# ADVANCES IN LLM

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## Could Bispecific Antibodies Be Used as Consolidation Treatment After R-CHOP for DLBCL?

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**H&O** What options are available for consolidation treatment after R-CHOP?

**ML** We have good data regarding the use of radiotherapy after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients who have stage III or IV diffuse large B-cell lymphoma (DLBCL) with substantial bulk. The definition of *bulk* has been a moving target, ranging from 7.0 to 7.5 cm depending on the clinical trial, but the definition does need to differ depending on whether we are talking about Hodgkin lymphoma or non–Hodgkin lymphoma.

Consolidative radiotherapy should be used differently in advanced-stage DLBCL than in early-stage DLBCL. In early-stage disease, we should plan to use radiotherapy as a consolidation treatment for patients who will be receiving a reduced number of cycles of induction chemotherapy. We need to be using a curative intent regimen in patients with early-stage disease, whether that consists of R-CHOP alone or rituximab plus anthracycline-based chemotherapy plus radiation therapy. The only exception would be patients meeting the criteria from the FLYER trial, which found that 4 cycles of R-CHOP were noninferior to 6 cycles of R-CHOP in young patients who had aggressive B-cell non-Hodgkin lymphoma and a favorable prognosis.[1] For these patients, it is reasonable to use this approach rather than a shorter course of chemotherapy plus consolidation radiotherapy.

We have not been able to prove a benefit with the use of medical oncology agents as consolidation therapy, however. The phase 3 ROBUST trial found a trend toward improved progression-free survival with use of the oral immunomodulatory therapy lenalidomide as consolidation therapy in DLBCL, but the difference was not statistically significant and occurred only in high-risk patients.[2] In addition, the use of lenalidomide adds extra toxicities and expense to treatment.

We also have shown that CD20 monoclonal antibodies such as rituximab are not effective as consolidation agents in DLBCL now that we are using them as part of induction treatment. In fact, the GOYA trial found that the seventh and eighth doses of rituximab or obinutuzumab (Gazyva, Genentech) did not improve outcomes even when used as part of induction therapy.[3] It is unfortunate that global trials of DLBCL continue to use 8-cycle rather than 6-cycle regimens because treatment with 8 cycles is no longer considered the gold standard in the United States.

**H&O** What are the limitations of using radiation for consolidation treatment?

**ML** The main limitation is location. Our precision has become much better, which has expanded the locations that can be radiated, but location continues to define whether we can complete therapy in many cases. If we cannot do radiation therapy, patients will need to complete all 6 cycles of R-CHOP unless they meet the FLYER criteria.

**H&O** What are the potential benefits of using bispecific antibodies as consolidation treatment?

**ML** I predict that bispecific antibodies will be used as an extension of induction therapy in the frontline setting. Some people might call this consolidation treatment, but I use that term only when we are using this therapy to improve the depth of remission of patients who are in a metabolic complete response. I refer to the old leukemia principles of induction, consolidation, and maintenance as phases of care on a continuum.

Bispecific antibodies have the potential to add benefit to CHOP, just as rituximab and now polatuzumab vedotin (Polivy, Genentech) have been shown to do. Ongoing trials are comparing bispecific antibody regimens with R-CHOP or with polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP): OLYMPIA-5 (NCT06149286), EPCORE DLBCL-2 (NCT05578976), and SKYGLO (NCT06047080). One advantage of bispecific antibodies is that they appear to be just as effective in patients who have double-hit biology—meaning high-grade B-cell lymphomas with *MYC* and *BCL2* rearrangement—as in the non–double-hit population.

If a patient is not in complete response after induction, I would consider that a failure of primary therapy, and the next step would be second-line therapy rather than consolidation. This is an area where semantics really matter, especially as we talk about novel therapies such as bispecific antibodies, for which we have data in the second-line population. For example, the phase 3 STARGLO trial has shown that the bispecific antibody glofitamab (Columvi, Genentech) plus gemcitabine and oxaliplatin (GemOx) improves overall survival in comparison with rituximab plus GemOx.[4] But again, that is second-line treatment and not consolidation treatment.

If we do develop studies that look at bispecific antibodies as true consolidation treatment, I would expect this approach to be useful only in certain subtypes of patients. A patient in whom a cure has already been achieved with 6 cycles of a bispecific antibody does not need a seventh, eighth, ninth, or 10th dose of that agent because that is just adding more toxicity than is necessary. Patients in whom a cure has already been achieved may not require consolidation, so we need to take a risk-adapted approach.

**H&O** What are the most important studies looking at the use of bispecific antibodies in DLBCL?

**ML** The most important studies looking at the use of bispecific antibodies in DLBCL are the randomized phase 3 SKYGLO and EPCORE DLBCL-2 trials. SKYGLO is enrolling previously untreated patients with CD20-positive DLBCL and randomizing them to Pola-R-CHP with or without glofitamab. Patients in the glofitamab plus Pola-R-CHP group will receive Pola-R-CHP in cycles 1 through 6 and glofitamab in cycles 2 through 8, and patients in the Pola-R-CHP group will receive Pola-R-CHP during cycles 1 through 6 and rituximab in cycles 7 and 8.

EPCORE DLBCL-2 is enrolling patients with newly diagnosed DLBCL; patients are being randomly assigned to either the bispecific antibody epcoritamab (Epkinly, Genmab/AbbVie) plus R-CHOP or R-CHOP alone.

**H&O** What are the adverse events that we worry about most with bispecific antibodies?

**ML** The long-term adverse event that we worry about most with bispecific antibodies is infection, which can be severe and long-lasting. Shorter-term adverse events that we worry about include cytokine release syndrome, which appears to be less frequent if we introduce the bispecific agent later in the treatment regimen. We should have even better data regarding this adverse event after we see the results of SKYGLO and EPCORE DLBCL-2.

***Disclosures***

*Dr Lunning has done consulting for AbbVie, ADC Therapeutics, AstraZeneca, BeOne Medicines, Bristol Myers Squibb, Genentech, Genmab, Incyte, Johnson & Johnson, Kite Pharma, Lyell Immunopharma, Loxo Oncology, Pfizer, Recordati Rare Diseases, and Secura Bio.*

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