

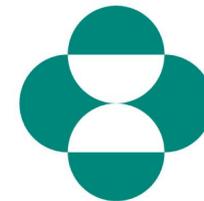
**ESMO PRECEPTORSHIP ON
IMMUNO-ONCOLOGY**

**2-3 NOVEMBER 2018
ZURICH, SWITZERLAND**

ESMO wishes to thank the following companies for supporting
this ESMO Preceptorship Programme



Bristol-Myers Squibb



MSD

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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO PRECEPTORSHIP ON IMMUNO-ONCOLOGY

2-3 NOVEMBER 2018
ZURICH, SWITZERLAND

DEMOGRAPHIC DATA

| | |
|--------------|-----------|
| Participants | 59 |
| Faculty | 13 |
| Total | 72 |

Participants Gender

| | | |
|--------|----|---------------|
| Female | 38 | 64.41% |
| Male | 21 | 35.59% |

Participants Country breakdown

| | |
|--------------------|---|
| Italy | 9 |
| United Kingdom | 8 |
| Russian Federation | 7 |
| Spain | 7 |
| Portugal | 5 |
| Romania | 3 |
| Ukraine | 3 |
| Denmark | 2 |
| Germany | 2 |
| Greece | 2 |
| Ireland | 2 |
| Switzerland | 2 |
| Armenia | 1 |
| Belgium | 1 |
| Georgia | 1 |
| Latvia | 1 |
| Montenegro | 1 |
| Serbia | 1 |
| Slovenia | 1 |

Immunotherapy of cancer

Some historical background

Rolf Stahel
University Hospital
Zürich, Switzerland

Zürich, 2.11.2018

4 | Disclosures

Consultant or Advisory Role in the last two years

I have received honoraria as a consultant at advisory boards from Abbvie, Astra Zeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

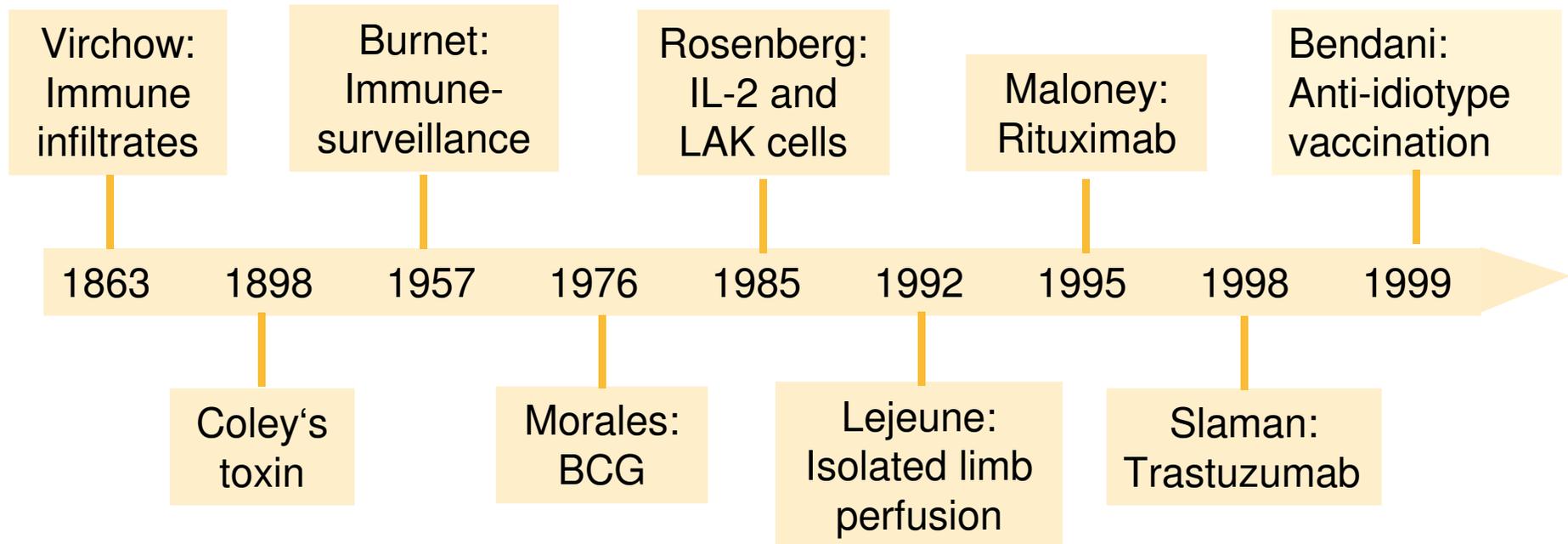
Speaker Honoraria in the last two years

I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, MSD and Roche.

DMC in the last two years

Roche and Takeda

5 | History of cancer immunotherapy before the immune checkpoint inhibitors



6 | 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

7 | Coley's toxin

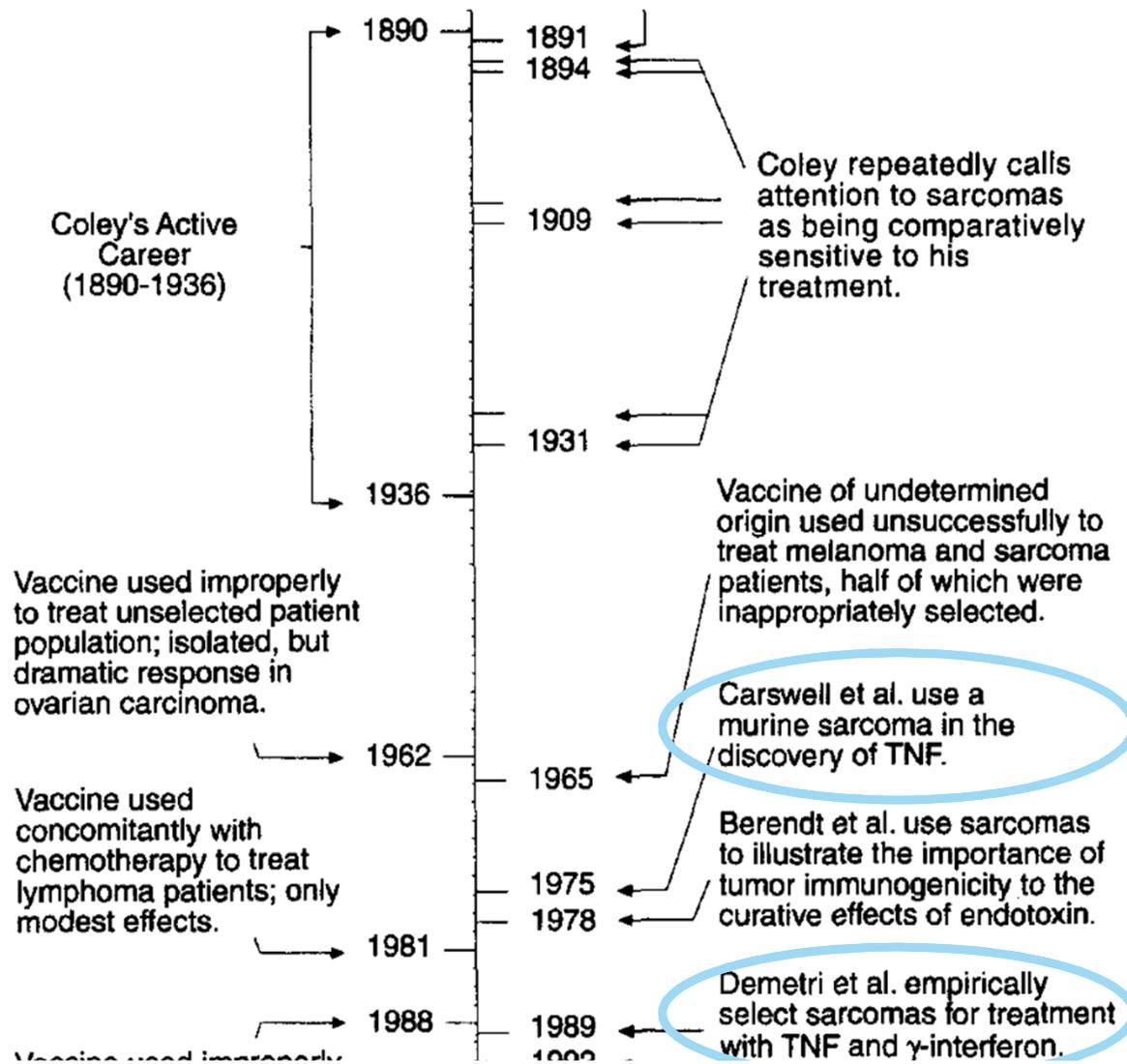
- Induction of erysipelas by direct inoculation with streptococci



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).

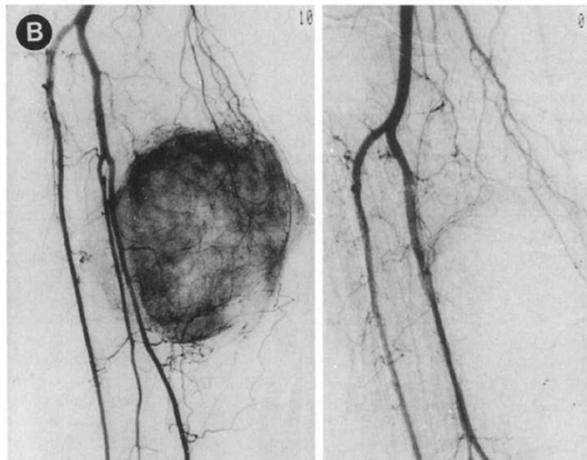
- Coley's toxin: Heat inactivated mixture of streptococci and serratia
About 900 patients treated, most inoperable sarcoma, 10% response rate.
Treatment associated high fever

William Coley, 1909



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.

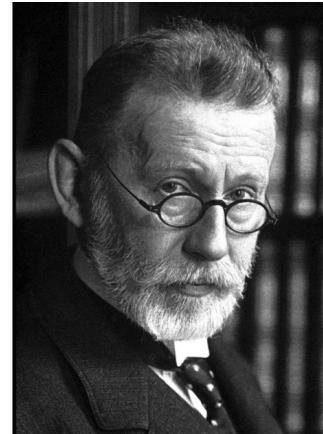
J Clin Oncol 14:2653-2665. © 1996 by American Society of Clinical Oncology.

10 | 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

11 | Immune surveillance of tumours

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



12 | 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”



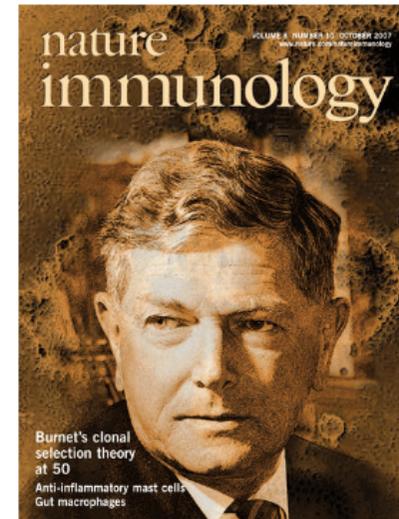
Lewis Thomas

13 | Immune surveillance of tumours

- *Sir Macfarlane Burnet, 1964*

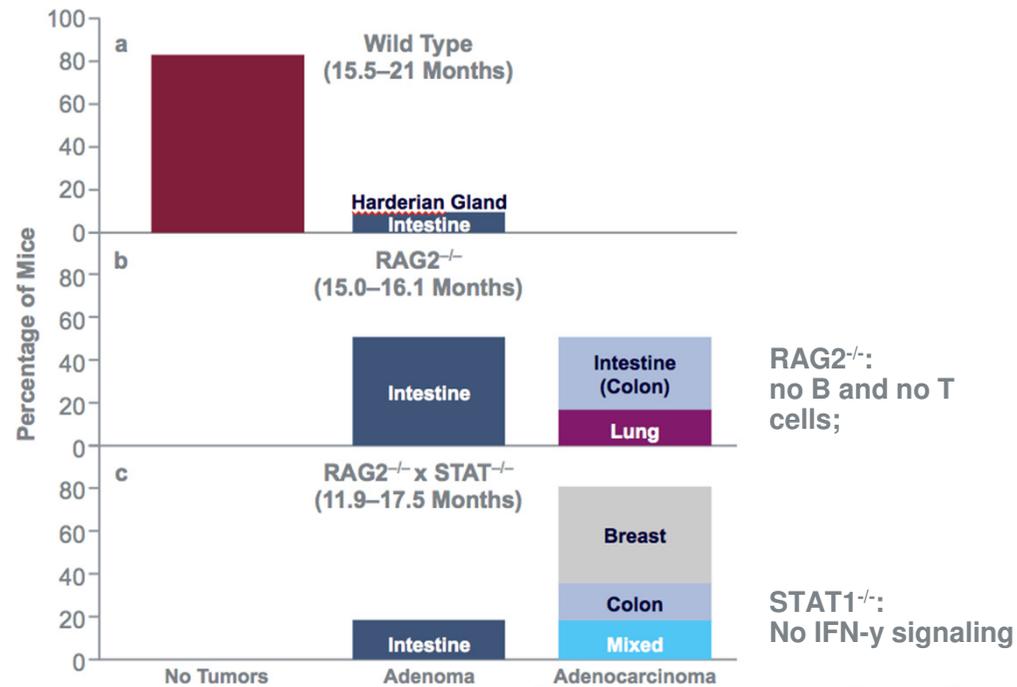
“...in animals, ..., inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy.

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.”



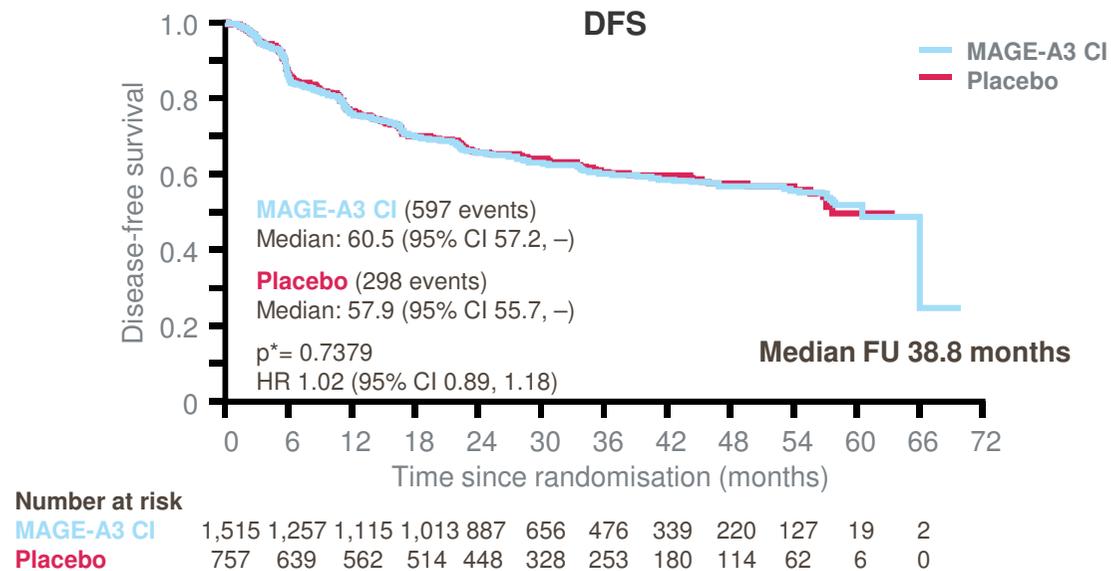
14 | Interferon-gamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity

Sponaneous carcinomas in immunodeficient mice



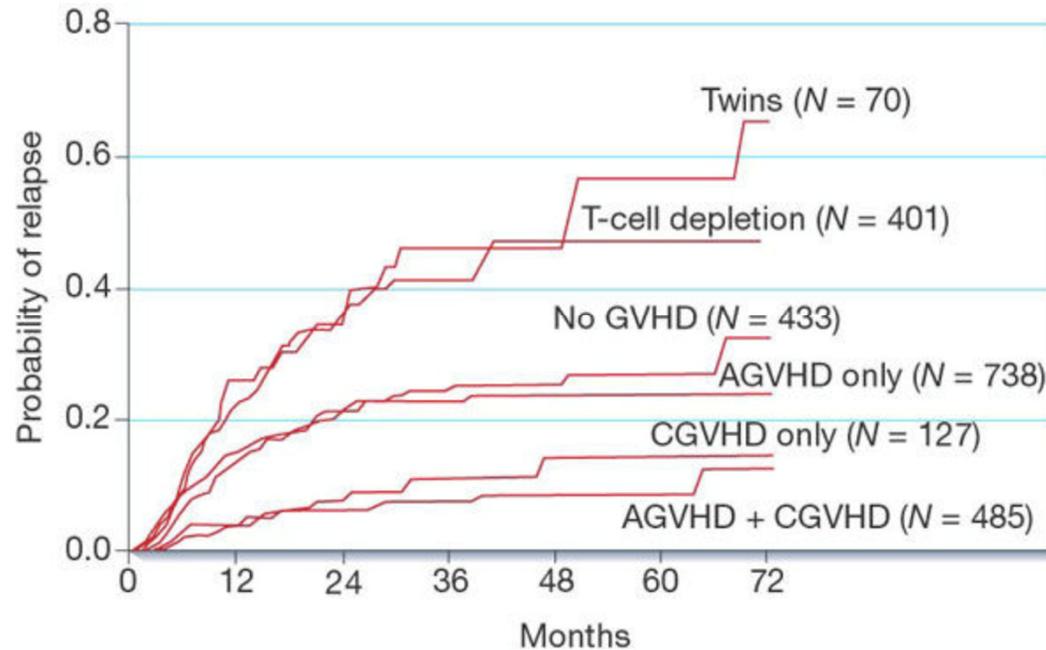
Shankaran, ..., Old, Schreiber, Nature 2001

15 | 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



Vansteenkiste, ESMO 2014

16 | Haematopoietic cell transplantation as immunotherapy

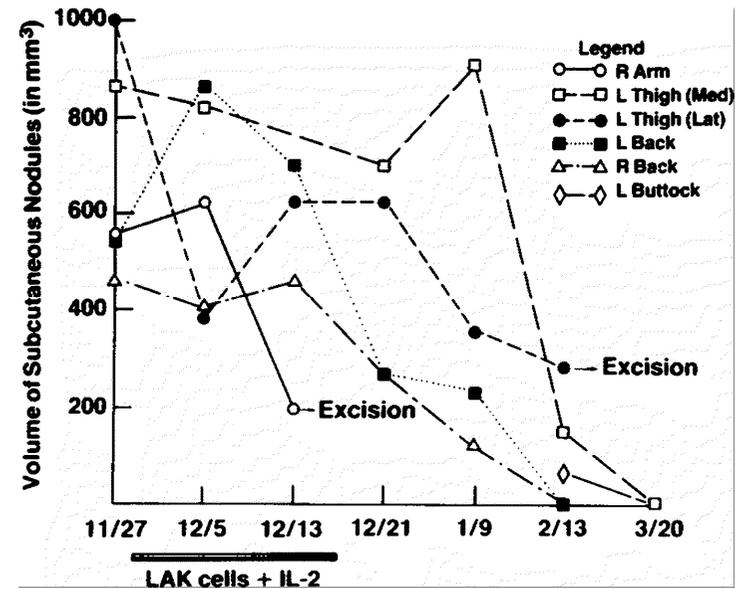


Relapse rates of acute leukemia are least in patients who develop both acute and chronic graft-versus-host disease (AGVHD + CGVHD), higher in those who develop no clinically evident GVHD, and higher still if T cells are depleted from the marrow graft or in recipients of twin transplants

Appelbaum, Nature 2001

17 | Cytokines in immunotherapy: The example of IL-2 and LAK cells

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



18 | Cytokines in immunotherapy: The example of IL-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 |

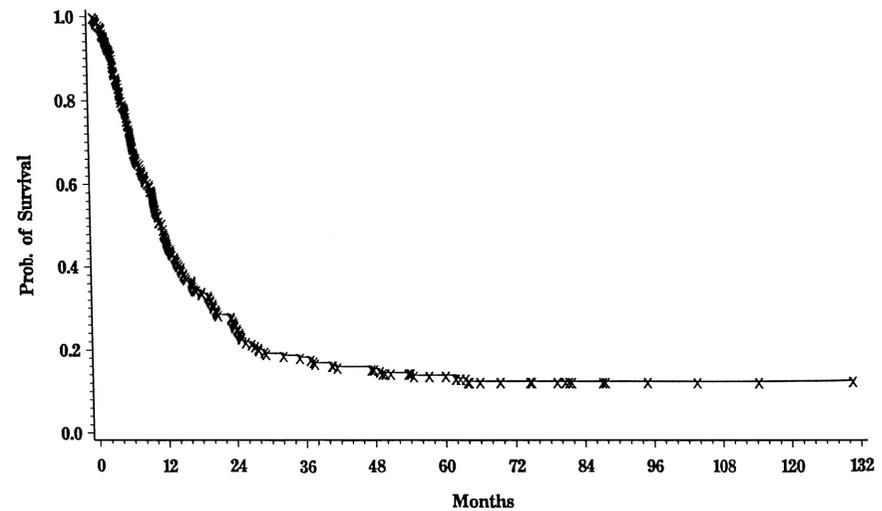
19 | Tolerance and effectiveness of recombinant interleukin-2 (r-met Hu IL-2 [ala-125]) and lymphokine-activated killer cells in patients with metastatic solid tumors

- 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

20 | High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993

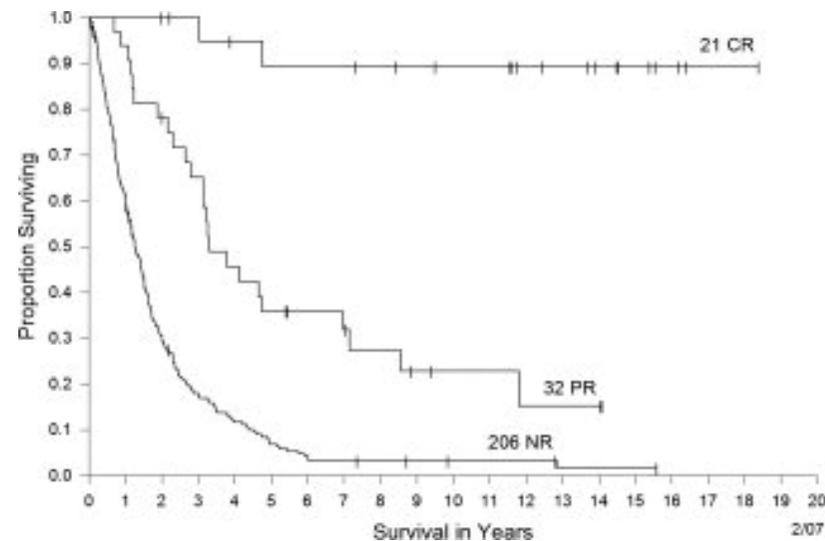
- 270 patients treated, RR 16% including 6% CRs
- 12 patients (28% of responding patients) remain disease free
- 6 patients died as related to treatment



Atkins, JCO 1999

21 | 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

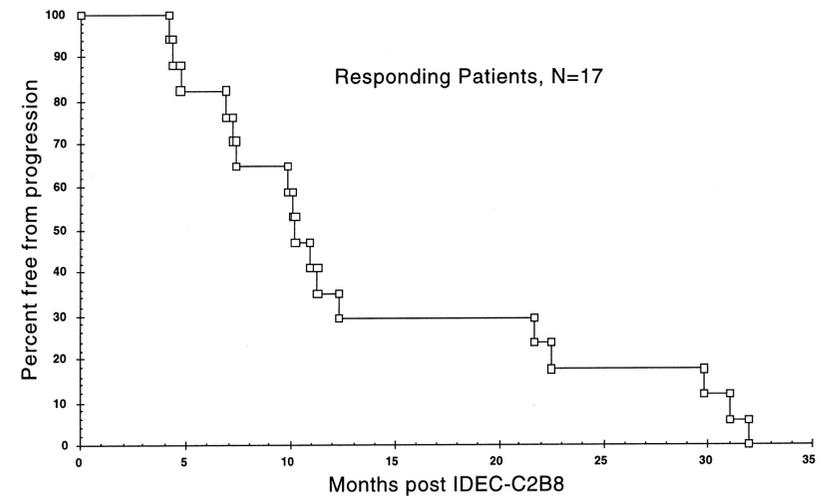


Klapper, Cancer 2008

22 | 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

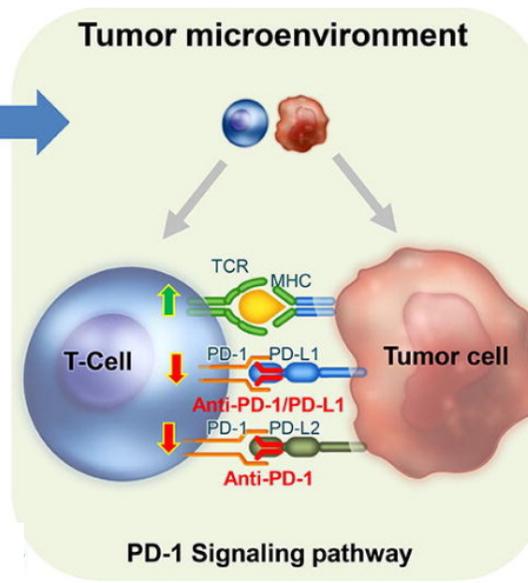
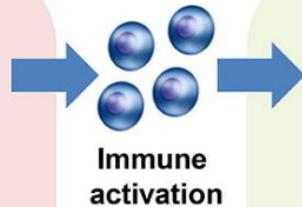
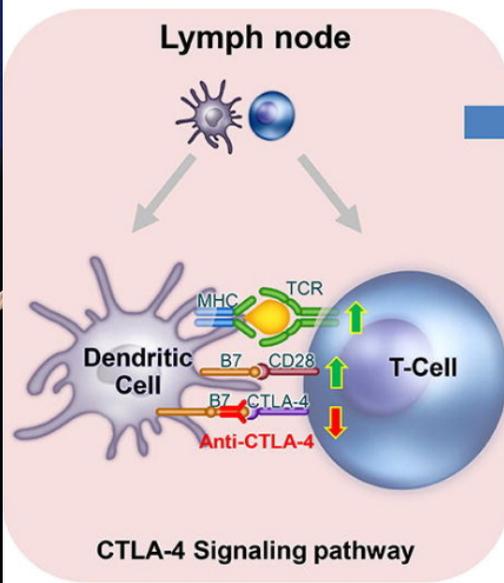


23 | Monoclonal antibodies in cancer therapy

- *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.”

24 | CTLA-4 and PD1/PD-L1 axis

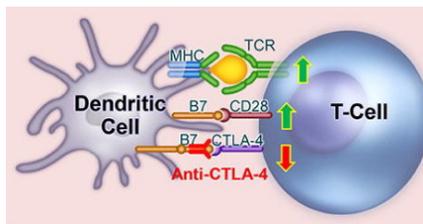


25 | CTLA-4

A new member of the immunoglobulin superfamily – CTLA-4

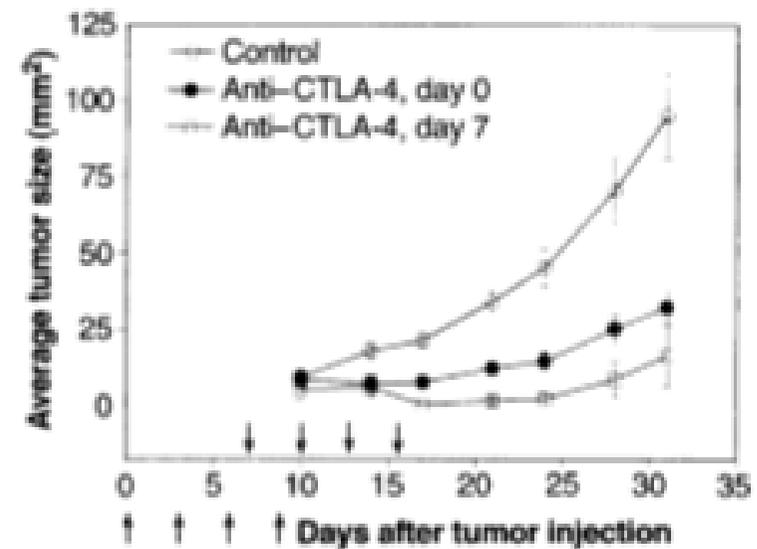
Brunet, ..., Golstein, Nature 1987

CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation



Matthew, ..., Allison, JEM 1995

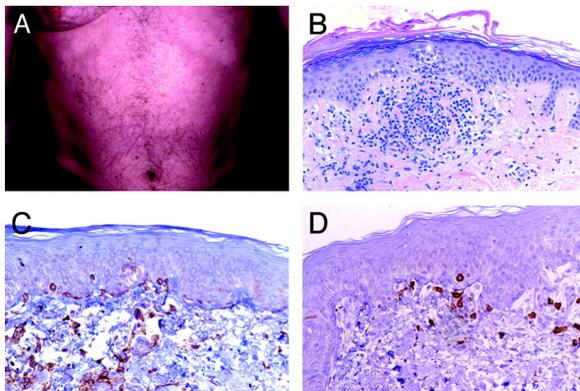
Enhancement of antitumor immunity by CTLA-4 blockade



Leach, ..., Allison, Science 1996

26 | 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.

Stephen Hodi, PNAS 2003

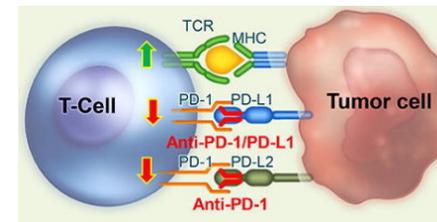
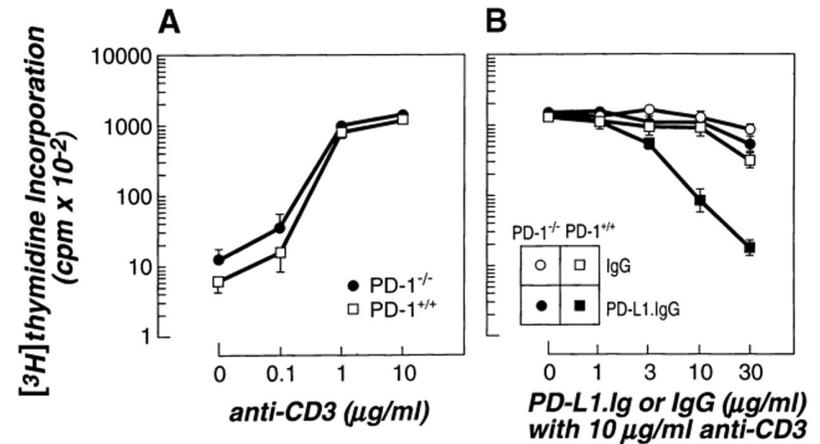
27 | PD-1

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death

Ishida, ..., Honjo, EMBO Journal, 1992

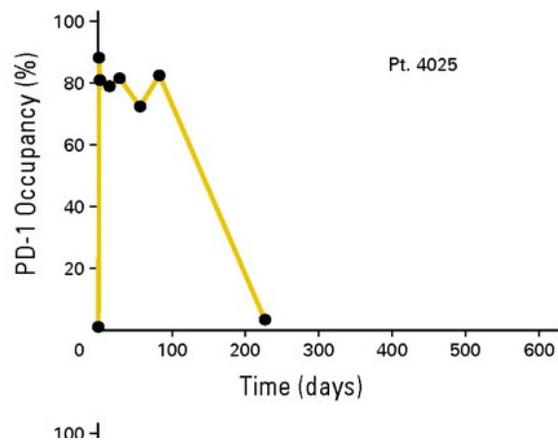
Engagement of PD-1 immunoinhibitory receptor by a novel B7 family member (PD-L1) leads to negative regulation of lymphocyte activation

Freeman, ..., Honjo, JEM Journal, 2000

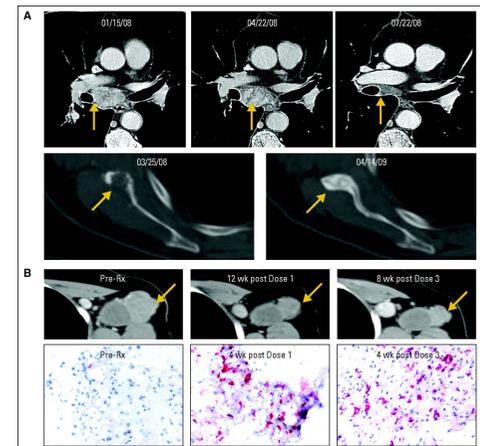


28 | Phase I study of single agent anti-PD1 in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates

T-cell occupancy of a patient receiving 10 mg/kg nivolumab



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



Brahmer, JCO 2010

29 | Immunotherapeutic approaches

