Vol. 28, No. 2, 2025

JOURNAL of MANAGED CARE MEDICINE

Educating Medical Directors of Employers, Health Plans and Provider Systems

FEATURED ARTICLES INCLUDE:

Evolving Considerations in Treatment and Management of HR+/HER2- Breast Cancer: Expert Insights on the Role of Emerging Targeted Therapies

Implementing New Data and Evolving Standards in Advanced Renal Cell Carcinoma: Optimizing Outcomes with Novel Targeted Therapies

Informed Managed Care Decision-Making in the Management of Endometrial Cancer: Optimizing Immunotherapy for Improved Patient Outcomes

Editorial Review Board

JMCM

JOURNAL OF MANAGED CARE MEDICINE

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

EDITOR-IN-CHIEF
Thomas Morrow, MD

PUBLISHER
Jeremy Williams

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

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

GRAPHIC DESIGN
Douglas Murphy Communications

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

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

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

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 28, No. 2, 2025

TABLE OF CONTENTS

Evolving Considerations in the Treatment and Management of HR+/HER2- Breast Cancer: Expert Insights on the Role of Emerging Targeted Therapies

Lee Schwartzberg MD, FACP

This journal article is supported by educational grants from AstraZeneca; Genentech; Merck

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 breast cancer has changed dramatically over the years with the identification of various subtypes and genetic mutations which increase risk or are drivers of tumor cell growth. The treatment of metastatic breast cancer is evolving with the introduction of various targeted therapies aimed at these genetic mutations.

Key Points

- Biomarker testing is important to identify those patients who might benefit from targeted therapies.
- Mutations in PIK3CA are common in HR+HER2- mBC.
- PIK3CA inhibitors in combination with other targeted therapies will play an increasingly key role in those with these mutations.

IN 2025, AN ESTIMATED 316,950 WOMEN and 2,800 men in the United States will be diagnosed with invasive breast cancer, and 42,170 women and 510 men are projected to die from the disease.[1] The lifetime risk of breast cancer for women is 12.6 percent and it remains the most common cause of cancer in women.

Breast cancer is composed of biologically distinct subgroups. These include hormone receptor positive/human epidermal growth factor receptor two negative (HR+/HER2–), HR+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC). HR+/HER2- is the most common subtype (Exhibit 1). Each of these subtypes is treated differently.

Multiple germline mutations have been shown to increase the risk of breast cancer. BRCA1, BRCA2, and PALB2 are the most common high-risk mutations and ATM and CHEK2 are the most common moderate-risk mutations. The American Society of Clinical Oncology (ASCO) guidelines recommend BRCA1/2 mutation testing be offered to all newly diagnosed patients with breast cancer, who are 65 years of age or less and select patients over 65 years of age, based on personal history, family history, ancestry, or eligibility for poly(ADP-ribose) polymerase (PARP) inhibitor therapy.[2] The National Comprehensive Cancer Network (NCCN) Guidelines provide a similar recommendation.[3]

Germline BRCA mutations occur in both HR+/HER2– and TNBC subtypes. Most cases (greater than 80%) are found in patients with HER2– disease. BRCA1 or BRCA2 gene mutations impair DNA

Exhibit 1: Breast Cancer Subgroups

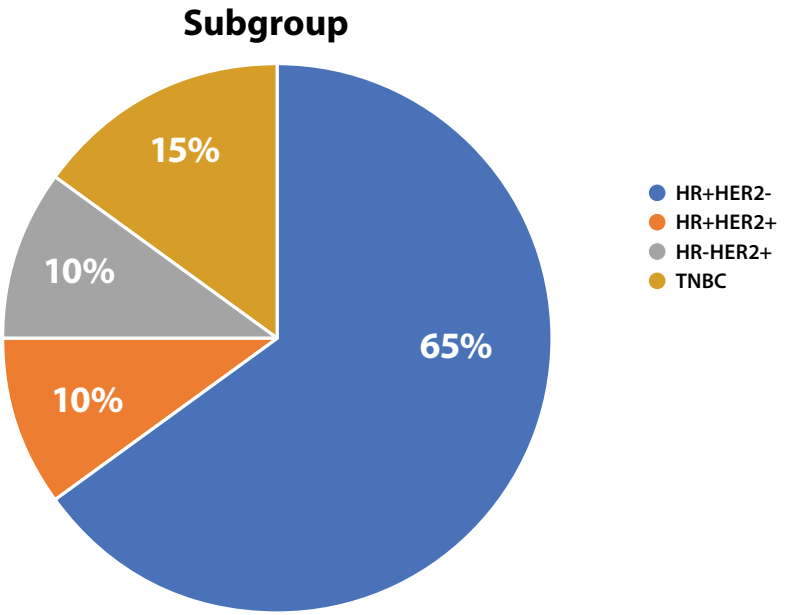
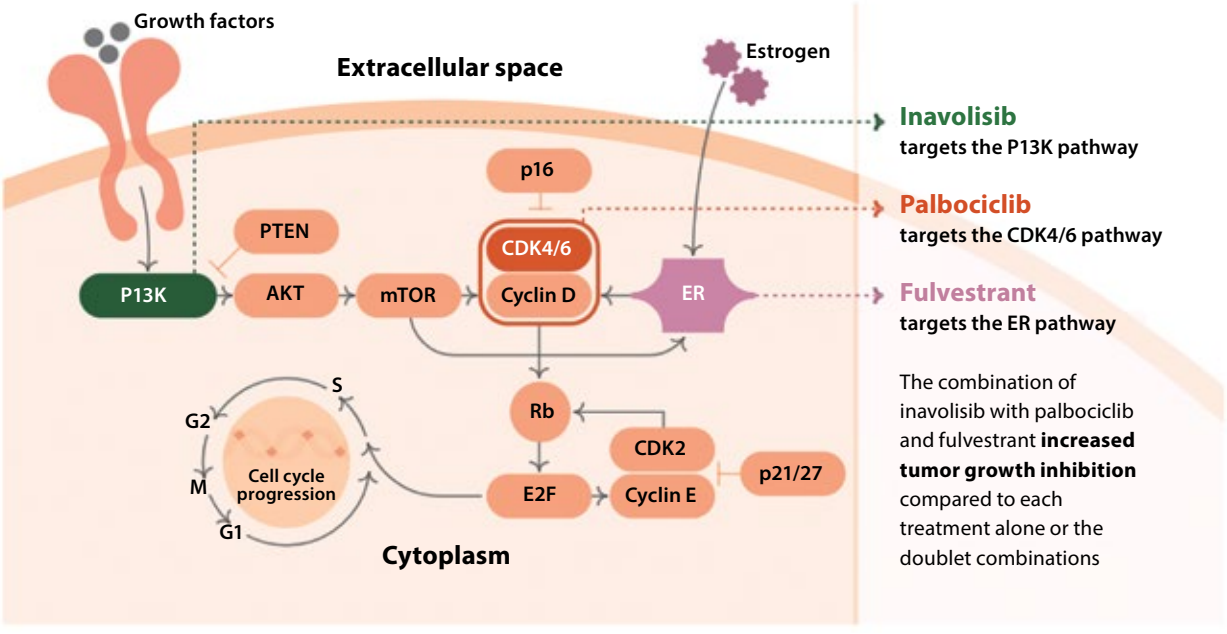


Exhibit 2: Intersection of PI3K, CDK4/6, and Estrogen Receptor Pathways[4]



AKT = alpha serine/threonine-protein kinase; CDK2 = cyclin-dependent kinase 2; CDK4/6 = cyclin-dependent kinase 4/6; E2F = E2F transcription factors; ER = estrogen receptor; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; mTOR = mechanistic target of rapamycin; PI3Ka = phosphatidylinositol 3-kinase alpha; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog deleted on chromosome 10; Rb = retinoblastoma protein

Exhibit 3: Targeted Therapies for PIK3CA Mutations in Recurrent Unresectable or Metastatic Disease[3]

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
HR-positive HER2-negative	*PIK3CA* activating mutation	NGS,PCR	Inavolisib + palbociclib + fulvestrant	Category 1	Useful in certain circumstances first-line therapy
HR-positive/ HER2-negative	*PIK3CA* activating mutation	NGS,PCR	Alpelisib + fulvestrant	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative	*PIK3CA* or *AKT1* activating mutations or *PTEN* alterations	NGS,PCR	Capivasertib + fulvestrant	Category 1	Preferred second- or subsequent-line therapy in select patients

repair leading to homologous repair deficient (HRD) cells. PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in HRD cells and two (olaparib, talazoparib) are currently approved for treating germline BRCA mutated metastatic breast cancer (mBC).

Other mutations are common in mBC. Approximately 40 percent of those with HR+/ HER2- mBC have mutations in PIK3CA. PIK3CA activation mutations are associated with poor prognosis. Inavolisib is a highly potent and selective inhibitor of the alpha isoform of the p110 catalytic subunit of PIK3CA that also promotes the degradation of mutated p110α. *In vitro*, it also inhibited phosphorylation of the downstream target AKT, reduced cellular proliferation, and induced testing for PIK3CA, among other mutations, in those with mBC.[4]

Inavolisib plus palbociclib, an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, and fulvestrant, an estrogen receptor antagonist, showed synergistic activity in preclinical models and promising antitumor activity in early-phase trials. This combination targets three different pathways of tumor cell growth in breast cancer (Exhibit 2).[4] In prior studies with other PIK3CA inhibitors (alpelisib) and fulvestrant, there was an improved progression-free survival (PFS) with the combination over fulvestrant alone in the HR+, HER-, metastatic breast cancer population with progression on or after an aromatase inhibitor (11.0 months versus 5.7 months).[5] In the final overall survival (OS) results from this trial, median OS was 39.3 months for alpelisib-fulvestrant and 31.4 months for placebo-fulvestrant but was not statistically significant ($p = 0.15$).[6]

In a Phase III, double-blind, randomized trial, inavolisib (at an oral dose of 9 mg once daily) plus palbociclib and fulvestrant (inavolisib group) was compared to placebo plus palbociclib and fulvestrant (placebo group) in 161 patients with PIK3CA-mutated, HR+, HER2- locally advanced or metastatic breast cancer who had relapsed during or within 12 months after the completion of adjuvant endocrine therapy. The included subjects had either primary or secondary endocrine therapy (ET) resistance. Primary endocrine resistance is defined as disease relapse while on the first two years of adjuvant ET, or progressive disease within first six months of first-line ET for mBC, while on this therapy.[7] Secondary endocrine resistance is defined as relapse while on adjuvant ET, but after the first two years, or relapse, within 12 months of completing adjuvant ET, or progressive disease within six months after initiating ET for mBC, while on ET.[7] In this trial, the median PFS was 15.0 months (95% confidence interval [CI], 11.3 to 20.5) in the inavolisib group and 7.3 months (95% CI, 5.6 to 9.3) in the placebo group (hazard ratio for disease progression or death, 0.43; 95% CI, 0.32 to 0.59; $p < 0.001$).[8] An objective response occurred in 58.4 percent of the patients in the inavolisib group and in 25.0 percent of those in the placebo group. Interim OS was better in the inavolisib group compared to placebo group (not yet reached versus 31.1 months, $p = 0.03$). Final OS data have not yet been published. The incidence of Grade 3 or 4 adverse events including neutropenia was 80.2 percent in the inavolisib group and 78.4 percent in the placebo group; hyperglycemia, 5.6 percent and 0 percent; stomatitis or mucosal inflammation, 5.6 percent and 0 percent; and diarrhea, 3.7 percent and 0 percent. Discontinuation for adverse events

occurred in 6.8 percent of the patients in the inavolisib group and in 0.6 percent of those in the placebo group.

Inavolisib was approved by the FDA in January 2025. It is indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR+, HER2-, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. The triple combination is a Category 1 NCCN recommendation as first-line therapy for unresectable local or regional or metastatic breast cancer when PIK3CA mutations are present and disease progression has occurred on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion (Exhibit 3).[3]

Conclusion

Targeted therapies have made a substantial impact on the treatment of metastatic breast cancer. Biomarker testing is important to identify those patients who might benefit from these therapies.

Alterations in PIK3CA are common in HR+HER2- mBC and all patients should undergo comprehensive genomic testing at diagnosis of metastatic disease. PIK3CA inhibitors in combination with other targeted therapies will play an increasingly key role in those with these mutations.

Lee Schwartzberg MD, FACP is a Professor of Clinical Internal Medicine at the University of Nevada in Reno and Chief of Medical Oncology and Hematology at the Renown Health-Pennington Cancer Institute in Reno, NV.

References

1. American Cancer Society. Cancer Facts & Figures 2025. Available at cancer.org. Accessed 4/22/2025.
2. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline testing in patients with breast cancer: ASCO-Society of Surgical Oncology Guideline. *J Clin Oncol*. 2024;42(5):584-604.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. Version 4.2025. Available at nccn.org. Accessed 4/22/2025.
4. Brufsky AM, Dickler MN. Estrogen receptor-positive breast cancer: Exploiting signaling pathways implicated in endocrine resistance. *Oncologist*. 2018;23(5):528-39.
5. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-40.
6. André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Final overall survival results from SOLAR-1. *Ann Oncol*. 2021;32(2):208-17.
7. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast*. 2014;23(5):489-502.
8. Turner NC, Im SA, Saura C, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast Cancer. *N Engl J Med*. 2024;391(17):1584-96.

Implementing New Data and Evolving Standards in Advanced Renal Cell Carcinoma: Optimizing Outcomes with Novel Targeted Therapies

Bradley McGregor, MD

This journal article is supported by an educational grant from AVEO Pharmaceuticals

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

Summary

The treatment of advanced renal cell carcinoma (RCC) has evolved dramatically over the last decade. Combination therapy with immunotherapy and oral tyrosine kinase inhibitors or dual immunotherapy has replaced targeted agent monotherapy as first-line treatment. Both of these strategies are improving overall survival.

Key Points

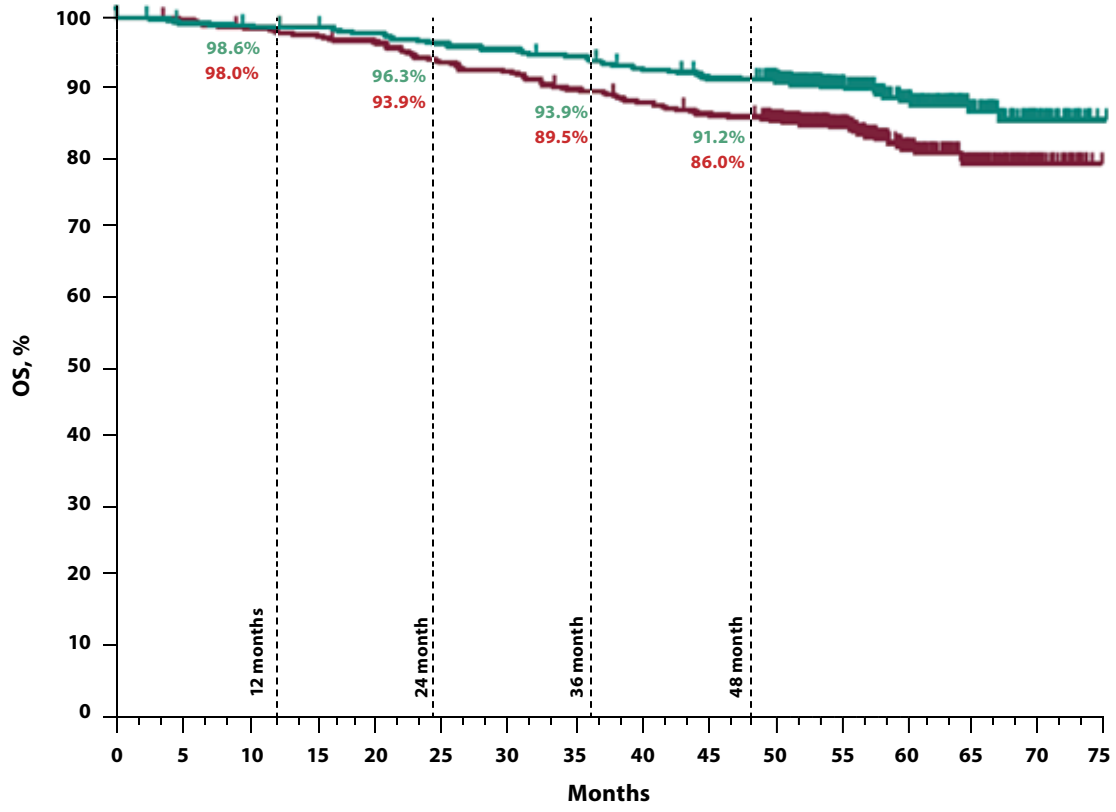
- Adjuvant immunotherapy is an option post-surgical resection for patients who meet certain criteria to reduce risk of metastatic disease.
- First-line treatment of advanced RCC is now combination therapy.
- The choice of which combination to use will depend on many factors.
- Second-line therapy is dictated by front line-treatment.
- Tivozanib and belzutifan are two newer options for later lines of therapy.

RENAL CELL CARCINOMA (RCC) IS THE most common type of kidney cancer in adults and accounts for 80 percent of all cases of kidney cancer.[1] Approximately 70 percent of RCC cases are of clear cell histology.[1] In 2025, about 80,980 new cases of kidney cancer will be diagnosed and about 14,510 people will die from this disease.[2] The five-year survival rate is 78.6 percent.

The best way to treat metastatic RCC is to prevent it. Adjuvant therapy after first-line resection of RCC can reduce risk of recurrence and help patients live longer. Anti-vascular endothelial growth factor (VEGF) tyrosine kinases inhibitors (TKIs) were initially shown to work well in advanced disease but were then investigated in earlier stage disease. Unfortunately, none of the trials showed that patients lived any longer with one year of adjuvant TKI therapy and there were significant adverse events. One small trial did show a small disease-free survival (DFS) benefit of one year with sunitinib but overall survival (OS) was not improved.[3] Thus, sunitinib delayed recurrence but did not improve survival. Subsequently, checkpoint immunotherapy was investigated as adjuvant therapy. Of the five trials with nivolumab, nivolumab/ipilimumab, atezolizumab, and pembrolizumab, only the pembrolizumab trial was positive.[4] In this trial in intermediate-high and high-risk clear cell RCC, adjuvant pembrolizumab 200 mg every three weeks for up to 17 cycles (approximately 1 year) or until recurrence or unacceptable toxic events improved OS compared to placebo (hazard ratio for death, [HR] 0.62; p = 0.005; Exhibit 1).[5] The estimated overall survival at 48 months was 91.2 percent in the pembrolizumab group, as compared with 86.0 percent in the placebo group. Adjuvant pembrolizumab did not eliminate the risk of recurrence and there was also about a 30 percent risk of recurrence in this trial. This was the first trial to show giving therapy after RCC resection helped patients live longer but there were significant adverse events with immunotherapy and 10 percent of patients had to discontinue therapy due to these adverse events.

There are some unanswered questions about adjuvant therapy. Given the other negative adjuvant immunotherapy trials, clinical criteria from the

Exhibit 1: Overall Survival with Adjuvant Pembrolizumab[5]



No. at risk

Pembro	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9 to 74.5)		

HR 0.62 (95% CI 0.44 to 0.87); *p* = .002*

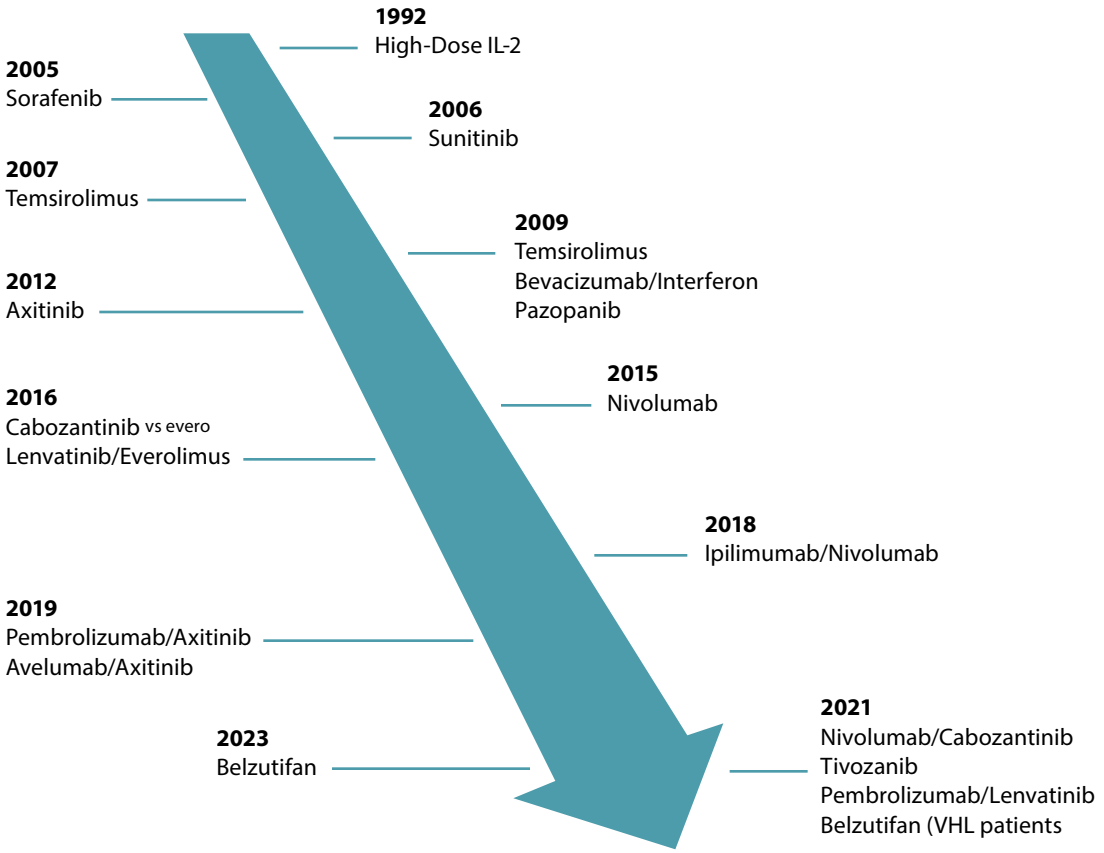
***denotes statistical significance.** P-value boundary for OS at IA3 was 0.0072 (1-sided per Lan-DeMets O'Brien-Fleming spending approximation "-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

positive trial are key for choosing the correct patients. Adjuvant therapy should be offered to those with clear cell RCC who meet the inclusion criteria from the trial:

- Intermediate-high risk RCC: pT2, Grade 4 or sarcomatoid, N0, M0; pT3, Any Grade, N0, M0;
- High- risk RCC: pT4, Any Grade N0, M0; pT Any stage, Any Grade, N+, M0; M1 no-evidence of disease in RCC participants who present not only with the primary kidney tumor but also solid, isolated, soft tissue metastases that can be completely resected at one of the following: the time of nephrectomy (synchronous) or, one year or less from nephrectomy (metachronous).

Currently these are the only criteria for selecting patients for adjuvant pembrolizumab; there is not yet a good biomarker to guide adjuvant treatment selection.

Exhibit 2: Systemic Treatment of Advanced RCC Over the Years



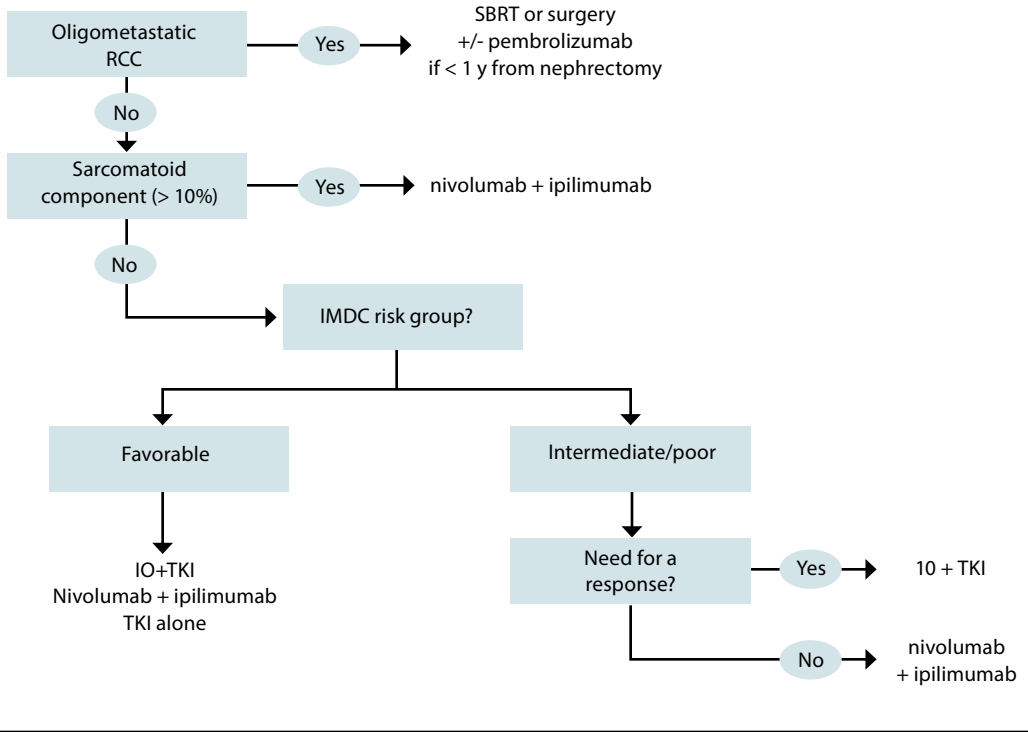
About 30 percent of patients with localized RCC will develop metastatic disease after initial treatment. In choosing therapy for metastatic disease it is first important to decide if this is a local recurrence which can be resected, ablated, or radiated. Aggressive local therapy can render many patients with no evidence of disease.

The systemic treatment paradigm for advanced disease has undergone a dramatic transformation in recent years (Exhibit 2). In the past, chemotherapy was shown to not be effective. Now the combination of targeted therapy (TKIs) and immunotherapy or dual immunotherapy is the standard of care in patients with metastatic clear cell RCC.[1] Therapy is chosen based on risk factors such as performance status, laboratory measurements, and time since initial treatment all of which place a patient in favorable, intermediate, or poor prognostic categories.[6]

Dual immunotherapy is nivolumab, a programmed death one (PD-1) inhibitor, in combination with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab. In the Phase III CheckMate 214 trial there was a significantly higher OS and objective response rate (ORR) with the immunotherapy combination (NIVO+IPI) compared with sunitinib.[7] With eight years of median follow-up, the HR for OS with NIVO+IPI versus sunitinib was 0.72 in intention to treat patients, 0.69 in intermediate/poor-risk patients, and 0.82 in favorable risk patients.[8] The combination shrinks the tumor in 40 percent of patients but does not work in 20 percent of patients. Importantly, it eliminates the tumor in 12 percent of patients and these are patients with Stage 4 RCC who are being cured with this combination. The FDA approved this combination for intermediate and poor-risk patients based on the trial design but in the long-term follow-up of this trial, survival trends towards the combination also occurred in those with favorable disease. Overall, the combination of nivolumab and ipilimumab offers the opportunity for durable response irrespective of risk factors.

One factor for which patients do much better with dual immunotherapy is sarcomatoid histology.

Exhibit 3: An Approach to First-Lline Treatment of Advanced RCC



SBRT = stereotactic body radiation therapy; IO = immunotherapy; TKI = tyrosine kinase inhibitor; IMDC = International Metastatic RCC Database Consortium

Sarcomatoid RCC tumors are characterized by an immune-inflamed phenotype with activation of immune pathways, increased expression of APM genes, increased cytotoxic immune infiltration, and high expression of programmed death ligand one (PD-L1) on tumor cells.[9] With nivolumab/ipilimumab, those with sarcomatoid tumors have a 20 percent complete response rate.[7]

An issue with nivolumab/ipilimumab is its use in very ill patients who may progress on this combination and not be eligible for another line of therapy. The 20 percent progressive disease rate with the combination is significant. This combination is given for two years and is then stopped unlike the next combination discussed.

The next evolution of therapy was immunotherapy combined with oral TKIs which are both given till disease progression or intolerable adverse events. In the Keynote-426 trial, treatment with pembrolizumab plus axitinib resulted in significantly longer OS and progression-free survival (PFS) compared to sunitinib, the prior standard of care, in the first-line setting for metastatic RCC.[10] At a median follow-up of 43 months, ORR with pembrolizumab/axitinib and sunitinib was 60 percent versus 40 percent, respectively.[11] Benefit with pembrolizumab/axitinib versus sunitinib was maintained for OS (HR 0.73) and PFS (HR 0.68). The median duration of response was 24 months versus 15 months, respectively. Twelve percent of subjects had progressive disease on pembrolizumab/axitinib. The longer-term OS curves show an upfront benefit of the combination but the curves merge over time.

In the CheckMate 9ER trial which compared nivolumab plus cabozantinib with sunitinib in a similar patient population to the pembrolizumab/axitinib trial, the median PFS was 16.6 months with the combination and 8.4 months with sunitinib ($p < 0.001$).[12] Median OS favored nivolumab/cabozantinib versus sunitinib (49.5 versus 35.5 months; HR 0.70). ORR was 56 percent versus 28 percent; 13 percent versus 5 percent of patients achieved a complete response, and the median duration of response was 22.1 months versus 16.1 months, respectively. PFS and OS favored nivolumab/cabozantinib across intermediate-, poor-, and intermediate/poor-risk subgroups; higher ORR and complete response rates were seen with nivolumab/cabozantinib regardless of risk subgroup. Nivolumab was given for up to two years in this trial. This trial used a lower dose of cabozantinib than currently FDA approved.

In the CLEAR trial, lenvatinib plus pembrolizumab was compared to lenvatinib plus everolimus or sunitinib.[13] The median OS was 53.7 months with

lenvatinib/pembrolizumab versus 54.3 months with sunitinib; 36-month OS rates were 66.4 percent and 60.2 percent, respectively. The median PFS was 23.9 months with lenvatinib/pembrolizumab and 9.2 months with sunitinib (HR, 0.47). ORR also favored the combination over sunitinib (71.3% versus 36.7%; relative risk 1.94). The complete response rate with this combination was 18.3 percent and the progressive disease rate was 5.4 percent, the lowest rate seen with any of the combination regimens. Treatment-emergent adverse events occurred in more than 90 percent of patients who received either treatment.

There are no head-to-head trials of dual immunotherapy or immunotherapy/TKI combinations so it is impossible to say any one combination is more effective. Immunotherapy/TKI combinations are FDA approved across various risk categories. There is controversy among specialists whether those with favorable-risk disease need more aggressive combinations rather than just a TKI. The fact that some of the immunotherapy/TKI combinations are continued for many years has its own complications including continued adverse event risk and the need for long-term management of adverse events. Exhibit 3 shows an approach to choosing therapy for first-line management of advanced disease. A major area of controversy is what to do with patients who have disease recurrence after adjuvant immunotherapy and this is yet to be resolved.

With second-line therapy for advanced RCC, there are numerous options and a choice will depend on prior therapy. There are no Phase III randomized trials of second-line treatment post-immunotherapy so the NCCN Guidelines do not have a preferred regimen.[1] If the patient has never received immunotherapy, immunotherapy is an option. A TKI should be chosen for those who have progressed on immunotherapy. Importantly immunotherapy should be discontinued in the advanced RCC setting if disease progression occurs; this being based on a randomized trial which showed no benefit to continuing the immunotherapy in this setting.[14]

Tivozanib is a newer TKI option for patients who received two or more prior systemic therapies. It inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2 and VEGFR-3 and inhibits other kinases including c-kit and PDGFR β at clinically relevant concentrations. Tivozanib was compared to sorafenib in those with advanced RCC previously treated with two systemic treatments (including at least one previous treatment with a TKI), measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1, and an Eastern Cooperative Oncology Group performance status of 0 or 1. At a median follow-up of 19.0 months, median PFS was significantly longer with tivozanib (5.6 months) than with sorafenib (3.9 months, $p = 0{\cdot}016$).[15] In the long-term follow-up report, PFS rates up to 48-months are consistently higher with tivozanib compared to sorafenib (12% versus 2% and 7.6% versus 0% at 3 years and 4 years, respectively).[16] Interestingly with this agent is that about 20 percent of patients, who are on at least third-line therapy, can maintain a disease response for a significant amount of time. This agent is dosed three weeks on and one week off and is a well-tolerated TKI. It has fewer off-target adverse events compared to older TKIs.

Belzutifan is a novel hypoxia-inducible factor two (HIF2) inhibitor which was initially FDA approved for patients with von Hippel-Lindau (VHL) disease who required therapy for associated RCC, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery. It was then FDA approved in early 2025 for advanced clear cell RCC following immunotherapy and a TKI. HIF2 is upregulated in clear cell RCC. At the first interim analysis of a Phase III trial comparing belzutifan to everolimus (median follow-up, 18.4 months), the median PFS was 5.6 months in both groups; at 18 months, 24.0 percent of the participants in the belzutifan group and 8.3 percent in the everolimus group were alive and free of progression (two-sided $p = 0.002$).[17] The ORR was 21.9 percent of the participants in the belzutifan group and 3.5 percent in the everolimus group ($p < 0.001$). At the second interim analysis (median follow-up, 25.7 months), the median OS was 21.4 months in the belzutifan group and 18.1 months in the everolimus group; at 18 months, 55.2 percent and 50.6 percent of the participants, respectively, were alive (HR, 0.88; two-sided $p = 0.20$, which did not meet the prespecified significance criteria). This agent has different adverse events as it targets HIF2. Anemia and hypoxia are common. There are ongoing trials combining HIF2 inhibitors and TKI which may become a standard of care in the future.

Conclusion

Therapy for RCC has dramatically evolved. Immunotherapy is an option in adjuvant settings for patients who meet the criteria from the clinical trial. Combination therapies are standard of care in first-line treatment of metastatic disease and second-line therapy is dictated by front-line treatment. Tivozanib is a well-tolerated TKI which is an option in the second-line or later. Belzutifan offers a novel agent with unique toxicity profile. Trials are ongoing which will further change the RCC treatment standard of care.

Bradley McGregor, MD is an Assistant Professor of Medicine at Harvard Medical School and Director of Clinical Research at the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute in Boston, MA.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 3.2025. Available at www.nccn.org. Accessed 04/23/2025.
2. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Available at seer.cancer.gov/statfacts/html/kidrp.html. Accessed 4/23/2025.
3. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375:2246-54.
4. Riveros C, Huang E, Ranganathan S, et al. Adjuvant immunotherapy in renal cell carcinoma: a systematic review and meta-analysis. *BJU Int*. 2023;131(5):553-61.
5. Choueiri TK, Tomczak P, Park SH, et al. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. *N Engl J Med*. 2024;390(15):1359-71.
6. Heng DY, Xie W, Regan MM, et al. External validation, and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: A population-based study. *Lancet Oncol*. 2013;14(2):141-8.
7. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-90.
8. Tannir NM, Albigès L, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: Extended 8-year follow-up results of efficacy and safety from the Phase III CheckMate 214 trial. *Ann Oncol*. 2024;35(11):1026-38.
9. Bakouny Z, Braun DA, Shukla SA, et al. Integrative molecular characterization of sarcomatoid and rhabdoid renal cell carcinoma. *Nat Commun*. 2021;12(1):808.
10. Rini BI, Plimack ER, Stus V, et al, for the KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380 (12):1116-27.
11. Plimack ER, Powles T, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib as first-line treatment of advanced renal cell carcinoma: 43-month follow-up of the Phase III KEYNOTE-426 study. *Eur Urol*. 2023;84(5):449-54.
12. Powles T, Burotto M, Escudier B, et al. Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended follow-up from the Phase III randomized CheckMate 9ER trial. *ESMO Open*. 2024;9(5):102994.
13. Motzer RJ, Porta C, Eto M, et al. Lenvatinib plus pembrolizumab versus sunitinib in first-line treatment of advanced renal cell carcinoma: Final prespecified overall survival analysis of CLEAR, a Phase III study. *J Clin Oncol*. 2024;42(11):1222-8.
14. Pal SK, Albiges L, Tomczak P, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): A multicenter, randomized, open-label, Phase III trial. *Lancet*. 2023;402(10397):185-95.
15. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): A Phase III, multicenter, randomized, controlled, open-label study. *Lancet Oncol*. 2020;21(1):95-104.
16. Atkins MB, Verzoni E, Escudier B, et al. Long-term PFS from TIVO-3: Tivozanib (TIVO) versus sorafenib (SOR) in relapsed/refractory (R/R) advanced RCC. *J Clin Oncol*. 2022;40(6_suppl):Abstract 362.
17. Choueiri TK, Powles T, Peltola K, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. *N Engl J Med*. 2024;391(8):710-21.

Informed Managed Care Decision-Making in the Management of Endometrial Cancer: Optimizing Immunotherapy for Improved Patient Outcomes

Bradley J. Monk, MD, FACS, FACOG

This journal article is supported by an educational grant from GlaxoSmithKline

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

Summary

Immunotherapy with checkpoint inhibitors has become a promising treatment option for treating advanced endometrial cancer. While initially used in the second-line or later setting, these therapies are being used in combination with standard of care chemotherapy in the first-line treatment setting. Improvements in progression-free survival and overall survival are being shown with immunotherapy/chemotherapy combinations.

Key Points

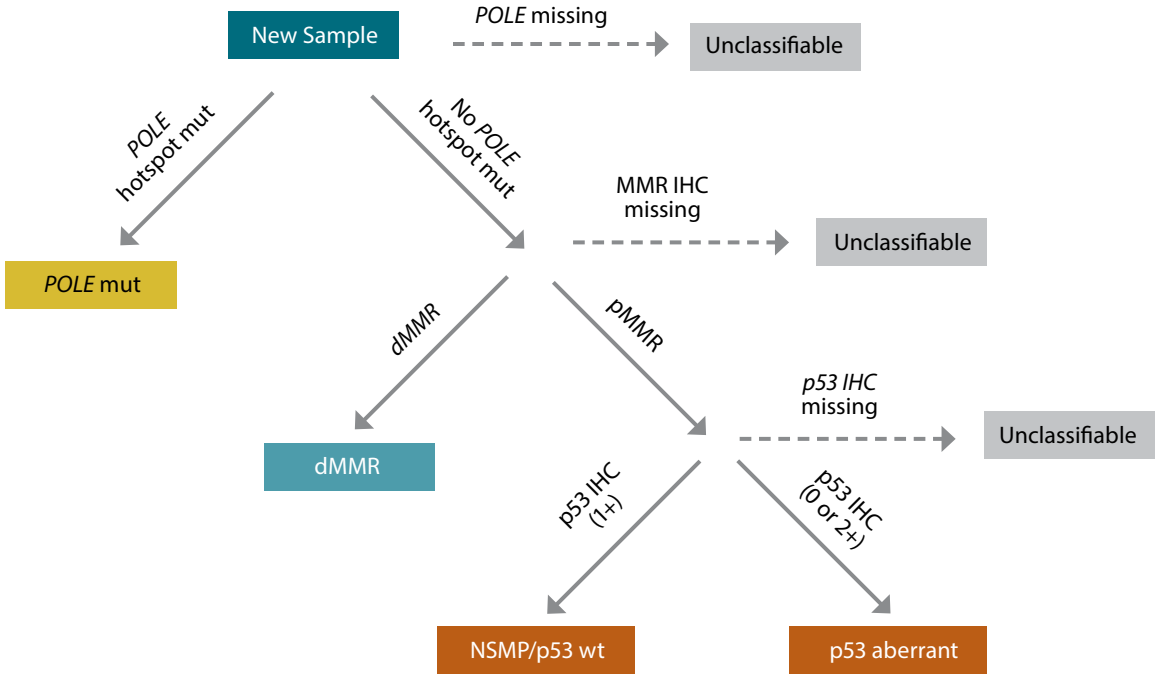
- Immunotherapy plus chemotherapy is indicated in first-line systemic treatment of advanced endometrial cancer.
- Patients with dMMR endometrial cancers should receive immunotherapy because this group achieves the most benefit.
- Single-agent immunotherapy is an option for recurrent disease if the patient is immunotherapy naïve.
- In second-line treatment of pMMR immunotherapy naïve recurrent endometrial cancer, pembrolizumab plus lenvatinib is FDA approved as well as NCCN recommended.

UTERINE CANCER IS MOST COMMON AND most lethal gynecologic cancer among women in the United States. In 2024, it accounted for 7 percent of cancer cases and 5 percent of cancer deaths among women.[1] Endometrial cancer is the most common uterine cancer accounting for 95 percent of cases.

There is a 3.1 percent cumulative lifetime risk for endometrial cancer in the general population and the median age at diagnosis is 63 years.[2] Fortunately, it is usually confined to the uterus at diagnosis resulting in a five-year survival of 81 percent. Unfortunately, the incidence of endometrial cancer has been increasing at a rate of 1.7 percent annually (2010 to 2019).[2,3] Additionally, the rate among African Americans has been increasing at 2 percent annually. Uterine cancer mortality rate ratio for African American patients compared with White patients increased from 1.83 (1.77 to 1.89) from 1990 to 1994 to 1.98 in 2015 to 2019 (95% CI, 1.93 to 2.02).[4]

One advance in the treatment of endometrial cancer is molecular profiling. It is recommended in newly diagnosed endometrial cancer because it allows for a more precise classification of the tumor, based on its genetic characteristics, which can significantly impact treatment decisions. Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups associated with differing clinical prognoses: POLE mutations, microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and aberrant p53 protein (Exhibit 1).[5,6] These four molecular subgroups may respond to therapy differently and therefore may require escalation or de-escalation of

Exhibit 1: Endometrial Cancer Molecular Classification Algorithm[5,6]



POLE = polymerase epsilon; dMMR = mismatch repair deficient;
ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2;
IHC = immunohistochemistry; mut = mutated; NSMP = no specific molecular profile;
pMMR = proficient MMR; PR = progesterone receptor;
TMB-H = tumor mutational burden-high; wt = wild type.

Exhibit 2: Predictive and Prognostic Value of Key Biomarkers[6,7]

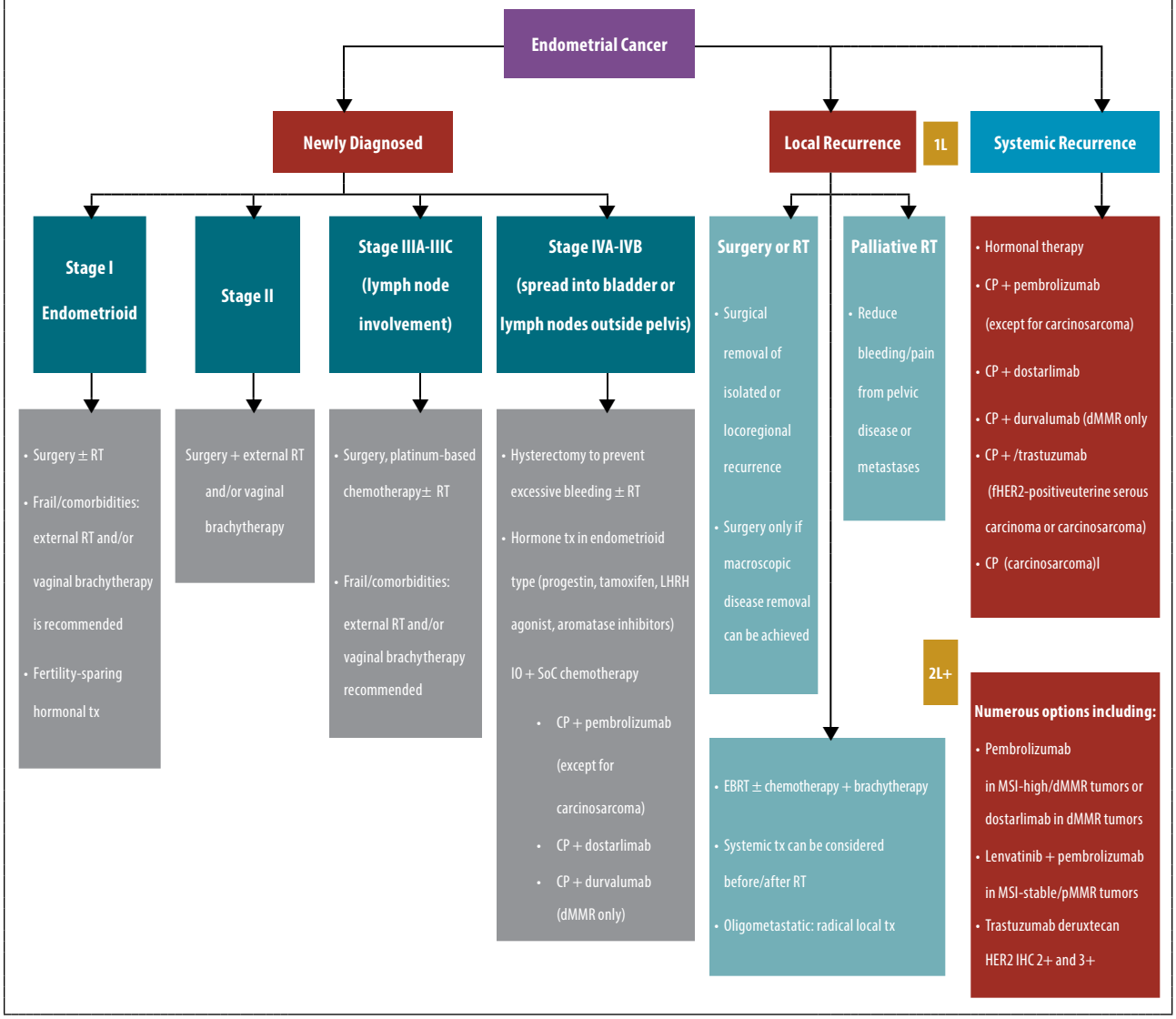
Biomarker	FDA-Approved Biomarker in EC	Predictive of Response	Prognostic
dMMR (MSI-H)	Yes	Yes	Intermediate
ER/PR	No	Yes	ER+ favorable
HER2+	No	Yes	Unfavorable
p53	No	Yes	p53 abnormal unfavorable
POLE	No	–	Favorable

EC = endometrial cancer; MSI = microsatellite instability; ER = estrogen receptor; PR = progesterone receptor;
dMMR = mismatch repair deficient; HER2 = human epidermal growth factor receptor 2; POLE = polymerase epsilon

therapy.[5] Beyond the four subtypes, other molecular biomarkers may influence clinical behavior and response to targeted therapies. These include beta-catenin, HER-2 amplification, PI3K/mTOR/AKT alterations, L1CAM, hormone receptor expression, tumor mutational burden, and ARID1A.[6] Exhibit 2 outlines the predictive and prognostic value of the key biomarkers.[6,7]

Historically treatment guidelines have recommended platinum-based chemotherapy (carboplatin + paclitaxel) as preferred first-line treatment of advanced or recurrent endometrial cancer. Immunotherapy is the most recent therapeutic breakthrough in endometrial cancer

Exhibit 3: Treatment Algorithm for Endometrial Cancer[5]



IO = immunotherapy; RT = radiation therapy; tx = treatment; SoC = standard of care; CP = carboplatin/cisplatin paclitaxel, dMMR = deficient mismatch repair; MSI = microsatellite instability-high

treatment. Immunotherapy was initially used in 2017 as second-line or later therapy but has now moved into first-line therapy in combination with standard of care chemotherapy in the advanced or recurrent disease setting. Exhibit 3 outlines the current National Comprehensive Cancer Network (NCCN) treatment options for endometrial cancer.[5]

The two approved checkpoint immunotherapies for endometrial cancer are dostarlimab and pembrolizumab. Exhibit 4 shows their FDA-approved indications.[8-10] In the second-line setting in previously treated advanced MSI-H/dMMR endometrial cancer, pembrolizumab monotherapy produced robust and durable antitumor activity and encouraging survival outcomes with manageable toxicity in an open label, single arm trial. The objective response rate was 48 percent (95% CI, 37 to 60), and median duration of response was not reached (2.9 to 49.7+ months).[11] Median progression-free survival (PFS) was 13.1 months, and median overall survival (OS) was not reached. In a single arm, open label trial in previously treated advanced endometrial cancer, dostarlimab also demonstrated durable antitumor activity in both dMMR/MSI-H (overall response rate, ORR 43.5%) and proficient mismatch repair (pMMR, ORR 14.1%) disease with a manageable safety profile.[12]

In the first-line setting, checkpoint immunotherapy

Exhibit 4: FDA Indications for Immunotherapy in Endometrial Cancer[8-10]

Agent	Indications
Dostarlimab	• in combination with carboplatin and paclitaxel, followed by dostarlimab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer. • as a single agent for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation.
Durvalumab	• in combination with carboplatin and paclitaxel followed by durvalumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR) as determined by an FDA-approved test.
Pembrolizumab	• in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma. • in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. • as a single agent for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

has been studied in combination with standard of care chemotherapy. In subjects with advanced (Stage III, IVA, IVB) or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer PFS than with chemotherapy alone. In the 12-month analysis, Kaplan-Meier estimates of PFS in the dMMR cohort were 74 percent in the pembrolizumab group and 38 percent in the placebo group (hazard ratio for progression or death, 0.30; $p < 0.001$), a 70 percent difference in relative risk.[13] In the pMMR cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo (hazard ratio, 0.54; $p < 0.001$). For those with dMMR status, the median OS was not reached in either study arm (HR, 0.55; $p = .0617$).[14] For those with pMMR status, the median OS was 27.96 months in the pembrolizumab arm compared with 27.37 in the placebo arm (HR, 0.79; $p = .1157$).

In one trial, dostarlimab in combination with carboplatin-paclitaxel demonstrated a statistically significant and clinically meaningful PFS and

OS benefit in the overall population of patients with primary advanced or recurrent endometrial cancer while demonstrating an acceptable safety profile. At the first interim analysis, the trial met one of its dual primary endpoints with statistically significant PFS benefits in both the dMMR/MSI-H (HR 0.28, $p < 0.0001$) and overall populations (HR 0.64, $p < 0.0001$).[15] In the overall population, with 51 percent maturity, there was a statistically significant reduction in the risk of death (HR 0.69, $p = 0.0020$) in patients treated with dostarlimab plus carboplatin-paclitaxel versus carboplatin-paclitaxel alone.[16] The risk of death was lower in the dMMR/MSI-H population (HR 0.32, nominal $p = 0.0002$) and a trend in favor of dostarlimab was seen in the pMMR population (HR 0.79, nominal $p = 0.0493$).

Overall, PFS outcomes in the dMMR cohort were similar in both the pembrolizumab and dostarlimab trials, with a 70 percent reduction in the risk of PD or death with pembrolizumab and a 72 percent reduction with dostarlimab. OS outcomes are not yet final but the dostarlimab trial has shown reduced risk of death in the dMMR population. Pooled data from the two trials indicate that standard of care chemotherapy plus immunotherapy enhances OS compared to chemotherapy alone in all patient groups (HR 0.75, 95% CI 0.63 to 0.89).[17] It should be noted that durvalumab is also FDA approved as first-line therapy in combination with chemotherapy but only in the dMMR population and is a Category 1 option in the NCCN Guidelines.[5,10]

Pembrolizumab has also been studied in the second-line setting in combination with lenvatinib (an inhibitor of various kinases implicated in pathogenic angiogenesis), tumor growth, and cancer progression. Overall survival (18 versus 12.2 months), PFS (6.7 versus 3.8 months), and ORR (32.4% versus 15.1%) favored lenvatinib plus pembrolizumab in all subgroups in the clinical trial.[18] This combination is a second-line option for MSI-stable/pMMR advanced endometrial cancer in the NCCN Guidelines.[5] This combination is currently under study in first-line management.

Overall, both dostarlimab and pembrolizumab in combination with standard of care chemotherapy are NCCN Level 1 recommended options for first-line treatment of advanced disease regardless of proficiency status. Both are second-line monotherapy options for dMMR tumors and pembrolizumab in combination lenvatinib is an option for pMMR tumors. There is a question of what to do after first-line immunotherapy when disease recurs. A second course of immunotherapy is an unproven and potentially toxic option.

An option for second-line or later therapy for patients who are HER2 positive is an antibody drug conjugate (ADC). HER2 expression is seen in a wide range of solid tumors, including gynecological tumors, and is associated with a biologically aggressive phenotype. High levels of HER2 expression (HER2 immunohistochemistry [IHC] 3+) have been found in 6 to 17 percent of endometrial tumors but HER2-low (1 or 2+) has been found in 13.0 to 46.5 percent.[19,20] HER2-low is a newly defined category with HER2 1+ or 2+ expression by IHC and lack of HER2 gene amplification measured by *in situ* hybridization (ISH). In one trial, trastuzumab deruxtecan demonstrated clinically meaningful ORR, PFS, and OS in HER2-expressing tumors, with particular benefit in gynecological tumors.[21] In the endometrial cancer cohort, median PFS was 11.1 months and median OS was 26.0 months. More data are needed to confirm the findings of the trial. Study was limited by the small number of endometrial cancer patients and its single-arm, open-label design, there was no companion diagnostic, the population was ill defined and a Phase III confirmatory trial was not initiated. The NCCN Guidelines includes trastuzumab deruxtecan as a second-line or later option for HER2-positive (IHC 3+/2+) endometrial cancer.[5]

Other ADCs with various molecular targets are being studied in endometrial cancer. One under investigation targets trophoblast cell surface antigen 2 (TROP2), which is overexpressed in patients with endometrial cancer and is associated with worse prognosis. Sac-TMT (also known as MK-2870/SKB264) is a novel antibody-drug conjugate composed of an anti-TROP2 antibody coupled to a cytotoxic belotecan derivative via a novel linker. The ENGOT-en23/GOG-3095/MK-2870-005 study is evaluating sac-TMT monotherapy against physician's choice chemotherapy in patients who had received prior chemotherapy and/or immunotherapy.[22]

Conclusion

Immunotherapy plus chemotherapy is indicated in first-line systemic treatment of advanced endometrial cancer. Patients with dMMR endometrial cancers should receive immunotherapy because this group achieves the most benefit. Single-agent immunotherapy is an option for recurrent disease if the patient is immunotherapy naïve. Trastuzumab deruxtecan is an option in prior treated patients with HER2 positive disease but many questions remain and confirmatory studies are required. In second-line treatment of pMMR immunotherapy naïve recurrent endometrial cancer, pembrolizumab plus lenvatinib is FDA approved as well as NCCN recommended.

Bradley J. Monk, MD, FACS, FACOG is Medical Director of Late-Phase Clinical Research at the Florida Cancer Specialists and Research Institute in West Palm Beach, FL. He is also Vice President and Member of the Board of Directors GOG-Foundation and Director GOG-Partners.

References

1. American Cancer Society. Cancer Facts & Figures. 2024. Available at cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures.pdf. Accessed 3/6/2025.
2. National Cancer Institute. Cancer Stat Facts: Uterine Cancer. Available at seer.cancer.gov/statfacts/. Accessed 3/6/2025.
3. Giaquinto AN, Broaddus RR, Jemal A, Siegel RL. The changing landscape of gynecologic cancer mortality in the United States. *Obstet Gynecol*. 2022;139(3):440-2.
4. Clarke MA, Devesa SS, Harvey SV, Wentzensen N. Hysterectomy-corrected uterine corpus cancer incidence trends and differences in relative survival reveal racial disparities and rising rates of non-endometrioid cancers. *J Clin Oncol*. 2019;37(22):1895-908.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Uterine Neoplasms. Version 2.2025. Available at nccn.org. Accessed 3/6/2025.
6. Walsh CS, Hacker KE, Secord AA, et al. Molecular testing for endometrial cancer: An SGO clinical practice statement. *Gynecol Oncol*. 2023;168:48-55.
7. Berg HF, Engerud H, Myrvold M, et al. Mismatch repair markers in preoperative and operative endometrial cancer samples; expression concordance and prognostic value. *Br J Cancer*. 2023;128(4):647-55.
8. Pembrolizumab (Keytruda®) package insert. 1/2025.
9. Dostarlimab (Jemperli®) package insert. 8/2024.
10. Durvalumab (Imfinzi®) package insert. 2/2025.
11. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: Results from the KEYNOTE-158 study. *J Clin Oncol*. 2022;40(7):752-61.
12. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: Interim results from GARNET-a Phase I, single-arm study. *J Immunother Cancer*. 2022;10(1):e003777.
13. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. *N Engl J Med*. 2023;388(23):2159-70.
14. Eskander RN, Sill M, Miller A, et al. Overall survival, progression-free survival by PD-L1 status, and blinded independent central review results with pembrolizumab plus carboplatin/paclitaxel (CP) versus placebo plus CP in patients with endometrial cancer: results from the NRG GY018 trial. Presented at: 2024 SGO Annual Meeting for Women's Cancer; March 15-18, 2024; San Diego, CA.
15. Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. *N Engl J Med*. 2023;388(23):2145-58.
16. Powell MA, Bjørge L, Willmott L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. *Ann Oncol*. 2024;35(8):728-38.
17. Bogani G, Monk BJ, Powell MA, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. *Ann Oncol*. 2024;35(5):414-28.
18. Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus pembrolizumab in previously treated advanced endometrial cancer: Updated efficacy and safety from the randomized Phase III study 309/KEYNOTE-775. *J Clin Oncol*. 2023;41(16):2904-10.
19. Uzunparmak B, Haymaker C, Raso G, et al. HER2-low expression in patients with advanced or metastatic solid tumors. *Ann Oncol*. 2023;34(11):1035-46.
20. Halle MK, Tangen IL, Berg HF, et al. HER2 expression patterns in paired primary and metastatic endometrial cancer lesions. *Br J Cancer*. 2018;118(3):378-87.
21. Meric-Bernstam F, Makker V, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 Phase II trial. *J Clin Oncol*. 2024;42(1):47-58.
22. Mirza MR, Martin-Babau J, Bologna A, et al. A Phase III, randomized, open-label, multicenter study of sacituzumab tirumotecan (sac-TMT) monotherapy vs treatment of physician's choice chemotherapy in patients with endometrial cancer who have received prior chemotherapy and immunotherapy: ENGOT-en23/GOG3095/MK-2870-005. Abstract. *Ann Oncol*. 2024;35(Suppl 2):S592.

Best Practices in the Treatment and Management of HER2-Positive and HER2-LOW Advanced Breast Cancer: Expert Managed Care Strategies for Improved Clinical and Economic Outcomes

Reshma L. Mahtani, DO

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

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

Summary

HER2 targeted therapies have dramatically changed outcomes for patients with HER2+ breast cancer. A HER2 targeted antibody drug conjugate is now approved for low and ultralow expression of HER2 in metastatic breast cancer which will provide further benefits.

Key Points

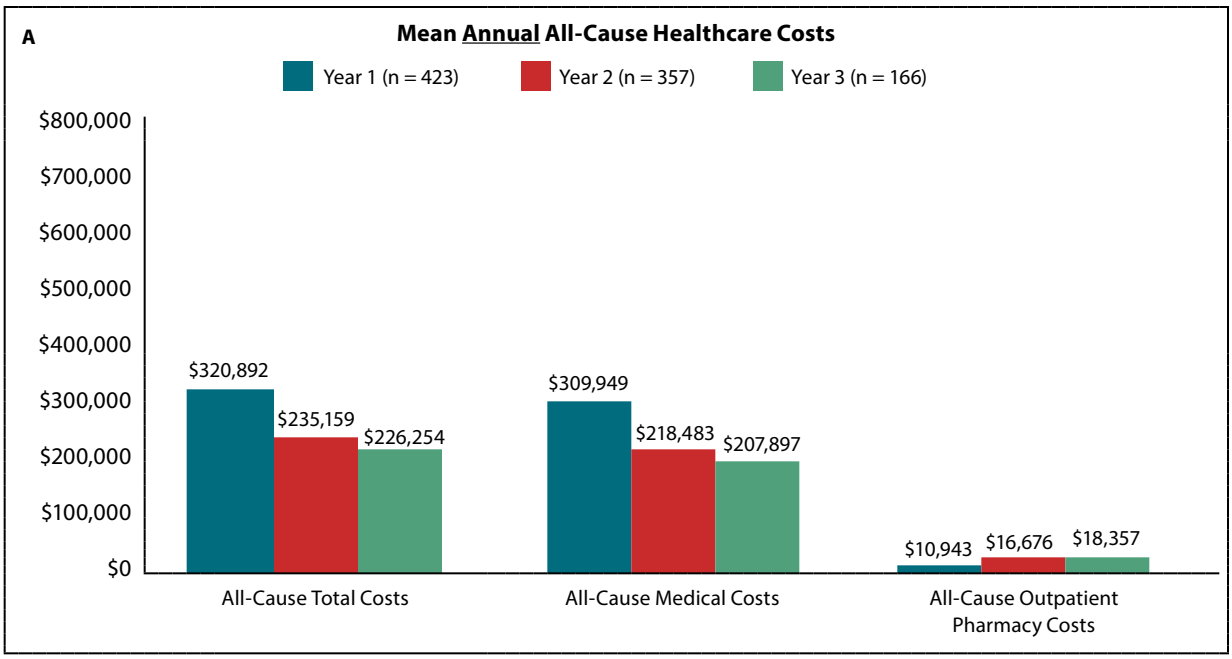
- HER2 targeted therapies have led to prolonged survival and have changed the natural history of advanced stage HER2+ breast cancer.
- HER2-low and -ultralow breast cancer are now targetable.
- Better biomarkers/assays are needed to define the new subtypes and optimize patient selection.

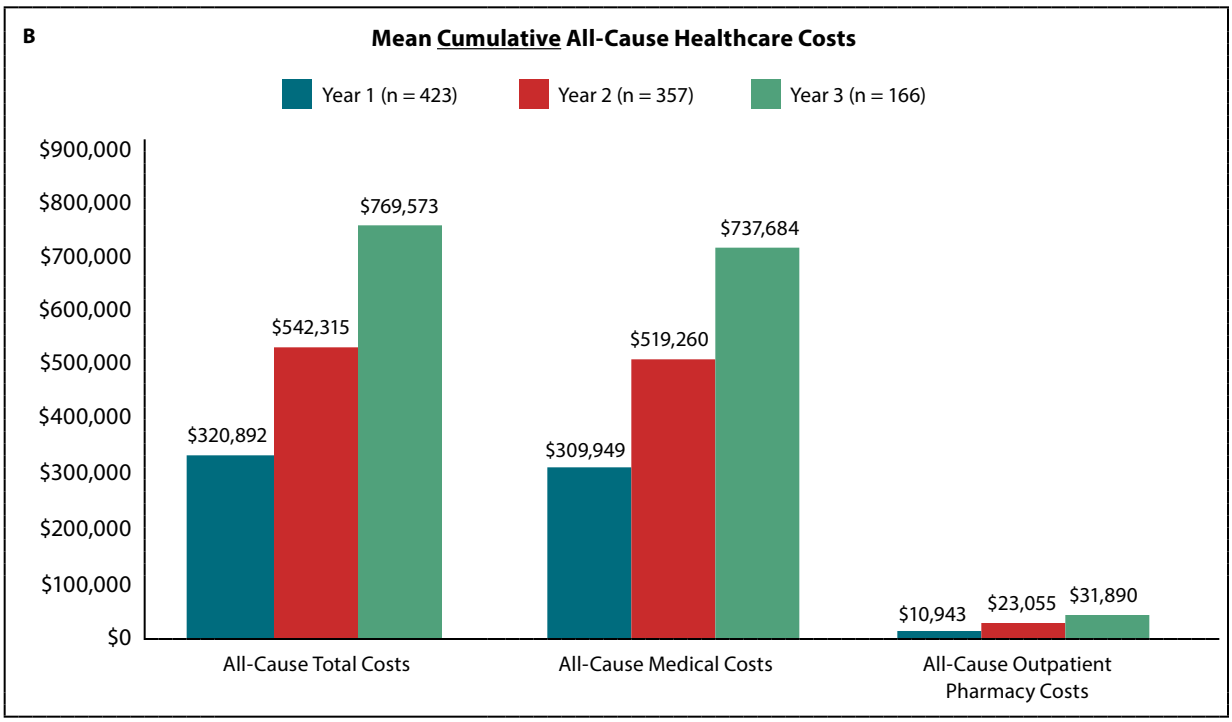
APPROXIMATELY 14 PERCENT OF THE 300,000 cases of breast cancer diagnosed in the United States every year are positive for human epidermal growth factor receptor two overexpression (HER2+).[1] HER2+ breast cancer is an aggressive, fast-growing disease but HER2 targeted drugs have reverted the negative prognostic impact of HER2 overexpression. Survival with HER2+ disease is now equivalent to that of hormone receptor positive (HR) disease.[2]

There are now eight HER2 targeting therapies approved by the FDA. Treatment of HER2-positive metastatic breast cancer (mBC) results in long-term therapy, with several lines of different medications, and causes substantial economic burden. In a claims data study, the mean annual total all-cause costs per patient with mBC in years one, two and three were $320,892 (standard deviation [SD]: $224,343), $235,159 (SD: $185,287), and $226,254 (SD: $197,901), respectively (Exhibit 1).[3] The mean annual total breast cancer-related costs were $240,048 (SD: $151,230), $175,631 (SD: $148,058), and $165,506 (SD: $159,374) in years one, two, and three respectively. A major portion of breast cancer-related costs were associated with HER2-targeted treatment. Because of the substantial cost for treating mBC, it is important to try to prevent metastatic disease by appropriately treating earlier stages of the disease. In the metastatic setting, appropriate sequencing of therapies is one way to limit cost.

Standard first-line treatment for HER2+ mBC is trastuzumab and pertuzumab which target HER2 in diverse ways together with chemotherapy due to improved overall survival (OS) compared to older regimens. In a pivotal trial (Cleopatra), median OS was 57.1 months in those receiving pertuzumab/trastuzumab/docetaxel and 40.8 months in those receiving placebo/trastuzumab/docetaxel (hazard ratio [HR], 0.69); eight-year landmark overall

Exhibit 1: Mean Annual and Cumulative All-Cause Healthcare Costs[3]

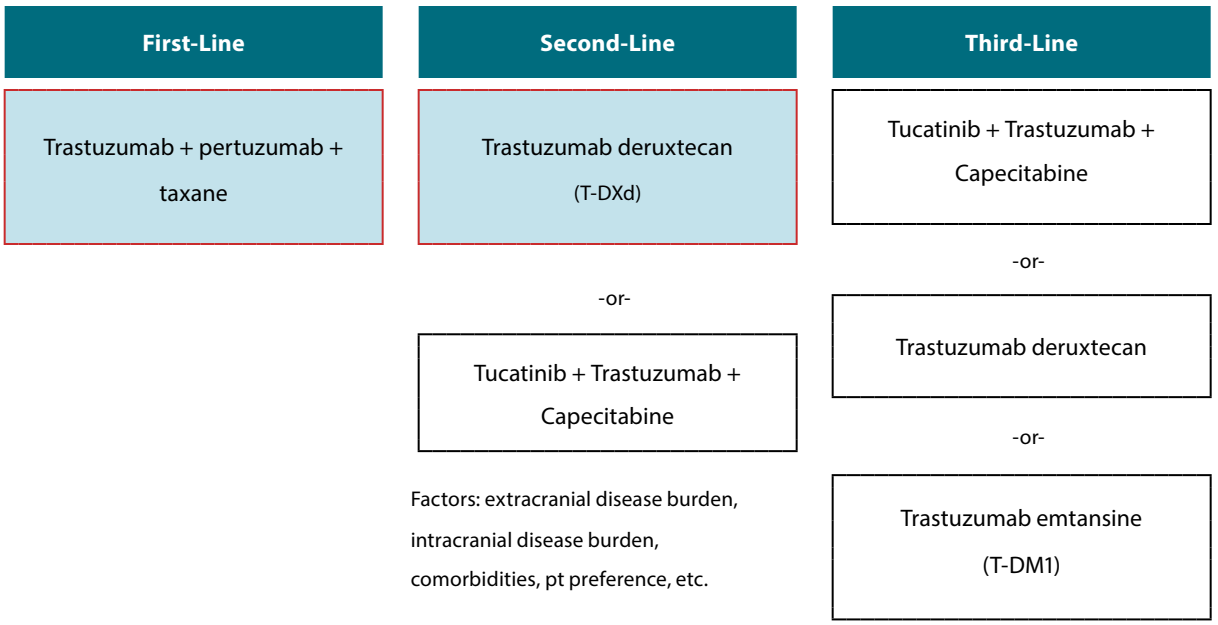




survival rates were 37 percent in the pertuzumab group and 23 percent in the placebo group.[4] Docetaxel, paclitaxel, or nab-paclitaxel can be chosen as the chemotherapy component as each produce similar OS results.[5] Selecting paclitaxel and nab-paclitaxel can make the trastuzumab/pertuzumab/chemotherapy regimen more tolerable. Pertuzumab causes significant diarrhea which must be identified and managed adequately with dietary changes, hydration, and anti-diarrheal medication.

Second-line treatment is now trastuzumab deruxtecan instead of the previous standard of care trastuzumab emtansine based on a comparison trial. Both are antibody-drug conjugates (ADC) but

Exhibit 2: Current Standard of Care for HER2-Positive mBC[8]



trastuzumab deruxtecan also can kill neighboring non-HER2+ tumor cells (bystander killing) due to high cell membrane permeability. Additionally, it delivers a higher chemotherapy payload than ado-trastuzumab emtansine. In the trial comparing trastuzumab deruxtecan and traztusumab emtansine in patients with HER2+ mBC previously treated with trastuzumab and a taxane, the percentage of those who were alive without disease progression at 12 months was 75.8 percent with trastuzumab deruxtecan and 34.1 percent ado-trastuzumab emtansine (HR, 0.28; $p < 0.001$).[6] The percentage of patients who were alive at 12 months was 94.1 percent and 85.9 percent, respectively (HR, 0.55; prespecified significance boundary not reached). At the final data analysis, median progression-free survival (PFS) was 29.0 versus 7.2 months (HR, 0.30), the 36-month PFS rate was 45.7 percent versus 12.4 percent and median OS was 52.6 versus 42.7 months (HR, 0.73) with trastuzumab deruxtecan versus trastuzumab emtansine, respectively.[7] First-line treatment of mBC studies are ongoing with trastuzumab deruxtecan because of the substantial benefit seen in second-line treatment.

Trastuzumab deruxtecan is a highly emetogenic ADC and triple anti-emetic prophylaxis should be used to reduce issues. Drug-related interstitial lung disease (ILD) occurs in about 10 percent of patients treated with this agent which is higher than with trastuzumab emtansine. In early trials with trastuzumab deruxtecan, there were deaths from ILD. There are guidelines published for identifying and managing drug-related ILD.

There is a high unmet need for better treatments in those with brain metastases which occur in up to 50 percent of HER2+ mBC patients. There are accumulating data which show that trastuzumab deruxtecan can penetrate the brain and in the trial discussed earlier, there was a 64 percent response rate in the brain.[6]

Tucatinib, a HER2 tyrosine kinase inhibitor, is also an option for brain metastases. In combination with trastuzumab and capecitabine, tucatinib is preferred in the National Comprehensive Cancer Network (NCCN) Guideline in those with both systemic and central nervous system (CNS) progression for third-line treatment because of improved OS compared to a regimen without tucatinib.[8] It is also an option in second-line treatment if brain metastases are present (Exhibit 2).[8]

In the HER2Climb trial of third-line or later treatment, tucatinib/trastuzumab/capecitabine treatment produced a median OS of 24.7 months versus 19.2 months for placebo/ trastuzumab/ capecitabine [HR, 0.73; $p = 0.004$] and a survival rate at two years of 51 percent and 40 percent,

Exhibit 3: Comparing HER2-positive, HER2-low, and HER2-ultralow[11]

Feature	HER2-Positive	HER2-Low	HER2-Ultralow
HER Status (IHC)	IHC 3+ or IHC 2+ with positive FISH	IHC 1+ or IHC 2+ with negative FISH	IHC 0 with faint or incomplete membrane staining
FISH (Fluorescence *In Situ* Hybridization)	Amplified (positive)	Not amplified (negative)	Not amplified (negative)
Prevalence	14% of breast cancers	~ 45% to 55% of breast cancers	~ 5% to10% (emerging category)
Hormone Receptor (HR) Status	Can be HR+ or HR–	Mostly HR+	Predominantly HR+
Biological Distinction	High HER2 protein overexpression/gene amplification	Low protein expression without amplification	Very low expression, borderline detectable
Diagnostic Challenge	Clear criteria	Subject to variability in IHC interpretation	Difficult to distinguish from HER2-0

IHC = immunohistochemistry

respectively.[9] In a secondary analysis of patients with brain metastases, risk of progression was reduced by 52 percent and risk of death in patients by 42 percent.[10] The HER2 specificity of tucatinib reduces off target adverse events, particularly those related to epidermal growth factor receptor effects (i.e., rash, diarrhea).

The most recent advance in HER2-related disease is the approval of trastuzumab deruxtecan for HER2-low and HER2-ultralow disease. HER2-positive is defined as an immunohistochemistry (IHC) score of 3+ or FISH positive whereas the HER2-low category includes those who have borderline of 1+ and 2+ scores and HER2-ultralow has an IHC score of 0 with faint or incomplete membrane staining (Exhibit 3).[11] Approximately 55 percent of people with mBC fall into the HER2-low category.[12] Low HER2 expression occurs predominately in HR positive breast cancer (85% to 90%) and has previously not been actionable. HER2-low appears to be prognostically and biologically indistinct from HER2-zero breast cancer.[13] There are issues with unreliable scoring by IHC and fluctuating expression over time which complicates identifying the HER2-low and HER2-ultralow population.

In the DESTINY-Breast 04 trial, patients with previously treated HER2-low mBC who were treated with trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy alone. The benefits of trastuzumab deruxtecan in HER2-low appear related to the bystander effect of this ADC. The median PFS was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice chemotherapy group (HR, 0.51; $p < 0.001$), and OS was 23.9 months and 17.5 months, respectively (HR, 0.64; $p = 0.003$).[14] Based on this study, this agent was FDA approved for adults with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/FISH negative) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

As of January 2025, trastuzumab deruxtecan is also FDA approved for HER2-ultralow unresectable or metastatic breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting. This approval was based on results from the DESTINY Breast 06 trial which included both HER2-low and HER2-ultralow HR positive mBC that had been previously treated with one or more lines of endocrine-based therapy and no previous chemotherapy for metastatic breast cancer. This trial included 713 subjects with HER2-low disease and 153 with HER2-ultralow. Among the patients with HER2-low disease, the median PFS was 13.2 months in the trastuzumab deruxtecan group and 8.1 months in the physicians' choice chemotherapy group (HR,

0.62; $p < 0.001$); the results were consistent in the exploratory HER2-ultralow population (13.2 versus 8.3 months).[15] Data for OS in the overall population are immature (28.9 versus 27.4 months).[16]

The DESTINY Breast 08 trial is also looking at various combinations with trastuzumab deruxtecan to maximize benefit in the HER2-low population. Several other ADC are under evaluation for HER2 positive and HER2-low disease including trastuzumab duocarmazine and disitamab vedotin.[17] ADCs are also being investigated in combination with immunotherapy and other classes of medications. Newer methods of identifying low levels of HER2 expression are under investigations including quantitative fluorescence and machine learning-based image analysis to reduce interobserver variability.

Conclusion

The newly defined HER2-low and HER2-ultralow breast cancer subtypes represent a paradigm shift and a challenge to the previous binary system of HER2 classification in breast cancer. HER2-low and -ultralow are targetable by the new generation of HER2 targeting ADCs providing treatment options for patients who previously would not have been eligible for this class of therapy. The new subgroups highlight the need for better biomarkers/assays to define these subgroups and optimize patient selection. Numerous other agents and combinations targeting HER2 and other drivers of this cancer are on the horizon.

Reshma L. Mahtani, DO is the Chief of Breast Medical Oncology at the Miami Cancer Institute at Baptist Health South Florida and and oncologist in Plantation, FL.

References

1. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer Subtypes. Available at seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed 4/27/2025.
2. Grinda T, Antoine A, Jacot W, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open*. 2021;6(3):100114.
3. Mahtani R, Oestreicher N, Lalla D, Health care resource utilization and costs for metastatic breast cancer patients newly treated with human epidermal growth factor receptor 2 (HER2)-targeted agents. *Clin Breast Cancer*. 2022;22(4):e488-e496.
4. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): End-of-study results from a double-blind, randomized, placebo-controlled, Phase III study. *Lancet Oncol*. 2020;21(4):519-30.
5. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. *Ann Oncol*. 2021;32(10):1245-55.
6. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-54.
7. Cortés, J., Hurvitz, S.A., Im, SA. et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: Long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med*. 2024;30:2208-15.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 4.2025. Available at nccn.org. Accessed 4/27/2025.
9. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): Final overall survival analysis. *Ann Oncol*. 2022;33(3):321-9.
10. Lin NU, Borges V, Anders C, et al. Intracranial efficacy, and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-9.
11. Franchina M, Pizzimenti C, Fiorentino V, et al. Low and ultra-low HER2 in human breast cancer: An effort to define new neoplastic subtypes. *Int J Mol Sci*. 2023;24(16):12795.
12. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: Pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-62.
13. Chen Z, Jia H, Zhang H, et al. Is HER2 ultra-low breast cancer different from HER2 null or HER2 low breast cancer? A study of 1363 patients. *Breast Cancer Res Treat*. 2023;202(2):313-23.
14. Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20.
15. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-22.
16. Study of Trastuzumab deruxtecan (T-DXd) vs investigator's choice chemotherapy in HER2-low, hormone receptor positive, metastatic breast cancer (DB-06). ClinicalTrials.gov ID NCT04494425. Available at clinicaltrials.gov/study/NCT04494425?tab=results. Accessed 4/27/2025.
17. Ferraro E, Drago JZ, Modi S. Implementing antibody-drug conjugates (ADCs) in HER2-positive breast cancer: State of the art and future directions. *Breast Cancer Res*. 2021;23(1):84.

Innovative Approaches in the Treatment and Management of Myelofibrosis: Managed Care Insights on the Evolving Role of JAK Inhibitors

Gary M. Owens, MD

This journal article is supported by an educational grant from GlaxoSmithKline

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

Summary

Myelofibrosis is a rare type of blood cancer where bone marrow is replaced by fibrous scar tissue. Myelofibrosis is characterized by numerous systemic symptoms, which may progress to leukemia. Fortunately for patients, new and emerging therapies, including JAK inhibitors, are available.

Key Points

- The only cure for myelofibrosis is allogeneic hematopoietic stem cell transplantation for which many patients are ineligible.
- Slowing disease progression and reducing symptom burden for patients are the main treatment goals.
- Four JAK inhibitors are FDA approved for myelofibrosis.

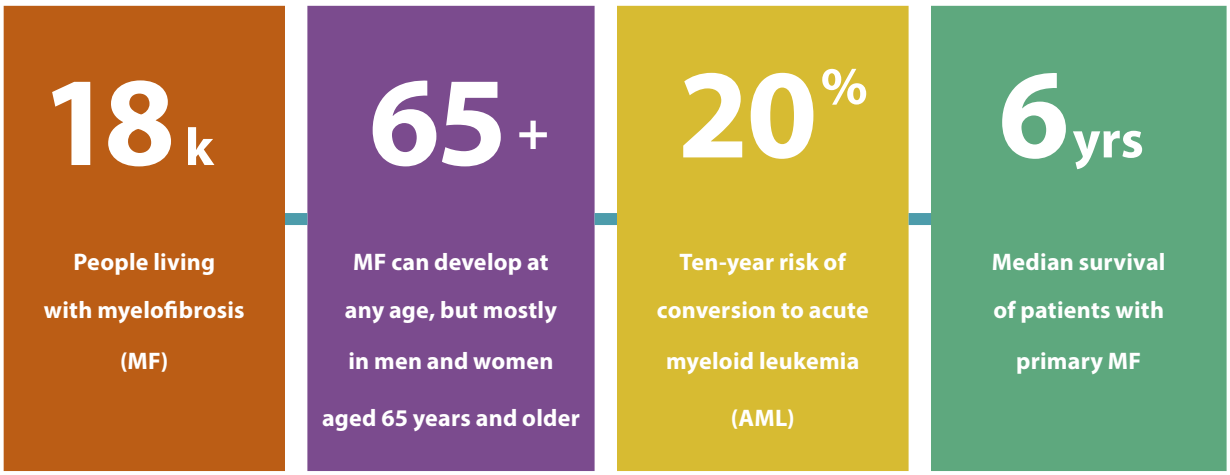
PRIMARY MYELOFIBROSIS (MF) IS A CLONAL disorder arising from the neoplastic transformation of early hematopoietic stem cells.[1] It is categorized as a chronic myeloproliferative disorder, together with chronic myelogenous leukemia, polycythemia vera, and essential thrombocytosis. Secondary MF can also result as a progression of polycythemia vera (post-PV-MF) or essential thrombocythemia (post-ET-MF). The manifestations of primary MF, post-PV-MF and post-ET-MF are virtually identical and treatment is the same for all three.[2]

The exact cause of MF is unknown but it is thought to arise from a somatic mutation of a pluripotent hematopoietic stem/progenitor cell.[3] Deposition of reticulin and collagen fibrosis in the bone marrow is believed to be mediated by the mutated hematopoietic stem/progenitor cell. Fibrosis results in an impaired microenvironment favoring malignant over normal hematopoiesis.

A major hallmark of MF is a significant elevation in circulating pro-inflammatory cytokines which are a consequence of the malignant clone and responsible for symptoms. These cytokines also modify the bone marrow microenvironment, promoting malignant hematopoiesis. Approximately 50 to 60 percent of patients with MF have clonal karyotypic abnormalities at diagnosis resulting from Janus kinase 2 (JAK2), myeloproliferative leukemia (MPL) and calreticulin (CALR) mutations.[3] Constitutive activation of the JAK/STAT pathway appears to be an important pathogenetic event in patients with myeloproliferative disorders such as MF. Mutations commonly affect the JAK/STAT pathway, including those that occur directly in JAK2 such as the JAK2V617F mutation, or indirectly, such as those in MPL, which encodes the thrombopoietin receptor, or in CALR, which may activate STATs through an unknown mechanism.

Primary myelofibrosis is an uncommon disease, with an annual incidence of approximately 1.5 cases per 100,000 individuals in the United States (U.S.).[4] It is more common in Whites, Ashkenazi Jews, and

Exhibit 1: Myelofibrosis by the Numbers[5]



men. The median age at diagnosis is 65 years, but about 22 percent of cases occur in those less than 56 years of age. It can occur in children and usually occurs in the first three years of life. Unfortunately, there is a significant risk of MF transforming into acute myeloid leukemia (AML) and survival after MF diagnosis is poor (Exhibit 1).[5] About 20 percent of those with MF will progress to AML over a 10-year period.

The signs of MF include anemia, thrombocytopenia, leukopenia, bone marrow fibrosis, extramedullary hematopoiesis, leukoerythroblastosis and teardrop-shaped red blood cells in peripheral blood, and hepatosplenomegaly. Constitutional symptoms include tiredness, weakness, shortness of breath with mild exertion, abdominal discomfort or pain, fever, night sweats, weight loss, bone pain, and pruritus.

The World Health Organization diagnostic criteria for MF includes three major criteria and four minor criteria. Diagnosis requires meeting all three major criteria and at least two minor criteria (Exhibit 2).[6] About one-fourth of patients with primary MF are asymptomatic at the time of diagnosis. In these patients, the diagnosis is found by detecting splenomegaly or checking blood cell counts for an unrelated cause. An extensive workup including molecular testing of blood for JAK2 V617F, CALR, and MPL mutations is required for diagnosis and before treatment.[7] About 50 percent of patients have the JAK2 V617F mutation, while 25 percent have a mutation in the CALR gene, and 5 to 10 percent have a MPL gene mutation.[4]

Treatment of MF is guided by prognosis, as assessed by clinical and/or pathologic features using a mutation-based model. Several prognostic models are used in the U.S. The National Comprehensive Cancer Network (NCCN) Guidelines recommends use of the Mutation-enhanced International Prognostic Scoring System (MIPPS70, MIPSS70+ v2.0), Dynamic International Prognostic Scoring System (DIPSS, if karyotype is not available), or DIPSS-Plus (if molecular testing not available).[7] Precision and reproducibility of various models differ, and prognostic categories do not match precisely across models. These models stratify patients into low-, intermediate-, or high-risk or lower/higher-risk categories. The greater the risk category, the lower the median overall survival (OS).

Historically, therapy for primary MF was supportive of patients receiving transfusions as needed. Thrombocytosis could be managed with hydroxyurea and other palliative agents. Currently, asymptomatic, lower-risk patients are managed with observation. Allogeneic hematopoietic stem cell transplantation (ASCT) is the only treatment which has the potential for cure but many patients are ineligible because of comorbidities. The NCCN Guidelines note that evaluation for ASCT is recommended for patients with low platelet counts or complex cytogenetics.[7] Identification of higher-risk mutations may be helpful in the decision-making regarding ASCT for patients with MF.[7] The approval of four JAK inhibitors for the treatment of MF has changed the treatment approach. Exhibit 3 shows the NCCN recommended first-line treatment based on prognostic risk and other factors.[7]

Ruxolitinib, a potent and selective JAK 1 and 2 inhibitor, was the first FDA approved for MF. Its 2011 approval was based on the results of the COMFORT-I and COMFORT-II trials.[8,9] In the

Exhibit 2: Myelofibrosis Diagnostic Criteria[6]

Major criteria:	• Megakaryocyte proliferation and atypia accompanied by reticulin and/or collagen fibrosis or, in the absence of reticulin fibrosis, the megakaryocyte changes accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis. • Not meeting WHO criteria for chronic myeloid leukemia polycythemia vera, myelodysplastic syndrome, or other myeloid neoplasm. • Demonstration of JAK2V617F or other clonal marker, or no evidence of reactive bone marrow fibrosis.
Minor criteria:	**· Leukoerythroblastosis** **· Elevated serum LDH level** **· Anemia** **· Palpable splenomegaly**

COMFORT-1 trial, 219 patients with intermediate-2 or high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF received oral ruxolitinib or the best available therapy.[8] The primary end point and key secondary end point of the study were the percentage of patients with at least a 35 percent reduction in spleen volume at week 48 and at week 24, respectively, as assessed with the use of magnetic resonance imaging or computed tomography. A total of 28 percent of the patients in the ruxolitinib group had at least a 35 percent reduction in spleen volume at week 48, as compared with 0 percent in the group receiving the best available therapy ($p < 0.001$); the corresponding percentages at week 24 were 32 percent and 0 percent ($p < 0.001$). At 48 weeks, the mean palpable spleen length had decreased by 56 percent with ruxolitinib but had increased by 4 percent with the best available therapy. The median duration of response with ruxolitinib was not reached with 80 percent of patients still having a response at a median follow-up of 12 months. Patients in the ruxolitinib group had an improvement in overall quality-of-life measures and a reduction in symptoms associated with myelofibrosis. The most common hematologic abnormalities of Grade 3 or higher in either group were thrombocytopenia and anemia, which were managed with a dose reduction, interruption of treatment, or transfusion. Two cases of AML were reported in the best available therapy group.

In the COMFORT-2 trial, those with intermediate-2 or high-risk MF were randomized to twice-daily oral ruxolitinib (155 patients) or placebo (154 patients).[9] The primary end point was the proportion of patients with a reduction in spleen volume of 35 percent or more at 24 weeks. Secondary end points included the durability of response, changes in symptom burden (assessed by the total symptom score), and OS. The primary end point was reached in 41.9 percent of patients in the ruxolitinib group as compared with 0.7 percent in the placebo group ($p < 0.001$). A reduction in spleen volume was maintained in patients who received ruxolitinib. Sixty-seven percent of the patients with a response had the response for 48 weeks or more. There was an improvement of 50 percent or more in the total symptom score at 24 weeks in 45.9 percent of patients who received ruxolitinib as compared with 5.3 percent of patients who received placebo ($p < 0.001$). Thirteen deaths occurred in the ruxolitinib group as compared with 24 deaths in the placebo group (hazard ratio, 0.50; 95% confidence interval, 0.25 to 0.98; $p = 0.04$). Eleven percent in the ruxolitinib group and 10.6 percent in the placebo group discontinued therapy because of adverse events. Among patients who received ruxolitinib, anemia and thrombocytopenia were the most common adverse events, but they rarely led to discontinuation. Two patients had transformation into AML and both were in the ruxolitinib group.

Importantly, long-term data from these two trials showed improvements in OS. The risk of death was

Exhibit 3: Myelofibrosis Treatment Recommendations[7]

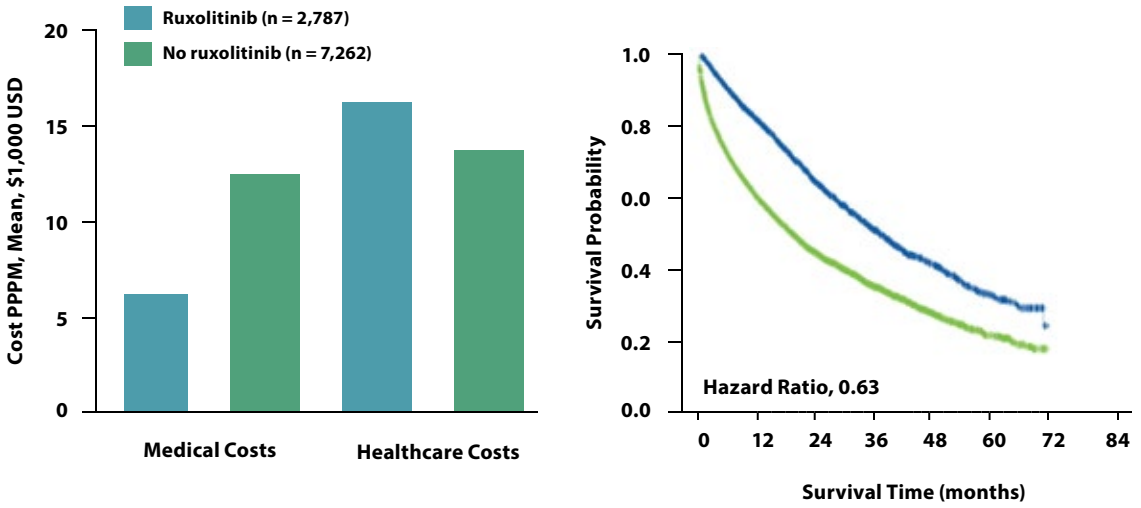
Prognostic Risk/Other Factors	First-Line
Lower, symptomatic	Clinical trial Useful in certain circumstances: Ruxolitinib, Peginterferon alfa-2a, Hydroxyurea, if cytoreduction would be symptomatically beneficial, Pacritinib (if platelets < 50 x 10^9/L), Momelotinib (Category 2B)
Higher, platelets < 50 x 10^9/L, transplant candidate	Allogenic HCT
Higher, platelets < 50 x 10^9/L, not transplant candidate	Clinical trial OR Pacritinib (Category 1, preferred) OR Momelotinib (Category 2B)
Higher, platelets ≥ 50 x 10^9/L, not transplant candidate, symptomatic splenomegaly and/or symptomatic	Clinical trial OR Ruxolitinib (Category 1) OR Fedratinib (Category 1) OR Momelotinib OR Pacritinib (Category 2B)

reduced by 30 percent among patients randomized to ruxolitinib compared with patients in the control group (median OS, 5.3 versus 3.8 years, respectively; hazard ratio [HR], 0.70 [95% CI, 0.54-0.91]; p = 0.0065).[10] After correcting for crossover, the OS advantage was more pronounced for patients who were originally randomized to ruxolitinib compared with patients who crossed over from control to ruxolitinib (median OS, 5.3 versus 2.3 years; HR [ruxolitinib versus RPSFT], 0.35 [95% CI, 0.23 to 0.59]). Ruxolitinib provided a survival benefit irrespective of baseline anemia status or transfusion requirements at week 24.

Fedratinib was the second JAK inhibitor approved in 2019 for adults with intermediate-2 or high-risk primary MF and secondary MF. Approval was based on a trial in 289 patients who were randomized to receive fedratinib 500 mg (n = 97) or 400 mg (n = 96) or placebo (n = 96) once daily for at least 24 weeks.[11] The primary end point was spleen response (35% or more reduction in volume) at week 24 and confirmed four weeks later. The primary end point was achieved by 36 percent and 40 percent in the fedratinib 400-mg and 500-mg groups, versus 1 percent in the placebo group (p < .001). The main secondary end point was symptom response (50% or more reduction in total symptom score, assessed using the modified Myelofibrosis Symptom Assessment Form). Symptom response rates at week 24 were 36 percent, 34 percent, and 7 percent, respectively (p < .001). Common adverse events with fedratinib treatment were anemia, gastrointestinal symptoms, and increased levels of liver transaminases, serum creatinine, and pancreatic enzymes. Encephalopathy was reported in four women who received fedratinib 500 mg/d. A diagnosis of Wernicke encephalopathy was supported by magnetic resonance imaging in three cases and suspected clinically in one case. This agent should not be given to patients with a platelet count of 50,000 or less, severe liver impairment, or being treated with strong or moderate CYP3A4 inducers or dual CYP3A4 and CYP2C19 inhibitors.

A third JAK inhibitor, pacritinib, was FDA approved in March 2022 and is the first treatment for adults with MF and severe thrombocytopenia (platelet count less than 50,000). This agent is an oral JAK inhibitor that inhibits JAK2 and FLT3, as well as CSFIR and IRAK1. Approval was based on the PERSIST-1 and PERSIST-2 Phase III trials.[12,13] In the first trial, patients with higher-risk MF (with no exclusions for baseline anemia or thrombocytopenia) were randomly assigned (2:1) to receive oral pacritinib 400 mg once daily or best available therapy (BAT) excluding other JAK2 inhibitors until disease progression or unacceptable toxicity.[12] Pacritinib therapy was well tolerated and induced significant and sustained spleen volume and symptom reduction, even in patients with severe baseline cytopenias. Positive results of this trial, led to the second trial which compared pacritinib and best available therapy (BAT) including ruxolitinib. In the second trial, the most common BAT was ruxolitinib (45%), followed by hydroxyurea and watchful-waiting.[13] The intention-to-treat efficacy

Exhibit 4: Cost Effectiveness of Ruxolitinib[20]



population from this trial included 75 patients randomized to pacritinib once daily, 74 patients randomized to pacritinib twice daily, and 72 patients randomized to BAT. Pacritinib (arms combined) was more effective than BAT for 35 percent or more spleen volume reduction (18% versus 3%; p = .001) and had a non-significantly greater rate of 50 percent or more reduction in total symptom score (25% versus 14%; p = .08). Pacritinib twice daily led to significant improvements in both end points over BAT (35% or more SVR: 22% versus 3%; p = .001; 50% or more reduction in symptoms: 32% versus 14%, p = .01). Clinical improvement in hemoglobin and reduction in transfusion burden were greatest with pacritinib twice daily. For pacritinib once daily, pacritinib twice daily, and BAT, the most common (more than 10%) Grade 3 or 4 adverse events were thrombocytopenia (31%, 32%, 18%), and anemia (27%, 22%, 14%). Discontinuation for adverse events occurred in 14 percent, 9 percent, and 4 percent. The authors concluded that in patients with MF and thrombocytopenia, including those with prior anti-JAK therapy, pacritinib twice daily was more effective than BAT, including ruxolitinib, for reducing splenomegaly and symptoms. Data from this trial led to the preferred Category 1 NCCN recommendation for higher risk non-transplant candidates with thrombocytopenia (Exhibit 3).[7] Strong CYP3A4 inhibitors or inducers are contraindicated in combination with pacritinib; moderate CYP3A4 inhibitors or inducers should be avoided. Pacritinib should be avoided in patients with moderate or severe liver impairment or kidney disease.

The most recent (September 2023) FDA approval is for momelotinib for treatment of intermediate- or high-risk MF, including primary or secondary disease. Momelotinib is a dual JAK1/JAK2 and ACVR1 inhibitor. In the first study used for approval, the safety and efficacy of momelotinib versus ruxolitinib was compared in 432 high risk or intermediate-2 risk or symptomatic intermediate-1 risk MF patients who had not received prior treatment with a JAK inhibitor.[14] Subjects were randomly assigned to receive 24 weeks of treatment with momelotinib 200 mg once daily or ruxolitinib 20 mg twice a day (or per label). A 35 percent or more reduction in spleen volume at week 24 was achieved by a similar proportion of patients in both treatment arms being 26.5 percent of the momelotinib group and 29 percent of the ruxolitinib group (noninferior; p = .011). A 50 percent or more reduction in the total symptom score was observed in 28.4 percent and 42.2 percent of patients who received momelotinib and ruxolitinib, respectively, indicating that non-inferiority was not met (p = .98). Transfusion rate, transfusion independence, and transfusion dependence were improved with momelotinib (all with nominal $p \leq .019$). The most common Grade 3 or greater hematologic abnormalities in either group were thrombocytopenia and anemia. Grade 3 or greater infections occurred in 7 percent of patients who received momelotinib and 3 percent of patients who received ruxolitinib. Treatment-emergent peripheral neuropathy occurred in 10

percent of patients who received momelotinib (all Grade 2 or less) and 5 percent of patients who received ruxolitinib (all Grade 3 or less). Another trial compared momelotinib to danazol for 24 week in 195 patients with primary or secondary MF.[15] A significantly greater proportion of patients in the momelotinib group reported a 50 percent or more reduction in symptom score than in the danazol group (25% versus 9%, $p = 0.0095$). Thirty-one percent of the momelotinib group was transfusion free compared with 20 percent of the danazol group at the end of 24 weeks. The most frequent Grade 3 or higher adverse events with momelotinib and danazol were hematological abnormalities—anemia (61% versus 75%) and thrombocytopenia (28% versus 26%). The most frequent non-hematological Grade 3 or higher adverse events were acute kidney injury (3% versus 9%) and pneumonia (2% versus 9%).

MF is associated with significant economic burden to the health system, patients, and their families.[16] The costs of treating MF were already substantial before the introduction of JAK inhibitors. Compared to age-gender matched comparisons without myeloproliferative neoplasms (MPN), inpatient, outpatient, emergency room visits, and pharmacy costs, as well as overall healthcare expenditures, were significantly higher in patients with MF.[17] Total annual costs were $54,168 compared to matched control costs of $10,203 in 2014. Primary drivers of costs of MF treatment are hospitalizations and medications.[18] With the introduction of JAK inhibitors, the cost of treating myeloproliferative disorders has been growing steadily. The market for medications for these disorders is expected to continue to grow at about 5.9 percent from 2025 to 2030.[19] Availability of novel drugs along with the aging U.S. population is creating market growth.

JAK inhibitors may be cost effective in treating MF. One cost-effectiveness study, using U.S. Medicare data, found ruxolitinib is associated with reduced healthcare resource utilization and direct costs of medical care in addition to increased survival (Exhibit 4).[20]

Managing the cost of oncology medications is a major payor concern but this can be a complicated process. There are many reasons why managing these medications is difficult including patient complexity, rapidly changing science, government regulations, and push back from providers and patient advocacy groups.[21] Pathways are one potential area of consideration by managed care. However, this process becomes challenging in areas where clinical and economic evidence are rapidly evolving similar to MF. One major issue to consider in developing an MF pathway is that the majority of trial data is based on symptom scores, spleen volume, and other measures, the benefits of which are harder to quantify than items such as OS and progression-free survival (PFS) used in most oncology treatment clinical trials. Additionally, these agents received accelerated approvals based on small trials; decisions on choosing agents would be required without confirmatory trials completion. Other challenges include age and fitness of trial subjects compared with real-world patients, factoring in toxicities and their treatment, choosing between medication cost versus overall cost of care, factoring in quality of life, and personalization of care versus standardization. These are only a few of the challenges that need to be further explored in MF and many other cancers where the evidence is rapidly evolving.

The treatment of MF will become more complicated in the future. Both existing approved medications for other indications and new molecules targeting additional pathways are being studied for MF. Examples of those that target pathways other than the JAK-STAT pathway include immunomodulators (pomalidomide), apoptosis (navitoclax, KRT-232, LCL-161, imetelstat), epigenetic modulation (CPI-0610, bomedemstat), the bone marrow microenvironment (PRM-151, AVID-200, alisertib), and signal transduction pathways (parsaclisib, everolimus).[22]

Conclusion

The only cure for myelofibrosis is ASCT for which many patients are ineligible. Slowing disease progression and reducing symptom burden for patients are the main treatment goals. JAK inhibitors provide managed care professionals and clinicians more options for treating this patient population but there are cost considerations which need to be addressed. Activation of the Janus-associated kinase (JAK)/signal transducers and activators of the transcription pathway has been shown to play a crucial role in disease development and progression of myelofibrosis.

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

References

1. Greenfield G, McMullin MF, Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. *J Hematol Oncol.* 2021;14(1):103.

2. Masarova L, Verstovsek S. The evolving understanding of prognosis in post-essential thrombocythemia myelofibrosis and post-polycythemia vera myelofibrosis vs primary myelofibrosis. *Clin Adv Hematol Oncol.* 2019;17(5):299-307.

3. Zahr AA, Salama ME, Carreau N, et al. Bone marrow fibrosis in myelofibrosis: Pathogenesis, prognosis, and targeted strategies. *Haematologica.* 2016;101(6):660-71.

4. Leukemia and Lymphoma Society. Myelofibrosis Facts. Available at lls.org. Accessed 2/21/2025.

5. MPN Research Foundation. Myelofibrosis. Available at mpnresearchfoundation.org/primary-myelofibrosis-pmf. Accessed 2/21/2025.

6. Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J.* 2018;8(2):15.

7. Nation Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 2.2024. Available at nccn.org. Accessed 2/21/2025.

8. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366(9):787-98.

9. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807.

10. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol.* 2017;10(1):156.

11. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: A randomized clinical trial. *JAMA Oncol.* 2015;1(5):643-51.

12. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): An international, randomized, Phase III trial. *Lancet Haematol.* 2017;4(5):e225-e236.

13. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: A randomized clinical trial. *JAMA Oncol.* 2018;4(5):652-9.

14. Mesa RA, Kiladjian JJ, Catalano JV, et al. SIMPLIFY-1: A Phase III randomized trial of momelotinib versus ruxolitinib in janus kinase inhibitor-naïve patients with myelofibrosis. *J Clin Oncol.* 2017;35(34):3844-50.

15. Verstovsek S, Gerds AT, Vannucchi AM, et al. Momelotinib versus danazol in symptomatic patients with anemia and myelofibrosis (MOMENTUM): Results from an international, double-blind, randomized, controlled, Phase III study. *Lancet.* 2023 ;401(10373):269-80.

16. Tang D, Taneja A, Rajora P, Patel R. Systematic literature review of the economic burden and cost of illness in patients with myelofibrosis. *Blood.* 2019;134 (Supplement_1):2184.

17. Mehta J, Wang H, Fryzek JP, et al. Health resource utilization and cost associated with myeloproliferative neoplasms in a large United States health plan. *Leuk Lymphoma.* 2014;55(10):2368-74.

18. Copher R, Kee A, Gerds A. Treatment patterns, health care resource utilization, and cost in patients with myelofibrosis in the United States. Oncologist. 2022;27(3):228-35.

19. Myeloproliferative Disorders Drugs Market Size, Share & Trends Analysis Report by Indication (Ph+ Chronic Myelogenous Leukemia (CML)), By Treatment Type, By End Use, By Region, And Segment Forecasts, 2025 – 2030. Available at grandviewresearch.com/industry-analysis/myeloproliferative-disorders-drugs-market. Accessed 2/21/2025.

20. Gerds AT, Yu J, Shah A, et al. Ruxolitinib for myelofibrosis in elderly non-transplant patients: Healthcare resource utilization and costs. *J Med Econ.* 2023;26(1):843-9.

21. Runyan A, Banks J, Bruni DS. Current and future oncology management in the United States. *J Manag Care Spec Pharm.* 2019;25(2):272-81.

22. Rare Disease Advisor. Myelofibrosis (MF). Available at rarediseaseadvisor.com/therapies/myelofibrosis-experimental-therapies. Accessed 2/21/2025.

New Horizons in the Treatment and Management of Amyotrophic Lateral Sclerosis: Managed Care Insights on the Role of Novel Oral Therapy Options

Jinsy A. Andrews, MD, MSc, FAAN

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

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

Summary

Diagnosis of ALS needs to be achieved as soon as possible so therapy can be implemented. Although there are three treatment options for ALS which slow functional decline and improve survival, more therapies are needed. Emerging genetic information is providing multiple targets for therapy development.

Key Points

- People suspected of having ALS should be referred to a specialty center as quickly as possible.
- Tools such as ThinkALS can help with earlier referral by general neurologists to ALS specialists.
- The FDA-approved therapies are intended to be used in combination and should be initiated as soon as possible.
- Genetic testing has become more important with the introduction of one targeted therapy and with many more being investigated.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) was first described in 1874 and genetic mutations, which lead to familial ALS, were first described in 1993 but the first ALS specific medications were not approved until 1995. The pathology of ALS involves atrophy of muscle fibers, which are denervated as their corresponding anterior horn cells degenerate (amyotrophy) and hardening of the anterior and lateral columns of the spinal cord as motor neurons in these areas degenerate and are replaced by fibrous astrocytes (lateral sclerosis). ALS affects upper and lower motor neurons which causes muscle weakness, disability, and eventually death. Patients lose their ability to move, speak, take anything orally, and breathe unassisted.

The goal of currently available treatment is to prevent progression of disease to other body regions and delay time to disability milestones. Riluzole, the first FDA-approved disease-modifying therapy for ALS, is given orally and blocks release of glutamate and modulates sodium channels which appear to be neuroprotective. It is available as tablet, liquid, or film—the liquid and film are helpful for patients with swallowing difficulties. From the trials used for FDA approval, riluzole prolongs median tracheostomy-free survival by two to three months more than placebo in patients younger than 75 years of age with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[1,2] A retrospective review of riluzole evaluated whether the benefit of riluzole occurs in the earlier or later stages of the disease and found riluzole primarily prolonged survival in the last clinical stage of ALS.[3] This study could not determine treatment effects at Stage 1 (patients came in as Stage 2 or

later per eligibility criteria of probable or definite ALS and could have had symptoms for up to five years). The most benefit in this patient population was in moving from Stage 4 disease (nutritional or respiratory failure) to Stage 5 (death). The ALS stage at which benefit occurs is important for counseling of patients before starting treatment. The thinking in the clinical community is earlier treatment may have a bigger impact with riluzole. A meta-analysis of population studies, which compared riluzole to placebo, found significant differences in median survival between the two groups, ranging from six to 19 months.[4] This is longer than the two- to three-month survival benefit observed in the pivotal clinical trials of riluzole. In another analysis using a real-world dataset, riluzole reduced risk of death uniformly, regardless of time from onset to treatment, and duration of treatment.[5] Earlier treatment with riluzole may be associated with greater absolute survival gain and early diagnosis of ALS will facilitate early treatment and is expected to improve survival.

Intravenous edaravone was approved by the FDA in 2017 to slow the functional decline in patients with ALS. Edaravone in combination with riluzole slowed the rate of disease progression by 33 percent at six months compared to the rate of disease progression for patients in the placebo group.[6] An open label extension of this trial out to 24 weeks found there was a clear benefit in those who had edaravone initiated earlier (at beginning of placebo controlled trail) compared with those switched from placebo to edaravone at end of the controlled trial.[7] Again, early intervention with therapy provided the most benefit.

This agent was initially given as a once daily intravenous infusion on a complicated cycle. Because of difficulties with administration, the uptake of this agent was limited until an oral formulation was approved in 2022. The oral formulation eliminated the complications of long-term intravenous line management in this debilitated population. The oral formulation was brought to market based on pharmacokinetic equivalence studies and not efficacy studies. In 2024, data from a Phase III clinical trial of an investigational oral edaravone formulation (FAB122, 100 mg once daily) combined with standard of care treatment in ALS patients did not meet primary or key secondary endpoints over 48 weeks compared to placebo.[8] No significant benefit in slowing the disease progression as measured by change from baseline in the ALS functional rating scale-revised (ALSFRS-R) score was found. Additionally, no improvement over placebo in long-term survival was observed at 48 weeks and 72 weeks in a subgroup of patients. This study used a different dose of edaravone and patient population than prior studies and is yet to be published.

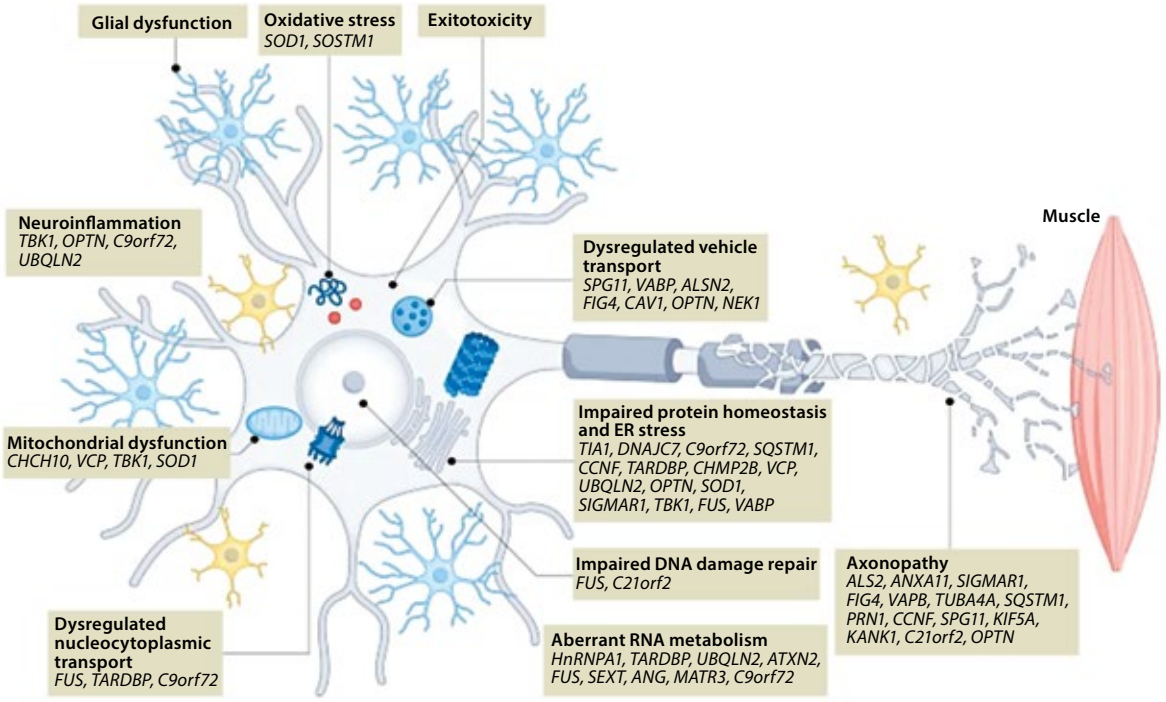
The third treatment approved for ALS was a combination of sodium phenylbutyrate/taurursodiol (PBT). The combination targeted mitochondrial dysfunction and endoplasmic reticular stress. This combination appears to act by blocking cell death pathways in mitochondria and in the endoplasmic reticulum. In the trial used for FDA approval in 2022, PBT reduced functional decline on the ALSFRS-R by 25 percent over 24 weeks compared to placebo.[9] In a modified intention-to-treat analysis, the mean rate of change in the ALSFRS-R score was -1.24 points per month with the active drug and -1.66 points per month with placebo (difference, 0.42 points per month; $p = 0.03$).[9] Trial participants had definite ALS and an onset of symptoms within the previous 18 months and were on background ALS therapies (edaravone, riluzole). A long-term survival analysis of this trial found the median overall survival was 25.0 months among participants originally randomized to PBT and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; $p = .023$).[10] Initiation of PBT treatment at baseline resulted in a 6.5-month longer median survival as compared with placebo. When the groups that initially received PBT (and continued) was compared to those who received placebo and crossed over to PBT, the best survival was in those who started the therapy earlier in the disease process.

This combination was FDA approved based on the single Phase II trial just discussed but a global Phase III trial to confirm the benefit of PBT was started before FDA approval. Unfortunately, the Phase III trial did not show functional benefit over 48 weeks so the manufacturer withdrew the product from the market in April 2024. This withdrawal occurred before the trial data was presented publicly. This trial had a different population from the Phase II trial and survival data was not available when the decision to remove it from the market was made. However, there may be a subset of patients that may be responders and additional data are pending. Taurursodiol as a single agent is also under investigation.

For patients with ALS, riluzole remains an important first-line therapy. Edaravone is meant to be added and used in combination with riluzole. Both appear to work better when initiated earlier in the course of the disease and therefore any delay in diagnosis and medication access can cause irreversible loss of function and progression of the disease.

Advances in large-scale genomic analyses have uncovered a variety of causative genes and risk

Exhibit 1: Gene Variants Mapped to Key Pathogenic Mechanisms[11]



factors for ALS. These gene variants map onto key pathogenic mechanisms and are targets for gene therapy (Exhibit 1).[11] The first gene therapy for ALS is tofersen, an intrathecally administered antisense oligonucleotide that targets superoxide dismutase 1 (SOD1) mRNA to reduce the synthesis of SOD1 protein in those with a SOD1 mutation (SOD1-ALS) which occurs in 1 to 2 percent of ALS cases. Preventing the build-up of SOD1 protein may help preserve motor neuron function. Tofersen was approved by the FDA in April 2023. One SOD1 mutation (A5V) causes a very aggressive form of ALS with a less than one-year prognosis. This mutation is autosomal dominant and occurs in every generation of an affected family.

In the Phase III trial used to conditionally approve tofersen, it led to greater reductions in concentrations of SOD1 in the cerebral spinal fluid and of neurofilament light chains in plasma than placebo.[12] In the faster-progression subgroup (primary analysis), the change to week 28 in the ALSFRS-R score was -6.98 with tofersen and -8.14 with placebo (difference, 1.2 points; p = 0.97). A total of 95 participants (88%) entered an open-label extension. At 52 weeks, the change in the ALSFRS-R score was -6.0 in the early-start cohort and -9.5 in the delayed-start cohort (difference, 3.5 points; 95% CI, 0.4 to 6.7). Tofersen was given every 28 days after three loading doses 14 days apart. Lumbar puncture-related adverse events were common in the clinical trial. Serious adverse events (myelitis, radiculitis, papilledema, and increased intracranial pressure, and aseptic meningitis) have occurred. It is FDA approved for the treatment of adults with SOD1 ALS and this indication is approved under accelerated approval based on the reduction in plasma neurofilament light chain.[13] Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). Clinicians are seeing significant benefit with this agent especially in individuals started on therapy within six months of symptom onset. Thus, it is critically important to initiate tofersen as soon as possible as this therapy can potentially stop progression or reverse weakness if initiated early in the disease. This therapy is intended to be used in combination with other treatments available for ALS.

For managed care, applying stringent eligibility criteria for ALS medications is inaccurate and not in alignment with FDA label indication for access to medications. Some plans restrict these medications to only those patients who met the study inclusion criteria, however, due to disease heterogeneity with ALS, all those with ALS should have access to these

Exhibit 2: Selected Agents in ALS Clinical Trial Pipeline

Platform Trial (U.S.)	Phase 3	Cell Therapies
• Zilucoplan (A)	**Ibudilast/MN 166***	**Allo T cell (CK0803/Cellenkos)***
• Verdiperstat (B)	Masitinib+	**Autologous TH2/Treg cell (Rapa 501)***
• CNM-Au8 (C)+	Nicotinamide Riboside/Pterostilbene (Norway)+	Autologous T cell+ IL2 (Coya)+
• Pridopidine (D)+	Triumeq* (Australia)	Human glial progenitor cell (Q cell)++
• Trehalose (E)	TUDCA (European Union)+	**CNS10-NPC-GDNF (human neural progenitor cells)***
• **ABBV-CLS-7262 (F)+**		Autologous bone marrow derived MSC-NTF (Debamestrocel/NurOwn)++
• **DNL363 (G)***		Lenzumestrocel (Korea)+ Autologous bone marrow derived MSC
		Adipose derived MSC (Mayo Clinics)+

*recruiting (U.S. recruiting trials in red); ++not yet recruiting; +active
Data from clinicaltrials.gov, 2/2024

medications. Failure of riluzole should not be a part of prior authorization criteria for edaravone. Diagnosis of SOD1 mutation for tofersen access is the only reasonable restriction. Combination therapy should not be restricted due to the differing mechanisms of actions. Delays related to coverage hurdles can also delay the start of medication which may put the patient on a pathway of faster progression.

There are numerous treatments under investigation so the future of ALS treatment is going to be increasingly complicated. Treatments targeting additional gene mutations in ALS, mechanisms associated with motor neuron degeneration, nerve and muscle communication, muscle response to diminished nerve input, neuroprotection of nerve cells, delivering protective factors to the motor neurons and the support cells surrounding the motor neurons (glial cells) are all under investigation. There are also numerous gene and cell directed therapies under investigation. Exhibit 2 shows selected agents in the pipeline. Already approved therapies are allowed in most clinical trials, however, people with ALS must be on a stable dose for 30 or more days before entering clinical trials. Most clinical trials have 'date from symptoms onset' criteria and delays in access to approved therapies will delay time to entry into clinical trials and inadvertently cause people with ALS to be ineligible for a clinical trial.

A new frontier in targeting ALS earlier is evaluating at risk individuals or gene carriers. Serum neurofilament light is being evaluated as a potential biomarker of presymptomatic ALS.[14] Tofersen is being evaluated in clinically presymptomatic SOD1 variant carriers. This frontier is moving ALS treatment into precision medicine.

Another innovation in ALS treatment is the use of platform trials with a goal of screening various drugs rapidly and efficiently, and to determine next steps in clinical development. An example in the United States is the HEALEY ALS platform trial which is testing multiple investigational products in parallel and sequentially.[15] Platform trials have considerable operational and statistical efficiencies compared with typical randomized controlled trials due to their use of shared infrastructure and shared control data.

A new era of collaboration, partnerships, research coordination, big data, harnessing technology, innovation, and open science for ALS is occurring. The Accelerating Access to Critical Therapies for

Exhibit 3: Think ALS — Tool for Clinicians

COULD THIS BE ALS?

PROGRESSIVE and ASYMMETRIC MUSCLE WEAKNESS

without radicular pain or sensory loss

A: LIMB ONSET OR FEATURES

- ☐ Ankle weakness, finger weakness or proximal arm or leg weakness
- ☐ Muscle atrophy (especially around the thumb)
- ☐ Fasciculations and cramps in a weak limb (look for deltoid, scapular, triceps, thigh regions)

B: BULBAR ONSET OR FEATURES

- ☐ Slow or slurred speech
- ☐ Dysphagia to liquids and/or solids (coughs frequently with water)
- ☐ Pseudobulbar affect/emotional lability
- ☐ Excessive saliva or pharyngeal mucus secretions
- ☐ Tongue fasciculations or atrophy (best assessed when tongue fully relaxed in floor of mouth)

C: SUPPORTING ALS

+

- ☐ Family history of ALS or dementia
- ☐ Progressive unintentional weight loss, with muscle weakness
- ☐ Unexplained neck weakness
- ☐ Unexplained frequent falls and gait abnormalities
- ☐ Orthopnea or hemidiaphragm weakness
- ☐ End-of-the-day worsening in speech and weakness
- ☐ Hyperreflexia with presence of atrophy and weakness

D: AGAINST ALS

×

- ☐ Presence of isolated radicular pain
- ☐ Symmetric proximal OR distal limb weakness
- ☐ Cog wheel rigidity
- ☐ Prominent sensory loss
- ☐ Isolated fasciculations or cramps without weakness
- ☐ Rapid onset with no progression

think ALS if patient has:

AT LEAST ONE feature in **CATEGORY A** or **B**, AND NO features in **CATEGORY D**

Additional presence of AT LEAST ONE feature in **CATEGORY C** strengthens ALS suspicion

Consider urgent referral to multidisciplinary ALS center!

Please state clearly in your referral **"CLINICAL SUSPICION FOR ALS"**

Most ALS Centers can accommodate **URGENT ALS** referrals within 2 weeks!

To find a Multidisciplinary ALS Center near you, visit THINKALS.ORG

ALS (ACT for ALS) bill is making $100,000,000 available each fiscal year from 2022 to 2026 to build new pathways to fund early access to ALS investigational therapies, accelerate ALS and neurodegenerative disease therapy development through public-private partnership, and increase research on, and development of, interventions for rare neurodegenerative diseases through a new FDA research grant program. Several trials have already been funded through ACT for ALS. In 2022, the FDA and NIH announced the launch of the Critical Path for Rare Neurodegenerative Diseases, a public-private partnership aimed at advancing the understanding of neurodegenerative diseases and fostering the development of treatments for ALS and other rare neurodegenerative diseases. The FDA has developed a five-year action plan describing actions intended to foster the development of safe and effective drugs that improve and/or extend the lives of people living with ALS and other rare neurodegenerative diseases and facilitate access to investigational drugs for ALS and other rare neurodegenerative diseases.[16] Grants and contracts will be awarded to public and private entities to cover costs of research on, and development of, interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children through the FDA Office of Orphan Products Development. An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine is conducting a study to identify and recommend key actions for the public, private, and nonprofit sectors to undertake and make ALS a livable disease within a decade.[17]

Access for ALL ALS is the first large-scale multicenter National Institute of Neurological Disorders and Stroke-funded ALS Consortium.[18] The consortium will be led by principal investigators at the Sean M. Healey and AMG Center for ALS at Massachusetts General Hospital, the Barrow Neurological Institute, Columbia University, and Georgetown University. Access for ALL ALS is designed to lead optimized, prospective, observational, longitudinal studies. This consortium will create and develop a best-in-class, widely accessible longitudinal natural history and biomarker study; community engagement strategies; disseminated ALS study methodology, a large openly shared prospectively created portal and biobank, and new clinical outcome assessments. The plan is to enroll over 2,000 symptomatic people with ALS controls, and asymptomatic people at genetic risk of ALS.

Clinician education initiatives focused on ALS are crucial for general neurologists because early recognition and timely referral to specialized ALS clinics are vital for optimal patient care. The time to diagnosis in ALS remained steady at a mean 12 to 15 months from 1996 to1998 to 2000 to 2018. Based on 2011 to 2021 Medicare claims, the mean time from first neurologist consult to confirmed ALS diagnosis was 9.6 months for ALS/neuromuscular specialists and 16.7 months for nonspecialist neurologists.[19] Given that an average ALS patient lives only three to five years from symptom onset, they are spending one-third of their survival time just trying to obtain a diagnosis.[20] The ThinkALS tool was developed by the ALS Association to significantly improve diagnosis speed by providing a structured approach to identify potential ALS cases among general neurology practices, allowing for faster access to multidisciplinary treatment and support for patients (Exhibit 3).[21]

Conclusion

People suspected of having ALS should be referred to a specialty center as quickly as possible for earlier diagnosis because earlier diagnosis allows earlier initiation of approved therapies which are meant to be taken in combination. Genetic testing is increasingly important and should be standard of care since there is an available treatment for SOD1-ALS and several investigational therapies are targeting C9ORF72, FUS, and other rare mutations. It is critical that people with SOD1-ALS gain access to tofersen as early as possible. Clinical trials are being performed with those who are asymptomatic and at risk for ALS (asymptomatic gene carriers). Innovation in clinical trials is ongoing with adaptive designs for identifying target responder groups, improving outcome measures, and identifying exploratory endpoints and biomarkers to be shared in a repository for the community.

Jinsy A. Andrews, MD, MSc, FAAN is Director of Neuromuscular Clinical Trials and an Associate Professor of Neurology at the Columbia University Irving Medical Center. She is also the Co-Chair of the NEALS Consortium in New York, NY.

References

1. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-91.

2. Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet*. 1996; 347(9013):1425-31.

3. Fang T, Al Khleifat A, Meurgey JH, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: A retrospective analysis of data from a dose-ranging study. *Lancet Neurol*. 2018;17(5):416-22.

4. Andrews JA, Jackson CE, Heiman-Patterson TD, et al. Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis. *Amyotroph*

Lateral Scler Frontotemporal Degener. 2020;21(7-8):509-18.

5. Thakore NJ, Lapin BR, Mitsumoto H, Pooled Resource Open-Access Als Clinical Trials Consortium. Early initiation of riluzole may improve absolute survival in amyotrophic lateral sclerosis. *Muscle Nerve*. 2022;66(6):702-8.
6. Writing Group on Behalf of The Edaravone ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: A randomized, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-12.
7. Writing Group on Behalf of The Edaravone (MCI-186) ALS 19 Study Group. Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener.* 2017;18(sup1):55-63.
8. Ferrer reports top-line results from Phase III ADORE study in ALS. Available at ferrer.com/en/results-study-ADORE-ALS. Accessed 2/25/2025.
9. Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. *N Engl J Med*. 2020;383(10):919-30.
10. Paganoni S, Hendrix S, Dickson SP, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle Nerve*. 2021;63(1):31-9.
11. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. *Nat Rev Drug Discov*. 2023;22(3):185-212.
12. Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. *N Engl J Med*. 2022;387(12):1099-110.
13. Tofersen (Qalsody®) package labeling. Biogen MA Inc. 4/2023.
14. Benatar M, Wuu J, Andersen PM, et al. Neurofilament light: A candidate biomarker of presymptomatic amyotrophic lateral sclerosis and phenoconversion. *Ann Neurol*. 2018;84(1):130-9.
15. Quintana M, Saville BR, Vestrucci M, et al. Design and statistical innovations in a platform trial for amyotrophic lateral sclerosis. *Ann Neurol*. 2023;94(3):547-60.
16. FDA. Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis. Available at fda.gov/media/159372/download. Accessed 2/25/2025.
17. National Academies of Sciences, Engineering, and Medicine. Amyotrophic Lateral Sclerosis: Accelerating Treatments and Improving Quality of Life. Available at nationalacademies.org/our-work/amyotrophic-lateral-sclerosis-accelerating-treatments-and-improving-quality-of-life. Accessed 2/25/2025.
18. Berry JD, Paganoni S, Harms MB, et al. Access for ALL in ALS: A large-scale, inclusive, collaborative consortium to unlock the molecular and genetic mechanisms of amyotrophic lateral sclerosis. *Muscle Nerve*. 2024;70(6):1140-50.
19. Dave KD, Oskarsson B, Yersak J, et al. Contributions of neurologists to diagnostic timelines of ALS and thinkALS as an early referral instrument for clinicians. *Amyotroph Lateral Scler Frontotemporal Degener.* 2024:1-10.
20. Dotinga R. New Clinician Tool Aims to Stop ALS Diagnosis Delays. October 22, 2024.
21. ALS Association. thinkALS™ for Faster Diagnosis. Available at als.org/thinkals. Accessed 2/25/2025.

Recent Advances in the Treatment and Management of Multiple Myeloma

Ravi Vij, MD, MBA

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

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

Summary

Multiple myeloma (MM) management has evolved dramatically in the past decade with new, more effective, and less toxic therapies. Quadruple therapy with proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and dexamethasone is the standard first-line regimen for transplant eligible patients whereas triple therapy, without the proteasome inhibitor, is standard for non-transplant eligible. Very effective options for relapsed/refractory disease are also now available including CAR-T and bispecific antibody therapies.

Key Points

- Initial treatment with a four-drug combination including a CD38 monoclonal antibody with ASCT followed by maintenance provide the best chance for a deep and long-lived remission.
- In those not eligible for transplant, a three-drug regimen is standard of care.
- For second- to fourth-line therapy, multidrug combinations are available options but CAR-T cells have also gained FDA approval for these patients.
- CAR-T cells and bispecifics are changing the landscape of treatment for later lines of therapy.

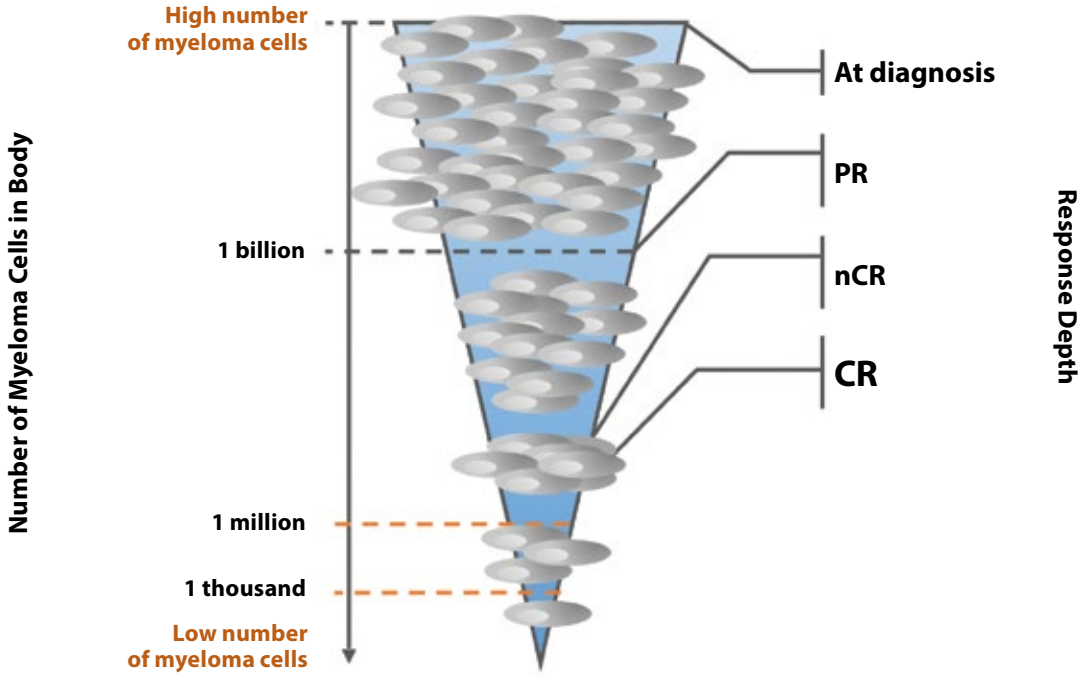
MULTIPLE MYELOMA (MM) IS THE SECOND most common blood cancer.[1] An estimated 35,780 new cases and 12,540 deaths occurred in the United States (U.S.) in 2024. The five-year survival rate is 61.1 percent and the median age at diagnosis is 69 years.

The treatment paradigm for newly diagnosed active MM begins with determining whether a patient is eligible for an autologous stem cell transplant (ASCT). About 20 percent of new MM cases in the U.S. are treated with transplant. Those who are transplant eligible receive induction, transplant, and then maintenance treatment but those not eligible receive induction and maintenance therapy only.[2,3] The goal of treating newly diagnosed MM, whether ASCT eligible or ineligible, is to gain the best depth of response to prolong the first progression-free survival (Exhibit 1).[4]

Depth of response to initial therapy correlates with long-term outcomes. Minimal residual disease (MRD, defined as less than 10^{-5} MM cells) should be achieved with first-line therapy if possible because MRD is a strong predictor of progression-free survival (PFS) and overall survival (OS).[5,6] Because the current treatments are so effective, patients can go six or seven years without disease progression or recurrence. The FDA is considering whether to use MRD rates as the primary factor for approving new therapies for MM rather than OS because of the time required to determine OS.

Treatment regimens for newly diagnosed and relapsed/refractory (RR) MM generally consist of several backbone agents and oral dexamethasone.[3] Dexamethasone has a therapeutic effect on MM cells. Trials have shown that more backbone agents are better than just one agent in improving

Exhibit 1: Goal of Front-Line Therapy Is Deep Response[4]



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

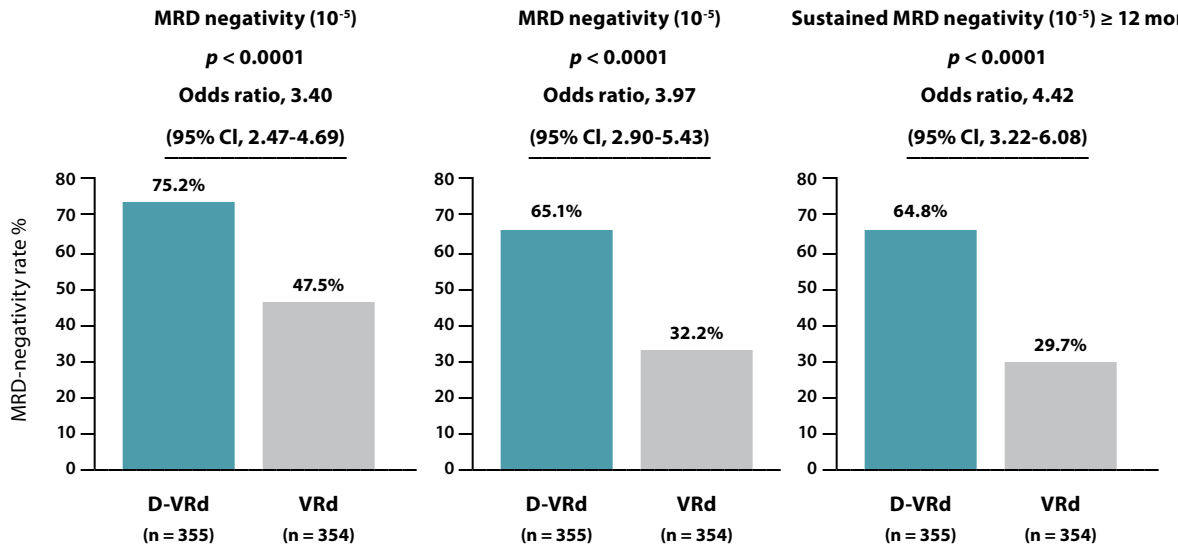
PFS. Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors which induce apoptosis of MM cells. Lenalidomide and pomalidomide are immunomodulators which induce immune responses, prevent inflammation, and enhance the activity of T cells and natural killer (NK) cells. Daratumumab and isatuximab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

For the transplant eligible population, the four-drug combination of daratumumab, bortezomib, lenalidomide, and dexamethasone is the preferred Category 1 regimen in the National Comprehensive Cancer Network (NCCN) Guidelines.[3] This regimen became standard of care based on a trial, in 709 transplantation-eligible patients with newly diagnosed MM, comparing the four-drug regimen and lenalidomide maintenance (D-VRd group) to bortezomib/lenalidomide/dexamethasone with lenalidomide maintenance (VRd group) which found significant improvement in PFS with four-drug regimen.[7] The estimated percentage of patients with PFS at 48 months was 84.3 percent in the D-VRd group and 67.7 percent in the VRd group (hazard ratio for disease progression or death, 0.42; $p < 0.001$). The percentage of patients with a complete response or better was higher in the D-VRd group than in the VRd group (87.9% versus 70.1%, $p < 0.001$), as was the percentage of patients with MRD-negative status (75.2% versus 47.5%, $p < 0.001$). Exhibit 2 shows the MRD-negative rates at two levels and the sustained MRD-negative rates.[7] Death occurred in 34 patients in the D-VRd group and 44 patients in the VRd group. Grade 3 or 4 adverse events occurred in most patients in both groups and the most common were neutropenia (62.1% with D-VRd and 51.0% with VRd) and thrombocytopenia (29.1% and 17.3%, respectively). Serious adverse events occurred in 57.0 percent of the patients in the D-VRd group and 49.3 percent of those in the VRd group.

The preferred maintenance therapy in transplant candidates is lenalidomide which continues until disease progression. Dual maintenance with bortezomib or daratumumab and lenalidomide is recommended for high-risk MM.[3] For nontransplant candidates, the NCCN preferred regimens are daratumumab/lenalidomide/dexamethasone (Category 1), isatuximab/bortezomib/ lenalidomide/ dexamethasone (for patients less than 80 years of age who are not frail, Category 1), and lenalidomide/ bortezomib/dexamethasone (Category 1).[3] These regimens are continued until disease progression.

After initial treatment, most patients will eventually have a disease relapse. The selection of

Exhibit 2: Minimal Residual Disease Negativity Rates with Four versus Three Medications[7]



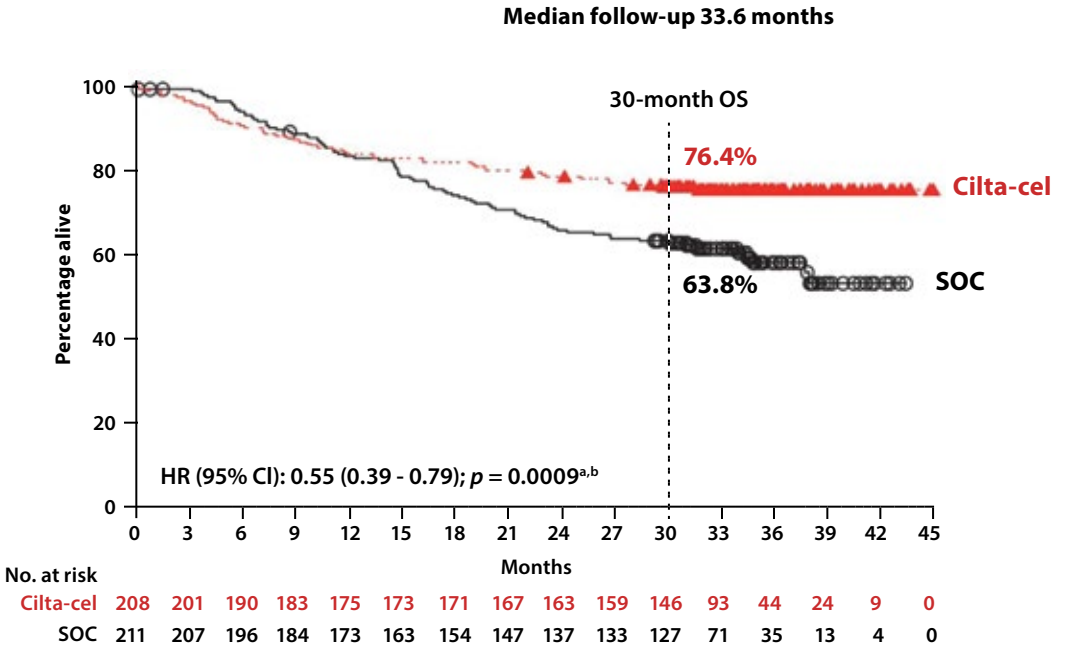
treatment for R/R MM is influenced by whether the relapse is early or late, patient factors, and prior treatments. Early relapses are those which occur within 12 months of initial treatment. Various treatment options for R/R MM are available and patients can receive multiple lines of therapy. Options include enrollment in a clinical trial, stem cell transplant, repeating first-line treatment, switching to a second-generation agent in the same drug class (e.g., lenalidomide to pomalidomide), switching to an alternative drug class, or two new classes—chimeric antigen receptor (CAR)-T cell therapy and bispecific antibodies.

Three-drug regimens are preferred over two-drug regimens. Recent studies favor the use of daratumumab or isatuximab as part of a triple regimen for R/R MM based on overall response rates and many clinicians believe adding anti-CD38 monoclonal antibodies produces the most potent regimens.[8-11] The NCCN Guidelines list several daratumumab or isatuximab regimens as Category 1 preferred regimens but also include other Category 1 regimens without these agents.[3] There is no standardization on which regimen to use first. The selected regimen will depend on which class of medication the disease has become refractory against and patient disease characteristics.

The treatment of R/R MM has changed with the FDA approval of two CAR-T therapies. Idecabtagene vicleucel (ide-cel), which targets B-cell maturation antigen (BCMA), was the first FDA approved CAR-T treatment for R/R MM in 2021. Although initially studied in patients treated with multiple prior regimens, the most recent study was in patients treated with two to four prior regimens (prior daratumumab, proteasome inhibitor, and immunomodulator containing regimen). Traditionally, outcomes have been poor in triple-class-exposed R/R MM. In the Phase III KarMMa-3 trial at median follow-up of 30.9 months, ide-cel improved median PFS versus standard regimens (13.8 versus 4.4 months; HR 0.49).[12] PFS benefit with ide-cel versus standard regimens was observed regardless of number of prior lines of therapy, with greatest benefit after two prior lines (16.2 versus 4.8 months, respectively). A complete response was seen in 44 percent of those treated with ide-cel compared to 5 percent in the standard regimen group. The patient-centric design of the trial allowed crossover from standard regimens to ide-cel upon progressive disease (56% of subjects), confounding OS interpretation. At interim analysis, median OS was 41.4 versus 37.9 months and median OS in both arms was longer than historical data (9 to 22 months). Two prespecified analyses adjusting for crossover showed OS favoring ide-cel.[12] The OS data are not yet final for this trial. This CAR-T is FDA approved for R/R MM after two or more prior lines of therapy including an immunomodulator, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and is preferred Category 1 in the NCCN Guidelines for this indication.[3]

Ciltacabtagene autoleucel (cilta-cel) is another BCMA directed CAR-T therapy. In an open label

Exhibit 3: Overall Survival with Ciltacabtagene Autoleucel Compared to Standard of Care[14]



[a] Log-rank test. *p*-value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter = 2
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable
cilta-cel = ciltacabtagene autoleucel; HR = hazard ratio; OS = overall survival; SOC = standard of care.

Phase Ib/II study in patients with R/R MM who had received three or more previous lines of therapy, at a median follow-up of 27.7 months, 82.5 percent of patients achieved a stringent complete response.[13]. Median PFS and OS were not reached. The 27-month PFS and OS rates were 54.9 percent and 70.4 percent, respectively. The results of this trial led to Phase III trials.

In a Phase III trial (Caritude-4) which has not yet been published, cilta-cel treatment reduced the risk of death by 45 percent compared to standard of care (pomalidomide/bortezomib/ dexamethasone or daratumumab/pomalidomide/dexamethasone) in patients with lenalidomide-refractory multiple myeloma and at least one prior line of therapy.[14] At a median follow-up of 33.6 months, the 30-month OS rate with ciltacabtagene autoleucel was 76.4 percent compared with 63.8 percent with SOC (HR, 0.55; *p* = .0009, Exhibit 3).[14] The median OS with the CAR-T therapy has not been reached. In the intention-to-treat (ITT) population, the MRD negativity rate with 10^{-5} sensitivity was 62.0 percent in the ciltacabtagene autoleucel arm and 18.5 percent in the standard of care arm. Cilta-cel is recommended in the NCCN Guidelines after one prior line of therapy including an immunomodulator and a proteasome inhibitor, and refractory to lenalidomide (category 1).[3]

CAR-T therapy does have some significant adverse events. Common adverse events include neutropenia, anemia, thrombocytopenia, leukopenia, and lymphopenia. Cytokine release syndrome is also common. Both approved CAR-T have black box warnings related to cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, prolonged cytopenia, and secondary hematological malignancies.

Because many cases of second-line treatment are for biological progression only, there will be few cases of R/R MM treated with CAR-T therapy in the second-line. For third- or fourth-line, especially in triple exposed patients, CAR-T therapy offers significant improvements in outcomes in a one-and-done treatment approach. Patients value the opportunity to go several years without needing any more treatment. With the standard regimens, the patient may be making once-a-week visits to a healthcare facility or lab testing for years. The CAR-T

therapies are going to be used more frequently but there are challenges to their widespread use, including toxicity, manufacturing time, and cost. Numerous other CAR-T-based treatments for R/R MM are under study.

Although initially FDA approved in 2019, selinexor is one agent which has been gaining use in the R/R setting because new dosing recommendations produce lower rates of gastrointestinal adverse events. Selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, cell cycle arrest, and apoptosis of cancer cells. It is approved for use in combination with bortezomib and dexamethasone for second-line treatment (Category 1, Other Recommended Regimen in NCCN Guidelines) and in combination with dexamethasone for fifth-line therapy in disease refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Selinexor does not impair T cell activity so it preserves the ability to use CAR-T cell therapy which is another reason for an uptick in its use.

There are many options for heavily pretreated patients with R/R MM. The NCCN Guidelines list CAR-T therapy preferred for those with R/R MM treated with three or more prior lines of therapy or bispecific antibodies after at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD. Three bispecific T-cell-engager antibodies have been FDA approved for R/R MM. With these agents, one side of the antibody binds to proteins on the myeloma cell and the other side binds to T cells allowing the T cell to kill the MM cell.

Belantamab mafodotin was the first bispecific BCMA-directed antibody FDA approved in August 2020 for the treatment of adult patients with R/R MM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulator but it was withdrawn from the market by the manufacturer in late 2022 because of results from a Phase III trial showing lack of PFS benefit. Teclistamab and elranatamab, both BCMA-directed, and talquetamab, G protein-coupled receptor 5D (GPRC5D)-directed, were FDA approved in 2022–2023 for the same indication as belantamab mafodotin. Also, similar to belantamab, these three agents were approved under accelerated approval based on response rate and continued approval is contingent on data from confirmatory trials. The bispecifics produce a substantial response rate (60% to 70%, 45% complete response) in a difficult to treat group.[15-17] In the past the average response duration in heavily pretreated patients was three months and duration of response with the bispecifics and CAR-T can be two or more years. Similar to CAR-T therapies, the bispecifics can cause significant adverse events which require monitoring. The bispecifics cause a higher rate and longer duration of immune suppression than CAR-T therapy and thus there is a considerable risk of infections, especially opportunistic infections. Patients receiving a bispecific should get *pneumocystis* and herpes prophylaxis. These agents carry a black box warning about cytokine release syndrome and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome, which can be fatal. Dosing with the bispecific requires starting at low doses and ramping up over time to reduce risk of cytokine release syndrome. Additional bispecific and trispecific antibodies are under study.

Bispecifics and CAR-T therapy have not yet been directly compared in trials. Bispecifics do not need to be individualized or engineered, and they can have a variety of targets. Unlike CAR-T, there is less delay in starting bispecific therapy but bispecifics are not a one-and-done therapy. Rather, they are given on a continued schedule. Most prescribing of bispecifics for MM is currently done at academic medical centers, however, once a patient has reached a stable dose, their care can be taken over by a community hematologist/oncologist.

Sequencing BCMA targeting CAR-T and BCMA targeting bispecifics are issues. The available data suggests that a BCMA targeting bispecific can be used before CAR-T without impacting outcome but not the other way around. It is not yet known if a patient can be treated with one of these and then receive therapy targeting something else and then go back to a BMCA targeting therapy. Because talquetamab targets something other than BCMA, it should be able to be used before or after CAR-T without impacting outcomes. This agent does have some unique adverse events related to its target including major rashes, brittle nails, nail loss, loss of taste and saliva, and difficulty swallowing.

Additional agents for MM treatment are on the horizon. One example is iberdomide, an investigational immunomodulator which is a potent cereblon E3 ligase modulator.[18] This is the same mechanism of action as lenalidomide and pomalidomide but this agent is more potent. In triple-class refractory disease in combination with dexamethasone, the overall response rate with this agent was 32 percent.[19]

Over the years MM has not been thought of as a curable malignancy but with the newer treatments about 5 percent of patients are being cured with transplants. Also, newly diagnosed patients are living 10 or more years with their disease which was fatal much sooner in the past.

Conclusion

The treatment of multiple myeloma has evolved quickly over the past decade. Initial treatment with a four-drug combination including a CD38 monoclonal antibody with ASCT followed by maintenance provides the best chance for a deep and long-lived remission. For second- to fourth-line therapy, multidrug combinations are available options but CAR-T cells and bispecifics have also gained FDA approval for these patients. For patients with multiple myeloma, the best is yet to come!

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

References

1. National Cancer Institute. Cancer Stat Facts: Myeloma. Available at seer.cancer.gov/statfacts/html/mulmy.html. Accessed 3/21/2025.
2. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2021;32(3):309-22.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 1.2025. Available at nccn.org. Accessed 3/21/2025.
4. Mailankody S, Korde N, Lesokhin AM, et al. Minimal residual disease in multiple myeloma: Bringing the bench to the bedside. *Nat Rev Clin Oncol*. 2015;12(5):286-95.
5. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): Final analysis of an open-label, randomized, Phase II trial. *Lancet Haematol*. 2023;10(10):e825-e837.
6. Costa LJ, Chhabra S, Medvedova E, et al. Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): Final report of the multicenter, single-arm, Phase II trial. *Lancet Haematol*. 2023;10(11):e890-e901.
7. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-13.
8. Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): Updated outcomes from a randomized, multicenter, open-label, Phase III study. *Lancet Oncol*. 2022;23(1):65-76.
9. Minakata D, Fujiwara SI, Yokoyama D, et al. Relapsed and refractory multiple myeloma: A systematic review and network meta-analysis of the efficacy of novel therapies. *Br J Haematol*. 2023;200(6):694-703.
10. Martin T, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase III study. *Blood Cancer J*. 2023;13(1):72.
11. Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;391(17):1597-609.
12. Ailawadhi S, Arnulf B, Patel K, et al. Ide-cel vs standard regimens in triple-class-exposed relapsed and refractory multiple myeloma: Updated KarMMa-3 analyses. *Blood*. 2024;144(23):2389-401
13. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti-b-cell maturation antigen chimeric antigen receptor t-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. *J Clin Oncol*. 2023;41(6):1265-174.
14. Mateos M-V, San-Miguel J, Dhakal, et al. Overall survival (OS) with ciltacabtagene autoleucel (Cilta-cel) versus standard of care (SoC) in lenalidomide (Len)-refractory multiple myeloma (MM): Phase 3 CARTITUDE-4 study update. Presented at: 2024 International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA – 65.
15. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232-44.
16. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2022;387(6):495-505.
17. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: Phase II MagnetisMM-3 trial results. *Nat Med*. 2023;29(9):2259-67.
18. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia*. 2020;34(4):1197-201.
19. Lonial S, Popat R, Hulin C, et al. Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): A multicenter, multicohort, open-label, Phase I/II trial. *Lancet Haematol*. 2022;9(11):e822-e832.

Elevating Optimal Care for Prostate Cancer: Applying Personalized Treatment Options to Improve Outcomes

Scott T. Tagawa, MD, MS, FASCO, FACP

This journal article is supported by educational grants from Janssen Biotech, Inc.; Novartis Pharmaceuticals Corporation

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

Summary

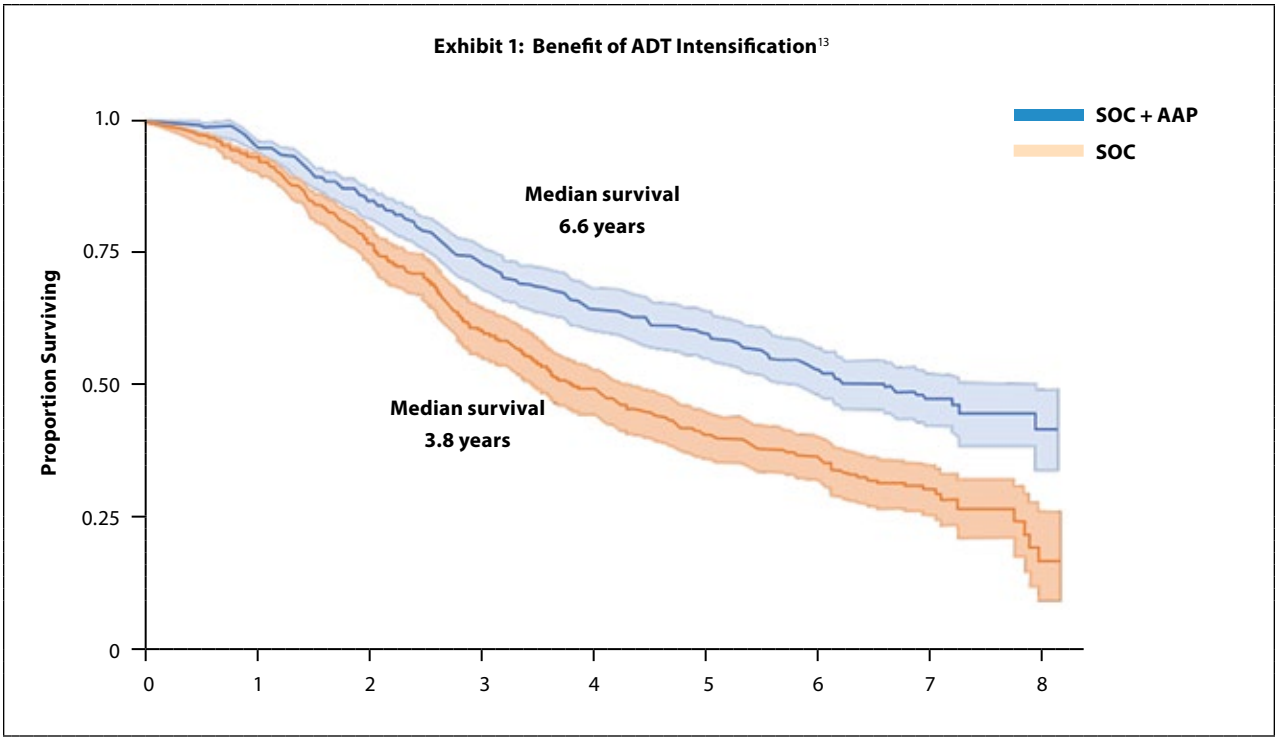
In the past, hormonal therapies were the only option for managing the later stages of prostate cancer. Numerous systemic therapies for hormone sensitive and resistant disease are now available that increase quantity and quality of life. Early intensification of androgen directed therapy leads to more significant survival benefits.

Key Points

- Androgen receptor pathway inhibitors in combination with androgen deprivation therapy and taxane-based chemotherapy provide the best survival in mCSPC and is the standard of care.
- The choice of therapy in metastatic disease will depend on prior therapy and selected biomarkers such as BRCA1/2 mutations, DNA repair deficiencies, and PSMA.
- A radiopharmaceutical is now available to target PSMA positive metastatic CRPC.

THE MANAGEMENT OF ADVANCED PROSTATE cancer has changed greatly in the last 25 years. Beginning in the early 2000s, docetaxel- and cabazitaxel-based chemotherapy was found to improve survival and quality of life in those with metastatic castrate resistant prostate cancer (mCRPC).[1] Chemotherapy then moved forward into the first-line setting for metastatic castrate sensitive disease (mCSPC). Taxanes (docetaxel, cabazitaxel) are the only class of chemotherapy with demonstrated survival benefit in CSPC. Docetaxel leads to prolongation of survival in men with metastatic CSPC and CRPC. Cabazitaxel leads to prolongation of survival in men with mCRPC following docetaxel. Each taxane has a similar toxicity profile with myelosuppression, fatigue, neuropathy, diarrhea, and alopecia being common.

Subsequently, androgen deprivation therapy (ADT) plus docetaxel was found to be superior to ADT alone for overall survival (OS) and progression-free survival (PFS) in mCSPC.[2] In terms of ADT, a bilateral orchiectomy, luteinizing hormone-releasing hormone (LHRH) analog, or estrogen are equally effective in prostate cancer. Of those three types of treatment, an LHRH analog is most used in the United States (U.S.). LHRH analogs include LHRH agonists (e.g., leuprolide, goserelin, triptorelin, histrelin) and gonadotropin-releasing hormone (GnRH) antagonists (e.g., degarelix, relugolix). Incidentally, because LHRH is a type of GnRH, and its primary action is to stimulate the release of LH, the terms are often used interchangeably. When an LHRH analog is started, there is an initial testosterone surge followed by suppression of testicular testosterone



SOC = standard of care; AAP = abiraterone acetate and prednisone

production. To avoid a disease flare from the surge, anti-androgens are typically given briefly at the beginning of therapy. The anti-androgens include bicalutamide, flutamide, and nilutamide which have competitive inhibition of androgen reception. With a GnRH antagonist, there is an immediate reduction in testosterone production in the testes.

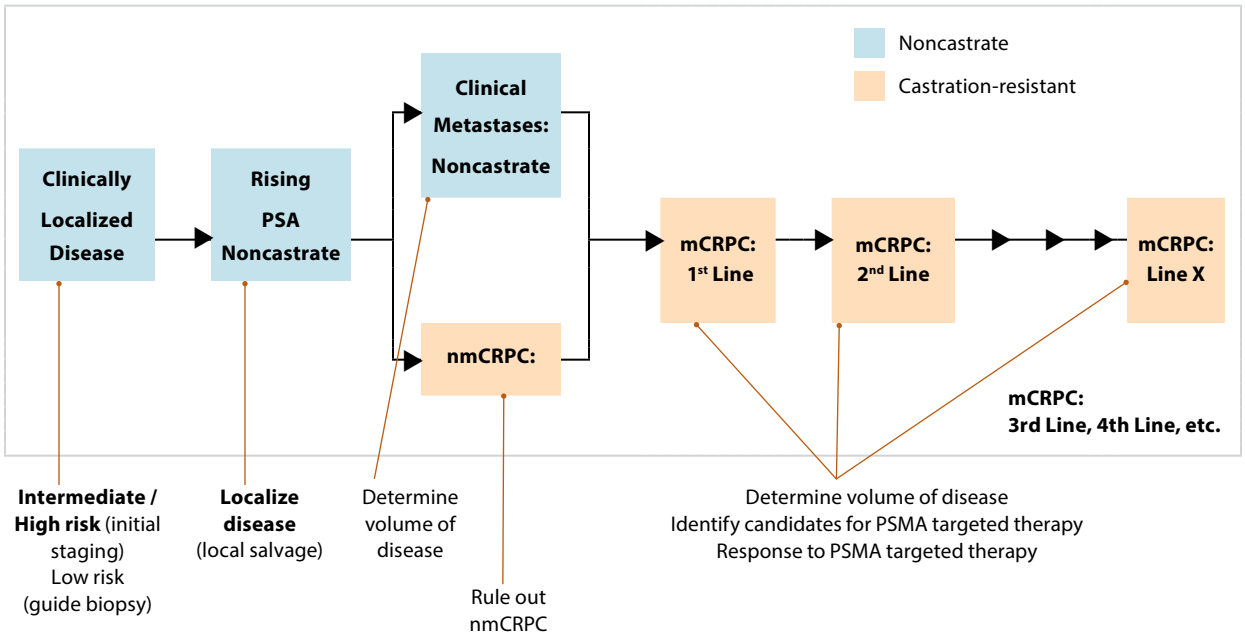
Androgen receptor pathway inhibitors (ARPI) play a significant role in managing advanced prostate cancer. Abiraterone, an androgen biosynthesis inhibitors that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), yields superior OS in post-docetaxel mCRPC, chemo-naïve minimally symptomatic mCRPC, and mCSPC.[3-6] Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide, apalutamide, and darolutamide are inhibitors of androgen binding to androgen receptors. Enzalutamide yields superior OS than placebo in post-docetaxel mCRPC and chemo-naïve minimally symptomatic mCRPC.[7,8] All three improve metastases-free survival and OS in nmCRPC.[9-11] Using these agents earlier in the disease process at the mCSPC stage produces magnified improvements in OS compared with using them later.[12-15] This translates to about three additional years of survival (Exhibit 1).[13]

Triple therapy with docetaxel, ADT, and ARPI is even better than docetaxel/ADT or ARPI monotherapy in terms of OS.[16] Triple therapy or what is known as ADT intensification is now standard of care but ADT/ARPI is the minimum that a patient should be receiving. Unfortunately, many men are not getting appropriate care. Although things have improved in recent years, approximately 50 percent of men are still getting inferior treatment.[17]

Other treatments for mCRPC include radium-223 for symptomatic bone metastases, immunotherapy for a few patients (sipuleucel-T for asymptomatic or minimally symptomatic patients with no liver metastases and life expectancy of six months or more, or pembrolizumab for the 3 percent of patients with microsatellite instability high or deficient mismatch repair), poly ADP-ribose polymerase (PARP) inhibitors for those with tumors with homologous recombination repair deficiency (HRD), combination therapy with PARP and ARPI, and lutetium Lu 177 for prostate-specific membrane antigen (PSMA)-positive disease.

Twenty-three percent of mCRPC cases have somatic DNA repair alterations and 11.8 percent of men have germline DNA repair defects such as BRCA mutations.[18] PARP inhibitors compared to enzalutamide or abiraterone have been shown to

Exhibit 2: Benefits of PSMA-PET[27]



improve OS in mCRPC with DNA repair defects. In a study of olaparib, the improved OS was in those BRCA1, BRCA2, or ATM mutations (19.1 versus 14.7 months) and in the overall population with and without those mutations (17.3 versus 14.0 months).[19] Rucaparib improved PFS when compared to physician choice of therapy (docetaxel or abiraterone or enzalutamide) in mCRPC patients with BRCA1, BRCA2 or ATM mutations.[20] Olaparib and rucaparib are both FDA approved as monotherapy for mCRPC with selected mutations.

Synthetic lethality of tumor cells is increased when PARP inhibition is combined with ARPI. Thus, PARP inhibitors have been studied in combination with ARI for mCRPC. The combination of olaparib with abiraterone as first-line therapy in mCRPC, regardless of HRR mutation status, led to a 34 percent risk reduction of progression or death and 8.2 month improvement in imaging based PFS.[21] Similar results were seen with the combination of niraparib and abiraterone which reduced risk of progression or death by 47 percent in those with BRCA 1 or 2 mutation.[22] Whereas both trials report significant imaging-based PFS benefit, the OS data did not show a benefit. A randomized, double-blind, Phase III trial of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line therapy in men with asymptomatic or mildly symptomatic mCRPC receiving ongoing ADT also resulted in clinically meaningful and statistically significant improvement in imaging based PFS versus enzalutamide.[23] Trial subjects may have had previous treatment (docetaxel or abiraterone, or both) in the castration-sensitive setting. The combination therapy reduced the risk of death by 20.4 percent compared to enzalutamide alone, with a median overall survival of 45.8 months versus 37.0 months.[24] The population studied in these trials is not the future state of mCRPC as more and more patients over time will have ADT intensification in the non-metastatic disease and mCSPC setting. The combination of talazoparib with enzalutamide, olaparib with abiraterone, and niraparib with abiraterone are currently FDA approved. The group of current patients who would be receiving these combinations will be limited because of prior ARPI exposure. The use of a second ARPI in those with prior exposure has not been shown to be effective.

PSMA is the single most well-established, prostate-restricted, cell membrane target known. The distribution of PSMA is mostly limited to prostate and prostate cancer thus PSMA is a target of high interest in the current era, especially important for higher grade, metastatic tumors

that grow despite hormonal therapy. PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in more than 80 percent of men with metastatic disease.[25,26] PSMA-PET scans are a very sensitive imaging technique for prostate cancer which address imaging deficiencies in prostate cancer (Exhibit 2).[27] PSMA-PET scans provide molecular-level imaging, allowing for more precise staging and restaging of prostate cancer compared to conventional imaging techniques such as CT, MRI, and bone scans. PSMA-PET scans are highly sensitive, meaning they can detect very small tumors or metastases that may be missed by other imaging methods. Thus, it can be used to show a patient actually has metastatic disease instead of nmCRPC. Importantly, PSMA-PET identifies patients for PSMA targeted therapy.

Lutetium Lu 177 vipivotide tetraxetan, a radiopharmaceutical, is the first PSMA targeted therapy. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to the cells, as well as to surrounding cells, and induces DNA damage leading to cell death. In the Phase III trial used for FDA approval, lutetium Lu 177 vipivotide tetraxetan plus standard care compared to standard care significantly prolonged both imaging-based PFS (8.7 versus 3.4 months; $p < 0.001$) and OS (15.3 versus 11.3 months; $p < 0.001$).[28] This radiopharmaceutical is indicated for the treatment of men with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. The National Comprehensive Cancer Network (NCCN) Guidelines list this therapy as a Category 1 treatment option for patients with one or more PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy.[29]

Many PSMA targeting agents are on the horizon. In addition to mCRPC, these agents are being studied earlier in the disease process including chemotherapy-naïve mCRPC. They are also being studied with radiosensitizers, chemotherapy, PARP inhibitors, immunotherapy, and ARPI to improve efficacy.

Conclusion

There are many more categories of therapy for the treatment of advanced prostate cancer available today than 25 years ago. These therapies have not only improved the quantity of life (overall survival) but many have improved the quality of life.

Scott T. Tagawa, MD, MS, FASCO, FACP is a Professor of Medicine and Urology and Medical Director of the Genitourinary Oncology Research Program at Weill Cornell Medicine. He is also an Attending Physician at New York-Presbyterian, Weill Cornell Medical Center in New York, NY.

References

1. Riaz IB, Sweeney CJ. The role of chemotherapy in metastatic prostate cancer. *Curr Opin Urol*. 2022;32(3):292-301.
2. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate Cancer. *N Engl J Med*. 2015;373(8):737-46.
3. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomized, double-blind, placebo-controlled Phase III study. *Lancet Oncol*. 2015;16(2):152-60.
4. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-60.
5. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-51.
6. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: A meta-analysis of primary results from two randomized controlled Phase III trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447-60.
7. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-97.
8. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-33.
9. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-74.
10. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-18.
11. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-46.
12. James ND, Clarke NW, Cook A, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomized trial (NCT00268476). *Int J Cancer*. 2022;151(3):422-34.
13. Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2022;40(15):1616-22.
14. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med*. 2019;381(2):121-31.
15. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24.
16. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132-42.
17. Heath EI, Dyson GE, Cackowski FC, et al. Treatment Intensification patterns and utilization in patients with metastatic castration-sensitive prostate cancer. *Clin Genitourin Cancer*. 2022;20(6):524-32.
18. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-53.
19. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-102.
20. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. *N Engl J Med*. 2023;388(8):719-32.

21. Clarke NW, Armstron AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med Evid*. 2022;1(9):EVIDoa2200043.

22. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2023;41(18):3339-51.

23. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): A randomized, placebo-controlled, Phase III trial. *Lancet*. 2023;402(10398):291-303.

24, Agarwal N, Azad AA, Carles J, et al. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the Phase III TALAPRO-2 trial. *J Clin Oncol*. 2005:43 (suppl 5):abstr LBA18.

25. Pomykala KL, Czernin J, Grogan TR, et al. Total-body 68Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients: Potential impact on bone scan guidelines. *J Nucl Med*. 2020;61(3):405-11.

26. Hope TA, Aggarwal R, Chee B, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nucl Med*. 2017;58(12):1956-61.

27. Combes AD, Palma CA, Calopedos R, et al. PSMA PET-CT in the diagnosis and staging of prostate cancer. *Diagnostics (Basel)*. 2022;12(11):2594.

28. Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-103.

29. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 2.2025. Available at nccn.org. Accessed 5/2/2025.

Informed Managed Care Decision-Making in the Management of Chronic Lymphocytic Leukemia: Optimizing Clinical and Economic Outcomes with BTK Inhibitors

Ryan Jacobs, MD

This journal article is supported by educational grants from Lilly; AstraZeneca; BeiGene

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

Summary

Over the last 10 years, the treatment of CLL has moved from non-specific chemo-immunotherapy to targeted therapies; specifically BTK inhibitors. Oral regimens with BTK inhibitors are favorable treatment options for the majority of CLL patients.

Key Points

- The covalent BTK inhibitors have similar efficacy but acalabrutinib and zanubrutinib have an advantage of fewer adverse events.
- Patients' disease can be controlled for 10 years or more with these agents.
- A time limited regimen of acalabrutinib and venetoclax is the most recent innovation.
- A non-covalent BTK inhibitor is now available to combat certain mutations that lead to disease progression.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23 and the diagnosis requires a $5x10^9$/L or more clonal B cell count.[1] CLL is the most common type of leukemia diagnosed in the United States (U.S.). In 2025, an estimated 23,690 patients will be diagnosed with CLL and the average age at diagnosis is 70 years.[2]

CLL develops from cumulative insults on the DNA of B lymphocytes over time. It is found incidentally based off a blood draw for other reasons in about 50 percent of cases. The precursor, monoclonal B cell lymphocytosis, and CLL without active disease, are managed with observation.

Treatment for CLL is initiated once the patient has active disease. Exhibit 1 shows the criteria for initiating therapy.[1] Currently, there are no data showing that treating CLL earlier rather than waiting for active disease provides any survival benefit. Although CLL-targeted treatments are well tolerated, adverse events can occur which are other reasons to postpone treatment. Many times, based on symptoms interfering with their quality of life, it is the patient saying it is time to start treatment.

Treatment has advanced over the years from cytotoxic chemotherapy to chemo-immunotherapy to small molecule inhibitors. Now, chemotherapy is rarely, if ever, an appropriate treatment. First-line therapy for most patients is either continuous oral Bruton's tyrosine kinase inhibitor (BTKi) until disease progression or unacceptable toxicity or limited duration use of oral venetoclax in combination with injectable obinutuzumab. The goals when using these therapies are disease control over decades as few patients will have their disease cured. With current therapy, most patients can live

Exhibit 1: Criteria for Initiation of Treatment[1]

Active Disease

Active disease is defined as having ≥ 1 of the following:

- Hemoglobin < 10 g/dL
- Platelet count < 100 x 10^9/L
- Symptomatic or functional extranodal involvement
- Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids
- Lymphocyte doubling time < 6 months
- Bulky disease (spleen ≥ 6 cm beneath costal margin, lymph nodes ≥ 10 cm)

Symptoms

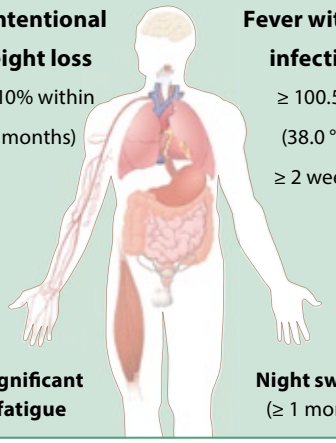


Exhibit 2: NCCN Guidelines for First Line Treatment of CLL[4]

	With or Without del(17p)/TP53 Mutation
Preferred (Category 1)	• Acalabrutinib ± obinutuzumab • Zanubrutinib • Venetoclax + obinutuzumab • Venetoclax + acalabrutinib ± obinutuzumab

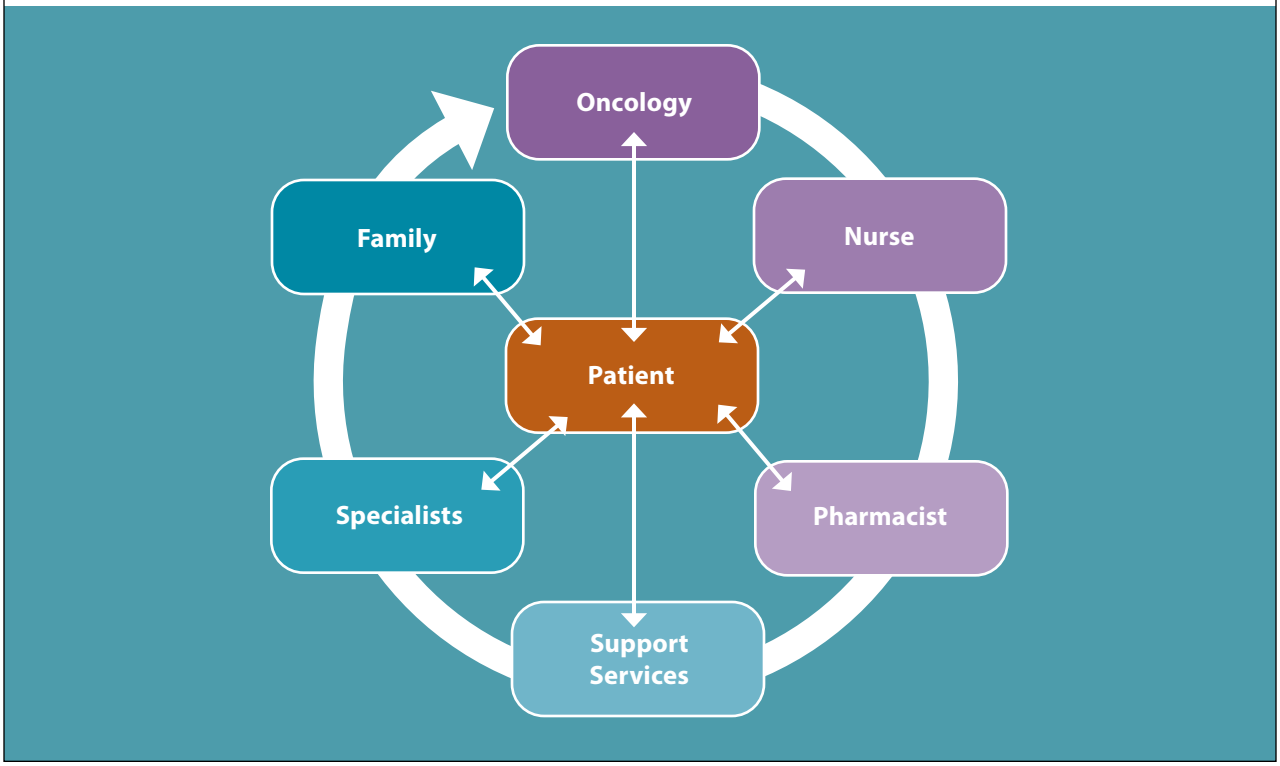
out their normal life expectancy.[3]

The choice of first-line therapy has become more complicated with the various available treatment and clinical trial options. The clinician and patient conversations for choosing therapy can be extensive. The National Comprehensive Cancer Network (NCCN) Guidelines include two BTKi category 1, preferred choices (acalabrutinib, zanubrutinib) or the time limited venetoclax/obinutuzumab for one year or time limited venetoclax/acalabrutinib with or without obinutuzumab (Exhibit 2).[4] Ibrutinib, the first BTKi, is no longer considered first-line because of significant adverse events, especially atrial fibrillation, compared to the other available BTKi. The dominant treatment in the U.S. is BTKi monotherapy, which is easier to manage than venetoclax/obinutuzumab, especially for community oncology settings. The combination regimen requires frequent laboratory monitoring and long infusion center visits for obinutuzumab. This combination is more likely to be used in cancer specialty centers.

Prognostic markers in CLL can be helpful in choosing between BTKi and combination therapy. These include del17p mutation, immunoglobulin heavy chain variable region (IgHV) mutational status, tumor suppressor protein 53 (TP53) mutation analysis, and complex karyotype. BTKi appear to be a better choice among those with del17p, which occurs in about 15 percent of patients. IgHV mutation status is an evolving area. Unmutated IgHV is a marker for poor survival with chemotherapy and progression-free survival (PFS) response with venetoclax/obinutuzumab appears to be less than with BTKi.[5,6]

Ibrutinib was the first BTKi approved by the FDA (2014) followed by zanubrutinib (2018), acalabrutinib (2023), and pirtobrutinib. Acalabrutinib has the lowest off-target activity, which can lead to significant adverse events. The longest-term data on overall survival (OS) is with ibrutinib, showing over 10 years of response. The OS at 117 months was 58.5 percent for all patients, 73.8 percent for treatment-naïve patients, and 54.1 percent in patients with TP53 alterations.[7] Among patients with TP53 alterations receiving frontline ibrutinib (N = 34), the mPFS was 81 months with an OS of 69.7 percent at 117 months.[7] Up to six years of follow-up are available for acalabrutinib. In the first-line treatment trial with acalabrutinib, obinutuzumab was given for six months along with acalabrutinib in one subgroup.[8] The addition of obinutuzumab does appear to improve PFS but most clinicians are not adding the obinutuzumab to acalabrutinib therapy because of the difficulty with infusions.

Exhibit 3: Shared Decision-Making in Oncology



A comparison trial of acalabrutinib versus ibrutinib (Elevate RR) found the two agents noninferior with a median PFS of 38.4 months in both arms.[9] All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; p = .02) and median OS was not reached in either arm. The discontinuation rate for adverse events was lower in this trial with acalabrutinib (14.9% versus 22.3%).

Zanubrutinib has also been compared to ibrutinib in the relapsed/refractory CLL setting. In the Alpine study, zanubrutinib was compared to ibrutinib in relapsed or recurrent CLL. At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to PFS (hazard ratio for disease progression or death, 0.65; p = 0.002).[10] At 24 months, PFS rates were 78.4 percent in the zanubrutinib group and 65.9 percent in the ibrutinib group. Thirty-six-month PFS rates were 64.9 percent and 54.8 percent and OS rates were 82.5 percent and 79.6 percent.[11] Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer PFS than those who received ibrutinib (hazard ratio for disease progression or death, 0.53). PFS across other major prognostic subgroups consistently favored zanubrutinib. A lower rate of atrial fibrillation/flutter was observed with zanubrutinib compared to ibrutinib (2.5% versus 10.1%; p = .0014) and major bleeding rates were also lower (2.9% versus 3.9%), as were adverse events leading to treatment discontinuation (7.8% versus 13.0%, respectively) or death (3.9% versus 5.8%). Neutropenia occurred more often with zanubrutinib (28.4% versus 21.7%). The toxicities where clinicians see differences among the BTKi are atrial fibrillation (ibrutinib), bleeding (ibrutinib), headaches (acalabrutinib), hypertension (zanubrutinib), and neutropenia (zanubrutinib).

The newest regimen recommended by the NCCN Guidelines is venetoclax plus acalabrutinib with or without obinutuzumab for a time-limited duration. In a single arm Phase II trial studying frontline time-limited, minimal residual disease (MRD)-guided triplet therapy with acalabrutinib, venetoclax, and obinutuzumab, patients were treated in 28 day cycles.[12] Acalabrutinib monotherapy was given orally at 100 mg twice daily for cycle 1, then combined for six cycles with intravenous obinutuzumab (100 mg on cycle 2 day one, 900 mg on day two, 1,000 mg on day eight, and 1,000 mg on day 15 and on day one of cycles 3 to 7). From the beginning of cycle 4, oral venetoclax was dosed daily using an accelerated ramp-up from 20 mg on day one to 400 mg by day 22 and continued at this dose thereafter. Patients

continued acalabrutinib 100 mg twice daily and venetoclax 400 mg once daily until day one of cycle 16 or day one of cycle 25. If the patient had undetectable MRD in the bone marrow they were given the option to discontinue therapy at the start of cycle 16 (if also in complete remission) or at the start of cycle 25 (if at least in partial remission). The primary endpoint was complete remission with undetectable MRD in the bone marrow (less than 1 CLL cell per 10,000 leucocytes), at cycle 16 day one. Median follow-up was 27.6 months. At cycle 16 day one, 14 (38%) of 37 participants had a complete remission with undetectable MRD in the bone marrow. The most common Grade 3 or 4 hematological adverse event was neutropenia (43%).

AMPLIFY is on ongoing Phase III study assessing the efficacy and safety of fixed-duration acalabrutinib-venetoclax (±obinutuzumab) versus investigator's choice of chemoimmunotherapy in fit patients with treatment naïve CLL.[13] In this trial, acalabrutinib-venetoclax (acalabrutinib 100 mg BID [cycles 1 to 14]; venetoclax QD [cycles 3 to 14 with five-week dose ramp-up [20 to 400 mg]), acalabrutinib-venetoclax-obinutuzumab (dosing as above, plus intravenous obinutuzumab 1,000 mg cycles 2 [days 1, 8, and 15] and 3 to 7 [day 1]), or investigator's choice of fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR) per standard dosing protocol (cycles 1 to 6) was used. The included subjects had Eastern Cooperative Oncology Group performance-status score of 0 to 2 and did not have a 17p deletion or TP53 mutation; 58.6 percent had unmutated IGHV. Estimated 36-month PFS at a median follow-up of 40.8 months was 76.5 percent with acalabrutinib-venetoclax, 83.1 percent with acalabrutinib-venetoclax-obinutuzumab, and 66.5 percent with chemoimmunotherapy (hazard ratio for disease progression or death with acalabrutinib-venetoclax versus chemoimmunotherapy, 0.65, $p = 0.004$; for the comparison of acalabrutinib-venetoclax-obinutuzumab with chemoimmunotherapy, $p < 0.001$). Estimated 36-month OS was 94.1 percent with acalabrutinib-venetoclax, 87.7 percent with acalabrutinib-venetoclax-obinutuzumab, and 85.9 percent with chemoimmunotherapy. Neutropenia, the most common adverse event of clinical interest of Grade 3 or higher, was reported in 32.3 percent, 46.1 percent, and 43.2 percent in the three groups, respectively. Death from coronavirus disease was reported in 10, 25, and 21 patients in the three groups, respectively. Based on estimated 36-month survival data and adverse events, it appears acalabrutinib and venetoclax are a viable time-limited treatment option and are now included in the NCCN Guidelines. This trial will not be completed until 2027.

One issue with BTKi is the development of resistance. Ibrutinib, acalabrutinib, and zanubrutinib are all irreversible covalent BTKi which bind to the C481 site on BTK for their mechanism of action. C481S mutations are common and confer resistance to all covalent BTKi. Patients who have disease progression on a covalent BTKi should not be switched to an alternative covalent BTKi because of this common resistance mechanism.

Reversible, non-covalent BTKi are the next evolution of CLL therapy. They exert their inhibition of BTK by different mechanisms than covalent BTKi. They do not act by binding to the C481 site on BTK and therefore offer a potential alternative therapeutic option to patients who have developed acquired resistance due to BTK C481 mutations following prior therapy with a covalent BTKi. Several other mutations have also shown up with acalabrutinib and zanubrutinib therapy which may or not be susceptible to non-covalent BTKi.

Pirtobrutinib is the first highly selective, non-covalent, reversible BTK inhibitor to be approved by the FDA (12/2023); it blocks the ATP binding site of BTK. The NCCN Guidelines recommend it for second-line or third-line therapy in cases of resistance or intolerance to prior covalent BTKi therapy.[4] Pirtobrutinib is a very selective inhibitor which also helps lower the rate of adverse events. In a trial evaluating pirtobrutinib in 317 patients with CLL, including 247 who had previously received a BTKi, the median number of previous lines of therapy was three (range, 1 to 11), and 40.5 percent had also received a B-cell lymphoma 2 inhibitor such as venetoclax.[14] The median PFS was 19.6 months. The most common adverse events were infections (71.0%), bleeding (42.6%), and neutropenia (32.5%). At a median duration of treatment of 16.5 months, some adverse events that are typically associated with BTKi occurred infrequently, including hypertension (14.2% of patients), atrial fibrillation or flutter (3.8%), and major hemorrhage (2.2%). Only 2.8 percent discontinued pirtobrutinib owing to a treatment-related adverse event. In this trial, pirtobrutinib showed efficacy in patients with heavily pretreated CLL who had received a covalent BTK inhibitor. Novel resistance mechanisms are now showing up with the use of pirtobrutinib which will have to be tackled in the future.[15]

Involving the patient in their care is a way to achieve the long-term survival outcomes seen in clinical trials. Shared decision-making is a way to involve the patient and this has been shown to improve patient outcomes in CLL treatment. Shared decision-making needs to be patient-centered

and include all the essential healthcare providers (Exhibit 3). Communication among everyone is key to success. For example, because the BTKi have many drug-on-drug interactions, patients receiving these agents can be educated to contact their pharmacist before starting any new medications. Cost of these agents and prescription coverage may be issues in keeping patients on these agents. Tapping into support services such as co-pay assistance may be needed.

Conclusion

Early results with oral small-molecule inhibitors in CLL are extremely promising. Small-molecule inhibitors provide favorable treatment options for the majority of CLL patients, most notably high-risk, elderly, and/or comorbid patients and those with relapsed disease. It is important to incorporate shared decision-making when developing care plans with patients, family members, and/or caregivers.

Ryan Jacobs, MD is Director, Division of Lymphoma Therapy and Research in the Department of Hematologic Oncology, Cellular Therapy and Blood Disorders at the Levine Cancer Institute/Atrium Health in Charlotte, NC. He is also an Associate Professor of Internal Medicine at Wake Forest University School of Medicine in Winston-Salem, NC.

References

1. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60.
2. National Cancer Institute. Cancer Stat Facts: Leukemia—Chronic Lymphocytic Leukemia (CLL). Available at seer.cancer.gov/statfacts/html/clyl.html. Accessed 3/11/2025.
3. Burger JA, Kay NE, Allan JN, et al. Treatment with first-line ibrutinib improves overall survival in patients with chronic lymphocytic leukemia (CLL) and high-risk genomic features to rates approximating an age-matched us population: Pooled analysis of Phase III trials with 10 years of follow-up. *Blood*. 2024;144 (Supplement 1):4615.
4. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. Version 2.2025. Available at nccn.org. Accessed 3/11/2025.
5. Al-Sawaf O, Zhang C, Jin HY, et al. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun*. 2023;14(1):2147.
6. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia*. 2022;36(4):1171-5.
7. Itsara A, Sun C, Bryer E, et al. Long-term outcomes in chronic lymphocytic leukemia treated with ibrutinib: 10-year follow-up of a Phase II study. *Blood*. 2023;142(Supplement 1):201.
8. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: 6-Year follow-up of Elevate-TN. *Blood*. 2023;142(Supplement 1):636.
9. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized Phase III trial. *J Clin Oncol*. 2021;39(31):3441-52.
10. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-32.
11. Brown JR, Eichhorst B, Lamanna N, et al. Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL: Final comparative analysis of ALPINE. *Blood*. 2024;144 (26):2706-17.
12. Davids MS, Lampson BL, Tyekucheva S, et al. Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukemia: A single-arm, open-label, Phase II study. *Lancet Oncol*. 2021;22(10):1391-402.
13. Brown JR, Seymour JF, Jurczak W, et al. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. *N Engl J Med*. 2025;392(8):748-62.
14. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukemia. *N Engl J Med*. 2023;389(1):33-44.
15. Montoya S, Thompson MC. Non-covalent Bruton's tyrosine kinase inhibitors in the treatment of chronic lymphocytic leukemia. *Cancers (Basel)*. 2023;15(14):3648.

2025 CORPORATE PARTNERS

PLATINUM

AbbVie
Daiichi Sankyo
Gilead Sciences
Medtronic
Menarini Silicon Biosystems
Nevro Corporation
Pfizer Biopharmaceuticals Group
Takeda Pharmaceuticals
Verrica Pharmaceuticals

GOLD

Aveo Oncology
Bristol Myers Squibb
Boston Scientific Corporation
BridgeBio
C2N Diagnostics
CVRx
DJO / Enovis
Ferring Pharmaceuticals, Inc.
Foundation Medicine
GE Healthcare
Genentech
Jazz Pharmaceuticals
Lantheus Medical Imaging
Lucid Diagnostics
Mitsubishi Tanabe Pharma America
Pharmacosmos
Recor Medical
Sumitomo Pharma America, Inc
Theranica
ViiV Healthcare

SILVER

Ambry Genetics
BillionToOne
Biodesix
CareDx
CorMedix, Inc.
Currax Pharmaceuticals, Inc.
Exagen, Inc.
EyePoint Pharmaceuticals
HepQuant
Intercept Pharmaceuticals, Inc.
Koya Medical, Inc.
LivaNova
Lynx DX
Mindera Health
Myriad Genetic Laboratories
Nalu Medical
Ocular Therapeutix
Otsuka America Pharmaceuticals
Pacira Pharmaceuticals
Podimetrics, Inc.
Pyros Pharmaceuticals, Inc.
Sobi – North America
SPR Therapeutics
Syndax Pharmaceuticals, Inc.
Veracyte

NAMCP
MEDICAL DIRECTORS INSTITUTE

For more information about Corporate Partnership with NAMCP, please call 804-527-1905.

NOVEMBER 6–7
CAESARS PALACE
Las Vegas

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

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

2025 FALL MANAGED CARE FORUM

PRESENTED BY:

NAMCP
WHERE MEDICAL DIRECTORS TRANSFORM KNOWLEDGE INTO IMPROVED OUTCOMES
www.namcp.org

AAIHDS AAMCN
American Association of Managed Care Nurses

SEE YOU THERE!

REGISTER TODAY

CME/NCPD CREDITS AVAILABLE

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