

# Understanding Treatment Options in MCL

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The goal of this resource is to increase your understanding of your mantle cell lymphoma (MCL) and your treatment options for MCL. Better knowledge and understanding of your MCL make you better equipped to partner in treatment decision-making with your oncology care team.

The treatment of MCL has evolved substantially over the years. Historically, many younger, fit people with MCL requiring treatment initially receive dose-intensified or conventional chemoimmunotherapy (CIT), often followed by autologous stem cell transplant (ASCT), a procedure whereby an individual's own bone marrow is replaced by their own stem cells to form new bone marrow that produces healthy cells.

For older or unfit people with symptomatic MCL, dose-intensified or conventional CIT and ASCT are not considered because they are typically too toxic to tolerate. The treatment of older or unfit people with MCL includes less intensive CIT regimens.

Currently, the initial treatment landscape, for people with MCL requiring treatment, has advanced with the incorporation of novel targeted therapies, particularly covalent BTK inhibitors. The emergence of targeted therapies has expanded treatment options and improved tolerability.

Of note, not all people with MCL require treatment immediately after diagnosis. Your oncology care team may recommend treatment based on factors such as disease characteristics, symptomatology and stage, age, level of fitness, and history of specific comorbid conditions. The decision about if and when to start treatment is usually best handled using a shared decision-making process involving the oncology care team as well as you and your family and/or friends. This resource was developed specifically for symptomatic people with MCL requiring treatment.

You will want as much information as possible about your MCL before treatment is initiated. If you do not have all this information yet, ask your oncology care team to help you fill out this checklist with answers about your diagnosis.

## Commonly Used Approved Treatments for MCL

| Treatment                 | Mechanism                                                                                                                                                                                                                                                                     | Approval                                                                                                 |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Chemoimmunotherapy (CIT)* | CIT regimens include a combination of cytotoxic drugs (chemotherapy and immunotherapy) that target rapidly dividing cells via damaging their DNA or interference with the cell cycle; in addition, CIT regimens include an antibody that targets CD20 on the MCL cell surface | Approved by the EMA and FDA for use in previously untreated and previously treated MCL                   |
| Acalabrutinib             | Covalent BTK inhibitor (selective treatment that targets BTK and abnormal signaling in MCL cells leading to disruption of cancer cell growth and promotion of cancer cell death)                                                                                              | Approved by the EMA and FDA for use in previously untreated and previously treated MCL                   |
| Ibrutinib                 | Covalent BTK inhibitor                                                                                                                                                                                                                                                        | Approved by the EMA for use in previously untreated (in combination with CIT) and previously treated MCL |
| Zanubrutinib              | Covalent BTK inhibitor                                                                                                                                                                                                                                                        | Approved by the FDA for use in previously treated MCL                                                    |

| Treatment                 | Mechanism                                                                                                                                                                                           | Approval                                                                                                                                                              |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pirtobrutinib             | Noncovalent BTK inhibitor (novel selective treatment that targets BTK and abnormal signaling in MCL cells leading to disruption of cancer cell growth and promotion of cancer cell death)           | Approved by the EMA and FDA for use in previously treated MCL (after previous exposure to a covalent BTK inhibitor)                                                   |
| Brexucabtagene autoleucel | CAR T-cell therapy (genetic reprogramming of the patient's own immune T-cells to target and destroy MCL cells)                                                                                      | Approved by the EMA and FDA for use in previously treated MCL                                                                                                         |
| Lisocabtagene maraleucel  | CAR T-cell therapy                                                                                                                                                                                  | Approved by the EMA and FDA for use in previously treated MCL (after previous exposure to a BTK inhibitor)                                                            |
| Sonrotoclax               | BCL-2 inhibitor (works by blocking the BCL-2 protein, which leads to cancer cell death)                                                                                                             | Approved by the FDA for use in previously treated MCL (including previous exposure to a BTK inhibitor)                                                                |
| Venetoclax                | BCL-2 inhibitor                                                                                                                                                                                     | Not approved by the EMA or FDA for MCL; however, it may be considered for use for del(17p) or TP53-mutant disease after failure of B-cell receptor pathway inhibitors |
| Bortezomib                | Proteasome inhibitor (works by triggering cancer cell death)                                                                                                                                        | Approved by the EMA for previously untreated MCL (in combination with CIT), and by the FDA for use in MCL                                                             |
| Glofitamab                | Bispecific monoclonal antibody (works by simultaneously binding to CD20 on malignant B-cells and CD3 on healthy T-cells, leading to destruction of cancer cells by the patient's own immune system) | Currently investigational and not yet approved by the EMA or FDA for MCL                                                                                              |

EMA, European Medicines Agency; FDA, Food and Drug Administration.

\*There are several available CIT regimens, including bendamustine/rituximab (BR), rituximab/cyclophosphamide/doxorubicin/vincristine (R-CHOP), rituximab/bendamustine/low-dose cytarabine (R-BAC), rituximab/dexamethasone/cytarabine/oxaliplatin (R-DHAOX), and rituximab/cyclophosphamide/doxorubicin/prednisone (R-CAP).

Of note, many younger and fit people who are newly diagnosed with symptomatic MCL can now avoid ASCT after initial treatment. This is primarily based on the results from the phase III TRIANGLE trial that investigated CIT with or without ibrutinib, a covalent BTK inhibitor, with or without ASCT followed by maintenance therapy for ASCT-eligible patients aged 65 years or younger with previously untreated stage II-IV MCL who are suitable to receive aggressive chemotherapy. In this trial, the lack of an overall survival advantage with the addition of ASCT to ibrutinib plus CIT followed by maintenance therapy indicated that ASCT plays no significant role when treating younger and fit people with MCL if a covalent BTK inhibitor can be added in the initial and maintenance treatment phases of treatment.

Also, many older people who are newly diagnosed with MCL requiring treatment can now receive targeted therapy in addition to a less intensive CIT regimen. This is based on the results from the phase III ECHO trial, which investigated the efficacy and safety of a less aggressive CIT regimen with or without acalabrutinib, another covalent BTK inhibitor, followed by maintenance therapy for patients aged 65 years or older with previously untreated MCL who were ineligible for ASCT. The clinical outcomes, including progression-free survival, were significantly improved with the inclusion of acalabrutinib in the initial and maintenance treatment phases.

## My Life Concerns

### What do I need to tell my doctor?

Think carefully about your personal expectations, desires, and hopes for treatment and how treatment will affect your lifestyle. Are there events you do not want to miss or activities you would prefer not to give up? Will work or family situations make it difficult to be available for treatment? How will you get to and from the clinic? How often will you need to visit the clinic for treatment? How far away from the treatment center do you live? Do you have a reliable social/familial support system? Do you need help speaking with loved ones? Do you have concerns about the financial burden of treatment? What other concerns or fears do you have?

Make notes about the things you want to discuss with your healthcare professionals. Your satisfaction with treatment requires weighing all the factors for medical success, a good quality of life during and after treatment, and ultimately, a happy life. You may need to give more weight to some factors vs the others from time to time. Knowing and acknowledging the things that you value more will help you do this successfully.

The following table includes some of the key factors to consider regarding the available treatment options for MCL.

| Treatment                                                                                        | Mechanism                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| How is the treatment administered? (orally, intravenously, subcutaneously)                       | <ul style="list-style-type: none"><li>• CIT includes multiple agents (chemotherapy and immunotherapy) administered intravenously</li><li>• BTK inhibitors are oral medications</li><li>• BCL-2 inhibitors are oral, and under certain circumstances can be recommended in combination with a covalent BTK inhibitor</li><li>• Bortezomib is administered intravenously or subcutaneously and is recommended in combination with CIT</li></ul>                                                                                      |
| What is the duration of treatment? (for a limited time, or continuously)                         | <ul style="list-style-type: none"><li>• CAR T-cell therapy is a single, 1-time intravenous infusion (typically requiring a hospital stay ranging from 10 days to 4 weeks after infusion)</li><li>• BTK inhibitors are usually taken continuously until the drug becomes unacceptably intolerable, or until the drug no longer controls the disease. Under certain circumstances (such as when taken in combination with aggressive CIT as initial treatment), time-limited covalent BTK inhibitor use may be recommended</li></ul> |
| What are the common side effects?                                                                | <ul style="list-style-type: none"><li>• Different treatment regimens have different side effect profiles; these should be discussed with your oncology care team before deciding on a treatment regimen</li></ul>                                                                                                                                                                                                                                                                                                                  |
| How may other illnesses (comorbidities) and concomitant medications affect my treatment options? | <ul style="list-style-type: none"><li>• Presence or history of other medical conditions and medications currently being taken can influence the choice of treatment</li></ul>                                                                                                                                                                                                                                                                                                                                                      |
| How may previous therapy affect possible subsequent therapies?                                   | <ul style="list-style-type: none"><li>• At present, it is unclear if any individual with MCL can truly be cured of the disease (currently, MCL is regarded as an incurable disease)</li><li>• Hence, most patients will need more than 1 therapy</li><li>• It is, therefore, best to understand how a prior therapy might affect subsequent treatment options</li></ul>                                                                                                                                                            |
| What are your financial circumstances?                                                           | <ul style="list-style-type: none"><li>• Will the medication be covered by your insurance? What is your "out of pocket" expense limit?</li><li>• If treatment is not covered or only partially covered, it is important to consider other means to obtain the treatment</li><li>• Discuss all financial constraints with your oncology care team, who may be able to assist through other means, such as informing you about available medication assistance programs</li></ul>                                                     |

## My Upcoming Treatment

### What do I need my doctor to tell me?

The following questions were identified by a panel of 5 renowned experts in MCL as the key factors that help to guide treatment selection. If your answer to any question is "I don't know," consult with your specialist or a member of your oncology care team to obtain the answer. As you learn more about MCL, you will become more confident in treatment decision-making for your disease. Working together with your oncology care team can make sure your health and treatment are balanced with all the other parts of your life.

Note that biomarker testing before treatment is one of the most important things you can do for your MCL. Obtaining the appropriate biomarker tests at the right time will guide treatment decisions and help predict how aggressively the disease might behave in the future.

#### What is the disease setting?

- ☐ Newly diagnosed, symptomatic
- ☐ Symptomatic relapsed/refractory
- ☐ I don't know

#### What is your age at the time of diagnosis or disease relapse?

- ☐ <65 years
- ☐ 65–70 years
- ☐ >70 years

#### What is your level of fitness (including considerations for your age, performance status, and preexisting comorbidities)?

- ☐ Fit
- ☐ Unfit
- ☐ Frail
- ☐ I don't know

**Does your disease have any high-risk feature(s) (including at least 1 of the following: *TP53* gene mutation, p53 protein overexpression; del(17p) chromosomal abnormality, Ki-67 proliferation index greater than 30%, blastoid or pleomorphic morphology, high Mantle Cell Lymphoma International Prognostic Index (MIPI) score; or if relapsed/refractory disease, the time to MCL progression from diagnosis to the completion of first-line therapy is less than 24 months)?**

- ☐ Yes
- ☐ No
- ☐ I don't know

#### Do you have uncontrolled hypertension, atrial fibrillation, and/or are you currently receiving warfarin anticoagulant therapy?

- ☐ Yes
- ☐ No
- ☐ I don't know

## If You are Considering Second-line Therapy

Which treatment did you receive in the frontline for your MCL (either off or on a clinical trial setting)?

- ☐ Chemotherapy followed by ASCT ± rituximab maintenance therapy
- ☐ Aggressive chemotherapy + covalent BTK inhibitor followed by ASCT followed by covalent BTK inhibitor ± rituximab
- ☐ Aggressive chemotherapy + covalent BTK inhibitor **without** ASCT followed by covalent BTK inhibitor ± rituximab
- ☐ BR + acalabrutinib followed by rituximab + acalabrutinib
- ☐ Chemotherapy-free doublet or triplet regimen ± maintenance therapy
- ☐ R-DHAP or R-CHOP or VR-CAP or BR or R-BAC ± rituximab maintenance therapy
- ☐ Rituximab monotherapy
- ☐ Other
- ☐ I don't know

## If You are Considering Third-line or Later-line Therapy

Which treatments have you previously received for your MCL (either off or on a clinical trial setting)?

- ☐ Covalent BTK inhibitor-based therapy ± ASCT followed by CAR T-cell therapy
- ☐ Covalent BTK inhibitor-based therapy ± ASCT followed by pirtobrutinib
- ☐ Covalent BTK inhibitor-based ± ASCT followed by glofitamab or sonrotoclax ± zanubrutinib
- ☐ Covalent BTK inhibitor-based ± ASCT followed by 1 other prior therapy
- ☐ Chemotherapy ± ASCT followed by 1 other therapy (**NOT** including a BTK inhibitor)
- ☐ Chemotherapy ± ASCT followed by 1 other therapy (including a BTK inhibitor)
- ☐ Chemotherapy ± ASCT followed by venetoclax ± covalent BTK inhibitor-based therapy
- ☐ Chemotherapy ± ASCT followed by bortezomib ± rituximab or obinutuzumab ± chemotherapy
- ☐ Any other therapy (**NOT** including a BTK inhibitor) and lenalidomide ± rituximab or obinutuzumab
- ☐ Other
- ☐ I don't know

If you are a healthcare professional, you can find our interactive treatment decision-making support tool [here](#).

Patients may also find this tool a useful educational resource in collaboration with their healthcare professional.

