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Recent Advances in the Treatment and Management of Ovarian Cancer: Expert Perspectives on the Evolving Role of PARP Inhibitors

Diagnosing and Treating Excessive Daytime Sleepiness in Narcolepsy or Obstructive Sleep Apnea

Navigating an Increasingly Complex Treatment Paradigm in the Management of HER2-Positive Advanced Breast Cancer: An In-Depth Look at New and Emerging Therapies

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TABLE OF CONTENTS

Recent Advances in the Treatment and Management of Ovarian Cancer: Expert Perspectives on the Evolving Role of PARP Inhibitors

Robert L. Coleman, MD, FACOG, FACS

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

Summary

Patient outcomes with ovarian cancer have been improving over the last several years. One factor in survival improvement is the introduction of poly ADP ribose polymerase (PARP) inhibitors. These agents are now most frequently used as maintenance therapy after an initial response to chemotherapy, but their use alone and in various combinations will continue to expand over the next few years.

Key Points

- All patients with ovarian cancer should have genetic testing for treatment selection.
- Maintenance with PARP inhibitors is recommended for many patients who have an initial complete or partial response to platinum-based chemotherapy.
- The use of these agents continues to expand.

OVARIAN CANCER IS AN UNCOMMON tumor primarily diagnosed in women 55 years of age and older. The primary site of origin is likely the fallopian tube and most are serous tumors. Unfortunately, 75 percent of tumors are advanced stage (III/IV) at the time of diagnosis. The incidence of ovarian cancer declined 30 percent from 2001 to 2018 in the United States (U.S.).[1] During this same time period there was also a 27 percent decline in mortality. Because women are living longer with this cancer, the prevalence increased 40 percent. One contributor to the changes in mortality and prevalence was the introduction of poly ADP ribose polymerase (PARP) inhibitors in 2014.

Principle interventions are surgery and chemotherapy, but the risk of relapse after initial treatment is high (~70%). There are no curative options in recurrence or metastatic disease but various treatments including chemotherapy, immunotherapy, and PARP inhibitors are available.

Germline breast cancer gene protein (BRCA) mutations are found in about 15 to 20 percent of new diagnoses. BRCA is the only predictive biomarker for developing ovarian cancer despite hundreds of prognostic biomarkers. BRCA is involved in repairing breaks in double-stranded DNA through homologous recombination (HR). Cells with BRCA mutations have homologous recombination deficiency (HRD) but can repair DNA through base-excision repair (non-homologous repair) but use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer.[2] PARP is involved in base-excision repair and blocking PARP with PARP inhibitors causes synthetic lethality in cells with deficient HRD because these cells can no longer repair DNA through non-homologous repair.[3] About 50 percent of epithelial ovarian cancers exhibit HRD, which is caused by BRCA and other mutations (Exhibit 1).[4]

All women with high-grade serous ovarian cancer regardless of family history should have genetic testing. Testing at the time of diagnosis is important because of the availability of olaparib for first-line maintenance therapy after chemotherapy; previously PARP inhibitors were only indicated for recurrent

Exhibit 1: Homologous Repair Deficiency in Ovarian Cancer[4]

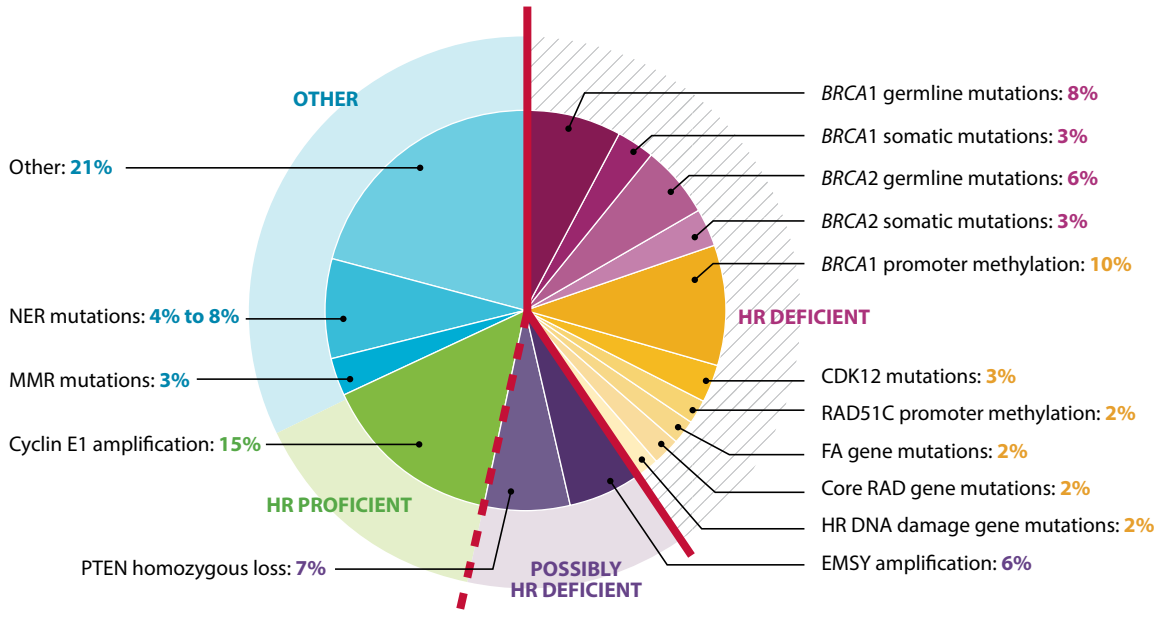


Exhibit 2: Genetic Testing[5-8]

Leading oncology societies recommend testing all women with ovarian cancer

NCCN	SGO	ASCO	ESMO
Genetic counseling and testing should be considered in women with a history of ovarian carcinoma, fallopian tube cancer, or primary peritoneal cancer	Women diagnosed with epithelial ovarian, tubal and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history	Genetic counseling and testing should be considered in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer even in the absence of family history	Patients with high-grade tumors should be tested for a germline *BRCA* mutation. Consideration should be given to testing tumors for a somatic *BRCA* mutation

NCCN = National Comprehensive Cancer Network; SGO = Society of Gynecologic Oncology
ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology

disease. Exhibit 2 outlines the recommendations from various professional organizations.[5-8] The recommended sequence is tumor BRCA first (larger population) and germline testing second with genetic counseling relative to patient and first-degree relatives' risk of other cancers and need for testing. Importantly up to 41 percent of patients with a BRCA mutation do not have a family history of ovarian cancer, thus family history should not be relied on as the only indicator for BRCA testing as it leads to significant under identification.[9]

Exhibit 3 shows the efficacy of PARP inhibitors in ovarian cancer for maintenance or treatment from the main trials and the FDA-approved indications.[10-16] Treatment is for recurrent disease instead of chemotherapy and provides a modest response rate and short duration of response. Maintenance is given after response to platinum-

Exhibit 3: PARP Inhibitors in Ovarian Cancer[10-16]

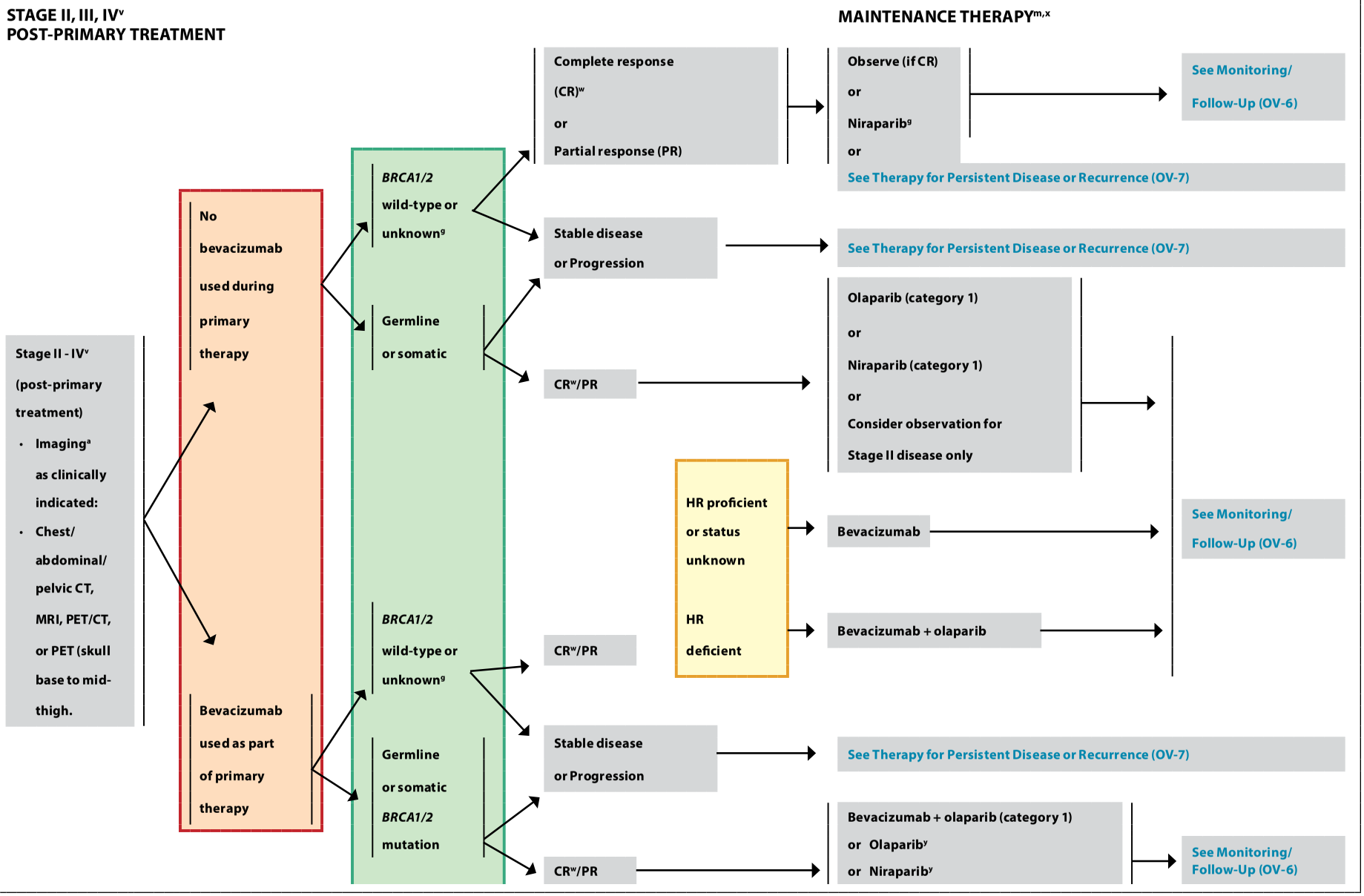
Agent	Dosing	FDA-Approved Indications	Setting/Efficacy/Trial
Niraparib	300 mg QD	**Treatment:** HRD ovarian cancer, > 3 prior therapies **Maintenance:** First-line after partial or complete platinum response. Platinum-sensitive ovarian cancer after response to platinum-based therapy.	**Treatment:** 20% ORR 8.3 months DOR **Maintenance:** 15.5 months PFS difference (gBRCAm); 9.1 months (HRD), 5.4 months (gBRCA-)
Olaparib	300 mg BID	**Treatment:** gBRCAm ovarian cancer, > 3 prior therapies **Maintenance:** Platinum-sensitive ovarian cancer after response to platinum-based therapy. First-line after partial or complete platinum response if gBRCAm or sBRCAm. First-line after partial or complete platinum response with bevacizumab in HRD ovarian cancer.	**Maintenance:** 13.6 months PFS difference (gBRCAm) **Maintenance:** 70% lower risk of disease progression or death compared to placebo. 3-year PFS 60% versus 27% with placebo **Treatment: (400 mg BID)** 26% ORR 42% SD8w
Rucaparib	600 mg BID	**Treatment:** gBRCAm/sBRCAm ovarian cancer, > 2 prior therapies **Maintenance:** Platinum-sensitive ovarian cancer after response to platinum-based therapy.	**Maintenance:** 11.2 months PFS difference (gBRCAm), 8.2 months (HRD); 5.4 months (ITT) **Treatment:** 54% ORR 9.2-month DOR

gBRCAm = germline BRCA mutation; sBRCAm = somatic BRCA mutation PFS = progression-free survival;
SD8W = stable disease for 8 weeks; ITT = Intent to Treat; ORR = overall response rate; DOR = duration of response

based chemotherapy in Stage II, III, and IV disease. The role of maintenance therapy is to delay disease progression, postpone the need for subsequent chemotherapy, and potentially improve the long-term survival of patients who achieve a response to platinum-based chemotherapy. Survival data from the maintenance setting are not yet available; PARP inhibitors do improve progression-free survival (PFS). The National Comprehensive Cancer Network (NCCN) Guideline recommendations for maintenance are shown in Exhibit 4.[17] Although rucaparib has a maintenance indication, it is not yet included in the NCCN Guidelines for this use.

The future with PARP inhibitors is to make them more effective through combination with other agents, find ways to overcome resistance, and make them work when they should not (non-HRD disease). Combinations of PARP inhibitors and chemotherapy (DNA-damaging agents), immune checkpoint inhibitors, and radiation therapy are under investigation as first-line primary treatment and for later-lines of therapy. Various agents to overcome PARP inhibitor resistance are also under development. To expand the number of patients who could benefit from a PARP inhibitor, methods of inducing HRD in HR-proficient tumors are also being investigated. Recycling these agents for maintenance after platinum treatment for a relapse while on PARP inhibitor maintenance is another area of investigation. One trial showed that, in a heavily pretreated ovarian cancer population, rechallenge with maintenance olaparib following response to platinum-based chemotherapy provided a statistically significant improvement in PFS compared with placebo, regardless of BRCAm status.[18] Data from this trial have not yet been published.

Exhibit 4: NCCN Guidelines Version 1.2021 — Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer



[a]Imaging performed with oral and IV contrast unless contraindicated.
[g]In the absence of a *BRCA1/2* mutation, homologous recombination (HR) status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy (See OV-B).
[m]See Principles of Systemic Therapy (OV-C) and management Reactions (OV-D).
[v]Post-primary treatment recommendations for Stage II to IV high-grade serous or Grade 2/3 endometrioid carcinoma; consider for clear cell carcinoma or carcinosarcoma with a BRCA1/2 mutation.
[w]No definitive evidence of disease.
[x]Data are limited for maintenance therapy with a PARPi for patients with Stage II disease.
[y]After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARPi (olaparib or niraparib) for patients with a germline or somatic *BRCA1/2* mutation. However, based on the magnitude of benefit of PARPi maintenance therapy for other subgroups, single-agent PARPi can be considered.

Conclusion

PARP inhibitors are continuing to transform ovarian cancer patient outcomes. Genetic testing, irrespective of family history, is essential to identify eligible patients and provide benefit through treatment and counseling. The future of ovarian cancer management is bright with many different avenues for expanding the use of PARP inhibitors.

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Diagnosing and Treating Excessive Daytime Sleepiness in Narcolepsy or Obstructive Sleep Apnea

Suresh Kotagal, MD

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

Summary

Daytime sleepiness can be a safety and quality of life issue. Two important treatable causes are narcolepsy and obstructive sleep apnea (OSA). Several pharmacologic agents are available to manage narcolepsy and some of these are useful in managing residual daytime sleepiness related to OSA.

Key Points

- A diagnostic delay is quite common with narcolepsy.
- Medications such as oxybates, pitolisant and solriamfetol, are more efficacious than methylphenidate, amphetamines, modafinil and armodafinil for narcolepsy.
- Residual daytime sleepiness is an important comorbidity of OSA.
- Modafinil, armodafinil, and solriamfetol may be prescribed as adjuncts to enhance daytime alertness and improve quality of life in OSA.

DAYTIME SLEEPINESS IS A PROBLEM FOR many people and the consequences of daytime sleepiness are numerous.[1] Decreased attention and concentration, emotional lability, increased utilization of inpatient and ambulatory health services, and impaired productivity at work and school have all been documented. Daytime sleepiness is also a public health hazard (e.g., driving-related accidents, workplace accidents). It is also linked to depression and increased risk of substance abuse in teens.

Daytime sleepiness is assessed clinically and with sleepiness and quality of life survey instruments, actigraphy, and nocturnal polysomnography. The differential diagnosis for daytime sleepiness is abnormal sleep hygiene, circadian rhythm disorder, depression, anxiety, medications, structural brain lesions, idiopathic hypersomnia, Kleine-Levin syndrome, narcolepsy, and obstructive sleep apnea (OSA). Clinical assessment can identify that a patient is visibly sleepy, apathetic, anxious, or depressed. The Epworth Sleepiness Scale (ESS) is the major validated instrument for assessing daytime sleepiness.[2] Actigraphy is a validated method of objectively measuring sleep parameters and average motor activity over a period of days to weeks using a noninvasive accelerometer. It helps understand sleep-wake habits in the ambulatory environment but is generally not covered by third-party payers. A nocturnal polysomnogram is indicated and utilized in the routine investigation of daytime sleepiness. Polysomnography, also called a sleep study, is a comprehensive test used to diagnose sleep disorders. Polysomnography records brain waves, blood oxygen, heart rate and breathing, as well as eye and leg movements during the study. Two other measures are the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT). The MSLT measures the mean speed with which the patient falls asleep during multiple daytime naps. Time from "lights out" to sleep onset on an electroencephalogram (EEG) is defined as sleep latency. The patient should be medication-free for at least two weeks to accurately assess MSLT. Normal is more than 10 minutes and in narcolepsy it is less than eight minutes. The MWT measures how long a patient can stay awake in a dark, quiet environment during the daytime while an EEG is

Exhibit 1: Narcolepsy Subtypes[3]

Type 1	Type 2
• Excessive daytime sleepiness	• Excessive daytime sleepiness
• Disturbed night sleep	• Disturbed night sleep
• Hypnagogic hallucinations	• Hypnagogic hallucinations
• Sleep paralysis	• Sleep paralysis
• Cataplexy	• No cataplexy
• Central nervous system orexin is low (< 110 pg/ml)	• Central nervous system orexin is normal

Exhibit 2: Step-Wise Process for Accurately Diagnosing Narcolepsy

- **Step 1** Sleep diaries for 10 to 14 days to record sleep and awake habits.
- **Step 2** Wrist actigraphy for 10 to 14 days to exclude confounders like inadequate sleep time or circadian rhythm sleep wake disorders.
- **Step 3** Nocturnal polysomnogram (PSG), to exclude other sleep disorders and document abnormal patterns of REM sleep.
- **Step 4** Multiple sleep latency test (MSLT) the day after PSG to establish excessive sleepiness and presence of sleep-onset REM periods.
- **Step 5** Urine drug screen during MSLT to exclude drug-seeking behaviors.

being monitored. A sleep latency of 28 to 30 minutes suggests satisfactory daytime alertness. The MWT is conducted while the patient is receiving treatment to enhance alertness. Polysomnography, MSLT, and MWT are performed in sleep centers.

Narcolepsy is a chronic sleep disorder characterized by overwhelming daytime drowsiness and sudden attacks of sleep. There are two types of narcolepsy (type 1 and type 2) which are distinguished by orexin levels and cataplexy (Exhibit 1).[3] Cataplexy, the abrupt loss of tone in extensor groups of muscles (neck, trunk, and lower extremities), may lead to loss of balance, falls, accidents, and social embarrassment. Exhibit 2 shows a five-step process to accurately diagnose narcolepsy.

In an analysis from Symphony Health claims data, the prevalence of narcolepsy in the United States (U.S.) was 38.9 per 100,000 in 2013 and 44.3 per 100,000 in 2016, a 14 percent increase.[4] This prevalence is slightly more than rheumatoid arthritis and slightly less than multiple sclerosis. The increase in prevalence may be due to increased awareness leading to increased diagnosis.

The onset of narcolepsy often occurs during childhood or adolescence (62%).[5] Few people are diagnosed after age 35. Typically, there is a long lag between onset of symptoms and clinical diagnosis. In one survey, most participants reported receiving a diagnosis of narcolepsy more than one year after symptom onset.[5] The strongest predictor of this delayed diagnosis was pediatric onset of symptoms (odds ratio = 2.4, $p < 0.0005$).

There are several reasons why narcolepsy is under-diagnosed. Sleepy children are misdiagnosed as being "hyperactive" or mistaken to be lazy and unmotivated. Though mood swings and apathy are manifestations of hypersomnia, they can be mistaken as manifestations of depression. In adults, chronic sleepiness is generally under-recognized as a neurological symptom due to insufficient awareness by health providers. Also, cataplexy can be subtle and easily overlooked. Lastly, there is limited access to sleep centers and sleep specialists who are skilled at diagnosing narcolepsy.

The exact cause of narcolepsy is unknown but it is thought to be caused by a lack of orexin (also known as hypocretin), which regulates wakefulness.

Exhibit 3: Pharmacologic Options for Narcolepsy[10]

Drug	Sleepiness	Cataplexy	Disturbed Night Sleep	FDA Indications
Modafinil/armodafinil	++	No effect		Excessive daytime sleepiness (EDS) in adult patients with narcolepsy or obstructive sleep apnea (OSA).
Pitolisant (Wakix®)	+++	++		EDS or cataplexy in adult patients with narcolepsy.
Sodium oxybate (Xyrem®)	++	+++	++	Cataplexy or EDS in patients 7 years of age and older with narcolepsy.
Calcium, magnesium, potassium, and sodium oxybates (Xywav®)	++	+++	++	Cataplexy or EDS in patients 7 years of age and older with narcolepsy. Idiopathic Hypersomnia (IH) in adults.
Solriamfetol (Sunosi®)	++	No effect		EDS associated with narcolepsy or OSA.
Venlafaxine/clomipramine	No effect	+		None related to narcolepsy or OSA.
Methylphenidate	++	No effect		Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

The lack of orexin is thought to be caused by the immune system mistakenly attacking the cells that produce orexin or the receptors that allow it to work.[6] Histamine function is also altered in type 1 narcolepsy. Narcolepsy patients and knockout mice show a marked increase in histaminergic neurons in the tubero-mamillary region.[7] This change in histamine function may be a compensatory mechanism to overcome lack of orexin. Histamine agonists are now available for enhancing alertness.

In a community-based study of narcolepsy comorbidities, both at diagnosis and after prolonged follow-up, persistent comorbidities were revealed, including obesity, OSA, chronic low-back pain, psychiatric disorders in general, and endocrinopathies.[8] The comprehensive management of narcolepsy requires monitoring and managing these important associated health conditions. Narcolepsy type 1 is strongly associated with obesity.[9] The obesity is present at symptom onset and is not caused by concomitant medications. The narcolepsy knockout-mouse model is also obese. Obesity may be related to orexin deficiency; binge eating and hyperphagia occur in some with type 1 narcolepsy.

General supportive measures for managing narcolepsy include regular sleep-wake schedules, brief planned naps during the day, regular exercise, psychological counseling, extra help at school with modifications in the academic program if needed, and dietary management for weight loss or to prevent further weight gain. Initially, medication management targets the symptom that is most bothersome to the patient, either sleepiness or cataplexy (Exhibit 3).[10] For sleepiness, starting with traditional stimulants (methylphenidate, modafinil, armodafinil) is reasonable. For cataplexy, starting with an oxybate is reasonable. At present, newer medications (solriamfetol and pitolisant) are prescribed when first-line agents have not been effective. Clinicians can consider adding a selective serotonin reuptake inhibitor (SSRI) for coexisting depression.

The two available oxybate preparations enhance activity of the gamma amino butyric acid (GABA) system in the central nervous system (CNS). The active moiety is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death. In narcolepsy, oxybate leads to slow wave sleep increases, sleep architecture stabilization, and diminished disruptions of nighttime sleep. Both daytime sleepiness and cataplexy are improved. These are liquid formulations that need to be administered in two nightly doses and administration timing is critical. The current oxybate formulations require twice nightly dosing, with doses given two and one-half to four hours apart. This is due to rapid absorption and elimination of the drug and may

Exhibit 4: Risk Stratification for OSA[12]

	0 Points	1 Point
Do you snore loudly?	No	Yes
Do you often feel tired, fatigued, or sleepy during the daytime?	No	Yes
Has anyone observed you stop breathing during sleep?	No	Yes
Do you have (or are you being treated for) high blood pressure?	No	Yes
BMI	≤ 35 kg/m^2	> 35 kg/m^2
Age	≤ 50 years	> 50 years
Neck circumference	≤ 40 cm	> 40 cm
Gender	Female	Male

STOP-BANG score to risk-stratify probability of having OSA.

A score of < 3 indicates a low risk of OSA, while a score of ≥ 3 indicates a high risk of OSA.

be associated with non-adherence to the treatment regimen. Because of potential drug diversion issues, the oxybates are dispensed through a centralized pharmacy.

The sodium oxybate product has a very high sodium content (1,640 mg in a 9-gm dose). The multi-salt product has a much lower sodium content (131 mg in a 9-gm dose) and is preferred in those with hypertension or other reasons for limiting sodium intake. Both products have similar efficacy and adverse event profile; they reduce cataplexy attacks (treatment effect difference: 2.4 to 12 per week) and ESS score (2 to 5 points). A once nightly sodium oxybate product that has both an immediate-release and extended-release component is under investigation.

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI). Compared to placebo, this agent produced statistically significant improvements on the MWT (7.7 minutes) and on the ESS (3.8 points) at 12 weeks. Pitolisant is a histamine-3 (H3) receptor antagonist/inverse agonist. This agent improves ESS score (2.2 to 3.1) and cataplexy (2 per week).

There are some limitations in our current narcolepsy drug treatment recommendations. Quality of life measures have not been consistently evaluated in clinical trials, especially for the older preparations such as methylphenidate and the amphetamines. Impact of hypersomnia on social life, and the cost of drug treatment are not routinely taken into consideration by all parties concerned. Head-to-head comparisons about treatment efficacy are lacking. The oxybates, pitolisant, solriamfetol are more efficacious than methylphenidate, amphetamines, modafinil and armodafinil but because of cost the stimulants are used more often. In pediatrics, except for oxybates and methylphenidate, the prescription of narcolepsy drugs is on an "off-label" basis.

Obstructive sleep apnea (OSA) occurs both by itself and as a comorbidity of narcolepsy. It is partial (hypopnea) or complete upper airway occlusion (apnea) during sleep, with associated 4 percent or greater oxygen desaturation. It affects about 5 percent of adults in the U.S. Mild OSA [apnea hypopnea index (AHI) > 5] is found in 17 percent of individuals and moderate to severe OSA (AHI > 20) is found in about 7 percent.[11] Age, gender, and body mass index have a major impact on prevalence. Exhibit 4 shows a risk stratification for OSA.[12]

In OSA, recurrent oxygen desaturation leads to increased sympathetic activity with vasoconstriction, tachycardia, increased blood pressure, supraventricular tachycardia, and ventricular ectopy. Repeated closing and opening of the upper airway activates inflammation resulting in a release of inflammatory mediators, leptin resistance and hyperinsulinemia, and increased platelet adhesiveness which increases risk for diabetes and cardiovascular disease. Sleep fragmentation occurs as a consequence of hypoxia. Most patients who have daytime sleepiness, have an ESS score of > 10.

Positive airway pressure (PAP) is the first-

line treatment of choice. Unfortunately, PAP is associated with non-adherence in about one-third of users. Even despite adequate treatment of OSA, daytime sleepiness persists in about 12 to 65 percent of patients.[13,14] Residual excessive daytime sleepiness (REDS) is defined as a score of 11 or more on the ESS even when breathing and oxygenation parameters during sleep are normalized by successful OSA therapy. In a French study, the estimated prevalence of REDS was 6 percent after controlling for continuous positive airway pressure (CPAP) usage greater than six hours per day, depression, restless leg syndrome, and medications.[15]

A meta-analysis of 13 randomized controlled trials found no significant differences in overall and psychological quality of life (QOL) comparing values of PAP treated patients with controls, however, physical QOL improved.[16] One study found that long-term improvement in QOL might occur with the use of CPAP in people with severe and possibly moderate sleep apnea.[17] Improving REDS may improve QOL in OSA that is treated with PAP.

Modafinil and armodafinil improve subjective and objective daytime sleepiness in those with residual EDS. In OSA, modafinil/armodafinil improved the ESS score (2.2 points, 95% CI 1.5 to 2.9) and the MWT over placebo (3 min).[18] Modafinil/armodafinil tripled adverse events and doubled adverse events leading to withdrawal but did not increase serious adverse events (hospitalizations or death). In one randomized trial, modafinil significantly improved subjective sleepiness in patients with untreated mild to moderate OSA.[19] The size of this effect is clinically relevant at 3 to 4 ESS points of improvement compared with only 1 to 2 points in CPAP clinical trials. Driving simulator performance and reaction time also improved on modafinil.

In REDS related to OSA, solriamfetol reduced ESS by 1.6 points.[20] The Patient Global Impression of Change, and the Clinical Global Impression of Change also improved in the treatment group. Transient adverse events were headache, nausea, and insomnia. Long-term solriamfetol treatment was associated with clinically meaningful, sustained improvements in functional status, work productivity, and QOL for up to 52 weeks in one trial that included both those with narcolepsy and OSA.[21] Adverse events were similar between narcolepsy and OSA. Common adverse events (≥ 5%) were headache, nausea, insomnia, dry mouth, anxiety, and decreased appetite.

Pitolisant, used as adjunct to CPAP therapy for OSA with REDS, despite good CPAP adherence, significantly reduced subjective and objective sleepiness and improved participant-reported outcomes and physician-reported disease severity.[22] ESS significantly decreased with pitolisant compared with placebo (-2.6; $p < .001$), and the rate of responders to therapy (ESS ≤ 10 or change in ESS ≥ 3) was significantly higher with pitolisant (71.0% versus 54.1%; $p = .013$). Adverse event occurrence (headache and insomnia) was higher in the pitolisant group compared with the placebo group (47.0% and 32.8%, respectively; $p = .03$). No cardiovascular or other significant safety concerns were reported. Pitolisant is not currently FDA approved for EDS in OSA.

Conclusion

A diagnostic delay is quite common with narcolepsy. Patients with narcolepsy should be screened systematically and treated for medical or psychiatric comorbidities and quality of life issues. Medications such as oxybates, pitolisant, and solriamfetol are more efficacious than methylphenidate, modafinil, and armodafinil but head-to-head trials are lacking. Sleep medicine specialists, patient support groups and third-party payers need to work together to achieve optimum outcomes.

Residual daytime sleepiness is an important co-morbidity of OSA that impacts QOL. Pharmacological agents such as modafinil, armodafinil, and solriamfetol may be prescribed as adjuncts to enhance daytime alertness and improve QOL.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of HER2-Positive Advanced Breast Cancer: An In-Depth Look at New and Emerging Therapies

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

Summary

The treatment of human epidermal growth factor two (HER2) positive metastatic breast cancer continues to evolve. Significant survival increases have occurred with the development of HER2-targeted therapies. Recent changes to the treatment guidelines have updated the recommended second-line therapy.

Key Points

- First-line therapy is pertuzumab, trastuzumab, and docetaxel or paclitaxel.
- Second-line therapy is now fam-trastuzumab deruxtecan.
- There are many options for third-line and beyond therapy.
- Identifying HER2-low disease and treatment with antibody-drug conjugates is a paradigm shift in managing metastatic breast cancer.

OVER THE LAST SEVERAL YEARS, THERAPY advancements have led to significant survival gains in human epidermal growth factor two positive (HER2+) breast cancer, such that it now has the best overall survival of all types of breast cancer.[1] Neratinib, tucatinib, fam-trastuzumab deruxtecan, and margetuximab have all been FDA approved for HER2-positive metastatic breast cancer (HER2+ mBC) since 2019.

First-line treatment for HER2+ mBC is pertuzumab, trastuzumab, and docetaxel (paclitaxel if not eligible for docetaxel) (Exhibit 1).[2] The addition of pertuzumab to the previous standard of care for first-line treatment of trastuzumab and docetaxel improved landmark eight-year overall survival (OS) by 14 percent.[3]

Until recently, the antibody-drug conjugate (ADC) ado-trastuzumab emtansine was the preferred second-line therapy because it improved median OS by 5.8 month compared to lapatinib/capecitabine.[4] It is now a category 2A other recommended regimen because of recent data on fam-trastuzumab deruxtecan, another ADC. Exhibit 2 shows how an ADC kills HER2+ cancer cells by delivering chemotherapy directly into HER2+ cells and by bystander killing afterwards if the chemotherapy is cell membrane permeable.[5] Fam-trastuzumab deruxtecan has the ability to kill neighboring non-HER2+ tumor cells (bystander killing) because of high cell membrane permeability and this has led to it also being evaluated in non-HER2+ breast cancer. It also delivers a higher drug payload than ado-trastuzumab emtansine. In a heavily pretreated HER2 mBC population, there was a 61 percent response rate with this agent with a 6 percent complete response and a 14.8-month duration of response in a nonrandomized study which led to FDA-accelerated approval.[6] The estimated median OS was 24.6 months with 85 percent of patients alive at 12 months and 74 percent at 18 months. Importantly, however, this agent can cause interstitial lung disease which has led to some deaths. This agent is being studied against ado-trastuzumab emtansine in the second-line setting in patients with HER2 mBC previously treated with trastuzumab and a taxane in a Phase III open

Exhibit 1: NCCN® Guidelines[2]

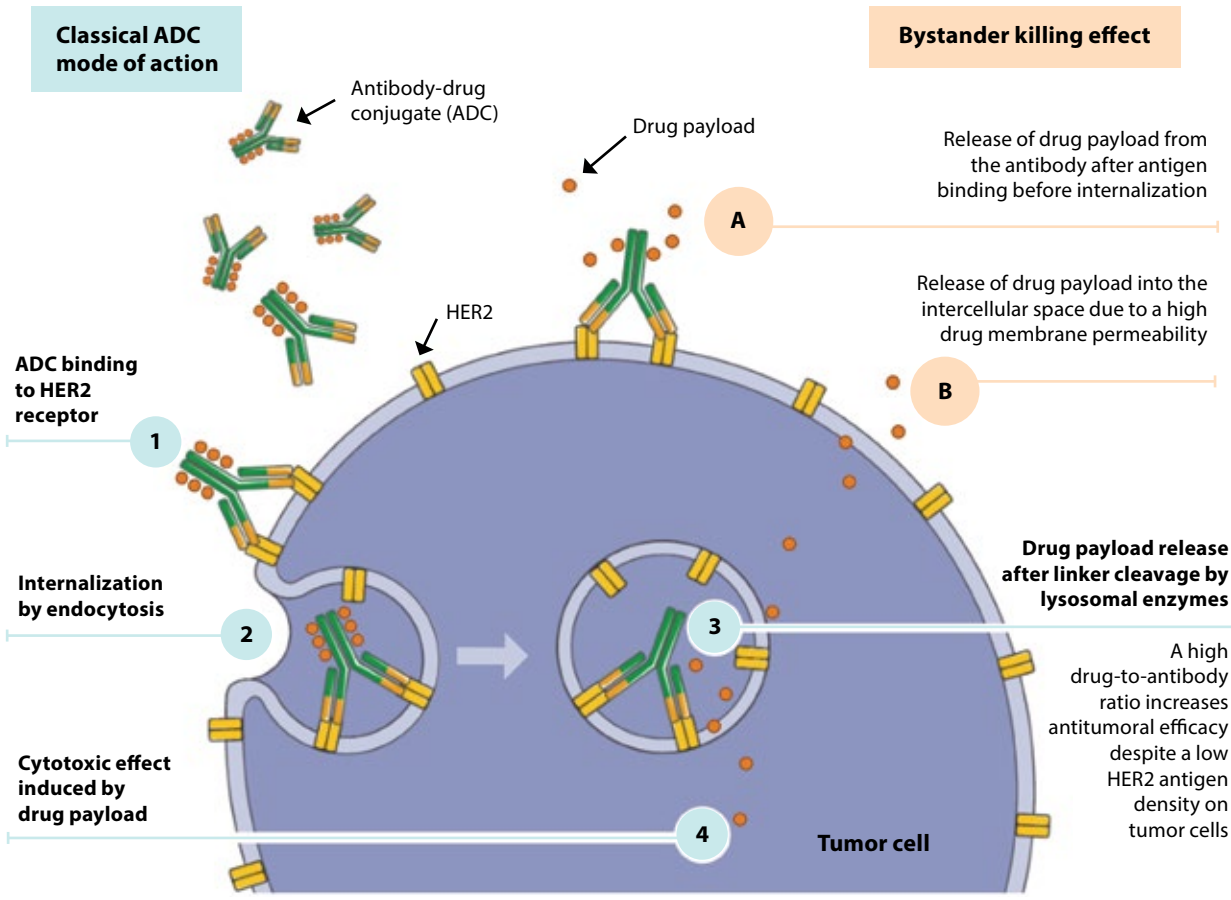
Setting	Regimen	NCCN Category of Preference (Category of Evidence)
First-Line	Pertuzumab + trastuzumab + docetaxel	Preferred regimen (1)
	Pertuzumab + trastuzumab + paclitaxel	Preferred regimen (2A)
Second-Line	Fam-trastuzumab deruxtecan-nxki	Preferred regimen (1)
	Ado-trastuzumab emtansine (T-DM1)	Other recommended regimen (2A)
Third-Line and Beyond	Tucatinib + trastuzumab + capecitabine	Other recommended regimen (1) (Preferred in patients with both systemic and CNS progression in the third-line setting and beyond; may be given second-line)
	Trastuzumab + docetaxel or vinorelbine	Other recommended regimen (2A)
	Trastuzumab + paclitaxel ± carboplatin	Other recommended regimen (2A)
	Capecitabine + trastuzumab or lapatinib	Other recommended regimen (2A)
	Trastuzumab + lapatinib (without cytotoxic therapy)	Other recommended regimen (2A)
	Trastuzumab + other agents	Other recommended regimen (2A)
	Neratinib + capecitabine	Other recommended regimen (2A)
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine	Other recommended regimen (2A)

label trial. Preliminary data from this trial has been presented at a professional meeting but is not yet published.[7] Median progression-free survival (PFS) was not reached for fam-trastuzumab deruxtecan versus 6.8 months for ado-trastuzumab emtansine; PFS improvements favored fam-trastuzumab deruxtecan in all subgroups. The estimated 12-month OS event rates were 94.1 percent versus 85.9 but this was not statistically significant based on preset cut points. Median treatment duration was 14.3 months (range, 0.7 to 29.8) versus 6.9 months (range, 0.7 to 25.1). Similar rates of treatment-related adverse events occurred with the two agents and no drug-related deaths occurred. Adjudicated drug-related interstitial lung disease (ILD) occurred in 10.5 percent of patients with fam-trastuzumab deruxtecan (9.7% Grade 1/2; 0% Grade 4/5) versus 1.9 percent with ado-trastuzumab emtansine (all Grade 1/2). The encouraging OS trend at the time of the first interim analysis led to fam-trastuzumab deruxtecan being recommended over the other ADCs for second-line HER2 mBC. The 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 pertuzumab which is also an FDA-approved indication.[2]

Prognosis worsens as patients progress through multiple regimens in the metastatic setting. Median PFS decreases with each line of therapy from 18.5 months with first-line pertuzumab, trastuzumab, and docetaxel to 9.6 months with ado-trastuzumab emtansine.[3,4] Treatment decisions for third-line and beyond should reflect risks and benefits of treatment, presence of brain or visceral metastases, patient performance status, and patient preferences.[2] Multiple lines of therapy are appropriate as long as the patient has a reasonable performance status and is willing to receive therapy.

Tucatinib is a selective HER2 inhibitor and neratinib is an irreversible pan-HER inhibitor (HER 1, 2, 4). These two small-molecule tyrosine kinase inhibitors are additions to lapatinib, a reversible inhibitor of HER1 and HER2, which was previously approved. These agents bind to the intracellular tyrosine kinase domains of HER2 and other HER receptors. Exhibit 3 shows where these agents work compared to pertuzumab, trastuzumab, and ado-trastuzumab emtansine.[8] Because of a high rate of diarrhea and only modest improvements in PFS and OS compared to lapatinib, neratinib use is reserved for later-line use. Tucatinib appears

Exhibit 2: Mechanism of Action of HER2-Directed Antibody Drug Conjugate[5]

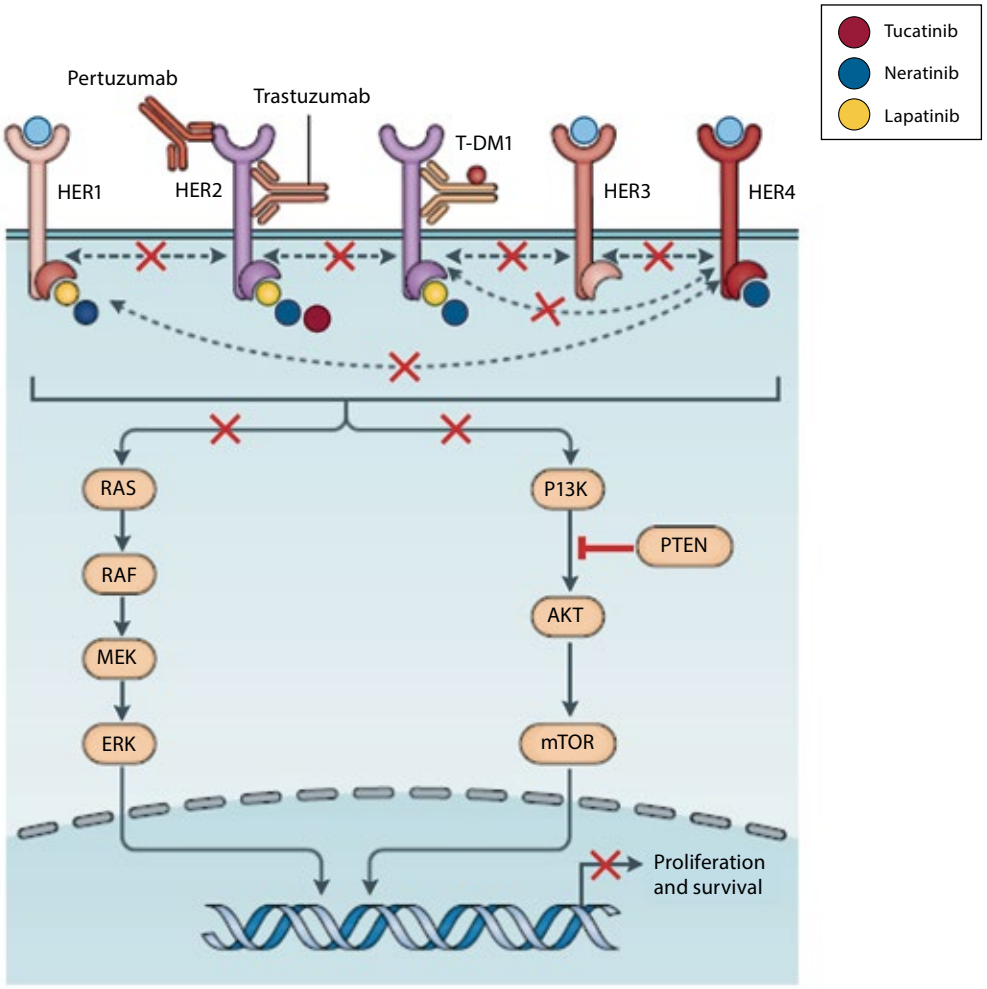


ADC = antibody-drug conjugate

particularly useful for third-line therapy when the patient has brain metastases. Breast cancer has the second highest incidence of brain metastasis among all cancers with about 36 percent of those with HER2 mBC developing them.[9] Tucatinib combined with trastuzumab and capecitabine significantly improved PFS and OS compared to trastuzumab/capecitabine/placebo in the third-line setting with 45 percent of the subjects having previously untreated brain mets.[10] The overall response rate for brain metastases was 47.3 percent versus 20 percent with placebo/trastuzumab/capecitabine. The risk of developing new central nervous system lesions or death was reduced by 48 percent in all patients with or without brain metastases with tucatinib addition. The combination of tucatinib/trastuzumab/capecitabine is a category 1 recommendation for third-line treatment.[2] The NCCN Guidelines also note that tucatinib/trastuzumab/capecitabine is an option as second-line treatment, especially for those with brain metastases.

Margetuximab in combination with chemotherapy was FDA approved in December 2020 for the treatment of adult patients with HER2 mBC who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. This monoclonal antibody was designed to improve immune system response over trastuzumab. The SOPHIA Phase III randomized open-label trial compared margetuximab plus chemotherapy to trastuzumab plus chemotherapy. Eligible patients had disease progression on two or more prior anti-HER2 therapies and one to three lines of therapy for metastatic disease. Interim median OS was 21.6 months with margetuximab versus 19.8 months with trastuzumab ($p = 0.33$); at the second interim OS analysis, median OS was 21.6 versus 19.8 months and in CD16A F allele carriers 23.7 versus 19.4 months.[11,12] Margetuximab appears to be most efficacious in patients with a CD16A-185 F genetic mutation of the FC receptor; the OS benefit is approximately four months compared to

Exhibit 3: HER2-Targeted Tyrosine Kinase Inhibitors[8]



T-DM1 = ado-trastuzumab emtansine

two months in those without the mutation. This particular mutation reduces binding of trastuzumab and thus reduces its efficacy. In patients without this mutation, the two agents appear similarly effective. The CD16A-185 F mutation is found in about 80 percent of patients.

Several agents are under investigation for HER2 mBC. One of these agents is another ADC, vic-trastuzumab duocarmazine. In the global Phase III TULIP trial in HER2 mBC, treatment with vic-trastuzumab duocarmazine significantly improved PFS in comparison with standard chemotherapy in previously treated patients (7.0 months versus 4.9 months).[13] Ocular toxicity was the most prevalent safety event but interstitial lung disease was reported including Grade 3 or worse events in 2.4 percent patients.

There is a paradigm shift ongoing in the definition of HER2 status in breast cancers.[14] HER2-low, which is on the spectrum between HER2-negative and HER2-positive, is being investigated as a potential biomarker for ADC efficacy. The vast majority of HER2-low tumors have low HER2 signaling which makes them vulnerable to HER2-targeted therapies but there is a large biological heterogeneity of HER2-low disease and a need to implement reproducible and sensitive assays to measure low HER2 expression.[15] A Phase III trial in HER2-low mBC (DESTINY-BREAST04) found that fam-trastuzumab deruxtecan improved median PFS by 4.8 months and median OS by 6.6 months compared with standard single-agent chemotherapy in a patient population already treated with one to two prior lines of chemotherapy for metastatic disease.[16]

Roughly 50 percent of patients with breast cancer are classified with HER2-low expression based on their immunohistochemistry (IHC) and/or in situ hybridization (ISH) findings (i.e., IHC 1+ or IHC 2+/ISH-). Based on historically poor responses of HER2-negative disease to HER2-targeted therapies, this group of patients ends up placed into the larger HER2-negative category on the pathology reports used by medical oncologists to determine treatment. Not all HER2-targeted agents function the same way, which explains why fam-trastuzumab deruxtecan succeeded where other HER2-targeted agents have failed. Whereas monoclonal antibodies or small-molecule tyrosine kinase inhibitors directed against HER2 work by blocking the oncogenic signaling activity of HER2, an ADC simply relies on HER2 to serve as a homing beacon for the delivery of highly cytotoxic chemotherapy and in the case of fam-trastuzumab deruxtecan, the deruxtecan can cross back out of the HER2-positive cell and kill other adjacent cells. Two studies are currently ongoing, DESTINY-Breast06 (NCT04494425) and DAISY (NCT04132960), to determine the minimum IHC HER2 expression threshold for fam-trastuzumab deruxtecan activity. Once the DESTINY-Breast 04 trial is published, the NCCN Guidelines will likely recommend use in those with HER2-low disease, however, clinicians may have already adopted use based on the preliminary data presentation.

Conclusion

First-line therapy for HER2 mBC continues to be chemotherapy plus HER2 targeting agents. Second-line therapy is now an ADC with the bystander killing ability. There are many options for third-line and beyond therapy but duration of response declines with each line of therapy. A new change in HER2 mBC management is the identification of HER2-low disease and treatment with fam-trastuzumab deruxtecan.

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Patient-Focused Treatment Decisions in the Management of Multiple Sclerosis

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http://www.namcp.org/home/education, and then click the activity title.

Summary

The treatment of multiple sclerosis (MS), a disabling immune-mediated disease, continues to evolve. There are numerous effective disease-modifying therapies which vary in efficacy, safety, and tolerability. Treatment targets are changing to better define disease activity and optimally prevent long-term disability.

Key Points

- Treating early with effective disease-modifying therapy and having a low threshold to switch and/or escalate therapy are key to managing MS.
- There is no-one-size-fits-all philosophy in choosing treatment.
- Treatment is selected while balancing efficacy, safety, and tolerability for each patient in a shared decision-making format.
- Current clinical and paraclinical biomarkers can be helpful for assessing treatment success or failure, although combining outcomes may be more informative.

MULTIPLE SCLEROSIS (MS) IS AN IMMUNE mediated inflammatory disease of myelin, the insulating sheath around axons. Characterized by inflammatory plaques or scars in the deep white matter of the brain and spinal cord, it is the most common cause of non-traumatic neurologic disability in young adults.

In MS, auto-reactive T lymphocytes and B cells attack myelin causing demyelination and axonal/neuronal injury. Irreversible axonal damage occurs from the onset of disease but is clinically silent until a threshold of axonal loss is exceeded. Inflammation predominates in the early phases of the disease.

There are four clinical subtypes of MS and one possible MS precursor. Radiologically isolated syndrome (RIS) is evidence of central nervous system (CNS) damage suggestive of MS on magnetic resonance imaging (MRI) but no clinical symptoms and clinical evidence of demyelinating disease (a current criterion for MS diagnosis) is lacking.[1] This is found incidentally when a person has a MRI for an unrelated medical indication. Thirty to 50 percent of those with RIS will progress to MS within five years.[2] Clinically isolated syndrome (CIS) is the first acute or subacute episode of neurologic disturbance of the type seen in MS and is due to a single white matter lesion.[3] Up to 85 percent of MS cases start with CIS which most commonly presents as optic neuritis, partial myelitis, or brainstem/cerebellar syndrome and should be treated as MS. Relapsing-remitting MS (RRMS) are episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery and no apparent progression of disease.[4] RRMS can be further characterized as active or not active and worsening or stable. Primary progressive and secondary progressive are the other two subtypes.

Most patients with MS who are untreated will develop disability. To prevent disability, prompt treatment within the first few years of symptom development is key to preserving as much function as possible. The available treatments are effective in RRMS but not as effective in progressive disease and do not restore damaged tissue. Another reason to treat early is that symptoms and relapses correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early RRMS.

Exhibit 1: Comparing Disease-Modifying Treatments for MS[5-17]

Drug	Potency	Safety	Tolerability	NEDA
Natalizumab	+++	+ or +++*	+++	30% over placebo 75.4% over four years (open label, single arm)
Ocrelizumab Ofatumumab	+++	++	+++	Ocrelizumab: 21% over IFNβ Ofatumumab: 36.6% over teriflunomide
Alemtuzumab	+++	+	+++	15% over IFNβ
Cladribine	+++	+	++	28% over placebo (at 96 weeks)
Fingolimod Siponimod Ozanimod Ponesimod	++	++	+++	Fingolimod: 20% over placebo > dimethyl fumarate in DMT experienced patients 59.6% NEDA-3, 37.5% NEDA-4 (single arm) Siponimod: not reported Ozanimod: 7.6% over IFN Ponesimod: 8.6% over teriflunomide
Dimethyl fumarate Diroximel fumarate	++	++	++	Dimethyl fumarate: 13% over placebo and equal to fingolimod in naïve patients, 6% over glatiramer Diroximel fumarate: not reported
Glatiramer	+	+++	+++	12% to 19% over placebo 2% over IFNβ
IFNβ's	+	+++	++	19% over placebo
Teriflunomide	+	++	+++	9% over placebo

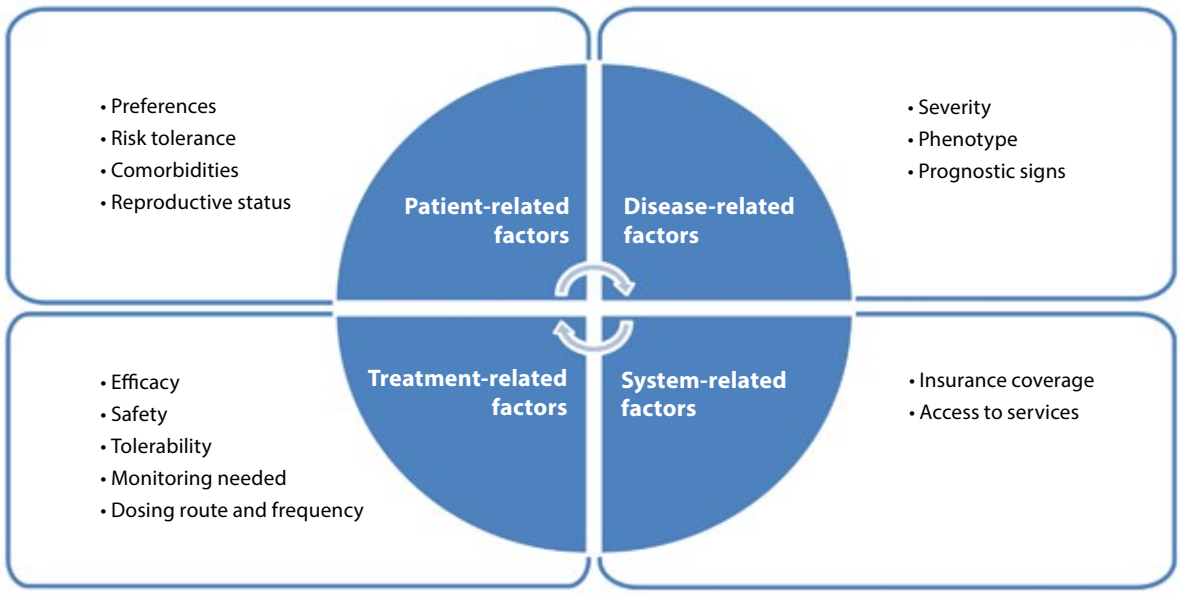
NEDA = no evidence of disease activity; IFN = interferon
Subjective ratings: + = low (worst), ++ = moderate, +++ = high (best)
* Depends on John Cunningham Virus status. Negative JCV best safety; Positive JCV worst safety

Disease-modifying treatment (DMT) helps minimize axonal injury, which yields irreversible disability. Clinically symptomatic relapses and paraclinical findings on MRI, optical coherence tomography (OCT), and cerebrospinal fluid analysis are associated with risk of disease activity and disability and are used to measure efficacy of DMT. OCT is a newer method for analyzing neurodegeneration by capturing thinning of the retinal nerve fiber layer.

The MS neurotherapeutic landscape is plentiful and expanding. Newer DMTs appear to be more effective than older general immunosuppressants but have additional short- and long-term safety concerns. All of the FDA-approved therapies reduce annual relapse rate, accumulation of disability, and MRI evidence of disease but their potencies, safety, and tolerability vary. Exhibit 1 presents those three issues on a relative + to +++ scale along with No Evidence of Disease Activity (NEDA) rates from clinical trials.[5-17] Most trials have measured NEDA-3 (no relapses, no disability progression, and no MRI activity) but some also have measured NEDA-4. NEDA-4 is defined as meeting all NEDA-3 criteria plus having an annualized brain volume loss (a-BVL) of ≤ 0.4 percent and may be a better predictor of long-term outcomes. Natalizumab, ocrelizumab, ofatumumab, alemtuzumab, and cladribine are the most potent agents but also have the most safety risks.

Therapy selection is a balance between DMT efficacy, safety, and tolerability and various disease, patient, and health-system-related factors (Exhibit 2).[18] Treatment decisions should be made using a

Exhibit 2: Considerations in Treatment Selection[18]

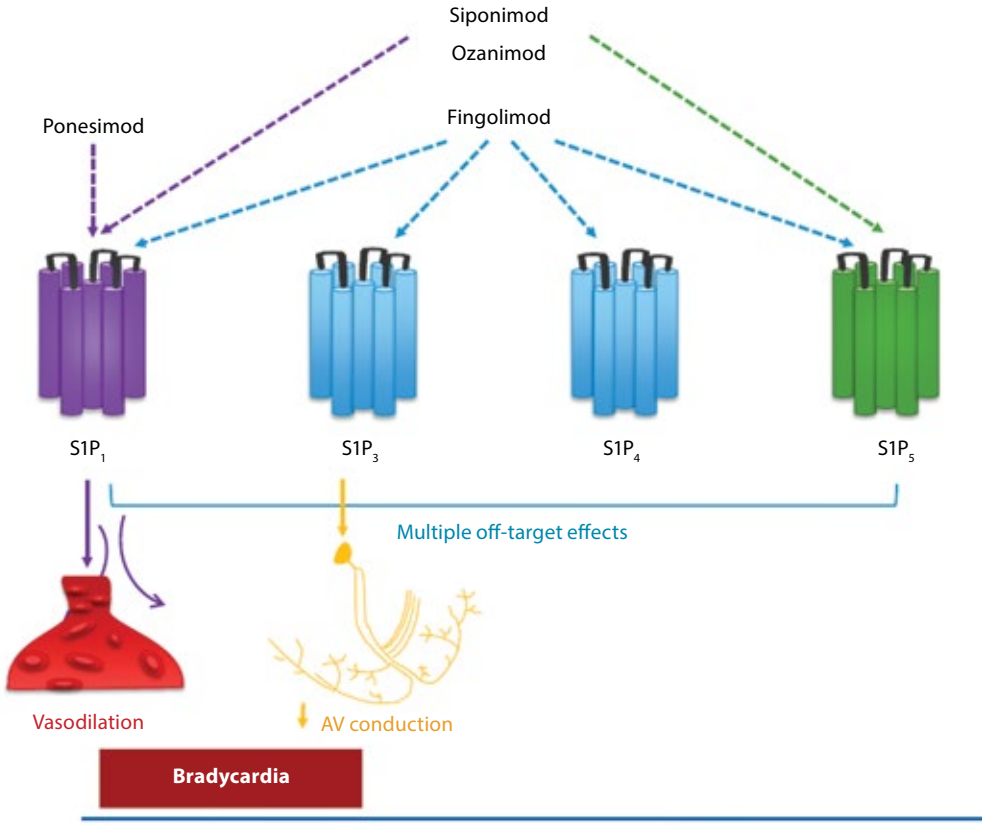


shared-decision process between the patient and clinician. Therapy should be tailored to an individual patient's prognosis and risk for disability worsening. MRI findings are an excellent prognostic predictor and very good early predictor of treatment response.

Traditionally, MS has been treated with an escalation approach, starting patients on a modestly effective DMT, and subsequently escalating to a higher efficacy DMT when there is evidence of clinical and/or radiologic breakthrough activity. With the development of higher efficacy therapies and emerging data showing the potential positive long-term impact of these therapies when started earlier in the disease course, many clinicians have shifted to an early aggressive treatment approach (induction approach) in which patients are initially started on a higher efficacy DMT.[19] It is now standard of care to begin patients with concerning prognostic features on high-efficacy therapies. An active escalation approach may be appropriate in patients with lower-risk prognostic features. No study so far has demonstrated worse outcomes by trying a therapy for six to 12 months and escalating for evidence of disease activity but trials are ongoing to better evaluate induction versus escalation.[20,21]

The sphingosine 1-phosphate (S1P) receptor modulators class is one area of significant treatment expansion with four available agents since the approval of ponesimod in 2021. S1P regulates diverse cellular responses involved in immunity, heart rate, smooth muscle tone, and endothelial barrier function. Subtype 1 S1P receptors (S1P1) are expressed on the surfaces of lymphocytes and are important in regulating egression from lymph nodes.[22] In MS, the S1P receptor modulators indirectly antagonize the S1P1 receptor's function and sequester lymphocytes in lymph nodes resulting in the depletion from the circulation and hence immunosuppression.[23] Fingolimod was the first S1P agent approved in the United States (U.S.) in 2010 for relapsing MS. As shown in Exhibit 3, the newer generation agents, unlike fingolimod, interact with fewer S1P pathways and thus cause lower rates of off-target effects (including bradycardia and atrioventricular block). The selective S1P agents have the advantage of shorter half-lives and more rapid lymphocyte recovery post discontinuation. These differences allow flexibility in retreatment with other agents, aiding in washout to treat potential opportunistic infections, and addressing other treatment-related complications or eliminating the drug in unplanned pregnancy.[24] All four S1P receptor modulators are FDA approved for RRMS and all but fingolimod for active secondary-progressive MS. Ozanimod is also approved for moderate to severe active ulcerative colitis. The three newer agents have all been shown to be disease modifying with reduced CNS lesions, annualized relapse rate, and brain volume loss; none

Exhibit 3: Off-Target Effects of S1P Receptor Modulators



have been directly compared to each other.

No evidence of disease activity has become a treatment target in MS management but some have raised concerns that achieving NEDA is not enough for more subtle, progressive disease. For example, a patient with MS who has no new relapses, no new MRI lesions, and stable disability scores would be considered to have NEDA but may be struggling more at work and at home because of debilitating fatigue and worsening processing speed which suggest that the disease is not optimally controlled. Progression Independent of Relapsing Activity (PIRA) is an emerging target for therapy and was first introduced in 2018. It is defined as worsening disability (as measured by a valid scale) independent of relapses (within a defined period or in relapse-free patients). Patients with MS acquire disability either through relapse-associated worsening or PIRA. Studies have demonstrated that PIRA is common, occurs frequently in early MS, and happens even with highly effective MS therapies.[25] Overall, about half of disability worsening in RRMS occurs because of PIRA. Some studies are starting to report PIRA rates. For example, compared with teriflunomide, ofatumumab reduced six-month PIRA by 56 percent.[17] If a patient is not achieving adequate disease control with a given therapy, clinicians need to consider switching DMT. A different mechanism of action agent should be chosen. Exhibit 4 also shows other reasons why a change in therapy may be needed.

Numerous avenues of treatment are under investigation for managing MS including finding safer but highly-effective agents. Anti-CD20-mediated B-cell depletion via ocrelizumab and ofatumumab effectively treats MS but recent data shows that antibody-mediated extinction of B cells as a lasting immune suppression harbors the risk of humoral deficiencies over time.[26] Accordingly, more selective, durable, and reversible B-cell-directed MS therapies are needed.

Bruton's tyrosine kinase (BTK) inhibitors are the most recent class of B-cell-directed medications to be investigated for MS treatment. BTK is an enzyme

Exhibit 4: Reasons to Consider Switching Disease-Modifying Therapy

- Breakthrough disease activity
  - Definite relapses.
  - MRI activity (new/enlarging T2 lesions and/or Gaudium enhancing lesions), even if asymptomatic.
  - Examination changes suggestive of disability progression.
- Adverse events/intolerance
- Sub-optimal adherence
- JCV Ab seroconversion (e.g., natalizumab)
- NAb development (e.g., IFN beta, natalizumab)

JCV = John Cunningham virus; Nab = neutralizing antibodies

Exhibit 5: Clinical Trials – BTK Inhibitors

	EVOBRUTINIB	TOLEBRUTINIB (SAR442168)			FENEBRUTINIB	
PHASE II TRIAL	EVOLUTION 1: RMS EVOLUTION 2: RMS	GEMINI 1: RMS GEMINI 2: RMS	HERCULES: *NRSPMS	PERSEUS: PPMS	FENhance 1: RMS FENhance 2: RMS	FENtrepid: PPMS
INTERVENTIONS	75 mg BID Placebo	Tolebrutinib (dose not reported) Placebo	Tolebrutinib (dose not reported) Placebo		Fenebrutinib 600 mg Placebo	Fenebrutinib (dose not reported) Placebo
ACTIVE COMPARATOR	Teriflunomide	Teriflunomide	None		Teriflunomide	Ocrelizumab
PRIMARY OUTCOMES	ARR	ARR up to 36 months	Six-month CDP		ARR (up to 96 weeks) Time to 12-week CDP	Time to 12-week CDP
ESTIMATED COMPLETION	Primary: 2023 Total: 2026	2023	2024		2024	Primary: 2025 Total: 2028

RMS = relapsing multiple sclerosis; PPMS = primary-progressive multiple sclerosis; NRSPMS = non-relapsing secondary-progressive multiple sclerosis; ARR = annualized relapse rare; CDP = confirmed disability progression

centrally involved in B-cell receptor signaling and BTK inhibition inhibits antigen-triggered activation and maturation of B cells as well as their release of pro-inflammatory cytokines. BTK inhibition also functionally impairs the capacity of B cells to act as antigen-presenting cells for the development of encephalitogenic T cells; this resulted in a significantly reduced MS severity in mice. In contrast to anti-CD20, BTK inhibition silenced this key property of B cells in MS without impairing their frequency or functional integrity.

Evobrutinib is a selective oral BTK inhibitor that has been shown to inhibit B-cell activation both in vitro and in vivo and is one of three agents being investigated for MS. In a Phase II trial, patients with RRMS who received 75 mg of evobrutinib once daily had significantly fewer enhancing lesions during weeks 12 through 24 than those who received placebo.[27] No significant difference from placebo was seen in the annualized relapse rate or disability progression at any dose and evobrutinib can elevate liver enzymes. Exhibit 5 summarizes the ongoing clinical trials with BTK inhibitors in MS. Emergence of BTK inhibitors with a unique mechanism of action will increase options for patients with relapsing and progressive MS and these agents have an encouraging safety profile.

Conclusion

The MS neurotherapeutic landscape is rapidly evolving and becoming more complex. Treating early with effective DMT and having a low threshold to switch and/or escalate therapy are key. There is no more one-size-fits-all philosophy in choosing treatment; treatment is selected while balancing efficacy, safety, and tolerability of DMTs for each patient in a shared decision-making format. Current clinical and paraclinical biomarkers can be helpful for assessing treatment success or failure, although combining outcomes may be more informative (NEDA and/or PRIA).

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Evolving Considerations in the Treatment and Management of Amyotrophic Lateral Sclerosis: Optimizing Strategies for Slowing Disease Progression

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

Summary

Amyotrophic Lateral Sclerosis (ALS) continues to be a fatal disease, but there are disease-modifying medications which can improve survival. Numerous critical therapies including disease-modifying and symptomatic treatment make this a complicated disease to manage that requires multidisciplinary care.

Key Points

- ALS needs to be diagnosed early and therapy initiated quickly.
- The goal is to prevent existing motor neurons from early death.
- Care of these complicated patients is best done in a specialty center.
- More and better ways to diagnosis and manage this disease are needed.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a progressive fatal neurodegenerative disease that affects upper and lower motor neurons. ALS and other neurodegenerative disorders are similar in that they affect similar patient populations and have an unknown cause and no cure. There is a highly predictable prognosis in most patients and unique loss of function with an eventual inability to move, speak, eat, and breathe. Some neurologic functions, including cognition, extraocular movements, bowel and bladder function, and sensation, are typically not affected in ALS patients.

The prevalence of ALS in the United States (U.S.) is 5.2 per 100,000, with an incidence of 1.7 per 100,000, reflecting short-average survival.[1-3] In the U.S., Caucasians have a higher rate of the disease than other ethnic groups and men have a higher rate than women (3:2).[3] An estimated 30,000 individuals in the U.S. have ALS. The five-year survival rate is 25 percent and 10-year survival is approximately 10 percent. Genetic factors cause 5 to 10 percent of cases [familial ALS (fALS)] and 90 to 95 percent of cases are considered sporadic (sALS).[1]

ALS has a major impact on a patient's and their caregiver's quality of life and financial status. This fatal diagnosis leads to tremendous emotional distress and anxiety. Patients have difficulty transitioning from being the main financial supporter of the family to being a dependent family member. The pace of disease progression can outpace learning and coping. For example, the patient may initially need a leg brace to manage foot drop. Just when they have mastered the brace, their progression to needing a walker occurs and then they may need to quickly proceed to a wheelchair. Families and caregivers have high physical and psychological burdens, anxiety, depression, distress, and low quality of life. Eventually the home becomes a "mini-hospital."

As shown in Exhibit 1, there are significant direct medical costs of caring for the individual with ALS. Annual direct and indirect cost per patient was estimated to be $69,475 in 2015, which was before the approval of edaravone which costs approximately $148,000 annually.[4] The estimated annual national economic burden (including medical, nonmedical, and indirect costs) of ALS in the U.S. ranges from $256 million to $1.023 billion (2010 U.S. dollars)

Exhibit 1: Cost of ALS for Patients

Direct Costs
• Potentially avoidable surgical treatments.
• Diagnostic process.
• Multidisciplinary ALS Clinic.
• FDA-approved disease-modifying medications.
• Symptomatic treatment.
• Durable medical devices.
• ER visits and hospital admissions.
• Professional aid and home care.
• Augmentative and alternative communication (AAC) devices.
• Nutritional care and gastrostomy.
• Non-invasive ventilator (NIV) and respiratory care.
• Palliative care/hospice care.
• Tracheostomy invasive ventilator (TIV).
Indirect Costs
• Loss of wages for patient and family caregivers.
• Emotional toll.

depending on which prevalence numbers are used.[4,5] Medical costs increase rapidly with each disability milestone. In one analysis of claims, annual costs were $10,000 nine months before diagnosis, $58,973 by 15 months after diagnosis, and $76,179 by the time of hospice care.[6] A case study that collected all expenses related to the cost of care for an individual patient over a 10-year period (2001–2010) found that the total disease-duration costs were $1,433,992 (85% paid by insurance, 9% paid by family, 6% paid by charities).[7] The highest costs were for in-home caregivers ($669,150), ventilation ($212,430) and hospital care ($114,558).

There are many unmet needs in ALS treatment. An understanding of the pathologic process and what initiates it needs to be discovered in order for a cure to be found. If a cure is not available, more effective disease-modifying medications are needed. Diagnostic and prognostic biomarkers need to be developed. Methods for early diagnosis of ALS need to be found so medication can be started quickly. Reduced financial and psychosocial burden for patients and families is needed. Multidisciplinary ALS clinics need to be available for every patient with ALS and the costs for those clinics have to be appropriately reimbursed. The U.S. needs a comprehensive care package and full support from insurance companies for those who have ALS (something akin to the Rare and Intractable Disease Act in Japan).[8]

Currently, there is significant delay in making an ALS diagnosis. In one study, the diagnostic delay for the U.S. Medicare population was 2.5 years in limb-onset patients and 1.25 years in bulbar-onset patients.[9] A more recent trial found a diagnostic delay of about 12 months occurs in non-ALS clinic settings compared to ALS clinics (~9 months).[10] Unmodifiable factors (comorbidities, familial ALS, bulbar onset, and progression rate) as well as modifiable factors (early referral to the neurologist and the evaluation in an ALS referral center) have an independent effect in the diagnostic delay.[10] Diagnostic delay mainly results from delayed referral from non-neurologist physicians to a neurologist.[10,11]

If patients are diagnosed earlier, they can begin treatment sooner and benefit from the survival extension and delay of disease-progression benefits offered by current and future therapies. Effective neuroprotective treatment must be given when motor neurons are still alive and functioning. Diagnostic difficulties come from the subtle initial presentation of the disease. Initially, ALS may involve degeneration and death of only upper motor neurons (UMN) or lower motor neurons (LMN), but it eventually progresses to involve both UMN and LMN. The UMN are the large cortical neurons originating in the motor cortex. These neurons descend through the pyramidal tract to synapse with LMN. The LMN are located in the brainstem and the ventral spinal cord and provide direct innervation of the voluntary skeletal muscles of the head, neck, limbs, and respiratory system. Most people with ALS have limb-onset disease and first feel muscle cramps, spasms, or twitching (fasciculations) in one of their arms or legs which could be caused by any number of diseases.[12] Other early signs include weakness in the hands and feet or loss of balance. About 25 percent of people with ALS first have trouble talking and begin to slur their words (bulbar-onset ALS). Patients may also have difficulty holding their head up or maintaining posture.

No direct pathologic mechanism for ALS development has been identified. Most experts agree that various factors including oxidative stress linked to free radical formation, mitochondrial dysfunction, derangements in cytoskeletal protein and glutamate metabolism, glial cell pathology, defects in axonal transport, protein aggregates, and RNA processing are involved.[13-15] Several of the genetic risk factors for ALS are involved in the RNA

Exhibit 2: Symptomatic Treatment for ALS

Medications	Purpose	Actions	Efficacy	Safety	Utility
Glycopyrrolate Atropine	Sialorrhea	Anti-muscarinic	Limited	Constipation, cardiac	Common
Botox	Sialorrhea	Cholinergic blocking	Fine for a few months	Potential weakness	Selected usage
Baclofen	Spasticity Muscle cramps	Central reflex inhibitor	First choice, limited benefits	Drowsiness, fatigue, weakness	Common
Nuedexta® **(Dextromethorphan/ quinidine)**	Pseudobulbar Affect (PBA)	Anti-glutamate lambda receptor	Good	Cardiac, ataxia	Common
Mexiletine	Muscle cramps	Neuron/Muscle membrane	Fair	Cardiac	Rare
Modafinil	Fatigue	Dopamine reuptake inhibitor	Fair	Insomnia	Rare

processing metabolic pathway, and aggregation of proteins involved in RNA metabolism has been seen in most forms of ALS.

Biomarkers are a possible solution to earlier diagnosis; neurofilament light chain protein (NfL) is currently the most accurate cerebrospinal fluid biomarker in ALS in terms of both diagnostic and prognostic value.[16,17] Genetic tests can also facilitate early diagnosis. New diagnostic criteria for ALS have been proposed but these do not pointedly specify the use of either genetic tests or NfL.[18] The guidelines state that investigations excluding other disease processes have to be done and that the appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle electromyography (EMG), magnetic resonance imaging (MRI) or other imaging, fluid studies of blood or cerebrospinal fluid (CSF), or other modalities as clinically necessary. Unfortunately, the importance of NfL measurement is not appreciated by clinicians nor is this test widely available.

Other barriers to early and accurate diagnosis include that general neurologists are not sufficiently knowledgeable about ALS or are not ready to discuss the potential diagnosis with the patient. ALS experts may not be keen to make an early diagnosis because the benefits of early diagnosis and treatment may not be fully recognized. Lastly, patients are not particularly interested in receiving an early diagnosis, partly due to fear and denial. Essentially, no parties are thinking toward making an ALS diagnosis in an expeditious manner.

Treatment of ALS encompasses symptomatic management, disease-modifying treatment, and management of mobility and breathing issues. Symptomatic management is important in maintaining quality of life. Clinicians need to identify symptoms that bother the patient and aggressively manage those. These can be psychological, musculoskeletal (cramps), gastrointestinal, pulmonary, emotional (pseudobulbar affect), and others (fatigue, insomnia, drooling, etc.). The easiest and safest symptomatic medications should be tried before those with potentially more adverse events and more difficult management (Exhibit 2).

Riluzole (Rilutek®, Tiglutik®) and edaravone (Radicava®) are the two FDA-approved disease-modifying treatments approved for ALS treatment. For both drugs, the mechanism of action remains unknown; it appears to be a neuroprotective effect via inhibition of glutamatergic neurotransmission for riluzole and scavenging of free radicals for edaravone.

Riluzole was the first FDA-approved disease-modifying therapy for ALS in 1995. It is a benzothiazole given orally that blocks release of glutamate and modulates sodium channels. In clinical trials, riluzole prolongs median tracheostomy-free survival by two to three months compared to placebo in patients younger than 75 years of age with definite or probable ALS who have

Exhibit 3: Critical Therapies in ALS

- Multidisciplinary Specialty Clinic – the principal location for the best patient care and management.
- Disease-modifying treatments – early start is far more effective.
- Durable medical equipment (walker, wheelchair, mechanical wheelchair, hospital bed, stair climber, Hoyer lift, wheelchair ramp, etc.) - Increasing levels needed as disease progresses.
- Fall prevention – Frequent falls result in fractures and other costly injuries.
- Augmentative and alternative communication devices, computer systems – for communication as speech is lost.
- Nutritional care – for dysphagia/poor oral intake, loss of muscle, weight loss; dehydration and weight loss are predictors of poor prognosis.
- Percutaneous endoscopic gastrostomy (PEG) – no one wants this but a necessary method to maintain weight; can be done safely even among those who have poor breathing.
- Non-invasive ventilator (NIV) (BiPAP®) – for poor sleep, orthopnea, low 0_2 saturation, low forced vital capacity (FVC).
- Cough assist – for poor cough and inability to clear secretion.
- Palliative care and home hospice.

had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[19,20] Real-world data from 10 clinical ALS databases have shown improvements in median survival of more than 19 months.[21] Another real-world investigation, including 15 retrospective population studies, which compared riluzole and riluzole-free ALS patients, found significant differences in median survival between the two groups, ranging from six to 19 months.[22]

The American Academy of Neurology (AAN) practice parameter states that riluzole should be offered to slow disease progression in patients with ALS (Level A evidence).[23] It is most effective in the initial stages of the disease. Approximately 80 percent of patients are currently taking riluzole, however, at an annual cost of $25,000 yearly, the cost is the main reason some patients are not receiving the medication.

Edaravone (Radicava®) was approved by the FDA in 2017 to slow the functional decline in patients with ALS. Edaravone is an intravenous antioxidant that was studied in two randomized trials in Japan. 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.[24] The second trial was done in 137 people who showed some degree of impairment in each of the ALS Functional Rating Scale-revised (ALSFRS-R) domains, had an forced vital capacity (FVC) ≥ 80 percent 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.[25] The cost of edaravone is estimated to be around $148,000 per year. No real-world studies of edaravone are available, due to only a few years' experience with this intravenous medication.

The manufacturer of edaravone provides support to assist with the insurance approval process, however, it is time-consuming and costly for nurses and coordinators to obtain insurance approval. There are active post-approval (Phase IV) studies for biomarkers and benefits of edaravone; similar studies for riluzole have never been undertaken. Development of oral edaravone is also underway but it may be many years away.

Numerous therapies are under investigation as disease-modifying therapies for ALS. Ultra-high-dose methylcobalamin and sodium phenylbutyrate-taurursodiol are the two that are actively being studied. In a Phase II/III study of ultra-high-dose methylcobalamin, placebo, 25 mg or 50 mg of methylcobalamin intramuscularly were compared in 373 patients with ALS. No significant differences were detected in either primary endpoint (time interval to death or full ventilation support and changes in the ALSFRS-R score).[26] 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. The incidence of treatment-related adverse events was similar and low in all groups. Sodium phenylbutyrate–taurursodiol resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks in one recent Phase II trial.[27] In a survival analysis of this trial, the median overall survival was 25.0 months among participants receiving the fixed dose combination and 18.5 months among those receiving placebo (hazard ratio, 0.56; 95% confidence interval, 0.34 to 0.92; $p = .023$).[28] The results of this trial suggest that sodium phenylbutyrate–taurursodiol has both functional and survival benefits in ALS. Longer and larger trials are necessary to fully evaluate the efficacy and safety of sodium phenylbutyrate–taurursodiol in persons with ALS. Exhibit 3 summarizes the critical therapies in ALS. Patients should be cared for in a multidisciplinary specialty clinic if possible; unfortunately, many patients live far from such a clinic.

Conclusion

This devastating disease needs to be diagnosed early and therapy initiated quickly. The goal is to prevent existing motor neurons from early death. Numerous critical therapies including disease-modifying and symptomatic treatment make this a complicated disease to manage that requires multidisciplinary care. More and better ways to diagnosis and manage this disease are needed.

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Patient-Focused Treatment Decisions in the Management of Non-Small Cell Lung Cancer

Gary M. Owens, MD

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

Summary

Non-small cell lung cancer (NSCLC) is a common and still highly fatal cancer for those with advanced disease. Treatment approaches for this disease are evolving rapidly and have become highly personalized. Agents targeting driver mutations and immunotherapy agents are standard of care in most patients.

Key Points

- Despite numerous advances in treatment, lung cancer remains the number one cause of death among solid organ tumors.
- NSCLC is the most common form of lung cancer.
- The treatment of NSCLC is now highly personalized.
- For those without identified driver mutations, immunotherapy is the standard of care in first-and later-line therapy.
- Those with driver mutations should be offered personalized therapy with the appropriate agent that targets the driver mutation if available.

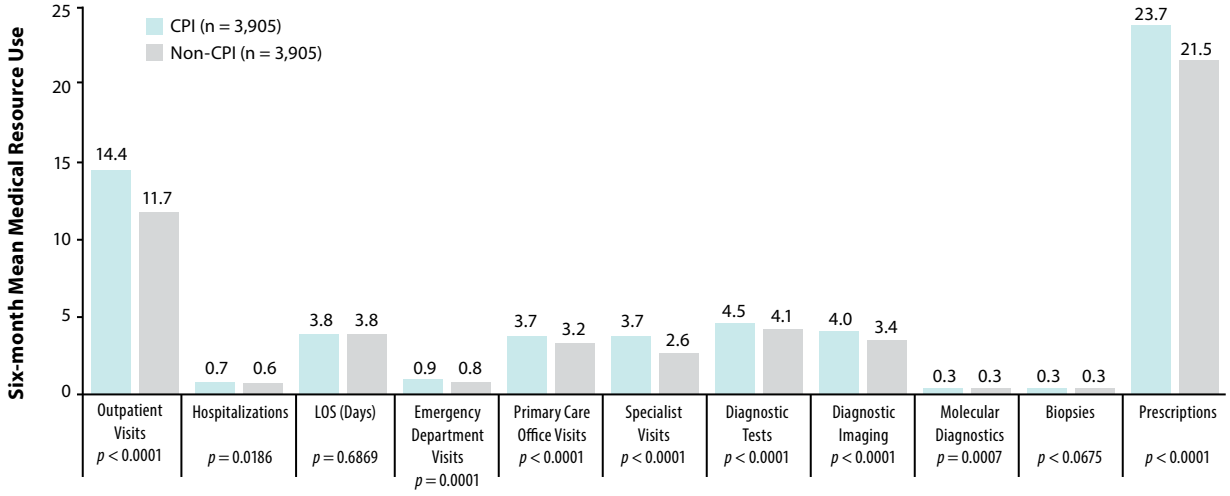
LUNG CANCER IS THE SECOND MOST common cancer in both men and women and the most common type of lung cancer is non-small cell lung cancer (NSCLC) accounting for 85 percent of cases.[1] Around 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women.[2] In recent years, lung cancer deaths have begun to decline in both men and women, reflecting a decrease in smoking.

The majority of patients with NSCLC are diagnosed at advanced stages, where chemotherapy has only limited efficacy, and at a price of significant toxicity. The advent of molecular-targeted therapies against driver oncogenes have altered the therapeutic landscape for subsets of oncogene-driven NSCLC. Immunotherapy with checkpoint inhibitors, including antibodies against programmed death one (PD-1), programmed death ligand one (PD-L1) and cytotoxic T lymphocyte associated protein four (CTLA4), can confer a durable response in a subset of patients – particularly those without driver mutations. Despite these life-prolonging advances, the majority of patients acquire resistance to therapies through a variety of mechanisms, resulting in cancer progression.

The National Institutes of Health (NIH) estimates that cancer care cost the United States (U.S.) an overall $190 billion in 2015, $21.1 billion (11%) of which was due to lung cancer.[3] Lost productivity due to early death from cancer led to an additional $134.8 billion of cost in 2005, $36.1 billion of which was caused by lung cancer. By 2020 the cost of cancer care had increased to $209 billion.[4] Likewise, lung cancer medical cost in the U.S. by 2020 had increased to almost $24 billion (11.5% increase). In 2020, lung cancer was the third most costly cancer. Healthcare spending for these patients is driven by outpatient visits and prescription therapeutics. Exhibit 1 shows a comparison of all-cause medical resource utilization per patient with NSCLC in cohorts treated with a checkpoint inhibitor immunotherapy (CPI) or with non-CPI treatment.[5]

For all this spending on NSCLC treatment,

Exhibit 1: NSCLC Cost Drivers[5]



CPI = checkpoint inhibitor immunotherapy; LOS = length of stay

there have been survival benefits. Population-level mortality from NSCLC in the U.S. fell sharply from 2013 to 2016, and survival after diagnosis improved substantially – driven by targeted therapies and immunotherapy. There may be unwanted patient consequences of higher priced therapies. Financial toxicity (FT) refers to the detrimental effects of the excess financial strain caused by the diagnosis of cancer on the well-being of patients, their families and society (Exhibit 2).[6] With continued escalation in the costs of cancer treatment, FT has become an important consideration in recent cancer care. Patients with Stage I, II, or III NSCLC are generally treated with curative intent using surgery, chemotherapy, radiation therapy (RT), or a combined-modality approach. The role of immunotherapy agents and targeted therapy against driver mutations as adjuvant therapy are becoming increasingly important in this setting. Systemic therapy is indicated for patients who present with advanced disease, including those who present with metastases (Stage IV) but advanced disease is not typically curable. For patients with a solitary metastasis, surgical resection or definitive irradiation of the metastasis may be appropriate. Key factors that influence the choice of initial therapy for advanced NSCLC include presence or absence of a driver mutation for which a specific inhibitor is available, presence of a high level of PD-L1 expression as a biomarker for immunotherapy efficacy, extent of disease (including the number and sites of metastases), the presence or absence of symptoms related to a specific site of metastasis, and squamous versus nonsquamous histology.[7,8] Exhibit 3 summarizes treatment selection based on mutations and PD-L1 expression.[8]

Molecular testing is central to selection of effective therapeutic options in NSCLC. The most useful biomarkers for predicting the efficacy of targeted therapy in advanced NSCLC are somatic genome alterations (driver mutations). These mutations occur in cancer cells within genes encoding for proteins critical to cell growth and survival. Driver mutations are typically not found in the germline (noncancer) genome of the host and are usually mutually exclusive (i.e., a cancer is unlikely to have more than one driver mutation). Methods for screening NSCLC patients for driver mutations and other abnormalities are continually evolving and there is no single-standard platform for testing. Features that make a platform clinically useful are fast turnaround time (two weeks or less), cost efficiency, ability to be performed on clinically available samples, and semi-automation, eliminating reliance upon a single operator.[9] Driver mutations occur with varying frequency in NSCLC (Exhibit 4).[9]

If targetable mutations are present, targeted therapy is first-line for those patients because these therapies are significantly more effective than standard therapies in those with driver mutations; immunotherapy is relatively ineffective in these populations and may pose a risk of toxicity if exposure is sequential.[8,10] Activating KRAS mutations, which activate a number of downstream

Exhibit 2: Financial Toxicity Related to Cancer Care[6]

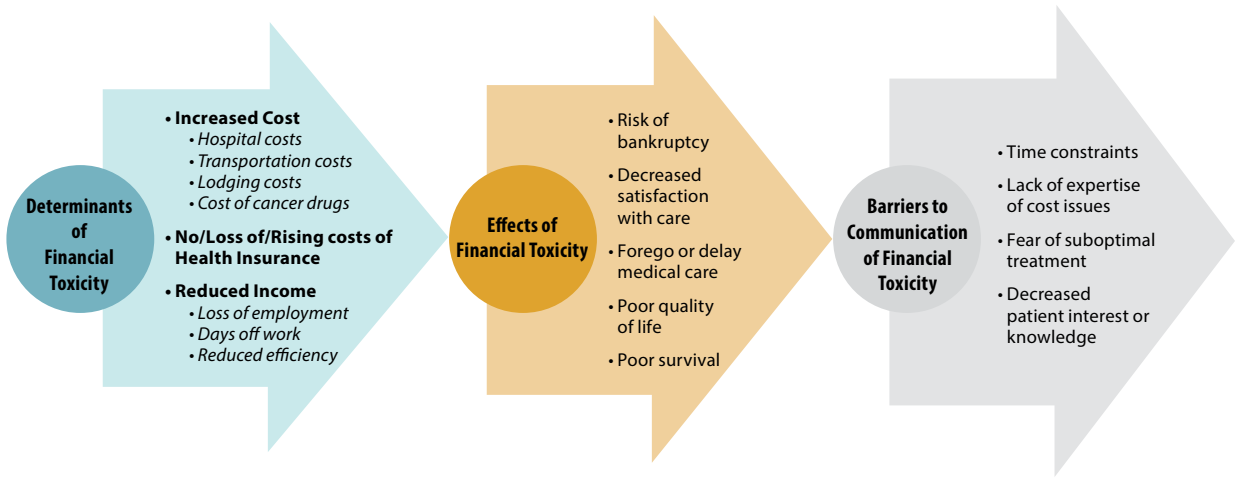


Exhibit 3: Advanced Disease Treatment[8]

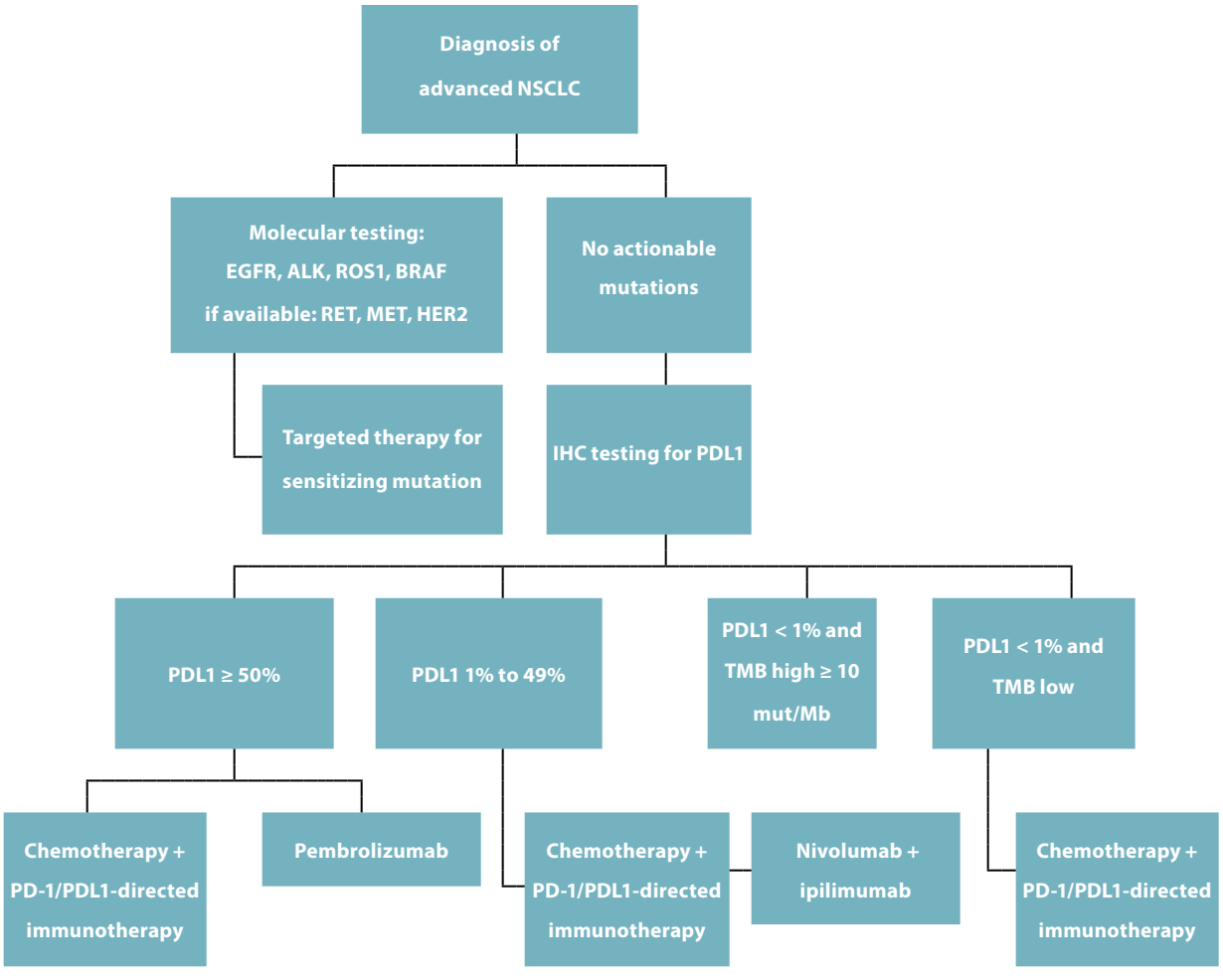
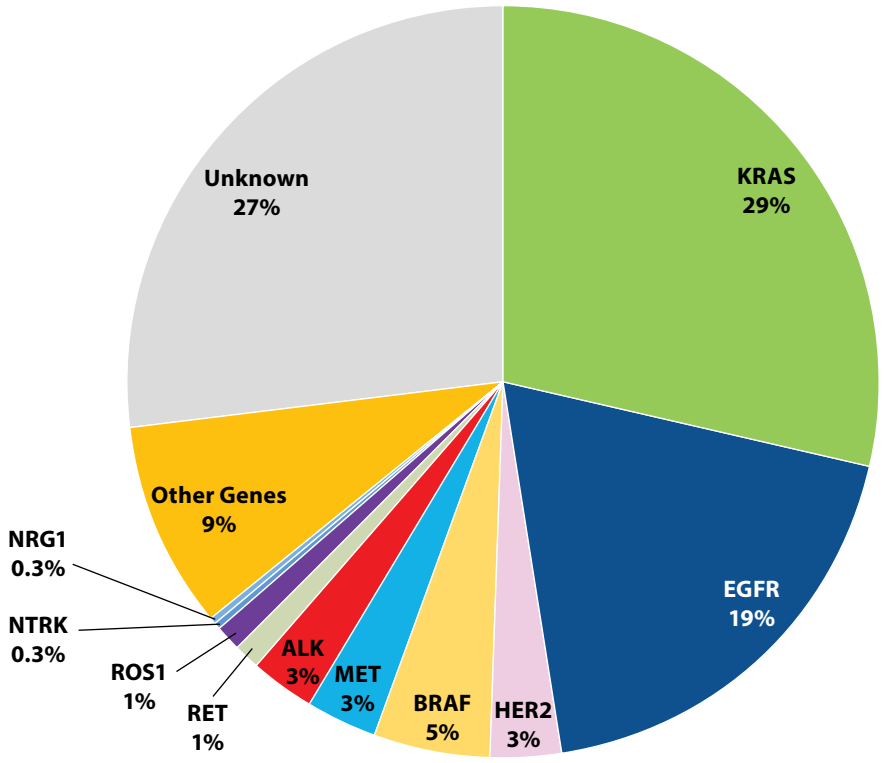


Exhibit 4: NSCLC Driver Mutations[8,9]



KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
EGFR = epidermal growth factor receptor
HER2 = human epidermal growth factor receptor
BRAF = v-Raf murine sarcoma viral oncogene homolog B
MET = MET proto-oncogene, receptor tyrosine kinase or hepatocyte growth factor receptor
ALK = anaplastic lymphoma kinase
ROS1 = ROS proto-oncogene 1
NTRK = neurotrophic tropomyosin-related kinase
NRG1 = neuregulin 1

signaling pathways, are found in approximately 29 percent of NSCLC cases in the U.S. and are generally associated with smoking. The focus of targeted therapeutics for patients with KRAS-mutated lung cancer has been against downstream effectors of activated KRAS. In 2021, sotorasib became the first targeted agent with regulatory approval for KRAS G12C-mutated NSCLC. It is FDA approved for patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, who have received at least one prior systemic therapy. In a Phase I trial in a heavily pretreated patient population (59 patients, 3 to 11 prior lines of therapy), sotorasib treatment resulted in a confirmed objective response (complete or partial response) in 32.2 percent and disease control (objective response or stable disease) in 88.1 percent.[11] Median progression-free survival (PFS) was 6.3 months. A Phase II trial, in which the majority (88%) of subjects had already received platinum-based chemotherapy and immunotherapy, an objective response was observed in 37.1 percent, including 3.2 percent who had a complete response.[12] The median duration of response was 11.1 months. Disease control occurred in 80 percent. The median PFS was 6.8 months, and the median overall survival (OS) was 12.5 months.

Mutations in the epidermal growth factor receptor (EGFR) are observed in approximately 19 percent of NSCLC. In Asian populations, the incidence of EGFR mutations is higher, up to 62 percent. Presence of an EGFR-activating mutation confers a more favorable prognosis and strongly predicts for sensitivity to EGFR targeting tyrosine kinase inhibitors (TKIs). Unlike activating mutations in

EGFR, amplification of EGFR does not predict improved outcomes with EGFR inhibitors. Targeted therapy should be used ahead of chemotherapy and immunotherapy in EGFR-positive NSCLC.[8] First-generation (erlotinib, gefitinib) and second-generation (afatinib, dacomitinib) TKIs have been standard of care for initial management of EGFR mutated NSCLC. Third-generation (osimertinib) has demonstrated improved outcomes over first- and second-generation TKIs. In 2021, amivantamab, an EGFR and MET receptor directed bispecific antibody was approved for EGFR exon 20 insertion-mutated NSCLC that progressed on chemotherapy (either with or without immunotherapy). Also in September 2021, mobocertinib was approved by the FDA for a similar indication. Both are recommended therapies in the National Comprehensive Cancer Network (NCCN) Guidelines.[8]

Choice of a first- or second-generation EGFR TKI should be individualized according to patient and provider preferences. Available data suggest that erlotinib, gefitinib, afatinib, and osimertinib all have efficacy in EGFR-mutant lung cancer and are well tolerated. Some data suggest that afatinib may yield the strongest disease outcomes but may also cause the most adverse events. Newer data demonstrate improved survival outcomes with front-line osimertinib compared with gefitinib or erlotinib and is the preferred agent in the NCCN Guidelines.[8,13]

For patients with completely resected EGFR-mutated NSCLC that is either Stage IB with high-risk features (e.g., lymphovascular invasion, poor differentiation, etc.) or Stage II to IIIA, adjuvant osimertinib may be used, and continued until progression or unacceptable toxicity, for up to three years. Two-year disease-free survival (DFS) rates in this setting were 89 percent with osimertinib and 53 percent with placebo.[14] Notably, the strong DFS advantage observed with osimertinib persisted across all patient subgroups, including those patients who received adjuvant chemotherapy and those who did not. Although adjuvant osimertinib treatment improves DFS in EGFR-mutated NSCLC, an improvement in OS has not been demonstrated at this point.

MET is a tyrosine kinase receptor for hepatocyte growth factor. MET abnormalities include MET exon-14-skipping mutations (3% of lung adenocarcinomas) and MET gene amplification (2% to 4% of treatment-naïve NSCLC, 5% to 20% of EGFR-mutated tumors) that have acquired resistance to EGFR inhibitors.[9] FDA-approved agents for MET exon-14-skipping include capmatinib and tepotinib. For those with high MET amplification, there are no approved agents, but capmatinib and crizotinib are used off label with some frequency.

Fusions involving one of three tropomyosin-related kinases (TRK) occur across many tumor types. Neurotrophic tropomyosin-related kinase (NTRK) gene fusion is rare in NSCLC (0.3%). Larotrectinib is FDA approved for treating advanced tumors that have all of the following characteristics:

- harbor an NTRK gene fusion.
- lack a known acquired resistance mutation.
- have no satisfactory alternative treatments available.
- have progressed following treatment.

Entrectinib is a dual NTRK and ROS proto-oncogene 1 (ROS1) inhibitor that is also FDA approved in this setting. ROS1 mutations occur in about 1 percent of NSCLC cases.

The rapid development of personalized therapies for NSCLC has transformed the treatment landscape and brightened the long-term outlook for many patients but at a substantial financial cost. Current value assessments for targeted therapies may need revision. Payers need to better define and understand the key aspects and attributes of personalized therapies that should be considered in any assessment of their value. Payers need to address evidence gaps in existing value frameworks given the unique properties of patient outcomes with this approach. A better characterization of the benefit of personalized treatment will allow a more thorough assessment of its benefits and provide a template for the design of management programs and a roadmap for healthcare insurers to optimize coverage for patients with NSCLC.

Payers also need to consider alternate stakeholder perspectives when making value decisions. While many payers require a focus on the health sector specific costs, to fully understand the costs and benefits of a particular targeted therapy to society, inclusion of a societal perspective (accounting for caregiver costs, productivity gains/losses, etc.) in cost-effectiveness analyses may be warranted. From the patient perspective, addressing the outcomes that "matter" to patients can help decision-makers compare drugs within the same disease state.[15] The value of hope in cancer treatment has been identified as an area needing more research to quantify, but it is conceptually intuitive and very relevant to personalized care.[16] A patient with cancer facing a terminal diagnosis may be willing to risk taking a more novel therapy if his or her chances include the possibility of durable response and even functional cure. Any innovation that can extend life (even at the same or worse quality of life) may give a patient a chance to live long enough for a new treatment to

develop, and possibly cure.

Payers may need to leverage patient-reported outcomes, real-world evidence, and other tools to expand the knowledge base and continuously improve patient outcomes from personalized approaches. From such analyses, payers and providers together must develop careful patient selection that ensures treatments are provided only to those patients most likely to benefit. Once the benefits are established for personalized approaches in the adjuvant and neo-adjuvant settings, thereby reducing the incidence of late-stage cancers, there will be additional cost offsets for these costly therapies.

Conclusion

NSCLC is the most common form of lung cancer. Despite numerous advances in treatment, lung cancer remains the number one cause of death among solid organ tumors. The treatment of NSCLC is now highly personalized. For those without identified driver mutations, immunotherapy has become the standard of care in first- and later-line therapy. Numerous tumor driver mutations have been identified in NSCLC and those with driver mutations should be offered personalized therapy with the appropriate agent that targets the driver mutation. The number of actionable driver mutations continues to increase as new agents are developed. These agents improve survival but increase cost and create evaluation challenges for payers.

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Patient-Focused Treatment Decisions in the Management of Overactive Bladder

David A. Ginsberg, MD

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

Summary

Overactive bladder (OAB) is a common problem that causes significant quality of life impacts. There are two major classes of oral medication for this condition with the newer class of β3-adrenergic receptor agonists causing fewer adverse events, especially in the elderly. A clinical care pathway is one way to improve clinical and economic outcomes.

Key Points

- Identifying and treating OAB is important.
- Patient education and appropriate expectations of treatment are important for achieving good outcomes.
- Antimuscarinics have been associated with increased rates of dementia and thus should be avoided in the middle-aged and older patients.
- A clinical care pathway can be used to improve outcomes in OAB treatment.

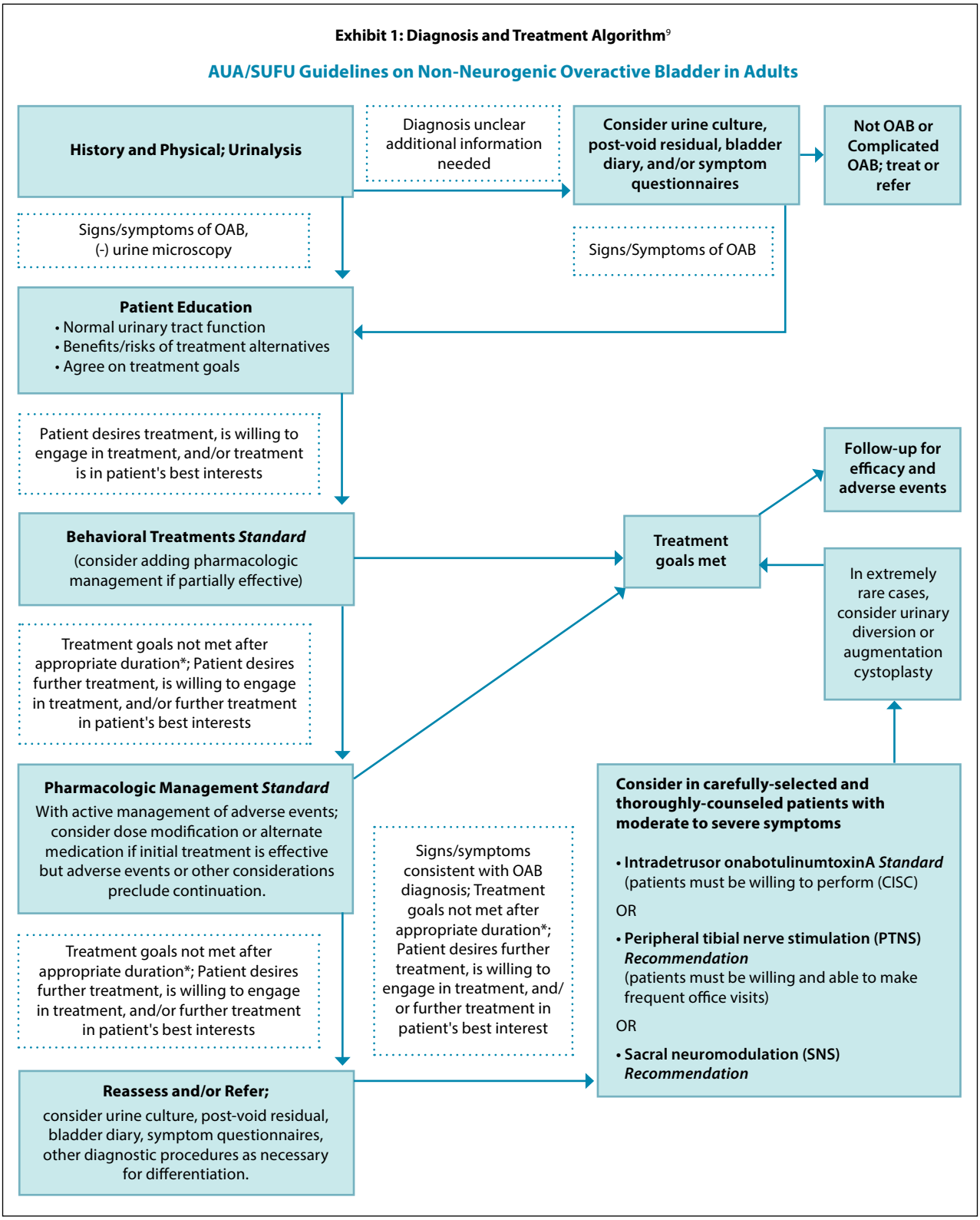
OVERACTIVE BLADDER (OAB) IS A SYMPTOM-based diagnosis. It is characterized by urinary urgency, usually accompanied by frequency and nocturia with or without urgency urinary incontinence, in the absence of a urinary tract infection (UTI) or other pathology. OAB symptoms occur due to the failure of the bladder to store urine normally.

In the United States (U.S.), the prevalence of OAB is estimated at 16 percent in both men and women.[1] Women more commonly seek care as they may be bothered more by the symptoms and are more likely to be incontinent with OAB. The prevalence of OAB increases with age in both men and women; many patients are younger than some people may believe with large prevalence rates in those aged 45 to 65 years. OAB is as prevalent as chronic diseases such as arthritis, allergic rhinitis, and sinusitis and is more prevalent than heart disease, asthma, and diabetes.[1]

In the U.S., annual OAB cost burden has been estimated to be $65.9 billion.[2] The all-cause annual direct cost of managing patients with OAB is up to twice as high than those without OAB.[3] The OAB-specific costs are a small proportion compared to the secondary costs of OAB-related comorbidities and complications (falls, urinary tract infections, skin rashes, depression, and anxiety). A recent retrospective review of Medicare claims found that long-term care residents with OAB have significantly more healthcare resource utilization compared with patients without OAB.[4] The mean annual direct total cost was $57,984 in the OAB cohort compared with $54,285 in the non-OAB cohort. The annual cost of OAB in nursing homes was estimated at $793 million. Adjusted analyses revealed that the OAB cohort was 9 percent more likely to have hospitalization and emergency department visits, 15 percent more likely to have outpatient visits, 27 percent more likely to have physician visits, and 12 percent more likely to have prescriptions compared with the non-OAB cohort. In addition to the financial burden, OAB impacts all aspects of quality of life including physical, social, sexual, and psychological.

Lack of patient education is a significant barrier to successful outcomes for the OAB patient. Patients need education on lower urinary tract function and the benefits and risks of treatments. The goal is to reduce, manage or eliminate OAB symptoms to improve quality of life but the treatments are not a cure. Acceptable symptom control may require

Exhibit 1: Diagnosis and Treatment Algorithm[9]



*Appropriate duration is 8 to 12 weeks for behavioral therapies and 4 to 8 weeks for pharmacologic therapies.
The complete OAB Guideline is available at www.AUAnet.org/Guidelines.

Exhibit 2: FDA Approved OAB Medications

Antimuscarinics
• Oxybutynin immediate/extended-release (Ditropan®/Ditropan XL®)
• Tolterodine immediate/extended-release (Detrol®/Detrol® LA)
• Oxybutynin patch/gel (Oxytrol/Gelnique)
• Trospium immediate/extended-release (Sanctura®/Sanctura XR®)
• Solifenacin (Vesicare®)
• Darifenacin (Enablex®)
• Fesoterodine (Toviaz®)
Beta Agonists
• Mirabegron (Myrbetriq®)
• Vibegron (Gemtesa®)

trials of multiple different therapies. It is important to educate patients on the goal and to manage expectations. Without appropriate education, appropriate expectations, and proactive adverse event management, there is a high rate of therapy discontinuation.

Proactive OAB screening does not occur very often. In one study, 85 percent of women discussing their incontinence symptoms with their healthcare provider had to raise the issue themselves.[5] Over 50 percent of women who discussed OAB with a healthcare provider waited more than one year to seek treatment and only 34 percent of patients diagnosed with OAB receive treatment. In a population-based survey, 60 percent of those with OAB symptoms had discussed OAB with a provider, and 73 percent were not getting the help they needed or requested.[6] Those affected by OAB may also not seek care. Even among nurses with high healthcare literacy, only 16 percent of those with urinary incontinence had sought out care over a two-year period.[7] Just getting an OAB diagnosis has a positive impact on knowledge, communication, and management.[8]

The American Urological Association (AUA) has published guidelines on managing OAB in adults.[9] Exhibit 1 provides an overview of the treatment of OAB from the guidelines.[9] The goal of treatment is to reduce frequency, urgency, and urinary incontinence and increased voided volume while minimizing adverse events. Behavioral therapies are recommended as first-line treatment for all patients and can be combined with pharmacologic management for better efficacy. Behavioral therapies should be evaluated in eight to 12 weeks. For second-line therapy, β3-adrenergic receptor agonists or antimuscarinics are recommended. Four to six weeks of oral therapy is needed for efficacy to be evaluated. Dose modification or a switch to a different medication is recommended in the case of inadequate efficacy or poor tolerability. Combination of the two classes is also an option because they have different mechanisms of action. Recommended third-line therapies include intradetrusor onabotulinumtoxin A, peripheral tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS). Additional treatments may include indwelling catheters and augmentation cystoplasty or urinary diversion for severe, refractory, complicated OAB patients.

Numerous antimuscarinic agents and two β3-adrenergic receptor agonists are currently available for treating OAB (Exhibit 2). There is no compelling evidence for differential efficacy across the various antimuscarinic agents. The choice of an initial antimuscarinic agent will depend on factors such as prior antimuscarinic use, past adverse events, patient preferences, comorbidities, other concomitant medications, cost, and insurance coverage and/or restrictions.

There are several issues with antimuscarinic agents in the treatment of OAB. They primarily improve symptoms rather than resolve all OAB symptoms. Adverse events are the major issue – dry mouth, constipation, and cognitive decline, especially in the elderly. Antimuscarinics are on the Beers list of agents that should not be used in the elderly. A study from England found there were significant increases in dementia risk with use of bladder antimuscarinic drugs and other strong anticholinergic medications.[10] The findings from this trial would suggest that anticholinergics should not be used at all in those who are 55 or older, especially in the long-term. A study using Medicare claims data involving long-term care residents aged ≥ 65 years with OAB found that anticholinergic burden increased healthcare resource utilization.[11] Most residents (87.2%) had some level of cumulative anticholinergic burden (low 18.0%, moderate 41.9%, and high 27.3%). All types of resource utilization were higher among those with any level of anticholinergic burden than those with no burden. The outpatient, emergency room, and physician costs tended to be higher with increasing anticholinergic burden. This study concluded that targeted efforts towards reducing anticholinergic burden among residents with OAB may result in decreases in costs and resource utilization and is

Exhibit 3: The SUFU Clinical Care Pathway Patient Road Map

Begin your path to managing your OAB

1

See Your Healthcare Provider

2

- Evaluation
- Optional Tests
- Patient Education and Expectations

First Steps or Initial Conservative Therapy

3

- Lifestyle
- Dietary Modifications
- Fluid Management
- Pelvic Floor Exercise
  - Patient Aids
- Maybe Combined with a Bladder Medication

(under construction)

Second Steps

4

Talk to your provider about a bladder medication.

If you have adverse events, there are aids to help.

(under construction)

It's been 4 to 8 weeks

Are you better?

Are you tolerating the meds?

YES

STOP!

You are doing great.

Keep up the good work.

Make sure to follow-up with your provider on a regular basis and your prescription stays current.

NO

It might be time to talk to your provider about adjusting the dose or trying another medication for 4 to 8 weeks.

It's been another 4 to 8 weeks.

Are you better?

Ate you tolerating the meds?

YES

STOP!

You are doing great.

Keep up the good work.

Make sure to follow-up with your provider on a regular basis and your prescription stays current.

NO

It might be time to consider advanced therapies.

If you are not seeing an OAB specialist now might be the time to see one.

Advanced Therapies

5

Talk with your OAB specialist on which is best for you.

- InterStim®
- BOTOX®
- NURO-PTNM®
- Urgent PC®

NO

Are you better?

Have you reached your goals?

YES

STOP!

You are doing great.

Keep up the good work.

Make sure you stick with it and see your provider on a regular basis.

yet another reason not to use antimuscarinics in older adults.

Unfortunately, managed care policies typically require the use of one or more antimuscarinics before more expensive agents can be used. No professional organization OAB guideline supports requiring antimuscarinic use before other agents. This is likely a self-defeating policy because of the potential for increased costs related to managing the adverse events and lack of control of OAB.

Mirabegron and vibegron are once daily oral beta agonist agents with no anticholinergic adverse events. These agents increase relaxation of the bladder muscles rather than inhibit contraction which makes issues with excess urine retention less likely. Mirabegron is not recommended when a patient has severe uncontrolled hypertension but vibegron does not have this warning. Both cost more than the older generic antimuscarinics but the impact of cognitive decline with those needs to be considered. Persistence and adherence have been found to be better with mirabegron compared to antimuscarinic agents.[12]

If cost is not an issue, mirabegron or vibegron should be the first-choice medications. If clinicians have to use an anticholinergic first because of insurance coverage, the best choices are solifenacin and fesoterodine which are once daily and titratable. If a generic has to be selected, tolterodine extended release or solifenacin are the best tolerated options. Combination therapy with a low-dose antimuscarinic and mirabegron is an option if more improvement is needed and the patient can afford and tolerate adverse events. The combination of 5 mg solifenacin with 50 mg mirabegron was superior to either of these alone in terms of number of micturitions per day and episodes of incontinence.[13,14]

Many patients are not satisfied with their OAB therapy. They are jumping from one OAB medication to another, or giving up on treatment, or not making it to further therapy, or getting incorrect information. In one U.S. survey study when only antimuscarinics were available, 49 percent of people stopped therapy because they were not satisfied with the results and 21 percent did not tolerate the medication.[15] A clinical care pathway (CCP) that helps better educate patients on the various treatment options could help improve OAB therapy selection, improve medication adherence, reduce risk of adverse events, improve patient satisfaction with care, and improve control of OAB.

The Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) developed a CCP in response to a lack of good evidence-based pathways. The OAB CCP helps primary care providers by providing tools to easily educate patients, set expectations, and understand the next steps if initial therapy fails. It can also help urologists and gynecologists because not all are OAB experts. A major cost benefit of the CCP is to discourage unnecessary testing in the diagnostic process. The components of the CCP include a flow diagram illustrating clinical management pathway, a patient road map, education handouts on various aspects of behavior management and lifestyle therapies, and a website (sufuorg.com/resources/overactive-bladder-ccp.aspx). The patient road map (Exhibit 3) and handouts can be used to educate patients, provide tangible outline of times and expectations for each therapeutic option, and provide insight if current therapy is not satisfactory and it is time to consider alternative options. An additional component to the CCP is a smart phone application (My Bladder) for patients to track symptoms, behavior modifications, and medication adherence. The application can also provide reminders to undertake behavior modification and take medications.

Conclusion

It is important for clinicians to screen patients for urinary symptoms to identify possible OAB. The right treatment for the right patient needs to be selected and therapy progressed if symptoms are not controlled. Antimuscarinics have been associated with increased rates of dementia and thus should be avoided in the middle-aged and older patients. Patient education and appropriate expectations are key to successful outcomes. Use of a well-done clinical pathway should allow for optimization of treatment and outcomes.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Advanced Renal Cell Carcinoma: A Close Look at New and Emerging Combinations

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

Summary

Advanced renal cell carcinoma remains incurable but there are numerous treatment options available. Important gains in survival have been made since the early 2000s with the introduction of targeted therapies and especially with the addition of immunotherapy to the standard regimen.

Key Points

- Standard first-line treatment for advanced renal cell carcinoma is a combination of targeted therapy and checkpoint immunotherapy or dual checkpoint immunotherapy.
- The choice of regimens for any line of therapy is guided by strength of evidence, toxicity profile, patient comorbidities, patient and physician preference, and financial concerns.
- With the multitude of possible therapeutic sequences, a definitive resolution in preferred sequence is unlikely.
- Molecular biomarkers to select for efficacy and toxicity are not yet in clinical use.

RENAL CELL CARCINOMA (RCC) IS NOT just one disease; there are eight known types but the majority of cases (75%) are clear cell RCC (ccRCC) which is the focus of this article. The median age of diagnosis for ccRCC is 62 years.

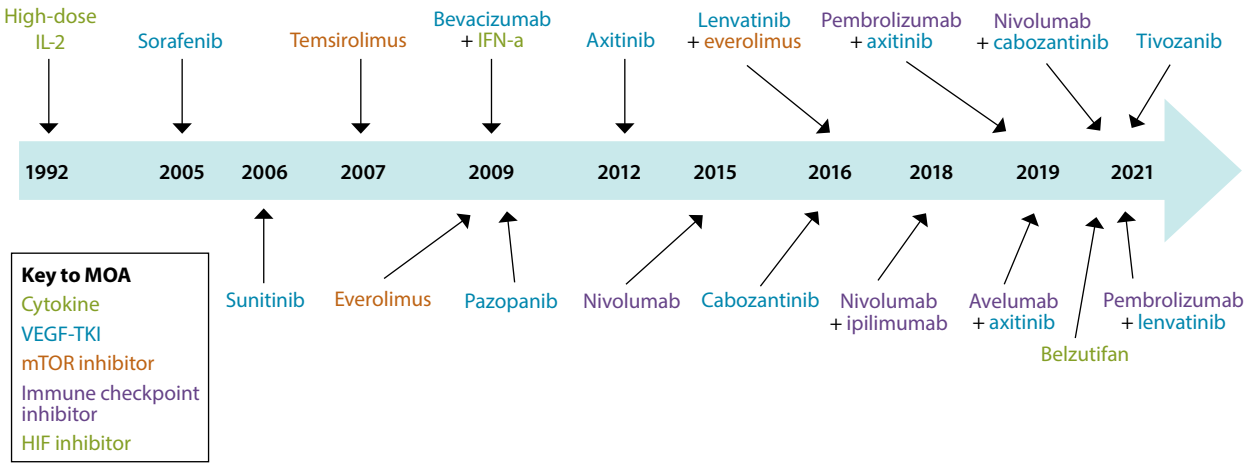
Unlike many other cancers, the majority of RCC cases are diagnosed when the disease is still localized to the kidney (56%); only 16 percent of cases are metastatic at diagnosis.[1] RCC can often be cured by surgical resection if it is diagnosed and treated whilst still localized to the kidney and the immediate surrounding tissue. With surgical treatment about 60 percent of patients are cured and 40 percent go on to eventually develop metastatic disease.

Treatment for advanced RCC is selected based on the International Metastatic Renal Cell Carcinoma Disease Consortium (IMDC) risk model which predicts survival with metastatic disease. Risk factors for a poor prognosis in RCC include a Karnofsky Performance status < 80 percent, time of diagnosis to therapy less than one year, anemia, hypercalcemia, neutrophilia, and thrombocytosis.[2] Those with no risk factors have a favorable prognosis, risk factors 1 to 2 have an intermediate prognosis, and risk factors 3 to 6 have a poor prognosis. Median overall survival (OS) for favorable risk is 43 months, intermediate risk is 22 months, and poor risk is eight months.[2]

In those with metastatic disease, therapeutic targets are vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), hypoxia-inducible factor (HIF) and the immune system. Exhibit 1 shows the dramatic expansion of treatment options for RCC since 2000. All approvals are based on data from ccRCC trials and not on studies of other histologies.

Treatment goals are to produce a durable complete response in the shortest time possible to lead to cure, prolong survival and treatment-free survival, improve quality of life, minimize adverse events,

Exhibit 1: FDA Approvals in Renal Cell Carcinoma



VEGF-TKI = vascular endothelial growth factor tyrosine kinase inhibitor;
mTOR = mammalian target of rapamycin;
HIF = Hypoxia-inducible factor inhibitor

reduce duration of therapy, and reduce cost. In a real-world study conducted by the IMDC consortium, only 51.4 percent of patients were able to receive a second-line therapy and the rate continued to drop substantially for the third- and fourth-lines.[3] Hence, the selection of most optimal therapy at a given time point is extremely important, as many patients especially those in the intermediate and poor-risk category may not survive long enough to receive a subsequent-line of therapy.

For several years, the first-line therapy for RCC was a VEGF tyrosine kinase inhibitor (TKI), primarily sunitinib. Based on numerous studies showing improved survival compared to VEGF-TKI alone, first-line therapy now is a VEGF-TKI plus checkpoint immunotherapy for those with favorable risk. This combination is also category 1 for those with poor/intermediate risk. Dual immunotherapy with ipilimumab and nivolumab are also an option in poor/intermediate risk but may cause more immune-related adverse events than the VEGF-TKI/immunotherapy combination. The recommended therapies for first and subsequent lines of therapy from the National Comprehensive Cancer Network (NCCN) Guidelines are shown in Exhibit 2.[4]

Data from the first-line trials of the preferred options in advanced RCC are shown in Exhibit 3.[5-10] Importantly, there are no head-to-head trials with any of these regimens. Thus, selecting first-line therapy is complicated with so many viable options. The selection of first-line treatment for metastatic RCC should be guided by individual patient characteristics combined with a vision for treatment sequencing to optimize survival.[11] The first question to consider when selecting a first-line regimen is whether the patient would be a suitable candidate for ipilimumab. Some studies have suggested that ipilimumab has limited activity after disease progression on immunotherapy-based regimens, so if ipilimumab is a desired component of the treatment sequence, it should preferably be administered as first-line in combination with nivolumab.[11] First-line nivolumab plus ipilimumab may be preferred in patients with intermediate- or poor-risk disease who do not have an urgent need for reduction in tumor volume as suggested by the NCCN guidelines.[4] First-line immunotherapy/VEGF-TKI can be selected for patients who have favorable risk, have an urgent need for reduction in tumor volume, or have highly symptomatic disease, especially if they may not get a chance to receive a second-line therapy or have preexisting autoimmune disease precluding ipilimumab therapy. Lenvatinib plus pembrolizumab should be considered for patients with a strong desire for a complete response, irrespective of toxicity, or who need an urgent response but can also tolerate lenvatinib.[11] In contrast, pembrolizumab plus axitinib or nivolumab plus cabozantinib are better tolerated regimens.

Prior exposure to various therapies has an impact on subsequent-line choices. Cabozantinib has activity as a single agent after disease progression on nivolumab plus ipilimumab or pembrolizumab plus axitinib and is the preferred agent for second-

Exhibit 2: Treatment Selection in Advanced Clear Cell RCC[4]

Options for First-Line Therapy			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful Under Certain Circumstances**
Favorable	• Axitinib + pembrolizumab (category 1) • Cabozantinib + nivolumab (category 1) • Lenvatinib + pembrolizumab (category 1)	• Nivolumab + ipilimumab • Axitinib + avelumab • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance • Axitinib (category 2B) • High-dose IL-2[a](category 2B)
Poor/Intermediate	• Axitinib + pembrolizumab (category 1) • Cabozantinib + nivolumab (category 1) • Nivolumab + ipilimumab (category 1) • Lenvatinib + pembrolizumab (category 1) Cabozantinib	• Axitinib + avelumab • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[a] (category 3) • Temsirolimus (category 3)

Subsequent Therapies		
Preferred Regimens	**Other Recommended Regimens**	**Useful Under Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab • Cabozantinib + nivolumab • Ipilimumab + nivolumab • Lenvatinib + pembrolizumab • Pazopanib • Sunitinib • Tivozanib (category 1) • Axitinib + avelumab (category 3)	• Everolimus • Bevacizumab (category 2B) • High-dose IL-2a (category 2B) • Sorafenib (category 3) • Temsirolimus (category 2B) • Belzutifan (category 2B)

[a]Patients with excellent performance status and normal organ function.
Recommendations are Category 2A unless otherwise noted.

line therapy in the NCCN Guidelines.[4] The activity of cabozantinib after progression on lenvatinib plus pembrolizumab is not yet known and an overlapping spectrum of tyrosine kinases targeted by cabozantinib and lenvatinib raises concern for cross-resistance.

One of the newest agents for RCC is belzutifan, a hypoxia-inducible factor (HIF) inhibitor, which is FDA approved for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Lack of functional VHL protein in those with VHL disease results in stabilization and accumulation of HIF-2α. Upon stabilization, HIF-2α translocates into the nucleus and interacts with HIF-1β to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes. Ninety percent of those with sporadic ccRCC have defective VHL protein. In a Phase II trial, 49 percent of patients

Exhibit 3: Cross-Trial Comparison of First-Line Trials in Advanced RCC[5-10]

	CheckMate 214		KEYNOTE-426		CheckMate 9ER		CLEAR		
	Nivo/ipi (n = 550)	Sun (n = 546)	Pembro/ax (n = 432)	Sun (n = 429)	Nivo/cabo (n = 323)	Sun (n = 328)	Len/pembro (n = 355)	Len/Eve (n = 357)	Sun (n = 357)
Primary endpoint	OS, PFS Int/Poor*		OS, PFS ITT		PFS ITT		PFS ITT		
Median follow-up	55 mo		30.6 mo		18.1 mo		26.6 mo		
mOS	NR	38.4 mo	NR	35.7 mo	NR	NR	NR	NR	NR
OS HR	0.69		0.68		0.60		0.66	1.15	
95% CI	0.59 – 0.81		0.55 – 0.85		0.40 – 0.89		0.49 – 0.88	0.88 – 1.50	
mPFS	12.2 mo	12.3 mo	15.4 mo	11.1 mo	16.6 mo	8.3 mo	23.9 mo	14.7 mo	9.2 mo
PFS HR	0.89		0.71		0.51		0.39	0.65	
95% CI	0.76 – 1.05		0.60 – 0.84		0.41 – 0.64		0.32 – 0.49	0.53 – 0.80	
ORR	39.1%	32.4%	60.0%	40.0%	55.7%	27.1%	71.0%	53.5%	36.1%
CR	10.7%	2.6%	9.0%	3.0%	8.0%	4.6%	16.1%	9.8%	4.2%
PR	28.4%	29.9%	51.0%	37.0%	47.7%	22.6%	54.9%	43.7%	31.9%
PD	17.6%	14.1%	11.0%	17.0%	5.6%	13.7%	5.4%	7.3%	14.0%
Prognostic groups, Fav/Int/Poor	23/61/17%	23/61/16%	32/55/13%	31/57/12%	23/58/19%	22/57/21%	27/64/9%	28/64/9%	27/64/9%
% dose reduction	NA	NA	NA	NA	56.3%	51.6%	69.0%	73.0%	50.0%
% discontinue Rx, 1st drug, 2nd drug, both	22.7%	13.1%	21/20/7%	12.0%	6.6/7.5/5.6%	16.9%	26/29/13%	22/25/19%	14.0%
% ≥ G3 TRAE	48.0%	64.0%	67.0%	62.0%	61.0%	51.0%	72.0%	73.0%	59.0%

Nivo = nivolumab; Ipi = ipilimumab; Sun = sunitinib; Pembro = pembrolizumab; ax = axitinib; cabo = cabozantinib; Len = lenvatinib; Eve = everolimus; mOS = median overall survival; mPFS = median progression-free survival; mo = months; Int = intermediate; ITT = intention to treat; NR = not reported; HR = hazard ratio; CI = confidence interval; ORR = overall response rate; CR = complete response; PR = partial response; PD = progressive disease; Fav = favorable; Rx = medication; G3 = grade three; TRAE = treatment-related adverse events.

with defective VHL and RCC had a partial response to this agent and 56 percent of the responders continued to benefit for 12 months or more.[12]

Biomarkers for efficacy or safety to the various treatments for RCC are not yet available. Unlike with other cancers, programmed death ligand one (PD-L1) expression levels have not been shown to be predictive of response to immunotherapy. PD-L1 levels may be useful to define the relative-risk of progression versus response with dual-immunotherapy versus immunotherapy/VEGF-TKI but this is still under investigation.[13]

Conclusion

The advanced RCC treatment landscape has been evolving rapidly. There are now multiple first-line, category 1 NCCN recommended options and multiple options for second-line and beyond therapy. The choice of regimens is guided by strength of evidence, toxicity profile, patient comorbidities, patient and physician preference, and financial concerns. With the multitude of possible therapeutic sequences, a definitive resolution in preferred sequence is unlikely. Molecular biomarkers to select for efficacy and toxicity are not ready for clinical use but will hopefully make precision

medicine possible in the near future. Clinical trial enrollment should be offered to patients for every-line therapy since cure is unlikely with current therapy.

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Optimizing Psoriasis Care: Key Advances for Current and Novel Therapies

Paul S. Yamauchi, MD, PhD

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

Summary

Biologic agents have shifted the treatment paradigm in psoriasis, offering long-term safety and efficacy to those with moderate to severe disease. The IL-17 and IL-23 agents are the most effective classes and are generally well tolerated.

Key Points

- The goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life.
- Patient preference should be considered when selecting therapy.
- Moderate to severe disease requires phototherapy, systemic agents, or biologics to achieve control.

PSORIASIS IS A CHRONIC RELAPSING immune-mediated inflammatory disease.[1] The most common type is characterized by psoriatic plaques with erythema, induration (thickness), desquamation (scaling), and affects multiple parts of the body. Psoriasis causes significant clinical, social, emotional, and economic burden and has multiple associated comorbidities related to systemic inflammation (Exhibit 1).[1,2] Other comorbidities beyond those shown in the exhibit include sleep apnea, Crohn's Disease, cancer, nonalcoholic steatohepatitis, chronic obstructive pulmonary disease (COPD), and kidney disease. Up to 30 percent of patients with psoriasis develop psoriatic arthritis, usually 10 to 15 years after onset of psoriasis, which can lead to significant joint damage and pain.

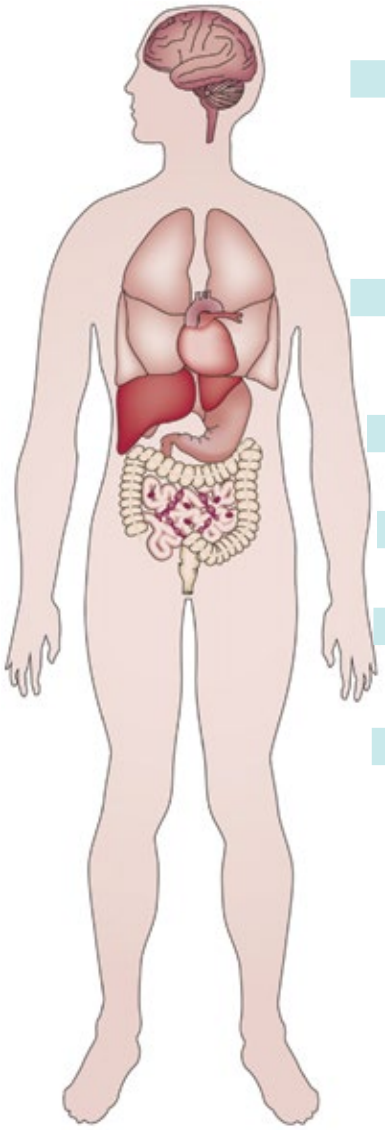
The age of onset is bimodal with the first peak in the second to third decade of life and second peak incidence after 50 years of age. Onset at less than 15 years of age may indicate more severe, resistant disease. Up to one-third of patients report a family history of the disease and several genetic markers have been identified.

Psoriasis is thought to be triggered by an event such as stress, or infection, or medications, in a genetically susceptible individual. The inflammatory process is perpetuated by tumor necrosis factor (TNF) and various interleukins (IL) including 1beta, 2, 6, 12, 17A, 17F, 22, 23.[3,4] TNF, IL-12, IL-17, and IL-23 are all targeted by currently approved biologics.

The severity of psoriasis is assessed based on the body surface area (BSA) affected. Mild is considered 1 to 3 percent BSA affected, moderate 3 to 10 percent, and severe more than 10 percent affected. Location also determines severity. Patients may have scalp, hands, feet, groin, and skin folds affected which are less than 10 percent of BSA but are very disabling. This is especially true of hands and feet. The Psoriasis Area Severity Index (PASI) is used in clinical trials to assess medication efficacy. The PASI score is composed of scores for erythema, induration, scaling, and surface area in each body region. A PASI score over 12 (out of 72) is considered moderate to severe disease. Clinical trial endpoints can range from PASI 50 to PASI 100 which indicates 50 to 100 percent improvement in the score. Investigator or physician global assessment (IGA/PGA) score change is also used in clinical trials.

Treatment goals in psoriasis are to clear the skin of lesions, minimize adverse events, enhance patient quality of life, and address comorbidities.[1] Dermatologists should screen for joint involvement in their psoriasis patients and collaborate with rheumatologists to adequately manage both skin and

Exhibit 1: Individuals with Psoriasis are at Risk of Developing Other Chronic Comorbid Conditions[1,2]



Depression/Anxiety	↑ risk of poor self-esteem, psychological stress, and anxiety due to their psoriasis
Cardiovascular Disease	39% ↑ risk of CV mortality 70% ↑ risk of MI 56% ↑ risk of MI
Obesity	346% ↑ risk (mild psoriasis) 123% ↑ risk (severe)
Metabolic Syndrome	22% ↑ risk (mild) 98% ↑ risk (severe)
Diabetes	14% ↑ risk (mild) 46% ↑ risk (severe)
Psoriatic Arthritis	↑ 30 % of patients 10 to 15 years after onset of psoriasis

CV = cardiovascular; MI = myocardial infarction

joint involvement over the long-term. Patients should be involved in treatment decision making and their preferences considered when selecting therapy.[1] The options for treatment are outlined in Exhibit 2. Mild psoriasis can be managed with topical agents but moderate to severe disease requires phototherapy, systemic agents, or biologics to achieve control. Phototherapy with or without crude coal tar or acitretin can be very effective for many patients but it is time consuming, not widely available, and may not be effectively reimbursed by health insurance (i.e., large copay per session). Methotrexate and cyclosporin are non-specific immunosuppressants with significant toxicities which do not specifically target the underlying pathology of psoriasis; these agents have been replaced with biologics. The biologics available for use in psoriasis and psoriatic arthritis are shown in Exhibit 3. Two oral small molecule drugs are also available. Apremilast, a PDE4 inhibitor, is FDA approved for psoriasis and psoriatic arthritis and tofacitinib, a Janus kinase inhibitor, is approved for psoriatic arthritis. If a patient has psoriatic arthritis, an agent studied in this condition and FDA approved should be selected.

The most recent FDA-approved agent is tapinarof cream, an aryl hydrocarbon receptor agonist indicated for the topical treatment of plaque psoriasis in adults. The aryl hydrocarbon receptor is highly expressed among epithelial and immune system cells of the skin and plays a role in regulating

Exhibit 2: Therapeutic Options for Psoriasis

Mild Disease	Moderate to Severe Disease
• Moisturizers	• Phototherapy
• Topical corticosteroids	• Goeckerman regimen (ultraviolet B light and crude coal tar)
• Topical Vitamin D Analogues	• PUVA
• Calcipotriene	• Ultraviolet B (UVB) light
• Betamethasone plus calcipotriene ointment	• Narrowband (NB-UVB)
• Calcipotriol	• Broadband
• Topical Retinoids	• Narrow band UVB laser
• Tazarotene cream or gel	• Excimer
• Topical immunomodulators	• Systemic Therapy
• Pimecrolimus	• Methotrexate
• Tacrolimus	• Cyclosporine
• Topical aryl hydrocarbon receptor agonist	• Acitretin (combine with PUVA or UVB)
• Tapinarof	• Biologics
• Shampoos	• TNF inhibitor
• Clobetasol shampoo	• IL-12/23 inhibitor
• Ketoconazole shampoo	• IL-17 inhibitor
• Ciclopirox shampoo	• IL-23 inhibitor
• Salicylic acid shampoo	• PDE4 inhibitor
• Tar shampoo	

skin barrier function and immune response. In the two trials with this agent, 36 and 40 percent of patients achieved clear or almost clear skin by PGA compared with 6 percent with vehicle placebo and 36.1 percent and 47.6 percent achieved PASI 75 compared to 10.2 percent and 6.9 percent.[5] The most common adverse reactions with this agent are folliculitis, contact dermatitis, and pruritus.

Exhibit 4 compares the PASI 75, 90, and 100 rates from the various trials used for FDA approval of the biologics and apremilast. Although the rates shown are not from head-to-head trials, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab appear to be the most effective for skin clearing. Systemic reviews have reached this same conclusion.[6,7] These agents are also more effective than TNF inhibitors or ustekinumab in the available head-to-head trials.[8-14] In one comparison between two of the highly effective agents for psoriasis, ixekizumab and guselkumab were found to be noninferior to each other at 24 weeks.[15] Guselkumab showed superior long-term efficacy based on PASI 90 at week 48 when compared with secukinumab for treating moderate to severe psoriasis (84% versus 70%) with similar rates of adverse events.[16] Ixekizumab and secukinumab have also been shown to be more effective than adalimumab for psoriatic arthritis.[17,18]

All of the biologic agents increase the risk for infections. Exhibit 5 shows some of the other safety issues and warnings included in the package labeling for each agent. Apremilast, because of lower impact on the immune system, does not appear to increase risk of infections but does cause diarrhea, nausea, and headache.

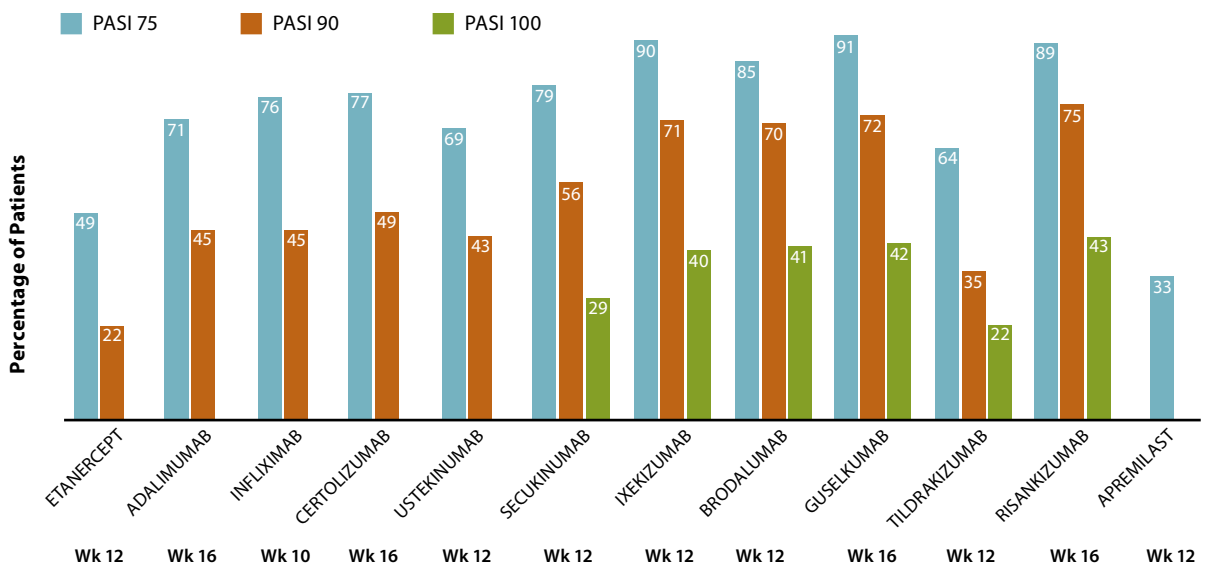
Several additional agents are under investigation. Bimekizumab selectively neutralizes the function

Exhibit 3: Biologic Agents Approved for Psoriasis and Psoriatic Arthritis

Type	Generic Name	FDA-Approved Indication
TNF-alpha Inhibitor	Etanercept	PsO and PsA
	Adalimumab	PsO and PsA
	Infliximab	PsO and PsA
	Golimumab	PsA
	Certolizumab pegol	PsO and PsA
IL-12/23 Inhibitor	Ustekinumab	PsO and PsA
IL-17A Inhibitor	Secukinumab	PsO and PsA
	Ixekizumab	PsO and PsA
IL-17 Receptor Inhibitor	Brodalumab	PsO
T cell Inhibitor	Abatacept	PsA
IL-23 Inhibitor	Guselkumab	PsO
	Tildrakizumab	PsO
	Risankizumab	PsO

PSO = psoriasis; PsA = psoriatic arthritis

Exhibit 4: Comparing Agents for Moderate to Severe Plaque Psoriasis



Data from FDA-approved package labeling
Not based on head-to-head trials

of IL-17A and IL-17F. In trials it produced better results than adalimumab, secukinumab, and ustekinumab.[19-21] Approximately 60 percent of patients achieve PASI 100 with this agent. Like other IL-17 inhibitors, bimekizumab increases risk for oral candida infections. Deucravacitinib is a first-in-class, oral, selective tyrosine kinase 2 (TYK2) inhibitor which inhibits signaling of IL-23, IL-12, and Type 1 interferon – key cytokines involved in the pathogenesis of multiple immune-mediated

Exhibit 5: Safety Considerations for Biologics

TNF Inhibitors
• Serious and opportunistic infections
• Tuberculosis warning
• Malignancies/lymphomas
• CHF exacerbation or new onset
• Demyelination
• Hepatitis B worsening if active
• Paradoxical skin reactions
IL-12/23 inhibitors
• Serious infections
• Malignancies/lymphomas
• Reversible posterior leukoencephalopathy syndrome (Extremely rare)
IL-17 inhibitors
• Infections
• Candidiasis
• Worsening and new onset of inflammatory bowel disease
• Suicide/depression warning (brodalumab)
IL-23 inhibitors
• Infections

diseases. A new drug application has been submitted to the FDA for use in moderate to severe psoriasis but it is also being studied in psoriatic arthritis, lupus and inflammatory bowel disease.[22] In the two trials being used for FDA approval, it was better than placebo and apremilast and had similar safety to apremilast (PASI 75 – 53.6% and 58.7%, placebo 9.4% and 12.7%, apremilast 40.2% and 35.1%).[23]

Topical roflumilast, a selective phosphodiesterase 4 (PDE4) inhibitor, is also being evaluated for psoriasis. Roflumilast is already FDA approved as an oral agent for reducing exacerbations in COPD. Roflumilast cream administered once daily to affected areas of psoriasis was superior to vehicle cream in leading to a state of clear or almost clear skin at six weeks.[24]

Conclusion

Multiple treatment options are now available for managing psoriasis. The primary goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life. Patient preference should be considered when selecting therapy. Moderate to severe disease requires phototherapy, systemic agents, or biologics to achieve control.

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Recent Advances in Novel Biologics in the Management of Psoriatic Arthritis: Elevating the Standard of Care

Gary M. Owens, MD

For a CME/CEU version of this article, please go to
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Summary

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the joints and the connection of tendons and ligaments to bone which can cause permanent joint damage. There are a growing number of targeted treatments including biologics which stop disease progression, lessen pain, and protect joints by modifying the underlying inflammatory pathology. Because these agents have significant financial costs, managed care needs strategies to manage these costs.

Key Points

- Available treatments are rapidly expanding for PsA and treatment guidelines are evolving, but often lack sufficient data to make firm recommendations.
- Treatment strategies should not only focus on the primary diagnosis, but also on the associated comorbidities.
- Treat-to-target is emerging as an effective goal of therapy.
- The treatments for PsA are often high-cost.
- Cost management strategies need to evolve.

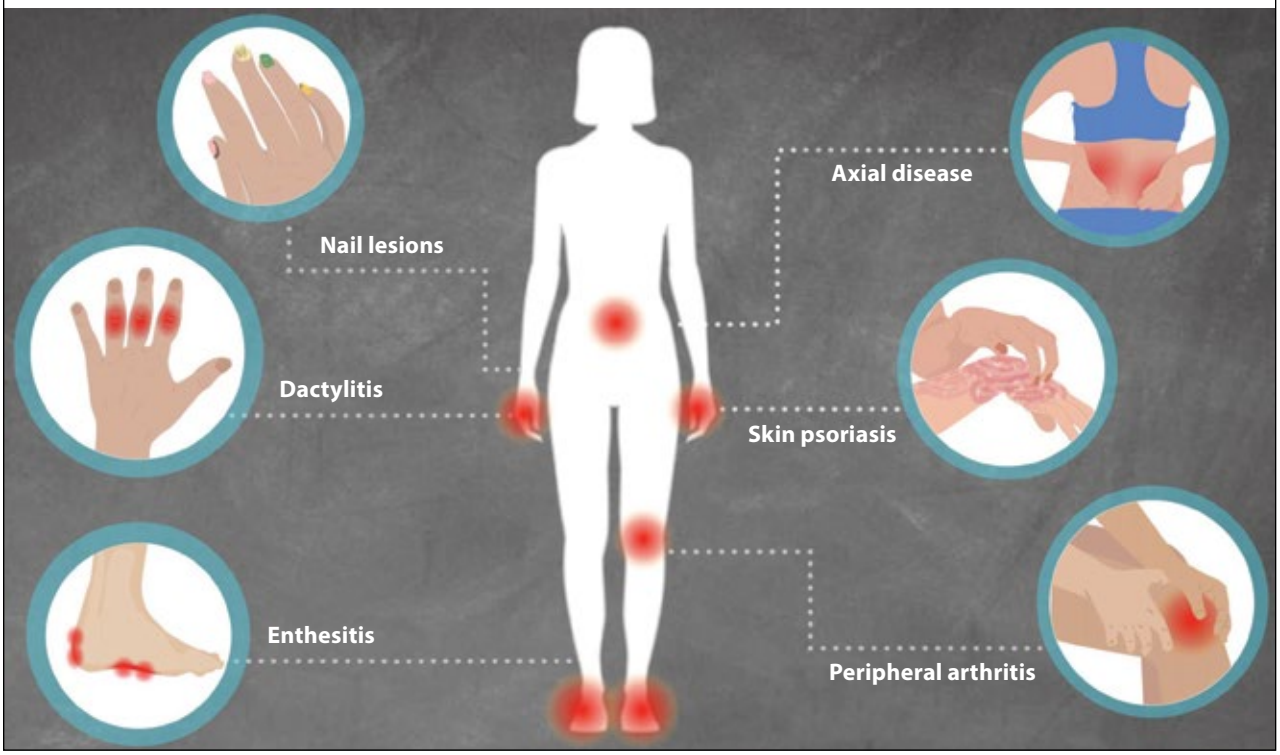
PSORIATIC ARTHRITIS (PsA) IS A CHRONIC inflammatory arthritis that develops in about 30 percent of people with psoriasis.[1] The association between psoriasis and arthritis was first made in the mid-19th century but PsA was not clinically distinguished from rheumatoid arthritis until the 1960s.

PsA is a chronic disease of the joints and the entheses (sites of attachment of tendon and ligaments to bone), including those of the axial skeleton. The affected areas of the body are shown in Exhibit 1. The course of PsA is usually characterized by flares and remissions. The patterns of PsA involvement are asymmetrical oligoarticular arthritis, symmetrical polyarthritis, distal interphalangeal arthropathy, arthritis mutilans, and spondylitis with or without sacroilitis.[1] Arthritis mutilans, known as the pencil-in-cup deformity, is the most severe form of PsA and occurs in 5 percent of people with PsA and affects mainly fingers and toes.

According to the National Psoriasis Foundation, PsA affects about one million people in the United States (U.S.), or about 30 percent of all persons with psoriasis.[2] Studies have shown variable rates among those with psoriasis and the exact frequency of the disorder remains uncertain, with the estimated rate ranging from 5 to 30 percent. Since the late 20th century, the incidence of psoriatic arthritis appears to have been rising in both men and women.[3] Reasons for the increase are unknown, but it may be related to a true change in incidence or to a greater overall awareness of the diagnosis by clinicians.

Race predilection in psoriatic arthritis has not been well studied. Whites are known to be affected more commonly than are persons of other racial groups. PsA characteristically develops in those

Exhibit 1: Domains of PsA



aged 35 to 55 years, but it can occur at almost any age. The male-to-female ratio is one to one.[4] Male patients were found to be more likely to exhibit axial involvement and radiographic joint damage. Female patients were more likely to experience impaired quality of life and severe limitations in function.

Psoriasis precedes the onset of PsA in 60 to 80 percent of patients (occasionally by 20 years, but usually by less than 10 years). In 15 to 20 percent of patients, arthritis appears before psoriasis. Occasionally, arthritis and psoriasis appear simultaneously. In some cases, patients may experience only stiffness and pain, with few objective findings. The musculoskeletal symptoms are usually insidious in onset.

There are no specific diagnostic tests for PsA and diagnosis is based on clinical and radiologic findings.[5] Importantly, PsA should be suspected in any patient with psoriasis who has joint complaints. Radiologic features can help to distinguish psoriatic arthritis from other causes of polyarthritis, such as rheumatoid arthritis (RA). Characteristic laboratory abnormalities in patients with PsA are elevations of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Differentiating PsA from RA can be difficult but rheumatoid factor and antinuclear antibodies are negative in PsA.

Epidemiological studies have shown that PsA patients are often affected by numerous comorbidities that carry significant morbidity and mortality, including diabetes mellitus, obesity, metabolic syndrome, cardiovascular disease, osteoporosis, inflammatory bowel disease, autoimmune eye disease, non-alcoholic fatty liver disease, depression, and fibromyalgia.[6] Part of the reason for the high rate of comorbidities is the systemic inflammation of the disease.

PsA can be a costly disease to manage. A claims database study using 2009 through 2020 data found that annual all-cause healthcare costs per patient were $29,742 for those with PsA, $11,062 for those with only psoriasis, and $7,470 for a control group with neither PsA or psoriasis.[7] All-cause healthcare costs increased over time and were significantly greater among the PsA group compared to the psoriasis ($p < 0.0001$) and control ($p < 0.0001$) groups. Across all categories of healthcare resources, utilization was greatest among patients with PsA and lowest in the control group. The majority of costs for PsA are outpatient visits and prescription medications.

There are multiple guidelines available for managing PsA. The American College of

Exhibit 2: Targeted Therapy in PsA

Agent	Target	Also has Psoriasis Indication	Indication for Axial Disease
Abatacept	CD80/86	No	None
Apremilast	PDE4	Yes	None
Tofacitinib	JAK 1/3	No	AS
Upadacitinib	JAK 1/3	No	None
Etanercept	TNF-α	Yes	AS
Infliximab	TNF-α	Yes	AS
Adalimumab	TNF-α	Yes	AS
Golimumab	TNF-α	No	AS
Certolizumab	TNF-α	Yes	AS and nr-AxSpA
Ustekinumab	IL-12/23	Yes	None
Guselkumab	IL-23	Yes	None
Secukinumab	IL-17A	Yes	AS and nr-AxSpA
Ixekizumab	IL-17A	Yes	AS and nr-AxSpA

CD = cluster of differentiation; PDE4 = phosphodiesterase 4; JAK = janus kinase; TNF = tumor necrosis factor; IL = interleukin; AS = ankylosing spondylitis; nr-AxSPA = Non-Radiographic Axial Spondyloarthritis

Rheumatology/National Psoriasis Foundation (ACR/NPF), the American Academy of Dermatology (AAD), and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) are the major guidelines used in the U.S.[8-10]

One component of the guidelines is managing comorbidities. The AAD psoriasis guidelines recommend cardiovascular risk assessment (screening for hypertension, diabetes, and hyperlipidemia) according to national guidelines for all patients with psoriasis (which includes all with PsA).[9] Patients with psoriasis should be informed about their increased risk for metabolic syndrome and have their obesity status determined according to national guidelines. All patients with psoriasis should have screening lipid tests and fasting blood glucose and/or hemoglobin A1C performed by a healthcare provider according to national guidelines.

As far as treatment goes, the American College of Rheumatology guidelines state that evidence does not support one single approach and there should be informed decision making with the patient in selecting therapy.[8] Treatment options include targeted therapies (biologics, phosphodiesterase 4 inhibitors, and Janus kinase inhibitors), methotrexate, and nonsteroidal anti-inflammatories (NSAIDs). The targeted agents shown in Exhibit 2 modify various aspects of the underlying inflammatory process of PsA and stop disease progression, lessen pain, and protect joints. The treatment guidelines leave room for individualized therapy using important considerations including the presence or absence of comorbidities (inflammatory bowel disease, uveitis, diabetes), serious infections, response to prior treatments, and physical examination, including assessment of the peripheral joints (including for dactylitis), the entheses, the spine, the skin, and the nails. Healthcare providers and patients must also take into consideration the patient's functional status in choosing the optimal therapy for an individual at a given point. Patients benefit from evaluation and treatment early in the disease to prevent joint damage.

A treat-to-target approach should be employed for peripheral and axial arthritis, with a target of remission/inactive disease or, alternatively, low/minimal disease activity. The benefits of this strategy were supported by a randomized, multicenter, open-label trial in the United Kingdom involving 206 patients.[11] Patients with early PsA who were assigned

to tight control were significantly more likely to achieve a 20 percent reduction in symptoms and affected joints (ACR20) at 48 weeks compared with patients receiving standard care (44% versus 18%).

For mild disease (involving less than four joints, no radiological evidence of damage, and minimal discomfort or functional impairment), initiating treatment with an NSAID is reasonable. For moderate disease, apremilast, an inhibitor of phosphodiesterase 4 (PDE4) may be reasonable. In patients with more severe PsA but nonerosive inflammatory arthritis, particularly those with multiple comorbidities, apremilast may be an option if biologics are not indicated. It should not be used in patients with erosive disease, as the capacity of apremilast to prevent joint damage has not been established. In patients presenting with severe disease who already have erosive disease and functional limitation, a TNF inhibitor should be first-line therapy, rather than a conventional nonbiologic disease-modifying agent (DMARD) such as methotrexate.[8] In patients whose joint counts do not improve substantially after three months of treatment with a conventional nonbiologic DMARD or who still have more than three tender and swollen joints, a TNF inhibitor rather than sequential trials of other conventional DMARDs should be used. In patients with peripheral arthritis who experience an inadequate response to an initial TNF inhibitor, use a second TNF inhibitor, a different class of biologic agent (IL-12/23 or IL-17), or a JAK inhibitor can be initiated. Patients with axial disease (ankylosing spondylitis or non-radiographic axial spondyloarthritis) should be treated with a biologic with data and an FDA indication for axial disease (Exhibit 2).

There is scant comparative data on the biologics in PsA to influence treatment selection. In one comparison trial, ixekizumab (interleukin 17A inhibitor) was non-inferior for ACR50 response compared to adalimumab (TNF inhibitor, 51% versus 47%) and superior for PASI100 (100% clearing of psoriasis skin lesions, 60% versus 47%; $p = 0.001$).[12] Ixekizumab produced greater response in additional PsA, skin, nail, treat-to-target, and quality-of-life outcomes. Serious adverse events were reported in 8.5 percent with adalimumab and 3.5 percent with ixekizumab. Data from this study would suggest that IL-17A inhibitors may produce better outcomes with fewer adverse events than TNF inhibitors.

The number of available treatments for PsA and potential treatment variables continues to increase. Many treatments for PsA also have FDA approvals for other inflammatory diseases. Seven of the top ten specialty medications by gross spend, according to RxBenefits' 2020 book of business analysis are used to treat PsA and/or psoriasis, in addition to other inflammatory diseases.[13] Formulary management of this area is essential. This is a highly competitive area with significant price and contracting competition.

In a 2020 real-world data study, initial treatment for PsA was mostly methotrexate monotherapy, even without guideline recommendations for first-line use of methotrexate.[14] Approximately one in four treatment-naïve patients initiated a TNF inhibitor monotherapy as the first treatment for PsA. Treatment with biologic monotherapy and combination therapy with oral small molecules particularly methotrexate, were the most common second-line regimens. This study found that biologics are the primary cost driver in PsA pharmacologic therapy.

To manage costs and outcomes, payers need to create a careful balance of patient needs with evolving treatment guidelines. They need to manage formularies to provide all available classes of drugs, use available data to drive contracting strategies for preferred agents, and recognize that comparative data may be incomplete (as the guideline makers have noted). Real-world data may help drive formularies but is often not contemporaneous. Payers need to continue to review and update formularies as new treatment options become available and new data emerge.

Conclusion

Psoriatic arthritis is an inflammatory arthritis with many associated comorbidities and which may present in many different forms. Available treatments are rapidly expanding for PsA and treatment guidelines are evolving, but often there is a lack of sufficient data to make firm recommendations of one agent or class over another. Treatment strategies should not only focus on the primary diagnosis, but also on the associated comorbidities. Treat-to-target is emerging as an effective goal of therapy. The treatments for PsA are often high-cost. Management strategies need to evolve using a combination of guideline recommendations, clinical data, and real-world data when available.

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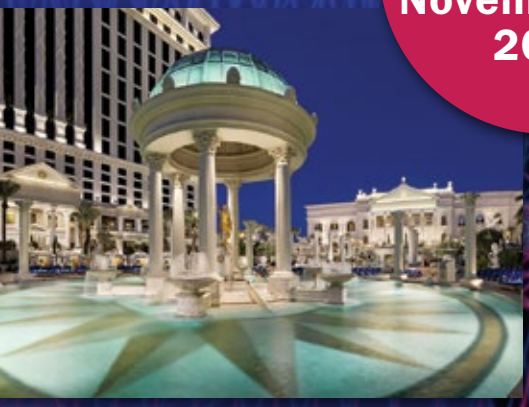

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