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Innovative Approaches in Treatment and Management of Advanced Colorectal Cancer

Overcoming Barriers to the Optimal Management of Acute Myeloid Leukemia

New Horizons in Acute Pain Relief: A Close Look at the Role of New and Emerging Non-Opioid Therapies

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Innovative Approaches in Treatment and Management of Advanced Colorectal Cancer

Richard Kim, MD

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Summary

The treatment of advanced colorectal cancer has dramatically changed with the identification of multiple genetic mutations which drive the cancer and markers for identifying tumors which will respond to checkpoint inhibitor immunotherapy. Next generation sequencing is required for all patients with advanced disease to identify the best treatment.

Key Points

- Next generation sequencing should be done on every patient with metastatic CRC.
- Available FDA-approved regimens include checkpoint inhibitor immunotherapy for those with dMMR/MSI-H/POLE/POLD1, BRAF inhibitor plus anti-EGFR plus chemotherapy for BRAF V600E, triple regimens for HER2 positive disease, anti-KRAS plus anti-EGFR for KRAS G12C, and several agents for gene fusion mutations.
- In the refractory setting with no actionable mutations, oral oncolytic options include trifluridine/tipiracil plus bevacizumab, regorafenib, or fruquintinib.

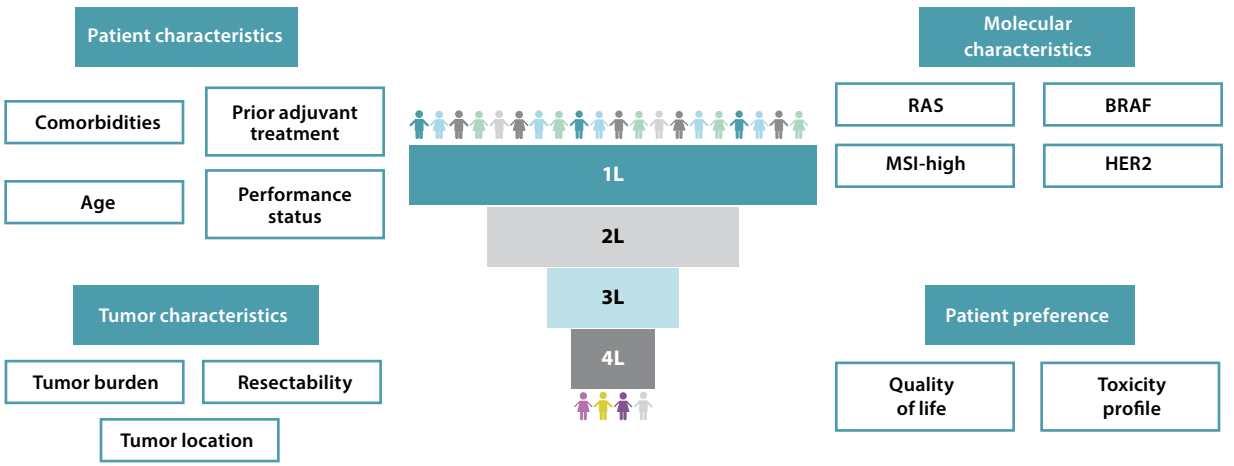
COLORECTAL CANCER (CRC) IS THE THIRD most diagnosed cancer in men and second most in women in the United States (U.S.). CRC is the second most common cause of cancer death. In 2025, 154,270 people will be diagnosed and 52,900 will die from CRC in the U.S.[1] About 60 percent of cases are already advanced (regional/distant stage) at diagnosis. Five-year survival rates drop from approximately 90 percent with localized disease to approximately 15 percent with metastatic disease.

Late-stage diagnosis, certain genetic/molecular alterations, comorbidities, and limits in healthcare access are all factors contributing to poor prognosis in CRC. Limited screening in underserved race/ethnicity and socioeconomic groups leads to advanced presentation.[2] KRAS and BRAF mutations confer more aggressive tumor behavior and resistance to certain therapies. Older patients with comorbidities tolerate treatment poorly and thus have worse outcomes.[3] Barriers to timely care such as lack of insurance or a rural setting can lead to limited screening and delayed therapy.

Metastatic CRC (mCRC) causes significant clinical and personal burden. There are high rates of inpatient admissions for metastatic disease (approximately 80% of patients). Bowel obstruction and liver metastases are two causes of significant morbidity.

Economic costs of treating mCRC are high. Key contributors to the inflated costs are advanced therapies, multiple lines of treatment, and end-of-life/palliative care. Targeted agents and immunotherapies are costly medications. In one trial, medical and prescription charges for patients with mCRC ($353,255 and $5,745) were nearly double those for non-mCRC ($182,000 and $2,406), as were out-of-pocket expenses ($4,032 versus $2,144 for medical; $319 versus $188 for prescriptions).[4] Many patients with mCRC undergo second, third, and even more lines of therapy leading to cumulative

Exhibit 1: What Influences Treatment Choices in mCRC?[5]



expense. Each line of therapy also has costs for ongoing supportive care such as managing toxicities and monitoring. Intensive hospital use can occur in the final weeks of life if palliative care is delayed. Earlier hospice enrollment has the potential for cost savings and quality of life benefits.

In terms of treatment, various patient, tumor, molecular characteristic factor and patient preference affect treatment selection (Exhibit 1).[5] Considering all these influences results in therapy tailored according to individual patient needs. The National Comprehensive Cancer Network (NCCN) Guidelines recommend treatment based on molecular testing for mismatch DNA repair proficiency (pMMR) or deficiency (dMMR), high microsatellite instability (MSI-H) DNA polymerase epsilon (POLE)/DNA polymerase beta (POLD1) mutations, and KRAS, BRAF mutations, and other less common mutations.[6] All patients with mCRC should be tested for these biomarkers at diagnosis.

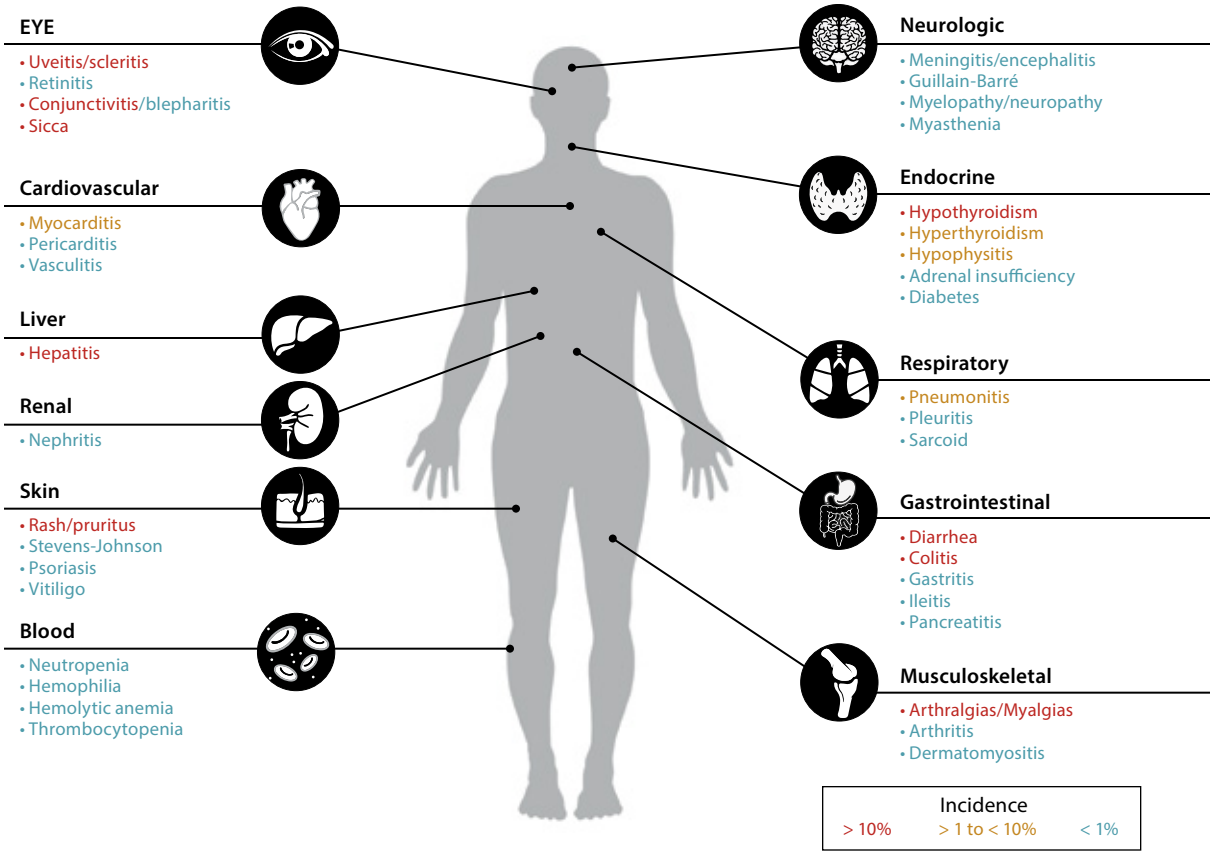
Tumors with dMMR, MSI-H, or POLE/POLD1 mutations correspond with a hypermutated phenotype that is highly sensitive to checkpoint inhibitor immunotherapy. dMMR is found in about 15 percent of all CRC, including 3 to 5 percent of mCRC. Somatic POLE mutations are found in approximately 2 to 8 percent of patients with CRC (mostly in pMMR disease). POLD1 mutations are very rare and mostly occur in dMMR/MSI-H CRC.

In patients with dMMR/MSI-H/POLE/POLD1 mCRC, checkpoint inhibitor immunotherapy is recommended as first-line therapy, if the patient is eligible for immunotherapy based on comorbidities and has not received prior immunotherapy in the non-metastatic setting.[6] Nivolumab in combination with ipilimumab, pembrolizumab, and dostarlimab are the FDA-approved and NCCN included options.[6-9] The options improve progression-free survival (PFS) and overall survival (OS) with less toxicity than chemotherapy.

Checkpoint inhibitor immunotherapy use is associated with a spectrum of adverse events related to a mechanism of action that is quite different from other systemic therapies. By unbalancing the immune system, immunotherapies cause dysimmune toxicities—immune-related adverse events (irAEs) that involve the gut, skin, endocrine glands, liver, and lung, but can potentially affect any tissue (Exhibit 2). Adverse events/toxicities from checkpoint inhibitors are not only caused by a different mechanism but are treated differently than chemotherapy-related adverse events.

There is currently no way to predict who will develop irAEs. Onset of irAEs is typically two to three months after starting the medication, but they can arise as long as two years after therapy is discontinued. Patients have to be educated to contact the oncology team if any symptoms develop, if they are admitted to hospital, or if they begin any new medications. Clinicians have to maintain an elevated level of suspicion for irAEs when new symptoms develop. Immunotherapy treatment can usually be continued in the presence of mild irAEs with close monitoring. However, moderate-to-severe irAEs may be associated with severe declines in organ function and quality of life, with fatal outcomes being reported. In addition to holding or discontinuing therapy, corticosteroids in escalating

Exhibit 2: Spectrum of Immune Related Adverse Events



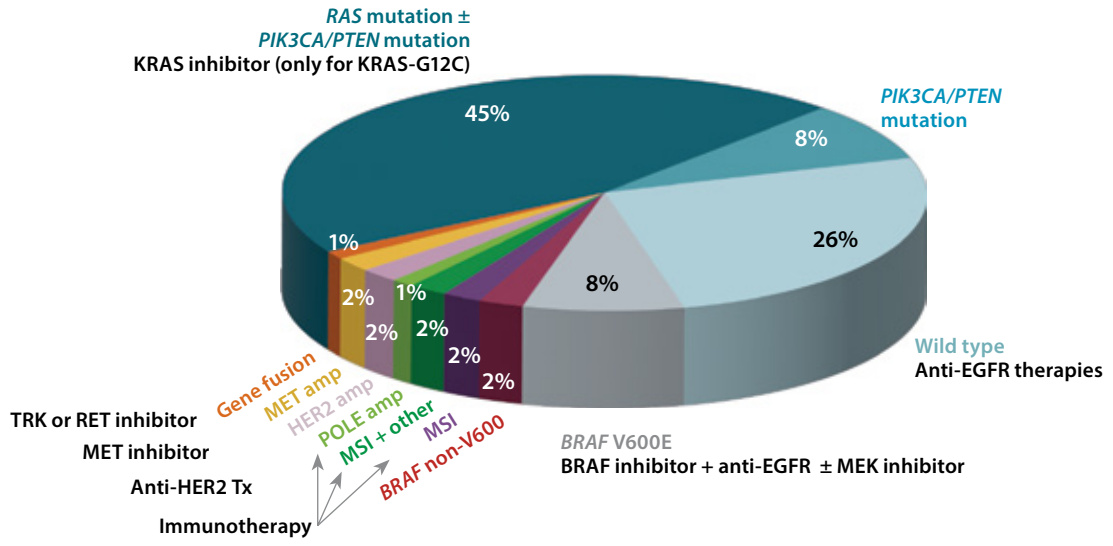
doses are used to manage moderate-to-severe irAEs. Prolonged corticosteroid tapers help prevent flare-ups or relapses of immune toxicity.

A multidisciplinary approach is required to manage checkpoint immunotherapy and irAEs to optimize patient outcomes. In addition to education about irAEs, clinicians need to address patient goals and expectations of treatment on overall prognosis.

Various cancer driving genetic mutations are found in mCRC and many of these have FDA-approved targeted therapies (Exhibit 3).[10,11] BRAF mutation occurs in about 8 percent of cases and has poor prognosis with median survival of approximately one year without targeted treatment.[12] The V600E mutation is found in about 90 percent of tumors with a BRAF alteration. Encorafenib, a BRAF V600E inhibitor, is used in those with this mutation in combination with an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab) with or without standard chemotherapy (FOLFOX). Encorafenib plus cetuximab plus FOLFOX is the first line, NCCN preferred for BRAF V600E mutant mCRC based on longer PFS (median, 12.8 versus 7.1 months; hazard ratio for progression or death, 0.53; $p < 0.001$) and OS (median, 30.3 versus 15.1 months; hazard ratio for death, 0.49; $p < 0.001$) compared to standard care.[13]

Human epidermal growth factor receptor two (HER2) overexpression occurs in 2 to 6 percent of mCRC cases. It strongly correlates with a lack of RAS and BRAF mutations, occurs mostly in left-sided colon cancer, and may confer resistance to anti-EGFR therapies.[14] In mCRC, HER2 targeted approaches for second line or later are combinations of anti-HER2 agents (trastuzumab plus lapatinib or pertuzumab or tucatinib) or the antibody drug conjugate fam-trastuzumab deruxtecan. In a small Phase II study, trastuzumab plus tucatinib produced an overall response rate of 38 percent and a median duration of response of 12.4 months.[15] Similar response rates are seen with pertuzumab (32%) and lapatinib (30%).[16,17] Fam-trastuzumab deruxtecan

Exhibit 3: Molecular Classification of CRC and Associated Targeted Therapies[10,11]



has an indication for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. In a multicenter, open-label, Phase II trial assessing the efficacy and safety of this agent in patients with HER2-expressing mCRC that progressed after two or more prior regimens, median PFS, OS, and duration of response were 6.9, 15.5, and 7.0 months, respectively in the IHC3+ group.[16] The patients in this trial had received a median of four prior regimens. All these options for HER2+ mCRC have only been studied in small trials in heavily pretreated patients.[16-18]

KRAS G12C mutations only occur in 1 to 3 percent of those with mCRC. A glycine to cysteine substitution locks the KRAS protein in its active state, preventing its normal off signal, and causing continuous activation of growth pathways leading to uncontrolled cell proliferation, survival, and tumor growth. Treatment options for second line or later for KRAS G12C mCRC are dual anti-EGFR and KRAS G12C inhibition for synergistic antitumor activity and reduced resistance. Adagrasib and sotorasib are the two oral small-molecule inhibitors of mutant KRAS G12C protein. Cetuximab and panitumumab are the anti-EGFR agents which have been studied in combination with anti-KRAS G12C agents. Similar to HER2+ agents, these therapies have been studied in small trials in heavily pretreated patients.[19,20] The KRAS G12C inhibitors have accelerated FDA approval which is conditional.

Less than 1 percent of mCRCs harbor actionable fusion genes but these are characterized by poor prognosis on standard therapy. Larotrectinib targets NTRK fusions; repotrectinib targets NTRK and ROS1 fusions; entrectinib, targets NTRK, ALK and ROS1 fusions; and selpercatinib is available for RET fusions. The NCCN Guidelines include each of these for second-line treatment or later mCRC treatment.[6]

For mCRC that has progressed through all the other available options, oral oncolytic options include trifluridine/tipiracil with or without intravenous bevacizumab, regorafenib, or fruquintinib. The combination of trifluridine/tipiracil works by delivering trifluridine into cancer cell DNA, disrupting cell replication through DNA damage, while tipiracil prevents trifluridine rapid breakdown and boosting its effectiveness as an antimetabolite by inhibiting thymidine phosphorylase. Trifluridine/tipiracil with bevacizumab improves response compared to trifluridine/tipiracil alone and the NCCN Guidelines recommend the addition of bevacizumab.[6,21]

Regorafenib is a multi-kinase inhibitor that blocks several proteins crucial for cancer growth, working by targeting tumor cells and their environment to inhibit proliferation, angiogenesis, and metastasis. It hits vascular endothelial growth factor receptors (VEGFRs), stromal receptors (PDGFR, FGFR), and oncogenic kinases (KIT, RET, BRAF). Regorafenib confers an OS benefit in patients with refractory mCRC; however, its adverse event profile has limited its use. Slowly escalating the dose is one way to

improve tolerance. [22]

Fruquintinib, a highly selective and potent oral inhibitor of VEGFR 1, 2, and 3, has been studied against placebo in patients with heavily pretreated mCRC in a randomized, double blind, Phase III trial.[23] The included subjects had received all current standard approved cytotoxic and targeted therapies and progressed on or were intolerant to trifluridine-tipiracil or regorafenib, or both. Median OS was 7.4 months in the fruquintinib group versus 4.8 months in the placebo group (hazard ratio 0.66, $p < 0{\cdot}0001$). Grade 3 or worse adverse events occurred in 286 (63%) of 456 patients who received fruquintinib and 116 (50%) of 230 who received placebo; the most common Grade 3 or worse adverse events in the fruquintinib group included hypertension (14%), asthenia (8%), and hand-foot syndrome (6%). There was one treatment-related death in each group (intestinal perforation in the fruquintinib group and cardiac arrest in the placebo group).

Conclusion

Next generation sequencing should be done on every patient with mCRC. Currently there are several available targets with FDA-approved regimens including checkpoint inhibitor immunotherapy for those with dMMR/MSI-H/POLE/POLD1, BRAF inhibitor plus anti-EGFR plus chemotherapy for BRAF V600E, triple regimens for HER2 positive disease, anti-KRAS and anti-EGFR for KRAS G12C, and several agents for gene fusion mutations. In the refractory setting with no actionable mutations, oral oncolytic options include trifluridine/tipiracil plus bevacizumab, regorafenib, or fruquintinib.

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Overcoming Barriers to the Optimal Management of Acute Myeloid Leukemia

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Summary

AML is the most common acute leukemia affecting adults. Numerous treatments with improved efficacy and safety have become available in the past several years. With so many new options available, and more to come, the treatment paradigm in AML has drastically changed and continues to evolve.

Key Points

- New therapies for AML are improving outcomes.
- AML care, especially for older adults, has shifted toward the outpatient setting with oral regimens.
- Unique toxicity profiles of these potent medications and high acuity of AML patients require resources and excellent communication for optimal management in the community.
- The excessive cost of oral AML medications is a major cost-containment challenge.

ACUTE MYELOID LEUKEMIA (AML) IS THE most common form of acute leukemia in adults with an estimated 22,010 cases in the United States (U.S.) in 2025 but is rare overall, accounting for only about 1 percent of all cancers.[1] The median age at diagnosis is 69 years. Despite significant advances in understanding AML and numerous treatment options, the five-year relative survival is only 32.5 percent. Over the last decade, the median survival of those over 65 years of age has been measured in months rather than years.

Numerous cytogenetic abnormalities and molecular mutations are associated with AML which aid in prognostication and risk stratification of the disease.[2] Based on the highly heterogeneous nature of the disease and cytogenetic profile, patients with AML can be stratified into favorable, intermediate, and adverse-risk groups (Exhibit 1).[3] Favorable-risk AML is more responsive to traditional chemotherapy and is often curable. Adverse-risk AML can often be put into remission but often recurs. Bone marrow transplant is a potential curative treatment for adverse-risk disease.

Traditionally, the approach to treating AML was to treat those who were in better physical shape with intensive induction chemotherapy followed at remission by additional chemotherapy or allogenic stem cell transplant. Those who could not tolerate nor want this regimen were given supportive care. The intensive curative intent regimens with or without a stem cell transplant remain the most effective options for those who can tolerate such therapy. The major changes in AML treatment have occurred for those who are unable to tolerate intensive therapy. Treatment today is selected based on patient and disease characteristics and a comprehensive genomic profile (Exhibit 2). The treatment regimen for those who are fit remains intensive chemotherapy possibly with targeted therapies; for those unfit, oral regimens containing venetoclax and a hypomethylating agent or targeted agents are primarily chosen. Therapy is beginning to move into triple and quadruple regimens to better attack the disease in those who are both fit and unfit.

Several oral therapies have changed the AML treatment landscape for those who are unable or

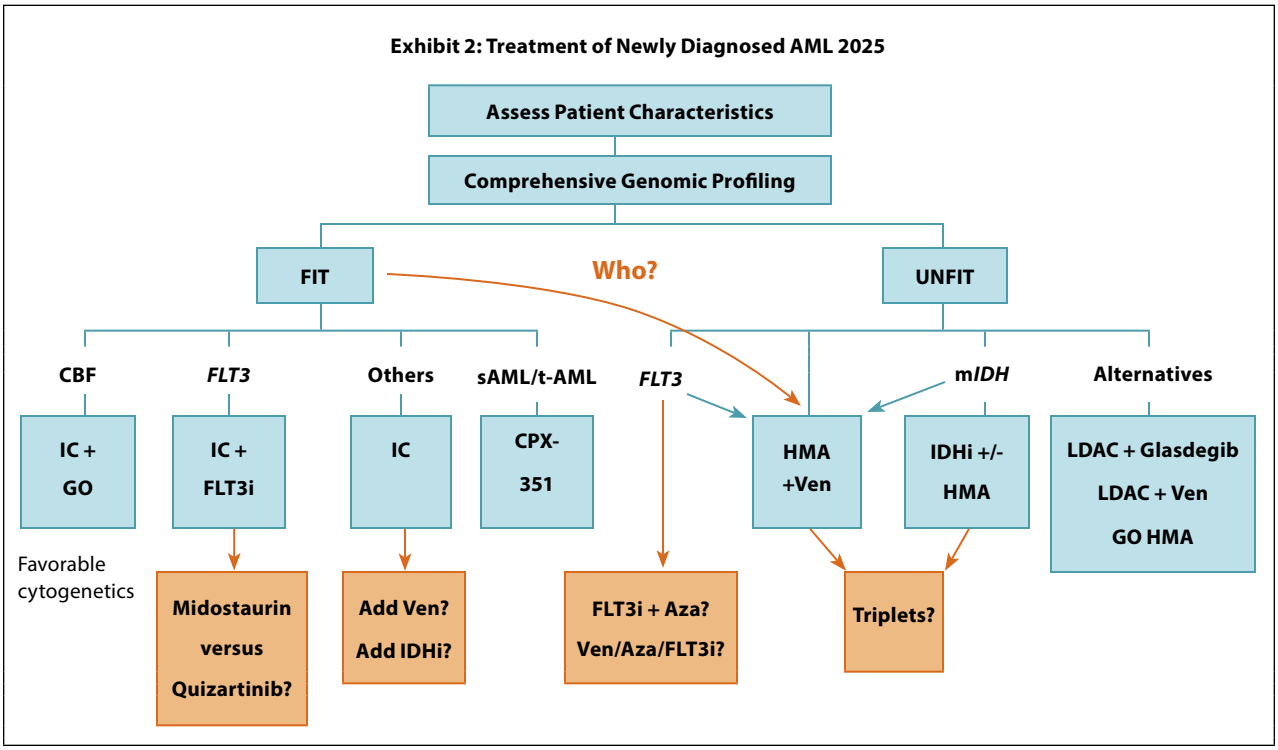
Exhibit 1: European LeukemiaNet Cytogenetic-Molecular Classification of AML[3]

Risk Category	Cytogenetic Abnormality
Favorable prognosis	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mutated NPM1 without *FLT3-ITD* • bZIP in-frame mutated *CEBPA*
Intermediate prognosis	• t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Wild-type *NPM1 with FLT3-ITD* (without adverse-risk genetic lesions) • Mutated *NPM1 with FLT3-ITD* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse prognosis	• t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • –5 or del(5q); –7; –17/*abn(17p)* • Complex karyotype and monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2* • Mutated *TP53*

unwilling to receive chemotherapy-based treatment and for those with specific mutations. Eleven oral therapies have been approved since 2017, with one of these (ziftomenib) being approved in late 2025. Agents are available targeting common mutations such as FMS-like tyrosine kinase 3 (FLT3) mutation and isocitrate dehydrogenase 1 (IDH1) mutation. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation. FLT3 ITD mutations occur in 20 to 25 percent of AML cases and result in poor prognosis and high rates of relapse after treatment while FLT3 TKD mutations occur in 5 to 10 percent of cases.[4] Midostaurin was the first FLT3 inhibitor shown in improve survival in FLT3+ AML.[5] Quizartinib, a second generation FLT3 inhibitor that is more potent and more selective, is indicated for first-line treatment of FLT3 ITD positive AML. This agent and midostaurin improve overall survival (OS) in first-line treatment of FLT3 ITD positive AML.[5,6] Median OS with quizartinib for three years after the end of chemotherapy was 31.9 months versus 15.1 months for placebo (hazard ratio 0.78, $p = 0 \cdot 032$).[6] The presence of an FLT3 mutation is an indication for incorporation of FLT3 inhibitors with induction and consolidation chemotherapy in fit patients and followed by the FLT3 inhibitor maintenance.

One question is whether to choose midostaurin or quizartinib. The hazard ratios in the clinical trials with these two agents were very similar (0.77 and 0.776) but no head-to-head trials are available. A matching adjusted indirect comparison (MAIC) using data from the clinical trials did not find statistically significant complete response (CR) and OS differences, however, the MAIC did reveal that quizartinib generated a significantly reduced risk of relapse which suggests a deeper and longer duration of CR.[7] Midostaurin does have an advantage of being effective against the FLT3 TKD mutation that quizartinib does not.

A recently published study of quizartinib in combination with standard induction and consolidation chemotherapy in patients with newly diagnosed FLT3-ITD-negative AML showed that this agent improved OS. Median OS was not reached at 29.3 months in the quizartinib and placebo arms, respectively ($p = .012$); three-year OS rates were 60.8 percent and 45.7 percent.[8] Quizartinib has high binding affinity to ITD and wild-type (WT) FLT3 which is why it would be effective in FLT3 ITD-



CBF = core binding factor; IC = intensive chemotherapy; GO = gemtuzumab ozogamicin; FLT3i = FLT3 inhibitor;
sAML/t-AML = secondary or treatment related AML; HMA = hypomethylating agent- azacitidine or decitabine; AZA = azacitidine;
Ven = venetoclax; LDAC = Low-Dose Cytarabine
Red highlighted items are changing areas of practice

negative AML. It is currently being studied head-to-head against chemotherapy for newly diagnosed FLT3 ITD-negative AML.

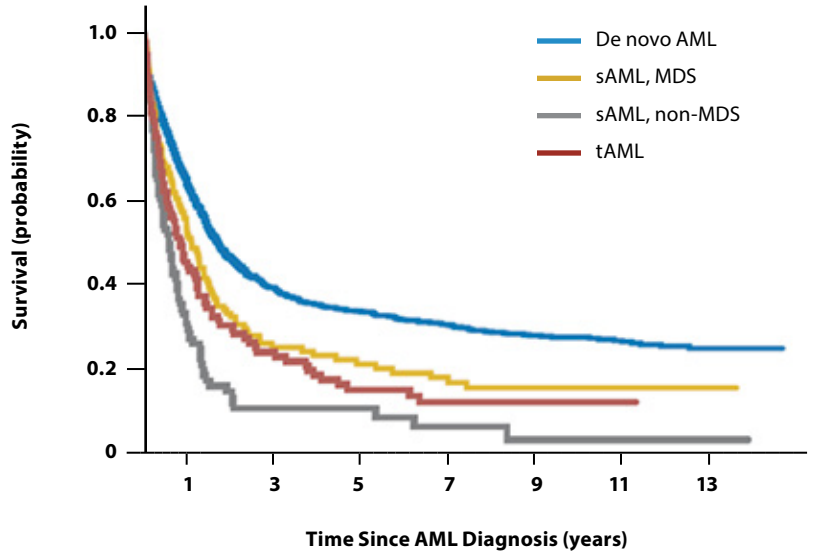
Gilteritinib is another FLT3 inhibitor effective against ITD and TKD mutations which is only approved for relapsed/refractory (R/R) AML. It does improve OS in the R/R setting compared to salvage chemotherapy (9.3 versus 5.6 months).[9] It has also been studied as post-transplant maintenance for FLT3 ITD+ AML.[10] Although relapse-free survival (RFS) was higher in the gilteritinib arm, the difference was not statistically significant (hazard ratio [HR] 0.679, two-sided p = .0518). However, 50.5 percent of participants had measurable residual disease (MRD) positivity pre- or post-transplant; gilteritinib was beneficial in this population (HR 0.515, p = .0065). Those MRD negative showed no benefit from gilteritinib maintenance (HR 1.213, p = .575). Because of the risk of recurrence, gilteritinib is often given as maintenance in the MRD positive post-transplant population.

Triplet therapy is also being explored in FLT3+ AML. Azacitidine, venetoclax, and gilteritinib were studied in a Phase I single-arm trial which showed 65 percent of evaluable patients achieved FLT3-ITD MRD negativity within four cycles. With a median follow-up of 19.3 months, the median RFS and OS have not been reached and the 18-month RFS and OS rates are 71 percent and 72 percent, respectively.[11] Phase II trials of this triplet regimen are ongoing.

Approximately 8 percent of patients with AML have an IDH1 mutation and 12 percent have an IDH2 mutation.[12] IDH is an enzyme in the citric acid cycle. Mutant IDH1 or IDH2 produces 2-hydroxyglutarate, an oncometabolite, which alters DNA methylation and leads to a block in cellular differentiation. Olutasidenib is the newest IDH1 inhibitor, joining ivosidenib. Olutasidenib is currently FDA-approved for IDH1+ R/R AML, whereas ivosidenib is approved for newly diagnosed or R/R IDH1+ AML. Ivosidenib in combination with azacitidine in newly diagnosed IDH1 mutated AML improved median OS significantly over azacitidine alone (24.0 versus 7.9 months) in older patients who were not fit enough for even low-intensity chemotherapy.[13] Enasidenib is FDA-approved for IDH2+ R/R AML.

The newest oral-targeted therapy in AML is menin inhibitors. Menin is a critical oncogenic cofactor in leukemias driven by lysine methyltransferase 2A gene (KMT2A) rearrangements and nucleophosmin

Exhibit 3: Prognosis of Secondary AML[18]



No. at risk					
De novo	799	413	293	207	140
sAML, MDS	71	27	20	14	12
sAML, non-MDS	26	7	6	3	1
tAML	46	22	12	8	4

sAML = secondary acute myeloid leukemia; MDS = myelodysplastic syndromes; tAML = treatment related

1 (NPM1) mutations. Revumenib is FDA-approved for R/R AML with a KMT2A translocation in adult and pediatric patients aged one year and older. It works by disrupting the interaction between menin and KMT2A proteins, which prompts leukemia cells to differentiate into normal cells. In adult AML patients, KMT2A gene rearrangements are found in 3 percent of *de novo* AML and in 10 percent of therapy-related AML cases.[14] The prevalence is much higher in acute leukemias found in infants. Ziftomenib, FDA-approved in November 2025, is approved for R/R AML with a susceptible NPM1 mutation. NPM1-mutated AML is common and found in 30 percent to 35 percent of adult AML cases, making it the most common genetic abnormality in adult AML.[15] This mutation is less frequent in childhood AML, accounting for only about 2 to 8 percent of cases. Several other menin inhibitors are in development.

One of the most used oral agents in patients who are unfit for chemotherapy is venetoclax. Venetoclax promotes apoptosis by selectively inhibiting B-cell lymphoma two (BCL-2). In AML, overexpression of BCL-2 enables cancer cells to evade apoptosis via sequestering proapoptotic proteins. Venetoclax selectively binds to BCL-2, thereby freeing proapoptotic proteins to initiate apoptosis. In combination with azacitidine, a hypomethylating agent used alone in the past, venetoclax significantly improves OS in first-line treatment of AML in patients not eligible for intensive chemotherapy.[16] This combination has become the standard of care first-line agent for many patients with newly diagnosed AML.

There are several issues with venetoclax use in AML. There is limited efficacy in p53 mutant AML. Efficacy in patients who develop AML but were treated with a hypomethylating agent for an antecedent hematological disorder is unclear. Lastly, venetoclax is a highly myelosuppressive medication administered in an outpatient setting which can lead to many adverse events.

In addition to myelosuppressive issues with venetoclax and other agents, the other newer therapies for AML have some unique adverse events of which clinicians, encountering patients with AML in the community, need to be aware. For example, IDH inhibitors and menin inhibitors can cause differentiation syndrome (DS) which is a serious potentially fatal adverse event. These therapies can produce drug-induced differentiation of leukemic cells. Proliferation of differentiated

leukemic cells can alter cytokine balance, leading to tissue damage and inflammation. Signs and symptoms of DS include unexplained fever, dyspnea, pleural or pericardial effusions, pulmonary infiltrates, hypoxia, and acute kidney injury. DS occurs in 10 to 15 percent of patients treated with an IDH inhibitor and 32 percent of those treated with revumenib. The median time to DS is 30 days after starting therapy but can be much longer. Treatment is corticosteroids, supportive care, and holding the IDH inhibitor. Another example of a unique adverse event is QT prolongation syndrome with revumenib. Other usual adverse events of cancer treatment such as nausea, vomiting, thrombocytopenia, and neutropenia also commonly occur. Patients and clinicians need to understand the potential adverse events of these potent oral cancer treatments and how to manage them in the community.

Another area where treatment option improvements have occurred is with secondary AML. Secondary AML can develop from myelodysplastic syndrome (MDS), prior treatment of AML (tAML), or myeloproliferative neoplasms (MPNs). Numerous mutations are commonly seen in secondary AML.[17] Secondary AML has a worse prognosis than *de novo* AML (Exhibit 3).[18]

Liposome-encapsulated cytarabine/daunorubicin is a treatment option for secondary AML which was FDA-approved in 2017. It was designed to provide optimal delivery of a specific ratio of cytarabine to daunorubicin (5:1), that has been shown to be synergistic *in vitro*. Compared to standard non-liposomal versions of the same two chemotherapies, the liposomal version produced significantly longer median OS, better remission rates, and improved opportunity for stem cell transplant in newly diagnosed secondary AML in those aged 60 to 75 years who were fit for chemotherapy.[19] Median OS was 9.56 months with the liposomal compound and 5.95 months with the standard chemotherapy. A real-world outcome study supported the benefits of liposome-encapsulated cytarabine/daunorubicin. With a median follow-up of three years, the median OS was 13.3 months in those treated with this therapy for secondary AML. The median OS was 20.4 months versus 12.9 months for patients with MRD negative or positive at the end of therapy, respectively (p = .006).[20] In a multivariate analysis, MRD positive was associated with a poorer OS (HR 2.6, p = .013). There was a trend toward a better median OS in patients who underwent hematopoietic stem cell transplantation with MRD negative (not reached versus 26.0 months; p = .06). Achievement of MRD negativity contributed to the improvement of OS in the overall population and, maybe, in patients receiving transplants. Numerous studies with this therapy are ongoing, including treating newly diagnosed adverse cytogenetic AML, high-risk MDS, secondary AML, and in combination with other agents.

Clinicians are always considering what is the best therapy for a given patient. A real-world study compared outcomes with liposome-encapsulated cytarabine/daunorubicin and venetoclax/azacitidine in patients with newly diagnosed AML who were considered fit enough for chemotherapy (i.e., they met the inclusion criteria used in the liposome-encapsulated therapy studies).[21] This retrospective medical records study included 217 patients who received chemotherapy and 439 who received venetoclax/azacitidine. Patients receiving oral therapy were older, more likely to be treated in the community, and more likely to have a diagnosis of *de novo* AML. Other baseline covariates were not statistically significantly different between the groups. Median OS for all patients was 12 months and did not differ statistically based on therapy (13 months for chemotherapy versus 11 months for venetoclax/azacitidine; HR, 0.88, p = .22). OS was similar across multiple sensitivity analyses. In terms of safety, early mortality was similar (10% versus 13% at 60 days). However, documented infections were higher with chemotherapy as were rates of febrile neutropenia. Hospital length of stay, including any admission before the next cycle of therapy, was more than twice as long for chemotherapy. Prospective randomized studies with careful attention to side events, quality of life, and impact on transplant outcomes are needed in these populations to determine the best treatment option.

The new oral agents approved since 2017 have led to a paradigm shift from a binary choice of intense chemotherapy or supportive care to various options including intense chemotherapy with or without targeted agents, oral but potent therapies for those who only received supportive care in the past, and options for R/R disease and secondary AML. Much of AML care has shifted from hospitals to the home with the introduction of so many oral agents.

Challenges in this transition to primarily outpatient care are numerous. These include long travel distances to the primary treatment center for patients, education of community-based oncologists in the management of less familiar diseases, the need for frequent visits to community oncologists, and resource strains (e.g., blood products). Transportation costs for patient/families, communication with tertiary specialists, and accessibility of medical records between primary treating centers and community-based providers

are all substantial issues to overcome. There are questions whether these challenges affect overall efficacy of the treatment regimens and negatively impact any potential cost savings.

The cost of care for traditionally chemotherapy treated AML patients is driven by inpatient costs.[22] Innovations such as liposomal cytarabine/daunorubicin, although more expensive than either agent alone, may improve cost effectiveness through improved efficacy or reduced adverse events. A budget impact analysis for a hypothetical one-million-member health plan, where 15.1 members would receive intensive induction for newly diagnosed secondary AML annually, found that induction treatment with liposomal cytarabine/daunorubicin instead of a non-liposomal regimen would have a limited economic impact on the budget of commercial health plans and may result in cost offsets, particularly in patients who respond to therapy.[23]

Even without chemotherapy, treatment of AML can be costly. One study from 2018 found the average cost for care of an older AML patient was $25,000 per month, this was when monthly medication costs were $450, and this amount has increased significantly since then.[24] Assuming an average 10-month life expectancy for AML patients over 60 years of age, who are the primary group for lower intensity therapy, this equates to a cost of $250,000 for AML care over the average life of a patient or an estimated $4.8 billion for all the older AML patients in the U.S.

The new oral medications are now the primary cost driver of AML care where annual costs can be almost $200,000. A few cost-effectiveness studies of the new therapies have been published. An analysis of midostaurin plus standard chemotherapy compared to chemotherapy alone in the treatment of newly diagnosed FLT3-mutated AML found midostaurin to be a cost-effective addition, from a U.S. third-party payer perspective.[25] In another analysis, venetoclax/azacitidine was compared to azacitidine alone for use in older, unfit people for first-line treatment from a U.S. third party perspective.[26] Over a lifetime horizon, venetoclax/azacitidine versus azacitidine led to gains of 1.89 life years (LYs, 2.99 versus 1.10, respectively) and 1.45 quality adjusted life years (QALYs, 2.30 versus 0.84, respectively). Patients receiving venetoclax/azacitidine incurred higher total lifetime costs ($250,486 versus $110,034). The combination was cost effective with incremental cost-effectiveness ratios (ICERs) for venetoclax + azacitidine versus azacitidine at $74,141 per LY and $96,579 per QALY gained. Also gilteritinib compared to chemotherapy for R/R FLT3 mutated AML was found to be cost effective.[27] Ivosidenib in combination with azacitidine for newly diagnosed, older or intensive chemotherapy-ineligible patients with *IDH1*-mutated AML, was found not to be cost effective at current prices (ICER $252,782/QALY).[28] Although CPX-351 has demonstrated superior efficacy and an acceptable safety profile in randomized Phase III clinical trials compared with conventional chemotherapy, it was shown unlikely to be cost-effective for most older patients with acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) or therapy-related AML (t-AML) under current pricing.[29]

In addition to the high acquisition costs of the medications, there are other barriers to cost savings in AML with the newer medications. Outpatient therapies are still complex and potent, which could lead to a higher risk of adverse events and hospitalization amongst patients cared for by less experienced clinicians. AML remains a disease with very limited curative potential, but this is changing. As people live longer with the disease, they will accumulate financial toxicity from their therapies. Extremely high medication prices make it mandatory to manage patients appropriately such that any savings are not offset by increased hospitalization rates. Few treatment strategies currently employ discontinuation of oral or maintenance therapies. These therapies continue until disease progression. There are questions whether adoption of "new" new generation drugs over "old" new generation drugs mitigate cost benefits (e.g., quizartinib over midostaurin). In addition, studies are needed on patient financial burden of the newer medications and the impact on therapeutic outcomes.

Conclusion

Multiple new therapies for AML are improving outcomes and have shifted care toward the outpatient setting, especially for older adults. Unique toxicity profiles for many of the new medications, along with high acuity of AML patients, require resources and excellent communication for optimal management in the community. The excessive cost of outpatient AML medications, especially as outcomes improve and patients live longer, provides a major challenge to cost containment. Patient financial burden of new oral AML medications and effects on outcomes should be the focus of future research. Modeling costs for limited time, more intensive therapy and long-term chronic therapy need to be compared.

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New Horizons in Acute Pain Relief: A Close Look at the Role of New and Emerging Non-Opioid Therapies

Jeffrey Gudin, MD

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

Summary

Initiating therapies that address the underlying pathophysiology of pain can lead to improved pain control and avoid risks associated with conventional therapies, such as opioid addiction. Emerging therapies for pain management focus on novel targets within the pain signaling pathways to provide effective pain relief with fewer adverse events, but these multimodal, non-opioid therapies are often underused or not yet FDA-approved.

Key Points

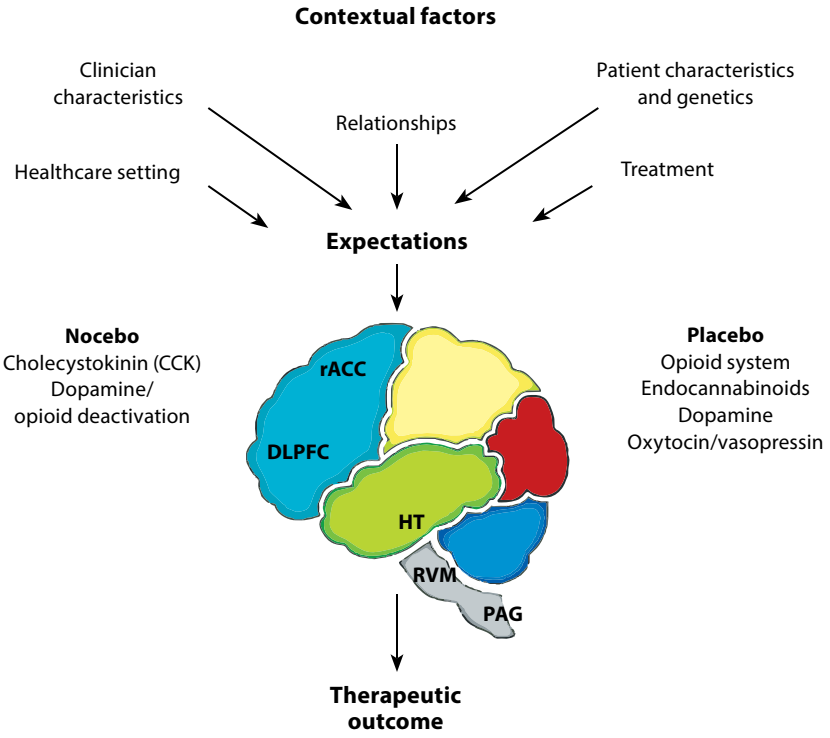
- Efforts to identify safe and effective analgesics continue.
- Opioids remain an important option for the treatment of severe pain.
- One novel analgesic has been approved.
- Novel analgesics should change the landscape and improve safety and tolerability of analgesics.
- Multimodal medications complemented by nonpharmacological therapies should be used to manage acute pain adequately and prevent chronic pain.

THERE IS A SIGNIFICANT DIFFERENCE between acute and chronic pain. They are differentiated temporally with fundamentally different underlying mechanisms. Acute pain occurs when noxious stimuli, such as an injury or surgery perceived by the peripheral nervous system are transmitted proximally and modulated by the central nervous system (CNS). Patients with acute pain can have elevated blood pressure and heart rate and may be sweating. On the other hand, chronic pain, which involves a complex interplay of ion channels, receptors, neurotransmitters, and neural systems, is associated with aberrant pain signal processing and interpretation and, as such, is much more challenging to treat than acute pain. Neuroplasticity may cause maladaptive changes with peripheral and central sensitization leading to persistent pain. In a small percentage of patients with acute pain, the nervous system goes haywire and starts to generate pain messages on its own. Prompt and effective treatment of acute pain may interrupt potential chronic pain.

The sensory experience of pain is surprisingly complex because the interactions between afferent inputs and their processing across the peripheral and CNSs involve affective-motivational components. In most individuals, the experience of and susceptibility to pain results from a complex interaction among several genetic variants involved in different steps of neuronal nociceptive processing with additional contributions of other genetic and psychosocial factors, expectations, and prior learning (Exhibit 1). Overall, everyone experiences pain differently.

On functional brain MRI, expectations for decreased pain significantly reduce subjective experience of pain and activation of pain-related

Exhibit 1: Factors in Pain Perception and Therapeutic Outcome of Pain Management



brain regions and expectations for significant pain increase activation.[1] It has been shown that preoperative patient education and patient preparedness are associated with less postoperative use of opioids.[2]

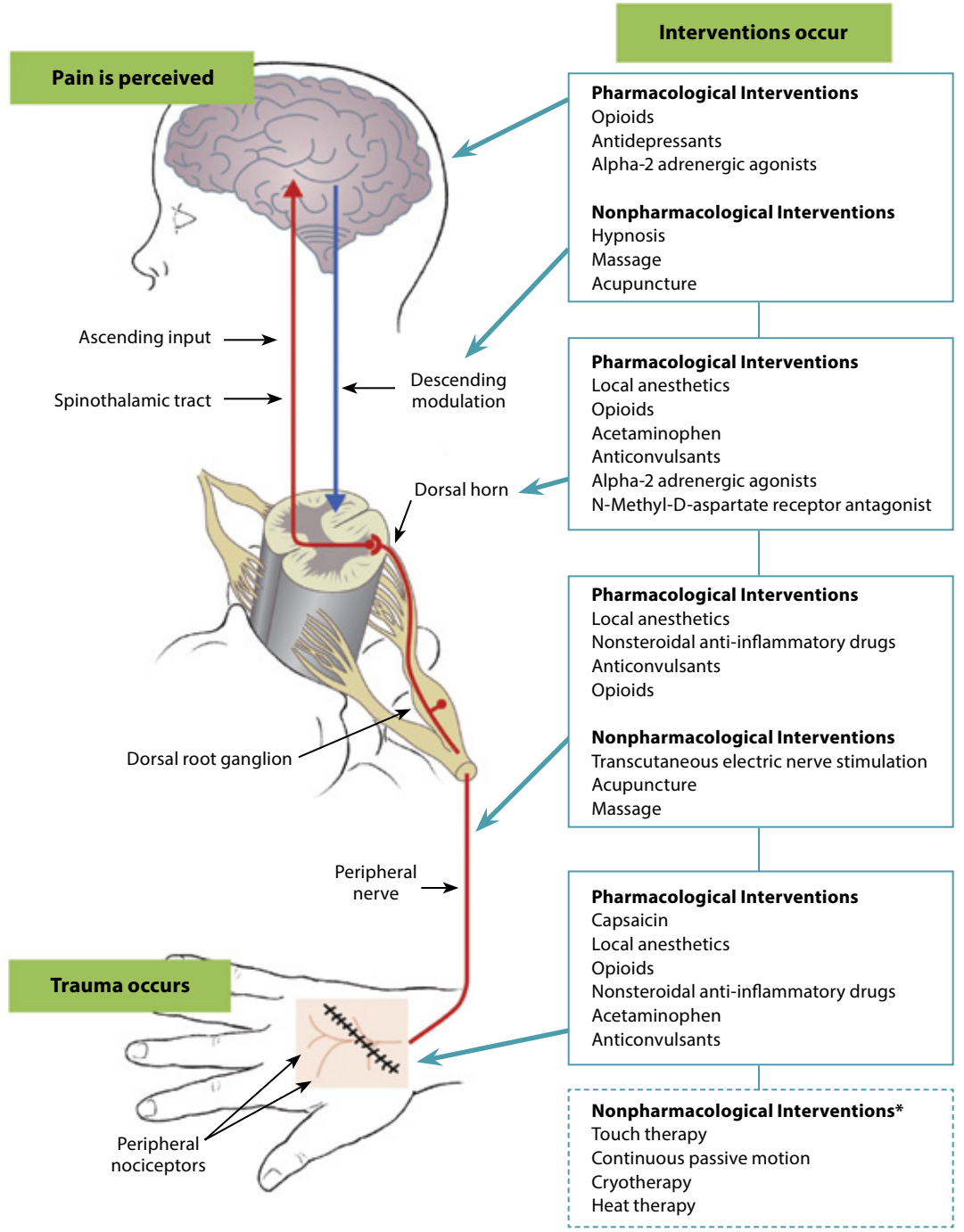
Another demonstration of the effect of expectations on pain is in the use of placebos. Placebos are effective for pain, anxiety, and depression. A meta-analysis of four small studies involving open-label placebo (OLP)—the patient knows what they are getting—for chronic low back pain demonstrated a modest reduction in pain on the numerical rating scale (mean difference = -0.62; 95% confidence interval: -1.09 to -0.14; $p = 0.01$; I2 = 31%) with placebo.[3] These findings, even if small, suggest potential benefits of OLP for pain reduction, with clinical relevance of the effect size being important depending on the clinical context and the patient's perspective. It is unethical to give placebo for treating acute pain outside of clinical trials.

Acute pain is a primary reason for healthcare visits and many hospitalized patients experience acute pain during their stay. Acute postsurgical pain, which occurs in about 80 percent of surgery patients, is a common form of acute pain and can be severe.[4] Over one-third (38%) of unexpected hospital readmissions following ambulatory surgery are due to pain.[5] Uncontrolled pain increases the risk of morbidity, dysfunction, decreased quality of life, impaired sleep, delayed recovery time, higher associated healthcare costs, and increased consumption of medications including opioids.[6] As noted previously, uncontrolled acute pain can become chronic, which is far more challenging to treat.[7]

There are challenges in adequately managing acute pain. The first is to assess the degree of pain present. Pain is often underreported and many clinicians do not have good assessment skills for pain. The assessment tools for pain commonly used in non-pain specialist practices are mostly unidimensional subjective assessment scales such as the 0 to 10 scale (i.e., how is your pain from a one of no pain to a 10 of most severe pain ever experienced). Pain specialists use assessment tools that consider function, ability to work, and daily changes. There are no commonly used objective measurement tools for pain.

Challenges in treating acute pain are the fear of adverse events and addiction with opioids and belief that most pain is transient and will go away on its own without consequences. Reluctance to prescribe opioids has increased because of the opioid crisis in the United States (U.S.). Between 2011

Exhibit 2: Where Analgesics and Nonpharmacologic Therapies Work



and 2020, opioid prescribing in the U.S. declined 44 percent.[8] Declines were especially prevalent among primary care providers. Physicians are reluctant to prescribe opioids or take on patients who are opioid-prescribed and, thus, are confronted with the challenges of treating pain patients responsibly in an environment of decreasing opioid prescribing. In one survey 72 percent of physicians worried that chronic pain patients may turn to illicit drugs.[9] As misuse and illicit opioid use increased, many primary care providers turned to gabapentin as an alternative pain therapy. Seventy-eight percent of physicians surveyed said that to avoid prescribing opioids for the treatment of pain, they

Exhibit 3: Limitations Associated with Traditional Oral Pain Therapies

- Acetaminophen
  - Hepatic, renal toxicity
- NSAIDs
  - Hepatic, renal, gastrointestinal, cardiovascular, and platelet toxicities.
- Opioids
  - Sedation, dizziness, nausea/vomiting, constipation, physical dependence, tolerance, respiratory depression, addiction, overdoses/deaths.
- Antidepressants
  - Dry mouth, blurred vision, constipation, urinary retention, drowsiness, dizziness, weight gain, cardiac arrhythmias, serotonin syndrome, reduced libido, erectile dysfunction
  - SNRI effective for chronic pain syndromes (fibromyalgia, chronic back pain, and neuropathic pain
- Anticonvulsants
  - Dizziness, blurred vision, weight gain, rash, hepatic toxicity, Stevens-Johnson syndrome, sexual dysfunction
  - Effective for neuropathic pain but not for musculoskeletal pain

often prescribed gabapentin, however, 34 percent were concerned about the potential misuse of gabapentin.[9] Gabapentin does work for some types of pain but not for every type of pain and there can be abuse issues.

In most other countries, opioids are only used for severe pain. Although taking opioids, including after surgery, exposes patients to the risk of prolonged opioid use, they remain an important option for the treatment of acute pain, especially severe pain. Our challenge as clinicians is that although effective, opioids are associated with adverse drug events which, in turn, are associated with higher medical costs. There is a clear unmet need for effective analgesics that lack systemic and behavioral adverse events. The holy grail of pain management is to find a medication that treats severe pain without all the negative aspects of opioids (abuse, diversion, addiction, respiratory depression, overdoses, deaths, etc.).

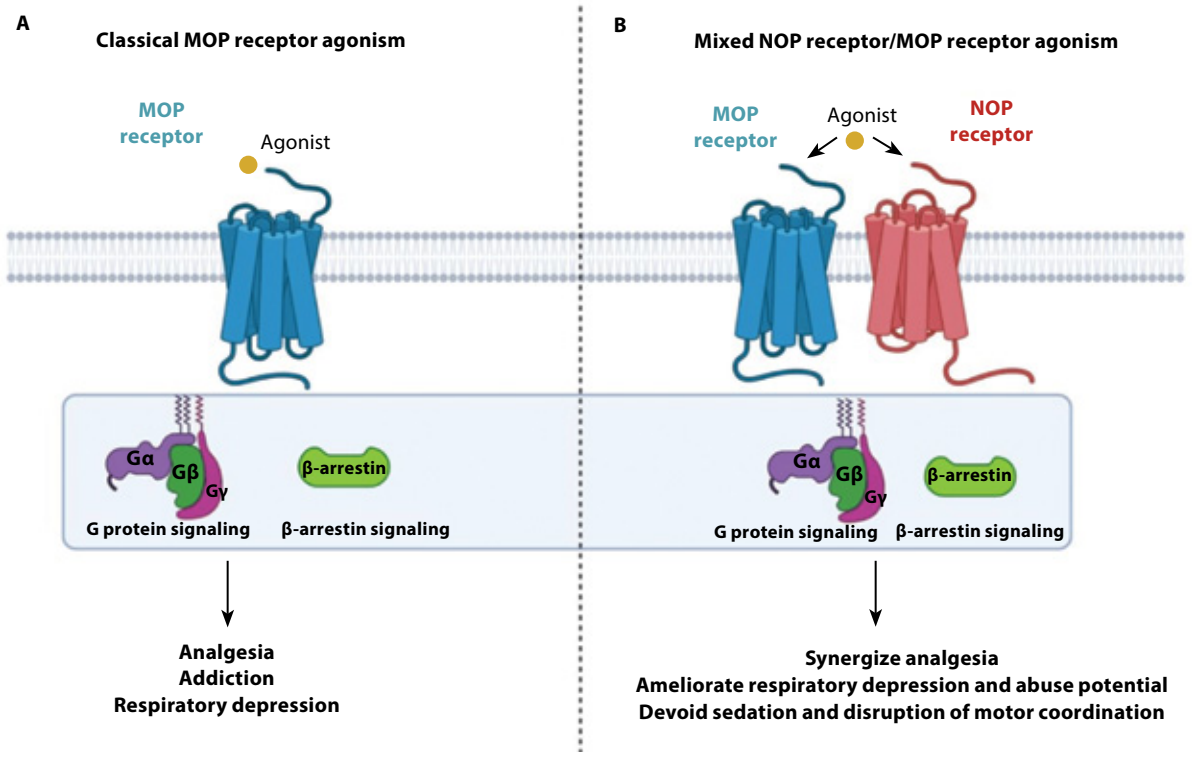
Options for acute pain management are nonpharmacologic treatments, acetaminophen, non-steroidal anti-inflammatories (NSAIDS), opioids (traditional and abuse deterrent formulations), opioid like molecules (tramadol, tapentadol), adjuvants, topicals, antidepressants, anticonvulsants, nerve blocks, and implantable therapies. Exhibit 2 shows where each of the options work in the pain pathways. Combinations of therapies are in many cases necessary to adequately manage acute pain. There are limitations with all the current options. Exhibit 3 highlights some of the issues with oral medications.

Abuse deterrent formulations of opioids prevent tampering and non-oral routes of administration (i.e., injection) but patients nor payers want to use these due to inflated costs. Prescribers are not fans because of prior authorization requirements and access issues. These formulations do not prevent oral overconsumption which is the most usual form of opioid abuse in the U.S. Overall, these formulations are little used.

One abuse deterrent formulation opioid which also has overdose protection (PF614-MPAR) is under study.[10] This is a combination product of a trypsin activated abuse protection-oxycodone prodrug, PF614, and the trypsin inhibitor nafamostat. Because exposure to trypsin in the gastrointestinal tract is required to activate PF614 for the release of oxycodone, drug activity is not generated if the drug is injected or snorted. The addition of nafamostat adds overdose protection if more than three tablets are taken at once. If approved, this would be the first overdose protection opioid.

The Non-Opioids Prevent Addiction in the Nation or NoPain act was passed in January of 2025 with bipartisan support.[11] This act aimed to temporarily expand access to non-opioid treatments for post-surgical pain by introducing separate Medicare reimbursement at 106 percent of the average sales price for treatments, medications, and devices used in the outpatient setting including hospital outpatient departments and ambulatory surgery

Exhibit 4: Bifunctional Opioids are Those That Target More Than One Opioid Receptor



MOP = mu opioid; NOP = nociceptin/orphanin FQ

centers. Commercial plans should follow suit.

The future of analgesics is bright. There are many different analgesic targets which have been discovered and many pain disorders have been mapped to mutations in genes encoding ion channels involved in pain modulation. It seems likely that aberrant peripheral or central ion channel activity underlies many pathological pain conditions. Voltage-gated sodium channels (VGSCs) are responsible for driving neuronal excitability in both the central and peripheral nervous system. Inhibitors prevent sodium ions from passing through cell membranes, which can slow electrical impulses and reduce cell excitability. Classes of medications that target VGSCs include antiarrhythmics, anticonvulsants, local anesthetics, and analgesics.

VGSCs are the primary target of local anesthetics such as lidocaine. Unfortunately, local anesthetics are not isoform-specific and thus, they can produce clinically relevant side events when given systemically. Immediate release and extended-release local anesthetics have been proven beneficial for improving pain and minimizing opioid use postoperatively. Topical lidocaine preparations are also beneficial for acute and chronic musculoskeletal and neuropathic pain. An example of a long-acting local anesthetic is bupivacaine liposome injectable suspension. It is indicated to produce postsurgical local analgesia via infiltration in patients six years of age and older and regional analgesia via an interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and for adductor canal block in adults. In a study comparing bupivacaine liposome injectable suspension with bupivacaine in total knee arthroplasty as an adductor canal block, the long-acting product produced superior analgesia on cumulative pain scores with 23 percent less postsurgical opioid consumption.[12] The challenge for managed care is the cost of the extended release local anesthetics compared to the shorter acting local anesthetics.

A 5.4 percent lidocaine topical system (SP-103), which contains a triple strength of an existing FDA-approved topical lidocaine product currently approved for post-herpetic neuralgia, is under investigation for acute low back pain.[13] It is in Phase III trials currently for this and other indications.

A first-in-class non-opioid, suzetrigine, was FDA-

approved in January 2025 and is a sodium channel blocker highly selective for sodium channel protein type 10 subunit α (Nav1.8). There are nine different known sodium channels in the body. By inhibiting Nav1.8, suzetrigine blocks sodium ions from entering pain-sensing neurons, disrupting the initiation and propagation of action potentials and reducing pain signal transmission from the peripheral nervous system to the CNS.[14] It does not interact with mu receptors, which are associated with addiction.[15] There is no evidence that it has addictive potential based on available data, including the mechanism of action, preclinical data, and clinical adverse event data and it is not a controlled substance. Suzetrigine was granted FDA Fast Track and Breakthrough Therapy designations in moderate-to-severe acute pain. Safety, tolerability, and efficacy with a favorable benefit/risk profile were demonstrated in three Phase III studies and two Phase II studies in moderate-to-severe acute pain, as well as positive results and a well-tolerated profile in a Phase II study in patients with painful diabetic peripheral neuropathy. In a trial comparing suzetrigine (100 mg, then 50 mg every 12 h), hydrocodone/acetaminophen (5/325 mg every 6 h), or placebo for 48 hours after abdominoplasty or bunionectomy, suzetrigine produced statistically significant and clinically meaningful reduction in pain versus placebo and was similar to hydrocodone/acetaminophen.[16] Adverse events include pruritus, muscle spasms, increased creatine phosphokinase, and rash.

Numerous novel oral analgesic agents are currently investigational including additional agents targeting gated sodium channels and agents targeting gamma-aminobutyric acid (GABA), N-methyl-d-aspartate (NMDA), calcium channels, nerve growth factor, serotonin, and transient receptor potential cation channel subfamily V member 1 (TRPV1). An example close to market is cebranopadol, a bispecific nociceptin/orphanin FQ peptide receptor and mu opioid receptor agonist. These receptors are partially homologous to each other, and they play both complementary and distinct roles to modulate pain biology pathways. Bispecific opioid receptor agonists (Exhibit 4) show an improved safety profile including for lower rates of respiratory depression. Cebranopadol targets different receptors than tramadol and tapentadol in addition to mu opioid receptors as agonists. Tramadol affects both serotonin and norepinephrine reuptake, while tapentadol primarily inhibits norepinephrine reuptake. Cebranopadol is currently being investigated for the treatment of acute pain, chronic pain, and neuropathic pain. Positive topline results from ALLEVIATE-1 (abdominoplasty) and ALLEVIATE-2 (bunionectomy) have been reported by the manufacturer but have not yet been published. ALLEVIATE-1, a multicenter, randomized, double-blind, placebo-and active-controlled Phase III study evaluated the efficacy of cebranopadol compared with placebo for moderate-to-severe acute pain after abdominoplasty.[17] Cebranopadol met the primary endpoint of reduction in pain intensity as measured by the Pain Numeric Rating Scale area under the curve from two to 48 hours.

Oxycodone showed more pain relief versus placebo but less than cebranopadol. Therapy was well tolerated with a favorable safety profile and no serious adverse events. The most common adverse event was nausea. Studies have shown a significantly lower abuse potential than Schedule II (oxycodone) and Schedule IV (tramadol) opioids, as well as 25 percent less respiratory depression and slower onset of respiratory depression as compared to oxycodone in recreational opioid users.[18] An intranasal study using a supratherapeutic dose of 1,000 ug cebranopadol (2.5 times higher than the therapeutic dose for the treatment of pain) was significantly less likeable compared to 40 mg oxycodone when crushed and snorted.[19] This agent has the potential to not cause the detrimental side events seen with opioids such as physical dependence and misuse, lower risk of respiratory depression, and has simple once-a-day dosing that will not require adjustment for food, renal or hepatic impairment, or tapering at the end of therapy.

Conclusion

Efforts to identify safe and effective analgesics without the complications of opioids continue. Opioids remain an important option for the treatment of severe pain. Novel analgesics in development should change the landscape and improve safety and tolerability of analgesics. Clinicians need to continue to employ multimodal medications complemented by nonpharmacological therapies to manage acute pain and prevent chronic pain.

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Delaying the Progression of Type 1 Diabetes: Managed Care Considerations on the Role of New and Emerging Therapies

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Summary

Type 1 diabetes (T1D) is a costly disease with major long-term consequences. Early Identification through screening programs and monitoring for disease progression may reduce long-term consequences. One therapy that targets the underlying immune dysfunction can delay onset of overt T1D.

Key Points

- Early identification of T1D is important for reducing incidence of diabetic ketoacidosis (DKA) at diagnosis and retaining as much β-cell function as possible.
- Waiting until patients are symptomatic results in poorer disease control.
- A medication for delaying development of T1D in those with Stage 2 disease is now available. Numerous other medications and therapies are under development.

TYPE 1 DIABETES (T1D) IS AN AUTOIMMUNE disease where the body's immune system mistakenly attacks and destroys the insulin-producing β-cells in the pancreas. It affects 1.5 million people in the United States (U.S.) and about 60,000 new cases are diagnosed annually. Importantly, only 18 percent of cases are diagnosed in children, with the majority of cases occurring in those over 18 years of age.

T1D is a costly disease both financially and clinically. In 2024, the total financial cost of T1D in the U.S. was $53 billion. This includes $31 billion in direct medical costs and $22 billion in indirect costs. The total estimated out-of-pocket cost for a single patient with insurance coverage is $5,700 and $35,700 without insurance.

People with T1D live shorter lives due to their disease. The long-term complications of T1D are well known. Microvascular complications include retinopathy, nephropathy, and neuropathy. Cardiovascular disease is the major macrovascular complication and the cause of death in 80 percent of cases. Studies have shown over the years that insulin therapy that keeps blood glucose in range at least 60 percent of the time for six years can reduce diabetic complications significantly. Retinopathy decreased by 76 percent, nephropathy by 39 percent, neuropathy by 60 percent, and heart disease by 40 percent. Improved diabetes care has led to reduced rates of these diseases, especially severe retinopathy, and nephropathy but there is still room for improvement.

The disease process of T1D occurs over several years as the functional β-cell mass declines (Exhibit 1).[1] Stage 1, the preclinical stage, is characterized by the onset of autoimmune β-cell destruction and insulitis caused by immune-mediated destruction. This stage is asymptomatic and characterized by normal fasting glucose, normal glucose tolerance, and the presence of at least two different pancreatic autoantibodies. In Stage 2, a significant amount of β-cell dysfunction has already occurred, leading to dysglycemia but individuals remain asymptomatic. Stage 3 is characterized by the clinical onset of disease where individuals present with symptomatic hyperglycemia.

Exhibit 1: Stages of Type 1 Diabetes[1]

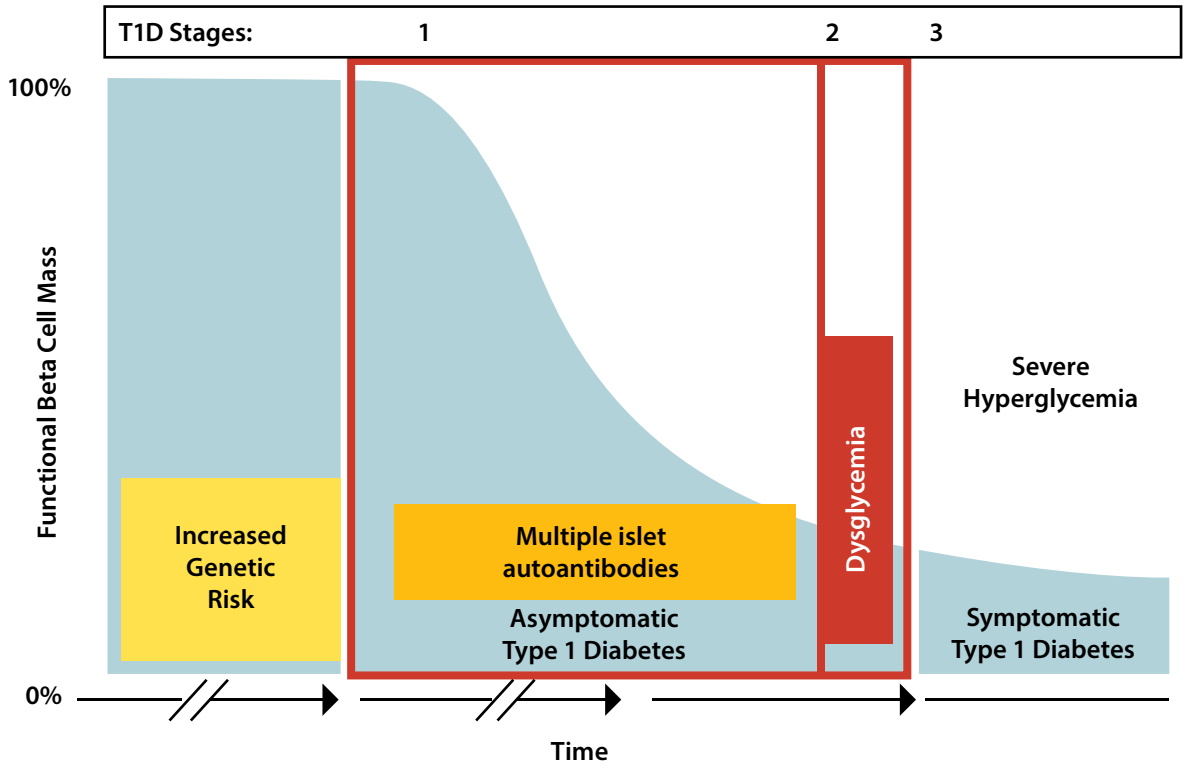

Exhibit 2: Common Misconceptions About T1D

• *'Nobody in my family has it'* – 90% of cases have no affected family.
• *'It is uncommon in non-whites'* – the rates are only slightly lower.
• *'My child is very active and not obese'* – not protective factors.
• *'Teenagers/young adults progress slowly to overt diabetes'* – progress can be rapid.
• *'Best test to diagnose is OGTT'* – A1C or random blood glucose would help.
• *'Nothing can be done until there are symptoms'* – preventing diabetic ketoacidosis saves lives, the brain, $$$, stress, and future trouble.

Identifying asymptomatic T1D in genetically susceptible people would be ideal but most patients are not diagnosed until severely symptomatic with diabetic ketoacidosis (DKA). In two studies in children, 40 to 62 percent had DKA at diagnosis.[2,3] In addition to lack of symptoms early in the disease, sometimes clinicians do not recognize the possibility of T1D and there are many misconceptions about the disease among the public and clinicians (Exhibit 2).

DKA at diagnosis predicts poor long-term glycemic control.[4] Compared to children without DKA, glycosylated hemoglobin (A1C) tracked 1.4 percent (15.3 mmol/mol) higher in those with severe DKA ($p < 0.0001$) and 0.9 percent (9.8 mmol/mol) higher in those with mild-to-moderate DKA at diagnosis ($p < 0.0001$). These results were independent of ethnic minority status or lack of health insurance at diagnosis that predicted higher A1C by 0.5 percent (5.5 mmol/mol; $p < 0.0001$) and 0.2 percent (2.2 mmol/mol; $p < 0.0001$), respectively. Other deleterious outcomes of DKA include acute neurological damage, chronic neurocognitive

Exhibit 3: Pathways to be Screened in the U.S.

	Where do you LIVE to participate?	What AGES can be screened?	Screen for T1D	Screen for CELIAC	Requires ORDER from HCP	Islet autoantibodies included	Assay used screening –>confirmation
Research Based Screening Programs							
ASK	United States	1 to < 18 years	✓	✓	No	GADA,IAA, IA-2A, ZnT8A	**ECL –>RBA+ECL**
CASCADE	Washington State	Newborn to 7 years	✓	✓	No	GADA,IAA, IA-2A, ZnT8A	**RBA –>LIPS**
PLEDGE	Sanford Health (ND, SD, MN)	Newborn to < 6 years and 8 to < 17 years	✓	✓	No	GADA,IAA, IA-2A, ZnT8A	**RBA –>ECL**
TrialNet	United States and International	2.5 to 45 years with parent, brother/sister, or child with T1D **– OR –** 2.5 to 20 years with aunt/uncle, cousin, grandparent, niece/nephew, or half-sibling with T1D	✓	☒	No	GADA,IAA, IA-2A, ZnT8A, ICA	**RBA** **IFA for ICA**
Consumer Laboratory							
Enable Biosciences	United States (except NY and PA)	Over 1 year	✓	☒	No	GADA, IAA, IA-2A	ADAP
Clinical Laboratory							
LabCorp	United States	All ages	✓	✓	Yes	GADA,IAA, IA-2A, ZnT8A	ELISA(GADA, IAA, IA-2A, ZnT8A) IFA (ICA)
Mayo Laboratories	United States	All ages	✓	✓	Yes	GADA,IAA, IA-2A, ZnT8A	ELISA (ZnT8), RBA (GADA, IAA, IA-2A, ZnT8A)
Quest	United States	All ages	✓	✓	Yes	GADA,IAA, IA-2A, ZnT8A	ELISA (GADA, IA-2A, ZnT8A) RBA (IAA) IFA (ICA)

ADAP = antibody detection by agglutination polymerase chain reaction; ECL = electrochemiluminescence; ELISA = enzyme-linked immunosorbent assay; GADA = glutamic acid decarboxylase antibody; IAA = insulin antibody; IA-2A = islet antigen-2 antibody; IFA = immunofluorescence assay; LIPS = luciferase immunoprecipitation systems; RBA = radio-binding assay; ZnT8a = zinc transporter antibody; ICA = islet cell antibody.

deficits from brain edema, significant management costs, and trauma to the child and family.

Screening for T1D is important to prevent DKA at clinical diagnosis and earlier diagnosis means more residual insulin secretion resulting in lower A1C and fewer complications. General population screening has been shown to reduce the DKA rate at diagnosis to the 3.8 to 5.8 percent.[5,6] Earlier diagnosis can delay insulin dependence. Sensitive and specific screening tools are available. Islet autoantibodies are the only clinically validated markers of pre-diabetic autoimmunity. Nearly all individuals who test positive for two or more persistent islet autoantibodies will develop overt clinical T1D. The American Diabetes Association (ADA) recommends that first- and second-degree relatives of individuals with T1D be screened and offered T1D autoantibody testing.[7] Screening cannot be limited to relatives of people with T1D because they represent only 10 to 15 percent of new diagnoses. Clinically acceptable groups for screening also include people with an autoimmune condition, and their relatives and those with dysglycemia or symptoms suggesting undiagnosed diabetes. Universal screening of children, adolescents and some adults will be accepted soon. Exhibit 3 outlines pathways to screening in the U.S.

Celiac disease screening is noted in Exhibit 3 because there is a strong connection between T1D

Exhibit 4: Diagnostic Criteria for Type 1 Diabetes[10]

	Stage 1 Pre-symptomatic	Stage 2 Pre-symptomatic	Stage 3 Symptomatic
Diagnostic criteria	**Multiple islet autoantibodies** **Normoglycemia**	**Islet autoantibodies** **Dysglycemia:** • FPG 100 to 125 mg/dL (IFG) • 2-h PG 140 to 199 mg/dL (IGT) • A1C 5.7% to 6.4% or ≥ 10% increase in A1C	**Clinical symptoms and RBG ≥ 200 mg/dL** **Diabetes by standard criteria:** • FPG ≥ 126 mg/dL or • 2-h PG ≥ 200 mg/dL, or • A1C ≥ 6.5%

FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; PG = post-prandial glucose; A1C = glycosylated hemoglobin; RBG = random blood glucose

and celiac disease; both are autoimmune conditions that share a common genetic background and often occur together. People with T1D are at a significantly higher risk of developing celiac disease, with estimates suggesting a rate of 5 percent compared to about 1 percent in the general population.[8]

There are many barriers to general population screening in the U.S. There is low community awareness of T1D, compared to T2D, and there is a lack of routine screening approval by professional societies, the U.S. Preventive Services Task Force, and insurance companies, which means unreimbursed cost. Fragmentation of primary pediatric care is another barrier. Lastly, healthcare providers require a large amount of focused education and resources to implement screening programs.

One analysis has shown that presymptomatic T1D screening may be cost effective, in areas with a high prevalence of DKA and an infrastructure facilitating screening and monitoring, if the benefits of avoiding DKA events and improved A1C persist over long-run time horizons.[9] Incremental budget impact estimates range from $0.50 to $1.40 per-member per-month in added costs.

Exhibit 4 shows the diagnostic criteria for T1D.[10] The ADA has published consensus guidance for monitoring individuals with pre-Stage 3 T1D to identify disease progression.[11] As more people are being identified with early stage T1D, there is significant interest in being able to prevent or delay progression. The first medication, teplizumab, was FDA-approved in 2022 to delay the onset of insulin-dependent (Stage 3) T1D in adults and children aged eight years and older with Stage 2 T1D. It is an Fc receptor-nonbinding anti-CD3 monoclonal antibody that works by binding to T cells and altering their signaling, which slows the autoimmune destruction of β-cells. In a Phase II, randomized, placebo-controlled, double-blind trial, teplizumab was given to relatives of patients with T1D who were autoantibody-positive (Stage 2) and thus high-risk for Stage 3. Patients were randomly assigned to a single 14-day course of teplizumab, or placebo, and follow-up for progression to clinical T1D with the use of oral glucose-tolerance tests at six-month intervals. A total of 76 participants (72% of whom were 18 years of age or less) underwent randomization (44 to the teplizumab group and 32 to the placebo group). The median time to the diagnosis of T1D was 48.4 months in the teplizumab group and 24.4 months in the placebo group; the disease was diagnosed in 43 percent of the participants who received teplizumab and in 72 percent of those who received placebo.[12] The hazard ratio for the diagnosis of T1D (teplizumab versus placebo) was 0.41 (95% confidence interval, 0.22 to 0.78; $p = 0.006$ by adjusted Cox proportional-hazards model). The annualized rates of diagnosis of diabetes were 14.9 percent per year in the teplizumab group and 35.9 percent per year in the placebo group. The most common adverse events with this agent are rash, transient lymphopenia, and headache. This was the first study to show that any medication can delay T1D diagnosis, a median of two-years, in adults and children at elevated risk.

In an extended follow-up (923-day median) of this

study, the median times to diagnosis were 59.6 and 27.1 months for teplizumab- and placebo-treated participants, respectively (HR = 0.457, p = 0.01).[13] Fifty percent of teplizumab-treated people remained diabetes-free but only 22 percent of the placebo-treated did so. Teplizumab treatment improved β-cell function, reflected by average on-study C-peptide area under the curve (AUC), 1.94 versus 1.72 pmol/ml; p = 0.006. Drug treatment reversed a decline in insulin secretion before enrollment, followed by stabilization of the declining C-peptide AUC seen with placebo treatment. The changes in C-peptide with teplizumab treatment were associated with increases in partially exhausted memory KLRG1+TIGIT+CD8+ T cells (r = 0.44, p = 0.014) that showed reduced secretion of interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα). A single course of teplizumab had lasting effects on delay of T1D diagnosis and improved β-cell function in high-risk individuals.

Teplizumab is given by intravenous infusion once daily over a 14-day period in an escalating dosage regimen. It is only now gaining recognition with most third-party payers and Medicaid covering therapy. It is expensive with a wholesale price of $14,410.95 per vial. The total course of therapy for patients with a body surface area (BSA) 1.94 or less is $201,753.34.

There are numerous other therapies under development to prevent or delay T1D. Antigen specific, β-cell and T-cell immune modulators, other immune modulators, cell transplantation, and gene therapies are all in various stages of investigation. Some agents already approved for other autoimmune diseases are in trials for T1D prevention including golimumab, abatacept, ustekinumab, and baricitinib. For example, golimumab, an anti-TNFα monoclonal antibody, given over one year in new-onset Stage 3 T1D in children and young adults resulted in better endogenous insulin production and less exogenous insulin use than placebo.[14]

Verapamil, an old calcium channel blocker antihypertensive, is being studied because calcium channel blockade reduces thioredoxin-interacting protein overexpression which induces pancreatic β-cell apoptosis. In a small trial in children and adolescents aged seven to 17 years with newly diagnosed T1D, verapamil partially preserved stimulated C-peptide secretion at 52 weeks from diagnosis compared with placebo.[15] At the end of the one-year trial, those treated with verapamil had 30 percent more insulin production.

For anyone who wishes to learn more about T1D, the StopT1D program (stopT1Dprogram.org) offers a comprehensive educational program for healthcare providers and a separate program for non-healthcare providers.

Conclusion

Identifying T1D as early as possible in the disease process is important for reducing the incidence of DKA and retaining as much β-cell function as possible. Waiting until patients are symptomatic results in poorer disease control. There is now one medication for delaying development of T1D in those with Stage 2 disease. Many other medications will make it to market in the next few years.

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Best Practices in the Treatment and Management of Chronic Lymphocytic Leukemia: Improving Clinical and Economic Outcomes with BTK Inhibitors

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Summary

In the last 10 years there has been a revolutionary change in the way CLL is treated with targeted agents instead of chemotherapy. Combination of these targeted agents is further changing first-line treatment.

Key Points

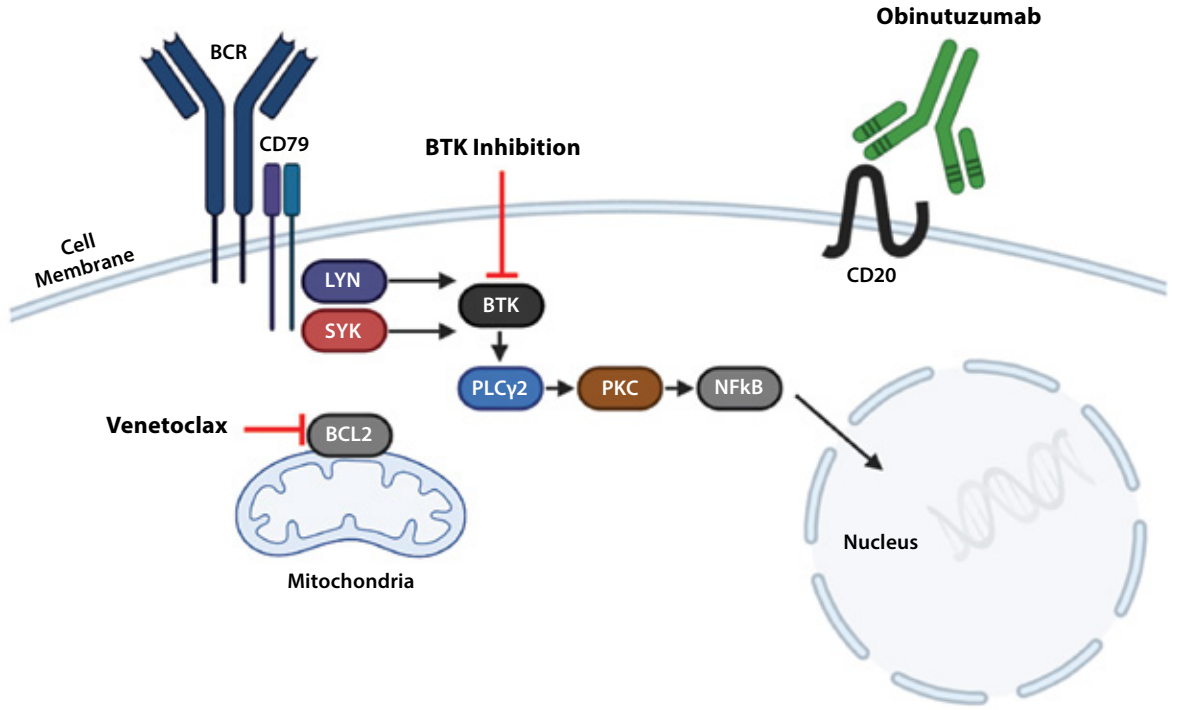
- With CLL therapies, patients are living longer with less toxicity.
- Many new medications, used in new combinations, are currently being developed in CLL.
- Clinicians are looking forward to utilizing an all-oral time-limited option.
- Clinical trials should continue to be prioritized.
- Economic toxicity from CLL treatment remains a real concern.

B CELL SIGNALING IS CRUCIAL FOR NORMAL B-cell development and adaptive immunity. In chronic lymphocytic leukemia (CLL), B cells are chronically activated leading to cell division and long cell life (Exhibit 1). Bruton's tyrosine kinase (BTK) is a key signaling pathway which is targeted, with oral BTK inhibitors (BTKi)—ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib. B cell lymphoma 2 (BCL2) is overexpressed in CLL, helping cells survive longer and resist chemotherapy. By inhibiting BCL2, venetoclax leads to the release of pro-apoptotic proteins, triggering programmed cell death in cancer cells. CD-20 is overexpressed on CLL cells so a third treatment is an injectable anti-CD20 monoclonal antibody, obinutuzumab. These three classes have significantly improved and extended the life of patients with better efficacy and less toxicity compared to chemoimmunotherapy. Long-term overall survival (OS) in those treated with a BTKi (ibrutinib) first line has been shown to match survival for age matched cohorts without CLL.[1]

The choice of initial therapy for patients with symptomatic or advanced CLL is made based on patient and tumor characteristics, patient preference, and goals of therapy.[2] The two major treatment approaches for CLL first-line therapy are continuous BTKi until disease progression, or time limited administration of venetoclax in combination with acalabrutinib and/or obinutuzumab (Exhibit 2).[2] Ibrutinib is no longer preferred in the National Comprehensive Cancer Network (NCCN) Guidelines because of higher rates of adverse events (AEs) compared to the other BTKi in head-to-head trials. Currently, chemotherapy and chemoimmunotherapy have a very limited role in the treatment of CLL and are rarely used.

The first-line treatment choice between a BTKi, venetoclax/obinutuzumab, or acalabrutinib/venetoclax/with or without obinutuzumab is currently based on patient age, comorbidities,

Exhibit 1: Mechanism of Action of Targeted Agents



disease biology, status (treatment naïve, relapsed/refractory), and patient preference. In addition, the financial impact of a given choice and potential adherence issues also must be considered. Patient preference is most important in selecting therapy for several reasons. The patient is the one who will be treated and our treatments, no matter which approach is chosen, work well for most patients. There are currently no randomized Phase III trials comparing all the main therapeutic approaches in the treatment naïve setting. Ongoing trials may settle the question of whether continuous or time-limited therapy is the best.

Some clinicians favor continuous BTKi for older patients because most data are in the older age group. Continuous therapy is also an option for those who want a less intensive upfront regimen (no infusions, less monitoring, less time off life or work). Patients on continuous BTKi can be seen every three months, whereas those on time-limited therapy have to be seen more frequently, initially for monitoring. Venetoclax time-limited therapy is favored in younger patients because of cumulative toxicity of BTKi over time and in those with good-risk disease based on data in patients with TP53 aberrations from the CLL14 trial.[3] Venetoclax time-limited therapy without a BTKi may be favored in patients with significant pre-existing cardiovascular disease. Time-limited therapy may also be preferred for financial reasons. Kidney function must be assessed before venetoclax or obinutuzumab-based therapy due to risk for tumor lysis syndrome (TLS).

Second generation BTKi (acalabrutinib, zanubrutinib) were designed with different binding-profiles and improved selectivity to decrease the observed "off target" effect of ibrutinib (Exhibit 3).[4] Off-target interactions with tumor necrosis factor-alpha converting enzyme (TEC) and human epidermal growth factor receptors 2 and 4 (HER2, HER4) are thought to contribute to cardiovascular-related AEs, such as atrial fibrillation (AF).[5] Acalabrutinib was FDA-approved for first-line treatment of CLL based on the results of the Elevate-TN trial.[6] In this trial, acalabrutinib 100 mg bid continuous until progression as monotherapy (A) or with obinutuzumab (AO) for six cycles was compared to chlorambucil/obinutuzumab (CO) for six cycles. At six years of follow-up, median progression-free survival (PFS) was not reached (NR) for AO and A versus 27.8 months for CO (both comparisons $p < .0001$); estimated 72-month overall PFS rates were 78.0 percent, 61.5 percent, and 17.2 percent, respectively. Median OS was not reached by six years for all treatments, with significantly longer OS for

Exhibit 2: NCCN Guidelines for First Line CLL Treatment[2]

CLL/SLL without del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]

Preferred	Other Recommended	Useful in Certain Circumstances
• BCL2i-containing regimens › Venetoclax/Acalabrutinib[j] ± Obinutuzumab (fixed duration)[h] (category 1) › Venetoclax + Obinutuzumab (fixed duration) (category 1) • cBTKi-based regimens[i,j] › Acalabrutinib (continuous) ± Obinutuzumab (category 1) › Zanubrutinib (continuous) (category 1)	• BCL2i-containing regimens › Venetoclax/Ibrutinib[j] (category 1; fixed duration)[k] › Venetoclax/Ibrutinib[j] (category 1; MRD-guided)[l]	• BCL2i-containing regimens › Venetoclax/Zanubrutinib[j] (MRD-guided)[m] • cBTKi-based regimens[i,j] › Ibrutinib[n] (continuous) (category 1) › Ibrutinib (continuous) + anti-CD20 mAb (category) 2B)[o] • High-dose methylprednisolone (HDMP) + anti-CD20 mAb[o] (category 2B; category 3 for patients < 65 years without significant comorbidities) • Consider only when cBTKi and BCL2i are not available or not feasible › Bendamustine[p] + anti-CD20 mAb[o,q] › FC (Fludarabine/Cyclophosphamide)[r,s,t] + Rituximab › Chlorambucil[u] + Obinutuzumab › Obinutuzumab

CLL/SLL with del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]

Preferred	Other Recommended	Useful in Certain Circumstances
• BCL2i-containing regimens › Venetoclax + Obinutuzumab (fixed duration) › Venetoclax/Acalabrutinib + Obinutuzumab (MRD-guided)[v] › Venetoclax/Zanubrutinib[j] (MRD-guided)[m] • cBTKi-based regimens[i,j] › Acalabrutinib (continuous ± Obinutuzumab) › Zanubrutinib (continuous)	• BCL2i-containing regimens › Venetoclax/Ibrutinib[j,w] (fixed duration)	• cBTKi-based regimens[i,j] › Ibrutinib[n] (continuous) • HDMP + anti-CD20 mAb[o] • Consider only wen cBTKi and BCL2i are not available or not feasible › Obinutuzumab

AO versus CO (p = .0349). Estimated 72-month OS rates were 83.9 percent, 75.5 percent, and 74.7 percent for AO, A, and CO, respectively. Importantly, this trial was not designed to evaluate AO against A. Many clinicians do not use the combination of AO because obinutuzumab must be given by infusion and has risks for infusion reactions and tumor lysis syndrome. The combination acalabrutinib and obinutuzumab may be used when a patient needs rapid symptom control.

Exhibit 3: Comparing Selectivity of First and Second Generation BTK Inhibitors[4]

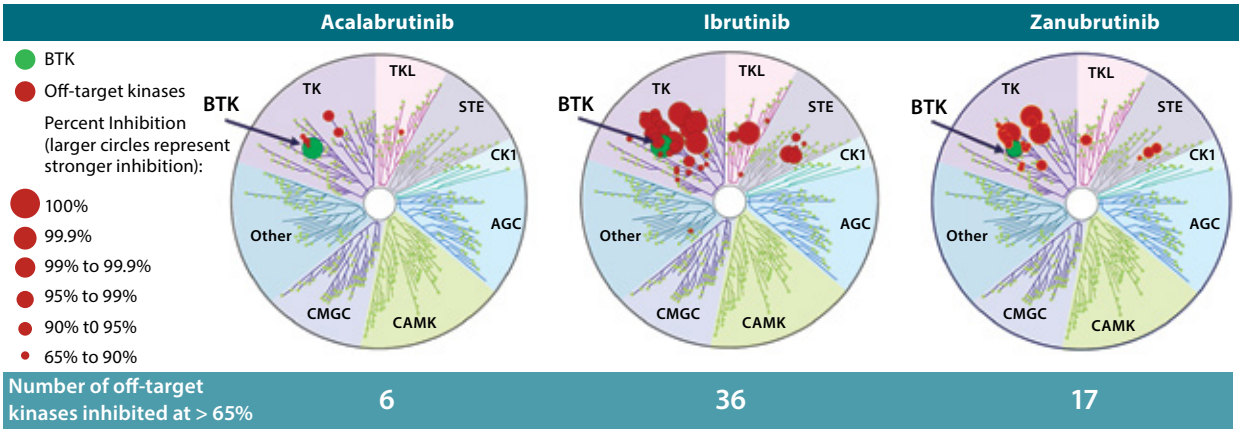
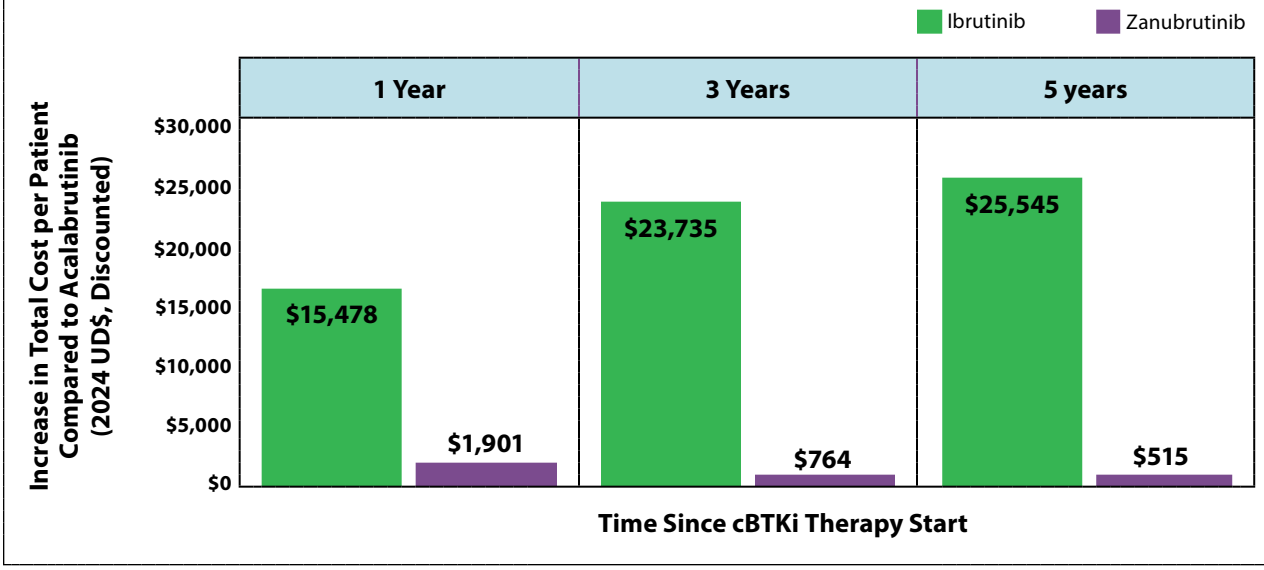


Exhibit 4: Cost impact of BTK inhibitor selection in Medicare patients with CLL[14]



Positive numbers indicate cost saving with acalabrutinib; negative numbers indicate increased cost with acalabrutinib.
AE = Adverse Event; cBTKi = Covalent Bruton's Tyrosine Kinase inhibitor; CLL = Chronic Lymphocytic Leukemia

Comparable results were shown when zanubrutinib was compared to bendamustine/rituximab (BR) as first-line therapy. At five-year follow-up, median OS was not reached in either treatment arm; estimated OS rates were 85.8 percent and 85.0 percent in zanubrutinib- and BR-treated patients, respectively.[7] The advantage of the BTKi regimen was a lower rate of significant AEs. The most common Grade 3 or worse AE was neutropenia (11% zanubrutinib versus 51% BR). Serious AEs occurred in 37 percent and 50 percent, respectively. Overall, the efficacy of acalabrutinib and zanubrutinib appear similar but no head-to-head trials exist. In choosing between the two, AEs may be a consideration. For example, zanubrutinib does appear to cause a higher rate of hypertension than acalabrutinib.[8]

The combination of venetoclax and obinutuzumab as a first-line treatment was established in the CLL14 and GAIA/CLL13 trials.[9,10] The six-year OS rate in the CLL14 trial was 78.7 percent in the venetoclax-obinutuzumab and 69.2 percent in the chlorambucil-obinutuzumab arm (HR, 0.69; p = .052).[9] This trial suggested that time-limited therapy produced worse results in those with TP53 mutation or 17p deletions but the data were based on only 25 patients and OS data are not yet available. There must be discussion with patients with high-risk disease as to whether time-limited therapy is appropriate. As shown in

Exhibit 2, there are no Category 1 recommended regimens for those with TP53 mutation or 17p deletions. Other trials are looking at which regimens are best for those with high-risk disease; for now, most clinicians recommend continuous therapy for those with high-risk CLL.

Doublet (BTKi/BCL2i) and triplet (BTKi/BCL2i/Anti-CD20) regimens are currently being studied as ways to improve time-limited therapy. Some data show that triplet regimens are more toxic than doublet and may only be acceptable for younger patients. Acalabrutinib in combination with venetoclax with or without obinutuzumab is currently included in the NCCN Guidelines as a first-line, Category 1, preferred option for those without 17p deletion/TP53 mutation.[2] This combination was added to the guidelines based on results from the AMPLIFY trial, a Phase III, open-label trial of first-line combination therapy in fit patients who did not have a 17p deletion or TP53 mutation.[11] Patients received acalabrutinib/venetoclax [(AV), acalabrutinib, cycles 1 to 14; venetoclax, cycles 3 to 14], acalabrutinib-venetoclax-obinutuzumab [(AVO), as above, plus obinutuzumab, cycles 2 to 7], or chemoimmunotherapy with the investigator's choice of standard chemoimmunotherapy (cycles 1 to 6). The median age in this trial was 61 years (range, 26 to 86) which is young compared to a typical CLL trial where the median age is around 65. Estimated 36-month PFS at a median follow-up of 40.8 months was 76.5 percent with AV, 83.1 percent with AVO, and 66.5 percent with chemoimmunotherapy (AV versus chemoimmunotherapy, $p = 0.004$; AVO with chemoimmunotherapy, $p < 0.001$). This trial was not designed to assess AV versus AVO. Estimated 36-month OS was 94.1 percent with AV, 87.7 percent with AVO, and 85.9 percent with chemoimmunotherapy; there were multiple deaths from COVID in the AVO group early in the study which may account for the difference in OS. Median OS data are not yet available for this trial. Neutropenia, the most common AE of Grade 3 or higher, was reported in 32.3 percent, 46.1 percent, and 43.2 percent in the three groups, respectively. Overall number of Grade 3 AEs (69.4% versus 53.6%), Grade 3 or higher infections (23.6% versus 12.4%), and AEs leading to treatment discontinuation (20.1% versus 7.9%) were higher with AVO compared to AV. Based on this trial, AVO should likely be reserved for use in younger patients who are better able to tolerate the AEs. Also, patients with unmutated immunoglobulin heavy chain variable (IGHV) who received AV did not do as well as those with mutated IGHV; more data is needed before determining best therapy based on IGHV mutation status.

Because the AMPLIFY study included a chemoimmunotherapy arm, patients with high-risk disease were excluded. Subsequent to this trial, AVO was studied in high-risk patients with and without TP53-aberrant disease (del[17p] or TP53 mutation) in a small single arm study. Four-year PFS and OS for patients with or without TP53 aberration were 70 percent/96 percent and 88 percent/100 percent, respectively.[12] In terms of time-limited therapy, clinicians may be replacing venetoclax/obinutuzumab with acalabrutinib/venetoclax which is an all-oral regimen that avoids infusions and potential infusion reactions. The combination is not yet FDA-approved but is included in the NCCN Guidelines. Time-limited therapy with AV should not be given to someone with unmutated IGHV. AVO can be considered for young patients with high-risk disease.

There are not much data on the best sequencing of BTKi and venetoclax-based regimens. Using real-world data, BTKi-based therapy has been shown to be effective after venetoclax-based therapy and the other way around.

Because most patients will eventually develop disease progression or relapse after time-limited therapy, second-line therapy depends on which regimen was given as first-line therapy. The preferred choices for second-line therapy are venetoclax/obinutuzumab or monotherapy with acalabrutinib or zanubrutinib or pirtobrutinib; which agent selected will depend on what the patient received first line. Pirtobrutinib is the first non-covalent BTKi FDA-approved and blocks the ATP binding site of BTK. It is FDA-approved for adults with relapsed or refractory CLL who have previously been treated with a covalent BTKi; it is active against C481-mutated BTK which is a common cause of disease progression while on a covalent BTKi. Pirtobrutinib also has less off-target AEs compared to acalabrutinib and zanubrutinib and is an excellent choice for patients who have not been able to tolerate these agents. Pirtobrutinib has been shown to be effective after either a covalent BTKi or venetoclax.[13]

There are clinical and economic barriers to the use of current therapies. The main clinical barrier is the presence of cardiac disease in a patient which can limit use of BTK inhibitors. There are ways to mitigate cardiovascular risk. For patients with underlying cardiac disease, it is important that cardiology be engaged early. For already existing atrial fibrillation, most clinicians try to avoid BTKi. If avoiding is not possible, atrial fibrillation should be controlled before therapy initiation. Because of bleeding risk with BTKi, patients on anti-platelet therapy should have the need for continuation

evaluation. If a patient develops hypertension while on a BTKi, a switch to a different one may be helpful. If a patient develops a new cardiac toxicity while on treatment, dose holds, dose reductions, or a switch in agent may manage the issue.

The main clinical barrier with venetoclax is the need for TLS monitoring. Unfortunately, there is no way around this. For patients at elevated risk for TLS because of large disease burden, a BTK inhibitor therapy can be started first to reduce burden before starting venetoclax. A scan before starting venetoclax can confirm reduced burden and the patient may be able to avoid hospitalization when starting venetoclax. In patients receiving obinutuzumab, corticosteroids can be given three days prior to infusion to minimize infusion reactions. Diarrhea secondary to venetoclax can be managed with loperamide. If neutropenia develops, it can be from venetoclax which requires dose hold or reduction or from CLL itself. If due to CLL, venetoclax is continued and GCSF is given for support.

Financially, CLL is costly for both payers and patients. In 2024, the annual wholesale costs for acalabrutinib, ibrutinib, and zanubrutinib were $186,979, $213,677, and $183,303, respectively.[14] In an economic analysis from a Medicare perspective, acalabrutinib showed cost savings of $16,919 per Medicare patient ($313 million across all Medicare patients with CLL) versus ibrutinib over one year, driven by lower treatment cost ($12,224 decrease) and lower AE cost ($4,695 decrease). Differences in AE costs were driven by differences in unadjusted rates of Grade 3 or greater atrial fibrillation (1.1% acalabrutinib versus 5.2% ibrutinib), hypertension (2.8% versus 8.1%), and infections (16.2% versus 20.6%) in treatment naïve patients, and hypertension (4% versus 9%), diarrhea (1% versus 5%) and neutropenia (20% versus 23%) in relapsed/refractory patients. Compared to zanubrutinib, acalabrutinib showed cost savings of $2,529 per patient ($47 million across all Medicare patients with CLL). Higher acalabrutinib treatment cost versus zanubrutinib ($1,683 increase) was offset by savings from lower AE cost ($4,212 decrease). Differences in AE costs were driven by differences in hypertension and infections in the treatment naïve group (2.8% acalabrutinib versus 9.2% zanubrutinib; 16.2% versus 23.8%) and hypertension and infections (4.0% versus 16.4%; 31.0% versus 35.5%) in the relapsed refractory group. Overall cost savings per CLL patient with acalabrutinib versus ibrutinib and zanubrutinib were maintained over three- and five-year time horizons (Exhibit 4).[14]

A real-world study using Optum Clinformatics Data Mart examined all-cause and CLL-specific healthcare resource utilization (HRU) and costs of patients initiated on venetoclax or BTKi in the second-line setting.[15] Of 280 patients (median age 75.5 years), 64.6 percent and 35.4 percent received BTKi- versus venetoclax-based regimens, respectively. Most BTKi-treated patients received monotherapy (88.4%), whereas 62.3 percent of venetoclax-treated patients received combination therapy with anti-CD20 agents. The median duration of second-line therapy was 11.6 and 11.0 months for BTKi and venetoclax cohorts, respectively. All-cause total costs were lower for venetoclax versus BTKi (-$2,497.64 to $1,006.77 respectively in U.S. dollars; $p = .01$), driven by lower medication costs offsetting medical costs; trends were similar for CLL-specific estimates. Outpatient HRU was higher for venetoclax versus BTKi. Overall, venetoclax was associated with total monthly cost savings versus BTKis, illustrating the economic value of time-limited venetoclax-based regimens in the second-line setting. In the same study, 6 percent of the average total patient-per-month costs were out-of-pocket costs which equated to $1,012 per month.

Ways to mitigate the economic cost for patients include choosing time-limited therapy, delaying the start of therapy to coincide when insurance maximums occur, utilizing co-pay discount programs, and foundation grants. For example, the Lymphoma Research Foundation provides Patient Aid Grants to support individuals undergoing treatment for lymphoma and CLL. Clinical trials are also an option which often provide free medication. The new cap on Medicare part D costs to $2,000 should help minimize patient out-of-pocket costs. It is unclear if governmental negotiation of prices will make a difference for patients.

Conclusion

With CLL therapies, patients are living longer with less toxicity. Many new medications, used in new combinations, are currently being developed in CLL. Clinicians are looking forward to utilizing an all-oral time-limited option. Clinical trials should continue to be prioritized. Economic toxicity from CLL treatment remains a real concern.

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Elevating Women's Care with Optimal Treatment Strategies for Menopause and Vasomotor Symptoms

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

Summary

Symptoms of menopause have an overwhelming impact on women and cost those women, the healthcare system, employers, and society significantly. In additional to hormone therapy, new non-hormonal medications targeted at the underlying pathophysiology of vasomotor symptoms are now available.

Key Points

- Hormone therapy is the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause.
- Hormone therapy prevents bone loss and fracture.
- Oral or transdermal hormone therapy should not be started after age 60 or 10 years past menopause.
- For women with contraindications or personal preference not to use hormone therapy, there are good non-hormonal treatment options available.

MENOPAUSE IS A UNIVERSAL EXPERIENCE for 51 percent of the world's population. It is defined as no menstrual cycle for 12 consecutive months and is a retrospective diagnosis. The mean age is 52 years but any age over 45 years is considered normal. Early menopause is between ages 40 and 45 years. Menopause before the age 40 is considered premature and, because these women are physiologically different, they need to be treated differently and as having an estrogen deficient state. Perimenopause is the six- to 10-year time span leading up to menopause during which many women have symptoms.

Many symptoms are associated with the menopause transition (Exhibit 1).[1] Seventy-five percent of women have vasomotor symptoms (VMS) or hot flashes associated with perimenopause and menopause. About 10 percent have severe VMS which significantly affect quality of life. Typical duration of VMS is from seven to 10 years but 30 percent of women can have symptoms for more than a decade. VMS starts earlier and lasts longer in Black women and can include other symptoms such as palpitations. VMS is worse in women who are obese.

Menopause is not just VMS. Other symptoms such as brain fog and mood changes have significant impact. Sleep disturbances and night sweats can be some of the first symptoms. There are many unmet needs in managing these wide-ranging symptoms in women who are in their early 50s, who are still in their productive phase of life and not getting relief for their suffering.

It is important to know that women drive the global economy, are a vital part of the global workforce, and thus, menopause has a significant economic impact. Menopause symptoms have been linked with 12.2 percent lower hourly and 10.9 percent lower annual productivity.[2] The 2010 U.S. National Health and Wellness Survey identified a link between the severity of VMS and lost work productivity.[3] This report also found higher adjusted

Exhibit 1: Many Symptoms Are Associated with the Menopause Transition[1]

- Hot flashes/Night sweats
- Sleep disruption
- Joint aches
- Palpitations
- Breast pain
- Vaginal dryness
- Pain with sex
- Urinary incontinence
- Nocturia
- Brain fog/memory problems
- Mood changes including depressed mood and anxiety

rates of presenteeism in women with severe (24%) and moderate (14%) VMS versus those with mild symptoms (4%). The Hormones and Experiences of Aging study reported that 13 percent of women reported at least one adverse work outcome and 11 percent had missed one or more days of work in the prior year due to menopause symptoms.[4] The mean number of days missed per year was three. Adverse work outcomes were driven by psychological symptom domain. Lost work productivity impacts society, employers, and women with lost opportunities for advancement and increased financial insecurity. Based on workdays missed due to menopause symptoms, the estimated annual loss is $1.8 billion in the United States (U.S.). Importantly, menopause is not a disability or a disease, but it is important that employers understand that there are opportunities to help women seek treatment for their symptoms which would improve their work productivity. The annual excess direct medical costs of menopause are $1,346 per woman.[5] Costs including direct and indirect medical expenses are estimated at $26 billion annually.

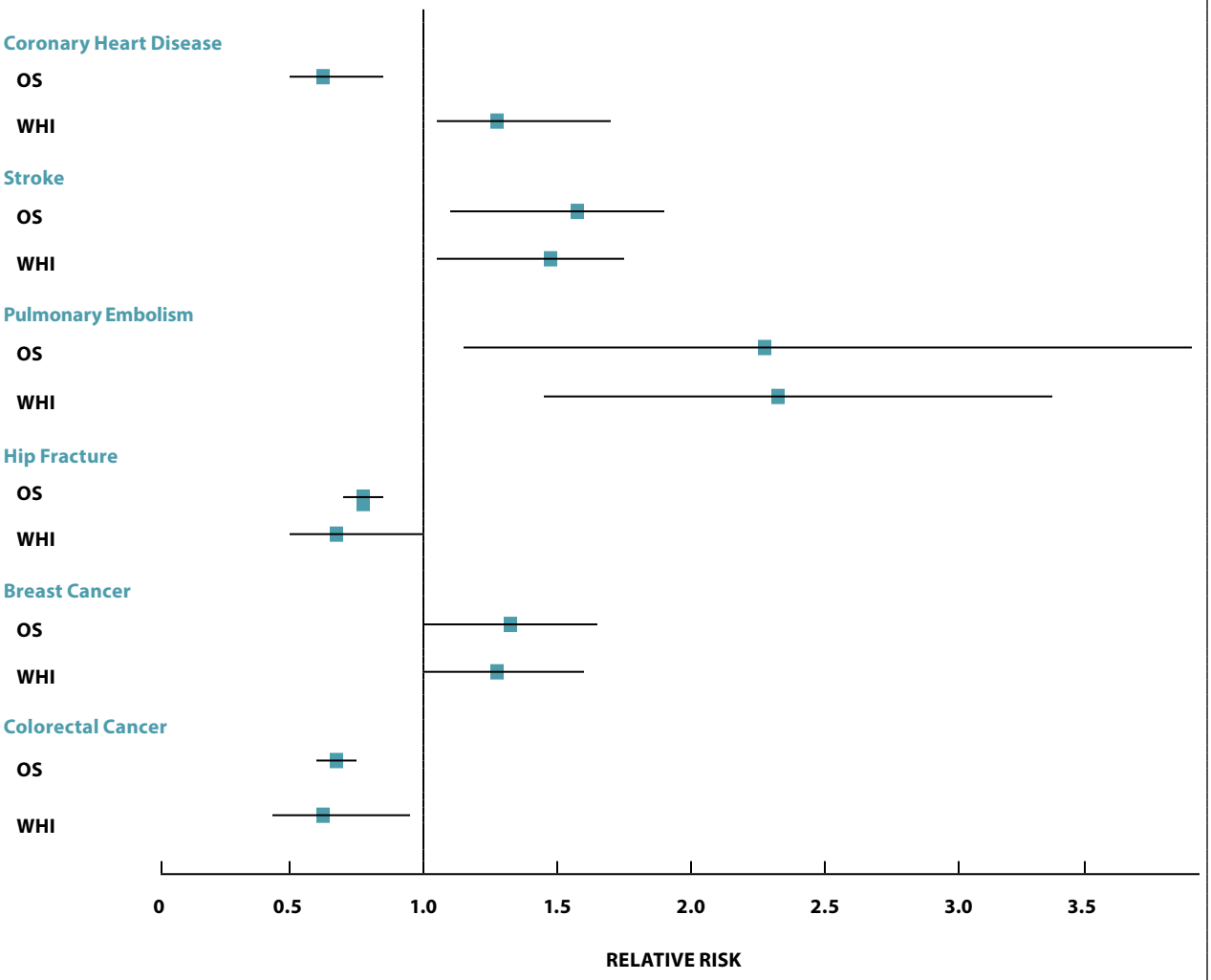
In the past, estrogen therapy seemed a logical answer to menopause symptoms based on menopause being associated with decreased estrogen and accelerated cardiovascular disease. Ergo, it was assumed giving estrogen would be cardioprotective. Observational studies, which enrolled women close to the average age of menopause, suggested that hormone therapy (HT) reduced the incidence of coronary heart disease (CHD), fractures, and colorectal cancer, but may increase the incidence of endometrial cancer, breast cancer, stroke, and venous thromboembolism. HT for menopause was the most prescribed medication in women. Then in the 1990's, the Women's Health Initiative (WHI) clinical trial was started to determine whether HT prevented heart disease and other chronic diseases. This trial randomized women with an intact uterus to conjugated equine estrogens (CEE) 0.625 mg/d plus medroxyprogesterone acetate (MPA) 2.5 mg/d (n = 8,506) or placebo (n = 8,102) and women with prior hysterectomy to CEE alone 0.625 mg/d (n = 5,310) or placebo (n = 5,429). The intervention lasted a median of 5.6 years in the CEE plus MPA trial and 7.2 years in the CEE alone trial with 13 years of cumulative follow-up until September 30, 2010. Since this was a double-blind placebo trial, women could not have symptoms of menopause and by design the average age was 62 years. Notably, except for the divergent findings about CHD, the WHI findings were largely concordant with the prior observational studies supporting estrogen use (Exhibit 2).[6] After this and other studies, cardiology groups recommended that HT no longer be prescribed to prevent heart disease and prescribers became reluctant to prescribe HT for menopause symptoms and women became reluctant to use the same. Hormone therapy prescribing rates are dismally low in the U.S. with less than 4 percent of women receiving such therapy.[7] Even though the WHI study is over two decades old, it still significantly depresses appropriate HT prescribing.

Further analyses of the WHI initiative have clarified when HT should be used. In the 50- to 59-year age group in the WHI study, the absolute risk of CHD was only modestly higher in those who took combination therapy and lower in those who took only estrogen compared to placebo.[8]

Currently, HT should not be started after age 60 because of the increased risk of CHD. Estrogen can have both positive and negative effects on the cardiovascular system. The impact of these effects varies by when HT is started relative to menopause. Estrogen has potentially beneficial effects on lipid parameters, such as reducing low-density lipoprotein cholesterol (LDLC) and increasing high-density lipoprotein cholesterol (HDLC), facilitating nitric oxide-mediated vasodilation, and inhibiting the response of blood vessels to injury and the development of atherosclerosis.[9]

Negatively, estrogen increases triglycerides and inflammatory markers such as C-reactive protein (CRP) and has many prothrombotic effects, such as increasing circulating levels of prothrombin and decreasing antithrombin III contributing to an increased risk of venous thromboembolic events.

Exhibit 2: Comparison of Observational Studies (OS) and Women's Health Initiative Study (WHI)[6]



Importantly, many of these effects of estrogen are mediated by first-pass effects on the liver, and thus result from oral but not transdermal administration of HT. In early atherosclerosis, the positive benefits of HT predominate whereas with established atherosclerosis (especially after age 60) estrogen's negative effects predominate. Overall, the risk of heart disease is low in women who do not have contraindication and start HT early after menopause.

Transdermal estrogen therapy may have advantages over oral therapy. Avoiding first-pass metabolism in the liver with transdermal therapy produces less effect on clotting factors, triglycerides, CRP, sex hormone binding globulin, blood pressure, and mammographic breast density.[10-12] There are no large-scale randomized trials assessing relative safety; these possible advantages are based predominately on small trials and observational data. Transdermal therapy can also be more convenient for the patient with weekly or biweekly administration compared to daily dosing with oral therapy. Many menopause specialist prefer prescribing transdermal therapy over oral estrogen.

Risk of breast cancer is another factor in selecting HT and is the most common concern of women considering HT. The risk related to HT use is low at less than one additional case per 1,000 women per year of use and is similar to that of certain modifiable risk factors (i.e., 2 daily alcoholic beverages, obesity, low physical activity).[13] After five years of HT, the risk is three cases per 1,000 and most cancers are being picked up very early because the women are being assessed yearly for appropriateness of continuing HT and possible adverse events. Risk is less with estrogen alone compared to combination therapy. In the WHI, there was greater breast cancer risk with

Exhibit 3: Approach to Hormone Therapy (HT) and Atherosclerotic Cardiovascular Disease (ASCVD)[14]

1. Evaluate Age, Time since Menopause and Symptoms

< 10 years from final menstrual cycle or < 60 years old + Bothersome Vasomotor Symptoms

2. ASCVD Risk Assessment and exclude HT Contraindications

ASCVD Risk Factors

- Hyperlipidemia
- Hypertension
- Diabetes
- Family history of premature CVD
  CVD in first-degree relative
  men < 55 or women
  < 65 years of age)
- Obesity (BMI) > 30
- Physical inactivity
- Cigarette smoking
- Coronary calcification (CAC 1-99
  moderate risk; CAC > 100 high risk
- History of preeclampsia
- History of systemic autoimmune
  collagen-vascular disease (e.g.,
  Lupus or Rheumatoid Arthritis)

Contraindications for systemic HT:

- Coronary heart disease, stroke, TIA
- Breast or endometrial cancer
- History of pulmonary embolus, venous
  thrombosis or clotting disorder
- Active liver disease
- Undiagnosed abnormal vaginal bleeding

3. Evaluate Risk Category

May consider HT

ASCVD risk <5% (low risk) and ≤1 CVD risk factor

May consider HT, transdermal formulation

ASCVD risk 5 to 10% or Low ASCVD < 5%, however ≥ 2 CVD risk factors

4. Follow up

TIA = transient ischemic attack; BMI = body mass index; CAC = coronary artery calcium

regimens containing a progestogen (specifically medroxyprogesterone acetate) versus regimens containing only estrogen (particularly conjugated estrogens).

The North American Menopause Society recommends HT for appropriate menopausal symptoms based on an individual patient evaluation.[7] The best candidate for HT is a woman under 60 years of age or 10 years or less past final menstrual period who has bothersome symptoms (VMS, mood, sleep), bone density concerns, or a personal preference to use HT. There should not be excess cardiovascular or breast cancer risk and no other contraindications. Exhibit 3 presents an approach to evaluating a patient for HT.[14] The transdermal route of administration should be considered for those with moderate atherosclerotic cardiovascular disease (ASCVD) risk and HT should potentially be avoided in those at elevated risks. Hormones should not be used to prevent CVD.

Menopause hormone therapy options are outlined in Exhibit 4. In women without a uterus, unopposed estrogen (oral, transdermal, or vaginal) can be used. With a uterus, a progestin or progesterone must be used to prevent endometrial hyperplasia and an eight-fold increase in endometrial cancer risk with unopposed estrogen. Transdermal progesterone cream, which is available without a prescription, will not provide sufficient blood levels to inhibit endometrial growth. Oral progesterone options include medroxyprogesterone and micronized progesterone. These can be given daily or on a cyclical basis. Transdermal progestin is available in a combination patch with estrogen but these formulations have limited dosing options. Intrauterine progesterone systems and vaginal gels are not FDA-approved for, nor should they be recommended for, endometrial protection in estrogen users.

The genitourinary syndrome of menopause (GSM) is associated with menopause-related estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and includes vaginal atrophy and major dryness. GSM symptoms will affect at least 50 percent of menopausal women. Symptoms do not improve without treatment and they are chronic and progressive. Treating GSM is important for not only vaginal and sexual health

Exhibit 4: Menopause Estrogen Therapy Options

- **Transdermal Estradiol**
  - Estradiol patches
    - Release rates (mg/24 hour):
    - 0.014*, 0.025, 0.0375, 0.05, 0.06, 0.75. 0.1
    - Change 1-2 x week depending on product formulation
  - Estradiol topical gels and emulsions
    - 0.012 – 1.25 mg foil packet or metered dose pump once daily
- **Oral Estrogen**
  - Conjugated Estrogen
    - 0.3, 0.45, 0.625, 0.90 mg once daily
  - Estradiol
    - 0.5, 1 mg once daily

* Indicated only for prevention of osteoporosis

but also for urinary health. Women with GSM have many more significant and potentially dangerous urinary infections. Vaginal products have minimal systemic absorption so a progesterone is not needed if only local vaginal estrogen is used. When HT is considered solely for GSM, local vaginal estrogen is recommended.[7] Low-dose vaginal estrogen preparations include creams, tablets, rings, and a soft gel insert. Oral estrogen does not always work for GSM so vaginal products may need to be added. Vaginal estrogen does not have the same restrictions of oral/transdermal being started before age 60, but it can be used at any age to manage GSM.

Non-hormonal agents are available for managing menopausal symptoms. These are important considerations for women who are poor candidates for HT. This includes women with a history of prior estrogen sensitive cancers (breast/endometrium), stroke, myocardial infarction, pulmonary embolus, venous thrombosis, clotting disorder, inherited high-risk for venous thromboembolic event (VTE), or severe active liver disease. Physiology of vasomotor symptoms is important in understanding the non-hormonal agents. The KNDy (kisspeptin, neurokinin B and dynorphin) neuronal plexus has direct effects on the adjacent hypothalamic thermoregulatory center which regulates body temperature.[15] Loss of feedback regulation of hypothalamic gonadotropin release hormone (GnRH) occurs during menopause. Vasomotor symptoms are triggered by hyperactivity of the KNDy neuron plexus leading to hypersecretion of neurokinin B. Neurokinin B receptor blockade has been found to reduce hot flashes.

Fezolinetant is an oral neurokinin 3 (NK3) receptor antagonist that was FDA-approved in 2023 for treatment of moderate-to-severe vasomotor symptoms due to menopause. In two 12-week Phase III randomized, placebo-controlled trials of fezolinetant 30 and 45 mg/d, both doses statistically significantly reduced VMS frequency and severity at weeks four and 12 versus placebo.[16] This was a decrease of 2.5 to three VMS per day over placebo response. It is important to note that there is a known 30 percent placebo response rate in VMS trials. Efficacy was maintained out to 52 in extensions of these two trials. Fezolinetant is available as a 45-mg tablet for daily dosing. A boxed warning was added to the fezolinetant package labeling in December 2024 related to potential hepatotoxicity and elevations in serum transaminase concentrations of more than three times the upper limit normally occurring in clinical trials. Liver function tests need to be performed before initiation, monthly for the first three months of therapy, and six and nine months after initiation. Real-world experience shows rare cases of hepatotoxicity. Headaches are the most common adverse event. Others include abdominal pain, diarrhea, insomnia, and back pain.

A second agent, elinzanetant, was approved by the FDA in 2025 for the treatment of moderate-to-severe vasomotor symptoms due to menopause. It is a selective neurokinin-1,3 (NK1,3) receptor antagonist. This agent was also evaluated in two Phase III, randomized, double-blind trials.[17] It significantly reduced VMS frequency and severity at weeks four and 12. The VMS frequency reduction was 3.0 to 3.3 per day. Additionally, there was significantly improved sleep and menopause-related quality of life. The most common adverse events were headaches, fatigue, dizziness, and somnolence. This agent also has a warning about potential hepatic transaminase increases but no liver toxicity was noted in the trials.

Elinzanetant, as a dual NK1,3 receptor antagonist, may be a better choice for improving sleep disturbances related to menopause than NK3 receptor antagonism seen with fezolinetant. NK3 receptor antagonism reduces VMS. NK1 receptor antagonism promotes sleep and vasodilatation.[18] Thus there may be synergy between NK1 and NK3 receptor antagonism to improve both sleep and VMS. NK1 receptor antagonism has also been shown in an animal model to reduce the visceral fat accumulation associated with loss of estrogen. The two NK antagonists have not been studied head-to-head.

There are other non-hormonal options. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), 7.5mg daily has an FDA indication for the

treatment of moderate-to-severe VMS. Other SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRI) have also been studied for VMS. Gabapentin has been shown to reduce VMS by 50 to 60 percent and has been used off-label at a dose of 600-900 mg/day. Pregabalin is not recommended for VMS because of adverse events and controlled-substance prescribing restrictions.[7] Due to significant adverse events and no recent studies showing greater benefit than placebo, clonidine is also not recommended. Non-pharmacologic therapies supported by the guidelines for managing menopause symptoms include weight loss (Level II), cognitive-behavioral therapy (Level I), and clinical hypnosis (Level I).[7]

Conclusion

The cost of menopausal symptoms to women, the healthcare system, employers, and society are staggering. There is a critical need to improve the medical treatment provided to women with menopause symptoms. Hormone therapy is the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. For genitourinary syndrome of menopause not relieved with nonhormone therapies, low-dose vaginal estrogen is available and recommended and does not have the same restrictions of oral/transdermal being started before age 60 years. For women with contraindications or personal preference not to use hormone therapy, there are good non-hormonal treatment options available.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Non-Small Cell Lung Cancer

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Summary

The introduction of targeted therapy for specific genetic mutations which drive this cancer and immunotherapy have changed the management of advanced non-small cell lung cancer (NSCLC) in recent years. The treatment paradigm for NSCLC continues to evolve as these agents are now being used in early-stage resectable disease.

Key Points

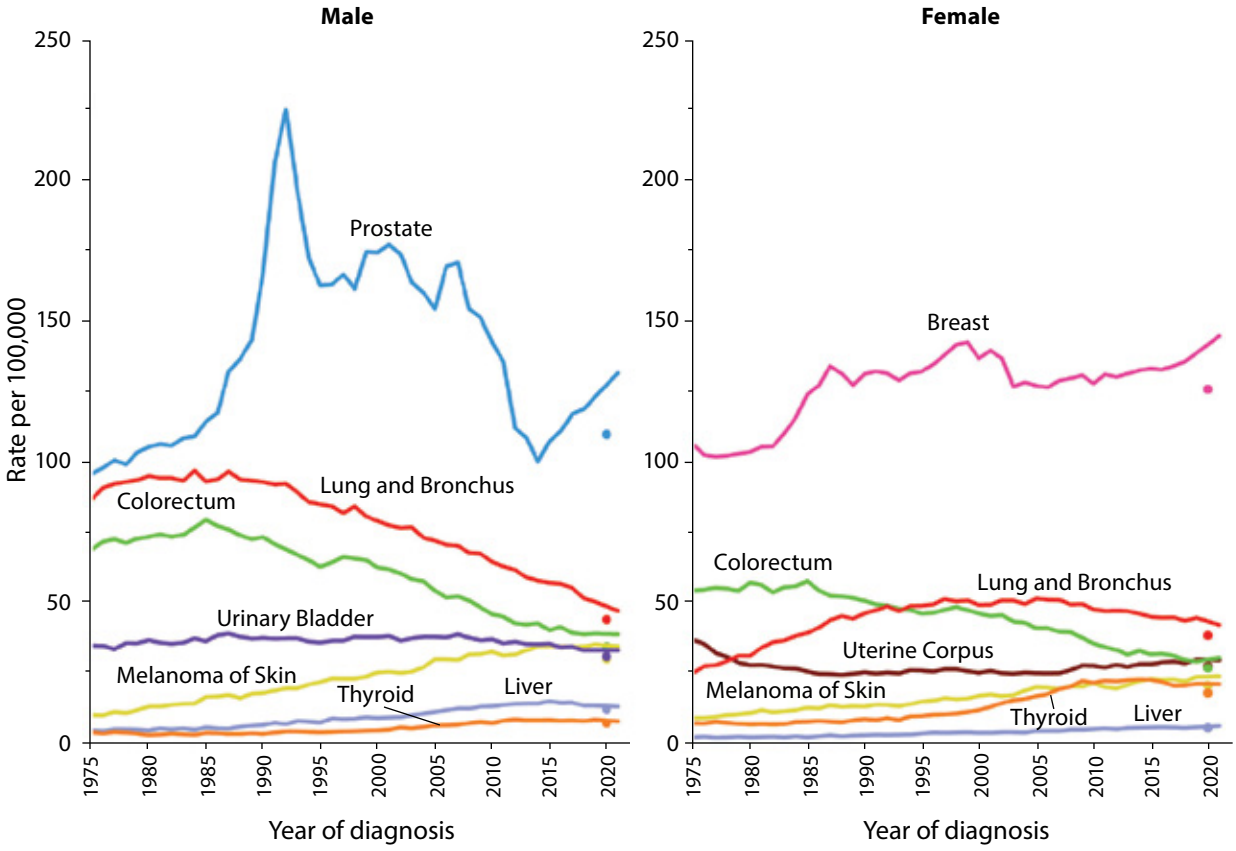
- Targeted therapies are first-line for those with advanced disease and actionable genetic mutations.
- Immunotherapy with or without chemotherapy is the first-line option for those with PD-L1 expression and no actionable mutations.
- Targeted therapies and immunotherapy are used in early-stage NSCLC to delay recurrence and improve survival.
- Managed care must find a way to better evaluate the value of new treatments.

LUNG CANCER IS THE SECOND MOST common cancer in both men and women in the United States (U.S.).[1] In 2025, an estimated 245,700 cases of lung cancer will be diagnosed and 130,200 people will die from this cancer. Lung cancer deaths have been declining in both men and women, reflecting decreases in smoking, but are still the leading cause of cancer deaths (Exhibit 1).[1] Lung cancer is the most common cause of cancer death for most ethnic groups.

Driver mutations and programmed cell death ligand 1 (PD-L1) expression are two key factors in initial treatment selection for advanced (Stage IV) NSCLC. Others include the extent of disease, including the number and sites of metastases, squamous versus nonsquamous histology, performance status, comorbidities, and brain or liver metastases.[2] If a patient with advanced NSCLC has targetable mutations, targeted therapy is first-line. 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, for those without targetable mutations.

Molecular testing identifies patients with advanced NSCLC who may benefit from targeted therapy or immunotherapy. The National Comprehensive Cancer Network (NCCN) Guidelines list specific mutations which should be tested for at the time of diagnosis, but also strongly advises broad molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials.[2] About

Exhibit 1: Lung Cancer Rates Over Time in Men and Women[1]



75 percent of NSCLC tumors harbor genomic alterations amenable to targeted therapy with the most common mutations being KRAS and EGFR (Exhibit 2).[3] The American Society of Clinical Oncology (ASCO) and NCCN Guidelines both include recommendations for which targeted agent to select depending on the mutation found.[2,4]

Epidermal growth factor receptor (EGFR) mutations, particularly in exons 19 and 21, are significant drivers in NSCLC. EGFR auto-phosphorylation triggers EGFR-dependent downstream signaling pathways, similar to PI3K and RAS which promote cell growth and proliferation.[5] Activating mutations (exon 19 deletions and the L858R point mutation in exon 21) comprise 90 percent of EGFR mutations found in NSCLC and are well defined as strong predictors for good clinical response to an EGFR tyrosine kinase inhibitor (TKI).[6] EGFR exon 20 insertion mutation occurs in about 3 percent of NSCLC cases and is more commonly found in people who have never smoked or are Asian.

An EGFR TKI is first-line therapy for a patient with activating EGFR mutations as these agents produce better overall survival (OS) than chemotherapy.[2] Osimertinib is a preferred EGFR TKI for exon 19 deletion or exon 21 L858R mutations because it overcomes T790M resistance mutations (which are common), penetrates the central nervous system, and produces better progression-free survival (PFS) compared to older EGFR TKI. Osimertinib monotherapy, osimertinib plus carboplatin or cisplatin and pemetrexed, or lazertinib plus amivantamab are all Category 1 preferred agents in the NCCN Guidelines.[2] In patients with exon 19 deletion or exon 21 L858R, osimertinib improved OS relative to standard of care (38.6 versus 31.8 months; HR 0.80).[7] When combined with platinum/pemetrexed chemotherapy, there was an improved PFS compared to osimertinib alone (29.4 versus 19.9 months; HR 0.62).[8]

Amivantamab, a bispecific EGFR and cMET antibody, and lazertinib, a third-generation EGFR TKI that irreversibly inhibits EGFR by forming a covalent bond to the Cys797 residue in the ATP-

Exhibit 2: Driver Mutations in NSCLC[3]

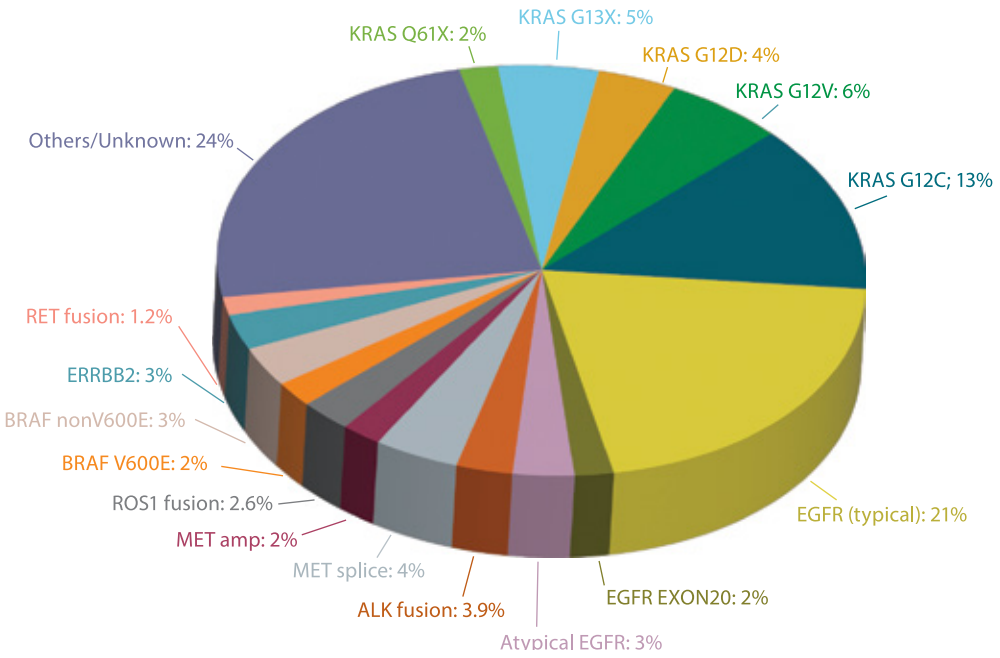
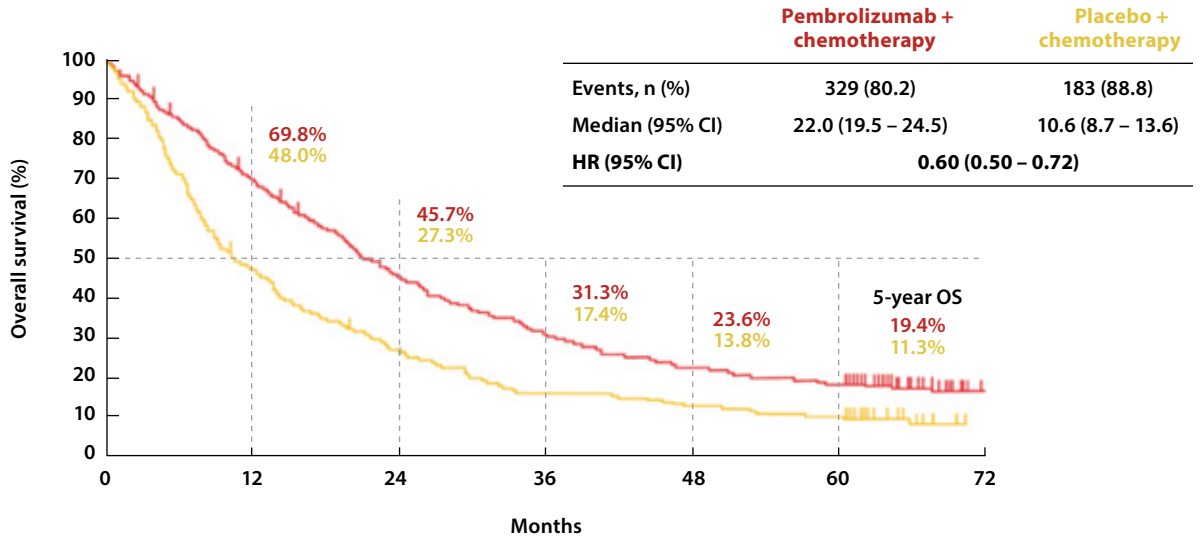


Exhibit 3: Keynote 189 Five-year Overall Survival[13]



	Pembrolizumab + chemotherapy	Placebo + chemotherapy
Events, n (%)	329 (80.2)	183 (88.8)
Median (95% CI)	22.0 (19.5 – 24.5)	10.6 (8.7 – 13.6)
HR (95% CI)	0.60 (0.50 – 0.72)	

binding site, improved PFS compared to osimertinib (23.7 versus 16.6 months; $p < 0.001$).[9] Final OS data from this trial are not yet available. This combination may become preferred over osimertinib once more data are available. For EGFR S768I, L861Q, and/or G719X mutations, afatinib or osimertinib are the preferred first-line agents.

For exon 20 insertion mutation (which is not an activating mutation), the NCCN Guidelines recommend amivantamab in combination with carboplatin/pemetrexed as preferred first-line therapy for nonsquamous disease. In patients with advanced NSCLC with EGFR exon 20 insertions, who had not received previous systemic therapy,

Exhibit 4: Approved Immunotherapy Agents for Neoadjuvant/Adjuvant Therapy

Drug	Indication
Pembrolizumab	Approved for resectable NSCLC with chemo for neoadjuvant and single agent for adjuvant therapy.
Atezolizumab	Adjuvant treatment following surgery and platinum-based chemotherapy for adults with Stage II - III A non-small cell lung cancer (NSCLC) whose tumors express PD-L1 ≥ 1%.
Nivolumab	Neoadjuvant with chemo followed by single-agent nivolumab after surgery as adjuvant treatment, for adults with resectable NSCLC and no known EGFR mutations or ALK rearrangements.
Durvalumab	With chemo for resectable Stage IIA to IIIB tumors with no known EGFR mutations or ALK rearrangements for neoadjuvant and single agent for adjuvant.

Exhibit 5: The Challenges in Oncology Management[24]

Challenges	Payers Selecting Challenge		Lives Represented by Payers Selecting Challenge	
	n	%	n (millions)	%
It is difficult to compare products and select a preferred one.	19.0	90	115.7	95
The patient population is too complex; physicians need to maintain the ability to choose.	13.0	62	102.9	85
The evidence is not mature enough.	12.0	57	72.9	60
Government regulations prevent me from managing this category.	14.0	67	69.2	57
I will receive physician pushback if I manage this category.	11.0	52	49.1	40
There are limited therapeutic agents in this category.	9.0	43	38.5	32
Patient advocacy groups.	7.0	33	32.8	27
Other organizations do not manage this category.	5.0	24	29.0	24
Science advances too quickly.	5.0	24	27.2	22

Note: This table reflects responses from 21 payers, representing 121.5 million lives.

amivantamab plus chemotherapy improved PFS better than chemotherapy alone (11.4 versus 6.7 months; $p < 0.001$).[10] Final survival data from this trial are not yet available. Another trial of the same combination versus chemotherapy alone found comparable results (15.5 versus 6.6 months).[11] For adenocarcinoma or squamous NSCLC with an exon 20 insertion mutation, chemotherapy is the preferred first-line therapy.[2]

For management of NSCLC without an identifiable driver mutation, immune checkpoint inhibitors targeting PD-1 or PD-L1 have become a routine part of the clinical approach. 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.[2,12] The ASCO guidelines provide a strong recommendation based on high quality evidence for pembrolizumab, cemiplimab, or atezolizumab for the 50 percent or more population and the use of these immunotherapies with chemotherapy is a weak recommendation based on moderate evidence.[12] For patients with PD-L1 expression less than 50 percent, the combination of a platinum-doublet chemotherapy and a checkpoint inhibitor is standard. For those with 1 to 49 percent expression, the ASCO guidelines recommend pembrolizumab or cemiplimab plus chemotherapy as a strong recommendation based on moderate evidence.[12]

Improvement in long-term survival is a primary reason for immunotherapy being recommended in those positive for PD-L1 expression without driver mutations. Five-year OS rates comparing pembrolizumab chemotherapy combination to

chemotherapy alone were 19.4 percent versus 11.3 percent (Exhibit 3).[13] OS improvements were observed in all PD-L1 categories, with the greatest numerical differences observed in 50 percent or greater PD-L1-expressing tumors. Similar five-year OS data was recently presented but not yet published with cemiplimab plus chemotherapy compared to chemotherapy alone (19.4% versus 8.8%).[14]

The treatment of NSCLC in earlier stages is also evolving. Patients with Stage I, II, or III NSCLC are at substantial risk for recurrence and death even after complete surgical resection.

Approximately 25 percent of patients with Stage IB, 35 to 50 percent of Stage II, and a greater percentage of those with Stage III NSCLC eventually recur and die. Treatment of early-stage disease includes resection, platinum-based chemotherapy, radiotherapy, and adjuvant immunotherapy with checkpoint inhibitors or targeted therapy post-resection. Treatment approaches for unresectable Stage III NSCLC are less well defined. Exhibit 4 shows the FDA approvals of immunotherapy for resectable, early-stage disease.

Clinical trials have consistently shown that incorporating checkpoint immunotherapy into the early-stage treatment regimen (either before or after surgery) significantly extends the time patients live without their cancer returning.[15-17] This benefit is particularly pronounced compared to traditional chemotherapy alone, which offers only modest (4 to 5%) improvements in five-year survival rates. Adjuvant and neoadjuvant immunotherapy may also improve OS. Thirty-six-month OS in one pembrolizumab trial was 71 percent in the pembrolizumab group and 64 percent in the placebo group.[18]

NSCLC costs are driven primarily by outpatient visits and medication costs, especially for immunotherapy and targeted agents.[19] Medication costs account for 50 percent of cancer care costs as almost every newly approved cancer drug has an annual cost greater than $120,000.[20,21] Although costly to treat, society appears to be benefiting from the increased costs. In one study, population-level mortality in the U.S. from NSCLC fell sharply from 2013 to 2016, and survival after diagnosis improved, which was driven by new therapies.[22] Survival trends over this period of time improved broadly by gender and race/ethnicity. Despite improvements in survival, financial toxicity is a real concern. Financial toxicity is the detrimental effect of the excess financial strain caused by the diagnosis of cancer on the well-being of patients and is becoming an important consideration in cancer care.[23]

Managing cancer medications has been difficult for payers. In a 2019 survey, 21 payers were asked about general oncology product management, use of specific management tools, management challenges, and expected use of specific management tools. When compared with other high-cost disease areas such as diabetes, multiple sclerosis, bleeding disorders, rheumatoid arthritis, psoriasis, and hepatitis C virus, oncology was rated as the highest budget impact category. The top five challenges to payers for oncology management were difficulty comparing products, complex patient population, lack of mature evidence, government regulations, and physician pushback (Exhibit 5).[24]

Conclusion

The treatment of advanced NSCLC continues to evolve. For those patients with selected driver mutations, targeted therapy is the initial therapy choice. Immunotherapy is the treatment option for many patients without driver mutations. The management of early-stage NSCLC is being changed through use of targeted therapy and immunotherapy. Payers still struggle with managing the use of these agents and their impact on treatment costs.

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Keeping Pace with the Rapid Advancements in the Treatment and Management of nAMD and DME: Expert Managed Care Strategies on the Role of Anti-VEGF Therapies

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Summary

Age-related macular degeneration and diabetic retinopathy are two common causes of vision loss. Preventing this loss is possible if either condition is identified, however, some treatments have significant treatment burden. Advances have been made in improving treatment burden with extended dosing intervals and more therapies are on the horizon.

Key Points

- Treatment of nAMD and DR requires frequent intravitreal injections but these can significantly help vision.
- Adherence and treatment burden can be an issue.
- Aflibercept 8 mg and faricimab help to extend the interval between injections.
- Upcoming therapies may help extend patients even longer or treat disease with a single injection.

NEOVASCULAR (WET) AGE-RELATED MACULAR degeneration (nAMD) is the leading cause of severe decrease in visual acuity in people older than 50 years of age.[1] It is estimated that 18.3 million people in the United States (U.S.) are living with early-stage AMD and 1.89 million have late-stage AMD and these numbers are expected to increase significantly as the U.S. population ages.[2] Exhibit 1 shows the classification of AMD based on clinical findings.[3,4]

The standard treatment for nAMD is intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors. Aflibercept 2 mg, aflibercept 8 mg, brolucizumab, ranibizumab, faricimab, and compounded bevacizumab (off-label) are the available options. Many clinical trials have shown significant efficacy of intravitreal injections with stabilized or improved vision. More frequent physician visits and intravitreal injections are associated with greater effectiveness and improvement in vision.[5]

Frequent visits, especially monthly, can be challenging for patients. From one survey, the time commitment of injections is the biggest adherence barrier for patients (Exhibit 2).[6] On average, patients in this survey were affected by 3.1 barriers. High patient burden results in poor adherence which leads to vision loss that would not otherwise occur. A real-world study in eight countries found that visual acuity improvement with intravitreal injections falls off after about four months of therapy—likely because of nonadherence.[7] Overall, real-world challenges of AMD include high patient burden, need for potentially lifelong injections, improvements in vision and absence of fluid may not be maintained long-term, need for repeated imaging, and increased risk for complications with frequent injections. Fewer injections are administered in

Exhibit 1: Classification and Clinical Findings of AMD[3,4]

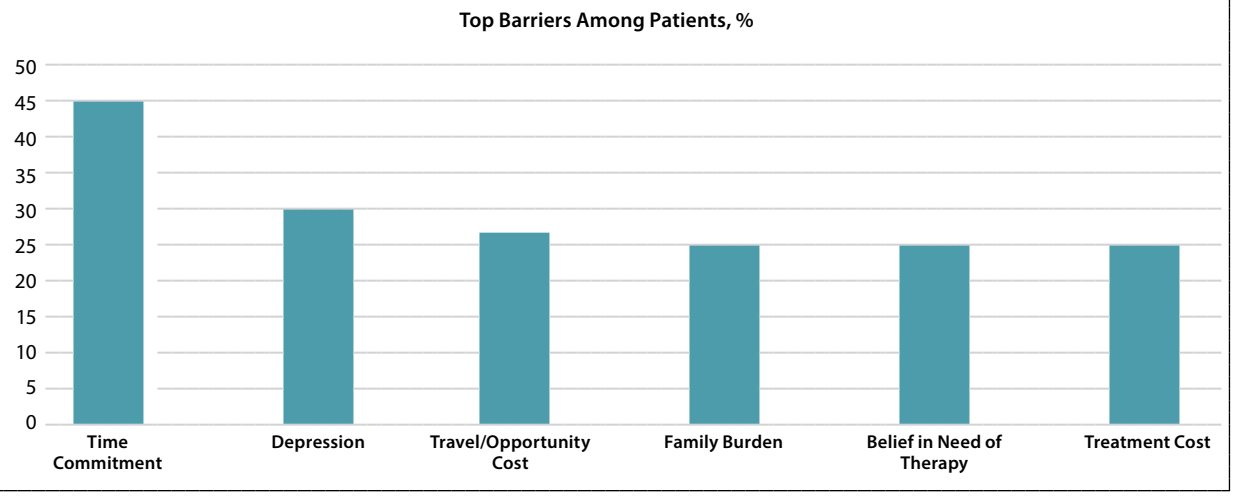
Classification	Clinical Findings
No AMD	No drusen and no RPE abnormalities
Normal aging changes	Drusen ≤ 63 µm and no RPE abnormalities
Early AMD	Drusen > 63 µm and ≤ 125 µm and no RPE abnormalities
Intermediate AMD	Drusen > 125 µm and/or RPE abnormalities
Late AMD	GA and/or nAMD

Drusen Size

Small: < 63 µm
Medium: 64 – 124 µm
Large: > 125 µm

GA = geographic atrophy; RPE = retinal pigment epithelium; nAMD = neovascular age-related macular degeneration.

Exhibit 2: Adherence Barriers in Patients[6]



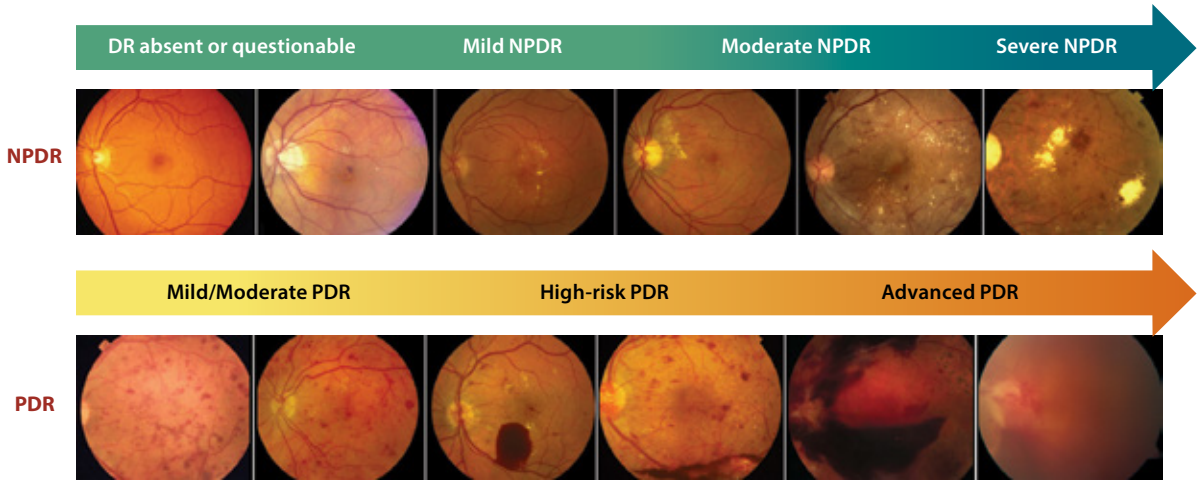
clinical practices compared with clinical trials where the benefits have been shown.

The challenges of AMD have spurred exploration of alternate dosing strategies and less burdensome treatments with longer half-lives. Longer duration anti-VEGF agents have been developed. These include aflibercept 8 mg and faricimab. An implantable port delivery system that can deliver medication continuously to the eye is also FDA-approved.

Aflibercept 8 mg is a higher dose version of aflibercept which can be given every 12 to 16 weeks with similar best corrected visual acuity (BCVA) and central subfield thickness (CST) when compared to aflibercept 2 mg every eight weeks.[8] Eighty percent of patients in the comparison trial were able to be dosed every 16 weeks or longer and 53 percent of those had a dosing interval of 20 or 24 weeks. Extend and treat is an approach used with anti-VEGF injections. Once a patient has no disease activity, their dosing interval can be extended. If disease activity is detected at a follow-up visit, the dosing interval is shortened. Being able to control nAMD with three or four injections a year is a substantial change in thinking in ophthalmology and a huge benefit for patients.

Faricimab is a long-acting dual-mechanism antibody with two different antigen-binding fragment regions; one which targets VEGF and the other targeting angiopoietin-2. In a trial comparing aflibercept 2 mg every eight weeks and faricimab 6 mg every 16 weeks using a treat-and-extend regimen, at two years those in the faricimab group achieved disease control with fewer injections.[9] About 63 percent of those in the faricimab group were able to achieve 16 week or greater dosing at the end of two years. Although it was not part of

Exhibit 3: Stages of Diabetic Retinopathy[13]



NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

the study, a post-hoc analysis determined that more than 50 percent of faricimab group met criteria for every 20-week dosing.

The third way to extend the dosing interval is with a ranibizumab port delivery system (PDS). The PDS is a permanent refillable intraocular implant surgically placed in the eye which releases 100 mg/mL ranibizumab into the vitreous in a controlled manner over six months. Refills of the implant are possible in the office setting. This system reduces the risk of frequent intravitreal injections but has not been widely adopted because of the need for surgical implantation and the risks of eye surgery.[10]

In development for nAMD are a long-acting hydrogel delivery platform (HDP) and gene therapy.[11] The HDP uses a preservative-free, biodegradable, polyethylene glycol network implanted in the eye to create sustained-release therapy. The meshwork traps medication and, when administered, it hydrates and dissolves to release the bound medication into surrounding tissue for six months or longer. Post-delivery, the hydrogel biodegrades and is cleared from the body.

Gene therapy offers the potential to treat nAMD with a one-time office visit. The modified gene is delivered to the target cells using a modified virus (vector). Once the gene is inserted within the DNA, the cells produce anti-VEGF protein on their own, thereby delivering long-term expression of therapeutic levels of anti-VEGF protein in the eye. Sustained delivery of anti-VEGF protein would facilitate better disease control in patients with nAMD and decrease clinic visits and other treatment burdens.

Diabetic retinopathy (DR) is another issue which may be treated with anti-VEGF therapies. Twenty-eight percent of adults with diabetes, 40 years of age or older, have DR and it is the leading cause of blindness for adults aged 20 to 74 years. Risk factors for DR include duration of diabetes, poor disease control, hypertension, nephropathy, obesity, hyperlipidemia, smoking, and pregnancy.[12] Every 1 percent increase in hemoglobin A1C levels corresponds to a 50 percent increased risk of diabetic macular edema (DME). As DR worsens it begins to affect quality of life through increasing visual difficulties. Exhibit 3 shows the stages of DR from mild non-proliferative diabetic retinopathy (NPDR) to advanced proliferative DR (PDR).[13]

Five to 10 percent of patients with diabetes and no retinopathy will progress to retinopathy within one year and 5 percent to 10 percent with mild NPDR will also progress within one year. Mild NPDR is defined as very mild microaneurysms only or some mild hemorrhages. Those with mild NPDR should be seen annually for follow-up. Moderate NPDR includes marked hemorrhages and microaneurysms. Peripheral lesions (cotton wool spots, venous beading) increase the risk of progression. These patients should be seen every six months. As many as 16 percent of patients with moderate NPDR can progress to proliferative disease within four years. Severe or very severe NPDR is defined by a 4-2-1 rule—marked hemorrhage in all four quadrants, venous beading in two or more quadrants, and marked intraretinal microvascular abnormalities

in one quadrant. Severe NPDR meets any one of the criteria and very severe meets two of three criteria. These patients should be followed every three to four months. Between 15 percent (severe NPDR) and 45 percent (very severe) of patients progress to high-risk PDR within one year. Most of these patients should be referred to a retina specialist—many patients may already have neovascularization.

Proliferative diabetic retinopathy (PDR) has retinal neovascularization of the optic disc or elsewhere. Response to ischemia from capillary closure results in vessels growing onto lattice of vitreous. These new vessels are fragile and easily ruptured. Neovascularization is divided into high risk and low risk. High risk requires immediate treatment. Treatment of retinopathy is possible with anti-VEGF therapy or pan retinal photocoagulation laser for PDR and moderate/severe NPDR with diabetic macular edema.

Diabetic macular edema (DME) is a subset of DR that can happen at any stage and is characterized by vascular leakage and vision loss. Because the risk of visual loss is greatest if macular edema is at the center of the macula, DME is subdivided as either center involved (CI-DME) or noncenter-involved (NCI-DME). CI-DME is treated with intravitreal anti-VEGF agents. Both aflibercept 8 mg and faricimab have been shown effective for managing DME with extended dosing intervals.[14,15] Tyrosine kinase inhibitors, hydrogel delivery platforms, and gene therapy are also being studied in DME and DR.

Unfortunately, despite recommendations for a yearly dilated eye exam in everyone with diabetes, adults aged 18 years and over, with diagnosed diabetes, who received a dilated eye exam within the past year, was only 66 percent in 2023.[16] Numerous barriers to getting eye care for those with diabetes have been identified. In one study, the most reported reasons for not receiving eye care were "no need" and "cost or lack of insurance" (39.7% and 32.3%, respectively).[17] Other reasons were "no eye doctor," "no transportation" or "could not get appointment" (6.4%), and "other" (21.5%). Additionally, only about half of those with diagnosed DR are currently being treated. Managed care can have an impact on improving eye exam rates among those with diabetes diagnosed. System based efforts to improve screening rates include utilization of electronic medical records, system alerts, educational programs, and combination of primary care and eye care services into single facilities.

Five major technological advances in imaging have led to improved DR detection. These are fundus photography, optical coherence tomography (OCT), OCT-angiography, telemedicine, and artificial intelligence. Fundus photography uses a specialized camera to capture detailed images of the back wall of the eye, including the retina, optic nerve, and blood vessels. The two types are standard and ultra-widefield. Ultra-widefield improves the rate of DR detection through telemedicine.[18] OCT is a non-invasive imaging technique that uses light to create high-resolution, cross-sectional images of the retina and other tissues. OCT-angiography uses motion contrast from repeated scans to visualize blood flow in the retina, unlike standard OCT which only shows structure. It works by detecting the movement of red blood cells between rapidly acquired scans, allowing it to create an angiogram. Telemedicine is one way to improve DR screening rates because it eliminates some barriers, such as transportation.[19] Artificial intelligence-based grading of retinal images can improve sensitivity and specificity of DR diagnosis. It can be used to determine when a primary eye-care patient should be referred to a retina specialist rather than referring all patients with diabetes—especially in environments where eye care resources are scarce. Although AI platforms for DR exist, some challenges that need to be overcome include insufficient image quality and reimbursement.

Conclusion

Treatment of nAMD and DME requires frequent injections but this can significantly help vision. Adherence and treatment burden can be an issue. Current FDA-approved therapies (Aflibercept 8 mg and Faricimab) help to extend patients longer between injections. Upcoming therapies may help extend patients even longer or treat disease with a single injection. There have been incredible treatment advances in the retina treatment field of retina, with the future even more exciting.

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Best Practices in the Treatment and Management of HR+/HER2- Breast Cancer

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

Summary

Over the past three decades, extensive and advocate-driven breast cancer research has led to extraordinary progress in the understanding of the disease. This has resulted in the development of more targeted and less toxic treatment principally for women with hormone receptor positive/human epidermal growth factor negative breast cancer, especially in the setting of advanced and metastatic disease. There are now many options which allow multiple lines of therapy, even in late-stage disease.

Key Points

- The role of the CDK4/6 inhibitors in both metastatic and early-stage disease is well established and supported by significant PFS and OS data.
- Choice of CDK4/6 inhibitor needs to be individualized based on patient-level evaluation of adverse event risk and out-of-pocket costs.
- A TROP2 directed ADC for later-line therapy is now available.

BREAST CANCER IS THE MOST COMMON cancer in women, excluding skin cancer. In 2025, an estimated 316,000 people in the United States (U.S.) will be diagnosed with invasive breast cancer.[1] Breast cancer is the second most common cause of cancer death in women with an estimated 42,170 deaths in 2025. Metastatic breast cancer will cause most of those deaths. Six percent of women have metastatic disease when they are first diagnosed.

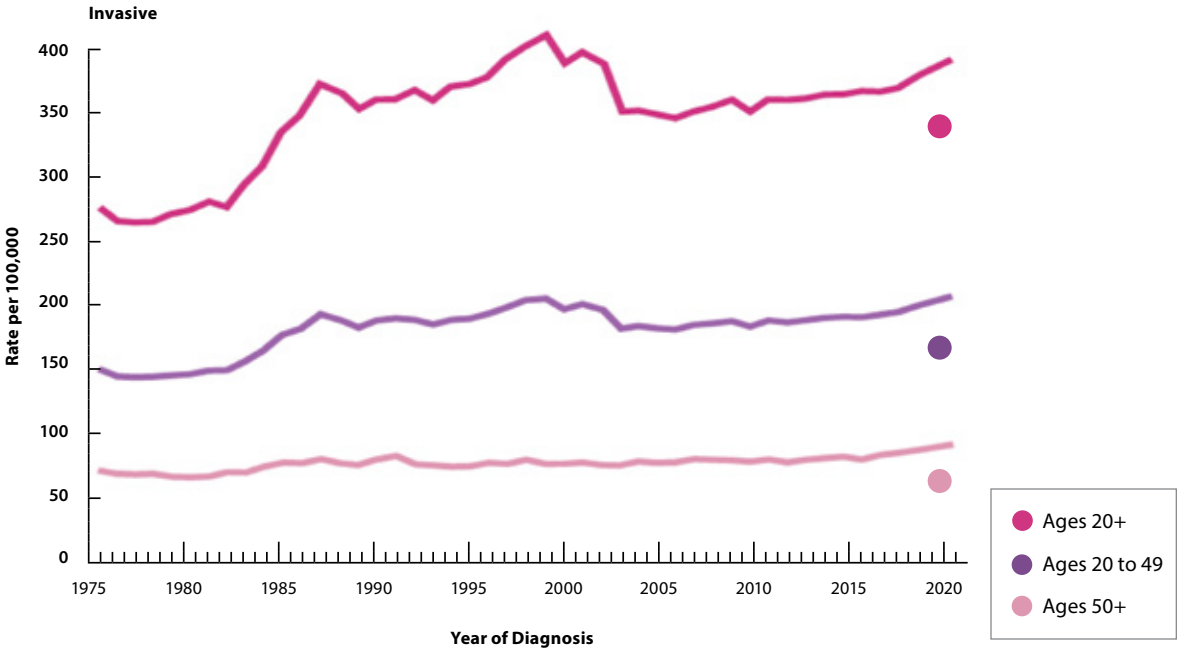
The incidence of breast cancer has been increasing slowly (Exhibit 1).[2,3] About one in eight U.S. women (~13%) will develop invasive breast cancer over the course of their lifetime.[4] There are about 4 million women with a history of breast cancer in the U.S., including women currently being treated and those who have completed 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.[5] About 5 to 10 percent of breast cancers can be linked to known gene mutations. Mutations in the BRCA1 and BRCA2 genes are the most common. On average, women with a BRCA1 mutation have up to a 72 percent lifetime risk of developing breast cancer. For women with a BRCA2 mutation, the risk is 69 percent. Breast cancer that is positive for the BRCA1 or BRCA2 mutations tends to develop more often in younger women. However, 85 percent of breast cancers occur in women who have no family history of breast cancer.

In general, breast cancer can be broken down into three biologic subgroups, each of which has a direct bearing on treatment choices. This includes those that express the estrogen receptors (ER), those that express the human epidermal growth factor receptor 2 (HER2), and those that do not express either of these, or the progesterone receptor (triple-negative). HER2 disease can be positive or negative for ER expression. The focus for this article is hormone receptor positive (HR+)/HER2- breast cancer.

Some of the most significant progress in treating breast cancer has been the use of adjuvant therapies before or after surgical resection in early-stage disease. Adjuvant breast cancer therapies are designed to treat micrometastatic disease that has escaped the breast and regional lymph nodes but has

Exhibit 1: Invasive Breast Cancer Incidence in Women[2,3]



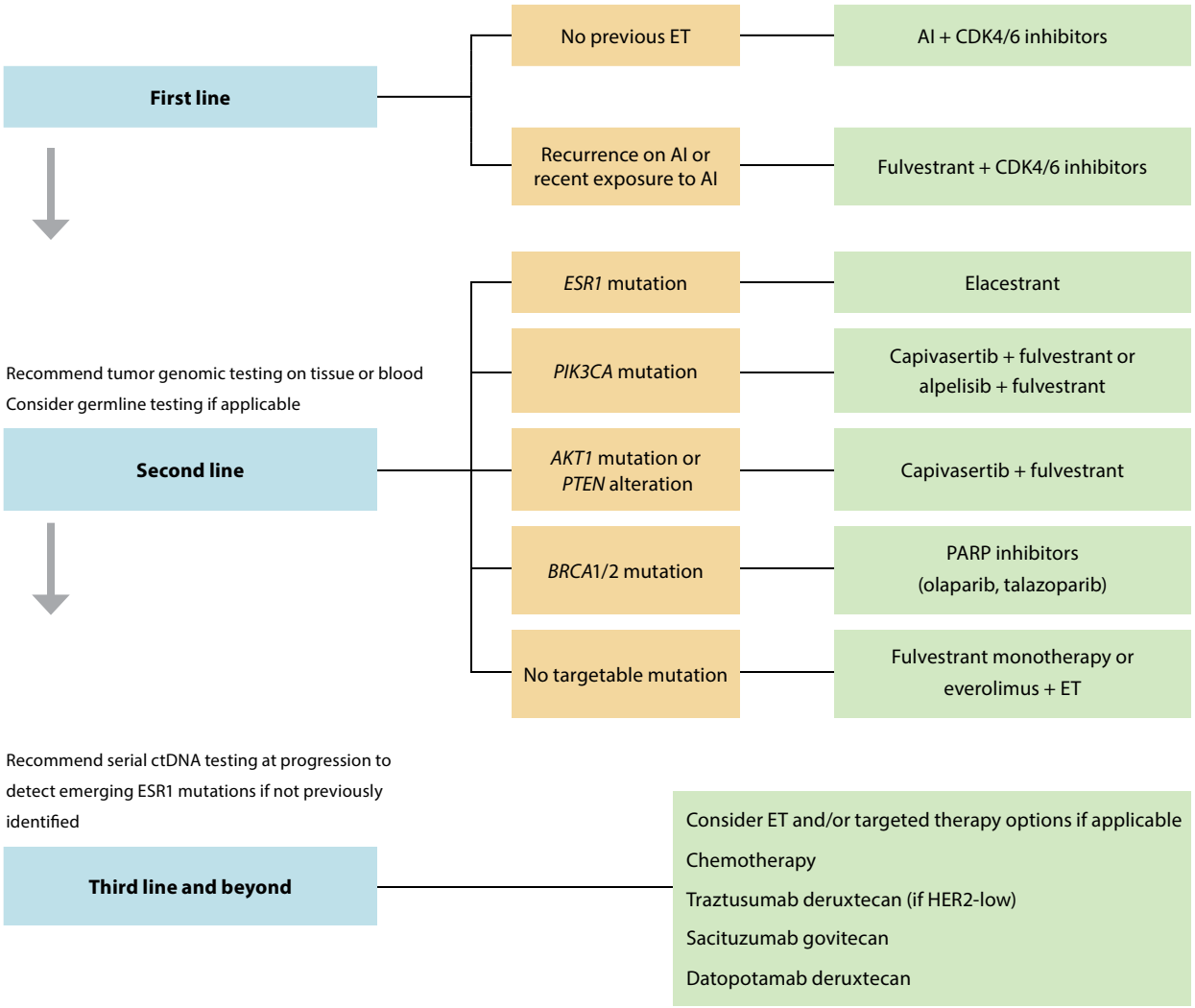
yet established identifiable metastasis. Depending on the model of risk reduction, adjuvant therapy has been estimated to be responsible for 35 to 72 percent of the decrease in mortality. In HR+/HER2- disease, there are many different adjuvant therapies which can be used including endocrine therapy (ET), cyclin-dependent kinase (CDK) 4/6 inhibitors, chemotherapy, and radiation.

The major focus in HR+/HER2- disease is to deplete estrogen. This can be done through surgical or pharmacologic oophorectomy in premenopausal women or with aromatase inhibitors [(AI), anastrozole, letrozole, exemestane] in postmenopausal women or the use of selective ER modulators (tamoxifen or raloxifene), or selective ER down-regulators (fulvestrant and elacestrant). Beyond agents that directly target estrogen, there is use of targeted agents which include CDK4/6 inhibitors, everolimus (an inhibitor of mTOR), alpelisib (tumor PIK3CA mutations), and for advanced disease, TROP2-directed antibody drug conjugate.

Patients with ER-positive metastatic breast cancer often respond to estrogen depletion therapy, also called ET, alone or in combination with targeted agents, which can reduce tumor burden and symptoms with generally fewer side events and toxicities than chemotherapy.[6,7] Modern ETs appear to prolong progression and possibly survival compared with older ETs. However, few if any patients with metastatic breast cancer will be cured, and the goal of therapy is principally, palliation. Patients will typically go through multiple lines of therapy with metastatic disease. A general approach to treatment is shown in Exhibit 2.[8]

CDK4/6 inhibitors interrupt the process through which breast cancer cells divide and multiply by targeting cyclin-dependent kinases 4 and 6. They block cell-cycle progression in the middle of the G1 phase. Palbociclib, ribociclib, and abemaciclib are the three FDA-approved options. In 2015, palbociclib became the first CDK4/6 inhibitor to receive accelerated FDA approval for HR+/HER2- breast cancer treatment. The current indications for this agent are treatment of advanced or metastatic breast cancer (mBC) in combination with an AI as initial endocrine-based therapy, or fulvestrant in patients with disease progression following ET. It is also approved for use in combination with inavolisib and fulvestrant for the treatment of adult patients with endocrine-resistant, PIK3CA-mutated, HR+/HER2-, locally advanced or mBC following recurrence on or after completing adjuvant ET. In combination with letrozole, palbociclib improved median progression-free survival [(PFS), 20.2 versus 10.2 months; one-sided $p = 0.0004$] but did not statistically improve median overall survival [(OS), 49.8 versus 53.8 months; one-sided $p = .21$).[9,10] In combination with

Exhibit 2: Current Treatment Approaches for Metastatic HR+/HER2- Breast Cancer[8]

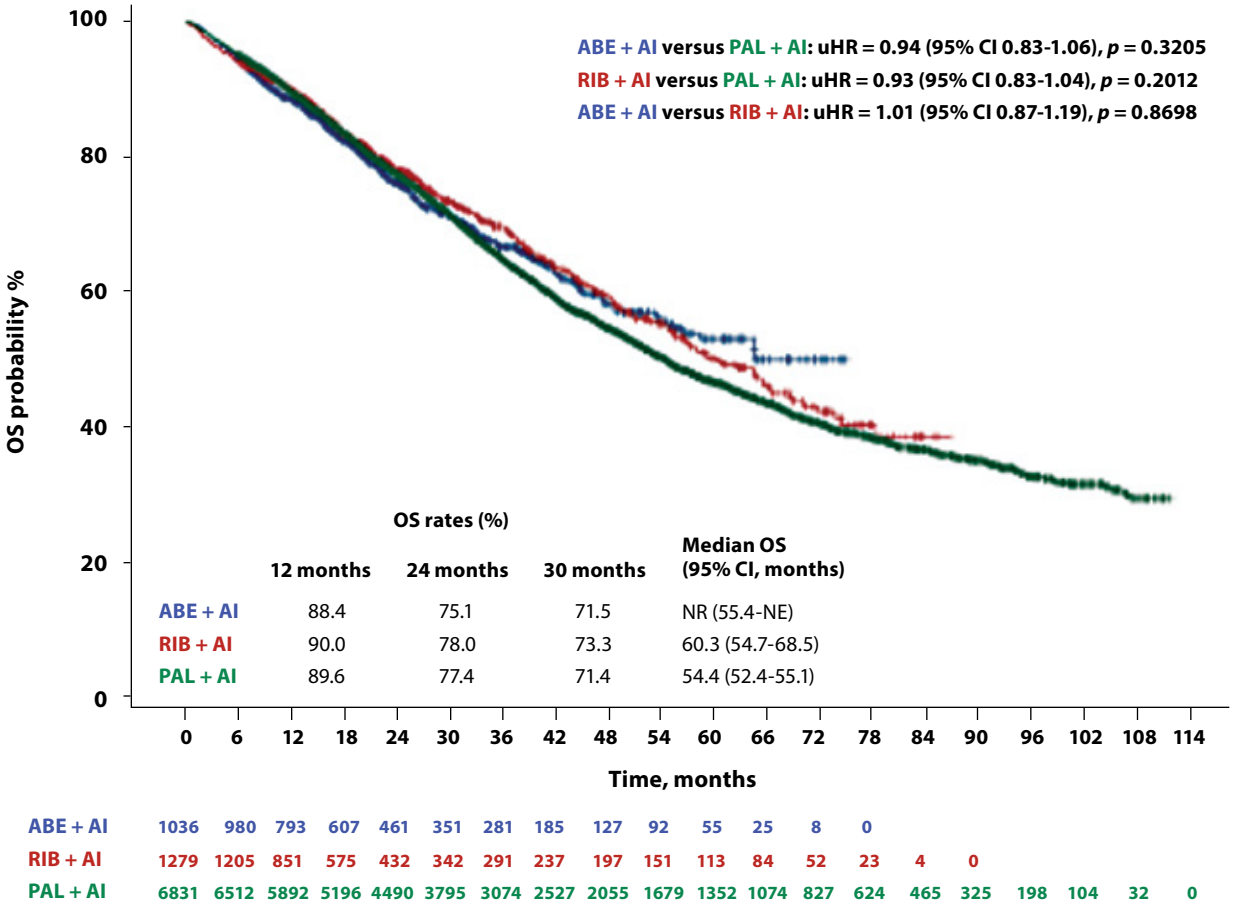


ET = endocrine therapy; AI = aromatase inhibitor; CDK = cyclin dependent kinase

fulvestrant in patients with disease progression following ET, palbociclib improved OS. Median OS was 34.9 months in the palbociclib/fulvestrant group and 28.0 months in the placebo/fulvestrant group [hazard ratio (HR) for death, 0.81; $p = 0.09$; absolute difference, 6.9 months).[11] The most common adverse events (incidence 20% or more) in combination with either letrozole or fulvestrant were neutropenia, blood creatinine increased, hemoglobin decreased, platelets decreased, infections, elevated liver function tests, fatigue, nausea, stomatitis, diarrhea, and alopecia.

Ribociclib, first FDA-approved in 2017, is indicated for the treatment of adults with HR+/HER2- advanced or mBC in combination with an AI as initial endocrine-based therapy or with fulvestrant as initial endocrine-based therapy or following disease progression on ET. It was approved in 2024 in combination with an AI for the adjuvant treatment of adults with HR+/HER2- Stage II and III early breast cancer at substantial risk of recurrence, including those with node-negative (N0) disease. For first-line therapy, this agent improved PFS when given in combination with letrozole versus letrozole alone. After 18 months, median PFS was 25.3 months for ribociclib/letrozole and 16.0 months for placebo/letrozole.[12] At median follow-up of 6.6 years, median OS was 63.9 months with ribociclib/letrozole and 51.4 months with placebo/letrozole (HR for death, 0.76; two-sided $p = 0.008$).[13] In combination with

Exhibit 3: Real-World Overall Survival with CDK4/6 Inhibitor plus Aromatase Inhibitors[20]



fulvestrant in treatment-naïve patients and those who relapsed after ET, ribociclib improved both PFS and OS.[14,15] The estimated OS at 42 months was 57.8 percent in the ribociclib/fulvestrant group and 45.9 percent in the placebo/fulvestrant group, for a 28 percent difference in the relative risk of death (HR, 0.72; $p = 0.00455$).[15] In early stage breast cancer, ribociclib plus a nonsteroidal AI [(NSAI), letrozole or anastrozole] as compared with NSAI alone provided a significant invasive disease-free survival benefit. At three years, invasive disease-free survival was 90.4 percent with ribociclib/NSAI and 87.1 percent with NSAI (HR for invasive disease, recurrence, or death, 0.75; $p = 0.003$).[16]

The adverse event profile of ribociclib is similar to palbociclib. The most common (incidence 20% or more) adverse events are leukopenia, neutropenia, lymphopenia, hemoglobin decreased, elevated liver function tests, infections, nausea, creatinine increased, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, back pain, and glucose decreased. Neutropenia and leukopenia are the most common all-grade and severe (Grades 3/4) adverse events reported.

Abemaciclib, the third CDK4/6 inhibitor, was initially FDA-approved in 2017. It is now indicated in combination with ET (tamoxifen or an AI) for the adjuvant treatment of adult patients with HR+/HER2- node-positive, early breast cancer at high risk of recurrence, in combination with an AI as initial endocrine-based therapy for the treatment of adult patients with HR+/HER2- advanced or mBC, in combination with fulvestrant for the treatment of adult patients with HR+/HER2- advanced or mBC with disease progression following ET, and as monotherapy for the treatment of adult patients with HR+/HER2- advanced or mBC with disease progression following ET and prior chemotherapy in the metastatic setting. Treatment with abemaciclib plus fulvestrant resulted in a statistically significant median OS improvement of 9.4 months for patients with HR+/HER2- advanced disease who progressed

after prior ET regardless of menopausal status.[17]As first-line therapy, after a median follow-up of 8.1 years, median OS was 66.8 versus 53.7 months for abemaciclib/anastrozole or letrozole versus placebo/anastrozole or letrozole.[18] Two years of adjuvant abemaciclib therapy combined with ET improved invasive disease-free survival and distant relapse-free survival at the five-year interim analysis; despite fewer deaths in the abemaciclib/ET arm compared with the ET-alone arm (208 versus 234), statistical significance was not reached for OS.[19] Abemaciclib has a similar adverse event profile to the others with the most common adverse reactions (incidence 20% or more) of diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

A retrospective study using real-world data from the Flatiron Health database examined OS outcomes among patients with HR+/HER2- mBC aged 18 years or more who at mBC diagnosis started first-line CDK4/6 inhibitor therapy. In this study, 6,831, 1,279, and 1,036 received palbociclib/AI, ribociclib/AI, or abemaciclib/AI, respectively. This study defined OS as months from start of index treatment to death. After baseline characteristics were balanced between treatment groups, no significant OS differences were found between treatment groups [ribociclib versus palbociclib: adjusted hazard ratio (aHR) 0.98, p = 0.7531; abemaciclib versus palbociclib: aHR 0.95, p = 0.4292; abemaciclib versus ribociclib: aHR 0.97, p = 0.6956; Exhibit 3].[20]

The authors of this study suggested that these findings together with other factors such as safety and quality of life are helpful in the selection of CDK4/6 inhibitor combination therapy for patients with HR+/HER2- mBC.

Although oral medications, the CDK4/6 inhibitors are potent medications that can have significant adverse events. One way to optimize use of this class is to prospectively monitor for and manage adverse events. Neutropenia is common, especially with palbociclib and ribociclib, and can be managed with dose modifications and supportive care similar to colony-stimulating factors (G-CSF). Notable adverse events with ribociclib are QT prolongation and elevation in liver function tests. Abemaciclib is particularly associated with diarrhea, which can be severe. It can be managed with anti-diarrheal medications and dose modifications. Patients should be instructed to initiate antidiarrheal therapy at the first sign of loose stools, increase oral fluids, and notify their healthcare provider. Nausea and vomiting can be managed with antiemetics. Fatigue is a common issue which can be managed with supportive care and lifestyle adjustments.

Overall, CDK4/6 inhibitors, when combined with ET, are a standard first-line treatment for hormone HR+/HER2- advanced or mBC significantly improving PFS and OS. The use of adjuvant abemaciclib and ribociclib in early breast cancer have been added to the American Society of Clinical Oncology and National Comprehensive Care Network Guidelines.[21,22] CDK4/6 inhibitors are expensive, and the cost-effectiveness of their use in early-stage breast cancer is a topic of ongoing discussion.

TROP2-directed antibody-drug conjugates (ADCs) are another advance for later-line therapy in HR+/HER2- mBC. ADCs consist of three main parts—antibodies responsible for selectively recognizing cancer cell surface antigens, cytotoxic payloads responsible for killing cancer cells, and linker used to connect antibodies with payloads. After the complex enters the cell, lysosome fusion with endosome causes linker cleavage in the cell, releasing and activating small molecule cytotoxic drugs. After the drug is released into the cytoplasm, it can kill tumor cells without causing major damage to other cells in the body.

Datopotamab-deruxtecan is a Trop-2-directed antibody and topoisomerase inhibitor conjugate that was FDA-approved in January 2025. TROP2 is a transmembrane glycoprotein that is overexpressed in a wide range of cancers including breast cancer. Datopotamab-deruxtecan is indicated for the treatment in adult patients with HR+/HER2- advanced or mBC who have received prior ET and chemotherapy for unresectable or metastatic disease. It is also indicated for one type of non-small cell lung cancer and is being studied in triple negative breast cancer. Approval was based on a Phase III, open-label, randomized trial which compared this ADC with investigator choice chemotherapy (ICC).[23] Prior use of CDK4/6 inhibitors was not required. Median PFS was 6.9 months with datopotamab-deruxtecan versus 4.9 months with ICC. Final OS data for this trial is not yet available. The rate of Grade 3 or worse adverse events with the datopotamab-deruxtecan was lower than ICC (20.8% versus 44.7%). The most common events (any Grade; Grade 3 and higher) were nausea (51.1%; 1.4%) and stomatitis (50%; 6.4%) with datopotamab-deruxtecan and neutropenia (42.5%; 30.8%) with ICC.

The cost of cancer continues to increase dramatically with approval of new expensive therapies and managed care continues to struggle with controlling these costs. Those with breast cancer have a significant cost burden from their treatment. In 2019, breast cancer had the highest

out-of-pocket cost of any cancer.[24] A retrospective cohort study including patients from a national specialty pharmacy with a diagnosis of breast cancer who received CDK4/6 inhibitor for treatment found that secondary insurance largely affected final patient out-of-pocket costs for these agents.[25] When analyzing patient reported side events, over 60 percent of the study population did not experience an ADE during the study time period. Ribociclib had the fewest number of reported side events with abemaciclib patients reporting the most. In general, reported ADE profiles were similar across all three medications. The authors noted that real-world safety data and out-of-pocket patient costs in addition patient specific comorbidities should be considered when developing a treatment plan that includes a CDK4/6 inhibitor.

Conclusion

Newer therapies for early and advanced disease are changing the prognosis for many patients with breast cancer. The role of the CDK4/6 inhibitors in both metastatic and early-stage disease is well established and supported by significant PFS data and some OS data. The choice of CDK4/6 inhibitor needs to be individualized based on patient evaluation of adverse event risk and out-of-pocket costs. Newer drugs such as the TROP2 directed ADC for later-line therapy are now available. Payers will need to manage access, outcomes, and cost very carefully in this disease state with the introduction of these game-changing therapeutic options.

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Addressing the Barriers to Optimized HIV Management: Navigating ART and PrEP Decision-Making for Improved Clinical and Economic Outcomes

David Alain Wohl, MD

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Summary

Preventing and treating HIV are important issues for managed care. Unfortunately, despite good options and improvements over the years, many people at risk for HIV infection are not receiving preventative therapy. Long-acting antiretroviral medications are options for improving both prevention and treatment and will be increasingly used.

Key Points

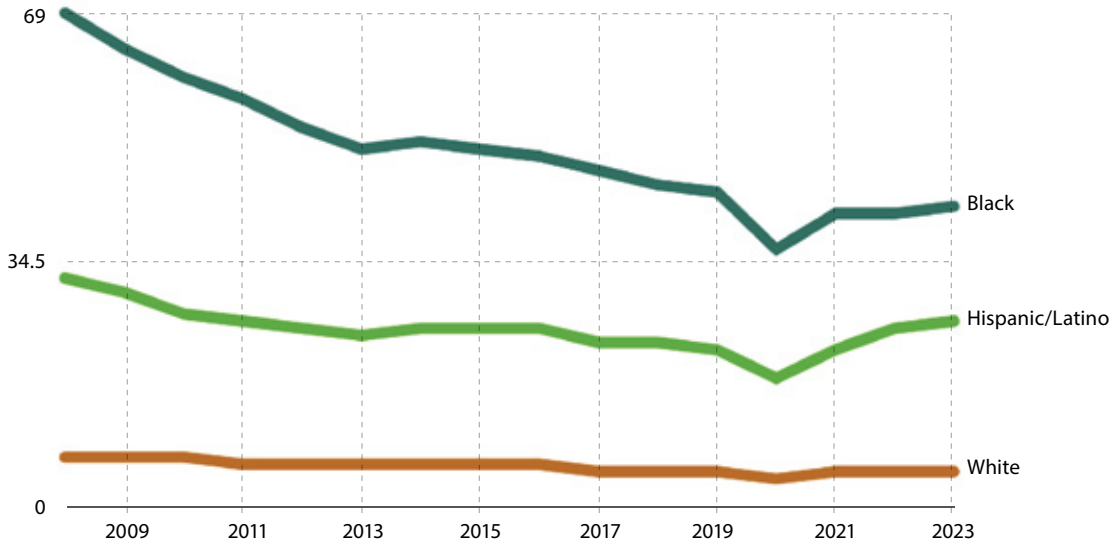
- Advances in prevention and treatment of HIV have led to reductions in new cases and increases in survival.
- Oral PrEP has fixed limitations that can be addressed with long-acting agents.
- Cost and logistics are challenges to injectable PrEP.
- Lenacapavir every six months will be a game-changer for PrEP uptake and adherence.
- Treatment is also leaning toward long-acting injectables.
- The frequency of injections limits uptake as do access barriers including prior authorizations and formulary restrictions.
- Super long-acting agents will shift the field and practice.

HIV INFECTIONS CONTINUE TO BE AN issue in the United States (U.S.). Exhibit 1 shows the new diagnosis rate since 2008.[1] Progress in HIV prevention continues to occur with an estimated 12 percent decline in cases between 2018 and 2022 (most recent year for available data).[2] In 2022, an estimated 31,800 people acquired HIV in the U.S.

HIV diagnoses are not evenly distributed across states and regions. The highest rates of new diagnoses continue to occur in the South. HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities, gay, bisexual, and other men who have sex with men (MSM).[2] Between 2018 and 2022, there was a 20 percent increase in the rate among Hispanic and Latino MSM. Effective treatment of known HIV infections (undetectable viral load) does help prevent transmission of the disease. For those at risk who are not currently infected, pre-exposure prophylaxis (PrEP) is very effective, when used correctly, at infection prevention.

About 2.5 million people in the U.S. are estimated to be at risk for HIV infection and eligible for PrEP.[3] In 2024, 23 percent of the at-risk population was receiving PrEP.[4] There was a 17 percent increase in uptake from 2023 to 2024. There are persistent disparities in PrEP use, especially among Black, Hispanic/Latino, the young, female, and Southern populations. Low rates of PrEP use have been tied to lower socioeconomic and educational status.

Exhibit 1: HIV New Diagnosis Rate Per 100,000 (2008 to 2023)



Improved equity in PrEP use would be impactful on the U.S. HIV epidemic. Persons most at-risk of acquiring HIV should have the highest levels of access to PrEP.[5] Despite its effectiveness, PrEP uptake and adherence can be hindered by factors such as stigma, fear of side events, cost concerns, and difficulty accessing culturally competent healthcare services, particularly for transgender people and people of color.[5,6] Additionally, even when someone starts on oral PrEP, discontinuation rates are high.

FDA-approved options for PrEP include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and integrase inhibitors. Oral PrEP regimens are emtricitabine/tenofovir disoproxil fumarate and emtricitabine/tenofovir alafenamide. Long-acting injectable cabotegravir (LA-CAB) every two months and long-acting lenacapavir (LA-LEN) twice yearly are the two available integrase inhibitor regimens.

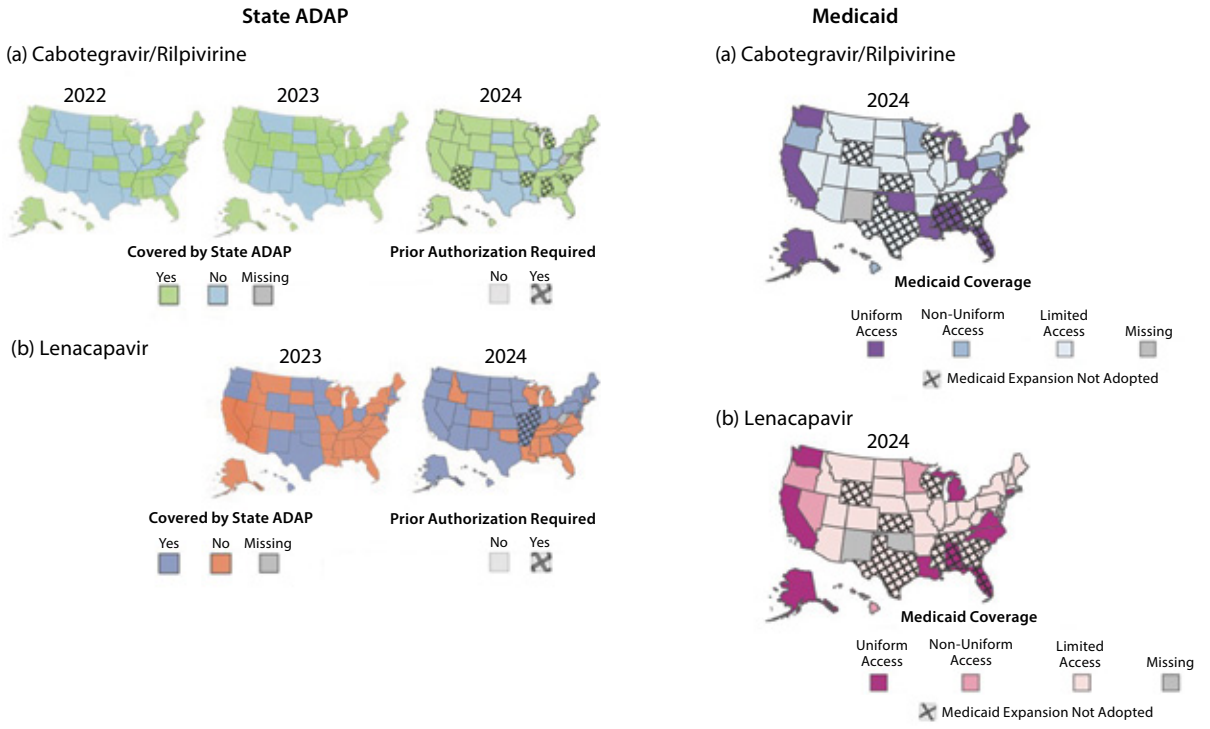
Long-acting injectable PrEP holds promise for improving adherence. Clinical trials showed LA-CAB is highly effective and improves adherence over daily oral PrEP, with high injection coverage (91% to 93%).[7] Real-world data are also showing good adherence and persistence.[8,9] In a trial assessing the integration of LA-CAB for PrEP across 17 clinics in the U.S. among a diverse population of MSM and transgender men, no cases of HIV acquisition were observed through 12 months.[9] The trial included 26 percent Black and 38 percent Hispanic/Latino participants. Twenty-two percent of the participants had not received oral PrEP in the six months prior to entering the trial. Persistence on LA-CAB was 85 percent at six months and 72 percent at 12 months.

Injectable lenacapavir (LA-LEN) was originally approved by the FDA for use in heavily treated people with HIV but was approved in 2025 for PrEP. It is highly effective in preventing HIV infection compared to oral PrEP.[10,11] In one trial, among 3,265 participants, HIV infections occurred in two participants in the lenacapavir group (0.10 per 100 person-years) and in nine participants in the daily oral emtricitabine-tenofovir disoproxil fumarate group (0.93 per 100 person-years).[11] The background HIV incidence in the screened population (4,634 participants) was 2.37 per 100 person-years. Adherence was also better with LA-LEN than oral therapy. A once-a-year dosing intramuscular formulation of lenacapavir is currently under study.

Long-acting injectable PrEP can overcome some of the barriers of oral PrEP. Unfortunately, implementation of long-acting PrEP is complicated by barriers related to health insurance processes, staffing and administrative support, drug costs and acquisition, and access for individuals who are uninsured.[12]

A major issue with HIV prevention is decreasing government support for HIV-related data collection and funding for prevention programs and Medicaid. Without accurate data, prevention programs cannot be targeted to the populations most in need. Many of the prevention programs may also disappear because of funding loss. Court cases have also challenged coverage of preventative services, such as PrEP, required by the Affordable Care Act. All these

Exhibit 2: Nationwide coverage of LA-ART by State AIDS Drug Assistance Program (ADAP) and Medicaid[22]



factors combined may lead to a surge in HIV cases.

In 2022 an estimated 1.2 million people were already infected with HIV.[2] About 87 of every 100 of those infected are diagnosed. In terms of treating diagnosed HIV cases, 76 percent have received some HIV care, 54 percent are retained in care, and 62 percent were virally suppressed and thus unable to transmit the disease. Viral suppression is lower in people with HIV who are Black or Hispanic/Latino. For a variety of reasons, people cannot stay in care and be adherent with treatment. The overall goal of HIV treatment is to get at least 95 percent of those infected to be undetectable.

The good news is that very good antiretroviral therapy (ART) is available, clinicians know how to use these medications, and there are evidence-based guidelines for treatment.[13] The combination of these factors has dramatically improved care for those with HIV. It is now a chronic disease rather than a death sentence for those who can access and stay in care.

The most common ART used for initial treatment of newly diagnosed HIV is bictegravir/tenofovir alafenamide/emtricitabine which is available as a single tablet given once daily. This is one of three initial regimen recommendations from the treatment guidelines and has a high barrier to resistance development. Long-term (5-year) data are available on the efficacy of this combination showing maintenance of high levels of virologic suppression (~99%).[14] A real-world study found that 97 percent of those initially started on this combination were virologically suppressed and 95 percent maintained therapy at one year.[15] It has been hard for other products to dislodge bictegravir/tenofovir alafenamide/emtricitabine as the first choice for treatment.

Long-acting injectables are one way to get around daily medication which can be an adherence challenge for some patients and a daily reminder of infection. Long-acting injectable cabotegravir and rilpivirine (LA-CAB/RPV) is given as two intragluteal injections every four to eight weeks. The value for the patient is only thinking about their HIV treatment six to 12 days a year. LA-CAB/RPV is currently only indicated for those who are virologically suppressed with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. In studies so far, about 85 percent of patients are coming back on time for injections and 97 to 99 percent are achieving viral suppression.[16-18]

About 16 percent of patients discontinue therapy and in one study 20 percent of those who stopped therapy did so because of injection pain.[19] Studies in

homeless and nonadherent populations are showing results better than oral ART.[20,21] About 10 percent of patients in HIV clinics are receiving LA-CAB/RPV.

In a study assessing access to long-acting injectable ART among uninsured and low-income persons with HIV, nearly one in five AIDS Drug Assistance Program (ADAP) clients (19%) lived in a state whose ADAP formulary did not cover LA-CAB/RPV.[22] Within one month of FDA approval (by January 2023), LA-LEN, as a treatment for heavily treatment-exposed patients and not as PrEP, was added to the formulary of 35 percent responding state ADAPs. That number increased to 70 percent by January 2024. Data on current formulary inclusion of LA-LEN for PrEP are not available. LA-CAB/RPV was not covered without prior authorization by 26 state Medicaid programs and not covered at all by 15 state ADAP (Exhibit 2).[22] In August 2024, 23 percent of state Medicaid plans provided uniform coverage of LA-LEN with no prior authorization. There are more long-acting injectables under investigation which will be given even less frequently than every six months.

Conclusion

Advances in prevention and treatment of HIV have led to reductions in new cases and increases in survival. Oral PrEP has fixed limitations that can be addressed with long-acting agents. Cost and logistics are challenges to injectable PrEP. Lenacapavir every six months will be a game-changer for PrEP uptake and adherence. Treatment is also leaning toward long-acting injectables but the frequency of injections limits uptake as do access barriers including prior authorizations and formulary restrictions. Like prevention, super long-acting agents will shift the field and practice.

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