



Guidelines



Large B-cell lymphoma: The LYSA pragmatic guidelines

Pierre Sesques^a, Guillaume Manson^b, Sydney Dubois^{c,1}, Francois Xavier Gros^{d,1},
 Gabriel Brisou^{e,1}, Clémentine Sarkozy^{f,1}, Sophie Bernard^{g,1}, Estelle Bourbon^a,
 Luc Matthieu Fornecker^h, Eric Durotⁱ, Laurent Martin^j, Catherine Chassagne-Clément^k,
 Francisco Llamas Gutierrez^l, Charlotte Syrykh^m, Marie-Hélène Delfau-Larueⁿ,
 Salim Kanoun^o, Laetitia Vercellino^p, Caroline Bodet-Milin^q, Haifa Bahri^r, Jules Zhang Yin^s,
 Arthur Dony^t, Laure Lebras^u, Marlène Ochmann^v, Marine Baron^w, Hélène Monjanel^x,
 Ronan Le Calloch^y, Fabien Claves^z, Youlia Kirova^{aa}, Christian Gisselbrecht^{ab},
 Stéphanie Guidez^{ac}, Jean Baptiste Bossard^{ad}, Roberta Di Blasi^{ae}, Caroline Delette^{af},
 Ludovic Fouillet^{ag}, Maryem Rhomdani^{ah}, Maya Belhadj^{ai}, Gilles Crochet^{aj}, Sandy Amorim^{ak},
 Firas Safa^{al}, Laurianne Drieu La Rochelle^{am}, Julie Abraham^{an}, Catherine Thieblemont^p,
 Fabrice Jardin^b, Robin Noel^e, Sébastien Bailly^{ao}, Loïc Renaud^{ap}, Yann Guillermin^u,
 Baptiste Delapierre^{aq}, Sylvain Choquet^w, Louise Roulin^{ar}, Sylvain Lamure^{u,as},
 Lionel Galicier^{at}, Yassine Al Tabaa^{au}, Carole Soussain^f, Romain Guïèze^{ao}, Roch Houot^b,
 Benoit Tessoulin^{av,*}

^a Department of Hematology, Hospices Civils de Lyon, Hôpital Lyon-Sud, Claude Bernard Lyon 1 University, Lyon, France

^b Department of Hematology, Centre Hospitalier Universitaire de Rennes, Université de Rennes, INSERM U1236, Rennes, France

^c Department of Hematology, Centre Henri Becquerel, Rouen, France; Université Rouen Normandie, INSERM U1245, Rouen, France

^d Department of Hematology-Transplantation, CHU de Bordeaux, Pessac, France

^e Department of Onco-Hématology, Institut Paoli-Calmettes, Marseille, France

^f Department of Hematology, Institut Curie, Saint-Cloud, France

^g Department of Hematology, Centre Hospitalier de la Côte Basque, Bayonne, France

^h Department of Hematology, Institut Cancérologie Strasbourg Europe, Strasbourg, France

ⁱ Department of Hematology, CHU de Reims, Reims, France

^j Department of Pathology, CHU de Dijon, Dijon, France

^k Department of Pathology, Centre Régional de Lutte Contre le Cancer Centre Léon Bérard, Lyon, France

^l Department of Pathology, CHU de Rennes, Rennes, France

^m Department of Pathology, CHU Toulouse, Toulouse, France

ⁿ Laboratoire d'Hématologie, AP-HP, Hôpital Henri-Mondor, Créteil, France

^o Department of Nuclear Medicine, Institut Universitaire du Cancer de Toulouse, Toulouse, France

^p Department of Nuclear Medicine, AP-HP, Saint-Louis, Paris, France; Université Paris Cité, Paris, France

^q Department of Nuclear Medicine, CHU de Nantes, Nantes, France

^r Department of Nuclear Medicine, Centre Régional de Lutte Contre le Cancer Centre Léon Bérard, Lyon, France

^s Department of Nuclear Medicine, Clinique Sud Luxembourg, Vivalia, Belgique, Arlon, France

^t Department of Hematology, CH Métropole Savoie, Chambéry, France

^u Department of Hematology, Centre Régional de Lutte Contre le Cancer Centre Léon Bérard, Lyon, France

^v Department of Hematology, CHU d'Orléans, Orléans, France

^w Department of Hematology, AP-HP, Pitié Salpêtrière, Paris, France

^x Department of Hematology, CH Henri Mondor, Aurillac, France

^y Department of Hematology, CH Quimper, Quimper, France

^z Department of Hematology, CHU Grenoble, Grenoble, France

^{aa} Department of Radiation Oncology, Institut Curie, Paris, France

^{ab} Department of Hematology, IUH - Institut Universitaire d'Hématologie Saint Louis, Paris, France

^{ac} Department of Hematology, CHU de Poitiers, Poitiers, France

^{ad} Department of Hematology, CH Lens, Lens, France

^{ae} Department of Hematology, AP-HP, Saint Louis, Paris, France

* Correspondence to: Department of Hematology, CHU de Nantes, Université de Nantes, CRCI²NA, France 1 place Alexis-Ricordeau, Cedex 1, Nantes 44093, France.
 E-mail address: Benoit.TESSOULIN@chu-nantes.fr (B. Tessoulin).

^{af} Department of Hematology, CHU Amiens, Amiens, France^{ag} Department of Hematology, CHU Saint Etienne, Saint Etienne, France^{ah} Department of Hematology, Centre Hospitalier d'Argenteuil Victor Dupouty, Argenteuil, France^{ai} Department of Hematology, CHU Saint Pierre, France^{aj} Department of Hematology, CHU UCL Namur, Belgique, Namur, France^{ak} Department of Hematology and cellular therapy, Hôpital Saint Vincent de Paul, Lille, France^{al} Department of Hematology, CH du Mans, Le Mans, France^{am} Department of Hematology, CHU Tours, Tours, France^{an} Department of Hematology, CHU Limoges, Limoges, France^{ao} Department of Hematology, CHU Clermont-Ferrand, Clermont-Ferrand, France^{ap} Department of Hematology, Gustave Roussy, Villejuif, France^{aq} Department of Hematology, CHU de Caen, Caen, France^{ar} Department of Hematology, AP-HP, Centre Henri Mondor, Créteil, France^{as} Service d'onco-hématologie, Hôpitaux Nord Ouest, Villefranche sur Saone, France^{at} Department of Hematology, AP-HM, La Timone, Marseille, France^{au} Scintidoc Nuclear Medicine Center, Clinique Clémentville, Montpellier, France^{av} Department of Hematology, CHU de Nantes, Université de Nantes, CRCI²NA, Nantes, France

ARTICLE INFO

Keywords:

Large B-cell lymphoma

Guidelines

LYSA

Level of evidence

ABSTRACT

The management of large B-cell lymphomas (LBCL) has undergone major changes over the last 5 years. These changes reflect the availability of new therapies (immunotherapies, cell therapies, targeted molecules), but also a better compartmentalization of the entities and their specific clinical characteristics. Numerous first-, second- and third-line therapeutic strategies are available, and each practitioner is committed to selecting the treatment that offers the best balance between efficacy and toxicity. Advances in the understanding of LBCL biology, coupled with improvements in diagnostic and monitoring tools and therapeutic approaches, have significantly enhanced patient outcomes in recent years. In this article, we present a set of pragmatic guidelines developed by the LYSA (Lymphoma Study Association) for the management of LBCL. These guidelines address key aspects of diagnosis, staging, response evaluation, and treatment, integrating the latest evidence from clinical trials, expert consensus, and real-world practice. They aim to provide clinicians with a clear, practical framework to optimize care for patients with LBCL, ensuring that the best available evidence is translated into clinical practice.

1. Introduction

Large B-cell lymphoma (LBCL) is the most common aggressive B-cell malignancy. It is considered a curable disease for most patients treated with frontline immunochemotherapy. However, a significant proportion (30 %) of patients are refractory or relapse within a short period of time [1]. In recent years, immunotherapies such as chimeric antigen receptor T-cells (CAR T-cells) or bispecific antibodies (BiAb) have revolutionized the treatment of chemo-refractory patients. Moreover, LBCLs encompass a large number of specific situations that are related to the patient's medical history, the molecular characteristics of the disease or a particular clinical presentation. Herein, the LYmphoma Study Association (LYSA) group proposes consensus guidelines that reflect the best available evidence-based medicine while considering reasonable proposals that have been widely adopted and are applied in clinical practice by LYSA experts in the field.

Levels of evidence and grades of recommendations have been applied according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) nomenclature [2].

1) Diagnosis and staging

1.1. Biological and anatomopathological diagnosis

Lymph node surgical excisional biopsy remains the gold standard for lymphoma diagnosis [3–7]. Core-needle biopsy represents an alternative method which is acceptable for frail patients, or for inaccessible or high-risk sites in the case of surgical biopsy. Fine-needle aspiration and flow cytometry should not be used as the only diagnostic tool [8,9].

All primary diagnoses should be reviewed by an expert hematopathologist [7,10] and be made according to the international classifications of hematolymphoid neoplasms (2022 WHO-HAEM5 and ICC [11,12]). The main challenge in diagnosing diffuse large B-cell

lymphoma (LBCL) NOS is to exclude all other aggressive B-cell neoplasms requiring another therapeutic strategy [12,13]. In that respect, a minimal immunohistochemical panel is required, with the use of other ancillary analyses depending on anatomopathological features (Supplementary table 1).

LBCL NOS is a heterogeneous disease that can be subdivided into morphological variants, phenotypic subtypes, and molecular subgroups. Among them, only the cell-of-origin (COO) subtypes (germinal center B-cell [GCB] and activated B-cell [ABC]) are formally recognized in both the 2022 WHO-HAEM5 and ICC classifications [12,13] and should be mentioned in the histological report conclusion. While gene expression profiling is the gold standard for subtyping LBCL NOS according to COO [14,15], immunohistochemistry (ICH) surrogates such as the Hans algorithm have been developed for standard clinical practice [16]. Nonetheless, COO designation is insufficient to fully capture the biological complexity of LBCL NOS and recent molecular profiling studies have identified 5–7 functional genetic subgroups [17–20]. However, no unified concept has been established so far, precluding its use in standard clinical practice at the present time [12,13]. Double expressor (MYC/BCL2) phenotypic status carries an adverse prognosis but may not be independent of the prognostic impact of mutation subgroups [21–23].

FISH testing of *MYC*, *BCL2* and *BCL6* translocation status is recommended in all LBCL and, especially, for all patients GCB COO, to identify LBCL HGBL with *MYC* and *BCL2* rearrangements [12,13,24,25]. A cost-effective approach would be to analyze cases for *MYC* rearrangement first, and to perform *BCL2* and *BCL6* FISH testing in *MYC*-rearranged cases only. Of note, whereas in both 2022 WHO-HAEM5 and ICC classifications LBCL/HGBL with *MYC* and *BCL2* rearrangements are recognized as a separate more aggressive entity, LBCL with *MYC* and *BCL6* rearrangements seem more heterogeneous [26]. The partner gene may be assessed as *MYC* translocation to an IG gene provides inferior outcomes. [27,28]

ctDNA at baseline can be proposed as an exploratory parameter but its relevance for routine use in diagnosis and staging should be further

¹ Authors contributed equally to the work

evaluated in prospective studies [29].

1.2. Expert point of view

Histology should be performed at diagnosis and subsequent relapse:

- Lymph node surgical excisional biopsy is the gold standard for the primary diagnosis (IVA).
- Core-needle biopsy is acceptable when surgical approach is impracticable and at relapse (VB).
- All cases should be reviewed by an expert hematopathologist (IVA).
- The minimal immunohistochemistry panel recommended includes two B-cell markers (including CD20), CD5, CD10, BCL6, MUM1, MYC, BCL2, Ki67 and EBER (VA).
- The histological report should include the COO subtype by IHC (Hans algorithm) (I A).
- Specifying double expressor status is optional (IVC).
- FISH testing of MYC + /- BCL2 translocation status is recommended in all aggressive B-cell lymphomas, especially in those of GCB subtype (IVA).

1.3. Initial assessment

Pre-treatment clinical assessment and investigations are summarized in Table 1.

For prognostic evaluation, the International Prognostic Index (IPI) can be calculated [30]. The IPI has been revised in the era of rituximab with the R-IPI consisting of a redistribution of the IPI factors [31]. Although the National Comprehensive Cancer Network IPI (NCCN-IPI) has improved discrimination among high-risk patients [32,33], the IPI is still the most widely used prognostic index for stratifying patients (Supplementary table 2). Considering the very similar metrics of IPI and age-adjusted IPI (aaIPI) in the elderly setting in terms of prognostication, aaIPI is widely used in patients both < 60 y.o and > 60 y.o. [34,35]. Of note, comorbidity screening scales (G8 assessment) should be introduced for frail patients.

1.4. Bone Marrow Involvement (BMi)

PET/CT can detect easily focal involvement and has shown better sensitivity than bone marrow biopsy (BMB) to determine BMi at LBCL diagnosis, with focal and intense skeletal uptakes being indicators of suspected BMi [36–38]. PET/CT has thus eliminated the need for systematic BMB in LBCL [36,37]. Of note, BMi in LBCL is either concordant (BMi by LBCL) or discordant (BMi by low-grade B-cell lymphoma), the latter of which has not been shown to be an IPI-independent prognostic marker, as opposed to concordant BMi [39].

Table 1

Pre-treatment assessment.

Clinical assessment	Laboratory tests	Pre-treatment interventions
Presence of B symptoms (fever, night sweats, unexplained weight loss, fatigue)	CBC, CMP, LDH, Coagulation Tests	ECG + evaluation of cardiac ejection fraction (TTE or isotopic ejection fraction)
Prior history of malignancy	HIV/Hepatitis B testing	Fertility preservation when applicable
Examination of peripheral nodal groups and HSMG	Pregnancy test in women of child-bearing age	CVC (PICC line or port)

HSMG: hepatosplenomegaly; CBC: complete blood count; CMP: comprehensive metabolic panel; LDH: lactate dehydrogenase; HIV: human immunodeficiency virus; ECG: Electrocardiogram; TTE: trans-thoracic echocardiogram; CVC: central venous catheter; PICC: peripherally inserted central cathete

1.5. CNS involvement (CNSi)

Establishing CNSi relies on brain MRI and cerebrospinal fluid analysis (CSF) at baseline and should be performed in LBCL patients with high risk of CNSi or clinical symptoms indicative of potential CNSi. CNS-IPI was established to stratify CNS relapse risk [40] but might underestimate this risk in patients with specific involved sites such as testis, kidney, adrenal gland, breast [41–44] and patients with ≥ 3 involved extranodal sites [45]. LBCL in proximity of the CNS (craniofacial and epidural masses) is also at risk of CNSi via contiguous infiltration although studies in the Rituximab era have shown significantly diminished CNS relapse rates [46,47].

When performed, CSF analysis must include cytology and flow cytometry (FCM) [48]. Depending on availability, we recommend considering CSF IL-6 and IL-10 level dosage, CSF cfDNA and detection of clonotypic Ig gene rearrangements [49–52].

Expert point of view:

- BMB for initial LBCL staging is not mandatory (IA).
- Establishing baseline CNSi should be performed in patients presenting neurological symptoms, high CNS-IPI (≥4) (IA), specific involved sites (testis, kidney, adrenal gland, breast) or ≥ 3 involved extranodal sites (IIIA).
- Establishing baseline CNSi should include whenever possible brain MRI, CSF cytology and FCM (IIIA), as soon as possible in the disease management.
- Depending on availability, clinicians should consider IL-6 and IL-10 dosage in CSF, CSF ctDNA and clonotypic Ig rearrangement detection (IIIA).

1.6. Role of positron emission tomography (PET) in the overall management of LBCL

PET/CT plays many roles in standard clinical practice for: staging and restaging [36,53–55], prognostics, treatment choice and response assessment [56–58]. Deauville Score compared with CT alone, the sensitivity and specificity of FDG-PET for lesion detection exceed 95 %, leading to stage modifications in 20–30 % of cases (mainly upstaging) and changes in therapeutic management in about 15 % of cases [53,59].

Baseline total metabolic tumor volume (TMTV) shows a strong prognostic value, but the absence of consensus on segmentation methods has prevented its validation for routine clinical use. The absolute SUVmax > 4 threshold method seems to be promising [60]. Combining TMTV with other parameters, both metabolic (such as Dmax) and clinical, should be validated in prospective cohorts [58, 61–63].

Derived from the GAINED study (a randomized phase 3 trial comparing obinutuzumab to rituximab), relevance of a previously determined deltaSUVmax PET0–2 (> 66 % vs ≤ 66 %) and PET0–4 (> 70 % vs ≤ 70 %) (rather than DS) for interim assessment of first-line, high-risk LBCL therapeutic response has been validated [56,64–66]. In the case of baseline SUVmax < 10, interim evaluation should be performed with Deauville scale (with DS 1–3 considered negative) [57].

The prognostic value of iPET has been widely demonstrated in LBCL for early identification of non-responders [67]. A large meta-analysis on almost 1700 *de novo* LBCL demonstrated that iPET after 2 cycles identified responders, and iPET after 4 cycles, using DeltaSUVmax, best identified non-responders [68]. Thus, the deltaSUVmax approach should be applied to patients with disseminated disease eligible to intensive treatment, regardless of their age.

In other cases, interpretation of iPET must be reported using the Deauville scale and Lugano classification in medical records [69].

FDG-PET is considered the reference exam for routine evaluation of end-of-treatment response in LBCL to ensure complete metabolic response, using DS and Lugano classification [70]. In case of partial metabolic response of persistent FDG uptake without definitive proof of

disease, follow-up FDG PET or biopsy can be useful to rule out later progression denoting evolutive disease.

FDG-PET has a low positive predictive value in the systematic follow-up of patients with a complete metabolic response after first-line immunochemotherapy and is not cost-effective [71–73].

1.7. Assessment of response to immuno-therapies (CAR T-cells and bispecific antibodies)

FDG-PET is performed before lymphodepletion and infusion of CAR T-cells to serve as baseline imaging. It allows assessment of bridging therapy efficacy and determines TMTV [57,74–77]. It also serves as a reference to evaluate treatment response, which can be performed as soon as 1 month after infusion. DS remains relevant in this context, with DS1–3 associated with durable response and DS5 mostly associated with adverse prognosis [78–80]. In patients with partial response or stable disease, persistent intense FDG uptake ($SUV_{max} > 10$) correlates with later progression [81,82].

Later follow-up at 3 months is recommended to confirm response, especially in patients with $DS \geq 4$ [78,80,83]. Given the existence of inflammatory or infectious processes, multidisciplinary evaluation and histological documentation is recommended in equivocal cases [84,85].

There is no study fully dedicated to FDG-PET interpretation or value in the context of bispecific antibodies, but all pivotal studies used FDG-PET as assessment tool.

Determination of baseline TMTV and Dmax can be proposed as exploratory parameters and their relevance for patients' risk stratification should be further evaluated in prospective studies. Determination of the optimal timepoints and duration of follow-up in patients receiving bispecific antibodies should be further studied.

1.8. Expert point of view

- Baseline FDG-PET is required for initial staging (gold standard) (IA).
- Interim FDG-PET is recommended after 4 cycles (Delta SUV max and DS) to identify early responders from non-responders (IA).
- FDG-PET-driven therapeutic strategies in first line DLBCL are relevant (IA).
- The use of Delta SUVmax (Simplified Gained Criteria) is recommended for patients with disseminated disease who are deemed eligible for CAR T and/or intensive treatment when baseline SUVmax is > 10 (IA).
- In localized disease, iPET is recommended for determining chemosensitivity, using Deauville scale and Lugano classification (IIA).
- Evaluation of end-of-treatment response is required, in order to ensure complete metabolic response, using DS and Lugano classification (IA).
- FDG-PET (nor CT TDM) should not be performed for systematic follow-up of patients with complete metabolic response after front-line therapy (IIB).

2) Frontline therapy

1.9. aaIPI= 0 without Bulky tumor

Localized LBCL is a specific subtype generally defined by stage I or II disease without a bulky mass (< 7.5 cm). Numerous strategies are available: standard R-CHOP, abbreviated R-CHOP or the historical combination of 3 R-CHOP+ Involved Site (IS) radiotherapy [86].

Patients should be stratified according to the presence of adverse prognostic factors such as defined by the age-adjusted IPI (aaIPI).

Low risk patients without adverse risk factors, aaIPI= 0, have a favorable prognosis and can be treated with abbreviated immunochemotherapy [87,88]. Indeed, the FLYER trial demonstrated that 4 R-CHOP+ 2 Rituximab versus 6 R-CHOP are non-inferior [87]. The LNH 02–03 trial established that radiotherapy can be spared in patients

obtaining a complete remission (CR) after 4 or 6 R-CHOP [89].

PET-guided treatments for abbreviated sequences can be performed. Patients in CR after recommended interim PET (iPET, after 2 or 3 cycles, DS1–2–3) have an excellent prognosis and can be treated with only 4 R-CHOP [90,91] (Figure 1 A). Patients with positive iPET have less favorable outcomes. The management of these patients remains to be fully clarified with three options: reassessment after 4 cycles, administration of 6 R-CHOP or radiotherapy. Taking into account that the use of radiotherapy in this context mainly relies on retrospective studies and that no randomized controlled trial comparing both strategies is available, the data is insufficient to choose between the two strategies [92].

For patients with DS4 evaluation at required end of treatment (EOT) PET (i.e. 4 cycles), considering the high risk of false positive findings, several options may be considered, none of which have been directly compared/evaluated: biopsy of residual uptake, addition of two more R-CHOP cycles (i.e. a total of 6 courses) with a follow-up PET, or radiotherapy. For patients with DS5 findings at the EOT (i.e. 4 cycles), a biopsy should be performed to rule out lymphoma persistence.

Patients with adverse risk factors (aaIPI ≥ 1) or bulky disease were mostly excluded from trials comparing abbreviated R-CHOP vs standard R-CHOP. Hence, these patients should be treated like advanced-stage patients.

1.10. Expert point of view

Patients without adverse risk factors (aaIPI=0, no bulk) should receive 4 cycles of R-CHOP if in CMR at iPET (after 2 cycles), without additional radiotherapy (IB).

- For patients not achieving CMR at EOT, several options should be weighted and one cannot be clearly recommended over the others: biopsy to assess refractory disease, two more R-CHOP cycles with new EOT PET, or radiotherapy.

1.11. aaIPI ≥ 1 and/or with Bulky tumor

Many approaches have been attempted in randomized trials to improve outcomes of the R-CHOP regimen (Supplementary table 3).

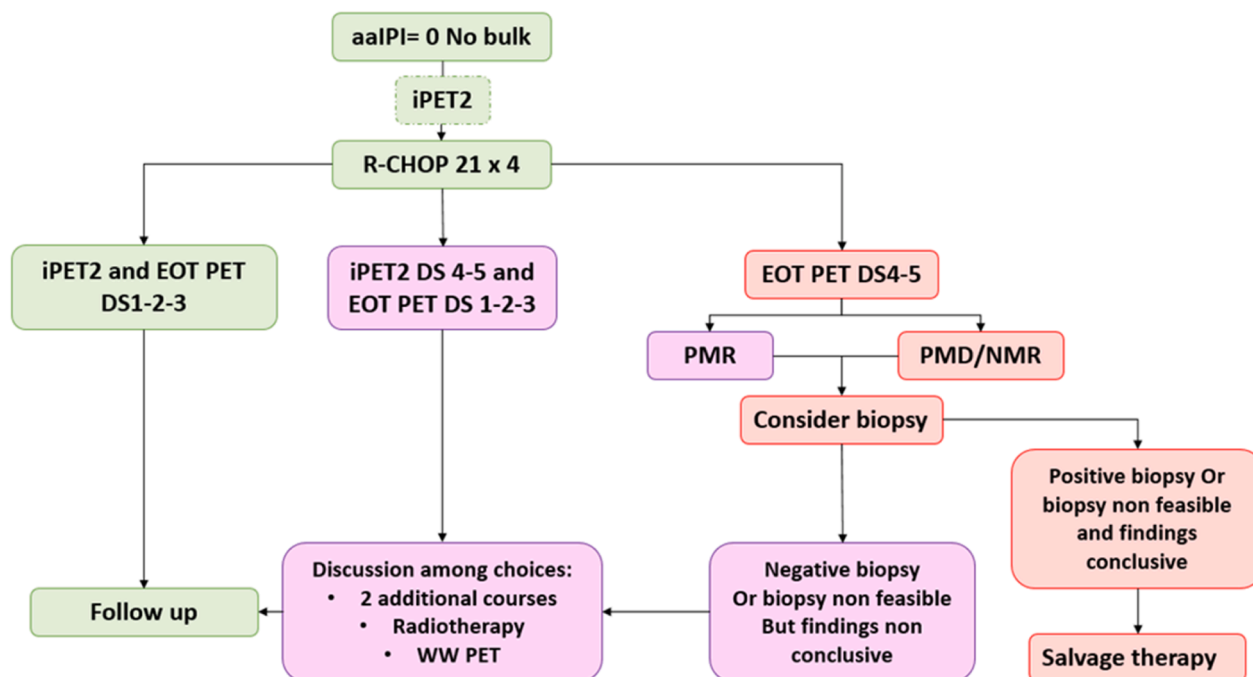
The R-ACVBP regimen is an intensive regimen and was the only regimen offering a survival advantage over R-CHOP in patients with an age-adjusted IPI score of 1, especially in non-GCB patients. However, its use has been limited due to side effects and significant toxicity [93]. No dose-dense R-CHOP regimen (every 14 days) has demonstrated superiority over a D21 interval in the Rituximab era [94,95].

The R-CHOP backbone has been the standard of care (SOC) for the last 20 years and has undergone various changes: 6 R-CHOP+ 2R, 8 R-CHOP, 6 R-CHOP. The latest has become the standard arm of the main ongoing first-line studies combining new drugs (Bispecific Antibodies, Golcadomide, etc.) with R-CHOP (Figure 1B). Of note, PET-guided strategies (such as GAINED trial) showed interesting results (overall, PFS of 77.5 % at 4y for the whole population), in a selected set of patients, but it must be noted that many patients did not undergo the planned ASCT consolidation and there was no control arm with “non-iPET” guided strategy [56].

Recently, the POLARIX study which compared Polatuzumab (antiCD79b conjugated antibody-R-CHP to R-CHOP in patients with IPI 2–5, showed a significant PFS benefit.), and has been approved by FDA and EMA, but may not be available in every healthcare-system. Notably, there was a significant improvement of both PFS and OS in patients with ABC subtype (as determined by GEP) [96]. The value of R-CHP-pola in GCB patients including DH and darkzone LBCL remains to be further explored

No strong evidence supports the systematic use of a low-dose debulking chemotherapy (i.e. “COP”) before intensive therapy but pre-dose with steroids, vincristine should be discussed on a case-by-case basis, according to age and/or comorbidities, especially in the elderly

A. Management of patients with aaIPI=0 without bulky disease



B. Management of aaIPI≥1 and/or with bulky disease

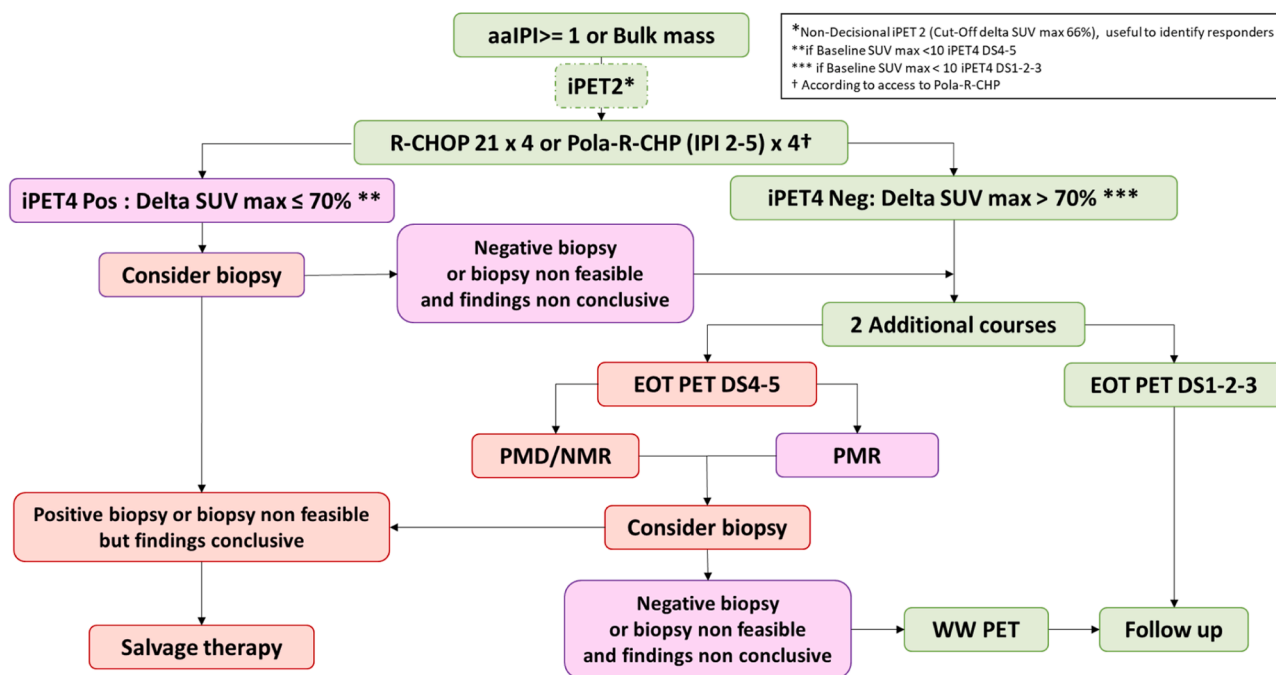


Fig. 1. Management of first-line treatment for large B-cell lymphoma. Management of patients with aaIPI= 0 without bulky disease. B. Management of aaIPI≥ 1 and/or with bulky disease. Abbreviations: aaIPI: age-adjusted International Prognostic Index; DS: Deauville score; DeltaSUVmax: change in SUVmax between baseline PET and and iPET; EOT: End of treatment; iTEP: Interim PET; LBCL: large B-cell lymphoma; Neg: negative; NMR: Non-metabolic Response; PET: Positron emission tomography; PMR: Partial metabolic response; PMD: Progressive metabolic disease; Pos: Positive; Pola-R-CHP: Polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone, R-CHOP 21: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, delivered every 21 days; SUVmax: standardized uptake value maximum, W&W: watch and wait.

setting.

1.12. Expert point of view

- The treatment of aaIPI ≥ 1 LBCL relies on 6 cycles of R-CHOP-21 for eligible patients (IA).
- PET should be used to guide therapy. We recommend performing iPET after 4 cycles of immunochemotherapy (IIIB).

PET4 should distinguish patients who achieve a CMR (DS1–3) or good partial metabolic response (PMR) (DS4–5 with $\Delta\text{SUV}_{\text{max}} \text{ PET4} > 70\%$) from those with progressive metabolic disease (PMD), no metabolic response (NMR) or an insufficient PMR (DS4–5 with $\Delta\text{SUV}_{\text{max}} \text{ PET4} \leq 70\%$). Patients in the latter group should undergo rebiopsy, and if findings are positive (e.g., showing lymphomatous proliferation, as previously described), they should be referred for salvage treatment.

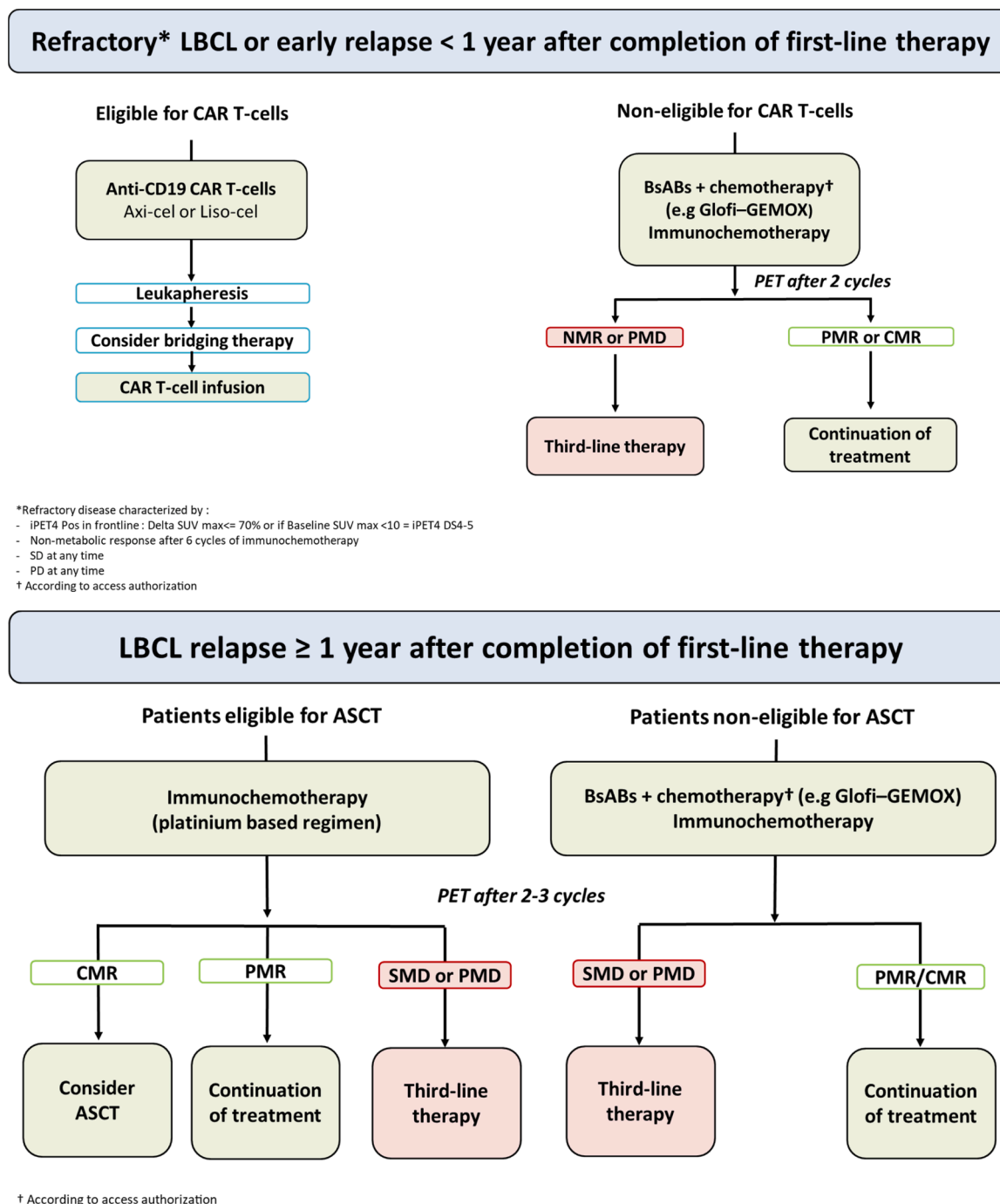


Fig. 2. A. Management of second-line treatment for large B-cell lymphoma: Management of refractory* or early-relapsing (<12 months) patients. Abbreviations: Axi-cel: axicabtagene ciloleucel; BsAbs: Bispecific monoclonal antibody; CAR T-cells: chimeric antigen receptor T cells; CMR: Complete metabolic response; GEMOX: Gemcitabine-oxaliplatin; Glofi: Glofitamab; liso-cel: lisocabtagene maraleucel; LBCL: large B-cell lymphoma; NMR, Non-metabolic response; PMR: Partial metabolic response; PMD, Progression metabolic response. **B. Management of second-line treatment for large B-cell lymphoma: Management of late-relapsing (≥ 12 months) patients.** Abbreviations: ASCT: Autologous stem cell transplantation; BsAbs: Bispecific monoclonal antibody; CMR: Complete metabolic response; GEMOX: Gemcitabine-oxaliplatin; Glofi: Glofitamab; liso-cel: lisocabtagene maraleucel; LBCL: large B-cell lymphoma; NMR, Non-metabolic response; PET: Positron emission tomography; PMR: Partial metabolic response; PMD, Progression metabolic response; SMD, Stable metabolic response.

1.13. CNS prophylaxis in LBCL

So far, only retrospective studies addressed the efficacy of CNS prophylaxis using either intrathecal chemotherapy or intravenous high-dose (HD) methotrexate (at the end of treatment or intercalated). All reports except one failed to demonstrate a benefit of prophylaxis for reducing the incidence of CNS relapse [97,98], while toxicities were underlined. The subgroups were frequently underpowered to draw other definitive conclusions in this very-high risk population. Because CNS screening was heterogeneous in the different reports, we cannot formally rule out that occult CNS involvement was missed and might have reduced the effectiveness of the prophylaxis.

1.14. Expert point of view

- CNS-involvement for high-risk patients must be ruled out by a systematic and thorough examination.
- CNS prophylaxis (prophylactic intrathecal or systemic chemotherapy) for high risk patients is not systematically recommended, except for patients with testicular lymphoma involvement (IVA).

3) Treatment of relapsed or refractory large B-cell lymphoma in the second line setting

Among the 30–40 % of the patients who relapse after the frontline therapy [99–102], 75 % experience early progression (< 1 year) after the completion of first-line immunochemotherapy. [103]. Among these early progressive patients, the ones with primary progressive disease (i. e. stable disease (SD) or progressive disease (PD) during or by the end of frontline therapy) display dismal prognosis [101].

Standard of care for R/R LBCL patients has mainly relied on intensive regimens with platinum-salts & ASCT (if eligible). A small fraction of these patients (25–30 % in CORAL randomized study and in EBMT registry), can experience complete response after the salvage treatment and can be candidate to consolidation with autologous stem cell transplantation [99,104–106].

Two randomized trials comparing the SOC salvage therapy followed by ASCT to CAR T-cell strategies for LBCL patients relapsing within 12 months of their frontline therapy demonstrated better efficacy of both axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) [107–109]. These data demonstrated that CAR T-cells produce durable remissions in 40–50 % of LBCL patients treated in 2nd line and led to the approval of axi-cel and liso-cel for LBCL patients who are refractory or relapse within 12 months of frontline therapy. Furthermore, phase II studies with axi-cel and liso-cel demonstrated a similar efficacy and an acceptable safety profile in transplant-ineligible patients [110,111], leading to axi-cel and liso-cel approval in this situation (Fig. 2A).

Expert point of view:

- For LBCL patients with refractory disease or early relapses (<12 months), who are deemed eligible for CAR T-cells, Axi-cel and liso-cel represent the standard of care (IA).
- For patients with late relapses (> 12 months), salvage immunochemotherapy remains the preferred option and chemo-sensitive patients (CMR evaluated after 2 or 3 cycles) should receive ASCT, if eligible (IA).

1.15. How to define patients not eligible for CAR T-cell therapy?

CAR T-cell therapy eligibility criteria were initially derived from pivotal clinical trials [112,113]. A definitive answer should result from a joint discussion between the CAR T-cells center and the referral center, in order not to dismiss a potentially curative option too quickly. Clinical experience gathered from transplant-ineligible patients demonstrated the feasibility of CAR T-cell therapy in patients with mildly impaired organ functions [110,111]. The occurrence of specific acute toxicities in 2nd-line patients receiving CAR T-cells is much better than in third-line

patients. Among the reasons for this better tolerance, we note a much better general condition of patients with better tolerance profile (especially liso-cel with low rates of CRS (50 % all grades with only 2–5 % of severe CRS) and neurotoxicities (less than 20 % all grades and 5–10–15 % of severe neurologic events) [111,114]. Moreover, CAR T-cells have also shown good efficacy and a favorable toxicity profile in older patients (>75 years old) [115]. Furthermore, specific adaptations of the lymphodepleting regimen showed feasibility of CAR T cell therapy in patients with renal impairment [116–118]. In Table 2, we propose “no go” and “slow go” criteria to help practicing clinicians in deciding when to refer a patient for CAR T-cell therapy.

Expert point of view:

- No clear age limit can be drawn to define CAR T-cell eligibility (IVA).
- CAR T-cell therapy should be proposed as broadly as possible in the 2nd line setting to optimize the odds of a successful therapy (IVA).
- Tumor board meetings with expert multidisciplinary teams should be held to discuss difficult situations on a case-by-case basis (VA).

1.16. Referral to CAR T-cell center

Networking culture shared by both referral and CAR-T cell centers should provide fair access to CAR T-cells to all patients. The referral process should be efficient enough to minimize the brain-to-vein time (ie, time between referral and infusion), and the vein-to-vein time (ie, time between leukapheresis and infusion), which is associated with better outcomes [119]. Every effort should be made to reduce this time interval, including prompt referral to a CAR-T cell center and urgent consultation slots. Steps of the CAR-T journey are shared between the referral center and the CAR-T center (Supplementary figure 1).

1.17. Holding therapy

Patients may relapse with rapidly progressive mass or critical location of disease and may need a holding-therapy (HT) before leukapheresis. Even though current evidence on the impact of HT on CAR-T cell outcome is limited, HT should be avoided given the potential deleterious effect of recent chemotherapy on the quality of the apheresis product [120] [120–122]. When HT is necessary, HT should avoid the use of bendamustine, given its deleterious and long-lasting impact on T-cell fitness, which may compromise subsequent CAR T-cell manufacturing and efficacy [123]. Alternative bridging approaches should therefore be preferred in this setting

1.18. Bridging therapy

The primary aim of bridging therapy (BT) is to maintain disease control during the CAR T-cells manufacturing period. BT has been frequently used (>60 % of patients) in clinical trials (except with axi-cel) as well as in real-world studies [112,122,124–129]. There is no consensus on identifying patients who require BT or on the optimal choice of BT. Decisions are often based on physicians' perceptions of patient fitness, regimens already received and disease progression. BT is typically proposed for patients with high-risk features for CAR T-cell failure, such as poor performance status, bulky disease, high LDH levels, extra-nodal involvement, and rapid progression [127,128,130]. Of note, targeted bridging with radiotherapy could be considered even with chemo-refractory disease. Current recommendations suggest a washout period of 12 weeks after bendamustine, 2 weeks for other chemotherapies, 7 days for corticosteroids or lenalidomide, and 5 half-lives for targeted agents (such as BTK inhibitors, venetoclax...) [131]. These measures aim to optimize T-cell collection and ensure CAR T-cell efficacy. The role and impact of BT has been studied mainly in patients who received CART cells in third line and available data suggest that BT is generally safe, with minimal mortality or toxicity [127,128,132]. Better disease control limits high-grade CRS/ICANs rates, or immune effector

Table 2

CAR T-cell therapy ineligibility criteria.

NO GO	SLOW GO
❖ PS 4** ❖ Loss of autonomy ❖ Severe organ failure* ❖ Decompensated organ failure* ❖ Active/uncontrolled infection ❖ Dementia/ severe cognitive impairment	✓ PS 2-3 ** ✓ Age over 80 years old ✓ Patient that would be unable to undergo intensive care: to be discussed on a case-by-case basis with the intensive care unit ✓ Moderate organ failure* ✓ Rapidly progressive disease

* To be evaluated in collaboration with the CAR T-cell center on a case by case basis

** Altered performance status linked to disease symptoms does not formally exclude patients

cell-associated hematotoxicity (ICAH) at day 30 or day 180 [127,128,132–134]. However, the ORR to BT is low, between 20 % and 45 % after chemotherapy [126,128,133] and 65 % after radiation therapy [128]. No significant differences in disease response, progression-free survival (PFS), or overall survival (OS) have been observed between BT and no-BT groups in multivariate analyses or after propensity score matching, nor across different BT types [127,130,132,135]. However, achieving a complete or partial response with BT has been associated with better outcomes [122,128,133]. Whether this favorable prognosis is the effect of BT itself or reflects a more treatment-sensitive disease is currently unknown.

Expert point of view:

- HT should be avoided whenever possible, by improving the referral process and reducing both brain-to-vein and vein-to-vein times (expert recommendations).
- BT is indicated to control rapidly progressive disease during manufacturing, but current evidence is insufficient to retain BT as a way to improve post-CAR-T outcome (efficacy and toxicity) (IVB).
- Bendamustine should be avoided as holding therapy due to its deleterious impact on T-cell fitness. Adequate washout before leukapheresis and infusion is recommended: 12 weeks for bendamustine, 2 weeks for other chemotherapies, 7 days for corticosteroids/lenalidomide, and 5 half-lives for other agents (targeted therapies).

1.19. Treatment of CAR T-ineligible patients

CAR T-ineligible patients represent a substantial proportion of patients that are under-represented in clinical trials but carry poor outcome in the real life setting when CAR T-cell therapy appears to be infeasible. Generally, we propose either less intensive chemo-immunotherapy regimens, clinical trials or best supportive care to these patients (Fig. 2B, Supplementary table 4).

1.20. Bispecific antibodies

Bispecific antibodies (BiAbs) associated to chemotherapy or targeted molecules will be an option when available. The European Commission and the China Commission has granted marketing authorisation for glofitamab in combination with gemcitabine and oxaliplatin for the treatment of adult patients with refractory or relapsed diffuse large unspecified B-cell lymphoma (LBCL NOS) who are ineligible for autologous stem cell transplantation (ASCT) based on the STARGLO phase III study [136,137]. Recent landmark analysis has demonstrated that an estimated 82.4 % of patients reaching CR at EOT would remain disease free 12 months after EOT [138].

1.21. Expert point of view

- For patients with chemo-sensitive diseases (late relapse), standard chemo-immunotherapy with good safety profile should be considered
- Glofitamab-GemOx can be proposed for CAR T/ASCT-ineligible patients (IA)

4) Management of LBCL ≥ 3 L

Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy was approved in 2018 for third-line (3 L) therapy of LBCL, producing durable remissions in around 30–40 % of patients [112,113,125,139–141] (Figure 3). The recent approval of these cellular therapies in the second-line setting has left two primary options in the third line, including – if not received in second line- CAR-T cells or BiAbs. For T cell engager (ie, CAR Tcells or BiAbs)-ineligible patients, a few combinations of immuno-targeted therapies could be available.

1.22. CAR T-cell therapy eligible patients

In France, two anti-CD19 CAR T products are currently available in the third line (if not received in second line): axi-cel [112], and tisa-gencleleucel (tisa-cel) [124]. In the absence of current reimbursement in European countries in 3L+, the third approved CAR T-cell product, liso-cel, will not be discussed any further.

Axi-cel offers significant improvement in PFS and OS when compared to tisa-cel [126,142]. However, it is associated with a higher occurrence and severity of cytokine release syndrome (CRS), neurotoxicity (immune effector cell associated neurotoxicity syndrome, ICANS) and cytopenia (immune effector cell-associated haematotoxicity, ICAHT) as compared with tisa-cel [142,143]. In this view, tisa-cel may be favored for older and frailer patients, or those with preexisting neurological disease, given its more favorable safety profile.

CAR T-cells have demonstrated greater efficacy in terms of CR and PFS than BiAbs, although with an increased incidence of adverse events, even when limiting BiAb cohorts to non-CAR T-experienced patients [144]. Discrepancies between patients' profiles among the respective trials cannot be ruled out.

Expert point of view:

- In the third or later-line, CAR T-cells (Axi-cel and Tisa-cel) are the preferred 3rd-line treatment option for CAR-T naïve patients (IIA).
- Axi-cel offers improved overall survival over tisa-cel, but with a higher risk of toxicity (IVA).

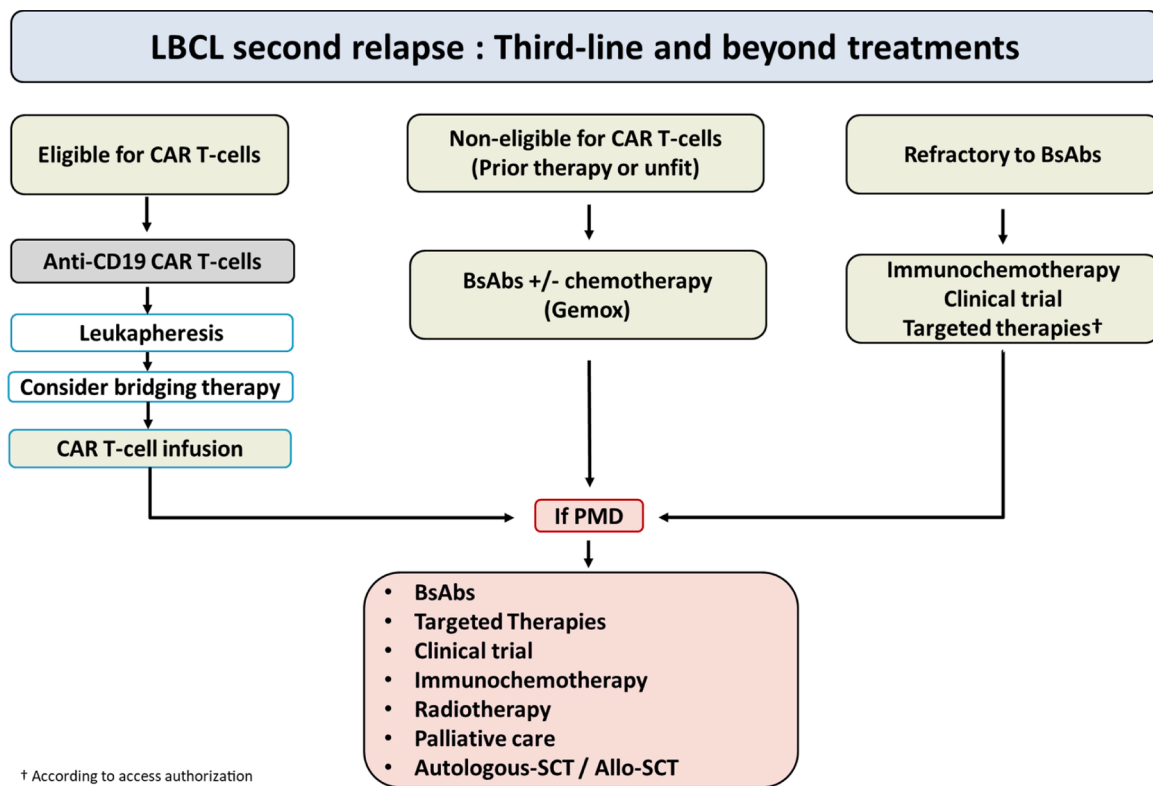


Fig. 3. Management of third-line treatment for large B-cell lymphoma. Abbreviations: Allo-SCT: Allogeneic Stem Cell Transplantation; BsAbs: Bispecific monoclonal antibody; CAR T-cells: chimeric antigen receptor T cells; LBCL: large B-cell lymphoma; PMD, Progression metabolic response.

1.23. CAR T-cell therapy-ineligible patients

For patients who are not eligible for CAR T-cells (unfit for or in relapse or refractory post CAR T-cells), several BiAbs have been approved and recently established as the preferred therapeutic class in the third line setting. In particular, the antiCD20xCD3 antibodies epcoritamab and glofitamab have been approved based on efficacy data reported in phase 2 trials [145–149]. Odronektamab is a third antiCD20xCD3 bispecific that has shown a similar rate of response, and is approved by the EMA [150]. In both trials, most CRs were reached at the time of first evaluation performed by PET-CT after 2 cycles, and duration of response was highly correlated to the quality of response (CR versus PR versus SD). These data suggest that in the absence of a complete response or at least a partial response after the second cycle, continuation of treatment should be considered based on the clinical benefit obtained. Of note, tumor flare reactions can be observed within the first few days of therapy. While high-grade CRS and ICANS can occur with bispecifics, the rate of these complications remains low (<10 %) in comparison to CAR T-cells [151], and multiple mitigation strategies are recommended in this setting (eg, Dexamethasone in premedication -before BiAbs infusion- or in prophylaxis -after BiAbs infusion- is preferred over other steroids) [145–147,152,153]. The choice should be made based on the rhythm of administration, treatment duration and patient preference.

Expert point of view:

- Bispecific antibodies are the preferred third-line treatment for patients who are ineligible for CAR T-cell therapy, in monotherapy (IIIC) or with chemotherapy (GemOx) (IA).
- The use of dexamethasone is recommended for the premedication and/or prophylaxis of CRS and ICANS during treatment with bispecific antibodies (IIIA).

1.24. For patients failing T-cell engagers (CAR T-cells / BiAbs)

For patients who relapse after CAR T-cells and/or BiAbs (i.e. in the fourth line setting), there are no standard recommended options and enrollment in a clinical trial (CT) is preferred whenever possible. Salvage regimens should be adapted to age, performance status, comorbidities, prior lines of therapy and disease presentation. Several options, such as Polatuzumab-vedotin-BR, Loncastuximab tesirine, or Tafasitamab and lenalidomide combinations are EMA/FDA approved [154,155]. More recently, Brentuximab-Vedotin associated to Lenalidomide and Rituximab demonstrated superiority in terms of OS over R² [156]. Other targeted therapy combinations have shown clinical activity and can be considered. Both chemo-free regimen IR² [157] (ibrutinib, lenalidomide and rituximab) and ViPOR [86] (venetoclax, ibrutinib, prednisone, obinutuzumab and lenalidomide) regimens showed significant ORR rates (47 % and 54 %, respectively), with manageable safety profiles. However, these combinations are not approved yet and have not been evaluated after CAR-T cell or BiAb. For patients who remain chemo-sensitive (i.e. late relapse), classic immunochemotherapy based salvage regimens can also be proposed [158–161] and the place of ASCT in patients who received CAR-T in second line or third line and who would respond to chemotherapy in fourth line, could be discussed.

Last but not least, allogeneic stem cell transplantation could be considered as a treatment modality for fit adults without major comorbid conditions whose disease can be controlled with emerging treatment modalities [162].

Expert point of view:

For patients relapsing after CAR T-cells and bispecific antibodies, enrollment in a clinical trial is preferred when possible (IVA).

5) Particular situations

1.25. Frail patients

Frailty refers to a patient's comorbidity or condition that might

impair the tolerance of anti-tumoral treatment. The recommendations are summarized in Table 3.

Table 3
Therapeutics adaptation for frail patients.

Condition	Recommendation	Findings
Elderly (> 80 years or < 80 and frail)	- To use a prephase treatment with corticosteroids and/or vincristine and/or rituximab [165,175,176]- To perform a geriatric evaluation after prephase [165]- To treat with R-miniCHOP [165,176,177]- To avoid CNS involvement screening and prophylaxis- To treat with CAR T cell therapy after a careful multidisciplinary evaluation [178]- To adapt Methotrexate dose as a function of the plasmatic level at 24 h of the administration (refer to Supplementary table 5)	Lin et al., 2022: prospective pilot, Rituximab prephase, 5-year OS 81 % Oberic et al., 2021: phase 3, Vincristine prephase, R-miniCHOP x 6, 2-years OS 66 % Peyrade et al., 2011: phase 2, R-miniCHOP x 6, 2-years OS 59 % Peyrade et al. 2017: Phase 2, Vincristine prephase, O-miniCHOP x6, 2-y OS 65 % Menez et al., 2024: retrospective, CD19 CAR T cell, mOS 12.7 months
Cardiac dysfunction (left ventricle ejection fraction < 50 %)	To replace R-CHOP with one of these regimens: - R-GEMOX: rituximab, gemcitabine and oxaliplatin[179]- R-COMP: non-pegylated liposomal doxorubicin instead of doxorubicin [180]- R-GCVP: gemcitabine instead of doxorubicin [181]- R-CEOP: etoposide instead of doxorubicin [182] - R-Bendamustine [183]	Shen et al., 2018: phase 2, R-GEMOX x 6, 3-y OS 65 % Luminari et al., 2010: phase 2, R-COMP x 6, 3-y OS 72 % Fields et al., 2014: phase 2, R-GCVP x 6, 2-y OS 56 % Moccia et al., 2021: retrospective, R-CEOP, 5-y OS 47 % Storti et al., 2018: phase 2, R-Bendamustine x 4–6, 2-y OS 51 %
Hemodialysis[184]	- Drugs to be administered after hemodialysis: bendamustine, carboplatin (AUC x 25), cisplatin (50 % reduction), cyclophosphamide (25 % reduction), doxorubicin, oxaliplatin (30 % dose reduction), vincristine- Drugs to be administered before hemodialysis: cytarabine (4–5 h), gemcitabine (6–12 h)- Drugs to be administered either before or after hemodialysis: etoposide (50 % dose reduction), rituximab- To start with 100 mg/m ² and adapt Methotrexate dose as a function of the plasmatic level at 24 h of the administration (refer to supplementary table 5)	Yasuda et al. 2021: review of the literature based on cases series.
Obesity (BMI > 30 kg/m²)	- To cap vincristine at 2 mg [171,185]- No dose limitation for other chemotherapy agents' for BSA> 2 sqm[185,186]	Griggs et al., 2021: ASCO guidelines based on literature review.Weis et al., 2020: retrospective study, 41 % grade 2 + neuropathy with vincristine 2 mg/m² vs 84 % when uncapped. Chan et al., 2016: retrospective, no increased incidence of toxicity with uncapped R-CHOP (except for vincristine).

1.25.1. Elderly (>80y.o., >75y.o. with comorbidities)

LBCL in elderly patients are characterized by more aggressive features including a higher prevalence of the ABC subtype [163,164], MYD88 mutations, higher association with EBV and display more extra-nodal involvement and a higher IPI score.

IPI and/or aa-IPI are usable in LBCL patients > 80 years old. However, several dedicated scoring systems presented in Table 4 have been proposed that outperform IPI / aa-IPI. When performed, geriatric assessment should take place after a prephase based on corticosteroids and vincristine [165]. R-miniCHOP is the preferred regimen for patients older than 80 years, or unfit patients under 80 years [165]. No CNS prophylaxis is recommended [166].

1.25.2. Cardiac dysfunction

The use of anthracyclines should be avoided for patients with cardiac dysfunction (LVEF < 50 %), and alternative regimens listed in the Table 3 should be preferred to R-CHOP. For patients with a cardiac condition and preserved cardiac function, we recommend close monitoring with echocardiographic imaging and, if available, to refer patients to a cardio-oncologist [167].

1.25.3. Renal insufficiency

In case of altered renal function, R-CHOP regimen and oxaliplatin based protocols are safe and do not need adaptation [168]. For patients

Table 4
Selected prognostic scoring systems dedicated to elderly patients with DLBCL in first line.

Reference	Items included in the score	Median age (y)	Training/ external validation (n)	Filed of application
SENIOR-IPI [187] (Dubois et al, 2024)	- number of years over 80 years old - number of aaIPI predictors - LDH> 3 N - albumin < 35 g/LWith weighting coefficients	83	396/140	Age > 80 y Eligible for R-chemo
Geriatric Prognostic Index [188] (Isaksen et al, 2023)	- ADL- CCI- GNRI- Age > 85 y	76	365/193	DLBCL≥ 70 y.o. Eligible for R-CHOP or R-miniCHOP, Outperforms IPI, R-IPI, NCCN-IPI
Simplified Geriatric Assessment [189] (Merli et al, 2021)	- sGA- ADL- IADL- CIRS-G- IPI- Hemoglobin level	76	1065/328	1st line and palliative care Can be performed in 10 min by hematologist
GETALMO index [190] (Pardal et al, 2018)	- Age- R-IPI- CIRS	83	252 (205 treated with R-chemo)	1st line R-CHOP based
ACA index [191] (Miura et al, 2017)	- Age- Albuminemia- CCL	75	836	Age > 65 years1st line R-CHOP based
MNA [192] (Soubeyran et al, 2012)	- Sex- Localized/ advanced stage- Time Get-up/go, cutoff 20 s	77.5	348 (including 105 NHL)	Risk of death at 6 months after treatment

Abbreviations: aa-IPI age-adjusted international prognosis index, LDH lactate dehydrogenase, ADL activities of daily living, CCL Charlson comorbidity index, GNRI geriatric nutritional risk index, IPI international prognosis index, R-IPI revised international prognosis index, NCCN-IPI national comprehensive cancer network international prognosis index, sGA simplified geriatric assessment, IADL instrumental activities of daily living, CIRS-G cumulative illness rating scale-geriatric, MNA mini-nutritional assessment.

undergoing hemodialysis, there are few studies and mostly case series about dosing and schedule of chemotherapy, reviewed by Yasuda and colleagues in 2021, Table 4 [169]. Methotrexate (MTX) prophylaxis should be avoided for mild impairment. In curative intent, methotrexate can be adapted as a function of the degree of renal insufficiency and the plasmatic level 24 h after infusion as proposed in Supplementary table 5. Bendamustine-based lymphodepletion could be used for patients with impaired renal function, without clear impact on CAR T-cell expansion and toxicities.

1.26. Obesity

Drug metabolism and distribution may be different in obese patients and traditionally chemotherapy used to be capped for a body surface area of 2m². With the increased incidence of obesity, data has emerged regarding the suboptimal treatment of obese patients [170]. In 2021, the American Society of Clinical Oncology guidelines recommended using full weight-based cytotoxic chemotherapy doses [171], except for vincristine [172].

1.27. T-cell engager immunotherapies (CAR T-cells / BiAbs) in R/R frail patients

Data regarding the safety of novel therapeutics in this patient population are emerging. In phase 2 studies, glofitamab was given up to 90 years old [173], and epcoritamab up to 83 years [174]. In both studies, age had no impact on response but infectious toxicities should be closely monitored.

There are few data concerning elderly patients treated by CAR T-cells. Phase 2 and 3 trials of axicabtagene ciloleucel and tisagenlecleucel included patients up to 80 years and age did not appear to be a risk for failure [193–195]. Lisocabtagene maraleucel has a remarkable safety profile and the phase 2 study included patients up to 86 years old. Case series of selected patients treated in the SOC showed encouraging outcomes in the population of patients > 80 years [196].

Expert point of view:

- A geriatric evaluation should be recommended for elderly patients if available (IIB), after a prephase (IB).
- R-miniCHOP is recommended after 80 years (IB).
- Anthracycline-free regimen and optimization of cardiologic treatment are recommended in case of impaired cardiac function (IIIB).
- We recommend not to limit drug dosing for obese patients, except for vincristine (IVB).
- In case of altered renal function, R-CHOP regimen and oxaliplatin based protocols are safe and do not need adaptation (IVB).
- No definitive age threshold should apply to elderly patients regarding T-cell engager agents and CAR T-cells (IIIB).

1.28. Testicular lymphomas

For patients with localized (I-II) testicular LBCLs, a sequence of 6 R-CHOP-21 is the preferred option.

Testicular lymphoma represents a subgroup of DLBCLs with a known high risk of CNS recurrence, for which there is definite consensus on CNS prophylaxis, which is considered mandatory. The efficacy of HD-MTX depends on drug dose: doses at 1.5–3 g/m² result in tumoricidal levels in the brain parenchyma and cerebrospinal fluid.

However, IV prophylaxis (ie HD-MTX) but not IT (ie intrathecal) improved survival without reducing the risk of CNS relapse in a retrospective series patients with testicular lymphoma, with or without rituximab [197]. Although liposomal cytarabine may optimize the IT chemotherapy in IELSG 30 (compared to IT-MTX), the compound was permanently withdrawn from the market because of persistent manufacturing process problems.

For all these reasons, in testicular lymphoma, CNS-prophylaxis is

based on 2 Cycles of HD-MTX after R-CHOP completion [198].

We opted for a total of 2 cycles of MTX at a dose of 3g/m². We considered this approach safe and well tolerated, while also maintaining a good balance between risk and benefit.

Notably, the administration HD-MTX was planned at the end of chemoimmunotherapy to prevent an adverse impact of MTX toxicity on the regular and complete delivery of the R-CHOP program.

Consolidative testicular radiation therapy (30–30.6 Gy/15–17 fractions with a testosterone level check before starting treatment) of the contralateral testicle at the end of treatment is strongly recommended to reduce the risk of local relapse [198,199]. The benefit of consolidation radiotherapy to involved inferior diaphragmatic nodes in stage II is not demonstrated.

For patients with disseminated disease (stage III or IV), we lack evidence to propose a different therapeutic strategy than in localized disease. The treatment should then rely on 6 cycles of R-CHOP, 2 cycles of HD-MTX, and consolidative contralateral testicular radiation therapy should be proposed.

Expert point of view:

For stage 1 or 2 primary testicular lymphomas:

- R-CHOP for 6 cycles should be used in primary testis lymphoma in 1st line (IIA).
- Add 2 cycles of HD-MTX 3g/m² (CNS prophylaxis) after R-CHOP completion (IIA).
- No IT prophylaxis is recommended.
- Contralateral testis radiotherapy is strongly recommended (IA).

For stage III or IV primary testicular lymphoma:

1.29. Same therapeutic strategy than stage 1–2 PTL (IIIB)

1.29.1. Secondary CNS lymphoma (SCNSL)

SCNSL refers to systemic LBCL disseminated in CNS compartment at diagnosis or relapse. SCNSL is a rare but aggressive presentation and is associated with a shorter OS. It affects about 4–6 % of LBCL patients [200–202].

At initial presentation.

Knowledge of CNS localization at diagnosis is crucial as most of 1st line chemotherapy molecules do not cross the blood brain barrier (BBB). Association of R-CHOP-HD-MTX for 6 cycles has shown good results [203–206]. R-CHOP alone can be proposed for the 1st cycle, depending on the clinical presentation, to limit toxicity. An anthracycline-free, but potentially more toxic regimen such as MATRix-R-ICE [207] can be used. Consolidation with aged-adapted Thiotepa-based conditioning regimen followed by ASCT should be proposed to all fit patients until 65–70 years old who obtained a complete response (CR) after immunochemotherapy. For patients reaching a PR, a CR should be achieved whenever possible with a salvage regimen prior intensification (R-DHAC, R-ICE) (Figure 4).

(Figure 4). Autologous stem cell transplantation is feasible in selected patients over 70 years of age, provided they are carefully assessed for comorbidities and functional status [208].

Expert point of view:

- R-CHOP-HD-MTX for 6 cycles should be used in LBCL with CNS localization in 1st line (IVB).
- Eligible patients should benefit from ASCT-consolidation (IVB).

1.29.2. At relapse/progression

SCNSL is a rare but aggressive disease, for which relapse occurs frequently, with a poor prognosis. At relapse, SCNSL can be isolated or associated with systematic relapse and usually occurs in the few months after diagnosis (early relapses) suggesting occult disease at diagnosis [209].

For isolated CNS relapses, HD-MTX based therapies (such as R-MPV

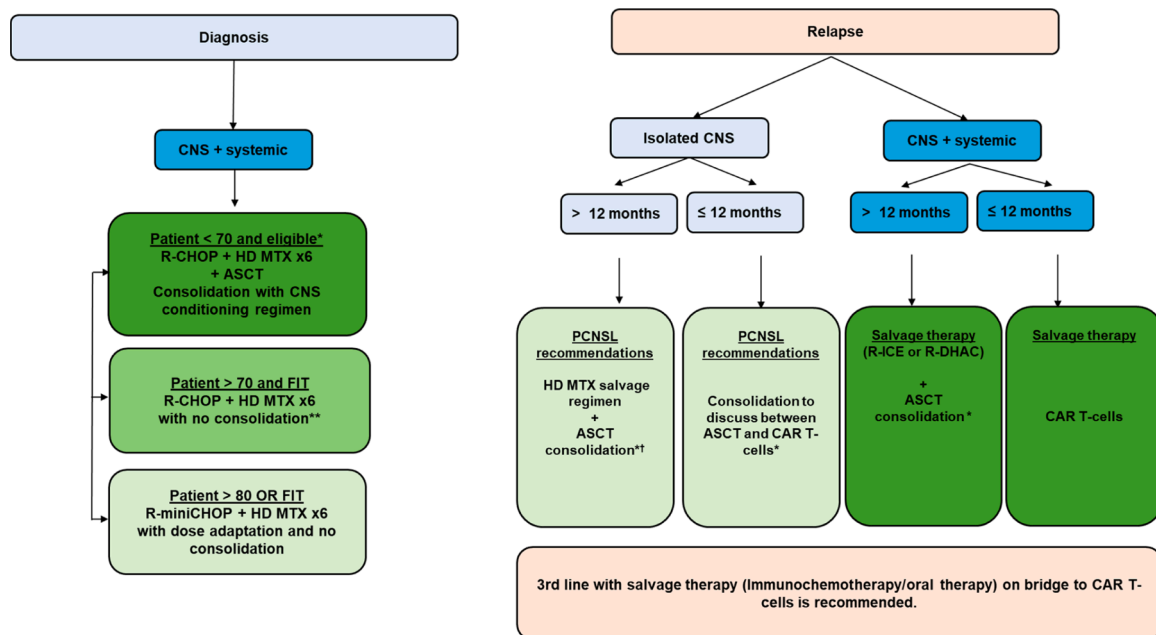


Fig. 4. Management of secondary central nervous system lymphoma - Adapted from LOC guidelines. * Eligible patients for ASCT consolidation: no prior ASCT in frontline, PS= 0–1, good renal and cardiac functions, CSP collect, thiotepa-based conditioning regimen eligible. ** ASCT consolidation is feasible in selected > 70 y.o. patients (age-adjusted thiotepa-based intensive regimen). † For isolated CNS relapses in patients under 60 years of age, low-dose radiotherapy (23.4 Gy) may be considered in cases achieving complete remission and ineligible for ASCT. Abbreviations: ASCT: Autologous stem cell transplantation; CAR T-cells: chimeric antigen receptor T cells; CNS: central nervous system; HD: High dose; MTX: methotrexate; PCNSL: Primary central nervous system lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, delivered every 21 days; R-Cyta: rituximab- cytarabine; R-DHAC: rituximab, dexamethasone, cytarabine, oxaliplatin; R-ICE: rituximab, ifosfamide, carboplatin,etoposide.

or MATRix) [210,211], with intensive consolidation with ASCT are the best options for eligible patients. For patients under 60 years of age, low-dose radiotherapy (23.4 Gy) may be considered for consolidation after achieving complete remission, if deemed ineligible for ASCT.

For concomitant systemic and CNS relapse, combination of drugs with CNS and systemic diffusion (eg R-ICE, R-DHAX or MATRix-R-ICE) as a bridge to CAR T-cells (relapse < 12 months) or ASCT (>12 m after 1 L) seems to be the best option for eligible patients. For those with a later relapse (> 12 months), the recommended consolidation is thiotepa-based (dosing is to be age-adjusted) ASCT for eligible patients

For ineligible patients for intensive therapy, immunochemotherapy with HD-MTX could be proposed if possible, or oral therapies. Due to poor prognosis, best supportive care can also be considered as a valuable option. First available data [212] show CNS diffusion of bispecific antibodies with potential clinical efficacy. These data are promising for patients in relapse or who cannot benefit from therapeutic intensification. Intrathecal chemotherapy has not shown significant benefit in this situation.

Expert point of view:

- Isolated CNS relapses should be treated like PCNSL (IIB).
- In case of chemo-sensitive disease, consolidation with ASCT is the preferred option.
- Chemorefractory SCNSL associated with systemic relapse should benefit from novel approaches (ie CAR T-cells) adapted to the time of relapse (IICG).

1.30. High Grade B Cell lymphoma (HGBL)

HGBL often present aggressive features, with high IPI and frequent CNS involvement and an adverse prognosis when exhibiting a MYC/BCL2 rearrangement. The two recent histological classifications underline the importance of MYC FISH testing theoretically for any diagnosis of LBCL-NOS, which, if positive, should be followed by the analysis of

BCL2 and BCL6.

First-line treatment with R-CHOP yields inferior outcomes in HGBL (double/triple hit) than in LBCL-NOS [213]. However, the administration of more intensive treatments (including first-line intensification with autologous stem cell transplantation) remains controversial due to significant toxicity and unproven clinical benefit [214]. Based on a phase 2 trial and real-world setting reports, we recommend a first-line treatment with either R-CHOP or Da-EPOCH-R for patients with disseminated HGBL (double/triple hit) [213,215–217]. In limited stage, R-CHOP treatment may be sufficient [218].

Due to the high risk of relapse, response to immunochemotherapy should be closely monitored (iPET required). In relapsed or refractory diseases, CD19 CAR T-cell therapy appears to be a promising option, potentially able to overcome the poor prognosis of HGBL [219].

Expert point of view:

- Patients with HGBL-DH MYC/BCL2 or HGBL-TH should be treated with either R-CHOP (IA) (or DA EPOCH-R if eligible) and response to immunotherapy should be closely monitored (IIB).
- In case of relapse, treatment with CAR-T cell should be proposed (IVA).

1.31. Lymphoma treatment for HIV infected patients

Lymphomas are the second leading cause of death during HIV infection and multidisciplinary management is recommended. Treatment is based on the combination of effective antiretroviral (ARV) treatment and optimal hematological care. The most important point is to treat HIV positive patients as HIV negative patients and to consider the infection as a comorbidity [220,221].

ARV treatment must be initiated or optimized as soon as the lymphoma is diagnosed to allow for rapid control of HIV replication, with close monitoring. Interactions between ARV treatment and chemotherapy must be anticipated, and ARV treatment must be adapted if

necessary (drug dosages) [222].

As for other LBCL patients, FDG/PET is the reference for staging and response assessment. Of note, opportunistic infections or lymphoid hyperplasia lesions linked to active HIV replication can cause false positives.

- Standard R-CHOP is recommended as 1st line treatment. In patients with $CD4 < 50/mm^3$, the addition of rituximab is associated with excess infectious mortality without a gain in survival. For these patients, CHOP is recommended but addition of rituximab can be discussed in the absence of active opportunistic infection and if good control of the HIV infection is thought to be rapidly obtained [223].
- EBV-positive PCNSL in very immunocompromised subjects ($CD4 < 100/mm^3$, non-controlled HIV infection or recent HIV diagnosis) should be treated by prioritizing immune reconstitution through ARV treatment. Mono-chemotherapy with methotrexate is probably sufficient, but can potentially be associated to rituximab.
- PCNSL in subjects with well-controlled HIV infection and EBV-negative PCNSL should be treated as in HIV-negative patients.

Persistence of contrast enhancement in MRI after treatment is common and should not systematically lead to salvage therapy [224].

The use of cell therapies or T-cell engagers, whether ASCT, axi-cel or liso-cel or bispecific antibodies, is possible [225].

Systematic monitoring of the CMV viral load should be proposed for patients with $CD4 < 100/mm^3$. Secondary neurological disorders are more frequent. There is no consensus on the indications for an initial CSF study; these must be broad. The indications and modalities of prophylaxis for a neurological relapse are the same as for patients without HIV infection.

Expert point of view:

- The patient's prognosis is associated with the control of his HIV infection. Adjustment of ARV treatment in conjunction with the infectiologist/pharmacist is essential (IIB).
- There is no systematic recommendation for CNS initial evaluation and prophylaxis in HIV-positive patients but it should be performed as for immunocompetent patients (IVB).
- In 1st line, R-CHOP is the reference treatment (IIA), except for patients with $CD4 < 50/mm^3$ (IIA) without rapidly expected infectious disease control (Rituximab will be omitted).
- EBV+ PCNSL treatment is based on immune reconstitution thanks to ARV, with HD-MTX alone if necessary (IIIA).

1.32. Chronic lymphocytic leukemia (CLL) aggressive transformation: richter transformation

LBCL is the most common histology of Richter Transformation (RT) (2–10 % of cases) [226–228]. Pathological examination, ideally performed from an excisional biopsy, is necessary to exclude differential diagnoses [229]. Note that Richter-like transformations have been reported in patients who have temporarily interrupted ibrutinib [230].

The outcome of patients with RT-LBCL is dismal, with median OS generally shorter than 12 months. RT-DLCBL is generally clonally related to the underlying CLL (85 % of cases), which is associated with shorter survival. It is therefore of the utmost importance to determine clonal relationship through *IGHV* locus sequencing obtained from RT-LBCL tissue and CLL cells. Indeed, together with *TP53* alterations, clonal relation guides therapeutic decisions.

In a prospective trial, the R-CHOP21 regimen only yielded a low 7 % CR rate. For patients with clonally related RT-DLBCL, enrollment in clinical trials remains the recommended option [231].

Immunotherapies have recently shown encouraging results in phase 2 studies such as immune checkpoint inhibitors in combination with iBTK or iBLC2, or bispecific T-cell engagers [173, 174].

In relapse setting, a retrospective series of patients treated with anti-

CD19 CAR T-cells, show a 63 % ORR, with 46 % achieving CR [232].

Despite promising advances, overall survival remains poor and transplantation strategies should be considered in eligible patients with limited subsequent options, according to the risk of relapse [233,234].

Despite promising advances, overall survival remains poor and allogeneic stem cell transplantation [234,235] strategies should be considered in eligible patients with limited subsequent options, according to the risk of relapse.

On the other hand, patients with clonally unrelated RT-DLBCL have a good prognosis and their management should be similar to those with *de novo* LBCL.

Expert point of view:

- Clonal relationship based on the comparison of *IGHV* sequences in CLL vs Richter tissue is highly recommended to tailor the treatment.
- Frontline management of RT-LBCL should consider enrollment into clinical trials for clonally related RT.
- R-CHOP21 is the option by default but evaluation and collective decision for use of off-label drug should be discussed given the poor prognosis after standard chemotherapy.
- CAR T-Cells (for refractory or relapse within 12 months after the completion of first line RT-LBCL patients), and allogeneic stem cell transplantation (for all R/R RT-LBCL patients) are interesting and potent options (IVB).

1.33. Other transformed indolent lymphomas

Histological transformation of follicular lymphoma (tFL) occurs in 10–70 % of patients over time, with a risk of 1–2 % per year in the rituximab era [236]. A new biopsy should be performed whenever a clinical or radiological transformation is suspected [237]. In onset (at diagnosis or after a period of watch and wait), the first-line treatment is the same as that of *de novo* aIPI ≥ 1 LBCL with R-CHOP-like immunochemotherapy [238]. Prognosis seems to be better for patients who experienced the transformation before any therapy for FL [239].

In relapse situation, after a first line of treatment for FL, we recommend a salvage therapy with immuno-chemotherapy (R-CHOP for patients not treated with anthracyclines in 1st line, or R-DHA-X/R-ICE for others). Consolidation with ASCT could be discussed for eligible patients already exposed to anthracyclines and with a relapse > 12 months. For early relapse, CAR T-cell eligibility must be discussed in the same way as LBCL with excellent results [240].

Subsequent relapses should, if possible, benefit from histological documentation to demonstrate whether or not they have transformed and to adapt therapeutic options. In cases of transformed relapses, the same options should be offered as for LBCL, notably BiAbs, that have shown interesting results in these patients [241].

Expert point of view:

- A new biopsy should be performed whenever a clinical or radiological transformation is suspected (IA).
- Histological transformation of non-Hodgkin lymphoma leads to modify treatments strategies, patient with HT could earlier benefit of CAR T-cells or BiAbs (IIIA).

1.34. Intravascular large B-cell lymphoma (IVLBCL)

IVLBCL is a rare and aggressive subtype of LBCL, characterized by the selective growth of malignant B cells within small- to medium-sized blood vessels. It typically affects elderly patients and frequently presents with extranodal localizations, most notably the central nervous system (≈ 30 % of cases), the lungs, and the skin [242]. The disease is associated with an unfavorable prognosis. Rituximab, although a key component of therapy, can induce severe infusion reactions, which may be reduced by delaying its administration until 2–3–7 days after the first cycle of chemotherapy [243,244]. Given the elevated risk of CNS involvement,

intensified regimens have been explored. A phase 2 study that combined intrathecal treatment and high-dose methotrexate (2 cycles) with an R-CHOP backbone (6 cycles) reported encouraging outcomes with a low incidence (3 %) of secondary CNS involvement [245].

1.35. T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)

THRLBCL is a rare and aggressive variant of diffuse large B-cell lymphoma, characterised by predominance of reactive T cells and histiocytes over malignant B cells. It predominantly affects middle-aged individuals and often presents with advanced-stage disease involving extranodal sites such as the spleen, liver, and bone marrow. Histologically, it is distinguished by a paucity of neoplastic B cells amidst a dense infiltrate of reactive T cells and histiocytes. This unique microenvironment poses significant challenges for immunotherapies. Subset of cases of THRLBCL are known to transform from nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) [246]. Standard treatments, including chemotherapy regimens like R-CHOP, have demonstrated limited efficacy [247]. Recent studies have explored the use of CAR-T therapy in THRLBCL with a 2-year overall survival rate of 42 % and a progression-free survival rate of 29 % [248,249]. However, these outcomes are less favorable compared to other LBCL subtypes.

CRediT authorship contribution statement

Pierre Sesques: Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization; Guillaume Manson: Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization; Sydney Dubois: : Writing – original draft, Validation, Supervision; Francois Xavier Gros: : Writing – original draft, Validation, Supervision; Gabriel Brisou: : Writing – original draft, Validation, Supervision; Clémentine Sarkozy: : Writing – original draft, Validation, Supervision; Sophie Bernard: : Writing – original draft, Validation, Supervision; Estelle Bourbon: Writing, Validation; Luc Matthieu Fornecker: Writing, Validation; Eric Durot: Writing, Validation; Laurent Martin: Writing, Validation; Catherine Chassagne-Clément: Writing, Validation; Francisco Llamas Gutierrez: Writing, Validation; Charlotte Strykh: Writing, Validation; Marie-Hélène Delfau-Larue: Writing, Validation; Salim Kanoun: Writing, Validation; Laetitia Vercellino: Writing, Validation; Caroline Bodet-Milin: Writing, Validation; Haifa Bahri: Writing, Validation; Jules Zhang Yin: Writing, Validation; Arthur Dony: Writing, Validation; Laure Lebras: Writing, Validation; Marlène Ochmann: Writing, Validation; Marine Baron: Writing, Validation; Hélène Monjanel: Writing, Validation; Ronan Le Calloch: Writing, Validation; Fabien Claves: Writing, Validation; Youlia Kirova: Writing, Validation; Christian Gisselbrecht: Writing, Validation; Stéphanie Guidez: Writing, Validation; Jean Baptiste Bossard: Writing, Validation; Roberta Di Blasi: Writing, Validation; Caroline Delette: Writing, Validation; Ludovic Fouillet: Writing, Validation; Maryem Rhomdani: Writing, Validation; Maya Belhadj: Writing, Validation; Gilles Crochet: Writing, Validation; Sandy Amorim: Writing, Validation; Firas Safa: Writing, Validation; Laurianne Drieu La Rochelle: Writing, Validation; Julie Abraham: Writing, Validation; Fabrice Jardin: Writing, Validation; Robin Noel: Writing, Validation; Sébastien Bailly: Writing, Validation; Loïc Renaud: Writing, Validation; Yann Guillermin: Writing, Validation; Baptiste Delapierre: Writing, Validation; Sylvain Choquet: Writing, Validation; Louise Roulin: Writing, Validation; Sylvain Lamure: Writing, Validation; Lionel Galicier: Writing, Validation; Yassine Al Tabaa: Writing, Validation; Carole Soussain: Writing, Validation; Romain Guizèze: Writing, Validation; Roch Houot: Writing, Validation; Benoit Tessoulin: Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization

Funding statement

This manuscript did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

PS has received honoraria from AbbVie, BMS, Chugai, Janssen, Kite/Gilead, Novartis and Roche.

GM received honoraria from Abbvie, Takeda, Kite-Gilead, Roche, Novartis, BMS

BT received honoraria from Abbvie, BMS, Lilly, Kite/Gilead and Incyte; travel accommodation from Kite/Gilead, Roche, Abbvie, Incyte.

SD has received honoraria from Takeda and Abbvie.

LV has received honoraria from Janssen, Takeda, BMS, Beigene and AbbVie

JBB has received honoraria from Abbvie, Gilead, Janssen and Takeda

LGL received honoraria from Recordati: Kite/Gilead, acted as consultant for Pixilib and Genmab; received hospitality from MSD France, Siemens Healthcare and Sanofi Aventis.

R.H. has received honoraria from Sanofi, Kite/Gilead, research grant from Novartis, Bristol-Myers Squibb/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, Abbvie, and travel accommodation from Janssen, Roche, Pfizer, and is a member on an entity's Board of Directors or advisory committees of Kite/Gilead and Sanofi, Novartis, Eusapharma, Sanofi, Lilly, Bristol-Myers Squibb/Celgene, Tessa Therapeutics, Abbvie and Roche.

All remaining authors have declared no conflicts of interest.

Acknowledgments

The authors thank Roch Houot, Catherine Thieblemont, Franck Morschhauser and Emmanuel Bachy who reviewed this manuscript for the LYSA Scientific Committee.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116070.

References

- [1] Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trnány M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. 27 janv N Engl J Med 2022;386(4):351–63.
- [2] Schünemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso-Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE – a statement by the GRADE guidance group. 1 juill J Clin Epidemiol 2023;159:79–84.
- [3] Gonçalves M de C, de Oliveira CRGCM, Sandes AF, Rodrigues CA, Novis Y, Viana PCC, et al. Core needle biopsy in lymphoma diagnosis: the diagnostic performance and the role of the multidisciplinary approach in the optimization of results. Am J Surg Pathol 1 janv 2023;47(1):111–23.
- [4] Krarup Sigaard R, Wennervaldt K, Munksgaard L, Rahbek Gjerdrum LM, Homøe P. Core needle biopsy is an inferior tool for diagnosing cervical lymphoma compared to lymph node excision. Acta Oncol Stock Swed juill 2021;60(7): 904–10.
- [5] Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol J Eur Soc Med Oncol sept 2015;26 (5):v116–25.
- [6] Chaganti S, Illidge T, Barrington S, Mckay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol juill 2016;174(1):43–56.
- [7] Strykh C, Chaouat C, Poullot E, Amara N, Fatacccioli V, Parrens M, et al. Lymph node excisions provide more precise lymphoma diagnoses than core biopsies: a French Lymphopath network survey. Blood 15 Déc 2022;140(24):2573–83.
- [8] Caraway NP. Evolving role of FNA biopsy in diagnosing lymphoma: past, present, and future (juill) Cancer Cytopathol 2015;123(7):389–93.
- [9] Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. 1 août J Clin Oncol J Am Soc Clin Oncol 2004;22(15): 3046–52.

- [10] Laurent C, Baron M, Amara N, Haioun C, Dandoit M, Maynadié M, et al. Impact of Expert Pathologic Review of Lymphoma Diagnosis: Study of Patients From the French Lymphopath Network. *J Clin Oncol J Am Soc Clin Oncol* 20 juin 2017;35(18):2008–17.
- [11] Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. 15 Blood sept 2022;140(11):1229–53.
- [12] Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB de O, Berti E, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: lymphoid neoplasms (juill) *Leukemia* 2022;36(7):1720–48.
- [13] Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. 15 Blood sept 2022;(11):1229–53. 140.
- [14] Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. 19 août Proc Natl Acad Sci USA 2003;100(17):9991–6.
- [15] Scott DW, Wright GW, Williams PM, Lih CJ, Walsh W, Jaffe ES, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood* 20 Févr 2014;123(8):1214–7.
- [16] Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 1 janv 2004;103(1):275–82.
- [17] Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, Wang JQ, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. 12 avr N Engl J Med 2018;378(15):1396–407.
- [18] Chapuy B, Stewart C, Dunford AJ, Kim J, Kamburov A, Redd RA, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med* mai 2018;24(5):679–90.
- [19] Wright GW, Huang DW, Phelan JD, Coulbaly A, Roulland S, Young RM, et al. A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. 13 avr Cancer Cell 2020;37(4):551–568.e14.
- [20] Lacy SE, Barrans SL, Beer PA, Painter D, Smith AG, Roman E, et al. Targeted sequencing in DLBCL, molecular subtypes, and outcomes: a Haematological Malignancy Research Network report. 14 mai Blood 2020;135(20):1759–71.
- [21] Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol J Am Soc Clin Oncol* 1 oct 2012;30(28):3452–9.
- [22] Staiger AM, Ziepert M, Horn H, Scott DW, Barth TFE, Bernd HW, et al. Clinical Impact of the Cell-of-Origin Classification and the MYC/ BCL2 Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group. 1 août J Clin Oncol J Am Soc Clin Oncol 2017;35(22):2515–26.
- [23] Meriranta L, Pasanen A, Alkopsi A, Haukka J, Karjalainen-Lindsberg ML, Leppä S. Molecular background delineates outcome of double protein expressor diffuse large B-cell lymphoma. 11 août Blood Adv 2020;4(15):3742–53.
- [24] Alduaij W, Collinge B, Ben-Neriah S, Jiang A, Hilton LK, Boyle M, et al. Molecular determinants of clinical outcomes in a real-world diffuse large B-cell lymphoma population. 18 mai Blood 2023;141(20):2493–507.
- [25] Davies AJ. The high-grade B-cell lymphomas: double hit and more. 19 déc Blood 2024;144(25):2583–92.
- [26] Rosenwald A, Bens S, Advani R, Barrans S, Copie-Bergman C, Elsensohn MH, et al. Prognostic Significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: a study by the lungenburg lymphoma biomarker consortium. 10 déc J Clin Oncol J Am Soc Clin Oncol 2019;37(35):3359–68.
- [27] Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol* sept 2014;166(6):891–901.
- [28] Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. 9 oct Blood 2014;124(15):2354–61.
- [29] Kurtz DM, Scherer F, Jin MC, Soo J, Craig AFM, Esfahani MS, et al. Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma. *J Clin Oncol J Am Soc Clin Oncol* 1 oct 2018;36(28):2845–53.
- [30] International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. 30 sept N Engl J Med 1993;329(14):987–94.
- [31] International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. 30 sept N Engl J Med 1993;329(14):987–94.
- [32] Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPi) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* 6 Févr 2014;123(6):837–42.
- [33] Ruppert AS, Dixon JG, Salles G, Wall A, Cunningham D, Poeschel V, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. 4 juin Blood 2020;135(23):2041–8.
- [34] Advani RH, Chen H, Habermann TM, Morrison VA, Weller EA, Fisher RI, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPi). *Br J Haematol* oct 2010;151(2):143–51.
- [35] Jelacic J, Juul-Jensen K, Bukumiric Z, Runeson Simonsen M, Kragh Jørgensen RR, Roost Clausen M, et al. Validation of prognostic models in elderly patients with diffuse large B-cell lymphoma in a real-world nationwide population-based study - development of a clinical nomogram. *Ann Hematol* janv 2025;104(1):433–44.
- [36] Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubreau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. *août J Nucl Med Publ Soc Nucl Med* 2013;54(8):1244–50.
- [37] Khan AB, Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, Morris T, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. 4 juill Blood 2013;122(1):61–7.
- [38] Adams HJA, Kwee TC, de Keizer B, Fijnheer R, de Klerk JMH, Nievelstein RAJ. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* mars 2014;41(3):565–74.
- [39] Sehn LH, Scott DW, Chhanabhai M, Berry B, Ruskova A, Berkahn L, et al. Impact of concordant and discordant bone marrow involvement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol J Am Soc Clin Oncol* 10 avr 2011;29(11):1452–7.
- [40] Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *J Clin Oncol J Am Soc Clin Oncol* 10 sept 2016;34(26):3150–6.
- [41] Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruner G, Yuen K, et al. Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. févr Ann Oncol J Eur Soc Med Oncol 2008;19(2):233–41.
- [42] Villa D, Connors JM, Sehn LH, Gascoyne RD, Savage KJ. Diffuse large B-cell lymphoma with involvement of the kidney: outcome and risk of central nervous system relapse. *Haematol* juill 2011;96(7):1002–7.
- [43] Kim YR, Kim JS, Min YH, Hyunyon D, Shin HJ, Mun YC, et al. Prognostic factors in primary diffuse large B-cell lymphoma of adrenal gland treated with rituximab-CHOP chemotherapy from the Consortium for Improving Survival of Lymphoma (CISL). 13 août J Hematol Oncol J Hematol Oncol 2012;5:49.
- [44] Kridel R, Telio D, Villa D, Sehn LH, Gerrie AS, Shenker T, et al. Diffuse large B-cell lymphoma with testicular involvement: outcome and risk of CNS relapse in the rituximab era. *Br J Haematol* janv 2017;176(2):210–21.
- [45] El-Galaly TC, Villa D, Michaelsen TY, Hutchings M, Mikhaeel NG, Savage KJ, et al. The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An international multicenter study of 1532 patients treated with chemoimmunotherapy. *Eur J Cancer Oxf Engl* 1990 avr 2017;75:195–203.
- [46] Murawski N, Held G, Ziepert M, Kempf B, Viardot A, Hänel M, et al. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. 31 juill Blood 2014;124(5):720–8.
- [47] Lee GW, Go SI, Kim SH, Hong J, Kim YR, Oh S, et al. Clinical outcome and prognosis of patients with primary sinonasal tract diffuse large B-cell lymphoma treated with rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy: a study by the Consortium for Improving Survival of Lymphoma (avr) *Leuk Lymphoma* 2015;56(4):1020–6.
- [48] Wilson WH, Bromberg JEC, Stetler-Stevenson M, Steinberg SM, Martin-Martin L, Muñiz C, et al. Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt lymphoma. *Haematol* juill 2014;99(7):1228–35.
- [49] Gu J, Huang X, Zhang Y, Bao C, Zhou Z, Tong H, et al. Cerebrospinal fluid IL-6 and IL-10 as promising diagnostic and therapeutic prognostic biomarkers for secondary central nervous system lymphoma. 22 nov BMC Cancer 2024;24(1):1443.
- [50] Song Y, Zhang W, Zhang L, Wu W, Zhang Y, Han X, et al. Cerebrospinal Fluid IL-10 and IL-10/IL-6 as Accurate Diagnostic Biomarkers for Primary Central Nervous System Large B-cell Lymphoma. 7 déc Sci Rep 2016;6:38671.
- [51] Mutter JA, Alig SK, Esfahani MS, Lauer EM, Mitschke J, Kurtz DM, et al. Circulating Tumor DNA Profiling for Detection, Risk Stratification, and Classification of Brain Lymphomas. *J Clin Oncol J Am Soc Clin Oncol* 20 mars 2023;41(9):1684–94.
- [52] Olszewski AJ, Chorzalska AD, Petersen M, Olila TA, Zayac A, Kurt H, et al. Detection of clonotypic DNA in the cerebrospinal fluid as a marker of central nervous system invasion in lymphoma. 28 déc Blood Adv 2021;5(24):5525–35.
- [53] Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol J Am Soc Clin Oncol* 20 sept 2014;32(27):3048–58.
- [54] Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, Avivi I, et al. 18F-FDG avidity in lymphoma readdressed: a study of 766 patients (janv) *J Nucl Med Publ Soc Nucl Med* 2010;51(1):25–30.
- [55] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol J Am Soc Clin Oncol* 20 sept 2014;32(27):3059–68.
- [56] Le Goull S, Ghesquière H, Oberic L, Morschhauser F, Tilly H, Ribrag V, et al. Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase 3 study by LYSA. 29 avr Blood 2021;137(17):2307–20.

- [57] Itti E, Blanc-Durand P, Berriolo-Riedinger A, Kanoun S, Kraeber-Bodéré F, Meignan M, et al. Validation of the Δ SUVmax for Interim PET Interpretation in Diffuse Large B-Cell Lymphoma on the Basis of the GAINED Clinical Trial. *J Nucl Med Publ Soc Nucl Med* Nov 2023;64(11):1706–11.
- [58] Mikhaeel NG, Smith D, Dunn JT, Phillips M, Møller H, Fields PA, et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. *Eur J Nucl Med Mol Imaging* juill 2016;43(7):1209–19.
- [59] Ngeow JYY, Quek RHH, Ng DCE, Hee SW, Tao M, Lim LC, et al. High SUV uptake on FDG-PET/CT predicts for an aggressive B-cell lymphoma in a prospective study of primary FDG-PET/CT staging in lymphoma. *Ann Oncol J Eur Soc Med Oncol sept 2009;20(9):1543–7*.
- [60] Boellaard R, Buvat I, Nioche C, Ceriani L, Cottreau AS, Guerra L, et al. International Benchmark for Total Metabolic Tumor Volume Measurement in Baseline 18F-FDG PET/CT of Lymphoma Patients: A Milestone Toward Clinical Implementation. 3 sept *J Nucl Med Publ Soc Nucl Med* 2024;65(9):1343–8.
- [61] Thieblemont C, Chartier L, Dührsen U, Vitolo U, Barrington SF, Zaucha JM, et al. A tumor volume and performance status model to predict outcome before treatment in diffuse large B-cell lymphoma. 13 déc *Blood Adv* 2022;6(23):5995–6004.
- [62] Cottreau AS, Meignan M, Nioche C, Capobianco N, Clerc J, Chartier L, et al. Risk stratification in diffuse large B-cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT. *Ann Oncol J Eur Soc Med Oncol mars 2021;32(3):404–11*.
- [63] Eertink JJ, van de Brug T, Wiegiers SE, Zwezerijnen GJC, Pfaehler EAG, Lugtenburg PJ, et al. 18F-FDG PET baseline radiomics features improve the prediction of treatment outcome in diffuse large B-cell lymphoma. *févr Eur J Nucl Med Mol Imaging* 2022;49(3):932–42.
- [64] Lin C, Itti E, Haïoun C, Petegnief Y, Luciani A, Dupuis J, et al. Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. *J Nucl Med Publ Soc Nucl Med Oct 2007; 48(10):1626–32*.
- [65] Casasnovas RO, Meignan M, Berriolo-Riedinger A, Bardet S, Julian A, Thieblemont C, et al. SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. 7 juill *Blood* 2011;118(1):37–43.
- [66] Rekowski J, Hüttmann A, Schmitz C, Müller SP, Kurch L, Kotzerke J, et al. Interim PET Evaluation in Diffuse Large B-Cell Lymphoma Using Published Recommendations: Comparison of the Deauville 5-Point Scale and the Δ SUVmax Method. *J Nucl Med Publ Soc Nucl Med janv 2021;62(1):37–42*.
- [67] Burggraaf CN, Eertink JJ, Lugtenburg PJ, Hoekstra OS, Arens AIJ, de Keizer B, et al. 18F-FDG PET Improves Baseline Clinical Predictors of Response in Diffuse Large B-Cell Lymphoma: The HOVON-84 Study. *J Nucl Med Publ Soc Nucl Med juill 2022;63(7):1001–7*.
- [68] Eertink JJ, Burggraaf CN, Heymans MW, Dührsen U, Hüttmann A, Schmitz C, et al. Optimal timing and criteria of interim PET in DLBCL: a comparative study of 1692 patients. 11 mai *Blood Adv* 2021;5(9):2375–84.
- [69] Meignan M, Gallamini A, Itti E, Barrington S, Haïoun C, Polliack A. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. *Leuk Lymphoma oct 2012;53(10):1876–81*.
- [70] Kostakoglu L, Martelli M, Sehn LH, Belada D, Carella AM, Chua N, et al. End-of-treatment PET/CT predicts PFS and OS in DLBCL after first-line treatment: results from GOYA. 9 mars *Blood Adv* 2021;5(5):1283–90.
- [71] Suh KJ, Kim KH, Kim R, Byun JM, Kim M, Park JH, et al. Costs and clinical outcomes of patients with diffuse large B-cell lymphoma in first remission: role of PET/CT surveillance (juill) *Korean J Intern Med* 2019;34(4):894–901.
- [72] Avivi I, Zilberlicht A, Dann EJ, Leiba R, Faibish T, Rowe JM, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *Am J Hematol mai 2013;88(5):400–5*.
- [73] El-Galaly TC, Jakobsen LH, Hutchings M, de Nully Brown P, Nilsson-Ehle H, Székely E, et al. Routine Imaging for Diffuse Large B-Cell Lymphoma in First Complete Remission Does Not Improve Post-Treatment Survival: A Danish-Swedish Population-Based Study. 1 déc *J Clin Oncol J Am Soc Clin Oncol* 2015;33(34):3993–8.
- [74] Locke FL, Oluwole OO, Kuruvilla J, Thieblemont C, Morschhauser F, Salles G, et al. Axicabtagene ciloleucel vs standard of care in second-line large B-cell lymphoma: outcomes by metabolic tumor volume. 13 juin *Blood* 2024;143(24):2464–73.
- [75] Dean EA, Mhaskar RS, Lu H, Mousa MS, Krivenko GS, Lazaryan A, et al. High metabolic tumor volume is associated with decreased efficacy of axicabtagene ciloleucel in large B-cell lymphoma. 28 juill *Blood Adv* 2020;4(14):3268–76.
- [76] Vercellino L, Di Blasi R, Kanoun S, Tessoulin B, Rossi C, D'Aveni-Piney M, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. 24 nov *Blood Adv* 2020;4(22):5607–15.
- [77] Bailly C, Carlier T, Tessoulin B, Gastinne T, Kraeber-Bodere F, Le Gouill S, et al. Prognostic value of FDG-PET/CT response for patient selection before chimeric antigen receptor-T-cells therapy in non-Hodgkin lymphoma. *Hematol Oncol oct 2022;40(4):796–800*.
- [78] Galtier J, Vercellino L, Chartier L, Olivier P, Tabouret-Viaud C, Mesguich C, et al. Positron emission tomography-imaging assessment for guiding strategy in patients with relapsed/refractory large B-cell lymphoma receiving CAR T cells. *Haematol 1 janv 2023;108(1):171–80*.
- [79] Sesques P, Tordo J, Ferrant E, Safar V, Wallet F, Dhompas A, et al. Prognostic Impact of 18F-FDG PET/CT in Patients With Aggressive B-Cell Lymphoma Treated With Anti-CD19 Chimeric Antigen Receptor T Cells. 1 août *Clin Nucl Med* 2021;46(8):627–34.
- [80] Kuhn A, Roddie C, Kirkwood AA, Menne T, Cuadrado M, Marzolini MAV, et al. Early FDG-PET response predicts CAR-T failure in large B-cell lymphoma. 11 janv *Blood Adv* 2022;6(1):321–6.
- [81] Breen WG, Young JR, Hathcock MA, Kowalchuk RO, Thorpe MP, Bansal R, et al. Metabolic PET/CT analysis of aggressive Non-Hodgkin lymphoma prior to Axicabtagene Ciloleucel CAR-T infusion: predictors of progressive disease, survival, and toxicity. 18 août *Blood Cancer J* 2023;13(1):127.
- [82] Al Zaki A, Feng L, Watson G, Ahmed SA, Mistry H, Nastoupil LJ, et al. Day 30 SUVmax predicts progression in patients with lymphoma achieving PR/SD after CAR T-cell therapy. 10 mai *Blood Adv* 2022;6(9):2867–71.
- [83] Cohen D, Luttwak E, Beyar-Katz O, Hazut Krauthammer S, Bar-On Y, Amit O, et al. 18F]FDG PET-CT in patients with DLBCL treated with CAR-T cell therapy: a practical approach of reporting pre- and post-treatment studies. *févr Eur J Nucl Med Mol Imaging* 2022;49(3):953–62.
- [84] Vercellino L, Betterli S, Blanc E, de Kerviler E, Cristinelli C, Merlet P, et al. Patterns of metabolic response in patients receiving commercial CAR T-cells for relapsing/refractory aggressive B cells lymphoma. 1 nov *Br J Radio* 2024;97(1163):1755–64.
- [85] de Boer JW, Pennings ERA, Kleinjan A, van Doesum JA, Spanjaart AM, Mutsaers PGJ, et al. Inflammatory reactions mimic residual or recurrent lymphoma on [18F]FDG-PET/CT after CD19-directed CAR T-cell therapy. 14 nov *Blood Adv* 2023;7(21):6710–6.
- [86] Persky DO, Unger JM, Spier CM, Stea B, LeBlanc M, McCarty MJ, et al. Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014. 10 mai *J Clin Oncol* 2008;26(14):2258–63.
- [87] Poeschel V, Held G, Ziepert M, Witzens-Harig M, Holte H, Thurner L, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet DéC* 2019;394(10216):2271–81.
- [88] Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. 11 janv *Blood* 2018;131(2):174–81.
- [89] Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. 11 janv *Blood* 2018;131(2):174–81.
- [90] Bologna S, Vander Borcht T, Briere J, Ribrag V, Damaj GL, Thieblemont C, et al. EARLY POSITRON EMISSION TOMOGRAPHY RESPONSE-ADAPTED TREATMENT IN LOCALIZED DIFFUSE LARGE B-CELL LYMPHOMA (AAPI=0): RESULTS OF THE PHASE 3 LYSA LNH 09–1B TRIAL (juin) *Hematol Oncol* 2021; 39(S2).
- [91] Persky DO, Li H, Stephens DM, Park SI, Bartlett NL, Swinnen LJ, et al. Positron Emission Tomography-Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001. 10 sept *J Clin Oncol* 2020;38(26):3003–11.
- [92] Sehn LH, Scott DW, Villa D, Gerrie AS, Freeman CL, Aquino Parsons C, et al. Long-Term Follow-up of a PET-Guided Approach to Treatment of Limited-Stage Diffuse Large B-Cell Lymphoma (DLBCL) in British Columbia (BC). 13 nov *Blood* 2019; 134(ement 1):401.
- [93] Récher C, Coiffier B, Haïoun C, Molina TJ, Fermé C, Casasnovas O, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial (nov) *Lancet* 2011;378(9806):1858–67.
- [94] Delarue R, Tilly H, Mounier N, Petrella T, Salles G, Thieblemont C, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial (mai) *Lancet Oncol* 2013;14(6):525–33.
- [95] Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. 25 mai *Lancet Lond Engl* 2013;381(9880):1817–26.
- [96] Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N Engl J Med janv 2022;386(4):351–63*.
- [97] Lewis KL, Jakobsen LH, Villa D, Smedby KE, Savage KJ, Eyre TA, et al. High-Dose Methotrexate as CNS Prophylaxis in High-Risk Aggressive B-Cell Lymphoma. 10 déc *J Clin Oncol* 2023;41(35):5376–87.
- [98] Ong SY, De Mel S, Grigoropoulos NF, Chen Y, Tan YC, Tan MSY, et al. High-dose methotrexate is effective for prevention of isolated CNS relapse in diffuse large B cell lymphoma. 12 août *Blood Cancer J* 2021;11(8):143.
- [99] Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. *N Engl J Med [Internet]. 3 mars 2021 [cité 23 avr 2021]; Disponible sur: <https://www.nejm-org.proxy.insermbiblio.inist.fr/doi/10.1056/NEJMra2027612>*.
- [100] Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. 14 déc *N Engl J Med* 2021;0(0).
- [101] Bock AM, Mwangi R, Wang Y, Khurana A, Maurer MJ, Ayers A, et al. Defining primary refractory large B-cell lymphoma. 26 juin *Blood Adv* 2024;8(13):3402–15.
- [102] Maurer MJ, Ghesquières H, Jais JP, Witzig TE, Haïoun C, Thompson CA, et al. Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related

- Outcome in Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy. 1 avr J Clin Oncol 2014;32(10):1066–73.
- [103] Westin J, Sehn LH. CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift?. 5 mai Blood 2022;139(18):2737–46.
- [104] Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trnny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study (Janv) Bone Marrow Transpl 2016;51(1):51–7.
- [105] Shadman M, Pasquini M, Ahn KW, Chen Y, Turtle CJ, Hematti P, et al. Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission. Blood 3 mars 2022;139(9):1330–9.
- [106] Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trnny M, et al. Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era. 20 sept J Clin Oncol 2010;28(27):4184–90.
- [107] Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. 17 févr N Engl J Med 2022;386(7):640–54.
- [108] Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. 13 juill N Engl J Med 2023;389(2):148–57.
- [109] Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of phase 3 TRANSFORM study. 21 déc Blood 2022. 21 déc.
- [110] Houot R, Bachy E, Cartron G, Gros FX, Morschhauser F, Oberic L, et al. Axicabtagene ciloleucel in large B cell lymphoma ineligible for autologous stem cell transplantation: the phase 2 ALCANTER trial. 14 sept Nat Med 2023;1–9. 14 sept.
- [111] Sehgal A, Hoda D, Riedell PA, Ghosh N, Hamadani M, Hildebrandt GC, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. 1 août Lancet Oncol 2022;23(8):1066–77.
- [112] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. 28 déc N Engl J Med 2017;377(26):2531–44.
- [113] Schuster S.J., Bishop M.R., Tam C.S., Waller E.K., Borchmann P., McGuirk J.P., et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med [Internet]. 1 déc 2018 [cité 15 janv 2021]; Disponible sur: <https://www.nejm-org.proxy.insermbiblio.inist.fr/doi/10.1056/NEJMoa1804980>.
- [114] Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. 6 avr Blood 2023;141(14):1675–84.
- [115] Guffroy B, Bachy E, Di Blasi R, Guedon H, Le Bras F, Yakoub-Agha I, et al. A Real-World Weighted Comparison of Tisagenlecleucel and Axicabtagene Ciloleucel CAR T Cells in Relapsed or Refractory Diffuse Large B Cell Lymphoma Aged 75 Years and Older: A Lysa Study from the Descar-T Registry. 5 nov Blood 2024;144(ement 1):3129.
- [116] Ghilardi G, Chong EA, Svoboda J, Wohlfarth P, Nasta SD, Williamson S, et al. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. 1 sept Ann Oncol 2022;33(9):916–28.
- [117] Ong SY, Pak S, Mei M, Wang Y, Popplewell L, Baird JH, et al. Bendamustine lymphodepletion is a well-tolerated alternative to fludarabine and cyclophosphamide lymphodepletion for axicabtagene ciloleucel therapy for aggressive B-cell lymphoma. Am J Hematol 2023;98(11):1751–61.
- [118] Lickefett B., Chu L., Ortiz-Maldonado V., Warmuth L., Barba P., Doglio M., et al. Lymphodepletion – an essential but undervalued part of the chimeric antigen receptor T-cell therapy cycle. Front Immunol [Internet]. 22 déc 2023 [cité 17 sept 2024];14. Disponible sur: <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1303935/full>.
- [119] Locke FL, Hu ZH, Siddiqi T, Jacobson CA, Nikiforow S, Ahmed S, et al. Real-World Impact of Time from Leukapheresis to Infusion (Vein-to-Vein Time) in Patients with Relapsed or Refractory (r/r) Large B-Cell Lymphoma (LBCL) Treated with Axicabtagene Ciloleucel. 15 nov Blood 2022;140(ement 1):7512–5.
- [120] Ghobadi A, Munoz J, Westin JR, Locke FL, Miklos DB, Rapoport AP, et al. Outcomes of subsequent antilymphoma therapies after second-line axicabtagene ciloleucel or standard of care in ZUMA-7. 11 juill Blood Adv 2024;8(11):2982–90.
- [121] Dahiya S, Spiegel JY, Lee D, Mohammed T, Lutfi F, Goyal A, et al. Second-Line Chimeric Antigen Receptor T Cell Therapy (CAR-T) As Standard of Care for Relapsed-Refractory Large B-Cell Lymphoma (LBCL). 2 nov Blood 2023;142(ement 1):4876.
- [122] Bücklein V, Perez A, Rejeski K, Iacoboni G, Jurinovic V, Holtick U, et al. Inferior Outcomes of EU Versus US Patients Treated With CD19 CAR-T for Relapsed/Refractory Large B-cell Lymphoma: Association With Differences in Tumor Burden, Systemic Inflammation, Bridging Therapy Utilization, and CAR-T Product Use. 11 juill HemaSphere 2023;7(8):e907.
- [123] Iacoboni G, Navarro V, Martín-López AA, Rejeski K, Kwon M, Jalowicz KA, et al. Recent Bendamustine Treatment Before Apheresis Has a Negative Impact on Outcomes in Patients With Large B-Cell Lymphoma Receiving Chimeric Antigen Receptor T-Cell Therapy. 10 janv J Clin Oncol J Am Soc Clin Oncol 2024;42(2):205–17.
- [124] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 3 janv 2019;380(1):45–56.
- [125] Abramson, Palomba JS, Gordon LI ML, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. 19 sept Lancet 2020;396(10254):839–52.
- [126] Bachy E, Le Guill S, Di Blasi R, Sesques P, Manson G, Cartron G, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med oct 2022;28(10):2145–54.
- [127] Jain MD, Jacobs MT, Gao F, Nastoupil LJ, Spiegel JY, Lin Y, et al. Bridging therapy with axicabtagene ciloleucel for large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. 27 févr Blood Adv 2024;8(4):1042–50.
- [128] Roddie C, Neill L, Osborne W, Iyengar S, Tholouli E, Irvine D, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. 16 juill Blood Adv 2023;7(12):2872–83.
- [129] Cook M. Real-World Evidence in the United States (US) of the Impact of Bridging Therapy Prior to Axicabtagene Ciloleucel (Axi-Cel) for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma (R/R LBCL). In ASH: 2023 [cité 1 déc 2024]. Disponible sur: <https://ash.confex.com/ash/2023/webprogram/Paper175034.html>.
- [130] Paillasa J, Vercellino L, Di Blasi R, Bernard S, Moatti H, Bommier C, et al. Impact of Bridging Chemotherapy on Clinical Outcomes of CD19 CAR T Therapy in Relapse/Refractory Diffuse Large B-Cell Lymphoma in Real World Experience. 13 nov Blood 2019;134(ement 1):2886.
- [131] Qayed M, McGuirk JP, Myers GD, Parameswaran V, Waller EK, Holman P, et al. Leukapheresis guidance and best practices for optimal chimeric antigen receptor T-cell manufacturing. Cytotherapy Sept 2022;24(9):869–78.
- [132] Lutfi F, Holtzman NG, Kansagra AJ, Mustafa Ali M, Bukhari A, Yan J, et al. The impact of bridging therapy prior to CD19-directed chimeric antigen receptor T-cell therapy in patients with large B-cell lymphoma. Br J Haematol 2021;195(3):405–12.
- [133] Khurana A, Hathcock M, Bansal R, Wang Y, Paludo J, Villasboas JC, et al. Response to Bridging Therapy As a Predictor of Outcomes for Chimeric Antigen Receptor Therapy in Large B-Cell Lymphoma. 5 nov Blood 2021;138(ement 1):3841.
- [134] Sesques P, Kirkwood AA, Kwon M, Rejeski K, Jain MD, Di Blasi R, et al. Novel prognostic scoring systems for severe CRS and ICANS after anti-CD19 CAR T cells in large B-cell lymphoma. 6 août J Hematol Oncol J Hematol Oncol 2024;17(1):61.
- [135] Muñoz J, Hu ZH, Kanters S, Limbrick-Oldfield EH, Miao H, Spooner C, et al. Real-World Bridging Therapy (BT) of Patients with Relapsed or Refractory (r/r) Large B-Cell Lymphoma (LBCL) Treated with Chimeric Antigen Receptor (CAR) T-Cell Therapy: A Systematic Literature Review (SLR) and Meta-Analysis. 15 nov Blood 2022;140(ement 1):4627–9.
- [136] Abramson JS, Ku M, Hertzberg M, Huang HQ, Fox CP, Zhang H, et al. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. 16 nov Lancet Lond Engl 2024;404(10466):1940–54.
- [137] Brody JD, Jørgensen J, Belada D, Costello R, Trněný M, Vitolo U, et al. Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial. 10 avr Blood 2025;145(15):1621–31.
- [138] Abramson JS, Ku M, Hertzberg M, Fox CP, Herbaux C, Huang H, et al. 76 | GLOFITAMAB PLUS GEMCITABINE AND OXALIPLATIN (Glofit-GemOx) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): 2-YEAR FOLLOW-UP OF STARGLO. Hematol Oncol 2025; 43(S3). e76.70093.
- [139] Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. 1 janv Lancet Oncol 2019;20(1):31–42.
- [140] Schuster SJ, Tam CS, Borchmann P, Worel N, McGuirk JP, Holte H, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. 1 oct Lancet Oncol 2021;22(10):1403–15.
- [141] Abramson JS, Palomba ML, Gordon LI, Lunning M, Wang M, Arnason J, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. Blood 1 Févr 2024;143(5):404–16.
- [142] Gauthier J, Gazeau N, Hirayama AV, Hill JA, Wu V, Cearley A, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. 30 juill Blood 2022;139(26):3722–31.
- [143] Rejeski K, Jain MD, Shah NN, Perales MA, Subklewe M. Immune effector cell-associated haematotoxicity after CAR T-cell therapy: from mechanism to management (juin) Lancet Haematol 2024;11(6):e459–70.
- [144] Kim J, Cho J, Lee MH, Yoon SE, Kim WS, Kim SJ. CAR T cells vs bispecific antibody as third- or later-line large B-cell lymphoma therapy: a meta-analysis. Blood 8 août 2024;144(6):629–38.
- [145] Thieblemont C, Karimi YH, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, et al. Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from the pivotal EPCORE NHL-1 trial. Leuk Déc 2024;38(12):2653–62.
- [146] Song Y.Q., Zhang H.L., Huang H.Q., Zhang Q.Y., Jing H.M., Wang C., et al. Glofitamab monotherapy induces high complete response rates and manageable safety in Chinese patients with heavily pretreated relapsed or refractory diffuse large B-cell lymphoma. Haematologica [Internet]. 19 oct 2023 [cité 4 févr 2025]; Disponible sur: <https://haematologica.org/article/view/haematol.2023.283802>.

- [147] Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. 15 déc N Engl J Med 2022;387(24):2220–31.
- [148] Izutsu K, Kumode T, Yuda J, Nagai H, Mishima Y, Suehiro Y, et al. Subcutaneous epcoritamab monotherapy in Japanese adults with relapsed/refractory diffuse large B-cell lymphoma. *Cancer Sci* Dec 2023;114(12):4643–53.
- [149] Cartron G, Houot R, Al Tabaa Y, Le Bras F, Ysebaert L, Choquet S, et al. Glofitamab in refractory or relapsed diffuse large B cell lymphoma after failing CAR-T cell therapy: a phase 2 LYSA study. 3 avr Nat Cancer 2025.
- [150] Tawfik A, Min Kim T, Cho SG, Jarque I, Iskierka-Jażdżewska E, Poon M, et al. P1115: ODRONEXTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: RESULTS FROM A PRESPECIFIED ANALYSIS OF THE PIVOTAL PHASE 2 STUDY ELM-2. 8 août HemaSphere 2023;7(S3):e50570ac.
- [151] Kim J, Cho J, Lee MH, Yoon SE, Kim WS, Kim SJ. CAR T cells vs bispecific antibody as third- or later-line large B-cell lymphoma therapy: a meta-analysis. *Blood* 8 août 2024;144(6):629–38.
- [152] Falchi L, Hutchings M, Carlo-Stella C, Morschhauser F, Dickinson M, Cartron G, et al. Dexamethasone is associated with reduced frequency and intensity of cytokine release syndrome compared with alternative corticosteroid regimens as premedication for glofitamab in patients with relapsed/refractory large B-cell lymphoma. 1 avr Haematologica 2025;110(4):999–1004.
- [153] Vose JM, Feldman T, Chamuleau MED, Kim WS, Lugtenburg P, Kim TM, et al. Mitigating the Risk of Cytokine Release Syndrome (CRS): Preliminary Results from a DLBCL Cohort of Epcore NHL-1. 2 nov Blood 2023;142(ement 1):1729.
- [154] Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, et al. Polatumumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. 25 janv Blood Adv 2022;6(2):533–43.
- [155] Duell J, Abrisqueta P, Andre M, Gaidano G, Gonzales-Barca E, Jurczak W, et al. Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: final 5-year efficacy and safety findings in the phase II L-MIND study. *Haematol* 31 août 2023;109(2):553–66.
- [156] Bartlett NL, Hahn U, Kim WS, Fleury I, Laribi K, Bergua JM, et al. Brentuximab Vedotin Combination for Relapsed Diffuse Large B-Cell Lymphoma. 20 mars J Clin Oncol J Am Soc Clin Oncol 2025;43(9):1061–72.
- [157] Goy A, Ramchandren R, Ghosh N, Munoz J, Morgan DS, Dang NH, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. 26 sept Blood 2019;134(13):1024–36.
- [158] Moccia AA, Hitz F, Hoskins P, Klasa R, Power MM, Savage KJ, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. 1 févr Leuk Lymphoma 2017;58(2):324–32.
- [159] Barton S, Hawkes EA, Cunningham D, Peckitt C, Chua S, Witherspoon A, et al. Rituximab, Gemcitabine, Cisplatin and Methylprednisolone (R-GEM -P) is an effective regimen in relapsed diffuse large B-cell lymphoma. *Eur J Haematol* mars 2015;94(3):219–26.
- [160] Aussetat G, Maucourt-Boulch D, Rey P, Safar V, Karlin L, Elsensohn MH, et al. Rituximab in combination with adapted-dose of ifosfamide and etoposide as salvage treatment in elderly refractory/relapsed diffuse large B-cell lymphoma patients non-candidate for high dose therapy: a retrospective study. 23 févr Leuk Lymphoma 2022;63(3):599–607.
- [161] Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas RO, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. 1 nov Haematologica 2013;98(11):1726–31.
- [162] Zurko J, Ramdial J, Shadman M, Ahmed S, Szabo A, Iovino L, et al. Allogeneic transplant following CAR T-cell therapy for large B-cell lymphoma. 14 juill Haematologica 2022;108(1):98–109.
- [163] Klapper W, Kreuz M, Kohler CW, Burkhardt B, Szczepanowski M, Salaverria I, et al. Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. 23 févr Blood 2012;119(8):1882–7.
- [164] Mareschal S, Lanic H, Ruminy P, Bastard C, Tilly H, Jardin F. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. *dec Haematologica* 2011;96(12):1888–90.
- [165] Oberic L, Peyrade F, Puyade M, Bonnet C, Dartigues-Cuillères P, Fabiani B, et al. Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older. 10 avr J Clin Oncol J Am Soc Clin Oncol 2021;39(11):1203–13.
- [166] Cabannes-Hamy A, Peyrade F, Jardin F, Emile JF, Delwail V, Mounier N, et al. Central nervous system relapse in patients over 80 years with diffuse large B-cell lymphoma: an analysis of two LYSA studies. *Cancer Med* 2018;7(3):539–48.
- [167] Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart Br Card Soc* juin 2018;104(12):971–7.
- [168] Lignon J, Sibon D, Madelaine I, Brice P, Franchi P, Briere J, et al. Rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX) is an effective and safe salvage regimen in relapsed/refractory B-cell non-Hodgkin lymphoma. *août Clin Lymphoma Myeloma Leuk* 2010;10(4):262–9.
- [169] Yasuda H, Yasuda M, Komatsu N. Chemotherapy for non-Hodgkin lymphoma in the hemodialysis patient: A comprehensive review (juill) *Cancer Sci* 2021;112(7):2607–24.
- [170] Gay C, Delarue R, Milpied N, Oberic L, Coiffier B, Boussetta S, et al. Impact of doxorubicin dose capping on the outcome of DLBCL patients with elevated body surface area. 18 mai Blood 2017;129(20):2811–3.
- [171] Griggs JJ, Bohlke K, Balaban EP, Dignam JJ, Hall ET, Harvey RD, et al. Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update. 20 juin J Clin Oncol J Am Soc Clin Oncol 2021;39(18):2037–48.
- [172] Weis TM, Marini BL, Nachar VR, Brown AM, Phillips TJ, Brown J, et al. Impact of a vincristine dose cap on the incidence of neuropathies with DA-EPOCH-R for the treatment of aggressive lymphomas (mai) *Leuk Lymphoma* 2020;61(5):1126–32.
- [173] Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. 15 déc N Engl J Med 2022;387(24):2220–31.
- [174] Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. 20 avr J Clin Oncol J Am Soc Clin Oncol 2023;41(12):2238–47.
- [175] Lin RJ, Owens CN, Drill E, Iannotta A, Oliveros M, Schick DL, et al. Prephase rituximab/prednisone therapy and aging-related, proinflammatory cytokine milieu in older, vulnerable patients with newly diagnosed diffuse large B-cell lymphoma. *Haematologica* 2022;107(5):1144–52.
- [176] Peyrade F, Bologna S, Delwail V, Emile JF, Pascal L, Fermé C, et al. Combination of ofatumumab and reduced-dose CHOP for diffuse large B-cell lymphomas in patients aged 80 years or older: an open-label, multicentre, single-arm, phase 2 trial from the LYSA group (janv) *Lancet Haematol* 2017;4(1):e46–55.
- [177] Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial (mai) *Lancet Oncol* 2011;12(5):460–8.
- [178] Menez S, Bourbon E, Gounot R, Tudesq JJ, Moya N, Houot R, et al. CAR T-cells in very elderly (≥ 80 years) lymphoma patients: a DESCAR-T analysis. *dec Leuk Lymphoma* 2024;65(13):2048–51.
- [179] Shen QD, Zhu HY, Wang L, Fan L, Liang JH, Cao L, et al. Gemcitabine-oxaliplatin plus rituximab (R-GemOx) as first-line treatment in elderly patients with diffuse large B-cell lymphoma: a single-arm, open-label, phase 2 trial. 1 juin Lancet Haematol 2018;5(6):e261–9.
- [180] Luminari S, Montanini A, Caballero D, Bologna S, Notter M, Dyer MJS, et al. Nonpegylated liposomal doxorubicin (Myocet™) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EUR018 trial. *Ann Oncol J Eur Soc Med Oncol* juill 2010;21(7):1492–9.
- [181] Fields PA, Townsend W, Webb A, Counsell N, Pocock C, Smith P, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. 1 févr J Clin Oncol J Am Soc Clin Oncol 2014;32(4):282–7.
- [182] Moccia AA, Schaff K, Freeman C, Hoskins PJ, Klasa RJ, Savage KJ, et al. Long-term outcomes of R-CEOP show curative potential in patients with DLBCL and a contraindication to anthracyclines. 8 mars Blood Adv 2021;5(5):1483.
- [183] Storti S, Spina M, Pesce EA, Salvi F, Merli M, Ruffini A, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the Fondazione Italiana Linfomi. *août Haematologica* 2018;103(8):1345–50.
- [184] Yasuda H, Yasuda M, Komatsu N. Chemotherapy for non-Hodgkin lymphoma in the hemodialysis patient: A comprehensive review (juill) *Cancer Sci* 2021;112(7):2607–24.
- [185] Weis TM, Marini BL, Nachar VR, Brown AM, Phillips TJ, Brown J, et al. Impact of a vincristine dose cap on the incidence of neuropathies with DA-EPOCH-R for the treatment of aggressive lymphomas (mai) *Leuk Lymphoma* 2020;61(5):1126–32.
- [186] Chan H, Jackson S, McLay J, Knox A, Lee J, Wang S, et al. Obese non-Hodgkin lymphoma patients tolerate full uncapped doses of chemotherapy with no increase in toxicity, and a similar survival to that seen in nonobese patients (nov) *Leuk Lymphoma* 2016;57(11):2584–92.
- [187] Dubois S, Cherblanc F, Belot A, Oberic L, Ghesquieres H, Haioun C, et al. Senior-IP: An Easily Applicable and Meaningful Prognostic Index for First-Line LBCL Patients Older Than 80 Years Treated with Age-Adapted Immunochemotherapy. 5 nov Blood 2024;144:649.
- [188] Isaksen KT, Galleberg R, Mastroianni MA, Rinde M, Rusten LS, Barzenje D, et al. The Geriatric Prognostic Index: a clinical prediction model for survival of older diffuse large B-cell lymphoma patients treated with standard immunochemotherapy. 1 sept Haematologica 2023;108(9):2454–66.
- [189] Merli F, Luminari S, Tucci A, Arcari A, Rigacci L, Hawkes E, et al. Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. 10 avr J Clin Oncol J Am Soc Clin Oncol 2021;39(11):1214–22.
- [190] Pardo E, Díez Baeza E, Salas Q, García T, Sancho JM, Monzón E, et al. A new prognostic model identifies patients aged 80 years and older with diffuse large B-cell lymphoma who may benefit from curative treatment: A multicenter, retrospective analysis by the Spanish GELTAMO group. *Am J Hematol* juill 2018;93(7):867–73.
- [191] Miura K, Konishi J, Miyake T, Makita M, Hojo A, Masaki Y, et al. A Host-Dependent Prognostic Model for Elderly Patients with Diffuse Large B-Cell Lymphoma (mai) *Oncologist* 2017;22(5):554–60.
- [192] Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. 20 mai J Clin Oncol J Am Soc Clin Oncol 2012;30(15):1829–34.

- [193] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med* 3 janv 2019;380(1):45–56.
- [194] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *28 N Engl J Med* 2017;377(26):2531–44.
- [195] Neelapu SS, Jacobson CA, Oluwole OO, Munoz J, Deol A, Miklos DB, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. *4 juin Blood* 2020;135(23):2106–9.
- [196] Menez S, Bourbon E, Gounot R, Tudesq JJ, Moya N, Houot R, et al. CAR T-cells in very elderly (≥ 80 years) lymphoma patients: a DESCAR-T analysis. *Leuk Lymphoma* Dec 2024;65(13):2048–51.
- [197] Mannisto S, Vähämurto P, Pollari M, Clausen MR, Jyrkkö S, Kellokumpu-Lehtinen PL, et al. Intravenous but not intrathecal central nervous system-directed chemotherapy improves survival in patients with testicular diffuse large B-cell lymphoma. *Eur J Cancer Oxf Engl* 1990 juill 1991;115:27–36.
- [198] Conconi A, Chiappella A, Ferreri AJM, Stathis A, Botto B, Sassone M, et al. IELSG30 phase 2 trial: intravenous and intrathecal CNS prophylaxis in primary testicular diffuse large B-cell lymphoma. *26 mars Blood Adv* 2024;8(6):1541–9.
- [199] Ollila TA, Olszewski AJ. Radiation therapy in primary testicular lymphoma: does practice match the standard of care? *Leuk Lymphoma*. Févr 2019;60(2):523–6.
- [200] Boehme V, Zeynalova S, Kloess M, Loeffler M, Kaiser U, Pfreundschuh M, et al. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma—a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). *Ann Oncol J Eur Soc Med Oncol* janv 2007;18(1):149–57.
- [201] Wilson MR, Eyre TA, Martinez-Calle N, Ahearne M, Parsons KE, Preston G, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: an analysis of toxicity and impact on R-CHOP delivery. *11 août Blood Adv* 2020;4(15):3586–93.
- [202] Frontzek F, Renaud L, Dührsen U, Poeschel V, Bernard S, Chartier L, et al. Identification, risk factors, and clinical course of CNS relapse in DLBCL patients across 19 prospective phase 2 and 3 trials—a LYSA and GLA/ DSHNHL collaboration. *Leuk Oct* 2024;38(10):2225–34.
- [203] Damaj G, Ivanoff S, Coso D, Ysaebert L, Choquet S, Houillier C, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. *Haematol Sept* 2015;100(9):1199–206.
- [204] Perry C, Ben Barouch S, Goldschmidt N, Sarid N, Herishanu Y, Shvidel L, et al. Characteristics, management and outcome of DLBCL patients, presenting with simultaneous systemic and CNS disease at diagnosis: A retrospective multicenter study. *Am J Hematol sept* 2019;94(9):992–1001.
- [205] Fleming M, Huang Y, Dotson E, Bond DA, Reneau J, Epperla N, et al. Outcomes of patients with diffuse large B-cell and high-grade B-cell lymphomas with synchronous CNS and systemic involvement at diagnosis treated with high-dose methotrexate and R-CHOP: a single-center retrospective study. *Ther Adv Hematol* 2022;13. 2040620722112900.
- [206] Nijland M, Jansen A, Doorduyn JK, Enting RH, Bromberg JEC, HC Kluin-Nelemans. Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma. *Leuk Lymphoma sept* 2017;58(9):1–6.
- [207] Ferreri AJM, Doorduyn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRIX-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *févr Lancet Haematol* 2021;8(2):e110–21.
- [208] Schorb E, Isbell LK, Kerkhoff A, Mathas S, Braulke F, Egerer G, et al. High-dose chemotherapy and autologous haematopoietic stem-cell transplantation in older, fit patients with primary diffuse large B-cell CNS lymphoma (MARTA): a single-arm, phase 2 trial. *1 mars Lancet Haematol* 2024;11(3):e196–205.
- [209] Qualls D, Abramson JS. Advances in risk assessment and prophylaxis for central nervous system relapse in diffuse large B-cell lymphoma. *Haematol janv* 2019;104(1):25–34.
- [210] Schorb E, Fox CP, Kasenda B, Linton K, Martinez-Calle N, Calimeri T, et al. Induction therapy with the MATRix regimen in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system - an international study of feasibility and efficacy in routine clinical practice. *Br J Haematol juin* 2020;189(5):879–87.
- [211] Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol J Am Soc Clin Oncol* 1 nov 2013;31(31):3971–9.
- [212] Godfrey JK, Gao L, Shouse G, Song JY, Pak S, Lee B, et al. Glofitamab stimulates immune cell infiltration of CNS tumors and induces clinical responses in secondary CNS lymphoma. *25 juill Blood* 2024;144(4):457–61.
- [213] Goyal G, Magnusson T, Wang X, Roose J, Narkhede M, Seymour E. Modern, real-world patterns of care and clinical outcomes among patients with newly diagnosed diffuse large B-cell lymphoma with or without double/triple-hit status in the United States. *1 avr Haematologica* 2023;108(4):1190–5.
- [214] McMillan AK, Phillips EH, Kirkwood AA, Barrans S, Burton C, Rule S, et al. Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3-5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: results of a phase 2 UK NCRI trial. *Ann Oncol J Eur Soc Med Oncol sept* 2020;31(9):1251–9.
- [215] Reagan PM, Davies A. Current treatment of double hit and double expressor lymphoma. *8 déc Hematol Am Soc Hematol Educ Program* 2017;2017(1):295–7.
- [216] Laude MC, Lebras L, Sesques P, Ghesquieres H, Favre S, Bouabdallah K, et al. First-line treatment of double-hit and triple-hit lymphomas: Survival and tolerance data from a retrospective multicenter French study. *1 mars Am J Hematol* 2021;96(3):302–11.
- [217] Dunleavy K, Fanale MA, Abramson JS, Noy A, Caimi PF, Pittaluga S, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. *déc Lancet Haematol* 2018;5(12):e609–17.
- [218] Torka P, Kothari SK, Sundaram S, Li S, Medeiros LJ, Ayers EC, et al. Outcomes of patients with limited-stage aggressive large B-cell lymphoma with high-risk cytogenetics. *28 janv Blood Adv* 2020;4(2):253–62.
- [219] Phina-Ziebin X, Bachy E, Gros FX, Di Blasi R, Herbaux C, Bay JO, et al. Outcome of high-grade B-cell lymphoma compared with other large B-cell lymphoma after CAR-T rescue: a DESCAR-T LYSA study. *19 mai Blood Adv* 2025;9(10):2500–10.
- [220] Besson C, Lancar R, Prevot S, Algarte-Genin M, Delobel P, Bonnet F, et al. Outcomes for HIV-associated diffuse large B-cell lymphoma in the modern combined antiretroviral therapy era. *28 nov AIDS Lond Engl* 2017;31(18):2493–501.
- [221] Hübel K, Bower M, Aurer I, Bastos-Oreiro M, Besson C, Brunnberg U, et al. Human immunodeficiency virus-associated Lymphomas: EHA-ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *HemaSphere sept* 2024;8(9):e150.
- [222] Barta SK, Xue X, Wang D, Tamari R, Lee JY, Mounier N, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. *7 nov Blood* 2013;122(19):3251–62.
- [223] Noy A. Optimizing treatment of HIV-associated lymphoma. *24 oct Blood* 2019;134(17):1385–94.
- [224] Lurain K, Uldrick TS, Ramaswami R, Polizzotto MN, Goncalves PH, Widell A, et al. Treatment of HIV-associated primary CNS lymphoma with antiretroviral therapy, rituximab, and high-dose methotrexate. *5 nov Blood* 2020;136(19):2229–32.
- [225] Abramson JS, Irwin KE, Frigault MJ, Dietrich J, McGree B, Jordan JT, et al. Successful anti-CD19 CAR T-cell therapy in HIV-infected patients with refractory high-grade B-cell lymphoma. *1 nov Cancer* 2019;125(21):3692–8.
- [226] Tsimberidou AM, O'Brien S, Khouri I, Giles FJ, Kantarjian HM, Champlin R, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *20 mai J Clin Oncol J Am Soc Clin Oncol* 2006;24(15):2343–51.
- [227] Wang Y, Tschautscher MA, Rabe KG, Call TG, Leis JF, Kenderian SS, et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. *Haematol mars* 2020;105(3):765–73.
- [228] Ryan CE, Davids MS. Practical Management of Richter Transformation in 2023 and Beyond (janv) *Am Soc Clin Oncol Educ Book* 2023;(43):e390804.
- [229] Gine E, Martinez A, Villamor N, Lopez-Guillermo A, Camos M, Martinez D, et al. Expanded and highly active proliferation centers identify a histological subtype of chronic lymphocytic leukemia (« accelerated » chronic lymphocytic leukemia) with aggressive clinical behavior. *1 sept Haematologica* 2010;95(9):1526–33.
- [230] Barnea Slonim L, Ma S, Behdad A, Chen Q. Pseudo-Richter transformation of chronic lymphocytic leukaemia/small lymphocytic lymphoma following ibrutinib interruption: a diagnostic pitfall. *Br J Haematol [Internet]*. oct 2020 [cité 15 oct 2024];191(1). Disponible sur: <https://onlinelibrary.wiley.com/doi/10.1111/bjh.16948>.
- [231] Langerbeins P, Busch R, Anheier N, Dürig J, Bergmann M, Goebeler M, et al. Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation. *Am J Hematol [Internet]*. déc 2014 [cité 26 nov 2024];89(12). Disponible sur: <https://onlinelibrary.wiley.com/doi/10.1002/ajh.23841>.
- [232] Kittai AS, Bond D, Huang Y, Bhat SA, Blyth E, Byrd JC, et al. Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter Transformation: An International, Multicenter, Retrospective Study. *J Clin Oncol* 10 juin 2024;42(17):2071–9.
- [233] Herrera AF, Ahn KW, Litovich C, Chen Y, Assal A, Bashir Q, et al. Autologous and allogeneic hematopoietic cell transplantation for diffuse large B-cell lymphoma-type Richter syndrome. *28 sept Blood Adv* 2021;5(18):3528–39.
- [234] Güeüz E, Eikema DJ, Koster L, Schetelig J, Sengeloev H, Passweg J, et al. Allogeneic hematopoietic stem-cell transplantation for patients with Richter transformation: a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT (juill) *Bone Marrow Transpl* 2024;59(7):950–6.
- [235] Herrera AF, Ahn KW, Litovich C, Chen Y, Assal A, Bashir Q, et al. Autologous and allogeneic hematopoietic cell transplantation for diffuse large B-cell lymphoma-type Richter syndrome. *28 sept Blood Adv* 2021;5(18):3528–39.
- [236] Fischer T, Zing NPC, Chiattoni CS, Federico M, Luminari S. Transformed follicular lymphoma. *Ann Hematol janv* 2018;97(1):17–29.
- [237] Al-Tourah AJ, Gill KK, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *10 nov J Clin Oncol J Am Soc Clin Oncol* 2008;26(32):5165–9.
- [238] Gleeson M, Hawkes EA, Peckitt C, Wotherspoon A, Attygalle A, Sharma B, et al. Outcomes for transformed follicular lymphoma in the rituximab era: the Royal Marsden experience 2003–2013. *Leuk Lymphoma août* 2017;58(8):1805–13.
- [239] Rusconi C, Anastasia A, Chiarenza A, Marcheselli L, Cavallo F, Rattotti S, et al. Outcome of transformed follicular lymphoma worsens according to the timing of transformation and to the number of previous therapies. A retrospective multicenter study on behalf of Fondazione Italiana Linfomi (FIL). *Br J Haematol mai* 2019;185(4):713–7.
- [240] Stephan P, Di Blasi R, Roulin L, Galtier J, Calvani J, Meignin V, et al. TRANSCAR: Real-World outcomes of CD19CAR T Cell Therapy in relapsed/refractory transformed indolent lymphomas. *Blood Adv* 2025. bloodadvances.2025015834.

- [241] Stephan P. Real-World Outcomes of CD20xCD3 Bispecific Antibody Therapy in Adult Patients with Relapsed/Refractory Transformed Indolent Lymphoma. In: Poster #243. Lugano, Switzerland; 2025.
- [242] Ferreri AJM, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the « cutaneous variant ». *Br J Haematol* oct 2004;127(2):173–83.
- [243] Ferreri AJM, Dognini GP, Bairey O, Szomor A, Montalbán C, Horvath B, et al. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in « Western » patients with intravascular large B-cell lymphoma. *Br J Haematol* oct 2008;143(2):253–7.
- [244] Shimada K, Matsue K, Yamamoto K, Murase T, Ichikawa N, Okamoto M, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. 1 juill *J Clin Oncol J Am Soc Clin Oncol* 2008;26(19):3189–95.
- [245] Shimada K, Yamaguchi M, Kuwatsuka Y, Matsue K, Sato K, Kusumoto S, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): long-term results of a multicentre, single-arm, phase 2 trial. *EclinicalMedicine* Févr 2025;80: 103078.
- [246] Ollila TA, Reagan JL, Olszewski AJ. Clinical features and survival of patients with T-cell/histiocyte-rich large B-cell lymphoma: analysis of the National Cancer Data Base. *déc Leuk Lymphoma* 2019;60(14):3426–33.
- [247] Baird K. Clinical Features and Outcomes of Patients with T-Cell/Histiocyte-Rich Large B-Cell Lymphoma: A Single-Center Analysis. In ASH; 2024 [cité 6 oct 2025]. Disponible sur: https://ash.confex.com/ash/2024/webprogram/Paper211784.html?utm_source=chatgpt.com.
- [248] Pophali PA, Fein JA, Ahn KW, Allbee-Johnson M, Ahmed N, Awan FT, et al. CD19-directed CART therapy for T-cell/histiocyte-rich large B-cell lymphoma. 22 oct *Blood Adv* 2024;8(20):5290–6.
- [249] Axel Andre, Emmanuel Bachy, Guillaume Cartron, Franck Morschhauser, Olivier Tournilhac, François Lemonnier, et al. ANTI-CD19 CAR-T CELL THERAPY IN RELAPSED/REFRACTORY T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA (THRLBCL): INSIGHTS FROM THE FRENCH DESCAR-T REGISTRY, A LYSA STUDY. In Milan; 2025.