Can we cure adult T cell leukemia/lymphoma?

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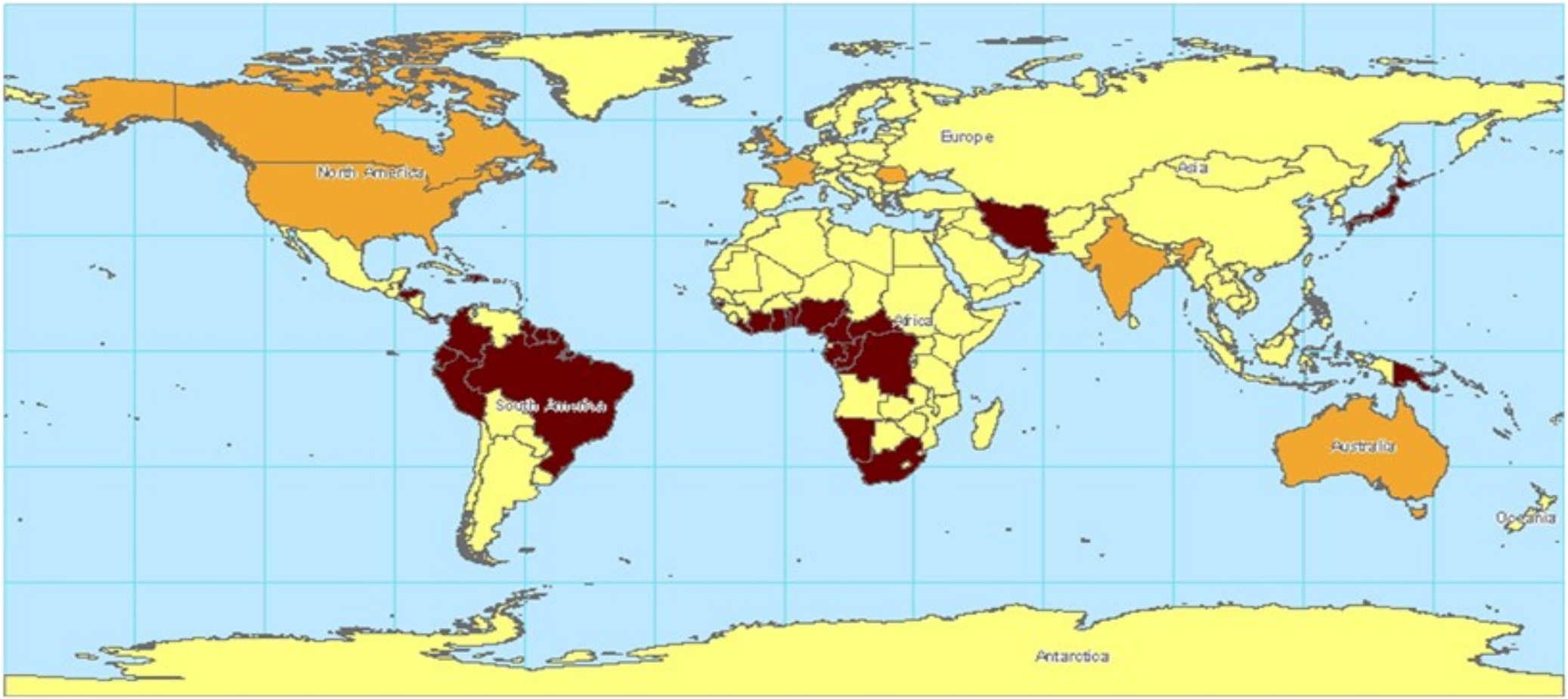
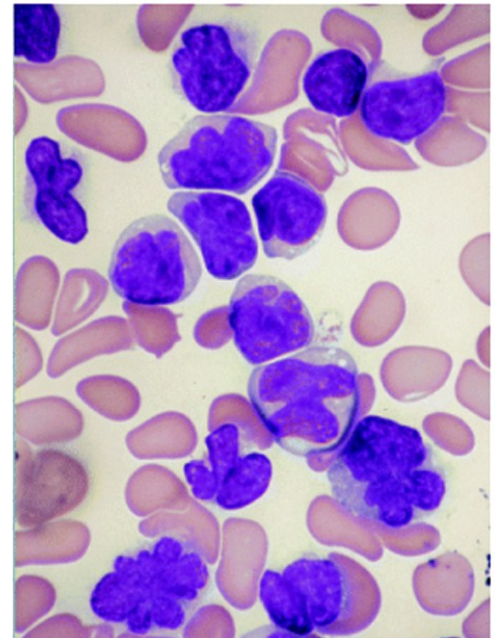
Beirut-Lebanon

HTLV-I infects 15-20 millions individuals worldwide.



Adult T cell leukemia/lymphoma (ATL)

- **Aggressive proliferation of mature activated T cells**
- **Secondary to HTLV-I infection**
- **Poor prognosis due to an intrinsic resistance to chemotherapy and the associated severe immunosuppression**
- **Malignant hypercalcemia**



ATL SURVIVAL DATA

	Smoulder. n=45	Chronic n=152	Lymphoma n=156	Acute n=465
Alive%	77.8	55.9	27.6	19.4
Non Treat %	66.7	28.9	3.2	9.2
Med Surv	N.R.	24.3	10.2	6.2
2 Y. Surv %	77.7	52.4	21.3	16.7
4 Y. Surv %	62.8	26.9	5.7	5.0

Shimoyama et al 1992

Chemotherapy for ATL

Polychemotherapy

- 1st Generation (PR+CR=15-30%)
- VEPA (VCR, CPM, PDN, ADM),
- VEPAM (VEPA+MTX)
- 2d Generation (Sequential chemotherapies) (CR+PR=45%)
- VEPA-B (VEPA + bleo)/M-FEPA (VDS, CPM, PDN, ADM)/VEPP-B (VCR, CPM,Procarbazine, PDN, Bleo)
- RCM + Growth Factors
- CDE (continuous infusions)
- LSG15 (Yamamda et al , 2001) (in acute ATL: CR<20%, median 10.5 m, renal failure excluded)

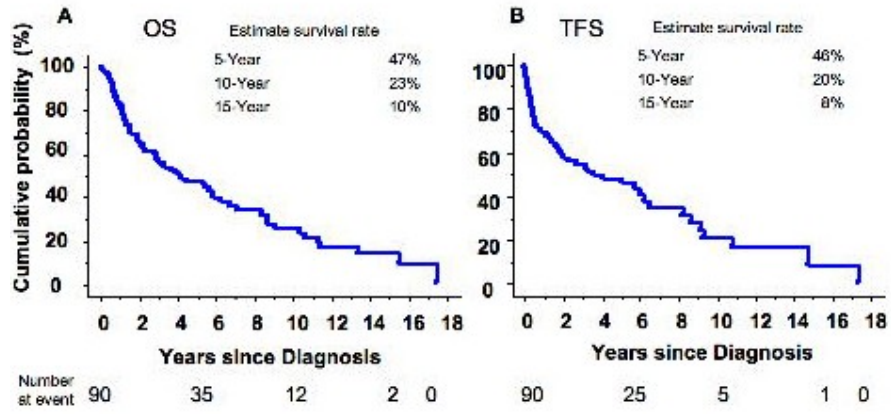
→ 4 years Survival < 10%

Long-term study of indolent adult T-cell leukemia-lymphoma (ATL)

Yumi Takasaki,[1,2] Masako Iwanaga,[2] Yoshitaka Imaizumi,[2] Masayuki Tawara,[1,2] Tatsuro Joh,[1,2] Tomoko Kohno,[4] Yasuaki Yamada,[3] Shimeru Kamihira,[3] Schuichi Ikeda,[5] Masao Tomonaga,[1] and Kunihiro Tsukasaki[2]

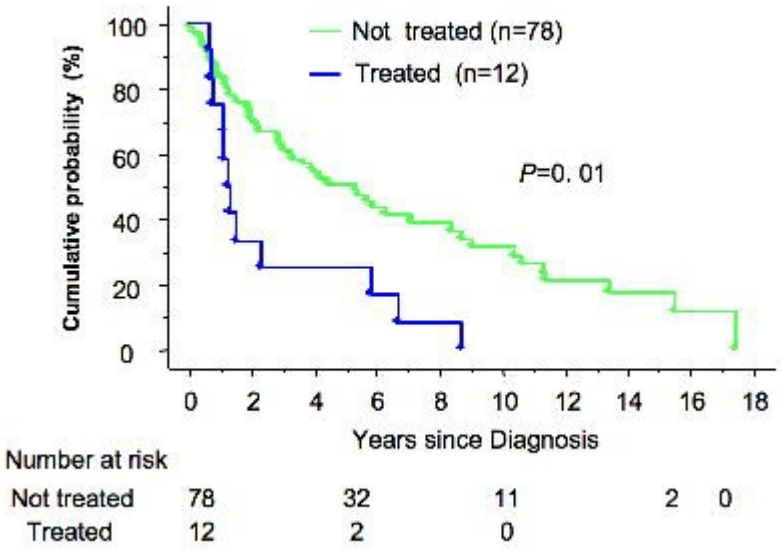
Table 1. Distribution of patients in three decades from 1974 to 2003.

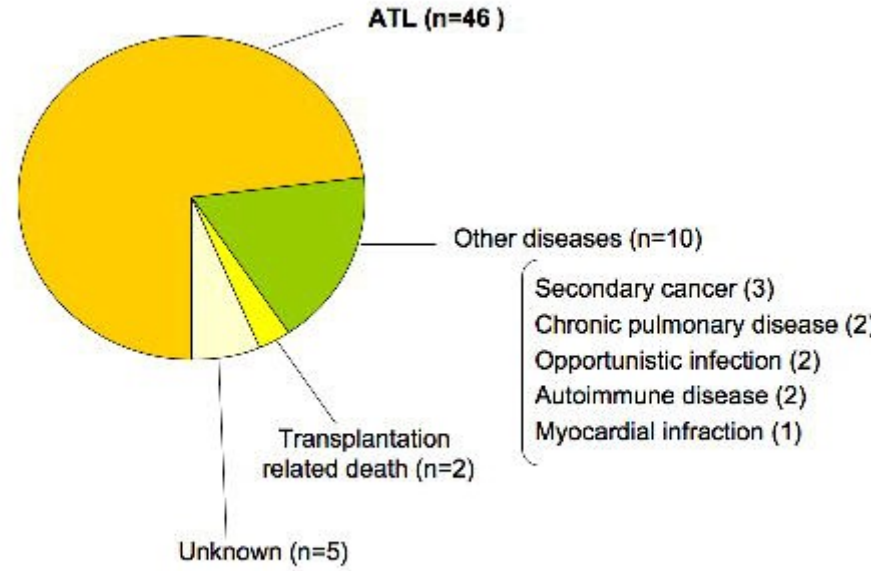
Year	Total	Smoldering type no, (% of Total)	Chronic type no, (% of Total)
1974–1983	19	2 (10.5)	17 (89.5)
1984–1993	35	7 (20.0)	28 (80.0)
1994–2003	36	16 (44.4)	20 (55.6)
All years	90	25 (27.8)	65 (72.2)



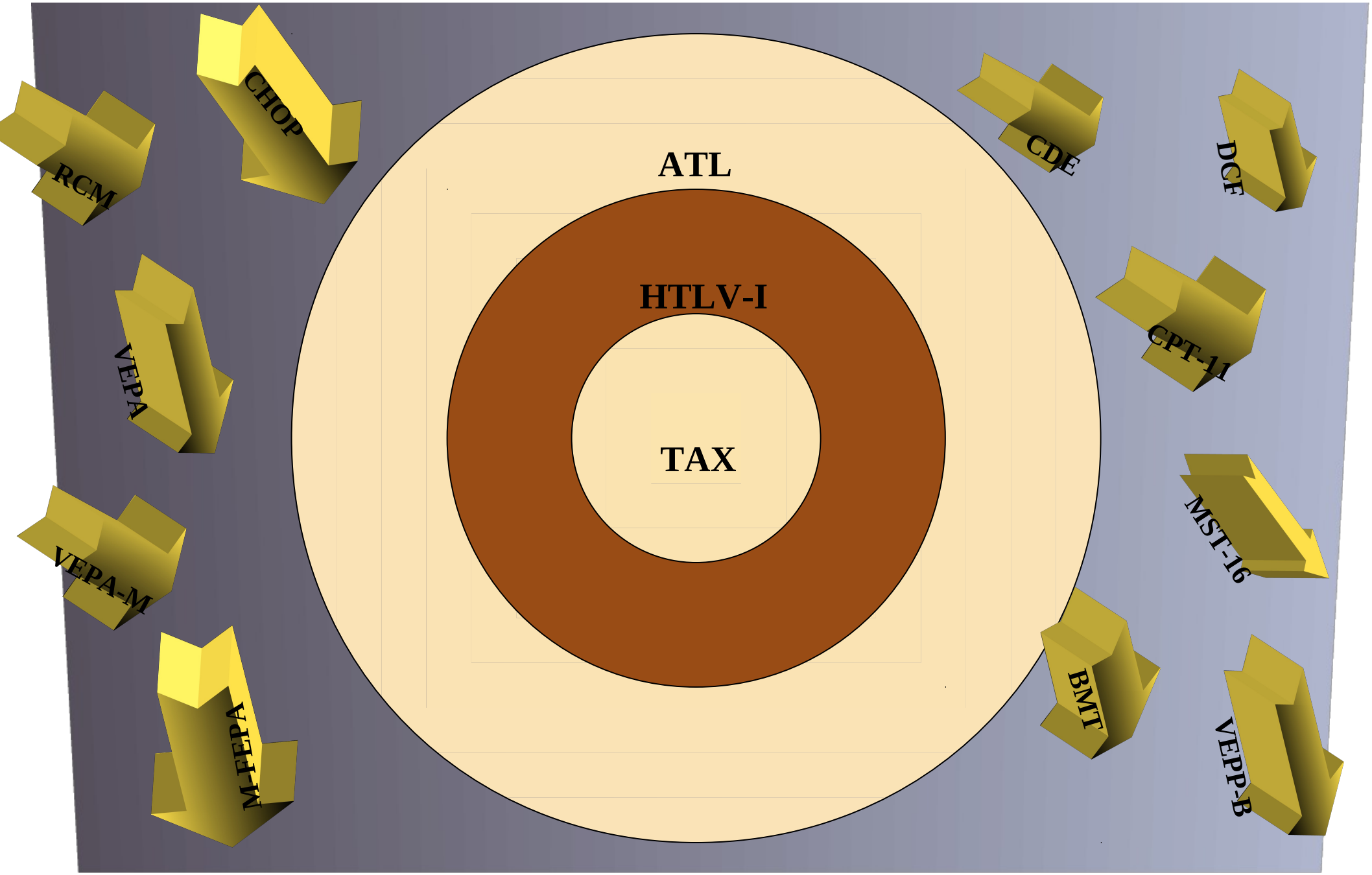
Takasaki Blood 2010

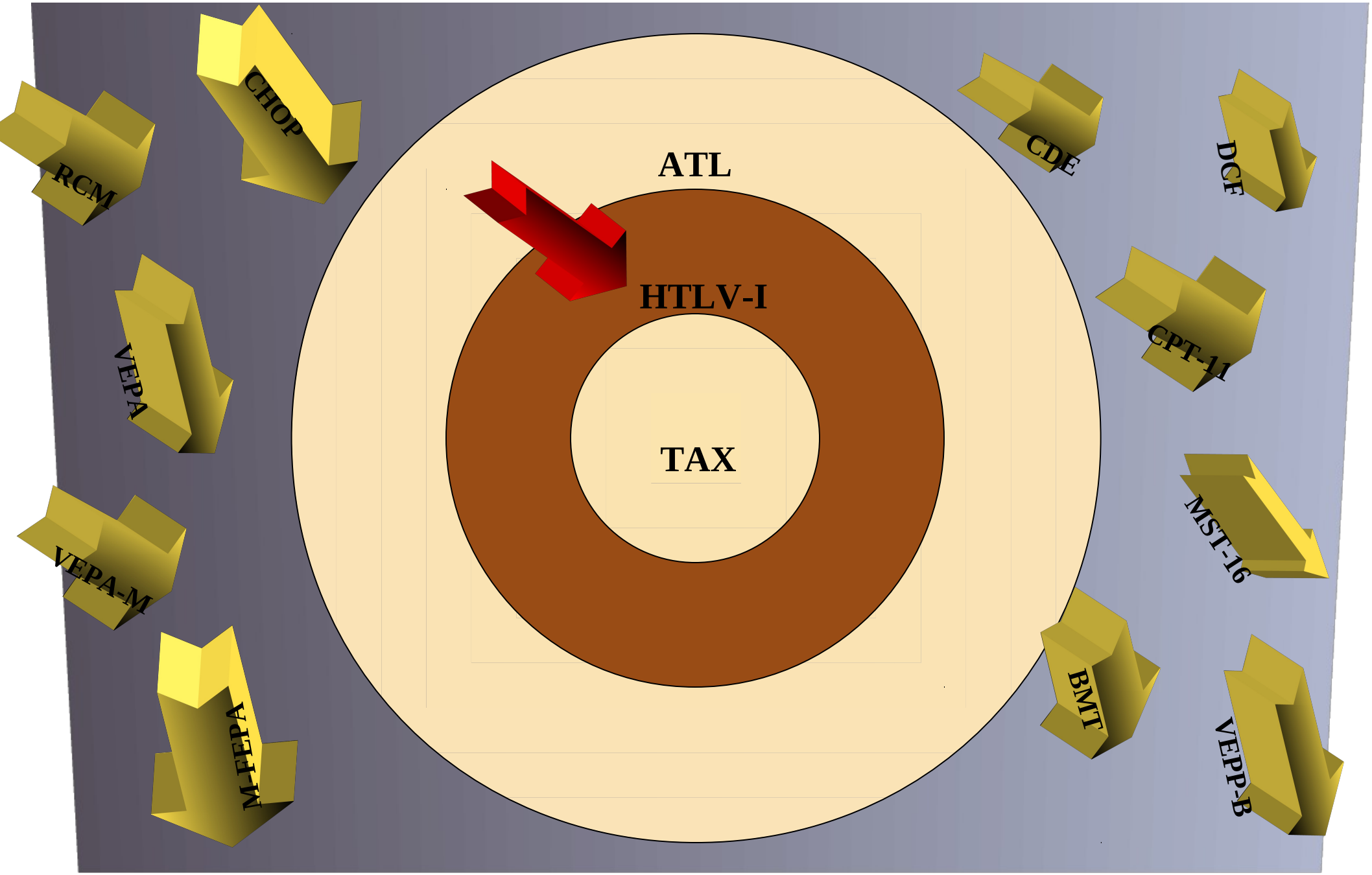
Smoldering/chronic ATL





Takasaki Blood 2010


ATL
HTLV-I
TAX
CHOP
RCM
VEPA
VEPA-M
M-IEPA
CDE
DCF
CPT-11
MST-16
BMT
VEPP-B


ATL
HTLV-I
TAX
CHOP
RCM
VEPA
VEPA-M
M-LEPA
CDE
DCF
CPT-11
MST-16
BMT
VEPP-B

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Adult T-Cell Leukemia–Lymphoma with a Combination of Interferon Alfa and Zidovudine

Parkash S. Gill, M.D., William Harrington, Jr., M.D., Mark H. Kaplan, M.D., Raul C. Ribeiro, M.D., John M. Bennett, M.D., Howard A. Liebman, M.D., Marjorie Bernstein-Singer, M.D., Byron M. Espina, A.B., Lisa Cabral, R.N., Steven Allen, M.D., Steven Kornblau, M.D., Malcolm C. Pike, Ph.D., and Alexandra M. Levine, M.D.

N Engl J Med 1995; 332:1744-1748 | June 29, 1995

ORIGINAL ARTICLE

Brief Report

Treatment of Adult T-Cell Leukemia-Lymphoma with Zidovudine and Interferon Alfa

Olivier Hermine, Didier Bouscary, Antoine Gessain, Pascal Turlure, Veronique Leblond, Nathalie Franck, Agnes Buzyn-Veil, Bernard Rio, Elisabeth Macintyre, Francois Dreyfus, and Ali Bazarbachi

N Engl J Med 1995; 332:1749-1751 | June 29, 1995

VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

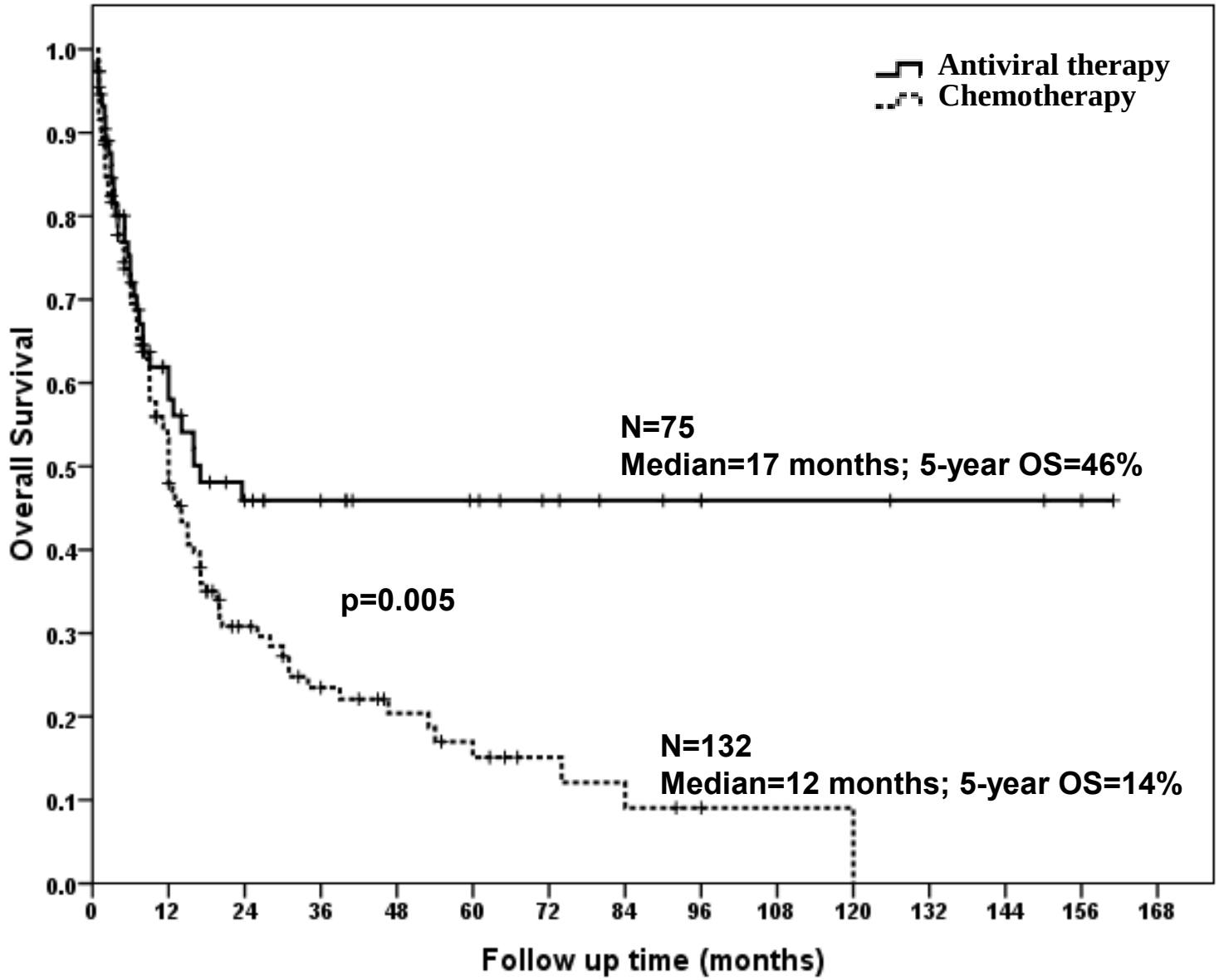
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Meta-Analysis on the Use of Zidovudine and Interferon-Alfa in Adult T-Cell Leukemia/Lymphoma Showing Improved Survival in the Leukemic Subtypes

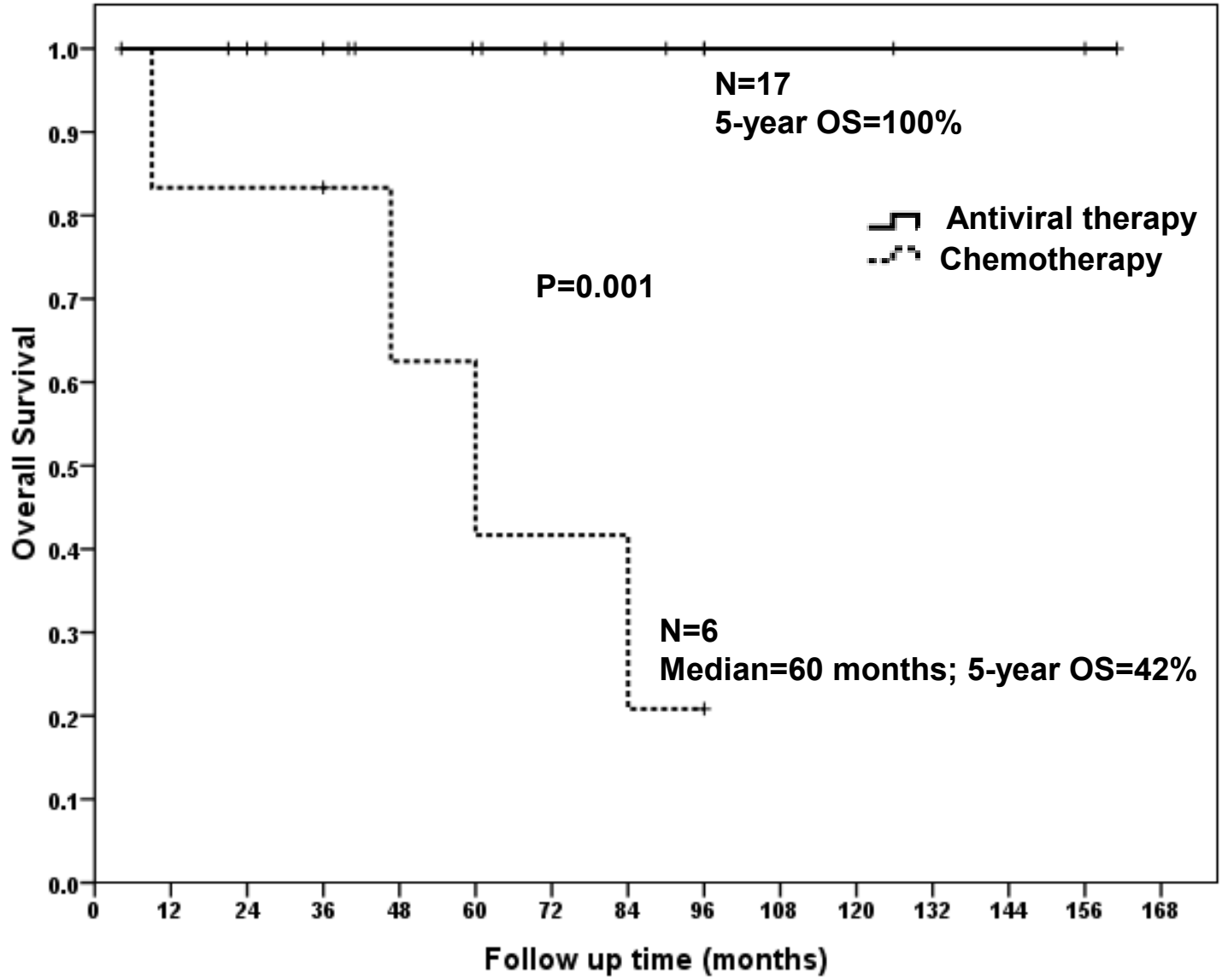
Ali Bazarbachi, Yves Plumelle, Juan Carlos Ramos, Patricia Tortevoye, Zaher Otrock, Graham Taylor, Antoine Gessain, William Harrington,† Gérard Panelatti, and Olivier Hermine

Effect of first line antiviral therapy: all patients



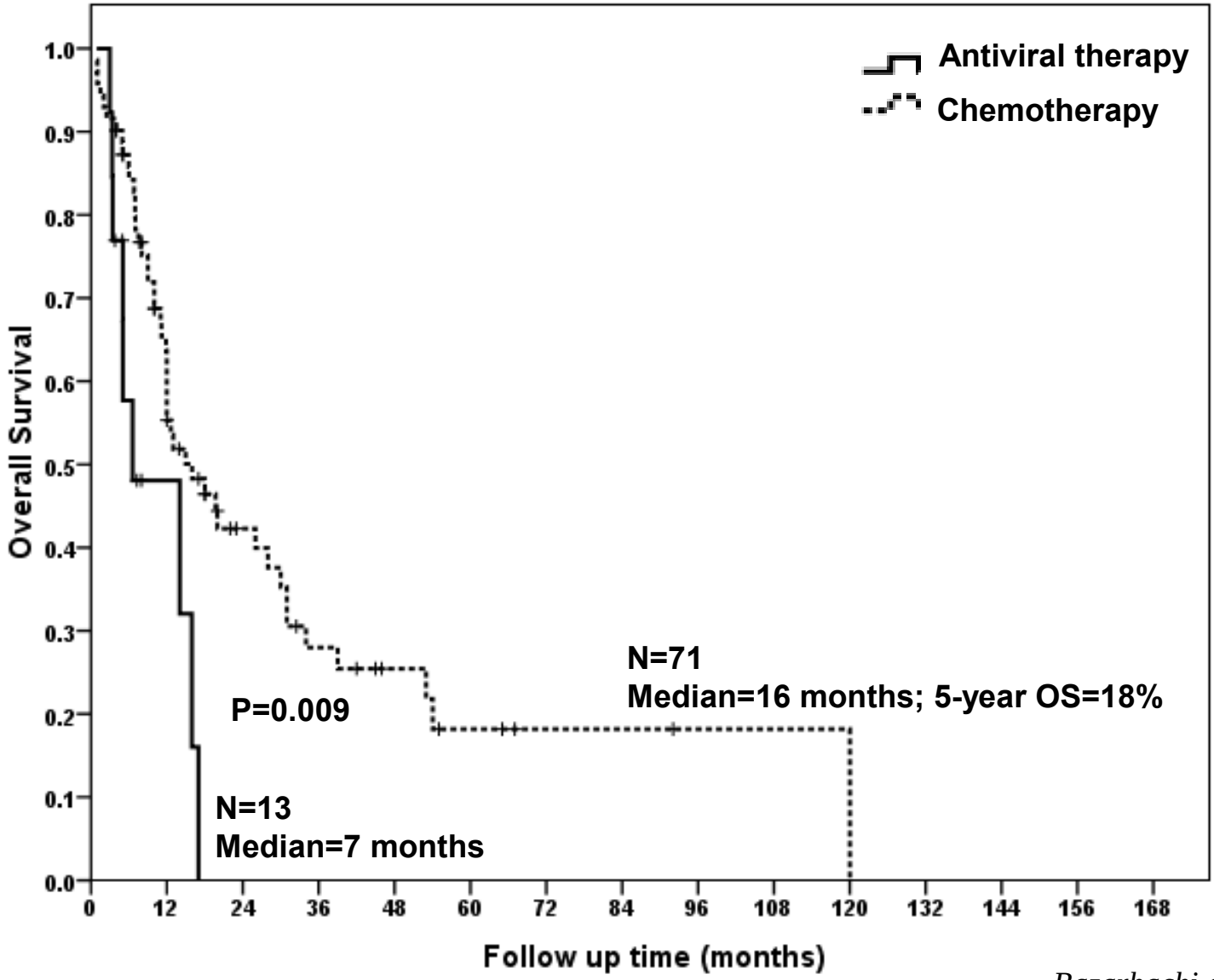
Bazarbachi et al. J. Clin. Oncol. 2010

First line antiviral therapy resulted in 100% long term survival in chronic/smouldering ATL



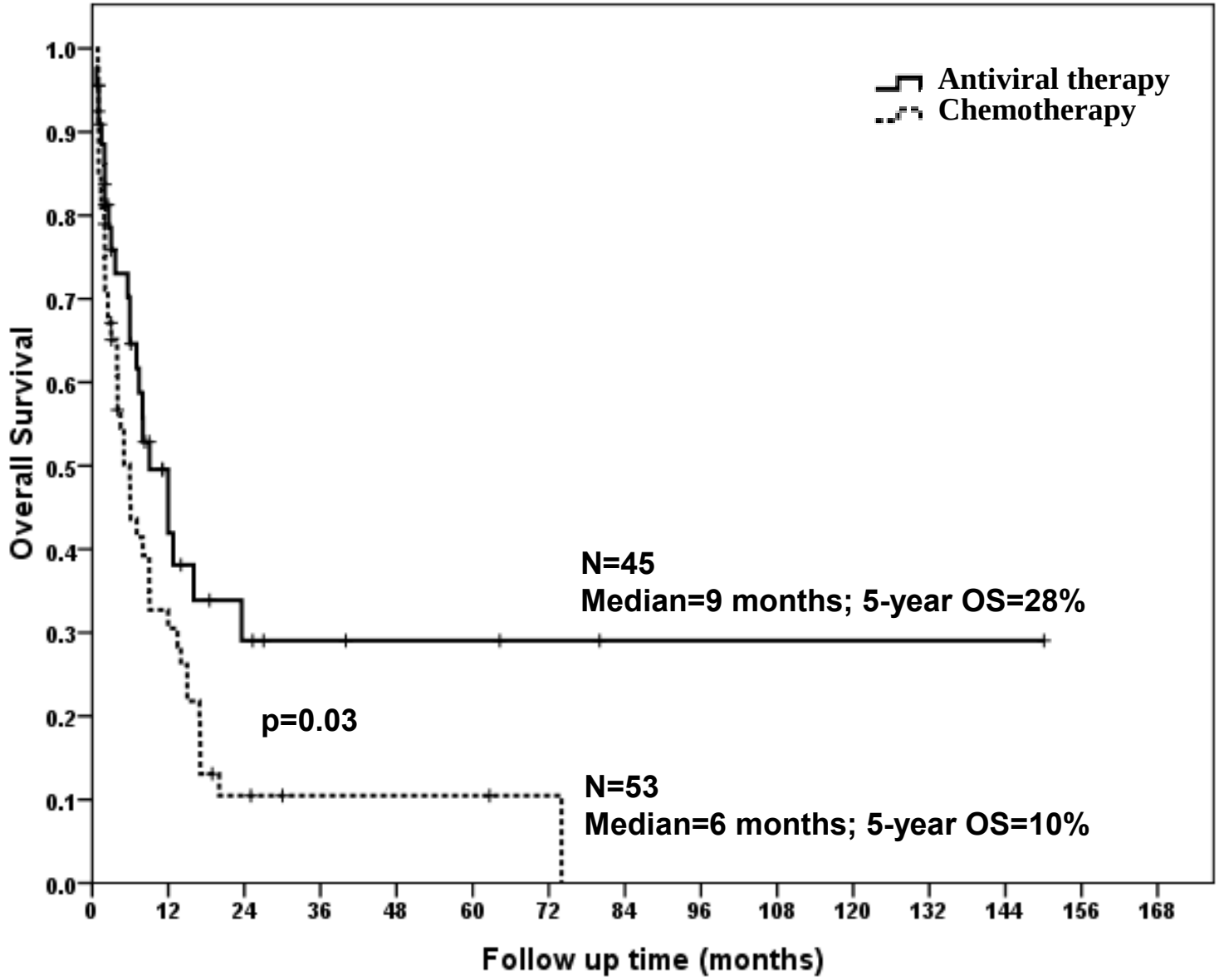
Bazarbachi et al. J. Clin. Oncol. 2010

First line antiviral therapy has no effect in ATL lymphoma



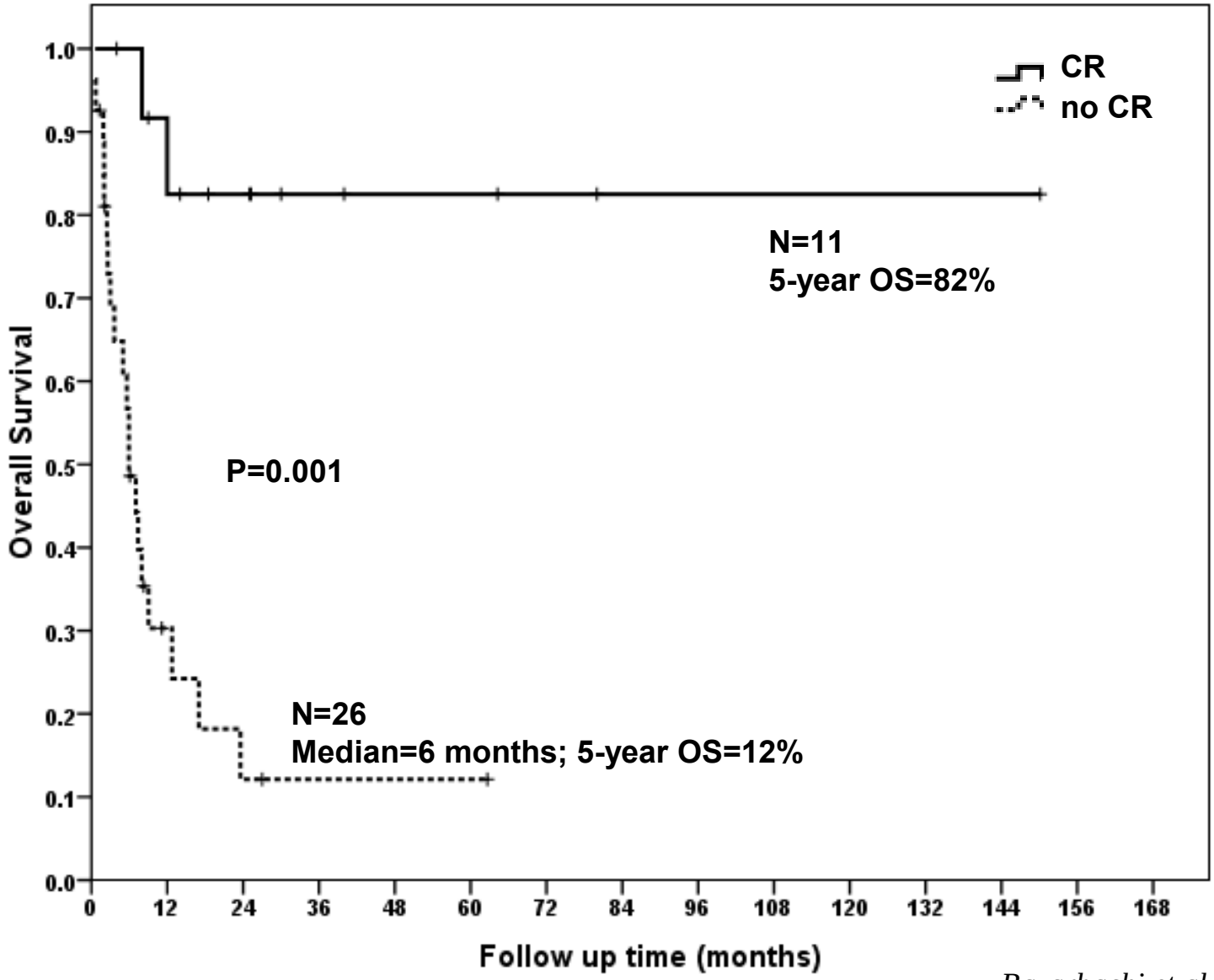
Bazarbachi et al. J. Clin. Oncol. 2010

Antiviral therapy improves OS in acute ATL



Bazarbachi et al. J. Clin. Oncol. 2010

Achievement of complete remission on first line antiviral therapy is critical for long term survival in patients with acute ATL



Bazarbachi et al. J. Clin. Oncol. 2010

	Univariate analysis			Multivariate analysis		
Variables	**P Value**	**Unadjusted Hazard Ratio**	**95% CI**	**P value**	**Adjusted Hazard Ratio**	**95% CI**
Sex Male (female)	0.736	1.06	(0.75, 1.50)			
Age (>50 y.o) <50 y.o.	0.591	0.90	(0.63, 1.30)			
ATL subtype (chronic/smouldering) Acute Lymphoma	 <0.001 <0.001	 13.6 8.30	 (4.89, 7.87) (2.97, 23.2)	 <0.001 0.001	 14.70 7.60	 (4.47, 48.36) (2.27, 25.46)
Lymphadenopathy (No) Yes	0.173	1.40	(0.86, 2.26)			
Hepatomegaly (No) Yes	0.008	1.67	(1.14, 2.44)			
Splenomegaly (No) Yes	0.040	1.50	(1.02, 2.22)			
Skin involvement (No) Yes	0.344	0.81	(0.53, 1.24)			
Serum LDH level (<2) >2N	<0.001	2.09	(1.43, 3.07)			
Hypercalcemia (No) Yes	<0.001	1.95	(1.36, 2.79)	0.183	1.28	(0.89, 1.85)
First line therapy (Chemotherapy alone) Antiviral alone Chemotherapy then antiviral	 0.004 0.370	 0.52 0.83	 (0.34, 0.81) (0.55, 1.25)	 0.021 0.083	 0.55 0.68	 (0.33, 0.91) (0.44, 1.05)

Bazarbachi et al. J. Clin. Oncol. 2010

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Bazarbachi et al. J. Clin. Oncol. 2010

When AZT/IFN does not work?

- After chemotherapy; relapsed/refractory
- Suboptimal doses of AZT and/or IFN are used
- Rapid dose reduction/discontinuation because of side effects or hematological toxicity
- ATL lymphoma or bulky disease (chemotherapy should be added)
- Intrinsic resistance (p53 mutation; IRF overexpression)

Proposed mechanism of action

- Evidence against a direct cytotoxic effect

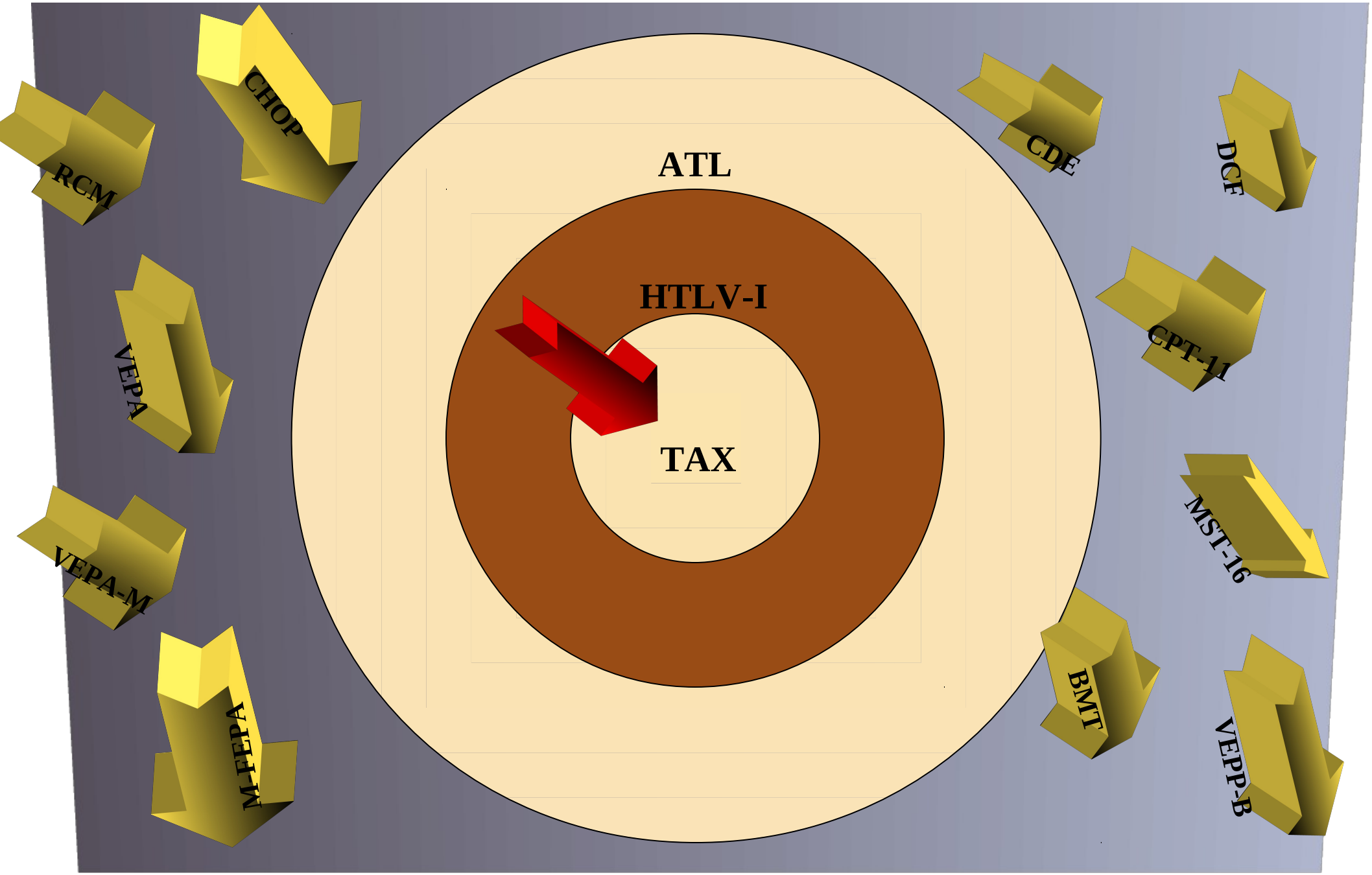
- p53 dependent inhibition of telomerase

- Direct antiviral effect (AZT on RT and IFN on virus assembly) but on which targets?

→ No HTLV-I replication in ATL cells

→ Inhibition of de novo infection of CD4 and dendritic cells (in vivo micro-environment: support for ATL cells)

→ Inhibition of de novo infection of CD8 cells (immuno-modulatory effect)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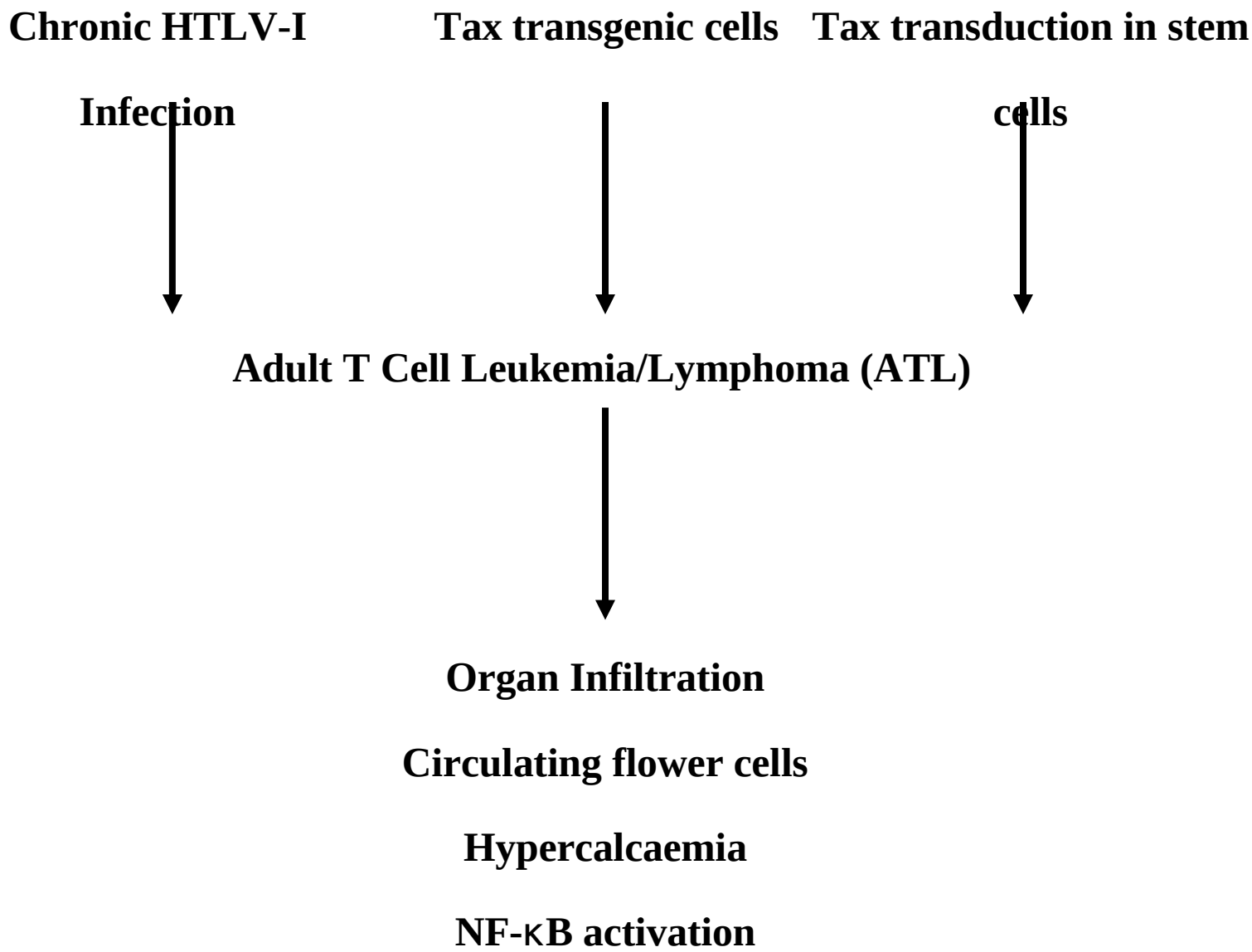

Chronic HTLV-I Infection
Tax transgenic cells
Tax transduction in stem cells
Adult T Cell Leukemia/Lymphoma (ATL)
Organ Infiltration
Circulating flower cells
Hypercalcaemia
NF-κB activation

Arsenic/interferon specifically reverses 2 distinct gene networks critical for the survival of HTLV-1–infected leukemic cells

Rihab Nasr, Andreas Rosenwald, Marwan E. El-Sabban, Bertrand Arnulf, Pierre Zalloua, Yves Lepelletier, Françoise Bex, Olivier Hermine, Louis Staudt, Hugues de Thé, and Ali Bazarbachi

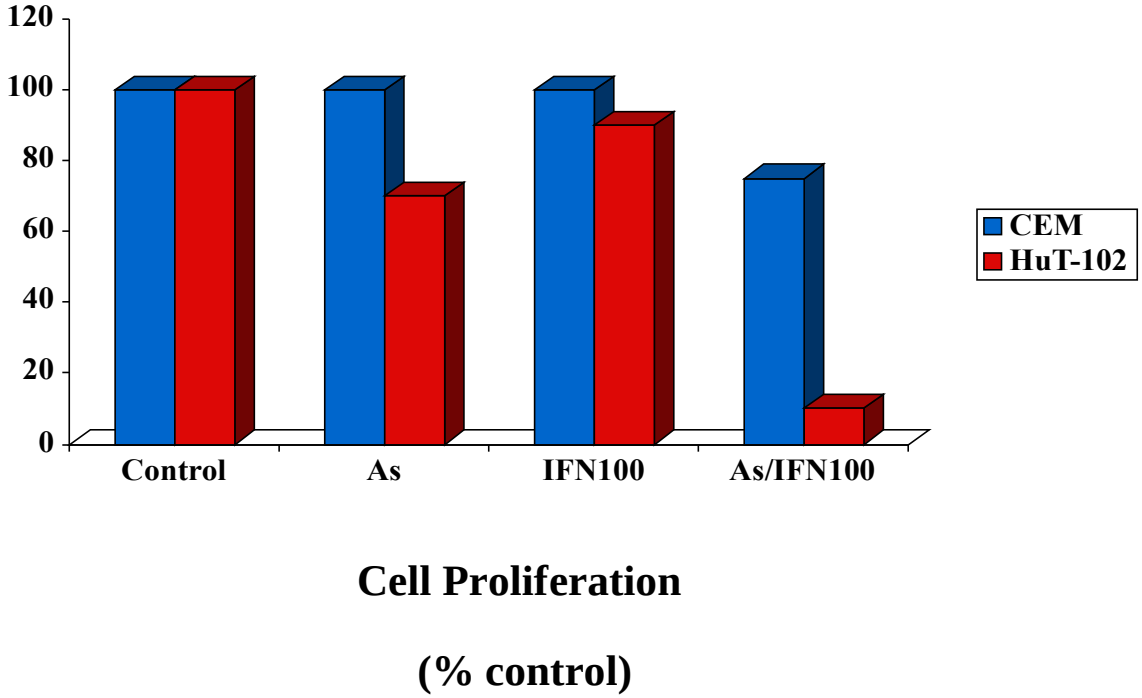
Arsenic-interferon-α–triggered apoptosis in HTLV-I transformed cells is associated with Tax down-regulation and reversal of NF-κB activation

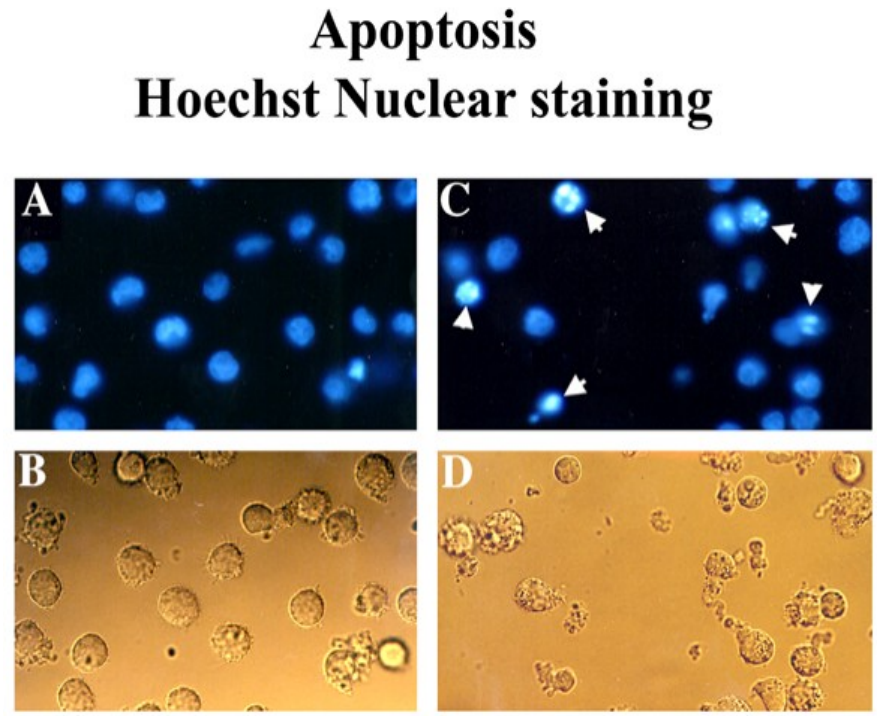
Marwan E. El-Sabban, Rihab Nasr, Ghassan Dbaibo, Olivier Hermine, Nour Abboushi, Frédérique Quignon, Jean Claude Ameisen, Françoise Bex, Hugues de Thé, and Ali Bazarbachi

Arsenic Trioxide and Interferon-alpha Synergize to Induce Cell Cycle Arrest and Apoptosis in Human T-Cell Lymphotropic Virus Type I-Transformed Cells

Ali Bazarbachi, Marwan E. El-Sabban, Rihab Nasr, Frédérique Quignon, Christian Awaraji, Joelle Kersual, Laurent Dianoux, Yael Zermati, Joud H. Haidar, Olivier Hermine and Hughes de Thé

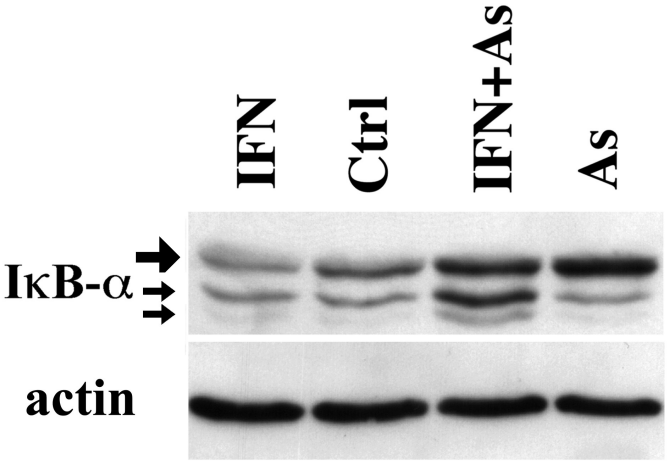
Synergistic effect of arsenic trioxide and interferon alpha on cell growth and apoptosis of HTLV-I transformed cells



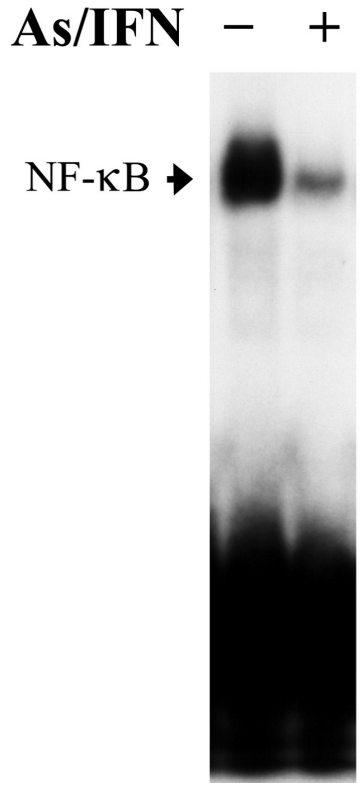


Bazarbachi et al. Blood 1999

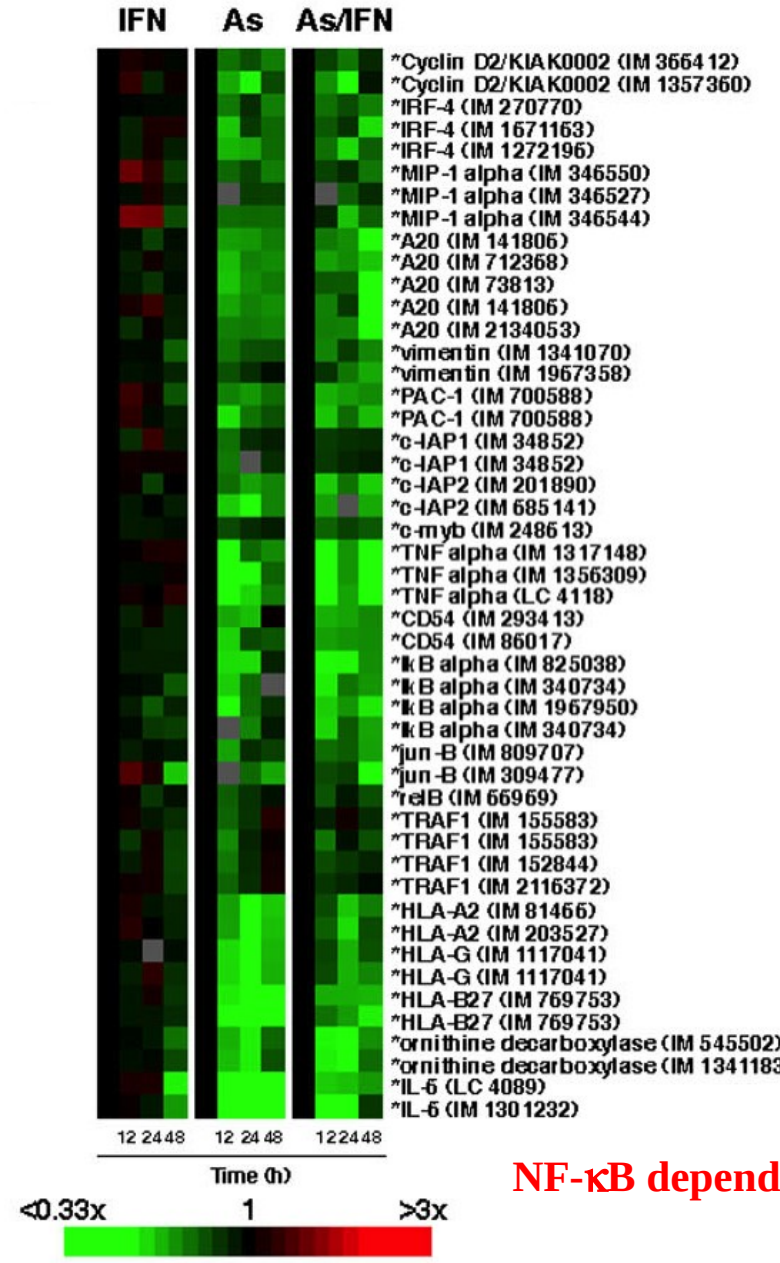
Arsenic/IFN reverse NF-κB activation



Western blot



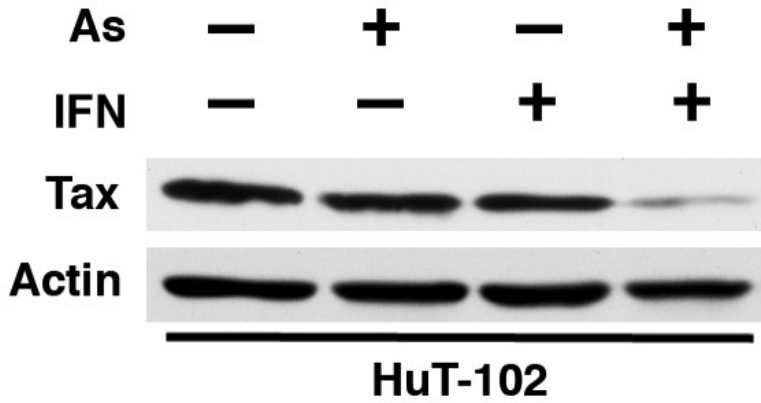
Gel shift

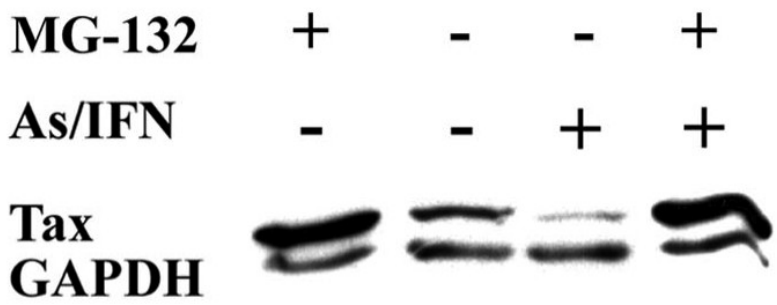


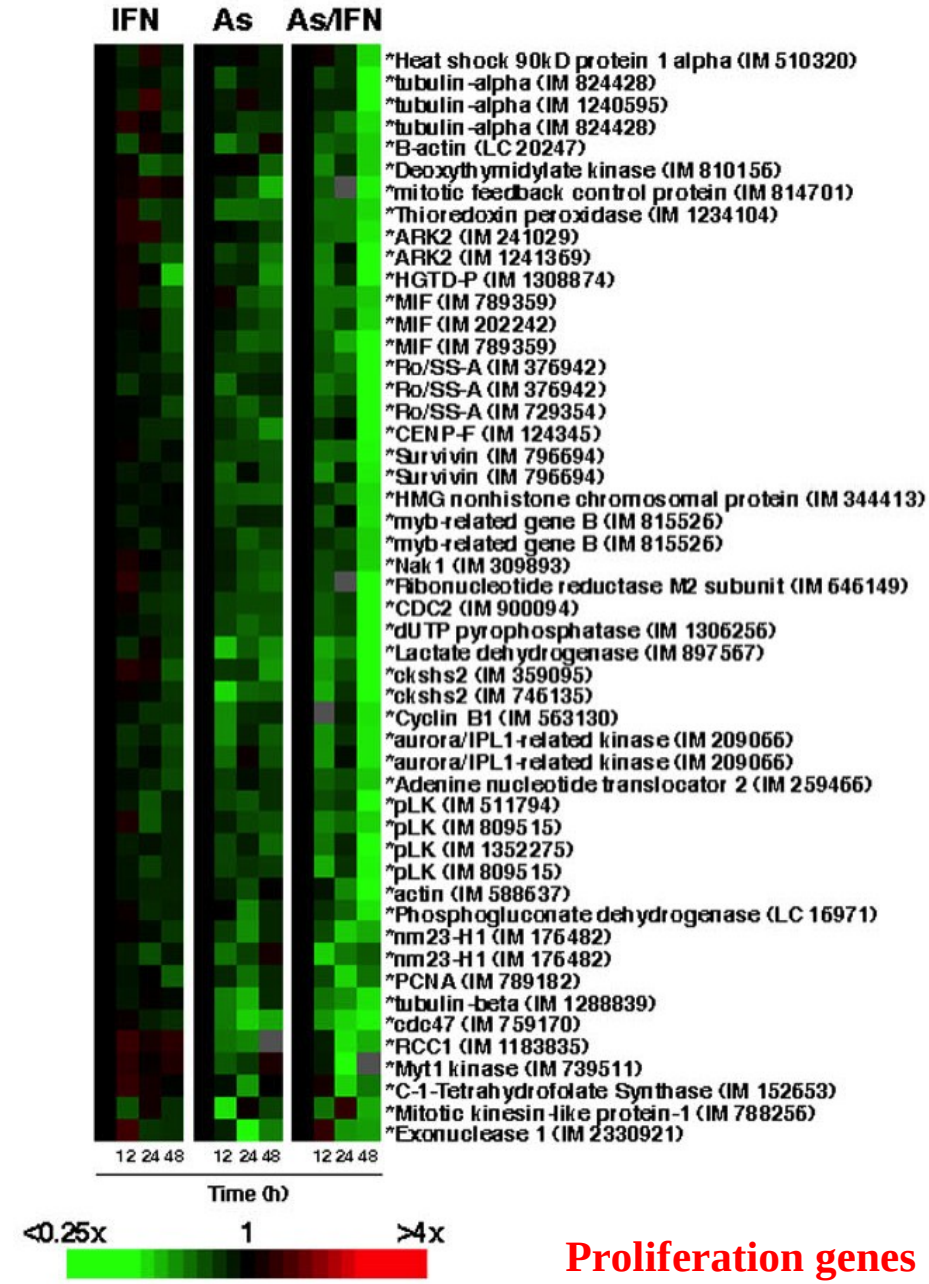
NF-κB dependent genes

El-Sabban et al. Blood 2000; Nasr et al. Blood 2003

Arsenic/IFN induce Tax degradation by the proteasome

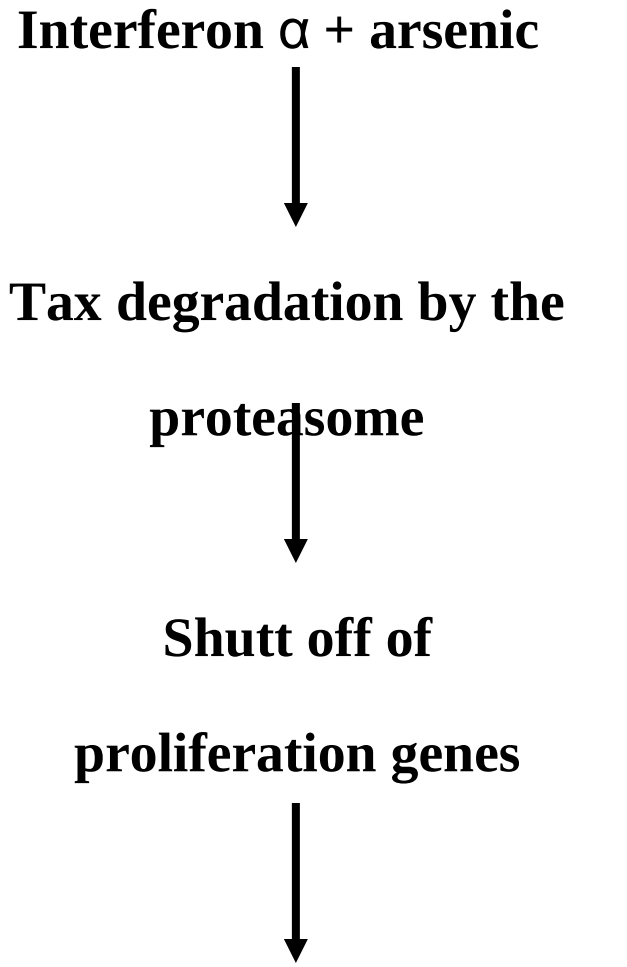




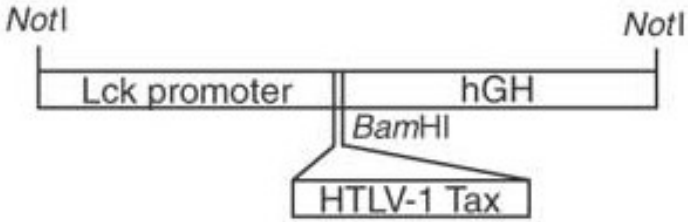


Proliferation genes

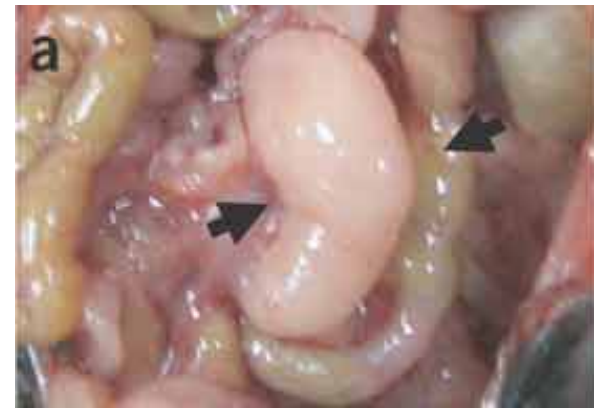
El-Sabban et al. Blood 2000; Nasr et al. Blood 2003


Interferon α + arsenic
Tax degradation by the proteasome
Shutt off of proliferation genes
Cell cycle arrest and apoptosis

Animal Model: Tax transgenics develop murine ATL



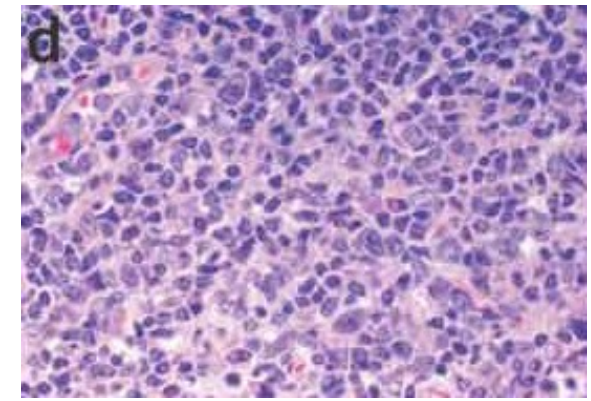
Transgenic mice were generated expressing Tax under the control of the LcK proximal promoter, which restricts expression to developing thymocytes



Mesenteric Tumor

Marked splenomegaly

Normal mouse



Bone Marrow

Hasegawa et al., Nature Medecine 2006

Murine ATL: transplantation model into SCID mice

Tax transgenic mice

↓ **18 months**

ATL like disease

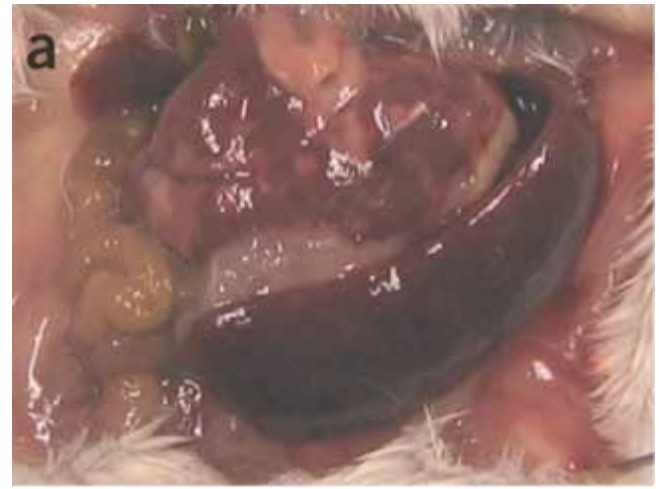
↓

Malignant lymphoma cells injected in

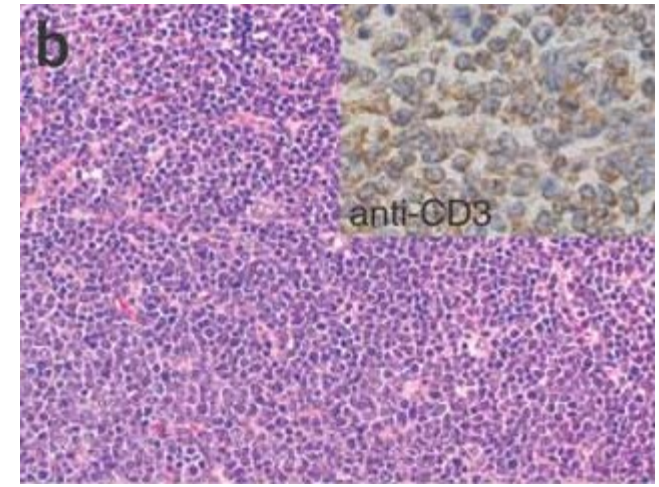
SCID mice

↓ **4 weeks**

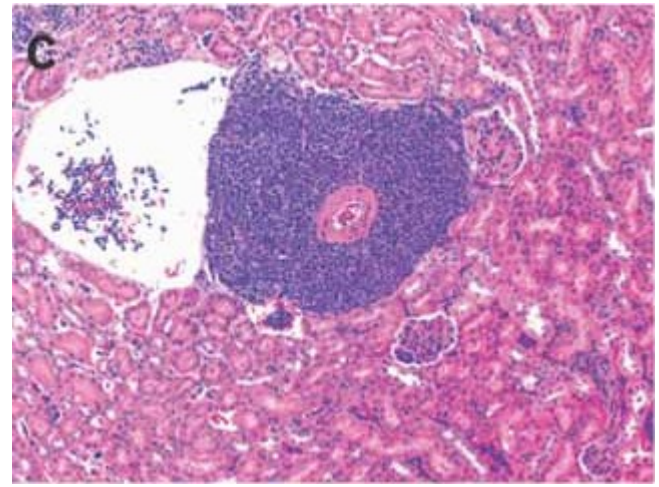
ATL like disease



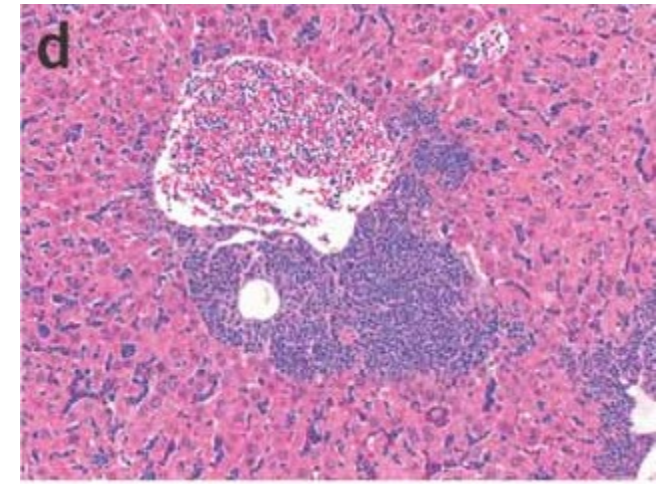
Gross Splenomegaly



CD3 positive staining



Liver



Kidney

Hasegawa et al., Nature Medecine 2006

Published December 6, 2010

JEM

Brief Definitive Report

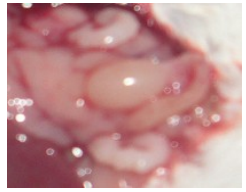
Therapy-induced selective loss of leukemia-initiating activity in murine adult T cell leukemia

Hiba El Hajj,[1] Marwan El-Sabban,[2] Hideki Hasegawa,[4,5] Ghazi Zaatari,[3] Julien Ablain,[6] Shahrazad T. Saab,[3] Anne Janin,[7] Rami Mahfouz,[3] Rihab Nasr,[1] Youmna Kfoury,[1] Christophe Nicot,[8,9,10] Olivier Hermine,[11] William Hall,[5] Hugues de Thé,[6] and Ali Bazarbachi[1]

Low level of Tax expression in murine and human ATL

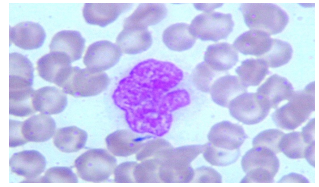
Normal mouse

Marked splenomegaly

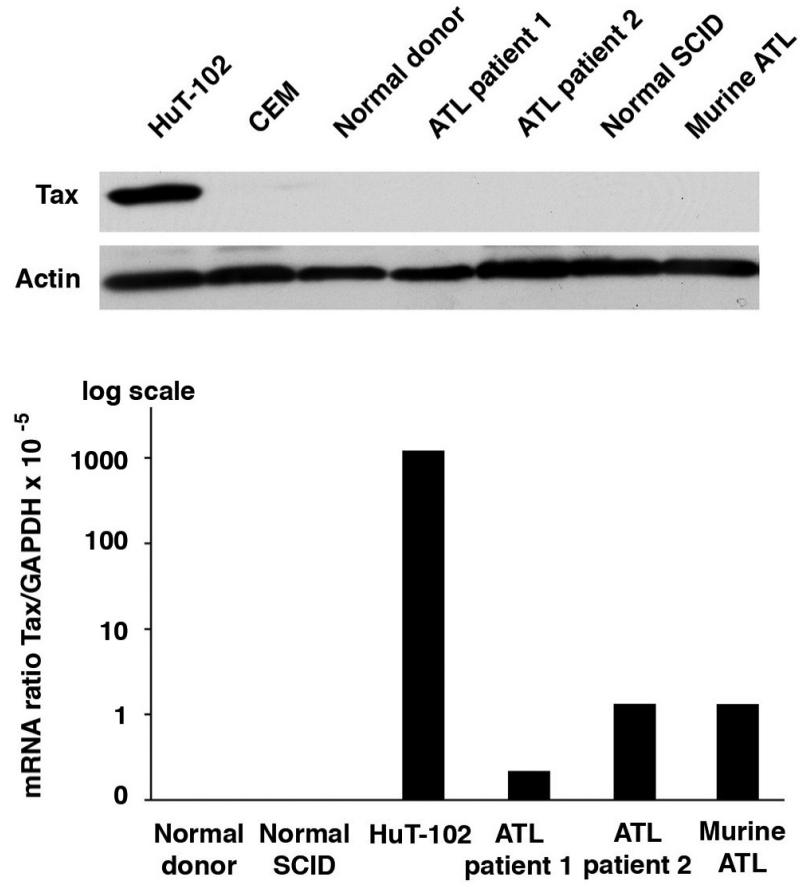


Mesenteric

Tumor

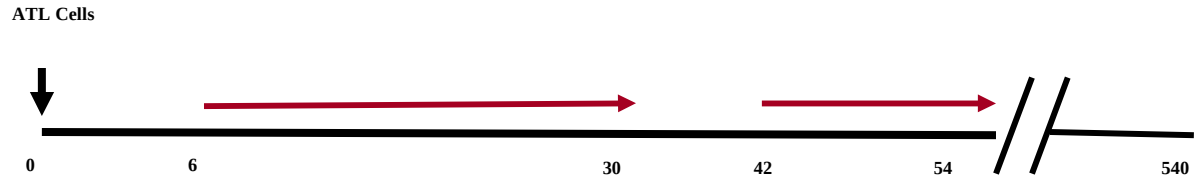


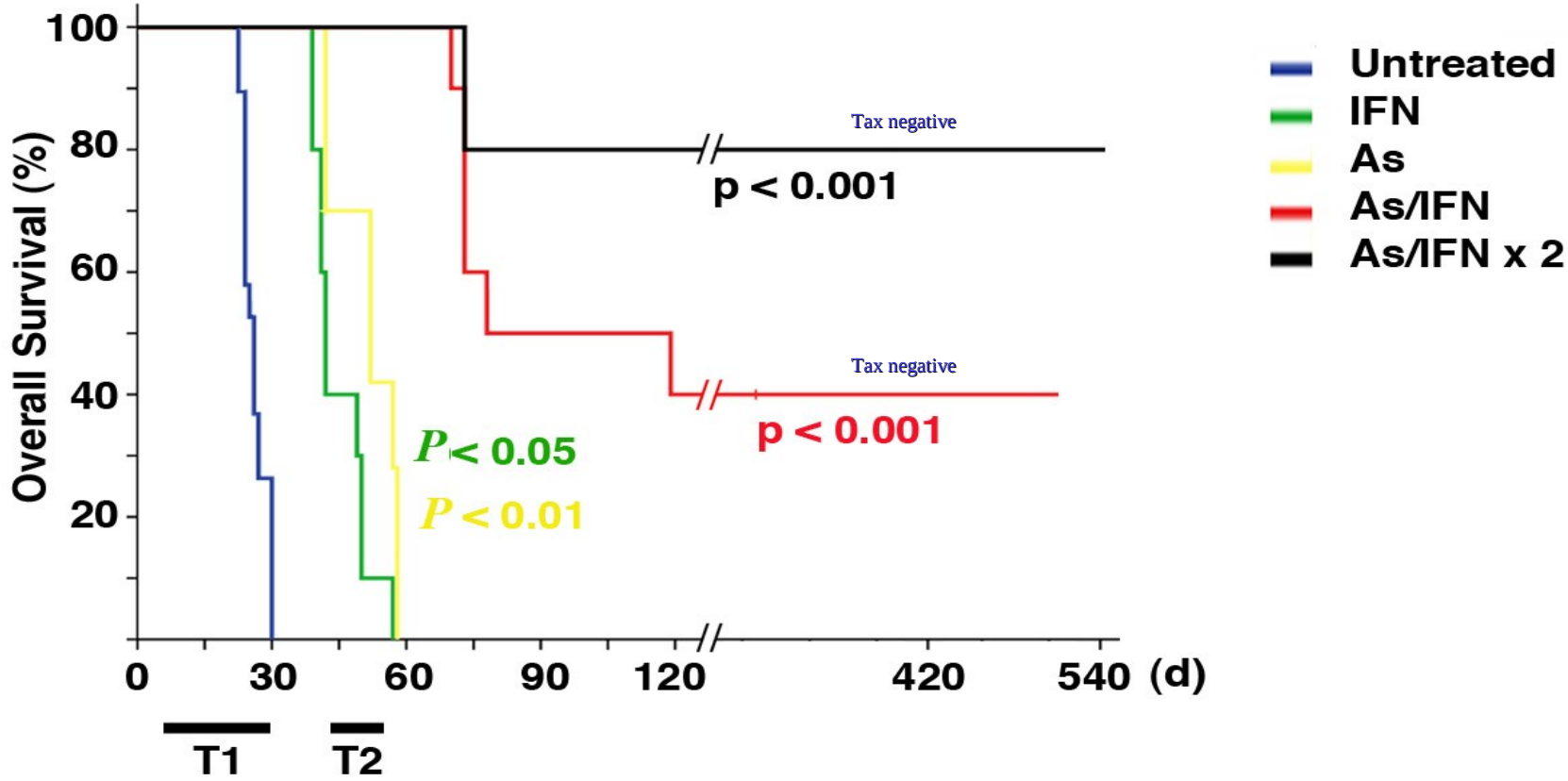
Flower cells



El Hajj et al. J Exp. Med. 2010; 207:2785-92

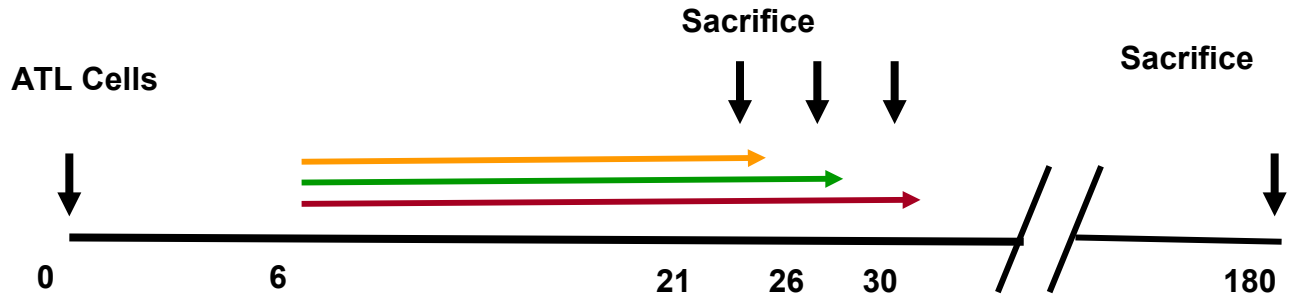
Arsenic/IFN cure murine ATL

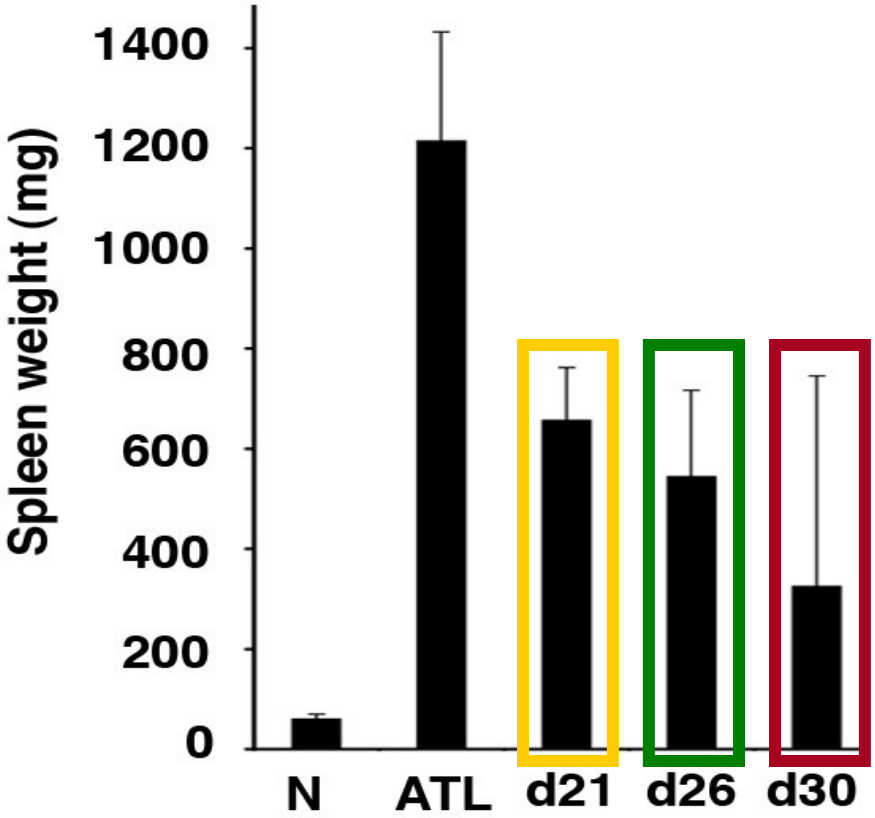


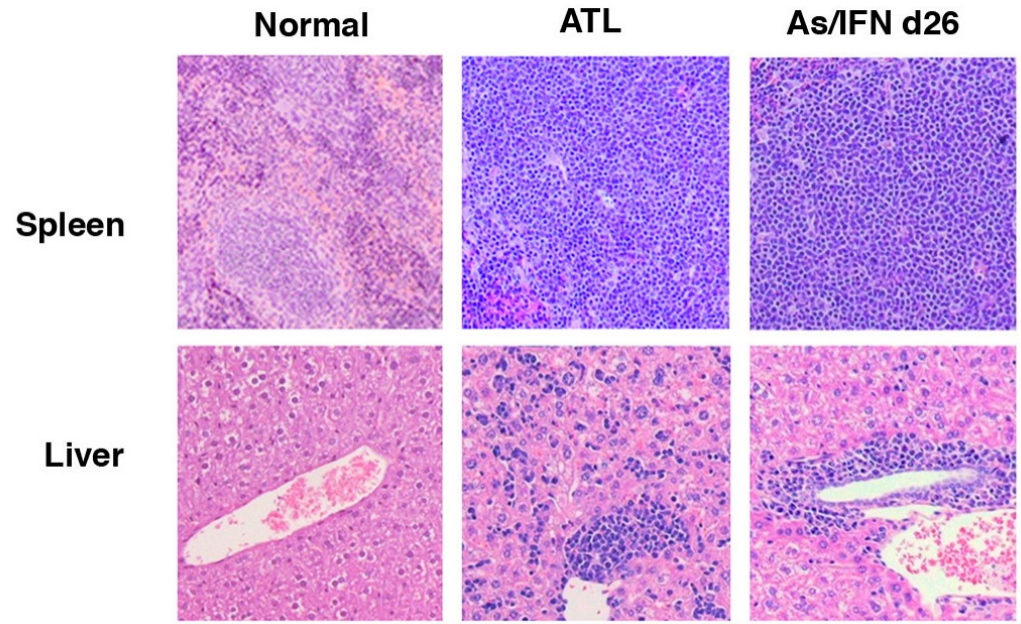


El Hajj et al. J Exp. Med. 2010; 207:2785-92

Arsenic/IFN modestly affects spleen weight

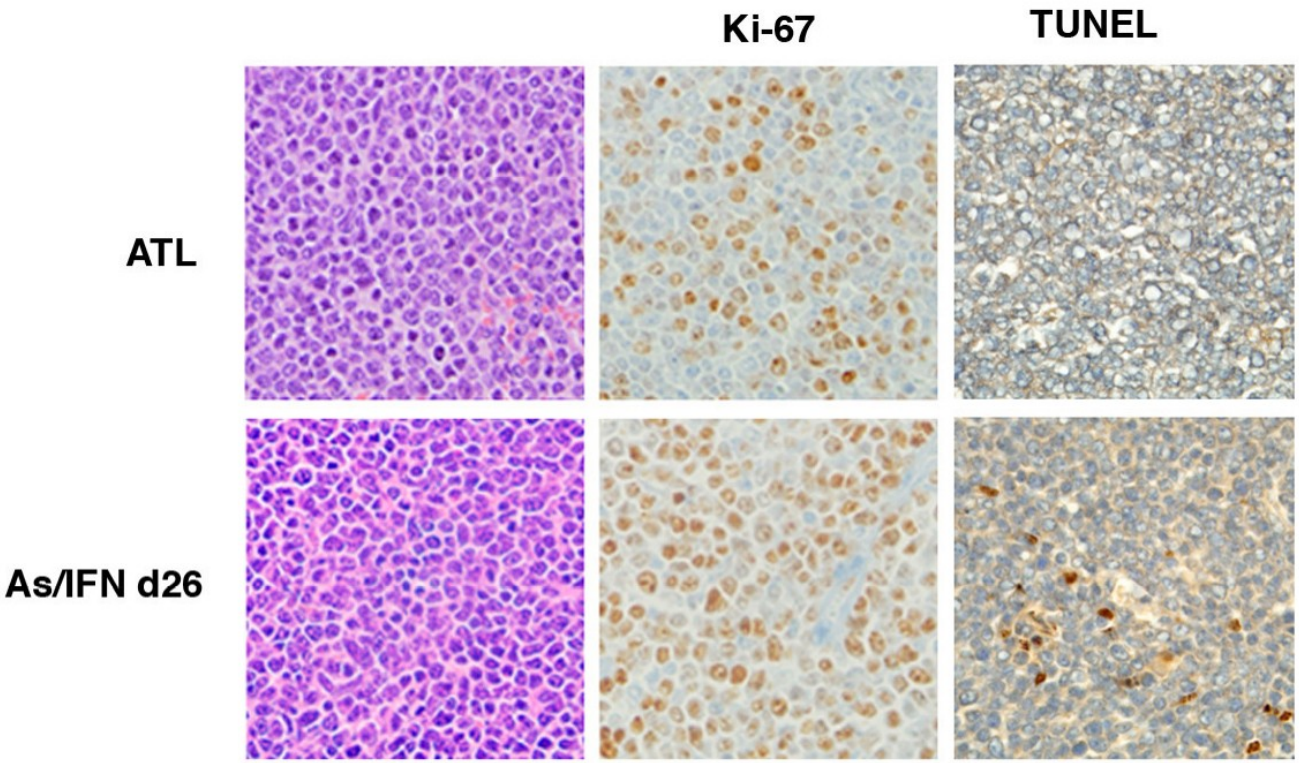


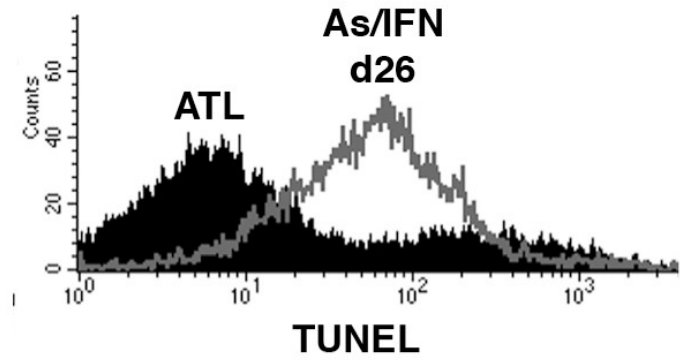




El Hajj et al. J Exp. Med. 2010; 207:2785-92

Arsenic/IFN modestly decreases mitotic activity and induces delayed apoptosis

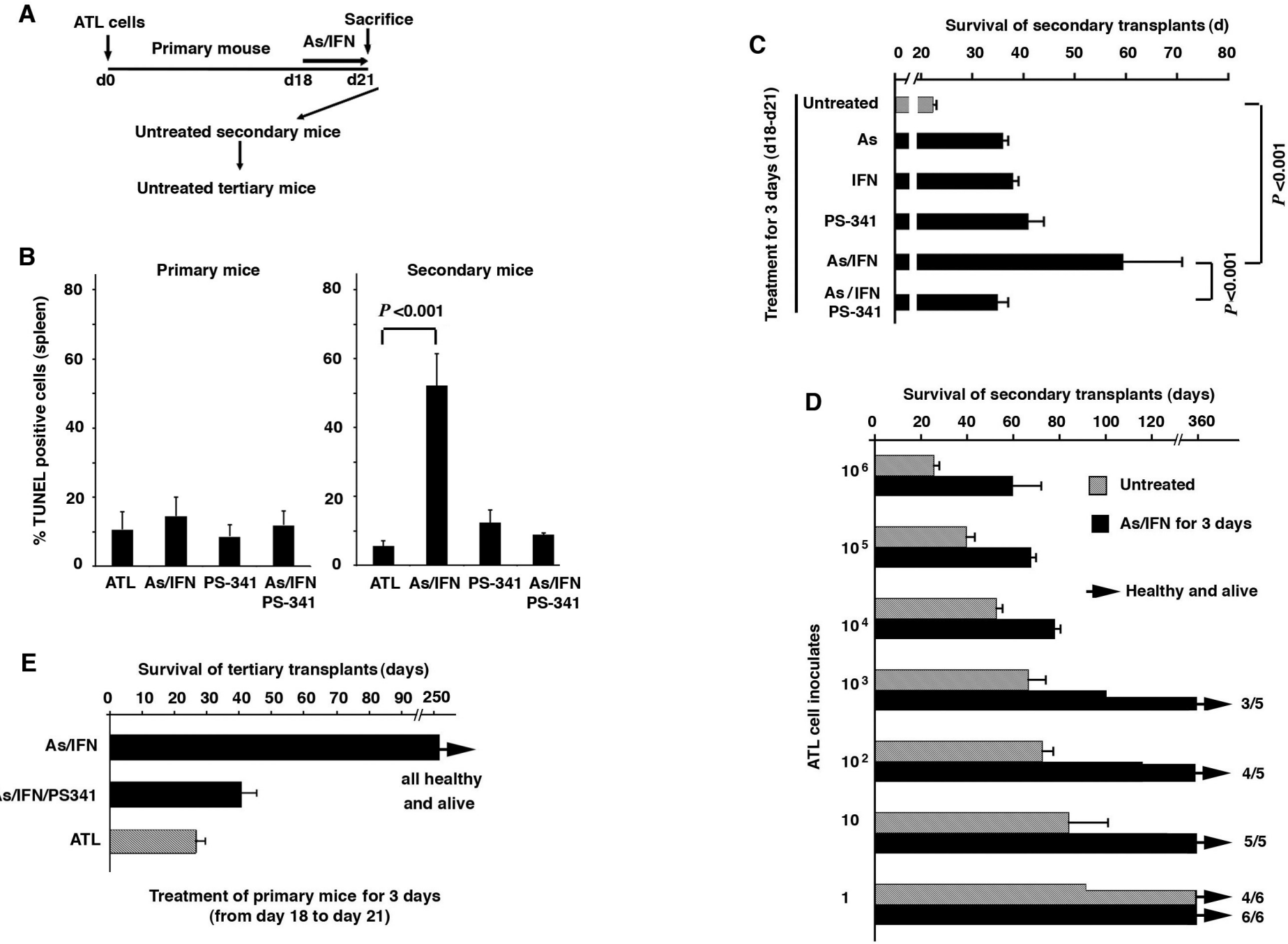




El Hajj et al. J Exp. Med. 2010; 207:2785-92

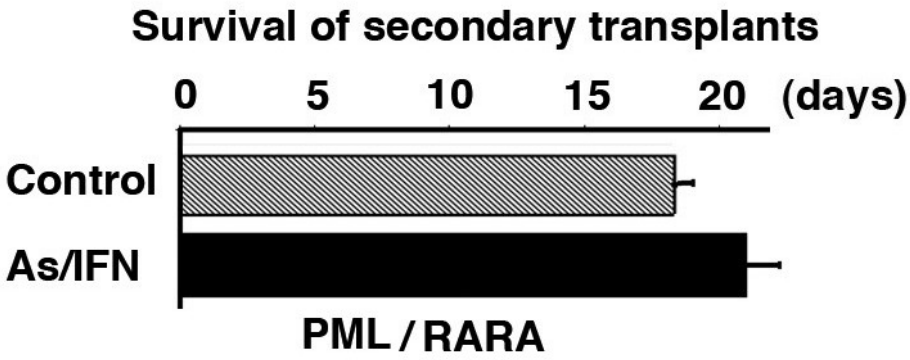
Leukemia initiating cells?

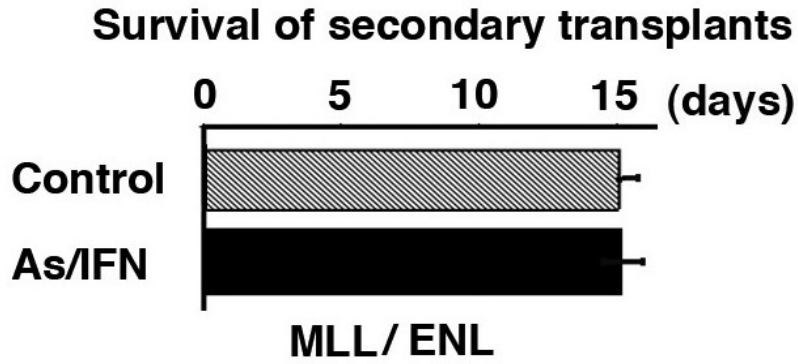
Transplantation model

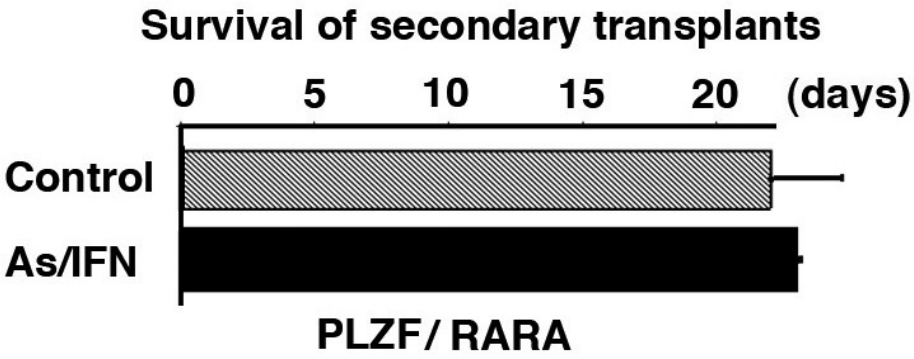


El Hajj et al. J Exp. Med. 2010; 207:2785-92

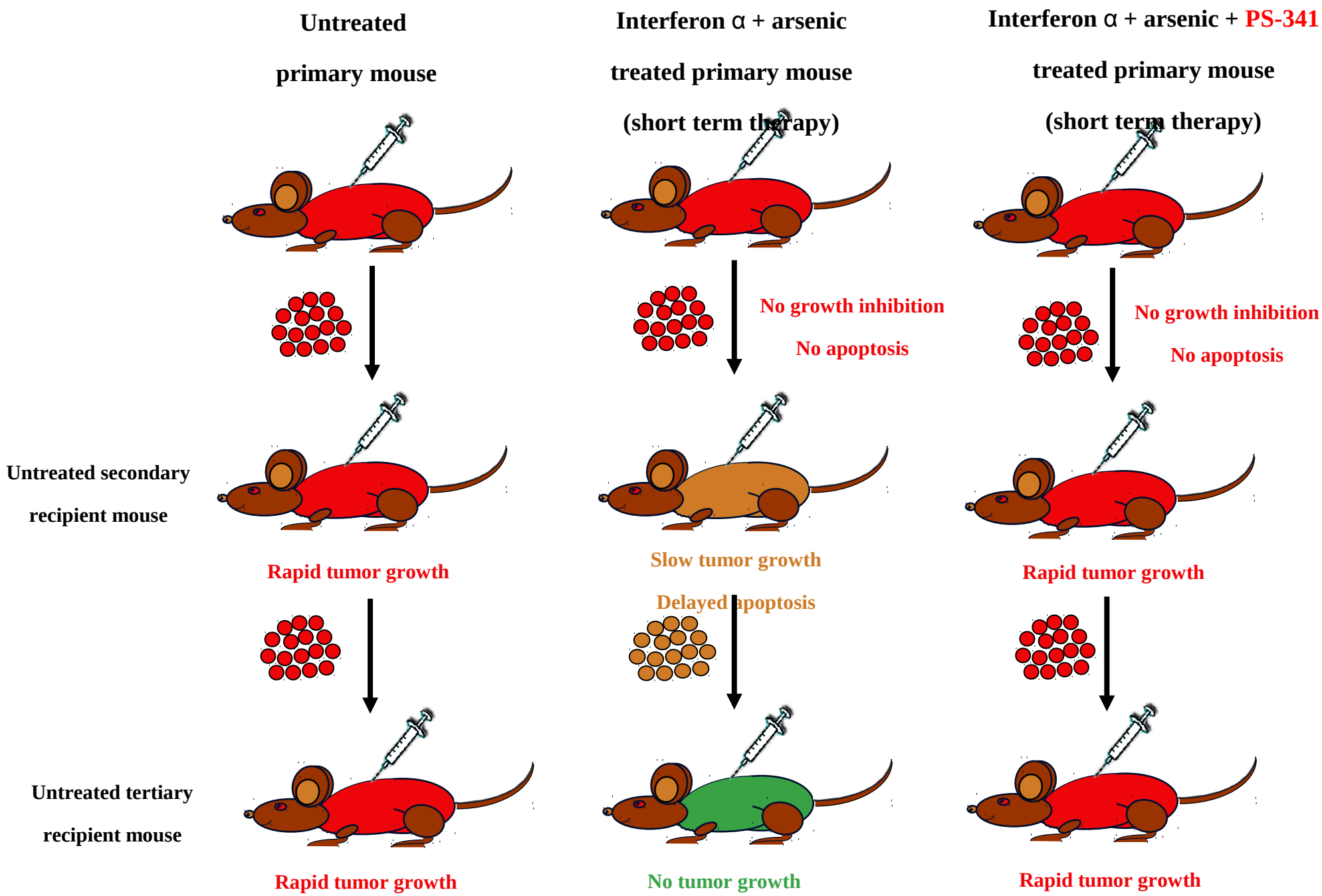
No effect of Arsenic/IFN on LIC activity in other murine leukemias

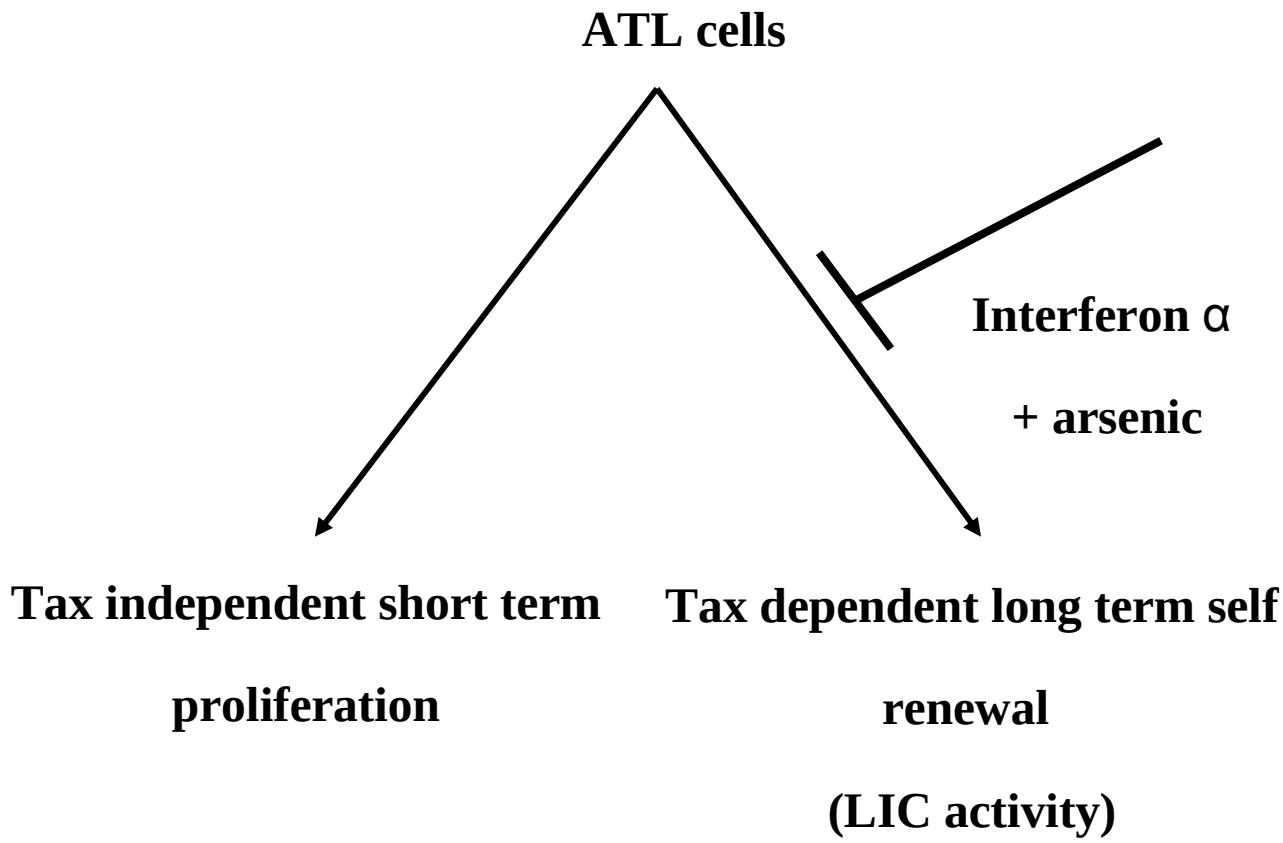






El Hajj et al. J Exp. Med. 2010; 207:2785-92


Untreated
primary mouse
Interferon α + arsenic
treated primary mouse
(short term therapy)
Interferon α + arsenic + PS-341
treated primary mouse
(short term therapy)
No growth inhibition
No apoptosis
No growth inhibition
No apoptosis
Untreated secondary
recipient mouse
Rapid tumor growth
Slow tumor growth
Delayed apoptosis
Rapid tumor growth
Untreated tertiary
recipient mouse
Rapid tumor growth
No tumor growth
Rapid tumor growth


ATL cells
Interferon α
+ arsenic
Tax independent short term proliferation
Tax dependent long term self renewal
(LIC activity)

Proposed model

- Long term leukemia initiating activity: Tax dependent
- Short term proliferation: Tax independent
- Arsenic/IFN: Proteasome dependent Tax degradation
  → exhaustion of long term leukemia initiating activity
  → initial proliferation then delayed apoptosis
  → Cure

blood

Prepublished online May 1, 2009;
doi:10.1182/blood-2009-03-211821

Phase II study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic ATL

Ghada Kchour, Mahdi Tarhini, Mohamad-Mehdi Kooshyar, Hiba El Hajj, Eric Wattel, Mahmoud Mahmoudi, Hassan Hatoum, Hossein Rahimi, Masoud Maleki, Houshang Rafatpanah, S.A.Rahim Rezaee, Mojtaba Tabatabaei Yazdi, Abbas Shirdel, Hugues de The, Olivier Hermine, Reza Farid and Ali Bazarbachi

Response and follow up of patients after Arsenic/AZT/IFN

Patient number	Response day 30	Relapse/ progression	Progression free survival (months)	Status at last Follow up	Survival status	Survival (months)
1	VGPR	**No**	15+	**CR**	**Alive**	15+
2	PR	**No**	15+	**CR**	**Alive**	15+
3	VGPR	**No**	12+	VGPR*	**Alive**	12+
4	PR	**No**	10+	**CR**	**Alive**	10+
5	VGPR	**No**	8+	**CR**	**Alive**	8+
6	PR	**No**	3+	**CR**	**Alive**	3+
7	PR	**No**	8+	**CR**	**Alive**	8+
8	VGPR	**No**	4+	**CR**	**Alive**	4+
9	VGPR	**No**	5+	VGPR**	**Alive**	5+
10	PR	**No**	2+	PR***	**Alive**	2+

* 8% atypical lymphocytes on peripheral blood smear

** 6% atypical lymphocytes on peripheral blood smear

*** lymphocytosis decreased from 185000 to 6400

Kchour et al. Blood 2009

Skin lesions patient 2

Before **After 2 weeks** **After 4 weeks**

Kchour et al. Blood 2009

Skin lesions patient 3

Before **After 4 weeks**

Kchour et al. Blood 2009

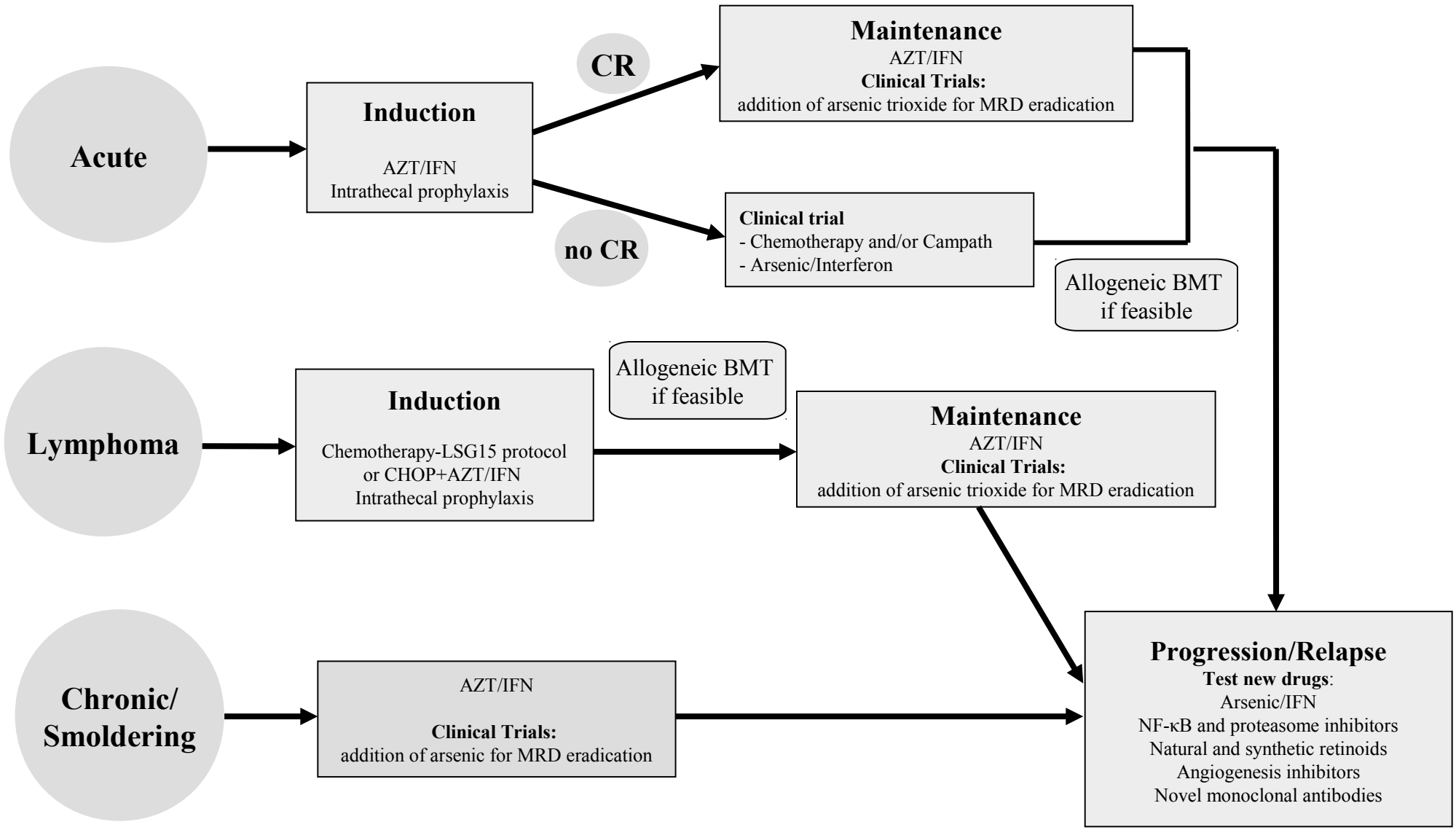
Follow up of ATL patients after stopping treatment in complete remission

Diagnosis	Treatment	Follow up after stopping treatment
Chronic ATL	IFN/AZT	Progression after 1 months
Chronic ATL	IFN/AZT	Progression after 3 months
Acute ATL	IFN/AZT	Progression after 3 months
Lymphoma	IFN/AZT	Progression after 5 months
Chronic ATL	IFN/AZT	Progression after 11 months
Chronic ATL	Arsenic/IFN/AZT	Progression after 1 month
Chronic ATL	Arsenic/IFN/AZT	Progression after 5 months
Chronic ATL	Arsenic/IFN/AZT	Progression after 6 months
Chronic ATL	Arsenic/IFN/AZT	**CCR** after 7 months follow up
Chronic ATL	Arsenic/IFN/AZT	**CCR** after 7 months follow up
Chronic ATL	Arsenic/IFN/AZT	**CCR** after 18 months follow up

Arsenic in Maintenance Therapy (ongoing study)

- 11 ATL patients treated with arsenic/IFN after chemo +/- AZT/IFN.
- ATL subtype: lymphoma (3), chronic (3) and acute (5).
- Disease status: CR=4 (3 lymphoma, 1 acute), PR=2 (1 acute, 1 chronic) and progression=5 (3 acute, 2 chronic).
- 6 patients died, and all were progressing at time of arsenic initiation.
- 5 patients survived : 3 lymphomas in CR (25, 31 and 46 m. FU), 1 acute in CR (9 m. FU) and 1 one chronic in PR (39 m. FU).

Suarez and Hermine



Bazarbachi et al. How I treat ATL BLOOD 2011 June 14 [Epub ahead of print]

AUB American University of Beirut

الجامعة الأميركية في بيروت

Hiba El Hajj

Youmna Kfoury

Zeina Dassouki

Zaher Otrock

Roudaina Nasser

Kazem Zibara

Shahrazad Saab

Mahdi Tarhini

Rihab Nasr

Nadine Darwiche

Ghassan Dbaibo

Ghazi Zaatari

Rami Mahfouz

Raghida Abou Merhi

Marwan El Sabban

Hôpital Necker

Olivier Hermine

Felipe Suarez

Hôpital St. Louis

Ali Saib

Estelle Chiari

Marie Claude Guillemin

Noemie Renault

Marie Louise Giron

Niclas Setterblad

Julien Ablain

Institut Pasteur

Patricia Tortevoye

Antoine Gessain

ENS Lyon

Renaud Mahieux

Institut Cochin

Claudine Pique

CHU Fort de France

Yves Plumelle

Gerard Panelatti

University College Dublin

Hideki Hasegawa

University of Miami

Juan Carlos Ramos

William Harrington

Imperial College London

Graham Taylor

Guys and St-Thomas

Paul Fields

Kansas University

Christophe Nicot

Mashhad Iran

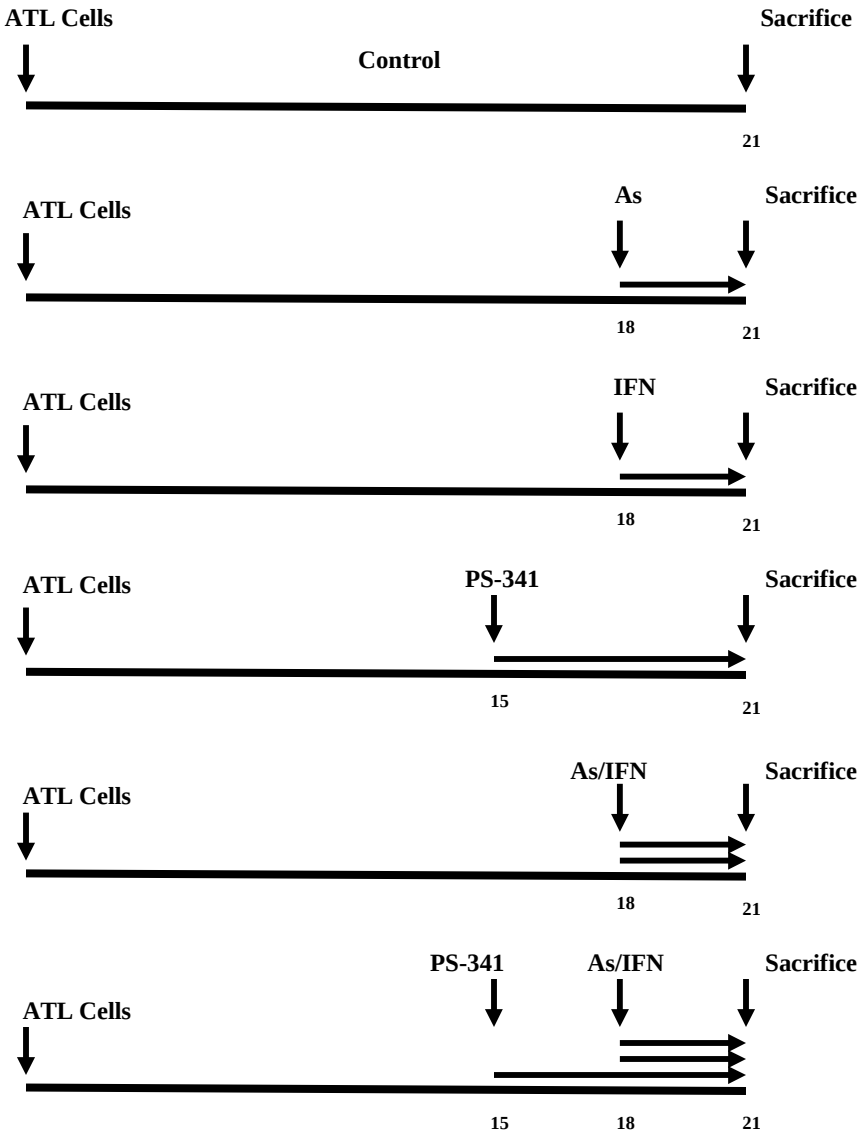
Ghada Kchour

Mahdi Tarhini

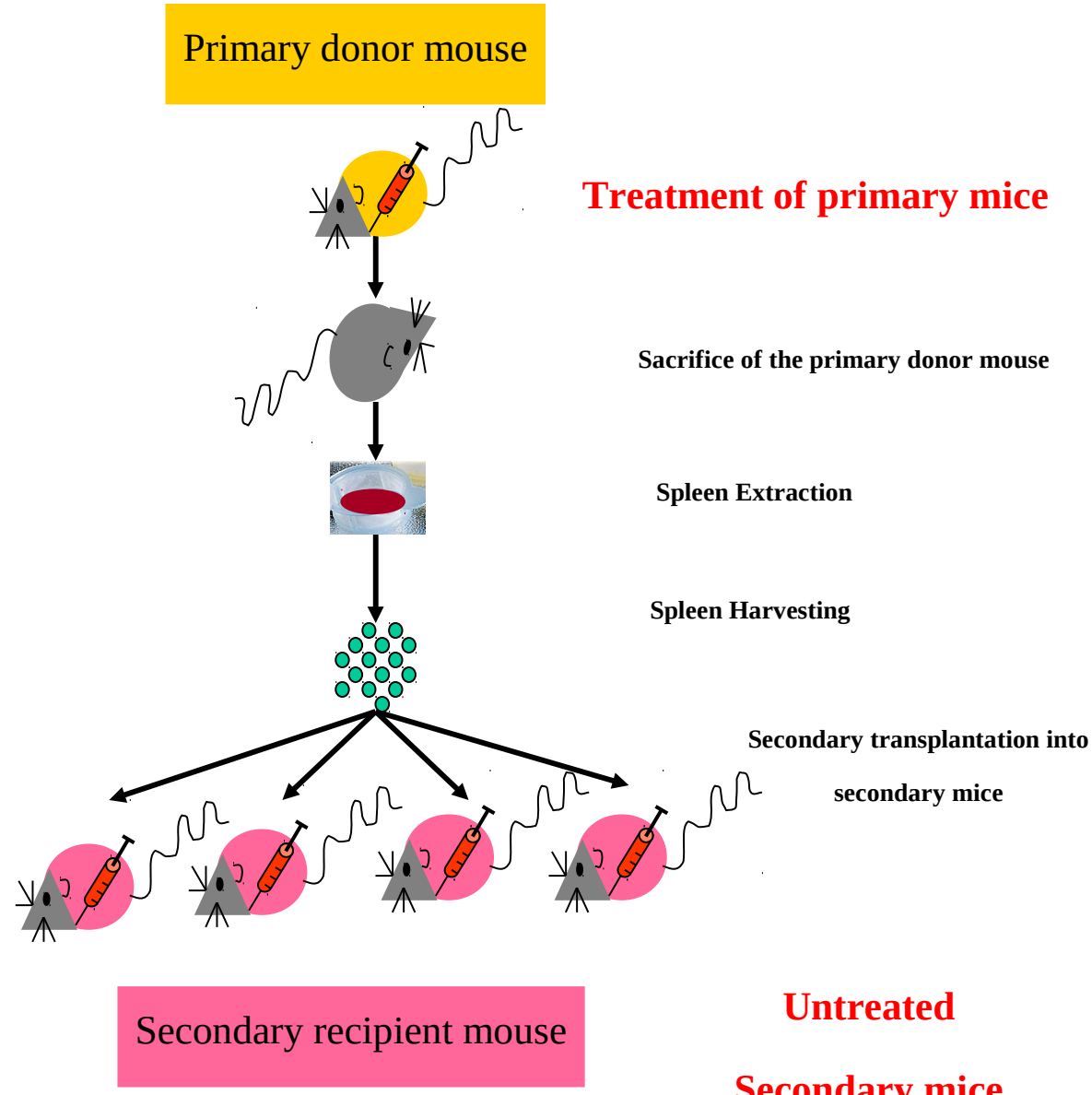
Mohamad Mehdi Khoshyar

Abbas Shirdel

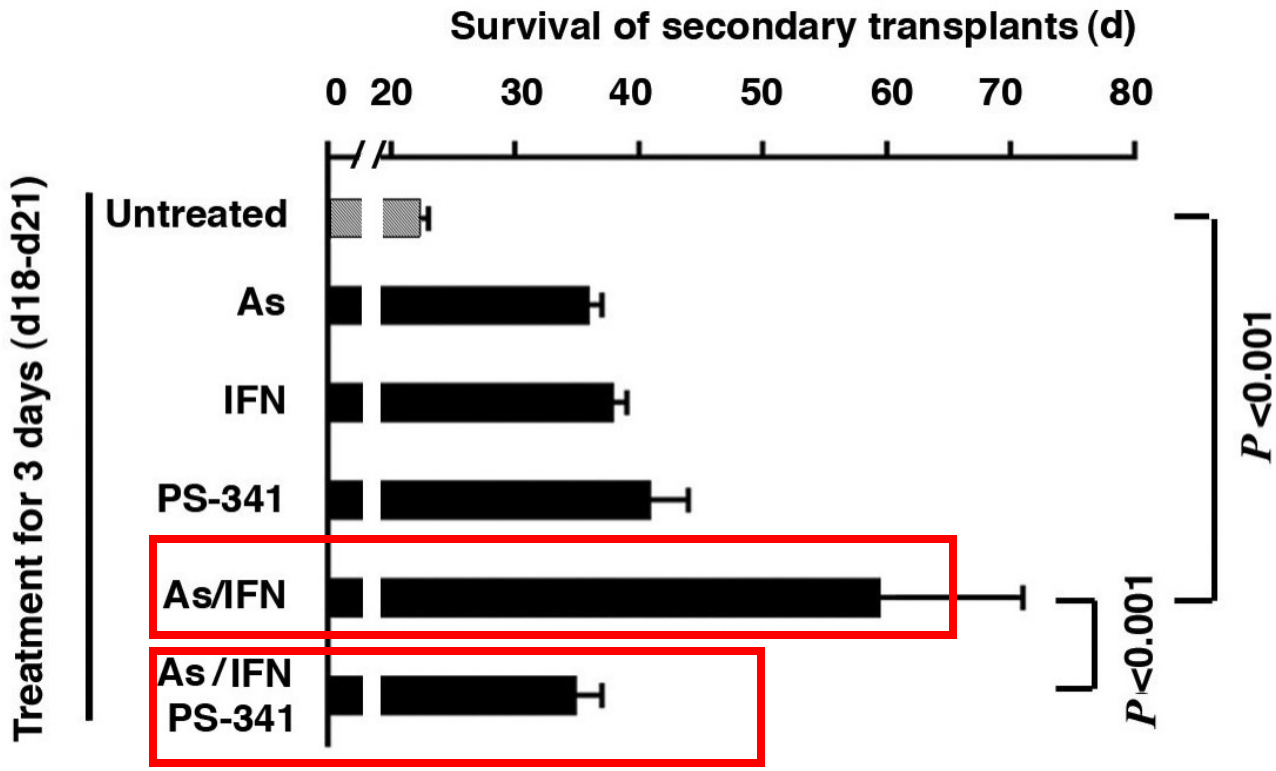
Secondary transplantation after 3 days of treatment



Treatment of primary mice



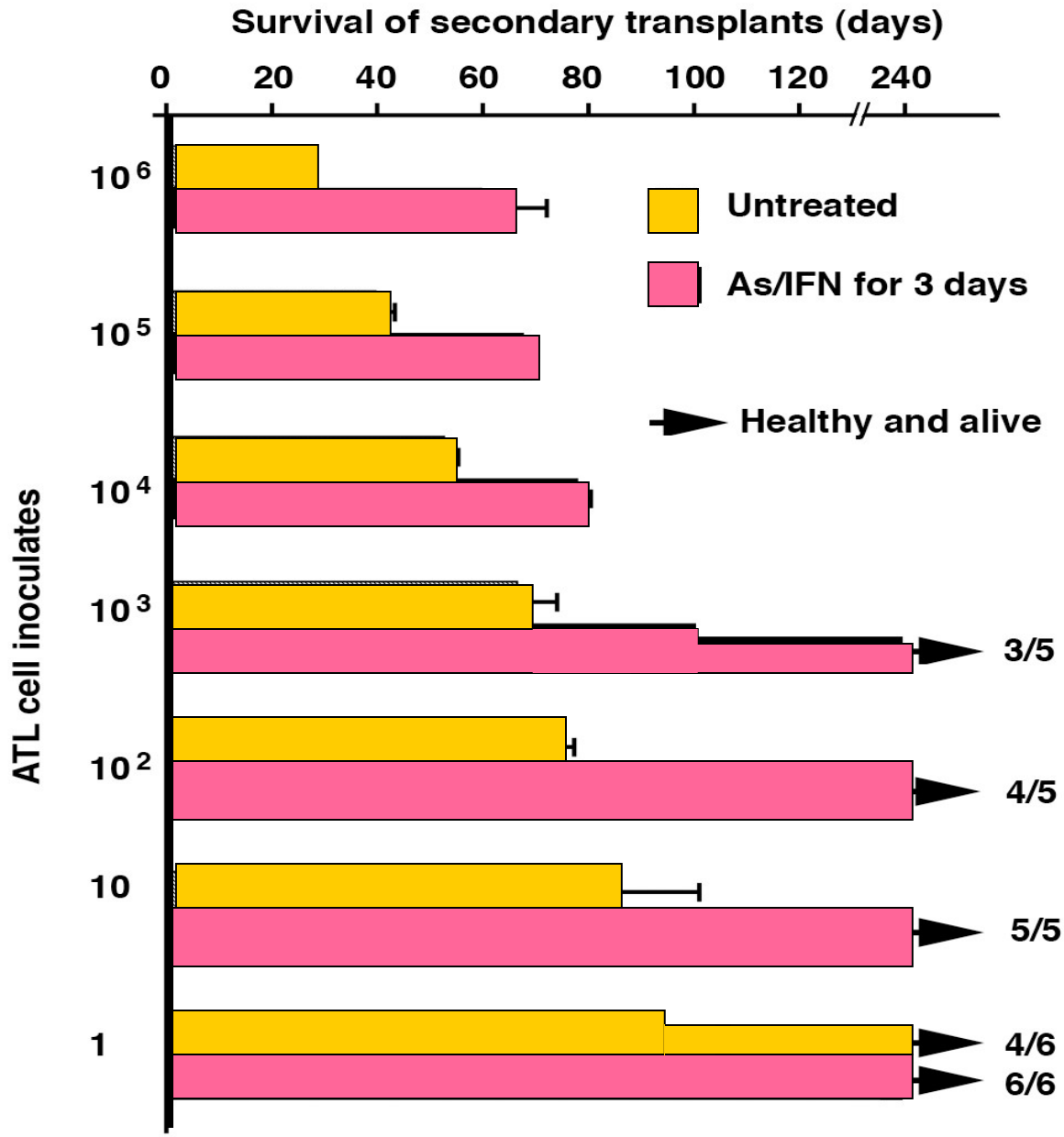
Secondary transplantation



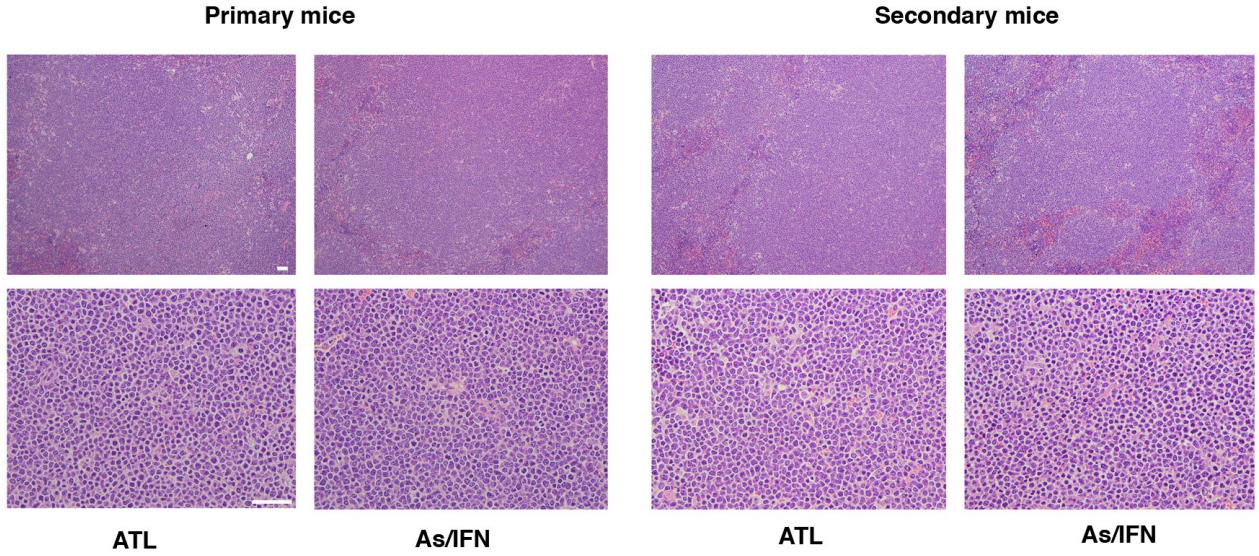
A dramatic increase in survival of secondary recipients from As/IFN strongly suggests that it specifically targets ATL LIC activity

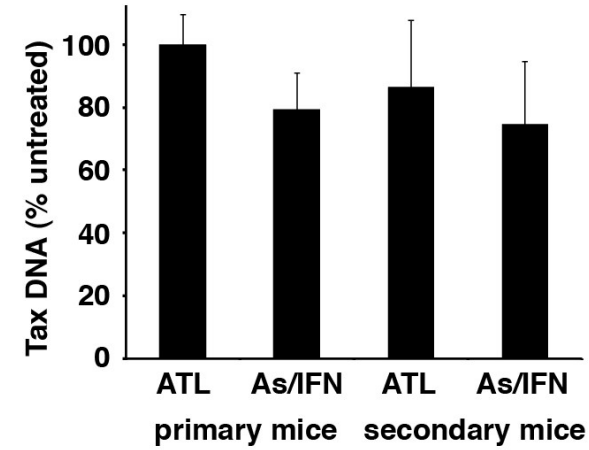
Protection of LICs with proteasome inhibition (role of Tax in eradication of LIC activity)

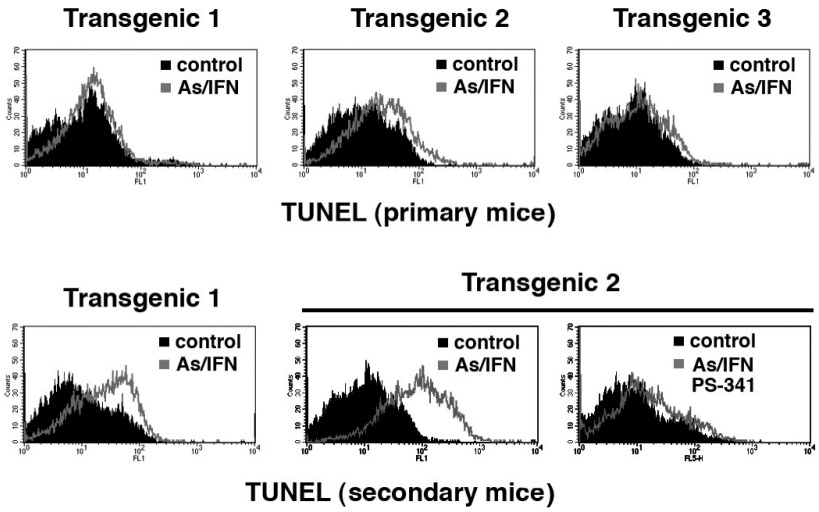
Arsenic/IFN decreased LIC activity by 500 to 1000X

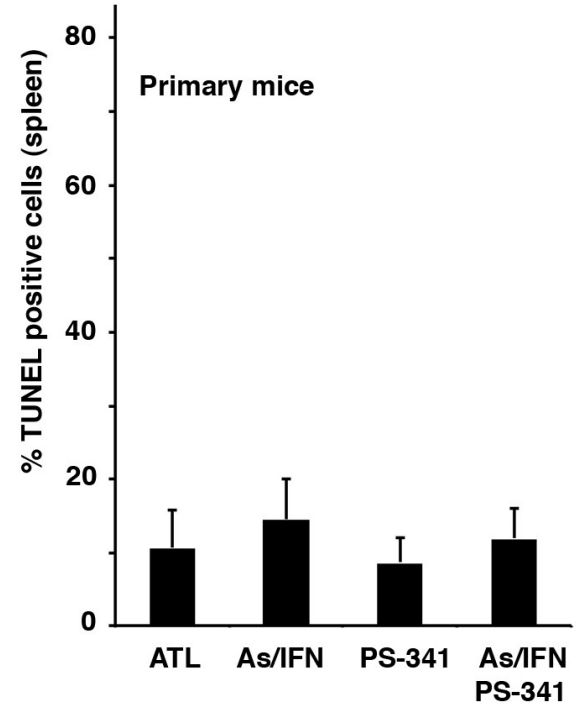


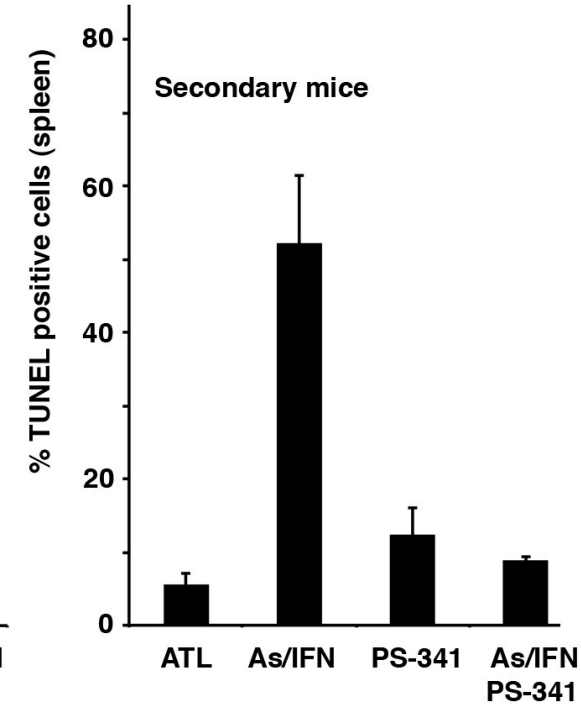
Arsenic/IFN (3 days) induces delayed apoptosis in secondary



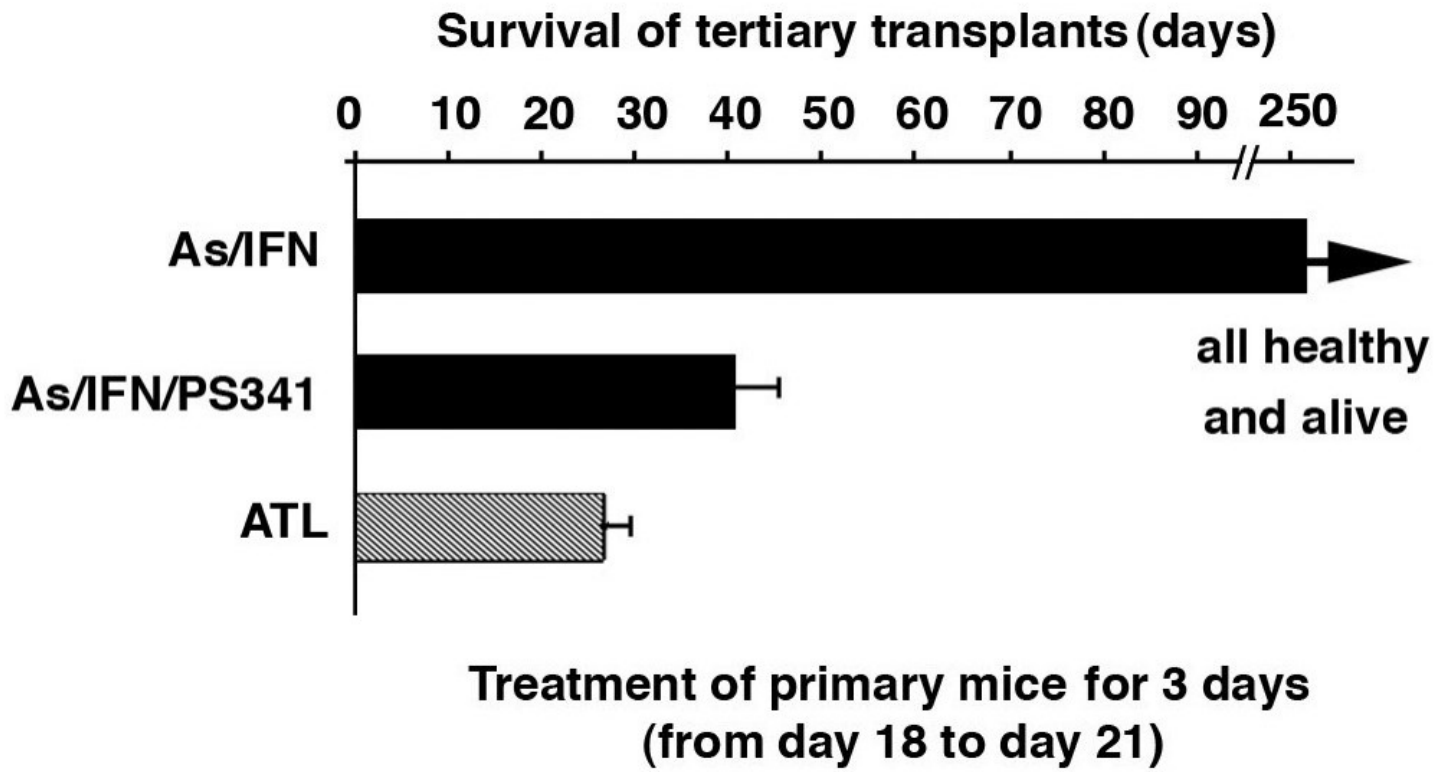




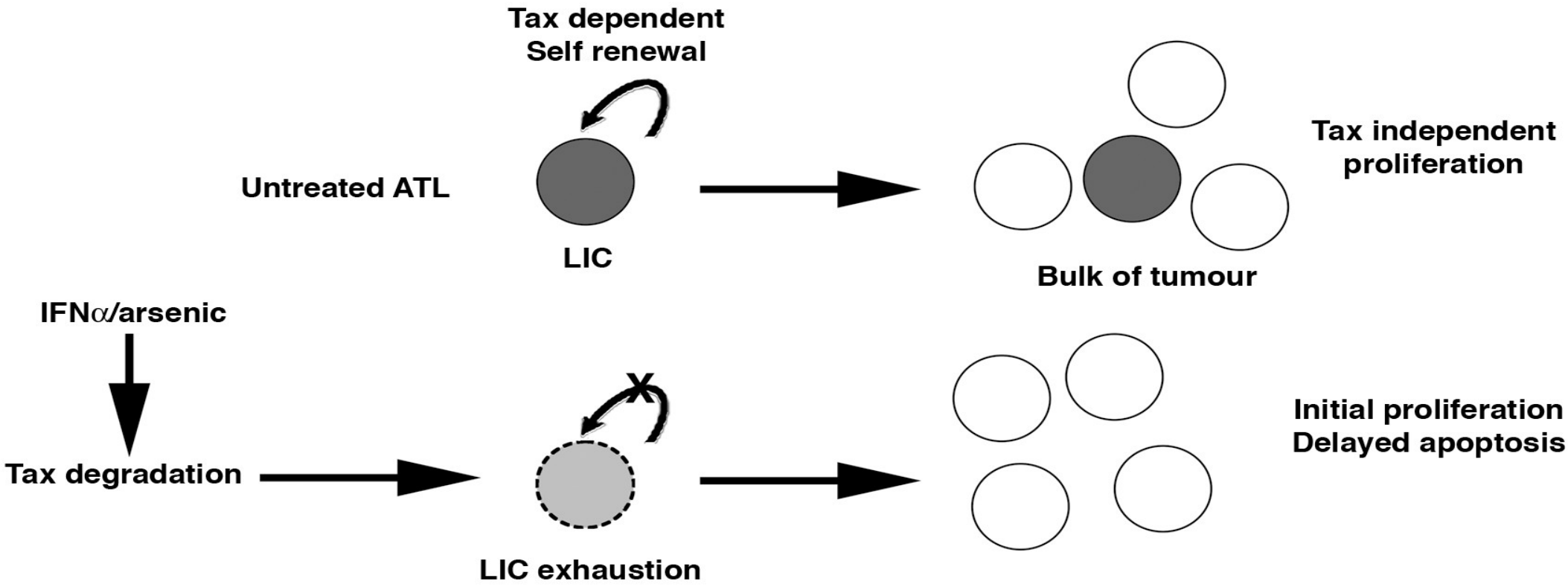




A complete loss of LIC activity in tertiary transplanted arsenic/IFN mice



Proposed model

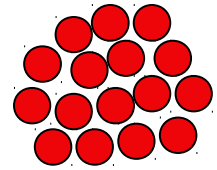


Interferon α + arsenic

treated primary mouse

Short term therapy

(3 days)

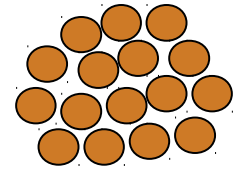


No growth inhibition

No apoptosis

Untreated secondary

recipient mouse

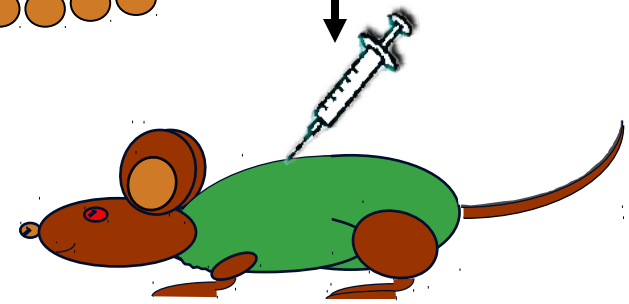


Slow tumor growth

Delayed apoptosis

Untreated tertiary

recipient mouse



No tumor growth