Historical overview of immunotherapy

Before introduction of immune checkpoint inhibitors

John B.A.G. Haanen, MD PhD

My disclosures

- I have provided consultation, attended advisory boards, and/or provided lectures for: **Pfizer, Bayer, MSD, BMS, IPSEN, Novartis, Roche/Genentech, Neon Therapeutics, Celsius Therapeutics, Gadeta BV, Immunocore, Seattle genetics** for which NKI received honoraria

- Through my work NKI received grant support from **BMS, MSD, Novartis** and **Neon Therapeutics**

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Historical background

examples of immunotherapy and their impact on survival

- **Coley's toxine and spin-off**
- Allogeneic bone marrow and peripheral stem cell transplantations
  - Hematological malignancies
  - (Solid tumors)
- High dose interleukin-2 and LAK cell therapy
  - Metastatic melanoma
  - Metastatic clear cell renal cell cancer
- Adoptive cell therapy with TIL

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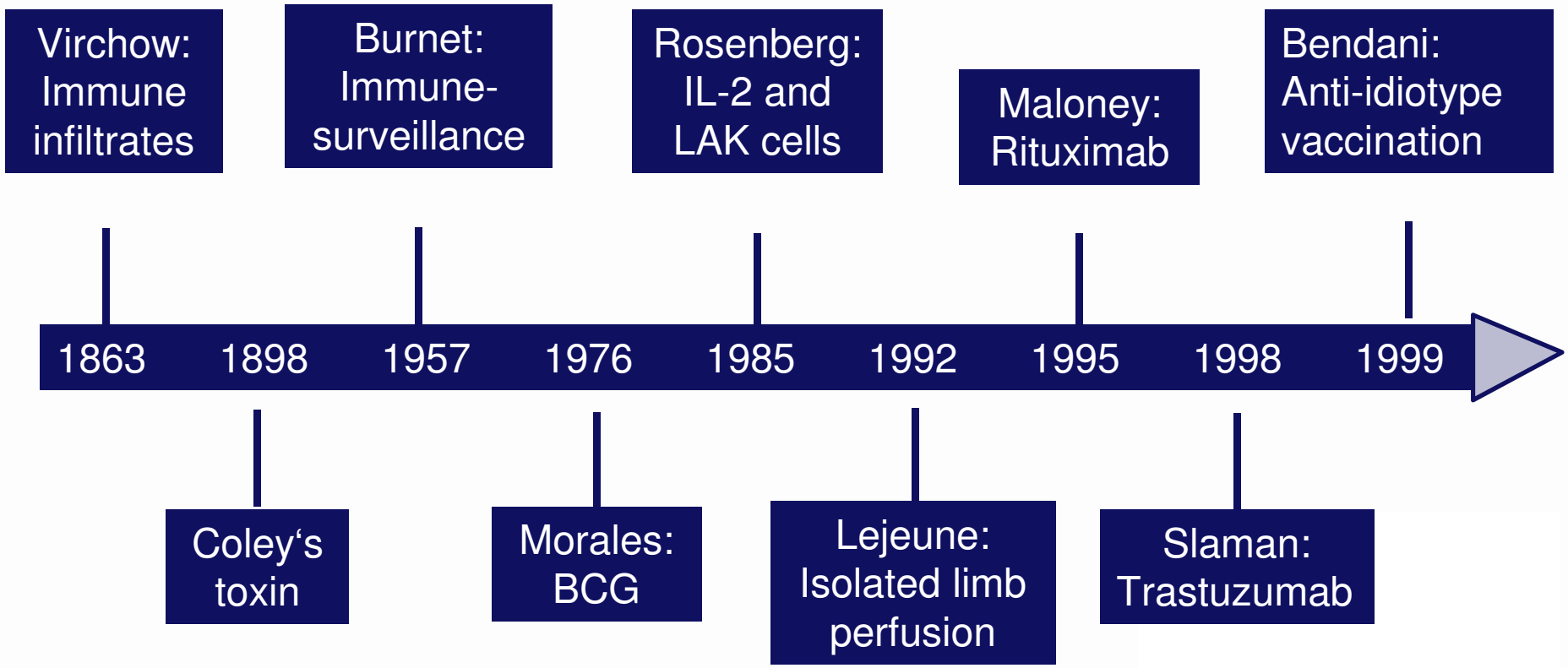
History of cancer immunotherapy



Courtesy of R. Stahel

Coley's toxin

William Coley, 1893

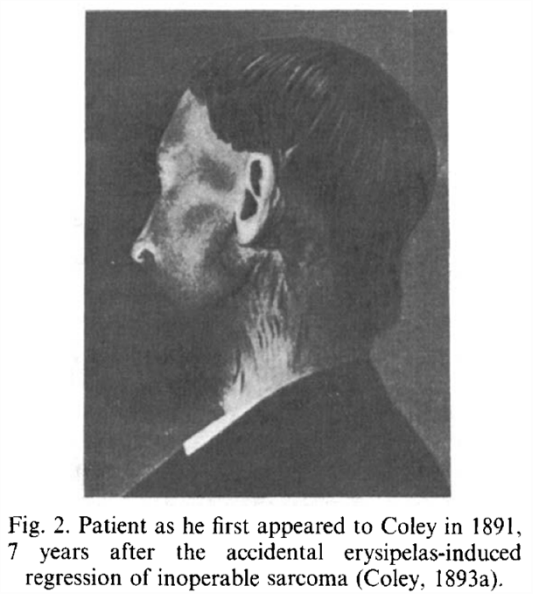


Fig. 2. Patient as he first appeared to Coley in 1891, 7 years after the accidental erysipelas-induced regression of inoperable sarcoma (Coley, 1893a).

Complete remission of a sarcoma in a patient after 2 episodes of erysipelas caused by streptococcus pyogenes

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Courtesy of R. Stahel

Coley's toxin

- Induction of erysipelas by direct inoculation with streptococci

Fig. 3. First patient Coley treated by deliberate induction of erysipelas (Coley, 1896a). Large lesion on neck broke down and disappeared under treatment; see text for description. Patient remained well for 8 years, then died of recurrence (Coley, 1909).

- Coley's toxin: Heat inactivated mixture of streptoccoci and serratia
  About 900 patients treated, most inoperable sarcoma, 10% response rate. Treatment associated high fever

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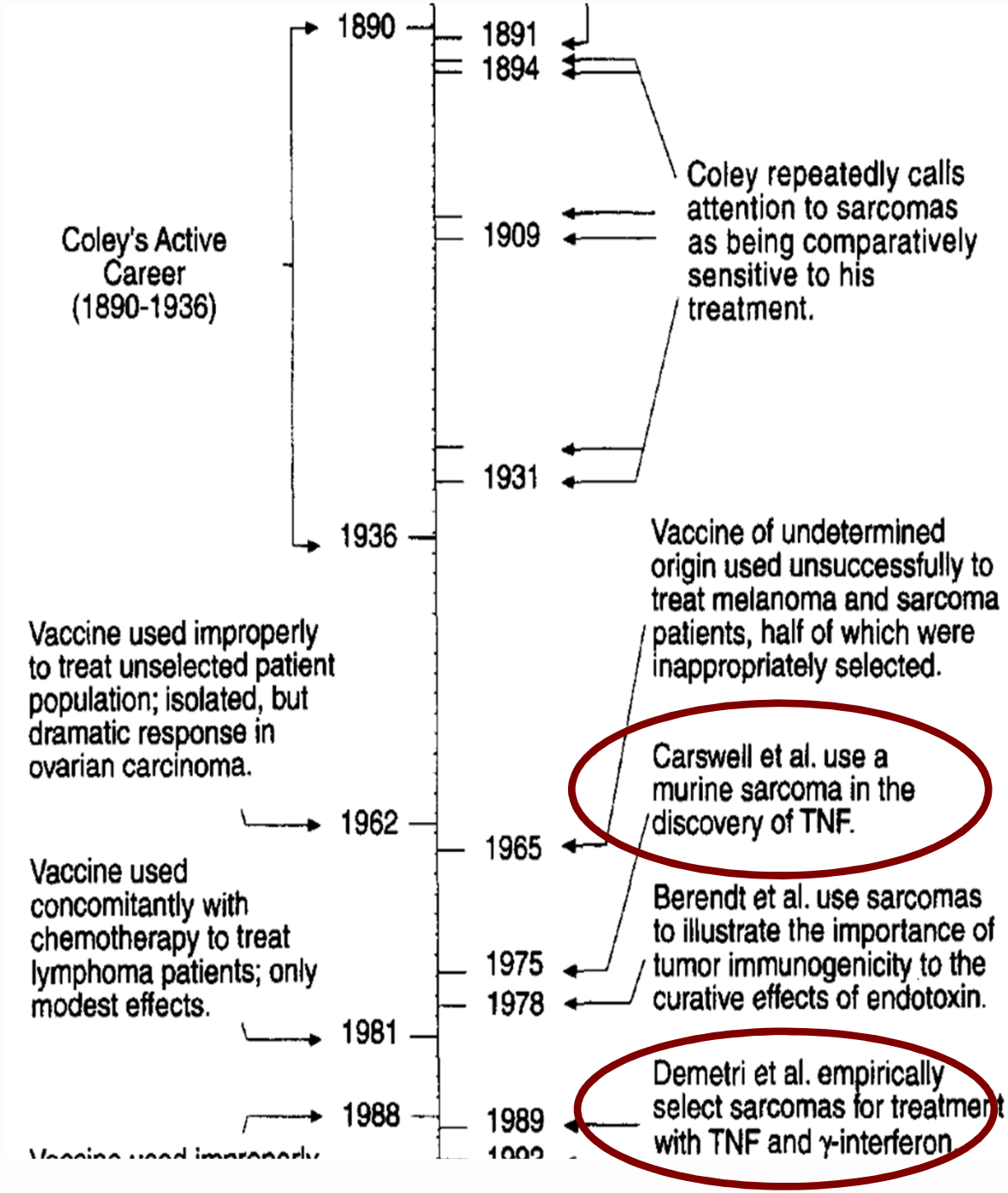
William Coley, 1909

Courtesy of R. Stahel



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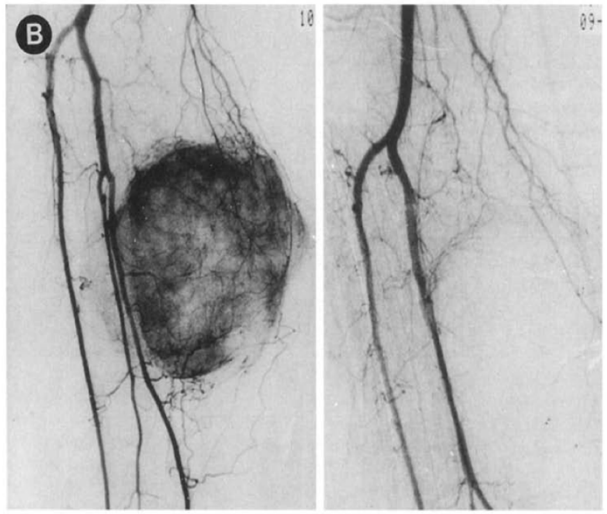
Courtesy of R. Stahel

Isolated Limb Perfusion With High-Dose Tumor Necrosis Factor-α in Combination With Interferon-γ and Melphalan for Nonresectable Extremity Soft Tissue Sarcomas: A Multicenter Trial

By Alexander M.M. Eggermont, Heimen Schraffordt Koops, Danielle Liénard, Bin B.R. Kroon, Albertus N. van Geel, Harald J. Hoekstra, and Ferdy J. Lejeune



Conclusion: **ILP with TNF, IFN, and melphalan is a safe and highly effective induction biochemotherapy procedure that can achieve limb salvage in patients with nonresectable extremity STS. TNF is an active anticancer drug in humans in the setting of ILP.**

J Clin Oncol 14:2653-2665. © 1996 by American Society of Clinical Oncology.

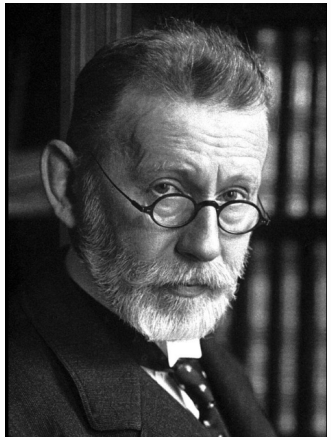
Immunotherapy with BCG

- *Raymond Pearl, Amer J Hyg 1929:* Lower incidence of cancer in patients with TB
- *Lloyd Old, Nature 1959:* Mice infected with BCG have resistance to transplantable tumors
- *Burton Zbar, JNCI 1971*: Suppression of tumor growth in mice at the site of infection with BCG
- *George Mathé, 1968:* Adjuvant BCG in children with acute lymphoblastic leukemia
- *Donald Morton, Surgery 1970:* Intralesional treatment of melanoma metastases with BCG
- *Alvaro Morales, J Urol 1976:* Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors

Courtesy of R. Stahel

Immune Surveillance of Tumours

- *Paul Ehrlich 1909:* the immune system might repress a potential overwhelming frequency of carcinomas



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Courtesy of R. Stahel

Immune Surveillance of Tumours

Lewis Thomas 1957:
"… the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease, thereby maintaining tissue homeostasis in complex multicellular organisms"

1982 Lewis Thomas:
"the greatest trouble with the idea of immunosurveillance is that it cannot be shown to exist in experimental animals"

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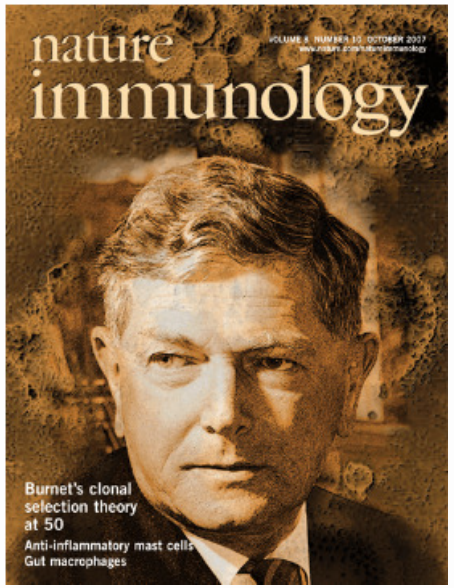
Courtesy of R. Stahel

Immune Surveillance of Tumours

Sir Macfarlane Burnet, 1964

"…in animals, …, inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy.

It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character."



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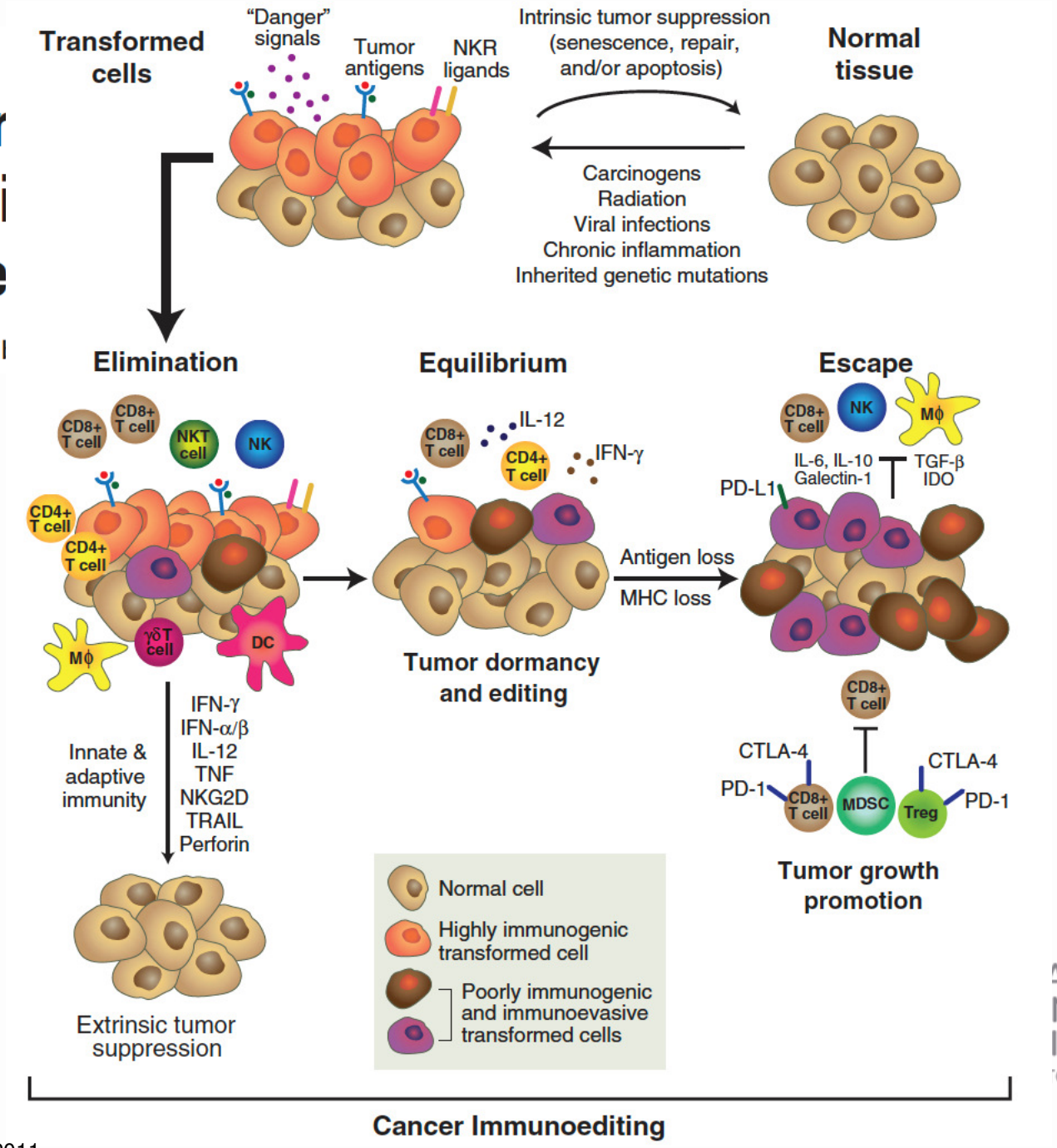
REVIEW

Cancer Immuni Suppre

Robert D. Schreil



Schreiber et al., Science 2011

Historical background

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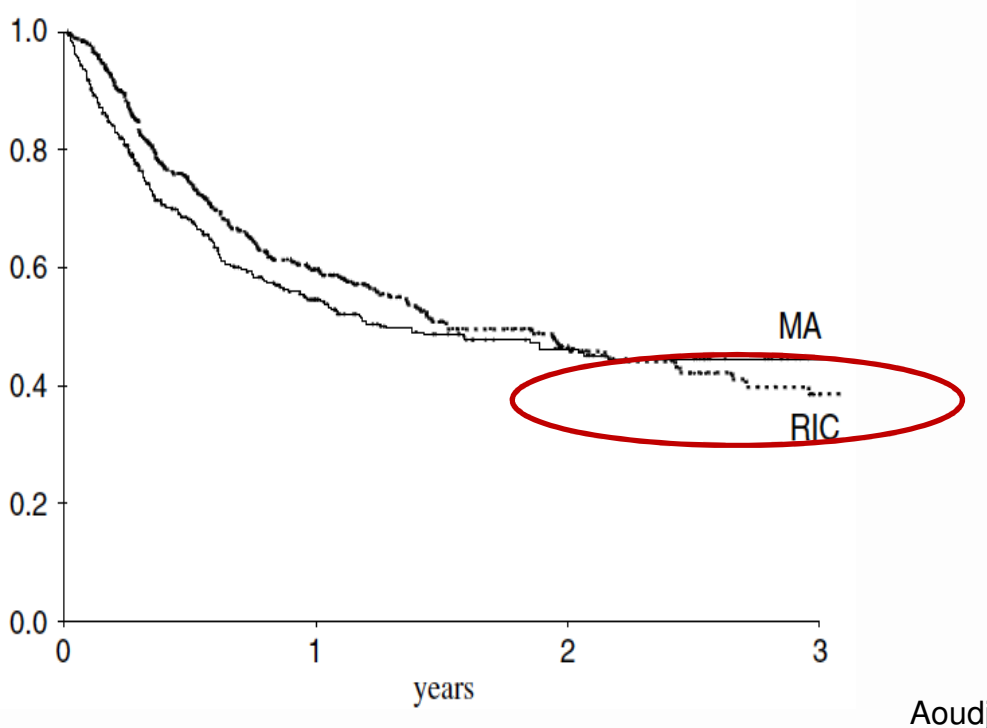
Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT)

M Aoudjhane[1], M Labopin[1], NC Gorin[1], A Shimoni[1], T Ruutu[1], H-J Kolb[1], F Frassoni[1], JM Boiron[1], JL Yin[1], J Finke[1], H Shouten[1], D Blaise[1], M Falda[1], AA Fauser[1], J Esteve[1], E Polge[1], S Slavin[1], D Niederwieser[1], A Nagler[1] and V Rocha[1] on behalf of the Acute Leukemia Working Party of EBMT[2]

OS comparing RIC and MA PSCT from HLA identical siblings



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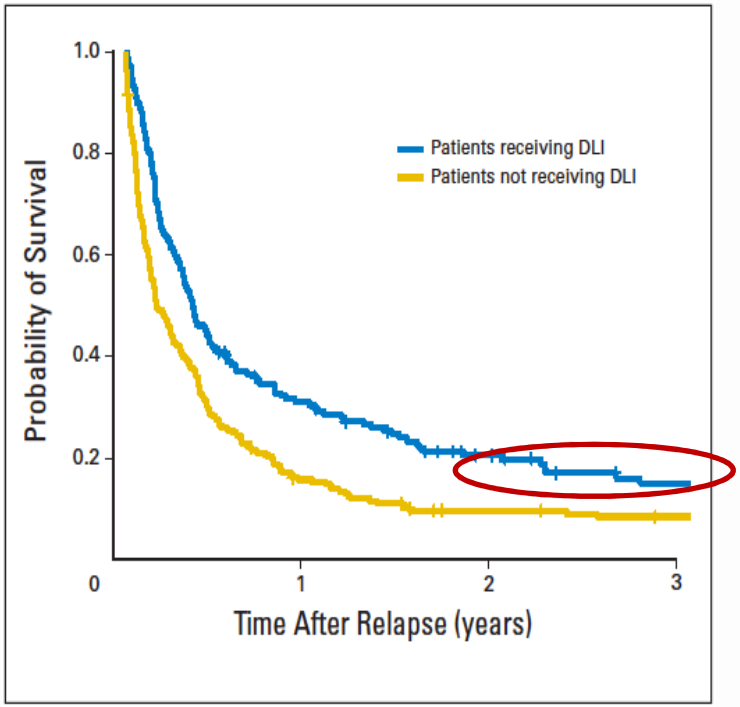
Aoudjhane et al., Leukemia 2005;

Donor Lymphocyte Infusion in the Treatment of First Hematological Relapse After Allogeneic Stem-Cell Transplantation in Adults With Acute Myeloid Leukemia: A Retrospective Risk Factors Analysis and Comparison With Other Strategies by the EBMT Acute Leukemia Working Party

Christoph Schmid, Myriam Labopin, Arnon Nagler, Martin Bornhäuser, Jürgen Finke, Athanasios Fassas, Liisa Volin, Günham Gürman, Johan Maertens, Pierre Bordigoni, Ernst Holler, Gerhard Ehninger, Emmanuelle Polge, Norbert-Claude Gorin, Hans-Jochem Kolb, and Vanderson Rocha



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Schmid et al., JCO 2007

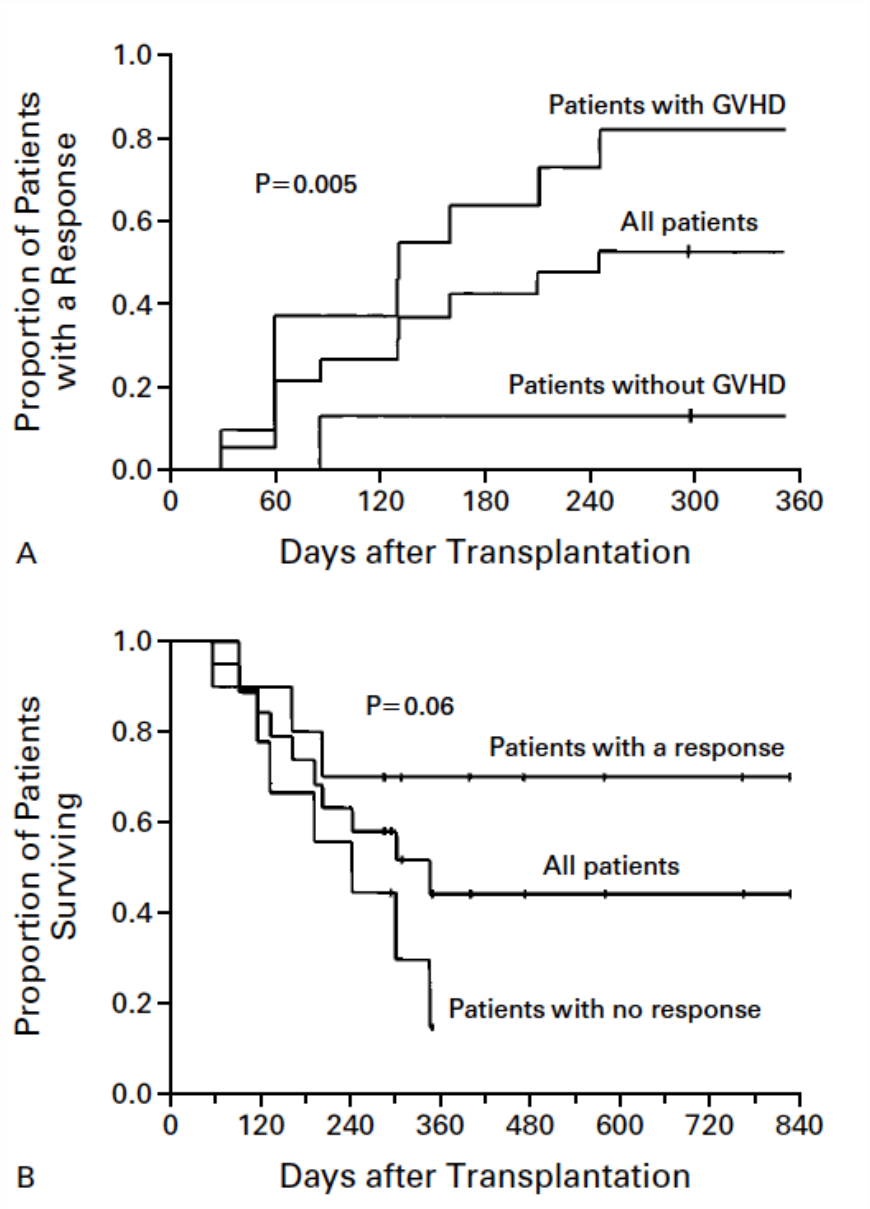
The New England
Journal of Medicine

VOLUME 343 SEPTEMBER 14, 2000 NUMBER 11

REGRESSION OF METASTATIC RENAL-CELL CARCINOMA AFTER NONMYELOABLATIVE ALLOGENEIC PERIPHERAL-BLOOD STEM-CELL TRANSPLANTATION

RICHARD CHILDS, M.D., ALLEN CHERNOFF, M.D., NATHALIE CONTENTIN, M.D., ERKUT BAHCECI, M.D., DAVID SCHRUMP, M.D., SUSAN LEITMAN, M.D., ELIZABETH J. READ, M.D., JOHN TISDALE, M.D., CYNTHIA DUNBAR, M.D., W. MARSTON LINEHAN, M.D., NEAL S. YOUNG, M.D., AND A. JOHN BARRETT, M.D.

Outcome of mRCC patients treated with allogeneic PSCT



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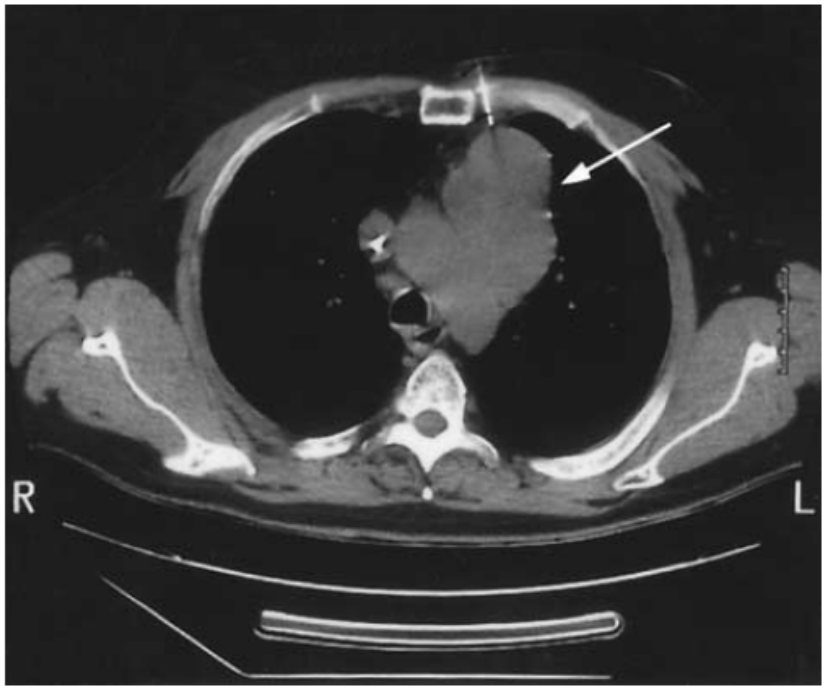
Childs et al., NEJM 2000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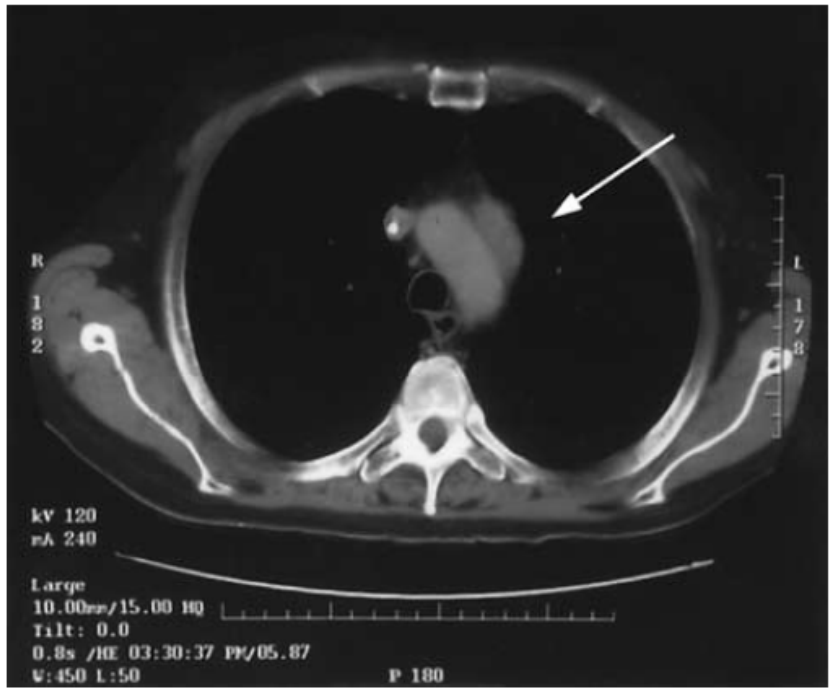
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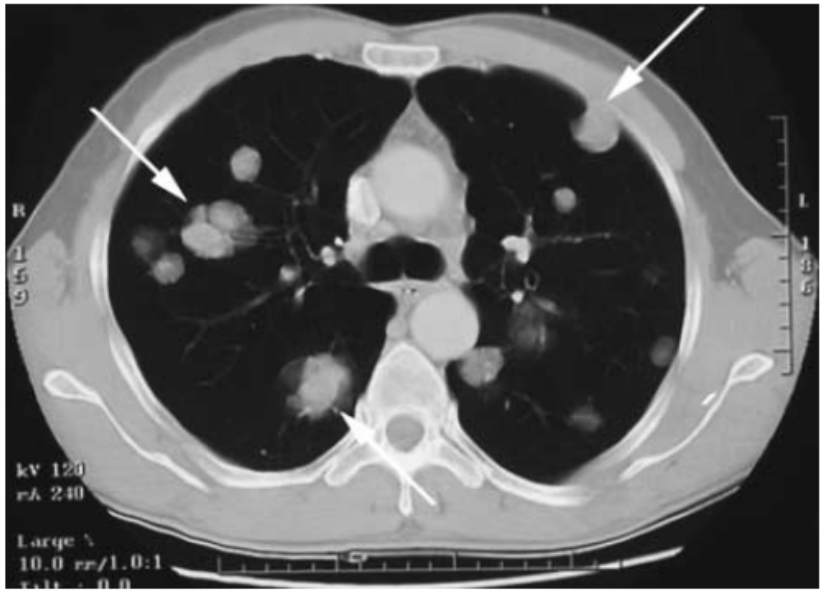
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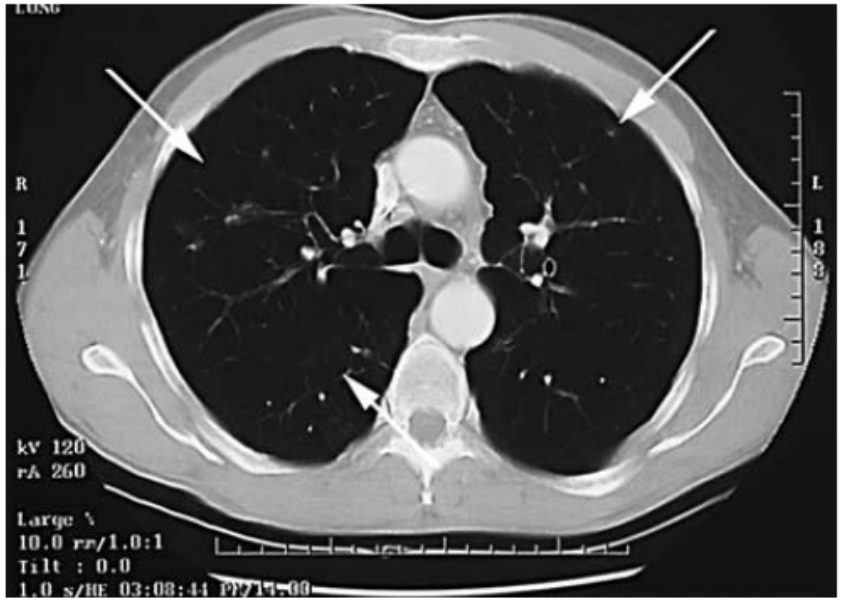
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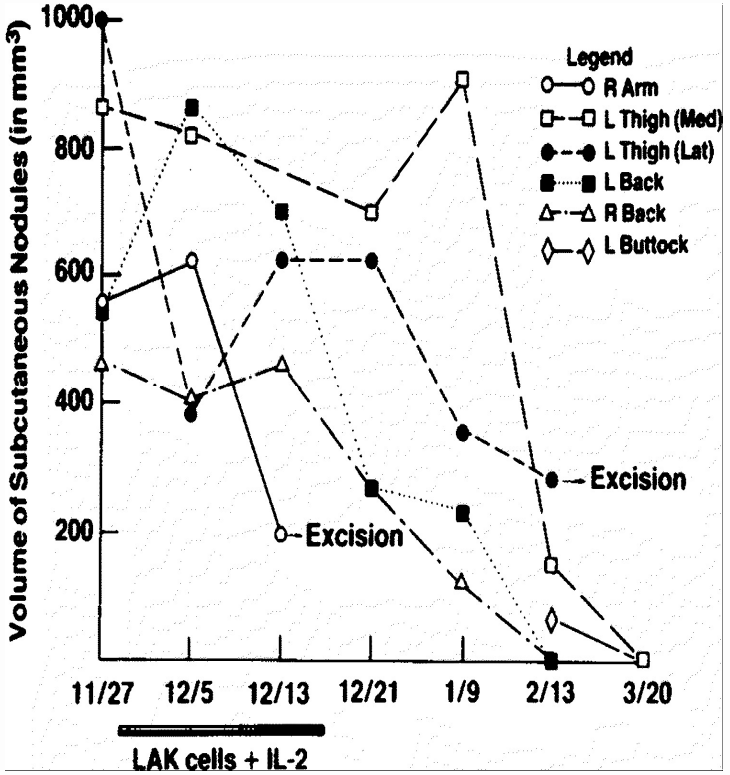
LAK cell therapy and Interleukin-2

Steven Rosenberg, NEJM 1985:
Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer



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LAK cell therapy in combination with interleukin-2

Steven Rosenberg, NEJM 1985:
Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer

Table 2. Toxicity of Therapy with LAK Cells and Interleukin-2

Side Effect	No. of Patients
Malaise	25
Fever	22
Chills	19
Nausea or vomiting	21
Diarrhea	18
Confusion	8
Weight gain (>10%)	16
Dyspnea	20
Erythema or rash	17
Pruritus	16
Glossitis	14
Nasal congestion	13
Serum creatinine >2 mg/dl	12
Serum bilirubin >2 mg/dl	16
Eosinophilia >5%	24
Anemia requiring transfusion	24
Thrombocytopenia (<50,000/mm^3)	11

Tolerance and effectiveness of recombinant interleukin-2 and lymphokine-activated killer cells in patients with metastatic solid tumors

- 26 patients with metastatic solid tumors, including 14 renal cell carcinomas, seven melanomas, three extragonadal germ cell tumors refractory to chemotherapy and two colon carcinomas
- Capillary leak syndrome with hypotension and impaired renal function and CNS toxicity were the major reasons for dose modification
- Partial responses were documented in three renal cell carcinomas and one melanoma. The median response duration was 5.5 (range 1-6) months.

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Stahel, Eur J Cancer Clin Oncol 1989

High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

By Michael B. Atkins, Michael T. Lotze, Janice P. Dutcher, Richard I. Fisher, Geoffrey Weiss, Kim Margolin, Jeff Abrams, Mario Sznol, David Parkinson, Michael Hawkins, Carolyn Paradise, Lori Kunkel, and Steven A. Rosenberg

Randomized Study of High-Dose and Low-Dose Interleukin-2 in Patients With Metastatic Renal Cancer

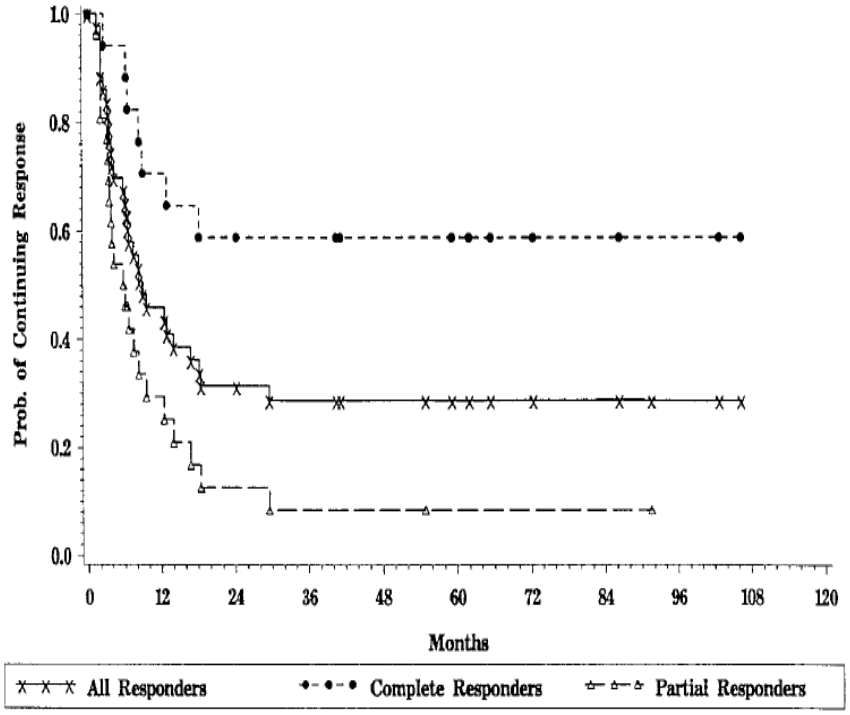
By James C. Yang, Richard M. Sherry, Seth M. Steinberg, Suzanne L. Topalian, Douglas J. Schwartzentruber, Patrick Hwu, Claudia A. Seipp, Linda Rogers-Freezer, Kathleen E. Morton, Donald E. White, David J. Liewehr, Maria J. Merino, and Steven A. Rosenberg

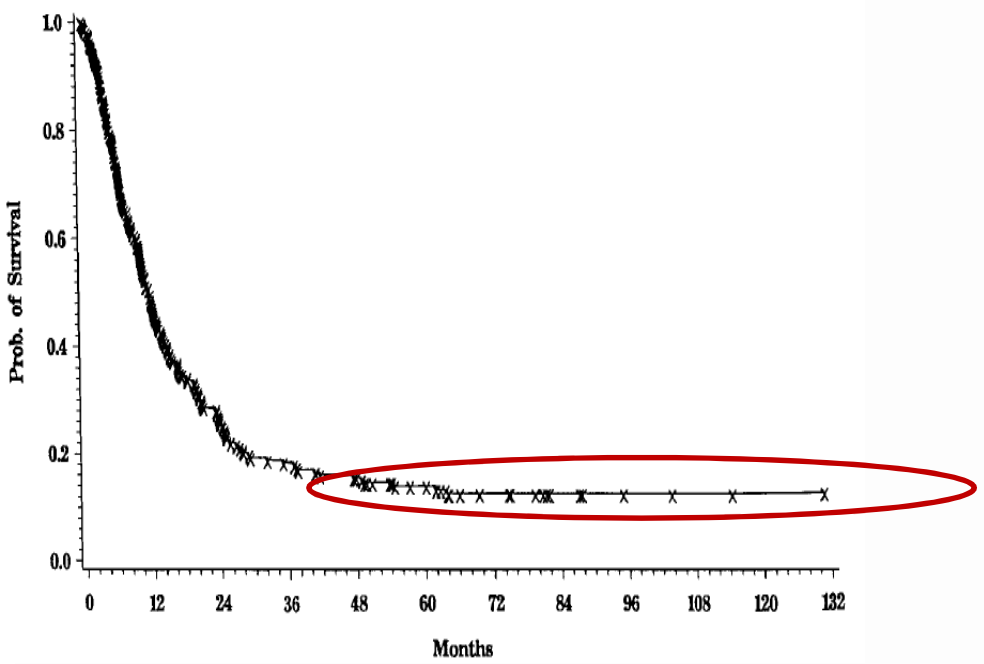
Randomized Phase III Trial of High-Dose Interleukin-2 Versus Subcutaneous Interleukin-2 and Interferon in Patients With Metastatic Renal Cell Carcinoma

David F. McDermott, Meredith M. Regan, Joseph I. Clark, Lawrence E. Flaherty, Geoffery R. Weiss, Theodore F. Logan, John M. Kirkwood, Michael S. Gordon, Jeffrey A. Sosman, Marc S. Ernstoff, Christopher P.G. Tretter, Walter J. Urba, John W. Smith, Kim A. Margolin, James W. Mier, Jared A. Gollob, Janice P. Dutcher, and Michael B. Atkins

Atkins et al., JCO 1999; Yang et al., JCO 2003; McDermott et al., JCO 2005

Overall Survival of patients with metastatic RCC treated with high dose IL-2





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Atkins et al., JCO 1999

Durability of Complete Responses in Patients With Metastatic Cancer Treated With High-Dose Interleukin-2

Identification of the Antigens Mediating Response

Steven A. Rosenberg, MD, PhD,* James C. Yang, MD,* Donald E. White, MS,* and Seth M. Steinberg, PhD†

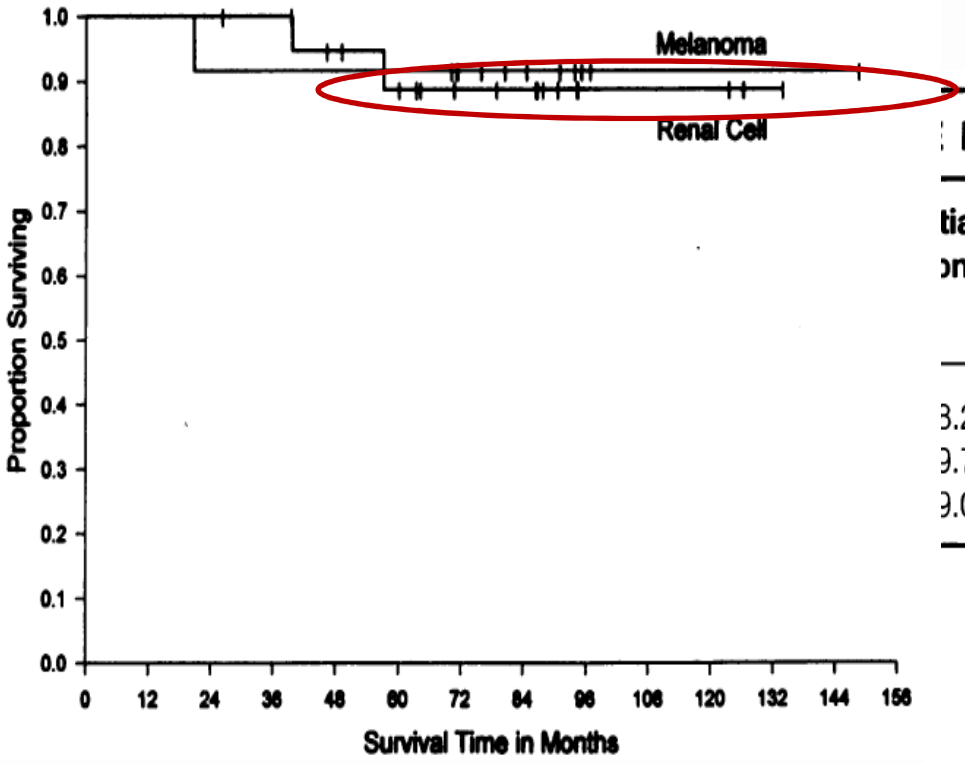

Table 2 BOLUS IL-2

Diagnosis	tial onse	Total
Melanoma	3.2)	27 (14.8)
Renal cancer	9.7)	43 (19.0)
Total	9.0)	70 (17.1)

Rosenberg et al. Ann Surg 1998

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Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

Mark E. Dudley,[1] John R. Wunderlich,[1] Paul F. Robbins,[1] James C. Yang,[1] Patrick Hwu,[1] Douglas J. Schwartzentruber,[1] Suzanne L. Topalian,[1] Richard Sherry,[1] Nicholas P. Restifo,[1] Amy M. Hubicki,[1] Michael R. Robinson,[2] Mark Raffeld,[3] Paul Duray,[3] Claudia A. Seipp,[1] Linda Rogers-Freezer,[1] Kathleen E. Morton,[1] Sharon A. Mavroukakis,[1] Donald E. White,[1] Steven A. Rosenberg[1]*

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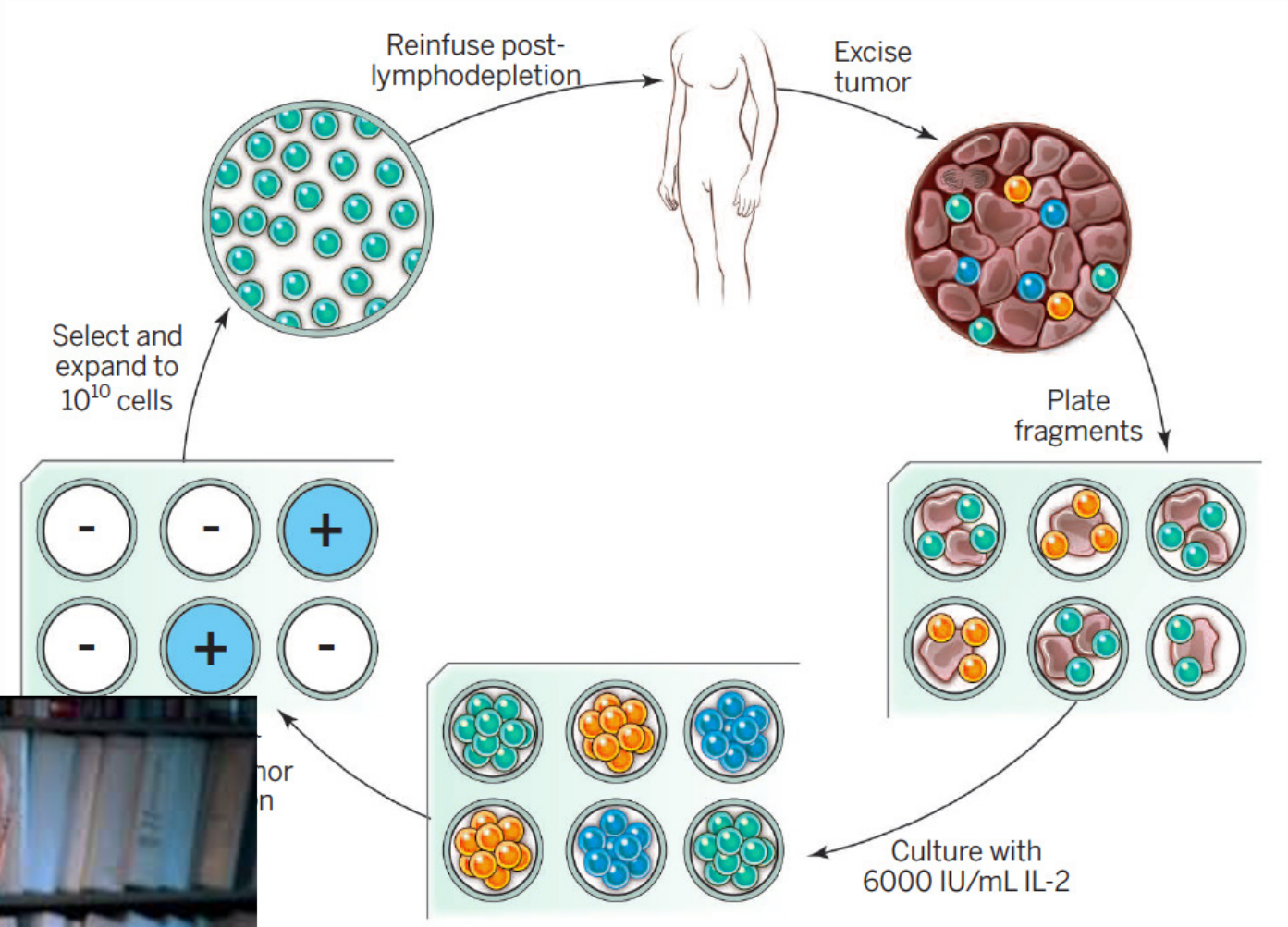
Dudley et al., Science 2002

Scheme for TIL therapy



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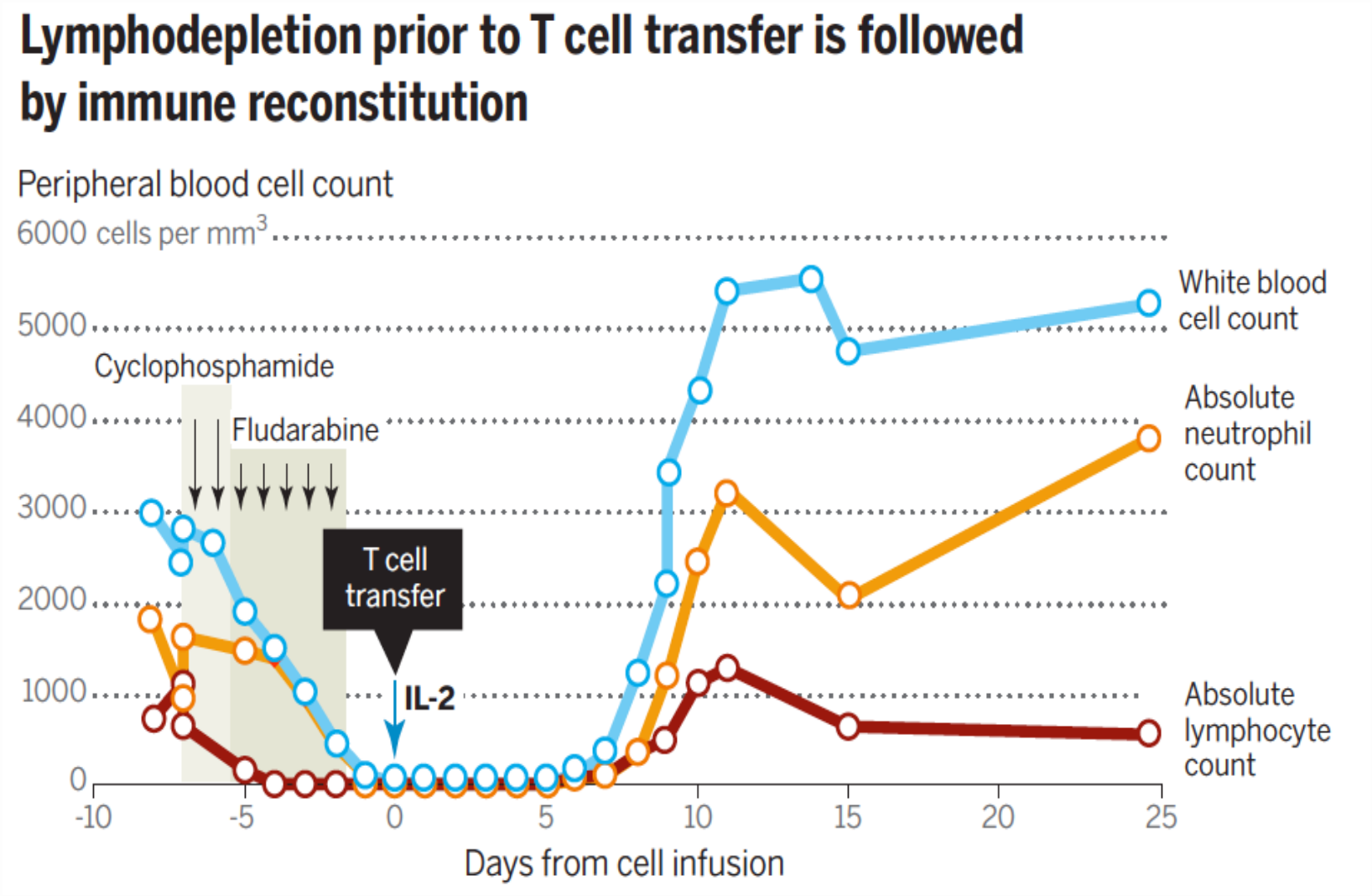
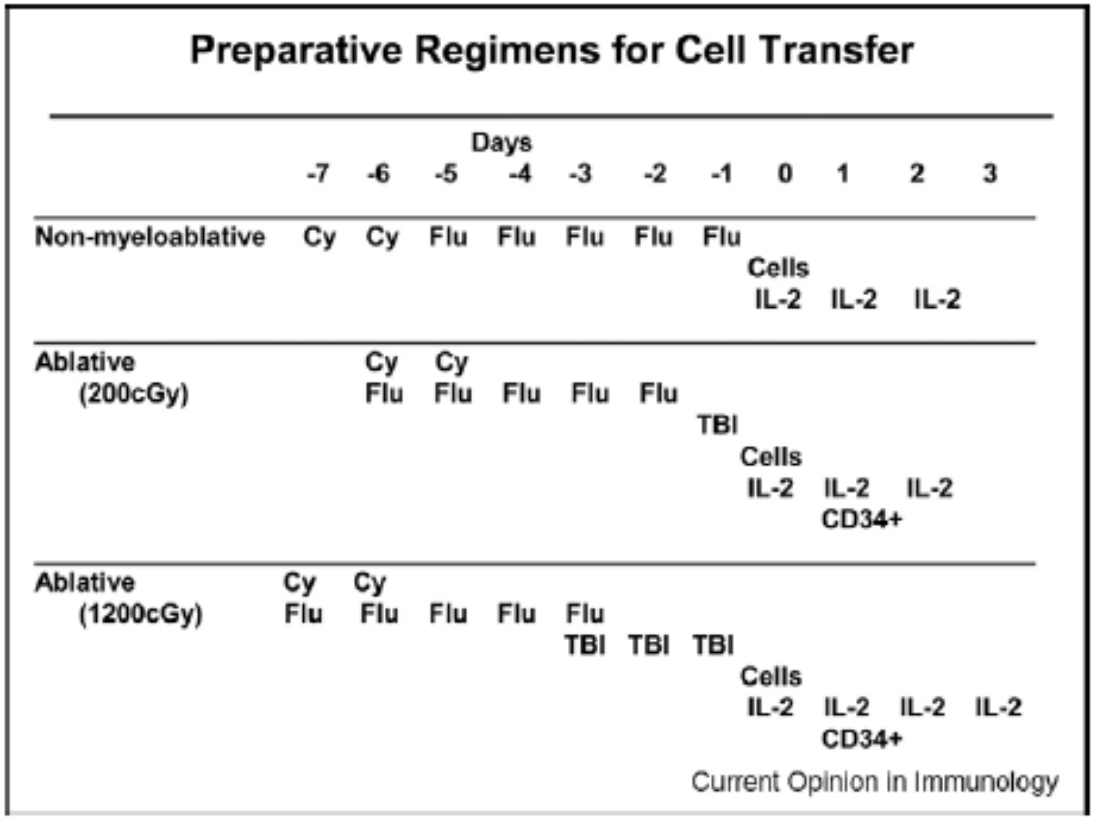


Rosenberg & Restifo Science 2015



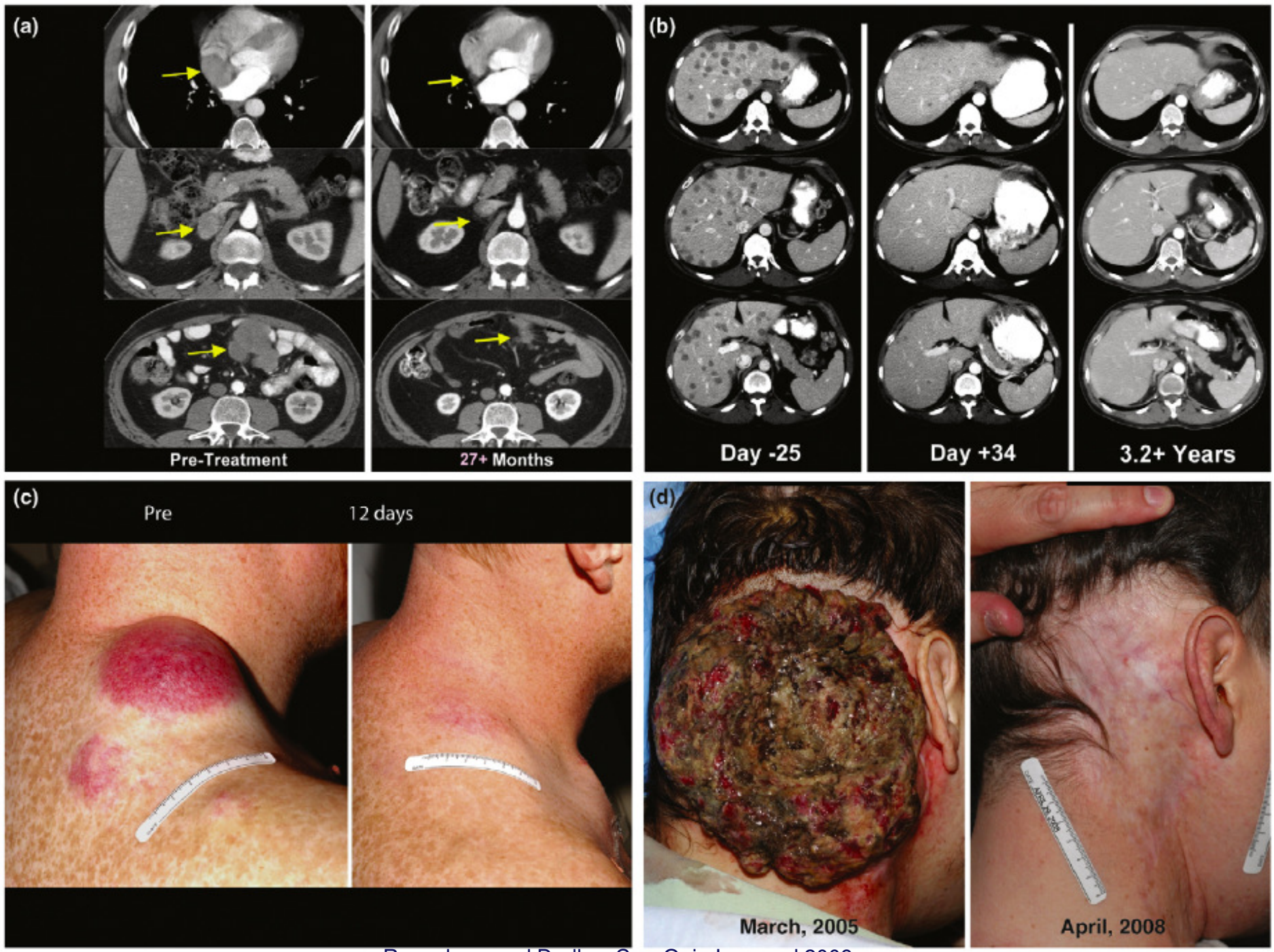
Cell transfer therapy.[a]

Treatment	Total	PR	CR	OR (%)
No TBI	43	17 (77+, 45+, 34+, 29, 28, 14, 13, 11, 8, 8, 7, 4, 3, 3, 2, 2, 2)	3 (75+, 70+, 60+, 59+)	21 (49%)
200 cGy TBI	25	11 (45+.41+.35+.14 10, 6, 5, 5, 4, 3, 3)	2 (49+, 38+)	13 (52%)
1200 cGy TBI	25	11 (26+, 19+, 19+, 19+, 13, 7, 6, 6, 5, 4, 3)	7 (29+, 19, 25+, 25+, 19+, 19+, 18+)	18 (72%)

52 responding patients: 42 had prior IL-2, 21 had prior IL-2+ chemotherapy.

[a] All patients with metastatic melanoma received a preparative regimen of cyclophosphamide (60 mg/kg/day × 2d) and fludarabine (25 mg/m^2/day × 5d) either with no total body irradiation (TBI) or with 200 or 1200 cGy TBI followed by the administration of autologous TIL plus IL-2 (720,000 IU/kg q 8 h).

Rosenberg and Dudley. Curr Opin Immunol 2009



Rosenberg and Dudley. Curr Opin Immunol 2009

Summary

- Over more than 100 years the role of the immune system in defense against cancer has established
- Immunotherapy of cancer has slowly developed into an effective treatment for few patients, sometimes with severe toxicities
- Currently, with the arrival of immune checkpoint blockers and new modalities of adoptive cell therapy (CARs), immunotherapy has led to a paradigm shift in the treatment of cancer

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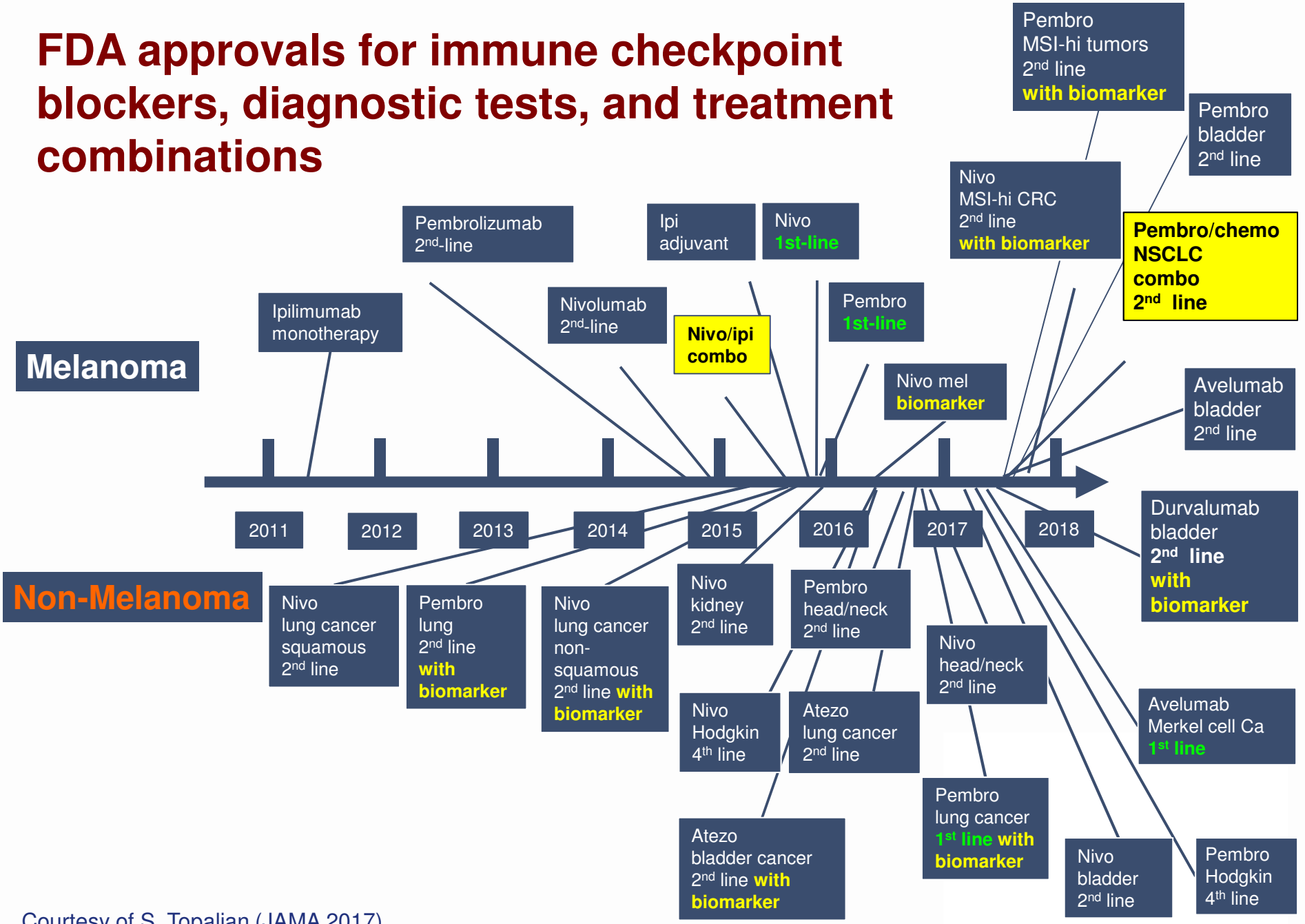
FDA approvals for immune checkpoint blockers, diagnostic tests, and treatment combinations



Courtesy of S. Topalian (JAMA 2017)