**MYD88^{L265P} and CD79B double mutations type (MCD type) of diffuse large B-cell lymphoma: mechanism, clinical characteristics, and targeted therapy**

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**Abstract:** MYD88/CD79B-mutated (MCD) genotype is a genetic subgroup of diffuse large B-cell lymphoma (DLBCL) with the co-occurrence of MYD88^{L265P} and CD79B mutations. MCD genotype is characterized by poor prognosis and extranodal involvement especially in immune-privileged sites. MCD model is dominated by activated B-cell (ABC)-like subtype of DLBCLs. It is generally accepted that the pathogenesis of MCD DLBCL mainly includes chronic active B-cell receptor (BCR) signaling and oncogenic MYD88 mutations, which drives pathological nuclear factor kappa B (NF-κB) activation in MCD lymphoid malignancies. CD79B and MYD88^{L265P} mutations are frequently and contemporaneously founded in B-cell malignancies. The collaboration of the two mutations may explain the unique biology of MCD. Meanwhile, standard immunochemotherapy combine with different targeted therapies worth further study to improve the prognosis of MCD, according to genetic, phenotypic, and clinical features of MCD type. In this review, we systematically described mechanism, clinical characteristics, and targeted therapy of MCD DLBCL.

**Keywords:** CD79B, chronic active BCR signaling, diffuse large B-cell lymphoma, MYD88, NF-κB

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**Introduction**

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous diagnostic type of lymphomas which consists of molecularly distinct subtypes differing in genetic aberrations, pathogenesis, clinical manifestation, and prognosis. Presently, gene expression profile-based molecular classification of DLBCL mainly distinguishes following subtypes: activated B-cell (ABC)-like lymphoma, germinal-center B-cell (CGB)-like lymphoma. A novel genetic classification system of DLBCL, which was uncovered by R. Schmitz et al. in 2018, distinguished four prominent categories (MCD, BN2, N1, and EZB) that differ phenotypically and genetically. MCD is a genetic subtype of DLBCLs with the coexisting of MYD88^{L265P} and CD79B mutations occurring in around 8% of DLBCLs overall, which is dominated by ABC subgroup of DLBCLs and particularly prone to extranodal sites. Myeloid differentiation primary response protein 8 (MYD88), an adaptor protein for the Toll/interleukin-1 receptor (TIR), has been mainly discovered as a common somatic mutation in Waldenström’s macroglobulinemia (100%) and 39% of ABC DLBCLs. A single amino acid replacement that changes a leucine residue at position 265 of the MYD88 coding region to proline (L265P) was most frequent type of nucleotide variant accounting for 75% of the MYD88 mutations. The co-occurrence of mutations in CD79B and MYD88 indicates a distinct molecular pathogenesis of MCD, which influence key proteins for BCR and TLR signaling, respectively.

Meanwhile, MCD is featured by great heterogeneity among different types and primary sites of lymphoma. The concurrence of MYD88 and MYD88^{L265P} and CD79B double mutations type (MCD type) of diffuse large B-cell lymphoma: mechanism, clinical characteristics, and targeted therapy

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CD79B mutations enriched for primary extranodal diffuse large B-cell lymphomas especially in immune-privileged sites (including 48–56% primary central nervous system (CNS) and 19–27% primary testicular DLBCL) and 33% of Waldeyer’s ring and paranasal sinuses (ENT).7–11 In addition, MCD type also occurs in 14% of Primary Adrenal DLBCL,12 11–25% of primary breast DLBCL, 20% of intravascular large B-cell lymphoma,13 and <56% of primary cutaneous DLBCL-leg type.14 Conversely, this type is few or inexistence in other DLBCL subtypes, such as gastrointestinal DLBCL15,16 and nodal lymphoma. See Table 1 for details.

This review summarizes molecular mechanism and clinical features of DLBCL with the concurrence of MYD88 and CD79B mutations, meanwhile discusses their clinical implications for mechanism-based therapeutics.

**Oncogenic aberrations and pathogenesis signaling**

**Oncogenic MyD88 mutations and NF-κB activation**

MYD88 is an adaptor protein that mediates the interleukin-1 (IL-1) receptors as well as the Toll-like receptors (TLRs) signaling to activate the NF-κB activation.20 IL-1/Toll receptors participate in host responses to invasion and infection from outside, which recognize multiple pathogen-associated molecular patterns (PAMPs) from bacteria and viruses.21,22 TIR is a common domain of IL-1 receptors and TLRs, which will undergo a conformational change after receptor binding and then combine with the C-terminal TIR domain of MyD88 via TIR–TIR interactions.23 Structurally, MYD88 contains its TIR domain, an N-terminal death domain (DD) and a short intermediate domain (ID). Through the N-terminal DD, MYD88 connects with IRAKs (IRAK1, 2, 4) and recruits the E3 ubiquitin ligase tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), forming a high-molecular weight signaling complex (Myddosome).24 The interaction of TRAF6 and IRAK1 activates the downstream signalings and then triggers canonical B-cell receptor (BCR)-dependent nuclear factor κB (NF-κB) activation.25 NF-κB is considered as a family of transcription factors and its oncogenic function in human lymphomas has been established by genetic evidence and mouse models.26 Aberrant NF-κB activation has been stated in a series of lymphoid malignancies, including the ABC-like subtype of diffuse large B-cell lymphoma (ABC DLBCL), Hodgkin lymphoma (HL), PMBL, lymphomas of the
mucosa-associated lymphoid tissue (MALT lymphoma), and multiple myeloma (MM).\textsuperscript{27–30} The ABC DLBCL subtype depends on constitutive NF-κB signaling to block apoptosis but the GCB subtype of DLBCL does not.\textsuperscript{31} Recurrent genetic lesions driving pathological NF-κB activation include (1) mutations in the BCR subunit CD79B in ABC DLBCL, (2) activating mutations in the CARD11 coiled-coil (CC) domain, (3) mapping of MYD88 mutations acquired in human lymphoma, and (4) loss of A20.\textsuperscript{32}

The affection of MYD88 on ABC DLBCLs was initially discussed in 2011. The essential function of MYD88 on ABC DLBCL survival was revealed by RNA interference screening. About 29\% of ABC DLBCLs carry the p.L265P mutation in the hydrophobic core of the MYD88 TIR domain leading to NF-κB activity elevating.\textsuperscript{5} Gero Knittel \textit{et al.}\textsuperscript{33} also found that B-cell-specific expression of MYD88 p.L252P is sufficient to trigger the development of DLBCL in mice. In addition, they confirmed that BCL2 amplifications frequently co-occurred with MYD88 mutations. A recent study also showed that MYD88 and Bcl2-driven mouse model resembled features of human ABC DLBCL. The MYD88 mutation cooperates with BCL2 amplifications in ABC DLBCL lymphomagenesis.\textsuperscript{33,34} Furthermore, mutation of the TIR adapter molecule MYD88 could also promote the production of interferon β (IFN-β), which have both autocrine and immunomodulatory function.\textsuperscript{35}

\textit{Chronic active BCR signaling}

CD79A (Ig-α) and CD79B (Ig-β) formed a CD79A/CD79B heterodimer by a disulfide bond mediating chronic BCR signaling.\textsuperscript{36} CD79A/B divides into membrane and cytoplasmic regions. On one hand, CD79A/CD79B heterodimers associate covalently with antigen-binding IgH and IgL chains of BCR in membrane regions. On the other hand, within the cytoplasmic domains, CD79A/B has immunoreceptor tyrosine–based activation motifs (ITAMs) that are critical for initiating an intracellular signaling cascade in response to receptor involvement.\textsuperscript{37,38} As we know, BCR plays an irreplaceable role in B-cell antigen-mediated activation, proliferation, and differentiation. Antigen binding promotes tyrosine phosphorylation of the ITAMs of CD79A/B by SRC-family kinases. Phosphorylated ITAMs recruit SYK through interacting with their tandem SH2 domains, resulting in SYK auto-phosphorylation, and initiating the intracellular signaling cascade.\textsuperscript{39,40}

BCR signaling plays a crucial part in pathogenic mechanism of lymphomas for its participation in the activation of the NF-κB pathway. R. Eric Davis \textit{et al.} found that knockdown of the essential BCR subunits CD79A/B or of downstream signaling effectors, such as Bruton’s tyrosine kinase (BTK) and SYK, decreased the expression of NF-κB target genes. Yosef Refaeli \textit{et al.}\textsuperscript{42} provided direct evidence for the role of the BCR in the genesis of B-cell lymphomas through mouse model reconstruction.

Mutations that influence the ITAMs of CD79B occur in more than 20\% of ABC DLBCLs.\textsuperscript{41} CD79B mutations alone could not stimulate the NF-κB pathway in ABC DLBCL cells. CD79B mutations increase surface expression of the BCR and reduce activation of the tyrosine kinase LYN, therefore increasing surface IgM and causing B-cells to respond improperly to BCR stimulation through foreign or self-antigens.\textsuperscript{41,44} LYN promotes BCR internalization and mediates negative feedback on BCR signaling.\textsuperscript{45} Normally, B-cells are resistant to self-antigens and will occur anergy or apoptosis when their receptors are repeatedly engaged by self-antigens. Instead, CD79B ITAM mutations form prominent BCRs clustering on the ABC DLBCLs cell surface. Then combination of BCRs to self-antigens actives chronic active BCR signaling and maintains the malignant survival of ABC DLBCL cells.\textsuperscript{46}

\textit{Synergistic cooperation between MYD88L265P and CD79B mutations.} Simultaneous detection of CD79B and MYD88 mutations in B-cell tumors is frequent, among patients with a MYD88L265P mutation, 34\% had a coincident CD79B/A mutation.\textsuperscript{5} The cooperation of these two mutations may explain clinical features of MCD DLBCLs. Normally, B-cells would down-regulate their surface BCR expression and then occurs anergy or apoptosis after long-term exposure to self-antigens. Low surface IgM expression can be regarded as checkpoints. The body make those self-reactive B-cells apoptosis through IgM expression, thereby preventing the occurrence of immune system tumors.\textsuperscript{43} Surface BCR density is regulated by many factors by controlling IgM antigen receptor synthesis and transport.\textsuperscript{47}
The expression of MYD88<sup>L265P</sup> block surface BCR transport and accumulation on the surface thus reduce their surface IgM, which is similar to chronic repeated exposure to self-antigen. Therefore, MYD88<sup>L265P</sup> alone is insufficient to break tolerance checkpoints. On the contrary, CD79 mutations maintain high BCR levels at the cell surface, which may change the response of B-cell to self-antigen from apoptosis into proliferation. Collectively, the combination of CD79B and MYD88<sup>L265P</sup> mutations cooperates to induce B-cell to differentiate into plasma cells and break tolerance checkpoints in B-cells in peripheral blood lymphoid tissue. 48

Another mechanism about how these two mutations work together was proposed by James D. Phelan et al. in 2018. They proposed that My-T-BCRsupercomplex, which comprised of the BCR, TLR9, MYD88, and associated signaling mediators, could coordinate NF-κB signaling and promote dependence on BCR signaling in the subgroup of ABC DLBCL belonging to the MCD. 49

**Clinical presentation**

**Advantaged pathogenesis of MCD genotype in immune-privileged microenvironment**

As mentioned above, MCD lymphoma has distinctive clinical and biological features. MCD lymphoma mainly occurs in the CNS, testis, and other immune barrier tissues. Organ-specific microenvironment is very important for the occurrence of tumor. 50 Recent studies have shown that CD79B and MYD88 mutations do not usually coexist with BCL2, BCL6, and cMYC, or Epstein–Bar virus infection. 6,51 This is consistent with the characteristic that MCD lymphoma usually appears in barrier-protected tissues. In these tissues, stimulation by TLR ligands endows lymphoma-initiating cells with a selective growth advantage. Notably, the ABC subtype of DLBCL seems to be more dependent on the chronic BCR signal driven by autoantigens. 46 The existence of CD79b (or other BCR pathway) mutation may cause chronic active BCR signal, which may further improve the selective growth of cancer cells in these relatively stimulus poor microenvironments. Immune barrier improves the possibility of autoimmune leading to tumor, forming an immunologically specific environments, though avoiding external immunity.

**Distinctive biological features linked to immune evasion and extranodal involvement**

Wright et al. 52 hypothesized that there is a link of MCD genotype and immune evasion. MCD tumors were featured by having one or more lesions that damage MHC class-I antigen presentation or activate T and NK cells. Immune evasion could be explained by following several mechanisms (1) MHC class I or TAP1 inactivation, (2) decreased NK activation for CD58 inactivation, and (3) diminished T-cell activation result from gene fusions encoding programmed death ligand 1 (PD-L1) and PD-L2. 53,54 Immune evasion and immunologic barrier allows MCD DLBCL become ‘invisible’ to immune surveillance.

As for extranodal involvement (END), Rong Shen established Zebrafish models to reveal the binding of MYD88 mutations and invasion of the kidneys and gonads. MYD88 has been confirmed as important biomarker of ENI in DLBCL in their research. 55 Moreover, Schrader et al. 13 also found that intravascular large B-cell lymphoma owns high prevalence of MYD88 and CD79B mutations, predominantly involving the skin and the CNS. Besides, dysregulation of 'homing' of lymphoma cells with carcinogenic MYD88 and/or CD79 mutations may be another mechanism for the site-specific differences in the incidence of these mutations observed in DLBCL. 56 Generally, activating mutations in MYD88 and CD79B have been proved as significant molecular drivers of pathogenic mechanism of lymphomas in immune-privileged sites, including the CNS and testes. 51

**Morphologic features of MCD-type DLBCL**

A study about primary adrenal DLBCL may provide morphologic clues for lymphoma owning both MYD88 and CD79B mutations. The neuroendocrine carcinoma–like type (NEC-like type) indicated CD79B mutation, while the RS-like cell type was associated with MYD88<sup>L265P</sup>. Therefore, biphasic type suggests MYD88<sup>L265P</sup> and CD79B double mutations, which was also observed in primary breast DLBCL. 12

**Outcome and therapy**

A multicenter large-scale study reported that MCD-type DLBCL cases have relatively poor prognosis. 3 The reasons are multiple and still controversial. A recent study found that MYD88 suggested inferior survival outcomes. (MYD88-mutated DLBCLs had a significantly inferior 5-year overall
survival (OS) ($p=0.019$) and inferior 5-year progression-free survival (PFS) ($p=0.049$; HR 1.46). In this research, the prognostic importance of CD79B mutations disappeared in the multivariable analysis.6 But in other study, CD79B mutation or the interaction of MYD88L265P and CD79B mutation could have contributed to the bad outcome.57,58 The MYD88L265P mutations were also significantly associated with old age, ENI, and ABC origin.59

RCHOP regimen, which includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, is currently the standard regimen for DLBCL that can achieve complete remission (CR) in nearly 80% of patients.60,61 However, MCD tumors often secondarily involved immune-privileged sites. Extranodal especially CNS involvement increases the difficulty of treatment. The rate of 5-year overall survival is 40% in all diffuse large B-cell lymphomas and is 37% in the ABC subtype of DLBCL.52 Therefore, it is necessary to prescribe regimen according to the unique biological and clinical characteristics of MCD. Target therapy and early treatment to prevent CNS infiltration are valuable to be discussed for MCD models. See Table 2 for details and following.

**Potential therapeutic targets**

*The inhibition of transducer and activator in MYD88 mutation pathway.* Lenalidomide is an immunomodulatory drug that downregulates interferon regulatory factor 4 (IRF4) and its regulatory partner SPIB in treatment of ABC DLBCL, which amplify pro-survival NF-κB signaling.68 Meanwhile, lenalidomide kills ABC DLBCL cells by increasing production of IFN-β. The oncogenic MYD88 mutation-induced IFN-β production, which promotes cell cycle block and apoptosis.69 Therefore, lenalidomide could be considered to a potential therapeutic choose. Lenalidomide inhibits NFκB as well as the PI3K/AKT pathway.67

Conclusively, lenalidomide owns both direct cytotoxicity to lymphoma cells and indirect modulation of the lymphoma immune microenvironment. A recent study also revealed that lenalidomide is an active agent which had higher response in relapsed/refractory DLBCL in non-germinal center B-cell-like phenotype.62 In an open-label, multicenter, phase-1b/2 study, ibrutinib plus lenalidomide and rituximab demonstrated promising activity in patients with non-GCB DLBCL.63

**IRAK4 kinase is a novel therapeutic target in the ABC DLBCLs.** As mentioned above, MYD88 mutant isoforms form a stable signaling complex containing IRAK4 and IRAK1. IRAK4 kinase inhibition could impact carcinogenesis of MYD88L265P by down-modulating survival signals, including NF-κB and autocrine IL-6/IL-10 involvement of the JAK-STAT3 pathway.70

**High response rate to BTK-inhibitor ibrutinib.** Ibrutinib is an inhibitor of BTK that blocks NF-κB activation downstream of BCR signaling, especially in tumors with CD79B mutations and MYD88 mutated subtypes.64 In a phase-1b study, Lionakis et al. also put forward a view that DLBCL with MYD88L265P and CD79B mutations had significantly higher response rates 4/5 (80%) to ibrutinib, indicating that B-cell lymphomas with these mutations may rely more on BCR signaling.64,72 Christian Grommes et al. revealed monotherapy activity of ibrutinib in patients with relapsed or treatment-refractory PCNSL. Meanwhile, a possible ibrutinib resistance mechanism was proposed, in which CD79B appears to attenuate the ‘addiction’ of BTK by providing redundant survival signals.73 Besides, it is known that mutations in ibrutinib resistance exist in the CC domain of CARD11.64,74 It is reasonable to speculate that the simultaneous mutation of MYD88 may increase susceptibility to ibrutinib. It has been reported that MYD88 could improve the sensitivity of respondence to ibrutinib in Waldenstrom’s macroglobulinemia (WM).75

**JAK-STAT pathway is an attractive therapeutic target for MCD malignancies**

Janus kinase (JAKs) signaling is triggered by autocrine production of IL-6 and IL-10, which is a feature of MCD models. JAKs phosphorylate STAT family members regulating gene expression to promote the tumor cell proliferation and
survival in ABC DLBCL.\textsuperscript{76,77} JAK1 inhibitor in combination with the BTK-inhibitor ibrutinib reduced IRF4 levels and worked together to kill ABC DLBCL cells.\textsuperscript{78} In addition, activation of the phosphatidylinositol 3-kinases (PI3K) pathway is an essential driver of the development of MCD lymphomas.\textsuperscript{79} As a phase-1 study mentioned, a selective JAK1 inhibitor itacitinib (INCB039110) in combination with a PI3K inhibitor showed promising results in nongerminal center B-cell like DLBCL.

### Table 2. Potential therapeutic targets of MYD88/CD79B-mutated (MCD) genotype.

| Clinical trial   | Therapeutic targets | Gene expression signal | Combined regimen | Drug                        | Outcome                                                                 |
|------------------|---------------------|------------------------|------------------|-----------------------------|-------------------------------------------------------------------------|
| Retrospective study\textsuperscript{62} | IRF4 SPIB IFN-β     | MYD88 pathway          | Single-agent lenalidomide | Lenalidomide                | ORR was 9/17 (52.9%) in ABC                                              |
| phase 1b study\textsuperscript{63} | IRF4                | MYD88 pathway          | Ibrutinib plus lenalidomide and rituximab | Lenalidomide | ORR was 11/17 (65%) in non-GCB                                          |
| NA               | IRAK4 kinase        | MYD88 pathway          | NA                | IRAK kinase inhibitors ND-2158 or ND-2110 | –                                                                       |
| Phase-1b study\textsuperscript{64}  | Bruton’s tyrosine kinase (BTK) | BCR signaling        | Single-agent ibrutinib   | BTK-inhibitors ibrutinib   | MCD has higher response rates 4/5 (80%) to ibrutinib                      |
| Phase-2 study\textsuperscript{65} | BTK                 | BCR signaling          | Ibrutinib monotherapy | BTK-inhibitors ibrutinib   | ORR was 10/18 (56%) with relapse/refractory PCNSL or PVRL               |
| Phase-1 study\textsuperscript{66}  | Autocrine IL-6/IL-10 IRF4 | JAK-STAT pathway | A selective JAK1 inhibitor itacitinib (INCB039110) in combination with a PI3K inhibitor | JAK1 inhibitor itacitinib and PI3K inhibitor | Response 4/13 (31%) in nongerminal center B-cell like DLBCL               |

ABC, activated B-cell; BCR, B-cell receptor; DLBCL, diffuse large B-cell lymphoma; IL, interleukin; IFN-β, interferon β; IRAK, interleukin receptor-associated kinase; IRF4, interferon regulatory factor 4; JAK, Janus kinase; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MCD, MYD88/CD79B; PCNSL, primary central nervous system lymphoma; ORR, objective response rate; PI3 K, phosphatidylinositol 3-kinases; PVRL, primary vitreoretinal lymphoma.

Use of small molecules and immune checkpoint inhibitors is important. Ollila et al.\textsuperscript{82} found that DLBCL with CNS recurrence could be predicted better on a molecular basis, mainly divided into two categories (hc-MCD subtype and subgroup with double-hit biology or TP53 mutations).

The remarkable efficacy of ibrutinib for PCNSL has been confirmed by multiple studies.\textsuperscript{64,65,73} Substantially higher response to ibrutinib is closely related to mutations in two pathways in MCD type compared with systemic lymphomas.

### Heterogeneous therapeutic management strategies

**Central nervous system.** CNS prophylaxis via high-dose methotrexate (HD-MTX; 3–8 g/m\(^2\)) or intrathecal MTX is more effectively for MCD DLBCL, which account for about 50%. HD-MTX-based therapy can be considered for fit patients with appropriate conditions. Consolidation therapy is suitable for those who are well enough to tolerate high-dose chemotherapy (HDC) and/or autologous stem cell transplantation (ASCT).\textsuperscript{81} However, the best strategy to prevent CNS relapse remains to be defined.
Immunomodulatory drugs (IMiDs) have been demonstrated to cross the blood–brain barrier, such as lenalidomide and pomalidomide. On the contrary, IMiDs inhibit NF-κB, explaining the advanced therapeutic activity in MCD type of PCNSL. There are several clinical trials exploring the efficacy of IMiDs. Meanwhile, ibrutinib (BTK inhibitor) and lenalidomide (IMiD) have been included in the NCCN Guidelines for consideration as salvage therapies.

**Testis.** So far, surgery, chemotherapy, and radiotherapy are effective means for the treatment of primary testicular diffuse large B lymphoma (PT-DLBCL). However, distant recurrences of the external nodes, particularly in the CNS and the contralateral testis, remain the greatest therapeutic challenges. A multicenter phase-II prospective study found that R-CHOP21 regimen combined with intrathecal methotrexate (IT-MTX) and locoregional RT related to a good outcome in patients with primary testicular lymphoma.

MCD type accounted for around 19–27% of the testicular DLBCL as mentioned above. Carrying oncogenic MYD88 and/or CD79 mutations could further promote the selective growth of the cancer cells in the immune-privileged microenvironment. This alerts us to the importance of CNS prevention for this type of lymphoma. MCD type of PT-DLBCL may benefit from target therapy such as IRAK kinase inhibitors and BTK.

**Other extranodal sites.** The other types of extranodal sites are relatively rare, and the therapeutic targets provided by the MCD gene type (detailed below) may provide new clue for the following types of lymphoma.

Primary adrenal diffuse large B-cell lymphoma (PA-DLBCL) and primary breast diffuse large B-cell lymphoma (PB-DLBCL): The adrenal glands and breast DLBCL similar pathologic types – the biphasic type (in other world, RS-like cells were scattered in the NEC-like background) as mentioned above. PA-DLBCL is characterized with elderly male predominance, advanced clinical stage and poor prognosis. Patients with RS-like cells PA-DLBCL were more likely to involve CNS and the CNS-directed prophylactic interventions should be used in conjunction with initial therapy.

Intravascular large B-cell lymphoma: intravascular large B-cell lymphoma may potentially involve any organ (CNS and skin, etc). Additional researches could be performed to assess whether patients with IVLBCL are more sensitive to treatment with ibrutinib. Analysis of survival conducted by Anne M. R. Schrader et al. found that MYD88 and/or CD79B did not seem to influence disease-specific survival (log-rank $p = 0.64$).

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT): surgery and radiotherapy are still the standard treatments in isolated cutaneous lesions. The therapy of relapsed disease is same to that for relapsed systemic ABC DLBCL. A case was treated with lenalidomide monotherapy and achieved a well curative effect.

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