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REVIEW

Enhancing Immunotherapy in Diffuse Large B-Cell Lymphoma: The Synergistic Potential of Metabolic Checkpoint Inhibitors and Immunomodulation

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Abstract: For many patients with diffuse large B-cell lymphoma (DLBCL), frontline chemoimmunotherapy is curative; nonetheless, up to 40% of patients develop relapse or refractory disease. Immunotherapeutic approaches, such as immunomodulatory drugs, bispecific antibodies and chimeric antigen receptor T-cell therapy, have improved outcomes for relapsed/refractory DLBCL over the past ten years. However, treatment failure is still frequent because of tumor antigen loss, T-cell dysfunction, and an immunosuppressive tumor microenvironment (TME). DLBCL is a highly metabolically active cancer that impairs efficient anti-tumor immune responses by depleting vital nutrients and producing immunosuppressive metabolites such lactate, adenosine, and kynurenine. Targeting metabolic checkpoints, such as glutamine metabolism, indoleamine 2,3-dioxygenase, adenosine signaling, and lactate transport, may remodel the TME and improve the effectiveness of immunotherapy, according to new research. The immune metabolic interaction that restricts long-lasting responses is the main topic of this study, which summarizes current immunotherapeutic strategies in DLBCL. To improve T-cell fitness and overcome immunotherapy resistance, we critically assessed the preclinical and early clinical data supporting metabolic checkpoint inhibition. We also emphasize translational issues and potential future paths for logical combination treatments. Importantly, this review distinguishes itself from existing literature by specifically focusing on the integration of metabolic checkpoint inhibition with established immunotherapies in DLBCL, an area that remains underexplored. While preclinical data are promising, clinical evidence for many metabolic checkpoint inhibitors in DLBCL remains limited, and further prospective clinical studies are required to validate their therapeutic potential.

Keywords: DLBCL, immunomodulatory drugs bispecific antibodies, CAR-T cells therapy, metabolic checkpoints

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent form of non-Hodgkin lymphoma (NHL) accounting for about 30–40% of all cases globally. Its defining feature is the proliferation and widespread infiltration of large neoplastic B cells into lymph nodes and extra nodal sites such as the testis, bone marrow, central nervous system, and gastrointestinal tract.[1] DLBCL can arise *de novo* or transform from indolent lymphomas, such as follicular lymphoma or chronic lymphocytic leukemia (Richter transformation). Its aggressive nature is reflected in its characteristically rapidly enlarging lymphadenopathy and constitutional symptoms such as fever, drenching night sweats, and weight loss. DLBCL primarily affects older adults, with a median age at diagnosis of 60 to 70 years with a slight male preponderance. There is significant geographic variation with Western countries typically having a higher prevalence of this lymphoma compared to Asian countries.[2] Numerous immunological, genetic, and environmental factors, such as autoimmune disease, immunosuppression, chronic infections (including hepatitis C and Epstein-Barr virus), and a family history of lymphoma, all affect the chance of developing DLBCL. Advancements in diagnostic methods and population ageing have led to an increase in the prevalence of DLBCL over recent decades, highlighting the necessity of strong epidemiological surveillance as well as preventative measures in high-risk populations.[3]

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The malignant transformation of B cells in DLBCL is a result of complex interactions between dysregulated signaling pathways, epigenetic modifications, and genetic abnormalities. Important pathogenic events include chromosomal translocations involving the *BCL6, BCL2*, and *MYC* genes, mutations in JAK/STAT and NF-κB pathways, and a failure of immune surveillance. DLBCL has a diverse clinical history and responsiveness to treatment because of its high degree of genetic diversity.[4] The disease can be broadly divided into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subgroups due to differences in cellular origin and molecular characteristics, based on transcriptomics. The GCB subtype typically has a better prognosis than the ABC subtype because constitutive activation of the NF-κB pathway together with other survival indicators makes the ABC subtype less responsive to conventional treatments and produces worse outcomes.[5] A distinct subset of high-grade B-cell lymphomas with aggressive clinical behavior are those that have MYC and BCL2 and/or BCL6 rearrangements; these lymphomas are generally referred to as "double-hit" or "triple-hit" lymphomas. These prognostic and predictive biomarkers form the basis of classifying DLBCL cases to facilitate risk assessment and treatment planning.[6] Up until recently most patients received treatment first-line with combination chemoimmunotherapy: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). After numerous clinical trials that had investigated the potential benefit of added targeting therapies (eg. ibrutinib, bortezomib) with little benefit, recent data has support the replacing vincristine by polatuzumab, particularly for patients with the ABC subtype.[7] While DLBCL is potentially curable with these therapies in 60–70% of patients, between 30–40% have disease that is refractory to these treatments or experience disease recurrence in the month/years following an initial complete or partial remission.[6] Immunotherapies have emerged as highly effective with durable responses in this setting, going some way to meet the unmet needs of relapsed/refractory (R/R) DLBCL. Despite this many patients still relapse, necessitating the development of novel therapeutic approaches.

In this review, we specifically examine the emerging interface between metabolic reprogramming and immunotherapy in DLBCL, highlighting how metabolic checkpoint inhibitors may enhance current immunotherapeutic strategies. This focus provides a novel perspective compared to prior reviews, which have largely considered these approaches independently.

CAR T-Cells for the Treatment of DLBCL

One of the most impactful immunotherapies to enter the DLBCL treatment space over the last decade or so have been chimeric antigen receptor (CAR) T cells. These are autologous (ie. the patient's own) T cells that have been engineered to express synthetic receptors that target lymphoma-associated antigens, most frequently CD19. MHC-independent tumor recognition is made possible by these receptors, which integrate intracellular signaling patterns with antigen-recognition domains. The CAR T cells then target the malignant B cells post-infusion, releasing granzyme and perforin to kill the tumor cells, as well as producing pro-inflammatory cytokines and enlisting bystander immune populations.[8] The therapeutic potential of this therapy has been highlighted by clinical studies like ZUMA-1 (axicabtagene ciloleucel; axi-cel) and JULIET (tisagenlecleucel), which have demonstrated overall response rates of 50–70% and permanent complete responses in 30–40% of heavily pretreated patients.[9,10] Recently, the ZUMA-7 study compared the anti-CD19 CAR T cells axi-cel to the longstanding standard care for 2nd line relapsed DLBCL: two or three cycles of chemoimmunotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation.[11] Notably, axi-cel treatment led to significant improvements in event-free survival and response as compared with standard care establishing the CAR T cells as the treatment of choice for patients relapsing after chemoimmunotherapy, particularly within the first 12 months. Despite these success there still remains significant unmet need as many patients still relapse, typically as a result of antigen escape via CD19 deletion or downregulation.[12,13] Furthermore, toxicities continue to be a significant challenge with side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) limiting the populations of patients in which they can be safely used.[14]

Bispecific Antibodies for the Treatment of DLBCL

A second strategy has been to develop "bispecific antibodies" (bsAbs) that work by bringing T-cells and B-cells together to eliminate the lymphoma cells. They bind to an antigen on the B-cells (commonly CD20) and CD3 on T-cells, resulting in the formation of an "immunological synapse" between them that activates the T-cells, causing

them to proliferate and release of cytotoxic granules (granzymes and perforin) to kill the CD20-expressing B-cells.[15] An advantage of bsAbs is that, unlike CAR T-cells treatment, they do not require ex vivo T-cell modification and can be administered off-the-shelf. This can be critical in some patients with DLBCL with rapidly progressive disease where the delays during T-cell apheresis and CAR T cells manufacture (typically ~ 3 weeks) can represent significant clinical risk.[16] Several bsAbs have been tested in R/R DLBCL in clinical trials, demonstrating encouraging efficacy with manageable toxicity profiles. Odronextamab, glofitamab, epcoritamab, and mosunetuzumab are some of the well-known bsAbs under investigation.[17] Glofitamab is a 2:1-configured CD20xCD3 bsAb that increases potency and avidity by bivalently binding to CD20. In a Phase II study, Glofitamab demonstrated a total response rate (CR) of 39.4% with an overall response rate (ORR) of nearly 51.6% in patients with R/R DLBCL who had received significant pre-treatment, including CAR T-cell treatment. Its promise as a salvage treatment was highlighted by the persistent median duration of response, which had a 12-month progression-free survival (PFS) rate of approximately 37%.[18] Epcoritamab, a subcutaneously administered CD20xCD3 bsAb, has shown efficacy in R/R DLBCL, including in patients with prior exposure to CAR T cells, with an ORR of 63% and a CR rate of 39% in the EPCORE NHL-1 study.[19] Reduced peak cytokine levels associated with its subcutaneous administration may reduce the incidence and severity of cytokine release syndrome (CRS), a major adverse effect of T-cell-involved therapies.[20] Early-phase trials have demonstrated the anticancer activity of mosunetuzumab and odronextamab, with tolerable tolerability profiles and ORRs ranging from 35 to 60%. The versatility of bsAb treatment in DLBCL has been highlighted by the efficacy of odronextamab in the CAR T-cell-exposed and CAR T cells-naïve populations.[21] Notably, mosunetuzumab has gained provisional European Medicines Agency (EMA) clearance for R/R follicular lymphoma and is being studied in DLBCL.[22] These clinical results demonstrate the wide-ranging therapeutic potential of bsAbs in DLBCL, exhibiting effectiveness in a variety of patient demographics, including those with resistant or relapsed illness. As with CAR T cells, patients do experience toxicities with CRS and ICANS both being observed, albeit less frequently and of lower severity than seen with CAR T cells. The major disadvantage of bsAb treatment compared to CAR T cells is that they are ongoing treatments that require repeated dosing, whereas CAR T cells are typically a "one-shot" approach and can persist and mount anti-tumor responses months or years after initial infusion. Optimizing the safety and efficacy profile of bsAb treatment in DLBCL will require ongoing improvements to dose and monitoring in clinical trials, with particular attention to combination therapies and sequencing approaches.[23]

Immunomodulatory Drugs for DLBCL

A further group of agents with immunotherapy activity are the immunomodulatory drugs (IMiDs). After initial development in multiple myeloma, subsequent studies have demonstrated clinical activity in several of the lymphomas, including DLBCL. Lenalidomide is a second-generation IMiD that primarily works by attaching to the E3 ubiquitin ligase cereblon to promote ubiquitination and degradation of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3).[24] This has a number of effects on the immune microenvironment, including to increased natural killer (NK) cell activity, and promotion of T-cell activation, proliferation and interleukin-2 (IL-2) synthesis.[25,26] Lenalidomide also acts to enhance immunological synapse formation between T cells and malignant B cells (24), while reducing the impact of immunosuppressive populations such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (T_{regs}), to foster a more pro-inflammatory microenviroment.[25,26] Notably, lenalidomide also has direct anti-lymphoma actions in addition to its immunomodulatory effects. For example, it acts to downregulate pro-survival signals mediated by B-cell receptor (BCR) pathways, something that the ABC subtype of DLBCL is particularly sensitive to these tumor-intrinsic effects.[25–27] The effectiveness of lenalidomide in non-Hodgkin lymphomas has been assessed in clinical trials including AUGMENT and ROBUST, with results differing depending on the subtype.[28] In DLBCL, the ABC subtype appears to benefit the most, since its immunostimulatory properties are complemented by its efficacy against BCR-driven pathways.[29] Although lenalidomide produces moderate results when used alone, better overall response rates and longer-lasting remissions have been noted when paired with rituximab, checkpoint inhibitors, and/or bsAbs. To maximize T-cell fitness and therapeutic effect, sequencing techniques have also been suggested, such as priming with lenalidomide prior to administering bsAb.[30]

The Tumor Microenvironment in DLBCL

A key feature of DLBCL is that it is a highly metabolically active tumor, a feature that underpins the utility of fludeoxyglucose (FDG) positron emission tomography (PET) for the diagnosis, staging and response assessment of this lymphoma. The immune milieu is directly impacted by this metabolic reprogramming, which can promote immunological evasion and treatment resistance. Furthermore, DLBCL is distinguished by metabolic heterogeneity, with subtypes relying on distinct energy pathways based on molecular characteristics and microenvironmental limitations.[31] Some subtypes have high glycolytic activity, which is characterized by elevated lactate formation and glucose absorption in accordance with the Warburg effect.[32] This causes the TME to become acidified, which hinders the action of cytotoxic immune cells and promotes immune suppression.[33,34] In contrast other subtypes of DLBCL exhibit increased mitochondrial activity with OXPHOS and glutaminolysis to maintain redox equilibrium and tolerance to oxidative stress.[35] By generating glutathione, glutamate metabolism strengthens antioxidant defenses and encourages the production of amino acids and nucleotides. Together, glutaminolysis, OXPHOS, and glycolysis demonstrate how metabolically flexible DLBCL cells can be, allowing them to proliferate in low-oxygen and low-nutrition environments. Adding to this adaptability, it has been depicted that hypoxia has a significant action in the immunosuppressive remodeling in TME.[36] Rapid tumor development and an inadequate vasculature produce a hypoxic environment that stabilizes hypoxia-inducible factors (HIFs), especially HIF-1α, which restrict mitochondrial respiration to further shift cellular metabolism toward glycolysis.[37] By upregulating immune checkpoint molecules such PD-L1 and immunosuppressive cytokines, this alteration not only enhances immune evasion but also supports tumor-cell survival.[38] Moreover, the CD39/CD73 axis is also activated by hypoxia, leading to the accumulation of extracellular adenosine, which increases the activity of T_{regs} and decreases the function of effector T-cells and NK cells.[39] These mechanisms work together to produce an immunologically cold environment that promotes treatment resistance.[40] These metabolic and immunosuppressive interactions within the DLBCL TME are summarized in Figure 1.

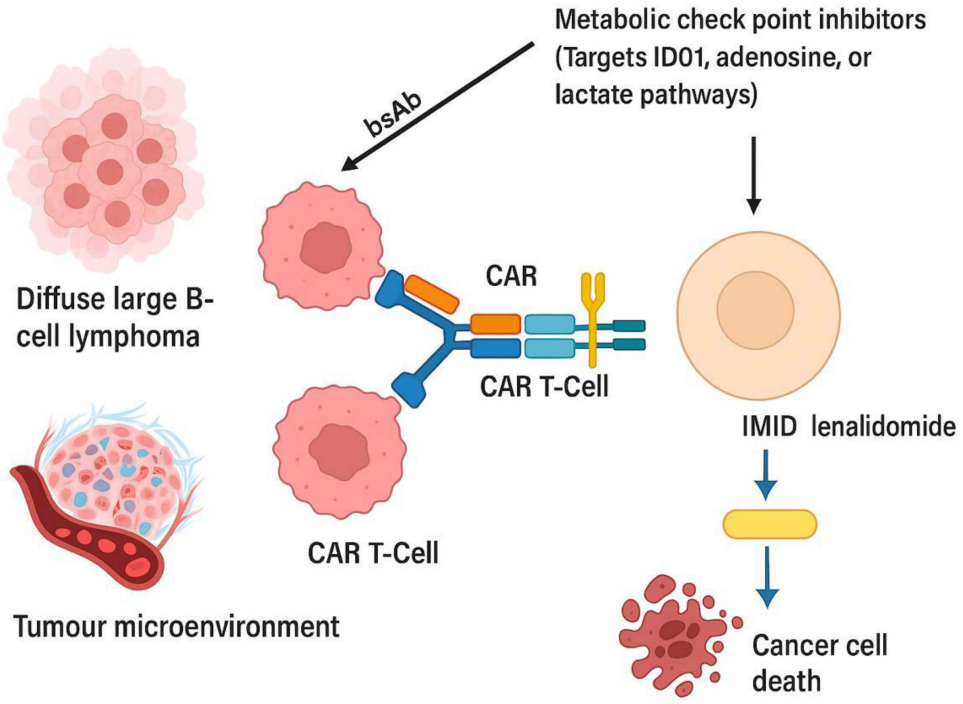

Figure 1 Overview of metabolic and immunological interactions in the DLBCL tumor microenvironment and therapeutic targeting strategies.

Notes: DLBCL cells exhibit metabolic reprogramming characterized by increased glycolysis, glutaminolysis, and oxidative phosphorylation, leading to accumulation of immunosuppressive metabolites such as lactate, adenosine, and kynurenine. These metabolites impair cytotoxic T-cell and natural killer (NK) cell function and promote Treg expansion. Key metabolic checkpoints include indoleamine 2,3-dioxygenase 1 (IDO1), arginase, monocarboxylate transporters (MCT1/4), and the CD39/CD73–adenosine axis. Immunotherapeutic modalities including CAR T cells, bsAbs, and IMiDs aim to restore anti-tumor immunity but are limited by the immunosuppressive TME. MCIs may enhance these therapies by restoring T-cell metabolic fitness and reducing immunosuppression.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; TME, tumor microenvironment; CAR, chimeric antigen receptor; bsAbs, bispecific antibodies; IMiDs, immunomodulatory drugs; IDO1, indoleamine 2,3-dioxygenase 1; MCI, Metabolic checkpoint inhibitors; MCT, monocarboxylate transporter; NK, natural killer; Treg, regulatory T cell.

Immune function is significantly impacted by the competition between immune effector cells and DLBCL cells for vital nutrients. Tumor cells utilize glucose and amino acids, which leads to nutritional depletion of the TME that inhibits T-cell proliferation and cytokine production.[41] Tryptophan is depleted by IDO activity in DLBCL, resulting in kynurenine, which decreases cytotoxic T-cell function and encourages T_{reg} differentiation.[42] Lactate buildup in the TME decreases CD8+ T- and NK-cell activity, and dendritic cell activation, whereas extracellular potassium from tumor necrosis weakens the antitumor response by blocking T-cell receptor signalling.[43] In the DLBCL microenvironment, innate immune cells also are essential for maintaining immune suppression via metabolic and signaling mechanisms. Tumor-associated macrophages (TAMs), typically exhibit an M2-like phenotype, secreting anti-inflammatory cytokines such as TGF-β and IL-10, and facilitating tissue remodeling, angiogenesis, and immune evasion through their oxidative metabolism and fatty acid oxidation (FAO).[44] Myeloid-derived suppressor cells (MDSCs), which are prevalent in peripheral blood and the TME of DLBCL patients, use arginase and inducible nitric oxide synthase (iNOS) to break down arginine and produce nitric oxide to restrict T-cell proliferation and activation. Additionally, MDSCs generate peroxynitrite and reactive oxygen species (ROS), which obstruct effective immune responses by interfering with T-cell receptor communication.[45] In addition to these impacts, stromal elements in lymphoid tissue actively modify the TME by means of cytokine signaling and metabolic interactions. DLBCL cells have a dynamic relationship with stromal cells such as cancer-associated fibroblasts (CAFs) as well as follicular dendritic cells, which generate chemokines such CXCL12 and CCL19 that regulate immune cell trafficking and enhance the survival and spread of lymphoma cells.[46] Among the cytokines produced by tumor and stromal cells, TNF-α, IL-6, and IL-10 further modulate immunosuppressive or metabolic support. For instance, IL-6 stimulates immunosuppressive myeloid populations to proliferate and DLBCL cells to engage in glycolytic activity by triggering STAT3 signaling.[47] The combination of these interactions creates a metabolically unfavorable and immunologically suppressive milieu that encourages tumor development and presents a significant challenge to effective immunotherapy.[48]

Metabolic Checkpoint Inhibition in DLBCL

Given the complex interplay between immunological dysfunction and metabolic abnormalities in DLBCL, investigation of metabolic checkpoint inhibitors (MCIs) as a treatment approach to boost anti-tumor activity and restore immune surveillance is an intriguing and relatively new approach.[49] Several studies have examined the potential for targeting the adenosine axis (CD73, CD39, A2A receptors), lactate metabolism, glutaminase, arginase, and IDO1 (indoleamine 2,3-dioxygenase) to enhance anti-cancer immune response. These inhibitors can restore immunological resistance by reviving cytotoxic T- and NK-cell activity, decreasing nutritional competition, and blocking metabolite-driven immunosuppression.[50] In hematologic malignancies such as DLBCL, MCIs may improve treatment effectiveness when combined with immunotherapies, by addressing on both immunological and metabolic vulnerabilities inside the TME.[51]

A particular area of interest has been the tryptophan-kynurenine pathway. Tumors use this pathway, which is controlled by IDO1 and IDO2, as a vital metabolic checkpoint to create immunological tolerance. Tryptophan depletion from increased levels of IDO1 causes T-cell anergy, while kynurenine buildup triggers immunosuppressive pathways mediated by the aryl hydrocarbon receptor (AhR).[52] In DLBCL, higher IDO1 expression is linked to a worse prognosis and less T-cell infiltration. Preclinical studies have demonstrated that IDO1 inhibitors enhance anti-tumor immunity, enhance T-cell proliferation and reduce T_{reg} infiltration.[53] Epacadostat is a potent and selective IDO1 inhibitor, originally developed to counteract tumor-induced immunosuppression. When used alongside bispecific antibodies (bsAbs) that engage CD3 and tumor-associated antigens, and immune checkpoint inhibitors like anti-PD-1/PD-L1, epacadostat may help restore T-cell functionality, enhance cytotoxic responses, and overcome TME-driven resistance. This tri-modality approach has the potential to improve outcomes in patients with relapsed and refractory DLBCL.[54] Early-phase studies employing epacadostat, and the other IDO inhibitors indoximod and navoximod, have shown the ability to transform immune cell morphologies and decrease kynurenine levels in patients.[55] However, the effectiveness of immunotherapy/IDO inhibitor combinations has been questioned by the ECHO-301/KEYNOTE-252 study, since epacadostat with pembrolizumab did not improve progression-free survival in melanoma patients.[56] Despite this, a small number of cohort studies have shown promising immune activation in hematologic settings, with increased CD8+ T-cell infiltration and a reduction in T_{regs} in the TME.[57] However, robust clinical evidence in DLBCL

remains limited, and the efficacy of IDO1 inhibition in this disease will require validation in well-designed prospective clinical trials. The current status of metabolic and immunotherapeutic interventions in DLBCL is summarized in Table 1.

Another MCI target is the enzyme arginase, mostly generated by myeloid-derived suppressor cells (MDSCs), thereby reducing arginine in the TME, thus impairing T-cell activity and proliferation. In addition to MDSCs, tumor-associated macrophages also promote immunosuppressive arginine metabolism in DLBCL, impeding

Table 1 Summary of Metabolic and Immunotherapeutic Interventions in DLBCL

Therapeutic Area	Key-Agents	Patient Population/ Trial Context	Phase	Key Outcomes / Findings	Key Refs
IDO1-Inhibition	Epacadostat, Indoximod, Navoximod	Melanoma (ECHO-301); early hematologic malignancy cohorts including DLBCL	Phase III (melanoma); Phase I/II (hematologic)	No PFS benefit in melanoma (ECHO-301); in hematologic malignancies, associated with ↓ Tregs, ↑ $CD8^+$ T-cell infiltration, and modulation of kynurenine levels; no definitive efficacy data in DLBCL	[52,54,55]
CB-1158 (Arginase inhibitor)	CB-1158 (Arginase inhibitor)	Preclinical lymphoma models; early solid tumor trials	Preclinical / Phase I	Restores arginine availability; enhances T-cell proliferation and function; reverses myeloid-mediated immunosuppression; DLBCL-specific clinical data pending	[58]
Glutamine Metabolism Inhibition	CB-839 (Telaglenastat)	Relapsed/refractory DLBCL; solid tumors and AML	Phase I	- Modest activity as monotherapy (mainly stable disease); acceptable safety profile; strong preclinical rationale for combination with immunotherapy	[31,59]
Lactate Metabolism Inhibition	AZD3965 (MCT1 inhibitor); LDHA inhibitors (eg., FX11)	Advanced solid tumors and lymphomas including DLBCL	Phase I	Well tolerated; limited single-agent efficacy; compensatory MCT4 upregulation observed; preclinical data suggest improved T-cell infiltration when combined with immunotherapy	[60–62]
Adenosine Pathway Inhibition	CPI-444 (A2AR antagonist); CD73/ CD39 inhibitors	Solid tumors; preclinical lymphoma models	Phase I / Preclinical	Restores effector T-cell function; enhances $CD8^+$ T-cell infiltration; synergizes with PD-1 blockade and T-cell–engaging therapies in preclinical models	[63–65]
Combination Therapy: Bispecific Antibodies+MCIs	Glofitamab, Epcoritamab +MCIs (IDO1 inhibitors, CB-839,AZD3965, etc)	Preclinical lymphoma models	Preclinical	MCIs improve T-cell metabolic fitness, reduce exhaustion, and enhance bsAb-mediated cytotoxicity; no published DLBCL-specific clinical trials to date	[50,53]
Combination: CAR T Cells + MCIs	CAR T + MCT1, A2AR, glutaminase inhibitors	Preclinical B-cell malignancy models	Preclinical	Improved CAR T persistence, cytokine production, and antitumor efficacy; potential to overcome metabolic resistance in hostile TMEs	[62,65]
Immune Checkpoint Inhibitors + MCIs + Combination Therapy	Anti- PD-1/PD-L1 antibodies combined with indoximod	Solid tumors; exploratory hematologic cohorts	Phase I/II	Mixed efficacy; improved immune activation in select contexts; DLBCL-focused trials remain limited	[53,55]

Abbreviations:AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IDO, indoleamine 2,3-dioxygenase; LDHA, lactate dehydrogenase A; MCI, metabolic checkpoint inhibitor; MCT, monocarboxylate transporter; ORR, overall response rate; PFS, progression-free survival; TME, tumor microenvironment.

effective immune responses.[58] Preclinical models have exhibited that arginase inhibitors such as CB-1158 can improve T- cell activation and block tumor growth. Inhibitors of arginase are presently being assessed in early-stage clinical trials for hematological cancers including DLBCL. As the effectiveness of immunological-based treatments like bispecific antibodies or CAR T-cell therapy can be jeopardized by arginine deficiency, arginase inhibition can be expected improve T-cell activity and reverse immunosuppression within the TME, making them a promising adjuvant in combination with existing immunotherapies.[63]

A further exciting prospect is the adenosine pathway, mediated by the enzymes CD39 and CD73 which act in succession to convert ATP into adenosine, which acts on its receptors A2AR and A2BR. Increased expression of CD39 and CD73 raises the concentration of extracellular adenosine in the TME, inhibiting T-cell effectiveness and cytokine production. By lowering T- or NK-cell responses, the elevated adenosine levels in the lymphoma microenvironment aid tumor immune evasion.[64] Researchers have developed a selective antagonist of A2AR, CPI-444, to combat adenosine-mediated immunosuppression in the TME. Blocking A2AR with CPI-444 has been shown to improve tumor infiltration by CD8+ T cells, restore effector T-cell function, and work in concert with other immunotherapies like PD-1/PD-L1 blockade or bispecific antibodies in preclinical murine models, including in lymphomas.[65] Because of this, A2AR inhibition is a potentially useful addition to combination treatments for DLBCL, especially in immunosuppressive TMEs with elevated adenosine levels. Drugs like CPI-444 may enhance CAR T cells and bsAb-driven T-cell responses and demonstrate clinical efficacy by blocking this metabolic immunological checkpoint.[66]

Lactate, a product of tumor glycolysis, builds up in the TME and contributes to immunological dysfunction and acidosis by preventing T-cell proliferation and cytokine production. DLBCL frequently exhibits increased lactate dehydrogenase A (LDHA), which supports the glycolytic phenotype and is associated with aggressive illness, likely reflecting that fact that LDHA expression is controlled by the *MYC* oncogene.[60] The Warburg metabolism exhibited by many tumors including DLBCL results in high intracellular lactate levels that are subsequently exported by monocarboxylate transporters (mostly MCT1 and MCT4). This metabolic inhibition can be repaired by inhibiting MCT1 and LDHA (lactate dehydrogenase A), which has been demonstrated to improve CD8+ T-cell infiltration and function in preclinical studies. Patients with relapsed/refractory DLBCL and advanced solid tumors participated in the first-in-human clinical trial of the selective MCT1 blocker, AZD3965. Although the medication was generally well tolerated, its clinical efficacy as monotherapy was limited. Although there were some patients with stable disease, there were no discernible objective responses.[61] Crucially, further work has shown that MCT1 inhibition might cause MCT4 to be upregulated in response, which could lessen the effectiveness of MCT1 as a stand-alone treatment.[62] Considering these drawbacks, a logical approach could be to combine MCT1 inhibitors with immunotherapies, including bsAbs. Particularly in metabolically hostile or "cold" DLBCL subtypes, MCT1 inhibition may prime the TME to be more responsive to bsAb-driven T-cell cytotoxicity by reducing lactate-mediated immunosuppression. This combination strategy might also enable reduced bsAb dosage, which could lower toxicities linked to cytokine release. Given the compensatory upregulation of MCT4 following MCT1 inhibition, dual inhibition of MCT1 and MCT4 has emerged as a potential strategy to more effectively disrupt lactate transport and overcome metabolic resistance. Preclinical studies suggest that this approach may enhance intratumoral immune activation and improve the efficacy of immunotherapies; however, clinical validation is currently lacking.

Both tumor growth and T-cell activity depend on glutamine, resulting in metabolic competition in the TME. Glutamine dependence or "addiction" has been demonstrated to be a particular feature of MYC-transformed cells offering a potential therapeutic opportunity.[67] This led to the developed of inhibitors of glutamine metabolism, such as the glutaminase inhibitor CB-839 (telaglenastat), which have demonstrated anti-tumor effect in preclinical DLBCL models. However, CB-839 showed poor efficacy as a monotherapy in relapsed/refractory DLBCL in early-phase clinical trials, with the majority of patients only obtaining stable disease, although it was typically well tolerated.[59] The combination of CB-839 with immunotherapies such as CAR T, bsAbs and IMiDs may act synergistically to enhance anti-lymphoma immune responses. The challenge will be that metabolic inhibitors such as CB-839 may also affect T-cell function which may limit their clinical effectiveness; however, it may just be the case of finding an effective "therapeutic window" as with many other anti-cancer agents.[68] The current status of the clinical testing of MCIs in lymphoma is summarized in Table 2.

Table 2 Overview of Clinical Studies Investigating Metabolic Checkpoint Inhibitors in DLBCL

Target/Pathway	Combination	Patient Population	Sample Size (n)	ORR (%)	CR (%)	PFS	Key References
IDO1	± anti–PD-1	Relapsed/refractory DLBCL	30–60	Limited activity	Low	Not mature	[52,54,55]
Arginase	+ pembrolizumab	Advanced malignancies (incl. lymphoma subset)	Small subset	Preliminary activity	Not defined	Not mature	[58]
Adenosine (CD73/ CD39)	+ durvalumab	Advanced cancers	Small subset	Modest	Low	Not mature	[63–65]
Lactate (MCT1)	Monotherapy / combinations	Advanced cancers (incl. lymphoma)	Small cohort	Early signals	Not defined	Not mature	[60–62]
Glutamine metabolism	+ rituximab-based therapy	Hematologic malignancies	Limited DLBCL data	Early activity	Not defined	Not mature	[31,59]
Multiple pathways	+ CAR-T / bsAbs (emerging)	DLBCL	N/A	Not established	N/A	N/A	[50,53]

Notes: Despite compelling preclinical evidence supporting the role of metabolic reprogramming in tumor immune evasion, translation into clinical benefit remains limited. Most available data derive from early-phase trials with small sample sizes or heterogeneous patient populations, and DLBCL-specific outcomes are often underreported. Consequently, while early signals of activity have been observed, the overall efficacy of these approaches remains uncertain. These limitations highlight a critical need for well-designed, disease-specific clinical trials and biomarker-driven strategies to better define the role of metabolic targeting in DLBCL. **Abbreviations**: ORR, overall response rate; CR, complete response; PFS, progression-free survival. Data for DLBCL-specific cohorts remain limited, and many findings derive from early-phase trials requiring further validation.

Further Considerations: Predictive Biomarkers and Toxicity

Identifying predictive biomarkers will be essential to guide patient selection for metabolic-immunotherapy combinations in DLBCL. IDO1 expression has been associated with poor prognosis and may serve as a potential biomarker for response to IDO1 inhibition.Metabolic subtyping of DLBCL, including glycolytic versus oxidative phenotypes, may also inform therapeutic vulnerabilities and guide the use of specific metabolic inhibitors.Furthermore, immune profiling, including assessment of T-cell infiltration, immune checkpoint expression, and cytokine signatures, may help predict responsiveness to combination strategies. In addition, focusing on metabolic biomarkers in the tumor biopsy or even within patient's serum may also provide valuable information to guide therapeutic decision-making.[69,70] Despite these promising avenues, biomarker-driven approaches in DLBCL remain underdeveloped and require further validation in clinical studies. This is an important question due potential toxicity concerns, meaning that it will be critical to identify which patients are most likely to benefit from these treatments. In particular, while combining MCIs with immunotherapies offers significant therapeutic promise, it also raises important safety considerations. Immune-related toxicities such as CRS and ICANS, already observed with CAR T-cell and bsAbs, may be exacerbated by metabolic modulation. Additionally, systemic targeting of metabolic pathways such as glutamine metabolism or lactate transport may affect not only tumor cells but also activated immune cells, potentially impairing T-cell proliferation and function. Mitigation strategies may include careful dose optimisation, sequential rather than concurrent administration, and patient selection based on metabolic and immunological biomarkers as above. Further clinical studies are required to define the therapeutic window and safety profile of these combination approaches.

Conclusion

DLBCL is an aggressive high-grade form of lymphoma which requires metabolic reprogramming to facilitate its fast growth. This results in the depletion of vital nutrients from the TMA and build-up of immunosuppressive metabolites which can promote immune evasion and reduce the efficacy and durability of modern immunotherapies. The metabolic changes that lead to T-cell dysfunction and immunological evasion include elevated IDO activity, adenosine and lactate buildup, and altered glutamine metabolism. Targeting these metabolic checkpoints offers an approach to improve T-cell fitness and to boost the effectiveness of immunotherapies. There is preclinical and preliminary clinical evidence that metabolic checkpoint inhibitors can alter the immunological landscape in B-cell malignancies. These inhibitors have

demonstrated synergistic potential when combined with immunotherapies, leading to improved anti-tumor efficacy in preclinical models, decreased immunosuppressive metabolite levels, and increased T-cell activation. Future research directions include determining the optimal sequencing and dose for combination therapy, identifying biomarkers for patient stratification, and developing clinical studies to understand the safety and its effectiveness of combinatorial strategies.[71–74] Recent studies have further highlighted the role of metabolic-immune interactions in shaping therapeutic responses in lymphoma, supporting continued investigation of combinatorial strategies.

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