Vol. 27, No. 2, 2024

JOURNAL of MANAGED CARE MEDICINE

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Implementing New Data and Evolving Standards in HER2-Negative Breast Cancer: Expert Strategies on the Expanding Role of Targeted Therapy

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

Managed Care Considerations in the Management of Amyotrophic Lateral Sclerosis: A Closer Look at the Emerging Role of Oral Therapy Options

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JOURNAL OF MANAGED CARE MEDICINE

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GRAPHIC DESIGN
Douglas Murphy Communications

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

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

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 27, No. 2, 2024

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Implementing New Data and Evolving Standards in HER2-Negative Breast Cancer: Expert Strategies on the Expanding Role of Targeted Therapy

Banu Arun, MD

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

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Summary

Targeting BRCA mutations with PARP inhibitors can increase progression-free survival in women with metastatic breast cancer who have these mutations. Unfortunately, this type of therapy has not yet been shown to improve survival. Using PARP inhibitors earlier in the disease process may significantly delay the time to recurrence.

Key Points

- PARP inhibitors are the first-line standard of care for metastatic BRCA-mutated breast cancer.
- Olaparib is a standard of care as an adjuvant in early breast cancer in certain patients.
- Tackling resistance to these agents is a major area of need and research.

APPROXIMATELY 300,000 CASES OF BREAST cancer are diagnosed annually in the United States.[1] Hormone receptor positive disease is the most common type followed by human epidermal growth factor receptor two (HER2) positive, and then triple-negative breast cancer. Between 5 percent and 10 percent of all cases will be in patients with a breast cancer (BRCA) gene mutation. Germline mutation (gBRCA) is found in up to 23 percent of patients with triple-negative breast cancer (TNBC) and in 5 percent of patients with hormone receptor positive disease. BRCA-related breast cancer is typically a high grade, poorly differentiated cancer.[2]

Overall, TNBC accounts for 12 percent of breast cancer cases. TNBC tends to be diagnosed at a much earlier age, recurrence occurs earlier after surgical removal compared to other subtypes, and survival is lower than with other subtypes.[3] In addition to Black women, TNBC is more likely to be in those with BRCA1 or BRCA2 mutation.

Biomarkers that can now be targeted in metastatic TNBC (mTNBC) include BRCA1/BRCA 2 mutation, programmed death ligand one (PD-L1) expression and other markers of immunotherapy response (MSI-H, TMB-H), HER2-low expression, and various other mutations such as NTRK and RET which have FDA-approved therapies. The focus of this article is BRCA mutation targeting.

BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination.[4] If BRCA1 or BRCA2 are mutated, damaged DNA may not be repaired properly, and damaged cells can multiply out of control leading to various cancers. Poly-ADP ribose polymerase (PARP) is involved in base-excision repair. Cells with BRCA mutations have nonfunctional homologous recombination but can repair DNA through base-excision repair (non-homologous repair). The National Comprehensive Cancer Network (NCCN) recommendations for BRCA testing are shown in Exhibit 1.[5]

Exhibit 1: Testing for BRCA1/2 Mutations[5]

Patients diagnosed at ANY AGE with breast cancer and any of the following:

- To aid adjuvant therapy decision-making using olaparib in high-risk early breast cancer.
- To aid systemic therapy decision-making using PARP inhibitors in the metastatic setting.
- TNBC histology.
- Lobular breast cancer and personal/family history of diffuse gastric cancer.
- Male breast cancer.
- ≥ 1 close male relative with breast cancer.

Patients with personal history of breast cancer and ≥ 1 of the following:

- Aged ≤ 45 years at diagnosis
- Aged 46 to 50 years at diagnosis, plus any:
  - Family history (unknown or limited).
  - Multiple primary breast cancers at any time interval.
  - ≥ 1 close blood relative diagnosed at any age with breast, ovarian, pancreatic, or prostate cancer.
- Aged ≥ 51 years at diagnosis plus any of the following:
  - ≥ 1 close blood relative aged ≤ 50 years with breast cancer.
  - ≥ 1 close blood relative diagnosed at any age with ovarian or pancreatic cancer.
  - Close male relative with breast cancer or high-risk prostate cancer.
  - ≥ 3 total breast cancer diagnoses in patient/close blood relative.
  - ≥ 2 blood relatives with breast cancer or prostate cancer.
- Ashkenazi Jewish ancestry.

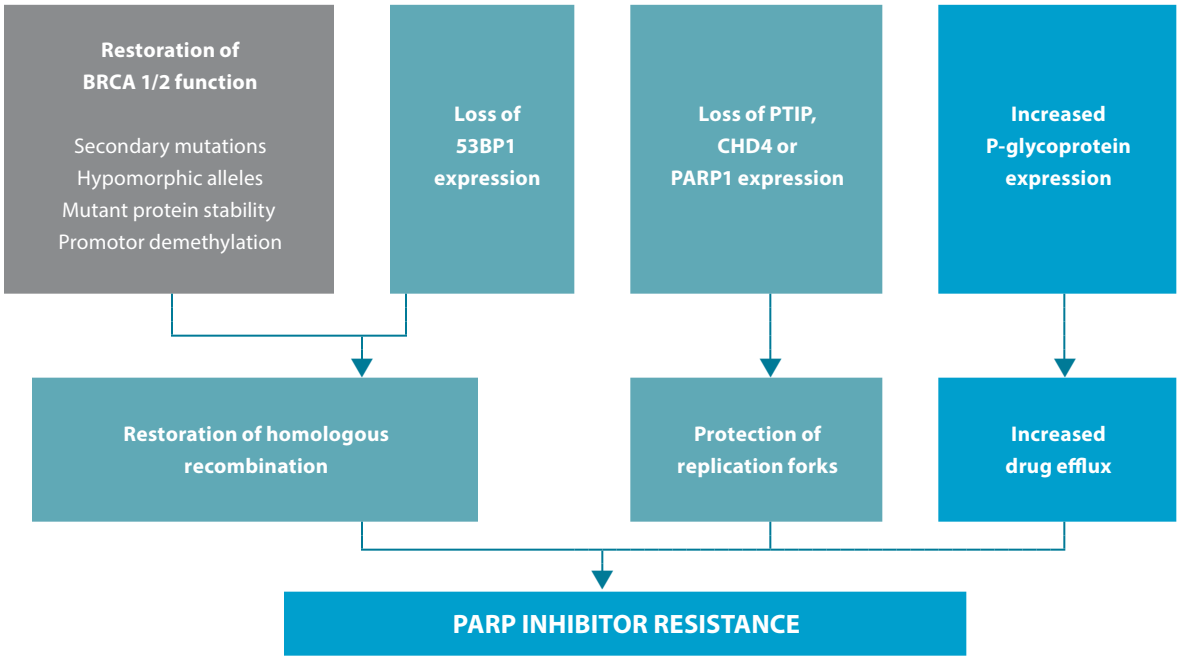
PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in cells deficient in homologous recombination including those with BRCA mutation.[4] Although others are available for other indications, two PARP inhibitors, olaparib and talazoparib, are FDA approved for treating gBRCA-mutated mBC.

Based on results from the OlympiAD trial (HER2 negative, gBRCA-mutated mBC treated with no more than 2 prior lines of chemotherapy), olaparib was FDA approved for treating gBRCA mutated mBC. Olaparib 300mg twice a day was compared to standard of care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the chemotherapy group (7.0 months versus 4.2 months; $p < 0.001$).[6] Final median overall survival (OS) was 19.3 months with olaparib versus 17.1 months with chemotherapy which was not statistically significant.[7] Olaparib was better tolerated than chemotherapy and those who received it had a better quality of life. Patients who had not had prior chemotherapy in the metastatic setting achieved a 7.9 month longer median survival with olaparib than those who received chemotherapy.[6] Overall, olaparib monotherapy provided a significant benefit over standard therapy with a better median PFS but not a better survival benefit.

Talazoparib was evaluated in the Phase III Embraca trial in which subjects had no more than three prior lines of chemotherapy but had to have been treated with a taxane and anthracycline. Talazoparib 1 mg once a day was compared to standard of care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[8] Median OS was 19.3 months with talazoparib versus 19.5 months which, as with olaparib, was not statistically significant.[9] The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). As with olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS and was well tolerated.

Although PARP inhibitors are currently used in the mBC setting as monotherapy, combination with

Exhibit 2: Mechanisms of PARP Inhibitor Resistance in BRCA1/2-Associated Cancers[13]



chemotherapy is being studied. BRCA-mutated breast cancers are sensitive to both PARP inhibitors and platinum agents owing to deficiency in homologous recombination repair of DNA damage. Veliparib, an investigational PARP inhibitor, is being studied in combination with carboplatin/paclitaxel in the metastatic gBRCA-mutated setting. Initial results found that the combination improved PFS (14.5 versus 12.6 months) compared to chemotherapy alone.[10] PARP inhibitors are being studied in combination with chemotherapy, in combination with immunotherapy, and for treatment in those with other homologous recombination pathway gene mutations other than BRCA.

For mTNBC, PARP inhibitors or platinum-based chemotherapy are the first-line preferred options in those with gBRCA mutation who are not candidates for checkpoint immunotherapy based on PD-L1 expression.[5] PARP inhibitors, if not previously used, are the preferred therapy for second-line therapy in those who have gBRCA mutation.

Olaparib is also used in earlier stages as adjuvant therapy in those with gBRCA mutations and high-risk early disease. In the trial leading to FDA approval for this indication, adjuvant olaparib for one year was compared to placebo. The four-year OS was 89.8 percent in the olaparib group and 86.4 percent in the placebo group (Δ 3.4%, 95% CI -0.1% to 6.8%).[11] Four-year invasive disease-free survival was 82.7 percent versus 75.4 percent, respectively, and four-year distant disease-free survival was 86.5 percent versus 79.1 percent, respectively. The NCCN Guidelines recommend clinicians consider addition of adjuvant olaparib for one year for those with gBRCA mutations and TNBC, if any tumors greater than 2 cm or any positive nodes after adjuvant chemotherapy or residual disease after preoperative chemotherapy.[5] It is also recommended for those with gBRCA mutations and HR-positive, HER2-negative tumors if ≥ 4 positive lymph nodes after adjuvant chemotherapy or residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥ 3. There are some issues with selecting adjuvant therapy in gBRCA-mutated early breast cancer.

Pembrolizumab immunotherapy is also an adjuvant option for TNBC and combinations of a PARP inhibitor and pembrolizumab have been studied in other settings but not this particular one.[12] It is not yet known if the combination or sequential use would be better for delaying recurrence. PARP inhibitor resistance does develop and is a clinical challenge. Forty to 50 percent of patients do not respond initially to a PARP inhibitor and those that respond eventually progress and are not cured. Some of the identified mechanisms of resistance

are shown in Exhibit 2.[13] More studies are needed to determine if PARP inhibitor resistance can be prevented or delayed.

Conclusion

PARP inhibitors are the first-line standard of care for metastatic BRCA-mutated breast cancer. They are also standard of care as an adjuvant in early breast cancer in certain patients. Tackling resistance to these agents is a major area of need and research.

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

Akshay S. Desai, MD, MPH

This journal article is supported by an educational grant from Merck Sharp & Dohme LLC

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Summary

The management of heart failure has changed significantly over the past few years. Based on recent trials, a four-medication strategy is recommended for those with reduced ejection fraction and a newer therapy is recommended for those with preserved ejection fraction. The recommended agents have been shown to reduce morbidity, mortality, and especially hospitalizations related to heart failure.

Key Points

- Patients with symptomatic HFrEF and HFmrEF should be rapidly initiated on four medications (ARNI/BB/MRA/SGLT2i) in the absence of contraindications.
- Treatment of HFpEF should begin with an SGLT2i, with consideration of additional agents in selected patients.
- In patients with HFimpEF, continuation of GDMT is appropriate, even if asymptomatic.
- Addition of SGLT2i may be appropriate if ongoing HF symptoms.

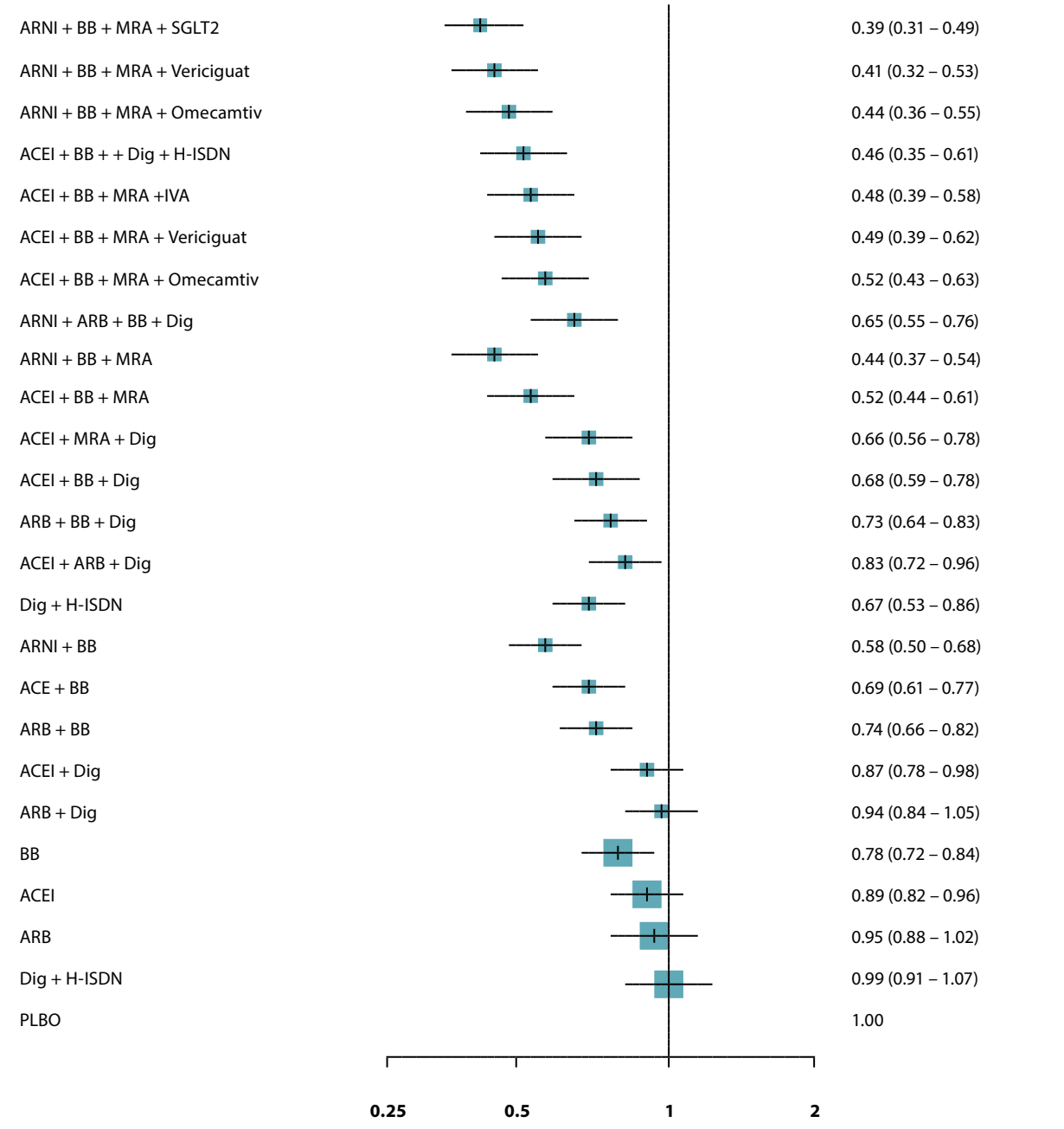
APPROXIMATELY 6.7 MILLION AMERICANS over 20 years of age have heart failure (HF), and the prevalence is expected to rise to 8.5 million by 2030.[1] Approximately 33 percent of the United States adult population is at-risk for HF (Stage A HF) and 24 to 34 percent have pre-HF (Stage B HF).[2] HF mortality rates have been increasing since 2012. Black, American Indian, and Alaska Native individuals have the highest all-cause age-adjusted HF mortality rates compared with other racial and ethnic groups. From 2010 to 2020, HF mortality rates have increased for Black men and women at a rate higher than any other racial or ethnic group, particularly for individuals below the age of 65 years.[2]

In 2010 dollars, the total direct medical costs of HF are projected to increase to $53 billion by 2030 and the total costs, including indirect costs for HF, are estimated to increase to $70 billion.[1] A large proportion of the expense of treating HF comes from hospitalizations. Rates of HF hospitalizations increased from 2014 to 2017.[2] This increase was consistent between age groups and sexes, with the highest rates being among Black patients.

The classification of HF is based on left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HPrEF) is defined as a LVEF of less than 40 percent and HF with preserved ejection fraction (HFpEF) has an EF of 50 percent or greater and both lead to hospitalizations.[3,4] HF with midrange EF (HFmrEF) is when the EF is between 41 and 49 percent and is treated the same as HFrEF.

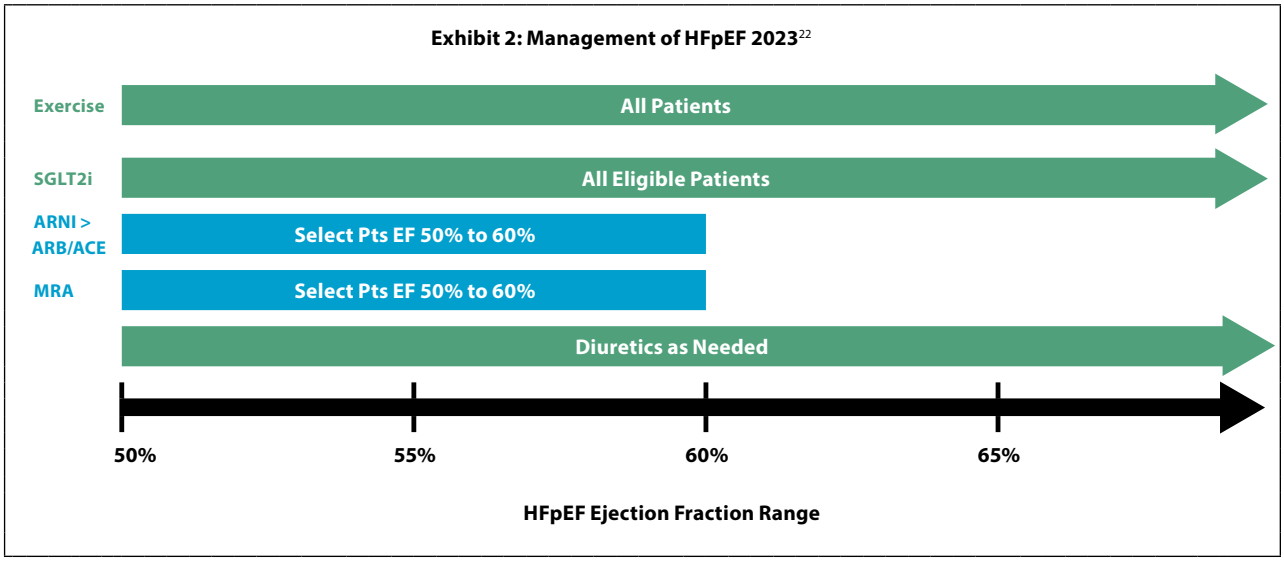
Treatment of HF has significantly evolved over the past 25 years. No matter the type of HF, patients should receive guideline-directed medical therapy (GDMT). The main classes of therapy are angiotensin

Exhibit 1: Comprehensive Medical Therapy for HFrEF Improves Survival[15]



receptor blocker/neprilysin inhibitor combination (ARNI), beta blockers (BB), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 inhibitor (SGLT2i). Each of these agents play a role in modifying the pathophysiology of HF and have been shown to reduce morbidity and mortality.

Patients with symptomatic HFrEF (including HFmrEF) should be rapidly initiated on the four-medication (ARNI/BB/MRA/SGLT2i) standard of care in the absence of contraindications.[5,6] In patients hospitalized for HF, predischarge initiation of ARNI is recommended as de novo therapy or for patients already on and tolerating angiotensin converting



enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB). This recommendation is based on results of the PIONEER-HF trial showing improved outcomes.[7,8]

ARNI has replaced ACE-I and ARB in the first-line management of HF because of the benefits in reducing cardiovascular death, HF hospitalization, and overall mortality.[9] Another benefit of ARNI is reverse remodeling which has been shown in two trials.[10,11] In the Prove-HF trial, continued reverse modeling, and EF improvement was shown at 12 months.[11]

The SGLT2i medication class was originally developed to treat type 2 diabetes but due to FDA-required studies related to cardiovascular disease (CVD) risk and diabetes medications, these agents now have FDA-approved labeling to reduce the risk of CVD death and hospitalization for HF in adults with HF in addition to an indication for reducing risk of CVD death in those with type 2 diabetes. In the DAPA-HF and EMPEROR-Reduced trials where the subjects had HFrEF, SGLT2i compared with placebo reduced the composite of CVD death or HF hospitalization by approximately 25 percent.[12,13] The benefit in reduction of HF hospitalization was significant (30%) in these trials. Sotagliflozin is the newest agent in the SGLT2i class and is also FDA approved for type 2 diabetes and HF. In patients with diabetes and recent worsening HF, sotagliflozin therapy, initiated before or shortly after hospital discharge, resulted in a significantly lower total number of deaths from cardiovascular causes, hospitalizations, and urgent visits for HF than placebo.[14]

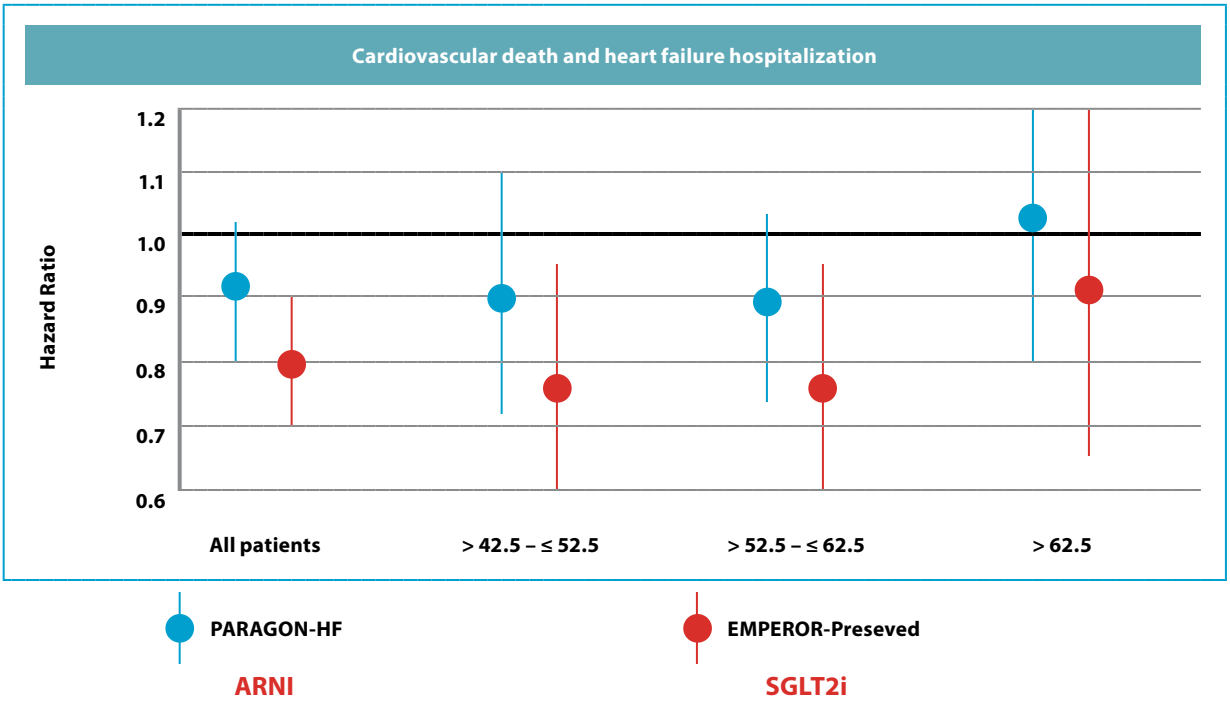
GDMT has been shown to improve longevity in HFrEF (Exhibit 1).[15] For a 55 year old, GDMT with ARNI/BB/MRA/SGLT2i compared to ACE-I or ARB with BB provides an 8.3 year benefit.[16] GDMT also reduces risk of sudden cardiac death.[17,18] Beyond the standard four-medication regimen, additional therapies may benefit some patients; these include ivabradine, vericiguat, omega-3 poly unsaturated fatty acid supplementation, digoxin, and potassium binders. These are typically added after optimization of the four-medication regimen.

Unfortunately, GDMT is underutilized in the general population for HFrEF.[19,20] Many varied reasons for this underutilization have been postulated.[21] Managed care can have a significant impact on this treatment gap by identifying patients with HFrEF who are not receiving GDMT, especially those with a recent HF hospitalization and targeting these patients for therapy improvements.

Although patients with HFpEF (LVEF ≥ 50) comprise half of those with chronic HF, there has been significant unmet clinical needs. Unlike HFrEF, there are limited evidence-based therapies to reduce morbidity and mortality. Treatment has been focused on management of congestion and comorbidities.

In recent years, large trials have been done in the HFpEF population with ARNI, SGLT2i and MRA. Treatment of HFpEF should begin with an SGLT2i, with additional consideration of ARNI and MRA in selected patients (e.g., recently hospitalized patients, those with elevated natriuretic peptides). Exhibit 2 shows recommendations based on current data.[22] The recommendation for SGLT2i therapy for all patients comes from comparing data from the separate trials with ARNI (Paragon-HF) and empagliflozin (Emperor-Preserved) in HFpEF which seem to indicate improved outcomes with SGLT2i (Exhibit 3).[23,24] Additional support comes

Exhibit 3: Comparing ARNI and SGLT2i in HFpEF[23,24]



from the Deliver trial.[25] A meta-analysis of these trials found a 20 percent relative risk reduction of cardiovascular death or first hospitalization for HF with the SGLT2i.[26] There were consistent reductions in these endpoints across LVEF range, including among LVEF ≥ 60 percent.

In patients who have HF with improved EF (HFimpEF, previous EF≤ 40 percent but improved to > 40% with treatment), the American Heart Association guidelines recommend GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic.[5] In a prespecified analysis of the Deliver trial, of a total of 6,263 participants with symptomatic heart failure and a EF > 40 percent, 1,151 (18%) had HFimpEF.[27] In participants with HFimpEF, dapagliflozin reduced the primary composite outcome (hazard ratio [HR] = 0.74), first worsening HF events (HR = 0.84), CVD death (HR = 0.62) and total worsening HF events (rate ratio = 0.68). These data suggest that patients with HFimpEF who are symptomatic and who are not already on an SGLT2i may benefit from the addition of one to previously instituted therapies to further reduce morbidity and mortality.

Additional therapies for HF are on the horizon. One example is finerenone, a nonsteroidal MRA which is already FDA approved to reduce the risk of sustained kidney function decline, end stage kidney disease, CVD death, non-fatal myocardial infarction, and hospitalization for HF in adult patients with chronic kidney disease associated with type 2 diabetes. It is being evaluated for HF treatment in those without diabetes.

Conclusion

Patients with symptomatic HFrEF and HFmrEF should be rapidly initiated on four medications (ARNI/BB/MRA/SGLT2i) in the absence of contraindications. Treatment of HFpEF should begin with an SGLT2i, with additional consideration of ARNI and MRA in selected patients. In patients with HFimpEF, continuation of GDMT is appropriate, even if asymptomatic. Addition of SGLT2i may be appropriate if these patients have ongoing HF symptoms.

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Managed Care Considerations in the Management of Amyotrophic Lateral Sclerosis: A Closer Look at the Emerging Role of Oral Therapy Options

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This journal article is supported by an educational grant from Mitsubishi Tanabe Pharma America

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Summary

Amyotrophic lateral sclerosis remains an incurable and devastating disease, however disease-modifying agents are now available to improve quality of life, slow disease progression, and improve survival. The disease needs to be diagnosed as soon as possible and therapy initiated promptly to save neurons.

Key Points

- Early diagnosis is essential.
- Early initiation of disease-modifying therapies, typically used in combination, is the key to slowing disease progression and prolonging survival.
- Multi-disciplinary care which provides effective nutritional interventions, respiratory care interventions, and aggressive symptomatic management is also vitally important.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a rare incurable progressive neurodegenerative disorder affecting upper and lower motor neurons and bulbar neurons. ALS and other neurodegenerative disorders are similar because they affect similar patient populations, have an unknown cause and no cure. ALS leads to the inability to move, speak, eat, and eventually breathe. Cognition, extraocular movements, bowel and bladder function, and sensation are typically not affected in ALS patients.

Risk factors for ALS are shown in Exhibit 1.[1,2] Approximately 10 percent of cases are genetically based (familial ALS, [fALS]) and the rest are considered sporadic (sALS). With ALS there is a highly predictable prognosis in about half of the patients but it is inevitably fatal in all patients. Life expectancy is typically two to five years after diagnosis.[3,4] Approximately 10 percent of those with the condition will live 10 years, and 5 percent will live for 20 or more years.[4] The incidence of ALS is between one and three per 100,000 and prevalence is 4.8 per 100,000.[5] Approximately 31,000 Americans have ALS with males slightly predominate (1.5:1).[5]

In the United States (U.S.), non-Hispanic Caucasians are the most frequently affected group (75% to 77% of cases).[6,7] Compared with non-Hispanic Caucasians, Black patients have been shown to have a 64 percent increase in diagnostic delay, worse disease and poorer ventilatory condition at the time of diagnosis.[8]

Economic, racial, cultural, and religious factors are critical elements which determine access and availability of ALS care and research. The high percentage of individuals living more than 50 miles from the nearest specialized clinic underscores one of the many challenges of ALS.[7] Having better access to care, whether at an ALS clinic or through other

Exhibit 1: Risk Factors for ALS[1,2]

- Genetics
- Heavy metals
- Agricultural chemicals (pesticides, herbicide, etc.)
- Excessive physical activity
- Military service
- Professional sports
- Chronic head trauma
- Smoking

Exhibit 2: Early Signs and Symptoms to Suspect ALS

- Rapid, unintentional weight loss of undetermined cause
- Unexplained fatigue
- Unexplained shortness of breath
- Undetermined speech problems or swallowing problems
- Focal (arm, hand, leg) weakness **without pain**
- Fasciculations or muscle cramps with weakness

modalities, is the key to increasing survivability and obtaining appropriate end-of-life treatment and support for people with ALS.

In terms of disease burden, ALS has a major impact on patients and caregivers. Due to the widespread effects of the disease, ALS causes major disability as it progresses. The receipt of a fatal diagnosis is devastating and leads to tremendous emotional distress and anxiety. Patients have difficulty transitioning from a financial supporter of the family to a dependent family member. The pace of disease progression can outpace learning and coping. Families and caregivers have high physical and psychological burdens, anxiety, depression, distress, and low quality of life (QOL).

In addition to the QOL impact, ALS causes significant financial burden. Medical costs are substantial and increase rapidly as disability worsens.[9] The annual total cost per patient has been estimated to be $69,475 and the total disease-duration costs have been estimated at $1,433,992 with 85 percent paid by insurance, 9 percent paid by families, and 6 percent paid by charities. The highest healthcare costs are for in-home caregivers ($669,150), ventilation ($212,430), and hospital care ($114,558). The national economic burden of ALS in the U.S. is estimated at $279 million to $472 million annually.[10]

At the beginning, ALS may involve degeneration and death of only upper motor neurons (UMN) or lower motor neurons (LMN), but it eventually progresses to involve both. As with many other degenerative diseases, ALS has a very long preclinical process.[11] Motor neurons are already markedly depleted when weakness is detected, even when muscle strength is normal. Someone can have normal muscle strength and a 30 percent to 50 percent neuronal loss. When weakness is detected, 80 percent of neurons can be depleted. Thus, early diagnosis is important if there is any hope of slowing the disease progression.

Early in the disease motor neurons are still alive and functioning and therapies are still effective but it can be difficult to make an early diagnosis. It takes approximately 12 months from onset of new progressive weakness to receive a definitive diagnosis of ALS.[12] During this diagnostic delay, patients see many different providers, receive several different diagnoses, and may undergo unnecessary surgical procedures. Fasciculations and muscle cramps often precede motor function symptoms so updates to ALS diagnostic criteria by the International Federation of Clinical Neurophysiology, the World Federation of Neurology, the ALS Association, and the Motor Neuron Disease Association include the use of electromyography (EMG) to identify fasciculation which can be an early marker of ALS.[13] Exhibit 2 lists some early signs and symptoms which should lead primary care providers and non-ALS specialists to consider ALS.

In addition to various medications for managing symptoms like sialorrhea, spasticity, and muscle cramps there are three FDA-approved orals, one injectable, and one intrathecal disease-modifying treatment. Riluzole (oral) and edaravone (oral and injectable) have been around for several years. For both medications, the mechanism of action in relation to ALS remains unknown. It appears to be a neuroprotective effect via inhibition of glutamatergic neurotransmission and anti-excitotoxic effect for riluzole and reduced oxidative stress through scavenging of free radicals for edaravone.

Riluzole prolongs median tracheostomy-free survival by about three months compared to placebo in patients younger than 75 years of age with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[14,15] FVC is the most used measure of respiratory muscle function for prediction of ALS survival and disease progression. Real-world data has shown improvements in median survival times of more than 19 months.[16] The American Academy of Neurology (AAN) ALS practice parameter states that riluzole should be

offered to slow disease progression in patients with ALS (Level A evidence).[17] It is probably more effective in the early stages of the disease which is another reason that early diagnosis is important.[18] The majority of patients with ALS are currently taking this medication which costs about $1,000 per year.

Edaravone was approved by the FDA in 2017 to slow the functional decline in patients with ALS. The first trial in patients within three years of symptom onset showed no benefit over placebo but a post-hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.[19] A second trial included 137 people who showed some degree of impairment in each of the ALS Functional Rating Scale-revised (ALSFRS-R) domains, had an FVC at 80 percent or more of expected value, were within two years of symptom onset, and had a further decline of –1 to –4 ALSFRS-R points during a 12-week observation period. For this subset of patients, edaravone slowed the rate of disease progression, as measured by a decrease in ALSFRS-R score, by 33 percent at six months compared to the rate of disease progression for patients in the placebo group.[20] In a real-world analysis, edaravone treatment in a large predominantly riluzole-treated U.S. cohort was associated with prolonged overall survival (~ 6 months) compared with not using edaravone.[21] Data from adequately powered randomized controlled trials are needed to support this finding. The disadvantage of edaravone is the annual cost (~$170,000 per year). Edaravone has not yet been included in the AAN practice guidelines.

The newest FDA-approved (September 2022) oral therapy for ALS is a combination of sodium phenylbutyrate and taurursodiol which is thought to mitigate endoplasmic reticulum stress and mitochondrial dysfunction. It is given as 3g of sodium phenylbutyrate and 1g of taurursodiol once a day for three weeks and then twice a day. A multicenter, randomized, double-blind trial in 137 subjects with definite ALS and onset of symptoms within the previous 18 months compared sodium phenylbutyrate-taurursodiol to placebo. The combination resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks (0.42 points per month difference; $p = 0.03$).[22] Most participants (77%) were receiving riluzole or edaravone at or before trial entry, with 22 percent of sodium phenylbutyrate-taurursodiol group and 40 percent of placebo group receiving both. In an open label extension trial of the randomized trial, median overall survival was 25.0 months among participants originally randomized to the combination and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; 95% confidence interval [CI], 0.34 to 0.92; $p = .023$).[23] Gastrointestinal issues were the primary adverse events. The clinical practice guidelines do not yet include this agent and the cost is about $158,000 per year.

It will take several years to evaluate whether the edaravone and sodium phenylbutyrate-taurursodiol can reduce overall medical expenditures in addition to improving survival. Being able to delay the use of feeding tubes and non-invasive and invasive ventilation may produce cost savings but this needs to be examined. The impact on overall QOL also needs to be studied.

In an analogy from the cancer field—one would need more approved medications, each of which may have only small benefit, but an additive benefit can be obtained by combining approved medications, provided combined side events are not significant issues.

Ultra-high doses of intramuscular methyl-cobalamin are also being evaluated as an ALS treatment. In a trial in 373 patients with ALS (duration ≤ 36 months) which compared placebo, 25mg and 50mg of methylcobalamin daily, the primary endpoints of the time interval to primary events (death or full ventilation support) and changes in the ALSFRS-R score from baseline to week 182 showed no significant differences with either of the three interventions.[24] However, post-hoc analyses of methylcobalamin-treated patients diagnosed and entered early (≤ 12 months' duration) showed longer time intervals to the primary event ($p < 0.025$) and less decreases in the ALSFRS-R score ($p < 0.025$) than the placebo group. In this trial, 89 percent of the subjects were also receiving riluzole. A trial in 130 patients within one year of symptom onset compared intramuscular injection of methylcobalamin (50mg) or placebo twice weekly for 16 weeks.[25] The least square means difference in ALSFRS-R total score at week 16 of the randomized treatment period was 1.97 points greater with methylcobalamin than placebo (-2.66 versus -4.63; 95% CI, 0.44 to 3.50; $p = .01$) supporting the findings of the prior trial. Eighty-nine percent of the methylcobalamin group and 91 percent of placebo group were also taking riluzole. Compared to the FDA-approved therapies, intramuscular methylcobalamin is very inexpensive.

The FDA approved the first antisense oligonucleotide (ASO) for treating a rare form of ALS – superoxide dismutase 1 (SOD1) mutated ALS in April 2023. Approximately 2 percent of ALS cases are associated with mutations in the SOD1 gene (it is estimated there are fewer than 500 patients with SOD1-ALS in the U.S.).[26] Tofersen is an ASO given

by intrathecal administration that mediates the degradation of messenger RNA to reduce SOD1 protein synthesis. Per the FDA, the approval was based on a reduction in plasma neurofilament light (NfL), a blood-based biomarker of axonal injury and neurodegeneration.[26] In the trial used for approval, adults with SOD1 ALS were assigned in a two to one ratio to receive eight doses of tofersen (100 mg) or placebo over a period of 24 weeks. A total of 72 participants received tofersen (39 predicted to have faster progression), and 36 received placebo (21 predicted to have faster progression). Tofersen led to greater reductions in concentrations of SOD1 in cerebrospinal fluid and of neurofilament light chains in plasma than placebo. In the faster-progression subgroup (primary analysis), the change to week 28 in the ALSFRS-R score was -6.98 with tofersen and -8.14 with placebo (difference, 1.2 points; 95% CI, -3.2 to 5.5; $p = 0.97$).[27] A total of 95 participants (88%) entered the open-label extension. At 52 weeks, the change in the ALSFRS-R score was -6.0 in the early-start cohort and -9.5 in the delayed-start cohort (difference, 3.5 points; 95% CI, 0.4 to 6.7); non-multiplicity-adjusted differences favoring early-start tofersen were seen for other end points.[27] Lumbar puncture-related adverse events were common and serious neurologic adverse events occurred in 7 percent of tofersen recipients. This agent is given as three initial 100 mg intrathecal doses administered at 14-day intervals, followed by a maintenance dose of 100 mg every 28 days.

Because the care of patients with ALS is complex, it is best accomplished in a multidisciplinary clinic which has been shown to prolong survival by eight to 10 months and improve QOL.[28-30] Major advantages of multidisciplinary care is effective and aggressive symptomatic treatment, nutritional management, and respiratory care. Other advantages include management sensitive discussions regarding diagnosis with patients, problem solving by multiple experts, minimized patient travel time visiting different professionals or therapists, highly specialized healthcare professionals, and clinical research and trials which can be effectively performed. There are more than 100 ALS Centers in the U.S., but some areas of the country lack these clinics. The major disadvantages of multidisciplinary care are the high cost and the tiring of both patients and providers. The AAN practice parameters recommend patients with ALS should be considered for referral to a specialized multidisciplinary ALS clinic to optimize healthcare delivery (Level B), prolong survival (Level B), and enhance quality of life (Level C).[31]

Conclusion

Early diagnosis and initiation of disease-modifying treatment is especially important in having the most impact on the disease. Currently approved medications for ALS (riluzole, edaravone, and sodium phenylbutyrate-taurursodiol) all delay functional progression and/or prolong survival, when initiated early. Once diagnosed, a combination of disease-modifying therapies, aggressive symptomatic treatment, and nutritional and respiratory care in a multidisciplinary clinic improve overall QOL and prolong survival in patients with ALS.

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

David Alain Wohl, MD

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

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Summary

Prevention and treatment of HIV infection continues to evolve. Adherence to both preventives and antiretroviral therapy is important to efficacy in preventing infection and producing viral suppression. Long-acting options are now available which may help optimize outcomes.

Key Points

- There are barriers in getting the appropriate people on HIV preventives and keeping those who start prevention adherent.
- Improvements have been made in diagnosis, care engagement, treatment, and viral suppression rates but there is a need for additional improvement to reach goal rates of 95 percent.
- Long-acting injectables are an option for prevention and treatment in those who have adherence issues or wish to avoid daily medication.

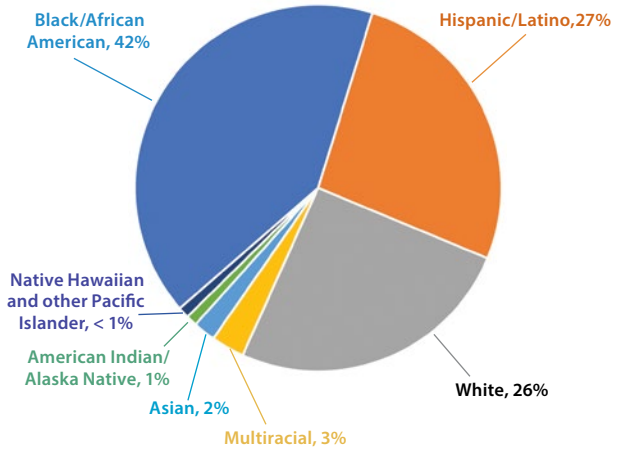
HIV INFECTIONS CONTINUE TO BE AN ISSUE in the United States (U.S.). In 2020, there were 30,635 new cases diagnosed.[1] This was a 17 percent decrease in new diagnoses compared with 2019. This is possibly due to disruptions in clinical care services, hesitancy in accessing healthcare services, and shortages in material for early HIV testing during the COVID-19 pandemic. Between 2016 and 2019, new diagnoses decreased by an average of 2.6 percent per year.

HIV disproportionately impacts certain groups and areas of the country. People of color and men who have sex with other men account for most new cases (Exhibit 1).[1] Almost 60 percent of new HIV diagnoses are in people younger than 35 years of age, however, over half of people living with HIV are 50 years of age or older.[1] The majority of those infected with HIV reside in the southern states.

Every single new case of HIV represents a failed opportunity to prevent the disease. There are great tools to prevent infection but they are not being used as widely as they should be. Pre-exposure prophylaxis (PrEP) is very effective in preventing HIV infection but is underutilized with only about 25 percent of those who have an indication (risk behaviors) currently receiving.[2] In the South, only 5 percent are receiving. Populations of color across the U.S., and women are less likely to receive PrEP. Also, the younger age group currently contracting HIV is less likely to receive PrEP.

The CDC and International Antiviral Society-USA Panel recommend that PrEP be discussed with all sexually active adults and adolescents.[3,4] PrEP should be offered to individuals who are at substantial risk of HIV acquisition. Oral emtricitabine and tenofovir disoproxil fumarate (FTC/TDF), emtricitabine and tenofovir alafenamide (FTC/TAF) and injectable cabotegravir are the FDA-approved options. The oral

Exhibit 1: 2020 New HIV Diagnoses by Demographics and Transmission Category[1]

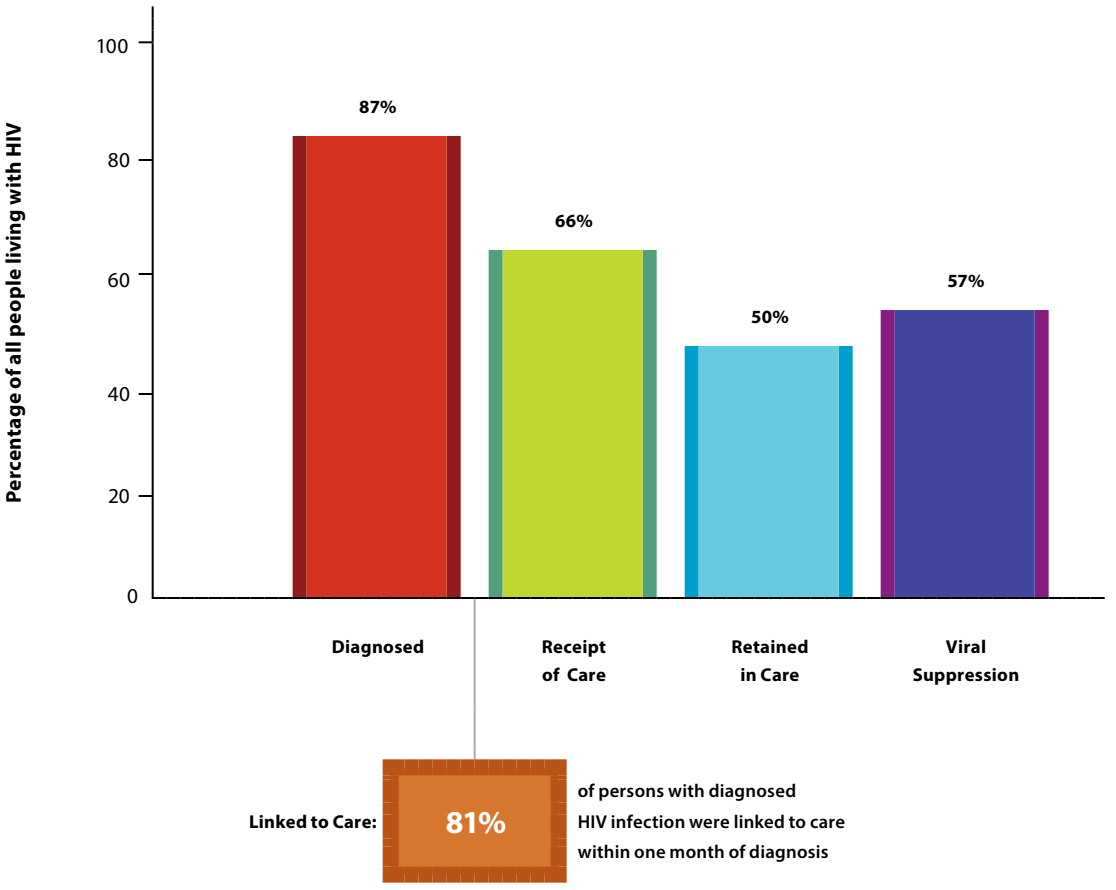


Transmission Category, n (%)	Males	Females	Total
Male-to-male sexual contact	20,758 (68)	NA	20,758 (68)
Injection drug use	1,198 (4)	857 (3)	2,055 (7)
Male-to-male sexual contact and injection drug	1,109 (4)	NA	1,109 (4)
Heterosexual contact	2,051 (7)	4,575 (15)	6,626 (22)
Perinatal	9 (< 1)	51 (< 1)	60 (< 1)
Other	20 (< 1)	7 (< 1)	27 (< 1)

agents are taken daily and on demand use of FTC/TDF is also an option. TAF has some advantages over TDF with fewer bone and kidney-related adverse events, however, the FTC/TDF generic is the most used in the U.S.[5]

Importantly, oral PrEP only works if taken. Adherence can be an issue which impacts efficacy. There are few people who can faithfully take a tablet every day. In one trial, over half of the participants did not use FTC/TDF consistently and had much

Exhibit 2: Prevalence-based HIV Care Continuum, U.S., and Six Dependent Areas, 2019[9]



higher rates of HIV compared to adherent patients.[6] Long-acting injectable cabotegravir given every two weeks is an alternative for those who have daily dosing adherence difficulty. Two trials have shown lower HIV infection rates with the injection compared to daily FTC/TDF due to differences in adherence.[7,8] For cabotegravir to be effective, the patient must be adherent to the every two-week injection regimen. In one of the comparison trials, Black people had lower efficacy than Whites with both cabotegravir and FTC/TDF because of lower oral adherence and lower rates of on-time injections.

In terms of those already infected, there are about 1.2 million people living with HIV in the U.S. Exhibit 2 shows that for some points on the continuum of care the U.S. is doing reasonably well and not so well on others.[9] The UNAIDS 2025 goals are 95 percent diagnosed, 95 percent on treatment, and 95 percent virally suppressed.[10] A fourth proposed goal is 90 percent with good health-related quality of life and well-being.

Viral suppression, which is required to prevent spread, is the rule where antiretroviral therapy (ART) is accessible and people in care are receiving it. There are differences across states in the availability of resources to get people tested, into care, and virally suppressed.[9] One group which stands out for having lower rates of viral suppression are those who use injectable drugs.[9]

Because HIV therapy continues to evolve, the guidelines for managing HIV are living documents which should be consulted frequently for changes.[11] The guidelines cover diagnosis, initiating therapy, disease and medication monitoring including recommended frequency, adjusting therapy if undetectable levels are not achieved, and managing multidrug resistance, among other topics. There are now 25 different antiretroviral agents available for treating HIV.

A few to spotlight are some of the newer agents. Long-acting injectable cabotegravir and rilpivirine is a two-medication regimen indicated as a complete regimen for the treatment of HIV infection in adults to replace the current ART 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 is equivalent to once daily oral regimens.[12,13] Injectable therapy is given as every one- or two-month intramuscular injections (each medication requires a separate injection) after an initial oral lead-in regimen. A small percentage of people (~1%) treated with this combination will develop resistance and have virologic failure even with on-time injection.

Several therapies have been approved for use with other ART for highly treated experienced (HTE) patients with multidrug resistance (MDR). Luckily, the rate of HTE patients with MDR running out of therapeutic options is declining because of improved therapies used early in therapy. Fostemsavir is a first-in-class attachment inhibitor given orally twice daily. After enzymatic activation to the active molecule temsavir, it binds to gp120 which prevents viral entry into CD4 cells, effectively stopping viral replication of the HIV virus. This agent has been shown to have long-term efficacy and safety in this difficult to treat population.[14]

Lenacapavir is a first-in-class HIV capsid inhibitor approved in late 2022 for HTE patients with MDR. Interestingly, this agent is started with both oral and subcutaneous loading doses and then subcutaneous doses are given every six months. It has to be taken with additional ART. Future treatment options are long-acting lenacapavir with other injectable long-acting agents to form a complete regimen as a long-acting option for those who are not HTE or with MDR.

Because HIV is no longer a death sentence when treated appropriately, those living with HIV have almost normal life spans. As people with HIV age, they develop comorbidities more than those without HIV. In one study, the risk for onset of diabetes, lung disease, cardiovascular disease, cancer, neurocognitive disorders, and hypertension was 10 percent to 80 percent higher among those living with HIV compared to people who are HIV-negative, even after controlling for pre-existing conditions, demographics and behavioral difference.[15] This may be due to the infection itself, past or present HIV treatments, and/or belonging to a marginalized population lacking healthcare access. Although the life expectancy of adults with HIV infection may be near that of individuals without HIV infection, the comorbidity-free years are significantly less.[16]

Conclusion

There are challenges in preventing and treating HIV to achieve 95 percent goals. Making sure that disproportionately affected populations achieve these goals is especially important. Adherence with prevention can be an issue but a long-acting injectable is an option for those who have issues or wish to avoid daily medication. Likewise, long-acting injectables are options for treatment in those with the same issues.

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Overcoming Barriers to Adolescent and Adult Immunizations: Practical Strategies for Improved Outcomes in Suboptimal Vaccination Practice

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This journal article is supported by an educational grant from Merck Sharp & Dohme LLC

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Summary

Despite safe and effective vaccines for numerous diseases and nationally accepted guidelines, the rates of vaccination for many vaccines have significant room for improvement. There are some vaccines for which recommendations have changed and the first vaccines against respiratory syncytial virus (RSV) have been approved.

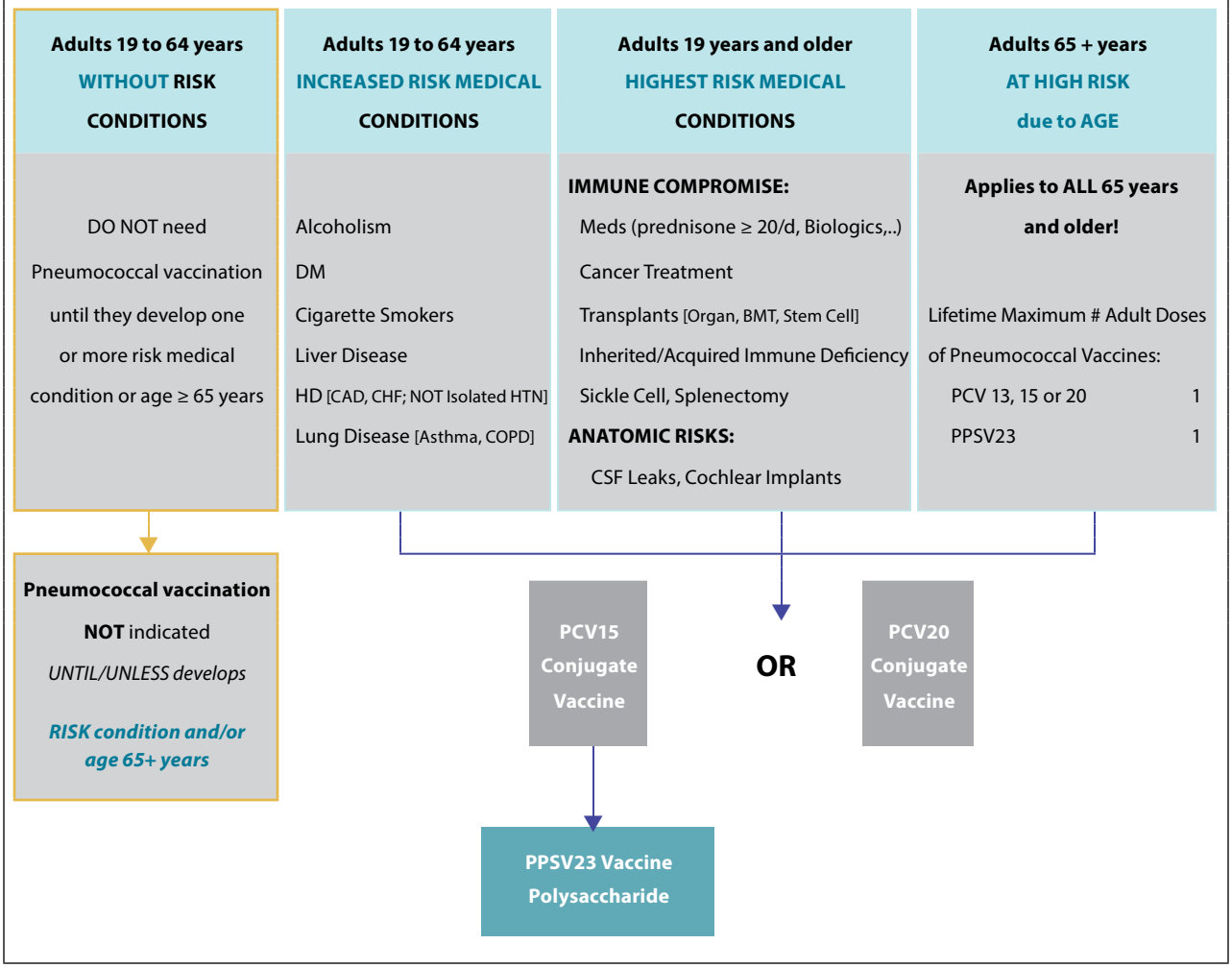
Key Points

- Vaccination rates need to be improved.
- Clinicians and payers need to work to overcome barriers to vaccination.
- Pneumococcal vaccine recommendations have been simplified.
- Two new RSV vaccines are now available.

THE RECOMMENDATIONS FOR PNEUMOcoccal vaccination have been simplified and new pneumococcal vaccines have been developed because of the change of prevalent infecting serotypes. Pneumococcus species cause approximately 400,000 cases of pneumonia, meningitis, otitis media, and sinusitis annually. Invasive infections (bacteremia, meningitis, and sepsis) are those which concern us most and which lead to major morbidity and mortality. Pneumococcal infection leads to 445,000 hospital admissions and 22,000 deaths annually in the United States (U.S.). There is a bimodal distribution of invasive pneumococcal infections with peaks in babies and older adults.[1] The incidence of pneumococcal infections also increases with the presence of chronic conditions such as diabetes, heart disease, lung disease, and immunocompromisation.[2,3]

The recommendations for who should receive pneumococcal vaccination have been simplified.[4,5] There are currently three pneumococcal conjugate vaccines (PCV-13, PCV-15, PCV-20) and 23-valent pneumococcal polysaccharide vaccine (PPSV-23). PCV-13 is no longer recommended for use in adults. All adults aged 65 years or older or those aged 19 to 64 years with risk factors, who have never received a prior pneumococcal vaccine, should receive one dose of PCV15 or PCV20. If PCV15 is used, one dose of PPSV23 is given at least one year later (clinicians may use a minimum interval of eight weeks for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak). Exhibit 1 outlines the recommendations by risk group.[5] For patients who had a prior pneumococcal vaccine at some point, clinicians should consult the guidelines to determine if a patient needs additional vaccination. A mobile app from the CDC, PneumoRecs VaxAdvisor, helps vaccination providers quickly and easily determine which pneumococcal vaccines a patient needs and when. The app incorporates recommendations for all ages so internists, family physicians, pediatricians, and pharmacists alike will

Exhibit 1: Adult Pneumococcal Vaccine: Risk Groups and Recommendations 2023[5]



CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; BMT = bone marrow transplant; CSF = cerebral spinal fluid

find the tool beneficial. There is significant room for improvement in pneumococcal vaccine rates. Only about 20 percent of the 19 to 64 age group with indications for the vaccine and 60 percent of the aged over 65 group are vaccinated.[6] These rates have not changed significantly since 2010.

Of the universally recommended vaccines for adolescents, the HPV vaccine is the first and only cancer preventing vaccine but is underutilized. HPV infection with oncogenic subtypes is responsible for a tremendous number of cancers, including over 99 percent of cervical cancer cases, but to be most effective vaccination needs to occur before any exposure to HPV occurs.[7] Although typically thought of as sexually transmitted, genital HPV can spread through the anogenital region via skin-to-skin contact and condoms are only partially effective in preventing transmission. Some adolescents have tested positive for vaginal HPV prior to first vaginal sexual intercourse.[8]

HPV induces persistent infection without early complications to the host (i.e., asymptomatic). It evades an acute immune system response and there is minimal inflammation, no cell death, no blood viremic phase, and the infection is only epithelial. Approximately 90 percent of those infected mount an innate and humoral immune-mediated viral clearance.[9] Some neutralizing antibodies are produced but are inefficient and will not reliably prevent future infection. Those who do not clear the infection are those at risk for cancer.

Adolescents and young adult males should be major targets for HPV vaccination campaigns. Genital HPV prevalence is higher in males than in females and does not decrease with age as it does in females.[10,11] Additionally, the incidence of HPV-

related oral pharyngeal carcinomas is increasing and these are three times more common in men.[12]

HPV vaccination, along with cervical cancer screening programs, are reducing the incidence of cervical cancer in the U.S. In a 12-year follow-up on the long-term efficacy of the earlier 4 valent HPV vaccine in females aged 16 to 23 years, the vaccine was 100 percent effective in preventing cervical, vulvar, and vaginal cancer.[13] With increasing vaccination rates, data are also showing reduced rates of HPV even in those who have not received the vaccine, thus demonstrating herd effect. HPV vaccination is recommended for both males and females from age nine or 11 through age 26 years.[14] The target age is 11 to 12 years. Those 27 to 45 years who were not vaccinated in the past can decide to be vaccinated based on shared decision-making. In 2022, only 62.9 percent of 13- to 17-year-olds were up-to-date on HPV vaccination.[15]

In addition to parents being reluctant to vaccinate their children against a sexually transmitted disease, clinicians can be a barrier to HPV vaccination. In a survey of physicians, only 73 percent reported recommending HPV vaccine as highly important and only 13 percent of physicians perceived HPV vaccine as being highly important to parents compared with 74 percent for Tdap and 62 percent for meningococcal vaccine.[16] Among physicians with a preferred order for discussing adolescent vaccines, 70 percent discussed HPV vaccine last.

Respiratory syncytial virus (RSV) vaccines have recently been approved. RSV infects nearly everyone by age three and reinfects everyone throughout their lives. Though most infections are mild, 2 to 3 percent of infants are hospitalized. RSV bronchiolitis is a leading cause of hospitalization for those under five years of age. RSV is also a cause of death for older adults.

RSV vaccine development began decades ago without success. New vaccine technology combined with greater understanding of RSV infectious molecular clones has led to a new era of RSV vaccines. A recombinant RSV glycoprotein F stabilized in pre-fusion conformation (RSVPreF3) as the antigen component vaccine was FDA approved in June 2023. This vaccine is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older. A bivalent recombinant RSV vaccine (PreF A and PreF B) was FDA approved in August 2023 for individuals 60 and older to prevent LRTD and for pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through six months of age.

The CDC recommends that adults 60 years of age and older have the option to receive a single dose of RSV vaccine, based on discussions between the patient and their healthcare provider.[17] There are two options for protection of infants against RSV—maternal vaccine and preventive antibodies given to the infant. Only one of these options is needed for most babies to be protected. The CDC recommends a single dose of RSV vaccine for pregnant individuals from week 32 through week 36 of pregnancy.[17] RSV vaccination is recommended to be given from September through January for most of the U.S. In some locations (the territories, Hawaii, Alaska, and parts of Florida), the timing of vaccination may vary as RSV circulating in these locations differs from the timing of the RSV season in the rest of the U.S.

In addition to being effective, vaccines are safe. No vaccine is 100 percent safe but nothing is. Nearly all vaccine-adverse events are very mild and include pain at the injection site, sore arm, redness, and fever. The risk of a serious adverse event from disease is far greater than the risk from vaccination. People are at far greater risk of an adverse outcome from riding in a car, crossing the street, or choking on food than from a vaccine. Vaccine safety is monitored carefully in the U.S. with a combination of post-licensure manufacturer monitoring, Vaccine Safety Datalink, and the Vaccine Adverse Event Reporting System (VAERS). Overall, vaccines have been found to be extremely safe and most safety issues are of limited clinical significance.[18]

Because of many factors, rates for most vaccinations for adults and adolescents have significant room for improvement. One of the biggest contributors to lack of vaccination is that clinicians do not strongly and clearly recommend vaccination. A strong, consistent presumptive recommendation rather than a participatory approach should be used. Clinicians should state "Today, you are due for two vaccines, HPV and pneumococcal, someone will be right in to administer those vaccines." rather than ask "Do you want to get the pneumococcal vaccines today?" In addition to a lack of a strong, clear recommendation, other things clinicians or practices do can provoke doubt in patients. These include following invalid contraindications to immunization (low-grade fevers, mild illness), providing reading material rather than directly discussing individual vaccines, equivocating on recommendations or answers, and inconsistent recommendations from the clinical team.[19]

Conclusion

Providers, health systems, and payers can work together to improve recommended vaccination rates

and identify those patients who need to catch-up on missed vaccines. Every time a patient encounters the healthcare system represents an opportunity to discuss, encourage, and offer vaccinations.

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Moving Beyond the Challenges of Insomnia: New Opportunities in an Expanding Therapeutic Landscape

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This journal article is supported by an educational grant from Idorsia Pharmaceuticals US

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Summary

Insomnia is a frequent problem in adults and can become chronic. The burden of insomnia is significant so it should be identified and treated.

Key Points

- Healthy sleep habits and cognitive behavioral approaches are the preferred first-line therapy.
- Medications that have sleepiness as an adverse event are frequently used off-label for insomnia.
- Orexin antagonists are newer pharmacotherapy options which have been shown to be safe and effective and are FDA approved for insomnia.

MANY ADULTS HAVE INSOMNIA WHICH may be acute or chronic. Prevalence is approximately 30 percent in the general population with 6 percent to 10 percent of the population having associated symptoms of daytime functional impairment.[1] Insomnia prevalence in clinical practices is up to 50 percent. The diagnostic criteria for insomnia disorder includes sleep difficulties three or more nights per week lasting for three or more months (Exhibit 1).[2,3] Components of insomnia disorder are dissatisfaction with sleep quantity or quality, daytime consequences of poor sleep, and sleep difficulty despite adequate opportunity for sleep.

Not everyone who has a sleepless night develops insomnia disorder. One natural history study showed that good sleepers can develop chronic insomnia (~1.8%) and 6.8 percent of those with acute insomnia develop chronic insomnia over one year.[4] Another study found that insomnia predicts more insomnia. Of those people with insomnia at the beginning of the study, 72 percent still had insomnia after three years.[5]

The clinical and economic burden of insomnia are substantial. There is increased risk of psychiatric disorders (depression, anxiety), cognitive decline including dementia, accidents (including motor vehicle, on the job, at home), and medical comorbidities including cardiovascular disease, diabetes, and obesity.[6-10] Insomnia in the context of mental health disorders can be successfully treated, and when sleep problems are treated, other mental health problems tend to lessen.[8] There are also higher rates of healthcare utilization, absenteeism and presenteeism, and poor occupational performance in those with insomnia compared to those without. Overall incremental healthcare costs of sleep disorders in the United States (U.S.) have been estimated at $94.9 billion.[11] Because of both financial and work performance costs, employers have an economic stake in their employee's sleep.[12]

There are no standard insomnia screening tools in primary care. Clinicians have the option to use other tools which ask questions about sleep such as the Patient Health Questionnaire (PHQ-9). The most practical approach and best practice is to add sleep questions to the routine review of systems.[13]

Insomnia treatment consists of a personalized treatment plan which includes healthy sleep habits, cognitive behavioral therapy specific for insomnia (CBT-I) and may include medications at the same

Exhibit 1: Key Insomnia Disorder Diagnostic Criteria[2,3]

Insomnia Complaint
Difficulty initiating sleep
Difficulty maintaining sleep
Early-morning awakening
Daytime Consequences or Impairment
Fatigue or malaise
Attention, concentration or memory
Performance (social, family, occupational, academic)
Mood disturbance/irritability
Daytime sleepiness
Behavioral disturbances (hyperactivity, impulsivity, aggression)
Motivation, energy or initiative
Concerns or dissatisfaction with sleep

Adequate
Opportunity
Circumstances
Frequency
At least three nights per week
Duration
At least three months
Not better explained by
Another sleep-wake disorder
Effects of a substance or medication
Coexisting mental disorders or medical conditions

Exhibit 2: Current Regulatory-Approved Insomnia Treatment Medications

- **Benzodiazepine receptor agonists B**
  - Benzodiazepine hypnotics (triazolam, flurazepam, etc.)
  - Nonbenzodiazepine hypnotics (eszopiclone, zaleplon, zolpidem)
- **Melatonin receptor agonist**
  - Ramelteon
- **Selective histamine receptor antagonist**
  - Low dose doxepin
- **Dual orexin/hypocretin receptor antagonist (DORA)**
  - Suvorexant
  - Lemborexant
  - Daridorexant

time or after CBT-I is not effective. Although CBT-I and healthy sleep habits are the first-line treatments for insomnia, the availability of CBT-I across the U.S. has been an issue. Companies are now offering CBT-I services delivered via smartphone applications under the supervision of a healthcare professional to employers to help reduce sleep disorder-related costs. Digital CBT-I has shown moderate or better benefits in trials in different populations.[14,15]

In terms of pharmacotherapy, one study found that the use of prescription medications for sleep disturbance declined nationally from 2013 to 2018.[16] The authors suggested the results were a possible effect of efforts to curb over-prescription and encourage judicious use of these agents.[16] However, the primary decline was in prescription medications specifically approved by the FDA for sleep. This study did not distinguish use among the many different FDA-approved agents. Use of medications with sedation as an adverse event used off-label continued steadily during the study time period.

The most used prescription medications for sleep are trazodone and zolpidem. Only zolpidem is approved by the FDA for sleep. Other sedating medications are also commonly prescribed but there is limited data on efficacy, dosing, and risk with the use of sedating medications off-label for insomnia. Diphenhydramine and melatonin are the commonly used non-prescription medications. The anticholinergic effects of diphenhydramine and other sedating antihistamines cause significant issues for many people, especially the elderly.

Exhibit 2 shows the available classes of FDA-approved medications for insomnia. Dual orexin receptor antagonists (DORAs) are the newest class of sleep medication. Orexins are neuropeptides which regulate arousal, wakefulness, and appetite. Elevated orexin levels have been shown in insomnia disorder and low orexin levels are found in narcolepsy.[17] Blocking the binding of wake-promoting orexin to its receptors is thought to suppress the wake drive.

Suvorexant was the first DORA to be approved by the FDA for insomnia in 2014. Lemborexant was approved in 2019 and daridorexant in 2020. These agents have been shown to decrease sleep latency and time awake during the night and increase total sleep time.[18-21] In older adults, lemborexant does not seem to impair cognition nor postural stability and

Exhibit 3: Available DORA Key Characteristics

	SUVOREXANT	LEMBOREXANT	DARIDOREXANT
Approval	2014	2019	2022
Indication	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance
Available doses	5, 10, 15, 20	5, 10	25, 50
Contraindications	Narcolepsy	Narcolepsy	Narcolepsy
Most common adverse reaction	Somnolence	Somnolence	Headache, fatigue, somnolence
Pharmacokinetics – Half-life (hours)	12	17, 19	8
DEA Schedule	IV	IV	IV

Exhibit 4: FDA-approved Indications for each Medication

Medication	Unspecified Insomnia	Sleep Onset	Sleep Maintenance	Early Awakening
Estazolam		✓	✓	✓
Flurazepam		✓	✓	✓
Quazepam		✓	✓	✓
Temazepam	✓			
Triazolam	✓			
Eszopiclone		✓	✓	
Zaleplon		✓		
Zolpidem		✓		
Zolpidem ER		✓	✓	
Zolpidem spray		✓		
Zolpidem sublingual		✓		
Zolpidem sublingual-MONT			✓	
Ramelteon		✓		
Low-dose doxepin			✓	
Suvorexant		✓	✓	
Lemborexant		✓	✓	
Daridorexant		✓	✓	

MONT = Middle of the night

Exhibit 5: DEA Class and Most Common Side Events for each Medication

Medication	DEA Class	Most Common Side Events
Estazolam	IV	Somnolence, hypokinesia, dizziness, abnormal coordination
Flurazepam	IV	Dizziness, drowsiness, lightheadedness, loss of coordination, staggering, falling
Quazepam	IV	Drowsiness, headache
Temazepam	IV	Drowsiness, dizziness, lightheadedness, difficulty with coordination
Triazolam	IV	Drowsiness, headache, dizziness, "pins & needles," coordination difficulty, lightheadedness
Eszopiclone	IV	Unpleasant taste, headache, somnolence, rash, respiratory and viral infections, dizziness, dry mouth, anxiety, hallucinations
Zaleplon	IV	Drowsiness, lightheadedness, dizziness, "pins & needles," difficulty with coordination
Zolpidem	IV	Drowsiness, dizziness, diarrhea, drugged feeling
Zolpidem ER	IV	Headache, next-day somnolence, dizziness
Zolpidem spray	IV	Drowsiness, dizziness, diarrhea, drugged feeling
Zolpidem sublingual	IV	Drowsiness, dizziness, diarrhea, drugged feeling
Zolpidem sublingual-MONT	IV	Headache, nausea, fatigue
Ramelteon	—	Somnolence, dizziness, fatigue, nausea, exacerbated insomnia
Low-dose doxepin	—	Somnolence/sedation, nausea, upper respiratory tract infection
Suvorexant	IV	Somnolence
Lemborexant	IV	Somnolence
Daridorexant	IV	Headache, fatigue, somnolence

MONT = Middle of the night

in addition, patients taking lemborexant are easy to awaken.[22,23] Daridorexant at the highest dose of 50 mg at bedtime has been shown to improve daytime functioning in those with insomnia disorder.[21] All three are FDA approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. All three have the same warnings in the package labeling: central nervous system depressant effects and daytime impairment; worsening of depression and/or suicidal ideation; complex sleep behaviors – sleep paralysis, hypnagogic hallucinations, and cataplexy-like symptoms; compromised respiratory function; and a need to evaluate for comorbid diagnoses.

Exhibit 3 compares the key characteristics of DORAs. The main difference is in the pharmacokinetic half-lives but all three have the potential for dose dependent daytime sedation. Long-term use (out to 12 months) has been shown to be safe and effective.[24] The FDA-approved DORAs are Schedule IV controlled substances. Abuse liability is determined by "drug liking" studies with daytime doses given to recreational sedative drug users. No physical dependence or withdrawal effects were found with these agents or misuse in the community since they became available. It is now

known that orexins have a significant role in neural reward circuitry and research supports potential therapeutic benefits of DORA in the treatment of substance use disorders (cocaine, opioids, alcohol, nicotine, and cannabinoids).[25] Hopefully, the DEA and FDA will eventually change these agents to no longer be controlled substances.

Seltorexant is an investigational single orexin receptor antagonist (2-SORA). It is a selective antagonist of the orexin OX receptor and is currently in Phase III trials.[26] The differences in sleep architecture and insomnia benefit between DORA and 2-SORA compounds is under investigation.

Selecting an agent for an individual patient will depend on concomitant diseases, the specific insomnia issue (difficulty falling asleep, sleep maintenance issue, or early awakening), patient age, potential adverse events, and abuse potential of the selected agent. Avoidance of benzodiazepines in those with substance abuse issues and in the elderly who are at risk of adverse events (falls, excessive sedation, cognitive impact) is recommended. Ramelteon and low-dose doxepin are the only agents which are not Schedule IV controlled substances. Exhibit 4 shows the FDA-approved indications for each medication.

Conclusion

Insomnia is a frequent problem in adults and can become chronic. The burden of insomnia is significant so clinicians should screen for sleep issues. Numerous treatment options are available and effective but cognitive behavioral approaches are the preferred first-line therapy. Orexin antagonists are newer pharmacotherapy options.

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The Impact of PCSK9 Modulation on Cardiovascular Outcomes in Lipid Management: Recent Advances and Managed Care Considerations

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This journal article is supported by an educational grant from Novartis Pharmaceuticals Corporation

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Summary

There is significant room to improve lipid management and cardiovascular outcomes. Non-statin agents like those targeting PCSK9 have a role in reducing gaps in lipid control.

Key Points

- Despite progress, there are still some significant gaps in care.
- Systems approaches to improving secondary prevention can make a significant impact on cardiovascular outcomes.
- Non-statin agents provide options for LDL-C lowering in the not at goal/residual-risk and intolerant population.
- Accurately identifying statin intolerance is an important healthcare challenge.

DESPITE CONSIDERABLE PROGRESS OVER the years, significant gaps in care with lipid lowering therapies remain. There are issues with statin titration and although patients may get started on therapy, many times their dose is never titrated to an appropriate dose to achieve guideline-directed low-density lipoprotein cholesterol (LDL-C) targets. Another issue is the failure to monitor LDL-C values adequately. There has also been resistance to the use of non-statin therapies in combination with statins.

One major gap is the appropriate treatment of patients with a recent myocardial infarction (MI). Hospital discharge prescription rates of recommended high-intensity statin dosing have been improving in the Medicare population since 2011 (30% to 79%).[1] Despite improvements in appropriate prescribing, patients are not persisting with, or being adherent to, their statin therapy.[2,3] Only 40 percent of patients remain on a statin within two years after having an MI.[2] Among all people taking statins in the United States (U.S.), about 80 percent remain on the medication and about 60 percent are taking the medication correctly.[3] Another gap is the use of statins in those with peripheral artery disease (PAD). PAD is associated with increased risk for atherosclerotic cardiovascular disease (ASCVD) events. Despite proven safety and effectiveness, the use is very low (34%).[4]

The LDL-C goal for those with ASCVD is < 70 mg/dL and some experts consider even lower goals. Almost a million recurrent ASCVD events could be averted over 10 years if all U.S. adults with ASCVD achieved and maintained an LDL-C < 70 mg/dL.[5] This is a 22.5 percent reduction in events. Another trial found if all patients hospitalized for an MI were to receive guideline-recommended therapy, a 21.6 percent (95% confidence interval [CI], 20.5% to 23.6%) relative risk reduction would occur over three years.[6] Unfortunately, this study found that among 279,395 patients with an MI hospitalization in the U.S. during 2018 and 2019 (mean age 75 years, mean LDL-C 92 mg/dL), only 27.3 percent were receiving guideline-recommended cholesterol-lowering therapy. The potential impact of all the lipid treatment gaps on health outcomes cannot be ignored. This is an area for managed care to assist

Exhibit 1: Types of Cardiovascular Outcomes[8]

Endpoint	Evolocumab (N = 13,784)	Placebo (N = 13,780)	HR (95% CI)
	Three year Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc.	**12.6**	**14.6**	**0.85 (0.79 – 0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73 – 0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88 – 1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65 – 0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66 – 0.95)**
Hosp. for unstable angina	**2.2**	**2.3**	**0.99 (0.82 – 1.18)**
Coronary revasc.	**7.0**	**9.2**	**0.78 (0.71 – 0.86)**
Urgent	3.7	5.4	0.73 (0.64 – 0.83)
Elective	3.9	4.6	0.83 (0.73 – 0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91 – 1.19)**

CVD = cardiovascular disease; MI = myocardial infarction; UA = unstable angina; revasc = revascularization

in improving care and reducing events. Systems approaches to improving secondary prevention afford the opportunity to make the largest impact on cardiovascular outcomes.

Early and adequate intensification of LDL-C lowering therapy beyond statins is important to address ASCVD event risk.[7] The addition of a proprotein convertase subtilisin kexin type 9 (PCSK9) targeting agent is one way to address residual ASCVD event risk after maximizing statin therapy. Alirocumab and evolocumab are two PCSK9 inhibitor monoclonal antibodies approved for use in the U.S.—they were both approved in 2015. PCSK9 inhibitors interfere with the binding of PCSK9 to the LDL receptor (LDL-R) on the surface of hepatocytes, leading to higher hepatic LDL-R expression and lower plasma LDL-C levels

In a large trial in high-risk stable patients with established ASCVD (prior MI, prior stroke, or PAD) who had LDL-C ≥ 70 mg/dL on a background of high- or moderate-intensity statin, evolocumab lowered LDL-C levels to a median of 30 mg/dL and significantly reduced the risk of the primary endpoint (9.8% versus 11.3%; hazard ratio, 0.85; 95% CI, 0.79 to 0.92; $p < 0.001$) and the key secondary endpoint (5.9% versus 7.4%; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $p < 0.001$) compared to placebo.[8] The primary efficacy endpoint was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy endpoint was the composite of cardiovascular death, MI, or stroke. Exhibit 1 compares the event rates in the evolocumab and placebo groups.[8] Overall, there was a 25 percent reduction in CVD death, MI, or stroke after one year of therapy. This trial confirmed what is known from many other trials—the lower the LDL-C, the lower the CVD event rate.

The open label extension of this evolocumab trial found that LDL-C reduction was maintained with continued therapy. Long-term LDL-C lowering with evolocumab was associated with persistently low rates of adverse events for more than eight years and did not exceed those observed in the original placebo arm during the parent study and led to further reductions in cardiovascular events compared with delayed treatment initiation.[9]

Alirocumab was studied in a large trial in patients who had an acute coronary syndrome within past 12 months (LDL-C level ≥ 70 mg/dL, non-HDL-C at least 100 mg/dL, or an apolipoprotein B at least 80 mg/dL), and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose.[10] At 2.8 years, a composite primary endpoint (death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) event occurred in 9.5 percent in the alirocumab group and in 11.1 percent in the placebo group (hazard ratio, 0.85; 95% CI, 0.78 to 0.93; $p < 0.001$). The absolute benefit of alirocumab with respect to the composite primary endpoint was greater among patients who had a baseline LDL-C level of ≥ 100 mg/dL than among patients who had a lower baseline level.

Exhibit 2: Definition Of Statin-Associated Muscle Symptoms (SAMS)[18]

- **Myalgia** – unexplained muscle discomfort often described as "flu-like" symptoms with normal CK level
- **Myopathy** – muscle weakness
- **Myositis** – muscle inflammation often with muscle enzyme elevations
- **Myonecrosis** – elevation in muscle enzymes, severity graded by elevation of CK level above pre-treatment baseline levels or ULN.
- **Clinical rhabdomyolysis** – muscle injury with myoglobinuria and/or acute renal failure

Unfortunately, momentum for PCSK9 inhibitor monoclonal antibody use was lost after the publication of the large clinical trials due to the price of these agents. The manufacturers have lowered the price by about 60 percent but these agents remain underutilized despite their safety and benefit. The rate of PCSK9 inhibitors is good in those with the severest forms of hypercholesterolemia, but other patients would also benefit from these agents. Additionally, there are racial and socioeconomic disparities in the use of PCSK9 inhibitors and the other main non-statin agent, ezetimibe.[11,12]

A third PCSK9 targeting agent was approved by the FDA in 2021. Inclisiran is a small interfering RNA (siRNA) directed to PCSK9 messenger RNA (mRNA). By binding to the mRNA precursor of PCSK9, inclisiran inhibits PCSK9 gene expression, resulting in increased hepatocyte recycling and membrane expression of LDL receptors and decreased levels of LDL-C. Inclisiran produces about a 50 percent reduction in LDL-C which is lower than the approximately 60 percent with PCSK9 monoclonal antibodies.[13] Thus, for patients with LDL-C greater than 190 on background statins, the monoclonal antibodies would be more likely to achieve goal. Continued LDL-C control and safety have been shown out to four years of use.[14] CVD outcomes are not yet available with inclisiran and the ORION4, VICTORION-2 Prevent, and VICTORION Plaque long-term outcome trials are ongoing.

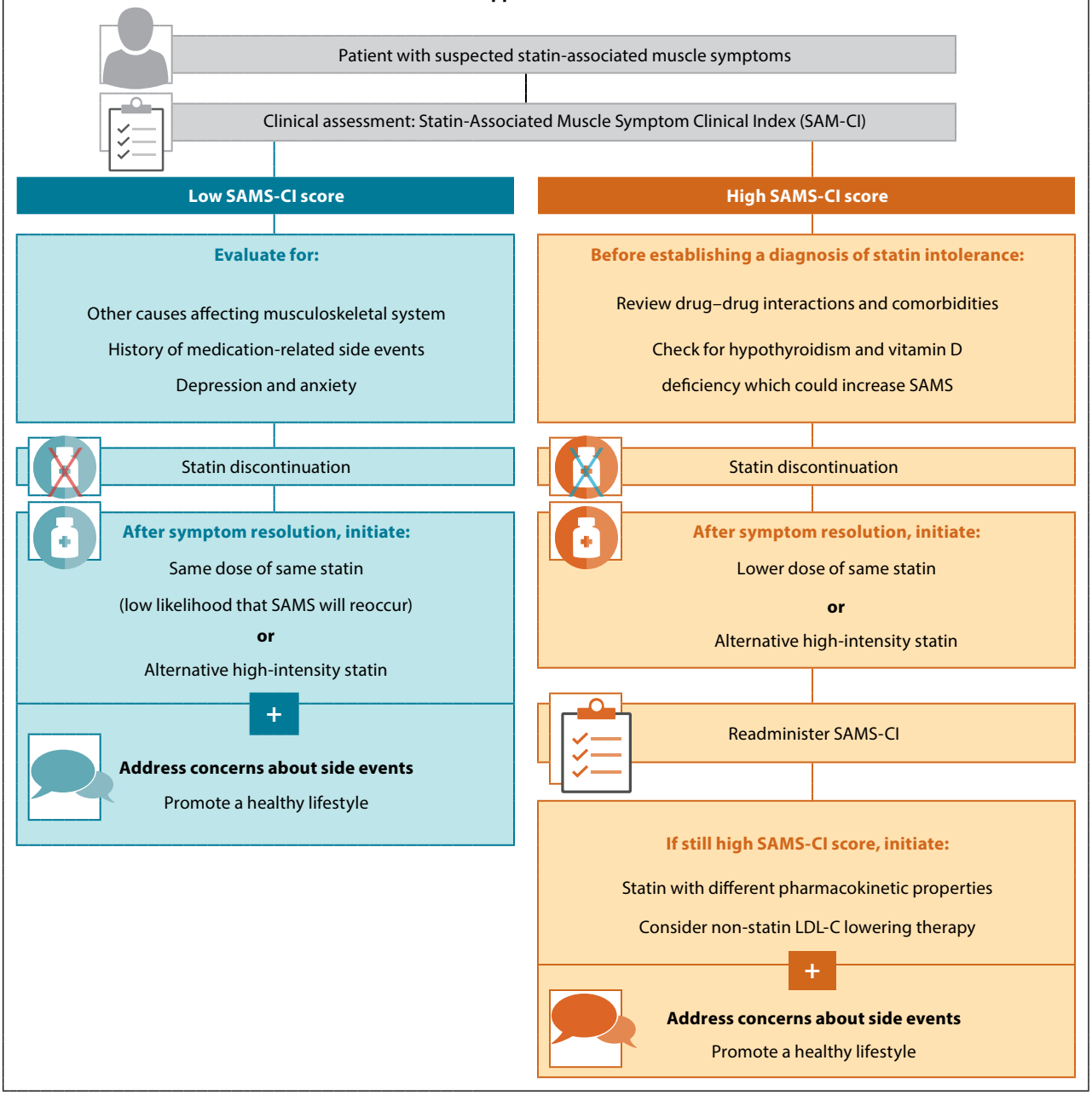
Inclisiran is given every six months by a healthcare provider compared to every two to four weeks self-injection with the monoclonal antibodies. It is an option for those who have had an allergic reaction to one of the monoclonal antibodies or where the patient has difficulty with the injection of the monoclonal antibodies (severe hand arthritis). The main adverse event of the PCSK9 targeting agents is injection site reaction.

Beyond the use of non-statin therapies in those who need additional LDL-C lowering after maximization of statin therapy group, is the group of those who have statin intolerance. Statin intolerance is a common reason for people to not achieve LDL-C goals because they cannot tolerate high-intensity dosing. A large retrospective cohort study found that patients who were statin intolerant had a 36 percent higher rate of recurrent MI than those adherent to statin therapy (HR 1.50; 95% CI, 1.30 to 1.73; $p < .001$) and a 43 percent higher rate of CVD events (HR 1.51; 95% CI, 1.34 to 1.70; $p < .001$).[15] In a trial using integrated healthcare system data, patients with stain intolerance were less likely to reach LDL-C goals, incurred higher healthcare costs, and experienced a higher risk for nonfatal CV events than patients without statin intolerance.[16] Overall, statin intolerance is associated with high healthcare costs. Reduction in overall healthcare costs may be higher than reported with a therapy that is more effective than statins. These results may encourage health systems to invest resources to re-challenge patients with statin adverse events and to increase the use of non-statin lipid-lowering medications in the truly intolerant population.

It is important to clarify stain intolerance. Statin intolerance is defined as the inability to tolerate at least two different statins (one statin at the lowest starting average daily dose and the other statin at any dose). Intolerance is associated with confirmed, intolerable statin-related adverse events or significant biomarker abnormalities; symptom or biomarker change resolves or significantly improves upon dose decrease or discontinuation; and symptom or biomarker changes that are not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance.[17]

Adverse events are commonly reported with statins and can frequently result in therapy discontinuation. Many symptoms that patients report are not related to the therapy (temporally or known adverse events) or do not go away subsequent to stopping therapy. In addition to stopping therapy due to an adverse event, patients can be reluctant to be re-challenged with another statin. Clinicians need to be rigorous in evaluating whether reported adverse

Exhibit 3: Clinical Approach to a Patient with SAMS[19]



events, especially muscle-related complaints, which are most common, are really related to the statin therapy. Exhibit 2 shows the definitions of statin associated muscle symptoms from the National Lipid Association.[18] Exhibit 3 offers an approach to this evaluation.[19] This approach uses the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) which considers pattern and location of muscle symptoms, timing in relation to statin initiation, improvement of symptoms after discontinuation, and effects of re-challenge.[20]

For those who are truly statin intolerant, the non-statin therapies are an option and will increase the likelihood of those patients achieving LDL-C goals. Among patients with statin intolerance akin to muscle-related adverse events, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks.[21] In this trial, 42.6 percent of patients with statin-associated muscle symptoms developed complaints when re-challenged blinded with atorvastatin 20 mg, but not placebo. This demonstrated that 57 percent of people who entered the trial as statin intolerant were not really intolerant. In this trial patients with

a history of statin-associated muscle symptoms receiving PCSK9 inhibitors rarely discontinued therapy due to muscle symptoms (ezetimibe 6.8%, evolocumab 0.7%).[21] A study comparing alirocumab and ezetimibe in statin-intolerant patients had a similar design.[22] Alirocumab produced greater LDL-C reductions than ezetimibe in statin-intolerant patients, with fewer skeletal-muscle adverse events compared to atorvastatin.

A 2022 expert consensus decision pathway from the American College of Cardiology provides information on the role of non-statin therapies for managing ASCVD risk and also provides guidance for clinicians in selecting therapy and managed care in managing this group of agents.[23]

Conclusion

Overall, statins are highly efficacious cholesterol-lowering therapies with proven benefits in lowering cardiovascular events. Despite progress, there are still some significant gaps in care. Systems approaches to improving secondary prevention afford the opportunity to close some of these gaps and make a significant impact on cardiovascular outcomes. Non-statin agents provide options for LDL-C lowering in the not at goal/residual risk and intolerant population. Accurately identifying statin intolerance is an important healthcare challenge that involves validated screening tools and rechallenge.

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Informed Managed Care Decision-Making in the Treatment and Management of Ovarian Cancer: Optimizing the Impact of PARP Inhibitors for Improved Outcomes

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

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Summary

Poly (ADP-ribose) polymerase (PARP) inhibitors for maintenance and treatment of advanced ovarian cancer has led to significant changes in the treatment paradigm for this disease. First-line maintenance therapy with PARP inhibitors with or without bevacizumab after platinum-based chemotherapy response is improving progression-free survival (PFS) which will hopefully translate to continued improvements in overall survival.

Key Points

- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure.
- The absolute PFS benefit shown in first-line treatment compared with later lines highlights the importance of introducing PARP inhibitors as early as possible.
- Clinical trials have demonstrated a PFS benefit from PARP inhibitor maintenance in patients with newly-diagnosed ovarian cancer.

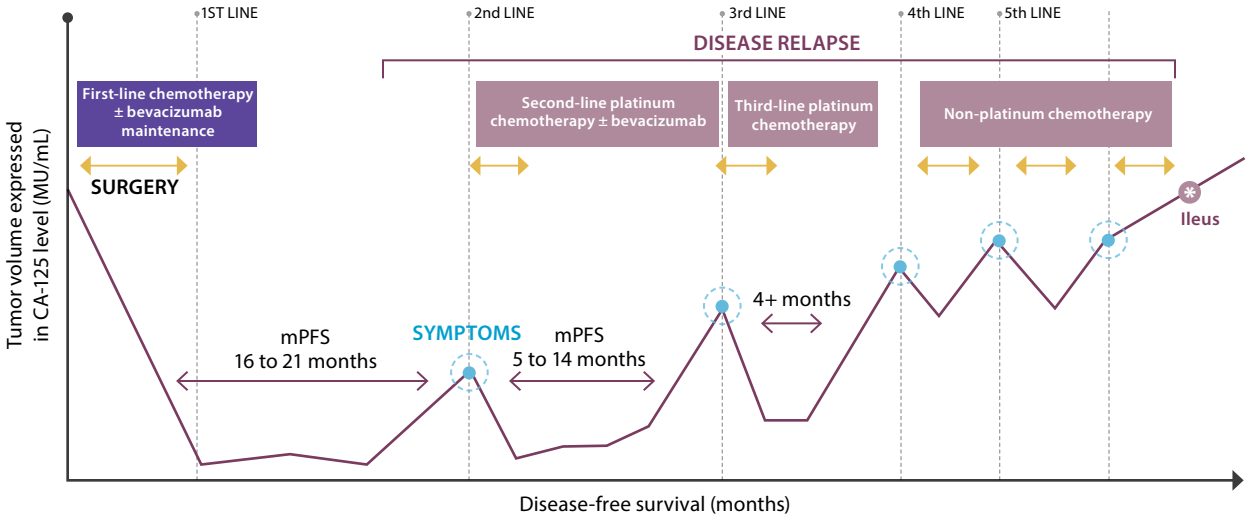
AN ESTIMATED 19,710 WOMEN WERE diagnosed with ovarian cancer in 2023 and 13,270 deaths occurred.[1] About 55 percent of newly diagnosed women will already have advanced disease. Most patients with advanced ovarian cancer relapse within three years following first-line multimodal therapy of surgery and chemotherapy.[2] Five-year survival for those with advanced disease is 31.5 percent.[1] There is a significant need for better first-line treatment to improve outcomes for women with advanced ovarian cancer.

Advanced ovarian cancer is characterized by multiple relapses. In the past, each relapse was treated with another line of chemotherapy but this approach is associated with cumulative toxicity while remission periods decrease (Exhibit 1). Once the disease relapses after first-line treatment, it is largely incurable. Thus, first-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure. Resection of as much disease as possible is the goal of surgery for advanced disease. Studies have shown that postoperative residual disease reduces five-year survival compared to zero residual disease.[4,5]

Considerable progress has been made in the management of ovarian cancer since 2003. One major advance was the introduction of PARP inhibitors for BRCA-mutated ovarian cancer in 2018 and the subsequent use of these agents in cases beyond BRCA-mutation. PARP inhibition selectively targets tumors with homologous recombination deficiency (HRD). PARP inhibitors trap PARP enzymes on DNA, causing cancer-specific cell death in tumors with HRD (Exhibit 2).[6]

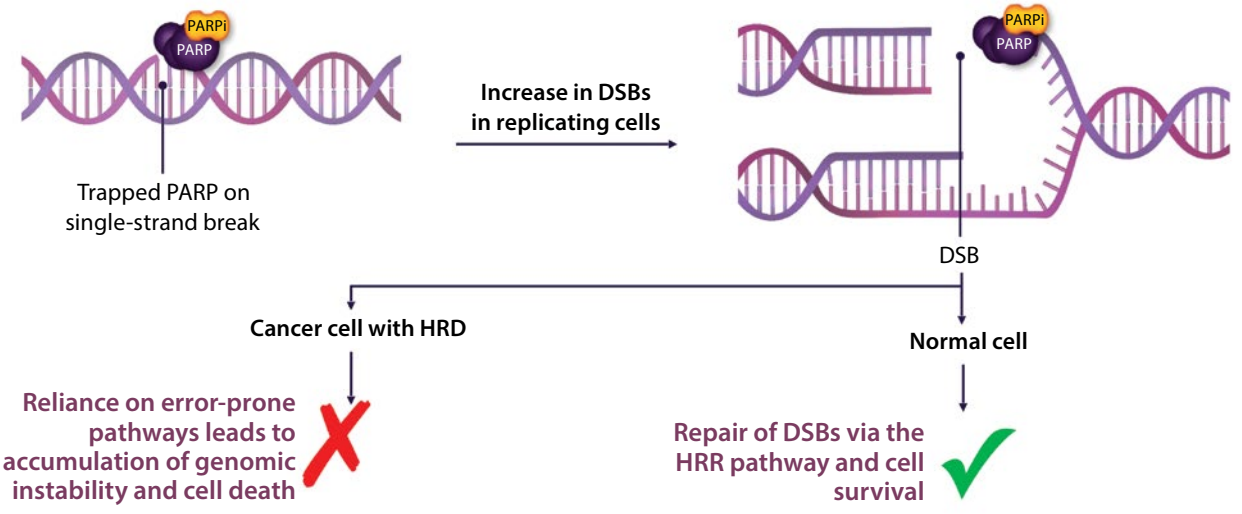
PARP inhibitors were initially used for relapsed advanced disease. Earlier use of PARP inhibitors

Exhibit 1: Multiple Lines of Chemotherapy is Associated with Cumulative Toxicity and Shortening Remission Periods[3]



CA-125 =cancer antigen 125; mPFS = median progression-free survival

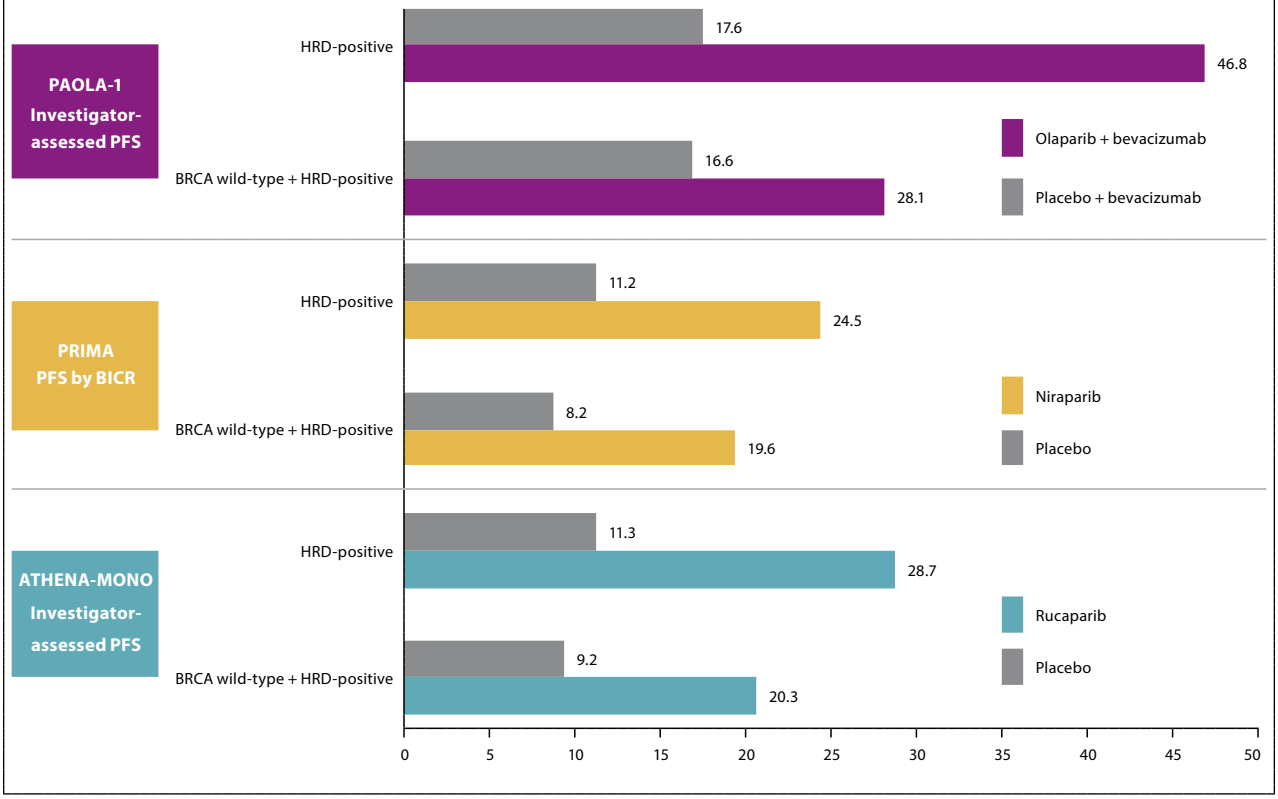
Exhibit 2: Mechanism of Action of PARP Inhibitors[6]



DSB = double strand break; HRR = homologous recombination repair

in newly diagnosed advanced disease offers the opportunity for a greater number of patients to benefit. The PFS benefit of 42.2 months shown in SOLO1 (maintenance in BRCA-mutated, newly diagnosed, advanced ovarian cancer with a complete or partial clinical response after platinum-based chemotherapy) compared with SOLO2 (maintenance in platinum-sensitive, relapsed ovarian cancer with a BRCA1 or 2 mutation and at least two lines of previous chemotherapy) benefit of 13.3 months highlights the importance of introducing PARP inhibitors as early as possible.[7,8] In SOLO1, olaparib first-line maintenance showed a 70 percent reduction in the risk of disease progression or death versus placebo in the BRCA-mutated population, which was sustained with long-term follow-up at

Exhibit 3: Greatest PFS Benefit from PARP Inhibitor Maintenance is in Biomarker-positive Populations[9-12]



five years.[7] The PFS benefit was sustained beyond the two-year duration of maintenance therapy. The seven-year median OS result from this trial did not reach statistical significance (at a prespecified $p < 0.0001$) but was clinically meaningful (not reached versus 75.2 months). Olaparib first-line maintenance also delayed time to first systemic therapy (64 versus 15.1 months).

Another advance in the use of PARP inhibitors as first-line maintenance is the addition of bevacizumab to the maintenance regimen. In PAOLA-1, olaparib for two years plus bevacizumab significantly improved PFS versus bevacizumab in the intention to treat and HRD-positive patient populations, while no additional benefit was observed in HRD-negative patients.[9] Olaparib plus bevacizumab improved median OS compared to bevacizumab alone (56.5 versus 51.6 months) at five years.[10] In the HRD-positive population, OS rate was higher with olaparib plus bevacizumab (HR 0.62, 65.5% versus 48.4%); the best five-year OS rate was in the BRCA-mutated group (73.2%). Updated PFS also showed a higher proportion of olaparib plus bevacizumab patients without relapse (HR 0.41, 46.1% versus 19.2%).[10]

Two other PARP inhibitors, niraparib and rucaparib, have also been studied for first-line maintenance. Niraparib maintenance in the PRIMA trial demonstrated a greater PFS benefit in the HRD-positive population compared with the HRD-negative population.[11] Rucaparib maintenance also produced a PFS benefit in those with or without HRD in the ATHENA-MONO trial.[12] As shown in Exhibit 3, the greatest PFS benefit with PARP inhibitor maintenance is seen in biomarker-positive populations.[9-12]

There are no randomized clinical trial data yet available to directly demonstrate the efficacy contribution of bevacizumab to first-line PARP inhibitor maintenance. The PAOLA-1 trial did not include an olaparib alone treatment arm. Ongoing trials are studying a direct comparison of a PARP inhibitor with and without bevacizumab. Until that evidence is available, one can look at the survival estimates for olaparib trials that did and did not include bevacizumab to try to determine the benefit of bevacizumab addition. Kaplan–Meier estimates of OS at five years were similar in the BRCA-mutated subgroups of PAOLA-1 (73.2% with olaparib/bevacizumab versus 53.8% with placebo/bevacizumab) and in SOLO1 (73.1% olaparib versus 63.4% placebo), despite patients in PAOLA-1 having less favorable prognostic features.[7,9,10] Compared

with the population enrolled into SOLO1, the PAOLA-1 population had a higher proportion of patients with Stage IV disease, a history of neoadjuvant chemotherapy, or residual disease after surgery. The contribution of bevacizumab to first-line PARP inhibitor maintenance was examined using a population-adjusted indirect treatment comparison of PAOLA-1 and SOLO1.[13] Adding bevacizumab to olaparib was associated with a numerical improvement in PFS compared with olaparib alone (hazard ratio 0.71; 95% confidence interval 0.45 to 1.09).

The current National Comprehensive Cancer Network (NCCN) Guidelines recommend PARP inhibitor maintenance for all patients with or without BRCA mutation who have complete or partial response to first-line treatment which did not include bevacizumab.[14] Bevacizumab addition to PARP inhibition is recommended in patients who had bevacizumab as part of primary therapy in those with BRCA mutation or HRD and complete or partial response to first-line therapy. Olaparib plus bevacizumab is a Category 1 recommendation.

Approximately 20 percent of patients with ovarian cancer harbor a BRCA mutation making maintenance treatment selection easy for this group. HRD, which includes BRCA mutation, is present in approximately 50 percent of newly-diagnosed, high-grade, epithelial ovarian cancers. In testing for HRD, homologous recombination repair (HRR) gene panels are 'cause' assays, whereas genomic instability tests are 'effect' assays. HRR gene panels identify pathogenic mutations in HRR genes. Genomic instability tests look for the effect of HRR loss and quantify genomic aberrations that are characteristic of HRD. Genomic instability tests should be done in combination with BRCA testing. In the first-line maintenance setting, HRD genomic instability clearly predicts the magnitude of PARP inhibitor benefit.[9-11] HRD kits and laboratory developed tests are being developed by diagnostic companies and the academic community to provide accurate HRD testing options.

Conclusion

First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure. The absolute PFS benefit shown in first-line treatment compared with later lines highlights the importance of introducing PARP inhibitors as early as possible. Clinical trials SOLO1, PAOLA-1 and PRIMA have demonstrated a PFS benefit from PARP inhibitor maintenance in patients with newly-diagnosed ovarian cancer.

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Managed Care Considerations in the Treatment of HER2-Positive Advanced Breast Cancer: A Closer Look at Recent Advances for Improved Patient Outcomes

Shanu Modi, MD

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

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Summary

HER2 targeted therapies have revolutionized outcomes for patients with HER2+ breast cancer. Next generation ADCs with advanced pharmaceutical properties also offer the potential role to expand the target landscape and target thresholds beyond HER2+ breast cancer.

Key Points

- Novel agents have led to prolonged survival and have changed the natural history of advanced stage HER2+ breast cancer.
- Novel agents also hold promise for CNS treatment for HER2+ disease with brain metastases.
- HER2-low breast cancer is now targetable.

OF THE 300,000 CASES OF BREAST CANCER diagnosed in the United States (U.S.) every year, approximately 14 percent are positive for human epidermal growth factor receptor two overexpression (HER2+).[1] HER2+ breast cancer is an aggressive, fast-growing disease. Prior to the introduction of the first HER2+ targeted therapy in 1998 it resulted in shorter disease-free survival and overall survival (OS) compared to HER2-negative breast cancer. HER2-targeted drugs have reverted the negative prognostic impact of HER2 overexpression. In one treatment database, the median OS in 2008 was 39 months which improved to 58 months by 2013 and in 2016 was not reached during a 65.5-month follow-up.[2] Survival with HER2+ breast cancer is now equivalent to that of hormone receptor positive (HR) disease.

Exhibit 1 shows the evolution of HER2 targeting agents for metastatic disease. Trastuzumab and pertuzumab, which target HER2 in separate ways are now given together with chemotherapy as standard first-line treatment for HER2+ metastatic breast cancer (mBC) due to improved OS (Exhibit 2). In a pivotal trial (Cleopatra), median OS was 57.1 months in those receiving pertuzumab/trastuzumab/docetaxel and 40.8 months in those receiving placebo/trastuzumab/docetaxel (hazard ratio [HR] 0.69). The eight-year landmark overall survival rates were 37 percent in the pertuzumab group and 23 percent in the placebo group.[3] Docetaxel, paclitaxel, and nab-paclitaxel can be chosen as the chemotherapy component and each produces similar results.[4] For those patients who are also HR positive, one study has suggested some select patients may benefit from hormone targeted therapy plus trastuzumab/pertuzumab without induction chemotherapy.[5]

Second-line treatment is now fam-trastuzumab

Exhibit 1: Timeline of HER2-Targeted Therapy Approvals for Metastatic Breast Cancer

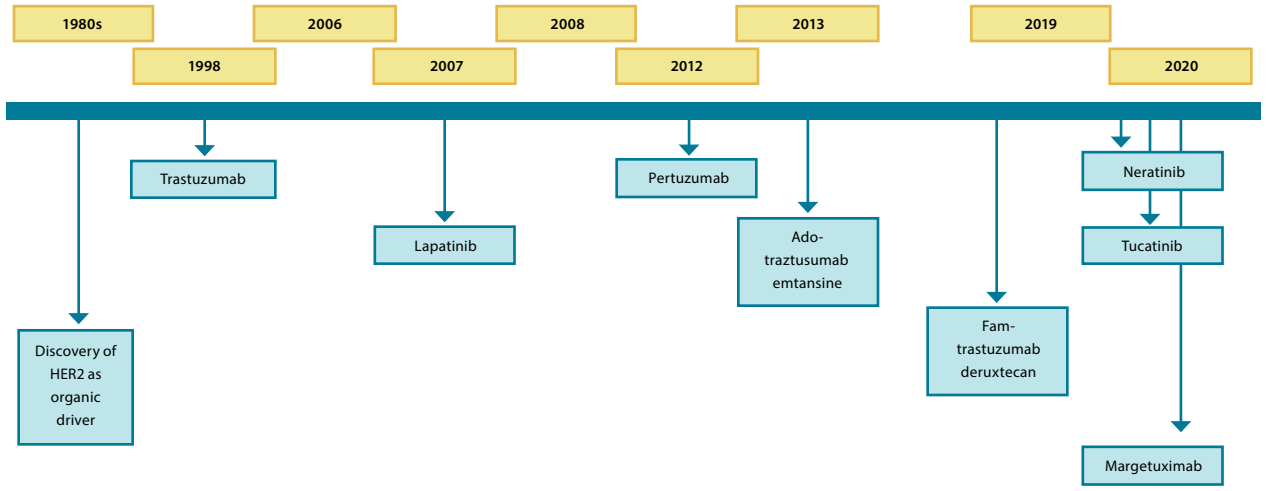
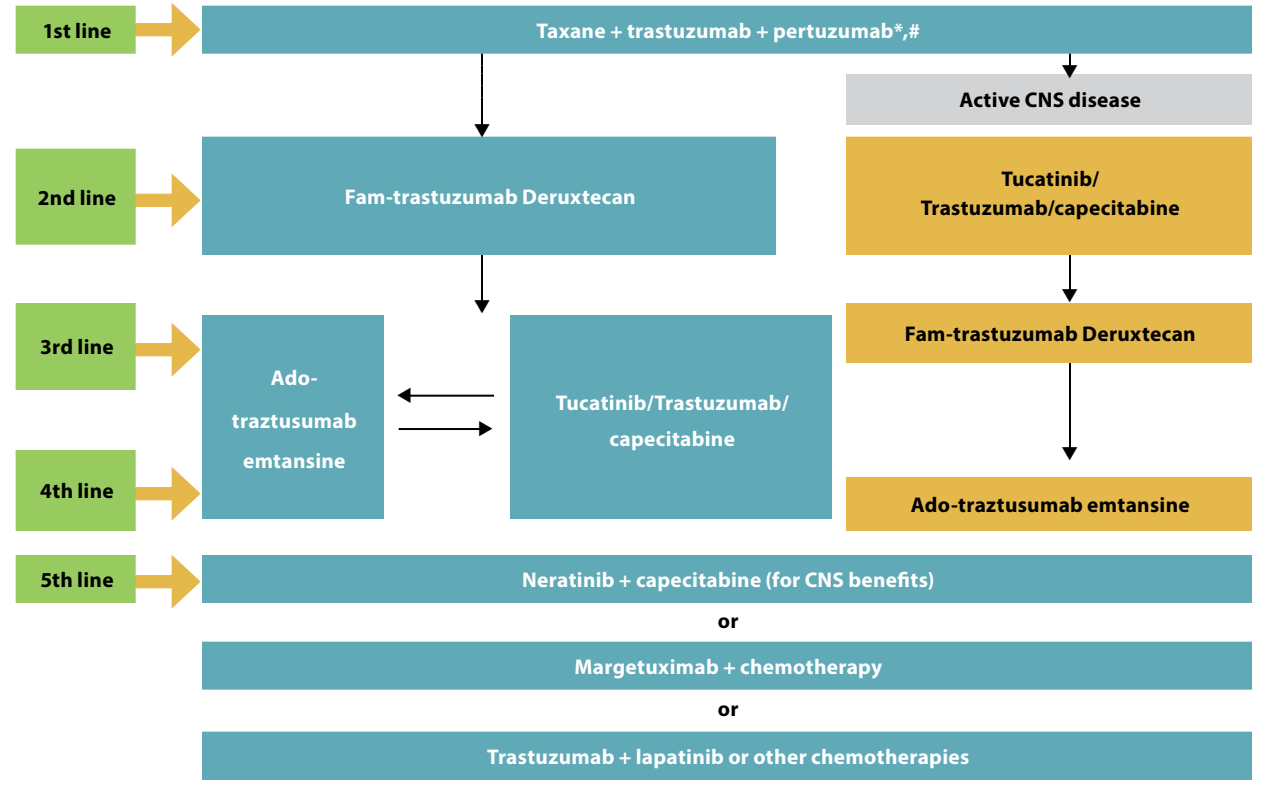


Exhibit 2: An Approach to Therapy for Metastatic HER2+ Breast Cancer



* Aromatase inhibitor/trastuzumab/pertuzumab in select cases and for maintenance in ER+ disease;
# endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

deruxtecan instead of the previously recommended ado-trastuzumab emtansine. Both are antibody-drug conjugates (ADC) but fam-trastuzumab deruxtecan also can kill neighboring non-HER2+ tumor cells (bystander killing) because of high cell membrane permeability and it delivers a higher chemotherapy payload than ado-trastuzumab emtansine. In a trial comparing fam-trastuzumab deruxtecan and ado-traztusumab emtansine in patients with HER2+ mBC previously treated with

trastuzumab and a taxane, the percentage of those who were alive without disease progression at 12 months was 75.8 percent with fam-trastuzumab deruxtecan and 34.1 percent with ado-trastuzumab emtansine (HR for progression or death from any cause, 0.28; $p < 0.001$).[6] The percentage of patients who were alive at 12 months was 94.1 percent and 85.9 percent, respectively (HR for death, 0.55; prespecified significance boundary not reached). The National Comprehensive Cancer Network (NCCN) Guidelines note that fam-trastuzumab deruxtecan can be considered as first-line treatment for those patients with rapid progression within six months of neoadjuvant or adjuvant therapy (12 months for a pertuzumab containing regimen).[7] First-line treatment of metastatic disease and neoadjuvant/adjuvant studies are ongoing with this agent.

There are still some issues to resolve with fam-trastuzumab deruxtecan. Drug-related interstitial lung disease occurs in about 10 percent of patients. Identifying the pathophysiology of this adverse event and ways to avoid it are needed. Determining if there is reversibility and whether patients could be retreated is also needed. Other issues to resolve with this agent include whether moving use into the first-line setting for HER2+ mBC will increase survival and long-term remissions, identifying combination strategies to maximize outcomes, and understanding mechanisms of resistance. An understanding of the potential role of fam-trastuzumab deruxtecan in HER2+ early breast cancer is under investigation.

Oral tyrosine kinase inhibitors (tucatinib, neratinib, lapatinib) are treatment options in the third-line. Tucatinib in combination with trastuzumab and capecitabine is preferred in the NCCN guideline in those with both systemic and central nervous system (CNS) progression for third-line treatment.[7] This combination is also an option instead of fam-trastuzumab deruxtecan in second-line treatment if CNS disease is present. Tucatinib is preferred over the TKI because of increased specificity for HER2, demonstrated CNS activity, and improved OS compared to a regimen without tucatinib. The HER2 specificity reduces off-target adverse events, particularly those related to epidermal growth factor receptor effects (rash, diarrhea). CNS activity is important because up to 50 percent of those with HER2+ mBC will develop brain metastases. In the HER2Climb trial of third-line or later treatment, tucatinib/trastuzumab/capecitabine treatment produced a median duration of OS of 24.7 months versus 19.2 months for placebo/trastuzumab/capecitabine (HR for death: 0.73, $p = 0.004$) and OS at two years was 51 percent and 40 percent, respectively.[8] In a secondary analysis of patients with brain metastases, risk of progression was reduced by 52 percent and risk of death in patients by 42 percent.[9]

The most recent advance in HER2-related disease is the approval of fam-trastuzumab deruxtecan for HER2-low disease. HER2+ is defined as an immunohistochemistry (IHC) score of 3+. The HER2-low category includes those who have borderline of 1+ and 2+ scores. Approximately 55 percent of people with HER2-negative breast cancer fall into this HER2-low category.[10] Low HER2 expression occurs predominately in hormone receptor positive breast cancer (85% to 90%) and has previously not been actionable. In the DESTINY-Breast04 trial, patients with previously treated HER2-low mBC who were treated with fam-trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy alone.[11] The median PFS was 10.1 months in the fam-trastuzumab deruxtecan group and 5.4 months in the physician's choice chemotherapy group (HR for disease progression or death, 0.51; $p < 0.001$), and OS was 23.9 months and 17.5 months, respectively (HR for death, 0.64; $p = 0.003$). Based on this study, this agent is now FDA approved for adults with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/in situ hybridization negative) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy. It is the new standard of care for HER2-low mBC and is a NCCN recommendation.

Fam-trastuzumab deruxtecan is also under study in chemotherapy naïve, hormone receptor positive, HER2-ultralow breast cancer. The DESTINY Breast 08 trial is also looking at various combinations with this agent to maximize benefit in the HER2-low population. Several other ADC are under evaluation for HER2-low disease including trastuzumab duocarmazine and disitamab vedotin.[12]

Conclusion

Novel agents have led to prolonged survival and have changed the natural history of advanced stage HER2+ breast cancer. Novel agents also hold promise for CNS treatment for HER2+ disease with brain metastases. HER2-low breast cancer is now targetable. Understanding mechanisms of resistance and sequencing will be key to optimizing and personalizing HER2 therapies in the future.

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Optimizing Outcomes in the Management of Multiple Myeloma: Key Managed Care Considerations on the Evolving Role of Anti-CD38 Therapy

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This journal article is supported by an educational grant from Sanofi

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Summary

Treatment of multiple myeloma has evolved quickly over the past decade. Effective combinations of therapies have revolutionized management and are providing improvements in survival.

Key Points

- Four-drug combinations including a CD38 monoclonal antibody with stem cell transplant followed by maintenance provide the best chance for a deep and long-lived remission.
- At relapse, multidrug combinations are again preferred treatment.
- Several new classes of drugs including CAR-T cells and bispecifics are emerging for the triple-class refractory population.

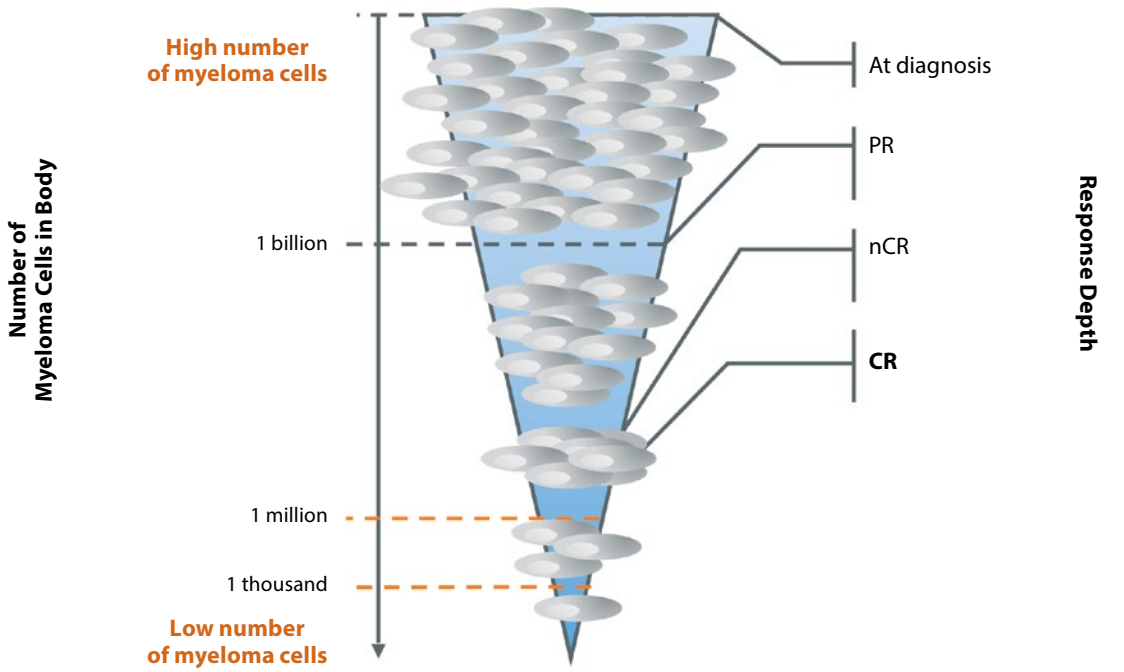
MULTIPLE MYELOMA (MM) IS AN uncommon cancer of plasma cells and is the second most common blood cancer in the United States (U.S.). The American Cancer Society's estimate for the U.S. in 2024 is that 35,780 new cases will be diagnosed (19,520 in men and 16,260 in women) and 12,540 deaths are expected to occur (7,020 in men and 5,520 in women).[1] In the U.S., the average lifetime risk of getting multiple myeloma is about 1 in 103 for men and about 1 in 131 for women. The median age at diagnosis is 69 years.

The goal of first-line therapy is a sustained remission with a deep cellular response (Exhibit 1).[2] As a result of the availability of effective drugs, many patients with MM now achieve good responses to treatment, with approximately 75 percent achieving a near-complete (nCR) or complete response (CR). Complete response (negative immunofixation results in serum and urine, disappearance of any soft-tissue plasmacytomas, and < 5% plasma cells in bone marrow) to therapy is associated with improved progression-free survival (PFS) and overall survival (OS), especially if the CR status is maintained. Complete remission sustained three years from treatment initiation is a powerful surrogate for extended survival in MM.[3]

Minimal residual disease (MRD) refers to the small number of cancer cells that remain in the body after treatment. An MRD-negative result means that no disease was detected after treatment. Studies have shown that patients with MM who achieve an MRD-negative status after treatment live longer without disease progression. According to the International Myeloma Working Group criteria, the minimum sensitivity level for the definition of MRD negativity is set at 1 in 10^5 nucleated cells (e.g., meaning that no tumor cell could be detected within 100,000 bone marrow cells).[4]

The primary medications used in MM treatment are proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors

Exhibit 1: Response Depth[2]



PR = partial response; nCR = near complete; CR = complete response

which induce apoptosis of MM cells. Lenalidomide and pomalidomide are immunomodulators which induce immune responses, prevent inflammation, and enhance the activity of T cells and natural killer (NK) cells. Daratumumab and isatuximab are anti-CD38 monoclonal antibodies—CD38 is overexpressed on MM cells.

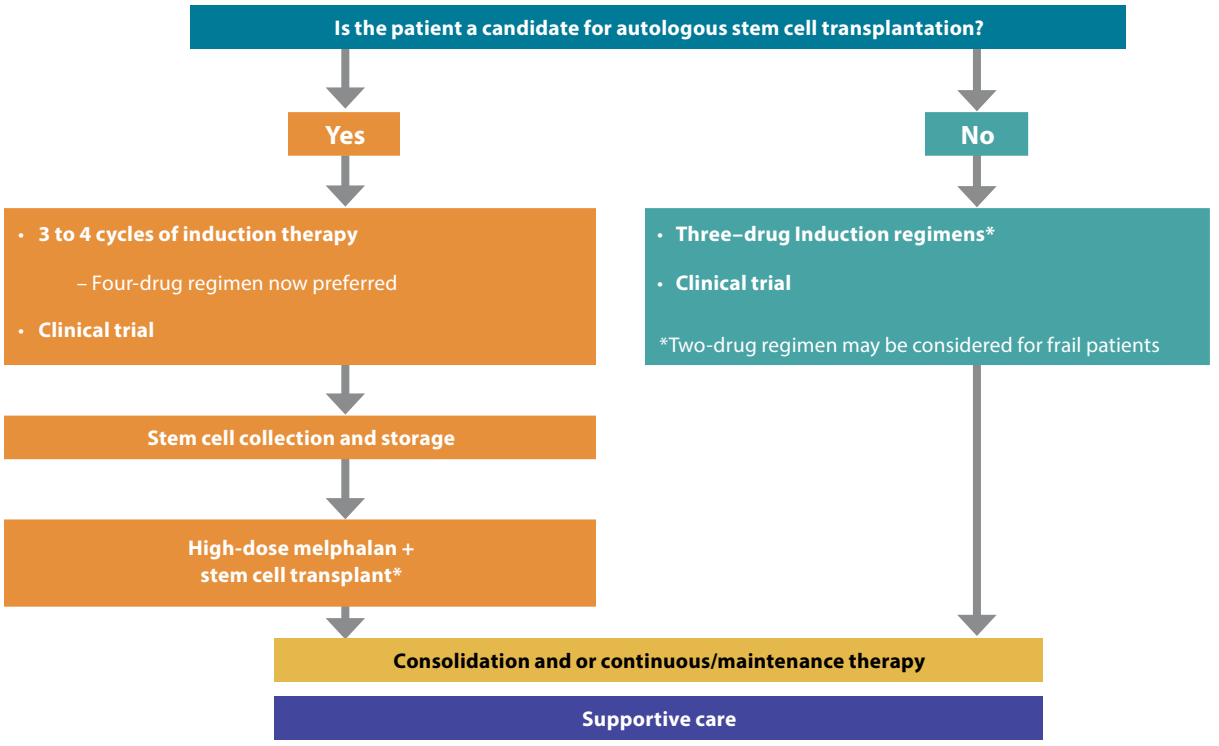
The initial treatment approach to choosing first-line therapy for MM begins with considering whether the patient is eligible for autologous stem cell transplantation (ASCT, Exhibit 2). Only about one-third of patients undergo ASCT. The National Comprehensive Cancer Network (NCCN) preferred primary therapy for newly diagnosed transplant candidates is bortezomib/lenalidomide/dexamethasone (category 1); daratumumab/lenalidomide/bortezomib/dexamethasone is currently an "other recommended regimen".[5]

Many clinicians choose the four-drug regimen including daratumumab based on higher rates of CR and MRD negativity compared with the standard of care in the clinical trials. The Cassiopeia trial evaluated daratumumab/bortezomib/thalidomide/dexamethasone versus bortezomib/thalidomide/dexamethasone.[6] Thalidomide is used in Europe instead of lenalidomide. The four-drug regimen improved PFS and appears to be improving OS(41 versus 72 deaths over three years, final results have not yet been published). The Griffin trial compared daratumumab/bortezomib/lenalidomide/dexamethasone to bortezomib/lenalidomide/dexamethasone with maintenance therapy after ASCT consolidation.[7]

The primary endpoint, stringent complete response (sCR) rate by the end of post-ASCT consolidation, favored four drugs versus three drugs (42.4% versus 32.0%; odds ratio, 1.57; 95% confidence interval, 0.87 – 2.82; one-sided $p = .068$) and met the prespecified one-sided α of 0.10. With longer follow-up (median, 22.1 months), responses deepened. sCR rates improved (62.6% versus 45.4% respectively; $p = .0177$), as did MRD-negativity rates in the intent-to-treat population (51.0% versus 20.4%; $p < .0001$). Respective 24-month PFS rates were 95.8 percent and 89.8 percent. There was a clinically meaningful 55 percent reduction in the risk of disease progression or death.[8] The separation of the PFS curves occurred beyond one year of maintenance therapy. Grade 3 and 4 hematologic adverse events were more common with the four-drug regimen. More infections also occurred with the four-drug regimen, but Grade 3 and 4 infection rates were similar.

The other anti-CD38 agent, isatuximab, has also been investigated in a four-drug regimen. Addition of isatuximab to lenalidomide, bortezomib, and

Exhibit 2: Initial Treatment Approach



*In certain circumstances, consideration for a tandem transplant

dexamethasone for induction therapy improved rates of MRD negativity with no new safety signals in patients with newly diagnosed transplantation-eligible MM. MRD negativity after induction therapy was reached in 50 percent of patients in the isatuximab group versus 36 percent in the control group (or, 1·82; 95% CI 1·33 – 2·48; $p = 0·00017$).[9]

The MASTER trial combined daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) in newly diagnosed MM using MRD by next-generation sequencing (NGS) to inform the use and duration of Dara-KRd post-ASCT in patients with two consecutive MRD-negative assessments in a single-arm Phase II trial.[10] Of the 123 participants, 43 percent had no high-risk chromosome abnormalities (HRCAs) for relapse, 37 percent had one HRCA, and 20 percent had two or more HRCAs. For participants with evaluable MRD by NGS, 81 percent reached MRD negativity (78% with no HRCAs, 86% with one, and 79% with two or more HRCAs). Seventy-one percent had two consecutive MRD-negative measurements and were able to stop maintenance. The 36-month PFS was 88 percent (95% with no HRCAs, 79% with one, and 50% for those with two or more). For the participants who stopped maintenance, the 24-month cumulative incidence of progression from cessation of therapy was 9 percent for participants with no HRCAs, 9 percent with one, and 47 percent with two or more HRCAs. Sixty-one participants remained free of therapy and MRD negative as of February 7, 2023.[11] The authors concluded that this approach provided positive outcomes and a pathway for treatment cessation in most patients with newly diagnosed MM.[11] Outcomes for patients with ultra-high-risk MM, defined as those with two or more HRCAs, remain unsatisfactory, and these patients should be prioritized for trials with early introduction of therapies with novel mechanisms of action.

For the non-transplant eligible patient, the recommended regimen is a three-drug combination of bortezomib/lenalidomide/dexamethasone or daratumumab/lenalidomide/dexamethasone.[5] Both are Category 1 recommendations. No trials have directly compared these two regimens. Most patients with MM will relapse at some point after initial treatment. Indications for treatment of relapsed disease are shown in Exhibit 3.[12] The regimen chosen will depend on the duration of response from prior treatment, genetic profile of the MM cells, previous treatments, and their toxicity in the patient, and various patient factors (pre-existing

Exhibit 3: Indications for Treatment at Relapse in Multiple Myeloma[12]

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

toxicity, age, concomitant conditions, general health, preferences). There are numerous options for multiple lines of therapy.

Patients with MM refractory to PIs, immunomodulatory agents, and anti-CD38 mAb have a poor prognosis.[13,14] Prior options included conventional chemotherapy, salvage ASCT, recycling previous regimens, and clinical trials. Treatment of this group has changed dramatically with the approval of chimeric antigen receptor (CAR-T) cells (ciltacabtagene autoleucel and idecabtagene vicleucel) and bispecifics (elranatamab, talquetamab, teclistamab). All are indicated for the treatment of adult patients with relapsed or refractory MM after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody and are Category 1 recommendations in the NCCN Guidelines.[5] Ciltacabtagene autoleucel, approved in 2022, and idecabtagene vicleucel, approved in 2021, are B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. Elranatamab and teclistamab are bispecific BCMA-directed CD3 T cell engagers which bind to BCMA on plasma cells, plasmablasts, and MM cells and CD3 on T cells leading to cytolysis of the BCMA-expressing cells. Talquetamab is a bispecific G protein-coupled receptor class C group 5 member D (GPRC5D)-directed CD3 T cell engager that binds to the CD3 receptor expressed on the surface of T cells and GPRC5D expressed on the surface of MM cells and non-malignant plasma cells, as well as healthy tissues such as epithelial cells in keratinized tissues of the skin and tongue. There are also numerous other bispecifics under investigation.

All of these new agents can cause significant adverse events and have black box warnings about cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both CRS and ICANS can be life-threatening or fatal. The CAR-T therapies also have additional black box warnings including potentially fatal hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) These agents are only available through restricted programs under Risk Evaluation and Mitigation Strategies.

Conclusion

Treatment of myeloma has evolved quickly over the past decade. Four-drug combinations including a CD38 monoclonal antibody with ASCT followed by maintenance provide the best chance for a deep and long-lived remission. At relapse, multidrug combinations are again preferred treatment. Several new classes of drugs including CAR-T cells and bispecifics are emerging for the triple class refractory population. The best is yet to come with additional therapies on the way.

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Evolving Considerations in the Treatment and Management of Advanced Non-Small Cell Lung Cancer

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This journal article is supported by educational grants from Sanofi; Merck Sharp & Dohme LLC

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Summary

Targeted therapies are the first-line therapy of choice for patients with advanced non-small cell lung cancer (NSCLC) who have targetable tumor mutations, but immunotherapy alone, or in combination with chemotherapy, is the first-line choice for most patients with NSCLC. Both immunotherapy and targeted therapies have improved outcomes in advanced-stage NSCLC.

Key Points

- Selected genetic mutations, tumor histology, and programmed death ligand one (PD-L1) expression are factors that drive therapy choice.
- Targeted therapy is first-line for those with selected genetic mutations.
- Immunotherapy plus platinum-based chemotherapy doublets is standard for those without mutations.
- Anti-angiogenic therapy can enhance the impact of immunotherapy.

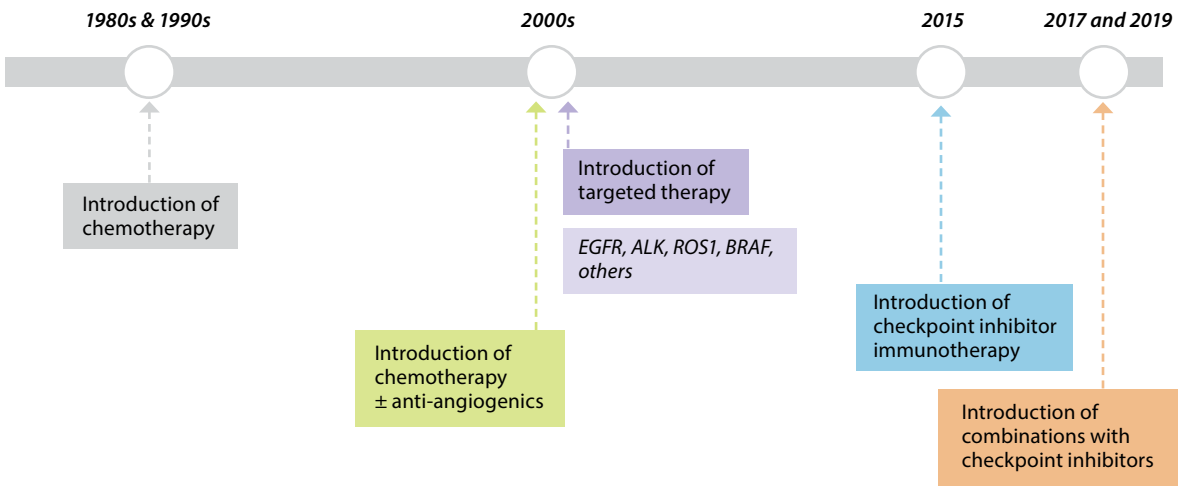
IN 2024, THE AMERICAN CANCER SOCIETY estimates that 234,580 new cases of lung cancer will be diagnosed and 125,070 deaths will occur.[1] Lung cancer is the most common cause of cancer-related mortality in the United States and accounts for more deaths than breast, prostate, and colorectal cancers combined.[1] The median age at diagnosis is 70 years and the major risk factor is smoking. Approximately 30,000 never-smoking Americans will develop lung cancer this year. Lung cancer is typically diagnosed at the later stages of the disease because lung cancer screening is not routinely practiced. Lung cancer is a very heterogeneous disease in terms of histology and molecularity. Non-small cell lung cancer is the most common histological type.[2,3]

Treatment of advanced or metastatic NSCLC has evolved significantly from chemotherapy alone to targeted therapy aimed at the various genetic mutation disease drivers and immunotherapy (Exhibit 1). The combination of chemotherapy and anti-angiogenics with checkpoint inhibitor immunotherapy are the most recent advances since 2017.

The treatment of NSCLC causes a high economic burden. Total costs have been increasing since 2015, driven by outpatient costs for systemic therapy which might reflect the greater use of immunotherapy for advanced NSCLC. In 2018, the total mean cost for NSCLC treatment was $250,942 per person per year.[4]

The major factors in selecting therapy for lung cancer are tumor histology (squamous versus nonsquamous disease), programmed death one ligand (PD-L1) expression, driver mutations (EGFR, ALK, ROS1, BRAF, etc.), performance status, comorbidities, and brain or liver metastases. Genomic testing is especially important because survival is about one-year better in those with targetable mutations who receive appropriate targeted therapy,

Exhibit 1: Evolving Landscape of NSCLC Treatment



compared with those who do not receive targeted therapy for a known mutation, or have no targetable mutations.[5] The National Comprehensive Cancer Network (NCCN) Guidelines note that although PD-L1 expression can be elevated in patients with an oncogenic driver, targeted therapy should take precedence over first-line immunotherapy treatment.[6] The guidelines recommend testing for EGFR, KRAS, BRAF, ERBB2 (HER2), and MET exon 14 skipping mutations; ALK, RET, and ROS1 rearrangements; NTRK1/2/3 gene fusion; and PD-L1 expression in eligible patients with advanced or metastatic NSCLC.[6] Liquid biopsy (plasma) testing is an option per the guidelines if tissue is inadequate.

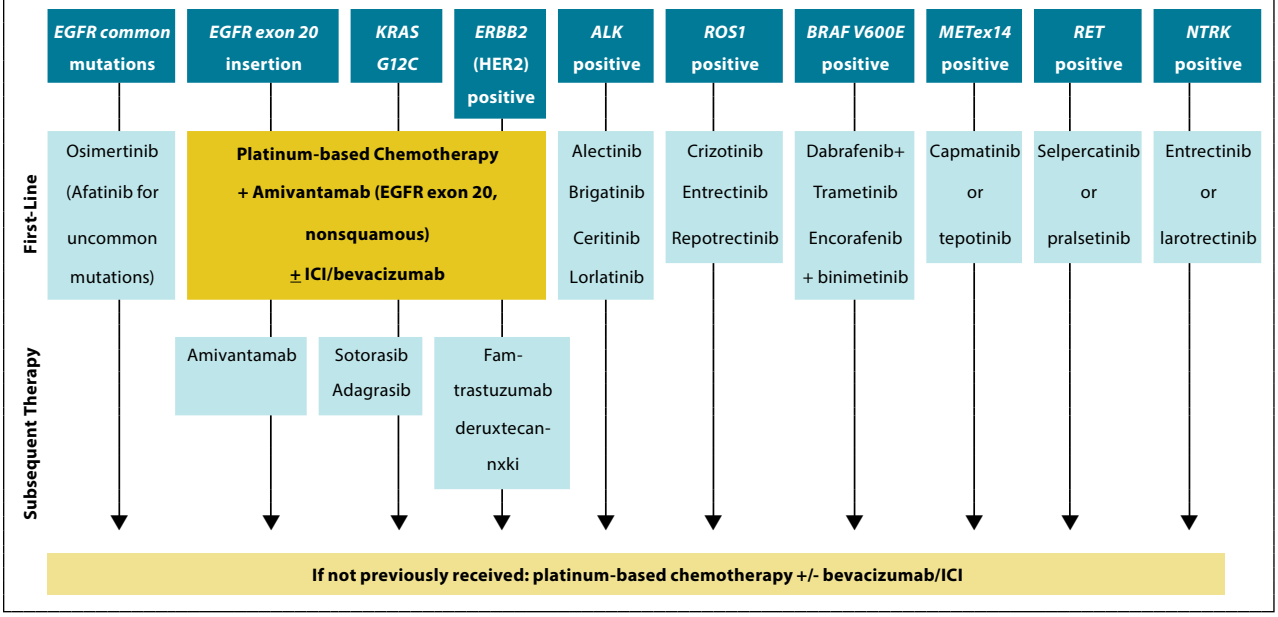
Importantly, comprehensive genomic testing at the time of diagnosis in Stage IV NSCLC (nonsquamous and selected squamous) is the standard of care and is not an option. Not identifying all actionable alterations is bad medicine. One real-world study of community oncology practices found that only 22 percent of those with advanced NSCLC were tested for the four main mutations and only 7 percent were tested for the seven for which targeted therapy was available at the time of the study.[7] This study also found underutilization of targeted therapies and immunotherapy being used first-line in those with targeted mutations. There are challenges to getting appropriate genomic testing. Following guideline recommendations for integrating liquid biopsy testing can mitigate tissue testing related challenges, reduce testing turn-around time, and increase detection of actionable biomarkers.[8-10]

If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment, except in the case of certain mutations where chemotherapy is first-line (Exhibit 2).[6] Epidermal growth factor receptor (EGFR) mutations are the most common genomic finding, occurring in 30 percent of NSCLC cases. Osimertinib is the tyrosine kinase inhibitor (TKI) of choice for common EGFR mutations (exon 19 and L858R). Afatinib is approved for uncommon mutations (G719X, L816Q, S786I) and is an option. One therapy is available for EGFR exon 20 insertion mutations, amivantamab, which is given with first-line platinum-based chemotherapy if nonsquamous disease is present.[6] It is given second-line at progression for adenocarcinoma or if not previously used.

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

In patients who had greater than 50 percent expression of PD-L1 on their tumor and no targetable mutations, first-line immunotherapy for advanced NSCLC with pembrolizumab, atezolizumab, or cemiplimab improves overall survival (OS) and progression-free survival (PFS).[11-13] Immunotherapy

Exhibit 2: Targeted Therapies for Molecular Biomarker–Positive Advanced NSCLC[6]



ICI = immunotherapy

Exhibit 3: Stage I-III NSCLC Adjuvant/Neoadjuvant Therapy

• Adjuvant
◦ Osimertinib in EGFR mutation in resected stage IB-IIIA
◦ Atezolizumab in PD-L1+ stage II-IIIA NSCLC following chemotherapy
◦ Pembrolizumab in stage IB-IIIA NSCLC following chemotherapy
• Neoadjuvant
◦ Nivolumab plus chemotherapy in > 4 cm or node positive NSCLC
• Unresectable Stage III following concurrent chemoradiation
◦ Durvalumab

has also been studied in those with PD-L1 expression of 1 to 49 percent. Pembrolizumab monotherapy is an option in those with lower PD-L1 expression especially for a frail patient but most clinicians prefer using immunotherapy in combination with chemotherapy because of a 20 to 25 percent better overall response rate compared to immunotherapy alone. Overall, monotherapy with immunotherapy is an acceptable standard for high PD-L1 expressors (> 90%) but may not be optimal for all high expressors (high tumor volume, heavy symptom burden). Low expressors or PD-L1 negative patients are best served with chemo-immunotherapy combinations.

There is a rationale for combining immunotherapy, chemotherapy, and anti-angiogenics (bevacizumab) in nonsquamous NSCLC.[14-19] Bevacizumab causes excess bleeding adverse events in squamous disease and should not be used in this group. The critical role of angiogenesis in promoting tumor growth and metastasis and consequently blocking this pathway as a therapeutic strategy has demonstrated great clinical success for the treatment of cancer but it has also been discovered that bevacizumab has effects in reprogramming the tumor milieu from an immunosuppressive to an immune permissive microenvironment in human cancers.[14] Atezolizumab and pembrolizumab have been studied in these triple combinations and the combination using atezolizumab is a Category 1 other recommended option in the NCCN Guidelines.[6] For example, the addition of atezolizumab to chemotherapy plus bevacizumab significantly improved PFS (8.3 versus 6.8 months) and OS (19.2 versus 14.7 months) among patients with metastatic nonsquamous NSCLC compared to bevacizumab/chemotherapy, regardless of PD-L1 expression and EGFR or ALK genetic alteration status.[20] The triple combination of chemotherapy, bevacizumab, and atezolizumab has also demonstrated a median survival benefit in NSCLC patients with liver metastases.[21]

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

to help identify patients at the time of diagnosis who will derive benefit from immunotherapy. For those patients with advanced NSCLC who have no driver mutations and are ineligible for immunotherapy, chemotherapy is the standard of care. Chosen regimens will depend on whether the disease is squamous or nonsquamous.

Another advance in NSCLC treatment is earlier use of immunotherapy or targeted therapy. Immunotherapy and one targeted therapy are also indicated as adjuvant or neoadjuvant therapy in selected patients with earlier stage disease. Exhibit 3 outlines these indications. Earlier use of these agents will impact treatment selection if the disease recurs.

Future therapies for NSCLC are antibody-drug conjugates (ADCs). Trastuzumab deruxtecan, is the only ADC currently FDA approved for use in NSCLC and is used to treat HER2-mutated disease. ADCs combine the specificity of monoclonal antibodies with the cytotoxic effects of chemotherapy. Several ADCs are currently in clinical trials for NSCLC. Other targets beyond HER2 are TROP2, CEACAM5, and MET. Several novel methods are underway to improve the safety and efficacy of ADCs, which include increasing the drug antibody ratio, increasing the potency of the chemotherapy payload, using more innovative payloads, and replacing the antibody.

Conclusion

Advanced NSCLC is an increasingly complex disease where several factors drive therapeutic choices. Targeted therapy should be used first in most patients with a targetable genetic mutation. Platinum-based doublets in combination with immunotherapy is a standard treatment for most patients with advanced NSCLC without targetable mutations. Bevacizumab appears to enhance the impact of immunotherapy and may be added to the regimen for selected patients.

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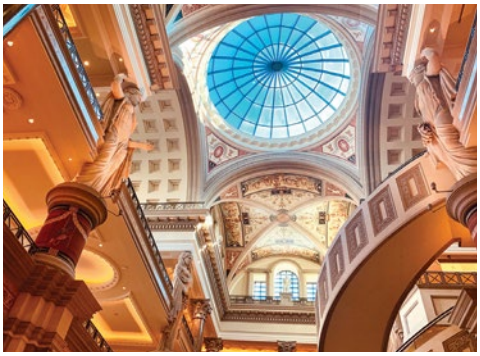

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