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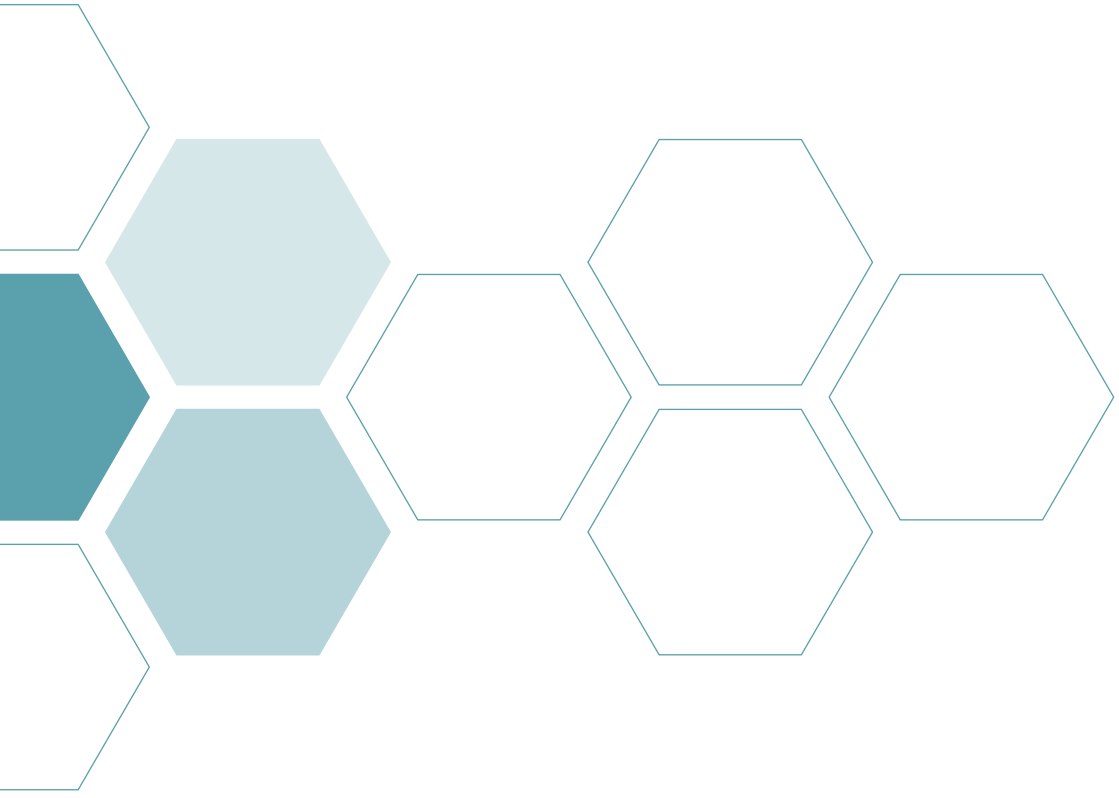
Educating Medical Directors of Employers, Health Plans and Provider Systems



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Recent Advances in Treatment and Management of Advanced Non-Small Cell Lung Cancer

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New Insights into the Management of Metastatic Bladder Cancer: Expert Strategies and Treatment Considerations for Managed Care

Jones T. Nauseef, MD, PhD

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Summary

The first-line systemic treatment of metastatic bladder cancer has recently changed. Platinum-based chemotherapy, which has been the standard for many years, has been replaced by an antibody-drug conjugate in combination with immunotherapy. This new regimen significantly improves survival with a lower rate of significant adverse events.

Key Points

- Molecular testing, patient factors, and prior therapies impact treatment selection options.
- Toxicities of systemic therapy and local treatment cause morbidity and excessive costs.
- Enfortumab vedotin in combination with pembrolizumab has replaced platinum-based chemotherapy combinations as the standard of care for first-line treatment.

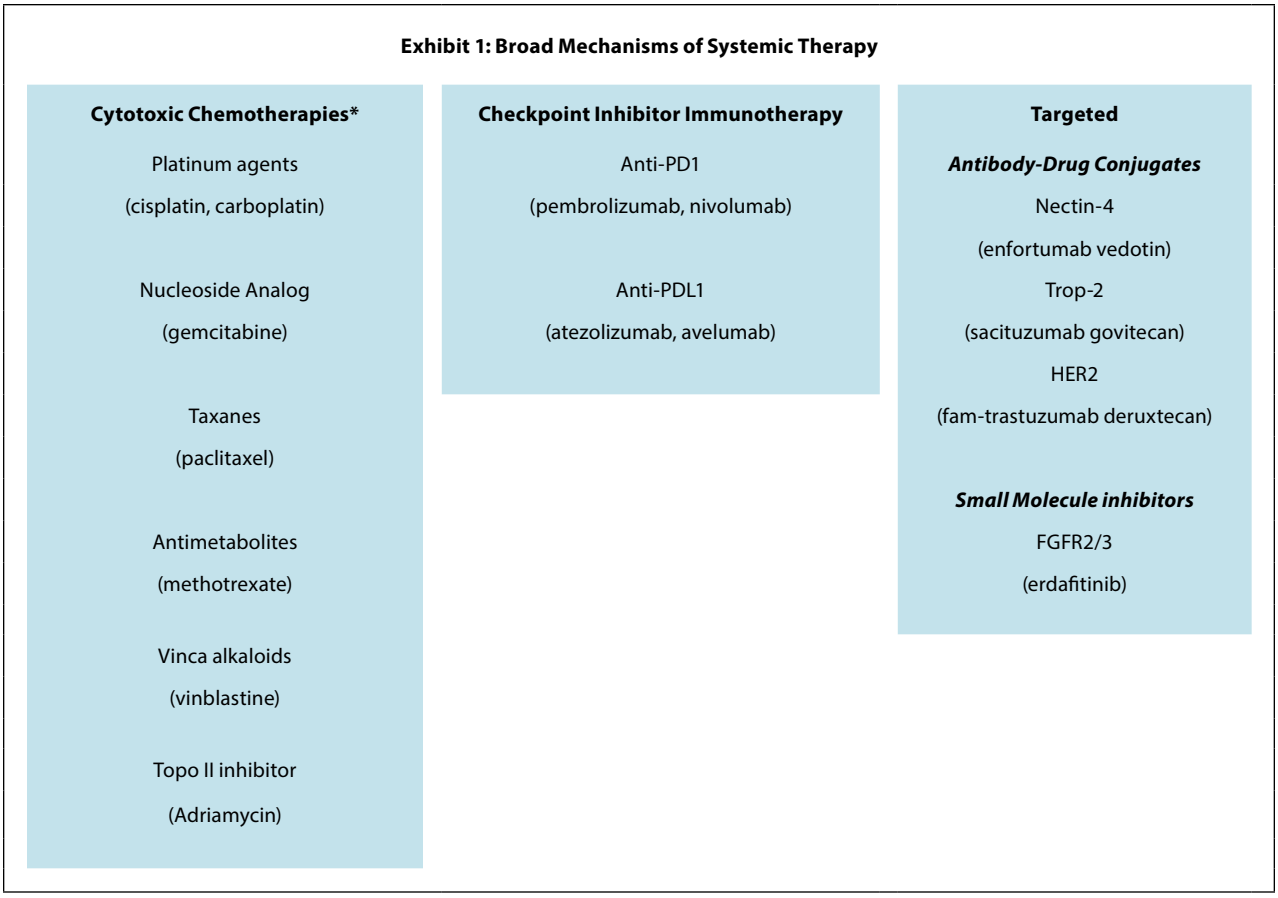
IN 2024, AN ESTIMATED 83,190 PEOPLE WILL be diagnosed with bladder cancer in the United States (U.S.) and 16,840 deaths will occur.[1] Bladder cancer accounts for 4.2 percent of new cancer cases and is more common in men than women. The rate of this cancer and the death rate has been slowly declining. Risk factors for bladder cancer include tobacco smoking, increased age, exposures (radiation, arsenic, chlorine, workplace chemicals), inflammation, prior cancer therapy, and germline syndromes. The five-year overall survival is now 78.4 percent.

The management of bladder cancer is multimodal. Non-muscle invasive disease (Stages 0 – 1) is managed locally via serial resection and intra-bladder therapy (e.g., chemotherapy, Bacillus Calmette-Guerin).[2] Muscle-invasive disease (Stages II – III) is managed with systemic therapy and bladder surgery. Systemic therapy may include neoadjuvant and adjuvant treatments, including cisplatin-based chemotherapies. Locally advanced or metastatic disease (Stage IV) is treated with radiation, chemotherapy, and other systemic therapies. Five percent of patients have metastatic disease at the time of diagnosis. Additionally, half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status.[2] Local recurrences account for 10 percent to 30 percent of relapses, whereas distant metastases are more common.[2]

Exhibit 1 shows the three broad categories of systemic therapies. The choice of treatment requires assessing the patient's performance status and co-morbidities, the goal of treatment (curative versus palliative), and prior therapies including platinum and immunotherapy.

The development of antibody-drug conjugates (ADCs) is one of the advances in managing bladder

Exhibit 1: Broad Mechanisms of Systemic Therapy



*Traditional delivery
PD = programmed death; PDL = programmed death ligand; FGFR = fibroblast growth factor receptor

cancer. An ADC combines a monoclonal antibody (mAb) with a cytotoxic drug. The mAb binds to specific proteins or receptors on cancer cells allowing the cytotoxic drug to enter the cells and kill them. ADCs are designed to target tumor cells with minimal damage to normal cells.

Three ADCs are currently available for treating bladder cancer and others are being investigated. Enfortumab vedotin is a nectin-4-directed antibody and monomethyl auristatin-E, a microtubule inhibitor conjugate, indicated in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer as a single agent and for those with locally advanced or metastatic urothelial cancer who have previously received checkpoint inhibitor immunotherapy and platinum-containing chemotherapy, or who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy. Sacituzumab govitecan is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for locally advanced or metastatic bladder cancer previously treated with a platinum-containing chemotherapy and a checkpoint inhibitor. Fam-trastuzumab deruxtecan is indicated for adult patients with unresectable or metastatic HER-2 positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

The NCCN Guidelines recommend that molecular/genomic testing be performed for Stages IVA and IVB bladder cancer and may be considered for Stage IIIB.[2] Molecular/genomic testing should be conducted early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility. At a minimum, testing should include analysis for fibroblast growth factor receptor (FGFR) genetic alterations and human epidermal growth factor receptor two (HER2) overexpression by immunohistochemistry (IHC). Bladder cancer is the third-highest mutated cancer.[2] More than 90 percent of patients will have at least one clinically

Exhibit 2: NCCN Guidelines for First-Line Systemic Therapy in Locally Advanced or Metastatic Disease[2]

	2024	2023
Cisplatin eligible	**Preferred Regimens** • Pembrolizumab and enfortumab vedotin (category 1) **Other Recommended Regimens** • Gemcitabine and cisplatin (category 1) followed by avelumab maintenance therapy (category 1) • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy (category 1)	**Preferred** Gemcitabine and cisplatin (category 1)
Cisplatin ineligible	**Preferred Regimens** • Pembrolizumab and enfortumab vedotin (category 1) **Other Recommended Regimens** • Gemcitabine and carboplatin followed by avelumab maintenance therapy (category 1)	**Preferred** Gemcitabine and carboplatin (category 1) Pembrolizumab (locally advanced or metastatic UC not eligible for any platinum-containing chemotherapy) Pembrolizumab and enfortumab vedotin

Guidelines also include "useful in certain circumstances" regimens. Only preferred regimens shown for 2023.

relevant finding with the most common being CDKN2A (34%), FGFR3 (21%), PIK3CA (20%), and HER2 (17%).[3]

The National Comprehensive Cancer Network (NCCN) preferred regimen for first-line systemic therapy, in locally advanced or metastatic disease for both cisplatin eligible and ineligible, significantly changed in 2024 (Exhibit 2).[2] Based on the results of the Phase III EV-302 trial, the combination of pembrolizumab plus enfortumab vedotin is now the preferred first-line systemic therapy option for patients with advanced or metastatic bladder cancer, regardless of whether they are eligible for cisplatin. The EV-302 trial randomized 886 patients with previously untreated locally advanced or metastatic disease to either enfortumab vedotin plus pembrolizumab or gemcitabine in combination with either cisplatin or carboplatin (the prior standard of care).[4] After a median follow-up of 17.2 months, median progression-free survival (PFS) was significantly longer with enfortumab vedotin plus pembrolizumab compared to chemotherapy (12.5 months versus 6.3 months; $p < .001$). Median overall survival (OS) was also significantly longer with enfortumab vedotin plus pembrolizumab (31.5 months versus 16.1 months; $p < .001$). Confirmed overall response rates were 67.7 percent and 44.4 percent for enfortumab vedotin plus pembrolizumab and chemotherapy, respectively ($p < .001$), with complete responses observed in 29.1 percent and 12.5 percent, respectively. Treatment-related adverse events of Grade 3 or greater occurred in 55.9 percent of patients receiving enfortumab vedotin plus pembrolizumab and 69.5 percent of those receiving chemotherapy.

There are numerous options for second-line therapy and beyond. For those with FGFR mutated tumors, erdafitinib is an NCCN preferred option for both cisplatin eligible and ineligible patients.[2] As noted previously, FGFR3 mutations occur in 21 percent of those with advanced bladder cancer; FGFR2 alterations occur less commonly.[3] In a Phase III trial of erdafitinib compared with chemotherapy in patients with metastatic bladder cancer with susceptible FGFR3/2 alterations who had progression after one or two previous treatments that included a checkpoint inhibitor immunotherapy, erdafitinib therapy resulted in significantly longer OS than chemotherapy (12.1 months versus 7.8 months; hazard ratio for death, 0.64; 95% confidence interval

[CI], 0.47 to 0.88; $p = 0.005$) with a similar rate of significant adverse events.[5]

Bladder cancer is a costly disease to treat. In 2015 before the advent of costly checkpoint inhibitor immunotherapy and ADC use in bladder cancer, the overall annual costs in the U.S. were $7.93 billion.[6] Newer therapies, management of disease recurrence, systemic and surgical treatment complications including medication adverse events, and infusion costs contribute significantly to the high cost of care.[6] All-cause healthcare costs are significantly higher for patients with severe adverse events versus those without, with an adjusted mean incremental cost difference of $6,130 per member per month ($p < 0.001$).[7] High-value interventions are those treatments that improve recurrence-free and OS at minimal additional toxicity. The new standard of care for first-line treatment of metastatic disease does improve OS with less toxicity than the prior standard.

Conclusion

Bladder cancer management is multimodal with frequent recurrences and commonly aggressive tumor behavior. Molecular testing, patient factors, and prior therapies impact treatment selection options. Toxicities of systemic and surgical treatment confer morbidity requiring use of healthcare, resulting in excessive costs. Combination therapy that avoids the use of platinum (enfortumab vedotin + pembrolizumab) has replaced chemotherapy combination as the standard of care for first-line treatment.

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Recent Advances in Treatment and Management of Advanced Non-Small Cell Lung Cancer

Gary M. Owens, MD

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

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

Summary

Dramatic changes have taken place in managing advanced non-small cell lung cancer in recent years. These include the introduction of targeted therapy for specific genetic mutations which drive this cancer.

Key Points

- Targeted therapies are first-line for those with advanced disease and actionable genetic mutations.
- Newer targets are the future of treatment.
- Managed care must find a way to better evaluate the value of new treatments.

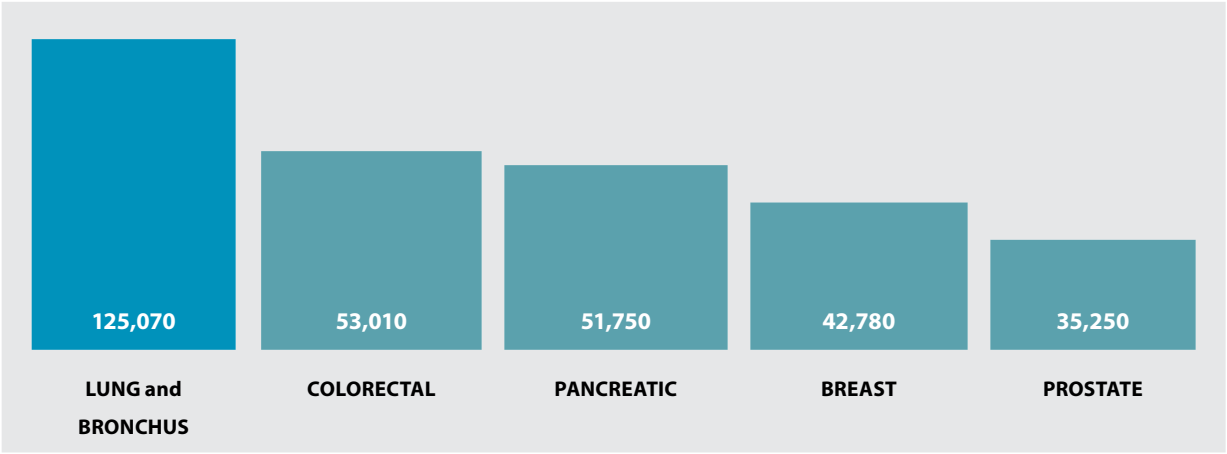
LUNG CANCER IS THE SECOND MOST common cancer in both men and women in the United States (U.S.).[1] In 2024, an estimated 234,580 cases of lung cancer will be diagnosed and 125,070 people will die from this disease. It is the most common cause of cancer death (Exhibit 1).[1] Lung cancer deaths have been declining in both men and women, reflecting decreases in smoking, but are still the leading cause of cancer deaths. The most common type of lung cancer is non-small cell lung cancer (NSCLC). It accounts for 85 percent of cases. NSCLC typically grows and spreads slower than small cell lung cancer.

In 2020, lung cancer was the third most costly cancer.[2] With NSCLC, costs are primarily driven by outpatient visits and medication costs, especially for checkpoint inhibitor immunotherapy and targeted agents.[3] Although costly to treat, society is benefiting from the increased costs. In one study, population-level mortality in the U.S. from NSCLC fell sharply from 2013 to 2016, and survival after diagnosis improved which was driven by new therapies.[4] Survival trends over this period of time improved broadly by gender and race/ethnicity. Despite improvements in survival, there may be financial toxicity for patients because of significant out-of-pocket expenses. Financial toxicity is the detrimental effect of the excess financial strain caused by the diagnosis of cancer on the well-being of patients and is becoming an important consideration in cancer care.[5]

The primary risk factor for developing NSCLC is smoking.[6] Other risk factors include second-hand smoke, radon exposure, heavy metal and hydrocarbon exposure, pulmonary fibrosis, genetic factors, alcohol, and prior radiation therapy. Signs and symptoms of lung cancer may include a persistent cough, coughing up blood (even a small amount), shortness of breath, chest pain, hoarseness, unintentional weight loss, and bone pain. These signs and symptoms are nonspecific—additionally, about 25 percent of people with lung cancer may have no signs or symptoms. Unfortunately, over 50 percent of cases are advanced at the time of diagnosis.[7] The basic diagnostic workup for lung cancer is shown in Exhibit 2.[8]

Molecular testing identifies patients with advanced NSCLC who may benefit from targeted therapy or immunotherapy. The National Comprehensive Cancer Network (NCCN) Guidelines lists specific

Exhibit 1: Lung Cancer is the Leading Cause of Cancer Death in the U.S.[1]



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. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. About 75 percent of NSCLC tumors harbor genomic alterations amenable to targeted therapy with the most common mutations being KRAS (29%) and EGFR (19%).[9] Exhibit 3 shows selected mutations and the recommended first-line agents from the NCCN Guidelines.[8]

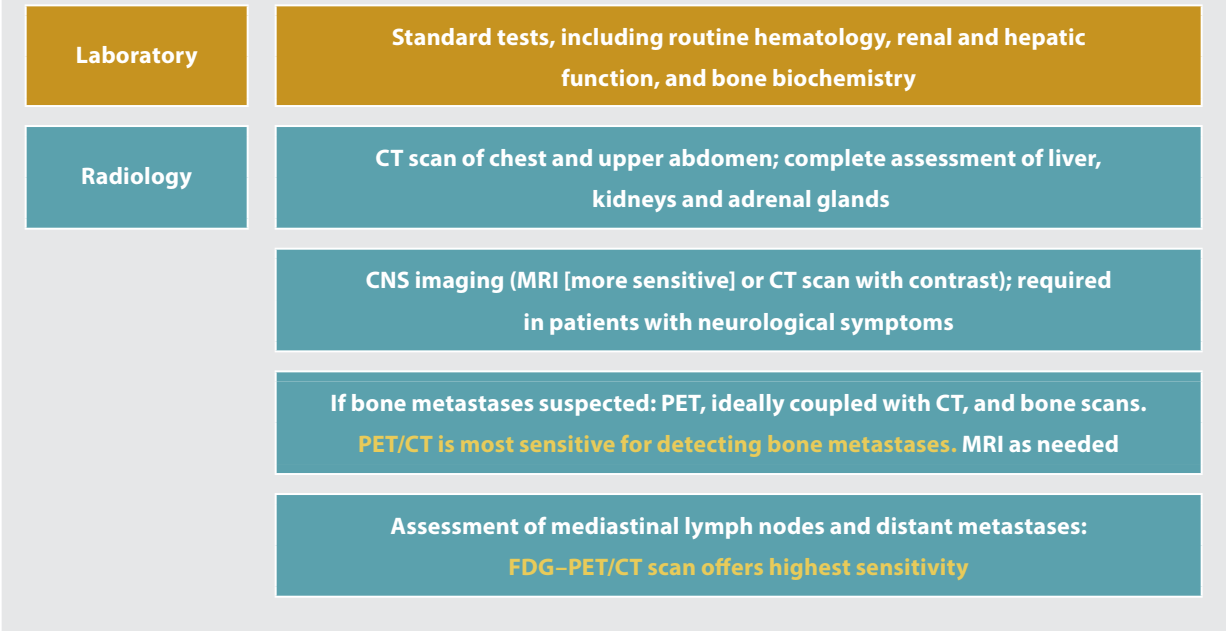
EGFR mutation was the first driver oncogene identified in lung cancer. EGFR is one of the four members of the human epidermal growth factor (HER) family transmembrane receptors (HER1/EGFR, HER2, HER3, and HER4). EGFR mutations are most common among non-smokers, young females, and Asians. Prevalence of EGFR oncogenes is 50 percent among Asian patients with lung adenocarcinoma and 15 percent among Western patients.[9] 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 EGFR tyrosine kinase inhibitors (TKIs).[10] EGFR exon 20 insertion mutation occurs in about 2 percent of NSCLC cases and is more commonly found in people who never smoked and Asians. EGFR exon 20 insertion mutations exhibit a unique configuration that renders them more resistant to EGFR TKIs. Rarer mutations including point mutations, deletions, insertions, and duplications occur within exons 18 to 25 of the EGFR gene in NSCLC and are associated with poor responses to EGFR TKI.

EGFR TKIs are first-line therapy for patients with activating EGFR mutations because these agents produce better overall survival than chemotherapy.[8] Osimertinib is the 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 TKIs. For EGFR S768I, L861Q, and/or G719X mutations, afatinib or osimertinib are the preferred first-line agents.

For an EGFR 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. Amivantamab is a bispecific EGFR and cMET antibody. In patients with advanced NSCLC with EGFR exon 20 insertions, who had not received previous systemic therapy, amivantamab plus chemotherapy improved PFS better than chemotherapy alone (median, 11.4 months and 6.7 months; $p < 0.001$).[11] At 18 months, PFS was reported in 31 percent of the patients in the amivantamab-chemotherapy group and in 3 percent of the chemotherapy group. A complete or partial response at data cutoff was reported in 73 percent and 47 percent, respectively ($p < 0.001$). Final survival data from this trial are not yet available. For adenocarcinoma or squamous NSCLC with an exon 20 insertion mutation, chemotherapy is the preferred first-line therapy in the guidelines.[8]

It should be noted the FDA-approved indications for amivantamab do not specify a histologic NSCLC restriction where the NCCN Guidelines

Exhibit 2: Basic Diagnostic Work-up for Lung Cancer[8]



recommend choosing based on nonsquamous disease. Amivantamab is approved by the FDA in combination with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as monotherapy for NSCLC with EGFR exon 20 insertion mutations which has progressed on or after platinum-based chemotherapy (second-line), and in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor. The newest indication for this agent is in combination with lazertinib, a third-generation EGFR TKI, for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. This combination may supplant first-line use of osimertinib based on a trial showing improved median PFS of 23.7 months versus 16.6 months.[12]

Driver mutations are one key factor in initial treatment selection for advanced NSCLC. Other key factors are the presence of a high level of programmed cell death ligand 1 (PD-L1) expression; the extent of disease, including the number and sites of metastases; squamous versus nonsquamous histology; performance status, comorbidities, and brain or liver metastases.[8] If a patient with advanced NSCLC has no targetable mutations, checkpoint inhibitor immunotherapy with or without chemotherapy and/or bevacizumab is the treatment option, depending on the expression of PD-L1, a biomarker of immunotherapy efficacy in NSCLC.

Many other targets are being studied for NSCLC treatment and carcinoembryonic antigen-related cell adhesion molecules (CEACAM) are one of these. There are 12 CEACAM proteins that impact cell function, including adhesion, differentiation, proliferation, and survival. CEACAM5 is involved in intercellular contact via both homophilic and heterophilic binding (with CEACAM1 or CEACAM6).[13] In early investigational studies, about 25 percent of patients with advanced nonsquamous NSCLC had high CEACAM5 levels.[14] CEACAM5 expression can be tested with tissue-based immunohistochemistry, using new or archival biopsy tissue. CEACAM5 is being studied as both a biomarker and as a therapeutic target using antibody-drug conjugates, bispecific antibodies, radioimmunotherapy, and chimeric antigen receptor T cells (CAR-T). Examples include cibisatamab, a bispecific antibody that targets CEACAM5 and CD3, and tusamitamab ravtansine, an antibody drug conjugate with a humanized

Exhibit 3: Selected Mutations and Recommended First-Line Therapy[8]

Genetic Mutation	Preferred First-Line Therapy
ALK Rearrangements	Alectinib or Brigatinib or Lorlatinib
EGFR exon 19 deletion, exon 21 L858R	Osimertinib
EGFR S768I, L861Q, and/or G719X	Afatinib or Osimertinib
EGFR exon 20 insertion	Amivantamab + Chemotherapy (nonsquamous) Chemotherapy (squamous and adenocarcinoma)
ROS1 Rearrangements	Crizotinib or Entrectinib or Repotrectinib
BRAF V600E Mutation	Dabrafenib + Trametinib or Encorafenib + Binimetinib
RET Rearrangements	Selpercatinib or Pralsetinib
KRAS G12C Mutation	Sotorasib or Adagrasib
NTRK Fusions	Larotrectinib or Entrectinib or Repotrectinib

antibody highly selective for CEACAM5 linked to a cytotoxic payload.

Payers have seen projections that estimate the cost of combination therapy with personalized approaches in the range of $250,000 to over $1 million per year. Payers view this cost as representative of the increasing and unsustainable cost of cancer care. Payers are not the only ones involved now, as their employer customers are demanding action on escalating costs as well.

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

One of the evidence gaps in value assessment to address is alternate stakeholder perspectives. There needs to be more research emphasis on the societal perspective when considering treatment value. Cost-effectiveness analyses should include both quality of life year (QALY) and no QALY adjustment so that absolute mortality reductions can be easily reported for decision-makers. Another gap to address is outcomes that are important to patients which can help decision-makers compare medications within the same disease state.[15] Hope is one outcome that matters to patients. The Professional Society for Health Economics and Outcomes Research (ISPOR) Special Task Force identifies the value of hope as an area needing more research to quantify. A cancer patient facing a terminal diagnosis may be willing to risk taking a more novel therapy if his or her chances include the possibility of durable response and even functional cure. For a cancer patient, any innovation that can extend life (even at the same or worse quality of life) may give a patient a chance to live long enough for a new treatment or even a cure to develop. Lastly, payers may need to leverage patient reported outcomes, real-world evidence, and other tools to expand the knowledge base and improve patient outcomes from personalized approaches.

Conclusion

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

providers together must develop careful patient selection that ensures treatments are provided only to those patients most likely to benefit.

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

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Novel HIV Prevention and Management Strategies: Optimizing PrEP and ART Managed Care Decision-Making for Improved Outcomes

Timothy Wilkin, MD, MPH

This journal article is supported by an educational grant from ViiV Healthcare

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

Summary

Despite considerable progress, HIV infections continue to be an issue in certain populations. Treatment with antiretroviral therapy is effective and safe. A newer long-acting injectable combination is an option for many patients and a long-acting injectable is also an option for prevention in at-risk groups.

Key Points

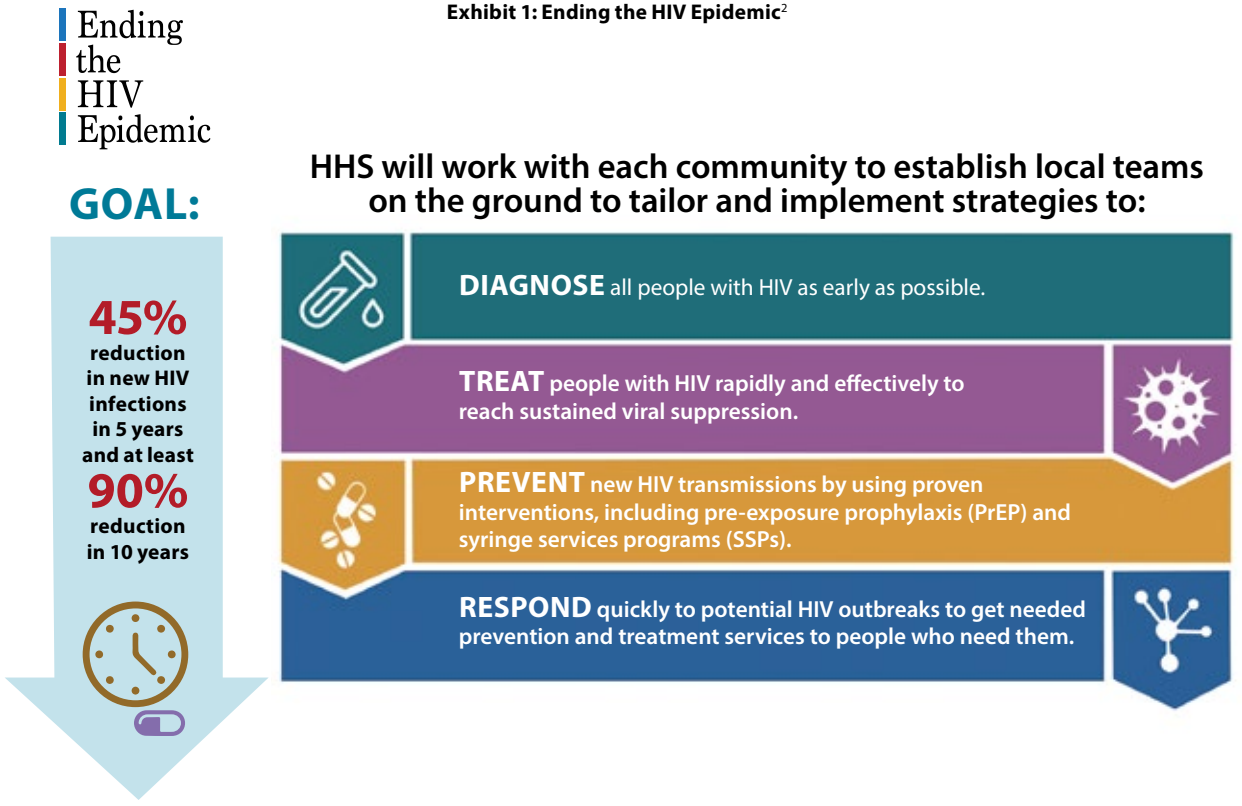
- Oral integrase inhibitor-based therapy is the standard of care for ART initiation.
- Long-acting CAB/RPV has demonstrated effectiveness and safety in a number of trials and has emerging data for use in viremic individuals.
- PrEP use is challenged by low uptake in key populations including women and African American men in the U.S.
- Long-acting CAB may help overcome some of the challenges with PrEP uptake and adherence.

APPROXIMATELY 1.2 MILLION PEOPLE IN the United States (U.S.) are living with HIV infection and about 13 percent of them do not know it.[1] In 2022, an estimated 31,800 people acquired HIV in the U.S. Estimated new HIV infections decreased 12 percent from 36,300 in 2018 to 31,800 in 2022. With diagnosis and appropriate treatment, the death rate from HIV has dramatically declined but those who are infected need to be identified.

The United States Ending the HIV Epidemic Initiative has four prongs—diagnosis, treat, prevent, and respond (Exhibit 1).[2] The goal is to reduce new HIV infections by 90 percent by 2030. This initiative focuses on those areas in the U.S. with the highest burden of new infections. About 50 percent of all new HIV diagnoses occur in 48 counties, Washington DC, and San Juan Puerto Rico across the country.

Gaps in care persist across the HIV care continuum in the U.S. For example, in 2018, 86 percent of those estimated to be infected were diagnosed, 65 percent of those diagnosed were linked to care, and 56 percent of those treated had viral suppression.[3] Things have improved since 2016 but work is still required. Groups who receive Ending HIV Epidemic funding have linked 84 to 86 percent of people newly diagnosed with HIV to medical care within 30 days.[4] As of 2023, a few groups have met the 2025 goal of linking 95 percent of newly diagnosed persons to HIV care. In several areas of the U.S., antiretroviral therapy (ART) is initiated at the time of testing which improves linkage to care and engages people in their care. There are still many barriers to people accessing care and achieving and maintaining viral suppression. These include youth discrimination,

Exhibit 1: Ending the HIV Epidemic[2]



substance use, mental health, poverty, stigma, medication adverse events, and general adherence issues such as forgetting medications.

Exhibit 2 shows the recommended initial ART regimens for treatment-naïve patients.[5] The HIV treatment guidelines are frequently updated so clinicians should always check for the most up-to-date recommendations. Two of the regimens are, a single tablet once daily which is a major improvement in patient burden over older regimens, and bictegravir/tenofovir alafenamide/emtricitabine, the most commonly selected initial therapy because it is a highly effective combination with a low rate of resistance development. Because some people at risk for HIV are now taking preventive agents (pre-exposure prophylaxis, PrEP), starting therapy requires consideration of which PrEP regimen has been used. Weight gain with the integrase inhibitor-based (i.e., bictegravir and dolutegravir) regimens is an issue for many patients which can have health significance. Women tend to gain more weight than men. The current standard of care is to still use the integrase inhibitor-based regimens while targeting weight with other interventions.

Long-acting injectable cabotegravir and rilpivirine (LA-CAB/RPV) is a two-medication injectable regimen indicated as a complete regimen for the treatment of HIV infection in adults to replace a current antiretroviral regimen in those who are virologically suppressed (HIV RNA less than 50 copies per mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This regimen has demonstrated effectiveness and safety in several trials and has emerging data for use in viremic individuals.[6-8]

Long-acting cabotegravir/rilpivirine is given as one- or two-month intramuscular injections (each medication requires a separate injection). If every two-month injections are planned, the first two injections are loading doses at one month intervals.[9] It was initially approved with a recommended oral lead in to assess tolerance but direct to injection has been shown to be equivalent to oral lead in plus injections.[10] An initial oral lead in regimen of cabotegravir and rilpivirine is now optional. Patients are typically offered both options and to choose with which they are most comfortable. Injection site reactions and pain on injection are the most common adverse events.

Virologic failure can occur with LA-CAB/PPV injections due to resistance mutations but the rate

Exhibit 2: Regimen Recommendations for Initial Antiretroviral Therapy (ART)[5]

- Bictegravir/tenofovir alafenamide/emtricitabine.
- Dolutegravir plus emtricitabine or lamivudine plus tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF].
- Dolutegravir/lamivudine,
  - Except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
- Darunavir/ritonavir or darunavir/cobicistat plus emtricitabine or lamivudine plus TAF or TDF,
  - For with a history of using cabotegravir and rilpivirine as PrEP, pending genotype/resistance testing.

Exhibit 3: CDC PrEP Recommendations[14]

	Daily Oral TDF/FTC	Daily Oral TAF/FTC	On Demand Oral TDF/FTC	Every 2 months LA-CAB
Cis Men	✓	✓	✓	✓
Cis Women	✓			✓
Trans women	✓	✓	✓	✓
Trans men	✓			✓
PWID	✓			
Renal disease		✓		✓

PWID = person who injects drugs

is low. Presence of at least two factors (rilpivirine resistance mutations, body mass index greater than 30 kg/m^2, HIV subtype A6/A1) is associated with virologic failure.[11] Longer two-inch needles should be used in those with BMI of 30 kg/m^2 or more to improve medication levels.[12]

One exciting development with this agent is for use in those who are unable to achieve viral suppression. It is thought that about 10 percent of patients with HIV who are treated do not achieve suppression for several reasons including housing instability, substance abuse, and mental illness. Using long-acting agents which do not depend on acquiring and taking medication daily is one way to bring the health and public health benefits of ART to these individuals. A study in a safety-net clinic in San Francisco had success in achieving viral suppression in a group with significant social challenges.[13] Although clinicians are trying this approach in patients who are not yet virally suppressed, they are having issues getting the combination covered in some settings because this is an off-label use. An ongoing Advancing Clinical Therapeutics Globally trial (A5359) is evaluating the use of LA-CAB/RPV in those with oral medication adherence challenges.

LA-CAB/RPV is primarily considered for switch regimens in those who have been suppressed for three to six months. Other switch regimens are also options, with reduced medication exposure for those with viral suppression, including dolutegravir-rilpivirine and dolutegravir-lamivudine. There are other things to consider when choosing between an oral regimen and injections. The long-acting regimen does not appear superior to once daily ART regimens and resistance can develop where there is no resistance development with bictegravir or dolutegravir/tenofovir alafenamide/emtricitabine. A subset of patients will prefer long-acting injections

Exhibit 4: PrEP Product Level Considerations

TDF/FTC or TAF/FTC	LA-CAB
Pros	**Pros**
• Options for daily and on-demand regimens.	• Superior to TDF/FTC in efficacy trials.
• Flexibility in implementation.	• Doesn't require daily adherence.
• Minimal clinical monitoring for most patients.	• Allows discretion in use.
• Available for all populations.	**Cons**
• Quarterly HIV testing.	• Increased visit frequency.
• Cost – generic TDF/FTC available.	• HIV testing requirements (frequency and type).
Cons	• Cost.
• Requires daily adherence or complex regimen.	• Resistance with breakthrough infections despite on-time injections.
• Pills may not be acceptable for all populations.	

to oral medications which can be a daily reminder of HIV infection. There are complexities with implementing in practices, including seeing patients six times a year compared to twice a year. Hopefully, LA-CAB/RPV will be an FDA-approved option for adherence challenged populations in the near future.

There are other investigational long-acting ART. Lenacapavir which is currently FDA approved for use in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current ART due to resistance, intolerance, or safety considerations, is given twice a year after an oral lead-in period. It is being evaluated for treatment naïve patients in combination with other antiretroviral agents. Islatravir, given as a once weekly dose, is in Phase III development for HIV treatment. It is being developed as part of a fixed-dose combination containing doravirine and islatravir and as a stand-alone agent.

For those people who are not yet infected but who are at risk for HIV infection, the main public health strategy in the U.S. is PrEP. The CDC recommends that all sexually active adults and adolescents should have PrEP discussed or considered as an option.[14] Exhibit 3 outlines the CDC recommended options for various groups.[14] Each regimen has been studied in different populations as indicated by the check marks.

There are some considerations in selecting among the four available PrEP regimens (Exhibit 4). Tenofovir disoproxil fumarate (TDF) can cause bone mineral density loss and renal dysfunction with long-term use but is less expensive; tenofovir alafenamide (TAF) does not cause these adverse events. On demand dosing is one way around long-term daily use of TDF; with this strategy the individual takes two tablets one hour before sexual activity and single doses at 24 and 48 hours afterwards. Many clinicians will use TDF in those under 45 years of age and TAF in those over 45 years.

The newest PrEP regimen is long-acting cabotegravir (LA-CAB) injection every two months. In a trial comparing LA-CAB with TDF/emtricitabine (FTC), the rate of HIV infection was 74 percent lower in African American men who have sex with men with LA-CAB—a group with a very high rate of HIV cases.[15] This data makes LA-CAB the preferred agent in this subpopulation, especially those who are younger.

Some considerations with implementing PrEP with LA-CAB are a need for HIV and viral load testing at every visit, additional visits compared to oral PrEP, and staffing requirements to manage the visits and lab testing. Additionally, there are issues on what to do if a patient misses or has a delayed injection. The patient can be covered with oral CAB or TDF/FTC or TAF/FTC.

Increasing PrEP coverage is one of the key prevention strategies outlined in the Ending the HIV Epidemic in the U.S. initiative. In 2022, 36 percent of people who could benefit from PrEP have had it prescribed, which was an improvement from 30 percent in 2021.[16] There is still a lack of uptake in selected groups. Uptake is highest at 94 percent among Caucasians, 24 percent in Hispanic/Latinos, and 13 percent in African Americans. Only 41 percent of at-risk men and 15 percent of women are receiving. Most new HIV infections are among gay

and bisexual men, the majority of whom are African Americans or Hispanic/Latino. About one-fifth of new HIV infections in 2021 were among women, and over half of those were among Black women. Age, racial/ethnic, and risk category disparities in PrEP discontinuation have also been identified.[17]

Conclusion

Oral integrase inhibitor-based therapy remains the standard of care for ART initiation. Long-acting CAB/RPV has demonstrated effectiveness and safety in a number of trials and has emerging data for use in viremic individuals. PrEP use is challenged by low uptake in key populations including women and African American men in the U.S. Long-acting CAB is highly effective for use as PrEP and may help overcome some of the challenges with uptake and adherence.

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Innovative Approaches in the Management of Chronic Lymphocytic Leukemia

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Summary

Chronic lymphocytic leukemia is a rare B cell cancer which affects primarily older people. Oral targeted therapies which change B cell signaling have replaced chemotherapy and chemoimmunotherapy as first-line treatment. Because patients will be taking these agents for many years, cost management solutions are needed.

Key Points

- Long-term data confirms safety and efficacy of the covalent BTK inhibitors.
- The covalent BTK inhibitors have similar efficacy but the selective agents have an advantage of fewer adverse events.
- Resistance mechanisms cause disease progression but a non-covalent BTK inhibitor is now available to achieve response and disease control in the presence of certain mutations.
- Fixed treatment duration approaches can mitigate overall cost without significant impairment to clinical outcomes.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) accounts for 1.0 percent of all cancers diagnosed in the United States (U.S.) annually.[1] Many patients with CLL are identified based on a routine blood draw which shows a high lymphocyte count. In 2024, an estimated 20,700 new cases of CLL and 4,400 deaths from CLL will occur. The five-year relative survival rate with CLL is 88.5 percent which has significantly improved over time. In the era of novel targeted agents, the five-year survival rate is predicted to increase to 90 percent. There are about 200,000 people living with CLL in the U.S.

CLL is a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23.[2] It is easy to diagnosis with flow cytometry and has a distinct immune-profile that is not seen in other diseases. A diagnosis of CLL requires a $5x10^9$/L or greater clonal B cell count. Small lymphocytic leukemia (SLL) is a subset of CLL with a less than $5x10^9$/L cell count but with documented nodal, splenic, or extramedullary involvement. SLL accounts for about 15 percent of cases. Hereafter only CLL is used since they are treated the same.

CLL is more common in adults with a median age at diagnosis of 70 years and is more common among men than women, particularly white men. For patients who are in their 70s when diagnosed, the new medications work so well that CLL will unlikely be the cause of their death. Molecular tests predict those patients who need to be treated immediately and those who can be observed.

B-cell receptor (BCR) signaling is crucial for normal B cell development and adaptive immunity. In CLL, malignant B cells display many features of normal mature B lymphocytes, including the expression of functional BCRs.[3] Thus various targeted treatments have been developed which alter this signaling. Targeted treatment options include oral

Exhibit 1: NCCN Recommended First-Line Regimens[8]

Type	Preferred First-Line
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Zanubrutinib
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (category 1) Venetoclax + obinutuzumab (category 1) Zanubrutinib (category 1)

Note: Guidelines also include other recommended regimens (including ibrutinib) and useful in certain circumstances regimens.

Bruton tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib), an oral B cell lymphoma 2 inhibitor (venetoclax), and an injectable anti-CD20 monoclonal antibody (obinutuzumab).

First-line CLL treatment has shifted away from chemo-immunotherapy (CIT) based approaches which combine chemotherapy and anti-CD20 agents to oral targeted therapy because of survival advantages and fewer short- and long-term adverse events. Currently, there are no targeted agents that can cure CLL. In the absence of a curative regimen, the therapeutic goal is to maximize patients' life span while effectively managing disease symptoms. Oral targeted therapy can control the disease for many years—patients are typically given BTK inhibitors until intolerance or disease progression occurs whereas venetoclax is used for a limited duration.

Although introduced initially for relapse/refractory disease, BTK inhibitors have moved to first-line therapy and transformed treatment of CLL by improving survival. Ibrutinib, the first BTK inhibitor to market, improves overall survival (OS) over chemotherapy and CIT in both older and younger patients. Long-term overall survival (OS) in those treated with ibrutinib first-line matches survival for age matched cohorts.[4-7] Ibrutinib also produces good survival results in those with high-risk features such as 17p deletion. The National Comprehensive Cancer Network (NCCN) Guidelines now recommend acalabrutinib and zanubrutinib, second generation agents, over ibrutinib for patients newly starting on BTK inhibitors (Exhibit 1).[8] Ibrutinib was moved from preferred regimens to other recommended regimens in the guidelines based on its toxicity profile compared to the other two BTK inhibitors. Dose reductions can be used to manage BTK inhibitor adverse events and have been shown not to impact outcomes. In patients who are already taking ibrutinib with no intolerance, ibrutinib can be continued until disease progression.

Acalabrutinib was the second BTK inhibitor approved. It is dosed twice daily to maintain BTK inhibition. A comparison trial of acalabrutinib versus ibrutinib (Elevate RR) found the two agents noninferior with a median progression-free survival (PFS) of 38.4 months in both arms.[9] All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; $p = .02$) and median OS was not reached in either arm. Final OS data have not yet been published. An advantage of acalabrutinib is lower rates of hypertension compared to the other BTK inhibitors.

Zanubrutinib was FDA approved for CLL in April 2023 after being approved in 2019 for several other indications. Unique to zanubrutinib, it can be dosed once or twice daily but still maintains BTK inhibition throughout the dosing interval even when given once daily. In the Alpine study, zanubrutinib was compared to ibrutinib in relapsed or recurrent CLL. At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to PFS (hazard ratio for disease progression or death, 0.65; $p = 0.002$).[10] At 24 months, PFS rates were 78.4 percent in the zanubrutinib group and 65.9 percent in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer PFS than those who received ibrutinib (hazard ratio for disease progression or death, 0.53); PFS across other major prognostic subgroups consistently favored zanubrutinib. The safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse

events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death. A lower rate of atrial fibrillation/flutter was observed with zanubrutinib compared to ibrutinib (2.5% versus 10.1%; $p = .0014$) and major bleeding rates were also lower (2.9% versus 3.9%), as were adverse events leading to treatment discontinuation (7.8% versus 13.0%, respectively) or death (3.9% versus 5.8%). Neutropenia occurred more often with zanubrutinib (28.4% versus 21.7%).

BTK inhibitors can be combined with anti-CD20 antibodies. With the combination of acalabrutinib with obinutuzumab (A+O), PFS is improved compared to acalabrutinib alone.[11] In the six-year follow-up report of this study, median OS was not yet achieved in both A+O and A arms and estimated 72-month OS rates were 68 percent and 72 percent, respectively.[12] Thus an OS benefit has not been shown with the combination and there are additional toxicities with the obinutuzumab addition including higher severe infection rates. High-risk patients do not have improved outcomes with the combination.

CLL B cell clones change over the course of the disease based on time, treatment pressures, and underlying biology resulting in treatment resistance mutations.[13] A sizable portion of patients treated with a BTK inhibitor eventually experience treatment failure due the development of resistance or intolerance. Ibrutinib, zanubrutinib and acalabrutinib are all irreversible, covalent BTK inhibitors which bind to the C481 site on BTK—50 to 60 percent of resistance mutations are with C481 and activating mutations downstream of BTK.[14] Reversible, non-covalent BTK inhibitors are the next evolution of CLL therapy. They exert their inhibition of BTK by different mechanisms to covalent BTK inhibitors. They do not act by binding to the C481 site on BTK, and therefore offer a potential alternative therapeutic option to patients who have developed acquired resistance due to BTK C481 mutations following prior therapy with a covalent BTK inhibitor. Pirtobrutinib is the first highly selective, non-covalent, reversible BTK inhibitor to be approved by the FDA—it blocks the ATP binding site of BTK.

Pirtobrutinib was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including another BTK inhibitor in January 2023 and for CLL in December of 2023. The NCCN Guidelines recommend it for second-line or third-line therapy in cases of resistance or intolerance to prior covalent BTK inhibitor therapy.[8] Pirtobrutinib is a very selective inhibitor which also helps lower the rate of adverse events. In a trial evaluating pirtobrutinib in 317 patients with CLL, including 247 who had previously received a BTK inhibitor, the median number of previous lines of therapy was three (range, 1 to 11), and 40.5 percent had also received a B-cell lymphoma 2 inhibitor such as venetoclax.[15] The percentage of patients with an overall response to pirtobrutinib was 73.3 percent (95% confidence interval [CI], 67.3 to 78.7), and the percentage was 82.2 percent (95% CI, 76.8 to 86.7) when partial response with lymphocytosis was included. The median PFS was 19.6 months (95% CI, 16.9 to 22.1). The most common adverse events were infections (71.0%), bleeding (42.6%), and neutropenia (32.5%). At a median duration of treatment of 16.5 months (range, 0.2 to 39.9), some adverse events that are typically associated with BTK inhibitors occurred infrequently, including hypertension (14.2% of patients), atrial fibrillation or flutter (3.8%), and major hemorrhage (2.2%). Only nine of 317 patients (2.8%) discontinued pirtobrutinib owing to a treatment-related adverse event. In this trial, pirtobrutinib showed efficacy in patients with heavily pretreated CLL who had received a covalent BTK inhibitor. Novel resistance mechanisms are now showing up with the use of pirtobrutinib which will have to be tackled in the future.[16] NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines BTK degradation with the immunomodulatory activity of an Ikaros and Aiolos degrader which is in early trials for CLL with BTK resistance.[17] Several other noncovalent BTK inhibitors are under investigation for CLL and other B-cell malignancies.

First-line treatment of CLL can be either BTK inhibitors (with or without anti-CD20 antibodies) until disease progression, or fixed duration venetoclax plus obinutuzumab. There are financial and toxicity benefits to a fixed duration treatment. Clinicians do not believe there is any detriment to fixed duration compared to continuous BTK inhibitors but there are no published trials that directly compare these approaches. One comparison trial is ongoing which is expected to produce data in 2025. In high-risk disease, B cell clones recover faster when treatment is stopped compared to low-risk disease, thus continuous BTK inhibitors may be the best choice but again head-to-head data are not yet available.

Treatment of CLL carries a significant financial burden. The main drivers of cost for CLL patients are infusions, outpatient visits, hospitalizations, adverse event management, and medication costs. Adoption of targeted agents has dramatically increased cost of CLL management due to high medication prices,

prolonged treatment duration, and an increased number of patients living longer because of medication efficacy.[18] Although CLL is an incurable disease, patients can live a long time with oral therapy. For example, with BTK inhibitors, a patient may be on this therapy for six to eight years before developing resistance or disease progression. The wholesale acquisition price of the BTK inhibitors is $14,000 to $20,000 monthly. Patients with Medicare Part D coverage may have a $900 per month out-of-pocket cost.

Fixed duration therapies like venetoclax or CIT compared to continuous BTK inhibitor therapy has similar costs in year one of treatment but decline in years two and three whereas the cost of the BTK inhibitor continues.[19] One approach currently being developed is to combine fixed duration BTK inhibitor and venetoclax to try to limit medication exposure and costs while also maximizing outcomes. This approach may become the first-line standard of care in appropriate patients.

Conclusion

Long-term data confirms safety and efficacy of the covalent BTK inhibitors. Head-to-head and indirect comparison data suggest similar efficacy across agents but with improved class effect adverse event profiles favoring selective agents. Selective agents have an advantage in lower rates of atrial fibrillation/flutter, cardiovascular deaths, and discontinuations due to adverse events. Resistance mechanisms cause disease progression but a non-covalent BTK inhibitor is now available to achieve response and disease control in presence of common C481 mutations. Costs for treating CLL are significant and fixed duration approaches can mitigate overall costs without significant impairment to clinical outcomes.

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New Developments in the Treatment and Management of Heart Failure: Managed Care Considerations on the Role of New and Emerging Therapies

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Summary

A quadruple medication strategy is now recommended for managing heart failure with a reduced ejection fraction. Two newer classes of medications which have been shown to improve morbidity, mortality, and hospitalization rates have been added to the regimen or replaced older agents.

Key Points

- ARNI + BB + MRA + SGLT2i are the standard of care for HFrEF.
- There are demonstrated benefits of ARNI and SGLT2i across the spectrum of EF below normal including those with HFmrEF and HFpEF.
- The increased upfront costs for novel therapies including ARNI and SGLT2i are likely offset by the improvements in morbidity, ultimately leading to cost-savings.

HEART FAILURE (HF) CAUSES MAJOR morbidity, mortality, and costs in the United States (U.S.). A major cost-driver is a high incidence of hospitalizations. There are about 6.7 million people in the U.S. with HF which results in over a million hospitalizations annually.[1] HF is the number one cause of hospitalization in those over 65 years of age and the 30-day HF readmission rate is 24 percent. Sixty percent of those hospitalized for HF will have a readmission within one year. Fifty percent of HF patients will die within five years of diagnosis. With the aging of the U.S. population, the impact of HF is expected to increase substantially.[2]

HF is classified by ejection fraction.[3] HF with reduced ejection fraction (HFrEF) has an EF less than or equal to 40 percent, HF with mildly reduced EF (HFmrEF) has EF between 41 and 49 percent, and HF with preserved EF (HFpEF) has EF greater than 50 percent. The primary focus of this article is HFrEF.

The four pillars of guideline directed medical therapy (GDMT) for optimal management of HFrEF are an angiotensin receptor blocker/neprilysin inhibitor combination (ARNI), a beta blocker (BB), a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i); see Exhibit 1.[4,5] Sacubitril/valsartan is the only available ARNI and is only available as a brand name product. Each of these agents plays a role in modifying the pathophysiology of HF and have been shown to reduce morbidity and mortality. Cumulative risk reduction in all-cause mortality over 24 months, if all evidence-based medical therapies are used, is a relative risk reduction of 72.9 percent and absolute risk reduction of 25.5 percent. The number needed to treat to prevent death with these four pillars is 3.9. Treatment with quadruple therapy is estimated to afford 2.7 additional years (for an 80-year-old) to 8.3 additional years (for

Exhibit 1: Quadruple HFrEF Therapy[4,5]

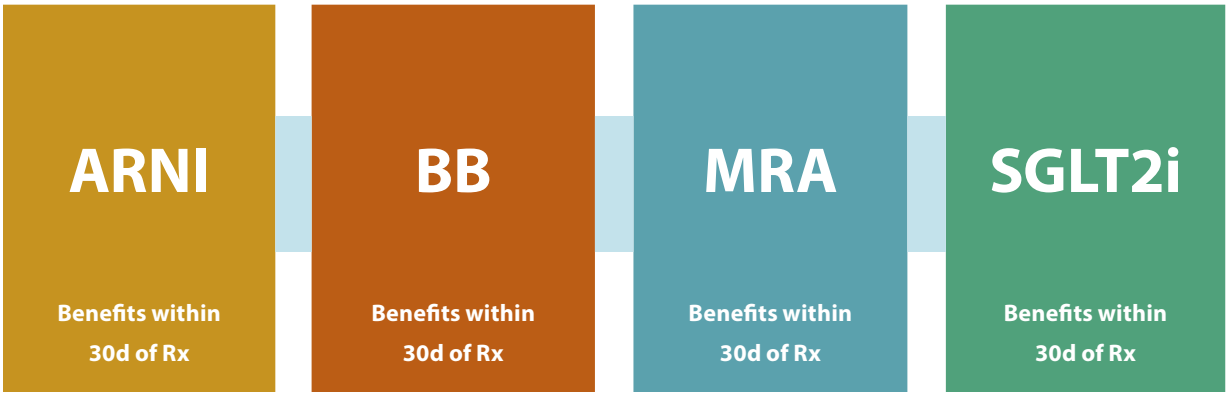
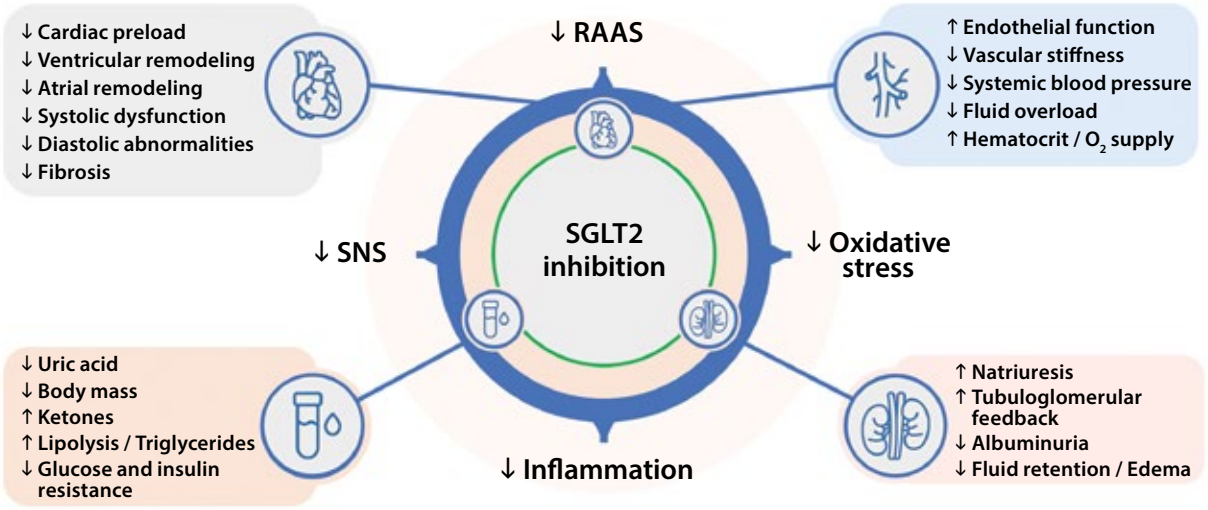


Exhibit 2: Direct and Indirect Actions of SGLT2 Inhibitors[9-11]

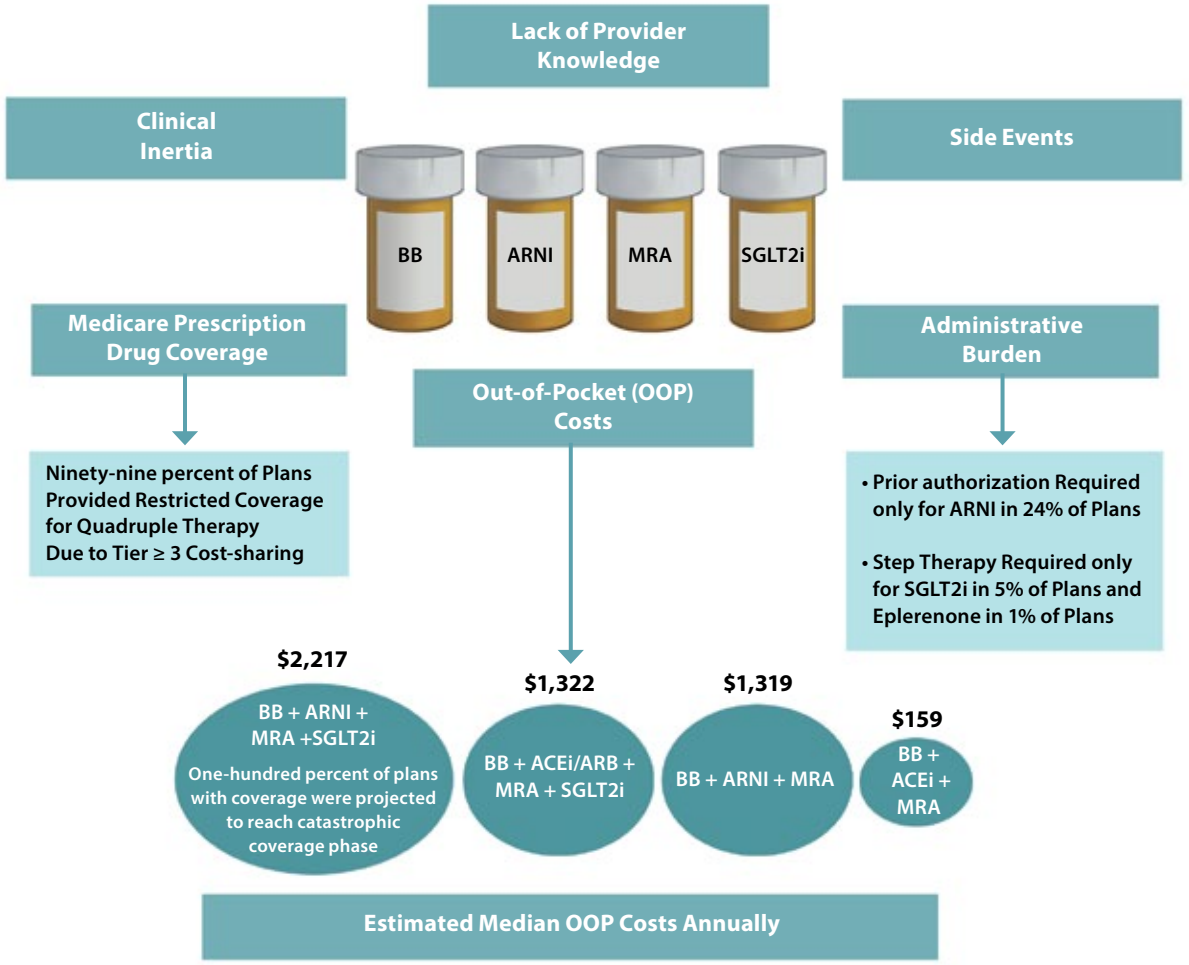


RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

a 55-year-old) free from cardiovascular death or first hospital admission for HF and 1.4 additional years (for an 80-year-old) to 6.3 additional years (for a 55-year-old) of survival compared with conventional therapy (angiotensin converting enzyme inhibitor [ACE-I] or angiotensin receptor blocker [ARB] plus a BB) when treating HfrEF.[6] The American College of Cardiology guidelines and their Decision Pathway for Optimization provide specifics on how to initiate therapy, starting and target doses, and adherence management.[4,5]

In the Paradigm-HF and Pioneer-HF trials, which both compared sacubitril/valsartan to enalapril, the ARNI was superior to enalapril in reducing the risks of death and of hospitalization for HF in those with HFrEF (EF < 40%) and reduced N-terminal pro-b-type natriuretic peptide (NT-proBNP) concentrations while improving cardiac function.[7,8] Indications for use of an ARNI are HFrEF (EF < 40%), New York Heart Association (NYHA) Class II or III HF, and administered in conjunction with a background of GDMT for HF for reduction of morbidity and mortality.[4] In patients with previous or current symptoms of chronic HFrEF, the use of ACE-I is beneficial to reduce morbidity and mortality when the use of ARNI is not feasible.

Exhibit 3: Barriers to Quadruple Therapy for HFrEF[18]



In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACE-I because of cough or angioedema and when the use of ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF NYHA Class II or III who are currently tolerating an ACE-I or ARB, replacement by ARNI is recommended to further reduce morbidity and mortality.

The SGLT2i medication class was originally approved to treat type 2 diabetes but because of FDA-required studies related to cardiovascular disease (CVD) risk and diabetes medications, these agents now have FDA-approved labeling for reducing CVD morbidity and mortality and HF hospitalizations. These medications have a wide range of direct and indirect actions which benefit HF (Exhibit 2).[9-11] Several RCTs in patients with type 2 diabetes and either established CVD or high risk for CVD have shown that SGLT2i prevent HF hospitalizations compared with placebo.[12-16] An overall 31 percent reduction in HF hospitalizations was noted irrespective of the presence or absence of preexisting HF, although only 10 percent to 14 percent of participants had HF at baseline. The benefit appears independent of the glucose-lowering effects. In the DAPA-HF and EMPEROR-Reduced trials where the subjects had HFrEF, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalization by approximately 25 percent. The benefit in reduction of HF hospitalization was significant (30%) in both trials. Risk of cardiovascular death was significantly lowered (18%) with dapagliflozin, as was risk of all-cause mortality (17%). Although no significant cardiovascular mortality benefit was observed with

Exhibit 4: Quadruple Therapy Provides Economic Value[4]

	Cost	Value Statement	QALYS
ARNI	$$$$	HIGH	< $60,000
ACE/ARB	$	HIGH	< $1,000
Beta-blockers	$	HIGH	< $1,000
MRA	$	HIGH	< $1,000
SGLT2i	$$$$	INTERMEDIATE	$60,000 to $90,000 (reduction in drug price would lead to QALY < $60,000)

QALY = quality adjusted life year

empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2i therapy was associated with a reduction in all-cause mortality and cardiovascular death.[17] The benefits in both trials were seen irrespective of baseline diabetes status. Furthermore, serious renal outcomes were less frequent, and the rate of decline in kidney function was slower in patients treated with SGLT2i. In patients with symptomatic chronic HFrEF, SGLT2i therapy is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[4]

There are significant barriers to implementing quadruple therapy for HFrEF (Exhibit 3).[18] One major barrier is that Medicare drug plans restrict coverage of quadruple therapy through cost sharing, with out-of-pocket costs that are substantially higher than generic regimens. Quadruple therapy may be unaffordable for many Medicare patients with HFrEF unless medication prices and cost sharing are reduced. Quadruple therapy does provide economic value and the 2022 ACC guidelines provide Value Statements for certain treatments with high-quality published economic analyses (Exhibit 4).[4] ARNI and two SGLT2i are on the list of medications selected by Medicare for price negotiations.[19]

ARNI and SGLT2i have also been evaluated across the spectrum of EF below normal. The 2023 ACC Expert Consensus Decision Pathway on Management of HFpEF recommends that ARNI be added for all women with HFpEF and men with EF between 55 and 60 percent.[20] In patients with HFpEF, SGLT2i can also be beneficial in decreasing cardiovascular mortality. EMPEROR-Preserved showed a significant benefit of the SGLT2i, empagliflozin, in symptomatic patients with HF with EF of more than 40 percent and elevated natriuretic peptides.[21] The 21 percent reduction in the primary composite endpoint of time to HF hospitalization or cardiovascular death was driven mostly by a significant 29 percent reduction in time to HF hospitalization (nonsignificant lower cardiovascular death [HR, 0.91; 95% CI, 0.76 to 1.0]), with no benefit on all-cause mortality. Empagliflozin also resulted in a significant reduction in total HF hospitalizations, decrease in the slope of the kidney function decline, and a modest improvement in quality of life at 52 weeks. Of note, the benefit was similar irrespective of the presence or absence of diabetes at baseline. The Deliver study with dapagliflozin showed similar results.[22] The 2023 ACC Expert Consensus Decision Pathway on Management of HFpEF recommends addition of SGLT2i for all patients with HfpEF.[20]

The EMPEROR-preserved and DELIVER trials also included patients with HF with mildly reduced EF (HFmrEF, EF 41to 49%) and showed benefit for reducing death and HF hospitalization in this population.[21,22] The ACC guidelines recommend SGLT2i as a 2B recommendation and the updated European Cardiology Society (ECS) guidelines recommend an SGLT2i (dapagliflozin or empagliflozin) in patients with HFmrEF to reduce the risk of HF hospitalization or CV death as a 1A recommendation.[4,23] The differences in these recommendations are based on when the guidelines were updated (2022 versus 2023). Use of any of the other main classes of HF medications in HFmrEF are a 2B recommendation in both the ACC and ESC guidelines.

HF is a progressive disease and high morbidity

and mortality are associated with worsening HF. Clinical clues that a patient may have worsening or advanced HF include persistent NYHA III-IV symptoms; two or more emergency department visits or hospitalizations for acute HF in past 12 months; high-risk biomarker profile (hyponatremia, very or persistently elevated troponin or NT-proBNP); inability to up-titrate GDMT because of hypotension (systolic ≤ 90 mm Hg), dizziness, or worsening renal function; onset of arrhythmias (atrial fibrillation, ventricular tachycardia); escalating doses of diuretics (e.g., > 160 mg/d furosemide) or persistent edema despite escalating diuretic doses; and/or need for intravenous inotropes.[24] The steps to address worsening HF include maximization of GDMT, consideration of devices for arrhythmias, percutaneous mitral valve repair, and cardiac rehabilitation; and additional medications such as hydral nitrates in African American patients, ivadarbine in those with heart rate of more than 70 beats per minute despite maximum beta blocker dosing, and vericiguat in those with recent HF hospitalization or need for intravenous diuretics, EF of less than 45 percent, and elevated BNP levels.[4] Patients with worsening HF and advanced HF should be referred to a comprehensive specialty HF program for maximization of GDMT and consideration for cardiac transplant, left ventricular assistive devices, palliative inotropic support, and palliative care, respectively.[4,24] The earlier in the HF disease process a patient is referred to specialty care the better.

One way to improve HF care is to implement a rapid up-titration of GDMT and close post-discharge follow-up when someone is hospitalized for HF. One trial found that an intensive treatment strategy of rapid up-titration of GDMT and close follow-up after an acute HF admission reduced symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or HF readmission compared with usual care.[25] By day 90 after hospital discharge, blood pressure, pulse, NYHA class, body weight, and NT-proBNP concentration had decreased more in the high-intensity care group than in the usual care group. Heart failure readmission or all-cause death up to day 180 occurred in 15.2 percent of the high-intensity care group and 23.3 percent of the usual care group (adjusted risk difference 8.1%; $p = 0{\cdot}0021$). When just examining HF readmission, there was 44 percent reduction in HF readmissions by 180 days. More adverse events did occur in the high-intensity care group (41%) than in the usual care group (29%) but similar incidences of serious adverse events (16% versus 17%) were reported in each group.

Conclusion

The landscape of medical therapies available for treatment of HFrEF, HFmrEF, and HFpEF continues to rapidly evolve. GDMT with ARNI/BB/MRA/SGLT2i is the standard of care for HFrEF. There are demonstrated benefits of ARNI and SGLT2i across the spectrum of EF below normal, which includes those with HFmrEF and HFpEF. The increased upfront costs for novel therapies including ARNI and SGLT2i are likely offset by the improvements in morbidity, ultimately leading to cost-savings.

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Addressing the Barriers to Optimal Adolescent and Adult Immunizations: Enhancing Confidence to Overcome Suboptimal Vaccination Practices

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Summary

Vaccinations are important for preventing disease. For most vaccines, concerted effort is needed to increase rates, especially given the rise in vaccine hesitancy and state regulations allowing personal/philosophical exemptions to school-based vaccine requirements.

Key Points

- Vaccines are an important public health initiative.
- Vaccine hesitancy has been increasing.
- Payers and providers need to focus efforts on adolescent and adult vaccines to boost rates.
- Payers and providers need to make joint efforts to educate, eliminate misunderstandings, and encourage patients to get appropriate vaccinations.

CHILDHOOD VACCINES SAVE AN ESTIMATED 42,000 lives every year in the United States (U.S.).[1] This is three times more lives saved than seat belts and child restraints combined.[2] Globally, 23 million deaths were averted between 2010 and 2018 by measles vaccinations alone.[3] Up to eight years after the introduction of human papilloma virus (HPV) vaccine, the oncogenic HPV prevalence was reduced by 83 percent among girls aged 13 to 19 years and precancerous lesions decreased by 51 percent among girls aged 15 to 19 years.[3]

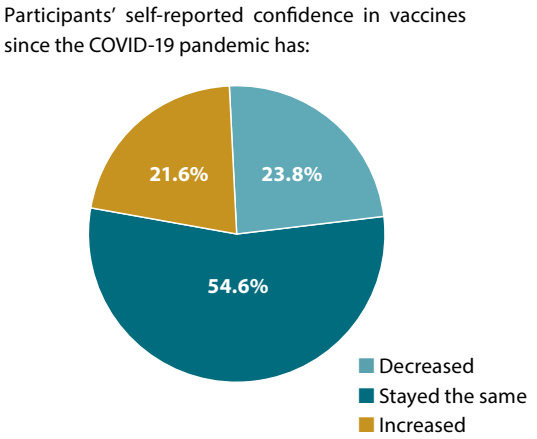
The COVID-19 pandemic impacted the rate of routine vaccinations for children, adolescents, and adults because of shutdowns.[4] By June through September 2020, the number of vaccine doses administered approached pre-pandemic baseline levels, but did not increase to the level that would have been necessary to catch up children who did not receive routine vaccinations on time.[5] Even without the impact of a pandemic, vaccination rates in adults lag those for children.[6]

Vaccine hesitancy has grown recently, especially with regards to the COVID-19 vaccines and routine childhood vaccines. One area where vaccine hesitancy in the U.S. is having an impact is with measles. There is an ongoing global spread of measles with over 140,000 measles deaths annually, mostly among unvaccinated or under vaccinated children less than five years of age.[7] In 2023, approximately 83 percent of the world's children received one dose of measles vaccine by their first birthday, well below the 2019 level of 86 percent. Measles was declared eliminated in the U.S. in 2000, but outbreaks have been occurring caused by importation of cases in unvaccinated people. As of October 24, 2024, there have been 15 outbreaks (defined as three or more related cases) reported in 2024, and 71 percent of cases (193 of 271) are outbreak-associated.[8] For comparison, four outbreaks were reported during 2023 and 49 percent of cases (29 of 59) were outbreak-

Exhibit 1: U.S. Measles Recent Cases[8]

Year	Cases
2024	271
2023	59
2022	121
2021	49
2020	13
2019	1,274
2018	381

Exhibit 2: Decrease in Vaccine Confidence[9]



associated. Exhibit 1 shows the recent yearly cases of measles.[8] Of the 2024 cases, 41 percent occurred in those under five years of age, 31 percent in those aged five to 19 years, and 28 percent in the over 20 years of age group. Eighty-nine percent of those infected were unvaccinated or had an unknown history.

Vaccine confidence has significantly declined since the onset of the pandemic. One study found an almost 24 percent decline when comparing pre- and post-pandemic surveys (Exhibit 2).[9] Confidence dropped across all demographic measures. The anti-vaccine community which questions vaccine safety and benefit includes over 400 websites, mass media personalities, and books which contribute to vaccine hesitancy.[10]

Managed care can work with clinicians to educate their members on how vaccines are evaluated for safety and how safety is continually monitored post-marketing through the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Data Link (VSD). In addition to education, clinicians can actively search for missed vaccines and seize opportunities for vaccination. Exhibit 3 shows various strategies for increasing vaccination rates.[11,12] Reminder systems, whether for patients or providers, are among the lowest-cost strategies to implement and the most cost effective in terms of additional people vaccinated.[12] Strategies based in settings such as schools and managed care organizations that reach the target population achieve additional vaccinations in the middle range of cost effectiveness.[12]

Healthcare providers can have a significant impact on vaccination rates by developing effective communication skills. An effective interaction between providers and patients can address the concerns of vaccine supportive individuals/parents and motivate a hesitant person towards vaccine acceptance.[13] Poor communication can contribute to rejection of vaccinations or dissatisfaction with care. The goals of a given interaction will vary, depending on a person's readiness to vaccinate. In all encounters, healthcare providers need to build rapport, accept questions and concerns, and facilitate valid consent. For the hesitant, late, or selective vaccinators, or refuser groups, strategies should include use of a guiding style and eliciting a person's own motivations to vaccinate while avoiding excessive persuasion and adversarial debates.

A presumptive or expectant approach can be effective. Here the provider states "you (or your child) are due to receive two vaccines today." For the vaccine hesitant, it may require extra time to address their concerns about safety and efficacy. Parents who exhibit doubts about immunizations for their children are not all the same and thus must be approached individually.[14] Safety is the most common concern over childhood vaccines; providers can contextualize the risks compared to the benefits without dismissing a parent's concern. Rather than attempting to overcome vaccination myths by convincing parents of the safety of vaccines, one study found that pro-vaccine messages are more effective if they work to convince parents of the dangers of failing to vaccinate their children.[15]

States allowing philosophical exemptions to school-required vaccines have significantly increased the number of unvaccinated children. Two years after Arkansas allowed these exemptions, vaccine exemptions increased over 50 percent with 95 percent being for philosophical reasons and have continued to increase since then.[16] However, vaccine-preventable disease clusters have not yet been linked to or identified in any population in

Exhibit 3: Strategies to Increase Vaccination[11,12]

Provider Behavior
- Assessment and feedback
- Patient communication – presumptive approach and motivational interviewing.

Clinical Processes
- Standing orders
- Reminders
- Recall systems
- Home visits

Public Health
- Immunization information systems
- Free vaccines
- School interventions
- Policy/Law

Patient Behavior
- Education
- Incentives
- Reducing costs

Arkansas with a high rate of vaccine exemptions.[17] In response to low vaccination rates, California implemented interventions to increase uptake of school-required vaccines including educational materials to school staff on the proper application of conditional admission for kindergartners who were not up-to-date on required vaccinations and elimination of personal belief exemptions.[18] These changes led to decreased size of clusters of under-vaccinated children and clusters in fewer schools.

Overall, healthcare providers should assess vaccination status of patients at all clinical encounters, clearly recommend needed vaccines, and offer needed vaccines or refer for vaccination if vaccines are not offered in that setting. Health systems and managed care can conduct vaccine needs assessments, measure vaccination rates, and perform continuous quality improvement to improve rates.

One example where vaccine coverage could be improved in the U.S. is with the HPV vaccine—the first cancer prevention vaccine. HPV infection with oncogenic subtypes is responsible for more than 90 percent of anal and cervical cancers, 70 percent of vaginal and vulvar cancers, 60 percent of penile cancers, and 70 percent of oropharyngeal cancers.[19-21] HPV infection results in an estimated 24 million active cases and 5.5 million new cases each year.[22]

HPV vaccine works by preventing infections prior to natural exposure. Thus, it is more effective at younger ages. Vaccine effectiveness estimates for younger adolescents ages nine to 14 years range from 74 to 93 percent and from 12 to 90 percent for adolescents ages 15 to 18 years (these estimates include rates for the older and current versions of the vaccine).[23] Thus the emphasis should be on early vaccination. As noted previously, the HPV vaccine has been shown to reduce the risk of HPV infection and precancerous changes. It also reduces the risk of invasive cervical cancer especially when given prior to age 17 years.[24] In 2007, Australia was one of the first countries to introduce an HPV vaccination program and has since achieved high vaccination coverage across both men and women. A modeling study found that if high-coverage vaccination and recommended HPV screening is maintained, at an elimination threshold of four new cases per 100,000 women annually, cervical cancer could be eliminated as a public health problem in Australia by 2066.[25]

The 9-valent recombinant vaccine, which replaced an earlier 4-valent version, is FDA approved for females nine through 45 years of age for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; cervical, vulvar, vaginal, and anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11. It is also FDA approved for males nine through 45 years of age for the prevention of anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11.

The ideal time to vaccinate against HPV is prior to any exposure through sexual contact. HPV vaccination is recommended at ages 11 to 12 years.[26] Catch-up HPV vaccination is recommended for all persons through age 26 who are not adequately vaccinated. Some adults ages 27 through 45 years may decide to get the HPV vaccine based on discussion with their clinician, if they were not adequately vaccinated when younger.

Unfortunately, the U.S. needs to continue to improve HPV vaccination rates. In 2022, only 38.6 percent of children aged nine to 17 years had received one or more HPV vaccine doses.[27] In 2023 in those aged 13 to 17 years, 59 percent of males and females were found to be up-to-date on HPV

Exhibit 4: Pneumococcal Vaccination for Adults[31]

Adults ≥ 50 years old

Complete pneumococcal vaccine schedules

Prior vaccines	Option A	Option B
None*	**PCV20 or PCV21**	**PCV15** → ≥1 year† → **PPSV23¶**
PPSV23 only at any age	≥1 year → **PCV20 or PCV21**	≥1 year → **PCV15**
PCV13 only at any age	≥1 year → **PCV20 or PCV21**	**NO OPTION B**
PCV13 at any age and PPSV23 at < 65 years	≥5 years → **PCV20 or PCV21**	

* Also applies to people who received PCV7 at any age and no other pneumococcal vaccines.

¶ If PPSV23 is not available, PCV20 or PCV21 may be used.

† Consider minimum interval (8 weeks) for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak (CSF) leak.

§ For adults with an immunocompromising condition, cochlear implant, or CSF leak, the minimum interval for PPSV23 is ≥ 8 weeks since last PCV13 dose and ≥ 5 years since last PPSV23 dose; for others, the minimum interval for PPSV23 is ≥ 1 year since last PCV13 dose and ≥ 5 years since last PPSV23 dose.

Shared clinical decision-making for those who already completed the series with PCV13 and PPSV23

Prior vaccines	Shared clinical decision-making option for adults ≥ 65 years old
Complete series: PCV13 at any age and PPSV23 at ≥ 65 yrs	≥5 years → **PCV20 or PCV21** — Together, with the patient, vaccine providers may choose to administer PCV20 or PCV21 to adults ≥ 65 years old who have already received PCV13 (but not PCV15, PCV20, or PCV21) at any age and PPSV23 at or after the age of 65 years.

vaccination.[28] Parental concerns about long-term safety, adverse events, age of child, and feeling their child is not at risk of an HPV-related disease are the primary reasons for parents avoiding having their adolescents vaccinated.[29,30]

Pneumococcal vaccination is another example of an area where vaccine rates could be improved. Invasive pneumococcal infection rates have declined with the introduction of the pneumococcal vaccines.[31] In 2021, pneumococcal vaccination coverage among adults aged 65 years and older was 70 percent and coverage among adults aged 18 to 64 years at increased risk was 30 percent. Currently there are three pneumococcal conjugate vaccines (PCV-15, PSV-20, PCV-21), and a 23-valent pneumococcal polysaccharide vaccine (PPSV-23). The PCV-21 vaccine is the most recent addition (June 2024). PCV21 does not contain certain serotypes that are included in other licensed pneumococcal vaccines but adds eight new serotypes. The recommendations for who should receive pneumococcal vaccination depends on risk, prior vaccination, and varies by age and underlying medical conditions and can be confusing for clinicians.[31] In a CDC survey, 38 percent of respondents disagreed or strongly disagreed with the statement "the current adult pneumococcal vaccine recommendations are easy to follow."[32] The CDC does offer a phone application (PneumoRecs VaxAdvisor) to help clinicians with appropriate recommendations.

Pneumococcal vaccine recommendations were updated in October 2024, to recommend pneumococcal vaccination for adults aged 50 years or older rather than starting at age 65 years.[31] Exhibit 4 shows the most recent recommendations for adults.[31] Younger adults may also need pneumococcal vaccination; clinicians should consult the guidelines for recommendations for those aged 19 to 49 years with immunocompromising conditions, cochlear implants, or cerebrospinal fluid leaks.

Conclusion

Vaccines are an important public health initiative. Unfortunately, vaccine hesitancy has been increasing in recent years. Payers and providers need to focus efforts especially on adolescent and adult vaccines to boost rates. Payers and providers will need to make joint efforts to educate, eliminate misunderstandings, and encourage patients to get appropriate vaccinations.

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Patient-Focused Treatment Decisions in the Management of Ovarian Cancer: Managed Care Considerations in the Evolving Role of PARP Inhibitors

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Summary

The management of advanced ovarian cancer has changed over the last decade, especially with the introduction of PARP inhibitors. Although initially approved as later-line treatment, these agents are now used for maintenance therapy after a complete or partial response to first-line platinum-based chemotherapy.

Key Points

- Genetic testing identifies those who would benefit the most from PARP inhibitors.
- PARP inhibitors have significant efficacy in first-line maintenance setting.
- Maximizing tolerability and adherence with PARP inhibitors is important.
- Cost management with this class of medication is challenging but the choice of therapy should be patient focused.

OVARIAN CANCER IS A CHALLENGING disease because most patients are not diagnosed until they already have advanced stage disease and recurrence after treatment is common.[1] Early-stage disease is very curable with an 85 to 95 percent survival rate, but even with locally invasive disease, survival drops substantially. Two-thirds of women surveyed in an Every Woman study had never heard of ovarian cancer or knew nothing about it.[2] One-quarter waited three months or more before visiting a doctor with their symptoms, and one in 10 waited more than six months.

In 2024, an estimated 19,680 cases of ovarian cancer will be diagnosed in the United States (U.S.), and 12,740 women will die from this cancer.[3] The rate of ovarian cancer has been declining in the U.S. since 1975 but part of this decline can be attributed to the use of oral contraceptives which reduce risk. Deaths from ovarian cancer also have been slowly declining since 2003. The five-year survival rate is 50.9 percent (2014 to 2020 data).

Ovarian cancer is very often a catastrophic disease. In 2019, the estimated economic burden of ovarian cancer in the U.S. was around $450 million, which includes out-of-pocket costs and patient time.[4] The average annual cost of ovarian cancer care varies by the phase of care with the first six months of care costing over $200,000, continuing care at $26,000 to $88,000, and end-of-life care at over $129,000.

Ovarian cancer is not one disease. The most common type is serous and 75 percent of cases are high-grade serous histology.[5] Endometrioid, clear cell, and mucinous are the other histological types. The other identifier of type is genetic. Breast cancer (BRCA) 1 and 2 mutated ovarian cancer is treated differently from cases without these mutations.

Exhibit 1: Advanced Ovarian Cancer First Line Maintenance[13]

Stage II to IV Post Primary Treatment		
No bevacizumab used in primary treatment	BRCA 1/2 wild type or unknown AND CR/PR	Observe OR Niraparib OR Rucaparib
	Germline or somatic BRCA 1/2 mutation AND CR/PR	Olaparib (category 1) OR Niraparib (category 1) OR Rucaparib OR Observe for some stage II CR
Bevacizumab used in primary treatment	BRCA 1/2 wild type or unknown - CR/PR - HR proficient	Bevacizumab
	BRCA 1/2 wild type or unknown - CR/PR - HR deficiency	Bevacizumab + olaparib (category 1) OR Bevacizumab + niraparib (if intolerant of olaparib)
	Germline or somatic BRCA 1/2 mutation AND CR/PR	Bevacizumab + olaparib (category 1) OR Bevacizumab + niraparib (if intolerant of olaparib) OR Single agent PARP inhibitor

CR = complete response; PR = partial response; HR = homologous recombination

The experience of the patient with this disease can be mapped out by following the CA125 levels which increase as the disease progresses. After surgery and radiation, levels decline and the patient hopes for a cure. Unfortunately, many patients have a relapse and then their hopes turn to remission. Chemotherapy is used for relapses to buy the patient time by inducing remission. The last season of this disease is the transition into maintaining quality of life near the end of life.

There have been multiple advances in the treatment of ovarian cancer since the late 1980s. Platinum-based chemotherapy (cisplatin, carboplatin), taxanes (paclitaxel), bevacizumab, immunotherapy, and poly (ADP-ribose) polymerase (PARP) inhibitors have all come to market for various stages of disease. Ovarian cancer treatment is based on three pillars—cytoreductive surgery, platinum-based chemotherapy, and targeted therapies. The development of PARP inhibitors has provided a substantial improvement in progression-free survival (PFS) and, hopefully, in overall survival (OS). Treatment is chosen based on histology, tumor genetic signature, remission duration after prior treatment, and the number of prior lines of therapy. First-line treatment is surgery (primary or interval debulking) and primary or neoadjuvant chemotherapy with carboplatin and paclitaxel. Bevacizumab may be added to chemotherapy and used as maintenance therapy until disease progression. At disease progression, another chemotherapy regimen will be tried; whether it will be platinum-based will depend

Exhibit 2: PARPi Cost Effectiveness[22]

Interventions	Results	Groups	Perspective	WTP Threshold
Maintenance therapy for platinum-sensitive recurrent ovarian cancer				
olaparib versus no maintenance	cost-effective	with gBRCA mutation non-gBRCA mutation	U.S. payer	$150,000/QALY
		all patients with gBRCA mutation	Taiwan (China) single-payer	$93,478/PF-LYS
	not cost-effective	non-gBRCA mutation with gBRCA mutation	U.S. societal	$50,000-$100.000/ PF-LYS
		with gBRCA mutation wild-type gBRCA	U.S. third-party payer	$50,000-$100.000/ PF-LYS
		all patients with gBRCA mutation non-gBRCA mutation	U.S. healthcare sector	$100,000/PF-LYS
		all patients with gBRCA mutation	Singapore healthcare system	$34,047/QALY
		with gBRCA mutation	Chinese healthcare system	$31,498.70/QALY
niraparib versus no maintenance	cost-effective	with gBRCA mutation non-gBRCA mutation	U.S. payer	$150,000/QALY
		all patients with gBRCA mutation	Taiwan (China) single-payer	$93,478/PF-LYS
	not cost-effective	non-gBRCA mutation		
		all patients with gBRCA mutation	U.S. healthcare sector	$100,000/PF-LYS
		non-gBRCA mutation with gBRCA mutation non-gBRCA mutation or HRD	U.S. societal	$100,000/ PF-LYS-QALY
rucaparib versus no maintenance	not cost-effective	with gBRCA mutation non-gBRCA mutation	U.S. payer	$150,000/QALY
olaparib versus niraparib	cost-effective	all patients with gBRCA mutation non-gBRCA mutation	Taiwan (China) single-payer	$93,478/PF-LYS
olaparib versus niraparib versus rucaparib	niraparib is most cost-effective, rucaparib is most non cost-effective	with gBRCA mutation non-gBRCA mutation	U.S. payer	$150,000/QALY
Maintenance therapy after first-line platinum-based chemotherapy for newly diagnosed ovarian cancer				
olaparib versus no maintenance	cost-effective	with gBRCA mutation	Italian NHS	€16,372/QALY
		with gBRCA mutation	U.S. third-party payer	$100,000/QALY
		with gBRCA mutation	Singapore healthcare payer	$43,799/QALY
		with gBRCA mutation	Spanish NHS	€25,000/QALY
	not cost-effective	with gBRCA mutation HRD without BRCA mutation with HRP	U.S. healthcare sector	$100,000/PF-LYS

(continued)

(continued)

niraparib versus no maintenance	cost-effective	all patients HRD group HRD without BRCA mutation	U.S. third-party payer	$100,000/QALY
	not cost-effective	with gBRCA mutation HRD without BRCA mutation with HRP	U.S. healthcare sector	$100,000/PF-LYS
olaparib+bevacizumab versus observation	not cost-effective	with gBRCA mutation HRD without BRCA mutation with HRP	U.S. healthcare sector	$100,000/PF-LYS
olaparib+bevacizumab versus bevacizumab	cost-effective	HRD group	U.S. healthcare system	$100,000/QALY

WTP = willingness to pay

on whether the disease is still platinum responsive. There are good data to say that chemotherapy should be discontinued at disease progression after two consecutive lines of therapy. Only about 3 percent of patients will benefit from a third-line of chemotherapy.[6] For those with BRCA mutation or other homologous repair deficiency (HRD) and a complete or partial response to first-line platinum-based chemotherapy for Stages II to IV, patients will receive maintenance treatment with a PARP inhibitor until disease progression occurs. Survival for those with BRCA mutation is typically longer than for those without because many more lines of therapy are an option.

BRCA 1 and 2 are tumor suppressor genes which encode proteins that are involved in homologous repair (HR) of double-strand breaks in DNA. The HR pathway corrects the double-stranded DNA breaks. Failure of HR in those with germline or somatic BRCA mutations or other forms of HRD leads to the use of alternative nonhomologous end joining (NHEJ) pathways of DNA repair. An error-prone mechanism of repair can lead to genetic instability.[7]Accumulation of such mutagenic events can lead to cancer.

Poly (ADP-ribose) polymerases plays a role in DNA repair through single-strand DNA break repair by NHEJ. Tumors defective in HR mechanisms may rely on PARP-mediated DNA repair for survival and are sensitive to its inhibition.[8] With a PARP inhibitor, the single strand breaks are not repaired and are converted into double-stranded breaks with cell replication with consequent accumulation of fragmented DNA incompatible with cellular viability. PARP inhibitors may also increase tumor sensitivity to DNA-damaging agents such as chemotherapy.

Germline BRCA mutations occur in approximately 25 percent of patients with epithelial ovarian cancers while somatic BRCA mutations are estimated at 5 to 7 percent.[9] BRCA 1 and 2 mutations and other DNA damage response deficiencies which would be susceptible to PARP inhibition are believed to affect up to 50 percent of high grade epithelial ovarian cancer cases.[10] All women diagnosed with ovarian cancer should have germline testing for BRCA1 and 2 plus other ovarian cancer susceptibility genes to steer treatment decisions.[11-13]

Olaparib was first approved for ovarian cancer in 2014 and since then rucaparib and niraparib have been approved. Other PARP inhibitors (talazoparib, veliparib) are FDA approved for other indications. Olaparib maintenance after complete or partial response to first-line chemotherapy in BRCA mutation positive patients led to a 70 percent reduction in risk of progression and the benefits continued even after patients stopped taking two years of maintenance.[14] There are also benefits to PARP inhibitor maintenance even in those who are HR-proficient. In a high risk for recurrence population, niraparib provided a clinically significant benefit in the HR-proficient subgroup with a 32 percent risk reduction in progression or death in addition to significant benefit in HRD subgroups.[15] Maintenance after first-line therapy provides more benefit than waiting to use a PARP inhibitor in later lines of therapy and the most benefit occurs in those with BRCA or HRD mutation. The National Comprehensive Cancer Network (NCCN) Guidelines recommend maintenance after first-line chemotherapy complete or partial response for disease Stages II to IV.[13] The choice of a PARP inhibitor will depend on whether bevacizumab was used during primary therapy and presence or absence of BRCA 1 or 2 mutation and HRD. Exhibit 1 shows the recommendations.[13] The NCCN Guidelines also include the use of PARP inhibitors as an option for maintenance after therapy for recurrence in platinum-sensitive disease (category 1 if not previously used).

Although the PARP inhibitors were previously used as treatment in second-line or later, there

appears to be a survival disadvantage in this setting. All three PARP inhibitors originally had an FDA-approved indication for treatment after two or more prior lines of therapy but these indications were voluntarily withdrawn in 2022 because of an approximately 30 percent increase in risk of death compared to chemotherapy based on the final results of the ARIEL-4 and SOLO-3 trials.[16]

Resistance to platinum-based chemotherapy and PARP inhibitors can occur through BRCA reversion mutations and restoration of homologous recombination.[17,18] One rucaparib trial found a 26 percent rate of reversion mutations.[19] Additionally PARP mutations and increases in drug efflux from cells are other sources of resistance. Overcoming resistance is a major area of ongoing research.

Maximizing tolerability and adherence with PARP inhibitors requires significant clinician effort. Adverse events such as nausea, fatigue, hypertension, and headache can lead many patients to discontinue therapy. Successful maintenance therapy requires allowing the patient to recover from chemotherapy before starting these agents. Monthly visits will also be required for laboratory testing. Patients should be educated on adverse events and ways to manage them. For example, for nausea, small frequent meals, good hydration, and gum or ginger can be helpful. Patients can also be given a prophylactic prescription for olanzapine 2.5mg every day to manage nausea. PARP inhibitors are thought to cause hypertension by altering sympathetic/parasympathetic tone which may require treatment.[20]

Cost management with PARP inhibitors is challenging. The cost of these agents range from $15,000 to $17,000 per month, which is cost prohibitive for a patient unless they have prescription drug coverage. The cost-prohibitive nature of these agents widens disparities among those with limited access to care.[21] The management of these agents is expected to increase in difficulty with many additional PARP inhibitors in clinical trials. Some cost-effectiveness studies have found them to be cost effective for maintenance therapy after response to first- or second-line chemotherapy at $100,000 to $150,000 per quality adjusted life year (QALY) from a U.S. payer perspective (Exhibit 2).[22] Genetic testing can improve cost effectiveness.

Patients will need to make a choice of whether they wish to pursue maintenance and are able to afford it. In a study measuring preferences of women with ovarian cancer regarding risks, side events, costs and benefits afforded by maintenance therapy with a PARP inhibitor, participants valued OS and monthly costs most highly, followed by risk of death from myelodysplastic syndromes and acute myeloid leukemia (MDS/AML, a rare adverse event), nausea, PFS, and fatigue.[23] Participants would accept 5 percent risk of MDS/AML if treatment provided 2.2 months additional OS or 4.8 months PFS. Participants would require gains of 2.6 months of PFS to accept mild treatment-related fatigue and 4.4 months to accept mild nausea. Clinicians need to get the focus on the patient when guiding them in decisions of whether to choose maintenance therapy.

Conclusion

The economic and clinical burdens of ovarian cancer are enormous. PARP inhibitors have significant efficacy in improving PFS in the first-line maintenance setting. Maximizing tolerability and adherence with PARP inhibitors requires significant effort. There is a challenge in optimizing cost management with this class of medication. Patient-centered decisions are where we need to be in choosing maintenance therapy.

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A New Era in the Treatment of Prostate Cancer: Integrating Personalized Therapies to Optimize Outcomes

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Summary

The management of prostate cancer has evolved based on the biology of disease which changes over time in response to therapy. The treatment of metastatic prostate cancer is becoming more personalized with genomics and prostate specific imaging available to select targeted therapies.

Key Points

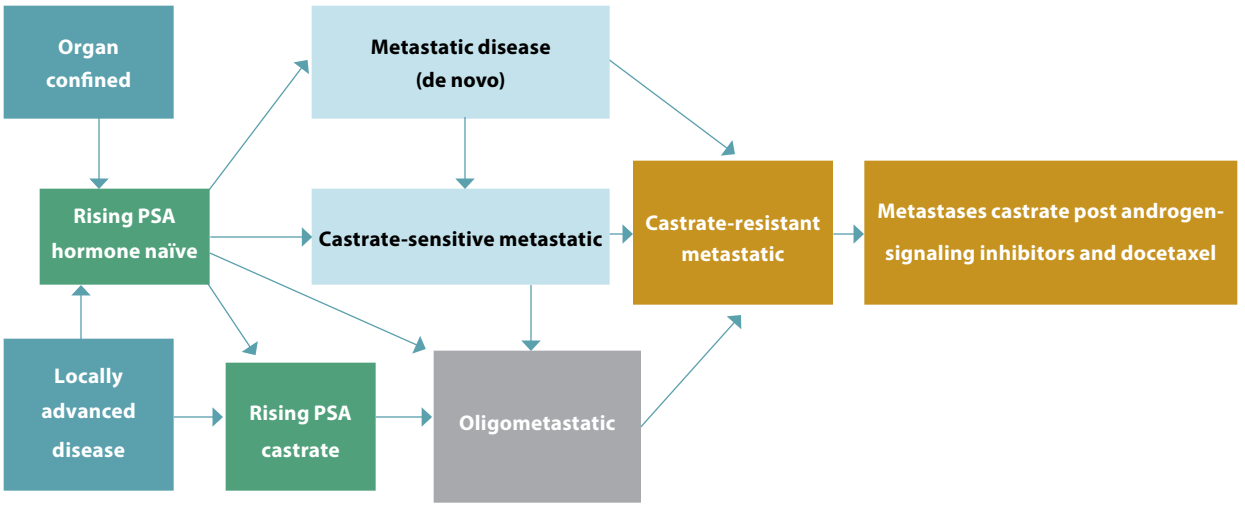
- The movement of therapies into earlier stages of disease complicates metastatic disease management.
- The impact of next generation imaging will be significant and challenging given limited prospective evidence to guide disease management.
- Optimal management of patients is expertise dependent and needs to be multidisciplinary.

THE CLINICAL STATES OF PROSTATE CANCER across the spectrum of disease are shown in Exhibit 1.[1] It is important to understand that each of these states are different and respond to treatment differently; there is also significant heterogeneity within each state. The various disease states and heterogeneity in addition to the impact of various treatments on the biology of the disease make treatment much more complicated than in the past. Some additional definitions are important. Prostate cancer with biochemical failure is a detectable, rising prostate specific antigen (PSA) post definitive local therapy. Non-metastatic castration-resistant prostate cancer (nmCRPC) has no evidence of metastatic disease on imaging, testosterone level of 50 ng/dL or less, and rising PSA. Metastatic castration-sensitive prostate cancer (mCSPC) is metastatic disease on imaging with a non-castrate testosterone level (> 50 ng/dL). Metastatic castration-resistant prostate cancer is metastatic disease on imaging, testosterone 50 ng/dL or less, and rising PSA or new metastases on imaging. Metastatic castration-resistant prostate cancer (mCRPC) is the main focus of this discussion.

Prostate cancer, especially advanced disease, is the only solid tumor managed by a village of clinicians. This includes community urologists, academic urologists, urologists in large urology group practices, medical oncologists, urologic medical oncologists, nuclear medicine specialists, and radiation oncologists. In absence of clear data supporting therapy sequence, which type of clinician a patient sees will impact what treatment they receive.

Innovations in advanced prostate cancer management that are impacting care include androgen deprivation therapy (ADT) intensification in the mCSPC, prostate cancer genomics, next generation imaging, and a new radiopharmaceutical. ADT intensification (i.e., using multiple androgen targeting agents) improves survival by almost two years in de novo high-volume mCSPC. This was paradigm shifting in managing advanced prostate

Exhibit 1: The Clinical States of Prostate Cancer[1]



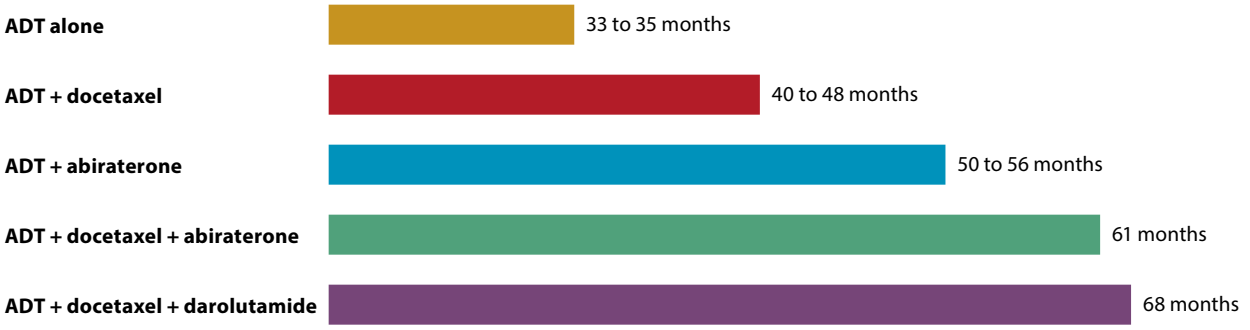
cancer. Triple therapy with ADT, docetaxel, and an androgen signaling inhibitor (ARI) provides the longest overall median survival over ADT alone, ADT plus docetaxel, and ADT plus abiraterone (Exhibit 2).[2-7] The improved survival in the mCSPC setting is significantly better than the survival effect of the many agents FDA approved for the mCRPC setting (2.4 to 4 months). Unfortunately based on retrospective data, triple therapy regimens are not being used in the community oncology setting in the United States (U.S.) for those with mCSPC despite the evidence of improved survival.[8,9] Up to two-thirds of patients are not receiving intensification. These therapies are well tolerated but not all patients will be appropriate candidates. The main reason for low rates of triple therapy use appears to be the clinician the patient sees for care. Overall, the number one thing which could move the needle in improving care and impacting overall survival in advanced prostate cancer is applying data that already exists. Managed care can have a role in identifying clinicians who may not be using the most up to date regimens and educating these individuals.

Treatments for mCRPC include chemotherapy (docetaxel, cabazitaxel), androgen signaling inhibitors (ARI), radium-223 for symptomatic bone metastases, lutetium Lu 177 for prostate-specific membrane antigen (PSMA)-positive metastases, immunotherapy for a small number of patients (sipuleucel-T for selected patients or pembrolizumab for tumors with microsatellite instability high or deficient mismatch repair), poly ADP-ribose polymerase (PARP) inhibitors for tumors with homologous recombination repair (HRR) deficiency, and combination therapy with PARP and ARI.[10] No data exists on the best sequencing of these agents partly because of heterogeneity of the disease and how prostate cancer is treated by so many different specialists. The choice of first-line treatment for mCRPC depends on many factors, including prior systemic treatments, site and extent of disease involvement, comorbidities, presence or absence of symptoms, genomics, and which clinician the patient sees. The earlier use of intensified ADT for mCSPC will have a major impact on therapeutic options in the mCRPC setting.

The new more sensitive imaging technique for prostate cancer is prostate-specific membrane antigen-positron emission tomography (PSMA-PET). PSMA is a well-established, prostate tissue-restricted, cell membrane target.[11] PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in more than 80 percent of men with metastatic disease.[12,13] The approved indications for PSMA-PET are assessment of patients with PSA only failure after definitive therapy, high-risk clinically localized disease, and PSMA expression status for therapy with lutetium Lu 177 vipivotide. Managed care coverage for PSMA-PET varies widely across the U.S.

Because of the increased sensitivity and specificity of PSMA-PET for detecting micro-metastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the National Comprehensive Cancer Network (NCCN) Guidelines state that conventional imaging is not

Exhibit 2: Impact of ADT Intensification[2-7]



a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective, front-line imaging tool for these patients.[10] It is important to note that all of the prostate cancer trials that led to FDA approvals of therapeutics except for the newest radiopharmaceutical utilized conventional CT/bone scans. Most ongoing clinical trials have not yet incorporated the new more sensitive imaging technique. Earlier detection of metastatic disease with this more sensitive imaging may not mean earlier therapeutic intervention is beneficial but may result in earlier intervention in any case. PSMA imaging is going to find many more metastatic cases than conventional imaging. In addition to over-treatment, PSMA imaging may result in under-treatment. Earlier detection may result in aborting planned curative intent therapies without data. Additionally, earlier detection may result in more therapy earlier with the potential for more toxicity without benefit. Adoption of next generation imaging is going to occur over time because these are much better tests which obviate the need for CT and bone scan.

The newest therapy for mCRPC is a radiopharmaceutical, lutetium Lu 177 vipivotide tetraxetan which was FDA approved in February 2022. It is indicated for the treatment of men with PSMA-positive mCRPC who have been treated with ARI and taxane-based chemotherapy. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to the cells, as well as to surrounding cells, and induces DNA damage leading to cell death. The trial that led to FDA approval found that lutetium Lu 177 vipivotide tetraxetan plus standard care compared to standard care significantly prolonged both imaging-based progression-free survival (PFS), (8.7 versus 3.4 months; $p < 0.001$) and overall survival (OS), (15.3 versus 11.3 months; $p < 0.001$).[14]

The NCCN Guidelines list this therapy as Category 1 treatment option for patients with one or more PSMA-positive lesions and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions, in those who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy.[10]

There is an evolving impact of genomics in prostate cancer treatment. Numerous guidelines support standard of care genomic testing for all patients with metastatic prostate cancer but unfortunately genomic testing is not as widely used as it should be. Targetable mutations may be either germline or somatic (tumor) and somatic DNA testing results may change over time due to the genetic instability of tumor DNA and these changes are identified by serial tumor or liquid biopsies.[15] Twenty-three percent of mCRPC cases have somatic DNA repair alterations and 11.8 percent of men have germline DNA repair defects such as BRCA mutations.[16] Those with a HRR gene mutation (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated previously with androgen receptor-directed therapy can receive a PARP inhibitor.[10] Immunotherapy with pembrolizumab is also an option for those who have received prior docetaxel and androgen receptor-directed therapy and who have microsatellite high, deficient mismatch

repair, or high tumor mutational burden.

PARP inhibitors compared to physician choice ARI therapy have been shown to improve OS in mCRPC. In a study of olaparib, the improved OS was in those BRCA1, BRCA2, or ATM mutations (19.1 versus 14.7 months) and in the overall population with and without those mutations (17.3 versus 14.0 months).[17] Rucaparib improved PFS when compared to physician choice of therapy (docetaxel or ARI) in mCRPC patients with BRCA1, BRCA2 or ATM mutations.[18] Olaparib and rucaparib are both FDA approved as monotherapy for mCRPC with these mutations. Most clinicians who manage mCRPC will only use PARP monotherapy in the setting of BRCA mutations since this is where the most benefit is seen. PARP inhibitors can be difficult for patients to tolerate, especially in the late metastatic disease stage, so ideally, they would be used earlier in the metastatic disease course but this requires earlier genomic testing.

There is preclinical data that suggests increased synthetic lethality of tumor cells when PARP inhibition is combined with ARI. Thus, PARP inhibitors have been studied in combination with ARI for mCRPC. The combination of olaparib with abiraterone as first-line therapy in mCRPC regardless of HRR mutation status led to a 34 percent risk reduction of progression or death and 8.2 month improvement in imaging-based PFS.[19] Similar results were seen with the combination of niraparib and abiraterone which reduced risk of progression or death by 47 percent in those with BRCA 1 or 2 mutation.[20] Both trials report significant imaging based PFS benefit, but the OS data did not show a benefit. A randomized, double-blind, Phase III trial of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line therapy in men with asymptomatic or mildly symptomatic mCRPC receiving ongoing ADT also resulted in clinically meaningful and statistically significant improvement in imaging-based PFS versus enzalutamide.[21] Subjects in this trial may have had previous treatment (docetaxel or abiraterone, or both) in the castration-sensitive setting. The OS data from this trial are still immature. The population studied in these trials is not the future state of mCRPC as more and more patients over time will have ADT intensification in the non-metastatic disease and mCSPC setting. Additionally, these studies do not address a key clinical/economic question of upfront combination versus sequenced therapy.

The combination of talazoparib with enzalutamide, olaparib with abiraterone, and niraparib with abiraterone are currently FDA approved. The talazoparib combination is approved for HRR mCRPC whereas olaparib and niraparib combinations are only approved for BRCA mutated mCRPC. The broader FDA approval of talazoparib plus enzalutamide as compared to olaparib/abiraterone or niraparib/abiraterone is a consequence of study design and not better outcomes. There is not going to be a large uptake of these combinations because most clinicians who practice evidence-based medicine and use ADT intensification will have already used ARIs in their patients in earlier stages. A study is ongoing evaluating talazoparib and enzalutamide earlier in mCSPC which may produce practice changing results.

As previously noted, multiple specialties are involved in the care of patients during their disease course. Urology and radiation oncology have a close working relationship in localized/locally advanced disease. Advanced disease is managed by a variety of clinicians with varying levels of experience. Introduction of more complex and potentially toxic regimens such as ADT and PARP combination complicate issues as uptake among different clinical specialties will impact therapeutic decision-making. Uptake of new data, new imaging, genomics, and therapeutics is more optimal with interdisciplinary care which should be encouraged for prostate cancer management.

Conclusion

Management of advanced prostate cancer is increasingly impacted by therapy administered earlier in the disease process and has become complicated because there is no standard sequence of therapeutic agents. The role of PARP inhibitors is evolving. The impact of next generation imaging will be significant and challenging given the limited prospective evidence to guide management. Overall, optimal management of patients is not specialty dependent, it is expertise dependent.

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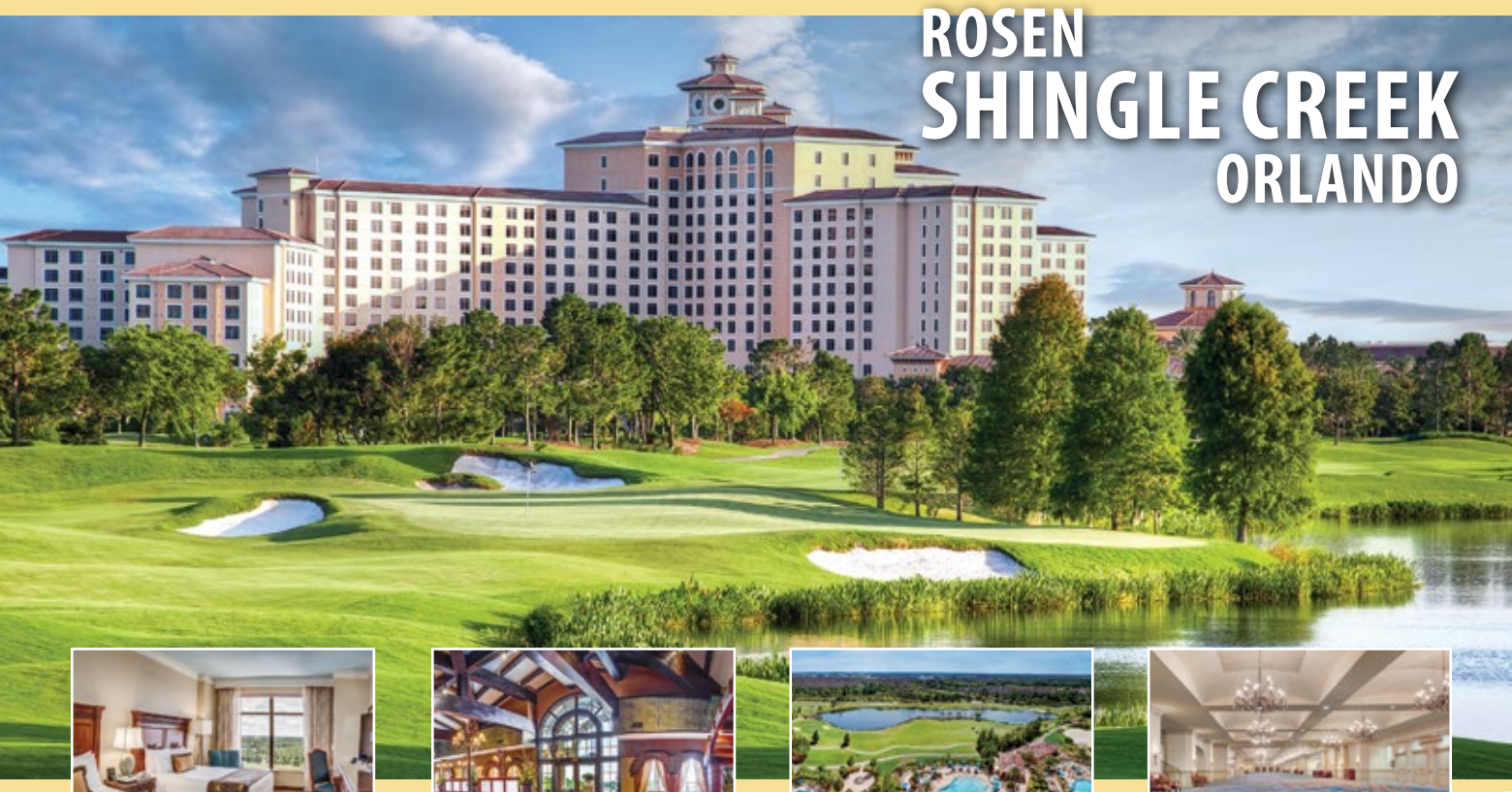

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Best Practices in the Diagnosis, Treatment, and Management of Patients with Epilepsy

Jerzy P. Szaflarski, MD, PhD

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Summary

The majority of those with epilepsy can achieve freedom from seizures with medications and surgery. The most benefit in seizure reductions is achieved with the first agent with lower chances of seizure control with subsequent agents. Selection of treatment depends on many medication and patient factors.

Key Points

- Sixty to 70 percent of patients will be seizure free with medications.
- For those who do not achieve this goal, reasons for continued seizures need to be considered and addressed.
- Neuromodulation devices are adjunctive treatment options.
- Epilepsy surgery is an option for carefully selected candidates.

A SEIZURE IS CAUSED BY A SUDDEN SURGE of abnormal electrical discharges from complex chemical changes in brain cells and can be a manifestation or symptom of many medical problems. There are both provoked seizures and unprovoked seizures. Epilepsy is the tendency to unprovoked recurring seizures not caused by any known medical condition. It is not a single entity or disease but a family of syndromes. Diagnostically, epilepsy is defined as two or more unprovoked seizures greater than 24 hours apart or one unprovoked seizure with risk of recurrent seizures or diagnosis of epilepsy syndrome.[1]

About 10 percent of the world's population will have a seizure in their lifetime thus about 800 million people will have a seizure at some point in their lives. Less than half of these patients will have multiple seizures and 2 to 3 percent will have epilepsy. About three million people in the United States have epilepsy.

After the first seizure, the risk of subsequent seizures is assessed to determine the need for anti-seizure medications (ASMs). The risk assessment includes a clinical history from the patient and others, family history of seizure disorders, electroencephalogram (EEG), CT scan in acute setting to identify potential causes such as a tumor, MRI for long-term prognostication, and laboratory testing for reversible causes.

The decision to start ASMs should be based on the probability of recurrence. The risk of recurrence after a first seizure is 40 to 52 percent and up to 90 percent in the elderly.[2,3] In another study 24 months after an initial seizure, a second seizure occurred twice as often in the control group (51%; no ASMs) than in those receiving therapy (25%).[4] The probability of seizure recurrence in untreated elderly patients was also higher in this study. The overall risk of a second seizure was 24.9 percent in the 16 to 60 age group and 39.1 percent in those over 60 years of age. In addition to older age, the presence of focal seizure, nocturnal seizure, history of prior brain injury, family history of epilepsy, abnormal neurological exam, epileptiform discharges on EEG, and neuroimaging abnormalities predict increased risk of seizure recurrence.[5]

There are numerous ASMs and the available agents can be divided into six categories based

Exhibit 1: Mechanisms of Anti-seizure Medications[6]

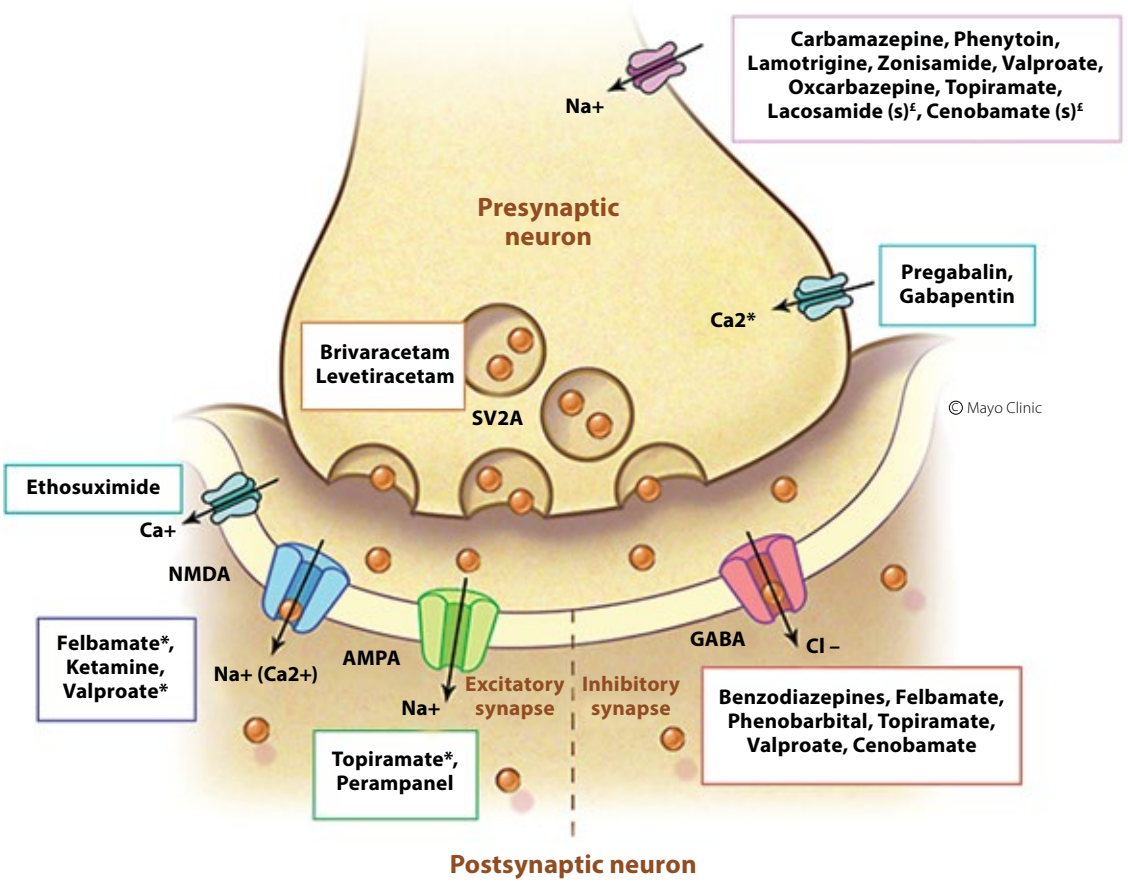


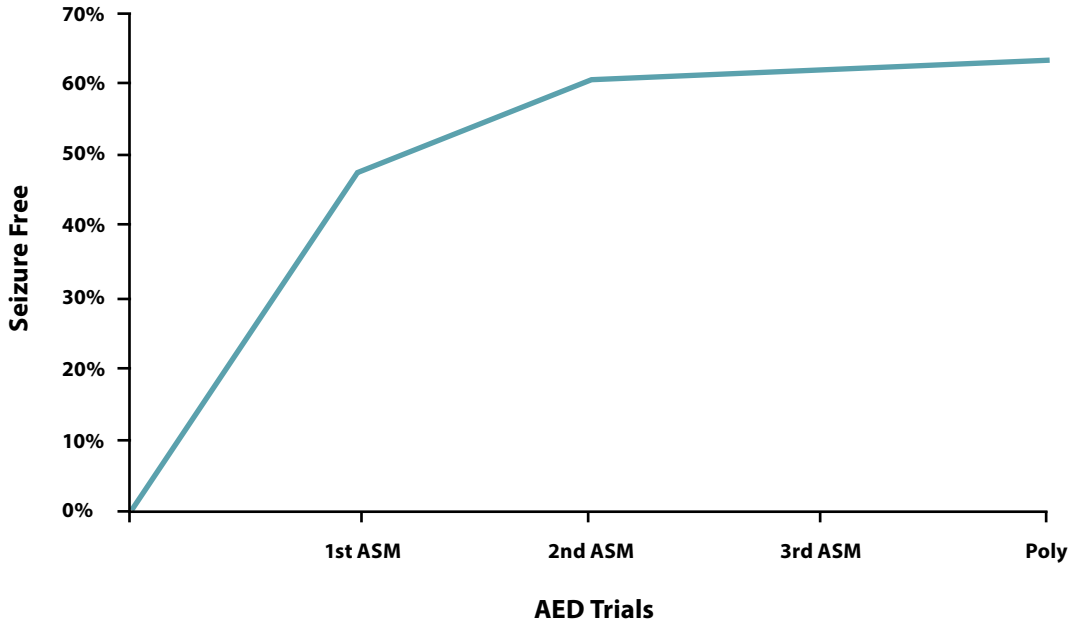
Exhibit 2: Factors to consider when selecting ASM[7]

- Seizure type
- Mechanism of action
- Adverse events
- Patient co-morbidities including mental health disorders
- Drug interactions
- Cost (brand versus generic)
- Formulation
- Dosing schedule
- Required monitoring

on mechanism of action (Exhibit 1).[6] Some ASMs mostly work for specific types of seizures (such as focal, absence, or myoclonic seizures) whereas others have some effectiveness for a wide variety of seizures.[7] In recent years, ASMs such as cannabidiol for less common seizure types, or syndromes such as Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex, and Dravet Syndrome have come to market. In addition to type of seizure and ASM mechanism of action, there are other factors to consider in selecting an initial agent (Exhibit 2).[7] The International League Against Epilepsy (ILAE) publishes a pocket card (ilae.org/files/dmfile/YES_PocketCard_Epi_med-v3.pdf) for helping clinicians select a first agent based on seizure type and modifying factors and there is an online tool (EpiPick.org) which uses the same pragmatic algorithm for medication selections.[8] For example, for generalized tonic clonic seizures, the ILAE recommends starting with valproic acid.

Comorbid mental health conditions are common with epilepsy and must be considered when choosing an ASM. Available data suggest that psychiatric comorbidity occurs in 20 percent to 40 percent of patients with epilepsy, with an even higher incidence in people with drug resistant epilepsy (DRE) and temporal lobe epilepsy.[9] Depression and anxiety are very common.

Exhibit 3: Diminishing Returns of Anti-seizure Medications[11]



Depression is the most common co-morbid psychiatric disorder. It may be more common in those under 30 years of age and is more frequent in those with DRE with up to 50 percent experiencing clinically significant symptoms during their lifetime. Additionally, there are higher rates of suicide among those with co-morbid depression. Depression and epilepsy have been linked to abnormal structure and/or function of the temporal, orbitofrontal, and inferior prefrontal areas of the brain and altered expression and action of certain neurotransmitters. Vocational and driving restrictions, social isolation, ASM adverse events, seizure unpredictability, lack of independence, and socioeconomic stress may significantly contribute to acute and chronic depressed mood.

Estimates of the life-time prevalence of overall anxiety in the epilepsy population may be as high as 22.8 percent compared with 5.6 percent in the general population. People with generalized anxiety disorders have an increased risk of epilepsy. It is difficult to discern between reactionary anxiety to epilepsy diagnosis and comorbid anxiety occurring in the setting of epilepsy. Stigma, concern over the unpredictability of seizures, and a lack of education regarding epilepsy itself have all been associated with a risk of anxiety. GABA may also play a leading role in the interplay between epilepsy and anxiety as GABAergic medications, such as valproic acid, barbiturates, and benzodiazepines, have both anti-convulsant and anxiolytic properties. The presence of anxiety is a predictor of worse quality of life in those with epilepsy.

Suicide attempts and complete suicide occur in 5.0 to 14.3 percent of people with epilepsy compared to 1.0 to 4.6 percent in the general population. The most consistent feature independently associated with suicide is the history of mood disorders. A history of suicide attempts should be elicited in all people with epilepsy since 10 to 20 percent of these individuals will successfully complete suicide within 10 years. The Mini-International Neuropsychiatric Interview (MINI) suicidality module is a solid screening tool for suicide risk. An expert task force of the ILAE notes that although some, but not all, ASMs can be associated with treatment-emergent psychiatric problems that can lead to suicidal ideation and behavior, the actual suicide risk is yet to be established, but it seems to be very low.[10] The risk of stopping ASMs or refusing to start ASMs is significantly worse and can result in serious harm including death of the patient. Overall, the task force noted that suicidality in epilepsy is multifactorial and different variables are operant. It is important for clinicians managing those with epilepsy to monitor mental health issues and suicidal thoughts.

As shown in Exhibit 3, patients have about a 50 percent chance of seizure freedom with the first ASM, regardless of which medication is chosen.[11] A second-line ASM produces about a 10 to 15 percent chance

of seizure freedom (again regardless of which agent is chosen). Moving on beyond second-line, there is only a 3 to 5 percent chance of seizure freedom. DRE may be defined as failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom.[1] Importantly, medication intolerance due to medication adverse events does not equal DRE. Management of DRE is a clinical challenge but for selected seizure types, surgery or neuromodulation may be helpful.

Surgical treatment is an option primarily for focal seizures, particularly those that are drug resistant. Focal seizures begin with an electrical discharge in one or two parts of the brain. While it starts in one area, it can spread to or involve other areas as well (secondary generalized).

Generalized seizures begin with widespread electrical discharge that involves the entire brain at once. Patients for whom surgical treatment is a possibility, an advanced evaluation is required. This may include ambulatory or video EEG monitoring with medication withdrawal, epilepsy protocol MRI to identify possible structural abnormalities (e.g., mesial temporal sclerosis and malformation of cortical development), advanced positive emission tomography (PET), other advance imaging tests, neuropsychological testing, and psychological evaluation. The goal of testing is to determine if the epileptogenic area of the brain can be identified and reached with surgical intervention.

Surgical treatment may include resection of the problematic area, laser interstitial thermal therapy (LITT), radiofrequency ablation (RFA), or neurostimulation device implantation. Surgical resection provides a 50 percent to 80 percent chance of seizure freedom depending on multiple factors.[12] Lesional ablation techniques (RFA, LITT) are minimally invasive with lower risks but lower chances of seizure freedom compared to surgical resection but can be used as staging procedures to establish safety and potential efficacy of larger ablation or resection. The procedures avoid the neurological, neuropsychological, and procedure-related complications of open surgery.

Neuromodulation or neurostimulator devices are other surgical options. Neuromodulation is the disruption and reconditioning of epileptogenic networks in the brain. Similar to a pacemaker that monitors and responds to heart rhythms, these devices can monitor and respond to brain activity. The three FDA-approved neuromodulation devices are relatively safe and well-tolerated. Deep brain stimulation (DBS) and vagal nerve stimulation (VNS) provide open-loop stimulation without recording capabilities. Responsive neurostimulation (RNS) provides closed-loop stimulation and storage of ambulatory electrocorticography (ECoG) data. All three modalities have an implantation (lesional) and long-term (cumulative) effect. Median reduction of seizures is 40 to 70 percent depending on duration of therapy. Responder rates appear higher for DBS and RNS (~ 70%) versus VNS (~ 40%). Overall, neuromodulation is currently used as an adjunct therapy to ASMs for epilepsy and not as a replacement.

Conclusion

For any patient with epilepsy, the approach to treatment needs to be personalized and consider personal, family, and societal factors. Sixty to 70 percent of patients will achieve seizure freedom with medical treatment. For the remaining 30 to 40 percent, reasons for continued seizures need to be considered and addressed. Neuromodulation treatments are mostly adjunct options to improve seizure frequency but epilepsy surgery can lead to seizure freedom in 50 to 75 percent of carefully selected candidates.

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Dexcom G7

better diabetes outcomes start at hospital discharge

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

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

Patients using Dexcom CGM resulted in:

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

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

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

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

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

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

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

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