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Immunotherapy in indolent Non-Hodgkin's Lymphoma

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ABSTRACT

Treatment of non-Hodgkin lymphoma (NHL) in general has improved over the years with the emergence of the monoclonal antibodies (MAB) therapy. NHL is divided into B cell NHL and T cell NHL. Treatment of NHL was based on the subtype of NHL and its staging. NHL is divided into aggressive and indolent NHL (iNHL). Subtypes of iNHL include: Follicular lymphoma (FL), Marginal zone lymphoma (MZL), Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL), Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, Nodal marginal zone lymphoma (NMZL), Splenic marginal zone lymphoma (SMZL). Chemotherapy was the main stay treatment of iNHL until the emergence of Rituximab, anti-CD20 MAB targeting CD-20 surface cell antigens that are present on B-cells lymphoma and not on precursor cells, mainly efficacious in B cell iNHL, It became the mainstay treatment in follicular lymphoma (FL) as a single agent modality or in combination with chemotherapy. The anti-CD20 Rituximab played an important role in the development of the treatment of iNHL to become FDA approved in 1997. It was also proven effective in multiple other types of lymphoma. MAB through targeting the cell surface antigen leads to a direct or immune mediated cytotoxicity. This carries few side effects, including allergic reactions. Other than that, a resistance mechanism to rituximab emerged by inducing a failure in the apoptosis mechanism. Alternative mechanisms of resistance included the presence of soluble antigens that could act by binding to the antibody present before the drug itself can bind the lymphoma cell. Thus, the interest in immunotherapy grew further to explore the possibility of conjugating an immune mediated drug to a radio-sensitizing agent in order to enhance the selectivity of the drug. Here came the development of 90Y-ibritumomab tiuxetan and 131I-tositumomab. After it, humanized anti-CD20 emerged ofatumumab, IMMU106 (veltuzumab) in 2005, and ocrelizumab which are considered as second generation anti-CD20 and 3rd generation anti-CD20 include AME-133v (ocaratuzumab), PRO131921 and GA101 (obinutuzumab). Also multiple other agents emerged targeting different surface cell antigens like CD52 (alemtuzumab), CD22 (unconjugated epratuzumab and calicheamicin conjugated CMC-544 [inotuzumab ozogamicin]), CD80 (galiximab), CD2 (MEDI-507 [siplizumab]), CD30 (SGN-30 and MDX-060 [iratumumab], Brentuximab vedotin), CD40 (SGN-40), and CD79b (Polatuzumab). Other agents include MAB targeting T-Cells like mogamulizumab, Denileukin Diftitox and BiTEs or bispecific T cell engagers like Mosunetuzumab, Glofitamab, and Epcoritamab. Moreover, further studies came up to evaluate the role of immunotherapy in combination chemotherapy as a pathway to evade the resistance mechanisms. Side effects of the treatment were mainly infusion related adverse reactions, myelosuppression in conjugated forms leading to immunosuppression and subsequently to infectious complications. Another important aspect in immunotherapy is the half-lives of the medication which is an important factor that can influence the evaluation of the response. The MAB treatment showed important benefit in the treatment of iNHL and it continuously shows how rapidly it can develop to provide optimum care and benefit to patients with iNHL.

1. Introduction

Indolent NHL includes multiple subtypes mainly divided into B cell NHL and T cell NHL. B cell NHL include: Follicular lymphoma (FL), Marginal zone lymphoma (MZL), Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL), Mantle cell Lymphoma (MCL), Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Lymphoplasmacytic lymphoma, Waldenström macroglobulinemia (WM), Nodal marginal zone lymphoma (NMZL), Splenic marginal zone lymphoma (SMZL) (Table 1) [1]. Treatment approaches are decided

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Table 1
Classifications and frequency of iNHL (40-50% on NHL), The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Type	Frequency %
Folicular lymphoma	22
Cutaneous T-cell lymphoma: Mycosis Fungoides and Sezary Syndrome	4
Marginal zone B-cell lymphoma (Nodal marginal zone lymphoma (NMZL), Nodal marginal zone lymphomaSMZL, MALT)	13
Waldenström macroglobulinemia (WM), Lymphoplasmacytic Lymphoma (LPL)	2
Small-cell lymphocytic Lymphoma (SLL), CLL	6
Mantle Cell Lymphoma (MCL)	1
Adult T-cell leukemia/lymphoma	1

selectively based on the lymphoma type/class/grade/stage [2]. FL is the most common iNHL [1]. Small percentage of iNHL present at early stages with localized disease [3]. Treatment of early stages constituted of close watch and wait strategy for symptoms free without any treatment and multiple studies have shown no benefit from early interference on the overall survival (OS) [2]. For stage I low grade FL curative approaches constituted of external beam radiation [2]. With the emergence of the Immunotherapy the treatment paradigm for iNHL changed over the years. It all started with the anti-CD20 MAB, rituximab which was a chimeric MAB that showed impressive results in the management of FL initially in relapsed/refractory (R/R) cases to be later evaluated in first treatment as single agent or in combination with chemotherapy or with targeted agents as venetoclax, ibrutinib or lenalidomide [5]. After it, humanized anti-CD20 emerged ofatumumab, IMMU106 (veltuzumab) in 2005, and ocrelizumab which are considered as second generation anti-CD20 and 3rd generation anti-CD20 include AME-133v (ocaratuzumab), PRO131921 and GA101 (obinutuzumab) [6]. Also multiple other agents emerged targeting different surface cell antigens like CD52 (alemtuzumab), CD22 (unconjugated epratuzumab and calicheamicin conjugated CMC-544 [inotuzumab ozogamicin]), CD80 (galiximab), CD2 (MEDI-507 [siplizumab]), CD30 (SGN-30 and MDX-060 [iratumumab], Brentuximab vedotin), CD40 (SGN-40), and CD79b (Polatuzumab). Other agents include MAB targeting T-Cells like mogamulizumab, Denileukin Diftitox and BiTEs or bispecific T cell engagers like Mosunetuzumab, Glofitamab, and Epcoritamab. [7,8]

The evolvement of immunotherapy continued by further investigation of the cell surface markers of B-cell lymphomas. It was found that almost all B-cells in FL are positive for monoclonal surface immunoglobulin (Ig), HLA-DR, pan-B cell antigens (CD19 and CD20), CD21, CD10, and CD79a and negative for CD5, where Small lymphocytic lymphoma (SLL) and B-cell chronic lymphocytic leukemia (B-CLL) are positive for HLA-DR, pan-B antigens (CD19, CD20, and CD22), CD23, weak sIgM±IgD, and CD5 and from here multiple MAB emerged targeting different cell surface antigen in the aim to provide better control on disease relapse and OS [8–10].

Targeting B-cells

1-a. Chimeric Anti-CD20 Monoclonal: Rituximab

B-cells express different cell surface antigens and this made them a target for different MAB. 1975 was the birth year for MAB. Immunotherapy was highly studied starting with anti-CD20, a MAB targeting a cell surface antigen, CD-20, of the B-cell lymphoma expressed homogenously among the B-cell and completely absent from precursor stem cells [4]. Rituximab as a chimeric anti-CD20 is crucial in the treatment on iNHL whether as first line or in R/R cases. It received its FDA approval in 1997 and the European authorization in 1998: 1st line as single agent [11], second line therapy [12], maintenance [13] or when combined with chemotherapy [14]. The mechanism of action of Rituximab can be summarized through 3 different pathways: complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) and complement dependent cellular cytotoxicity [15].

As a 1st line treatment in FL, Rituximab added to cyclophosphamide, vincristine and prednisone (R-CVP) showed an increase in the response rate from 57 % with CVP alone to 81% when rituximab was added and same results were proven when rituximab was added to other chemotherapy protocols like CHOP (cyclophosphamide, hydroxydaunorubicin, Vincristin, and prednisone), CHVP (cyclophosphamide, hydroxydaunorubicin, etoposide and prednisolone plus interferon-2) [4,11], [13].

In a phase III trial for the front-line treatment of FL, R-CVP was demonstrated to have an overall response rate (ORR) of 81% compared with 57% for patients treated with CVP alone, with a median time to treatment failure of 27 months versus 7 months[11]. The addition of rituximab to other chemotherapy regimens such CHOP and fludarabine-based regimens has also addressed improved treatment outcomes[11]. Rituximab was also studied in R/R iNHL where in an international trial it was compared between CHOP alone vs rituximab with CHOP in R/R iNHL the ORR was 85% with R-CHOP compared to 72% with CHOP alone and PFS was 33.1 months in rituximab arm compared to 20 months in CHOP alone ($P < 0.001$)[14]. Rituximab was also studied in combination with Bendamustin in BRIGHT and STILL trials as 1st line in iNHL considering its acceptable safety profile as chemotherapy free regimen in comparison to R-CHOP[15,16]. In Addition, it was studied in combination with lenalidomide followed by maintenance rituximab in RELEVANCE study in comparison to R-chemotherapy showing similar CR, ORR,PFS, OS yet better tolerable side effects[17] to become later FDA approved based on AUGMENT trial in R/R iNHL in FL and MZL[18]. Rituximab was also being studied as maintenance post combination chemo-immunotherapy in 1st line follicular lymphoma in the PRIMA phase 3 study where patients received rituximab every 8 weeks for 2 years and with a median follow-up of 36 months the PFS was 74.9% in the rituximab maintenance group compared to 57.6% in the observation group with a significant P value of <0.0001[19]. Rituximab was also studied in MCL, characterized by expression of the B-cell markers **CD19, CD20, CD22, CD79a and BSAP/PAX5**, where 638 patients with a mean age of 75 years at diagnosis, stage III/IV constituted 75% of the patients and 64% of them received rituximab in first line treatment[20]. 27 months was the median survival for chemotherapy alone, compared with 37 months for chemotherapy plus rituximab ($P < .001$)[20]. Lyma Trial was then performed to show the effectiveness of rituximab maintenance post ASCT in young patients with MCL after induction with chemo-immunotherapy regimens[21]. The 4 years PFS and OS were superior in the rituximab maintenance arm and the median OS and PFS was not reached in the rituximab maintenance arm[21]. In addition, Rituximab was shown to be effective in the treatment of splenic marginal zone lymphoma (SMZL), characterized by expression of **CD20^{+}, CD5^{-}, CD10^{-}, CD23^{-}**, with surface immunoglobulin light chain restriction, where the study was performed on 108 patients[22]. Treatment was initiated depending on the presence of absence of symptoms like: bulky/symptomatic splenomegaly, cytopenias, B symptoms, and autoimmune manifestations[17]. Rituximab was given at a 6 weekly infusions (375 mg/m^2) to be followed by maintenance every 2 months for 1 or 2 years based on response vs follow up alone[22]. The overall response rate was 92% and the 5- and 10-year OS rates were 93% and 85% respectively[22]. Freedom from progression (FFP) was significantly better with maintenance therapy: 5- and 9-year FFP rates were 79% and 76% for patients who received maintenance vs 52% and 42% for those who did not with a $P = .0006$[22]. As for the role of rituximab in frontline MALT patient, characterized by expression of CD20+, IgD−, IgM (>IgA>IgG)+, CD5−, CD10−, Bcl6−, cyclin D1, IELSG-19, phase 3 trial had patients randomized into 3 arms: chlorambucil monotherapy, rituximab monotherapy, and the combination of rituximab and chlorambucil[23]. The EFS, which was the primary end point, was not reached in the combination arm with good toleration[23]. Other than

that we have MZL that was studied in the phase 2 BRISMA/IELSG36 trial, where 45 patients with frontline splenic MZL were treated with R-Bendamustine, to get an ORR of 82%, CR 73%, and a 3-year PFS of 90%[24]. As for the side effects of rituximab, they most commonly happen after 1st infusion and are mostly related to infusion reactions including fever, chills, hypotension, arrhythmia, dyspnea and hypoxia with the risk of reactivation of hepatitis B virus as well as it contribute to the development of hypogammaglobulinema[12]. And from here, in order to enhance the side effects, the response rates and the half-lives of rituximab further investigation took place in this domain[25].

Rixathon, another chimeric anti-CD20 biosimilar was investigated in iNHL and it was compared to rituximab showing similar efficacy and functionality with only difference in the size and charge heterogeneity and glycosylation pattern[26,27]. Another biosimilar emerged in 2020, Ruxience as anti-CD20 that was FDA approved for the use in NHL where its effectiveness and safety was proven in the Reflections B3281006 study when compared directly to rituximab in low tumor burden FL where no difference was shown in its clinical benefits and safety profile [28].

Rituximab is also studied in WM/LPL, as WM cells express CD20[29]. The addition of rituximab to fludarabine and cyclophosphamide as well as to revlimid was also associated with increase in RR with well tolerated side effects[30–32]. Bendamustine with Rituximab combination was also evaluated in WM as well as in MCL[33]. MCL is managed based on age where less than 65-70 years are candidates for ASCT and above 65-70 years are treated without transplant, yet both are treated with chemoimmunotherapy[34]. Transplant eligible patients can be managed by different induction protocols based on different trials[34]. 3 Phase 2 trials discuss the use of R-HYPERCVAD and its efficacy in MCL in younger patients[34,35]. After 15-year follow-up (median, 13.4 years) the median failure-free survival improved from 4.8 to 6.5 years and OS improved from 10.7 years to 13.4 years[35]. The more used protocols include cytarabine in pretransplant induction of rituximab in combination with alternating cycles of maxi-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and high-dose cytarabine, followed by ASCT[34]. The 6-year PFS was 66% and the 6-year OS was 70%, and after 15-years of follow-up (median 11.4 years) the median PFS was 8.5 years and OS was 12.7 years[34,36]. In phase 2 French study it evaluated RCHOP/RDHAP (rituximab, cisplatin, cytarabine, dexamethasone) by randomizing patients to RCHOP or RCHOP/RDHAP, followed by ASCT[37]. After a median follow-up of 6.1 years, there was a significant improvement in TTF (9.1 vs 3.9 years, $P = .038$), although OS was not significantly different [34,37].As for older adults two randomized phase 3 trials established efficacy of BR, showing prolonged PFS with BR compared with RCHOP[38]. In addition, given bortezomib's efficacy in relapsed disease, a randomized phase 3 trial evaluated R-CHOP vs cyclophosphamide, doxorubicin, bortezomib, and prednisone (VR-CAP),and at a median follow-up of 40 months, VR-CAP had significantly improved PFS (24.7 vs 14.4 months, $P < .001$)[39].

1-b. Humanized Anti-CD20 Monoclonal Antibody: 2nd generation [ofatumumab, IMMU106 (veltuzumab), and ocrelizumab] **3rd generation** [AME-133v (ocaratuzumab), PRO131921 and GA101 (obinutuzumab)]

In the advances of overcoming the side effects of rituximab as a chimeric MAB causing infusion reaction side effects and requiring prolonged infusion time, humanized MAB came to birth with ofatumumab [40]. As a fully humanized antibody (Ab) it functions by recognizing the CD-20 and encircling both the small and large extracellular loops of CD-20 enhancing CDC and inducing apoptosis in a more effective manner than rituximab and it has been indicated in autoimmune diseases[41] as well as it was studied in HOMER phase 3 trial in R/R iNHL in comparison with rituximab and it showed no-superiority over rituximab[40]. Another humanized MAB IMMU-106 (veltuzumab) was also studied[5]. Its efficacy was proven through a phase1/2 study where the study population included relapsed iNHL as well as intermediate to aggressive B-Cell NHL showing ORR 53% and 40% CR[5]. Infusion related side effects as well as infusion time was reduced compared to rituximab showing promising results to be further studied in 1st line approaches[5]. Then came ocrelizumab as a 2nd generation humanized anti-CD20 MAB with the special criteria of increased binding affinity for the low-affinity variants of the FcγRIIIa receptor[41]. Its activity in iNHL was proven in a phase 1/2 of R/R FL after prior rituximab therapy where 47 patients received ocrelizumab with 3 sequential dose cohorts to show ORR of 36% with acceptable toxicity profile where mostly were grade 1/2 infusion related reactions and this makes it encouraging for use in rituximab R/R iNHL[41].

3rd generation Anti-CD20 humanized MAB include AME-133v (ocaratuzumab) which characterized by its increased affinity to CD20 and its enhanced vitro by ADCC activity[42]. A phase 1 study was performed in heavily pretreated FL where patients included received one of five dose-escalation cohorts of AME-133v showing an ORR of 22% and the median PFS was 25.4 weeks indicating promising results [23]. Another 3rd generation anti-CD20 MAB is PRO131921 also characterized by its increased ADCC and CDC compared to rituximab[43]. It was studied in a phase 1/2 as well where patients with R/R iNHL were infused PRO131921 weekly for 4 weeks at a dose escalation process based on safety ranging from 25 mg/m^2 to 800 mg/m^2, the ORR was 27% and it was noticed that higher AUC showed better response and thus better pharmacokinetic study would help improve the drug efficacy which can be implicated on other MAB[43].

Then came Obinutuzumab which is another humanized anti-CD20 monoclonal antibody and when compared to rituximab, it had an enhanced activity in direct non-apoptotic cell cycle arrest as well as a diminished level of CDC with increased ADCC and that it is mainly due to the benefit of the enhanced Fc–Fcγ receptor (FcγR) III interaction [6]. The GAUDI study as a phase 2 trial showed the efficacy of Obinutuzumab when combined with CHOP or when combined with FC (fludarabine and cyclophosphamide) reaching a CR rate of 64% and 50%, respectively with ORR 96% and 93% respectively where patients responding to Obinutuzumab were maintained on it for 2 years[44]. Gallium study compared Obinutuzumab based chemotherapy to rituximab based chemotherapy in first line treatment of FL, where responding patients were maintained on the antibody used for 2 years[45]. The 3-year PFS rate was 80.0% for Obinutuzumab arm compared 73.3% in rituximab arm[45] but infusion related adverse events were more common in Obinutuzumab arm[45]. It was also studied in GADOLIN study a phase 3 trial that included patients with iNHL that were refractory to rituximab where they received Obinutuzumab in combination with bendamustine vs bendamustine alone to be followed by Obinutuzumab maintenance showing improvement in PFS in the cohort receiving the combination arm where median PFS was not reached compared to 14.9 month in bendamustine monotherapy arm and it was associated with prolonged OS indicating that there is a new treatment option for rituximab refractory iNHL[46].

Obinutuzamb was also studied in CLL, rituximab as anti CD-20 in combination with chemotherapeutic agents was shown to be effective in fit newly diagnosed CLL patients, thus the CLL-11 trial was performed to assess the efficacy of obinutuzumab- chlorambucil combination in comparison to Rituximab-chlorambucil[42]. The combination treatments was superior to chlorambucil single agent in terms of response rates, OS and PFS[42]. Treatment with obinutuzumab–chlorambucil resulted in prolonged PFS as compared with rituximab–chlorambucil and higher rates of complete response (20.7% vs. 7.0%)[47]. Infusion related reaction were observed more with Obinutuzumab arm[47].

1-c Anti-CD20 Radioimmunotherapy: 90Y-ibritumomab tiuxetan and 131I-tositumomab

After the success that immunotherapy showed in the management of iNHL, radioisotopes were combined to MAB anti-CD20 to formulate 2

types of radio-immunotherapy drugs: 90Y-ibritumomab tiuxetan and 131I-tositumomab[48]. The association between anti-CD20 and radio-isotopes enhances the role of the medication and allows its infiltration into bulky and poorly vascularized tumors and thus it can help targeting radiation to tumor cells avoiding the exposure of normal cells[49]. The Y90 isotope can deliver a high energy level and has a has a path length of 5 to 10 mm and consequently it can target the cancerous cells and neighboring environment[49]. This combination have proven a CR of 26% and RR of 67% in a multicenter trial in relapsed low-grade or intermediate B-cell NHL[50]. In FL the ORR were 65% ORR with 20% CR yet it still caused severe infusion related reactions like rituximab as well as skin reactions in association with hematological toxicities like anemia, thrombocytopenia and mainly severe neutropenia adding to that the logistic problems for the preparation and the infusion of the drug [50]. In addition it carries a long term toxicity of inducing MDS/AML due to the toxicity induced on the bone marrow[49].

2- Anti CD-19 Antibodies:

B-cells express a transmembrane protein CD-19 that has been a cornerstone target in the CAR-T cell therapies on B-cell acute Lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Targeting CD-19 with a MAB has been an interest in R/R NHL. A humanized anti-CD19 MAB Tafasitamab (MOR208) has been evaluated in a phase 2 trial in patient with R/R B-NHL after progression on rituximab based therapy and the ORR including FL and MZL was 29%[51]. It is also being investigated in combination with Lenalidomide and Rituximab in phase 3 trial (InMIND) in comparison to R-R with placebo in R/R FL or MZL(NCT04680052).

3- Anti CD-22 Antibodies: Conjugated and Unconjugated

3.a. Non-FDA Approved: A MAB targeting the cell surface antigen of the B-cells CD-22 was investigated. It was called LL2 antibody, an IgG2a mouse MAB against CD22[52]. Epratuzumab is the humanized version of anti-CD22 and it is labeled with 131I and 111Indium/90Y for further specification to the tumor and it was studied in R/R aggressive NHL as well as in relapsed NHL[52]. Investigations took place in adding Epratuzumab to Rituximab alone showing ORR of 63% for iNHL with 56% CR[53]. It is only FDA approved as second line in CLL but associated with severe side effects[53].

3.b. FDA Approved: Like rituximab, anti-CD22 was also tried in a conjugated form, linked to 90Y-ibritumomab tiuxetan and 131I-tositumomab to potentiate its activity in killing the lymphoma cells, yet this holds an increase in the potential side effects mainly severe myelosuppresion[54]. One radio conjugated anti-CD20: 90Y- Epratuzumab was studied in a clinical trial as a once per week infusion for 2-4 weeks to show a good ORR in both indolent and aggressive lymphoma patients, ORR was 75% in indolent NHL[54]. Another important conjugated anti-CD22 is inotuzumab ozogamicin, an anti CD22 conjugated to an antitumor antibiotic Calicheamicin, the data on this drug is mainly in B-cell acute lymphoblastic leukemia (B-ALL) but there is data from a phase one study in aggressive NHL and from preclinical data that shows promising results to be further investigated but not yet in iNHL[55].

4. Anti CD-80: Galiximab

FL B-cells can be characterized by the presence of CD-80 membrane protein co-stimulatory molecule that helps in the regulation of the activation cascade of T-cells[56]. This molecular has been a target in FL through the anti-CD80 Galiximab that was studied in R/R FL as a single agent where minimal adverse events were noticed, and it was shown to have a longer half-life compared to rituximab[56]. The ORR was only 11% yet there was a decrease in the size of the tumor in 49% of the patients and what was interesting in this study is that the responses were noticed to be delayed where one patient achieved CR after 1 year of treatment initiation raising the possibility that galiximab would trigger an active immune response[56].

5- Anti-CD30: Brentuximab Vedotin (BV)

Brentuximab Vedotin as anti-CD30 was also studied in CD30 positive cutaneous T cell lymphoma (CTCL) in first line and in R/R cases as a single agent [57]. In a phase II open-label trial, BV was given to 48 patients with CD30(+) lymphoproliferative disorders mycosis fungoides (MF) to show an ORR of 73% and CR of 35%[57]. Brentuximab vedotin has also been investigated in ALCANZA trial in previously treated MF CD30 positive where patients were randomized to brentuximab vedotin 1•8 mg/kg once every 3 weeks, for up to 16 3-week cycles, or physician's choice of oral methotrexate 5–50 mg once per week or oral bexarotene 300 mg/m^2 once per day for up to 48 weeks[49]. There was an improvement in objective response observed at 4 month in brentuximab arm in comparison to other arms[58].

6- Others: Anti-CD52: Alemtuzumab, **Anti CD-40:** SGN-40 and HCD122, **Anti CD79b:** Polatuzumab

CD-52 is another cell surface antigen present profoundly on surface of B-and T-cells[59]. It was studied initially in CLL and then investigated in advanced-stage MF/Sezary syndrome and in peripheral T-cell lymphoma but not in iNHL[59,60]. Its applicability is limited but it is still considered the main therapy for T-cell prolymphocytic leukemia (T-PLL) [60]. It has a wide variety of side effects mainly reactivation of Cytomegalovirus, hemophagocytosis and neutropenia[60].

CD40 cell surface antigen is regularly expressed by normal B and T-lymphocytes as well as several types of malignant cells and there is also the CD40L (CD154) is less frequently expressed[9] and the soluble type of CD40L can be present and identified in the serum of disease patients with lymphoma and autoimmune diseases as well as with essential thrombocythemia[61]. Two antibodies have been studied: 1- SGN-40 which is a humanized IgG1 anti CD-40 antibody which works on inhibition of proliferation and induction of apoptosis[62], In a phase 1/2 trial to evaluate the safety of the drug where 111 patients were included divided between NHL (n = 74) and HL (n = 37). The ORR in patients with FL was 33.3% and with marginal zone lymphoma of mucosa-associated lymphatic tissue (MZL/MALT) was 42•9%[63].

HCD122 which is a humanized IgG1 anti-CD40 antagonistic monoclonal antibody which showed in vitro activity in CLL and iNHL mainly in FL[63].

Polatuzumab Vedotin, anti-CD79b antibody conjugated to monomethyl auristatin E, has been shown to be effective in R/R NHL mainly in FL and DLBCL in combination with rituximab or Polatuzumab with rituximab and bendamustin based on phase1/2 studies and it was FDA approved in June 2018 for R/R DLBCL[64]. It is also being investigated with combination with bendamustine and rituximab for the treatment for R/R FL or with rituximab alone (Table. 2)[64]. ROMULUS Trial investigated Polatuzumab in combination with rituximab vs Pinatuzumab (antiCD-22) in combination with Rituximab in patients with R/R DLBCL and FL[65]. In the R-Pina group 60% of DLBCL patients achieved objective response where 54% in R-pola achieved objective response [65], where objective response was higher in R-pola in the FL group than in R-pina group[65].Side effects were similar among both groups[65]. This shows that R-pina and R-pola combination can be potential treatment options in R/R DLBCL and FL[65].

B- Targeting B –cells (BiTEs and MAB)

Further development in immunotherapy include the emerging BiTEs or bispecific T cell engagers, which facilitated the role of immunotherapy[66]. Bispecific antibodies are mainly divided into 3 groups based on their targets: 1- antibodies targeting two different tumor antigens; 2- antibodies targeting one tumor antigen and one immune-related molecule; 3- antibodies targeting two immune-related molecules[66]. BiTEs are part of the second group because one BiTE molecule tends to target one CD3 molecule and one tumor antigen at same time[66]. We have 2 categories: Anti CD3/CD20 and Anti CD3/CD19:

1- **Anti CD3/CD20: Mosunetuzumab, Glofitamab, and Epcoritamab**

In **phase I/Ib GO29781 study that showed mosunetuzumab as a BiTes molecule anti CD-20 and Anti CD-3 demonstrated high response rates and durable complete remissions in people with** (R/

Table 2
Monoclonal antibody-based therapy for patients with i-NHL. PFS is recorded as rate or median. FL: follicular lymphoma, mo: months, yr: years, MALT: mucosa-associated lymphoid tissue, MZL: marginal zone, lymphoma, MCL: mantle cell lymphoma, SLL: small lymphocytic lymphoma, SMZL: splenic marginal zone lymphoma, WM: Waldenstrom's macroglobulinemia, LPL: lymphoplasmacytic lymphoma, PMBCL: primary mediastinal B cell lymphoma, GZL: gray zone lymphoma, PTLD: post-transplant lymphoproliferative disorder, PBL: plasmablastic lymphoma, Benda: bendamustine, Chlor: chlorambucil, R: rituximab, O: obinutuzumab, PoV: polatuzumab vedotin, PiV: pinatuzumab vedotin. NA

Target	Monoclonal Antibody	Study	Disease Entity	PFS
Anti CD-20				
Chimeric	Rituximab	PRIMA Trial: R-chemo +/- Maintenance [8]	FL	Median 10.5 vs 4.1 yr (P<0.0001)
		Relevance: R-Lenalidomide vs chemo [19]	Advanced FL	Rate:77 vs 78 at 3 yr (p=0.48)
		BRISMA/ IELSG36: R-BENDA[26]	Splenic MZL	Rate: 90% at 3 yr
		BRIGHT: R-BENDA vs R-CHOP/CVP [17]	iNHL (LPL, MZL, MCL, FL)	Rate:65.5 vs 31.2 at 5 yr (p=0.0025)
		STIL: R-BENDA vs R-CHOP[18]	iNHL (LPL, MZL, MCL, FL, SLL)	Rate: 69 vs 31 (p=0.001)
		IELSG-19: R-Chlor vs chlor vs R[25]	MALT	Median NR vs 8.3 vs 6.9 yrs (p=0.0119)
Humanized	**2nd generation**: Ofatumumab	HOMER: Ofatumumab vs Rituximab [31]	R/R iNHL (FL, MZL, SLL, WM)	Median 16.3 vs 21 mo (P=0.292)
	3rd generation: GA101 (obinutumumab)	Gallium: O-Chemo vs R-Chemo[36]	FL	Rate: 80 vs 73at 3 yr (P<0.0001)
		GADOLIN: O-Benda vs Benda[37]	R/R iNHL (FL, MZL, SLL, WM)	Median 25.8 vs 14.1 mo (P<0.0001)
Radiolabelled	90Y-ibritumomab tiuxetan	A multicenter trial in relapsed low-grade or intermediate B-cell NHL [14]	FL	Rate 20
	131I-tositumomab		FL	
Anti CD-19	Tafasitamab	Phase 2 trial [42]	RR NHL (FL, MZL, CLL, MCL, DLBCL)	Median 8.8 mo FL
Anti CD-22	Epratuzumab	R-Epratuzumab [44]	RR NHL (FL, MZL, SLL, LPL, DLBCL)	Median 3.5 yr
Anti CD-80	Galiximab	Phase 1/2 Study Galiximab[47]	R/R FL	Rate: 11
Anti CD-52	Alemtuzumab	Pilot study; Alemtuzumab [53]	R/R MF, SS	NA
Anti CD-30	Brentuximab Vedotin	Phase 2[49]	RR NHL (DLBCL, GZL, PMBL, FL, PTLD, PBL)	3.9 mo
CD-19/CD3	Blinatumumab	MT103-104 [63]	R/R NHL (FL, MCL, DLCBL, MZL)	Medisn 6.77 mo
CD20/CD3	Mosunetuzumab	Phase I/Ib GO29781[60]	R/R FL	11.8 mo
	Glofitamab	Phase 1 study in R/R B-cell NHL[61]	R/R NHL (FL, DLBCL, PMBCL)	Median 11.8 mo in FL
	Epcoritamab	Phase 1,2 trial in R/R NHL [62]	R/R NHL (FL, MCL, DLCBL)	Median 2.2 moRate

R) follicular lymphoma who have received at least two prior systemic therapies[67].We have Glofitamab as anti CD-20 and Anti CD-3 that is being investigated in phase 1 study in R/R B-cell NHL[68]. Epcoritamab is also another bispecific antibody anti-CD20 and anti CD-3 that was also studied in a phase ½ trial in R/R NHL as a Single-agent subcutaneous showing at a dose of 48 mg an overall response rate of 88%[69]. This shows future of immunotherapy development in this disease category.

1- Anti CD30/CD19: Blinatumumab

On premature and mature B cells of NHL we have the CD19 antigen. Initially the bispecific antibody, Anti CD3 and Anti CD19, Blincyto or Blinatumumab was FDA approved in R/R B-ALL in 2014[70]. It was evaluated in R/R NHL as monotherapy in MT103-104 and it showed improvement in response and OS in a dose escalation protocol where the benefit was mainly seen in a dose >60 mg/m2 with minimal side effects [70]. It is also being evaluation in a phase 1 study in combination with Lenalidomide[71].

C- Other Anti- T cells MAB: mogamulizumab, Denileukin Diftitox

Mogamulizumab as an Anti-CC Chemokine Receptor 4 Antibody has been FDA approved for R/R MF and SS after failure of at least one systemic therapy. This was based on the MAVORIC trial, phase 3, randomised controlled trial, where patients were randomized to mogamulizumab (n=186) or vorinostat (n=186), where the primary end point of PFS was reached in the mogamulizumab group 7.7 month compared to 7.1 month which represent a major therapeutic option in cutaneous T-cell lymphoma[72]. Other than that, Denileukin Diftitox a recombinant fusion protein targeting IL-2 receptor-expressing malignant T lymphocytes, was also studied in patients with stage IA to III, CD25 assay-positive cutaneous T-cell lymphoma (CTCL) including the mycosis fungoides and Sézary syndrome in a phase 3 trial in comparison with placebo where PFS was significantly prolonged in the DD groups (>2 years) in comparison to placebo (124years) with a significant P value of <0.001[73].

D- Future

Future therapies are being investigated as well in iNHL including different mechanism and the TNF-related apoptosis-inducing ligand)/ Apo2 (TRAIL) is one of them[74]. It includes 4 receptors to constitute a death protein that can induce the apoptosis of the malignant cell exclusively as it is not expressed on normal tissue rendering it an effective mechanism in targeting cancer cells[60]. TRAIL-R1 (mapatumumab [HGS-ETR1]) and -R2 (HGS-ETR2) are two MAB that are being studied in preclinical trial to validate the effectiveness of this pathway [75]. One additional aspect investigated in NHL is anti-angiogenesis, where there is increased angiogenesis in lymphoma and anti- vascular endothelial growth factors are being investigated mainly in aggressive subtypes of NHL and not in indolent[75].

Another future strategy in iNHL is the chimeric antigen receptor (CAR) T cells where the patient's T-cells are genetically modified to be able to fight the cancerous cells[76]. This technique has been further understood with the influence of CD19-specific CAR-T cells counter to the refractory B-cell malignancies[76]. It has been very efficacious in

B-cell ALL and showed promising results in aggressive B-cell NHL especially with the wide expression of CD19 on those cells, yet to be explored in iNHL[76]. Investigated CAR-T cells include lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel in aggressive NHL not yet in iNHL[76].

2. Conclusion

Major advances have been implemented in the management of NHL specifically in the iNHL. With the emergence of immunotherapy the response rates have been significantly changing over time. After targeting CD-20 studies evolved to target more cell surface antigens that are landmarks in iNHL and consequently causing a change in its management and improving the potential curability of relapsed cases. Future mechanisms are still under investigation and this is a wide domain of adventure worth of going through as it carries with it hope of cure rates for iNHL patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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