



# CANCER NEWS

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**From the Desk of Director Research**

Lymphoma is a type of blood cancer that develops in the lymphatic system, the body's disease fighting network. It is estimated that around 1,000 people worldwide are diagnosed with lymphoma every day. It is typically classified into two groups, Hodgkins lymphoma (HL) and non-Hodgkins lymphoma (NHL), although around 60 biologically distinct subtypes have been identified. While lymphoma is potentially fatal, some forms are curable and a patient's survival may be greatly enhanced by early diagnosis.

Lymphomas are a very complex group of diseases with differing behaviors and treatment options. While all lymphoma types can be cured or managed as a chronic disease, its complexity and variation do not allow for a one-size-fits-all treatment approach. Instead, it necessitates highly specialized and individualized approaches. The cause of the majority of lymphoma cases is unknown, however, there could be several factors that may influence one's risk of developing lymphoma. The relative effects of these factors in any given case of cancer vary and are very difficult to determine with accuracy at present.

Lymphoma biology and immunology have begun an exciting new era in cancer therapy. Unlike most other cancers, the treatment for most of the lymphomas is based on precise pathological subtype more than clinical and radiological stage at the time of diagnosis. The increasing availability of molecular tests has aided the diagnosis of lymphoma, in particular the differential diagnosis of HL and other haematologic malignancies. Lymphoma treatment and prognosis, especially for NHL, are heavily dependent on the disease type and staging. Standard therapy for lymphoma still consists of chemotherapy and radiotherapy, which are associated with short and long term toxicities. Discovery of new treatments for lymphoma that prolong survival and are less toxic than currently available agents represent an urgent unmet need. Emerging novel therapies, such as small molecule and antibodies that preferentially target tumor cells while potentially sparing normal cells, bring new hope to patients with lymphoma.

This issue of Cancer News highlights the newer advances in the field of lymphomas and features the regular articles, such as Special Feature, Guest Article, Watch-Out, Perspective, Research & Development, New Technologies, Clinical Trials, Globe Scan, Cancer Control and In Focus.

We are grateful to the contributions made by Dr Ajay Bapna, Head, Department of Medical and Pediatric Oncology, Bhagwan Mahaveer Cancer Hospital & Research Centre, Rajasthan.

The understanding of lymphomas and its management is changing rapidly. The 13<sup>th</sup> Annual International Conference "RGCON-2014" being organized by the Institute from February 15<sup>th</sup> to 16<sup>th</sup>, 2014 has its main theme as "Lymphoma-Biology to Therapy". It would be a perfect forum to interact with the eminent international and national faculty in this field.

Suggestions/ comments from the readers are welcome.

*Dr D C Doval*

**CONTENTS**

- **Special Feature:** Expanding Role of Immunotherapies in Lymphoma (Beyond Rituximab) [3-6]
- **Guest Article:** Overview and Advances in non-Hodgkin's Lymphoma Treatment [7-9]
- **Watch-Out:** Strategies for Improved Cancer Vaccines [9]
- **Perspective:** Role of PET-CT in the Management of Lymphoma [10-12]
- **Research & Development:** Alterations in Bone Mineral Density; 18 F-Fluorothymidine Uptake; Genome Sequencing; Novel Soluble-Receptor Marker [13]
- **New Technologies:** Breakthrough Therapy for Mantle Cell Lymphoma; Novel Diagnostic Tool for Hodgkin Lymphoma; Topical Drug for Cutaneous T-Cell Lymphoma [14]
- **Clinical Trials:** Drug-Antibody Pair for Non-Hodgkin Lymphoma; Lenalidomide with Rituximab & Bendamustine; Low-Intensity Chemotherapy for Burkitt's Lymphoma; Molecular Profiling for Peripheral T-Cell Lymphomas [15]
- **Globe Scan:** Autologous Stem Cell Transplantation; Genetic Predisposition to Lymphoma; Diabetes Mellitus in Lymphoma Patients; Patterns of Hospice Use [16]
- **Cancer Control:** Birth Characteristics and Risk of Lymphoma; Lymphoma Risk with Ongoing Intestine; Obesity and Diffuse Large B-Cell Lymphoma; UV Radiation and Risk of Hodgkin Lymphoma [17]
- **In Focus:** Double Hit, Triple Hit Lymphoma- Seek and Your Find [18-19]

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## SPECIAL FEATURE

## EXPANDING ROLE OF IMMUNOTHERAPIES IN LYMPHOMA (BEYOND RITUXIMAB)

Therapy for non-Hodgkin's lymphoma has progressed significantly over the last decades. However, a sizeable number of patients remain incurable, and novel therapies are needed. Because immunotherapy ideally offers target selectivity, an ever increasing number of immunotherapies, both passive and active, are under development. The champion of passive immunotherapy to-date is the anti-CD20 monoclonal antibody rituximab that revolutionized the standard of care for lymphoma.

## Passive Immunotherapy by Antibodies

**Anti-CD20 Antibodies:** Rituximab, a human–mouse chimeric IgG1 antibody that targets CD20, revolutionized the treatment of NHL and is now a standard component of first-line therapy. As a single agent or in combination with chemotherapy it improves the overall response rate (ORR), the duration of response and overall survival.

**Mechanisms of Action of Rituximab:** Rituximab depletes both normal and malignant B-cells. Four major mechanisms have been proposed for the action of rituximab:

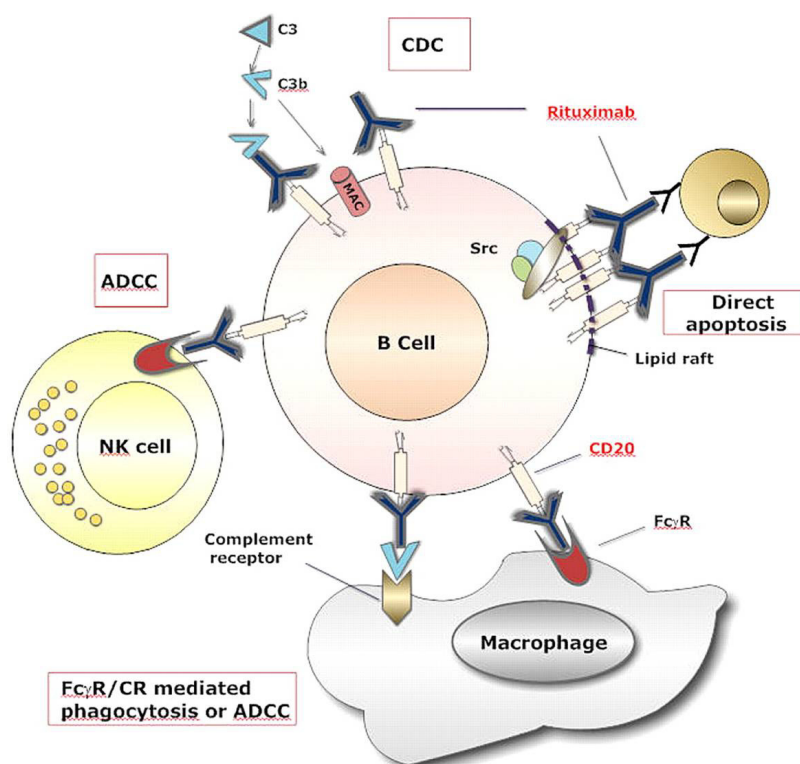
- i) Antibody-dependent cellular cytotoxicity (ADCC),
- ii) Phagocytosis,
- iii) Complement-dependent cytotoxicity (CDC),
- iv) Direct induction of apoptosis and “vaccination effect” resulting from cross-priming

## Rituximab Resistance

In spite of its success in lymphoma treatment, the effectiveness of rituximab is limited due to development of resistance with relapse of the disease. Rituximab resistance is mediated by both tumor and host factors. Lymphoma cells may develop resistance because of increased expression of complement regulatory proteins that impair CDC, blockade of ADCC by deposited C3b complement component, overexpression of anti-apoptotic proteins or down-regulation of pro-apoptotic proteins, and down-regulation of CD20 either through loss of expressions having rituximab/CD20 complexes by phagocytic cells, or antigenic modulation through internalization that has been previously believed to be of little significance. The relative contribution of these mechanisms to rituximab resistance remains to be determined in further clinical studies.

## Prospective Improvement of Anti-CD20 Antibody Therapy: Improvement of Rituximab Efficacy

- i) Rituximab-resistant lymphoma cells exhibit up-regulation of components of the **ubiquitin–proteasome** system.



Mechanisms of Action of Rituximab

**Table: New Generation Anti-CD20 mAbs**

Antibody	Characteristics	Activity compared with Rituximab	Phase of Development
Ofatumumab	Type 1, fully human	Increased CDC and slower off rate	FDA approved for CLL & Phase 3 trial in NHL
Veltuzumab	Type 1, humanised	Slower off rate	Phase 1 / 2 NHL
Ocrelizumab	Type 1, humanised	Increased ADCC and lower CDC	Phase 2 NHL
PR0131921	Type 1, humanized with modified Fc	Increased ADCC	Phase 1 / 2 NHL
AME-133v	Type 1, humanized with modified Fc	Increased ADCC	Phase 1 / 2 NHL
GA 101	Type 2, humanized with glycerol-engineered Fc	Increased ADCC and slower PCD	Phase 3 NHL

**Table: Targeting Other Lymphoma Antigens**

Antibody	Target	Characteristics	Phase of Development
Epratuzumab	CD22	Humanized anti-CD22 mAb	Phase II in NHL
Inotuzumab ozogamicin	CD22	Humanized anti-CD22 mAb conjugated with calicheamicin	Phase I/II in NHL
90Y- epratuzumabtetraxetan	CD22	Humanized anti-CD22 mAb conjugated with 90Y	Phase I/II in NHL
Brentuximab vedotin	CD30	Chimeric anti-CD30 mAb conjugated with vedotin	Phase II in HL
Lucatumumab	CD40	Fully human anti-CD40	mAb Phase I/II in NHL and HL
Alemtuzumab	CD52	Humanized anti-CD52 mAb FDA approved for resistant CLL,	phase III as first-line in CLL, phase II in DLBCL
Blinatumomab	CD19/CD3	Anti-CD19/anti-CD3 BiTE (bispecific T-cell engager)	Phase I in NHL

**Table: Phase III Clinical Trials of Id Vaccination in Follicular Lymphoma**

	NCI / Biovest	Genitope	Favrille
Production of Id protein	Hybridoma	Recombinant	Recombinant
Isotype of Id	IgM or IgG	IgG	IgG
Pre-vaccine therapy	PACE	CVP	Rituximab
Pre-vaccination status	CR	CR or PR	CR, PR, or SD
Randomized patients	117	349	287
Primary endpoint	DFS	PFS	TTP
Primary endpoint P	DFS	PFS	TT
Results	$p = 0.047$	NS	NS

Combination of **bortezomib with rituximab** is feasible as a salvage treatment in relapsed or refractory indolent lymphomas

- ii) A phase II study combining **oblimersen (Bcl-2 inhibitors)** with rituximab resulted in a promising response rate of 60% in FL patients, some of which were refractory to prior treatment with rituximab.
- iii) Agents as adjuncts added to rituximab to enhance ADCC. The toll-like receptor 9 (TLR9) agonist CpG oligonucleotide (ODN) combined with rituximab in a phase II study in patients with relapsed or refractory

follicular lymphoma showed clinical responses in 48% of patients.

### CD20 Antibody with Radioconjugates

Two radio conjugates of anti-CD20 mAbs are currently approved by the FDA-131I-tositumomab (Bexxar) and 90Y-ibritumomab tiutexan (Zevalin). In 5 clinical trials, patients with indolent NHL that were treated with one course of 131I-tositumomab demonstrated ORR ranging from 47 to 68% with complete response (CR) rates ranging between 20 and 38%. The 5 year-PFS was 17% with a median follow-up of 53 years.

In 90Y-ibritumomab tiuxetan-treated patients with relapsed/refractory NHL, in 4 clinical trials, 59(39%) of 153 patients with indolent FL had a long-term response (PFS of more than 1 year), and the median time to progression was 30.9 months.

### Active Immunotherapy

In comparison to passive immunotherapy with mAbs, active immunotherapy may induce a polyclonal response directed against multiple epitopes, hence limiting tumor escape that gives rise to relapse. On the other hand, the disadvantage of active immunotherapy is its reliance on the patient's immune system, which may be dysfunctional.

### Vaccination

The most thoroughly studied target for vaccination in lymphoma is the immunoglobulin Id. A major obstacle in production of Id vaccines is due to its patient-specific nature that requires the generation of a custom-made product. The Id may be used as either protein or DNA in therapeutic vaccines.

**The traditional rescue hybridization technique:** The Id protein is produced by fusing the lymphoma cells with mouse myeloma cells to generate Id-secreting hybridomas.

**Recombinant Id Protein:** Genes encoding the tumor-specific immunoglobulin variable regions are cloned by PCR, ligated into an expression vector and transfected into bacterial, plant, insect, or mammalian cells that then produce the Id protein.

**Id DNA Vaccination:** The immunoglobulin heavy and light chains are cloned and inserted into a plasmid vector for naked DNA injection.

**Prospective Improvement of Id Vaccines:** Increasing Id immunogenicity, delivery, and presentation. Increasing antigen immunogenicity, delivery, and presentation may improve the clinical outcome of Id vaccines.

The Id is currently chemically conjugated to KLH using glutaraldehyde (by extensive protein cross-linking via glutaraldehyde could destroy immunogenic epitopes and inhibit proteolytic processing) or a sulfhydryl-based Id-carrier protein conjugation system. Using maleimide chemistry enhanced the efficacy of Id-KLH vaccines. Liposomes are widely accepted as effective carriers for vaccines. Hence, incorporation of Id into cytokine-carrying liposomes has been proposed as a means to enhance Id delivery.

**DNA Vaccines:** Idiotypic DNA vaccines consist of a plasmid encoding the immunoglobulins in single chain

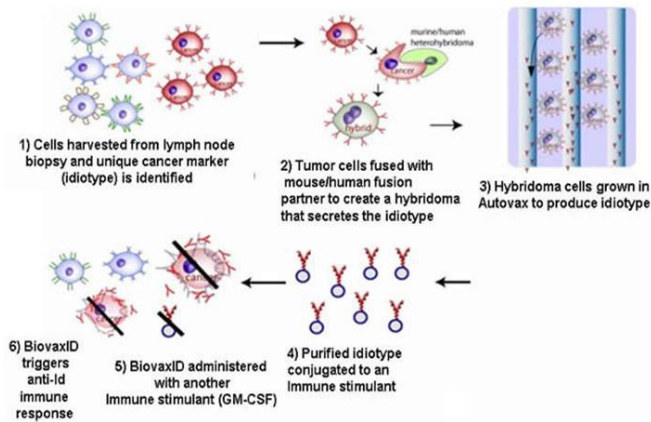
variable fragment. The DNA vaccine is injected into the skin or muscle, resulting in production of the protein by the patient's cells and presentation to the immune system. The failure to translate the success of DNA vaccination in pre-clinical models to the clinic is believed to be due to failure in delivery of DNA.

**DC Vaccines:** Dendritic cells loaded in vitro with antigen are attractive vehicles for therapeutic cancer vaccines. The FDA approval of sipuleucel-T, a DC vaccine against prostate cancer, provided a formal proof for the clinical efficacy of DC vaccines, and is likely to prompt development of this therapeutic modality.

**Combining Id Vaccines with New Adjuvants:** Increasing evidence argues that the success of an anti-cancer vaccine may rely on immune adjuvant stimulating effects. Hence, co-administration of vaccines with various adjuvants is being evaluated for improving vaccine performance. One promising class of adjuvants with potent immune stimulatory properties consists of CpG ODNs that are capable of activating antigen presenting cells, B-cells, and NK cells by engaging TLR9. B-cell malignancies are uniquely sensitive to CpG ODNs in that the malignant cells themselves express TLR9, thus responding to CpG ODNs by up-regulation of MHC and co-stimulatory molecules, and by proliferation that can lead to activation induced cell death.

**Tumor Cell Vaccines:** One drawback of Id vaccination is the restriction of the anti tumor response to a single antigen. Therefore, vaccine formulations based on autologous neoplastic cells have been investigated. These formulations might potentially induce autoimmunity, but have the advantage of widening the spectrum of target tumor-associated antigens. Unlike other malignant cells, B-lymphoma cells can be activated to express MHC class II and costimulatory cells, thus presenting their own tumor-associated antigens and elicit T-cell responses. Lymphoma cells are, therefore, excellent candidates for tumor cell-based vaccination. One approach to activate malignant B-cells is by ligation of CD40 via CD40-CD40 ligand (CD40L) interaction. This can be achieved either by mixing lymphoma cells with CD40L expressing cells or by engineering lymphoma cells to express CD40L. In phase I trial on patients with CLL, who received subcutaneous injections of autologous tumor cells transduced with both CD40L and IL-2, three patients (30%) had >50% reduction in the size of affected lymph nodes, suggesting that CD40-based immunotherapy may have clinical benefit.





*Individualized vaccine made from surface proteins of cancer cells induces an immune response against those cells*

**In Situ Vaccination:** To circumvent the logistical difficulty of *ex vivo* manufacture of a customized vaccine, an alternate approach of *in situ* vaccination has been developed. It consists of low-dose irradiation to a single lymphoma site, followed by intra-tumoral injection of CpG at the same site. This maneuver kills some tumor cells at the treated site, and the CpG activates nearby DCs, enhancing presentation of the released tumor antigens by the DCs. Residual viable lymphoma cells can also be activated by CpG and present the released antigens to T-cells. B-cell NHL are considered highly suited to this maneuver because they are sensitive to radiotherapy and because they express TLR9.

### Immune Checkpoint Intervention

#### Blockade of T-Cell Inhibitory Signals:

**i) Anti-CTLA-4mAb.** Cytotoxic T-lymphocyte antigen 4 (CTLA-4), a member of the CD28 family, is a key negative regulator of T-cell activation. It is inducibly expressed in conventional T-cells after activation and constitutively expressed in Treg. Blockade of CTLA-4 by mAbs enhanced T-cell activation, improved immune responsiveness to anti-cancer vaccines in preclinical studies, and had clinical activity against several types of cancer. The anti-CTLA-4 human mAb ipilimumab was approved by the FDA in 2011 to treat patients with late-stage melanoma. Ipilimumab has also been evaluated for treatment of B-cell lymphoma.

**ii) Anti-PD-1mAb.** Programmed death-1 (PD-1) is another T-cell inhibitory receptor that is inducibly expressed after activation of T-cells. Ligation of PD-1 by its ligands PD-L1 and PD-L2 inhibits T-cell activation. It has been demonstrated that PD-L1 is expressed by NHL and inhibits the activity of tumor-associated T-

cells, suggesting PD-L1 block is potentially useful strategy for lymphoma immunotherapy.

**Depletion of Treg:** Treg are implicated in the dampening of anti-tumor T-cell responses. Accumulated data indicate that the presence of Treg at the tumor site or in peripheral blood correlates with poor prognosis. In B-cell NHL, Treg at the tumor site have been shown to suppress activity of infiltrating CD4 and CD8 T-cells, suggesting that Treg depletion may enhance clinically beneficial anti-tumor responses. Denileukin difitox (Ontak) is a diphtheria toxin-IL-2 fusion protein shown to deplete Treg in several tumors.

### Conclusion

Rituximab improved tremendously the management of NHL, prolonging remission, and survival. However, resistance to rituximab leads to eventual relapse in most patients. Although several new generation anti-CD20 mAbs show improved mode of action compared to rituximab, their clinical efficacy in rituximab-refractory patients is disappointingly modest.

In the coming era of personalized medicine, it will become extremely important to determine which lymphoma patients are most likely to benefit from a particular therapy out of the existing therapeutic arsenal.

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(Dr Rayaz Ahmed, Consultant, Dept of Hemato-Oncology, RGCI&RC)

## GUEST ARTICLE

## OVERVIEW AND ADVANCES IN NON-HODGKIN'S LYMPHOMA TREATMENT

Non-Hodgkin's lymphomas are a group of related malignancies of lymphocytes. Some lymphomas are among the most rapid growing and aggressive of all cancers, whereas others are indolent and can be managed with an initial period of observation. In the year 1970, it was recognized that aggressive non-Hodgkin's lymphomas could sometime be cured with combination chemotherapy. Since then, there have been significant increase in knowledge of the biology, immunology, and genetics of these disorders that have led to improvement in diagnosis, classification and treatment.

In this chapter, we will discuss the treatment aspect of two most common lymphomas. Diffuse large B-cell lymphomas (DLBCL) are prototype of aggressive lymphomas and Follicular lymphomas (FL) are prototype of indolent lymphomas.

## Diffuse Large B-Cell Lymphoma (DLBCL)

It is the most common histological subtype which accounts for 30% approximately of all patients of NHL. It is an aggressive NHL variety. For patients with NHL, disease stage is determined using the Ann Arbor Staging system with Costwald modification. For treatment purpose patients with DLBCL are classified as having either limited stage or advanced disease.

## 1. Limited Stage Disease (Stage I or II)

This population accounts for 30-40% patients with DLBCL. Limited stage DLBCL is treated primarily with combined modality therapy consisting of abbreviated systemic chemotherapy (three cycles), the anti-CD 20 antibody rituximab and involved field RT. Alternatively, full course chemo-immuno therapy without treatment may be used. Patients with bulky (>10 cm) stage II disease and patients with stage IIB have a less favorable prognosis than those with non-bulky stage II disease. These patients are generally treated in a similar fashion to those with advanced stage disease. Combined modality therapy has less acute and hematologic toxicity. R-CHOP has become the preferred chemotherapy regimen for treatment of DLBCL.

**Role of involved field RT:** There have been four multi-institutional randomized trials comparing chemotherapy plus RT versus chemotherapy alone for patients with

limited stage DLBCL. These trials were actually done before the incorporation of rituximab in the treatment. These trials are SWOG 8736, GELA LNH 93-1, ECOG 1484 and GELA LNH 93-4. Taken together these studies suggest that combination therapy with abbreviated chemotherapy plus RT is at least as effective as a full course of the same chemotherapy. So far there are no randomized trials of abbreviated R-CHOP plus RT versus R-CHOP alone.

**Radiation dose:** The importance of radiation dose was examined in a phase III trial that included 640 sites of DLBCL (all stages were included). This trial assigned radiation at a lower doses (30 Gy in 15 fractions) or higher doses (40 to 45 Gy in 20-23 fractions). At a median follow up of 5.6 years, lower dose of radiation resulted in similar rates of in-field progression, progression-free survival and overall survival. Patients with non-bulky disease who have a complete response on PET scanning, radiation doses of 30-36 Gy produced excellent results. In comparison, for patients with initial bulky disease or persistent PET positive disease after chemotherapy, higher doses of RT (45-50 Gy) may be used.

**Follow up:** After completion of the initially planned treatment of DLBCL, patients should be evaluated to determine the disease response to treatment and be seen at periodic interval to monitor the treatment complications and assessed for possible relapse.

## 2. Advanced Stage Diffuse Large B Cell Lymphoma

These are the advanced stage DLBCL which cannot be contained within one irradiation field (usually Ann Arbor stage III or IV disease). This population accounts for 60-70 percent of patients with DLBCL. These are treated primarily with systemic chemotherapy and rituximab.

**Rituximab containing regimen:** The addition of rituximab to CHOP based therapy results in an approximately 10-15 percent overall increase in survival beginning at one year from initiation of therapy in patients of all ages with almost no increase in toxicity.

**Choice of chemotherapy regimen:** Prior to incorporation of rituximab containing regimen, CHOP was compared with many other anthracycline based regimen in prospective randomized trials. These regimens offered no improvement in remission rate, disease-free survival or overall survival, and were also associated with increased toxicity. Thus CHOP has been the preferred chemotherapy regimen. The optimal defined number of treatment cycles is unclear. No study has directly evaluated the appropriate numbers of cycles but administration of either six or eight cycles of R-CHOP is reasonable.

### 3. Patients with Cardiac Disease

This population may not be able to tolerate the use of an anthracycline since this agent is toxic for cardiac cells. Doxorubicin should not be administered to patients with a baseline LVEF < 30%. There is paucity of data to guide the choice of therapy in this population. However, etoposide can be used in place of doxorubicin.

For older patients (>60 years) with DLBCL full dose therapy should be encouraged. Patients who are unable to tolerate standard doses of R-CHOP - 21, may be considered in reduced dosage CHOP regimen (R-mini-CHOP).

**Hematopoietic stem cell transplantation consolidation in first remission:** In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation with either sequential chemotherapy or HSCT/ASCR. No difference in outcome was prospectively observed. A retrospective subset analysis showed that high risk patient showed improvement in disease-free survival and overall survival but this study was performed prior to rituximab based therapy.

Recently, several other randomized studies have prospectively evaluated the role of upfront HSCT/ASCR after rituximab containing therapies. These studies found no benefit to upfront HSCT/ASCR compared to first line rituximab based chemo-immunotherapy. The suggestion of benefit limited to high risk patients warrants further prospective studies. Currently, upfront HDCT/ASCR is recommended only in selected high risk patients.

### Follicular Lymphoma (FL)

It is the second most common type of non-Hodgkin lymphoma and is the most common of the indolent NHLs. Treatment of FL depends upon the stage of disease at presentation as evaluated by Ann Arbor staging system. For the treatment purpose FL are also divided into limited disease and advanced disease.

#### 1. Treatment of Limited Disease Follicular Lymphoma (FL)

Patients with localized (Stage I) disease are candidates for RT, which is curative in large percentage of patients. The management of patients with stage II FL is more variable; some treat as stage I and other like advanced disease. Approximately 15-30% of patients with follicular lymphoma will present with clinical stage I/II disease. For most patients with stage I or non-bulky stage II FL, initial treatment with RT is suggested rather than chemotherapy or initial period of observations.

RT is delivered to the involved lymphoid region at a dose of 24 Gy. Patients with Group IIIb FL and some patients with grade IIIa FL is treated as patients with aggressive lymphoma. It is unknown whether increasing therapy intensity for patients with bulky disease would improve outcome in this population.

### 2. Advanced Stage III/IV Follicular Lymphoma

Advanced stage disease includes disease on both sides of diaphragm (stage III) or diffuse involvement of one or more extra lymphatic tissue (stage IV). Overall 70-85 percent of patients present with advanced stage disease. Survival rates vary and can be estimated for the population using Follicular Lymphoma International Prognostic Index (FLIPI) score. Patients with advanced stage disease are usually not cured with conventional treatment. While remission can be attained, repeated relapses are common. Treatment focuses on the alleviation of symptoms and improvement of quality of life.

Asymptomatic patients can be observed initially. Once therapy is indicated, immunotherapy based treatment (rituximab) is preferred because it results in superior response rates, progression free survival and overall survival.

Indications for starting treatments in follicular lymphomas:

- i. Local symptoms due to progressive or bulky nodal disease.
- ii. Compromise of normal organ function due to progression.
- iii. B symptoms.
- iv. Presence of symptomatic extranodal disease e.g. effusion.
- v. Cytopenia due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia.
- vi. An increase in disease tempo.

#### 3. Radio-immunotherapy (RIT) in Management of FL

RIT with <sup>131</sup>I-tositumumab and <sup>90</sup>Y-ibritumumab tiuxetan has also been evaluated in patients with newly diagnosed as well as those with relapsed refractory FL. RIT is currently recommended only for patients who received first-line chemotherapy and not chemoimmunotherapy.

#### 4. Long Term Management - Maintenance Therapy

It refers to prolonged administration of agents with low toxicity profile in an attempt to prevent progressive disease. Maintenance rituximab has been investigated in



the treatment of low grade lymphoma. Maintenance therapy may convert some of the partial remission into complete remission. It is important to use one of the established regimens for maintenance e.g. rituximab every two months for a total of two years.

### 5. Hematopoietic Stem Cell Transplantation (HSCT)/ Autologous Stem Cell Rescue (ASCR) in Management of FL

HSCT/ASCR has been shown to prolong OS and DFS in patients with relapsed or refractory disease. The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first-line setting and found that EFS and survival after relapse were superior for patients treated with rituximab based regimens compared to chemotherapy only based second-line therapy followed by HSCT/ASCR in relapsed or refractory FL.

### Conclusion

Non-Hodgkin's lymphomas are common malignancies and often seen by primary care physicians as well as oncologists. Because lymphomas are frequently curable and often affect young individuals, a meticulous approach to diagnosis and staging is warranted. Any uncertainties regarding diagnosis should lead to review of biopsy material by an expert hematopathologist or consider a repeat biopsy if the diagnosis is unclear.

Once diagnosis is established, both aggressive DLBCL and indolent FL should receive evidence based treatment with strict adherence to protocol to achieve maximum benefit and chance of cure.

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## WATCH-OUT

### Strategies for Improved Cancer Vaccines

A biopharmaceutical company IBC Pharmaceuticals, Inc, primarily focusing on the development of monoclonal antibody based products for the targeted treatment of cancer, autoimmune and other serious diseases, was awarded US patent No. 8,562,988 for "Strategies for Improved Cancer Vaccines" on 22<sup>nd</sup> October 2013. The invention relates to methods and compositions for forming anti-cancer vaccine complexes. The anti-cancer vaccine complex is capable of inducing an immune response against xenoantigen expressing cancer cells, such as CD138.sup.negCD20.sup.+ MM stem cells, and inducing apoptosis of and inhibiting the growth of or eliminating the cancer cells. The allowed claims cover the use of bispecific antibodies targeting CD74, the major histocompatibility complex (MHC) class-II invariant chain, Ii, of immune cells, and CD20 to form a vaccine complex. Because immune cells such as dendritic cells express high levels of CD74, the bispecific antibody-vaccine complex is capable of inducing an immune response against CD20-expressing cancer cells, killing, inhibiting the growth of, or eliminating the cancer cells. This patent will expire in March 2026. This is an important patent protecting a new vaccine technology targeting dendritic cells for blood cancer treatment. This method also has the potential of including the use of a cytokine, such as interleukin-2, interleukin-12, or gamma-interferon.

*(USPTO, Dec 23, 2013)*



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## PERSPECTIVE

### ROLE OF PET-CT IN THE MANAGEMENT OF LYMPHOMA

Lymphomas are a group of heterogeneous but a potentially curative group of neoplasms. Over the years the diagnosis and evaluation of response to treatment have rapidly evolved side by side with its treatment protocols as a result of which there has been significant improvement in the cure rate and treatment related toxicities. To achieve this goal, first of all an accurate staging system is required along with predictive and prognostic factors to define optimal treatment strategy.

Prognostic factors include strong baseline risk factors and those which can be used early during therapy, being the predictive factors. Positron Emission Tomography with integrated computed tomography (PET-CT) is being widely used to investigate staging and evaluation of therapy response in lymphomas and may provide the means for such an individualized approach.

#### Histopathologic Lymphoma Subtypes

Knowledge of lymphoma subtypes is important because the power of glucose utilization varies among different lymphoma subtypes and is predictive of proper utilization and optimum yield of PET-CT studies. Most routinely glucose avid lymphomas are Hodgkin's lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, mantle cell lymphoma (MCL) and follicular lymphoma (FL). The sensitivity of detection by PET in these groups of lymphoma, across literature, has been in the range of 85-100%. The clinical usefulness of PET in the less common indolent lymphomas, including marginal zone lymphomas, chronic lymphocytic leukemia /small lymphocytic lymphoma (CLL /SLL) and lymphoplasmacytic lymphoma (LPL) is questionable as the glucose utilization in these groups of lymphomas is variable. The glucose avidity in these groups of lymphoma needs to be established by a baseline scan if PET is to be used for response evaluation. In the lymphomas of T-cell origin, glucose avidity is also variable. In these groups the nodal subtypes like peripherally T-cell lymphoma and anaplastic large cell lymphoma are the most reliable in terms of usefulness of PET-CT in their evaluation and utilization. In general, it has been seen that the glucose avidity correlates to the aggressiveness of lymphomas and therefore the intensity of tracer uptake or glucose avidity in an otherwise non-avid variety could be an indication of its histologic transformation.

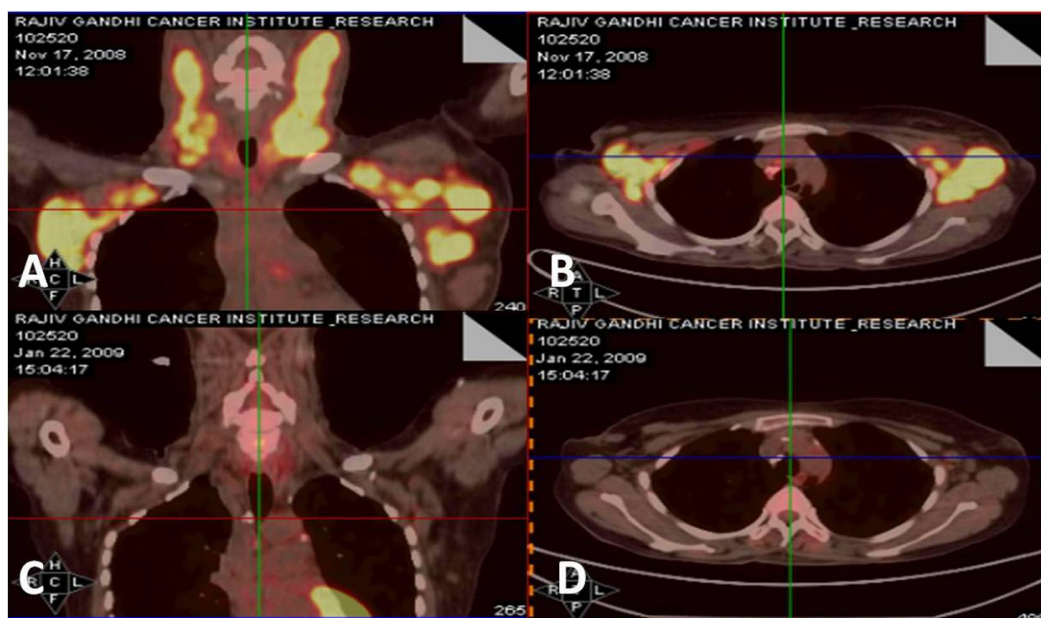
### Staging of Lymphoma

Traditionally, CT scan has been incorporated in the staging of lymphomas. CT is an anatomical modality which relies on size and location of the lymph nodes. For this reason it is difficult to differentiate between benign and malignant nodes. Enlarged lymph nodes could be reactive in nature and vice versa. Over the last few years numerous studies and meta analysis of studies in the literature have demonstrated that FDG PET-CT is more accurate in staging of lymphomas as compared to either PET or CT alone. Discord between PET & CECT findings occurs during staging in approximately 1/3<sup>rd</sup> of patients and although staging may be altered by being either upstaged or down-staged, there is alteration in the treatment protocol in few cases. Improvement in outcome is also not established in the literature as a result of these findings.

The International Harmonization Project (IHP) recommends a baseline scan in Hodgkin's lymphomas and DLBCL mainly because of their consistency in glucose avidity and being potentially curable. Routinely, FDG PET scan is not performed for other subtypes. In addition to the above, the NCCN guidelines recommend the use of FDG PET as an essential test in AIDS related B-cell lymphomas and in selected cases in FL, MZL & MCL.

#### PET in the Evaluation of Bone Marrow

In lymphomas, accurate assessment of bone marrow is crucial as it changes disease staging and can lead to alteration in therapeutic strategies. Bone marrow involvement is more commonly seen in NHL, especially in indolent subtypes and MCL. In contrast, 10% of Hodgkin's lymphoma patients have bone marrow involvement. Bone marrow biopsy which has been considered as a gold standard till now and a mandatory staging investigation, has been known to have a substantial false negative rate due to the fact that it does not evaluate marrow involvement outside the pelvis. Off late FDG-PET has been used for the evaluation of bone marrow with greater success, more so as it evaluates the marrow even outside the pelvis (iliac crest being the biopsy site). The sensitivity of detection varies in the range of 75% - 90% across literature in HL and NHL and about 50% in indolent lymphomas. Whether bone marrow biopsy can be reserved only for patients who have suspicious involvement of marrow in FDG-PET scan or as a routine as before needs to be decided. It should be remembered that reactive bone marrow also shows increased metabolic activity and thus interpretation of a positive finding is very important and pattern recognition plus



Figures A & B (Staging PET CT): Coronal and Axial FDG PET-CT fused images show metabolically active bilateral cervical and axillary lymphadenopathy. Figures C & D (Interim PET-CT): Coronal and Axial FDG PET-CT fused images show no metabolically active cervical and axillary lymphadenopathy, suggesting responder status.

experience plays an important role. Things are most challenging in the post therapy setting where reactive changes in the marrow induced by colony stimulating factors (i.e. G-CSF) may pose difficulty in interpretation. Therefore a sufficient period (usually 4-6 weeks) post treatment should be allowed before PET scan is done for proper interpretation of bone marrow.

### Response Evaluation / Interim Scan

FDG PET has been recognized as a surrogate marker of chemo sensitivity in both NHL & Hodgkin's disease. It is perceived that absence of metabolic activity during mid cycle predicts a longer progression free survival. Persistent metabolic activity at this point of time may show a higher relapse rate ranging from 50% - 100%, whereas in the other group, it is less than 10%. Studies in the literature show that this hypothesis can be used in routine clinical practice. It has also been shown that interim PET results appear to be a stronger predictive factor than the international prognostic score (IPS). There is, however limited evidence that changing treatment based solely on the interim PET results improves patient outcome.

### Response Evaluation at End of Treatment

In the post treatment scenario, the role of PET is predominantly in the characterization of a residual mass to distinguish between fibrosis and active disease. There is a definite role of PET in the prediction of recurrence in aggressive NHL and Hodgkin's disease after completion

of first-line chemotherapy. FDG PET is thus incorporated in the revised IWG criteria for response due to its ability to assess residual masses, eliminating the previous terminology of complete remission/unconfirmed (CRu). It is important to note that in addition to documenting whether PET has become negative, it is also important to see how soon during treatment it has become negative.

### During Surveillance

Following first line therapy a recurrence rate of 30%-50% has been reported in literature in advanced stage Hodgkin's disease and DLBCL. The sensitivity of PET in identifying relapses has been varied in the literature ranging from 60% - 100% in both groups irrespective of a persistent residual mass in CT scan. Due to clinically silent nature of the disease, Hodgkin's lymphoma relapses were detected earlier. The frequency of follow up scans is debatable and therefore a more patient centric approach needs to be taken rather than routine evaluation with PET during each visit. The pretest likelihood and the initial disease profile should be the important factors which should be considered in such cases. At the same time, since PET has a high negative predictive value, a psychological boost of a negative study during surveillance cannot be overlooked.

### Timing of FDG PET Imaging

In cases where a baseline PET is mandatory or desirable, it should be performed before initiation of any



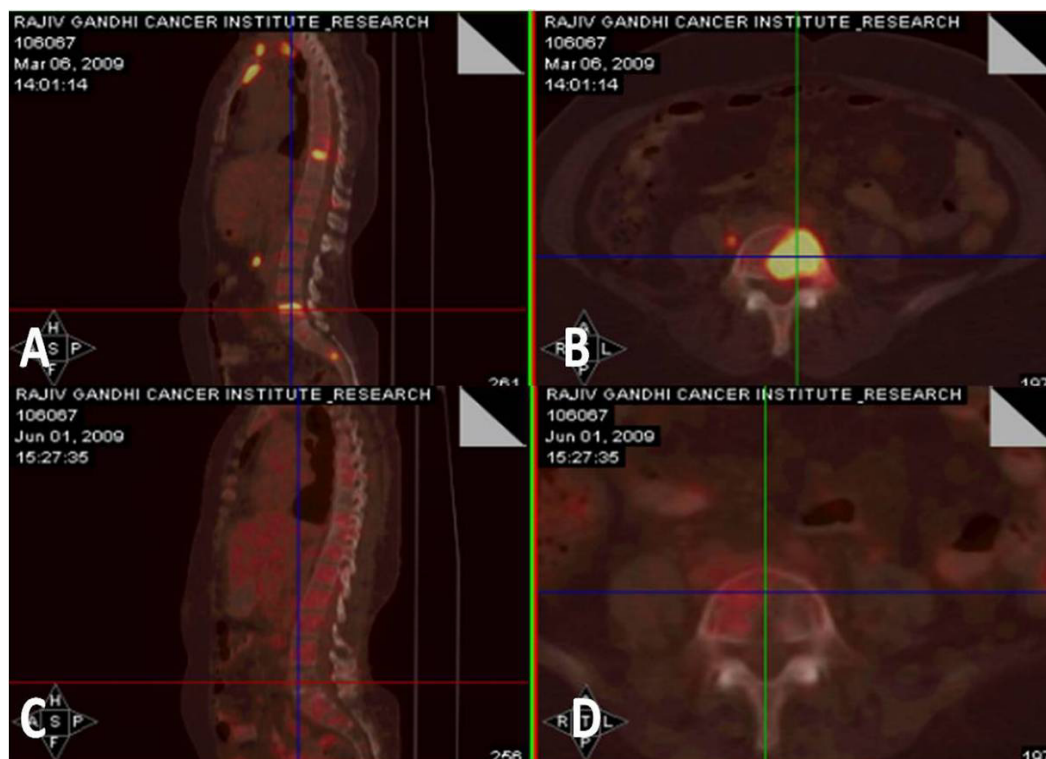


Figure A & B (Staging PET-CT): Sagittal and Axial FDG PET CT fused images show metabolically active bony lesions.  
 Figure C & D (Interim PET-CT): : Sagittal and Axial FDG PET CT fused images show no metabolically active bony lesions suggesting responder status

form of therapy, whether cytotoxic or otherwise. It is also recommended to schedule the baseline study after confirmation of histopathological diagnosis. Interim PET study should be done as early as possible after the desired chemotherapy cycle as false positive findings due to co-existent inflammatory changes appear later. Timing of scan at the end of treatment is more flexible and should be performed 3-4 weeks after systemic chemotherapy or even later to allow the inflammation to subside and minimize false positive result.

### Study Interpretation

Several parameters are used for interpretation of a PET study during interim evaluation and at the end of treatment. These may vary from visual interpretation, lesion to background ratio, to semi-quantitative measurement of standardized uptake value (SUV) and to more recent still to be established criteria, like metabolic tumor volume (MTV) and total lesion glycolysis (TLG). It is very important to understand that each institution should standardize their PET protocols for acquisition and processing and the same standardized protocol should be followed in serial studies. It assumes further importance when the change in SUV is used as a measure of response as reproducibility of SUV is

multifactorial and may vary from the dose of FDG, timing post injection and blood sugar estimation. As far as possible, these parameters need to be maintained between studies. Due to these variabilities, it is important that more than one parameter should be used for interpretation. We use percentage fall in SUV for the interim evaluation and visual interpretation in the end of treatment study and have standardized this in our institution. Recently proposed Deauville criteria yield a flexible reading scheme to adjust for the required treatment end-points.

### Deauville Criteria

Score 1 : No uptake  
 Score 2 : Uptake  $\leq$  mediastinum  
 Score 3 : Uptake  $>$  mediastinum but  $\leq$  liver  
 Score 4 : Uptake  $>$  liver at any site  
 Score 5 : Uptake  $>$  liver & new sites of disease  
 Score x : New a real of uptake unlikely to be related to lymphoma

A widely accepted semi-quantitative approach for lymphoma evaluation needs to be derived and it is desirable to standardize the quantitative parameters for each subtype.

(Dr PS Choudhury; Director & Dr Manoj Gupta; Consultant; Dept of Nuclear Medicine; RGCI&RC)

## RESEARCH & DEVELOPMENT

### Alterations in Bone Mineral Density

Bone mineral density (BMD) loss is poorly defined in lymphoma patients. A prospective, single-center study was conducted in 41 patients aged 18 years with previously confirmed lymphoma treated by chemotherapy. BMD was measured at baseline before initiating chemotherapy and 1 year later. Histological subtypes were predominantly diffuse large B-cell lymphoma (58%), mostly stage III-IV (54%). The mean BMD changes were:  $-2.7\% \pm 3.9\%$  for lumbar spine ( $P < 0.001$ ),  $-2.2\% \pm 7.6\%$  for femoral neck ( $P < 0.01$ ) and  $-2.6\% \pm 4.5\%$  for total hip ( $P < 0.0001$ ). Predictive factors of BMD loss at baseline were (i) at lumbar spine: female gender, higher lactate dehydrogenase level and lower creatinine clearance; (ii) at total hip: lower albumin, higher corrected serum calcium, lower alkaline phosphatase (AP) and autologous stem cell transplant; and (iii) at femoral neck: higher corrected serum calcium and lower bone AP. Adult patients with known lymphoma receiving chemotherapy experienced significant BMD loss at 1 year.

(*Ann Oncol*, Jan 8, 2014)

### <sup>18</sup>F-Fluorothymidine Uptake

Scientists have observed a disproportional <sup>18</sup>F-fluorothymidine (F-FLT) uptake in follicular lymphoma (FL) relative to its low cell proliferation. Immunohistochemical staining was performed to assess the pure DNA replication marker MIB-1 and markers of both DNA replication and repair like PCNA, TK-1 and RPA1 on lymph node biopsies of 27 FLs and 35 diffuse large B-cell lymphoma (DLBCL). In 7 FL and 15 DLBCL patients, <sup>18</sup>F-FLT-PET had been performed. <sup>18</sup>F-FLT uptake was lower in FL than in DLBCL (median SUV<sub>max</sub> 5.7 vs. 8.9,  $p = 0.004$ ), but the ratio of <sup>18</sup>F-FLT-SUV<sub>max</sub> to percentage of MIB-1 positive cells was significantly higher in FL compared with DLBCL ( $p = 0.001$ ). This is the first demonstration of a striking discordance between <sup>18</sup>F-FLT uptake in FL and tumor cell proliferation. The apparently high contribution of DNA repair to the <sup>18</sup>F-FLT signal in FL may hamper studies where <sup>18</sup>F-FLT is used to assess response to cytostatic therapy or to distinguish between FL and transformed lymphoma.

(*EJNMMI Res*, Jan 8, 2014)

### Genome Sequencing

Mantle cell lymphoma is a very aggressive and difficult to treat cancer originated in blood cells and lymph nodes. A team of scientists have presented the first comprehensive genomic analysis of this disease. The authors analyzed the genome of tumor cells at the onset of the disease and within several years after treatment, when the relapses occur. These analyses have discovered the implication of several genes in the progression of these lymphomas and some mechanisms generating resistance to chemotherapy. They also defined a group of patients with very rapid progression of the disease with mutations in *NOTCH1* and *NOTCH2* genes. These mutations could become therapeutic targets because there are already drugs blocking the activity of these genes which may be useful in complicated cases of mantle cell lymphoma. Researchers also identified a group of patients with a small number of mutations in the tumor whose disease progression was very slow. Thus, knowledge around the genome of these lymphomas might guide the selection of appropriate treatments for each patient. These studies should allow the application of genomic studies in clinical practice to improve the diagnosis and treatment of cancer patients.

(*Science Daily*, Oct 22, 2013)

### Novel Soluble-Receptor Marker

Researchers in Japan have reported that the soluble LDL receptor relative with 11 ligand-binding repeats (sLR11) is a promising biomarker for follicular lymphoma (FL). The fluctuation in serum sLR11 levels was evaluated compared with those of serum soluble urokinase-type plasminogen activator receptor (suPAR) and soluble interleukin-2 receptor (sIL-2R) in patients with non-Hodgkin's lymphoma (NHL). Serum sLR11, suPAR, and sIL-2R levels were measured using ELISA in 175 NHL patients and 57 healthy controls. The levels at diagnosis and at remission were evaluated in 64 paired samples. Serum sLR11 levels were significantly increased in FL, diffuse large B-cell lymphoma (DLBCL), and peripheral T-cell lymphoma patients compared with healthy controls. The receiver operating characteristic-area under the curve of serum sLR11 concentrations was equivalent to that of serum suPAR and sIL-2R concentrations in an early-stage DLBCL and FL. sLR11 may be a novel soluble receptor indicative of early-stage NHL, with potential use for evaluating therapeutic efficacy.

(*Clin Chim Acta*, Jan 3, 2014)

## NEW TECHNOLOGIES

### Breakthrough Therapy for Mantle Cell Lymphoma

The US Food and Drug Administration (FDA) has approved Imbruvica (ibrutinib) for the treatment of mantle cell lymphoma, a rare form of non-Hodgkin lymphoma. The drug is given to patients who have received at least one prior treatment. Imbruvica works by blocking a specific protein Bruton's tyrosine kinase (BTK) and blocking BTK inhibits malignant B-cell survival. Imbruvica is the second drug with breakthrough therapy designation to receive FDA approval. A drug is designated as breakthrough therapy whose preliminary clinical evidence indicates that the drug may offer a significant improvement over available therapies for patients with serious or life-threatening diseases. The drug's approval was based on a study of 111 patients who were daily given Imbruvica until their disease progressed or side effects became intolerable. The results showed about 66% of participants had their cancer shrink or disappear after the treatment. The new drug was also granted priority review and orphan-product designation as it revealed the potential of significant improvement in safety or effectiveness during treatment of a serious condition and intended to treat a rare disease, respectively. The most commonly occurring side effects were thrombocytopenia, diarrhoea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnoea, constipation, rash, abdominal pain, vomiting and decreased appetite etc.

*(US Food and Drug Administration, Nov 13, 2014)*

### Novel Diagnostic Tool for Hodgkin Lymphoma

The diagnosis of classical Hodgkin lymphoma (HL) is often difficult to establish due to the shortage of neoplastic component and necessity to perform immunostains on serial sections. GE Healthcare has launched the first lab developed test using MultiOmyx™, a ground-breaking new pathology platform to aid the differential diagnosis of HL. Offered through the company's Clariant Diagnostic Services, the first multiplexed single slide assay assesses the levels of nine proteins linked to HL for the detection of disease where conventional methods are either impractical or insufficient. The HL profile by MultiOmyx helps assessing nine unique antibodies (CD30, CD15, CD20, CD45, PAX5,

OCT2, BOB1, CD3, and CD79A) on a single formalin fixed paraffin embedded tissue section. MultiOmyx approach has similar staining characteristics as standard immunohistochemical stains with the added advantage that it may be performed on a single tissue section. In clinical validation, this single slide assay demonstrated high levels of accuracy, diagnostic reproducibility and high sensitivity of all immunofluorescent stains compared to traditional immunohistochemistry performed on the same samples. MultiOmyx allows for better correlation of results between stains, particularly in cases with rare Hodgkin cells as it allows direct comparison of multiple stains within same field of view. This may also be advantageous in small samples where full immunohistochemical profiles may not be possible. This novel methodology is practical for routine diagnosis and will likely be an aid to the improved diagnosis of HL.

*(www.multiomyx.com, Jul 10, 2013)*

### Topical Drug for Cutaneous T-Cell Lymphoma

The US Food and Drug Administration (FDA) has granted marketing approval to the orphan drug Valchlor (mechlorethamine) for the treatment of patients with Stage 1A and 1B mycosis fungoides-type cutaneous T-cell lymphoma (CTCL), who have received previous skin treatment. Valchlor is the first and only FDA-approved topical formulation of mechlorethamine which is also known as nitrogen mustard. Mechlorethamine is a chemotherapeutic agent formerly approved for intravenous treatment of mycosis fungoides, the most common type of CTCL. The approval of drug was based on a randomized study ever conducted in mycosis fungoides-type CTCL. This randomized, observer-blinded, non-inferiority pivotal trial compared Valchlor to a pharmacy-compounded mechlorethamine preparation in patients with stage IA-IIA mycosis fungoides-type CTCL. These patients had received at least one prior skin-directed therapy. The patients were not required to be refractory to or intolerant of prior therapies. In the study, 60% of patients with Valchlor had a confirmed response at 12 months which is defined as the reduction of at least 50% in the Composite Assessment of Index Lesion Severity score. However, 48% of patients treated with the compound control achieved a confirmed response. The most common adverse reaction to Valchlor is dermatitis, which in some cases may be severe and require dosing changes or discontinuation.

*(Ceptaris Therapeutics Inc., Aug 16, 2013)*



## CLINICAL TRIALS

### Drug-Antibody Pair for Non-Hodgkin Lymphoma

According to the results of an ongoing open-label phase II study from Dana-Farber Cancer Institute, the antibody-toxin compound, brentuximab vedotin (Adcetris), has shown compelling antitumor activity in relapsed or refractory non-Hodgkin lymphoma (NHL) including B-cell cancers such as diffuse large B-cell lymphoma (DLBCL). Till date, the trial has enrolled 62 patients of B-cell lymphomas, including 44 diagnosed with DLBCL, who have not responded to previous therapy and had never responded to any treatment. Evaluation was done in 43 patients of DLBCL, of which 40% of patients had an objective response to the drug with a median duration of 36 weeks, including some of more than eight months. A complete remission was seen in seven patients and ten patients had partial response. The drug had also caused adverse reactions like fatigue, nausea, low white blood counts, fever, diarrhea, peripheral sensory neuropathy etc. However, these results are encouraging enough to take the drug forward for DLBCL patients.

*(Scienc Daily, Dec 2013)*

### Lenalidomide with Rituximab & Bendamustine

A multicenter, phase I dose-escalation study was conducted by a Swiss group of clinical researchers to determine the maximum-tolerated dose of the lenalidomide in combination of rituximab and bendamustine for patients with aggressive B-cell lymphoma not eligible for front-line anthracycline-based chemotherapy or aggressive second-line treatment strategies. Total 13 patients were recruited in the trial who received rituximab (375 mg/m<sup>2</sup> on day 1), bendamustine (70 mg/m<sup>2</sup> on days 1 and 2), and lenalidomide was tested with a dose escalation of at three dose levels (10, 15, or 20 mg/day). Recommended dose was defined as one level below the dose-limiting toxicity (DLT) during the first cycle. Two DLTs occurred at the second dose level (15 mg/day) within the first cycle: one patient had prolonged grade 3 neutropenia, and one patient experienced grade 4 cardiac adverse event. Dose of lenalidomide of 10 mg/day in combination with rituximab 375 mg/m<sup>2</sup> on day 1 and bendamustine 70 mg/m<sup>2</sup> on days 1 and 2 was found to be well-tolerated regimen and recommended for a subsequent phase II trial.

*(Ann Hematol, Aug 2013)*

### Low-Intensity Chemotherapy for Burkitt's Lymphoma

A phase II trial was conducted by researchers at the National Cancer Institute in adult patients of Burkitt lymphoma (BL). Trial patients showed long-term survival rates more than 90% when treated with low-intensity chemotherapy regimens. Thirty patients with previously untreated BL were included over a 10-year period. Patients were divided into two groups based on their HIV status. HIV-negative patients (n=19) received dose-adjusted (DA)-EPOCH-R (Etoposide, Prednisone, Vincristine, Cyclophosphamide & Doxorubicin, Rituximab), whereas 11 HIV-positive patients received short-course-EPOCH-RR that included two doses of rituximab per treatment cycle with lower treatment intensity than DA-EPOCH-R. Results demonstrated that median follow-up was 86 and 73 months, the overall survival rates were 100% and 90% respectively, with DA-EPOCH-R and SC-EPOCH-RR. HIV positive patients had shown complete remissions even though they had more advanced disease. The toxicity was considerably less than that reported with standard treatment. These promising results suggest that this approach may be effective and worth investigating in certain economically challenged regions where BL is highly prevalent.

*(N Engl J Med, Nov 2013)*

### Molecular Profiling for Peripheral T-cell Lymphomas

Researchers from Italy had performed phase III diagnostic accuracy study, using molecular profiling to improve the classification of peripheral T-cell lymphomas (PTCL). The types of PTCL ie, PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL), have largely overlapping morphologic and phenotypic features, which make its diagnosis difficult. Total 244 patients with PTCL were recruited, including 158 PTCLs NOS, 63 AITLs, and 23 ALK-negative ALCLs. Molecular classifier (MC) in formalin-fixed paraffin-embedded (FFPE) samples was developed and validated in both FFPE and frozen tissues. The MC was used to differentiate AITL and ALK-negative ALCL from PTCL NOS in a training set. Mostly it enhanced the distinction of ALK-negative ALCL from PTCL NOS. Overall results showed that accuracy of the MC was remarkable: 98% to 77% for AITL and 98% to 93% for ALK-negative ALCL in test and validation sets of patient cases, respectively. Study revealed that MC could be used as additional tool in the diagnosis of PTCL.

*(J Clin Oncol, Aug 2013)*

## GLOBE SCAN

### Autologous Stem Cell Transplantation

This study was proposed to evaluate the efficacy of autologous peripheral blood hematopoietic stem cell transplantation (auto-PBHSCT) for patients with malignant lymphoma. From January 1992 to June 2012, 32 malignant lymphoma (ML) patients were treated with auto-PBHSCT in a hospital. The preconditioning regimens of total body irradiation (TBI) plus cyclophosphamide combined with etoposide/pharmorubicin were used in 50 patients, and the BEAM (BCNU+etoposide+Ara-C+melphalan) were used in the other 22 patients. The results showed that transplanted cells were engrafted and hematopoiesis was reconstituted in all patients. The transplantation related mortality was 4.2%. The median follow-up time was 63.5 months. 1-year OS rate was  $92.3 \pm 3.2\%$ . 3-years OS rate was  $81.4 \pm 4.9\%$ . 5-years OS rate was  $77.6 \pm 5.3\%$ ; and 10-years OS rate was  $68.9 \pm 6.8\%$ . It is concluded that auto-PBHSCT is effective for malignant lymphoma, and long time follow-up shows that the OS rate is still high.

(China: *Zhongguo Shi Yan Xue Ye Xue Za Zhi*; Nov 21, 2013)

### Genetic Predisposition to Lymphoma

New research shows that children with an inherited genetic defect in a critical anti-inflammatory pathway have a genetic predisposition to lymphoma. Among the hundreds of signaling pathways in the human immune system that guide the body's defense against infection, inflammation, and trauma, the interleukin-10 (IL-10) pathway plays a substantial role in regulating and safeguarding the intestinal tract. In rare cases, a genetic defect can appear in the IL-10 or in one of its receptors (IL-10R1 and IL-10R2) that turns off the pathway's normal protective function, resulting in the development of very-early-onset inflammatory bowel diseases (VEO-IBD) in children as young as two weeks old. Researchers began to investigate this potential linkage when five children between 5.5 and 6.5 years of age being monitored for VEO-IBD developed highly proliferative and severe cancer very similar to diffuse large B-cell lymphoma (DLBCL), an extremely rare form of blood cancer in children. The confirmed association between the IL-10 pathway and this rare pediatric lymphoma provides a

valuable tool to predict cancer risk in children with VEO-IBD so that doctors can take preventive action that may prevent the occurrence or reoccurrence of lymphoma.

(France: *Blood*; Oct 2, 2013)

### Diabetes Mellitus in Lymphoma Patients

Glucocorticoid-induced diabetes mellitus (GDM) is a major complication arising from corticosteroid administration, but there is lack of studies on GDM attributing to CHOP chemotherapy. The authors studied the incidence and risk factors for GDM development in patients with lymphoma during CHOP chemotherapy. 80 patients were analyzed with lymphoma treated with a CHOP regimen with or without rituximab between 2004 and 2012. Patients with a known history of DM were excluded. Among the 80 patients, 26 (32.5%) developed GDM. Researchers found that age  $\geq 60$  years, glycated hemoglobin (HbA1c) levels  $>6.1\%$ , body mass index (BMI)  $>30 \text{ kg/m}^2$ , prednisolone administration prior to chemotherapy, history of hypertension or hypertension at admission, and the presence of metabolic syndrome, were significant ( $p \leq 0.05$ ) factors associated with GDM development by univariate analysis. The results suggest a guideline for plasma glucose monitoring during CHOP chemotherapy in patients with no history of DM.

(Japan: *Support Care Lancer*, Dec 2, 2013)

### Patterns of Hospice Use

Hospice brings substantial clinical benefits to dying patients and families but is underutilized by patients dying of hematologic malignancies (HM). There are 70,000 deaths among US patients with hematologic malignancies yearly. The authors measured the use and length of stay (LOS) in hospice among patients with HMs at a large academic cancer center. Information included demographics, transplant, hospice type, LOS, and use of "expanded access" services. Fifty-nine patients were referred to hospice, and 53 utilized hospice services, 25% of 209 HM decedents. Thirty-five received home hospice and 18 used inpatient hospice. The median home hospice LOS was nine days (SD 13) and inpatient hospice six days (SD 10). Nine patients with "expanded access" hospice received only a few blood transfusions, and none received radiation. HM patients are referred late or never for hospice services. Studies evaluating earlier integration of palliative and hospice care with usual HM care are warranted.

(USA: *J Palliat Med*; Jan 2, 2014)

## CANCER CONTROL

### Birth Characteristics and Risk of Lymphoma

Researchers have found that birth characteristics may be a risk factor for childhood lymphoma. In a population-based study, scientist from the University of California, USA, identified 478 lymphoma cases diagnosed in children 0-5 years of age between 1988 and 2007; and 208,015 controls frequency-matched by birth year were randomly selected from birth records. It was found that compared to non-Hispanic whites, Hispanic children had an increased risk of Hodgkin lymphoma (HL). For all types of lymphoma, about two fold risk increase was observed with indicators for high risk pregnancies including tocolysis, fetopelvic disproportion and previous preterm birth. NHL risk doubled with the complication premature rupture of membranes (OR and 95% CI 2.18 [1.12, 4.25]) and HL with meconium staining of amniotic fluids (OR and 95% CI 2.55 [1.01, 6.43]). These data suggest that pregnancy related factors, such as intra-uterine infections and factors associated with preterm labor, may be involved in lymphomathogenesis.

*(Cancer Epidemiol, Dec 14, 2013)*

### Lymphoma Risk with Ongoing Intestine

People with celiac disease who had persistent damage to their intestines, were at higher risk of lymphoma than people whose intestines had healed. This was revealed by the scientists from Sweden and USA in a collaborative research study. Celiac disease is characterized by damage to the lining of the small intestine because of a reaction to eating gluten. It can reduce the ability to absorb nutrients. Celiac disease is treated with dietary changes to avoid gluten found in wheat, barley and rye, for example. The study was conducted by following 7,625 celiac disease patients from 28 Swedish pathology departments for an average of almost nine years. Those with ongoing intestinal damage had a larger risk of lymphoma—102.4 instances per 100,000 people versus 24.2 per 100,000 in the general population. Among those with celiac disease, the rate was 67.9 instances per 100,000 compared with 31.5 per 100,000 among patients whose intestines had healed.

*(ScienceDaily, Aug 5, 2013)*

### Obesity and Diffuse Large B-Cell Lymphoma

Scientists from Dana Farber Cancer Institute, USA, have suggested risk of diffused large B-cell lymphoma (DLBCL) with high BMI. A meta-analysis was performed to quantify the relative risk (RR) of DLBCL incidence in overweight and obese persons compared with normal weight individuals using the random-effects model. Overweight was defined as a BMI 25 to 29.9 kg/m<sup>2</sup>, and obesity was defined as a BMI of 30 kg/m<sup>2</sup>. The RR of DLBCL in overweight individuals was 1.14 (95% confidence interval [CI], 1.04-1.24; P=0.004), and in obese individuals, RR was 1.29 (95% CI, 1.16-1.43; P<0.001). The RR of DLBCL in overweight men and women was 1.22 and 1.27, respectively. The RR of DLBCL in obese men and women was 1.40 and 1.34, respectively. Meta-regression analysis showed a 14% increase in DLBCL incidence for each 10 kg/m<sup>2</sup> increase in BMI. It was concluded that an increased BMI is associated with higher RR of DLBCL regardless of sex. Also, there seems to be a linear association between BMI and DLBCL incidence.

*(Clin Lymphoma Myeloma Leuk, Nov 14, 2013)*

### UV Radiation and Risk of Hodgkin Lymphoma

Ultraviolet radiation (UVR) may be protective against the Hodgkin lymphoma (HL). Researchers from Institut National de la Santé et de la Recherche Médicale, France conducted pooled analysis on type and timing of UVR exposure and on disease subtypes by age, histology, and tumor-cell Epstein-Barr virus (EBV) status by selecting 1320 HL cases and 6381 controls. Lifetime, adulthood, and childhood UVR exposure and history of sunburn and sunlamp use were estimated. Statistically significant inverse associations with HL risk for UVR exposures during childhood and adulthood, sunburn history, and sunlamp use were found. Risks were significant only for EBV-positive HL (pooled odds ratio, 0.56; 95% confidence interval, 0.35 to 0.91 for the highest overall UVR exposure category), with a significant linear trend for overall exposure (P=0.03). Pooled relative risk estimates were not heterogeneous across studies. Increased UVR exposure may protect against HL, particularly EBV-positive HL. Plausible mechanisms involving UVR induction of regulatory T-cells or the cellular DNA damage response suggest opportunities for new prevention targets.

*(Blood, Nov 14, 2013)*



## INFOCUS

### DOUBLE-HIT, TRIPLE-HIT LYMPHOMA-SEEK AND YOU WILL FIND

In many B-cell lymphomas, chromosomal translocations are biologic and diagnostic hallmarks of disease. Chromosomal translocations involving the immunoglobulin genes are common in B-cell non-Hodgkin's lymphomas. Two common translocations involve the BCL2 and MYC genes. The t(14;18) (q32;q21) juxtaposes BCL2 at 18q21 with the immunoglobulin heavy chain (IGH) gene enhancer at 14q32, resulting in the overexpression of BCL2. The t(14;18) (q32;q21) is characteristic of follicular lymphoma, but also occurs in 20–30% of de novo diffuse large B-cell lymphoma. Translocations that involve MYC, including t(8;14) (q24;q32), t(2;8) (p12;q24), and t(8;22) (q24;q11), juxtapose MYC at 8q24 with the IGH,  $\kappa$ , and  $\lambda$  genes, respectively, and upregulate MYC. MYC translocations are a hallmark of Burkitt lymphoma, but are not specific, as they can occur in other B-cell lymphomas. MYC rearrangement is observed in 5–10% of diffuse large B-cell lymphomas and up to 50% of high-grade B-cell lymphomas other than Burkitt lymphoma.

B-cell lymphomas with MYC/8q24 rearrangement and IGH@ BCL2/t (14;18) (q32;q21) have been referred to as double-hit lymphoma. Double-hit lymphoma (DHL) has been defined by others as a B-cell lymphoma with MYC/8q24 rearrangement in combination with a translocation involving another gene, such as BCL2, BCL3, or BCL6, most common of which involves MYC and BCL2, also known as MYC/BCL2 DHL. Triple hit lymphoma (TH lymphoma) has been defined as a B-cell lymphoma with MYC/BCL2/BCL6 rearrangement (Fig 1).

Patients with MYC/BCL2 lymphoma can present de novo or be associated with follicular lymphoma. B-cell lymphoma with MYC/BCL2 is uncommon, representing <1% of all lymphomas and approximately 4% of high-grade B-cell lymphomas.

The Mitelman Database of Chromosome Aberrations in Cancer, February 2010 edition, published cytogenetic data on a wide variety of malignancies, including B-cell lymphomas.

**Table 1: DH and TH Lymphomas in the Mitelman Database**

DH Lymphomas	N	Percentage of All 326 DH Cases
BCL2+/MYC+	203	62
BCL6+/MYC+	26	8
BCL2+/BCL6+/MYC+	53	16
CCND1+/MYC+	34	10
BCL3+/MYC+	5	2
9p13+/MYC+	4	1
BCL3+/9p13+/MYC+TH	1	0
Total DH and TH cases	326	100

BCL2<sup>+</sup>/MYC<sup>+</sup> DH lymphomas formed the great majority of DH lymphomas (62%; Table 1). BCL6<sup>+</sup>/MYC<sup>+</sup> DH lymphomas were relatively rare (8% of all cases), and in fact TH lymphomas that involved MYC, BCL2 and BCL6 (16%) were more frequent than BCL6<sup>+</sup>/MYC<sup>+</sup> DH cases. In DLBCL, 25 of 139 cases (18%) had a BCL6 breakpoint, whereas 84 of 139 (60%) had a BCL2 breakpoint. A very strong preference for BCL2 involvement in DH lymphomas was also found by FISH and suggests a selective complementary role for MYC and BCL2.

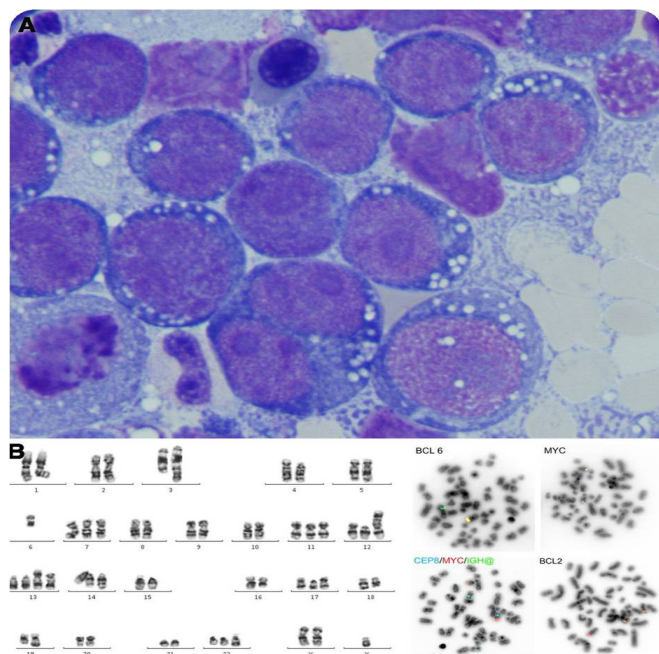
The morphological findings of MYC/BCL2 lymphomas show a spectrum, with most cases fitting best within the current World Health Organization system category of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma.

In series unselected by histology, between 30–40% of MYC/BCL2 double-hit lymphomas are classified as DLBCL, with rare cases classified as B-lymphoblastic lymphoma/leukemia or follicular lymphoma.

The diagnosis of DH/TH lymphoma is invoked to classify aggressive, mature B-cell neoplasms that fail to meet classical morphologic, immunophenotypic, and genetic definitions of Burkitt lymphoma or DLBCL.

### Clinicopathologic Features

Double-hit lymphomas bearing concurrent rearrangements of MYC/8q24 and BCL2/18q21 are clinically distinct from Burkitt lymphoma and DLBCL. The median age of diagnosis of MYC/BCL2 double-hit lymphomas is in the 6<sup>th</sup>–7<sup>th</sup> decade, significantly older than sporadic BL (4<sup>th</sup> decade) and younger than DLBCL (7<sup>th</sup> decade). Across series, MYC/BCL2 double-hit lymphomas tend to present with advanced stage (Ann Arbor III/IV), high or high-intermediate International



**Fig 1:** In the bone marrow aspirate, large blasts with deeply basophilic cytoplasm and numerous vacuoles resembling Burkitt cells (panel A) were present. Cytogenetic and fluorescence in situ hybridization analysis showed *MYC*, *BCL2* (double hit), and *BCL6* (triple-hit) rearrangements within a complex karyotype (panel B).

Prognostic Index (IPI), and increased LDH. There is a high frequency of extranodal disease, most commonly involving bone marrow/peripheral blood, central nervous system, or pleural effusions. When compared to IPI-matched DLBCL, only younger age (64 vs. 71 years), higher median LDH at presentation (727 U/L vs. 366 U/L), and increased frequency of bone marrow involvement (59% vs. 23%) are significantly associated with *MYC/BCL2* double-hit lymphomas. The median proliferation index of double-hit lymphomas approaches 90% but a wide range of proliferative index (40–100%) is noted even in disease that otherwise behaves in a clinically aggressive manner.

On routine cytogenetic analysis, double-hit lymphomas nearly always possess complex karyotypes, as defined by >2 numerical and/or structural aberrations. This context of chromosomal complexity is thought to be critical in determining the biological and clinical effects of *MYC* rearrangement.

### Treatment Outcomes

Double-hit lymphomas are highly resistant to standard chemotherapy, independent of regimen intensity or inclusion of rituximab. Median survival in recently published series ranges widely from 4.5 to 18.5 months but is significantly shorter compared to survival of

patients with Burkitt lymphoma or IPI-matched DLBCL. Double- and triple-hit lymphomas are chemosensitive aggressive B-cell lymphomas, but unlike Burkitt lymphoma and DLBCL they have a very high recurrence rate and are almost always fatal.

In their study of 303 patients with DLBCL, Barrans, et al. showed that overall survival at 2 years was significantly worse in patients with *MYC/8q24* rearrangements compared to those with unrearranged *MYC/8q24* (35% vs 61%). In a recent report from Argentina, the mean follow-up survival time of DH/TH lymphoma was 6.6 months, which was significantly short in comparison to DLBCL (31 months) and BL (30 months), respectively.

Across studies, patients treated with R-CHOP, R-hyper-CVAD, consolidation with either allogeneic stem cell transplantation or high-dose chemotherapy with autologous stem cell rescue did not impact survival.

### Conclusion

The importance of recognizing this double hit/triple hit lymphoma groups relies on its different clinical course, poor prognosis and shorter survival than DLBCL and BL. Based on clinical significance, it seems advisable to test all diffuse large B-cell and related lymphomas for *MYC* and other breakpoints. An accurate diagnosis is critical for risk stratification and to improve therapeutic approaches and outcomes.

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# LYMPHOMA

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