Evolution of Gene Therapy

- Gene therapy research is *experimental* - at a very early, immature stage
- Present methods and tools are nascent and still unrefined and also carry risk, but,
- The X-SCID gene transfer study has provided strong proof of principle for therapeutic efficacy - “clinical gene transfer research” has become “gene therapy”
- Should be subject to same risk/benefit analysis as other experimental procedures and therapies
- Great need for *more, not less*, effort to overcome scientific and medical obstacles
- Acknowledge difficulties and focus on solutions
- Recognize and applaud epochal advances already made

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 346:1185-1193 April 18, 2002 Number 16 Next ►

Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy

Salima Hacein-Bey-Abina, Ph.D., Françoise Le Deist, M.D., Ph.D., Frédérique Carlier, B.S., Cécile Bouneaud, Ph.D., Christophe Hue, B.S., Jean-Pierre De Villartay, Ph.D., Adrian J. Thrasher, M.D., Ph.D., Nicolas Wulffraat, M.D., Ricardo Sorensen, M.D., Sophie Dupuis-Girod, M.D., Alain Fischer, M.D., Ph.D., E. Graham Davies, M.D., Wietse Kuis, M.D., Ph.D., Lilly Leiva, Ph.D., and Marina Cavazzana-Calvo, M.D., Ph.D.

ABSTRACT

Background X-linked severe combined immunodeficiency due to a mutation in the gene encoding the common γ (γc) chain is a lethal condition that can be cured by allogeneic stem-cell transplantation. We investigated whether infusion of autologous hematopoietic stem cells that had been transduced in vitro with the γc gene can restore the immune system in patients with severe combined immunodeficiency.

ARTICLE

► Table of Contents
► Full Text of this article
► PDF of this article
► PDA version of this article
► Editor's Summary
► Supplementary Appendix 1
► Related Letters to the Editor

Related editorials in the

"Somatic gene therapy of human disease with retrovirus vectors is a new technology with potentially important medical benefits. Although it involves recombinant DNA technologies and modified retroviruses, proper design of the vectors and delivery systems removes most potential foreseen risks. Furthermore, even in the very remote possibility that there is a non-therapeutic biological effect of the treatment, it is unlikely to be a harmful one. Thus, *once very safe retrovirus vector-helper cell systems are constructed and in use, safety considerations should not hold up further human trials of retrovirus vectors*."

Howard Temin
Hum.Gene Ther. 1: 111 (1990)

“Random integration will obviously lead to occasional insertional mutagenesis through the interruption of vital cellular genes or through the insertion of retroviral regulatory sequences that modulate the expression of flanking cellular genes. To avert problems of promoter interference and to reduce the likelihood of insertional mutagenic events, a number of investigators have designed retrovirus vectors that are devoid of their own promoter and enhancer sequences and are therefore transcriptionally disabled.”

T. Friedmann
Science. 244: 1275-1281 (1989)

Setback Fall 2002-Winter 2003

- Two treatment-related cases of T-cell leukemia
  - Due to single copy provirus integration into or near known T cell leukemia oncogene LMO-2.
  - Presumed viral enhancer effect
  - ??role of γC protein.
- Response to chemotherapy, clinical remission

- Pending further data or extenuating circumstances, reviewed on a case-by-case basis, retroviral gene transfer studies for X-linked SCID should be limited to patients who have *failed identical or haploidentical stem-cell transplantation or for whom no suitable stem cell donor* can be identified. Case-by-case review would include appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

- *There are not sufficient data or reports of adverse events directly attributable to the use of retroviral vectors at this time to warrant cessation of other retroviral human gene transfer studies*, including studies for non-X-linked SCID. Such studies *may be justified* contingent upon appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

NIH RAC recommendation, Feb 2003

Winter 2005

- death of one child with leukemia. Second child in complete remission.
- a third instance of leuekemia-like clonal expansion, several (3) integrations, none in LMO-2
- rapid response to chemotherapy, complete remission
- remaining study subjects (9 France, 6 in England) immunologically reconstituted, alive and well, some into 6th year after treatment
- total experience - 18 patients (12 France, 6 England), 1 non-response, 17 immune reconstitutions, 3 life-threatening SAEs, 1 death

Regulatory Responses

- France - clinical hold by AFSSAPS, at request of investigators
  - safer vectors to reduce insertional mutagenesis, better understanding of vector/transgene contributions to leukemogenesis
- U.S. - FDA clinical hold on X-SCID; ADA-SCID and other retrovirus-based protocols may proceed
- Italy, Japan - ?
- England - study and patient accrual to continue
  - at present, clinical benefits outweigh risks of other therapies, BMT

The Heart of the Dilemma

- Severe risks in context of robust clinical *success*
- Retrovirus-mediated transduction of CD34+ cells with wild type γC gene is *effective treatment*, ?cure, of human X-SCID
- *Very* high risk of leukemia with current technology from unregulated growth- or survival advantage - risk is inherent in mechanisms of retroviral integration.
- What is this study - human experimentation or therapy? Viewing alternatives, when does high-risk experimentation become high-risk but justifiable therapy?
- Important to work toward improved methods, but what does one do while awaiting better technology?

Sound familiar? - not a new problem

- childhood lymphocytic leukemia
- Hodgkin’s Disease
- organ transplantation - bone marrow, heart, liver, kidney
- monoclonal antibodies

The New England

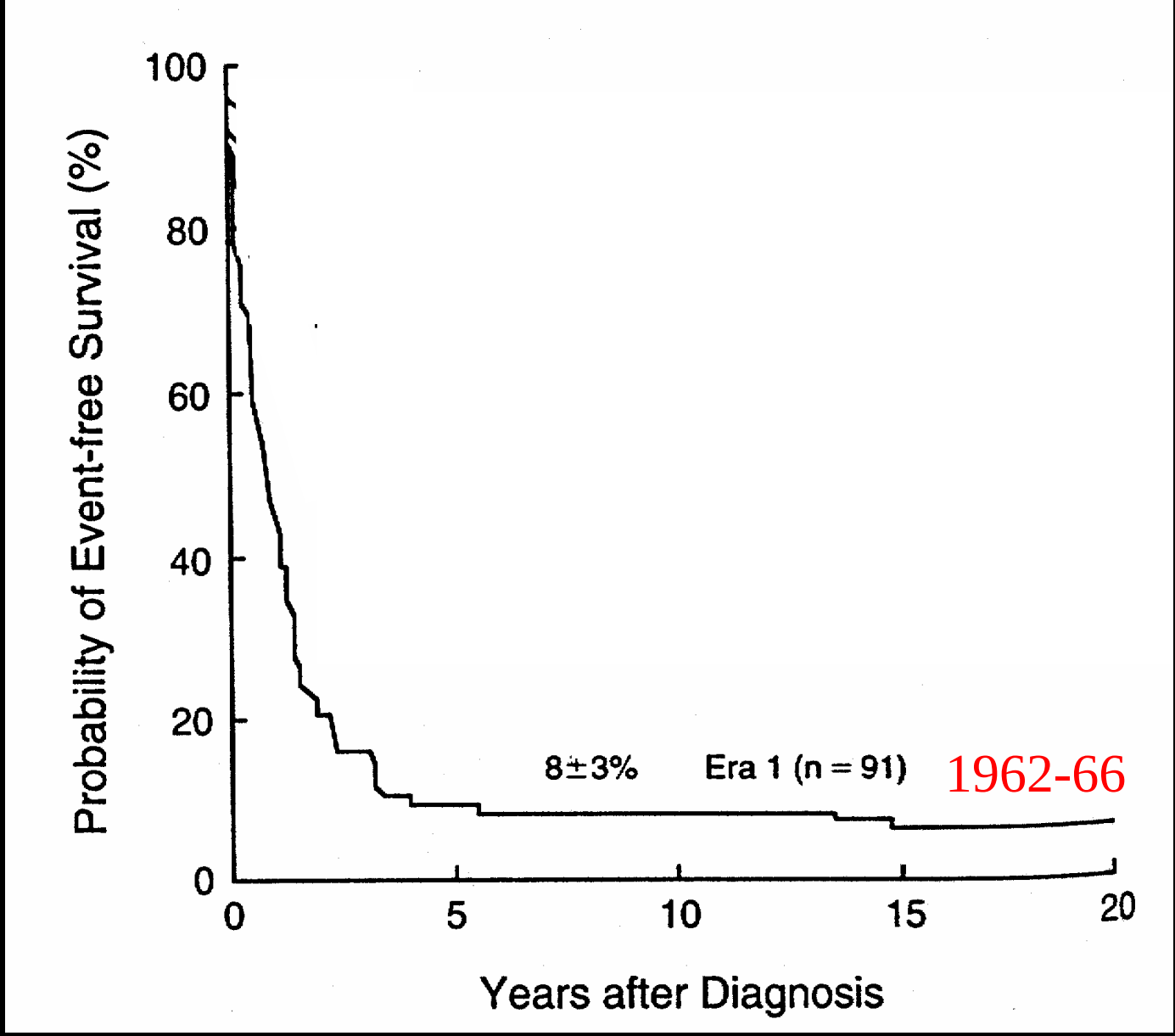
Journal of Medicine

Volume 238 JUNE 3, 1948 Number 23

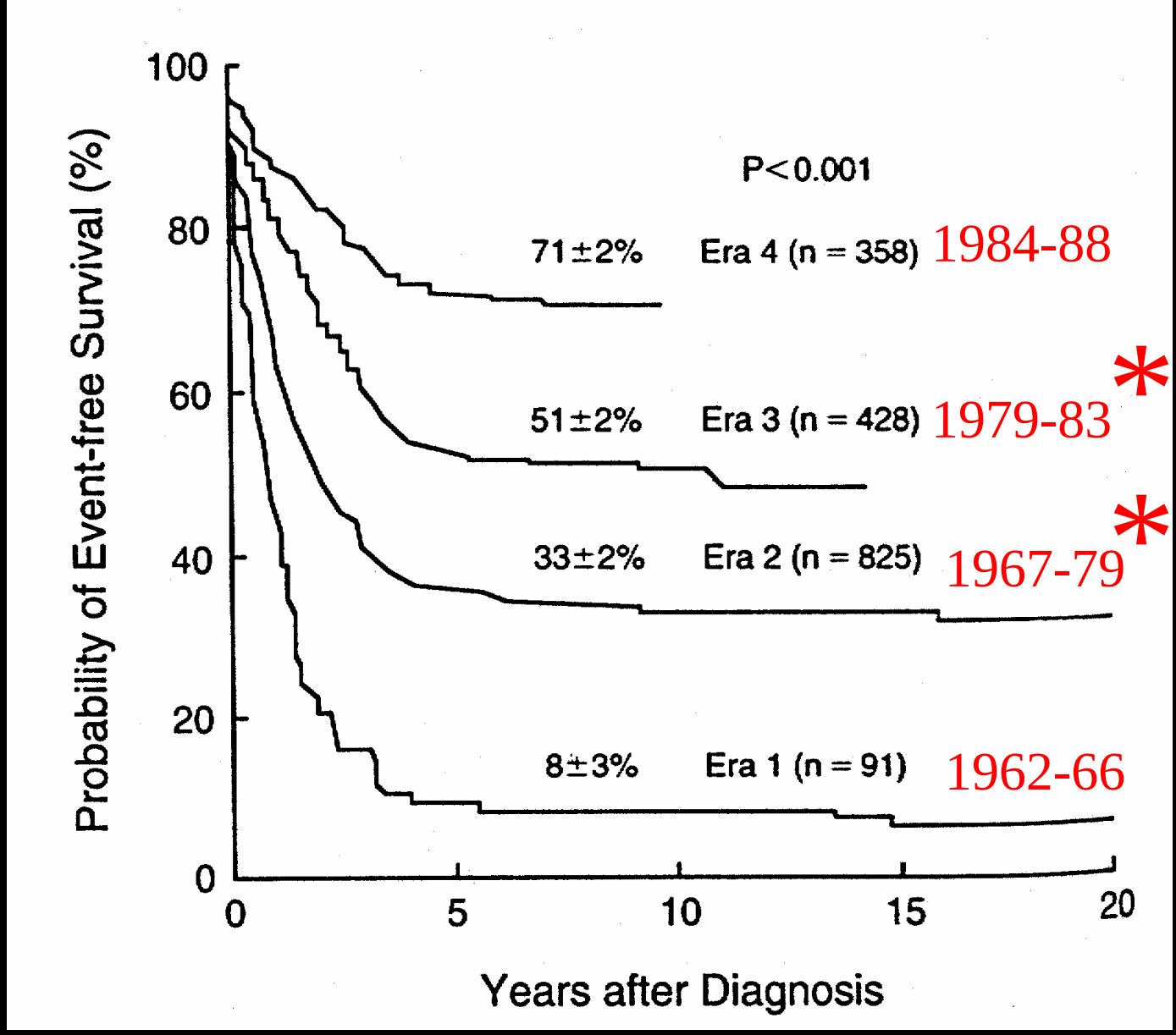
TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

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

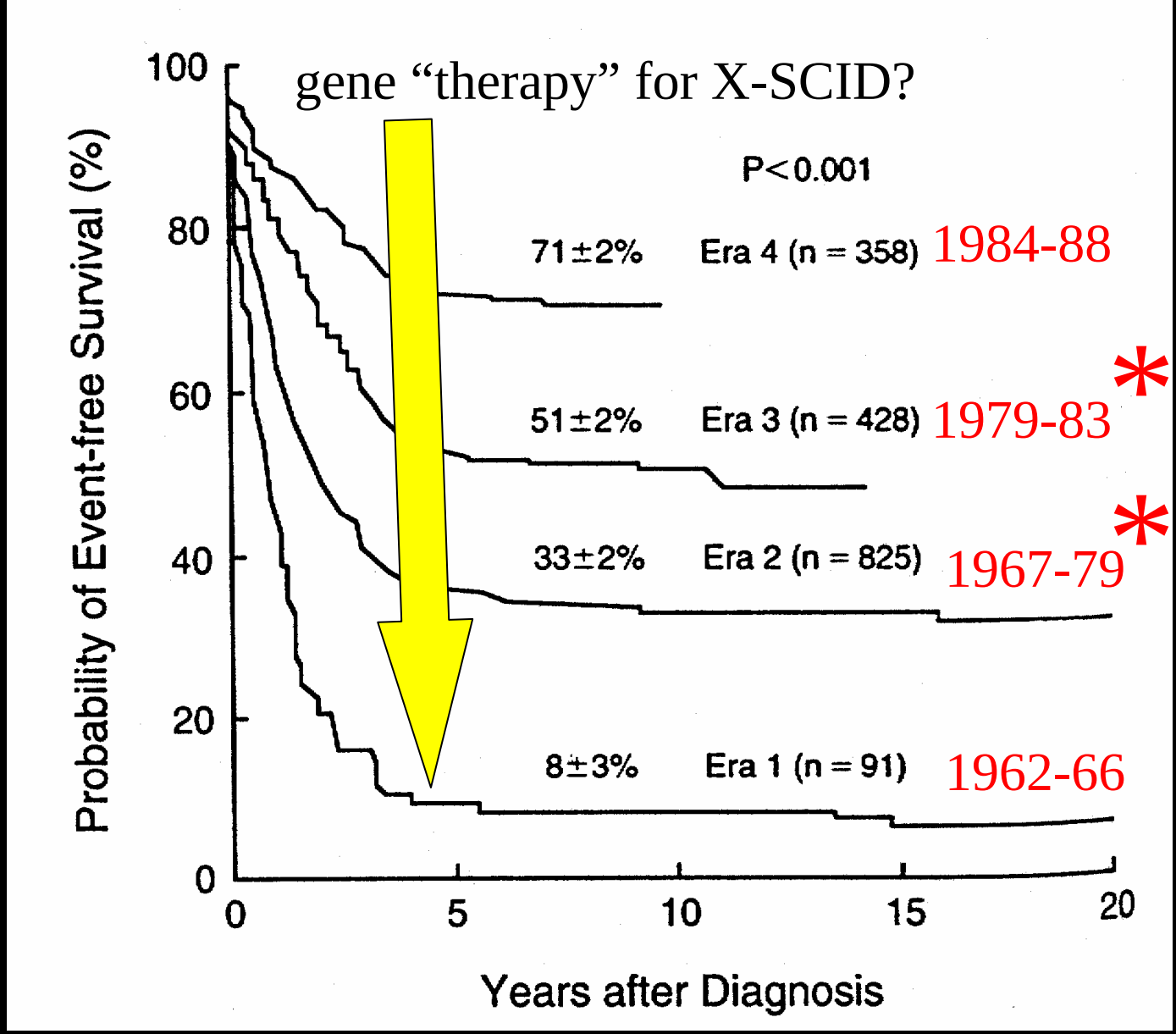


Pui CH: N Engl J Med 332: 1618-1630, 1995



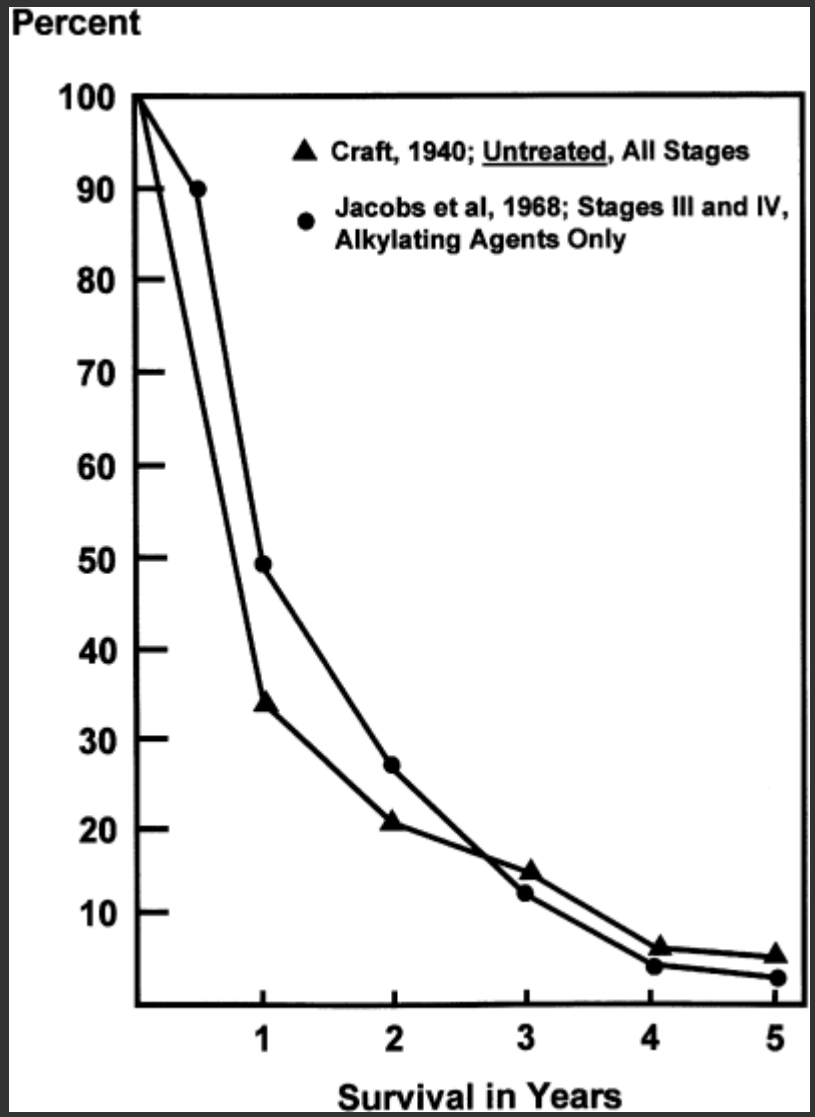
Pui CH: N Engl J Med 332: 1618-1630, 1995

* CNS prophylaxis, new chemotherapeutic agents

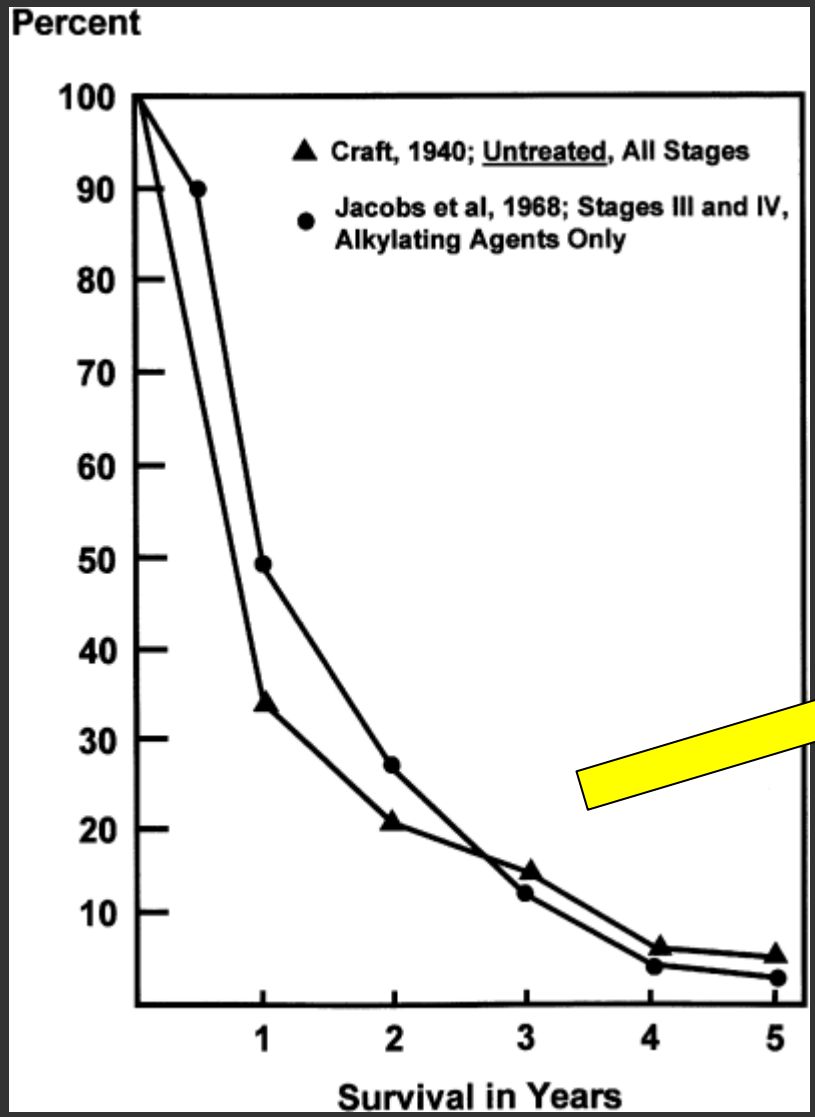


Pui CH: N Engl J Med 332: 1618-1630, 1995

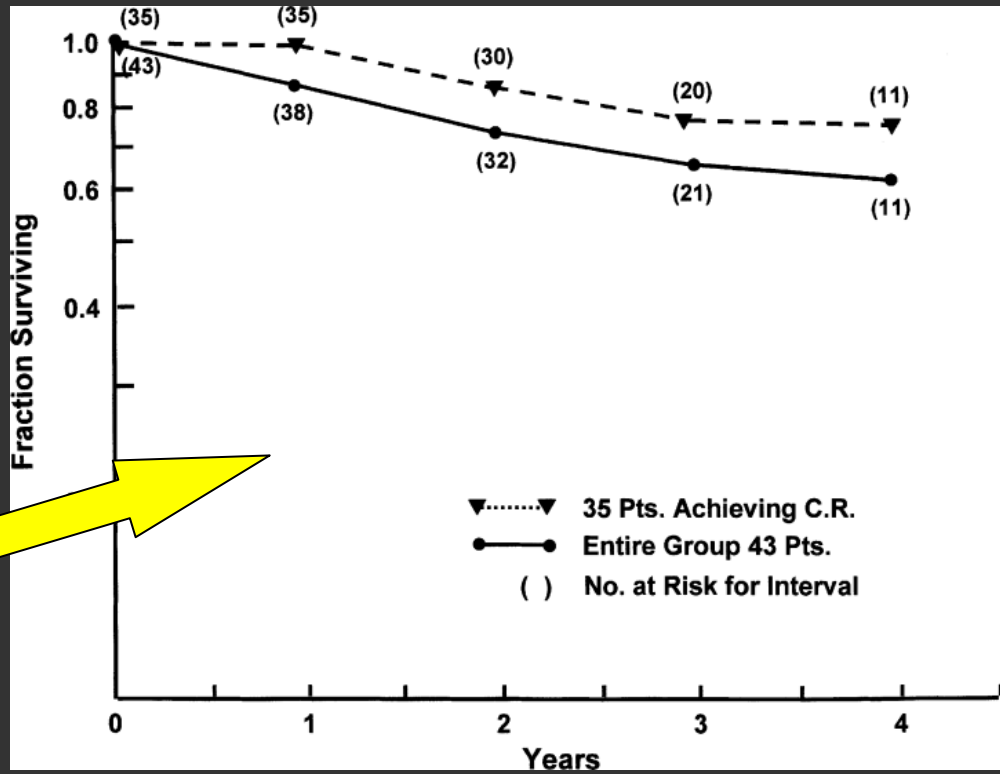
*CNS prophylaxis, new chemotherapeutic agents



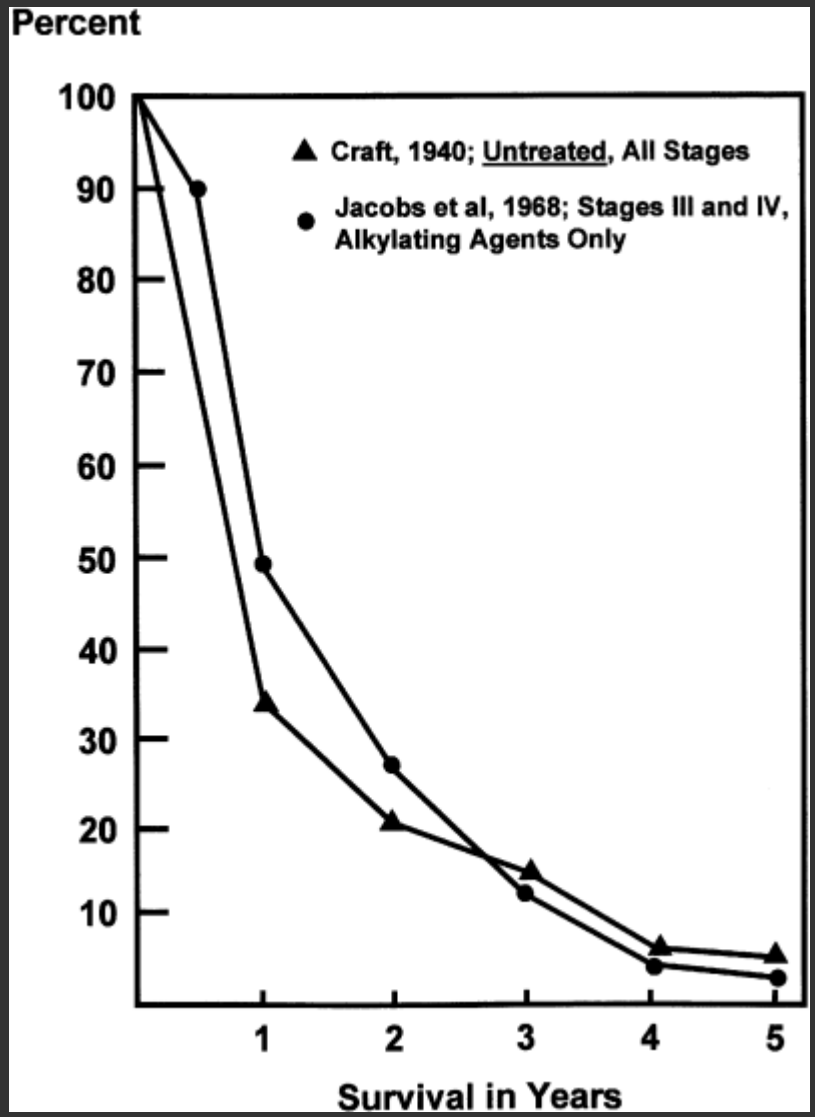
1963 - alkylating agent



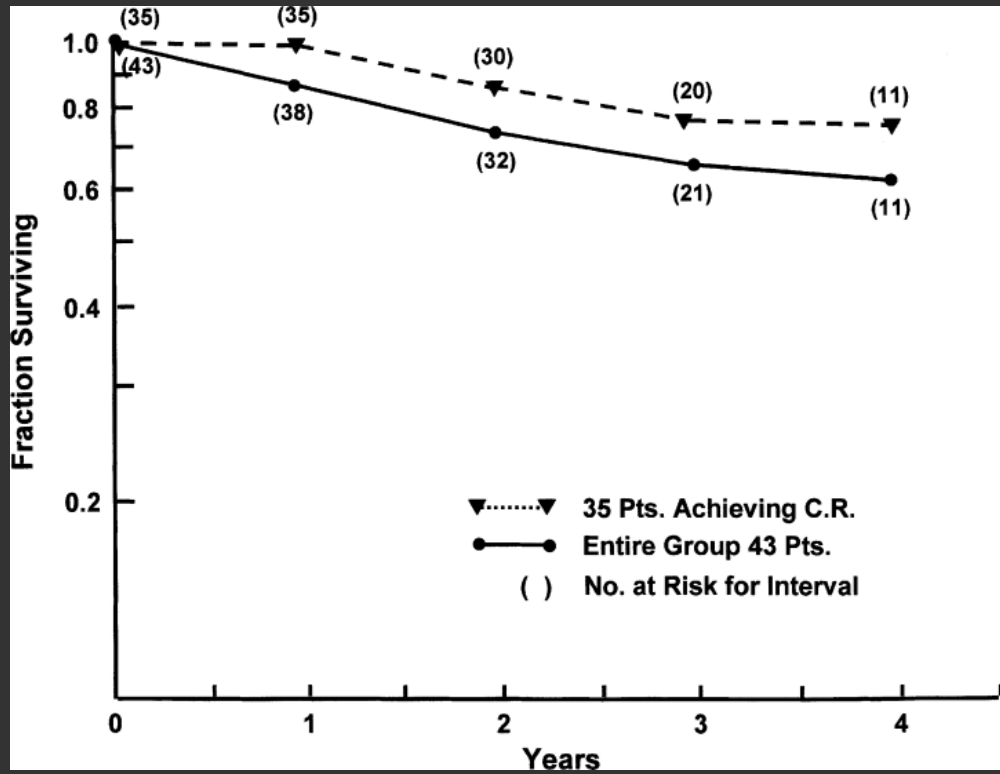
1963 - alkylating agent



1970 - MOPP combination Rx
DeVita et al.



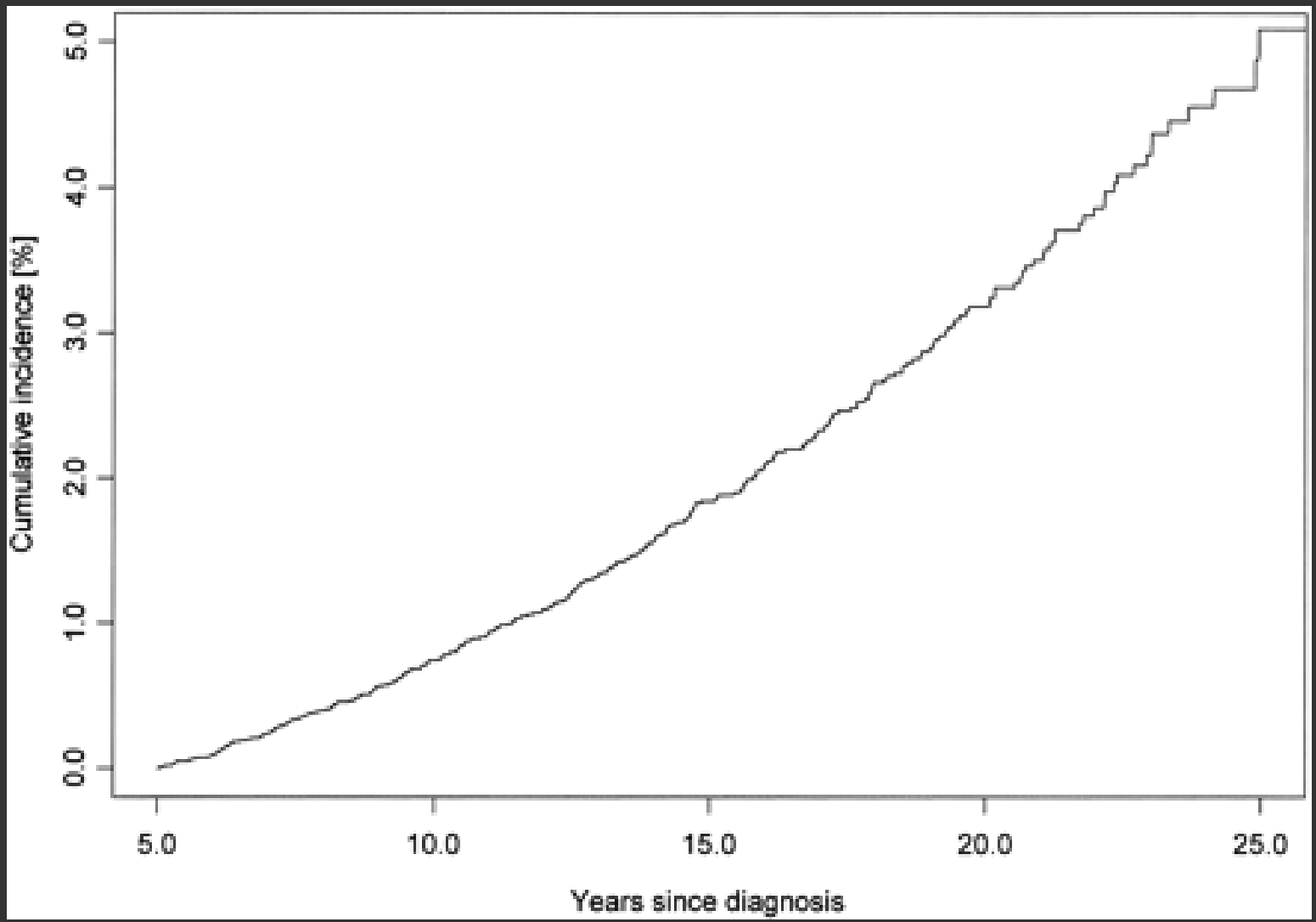
1963 - alkylating agent



1970 - MOPP combination Rx
DeVita et al.

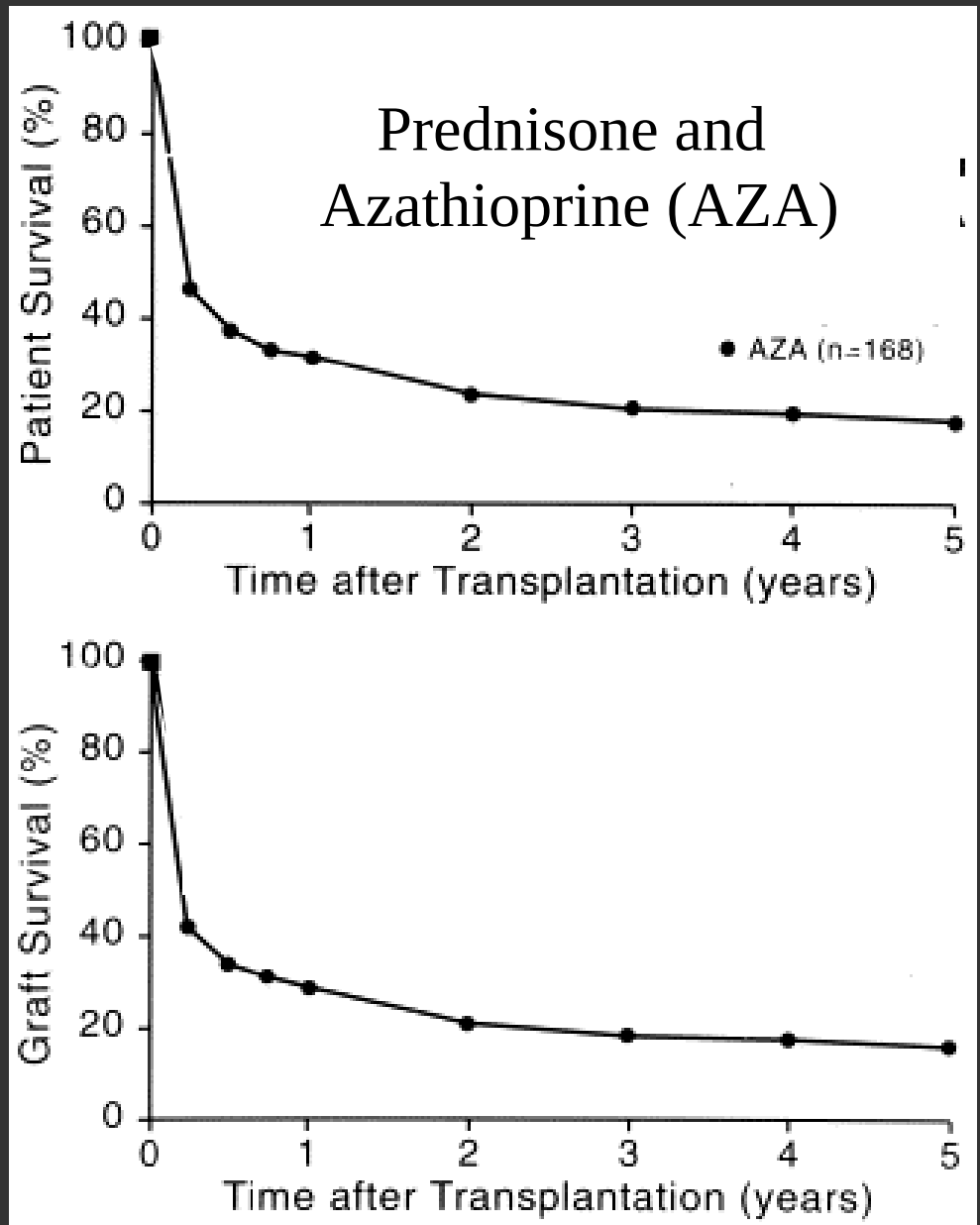
At a cost - “treatment-related leukemia” and other secondary cancers

At a cost - cumulative incidence of secondary cancers in treated childhood cancer



Neglia et al., JNCI , 2001

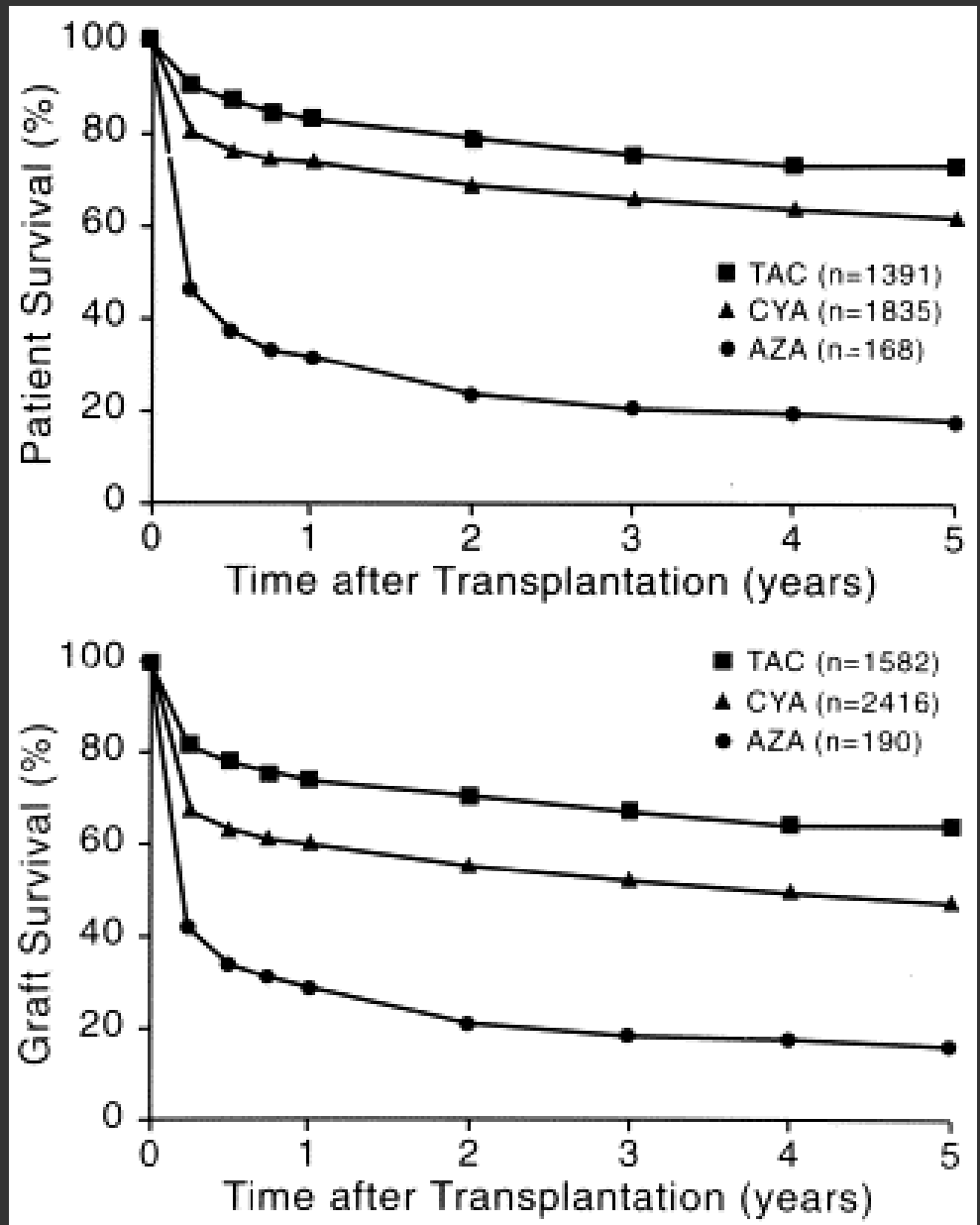
Immunosuppression for liver transplantation - 1963



Starzl

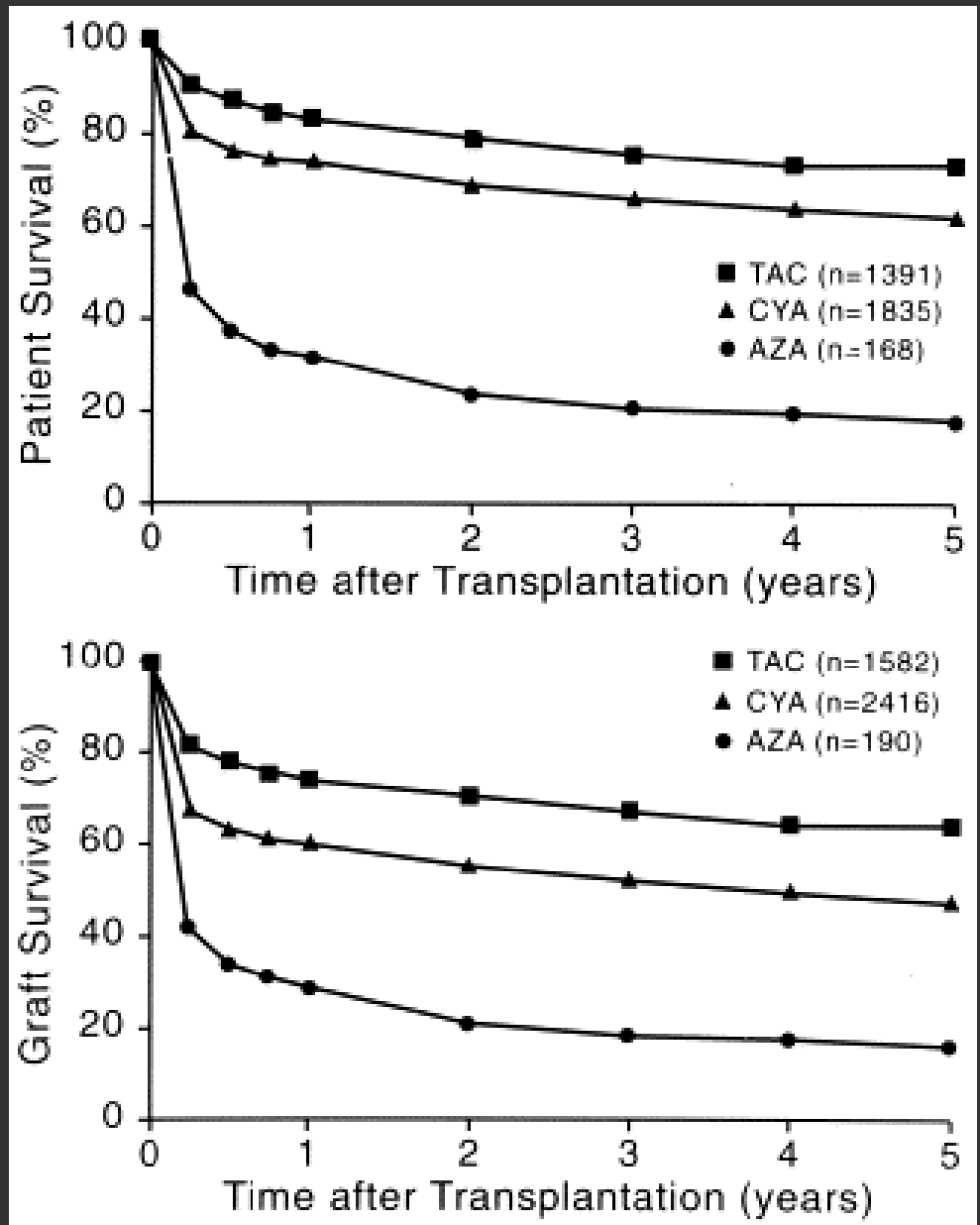
Improved immunosuppression for liver transplantation

cyclosporin (1980), other calcineurin inhibitors



Starzl

At a cost - renal failure, secondary malignancies



Starzl

Is human gene transfer experimentation different from other clinical research?

- far greater visibility and scrutiny at the most nascent stages of its development
- burden of its history - greater exaggeration of quick clinical delivery, undeliverable explicit and implicit promises
- Earlier and more powerful influence of commercial interests in delivery of immature technology to urgent clinical problems

Issues for RAC discussion

- criteria for proceeding with current studies?
  - vector modifications - insulators, suicide and ablation elements
  - prophylactic chemotherapy in X-SCID model?
  - what are goals of clinical “hold”? What should be done while awaiting improved and less hazaradous technology?
- define long-term research needs and goals?
  - vector design, choice of target cells, effects of integration site and provirus on proto-oncogene expression, oncogenic role of γC, targeted integration, prospective identification of transduced cells with prolferative, selective advantage, etc.
- how to achieve greater ethical clarity on transition from human experimentation to “therapy”
- new requirements in appendix M?

Specific immediate tasks for NIH RAC

- Affirm or modify Feb. 2003 RAC position on retrovirus-mediated gene transfer for X-SCID, other SCID
  - extend to other stable transducing systems - episomal (herpes, adenovirus, etc.)
- Anticipate effect of additional SAEs in X-SCID study
- Modify appendix M to include specific reference to:
  - minimized number of transduction events and transduced cell number, consistent with therapeutic effect?
  - elements to regulate levels of gene expression?
  - methods to ablate genetically modified cells, reverse their effects?
  - methods to test and archive grafted cells (prospectively, post-grafting) to detect inappropriate selection/expansion
- RAC review of impact of gene transfer technology and successful therapy on existing ethical and policy codes of human experimentation
  - when does high-risk experimentation become “therapy”?
  - policy conference(s)

A complex task for the RAC

- assist investigators to ensure high quality gene transfer clinical research studies and maximal patient protection
- ensure safety and compliance with principles of human experimentation
- prevent unjustifable exaggeration of

A danger of exuberant pessimism

- empathy and concern for participants in all clinical research, including gene transfer studies - those who wind up on the wrong side of the risk-benefit calculation
- appropriate determination to identify and solve technical problems of gene delivery and expression
- avoid the inverse of un-rigorous, exaggerated optimism of earlier clinical phase of gene transfer research
  - unrealistic attitude of *straightforward clinical application* to equally unrealistic attitude of insurmountable obstacles
- appropriate recognition of advances, development of effective, albeit wtill primitive and dangerous, therapy

Challenges to the RAC

- if some patients remain well, gene transfer for X-SCID constitutes effective treatment, possibly "preferred treatment", possibly even "standard of care"
- very likely inevitable serious harm
- an approximate measure of cost-benefit

Challenges to RAC

- existing technology,
  - question of balance of benefits and risks, as in all therapies, no matter how hazardous
- improve technology and increase safety
  - specify “safe” integration sites - too difficult for now
  - incorporate mechanisms of regulated gene expression - promising but very early technology
  - incorporate ”suicide”and ablation technology

Challenges to RAC - existing technology - wait for what?

- adverse events are inherent in non-specific integration and resulting insertional mutagenesis
- methods for site-specific integration not imminent
- the more efficient the gene transfer and expression, the greater the likelihood of harm
- effects of patient age, virus dose, mechanisms of oncogene dysregulation are important but will not be understood quickly

Possible further outcomes

- all subjects in current X-SCID studies will show serious harm, despite transient effective therapy
- some patients remain well, gene transfer for X-SCID constitutes effective treatment, possibly “preferred treatment”, possibly even “standard of care”
- serious harm very likely - even inevitable
- an approximate measure of cost-benefit

The dilemma - how should RAC proceed?

- with existing technology
  - question of balance of benefits and risks, as in all therapies, no matter how hazardous

The quandary - if and how to proceed?

- improved technology and increased safety - what is needed?
  - specific “safe” integration sites - too difficult for now.
  - incorporate mechanisms of regulated gene expression - promising but very early technology
  - incorporate ”suicide”, reversal and ablation technology

RAC actions - new appendix M points for retrovirus studies

- minimized number of transduction events and number of modified cells, consistent with therapeutic effect?
- incorporated elements to regulate levels of gene expression?
- incorporated methods to ablate genetically modified cells, reverse their effects?
- incorporated archiving and testing assays to detect cells undergoing inappropriate selection/expansion?

RAC actions - articulate ethical view of harmful treatment

- RAC symposium or policy conference - when does an immature and harmful treatment become preferred treatment? For instance, is current gene therapy for X-SCID different from early phase of treatment for Hodgkin’s disease

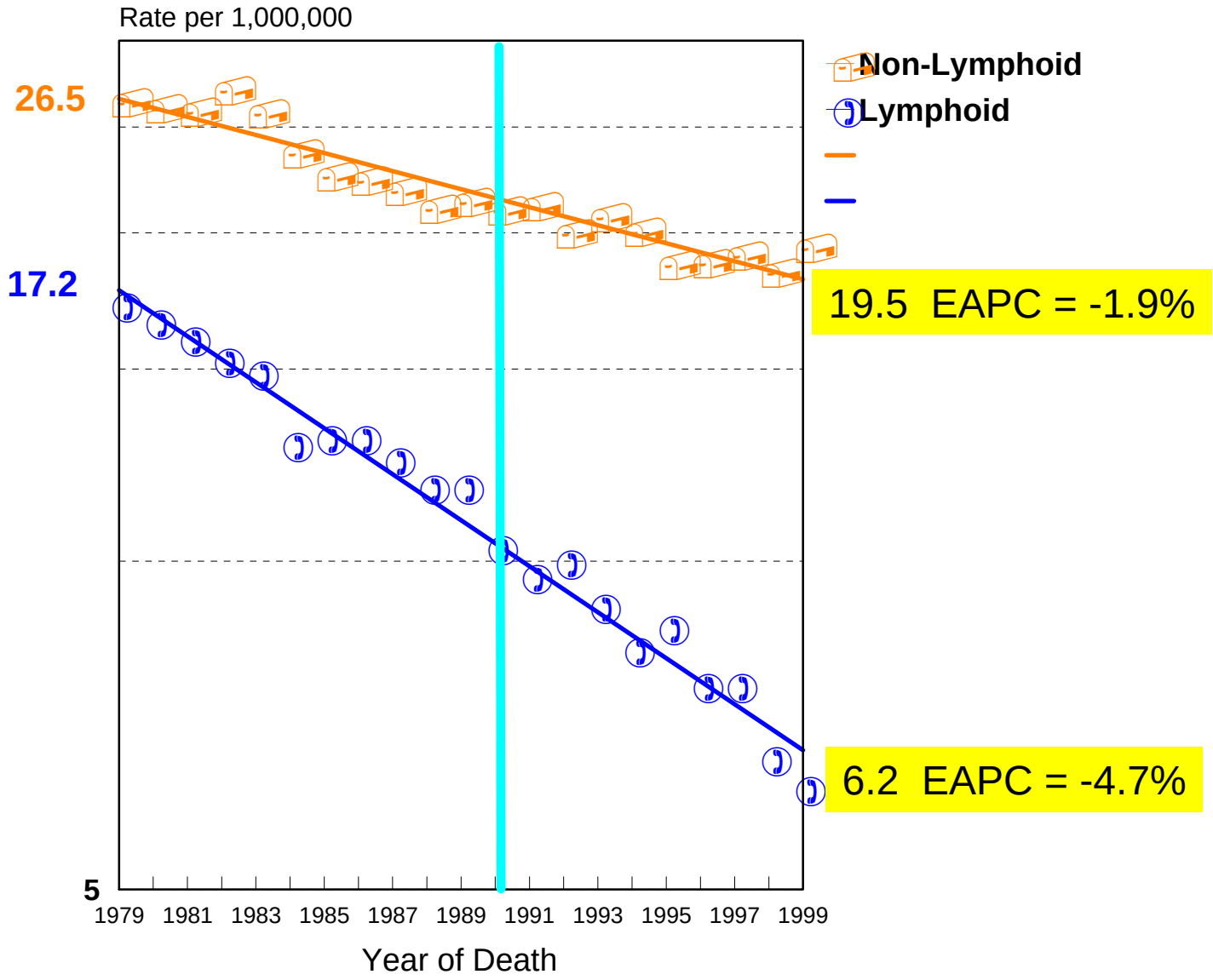
Different Rates of Decline in Mortality for Lymphoid (ALL, NHL, Hodgkin) versus non-Lymphoid Cancers

Does that sound familiar? Evolution of many other current therapies

The dilemma and challenge to RAC

- ex-vivo retrovirus-mediated transfer of γC into hematopoietic cells is effective therapy for X-SCID
- the therapy carries very high risk of harm
- are there ways to avert the harm in current study?
- in face of effective treatment of life-threatening disease, should long-term safety and other scientific studies be carried out before X-SCID and similar studies be continued with current technology?
- if not, what more do we need to know? Are any changes needed in RAC oversight mechanisms?

Lymphoid vs Non-Lymphoid Mortality (Age 0-14 Years) Both Sexes, All Races, 1979-1999



Smith , et al. Proc ASCO: 21, Abstr #1551. 2002

Rates are per 1,000,000 and age adjusted to the 2000 U.S. standard

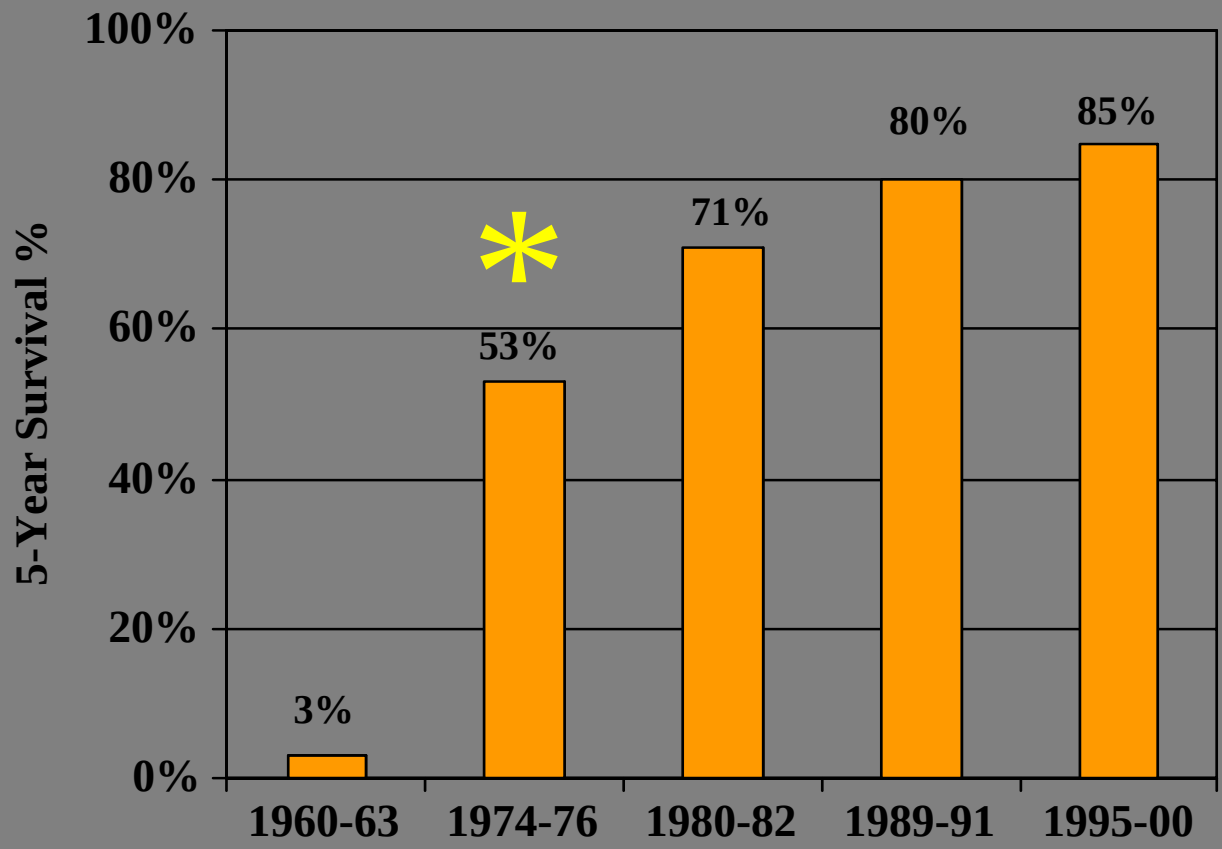
RAC recommendations and actions

- X-SCID
  - risk/benefit of genetic reconstitution compared with BMT
  - clinical “hold” - until when? what scientific/medical advances required?
  - how to proceed with current study - prophylactic chemotherapy?
- ADA-deficiency and other SCID diseases
- other retroviral/hematopoietic disease gene transfer models - is hematopoietic system a unique problem?
- any additional pre-clinical requirements of investigators (appendix M points to consider, recommendations to IRBs and IBCs)
- review of ethically acceptable research with human subjects (RAC policy conference). Does gene therapy stretch present codes (Nuremberg, Helsinki, Belmont Report, AMA, etc.)?

The beginnings of curative therapy for childhood ALL

- **1948**: Sidney Farber reported complete remissions with anti-folate therapy for children with ALL, but rare long-term survival
- **1958**: Report of randomized clinical trial of combination chemotherapy for children and adults with ALL
- **1963**: The use of maintenance therapy described

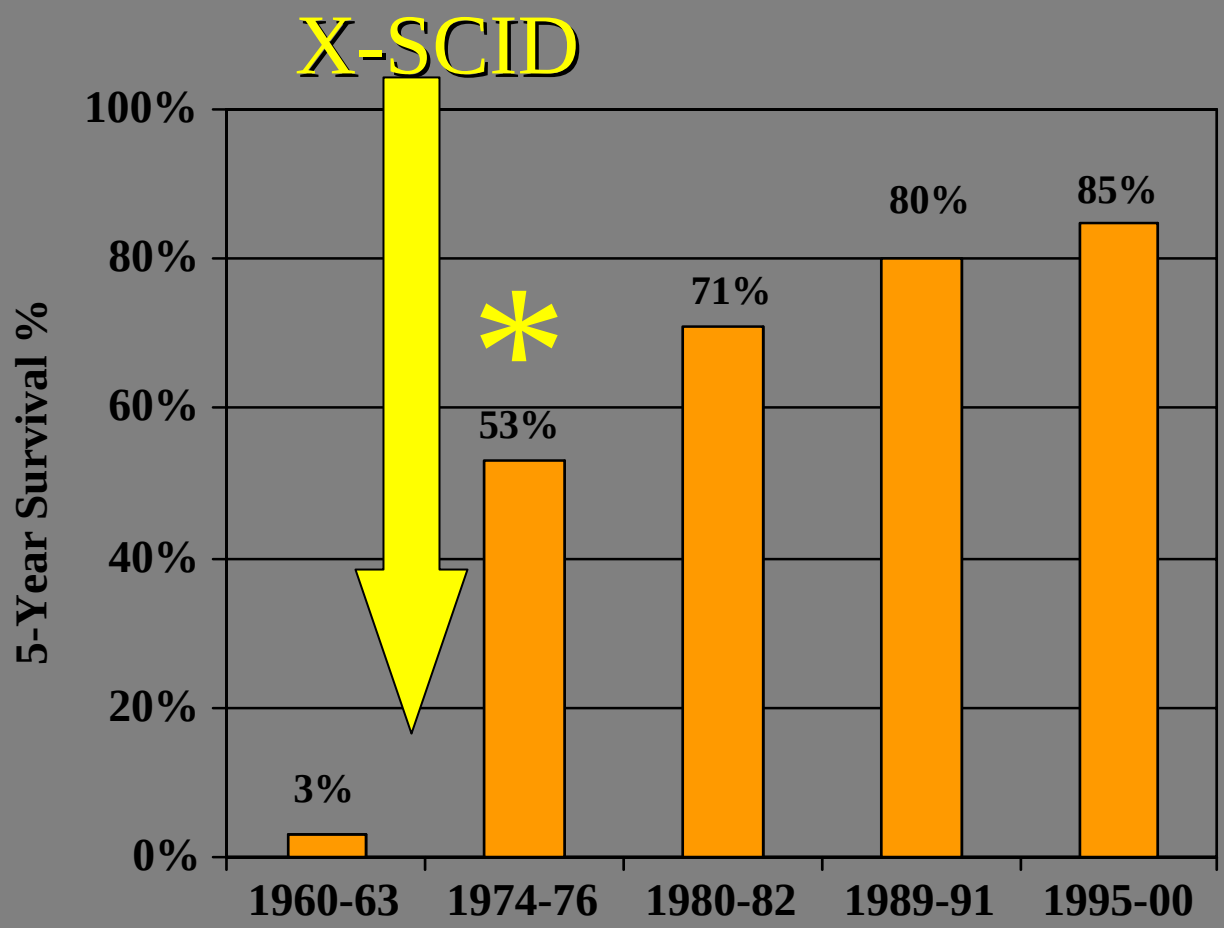
Childhood ALL Survival Rates: 1960-2000



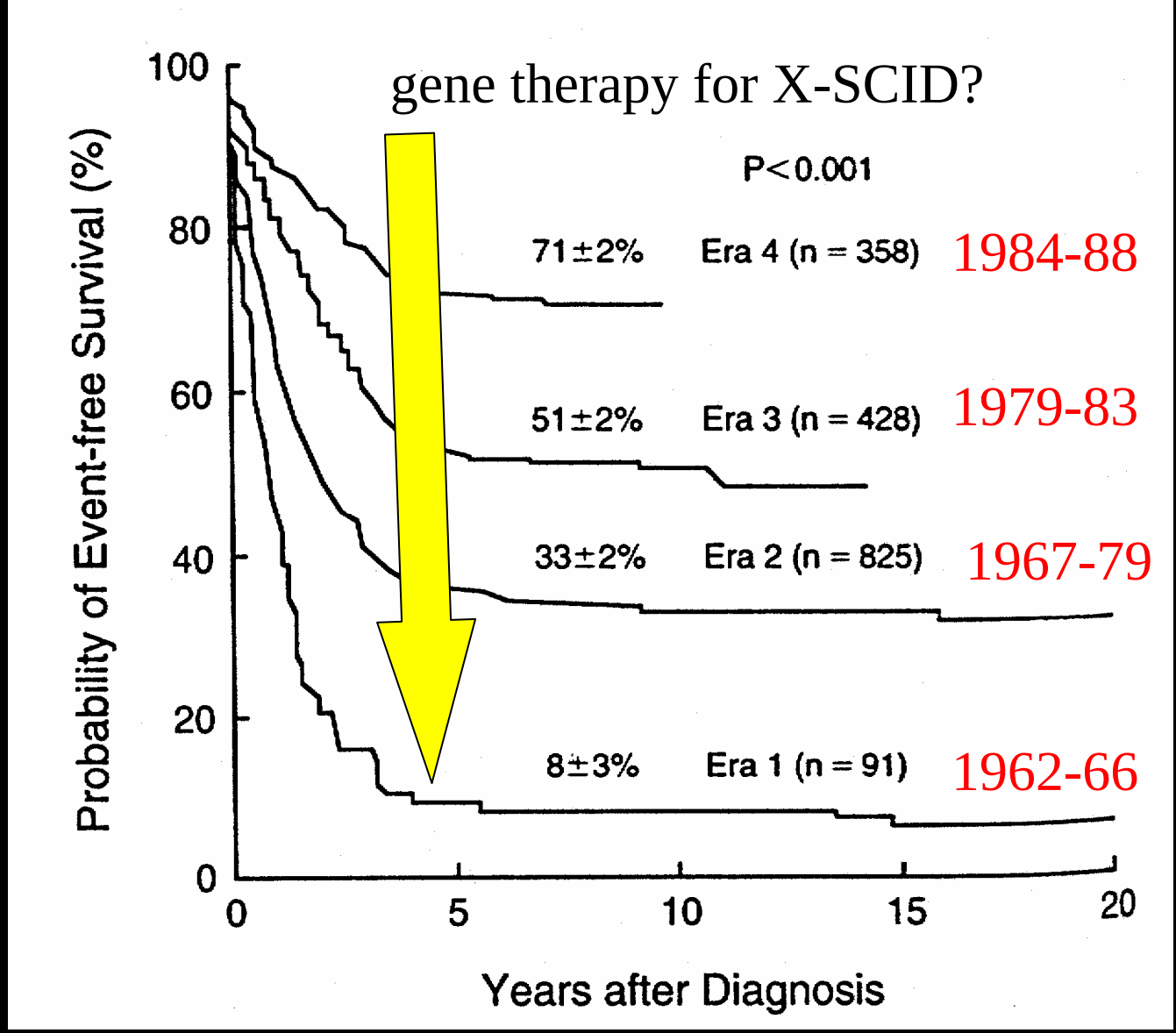
* CNS prophylaxis, new and increased experience with chemotherapeutic agents

Malcolm Smith NCI

Childhood ALL Survival Rates: 1960-2000



Malcolm Smith NCI



Pui CH: Childhood leukemias. N Engl J Med 332: 1618-1630, 1995

The general dilemma

- when does dangerous experimentation become acceptable, preferred, or even “standard of care” therapy ?
- what does one do while waiting for dangerous and imperfect therapy to improve?