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PROGRESS IN HEMATOLOGY

Current status and progress of lymphoma research in East Asian countries

Current status and progress of lymphoma management in China

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Abstract
Lymphoma is a large group of lymphoid hematopoietic malignancies including Hodgkin lymphoma and non-Hodgkin's lymphoma. The various subtypes of lymphoma are different in clinical features, response to treatment and prognoses. The relative frequency of specific subtypes of lymphoma varies geographically. The mature T cell lymphoma is much more common in East Asia compared with Western countries. Chemotherapy plays an important role in the treatment of lymphoma. With advances in understanding the biology and genetics of lymphoma, many new agents are used in the treatment of lymphoma. In mainland China, some new agents and new combination chemotherapy regimens showed high efficacy and good tolerability. Chidamide, a histone deacetylase inhibitor, has been approved for the treatment of relapsed or refractory peripheral T cell lymphoma by the China Food and Drug Administration. Anti-programmed death 1 antibodies and chimeric antigen receptor-engineered T cells have been explored for lymphoma immunotherapy in Chinese patients. Advances in the treatment have substantially increased the likelihood of cure for patients with lymphoma.

Keywords Lymphoma · Chemotherapy · New agents

Introduction

Lymphoma is a diverse group of malignancies that originates from either B, T or NK cells. According to the cancer statistics in 2013, the incidence of lymphoma was 4.2 per 100,000 and the mortality was 2.2 per 100,000 in mainland China [1], making it the eleventh most common cancer and the tenth leading cause of cancer death [2]. There are some differences in the distribution of lymphoma subtypes between East Asia and Western countries. The mature T/NK cell neoplasms display higher rates on the Asian continent than others [3, 4]. In mainland China, diffuse large B cell lymphoma (DLBCL) is still the most common subtype of lymphoma. Extranodal NK/T cell lymphoma, nasal type (ENKTL) is a common subtype and makes up 11–15% of all lymphoma [3, 4]. The treatment modalities for lymphoma include chemotherapy, radiotherapy, or their combinations. High-dose chemotherapy combined with autologous stem cell transplantation (HDC/ASCT) is still an important treatment strategy for high-risk or relapsed patients. Furthermore, advances in genetic analysis will provide new approaches in molecular targeted therapy. These new developments will improve the outcome of lymphoma patients.

Hodgkin lymphoma

Hodgkin lymphoma (HL) accounts for 8.6–13% of all lymphoma in mainland China [3, 4]. Currently, more than 80% of patients with newly diagnosed HL are likely to be cured. Patients with early-stage HL commonly receive abbreviated courses of chemotherapy followed by involved-field radiation therapy (IFRT). In contrast, patients with advanced-stage HL commonly receive prolonged courses of combination chemotherapy, with radiation therapy used only in selected cases.

For relapsed or refractory (R/R) patients who are ineligible for HDC/ASCT or those in whom HDC/ASCT have failed, treatment with brentuximab vedotin and anti-programmed death 1 (PD-1) antibodies could be considered.

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The phase II studies of pembrolizumab and nivolumab achieved overall response rates (ORR) of 69.0 and 66.3% in patients with R/R HL, respectively [5, 6]. In Hong Kong China, Chan et al. [7] indicated low-dose pembrolizumab was highly efficacious with minimal toxicity in five patients with R/R classical HL. Pembrolizumab was given with a median dose of 100 mg every 3 weeks and the ORR was 100% [7]. Nivolumab used in a low dose might similarly be efficacious. A patient received nivolumab at a fixed dose of 40 mg (about 0.55 mg/kg) every 2 weeks [8]. Complete remission (CR) was achieved after a cumulative dose of only 2.2 mg/kg [8]. Several anti-PD-1 antibodies are also developed in mainland China, such as IBI308 (NCT03114683), SHR-1210 (NCT0315425) and BGB-A317 (NCT03209973). Patients with R/R classical HL could participate in clinical trials to receive these anti-PD-1 antibodies treatment. The results of these clinical trials are worthy of expectation.

Non-Hodgkin's lymphoma

Diffuse large B cell lymphoma

In China, the most common subtype lymphoma is DLBCL [3, 4]. The initial treatment for patients with DLBCL is based on the histologic characteristics, the stage, the primary site and other prognostic factors. The most important advance in the management of DLBCL in the past two decades was the addition of rituximab to an anthracycline-containing chemotherapy regimen. The real-world study of rituximab plus chemotherapy as first-line treatment in Chinese patients with DLBCL showed the ORR and CR/unconfirmed CR (CRu) were 94.2 and 73.2%, respectively [9]. According to the retrospective study of Shanghai Lymphoma Research Group, there were significant differences between R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy for overall survival (OS 84.1 vs 70.2%, $p = 0.018$) and progression-free survival (PFS 81.5 vs 66.7%, $p = 0.015$), with the median follow-up of 86 months [10]. Hepatitis B virus (HBV) reactivation is a serious complication for patients with lymphoma treated with rituximab-containing chemotherapy. Antiviral prophylaxis can potentially prevent rituximab-associated HBV reactivation in patients with lymphoma and resolved hepatitis B [11]. Huang et al. [12] found among patients seropositive for the hepatitis B surface antigen with DLBCL receiving R-CHOP chemotherapy, the addition of entecavir compared with lamivudine resulted in a lower incidence of HBV-related hepatitis and HBV reactivation.

Due to the prominent efficacy and good tolerability of rituximab in the treatment of lymphoma, several new anti-CD20 monoclonal antibodies (mAbs) have been developed. Ofatumumab and obinutuzumab have been approved for the treatment of chronic lymphocytic leukemia (CLL) [13, 14]. In mainland China, the phase Ib study demonstrated obinutuzumab exposure was comparable in CLL, DLBCL and follicular lymphoma (FL) patients [15]. Pharmacokinetic characteristics of Chinese patients with B cell lymphomas are similar to those in non-Chinese patients [15]. SCT400 is a recombinant, human-mouse chimeric anti-CD20 IgG1 mAb. Phase I study demonstrated that SCT400 was safe and well tolerated in Chinese patients with CD20+ B cell non-Hodgkin's lymphoma (NHL) [16]. The pharmacokinetics and pharmacodynamics results of SCT400 were comparable to rituximab, and the preliminary efficacy data were encouraging [16]. HLX01 is a rituximab biosimilar produced in mainland China. The multicenter, randomized, phase III studies to compare the efficacy and safety of HLX01 (NCT02787239) or SCT400 (NCT02772822) with rituximab plus CHOP are ongoing in previously untreated subjects with CD20+ DLBCL.

Up-front HDC/ASCT following R-CHOP could improve the outcome of high-intermediate and high-risk DLBCL patients [17]. Absolute monocyte count is a prognostic indicator in patients with DLBCL after HDC/ASCT [18]. Dose-adjusted CHOP and ICE-based regimens are effective for autologous peripheral blood stem cell (APBSC) mobilization [19, 20]. Etoposide given at a dose of either 1.0 or 1.5 g/m^2 in combination with recombinant human granulocyte colony-stimulating factor (rhG-CSF) is also an effective and tolerable regimen for APBSC mobilization [21]. CBV (cyclophosphamide, carmustine and etoposide), BEAM (carmustine, etoposide, cytarabine and melphalan) and BEAC (carmustine, etoposide, cytarabine and cyclophosphamide) regimens are all optional high-dose chemotherapy before ASCT for NHL patients [22]. Shi et al. [22] demonstrated the estimated 5-year PFS in the CBV group (43.8%) was relatively inferior to the BEAM (66.7%) and BEAC (67.5%) groups, but the differences were not significant.

Chimeric antigen receptor (CAR)-engineered T cells are widely studied for cancer immunotherapy. Autologous T cells with re-engineered chimeric antigen receptors (CAR-T) have been successfully used for some patients with leukemia and lymphoma [23–26]. The multicenter ZUMA-1 phase I study showed autologous CD3ζ/CD28-based CAR-T therapy was safe in patients with refractory DLBCL [25]. The ORR was 71% ($n = 5/7$) and CR rate was 57% ($n = 4/7$) [25]. In the ZUMA-1 phase II study, the ORR was 76% (47% CR and 29% PR) at the time of report in the cohort 1 of 51 patients [26]. In recent years, more and more clinical trials from mainland China are registered at ClinicalTrials.gov. According to Liu et al. [27], there are 121 trials of CAR-T cells reported and/or registered at ClinicalTrials.gov for different cancer types from mainland China. The most common type of diseases in CAR-T trials are B cell malignancies [27].

Follicular lymphoma

FL is the most prevalent indolent NHL. The management of FL is mainly determined by histologic grading, clinical stage and tumor burden. For patients with stage I and II, the IFRT is recommended and usually results in long-lasting remission. While for patients with stage III and IV, systemic therapy could be taken into consideration. The watchful waiting is still an option for patients without symptoms or/and low tumor burden.

Hou et al. [28] compared the efficacy and safety of RFT (rituximab, fludarabine and pirarubicin) with RCTVP (rituximab, cyclophosphamide, pirarubicin, vindesine and prednisone) in 248 indolent B cell NHL patients in mainland China. There were no statistically significant differences in OS between treatment groups [28]. Compared with RCTVP regimen, RFT regimen was associated with superior PFS both in previously untreated and R/R patients [28]. But grades 3 and 4 hematological adverse events were more common in the RFT group [28]. The efficacy and safety of rituximab and bortezomib were evaluated in 60 Chinese patients with R/R indolent B cell NHL, including FL grades 1–2 ($n = 35$), CLL (n=16) and marginal zone lymphoma ($n = 9$) [29]. The ORR was 70.0%, with a CR/CRu rate of 31.7% [29]. The 2-year OS and PFS rates of all patients were 75.0 and 41.0%, respectively [29].

Mantle cell lymphoma

Mantle cell lymphoma (MCL) may have two different subtypes, which are indolent or aggressive. Asymptomatic indolent MCL patients with low tumor burden can be closely observed, deferring therapy to the time of disease progression. Currently, the recommended first-line treatment for young transplant eligible patients is cytarabine/rituximab-based combination chemotherapies followed by HDC/ASCT [30, 31]. The bendamustine and rituximab (BR) regimen is becoming an popular treatment option among the elderly population [31, 32].

Novel agents such as bortezomib, lenalidamide and ibrutinib are now available for the treatment of R/R disease. Bruton's tyrosine kinase (BTK) has been defined as a major mediator on B cell-receptor signaling pathway. A phase II study to evaluate the efficacy and safety of BGB-3111, a BTK inhibitor developed in mainland China, in patients with R/R MCL is ongoing (NCT03206970). Another BTK inhibitor CT-1530 is in phase I study for patients with R/R B cell NHL, CLL or Waldenstrom's macroglobulinemia (NCT02981745). Wu et al. [33] discovered a selective and potent BTK/mitogen-activated protein kinase interacting kinase (MNK) dual kinase inhibitor (QL-X-138) through a structure-based drug design approach. QL-X-138 exhibits covalent binding to BTK and non-covalent binding to MNK [33]. Compared to the BTK kinase inhibitor (PCI-32765) and the MNK kinase inhibitor (cercosporamide), QL-X-138 displays a stronger anti-proliferative effect against a variety of B cell cancer cell lines [33]. In Hong Kong China, Gill et al. [34] found oral arsenic trioxide-based regimen was effective with minimal toxicity for R/R MCL. Thirty-nine patients ineligible for HDC/ASCT were treated with arsenic trioxide, chlorambucil and ascorbic acid [34]. The ORR was 49% with a CR rate of 28% [34]. The median PFS and OS were 16 and 38 months, respectively [34].

Peripheral T cell lymphomas

Peripheral T cell lymphoma (PTCL) makes up 23–27% of all NHL cases in mainland China [3, 4], much higher than that in Western countries of 10–15% [35]. The most common subtype of PTCL in mainland China is ENKTL, followed by PTCL not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL) [3, 4]. PTCL represents a relatively rare group of heterogeneous NHL with a very poor prognosis. The anthracycline-based conventional chemotherapy remains standard treatment, but most patients are either refractory to initial therapy or eventually relapse. A systematic review and meta-analysis of front-line anthracycline-based chemotherapy for PTCL patients showed the CR rate ranged from 35.9% for enteropathy-type T cell lymphoma (ETTL) to 65.8% for ALCL [36]. The 5-year OS rate was 38.5% for all PTCL patients [36]. Frontline consolidation treatment with HDC/ASCT was associated with favourable outcomes in patients with PTCL [37–40]. CR to induction chemotherapy was a prognostic factor for survival [37–40].

In mainland China, some new regimens were explored as first-line therapy against PTCL. Li et al. [41] compared the efficacy and safety of GDPT (gemcitabine, cisplatin, prednisone and thalidomide) with standard CHOP regimen for patients with newly diagnosed PTCL. 103 patients were randomly allocated into the GDPT group or CHOP group [41]. Patients receiving GDPT chemotherapy achieved significant higher 2-year PFS rate (57 vs 35%, $p = 0.0035$) and OS rate (71 vs 50%, $p = 0.0001$) than those receiving CHOP chemotherapy [41]. The CR rate (52 vs 33%, $p = 0.0001$) and the ORR (67 vs. 49%, $p = 0.046$) in the GDPT group were higher than in the CHOP group [41]. Haemocytopenia was the predominant adverse effect [41]. Endostatin (endostar) is an endogenous inhibitor of angiogenesis. Zhang et al. [42] explored the efficacy and safety of recombinant human endostatin in

combination with CHOP in 15 PTCL patients. The ORR was 80%; 53.3% of patients achieved CR [42]. The CR rate was 100% (3/3) in AITL patients compared to only 36.4% (4/11) in PTCL-NOS patients [42]. The 5-year PFS and OS rates were 53 and 60%, respectively [42]. Grade 3–4 neutropenia was 86.7% [42].

The most significant progress in recent years has been the evaluation of novel agents in R/R PTCL, including: agents targeting the signal transduction pathways, agents of immunotherapy, histone deacetylase inhibitors, antifolate and nucleoside analogs. Thus, four agents (pralatrexate, brentuximab vedotin, romidepsin and belinostat) have been approved for the treatment of R/R PTCL by the US Food and Drug Administration (FDA). Chidamide (CS055) is a novel and orally active benzamide class of histone deacetylase inhibitor (HDACi) that selectively inhibits activity of HDAC1, 2, 3 and 10 [43, 44]. The pivotal phase II trial of Chidamide enrolled 83 Chinese patients with R/R PTCL, and 79 patients were eligible for efficacy assessment [45]. The ORR was 28% including 14% with CR/CRu [45]. Median PFS and OS were 2.1 and 21.4 months, respectively [45]. AITL patients tended to have higher ORR (50%) and CR/CRu rate (40%) [45]. Grade 3 to 4 adverse events were mainly thrombocytopenia (22%), leucopenia (13%) and neutropenia (11%), respectively [45]. The multicenter real-world study of Chidamide in 383 R/R PTCL patients confirmed the favorable efficacy and acceptable safety profile [46]. For patients receiving Chidamide monotherapy and Chidamide combined with chemotherapy, the ORR were 39.06 and 51.18%, respectively [46]. The China Food and Drug Administration (CFDA) has approved Chidamide for the treatment of R/R PTCL in December 2014. Novel agents approved by FDA or CFDA are summarized in Table 1 [45, 47–50].

In recent years, a variety of interesting novel combinations are also emerging. Several studies have evaluated the addition of a novel agent to CHOP-(like) chemotherapy in the front-line therapy [51–53]. The clinical trials of Chidamide combined with CHOP chemotherapy for newly diagnosed PTCL (NCT02809573) and Chidamide combined with ICE chemotherapy for R/R PTCL (NCT02856997) are ongoing.

Extranodal NK/T cell lymphoma, nasal type

ENKTL is specific subtype of PTCL with higher prevalence in East Asia. It comprises approximately 50% of PTCL in mainland China and only accounts for 4.3–5.1% in north America and Europe [3, 4, 35]. The upper respiratory tract, especially the nasal region, is the most common site of invasion [54]. A multicenter study of 1383 Chinese patients with NKTCL showed 92% of patients presented with early-stage disease [55]. The 5-year OS rate was 60.3% for all patients [55]. Stage, age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase and primary tumor invasion were important prognostic factors [55]. Jiang et al. [56] found Chinese patients with DDX3X mutations presented a poor prognosis. DDX3X mutants exhibited loss of suppressive effects on cell-cycle progression in NK cells, transcriptional activation of NF-κB and MAPK pathways [56].

Standard treatment for ENKTL patients has not been established. For patients with localized ENKTL, radiotherapy is widely administered and could achieve CR rates of up to 70% [57, 58]. However, radiotherapy alone seems inadequate for high-risk patients and the optimal treatment is combined chemoradiotherapy for these patients. In mainland China, some "sandwich" protocols, with earlier RT after an initial 2–3 cycles of chemotherapy followed by further "consolidation" cycles of chemotherapy, achieved good efficacy. The frontline use of "sandwich" chemotherapy regimens included LVP (L-asparaginase, vincristine and prednisone), GELOX (gemcitabine, oxaliplatin and L-asparaginase), P-Gemox (pegaspargase, gemcitabine and oxaliplatin) and LVDP (L-asparaginase, cisplatin, etoposide and dexamethasone) [59–62]. The ORR were 86.4–96.3%, and the CR rates were 74.1–86.8% [59–62]. Other studies demonstrated the DICE-L (cisplatin, ifosfamide, etoposide, dexamisone and L-asparaginase) chemotherapy followed by IFRT and

Table 1 Novel agents approved by FDA or CFDA for peripheral T-cell lymphoma

Agents	Mechanism	Approved diseases	ORR (%)	CR (%)	DOR (months)	OS (months)	References
Pralatrexate	Anti-metabolite	R/R PTCL	29	11	10.1	14.5	[47]
Romidepsin	HDACi	R/R PTCL	25	15	17	NA	[48]
Belinostat	HDACi	R/R PTCL	26	11	13.6	7.9	[49]
Chidamide	HDACi	R/R PTCL	28	14	9.9	21.4	[45]
Brentuximab vedotin	Antibody-drug conjugate	R/R ALCL	86	57	12.6	NA	[50]

ALCL anaplastic large cell lymphoma, *CR* complete response, *CFDA*, China Food and Drug Administration, *DOR* duration of response, *FDA* U.S. Food and Drug Administration, *HDACi* histone deacetylase inhibitor, *OS* overall survival, *ORR* objective response rate, *PTCL* peripheral T-cell lymphoma, *R/R* relapsed or refractory

Table 2 Treatment for extranodal natural killer/T-cell lymphoma, nasal type in China

Disease	Treatment	ORR (%)	CR (%	PFS	OS	Study/references
Newly diagnosed stage I/II	Sandwich LVP with RT	88.5	80.8	2 years: 80.6%	2 years: 88.5%	Phase II/[59]
Newly diagnosed stage I/II	Sandwich GELOX with RT	96.3	74.1	2 years: 86.0%	2 years: 86.0%	Prospective/[60]
Newly diagnosed stage I/II	Sandwich P-Gemox with RT	92.1	86.8	1 year: 86.7%	1 year: 86.6%	Retrospective/[61]
Newly diagnosed stage I/II	Sandwich LVDP with CCRT	86.4	83.3	3 years: 67.4%	3 years: 70.1%	Phase II/[62]
Newly diagnosed stage I/II	DICE-L followed by RT	100	90.9	5 years: 82.9%	5y:89.2%	Retrospective/[63]
Newly diagnosed stage I/II	RT followed by GDP	95	89	3 years: 77%	3 years: 85%	Retrospective/[64]
Advanced-stage, relapsed, or refractory	Modified SMILE vs CHOP	70 vs. 36	45.0 vs. 13	NA	NA	Retrospective/[66]
Newly diagnosed stage III/IV	DDGP vs SMILE	95 vs. 67	71 vs. 29	1 year: 86% vs. 38%	2 years: 74% vs. 45%	Prospective/[67]
Advanced-stage, relapsed, or refractory	P-gemox	80.0	51.4	3 years: 38.6%	3 years: 64.7%	Retrospective/[68]
Newly diagnosed, relapsed, or refractory	MESA	87	43.5	66%	2 years: 83.4%	Phase II/[69]
Stage I–IV	DIMG	74	41.7	NA	NA	Retrospective/[70]

CR complete response, *CCRT* concurrent chemoradiotherapy, *CHOP* cyclophosphamide doxorubicin vincristine and prednisone, *DDGP* dexamethasone cisplatin gemcitabine and pegaspargase, *DICE-L* cisplatin ifosfamide etoposide dexamisone and L-asparaginase, *DIMG* dexamethasone ifosfamide methotrexate and gemcitabine, *GELOX* gemcitabine oxaliplatin and L-asparaginase, *GDP* gemcitabine dexamethasone and cisplatin, *LVDP* L-asparaginase cisplatin etoposide and dexamethasone, *LVP* L-asparaginase vincristine and prednisone, *MESA* methotrexate etoposide dexamethasone and pegaspargase, *RT* radiotherapy, *NA* not available, *ORR* overall response rate, *OS*, overall survival, *PFS*, progression-free survival, *P-Gemox* pegaspargase gemcitabine and oxaliplatin, *SMILE* dexamethasone methotrexate ifosfamide L-asparaginase and etoposide

intensity-modulated radiation therapy followed by GDP (gemcitabine, dexamethasone and cisplatin) chemotherapy were both effective for the treatment of newly diagnosed stage I to II ENKTL [63, 64].

The prognoses of patients with stage III and IV disease are extremely poor and the 5-year OS rate is no more than 30% [55]. Chemotherapy is the main treatment for advanced ENKTL. Conventional CHOP or CHOP-like regimes appeared to be unsatisfactory. Several studies demonstrated that SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) regimen is associated with superior efficacy but much higher incidence of grade 4 toxicity [65]. In mainland China, many studies explored effective chemotherapy regimens for advanced-stage or R/R ENKTL. Yang et al. [66] indicated that the modified SMILE chemotherapy regimen markedly improved the OS and PFS rates compared with CHOP chemotherapy regimen. A randomized controlled multicenter study showed DDGP (dexamethasone, cisplatin, gemcitabine and pegaspargase) chemotherapy resulted in significant improvement in PFS, OS, and better tolerability compared with SMILE chemotherapy for newly diagnosed advanced ENKTL patients [67]. Other pegaspargase or gemcitabine-based combination regimens including P-gemox (gemcitabine, oxaliplatin and pegaspargase), MESA (methotrexate, etoposide, dexamethasone and pegaspargase) and DIMG (dexamethasone, ifosfamide, methotrexate and gemcitabine) also showed high efficacy [68–70]. The studies for the treatment of ENKTL in mainland China are summarized in Table 2. HDC/ASCT in combination with chemoradiotherapy may improve long-term outcomes in patients with newly diagnosed ENKTL [71]. For patients with R/R ENKTL failing L-asparaginase, PD-1 blockade with pembrolizumab is highly effective [72]. IBI308 is also used for the treatment of R/R ENKTL in phase II clinical trial (NCT03228836).

Conclusion

Although the understanding of the biology of lymphoma has greatly improved, clinical trials are still needed since many unanswered questions remain. In mainland China, HDACi Chidamide, anti-PD-1 antibodies, BTK inhibitors and anti-CD20 antibodies have been developed. Clinical trials are ongoing to use these new agents developed in mainland China for the treatment of HL, DLBCL, MCL and ENKTL (Table 3). These innovative approaches will improve outcomes in this group of diseases.

Table 3 New agents developed in China for lymphoma treatment

Agents	Mechanisms of action	Clinical trial status	Indications	ClinicalTrials.gov Identifier
IBI308	Anti-PD-1 antibody	Phase II	R/R classical HL	NCT03114683
IBI308	Anti-PD-1 antibody	Phase II	R/R ENKTL	NCT03228836
BGB-A317	Anti-PD-1 antibody	Phase II	R/R classical HL	NCT03209973
SHR-1210	Anti-PD-1 antibody	Phase I/II	R/R HL	NCT03250962
SHR-1210	Anti-PD-1 antibody	Phase I/II	R/R PMBCL	NCT03346642
SHR-1210	Anti-PD-1 antibody	Phase II	R/R classical HL	NCT03155425
SCT400	Anti-CD20 antibody	Phase III	Untreated CD20+ DLBCL	NCT02772822
HLX01	Rituximab Biosimilar	Phase III	Untreated CD20+ DLBCL	NCT02787239
BGB-3111	BTK inhibitor	Phase I	R/R B-cell lymphoma	NCT03189524
BGB-3111	BTK inhibitor	Phase II	R/R non-GCB DLBCL	NCT03145064
BGB-3111	BTK inhibitor	Phase II	R/R CLL/SLL	NCT03206918
BGB-3111	BTK inhibitor	Phase II	R/R MCL	NCT03206970
CT-1530	BTK inhibitor	Phase I	R/R B-NHL, CLL or WM	NCT02981745

R/R relapsed or refractory, *HL* Hodgkin lymphoma, *PMBCL* primary mediastinal large B-cell lymphoma, *ENKTL* extranodal NK/T cell lymphoma, nasal type, *DLBCL* diffuse large B-cell lymphoma, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *MCL* mantle cell lymphoma, *WM* Waldenstrom's macroglobulinemia, *B-NHL* B cell non-Hodgkin's lymphoma, *PD-1* programmed death 1, *BTK* bruton's tyrosine kinase

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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