lymphatics

MDPI

Review

Personalized Frontline Therapy in Diffuse Large B-Cell Lymphoma: Integrating Circulating Tumor DNA for Real-Time Adaptive Treatment Stratification

Vasisht Karri [1] and Samir Dalia [2,*]

[1] College of Osteopathic Medicine, Kansas City University, 2901 St. Johns Blvd, Joplin, MO 64804, USA; vasisht.karri@kansascity.edu
[2] Department of Medical Oncology, Mercy Hospital, 100 Mercy Way, Joplin, MO 64804, USA
* Correspondence: samir.dalia@mercy.net

Abstract

This review analyzed approximately 115 peer-reviewed studies published between 2010 and 2025, focusing on molecular subtyping and circulating tumor DNA (ctDNA)-guided approaches in Diffuse Large B-Cell Lymphoma (DLBCL). Evidence was synthesized from retrospective cohorts, prospective clinical trials, and translational studies, highlighting how molecular heterogeneity, clonal evolution, and the tumor microenvironment complicate classification and treatment. While molecular subtypes such as MCD, BN2, EZB, A53, and ST2 have improved prognostication, their routine use in clinical practice remains limited due to cost, complexity, and restricted access to sequencing platforms. Tumor-informed ctDNA assays show promise for minimal residual disease (MRD) monitoring and adaptive therapy, yet their predictive power for CAR-T therapy, bispecific antibodies, and checkpoint inhibitors is still incompletely understood. Overall, the literature converges on the need for integrated strategies combining ctDNA, molecular subtyping, and immune microenvironment analysis to personalize frontline therapy.

Keywords: diffuse large B-cell lymphoma; molecular heterogeneity; cell-of-origin; precision medicine; frontline therapy; mutational profiling; targeted therapy

Academic Editor: Hans Theodor Eich

Received: 2 August 2025
Revised: 4 September 2025
Accepted: 23 September 2025
Published: 17 October 2025

Citation: Karri, V.; Dalia, S. Personalized Frontline Therapy in Diffuse Large B-Cell Lymphoma: Integrating Circulating Tumor DNA for Real-Time Adaptive Treatment Stratification. *Lymphatics* **2025**, *3*, 34. https://doi.org/10.3390/lymphatics3040034

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma, accounting for nearly 30–40% of adult cases worldwide [1]. Despite being curable in many patients with standard chemoimmunotherapy such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), outcomes remain heterogeneous, with approximately one-third of patients experiencing relapse or refractory disease [2,3]. Furthermore, this heterogeneity reflects the underlying biological diversity of DLBCL.

Traditional prognostic tools, such as the International Prognostic Index (IPI), rely on clinical features including age, stage, lactate dehydrogenase levels, and performance status. While useful, these metrics fail to fully capture the molecular and genetic diversity driving patient outcomes. Early work using gene-expression profiling established the cell-of-origin (COO) framework—germinal center B-cell-like (GCB) vs. activated B-cell-like (ABC)—with prognostic separation [2]. These categories remain prognostically relevant but incompletely explain clinical variability [1,4].

Technological advances in circulating tumor DNA provided the first proof-of-concept that molecular residual disease can be detected noninvasively, often earlier than radiographic relapse [5]. In parallel, error-suppressed sequencing methods (e.g., CAPP-Seq) increased analytical sensitivity for low-frequency variants in plasma, enabling serial disease monitoring [6]. Large-scale tumor sequencing then revealed recurrent genetic drivers and networks that stratify DLBCL into reproducible genetic subtypes [7], while the emergence of CAR-T therapy provided durable remissions for a subset of relapsed/refractory patients [8].

Beyond COO, next-generation sequencing has delineated reproducible genetic subtypes defined by characteristic driver constellations and clinical behavior: MCD (co-mutated *MYD88L265P/CD79B*), BN2 (*BCL6* fusions/*NOTCH2* mutations), EZB (*EZH2* mutations/*BCL2* translocations), A53 (*TP53* alterations), and ST2 (*SGK1/TNFAIP3/TET2/TNFRSF14* lesions) [9–13]. To be specific, recurrent driver alterations have been identified across subtypes: *MYC*, *BCL2*, and *BCL6* rearrangements (double- or triple-hit lymphomas) predict particularly poor outcomes [11–13]; *EZH2* mutations and *BCL2* translocations define the EZB genomic subtype [9,10]; *MYD88ˆL265P* and *CD79B* mutations characterize the MCD subtype; *NOTCH2* and *BCL6* fusions define BN2; *TP53* loss drives the A53 subtype; and *SGK1/TET2/TNFAIP3* alterations underlie ST2 [9,10]. Epigenetic regulators, such as *CREBBP* and *EP300* mutations, frequently co-occur with GCB-DLBCL, while chromatin modifiers and NF-κB pathway activators are enriched in ABC-DLBCL [7]. In addition, circulating tumor DNA (ctDNA) has emerged as a sensitive, scalable window into disease burden and dynamics—detecting minimal residual disease (MRD) and anticipating relapse months before imaging in some settings [5,6,14,15]. Transcriptomic profiling further refines COO by integrating immune microenvironmental signatures, which can independently influence prognosis [16,17].

Despite this progress, the clinical translation of molecular subtyping remains constrained. Many classification studies are retrospective, rely on limited cohorts, and use heterogeneous sequencing methods, limiting generalizability [10]. Furthermore, costs, turnaround time, and uneven sequencing infrastructure hinder widespread adoption in community practice. Finally, while subtyping informs prognosis, predictive value for novel therapies—such as CAR-T cells, bispecific antibodies, and checkpoint inhibitors—remains incompletely defined [8–10].

This review aims to synthesize recent evidence on the molecular heterogeneity of DLBCL and the emerging role of circulating tumor DNA (ctDNA) as a tool for adaptive, real-time treatment stratification. We highlight how ctDNA can complement molecular subtyping by detecting minimal residual disease, guiding escalation or de-escalation strategies, and integrating tumor microenvironmental features to advance personalized frontline therapy.

2. Molecular Landscape of DLBCL

2.1. From Cell-of-Origin to Genomic Subtypes

The COO paradigm (GCB vs. ABC) remains clinically informative [1,3], but it incompletely captures heterogeneity. Next-generation sequencing has delineated reproducible genetic subtypes with distinct driver constellations and clinical behavior, notably MCD (*MYD88/CD79B*), BN2 (*BCL6* fusions/*NOTCH2*), EZB (*EZH2* mutations/*BCL2* translocations), A53 (*TP53* alterations), and ST2 (*SGK1/TNFAIP3/TET2/TNFRSF14*) [9,10]. These molecular layers coexist with high-risk cytogenetics (*MYC/BCL2/BCL6* rearrangements) and adverse protein co-expression [11–13], creating overlapping axes of risk. To consolidate nomenclature and highlight the evidence base behind each subtype, Table 1 lists defining alterations, typical clinical correlates, and supporting references.

Table 1. Molecular classifications of DLBCL and clinical correlates.

Subtype	Defining Alterations	Typical Clinical Correlates	Key References
MCD	*MYD88 L265P*, *CD79B* mutations	ABC-DLBCL enrichment; extranodal disease; inferior survival with R-CHOP	Chapuy et al., 2018 [9]; Schmitz et al., 2018 [10]
BN2	*BCL6* fusions, *NOTCH2* mutations	Intermediate prognosis; overlap with marginal-zone biology	Chapuy et al., 2018 [9]; Wright et al., 2020 [18]
EZB	*EZH2* mutations, *BCL2* translocations	GCB lineage; frequent double-hit; targetable *EZH2*	Schmitz et al., 2018 [10]; Lacy et al., 2020 [19]
A53	*TP53* mutations/deletions	Chemoresistance; very poor outcomes	Lacy et al., 2020 [19]; Wilson et al., 2021 [20]
ST2	*SGK1,TNFAIP3, TET2/TNFRSF14*	Favorable in some cohorts; microenvironment influence	Wright et al., 2020 [18]; Wilson et al., 2021 [20]

Legend: A53, *TP53*-mutated subtype; ABC, activated B-cell-like; BN2, *BCL6/NOTCH2* subtype; CAR-T, chimeric antigen receptor T-cell therapy; COO, cell-of-origin; ctDNA, circulating tumor DNA; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EZB, *EZH2/BCL2* subtype; *EZH2*, enhancer of zeste homolog 2; GCB, germinal center B-cell-like; MCD, *MYD88/CD79B* subtype; MRD, minimal residual disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ST2, *SGK1/TNFAIP3/TET2/TNFRSF14* subtype; TME, tumor microenvironment; *TP53*, tumor protein p53.

Table 1 outlines the five major molecular subtypes of DLBCL, integrating their defining genetic alterations with associated clinical features. These classifications, derived from next-generation sequencing studies, illustrate the heterogeneity of DLBCL and highlight potential therapeutic vulnerabilities, such as *EZH2* inhibition in EZB or BCR-targeting approaches in MCD. Importantly, while subtype-specific alterations correlate with distinct prognoses, their translation into routine clinical practice remains limited due to cost, complexity, and incomplete integration with evolving tumor biology.

2.2. Genetic Subtypes and LymphGen Classification

Building upon COO, integrated molecular taxonomies partition DLBCL by mutational and copy-number features with partial transcriptomic corroboration. MCD (co-mutated *MYD88L265P/CD79B*) implicates chronic-active B-cell receptor (BCR)/NF-κB signaling and extranodal tropism with inferior R-CHOP outcomes; BN2 (*BCL6* fusions/*NOTCH2*) overlaps with marginal-zone biology and shows intermediate prognosis; EZB (*EZH2* activating mutations with *BCL2* translocations) aligns with GCB and frequently intersects with DHL; A53 (*TP53*-inactivated) exhibits genomic instability and poor response to cytotoxic therapy; ST2 (e.g., *SGK1/TNFAIP3/TET2/TNFRSF14*) remains less well defined and appears sensitive to microenvironmental context [9,10]. The NIH-developed LymphGen algorithm stratifies individual cases probabilistically across these subtypes, facilitating research use and early clinical exploration, though platform harmonization and access to comprehensive sequencing remain barriers to routine deployment [10].

2.3. Prognostic Impact of Molecular Subtypes

COO classification alone distinguishes patients with markedly different survival outcomes: GCB-DLBCL patients treated with R-CHOP exhibit 5-year overall survival rates around 70–75%, compared to 40–50% in the ABC subtype [4,21]. The molecular mechanisms underlying these disparities include chronic active BCR signaling, NF-κB activation, and loss of tumor suppressor regulation in ABC-DLBCL, contributing to chemoresistance.

At a finer scale, genetic subtypes confer distinctive risks: The MCD subtype, enriched for *MYD88ˆL265P* and *CD79B* mutations, is associated with poor prognosis, frequent extranodal disease, and poor response to R-CHOP [9]. The A53 subtype, defined by *TP53* mutations and genomic instability, remains refractory to chemotherapy. Conversely, the

EZB subtype, although associated with double-hit lymphomas (DHLs), often responds initially to R-CHOP or R-EPOCH [10]. BN2 and ST2 represent intermediate or variable outcomes but continue to demonstrate clinical relevance as classification frameworks evolve. Moreover, intratumoral heterogeneity and clonal evolution modulate these risks over time—therapy can reshuffle subclonal dominance, rendering static, single-biopsy classifications incompletely predictive [7].

The recognition of DHL, defined by concurrent rearrangements of *MYC* and *BCL2/BCL6*, has shifted practice toward intensive regimens such as R-EPOCH [22]. Incorporating mutational data into prognostication models is expected to allow more accurate predictions than traditional IPI scoring alone.

3. Molecular-Driven Treatment Strategies

3.1. Emerging Targeted Agents

Targeted therapies have reshaped lymphoma care. Ibrutinib, a BTK inhibitor, has shown activity in ABC-DLBCL harboring *MYD88* and *CD79B* mutations, with improved progression-free survival in younger patients [23]. Lenalidomide, through modulation of NF-κB and immune signaling, demonstrated activity in ABC subtypes [24]. Tafasitamab, an anti-CD19 monoclonal antibody, in combination with lenalidomide, produced durable responses in relapsed/refractory disease [25]. Polatuzumab vedotin, targeting *CD79b*, demonstrated superior PFS when combined with R-CHP compared to R-CHOP in the POLARIX trial [18].

Emerging strategies also emphasize biological differences. For example, men with ABC-DLBCL often experience inferior outcomes with R-CHOP compared to women, potentially due to pharmacokinetic differences in rituximab clearance [26]. Sex, age, comorbidities, and ethnicity all influence therapy tolerability, highlighting the importance of embedding demographic and biological factors into personalized regimens.

3.2. Stratified Chemotherapy and High-Risk Scenarios

For DHL and other high-grade B-cell lymphomas, dose-adjusted R-EPOCH remains a frontline option, supported by studies showing improved complete remission rates in high-risk cohorts [19,22]. Integration of molecular subtype data into trial design is ongoing, with studies such as REMoDL-B (bortezomib in ABC), LYSA B05 (obinutuzumab vs. rituximab), and ctDNA-guided escalation/de-escalation designs under active investigation [5,27,28].

Nevertheless, randomized evidence is limited, and optimal tailoring of chemotherapy based on subtype or ctDNA remains investigational. These efforts reflect a broader need to harmonize molecular data, trial design, and real-world implementation.

4. Circulating Tumor DNA (ctDNA) in Frontline DLBCL

Circulating tumor DNA has emerged as a promising biomarker to complement tissue-based classifications by providing a dynamic measure of disease burden and treatment response. Ultrasensitive sequencing methods, such as CAPP-Seq, permit the detection of tumor-derived DNA at extremely low variant allele fractions, making it possible to quantify minimal residual disease with high precision [6]. Prospective studies have shown that ctDNA can detect molecular relapse months before it becomes apparent on imaging and can also provide a more refined assessment of remission depth at the completion of therapy [5,15,29].

Beyond its role in surveillance, ctDNA kinetics during treatment hold potential for adaptive decision-making. Several studies have demonstrated that patients who fail to clear ctDNA early in therapy are at substantially higher risk of treatment failure, in some cases with predictive performance exceeding that of interim PET imaging [14]. Ultralow-

frequency detection enabled by phased-variant or duplex error-suppression can reliably track molecular response even in low-burden settings, improving negative predictive value and reducing false positives [30]. These features suggest a response-adapted paradigm: (i) establish a baseline molecular fingerprint from tumor/WBC sequencing; (ii) obtain early on-treatment ctDNA to confirm biologic response; (iii) integrate end-of-therapy ctDNA to adjudicate remission depth and plan surveillance intensity; and (iv) use serial surveillance to detect preclinical relapse, ideally within trial frameworks that specify action thresholds for intervention. Moreover, the combination of all these findings suggest that serial ctDNA monitoring could form the backbone of response-adapted strategies.

For patients with favorable-risk biology who achieve rapid clearance, de-escalation may be considered to reduce toxicity, while persistent ctDNA positivity may identify candidates for clinical trials, antibody–drug conjugates, or early referral for cellular therapies. Although not yet incorporated into standard practice, this approach highlights how ctDNA could enable a more precise tailoring of frontline therapy once validated in prospective, randomized studies.

5. Molecular Subtypes, Immunotherapies and Biological Differences

Novel immunotherapies have transformed the treatment landscape in relapsed/refractory DLBCL, yet molecular subtypes and patient characteristics may influence efficacy. BTK inhibitors such as ibrutinib show preferential activity in MCD/BN2 tumors, where chronic active B-cell receptor signaling drives pathogenesis, though consistent frontline benefit remains unproven [9,23]. In addition, EZB tumors with *EZH2* mutations are rational candidates for epigenetic therapies such as tazemetostat, though most evidence is from early-phase trials [10].

Cell therapies have transformed relapsed/refractory DLBCL management. CAR-T therapies, such as axicabtagene ciloleucel, have achieved durable remissions in subsets of patients [8,31], though subtype-specific predictors of response remain unsettled. Subtype-specific correlates are under investigation, and ctDNA kinetics may provide additional tools to guide referral and assess depth of remission [8,31]. Bispecific antibodies (e.g., glofitamab, epcoritamab) have shown encouraging results post-CAR-T failure, yet molecular predictors of response are not defined [32–34].

Checkpoint inhibitors (PD-1 blockade) have limited but notable activity in select aggressive B-cell lymphomas; however, neither COO nor genetic subtype consistently predicts response, emphasizing the importance of integrating tumor microenvironmental signatures and ctDNA into predictive models [17,20].

Importantly, sex-based differences require greater attention as they add another dimension to precision therapy. Several pharmacokinetics studies demonstrate that rituximab clearance differs by sex, with men showing lower serum exposure and reduced benefit in some series, highlighting how pharmacology and immune responsiveness may interact with outcomes [26]. These observations support incorporating sex as a biological variable into trial design and therapeutic stratification [27]. Future trials should prospectively stratify by sex and other biological factors to better understand and address outcome disparities.

6. Practical Limits to Clinical Translation

Despite advances in molecular subtyping, several barriers limit the immediate translation of these approaches into routine clinical practice. One major challenge is intratumoral heterogeneity and clonal evolution. Diffuse large B-cell lymphoma often comprises multiple genetically distinct subclones within the same patient, and the selective pressures of therapy can shift clonal dominance over time. This dynamic biology blurs the neat boundaries established by classification systems and helps explain why molecular findings

may differ between biopsies taken at separate time points or disease sites. As a result, a single molecular snapshot may not fully capture the complexity of the disease, and rigid treatment assignments based on baseline profiling alone may be misleading [7].

Another limitation lies in the evidence base and its generalizability. Many of the studies that established current molecular classifications were retrospective in design and relied on relatively small or geographically restricted patient populations. Such limitations constrain the external validity of the findings and complicate efforts to harmonize classification systems across clinical settings [10]. In addition, cell-of-origin assignment and genomic subtyping are not consistently aligned across sequencing platforms, and variability in analytic pipelines further reduces cross-study comparability [10].

Operational considerations also pose substantial barriers. High-quality next-generation sequencing remains unevenly available, with turnaround times, costs, and the need for specialized bioinformatics expertise creating obstacles in many treatment settings. Insurance coverage and payer policies further restrict access, meaning that the full promise of molecular classification is often realized only in academic or tertiary care centers rather than in broader real-world practice [9,10].

Finally, current molecular taxonomies underweight the contribution of the tumor microenvironment. Increasing evidence demonstrates that immune and stromal cell signatures carry independent prognostic information and plausibly influence responses to immunotherapies. However, most classification systems remain focused primarily on tumor-intrinsic genetic programs, limiting their ability to predict outcomes in contexts where host immunity and stromal interactions are dominant drivers of response. Incorporating microenvironmental features alongside genomic subtyping may therefore represent an important next step in refining prognostic and predictive models [16].

7. Future Directions in Precision Oncology

The next frontier in DLBCL research lies in integrating multiple biological dimensions into unified clinical models. Emerging research efforts are focused on combining genomic data with real-time functional assays (e.g., ctDNA dynamics, single-cell sequencing) to develop dynamic risk models. Three complementary streams are poised to move precision forward.

Firstly, prospective adaptive trials that are subtype-aware and ctDNA-guided are needed to test clinically meaningful strategies: de-escalation for patients with early molecular clearance (to reduce long-term toxicity without compromising cure) and escalation for those with persistent ctDNA (e.g., adding a targeted agent, antibody–drug conjugate, bispecific, or cellular therapy), with PFS/OS and quality-of-life endpoints, plus molecular clearance as a coprimary or key secondary endpoint.

In addition, integrated models that combine genomic subtype, TME signatures, and ctDNA kinetics should be prospectively validated to improve risk discrimination over traditional clinical scores, while exploring predictive relationships with CAR-T, bispecifics, and checkpoint inhibitors [17,32].

Finally, operational equity is essential. Sequencing platforms and ctDNA assays remain inaccessible in many settings due to cost, turnaround time, and lack of reimbursement. Expanding sequencing and ctDNA access through streamlined logistics, payer coverage, and rapid turnaround will prevent precision tools from widening disparities. Ensuring equitable access to molecular diagnostics will be critical for translating precision medicine into real-world outcomes. All three streams should embed sex-aware design and pre-specified subgroup analyses, given the observed differences in outcomes and pharmacokinetics with rituximab-containing regimens [26,33].

In parallel, predictive correlatives for CAR-T, bispecifics, and checkpoint inhibitors must be validated, including exploration of ctDNA clearance as an early pharmacodynamic biomarker. Finally, a sex-stratified trial design will be essential to test how gender, immune response, and drug metabolism interact with therapy class and outcomes [26,33].

8. Conclusions

Diffuse large B-cell lymphoma is increasingly recognized as a family of biologically distinct diseases shaped by genomic alterations, clonal evolution, and the tumor microenvironment. Molecular classification, from COO to integrated genomic subtypes (MCD, BN2, EZB, A53, ST2), has advanced risk stratification and highlighted therapeutic vulnerabilities. Yet routine implementation remains constrained by cost, complexity, and lack of universal predictive benefit.

Tumor-informed ctDNA has emerged as a complementary, minimally invasive tool capable of detecting minimal residual disease, anticipating relapse, and refining depth-of-remission assessment. While still investigational, ctDNA offers a real-time window into disease dynamics and holds promise for guiding adaptive therapy.

Across the literature, several themes recur. First, intratumoral heterogeneity and clonal evolution complicate precise classification and demand adaptive strategies [7]. Second, the generalizability of molecular classifications is limited by retrospective cohorts and restricted sequencing availability [10]. Third, the tumor microenvironment and sex-specific biology remain under-integrated into prognostic and therapeutic models [16]. Fourth, the predictive value of subtypes for immunotherapies (CAR-T, bispecifics, checkpoint blockade) shows promise but is incompletely understood [8,20,31–34]. Finally, biological factors such as sex, age, and comorbidity can modulate therapeutic response, reinforcing the need for inclusive, stratified trial designs [26].

The consensus is clear: personalization of DLBCL therapy will require integrating molecular subtyping, ctDNA monitoring, and tumor microenvironment profiling into cohesive care models that are equitable and scalable. Future research must focus on prospective, adaptive trials that benchmark biomarker-informed strategies against standard-of-care, while systematically evaluating sex-specific and biologically distinct responses. Only through this integrated lens can the field move closer to precise, patient-centered therapy across diverse patient populations.

Author Contributions: Conceptualization, V.K. and S.D.; methodology, V.K.; software, V.K.; validation, V.K. and S.D.; formal analysis, V.K. and S.D.; investigation, V.K.; resources, V.K. and S.D.; data curation, V.K.; writing—original draft preparation, V.K.; writing—review and editing, V.K. and S.D.; visualization, V.K. and S.D.; supervision, S.D.; project administration, V.K. and S.D.; funding acquisition, V.K. and S.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Alizadeh, A.A.; Eisen, M.B.; Davis, R.E.; Ma, C.; Lossos, I.S.; Rosenwald, A.; Boldrick, J.C.; Sabet, H.; Tran, T.; Yu, X.; et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* **2000**, *403*, 503–511. [CrossRef]
2. Rosenwald, A.; Wright, G.; Chan, W.C.; Connors, J.M.; Campo, E.; Fisher, R.I.; Gascoyne, R.D.; Muller-Hermelink, H.K.; Smeland, E.B.; Giltnane, J.M.; et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N. Engl. J. Med.* **2002**, *346*, 1937–1947.

3. Coiffier, B.; Lepage, E.; Brière, J.; Herbrecht, R.; Tilly, H.; Bouabdallah, R.; Morel, P.; Van Den Neste, E.; Salles, G.; Gaulard, P.; et al. CHOP plus rituximab compared with CHOP alone in elderly patients with DLBCL. *N. Engl. J. Med.* **2002**, *346*, 235–242. [CrossRef] [PubMed]
4. Hans, C.P.; Weisenburger, D.D.; Greiner, T.C.; Gascoyne, R.D.; Delabie, J.; Ott, G.; Müller-Hermelink, H.K.; Campo, E.; Braziel, R.M.; Jaffe, E.S.; et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* **2004**, *103*, 275–282. [CrossRef] [PubMed]
5. Roschewski, M.; Dunleavy, K.; Pittaluga, S.; Morrhead, M.; Pepin, F.; Kong, K.; Shovlin, M.; Jaffe, E.S.; Staudt, L.M.; Lai, C.; et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: A correlative biomarker study. *Lancet Oncol.* **2015**, *16*, 541–549. [CrossRef] [PubMed]
6. Newman, A.M.; Bratman, S.V.; To, J.; Wynne, J.F.; Eclov, N.C.; Modlin, L.A.; Liu, C.L.; Neal, J.W.; Wakelee, H.A.; Merritt, R.E.; et al. An ultrasensitive method for quantitating circulating tumor DNA with CAPP-Seq. *Nat Med.* **2014**, *20*, 548–554. [CrossRef]
7. Dunleavy, K.; Pittaluga, S.; Maeda, L.S.; Kinda, S.B.; Gacina, P.; Perisa, V.; Prka, Z.; Dreta, B.; Galusic, D.; Holik, H.; et al. Dose-adjusted EPOCH-rituximab in aggressive B-cell lymphoma. *N. Engl. J. Med.* **2013**, *368*, 1408–1416. [CrossRef]
8. Petrich, A.M.; Nabhan, C.; Smith, S.M. MYC-associated and double-hit lymphomas: Outcomes and approaches. *Cancer* **2014**, *120*, 3884–3895.
9. Chapuy, B.; Stewart, C.; Dunford, A.J.; Kim, J.; Kamburov, A.; Redd, R.A.; Lawrence, M.S.; Roemer, M.G.M.; Li, A.J.; Ziepert, M.; et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat. Med.* **2018**, *24*, 679–690.
10. Schmitz, R.; Wright, G.W.; Huang, D.W.; Johnson, C.A.; Phelan, J.D.; Wang, J.Q.; Roulland, S.; Kasbekar, M.; Young, R.M.; Shaffer, A.L.; et al. Genetics and pathogenesis of DLBCL. *N. Engl. J. Med.* **2018**, *378*, 1396–1407. [CrossRef]
11. Johnson, N.A.; Slack, G.W.; Savage, K.J.; Connors, J.M.; Ben-Neriah, S.; Rogic, S.; Scott, D.W.; Tan, K.L.; Steidl, C.; Sehn, L.H.; 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.* **2012**, *30*, 3452–3459. [CrossRef]
12. Sarkozy, C.; Traverse-Glehen, A.; Coiffier, B. Double-hit and double-protein-expression lymphomas: Aggressive and refractory lymphomas. *Lancet. Oncol.* **2015**, *16*, e555–e567. [CrossRef]
13. Wilson, W.H.; Young, R.M.; Schmitz, R.; Yang, Y.; Pittaluga, S.; Wright, G.; Lih, C.J.; Williams, P.M.; Shaffer, A.L.; Gerecitano, J.; et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat. Med.* **2015**, *21*, 922–926. [CrossRef]
14. Reddy, A.; Zhang, J.; Davis, N.S.; Moffitt, A.B.; Love, C.L.; Waldrop, A.; Leppa, S.; Pasanen, A.; Meriranta, L.; Karjalainen-Lindsberg, M.L.; et al. Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma. *Cell* **2017**, *171*, 481–494. [CrossRef] [PubMed]
15. Kurtz, D.M.; Scherer, F.; Jin, M.C.; Soo, J.; Craig, A.F.M.; Esfahani, M.S.; Chabon, J.J.; Stehr, H.; Liu, C.L.; Tibshirani, R.; et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J. Clin. Oncol.* **2018**, *36*, 2845–2853. [CrossRef] [PubMed]
16. Simeonov, K.P.; Byrns, C.N.; Clark, M.L.; Norgard, R.J.; Martin, B.; Stanger, B.Z.; Shendure, J.; McKenna, A.; Lengner, C.J. Clinical and biological subtypes of B-cell lymphoma revealed by microenvironmental signatures. *Cancer Cell.* **2021**, *39*, 1422–1437.e10. [CrossRef]
17. Vitolo, U.; Trněný, M.; Belada, D.; Carella, A.M.; Chua, N.; Abrisqueta, P.; Demeter, J.; Demeter, J.; Flinn, I.W.; Hong, X.; et al. Obinutuzumab or rituximab plus CHOP in previously untreated diffuse large B-cell lymphoma: Final results from an open-label, randomized phase 3 study (GOYA). *Blood* **2016**, *128*, 470. [CrossRef]
18. Wright, G.W.; Huang, D.W.; Phelan, J.D.; Coulibaly, Z.A.; Roulland, S.; Young, R.M.; Wang, J.Q.; Schmitz, R.; Morin, R.D.; Tang, J.; et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. *Cancer Cell.* **2020**, *37*, 551–568. [CrossRef]
19. Lacy, S.E.; Barrans, S.L.; Beer, P.A.; Painter, D.; Smith, A.G.; Roman, E.; Cooke, S.L.; Ruiz, C.; Glover, P.; Van Hoppe, S.J.L.; et al. Targeted sequencing in DLBCL, molecular subtypes, and outcomes: A Haematological Malignancy Research Network report. *Blood.* **2020**, *135*, 1759–1771. [CrossRef]
20. Ren, W.; Wan, H.; Own, S.A.; Berglund, M.; Wang, X.; Yang, M.; Li, X.; Liu, D.; Ye, X.; Sonnevi, K.; et al. Genetic and transcriptomic analyses of diffuse large B-cell lymphoma patients with poor outcomes within two years of diagnosis. *Leukemia* **2024**, *38*, 610–620. [CrossRef]
21. Lenz, G.; Wright, G.; Dave, S.S.; Xiao, W.; Powell, J.; Zhao, H.; Xu, W.; Tan, B.; Goldschmidt, N.; Iqbal, J.; et al. Stromal gene signatures in large B-cell lymphomas. *N. Engl. J. Med.* **2008**, *359*, 2313–2323.
22. Bartlett, N.L.; Wilson, W.H.; Jung, S.H.; Hsi, E.D.; Maurer, M.J.; Pederson, L.D.; Polley, M.C.; Pitcher, B.N.; Cheson, B.D.; Kahl, B.S.; et al. Dose-Adjusted EPOCH-R Compared with R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J. Clin. Oncol.* **2019**, *37*, 1790–1799. [CrossRef] [PubMed]
23. Locke, F.L.; Ghobadi, A.; Jacobson, C.A.; Miklos, D.B.; Lekakis, L.J.; Oluwole, O.O.; Lin, Y.; Braunschweig, I.; Hill, B.T.; Timmerman, J.M.; et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1–2 trial. *Lancet Oncol.* **2019**, *20*, 31–42. [CrossRef] [PubMed]

24. Nowakowski, G.S.; Chiappella, A.; Gascoyne, R.D.; Scott, D.W.; Zhang, Q.; Jurczak, W.; Özcan, M.; Hong, X.; Zhu, J.; Jin, J.; et al. ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients with ABC-Type Diffuse Large B-Cell Lymphoma. *J. Clin. Oncol.* **2019**, *39*, 1317–1328. [CrossRef]
25. Davies, A.; Cummin, T.; Barrans, S.; Maishman, T.; Mamot, C.; Novak, U.; Caddy, J.; Stanton, L.; Kazmi-Stokes, S.; McMillan, A.; et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): An open-label, randomised, phase 3 trial. *Lancet Oncol.* **2019**, *20*, 649–662. [CrossRef]
26. Pfreundschuh, M.; Trümper, L.; Osterborg, A.; Pettengell, R.; Trneny, M.; Imrie, K.; Ma, D.; Gill, D.; Walewski, J.; Zinzani, P.L.; et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large B-cell lymphoma: A randomised controlled trial (MInT). *Lancet Oncol.* **2006**, *7*, 379–391. [CrossRef] [PubMed]
27. Yıldırım, M.; Kaya, V.; Demirpence, Ö.; Paydas, S. The role of gender in patients with diffuse large B-cell lymphoma: A meta-analysis. *Cancer Med.* **2015**, *4*, 1407–1416. [CrossRef]
28. Neelapu, S.S.; Locke, F.L.; Bartlett, N.L.; Lekakis, L.J.; Miklos, D.B.; Jacobson, C.A.; Braunschweig, I.; Oluwole, O.O.; Siddiqi, T.; Lin, Y.; et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N. Engl. J. Med.* **2017**, *377*, 2531–2544.
29. Sehn, L.H.; Salles, G. Diffuse large B-cell lymphoma: Current landscape. *N. Engl. J. Med.* **2021**, *384*, 842–858. [CrossRef]
30. Dickinson, M.; Carlo-Stella, C.; Morschhauser, F.; Bachy, E.; Corradini, P.; Iacoboni, G.; Khan, C.; Wróbel, T.; Offner, F.; Trněný, M.; et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N. Engl. J. Med.* **2022**, *387*, 2220–2231. [CrossRef]
31. Kurtz, D.M.; Soo, J.; Co Ting Keh, L.; Alig, S.; Chabon, J.J.; Sworder, B.J.; Schultz, A.; Jin, M.C.; Scherer, F.; Garofalo, A.; et al. Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA. *Nat. Biotechnol.* **2021**, *39*, 1537–1547. [CrossRef]
32. Tilly, H.; Morschhauser, F.; Sehn, L.H.; Friedberg, J.W.; Trněný, M.; Sharman, J.P.; Herbaux, C.; Burke, J.M.; Matasar, M.; Rai, S.; et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N. Engl. J. Med.* **2022**, *386*, 351–363. [CrossRef] [PubMed]
33. Budde, L.E.; Sehn, L.H.; Matasar, M.; Schuster, S.J.; Assouline, S.; Giri, P.; Kuruvilla, J.; Canales, M.; Dietrich, S.; Fay, K.; et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: A single-arm, multicentre, phase 2 study. *Lancet Oncol.* **2022**, *23*, 1055–1065. [CrossRef] [PubMed]
34. Lauer, E.M.; Mutter, J.; Scherer, F. Circulating tumor DNA in B-cell lymphoma: Technical advances, clinical applications, and perspectives for translational research. *Leukemia* **2022**, *36*, 2151–2164. [CrossRef] [PubMed]