware of the nocebo effect and adopt strategies to minimize it by being well-informed and confident about the existing evidence about biosimilars (Exhibit 4).[19]

There is a need for widespread patient education about biosimilars. Areas where education is needed include use of therapy in the specific disease, regulatory requirements, safety of biosimilars, delivery/administration of the agent, and insurance coverage. Advocacy groups and managed care organizations can play roles in this education.

Conclusion

For approval, a biosimilar undergoes extensive comparative analytical studies against a reference product and must demonstrate similar efficacy and safety. Biosimilars in inflammatory diseases are comparable in efficacy and safety to reference products in biologic-naïve patients and data supports switching from reference to biosimilar. There is accumulating evidence for reverse switching, multiple switching, and cross-switching among biosimilars. Clinicians need to address patient concerns about biosimilars through communication, shared decision-making, and patient education. Use of a lower cost biosimilar benefits others with a particular condition by allowing more people to be treated with an effective medication. Savings realized by using biosimilars may be redirected to pay for novel therapies that address unmet needs.

Allan Gibofsky, MD, JD, MACR, FACP, FCLM is a Professor of Medicine at Weill Cornell Medicine and Attending Rheumatologist and Director, Clinic for Inflammatory Arthritis and Biologic Therapy at the Hospital for Special Surgery in New York, NY.

References

1. U.S. Food and Drug Administration. Biological Product Definitions. Available at fda.gov/files/drugs/published/Biological-Product-Definitions.pdf. Accessed 5/30/2024.
2. U.S. Food and Drug Administration. Level 1: Foundational Concepts. Available at fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars#level1. Accessed 5/30/2024.
3. U.S. Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry. Department of Health and Human Services. 2015. Available at fda.gov/media/82647/download. Accessed 5/30/2024.
4. U.S. Food and Drug Administration. Biosimilar Product Information. Available at fda.gov/drugs/biosimilars/biosimilar-product-information. Accessed 5/30/2024.
5. Cardinal Health. 2022 Biosimilars Report: The U.S. Journey and Path Ahead. Available at: cardinalhealth.com. Accessed 5/30/2024.
6. Gibofsky A, McCabe D. U.S. rheumatologists' beliefs and knowledge about biosimilars: A survey. *Rheumatology (Oxford).* 2021;60(2):896-901.
7. Malter L, Jain A, Cohen BL, et al. Identifying IBD providers' knowledge gaps using a prospective web-based survey. *Inflamm Bowel Dis.* 2020;26(9):1445-50.
8. U.S. Food and Drug Administration. Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry. May 2019. Available at fda.gov/media/124907/download. Accessed 5/30/2024.
9. Jørgensen KK, Olsen IC, Goll GL, et al; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): A 52-week, randomized, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-16.
10. Goll GL, Jørgensen KK, Sexton J, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: Open-label extension of the NOR-SWITCH trial. *J Intern Med.* 2019;285(6):653-69.
11. Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: An international, randomized, double-blind, Phase III non-inferiority study. *Lancet*. 2019;393(10182):1699-707.
12. Emery P, Vencovský J, Sylwestrzak A, et al. A Phase III randomized, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis.* 2017;76(1):51-7.
13. Ribaldone DG, Caviglia GP, Pellicano R, et al. Effectiveness and safety of adalimumab biosimilar ABP 501 in Crohn's disease: an observational study. *Rev Esp Enferm Dig.* 2020;112(3):195-200.
14. Hanauer S, Liedert B, Balser S, et al. Safety and efficacy of BI 695501 versus adalimumab reference product in patients with advanced Crohn's disease (VOLTAIRE-CD): A multicenter, randomized, double-blind, Phase III trial. *Lancet Gastroenterol Hepatol.* 2021;6(10):816-25.
15. Kurti Z, Gonczi L, Lakatos PL. Progress with infliximab biosimilars for inflammatory bowel disease. *Expert Opin Biol Ther.* 2018;18(6):633-40.
16. Cohen J. What's holding back market uptake of biosimilars? Forbes.com. June 20, 2018. Available at forbes.com/sites/joshuacohen/2018/06/20/whats-holding-back-market-uptake-of-biosimilars/#16ec3554691a. Accessed 5/30/2024.
17. Peyrin-Biroulet L, Lönnfors S, Roblin X, et al. Patient Perspectives on Biosimilars: A Survey by the European Federation of Crohn's and Ulcerative Colitis Associations. *J Crohns Colitis.* 2017;11(1):128-33.
18. Pouillon L, Socha M, Demore B, et al. The nocebo effect: A clinical challenge in the era of biosimilars. *Expert Rev Clin Immunol.* 2018;14(9):739-49.
19. D'Amico F, Solitano V, Peyrin-Biroulet L, Danese S. Nocebo effect and biosimilars in inflammatory bowel diseases: what's new and what's next? *Expert Opin Biol Ther.* 2021;21(1):47-55.

Informed Managed Care Decision-Making in the Management of Acute Myeloid Leukemia: Optimizing Clinical and Economic Outcomes in an Evolving Paradigm

Amir T. Fathi, MD

This journal article is supported by educational grants from Jazz Pharmaceuticals; Abbvie

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

Summary

The last decade has brought significant advances in the treatment of Acute Myeloid Leukemia. Earlier, the only treatment for the disease was potent chemotherapy regimens and hematopoietic stem cell transplant but many patients were not eligible for these treatments because of underlying poor health or comorbidities. Effective, targeted oral therapies are now available and are providing improved survival outcomes for selected patients.

Key Points

- The treatment for many older or frail AML patients is now oral-targeted therapy when an appropriate mutation is present, or combination hypomethylation/venetoclax therapy.
- Maintenance therapy after first remission is also now an option for many patients and this will hopefully reduce the relapse rate.

ACUTE MYELOID LEUKEMIA (AML) IS A cancer of the blood and bone marrow with excess immature white blood cells and is the most common leukemia affecting adults. In 2024, there will be an estimated 20,800 cases in the United States and 11,220 deaths.[1] The median age at diagnosis is 69 years which makes it difficult to treat this disease because of the advanced age of over half of the patients. The five-year overall survival (OS) rate is 31.9 percent which is an increase from 29.5 percent in 2021.

The classification of leukemia by cell surface immunohistochemistry and chromosomal analysis first occurred in the 1960s and 1970s. The 2000s brought the identification of genetic mutations which drive the disease. Leukemia develops when there are genetic mutations in the myeloid cells, precursor cells of platelets, red blood cells and white blood cells derived from the hematopoietic stem cells. The genetic mutations prevent the myeloid cells from maturing normally and allow uncontrolled proliferation.

The traditional prognosis model of AML is based on patient factors such as age, medical co-morbidities, and functional status; whether the AML evolved from preceding marrow disease [e.g., myelodysplastic syndromes (MDS)]; and the presence of certain molecular characteristics based on cytogenetic and mutational analysis. An example favorable risk factor from molecular characteristics is mutated NMP1 without FLT3-ITD and an adverse-risk factor is complex karyotype. Based on the prognostic factors, patients are classified as having favorable, intermediate 1 or 2, or adverse-risk disease. Favorable disease has the longest disease-free survival after treatment and best OS and adverse-risk disease has the shortest.[2] Prognostication has become much more complicated as more mutations

have been identified in AML.[3] Depending on the underlying mutations and patient factors, each case of AML has a different course, prognosis, and best treatment.

Conventional treatment of AML uses various chemotherapy regimens to reboot the bone marrow with the hope that normal stem cells will replicate. Induction chemotherapy regimens (cytarabine and daunorubicin or idarubicin), which may be repeated twice, induce complete response (CR) in 75 percent of cases. This therapy is used in the more robust, younger patient. Unfortunately, 25 percent of patients do not respond to induction regimens and have refractory leukemia. After remission induction, consolidation therapy is given to destroy any remaining AML cells to attempt a cure. A cure is defined as five years without disease recurrence. Consolidation is done with either high-dose cytarabine (most common) or allogeneic hematopoietic stem cell transplant. Patients with a more favorable disease typically receive chemotherapy for consolidation because their leukemic cells are more sensitive to chemotherapy. Those with intermediate or adverse risk, who can tolerate a transplant, obtain a transplant for consolidation. When relapse occurs after initial treatment, various chemotherapy regimens have been tried with varying success. The five-year survival rate with relapsed AML is poor (< 55 years, 11% and > 55 years, 6%).[4]

The treatment landscape for AML has changed significantly with the approval of several oral therapies targeting the underlying mutations or factors which lead to abnormal cell production. Agents targeting isocitrate dehydrogenase (IDH), FMS-like tyrosine kinase 3 (FLT-3), and B-cell lymphoma two (BCL2) are FDA approved for treating AML. IDH proteins, essential to the Krebs Cycle, catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the cytoplasm (IDH1) and mitochondria (IDH2). Mutant IDH enzymes catalyze α-KG to 2-hydroxyglutarate (2-HG), which is an onco-metabolite and which accumulates in IDH-mutant tumors. 2-HG suppresses key enzymes for bone marrow cell differentiation. Approximately 8 percent of patients with AML have an IDH1 mutation and 15 percent have IDH2 gene mutations.[5,6]

IDH inhibitors which target IDH mutations are now FDA approved for treating IDH-mutated AML. These agents allow differentiation of the bone marrow cells that were previously stuck being immature. Enasidenib is an oral, selective inhibitor of mutant-IDH2 enzymes. IDH2 mutations occur in about 20 percent of patients with AML. Treatment of IDH2-mutated AML produced impressive results in relapsed/refractory AML (R/R AML), untreated AML not eligible for chemotherapy, and MDS. Median OS was 9.3 months, and for the 34 patients (19.3%) who attained CR, overall survival was 19.7 months.[7] There is minimal toxicity with this daily oral, non-chemotherapy agent. Enasidenib is currently FDA approved for treating R/R AML with an IDH2 mutation and is an option in the National Comprehensive Cancer Network (NCCN) Guidelines for this indication.[8] It is also recommended as an option for first-line therapy in those who are aged 60 years and older and who are not candidates for intensive remission induction therapies.[8]

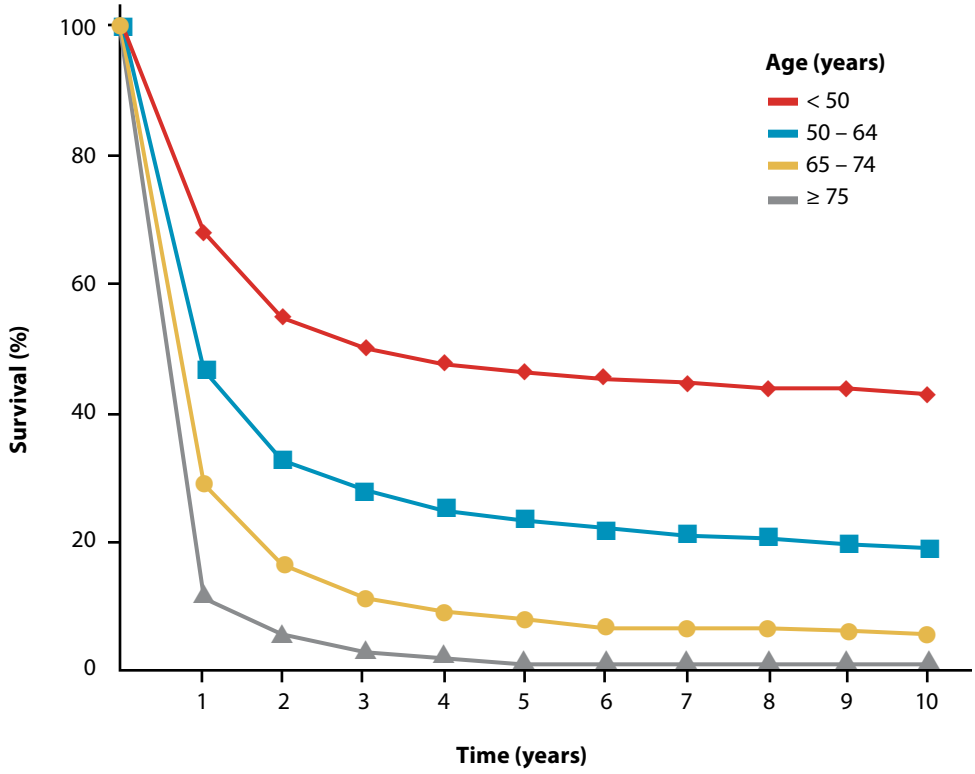
Ivosidenib targets IDH-1 and produces results similar to enasidenib in those with IDH1-mutated AML. IDH1 mutations occur in about 10 percent of patients with AML. In patients with advanced IDH1-mutated R/R AML, ivosidenib at a dose of 500 mg daily was associated with a low frequency of Grade 3 or higher treatment-related adverse events and with transfusion independence, durable remissions, and molecular remissions in some patients with CR.[9] Ivosidenib is FDA approved for treating adult patients with newly-diagnosed AML who are aged 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy and adult patients with R/R AML. The NCCN Guidelines recommend it as an option for those who cannot tolerate intensive induction, however, it is not the preferred therapy.[8] Overall, even patients who do not achieve CR with the IDH inhibitors have some benefits including reduced need for red blood cell transfusions, fewer clinic visits, fewer infections, and lower patient and caregiver treatment burden.

Olutasidenib is another IDH1 inhibitor similar to ivosidenib which was FDA approved in 2022 for R/R AML. The adverse events of this agent are similar to those of the other IDH-targeting agents. It is an option for R/R AML with IDH1 mutation.[8]

Differentiation syndrome, an overly robust differentiation of cells which leads to cytokine mediated weight gain, plural effusions, pulmonary infiltrates, hypoxia, and fever, can occur with IDH-inhibitor treatment. This is a potentially lethal clinical entity and occurs in 12 to 18 percent of enasidenib-treated patients with mutant-IDH2 R/R AML.[10] It can also occur with ivosidenib and olutasidenib and is treated with corticosteroids.

Another iteration of IDH1-targeting therapy was to add chemotherapy to one of these agents to attempt to improve survival in those unable to receive intense chemotherapy induction regimens. The combination of ivosidenib and azacitidine has been shown to improve survival. The median OS was

Exhibit 1: AML Survival by Age[18]



Relative survival by time and age for acute myeloid leukemia based on SEER data.

24.0 months with ivosidenib and azacitidine and 7.9 months with placebo and azacitidine (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; $p = 0.001$).[11]

FMS-like tyrosine kinase 3 (FLT-3) inhibitors are another class of targeted agents. FLT-3 is a tyrosine kinase enzyme that resides on the surface of cells and acts as a receptor. A ligand in the blood binds to the FLT-3 receptor to turn it off. When a FLT-3 mutation is present, the FLT-3 receptor is less sensitive to the ligand and thus the receptor is turned on all the time allowing cells to constantly multiply. FLT-3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD). FLT-3 ITD mutations occur in 25 to 30 percent of AML cases and result in poor prognosis and high rates of relapse.[12] FLT-3 TDK mutations occur in 5 percent to 10 percent of cases.

The first agents developed to target FLT-3 were aimed at numerous tyrosine kinases including sorafenib and midostaurin but these have significant toxicity because of their nonspecific effects. The addition of midostaurin to standard chemotherapy induction significantly prolonged OS and event-free survival among patients with AML and a FLT3 mutation. Median OS was 74.7 months for the combination therapy group and 25.6 months for the group that received only chemotherapy.[13] There was a 23 percent reduced risk of death in the midostaurin arm. At four years, 51.4 percent were alive in the midostaurin arm as opposed to 44.2 percent in the placebo arm. Midostaurin is FDA approved for treating adults with newly diagnosed FLT3 mutation positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

Gilteritinib is a next generation, more specific FLT-3 inhibitor. In the FLT-3 mutated R/R AML setting, the median OS in the gilteritinib group was significantly longer than the salvage chemotherapy group (9.3 months versus 5.6 months).[14] It is FDA approved for adult patients with FLT-3 mutated R/R AML but is also used in first-line treatment in addition to induction chemotherapy and consolidation. In a first-line study, the median overall survival time was 46.1 months with the combination regimen.[15]

Quizartinib, which targets FLT3-ITD mutation, was FDA approved in 2023. It is indicated

in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed FLT3-ITD AML and is an NCCN Category 1 recommendation.[8] The addition of quizartinib to standard chemotherapy with or without allo-HCT, followed by continuation monotherapy for up to three years, resulted in improved OS in adults aged 18 to 75 years with FLT3-ITD-positive newly diagnosed AML (31.9 versus 15.2 months).[16] Quizartinib is more potent and selective than midostaurin. It targets FLT3-ITD well but not the less common FLT3-TKD mutation variants in AML.

Maintenance therapy at remission to prevent relapse, especially post-bone marrow transplant and in those with FLT-3 mutation is a significant advance in therapy. This approach is now recommended in the NCCN Guidelines.[8] Maintenance is also being studied with IDH1 and IDH2 inhibitors.[17]

Most patients with AML are older (> 75 years) and the older the patient, the poorer their prognosis (Exhibit 1).[18] There are many reasons for this including poor performance status, preexisting heart and kidney disease, higher incidence of preceding bone marrow disease, higher rate of poor prognosis mutations, and higher rates of therapy-related morbidity and mortality. Older patients have a higher incidence of treatment-resistant disease, lower rates and duration of complete remission, shorter median OS, and are less likely to be eligible for allogeneic hematopoietic cell transplantation. Hypomethylating agents are less intensive treatments increasingly used for less robust or older patients, in whom it is better-tolerated, with lower rate of toxicity than traditional aggressive chemotherapy regimens. This therapy is typically administered in the clinic and can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden, and less commonly, remissions (~20%). However, responses are often transient, with leukemic progression and brief post-therapy survival.

Methyl groups which bind to DNA turn genes off and acetyl groups turn them on. In many patients with AML and MDS, genes are inappropriately turned off by methyl groups. The hypomethylating agents remove methyl groups and turn the genes for blood cell maturation back on. Intravenous decitabine and azacitidine are very well tolerated but these agents can take several months to work.

The next evolution of therapy was to try to identify other things that could be given with hypomethylating agents to improve remission rates while still having minimal adverse events. 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 the pivotal clinical trials evaluating venetoclax in combination with azacitidine in newly diagnosed people aged over 75 years ineligible for induction chemotherapy, the median OS was 14.7 months with combination therapy and 9.6 months with azacitidine alone.[19] The combination also significantly improved complete response rates. Venetoclax in combination with azacitidine or decitabine or low-dose cytarabine is FDA approved for and the standard of care for the treatment of newly-diagnosed AML in adults who are aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Improved survival with combination venetoclax and hypomethylating agents comes at the cost of increased rates of myelosuppression.

Oral azacitidine, approved in 2020, is for the continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and who are not able to complete intensive curative therapy. This approval was based on the results from the Quazar AML-001 study where median OS was significantly longer with azatadine maintenance than with placebo (24.7 months and 14.8 months, respectively; $p < 0.001$).[20] Median relapse-free survival was also significantly longer than with placebo (10.2 months and 4.8 months, respectively; $p < 0.001$).

Menin inhibitors are under investigation for treating R/R AML. These agents work differently from targeted therapies currently used in AML. Instead of blocking the activity of dysfunctional proteins, menin inhibitors stop the genes affected by KMT2A or NPM1 mutations from being expressed in the first place. Although several are under development, revumenib is farthest along in development, has been granted breakthrough status by the FDA, and will be reviewed by the FDA in fall 2024.[21]

Conclusion

The treatment for many older or frail AML patients is now oral targeted when an appropriate mutation is present or hypomethylation therapy. Maintenance therapy after first remission is also now an option for many patients and this will hopefully reduce the relapse rate. There is hope that the next decade will bring more approved AML therapies that continue to enhance outcomes.

Amir T. Fathi, MD is the Program Director for the Center of Leukemia at the Massachusetts General Hospital Cancer Center and an Assistant Professor of Medicine at Harvard Medical School in Cambridge, MA.

References

1. Cancer Stat Facts: Leukemia — Acute Myeloid Leukemia (AML). Available at seer.cancer.gov/statfacts/html/amyl.html. Accessed 5/21/2024.
2. Mrózek K, Marcucci G, Nicolet D, et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. *J Clin Oncol*. 2012;30(36):4515-23.
3. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-47.
4. Rowe JM, Tallman MS. How I treat acute myeloid leukemia. *Blood*. 2010;116(17):3147-56.
5. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009;361(11):1058-66.
6. Ward PS, Patel J, Wise DR, et al The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-34.
7. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-31.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2024. Available at nccn.org. Accessed 5/21/2024.
9. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-98.
10. Fathi AT, DiNardo CD, Kline I, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: Analysis of a Phase I/II study. *JAMA Oncol*. 2018;4(8):1106-10.
11. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519-31.
12. Garcia JS, Stone RM. The development of FLT3 inhibitors in acute myeloid leukemia. *Hematol Oncol Clin North Am*. 2017;31(4):663-80.
13. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-64.
14. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-40.
15. Pratz KW, Cherry M, Altman JK, et al. Gilteritinib in combination with induction and consolidation chemotherapy and as maintenance therapy: A Phase IB study in patients with newly diagnosed AML. *J Clin Oncol*. 2023;41(26):4236-46.
16. Erba HP, Montesinos P, Kim HJ, et al; QuANTUM-First Study Group. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukemia (QuANTUM-First): A randomized, double-blind, placebo-controlled, Phase III trial. *Lancet*. 2023;401(10388):1571-83.
17. Fathi AT, Kim HT, Soiffer RJ, et al. Multicenter Phase I trial of ivosidenib as maintenance treatment following allogeneic hematopoietic cell transplantation for IDH1-mutated acute myeloid leukemia. *Clin Cancer Res*. 2023;29(11):2034-42.
18. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. *J Clin Oncol*. 2014;32(24):2541-52.
19. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-29.
20. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-37.
21. Syndax Announces FDA Priority Review of NDA for Revumenib for the Treatment of Relapsed/Refractory KMT2Ar Acute Leukemia. March 26, 2024. Available at ir.syndax.com/news-releases/news-release-details/syndax-announces-fda-priority-review-nda-revumenib-treatment. Accessed 5/21/2024.

Integrating Novel Approaches to Psoriasis Management: Closing the Gap with Innovative Treatment Strategies

April W. Armstrong, MD, MPH

This journal article is supported by educational grants from Arcutis Biotherapeutics; Bristol Myers Squibb

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

Summary

The management of psoriasis has changed significantly over time. Numerous medications are now available for treating this immune-mediated disease which can make treatment selection challenging. Treatment selection depends on the severity and location of the disease and the presence of psoriatic arthritis.

Key Points

- Two new mechanism of action topicals are now available for managing mild disease.
- Numerous injectable biologics are available for managing moderate-to-severe disease with some approved for psoriatic arthritis.
- Two oral agents are available for moderate-to-severe disease.

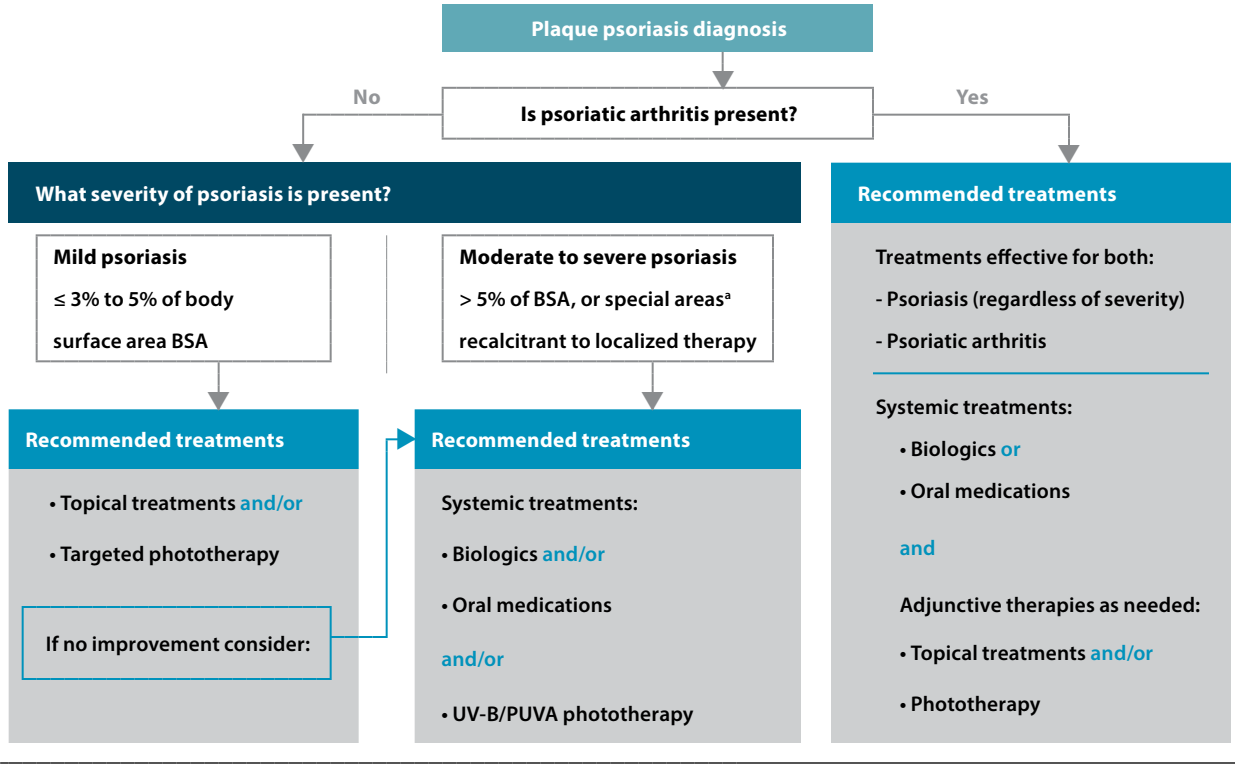
PSORIASIS IS THE MOST COMMON IMMUNE mediated disease. It affects 3 percent of United States adults which means over 7.5 million adults are affected.[1] Rates are highest in the Caucasian population. It is important to note that diagnosis in those with skin of color can be challenging, therefore, this population may be underrepresented in rate statistics.

Psoriasis can mimic several other skin conditions such as atopic dermatitis and seborrhea. Evaluation of a patient with potential psoriasis begins with a total body skin exam. This includes scalp, nails, intergluteal fold, and genital area which are all common areas of impact. Assessment of the chronicity and course are important to help distinguish psoriasis from other skin conditions. Mild psoriasis tends to be stable with occasional periods of exacerbation. Severe psoriasis has a greater likelihood of more severe and frequent flares. Symptoms of itch and pain, exacerbating or ameliorating factors such as sunlight, and family history of psoriasis are also evaluated. Screening for psoriatic arthritis is also important when suspecting psoriasis as up to 30 percent of those with psoriasis will develop psoriatic arthritis which can result in disabling joint destruction. Symptoms of psoriatic arthritis include pain in the joints and back, morning stiffness and/or swelling in joints, and stiffness in the back.

Psoriasis can be classified by morphology, location, and severity. Morphology subtypes include plaque (most common, 80%), guttate, erythrodermic, and pustular (generalized or localized). Location subtypes include inverse/intertriginous, palmoplantar, and nails. Severity ranges from mild (< 5% of body surface area affected) to moderate to severe. These classifications all overlap and a patient can change from one subtype to another.

Psoriasis is considered a T cell-mediated disease, with pathogenic T cells producing elevated levels of interleukin 17 (IL-17) in response to IL-23. Dendritic cells also produce tumor necrosis alpha (TNF-α) and IL-23 to help differentiate T cells into TH17 cells, which produce cytokines like IL-17, interferon

Exhibit 1: Overall Treatment Approach for Plaque Psoriasis[2]



[a] Special areas include scalp, palms, soles, genitalia, and nails.
PUVA indicates psoralen and UV-a.

gamma (IFN-γ), and IL-22. Several of these inflammatory cytokines are targeted by the FDA-approved oral and injectable biologic treatments. IL-17 and IL-23 appear to be the most important in psoriasis pathophysiology.

Because plaque psoriasis is most common and the majority of FDA-approved treatments are only approved for this subtype, the treatment discussion will focus on plaque psoriasis. Exhibit 1 illustrates the general approach to choosing treatment.[2] Mild disease is typically treated with topical therapies and/or targeted phototherapy. Moderate-to-severe disease requires more aggressive treatment. Disease that affects the scalp, palms, soles of feet, genitalia, or nails is also considered moderate-to-severe because of the disabling impact of disease in these areas. If a patient has psoriatic arthritis, systemic therapy is automatically started even if skin disease is mild.

Topicals for mild disease include corticosteroids, vitamin D, keratolytics, aryl hydrocarbon receptor inhibitor (tapinarof), and phosphodiesterase four inhibitor (roflumilast). The last two categories are new to the market and are effective non-steroidal agents which are more acceptable to patients compared to corticosteroids. The newer non-steroidal topicals have equivalent efficacy to mid-potency topical corticosteroids. To better manage psoriasis, an initiative-taking approach should be used with topical treatment instead of a reactive approach.[3] First, lesional areas should be treated until clear or almost clear and then proactive maintenance is started. This means treating areas that frequently recur or flare, but are now clinically quiescent, once or twice weekly to prevent flares. Dermatologists most often choose the newer non-steroidal topicals for initiative-taking approach to avoid the long-term adverse events of corticosteroids.

There are numerous oral therapies for plaque psoriasis which affect intracellular signal transduction pathways. Methotrexate is a nonspecific dihydrofolate reductase inhibitor and acitretin targets retinoid receptors. Cyclosporine is a calcineurin inhibitor which is used in crisis patients with very severe psoriasis. Currently, these agents are used infrequently for plaque psoriasis.

Apremilast is an oral phosphodiesterase four inhibitor that decreases pro-inflammatory (TNF-alpha, IL2, 12, 23) and increases anti-inflammatory (IL10) factors. It is FDA approved for adults with plaque psoriasis who are candidates for phototherapy

Exhibit 2: FDA-approved Biologics for Psoriasis

Drug Class	Agent	Indication
TNF antagonists	• Etanercept • Infliximab • Adalimumab • Certolizumab	Psoriasis, PsA
p40 IL-12/23 antagonist	• Ustekinumab	Psoriasis, PsA
IL-17 antagonists	• Ixekizumab • Secukinumab	Psoriasis, PsA
	• Brodalumab • Bimekizumab	Psoriasis
IL-23 antagonist	• Guselkumab • Risankizumab	Psoriasis, PsA
	• Tildrakizumab	Psoriasis

PsA = psoriatic arthritis; TNF = tumor necrosis factor; IL = interleukin

Exhibit 3: Choosing a Biologic

TNF inhibitors great in:

Psoriatic arthritis (peripheral and axial)

Pregnancy (certolizumab)

Avoid TNF inhibitors in:

Demyelinating disease

Hepatitis B

TNF inhibitors not preferred:

History of latent tuberculosis

Advanced heart failure

IL-17 inhibitors great in:

- Robust psoriasis efficacy
- Psoriatic arthritis (peripheral and axial)

Avoid IL-17 inhibitors in:

- Personal history of inflammatory bowel disease

Other consideration:

- Oral candidiasis

IL-23 inhibitors great in:

- Robust psoriasis efficacy
- Efficacy in psoriatic arthritis (guselkumab, risankizumab, and ustekinumab)
- Fewer injections

IL-23 inhibitors with evolving evidence:

- psoriatic arthritis involving spine

or systemic therapy (across all severities) and psoriatic arthritis. About 20 percent of those who started on apremilast will have diarrhea and nausea which can lead to therapy discontinuation.

The newest oral agent is deucravacitinib which inhibits tyrosine kinase two (TYK2). TYK2 is a key mediator of psoriasis pathophysiology through modulation of the IL-23/IL-17 axis. It also mediates signaling of IL-12 and Type 1 interferon. TYK2 and the Janus kinases (JAK1, JAK2, JAK3) are all in the same kinase family. Each member of the TYK2/JAK family contains an active and regulatory domain. The regulatory domains are more unique among the family members than the active domains. Deucravacitinib is an allosteric inhibitor of the TYK2 regulatory domain and thus has greater selectivity for TYK2 compared to JAK1, 2, and 3.[4] Due to deucravacitinib's selectivity, its package labeling does not include the black box warnings (infections, sudden cardiovascular death, malignancy, thrombosis) required by the FDA for JAK inhibitors.

In a comparison trial, deucravacitinib resulted in higher rates of clear or almost clear skin compared

to apremilast (58.4% versus 31%) at 16 weeks.[5] By the end of a year of treatment, 66 percent of patients on deucravacitinib had clear or almost clear skin. This agent also resulted in lower rates of adverse events and treatment discontinuation compared to apremilast. It is FDA approved for moderate-to-severe psoriasis. This agent is well tolerated, has no known drug interactions, and does not require any ongoing laboratory monitoring—it has become the main oral agent used for moderate-to-severe disease.

Some patients with moderate-to-severe psoriasis, especially with psoriatic arthritis, will require injectable biologics to adequately manage their disease. Four different mechanism of action classes are available. Exhibit 2 shows the FDA-approved agents in each class and those which are also approved for use in psoriatic arthritis. Bimekizumab, ixekizumab, and risankizumab are the most effective at achieving 100 percent reduction in the Psoriasis Area and Severity Index (PASI) and have the lowest number needed to treat (NNT) to achieve PASI 90 compared to the other approved injectable biologics.[6-8] In choosing between the various biologics, Exhibit 3 provides some areas where each group work the best and where they should be avoided.

Of note, bimekizumab, which was FDA approved in 2023, is different from the other approved IL-17 antagonists because it has dual specificity for IL-17A and IL-17F. It targets 3 dimers with high affinity (IL17A/A, IL17F/F, and IL17 A/F). It also inhibits the activation of the IL-17 receptor complex by these cytokines and the subsequent inflammatory cascade. In comparison trials, bimekizumab produces higher PASI 90 rates than ustekinumab, adalimumab, and secukinumab. In a network meta-analysis, bimekizumab demonstrated statistical superiority over all biologics in achieving PASI 90 and PASI 100 thresholds.[8]

Shared decision-making is especially important now with numerous treatment choices. Many clinicians will present the agent they feel is the best choice for a patient together with the reasons for that choice but will ask for the patient's feedback. Patients' buy-in for treatment selection is important for achieving optimal outcomes in psoriasis management.

Adherence with medications and annual dermatologic visits is also important for achieving optimal outcomes. Long-term adherence with medications can be an issue with proactive topical use for mild disease and oral or injectable therapies for moderate-to-severe disease. Consistently taking or using these medications can be an issue if the patient has success in clearing their skin—they lose incentive to continue. Education on the chronic nature of psoriasis and the importance of adherence to maintain improved skin is essential. Simplification of regimens is also important. Once-daily oral or infrequently dosed highly effective injectables are beneficial in improving adherence. Patients need to maintain at least a once-yearly visit with the dermatologist. This is especially important for maintaining access through managed care to their medications. If the appointment is missed, managed care approvals must be redone.

Conclusion

In managing psoriasis, treatment selection depends on the severity and location of disease and presence of psoriatic arthritis. Two mechanism of action topicals which avoid the long-term adverse events of corticosteroids are very effective for managing mild disease. Numerous injectable biologics are available for managing moderate-to-severe disease and some are approved for psoriatic arthritis.

Two oral agents are available for moderate-to-severe disease and once-daily TYK2 inhibitors are becoming the most commonly used oral treatment and are well tolerated.

April W. Armstrong, MD, MPH is a Professor and Chief of the Division of Dermatology at the University of California, Los Angeles.

References

1. Armstrong AW, Mehta MD, Schupp CW, et al. Psoriasis prevalence in adults in the United States. *JAMA Dermatol*. 2021;157(8):940-6.
2. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: A review. *JAMA*. 2020;323(19):1945-60.
3. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(2):432-70.
4. Wrobleski ST, Moslin R, Lin S, et al. Highly selective inhibition of tyrosine kinase 2 (TYK2) for the treatment of autoimmune diseases: Discovery of the allosteric inhibitor BMS-986165. *J Med Chem*. 2019;62(20):8973-95.
5. Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled Phase III POETYK PSO-1 trial. *J Am Acad Dermatol*. 2023;88(1):29-39.
6. Armstrong AW, Soliman AM, Betts KA, et al. Comparative efficacy and relative ranking of biologics and oral therapies for moderate-to-severe plaque psoriasis: A network meta-analysis. *Dermatol Ther (Heidelb)*. 2021;11(3):885-905.
7. Blauvelt A, Gooderham M, Griffiths CEM, et al. Cumulative clinical benefits of biologics in the treatment of patients with moderate-to-severe psoriasis over 1 year: A network meta-analysis. *Dermatol Ther (Heidelb)*. 2022;12(3):727-40.
8. Armstrong A, Fahrbach K, Leonardi C, et al. Efficacy of bimekizumab and other biologics in moderate to severe plaque psoriasis: A systematic literature review and a network meta-analysis. *Dermatol Ther (Heidelb)*. 2022;12(8):1777-92.

Keeping Pace with Rapid Advancements in the Treatment and Management of Multiple Myeloma

Ravi Vij, MD, MBA

This journal article is supported by educational grants from Janssen Biotech, Inc.; Sanofi; Karyopharm Therapeutics

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

Summary

The management of multiple myeloma (MM) in the past decade has been dramatically changed by new, more effective, and less toxic therapies. Triple therapy with proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies is now the standard treatment. Additional options for relapsed/refractory disease are now available.

Key Points

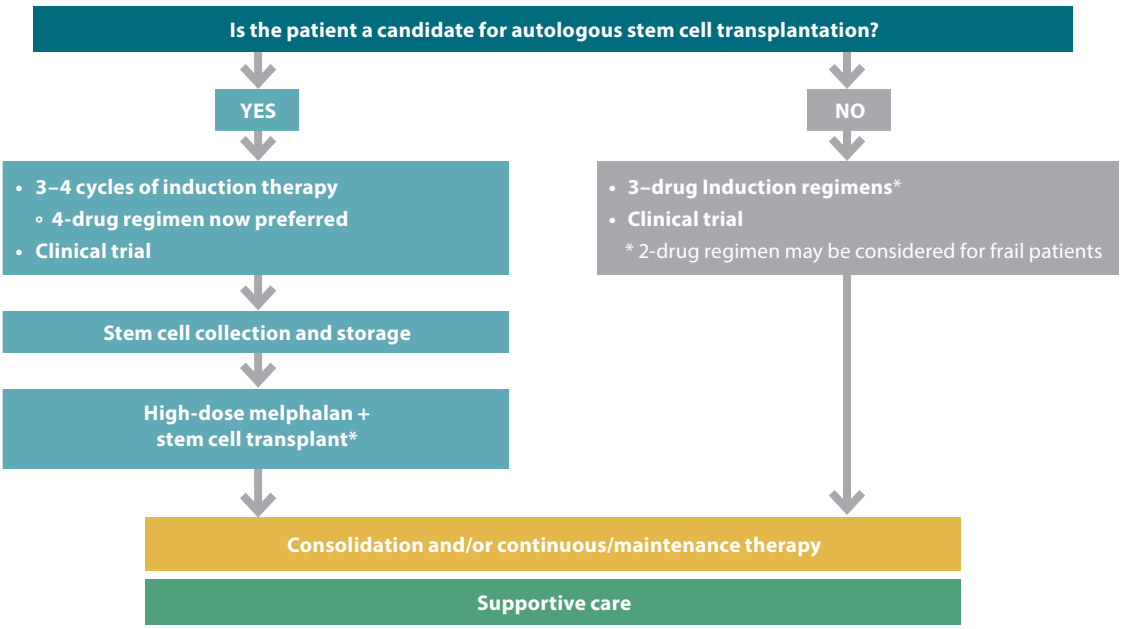
- Triple therapy with backbone agents is the standard of care.
- Bispecific antibodies and CAR-T therapies have been FDA approved for treating relapsed/refractory MM.
- Additional new agents are on the horizon.

MULTIPLE MYELOMA (MM) IS THE SECOND most common blood cancer.[1] In the United States during 2024, there will be an estimated 35,780 new cases and 12,540 associated deaths. The five-year survival rate is 61.1 percent and the median age at diagnosis is 69 years.

The treatment paradigm for newly diagnosed active MM begins with determining whether a patient is eligible for an autologous stem cell transplant (ASCT)—those not eligible receive induction and maintenance therapy (Exhibit 1).[2,3] The goal of treating newly diagnosed MM, whether ASCT eligible or ineligible, is to gain the best depth of response by using an effective induction regimen followed by consolidating the response with a transplant or medication and offering maintenance strategies to prolong the first progression-free survival (PFS1) benefit.[4] Minimal residual disease (MRD, defined as $< 10^5$ MM cells) should be achieved if possible because MRD is a strong predictor of progression-free survival (PFS) and overall survival (OS).[5,6]

Treatment regimens for newly diagnosed and relapsed/refractory MM generally consist of two or more treatment backbone agents and oral dexamethasone.[3] Dexamethasone has a therapeutic effect on MM cells. Trials have shown that more backbone agents are better than just one agent in improving PFS. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors which induce apoptosis of MM cells. Lenalidomide and pomalidomide are immunomodulators which induce immune responses, prevent inflammation, and enhance the activity of T cells and natural killer (NK) cells. Daratumumab and isatuximab are anti-CD38 monoclonal antibodies—CD38 is overexpressed on MM cells. Elotuzumab and selinexor are FDA approved for relapsed/refractory MM (R/R MM). Elotuzumab, a humanized IgG1 monoclonal antibody, directly activates NK cells through both the signaling lymphocytic activation molecule family member 7 (SLAMF7) pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). Selinexor reversibly inhibits nuclear export of tumor

Exhibit 1: Initial Treatment Approach[2,3]



* In certain circumstances, consideration for a tandem transplant

Exhibit 2: Indications for Treatment at Relapse in MM[7]

Clinical relapse
• Development of new soft tissue plasmacytomas or bone lesions
• Definite increase (≥ 50%) in size of existing plasmacytomas or bone lesions
• Hypercalcemia (≥ 11.5 mg/dL)
• Decrease in hemoglobin of ≥ 2 g/dL or to <10 g/dL due to myeloma
• Risk in serum creatinine by ≥ 2 mg/dL due to myeloma
• Hyperviscosity requiring therapeutic intervention
Significant biochemical relapse without clinical relapse
• Doubling of M-component in 2 consecutive measurements separated by 2 months with the reference value of 5 g/L;
or
• In 2 consecutive measurements, any of the following increases:
◦ Absolute levels of serum M protein by ≥ 10 g/L
◦ Urine M protein by ≥ 500 mg/24 h
◦ Involved FLC level by ≥ 20 mg/dL plus abnormal FLC ratio or by 25%, whichever is greater

suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells.

In transplant eligible patients, a four-drug primary induction regimen (daratumumab/bortezomib/lenalidomide/dexamethasone) is preferred by many clinicians but bortezomib/lenalidomide/dexamethasone is a Category 1 recommendation in the National Comprehensive Cancer Network (NCCN) Guidelines.[3] The four-drug regimen is another recommended regimen. For nontransplant candidates, the NCCN-preferred regimens are bortezomib/lenalidomide/dexamethasone or daratumumab/lenalidomide/dexamethasone. For either category of patient, the preferred maintenance therapy is lenalidomide which is continued until disease progression. Dual maintenance with bortezomib and lenalidomide is recommended for high-risk MM.

After initial treatment, most patients will have a disease relapse. Indications for retreatment are either clinical or biochemical (Exhibit 2).[7] The selection of treatment for R/R MM is influenced by whether the relapse is early or late, patient factors, and prior treatments.[8,9] Early relapse is one which occurs within 12 months of finishing initial treatment. The most crucial factor in choosing therapy for R/R

MM is that the selected therapy has been shown to produce stable disease or better and is well tolerated.

The treatment options at relapse are enrollment in a clinical trial, stem cell transplant, repeating first-line treatment, switching to a second-generation agent in same drug class (e.g., lenalidomide to pomalidomide), switching to alternative drug class, or two new classes—chimeric antigen receptor (CAR)-T cell therapy and bispecific antibodies. Patients can receive multiple line therapy for R/R MM. Recent studies favor the use of daratumumab as part of a triple regimen for R/R MM based on overall response rates.[10,11] The NCCN Guidelines list several daratumumab regimens as Category 1 preferred regimens but also include other Category 1 regimens without daratumumab.[3] The selected regimen will depend on which component the disease has become refractory against.

Patients who are triple or quad refractory to the backbone agents have very poor prognosis (median overall survival is 9 months).[12] Approaches in the past have been conventional chemotherapy, salvage autologous stem cell transplant, recycling previous regimens, and clinical trial, each of which have generally had short-lived efficacy.[13]

Several bispecific T-cell engager antibodies have been FDA approved for R/R MM. With these agents, one side of the antibody binds to proteins on the myeloma cell and the other side binds to T cells allowing the T cell to kill the MM cell. Belantamab mafodotin was the first bispecific B-cell maturation antigen (BCMA)-directed antibody FDA approved in August 2020 for the treatment of adult patients with R/R MM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent, however, it was withdrawn from market by the manufacturer in late 2022 due to results from a Phase III trial showing lack of PFS benefit. Teclistamab and elranatamab, are both BCMA directed, and talquetamab is a G protein–coupled receptor 5D (GPRC5D) directed, were FDA approved in 2022 and 2023 for the same indication as belantamab mafodotin. Also, like belantamab, these three agents were approved under accelerated approval based on response rate and continued approval is contingent on data from confirmatory trials.

Along with CAR-T cell therapies, these agents are listed as preferred therapy in the NCCN Guidelines for R/R MM after at least four prior therapies.[3] They produce a substantial response rate in a difficult to treat group but also can cause significant adverse events which require monitoring.[14-16] These agents carry a black box warning about cytokine release syndrome and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome which can be fatal. Additional bi-specific and tri-specific antibodies are under study.

CAR-T therapies are showing impressive activity in the R/R MM setting and the first ones for R/R MM have been FDA approved. Challenges to their widespread use remain, including toxicity, manufacturing time, and cost. Idecabtagene vicleucel, which targets BCMA, was the first FDA-approved CAR-T treatment for R/R MM in 2021. In a study in 33 patients who had received a median of seven prior therapies, the objective response rate was 85 percent, including 45 percent with complete responses.[17] Six of the 15 patients who had a complete response had a relapse after treatment. The median PFS was 11.8 months. All 16 patients who had a response (partial response or better) and who could be evaluated for MRD had MRD-negative status ($\leq 10^4$ nucleated cells). CAR-T cell expansion in the subjects was associated with responses, and CAR-T cells persisted up to one year after the infusion. In another Phase II trial in 128 R/R MM patients who had disease after at least three previous regimens, idecabtagene vicleucel treatment resulted in a 73 percent overall response rate; 33 percent had a complete response or better.[18] MRD-negative status ($< 10^5$ nucleated cells) was confirmed in 26 percent who were treated and 79 percent of those had a complete response or better. The median PFS was 8.8 months. Common toxic events include neutropenia, anemia, and thrombocytopenia. Cytokine release syndrome occurred in 84 percent. This CAR T is FDA approved for R/R MM after two or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and is preferred in the NCCN Guidelines for this indication.[3]

Ciltacabtagene autoleucel is another BCMA directed CAR-T therapy. In an open-label Phase Ib/II study in patients with R/R MM who had received three or more previous lines of therapy, the overall response rate was 97 percent, with 67 percent of patients achieving a stringent complete reponse.[19] The PFS rate was 77 percent with an 89 percent OS rate. Common adverse events include neutropenia, anemia, thrombocytopenia, leukopenia, and lymphopenia. Cytokine release syndrome is also common. There were six deaths due to treatment-related adverse events. Both approved CAR Ts have black box warnings related to cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, prolonged cytopenia, and secondary hematological malignancies. A follow-up

analysis at 18 months showed that responses were durable. The 18-month PFS and OS rates were 66.0 percent and 80.9 percent respectively, with no new observed safety signals.[20] Numerous other CAR-T based treatments for R/R MM are under study.

Bi-specifics and CAR-T therapy have not yet been directly compared in trials. Bi-specifics do not need to be individualized or engineered, and they can have a variety of targets. Unlike CAR T, there is less delay in starting bispecific therapy but bi-specifics are not a one-and-done therapy. Rather, they are given on a continued schedule.

Iberdomide is an investigational immunomodulator which is a potent cereblon E3 ligase modulator.[21] This is the same mechanism of action as lenalidomide and pomalidomide but this agent is more potent. In triple-class refractory disease in combination with dexamethasone, the overall response rate was 32 percent.[22]

Conclusion

Treatment of myeloma has evolved quickly over the past decade. Initial treatment with a four-drug combination including a CD38 monoclonal antibody with ASCT followed by maintenance provide the best chance for a deep and long-lived remission. At relapse, multidrug combinations are again preferred but CAR-T cells and bi-specifics are emerging for the refractory population.

Ravi Vij, MD, MBA is a Professor of Medicine in the section of Stem Cell Transplant and Leukemia at the Washington University School of Medicine in St. Louis, MO.

References

1. National Cancer Institute. Cancer Stat Facts: Myeloma. Available at seer.cancer.gov/statfacts/html/mulmy.html. Accessed 7/2/2024.
2. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2021;32(3):309-22.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 4.2024. Available at nccn.org. Accessed 7/2/2024.
4. Mailankody S, Korde N, Lesokhin AM, et al. Minimal residual disease in multiple myeloma: Bringing the bench to the bedside. *Nat Rev Clin Oncol*. 2015;12(5):286-95.
5. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): Final analysis of an open-label, randomized, Phase II trial. *Lancet Haematol*. 2023;10(10):e825-e837.
6. Costa LJ, Chhabra S, Medvedova E, et al. Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): Final report of the multicenter, single-arm, Phase II trial. *Lancet Haematol*. 2023;10(11):e890-e901.
7. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica*. 2016;101(4):396-406.
8. Goldschmidt H, Ashcroft J, Szabo Z, Garderet L. Navigating the treatment landscape in multiple myeloma: Which combinations to use and when? *Ann Hematol*. 2019;98(1):1-18.
9. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: Recommendations of the International Myeloma Working Group. *Leukemia*. 2016;30(5):1005-17.
10. Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): Updated outcomes from a randomized, multicenter, open-label, Phase III study. *Lancet Oncol*. 2022;23(1):65-76.
11. Minakata D, Fujiwara SI, Yokoyama D, et al. Relapsed and refractory multiple myeloma: A systematic review and network meta-analysis of the efficacy of novel therapies. *Br J Haematol*. 2023;200(6):694-703.
12. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-75.
13. Mikhael J. Treatment options for triple-class refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2020;20(1):1-7.
14. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232-44.
15. Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): A multicenter, open-label, single-arm, Phase I study. *Lancet*. 2021;398(10301):665-74.
16. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: Phase II MagnetisMM-3 trial results. *Nat Med*. 2023;29(9):2259-67.
17. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019;380(18):1726 37.
18. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384(8):705-16.
19. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A Phase Ib/II open-label study. *Lancet*. 2021;398:314-324.
20. Martin T, Usmani SZ, Berdeja JG, et al. Updated Results from CARTITUDE-1: Phase Ib/II study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in patients with relapsed/refractory multiple myeloma. *Blood*. 2021;138:549.
21. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia*. 2020;34(4):1197-201.
22. Lonial S, Popat R, Hulin C, et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): A multicenter, multicohort, open-label, Phase I/II trial. *Lancet Haematol*. 2022;9(11):e822-e832.

New Horizons in the Treatment and Management of Endometrial Cancer: Leveraging Immunotherapy for Improved Clinical and Economic Outcomes

Dario R. Roque, MD

This journal article is supported by an educational grant from GlaxoSmithKline

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

Summary

Immunotherapy is transforming the endometrial cancer treatment landscape. A growing body of evidence supports the integration of immunotherapy with chemotherapy as a first-line treatment strategy in selected patients.

Key Points

- Immunotherapy is used in combination with standard first-line chemotherapy for advanced or recurrent disease.
- This combination has demonstrated significant improvement in progression-free survival, particularly in dMMR patient population.
- A survival benefit has been shown in the dMMR population with dostarlimab.

IN THE UNITED STATES (U.S.), CANCER OF the endometrium is the most common cancer of the female reproductive organs and fourth most common cancer overall. The American Cancer Society estimates about 67,880 new cases of cancer of the uterus will be diagnosed in 2024 and 13,250 women will die.[1] The lifetime risk for a woman is one in 37. Excess weight is one risk factor, as each increase in body mass index of 5 kg/m^2 significantly increases a woman's risk of endometrial cancer.[2] The obesity epidemic in the U.S. has led to an increase in endometrial cancer cases.

Endometrial cancers have traditionally been divided into estrogen-dependent type I and the less common, clinically aggressive, estrogen-independent type II. Type II are rarer histologic subtypes, such as serous, clear cell, carcinosarcoma and undifferentiated/dedifferentiated. Exhibit 1 shows key differences in stage at presentation and survival. Type II cancers account for a disproportionate amount of endometrial cancer mortality (75%).[3]

In addition to survival differences based on type, there are racial/ethnic differences in survival regardless of initial stage at presentation. Black women have poorer survival at every stage of diagnosis, regardless of histologic subtype compared with non-Hispanic White women.

The percentage differences in survival range from 6 percent risk difference for local stage, low-grade endometrioid cancers to 59 percent lower survival for distant-stage clear-cell cancers.[4] There are also differences in stage at diagnosis, guideline concordant care, and surgical treatment based on race. With the status quo, 39.1 percent of black compared to 19.8 percent of white women die within five years, a 19.3 percent absolute difference.[5] Equal surgery rates would decrease the absolute difference in survival to 17.7 percent and equal stage at diagnosis would lower the difference to 12.9 percent. When both stage at diagnosis and rates of surgery are equal for Black and White women, the absolute difference in five-year survival between races would be 11.6 percent.

Exhibit 1: The Clinical Divide of Uterine Cancer

Feature	Type I	Type II
Stage at Presentation	I (73%)	I (54%)
	II (11%)	II (8%)
	III (13%)	III (22%)
	IV (3%)	IV (16%)
Survival by stage	I (85 – 90%)	I (50 – 80%)
	II (70%)	II (50%)
	III (40 – 50%)	III (20%)
	IV (15 – 20%)	IV (5 – 10%)

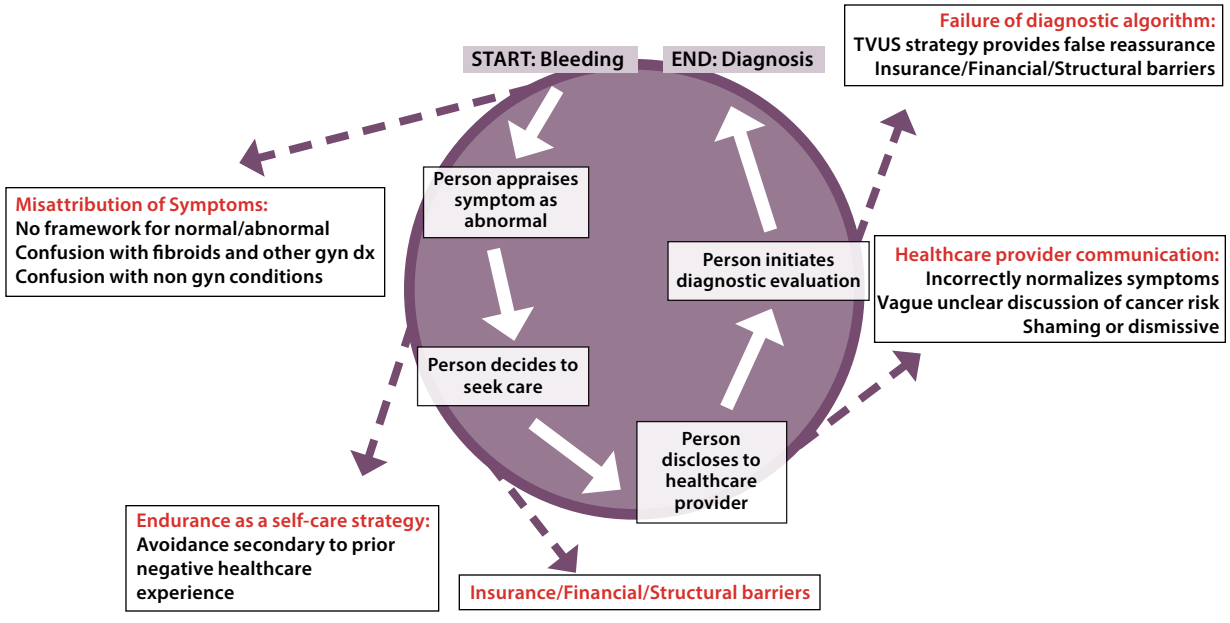
How post-menopausal bleeding (a common symptom of endometrial cancer) is evaluated by clinicians can be an issue. Transvaginal ultrasound to measure the thickness of the endometrium is a common starting point, however, the use of transvaginal ultrasound can lead to missed cases in those with fibroids. Fibroids, which are more common in Black women, can distort the quality of ultrasound images. Black women more often have high-risk cancer types that may cause less thickening of the endometrium than low-risk types. Transvaginal ultrasound can miss as many as 50 percent of cases in Black women and result in an eight-fold higher frequency of false negative results than reported for the general population.[6] Additionally, Black women have a higher risk for non-guideline adherent work-up.[7]

There are many ways in which the system can fail women seeking an answer for post-menopausal bleeding. Exhibit 2 illustrates where in the pathway from symptoms to diagnosis barriers occur. Clinicians and managed care need to work together to overcome these barriers.

Treatment modalities for endometrial cancer include surgery, chemotherapy, hormone therapy, radiation, and targeted therapy. The surgical approach is total hysterectomy with bilaterial salpingo-oophorectomy. A minimally invasive surgery (MIS) is now the standard of care for comprehensive surgical staging in patients with endometrial cancer and is endorsed by the National Comprehensive Cancer Network (NCCN), American College of Obstetrics and Gynecology, and the Society of Gynecologic Oncology.[8-10] MIS reduces blood loss, hospital stays, risk, and severity of complications compared to laparotomy. It can also improve cosmesis, quality of life, and help patients return to normal activities more quickly.

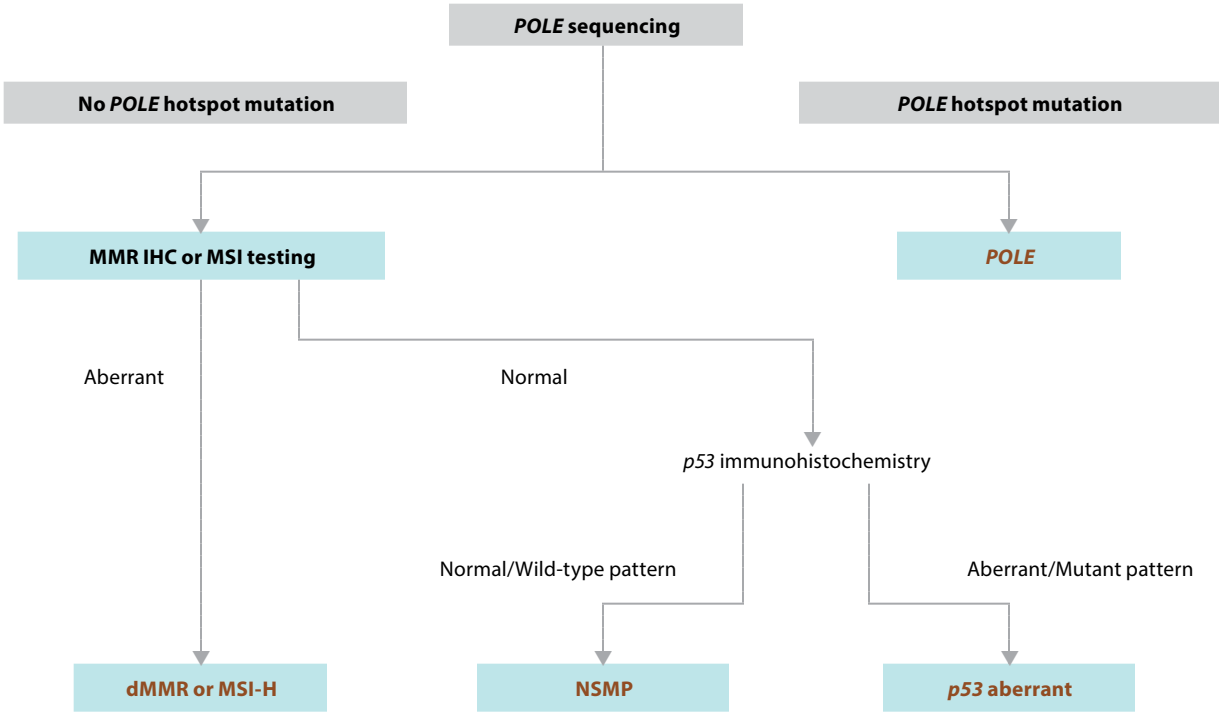
Sentinel lymph node (SLN) biopsy is the standard of care for staging instead of lymphadenectomy. There are excellent sensitivity/specificity and

Exhibit 2: Barriers to a Diagnosis of Endometrial Cancer



Gyn= gynecologic; dx = diagnosis; TVUS = transvaginal ultrasound

Exhibit 3: NCCN Biomarker Testing Recommendations for Endometrial Carcinoma[8]



reduced morbidity such as lymphedema with SLN compared to lymphadenectomy.[11-13] SLN biopsy is also cost effective compared to lymphadenectomy.[14]

Most women will require surgical treatment when diagnosed. Adjuvant systemic therapy is used after surgical therapy in Stage II – IV disease. The standard systemic therapy regimen has been carboplatin and paclitaxel since 2012. In those with uterine serous carcinomas which overexpress HER2, trastuzumab has been added to the chemotherapy regimen.

As with many other cancers, biomarker testing has come to the management of endometrial cancer. Exhibit 3 shows the current NCCN diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinoma. There are four distinct classifications based on this testing—polymerase-epsilon (POLE) mutated, microsatellite instability/deficient mismatch repair (MSI/dMMR), P53 aberrant, and non-specific molecular profile (NSMP).

Tumors which are POLE or MSI/dMMR are ultra mutated and hypermutated, respectively. POLE occurs in about 4 percent of cases and results in the lowest mortality rate of the four subtypes. MSI/dMMR occurs in about 40 percent of cases. Those with dMMR have a higher rate of distant recurrence and lower relapse-free survival compared to those with proficient MMR (pMMR).[15] P53 aberrant endometrial cancer has high copy numbers, is mostly serous histology, accounts for 19 percent of high-grade endometrioid carcinomas, and results in the highest mortality. Endometrial cancer without POLE mutations, MSI/dMMR, or P53 mutations, is classified as a NSMP subtype, accounting for approximately 50 percent of endometrial cancers. Its molecular characteristics include low cell mutation and low copy number variation, and its histologic subtype is mostly low-grade endometrial carcinoma. These subtypes are used for prognosis, staging, and treatment selection.

The International Federation of Obstetrics and Gynecology (FIGO) staging guidelines from 2023 use the presence of these subtypes to change staging of patients.[16] FIGO recommends complete molecular classification in all endometrial carcinomas and as potential influencing factors of adjuvant or systemic treatment decisions. If the molecular subtype is known, this is recorded in the FIGO stage by the addition of "m" for molecular classification, and a subscript indicating the specific molecular subtype. When molecular classification reveals P53 or POLE status in Stages I and II, this results in upstaging or

downstaging of the disease because of the prognostic implications of these particular subtypes.

MSI/dMMR subtype is the one area for which there are specific treatments. Because of the sensitivity of tumors with MSI/dMMR to the effects of immunotherapy, checkpoint inhibitors have been studied in this subtype of endometrial cancer and provide progression-free survival (PFS) benefits. Pembrolizumab and dostarlimab are the two checkpoint inhibitors which have FDA indications for endometrial cancer.

Checkpoint immunotherapy initially transformed the management of recurrent endometrial cancer post-platinum chemotherapy. The NCCN Guidelines include biomarker directed therapy options for recurrent disease after prior platinum-based therapy including neoadjuvant and adjuvant use.[8] For pMMR tumors, the combination of lenvatinib and pembrolizumab has been shown to improve PFS.[17] For tumor mutation burden high (TMB-H) tumors, pembrolizumab, and for MSI-H/dMMR tumors, pembrolizumab or dostarlimab monotherapy are options.[18-20] For patients who can still receive platinum-based chemotherapy at recurrence, either agent can be added to carboplatin/paclitaxel for Stage II – IV tumors. Pembrolizumab is not recommended for carcinosarcoma because these type of tumors were not included in the studies.

The next evolution of studies was to use immunotherapy with first-line treatment. These agents can be added to carboplatin/paclitaxel for first-line chemotherapy or adjuvant therapy after surgery. In women with Stage III or IV or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy was beneficial in improving PFS compared to chemotherapy alone in patients with and without dMMR. In the 12-month analysis of this study, Kaplan-Meier estimates of PFS in the dMMR cohort were 74 percent in the pembrolizumab group and 38 percent in the placebo group (hazard ratio for progression or death, 0.30; 95% confidence interval [CI], 0.19 to 0.48; $p < 0.001$), a 70 percent difference in relative risk.[21] In the pMMR cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo (hazard ratio, 0.54; 95% CI, 0.41 to 0.71; $p < 0.001$). While not as beneficial in the pMMR group, many clinicians still consider the use of immunotherapy with chemotherapy.

In a similar primary advanced or recurrent disease patient population, dostarlimab plus carboplatin/paclitaxel significantly increased PFS with a substantial benefit in the dMMR/MSI-H population compared to carboplatin/paclitaxel alone. In the dMMR/MSI-H population, estimated PFS at 24 months was 61.4 percent (95% CI, 46.3 to 73.4) in the dostarlimab group and 15.7 percent (95% CI, 7.2 to 27.0) in the placebo group (hazard ratio, 0.28; 95% CI, 0.16 to 0.50; $p < 0.001$).[22] In the overall population, PFS at 24 months was 36.1 percent (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1 percent (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; $p < 0.001$). Overall survival at 24 months was 71.3 percent (95% CI, 64.5 to 77.1) with dostarlimab and 56.0 percent (95% CI, 48.9 to 62.5) with placebo (hazard ratio, 0.64; 95% CI, 0.46 to 0.87). The overall survival (OS) at 24 months in the dMMR group was 83.3 percent versus 58.7 percent and in the pMMR was 67.7 percent versus 55.1 percent. Patients with carcinosarcoma were included in this trial which is why the NCCN Guidelines recommend dostarlimab over pembrolizumab in this population.[8] In this trial the dostarlimab was given as maintenance therapy for up to three years after the end of chemotherapy.

There are some unanswered questions about immunotherapy. One is how best to sequence therapy in pMMR patients. A study is needed to decide whether immunotherapy/chemotherapy should be used before or after chemotherapy. Another question is should lenvatinib/pembrolizumab remain standard second-line treatment in patients with pMMR who recur after immunotherapy/chemotherapy. Additionally, single-agent immunotherapy instead of combination with chemotherapy may be enough in those with dMMR, however, this needs to be studied. Immunotherapy versus trastuzumab in combination with chemotherapy in the HER2 positive, pMMR population also needs to be considered. The optimal duration of maintenance immunotherapy needs to be identified. Several studies are ongoing examining immunotherapy, including agents not currently used in endometrial cancer, in various combinations and patient populations to help address these questions.

A study evaluating treatment patterns, healthcare resource use and healthcare costs among newly diagnosed U.S. patients with endometrial cancer found that newly diagnosed patients generally received guideline-recommended treatment.[23] Using 2016 – 2018 data, mean per patient per month costs per line of therapy (LOT) were $14,601 for pre-treatment, $6,859 for LOT1, $10,649 for LOT2, and $9,206 for LOT3+. With recent changes in the treatment guidelines recommending earlier use of immunotherapy, the monthly cost will be higher. Treating patients more aggressively with immunotherapy/chemotherapy combinations in first-line therapy will hopefully reduce the number of patients requiring later lines of therapy.

Conclusion

Improving outcomes, reducing disparities, and reducing costs require increasing provider awareness and patient education. Early referral and access to a gynecologic oncologist for appropriate treatment selection, surgical intervention, and surgical staging will decrease the number of patients needing more than one line of treatment. Optimizing adjuvant treatment for patients with advanced disease using biomarker-based testing is important. Immunotherapy should be used in combination with standard first-line chemotherapy for advanced or recurrent disease because this combination has demonstrated significant improvement in PFS, particularly in the dMMR patient population where a survival benefit was also observed with dostarlimab.

Dario R. Roque, MD is an Associate Professor of Gynecologic Oncology in the Department of Obstetrics and Gynecology at the Northwestern University Feinberg School of Medicine in Chicago, IL.

References

1. American Cancer Society. Key Statistics for Endometrial Cancer. Available at cancer.org/cancer/types/endometrial-cancer/about/key-statistics.html. Accessed 6/4/2024.
2. Renehan AG, Tyson M, Egger M, et al. Body-mass index, and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569-78.
3. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer.* 2006;94(5):642-6.
4. Cote ML, Ruterbusch JJ, Olson SH, et al. The growing burden of endometrial cancer: A major racial disparity affecting Black women. *Cancer Epidemiol Biomarkers Prev.* 2015;24(9):1407-15.
5. Doll KM, Winn AN, Goff BA. Untangling the Black-White mortality gap in endometrial cancer: A cohort simulation. *Am J Obstet Gynecol.* 2017;216(3):324-25.
6. Romano SS, Doll KM. The impact of fibroids and histologic subtype on the performance of U.S., clinical guidelines for the diagnosis of endometrial cancer among Black women. *Ethn Dis.* 2020;30(4):543-52.
7. Doll KM, Khor S, Odem-Davis K, He H, et al. Role of bleeding recognition and evaluation in Black-White disparities in endometrial cancer. *Am J Obstet Gynecol.* 2018;219(6):593.e1-593.e14.
8. NCCN Clinical Practice Guidelines in Oncology. Uterine Neoplasms. Version 2.2024. Available at nccn.org. Accessed 6/4/2024.
9. American College of Obstetrics and Gynecology. Endometrial Cancer Practice Bulletin. Number 149. April 2015.
10. Hamilton CA, Pothuri B, Arend RC, et al. Endometrial cancer: A society of gynecologic oncology evidence-based review and recommendations. *Gynecol Oncol.* 2021;160(3):817-26.
11. Persson J, Salehi S, Bollino M, et al. Pelvic sentinel lymph node detection in high-risk endometrial cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. *Eur J Cancer.* 2019;116:77-85.
12. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, Method M, Ade M, Ivanova A, Boggess JF. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): A multicenter, prospective, cohort study. *Lancet Oncol.* 2017;18(3):384-92.
13. Helgers RJA, Winkens B, Slangen BFM, Werner HMJ. Lymphedema and post-operative complications after sentinel lymph node biopsy versus lymphadenectomy in endometrial carcinomas – A systematic review and meta-analysis. *J Clin Med.* 2020;10(1):120.
14. Suidan RS, Sun CC, Cantor SB, et al. Three lymphadenectomy strategies in low-risk endometrial carcinoma: A cost-effectiveness analysis. *Obstet Gynecol.* 2018;132(1):52-8.
15. Backes FJ, Haag J, Cosgrove CM, et al. Mismatch repair deficiency identifies patients with high-intermediate-risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: A prognostic biomarker. *Cancer.* 2019;125(3):398-405.
16. Berek JS, Matias-Guiu X, Creutzberg C, et al; Endometrial Cancer Staging Subcommittee, FIGO Women's Cancer Committee. FIGO staging of endometrial cancer: 2023. *Int J Gynaecol Obstet.* 2023;162(2):383-94.
17. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: An interim analysis of a multicenter, open-label, single-arm, Phase II trial. *Lancet Oncol.* 2019;20(5):711-8.
18. Marabelle A, Fakih M, Lopez J, et al. Association of tumor mutational burden with outcomes in patients with advanced solid tumors treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, Phase II KEYNOTE-158 study. *Lancet Oncol.* 2020;21(10):1353-65.
19. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. *J Clin Oncol.* 2022;40(7):752-61.
20. Oaknin A, Tinker AV, Gilbert L, et al. Clinical activity, and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: A nonrandomized Phase I clinical trial. *JAMA Oncol.* 2020;6(11):1766-72.
21. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. *N Engl J Med.* 2023;388(23):2159-70.
22. Mirza MR, Chase DM, Slomovitz BM, et al; RUBY Investigators. Dostarlimab for primary advanced or recurrent endometrial cancer. *N Engl J Med.* 2023;388(23):2145-58.
23. Nwankwo C, Shah R, Shah A, et al. Treatment patterns and economic burden among newly diagnosed cervical and endometrial cancer patients. *Future Oncol.* 2022;18(8):965-77.

Targeting New Strategies in Narcolepsy and Idiopathic Hypersomnia: Novel Approaches to Diagnosis and Treatment

Anne Marie Morse, DO, FAASM

This journal article is supported by educational grants from Jazz Pharmaceuticals; Avadel CNS Pharmaceuticals, LLC

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

Summary

Narcolepsy and idiopathic hypersomnia are rare sleep disorders which have a major impact on those affected due to dramatic daytime sleepiness. Several medications which promote wakefulness are available for treatment. Individualized treatment plans need to be developed to achieve the best outcomes.

Key Points

- Narcolepsy and idiopathic hypersomnia are related but distinct entities that are unified by the presence of excessive daytime sleepiness.
- Clinical guidelines offer a starting place for strategies to consider, but the patient should direct the personalized treatment plans for these disorders.

NARCOLEPSY AND IDIOPATHIC HYPERsomnia are typically pediatric onset diagnoses but there are significant delays in diagnosis. Both are rare diseases affecting one in 2,000 people which is a similar rate to multiple sclerosis. Both narcolepsy and idiopathic hypersomnia, even when treated, cause significant social and economic burden. A timely diagnosis is important because medical comorbidities can develop over time.

Narcolepsy is a neurologic disorder associated with the dysregulation of the sleep–wake cycle characterized by excessive daytime sleepiness (EDS), rapid eye movement (REM)-related phenomena, and disturbed nocturnal sleep.[1] Patients can have continual background sleepiness, involuntary sleep episodes (sleep attacks), and wakeful sleepiness (automatic behavior, microsleeps). The REM-related phenomena include cataplexy (transient change in muscle tone) which occurs in about 60 percent of those with narcolepsy, hypnagogic hallucinations in 67 percent, and sleep paralysis in 64 percent.[2] In children or in individuals within six months of onset, cataplexy manifests as spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.[3] In those with long-standing disease, cataplexy manifests as brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or strong emotion. Most patients have partial cataplexy rather than complete—where they may fall or slump out of a chair.[4] Nightmares and unpleasant frequent dreams are also REM-related phenomena. In narcolepsy, sleep onset REM periods occur within 15 minutes of falling asleep whereas they occur about 90 minutes after falling asleep in those without narcolepsy.

There are two types of narcolepsy—Type 1 (with cataplexy) and Type 2 (without cataplexy). Type 1 is caused by hypocretin deficiency which is due to autoimmunity and has cerebral spinal fluid (CSF) levels of hypocretin less than 110 pg/mL.[5] Hypocretin (also known as orexin) is an important regulator of sleep/wake behavior. Type 1 can be diagnosed by symptoms of excessive daytime sleepiness and an average sleep latency of less than eight minutes and

Exhibit 1: Idiopathic Hypersomnia

• **MSLT:**
• Average Sleep Latency of less than 8 minutes
• Less than 2 SOREMPs
• **Actigraphy:**
• 660 minutes or more of TST on average over 1-2 weeks
• **24-hour PSG:**
• 660 minutes or more of TST

MSLT = multiple sleep latency test; SOREMPs = sleep onset REM period; TST = total sleep time; PSG = polysomnography

two or more sleep onset REM periods (SOREMPs) on multiple sleep latency testing (MSLT) or a SOREMP on nocturnal polysomnography. The difference with Type 2 narcolepsy is that CSF hypocretin levels are not deficient. Spinal taps for hypocretin are not done frequently.

Narcolepsy can also be primary or secondary. Primary is caused by autoimmunity or an unknown factor. Secondary can be caused by multiple sclerosis, traumatic brain injury, stroke, brain neoplasm, Prader Willi syndrome, Niemann Pick Type C disease, Parkinson's disease, and others which can cause defects in brain signals for sleep.

Idiopathic hypersomnia (IH) is characterized by excessive sleep (11 or more hours), chronic daytime sleepiness, and cognitive dysfunction. Patients complain of sleep inertia (prolonged difficulty waking with repeated returns to sleep, irritability, automatic behavior, and confusion). Patients may have difficulty concentrating or thinking clearly throughout the day. The need to sleep can strike at any time, including while driving or working, which makes idiopathic hypersomnia potentially dangerous like narcolepsy. Idiopathic hypersomnia is not a deficiency of wakefulness like narcolepsy but is an overexaggeration of sleepiness. Diagnosing idiopathic hypersomnia requires ruling out other sleep disorders. Exhibit 1 shows the test results which suggest this sleep disorder.[5] There can be issues with using the MSLT for diagnosis. Sensitivity of MSLT for IH is documented to be as low as 12 percent and approximately 40 percent or more IH patients have MSLT of more than eight minutes. MSLT also has poor retest reliability with IH and narcolepsy Type 2.[6] Exhibit 2 shows the overlap and differences with narcolepsy IH. Unlike with narcolepsy, naps are not refreshing for those with IH.

Treating narcolepsy and IH is not just managing daytime sleepiness but also limiting the impact the disease has on quality of life, work/school, and social

Exhibit 2: Comparing Narcolepsy Type 1 and 2 and Idiopathic Hypersomnia

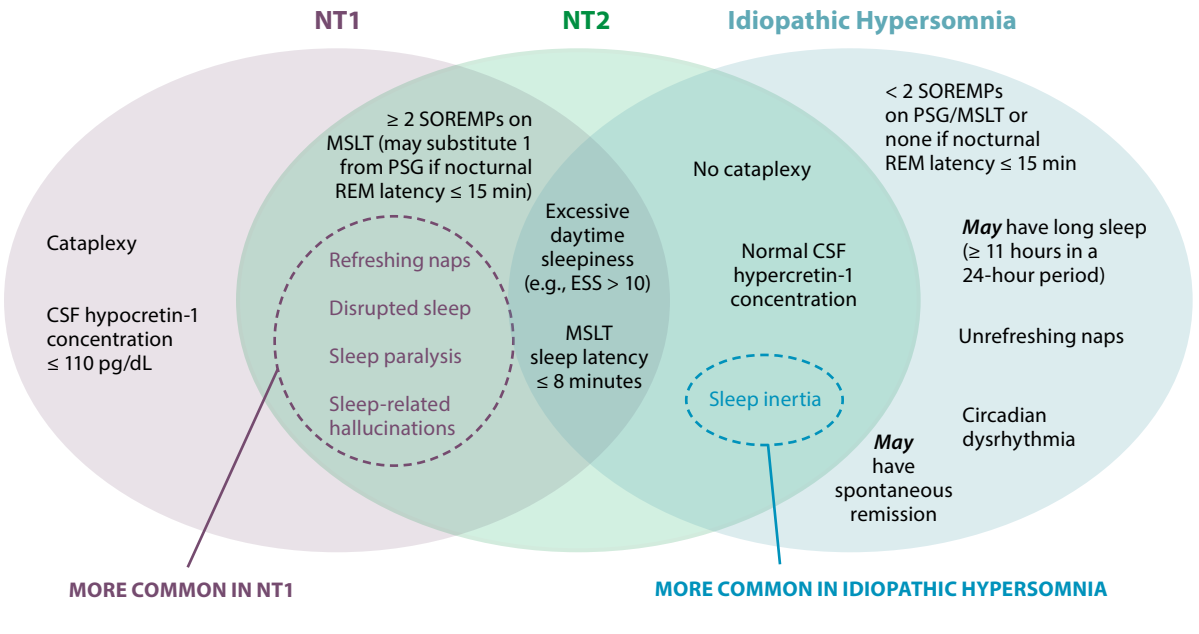


Exhibit 3: 2021 AASM Clinical Practice Guideline (Adults)[7]

NARCOLEPSY			Outcomes Showing Clinically Significant Improvement			
Intervention	**Recommendation**	**FDA Approval**	**EDS**	**Cataplexy**	**Disease Severity**	**QoL**
Modafinil	Strong	EDS in narcolepsy or shift work sleep disorder (≥ 17 years)	X		X	X
Pitolisant	Strong	EDS or cataplexy in narcolepsy (≥ 6 years)	X	X	X	
Oxybate	Strong	EDS or cataplexy in narcolepsy (≥ 7 years) IH (adults, low sodium)	X	X	X	
Solriamfetol	Strong	EDS in narcolepsy or OSA (adults)	X		X	X
Armodafinil	Conditional	EDS in narcolepsy, OSA, shift work sleep disorder(≥ 17 years)	X		X	
Dextro-amphetamine	Conditional	Narcolepsy, ADHD	X	X		
Methylphenidate	Conditional	ADHD (≥ 6 years)	X		X	
IDIOPATHIC HYPERSOMNIA			**Outcomes Showing Clinically Significant Improvement**			
Intervention	**Recommendation**	**FDA Approval**	**EDS**	**Cataplexy**	**Disease Severity**	**QoL**
Modafinil	Strong	EDS in narcolepsy or shift work sleep disorder (≥ 17 years)	X		X	
Clarithromycin	Conditional	Infections	X		X	X
Methylphenidate	Conditional	ADHD (≥ 6 years)			X	
Pitolisant	Conditional	EDS or cataplexy in narcolepsy (≥ 6 years)	X			
Oxybate	Conditional	EDS or cataplexy in narcolepsy (≥ 7 years) IH (adults, low sodium)	X			

aspects of life. Exhibit 3 shows the 2021 American Academy of Sleep Medicine guideline medication recommendations for managing narcolepsy and IH in adults.[7] No currently available medication impacts all aspects of either disease. Low-sodium oxybate is the only agent with an FDA-approved indication for IH—this indication was granted in 2023. The potential benefits of long-term low-sodium oxybate treatment of narcolepsy or IH include flexible optimization of dosing and regimen, improvement of quality of life and functioning, weight loss, and relative to sodium oxybate use, health benefits of reduced sodium content. Exhibit 4 compares the adverse events of each agent. It is important to note that pitolisant is the only non-scheduled wake promoting agent.

Exhibit 4: Adverse Event Profiles

Drug	Schedule	Adverse Events (most common in bold)
Pitolisant	–	**Headache**, insomnia, nausea, anxiety. *Warnings*: QT prolongation.
Sodium oxybate	III	Headache, **nausea**, dizziness, ↓ appetite, diarrhea, hyperhidrosis, anxiety, vomiting (adults), sedation, **weight loss**, worse obstructive sleep apnea. *Warnings: Central nervous system depression (black box), abuse or misuse (black box), depression and suicidality, confusion or anxiety,* ***parasomnias****.*
Modafinil	IV	**Headache**, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, dyspepsia. *Warnings: Serious rash (e.g., Stevens-Johnson syndrome), angioedema, anaphylaxis, multiorgan hypersensitivity, persistent sleepiness, psychiatric symptoms, known cardiovascular disease.* May have teratogenic effects.
Armodafinil	IV	**Headache**, nausea, dizziness, insomnia. *Warnings: Serious rash (e.g., Stevens-Johnson syndrome), angioedema, anaphylaxis, multiorgan hypersensitivity, persistent sleepiness, psychiatric symptoms, known cardiovascular disease.*
Solriamfetol	IV	Headache, nausea, ↓ appetite, insomnia, anxiety. *Warnings: ↑ blood pressure, ↑ heart rate, psychiatric symptoms.*
Methylphenidate	II	**Tachycardia, palpitations,** headache, insomnia, anxiety, hyperhidrosis, weight loss, ↓ appetite, dry mouth, nausea, abdominal pain. *Warnings: Central nervous system stimulant (black box), abuse potential (black box), serious cardiovascular events, ↑ blood pressure, ↑ heart rate, psychiatric symptoms, priapism, peripheral vasculopathy, growth retardation.*
Dextroamphetamine	II	**Palpitations, tachycardia, ↑ blood pressure**, cardiomyopathy, psychosis, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, ↑ motor and phonic tics, dryness of mouth, unpleasant taste, diarrhea, constipation, anorexia, weight loss, urticaria, impotence, changes in libido. *Warnings: Abuse potential (black box), serious cardiovascular events, sudden death, hypertension, psychiatric symptoms, growth retardation, visual disturbances.*

The guidelines note there are gaps in the treatment landscape.[7] Data are lacking for use of amphetamines which are commonly used and there are few comparative effectiveness studies. Standardized, validated outcome measures are not always used across studies. Outcome measures that reflect patient symptoms are needed.

Comorbidities are very common with narcolepsy and IH. Much higher rates of sleep apnea, cardiovascular disease, hypertension, diabetes, hyperlipidemia, migraine, anxiety, and depression are seen in this population compared to the general population.[8] In Type 1 narcolepsy, higher rates of metabolic and cardiovascular diseases are thought to occur because of hypocretin neurons participate in the regulation of metabolism, including appetite, energy expenditure, and autonomic regulation.[9]

Initial steps to maximize outcomes in those with

narcolepsy or IH include having patients keep a symptom diary and defining their goals for treatment. The symptom diary should also include how the symptoms disrupt their life, severity, cognitive/emotional state, and any other wellness concerns. In addition to stopping daytime sleepiness, all patients when surveyed would like treatment to allow them to be more productive, improve their sense of well-being, increase energy level, and improve memory or cognition.

Barriers to good outcomes include stigma that those with narcolepsy and IH are lazy, unnecessary treatment delays related to managed care approvals, lack of provider education on diagnosis, and access to specialist care. A significant barrier to adequate treatment of narcolepsy can be the managed care criteria for medication approval. For example, plan criteria states a patient must have 14 episodes of cataplexy in a two-week period of time in order to be treated with a particular medication. Plans should consider the impact on a patient who has at least one episode of cataplexy a week. A patient may fear holding her newborn baby because the overwhelming joy of the moment may lead to her having an attack and dropping the baby. Many managed care plans use study inclusion criteria for determining which patients are eligible for a particular medication. Clinical trial data help guide efficacy, safety, and approval of use, but study design should not dictate the user profile for a given agent.

Conclusion

Narcolepsy Types 1 and 2 and IH are related but distinct entities that are unified by the presence of excessive daytime sleepiness. Narcolepsy results in insufficient wakefulness and IH in exaggerated sleepiness. Guidelines offer a starting place for strategies to consider, but the patient should direct personalized treatment plans for both. Personalized treatment plans should start with the person being treated.

Anne Marie Morse, DO, FAASM is Director of the Division of Child Neurology, Director of the Division of Pediatric Sleep Medicine, and Program Director of Child Neurology Residency at the Janet Weis Children's Hospital and a Clinical Associate Professor, Neurology and Sleep Medicine at the Geisinger Commonwealth School of Medicine in Danville, PA.

References

1. American Academy of Sleep Medicine. Provider Fact Sheet. Narcolepsy. Available at aasm.org/wp-content/uploads/2022/07/ProviderFS-Narcolepsy.pdf. Accessed 7/12/2024.
2. Scammell TE. Narcolepsy. *N Engl J Med*. 2015;373(27):2654-62.
3. Ahmed I, Thorpy M. Clinical features, diagnosis, and treatment of narcolepsy. *Clin Chest Med*. 2010;31(2):371-81
4. National Institute of Neurological Disorders and Stroke. Narcolepsy. Available at ninds.nih.gov/health-information/disorders/narcolepsy. Accessed 7/12/2024.
5. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
6. Trotti LM. Twice is nice? Test-retest reliability of the Multiple Sleep Latency Test in the central disorders of hypersomnolence. *J Clin Sleep Med*. 2020;16(S1):17-18.
7. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2021;17(9):1881–93.
8. Gudka S, Haynes E, Scotney J, et al. Narcolepsy: Comorbidities, complexities, and future directions. *Sleep Med Rev*. 2022;65:101669.
9. Krahn LE, Zee PC, Thorpy MJ. Current understanding of narcolepsy 1 and its comorbidities: What clinicians need to know. *Adv Ther*. 2022;39(1):221-43.

Informed Managed Care Decision-Making in the Management of Hereditary Angioedema: Optimizing Clinical and Economic Outcomes in an Evolving Paradigm

Marc A. Riedl, MD, MS

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

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

Summary

Hereditary angioedema (HAE) is a rare, lifelong, disabling, and potentially life-threatening condition caused by a deficiency of C1 esterase inhibitor. Available treatments manage acute attacks and prevent future attacks. Numerous patient factors impact treatment selection.

Key Points

- Early recognition and diagnosis of HAE is critical.
- Every patient must have an acute HAE treatment plan.
- Long-term prophylactic treatment is considered on an individual basis.
- Newer therapies are highly effective and tolerable treatment options.
- Quality of life must be considered carefully when evaluating efficacy of the treatment plan.
- Continued collaboration is necessary to optimize access to effective HAE treatments.

ANGIOEDEMA, THE RESULT OF FLUID extravasation into deep dermis and subcutaneous tissues, is alarming to sufferers and a common reason they seek care at emergency rooms. One rare type of angioedema is hereditary angioedema (HAE). HAE has a prevalence of one in 50,000, can be difficult to diagnose, and is frequently misdiagnosed.

Diagnosis of HAE requires excluding other causes of angioedema (Exhibit 1).[1-3] About 50 percent of patients with HAE have previously had their conditions misdiagnosed—most commonly as allergic angioedema or appendicitis. The median delay in diagnosis is 10 years.[4] The challenge of getting an HAE diagnosis is that it is a rare condition with numerous and variable symptoms similar to more common conditions. Clinicians thinking of the diagnosis is often the greatest obstacle because clinicians often "see" through a highly specialized lens or specific time interval. Misdiagnosis results in marked delays in receiving the correct diagnosis during which time patients cannot access effective lifesaving treatment and this can result in unnecessary surgeries or even death.[5]

HAE attacks are characterized by non-itching angioedema. Attacks can be quite severe, affecting the face, oropharynx (causing risk of asphyxiation), extremities, gastrointestinal system, and genitourinary tract. These attacks have a rapid onset of minutes to hours, increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Importantly, HAE attacks are not an allergic process and thus are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine. In a patient survey, clinical symptoms started at a mean age of 11.2 (± 7.7) years.[4] In this survey, women had a more severe course of the

Exhibit 1: Causes of Angioedema[1-3]

- Foods, medications, insect stings (IgE-mediated allergy)
- Radiocontrast media (Non-IgE mediated)
- Chronic spontaneous urticaria/angioedema
- Physical urticaria/angioedema
- Aspirin and other nonsteroidals
- Angiotensin converting enzyme inhibitor-induced

- **C1-INH Deficiency**
  - Hereditary - Types I, II
  - Acquired (associated with B-cell lymphoma, monoclonal gammopathy of undetermined significance (MGUS), and anti-C1-INH autoantibodies)
- **Hereditary with normal C1-INH**
  - Factor XII
  - Angiopoietin-1
  - Plasminogen
  - Kininogen
  - Myoferlin
  - HS3ST6
  - Unknown
- **Idiopathic**
  - Histaminergic/Mast Cell-mediated
  - Non-histaminergic

disease than men and those with early in life onset of clinical symptoms were affected more severely than those with late onset.[4]

Attacks typically occur unpredictably and vary in frequency. There are several known triggers of attacks but only about 40 percent of individuals with HAE can identify the cause of an episode.[6] Common triggers include estrogen-containing oral contraceptives, hormone replacement therapy, emotional stress, infections, dental or surgical procedures, or physical trauma from accidents. In most cases, a family history of HAE is identified.

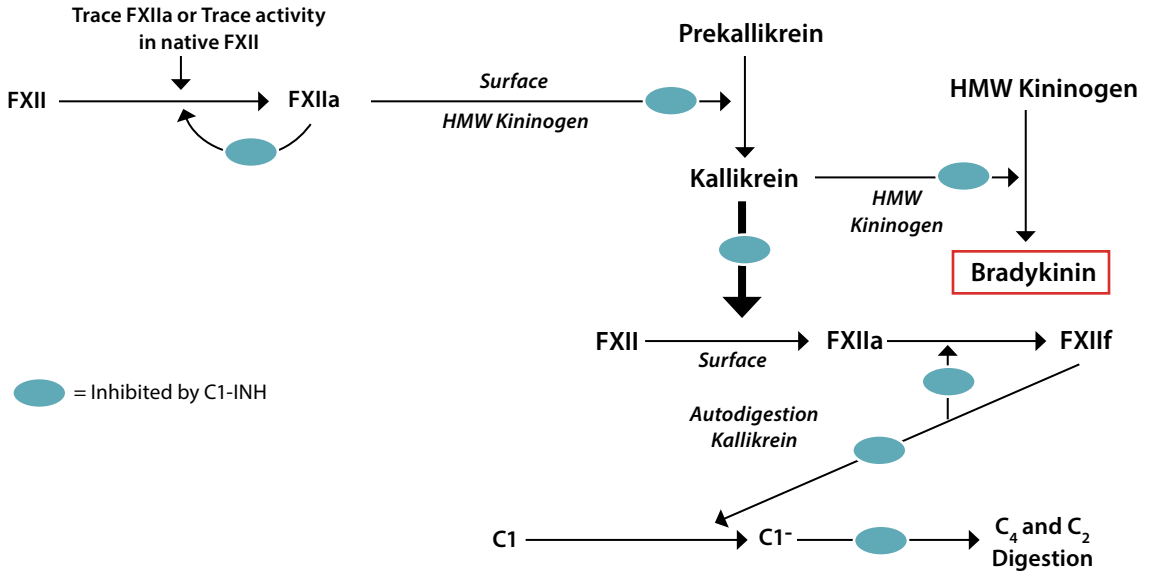
The skin and abdomen are the most common locations for HAE attacks followed by larynx.[7] With abdominal attacks, mild-to-severe pain, abdominal distension, tenderness, and vomiting occur. The symptoms can mimic other abdominal conditions, resulting in misdiagnosis and unnecessary surgery. Airway angioedema can cause death. In one survey, 1.3 percent of diagnosed patients died from asphyxiation and more importantly 31 percent of those undiagnosed also died.[8] Even if a patient has never had an airway attack, they need to be educated on this possibility and how to manage it.

Hereditary angioedema is associated with significant and multifaceted disease burden.[5,9] Many contributing factors include debilitating, painful, dangerous, and unpredictable symptoms; challenges in diagnosis; lack of access to effective treatment; and treatment burden. HAE also increases the risk of depression, anxiety, and loss of productivity. Patients can lose significant amounts of work and/or school time. Overall, HAE results in significant humanistic burden across physical and mental health domains and negatively impacts productivity.

Type 1 and Type 2 HAE are autosomal dominant diseases caused by C1 inhibitor (C1-INH) gene mutations which lead to deficiency in or dysfunctional C1-INH.[10] C1-INH inhibits all active enzymes of the bradykinin-forming cascade (Exhibit 2). With a C1-INH deficiency, bradykinin levels increase and bradykinin causes endothelial cell fluid extravasation through vasodilatation and increased vascular permeability.[11]

C1-INH functional assays are used to diagnose HAE. Type 1 HAE accounts for about 85 percent of cases and has low C4 level, C1-INH antigenic level, and C1-INH antigenic function. Type 2 HAE accounts for close to 15 percent of cases and has normal C1-INH antigenic level but low C4 level and C1-INH antigenic function. There are rare cases of C1-INH normal HAE which can be especially difficult to diagnose using functional assays. There is lot of work going on to use genetic mutation studies to diagnose these patients. Some of the possible genetic factors which can be mutated in C1-INH normal are shown in Exhibit 1. Families of those diagnosed with HAE should be screened for the disease.

Exhibit 2: Pathophysiology of Hereditary Angioedema



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 treatment 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.[2,7] All patients need on-demand treatment and many will also need long-term prophylaxis. Short-term prophylaxis should be prescribed for those with known triggers. Treatment for HAE must be individualized to provide optimal care and normalize quality of life.

Since 2009 there have been dramatic advances in available treatments for HAE for both acute attack treatment and prophylaxis. The available agents target bradykinin production or effects in several ways. Because newer agents have better safety and efficacy data, older therapies including androgens and tranexamic acid are no longer used first-line, except for the case of tranexamic acid which may be beneficial in those with C1-INH normal HAE.

Four agents are available for the acute treatment of an attack—intravenous plasma-derived C1-INH, intravenous recombinant C1-INH, subcutaneous ecallantide (kallikrein inhibitor), and subcutaneous icatibant (bradykinin-2 receptor antagonist). Only icatibant is FDA labeled for self-administration during an attack. Treatment of early symptoms of an attack, with any licensed therapy, results in milder symptoms and shorter duration of attack, compared with later treatment.[12] All acute therapies have been shown to be well-tolerated, with minimal risk of serious adverse events. All HAE attacks are considered for on-demand treatment and any attack affecting or potentially affecting the upper airway must be treated.[2] HAE attacks should be treated as early as possible and all patients must have sufficient medication for on-demand treatment of two attacks and always carry on-demand medication. All patients who are provided with icatibant must be taught to self-administer the medication. Patients must also be educated not to "save" on-demand medication just in case an attack worsens but to treat it as soon as possible.

Prophylactic treatments for HAE help patients prevent and reduce the frequency and severity of attacks (Exhibit 3). All currently available prophylactic agents are associated with breakthrough attacks, therefore, an acute treatment plan is essential for every patient when on prophylactic agents. Patients may also need additional prophylaxis before surgical procedures or other known triggers.

Subcutaneous administration of C1-INH is a significant advancement in therapy over intravenous administration because it does not require intravenous access which can become an issue over time with patients. It is effective in

Exhibit 3: HAE Prophylactic Therapies

Drug	Mechanism of Action	Route of Administration and Dosing Schedule	FDA-Approved Age Indication
Plasma-derived C1-INH (intravenous)	C1-INH: Inhibition of contact system activation.	Intravenous every 3-4 days	6 years of age and older
Plasma-derived C1-INH (subcutaneous)	C1-INH: inhibition of contact system activation.	Subcutaneous every 3-4 days	6 years of age and older
Lanadelumab	Monoclonal antibody: inhibition of plasma kallikrein activity.	Subcutaneous every 2 or 4 weeks; Dosing interval determined by age and response to treatment.	Ages 2 and older
Berotralstat	Small molecule: inhibition of plasma kallikrein activity.	Oral, once daily	Ages 12 and older

reducing attacks by about 90 percent compared to placebo in adults, adolescents, and children.[13,14] Subcutaneous administration also reduces the need for on-demand treatment. In one trial, the need for rescue medication was reduced from 5.55 uses per month in the placebo group to 1.13 uses per month in the 40-IU dose group and from 3.89 uses in the placebo group to 0.32 uses per month in the 60-IU dose group.[13] Prophylactic subcutaneous C1-INH improves patient quality of life compared with on-demand alone treatment.[15]

Lanadelumab, a human monoclonal antibody that targets plasma kallikrein to prevent angioedema in patients with HAE, was approved in the U.S. in 2018 as the first monoclonal antibody indicated for prophylactic treatment of HAE. Subcutaneous lanadelumab for 26 weeks significantly reduced the attack rate by approximately 78 percent and improved quality of life compared with placebo.[16] In children, the mean attack rate during treatment decreased by 94.8 percent from baseline (1.84 ± 1.53 to 0.08 ± 0.17) attacks/month, and 16 (76.2%) patients were attack-free.[17]

Berotralstat is an oral once daily plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years of age and older. Berotralstat demonstrated a significant reduction in attack rates at both 110 mg (1.65 attacks per month; $p = .024$) and 150 mg (1.31 attacks per month; $p < .001$) relative to placebo (2.35 attacks per month).[18]

The treatment guidelines recommend that patients be evaluated for long-term prophylaxis at every visit.[2,7] Disease burden and patient preference should be taken into consideration when considering prophylaxis. C1-INH (intravenous or subcutaneous), lanadelumab, or berotralstat are first-line. Long-term prophylaxis and androgens are considered second-line. The guidelines recommend modification of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease.

Management plans need to be individualized to lessen the burden of illness, aim to provide patients with HAE a normal quality of life, and consider treatment burden.[2] Overall, acute treatment and prophylaxis should be selected considering unique patient factors such as frequency of attacks, rapidity of attack progression, location of attacks (i.e., laryngeal), access to medical care, history of frequent hospitalization, treatment complications, and quality of life. Medication factors to consider include efficacy, safety, cost, route of administration, and patient preference/tolerability. The treatment plan needs to be assessed at least biannually and sometimes more often.

Quality of life is important with HAE. The disease has an impact on quality of life in between angioedema episodes and this has not always been considered by clinicians.[19] Unpredictability of the disease is stressful, limits educational/employment opportunities, causes disruption of social activities, and causes negative impact on family relationships. A higher frequency of attacks is associated with a higher burden of disease (physical, psychological, social). Despite advances in treatment, the burden of disease remains high.

Clinicians need to assess whether a patient's disease is being controlled, whether the patient feels they have control, whether they can do life activities, and whether they are able to be adherent with their medications. There are objective HAE specific disease

control and quality-of-life tools which clinicians can use to measure efficacy and benefit of therapy.[20,21] Overall studies show that those on prophylactic therapy have a reduced disease burden compared to those who receive on-demand treatment only.[22,23] Home treatment of attacks is replacing emergency-room treatment which can significantly reduce costs and disease burden. Additionally, fewer narcotics are being prescribed because attacks appear less severe when the disease is better controlled.[24]

Access to HAE specialists is a barrier to optimized care. Inequities in access are especially true for people living in rural areas of the U.S. About 50 percent of individuals with HAE live in a community with less than a 100,000 population. Challenges in managing HAE in the rural setting include obtaining a diagnosis of HAE, easy access to a physician with expertise in HAE, continuity of care, availability of telemedicine services, access to approved HAE therapies, patient education, and economic barriers to treatment.[25]

There are also system and socioeconomic barriers to optimize HAE care. Insurance providers and healthcare systems determine access to HAE treatment. There is significant variability in system support and reimbursement for HAE medications across the U.S. Unfortunately, regulatory approval does not equal access to medication. Additionally, patient burden may remain high despite reimbursement coverage due to such things as limits on on-demand medication quantities and limits on prophylaxis options. There are numerous additional agents being investigated for HAE. Examples in Phase III trials include deucrictibant (bradykinin B2 receptor antagonist), sebetralstat (plasma kallikrein inhibitor), and donidalorsen (antisense oligonucleotide to reduce pre-kallikrein expression).

Conclusion

Early recognition and diagnosis of HAE is critical to reducing morbidity and mortality by allowing development of an effective management plan. An acute HAE treatment plan is necessary for every patient. Long-term prophylactic treatment should be considered on an individual basis for patients—newer therapies are highly effective and tolerable treatment options. Quality of life must be considered carefully when evaluating the efficacy of the treatment plan. Continued collaboration among providers and managed care is necessary to optimize access to effective HAE treatments.

Marc A. Riedl, MD, MS is a Professor of Medicine and the Clinical Director of the U.S. HAEA Angioedema Center at the University of California, San Diego, CA.

References

1. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 Suppl):S51-131.
2. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-90.
3. Kesh S, Bernstein JA. Isolated angioedema: A review of classification and update on management. *Ann Allergy Asthma Immunol*. 2022;129(6):692-702.
4. Zanichelli A, Longhurst HJ, Maurer M, et al.; IOS Study Group. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Ann Allergy Asthma Immunol*. 2016;117(4):394-8.
5. Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. *Allergy Asthma Proc*. 2020;41(Suppl 1):S08-S13.
6. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267-74.
7. Busse PJ, Christiansen SC, Riedl MA, et al. U.S. HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-50.e3.
8. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks, and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692-7.
9. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329-36.
10. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105(3):541-6.
11. Zhao Y, Qiu Q, Mahdi F, et al. Assembly and activation of HK-PK complex on endothelial cells results in bradykinin liberation and NO formation. *Am J Physiol Heart Circ Physiol*. 2001;280(4):H1821-9.
12. Longhurst H. Optimum use of acute treatments for hereditary angioedema: Evidence-based expert consensus. *Front Med (Lausanne)*. 2018;4:245.
13. Longhurst H, Cicardi M, Craig T, et al; COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med*. 2017;376(12):1131-40.
14. Levy D, Caballero T, Hussain I, et al. Long-term efficacy of subcutaneous C1 inhibitor in pediatric patients with hereditary angioedema. *Pediatr Allergy Immunol Pulmonol*. 2020 1;33(3):136-41.
15. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2018;6(5):1733-41.e3.
16. Banerji A, Riedl MA, Bernstein JA, et al; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial. *JAMA*. 2018;320(20):2108-21.
17. Maurer M, Lumry WR, Li HH, et al; SPRING Investigators. Lanadelumab in patients 2 to less than 12 years old with hereditary angioedema: Results from the Phase III SPRING study. *J Allergy Clin Immunol Pract*. 2024;12(1):201-211.e6.
18. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled Phase III trial. *J Allergy Clin Immunol*. 2021;148(1):164-172.e9.
19. The Voice of the Patient. A series of reports from the U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative. Hereditary Angioedema. Public Meeting: September 25, 2017. Report Date: May 2018. Available at fda.gov.
20. Weller K, Donoso T, Magerl M, et al. Validation of the Angioedema Control Test (AECT)-A patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-57.e4.
21. Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. *Front Med (Lausanne)*. 2017;4:212.
22. Zarnowski J, Rabe M, Kage P, et al. Prophylactic treatment in hereditary angioedema is associated with reduced anxiety in patients in Leipzig, Germany. *Int Arch Allergy Immunol*. 2021;182(9):819-26.
23. Castaldo AJ, Jervelund C, Corcoran D, et al. Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. *Allergy Asthma Proc*. 2021;42(2):108-17.
24. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: Follow-up survey of U.S. physicians. *Ann Allergy Asthma Immunol*. 2021;126(3):264-72.
25. Riedl MA, Johnston DT, Anderson J, et al. Optimization of care for patients with hereditary angioedema living in rural areas. *Ann Allergy Asthma Immunol*. 2022;128(5):526-33.

Implementing New Data and Evolving Standards in HER2-Positive Advanced Breast Cancer: Applying the Latest Evidence to Improve Outcomes

Gary M. Owens, MD

This journal article is supported by educational grants from Daiichi Sankyo; AstraZeneca

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

Summary

Targeted therapy has transformed the treatment of HER2-positive metastatic breast cancer. The ability to target HER2-low disease has been the most recent evolution of management.

Key Points

- A significant percentage of women with breast cancer are eligible for HER2-targeted therapy.
- HER2-targeted therapies are used in the neoadjuvant, adjuvant, and metastatic disease settings.
- HER2-low is a new target for these therapies which will significantly expand the use of fam-trastuzumab deruxtecan, the only FDA-approved agent.

IN 2024, AN ESTIMATED 320,720 WOMEN and 2,800 men will be diagnosed with invasive breast cancer in the United States (U.S.).[1] In women, breast cancer is the most common cancer—excluding skin cancer—and is the second most common cause of cancer death.[2] It is estimated that 42,250 women will die from breast cancer in 2024.[1]

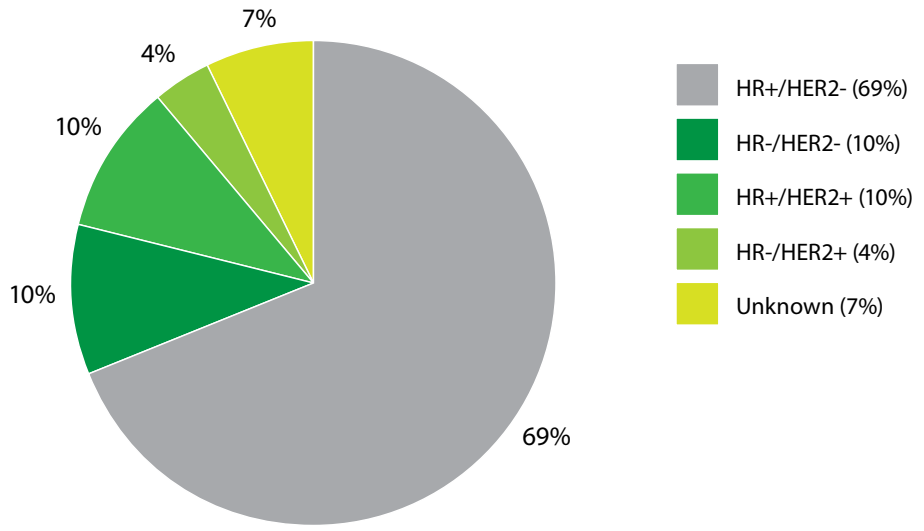
About one in eight U.S. women (~13%) will develop invasive breast cancer over the course of their lifetime.[2] There are currently more than four million women with a history of breast cancer in the U.S.[3] This includes women currently being treated and women who have finished treatment. A woman's risk of breast cancer nearly doubles if she has a first-degree relative (mother, sister, daughter) who has been diagnosed with breast cancer.

There are four main female breast cancer subtypes. In order of prevalence these are, hormone receptor positive (HR+)/human epidermal growth factor receptor two negative (HER2-), HR-negative/HER2-negative, HR-positive/HER2-positive, and HR-negative/HER2-positive (Exhibit 1).[4] Survival varies with each subtype and stage at diagnosis and overall five-year survival for breast cancer is 90.8 percent.

HER2 expression is an important prognostic and predictive biomarker in breast cancer. All patients with newly diagnosed primary or metastatic breast cancer should be tested for HER2 protein expression.[5] Immunohistochemistry (IHC) and/or gene expression by in situ hybridization (ISH) is used to measure HER2. Brease cancers are currently classified as HER2-positive when the HER2 expression is scored 3+ by IHC or an IHC score of 2+ with HER2 gene amplification identified by ISH. HER2 targeted agents have dramatically improved the clinical outcomes of HER2-positive breast cancer but many patients have HER2 scores less than three.

HER2-low disease is a newer concept. It is defined as an IHC score of 1+ or 2+ with a negative ISH result.[6] Historically, HER2-low was managed as HER2-negative disease and these patients had limited treatment options until recently. Approximately 65 percent of patients with breast cancer have an actionable level of HER2 expression when HER2-

Exhibit 1: Percent of Female Breast Cancer by Subtype[4]



HR = hormone receptor; HER2 = human epidermal growth factor receptor two

low disease is included.[7]

The cost of treating cancer in the U.S. has been increasing dramatically and the overall cost of treating breast cancer is higher than for other cancers.[8] Cost of care increases by disease stage with estimates of $48,477 for Stage 0 compared to $89,463 to $182,655 for Stage IV disease.[9] Patient out-of-pocket costs for breast cancer are substantial and were $3.14 billion in 2019.[10] Exhibit 2 shows the costs of HER2-targeted treatment specifically.[11] All cause healthcare cost are highest in year one, but remain substantial in years two and three. Patients treated with HER2-targeted agents incurred approximately $624,455 in breast cancer-related total costs over three years. Any new treatments for HER2 disease need to be evaluated and methodically managed to maximize the value of healthcare expenditures in a resource-constrained environment.[11]

HER2-positive tumors are eligible for HER2-pathway blockade agents. The choices include anti-HER2 monoclonal antibodies (trastuzumab, pertuzumab, and margetuximab), anti-HER2 antibody drug conjugates (trastuzumab emtansine, trastuzumab deruxtecan) and tyrosine kinase inhibitors (tucatinib, lapatinib and neratinib). These HER2-targeted agents have dramatically improved the clinical outcomes since their introduction. HER2-targeted therapies are used in the neoadjuvant (to shrink tumor before surgery), adjuvant (post-surgery), and metastatic disease settings.

Standard neoadjuvant therapy for patients with HER2-positive disease consists of chemotherapy and HER2-directed therapy—specifically trastuzumab with or without pertuzumab.[12] Patients who were treated with neoadjuvant chemotherapy and trastuzumab (with or without pertuzumab) are also treated with HER2-directed therapy in the adjuvant setting. The choice of therapy is chosen according to the response to neoadjuvant treatment. In the metastatic disease setting, the choice of HER2-directed therapy depends on prior therapies but there are several treatment options. Exhibit 3 outlines the recommendations by line of therapy from the National Comprehensive Cancer Network (NCCN) Guidelines.[5]

Antibody-drug conjugates (ADCs) are a new class of anticancer therapy. By combining the selectivity of monoclonal antibodies with the cytotoxic properties of chemotherapy, they improve the therapeutic index of antineoplastic agents.[13] An ADC is composed of an antibody, directed at a target antigen; a payload, typically a cytotoxic agent; and a linker, connecting the antibody to the payload. Fam-trastuzumab deruxtecan and ado-trastuzumab emtansine are the two ADCs which target the HER2.

In 2013, ado-trastuzumab emtansine was the first to be granted FDA approval. It combines trastuzumab with DM1, a derivative of the maytansinoid toxin, which inhibits tubulin polymerization. It significantly prolonged progression-free and overall survival with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.[14] In addition to being third-line for metastatic disease, it is considered the standard of care for patients with HER2-positive

Exhibit 2: All-Cause Cost per Year for HER2 Targeted Agents[11]

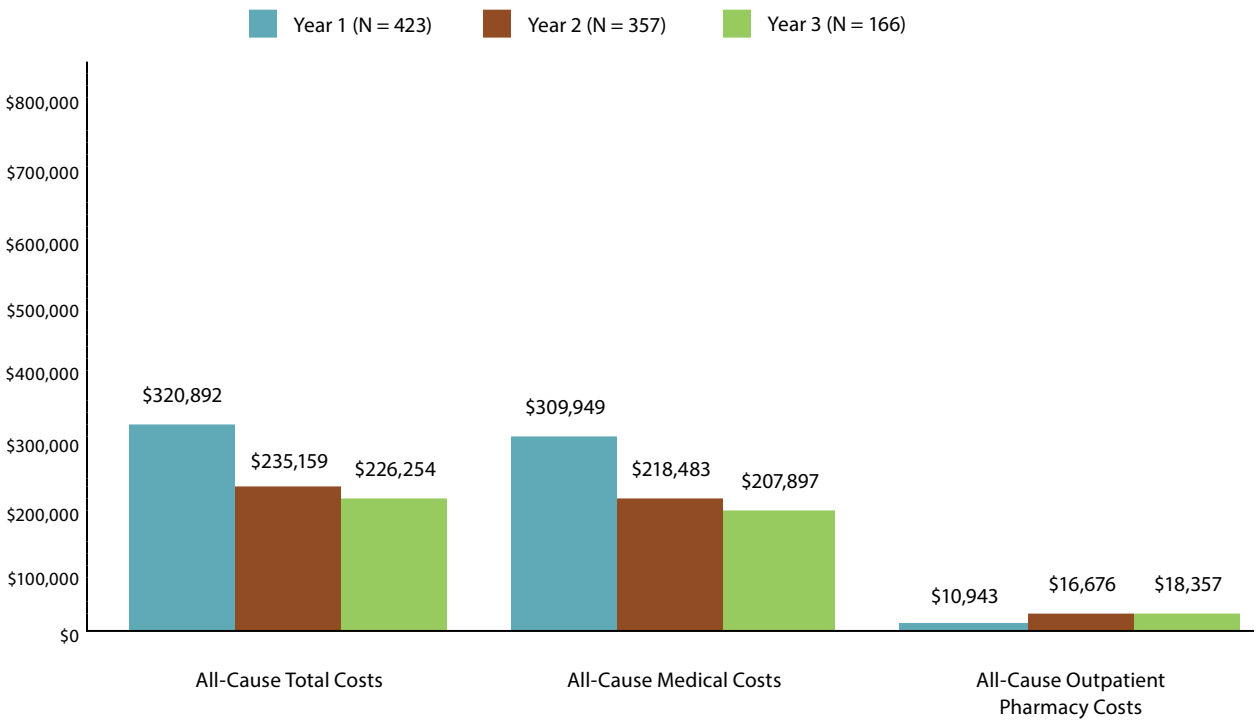


Exhibit 3: NCCN Guidelines for Advanced HER2+ Breast Cancer[5]

Setting	Regimen
First Line	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred) Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line	Fam-trastuzumab deruxtecan (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine (Category 1, preferred, option for second line especially with CNS disease) Ado-trastuzumab emtansine (T-DM1)
Fourth Line and Beyond (optimal sequence is not known)	Trastuzumab + docetaxel or vinorelbine Trastuzumab + paclitaxel ± carboplatin Capecitabine + trastuzumab or lapatinib Trastuzumab + lapatinib (without cytotoxic therapy) Trastuzumab + other chemotherapy agents Neratinib + capecitabine Margetuximab + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

disease with residual disease at the time of surgery in the post-neoadjuvant setting.[15]

Fam-trastuzumab deruxtecan is an ADC composed of trastuzumab, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor, deruxtecan. It is FDA approved for treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy. Compared to trastuzumab emtansine, fam-trastuzumab deruxtecan produced a significant improvement in overall survival in patients with HER2-positive metastatic breast cancer, as well as the longest reported median progression-free survival in this setting.[16] The results of this trial led to fam-trastuzumab deruxtecan being recommended as second-line therapy in the NCCN Guidelines and the other ADC was moved to third-line therapy.[5]

In the HER2-low setting, trastuzumab emtansine demonstrated poor activity among patients with heterogeneous and/or low HER2 expression but fam-trastuzumab deruxtecan has been shown effective.[17] The efficacy in HER2-low may be explained by a more potent cytotoxic payload, higher drug-to-antibody ratio, and/or the ability to elicit the so-called bystander effect. With fam-trastuzumab deruxtecan, the linker allows the release of membrane-permeable-free payload from target cells to enable the killing of neighboring cells regardless of their HER2 expression. In previously treated HER2-low advanced breast cancer, treatment with this agent resulted in significantly longer progression-free (4.7 months) and overall survival (6.5 months) than physician's choice of chemotherapy.[18] In 2022, it was approved for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

HER2-low has been reported to occur in 35.2 to 63.2 percent of cases of metastatic breast cancer.[6] The new paradigm of treating HER2-low metastatic disease with fam-trastuzumab deruxtecan will lead to significantly increased usage of this agent. A cost-effectiveness study found that from a third-party payer's perspective in the U.S., at the current price, this agent is a cost-effective alternative to chemotherapy for patients with HER2-low advanced breast cancer, at a willingness-to-pay threshold of $100,000 per quality-adjusted life-year.[19] Payers will need a strategy to manage this increased usage.

Conclusion

Given the evidence for major clinical benefit with HER2-targeted therapy, it is imperative that managed care methodically evaluate new agents and new uses of already approved agents to maximize the value of healthcare expenditures. There is an urgent need to develop therapies that will prevent the development of metastatic recurrences and delay progression as a potential approach to minimize healthcare resource utilization and costs for patients with HER2-positive metastatic breast cancer.

Gary M. Owens, MD is aPresident of Gary Owens and Associates in Ocean View, DE.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49.
2. American Cancer Society. Key Statistics for Breast Cancer. Available at cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html. Accessed 6/19/2024.
3. Breastcancer.org. Breast Cancer Facts and Statistics. Available at breastcancer.org/symptoms/understand_bc/statistics. Accessed 6/19/2024.
4. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer Subtypes Available at seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed 6/19/2024.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 3.2024. Available at nccn.org. Accessed 6/19/2024.
6. Zhang H, Peng Y. Current biological, pathological, and clinical landscape of HER2-low breast cancer. *Cancers (Basel).* 2022;15(1):126.
7. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: Pathological and clinical landscape. *J Clin Oncol.* 2020;38(17):1951-62.
8. National Cancer Institute. Financial Burden of Cancer. Available at progressreport.cancer.gov/after/economic_burden. Accessed 6/19/2024.
9. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. *Am Health Drug Benefits.* 2016;9(1):23-32.
10. Yabroff KR, Mariotto A, Tangka F, et al. Annual Report to the Nation on the Status of Cancer, Part 2: Patient economic burden associated with cancer care. *J Natl Cancer Inst.* 2021;113(12):1670-82.
11. Mahtani R, Oestreicher N, Lalla D, et al. Health care resource utilization and costs for metastatic breast cancer patients newly treated with human epidermal growth factor receptor 2 (HER2)-targeted agents. *Clin Breast Cancer.* 2022;22(4):e488-e496.
12. Martínez-Sáez O, Prat A. Current and future management of HER2-positive metastatic breast cancer. *JCO Oncol Pract.* 2021;17:594–604
13. Corti C, Giugliano F, Nicolò E, et al. Antibody-drug conjugates for the treatment of breast cancer. *Cancers* (Basel). 2021;13(12):2898.
14. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-91.
15. Von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617-28.
16. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomized, open-label, Phase III trial. *Lancet.* 2023;401(10371):105-17.
17. Nicolò E, Boscolo Bielo L, Curigliano G, Tarantino P. The HER2-low revolution in breast oncology: Steps forward and emerging challenges. *Ther Adv Med Oncol.* 2023;15:17588359231152842.
18. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387:9-20.
19. Shi D, Liang X, Li Y, Chen L. Cost-effectiveness of trastuzumab deruxtecan for previously treated HER2-low advanced breast cancer. *PLoS One.* 2023;18(8):e0290507.

2024 FALL MANAGED CARE FORUM

November 7–8 | Caesars Palace | Las Vegas

MEDICAL DIRECTORS, PHYSICIANS, NURSES, ADMINISTRATORS, and OTHER HEALTHCARE PROFESSIONALS

POPULATION HEALTH MANAGEMENT, BUSINESS, ONCOLOGY and GENOMICS,
BIOTECH and EMERGING MEDICAL TECHNOLOGIES TRACKS

PRESENTED BY: NAMCP — WHERE MEDICAL DIRECTORS TRANSFORM KNOWLEDGE INTO IMPROVED OUTCOMES — www.namcp.org

AAIHDS

AAMCN — American Association of Managed Care Nurses

CME/NCPD CREDITS AVAILABLE

Contact Jeremy Williams at jwilliams@namcp.org for more information.

Dexcom G7

better diabetes outcomes start at hospital discharge

Dexcom G7 is clinically proven to improve glycemic outcomes[1-5]

- >1% A1C reduction after 12 weeks[1,2,5]
- >1 hour increase in time in range for T1D and T2D after 12 weeks[1,2]
- Features to reduce rebound hyper- and hypoglycemia[6-8]

Patients using Dexcom CGM resulted in:

35%
(~$358 PPPM)
reduced diabetes-related inpatient admission costs[9]

~50%
reduced diabetes-related inpatient visits[10]

Smart devices sold separately. For a list of compatible devices, visit dexcom.com/compatibility.

To learn more about the Dexcom hospital discharge program, scan the QR code

PPPM = per patient per month; T1D = type 1 diabetes; T2D = type 2 diabetes.

BRIEF SAFETY STATEMENT: Failure to use the Dexcom G7 Continuous Glucose Monitoring System (G7) and its components according to the instructions for use provided with your device and available at https://www.dexcom.com/safety-information and to properly consider all indications, contraindications, warnings, precautions, and cautions in those instructions for use may result in you missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury. If your glucose alerts and readings from the G7 do not match symptoms, use a blood glucose meter to make diabetes treatment decisions. Seek medical advice and attention when appropriate, including for any medical emergency.

1 Beck RW, et al. *JAMA*. 2017;317(4):371-378. 2 Beck RW, et al. *Ann Intern Med*. 2017;167(6):365-374. 3 Martens T, et al. *JAMA*. 2021;325(22):2262-2272. 4 Laffel LM, et al. *JAMA*. 2020;323(23):2388-2396. 5 Welsh JB, et al. *J Diabetes Sci Technol*. 2024;18(1):143-147. 6 Dexcom G7 User Guide, 2023. 7 Acciaroli G, et al. *J Diabetes Sci Technol*. 2022;16(3):677-682. 8 Wilmot E. Dexcom G7: Unique Features and Correlational Improvements in Glycemic Control. Presented at the 16th International ATTD Conference on February 23, 2023. 9 Norman GJ, et al. *Diabetes Technol Ther*. 2022;24(7):520-524. 10 Hannah K, et al. *Diabetes*. 2023;72(Suppl 1):991-P.

Dexcom