Anaplastic lymphoma kinase is a tyrosine kinase that belongs to the insulin receptor superfamily. These neoplasms express the product of a fusion gene that incorporates the 3′ portion of ALK, which encodes a tyrosine kinase. The most common fusion partner for ALK is clathrin (CLTC-ALK). This is the product of t(2;17)(p23;q23).[6-8] Interestingly, in these cases a cytoplasmic and granular positivity is seen on immunohistochemistry. This is because clathrin encodes for a coated vesicle protein involved in the intracellular transport. Less commonly the fusion partner is a nucleophosmin that results from t(2;5)(p23;q35). In Anaplastic large cell lymphoma, this is the most common chimeric protein. The methods that can be used to detect these mutations are karyotyping, FISH and /or RT-PCR. Van Roosbroeck et al identified a cryptic SEC31A-ALK fusion, generated by insertion of 5′ end of SEC31A (4q21) upstream of the 3′ end of ALK.[9] Other genetic abnormalities that can be seen, include 5′ ALK gene deletion, duplication of the ALK gene region, additional copy of chromosome 2, complex karyotype with two independent ALK translocation t(X;2)(q21;q23) and t(2;12)(q23;q24.1).[10-12] All these show diffuse granular cytoplasmic positivity on immunohistochemistry. SQSTM1-ALK formed by translocation t(2;5)(q23.1;q35.3) shows a diffuse cytoplasmic ALK staining with ill demarcated spots.

ALK positive large B cell lymphoma have a dismal prognosis and poor response to chemotherapy as compared to ALK positive large cell lymphoma that has a 5 year survival rate approaching 80%. Overall survival is strongly associated with the clinical stage. Early stage patients tend to achieve longer overall survival than advanced stage patients. More than 76% of the documented cases were in stage III and IV. Laurent and colleagues have reported a 5 years survival rate of 25% with a median survival of 12 months in clinical outcome data of 31 patients.[13] Beltran and colleagues also calculated an 18 months median survival in patients with an advanced disease.[14] Most patients receive chemotherapy including CHOP, CHOEP, EPOCH and CVAD with few patients who also receive radiotherapy and hematopoietic stem cell transplantation. As CD20 is negative in this neoplasm, Rituximab is insufficient for the improvement of the outcome in these cases.[5] Researchers have been trying to find a new way to treat this disease and the answer lies in its molecular pathogenesis. Crizotinib is a small molecule ALK inhibitor that has shown great success in the treatment of lung cancers with EML4-ALK translocation. Cerchietti and his colleagues established the first CLTC-ALK positive DLBCL cell line and xenotransplant tumor mouse.[15] The in vivo studies in the mouse showed that CLTC-ALK positive B cell lymphomas respond well to ALK inhibitors. STAT3 phosphorylation has been strictly linked to the ALK expression in these neoplasms and would be one of the other molecular targets especially in cases with SQSTM1-ALK variant translocation.[16]