Immunotherapy of cancer
Some historical background

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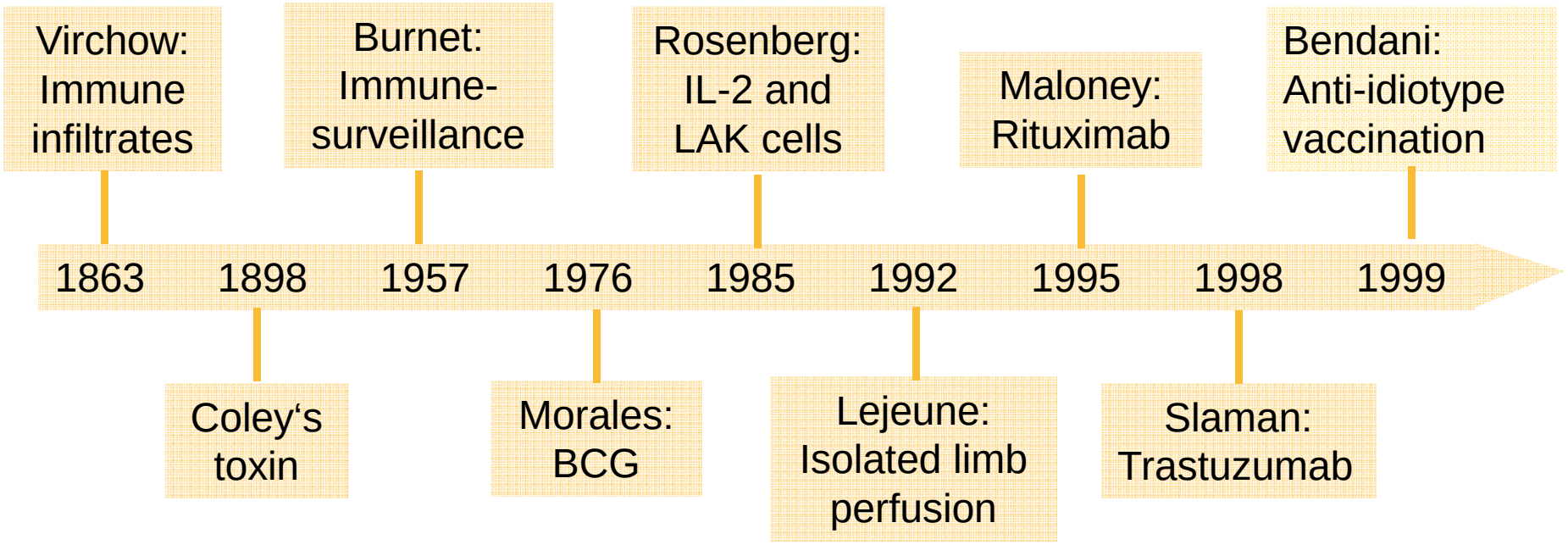
History of cancer immunotherapy before the immune checkpoint inhibitors



Coley's toxin

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

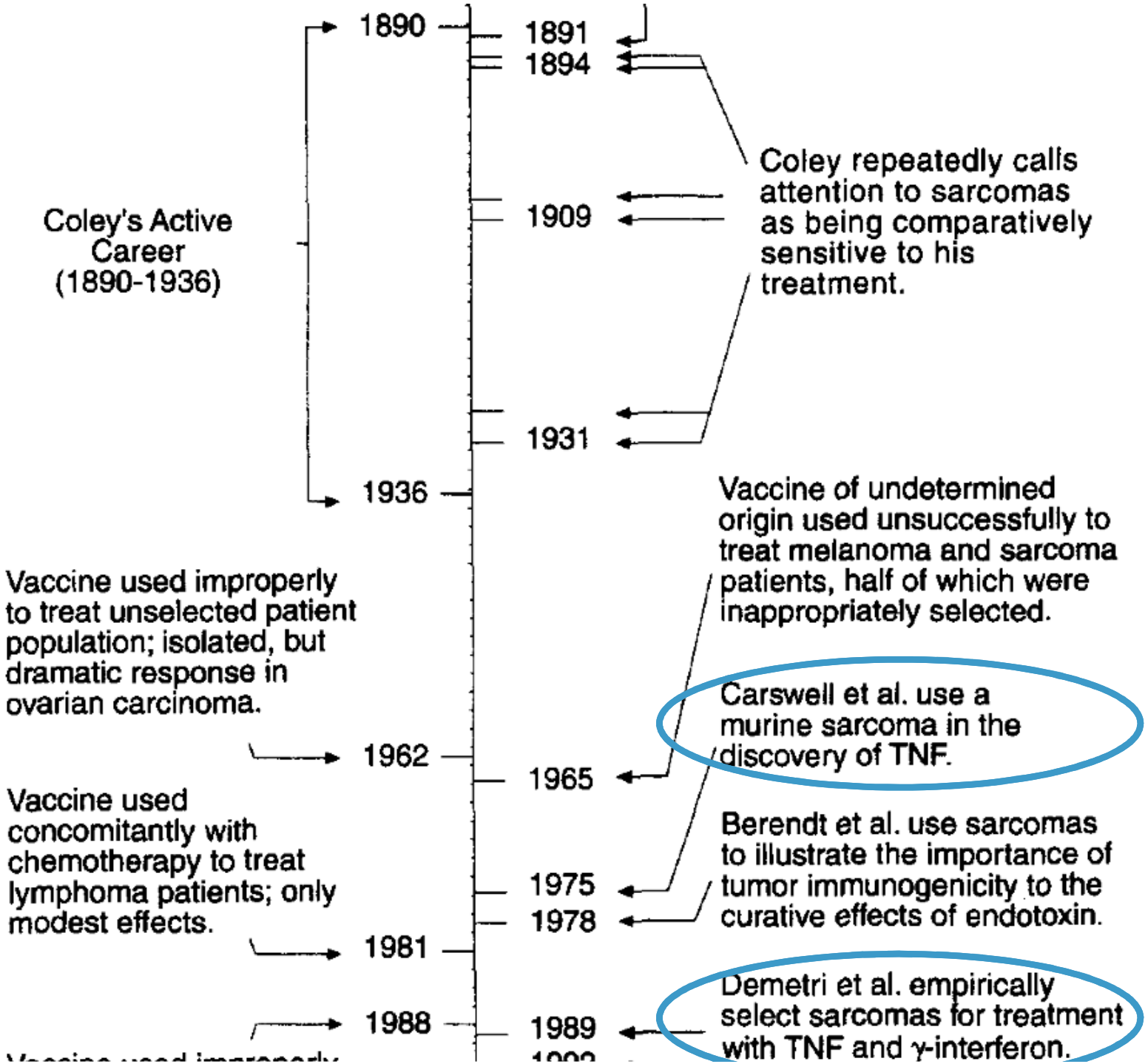
William Coley, 1893

Coley's toxin

- Induction of erysipelas
  by direct inoculation with
  streptococci

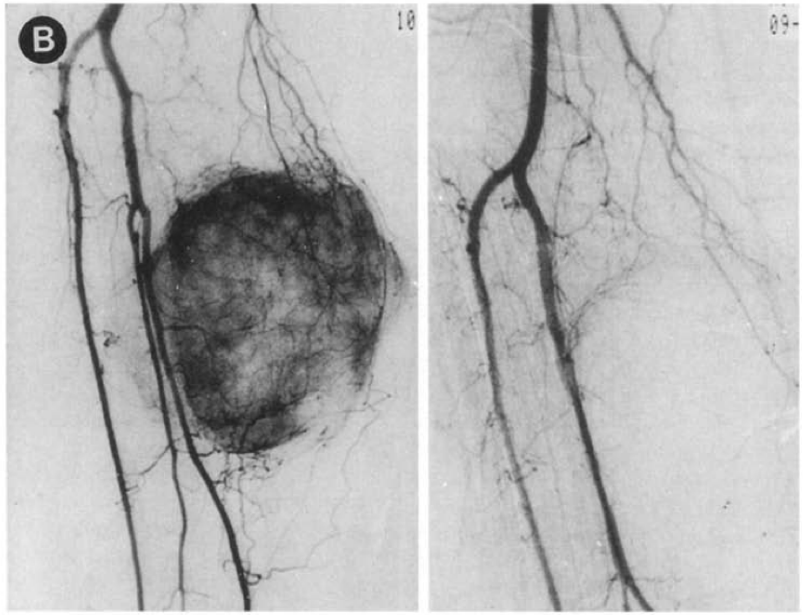
Fig. 3. First patient Coley treated by deliberate induction of erysipelas (Coley, 1896a). Large lesion on neck broke down and disappeared under treatment; see text for description. Patient remained well for 8 years, then died of recurrence (Coley, 1909).

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


1890
1891
1894
1909
1931
1936
1962
1965
1975
1978
1981
1988
1989
Coley's Active Career (1890-1936)
Coley repeatedly calls attention to sarcomas as being comparatively sensitive to his treatment.
Vaccine of undetermined origin used unsuccessfully to treat melanoma and sarcoma patients, half of which were inappropriately selected.
Vaccine used improperly to treat unselected patient population; isolated, but dramatic response in ovarian carcinoma.
Carswell et al. use a murine sarcoma in the discovery of TNF.
Vaccine used concomitantly with chemotherapy to treat lymphoma patients; only modest effects.
Berendt et al. use sarcomas to illustrate the importance of tumor immunogenicity to the curative effects of endotoxin.
Demetri et al. empirically select sarcomas for treatment with TNF and γ-interferon.

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.**

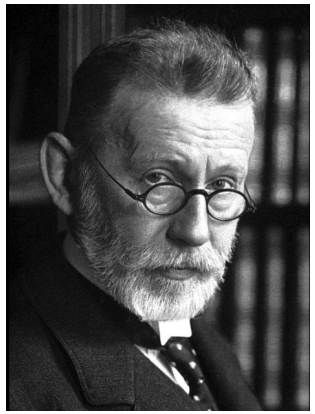
J Clin Oncol 14:2653-2665.

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
-

Immune Surveillance of Tumours

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



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 homoestastsis in complex multicellular organisms"

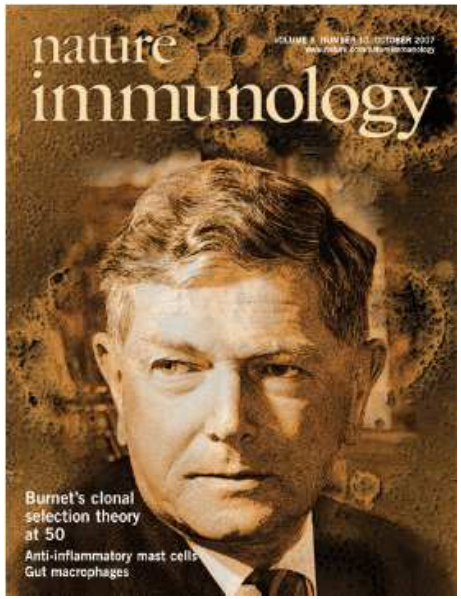
- *1982 Lewis Thomas:*
  "the greatest trouble with the idea of immunosurveillance is that it cannot be shown to exist in experimental animals"

Immune Surveillance of Tumours

Sir Macfarlane Burnet, 1964

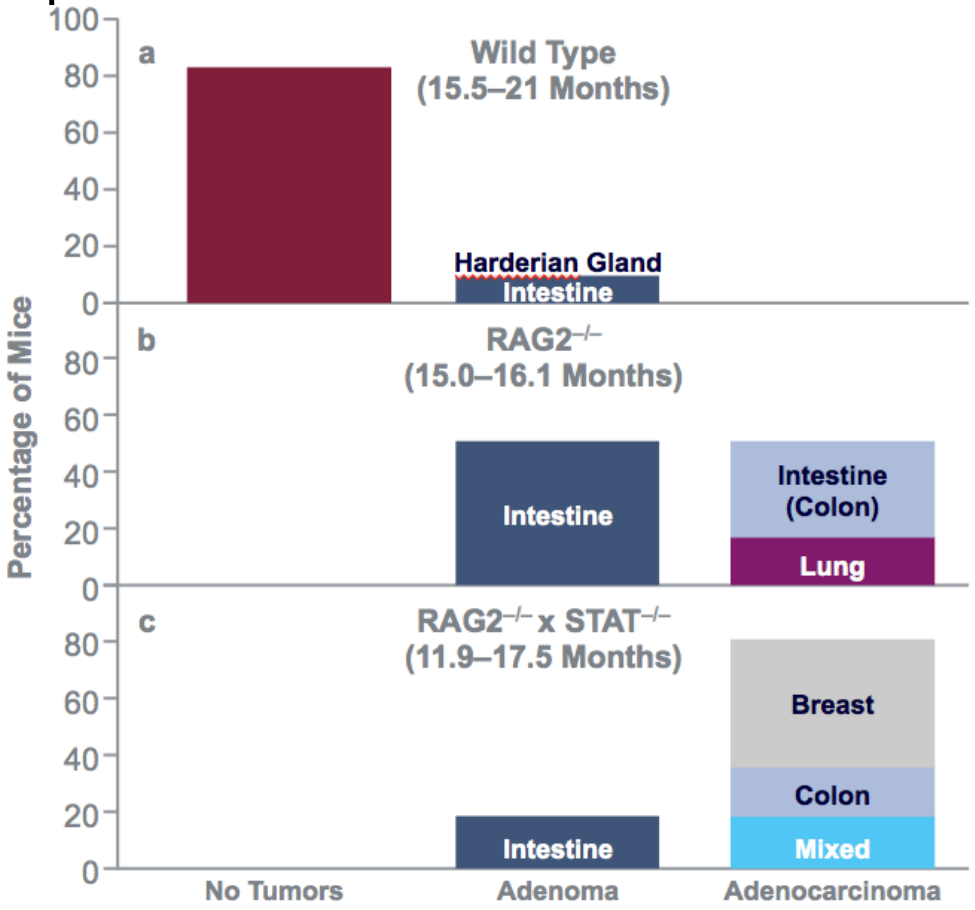
"…in animals, …, inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy.

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."



IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity

Sponaneous carcinomas in immundeficient mice



RAG2$^{-/-}$:
no B and no T cells;

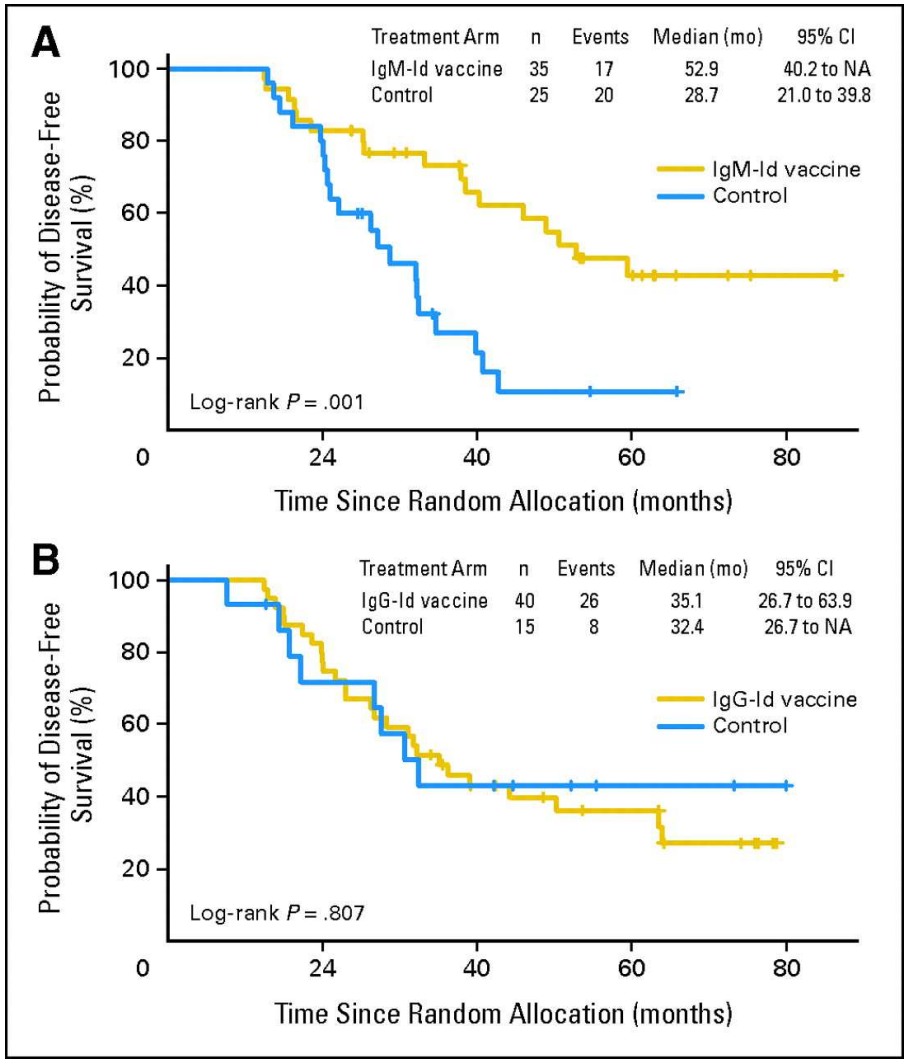
STAT1$^{-/-}$:
No IFN-γ signaling

Shankaran, …, Old, Schreiber, Nature 2001

Vaccines against cancer-associated antigens

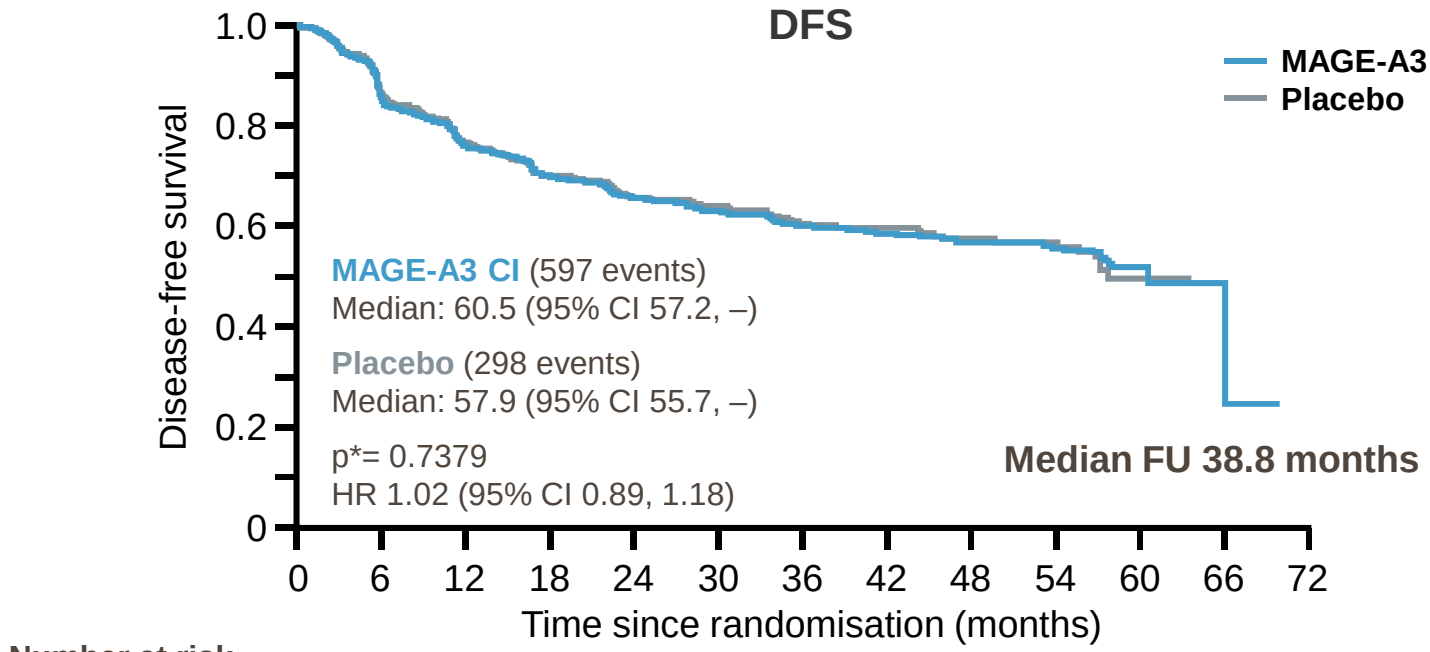
- *Maurizio Bendandi,… Larry Kwak, Nat Med 1999:* Complete molecular remissions induced by patient-specific vaccination plus granulocyte−monocyte colony-stimulating factor against lymphoma
- “The demonstration of molecular remissions, analysis of cytotoxic T lymphocytes against autologous tumor targets, and addition of granulocyte-monocyte colony-stimulating factor to the vaccine formulation provide principles relevant to the design of future clinical trials of other cancer vaccines administered in a minimal residual disease setting”

Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma



Schuster, JCO 2011

MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 as adjuvant therapy in resected MAGE-A3-positive NSCLC



Number at risk												
MAGE-A3 CI	1,515	1,257	1,115	1,013	887	656	476	339	220	127	19	2
Placebo	757	639	562	514	448	328	253	180	114	62	6	0

Vansteenkiste, ESMO 2014

Cytokines in immunotherapy: the example of IL2

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

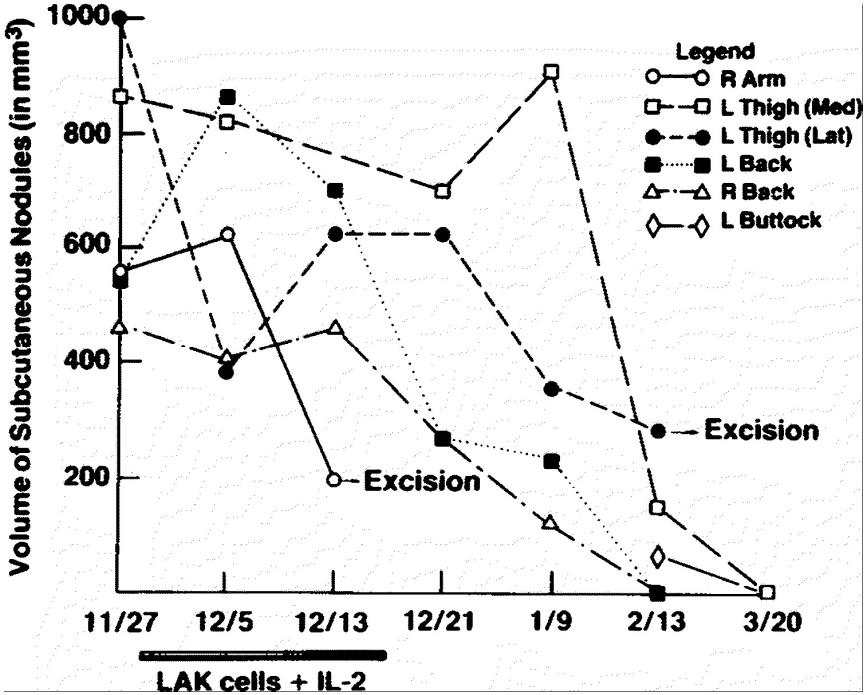


Table 2. Toxicity of Therapy with LAK Cells and Interleukin-2

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

Rosenberg, NEJM 1985

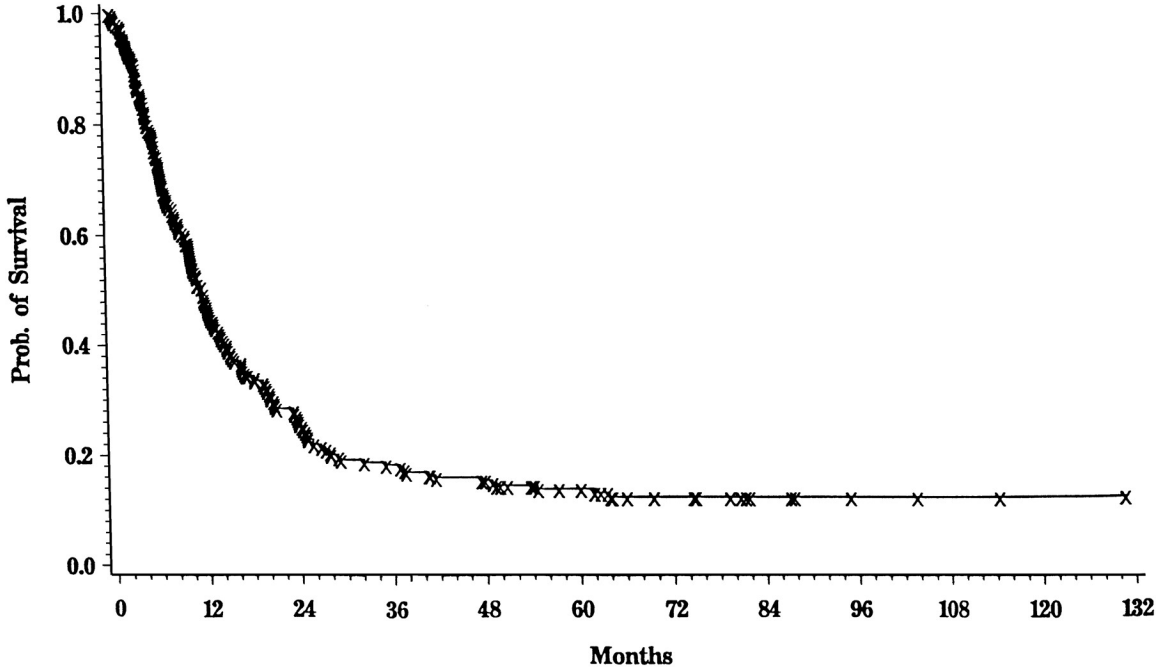
Tolerance and effectiveness of recombinant interleukin-2 (r-met Hu IL-2 [ala-125]) and lymphokine-activated killer cells in patients with metastatic solid tumors.

- 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.

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

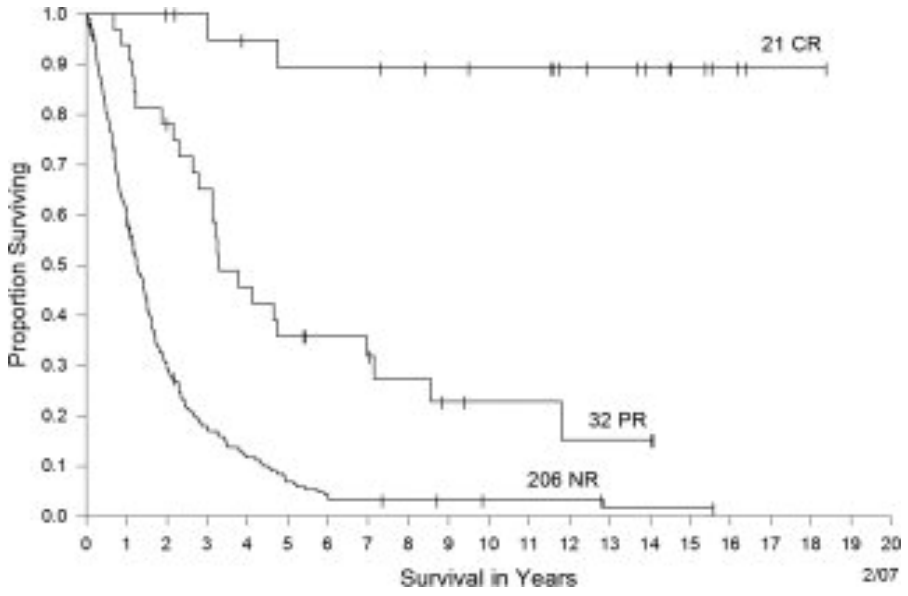
- 270 patients treated, RR 16% including 6% CRs
- 12 patients (28% of responding patients) remain disease free
- 6 patients died as related to treatment



Atkins, JCO 1999

High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006.

- 259 patients treated, RR 20%, including 23 (9%) with CR
- 19 pts remain disease-free
- 2 pts with treatment related mortality

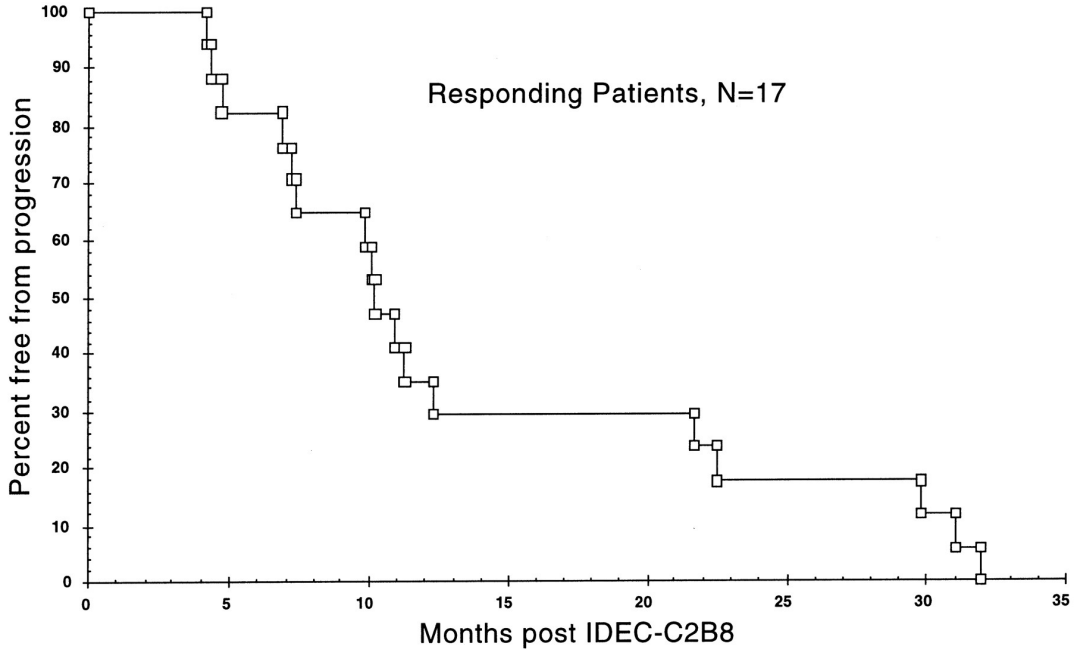


Klapper, Cancer 2008

Monoclonal antibodies in cancer therapy

- *David Maloney, Blood 1997:* IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma

17/37 responses in relapsed B-cell lymphoma



Monoclonal antibodies in cancer therapy

- *Mark Pegram, … Denis Slamon, JCO 1998:* Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody (trastuzumab) plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment.

  "The use of rhuMAb HER2 in combination with CDDP in patients with HER2/neu-overexpressing metastatic breast cancer results in objective clinical response rates higher than those reported previously for CDDP alone, or rhuMAb HER2 alone. In addition, the combination results in no apparent increase in toxicity."

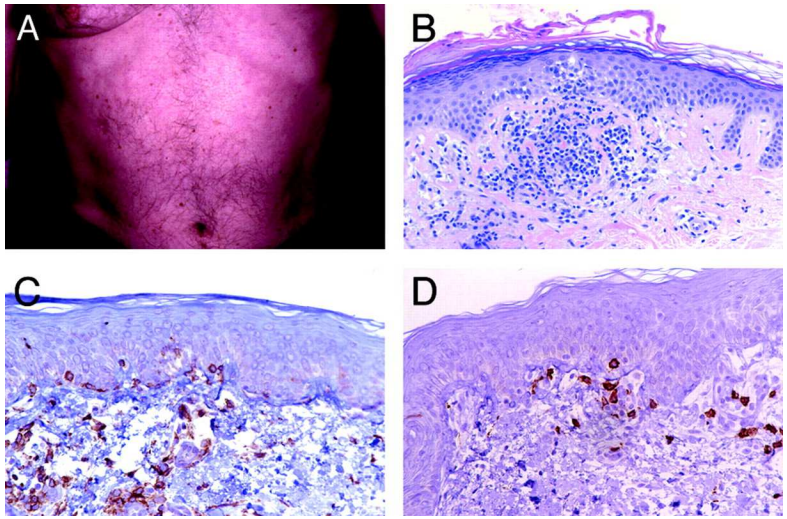
CTLA-4 and PD-1

- *Brunet , ..., Golstein, Nature 1978:*
  A new member of the immunoglobuline superfamily – CTLA-4
- *Ishida, ..., Honjo, EMBO Journal, 1992:*
  Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death

Immune checkpoint inhibition

- *Stephen Hodi, PNAS 2003:*
  Biologic activity of cytotoxic T lymphocyte-associated antigen-4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients

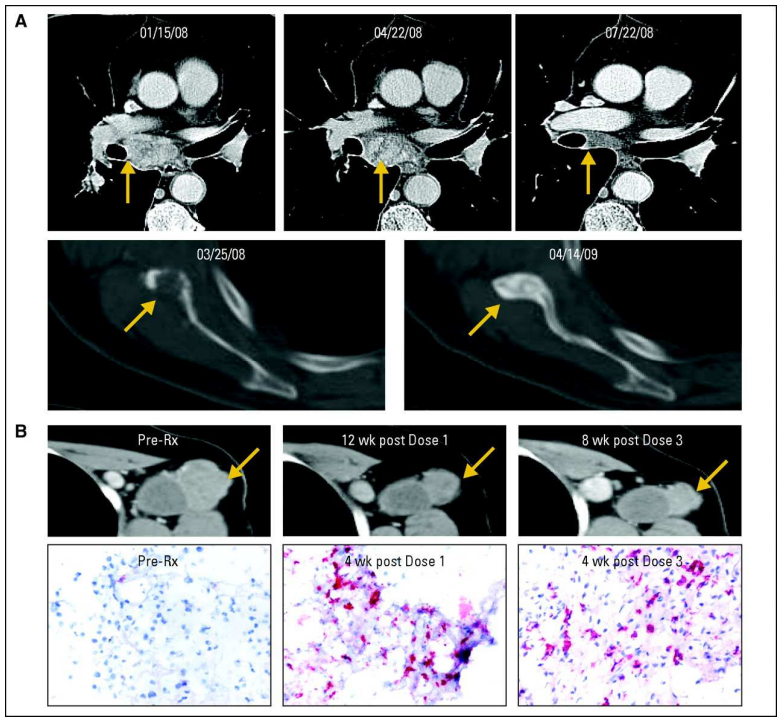
.... MDX-CTLA4 stimulated extensive tumor necrosis with lymphocyte and granulocyte infiltrates in 3 of 3 metastatic melanoma patients...



(A) Reticular erythematous rash. (B) Perivascular lymphocyte infiltrate extending into epidermis with interface dermatitis. (C) CD4+ T cells apposed to dying melanocytes. (D) CD8+ T cells apposed to dying melanocytes.

Immune checkpoint inhibition

- *Judy Brahmer, …, Suzanne TopalianJCO 1010:*
  Phase I study of single agent anti programmed death-1 in refractary solid tumors



Objective reponses in a patient with renal cell carcinom (A) and melanoma (B)

Immunotherapeutic approaches