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Treatment strategies for patients with diffuse large B-cell lymphoma

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is nowadays a curable disease with the frontline treatment R-CHOP, but 30–40% of patients are still unresponsive or relapse thereafter. In the recent era several upcoming new options are improving the therapeutic landscape for relapsed/refractory (R/R) DLBCL setting, first of all anti-CD19 chimeric antigen receptor T-cells (CAR-T) that already represent a standard of care as third-line therapy and are rapidly moving as second-line treatment for those who are refractory or early relapse after R-CHOP. Among these new therapies, the combinations polatuzumab plus rituximab and bendamustine, tafasitamab plus lenalidomide for transplant ineligible patients, and CD3xCD20 bispecific antibodies are the most relevant, but several other agents and strategies are on the way. On the other hand, in the last 20 years, several efforts have been spent in the attempt to ameliorate the outcome over R-CHOP for the frontline treatment of DLBCL shortening the interval between the cycles or intensifying treatment or adding novel drugs to R-CHOP without success, so far. Recent studies combining the anti-CD79b antibody-drug conjugate polatuzumab vedotin plus R-CHP and the anti-BCL2 agent venetoclax plus R-CHOP showed promising results. Preliminary data of new upcoming strategies characterized by a tailored therapy based on different molecular subtypes of DLBCL are encouraging, showing a benefit over the standard R-CHOP. In this manuscript, the literature data on the landscape of new therapies available and upcoming for both frontline and R/R settings of DLBCL will be critically reviewed.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of Non-Hodgkin lymphoma (NHL). The introduction of the anti-CD20 monoclonal antibody (moAb) rituximab in addition to chemotherapy substantially improved the outcome of DLBCL which nowadays is considered a curable disease with the standard frontline chemo-immunotherapy regimen rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP). However, only a part of patients can benefit from this treatment and 30–40% of them are still refractory or will relapse after initial response. In the last decade many efforts have been spent in the attempt to improve the outcome for patients affected by DLBCL over R-CHOP in the frontline, and with novel therapies for the relapsed/refractory (R/R) setting. This review focuses on new therapeutic strategies approved and under investigation for the treatment of advanced stage DLBCL in first line and relapsed/refractory settings. A literature search was performed for papers up to June 2022 PubMed, National Comprehensive Cancer Network and European Society of Medical Oncology guidelines and abstracts from main international conference proceedings, such as American Society of Hematology, American Society of Clinical Oncology, and International Conference of Malignant Lymphoma meetings.

Improvements over R-CHOP in frontline treatment

Several strategies have been adopted to ameliorate the efficacy of the frontline treatment for DLBCL (Table 1).

Increase in treatment intensity

One of the attempts applied to improve the frontline treatment is represented by the use of more intensive chemotherapy regimens.

First of all, the attempt to improve the efficacy of R-CHOP by shortening the interval between the cycles administered every 2 weeks,

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Table 1
Improvements over R-CHOP in frontline treatment.

Scheme (trial)	Study design	n	Median age (range)	Biological characteristics	ORR/CR (%)	PFS or EFS or DFS (%)	OS (%)	Primary endpoint	HR / P value
R-CHOP14 [1]	Phase III	540 *	61 (19–85)	All DLBCL	91/41	75.4 (2 y)	82.7 (2 y)	OS	0.9 / 0.3763
R-ACVBP (LNH03-2B) [2]	Phase III	196 *	47 (18–59)	All DLBCL	90/58	87 (3 y)	92 (3 y)	EFS	0.48 / 0.0015
Autologous transplantation (DLCL04) [3]	Phase III	199 *	48 (36–56)	All DLBCL	nd/76	71 (2 y)	78 (5 y)	FFS	0.65 / 0.012
R-DA-EPOCH (Alliance/ CALB50303) [7]	Phase III	262 *	58 (19–84)	All DLBCL	nd/nd	77.1 (2 y)	78.9 (2 y) ‡	PFS	0.93 / 0.65
G-CHOP [9]	Phase III	706 *	62 (18–86)	All DLBCL	77.4 / 56.7	69.6 (3 y) ‡	81.2 (3 y) ‡	PFS	0.92 / 0.39
R2-CHOP (E1412) [10]	Randomized phase II	145*	66 (24–92)	All DLBCL	97/72	75 (2 y)‡	87 (2 y)	PFS	0.67 / 0.03
R2-CHOP (ROBUST) [11]	Phase III	285*	65 (21–82)	ABC	91/69	75 (2 y)‡	79 (2 y)	PFS	0.85 / 0.29
VR-CHOP (PYRAMID) [12]	Randomized Phase II	103*	65 (20–83)	Non-GCB	96/56	82 (2 y)	93 (2 y)	PFS	0.73 / 0.611
VR-CHOP (REMoDL-B) [13]	Phase III	459*	63 (20–84)	All DLBCL	nd	75 (30 mo)	84 (30 mo)	PFS	0.86 / 0.28
Ibrutinib + R-CHOP (PHOENIX) [14]	Phase III	419*	63 (19–88)	Non-GCB	89/67	70 (2 y)‡	85 (2 y)‡	EFS	0.93 / 0.59
Pola-R-CHP (POLARIX) [15]	Phase III	440*	65 (19–80)	All DLBCL	85.5/78	76.67 (2 y)‡	88.7 (2 y)‡	PFS	0.73 / 0.02
Venetoclax + R-CHOP (CAVALLI) [16]	Phase II	206	65 (18–85)	All DLBCL	83/69	80 (2 y)	86 (2 y)	CR	–
R-CHOP + R maintenance (NHL13) [17]	Phase III	338 *	57(19–87)	All DLBCL or FL grade 3b (in first remission)	NA	80.1 (3 y) ^	92 (3 y) ^	EFS	0.79 / 0.1433
R-CHOP + enzastaurine maintenance (PRELUDE) [18]	Phase III	504 *	64.4 (22.4–88.7)	All DLBCL (in first remission)	NA	78 (2 y)	87 (2 y)	DFS	0.92 / 0.541
R-CHOP + everolimus maintenance (PILLAR-2) [19]	Phase III	372 *	64 (21–83)	All DLBCL (in first remission)	NA	77.8 (2 y)	90.7 (2 y)	DFS	0.92 / 0.276
R-CHOP + Lenalidomide maintenance (REMARC) [20]	Phase III	323 *	69 (58–80)	All aggressive B-cell Lymphomas	NA	75 (2 y)	87 (2 y) ‡	PFS	0.708 / 0.0135;

Abbreviations: ABC: activated B cell like subgroup; ACVBP: doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete response; DA-EPOCH: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DFS: disease free survival; DLBCL: diffuse large B cell lymphoma; EFS: event-free survival; FFS: Failure-free survival; FL: follicular lymphoma; G: Obinotuzumab; GCB: germinal center B cell like subgroup; HR: hazard ratio; mo: months; nd: not defined; NA: not applicable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R: rituximab; R2: rituximab plus lenalidomide; Pola-R-CHP: Polatuzumab, Rituximab, cyclophosphamide, doxorubicin, prednisone; VR: Bortezomib, rituximab; y: years.
^ from randomization.
*Considering experimental arm only.
‡Approximate data obtained from reported Kaplan-Meier curves.

instead of the standard 3 weeks interval, did not improve progression-free survival (PFS) or overall survival (OS) compared to the standard treatment [1].

In the LNH03-2B French study, 380 patients aged 18–59 years with untreated DLBCL and an age-adjusted international prognostic index (aa-IPI) score equal to 1 were randomized to receive standard R-CHOP or more intensive treatment with R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) repeated every 2 weeks. In detail R-ACVBP regimen consisted of an induction phase of 4 cycles of R-ACVBP with a subsequent consolidation phase containing different treatment sequences (2 cycles of methotrexate, 4 subsequent cycles of rituximab combined with etoposide and ifosfamide and finally 2 cycles of cytarabine, with each consolidation course being given at 2-week intervals) [2]. In addition, patients received intrathecal methotrexate on day 1 of the first 4 cycles in both study groups. This trial met its primary endpoint with a 3-year estimated event-free survival (EFS) of 81% in the R-ACVBP group and 67% in the R-CHOP group (hazard ratio [HR] 0.56, 95% CI 0.38–0.83; p = 0·0035). An increased 3-year estimated PFS (87% vs 73%; HR 0.48 [0.30–0.76]) and OS (92% vs 84%; HR 0.44 [0.28–0.81]) rates were also observed in the R-ACVBP group but with an increased rate of haematological side effects. The positive effect of the treatment was due to the lower rate of disease progression during the treatment phase and fewer relapses in patients who reached a complete response, but we don't know which phase of the R-ACVBP regimen improves the outcome. However, despite positive results over R-CHOP, the value of R-ACVBP is hampered by its improved efficacy only in a relatively favorable subgroup (i.e aa-IPI 1) and its increased toxicity that has limited its widespread use.

The role of high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT) as consolidation at first-line treatment has been investigated by three studies. In the DLCL04 trial by Chiappella *et al.* [3] 399 young patients (18–65 years) at high risk (aa-IPI score 2–3) were randomized with a 2x2 factorial design to receive a full course of rituximab-dose-dense chemotherapy at two different dose levels (R-CHOP or R-MegaCHOP) or an abbreviated course of rituximab-dose-dense chemotherapy followed by consolidation with R-MAD (rituximab, high-dose cytarabine, mitoxantrone and dexamethasone) and high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine and melphalan) followed by ASCT. The study met the primary endpoint reaching an improved 2-year failure-free survival (71% in the transplantation group vs 62% in the no-transplantation group; HR 0.65 [95% CI 0.47–0.91]). However, no difference in 5-year OS was observed between these two groups (78% vs 77%, HR 0.98 [0.65–1.48]) because of an effective salvage therapy with HDC and ASCT in case of relapse or progression. Similar data were reported by other two randomized studies investigating the role of HDC and ASCT as consolidation in first line over R-CHOP or R-CHOEP. In the first one intensification with HDC and ACST has shown an improvement in PFS but not in OS [4] and the second trial failed to demonstrate any benefit for the HDC over R-CHOEP [4,5]. Overall, these results do not support the use of HDC +

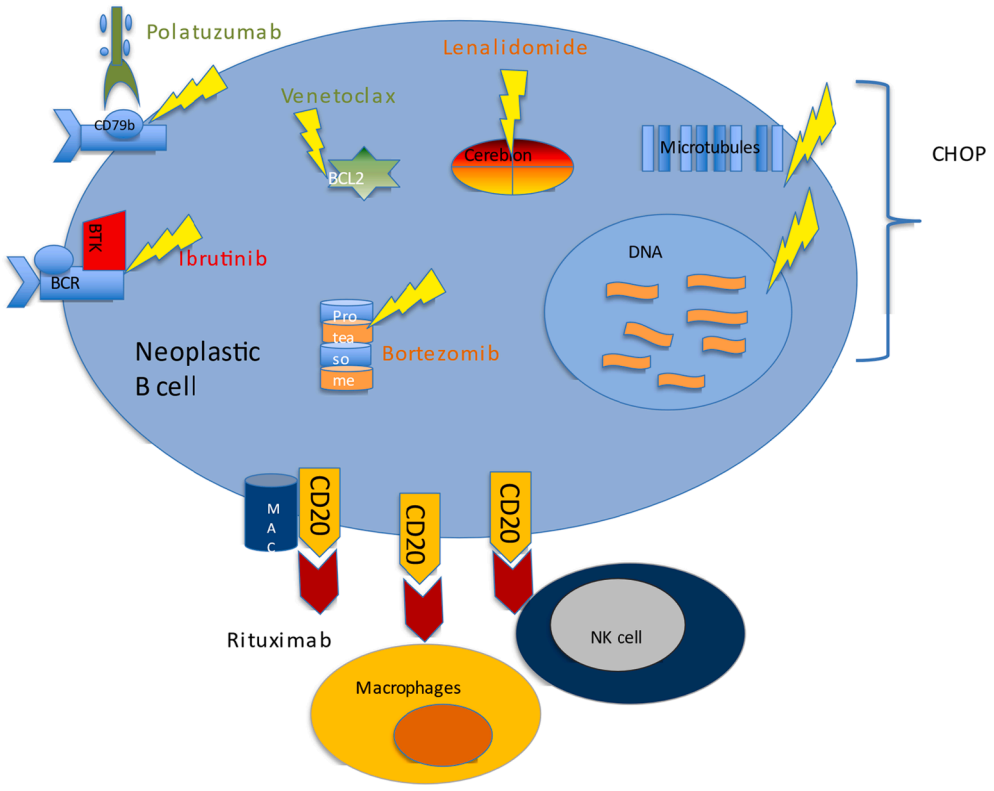

Fig. 1. Mechanism of action of R-CHOP plus 'X' drugs in frontline treatment of DLBCL. Several add-on therapies have been combined with the backbone R-CHOP. *Lenalidomide is an immunomodulant agent that blocks Cereblon, Bortezomib is a proteasome inhibitor, Ibrutinib is an antagonist of Bruton Tyrosine Kinase, Venetoclax blocks anti-apoptotic protein BCL-2 and Polatuzumab is an anti-CD79b antibody drug conjugate.*

ASCT as an upfront strategy in patients with poor prognosis DLBCL. A limited role of this strategy could be in selected patients with slow response to R-CHOP based on interim positron emission tomography (PET) evaluation as showed by Le Gouill et al. [6].

The Alliance/CALGB 50303 study compared 6 cycles of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) with standard R-CHOP as first-line therapy for DLBCL [7]. In this trial, the more intensive DA-EPOCH-R regimen did not show an improvement in PFS (2-year PFS rate 78.9% vs 75.5%) and OS (2-year OS rate 86.5% vs 85.7%) as compared with the standard R-CHOP with an increased rate of toxicities. In a post hoc analysis, patients with IPI score 3 to 5 showed a better PFS but no benefit in OS when receiving DA-EPOCH-R compared with patients in the R-CHOP arm. To note, the outcome in the standard arm was more favorable compared with historical controls and the authors suggested this was probably due to a potential patient selection bias and this may have masked the potential benefit in specific higher risk subgroups. In a retrospective study Dodero *et al.* [8] evaluated in 114 consecutive patients with double-expressor DLBCL (i.e. with *MYC* and *BLC2* protein overexpression) the same DA-EPOCH-R regimen versus R-CHOP. In the entire population of the study, these two regimens showed similar OS and PFS. However, patients younger than 65 years achieved a 2-year PFS of 82%, which was significantly better than the PFS observed with R-CHOP, suggesting a possible role of this treatment in this selected population. The efficacy showed only in the younger population may be explained by the higher cumulative dose of chemotherapy received in these patients.

Alternative anti-CD20 monoclonal antibody

The large, randomized phase III GOYA trial tested the efficacy of a second generation anti-CD20 moAb Obinutuzumab on DLBCL. In the study, 1418 untreated DLBCL were randomized to receive Obinutuzumab plus CHOP (G-CHOP) or the standard R-CHOP. No survival differences were observed in the two groups (3-year PFS rates were 70% in G-CHOP arm and 67% in the R-CHOP arm). Thus, the data did not support the use of Obinutuzumab in this setting unlike follicular lymphoma. [9].

R-CHOP plus 'X'

A different attractive strategy is to add novel biological drugs ('X') to the standard R-CHOP, either in the induction phase or as maintenance (Fig. 1).

Lenalidomide is an oral immunomodulatory drug that showed activity in R/R DLBCL and, in phase II single arm trials showed a benefit in frontline when combined with R-CHOP (R2-CHOP) particularly for non-germinal-center-B-cell-like (GCB) subtypes [21–23]. Thus, R2-CHOP was subsequently tested in two randomized studies in comparison with R-CHOP for untreated DLBCL. The phase II randomized trial E1412 from the Eastern Cooperative Oncology Group (ECOG)-ACRIN Cancer Research Group, on 349 patients demonstrated an improvement for the R2-CHOP arm both in OS and PFS for activated B-cell-like (ABC) subtype of DLBCL [10]. However, in the ROBUST phase III trial, which included 570 prospectively tested ABC-DLBCL patients, the addition of lenalidomide, administered with a slightly different schedule in respect of the E1412 trial (15 mg daily on days 1–15 of each 21-day cycle in ROBUST trial, 25 mg daily on days 1–10 of each cycle in E1412 trial), did not improve PFS, even if a PFS trend favoring R2-CHOP over placebo/R-CHOP was seen in patients with higher-risk disease (IPI score 3 or more) [11].

Similarly, the proteasome inhibitor Bortezomib added to R-CHOP (RB-CHOP) failed to show improved outcomes over R-CHOP in the phase II PYRAMID study and in the phase III REMoDL-B phase III trial, no differences were observed among the two arms in the latter study also stratifying patients according to the cell of origin (COO) classification. [12,13] Interestingly, PFS at 30 months in patients with double-hit

lymphoma was 38.9% after R-CHOP compared with 58.8% after RB-CHOP, although this result derived from a post-hoc analysis and the difference was not statistically significant.

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK) that has been approved for several B-cell malignancies and demonstrated an interesting activity in R/R ABC DLBCL, possibly related to the chronic activation of B-cell receptor and NF-κB patterns which characterize this COO subtype [24]. However, results from the randomized phase III PHOENIX trial that compared ibrutinib + R-CHOP and placebo + R-CHOP were disappointing with neither significant improvement in the primary endpoint (EFS) nor in the secondary endpoints. A pre-planned exploratory analysis identified a significant interaction between treatment and age: in patients younger than 60 years ibrutinib plus R-CHOP improved outcomes with manageable safety, while in older patients the addiction of ibrutinib was associated with increased toxicity, leading to compromised treatment administration and worse outcomes [14]. With the purpose of ameliorate PHOENIX results, the ongoing phase III trial ESCALADE (NCT04529772) restricts enrolment to young untreated non-GCB DLBCL (age $\leq$ 65 years) randomizing to receive R-CHOP or the combination R-CHOP plus Acalabrutinib, a selective second-generation BTK-inhibitor with less off-target toxicities [25].

Recently, the POLARIX trial investigated a modified regimen, in which vincristine was replaced by Polatuzumab vedotin (pola-R-CHP) [15]. Polatuzumab is an antibody-drug conjugate (ADC) moAb targeting CD79b, which is a component of the B-cell antigen receptor ubiquitously expressed on the surface of malignant B cells, combined with a protease cleavable link with the microtubule-disrupting agent monomethyl auristatin E (MMAE). Vincristine was excluded from the regimen due to the overlapping risk of neurological toxicities. In this phase III placebo-controlled trial pola-R-CHP reduced the risk of progression, relapse or death compared to the standard R-CHOP in patients with previously untreated intermediate-risk or high-risk DLBCL (IPI score 2 or higher). At two years the PFS was 76.7% versus 70.2% (HR 0.73, 95% CI 0.57–0.95). The exploratory subgroup analysis showed no clear benefit in patients younger than 60 years, those with GCB DLBCL, bulky disease or lower IPI score. Moreover, complete metabolic response was not different between the two arms and OS at 2 years did not differ significantly between the groups (88.7% versus 88.6%), but this can be probably deemed to the short follow-up and the subsequent effective treatments. However, future studies with a more matured follow-up are needed to clarify the heterogeneous effect of pola-R-CHP across different subgroups.

Encouraging results also come from the phase II CAVALLI trial that evaluated the use of Venetoclax, a selective *BCL-2* inhibitor, in addiction to R-CHOP, especially in the poor prognosis population with *BCL-2* overexpression [16]. Even if this was a single-arm non-randomized study, the authors compared results with matched R-CHOP controls from the GOYA study. PET-complete response (CR) rates, primary endpoint of this study, were 69% overall, 64% in the *BCL-2* population, and 66% in the double expressor population. Rates were similar to those in the GOYA cohort. Interestingly, 2-year PFS (secondary endpoint) was increased in the CAVALLI study compared to the matched GOYA control in the overall population, mainly driven by the *BCL-2* overexpression population (78% versus 62%; HR 0.55; 95% CI 0.34–0.89), suggesting a deeper and more durable response induced by Venetoclax. Adding Venetoclax also led to higher rates of hematologic toxicity and infection but these did not translate into an increased risk for toxic death and the dose intensity of R-CHOP in CAVALLI was maintained at a level similar to that in GOYA. So, this trial provides the rational to explore this combination in further phase III studies.

Finally, many drugs were studied as maintenance after the standard R-CHOP induction but results of this approach were not satisfying. Rituximab maintenance did not prolong EFS, PFS or OS in the NHL13 trial and similar results were achieved in the Prelude study with the selective protein kinase C β (PKCβ) inhibitor Enzastaurin and in the PILLAR-2 study with everolimus [17,19,26]. By contrast, in the REMARC study, lenalidomide maintenance for 24 months significantly prolonged PFS in elderly (60–80 years) patients (median PFS not reached for lenalidomide maintenance versus 58.9 months for placebo [HR 0.708; 95% CI, 0.537 to 0.933]) [20]. This result was consistent in all the analysed subgroups, but no improvement in OS was seen. This was the first randomized study showing that maintenance therapy can prolong PFS for patients with DLBCL after responding to R-CHOP, but more details to explain the mechanism of this advantage should be given.

Salvage chemotherapy and autologous stem cell transplantation

The standard therapeutic strategy for DLBCL patients R/R after R-CHOP is nowadays represented by platinum-based chemotherapy followed by HDC-ASCT.

In this setting, the role of ASCT was firstly assessed in 1995 when the PARMA trial [27] demonstrated an improvement in EFS and OS with two cycles of salvage chemotherapy (DHAP – dexamethasone, high-dose cytarabine and cisplatin) followed by HDC (BEAC – carmustine, etoposide, cytarabine and cyclophosphamide) and ASCT as compared with six cycles of DHAP alone.

Subsequently several trials tried to improve transplantation outcomes, mainly modifying salvage or conditioning regimens. In the phase III CORAL study [28] a salvage regimen with R-ICE (rituximab, ifosfamide etoposide and carboplatin) results in similar response rate (62.8% vs 63.5%) and no significant difference in EFS (26% vs 35% at 3 years) or OS (47% vs 51% at 3 years) as compared with R-DHAP. Moreover, this trial also included a second randomization to rituximab or placebo maintenance after ASCT with BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning regimen, demonstrating no different outcome. Due to this data, rituximab maintenance after ASCT cannot be recommended.

Similar results were also seen in the NCIC-CTG LY.12 trial where GDP (gemcitabine, dexamethasone and cisplatin) showed similar response rate (45.2% vs 44%), no difference in EFS and OS, with a reduced toxicity when compared with DHAP [18]. These studies also permitted to underline the most relevant prognostic factors affecting response rate in this setting. In the CORAL study, a relapse less than 12 months after diagnosis, an aa-IPI score at relapse (saaIPI) of more than 1 and prior rituximab treatment were associated with a worse prognosis. A retrospective analysis from the CORAL study also demonstrated the prognostic value of the COO status: GCB-like DLBCL seems to have a better response rate to R-DHAP than to R-ICE [29]. Thus, the aforementioned regimen showed similar results and the choice of salvage therapy should be done taking in consideration comorbidities, clinician experience and pathologic features, preferring R-DHAP especially in the GCB-like DLBCL.

Although no conditioning regimen has proven to be superior, BEAM is usually preferred [30]. Rituximab could also be included in the conditioning regimen, but no clear benefit was demonstrated [31].

As previously reported, the most important factors that impact post-transplantation outcomes are the response to first line therapy and salvage regimen. In the CORAL study [28] only 46% of patients who relapsed within 12 months from diagnosis responded to salvage treatment compared with 88% of response in patients whose relapse occurred after 12 months. This different response rate reflected in an extremely distinct EFS (23% vs 64% at 3 years, respectively). In addition, only half of the patients in CORAL and NCIC-CTG LY.12 [18,28] underwent ASCT, and this was mainly due to failure to salvage regimen. Also in the PET era, several studies showed that patients who cannot achieve a PET-negative status pre-transplantation had a higher risk of relapse [31].

In conclusion, ASCT still has a major role in the treatment of patients with R/R DLBCL, namely in late relapse and in chemo sensitive patients. However, especially in patients who relapsed within 12 months from diagnosis as in patients who did not achieve a PET-negative CR at transplantation, new strategies are required.

Chimeric antigen receptor T-cell (CAR-T) therapy

Prognosis for patients affected by DLBCL who fail R-CHOP and are transplant ineligible or R/R to HDC-ASCT is extremely unfavorable with standard chemotherapy options [32]. CAR-T is a recent effective treatment for B-cell malignancies including DLBCL. Anti-CD19 CAR-T cells consist of autologous T lymphocytes redirected against CD19 antigen by the introduction of a chimeric anti-CD19 T cell receptor (CAR) with a replication-incompetent retroviral vector. This treatment platform consists of a lymphodepleting chemotherapy (generally based on fludarabine plus cyclophosphamide or bendamustine) followed by a single CAR-T infusion. Three CAR-T products are currently available for DLBCL treatment: Axicabtagene ciloleucel (Axi-cel), Tisagenlecleucel (Tisa-cel) and Lisocabtagene maraleucel (Liso-cel), characterized by similar efficacy but some structural differences mainly derived to a different costimulatory domain (CD28 for Axi-cel, 4-1BB for Tisa-cel and Liso-cel) and a unique balanced CD4+/CD8 + ratio for Liso-cel. The three products demonstrated high effectiveness in DLBCL R/R after at least 2 prior lines in the three pivotal trials ZUMA-1 (Axi-cel), JULIET (Tisa-cel) and TRANSCEND NHL 001 (Liso-cel). Unless non-negligible peculiar toxicities mainly characterized by cytokine release syndrome (CRS) and neurotoxicity, deep and durable responses have been observed: ORR ranging from 52 to 83% with 40% to 58% of CR, median PFS 5.9 mo to NR and DOR 11 to 23 months among different trials [33–35]. CRS was observed in 93% of patients (11% grade $\geq$ 3) in ZUMA-1, 93% of CRS (21% grade $\geq$ 3) in JULIET and 42% (2% grade $\geq$ 3) in TRANSCEND NHL 001, while 64% of patients experienced neurotoxicity (32% grade $\geq$ 3) in ZUMA-1, 58% (12% grade $\geq$ 3) in JULIET and 30% (10% grade $\geq$ 3) in TRANSCEND NHL 001 [33–35]. Leaded by the impressive results from the three trials, Axi-cel, Tisa-cell and more recently Liso-cel have been approved by FDA and EMA as treatment for adult patients with DLBCL R/R after at least 2 prior lines of therapy. Thus, nowadays CAR-T are considered the gold-standard as third line treatment for R/R DLBCL. Real-life data both from US and Europe confirm their effectiveness in this setting [36–39].

CAR-T as second-line treatment

The impressive results of CAR-T as third line prompted to test them as second-line treatment for refractory DLBCL. Three large randomized phase III trials have been conducted comparing the three CAR-T products and salvage platinum-based chemotherapy regimens followed by HDC-ASCT (standard of care, SOC), in patients with refractory DLBCL, intended as non-responsive to frontline treatment or relapsed within 12 months [40–42]). ZUMA-7 trial (Axi-cel vs. SOC) and TRANSFORM trial (Liso-cel vs. SOC) randomized 359 and 194 patients, respectively, and demonstrated the superiority of the two CAR-T products in respect of SOC, both in terms of treatment responses (CR 65% vs. 32%, and 66% vs. 39%, respectively) and survival (median EFS 8.2 vs. 2 months, and 10.2 vs. 3.1, respectively) [41,42]. In contrast, in the BELINDA trial no differences between Tisa-cel and SOC have been observed: CR 28.4 vs. 27.5%, median EFS 3 months for both therapies [40]). The different results obtained from the trials may be partially explained by some differences in the study design including the non-permitted bridging therapy in ZUMA-7 which may have selected patients with less aggressive disease, and a longer manufacturing time for CAR-T in BELINDA trial [23.5 days in US (range 22–34 days) and 28 days in non-US countries (range 22–115 days)] in respect of ZUMA-7 (13 days) [40,42]. Interestingly, in the three trials patients aged more than 75 years have been enrolled (maximum age of 81 years in ZUMA-7, 79 in BELINDA and 2 patients >5 in TRANSFORM). The positive results from ZUMA-7 established a new therapy breakthrough for DLBCL leading Axi-cel to be the first FDA approved CAR-T product for the treatment of patients refractory to frontline therapy or relapsed within 12 months. Final results from TRANSFORM are pending.

Mechanisms of CAR-T treatment failure

More than one-third of R/R DLBCL patients is cured with CAR-T therapies, however, a relevant portion of them still relapses and experiences a poor outcome. [33–35] Many efforts are continuously spent to understand mechanisms of CAR-T failure and how to overcome them. To date, the known reasons for treatment failure are related to patient and disease features, characteristics of the CAR-T product and tumor cell mechanisms of escape.

Pre-infusion factors play a key role in CAR-T efficacy. The generation of the cellular products requires an adequate absolute lymphocyte count and a long manufacturing time that could reach up to 115 days in certain circumstances [40]. The first pre-infusion factor is mostly represented by the number of previous treatments; this could be overcome with the move up of the CAR-T treatments to the second line, as tested in ZUMA-7, BELINDA and TRANSFORM trials, or eventually in the first line as designed in ZUMA-12 trial, in which Axi-cel have been tested as part of frontline treatment for patients with high-risk DLBCL [43]). The second is a limiting factor in patients that suffer from a highly proliferative disease. In order to overcome that weak point, protocols for faster generation of CAR-T are moving to the clinic in the next years [44].

Characteristics of the product may vary and this can affect its antitumor activity. The efficacy of the CAR-T therapies is influenced by the phenotypic composition of the cellular product. CAR-T products enriched in central memory T cells are associated with a higher cytotoxic activity compared with products with a more differentiated phenotype of the T-Cell [45].

Another mechanism of CAR-T failure is related to their dysfunction with the reduction of the killing's potentiality. This factor can be related to an intrinsic dysfunctionality of the engineered T-Cell or to the exposition to an immunosuppressive tumor microenvironment. In this microenvironment, checkpoint inhibitors and anti-inflammatory molecules can lead to CAR-T exhaustion: one of the main determinants of the clinical outcome [34,46,47].

The last reason for CAR-T failure is related to heterogeneous tumor cell mechanisms of escape. The most known is represented by the antigen loss. The selective pressure of the CAR-T on a target antigen can lead to a loss of expression of the antigen itself. More than two-third of patients affected by Acute lymphoblastic leukemia, treated with a anti CD19 CAR-T, relapses with CD19 negative disease [48]. This phenomenon was less defined in Lymphoma until Neelapu *et al*, showed that up to 30% of NHL treated with Axi-cel relapse as CD19 negative [49]. The tumor cell 'lineage switch' is another intriguing event that can lead to CAR-T failure. This consists of the phenotypical change of the tumor in a different cell line to avoid the selective pressure of the CAR-T therapies. Of note in a recent report of Zhang *et al*. [50] a transdifferentiation from Mantle cell lymphoma to a poorly differentiated sarcoma is described.

Allogeneic stem cell transplantation in the CAR T-cell era

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was the first treatment to establish the role of adoptive cell therapy in the cure of hematologic malignancies. Allo-HSCT exploits the ability of donor cells to recognize tumor antigens and to mount an effective immune response. This capacity led allo-HSCT to be considered a potentially curative treatment also in DLCBL, especially in heavily pre-treated patients that relapse or progress after ASCT.

The European Society for Blood and Marrow Transplantation (EBMT) analysed 101 patients with DLBCL that underwent an allo-HSCT after a previous ASCT from 1997 to 2006. This study confirms an important role for allo-HSCT also in a cohort of challenging pre-treated patients with a 3-years non-relapse mortality (NRM) of 28.2%, 3-year PFS of 41.7% and 3-year OS of 53.8% [51]. This analysis also showed longer PFS for patients with a time to relapse after ASCT of more than 12 months. Conversely, this study showed no statistically significant difference between different conditioning regimens. Myeloablative

Table 2
Novel treatment combinations in R/R DLBCL.

Regimen (trial)	Study design	n	Population	ORR/CR (%)	PFS/ EFS	OS (%)	Grade ≥ 3 AEs (%) ˆ	Other specific-drug toxicities of any grade AEs (%)
Tafasitamab + Lenalidomide (L-MIND) [56]	Phase II	81	Transplant ineligible R/R DLBCL	60/43	50% at 1y	74 (1y)	Neutropenia (21), thrombocytopenia (5), febrile neutropenia (10), leukopenia (7), anaemia (7), and pneumonia (6)	pulmonary embolism (4),atrial fibrillation (2), and congestive cardiac failure (2) .
Mosunetuzumab [57]	Phase I/Ib	129 **	R/R B-NHL	34.9/19.4 **	Median 1.4 mo **	nd	Neutropena (25.4), Hypophosphatemia (15.2), anemia (9.1)	CRS (27.4; G3 1%), neurologic G3 (4.1)
Glofitamab [58]	Phase I	127 **	R/R B-NHL	41.1/28.8 ***	Median 2.9 mo **	nd	Neutropenia (25.1), thrombocytopenia (8.1),anaemia (7.6)	CRS (50.3), neurologic (43.3)
Epcoritamab [59]	Phase I/II	46 ***	R/R B-NHL	68/45 with full doses 12–60 mg ***	nd	nd	Anaemia (13), hypotension (6), fatigue (6), pyrexia (6)	CRS (59, all G1-2), neurologic (6)
Odronextamab [60]	Phase I	71 ***	R/R B-NHL	60/60 at doses ≥ 80 mg in pts with no prior CART; 33.3/ 23.8 at doses ≥ 80 mg in patients with prior CART	nd	nd	nd	CRS G3 (6.3), neurologic G3 (2.3)
Plamotamab [61]	Phase I	36 **	R/R B-NHL and CLL	ORR 33.3 at doses of 80–125 μg/kg **	nd	nd	Pyrexia (5.6), neutropenia (13.9), thrombocytopenia (8.3), hypokaliemia (5.6) **	CRS (11.1)
Pola-RB [62]	Phase Ib/II	192 *	Transplant ineligible R/R DLBCL	41.5/38.7	Median 9.2 mo	Median 12.4 mo	Neutropenia (32.5), thrombocytopenia (20.5), anaemia (12.6), infections (21.9)	–
Loncastuximab tesirine [63]	Phase I	139 ***	R/R B-NHL	42.3/23.4 ***	Median 2.8 mo ***	Median 7.5 mo ***	Neutropenia (39.7), thrombocytopenia (26.7), increased gamma-glutamyltransferase (21.3), anaemia (15.3), lymphopenia (6.6), phosphatase alkaline increase (6.6), febrile neutropenia (5.5), hypokaliemia (5.5)	–
Loncastuximab tesirine (LOTIS-2) [64]	Phase II	145	R/R DLBCL	48.3/24.1	Median 4.9 mo	Median 9.9 mo	Neutropenia (26), thrombocytopenia (18), increased gamma-glutamyltransferase (17), anaemia (10), leukopenia (9), lymphopenia (5), Hypophosphataemia (6)	–

Abbreviations: CART: chimeric antigen receptor T-cells; CLL: chronic lymphocytic leukemia; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B cell lymphoma; EFS: event-free survival; G: grade; mo: months; n: number; nd: not defined; NHL: non-Hodgkin Lymphoma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RB: rituximab, bendamustine; R/R; relapsed or refractory; y: years.
ˆ more frequent than 5%.
* considering experimental arm only.
** considering patients with aggressive B-NHL.
*** considering patients with DLBCL.
‡ Approximate data obtained from reported Kaplan-Meier curves.

conditioning (MAC) or reduced intensity conditioning (RIC) remain nowadays possible alternative choices in the absence of prospective randomized trial, with MAC that seems to be associated with lower rate of relapse but higher rates of NRM [52]. Aggressive disease with high tumor burden and an incomplete response to salvage therapies are probably situations where MAC should be preferred.

Even if allo-HSCT can provide durable disease control in some difficult to treat patients, some concerns about this procedure are still not completely resolved. In fact, infection rate and graft versus host disease (GVHD) yet impact in a relevant way on NRM and quality of life after allo-HSCT [53].

In recent years, CAR T-cell therapy revolutionized the landscape of cellular therapy options in DLBCL, offering a prominent alternative cellular immunological therapy in patients relapsing after ASCT and previously treated with multiple lines of therapy. CAR T-cells also permitted to overcome some issues typical of allo-HSCT. For example, CAR T-cell does not need disease control before the infusion, differently from allo-HSCT.

However, allo-HSCT can still play a role especially in patients who experienced failure after CAR T-cell. In addition, allo-HSCT should be recommended in situations where CAR-T cell cannot be suitable, such as in patients with impossibility to perform apheresis (i.e. patients with cytopenia) or in regions where CAR-T cell are not available [54].

In the future, allo-HSCT might be used as consolidation after CAR T-cell trying to improve outcomes especially in patients with a particularly poor prognosis or patients not achieving a CR. A strict collaboration with cellular therapy team will be crucial to early identify patients that could potentially benefit from this approach.

Furthermore, in this context, any effort to reduce NRM and toxicity should be pursued to transform allo-HSCT in a safer platform where other cellular therapy (not only CAR T-cell, but also Donor Lymphocyte Infusion) could be included to reach a better and better disease control [55].

Innovations in salvage treatment, beyond CAR-T

Apart from CAR-T other promising agents are coming in the landscape of the therapeutic options for R/R DLBCL (Table 2).

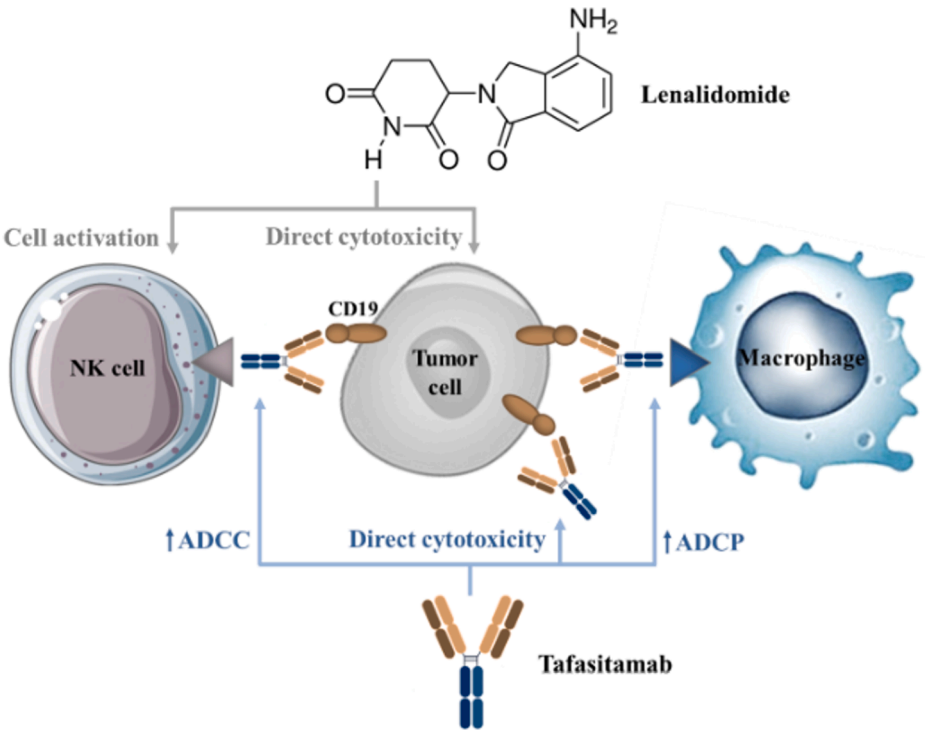

Fig. 2. Anti lymphoma effect of Tafasitamab plus Lenalidomide. Tafasitamab and Lenalidomide showed in vitro and in vivo synergic anti-B-cell lymphoma activity. The anti-tumor effect of the anti-CD19 monoclonal antibody Tafasitamab consists of direct cytotoxicity, antibody-dependent cell-mediated cytotoxicity via NK (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP). Lenalidomide presents direct cytotoxicity, enhances ADCC and stimulates interferon-ϒ secretion which lowers the NK cell activation threshold and increases NK cell proliferation by promoting interleukin-2 production.

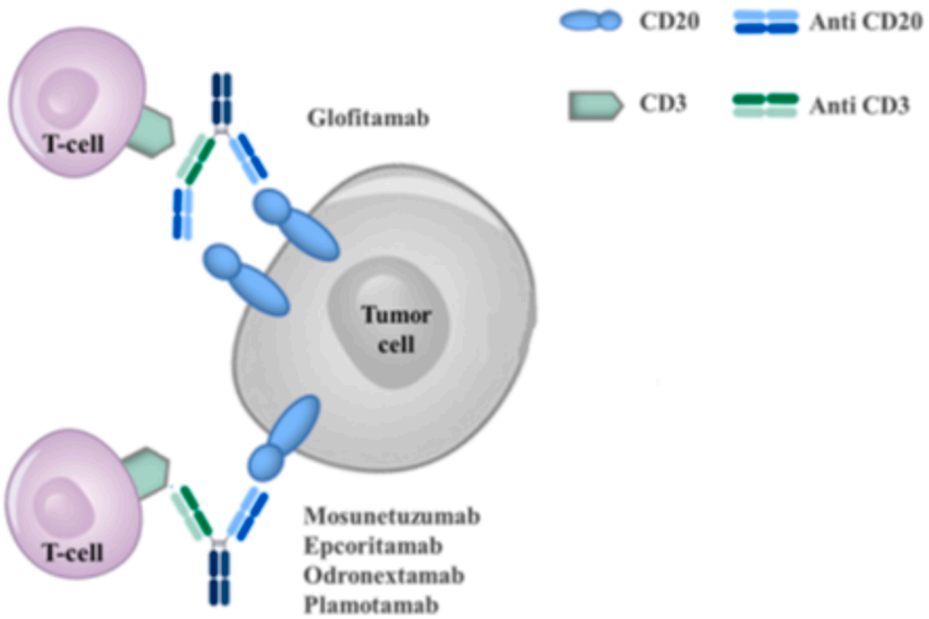

Fig. 3. Bispecific antibodies for treatment of Diffuse Large B cell Lymphoma. CD3xCD20 bispecific antibodies act engaging autologous T-cells against CD20 positive tumor B-cells. Mosunetuzumab, Epcoritamab, Odronextamab and Plamotamab are present a CD3-binding fragment and a single CD20-targeting fragment. Glofitamab is characterized by a 2:1 structure with two fragments directed to the CD20 antigen and a single CD3-binding fragment.

Tafasitamab + Lenalidomide

Tafasitamab is a Fc-enhanced humanized anti-CD19 moAb that showed in vitro and in vivo activity in B-cell malignancies and synergic effect with lenalidomide, which is able to enhance natural killer cell-meditated, antibody-dependent cellular cytotoxicity (Fig. 2) [65,66]. In the phase II multicentre single-arm L-MIND study the combination of tafasitamab plus lenalidomide (tafa + LEN) has been tested in R/R transplant ineligible DLBCL. [56] The schedule consisted of tafasitamab + lenalidomide for up to 12 months followed by tafasitamab alone until disease progression. This treatment resulted highly effective with 61% of ORR (CR 43%) and a median duration of response of 21.7 months (95% CI 21·7 to not reached) and with a reasonable toxicity profile. Based on these results, in mid-2020, the tafasitamab plus lenalidomide combination reached the accelerated approval by the Food and Drugs Administration (FDA) and European Medicine Agency (EMA) for treatment of transplant ineligible R/R DLBCL. Recently, an observational retrospective study RE-MIND2, compared patient outcomes from L-MIND trial with matched-paired patient populations treated with recommended NCCN and ESMO therapies for transplant ineligible R/R

DLBCL [67]. In a propensity score-based 1:1 matched analysis tafa + LEN showed better outcomes in terms of OS and ORR in respect of polatuzumab vedotin plus rituximab and bendamustine (Pola-BR) and rituximab + lenalidomide (R2), and comparable outcomes compared with anti-CD19 CAR-T, remarking its high effectiveness in the setting of R/R DLBCL with a limit of a retrospective comparison.

Bispecific antibodies

Bispecific antibodies (BsAb) are moAb that recognize two specific antigens or epitopes redirecting autologous T-cells against tumor cells (Fig. 3). Recently, different anti-CD20 BsAbs have been investigated for R/R DLBCL showing promising activity even in multirefractory patients, and manageable safety profiles with low rates of CRS and neurotoxicity events, mostly of grade 1–2 [68].

Mosunetuzumab is a full-length fully humanized IgG1 BsAb targeting CD3 on T-cells and CD20-positive B-NHL cells. Final results of the dose-escalation phase I/Ib study on a cohort of R/R indolent and aggressive B-NHLs have been recently presented by Budde *et al* [57]. They showed, across all drug-doses, an ORR of 34,9% (19.4% CR) for the aggressive B-NHL subgroup, with a duration of response (DOR) of 16.8 months for all responders (95% CI, 11.7 to not reached) and 20.4 months for patients in CR (95% CI, 16.0 to not reached). These promising results and the acceptable toxicities observed - no dose-limiting toxicities, 27.3% of CRS with only 1% of grade 3 and 4.1% of grade 3 neurotoxicity events - encouraged the conduction of the expansion part of the study, still ongoing.

Glofitamab is another molecule belonging to the CD3xCD20 BsAbs, characterized by a 2:1 structure composed of two fragments directed to the CD20 antigen and a single CD3-binding fragment. It is administered preceded by a single dose of obinutuzumab (1000 mg) with the purpose of reducing the mature circulating B-cells and minimizing the systemic cytokine release syndrome [69]. In the phase I trial including different heavily pretreated B-NHL subtypes considerable activity was observed in R/R DLBCL: ORR 41.1% (CR 28.8%) globally and ORR 55% (CR 42.1%) at doses $\geq$ 10 mg with 5.5 months of median DOR (95% CI, 4.4 months to not reached) and a median DOR not reached for patients obtaining CR, with a median observation period of 27.4 months [58]. The Pivotal phase II expansion results from a cohort of 155 R/R DLBCL treated with Glofitamab have been recently presented, and showed durable responses with 51.6% ORR (39.4% CR) and median DOR of 12.6 months (range 0–22). Patients were heavily pretreated and 52 out of 155 previously failed CAR-T [70].

Epcoritamab (GEN3013) represents the first subcutaneous CD3xCD20 BsAb which binds CD20 antigen on a different epitope in respect of the most common anti-CD20 moAbs. It showed a really manageable profile, with 59% of CRS events but all grade 1–2 and remarkable activity on R/R B-NHLs, including 68% of ORR (45% CR) on multirefractory DLBCL (with a median of 3 previous treatments) at full doses (12–60 mg) and 88% ORR (38% CR) at the final recommended dose of 48 mg [59]. Recent data from the phase II DLBCL expansion cohort of the pivotal trial (EPCORE NHL 1) confirm the activity of Epcoritamab in R/R DLBCL: in 157 patients enrolled (61 out of 157 R/R to CAR-T) a 63% ORR (39% CR) was reached, with a median DOR of 12 months [71].

Other CD3xCD20 BsAbs under investigation for R/R NHLs include odronextamab and Plamotamab whom data from early studies are encouraging. While studies on Plamotamab are still preliminary, in a phase I dose-escalation trial odronextamab showed durable responses on R/R B-NHLs, particularly when administered at doses greater than 80 mg, with 60% of ORR (60% CR) for the DLBCL subgroup not previously treated with CAR-T and 33.3% of ORR (23.8% CR) for patients R/R to CAR-T, with a median DOR of 10.3 months and 2.8 months, respectively [60,61]. Data from the phase I study on odronextamab prompted the conduction of a global phase II trial for R/R B-NHLs, that is currently ongoing.

Antibody-drug conjugates

In the R/R setting of DLBCL two compounds are obtaining a major role among ADCs.

Polatuzumab vedotin

The above mentioned Polatuzumab vedotin showed a certain activity as single-agent for B-NHLs, with good tolerance and neurotoxicity as the main treatment-emergent adverse event and was investigated in more advanced studies [72]. The combination polatuzumab vedotin plus rituximab and bendamustine (pola-BR) showed better efficacy in respect of the standard BR in the phase II-randomized trial by Sehn *et al.* [73] in terms of response (CR 40% vs. 17.5%) and long-term survival rates (median PFS 9.2 vs. 3.7 months; HR 0.36, and median OS 12.4 vs. 4.7 months; HR, 0.42, median follow up 22.3 months). These results leaded the FDA and EMA approval for pola-BR regimen for treatment of transplant-ineligible R/R DLBCL. In a recently published updated analysis with the addition of an extension cohort of 106 R/R DLBCL patients treated with pola-BR, the regimen confirmed its efficacy with 38.7% of CR and sustained survival rates, even if lower PFS rate was observed: median PFS 6.6 months, median OS 12.5 months [62]. Real word data with pola-BR in R/R DLBCL reported similar response rates with an ORR ranging between 48% and 60%, but with a much shorter PFS (3 to 5.6 months) [74,75]. Driven by the positive results of pola-BR several trials are investigating the efficacy of polatuzumab combined with other chemoimmunotherapy regimens such as rituximab plus ifosfamide, carboplatin and etoposide (polaR-ICE) as pre-ASCT salvage therapy for transplant-eligible patients and the comparison of polatuzumab plus rituximab, gemcitabine and oxaliplatin (pola-R-GemOx) vs. R-GemOx alone for transplant-ineligible R/R DLBCL in the phase III-trial POLARGO [76,77].

Loncastuximab tesirine

Loncastuximab tesirine is composed of a humanized anti CD19 moAb conjugated with the pyrrolobenzodiazepine dimer cytotoxic alkylating agent tesirine (SG3199). The compound demonstrated a safe toxicity profile in the phase I trial and, based on the results of the multicenter phase II LOTIS-2 trial, it obtained the accelerated FDA approval for treatment of R/R DLBCL in mid 2021 [63,64]. In the LOTIS-2 145 heavily pretreated DLBCL patients (with a median of 3 previous lines of treatment) were treated with loncastuximab tesirine given intravenously every 21 days for up to 1 year or until progression or unacceptable toxicity. The compound showed certain effectiveness with an ORR of 48.3% (CR 24.1%), a 9-month DOR of 64% and median PFS and OS of 4.9 and 9.9 months, respectively. A phase I multi-arm trial not yet recruiting will investigate the activity of loncastuximab tesirine combined with several chemotherapeutic or biological agents including gemcitabine, lenalidomide, polatuzumab vedotin or the PI3K inhibitor umbralisib in the setting of R/R B-NHLs [78]. In an attempt to improve its efficacy, loncastuximab tesirine has been also combined with Ibrutinib in a phase 2 single arm study in R/R DLBCL and Mantle Cell Lymphoma (LOTIS-3). Preliminary results in the first 35 patients have been recently reported showing an improvement of ORR 57.1% (CR 34.3%) [79]. More data with a longer follow-up are needed to show if the combined treatment will be better than the single agent.

Early adoption of immunotherapy

Positive results of innovative therapies such as tafa + LEN, BsAbs and CAR-T for R/R DLBCL prompted the attempt to introduce their use in the front-line setting.

In the First-MIND phase Ib trial patients with newly diagnosed DLBCL were randomized to receive tafa + R-CHOP or tafa + LEN + R-CHOP [80]. Both combinations showed acceptable toxicity, similar to those expected from standard R-CHOP. This prompted to launch a phase-III multicentre randomized double-blind trial (frontMIND)

comparing safety and efficacy of R-CHOP vs. the triplet regimen tafa + LEN + R-CHOP for untreated high-risk DLBCL that is ongoing [81].

In the field of CD3xCD20 BsAbs a number of compounds are under investigation in frontline in addition to the standard R-CHOP. In the subpopulation of untreated DLBCL of a trial including R/R B-NHLs and newly diagnosed high-risk DLBCL, the combination mosunetuzumab plus CHOP showed to be manageable with CRS not exceeding grade 2 and no neurotoxicity with 96% of ORR (CR 85%) among 27 evaluable patients [82]. The efficacy of mosunetuzumab as consolidation for DLBCL patients with unsatisfactory response after frontline R-CHOP (stable disease or PR) or mosunetuzumab +/- Polatuzumab vedotin as first-line for elderly/unfit patients considered not candidate for chemoimmunotherapy is under investigation in a phase I/II trial [83]. In a preliminary analysis of the latter ongoing trial good results were observed for mosunetuzumab monotherapy (arm B) with 58% of ORR and 42% of CR [84]. Glofitamab plus R-CHOP is under investigation in a phase Ib trial (NCT03467373) including R/R B-NHLs and newly diagnosed DLBCL. The very preliminary data of the safety run-in part of the DLBCL cohort showed a safe profile of the combination, with a single event of grade 1 CRS and no neurotoxicity events, and among patients evaluable for response 4/4 CRs were observed [85]. In a phase I/II trial safety and efficacy of Epcoritamab combined with various standard of care therapies for untreated and R/R B-NHLs is ongoing, including the combination Epcoritamab + R-CHOP for untreated high-risk DLBCL and Epcoritamab + Gemox for R/R DLBCL not eligible for transplantation or failing CAR-T. Preliminary data from a small number of 33 untreated high-risk DLBCL patients showed reasonable toxicities and encouraging anti-lymphoma activity for the combination Epcoritamab + R-CHOP, with 52% of CRS all grade $\leq$ 2 except one grade 3 and all evaluable patients (31) achieving early responses (ORR 100%, CMR 77%) [86]. In 27 R/R DLBCL patients Epcortimab + Gemox was preliminarily shown to be safe (CRS 70% all grade 1–2 except 1 grade 3) with a promising efficacy (ORR 92%, CMR 60%) [87].

Based on the good efficacy of anti CD19-CAR-T in R/R DLBCL in second or third line or beyond, this cellular therapy has been incorporated in early phase of treatment for high risk DLBCL. In the phase II ZUMA-12 trial patients with high-risk DLBCL, defined as IPI $\geq$ 3 or double/triple-hit histology and with an interim positive PET after 2 courses of an anti CD20 - antracicline-based regimen were treated with Axicabtagene ciloleucel (Axi-cel) [88]. Preliminary data of the study showed rapid and durable responses with 89% of ORR (78% CR), 12-month PFS, EFS, DOR and OS of 81%, 73%, 75% and 91%, respectively, and median PFS, EFS and DOR not reached with a median follow up of 15.9 months. These results prompted the design of further trials with the use of CAR-T in front-line for high-risk DLBCL, hypothesizing an increased benefit of their use for patients exposed to fewer prior therapies and likely with a more competent immune system.

Precision medicine and tailored therapeutic approaches

DLBCL is nowadays recognised to be a phenotypically and genetically heterogeneous disease. In the first instance, three distinct subtypes of DLBCL ABC, GCB and unclassified were defined, based on the COO, and subsequently recognised in the 2016 revision of the World Health Organization classification of lymphoid neoplasms [89,90]. More recently two independent studies, based on whole-exome sequencing and structural genomic abnormalities, defined two 'molecular classifications', dividing DLBCL in several subtypes characterized by targetable gene alterations and paving the way for a new era of precision medicine [91,92]. In a recent study by Wilson *et al* [93] an extended genomic analysis on non-GCB DLBCL patients from PHOENIX trial was performed with the aim to identify molecular subgroups with different sensitivity to the ibrutinib plus R-CHOP combination. The authors were able to divide the patients based on the classification by Schmitz *et al* [92] identifying cases defined as MDC, BN2 and N1 molecular subtypes. Young subjects (age $\leq$ 60 years) defined as MDC or N1 harbouring *MYD88*, *CD79b* or *NOTCH1* mutations, were more sensitive to Ibrutinib showing a significantly improved outcome when treated with the addition of ibrutinib in respect of those in the standard arm, with a 3-year EFS of 100% vs. 42.9% and 50% for the two subtypes, respectively. At the last International Conference of Malignant Lymphoma (16th ICML, Lugano, 2021) the preliminary findings of the Guidance-01 phase II trial were presented [94]. In this ambitious study 128 newly diagnosed DLBCL were divided into 6 subgroups using a simplified targeted-sequencing tool, including 4 subtypes previously described in the molecular classification by Schmitz *et al* [92] (MCD *like*, BN2 *like*, N1 *like*, EZB *like*), *TP53* mutated and others. Patients were subsequently randomized 1:1 to receive the standard R-CHOP or R-CHOP plus X, modulating the added compound based on the molecular subgroup: Ibrutinib for MCD like and BN2 like, the demethylating agent decitabine for *TP53* mutated, tucidinostat, a histone deacetylase inhibitor, for EZB like and Lenalidomide for N1 like and others. For the 107 evaluable patients at the time of the analysis better rates of responses were observed for the R-CHOP plus X cohort with 87% of CR vs. 66% for the standard cohort, ultimately translating in improved PFS (1-year PFS 96% and 79%, respectively, HR 0.22). Despite the limit of a small sample size, this "proof of concept" study may suggest a potential benefit for these tailored mechanism-based treatment strategies and encourage further investigations in this direction.

Conclusions

Since the introduction of R-CHOP many efforts were made to improve outcome of DLBCL. In the last decade much is changed and in the R/R setting new options ameliorated the life expectancy. The advent of CAR-T opened the doors of a new era for patients unresponsive to chemoimmunotherapy treatments; today they represent the standard III line therapy for R/R DLBCL and data from new studies allowed the approval for their use earlier during the treatment timeline as second line therapy in refractory or early relapse patients [41,42,88]. The combination pola-BR is a new option for transplant ineligible R/R cases improving outcome of cases for which there were no valid alternatives before [73]. More recently, novel agents are showing impressive results in treatment of unresponsive patients, among those tafa + LEN combination, already approved by FDA and EMA for the R/R setting and CD3xCD20 BsAbs which demonstrated efficacy even in heavily pretreated cases [56–60].

On the other hand, despite many trials were designed with the purpose to improve the frontline therapy outcome, after two decades the standard of care is still represented by R-CHOP. It is not easy to explain why the strategy of R-CHOP + X has failed despite many and different combinations. Targeting a single gene alteration based on a too simple subgrouping (GCB or ABC) could be not active enough leading the lymphoma cells to escape through other pathways. Indeed, DLBCL is more complex and heterogenous as shown by the more recent molecular classifications and novel-novel combinations with multiple new agents added to standard R-chemotherapy, possibly based on the presence of specific mutations could be an option with greater chance of success. Nevertheless, in the very recent era something is changing. With the POLARIX trial for the first time a combination R-CHOP plus X (i.e. pola-R-CHP) demonstrated an advantage over R-CHOP, and encouraging results came from the phase II CAVALLI trial in which the addition of venetoclax to the R-CHOP backbone, seems to improve outcome for the subset of poor prognosis population with *BCL-2* overexpression [65,66]. Furthermore, ongoing trials are testing the efficacy of the early use of the immunotherapy combinations resulted effective for R/R patients, combining them in frontline with R-CHOP, and this is the case of tafa + LEN in the First-MIND trial, and several trials adding CD3xCD20 BsAbs such as mosunetuzumab, epcoritamab and glofitamab.

In the future, the real breakthrough in the frontline therapy for DLBCL may be represented by the adoption of tailored individualized strategies, based on clinical and molecular characterization. The

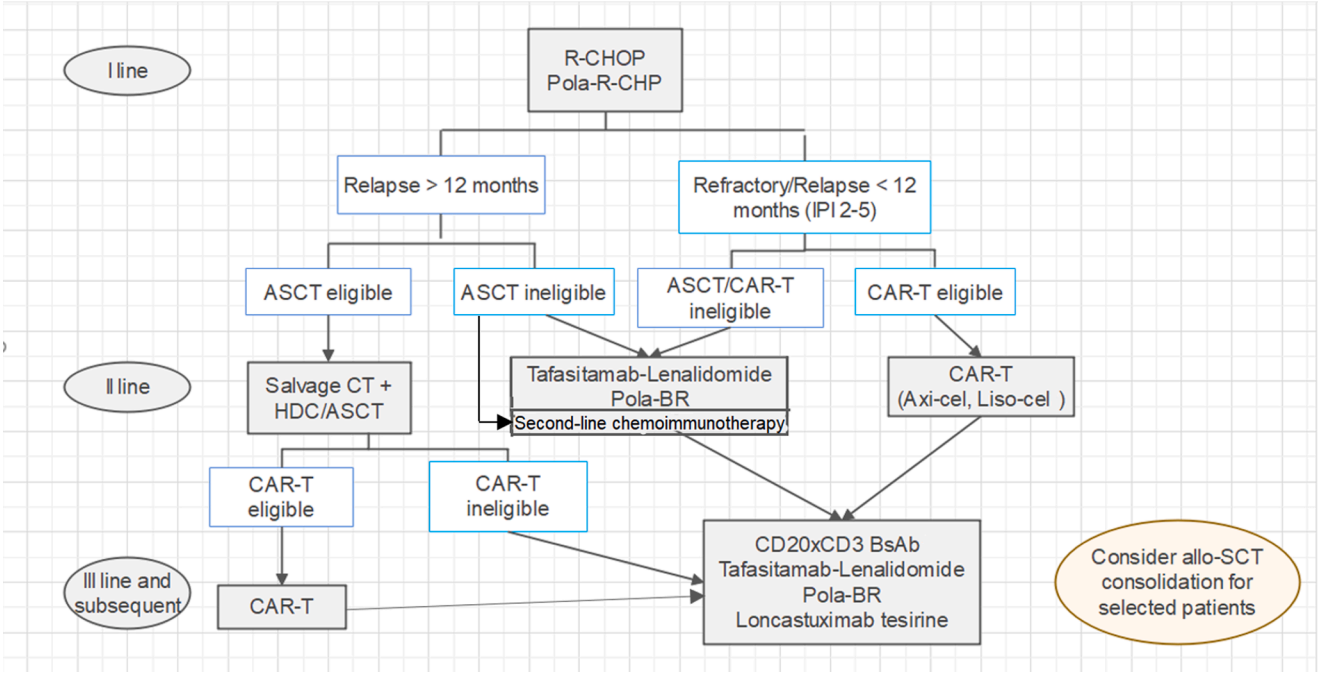

Fig. 4. Our proposal of treatment algorithm for DLBCL in 2022. In first line Pola-R-CHP could be considered as an alternative to R-CHOP. The choice of second line treatment should be assessed based on disease (relapse before or after 12 months) and patients characteristics (eligible or not to CAR-T and ASCT). CAR-T should be preferred for chemo-refractory disease, while salvage CT followed by HDC and ASCT still have a major role in chemo-sensitive disease. Tafasitamab plus lenalidomide and Pola-BR are evaluable options for patients who are ineligible to CAR-T and ASCT. Second-line chemoimmunotherapy i.e R-Gemox or others is still an option in patients not eligible to CAR-T and ASCT and chemosensitive (late relapse etc). In subsequent lines additional alternative treatment are BsAb, Tafasitamab + Lenalidomide, Pola-BR and loncastuzumab tesirine. Allo-SCT could be considered in this setting in selected patients. Abbreviations: ASCT: autologous stem cell transplant; BsAb: bispecific antibodies; BR: rituximab, bendamustine; CAR-T: chimeric antigen receptor T-cells; CHP: cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; HDC: high dose chemotherapy; IPI: international prognostic index; R: rituximab; Pola: Polatuzumab; SCT: stem cell transplant.

findings revealed from molecular analysis of PHOENIX trial by Wilson *et al* [93], and even more the preliminary results from the Guidance-01 trial suggest a move in this direction [94]. Further trials should be encouraged with molecular-based treatment strategies and the translation of advanced sequencing techniques into simplified platforms able to capture the relevant signatures of different genetics subgroups may be the next step to increase the feasibility of this approach.

Given the current dynamic landscape of new biological agents and innovative combinations a possible algorithm for the treatment of DLBCL in 2022 can be summarized in Fig. 4. But as a famous song said "the times they are a-changing" and this algorithm may require an update in the short future with the results of the ongoing studies (Fig. 4).

Authors' contributions

SP, MN, LP, PMMF and UV collected and interpreted data from literature, and wrote the manuscript. All authors reviewed and approved the final report.

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.

References

[1] Cunningham D, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381(9880):1817–26.
[2] Recher C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet 2011;378(9806):1858–67.
[3] Chiappella A, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. Lancet Oncol 2017;18(8):1076–88.
[4] Stiff PJ, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med 2013;369(18):1681–90.
[5] Schmitz N, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002–1). Lancet Oncol 2012;13(12):1250–9.
[6] Le Gouill S, et al. Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase 3 study by LYSA. Blood 2021;137(17):2307–20.
[7] Bartlett NL, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol 2019;37(21):1790–9.
[8] Dodero A, et al. Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma. Leukemia 2019;33(4):1047–51.
[9] Vitolo U, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol 2017;35(31):3529–37.
[10] Nowakowski GS, et al. Addition of lenalidomide to R-CHOP improves outcomes in newly diagnosed diffuse large B-cell lymphoma in a randomized phase II US intergroup study ECOG-ACRIN E1412. J Clin Oncol 2021;39(12):1329–38.
[11] Nowakowski GS, et al. ROBUST: a Phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol 2021;39(12):1317–28.
[12] Leonard JP, et al. Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. J Clin Oncol 2017;35(31):3538–46.
[13] Davies A, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet Oncol 2019;20(5):649–62.
[14] Younes A, et al. Randomized Phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal Center B-cell diffuse large B-cell lymphoma. J Clin Oncol 2019;37(15):1285–95.
[15] Tilly H, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med 2022;386(4):351–63.

[16] Morschhauser F, et al. A phase 2 study of venetoclax plus R-CHOP as first-line treatment for patients with diffuse large B-cell lymphoma. Blood 2021;137(5):600–9.
[17] Jaeger U, et al. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica 2015;100(7):955–63.
[18] Crump M, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014;32(31):3490–6.
[19] Witzig TE, et al. Adjuvant everolimus in high-risk diffuse large B-cell lymphoma: final results from the PILLAR-2 randomized phase III trial. Ann Oncol 2018;29(3):707–14.
[20] Thieblemont C, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2017;35(22):2473–81.
[21] Wiernik PH, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26(30):4952–7.
[22] Nowakowski GS, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. J Clin Oncol 2015;33(3):251–7.
[23] Vitolo U, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol 2014;15(7):730–7.
[24] Wilson WH, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21(8):922–6.
[25] *A Combination of Acalabrutinib With R-CHOP in Subjects With Previously Untreated Non-GCB DLBCL (ACE-LY-312)*. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04529772 (accessed Feb 6, 2022).
[26] Crump M, et al. Randomized, double-blind, phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. J Clin Oncol 2016;34(21):2484–92.
[27] Philip T, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333(23):1540–5.
[28] Gisselbrecht C, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28(27):4184–90.
[29] Thieblemont C, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol 2011;29(31):4079–87.
[30] Caballero MD, et al. BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. Bone Marrow Transplant 1997;20(6):451–8.
[31] Jagadeesh D, et al. Outcomes of rituximab-BEAM versus BEAM conditioning regimen in patients with diffuse large B cell lymphoma undergoing autologous transplantation. Cancer 2020;126(10):2279–87.
[32] Crump M, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130(16):1800–8.
[33] Locke FL, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol 2019;20(1):31–42.
[34] Schuster SJ, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380(1):45–56.
[35] Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396(10254):839–52.
[36] Nastoupil LJ, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US lymphoma CAR T consortium. J Clin Oncol 2020;38(27):3119–28.
[37] Pasquini MC, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv 2020;4(21):5414–24.
[38] Jacobson CA, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol 2020;38(27):3095–106.
[39] Bethge WA, et al. GLA/DRST real-world outcome analysis of CAR-T cell therapies for large B-cell lymphoma in Germany. Blood 2022.
[40] Bishop MR, et al. Second-line tisagenlecleucel or standard care in aggressive B-Cell lymphoma. N Engl J Med 2022;386(7):629–39.
[41] Kamdar M, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet 2022;399(10343):2294–308.
[42] Locke FL, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 2022;386(7):640–54.
[43] Neelapu SS, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. Nat Med 2022;28(4):735–42.
[44] Ghassemi S, et al. Rapid manufacturing of non-activated potent CAR T cells. Nat Biomed Eng 2022;6(2):118–28.
[45] Fraietta JA, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018;24(5):563–71.
[46] Neelapu SS, et al. Long-Term Follow-up ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients with Refractory Aggressive Non-Hodgkin Lymphoma (NHL). Blood 2017;130(Supplement 1).
[47] Kasakovski D, Xu L, Li Y. T cell senescence and CAR-T cell exhaustion in hematological malignancies. J Hematol Oncol 2018;11(1):91.
[48] Dourthe ME, et al. Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia. Leukemia 2021;35(12):3383–93.
[49] Neelapu SS, et al. CD19-loss with preservation of other B cell lineage features in patients with large B cell lymphoma who relapsed post-axi-cel. Blood 2019;134(Supplement_1).
[50] Zhang Q, et al. Transdifferentiation of lymphoma into sarcoma associated with profound reprogramming of the epigenome. Blood 2020;136(17):1980–3.
[51] van Kampen RJ, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol 2011;29(10):1342–8.
[52] Bacher U, et al. Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? Blood 2012;120(20):4256–62.
[53] Dreger P, et al. PTCy-based haploidentical vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL. Blood Adv 2019;3(3):360–9.
[54] Shah NN, Hamadani M. Is there still a role for allogeneic transplantation in the management of lymphoma? J Clin Oncol 2021;39(5):487–98.
[55] Carnevale-Schianca F, et al. Post-transplant cyclophosphamide and tacrolimus-mycophenolate mofetil combination governs GVHD and immunosuppression need, reducing late toxicities in allogeneic peripheral blood hematopoietic cell transplantation from HLA-matched donors. J Clin Med 2021;10(6).
[56] Salles G, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol 2020;21(7):978–88.
[57] Budde LE, et al. 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(5):481–91.
[58] Hutchings M, et al. 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(18):1959–70.
[59] Hutchings M, et al. 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(10306):1157–69.
[60] Bannerji R, et al. Odronextamab (REGN1979), a human CD20 x CD3 Bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-hodgkin lymphoma, including patients refractory to CAR T therapy. Blood 2020;136(Supplement 1):42–3.
[61] Patel K, et al. Preliminary safety and anti-tumor activity of XmAb13676, an anti-CD20 x anti-CD3 bispecific antibody, in patients with relapsed/refractory non-hodgkin's lymphoma and chronic lymphocytic leukemia. Blood 2019;134(Supplement_1).
[62] Sehn LH, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv 2022;6(2):533–43.
[63] Hamadani M, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood 2021;137(19):2634–45.
[64] Caimi PF, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021;22(6):790–800.
[65] Horton HM, et al. Potent in vitro and in vivo activity of an Fc-engineered anti-CD19 monoclonal antibody against lymphoma and leukemia. Can Res 2008;68(19):8049–57.
[66] Jurczak W, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Ann Oncol 2018;29(5):1266–72.
[67] Nowakowski GS, et al. Tafasitamab plus lenalidomide versus Pola-BR, R2, and CAR T: comparing outcomes from RE-MIND2, an observational, retrospective cohort study in relapsed/refractory diffuse large B-cell lymphoma. Blood 2021;138(Supplement 1).
[68] Novo M, et al. Antibody therapies for large B-cell lymphoma. Biologics 2021;15:153–74.
[69] Bacac M, et al. CD20-TCB with obinutuzumab pretreatment as next-generation treatment of hematologic malignancies. Clin Can Res 2018;24(19):4785–97.
[70] Dickinson M, et al. Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and $\geq$ 2 prior therapies: pivotal phase II expansion results. J Clin Oncol 2022;40(16_suppl).
[71] Thieblemont C et al. Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma: a phase 2 study. Presented at: 2022 EHA Annual Meeting; June 9-17, 2022; Vienna, Austria. Abstract LB2364. https://bit.ly/3xq326p.
[72] Palanca-Wessels MC, et al. Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. Lancet Oncol 2015;16(6):704–15.
[73] Sehn LH, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38(2):155–65.
[74] Segman Y, et al. Outcome of relapsed/refractory diffuse large B-cell lymphoma patients treated with polatuzumab vedotin-based therapy: real-life experience. Leuk Lymphoma 2021;62(1):118–24.

[75] Liebers N, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. Blood Adv 2021;5(13):2707–16.
[76] Haioun C et al. POLARGO: Randomized Phase III study of polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). J Clin Oncol, 2020;**38**(15_suppl): p. TPS8070-TPS8070.
[77] Vedotin P, Rituximab I. Carboplatin, and Etoposide (PolaR-ICE) as Initial Salvage Therapy for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma. ClinicalTrialsgov 2021. accessed Jan 24.
[78] A Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination With Other Anti-cancer Agents in Participants With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (LOTIS 7). ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04970901 (accessed Jan 30, 2022).
[79] Carlo-Stella C, et al. Planned interim analysis of a phase 2 study of loncastuximab tesirine plus ibrutinib in patients with advanced diffuse large B-cell lymphoma (LOTIS-3). Blood 2021;138:54.
[80] Belada D. et al. First-MIND: A phase Ib, open-label, randomized study to assess safety of tafasitamab (tafa) or tafa + lenalidomide (LEN) in addition to R-CHOP in patients with newly diagnosed DLBCL. Journal of Clinical Oncology, 2021. **39**(15_suppl): p. 7540-7540.
[81] Vitolo U, et al. frontMIND: A phase III, randomized, double-blind study of tafasitamab + lenalidomide + R-CHOP versus R-CHOP alone for newly diagnosed high-intermediate and high-risk diffuse large B-cell lymphoma. J Clin Oncol 2022;40(16_suppl).
[82] Phillips TJ, et al. Mosunetuzumab, a novel CD20/CD3 bispecific antibody, in combination with CHOP confers high response rates in patients with diffuse large B-cell lymphoma. Blood 2020;136(Supplement 1):37–8.
[83] Trial of Mosunetuzumab (BTCT4465A) as Consolidation Therapy in Participants With Diffuse Large B-Cell Lymphoma Following First-Line Immunochemotherapy and as Monotherapy or in Combination With Polatuzumab Vedotin in Elderly/Unfit Participants With Previously Untreated Diffuse Large B-Cell Lymphoma. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03677154 (accessed Feb 13, 2021).
[84] Olszewski AJ, et al. Single-agent mosunetuzumab is a promising safe and efficacious chemotherapy-free regimen for elderly/unfit patients with previously untreated diffuse large B-cell lymphoma. Blood 2020;136:43–5.
[85] Ghosh N, et al. Glofitamab Plus R-CHOP Induces High Response Rates with Minimal Cytokine Release Syndrome (CRS) in Patients (pts) with Relapsed/Refractory (R/R) Non-Hodgkin Lymphoma (NHL) and Previously Untreated (1L) Diffuse Large B-Cell Lymphoma (DLBCL): Preliminary Results from a Dose-Escalation and Safety Run-in Phase Ib Study. Blood 2021;138(Supplement 1).
[86] Falchi L, et al. First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): Phase 1/2 data update. J Clin Oncol 2022;40(16_suppl).
[87] Brody J, et al. Epcoritamab (epco) with gemcitabine + oxaliplatin (GemOx) in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) ineligible for autologous stem cell transplant (ASCT) induces high response rate even in pts failing CAR T therapy. J Clin Oncol 2022;40(16_suppl).
[88] Neelapu SS, et al. Primary analysis of ZUMA-12: a phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as first-line therapy in patients with high-risk large B-cell lymphoma (LBCL). Blood 2021;138:739.
[89] Alizadeh AA, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403(6769):503–11.
[90] Swerdlow SH, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127(20):2375–90.
[91] Chapuy B, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med 2018;24(5):679–90.
[92] Schmitz R, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med 2018;378(15):1396–407.
[93] Wilson WH, et al. Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL. Cancer Cell 2021;39(12):1643–1653.e3.
[94] Zhang M, et al. Genetic subtype guided rituximab-based immunochemotherapy improves outcome in newly diagnosed diffuse large B-cell lymphoma: first report of a randomized phase 2 study. Hematol Oncol 2021;39(S2).