



THE FDA MEDICAL PRODUCT REPORT

Page ____ of ____

A. Patient information

C. Suspect medication(s)

1. Patient identifier unknown In confidence	2. Age at time of event: adult Date of birth:	3. Sex () female () male	4. Weight unk lbs or kgs
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1. Name (give labeled strength & mfr/labeler, if known) #1 unspecified acetaminophen product #2 STI571
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B. Adverse event or product problem

2. Dose, frequency & route used #1 unknown dose, po #2 400-600 mg/day, po	3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 "chronically" #2 unknown date or duration
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1. X Adverse event and/or Product problem (e.g., defects/malfunctions)	() disability
2. Outcomes attributed to adverse event (check all that apply)	() congenital anomaly
(x) death unknown (mo/day/yr)	() required intervention to prevent permanent impairment/damage
() life-threatening	() other:
() hospitalization - initial or prolonged	

4. Diagnosis for use (indication) #1 unknown #2 chronic myeloid leukemia	5. Event abated after use: stopped or dose reduced #1 () Yes () No (X) N/A #2 () Yes () No (X) N/A
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3. Date of event unknown (mo/day/yr)	4. Date of this report 02/27/01 (mo/day/yr)
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6. Lot # (if known) #1 Unknown #2 unknown	7. Exp. date (if known) #1 Unknown #2 unknown	8. Event reappeared after reintroduction #1 () Yes () No (X) N/A #2 () Yes () No (X) N/A
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5. Describe event or problem

Literature report (Blood 2000;96(11):469a-Abstract #2021) of a phase II study of STI 571 in adult patients with Philadelphia chromosome positive chronic myeloid leukemia in accelerated phase. Two hundred and thirty-four patients with CML-AP were recruited from 18 centers in France, Germany, Italy, Switzerland, UK and USA between 8/99 and 3/00. STI571, an Abl tyrosine kinase inhibitor, was administered orally, initially at a daily dose of 400 mg/day and subsequently at a daily dose of 600 mg, on an outpatient basis. One patient died (DEATH) due to LIVER FAILURE within 11 days of initiating trial therapy. This was suspected to be related to the use of STI571. The patient had been taking an unspecified dose of acetaminophen chronically, and a possible DRUG INTERACTION between STI571 and acetaminophen was also suspected. No further information was provided regarding this patient's clinical course.

9. NDC # - for product problems only (if known)	10. Concomitant medical products and therapy dates (exclude treatment of event) unknown
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6. Relevant tests/laboratory data, including dates unknown

G. All manufacturers

1. Contact office - name/address (& mfrng site for devices) McNeil Consumer Healthcare Medical Affairs 7050 Camp Hill Road Ft. Washington, PA 19034	2. Phone number 215-273-7303	3. Report source: (check all that apply) () foreign () study (X) literature () consumer (X) health professional () user facility () comparative () distributor () other:
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4. Date received by manufacturer (mo/day/yr) 02/26/01	5. (A) NDA # 19-872 IND # PLA # pre-1938 () Yes OTC product (X) Yes
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7. Type of report (check all that apply) () 5-day (X) 15-day () 10-day () periodic (X) Initial () follow-up #	8. Adverse event term(s) DEATH LIVER FAILURE DRUG INTERACTION
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9. Mfr. report number 1513100A

E. Initial reporter

1. Name, address & phone # M. Talpaz MD Anderson Cancer Center 1515 Holcombe Boulevard Houston, TX 77030	DSS MAR 9 2001
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2. Health professional? (X) Yes () No	3. Occupation	4. Initial reporter also sent report to FDA () Yes () No (X) Junk
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clonogenic properties of infected cells. Δ STAT5B reduced anti-apoptotic activity of NPM/ALK in cells kept in growth factor and serum-free medium. Finally, mice injected with NPM/ALK+ BaF3 cells infected with the virus carrying Akt(K179M) or Δ STAT5B dominant-negative mutants survived significantly longer than mice inoculated with NPM/ALK+ cells infected with the empty virus. Necropsy has identified a wide-spread ALK+ lymphoma in lymph nodes and liver of the affected animals. Altogether, our data indicate that PI-3K/Akt and STAT5 pathways may play an important role in the NPM/ALK-mediated lymphomagenesis.

Abstract# 2018

NPM-ALK ASSOCIATED WITH ANAPLASTIC LARGE-CELL LYMPHOMA ACTIVATES THE PI3-KINASE/AKT ANTIAPOPTOTIC SIGNALING PATHWAY. Renyuan Y. Bai*,¹ Tao Ouyang*,¹ Cornelius Miething*,¹ Steve W. Morris*,² Christian Peschel*,¹ Justus Duyster.¹ ¹Department of Internal Medicine III, Technical University of Munich, Munich, Germany; ²Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA.

More than half of anaplastic large-cell lymphomas (ALCL) have a chromosomal translocation (t(2;5) that leads to expression of a hybrid protein comprised of the nuclear phosphoprotein nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK) that exhibits an unregulated tyrosine kinase activity. We have previously identified PLC- γ as a crucial downstream signaling molecule of NPM-ALK that contributes to its mitogenic potential. Here, we show that NPM-ALK recruits the C-terminal SH2 domain of the PI3-kinase p85 subunit. PI3-kinase assays revealed that the kinase is activated by NPM-ALK *in vivo* in turn activating PKB/Akt in NPM-ALK-expressing cells. Use of two specific PI-3-kinase inhibitors, wortmannin and LY294002, demonstrated the requirement of PI3-kinase for the growth of NPM-ALK-transformed cell lines, as well as a cell line established from an ALCL patient. Primary murine bone marrow retrovirally transduced with NPM-ALK showed a transformed phenotype which was reversible upon treatment with PI3-kinase inhibitors. Flow cytometric analysis revealed that wortmannin-treated NPM-ALK-transformed cell lines underwent apoptosis. Furthermore, apoptosis induced by overexpression of the proapoptotic molecule Bad could be partially blocked by the overexpression of NPM-ALK. Thus, NPM-ALK activates the antiapoptotic PI-3 kinase/Akt pathway, which likely contributes to the molecular pathogenesis of ALCL.

Abstract# 2019

T CELL LYMPHOPROLIFERATIVE DISORDERS (LPD) IN A SINGLE INSTITUTION: A 20-YEAR EXPERIENCE. Kerry J. Savage*, Randy D. Gascoyne, Mukesh Chhanabhai*, Nicholas J. Voss*, Joseph M. Connors. *British Columbia Cancer Agency, Vancouver, Canada.*

T cell neoplasms are heterogeneous. We reviewed 328 adult patients with LPDs with a T cell immunophenotype seen at the BC Cancer Agency over the past 20 y (age 15-87y; F:M 127:201). WHO categories included: angioimmunoblastic lymphoma (AILD) n (%) 10 (3), anaplastic large cell lymphoma (T) (ALCL) 36 (11), cutaneous ALCL (C-ALCL) 7 (2), enteropathy-associated T cell lymphoma (EATL) 7 (2), lymphoproliferative disorder of granular lymphocytes (LGL) 11 (3), lymphoblastic lymphoma (LBL) 28 (9), PTCL-unspecified (PTCL) 120 (37), mycosis fungoides (MF) 75 (23) and nasal T/NK-type (Nasal) 15 (5). The remainder, 19 (6) were comprised of T cell chronic lymphocytic leukemia/PLL 6, lymphomatoid papulosis (LyP) 6, HTLV1-type 3, and subcutaneous panniculitic-type (SCPTCL) 4. The median age at diagnosis ranged from 23-73 y. The IPI for diffuse large cell lymphoma was applied to the 4 subgroups with > 25 patients. Factor distribution varied markedly: ALCL 0-1, 50%; 2-3, 28%; 4-5, 22%; LBL 0-1, 25%; 2-3, 54%; 4-5, 21%; PTCL 0-1, 30%; 2-3, 47%; 4-5, 23%; MF 0-1, 84%; 2-3, 12%; 4-5, 4%.

Outcomes (subgroups with < 7 patients not shown; *not assessable)

Subtype	CR %	5 y OS %	5 y PFS %	IPI score (0-1) 5 y OS %	IPI score (2-3) 5 y OS %	IPI score (4-5) 5 y OS %
AILD	70	36	25	*	*	*
ALCL	53	48	27	66	21	31
C-ALCL	86	71	57	*	*	*
EATL	43	34	29	*	*	*
LBL	89	52	54	38	60	56
LGL	*	90	79	*	*	*
LyP	*	100	75	*	*	*
Nasal	60	16	9	*	*	*
PTCL	61	35	30	62	23	22
MF	*	70	54	79	30	33

C-ALCL, LBL, ALCL, LGL and MF had favorable prognoses. The 5y PFS (54%) in LBL closely approximated OS (52%), indicating that responses were durable. PTCL-unspecified had poor 5y OS (35%), PFS (30%), and med survival (2y). The IPI was predictive of survival for ALCL, PTCL and MF, but not LBL. However, it only identified 2 groups, low risk vs all others (high risk). Overall survival for most subtypes of PTCL is poor. More effective therapies are needed. A population within the ALCL, PTCL and MF subgroups defined using the IPI may have a more favorable prognosis.

Abstract# 2020

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA AILD-TL: AN HETEROGENEOUS ENTITY WITH REGARD TO LYMPHOCYTE CLONALITY AND EBV STATUS. Marie-Helene Delfau-Larue*,¹ Frederic Davi*,¹ Danielle Canioni*,¹ Pierre Dubus*,¹ Thierry Molina*,¹ Martine Raphael*,¹ Philippe Gaulard*,¹ Gilles Salles,¹ Elizabeth Macintyre,¹ *Groupe d'Etude des Lymphomes de l'Adulte.*

Though initially described as an immune disorder, AILD is now considered to be a T-cell lymphoma, based on the frequent finding of clonal T cell receptor (TCR) gene rearrangement. Since most studies were based on Southern blot analyses, the aim of this work was: 1) to reassess on a large series of patients the clonality status by PCR, for both T and B cells; 2) to evaluate the frequency of Epstein-Barr virus (EBV) infection. Eighty seven cases of AILD biopsies were studied. Clonality of T and B cells was analyzed by DNA amplification of TCR gamma and immunoglobulin heavy chain (Igh) genes respectively. The EBV genome was detected by Southern blot, and a terminal repeat probe was used to determine EBV clonality. A major (M), minor (m), or oligoclonal (o) TCR rearrangement was observed in 75/87 (86%) patients. Only 4/87 (5%) patients had polyclonal (P) T and B cells.

Clonal EBV	TCR M	TCR m/o	TCR P	Total	EBV	(+/-test)
IgH	15	6	5	26(30%)	13/2	6
IgB m/o	15	7	3	25(29%)	6/7	1
IgH P	22	10	4	36(41%)	3/14	1
Total	52(60%)	23(26%)	12(14%)	87	28/51(55%)	8

EBV genome was detected in only 28 of the 51 tested patients (55%). This is in contrast to most previous studies which show that over 90% of AILD are associated with EBV. Two third of EBV positive cases demonstrated both a TCR and Igh restricted repertoire. The viral load, evaluated by the intensity of the hybridization signal was variable. In 8 of the 9 cases with a strong EBV signal, a monoclonal infection pattern could be observed. Most of these cases (6/8) had a major B cell clone.

These data show that AILD demonstrate a continuous spectrum of polyclonal to clonal TCR gamma and Igh rearrangement, with an overall incidence of restriction of the Igh repertoire (59%) which is much higher than that previously detected by southern blot (20%). A similar spectrum of EBV infection, with EBV clonality correlating with a major Igh clone is in keeping with emergence of a B lymphoproliferation similar to that seen in immunosuppressed individual.

STI-571: BIOLOGY AND THERAPY

Abstract# 2021

A PHASE II STUDY OF STI 571 IN ADULT PATIENTS WITH PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA IN ACCELERATED PHASE. M. Talpaz,¹ R. T. Silver, B. Druker, R. Paquette, J. M. Goldman, S. F. Reese*,² R. Capdeville*, *The International STI571 Study Group.*³ MD Anderson Cancer Center, Houston, TX, USA; ²Novartis Pharma AG, Basel, Switzerland.

The Philadelphia (Ph) chromosome is present in 95% of patients with chronic myeloid leukemia (CML). The molecular consequence of this abnormality is the creation of the constitutively active tyrosine kinase, Bcr-Abl. STI571, an Abl tyrosine kinase inhibitor in clinical development, has shown significant activity with minimal toxicity in CML chronic phase patients who failed interferon therapy. To determine whether these promising results could be extended to CML accelerated phase (CML-AP), 234 patients with CML-AP were recruited for a phase II study at 18 centers in France, Germany, Italy, Switzerland, UK, and USA between August 99 and March 2000. Accelerated phase was defined as the presence of 1 or more of the following: $\geq 15\%$ but $< 30\%$ blasts in peripheral blood or bone marrow, or $\geq 20\%$ blasts plus promyelocytes in peripheral blood or bone marrow, or basophils $\geq 20\%$ in peripheral blood, or thrombocytopenia $< 100 \times 10^9/L$, not related to therapy. STI571 was administered orally, initially at a dose of 400 mg/day (30% of patients) and subsequently at a daily dose of 600 mg (70%), on an outpatient basis. The primary aim of the study is to determine the rate of hematological response. Complete response (CR) is defined as $< 5\%$ blasts in bone marrow with no circulating blasts with recovery of peripheral blood counts. No evidence of leukemia in blood or bone marrow without full peripheral blood recovery or return of chronic phase hematopoiesis are also considered hematological responses. Secondary endpoints include the safety and tolerability of STI571, the duration of hematologic response, overall survival, and cytogenetic response. Preliminary response data as assessed by the investigators is available on 154 patients who have been treated for at least 4 weeks. The overall hematological response rate at 4 weeks is 78%, including 22 patients who achieved a CR. The most frequently reported side effects have been mild to moderate nausea, vomiting, muscle cramps, edema, diarrhea and headache. Grade 3/4 neutropenia and thrombocytopenia according to NCI/CTC Criteria, has been observed in 40% and 18% of patients, respectively. One death due to liver failure occurring within 11 days of initiating trial therapy was suspected to be related with STI571. The patient had been taking acetaminophen chronically, and a possible drug interaction between STI571 and acetaminophen was also suspected. Data collection is ongoing and results with a maximum duration of follow-up of 15 months will be presented.

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