Promising Immunotherapeutic Modalities for B-Cell Lymphoproliferative Disorders

Subjects: Allergy

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Over Over the last few years, treatment principles have been changed towards more targeted therapy in many B-cell lymphoma subtypes and chronic lymphocytic leukemia (CLL). Immunotherapeutic modalities, namely monoclonal antibodies (mAbs), bispecific antibodies (bsAbs), antibody-drug conjugates (ADCs), and chimeric antigen receptor T (CAR-T) cell therapy commonly use B-cell-associated antigens (CD19, CD20, CD22, and CD79b) as one of their targets. T-cell engagers (TCEs), a subclass of bsAbs, work on a similar mechanism as CAR-T cell therapy without the need of previous T-cell manipulation. Currently, several anti-CD20xCD3 TCEs have demonstrated promising efficacy across different lymphoma subtypes with slightly better outcomes in the indolent subset. Anti-CD19xCD3 TCEs are being developed as well but only blinatumomab has been evaluated in clinical trials yet. Results are not so impressive as those with anti-CD19 CAR-T cell therapy. Antibody-drug conjugates targeting different B-cell antigens (CD30, CD79b, CD19) seem to be effective in combination with mAbs, standard chemoimmunotherapy, or immune checkpoint inhibitors. Further investigation will show whether immunotherapy alone or in combinatory regimens has potential to replace chemotherapeutic agents from the first line treatment.

Keywords: immunotherapy ; bispecific antibodies ; antibody-drug conjugates ; brentuximab vedotin ; polatuzumab vedotin ; mosenutuzumab ; epcoritamab ; glofitamab

1. Introduction

In the last decade, immunotherapy experienced a very rapid development and established itself as one of the fundamental parts of cancer treatment. Its main aim is to activate and encourage the body's own immune system to distinguish and destroy malignant cells [1]. In 1997, rituximab was the very first CD20-specific mAb to obtain regulatory approval, and rapidly became a key part of chemotherapeutic regimens (so-called chemoimmunotherapy) in the care for both B-cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukaemia (CLL) [2]. Since then, antibody drug-conjugates (ADCs), immune checkpoint inhibitors, and both bispecific and trispecific antibodies for CAR-T cell therapy have been developed. Each class of these immunotherapeutic modalities has a unique mechanism of action, structure, and pharmacokinetic properties which are reflected in their specific treatment-related toxicities.

Mature B-cell neoplasms are a diverse group of lymphoid disorders with varying clinical manifestations, pathologic features, and outcomes. Diffuse large B-cell lymphoma (DLBCL) along with follicular lymphoma (FL) represent the most common aggressive and indolent histological subgroups of B-NHL with the incidence of ~5.6/100.000/year and ~2.7/100.000/year respectively (https://seer.cancer.gov/statfacts/html/dlbcl.html accessed on 19 October 2021). Together they comprise 50% of all B-NHL cases [3]. Chronic lymphocytic leukemia is another indolent B-cell malignancy with an incidence of ~4.9/100.000/year (https://seer.cancer.gov/statfacts/html/dlbcl.html accessed on 19 October 2021), and accounts for 25–30% of newly diagnosed leukemias in the Western world [4]. Expression of tumor cell antigens varies according to diagnosis and may change during the treatment. Nevertheless, some markers such as B-cell-associated antigens (CD19, CD20, CD22, and CD79b) are commonly expressed on mature B-lymphocytes including neoplastic ones, and became targets for different immunotherapeutic modalities [5]. Despite that, molecules more selectively expressed on malignant cells and ideal targets on effector cells (e.g., T-cells, NK cells, APCs—antigen presenting cells, macrophages) are still being explored. Some of such antigens (CD30, CD47, CD37, CD70) will be described later in more detail.

2. Antibody-Drug Conjugates

Antibody-drug conjugates could be considered a bridge between conventional chemotherapy which eliminates all rapidly dividing cells and more targeted immunotherapy combining the best anti-tumor properties of each of them [6].

Antibody-drug conjugates consist of three main parts: the mAb, the cytotoxic payload, and the linker, which connects the two together. Monoclonal antibody serves as a transporter of the payload and binds to the specific antigen on the surface of tumor cells. The antigen then triggers the internalization of the whole complex via endocytosis, the linker is degraded by lysosomal enzymes and the payload is released. Upon release, the cytotoxic agent eliminates the tumor cell by various mechanisms, most often by DNA damage or interaction with microtubules [7][8]. Several ADCs (e.g., brentuximab vedotin) exert their anti-tumor toxicity also via bystander effect that is characterized as capability of the payload to permeate through cell membranes and kill neighboring cells, regardless of the presence of the target antigen [6].

Monoclonal antibody should be directed against antigen highly expressed on tumor cells and with limited or no expression on normal tissues to avoid excessive off target toxicity [7]. Payload is required to be highly toxic in subnanomolar concentrations, to be able to conjugate with the antibody, and to remain stable in physiological conditions [6][8]. Nevertheless, the essential components of ADC from the perspective of biochemical stability are linkers and there are two types of them (cleavable and non-cleavable) [9]. The first group has the cleavage site located between payload and monoclonal antibody and the “separation” process may occur within the endosome, lysosome or cytosol itself, while the second group needs complete proteolytic degradation of mAb backbone within the lysosome to release the payload [7][8][9]. Another important attribute of ADC in terms of efficacy and safety is drug-antibody ratio (DAR) which is defined by the number of cytotoxic molecules attached to mAb and relates to ADC’s homogeneity and conjugation strategies [7][8][10].

As of 2021, eleven ADCs have been approved by the US Food and Drug Administration (FDA) in various hematological and oncological indications (**Table 1**) [8][10][11]. And many other ADCs are undergoing various stages of clinical testing. Results of phase I/II clinical trials, summary of currently ongoing phase III clinical trials and chemotherapy free clinical trials of ADCs are to be found in **Table 2** and **Table 3**.

Table 1. Antibody-drug conjugates approved by FDA for hematooncological and oncological disorders.

ADC	Diagnosis
gemtuzumab ozogamicine (Mylotarg, Pfizer)	**acute myeloid leukemia**
brentuximab vedotin (Adcetris, Seagen/Takeda Oncology)	**classical Hodgkin lymphoma specific CD30+ T-cell lymphomas**
inotuzumab ozogamicin (Besponsa, Pfizer)	**acute lymphoblastic leukemia**
polatuzumab vedotin (Polivy, Roche)	**diffuse large B-cell lymphoma**
belantamab mafodotin (Blenrep, GlaxoSmithKline)	**multiple myeloma**
loncastuximab tesirine (Zynlonta, ADC Therapeutics S.A.)	**large B-cell lymphomas**
moxetumomab pasudotox (Lumoxiti, Astrazeneca)	**hairy cell leukemia**
trastuzumab emtansine (Kadcyla, Genentech, Roche)	**HER2-positive metastatic breast cancer**
trastuzumab deruxtecan (Enhertu, AstraZeneca/Daiichi Sankyo)	**HER2-positive breast cancer**
sacituzumab govitecan (Trodelvy, Immunomedics)	**triple-negative breast cancer**
enfortumab vedotin (Padcev, Astellas/Seattle Genetics)	**urothelial cancer**

Table 2. Antibody-drug conjugates-available results of phase I-III clinical trials; EN, estimated enrollment; ORR, overall response rate; CR, complete remission; PR, partial remission; NA, not available; mPF, median progression free survival; mOS, median overall survival; m, month; RR, relapse and/or refractory; Ph, phase; B-NHL, B-cell non-Hodgkin lymphoma; I, indolent; a, aggressive; N, number; DLBCL, Diffuse large B-cell lymphoma; FL, follicular lymphoma; GZL, gray zone lymphoma; PV, polatuzumab vedotin; BV, brentuximab vedotin; Lonca, Loncastuximab tesirine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHP, cyclophosphamide, doxorubicin, prednisone; R, rituximab; G, Obinutuzumab; BR, bendamustine, rituximab; BG, bendamustin, obinutuzumab; NR, not reached; NE, not evaluable; m, months.

Title	Diagnosis	EN	Regimen	ORR % (N)	CR % (N)	mPFS	mOS	Ph	Identifier Reference Status
POLATUZUMAB VEDOTIN									

Title	Diagnosis	EN	Regimen	ORR % (N)	CR % (N)	mPFS	mOS	Ph	Identifier Reference Status
A Study of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma	RR DLBCL RR FL	331	Arm 1: PV + BR Arm 2: PV + BG Arm 3: BR	45% (18/40) 41% (11/27) 18% (7/40)	40% (16/40) 30% (8/27) 18% (7/40)	7.6m 6.3m 2.0 m	12.4m 10.8m 4.7 m	I/II	NCT02257567 [12] ongoing, not recruiting
A Study of Polatuzumab Vedotin in Combination With Rituximab or Obinutuzumab, Cyclophosphamide, Doxorubicin, and Prednisone in Participants With B-Cell Non-Hodgkin's Lymphoma	RR B-NHL	90	Arm 1: PV + R-CHP Arm 2: PV + G-CHP	89% (40/45) 90% (19/21)	76% (34/45) 81% (17/21)	NE	NE	I/II	NCT01992653 [13] completed
A Study of Obinutuzumab, Polatuzumab Vedotin, and Lenalidomide in Relapsed or Refractory Follicular Lymphoma (FL) and Rituximab in Combination With Polatuzumab Vedotin and Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	RR DLBCL RR FL	116	PV+R+Len PV+G+Len	74% (36/49) 83% (38/46)	35% (17/49) 61% (28/46)	6.3m NE	10.9m NA	I	NCT02600897 [14] [15] ongoing, not recruiting
LONCASTUXIMAB TESIRINE									
Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2)	RR DLBCL	145	Lonca	48.3% (70/145)	24.8% (36/145)	4.9m	9.5m	II	NCT03589469 [16] ongoing, not recruiting
Study of ADCT-402 in Patients With Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL)	RR B-NHL	183	Lonca	45.6% (82/180)	26.7 (48/180)	3.1 m	8.3 m	I	NCT02669017 [17] Completed
Safety and Efficacy Study of Loncastuximab Tesirine + Ibrutinib in Diffuse Large B-Cell or Mantle Cell Lymphoma	RR DLBCL RR MCL	161	Lonca + ibrutinib	63.9% (23/36)	36.1% (13/36)	NA	NA	I/II	NCT03684694 [18] ongoing
BRENTUXIMAB VEDOTIN									
An Investigational Immuno-therapy Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas (CheckMate 436)	RR DLBCL RR PMBCL	146	BV + nivolumab	73% (22/30)	37% (11/30)	NA	NR	I/II	NCT02581631 [16] ongoing, not recruiting
Brentuximab Vedotin and Chemotherapy in CD30+ PMBL, Diffuse Large B-Cell, and Grey Zone Lymphoma Patients	ND DLBCL ND PMBCL ND GZL	32	BV + R-CHP	100% (29/29)	86% (25/29)	NA	NA	I/II	NCT01994850 [19] completed

Table 3. Antibody-drug conjugates-phase III ongoing clinical trials and phase I-II ongoing chemotherapy free clinical trials with no available results (NCT03677154, NCT03533283, NCT03671018 are included in **Table 4**; EN, estimated enrollment; RR, relapse and/or refractory; ND, newly diagnosed; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, follicular lymphoma; PV, polatuzumab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; miniCHOP, dose modified CHOP, CHP, cyclophosphamide, doxorubicin, prednisone; miniCHP, dose modified CHP; R, rituximab; Gem, gemcitabine; Ox, oxaliplatin; Len, lenalidomide; ICE, ifosfamide, carboplatin,

etoposide; PV, polatuzumab vedotin; BV, brentuximab vedotin; Lonca, loncastuximab tesirine; BR, bendamustine, rituximab.

ADC	Diagnosis	EN	Regimen	Phase	Identifier	Status
PV	RR DLBCL	216	Arm 1: PV+R-GemOx Arm 2: R-GemOx	III	NCT04182204	ongoing
PV	RR DLBCL	42	Arm 1: PV + BR Arm 2: BR	III	NCT04236141	ongoing, not recruiting
PV	ND DLBCL	1000	Arm 1: PV + R-CHP Arm 2: R-CHOP	III	NCT03274492	ongoing, not recruiting
PV	ND DLBCL ND FL	200	Arm 1: PV + R-miniCHP Arm 2: PV + R-miniCHOP	III	NCT04332822	ongoing
PV	RR DLBCL	334	Arm 1: PV + R-ICE Arm 2: R-ICE	III	NCT04833114	ongoing
Lonca	RR DLBCL	350	Arm 1: Lonca-R Arm 2: R-GemOx	III	NCT04384484	ongoing
BV	RR DLBCL	400	Arm 1: BV+R+Len Arm 2: R+Len	III	NCT04404283	ongoing
PV	RR MCL	63	PV + R+Ven+Hyalur + Ven+Hyalur©	I/II	NCT04659044	not yet recruiting
PV	RR B-NHL	252	Arm 1: PV + CC-220 + R Arm 2: CC-220 + Tafasitamab Arm 3: CC-220 + R-GDP	I/II	NCT04882163	not yet recruiting
PV	RR FL RR DLBCL	133	PV+Obi+Ven + Obi+Venμ PV+R+Ven + R+Ven*	I	NCT02611323	ongoing
Lonca	RR FL	150	Lonca + idelalisib	I	NCT04699461	ongoing

2.1. Antibody-Drug Conjugates Approved for the Treatment of B-Cell Non-Hodgkin Lymphomas

2.1.1. Polatuzumab Vedotin, POLIVY™, DCDS4501A, RG7596 (Roche)

Polatuzumab vedotin (PV) consists of a humanized IgG1 mAb against CD79b (B-cell receptor component) and a microtubule-disrupting agent MMAE (monomethyl auristatin E) conjugated by a protease-cleavable linker [20][21][22].

GO29365 (NCT02257567) was an open-label, international, multi-center, randomized, phase Ib/II clinical trial evaluating safety and efficacy of PV plus bendamustine and rituximab (BR) or bendamustine and obinutuzumab (BG) in relapsed/refractory (RR) DLBCL and FL setting compared to BR alone [12][22]. The results proved superiority of PV plus BR opposed to BR. Overall response rate (ORR) was 45% (18/40) versus 18% (7/40), complete response (CR) was 40% (16/40) versus 18% (7/40), duration of response (DOR) was 10.3 versus 4.1 months, median progression free survival (PFS) was 7.6 versus 2.0 months and overall survival (OS) was 12.4 versus 4.7 months in RR DLBCL, but there was no benefit in RR FL patients [12][21]. Based on the results of this study, PV in combination with BR was approved for the treatment of transplant ineligible RR DLBCL patients after at least one (Europe) or two (USA) prior lines of therapy in combination with BR in 2019 [23].

Polatuzumab vedotin in combination with CHP (cyclophosphamide, doxorubicin, prednisone) and rituximab (R) or obinutuzumab (G) were also investigated in treatment naïve DLBCL patients in a phase I/II clinical trial (NCT01992653) [13]. Sixty-six patients were included in the phase II part. Overall response rate was 89% (59/66) with CR of 77% (51/66). 12-month PFS and OS were 91% and 94%, respectively. There was no significant difference in efficacy between PV plus R-CHP or PV plus G-CHP cohorts. Based on these promising results, a phase III study comparing standard of care for newly diagnosed (ND) DLBCL, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), with PV-R-CHP (NCT03274492, Polarix) has been ongoing and the results are impatiently awaited.

Other PV combination investigated in RR DLBCL with available primary data is PV plus rituximab and lenalidomide [14]. DLBCL cohort in this phase Ib/II clinical trial (GO29834, NCT02600897) was characterized by the median age of 71 years (28–92) and median of 2 prior therapies. The investigator-assessed best overall response was 74% (36/49) with 35% (17/49) of CR. It is worth mentioning that CRs were durable with 82% (14/17) of patients remaining in remission at the cutoff date which is a promising sign in this difficult-to-treat population. The same clinical trial included also a RR FL arm

investigating PV plus obinutuzumab and lenalidomide and the interim results were presented at British Society for Haematology 2020 Virtual meeting [15]. Efficacy population included 56 highly pretreated patients (median of three prior lines of therapy). At the median follow-up of 15.1 months, the data are still immature, but investigator-assessed ORR was 83% (38/46) with CR of 61% (28/46) by Modified Lugano 2014 criteria. Twelve-month PFS was 83.4%. This triplet appears to be a potent option for RR FL patients. However, longer follow-up is warranted for either arm.

Preclinical data suggest synergistic anti-tumor effect of PV and venetoclax (inhibitor of anti-apoptotic Bcl-2 protein) when PV promotes MCL-1 (myeloid leukemia cell 1) degradation, a known mechanism of resistance to venetoclax (Ven) [24]. That was the rationale of a phase Ib/II study (GO29833, NCT02611323) investigating the combination of PV with Ven and G for RR FL patients [25]. Study population was highly pretreated (74% ≥ 2 prior therapies) and 55% of patients were double refractory (to anti-CD20 mAb and alkylating agent). Primary analysis was presented at ASCO (American Society of Clinical Oncology) Meeting 2021. At the end of induction, PET (positron emission tomography)-CR was 57% (28/49). Median PFS was not reached and 12-month PFS was 73% with a median follow up of 14.4 months [25]. These results look encouraging, but data from maintenance treatment and beyond will be crucial to determine the benefit for this patient population.

Another promising PV combination for RR B-NHL patients is with mosunetuzumab (bispecific antibody targeting CD20 and CD3) and will be discussed further in text.

2.1.2. Loncastuximab Tesirine, ZYNLONTA™, ADCT-402 (ADC Therapeutics S.A.)

Loncastuximab tesirine (lonca) comprises of a humanized anti-CD19 IgG1 mAb attached to DNA-damaging agent, pyrrolobenzodiazepine (PBD) dimer toxin, by a protease-cleavable linker [7][17].

In 2021, Hamadani et al. published final results of a phase I study investigating this ADC as a monotherapy in RR B-NHL (NCT02669017) [17]. Patients had received median of three prior lines of systemic therapy. Overall response rate was 45.6% (82/180) in all evaluable patients with CR of 26.7% (48/180). Median DOR (duration of response) was 5.4 months for the whole cohort and was not reached for DLBCL patients who achieved CR. As this was primarily the dose-escalation and dose-expansion study, recommended dose for a phase II trial (LOTIS-2, NCT03589469) aiming at RR DLBCL was determined as 150µg/kg every three weeks for two doses followed by 75µg/kg every three weeks [16]. Interim results showed ORR 48.3% (70/145) with 24.8% CR (36/145). Median DOR for responders (CR + PR; PR = partial remission) was 12.6 months and not reached for patients with CR. Median PFS and median OS were 4.9 and 9.5 months, respectively. Lonca showed efficacy even in high risk groups such as double or triple-hit, transformed or refractory DLBCL. These encouraging results led to the FDA approval of lonca monotherapy for large B-cell lymphomas (DLBCL, transformed DLBCL, high grade B-cell lymphoma) after at least 2 prior lines of therapy in April 2021 [26].

Besides monotherapy, lonca is currently being tested in combination with ibrutinib in RR DLBCL and RR MCL in phase I/II trial (LOTIS-3, NCT03684694). Preliminary results for 36 evaluable patients from a phase I part were recently presented at ICML (International Conference on Malignant Lymphoma) 2021 and the efficacy data looked promising with ORR of 63.9% (23/36) and CR of 36.1% (13/36) [18]. Another investigated combination includes lonca plus rituximab versus R-GemOx (rituximab, gemcitabine, oxaliplatin) for RR DLBCL patients in a phase III study (LOTIS-5; NCT04384484), but the results are not available yet [27]. Loncastuximab tesirine is also being considered for the treatment of RR FL in a phase II clinical trial (LOTIS-6; NCT04699461) opposed to idelalisib [28].

2.2. Other Antibody-Drug Conjugates Investigated in B-Cell Non-Hodgkin Lymphomas

2.2.1. Brentuximab Vedotin, ADCETRIS®, SGN-35 (Seagen/Takeda Oncology)

Brentuximab vedotin (BV) consists of a microtubule-disrupting agent MMAE, but this time covalently attached by a protease-cleavable linker to the humanized mAb directed against CD30 [29][30]. Transmembrane receptor CD30 can be found on classical Hodgkin lymphoma´s (cHL) Reed-Sternberg cells, on some T-cell malignancies and on a subset of DLBCL as well [20][30]. As of 2021, BV has been approved for the treatment of RR cHL, ND, and RR CD30+ systemic anaplastic large cell lymphoma and RR CD30+ cutaneous T-cell lymphoma [29][31][32][33][34].

Primary mediastinal large B-cell lymphoma (PMBCL) is a specific subtype of DLBCL which shares some characteristics with cHL, especially high CD30 expression [35]. That is why similar efficacy was expected from BV monotherapy in RR PMBCL patients. A phase II study investigating BV in this setting (NCT02423291) did not confirm this hypothesis with ORR of only 13.3% (2/15) and with no CR achieved. Therefore, BV alone is considered inactive in RR PMCBL. Nevertheless, Zinzani et al. presented the data of a phase I/II combination trial of BV with nivolumab (immune checkpoint inhibitor) in RR PMBL at ICML 2021 and the results were just the opposite (NCT02581631, CheckMate436) [36]. Thirty

highly pretreated patients were recruited with a median of two prior lines of therapy. Results from the extended median follow up of 33.7 months showed ORR of 73% (22/30) with CR of 37% (11/30). Median DOR was 31.6 months and median duration of CR and median OS have not been reached. As this combination proved its efficacy and long-term survival benefits, a phase II study of BV + nivolumab with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) for newly diagnosed ND PMBCL is currently underway (PACIFIC, NCT04745949).

Not only PMBCL, but CD30+ DLBCL and gray zone lymphoma (GZL) could be appropriate targets for BV combination therapy. In a phase 1/2 multicenter trial (NCT01994850), 29 patients with ND CD30+ B-cell lymphomas (22 PMBCL, 5 DLBCL, 2 GZL) were treated with 6 cycles of BV + R-CHP and 52% of patients followed consolidative radiotherapy [19]. Overall response rate was 100% with 86% CR and there was no difference between radiotherapy + or-cohort. At the median follow-up of 30 months, 2-year PFS and OS were 85% and 100%, respectively. These results are quite promising but should be regarded with caution due to the small study cohort.

At ICML 2021, preliminary results from a phase I combination trial of BV plus lenalidomide and rituximab for RR DLBCL were foreshadowed [37]. Among 37 evaluated patients, ORR was 56.7% (21/37) and median DOR was 13.2 months for the responding patients (CR+PR). The PFS and median OS reached 11.2 months and 14.3 months, respectively. It is worth mentioning that the results were similar between CD30+ and CD30 < 1% cohorts. Based on these promising outcomes, a phase III study comparing lenalidomide and rituximab plus BV/placebo in RR DLBCL setting was initiated (ECHELON-3, NCT04404283).

2.2.2. Naratuximab Emtansine, Debio1562, IMGN529 (Debiopharm)

Naratuximab emtansine (nara) represents a humanized anti-CD37 IgG1 antibody conjugated via a non-reducible thioether linker to a potent anti-mitotic agent—maytansinoid DM1 [7][38] Transmembrane protein CD37 has the highest abundance on mature B-cells and it is expressed only in a low level on T-cells and myeloid cells [7][39]. Under physiological condition, CD37 plays a role in normal B-cell activation and survival. On the other hand, it is highly expressed on most histological subtypes of B-NHL.

Naratuximab emtansine was evaluated in a phase I study (NCT01534715) in heavily pretreated RR NHL patients (median of three prior systemic regimens) and the results were encouraging with ORR 22% (4/18) in DLBCL cohort [38]. Based on these results, nara was selected for a phase II clinical trial in combination with rituximab for RR B-cell NHL patients (NCT02564744) [40]. Seventy-four RR DLBCL patients were evaluable for efficacy and ORR of 43.2% (32/74) with 32.4% (24/74) of CRs were observed in this group. Median DOR was not reached during median follow-up in responders of 13.7 months.

2.2.3. Other Antibody-Drug Conjugates

There are several ADCs that were tested in B-NHL setting but were not pursued further due to safety or efficacy reasons. Pinatuzumab vedotin (anti-CD22 mAb + MMAE) was initially investigated together with PV in a phase II study ROMULUS, but was abandoned thereafter for PV´s better results [41]. Camidanlumab tesirine (anti-CD25 mAb + PBD) is currently more extensively researched in cHL than B-NHL setting [42][43]. Coltuximab ravtansine (anti-CD19 mAb + microtubule disruptive agent DM4) showed only a moderate efficacy in RR DLBCL in contrast with another CD19 targeting agent—lonca [44][45]. Three CD70 targeting ADCs (SGN-CD70A, MDX-1203, vorsetuzumab mafodotin) raised safety concerns due to treatment-emergent toxicities [7][46][47][48]

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