Optimizing BTK Inhibition in Waldenström Macroglobulinemia

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Abstract

Bruton tyrosine kinase (BTK) inhibitors have become a standard of care in the treatment of patients with Waldenström macroglobulinemia (WM) and are the only medications approved by the FDA to treat these patients. As more patients with WM are treated with BTK inhibitors in the United States and worldwide, it is essential to optimize this therapy by selecting the patients who are more likely to benefit from it, and by managing the unique adverse effects associated with these agents. Herein, we propose a genomic-driven approach to selecting patients with WM who are more likely to experience fast, deep, and durable responses to BTK inhibitors, and provide practical strategies for managing adverse effects, including BTK inhibitor dose reductions, switching to other BTK inhibitors, and abandoning BTK inhibitor therapy. Ongoing clinical trials are evaluating covalent and noncovalent BTK inhibitors alone and in combination, as well as BTK degraders, with exciting results, making the horizon for BTK-targeting therapies in WM bright and hopeful.

J Natl Compr Canc Netw 2024;22(4):e247007
doi:10.6004/jnccn.2024.7007

Bruton tyrosine kinase (BTK) inhibitors have become a standard of care for treating patients with Waldenström macroglobulinemia (WM) and are arguably the most effective single-agent treatment for patients with this disease. As BTK inhibitors are used more frequently in daily practice, we must familiarize ourselves with the selection of patients more likely to benefit from such agents and with the management of adverse effects in order to optimize the use of these agents in WM.

BTK Inhibition in WM

Recurrent somatic mutations in *MYD88* and *CXCR4* characterize WM. More than 90% of patients with WM harbor a mutation in *MYD88* L265P, which activates BTK, HCK, and NF-kB, an essential signaling pathway that promotes survival advantage in malignant WM cells.[1–4] Approximately 40% of patients with WM also harbor mutations in *CXCR4*, subclonal to *MYD88*, which can be nonsense or frameshift. *CXCR4* mutations promote WM cell survival by activating PI3K, ERK, and AKT.[5–7]

Preclinical studies have shown that BTK inhibition promoted apoptosis of WM cell lines and primary cells, giving way to the clinical development of BTK inhibitors in WM.[4] The first experience with covalent BTK inhibitors in WM was a phase I clinical trial in which 3 of 4 patients attained a clinical response to ibrutinib.[8] This initial observation prompted a seminal phase II study in which 63 patients with previously treated WM received ibrutinib until disease progression or unacceptable toxicity.[9,10] In this study, 91% of patients attained a response, 79% a major response (partial response or better), and 30% a very good partial response (VGPR). The 5-year progression-free survival (PFS) rate was 54%. Compared with patients with *MYD88* and without *CXCR4* mutations, the patients with *CXCR4* mutations had lower rates of VGPR (9% vs 47%) and shorter PFS (5-year PFS rate, 38% vs 70%). Patients without *MYD88* mutations had an even lower VGPR rate (0%) and shorter PFS (median, 0.4 years). Another phase II study evaluating ibrutinib monotherapy in 30 patients with previously untreated WM[11,12] reported a major response rate of 87% and a VGPR rate of 30%, with a 4-year PFS rate of 76%. All patients harbored a *MYD88* mutation. Patients with *CXCR4* mutations had lower VGPR (14% vs 44%) and 4-year PFS rates (59% vs 92%) than patients without *CXCR4* mutations. The FDA approved ibrutinib for WM in 2015.

The phase III randomized INNOVATE study evaluated the combination of ibrutinib + rituximab (Arm A) against placebo + rituximab (Arm B) in 150 patients with WM randomized in a 1:1 fashion.[13,14] The combination of ibrutinib + rituximab induced a higher major response rate (76% vs 31%) and longer median PFS (not reached vs 20 months). There were lower VGPR rates to ibrutinib + rituximab in patients with *CXCR4* mutations (24%) and patients without *MYD88* mutations (27%) when compared with patients with *MYD88* and without *CXCR4* mutations (44%). There were no differences in PFS between genomic groups treated with ibrutinib + rituximab. The FDA approved the combination of ibrutinib + rituximab for WM in 2018. Arm C was a substudy of INNOVATE in which 31 patients with WM refractory to rituximab were exposed to ibrutinib monotherapy.[15,16] Major response and VGPR rates were 61% and 29%, respectively, and the median PFS was 39 months. Patients with *CXCR4* mutations had a shorter median PFS (19 months).

Novel covalent BTK inhibitors with higher potency and specificity for BTK than ibrutinib are under development. Acalabrutinib was evaluated in 106 patients with WM and induced a major response rate of 78%, a VGPR rate of 33% in previously treated patients, and an estimated 66-month PFS rate of 52%.[17,18] Patients without *MYD88* mutations had a lower VGPR rate (0%), but testing was performed in only 50 patients. No patients were tested for *CXCR4* mutations. The phase III randomized ASPEN study evaluated 102 patients on zanubrutinib versus 99 on ibrutinib (Cohort 1) and 28 patients without *MYD88* mutations on zanubrutinib (Cohort 2).[19–21] In Cohort 1, the rate of VGPR favored zanubrutinib at 36% versus ibrutinib at 25%, whereas the rate of VGPR or better was 31% in Cohort 2. Patients with *CXCR4* mutations had lower VGPR rates to zanubrutinib (21% vs 45%) and

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ibrutinib (10% vs 31%) than patients without *CXCR4* mutations. The 42-month PFS rate also favored zanubrutinib over ibrutinib (78% vs 70%). The 42-month PFS rate was lower in patients with *CXCR4* mutations on ibrutinib (49% vs 75%) and somewhat lower in those on zanubrutinib (73% vs 81%). The 42-month PFS rate was 53% in Cohort 2. The FDA approved zanubrutinib for treatment of WM in 2021. Orelabrutinib and tirabrutinib have also been shown to be safe and effective in WM, although experience with these agents is limited.[22,23]

Despite the deep and durable responses attained with BTK inhibitors in patients with WM, complete responses have not been observed in prospective clinical trials.

Therapy Selection Based on Genomic Profile

Based on *MYD88* and *CXCR4* mutational status, patients with WM can be divided into 3 groups: (1) those with *MYD88* mutations and without *CXCR4* mutations ($MYD88^{MUT}/CXCR4^{WT}$), which includes 50% to 60% of cases; (2) those with *MYD88* and *CXCR4* mutations ($MYD88^{MUT}/CXCR4^{MUT}$), which includes 30% to 40% of cases; and (3) those without *MYD88* and *CXCR4* mutations ($MYD88^{WT}/CXCR4^{WT}$), which includes <10% of cases.[24]

The $MYD88^{WT}/CXCR4^{WT}$ group had the lowest response rate and shortest PFS to ibrutinib monotherapy compared with the other genomic groups.[10,12] This group also had lower VGPR rates than the $MYD88^{MUT}$ group on ibrutinib + rituximab (INNOVATE) and acalabrutinib (<50% of the participants were tested for *MYD88* mutational status), but PFS appeared similar. The VGPR rate and PFS for this group on zanubrutinib were similar to the outcomes observed in the $MYD88^{MUT}$ group (ASPEN, Cohort 2). It is important to note that the *MYD88* mutational testing for the ibrutinib monotherapy studies was performed via allele-specific PCR (AS-PCR) on CD19-selected bone marrow cells, followed by *MYD88* sequencing if the more common *L265P* variant was not detected.[10,12] In the INNOVATE, acalabrutinib, and ASPEN studies, *MYD88* mutational studies were performed using next-generation sequencing (NGS) panels in unselected bone marrow cells with a lower detection sensitivity.[25] For this reason, we favor chemoimmunotherapy regimens in the $MYD88^{WT}/CXCR4^{WT}$ group.

The $MYD88^{MUT}/CXCR4^{MUT}$ group had lower VGPR rates than the $MYD88^{MUT}/CXCR4^{WT}$ group in the ibrutinib monotherapy, INNOVATE, and ASPEN studies. The time to major response was longer on ibrutinib monotherapy for the $MYD88^{MUT}/CXCR4^{MUT}$ group compared with the $MYD88^{MUT}/CXCR4^{WT}$ group. However, the time to major response was numerically faster in this group of patients in INNOVATE and ASPEN when compared with those in the ibrutinib monotherapy study. The median PFS for this group was also shorter than for the $MYD88^{MUT}/CXCR4^{WT}$ group in the ibrutinib monotherapy study, but no PFS differences were observed in the INNOVATE or ASPEN studies. There were differences in the *CXCR4* detection methods between studies, which may have affected the outcomes. In the ibrutinib monotherapy studies, *CXCR4* mutations were investigated using AS-PCR for nonsense mutations and Sanger sequencing for frameshift mutations in CD19-selected bone marrow cells.[10,12] The INNOVATE and ASPEN studies used NGS panels in unselected bone marrow cells. *CXCR4* mutations were not investigated in the acalabrutinib study. Based on these findings, we prefer chemoimmunotherapy regimens for patients with $MYD88^{MUT}/CXCR4^{MUT}$ status who need a fast response. However, for patients with $MYD88^{MUT}/CXCR4^{MUT}$ status who do not need a fast response, BTK inhibitors are a reasonable treatment option.

The $MYD88^{MUT}/CXCR4^{WT}$ group had higher VGPR rates, faster median time to response, and longer PFS in the ibrutinib monotherapy, INNOVATE, and ASPEN studies. BTK inhibitors and chemoimmunotherapy are reasonable options in this patient group. To avoid the risk of myeloid neoplasms, paradoxical serum IgM flare, and severe immunosuppression associated with chemoimmunotherapy, BTK inhibitor therapy should be considered in the frontline setting or in patients with relapsed disease who have not yet been exposed to BTK inhibitors.

Figure 1 shows a proposed genomics-driven treatment algorithm for patients with WM.

BTK Inhibitor–Associated Adverse Effects

Although many patients with WM benefit from BTK inhibitors, adverse effects such as atrial fibrillation, bleeding, cytopenias, hypertension, gastrointestinal symptoms, infections, and arthralgias can occur, albeit at different rates depending on the BTK inhibitor selectivity. The long-term report of ibrutinib in patients with treatment-naïve WM demonstrated that fatigue, upper respiratory tract infection, hematoma, atrial fibrillation, urinary tract infection, and rash were the most common grade ≥2 adverse events.[12] In another trial, patients with previously treated WM who received ibrutinib also had similar adverse effects.[10] The most common grade ≥3 adverse events of acalabrutinib in patients with WM included neutropenia, pneumonia, lower respiratory infection, anemia, and hyponatremia.[17] The most common grade ≥3 adverse events reported with zanubrutinib in ASPEN were neutropenia, anemia, hypertension, and thrombocytopenia.[26]

Adverse Event Management

Atrial fibrillation has been reported in 5% to 15% of patients with WM exposed to BTK inhibitors. For patients with suspected atrial fibrillation, we perform a 12-lead electrocardiogram to confirm the diagnosis. Once the diagnosis is confirmed, patients may be started on β-blockers if needed for rate control. Their risk of stroke can be estimated by the CHA_2DS_2-VASc scoring system to determine if anticoagulation is warranted. After a diagnosis of atrial fibrillation, a referral to a cardiologist is recommended to determine whether further interventions, such as cardiac ablation, are indicated and for ongoing medical management and cardiac monitoring. In most cases of atrial fibrillation, the BTK inhibitor can be continued if the arrhythmia is transient or well-controlled. Dose reduction or transition to a BTK inhibitor with a lower rate of atrial fibrillation may be considered.

Increased bleeding and bruising are almost universally reported with BTK inhibitors, because these agents affect platelet adhesion and aggregation. Concomitant anticoagulants or antiplatelet agents should be used judiciously, with dose reductions considered in patients with high risk of bleeding. Acute bleeding episodes should be managed with therapy cessation and platelet transfusions if indicated. Bleeding with surgical procedures can be prevented with temporary holds for a few to several days before and after the procedure. The drug-hold duration depends on the procedure's invasiveness and the patient's bleeding risk.

Cytopenias are commonly seen with BTK inhibitors. Neutropenia, which occurs more frequently with zanubrutinib, might require temporary treatment cessation or growth factor administration. In most cases, we favor the latter approach

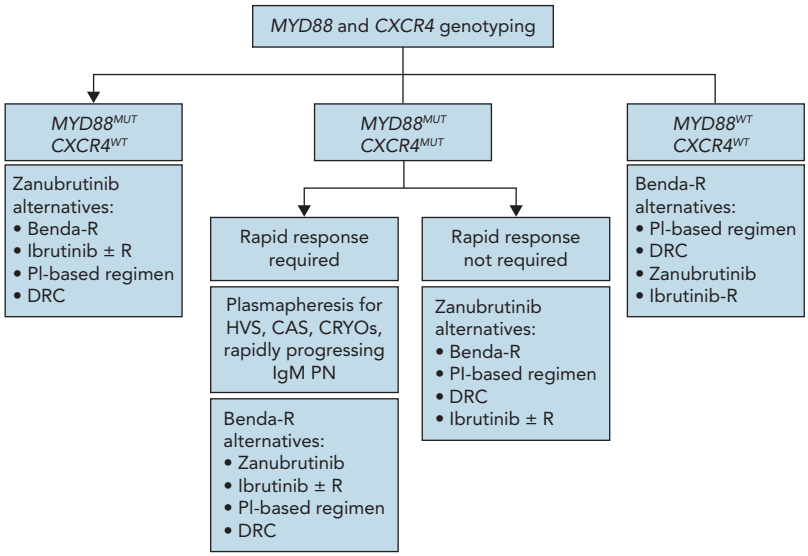

Figure 1. Proposed genomic-driven algorithm for the treatment of patients with Waldenström macroglobulinemia.
Abbreviations: Benda-R, bendamustine/rituximab; CAS, cold agglutinin syndrome; CRYOs, cryoglobulins; DRC, dexamethasone/rituximab/cyclophosphamide; HVS, hyperviscosity; PI, proteasome inhibitor; PN, peripheral neuropathy; R, rituximab.

because neutropenia improves with continued treatment. Thrombocytopenia is usually mild, with platelet counts between 100 and 150,000/μL. Typically, no interventions are needed. Anemia is rare, and other causes of anemia, especially iron deficiency, which can be seen in the context of BTK inhibitor therapy, should be evaluated and treated.

The risk of infections, especially upper respiratory infections, is increased with BTK inhibitors. In addition to universal precautions and the use of a facial mask, seasonal and age-appropriate vaccinations are strongly recommended. These include but are not limited to influenza, COVID-19, respiratory syncytial virus, varicella-zoster virus, and *Streptococcus pneumoniae*. Intravenous immunoglobulin (IVIG) can be used in patients with hypogammaglobulinemia (ie, serum IgG level <400 mg/dL) and a history of recurrent infections needing antibiotic therapy. IVIG therapy aims to decrease the number of clinically significant infections.

For significant rheumatologic symptoms, a transient medication hold may be sufficient to relieve symptoms, but persistent symptoms may require a dose reduction or referral to a rheumatologist to evaluate the underlying cause of symptoms, because autoimmune disorders, such as rheumatoid arthritis and psoriatic arthritis, occur at higher rates in patients with WM compared with the general population.

Gastrointestinal symptoms may be relieved by daily fiber supplementation, antidiarrheals, antacids, dietary changes, or changes in medication administration (eg, taking medication with/without food or at a different time of day). Patients with persistent symptoms should be referred to gastroenterology.

Approximately 20% of patients with WM who temporarily hold BTK inhibitors can experience withdrawal symptoms.[27] Onset is typically within 24 hours of the first missed dose, and the symptoms can include severe fatigue, night sweats, flu-like symptoms, and fever. The symptoms usually resolve within 12 hours of restarting BTK inhibitor therapy. In patients who experience withdrawal symptoms, low doses of prednisone (eg, 10 mg orally twice daily or 20 mg orally once daily) can be used to minimize the symptoms while the BTK inhibitor is held.

In cases of BTK inhibitor intolerance due to persistent symptoms of any kind, a dose reduction, change to another BTK inhibitor, or discontinuation of the BTK inhibitor can be considered (Figure 2).

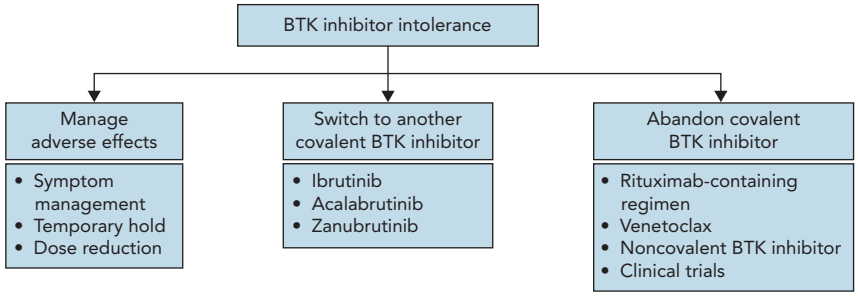

Figure 2. Proposed algorithm for the management of BTK inhibitor intolerance.
Abbreviation: BTK, Bruton tyrosine kinase.

Dose Reduction

A large single-center retrospective review evaluating 353 patients treated with ibrutinib found that 96 patients (27%) required a dose reduction due to adverse effects.[28] Dose reductions were more common in patients aged >65 years and females. The most common reasons for dose reduction were rheumatologic (myalgias, arthralgias, muscle cramping), cardiac (arrhythmia, hypertension, palpitations), nail/hair/skin changes, cytopenias, gastrointestinal (diarrhea, nausea, reflux), and bleeding/bruising. In 65% of cases, the adverse effect improved or resolved after the initial dose reduction. After dose reduction, the hematologic response was sustained or improved in 79% of patients, suggesting that ibrutinib doses can be safely reduced without compromising disease control. Prospective studies are required to confirm this finding and investigate the hematologic effects of dose reduction with other BTK inhibitors.

Change to Another BTK Inhibitor

If supportive care and dose reduction do not provide sufficient symptom relief, transition to a different BTK inhibitor can be considered, because these agents can have different side effect profiles. We do not recommend switching to another covalent BTK inhibitor if the disease is progressing on a covalent BTK inhibitor. In ASPEN, diarrhea, muscle spasms, hypertension, atrial fibrillation, and pneumonia were less frequent with zanubrutinib than ibrutinib, although neutropenia was more common with zanubrutinib.[26] Therefore, for these specific adverse effects, and potentially others, patients could consider changing BTK inhibitors, particularly transitioning to zanubrutinib from ibrutinib or acalabrutinib, as seen in a recent phase II study in which 67 patients with treatment-related toxicities from ibrutinib or acalabrutinib were switched to zanubrutinib.[29] After initiating zanubrutinib, 70% of ibrutinib-related and 83% of acalabrutinib-related intolerance events did not recur. Of those events that recurred, none of the symptoms recurred with a worse severity.

Discontinuation of BTK Inhibitors

Despite supportive care or medication adjustments, some patients require treatment discontinuation. Reasons for ibrutinib discontinuation have previously been reported in a single-center retrospective review of 189 patients with WM.[30] In this cohort, ibrutinib was stopped due to disease progression (14%), toxicity (8%), lack of response (3%), or other reasons (2%). Patients with a baseline platelet count of ≤100,000/μL or the presence of a *CXCR4* mutation had 4-fold increased odds of discontinuing ibrutinib. Survival in this cohort was higher in patients who began salvage therapy within 2 weeks of ibrutinib cessation. Additionally, 73% of patients who stopped ibrutinib therapy developed an IgM rebound.[30] Therefore, rapid initiation of subsequent therapy with close monitoring or bridging the next therapy with the BTK inhibitor should be considered due to the risk of IgM rebound and decreased survival with delay of salvage therapy initiation.

For patients treated with a BTK inhibitor as first-line therapy, standard chemoimmunotherapy can be used as subsequent therapy. Chemoimmunotherapy demonstrated significant efficacy in relapsed and refractory WM, with an overall response rate (ORR) of 90%.[31–33] Proteasome inhibitor–based regimens demonstrated an ORR >80% in this setting.[34–37] Outcomes with these regimens are not known to be affected by *CXCR4* mutational status.[37–40] In patients with IgM-only, asymptomatic disease progression who tolerate BTK inhibitor therapy, we advocate for continuing therapy beyond hematologic progression, because patients might derive clinical benefit for months to years after meeting disease progression criteria.

If patients have already received treatment with standard therapies, additional novel therapies, such as venetoclax, or clinical trial enrollment can be considered. Venetoclax was associated with an ORR of 84% in relapsed or refractory WM in a phase II trial that enrolled 32 patients, although the ORR was lower with prior BTK inhibitor use (75% vs 93%).[41] Times to minor (4.5 vs 1.4 months) and major response (8.5 vs 4.4 months) were longer with prior BTK inhibitor use. PFS was not impacted by prior BTK inhibitor exposure, however. The most common grade ≥2 adverse events were neutropenia, anemia, lymphopenia, nausea, diarrhea, and upper respiratory infection. Development of additional BCL-2 inhibitors, APG-2575 (ClinicalTrials.gov identifier: NCT04260217) and BGB-11417 (NCT05952037), is ongoing.

BTK Targeting Agents Under Development

Noncovalent BTK Inhibitors

The acquisition of *BTK* mutations (*C481S*), among other mechanisms, is associated with developing resistance to covalent BTK inhibitors in WM.[42,43] Noncovalent BTK inhibitors have shown efficacy in this setting. In the United States, pirtobrutinib was FDA-approved for treating relapsed or refractory mantle cell lymphoma. Pirtobrutinib is a highly selective reversible BTK inhibitor used in a study of 323 patients with multiple B-cell lymphomas, including WM.[44] This trial confirmed the efficacy and safety of pirtobrutinib in patients with prior resistance or intolerance to covalent BTK inhibitors and those with *BTK* C481S mutations. In the 78 patients with previously treated WM, the median number of prior therapies was 3 (range, 1–11), with 61 (78%) patients previously treated with a BTK inhibitor, of which 66% had discontinued due to disease progression.[45] The major response rate in the 55 patients with prior BTK inhibitor exposure was 64%. The most frequent adverse effects were fatigue, diarrhea, and contusion. The most common grade ≥3 adverse event was neutropenia. Rates of hypertension, hemorrhage, and atrial fibrillation were low. Based on these data, a trial combining pirtobrutinib and venetoclax in previously treated WM is ongoing (ClinicalTrials.gov identifier: NCT05734495).

In addition to pirtobrutinib, nemtabrutinib is being developed in WM. This noncovalent BTK inhibitor initially demonstrated in vitro and in vivo activity in CLL models with both wild-type *BTK* and C481S-mutated *BTK*.[46] A single-arm phase II trial that included multiple B-cell lymphomas demonstrated a similar side effect profile to other BTK inhibitors, including nausea, fatigue, and neutropenia, but also the unique drug-related effect of dysgeusia in 15% of patients.[47] A clinical trial using nemtabrutinib in hematologic malignancies, including WM, is underway (NCT04728893).

BTK Degraders

Despite the novelty of noncovalent BTK inhibitors, data have shown that additional *BTK* mutations (T474I, V416L, and L528W) may develop and render noncovalent BTK inhibitors ineffective.[48] In these cases, small molecule–induced protein degradation may allow for continued targeting of BTK.[49] The novel agent NX-5948 is a chimeric targeting molecule that contains a BTK hook linked to a cereblon harness and allows for ubiquitylation and proteasomal degradation of BTK.[50] Preclinical studies have shown successful

degradation of BTK, even in models with *BTK* C481S mutations. This molecule also has known central nervous system penetration, which may allow for future treatment of Bing-Neel syndrome, a rare condition in which WM cells gain access to the central nervous system causing neurologic deficits.[51] Preliminary data from a phase I trial using the BTK-targeted protein degrader NX-2127 in patients with relapsed or refractory B-cell malignancies have demonstrated a mean BTK degradation of 85%, resulting in decreased BCR signaling.[52] Clinical responses were seen despite the previous exposure to BTK inhibitors. Further development of this agent (ClinicalTrials.gov identifier: NCT04830137), as well as the BTK degraders NX-5948 (NCT05131022) and BGB-16673 (NCT05006716), is ongoing in patients with WM.

Conclusions

Many patients with WM will benefit from BTK inhibitor therapy. The fast, deep, and durable responses attained with these agents should be balanced against their unique side effect profile and the indefinite duration of therapy. BTK inhibitor therapy can be optimized by selecting patients who are more likely to benefit and by managing adverse effects.

Submitted September 8, 2023; final revision received January 2, 2024; accepted for publication January 9, 2024.

Disclosures: Dr. Sarosiek has disclosed receiving grant/research support from AbbVie, AstraZeneca, BeiGene, Cellectar Biosciences, Loxo Oncology, Pharmacyclics, and ADC Therapeutics; serving as a principal investigator for ADC Therapeutics; and serving as a consultant for BeiGene and Cellectar Biosciences. Dr. Castillo has disclosed receiving grant/research support from and serving as a principal investigator for AbbVie, AstraZeneca, BeiGene, Cellectar Biosciences, Loxo Oncology, and Pharmacyclics; serving as an advisory board member for AbbVie, BeiGene, Cellectar Biosciences, Mustang Bio, and Pharmacyclics; and serving as a consultant for AbbVie, AstraZeneca, BeiGene, Cellectar Biosciences, Janssen, Kite, Loxo Oncology, Mustang Bio, and Pharmacyclics.

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