

ΙΑΤΡΙΚΗ ΤΩΝ ΜΕΛΕΤΩΝ – ΙΑΤΡΙΚΗ ΣΤΗΝ ΚΟΙΝΟΤΗΤΑ

ΜΕΛΕΤΕΣ και "Μελέτες"

Clinical decision making: more than just an algorithm



23^ο Ετήσιο Σεμινάριο Συνεχιζόμενης
Ιατρικής Εκπαίδευσης
Νοσοκομείου «Ο Ευαγγελισμός»

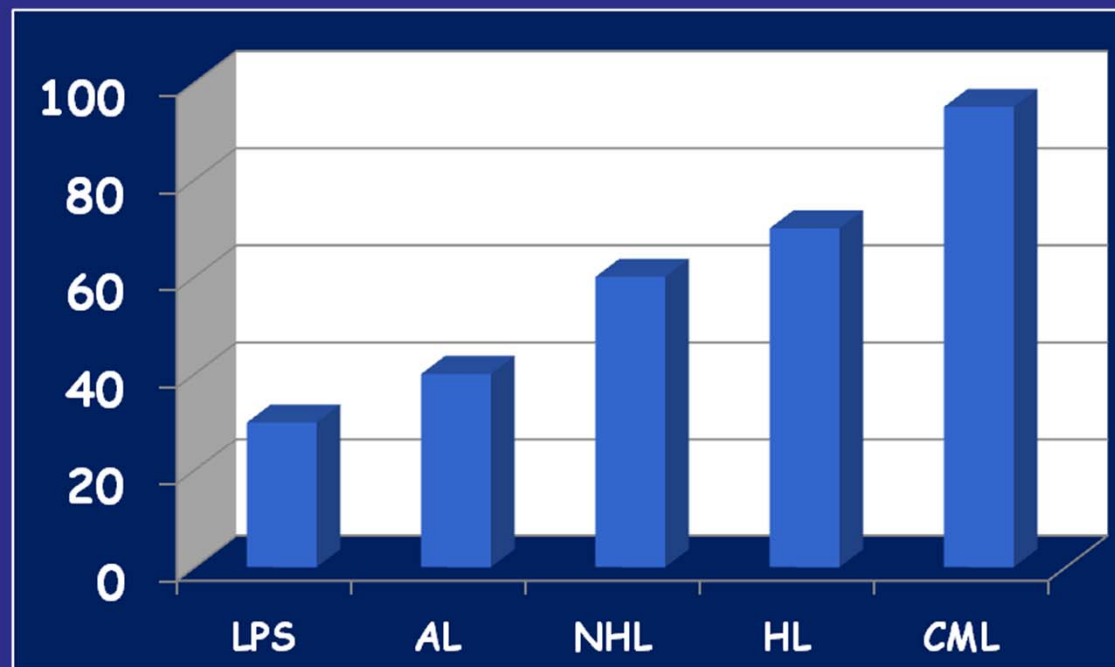


Αθήνα, 26 Φεβρουαρίου – 2 Μαρτίου 2018

Δεν υπάρχει σύγκρουση συμφερόντων
με τις παρακάτω χορηγούς εταιρείες:

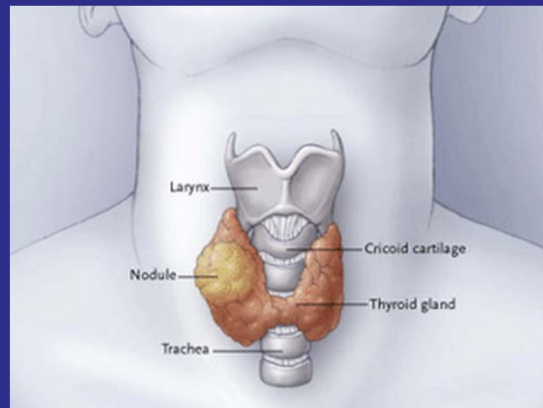
NOVARTIS, JANSSEN ONCOLOGY, ABBVIE,
BRISTOL-MYERS SQUIBB, MEDTRONIC,
TAKEDA, GENESIS, MSD, PFIZER, AMGEN,
ASTELLAS, GILEAD, AENORASIS, BAXTER,
BIANEX, WINMEDICA, ABBOTT, BIOSEP,
SANOFI, ANGELINI, DEMO, ELPEN,
EDWARDS, ROCHE, RONTIS, SPECIFAR, UCB,
ΥΓΕΙΟΔΥΝΑΜΙΚΗ, MAVROGENIS

ΙΑΤΡΙΚΗ ΣΤΗΝ ΚΟΙΝΟΤΗΤΑ





T. Kocher



Θυρεοειδεκτομή



Τραγικές συνέπειες !

*Δεν διαθέτουμε τίποτα το βεβαιωμένο,
παρά μόνο όσα μας αποκαλύπτει ο Θεός
Η προσευχή μπορεί να αντικαταστήσει την ανικανότητά μας
να ... αποτρέψουμε το θάνατο*

ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ

ΤΡΕΧΟΥΣΕΣ ΑΠΑΝΤΗΣΕΙΣ ΣΕ ΒΑΣΙΚΑ ΕΡΩΤΗΜΑΤΑ

ΔΙΑΔΙΚΑΣΙΕΣ ΕΛΕΓΧΟΥ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ



26943

ΕΦΗΜΕΡΙΣ ΤΗΣ ΚΥΒΕΡΝΗΣΕΩΣ

ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΔΗΜΟΚΡΑΤΙΑΣ

ΤΕΥΧΟΣ ΔΕΥΤΕΡΟ

Αρ. Φύλλου 1973
31 Δεκεμβρίου 2003

Ι. ΚΩΝΣΤΑΝΤΕΛΟΣ

**GUIDELINE FOR GOOD CLINICAL
PRACTICE June 1996**

ΕΝΤΙΜΟΤΗΤΑ

Ηθικά Παραπτώματα στην Έρευνα

Κ. Γαρδίκας

Sir Cyril Burt 1883-1971

Κληρονομικότητα της νοημοσύνης!

...

ΜΕΛΕΤΕΣ και "Μελέτες"

"Don't get too caught up in the deluge of data and statistics: it's time to reconnect with the patient."

Gianni Bonadonna 1995

CLICAL TRIALS AND TRAVAILS

Vincent T. DeVita 2003

The NEW ENGLAND
JOURNAL of MEDICINE

This article was retracted in June 2001.

High-Dose Chemotherapy With Hematopoietic Rescue as Primary Treatment for Metastatic Breast Cancer: A Randomized Trial

By W.R. Bezawada, L. Seymour, and R.D. Dansey

Purpose: The aims of this study were to compare in a randomized trial the results of high-dose versus conventional-dose chemotherapy as first-line treatment for metastatic breast cancer. The comparison included complete response (CR) rate, duration of response, and duration of survival.

Patients and Methods: Ninety patients were entered onto a study to compare two cycles of high-dose cyclophosphamide 2.4 g/m², mitoxantrone 35 to 45 mg/m², and etoposide (VP16) 2.5 g/m² (HD-CNV) versus six to eight cycles of conventional-dose cyclophosphamide 600 mg/m², mitoxantrone 12 mg/m², and vincristine 1.4 mg/m² (CNV) as first-line treatment for metastatic breast cancer. The high-dose regimen included either autologous bone marrow or peripheral-blood stem-cell rescue. All 90 patients are assessable.

Results: The response rates were significantly different. The overall response rate for HD-CNV was 43 of 45

(95%), with 23 of 45 patients (51%) achieving CR. Twenty-four of 45 patients (53%) who received conventional CNV have responded, with only two patients achieving CR. Both duration of response and duration of survival were significantly longer for patients who received HD-CNV. Toxicity of the high-dose therapy was moderate in most patients. Grade 2 to 3 mucositis and hematologic suppression that required supportive treatment was universal, but hematologic recovery to a neutrophil count more than 500/ μ L and platelet count more than 40,000/ μ L occurred at day 18 (median) after therapy.

Conclusion: HD-CNV appears to be a promising schedule that results in a significant proportion of CRs and increased survival in patients with metastatic breast cancer.

J Clin Oncol 13:2483-2489. © 1995 by American Society of Clinical Oncology.

DOSE OPTIMIZATION is a major determinant of the effectiveness of chemotherapy. The linear-log relationship between chemotherapy dose and cell kill¹ suggests that high-dose chemotherapy regimens should include agents that can be administered in doses at least double or more of those used in conventional-dose regimens. Although such high-dose treatment regimens have been shown to be effective even in patients refractory to conventional-dose treatments,²⁻⁵ the use of high-dose chemotherapy with bone marrow or peripheral-blood stem-cell support has not been directly compared with conventional-dose regimens as first-line treatment for metastatic breast cancer.

We have developed a new high-dose chemotherapy regimen that consists of cyclophosphamide, mitoxantrone, and etoposide (VP16) (HD-CNV) and present here the results of an ongoing randomized trial comparing this regimen with a conventional dose treatment schedule, of comparable drug composition.

PATIENTS AND METHODS

Details of the two chemotherapy schedules are listed in Table 1. The HD-CNV schedule was initially developed in a pilot study using escalating doses of mitoxantrone (25 to 50 mg/m²) together with cyclophosphamide (2.4 g/m²) and VP16 (2.5 g/m²). This study included 17 patients less than 51 years of age with recurrent or refractory stage 4 breast cancer after at least two and up to four prior chemotherapy regimens (including at least one taxane)-based chemotherapy schedule. In this pilot study, there was a response rate of 30 of 37 (81%), including four of 12 (33%) complete responses (CRs) among patients who survived more than 35 mg/m² of mitoxantrone, with reasonable toxicity and no mortality. Dose-limiting gastrointestinal toxicity was observed at a mitoxantrone dose of more than 45 mg/m².

The randomized study was first undertaken at the doses listed in Table 1. The aims of the study were to determine whether high-dose chemotherapy given to patients with metastatic breast cancer but without prior chemotherapy exposure could result in a CR rate $\geq$ 50%, the hypothesis being that only CR rates of this order are likely to have a substantial impact on survival. The study was thus designed to detect, with 80% power, an increase of the proportion of patients with CR of at least 20% over that which could be expected to result from conventional-dose treatment regimens. This statistical design requires 10 and 30 patients for the first phase of the study. Patients who entered the randomized study were 18 women $\geq$ 50 years of age with histologically or cytologically confirmed metastatic breast cancer T₁ to be eligible for the study, they had to have had no prior chemotherapy for metastatic disease, no prior radiotherapy, no prior steroids, and normal cardiac function as determined by multigated, radionuclide cardiac ejection fraction (MLGA $\geq$ 50%). Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less to be eligible for entry. Patients who relapsed or did not respond to prior hormone therapy were eligible. Randomization was performed by a random number, closed-envelope technique.

Patients on high-dose chemotherapy regimens received bone marrow support either by means of noncryopreserved autologous bone marrow (nine patients) or via peripheral-blood progenitor-cell support. Fourteen peripheral-blood progenitor-cell collections were performed following hematologic recovery after a priming dose of cyclophosphamide.

From the Department of Medicine, Division of Hematology/Oncology, University of Witwatersrand, South Africa.

Submitted January 11, 1995; accepted June 16, 1995.

Address reprint requests to W.R. Bezawada, MD, Department of Medicine, University of Witwatersrand Medical School, 7 York Rd, Parktown, Johannesburg, South Africa.

© 1995 by American Society of Clinical Oncology.
0732-183X/95/1324-2483/\$06.00

RETRACTION !

Retraction: A Genomic Strategy to Refine Prognosis in
Early-Stage Non-Small-Cell Lung Cancer.
N Engl J Med 2006;355:570-80.

March 2 2011

to the editor: We would like to retract our article...
... We deeply regret the effect
of this action on the work of other investigators.

The NEW ENGLAND
JOURNAL *of* MEDICINE

Πολλαπλούν Μυέλωμα PBSCT + Thalidomide vs PBSCTx2 ?

Tunisian Myeloma Study Group !

blood

2008 111: 1805-1810
Prepublished online Sep 17, 2007;
doi:10.1182/blood-2007-07-101212

Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial

Abderrahman Abdelkefi,¹ Saloua Ladeb,¹ Lamia Torjman,¹ Tarek Ben Othman,¹ Amel Lakhal,¹ Neila Ben Romdhane,² Halima El Omri,³ Moez Elloumi,⁴ Hatem Belaaj,⁵ Ramzi Jeddi,⁶ Lamia Aissaoui,⁷ Habib Ksouri,⁸ Assia Ben Hassen,⁹ Fahmi Msadek,¹ Ali Saad,⁷ Mohamed Hachi,⁹ Kamel Boukef,⁹ Ahlem Amouri,¹⁰ Hechmi Louzi,¹⁰ Koussay Dellagi,¹⁰ and Abdeladhim Ben Abdeladhim,¹ on behalf of the Tunisian Multiple Myeloma Study Group



From www.bloodjournal.org at HELLENIC SOCIETY OF HEMATOLOGY on June 10, 2008. For personal use only.

Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial

Abderrahman Abdelkefi,¹ Saloua Ladeb,¹ Lamia Torjman,¹ Tarek Ben Othman,¹ Amel Lakhal,¹ Neila Ben Romdhane,² Halima El Omri,³ Moez Elloumi,⁴ Hatem Belaaj,⁵ Ramzi Jeddi,⁶ Lamia Aissaoui,⁷ Habib Ksouri,⁸ Assia Ben Hassen,⁹ Fahmi Msadek,¹ Ali Saad,⁷ Mohamed Hachi,⁹ Kamel Boukef,⁹ Ahlem Amouri,¹⁰ Hechmi Louzi,¹⁰ Koussay Dellagi,¹⁰ and Abdeladhim Ben Abdeladhim,¹ on behalf of the Tunisian Multiple Myeloma Study Group

¹Centre National de Greffe de Moelle Osseuse, Tunis; ²Hôpital Le Flah, Tunis; ³Hôpital Farhat Hached, Sousse; ⁴Hôpital Hedi Chaker, Sfax; ⁵Hôpital Aziz Othmani, Tunis; ⁶Hôpital el Ghazal, Tunis; ⁷Université de médecine de Sousse, Hôpital Farhat Hached, Sousse; ⁸Unité Nationale de la Santé Publique, Tunis; ⁹Centre National de Transfusion Sanguine, Tunis; and ¹⁰Institut Pasteur de Tunis, Tunisia

From April 2003 to December 2006, 195 patients with de novo asymptomatic myeloma and younger than 65 years of age were randomly assigned to receive either tandem transplantation up front (arm A, n = 97) or one autologous stem-cell transplantation followed by a maintenance therapy with thalidomide (day + 86, 100 mg per day during 8 months) (arm B, n = 98). Patients included in arm B received a second transplant at disease progression. In both arms, autologous stem-cell transplantation was preceded by first-line therapy with thalidomide-dexamethasone and subsequent collection of peripheral blood stem cells with high-dose cyclophosphamide (cyclo) and granulocyte colony stimulating factor. Data were analyzed on an intent-to-treat basis. With a median follow-up of 32 months (range, 8–66 months), 3-year overall survival was 63% in arm A and 85% in arm B (P = .02). The 3-year progression-free survival was 63% in arm A and 85% in arm B (P = .02). Up-front single autologous transplantation followed by 8 months of maintenance therapy with thalidomide (with second transplant in relapse or progression) is a superior therapeutic strategy to that of multiple myeloma patients undergoing tandem transplantation in this setting. This study was registered at www.ClinicalTrials.gov as NCT00077605. (Blood. 2008;111:1805–1810)

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Introduction

Two prospective randomized studies have shown that relapse-free survival is superior in high-dose chemotherapy with autologous stem-cell transplantation (ASCT) compared with conventional therapy in multiple myeloma (MM).^{1,2} ASCT is now considered a standard option in young patients.³ The challenge of the French Multiple Myeloma (FMM) study was the first to show that 2 sequential ASCTs improved 7-year event-free survival (EFS) and overall survival (OS) rates in comparison with a single ASCT.⁴ Recently, the Bolognesi 96 clinical study has shown that in comparison with a single ASCT as up-front therapy for newly diagnosed multiple myeloma (MM), double ASCT offered superior complete response (CR) rate and EFS but failed to significantly prolong OS. Disease relapse after double ASCT was particularly evident among patients who did not achieve at least a very good partial response (VGPR) after one autotransplantation.⁵ Second ASCT given after relapse following a single ASCT has been used as a salvage therapy in many centers.^{6–11} Recently, a retrospective study has compared tandem ASCT up front with a strategy including planned second ASCT at relapse or progression followed by 8 months of maintenance therapy with thalidomide (with second transplant in relapse or progression) in multiple myeloma patients.¹² In this retrospective study, Morice et al¹² showed that a second ASCT performed before relapse and within 6 to 12 months of the first ASCT improved survival. While there have been no randomized trials to evaluate the benefit of second ASCT following relapse, it has been suggested that ASCT (after first relapse) may achieve the same outcome as transplantation following initial therapy.^{13–15} Indeed, Pfreundschuh et al¹³ showed that early transplantation improved EFS but did not affect OS when compared with delayed transplantation. Although MM remains incurable with conventional treatment, management of the disease recently has been transformed with the introduction of 3 novel agents: bortomizomib,¹⁶ thalidomide,¹⁷ and lenalidomide.¹⁸ These agents represent a new generation of treatments for MM that affect both specific intracellular signaling pathways and the tumor microenvironment.¹⁹ Thalidomide is an agent with immunomodulatory and antiangiogenic properties. Thalidomide plus dexamethasone^{20–22} is currently approved as frontline treatment of MM. Furthermore, several studies have shown that thalidomide is an effective maintenance therapy after ASCT in patients with MM.^{23–25}

Submitted July 14, 2007; accepted September 13, 2007. Republished online as Blood First Edition paper, September 17, 2007; DOI 10.1182/blood-2007-07-101212.

An inside Blood analysis of this article appears at the front of this issue. The online version of this article contains a data supplement.

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BLOOD, 16 FEBRUARY 2008 • VOLUME 111, NUMBER 4

1805

Ο εθνικός ήρωας στη Νότια Κορέα ήταν απατεώνας!

ΣΕΟΥΛ : Ο Χ.. εθνικός ήρωας για την έρευνά του στα βλαστοκύτταρα καταδικάστηκε για υπεξαίρεση κονδυλίων και για παράνομη αγορά ανθρωπίνων ωαρίων. ...Ο Χ. έδειξε μεταμέλεια και το δικαστήριο του επέβαλε ποινή φυλάκισης με τριετή αναστολή.

Με την απόφαση του δικαστηρίου γράφτηκε ο θλιβερός επίλογος στη σταδιοδρομία ενός ανθρώπου ο οποίος κάποτε χαρακτηρίστηκε ήρωας ...

Αίτια των Ηθικών Παραπτωμάτων

Κ. Γαρδίκας

Φιλοδοξία

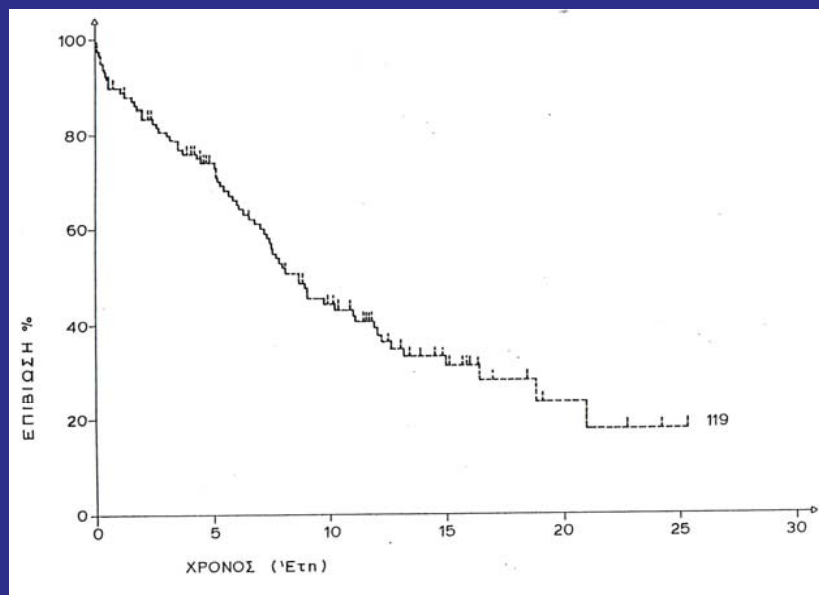
Εναγκαλισμός των εταιρειών

Publish or Perish

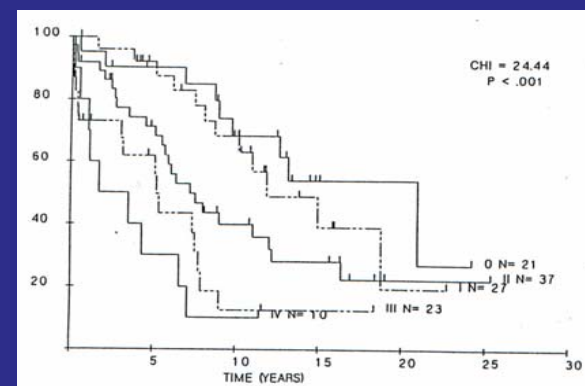
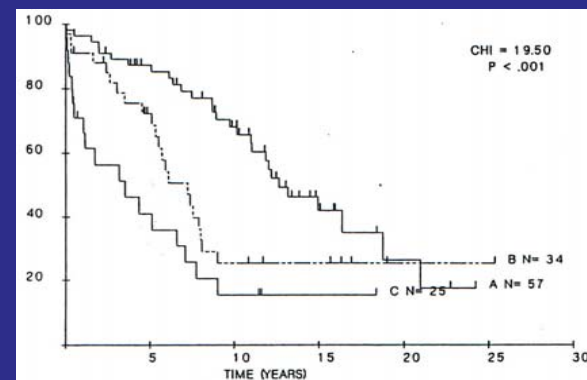
“Deadly Medicines and Organized Crime”

ΑΞΙΟΠΙΣΤΙΑ

Χρόνια Λεμφοκυτταρική Λευχαιμία

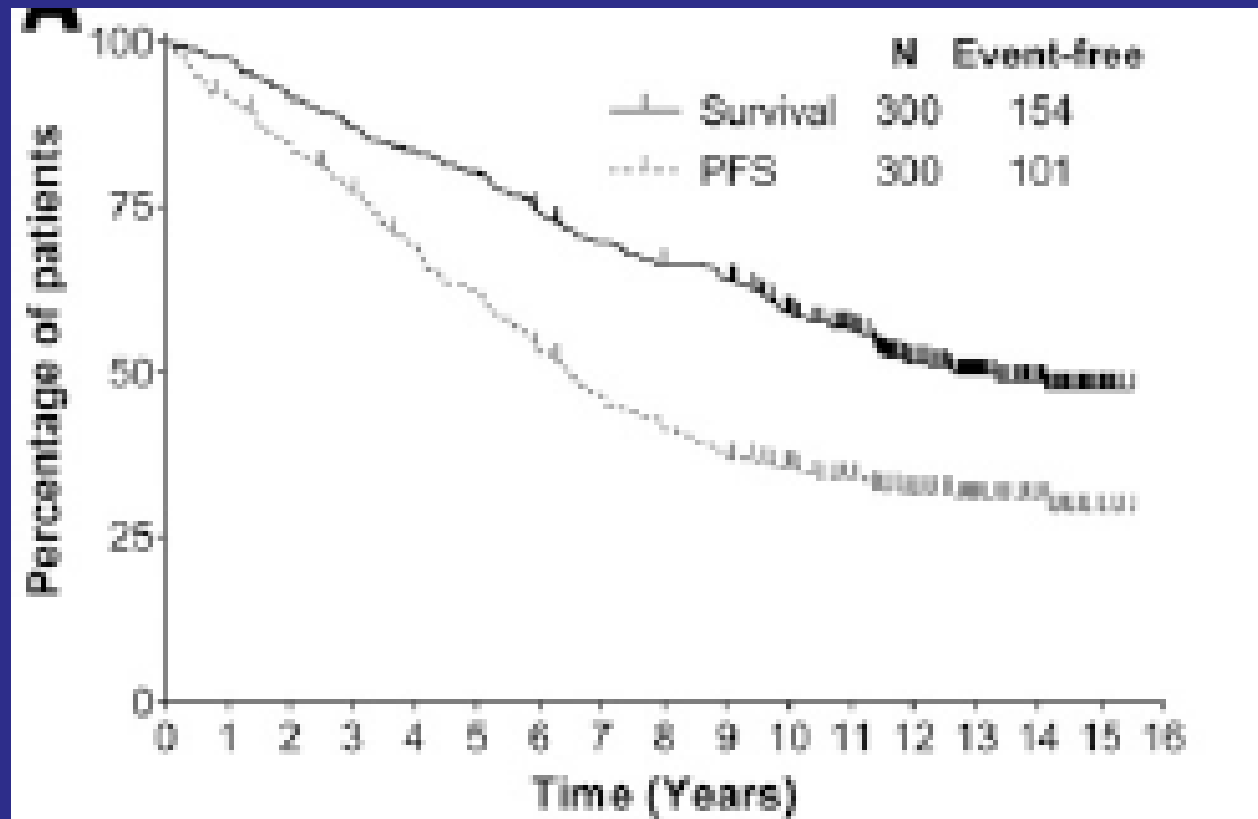


S. BARTHOLOMEW'S 1990



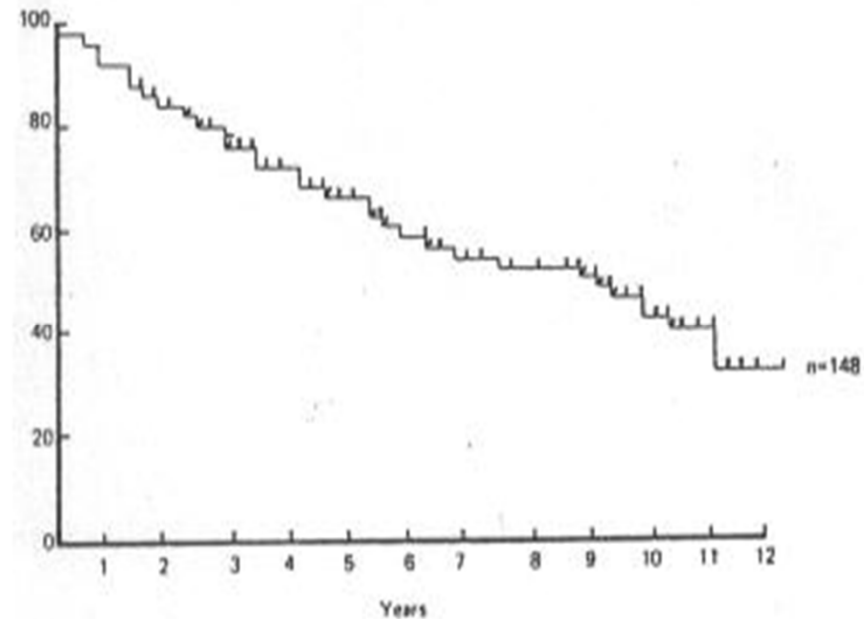
FCR Μετά 25 χρόνια

FCR holds up to the test
of time: CLL8 follow-up



MD Anderson 2016

Οζώδη Λεμφώματα '70 - '80



S. BARTHOLOMEW'S 1990

Οζώδη Λεμφώματα

Δοκιμές και Δοκιμασίες x 20 έτη

'80 - 2000

Table 1. More is better (and needs to be).

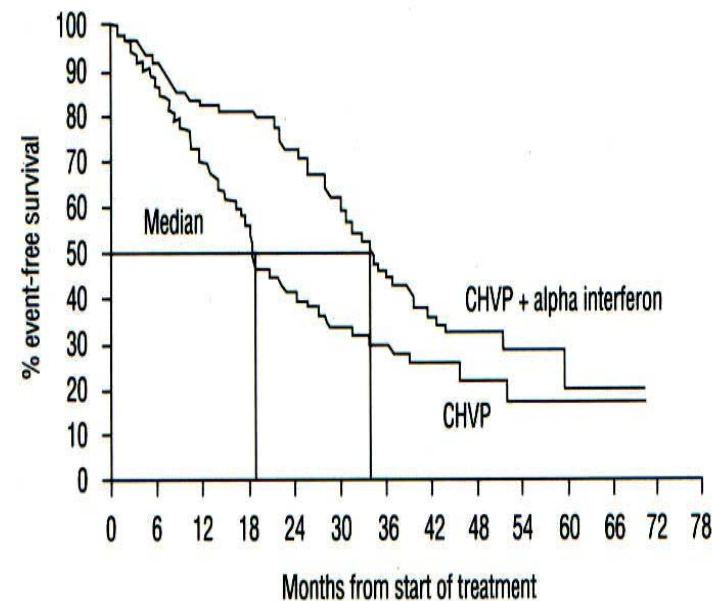
1. CVP	→ CY/TBI + ABMT	STANFORD
2. CHOP	→ CY/TBI + ABMT	DFCI (Nadler)
3. ProMACE-MOPP	↙ CY/TBI + ABMT ↘ RT	MSKI

Table 2. Biology is beautiful.

1. CYCLO ± IFNα		CALGB
2. COPA		ECOG
3. CVP	→ IFNα vs 0	EORTC
4. PDM		LOW GRADE GERMAN GROUP

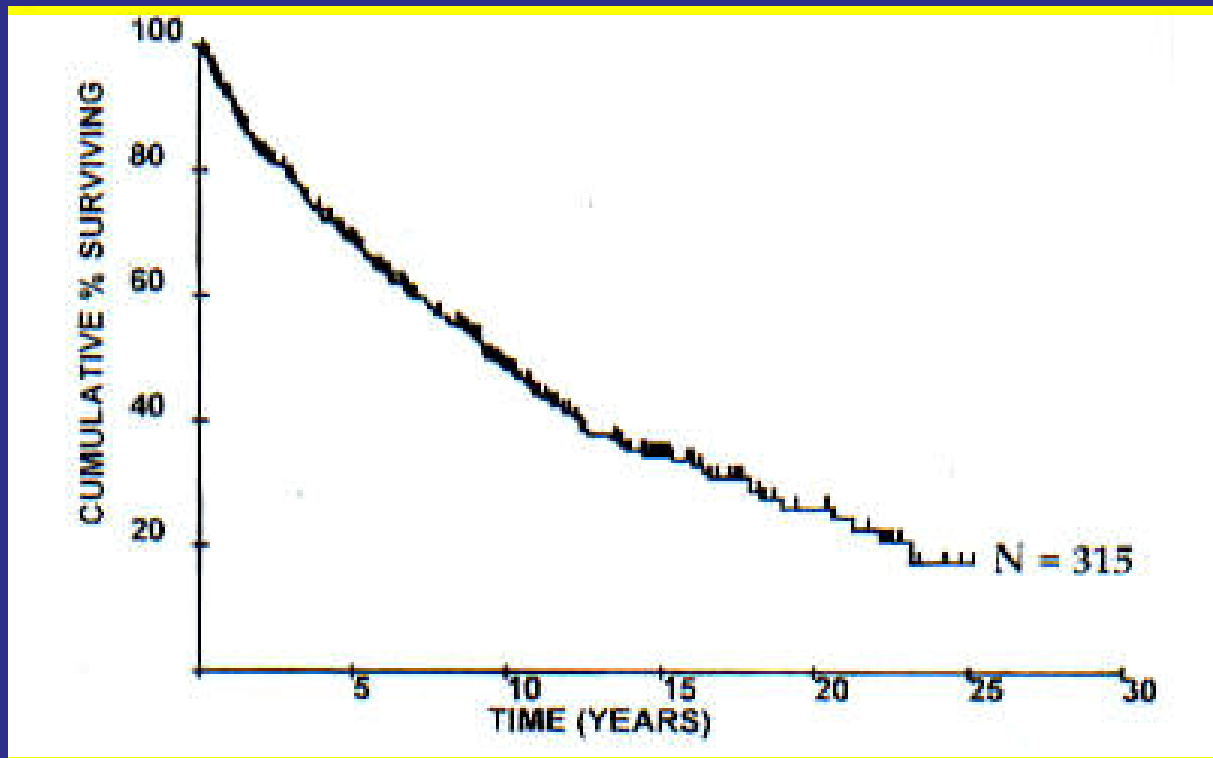
Table 3. The Texas solution (SWOG).

ProMACE-MOPP	→ CR	↙ IFNα ↘ 0
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Οζώδη Λεμφώματα

2000

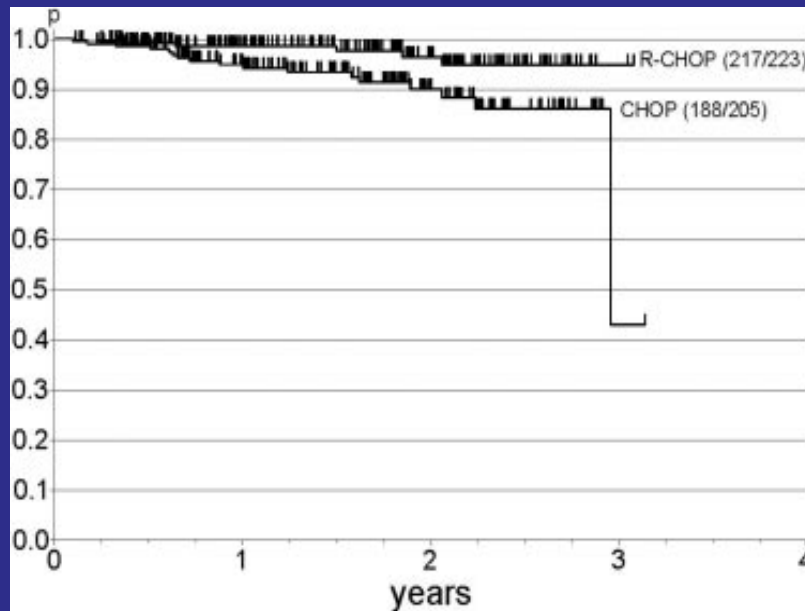


S. BARTHOLOMEW'S J. Apostolidis

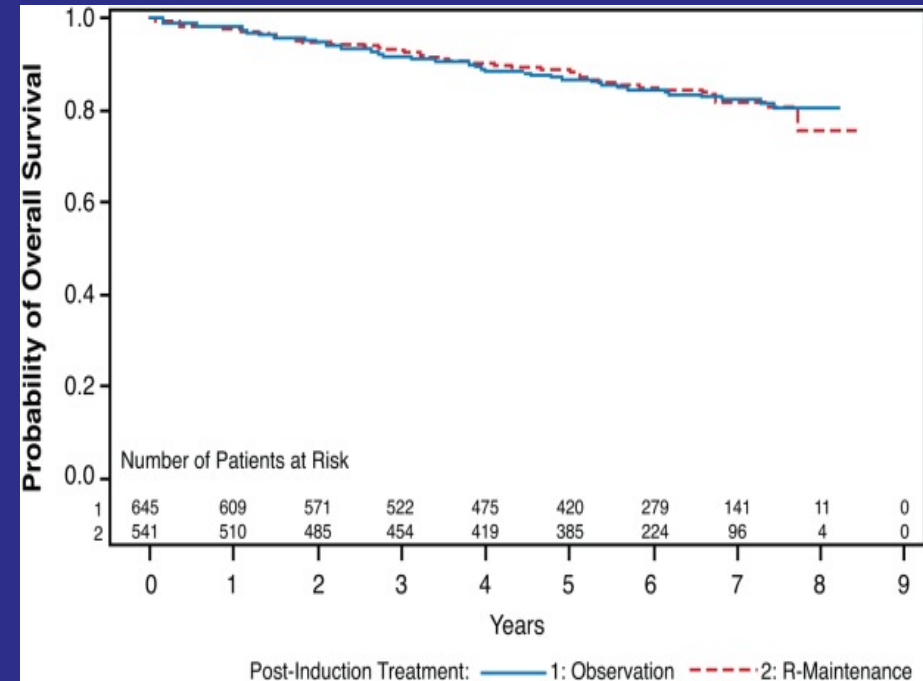
JOURNAL OF CLINICAL ONCOLOGY

Οζώδη Λεμφώματα

Rituximab... μετά 30 χρόνια



Hiddemann W. et al. 2005



National LymphoCare Study, 2014
2004-7, 2700 pts

The Search for Surrogate Endpoints in Trials in Diffuse Large B-Cell Lymphoma: The Surrogate Endpoints for Aggressive Lymphoma Project

ΣΥΓΚΡΙΤΙΚΕΣ ΜΕΛΕΤΕΣ

A CLINICAL TRIAL OF SANOCRY SIN IN PULMONARY TUBERCULOSIS¹

J. BURNS AMBERSON, JR., B. T. McMAHON AND MAX PINNER



**Silesian Terra Sigillata
1580**

1753 James Lind

controlled trial

Citrus - scurvy

1898 Johannes Fibiger

Alternate – allocation

Diphtheria antitoxin

1931 James Burns Amberson

Coin flip

Sanocrysin - tuberculosis

ΤΥΧΑΙΟΠΟΙΗΣΗ / ΠΡΟΟΠΤΙΚΕΣ ΜΕΛΕΤΕΣ



Sir Austin Bradford Hill
1897 - 1991

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
A MEDICAL RESEARCH COUNCIL INVESTIGATION



1962 Food, Drug, and Cosmetic Act

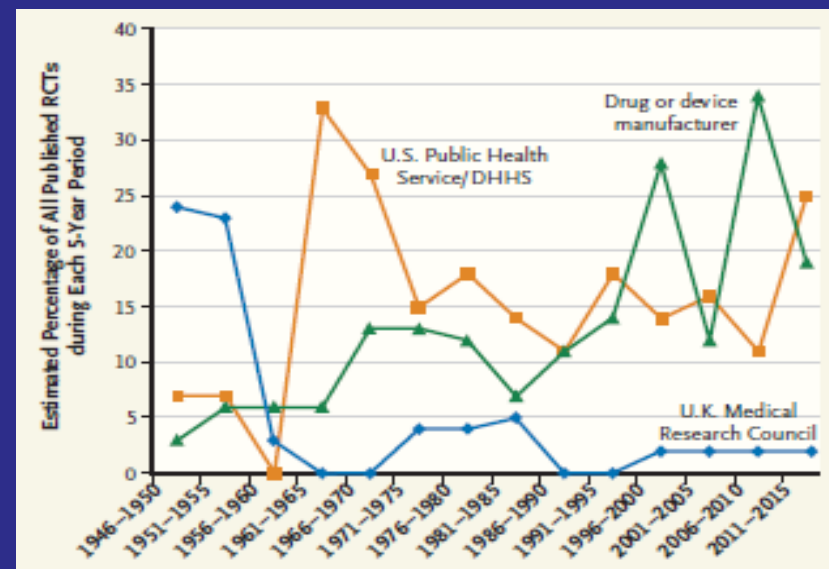
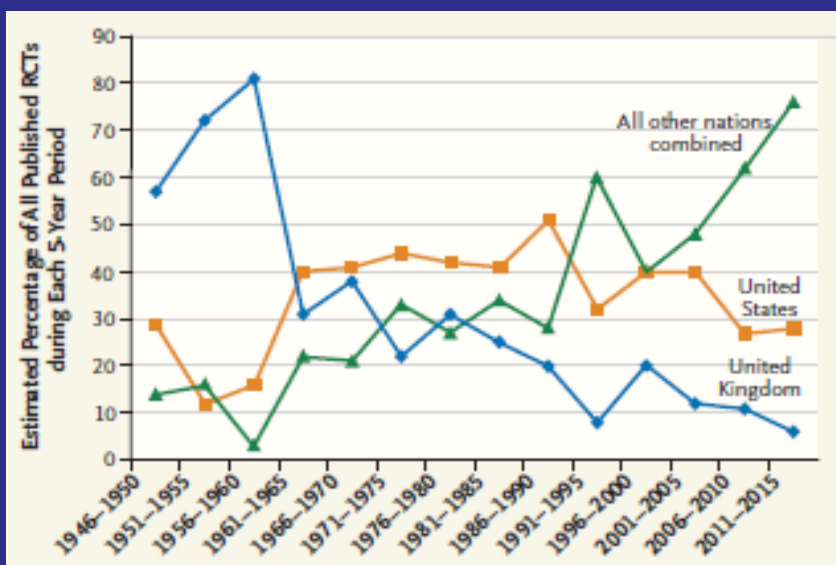
1970 Προοπτικές, Τυχαιοποιημένες
Μελέτες

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES,
AND THE HIERARCHY OF RESEARCH DESIGNS



The NEW ENGLAND
JOURNAL *of* MEDICINE

Χρηματοδότηση - Θέση Μελετών



*The NEW ENGLAND
JOURNAL of MEDICINE*

ΕΠΙΘΕΤΙΚΕΣ ΘΕΡΑΠΕΙΕΣ

'70 - 2000



Λέμφωμα Hodgkin

More is better

ABVD > MOPP 1975

MOPP - ABVD x12 !!

MOPP/ABV x8 !

BEACOPP x8

Μεγαθεραπεία !

2002 Λέμφωμα Hodgkin Αμφιβολίες...

EDITORIAL

**Advanced Hodgkin's Disease: ABVD Is Better,
Yet Is Not Good Enough!**

The NEW ENGLAND
JOURNAL *of* MEDICINE

Volker Diehl

ΣΧΕΔΙΑΣΜΟΣ

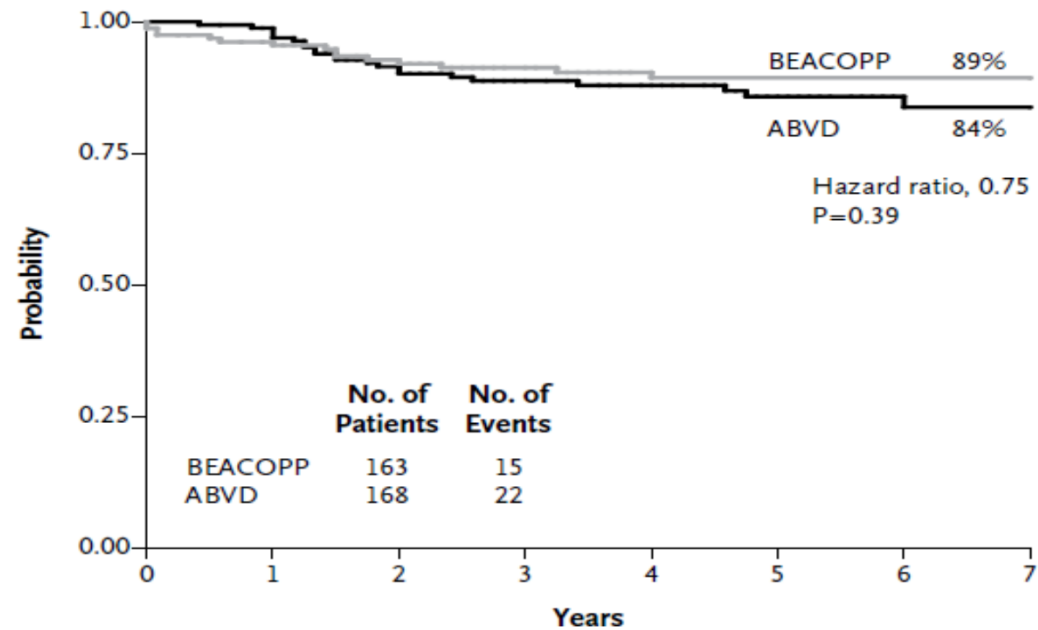
More is not necessarily better !



Hodgkin's Lymphoma — The Great Teacher

Joseph M. Connors, M.D.

B Overall Survival



The NEW ENGLAND
JOURNAL of MEDICINE

Επιθετικά Λεμφώματα

More is better?...2000

'70 CHOP > COP



m BACOD

MACOP - B

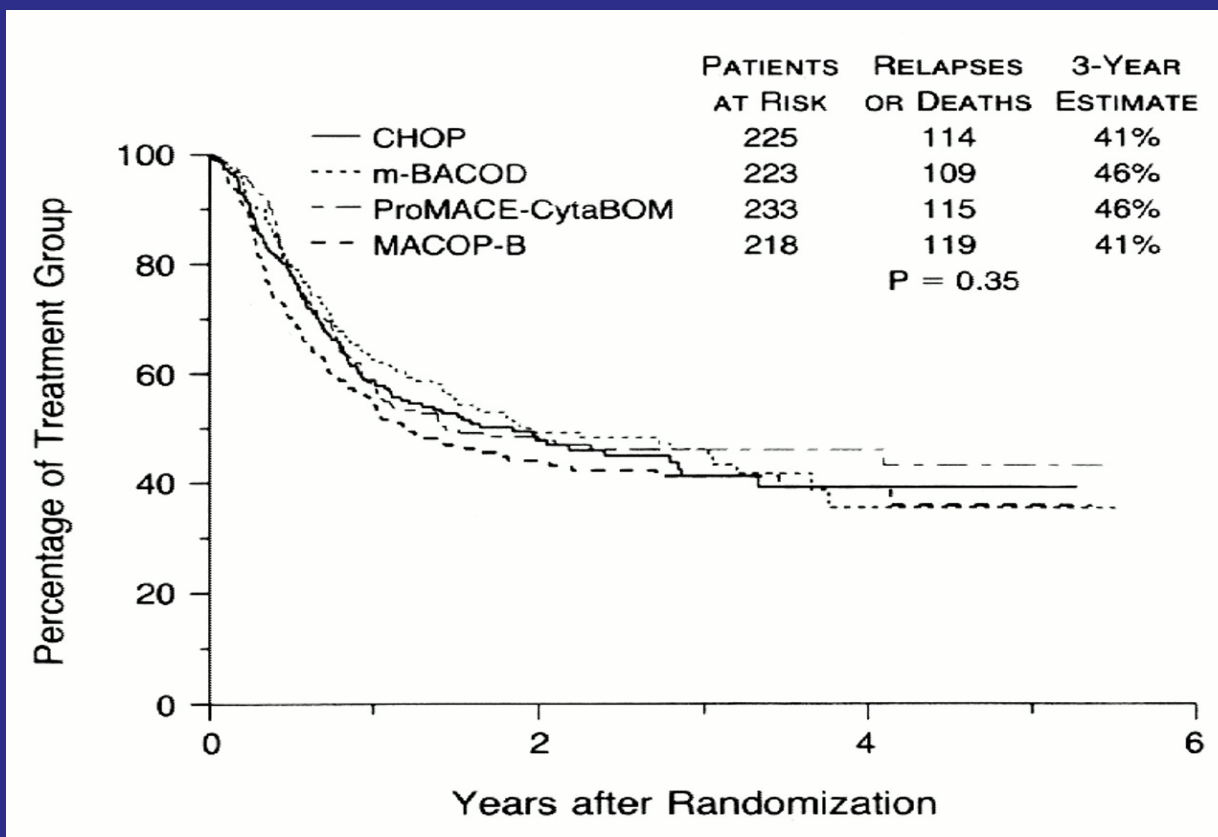
ProMACE - Cytabom



Μεγαθεραπεία !

Επιθετικά Λεμφώματα

1993 more is not better

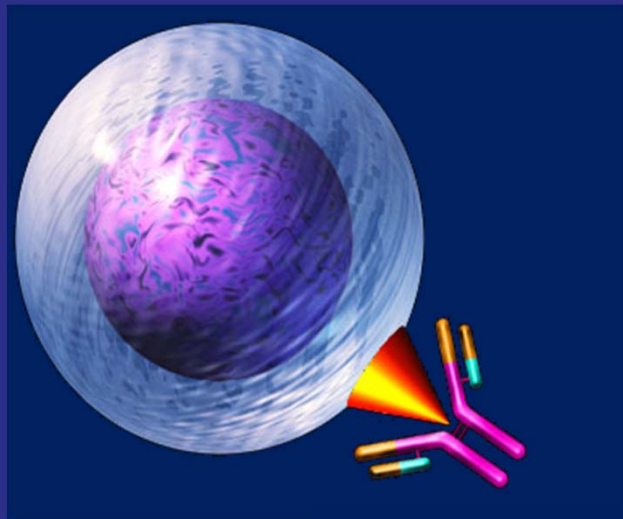


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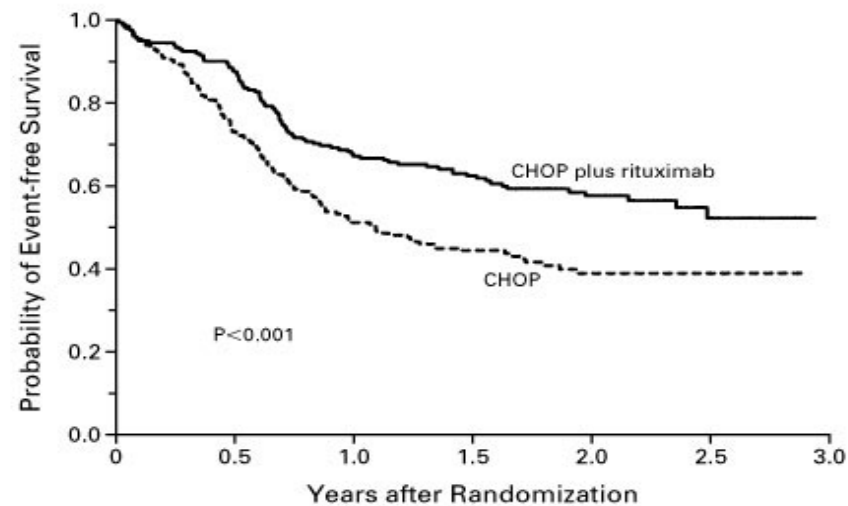
Fisher, R. I. et al. 1993

2000... the different is better

Ανοσοχημειοθεραπεία



Rituximab



No. AT Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

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The greatest derangement of
the mind is to believe in
something because one wishes
it to be so.

~ Louis Pasteur

AZ QUOTES

Έτσι, άλλα 15 χρόνια...
μήπως more is better?

- R/CHOP14
- R/CHOEP
- R/ACVBP
- R/DA-EPOCH

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 31, 2013

VOL. 369 NO. 18

Autologous Transplantation as Consolidation
for Aggressive Non-Hodgkin's Lymphoma

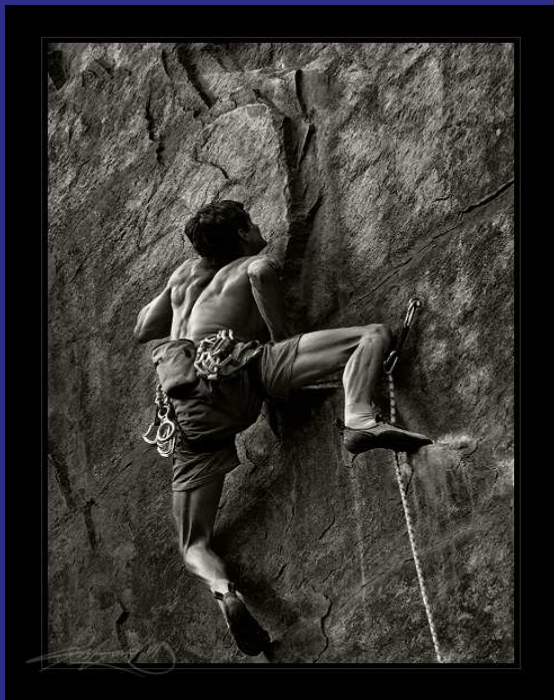
Myeloablation for Lymphoma — Question Answered?

Noel Milpied, M.D.

Κλινικές Μελέτες

Πολύτιμο Εργαλείο αλλά...

Επιλογή - Ασθενείς



Κάθε βεβαιότητα ότι οι προοπτικές μελέτες είναι η μόνη λύση
θα σήμαινε όχι ότι το εκκρεμές κλίνει προς μια κατεύθυνση
αλλά ότι είναι εκτός ελέγχου.

Sir Bradford Hill

Τι Πέραν των Τυχαιοποιημένων Κλινικών Μελετών ?

Z. Μέλλιος



ΣΤΟΝ ΠΡΑΓΜΑΤΙΚΟ ΚΟΣΜΟ

Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry

Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study

Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry

Μελέτες Παρατήρησης

Randomized Clinical Trials and Observational Studies:
Is There a Battle?

There are three principal means of acquiring knowledge: observation, reflection, and experimentation. Observation collects facts; reflection combines them; experimentation verifies the result of that combination.

Denis Diderot (1713-1784)

THE NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Pragmatic Trials

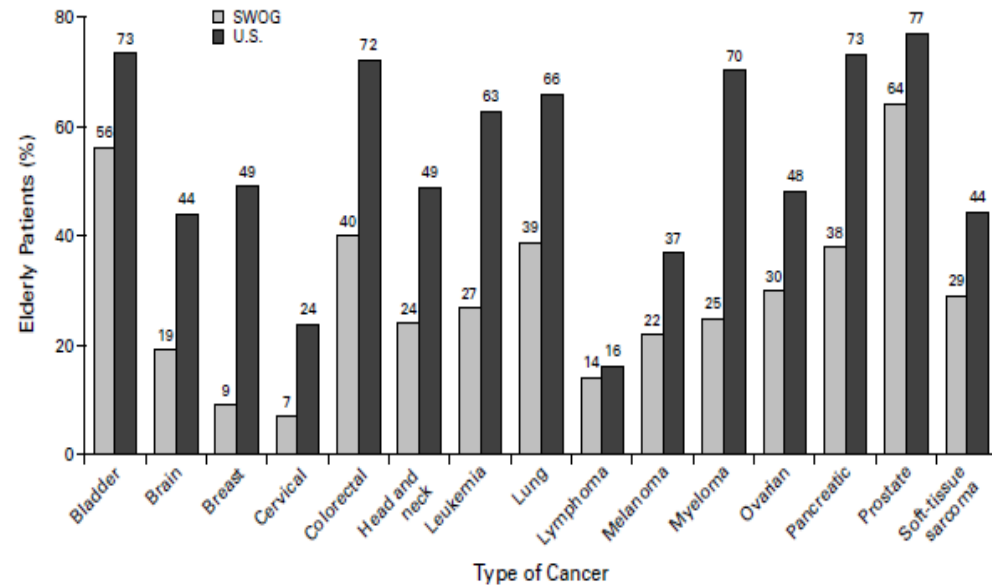
Ρεαλισμός των Μελετών

Pragmatic Trials

- Ερευνητές / Ασθενείς
- Θεραπευτική παρέμβαση
 - Παρακολούθηση
- Ανάλυση αποτελεσμάτων

Special Article

UNDERREPRESENTATION OF PATIENTS 65 YEARS OF AGE OR OLDER
IN CANCER-TREATMENT TRIALS



The NEW ENGLAND
JOURNAL of MEDICINE

Ηλικιωμένοι

TO THE EDITOR:

Survival outcomes in the very elderly with DLBCL prior to and after the introduction of rituximab: a US population-based study

Diffuse large B-cell lymphoma in the elderly

How to treat old MCL patients:
one size fits it all?

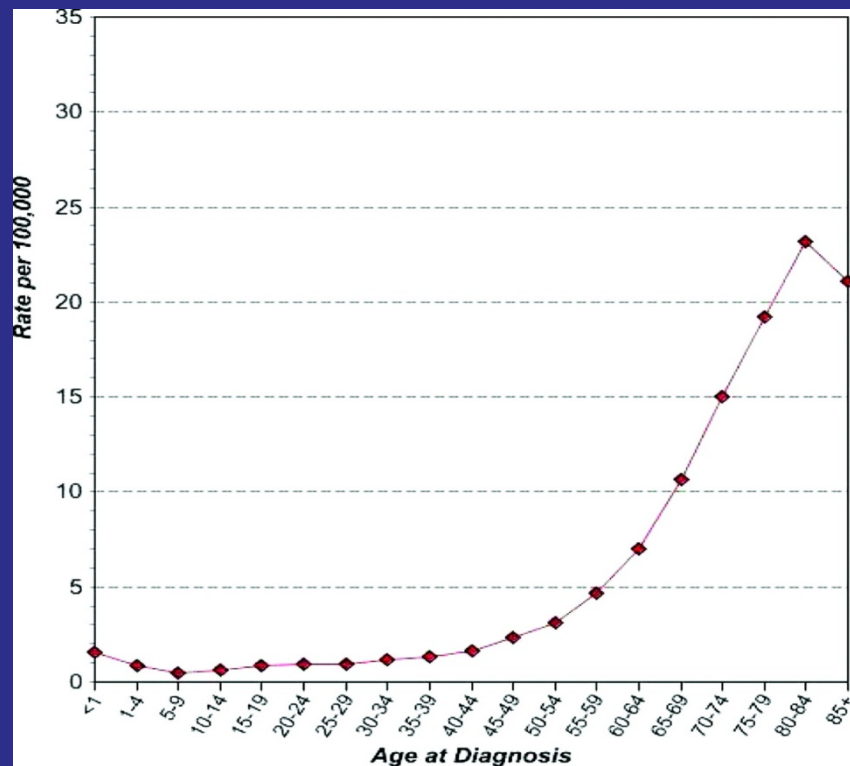
Treatment of Hodgkin
lymphoma in older patients

Treatment of older patients with chronic lymphocytic
leukemia: key questions and current answers

4th INTERNATIONAL CONFERENCE ON
HEMATOLOGIC MALIGNANCIES AT OLDER AGE: BIOLOGY AND THERAPY

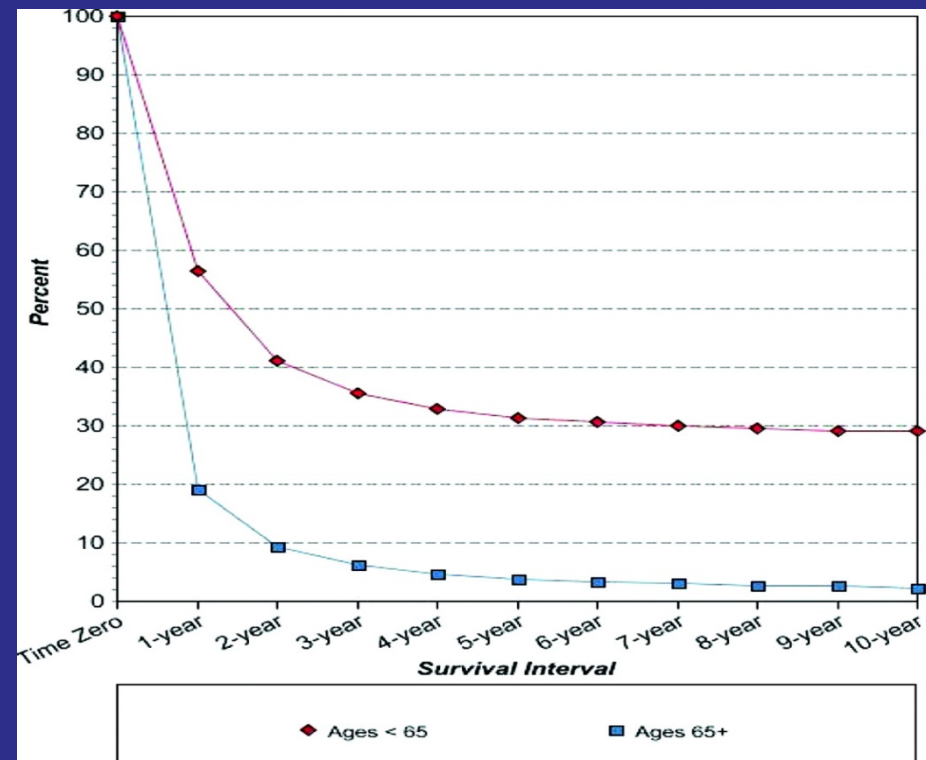
ΟΞΕΙΑ ΛΕΥΧΑΙΜΙΑ

Επίπτωση / Ηλικία 2000-2005



Juliusson, G. et al. Blood 2009;113:4179-4187

Survival rates for AML by age group, 1988-2004

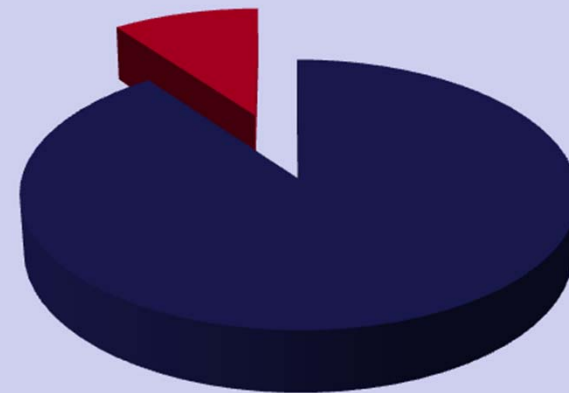


Klepin, H. D. et al. Oncologist 2009;14:222-232

"TOLERABLE" Toxicity ?

Chemoimmunotherapy Is Not Dead Yet in Chronic Lymphocytic Leukemia

Chemoimmunotherapy May Not Be Dead Yet in Chronic Lymphocytic Leukemia, But Fludarabine Plus Cyclophosphamide Plus Rituximab Is Potentially Facing Life Support



ΑΙΤΙΑ ΔΙΑΚΟΠΗΣ ΘΕΡΑΠΕΙΑΣ

ΣΤΙΣ ΜΕΛΕΤΕΣ ...Εξέλιξη της νόσου



ΣΤΟΝ ΠΡΑΓΜΑΤΙΚΟ ΚΟΣΜΟ... "Managable" Toxicity

Table 2. Reasons for discontinuation first KI

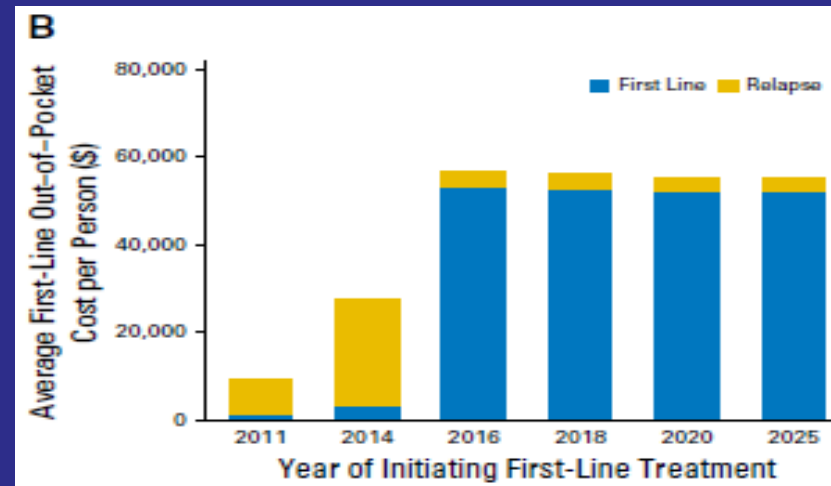
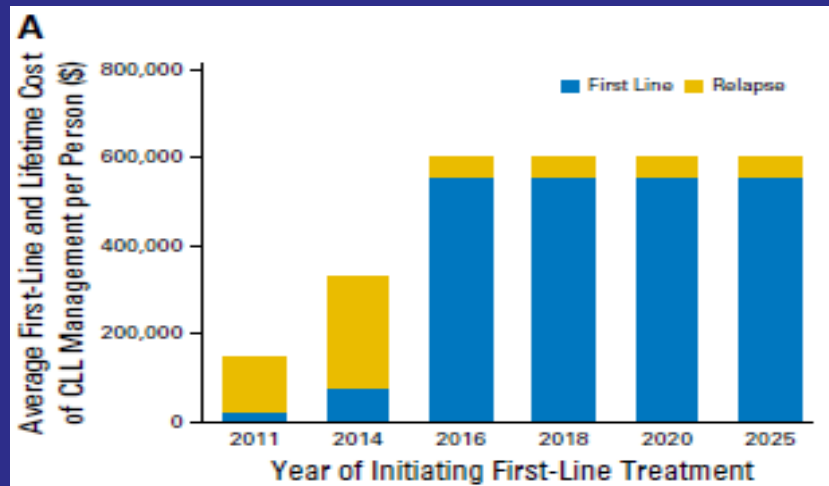
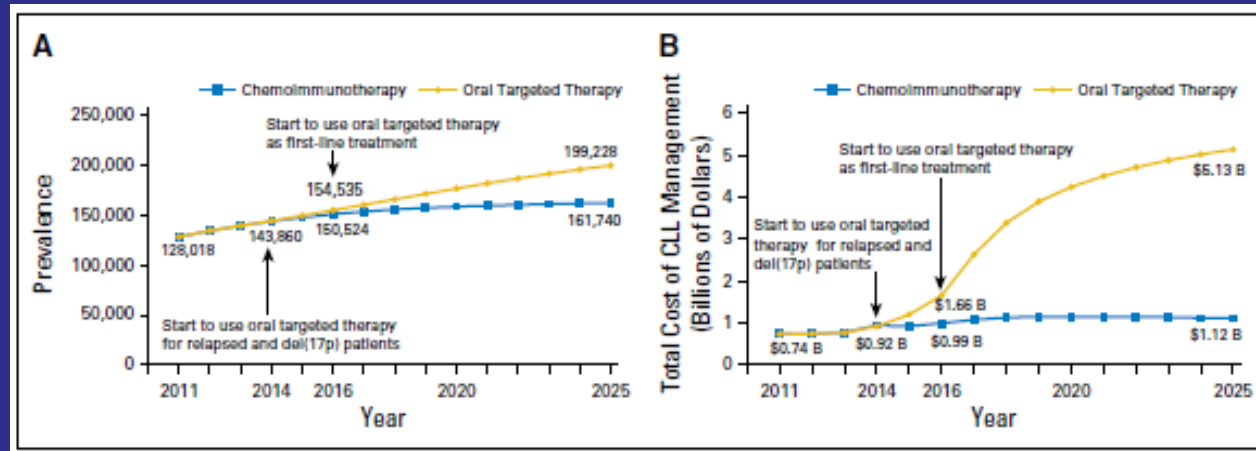
	Ibrutinib (n = 258 discontinuation events)	Idelalisib (n = 58 discontinuation events)
Toxicity	51.2% (n = 132)	44.8% (n = 26)
Progression	20.5% (n = 53)	27.6% (n = 16)
Other/death not secondary to progression	11% (n = 28)	6.9% (n = 4)
MD/patient preference	6.2% (n = 16)	17.2% (n = 10)
Richter's transformation	5.0% (n = 13)	3.5% (n = 2)
Stem cell transplant/CAR T cells	3.9% (n = 10)	0%
Secondary malignancy	1.1% (n = 3)	0%
Cost	1.1% (n = 3)	0%

Key Points

- Toxicity was the most common reason for discontinuation of ibrutinib or idelalisib in treated patients with CLL.
- KI-intolerant patients, but less so those with CLL progression, can be successfully treated with an alternate KI.

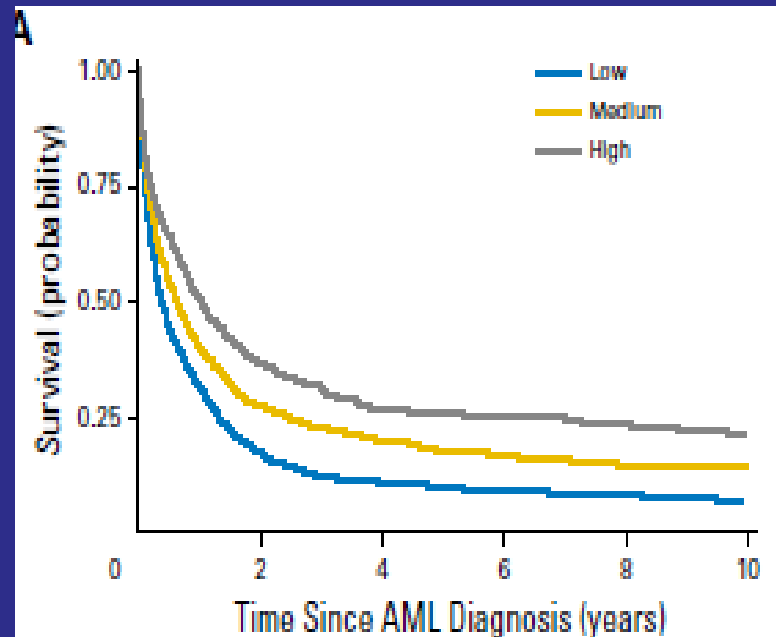
ΚΟΣΤΟΣ !

Justum Pretium



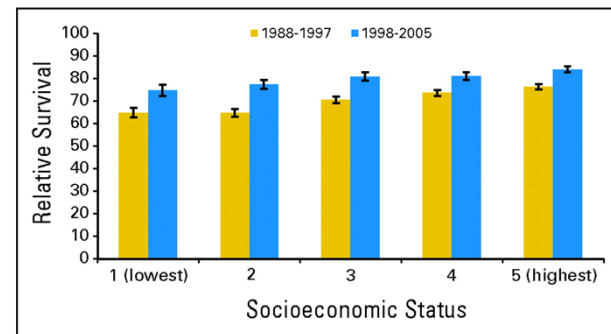
Κοινωνική / Οικονομική Κατάσταση

Οξεία Λευχαιμία



Οζώδη Λεμφώματα

Fig 1. Five-year relative survival by socioeconomic status and period of diagnosis, 1988 to 1997 and 1998 to 2005, California



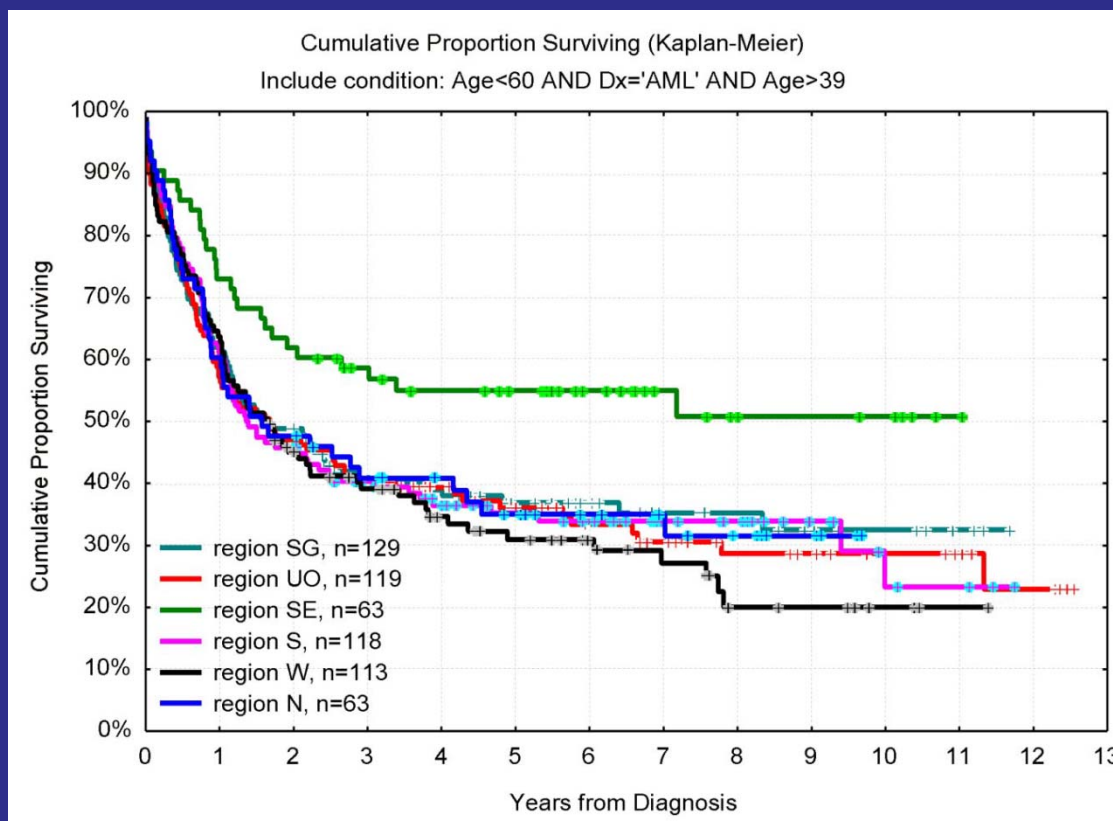
Keegan, T.H.M. et al. J Clin Oncol; 27:3044-3051 2009

Copyright © American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY

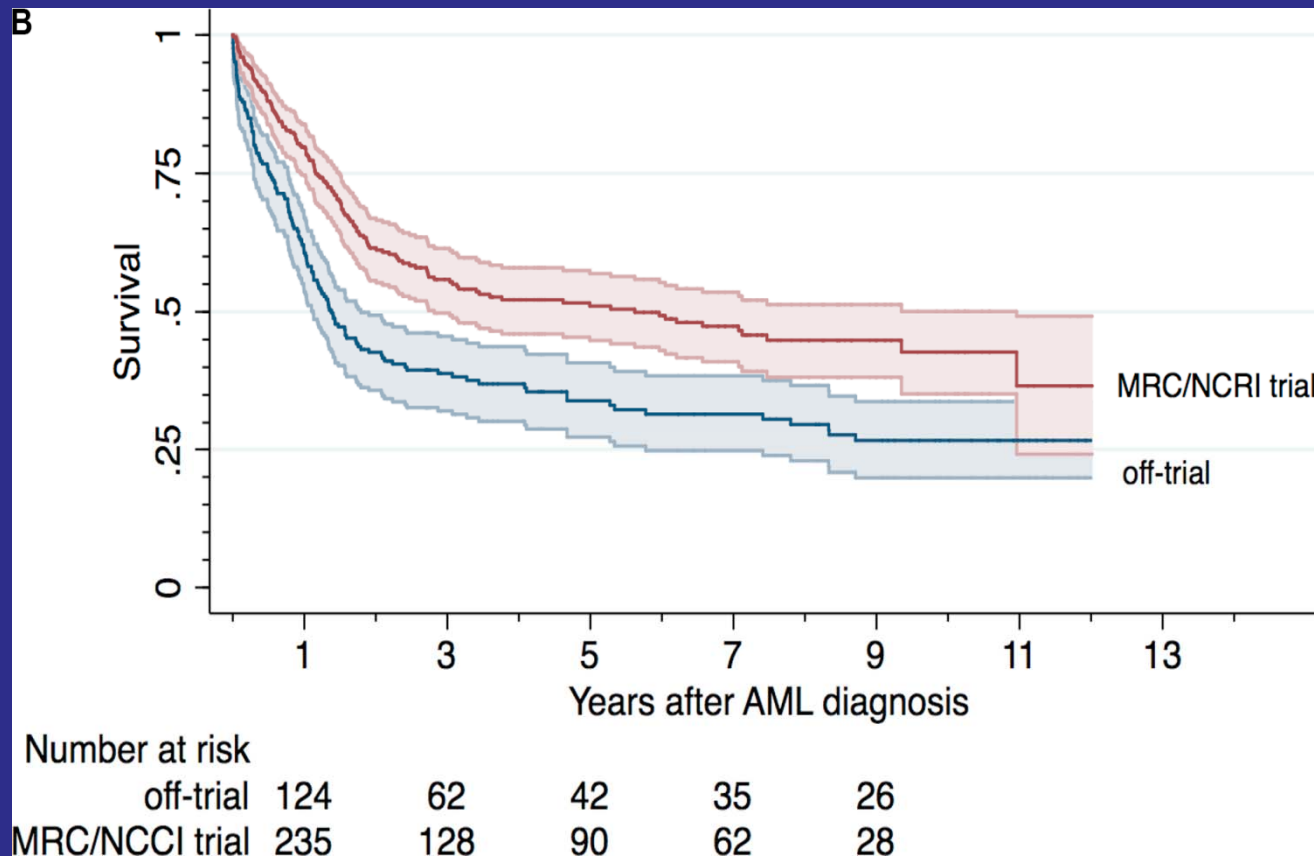
Οξεία Λευχαιμία / Γεωγραφική περιοχή

ACUTE MYELOID LEUKEMIA IN THE REAL WORLD



Juliusson G. et al. Swedish AL Registry, 2015

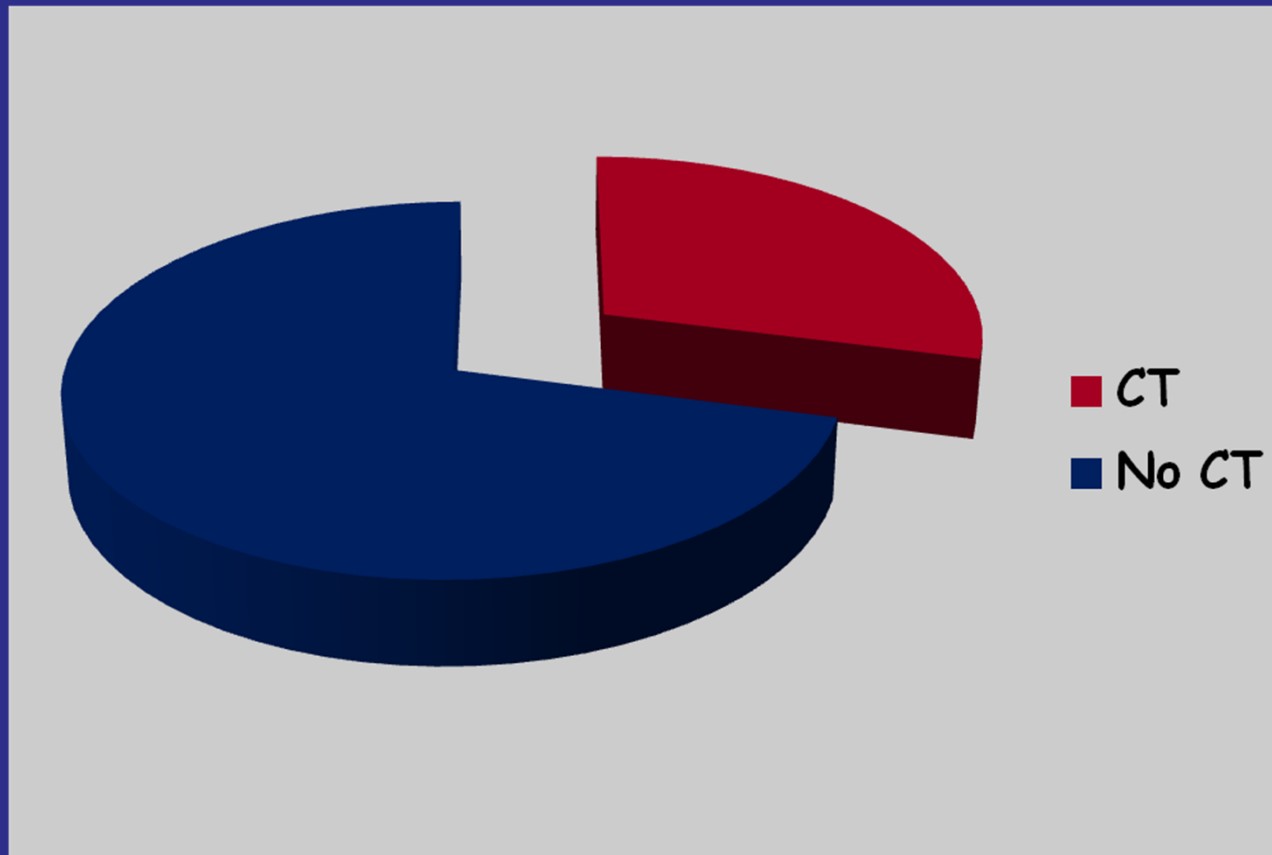
Οξεία Λευχαιμία 2000-2013 867 pts



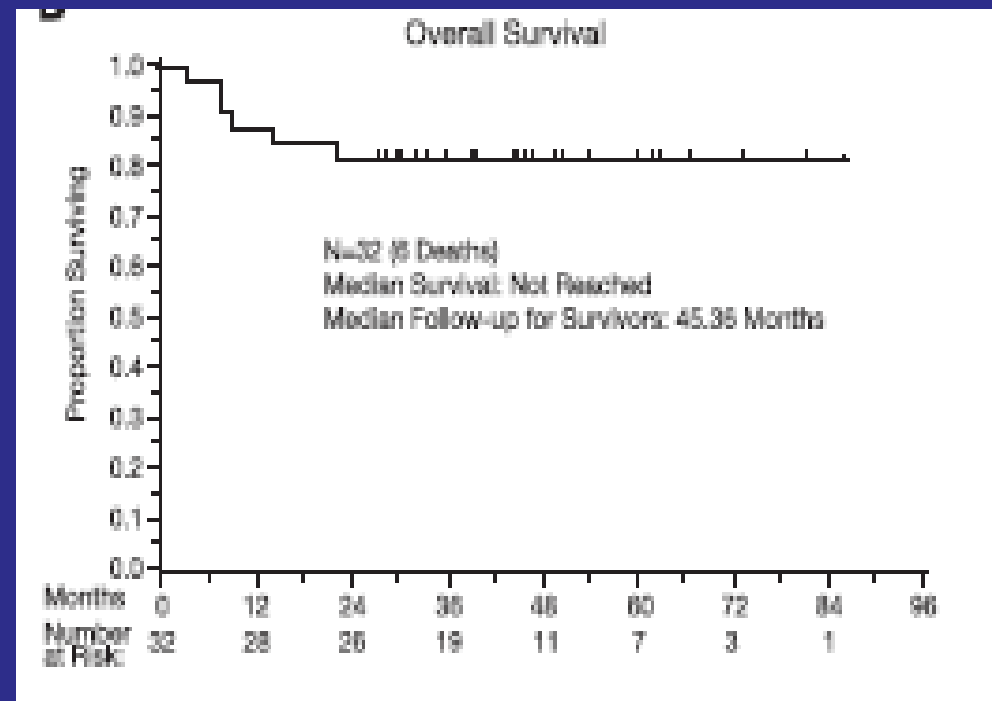
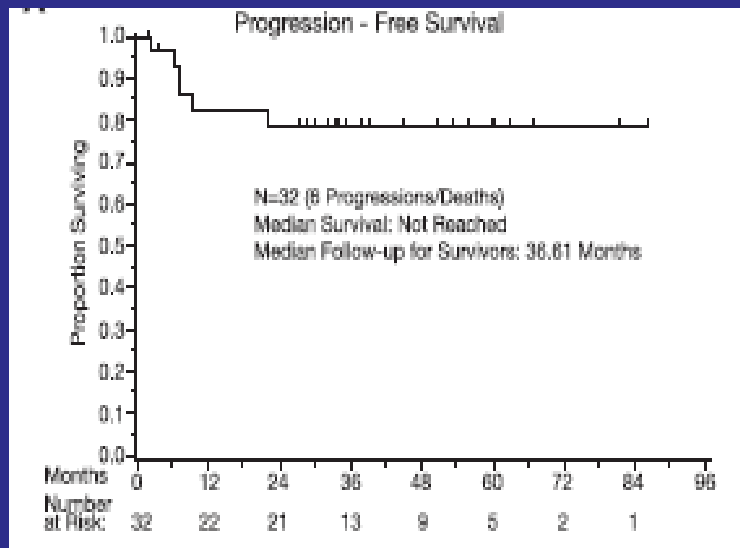
Danish National Leukemia Registry 2016

Οξεία Λευχαιμία

% Θεραπείας στον κόσμο των Ινδιών



Λεμφώματα ΚΝΣ στον κόσμο του Memorial

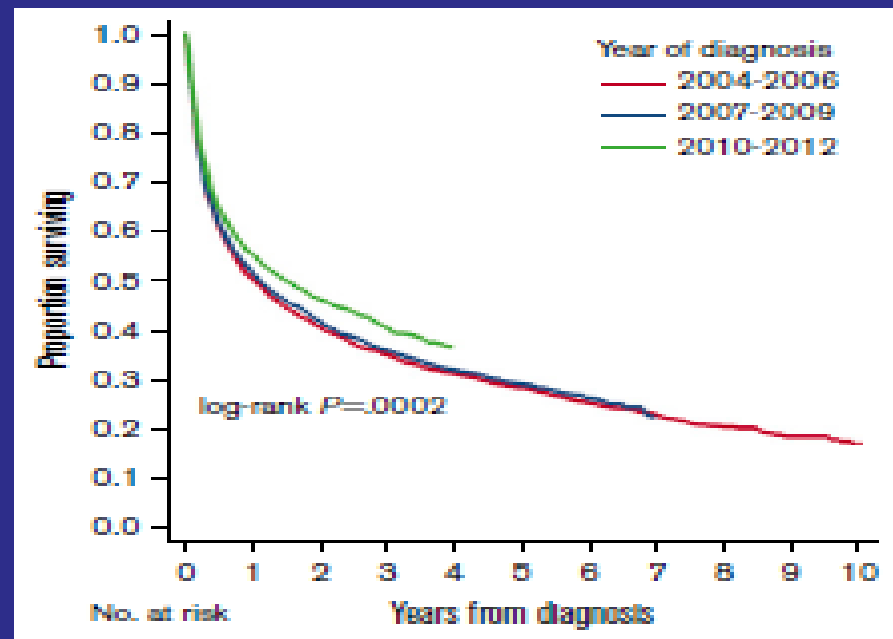
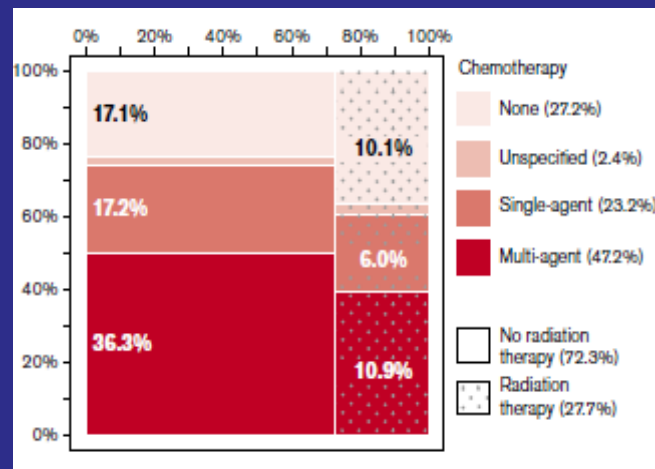


Omuro A. et al 2015

Λεμφώματα ΚΝΣ

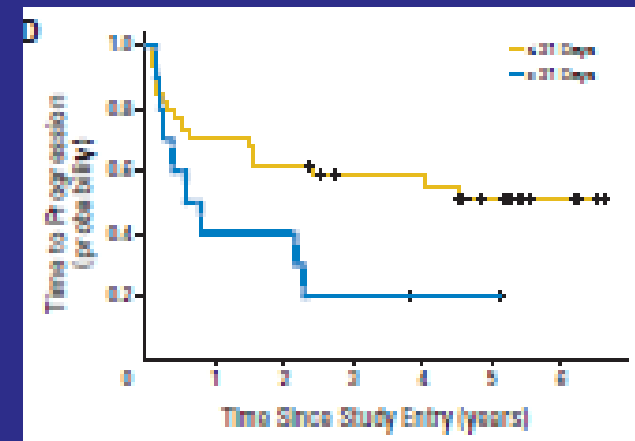
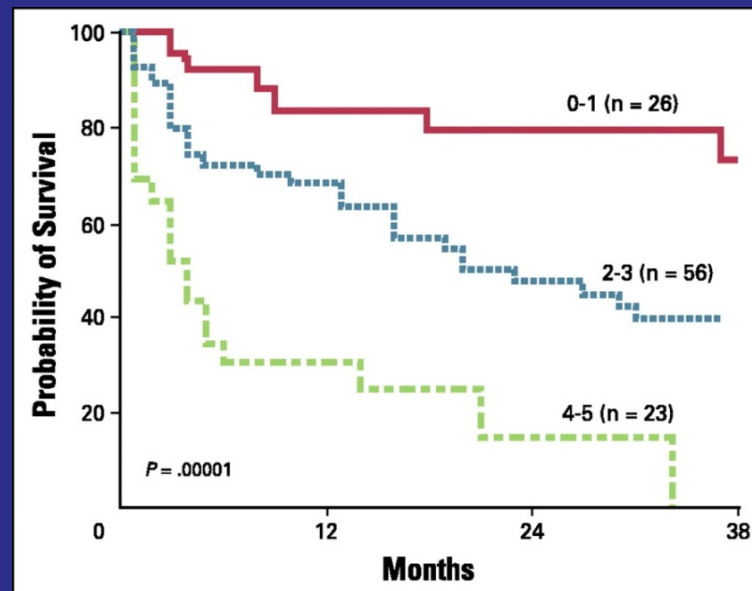
στον πραγματικό κόσμο

9165 -ve Pts ! National Cancer Database



Λεμφώματα ΚΝΣ στον πραγματικό κόσμο

- ✓ ΗΛΙΚΙΑ >60
- ✓ PS >1
- LDH >1
- CSF Protein
- ✓ Βαθιές εντοπίσεις



Batchelor T. et al.

CALGB 2013

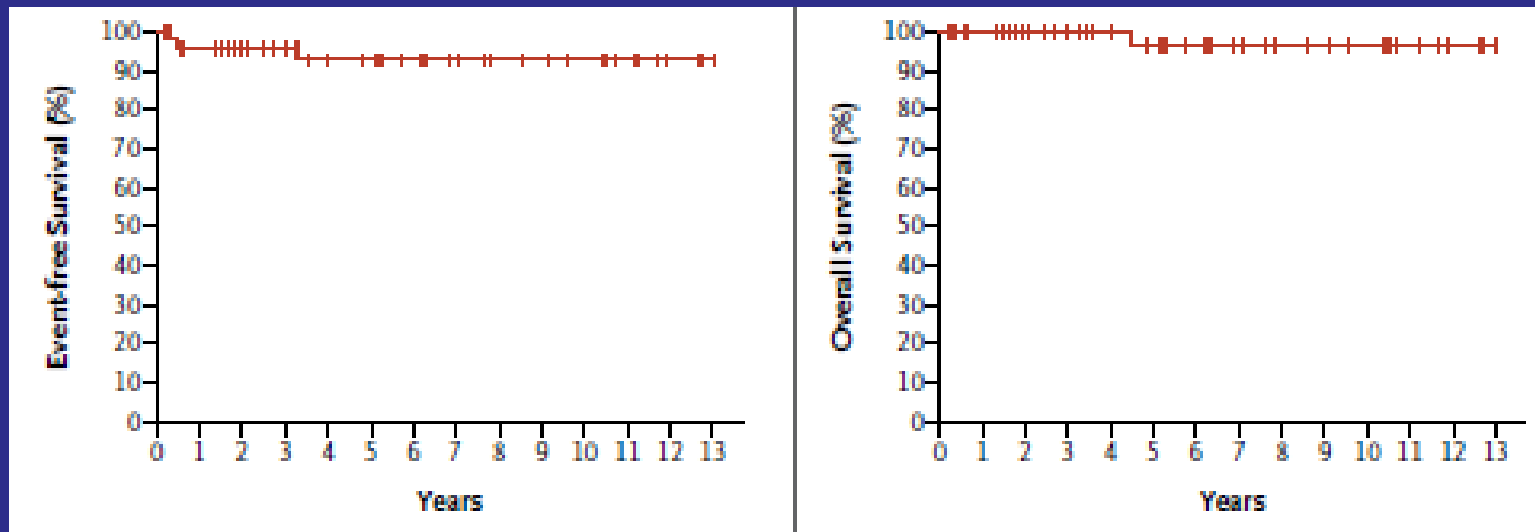
JOURNAL OF CLINICAL ONCOLOGY

Πρωτοπαθή Λεμφώματα Μεσοθωρακίου στον κόσμο του NCI

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose-Adjusted EPOCH-Rituximab Therapy
in Primary Mediastinal B-Cell Lymphoma



Dunleavy K. et al. 2013

Κριτήρια Επιλογής - Καταλληλότητας

Re-Evaluating Eligibility Criteria for Oncology Clinical Trials:
Analysis of Investigational New Drug Applications in 2015

Broadening Eligibility Criteria to Make Clinical Trials More
Representative: American Society of Clinical Oncology and
Friends of Cancer Research Joint Research Statement

Τί σημαίνει η επιβεβαίωση ή η απόρριψη του κύριου ερωτήματος που θέτει μια κλινική μελέτη

Χαρά Γιατρά
Αιματολογική και Λεμφωμάτων Κλινική/MMMO
Γ.Ν.Α. 'Ο Ευαγγελισμός'



ΕΡΜΗΝΕΙΑ ΑΠΟΤΕΛΕΣΜΑΤΩΝ

Εντυπώσεις... Πραγματικότητα

Progress in Cancer Care: The Hope,
the Hype, and the Gap Between Reality
and Perception

SUBSTANTIAL SIGNIFICANCE OF THE DIFFERENCE BETWEEN
SUBSTANTIAL AND SIGNIFICANT

FREEDOM FROM PROGRESSION-FREE SURVIVAL

IF THE DEATH RATE IS REDUCED, HOW COME THEY ALL DIED?

"TOLERABLE" TOXICITY

ΔΡΑΣΤΙΚΗ ΟΥΣΙΑ

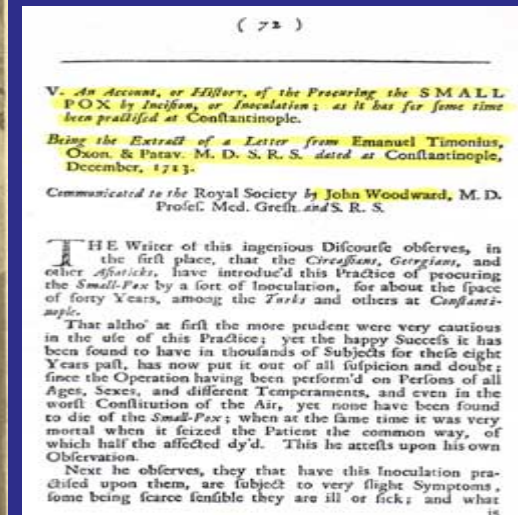


An Inquiry Into the Causes and Effects of the Variolæ Vaccinæ, Or Cow-Pox.1798

Edward Jenner 1749-1823



Εμβολιαμός του James Phillips (1796)





The New England Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 238

JUNE 3, 1948

Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§

ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.||

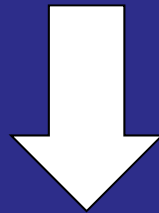
BOSTON

Brit. J. Haemat., 1961, 7, 73.

The Use of Chlorambucil and Steroids in the Treatment of Chronic Lymphocytic Leukaemia

D. A. G. GALTON, E. WILTSHAW, L. SZUR[‡] AND J. V. DACE

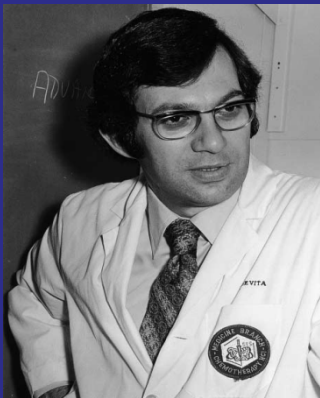
The Chester Beatty Research Institute (the Royal Cancer Hospital) and the Royal Marsden Hospital;* the Department of Radiotherapy, Hammersmith Hospital,† and the Department of Haematology, Postgraduate Medical School of London**



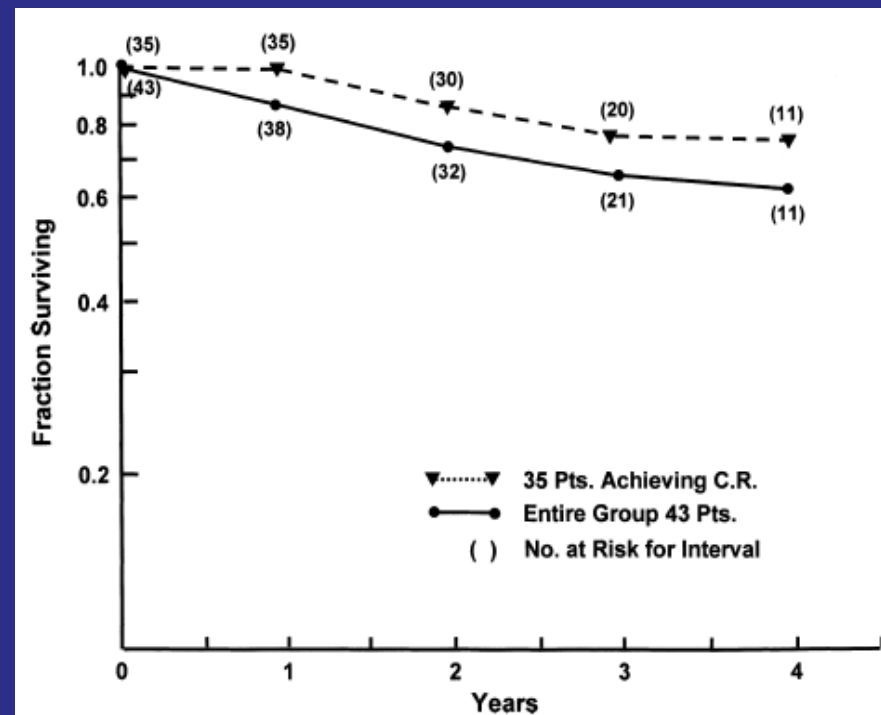
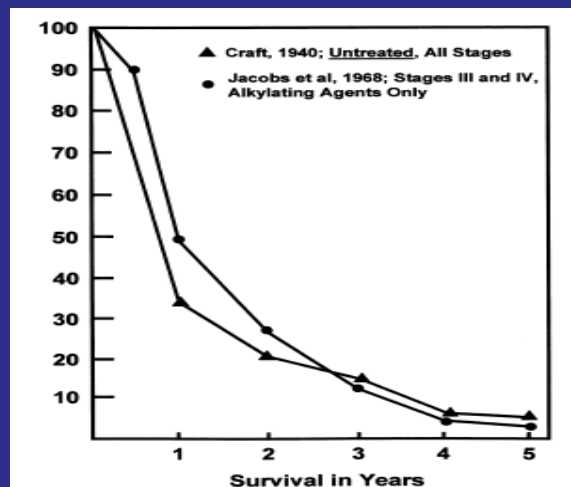
Chlorambucil + Rituximab / Obinutuzumab

Chlorambucil vs Ibrutinib !

ΜΟΡΡ - Λέμφωμα Hodgkin - '60



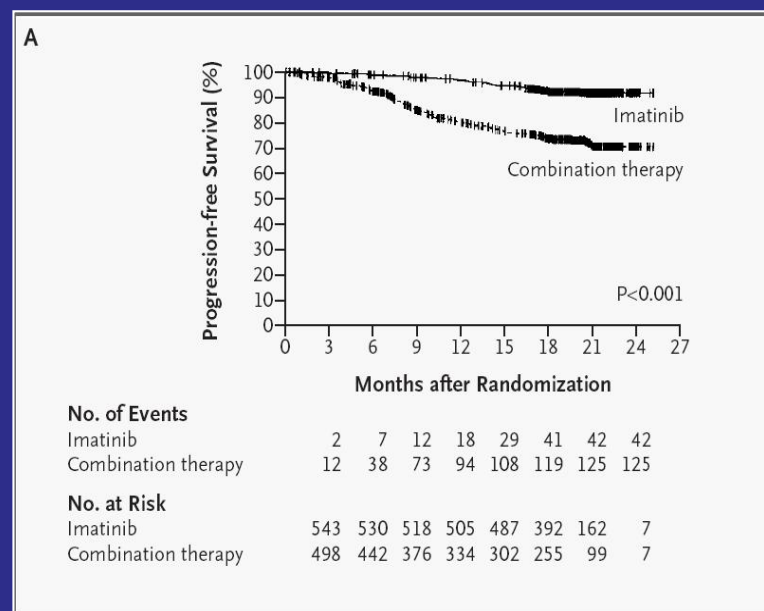
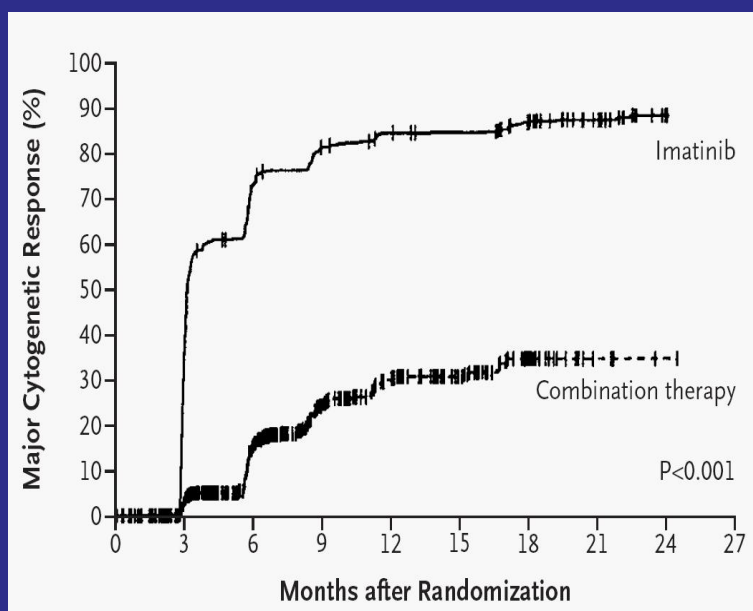
V. De Vita



Progress in the Treatment of Hodgkin's Lymphoma

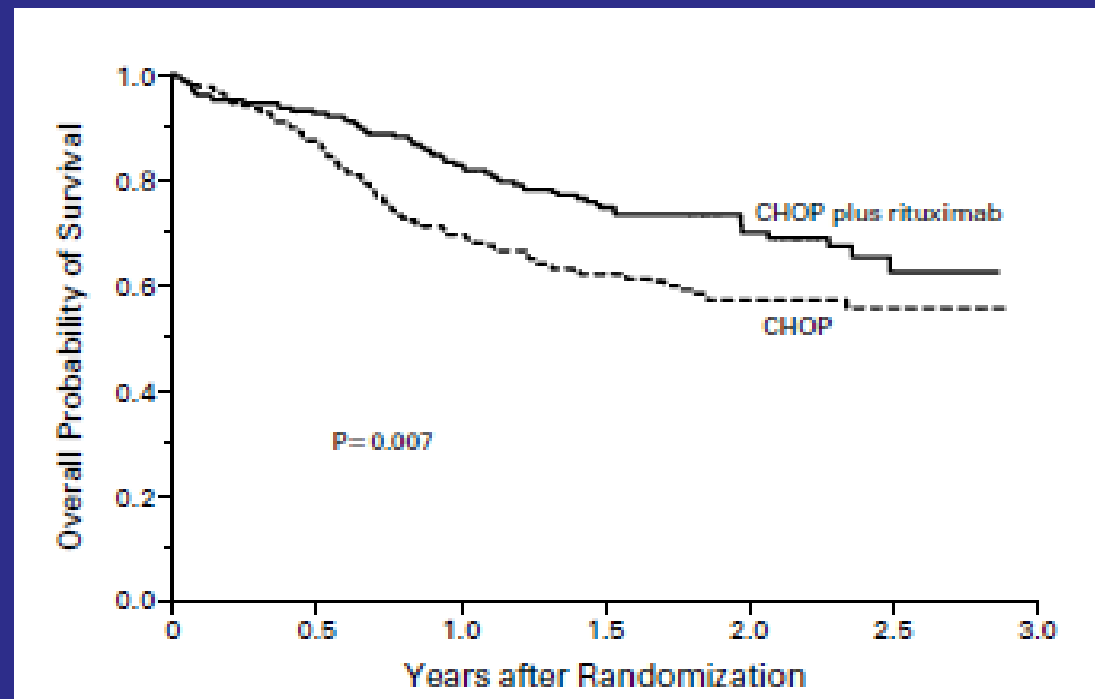
Dan L. Longo, M.D., and Vincent T. DeVita, Jr., M.D.

Imatinib XMA 2003



The NEW ENGLAND
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Rituximab - Λεμφώματα



Coiffier, B. et al. 2002

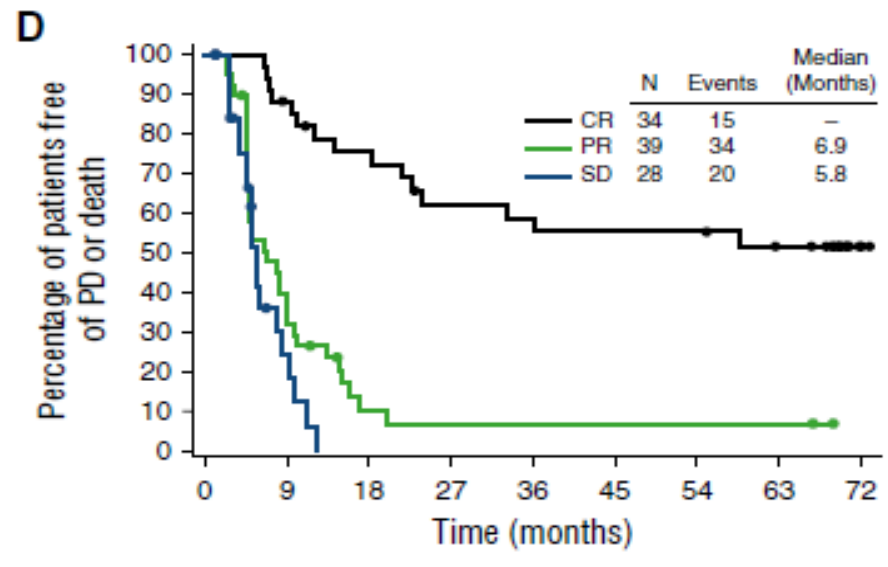
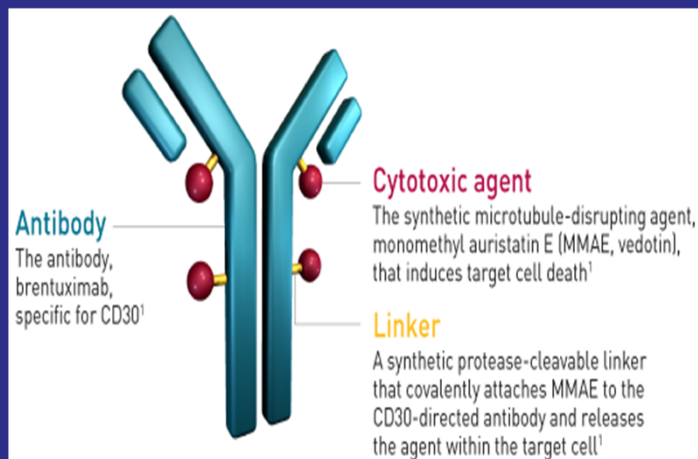
The NEW ENGLAND
JOURNAL of MEDICINE

Anti CD30 - Λέμφωμα Hodgkin

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas



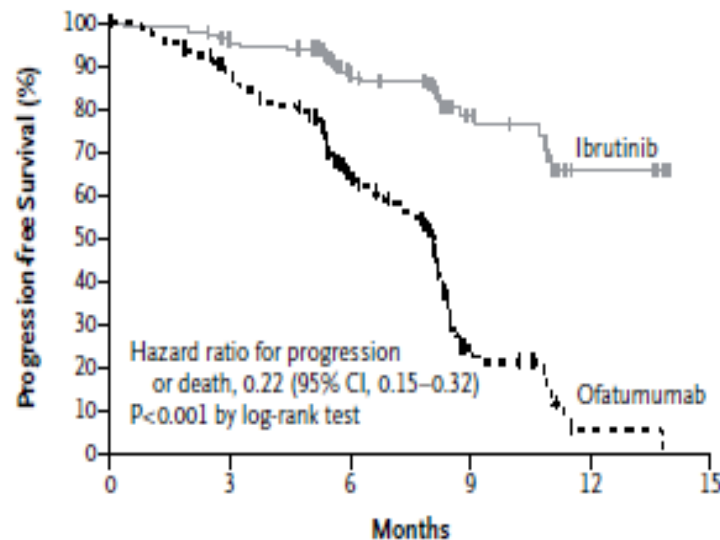
blood

Ibrutinib - XMM

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

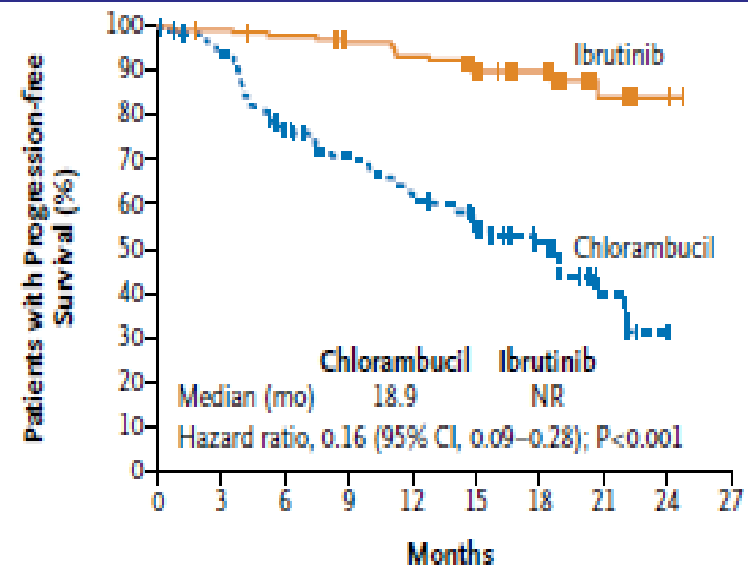


J. Byrd et al. 2014

THE NEW ENGLAND JOURNAL of MEDICINE

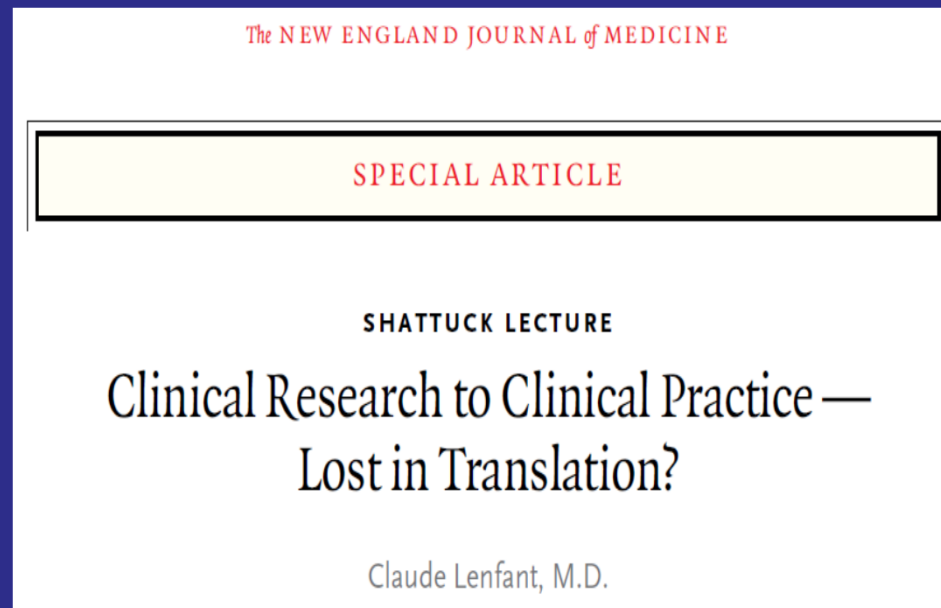
ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia



J. A. Burger et al. 2015

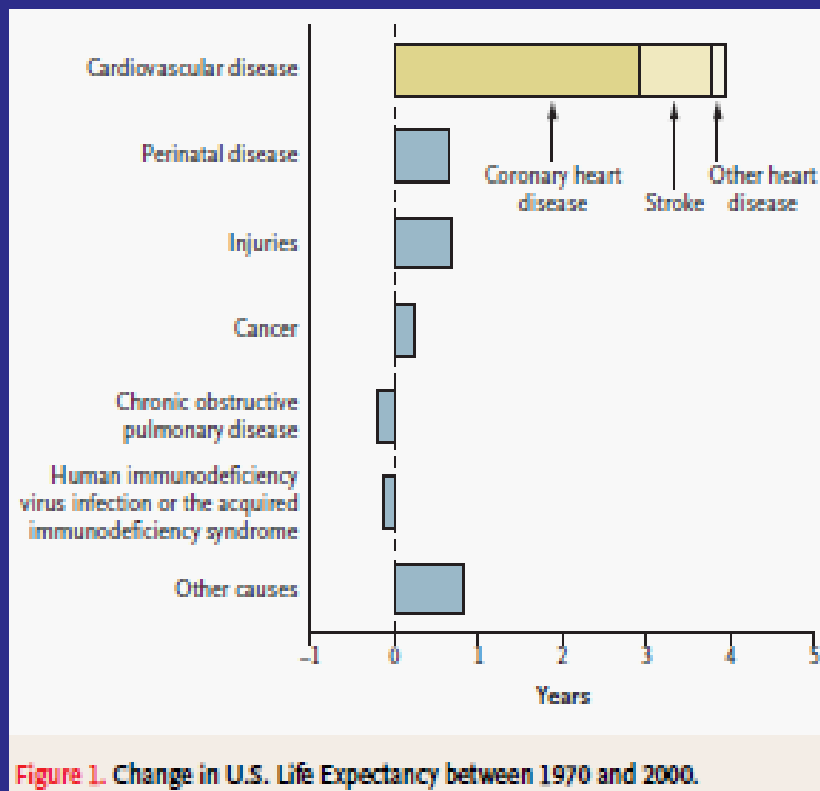
ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ: ΠΩΣ ΕΠΗΡΕΑΖΟΥΝ ΤΗΝ ΚΑΘΗΜΕΡΙΝΗ ΠΡΑΚΤΙΚΗ



ΤΣΩΝΗΣ ΙΩΑΝΝΗΣ, ΕΙΔΙΚΕΥΟΜΕΝΟΣ
ΑΙΜΑΤΟΛΟΓΙΑΣ

Από τις Μελέτες ... στην Κοινότητα Μήπως χανόμαστε στη μετάφραση ?

Medicine is Science and Art



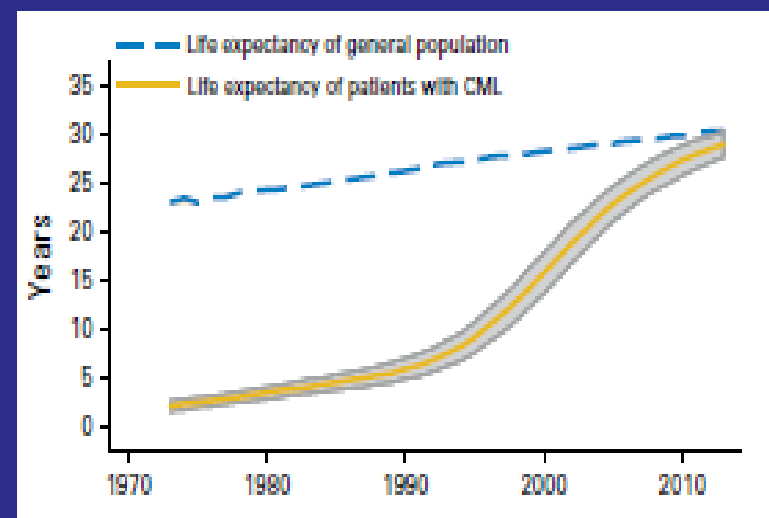
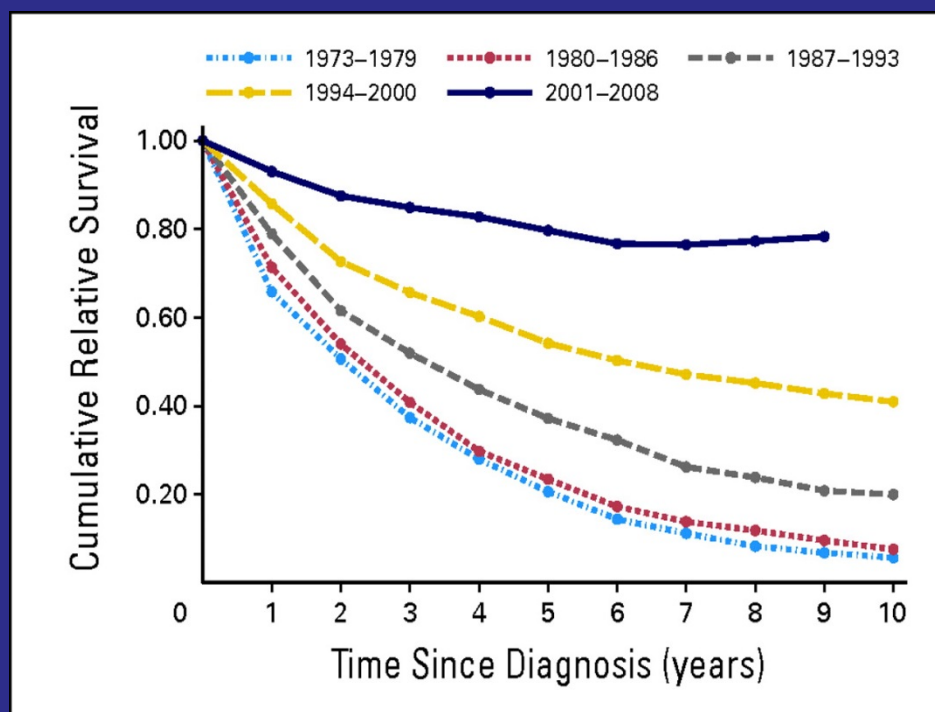
Που είναι όλη η σοφία που
χάσαμε μέσα στη γνώση;
Που είναι όλη η γνώση που
χάσαμε μέσα στην πληροφόρηση;

T.S. Eliot

Χρόνια Μυελογενής Λευχαιμία

Success story !

Swedish Cancer Registry 1973-2013, 2662 pts



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Björkholm M. et al. 2011

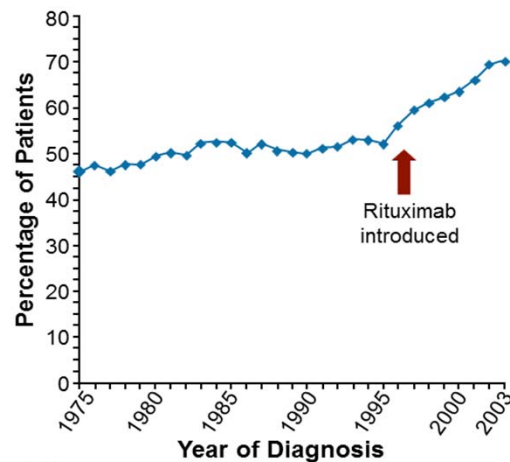
Bower H. et al. 2016

Λεμφώματα

ΙΝΔΙΕΣ

NHL: Increase in Survival Over Time

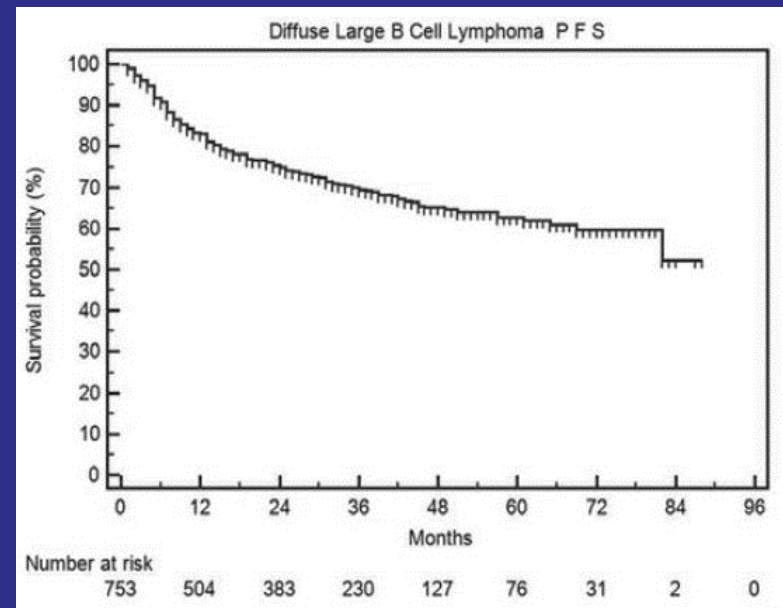
Rate of 5-Year Relative Survival, 1975-2003*



NHL = non-Hodgkin lymphoma.

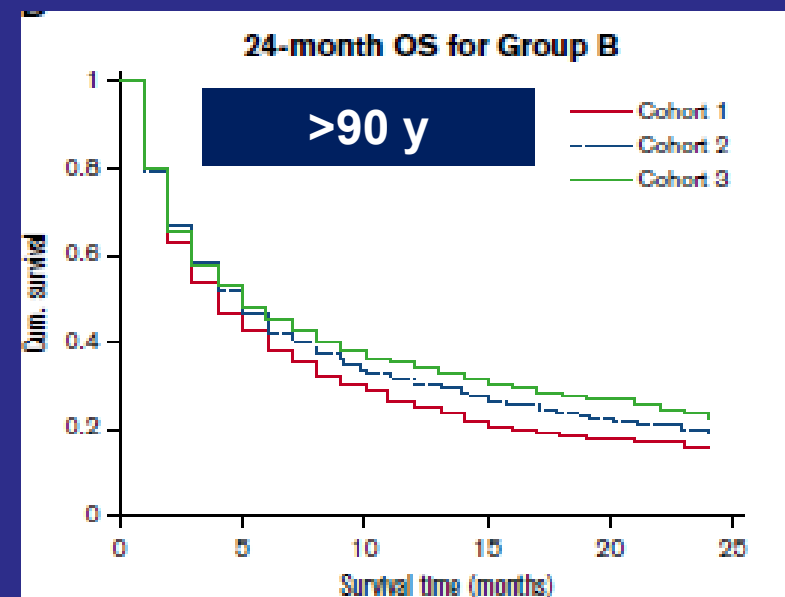
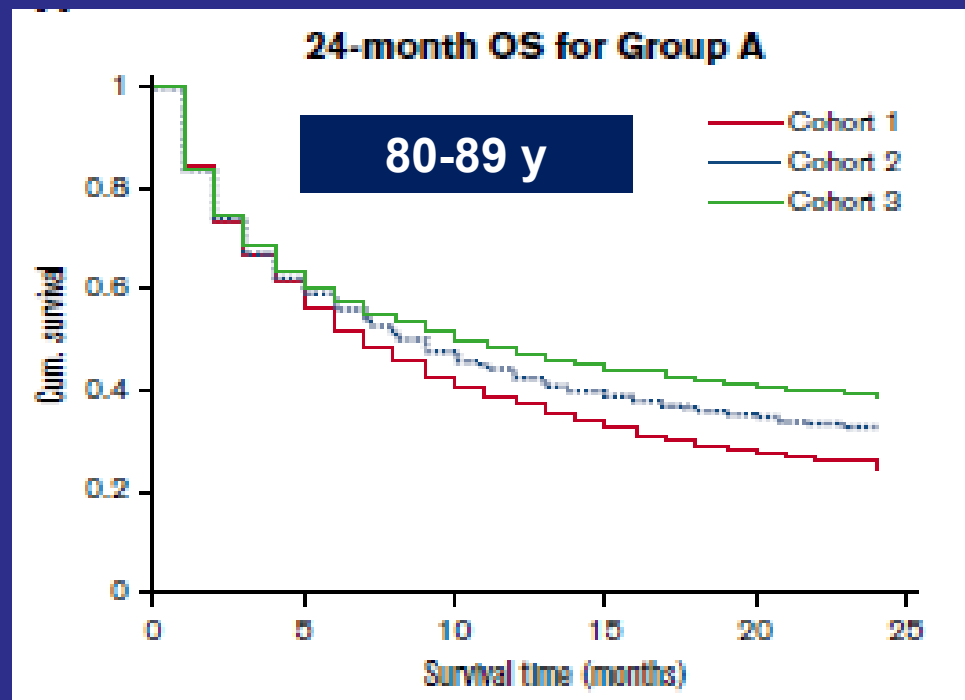
* Data represent patients of all ages, all races, and both sexes.

SEER Database. www.seer.cancer.gov.



Λεμφώματα - Υπερήλικες !

National Cancer Institute, 1983-2013 - 14396 pts



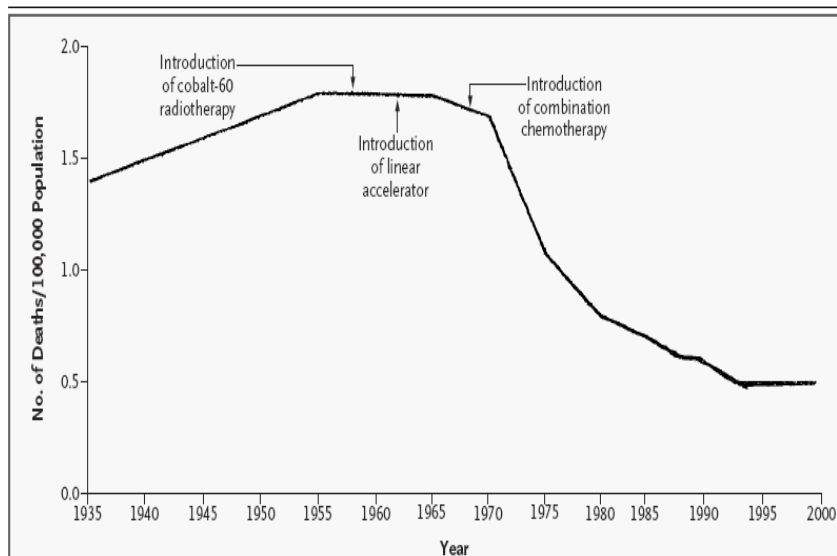
Gin U. and Martin MG 2017

Λέμφωμα Hodgkin

THE NEW ENGLAND JOURNAL of MEDICINE

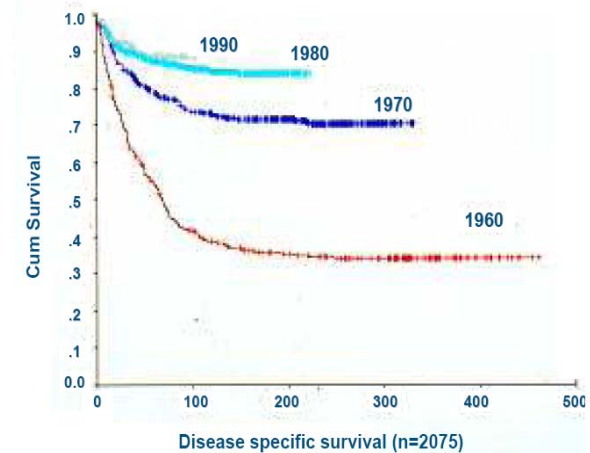
EDITORIAL

Progress in the Treatment of Hodgkin's Lymphoma



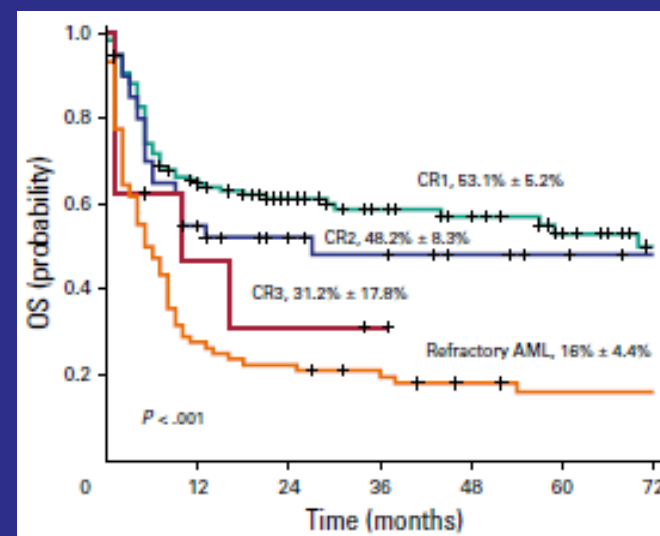
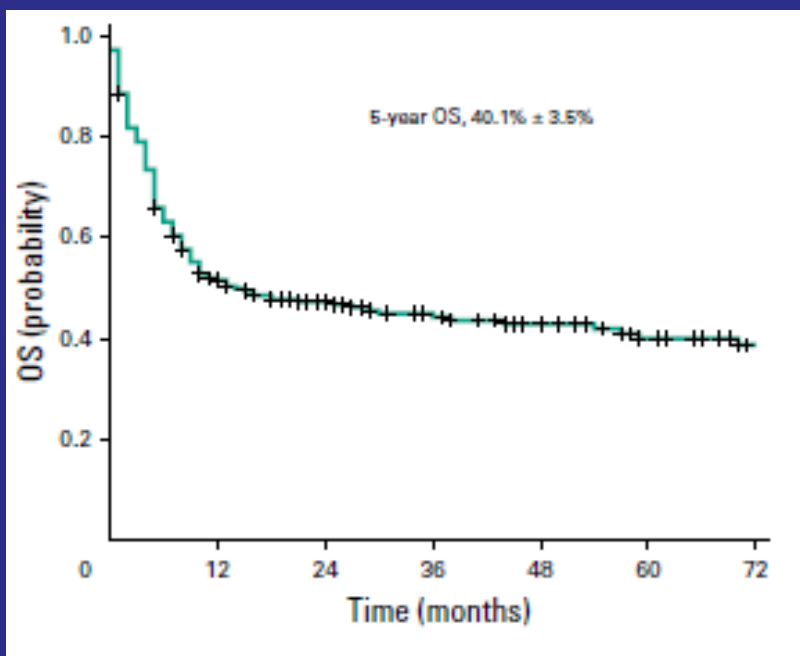
Rates of Death from Hodgkin's Disease, 1935 through 2000.

Values have been adjusted for the age of the 1970 population. Data are from the Surveillance, Epidemiology, and End Results Program and the National Cancer Institute.



GHSg

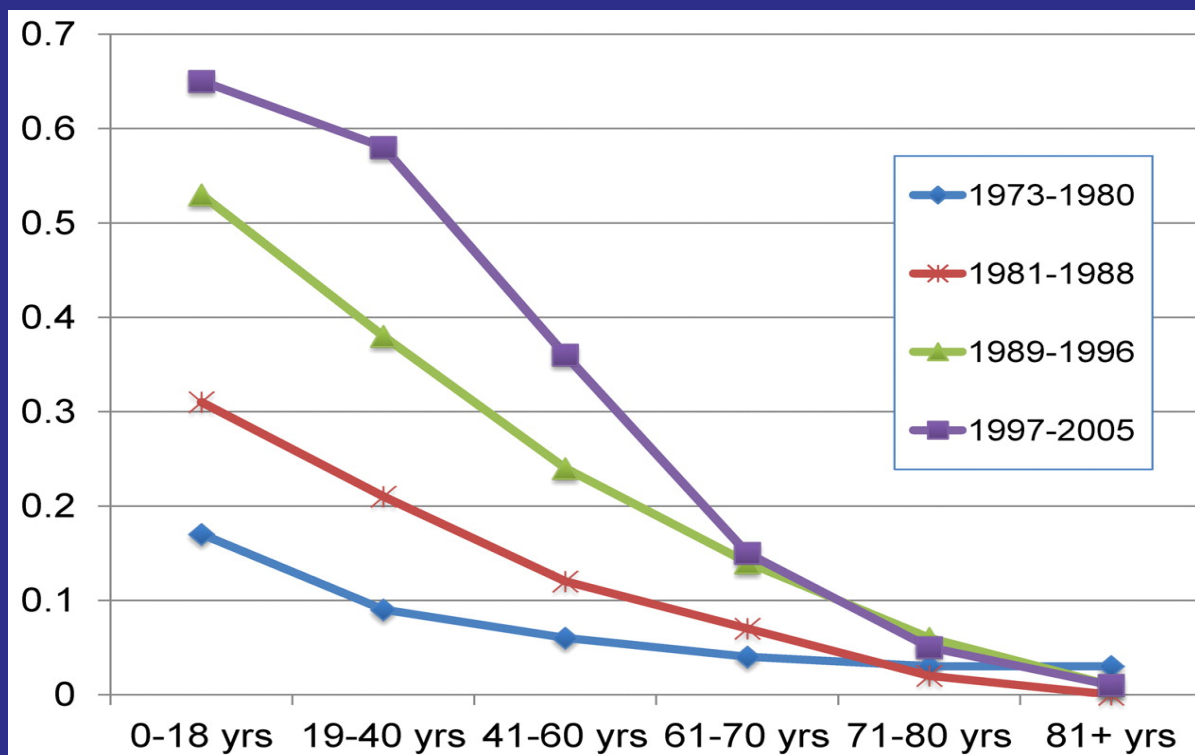
Οξεία Λευχαιμία / Αλ. Μεταμόσχευση Ινδίες



Journal of Global Oncology 2017

Οξεία Λευχαιμία

ACUTE MYELOID LEUKEMIA IN THE REAL WORLD



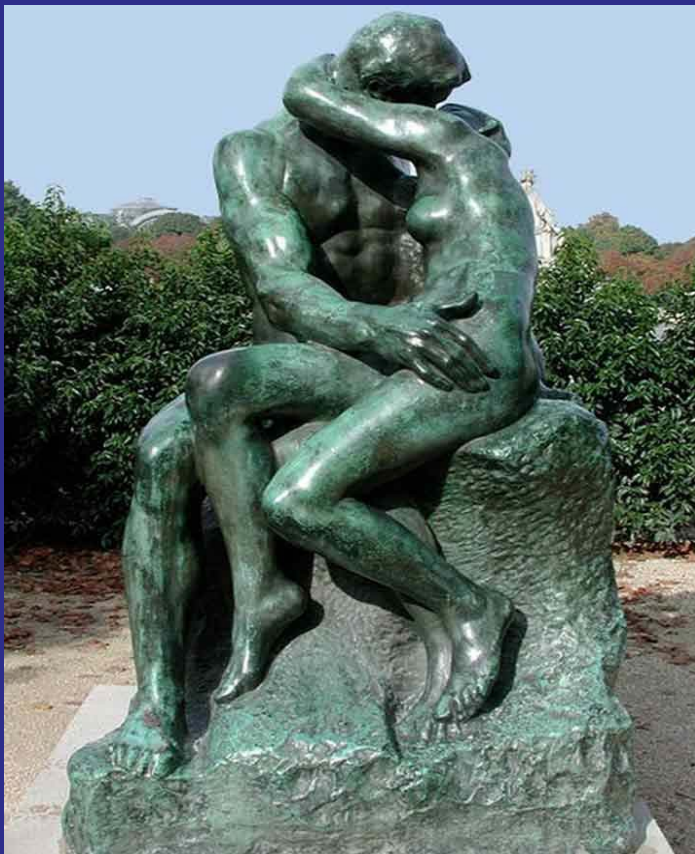
Juliusson G. et al. Swedish AL Registry 2015

Ιπποκράτης - Αφορισμοί

Ο βίος βραχύς, η δε τέχνη μακρή, ο δε
καιρός οξύς, η δε πείρα σφαλερή,
η δε κρίσης χαλεπή



ΑΠΟ ΤΙΣ ΜΕΛΕΤΕΣ ΣΤΗΝ ΚΟΙΝΟΤΗΤΑ



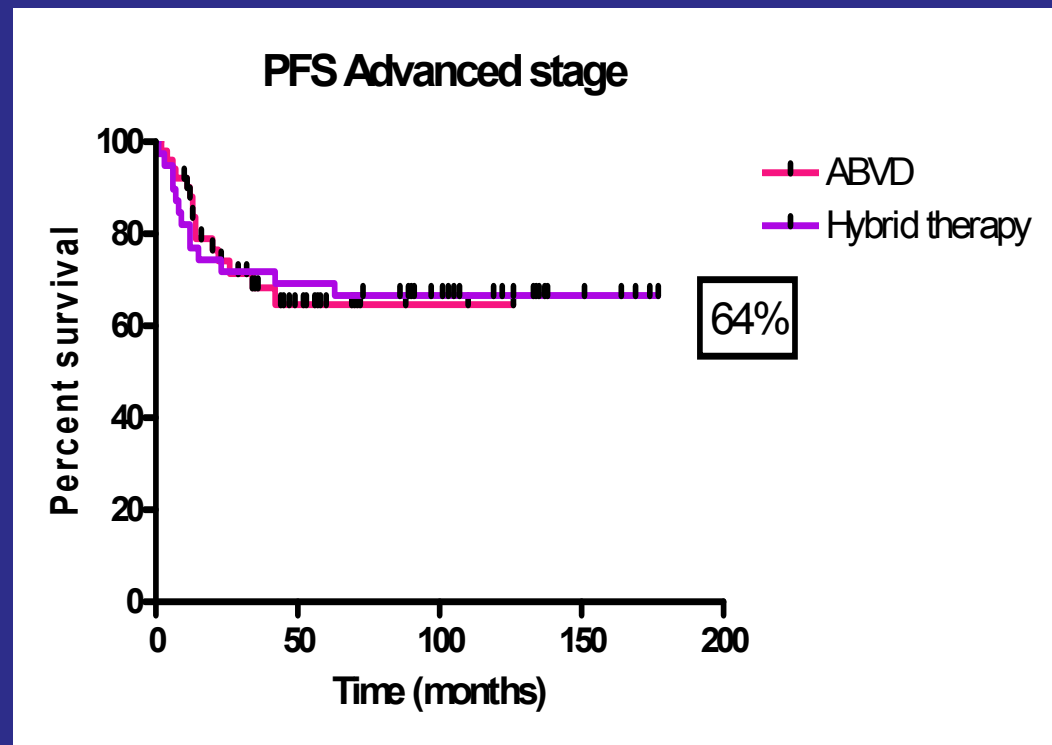
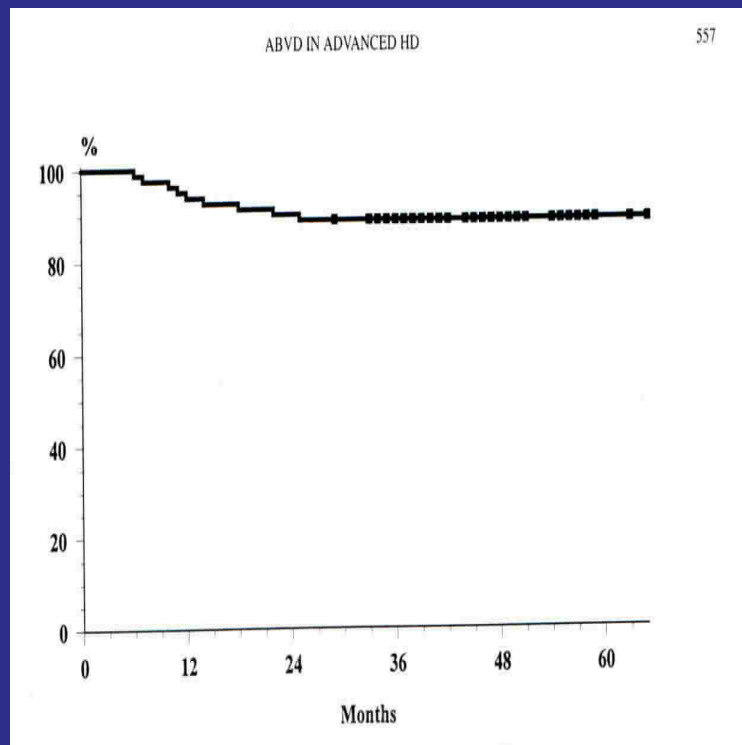
Αν οι μελέτες είναι
έντιμες, αξιόπιστες...

Αν προσέξουμε τη
μετάφραση...

YES WE CAN

Barak Obama

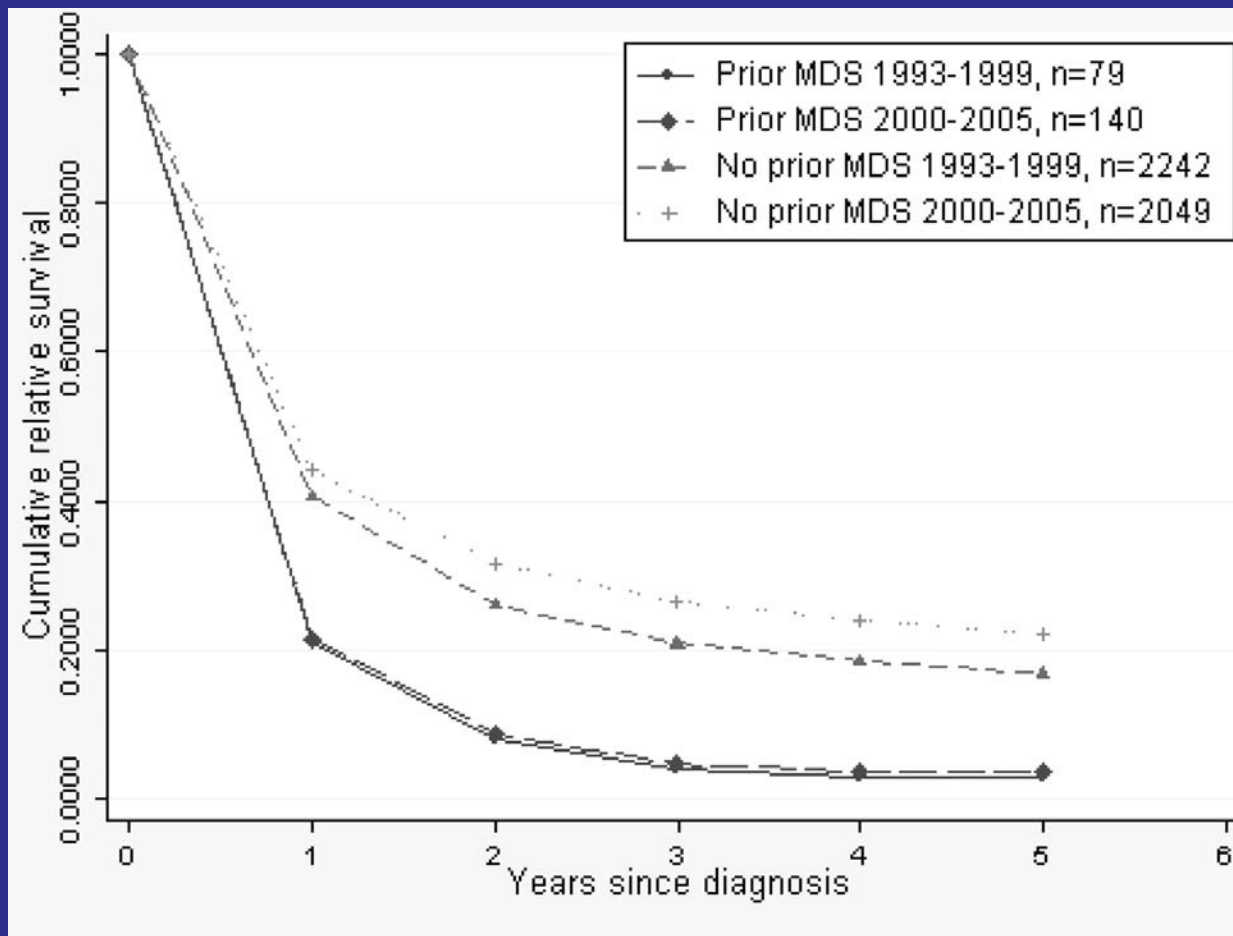
ΛΕΜΦΩΜΑ HODGKIN



ZINZANI 1998

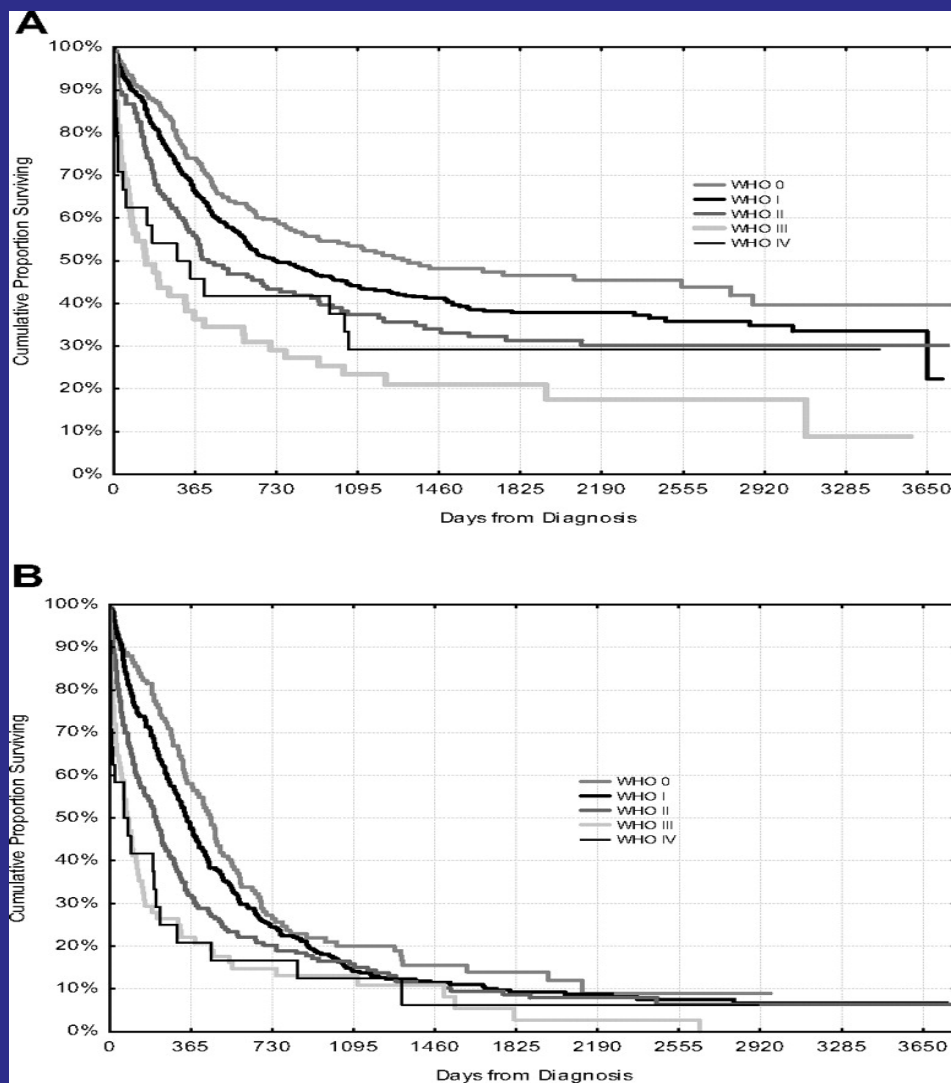
ΕΥΑΓΓΕΛΙΣΜΟΣ 1990-2006

Survival in AML MDS vs de novo AML



Derolf, A. R. et al. Blood 2009;113:3666-3672

**Overall survival according to WHO/ECOG performance status,
only patients fit for intensive treatment**



Juliusson, G. et al. Blood 2009;113:4179-4187

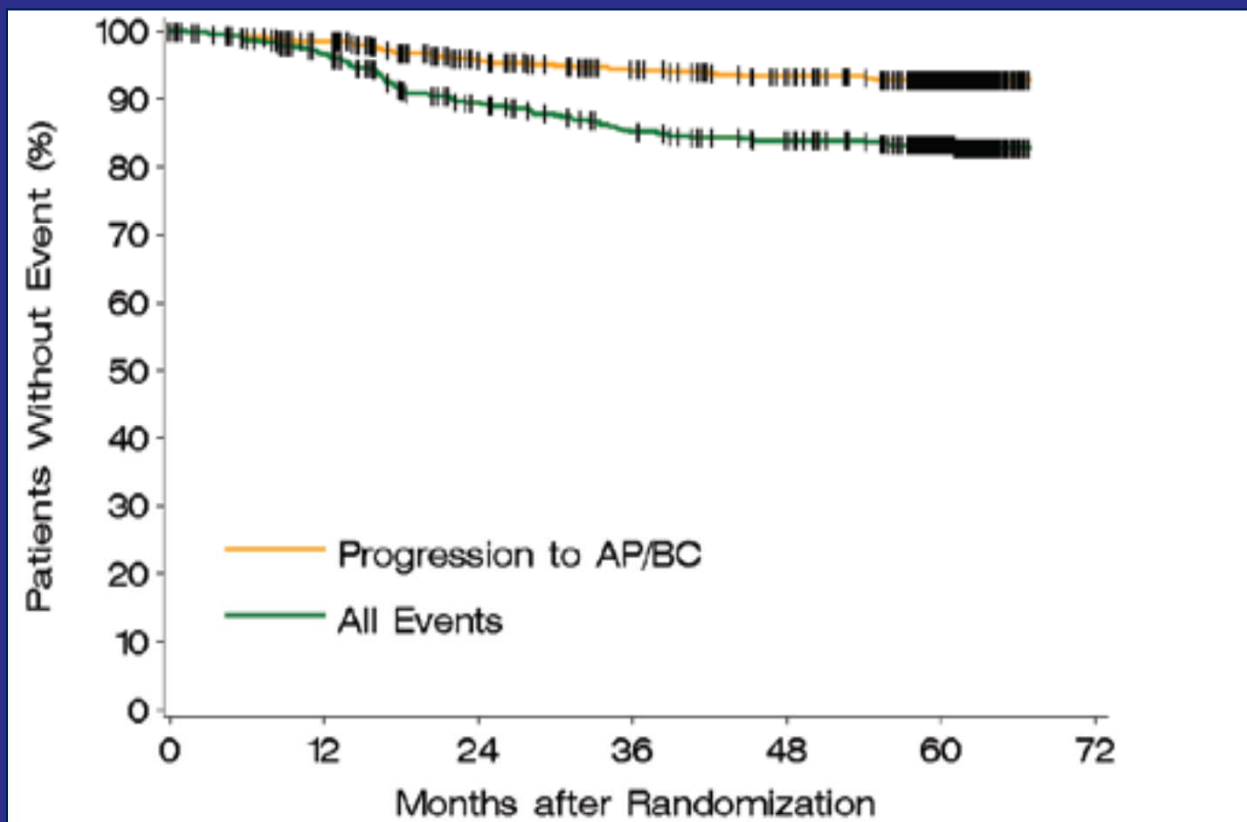
ΔΡΑΣΤΙΚΗ ΟΥΣΙΑ

ΧΡΟΝΙΑ ΜΥΕΛΟΓΕΝΗΣ ΛΕΥΧΑΙΜΙΑ



www.kepguru.hu

IMATINIB - IRIS 2006



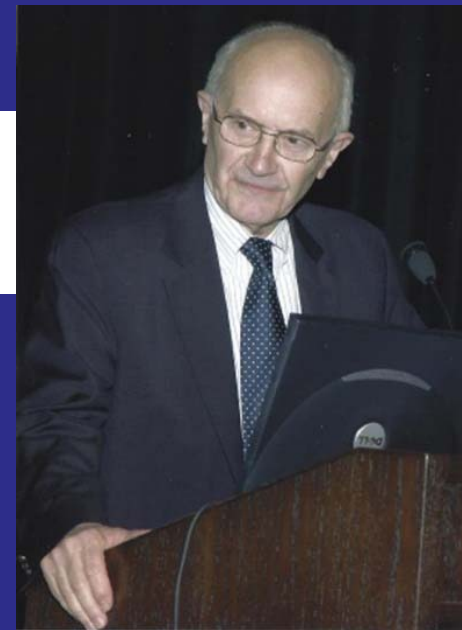
The NEW ENGLAND
JOURNAL *of* MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

**First-in-Human Clinical Trials — What We Can Learn
from Tragic Failures**

**The Search for Surrogate Endpoints in Trials in Diffuse Large
B-Cell Lymphoma: The Surrogate Endpoints for Aggressive
Lymphoma Project**



RETRACTION!

**Retraction: A Genomic Strategy to Refine Prognosis in
Early-Stage Non-Small-Cell Lung Cancer.
N Engl J Med 2006;355:570-80.**

to the editor: We would like to retract our article,
"A Genomic Strategy to Refine Prognosis in
Early-Stage Non-Small-Cell Lung Cancer," which
was published in the *Journal* on August 10, 2006.
Using a sample set from a study by the American
College of Surgeons Oncology Group (ACOSOG)
and a collection of samples from a study by the
Cancer and Leukemia Group B (CALGB), we have
tried and failed to reproduce results supporting
the validation of the lung metagene model described
in the article. We deeply regret the effect
of this action on the work of other investigators.

N Engl J Med March 2 2011

Από τον Θρίαμβο στην Τραγωδία



Οζώδη Λεμφώματα

'80

2000

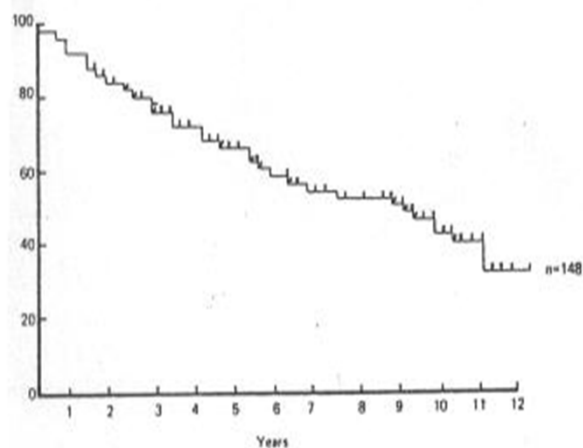


Table 1. More is better (and needs to be).

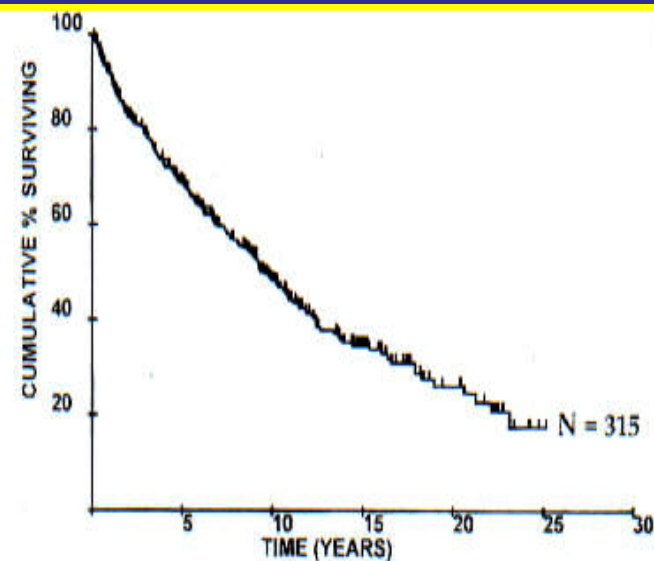
1. CVP	→	CY/TBI + ABMT	STANFORD
2. CHOP	→	CY/TBI + ABMT	DFCI (Nadler)
3. ProMACE-MOPP	↗	CY/TBI + ABMT	MSK
	↘	RT	

Table 2. Biology is beautiful.

1. CYCLO ± IFNa		CALGB
2. COPA	→ IFNa vs 0	ECOG
3. CVP		EORTC
4. FDM		LOW GRADE
		GERMAN GROUP

Table 3. The Texas solution (SWOG).

ProMACE-MOPP	→	CR	↗	IFNa
			↘	0

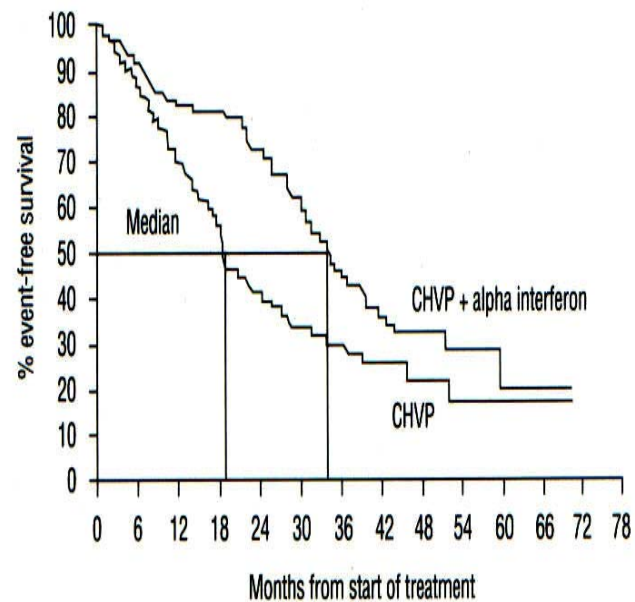


JOURNAL OF CLINICAL ONCOLOGY

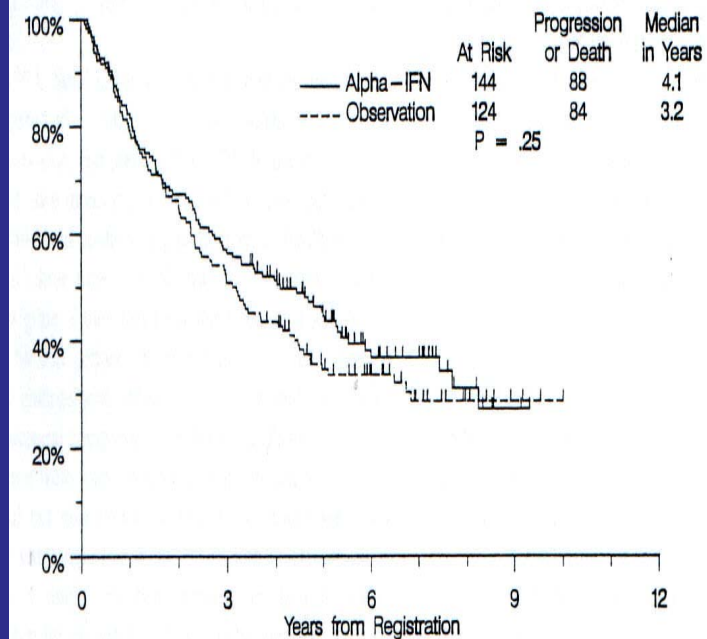
Οζώδη Λεμφώματα

INF vs Observation

1990



2000



Ο εθνικός ήρωας στη Νότια Κορέα ήταν απατεώνας!

- ΣΕΟΥΛ. Σε τριετή φυλάκιση με αναστολή καταδικάστηκε... της έρευνας για τα βλαστοκύτταρα.
- Ο 56χρονος Χουάνγκ Γου Σουκ, ο οποίος εθεωρείτο εθνικός ήρωας στη Νότια Κορέα, ..., καταδικάστηκε ωστόσο για υπεξαίρεση κονδυλίων και για παράνομη αγορά ανθρωπίνων ωαρίων. ...ο Χουάνγκ έδειξε μεταμέλεια και το δικαστήριο του επέβαλε ποινή φυλάκισης με τριετή αναστολή. ...
- Με την απόφαση του δικαστηρίου γράφτηκε ο θλιβερός επίλογος στη σταδιοδρομία ενός ανθρώπου ο οποίος κάποτε χαρακτηρίστηκε ήρωας ...

2009 Retraction !

From www.bloodjournal.org at HELLENIC SOCIETY OF HEMATOLOGY on June 19, 2009. For personal use only.

Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial

Abderrahman Abdelkefi,¹ Saloua Ladeb,¹ Lamia Torjman,¹ Tarek Ben Othman,¹ Amel Lakhal,¹ Neila Ben Romdhane,² Halima El Omri,³ Moez Eloumi,⁴ Hatem Belaj,⁴ Ramzi Jeddi,⁴ Lamia Alsaoui,⁵ Habib Ksouri,¹ Assia Ben Hassen,¹ Fahmi Msadek,⁶ Ali Saad,⁷ Mohamed Hsairi,⁸ Kamel Boukef,⁹ Ahlem Amouri,¹⁰ Hechmi Louzir,¹⁰ Koussay Dellagi,¹⁰ and Abdeladhim Ben Abdeladhim,¹ on behalf of the Tunisian Multiple Myeloma Study Group

¹Centre National de Greffe de Moelle Osseuse, Tunis; ²Hôpital La Rabta, Tunis; ³Hôpital Farhat Hached, Sousse; ⁴Hôpital Hédi Chaker, Sfax; ⁵Hôpital Aziza Othmana, Tunis; ⁶Hôpital militaire, Tunis; ⁷Laboratoire de cytogénétique, Hôpital Farhat Hached, Sousse; ⁸Institut National de la Santé Publique, Tunis; ⁹Centre National de Transfusion Sanguine, Tunis; and ¹⁰Institut Pasteur de Tunis, Tunisia

From April 2003 to December 2006, 195 patients with de novo symptomatic myeloma and younger than 60 years of age were randomly assigned to receive either tandem transplantation up front (arm A, n = 97) or one autologous stem-cell transplantation followed by a maintenance therapy with thalidomide (day + 90, 100 mg per day during 6 months) (arm B, n = 98). Patients included in arm B received a second transplant at disease progression. In both arms, autologous stem-cell transplantation was preceded

by first-line therapy with thalidomide-dexamethasone and subsequent collection of peripheral blood stem cells with high-dose cyclophosphamide (4 g/m²) and granulocyte colony stimulating factor. Data were analyzed on an intent-to-treat basis. With a median follow-up of 22 months (range, 6-46 months), the 2-year overall survival was 65% in arm A and 85% in arm B (*P* = .04). The 2-year progression-free survival was 57% in arm A and 85% in arm B (*P* = .02). Up-front single autologous transplantation fol-

lowed by 6 months of maintenance therapy with thalidomide (with second transplant in relapse or progression) is an effective therapeutic strategy to treat multiple myeloma patients and is superior to tandem transplant in this setting. This study was registered at www.ClinicalTrials.gov as (NCT00207700). (Blood. 2008;111:1805-1810)

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Introduction

Two prospective randomized studies have shown that recipients of high-dose chemotherapy with autologous stem cell transplantation (ASCT) have superior survival when compared with patients treated with conventional therapy.^{1,2} In both studies, patients were younger than 65 years, and as a result, single ASCT is now considered a standard option in younger patients.^{1,2}

The double-type triazepone doublet (TDM) was the first to demonstrate that 2 sequential ASCTs improved 7-year event-free survival (EFS) and overall survival (OS) rates in comparison with a single ASCT.⁴ Recently, the Bologna 96 clinical study has shown that in comparison with a single ASCT as up-front therapy for newly diagnosed multiple myeloma (MM), double ASCT effected superior complete response (CR) rate and EFS but failed to significantly prolong OS. Benefits offered by double ASCT were particularly evident among patients who did not achieve at least a very good partial response (VGPR) after one autotransplantation.⁵

Second ASCT given after relapse following a single ASCT has been used as a salvage therapy in many centers.⁶⁻¹¹ Recently, a retrospective study has compared tandem ASCT up front with a strategy including planned second ASCT at relapse or progres-

sion.¹² In this retrospective study, Morris et al¹² showed that a second ASCT performed before relapse and within 6 to 12 months of the first ASCT improved survival.

While there have been no randomized trials to evaluate the benefit of second ASCT following relapse, it has been suggested that ASCT (after first relapse) may achieve the same outcome as transplantation following initial therapy.¹³⁻¹⁵ Indeed, Fermand et al¹³ showed that early transplantation improved EFS but did not affect OS when compared with delayed transplantation.

Although MM remains incurable with conventional treatments, management of the disease recently has been transformed with the introduction of 3 novel agents: bortezomib,¹⁴ thalidomide,¹⁷ and lenalidomide.¹⁸ These agents represent a new generation of treatments for MM that affect both specific intracellular signaling pathways and the tumor microenvironment.¹⁹ Thalidomide is an agent with immunomodulatory and antiangiogenic properties. Thalidomide plus dexamethasone²⁰⁻²² is currently approved as frontline treatment of MM. Furthermore, several studies have shown that thalidomide is an effective maintenance therapy after ASCT in patients with MM.²³⁻²⁵

Submitted July 14, 2007; accepted September 18, 2007. Prepublished online as Blood First Edition paper, September 17, 2007; DOI 10.1182/blood-2007-07-101212.

An inside Blood analysis of this article appears at the front of this issue.

The online version of this article contains a data supplement.

BLOOD, 16 FEBRUARY 2008 • VOLUME 111, NUMBER 4

1805

From www.bloodjournal.org at HELLENIC SOCIETY OF HEMATOLOGY on June 19, 2009. For personal use only.

Retraction

Abdelkefi A, Ladeb S, Torjman L, Ben Othman T, Lakhal A, Ben Romdhane N, El Omri H, Eloumi M, Belaj H, Jeddi R, Alsaoui L, Ksouri H, Ben Hassen A, Msadek F, Saad A, Hsairi M, Boukef K, Amouri A, Louzir H, Dellagi K, Ben Abdeladhim A, on behalf of the Tunisian Multiple Myeloma Study Group. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. Blood. 2008;111:1805-1810.

The authors wish to retract the February 15, 2008, article cited above. The initial data available at the time the paper was published were inadequately collected. The first author, Abdeladhim Abdelkefi, was solely responsible for the errors. The authors present their deepest apologies to the scientific community and to the readers, reviewers, and editors of Blood for publishing these

data. The undersigned agreed to the retraction by notifying the journal.

Abderrahman Abdelkefi, Saloua Ladeb, Lamia Torjman, Tarek Ben Othman, Amel Lakhal, Neila Ben Romdhane, Halima El Omri, Moez Eloumi, Hatem Belaj, Ramzi Jeddi, Lamia Alsaoui, Habib Ksouri, Assia Ben Hassen, Fahmi Msadek, Ali Saad, and Mohamed Hsairi

BLOOD, 11 JUNE 2008 • VOLUME 111, NUMBER 24

6205

ΣΧΕΔΙΑΣΜΟΣ



RETRACTION !

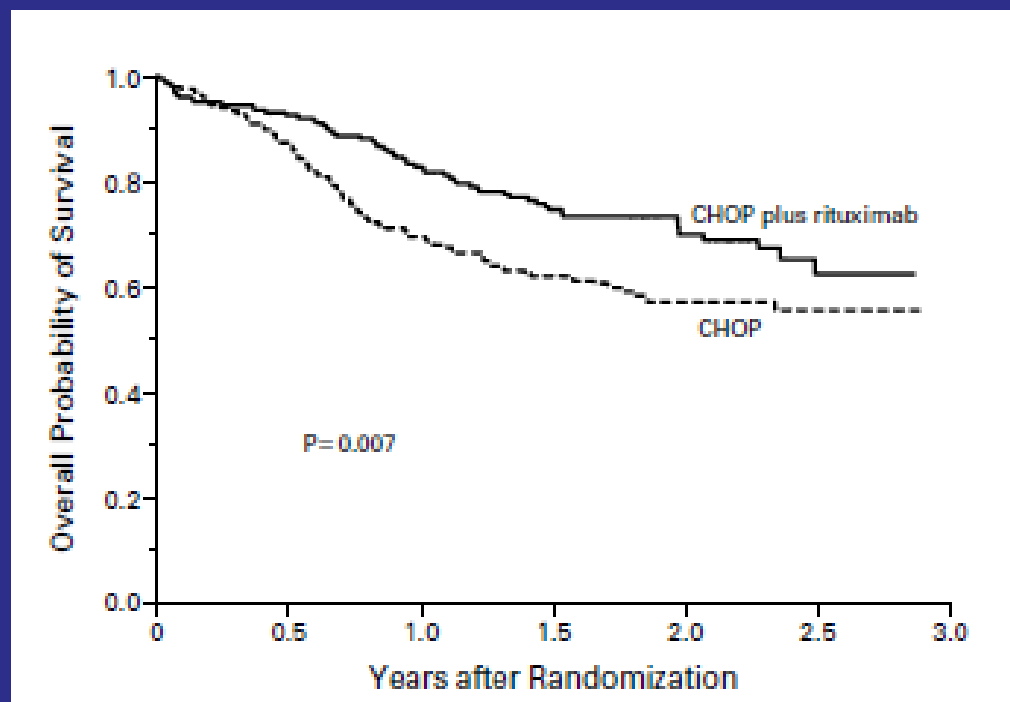
Retraction: A Genomic Strategy to Refine Prognosis in
Early-Stage Non-Small-Cell Lung Cancer.
N Engl J Med 2006;355:570-80.

March 2 2011

to the editor: We would like to retract our article,
"A Genomic Strategy to Refine Prognosis in
Early-Stage Non-Small-Cell Lung Cancer," which
was published in the *Journal* on August 10, 2006.
... We deeply regret the effect
of this action on the work of other investigators.

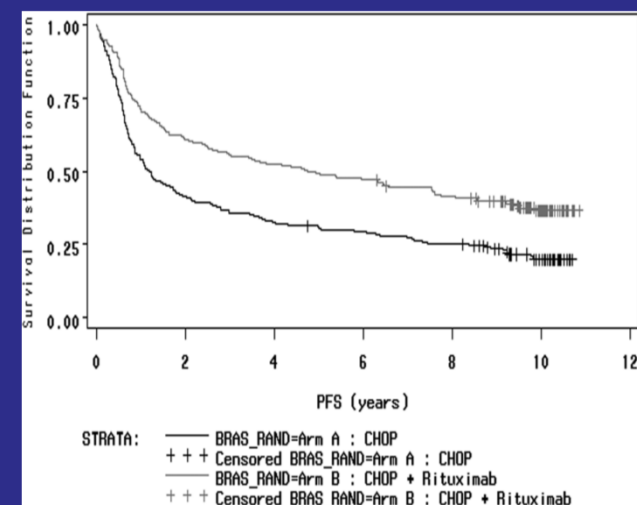
The NEW ENGLAND
JOURNAL of MEDICINE

Rituximab - Λεμφώματα



Coiffier, B. et al. 2002

The NEW ENGLAND
JOURNAL of MEDICINE



Coiffier, B. et al. Blood September 2010



23^ο Ετήσιο Σεμινάριο Συνεχιζόμενης
Ιατρικής Εκπαίδευσης
Νοσοκομείου «Ο Ευαγγελισμός»



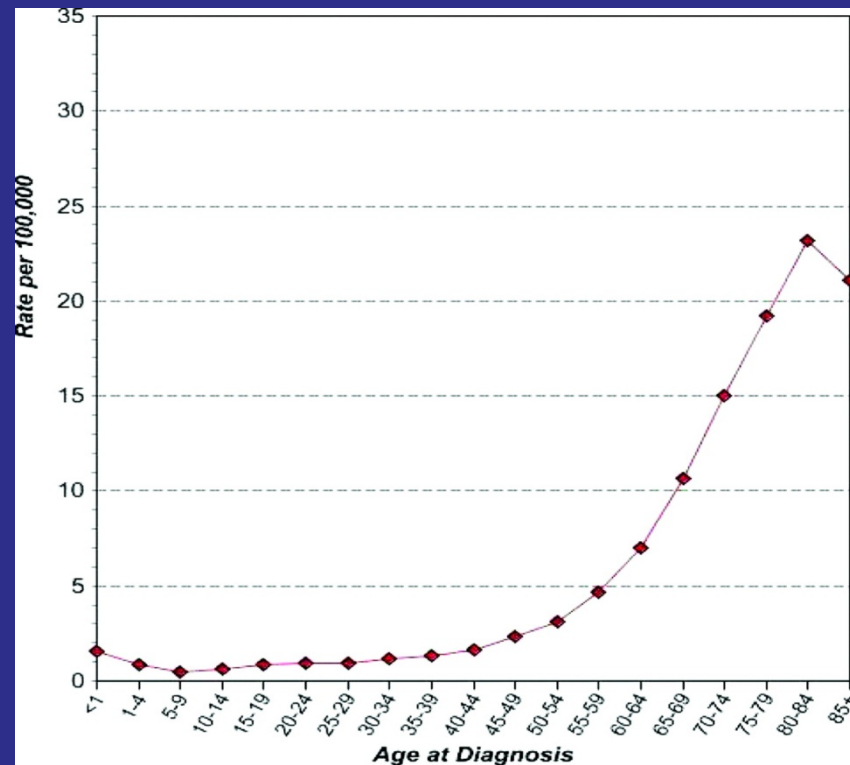
Αθήνα, 26 Φεβρουαρίου – 2 Μαρτίου 2018

Δεν υπάρχει σύγκρουση συμφερόντων
με τις παρακάτω χορηγούς εταιρείες:

NOVARTIS, JANSSEN ONCOLOGY, ABBVIE,
BRISTOL-MYERS SQUIBB, MEDTRONIC,
TAKEDA, GENESIS, MSD, PFIZER, AMGEN,
ASTELLAS, GILEAD, AENORASIS, BAXTER,
BIANEX, WINMEDICA, ABBOTT, BIOSEP,
SANOFI, ANGELINI, DEMO, ELPEN,
EDWARDS, ROCHE, RONTIS, SPECIFAR, UCB,
ΥΓΕΙΟΔΥΝΑΜΙΚΗ, MAVROGENIS

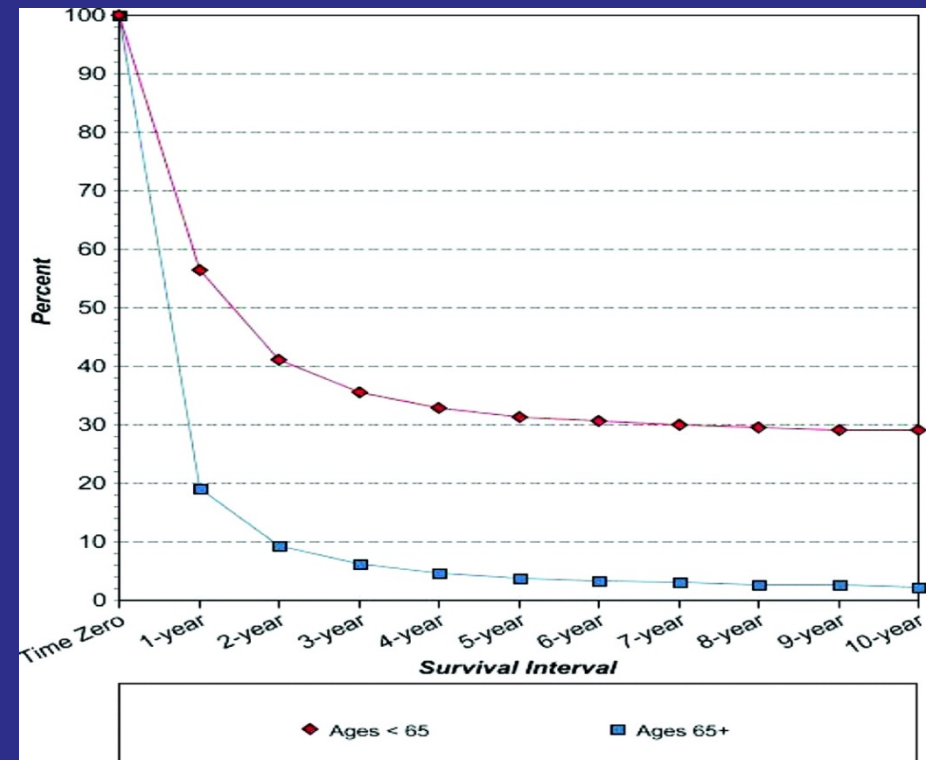
Οξεία Λευχαιμία

Επίπτωση / Ηλικία



Juliusson, G. et al. Blood 2009;113:4179

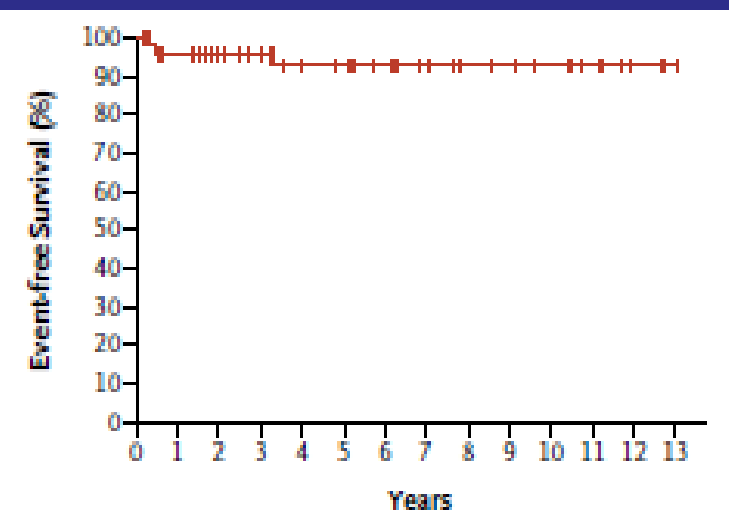
Επιβίωση / Ηλικία



Klepin, H. D. et al. Oncologist 2009;14:222-232

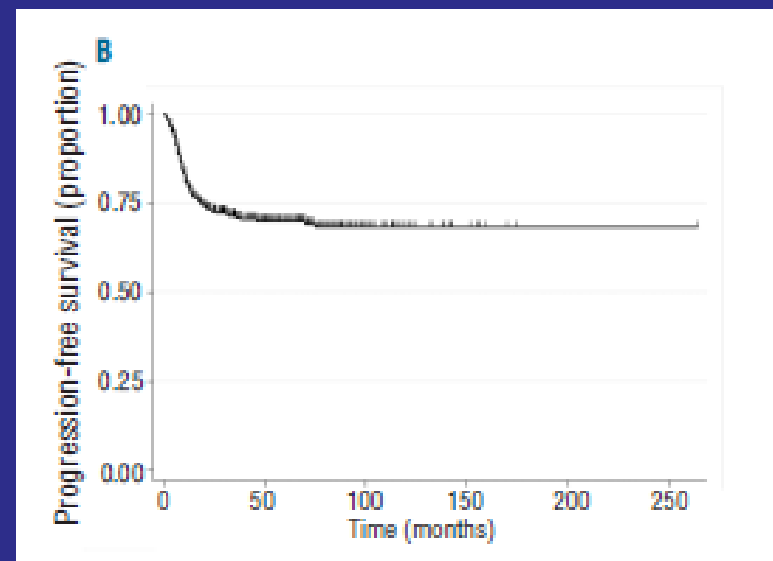
Πρωτοπαθή Λεμφώματα Μεσοθωρακίου

Στον κόσμο του NCI



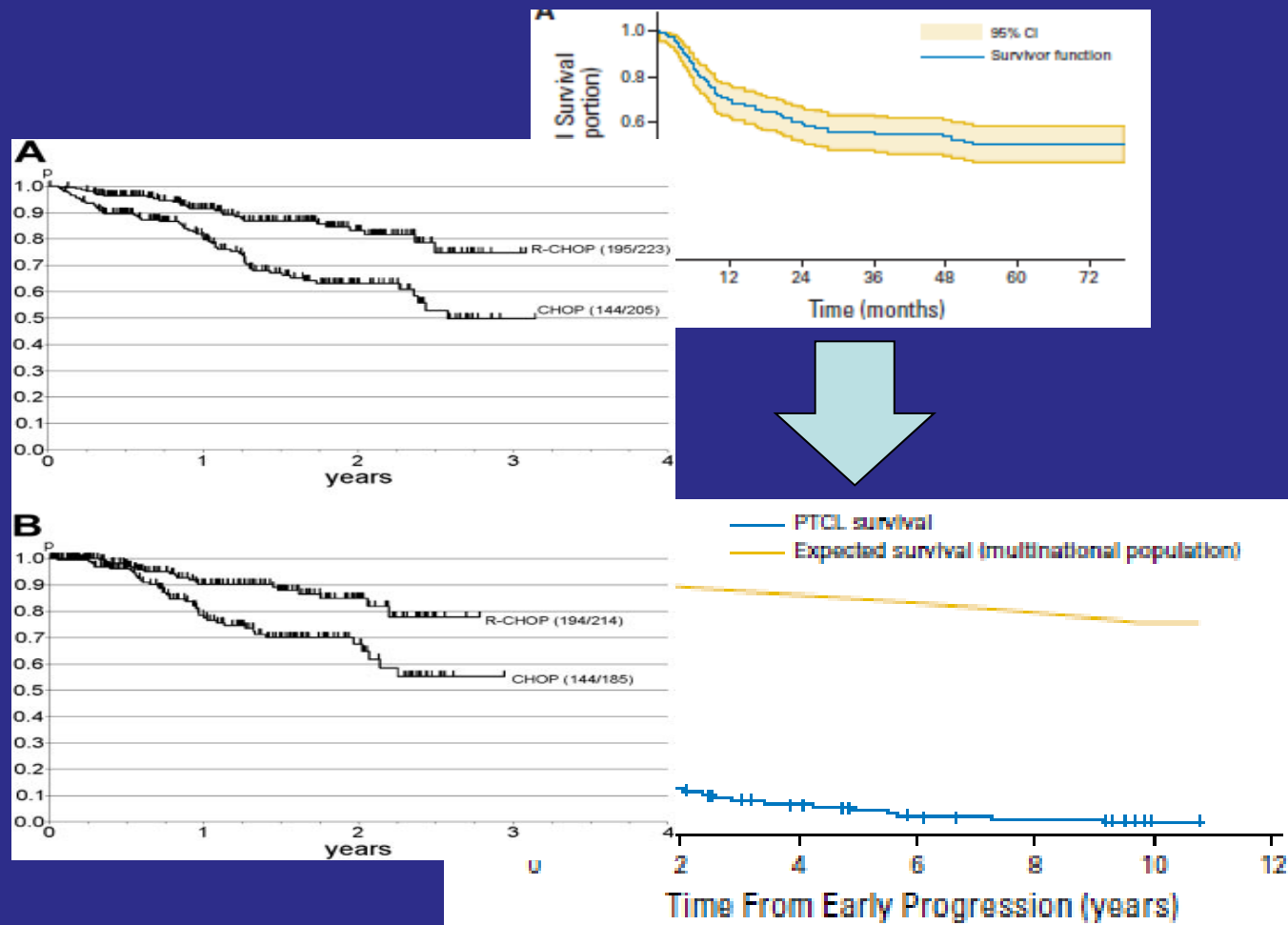
Dunleavy K. et al. 2013

Στην Ιαπωνία



PTCL

Από τις Μελέτες στον Πραγματικό κόσμο

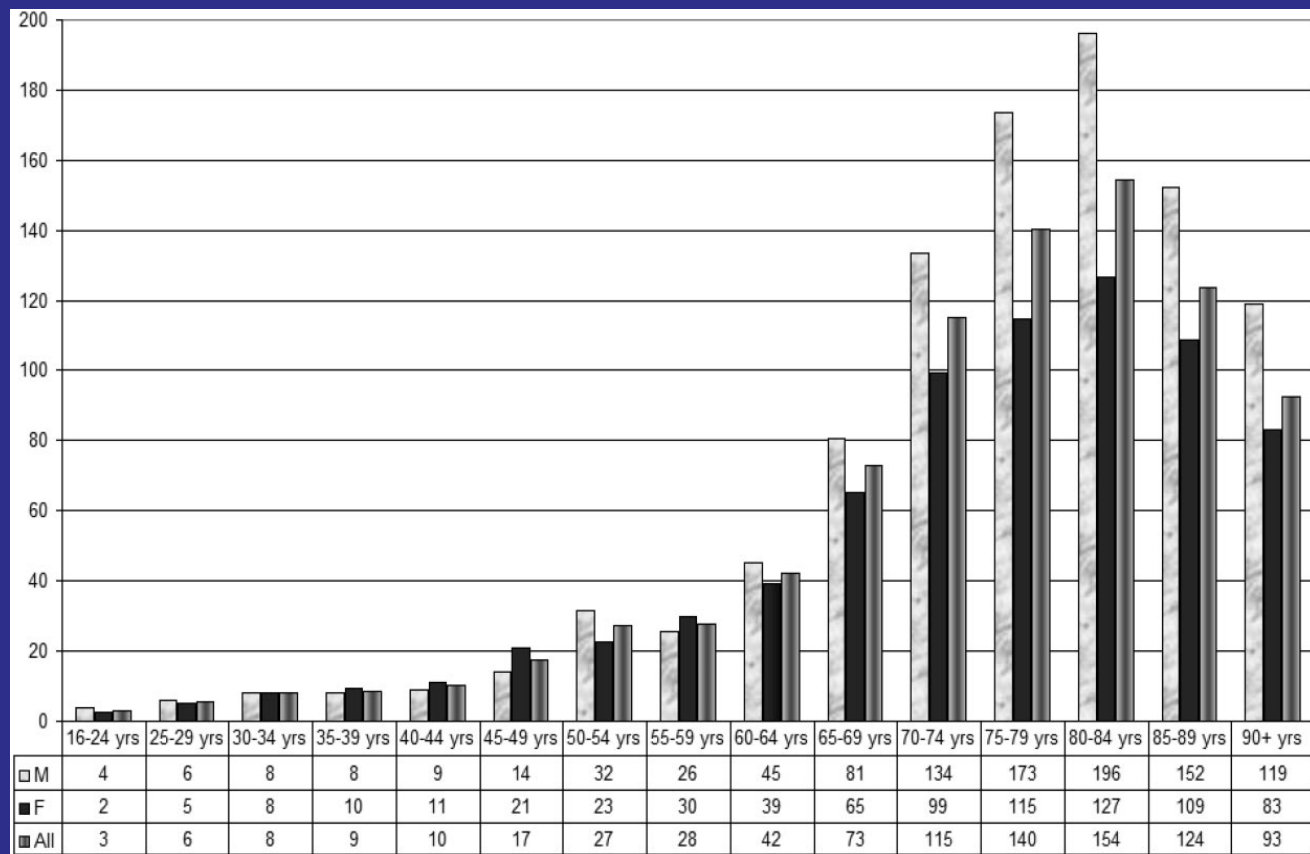


Mauer MJ. Et al. 2017

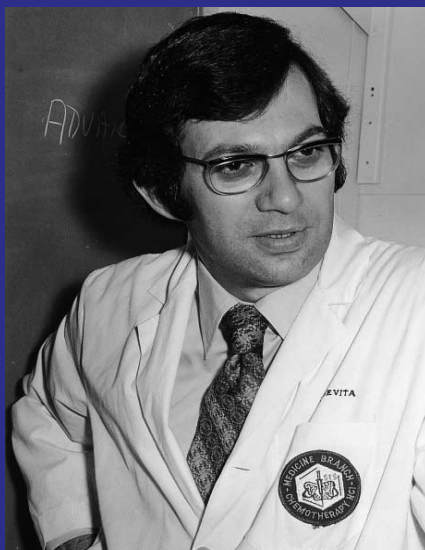
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



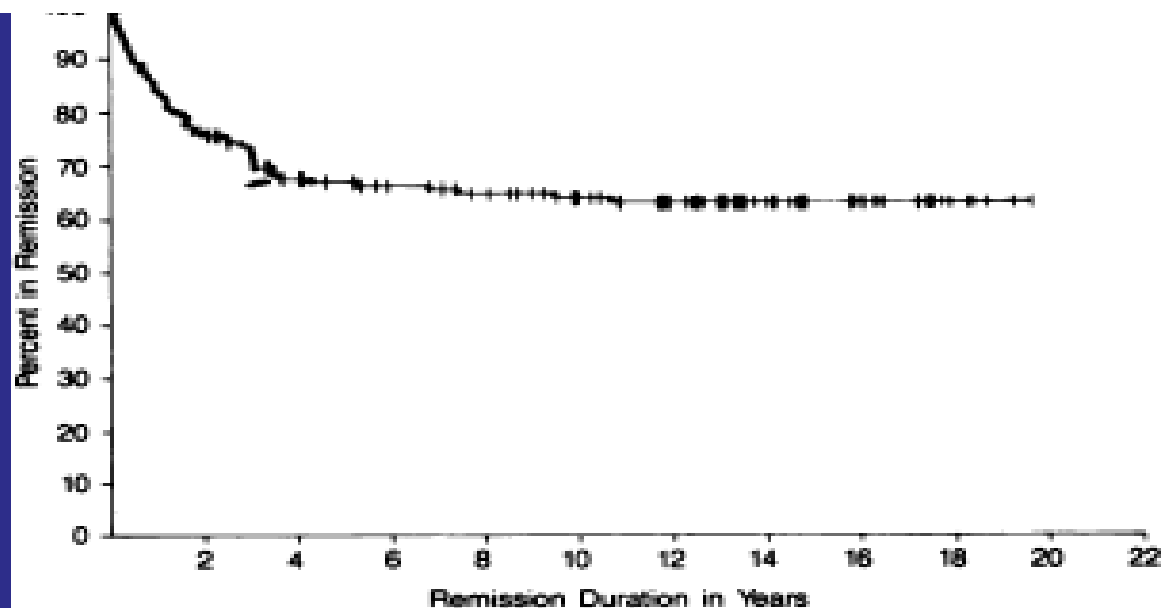


ΜΟΡΡ...20 Χρόνια αργότερα



Progress in the Treatment of Hodgkin's Lymphoma

Dan L. Longo, M.D., and Vincent T. DeVita, Jr., M.D.



JOURNAL OF CLINICAL ONCOLOGY