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A Systematic Review of Clinical Trials Focusing on Various Therapies to Treat Follicular Lymphoma

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ABSTRACT

Follicular lymphoma (FL) is a rare type of blood cancer that is rather challenging to diagnose at earlier stages. When detected at later stages of development, the treatment of FL will be much more difficult and less effective. In comparison, when the disease is diagnosed on time, cancer often responds well to treatment and generally can be managed; however, treatments for FL, regardless of when it's noticed, are generally volatile and risky, indicating the need for more effective and safe treatments. This paper reviews potential therapies for FL by analyzing clinical trial data of Chimeric Antigen Receptor T-cell therapies (CAR T-cell therapies), enzyme inhibitors, immunotherapies, and combination treatments. CAR T-cell therapies showed high response rates with strong efficacy but were associated with harmful side effects such as cytokine release syndrome (CRS). Similarly, immunotherapies were found to be effective, but they also showed risks of CRS. Enzyme inhibitors and combination therapies displayed several benefits of efficacy; even so, it also was affiliated with the risk of side effects. Many of these therapies, although promising, show significant safety risks, and thus, the need for additional research in developing safer and more effective treatments for FL is of great importance.

INTRODUCTION

Several possible treatments have been developed, though none of these have yet been proven to cure cancer completely. Despite this fact, many of these treatments show potential, displaying significant efficacy and/or safety. This systematic review aims to evaluate new FL therapies by examining clinical trials, which are studies that compare and evaluate the safety and efficacy of new possible treatments. This review is focused on Phase 2 clinical trials, as they usually provide experimental data and findings on a drug with 100 to 300 volunteer patients.[4] Clinical trials also look for key endpoints that are to be used to compare and evaluate the safety and efficacy of treatments.[5] These criteria involve the Overall Response (OR) which is the percentage of the patients with significant improvement in control of the disease, the Complete Response (CR) which is the percentage of the patients in whom the cancer has completely been eradicated, and the Partial Response (PR) which is the percentage that indicates those who a considerable reduction in the size of the tumors. The other endpoints include the Overall Response Rate (ORR), a sum of CR and PR to give an estimate of the treatment's overall efficacy, Progression-Free Survival (PFS), the time the patients live without developing a disease progression, and finally the

Duration of Response (DoR), which shows the length of time in which the tumor responds to treatment. This review will describe and analyze these endpoints and data for a few potential therapies for follicular lymphoma like CAR T-cell therapies, enzyme inhibitors, immunotherapies, combinations of the same, and multi-lines of treatment. Each of these therapies uses distinct mechanisms to target and address the proliferating cancer cells, and this review will evaluate their potential effectiveness in treating FL based on recent clinical trial data.

METHODS

This systematic review of FL was performed using PubMed. In the database, clinical trials evaluating different therapies for refractory and relapsed FL were researched. The clinical trials studied in this review were mostly phase 2 trials, which are intermediate steps in testing drugs. The search to find these trials included terms such as "refractory follicular lymphoma" and "relapsed follicular lymphoma,". Additionally, the search was filtered to the last 5 years (2019-2024). Many studies focused on patients with multiple lines of treatment who have had relapsed FL.

RESULTS

Table 1. Summary of therapies and clinical studies included in this review

Therapy	**Study/Phase**	**Patients**	**ORR**	**CR**	**Therapy**	**Study/Phase**	**Patients**	**ORR**	**CR**
Tisagenlecleucel	ELARA, Phase 2	98	86.20%	69.10 %	Idelalisib	Phase 2/3 studies	—	58%	6%
Lisocabtagene maraleucel	TRANSCEND NHL 001	256	73%	53%	Tazemetostat	Phase 2	99	69–78 %*	13%*
Mosunetuzumab	Phase 2	90	80%	60%	Zanubrutinib + obinutuzumab	ROSEWOOD, Phase 2	145	69%	39%
Epcoritamab	EPCORE NHL-1, Phase 2	118	82%	62.50 %	Lenalidomide + rituximab	AUGMENT, Phase 3	—	78%	34%
Glofitamab	Phase 1	171	71.40%	64.30 %	LEO CReWE	Multicenter cohort	441	70%	47%

CAR T-Cell therapies

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a new technique for various types of cancers, particularly B-cell lymphoma such as FL. The treatment genetically engineers a patient's T-cells (a type of immune cell) to target cancerous B-cells and inhibit growth.[4] Both Tisagenlecleucel and Lisocabtagene maraleucel are both examples of CAR-T therapies that target a specific protein found on the surface of B-cells to improve cancer response.

Tisagenlecleucel is an autologous CAR-T cell therapy designed to attack the CD19 protein, which is found on the surface of B-cells.[5] This treatment involves collecting T-cells from a patient, modifying them to recognize and kill CD19-positive cells, and returning the modified cells to the patient's bloodstream. Tisagenlecleucel was tested in the Phase 2 ELARA trial, enrolling 98 patients to test the effectiveness of the therapy in patients whose cancer was resistant to other forms of treatment. Patients had been previously treated with at least 2 lines of treatment, with a median of 4, meaning they were heavily treated. In the Phase 2 ELARA trial, Tisagenlecleucel had a Complete Response Rate (CRR) of 69.1%, and an Overall Response Rate of (ORR) (Figure 1A). The Progression-Free Survival (PFS) rate at 12 months was 67%, which means that two out of three patients were free from disease progression after 12 months (Figure 1A). While the treatment demonstrated an encouraging efficacy, it also showed a few concerning side effects. These include Cytokine Release Syndrome (CRS), which occurred in 49% of the patients, neurological side effects (headaches and dizziness) in 37.1%, and in a few cases, other more severe side effects like ICANS Immune Effector Cell-Associated Neurotoxicity Syndrome, which is a neurologically toxic condition (Figure 1A). Another common side effect was neutropenia, which was observed in 42.3% of the patients (Figure 1A). In total, 99% of patients experienced aftereffects, and 78.4% had one or more grade 3 or higher aftereffects at any time point during the trial.

Another CAR-T therapy that has also proven to be effective in treating FL is Lisocabtagene Maraleucel. Just like Tisagenlecleucel, Lisocabtagene Maraleucel is a CD19-targeted therapy whose mechanism of action is genetically transforming a patient's T-cells to recognize and kill off B-cells containing the CD19 protein.[6] But Lisocabtagene Maraleucel involves a slightly different strategy in employing two different methods to maximize T-cells, while Tisagenlecleucel uses one method.

In a Phase II trial titled ‘TRANSCEND’, Lisocabtagene Maraleucel was evaluated for its efficacy and safety among patients with refractory or relapsed lymphoma. In terms of efficacy, the results showed that lisocabtagene maraleucel was effective in treating B-cell lymphomas. After 256 patients were evaluated, it was determined that the objective response rate was 73%, with 53% achieving a complete response (Figure 1A). Additionally, the median progression-free survival was 6.8 months. This efficacy was consistent across various demographic groups, indicating the treatment's broad effectiveness.

The safety data, on the other hand, showed varying results. Treatment-emergent adverse events included neutropenia (63%), anemia (48%), and CRS (42%). A total of 127 patients (47%) experienced CRS, with a median onset of 5 days, while neurological events occurred in 30% of patients (Figure 1A). Despite

some severe adverse events, no patients died directly from CRS, although seven patients with treatment-emergent adverse events died from other causes. Overall, the study highlighted the need for significant safety improvements.

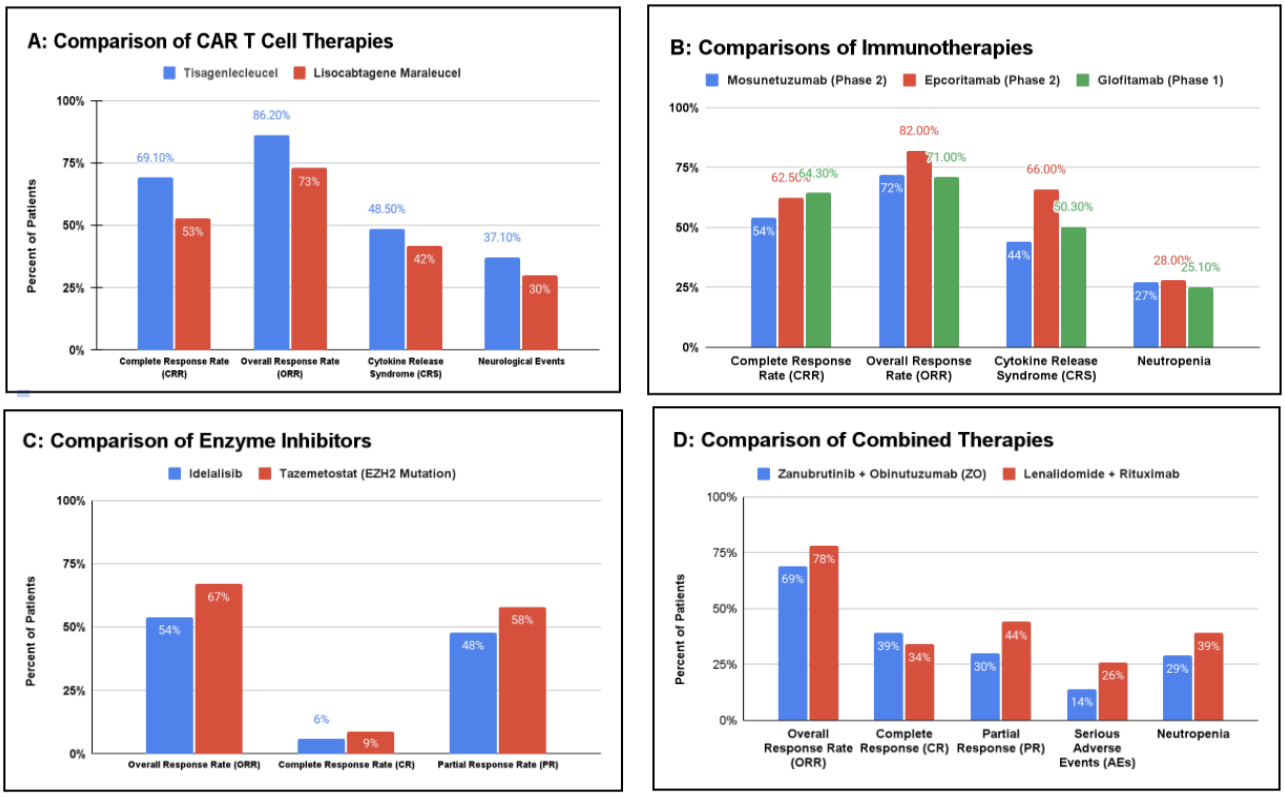


Figure 1. The Complete Response Rate indicates the proportion of patients who had fully recovered after treatment. The Overall Response Rate indicates the proportion of patients who had a response. In all of the studies, the percentages were calculated out of 100% of patients, meaning percentages are non-exclusive, and a patient experiencing an outcome can also be co-experiencing another outcome. **A)** A comparison of FL patient outcomes under CAR-T Cell therapies. Blue bars represent Tisagenlecleucel treatments and red bars represent Lisocabtagene Maraleucel treatments. As for the actual results, both Tisagenlecleucel and Lisocabtagene Maraleucel showed high overall response rates, with notable occurrences of cytokine release syndrome and neurological events. **B)** A comparison of FL patient outcomes undergoing immunotherapy. The blue bars represent mosunetuzumab treatments, the red bars represent epcoritamab treatments, and the green bars represent Glofitimab treatments. Epcoritamab and Glofitamab exhibited high overall and complete response rates, though cytokine release syndrome and neutropenia are observed across the treatments. **C)** A comparison of FL patient outcomes treated with enzyme inhibitors. Blue bars represent idelalisib treatments and red bars represent tazemetostat treatments. Idelalisib and Tazemetostat showed moderate overall response rates, with significantly low complete response rates. **D)** A comparison of FL patient outcomes undergoing drug combination

therapies. Blue bars represent zanubrutinib + obinutuzumab treatments and red bars represent lenalidomide + rituximab treatments. In terms of results, both combination therapies demonstrated notable overall response rates, with varying levels of serious adverse events and neutropenia.

Immunotherapies

Immunotherapies are similar treatments that specifically utilize the body's immune system to recognize and attack diseases. These therapies often involve the use of antibodies to target specific proteins in cancer cells to encourage the immune system to detect and destroy tumors. This category of treatment is identical to CAR T cell therapies in terms of how it approaches treating cancer, however, it differs in its mechanism. Many agents in this category have been developed, including mosunetuzumab, epcortiamab, and glofitmab.

The first agent, mosunetuzumab, simultaneously targets the proteins CD3 on T cells and CD20 on B cells to redirect the patient's immune system and eliminate cancerous B cells in a single treatment.[7] To evaluate this method, a study was held, testing mosunetuzumab in patients with relapsed or refractory FL. This phase 2 trial involved 90 adult patients with FL receiving mosunetuzumab in a structured dosing schedule over a 21-day cycle. These patients had relapsed/refractory FL and received at least 2 previous treatments, with a median of 3. At the median follow-up of 18.3 months, the study reported a significant CR rate of 60%, which was notably higher than expected (Figure 1B). Additionally, the ORR was also particularly high at 80%. For the PFS, the median was 17.9 months, and the median time to first respond was also early at 1.4 months. Safety-wise, the most common adverse event reported was CRS, occurring in 44% of patients (Figure 1B). Serious adverse events (SAEs) occurred in 47% of the subjects, which implies that nearly half of the patients experienced some form of severe complication. The second most frequent side effect was neutropenia, occurring in 29% of the patients (Figure 1B).

Another bispecific antibody targeting both the CD3 and CD20 proteins is epcoritamab.[8] While it shares the same target as mosunetuzumab, it differs in the way it structures and marks the CD3 and CD20 proteins. A 118-patient phase 2 clinical trial assessed both the safety and efficacy of epcoritamab across numerous dosing regimens. Patients had relapsed/refractory FL and received at least 2 previous lines of treatment. The results exhibited a high ORR of 82%, with 62.5% of patients experiencing complete response (Figure 1B). Interestingly, responses were noted relatively quickly, with signs of improvement within 1.4 months and complete responses within 1.5 months. At 18 months, 73.8% of patients experienced a durable complete response, with excellent progression-free survival. Epcoritamab was generally well-tolerated, though 18% of patients experienced at least one treatment-emergent adverse event (TEAE). The most common TEAE was CRS, occurring in 66% of the patients. Injection site reactions (57%), COVID-19 infections (40%), diarrhea (25%), neutropenia (28%), and fatigue (30%) were additional side effects (Figure 1B).

Finally, glofitamab is another novel bispecific antibody targeting CD3 and CD20, but in a 2:1 bivalent format so that it binds bivalently to CD20 on B cells but monovalently to CD3 on T cells. This design enables more effective T-cell recruitment to destroy cancerous B cells.[9] The phase 1 study includes

multiple types of B-cell lymphoma rather than only FL, and only patients with multiple previous treatments were included. In total, 171 patients with relapsed or refractory B-cell lymphoma showed encouraging results. The ORR was 71.4%, with a CR rate of 64.3% (Figure 1B). The median DOR was 5.5 months, and the median PFS was 2.9 months, showing its short-term effectiveness. Safety concerns for glofitamab included CRS, affecting 50.3% of patients. Other adverse events included neurological side effects (43.3%), neutropenia (25.1%), and infections (51.5%) (Figure 1B). As a whole, a large percentage of patients (58%) experienced serious adverse events (SAEs). These further prove the hazardous side effects associated with immunotherapy treatments; however, in all three trials, the efficacy was impressively high (Figure 1B).

Enzyme Inhibitors

Enzyme inhibitors are another form of cancer therapy designed to block some of the pathways that enable cancer cells to develop and grow. This form of therapy is aimed at specific enzymes that can help cancer cells grow and survive. Different enzyme inhibitors target different enzymes to treat cancer.

Idelalisib is a targeted therapy drug that binds to and inhibits an enzyme known as phosphoinositide 3-kinase (PI3K). PI3K is a key enzyme of the cell growth, survival, and metabolism pathway.[10] This enzyme has been reported to be overexpressed in multiple types of cancers, and its expression increases the proliferation and spread of cancer cells. Idelalisib was very promising at first. The study was a mix of phase 2 and 3 clinical trials and it featured patients who have relapsed/refractory indolent lymphoma and were treated previously. Results showed an ORR of 58% in the FL patients (Figure 1C). This later led to its approval in 2014 by the FDA. However, when Idelalisib began to be used more, safety issues started to rise. In particular, Idelalisib was associated with SAEs of severe liver toxicity, infection, and lung tissue inflammation. These safety issues were so severe that they ultimately resulted in the withdrawal of approval of the drug for FL treatment in 2022. Although it was initially successful, the negative side effects of the drug made it an unreliable treatment.

Another enzyme inhibitor, tazemetostat, was also studied for this review.[11] This therapy targets another enzyme, EZH2, one enzyme responsible for epigenetic control, a mechanism by which genes are expressed in varying ways without altering the actual DNA structure. In various cancers, including FL, EZH2 gets hyperactive, increasing cell proliferation. Tazemetostat blocks the activity of EZH2, enabling it to decelerate the growth of cancer cells. The phase 2 trial was conducted to assess the efficacy and safety of tazemetostat in patients with follicular lymphoma who had already received multiple previous therapies. The patients were divided to improve the analysis, according to their mutation status in EZH2: EZH2 mutant with 54 patients, and EZH2 wild-type cohort with 45 patients. In terms of efficacy, tazemetostat was promising. Furthermore, for patients who had the EZH2 mutation, the ORR was significant at 69%-78% of the patients responding (Figure 1C). The EZH2 wild-type subgroup had a much lower ORR at just 33-35 % of the patients responding. The disease control rate (DCR) was higher in the mutant group as well, with 98% of the patients showing disease control compared to 69% in the wild-type (Figure 1C). Of the EZH2 mutant group, 13% experienced a CR, or the cancer disappeared, and

56% experienced a partial response, or the tumor shrank. These findings make tazemetostat a promising treatment, especially for those who have EZH2 mutations.

Combinations of Different Treatments

Throughout this review, various types of different individual treatments have been discussed. Many of these treatments, however, seemed to exhibit some specific disadvantages. To address this profound issue, many professionals began to use combinations of treatments to get the best features out of each one. For instance, if a treatment happens to lead to a certain unwanted side effect, another treatment can be added to the combination to obviate this side effect. Using this idea, many treatments have been combined to treat FL safely and effectively.

An example of this mechanism includes the combination therapy of zanubrutinib and obinutuzumab (ZO).[12] Zanubrutinib is a selective enzyme inhibitor that blocks the BTK enzyme, which can increase the proliferation and survival of malignant B cells. By inhibiting BTK, zanubrutinib reduces the harmful impact on T cells, leading to improved patient outcomes. In this study, zanubrutinib is combined with obinutuzumab, an antibody that targets the CD20 protein on B cells, to address the toxicity that is often involved in zanubrutinib. To test the effectiveness of the ZO combination, a phase 2 clinical trial study was held and enrolled 145 patients, all of whom had previously undergone two or more therapies. Patients received a median of 3 previous lines of treatment. After a 20-month follow-up, the ZO combination demonstrated a promising ORR of 69% in patients with relapsed or refractory FL, with 39% of patients achieving a complete response (Figure 1D). The median PFS was an encouraging 2.8 months, and the time to respond averaged 12 months. Additionally, the duration of response for the combination was noted at 18 months, with 30% of patients showing a PR (Figure 1D). Regarding safety, the profile of the treatment was consistent with a variety of side effects such as neutropenia (29%), fatigue (15%), and pyrexia (13%) (Figure 1D). There were serious treatment-related AEs in 4% of the patients, and no treatment-related deaths were noted.

Similarly, a combination of lenalidomide and rituximab was also tested.[13] Lenalidomide is a type of immunotherapy that binds to a protein complex called cereblon that regulates immune cell activity. By binding to the protein complex, the immune response can be improved. In combination with rituximab, an anti-B-cell antibody, lenalidomide increases immune function by making immune cells more efficient at killing cancer cells marked by rituximab. This phase 3 study included patients who had received at least 1 previous systematic treatment. In terms of efficacy, the ORR of lenalidomide and rituximab was high at 78% (Figure 1D). The other main endpoints were also favorable for this combination since 34% experienced a CR and 44% had a PR (Figure 1D). The safety profile of both combinations was also covered in the trial. Interestingly, dose interruptions due to adverse events were significantly higher in the lenalidomide group at 64% (Figure 1D). Serious adverse events occurred in 26% of the patients, and overall, 9% of the patients who were reported in the lenalidomide trials had died (Figure 1D). The combination of rituximab and lenalidomide appeared effective, but it still involved a concerning safety profile.

Multi-Line Treatments

Multi-line treatments involve a sequential treatment using different agents. This approach was experimented with in a study that employed a three-line therapy strategy for patients with FL.[14] The initial line of treatment involved anti-CD20 antibody monotherapy, which is directed against the CD20 protein present on the surface of B-cells, a key component in the development of lymphoma. The second line involved a combination therapy of anti-CD20 antibodies, PI3K inhibitors, and lenalidomide. PI3K inhibitors attack important signaling pathways involved in cancer cell proliferation and survival, and lenalidomide works to block the formation of new blood vessels, thus inhibiting cancer spread. The final therapy in this multi-line therapy was hematopoietic stem cell therapy, in which the stem cells were collected either from the patient or the donor and then high-dose chemotherapy was given in a bid to destroy cancerous cells. In a phase 2 study that comprised 441 relapsed/refractory patients, it was shown that the three-line therapy produced a 70% ORR.

A CR was observed in almost half of the patients, 47%, which means the treatment was highly effective for a great majority of patients. The median PFS was 17 months, and 40% of the patients were progression-free at two years. The median DOR in responders was 19 months, indicating that a lot of patients who responded were able to maintain it for a lengthy duration. While the efficacy of the treatment was promising, the safety profile was concerning. Moreover, 26% of patients in the study died during therapy, and the majority of deaths were related to lymphoma progression. A 7% risk of disease transformation was also present, meaning that in a minority of cases, the FL converted to a more aggressive lymphoma. Although particular adverse events were not described in the published report, the administration of stem cell therapy and high-dose chemotherapy reveals that the regimen was associated with high toxicity, including possible infections, hematologic toxicity, and other severe side effects. These problems highlight the need for careful monitoring of patients and changes to improve the safety of this approach.

DISCUSSION

FL is certainly a volatile cancer that is difficult to treat while ensuring safety among the patients. Many treatments, regardless of their category, seemed to uphold significant efficacy but faced a dilemma in terms of safety and side effects.

The pattern of significant efficacy but high risk of side effects applied for both CAR T cell therapies that were discussed –tisagenlecleucel and lisocabtagene maraleucel.[6,7] Moreover, both tisagenlecleucel and lisocabtagene maraleucel demonstrated similar and high efficacy, with their CRR and ORR falling within the same range— 69.1% CRR and 86.2% ORR for tisagenlecleucel and 53% CRR and 73% ORR for lisocabtagene maraleucel. To go into further detail, both their levels of efficacy only contrasted by a short range below 16%. This is expected, as both are CAR T-cell therapies targeting the same malignancy through the same general method of genetically modifying cells. These treatments, however, were associated with a significant safety risk. CRS is the overwhelming release of certain immune cells called

cytokines into the bloodstream. When this occurs, the blood vessels get overwhelmed, and this can lead to organ failure and even death. CRS is a very severe disease, and both these treatments led to a significant number of patients being diagnosed with it: 48.5% for tisagenlecleucel and 42% for lisocabtagene maraleucel. Aside from these percentages being extremely high, they are both very similar in terms of their range. This may show that CAR-T cell therapies as a whole may be associated with the great risk of CRS, as it often changes conditions in the immune system. From these two trials, it can be concluded that CAR T-cell therapies are highly effective in treating FL, but given the risk of CRS, extended precautions and accommodations should be implemented when using these therapies in clinical trials.

Immunotherapies also demonstrated similar patterns to CAR T cell therapies. To elaborate, the three immunotherapies that were examined – mosunetuzumab, epcoritamab, and glofitamab – all displayed similar and high levels of efficacy: epcoritamab achieved the highest ORR of 82% and a CRR of 62.5%, Glofitamab followed closely with a CRR of 64.3% and ORR of 71%, while mosunetuzumab showed a slightly lower CRR of 54% and ORR of 72%.[8,9,10] This shows that immunotherapies, just like CAR T cell therapies, can efficiently treat patients. In regards to safety, all three therapies resulted in immense levels of CRS and the severe event 'neutropenia'. These safety concerns signal the need for close monitoring and management during treatment. Overall, immunotherapies tend to display trends very similar to CAR T cell therapies, as both exhibit high and comparable levels of efficacy along with increased but similar risks of CRS. This may be because both CAR T cell therapies and immunotherapies involve similar mechanisms of action, as they both modify T cells to target and destroy cancer cells, just in different ways. The similarities between the two categories, CAR T cell therapies and Immunotherapies, show how the modification of immune cells can be correlated to significant efficacy and CRS. From analyzing the results of various immunotherapies, it can be determined that when operating with them, researchers and pharmaceutical companies should pay close attention to immune system-related responses. The same idea can be applied to CAR T-cell therapies.

Enzyme inhibitors happened to show interesting results regarding the number of patients in the trial that experienced a complete response. Furthermore, the two enzyme inhibitors that were previously examined in the review–idelalisib and tazemetostat–both showed a significant ORR: 54% for Idelalisib and 67% for tazemetostat.[11,12] These results seem reasonable, given that both drugs block pathways critical to cancer cell survival and proliferation. When it came to the number of patients with a CR, however, the results were more modest, with Idelalisib showing only a 6% CR and tazemetostat showing 9%. In comparison to the previous two therapy categories mentioned, this critical response is extremely low. This shows that while these treatments can lead to improvements in tumor size or disease control, they are unlikely to result in the complete removal of tumors in patients. An additional concern with the enzyme inhibitors category is its frequent and distinct side effects. Moreover, something peculiar within both idelalisib and tazemetostat is their difference in the degree of their side effects. To further explain, both treatments encountered several side effects, but the ones associated with tazemetostat – fatigue and nausea – were not as severe as the side effects with idelalisib – severe liver toxicity or intense gastrointestinal issues. Enzyme Inhibitors, as a whole, seem to prove efficient in disease control, however, this therapy method seems to be less capable of completely removing cancer cells from patients and being consistent with its

side effects. This, overall, continues to show how enzyme inhibitor monotherapies may not be the most appropriate diagnosis for FL, as it is yet to show capability in completely extirpating cancerous cells.

Combinations of various treatment types were also heavily explored in previous parts of the review, which featured trials on 'zanubrutinib with obinutuzumab' (ZO) and 'lenalidomide with rituximab'.[13,14] For example, the zanubrutinib-obinutuzumab combination showed an ORR of 69%, with 39% of patients experiencing a complete response, while the lenalidomide-rituximab combination showed a higher ORR of 78%, with 34% of patients experiencing a complete response. Both therapies demonstrated efficacy in the same range, which would make sense given the fact that they both include immunotherapies in their regimens. The safety of the drugs, however, presented several differences. The zanubrutinib-obinutuzumab regimen, for example, had manageable side effects such as neutropenia (29%) and fatigue (15%), and only 14% of the patients had experienced SAEs. On the other hand, the lenalidomide plus rituximab combination was noted to be linked with neutropenia (39%) and a higher rate of serious adverse events (26%). The safety issues related to the lenalidomide and rituximab combination are possible because both of its components are immunotherapies. Both lenalidomide and rituximab are also immunotherapies, and when used together, these therapies may trigger immune activation even more and lead to an overactive immune response. In general, the combinations covered in this review tend to have similar efficacy results but variable safety results, possibly due to the specific constituent drugs of the combination and how they interact with each other. These results show how clinicians must exercise caution with the use of combination treatments since they can lead to harmful side effects.

The final treatment covered in this article, Multi-Line Treatments, also showed some intriguing results. Moreover, the three-line therapy that was observed included an anti-CD20 antibody, a combination of PI3K inhibitors, and a hematopoietic stem cell therapy that involves renewing and replacing the stem cell of the patient after high-dose chemotherapy (drug therapy that kills cells).[15] This three-line therapy led to a 70% ORR and 47% of patients achieving a CR. These results highlight significant efficacy, as almost half the patients had fully recovered, and the great majority had improvements in tumor size. While the initial results were promising, concerns arose as 26% of patients died during the trial, with most deaths attributed to lymphoma progression. This could be related to the patients' underlying conditions and the stage of their disease at the time of treatment. It’s possible that the 26% who passed away were already in critical condition when they started the therapy, which may have contributed to their deaths. However, of course, the exact reasons are hard to pinpoint and could involve a variety of factors, such as a specific component in the therapy or the condition of the patients before receiving treatment. Treatments given in separate lines to the same patient seemed to have many concerns related to the unusually significant number of patients that had died in the course. This could have been due to factors specific to the components used in the trial, but regardless, attention should be raised when combining treatments across multiple lines. This idea can also go for combination treatments, as both share similar mechanisms.

Despite the varying results across all the different types of treatments, directly comparing the efficacy and safety of different therapies for Follicular Lymphoma is challenging because of certain limitations. Primarily, the variables maintained in clinical trials are not always consistent in different clinical trials. In

other words, the patients, disease stages, timeframe, treatment protocols, and other aspects may not have been kept the same in different clinical trials, making it hard to form a definite conclusion. However, throughout the review, it is clear that safety risks, a major failure in all trials, should be addressed in treating FL. To elaborate, both CAR T-cell therapies and immunotherapies showed high rates of CRS in patients. This suggests that the process of specifically modifying cells to target cancer cells can trigger an overwhelming immune response, leading to higher levels of cytokines. Similarly, with combination treatments and multi-line treatments, unexpected outcomes, including death and high rates of serious adverse events, were noted, which further proves the volatility and risk present in combining different therapies. Enzyme inhibitors, another category in this review, also resulted in many incidences of CRS, just like Immunotherapies and CAR-T therapies. However, this category of treatment resulted in an extremely low number of patients with a CR that was unlike any of the other treatments/categories. All these trials show a common failure in addressing safety concerns across the many categories of treatments discussed in this review, though the trials did happen to differ in the specific outcomes.

CONCLUSION

In conclusion, although numerous treatment strategies for FL have shown notable effectiveness, the issue of patient safety is a great concern. CAR T-cell therapies such as Tisagenlecleucel and Lisocabtagene Maraleucel have shown high response rates, but the risk of severe side effects such as CRS shows how important it is to have safe monitoring of the immune system since most of the side effects observed in the trial were due to complications of aggressive immune responses. Similarly, immunotherapies like mosunetuzumab, epcoritamab, and glofitamab have excellent overall response rates, but their CRS and neurological side effects need to be better controlled. Enzyme inhibitors are also very risky from a safety point of view, although the specific inhibitors that were tested demonstrated significantly low rates of complete responses, but higher partial responses and control rates. This shows how enzyme inhibitors tend to manage cancer growth rather than remove it altogether. Another approach, combination therapies, where zanubrutinib was combined with obinutuzumab and lenalidomide with rituximab, was also effective but varied significantly in safety outcomes. This once again indicates the risks of combining treatments, where certain drug combinations result in unforeseen side effects. Based on this idea, it can be concluded that careful pre-planning is essential to combination design so treatment-related conflicts can be avoided. Then, multi-line treatments have excellent efficacy but a very high rate of lymphoma-related deaths. This result simply shows how some treatments can work for some people but not for others, reminding researchers of how variability in patient status or patient characteristics can affect treatment results. All these results prove that therapies for FL have progressed significantly in terms of effectiveness, but safety precautions and technology must be further enhanced. Though side effects are an inevitable accompaniment of cancer treatments, every effort should still be made to reduce the danger of severe complications through special alterations, methods, and surveillance. Future work is also attempting to address these issues with researchers testing pirtobrutinib with mosunetuzumab to see if the combination can effectively treat relapsed FL but also cause fewer problems like inflammation and CRS. Looking to the future, it must be the goal to develop FL treatments that resolve any significant safety concerns but still maintain a high level of effectiveness.

ABOUT THE AUTHOR

Kavinharish Thirumurugan is a high school student from Chandler, Arizona. His interests are in playing soccer and video editing. The journey of making this paper has been a major step towards discovering many of his passions and working towards the future. Looking ahead, he aims to pursue a career in biomedical research or engineering.

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