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Review Article

Frontline Treatment in Diffuse Large B-Cell Lymphoma (DLBCL) and the Futuristic Alternate Standard of Care for the First Line Therapy

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Abstract

Diffuse large B cell lymphoma (DLBCL) in the most common type of non-Hodgkin's lymphoma (NHL) in developed world, so far and approximately 60,000 new non-Hodgkin lymphoma (NHL) cases and 20,000 deaths have been estimated in the United States for 2010. In spite of novel therapeutic options have been suggested and successfully tried in patients with lymphoproliferative disorders, the standard first- line treatment for DLBCL has remained the same combination of chemotherapy and CD20 (activated-glycosylated phosphoprotein) targeting monoclonal antibody rituximab (R) with 30% to 40% chance of relapse after first line R-CHOP treatment. Diffuse large B-cell Lymphoma is a distinct histological type within mature B-cell NHL that is characterized by large tumor cells and aggressive clinical behavior. Several clinical trials have been designed to evaluate safety, efficacy and superior clinical benefit by adding novel agents, intensifying cycles of treatment or substituting rituximab with new CD20 targeting immunotherapies. Intensification of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy from 3- week interval cycles to 2- week interval cycles has already shown clinical benefit in a German trial but failed to show improved overall and disease free (DFS) survival in both elderly (60 to 80 years) and young patients in randomized phase 3 clinical trials. In the GELA study of R-CHOP versus CHOP front line therapy in elderly subjects, following R-CHOP treatment the 5-year event-free survival (EFS) was 47%, the 5-year progression free survival (PFS) was 54%, and the 5-year overall survival (OS) was 58%3. Namely, in a phase 2 randomized clinical trial (PYRAMID) as a first line treatment for non-Germinal Center Cell (GCB) subtype of DLBCL the results were in favor of R-CHOP and adding bortezomib was not found to improve DFS and OS significantly. Immunomodulatory agent lenalidomide is another attractive therapeutic option for non-GCB subtype of DLBCL. Statistically significant difference between non-GCB and GCB controls treated with standard R-CHOP alone in terms of progression-free survival (28% vs. 64%; P = .00029) and overall survival (46% vs. 74%; P = .000036) was reported while non-GCB and GCB treated with R-CHOP plus lenalidomide had similar rates of progression (60% vs. 59%; P = 0.83) and overall survival at 2 years (83% vs. 75%; P = .61). Despite these promising clinical results, further clinical studies, especially phase 3 randomized clinical trials are required to confirm the alternate competitive treatment for DLBCL patients. arious strategies have been implemented to improve the outcomes of diffuse large B-cell lymphoma (DLBCL. As such, molecular classification of DLBCL is not only important for prognostication, but moves to center stage for personalization of therapy for DLBC.). In recent years, remarkable advances have been achieved, based on the discovery of cell-of-origin in DLBCL and on more effective targeted agents. A number of early clinical trials evaluating combinations of novel

targeted agents with standard chemotherapy (R-CHOP) have been completed and have demonstrated the feasibility of this approach with encouraging efficacy.

Keywords: CD20 targeting monoclonal antibody rituximab; chemo-immunotherapy; CHOP; Lenalidomide; mTOR inhibitor everolimus; obinutuzumab, Ibrutinib; brentuximab-vendotin; progression-free survival (PFS); Overall survival (OS)

Introduction

Diffuse large B-cell Lymphoma is a distinct histological type within mature B-cell NHL that is characterized by large tumor cells and aggressive clinical behavior. Diffuse large B cell lymphoma (DLBCL) comprises specific subtypes, disease entities, and other not otherwise specified (NOS) lymphomas. This review will focus on DLBCL NOS because of their prevalence and their heterogeneity with respect to morphology, clinical presentation, biology, and response to treatment. Gene expression profiling of DLBCL [1]. This type accounts for approximately 31% of all newly diagnosed malignant lymphomas (Armitage, 1998). CHOP chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab on a 21-day schedule is a standard of care in newly diagnosed cases in most countries worldwide [2]; Ketterer, 2013). In the GELA study of R-CHOP versus CHOP front line therapy in elderly subjects, following R-CHOP treatment the 5-year event-free survival (EFS) was 47%, the 5-year progression free survival (PFS) was 54%, and the 5-year overall survival (OS) was 58% [2]. While approximately 50% to 60% of patients are cured [2,3] for those patients who are refractory or who progress following R-CHOP, treatment options are limited and outlook is poor; most die within the next two years. Since roughly 40% to 50% of patients are not cured on initial therapy, evaluating other front line treatment options is warranted. Other attempts to improve cure rate, including R-ACVBD, CHOEP, dose dense regimens (R-CHOP14), and high dose regimens (DA-EPOCH), have not replaced R-CHOP21 as a standard of care [4,5].

Biological and Clinical Significance of DLBCL Typing

Diffuse large B cell lymphoma (DLBCL) in the most common type of non-Hodgkin's lymphoma (NHL) in developed world, so far. Gene expression profiling (GEP) of DLBCL resulted in the identification of two major and clinically distinct subtypes that are classified based on cell of origin (COO) and are associated with differences in clinical outcome: GCB and non-GCB, which is further comprised of ABC and primary mediastinal B-cell types [6,7]. The activated B cell-like (ABC) subtype of diffuse large B cell lymphoma (DLBCL) is much less curable than the other common DLBCL subtypes—germinal center B cell-like (GCB DLBCL) and primary mediastinal B cell lymphoma (PMBL)—necessitating new therapeutic strategies [1-3]. Besides, there is a more aggressive subtype of DLBCL which has been reported to be 5% to 10% of all DLBCL cases and presents with both MYC and BCL2 or BCL6 gene re-arrangement and is so called double hit lymphoma [8]. Despite novel therapeutic options have been suggested and successfully tried in patients with lymphoproliferative disorders, the standard treatment for DLBCL has remained the same combination of chemotherapy and CD20 targeting monoclonal antibody rituximab with 30% to 40% chance of relapse after first line R-CHOP treatment. Based on the below two major factors the COO classifications which are considered more clinically relevant [9].

(1) The development of new real-time COO assessment methods, including immunohistochemistry (IHC) and Nanostrings technology and (2) The identification of novel agents with activity in a specific DLBCL subtype (particularly ABC DLBCL).

Several clinical trials have been designed to evaluate safety, efficacy and superior clinical benefit by adding novel agents, majority of which are in development as front-line treatment for DLBCL appear to specifically target the ABC subtype of DLBCL, through either the B-cell receptor (BCR) pathway or pathway(s) downstream of the BCR pathway. This review will include only agents that are already in advanced clinical trials [9].

S.No	Agents	Examples
1	Immunomodulators	Pomalidomide
2	Proteasome inhibitors	Carfilzomib, Marizomib, Ixazomib, Oprozomib
3	Alkylating agents	Bendamustine
4	Akt inhibitors	Afuresertib
5	Btk inhibitors	Ibrutinib
6	Cdk inhibitors	Dinaciclib
7	Histone deacetylase inhibitors	Panobinostat, Rocilinostat, Vorinostat
8	Il-6 inhibitors	Siltuximab
9	Kinesin spindle protein inhibitors	Filanesib
10	Monoclonal antibodies	Daratumumab, Elotuzumab, Indatuximab,

Table 02. Examples for the Novel Agents.

Intensification of CHOP chemotherapy from 3- week interval cycles to 2- week interval cycles has already shown clinical benefit in a German trial in patients older than 60 in pre-rituximab era [10]. However, intensified R-CHOP chemotherapy in a 2-week interval has failed to show improved overall and disease-free survival in both elderly (60 to 80 years) (the LNH03-6B study) and young patients in randomized phase 3 clinical trials [11,12].

Clinical benefit of adding etoposide to the R-CHOP backbone in R-dose adjusted EPOCH combination chemo-immunotherapy has also been evaluated in both phase 2 and phase 3 clinical trials. Despite the excellent phase 2 trial results reporting the time to progression and event-free survival of 100% and 94%, in GCB (Germinal Center Cell) subgroup and 67% and 58% in non-GCB cases of DLBCL at 62 months follow up, this combination has failed to show superior results in terms of DFS and OS between two study groups. Besides, more patients in DA-R-EPOCH were unable to complete course of treatment due to toxicity [13,14].

The concept of intensifying chemotherapy for better DFS and OS has also been validated in phase 3 clinical trial (LNH03-2B) by using R-ACVBP (dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by consolidation in adult patients with DLBCL below the age of 60 compared with standard R-CHOP. This study showed superior 3-year event free survival of 81% (95% CI 75-86) vs. 67% (59-73) in R-ACVBP study group in low and intermediate risk DLBCL patients. 3-year estimates of progression-free survival was 87% [95% CI, 81-91] vs 73% [66-79]; HR 0·48 [0·30-0·76]; p=0·0015) and overall survival 92% [87-95] vs 84%. However, serious adverse events were 3 times in study group (42% vs. 15%) with 38% incidence of febrile neutropenia in R-ACVBP group [4].

S.No	Regimen	Drugs
1	DA-R-EPOCH	Darbepoetin alfa, Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
2	R-ACVBP	Rituximab, Doxorubicin, CycloPhosphamide, Vindesine, Bleomycin, And Prednisone
3	EPOCH	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
4	R-CHOP	Rituximab, Doxorubicin, Cyclophosphamide, Vincristine, And Prednisone
5	R-CVP	Cyclophosphamide, Prednisone and Vincristine

Table 3. Details with Different Regimens.

Below are the drugs used as chemotherapy in treatment for DLBCL.

Drug	Standard [R]-CHOEP	[R]-High-CHOEP	[R]-Mega-CHOEP, cycle 1	[R]-Mega-CHOEP, cycles 2 and 3	[R]-Mega-CHOEP, cycle 4 (last)	Mode	Days
(R)ituximab	375 mg/m^2	375 mg/m^2	375 mg/m^2	375 mg/m^2	375 mg/m^2	IV infusion	Day 1
(C)yclophosphamide	750 mg/m^2	1400 mg/m^2	1500 mg/m^2	4500 mg/m^2	6000 mg/m^2	IV infusion	Day 1
(H)ydroxydaunorubicin	50 mg/m^2	65 mg/m^2	70 mg/m^2	70 mg/m^2	70 mg/m^2	IV bolus	Day 1
(O)ncovin	1,4 mg/m^2 (max 2 mg)	2 mg	2 mg	2 mg	2 mg	IV bolus	Day 1
(E)toposide	100 mg/m^2	175 mg/m^2	600 mg/m^2	960 mg/m^2	1480 mg/m^2	IV infusion	Days 1-3
(P)rednisone or **(P)**rednisolone	40 mg/m^2	100 mg	500 mg	500 mg	500 mg	PO qd	Days 1-5

Table 1. Doses of chemotherapy regimens.

	R-ACVBP group	R-CHOP group
Events for event-free survival	**40 (20%)**	**63 (34%)**
Unplanned treatment for lymphoma	15	14
Unplanned chemotherapy	13	10
Unplanned radiotherapy	2	4
Progression or relapse	19	43
Death	6	6
Events for progression-free survival	**28 (14%)**	**51 (28%)**
Progression of relapse	21	44
Death	7	7
Events for overall survival	**15 (8%)**	**31 (17%)**
Lymphoma*	8	22
Unrelated to lymphoma progression during treatment	5	3
Unrelated to lymphoma progression after treatment		
Second cancer	-	2
Cardiac cause	1	-
Pneumonitis	-	2
Gastric haemorrhage	-	1
Suicide	-	1
Unknown	1	-

Table 4. Analysis of endpoints in the intention-to-treat population Data are n (%) unless otherwise stated. R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone. *Deaths from lymphoma progression or related to treatment of relapse or progression.

Poor outcome of non-GCB subtype has suggested the possibility of improving DFS and OS by adding novel treatment modalities to the classic R-CHOP combination. Considering the molecular pathways responsible for tumor genesis and promotion of non-GCB subtype of DLBCL involving nuclear factor-kb, proteasome inhibitor bortezomib, specifically targeting this pathway considered an attractive novel agent, which combined with R-CHOP, may potentially improve DFS and OS in this specific subgroup of patients. However, several phase 2 clinical trials have failed to show clinical benefit in terms of DFS and OS. Differences in PFS and OS in patients with germinal center B-cell–like versus nongerminal center B-cell–like DLBCL were analyzed, and 2-sided 95% CIs were calculated. PFS and OS data were presented as Kaplan-Meier estimates in the figure 1 and figure 2.

Patients treated with the immunomodulatory agent lenalidomide (R) in combination with R-CHOP (R2-CHOP) achieved ORRs and CRs of 90% to 100% and 77% to 86%, respectively, in phase I and phase II trials [15-18]. In one phase II trial, the most frequent grade 3/4 hematologic adverse events (AEs) included neutropenia (31%), leukocytopenia (28%), and thrombocytopenia (13%); no grade 4 nonhematologic AEs were reported.36 Response to R2-CHOP in patients with GCB versus non-GCB DLBCL was similar in a phase II trial (32 tissue samples available), and the 2-year PFS was 71% and 81%, respectively.36 Interestingly, in a separate phase II trial involving patients with newly diagnosed DLBCL who were treated with R2-CHOP, the 2-year OS was 75% for patients with GCB DLBCL compared with 83% for non-GCB subtypes. In patients treated with R-CHOP alone, a 2-year OS of 78% and 46% was achieved in GCB and non-GCB subgroups, respectively, suggesting that the addition of lenalidomide can improve the poor prognosis usually reported in the non-GCB population in response to standard R-CHOP therapy (Fig. 1) [19].

Namely, in a phase 2 randomized clinical trial (PYRAMID) as a first line treatment for non-GCB subtype of DLBCL the results were in favor of R-CHOP and adding bortezomib was not found to improve DFS and OS significantly. Similar results has been reported in the United Kingdom REMoDLB clinical trial in which patients were randomly assigned after the first R-CHOP treatment to receive either R-CHOP Alone or in combination with bortezomib. There was still no difference in overall response rate or CR rates between R-CHOP and R-CHOP plus bortezomib, whereas the 2-year PFS at 78% was again higher than expected and interestingly identical in both the PYRAMID and GOYA studies [20-22].

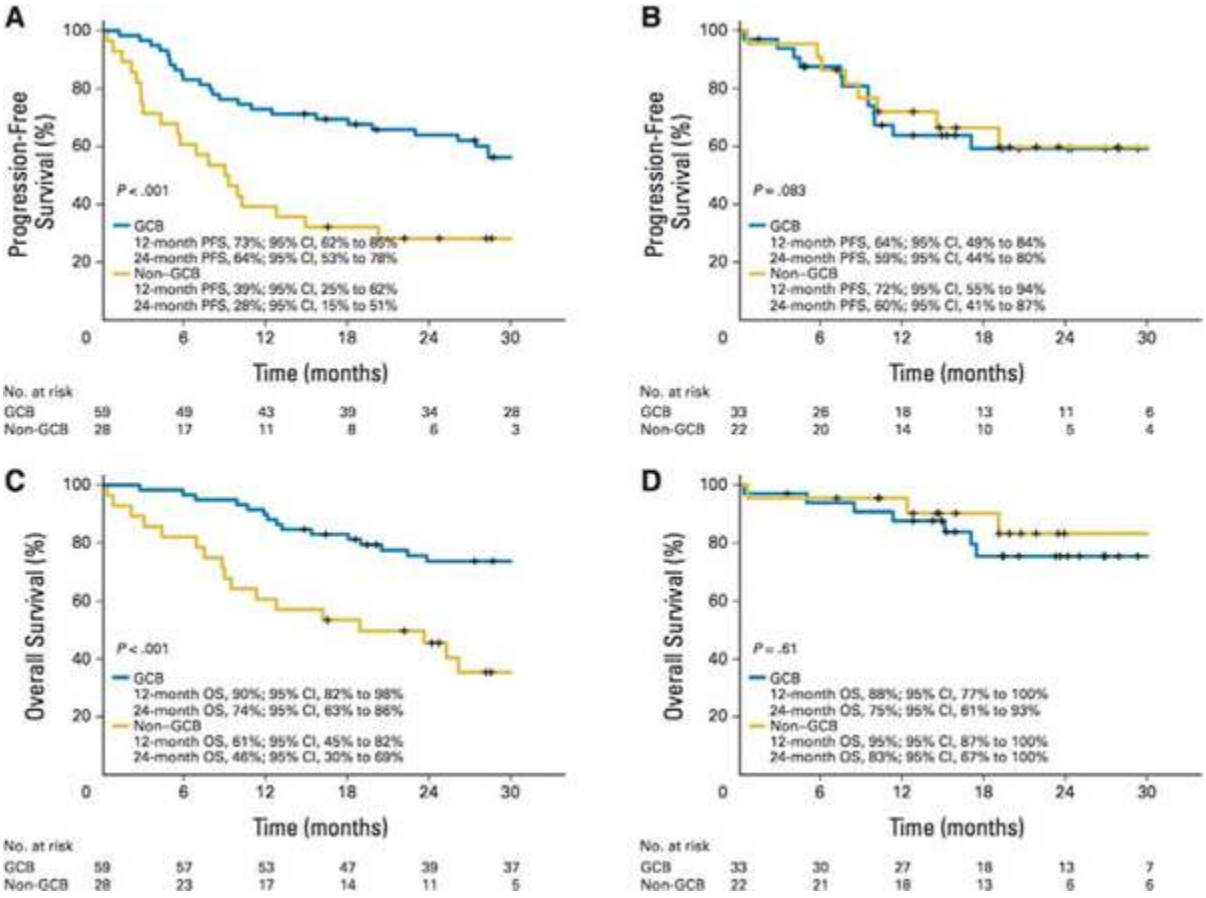

Figure 01. Outcomes of Patients Treated with R-CHOP or R2-CHOP according to GCB versus Non-GCB DLBCL Subtype Outcomes are shown for historic control patients treated with R-CHOP and study patients treated with R2CHOP based on germinal center B-cell (GCB) versus non-GCB diffuse large B-cell lymphoma (DLBCL) subtype. (A) Progression-free survival in patients treated with R-CHOP for non-GCB versus GCB DLBCL. (B) Progression-free survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL. (C) Overall survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL. (D) Overall survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL.

A combination of the proteasome inhibitor bortezomib and R-CHOP (VR-CHOP or Bor-RCHOP) was evaluated in patients with previously untreated DLBCL or mantle cell lymphoma. The evaluable ORR was 100%; 86% of patients exhibited CR or CR unconfirmed (CRu). In the intent-to-treat (ITT) population of 40 patients, ORR was 88%, and 75% had CR/CRu. The 2-year PFS was 64% and 2-year OS was 70% [23]. A current randomized phase II trial is designed to compare the effect of VR-CHOP versus R-CHOP on PFS (NCT00931918) [24], and an ongoing randomized phase III trial is investigating the efficacy of CHOP versus RV-CHOP in patients with DLBCL (REMoDL-B; NCT01324596) [25].

	DLBCL			MCL		
		%			%	
Response	No. of Patients	ITT (n – 40)	Evaluable (n = 35)	No. of Patients	ITT (n – 40)	Evaluable (n = 35)
Overall	35	88	100	29	81	91
CR+CRu	30	75	86	23	64	72
PR	5	13	14	6	17	19
SD	0	0	0	3	8	9
PD	0	0	0	0	0	0
Inevaluable*	5			4		

Table 5. R-CHOP and Bortezomib Treatment Response.

Abbreviations: R-CHOP: Rituximab Cyclophosphamide Doxorubicin Vincristine and Prednisone;

DLBCL: Diffuse Large B-cell Lymphoma;

MCL: Mantle Cell Lymphoma;

ITT: Intent to Treat;

CR: Complete Response;

CRu: Complete Response Unconfirmed;

PR: Partial Response;

SD: Stable Disease;

PD: Progression of Disease.

*Treatment was stopped due to toxic effects, withdrawal of consent by patients, investigator's decision, or death without progression before tumor response evaluation.

Immunomodulatory drugs (IMiDs) are structural and functional analogs of thalidomide that have immunomodulatory, antiangiogenic, and antitumor functions [26] Immunomodulatory agent like lenalidomide is another attractive therapeutic option for non-GCB subtype of DLBCL. Preclinical studies have demonstrated that lenalidomide selectively kills ABC lymphoma cells by augmenting interferon beta production. This augmentation is mediated through lenalidomide effects on interferon regulatory factor 4. After superior results of treatment with lenalidomide in relapsed, refractory DLBCL of non-GCB, phase 2 randomized clinical trial studied efficacy of adding oral lenalidomide to R-CHOP clearly showed that adding lenalidomide could overcome DFS and OS difference between non-GCB vs. GCB subtype of DLBCL that has been observed in patients received R-CHOP. Statistically significant difference between non-GCB and GCB controls treated with standard R-CHOP alone in terms of progression-free survival (28% vs. 64%; *P* = .00029) and overall survival (46% vs. 74%; *P* = .000036) was reported while non-GCB and GCB treated with R-CHOP plus lenalidomide had similar rates of progression (60% vs. 59%; *P* = 0.83) and overall survival at 2 years (83% vs. 75%; *P* = .61). Similarly, an open label, phase 2 clinical trial in elderly patients with newly diagnosed DLBCL (REAL07) reported a response rate of 92% and found the combination safe and effective in elderly group of patients· [27-29]. n a retrospective analysis of two phase II trials (NHL-002 and NHL-003), patients with aggressive relapsed/refractory NHL who received single-agent lenalidomide and prior autologous stem cell transplantation (ASCT) were compared with those who did not receive ASCT.

	GCB	Non-GCB
Lenalidomide cycles		
Median	2	4
Range	1-21	1-35
Response[a]		
CR	1 (4.3)	5 (29.4)[b]
PR	1 (4.3)	4 (23.5)
SD	7 (30.4)	0
PD	14 (60.9)	7 (41.2)
Unknown	0	1 (5.9)[c]
ORR (CR + PR)	2 (8.7)[d]	9 (52.9)[d]
PFS, mo		
Mean	3.3[e]	10.8[e]
95% CI	1.2-5.4	5.3-16.2
Median	1.7[e]	6.2[e]
95% CI	0.3-3.1	2.9-9.6

Table 6. Response to Lenalidomide Monotherapy.

Abbreviations: CI: Confidence Interval;

CR: Complete Response;

GCB: Germinal Left B-cell–like;

ORR: Overall Response Rate;

PD: Progressive Disease;

PET: Positron Emission Tomography;

PFS: Progression-Free Survival;

PR: Partial Response;

SD: Stable Disease.

As per 1999 Cheson criteria (PET scan excluded).

[b] One patient was originally assessed as SD, but subsequently reclassified as CR by the 2007 Cheson criteria (ie, PET negative for >12 months).

[c] One patient died during the first cycle before imaging studies.

[d] P ¼.006 non-CGB vs GCB.

[e] P ¼.004 non-CGB vs GCB.

Thirty-four patients (39%) with relapsed or refractory NHL and prior ASCT responded to lenalidomide; these included 12 of 87 (14%) patients with a CR/CRu and 22 of 87 (25%) with a PR. As summarized in detail in Table 2, responses occurred in 15 of 52 patients (29%) with DLBCL, 12 of 19 patients (63%) with MCL, and 6 of 10 patients with TL (60%). One patient (17%) with FL responded. Similar efficacy outcomes were confirmed through central review. For patients who had not received a prior transplant, the OR rate among all patients was 35%, with the following responses per histological disease: 26% for DLBCL (*n* = 82), 40% for MCL (*n* = 53), 38% for TL (*n* = 26), and 56% for FL (*n* = 18; data not shown) [30].

Response to lenalidomide by disease type among patients with relapsed or refractory aggressive NHL with a prior history of ASCT

stology	No. of patients	Response, n (%)					NEa
		ORR	CR/CRu	PR	SD	PD	
All patients with prior ASCT	87	34 (39)	12 (14)	22 (25)	21 (24)	25 (29)	7 (8)
Diffuse large B-cell lymphoma	52	15 (29)	5 (10)	10 (19)	13 (25)	20 (38)	4 (8)
Mantle cell lymphoma	19	12 (63)	5 (26)	7 (37)	6 (32)	1 (5)	0 (0)
Transformed lymphoma	10	6 (60)	2 (20)	4 (40)	1 (10)	3 (30)	0 (0)
Follicular lymphoma	6	1 (17)	0	1 (17)	1 (17)	1 (17)	3 (50)
Response as measured by central review							
All patients with prior ASCT	73	25 (34)	9 (12)	16 (22)	21 (29)	27 (37)	0 (0)
Diffuse large B-cell lymphoma	47	13 (28)	5 (11)	8 (17)	12 (26)	22 (47)	0 (0)

stology	No. of patients	Response, n (%)					NEa
		ORR	CR/CRu	PR	SD	PD	
Mantle cell lymphoma	14	8 (57)	3 (21)	5 (36)	4 (29)	2 (14)	0 (0)
Transformed lymphoma	8	4 (50)	1 (13)	3 (38)	3 (38)	1 (13)	0 (0)
Follicular lymphoma	4	0 (0)	0 (0)	0 (0)	2 (50)	2 (50)	0 (0)

1. ASCT, autologous stem cell transplantation; CR, complete response; CRu, complete response unconfirmed; NE, not evaluable or missing; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

2. *a* Reflects the number of patients with missing assessment or not evaluable (NE) by investigator.

Response as measured by investigator

In an ongoing, randomized, phase II/III clinical trial, the safety and efficacy of lenalidomide in relapsed/refractory DLBCL is being compared to the Investigator's choice (gemcitabine, oxaliplatin, rituximab, or etoposide) (NCT01197560) [31].

Lenalidomide has also been introduced as maintenance treatment for 24 months in elderly DLBCL patients achieving complete response with primary R-CHOP treatment in a phase 3 randomized clinical trial versus placebo (REMARC). This maintenance treatment showed significantly prolonged DFS in study group. This DFS improvement has been associated with higher chance of grade 3 or 4 neutropenia as well as higher chance of treatment discontinuation due to adverse effects (36% vs. 16%). Besides, no beneficial on OS has been observed with maintenance lenalidomide [29] Unlike lenalidomide, two other phase 3 randomized clinical trials using mTOR inhibitor everolimus versus placebo for one year (PILLAR-2) and oral protein kinase Cβ inhibitor enzastaurin versus placebo for 3 years and showed no difference in PFS or OS [32,33]. 36% and 30% patents in the study group in both REMARC (lenalidomide) and PILLAR-2 (everolimus) maintenance clinical trials discontinued treatment early due to the adverse events, respectively [32,34].

Considering more potent antibody-dependent cellular toxicity and greater induction of apoptotic effect that has been observed with obinutuzumab compared with rituximab, substituting obinutuzumab for rituximab has been evaluated in phase 2 and 3 clinical trials. GATHER has been the phase 2 clinical study of frontline treatment with obinutuzumab plus CHOP (G-CHOP) in newly diagnosed patients with advanced DLBCL that showed ORR of 88% and manageable toxicity. However, phase 3 clinical study of G-CHOP versus R-CHOP in newly diagnosed DLBC demonstrated no difference in relative progression-free survival (PFS) that was considered the primary end point. Moreover, higher rate of toxicity and particularly dose reductions and/or dose skipping in the obinutuzumab-CHOP (G-CHOP) arm were noted. The most commonly reported adverse event in obinutuzumab arm was infusion related reaction [33,35].

Ibrutinib, small molecule bruton kinase inhibitor which has already been approved in lymphoproliferative disorders, namely mantle cell lymphoma and chronic lymphocytic leukemia. An early phase 1b clinical trial in newly diagnosed patients with DLBCL showed 100% response in non-GCB subtype DLBCL. An ongoing phase 3 clinical trial (PHOENIX) is to evaluate the efficacy of ibrutinib plus R-CHOP with placebo plus R-CHOP in newly diagnosed non-GCB-subtype DLBCL. This trial has completed patient recruitment. The primary endpoint of the study is EFS [36,37].

Antibody-drug conjugate brentuximab-vendotin targeting CD30 expressing lymphomas has already been approved in aggressive T cell lymphomas and Hodgkin's disease in relapse, refractory setting. Safety and efficacy of brentuximab-vendotin in newly diagnosed DLBCL has been evaluated in a phase 2 randomized clinical study in combination with R-CHOP versus R-CHP (without vincristine) combination chemotherapy in intermediate-high and high risk clinical setting. In part 1 of this study, 51 patients were recruited to receive brentuximab vedotin 1.2 or 1.8 mg/kg plus CHOP. In part 2, patients with CD-30 expressing high-intermediate or high risk DLBCL enrolled to receive brentuximab vedotin 1.8 mg/kg plus RCHP. First part of this trial demonstrated the estimated 24-month progression-free survival of 79% for patients with CD30 expression compared with 52% among patients without detectable CD30 expression; 24-month overall survival was 92% (95% CI, 71-98) vs. 67% (95% CI, 44-82),

respectively. Of note, 73% of patients receiving brentuximab- vendotin in combination with R-CHOP presented treatment emergent peripheral neuropathy. Overall response rate for brentuximab-vendotin combined with R-CHP was reported to be 91%. Despite this promising clinical result, further clinical studies, especially phase 3 randomized clinical trials are needed to confirm the results of this early clinical study [38].

		Investigator Assessment	
End Point	**G-CHOP (n = 706)**		**R-CHOP (n = 712)**
Median observation time (range), months	29.0 (0.1-56.6)		28.9 (0.1-56.2)
Investigator-assessed PFS (primary end point)	n = 706		n = 712
Patients with event, No. (%)			
3-year PFS, %	201 (28.5)		215 (30.2)
Stratified HR (95% CI); P (log-rank)*	69.6		66.9
		0.92 (0.76 to 1.11); P = .3868	
OS	n = 706		n = 712
Patients with event, No. (%)	126 (17.8)		126 (17.7)
3-year OS, % (95% CI)	81.2 (77.9 to 84.1)		81.4 (78.1 to 84.3
Stratified HR (95% CI)*		1.00 (0.78 to 1.28)	
DFS in patients with investigator-assessed CR	n = 397		n = 369
Patients with event, No. (%)			
Stratified HR (95% CI)*	77 (19.4)		64 (17.3)
		1.27 (0.91 to 1.77	
Investigator-assessed EFS	n = 706		n = 712
Events, No. (%)	236 (33.4)		250 (35.1)
Stratified HR (95% CI)*		0.92 (0.77 to 1.11)	
Investigator-assessed response (with PET) at end of treatment†	n = 669		n = 665
ORR			
Proportion, No. (%)	518 (77.4)		518 (77.9)
Percentage difference (95% CI)		20.47 (25.01 to 4.08)	
CR			
Proportion, No. (%)			
Difference (95% CI)	379 (56.7)		396 (59.5)
		22.90 (28.27 to 2.48)	

Table 7. Summary of Efficacy End Points (intent-to-treat population) for G-CHOP v R-CHOP.

The anticonvulsant valproate in combination with R-CHOP in primary treatment of diffuse large B-cell lymphoma (DLBCL) stage II-IV, including a dose expansion cohort was initiated as an open label trial. R-CHOP was given at standard dose in 14 or 21 day cycles, 6 cycles. Valproate was given in escalating doses days 1-3, starting at 10 mg/kg every 8 hrs, by a standard 3+3 design. Prednisone was given days 1-5, R-CHOP on day 3. Response was evaluated according to the Lugano criteria. The primary outcome measure was establishment of maximum tolerable dose of valproate. Sensitization to rituximab and CHOP by pre-treatment with a Histone Deacetylase Inhibitors (HDAC) inhibitor which is a novel therapeutic strategy for the treatment of DLBCL. At a dose of 60 mg/kg, divided into 3 doses, the combination of valproate with R-CHOP is feasible in 1st line treatment of DLBCL. Higher doses of valproate were associated with intolerable auditory side effects. Early data show promising efficacy, which may

form the basis for a randomized phase III trial. The long-term efficacy of this regimen remains to be established by longer follow-up. Results showed in the phase I portion, the MTD of valproate was established as 20 mg/kg every 8 hrs (total 60 mg/kg). Toxicity was comparable to that of standard R-CHOP, without any impact on hematological toxicity. At the time of this report, the study is ongoing. After a median time of follow-up of 16 months, median PFS has not been reached out of 17 evaluable patients, and estimated PFS at 18 months is 77%. Common adverse events noticed at a dose of 80 mg/kg, 2 of 3 patients experienced tinnitus (grade 1 and 2) during the latter part of the treatment course. At a dose of 100 mg/kg, 1 of 5 patients developed hearing impairment, grade 1, after 3 cycles, which worsened to grade 2 after 4 cycles, leading to omission of valproate. One patient has died due to progressive lymphoma, 21 months after inclusion. By flow cytometry of fine needle aspirates from lymphoma lesions before and after 3 days of valproate, we could show significant upregulation of CD20 expression in 3 patients [38,39]. The study is still ongoing.

One open label trial was initiated to compare the efficacy and safety of Inotuzumab Ozogamicin in combination with R-CVP (Rituximab- Cyclophosphamide, Prednisone and Vincristine) with that of R-G-CVP for the treatment of Diffuse Large B Cell Lymphoma (DLBCL) in a population of patients not suitable for anthracycline based chemotherapy. There is no standard of care for the treatment of this group of patients. If demonstrated to be efficacious and safe to deliver this regimen will be further tested in a phase III trial to determine whether this should become the standard of care amongst patients with DLBCL not fit for anthracycline (R-CHOP). The primary outcome of this clinical study is Progression free survival (PFS) and the secondary outcomes are Overall Response Rate (ORR), Overall Survival (OS), Treatment, Toxicity, Quality Of Life, Performance Status Post Treatment and co-morbidities of the patient. Given that about 40% of cases of DLBCL occur in patients aged over 70 and the number of co-mobilities increases with age, research to investigate the optimal treatment of DLBCL in this group of patients is needed. R-CHOP remains the standard of care for most patients with DLBCL, anthracycline use is precluded in a proportion of these patients by a high risk of developing cardiotoxicity, especially congestive cardiac failure. Currently there is no standard of care for patients who are unfit for anthracycline treatment. It has been routine to omit the doxorubicin from R-CHOP, giving R-CVP instead. However, the outcome for patients treated with R-CVP is poor and attempts have been made to replace the doxorubicin with alternative agents. The trial will compare an experimental arm consisting of Inotuzumab Ozogamicin added to the standard immunochemotherapy regimen of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) with the control arm of gemcitabine added to the same combination (Gem-R-CVP). Study is still ongoing and no further analysis was performed [40].

Metformin [3] as an adjunct to RCHOP chemotherapy for patients with newly diagnosed diffuse large-B cell lymphoma was assessed with an open label single group assignment treatment study for evaluation of the safety and effectiveness. The primary outcomes of incidence of treatment-emergent adverse events and response rates and secondary outcomes of progression-free survival, overall survival, event-free survival, survival from diagnosis until death or progression, time to progression or relapse. Patients with newly diagnosed diffuse large-B cell Non Hodgkin lymphoma, irrespective of cell of origin status will receive metformin in combination to Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) chemotherapy for 6 cycles, until response evaluation as reported. Metformin will be added and administered in an outpatient basis, starting with 425 mg twice a day for 1 week, followed by 850 mg twice a day for 1 week, and lastly 850 mg every 8 hours maximum dose until re-staging. Laboratory tests will be performed serially. Study is still ongoing and no further analysis was performed [41].

Treatment of Yt90 Zevalin [6] in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) are effective as first line treatment in patients with bulky stage II or stage III or IV diffuse large B-cell lymphoma. A non-randomised, open label single group assignment treatment study with primary outcome of 2-year progression-free survival and overall survival of patients and secondary outcomes of response rate in patients 2-year progression-free survival, overall survival and response rate in BCL-2 positive patients was initiated. Radio-immunotherapy represents a significant advance over unlabeled immunotherapy for the treatment of patients with B-cell non-Hodgkin's lymphoma. The radio-biological effects associated with Yt90-labelled ibritumomab tiuxetan (Zevalin) include the induction of apoptosis and cell-cycle redistribution. The response rate tend to be higher in patients who have been treated with fewer prior therapies and Yt90-labelled ibritumomab tiuxetan may be suitable for use early in the course of therapy. Yt90-labelled ibritumomab tiuxetan has less non-hematologic toxicity than chemotherapy, with only minimal alopecia, mucositis, nausea, or vomiting, and a lower incidence of infections. Yt90-labelled ibritumomab tiuxetan regimen is routinely and safely given in an outpatient setting and is completed in 7-9 days and is thus more convenient to be used. This study has been terminated and no articles have been published yet [42].

Conclusion:

DLBCL is the most common type of NHL, the standard treatment with combination of rituximab and CHOP therapy is used as first line treatment. Competitive treatments that are being explored are the treatment of patients with lymphoproliferative disorders and several clinical trials have been initiated. Despite the positive results with the alterantives available for the treatment there has been showed no difference in PFS or OS in case of treatment with everolimus versus placebo for one year (PILLAR-2) and oral protein kinase Cβ inhibitor enzastaurin versus placebo [32,33]. Besides, no beneficial on OS has been observed with maintenance lenalidomide [34] and G-CHOP did not improve PFS compared with R-CHOP in patients with previously untreated DLBCL. Although these observations may help to inform and shape the direction of future research activities in patients with advanced-stage DLBCL, the need for improved therapeutic options therefore remains. A number of early clinical trials evaluating combinations of novel targeted agents with standard chemotherapy (R-CHOP) have been completed and have demonstrated the feasibility of this approach with encouraging efficacy. As such, molecular classification of DLBCL is not only important for prog-

nostication, but moves to center stage for personalization of therapy for DLBC.

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