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EDITORIAL

Recent advances in treatment of nodal and gastrointestinal follicular lymphoma

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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

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 gastrolienal FL cases are 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.

ANTIBODY-BASED THERAPY

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); loncastyximab 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 tesirineis (ADCT-402) is a noble antibody-drug conjugated to a cytotoxic dimer. After bindig 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 (LOTIS-2 study) of loncastaximab 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 I study of the combination of venetoclax plus obinutumab in previously untreated FL patients 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 rituximb biosimulators 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

Study	Target disease	No. of patients	Objective response rate	Complete response rate	Median progression-free survival	Overall survival	Adverse events or other subjects	Ref.
Tafasitamab plus lenalidomide phase-II L-MID	r/r DLBCL (no FL) > 35 mo follow up	*n* = 80	57.5% (*n* = 46/80)	40.0% (*n* = 32/80)	11.6 mo	33.5 mo	No unexpected toxicity	[14]
Phase-II ROMULUS, rituximab-polatuzumab *vs* rituximab-pinatuzumab	r/r FL	*n* = 42, *n* = 20, *n* = 21	70% (*n* = 14/20); 62% (*n* = 13/21)	45% (*n* = 9/20); 5% (*n* = 1/21)	Unknown	Unknown		[15]
Loncastuximab tesirine (ADTC-402) frontline therapy	Untreated FL	Total, DLBCL, MZL, FL	45.6%, 42.3%, 46.7%, 78.6%	26.7%	Unknown	Unknown	Median duration response: 5.4 mo	[16]
Magrolimab plus rituximab phase-Ib	r/r DLBCL; r/r FL	*n* = 22; DLBCL:15; FL: 7	50% (CR or PR); 40%, 71% (*n* = 5/7)	33%, 43% (*n* = 3/7)	Unknown	Unknown	90% response were on going, a median follow-up of 6.2 (DLBCL)/8.1 (FL) mo	[17]
Venetoclax plus obinutumab phase-I	Untreated FL	CT, PET/CT	87.5%, 84.2%	25.0%, 68.4%	77.8% (at one yr); 79.0% (at one yr); 73.2% (at 30 mo); 79.0% (at 30 mo)	Unknown; unknown		[19]
GALLIUM trial obinutuzumab + CTx rituximab + CTx	Untreated FL	*n* = 1202, *n* = 601, *n* = 601	88.5%, 86.9%	Unknown, unknown	80.0% (at 3 yr); 73.3% (at 3 yr)	Unknown, unknown	Obinutuzumab is better	[20, 21]

"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]. Mosnetuzumab, 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 lenaridomide; 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 abstruct.

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 Abstruct.

The results of a phase I/II trial of epcoritamab, 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 epcoritamab in combination with lenaridomide and rituximab in patients with r/r FL showed high efficacy, with an ORR of 100% and a CRR of 93%[28].

Odronextamab 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 Odronextamab 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%; Odronextamab 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. Recntly, the efficacy of the anti-PD-1 ligand (PD-L1) antibodies, atezolitumab and pembrolizumab, in FL has also attracted attention (Table 3).

Table 2 Summary of clinical trial results of bispecific T cell binding antibody therapies

Study	Target disease	No.of patients	Objective response rate	Complete response rate	Median progression-free survival	Overall survival	Adverse events or other subjects	Ref.
Mosunetuzumab alone, phase-I	r/r NHL (including FL and t-FL)	*n* = 157	66.2% (i B-NHL)	48.5% (i B-NHL)	Median duration of response 20.4 mo (i B-NHL	Unknown	G3 and higher in 71% of iNHL patients	[24]
Mosunetuzumab alone, phase-II	r/r FL (Grade 1-3a)	*n* = 90 (median follow-up was 18.3 mo)	Unknown	60% (*n* = 54/90) (14% higher than CRR with copanlisib), high efficacy	Unknown	Unknown	High efficacy	[25]
Mosunetuzumab with lenaridomide, phase-I	r/r FL	Unknown	92%	77%	Unknown	Unknown	G3 and higher in 30% of patients	In abstruct
Glofitamab alone, phase-I	r/r B-NHL (including r/r FL)	*n* = 155	65.7% (at the recommended phase-II dose)	57.1% (at the recommended phase-II dose)	Unknown	Unknown	CRS occurred in 50.3% of patients	[26]
Glofitamab alone *vs* glofitamab with obinutuzumab	r/r FL	Unknown	81%, 100%	70%, 74%	Unknown	Unknown	Combination has a better response rate	In Abstruct
Epcoritamab, phase-I/II	r/r B-NHL	*n* = 68	90% (full dose)	50% (full dose)	Unknown	Unknown	Pyrexia 69%, CRS 59%	[27]
Epcoritamab with lenaridomide and rituximab	r/r FL	Unknown	100%	93%	Unknown	Unknown	High efficacy is revealed	[28]
Odronextamab alone phase-I ELM-1 trial	r/r B-NHL (including r/r FL)	*n* = 145	91% (r/r FL)	72% (r/r FL)	Unknown	Unknown	CRS 28%	[29]

"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

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

"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

Lenaridomide is a typical oral immunomodulatory drug (IMiD) used to treat FL. Lenaridomide is a derivative of thalidomide with a similar structure. Lenaridomide 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[33]. The combination of lenaridomide 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 lenaridomide was administered.

A phase II study comparing lenaridomide alone with R2 (lenaridomide 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[34].

The results of the phase III AUGMENT study evaluating R2 (lenaridomide 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[35].

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[36].

In a single-arm phase II GALEN trial of patients with r/r FL, Obinutuzumab and lenaridomide were studied[37]. The patients received lenaridomide and obinutuzumab for 18 mo, followed by 1 year of obinutuzumab maintenance therapy[37]. 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 lenaridomide, 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[38]. Patients were randomized to receive 18 cycles of R2 therapy plus 6 cycles of rituximab maintenance therapy or a chemoimmunotherapy 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 chemoimmunotherapy in the front-line treatment of FL has been demonstrated [38].

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 boltezomib plus rituximab maintenance, and compared the efficacy among the three groups[39]. 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 lenaridomide 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[40]. In the future, the combination of lenalidomide and CD20 antibodies is expected to be the mainstay of front-line therapy for FL.

With the introduction of bendamustine, obinutuzumab, and 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[41].

With lenaridomide, 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 CONPOUNDS)

Bruton's tyrosine kinase inhibitor

Bruton'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

Study	Target disease	No.of patients	Objective response rate	Complete response rate	Progression-free survival	Overall survival	Adverse events or other subjects	Ref.
Randomized phase-II; lenaridomide alone (L) lenaridomide + rituximab (LR)	r/r FL	*n* = 91, *n* = 45 (L); *n* = 46 (LR)	53%, 76%	20%, 39%	Median time to progression: 1.1 yr (at 2.5 yr); 2.0 yr (at 2.5 yr)	Unknown		[34]
Phase-III AUGMENT lenaridomide + R (R2) *vs* lenaridomide + placebo	r/r FL; r/r MZL	*n* = 358; *n* = 180; *n* = 178	Unknown	Unknown	Median duration: 39.4 mo; 14.1 mo	Unknown	Grade 3 neutropenia of R2 is higher than L	[35]
Phase-IIIb MAGNIFY trial; R maintain after R2 additional lenarimide + rituximab (R2) 18 mo after R2	r/r FL; r/r MZL	*n* = 393	69% (R2)	40% (R2)	40 mo (similar to AUGMENT trial)	Unknown		[36]
Phase-II GALEN study; lenarimide + obinutuzumab (R2) 18 mo followed by obinutuzumab alone maintenance therapy 1 year	r/r FL	*n* = 68; evaluable	95% (at 2.6 yr)	38% (*n* = 33/86)	65% (at 2 yr)	87% (at 2 yr); 81% (*n* = 70/86); 84% (*n* = 72/86)		[37]
Phase-III RELEVANCE study, lenaridomide + rituximab (R2) + Rituximab maintenance therapy *vs* CTx (R-CHOP, BR, or R-CVP)	Untreated advanced FL	*n* = 1030; R-maintenance, *n* = 513; CTx, *n* = 517	Unknown	48%-53%, about the same	3 years-PFS 77%-78%, almost equal to superiority of R2 in F2 frontline not proven	Unknown		[38]
	Untreated advanced FL		Unknown	All 3 groups approximately 90%, about the same	3 yr PFS (5 yr median follow-up); -R 77%, BVR-R 82%, BR-LR 76% (higher in the R-maintenance group than in the R2 group) because of more discontinuations in the R2 group)	3 yr PFS (5 yr median follow-up), BR-R 87%, BVR-R 90%, BR-LR 84%		[39]
Single center phase-II frontline therapy; lenaridomide plus obinutuzumab	Untreated advanced FL	*n* = 90	98% (after a median follow-up of 22 mo)	92% (after a median follow-up of 22 mo)	2 yr-PFS 96 (after a median follow-up of 22 mo)	Unknown		[40]

"Unknown" means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; MZL: Marginal zone lymphoma; L: Lenaridomide; R: Rituximab; LR: Lenaridomide plus rituximab; R2: Lenaridomide 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.

of BTKi treatments for FL are listed in Table 5.

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 zanurutinib 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]. Zanurutinib 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

Study	Target disease	No. of patients	Objective response rate	Complete response rate	Progression-free survival	Overall survival	Adverse events or others	Ref.
Zanubrutinib (other BTKi) alone	r/r FL		36.4%	18.2%	Median PFS 10.4 mo (median follow-up 33.9 mo)	Unknown		[42]
Zanubrutinib phase-II	r/r MCL	83.7%	77.9%	Unknown	33.0 mo	Unknown		[43]
	r/r FL	n = 100	21.0% (poor)	Unknown	Unknown	Unknown		[47]
Ibrutinib with rituximab phase-II trial	Untreated FL, r/r FL	n = 13, n = 27	85% (arm-1), 75% (arm-2)	Unknown	62% of untreated FL, 26% of r/r FL, continued treatment	Unknown		[48]

"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 Obinutuzumab[50].

Although the single-agent activity of BTKis 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 ibrutinib was tested in a phase I/II study of venetolax plus ibrutinib 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 ideralisib, 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

Study	Targeted disease	No. of patients	Objective response rate	Complete response rate	Progression-free survival	Overall survival	Adverse events or others	Ref.
Tazemetostat alone, phase-II	r/r FL, EZH2-mut; FL, EZH2-wt. FL	*n* = 99, mut FL *n* = 45; wt FL *n* = 54	69% (EZH2 mut); 35% (EZH2 wt)	Unknown; unknown	Median PFS: 13.8 mo (EZH2 mut); 13.1 mo (EZH2 wt)	Unknown	G3 or higher 27%+, treatment discontinued at 8%	[54]
Tazemetostat (first EZH2 inhibitor) *vs* inderalisib, duvelisib, copanlishib, umbralisib	r/r FL, systematic literature review		Tazemetostat *vs* inderalisib 43% *vs* 56; duvelisib 48% *vs* 47; Kopanlisib 49% *vs* 61; umbralisib 57% *vs* 47; no significant difference in either case	Unknown	Unknown	Unknown	Predominantly reduced risk of adverse events compared to PI3Ki	[57]
Vorinostat (HDACi), phase-II	r/r Inhl + MCL, median with one or more prior treatment	*n* = 39 (r/r FL)	49%	Unknown	Median PFS, 20 mo	Unknown	G3 or higher 8%	[58]
Vorinostat + rituximab, phase-II	Untreated and r/r FL (4 or less prior treatment)	*n* = 22	46% (all patients); 67% (untreated pts); 41% (r/r FL)	Unknown	Median PFS, 29.2 mo (all patients); not reached (untreated pts); 18.8 mo (r/r FL)	Unknown		[59]
Mocetinostat, phase-II	r/r DLBCL, r/r FL	*n* = 41, *n* = 31	18.9% (r/r DLBCL), 11.5% (r/r FL)	Unknown	1.8-22.8 mo (DLBCL); 11.8-26.3 mo (FL)	Unknown	Fatigue (75.0%); nausea (69.4%); diarrhea (61.1%)	[60]

"Unknown" means data not shown, unknown information or not reached. r/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 r/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[58]. 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 r/r FL patients[59]. Another HDACi, mocetinostat, 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 r/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 kinaseb (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, ϒ, 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 r/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 r/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 r/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 r/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

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

"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; (i)NHL: (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 conpalisib has been approved for r/r FL after more than two lines of therapy. The phase II CHRONOS-1 study[70,71] of copanlisib 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 84%, 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

median PFS of 10.6 mo in a cohort of patients with FL after a median follow-up period of 27 mo[74]. Most recently, a phase II trial of Frontline with umbralisib and ubrituximab in untreated advanced FL patients was completed in Florida, the United States.

Parsaclisib is a potent δ isoform of the PI3Ki. The results of CITADEL-111, a phase Ib study in Japanese patients with relapsed/refractory B-cell lymphoma, showed an ORR of 100% in r/r FL and CR in two patients (22.2%), indicating efficacy. The results for MZL and DLBCL are shown in Table 7. Although potent, adverse events were frequent, requiring careful patient selection and implementation [75]. The Phase I/II trial of parsaclisib in patients with r/r FL showed an ORR of 71%. Grade 3 or higher adverse events were observed in 19% of all participants, and phase II trial is ongoing[76].

Zandelisib (ME-401) is a novel PI3-Kδ inhibitor, and phase I trials have recently been reported in Japanese patients with r/r iNHL. ORR was 100% and CR was 22% in 9 Japanese patients with r/r iNHL, and the median duration of response, progression-free survival, and time to response were 7.9 mo, 11.1 mo, and 1.9 mo, respectively. Neutropenia was the most common adverse event, with 55.6% (6/9) of the patients having neutropenia, and thrombocytopenia was the most common adverse event. In Japanese patients with r/r iNHL, zandelisib showed good antitumor efficacy[77]. The results of a study comparing zandelisib monotherapy with zandelisib plus rituximab combination therapy for r/r FL showed an ORR of 92% in the 60 mg group and 83% in the 180 mg group. Serious adverse events occurred in 21% and 8% of patients in the continuous- and intermittent-dose groups, respectively. There were no treatment-related deaths. The 60 mg once-daily intermittent dose was safe, with a low incidence of grade 3 or higher adverse events[78].

PI3Ki has also been considered in combination with conventional chemotherapy, immunotherapy, and other targeted therapies to achieve more potent therapeutic effects. Results of the phase III CHRONOS-4 trial comparing the efficacy and safety of Conpalisib in combination with BR or R-CHOP in patients with r/riNHL showed an ORR of 90% in the BR group and 100% in the R-CHOP group, with grade 3 or higher adverse events occurring in 70% of the BR group and 91% of the R-CHOP group[79]. Early clinical trials of PI3Ki in combination with other immune checkpoint inhibitors and IMiDs are currently underway.

Inderalisib-induced acute liver injury has also been reported and has been noted to be severe and potentially fatal[80]. In a phase I trial in patients with FL or MCL, the triple combination of inderalisib with lenaridomide and rituximab was discontinued early because of the excessive toxicity of all three drugs[81]. Combination therapy with other drugs, including inderalisib, is complicated for future treatment because of significant safety concerns owing to overtoxicity.

PI3K inhibitors were initially expected to have therapeutic effects, and various types of agents were developed, but due to the large number of adverse reactions, only zandelisib remains in Japan, for example, and clinical trials are continuing. We hope that the treatment effect for FL patients will improve in the future.

PI3K/mechanistic target of rapamycin inhibitor

Numerous studies have shown that somatic mutations in PI3K/Akt/mechanistic target of rapamycin (mTOR)-related genes may induce homeostatic activation of various types of cancer pathways, leading to dysregulation of tumor cell growth, growth, differentiation, metabolism, apoptosis, and other functions supporting tumor cell survival It has been shown[82].

Recently, dual inhibitors targeting two targets of the PI3K/PKB/mTOR signaling pathway have been developed and investigated for their therapeutic effects; PI3K/mTOR inhibitors not only inhibit cell proliferation but also promote cell apoptosis. They are also expected to be promising anticancer agents because of their high efficacy at low doses and low drug resistance[83].

The TOR inhibitors, temisirolimusm (TEM) and lenaridomide (LEN) combination therapy, overlapped within the PAM axis and were expected to have synergistic effects. the FL cohort was discontinued early due to low case numbers. the ORR and CRR of the DLBCL and exploratory cohorts were 26% and 13%, 64% and 18%, respectively. The ORR and CRR of the exploratory cohort for classical Hodgkin lymphoma (CHL) patients were 80% and 35%, respectively. Forty percent of CHL patients could be transferred to allogeneic transplant after TEM/LEN therapy. Grade 3 or higher hematologic adverse events were common, and three grade 5 adverse events occurred; TEM/LEN combination therapy was highly effective in advanced untreated lymphomas and especially in r/r CHL[84].

We look forward to the further development of new PI3K/Akt/mTOR dual inhibitors, and to the improvement of therapeutic results and progress as FL treatment agents through the accumulation of clinical trials.

CELL THERAPY

CAR-T cell therapy uses autologous T cells genetically engineered to attack cancer and other cells by introducing CARs.

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 remedy[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 t-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 aggresive 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 ibritumomab 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

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

"Unknown" means data not shown, unknown information or not reached. r/r: Refractory and relapsed; FL: Follicular lymphoma; t-FL: Transformed follicular lymphoma; (i)NHL: (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 checkups, 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 prognosis 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 chemotherapy (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 lenaridomide and anti-CD20 antibodies was effective in r/r FL treatment. In contrast, lenaridomide 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 obinutumab, a humanized anti-CD20 monoclonal antibody, have been developed and have demonstrated efficacy in FL. More recently, anti-PD-L1 antibodies such as atezolitumab 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*[9] have reported that most GI-FL cases are stage I, but metastasis or invasion of intra-abdominal lymph nodes (stage-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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REFERENCES

1 The world health organization classification of malignant lymphomas in japan: incidence of recently recognized entities. Lymphoma Study Group of Japanese Pathologists. *Pathol Int* 2000; **50**: 696-702 [PMID: 11012982 DOI: 10.1046/j.1440-1827.2000.01108.x]

2 **Jaffe ES**, Harris NL, Stein H, Vardiman J. World Health Organization Classification of Tumors: Tumors of the Hematopoietic and Lymphoid Tissues. 2001. [cited 20 April 2023]. Avaliable from: https://tumourclassification.iarc.who.int/welcome/

3 **Chihara D**, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, Tomotaka S, Morton LM, Weisenburger DD, Matsuo K. Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br J Haematol* 2014; **164**: 536-545 [PMID: 24245986 DOI: 10.1111/bjh.12659]

4 **d'Amore F**, Christensen BE, Brincker H, Pedersen NT, Thorling K, Hastrup J, Pedersen M, Jensen MK, Johansen P, Andersen E. Clinicopathological features and prognostic factors in extranodal non-Hodgkin lymphomas. Danish LYFO Study Group. *Eur J Cancer* 1991; **27**: 1201-1208 [PMID: 1835586 DOI: 10.1016/0277-5379(91)90081-n]

5 **Cirillo M**, Federico M, Curci G, Tamborrino E, Piccinini L, Silingardi V. Primary gastrointestinal lymphoma: a clinicopathological study of 58 cases. *Haematologica* 1992; **77**: 156-161 [PMID: 1398301]

6 **Yoshino T**, Miyake K, Ichimura K, Mannami T, Ohara N, Hamazaki S, Akagi T. Increased incidence of follicular lymphoma in the duodenum. *Am J Surg Pathol* 2000; **24**: 688-693 [PMID: 10800987 DOI:

10.1097/00000478-200005000-00007]
7 **Lewin KJ**, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. *Cancer* 1978; **42**: 693-707 [PMID: 354774 DOI: 10.1002/1097-0142(197808)42:2<693::aid-cncr2820420241>3.0.co;2-j]
8 **Filippa DA**, Lieberman PH, Weingrad DN, Decosse JJ, Bretsky SS. Primary lymphomas of the gastrointestinal tract. Analysis of prognostic factors with emphasis on histological type. *Am J Surg Pathol* 1983; **7**: 363-372 [PMID: 6869665 DOI: 10.1097/00000478-198306000-00008]
9 **Damaj G**, Verkarre V, Delmer A, Solal-Celigny P, Yakoub-Agha I, Cellier C, Maurschhauser F, Bouabdallah R, Leblond V, Lefrère F, Bouscary D, Audouin J, Coiffier B, Varet B, Molina T, Brousse N, Hermine O. Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review. *Ann Oncol* 2003; **14**: 623-629 [PMID: 12649111 DOI: 10.1093/annonc/mdg168]
10 **Hiddemann W**, Buske C, Dreyling M, Weigert O, Lenz G, Forstpointner R, Nickenig C, Unterhalt M. Treatment strategies in follicular lymphomas: current status and future perspectives. *J Clin Oncol* 2005; **23**: 6394-6399 [PMID: 16155025 DOI: 10.1200/JCO.2005.07.019]
11 **Conconi A**, Lobetti-Bodoni C, Montoto S, Lopez-Guillermo A, Coutinho R, Matthews J, Franceschetti S, Bertoni F, Moccia A, Rancoita PM, Gribben J, Cavalli F, Gaidano G, Lister TA, Montserrat E, Ghielmini M, Zucca E. Life expectancy of young adults with follicular lymphoma. *Ann Oncol* 2015; **26**: 2317-2322 [PMID: 26362567 DOI: 10.1093/annonc/mdv376]
12 **Ghielmini M**, Schmitz SF, Cogliatti SB, Pichert G, Hummerjohann J, Waltzer U, Fey MF, Betticher DC, Martinelli G, Peccatori F, Hess U, Zucca E, Stupp R, Kovacsovics T, Helg C, Lohri A, Bargetzi M, Vorobiof D, Cerny T. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood* 2004; **103**: 4416-4423 [PMID: 14976046 DOI: 10.1182/blood-2003-10-3411]
13 **Hiddemann W**, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, Reiser M, Metzner B, Harder H, Hegewisch-Becker S, Fischer T, Kropff M, Reis HE, Freund M, Wörmann B, Fuchs R, Planker M, Schimke J, Eimermacher H, Trümper L, Aldaoud A, Parwaresch R, Unterhalt M. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; **106**: 3725-3732 [PMID: 16123223 DOI: 10.1182/blood-2005-01-0016]
14 **Duell J**, Maddocks KJ, González-Barca E, Jurczak W, Liberati AM, De Vos S, Nagy Z, Obr A, Gaidano G, Abrisqueta P, Kalakonda N, André M, Dreyling M, Menne T, Tournilhac O, Augustin M, Rosenwald A, Dirnberger-Hertweck M, Weirather J, Ambarkhane S, Salles G. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. *Haematologica* 2021; **106**: 2417-2426 [PMID: 34196165 DOI: 10.3324/haematol.2020.275958]
15 **Morschhauser F**, Flinn IW, Advani R, Sehn LH, Diefenbach C, Kolibaba K, Press OW, Salles G, Tilly H, Chen AI, Assouline S, Cheson BD, Dreyling M, Hagenbeek A, Zinzani PL, Jones S, Cheng J, Lu D, Penuel E, Hirata J, Wenger M, Chu YW, Sharman J. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). *Lancet Haematol* 2019; **6**: e254-e265 [PMID: 30935953 DOI: 10.1016/S2352-3026(19)30026-2]
16 **Hamadani M**, Radford J, Carlo-Stella C, Caimi PF, Reid E, O'Connor OA, Feingold JM, Ardeshna KM, Townsend W, Solh M, Heffner LT, Ungar D, Wang L, Boni J, Havenith K, Qin Y, Kahl BS. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. *Blood* 2021; **137**: 2634-2645 [PMID: 33211842 DOI: 10.1182/blood.2020007512]
17 **Advani R**, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, Kline J, Roschewski M, LaCasce A, Collins GP, Tran T, Lynn J, Chen JY, Volkmer JP, Agoram B, Huang J, Majeti R, Weissman IL, Takimoto CH, Chao MP, Smith SM. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. *N Engl J Med* 2018; **379**: 1711-1721 [PMID: 30380386 DOI: 10.1056/NEJMoa1807315]
18 **Davies A**, Kater AP, Sharman JP, Stilgenbauer S, Vitolo U, Klein C, Parreira J, Salles G. Obinutuzumab in the treatment of B-cell malignancies: a comprehensive review. *Future Oncol* 2022; **18**: 2943-2966 [PMID: 35856239 DOI: 10.2217/fon-2022-0112]
19 **Stathis A**, Mey U, Schär S, Hitz F, Pott C, Mach N, Krasniqi F, Novak U, Schmidt C, Hohloch K, Kienle DL, Hess D, Moccia AA, Unterhalt M, Eckhardt K, Hayoz S, Forestieri G, Rossi D, Dirnhofer S, Ceriani L, Sartori G, Bertoni F, Buske C, Zucca E, Hiddemann W. SAKK 35/15: a phase 1 trial of obinutuzumab in combination with venetoclax in patients with previously untreated follicular lymphoma. *Blood Adv* 2022; **6**: 3911-3920 [PMID: 35537101 DOI: 10.1182/bloodadvances.2021006520]
20 **Marcus R**, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med* 2017; **377**: 1331-1344 [PMID: 28976863 DOI: 10.1056/NEJMoa1614598]
21 **Casulo C**, Herold M, Hiddemann W, Iyengar S, Marcus RE, Seymour JF, Launonen A, Knapp A, Nielsen TG, Mir F. Risk Factors for and Outcomes of Follicular Lymphoma Histological Transformation at First Progression in the GALLIUM Study. *Clin Lymphoma Myeloma Leuk* 2023; **23**: 40-48 [PMID: 36379880 DOI: 10.1016/j.clml.2022.09.003]
22 **Gmoshinskiĭ IV**, Mazo VK, Shaternikov VA. [Breakdown of the soluble soybean antigen in the digestive tract of adult rats]. *Vopr Pitan* 1986; 43-46 [PMID: 3532538]
23 **Yang L**, Zheng Z, Li N, Zheng B, Liu M, Cai H. Efficacy and safety of rituximab biosimilars or reference product as first-line treatment in patients with low-tumour-burden follicular lymphoma: A systematic review and meta-analysis. *J Clin Pharm Ther* 2022; **47**: 1923-1931 [PMID: 36345167 DOI: 10.1111/jcpt.13799]
24 **Budde LE**, Assouline S, Sehn LH, Schuster SJ, Yoon SS, Yoon DH, Matasar MJ, Bosch F, Kim WS, Nastoupil LJ, Flinn

IW, Shadman M, Diefenbach C, O'Hear C, Huang H, Kwan A, Li CC, Piccione EC, Wei MC, Yin S, Bartlett NL. Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study. *J Clin Oncol* 2022; **40**: 481-491 [PMID: 34914545 DOI: 10.1200/JCO.21.00931]

25 **Budde LE**, Sehn LH, Matasar M, Schuster SJ, Assouline S, Giri P, Kuruvilla J, Canales M, Dietrich S, Fay K, Ku M, Nastoupil L, Cheah CY, Wei MC, Yin S, Li CC, Huang H, Kwan A, Penuel E, Bartlett NL. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol* 2022; **23**: 1055-1065 [PMID: 35803286 DOI: 10.1016/S1470-2045(22)00335-7]

26 **Hutchings M**, Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, Salles G, Martínez-Lopez J, Crump M, Thomas DN, Morcos PN, Ferlini C, Bröske AE, Belousov A, Bacac M, Dimier N, Carlile DJ, Lundberg L, Perez-Callejo D, Umaña P, Moore T, Weisser M, Dickinson MJ. Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell-Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial. *J Clin Oncol* 2021; **39**: 1959-1970 [PMID: 33739857 DOI: 10.1200/JCO.20.03175]

27 **Hutchings M**, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, Lewis DJ, Sureda Balari A, Cunningham D, Oliveri RS, Elliott B, DeMarco D, Azaryan A, Chiu C, Li T, Chen KM, Ahmadi T, Lugtenburg PJ. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet* 2021; **398**: 1157-1169 [PMID: 34508654 DOI: 10.1016/S0140-6736(21)00889-8]

28 **Falchi L**, Lepp¨ AS, Wahlin BE, Nijland M, Christensen JH, De Vos S, Holte H, Linton KM, Abbas A, Wang LW, Dinh M, Elliott B, Belada D. Subcutaneous epcoritamab with rituximab + lenalidomide (R2) in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): Update from a phase 1/2 trial. *J Clin Oncol* 2022; **40** Suppl 16: 7524 [DOI: 10.1200/jco.2022.40.16_suppl.7524]

29 **Bannerji R**, Arnason JE, Advani RH, Brown JR, Allan JN, Ansell SM, Barnes JA, O'Brien SM, Chávez JC, Duell J, Rosenwald A, Crombie JL, Ufkin M, Li J, Zhu M, Ambati SR, Chaudhry A, Lowy I, Topp MS. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. *Lancet Haematol* 2022; **9**: e327-e339 [PMID: 35366963 DOI: 10.1016/S2352-3026(22)00072-2]

30 **Dickinson M**. Challenges in the development of bispecific antibodies for non-Hodgkin lymphoma. *Lancet Haematol* 2022; **9**: e314-e315 [PMID: 35366964 DOI: 10.1016/S2352-3026(22)00104-1]

31 **Palomba ML**, Till BG, Park SI, Morschhauser F, Cartron G, Marks R, Shivhare M, Hong WJ, Raval A, Chang AC, Penuel E, Popplewell LL. Combination of Atezolizumab and Obinutuzumab in Patients with Relapsed/Refractory Follicular Lymphoma and Diffuse Large B-Cell Lymphoma: Results from a Phase 1b Study. *Clin Lymphoma Myeloma Leuk* 2022; **22**: e443-e451 [PMID: 35031227 DOI: 10.1016/j.clml.2021.12.010]

32 **Nastoupil LJ**, Chin CK, Westin JR, Fowler NH, Samaniego F, Cheng X, Ma MCJ, Wang Z, Chu F, Dsouza L, Obi C, Mims J, Feng L, Zhou S, Green M, Davis RE, Neelapu SS. Safety and activity of pembrolizumab in combination with rituximab in relapsed or refractory follicular lymphoma. *Blood Adv* 2022; **6**: 1143-1151 [PMID: 35015819 DOI: 10.1182/bloodadvances.2021006240]

33 **Gandhi AK**, Kang J, Havens CG, Conklin T, Ning Y, Wu L, Ito T, Ando H, Waldman MF, Thakurta A, Klippel A, Handa H, Daniel TO, Schafer PH, Chopra R. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos *via* modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). *Br J Haematol* 2014; **164**: 811-821 [PMID: 24328678 DOI: 10.1111/bjh.12708]

34 **Leonard JP**, Jung SH, Johnson J, Pitcher BN, Bartlett NL, Blum KA, Czuczman M, Giguere JK, Cheson BD. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). *J Clin Oncol* 2015; **33**: 3635-3640 [PMID: 26304886 DOI: 10.1200/JCO.2014.59.9258]

35 **Leonard JP**, Trneny M, Izutsu K, Fowler NH, Hong X, Zhu J, Zhang H, Offner F, Scheliga A, Nowakowski GS, Pinto A, Re F, Fogliatto LM, Scheinberg P, Flinn IW, Moreira C, Cabeçadas J, Liu D, Kalambakas S, Fustier P, Wu C, Gribben JG; AUGMENT Trial Investigators. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2019; **37**: 1188-1199 [PMID: 30897038 DOI: 10.1200/JCO.19.00010]

36 **Coleman M**, Andorsky DJ, Yacoub A, Melear JM, Fanning SR, Kolibaba KS, Jason M, Lansigan F, Reynolds CM, Nowakowski GS, Gharibo M, Ahn E, Li J, Rummel MJ, Sharman JP. Patients with relapsed/refractory marginal zone lymphoma in the MAGNIFY phase IIIb interim analysis of induction R2 followed by maintenance. *Blood* 2020; **136** Suppl 1: 24-25 [DOI: 10.1016/j.htct.2021.10.167]

37 **Morschhauser F**, Le Gouill S, Feugier P, Bailly S, Nicolas-Virelizier E, Bijou F, Salles GA, Tilly H, Fruchart C, Van Eygen K, Snauwaert S, Bonnet C, Haioun C, Thieblemont C, Bouabdallah R, Wu KL, Canioni D, Meignin V, Cartron G, Houot R. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. *Lancet Haematol* 2019; **6**: e429-e437 [PMID: 31296423 DOI: 10.1016/S2352-3026(19)30089-4]

38 **Morschhauser F**, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, Fruchart C, Libby EN, Casasnovas RO, Flinn IW, Haioun C, Maisonneuve H, Ysebaert L, Bartlett NL, Bouabdallah K, Brice P, Ribrag V, Daguindau N, Le Gouill S, Pica GM, Martin Garcia-Sancho A, López-Guillermo A, Larouche JF, Ando K, Gomes da Silva M, André M, Zachée P, Sehn LH, Tobinai K, Cartron G, Liu D, Wang J, Xerri L, Salles GA; RELEVANCE Trial Investigators. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. *N Engl J Med* 2018; **379**: 934-947 [PMID: 30184451 DOI: 10.1056/NEJMoa1805104]

39 **Evens AM**, Hong F, Habermann TM, Advani RH, Gascoyne RD, Witzig TE, Quon A, Ranheim EA, Ansell SM, Cheema PS, Dy PA, O'Brien TE, Winter JN, Cescon TP, Chang JE, Kahl BS. A Three-Arm Randomized Phase II Study of Bendamustine/Rituximab with Bortezomib Induction or Lenalidomide Continuation in Untreated Follicular Lymphoma: ECOG-ACRIN E2408. *Clin Cancer Res* 2020; **26**: 4468-4477 [PMID: 32532790 DOI: 10.1158/1078-0432.CCR-20-1345]

40 **Nastoupil LJ**, Westin JR, Hagemeister FB, Lee HJ, Fayad L, Samaniego F, Ahmed S, Claret L, Steiner RE, Nair R, Parmar S, Rodriguez MA, Wang ML, Green MR, Neelapu SS, Fowler NH. Results of a Phase II study of obinutuzumab in

combination with lenalidomide in previously untreated, high tumor burden follicular lymphoma (FL). *Blood* 2019; **134** Suppl 1: 125 [DOI: 10.1182/blood-2019-129422]

41 **Wang Y**, Zhou S, Qi X, Yang F, Maurer MJ, Habermann TM, Witzig TE, Wang ML, Nowakowski GS. Efficacy of front-line immunochemotherapy for follicular lymphoma: a network meta-analysis of randomized controlled trials. *Blood Cancer J* 2022; **12**: 1 [PMID: 34987165 DOI: 10.1038/s41408-021-00598-x]

42 **Phillips T**, Chan H, Tam CS, Tedeschi A, Johnston P, Oh SY, Opat S, Eom HS, Allewelt H, Stern JC, Tan Z, Novotny W, Huang J, Trotman J. Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma. *Blood Adv* 2022; **6**: 3472-3479 [PMID: 35390135 DOI: 10.1182/bloodadvances.2021006083]

43 **Song Y**, Zhou K, Zou D, Zhou J, Hu J, Yang H, Zhang H, Ji J, Xu W, Jin J, Lv F, Feng R, Gao S, Guo H, Zhou L, Huang J, Novotny W, Kim P, Yu Y, Wu B, Zhu J. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. *Blood* 2022; **139**: 3148-3158 [PMID: 35303070 DOI: 10.1182/blood.2021014162]

44 **Byrd JC**, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S, Barr PM, Furman RR, Kipps TJ, Cymbalista F, Pocock C, Thornton P, Caligaris-Cappio F, Robak T, Delgado J, Schuster SJ, Montillo M, Schuh A, de Vos S, Gill D, Bloor A, Dearden C, Moreno C, Jones JJ, Chu AD, Fardis M, McGreivy J, Clow F, James DF, Hillmen P; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; **371**: 213-223 [PMID: 24881631 DOI: 10.1056/NEJMoa1400376]

45 **Sharman JP**, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, Kamdar M, Munir T, Walewska R, Corbett G, Fogliatto LM, Herishanu Y, Banerji V, Coutre S, Follows G, Walker P, Karlsson K, Ghia P, Janssens A, Cymbalista F, Woyach JA, Salles G, Wierda WG, Izumi R, Munugalavadla V, Patel P, Wang MH, Wong S, Byrd JC. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020; **395**: 1278-1291 [PMID: 32305093 DOI: 10.1016/S0140-6736(20)30262-2]

46 **Mato AR**, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, Fakhri B, Eyre TA, Lamanna N, Patel MR, Alencar A, Lech-Maranda E, Wierda WG, Coombs CC, Gerson JN, Ghia P, Le Gouill S, Lewis DJ, Sundaram S, Cohen JB, Flinn IW, Tam CS, Barve MA, Kuss B, Taylor J, Abdel-Wahab O, Schuster SJ, Palomba ML, Lewis KL, Roeker LE, Davids MS, Tan XN, Fenske TS, Wallin J, Tsai DE, Ku NC, Zhu E, Chen J, Yin M, Nair B, Ebata K, Marella N, Brown JR, Wang M. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet* 2021; **397**: 892-901 [PMID: 33676628 DOI: 10.1016/S0140-6736(21)00224-5]

47 **Gopal AK**, Schuster SJ, Fowler NH, Trotman J, Hess G, Hou JZ, Yacoub A, Lill M, Martin P, Vitolo U, Spencer A, Radford J, Jurczak W, Morton J, Caballero D, Deshpande S, Gartenberg GJ, Wang SS, Damle RN, Schaffer M, Balasubramanian S, Vermeulen J, Cheson BD, Salles G. Ibrutinib as Treatment for Patients With Relapsed/Refractory Follicular Lymphoma: Results From the Open-Label, Multicenter, Phase II DAWN Study. *J Clin Oncol* 2018; **36**: 2405-2412 [PMID: 29851546 DOI: 10.1200/JCO.2017.76.8853]

48 **Fowler NH**, Nastoupil L, De Vos S, Knapp M, Flinn IW, Chen R, Advani RH, Bhatia S, Martin P, Mena R, Davis RE, Neelapu SS, Eckert K, Ping J, Co M, Beaupre DM, Neuenburg JK, Palomba ML. The combination of ibrutinib and rituximab demonstrates activity in first-line follicular lymphoma. *Br J Haematol* 2020; **189**: 650-660 [PMID: 32180219 DOI: 10.1111/bjh.16424]

49 **Fowler NH**, Coleman M, Stevens DA, Smith SM, Venugopal P, Martin P, Phillips TJ, Agajanian R, Stephens DM, Izumi R, Cheung J, Slatter JG, Yin M, Hiremath M, Hunder NNH. Acalabrutinib alone or in combination with rituximab (R) in follicular lymphoma (FL). *J Clin Oncol* 2018; **36** Suppl 15: 7549

50 **Zinzani PL**, Mayer J, Auer R, Bijou F, de Oliverira AC, Flowers C, Merli M, Bouabdallah K, Ganly PS, Johnson R, Yuen S, Kingsley E, Tumyan G, Assouline SE, Ivanova E, Kim P, Huang J, Delarue R, Trotman J. Zanubrutinib plus Obinutuzumab (ZO) vs Obinutuzumab (O) monotherapy in patients (pts) with relapsed or refractory (R/R) follicular ltmphoma (FL): Primary analysis of the phase 2 randomized ROSEWOOD trial. *J Clin Oncol* 2022; **40** Suppl 16: 7510 [DOI: 10.1200/jco.2022.40.16_suppl.7510]

51 **Parikh A**, Gopalakrishnan S, Freise KJ, Verdugo ME, Menon RM, Mensing S, Salem AH. Exposure-response evaluations of venetoclax efficacy and safety in patients with non-Hodgkin lymphoma. *Leuk Lymphoma* 2018; **59**: 871-879 [PMID: 28797193 DOI: 10.1080/10428194.2017.1361024]

52 **Zinzani PL**, Flinn IW, Yuen SLS, Topp MS, Rusconi C, Fleury I, Le Dû K, Arthur C, Pro B, Gritti G, Crump M, Petrich A, Samineni D, Sinha A, Punnoose EA, Szafer-Glusman E, Spielewoy N, Mobasher M, Humphrey K, Kornacker M, Hiddemann W. Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma. *Blood* 2020; **136**: 2628-2637 [PMID: 32785666 DOI: 10.1182/blood.2020005588]

53 **Ujjani CS**, Lai C, Leslie LA, Ramzi P, Tan M, Wang S, Wang HK, Shim E, Swanson N, Broome CM, Gopal AK, Smith SD, Warren EH, Blue K, Kdiry S, Till BG, Lynch RC, Shadman M, Johnson M, Coye H, Shelby M, Tseng YD, Shustov A, Maloney DG, Cheson BD. Ibrutinib and venetoclax in relapsed and refractory follicular lymphoma. *Blood* 2020; **136** Suppl 1: 46-47 [DOI: 10.1182/blood-2020-136219]

54 **Morschhauser F**, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, Batlevi CL, Campbell P, Ribrag V, Damaj GL, Dickinson M, Jurczak W, Kazmierczak M, Opat S, Radford J, Schmitt A, Yang J, Whalen J, Agarwal S, Adib D, Salles G. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2020; **21**: 1433-1442 [PMID: 33035457 DOI: 10.1016/S1470-2045(20)30441-1]

55 **Chung C**. A Promising Future for Precision Epigenetic Therapy for Follicular and Diffuse Large B-Cell Lymphoma? *Blood Lymphat Cancer* 2022; **12**: 99-106 [PMID: 35959380 DOI: 10.2147/BLCTT.S282247]

56 **Barghout SH**, Machado RAC, Barsyte-Lovejoy D. Chemical biology and pharmacology of histone lysine methylation inhibitors. *Biochim Biophys Acta Gene Regul Mech* 2022; **1865**: 194840 [PMID: 35753676 DOI: 10.1016/j.bbagrm.2022.194840]

57 **Proudman D**, Nellesen D, Gupta D, Adib D, Yang J, Mamlouk K. A Matching-Adjusted Indirect Comparison of Single-Arm Trials in Patients with Relapsed or Refractory Follicular Lymphoma Who Received at Least Two Prior Systemic Treatments: Tazemetostat was Associated with a Lower Risk for Safety Outcomes Versus the PI3-Kinase Inhibitors Idelalisib, Duvelisib, Copanlisib, and Umbralisib. *Adv Ther* 2022; **39**: 1678-1696 [PMID: 35157216 DOI:

10.1007/s12325-022-02054-z]
58 **Ogura M**, Ando K, Suzuki T, Ishizawa K, Oh SY, Itoh K, Yamamoto K, Au WY, Tien HF, Matsuno Y, Terauchi T, Mori M, Tanaka Y, Shimamoto T, Tobinai K, Kim WS. A multicentre phase II study of vorinostat in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. *Br J Haematol* 2014; **165**: 768-776 [PMID: 24617454 DOI: 10.1111/bjh.12819]
59 **Chen R**, Frankel P, Popplewell L, Siddiqi T, Ruel N, Rotter A, Thomas SH, Mott M, Nathwani N, Htut M, Nademanee A, Forman SJ, Kirschbaum M. A phase II study of vorinostat and rituximab for treatment of newly diagnosed and relapsed/refractory indolent non-Hodgkin lymphoma. *Haematologica* 2015; **100**: 357-362 [PMID: 25596263 DOI: 10.3324/haematol.2014.117473]
60 **Batlevi CL**, Crump M, Andreadis C, Rizzieri D, Assouline SE, Fox S, van der Jagt RHC, Copeland A, Potvin D, Chao R, Younes A. A phase 2 study of mocetinostat, a histone deacetylase inhibitor, in relapsed or refractory lymphoma. *Br J Haematol* 2017; **178**: 434-441 [PMID: 28440559 DOI: 10.1111/bjh.14698]
61 **Vanhaesebroeck B**, Leevers SJ, Ahmadi K, Timms J, Katso R, Driscoll PC, Woscholski R, Parker PJ, Waterfield MD. Synthesis and function of 3-phosphorylated inositol lipids. *Annu Rev Biochem* 2001; **70**: 535-602 [PMID: 11395417 DOI: 10.1146/annurev.biochem.70.1.535]
62 **Bi L**, Okabe I, Bernard DJ, Nussbaum RL. Early embryonic lethality in mice deficient in the p110beta catalytic subunit of PI 3-kinase. *Mamm Genome* 2002; **13**: 169-172 [PMID: 11919689 DOI: 10.1007/BF02684023]
63 **Sasaki T**, Irie-Sasaki J, Jones RG, Oliveira-dos-Santos AJ, Stanford WL, Bolon B, Wakeham A, Itie A, Bouchard D, Kozieradzki I, Joza N, Mak TW, Ohashi PS, Suzuki A, Penninger JM. Function of PI3Kgamma in thymocyte development, T cell activation, and neutrophil migration. *Science* 2000; **287**: 1040-1046 [PMID: 10669416 DOI: 10.1126/science.287.5455.1040]
64 **Laffargue M**, Calvez R, Finan P, Trifilieff A, Barbier M, Altruda F, Hirsch E, Wymann MP. Phosphoinositide 3-kinase gamma is an essential amplifier of mast cell function. *Immunity* 2002; **16**: 441-451 [PMID: 11911828 DOI: 10.1016/s1074-7613(02)00282-0]
65 **Isidori A**, Loscocco F, Visani G, Paolasini S, Scalzulli P, Musto P, Perrone T, Guarini A, Pastore D, Mazza P, Tonialini L, Pavone V, De Santis G, Tarantini G. Real-life efficacy and safety of idelalisib in 55 double-refractory follicular lymphoma patients. *Br J Haematol* 2022; **199**: 339-343 [PMID: 36002151 DOI: 10.1111/bjh.18426]
66 **Gopal AK**, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, Flinn IW, Flowers CR, Martin P, Viardot A, Blum KA, Goy AH, Davies AJ, Zinzani PL, Dreyling M, Johnson D, Miller LL, Holes L, Li D, Dansey RD, Godfrey WR, Salles GA. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* 2014; **370**: 1008-1018 [PMID: 24450858 DOI: 10.1056/NEJMoa1314583]
67 **Gordon MJ**, Huang J, Chan RJ, Bhargava P, Danilov AV. Medical comorbidities in patients with chronic lymphocytic leukaemia treated with idelalisib: analysis of two large randomised clinical trials. *Br J Haematol* 2021; **192**: 720-728 [PMID: 32599655 DOI: 10.1111/bjh.16879]
68 **Coutré SE**, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, Li D, O'Brien SM, Pagel JM, Poleski MH, Sharman JP, Yao NS, Zelenetz AD. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma* 2015; **56**: 2779-2786 [PMID: 25726955 DOI: 10.3109/10428194.2015.1022770]
69 **Wang Z**, Zhou H, Xu J, Wang J, Niu T. Safety and efficacy of dual PI3K-δ, γ inhibitor, duvelisib in patients with relapsed or refractory lymphoid neoplasms: A systematic review and meta-analysis of prospective clinical trials. *Front Immunol* 2022; **13**: 1070660 [PMID: 36685572 DOI: 10.3389/fimmu.2022.1070660]
70 **Dreyling M**, Santoro A, Mollica L, Leppä S, Follows G, Lenz G, Kim WS, Nagler A, Dimou M, Demeter J, Özcan M, Kosinova M, Bouabdallah K, Morschhauser F, Stevens DA, Trevarthen D, Munoz J, Rodrigues L, Hiemeyer F, Miriyala A, Garcia-Vargas J, Childs BH, Zinzani PL. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. *Am J Hematol* 2020; **95**: 362-371 [PMID: 31868245 DOI: 10.1002/ajh.25711]
71 **Dreyling M**, Santoro A, Mollica L, Leppä S, Follows GA, Lenz G, Kim WS, Nagler A, Panayiotidis P, Demeter J, Özcan M, Kosinova M, Bouabdallah K, Morschhauser F, Stevens DA, Trevarthen D, Giurescu M, Cupit L, Liu L, Köchert K, Seidel H, Peña C, Yin S, Hiemeyer F, Garcia-Vargas J, Childs BH, Zinzani PL. Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2017; **35**: 3898-3905 [PMID: 28976790 DOI: 10.1200/JCO.2017.75.4648]
72 **Maharaj K**, Powers JJ, Achille A, Mediavilla-Varela M, Gamal W, Burger KL, Fonseca R, Jiang K, Miskin HP, Maryanski D, Monastyrskyi A, Duckett DR, Roush WR, Cleveland JL, Sahakian E, Pinilla-Ibarz J. The dual PI3Kδ/CK1ε inhibitor umbralisib exhibits unique immunomodulatory effects on CLL T cells. *Blood Adv* 2020; **4**: 3072-3084 [PMID: 32634240 DOI: 10.1182/bloodadvances.2020001800]
73 **Schweitzer J**, Hoffman M, Graf SA. The evidence to date on umbralisib for the treatment of refractory marginal zone lymphoma and follicular lymphoma. *Expert Opin Pharmacother* 2022; **23**: 535-541 [PMID: 35209784 DOI: 10.1080/14656566.2022.2043273]
74 **Fowler NH**, Samaniego F, Jurczak W, Ghosh N, Derenzini E, Reeves JA, Knopińska-Posłuszny W, Cheah CY, Phillips T, Lech-Maranda E, Cheson BD, Caimi PF, Grosicki S, Leslie LA, Chavez JC, Fonseca G, Babu S, Hodson DJ, Shao SH, Burke JM, Sharman JP, Law JY, Pagel JM, Miskin HP, Sportelli P, O'Connor OA, Weiss MS, Zinzani PL. Umbralisib, a Dual PI3Kδ/CK1ε Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2021; **39**: 1609-1618 [PMID: 33683917 DOI: 10.1200/JCO.20.03433]
75 **Fukuhara N**, Suehiro Y, Kato H, Kusumoto S, Coronado C, Rappold E, Zhao W, Li J, Gilmartin A, Izutsu K. Parsaclisib in Japanese patients with relapsed or refractory B-cell lymphoma (CITADEL-111): A phase Ib study. *Cancer Sci* 2022; **113**: 1702-1711 [PMID: 35201656 DOI: 10.1111/cas.15308]
76 **Forero-Torres A**, Ramchandren R, Yacoub A, Wertheim MS, Edenfield WJ, Caimi P, Gutierrez M, Akard L, Escobar C, Call J, Persky D, Iyer S, DeMarini DJ, Zhou L, Chen X, Dawkins F, Phillips TJ. Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies. *Blood* 2019; **133**: 1742-1752 [PMID: 30803990 DOI: 10.1182/blood-2018-08-867499]

77 **Goto H**, Izutsu K, Ennishi D, Mishima Y, Makita S, Kato K, Hanaya M, Hirano S, Narushima K, Teshima T, Nagai H, Ishizawa K. Zandelisib (ME-401) in Japanese patients with relapsed or refractory indolent non-Hodgkin's lymphoma: an open-label, multicenter, dose-escalation phase 1 study. *Int J Hematol* 2022; **116**: 911-921 [PMID: 36107394 DOI: 10.1007/s12185-022-03450-5]

78 **Pagel JM**, Soumerai JD, Reddy N, Jagadeesh D, Stathis A, Asch A, Salman H, Kenkre VP, Iasonos A, Llorin-Sangalang J, Li J, Zelenetz AD. Zandelisib with continuous or intermittent dosing as monotherapy or in combination with rituximab in patients with relapsed or refractory B-cell malignancy: a multicentre, first-in-patient, dose-escalation and dose-expansion, phase 1b trial. *Lancet Oncol* 2022; **23**: 1021-1030 [PMID: 35835137 DOI: 10.1016/S1470-2045(22)00333-3]

79 **Matasar MJ**, Dreyling M, Leppä S, Santoro A, Pedersen M, Buvaylo V, Fletcher M, Childs BH, Zinzani PL. Feasibility of Combining the Phosphatidylinositol 3-Kinase Inhibitor Copanlisib With Rituximab-Based Immunochemotherapy in Patients With Relapsed Indolent B-cell Lymphoma. *Clin Lymphoma Myeloma Leuk* 2021; **21**: e886-e894 [PMID: 34389273 DOI: 10.1016/j.clml.2021.06.021]

80 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012- [PMID: 31643176]

81 **Smith SM**, Pitcher BN, Jung SH, Bartlett NL, Wagner-Johnston N, Park SI, Richards KL, Cashen AF, Jaslowski A, Smith SE, Cheson BD, Hsi E, Leonard JP. Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: the Alliance for Clinical Trials in Oncology A051201 and A051202 phase 1 trials. *Lancet Haematol* 2017; **4**: e176-e182 [PMID: 28314699 DOI: 10.1016/S2352-3026(17)30028-5]

82 **Wu X**, Xu Y, Liang Q, Yang X, Huang J, Wang J, Zhang H, Shi J. Recent Advances in Dual PI3K/mTOR Inhibitors for Tumour Treatment. *Front Pharmacol* 2022; **13**: 875372 [PMID: 35614940 DOI: 10.3389/fphar.2022.875372]

83 **McCurdy A**, Visram A. The Role of Belantamab Mafodotin, Selinexor, and Melflufen in Multiple Myeloma. *Curr Hematol Malig Rep* 2022; **17**: 306-318 [PMID: 36417082 DOI: 10.1007/s11899-022-00682-4]

84 **Major A**, Kline J, Karrison TG, Fishkin PAS, Kimball AS, Petrich AM, Nattam S, Rao K, Sleckman BG, Cohen K, Besien KV, Rapoport AP, Smith SM. Phase I/II clinical trial of temsirolimus and lenalidomide in patients with relapsed and refractory lymphomas. *Haematologica* 2022; **107**: 1608-1618 [PMID: 34320785 DOI: 10.3324/haematol.2021.278853]

85 **Sharma N**, Reagan PM, Liesveld JL. Cytopenia after CAR-T Cell Therapy-A Brief Review of a Complex Problem. *Cancers (Basel)* 2022; **14** [PMID: 35326654 DOI: 10.3390/cancers14061501]

86 **Yassine F**, Murthy H, Ghabashi E, Kharfan-Dabaja MA, Iqbal M. Understanding the Etiology of Pancytopenias in the CAR T-Cell Therapy Setting: What We Know and What We Don't? *Hematol Oncol Stem Cell Ther* 2022; **15**: 122-130 [PMID: 36633964 DOI: 10.56875/2589-0646.1047]

87 **Goldsmith SR**, Ghobadi A, Dipersio JF, Hill B, Shadman M, Jain T. Chimeric Antigen Receptor T Cell Therapy versus Hematopoietic Stem Cell Transplantation: An Evolving Perspective. *Transplant Cell Ther* 2022; **28**: 727-736 [PMID: 35878743 DOI: 10.1016/j.jtct.2022.07.015]

88 **Gajra A**, Zalenski A, Sannareddy A, Jeune-Smith Y, Kapinos K, Kansagra A. Barriers to Chimeric Antigen Receptor T-Cell (CAR-T) Therapies in Clinical Practice. *Pharmaceut Med* 2022; **36**: 163-171 [PMID: 35672571 DOI: 10.1007/s40290-022-00428-w]

89 **Abramson JS**, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, Mehta A, Purev E, Maloney DG, Andreadis C, Sehgal A, Solomon SR, Ghosh N, Albertson TM, Garcia J, Kostic A, Mallaney M, Ogasawara K, Newhall K, Kim Y, Li D, Siddiqi T. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020; **396**: 839-852 [PMID: 32888407 DOI: 10.1016/S0140-6736(20)31366-0]

90 **Neelapu SS**, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, Hill BT, Smith MR, Deol A, Farooq U, McSweeney P, Munoz J, Avivi I, Castro JE, Westin JR, Chavez JC, Ghobadi A, Komanduri KV, Levy R, Jacobsen ED, Witzig TE, Reagan P, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Chang D, Wiezorek J, Go WY. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017; **377**: 2531-2544 [PMID: 29226797 DOI: 10.1056/NEJMoa1707447]

91 **Schuster SJ**, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT; JULIET Investigators. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med* 2019; **380**: 45-56 [PMID: 30501490 DOI: 10.1056/NEJMoa1804980]

92 **Chong EA**, Ruella M, Schuster SJ; Lymphoma Program Investigators at the University of Pennsylvania. Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy. *N Engl J Med* 2021; **384**: 673-674 [PMID: 33596362 DOI: 10.1056/NEJMc2030164]

93 **Jacobson CA**, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, Munshi PN, Casulo C, Maloney DG, de Vos S, Reshef R, Leslie LA, Yakoub-Agha I, Oluwole OO, Fung HCH, Rosenblatt J, Rossi JM, Goyal L, Plaks V, Yang Y, Vezan R, Avanzi MP, Neelapu SS. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol* 2022; **23**: 91-103 [PMID: 34895487 DOI: 10.1016/S1470-2045(21)00591-X]

94 **Mohty R**, Kharfan-Dabaja MA. CAR T-cell therapy for follicular lymphoma and mantle cell lymphoma. *Ther Adv Hematol* 2022; **13**: 20406207221142133 [PMID: 36544864 DOI: 10.1177/20406207221142133]

95 **Jacobson CA**, Chavez JC, Sehgal A, William BM, Munoz J, Salles GA. Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 mo from initiation of first anti-CD20-containing chemoimmunotherapy (POD24). *J Clin Oncol* 2021; **39** Suppl 15: 7515 [DOI: 10.1200/jco.2021.39.15_suppl.7515]

96 **Fowler NH**, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, Ghosh M, Popplewell L, Chavez JC, Bachy E, Kato K, Harigae H, Kersten MJ, Andreadis C, Riedell PA, Ho PJ, Pérez-Simón JA, Chen AI, Nastoupil LJ, von

Tresckow B, Ferreri AJM, Teshima T, Patten PEM, McGuirk JP, Petzer AL, Offner F, Viardot A, Zinzani PL, Malladi R, Zia A, Awasthi R, Masood A, Anak O, Schuster SJ, Thieblemont C. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med* 2022; **28**: 325-332 [PMID: 34921238 DOI: 10.1038/s41591-021-01622-0]

97 **Salles G**, Schuster SJ, Dreyling M, Fischer L, Kuruvilla J, Patten PEM, von Tresckow B, Smith SM, Jiménez-Ubieto A, Davis KL, Anjos C, Chu J, Zhang J, Lobetti Bodoni C, Thieblemont C, Fowler NH, Dickinson M, Martínez-López J, Wang Y, Link BK. Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. *Blood Adv* 2022; **6**: 5835-5843 [PMID: 35973192 DOI: 10.1182/bloodadvances.2022008150]

98 **Sarkozy C**, Maurer MJ, Link BK, Ghesquieres H, Nicolas E, Thompson CA, Traverse-Glehen A, Feldman AL, Allmer C, Slager SL, Ansell SM, Habermann TM, Bachy E, Cerhan JR, Salles G. Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts. *J Clin Oncol* 2019; **37**: 144-152 [PMID: 30481079 DOI: 10.1200/JCO.18.00400]

99 **Sehgal A**, Hoda D, Riedell PA, Ghosh N, Hamadani M, Hildebrandt GC, Godwin JE, Reagan PM, Wagner-Johnston N, Essell J, Nath R, Solomon SR, Champion R, Licitra E, Fanning S, Gupta N, Dubowy R, D'Andrea A, Wang L, Ogasawara K, Thorpe J, Gordon LI. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol* 2022; **23**: 1066-1077 [PMID: 35839786 DOI: 10.1016/S1470-2045(22)00339-4]

100 **St-Pierre F**, Gordon LI. Lisocabtagene maraleucel in the treatment of relapsed/refractory large B-cell lymphoma. *Future Oncol* 2023; **19**: 19-28 [PMID: 36651471 DOI: 10.2217/fon-2022-0774]

101 **Luminari S**, Manni M, Galimberti S, Versari A, Tucci A, Boccomini C, Farina L, Olivieri J, Marcheselli L, Guerra L, Ferrero S, Arcaini L, Cavallo F, Kovalchuk S, Skrypets T, Del Giudice I, Chauvie S, Patti C, Stelitano C, Ricci F, Pinto A, Margiotta Casaluci G, Zilioli VR, Merli A, Ladetto M, Bolis S, Pavone V, Chiarenza A, Arcari A, Anastasia A, Dondi A, Mannina D, Federico M; Fondazione Italiana Linfomi. Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study. *J Clin Oncol* 2022; **40**: 729-739 [PMID: 34709880 DOI: 10.1200/JCO.21.01234]

102 **Schmatz AI**, Streubel B, Kretschmer-Chott E, Püspök A, Jäger U, Mannhalter C, Tiemann M, Ott G, Fischbach W, Herzog P, Seitz G, Stolte M, Raderer M, Chott A. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. *J Clin Oncol* 2011; **29**: 1445-1451 [PMID: 21383289 DOI: 10.1200/JCO.2010.32.9193]

103 **Tari A**, Kitadai Y, Mouri R, Takigawa H, Asaoku H, Mihara K, Takata K, Fujihara M, Yoshino T, Koga T, Fujimori S, Tanaka S, Chayama K. Watch-and-wait policy versus rituximab-combined chemotherapy in Japanese patients with intestinal follicular lymphoma. *J Gastroenterol Hepatol* 2018; **33**: 1461-1468 [PMID: 29377265 DOI: 10.1111/jgh.14100]

104 **Yamamoto S**, Nakase H, Yamashita K, Matsuura M, Takada M, Kawanami C, Chiba T. Gastrointestinal follicular lymphoma: review of the literature. *J Gastroenterol* 2010; **45**: 370-388 [PMID: 20084529 DOI: 10.1007/s00535-009-0182-z]

105 **Takata K**, Okada H, Ohmiya N, Nakamura S, Kitadai Y, Tari A, Akamatsu T, Kawai H, Tanaka S, Araki H, Yoshida T, Okumura H, Nishisaki H, Sagawa T, Watanabe N, Arima N, Takatsu N, Nakamura M, Yanai S, Kaya H, Morito T, Sato Y, Moriwaki H, Sakamoto C, Niwa Y, Goto H, Chiba T, Matsumoto T, Ennishi D, Kinoshita T, Yoshino T. Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: a multicenter, retrospective analysis in Japan. *Cancer Sci* 2011; **102**: 1532-1536 [PMID: 21561531 DOI: 10.1111/j.1349-7006.2011.01980.x]

106 **Rohatiner A**, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, Lister TA, Norton A, Salem P, Shipp M. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol* 1994; **5**: 397-400 [PMID: 8075046 DOI: 10.1093/oxfordjournals.annonc.a058869]

107 **Watanabe T**. Treatment strategies for nodal and gastrointestinal follicular lymphoma: current status and future development. *World J Gastroenterol* 2010; **16**: 5543-5554 [PMID: 21105187 DOI: 10.3748/wjg.v16.i44.5543]

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