WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman

CHAPTER 11

Mature T- and NK-cell Neoplasms

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorders of NK cells
- Aggressive NK cell leukaemia
- EBV+ T-cell lymphoproliferative disorders of childhood
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Primary cutaneous gamma-delta T-cell lymphomas
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma (ALCL), ALK positive
Anaplastic large cell lymphoma (ALCL), ALK negative
ALCL was firstly described by Stein et al. (Blood, 66:848-58) in 1985.

The tumour - previously often misdiagnosed as malignant histiocytosis or metastatic involvement by occult carcinoma - was characterised by distinctive morphology, cohesive growth pattern, frequent intra-sinusoidal diffusion, and regular expression of the lymphoid activation molecule Ki-1/CD30.

At that time, no distinction was made among anaplastic large cell lymphoid tumours carrying T, null or B-cell phenotype.
Thanks to two Intercontinental Workshops held in Berlin in 1987 and 1988

**ALCL primary:**  systemic:

- common (CT)
- giant-cell rich (GCR)
- lympho-histiocytic (LH)
- small cells (SC)
- “Hodgkin-related” (HR)
- *of the skin*

**ALCL secondary:** after HL, PTCL, etc.
CTCT

LHLH

GCRGCR

Sheet of tumoural cells
Further histological variants:

- signet-ring cell
- sarcomatoid
- eosinophil-rich
- epithelioid cell-rich

t(2;5) (p23;q35)

- It is characteristic of most ALCLs (T-cell).  

- It causes the fusion of the ALCL kinase (ALK) and nucleophosmin (NPM) genes, by producing the hybrid gene NPM/ALK, which encodes for a chimeric 80 kD protein (NPM/ALK or p80).

- ALK protein over-expression is thought to play a role in the lymphomagenesis process.

- REAL Classification (Harris NL et al, Blood, 1994):

DLBCL, anaplastic variant;

ALCL T/null (CT, LH, SC, GCR) (primary systemic, cutaneous) = accepted entity;

ALCL Hodgkin’s-like (ex-HR) = provisional entity.
WHO Blue Book (2001):

- DLBCL, anaplastic variant;
- ALCL, T/null (about 3% of all lymphomas), primary, systemic;
- CD30\(^+\) lymphoid proliferations of the skin:
  - lymphomatoid papulosis A and B;
  - Lymphomatoid papulosis C;
  - primary CD30\(^+\) ALCL of the skin.
Not specifically recognised because of the lack of conclusive data.
# MATURE T-CELL AND NK-CELL NEOPLASMS

<table>
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<th>Condition</th>
<th>Code</th>
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<td>Chronic lymphoproliferative disorder of NK-cells</td>
<td>9831/3</td>
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<td>Aggressive NK cell leukaemia</td>
<td>9948/3</td>
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<td>Systemic EBV positive T-cell lymphoproliferative</td>
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<td>disease of childhood</td>
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<td>Sézary syndrome</td>
<td>9701/3</td>
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<td><strong>Primary cutaneous CD30 positive T-cell</strong></td>
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<td>lymphoproliferative disorders</td>
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<tr>
<td>Lymphomatoid papulosis</td>
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<td>Primary cutaneous anaplastic large cell lymphoma</td>
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<td>Primary cutaneous gamma-delta T-cell lymphoma</td>
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<td><strong>Primary cutaneous CD8 positive aggressive</strong></td>
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<td>epidermotropic cytotoxic T-cell lymphoma</td>
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<td><strong>Primary cutaneous CD4 positive small/medium</strong></td>
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<td>T-cell lymphoma</td>
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<td>Angioimmunoblastic T-cell lymphoma</td>
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<td><strong>Anaplastic large cell lymphoma, ALK negative</strong></td>
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### Translocations and fusion proteins involving the ALK gene in ALCL

<table>
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<th>Translocation</th>
<th>Frequency</th>
<th>Localization</th>
<th>Fusion Proteins</th>
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<tbody>
<tr>
<td>t(2;5)(p23;q35)</td>
<td>70-80%</td>
<td>Cytoplasmic/Nuclear nucleolar</td>
<td>NPM-ALK</td>
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<tr>
<td>t(1;2)(q25:p23)</td>
<td>10-20%</td>
<td>Cytoplasmic</td>
<td>TPM3-ALK</td>
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<td>t(2;3)(p23;q21)</td>
<td>2-5%</td>
<td>Cytoplasmic</td>
<td>TFGL/S-ALK</td>
</tr>
<tr>
<td>inv(2)(p23;q35)</td>
<td>2-5%</td>
<td>Cytoplasmic</td>
<td>ATIC-ALK</td>
</tr>
<tr>
<td>t(2;17)(p23;q23)</td>
<td>2-5%</td>
<td>Cytoplasmic</td>
<td>CLTC-ALK</td>
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<tr>
<td>t(2;19)(p23;q13,1)</td>
<td>-</td>
<td>Cytoplasmic</td>
<td>TPM4-ALK</td>
</tr>
<tr>
<td>t(2;2)(p23;q11-13)? or inv(2)(p23;q11-13)?</td>
<td>-</td>
<td>Nuclear membrane</td>
<td>RanBP2-ALK</td>
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<tr>
<td>t(X;2)(q11-12;p23)</td>
<td>-</td>
<td>Membranous</td>
<td>MSN-ALK</td>
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</table>
The oncogenic role of ALK fusion proteins

- ALK fusion proteins are induced to complex via their dimerization domain, leading to constitutive tyrosine kinase activation of ALK
- Transforming ability *in vitro*
- Tumorigenic role in transgenic mouse models
- Engagement of several intracellular pathways

Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in 5 cases.

L Lamant, S Pileri, E Sabattini, L Brugières, ES Jaffe and G Delsol

Anaplastic large-cell lymphoma

Giorgio Inghirami, MD, a,b Stefano A. Pileri, MD, c and the European T-Cell Lymphoma Study Group

Seminars in Diagnostic Pathology (2011) 28, 190-201
Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target

Roberto Chiarle\textsuperscript{1,2}, William J Simmons\textsuperscript{1}, Honjying Cai\textsuperscript{1}, Girish Dhall\textsuperscript{1,3}, Alberto Zamo\textsuperscript{14}, Regina Raz\textsuperscript{1}, James G Karras\textsuperscript{5}, David E Levy \textsuperscript{1} & Giorgio Inghirami\textsuperscript{1,2}

The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination

Roberto Chiarle\textsuperscript{1,2}, Cinzia Martinengo\textsuperscript{1,5}, Cristina Mastini\textsuperscript{1,3,5}, Chiara Ambrogio\textsuperscript{1,2}, Valentina D’Escamard\textsuperscript{4}, Guido Forni\textsuperscript{3} & Giorgio Inghirami\textsuperscript{1,2,4}

Anaplastic Lymphoma Kinase (ALK) in cancer pathogenesis.

Antonella Barreca\textsuperscript{1}, Elena Lasorsa\textsuperscript{1}, Ludovica Riera\textsuperscript{1}, Rodolfo Machiorlatti\textsuperscript{1}, Roberto Piva\textsuperscript{1,2}, Maurilio Punzoni\textsuperscript{3}, Ivo Kwee\textsuperscript{4}, Francesco Bertoni\textsuperscript{4}, Pier Paolo Piccaluga\textsuperscript{5}, Stefano A. Pileri\textsuperscript{5}, Giorgio Inghirami\textsuperscript{1,2} & the European T-Cell Lymphoma Study Group.
Anaplastic large cell lymphoma (ALCL), ALK-positive

G. Delsol
B. Falini
H.K. Müller-Hermelink
E. Campo
E.S. Jaffe
R.D. Gascoyne
H. Stein
M.C. Kinney

ALCL: Overall survival

%  
100  
80  
60  
40  
20  
0  
0  12  24  36  48  60  72  months

ALK+  
ALK-  

Male (n=228)  
Female (n=158)  

Age

Number of cases
ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project

Kerry J. Savage,1 Nancy Lee Harris,2 Julie M. Vose,3 Fred Ulrich,4 Elaine S. Jaffe,5 Joseph M. Connors,1 Lisa Rimsza,6 Stefano A. Pileri,7 Mukesh Chhanabhai,8 Randy D. Gascoyne,6 James C. Armitage,9 and Dennis D. Weisenburger,9 for the International Peripheral T-Cell Lymphoma Project

---

ALK+ Lymphoma: Clinico-Pathological Findings and Outcome

Brunangelo Falini, Stefano Pileri, Pier Luigi Zinzani, Antonino Carbone, Vittorina Zagonel, Chris Wolf-Peeters, Gregor Verhoeef, Fabio Menestrina, Giuseppe Todeschini, Marco Pauli, Mario Lazzarino, Roberto Giardini, Antonella Aiello, Hans-Dieter Foss, Iguaicyra Araujo, Marco Fizzotti, Pier-Giuseppe Pellicci, Leonardo Flenghi, Massimo F. Martelli and Antonella Santucci
Morphologic spectrum of "ALK+ ALCL"

- ALK+ hallmark cells
- ALK+ small cells (reservoir?)

ALCL - CT - mixed - SCV
- HL (perivascular) - LH

ALK-Positive Anaplastic Large Cell Lymphoma Mimicking Nodular Sclerosis Hodgkin’s Lymphoma

Report of 10 Cases

José Vassallo, MD, PhD,*† Laurence Lamant, MD, PhD,* Laurence Brugieres, MD, PhD,‡ Fanny Gaillard, MD, PhD,§ Elias Campo, MD, PhD,‖ Pierre Brousset, MD, PhD,* and Georges Delsol, MD*
Phenotype:

- **CD30**
- **T/null**
- **CD45**
- **EMA**
- **CD15**
- **Cytotoxic markers**
- **EBV**
ALCL, ALK+: variant morphologic patterns


12/13 common type

8/12 variant patterns

- Distinct molecular signature
- More advanced stage disease
- More frequent relapses
Anaplastic large cell lymphoma, ALK-negative (Provisional entity)
Undistinguishable morphologically and phenotypically
Histological variants do exist but the small cell one!
ALK⁻ anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK + ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project

Kerry J. Savage¹, Nancy Lee Harris², Julie M. Vose³, Fred Ullrich⁴, Elaine S. Jaffe⁵, Joseph M. Connors⁴, Lisa Rimsza⁶, Stefano A. Pileri⁷, Mukesh Chhanabhai⁸, Randy D. Gascoyne⁸, James O. Armitage³, Dennis D. Weisenburger, for the International Peripheral T-Cell Lymphoma Project⁹
Gene expression profiling uncovers molecular classifiers for the recognition of Anaplastic Large Cell Lymphoma within Peripheral T-cell neoplasms

JCO, 2010; 28:1583-90.

Roberto Piva\textsuperscript{1,2}, Luca Agnelli\textsuperscript{3*}, Elisa Pellegrino\textsuperscript{1*}, Katia Todoerti\textsuperscript{3}, Valentina Grosso\textsuperscript{1}, Ilaria Tamagno\textsuperscript{1}, Alessandro Fornari\textsuperscript{1}, Barbara Martinoglio\textsuperscript{4}, Enzo Medico\textsuperscript{4}, Alberto Zam\textsuperscript{5}, Fabio Facchetti\textsuperscript{6}, Maurilio Ponzoni\textsuperscript{7}, Eva Geissinger\textsuperscript{8}, Andreas Rosenwald\textsuperscript{9}, Hans Konrad Müller-Hermelink\textsuperscript{10}, Cristiane De Wolf-Peeters\textsuperscript{11}, Pier Paolo Piccaluga\textsuperscript{12}, Stefano Pileri\textsuperscript{10}, Antonino Neri\textsuperscript{5}, Giorgio Inghirami\textsuperscript{1,2}
Abstract submitted to ASH Meeting

Gene expression signatures that delineate biologic and prognostic subgroups in peripheral T-cell lymphoma

ALK- ALCL

8 different genetic lesions detected by RNAseq
(2 already reported by the Rochester Group, although at different rates)
Brief report

Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing

Andrew L. Feldman,1 Ahmet Dogan,1 David I. Smith,1 Mark E. Law,1 Stephen M. Ansell,2 Sarah H. Johnson,3 Julie C. Porcher,2 Nazan Özsan,4 Eric D. Wieben,5 Bruce W. Eckloff,5 and George Vasmatzis3

1Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; 2Division of Hematology, Mayo Clinic, Rochester, MN; 3Department of Molecular Medicine and Center for Individualized Medicine, Mayo Clinic, Rochester, MN; 4Department of Pathology, Ege University, Izmir, Turkey; and 5Advanced Genomics Technology Center, Mayo Clinic, Rochester, MN

The genetics of peripheral T-cell lymphomas are poorly understood. The most well-characterized abnormalities are translocations involving ALK, occurring in approximately half of anaplastic large cell lymphomas (ALCLs). To gain insight into the genetics of ALCLs lacking ALK translocations, we combined mate-pair DNA library construction, massively parallel (“Next Generation”) sequencing, and a novel bioinformatic algorithm. We identified a balanced translocation disrupting the DUSP22 phosphatase gene on 6p25.3 and adjoining the FRA7H fragile site on 7q32.3 in a systemic ALK-negative ALCL. Using fluorescence in situ hybridization, we demonstrated that the t(6;7)(p25.3;q32.3) was recurrent in ALK-negative ALCLs. Furthermore, t(6;7)(p25.3;q32.3) was associated with down-regulation of DUSP22 and up-regulation of MIR29 microRNAs on 7q32.3. These findings represent the first recurrent translocation reported in ALK-negative ALCL and highlight the utility of massively parallel genomic sequencing to discover novel translocations in lymphoma and other cancers. (Blood. 2011;117(3):915-919)
Peripheral T-cell lymphomas (PTCLs) are aggressive malignancies of mature T lymphocytes with 5-year overall survival rates of only -- 35%. Improvement in outcomes has been stymied by poor understanding of the genetics and molecular pathogenesis of PTCL, with a resulting paucity of molecular targets for therapy. We developed bioinformatic tools to identify chromosomal rearrangements using genome-wide, next-generation sequencing analysis of mate-pair DNA libraries and applied these tools to 16 PTCL patient tissue samples and 6 PTCL cell lines. Thirteen recurrent abnormalities were identified, of which 5 involved p53-related genes (TP53, TP63, CDKN2A, WWOX, and ANKRD11). Among these abnormalities were novel TP63 rearrangements encoding fusion proteins homologous to ΔNp53, a dominant-negative p63 isoform that inhibits the p53 pathway. TP63 rearrangements were seen in 11 (5.8%) of 190 PTCLs and were associated with inferior overall survival; they also were detected in 2 (1.2%) of 164 diffuse large B-cell lymphomas. As TP53 mutations are rare in PTCL compared with other malignancies, our findings suggest that a constellation of alternate genetic abnormalities may contribute to disruption of p53-associated tumor suppressor function in PTCL. (Blood. 2012;120(11):2280-2289)
**ALK- ALCL**

### Table

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<th>Type</th>
<th>p63</th>
<th>Ki67</th>
<th>CD30</th>
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<tr>
<td>PTCL, NOS</td>
<td>53  (27.9)</td>
<td>5/53 (9.4)</td>
<td>3/5 (60.0)</td>
</tr>
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<td>ALCL, ALK positive</td>
<td>21  (11.1)</td>
<td>0/21 (0.0)</td>
<td>— (—)</td>
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<tr>
<td>ALCL, ALK negative</td>
<td>32  (16.8)</td>
<td>4/32 (12.5)</td>
<td>3/4 (75.0)</td>
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<tr>
<td>ALCL, primary cutaneous</td>
<td>19  (10.0)</td>
<td>2/19 (10.5)</td>
<td>1/2 (50.0)</td>
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ALK- ALCL

**Wednesday, October 24th, 08.30 Key Note Lecture:**
New genetic findings in T-cell lymphomas. *Andrew Feldman*
Anaplastic Large Cell Lymphoma Associated With Breast Implants: A Report of 13 Cases

Aladily, Tariq N. MD*; Medeiros, L. Jeffrey MD*; Amin, Mitual B. MD†; Haiider, Nisreen MD‡; Ye, Dongjiu MD§; Azevedo, Sergio J. MD; Jorgensen, Jeffrey L. MD, PhD*; de Peralta-Venturina, Mariza MD§; Mustafa, Eid B. MD#; Young, Ken H. MD, PhD*; You, M. James MD, PhD*; Fayad, Luis E. MD**; Blenc, Ann Marie MD‡; Miranda, Roberto N. MD*

Abstract

We report 13 cases of anaplastic large cell lymphoma (ALCL) associated with breast implants. Patient age ranged from 39 to 68 years, and the interval from implant to ALCL was 4 to 29 years. All tumors were composed of large, pleomorphic cells that were CD30+ and ALK+, and all 7 cases assessed had monoclonal T-cell receptor γ-chain rearrangements. Two patient subgroups were identified. Ten patients presented with effusion surrounded by fibrous capsule without a grossly identifiable tumor mass. Nine patients had stage I and 1 had stage II disease. Eight patients underwent implant removal and capsulectomy. Four patients received chemotherapy and 4 radiation therapy. All patients were alive without disease at last follow-up. A second subgroup of 3 patients had effusion and a distinct mass adjacent to the implant. One patient had stage I and 2 stage II disease. One patient had a 3-year history of lymphomatoid papulosis, and 1 patient had a 1-year history of CD30+ T-cell lymphoma adjacent to the breast before the diagnosis of ALCL associated with breast implant. Two patients received chemotherapy and 1 radiation therapy. Two patients died 2 and 12 years after diagnosis, respectively. We conclude that the clinical behavior of ALCL associated with breast implants is heterogeneous. Patients who present with effusion without a distinct mass may have an indolent disease course, similar to CD30+ lymphoproliferative disorder of skin. In contrast, patients who present with a distinct mass may have advanced stage or possibly systemic disease and have a poorer prognosis.
Extranodal NK/T-cell Lymphoma, Nasal Type, Arising in Association With Saline Breast Implant

Expanding the Spectrum of Breast Implant–associated Lymphomas

Tariq N. Aladily, MD,* Bharat N. Nathwani, MD,† Roberto N. Miranda, MD,* Rina Kansal, MD,† C. Cameron Yin, MD, PhD,* Richard Protzel, MD,‡ Gary S. Takowsky, MD,§ and L. Jeffrey Medeiros, MD*

Abstract: Extranodal NK/T-cell lymphoma, nasal type, is a rare type of non-Hodgkin lymphoma that is most common in Asia and is driven by Epstein-Barr virus infection. These tumors usually arise in the nasal region; in rare cases they can involve extranasal sites, most often skin, with involvement of the breast being rare. Lymphomas arising adjacent to breast implants are rare, and most cases reported to date have been anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma. Here we report a 41-year-old white woman with bilateral saline breast implants placed for cosmetic reasons who almost 9 years later developed painful swelling at the right-breast implant site. Excisional biopsy revealed lymphoma composed of monomorphic large cells associated with necrosis and angioinvasion. Immunohistochemical analysis showed an aberrant, NK/T-cell immunophenotype with the lymphoma cells being CD2, CD3, CD56, partial CD30, granzyme B, TIA-1, CD4, CD5, CD7, and CD8. In situ hybridization analysis showed Epstein-Barr virus–encoded RNA within the neoplastic cells. Polymerase chain reaction analysis showed monoclonal T-cell receptor-γ chain gene rearrangement. These findings support the diagnosis of extranodal NK/T-cell lymphoma, nasal type. On the basis of our review of the literature, this case is unique. In addition, we believe this case is important to report, because it expands the spectrum of T-cell lymphomas that can be associated with breast implants and may be a forerunner of additional cases to follow.

Non-Hodgkin lymphomas are the most common nonepithelial neoplasms that involve the breasts, but lymphomas localized to and arising in the breasts are rare, accounting for <1% of all breast malignant neoplasms. In the United States and Western Europe, most lymphomas affecting the breast are of B-cell lineage, whereas T-cell lymphomas involving the breast represent <10% of all cases. Within the T-cell lymphoma group, a subset of lymphomas show a preferential association with breast implants, and most of these cases have anaplastic cytologic features, an aberrant T-cell immunophenotype with uniform expression of CD30, and absence of anaplastic lymphoma kinase (ALK), meeting the criteria for breast implant–associated anaplastic large cell lymphoma (ALCL).

Extranodal natural killer (NK)/T-cell lymphoma, nasal type, is a rare type of lymphoma that is most common in Southeast Asia and is rare in the United States. This neoplasm can have an NK-cell or a T-cell immunophenotype and is virtually always positive for Epstein-Barr virus (EBV), suggesting that EBV plays a pathogenic role. Most cases of nasal type extranodal NK/T-cell lymphoma arise in the upper aerodigestive tract, usually the nasal region, but approximately 5% to 10% of cases can arise at extranasal sites. The most common
ALK+ T/null ALCL

- CD45
- CD15
- EMA
- Cytotoxic markers
- PAX5/BSAP
- EBV
- PCR
Innovative therapies

- **Rapamycin - mTOR inhibition - miR101 counteraction.**
Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Anas Younes, M.D., Nancy L. Bartlett, M.D., John P. Leonard, M.D., Dana A. Kennedy, Pharm.D., Carmel M. Lynch, Ph.D., Eric L. Sievers, M.D., and Andres Forero-Torres, M.D.

BACKGROUND
Hodgkin’s lymphoma and anaplastic large-cell lymphoma are the two most common tumors expressing CD30. Previous attempts to target the CD30 antigen with monoclonal-based therapies have shown minimal activity. To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E (MMAE) was attached to a CD30-specific monoclonal antibody by an enzyme-degradable linker, producing the antibody–drug conjugate brentuximab vedotin (SGN-35).

METHODS
In this phase 1, open-label, multicenter dose-escalation study, we administered brentuximab vedotin (at a dose of 0.1 to 3.6 mg per kilogram of body weight) every 3 weeks to 45 patients with relapsed or refractory CD30-positive hematologic cancers, primarily Hodgkin’s lymphoma and anaplastic large-cell lymphoma. Patients had received a median of three previous chemotherapy regimens (range, one to seven), and 79% had undergone autologous stem-cell transplantation.

RESULTS
The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.

CONCLUSIONS
Brentuximab vedotin induced durable objective responses and resulted in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas in this phase 1 study. Treatment was associated primarily with grade 1 or 2 (mild-to-moderate) toxic effects. (Funded by Seattle Genetics; ClinicalTrials.gov number, NCT00430846.)

Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK centre

Short Title: Brentuximab vedotin in refractory CD30+ lymphomas

Adam Gibb1,2, Craig Jones1,2, Adrian Bloor1, Samar Kulkarni1, Tim Illidge1,2, Kim Linto,1,2 and John Radford1,2

Abstract
The CD30-targeted agent brentuximab vedotin has shown impressive activity in relapsed/refractory Hodgkin lymphoma and anaplastic large-cell lymphoma in phase II studies. We have treated 24 patients with relapsed/refractory disease enrolled onto a Named Patient Programme during 2010-11 at a single UK Centre. Overall response rate across all histologies was 67% (Hodgkin, 72%; anaplastic large cell, 60%), complete response rate 25% (Hodgkin, 17%; anaplastic large cell 60%), median progression-free survival 5.1 months and toxicity mild to moderate in the majority of cases. Six patients proceeded to allogeneic transplantation and one patient awaits this procedure. These results are similar to phase II data and show that brentuximab vedotin provides a bridge to allogeneic transplantation in approximately one quarter of patients refractory to conventional salvage therapies. Best response was seen after four doses so consideration of allogeneic transplantation should be made early and scheduled following the first assessment indicating response.
ALK+ ALCL

PDGFR blockade is a rational and effective therapy for NPM-ALK–driven lymphomas

Daniela Laimer1,25, Helmut Dolznig2,25, Karoline Kollmann3,25, Paul W Vesely4,24,25, Michaela Schlederer5, Olaf Merkel6,24, Ana-Iris Schiefer1, Melanie R Hassler1,7, Susi Heider1, Lena Amenitsch1, Christiane Thallinger7, Philipp B Staber8,9, Ingrid Simonitsch-Klupp1, Matthias Artaker10, Sabine Lagger10,24, Suzanne D Turner11, Stefano Pileri12, Pier Paolo Piccaluga12, Peter Valent13,14, Katia Messana15, Indira Landra15, Thomas Weichhart2, Sylvia Knapp16,17, Medhat Shehata13, Maria Todaro15, Veronika Sexl13, Gerald Höfler4, Roberto Piva15,18, Enzo Medico19,20, Bruce A Ruggeri21, Mangeng Cheng21, Robert Eferl22, Gerda Egger1, Josef M Penninger23, Ulrich Jaeger13, Richard Morigli5, Giorgio Inghirami15,19 & Lukas Kenner1,5

Received 23 July; accepted 10 September; published online 14 October 2012; doi:10.1038/nm.2966
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<tr>
<th>TCL subtype</th>
<th>cases included in TMA</th>
<th>PDGFRα</th>
<th>p-PDGFRα</th>
<th>PDGF-A</th>
<th>PDGF-B</th>
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<tbody>
<tr>
<td>PTCL/NOS</td>
<td>156</td>
<td>128/141</td>
<td>105/110</td>
<td>74/86</td>
<td>85/92</td>
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<tr>
<td>AITL</td>
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<td>21/22</td>
<td>20/23</td>
<td>23/24</td>
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<tr>
<td>ALCL ALK⁺</td>
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<td>10/12</td>
<td>13/13</td>
<td>9/12</td>
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<tr>
<td>ALCL ALK⁻</td>
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<td>8/10</td>
<td>6/6</td>
<td>7/9</td>
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<tr>
<td>MF</td>
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<td>28/28</td>
<td>28/28</td>
<td>5/5</td>
<td>7/8</td>
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<tr>
<td>EATL</td>
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<td>5/5</td>
<td>ne</td>
<td>3/3</td>
<td>2/2</td>
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<tr>
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<td>1/1</td>
<td>ne</td>
<td>ne</td>
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<table>
<thead>
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<th>PDGFRβ</th>
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<td>PTCL/NOS</td>
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<tr>
<td>AITL</td>
<td>0/15</td>
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<tr>
<td>ALCL ALK⁺</td>
<td>9/9</td>
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<tr>
<td>ALCL ALK⁻</td>
<td>15/20</td>
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</tbody>
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**ALK**+ ALCL

Anaplastic large-cell lymphoma

Giorgio Inghirami, MD, a,b Stefano A. Pileri, MD, c and the European T-Cell Lymphoma Study Group
Conditional deletion of JunB and cJun in transgenic mice in which the human NPM/ALK was put under the control of the murine CD4 promoter.
**ALK**⁺ ALCML

**TCL subtype** | **PDGFRA** positives/sample set | **PDGFRB** positives/sample set
---|---|---
PTCL/NOS | 128/141 | 4/38
AITL | 36/36 | 0/15
ALCL ALK⁺ | 77/79 | 53/71
ALCL ALK⁻ | 31/31 | 33/48
ALK+ ALC
ALKALK++ ALCLALCL

- Patient suffering from NPM
  - ALK+, ALK+, JunB+
  - cJun+, PDGFRA+, +
  - PDGFRB+, cPDGFRB+, c
  - Kit-- ALCL refractory to conventional first line chemotherapy and relapsed after autologous stem cell transplantation.

- Complete clinical remission with reduced tumor markers and normalized PDGFB levels within 10-14 days of imatinib therapy.

- Patient free of ALCL since 24 months after initiation of imatinib.
PP Piccaluga, E Sabattini, F Bacci, C Agostinelli, C Sagramoso, F Fuligni, M Rossi, S Righi, A Gazzola, T Sista, M Piccioli, MR Sapienza, C Mannu, F Fuligni, F Sandri, P Artioli, G De Biase, G Da Pozzo, C Tigrini, M Monari and D Bignami