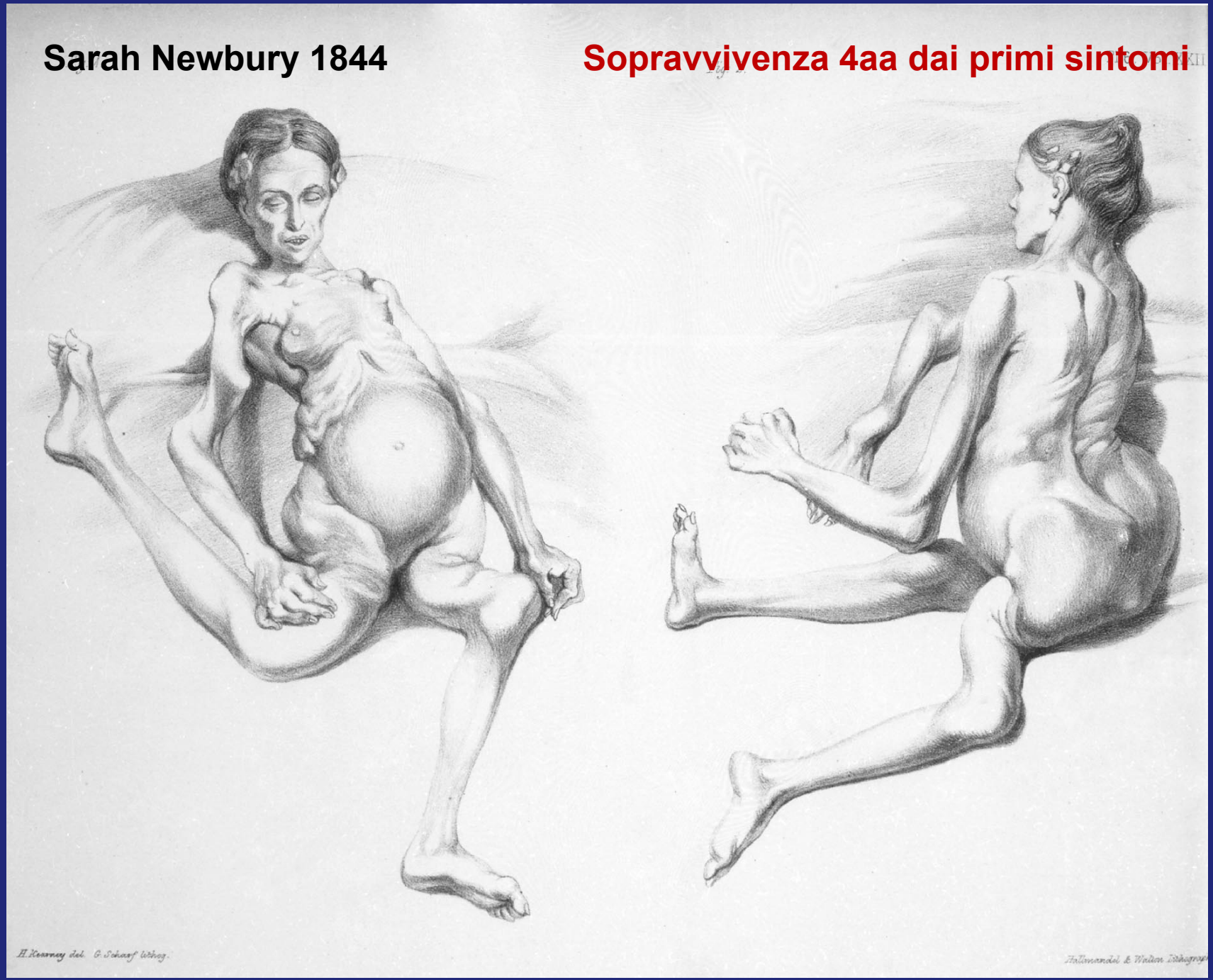
La prognosi del mieloma multiplo, oggi:

Da malattia inguaribile a malattia guaribile

Patrizia Tosi
UO Ematologia Rimini

Sarah Newbury 1844

Sopravvivenza 4aa dai primi sintomi



Multiple Myeloma. *Definition.* Multiple myeloma is a malignant tumor arising in the bone marrow which tends to occur in persons after the fifth decade. It is usually characterized by pain in the back and weakness, skeletal involvement especially of the trunk, pathological fractures, a normocytic anemia of moderate degree, and the presence of a peculiar type of protein (Bence-Jones) in the urine.

Although it has not received general acceptance, the most satisfactory tentative view is to consider multiple myeloma as a neoplastic process in which the myeloid cells are derived from the hematopoietic system. If this is true, the condition bears a close relationship to leukemia. The cells making up the tumors have been most commonly regarded as plasma cells although their identification is by no means definite. Possibly myeloma cells are a distinctive type, varying from all other forms.

Symptoms and Signs. The condition is observed twice as commonly in males as in females. Almost all cases occur after the age of forty years. Pain of a vague, intermittent, shifting type, often referable to the spine, is commonly the earliest evidence of the disease. As the condition progresses this frequently is a severe and dominant symptom. Tumors and pathologic fractures, usually in bones containing red marrow, are common. Changes in the spine causing compression of the spinal cord with its resultant neurological manifestations is not a rare complication.

Blood. A moderately severe normocytic or slight macrocytic normochromic anemia is almost always present. The leukocyte count is ordinarily normal, slightly elevated or diminished, and the differential formula is usually not disturbed or may reveal only an occasional abnormal white blood cell. Rarely have many plasma cells been observed in the blood stream but these, when present, have caused the condition to be regarded as a plasma cell leukemia.

A finding of great diagnostic importance is the presence of Bence-Jones protein in the urine, which appears in about two-thirds of the cases. It may occur occasionally in the urine of patients with leukemia and polycythemia. This protein precipitates at temperatures of 50° to 60° C.; further heating causes it to go into solution at about boiling, and on cooling it reappears. Its presence appears to be limited to pathologic conditions attacking the bone or bone marrow. There may be a pronounced hyperproteinemia, as indicated by plasma protein determinations, which are often found to be 10 Gm. per 100 cc. of plasma, or above; figures twice as high as this have been reported. This is due entirely to an increase in the globulin fraction. Autohemagglutination, or spontaneous clumping of the erythrocytes, occurs in some cases. This accounts for the tendency to striking rouleau formation and an accelerated sedimentation rate. Serum calcium is frequently elevated to levels of 12 to 16 mg. per cent, but the serum inorganic phosphates are usually normal.

In addition to those mentioned above, there are two diagnostic procedures which are of great importance: (1) sternal puncture, which usually reveals the presence of typical myeloma cells, and (2) roentgen ray examination which demonstrates the characteristic punched out areas, without evidence of bone regeneration, in the ribs, spine, clavicles, skull and the shoulder and pelvic girdles.

Prognosis and Treatment. The disease is uniformly fatal after an average duration of life of between two and three years. Occasionally the course is prolonged with remissions and exacerbations. Roentgen ray exposures should be employed in all cases, as it frequently gives worth-while symptomatic relief and may prolong life in some instances. This, with blood transfusions, is the only known therapeutic agent of recognized value. Otherwise the treatment is symptomatic.

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"Cyrus C. Sturgis"

Cecil Textbook of Medicine 7th Ed., 1948

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CLINICAL EXPERIENCES WITH SARCOLYSIN IN NEOPLASTIC DISEASES

By N. Blokhin, L. Larionov, N. Perevodchikova, L. Chebotareva, and N. Merkulova

Institute of Experimental Pathology and Therapy of Cancer, Academy of Medical Sciences of the U. S. S. R., Moscow, U. S. S. R.

Tumor	No. of patients	Immediate positive result		Negative result
		Complete regression of tumors	Considerable reduction of tumor size	
Seminoma and its metastases	23	11	8	4
Reticulum cell sarcoma	16	2	6	8
Ewing's tumor	13	4	6	3
Thymoma	1	1	—	—
Mixed tumors of the testis	9	—	5	4
Angioendothelioma	10	—	4	6
Primary carcinoma of liver	10	—	3	7
Multiple myeloma	6	—	3	3
Total	88	18	35	35

Annals NY Acad Sci 1958

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To illustrate the possibilities of persistent treatment we may cite the case of a patient with myelomatosis. Administration of sarcolysin was begun when the patient was in a very critical state, with multiple involvement of the skull, ribs, and pelvic bones, after the failure of radioactive phosphorus treatment. The patient's hemoglobin level was 27 per cent (Sahli), and there was 20 *pro mille* protein content in the urine.

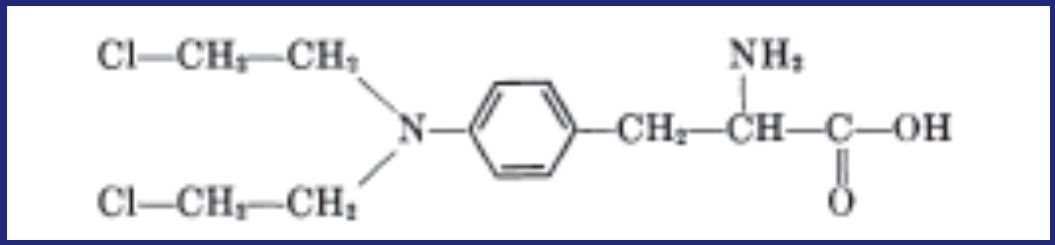
Three courses of sarcolysin treatment were carried out in succession with intervals of from 1 to 2 months.* The first course was conducted with doses of 30 to 40 mg. (total dose, 210 mg.). The single dose in the second and third course was enlarged to 50 mg. The total dose for the last two courses was from 250 to 270 mg. Because leukopenia occurred, repeated transfusions of blood and of suspensions of leukocytes and thrombocytes were carried out during and after treatment.

At the present time—that is, one year after the beginning of treatment and 6 months after the end of the third course—the patient has apparently recovered. He has gained 20 kg. in weight and is able to carry on intensive work as the director of a large plant. In the majority of bone defects a regeneration of bone tissue has occurred (FIGURE 1).

Annals NY Acad Sci 1958

EVALUATION OF NEW CHEMOTHERAPEUTIC AGENTS IN THE TREATMENT OF MULTIPLE MYELOMA. IV. L-PHENYLALANINE MUSTARD (NSC-8806)[1,2,3,4]

D. E. Bergsagel,[5] C. C. Sprague, C. Austin, and K. M. Griffith



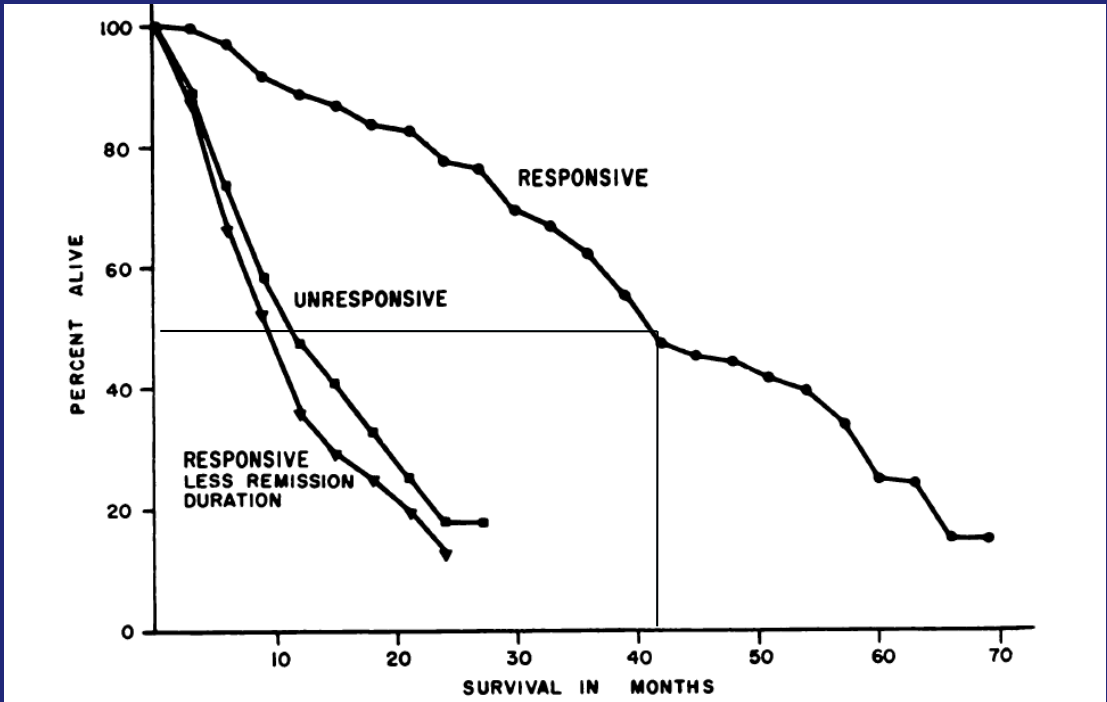
L-Phenylalanine mustard (L-PAM) has been administered orally at 0.2 mg./kg./day (total doses, 1.8 to 9.4 mg./kg.) in 38 courses to 24 patients with multiple myeloma. With total doses of 1.8 to 3.0 mg., leukopenia developed in 50% of the patients. Marked hematologic toxicity (leukopenia, thrombocytopenia, and a fall of more than 2.0 g.% in hemoglobin) was observed in 22 of the 34 courses in which the drug was continued until the white blood cell count fell below 3000 cells/mm.[3] Eight patients were "significantly improved," 6 showed improvement in 1 or more objective parameters, and there was no response in 10. The over-all therapeutic effectiveness was 58% with a standard error of 10.1%; the incidence of "significant improvement" was 33% with a standard error of 9.6%. No correlation which would aid in predicting a response to L-PAM was detected between the response to therapy and any factor related to the disease process.

Cancer chemotherapy reports 1962

BLOOD
The Journal of Hematology
JANUARY, 1968
Vol. XXXI, No. 1

Melphalan Therapy for Plasma Cell Myeloma

By RAYMOND ALEXANIAN, DANIEL E. BERGSAGEL, PHILIP J. MIGLIORE, WILLIAM K. VAUGHN AND CLIFTON D. HOWE



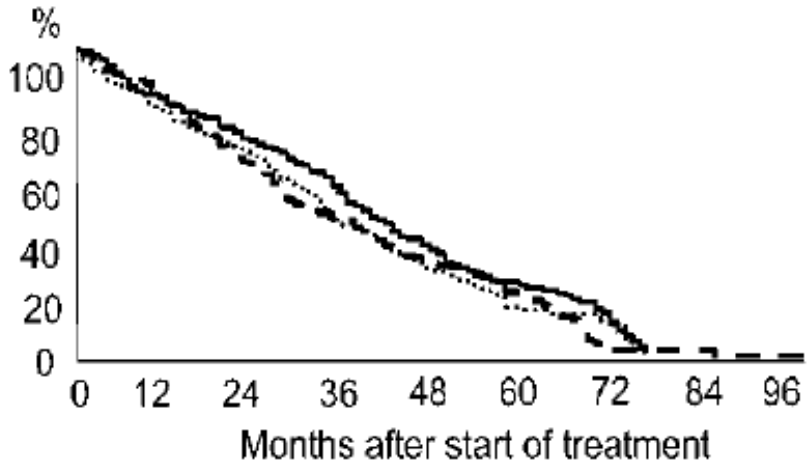
Melphalan-prednisone versus alternating combination VAD/MP or VND/MP as primary therapy for multiple myeloma: final analysis of a randomized clinical study

MICHELE CAVO, MONICA BENNI, SONIA RONCONI, MAURO FIACCHINI, ALESSANDRO GOZZETTI, ELENA ZAMAGNI, CLAUDIA CELLINI, PATRIZIA TOSI, MICHELE BACCARANI, SANTE TURA
WRITING COMMITTEE OF THE "BOLOGNA 90" CLINICAL TRIAL
Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, Italy

Monoclonal Gammapathies

research paper

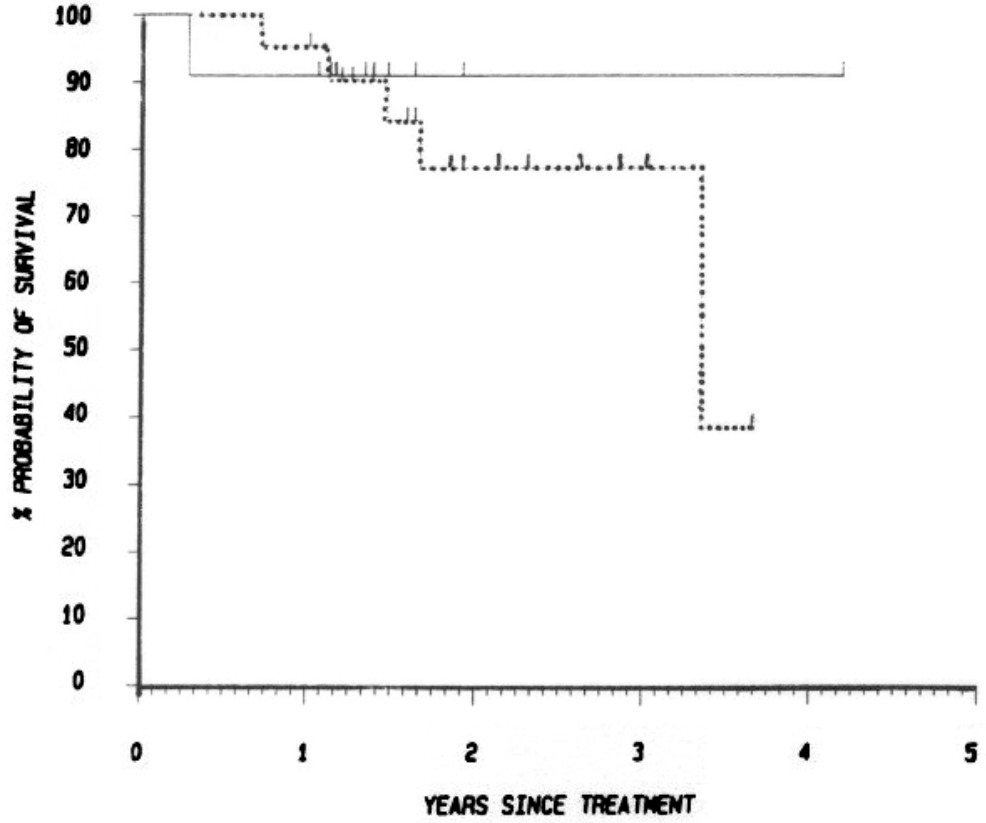
haematologica 2002; 87:934-942
http://www.haematologica.ws/2002_09/934.htm

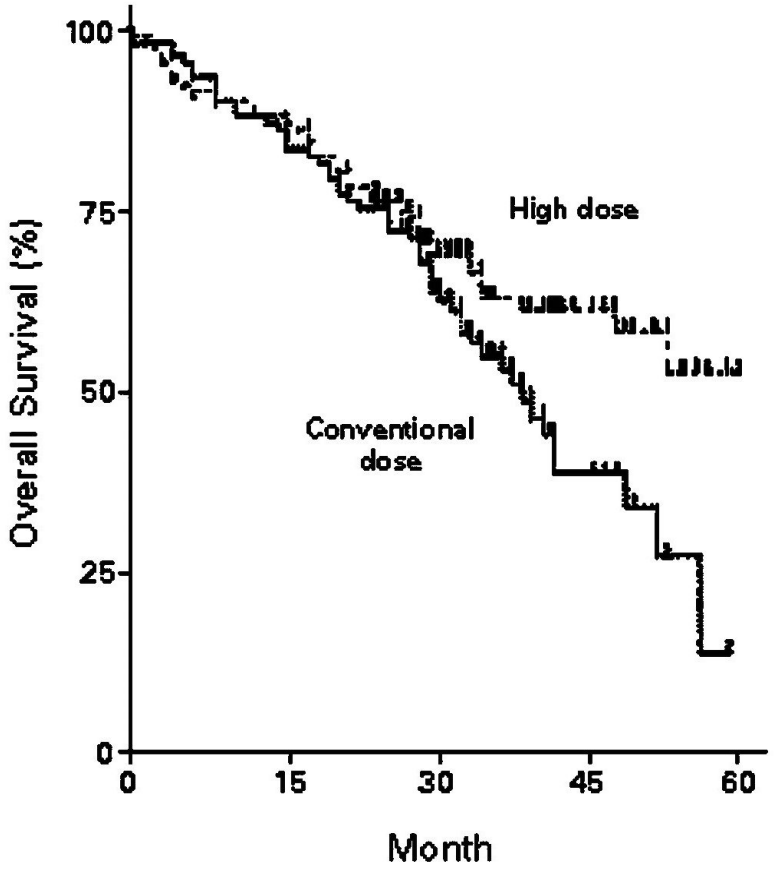


Median survival duration was 36.5 months with MP, 29 months with VAD/MP and 32.5 months with VND/MP. The dif-


Che cosa è cambiato?

La curva dose-risposta del Melphalan



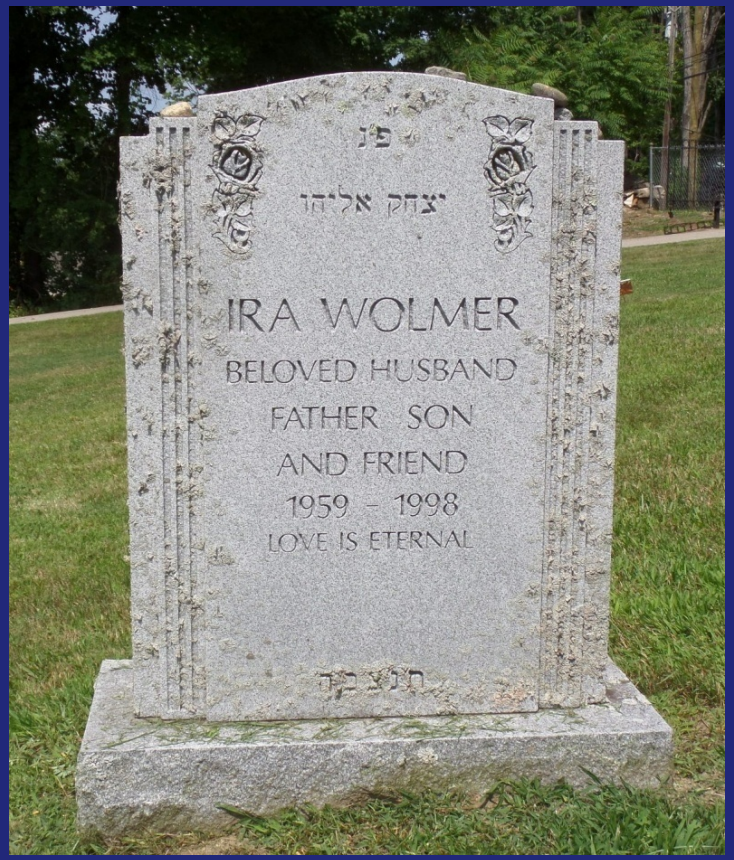


Selby et al, BR J Haematol 1987

Attal et al NEJM 1996

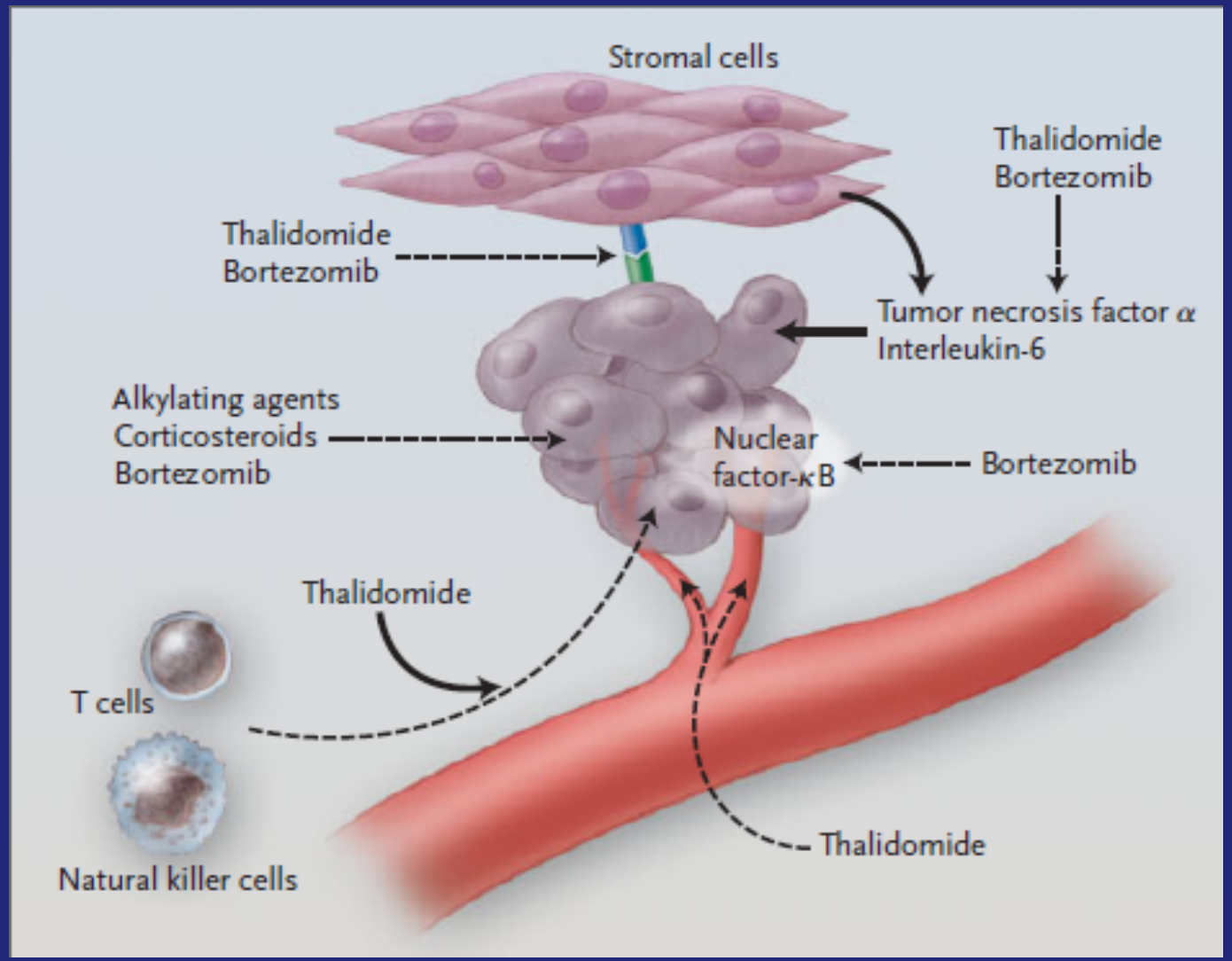
ANTITUMOR ACTIVITY OF THALIDOMIDE IN REFRACTORY MULTIPLE MYELOMA

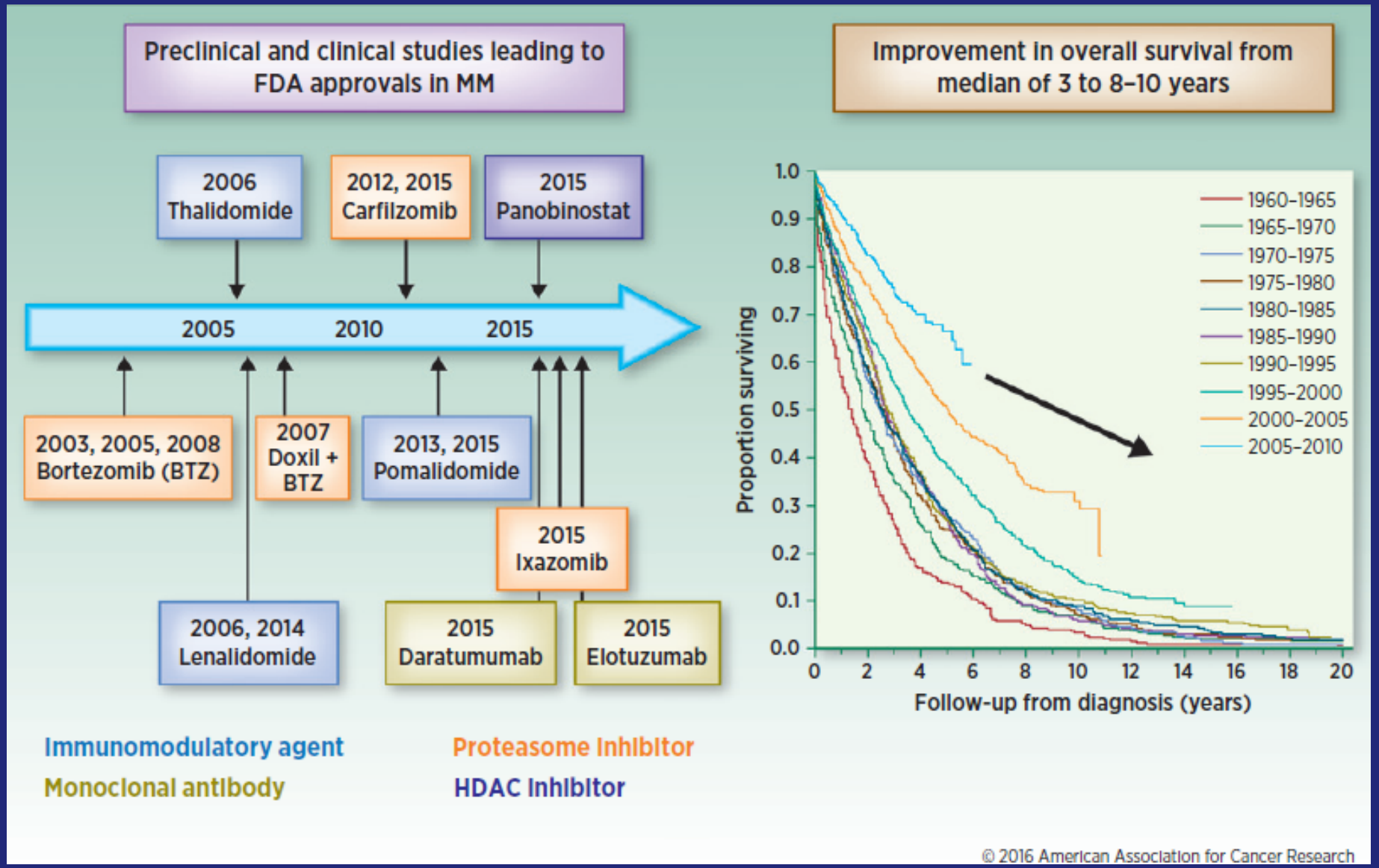
SEEMA SINGHAL, M.D., JAYESH MEHTA, M.D., RAMAN DESIKAN, M.D., DAN AYERS, M.S., PAULA ROBERSON, PH.D., PAUL EDDLEMON, B.S., NIKHIL MUNSHI, M.D., ELIAS ANAISSIE, M.D., CARLA WILSON, M.D., PH.D., MADHAV DHODAPKAR, M.D., JEROME ZELDIS, M.D., AND BART BARLOGIE, M.D., PH.D.



We are indebted to Beth Wolmer for her persistence in recommending the clinical evaluation of thalidomide in the treatment of multiple myeloma……

This article is dedicated to the memory of Ira Wolmer, M.D


Stromal cells
Thalidomide
Bortezomib
Thalidomide
Bortezomib
Tumor necrosis factor α
Interleukin-6
Alkylating agents
Corticosteroids
Bortezomib
Nuclear
factor-κB
Bortezomib
Thalidomide
T cells
Natural killer cells
Thalidomide



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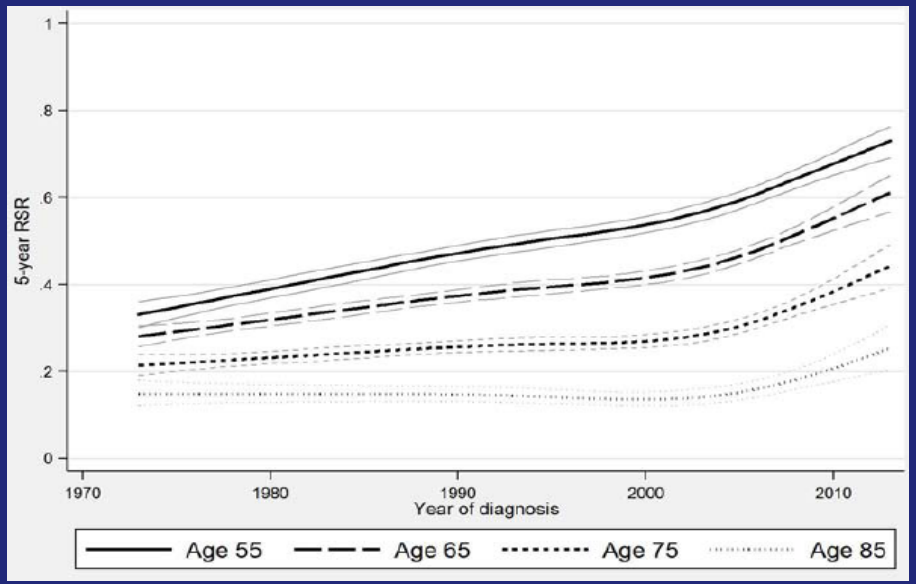
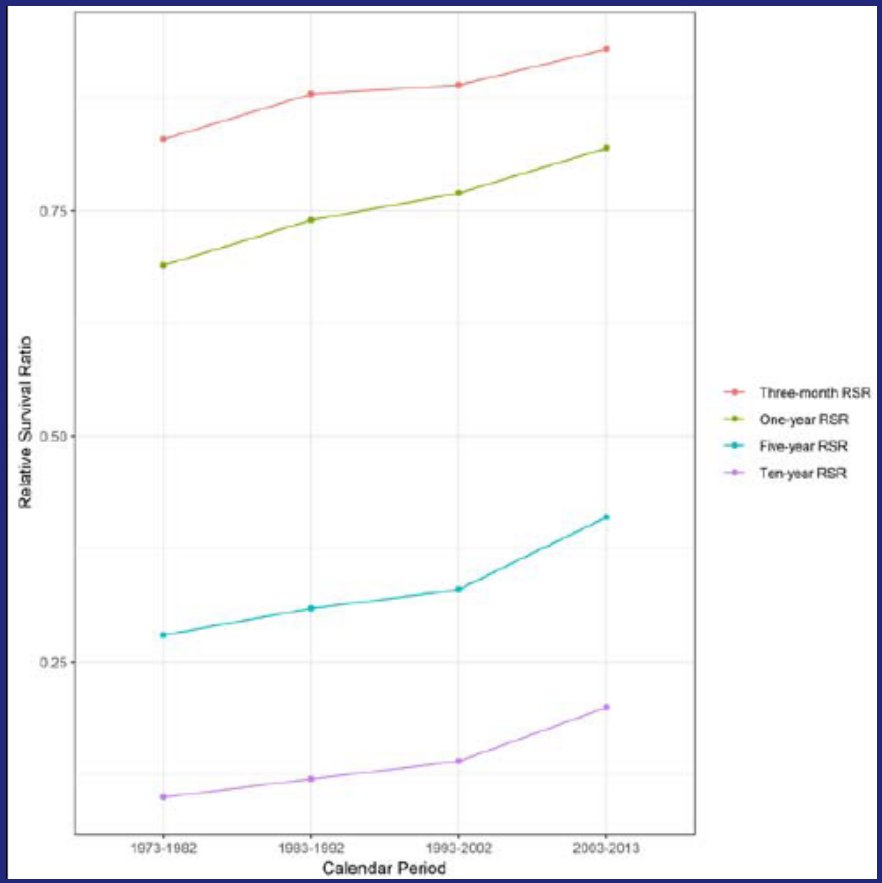
Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study

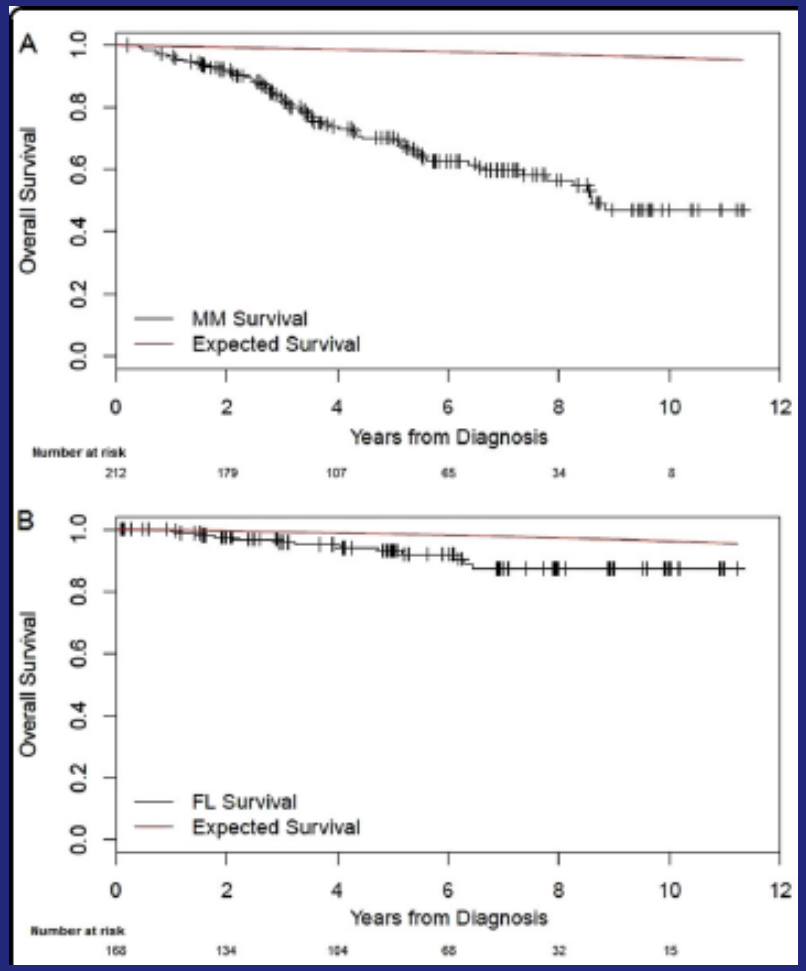
by Sigrun Thorsteinsdottir, Paul W. Dickman, Ola Landgren, Cecilie Blimark, Malin Hultcrantz, Ingemar Turesson, Magnus Björkholm, and Sigurdur Y. Kristinsson

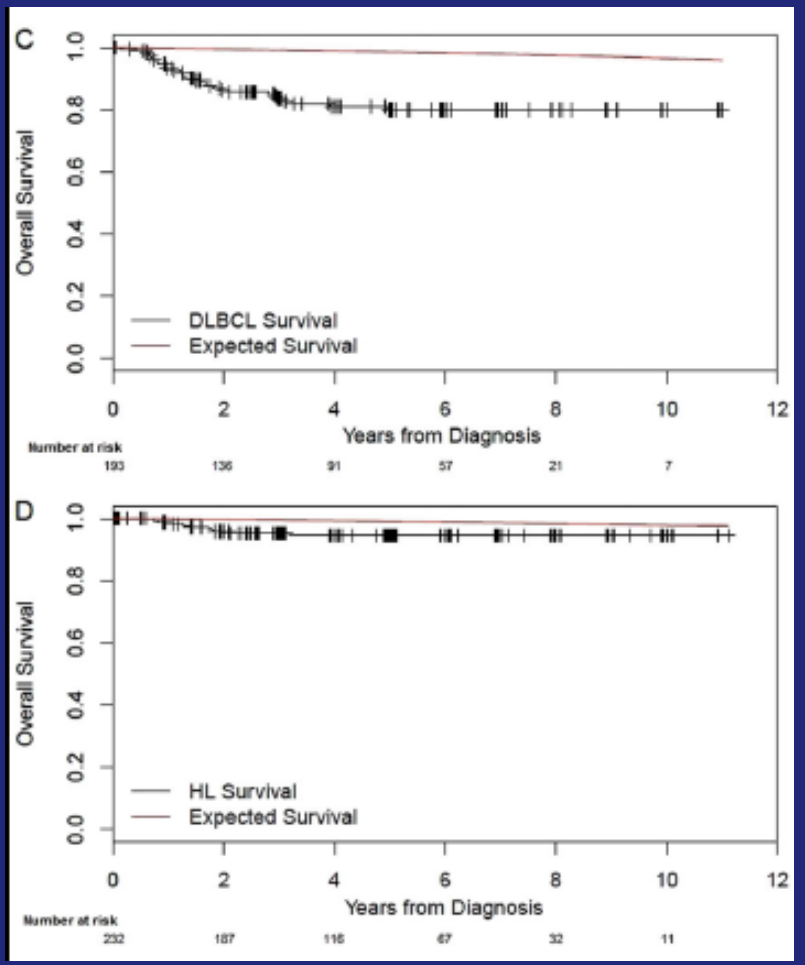




Haematologica 2018

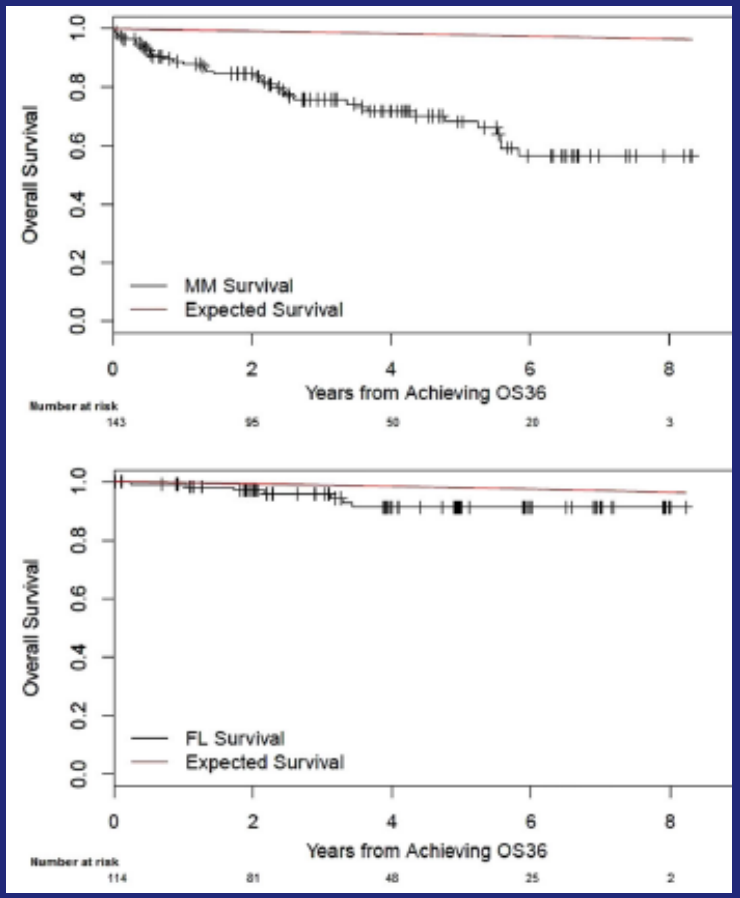
Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies

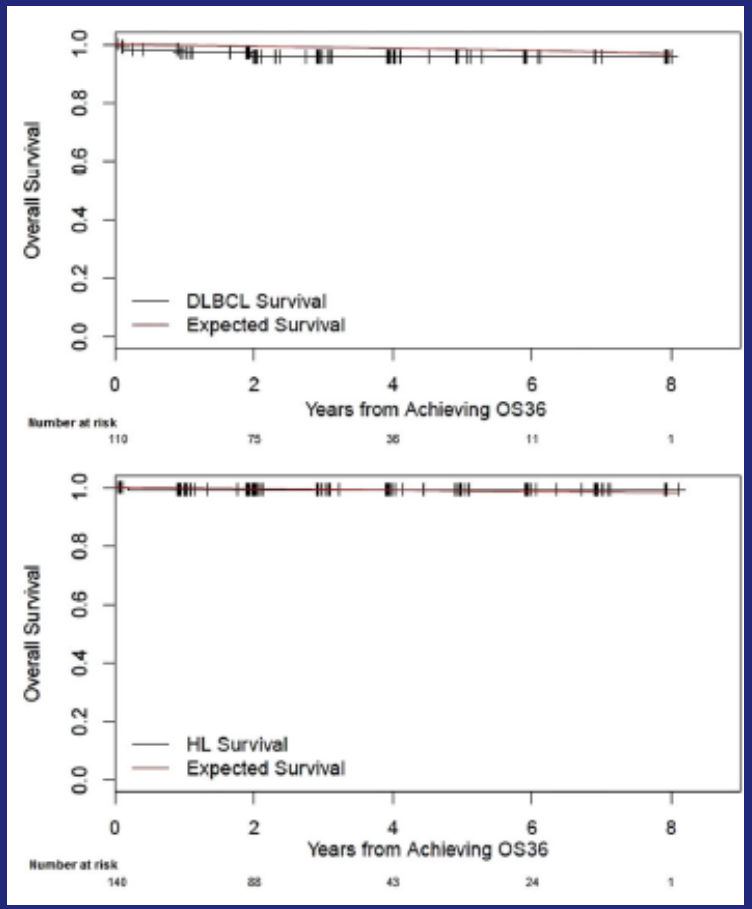




Ravi et al, Blood cancer journal 2018

Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies





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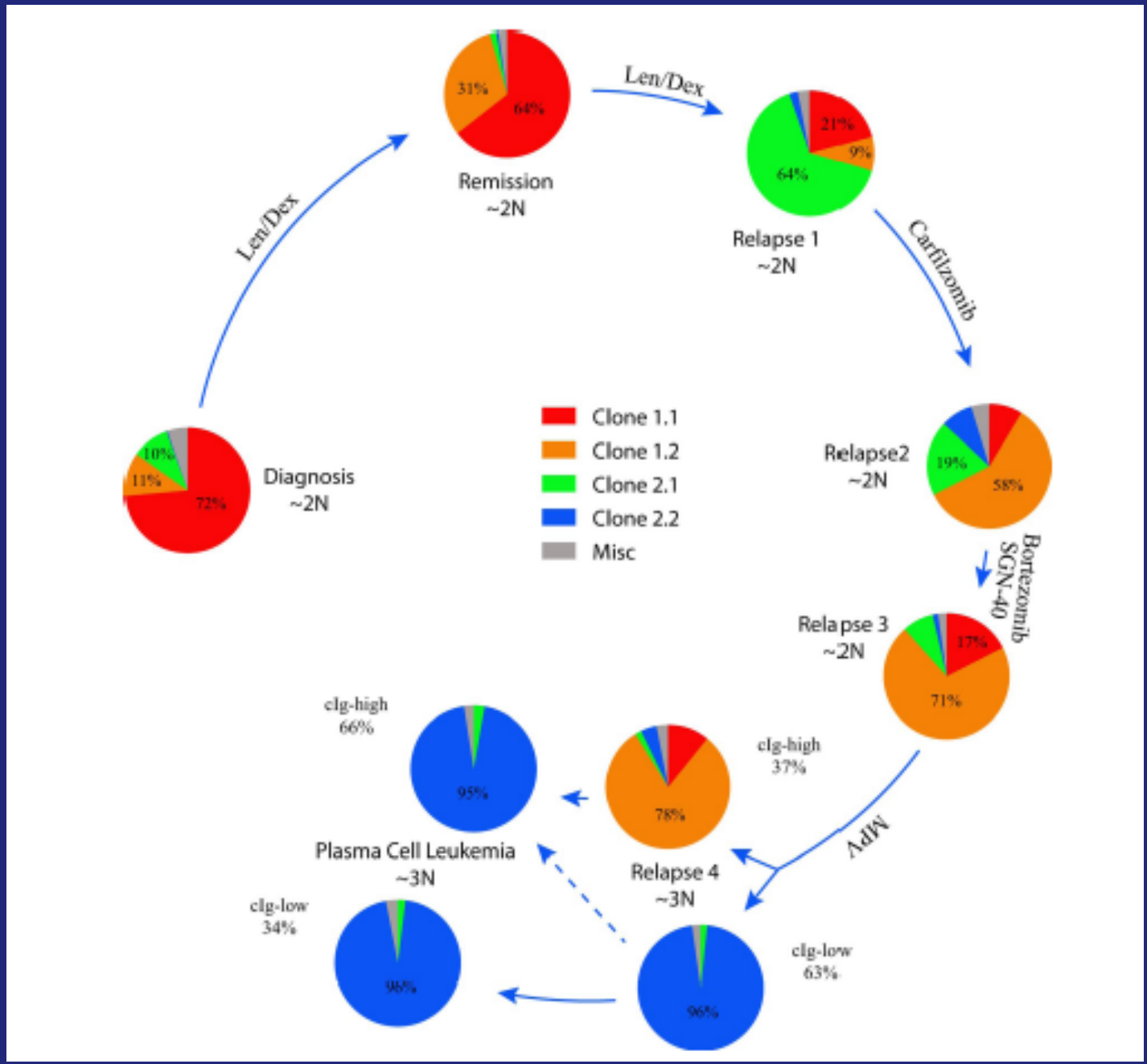
Len/Dex
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64%
Remission
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Len/Dex
21%
9%
64%
Relapse 1
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Carfilzomib
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10%
11%
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Diagnosis
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Clone 1.1
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Clone 2.2
Misc
Relapse2
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19%
58%
Bortezomib
SGN-40
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17%
71%
cIg-high
66%
95%
cIg-high
37%
78%
MPV
Plasma Cell Leukemia
~3N
Relapse 4
~3N
cIg-low
34%
96%
cIg-low
63%
96%

“pathway to cure”

Eradicazione del clone

- Metodiche per valutare l’efficacia del trattamento (MRD)

Trattamento precoce

- Nuovi criteri di inizio trattamento
- Studi sul MM smouldering

Identificazione dei pazienti ad alto rischio

- Trattamenti ad hoc (potenziamento dell’immunoterapia?)


impossible