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Recent advances in treatment of nodal and gastrointestinal follicular lymphoma

Takuya Watanabe

Abstract

Follicular lymphoma (FL) is the most common low-grade lymphoma, and although nodal FL is highly responsive to treatment, the majority of patients relapse repeatedly, and the disease has been incurable with a poor prognosis. However, primary FL of the gastrointestinal tract has been increasingly detected in Japan, especially due to recent advances in small bowel endoscopy and increased opportunities for endoscopic examinations and endoscopic diagnosis. However, many cases are detected at an early stage, and the prognosis is good in many cases. In contrast, in Europe and the United States, gastrointestinal FL has long been considered to be present in 12%-24% of Stage-IV patients, and the number of advanced gastrointestinal cases is expected to increase. This editorial provides an overview of the recent therapeutic advances in nodal FL, including antibody-targeted therapy, bispecific antibody therapy, epigenetic modulation, and chimeric antigen receptor T-cell therapy, and reviews the latest therapeutic manuscripts published in the past year. Based on an understanding of the therapeutic advances in nodal FL, we also discuss future possibilities for gastroenterologists to treat gastrointestinal FL, especially in advanced cases.

Key Words: Nodal and gastrointestinal follicular lymphoma; Antibody-based therapy; Bispecific antibody therapy; Phosphatidylinositol-3 kinase inhibitor; Epigenetic modulator; Chimeric antigen receptor-T cell therapy

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Core Tip: Primary gastrointestinal follicular lymphomas (FLs) have been increasingly detected in Japan, especially due to recent advances in small bowel endoscopy and increased opportunities for endoscopic examination and endoscopic diagnosis. Previously, many gastrointestinal FL cases were detected at an early stage, however, the number of advanced cases is expected to increase in the future. This editorial provides an overview of the recent therapeutic advances in nodal FL, including antibody-targeted therapy, bispecific antibody therapy, epigenetic mutations, and chimeric antigen receptor T-cell therapy, and we also discuss future possibilities for gastroenterologists to treat gastrointestinal FL, especially in advanced cases.

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INTRODUCTION

Follicular lymphoma (FL) is a typical indolent B-cell lymphoma that accounts for 10%-20% of all non-Hodgkin lymphomas (NHLs)[1]. Its incidence is increasing rapidly in Western and Asian countries[2]. In particular, the number of FL cases in Japan has recently increased[3]. FL is histopathologically classified as grades 1, 2, 3a, or 3b, with grade 3b usually treated as aggressive (intermediate/high-grade) lymphoma. Most patients present with enlarged lymph nodes, and 70%-85% of patients have advanced clinical stage III or IV disease at diagnosis, with a high rate of bone marrow involvement. The gastrointestinal tract is the most common site of extranodal NHL, accounting for 30-40% of primary extranodal NHL cases[4,5]; however, gastrointestinal FL (GI-FL) is rare, with a frequency of approximately 2% of GI-NHL[6-8]. However, in recent years, the number of patients with primary GI-FL has increased because capsule and double-balloon endoscopies of the small intestine have become common in Japan. Most GI-FL cases are stage I, but there are 3.4%-40.0% with metastasis or invasion to intra-abdominal lymph nodes (stage II), extensive extranodal organ (stage IV) to extensive extranodal organs or beyond the diaphragm (12%-24%) have been reported[9], and the number of advanced cases of GI-FL (stage III, IV) is expected to increase in the future. Hiddemann et al[10] reported the efficacy and prolonged overall survival (OS) of rituximab, an anti-CD20 monoclonal antibody, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in patients with advanced FL. Prior to the introduction of rituximab, the 50% survival period for FL patients was 7-10 years, recent reports have indicated that the 50% survival period exceeds 20 years for patients under 40 years of age at diagnosis[11]. Furthermore, progress has been made in the studies and clinical trials of combination therapies using other monoclonal antibodies and conventional chemotherapy combinations. In the last decade, new therapeutic agents for nodal FL have been developed, including antibody-targeted therapy, bispecific antibody therapy, epigenetic mutation, and chimeric antigen receptor (CAR)-T cell therapy, and many clinical trials of monotherapy and various combinations of two or three of these agents have been conducted, showing high response rates, progression-free survival (PFS). Many clinical trials have been conducted to evaluate the efficacy of single agents and combinations of two or three of these drugs, and have shown high response rates, PFS, and OS. However, the large number of new drugs has led to the creation of many combinations of these drugs, so there is still no definitive conclusion as to which combination is the best in terms of efficacy and safety, and what the optimal order of these therapies should be. We reviewed and summarized the recently reported therapeutic advances in nodal FL, especially the most recent therapeutic publications during the past year. We then discuss the possibilities and directions in which gastroenterologists should utilize and reflect on recent advances in the treatment of nodal FL in primary GI-FL.

Recent advances in the treatment of nodal FL

Radiation therapy used to be the first choice for the treatment of nodal FL when the lesions were localized or multiple but few in number, however, the choice of radiation therapy has been greatly reduced in recent years due to its strong adverse reactions, and chemotherapy, which has advanced significantly in the past 20 years, immunotherapy, which has fewer side effects, or their combination therapies have emerged.

This editorial describes recent advances in the treatment of advanced FL, primarily stage III or IV, with reference to tables summarizing them.
Monoclonal antibody-based therapy

Immunotherapy with rituximab and other anti-CD antibodies is highly effective in the treatment of FL and is superior and still central to current FL therapy. The objective response rate (ORR) with single-agent rituximab was 67% in untreated FL patients and 46% in previously treated relapsed FL patients [12].

A German Low-Grade Lymphoma Study Group conducted a randomized trial of CHOP alone vs rituximab plus CHOP (R-CHOP) in untreated advanced FLs. In a randomized comparison of CHOP monotherapy and R-CHOP combination therapy, the R-CHOP group significantly outperformed the CHOP group not only in time to failure but also in OS[13]. This evidence is important because it heralds the subsequent progress of combination therapy using anti-CD monoclonal antibody immunotherapy and other novel agents, in addition to conventional chemotherapy. Following rituximab administration, new antibody-based agents have been developed, including tafasitamab, an anti-CD19 antibody; polatuzumab vedotin, an anti-CD79b antibody-drug conjugate (ADC); loncastuximab tesirine, an ADC composed of a humanized antibody targeting the protein CD19; magrolimab, an anti-CD47 antibody; and obinutumab, a humanized anti-CD20 monoclonal antibody. Obinutumab, a humanized anti-CD20 monoclonal antibody, has been developed (Table 1).

Tafasitamab plus lenalidomide, which enhances NK cell activity and antibody-dependent cytotoxicity (ADCC), has been shown to be superior to the monotherapy[14].

Polatuzumab vedotin is a CD79b-directed ADC. In the phase II ROMULUS trial of relapsed and refractory (r/r) FL and diffuse large B-cell lymphoma (DLBCL), patients with FL were treated with rituximab plus polatuzumab (CD79-directed ADC) or rituximab plus pinatuzumab (CD22-directed ADC), and their efficacy was compared[15].

Loncastuximab tesirine (ADCT-402) is a noble antibody-drug conjugated to a cytotoxic dimer. After binding to the tumor cells the antibody is internalized, the cytotoxic drug is released, and the cancer cells are killed. The ORR in patients with FL in a phase I study was 78.6%; phase II findings (LOTS5-2 study) of loncastuximab tecilin in r/r DLBCL patients showed a good and sustained antitumor effect with an ORR of 48.3% and complete response rate (CRR) of 24.2%[16]. Clinical trials are currently underway for other carcinomas; a phase II study in combination with rituximab for r/r FL patients is ongoing in Florida, United States.

Magrolimab is a CD47-directed antibody, and a phase I study of its combination with rituximab in r/r lymphoma has been reported[17].

Obinutumab is a humanized anti-CD20 monoclonal antibody with low fucose content in the Fc region through glycosylation technology and the unique properties of a type-2 antibody. Phase 3 trials have shown improved efficacy in indolent non-NHL (iNHL) and chronic lymphocytic leukemia (CLL), and phase 2 trials of these therapeutic regimens have shown promising results in CLL, FL, and mantle cell lymphoma (MCL)[18].

Results of a phase II study of the combination of venetoclax plus obinutumab in previously untreated FL patients showed ORR and CRR were 87.5% and 25.0%, respectively, by CT evaluation; 84.2% and 68.4%, respectively, by PET/CT evaluation; 1-year PFS was 77.8% and 79%, respectively; 30-mo PFS was 73.2% and 79.0%, respectively and showed efficacy of the combination of venetoclax plus obinutumab[19]. However, in the GALLIUM trial, obinutuzumab had a better PFS than rituximab when combined with conventional chemotherapy as frontline therapy in previously untreated advanced FL patients[20]. Furthermore, transformed-FL (t-FL) patients with more aggressively transformed, more malignant potential had worse survival than r/r FL patients (2-year rate: 55.9% vs 83.1%). t-FL relapsed earlier than FL (median observation time: 0.8 years vs 2.3 years)[21].

Finally, we discuss the key points regarding recent rituximab biosimilars. In recent years, four rituximab biosimilars have been approved to date in Europe and the United States. CT-P10 is the first Rituximab biosimilar approved CT-P10 is as effective and safe as Rituximab in untreated FL with small tumor volume[22]. They also reported no statistically significant differences in efficacy and serious adverse events between the Rituximab biosimilar group and the reference drug, Mabusera[23]. The Japanese government’s policy for 2022 also states that biosimilar will be steadily promoted with a target value set by the end of 2022 based on the effect of medical cost optimization. It is expected that the use of rituximab biosimilars will be recommended and increased worldwide from the viewpoint of cost benefit in reducing the enormous medical costs in the future.

Antibody therapies against novel targets, such as CD19, CD79b, and CD47, as well as rituximab, an anti-CD20 monoclonal antibody and obinutumab, a humanized anti-CD20 monoclonal antibody, have been developed and have demonstrated efficacy in FL. Antibody targeted therapies to FL are innovative immunotherapy medication that offers great efficacy and safety for FL treatment. We have high expectations for improved outcomes in the near future.

Bispecific T cell binding antibody = bispecific antibody therapy

Bispecific T-cell binding antibodies (BTEs) = bispecific antibodies are molecules designed to bind to two or more different antigens, a powerful therapy that allows T cells to more precisely target specific tissues and cells. Summary of clinical trials of BTE treatment for FL is shown in Table 2.
Table 1 Summary of clinical trial results of monoclonal antibody-based therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Median progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or other subjects</th>
<th>Ref.</th>
</tr>
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<tr>
<td>Tafasitamab plus lenalidomide phase-II L-MID</td>
<td>r/r DLBCL (no FL) &gt; 35 mo follow up</td>
<td>n = 80</td>
<td>57.5% (n = 46/80)</td>
<td>40.0% (n = 32/80)</td>
<td>11.6 mo</td>
<td>33.5 mo</td>
<td>No unexpected toxicity</td>
<td>[14]</td>
</tr>
<tr>
<td>Phase-II ROMULUS, rituximab-polatuzumab vs rituximab-pituituzumab</td>
<td>r/r FL</td>
<td>n = 42, n = 20, n = 21</td>
<td>70% (n = 14/20); 62% (n = 13/21)</td>
<td>45% (n = 9/20); 5% (n = 1/21)</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>Loncastiximab tesirine (ADTC-402) frontline therapy</td>
<td>Untreated FL, Total, DLBCL, MZL, FL</td>
<td>45.6%, 42.3%, 46.7%, 78.6%</td>
<td>26.7%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Median duration response: 5.4 mo</td>
<td>[16]</td>
<td></td>
</tr>
<tr>
<td>Magrolimab plus rituximab phase-Ib</td>
<td>r/r DLBCL; r/r FL</td>
<td>n = 22; DLBCL:15; FL:7</td>
<td>50% (CR or PR); 40%; 71% (n = 5/7)</td>
<td>33%, 43% (n = 3/7)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>90% response were on going; a median follow-up of 6.2 (DLBCL)/8.1 (FL) mo</td>
<td>[17]</td>
</tr>
<tr>
<td>Venetoclax plus obinutuzumab phase-I</td>
<td>Untreated FL, CT, PET/CT</td>
<td>87.5%, 84.2%</td>
<td>25.0%, 68.4%</td>
<td>77.8% (at one yr); 79.0% (at 30 mo); 73.2% (at 30 mo)</td>
<td>Unknown</td>
<td>unknown</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>GALLIUM trial obinutuzumab + CTx rituximab + CTx</td>
<td>Untreated FL</td>
<td>n = 1202, n = 401, n = 401</td>
<td>88.5%, 86.9%</td>
<td>Unknown</td>
<td>80.0% (at 3 yr); 73.3% (at 3 yr)</td>
<td>Unknown</td>
<td>Obinutuzumab is better</td>
<td>[20], [21]</td>
</tr>
</tbody>
</table>

*Unknown” means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; DLBCL: Diffuse large B-cell lymphoma; MZL: Marginal zone lymphoma; (R-)CHOP: (Rituximab plus) cyclophosphamide, doxorubicin, vincristine, and prednisolone; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography; CTx: Traditional chemotherapy.

The BTEs most commonly used for FL treatment are CD3 and CD20, with Mosunetuzumab and Glofitamab being pioneering representative novel BTEs.

A phase I trial of single-agent mosunetuzumab in patients with r/r iNHL (including FL and t-FL) showed an ORR of 66% and a CRR of 49%, with grade 3 or higher adverse events in 71% of patients with low-grade lymphoma (r/r and t-FL, 96%)[24]. Mosunetuzumab, a CD20 × CD3 bispecific monoclonal antibody, showed a significantly higher CRR of 60% than that of the control group with copanlisib of 14%, when administered to patients with r/r FL, indicating high efficacy[25]. Mosunetuzumab was also studied in combination with lenalidomide; a phase I study of combination therapy in r/r FL patients showed an ORR of 92%, CR of 77%, and grade 3 or higher adverse events in 30% of patients in the abstract.

Glofitamab was observed to have a better response rate at higher dose levels in the r/r B-NHL (including indolent lymphoma of 25.7%) phase I trial, with an ORR of 65.7% and a CRR of 57.1%. CRS occurred in 50.3% of cases[26]. The results of a study comparing glofitamab with or without obinutuzumab in r/r FL showed an ORR of 81% and a CRR of 70% for glofitamab alone and 100% and 74% for the combination group in the Abstract.

The results of a phase I/II trial of epocritamab, an anti-CD3 and anti-CD20 BTE, in r/r NHL patients showed an ORR of 90% and a CRR of 50% in FL patients[27]. The results of a phase I/II study of epocritamab in combination with lenalidomide and rituximab in patients with r/r FL showed high efficacy, with an ORR of 100% and a CRR of 93%[28].

Odonextamab is a hinge-stabilized fully human IgG4-based CD20 × CD3 bispecificity antibody that binds to CD3 on T cells and CD20 on B cells. In the Odonextamab ELM-1 phase I study, patients with r/r FL who received 5 mg or more of odronextamab had an ORR of 91% and a CRR of 72%; Odonextamab monotherapy showed promising preliminary activity, especially in patients with long-standing previously treated BCL with sustained response[29,30].

BTE is a novel immunotherapy agent that shows high efficacy and safety for FL treatment. We would like to greatly anticipate further improvements in outcomes through future clinical trials.

**Anti-programmed death ligand 1 antibody**

Programmed death ligand 1 (PD-1) blockade enhances anti-tumor T cell function and ADCC in NK cells. Recently, the efficacy of the anti-PD-1 ligand (PD-L1) antibodies, atezolizumab and pembrolizumab, in FL has also attracted attention (Table 3).
Table 2 Summary of clinical trial results of bispecific T cell binding antibody therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Median progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or other subjects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosunetuzumab alone, phase-I</td>
<td>r/r NHL (including FL and t-FL)</td>
<td>n = 157</td>
<td>66.2% (i B-NHL)</td>
<td>48.5% (i B-NHL)</td>
<td>Median duration of response 20.4 mo (i B-NHL)</td>
<td>Unknown</td>
<td>G3 and higher in 71% of iNHL patients</td>
<td>[24]</td>
</tr>
<tr>
<td>Mosunetuzumab alone, phase-II</td>
<td>r/r FL (Grade 1-3a)</td>
<td>n = 90 (median follow-up was 18.3 mo)</td>
<td>Unknown</td>
<td>60% (n = 54/90) (14% higher than CRR with copanlisib), high efficacy</td>
<td>Unknown</td>
<td>Unknown</td>
<td>High efficacy</td>
<td>[25]</td>
</tr>
<tr>
<td>Mosunetuzumab with lenaridomide, phase-I</td>
<td>r/r FL</td>
<td>Unknown</td>
<td>92%</td>
<td>77%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>In abstract</td>
</tr>
<tr>
<td>Glofitamab alone, phase-I</td>
<td>r/r B-NHL (including r/r FL)</td>
<td>n = 155</td>
<td>65.7% (at the recommended phase-II dose)</td>
<td>57.1% (at the recommended phase-II dose)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>CRS occurred in 50.3% of patients</td>
<td>[26]</td>
</tr>
<tr>
<td>Glofitamab alone vs glofitamab with obinutuzumab</td>
<td>r/r FL</td>
<td>Unknown</td>
<td>81%, 100%</td>
<td>70%, 74%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Combination has a better response rate</td>
<td>In Abstact</td>
</tr>
<tr>
<td>Epcuritamab, phase-I/II</td>
<td>r/r B-NHL</td>
<td>n = 68</td>
<td>90% (full dose)</td>
<td>50% (full dose)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Pyrexia 69%, CRS 9%</td>
<td>[27]</td>
</tr>
<tr>
<td>Epcuritamab with lenaridomide and rituximab</td>
<td>r/r FL</td>
<td>Unknown</td>
<td>100%</td>
<td>93%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>High efficacy is revealed</td>
<td>[28]</td>
</tr>
<tr>
<td>Ondonxetamab alone phase-I ELM-1 trial</td>
<td>r/r B-NHL (including r/r FL)</td>
<td>n = 145</td>
<td>91% (r/r FL)</td>
<td>72% (r/r FL)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>CRS 28%</td>
<td>[29]</td>
</tr>
</tbody>
</table>

"Unknown" means data not shown, unknown information or not reached. r/r: Refractory and relapsed; (i)NHL: (Indolent) non-Hodgkin lymphoma; i B-NHL: Indolent B-cell non-Hodgkin lymphoma; FL: Follicular lymphoma; t-FL: Transformed follicular lymphoma; G: Grade; CRS: Cytokine release syndrome.

Table 3 Summary of clinical trial results of anti-programmed death ligand 1 antibody-based therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Median progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or other subjects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolitumab (anti-PD-1 antibody) plus obinutumab</td>
<td>Total</td>
<td>n = 49</td>
<td>Unknown</td>
<td>Unknown</td>
<td>12 mo</td>
<td>97% (at 3 yr)</td>
<td>23% in remission at median follow-up of 35 mo</td>
<td>[31]</td>
</tr>
<tr>
<td>phase-I</td>
<td>r/r FL</td>
<td>n = 26</td>
<td>54%</td>
<td>23%</td>
<td>9 mo</td>
<td>3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r/r DLBCL</td>
<td>n = 23</td>
<td>17%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab(anti-PD-L1antibody) plus rituximab</td>
<td>r/r FL (one or more prior therapy)</td>
<td>n = 30</td>
<td>67%</td>
<td>50%</td>
<td>12.6 mo</td>
<td>97% (at 3 yr)</td>
<td>23% in remission at median follow-up of 35 mo</td>
<td>[32]</td>
</tr>
</tbody>
</table>

"Unknown" means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; DLBCL: Diffuse large B-cell lymphoma; PD-1: Programmed death ligand 1.

The results of a phase I study of the combination of atezolizumab, an anti-PD-L1 antibody, and obinutumab showed an ORR of 54% (CRR: 23%) for r/r FL and r/r DLBCL and 17% (CRR: 4%) for DLBCL; PFS was 9 mo in the FL group and 3 mo in the DLBCL group[31]. In addition, a clinical trial of pembrolizumab, an anti-PD-1 monoclonal antibody, in combination with rituximab, an anti-CD20 monoclonal antibody, in r/r FL patients showed an ORR of 67% and CRR of 50%; median PFS was 12.6 mo, 3-year OS was 97%, and at a median follow-up of 35 mo 23% of patients were in remission[32]. Pembrolizumab in combination with rituximab as a novel therapeutic agent for r/r FL showed high efficacy and remission maintenance.
PD-1 blockade enhances anti-tumor T cell function and ADCC in NK cells, and its mechanism of action is more fundamental and makes more sense. We expect further improvement of the therapeutic effect of anti-PD-1 antibody therapy for FL patients.

**IMMUNOMODULATORS**

Lenalidomide is a typical oral immunomodulatory drug (IMiD) used to treat FL. Lenalidomide is a derivative of thalidomide with a similar structure. Lenalidomide is a derivative of thalidomide with a similar structure. It has both a “tumor-killing” effect by inhibiting the growth of hematological malignancies and inducing apoptosis, and an “immunomodulatory” effect by acting on immune cells and activating their immunity. The combination of lenalidomide and CD20 antibody was initially tested as a salvage therapy for r/r FL in combination with an anti-CD20 antibody; however, owing to its high efficacy, it was recently tested as a frontline therapy for patients with advanced, untreated FL, with good results. Table 4 lists clinical trials in which lenalidomide was administered.

A phase II study comparing lenalidomide alone with R2 (lenalidomide plus rituximab) in patients with r/r FL showed an ORR favoring the R2 group (35% vs 24%), with a median follow-up of 2.5 years. The time to progression (median) was also superior in the R2 group (2.0 years vs 1.1 years), but there was no significant difference in OS.

The results of the phase III AUGMENT study evaluating R2 (lenalidomide plus rituximab) in r/r FL and marginal zone lymphoma (MZL) showed a median PFS of 39 mo in the R2 group compared to 14 mo in the rituximab group, with no difference in OS.

The phase IIIb MAGNIFY trial investigated extended R2 treatment in patients with r/r FL and MZL. After 12 cycles of R2 treatment, patients were randomized to receive an additional 18 mo of R2 treatment or rituximab maintenance therapy. The R2 cohort had ORR of 69% and CRR of 40%. The median PFS was 40 mo, similar to that observed in the AUGMENT trial.

In a single-arm phase II GALLEN trial of patients with r/r FL, Obinutuzumab and lenalidomide were studied. The patients received lenalidomide and obinutuzumab for 18 mo, followed by 1 year of obinutuzumab maintenance therapy. After a median follow-up of 2.6 years, the ORR was 95%, 2-year PFS was 65%, and OS was 87%. No clinical trials have directly compared rituximab and obinutuzumab in combination with lenalidomide, and it is unclear which combination is superior in efficacy.

The phase III RELEVANCE trial of R2 as frontline therapy for advanced FL was conducted. Patients were randomized to receive 18 cycles of R2 therapy plus 6 cycles of rituximab maintenance therapy or a chemotherapy regimen including rituximab [R-CHOP, bendamustine plus rituximab (BR), or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP)]. The primary endpoints of the CR rate (48%-53%) and 3-year PFS (77%-78%) at 120 wk were similar; no superiority of R2 over chemotherapy in the frontline treatment of FL has been demonstrated.

The phase II E2408 trial randomized untreated FL patients into BR induction and R2 maintenance, BR induction and rituximab maintenance, or BR and the proteasome inhibitor bortezomib plus rituximab maintenance, and compared the efficacy among the three groups. The three groups had similar (approximately 90%) and high CRRs, and the 1-year disease-free survival was higher in the rituximab maintenance group (85%) than in the R2 group (67%), possibly due to a higher discontinuation rate due to adverse events in the R2 group.

A clinical trial of lenalidomide plus obinutuzumab as frontline therapy for patients with advanced untreated FL showed very good results, with an ORR of 98%, CR of 92%, and 2-year PFS of 96% after a median follow-up of 22 mo. In the future, the combination of lenalidomide and CD20 antibodies is expected to be the mainstay of frontline therapy for FL.

With the introduction of bendamustine, obinutuzumab, lenalidomide, which have shown high efficacy in maintenance therapy, front-line treatment of FL has improved and developed. However, how they can be combined to provide the best treatment has recently been studied by network meta-analysis of randomized controlled trials to compare treatment efficacy.

With lenalidomide, a further improvement in the therapeutic effect in FL patients was obtained when used in combination with other main agents. As one of the important combination drugs, it is expected to improve treatment outcomes in the future.

**MOLECULAR TARGETED THERAPIES (SMALL MOLECULE COMPOUNDS)**

**Bruno’s tyrosine kinase inhibitor**

Bruno’s tyrosine kinase (BTK) is a type of protein kinase that exists in immune cells and regulates B cell differentiation and activation upon stimulation from the B cell receptor (BCR). Since BCR signaling plays an important role in blood cancers such as B-cell NHL and CLL, BTK inhibitors have been expected to have therapeutic effects in these blood cancers including FL. The results of the clinical trials...
Table 4 Summary of clinical trial results of immunomodulator-based therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or other subjects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized phase-II; lenalidomide alone (L) lenalidomide + rituximab (LR)</td>
<td>r/r FL</td>
<td>$n = 91, n = 45$ (L); $n = 46$ (LR)</td>
<td>53%, 76%</td>
<td>20%, 39%</td>
<td>Median time to progression: 1.1 yr (at 2.5 yr); 2.0 yr (at 2.5 yr)</td>
<td>Unknown</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>Phase-III AUGMENT lenalidomide + R (R2) vs lenalidomide + placebo</td>
<td>r/r FL; r/r MZL</td>
<td>$n = 358; n = 180; n = 178$</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Median duration: 39.4 mo; 14.1 mo</td>
<td>Unknown</td>
<td>Grade 3 neutropenia of R2 is higher than L</td>
<td>[35]</td>
</tr>
<tr>
<td>Phase-IIIb MAGNIFY trial; R maintain after R2 additional lenalidomide + rituximab (R2) 18 mo after R2</td>
<td>r/r FL; r/r MZL</td>
<td>$n = 393$</td>
<td>69% (R2)</td>
<td>40% (R2)</td>
<td>40 mo (similar to AUGMENT trial)</td>
<td>Unknown</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>Phase-II GALEN study; lenalidomide + obinutuzumab (R2) 18 mo followed by obinutuzumab alone maintenance therapy 1 year</td>
<td>r/r FL</td>
<td>$n = 68$; evaluable</td>
<td>95% (at 2.6 yr)</td>
<td>38% ($n = 33/86$)</td>
<td>65% (at 2 yr)</td>
<td>87% (at 2 yr); 81% ($n = 70/86$); 84% ($n = 72/86$)</td>
<td>[37]</td>
<td></td>
</tr>
<tr>
<td>Phase-III RELEVANCE study, lenalidomide + rituximab (R2) + Rituximab maintenance therapy vs CTx (R-CHOP, BR, or R-CVP)</td>
<td>Untreated advanced FL</td>
<td>$n = 1030$; R- maintenance, $n = 513$; CTx, $n = 517$</td>
<td>Unknown</td>
<td>48%-53%, about the same</td>
<td>3 years-PFS 77%-78%, almost equal to superiority of R2 in F2 frontline not proven</td>
<td>Unknown</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td>Single center phase-II frontline therapy; lenalidomide plus obinutuzumab</td>
<td>Untreated advanced FL</td>
<td>$n = 90$</td>
<td>98% (after a median follow-up of 22 mo)</td>
<td>92% (after a median follow-up of 22 mo)</td>
<td>2 yr-PFS 96 (after a median follow-up of 22 mo)</td>
<td>Unknown</td>
<td>[40]</td>
<td></td>
</tr>
</tbody>
</table>

“Unknown” means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; MZL: Marginal zone lymphoma; L: Lenalidomide; R: Rituximab; LR: Lenalidomide plus rituximab; R2: Lenalidomide plus rituximab; (R-)CHOP: (Rituximab plus) cyclophosphamide, doxorubicin, vincristine, and prednisolone; BR: Bendamustine plus rituximab; (R-)CVP: (Rituximab plus) cyclophosphamide, vincristine and prednisolone; BR-R: BR induction followed by 2-year rituximab maintenance; BVR-R: BR with bortezomib and rituximab maintenance; BB-LR: BR followed by lenalidomide (1 year) with rituximab maintenance; CTx: Traditional chemotherapy.

Representative BTKi include, in order of oldest to youngest, first-generation ibrutinib, second-generation acalabrutinib and zanubrutinib, and third-generation piltobrutinib. These BTKi have shown high efficacy in B-cell NHL and CLL[42-46]. The efficacy of zanubrutinib monotherapy in patients with r/r FL was sluggish, with an ORR of 36.4% and CR of 18.2%. After a median follow-up of 33.9 mo, the median PFS was 10.4 mo[42]. On the other hand, a phase II study in r/r MCL showed that after a median follow-up of 35.3 mo, the ORR was 83.7%, the CRR was 79.9%, and the median PFS was 33.0 mo[43]. Zanubrutinib alone was highly effective in r/r MCL, however, limited in r/r FL.

The phase II DAWN trial evaluated the therapeutic efficacy of single-agent ibrutinib in patients with r/r FL; the ORR was 21% and did not meet the primary endpoint[47]. Frontline therapy was administered to investigate a combination of Ibrutinib and Rituximab. This phase II trial included two arms, both with ibrutinib 560 mg/d, with Rituximab in arm-1 starting at week 1 for four cycles per
Table 5 Summary of Clinical Trial Results of Bruton’s Tyrosine Kinase inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or others</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanubrutinib (other BTKi) alone</td>
<td>r/r FL</td>
<td></td>
<td>36.4%</td>
<td>18.2%</td>
<td>Median PFS 10.4 mo (median follow-up 33.9 mo)</td>
<td>Unknown</td>
<td>[42]</td>
<td></td>
</tr>
<tr>
<td>Zanubrutinib phase-II</td>
<td>r/r MCL</td>
<td>83.7%</td>
<td>77.9%</td>
<td>Unknown</td>
<td>33.0 mo</td>
<td>Unknown</td>
<td>[43]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>r/r FL</td>
<td>n = 100</td>
<td>21.0% (poor)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>[44]</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib with rituximab phase-II trial</td>
<td>Un-treated FL, r/r FL</td>
<td>n = 13, n = 27</td>
<td>85% (arm-1), 75% (arm-2)</td>
<td>Unknown</td>
<td>62% of untreated FL, 26% of r/r FL, continued treatment</td>
<td>Unknown</td>
<td>[45]</td>
<td></td>
</tr>
</tbody>
</table>

“Unknown” means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; PFS: Progression-free survival.

Week, and Rituximab in arm-2 starting at week 9. The ORR was 85% in arm-1 and 75% in arm-2[48].

Acalabrutinib is an effective BTKi for r/r MCL. Results of a phase I trial comparing acalabrutinib with or without rituximab as frontline therapy for untreated FL and salvage therapy for r/r FL, after a median follow-up of 22 mo, 62% of untreated FL patients and 26% of r/r FL patients remained on therapy and showed high tolerability[49].

Results of the randomized phase II ROSEWOOD trial in patients with r/r FL showed that combination therapy with zanubrutinib had better PFS than obinutuzumab alone. Zanubrutinib suggested to be more effective against r/r FL when used in combination with Obitutuzumab[50].

Although the single-agent activity of BTKi’s in FL is modest, their activity may be demonstrated when used in combination, and there is hope for their efficacy. We will keep a close eye on the future improvements in combination therapy with various combinations of new BTKs and other drugs in patients with FL.

**Pro-apoptotic pathway inhibitors (BCL2 inhibitor)**

Venetoclax selectively binds with strong affinity to BCL2, an anti-apoptotic protein involved in many blood cancers, and liberates apoptosis-promoting proteins, thus rapidly and irreversibly promoting apoptosis of blood cancer cells because BCL2 is overexpressed in FL. Venetoclax, a BCL2 inhibitor, has shown great promise. A phase I trial of venetoclax monotherapy was conducted in patients with FL, with an ORR of 38% and a median PFS of 11 mo[51]. The phase II CONTRALTO trial compared three groups of patients with r/r FL: Venetoclax plus rituximab, venetoclax plus BR, and BR in combination with venetoclax[52]. The CRR were 17%, 75%, and 69%, respectively; grade 3 or higher adverse events were extremely common in the venetoclax plus BR group (94%). r/r FL was included. In addition, combination therapy with ibritinib was tested in a phase I/II study of venetoclax plus ibritinib with an ORR of 69% and a CRR of 25%[53].

Since BCL2 is overexpressed in FL, BCL2 inhibitors are expected to have a fundamental antitumor effect on FL tumor cells in terms of their mechanism of action. We look forward to improving the therapeutic outcome of BCL2 inhibitors for FL patients in the near future.

**Epigenetic regulator**

Progress has been made in drug development that is active against blood cancers through the epigenetic regulation of gene expression, such as DNA methylation. The results of clinical trials of EZH2 treatments in patients with FL are listed in Table 6.

Tazemetostat is a small molecule that inhibits the activity of enhancer of zeste homolog 2 (EZH2), a methyltransferase of histones, etc. Tazemetostat inhibits the methylation activity of mutant EZH2, thereby inhibiting the methylation of lysine residue 27 of histone H3 and other methyltransferases. A phase II study of tazemetostat in EZH2-mutant and wild-type r/r FL patients showed a higher ORR in the EZH2-mutant cohort (69% vs 35%)[54]. It is important to note that higher activity was observed in patients with FL with high-risk characteristics. Currently, combination therapy for r/r FL with tazemetostat is under investigation in the phase II SYMPHONY-2 trial in combination with rituximab and in the phase Ib/III trial in combination with R2. Tazemetostat as a third, fourth, and subsequent treatment for FL and DLBCL patients, especially r/r FL, has a reduced risk of adverse events compared to the PI3K inhibitors idelalisib, duvelisib, copanlisib, and umbralisib, while the therapeutic efficacy and benefit were comparable[55-57].

More than 10 EZH2 inhibitors have recently entered clinical trials, including tazemetostat[56], and we look forward to improved outcomes in the future.
Table 6 Summary of clinical trial results of epigenetic regulators

<table>
<thead>
<tr>
<th>Study</th>
<th>Targeted disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or others</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tazemetostat alone, phase-II</td>
<td>t/r FL, EZH2-mut; FL, EZH2-wt; FL</td>
<td>n = 99, mut FL n = 45; wt FL n = 54</td>
<td>69% (EZH2 mut); 35% (EZH2 wt)</td>
<td>Unknown</td>
<td>Median PFS: 13.8 mo (EZH2 mut); 13.1 mo (EZH2 wt)</td>
<td>Unknown</td>
<td>G3 or higher 22%+, treatment discontinued at 8%</td>
<td>[54]</td>
</tr>
<tr>
<td>Tazemetostat (first EZH2 inhibitor) vs inderalisib, duvelisib, copanlisib, umbrelalisib</td>
<td>t/r FL, systematic literature review</td>
<td>Tazemetostat vs inderalisib 43% vs 56; duvelisib 48% vs 47; Kopanlisib 49% vs 61; umbrelalisib 57% vs 47; no significant difference in either case</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Predominantly reduced risk of adverse events compared to PI3Ki</td>
<td>[57]</td>
<td></td>
</tr>
<tr>
<td>Vorinostat (HDACi), phase-II</td>
<td>t/r Inhl + MCL, median with one or more prior treatment</td>
<td>n = 39 (t/r FL)</td>
<td>49%</td>
<td>Unknown</td>
<td>Median PFS, 20 mo</td>
<td>Unknown</td>
<td>G3 or higher 8%</td>
<td>[58]</td>
</tr>
<tr>
<td>Vorinostat + rituximab, phase-II</td>
<td>Untreated and t/r FL (4 or less prior treatment)</td>
<td>n = 22</td>
<td>46% (all patients); 67% (untreated pts); 41% (t/r FL)</td>
<td>Unknown</td>
<td>Median PFS, 29.2 mo (all patients); not reached (untreated pts); 18.8 mo (t/r FL)</td>
<td>Unknown</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Mocetinostat, phase-II</td>
<td>t/r DLBCL, t/r FL</td>
<td>n = 41, n = 31</td>
<td>18.9% (t/r DLBCL), 11.5% (t/r FL)</td>
<td>1.8-22.8 mo (DLBCL); 11.8-26.3 mo (FL)</td>
<td>Unknown</td>
<td>Fatigue (75.0%); nausea (69.4%); diarrhea (61.1%)</td>
<td>[60]</td>
<td></td>
</tr>
</tbody>
</table>

“Unknown” means data not shown, unknown information or not reached. t/r: Refractory and relapsed; FL: Follicular lymphoma; EZH2: Enhancer of zeste homolog 2; mt: Mutant; wt: Wild type; (i)NHL: (Indolent) non-Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; MZL: Marginal zone lymphoma; MCL: Mantle cell lymphoma; G: Grade; PI3Ki: Phosphoinositide 3 kinase inhibitor.

Vorinostat is a histone deacetylase inhibitor (HDACi). A phase II study of vorinostat in patients with t/r FL reported an ORR of 49%, with a median PFS of 20 mo. Grade 3 or greater adverse events were observed in 80% of the patients, mostly cytopenia[38]. Vorinostat was also evaluated in combination with rituximab, with an ORR of 50% and a CR of 41% in a phase II study of 22 untreated and t/r FL patients[59]. Another HDACi, moclertinostat, has shown poor efficacy, with an ORR of only 12% in patients with FL (n = 31) evaluated in a phase II trial of patients with t/r FL[60].

EZH2 inhibitors demonstrate effectiveness as an epigenetic regulator by the mechanism that inhibits the activity of methyltransferase of histones, etc. These agents are expected to further improve their therapeutic outcomes in the future, especially as a treatment for t-FL.

Phosphatidylinositol-3 kinase inhibitor

The BCR-mediated signaling pathway has been found to be permanently activated in B cell tumor cells, and inhibitors targeting molecules in the BCR signaling pathway are being developed.

Phosphatidylinositol-3 kinase (PI3K) is a lipid kinase that mediates the phosphorylation of the inositol ring 3 of inositol phospholipids, a membrane component[61]. Class I PI3Ks are heterologous. Class I PI3Ks are heterodimers that play important roles in signal transduction. Class 1 kinases are further divided into α, β, γ, and δ isoforms. For example, p110α and β are expressed in all cells, their knock out mouse is embryonic lethal[62]. p110γ is involved in neutrophil and macrophage migration[63] and mast cell degranulation[64]. This pathway is important in cancer, including B cell malignancies, and several small-molecule PI3K inhibitors (PI3Ki) have been developed for its treatment. The results of clinical trials of PI3K inhibitors in patients with t/r FL are listed in Table 7.

Idelalisib, a selective inhibitor of the delta isoform, was the first PI3Ki developed for the treatment of FL. In the European phase II DELTA study, idelalisib demonstrated the highest efficacy to date in t/r FL patients, with a median treatment duration of 10 mo (range 1-43) and an overall response rate of 73% [65].

In addition, a phase II open-label study of idelalisib in t/r iNHL, including FL, in the United States confirmed a response rate of 57% and a median PFS of 11 mo[66]. While idelalisib showed high efficacy against t/r FL, grade 3 or higher adverse events were observed in most participants (54%). Higher rates of adverse events have been observed in relatively young patients with less severe prior therapy, fewer complications, and stronger immune responses[67,68]. Fatal adverse events complicate the use of PI3K inhibitors.
Table 7 Summary of Clinical Trial Results of phosphoinositide 3 kinase inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events or others</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indelalisib, phase-II DELTA trial</td>
<td>r/r FL</td>
<td>n = 55</td>
<td>73% (highest ever reported)</td>
<td>Unknown</td>
<td>72% disease-free after 12 mo</td>
<td>80% alive after 12 months</td>
<td>54% of G3 or higher</td>
<td>[65]</td>
</tr>
<tr>
<td>Indelalisib phase-II open-labeled trial</td>
<td>r/r NHL (including FL), median of 4 lines prior therapy</td>
<td>(NHL, n = 72; FL, n = 42)</td>
<td>57%</td>
<td>Unknown</td>
<td>11 mo</td>
<td>Unknown</td>
<td>54% of G3 or higher</td>
<td>[66]</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>iNHL (including FL)</td>
<td>n = 187</td>
<td>70% good</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>63% of G3 or higher</td>
<td>[63, 69]</td>
</tr>
<tr>
<td>Compalisib, phase-II CHRONOS-I trial</td>
<td>r/r FL, median 3-lines of prior therapy</td>
<td>n = 142</td>
<td>59%</td>
<td>12%</td>
<td>11 mo (median)</td>
<td>43 mo (median)</td>
<td>G3 84%, 6 cases of G5 events</td>
<td>[70, 71]</td>
</tr>
<tr>
<td>Umbralisib, phase-II trial</td>
<td>iNHL (including FL), median 3-lines or more of prior therapy</td>
<td>n = 208 (FL = 117)</td>
<td>47.1% of (after a median follow-up of 27.7 mo)</td>
<td>Unknown</td>
<td>10.6 mo (median PFS)</td>
<td>Unknown</td>
<td>G3/4 neutropenia occurred in 19%</td>
<td>[74]</td>
</tr>
<tr>
<td>Parsaclisib, phase-Ib, CITADEL-111 trial</td>
<td>Japanese: r/r FL, r/r MZL; r/r DLBCL</td>
<td>n = 9; n = 2; n = 6</td>
<td>9 cases (= 100%); 2 cases (= 100%); 1 case (= 16.7%)</td>
<td>22.2% (n = 2/9); 100% (n = 2/2); 16.7% (n = 1/6)</td>
<td>Unknown</td>
<td>High incidence of adverse events-need to carefully select target patients</td>
<td>Neutropenia above G3 interrupted in 58.8% and reduced in 29.4%</td>
<td>[75]</td>
</tr>
<tr>
<td>Parsalisib phase-I/II (phase-II trial is ongoing)</td>
<td>r/r B-NHL</td>
<td>n = 72</td>
<td>71% (r/r FL); 78% (r/r MZL); 67% (r/r MCL); 30% (r/r DLBCL)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>G3 or higher neutropenia 6/9 (55.6%) diarrhea 3/9 (33.3%) and many events</td>
<td>[76]</td>
</tr>
<tr>
<td>Zandelisib (ME-401), phase-I trial</td>
<td>Japanese, r/r iNHL</td>
<td>n = 9</td>
<td>100% (n = 9/9)</td>
<td>22% (n = 2/9), median duration of response 7.9 mo; median time to response 1.9 mo</td>
<td>Unknown</td>
<td>G3 or higher neutropenia 6/9 (55.6%) diarrhea 3/9 (33.3%) and many events</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>Zandelisib alone vs zandelisib + rituximab</td>
<td>r/r FL</td>
<td>n = 12</td>
<td>92% (n = 11/12) in the 60 mg group; 83% (n = 5/6) in the 180 mg group</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>G3 or higher, high rate of 70% (BR), 91% (R-CHOP)</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>r/r iNHL, median 3-lines of prior therapy</td>
<td>n = 30 + BR (n = 19), vs + R-CHOP (n = 11)</td>
<td>90% (+ BR) vs 100% (+ R-CHOP)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>G3 or higher, high rate of 70% (BR), 91% (R-CHOP)</td>
<td>[79]</td>
</tr>
</tbody>
</table>

“Unknown” means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular Lymphoma; B-NHL: B-cell non-Hodgkin lymphoma; iNHL: Indolent non-Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; MZL: Marginal zone lymphoma; MCL: Mantle cell lymphoma.

Duvelisib is the first FDA-approved oral dual inhibitor of PI3K-δ and PI3K-γ. Wang et al[69] reported on the safety and efficacy of duvelisib, a dual PI3K-δ and γ inhibitor, in patients with relapsed and refractory lymphoid neoplasms in a systematic prospective clinical trial reviews and meta-analyses have been reported[63,69]. Although the ORR of 187 patients with iNHL including FL showed a good efficacy of 70%, the relatively high rate of grade 3 or higher adverse events (63%) is still a safety concern[63,69].

The high rate of adverse events associated with these two drugs has made it difficult to gain general acceptance for FL treatment. In such a situation, only compalisib has been approved for r/r FL after more than two lines of therapy. The phase II CHRONOS-I study[70,71] of compalisib in patients with r/r iNHL showed an ORR of 59%, CR of 12%, median PFS of 11 mo, and median OS of 43 mo. There was no increase in serious adverse events during the long-term follow-up period, although the rate of grade 3 or higher adverse events was as high as 44%, including 6 grade 5 events[70,71].

Umbralisib (TGR-1202) is an orally available, effective, potent and selective PI3-K δ and casein kinase-1-ε (CK1ε) inhibitor[72]. Umbralisib is a fourth-generation, late-stage PI3Ki that may play an important role in therapeutic algorithms[73]. The results of a phase II trial of r/r iNHL showed an ORR of 45% and...
Watanabe T. Current status and future development

CAR-T cell therapy is a highly effective, innovative, and revolutionary treatment for patients with r/r hematologic malignancies and shows great promise. When reinjected into the same patient, these CAR-
T cells trigger a T-cell-mediated immune response against the antigen-expressing malignancy and induce cell death. CAR-T cell therapy has recently been used in the treatment of iNHL such as FL and MCL. However, CAR T-cell therapy has a unique hematological toxicity, and post-treatment cytopenia is a major side effect[85,86].

Recent clinical trials have compared the efficacy and safety of three cell therapy modalities (autologous transplantation, allogeneic transplantation, and CAR-T with respect to their validity and rationale as therapeutic modalities[87]. In addition, there are various issues and barriers to the realization of CAR-T therapy, including complex logistics, manufacturing limitations, toxicity concerns, and economic burdens, which must be addressed and remedied[88]. The results of clinical trials on CAR-T cell therapy are summarized in Table 8.

Clinical trials of the autologous anti-CD19 CART agents axicabtagene ciloleucel (Axi-cell), tisagenlecleucel (Tisa-cell), and lisocabtagene maraleucel (Liso-cell) for r/r DLBCL containing approximately 20% transformed FL (Liso-cell) have shown high efficacy, with ORRs ranging from 52% to 82%[89-91]. Long-term follow-up has shown sustained remission in approximately 40% of the patients and high remission maintenance against r-FL[92]. The results of the Phase II ZUMA-5 trial showed that Axi-cells in r/r FL had a median follow-up of 18 mo, with an ORR of 94%, a CRR of 79%, and an estimated PFS of 66% at 18 mo, although the median PFS and OS were not reached. Grade 3 or higher adverse events were observed in 86%, with Grade-5 adverse events in 3%[93,94].

The results of the phase II ELARA trial showed an ORR of 86% and a CR of 69% after a median follow-up of 17 mo for Tisa-cell r/r FL. The results of the Phase II ELARA trial of Tisa-cell therapy for r/r FL showed an ORR of 86% and CR of 69% at a median follow-up of 17 mo[95-97]. It is important to note that the results of these trials showed that Tisa-cells had a higher sustained response in higher-risk patients with refractory, relapsed, and heavily pretreated FL[98].

Liso-cells are autologous anti-CD19 CAR-T cells. The results of a clinical trial as a second-line therapy for patients with r/r DLBCL not scheduled for hematopoietic stem cell transplantation showed high efficacy, with a median follow-up of 12.3 mo and an ORR of 80%. Grade 3 or higher adverse events ranged from 20%-48% for thrombocytopenia and 21% for serious adverse events[99]. Based on these results, Liso cells have the potential for future use in patients with r/r FL.

The TRANSFORM and PILOT trials demonstrated the high efficacy of Liso-cell in the second-line treatment of r/r large B-cell lymphoma. As a result, Liso-cell was approved as a third-line agent for aggressive B-cell lymphoma[100].

Expectations are high for the future development of CAR-T cell therapy as a fundamental therapeutic tool for FL.

**MOLECULAR RESPONSE ADAPTIVE THERAPY RESPONSE-ADOPTED POST-INDUCTION STRATEGY**

The FOLL12 study compared a standard 2-year rituximab maintain therapy arm with an experimental post-remission induction arm in patients with FL who responded to induction immunochemotherapy. In the experimental arm, post-induction treatment consisted of observation for patients with complete metabolic response (CMR) and minimal residual disease (MRD)-negative disease, four doses of rituximab for patients with CMR and MRD-positive disease until MRD-negative, and one dose of ibrutinomab tixetan for non-CMR patients, followed by three standard treatments with RM. Results showed that After a median follow-up of 53 mo, patients in the standard arm had significantly better PFS than those in the experimental arm (3-year PFS, 86% vs 72%; P < 0.001). All subgroups except non-CMR patients confirmed the superior PFS of the standard group vs the experimental group, with 3-year OS rates of 98% and 97% (95%CI, 95-99) in the reference and experimental groups, respectively[101]. In FL patients who benefited from induction therapy, standard 2-year rituximab maintenance therapy prolonged PFS after the induction of remission.

**Future prospects for nodal FL treatment**

Although FL progresses slowly and can be effective if treated, it is prone to recurrence and has been considered an incurable disease. Recently, however, research and progress in various new treatment modalities have been remarkable, and improvements in treatment outcomes have been confirmed. In addition, the direction of research is beginning to turn toward how to combine two or more of these anticancer agents, immune agents, immunomodulators, and CAR-T cell therapy, which have different mechanisms of action, and how to arrange the order of treatment in such combinations to obtain the best results. After discussing this important topic, I will conclude this section with the hope that the era of complete cure of FL will arrive in the future.

**Prospects for GI-FL treatment**

Based on an understanding of the recent advances in the treatment of nodal FL that have been discussed, the current status and future of GI-FL treatment and how gastroenterologists should treat
Table 8 Summary of clinical trials results of chimeric antigen receptor T-cell therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Target disease</th>
<th>No. of patients</th>
<th>Objective response rate</th>
<th>Complete response rate</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Adverse events and others</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene ciloleucel (Axi-cell), phase-II</td>
<td>r/r DLBCL, t-FL n = 101</td>
<td>82%</td>
<td>40%</td>
<td>Unknown</td>
<td>52% (overall survival rate at 18.8 mo)</td>
<td>Neutropenia 78%; anemia 43%; thrombocytopenia 38%</td>
<td>[90]</td>
<td></td>
</tr>
<tr>
<td>Tisagenleucel (Tisa-cell), phase-II JULIET trial</td>
<td>r/r DLBCL</td>
<td>n = 93</td>
<td>52%</td>
<td>40%</td>
<td>65% (relapse-free survival rate)</td>
<td>Unknown</td>
<td>CRS 22%; neurologic events 12%; infections 20%</td>
<td>[91]</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel (Axi-cell), phase-II</td>
<td>r/r iNHL (FL and MZL) after 2 or more treatment</td>
<td>n = 148, n = 124 (FL), n = 24 (MZL)</td>
<td>92%</td>
<td>74%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Serious adverse events (any grade) occurred in 50% of all</td>
<td>[93]</td>
</tr>
<tr>
<td>Tisagenleucel (Tisa-cell), phase-II ELARA trial</td>
<td>r/r FL (with 2 and more prior treatments)</td>
<td>n = 97</td>
<td>86.2%</td>
<td>69.1%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>CRS 48.5% (&gt; G3) neurological events 37.1% (&gt; G3)</td>
<td>[96]</td>
</tr>
<tr>
<td>Liscoabtagene maraleucel (Liso-cell), phase-II</td>
<td>r/r large BCL n = 61</td>
<td>80% (median follow-up 12.3 mo)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Neutropenia 48%, thrombocytopenia 20%, CRS 38%</td>
<td>[99]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Unknown” means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; t-FL: Transformed follicular lymphoma; iNHL: (Indolent) non-Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; BCL: B-cell lymphoma; MZL: Marginal zone lymphoma; CRS: Cytokine release syndrome.

Gastrointestinal FL in the future will be discussed.

FL is the most common low-grade lymphoma, and although nodal FL is highly responsive to treatment, the majority of patients relapse repeatedly, and the disease has been said to be incurable with a poor prognosis. In contrast, primary GI-FL has been detected and treated in a larger number of cases in Japan, especially due to recent advances in small bowel endoscopy and increased opportunities for endoscopic examinations, such as health checks, diagnostic imaging equipment, endoscopist examination techniques, and endoscopic diagnostic procedures. However, many cases are detected at an early stage, and many of them are at a later stage than those detected at an early stage, owing to the bias of reported cases, and the prognosis is excellent. Therefore, there is still a mainstream view that “watch and wait” is preferable, taking into account the adverse effects of treatment and the decline in patient quality of life. Schmatz et al[102] compared the progression of 63 stage I GI-FLs in the treatment, watch, and wait groups and reported no significant difference in PFS or OS. Tari et al[103] also reported no difference in progression in a study of GI-FL patients with low tumor volume divided between the “watch and wait” groups and the rituximab combination chemotherapy group. GI-FL is considered a potential candidate for “watch and wait” in many cases because of its pathological characteristics: The lesions are widely distributed and not amenable to local therapy, many patients are asymptomatic in the localized stage, and the degree of tumor extension and invasion is lower than that of nodal FL. The number of patients with nodal FL was high, and the degree of tumor progression and invasiveness was low. Yamamoto et al[104] have reported that 128 (66.3%) of 193 cases of GI-FL in Japan were stage I and 52 (26.9%) were stage II. The authors attribute this to the higher frequency of grade 1 lymphoma. However, we think that the reported cases may not necessarily represent the overall picture of GI-FL cases in Japan due to a large bias arising when they selected. In a Japanese multicenter study by Takata et al[105] in 125 patients with localized GI-FL, CR was observed in 61 (49%) out of 125 patients treated with Watch and Wait (33 patients), combination chemotherapy including rituximab (42 patients), rituximab alone (29 patients), surgical resection (4 patients), radiation therapy (1 patient), and Helicobacter pylori (H. pylori) eradication therapy (3 patients). pylori eradication therapy in three cases, 61 cases (49%) achieved CR, and by treatment method, 39/42 cases (93%) were treated with multi-agent chemotherapy including rituximab, 20/29 (69%) with rituximab alone, 1/4 (25%) with surgical resection, 0/1 case (0%) with radiation therapy, H. pylori eradication in 1/3 (33%), and Watch and Wait 1/33 (3%). The median follow-up was 40 mo (6-148 mo), with no primary deaths, a 5-year survival rate of 100%, a progression-free survival rate of 93 %, and very good results[105]. It should be noted that the Watch and Wait group had a CR rate of 3%, which was lower than the CR rate in the treatment group, excluding radiotherapy. Damaj et al[9] reported that most GI-FL are Stage I, but metastasis or invasion of intra-abdominal lymph nodes (Stage II) is 3.4%-40.0%, and extensive extranodal dissemination or transdiaphragmatic invasion (Stage IV) is reported in 12%-24% of GI-FL cases. The number of reports of advanced GI-FL cases (stages III and IV) is expected to increase further in the future. To understand the recent advances in the treatment of nodal FL, how should gastroenterologists treat gastrointestinal FL in the future? In early stage I cases, endoscopic resection of the gastrointestinal tract or surgical resection plus R-CHOP is the...
standard of care. The prognosis was good and the PFS and OS were excellent. The number of refractory and advanced GI-FL cases, grade 3b or higher at the cellular level, and stage II or higher are expected to increase in the future. These cases will likely be treated with the same advanced and recent therapeutic modalities for nodal FL, such as antibody-targeted therapy, bispecific antibody therapy, epigenetic mutation, and CAR T-cell therapy, as described previously. The importance of nodal and Gastrointestinal-FL treatments is expected to increase. The difference is that when GI-FL is treated, the risk of perforation of the gastrointestinal tract must always be considered because if perforation develops due to a decrease in tumor volume, subsequent peritonitis may develop, making the disease more severe, and subsequent treatment impossible to continue. After careful consideration of the risk of gastrointestinal perforation, surgical resection of the gastrointestinal lesion should be performed first, followed by adjuvant therapy. For postoperative recurrence, lymph node metastases outside the gastrointestinal tract, and other distant metastases, it is necessary to collaborate with hematology and gastrointestinal surgery departments to predict possible complications and changes in disease status due to treatment, such as in the treatment of nodal and r/r-FL, and to discuss a royal policy in collaboration with these departments. We look forward to the future development and progress of GI-FL treatment.

**Differences in treatment strategies between nodal FL and GI-FL**

Staging of nodal FL is determined using the Ann-Arbor clinical staging classification, while GI-FL is classified according to the Lugano staging classification[106], a modified version of the Ann-Arbor staging classification. Basically, the Lugano staging classification[106] should be followed to determine a treatment strategy similar to that for nodal FL. However, due to the characteristics of the gastrointestinal tract, a treatment strategy specific to gastrointestinal FL may be considered in the following cases, which differ from nodal FL.

First, and most importantly, one must be very mindful of gastrointestinal perforation due to the loss of tumor tissue associated with the mass reduction effect of treatment. Careful consideration should be given to the risk of gastrointestinal tract perforation before initiating any type of treatment.

In GI-FL cases, whether the distribution of lesions is unifocal or multifocal is important in the choice of treatment; Yamamoto et al[104] reported that in more than 70% of GI-FL patients with lesions in the gastrointestinal tract other than the small bowel, new secondary lesions were found in the small bowel. If the disease is found to be multifocal, immunochemotherapy may be the treatment of choice.

Primary FL in the gastrointestinal tract should be treated with surgical resection first, followed by postoperative chemotherpay (or combination chemotherapy and immunotherapy), depending on the extent of extension and invasion, if the lesions arise from deep submucosal layers and are localized within the wall, lumen, or regional lymph nodes. However, if the disease has invaded or spread beyond the gastrointestinal tract or has distant metastasis beyond the diaphragm, it is stage-4 according to the Lugano classification, and if there is no or little deterioration in quality of life due to gastrointestinal obstruction, local surgical resection is of course not indicated, and combination chemotherapy plus immunotherapy or immunomodulators is the chemotherapy plus immunotherapy or immunomodulators is the first choice.

In cases of extra-gastrointestinal primary disease with gastrointestinal involvement, surgical resection or radiotherapy should be considered if the disease is localized. If there are metastases in multiple organs or bone marrow, the disease is basically stage-4, and chemotherapy (plus immunotherapy) is the first choice.

In addition, other factors such as age, gender, site of disease, and extent of spread should determine the best overall treatment for each case of gastrointestinal FL that is most appropriate for the patient and that offers a better prognosis, especially longer treatment-free period and improved patient quality of life. Because gastrointestinal FL is an organ with “gastrointestinal” characteristics, the treatment strategy is often more controversial than that for nodal FL, and in a sense, the range of treatment options is wider.

In addition, the underlying nature of FL itself, which as a tumor is indolent in its extension, growth, and invasion, responds well to chemotherapy, but is prone to relapse and is currently incurable, further complicates and complicates the treatment options for gastrointestinal FL. The differences in treatment strategy between nodal FL and gastrointestinal FL are described in the author’s previous review[107], which should also be consulted.

In the future, the number of advanced-stage multifocal GI-FL cases will increase more and more, and the treatment strategy should be carefully determined by cooperating multiple physicians in each department, including gastroenterology, surgery, hematology, and radiology.

**CONCLUSION**

Treatment with Nodal-FL improved the ORR, CRR, PFS, and OS with the addition of rituximab, an anti-CD20 monoclonal antibody, to CHOP therapy, which was the standard chemotherapy regimen for malignant lymphomas 20 years ago. Maintenance therapy with an anti-CD20 antibody prolongs
remission. The last decade has seen remarkable progress with the addition of new therapeutic modalities such as antibody-targeted therapy, bispecific antibody therapy, epigenetic modulator therapy, CAR-T cell therapy, and conventional chemotherapy. The combination of lenalidomide and anti-CD20 antibodies was effective in r/r FL treatment. In contrast, lenalidomide shows good results as frontline therapy for untreated patients with advanced FL and may become a mainstay treatment modality. Antibody therapies against novel targets, such as CD19, CD79b, and CD47, as well as obinutuzumab, a humanized anti-CD20 monoclonal antibody, have been developed and have demonstrated efficacy in FL. More recently, anti-PD-L1 antibodies such as atezolizumab and pembrolizumab have also demonstrated efficacy in relapsed FL. PI3Kinase inhibitors are effective for treating FL and multiple relapsed lesions. However, the high number of adverse events associated with its toxicity complicates its future use as a combination therapy. As an epigenetic modulator treatment, tazemetostat showed more activity in r/r FL patients with higher risk characteristics. Vorinostat, a histone deacetylase inhibitor HDACi, is also a potential treatment for r/r FL patients. CAR-T cell therapy for FL and T-cell immune attack with bispecific antibodies have shown remarkable efficacy and are expected to become a fundamental therapy, as evidenced by the current approval of CAR-T cell therapy for relapsed and refractory FL in the United States. In Europe and the United States, Damaj et al. have reported that most GI-FL cases are stage I, but metastasis or invasion of intra-abdominal lymph nodes (stages II) is present in 3.4%-40.0% and extensive extranodal organ dissemination or involvement beyond the diaphragm (stage-IV) in 12%-24%. The number of advanced GI-FL cases (stages III and IV) is expected to increase further in the future. The number of refractory and advanced GI-FL cases, grade 3b or higher at the cellular level, and stage II or higher are expected to increase in the future. For these cases, recent advances in nodal FL, such as antibody-targeted therapy, bispecific antibody therapy, epigenetic mutation, and CAR-T cell therapy, as described above, should be considered as treatment options, but with careful attention to gastrointestinal perforation and cooperation among the departments of gastroenterology, hematology, and gastroenterological surgery need to work together.

FOOTNOTES

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 relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24
ciloleucel (axi-cel) in patients (pts) Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with

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CAR-T Therapy Setting: What We Know and What We Don’t?

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