ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

KATEDRA
ZA
ONKOLOGIJO

Slovensko
Zdravniško
Društvo

3. LIMFOMSKA ŠOLA

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Ljubljana, oktober 2023

PROGRAMME

Thursday 19.10.2023

Chairman: prof. Veronika Kloboves Prevodnik, dr. Gorana Gašljević

9.00 – 9.10: Opening speach (dr. Gašljević, prof. Kloboves Prevodnik)

9.00 – 9.45: 5th WHO classification of Lymphoid malignanices (prof. Andrew Wotherspoon, The Royal Marsden, England)

9.45 –10.00: A Proposal for the Performance, Classification, and Reporting of Lymph Node Fine-Needle Aspiration Cytopathology: The Sydney System (prof. Kloboves Prevodnik)

10.00 – 10.40: Treatment of ALL and flow cytometric analyses of MRD (prof. Michael Dworzak, St. Anna Kinderspital, Vienna, Austria)

10.40 – 11.00: Treatment of ALL – our centre experience (assist. prof.. Matevž Škerget, Dept. Of Hematology, University Clinical Centre Ljubljana, Slovenia)

11.00 – 11.30: Coffee break

11.30 – 12.30: Pathology and cytopathology workshops part I

Case1. Gazić Barbara, Klopčič Ulrika: T-cell lymphoblastic lymphoma vs thymoma in effusion as well as in small biopsies

Case 2. Gazić Barbara, Klopčič Ulrika: Nodal B-cell lymphoblastic lymphoma and its pitfalls in cytopathology

Case 3: Grčar-Kuzmanov Biljana, Kloboves Prevodnik Veronika: Classical Hodgkin lymphoma vs Primary mediastinal large B-cell lymphoma

Case 4. Grčar-Kuzmanov Biljana, Rode Aleš: Burkitt lymphoma vs diffuse large B-cell lymphoma

12.30 – 13.15: Lunch

13.15-14.15: Pathology and cytopathology workshops part II

Case 5. Gašljević Gorana, Jeričević Anja: Nodular lymphocyte predominant Hodgkin lymphoma vs T-cell/histiocyte rich large B-cell lymphoma

Case 6. Gašljević Gorana, Jeričevič Anja: Classical Hodgkins lymphoma vs Nodular

lymphocyte predominant Hodgkin lymphoma

Case 7. Wotherspoon Andrew: Criteria for transformation of MZL into DLBCL (Case 8. Car Milan, Rode Aleš: PEL versus PAL

Flow cytometry workshop in flow lab (3hours, parallel to patho workshop)

Friday 20.10.2023

Chairman: prof. Barbara Jezeršek Novaković, assist. prof. Lučka Boltežar

9.00 – 09.30: Molecular pathogenesis of DLBCL (prof. Andrew Wotherspoon, The Royal Marsden, England)

09.30 – 10.00: Risk stratification in DLBCL - clinical prognostic factors, molecular prognostic factors (prof. Thomas Melchardt, SALK, Paracelsus Medical University Salzburg, Austria)

10.00 – 10.15: First line treatment of DLBCL in regard to molecular pathogenesis (Milica Miljković, Institute of Oncology Ljubljana, Slovenia)

10.15 – 10.45: Coffee break

10.45 – 11.05: Favorable and unfavorable subtypes of DLBCL (dr. Gorana Gašljević, Urška Rugelj, Institute of Oncology Ljubljana, Slovenia)

11.05 – 11.25: Treatment of R&R DLBCL in regard to molecular pathogenesis (prof. Barbara Jezeršek Novaković, Institute of Oncology Ljubljana, Slovenia)

11.25 – 11.45: Treatment of R&R DLBCL – our centre experience (Maria Cristina Pirosa, Institute of Southern Switzerland, Switzerland)

11.45 – 12.05: Treatment of R&R DLBCL – our centre experience (assist. prof. Lučka Boltežar, Institute of Oncology Ljubljana, Slovenia)

12.05 – 12.30: Discussion

12.30 – 13.30: Lunch

13.30 – 15.00: Difficult cases presentations and discussion (assist. prof. Lučka Boltežar, Maria Cristina Pirosa, Institute of Southern Switzerland, Switzerland, Aleš C. Mihelač, Tina Zupančič, Anja Žižek, Institute of oncology, Ljubljana, Slovenia)

AVTORJI PRISPEVKOV V ZBORNIKU "3. LIMFOMSKA ŠOLA":

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prof. dr. Veronika Kloboves Prevodnik, dr.med., specialistka citopatologinja
Oddelek za citopatologijo, Onkološki inštitut Ljubljana

Aleš Christian Mihelač, dr.med., specialist hematologije
Sektor za internistično onkologijo, Onkološki inštitut Ljubljana

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KAZALO

Treatment of relapsed/refractory diffuse large B-cell lymphoma in regard to molecular classification

Prof. Barbara Jezeršek Novaković, MD, PhD

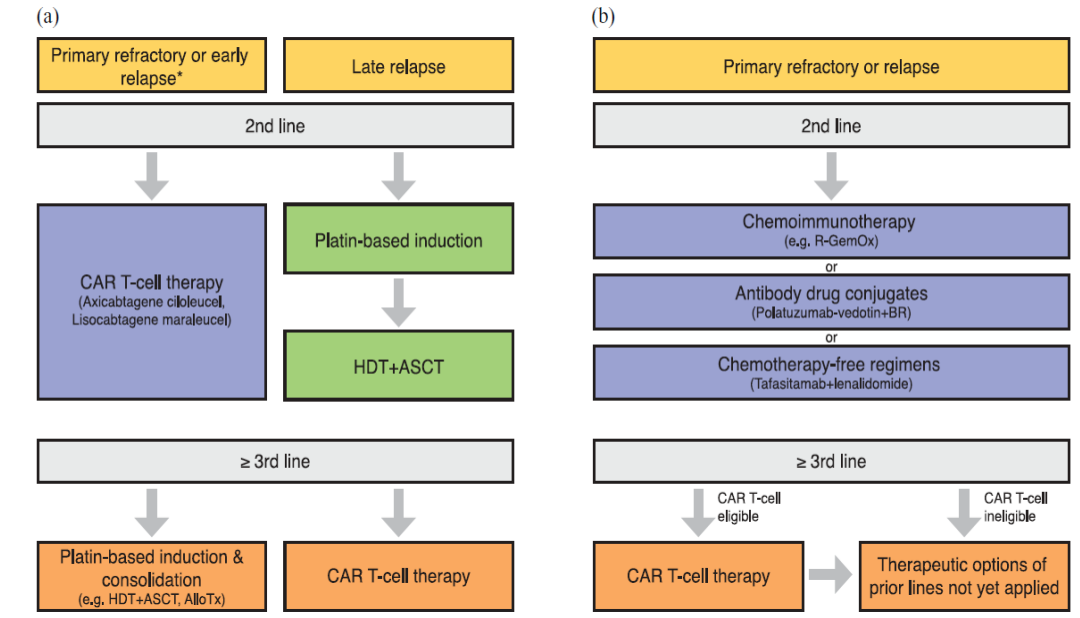
3rd Lymphoma School October 2023

Introduction: an overview of the current status of DLBCL treatment

DLBCL encompasses a wide variety of disease states ➡ to date characterized based on IHC methods ➡ limited prognostic value to clinicians, no alteration in treatment regimen.

The addition of R to CHOP ➡ last improvement in terms of treatment.
When disease becomes refractory ➡ regimens follow a standardized course with no individualization based on genotype.

Guidelines direct standardized R-CHOP as first line treatment (regardless of presentation or cellular markers), and refractory cases are treated uniformly with second line therapy in combination with HCT, CAR T-cell therapy, clinical trials, or finally palliative care.



Treatments agnostic for genetic diversity of the DLBCL. Treatments agnostic for internal disease mechanisms (as opposed to outward morphology or presence of basic cell markers). Indiscriminate therapy based on patient response.

Frontzek F et al. Current options and future perspectives in the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma. Ther Adv Hematol 2022, Vol. 13: 1–19.

Introduction: current trends

Research groups propose new strategies for categorizing DLBCL based on genetic abnormalities that are frequently found together ➡ to better predict disease course and to deliver targeted treatment.

Identification of genetic markers that alter disease course is essential:

- for implementation of effective treatment
- to indicate which patients may require less potent treatment or less invasive surveillance in looking for relapse.

Novel algorithms in combination with NGS have identified between 4 and 7 subgroups of DLBCL with potentially significant and actionable genetic alterations.

Subgroup by cell origin COO

IHC in combination with various algorithms have allowed the basic classification of DLBCL into two groups, ABC and GCB type, which has provided some prognostic insight into disease course without yielding much into targeted therapies for these distinct subtypes.

The heterogeneity of treatment outcomes, even among ABC and GCB subtypes, results from the specific pathways with altered regulation, expression, or end products that are not defined by classical subtyping.

The current ABC and GCB subtypes provide relatively little utility because they do not take in account the numerous changes that can occur within the genome that are not observable with IHC staining techniques.

Subgroup by cell origin COO

Activated B-cell like type (ABC): Cells tend to express common mutations and translocations, such as PRDM1 truncations or homozygous deletions. These cells show increased incidence of "chronic active" BCR signaling which is characterized by BCR clustering and autoreactive selfantigens as opposed to tonic signaling which is antigen independent and exhibits a lack of BCR clustering, as seen in GCB. MYD88 mutations conferring extranodal involvement, TNFAIP3 inactivation leading to uncontrollable NF-κB expression, and NOTCH1 mutations are seen almost exclusively in this subtype.

Germinal center B-cell like type (GCB): Cells are affected by the master regulator BCL6 similarly to ABC cells, but also are affected by more unique mutations. These possess an association with REL amplifications promoting lymphomagenesis, an almost exclusive presentation of t(14;18)(q32; q21) translocations leading to BCL2 activation and overexpression, and CREBBP mutation affecting the histone acetyltransferase domain leading to epigenetic dysregulation.

Subgroup by genetic alteration and signaling pathway

Molecular classification				
Wright	Schmitz	Lacy	Chapuy	Genetic alteration (% prevalance*)
BN2	BN2	NOTCH2	C1	*BCL6* (72.8%), *NOTCH2* (41.8%), *TNFAIP3* (51.6%), *DTX1* (50.0%), *CD70* (41.3%), *BCL10* (39.6%), *UBE2A* (30.4%), *TMEM30A* (26.7%), *KLF2* (21.7%), *SPEN* (21.7%)
A53	—	—	C2	*TP53* (86.8%), *B2M* (34.2), *TP53BP1* (27.0%), *CNPY3* (23.7%), *ING1* (15.8%), *NFKBIZ* (15.8%), *TP73* (13.2%)
EZB-MYC+ EZB-MYC−	EZB	BCL2	C3	*BCL2* (68.4%), *EZH2* (44.7%), *TNFRSF14* (66.2%), *KMT2D* (53.9%), *CREBBP* (52.7%), *REL* (34.3%), *FAS* (30.1%), *IRF8* (28.9%), *EP300* (27.8%), *MEF2B* (26.3%), *CIITA* (25.0%), *ARID1A* (22.9%), *GNA13* (22.5%), *STAT6* (21.1%), *PTEN* (20.0%)
ST2	—	TET2/SGK1 SOCS1/SGK1	C4	*TET2* (48.1%), *DUSP2* (44.4%), *ZFP36L1* (40.7%), *ACTG1* (37.0%), *SGK1* (37.0%), *ITPKB* (33.3%), *NFKBIA* (33.3%), *EIF4A2* (29.6%), *JUNB* (29.6%), *STAT3* (29.6%), *BCL2L1* (25.9%), *CD83* (25.9%), *DDX3X* (25.9%), *SOCS1* (25.9%), *CD83* (25.9%), *P2RY8* (22.2%), *RFTN1* (22.2%)
MCD	MCD	MYD88	C5	*MYD88* (66.2%), *CD79B* (50.0%), *PIM1* (92.5%), *HLA-B* (73.8%), *BTG1* (70.0%), *CDKN2A* (62.0%), *ETV6* (55.0%), *SPIB* (51.9%), *OSBPL10* (51.2%), *TOX* (48.1%), *BCL2* (48.1%), *BTG2* (43.8%), *MPEG1* (43.8%), *HLA-A* (43.0%), *HLA-C* (42.5%), *SETD1B* (41.8%), *KLHL14* (41.2%), *TBL1XR1* (35.0%), *GRHPR* (33.8%), *PRDM1* (32.5%), *CD58* (31.6%), *TAP1* (26.6%), *PIM2* (25.0%), *FOXC1* (21.2%), *IRF4* (20.0%)
N1	N1	—	—	*NOTCH1* (100%), *IRF2BP2* (43.8%), *ID3* (25.0%), *BCOR* (25.0%), *EPB41* (18.8%), *IKBKB* (18.8%), *ALDH18A1* (18.8%)

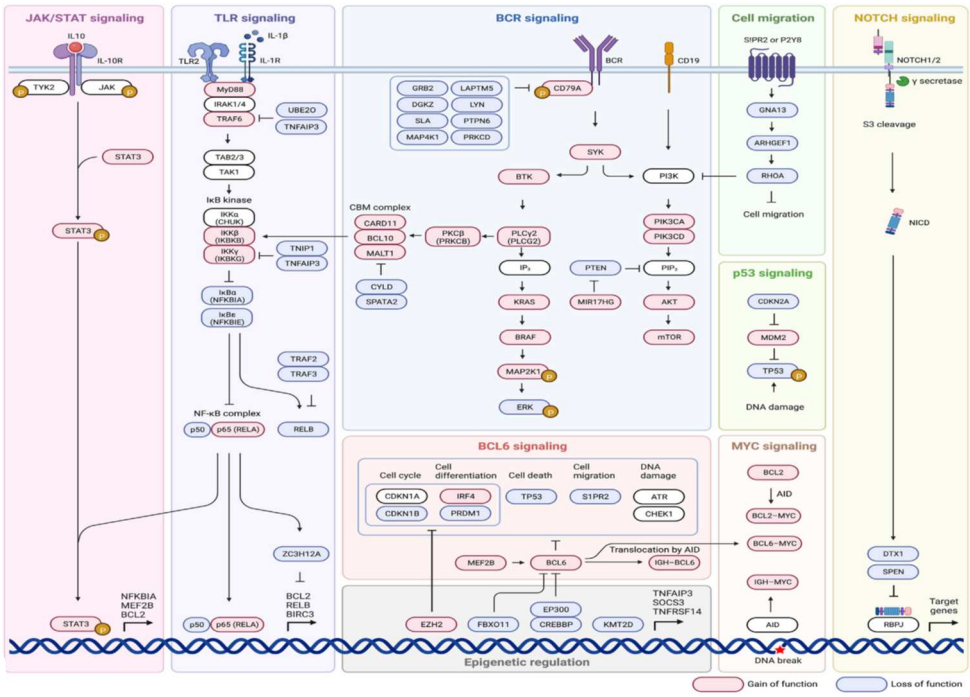
Shimkus G and Nonaka T (2023), Molecular classification and therapeutics in diffuse large B-cell lymphoma. Front. Mol. Biosci. 10:1124360.

Genetic alterations in DLBCL – major signaling pathway alteration in DLBCL

Major signaling pathways affected by genetic alteration in DLBCL:

- BCR signaling,
- PI3K-AKT-mTOR signaling,
- BCR dependent NF-κB activation,
- NF-κB signaling,
- TLR signaling,
- and the BCL2 anti-apoptotic family.

These pathways are related in their ability to evade apoptotic pathways, promote cell proliferation and gene expression, and confer lymphomagenesis.



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Alterations in epigenetic regulation that contribute to development of DLBCL

Equally important as mutations within genes themselves are changes in epigenetic regulators that alter expression of these genes.

Greater epigenetic heterogeneity is associated with poor clinical outcome and inhibitors of these mechanisms such as DNA methyltransferase and histone methyltransferase inhibitors may be a source of therapeutic intervention in DLBCL.

Alterations in other pathways

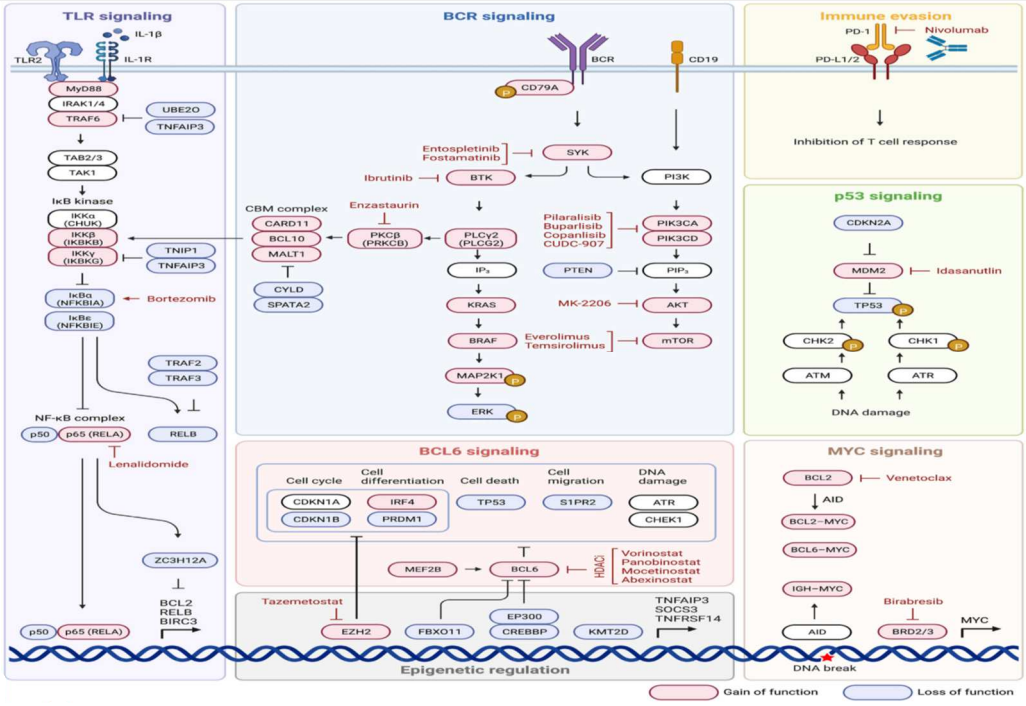
Various other pathways are involved in the continued survival, proliferation, and immune evasion of malignant DLBCL cells.

- Subtype N1 is based off alterations in NOTCH signaling.
- Germinal center homing pathways and migration are disrupted in EZB type cases.
- BCL6 signaling disruption is also found commonly in EZB subtype.
- TP53 mutations prevent cell death.
- MYC mutations are highly associated with MCD and BN2 type.
- Evasion of immune surveillance is seen across numerous DLBCL subtypes.

Targeted therapeutic strategies in DLBCL

Different therapies may be needed to target not only different pathways, but also the same pathway in different ways depending on how it was altered along its mechanism.

While these various subtyping methods may not be entirely clinically useful or relevant yet ➡ necessity to begin conceptually examining pharmaceuticals that could lead to outcomes superior to traditional R-CHOP when applied to these experimental subgroups.



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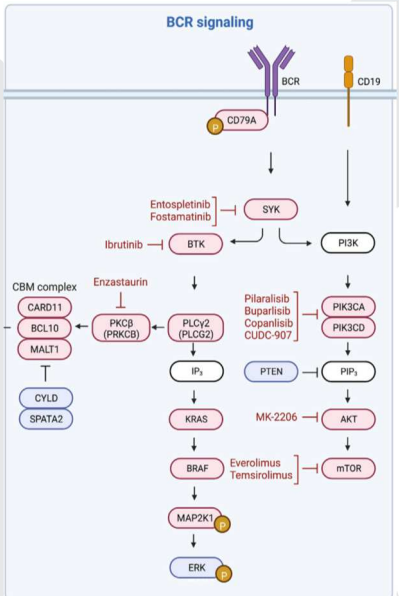
Targeted therapeutic strategies in DLBCL



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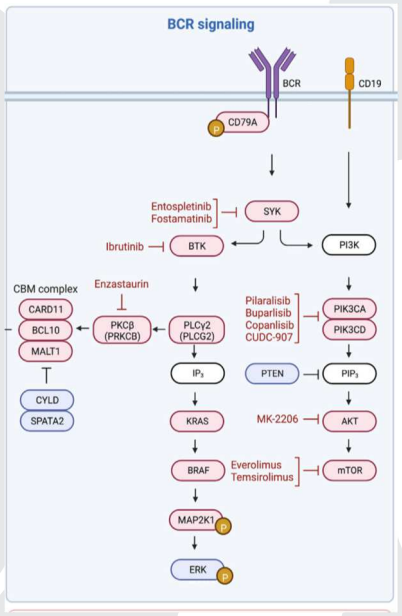
Targeting BCR signaling: Three targets of the BCR signaling pathway that are actionable by current drugs, are PKCβ, SYK, and Bruton's tyrosine kinase (BTK).

Enzastaurin is a selective PKCβ inhibitor which inhibits signal transduction and ultimate pathway activation, but efficacy has yet to be shown with this drug, and clinical failures have been attributed to mutations further down the pathway than at PKCβ. This drug may be of clinical use in patients with mutations specifically affecting PKCβ, so being able to detect mutations here would be essential in utilizing this treatment.

SYK inhibitor (SYKi) entospletinib has shown promise in clinical trials following BTK or PI3Kδ inhibitors, with a response rate of 69%.

Fostamatinib is another SYKi but has shown little clinical benefit, and likely caused side effects because it is a non-selective agent.

Targeted therapeutic strategies in DLBCL



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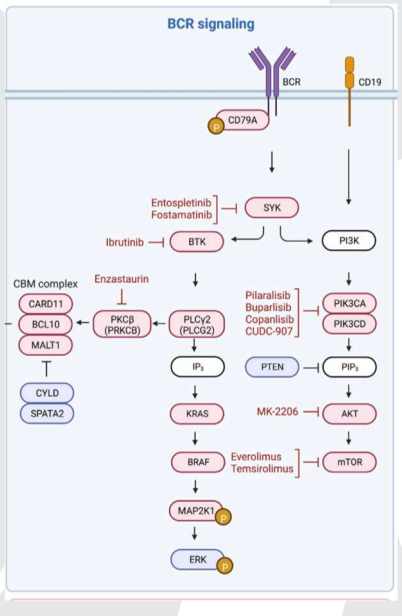
Another promising agent in this pathway is ibrutinib, a BTK inhibitor, and overall response rate in one monotherapy trial of refractory DLBCL with ibrutinib was 40% in ABC type and 5% in GBC type.
MYD subtype in combination with CD79A and CD79B mutations increased susceptibility to ibrutinib, 80% of responses had MYD88 mutation with concomitant CD79B mutation, while the wild type CD79A/CD79B provided protection from this intervention.

Targeted therapeutic strategies in DLBCL



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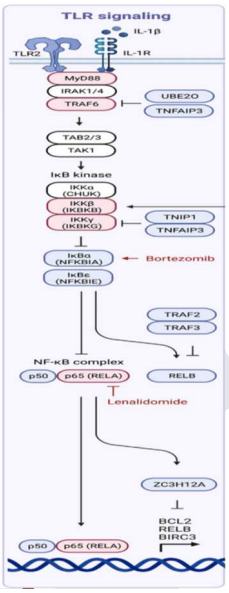
Targeting PI3K-AKT-mTOR: The PI3K-AKT-mTOR is another commonly active pathway in DLBCL with treatments that have shown promise in limited trials.

CUDC-907 is a small molecule that inhibits PI3K and HDAC, that showed a response rate of 64% in patients with DLBCL concurrent with MYC alteration. Other drugs targeting PI3K are pilaralisib, buparlisib, and copanlisib.

AKT inhibitor MK-2206 showed promise in preclinical models, but failed to show results in any of the patients treated in a phase II trial.

Two drugs showing some clinical significance are the mTOR inhibitors everolimus and temsirolimus, with positive responses observed, and one patient achieved a durable and complete response to the everolimus for years.

Targeted therapeutic strategies in DLBCL



Targeting NF-κB signaling: Lenalidomide acts on the NF-κB pathway by targeting the E3 ubiquitin ligase component of cereblon, and shows substantial activity in patients with relapsed or refractory DLBCL alone or in combination with other regimens. The greatest effects have been seen in patients with ABC DLBCL, and the addition of lenalidomide to CHOP treatment in patients with novel DLBCL seems to negate the negative prognostic implications of ABC DLBCL. Lenalidomide has also been shown to be effective as a maintenance therapy and prolong PFS in patients who respond to R-CHOP. Another mechanism for the utility of lenalidomide may be realized, aside from acting as a sole inhibitor of the NF-κB pathway, is through synthetic lethality.

Another drug acting on the NF-κB path is bortezomib which downregulates NF-κB through inhibition of proteasomal degradation of IκBα, but is has failed to show significant efficacy as a monotherapy or in addition to R-CHOP therapy.

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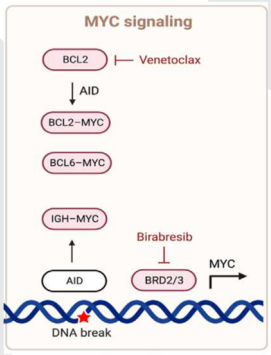
Targeted therapeutic strategies in DLBCL



Targeting BCL2 signaling: BCL2 expression is one of the most influential alterations in DLBCL and is already prognostically significant, as DLBCL with MYC and BCL2/BCL6 mutations are associated with a worse prognosis.

Venetoclax is a BCL2 inhibitor that was shown to have a complete response in 12% of patients when used as a monotherapy, and an overall response rate of 41% when used in combination with bendamustine plus rituximab. In patients with confirmed BCL2 mutations, venetoclax had a superior overall response rate when compared to R-CHOP in the matched population, suggesting the potential of venetoclax to improve outcomes in patients receiving R-CHOP.

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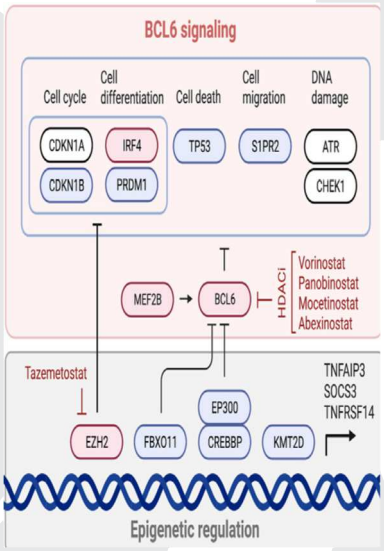
Targeted therapeutic strategies in DLBCL



Targeting epigenetic pathways: Gene regulation is another great target for manipulation since DLBCL displays frequent disruptions in histone-modifying enzymes and the general activity of genes.

Tazemetostat is an EZH2 inhibitor with an encouraging safety profile and response in both EZH2 wild-type and mutant relapsed/refractory DLBCL, with responses up to 60% in R/R DLBCL.

Histone deacetylase inhibitors (HDACi) such as vorinostat, panobinostat, mocetinostat, and abexinostat show potential benefit in certain patients with B-cell lymphoma when combined with other chemotherapies. Use of HDACi is proving useful especially in CREBBP-mutant cells, to restore acetylation of histones at transcriptional enhancer regions to enhance expression of tumor suppressor genes. HDACi's are also of interest in individuals with elevated MYC concurrent with elevated BCL2 levels, and can lead to induction of apoptosis through acetylated BCL6 accumulation.

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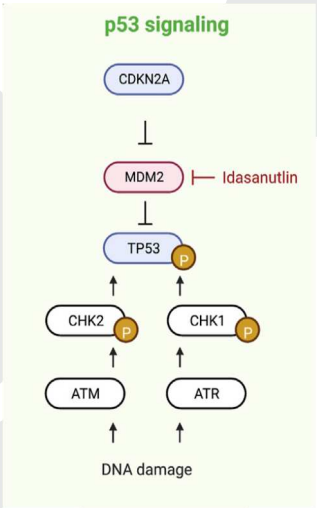
Targeted therapeutic strategies in DLBCL



Targeting p53 signaling:
MDM2 antagonist, idasanutlin, showed potent anti-tumor activity in both ABC and GCB cell lines and idasanutlin could be used as a novel drug in the clinical setting of DLBCL.

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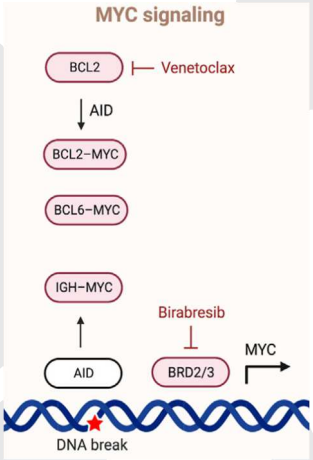
Targeted therapeutic strategies in DLBCL



Targeting MYC signaling: The ability to block overactive MYC transcription is of interest because of the genes' involvement in not only overall pathogenesis, but also its association with relapse and refractory DLBCL.

The BET protein family enhance MYC transcription by binding acetylated histones. BET inhibitors (BETi) interfere with BET-mediated MYC transcription through disruption of bromodomain-containing proteins which normally organize transcriptional machinery.

Birabresib specifically is a drug of interest, and functions through binding to the BRD2 and BRD3, limiting the transcription of MYC among other oncogenes.

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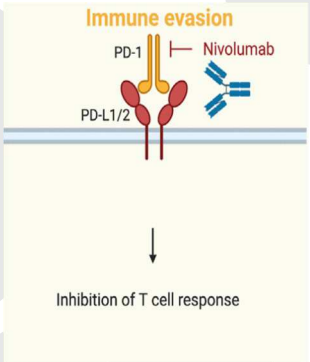
Targeted therapeutic strategies in DLBCL



Targeting immune evasion: Evasion of DLBCL immune surveillance is accomplished through various mechanisms, but PD-L1 (CD274) and PD-L2 (PDCD1LG2) dysregulation is one of the most notable from a therapeutic standpoint.

This pathway is targetable by antibodies that bind the PD-L1/2 ligand on the tumor cell, preventing it from binding PD-1/2 receptor and disabling immune escape. One such antibody is nivolumab, which has shown some promise in studies with ORR of 36% in patients with R/R DLBCL. Failure to respond has been attributed to the relatively small number of patients in the study who had 9p21.1 low level copy gains and amplifications. CD274 mutations may be predictive of response to anti-PD-L1 antibodies (pembrolizumab).

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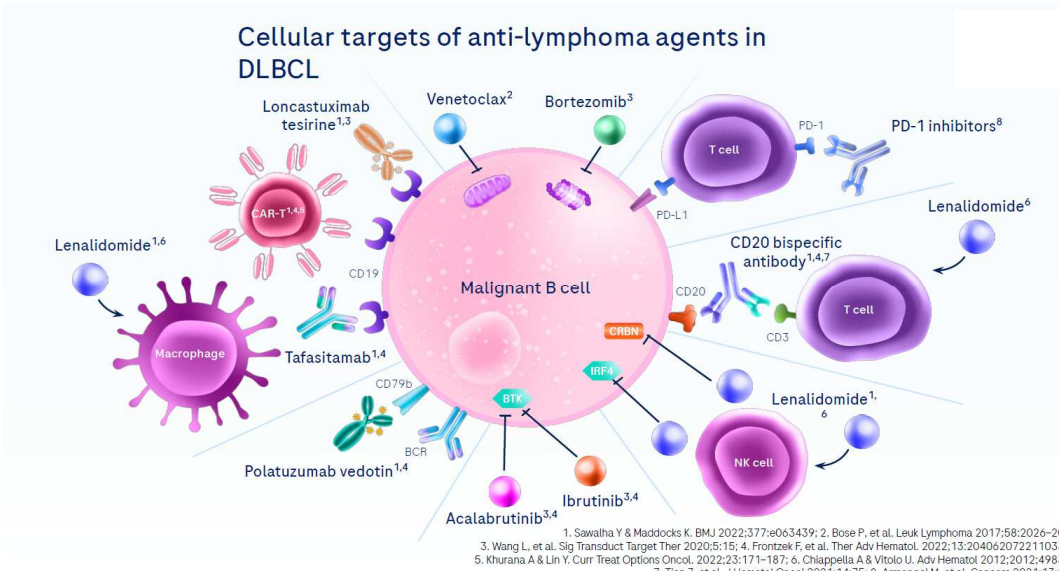

F Morschhauser. Treating DLBCL: Where are we now? ICML 2023 Roche symposium.

	Drug	Mechanism of Action	Clinical Trial	Outcome
ABC-DLBCL	Ibrutinib[64,66]	Bruton Tyrosine Kinase Inhibitor	Phase 1-2 R/R DLBCL	ORR: 37% (14/38) • MYD88/CD79 Mut: ORR: 80% (4/5)
			Phase 3 Upfront DLBCL Ibrutinib+R-CHOP vs. R-CHOP	ORR (ITT): 89.3% *vs.* 93.1% ($P = 0.0515$)
	Acalabrutinib[67,69,70]	Bruton Tyrosine Kinase Inhibitor	Phase 1-2 R/R DLBCL[67]	ORR: 24% (5/21)
			Phase I PRISM: Acalabrutinb+AZD9150 Acalabrutinib_AZD6738 Acalabrutinib+Magrolimab+ Rituximab Acalabrutinib+AZD5153	N/A (NCT03527147)
			Phase 1-2 Acalabrutinib + R-CHOP	N/A (NCT0400294)
			Phase 1-2 Acalabrutinib + R-EPOCH	N/A (NCT03571308))
	CA-4948[74,75]	IRAK4 Kinase Inhibitor	Phase 1	N/A, 1 PR (NCT03328078)
			Phase 1 CA-4948+Ibrutinb	N/A (NCT0332878)
	KT-413[76,77]	IRAK4/IMiD PROTAC	Pending	N/A
	JNJ-67856633[88]	MALT1 Inhibitor	Phase 1	N/A (NCT03900598)

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GC-DLBCL	Tazemetostat[121,122]	EZH2 Inhibitor	Phase 2	Closed After Interim Assessment (NCT01897571)
			Phase 1b/2	N/A (NCT02889523)
	Valemetostat[124]	EZH1/2 Inhibitor	Phase 1	ORR: 15% (R/R NHL)(NCT02732274)
	Fimepinostat[128-130]	HDAC/PI3K Inhibitor	Phase 1-2 Fimepinostat Fimepinostat+Venetoclax Fimepinostat+Rituxan Fimepinostat+Venetoclax+Rituxan	ORR: 55% (5/9) ORR: 23.3% (14/60 MYC-altered DLBCL) (NCT01742988)
	Venetoclax[136,137]	BCL2 Inhibitor	Phase 1 CAVALLI Study Venetoclax+R-CHOP	ORR: 87.5% (NCT02055820)
			Phase 1 ALLIANCE 51701 Venetoclax+DA-R-EPOCH	ORR: 97% (NCT03036904)

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Agnostic	PolatuzuambVedotin[138,139]	Antibody-Drug Conjugate against CD79b linked to MMAE	Phase 1b/2 Polatuzumab+BR vs. BR	Objective Response: 45.0% *vs.* 17.5% CR 40% *vs.* 17.5% OS 12.4 *vs.* 4.7 months (NCT02257567)
			Phase 3 Polatuzumab+R-CHP vs. R-CHOP	ORR: 85.5% *vs.* 83.8% CR: 78.0% *vs.* 74.0% Decrease risk in progression/relapse/death: HR: 0.73; 95%CI 0.57-0.95; *P* = 0.02 (NCT03274492)
	Tafasitamab[141-143]	Anti-CD19 monoclonal Ab	Phase 1-2 L-MIND Tafasitamab+Lenalidomide	ORR: 54% CR: 32% NCT02399085
			Phase 3 FIRST-MIND Tafasitamb+Lenalidomide+R-CHOP	N/A NCT04134986
	Loncastuximab tesirine[144]	Antibody-Drug conjugate against CD19	Phase 2	ORR: 48.3% CR: 24% PR: 24% (NCT03589469)
	Magrolimab[146,147]	Anti-CD47 monoclonal	Phase 1b in R/R DLBCL and FL	Objective Response: 40% DLBCL)

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Mosunetuzumab[147, 148]	CD3-CD20 BsAb	Phase I/Ib	ORR: 37% CR: 19% (NCT02500407)
		Phase Ib/II Mosunetuzumab+CHOP or Polatuzumab+CHP	N/A (NCT03677141)
Odronexatamab[149]	CD3-CD20 BsAb	Phase I	ORR: 60% (CAR T-cell Naïve) CR: 60% (CAR T-cell Naïve) ORR: 33.3% (Refractory CAR T-cell) CR: 23.8% (Refractory CAR T-cell) (NCT02290951)
Epicoritamab[150]	CD3-CD20 BsAb	Phase I/II	ORR: 100% (DLBCL) at 48mg CR: 28.6% (2/7) PR: 71.4% (5/7) (NCT03625037)
Glofitamab[151,152]	2:1 CD20-C3 BsAb	Phase I/Ib	ORR: 50% (aggressive NHL) CR: 29.2% (NCT03075696)
CMG1A46[153]	Trispecific Ab: CD19-CD20-CD3	Pending	N/A
Selinexor[170]	XPO-1 Mediated Nuclear Transport Inhibitor	Phase 2	ORR: 28% CR:12% (NCT02227251)

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Conclusion and future perspectives

DLBCL encompasses a wide array of disease mechanisms/presentations that have historically been and are currently, grouped into essentially two prognostic groups all with the same therapeutic indication.

Various novel ways to delineate cases of DLBCL have been proposed by groups such as Schmitz et al., Chapuy et al., Lacy et al., and Wright et al.. These systems have used various algorithms to group DLBCL by “constellations” of genetic alteration instead of examining and grouping each alteration individually, because it is the sum of the parts that leads to the specific disease state and that may point to specific treatment regimen.

Conclusion and future perspectives

New therapies derived from NGS acquired data are aimed at disrupting signaling pathways or modulating immune response, however the impact of these therapies can only be fully realized when we are able to categorize DLBCL into subtypes based on internal disease mechanism and not on outward morphology or presence of basic cell markers.

These internal mechanisms are the basis for future treatment modalities and the cessation of indiscriminate therapy based on patient response.

Conclusion and future perspectives

Mutations in pathways regulating BCR signaling, the PI3K-AKT-mTOR signaling pathway, BCR-dependent NF-κB signaling, NF-κB signaling, TLR signaling, and the BCL2 family are among the most influential when it comes to subdividing DLBCL cases into new subgroups.

The end result of these pathways - either overstimulation of pro-growth factors or inhibition of apoptotic pathways, leads to the same phenotypic result of continued cell growth and survival.

Even therapies directed specifically at these pathways may still fail if they treat steps further up the cascade than the mutation actually lies, so having the ability to identify and target multiple steps in these pathways will be a prerequisite to extend overall survival of these patients.

Conclusion and future perspectives

Dysregulation of genes involved in epigenetic regulation may also result in aberrant pathway activation or inactivation in many DLBCL cases, so exploring treatments directed at regulation of these pathways may also impact the outcomes.

Other pathways of interest with potential therapeutic interventions are the NOTCH signaling pathway, malignant cell migration, BCL6 signaling, p53 signaling, MYC signaling, and immune evasion through mutations in various receptors and ligands such as PD-L1 overexpression.

Therapies currently showing promise include ibrutinib in targeting BCR signaling, everolimus in the PI3K-AKT-mTOR pathway, lenalidomide in targeting NF-κB signaling, venetoclax in BCL2 signaling, tazemetostat in EZH2 epigenetic regulation, birabresib in targeting MYC signaling, and nivolumab in targeting immune evasion.

Conclusion and future perspectives

To progress in the treatment of DLBCL, a new classification system must first be implemented as part of guidelines that will provide a better prognostic information, and that may indicate which second line therapies might be effective when first line R-CHOP fails.

Availability of NGS for use in patients with DLBCL will also need to be increased in order to appropriately place a malignancy in its respective group applying novel algorithms. Larger quantities of data will also enable further differentiation which mutations are impactful on disease course, and which mutations may indicate a specific or targeted treatment.

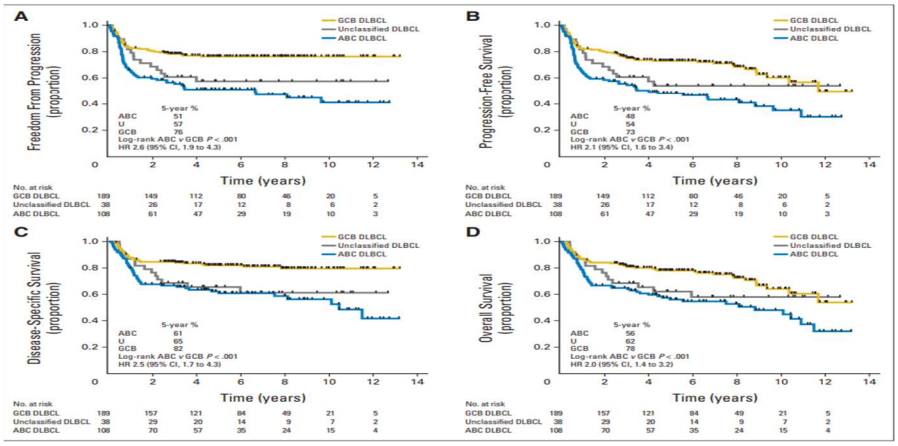
First line treatment of DLBCL in regard to molecular pathogenesis

Milica Miljković, medical oncologist
Institute of Oncology Ljubljana
19th and 20th October, Ljubljana, Slovenia

Classification by cell of origin (COO)

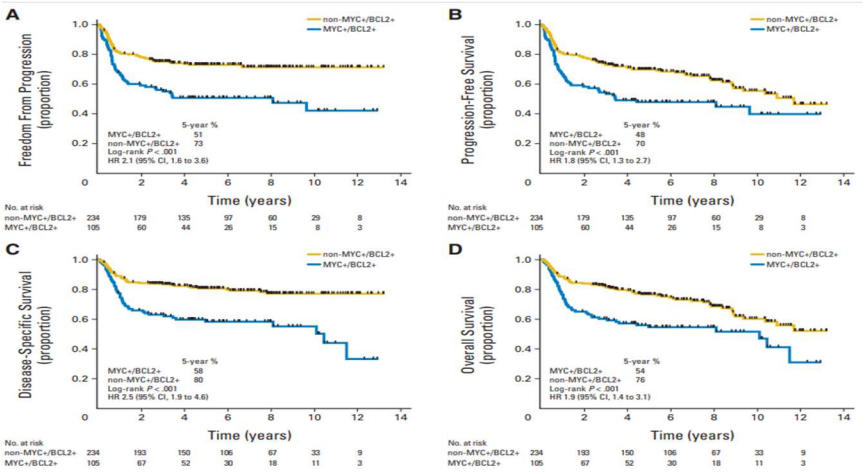
- Activated B-cell like type (ABC)
- Germinal center B-cell like type (GCB)
- Unclassified

Outcomes after treatment with R-CHOP according to COO



Scott DW. Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. J Clin Oncol 2015; 33: 2848. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)

Outcomes after treatment with R-CHOP according to MYC and BCL-2 expression (IHC)



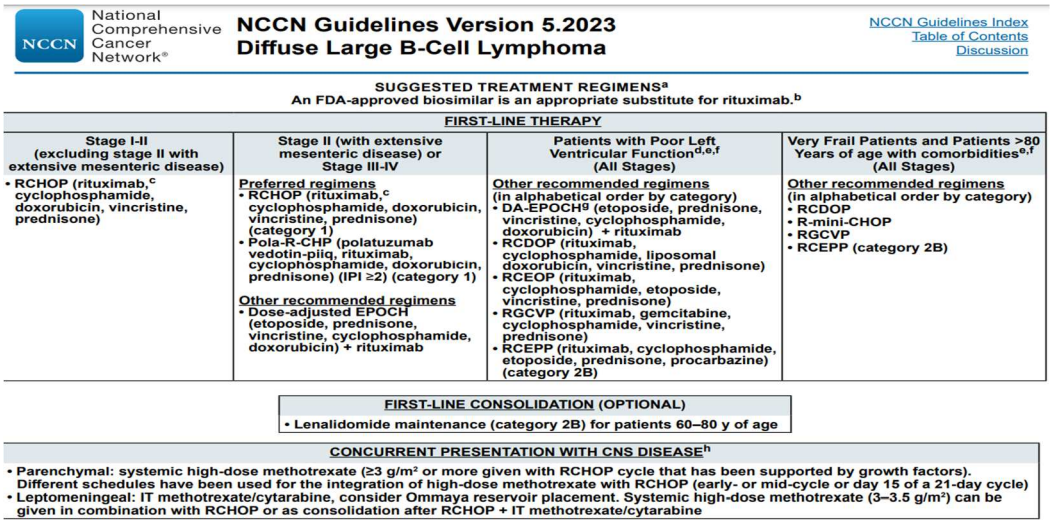
Scott DW. Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. J Clin Oncol 2015; 33: 2848. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), IHC-immunohistochemistry

Molecular classification of DLBCL

Molecular classification				
Wright	Schmitz	Lacy	Chapuy	Genetic alteration (% prevalance*)
BN2	BN2	NOTCH2	C1	*BCL6* (72.8%), *NOTCH2* (41.8%), *TNFAIP3* (51.6%), *DTX1* (50.0%), *CD70* (41.3%), *BCL10* (39.6%), *UBE2A* (30.4%), *TMEM30A* (26.7%), *KLF2* (21.7%), *SPEN* (21.7%)
A53	—	—	C2	*TP53* (86.8%), *B2M* (34.2), *TP53BP1* (27.0%), *CNPY3* (23.7%), *ING1* (15.8%), *NFKBIZ* (15.8%), *TP73* (13.2%)
EZB-MYC+ EZB-MYC−	EZB	BCL2	C3	*BCL2* (68.4%), *EZH2* (44.7%), *TNFRSF14* (66.2%), *KMT2D* (53.9%), *CREBBP* (52.7%), *REL* (34.3%), *FAS* (30.1%), *IRF8* (28.9%), *EP300* (27.8%), *MEF2B* (26.3%), *CIITA* (25.0%), *ARID1A* (22.9%), *GNA13* (22.5%), *STAT6* (21.1%), *PTEN* (20.0%)
ST2	—	TET2/SGK1 SOCS1/SGK1	C4	*TET2* (48.1%), *DUSP2* (44.4%), *ZFP36L1* (40.7%), *ACTG1* (37.0%), *SGK1* (37.0%), *ITPKB* (33.3%), *NFKBIA* (33.3%), *EIF4A2* (29.6%), *JUNB* (29.6%), *STAT3* (29.6%), *BCL2L1* (25.9%), *CD83* (25.9%), *DDX3X* (25.9%), *SOCS1* (25.9%), *CD83* (25.9%), *P2RY8* (22.2%), *RFTN1* (22.2%)
MCD	MCD	MYD88	C5	*MYD88* (66.2%), *CD79B* (50.0%), *PIM1* (92.5%), *HLA-B* (73.8%), *BTG1* (70.0%), *CDKN2A* (62.0%), *ETV6* (55.0%), *SPIB* (51.9%), *OSBPL10* (51.2%), *TOX* (48.1%), *BCL2* (48.1%), *BTG2* (43.8%), *MPEG1* (43.8%), *HLA-A* (43.0%), *HLA-C* (42.5%), *SETD1B* (41.8%), *KLHL14* (41.2%), *TBL1XR1* (35.0%), *GRHPR* (33.8%), *PRDM1* (32.5%), *CD58* (31.6%), *TAP1* (26.6%), *PIM2* (25.0%), *FOXC1* (21.2%), *IRF4* (20.0%)
N1	N1	—	—	*NOTCH1* (100%), *IRF2BP2* (43.8%), *ID3* (25.0%), *BCOR* (25.0%), *EPB41* (18.8%), *IKBKB* (18.8%), *ALDH18A1* (18.8%)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9936827/

First line therapy - NCCN



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

FIRST-LINE THERAPY

Stage I-II (excluding stage II with extensive mesenteric disease)	Stage II (with extensive mesenteric disease) or Stage III-IV	Patients with Poor Left Ventricular Function[d,e,f] (All Stages)	Very Frail Patients and Patients >80 Years of age with comorbidities[e,f] (All Stages)
• RCHOP (rituximab,[c] cyclophosphamide, doxorubicin, vincristine, prednisone)	Preferred regimens • RCHOP (rituximab,[c] cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1) • Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, prednisone) (IPI ≥2) (category 1) Other recommended regimens • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab	Other recommended regimens (in alphabetical order by category) • DA-EPOCH[g] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab • RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone) • RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone) • RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone) • RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine) (category 2B)	Other recommended regimens (in alphabetical order by category) • RCDOP • R-mini-CHOP • RGCVP • RCEPP (category 2B)

FIRST-LINE CONSOLIDATION (OPTIONAL)
• Lenalidomide maintenance (category 2B) for patients 60–80 y of age

CONCURRENT PRESENTATION WITH CNS DISEASE[h]
• Parenchymal: systemic high-dose methotrexate (≥3 g/m² or more given with RCHOP cycle that has been supported by growth factors). Different schedules have been used for the integration of high-dose methotrexate with RCHOP (early- or mid-cycle or day 15 of a 21-day cycle)
• Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement. Systemic high-dose methotrexate (3–3.5 g/m²) can be given in combination with RCHOP or as consolidation after RCHOP + IT methotrexate/cytarabine

https://www.nccn.org/guidelines/category_1

First line therapy - our practice

- R-CHOP or R-mini-CHOP or R-C(X)OP
- R-DA-EPOCH (high IPI score, ABC subtype or double hit)
- Polatuzumab-R-CHP (IPI score 3-5)
- HD MTX (3-5g/m2)
- Prophylactic intrathecal chemotherapy (IT): MTX+ARA-C+Dexamethason

*R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); R-C(X)OP (X= gemcitabine or etoposide); R-DA-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin); Polatuzumab - R- CHP (rituximab, cyclophosphamide, doxorubicin, prednisone); HD MTX – high dose of methotrexate;
IPI - international prognostic index; ABC–activated B cell like subtype; double hit - mutation of MYC and BCL-2

POLARIX (GO39942)

Primary analysis – global population

A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP vs R-CHOP in previously untreated patients with DLBCL

Study design overview

- **Double-blind, randomized controlled**
- Collaboration with LYSA
- NCT03274492

Patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

N=879

Stratification factors
- IPI score (2 vs 3–5)
- Bulky disease (≥7.5cm vs absence)
- Geographic region*

R 1:1

ARM A
Polatuzumab vedotin 1.8mg/kg
R-CHP + vincristine placebo
Q21D x 6 cycles
→ Rituximab 375mg/m^2 Cycles 7 & 8

1 Cycle=21 days

ARM B
R-CHOP + polatuzumab vedotin placebo
Q21D x 6 cycles
→ Rituximab 375mg/m^2 Cycles 7 & 8

Primary endpoint	PFS by INV
Key secondary endpoints	$EFS_{efficacy}$ by INV, PET CR at EOT by BICR, OS, and safety

*Western Europe, United States, Canada and Australia vs Asia vs Rest of World. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; $EFS_{efficacy}$, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion)

Tilly H, et al. New Engl J Med 2022;386:351–63.

Demographics and baseline characteristics were generally well balanced between arms-global ITT (1 of 3)

		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age, n (%) Age, years	>60 years Median (Min–Max)	300 (68.2) 65.0 (19–80)	308 (70.2) 66.0 (19–80)
Sex, n (%)	Male	239 (54.3)	234 (53.3)
ECOG PS, n (%)	0–1 2 Unknown	374 (85.0) 66 (15.0) 0	363 (82.7) 75 (17.1) 1 (0.2)
Geographic region, n (%)	Asia Rest of World Western Europe, United States, Canada, and Australia	81 (18.4) 57 (13.0) 302 (68.6)	79 (18.0) 59 (13.4) 301 (68.6)
IPI at screening, n (%)	2 3–5	167 (38.0) 273 (62.0)	167 (38.0) 272 (62.0)
Bulky disease, n (%)	Absent Present	247 (56.1) 193 (43.9)	247 (56.3) 192 (43.7)
Baseline LDH, n (%)	≤1 x ULN >1 x ULN Unknown	146 (33.2) 291 (66.1) 3 (0.7)	154 (35.1) 284 (64.7) 1 (0.2)

Tilly H, et al. New Engl J Med 2022;386:351–63.

Demographics and baseline characteristics were generally well balanced between arms-global ITT (2 of 3)

		Pola-R-CHP (N=440)	R-CHOP (N=439)
Bone marrow involvement at diagnosis, n (%)	Unknown Negative Positive	22 (5.0) 342 (77.7) 76 (17.3)	18 (4.1) 349 (79.5) 72 (16.4)
Ann Arbor Stage, n (%)	I or II III or IV	47 (10.7) 393 (89.3)	52 (11.8) 387 (88.2)
No. of extranodal sites, n (%)	0–1 ≥2	227 (51.6) 213 (48.4)	226 (51.5) 213 (48.5)

Tilly H, et al. New Engl J Med 2022;386:351–63.

Demographics and baseline characteristics were generally well balanced between arms – global ITT (3 of 3)

		Pola-R-CHP (N=440)	R-CHOP (N=439)
NHL histologic diagnosis (local diagnosis), n (%)	DLBCL NOS (including ABC and GCB) HGBL, (including NOS and DHL/THL) Other large B-cell*	373 (84.8) 43 (9.8) 24 (5.5)	367 (83.6) 50 (11.4) 22 (5.0)
COO,† n (%)		**N=330**	**N=338**
	ABC	102 (30.9)	119 (35.2)
	GCB	184 (55.8)	168 (49.7)
	Unclassified	44 (13.3)	51 (15.1)
Double-expressor lymphoma,† n (%)		**N=362**	**N=366**
	DEL	139 (38.4)	151 (41.3)
	Non DEL	223 (61.6)	215 (58.7)
Double/triple-hit lymphoma,† n (%)		**N=331**	**N=334**
	DH/TH+	26 (7.9)	19 (5.7)
	DH/TH-	305 (92.1)	315 (94.3)

*Other large B-cell lymphomas by local diagnosis included EBV+ DLBCL NOS, and T-cell/histiocyte rich large B-cell lymphoma.
†Based on central review, and percentages are based on biomarker evaluable population (i.e. by excluding patients with unknown status).

Tilly H, et al. New Engl J Med 2022;386:351–63.

Overall safety profile

AE, n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade AEs	426 (97.9)	431 (98.4)
Grade 3–4 AEs	251 (57.7)	252 (57.5)
SAEs	148 (34.0)	134 (30.6)
Grade 5 AEs	13 (3.0)	10 (2.3)
AEs leading to treatment discontinuation		
Any treatment	27 (6.2)	29 (6.6)
Polatuzumab vedotin/vincristine	19 (4.4)	22 (5.0)
AEs leading to dose reduction (any treatment)	40 (9.2)	57 (13.0)

- The safety profile of Pola-R-CHP was similar to that of R-CHOP
- Fewer AEs leading to dose reductions were observed in the Pola-R-CHP arm

Tilly H, et al. New Engl J Med 2022;386:351–63.

Most common adverse events (1 of 3)

All-grade incidence rate of ≥12% in any treatment arm

AE, n (%)	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Gastrointestinal disorders				
Nausea	181 (41.6)	5 (1.1)†	161 (36.8)	2 (0.5)
Vomiting	65 (14.9)	5 (1.1)†	63 (14.4)	3 (0.7)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Constipation	125 (28.7)	5 (1.1)†	127 (29.0)	1 (0.2)
Blood and lymphatic system disorders				
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Febrile neutropenia*	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)

- The most common AEs were consistent with R-CHOP therapy
- Grade 3–4 AEs were comparable between treatment arms and most were associated with myelosuppression

*Granulocyte-colony stimulating factor (G-CSF) administration was required during the first six cycles as primary prophylaxis of neutropenia: G-CSF prophylaxis was reported in 93.2% and 90.1% of patients in the R-CHOP and Pola-R-CHP arms, respectively; †With the exception of diarrhea, Grade 3–4 events for all gastrointestinal disorders were less than 2% in the Pola-R-CHP arm.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Most common adverse events (2 of 3)

All-grade incidence rate of ≥12% in any treatment arm

AE, n (%)	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Nervous system disorders				
Peripheral neuropathy†	230 (52.9)	7 (1.6)*	236 (53.9)	5 (1.1)
Headache	56 (12.9)	1 (0.2)*	57 (13.0)	4 (0.9)
Dysgeusia	49 (11.3)	0*	57 (13.0)	0
General disorders and administration site conditions				
Fatigue	112 (25.7)	4 (0.9)*	116 (26.5)	11 (2.5)
Pyrexia	68 (15.6)	6 (1.4)*	55 (12.6)	0
Asthenia	53 (12.2)	7 (1.6)*	53 (12.1)	2 (0.5)
Skin and subcutaneous tissue disorders				
Alopecia	106 (24.4)	0*	105 (24.0)	1 (0.2)

*Grade 3–4 events for all nervous system, general and skin disorders were less than 2% in the Pola-R-CHP arm;
†Data presented here refer to grouped term peripheral neuropathy, which included preferred terms: peripheral neuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, ear paresthesia, peroneal nerve palsy, skin burning sensation.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Most common adverse events (3 of 3)

All-grade incidence rate of ≥12% in any treatment arm

AE, n (%)	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Respiratory, thoracic and mediastinal disorders				
Cough	56 (12.9)	0	53 (12.1)	0
Metabolism and nutrition disorders				
Decreased appetite	71 (16.3)	5 (1.1)*	62 (14.2)	3 (0.7)
Investigations				
Decreased weight	55 (12.6)	4 (0.9)*	52 (11.9)	1 (0.2)

*Grade 3–4 events for all metabolism, musculoskeletal disorders and investigations were less than 2% in the Pola-R-CHP arm.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Safety summary (1 of 2)

Overall safety profile of Pola-R-CHP is similar to that of R-CHOP and consistent with the known risk of the individual study drugs[1]

Drug deliverability favors Pola-R-CHP vs R-CHOP[1]

- Lower incidence of AEs leading to any dose reduction in Pola-R-CHP (9.2% vs 13.0%)
- More patients received all planned doses of polatuzumab vedotin/vincristine in the Pola-R-CHP arm vs R-CHOP (91.7% vs 88.5%)

Rates of febrile neutropenia were higher with Pola-R-CHP vs R-CHOP (14.3% vs 8.0%) but this did not translate into greater overall rates of infection: Grade ≥3 infections were comparable (15.2% vs. 12.6%, respectively)[1]

- Similar FN rates reported in recent R-CHOP studies (9.0% to 15.2%)[2–4]
- Drug discontinuations (2.1% vs 2.3%), dose reductions due to infections/neutropenia (1.8% vs 2.5%) and G-CSF prophylaxis (90.1% vs 93.2%) were also comparable
- Grade 5 AEs were comparable between treatment arms

1. Tilly H, et al. New Engl J Med 2022;386:351–63; 2. Vitolo U, et al. J Clin Oncol 2017;35:3529–37;
3. Nowakowski GS, et al. J Clin Oncol 2021;39:1329–38; 4. Younes A, et al. J Clin Oncol 2019;37:1285–95.

Safety summary (2 of 2)

No significant differences in rates or severity of PN were observed in patients receiving Pola-R-CHP vs R-CHOP; most PN events were Grade 1[1,2]

- Fewer dose modifications as a result of PN were required for patients who received Pola-R-CHP than for those who received R-CHOP
- According to ClinRO and PRO data, PN appeared to occur later after initial exposure to Pola-R-CHP than to R-CHOP; however, the duration of neuropathy events was comparable in both treatment arms
- Patient and clinician assessments similarly demonstrated the temporal relationship between PN symptoms and their resolution

No new safety signals were detected[1]

1. Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Trněný M, et al. ASCO 2022. Poster P7561.

Pola-R-CHP | **R-CHOP**

HR 0.73 (p=0.02)

Pola-R-CHP → 27% reduction in risk of progression, relapse or death[1]

- Relapsing or being refractory to 1L treatment remain the main causes of morbidity and mortality in DLBCL[2]

1.Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Maurer MJ, et al. Ann Oncol 2018;29:1822–27.

Pola-R-CHP | **R-CHOP**

6.5% improvement[1]

Pola-R-CHP	R-CHOP
76.7%	70.2%
24 months	24 months
Progression-free survival	*Progression-free survival*

- Most relapses in patients with previously untreated DLBCL occur in the first 2 years, and outcomes with salvage therapy remain poor for a variety of patients[2]
- Landmark analysis at 24 months showed a clinically meaningful improvement in the number of patients avoiding relapse with Pola-R-CHP vs R-CHOP

1. Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Maurer MJ, et al. J Clin Oncol 2014;32:1066–73.

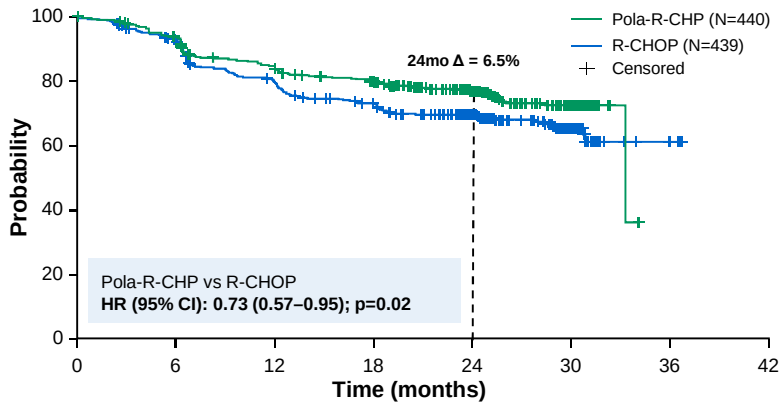
Investigator-assessed PFS (global ITT population)

	Pola-R-CHP (N=440)	R-CHOP (N=439)
No. of events, n (%)	107 (24.3)	134 (30.5)
Earliest contributing event, n		
Death	19	20
Disease progression or relapse	88	114
Stratified analysis*		
P-value (Log-rank)	0.02	
Hazard ratio (95% CI)	0.73 (0.57–0.95)	
12-month PFS rate† (95% CI)	83.9 (80.4–87.4)	79.8 (75.9–83.6)
24-month PFS rate† (95% CI)	76.7 (72.7–80.8)	70.2 (65.8–74.6)

*Stratified for IPI score (IPI 2 vs IPI 3–5), bulky disease (present vs absent), and geographical region (Western Europe, United States, Canada and Australia vs Asia vs Rest of World [remaining countries]);
†Kaplan–Meier estimate.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Investigator-assessed PFS (global ITT population)

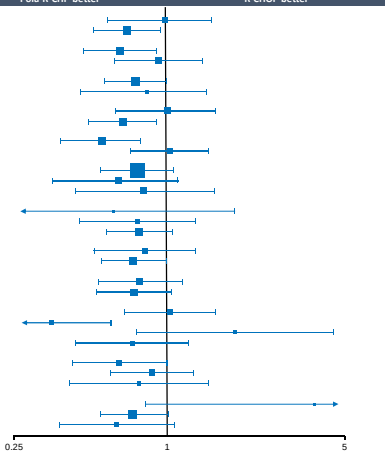


Number at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Tilly H, et al. New Engl J Med 2022;386:351–63.

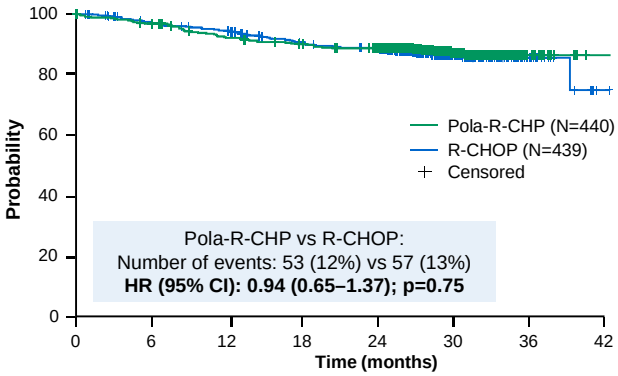
Investigator-assessed PFS by subgroup (global ITT, unstratified)

Baseline risk factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year rate	HR	95% Wald CI
Age group							
≤60	271	140	74.1	131	71.9	0.9	(0.6 to 1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5 to 0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5 to 0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6 to 1.4)
ECOG PS							
0–1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)
IPI 3–5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)
Geographic region							
W. Europe, US, Canada, Australia	603	302	78.6	301	72.0	0.8	(0.6 to 1.1)
Asia	160	81	74.3	79	65.6	0.6	(0.4 to 1.5)
Rest of world	116	57	70.8	59	67.3	0.9	(0.6 to 1.5)
Ann Arbor stage							
I–II	99	47	89.1	52	85.5	0.6	(0.2 to 1.8)
III	232	124	80.7	108	73.6	0.8	(0.5 to 1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6 to 1.1)
Baseline LDH							
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)
No. of extranodal sites							
0–1	453	227	80.2	226	74.5	0.8	(0.5 to 1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5 to 1.0)
Cell-of-origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)
Non DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8 to 17.6)
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)



Tilly H, et al. New Engl J Med 2022;386:351–63.

Overall survival (global ITT population)



Number at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

	Pola-R-CHP (N=440)	R-CHOP (N=439)
No. of events, n (%)	**53 (12.0)**	**57 (13.0)**
Earliest contributing event, n		
Death	53	57
Stratified analysis*		
p-value (Log-rank)	0.75	
Hazard ratio (95% CI)	0.94 (0.65–1.37)	
24 months OS rate† (95% CI)	88.7 (85.7–91.6)	88.6 (85.6–91.6)

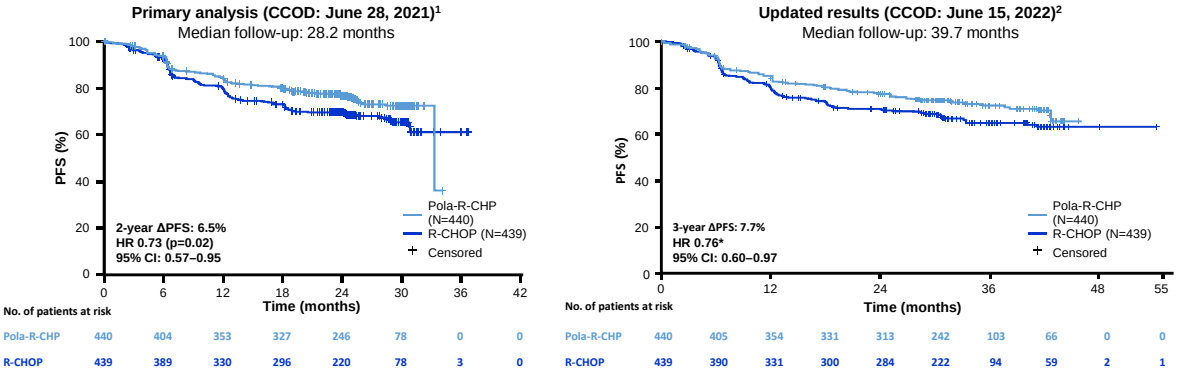
The final OS analysis will be performed (two-sided alpha boundary = 0.04) in the 2nd half of 2022. OS analysis was time-driven.
*Stratified for IPI score (IPI 2 vs IPI 3–5), bulky disease (present vs absent), and geographical region (Western Europe, United States, Canada and Australia vs Asia vs Rest of World [remaining countries]); †Kaplan–Meier estimate.

Tilly H, et al. New Engl J Med 2022;386:351–63.

Updated survival data

June 15th 2022 data cut-off

PFS with additional follow-up (global ITT population)



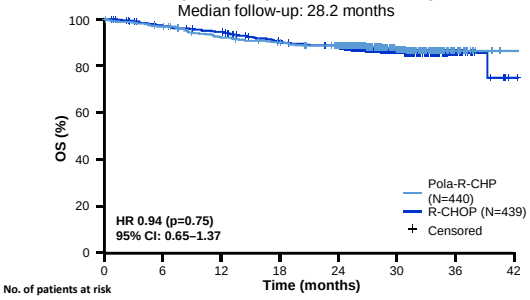
PFS benefit with Pola-R-CHP vs R-CHOP was maintained with longer follow-up (HR 0.76, 95% CI: 0.60–0.97)[2]

*Descriptive analysis only.

1. Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Herrera AF, et al. ASH 2022. Oral presentation 542.

OS with additional follow-up (global ITT population)

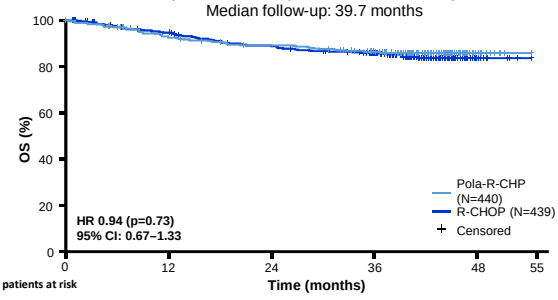
Primary analysis (CCOD: June 28, 2021)[1]
Median follow-up: 28.2 months



No. of patients at risk

Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

Updated results (CCOD: June 15, 2022)*[2]
Median follow-up: 39.7 months



No. of patients at risk

Pola-R-CHP	440	423	398	387	379	371	338	129	13	1
R-CHOP	439	415	403	382	372	361	329	124	18	1

- **OS remained similar between treatment arms with longer follow-up[2]**
- **No new safety signals** have been identified with longer follow-up compared with the primary analysis[2]

*Final analysis of OS at 3 years, prespecified per the study protocol.

1. Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Herrera AF, et al. ASH 2022. Oral presentation 542.

The impact of POLARIX

POLARIX is the first trial in over 20 years to show a meaningful improvement in the benefit-risk profile over R-CHOP in an international Phase III double-blind, randomized controlled trial

POLARIX demonstrated a positive benefit-risk profile that was sustained with longer follow-up. The risk of progressive disease or death was reduced at 2 years (HR 0.73, 95% CI: 0.57–0.95) and at longer follow-up (median follow-up: 39.7 months; HR 0.76, 95% CI: 0.60–0.97)

This global collaboration with LYSA and sites all over the world has led to a significant advancement for patients and the field of DLBCL, and supports the use of Pola-R-CHP in the initial management of DLBCL

Tilly H, et al. New Engl J Med 2022;386:351–63.

Treatment of DLBCL – our experience

ASSIST. PROF. LUČKA BOLTEŽAR, MD, PHD
INSTITUTE OF ONCOLOGY LJUBLJANA
OCTOBER 2023

Our institutional recommendations

1st line: R-CHOP, R-mini-CHOP, R-COEP, R-DA-EPOCH

2nd line: R-polatuzumab vedotin-bendamustin

3nd line: R-CBVPP, R-GemOx, R-IGEV…*CAR-T*

4th line: …….

Polatuzumab vedotin

Available (and reimbursed) in Slovenia since 30.12.2020

So far we treated 74 patients with polatuzumab vedotin

Year	Number of patients
2020	1
2021	19
2022	33
2023	23

Number of cycles	Number of patients
6	25
5	7
4	6
3	6
2	5
1	12

Therapeutic regimen	Number of patients
Rituximab-polatuzumab-bendamustin	71
Rituximab-polatuzumab	2
Rituximab-polatuzumab-CHP	1

Analyses 2015 - 2018

2015: 99 patients

2016: 103 patients

2017: 73 patients

2018: 76 patients

2019: *COVID*

2020: *COVID* + in the middle of 2020 → CAR-T

2021: 91 patients

Exclusion & Inclusion criteria

Transformation from low grade lymphomas, primary CNS lymphomas, primary mediastinal lymphoma, composite lymphoma

Intermediate between Hodgkin lymphoma and DLBCL and DLCBL and Burkitt lymphoma or Burkitt-like lymphomas

All patients who were treated only with palliative radiotherapy or referred to palliative care

→ Included all patients with at least one cycle of systemic treatment

Before CAR-T period

2015: 99 patients with DLBCL (8가), (26) 21 are treated with 2nd line treatment, 11 are treated with 3rd line treatment → 6 potential CAR-T patients (aged 56,65,67,67,70,74)

2016: 103 patients with DLBCL (9가), (18) 14 are treated with 2nd line treatment, 7 are treated with 3rd line treatment → 5 potential CAR-T patients (aged 40,69,69,72,74)

2017: 73 patients with DLBCL (6가), (7) 5 are treated with 2nd line treatment, 1 is treated with 3rd line treatment → 1 potential CAR-T patient (aged 61)

2018: 76 patients with DLBCL (6가), (15) 8 are treated with 2nd line treatment, 6 are treated with 3rd line treatment → 2 potential CAR-T patients (aged 57 in 59)

CAR-T period

Department of Hematology of University Clinical Centre of Ljubljana established Center of excellency with Novartis's help in the middle of 2020 → product: Kymriah

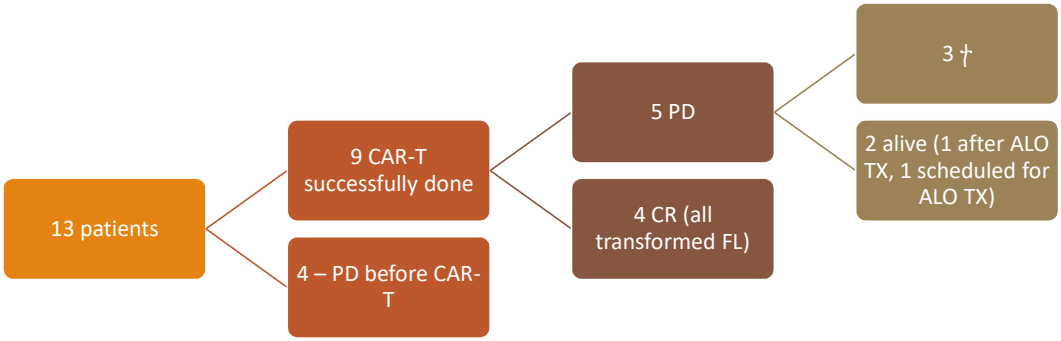
In 2021 we analyzed 91 patients with DLBCL: 14 are treated with 2nd line treatment, 2 are treated with 3rd line treatment → 1 potential CAR-T candidate, who died due to progressive disease before CAR-T administration

CAR-T period

Department of Hematology of University Clinical Centre of Ljubljana established Center of excellency with Novartis's help in 2020 → product: Kymriah

Since 2020 we had 17 potential patients for CAR-T treatment, presented at University Clinical Center tumor board → 4 were rejected by the hematologists, 13 were approved

→ Out of those 4 rejected, two were offered autologous transplantation, but none of them recieved it



9 patients with successfull CAR-T administration: aged 29 – 71 years

Median number of prior treatment lines: 2 (range 2-3)

7 patients with PS 0 and 2 with PS 1

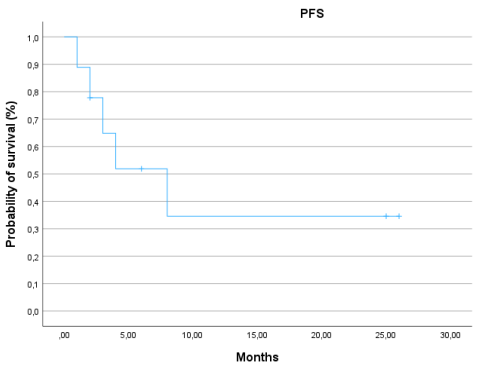
Histology	Number of patients
Transformed follicular lymphoma	5
DLBCL	2
Primary mediastinal B lymphoma	1
Richter's transformation	1
DLBCL *LPHL→DLBCL*	*3* *1*

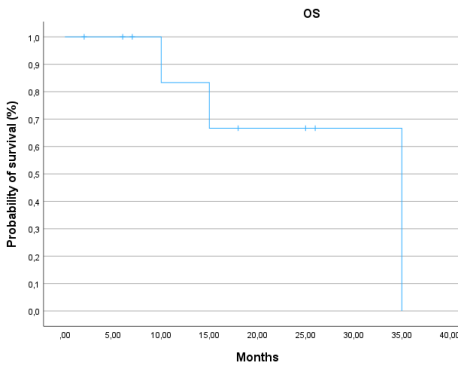
Bridging therapy regimen	Number of patients
IGEV	2
GemOx	1
R-DHAP	1
Brentuximab-R-IGEV	1
R-IGEV	1
R-CBVPP	1
Venetoclax + radiotherapy	1
GemOx + radiotherapy	1

Prognostic factors prior to CAR-T

Patient number	PS 2 or more	Resistance to bridging therapy	Bulky disease	2 or more extranodal localisations	CRP above normal level	LDH above normal level	Progressed after CAR-T
# 1	-	-	-	-	-	+	+
# 2	-	+	-	-	-	-	-
# 3	-	-	-	-	+	-	-
# 4	-	+	-	-	-	-	+
# 5	-	+	-	+	+	-	+
# 6	-	-	-	-	+	+	+
# 7	-	+	-	+	-	-	-
# 8	-	+	-	-	+	-	+
# 9	-	+	-	+	+	+	-
# 10	-	+	+	+	+	+	
# 11	-	+	-	+	+	+	
# 12	-	-	+	+	+	+	
# 13	-	-	-	-	+	-	

Vercellino et al, Blood Adv (2020)





Survival curves

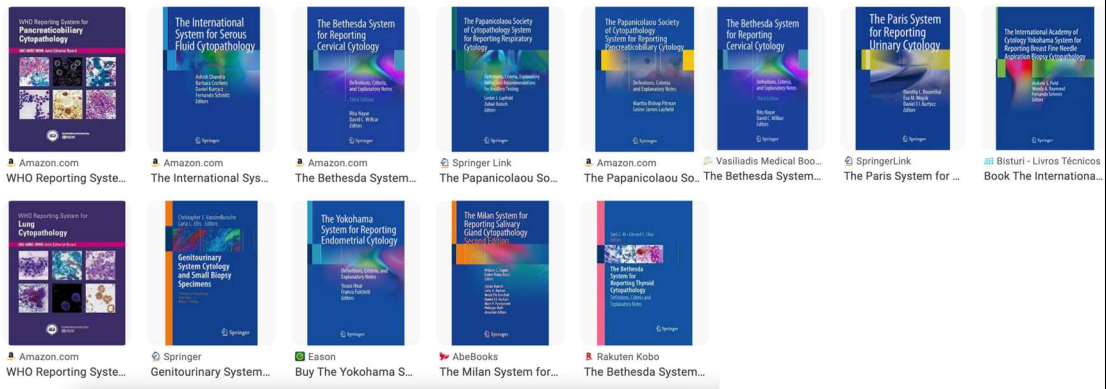
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Proposal for the Performance, Classification, and Reporting of Lymph Node Fine-Needle Aspiration Cytopathology: The Sydney System

Veronika Kloboves Prevodnik
Dept. of Cytopathology, Institute of Oncology Ljubljana

3rd Scool of Malignant Lymphomas, Institute of Oncology Ljubljana, 19th -20th October, 2023

Standardization in cytopathology



Classification of the disease and uniform reporting system are the basis for their multidisciplinary comprehension and treatment
(prof. Pio Zeppa at the European Congress of cytology, Budapest 2023)

What about lymph nodes?

- *Evaluation of lymph nodes by FNAB is* used in many institutions but it is not uniformly accepted mainly because of the lack of guidelines and a cytopathological diagnostic classification.
- Its role in lymphoma diagnostic is controversial and not widely accepted among clinicians and pathologists.

Standardization in lymph nodes cytopathology

- A steering committee of international cytopathologists involved in LN-FNAC met at the International Cytology Congress on May 2019 in Sydney, Australia, and decided to develop a system for reporting LN-FNAC.
- The project has received the endorsement and patronage of the International Academy of Cytology and the European Federation of the Cytology Societies.
- A Proposal for the Performance, Classification, and Reporting of Lymph Node Fine-Needle Aspiration Cytopathology: The Sydney System *(Acta Cytologica 2020;64:306–322)*

P. Zeppa at ECC in Budapest

The main aims of the proposed lymph nodes consensus system

- Provide **consensus guidelines and a framework of reference** to facilitate communication among cytopathologists, hematopathologists, clinicians, surgeons, and other healthcare providers.
- Define and identify lymph node FNAB
  - **indications,**
  - **preferred operators,**
  - **recommended performance,**
  - **analytical and preanalytical issues,**
  - **technical issues**
  - **basic diagnostic reporting categories and additional diagnostic information that can produce specific disease subtyping when possible.**
- Provide the key **diagnostic cytopathological features** of lesions that occur commonly in the various categories.

- Provide **recommendations on the components of standardized diagnostic reports** with the aim to improve reporting and communication between cytopathologists and clinicians.
- Provide **management recommendations** linked to the reporting categories with possible options that include the use of clinical and imaging follow-up, ancillary testing, and possible need of LN excision.
- Encourage **cytohistopathological correlations, cell storage, and research on neoplastic and non-neoplastic LN specimens.**
- Increase **lymph node-FNAC reliability**

Main goals of lymph nodes FNAB

- Lymph node identification (i.e. intramammary)
- Lymph node diagnosis (malignant/reactive) and avoid excisional biopsy for benign/reactive process
- Diagnosis and staging metastases and lymphomas
- Diagnosis and microbial culture material for infectious etiology
- Relieve anxiety for benign/reactive processes
- Cell collection for prognostic and predictive tests
- Cell collection for clinical trials or other research tests

Diagnostic approach in lymphadenopathy

- Two levels
  1. Clinical, imaging, serological
  2. FNAB, core needle biopsy or excissional biopsy

Clinical, imaging, and serological evaluation of lymphadenopathy

- Clinical evaluation of patients with lymphadenopathy may be a complex task for clinicians.
- Medical history and physical examination often suggest the cause of lymphadenopathy and, in most cases with a clear clinical context, the diagnosis and management of reactive lymphadenopathy is quite straightforward and FNAB, core needle biopsy or excisional biopsy are not indicated.
  - Age
  - Clinical history
  - The size (> 1 cm and for specific sites (SCL, popliteal, iliac, epitrochlear region > 0,5 cm), consistency and/or image findings (US).
  - Basic laboratory test (CBC, DBC, biochemical blood analytes: LDH, CRP, SR...
  - Serology (Toxoplasma, CMV...)

Indications for lymph node FNAB

- When the clinical and US presentation is less clear and serological data do not explain or do not match the clinical context, diagnostic imaging (CT...) and/or pathological evaluation are required (FNAB, core needle biopsy or excisional biopsy).
  - For the most frequent causes of lymphaedenopathy, such as **benign reactive hyperplasia, specific infections or a metastasis** from a known or unknown primary tumour, FNAB is an accurate, quick, and cost-effective procedure, often making excisional biopsy an unnecessary and costly alternative.
  - FNAB can **distinguish a benign from malignant entity**, or a **haematolymphoid from a non-haematolymphoid process**.
  - FNAB can be **the first-choice procedure** for patients who are poor candidates for surgical biopsy or with abnormal lymph nodes in deep or inaccessible locations.

Indications for core needle biopsy or excisional biopsy after FNAB

- Primary lymphomas/leukemia
- Inconclusive cytopathological diagnosis
- Prognostic and predictive markers which cannot be asses by cytopathological examination

Lymph node FNAB techniques and procedural considerations

- **Informed consent**
  - Based on the guidelines of the Internal Review Board or Ethics Committee of the involved institution
- **Operator**
  - Cytopathologist, radiologist, clinician
- **FNAB**
  - US guide recommended
  - Manual, CT, EUS, EBUS guide
- Rapid on site evaluation (**ROSE**)
- **Accurate triage of material for ancillary studies** (immunophenotypic and molecular)

Lymph node FNAB request

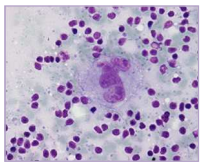
Table 1. LN-FNAC: clinical assessment and indications

LN-FNAC issues	Significant data		Course of action
Clinical context for requesting LN-FNAC	Single or multiple LN with no relevant history		Mandatory
	Single or multiple LN in known pathology		Mandatory
Clinical data to review when interpreting LN-FNAC	Age, symptoms, site, size, time of onset, imaging (US)	Generally not available!	Mandatory
	Remote and current medical history		Mandatory
	Basic serology (ESR, LDH, ToRCH complex, ANA, others)		Recommended
	Specific serology (known or suspected disease)		Recommended

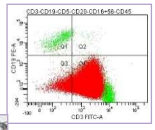
LN, lymph node; US, ultrasound; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; ToRCH, toxoplasmosis rubella

Acta Cytologica 2020;64:306–322

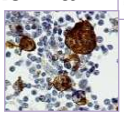
Cytopathological examination



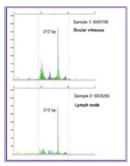
- **Microscopic evaluation** of MGG and Papanicolaou stained smears
- **Ancillary techniques**
  - **Flow cytometry**
    - Reactive hypoplasia/lymphoma/leukemia



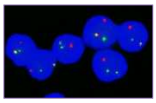
  - **ICC** on cytospins and cell blocks
    - Metastases, Hodgkin lymphoma



  - **Gene rearrangement studies** (Biomed II)
    - Especially for T-cell lymphomas



  - **FISH, CISH**
    - Specific translocations



  - **Infections**
    - Special stains, cell culture, PCR

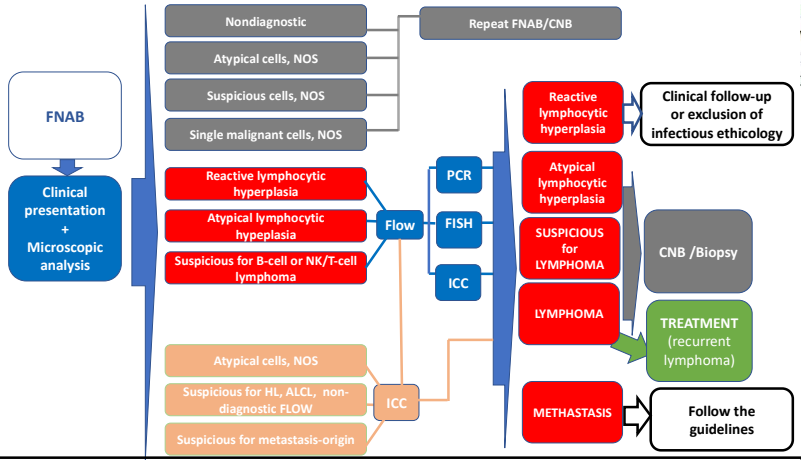
Proposed diagnostic reporting categories for lymph nodes FNAB

LN-FNAC issues	Diagnostic reporting categories	Course of action
1st diagnostic level	Inadequate/non-diagnostic	Mandatory
	Benign	Mandatory
	Atypical undetermined significance/atypical lymphoid uncertain significance (AUS/ALUS): possibly benign, not fully supported by cytology and ancillary techniques	Mandatory
	Suspicious: probably malignant, not fully supported by cytology and ancillary techniques	Mandatory
	Malignant (NHL, HL, metastases)	Mandatory
2nd diagnostic level (additional diagnostic information)	Provide specific etiology in reactive processes	Recommended if available
	NHL subtyping and specific diagnoses	Recommended if available
	HL	Recommended if available
	Specific primary tumor in metastases	Recommended if available

Acta Cytologica 2020;64:306–322

Recommendations

Post-LN-FNAC management recommendations	Inadequate/non-diagnostic	LN-FNAC repetition and/or CNB or excision
	Benign	Clinical follow-up/specific treatment (depending on diagnosis, e.g., antibiotics for bacterial infection)
	Atypical undetermined significance/atypical lymphoid uncertain significance (AUS/ALUS)	LN-FNAC repetition with acquisition of material for ancillary studies and/or CNB or excision
	Suspicious	LN-FNAC repetition with acquisition of material for appropriate ancillary studies and/or CNB or excision
	Malignant	Histological biopsy requested (note: histological for HL and NHL relapses or wn or clearly indicated primary particular sites, or in case of or specific clinical settings)



Acta Cytologica 2020;64:306–322

FNAB report

LN-FNAC issues	Procedures	Course of action
LN-FNAC report elements	Clinical data, site, imaging (US/CT) features	Recommended
	Procedure description: G-needle, guide, number of passes, ROSE, method, sample type(s), processing, staining	Suggested
	Basic diagnostic class (L1-L5)	Recommended
	Microscopic description, ancillary technique/s used	Suggested
	Secondary diagnosis or specific subtyping (if any)	Suggested
	Sample suitable (or not) for further studies (ICC, molecular) for predictive markers (possibly % content of the tumor)	Recommended
	Recommendations (follow-up for reactive, repetition-biopsy for undetermined/suspicious, biopsy for first diagnosis HL-NHL, and undetermined metastases)	Suggested
	Notes	If necessary

Acta Cytologica 2020;64:306–322

For external patients

Occasionally, mainly for general practitioner's

Risk of malignancy (ROM)

- **Many publications in last 3 years:** Gupta (2012), Vigliar (2021), Torres Rivas (2021), Ahuja 2022, Caputo 2022, Uzun 2022, Makarenko 2022, Shanmugasudaram 2023, Juanita 2023, Kanhe 2023)

	ROM (data from the literature), %	ROM (OIL)
Nondiagnostic	0.55-10.7	
Benign	0.2-9.38	
Atypical	37.5-100	
Suspicious	82.3-100	
Malignant	98.8-100	

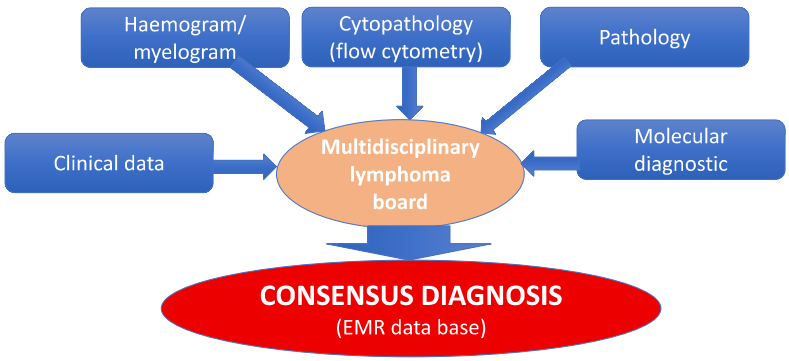
NOT AVAILABLE YET!

Conclusions

- Implementation of ***A Proposal for the Performance, Classification, and Reporting of Lymph Node Fine-Needle Aspiration Cytopathology: The Sydney System*** in daily practice worldwide will improve accuracy of lymph node FNAB results and its acceptance among clinicians and pathologists.

- At institute of Oncology Ljubljana the recommendations of the Sydney system has been part of our daily routine work long before their publishing and are also incorporated in The guidelines for diagnostic and treatment of malignant lymphomas of our hospital.

Conclusions



Multidisciplinary lymphoma bord at the Institute of Oncology Ljubljana

Thank you!

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

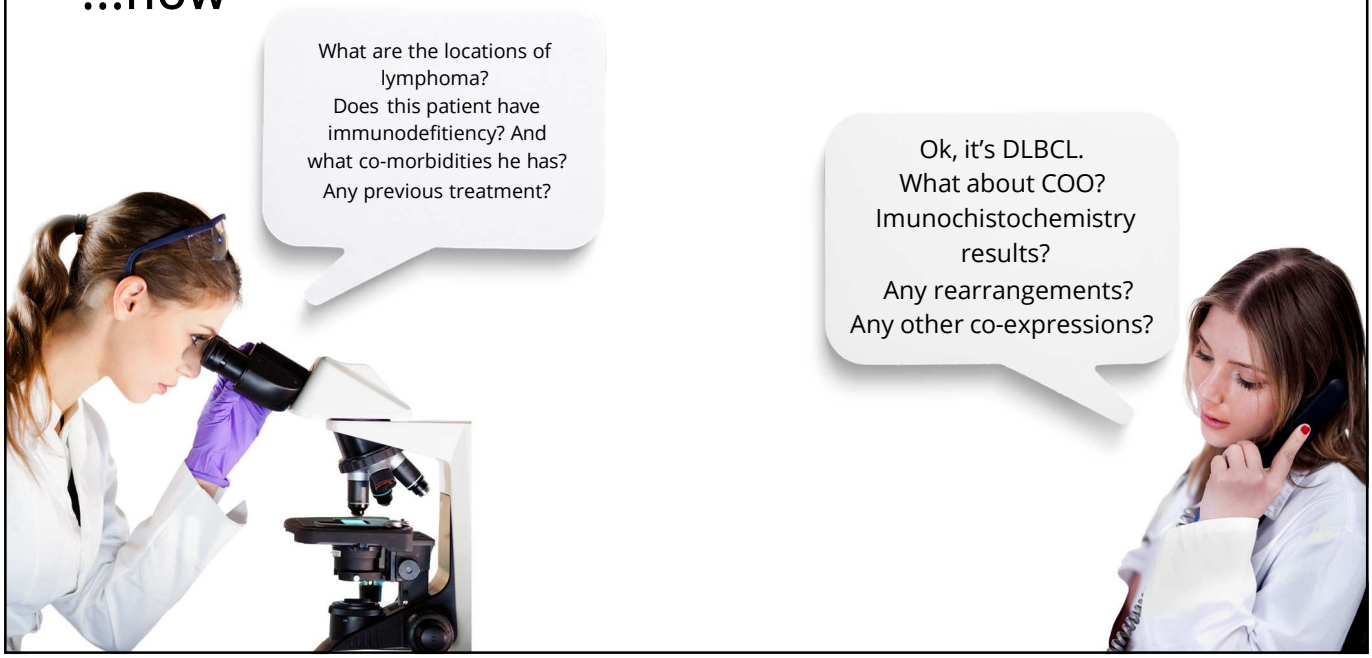
Favorable and unfavorable subtypes of DLBCL

Urška Rugelj, MD
Gorana Gašljević, MD, PhD
Institute of oncology Ljubljana

3rd School of Malignant Lymphomas,
Ljubljana, 20.10.2023

In the past...

...now

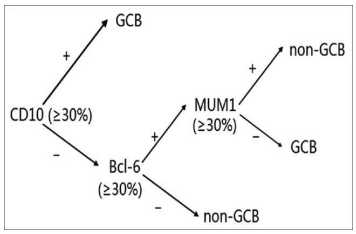


DLBCL - heterogeneus family

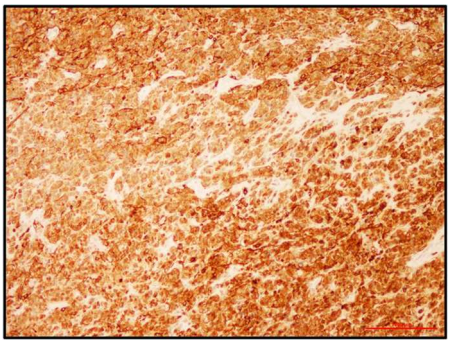
- Different prognostic and predictive factors in DLBCL are already know.
- The current standard of care - ChT with R-CHOP will not cure approx. 30%-40% of patient.
- IPI score does not include any biological features.
- Need to identify biomarkers to direct the treatment selections.
- Many biomarkers have been investigated, but few show suffitient prognostic power.

Cell Of Origin

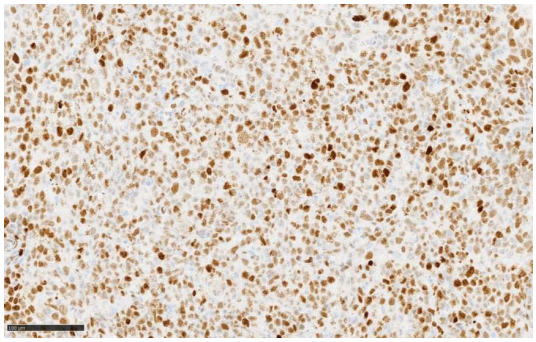
- Two main biologically distinct molecular subgroups of DLBCL based on GEP.
  - germinal center B-cell like (GCB)
  - activated B-cell like (ABC) or non-GCB
- IHC expression of CD10, MUM1 and BCL-6 (Hans algorithm)
- ABC subtype associated with worse prognoses compared to GCB



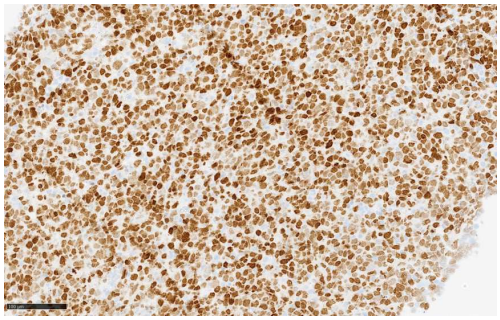
Lu, T.-X. et al.. Sci. Rep. 6, 20465; doi: 10.1038/srep20465 (2016).



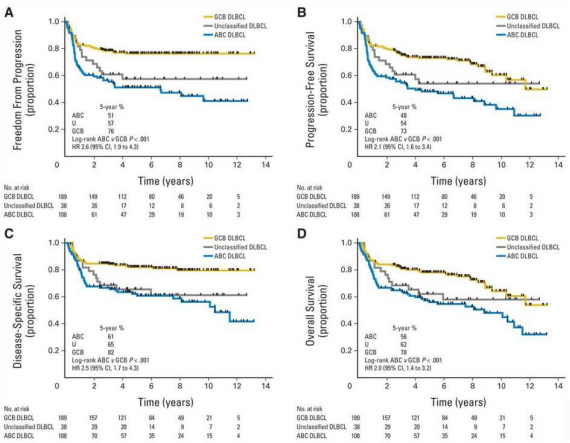
CD10



BCL6

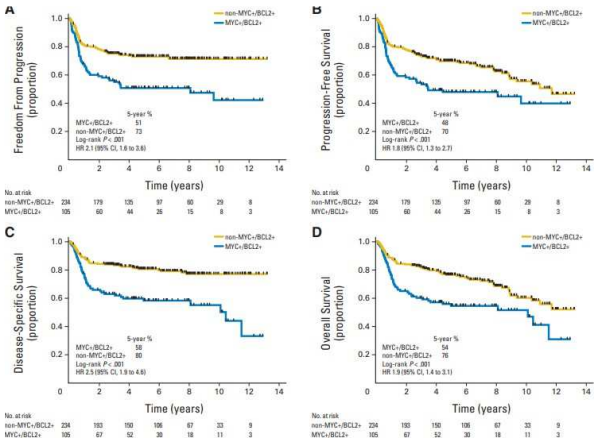


MUM - 1



GEP

IHC



Scott et al. J Clin Oncol. 2015, Sept. 10;33:2848-2856.

What about double positive GCB (CD10+, MUM1+) and triple negative non-GCB (CD10-, MUM1-, BCL6-) subtypes

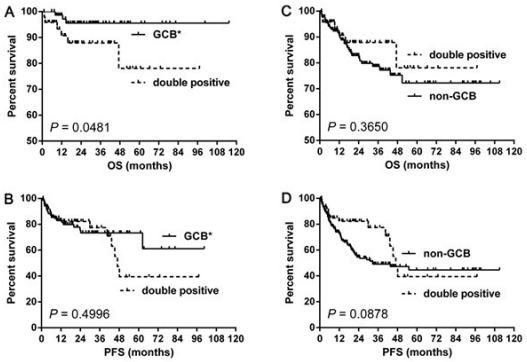


Figure 3. The survival difference between the double positive (CD10$^+$MUM1$^+$) group and GCB* or non-GCB group. The CD10$^+$MUM1$^-$ showed a better OS (**A**) but not PFS (**B**) than GCB*. However, the CD10$^+$MUM1$^+$ showed similar OS (**C**) and PFS (**D**) with non-GCB. Abbreviations: GCB: germinal center B-cell; GCB*: GCB without CD10$^+$MUM1$^+$ patients; OS: overall survival; PFS: progression-free survival.

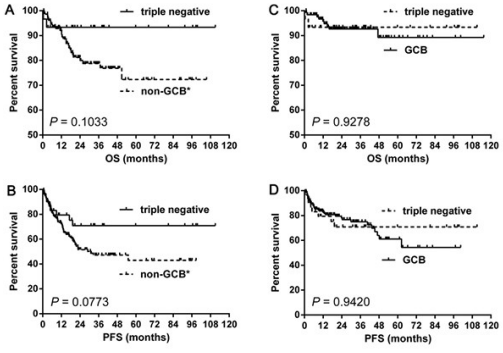
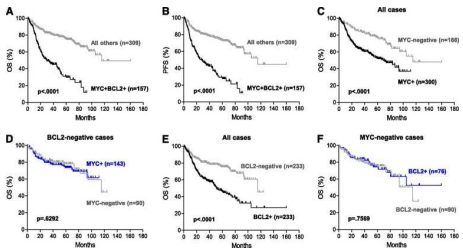


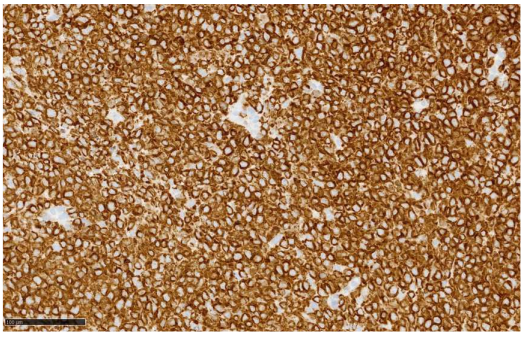
Figure 4. The survival difference between the triple negative (CD10$^-$Bcl6$^-$MUM1$^-$) group and non-GCB* or GCB group. The triple negative group tended to have better OS (**A**) and PFS (**B**) than non-GCB*. However, the triple negative group showed similar OS (**C**) and PFS (**D**) with GCB group. Abbreviations: GCB: germinal center B-cell; non-GCB*: non-GCB without triple negative patients; OS: overall survival; PFS: progression-free survival.

Lu, T.-X. et al. The distinct clinical features and prognosis of the CD10+ MUM1+ and CD10−Bcl6−MUM1− diffuse large B-cell lymphoma. Sci. Rep. 6, 20465; doi: 10.1038/srep20465 (2016)

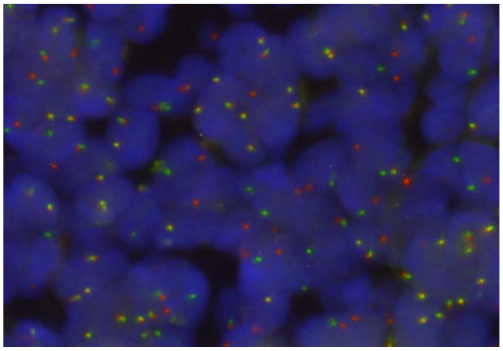
Double Hit/Double Expression Lymphomas

- 5-10% of DLBCL over-express MYC and BCL-2
  - BCL-2 over-expression plays a role in resistence to chemotherapy
    - 47%-58% of DLBCL
  - MYC over-expression is associated with increased proliferation.
    - 20-30% of DLBCL
- 5y OS and PFS when treated with R-CHOP <30%

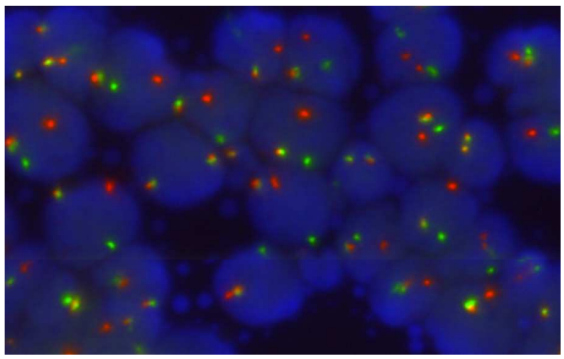




BCL2 (IHC+FISH)



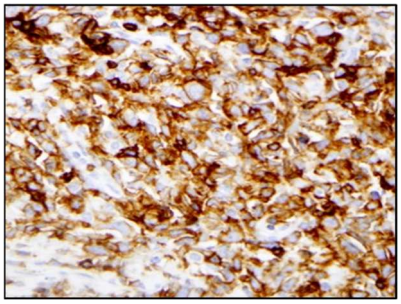
FISH c-myc

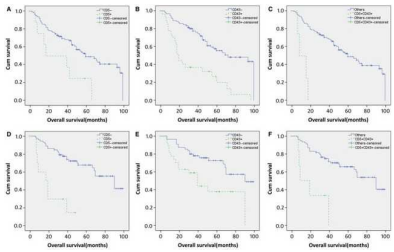


DLBCL with CD5/CD43 co-expression

- CD5 expressed in 5-10% de novo DLBCL
- CD43 expressed in approx. 25% of DLBCL
- Co-expression CD5/CD43 in approx. 5%

- The expression in studies correlates with higher IPI, higher Ki-67% and non-GCB phenotype
- All three variants predict poorer prognosis with (R)CHOP
  - CD5+ RR EFS: 3,30; OS 3,69
  - CD43+ RR EFS: 3,18; OS 2,89
  - CD5+/CD43+ RR EFS: 7,71; OS 6,25

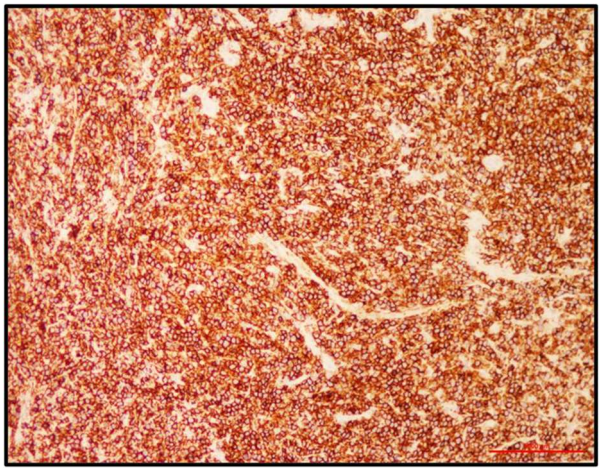




Ma X-B et all. Coexpression of CD5 and CD43 predicts worse prognosis in DLBCL. Cancer Med.2018

DLBCL with CD56 expression

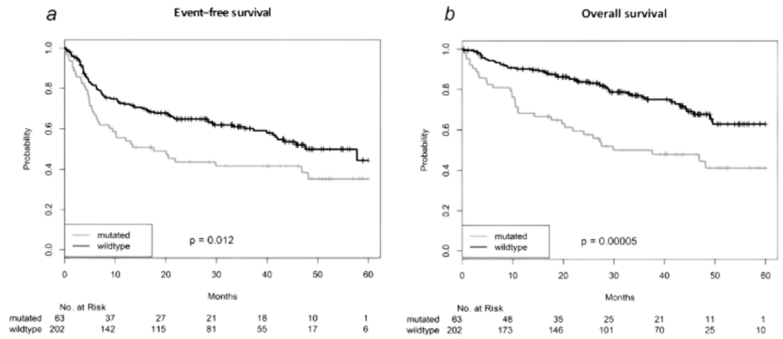
- Reported incidence 0,5 - 7% of DLBCL NOS
- Data are limited as it is not part of standard testing in B cell lymphoma
- A predictive marker in myeloma, AML and ALL
- More frequent with GCB subtype expressing CD10 and BCL-6
- May be related to more frequent extranodal involvement
- The reports suggest favorable prognostic value
  - A series from our Institution showed EFS and OS 100%



G.Gasljevic et al.. Radiol Oncol. 2023

DLBCL with TP53 mutation

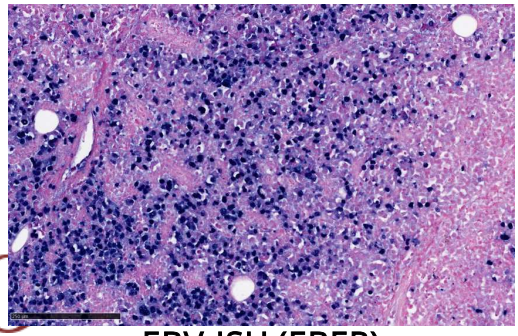
- Mutation of TP53 detected in 18% to 30% of LBCL
- Present in both GCB and non-GCB subtype
- Associated with lower response to R-CHOP (CR 62%) and lower 3y EFS (42%) and OS (50%)



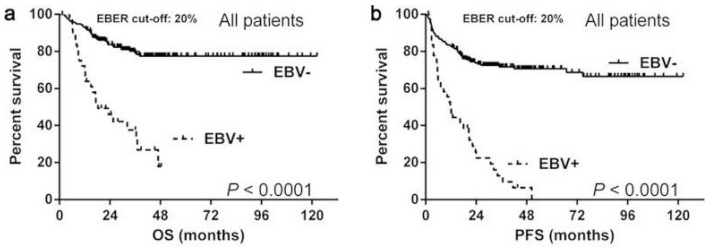
Zenz et al. Int. J. Cancer:141, 1381–1388 (2017)

EBV+/EBER DLBCL

- EBV infection is correlated to several types of lymphoma
- Associated with advanced stage, male patients, B simp., higher IPI, elevated LDH, extranodal involvement and non-GCB subtype
- Predicts poor EFS and shorter survival.



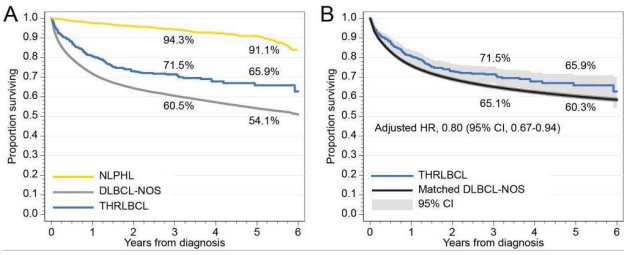
EBV-ISH (EBER)



Gao, Xiaojuan et al. PloS one vol. 13,6 e0199398. 19 Jun. 2018, doi:10.1371/journal.pone.0199398
Lu, Ting-Xun et al. Scientific reports vol. 5 12168. 23 Jul. 2015, doi:10.1038/srep12168

T-cell-rich/histiocyte-rich BCL

- 10% atypical B cells in a background rich in polyclonal T-cells
- 1-3% of DLBCL
- Aggressive clinical course, high risk of bone marrow involvement, hepatosplenomegaly, high rates of extranodal involvement



Instead of conclusion...

There are many more subtypes and subgroups according to molecular testing, NGS...

Due to its speed, good reliability, and widespread applicability, IHC will remain the gold standard for additional diagnosis of DLBCL for some time.

It is our task to further research and discover treatment modalities that will transform unfavorable lymphomas into favorable ones.

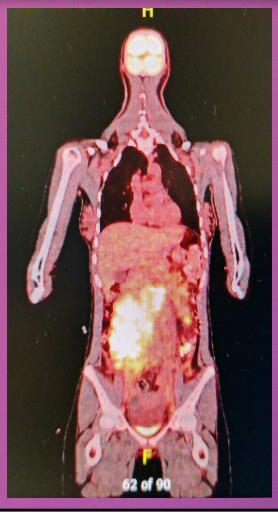
Clinical case of refractory DLBCL

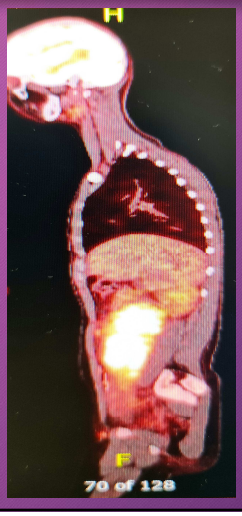
Aleš Christian Mihelač, MD
Institute of Oncology Ljubljana, Slovenia

Initial presentation

Patient	• 30-years old, female • Unremarkable medical history
Presentation of disease	• B-symptoms, enlarged lymph nodes in right groin, tumor mass in abdomen • On PET-CT retroperit. tumor mass (SUV max 28,8), several smaller lymph nodes above and below diaphragm, BM (10 %), psoas major muscle
Diagnosis	• Transformation of follicular lymphoma to diffuse large B-cell lymphoma, GCB molecular subtype • Primary clinical stage IV.B.E.X.
Laboratory	• Beside slightly elevated LDH unremarkable blood picture and biochemistry • International prognostic index (IPI) 3 points – high-intermediate risk group

Initial presentation – PET-CT





I. Line of Treatment

Therapy
- 8 cycles R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and methylprednisolone) in year 2021
- 4 prophylactic intrathecal chemotherapies (methotrexate, cytarabine and dexamethasone)

Response
- Complete remision on PET-CT
- All 4 cerebrospinal fluid samples negative on cytology

Aftermath
- Maintenance subcutaneous rituximab on 8 weeks schedule
- After 2 applications relapse, confirmed with CT scans and fine needle biopsy

II. and III. Line of Treatment

Therapy
- R-DHAP (rituximab, dexamethasone, high dose cytarabine and cisplatine), started in june 2022
- Favorable response, collection of stem cells for autologous bone marrow transplantation

Aftermath
- Prolonged Covid infections, 3rd cycle delayed for 2 months
- Confirmed relapse

Therapy
- R-IGEV (rituximab, ifosfamide, gemcitabine, vinorelbine), started in september 2022
- Very good response achieved

CAR-T
- 2nd relapse, patient already received several myelosupressive regimens
- Hematologists were consulted and an agreement was made, that she is a suitable candidate for CAR-T cell therapy, which she received in november 2022

IV. Line of Treatment

Relapse
- In february 2023, 3rd relapse was confirmed
- Relapse in the right ureter, the only site of relapse according to all diagnostic studies
- Radical irradiation of single relapse site with a dose of 40 Gy in april 2023

Relapse
- Despite all interventions 4th relapse was confirmed with large tumor retroperitoneal and mesenterial masses after 2 months

Therapy
- R-pola-benda (rituximab, polatuzumab and bendamustine) with addition of prophylactic intrathecal chemotherapies was introduced
- After 1st cycle progress of disease, chemotherapy with R-IGEV was reintroduced
- PET-CT after 4 cycles showed complete metabolic remission.

Future considerations

Current status

- Malnourishment
- Stable laboratory results

Plan of treatment

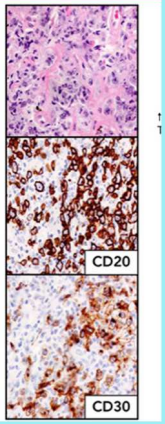
- Candidate for allogenic stem cell transplantation in Zagreb, Croatia

Overview of treatments

20.10.2023, Institute of Oncology Ljubljana

3rd school of malignant lymphomas

Clinical case presentation



Anja Žižek, dr.med

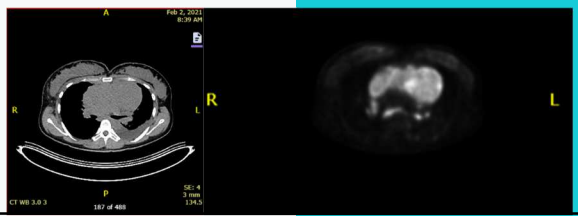
36-year-old female

- Pharmacist with 2 children (2,5-year-old, 6-month- old)
- Family history: mother had breast cancer
- Past history: eczema skin changes last 2 years on both arms (unkown cause)
- December 2020: COVID-19 disease → negative test after 1 week, but still persisting dyspnea, new onset of pain under right scapula, in pelvis and in left lower part of chest
- Coughing, night sweats, loss of 4 kg in 1,5 month
- Examination: palpable lymph nodes in both SCL region (1,5 cm), right axila (4cm infiltrate), left axila (3 cm)
- RTG p.c. (january 2021): widened mediastinum (15 cm), small left sided pleural effusion
- CT of thorax, abdomen with contrast (January 2021): large solid formation in mediastinum, pressing on VCS, numerous enlarged lymph nodes
- LDH 4,67

Diagnosis: histopathological examination (right axillary lymph node, 29.1.2021) and other investigations:
primary mediastinal large-B cell lymphoma

- **MIB-1 80%**
- **without bcl-2, bcl-6 and myc translocation**

- **Bone marrow biopsy and aspiration: no lymphoma infiltration**
- **PET-CT (2.2.2021): widened mediastinum (X=15 cm, SUV max 19,4), infiltration of lymph nodes: both SCL regions, axillae, intercostal, abdomen; infiltrates in lungs?, clear infiltrations in left pleura, pleural effusion and bones (skull, mandibula, iliac bone, femur)**
  - **Primary clinical stage: IV.B.X, IPI 3**



Treatment

- ❑ **1st line treatment: 6 x R- DA- EPOCH** (4x level 1, 2xlevel 2, finished by the end of May 2021), 5 x zoledronic acid, 2x IT, CSF negative
- ❑ CT of neck, thorax, abdomen with contrast before 6th cycle: 5,9 x 2,1 x 8,5 cm formation in anterior mediastinum
- ❑ PET-CT: **CR** (DS 3 only in upper retrosternal mediastinum).
- ❑ Lymphoma council: no further treatment, repeat PET-CT after 3 months

- November 2021 - PET-CT: disease progression: 2 formations in anterior mediastinum (7 cm, SUV max 18), new infiltrate in 5th left rib (SUV max 25)
- US-guided cytological puncture of tumor → **Refractory large B cell lymphoma, CD 19+** in anterior mediatinum: **large-B-cell lymphoma, high expression of CD20+, MIB-1 70%**

- ❑ **2nd line treatment: 3 x DHAP** → after 1 cycle collection of stem cells for ASCT
  - ❑ January 2022 - PET-CT: disease progression in anterior mediastinum, new infiltrate in right paratracheal lymph node (DS 5)
- ❑ **Bridging therapy : 2 x R - IGEV**
  - ❑ March 2022 - PET-CT: PR in anterior mediastinum, retrosternal and parasternal space (DS 4)

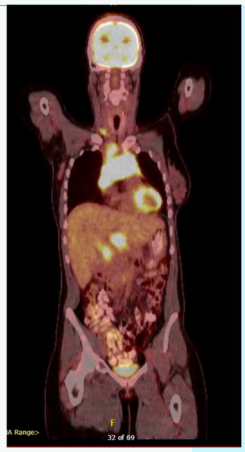
Continuation of treatment

June 2022 - biopsy of lymph node in right SCL region: mature highly malignant B cell lymphoma, morphological and immunophenotypically similar to primary biopsy. Immunohistochemical features: CD19+, CD23+, p63+, p53+, bcl-2+, bcl-6+, CD30 < 1%

- Negative: CD20, CD3, CD5. EBV -.
- MIB-1 at least 70%

February 2023 - biopsy of lesion in liver: large-B-cell lymphoma, CD19+, partial CD23+, 30% of cells is CD30+

- Negative: CD20, CD10, Cyclin D1 and CD5.
  - → MIB-1 > 90%.
  - → PD-L1 clone 142: 1%
  - → PD-L1 clone 22C3: 70%.



3rd line: CAR-T cell therapy (23.3.2022)

- Fever, occasional chest pain, night sweats
- May 2022 - PET-CT: **severe progression** of disease: infiltrated whole mediastinum (9,9 x 16 cm, SUV max 18), new infiltrates in liver hilus, at head of pancreas, aortocaval (SUV max 17)

4th line: 2 x CBVPP

July 2022 - PET-CT: new, <1cm in diameter, hypodense lesions in liver (SUV max 5,8), other localisations: PR

- MR of liver: diffuse lesions, ~ 10mm → characteristics of malignant growth

5th line: 3 x polatuzumab-bendamustin (+ venetoclax 200mg in 2nd and 3rd cycle)

- After 2nd cycle - PET-CT in September 2022: **CR**
- Prolonged pancytopenia + parainfluenza infection
- **November 2022: allogenic SCT, conditioning with TBF protocol, imunosupression: ATG, mycophenolat, cyclosporine.**

➔ January 2023 - PET-CT: hypermetabolic, 1-2 cm large lesions in liver (SUV max 10,5), hypermetabolic lymph nodes in mediastinum, retroperitoneal lymph nodes → **relapse of disease**
➔ Reducing immunosupression!

February 2023 - biopsy of lesion in liver: large-B-cell lymphoma, CD19+, partial CD23+, 30% of cells are CD30+

- Negative: CD20, CD10, Cyclin D1 and CD5.
  - ➔ MIB-1 > 90%.
  - ➔ PD-L1 clone 142: 1%
  - ➔ PD-L1 clone 22C3: 70%.

Hematology and Lymphoma council:
→ **6th line therapy (16.3.2023 - 1.8.2023)**
Day 1: brentuximab-vedotin 1,8 mg/kg IV (7x)
Day 8: nivolumab 240 mg IV (6x)
Repeat every 21 days.

PET-CT after 4th cycle: CR

Adverse effects

- After 2nd dose of brentuximab vedotin →small fiber sensory neuropathy: severe burning pain in feet→ ↓ dose of brentuximab to 1,2 mg/kg
- Itching skin eczema on elbow, clavicula, neck → corticosteroid creme
- After 6th cycle: **TSH 112 MIU/L, FT4 3,1 pmol/L, FT3 3,8,** asymptomatic → Levothyroxine 50 mcg
  - → **ICI induced hypothyroidism**

Avgust 2023: severe pancytopenia

- **Fever, severe fatigue, respiratory infection → azythromicin and AMX/SMX**
- **Numerous blood and platelets transfusions**
- **Platelet antibodies: +**
- **Ineffective platelet transfusions-> ITP?**
- **Tranexamic acid**
- **increasing LDH**

Leukocytes	0,39
Hemoglobin	66
MCV	98
Trombocytes	2
LDH	**37**
TSH	15, pT3 3,7, pT4 12,6
feritin	21341
TAG	2,51
CRP	55, PCT 0,48
Bilirubin	19

PET-CT - end of August 2023

- new diffuse accumulation of 18F-FDG in **enlarged spleen (SUV max 6,6) and liver (SUV max 3,8), bone marrow (SUV max 3-4)**
- no pathological accumulation in lymph nodes (DS 2)

BONE MARROW EXAMINATION - 30.8.2023:

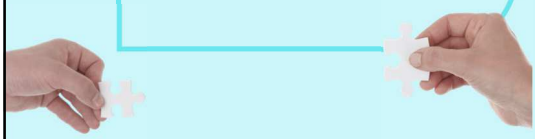
- **Citology:** no lymphoma cells.
- **Histology:** toxic mielopathy due to specific oncology treatment, no hemophagocytosis. Few individual (max 3-4) transformed B cells - etiology? Minimal infiltration of large B-cell lymphoma?

Microbiology results:

- PCR - CMV, EBV: negative
- Parvovirus B19: IgG positive (16), IgM negative
- PCR - RV panel: negative
- Induced sputum - *Pneumocystis jirovecii:* negative
- Beta-D-glukan, Aspergillus galactomanan: negative
- Populations of T-lymphocytes: decreased all values including NK cells
- sIL-2r: 5470 U/ml
- Sputum: normal bacterial microbiota
- Blood cultures: negative
  - Coombs test-direct: +
  - Coombs test-indirect: -
  - 4.9. → Blood transfusion center: **new anti-E antibodies against donor erythrocytes**
    - 2 units of blood transfusions without E antigen, tocilizumab 440 mg → appropriate ↑Hb: 90

HLH - 2004 criteria (at least 5 out of 8 criteria)

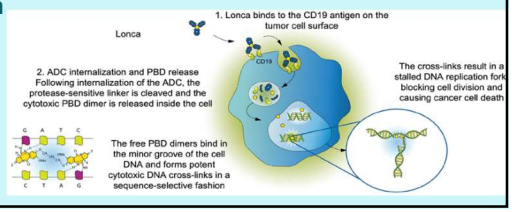
1. Fever
2. **Splenomegaly**
3. **Cytopenia (in at least 2 of the 3 cell lines**
   a. Hb < 90mg/dl
   b. Platelet counts < 100
   c. neutrophils count < 1
4. **↑TAG** or ↓fibrinogen
5. Low or absent NK-cell activity
6. **Ferritin level >500 ug/L**
7. **sCD25r level >2400 U/ml**
8. Hemophagocytosis in bone marrow, spleen, or lymph nodes



Haemophagocytic lymphohistocytosis secondary to immune checkpoint inhibitor therapy

→ Therapy:

- 31.8.2023 - start of **Dexamethasone 16 mg p.o.** → slowly tapering of dose
- During hospitalization: 4 units of blood transfusions, 2 units of blood transfusion without E antigens, 5 units of platelet transfusion
- Sent application for compassionate use of loncastuximab tesirine → rejected due to pancytopenia



31.8. - 25.10.: Dexamethasone 16 mg/day (2 weeks)
→ 8 mg/day (2 weeks)
→ 4 mg/day (2 weeks)
→ 2 mg/day (1 week)
→ 2 mg every second day

1.9.2023		11.9.2023	
Leukocytes	1,84	Leukocytes	2,93
Hemoglobin	88	Hemoglobin	76
MCV	92	MCV	90
Platelets	8·	Platelets	3
Neutrophils	1,4 x 10^9/L	Neutrophils	2,38 x 10^9/L
Lymphocyte	0,29 x 10^9/L	Lymphocyte	0,32 x 10^9/L
Reticulocytes	4,7 x 10^9/L	Reticulocytes	
LDH	**45 ukat/L**	**LDH**	**15 ukat/L**
TSH	15, pT3 3,7, pT4 12,6	TSH	0,927, pT3 3,2, pT4 21
feritin	35043	feritin	11358
CRP	64 PCT 0,756	CRP	1,2
Bilirubin	19	Bilirubin	19

Date	**s-IL2-R** (158 - 623 U/ml)
29.8.2023	5470
4.9.2023	5313
25.9.2023	1398

Last visit- 9.10.2023

History:

- well-being, going for a walk, good appetite
- no fatigue
- active at home and around the house
- no B-symptoms, bleeding, dispnea or cough

- Muscle cramps at night
- dull pain in lumbar region, which is spreading to chest in last two days

- Future: PET-CT after completion of treatment with dexamethasone

Leukocytes	2,35
Hemoglobin	100
MCV	104,4
Platelets	14
Neutrophils	1,49 x 10^9/L
Lymphocytes	0,42 x 10^9/L
Bilirubin	9
LDH	5,71
TAG	4,03
Feritin	3773
CRP	< 0,6
TSH	1,65 mIU/L
FT3	3 pmol/L
FT4	19,6 pmol/L

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
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Nine–years up-to-date treatment of follicular lymphoma transformed to diffuse large B-cell lymphoma

Tina Zupančič
Prof. Barbara Jezeršek Novaković, PhD

Third school of malignant lymphomas, Institute of Oncology Ljubljana
October, 2023

Patient presentation

WBC: 4,97 x 10^9/L (normal 4,0 – 10,0)
HB: 159 g/L(normal 130 – 170)
PLT: 188 x 10^9 /L (normal 150 – 410)
Creat: 98 µmol/L (normal 59 – 104)
LDH: 2,71 µkat/L (normal < 4,13)

❖**November 2014**

- 42-year-old male
- Familly history negative for heamatological diseases
- No commorbidities, PS 0
- No B symptoms
- Axillar lymphadenopathy - lymph node biopsy confirmed low grade follicular lymphoma (FL)
- IV A.X. (lymph nodes of the neck, axilla, *large retroperitoneal mass (X) causing obstruction of the right kidney,* bone marrow positive for FL)
- FLIPI low risk
- **Interested in alternative medicine**

First and second line

WBC: 4,82 x 10^9/L (normal 4,0 – 10,0)
HB: 100 g/L (normal 130 – 170)
PLT: 125 x 10^9 /L (normal 150 – 410)
LDH: 10,34 µkat/L (normal < 4,13)
PS: 0

❖**December 2014**

- Radiotherapy to the retroperitoneal mass 2x2 Gy

❖**April – October 2015**

- Transformation to diffuse large B-cell lymphoma (DLBCL) in abdominal mass
- 8 cycles of R-CHOP (cyclophosphamide, doxorubicine, vincristine, metilprednisolone)
- Partial remission on PET CT reached
- Consolidation radiotherapy indicated, but patient DECLINED
- Rituximab maintenance for 6 cycles

WBC: 3,13 x 10^9/L (normal 4,0 – 10,0)
HB: 161 g/L (normal 130 – 170)
PLT: 183 x 10^9 /L (normal 150 – 410)
LDH:2,39 µkat/L (normal < 4,13)
PS:0

❖**November 2016**

- Lymph node on neck - cytological relapse of FL confirmed
- Multiple cytological punctions were suggested, but he DECLINED
- Radiotherapy on multiple sites was suggested, again he DECLINED

Third line

WBC: 6,63 x 10^9/L (normal 4,0 – 10,0)
HB: 136 g/L (normal 130 – 170)
PLT: 210 x 10^9 /L (normal 150 – 410)
LDH: 2,68 µkat/L (normal < 4,13)
PS: 0

❖**February – April 2020**

- Massive clinical progression on right side of scalp and neck and other sites
- Citology confirmed DLBCL, CD 20 positive
- 3 cycles R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone; after 2 cycles hearing immparement and cisplatin switch for oxaliplatin) and planned for autologous TX
- Just before cytoreduction chemotherapy for autologous TX clinical progression at jugulum – confirmed DLBCL, CD 20 **negative**!

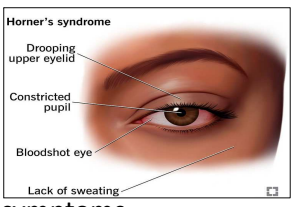
Fourth line

WBC: 3,39 x 10^9/L (normal 4,0 – 10,0)
HB: 98 g/L (normal 130 – 170)
PLT: 158 x 10^9 /L (normal 150 – 410)
LDH: 3,71 µkat/L (normal < 4,13)
PS: 0

❖**April 2020**

- First cycle of IGEV (ifosfamide, gemcitabine, vinorelbine)
- Presented for CAR-T therapy
- 14. 5. 2020 leukapheresis for CAR-T performed
- Totally 3 cycles of IGEV and **complete response** confirmed on PET CT
- 1. - 7. 7. 2020 Lymphodepletion (cyclophosphamide, fludarabine) and CAR-T (2,6 x 10^9) infussion
- No major complications
- Remission for 8 months!
- **First patient in Slovenia!**

Fifth line



WBC: 4,40 x 10^9/L (normal 4,0 – 10,0)
HB: 147 g/L (normal 130 – 170)
PLT: 150 x 10^9 /L (normal 150 – 410)
LDH: 4,14 µkat/L (normal < 4,13)
PS: 0

❖**February - april 2021**

- Right-sided Horner's syndome, no B symptoms
- PET CT: higher SUV on right apical pleura (6,4)
- VATS biopsy of apical pleura confirmed DLBCL, GCB phenotype, double expressor, CD 20 **negative**, CD 19 40%

❖**May 2021**

- Polatuzumab-bendamustine was started and he was presented for allogenic TX
- All necessary procedures for allogenic TX were performed and brother was a suitable donor
- After 2 cycles (patient missed one cycle due to cellulitis and personal preferences) **complete response** on PET CT (july) confirmed
- DECLINED further treatment
- Declinded COVID-19 vaccination

Follow up

❖**September 2021**

- No B symptoms, PS 0
- No lymphadenopathy
- LDH: 4,1 ukat/L (normal < 4,13)

❖**February 2022**

- PET/CT: Higher SUV in skin and fat tissue of right side of scalp

❖**April 2022**

- No B symptoms, PS 0
- Clinically not suspicious for progression
- LDH 3,55 ukat/L (normal < 4,13)

Sixth line

WBC: 4,38 x 10^9/L (normal 4,0 – 10,0)
HB: 151 g/L (normal 130 – 170)
TBC: 226 x 10^9 /L (normal 150 – 410)
LDH: 11,36 µkat/L (normal < 4,13)
PS: 0-1

❖**September/november 2022**

- Clinically evident progression on right side of neck and scalp *(10 cm large induration of skin and lymph nodes)*
- Denied B symptoms
- Citology of infiltrat and node confirmed DLBCL, CD 20 weakly positive
- PET CT: massive progression – including mass in pericard, infiltration of stomach, multiple sites in lungs and bones, many sites of lymph nodes
- Polatuzumab-rituximab-bendamustine, intratecal application (MTX, AraC, Dexa) and zolendronic acid for 3 cycles
- According to PET CT mixed response (progression and stable disease)

Seventh line

WBC: 3,45 x 10^9/L (normal 4,0 – 10,0)
HB: 100 g/L (normal 130 – 170)
TBC: 185 x 10^9 /L (normal 150 – 410)
LDH: 14,81 µkat/L (normal < 4,13)
PS: 1-2

❖*A request was made for compassionate use of glofitamab (available in Slovenia at that time) – it was denied due to newly confirmed negative CD 20 status*

❖**February - april 2023**

- CBVPP (carmustine, cyclophosphamide, vinblastine, procarbazine, prednisone) for 4 cycles and 3 intratecal applications (*complication - Klebsiella pneumoniae sepsis)*
- PET CT again showed mixed response (progression and stable disease)
- Radiotherapy of the progressed sites with continuity of CBVPP proposed – DECLINED radiotherapy (but performed CT simulations)
- Turned to alternative medicine
- Patient died (at home) in june 2023

Conclusions

- In 9 years 7 lines used according to up-to-date treatment, although not all possibilities were used
- Non-compliant patient, prone to alternative treatment
- Despite all, patient remained in good performance status and enjoyed high quality of life
- First patient to receive CAR-T therapy in Slovenia

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