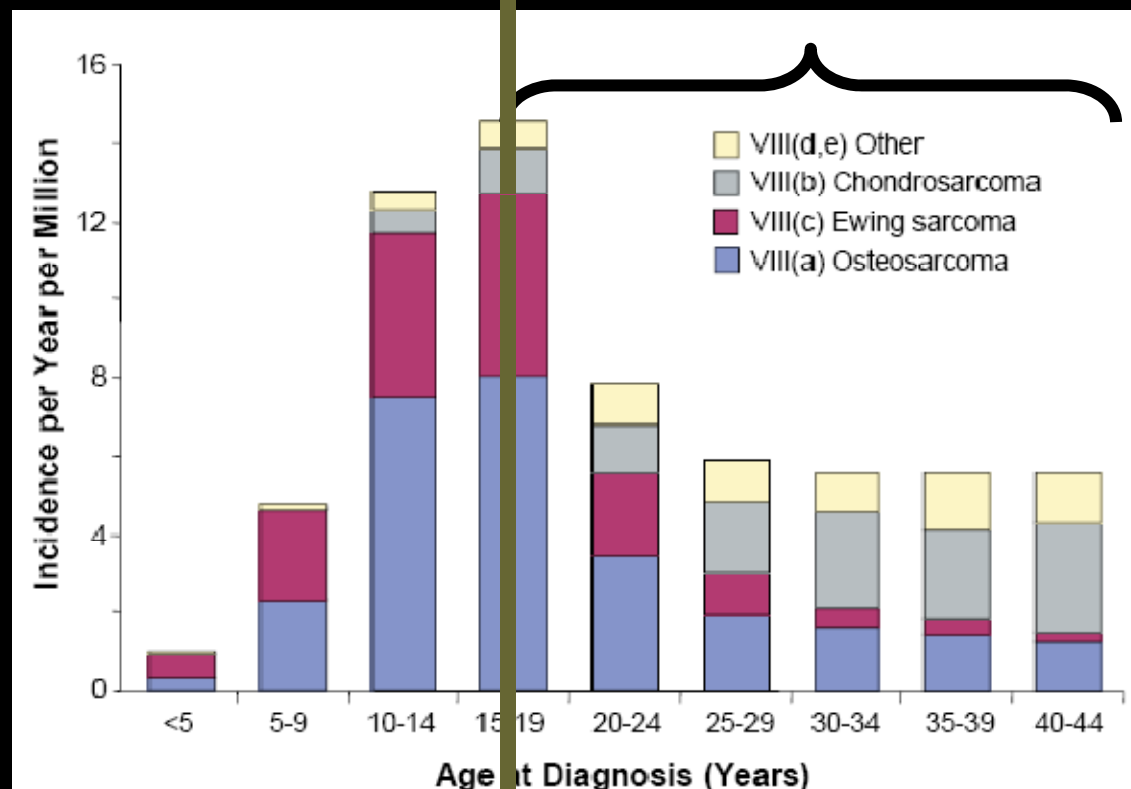


CHEMOTHERAPY FOR BONE SARCOMAS

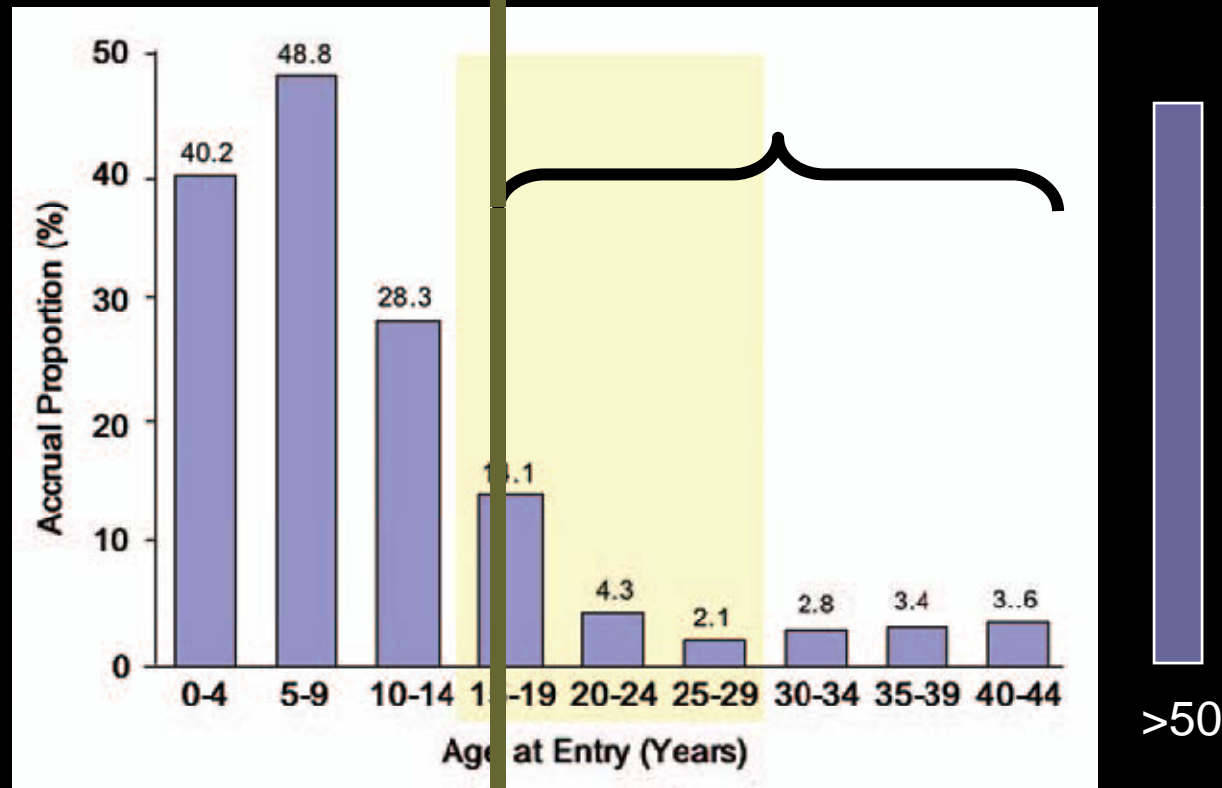
ABHA GUPTA, MD

PRINCESS MARGARET HOSPITAL
HOSPITAL FOR SICK CHILDREN

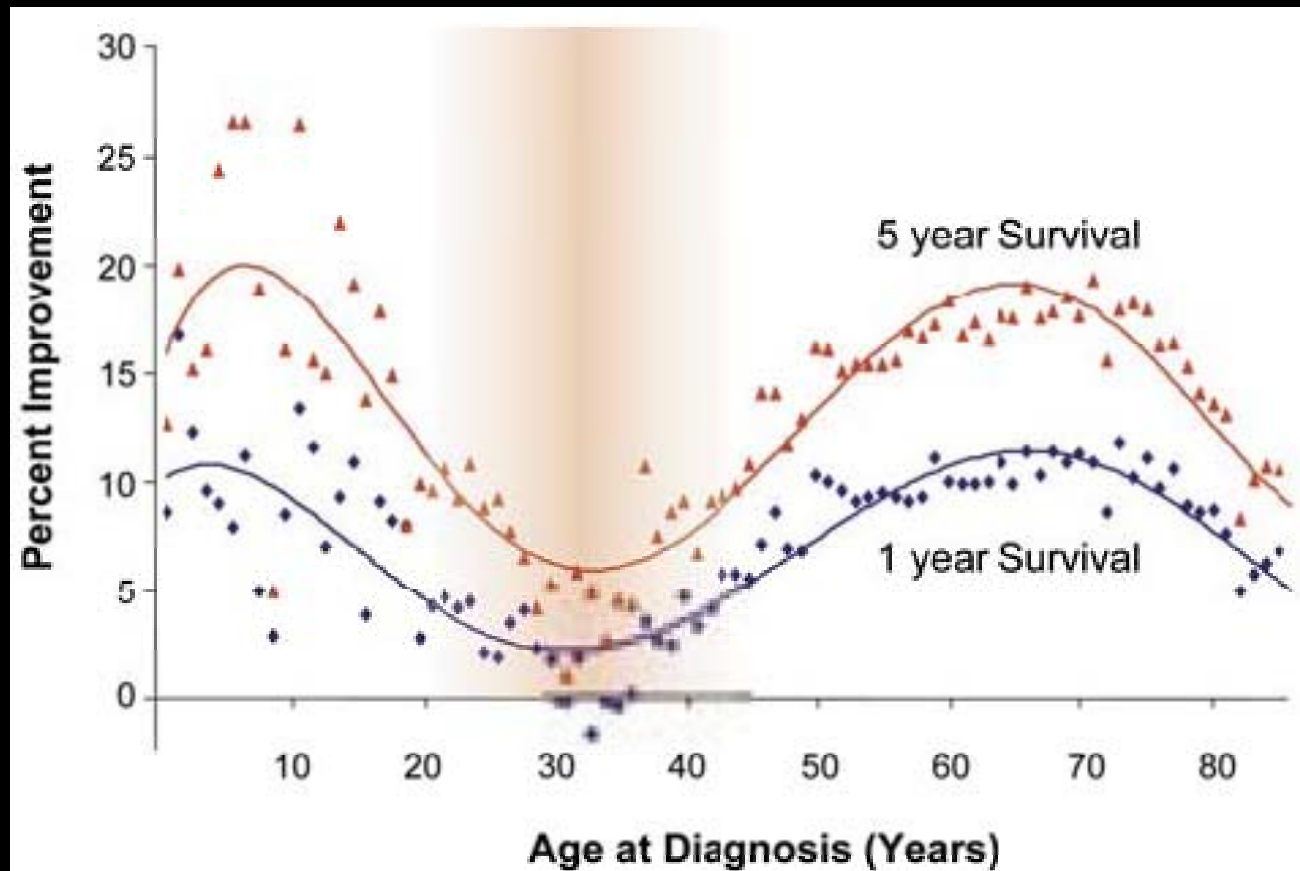
Incidence of Bone Sarcomas, SEER 1975-2000



Proportion of Newly Diagnosed Patients Accrued to National Trials, 1997-2003



Change in Relative Survival, SEER 1995–1999 vs. 1975–1979



“The Lost Tribe”

NEWSFOCUS



Survival in young adults with cancer shows little change across decades. Why is that, and how can the disease be pushed back?

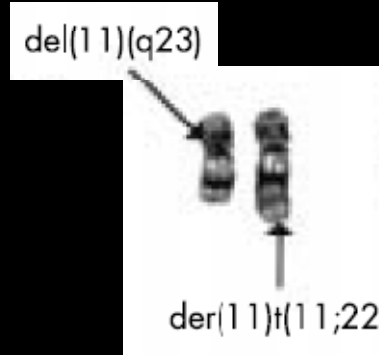
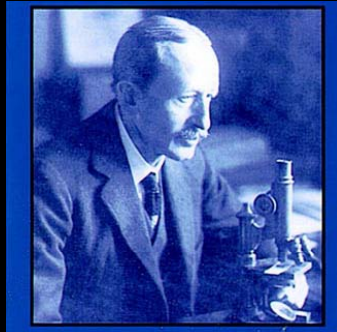
In Their Prime, And Dying of Cancer

sciencemag.org on October 19, 2007

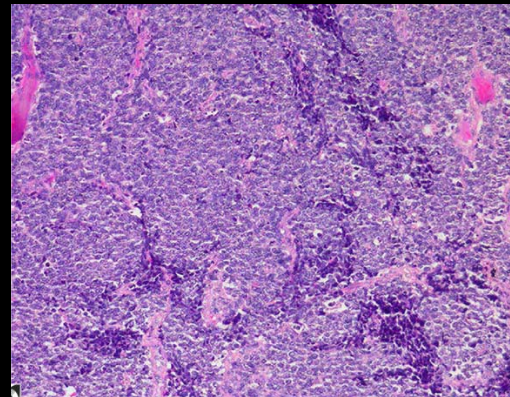
In Canada, each year...

| | | | |
|----------|--------|---------------------|----|
| Prostate | 25,000 | <u>Bone Sarcoma</u> | |
| Lung | 24,000 | Age 0-14 | 35 |
| Breast | 23,000 | Age 20-44 | 75 |
| Colon | 21,000 | Age 15-19 | ? |



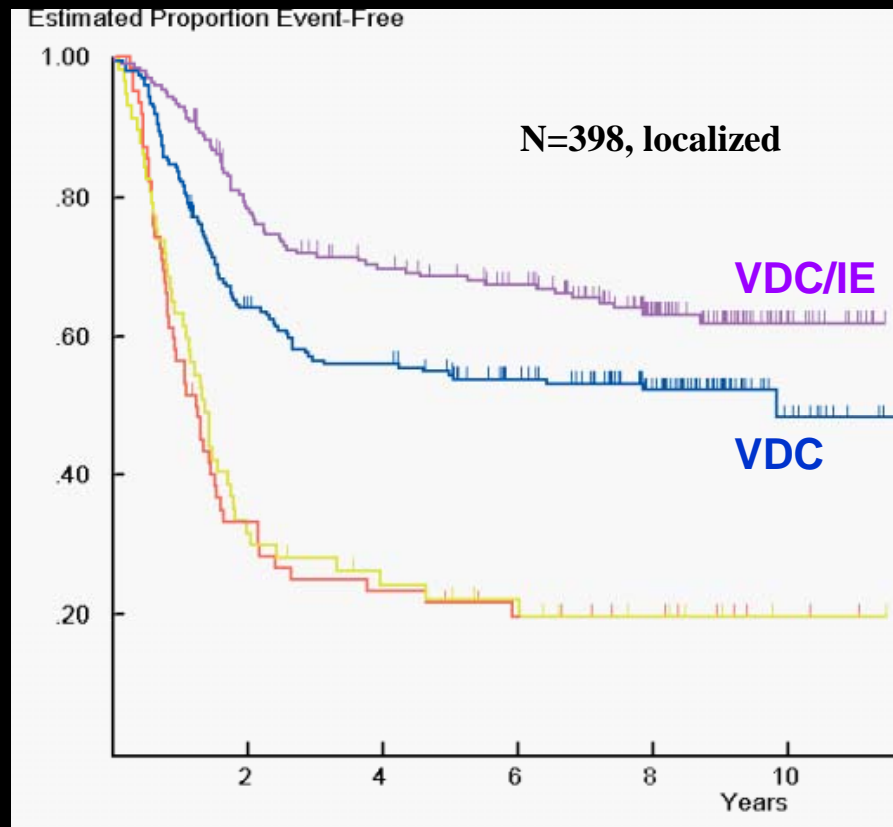


Ewing's Sarcoma



Therapeutic Strategy: Increasing Drugs

Addition of IE to VDC Improves Survival in Localized Ewing's Sarcoma



5 yr EFS: 54% vs. 69%,
 $p=0.005$

'Pediatric' Therapy

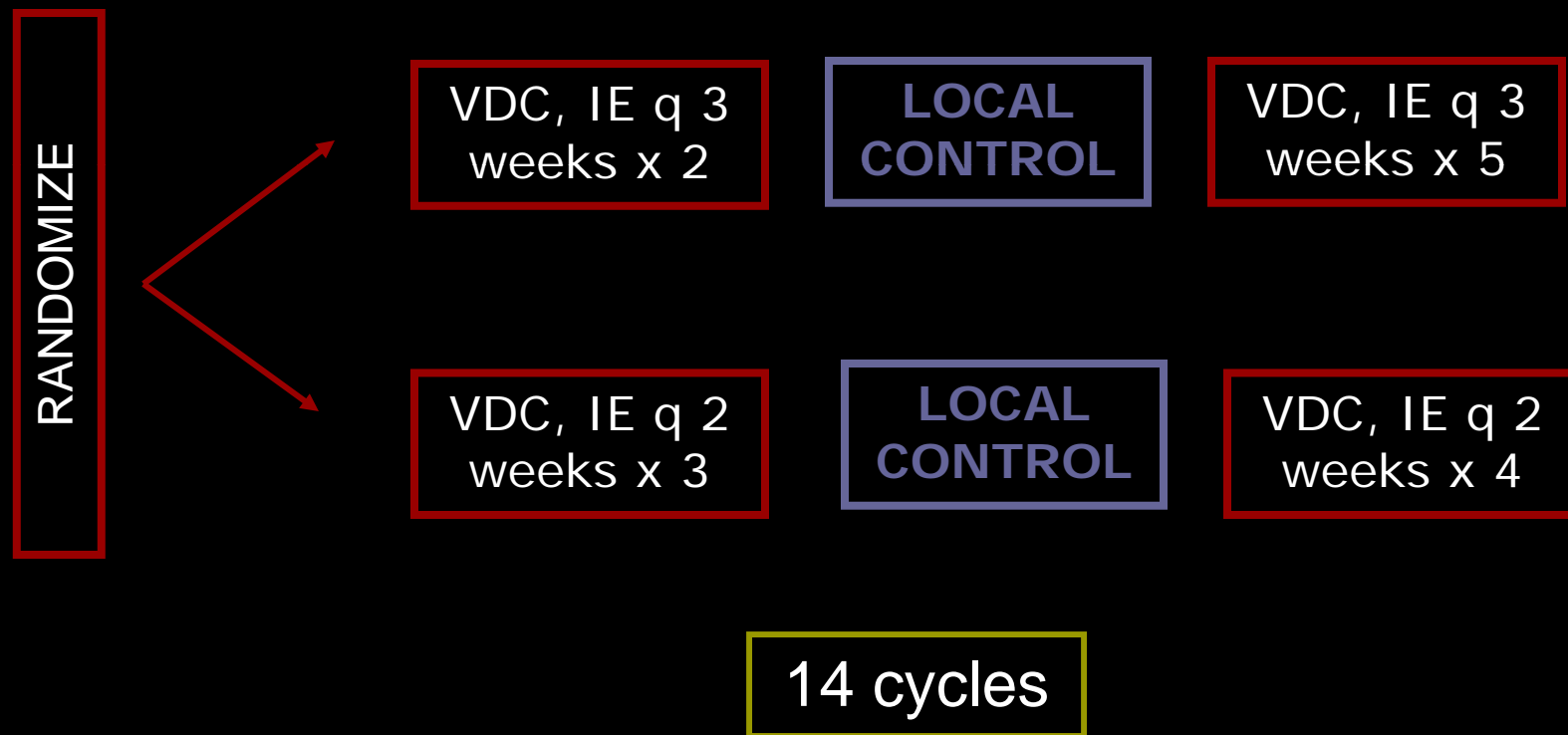
- 5 cycles of VDC
- 8 cycles of IE
- 4 cycles of VC
- ADR = 375 mg/m²

17 cycles

13% > age 18
Unclear benefit of IE in adults

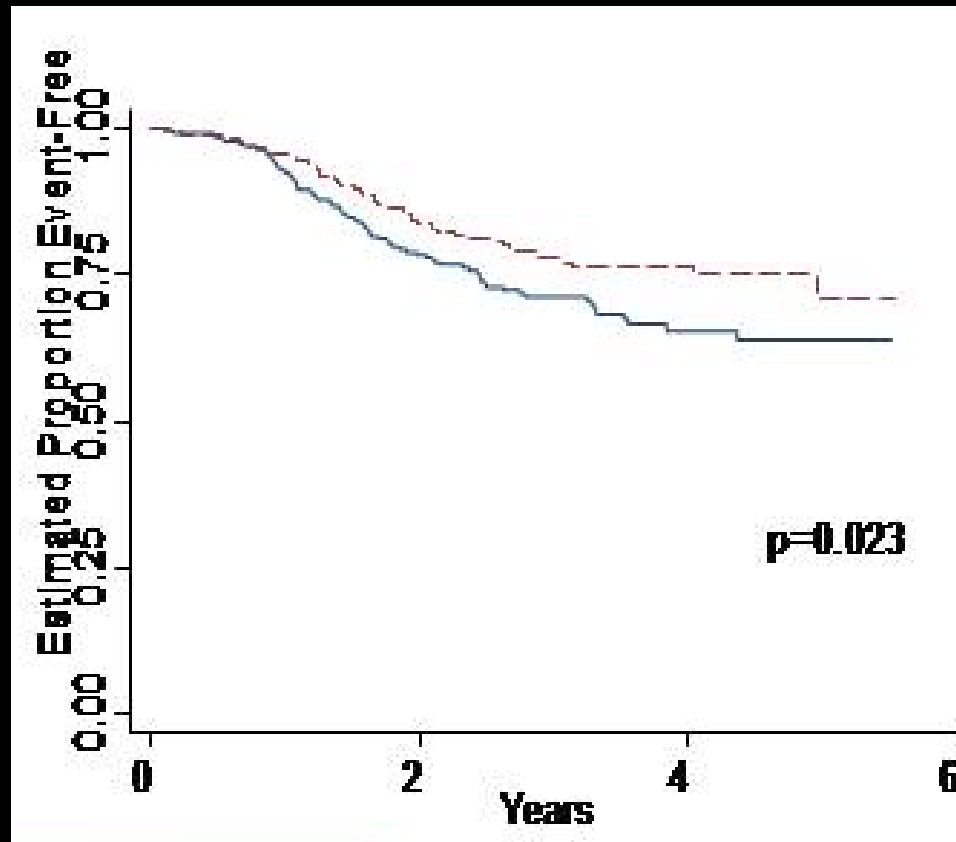
Therapeutic Strategy: Increasing dose Intensity

Randomized Comparison of q2 week vs. q3 week Chemotherapy



25% ↑ dose intensity; no increase toxicity. Improved EFS.

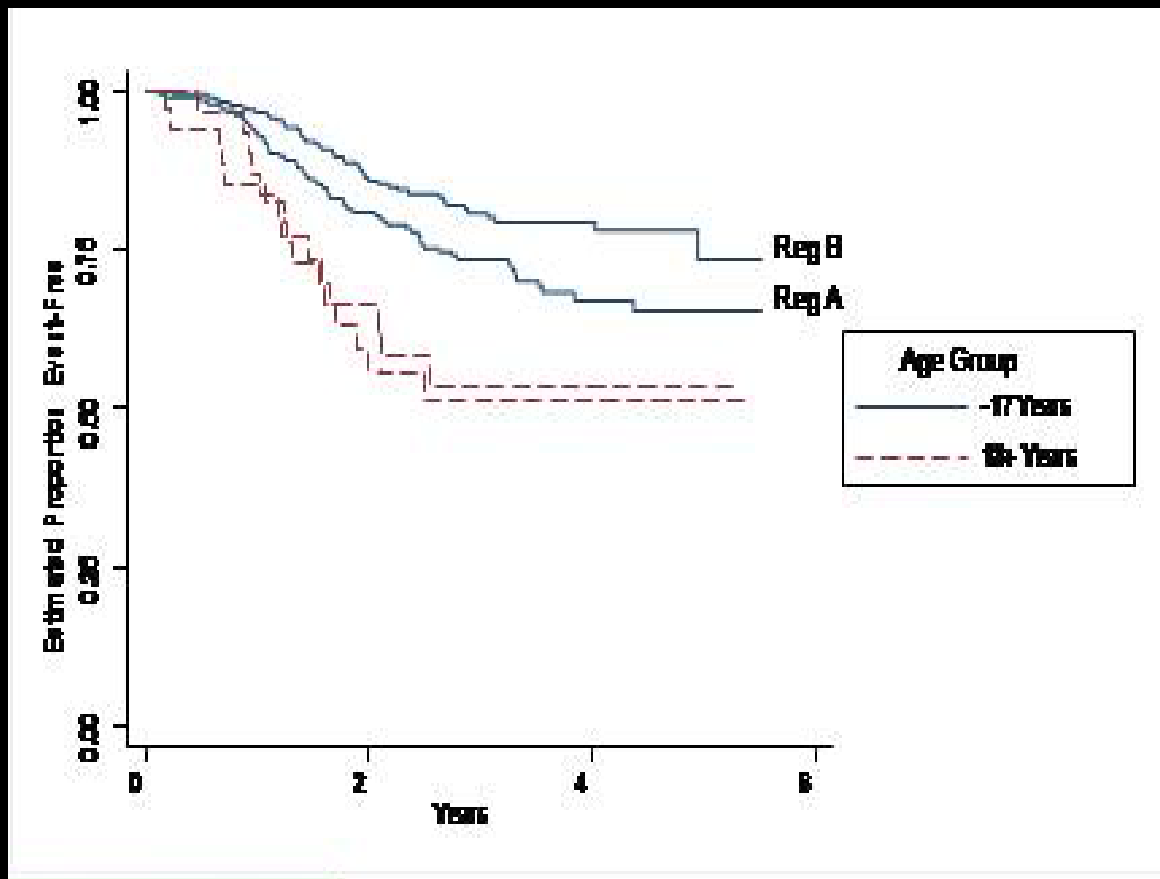
n = 568



3 yr EFS:
65% vs. 76%

Small numbers Limit Power in Adults

“...should give them benefit of the doubt”



13% > age 17

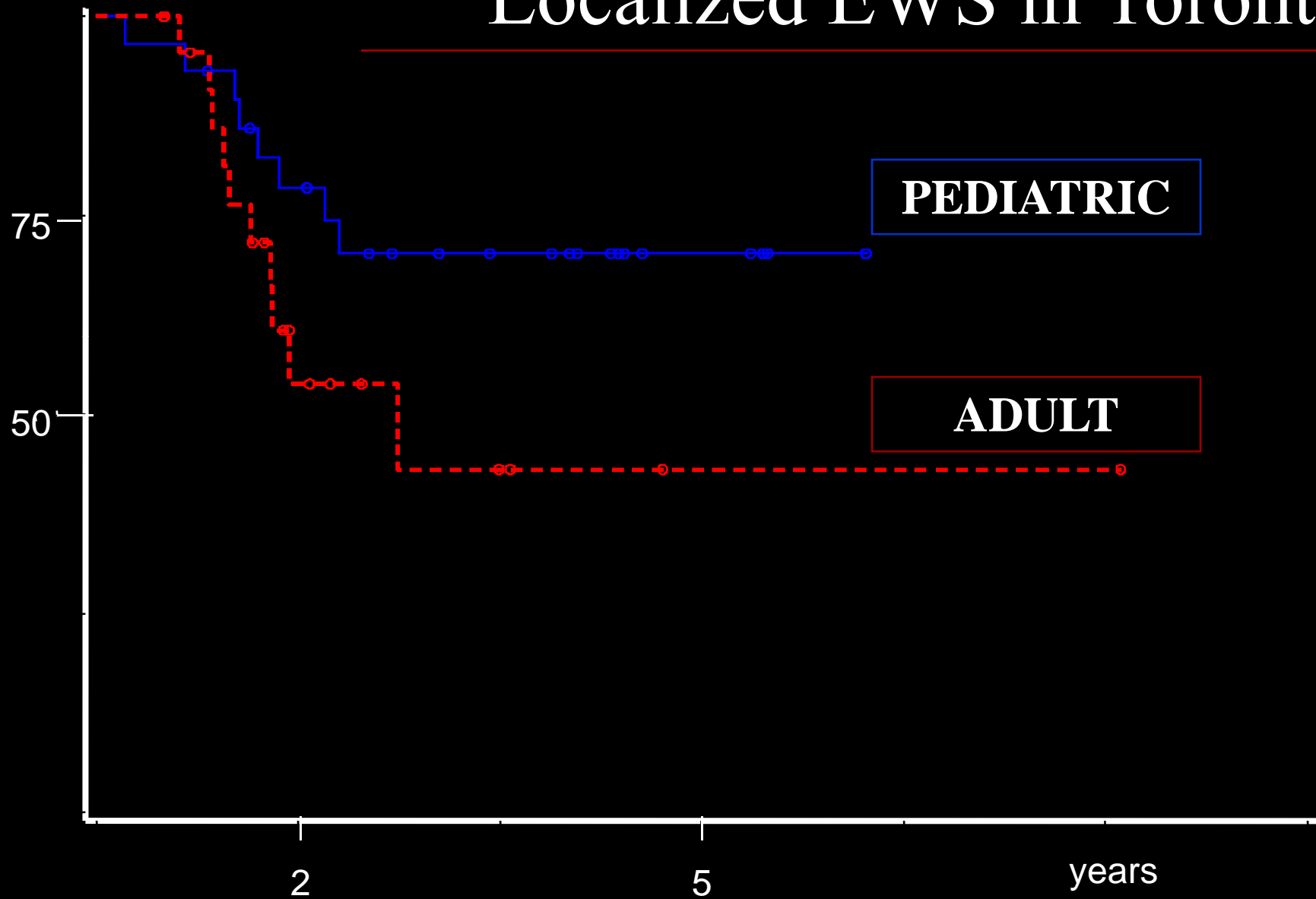
Ewing's Sarcoma in Toronto



- 10 cycles of VDC alternating with IE
- ADR = 375 mg/m²
- 17 cycles of VDC alternating with IE
- ADR = 375 mg/m²

Localized EWS in Toronto

EFS



PEDIATRIC

ADULT

years

Multivariable Analysis of Prognostic Features for EFS

| Parameter | HR | 95% C.I. | p |
|------------------------|------|--------------|-------|
| Total Dose Ifosfamide | 0.97 | (0.95, 0.98) | 0.002 |
| Pelvic Primary | 2.12 | (1.1, 4.26) | 0.03 |
| Total Dose Doxorubicin | 0.56 | (0.33, 0.94) | 0.03 |

Is Age an Independent Prognostic Factor in Ewing's Sarcoma?

■ Yes

- Craft JCO 1998
- Cotterill JCO 2000
- Bacci JCO 2000
- Grier NEJM 2003

■ No

- Oberlin Proc ASCO 1996
- Verrill JCO 1997
- Fizazi JCO 1998
- Paulussen JCO 2001

Ewing's in First Relapse

Irinotecan 20 mg/m² x 5

OR = 30%

Temozolomide 100 mg/m² x 5

Wagner 2004, 2007

CPM 250 mg/m² x 5

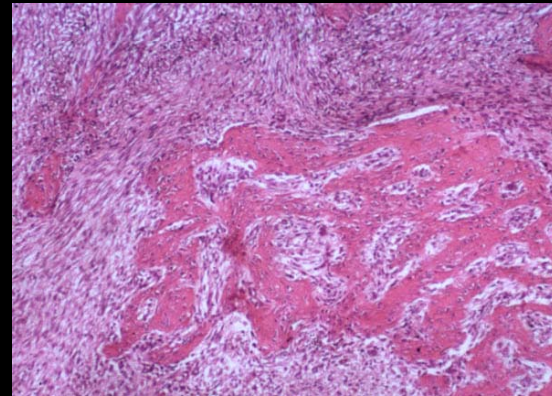
OR = 33 – 57%

Topotecan 0.75 mg/m² x 5

Jurgens 2006, Saylor 2001, Bernstein 2006

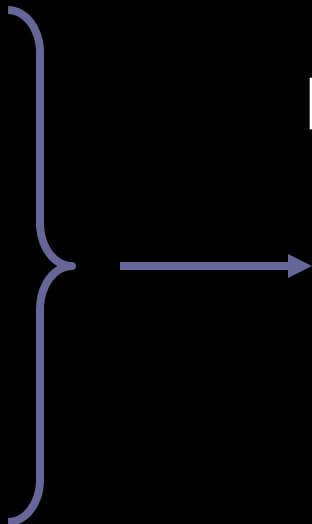
Upfront therapy

Osteosarcoma



Active Agents in Osteosarcoma

- Doxorubicin
- Cisplatin
- Methotrexate
- [Ifosfamide]



Despite various doses,
combinations, pre-op,
post-op, North
America, Europe...

...survival of localized osteosarcoma
has not changed in >20 years

Winkler JCO 1984

- COSS-80

EFS 68%

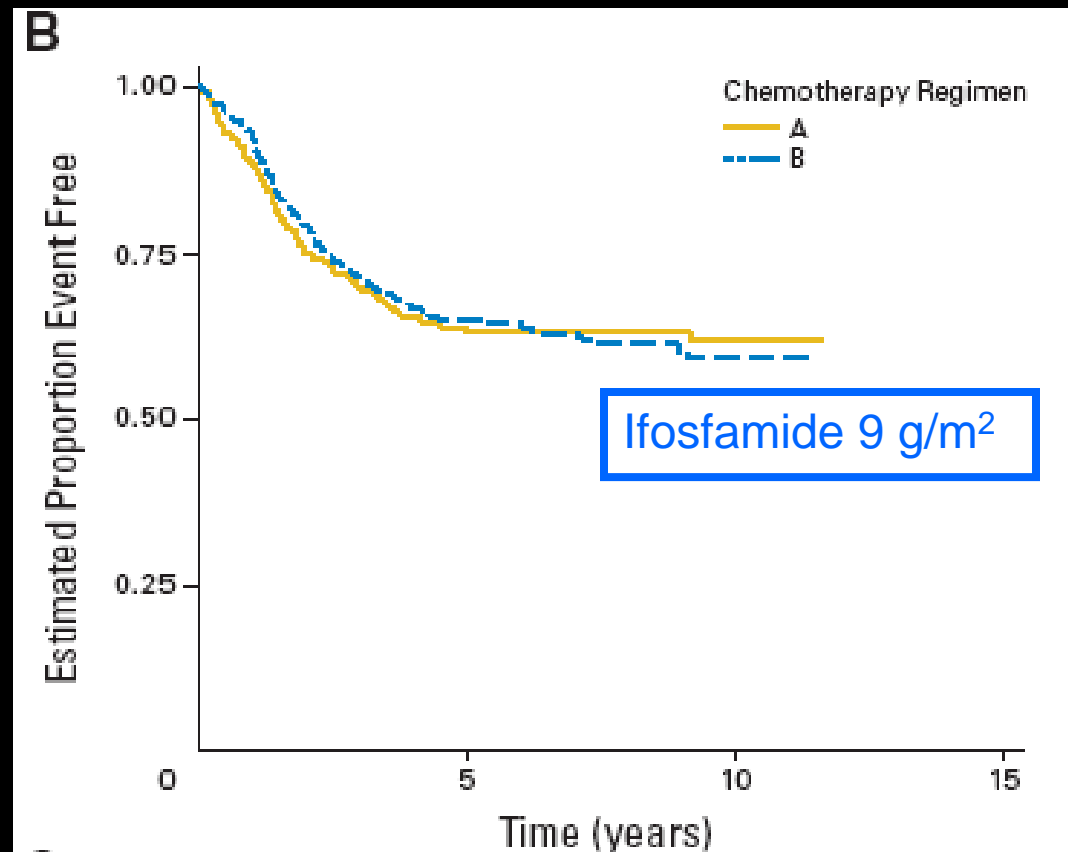
Meyers JCO 2005

- POG-9351

EFS 71%

Add Ifosfamide: no difference

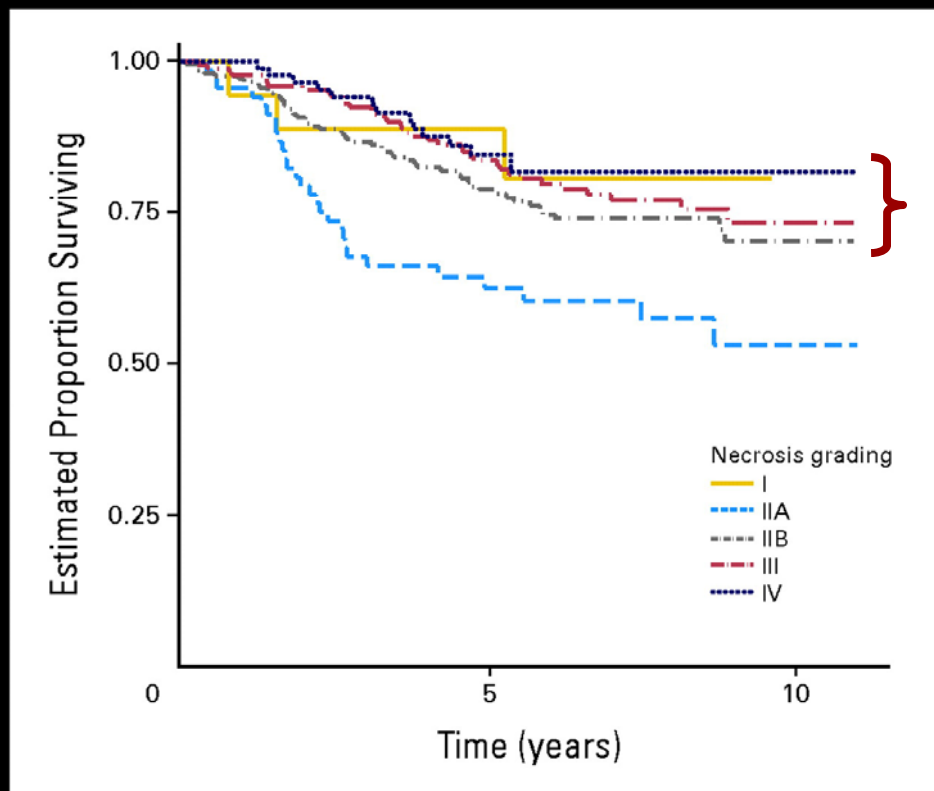
Median
age = 13



Therapeutic Strategy: Improve % Necrosis



After induction chemotherapy, necrosis in primary tumour at definitive surgical resection is correlated with event-free survival



> 95%
necrosis



Changing % Necrosis: no difference

- Patients randomized to MA vs. MIE pre-op
 - Ifosfamide = 12 g/m²
 - proportion of patients with favorable necrosis increased from 39% to 56%
 - No effect on survival

Therapeutic Strategy: Dose Intensity

Increasing dose intensity from q3w to q2w: no difference

- AP x 6
- Surgery at week 6
- Proportion of patients with favorable (>90%) necrosis increased from 36 to 50%
- No impact on EFS or OS

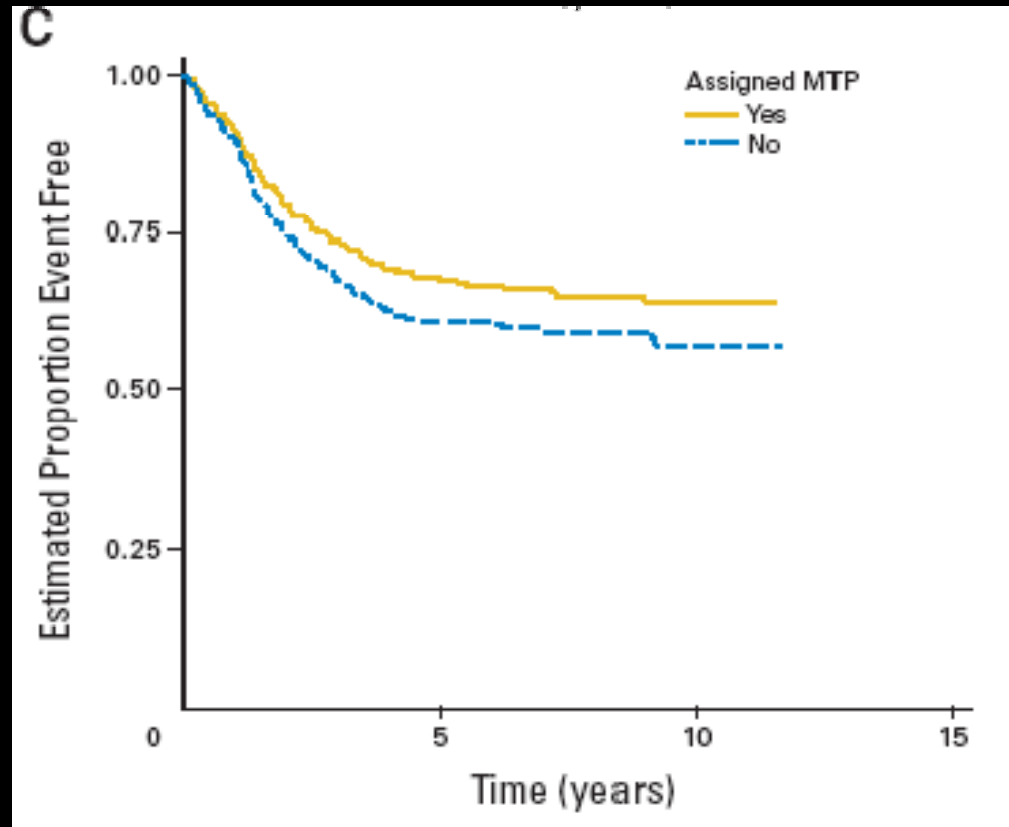
Therapeutic Strategy: Immunotherapy

Immunotherapy in Osteosarcoma

- Wound infection improves survival

Liptak Vet Surgery 2006

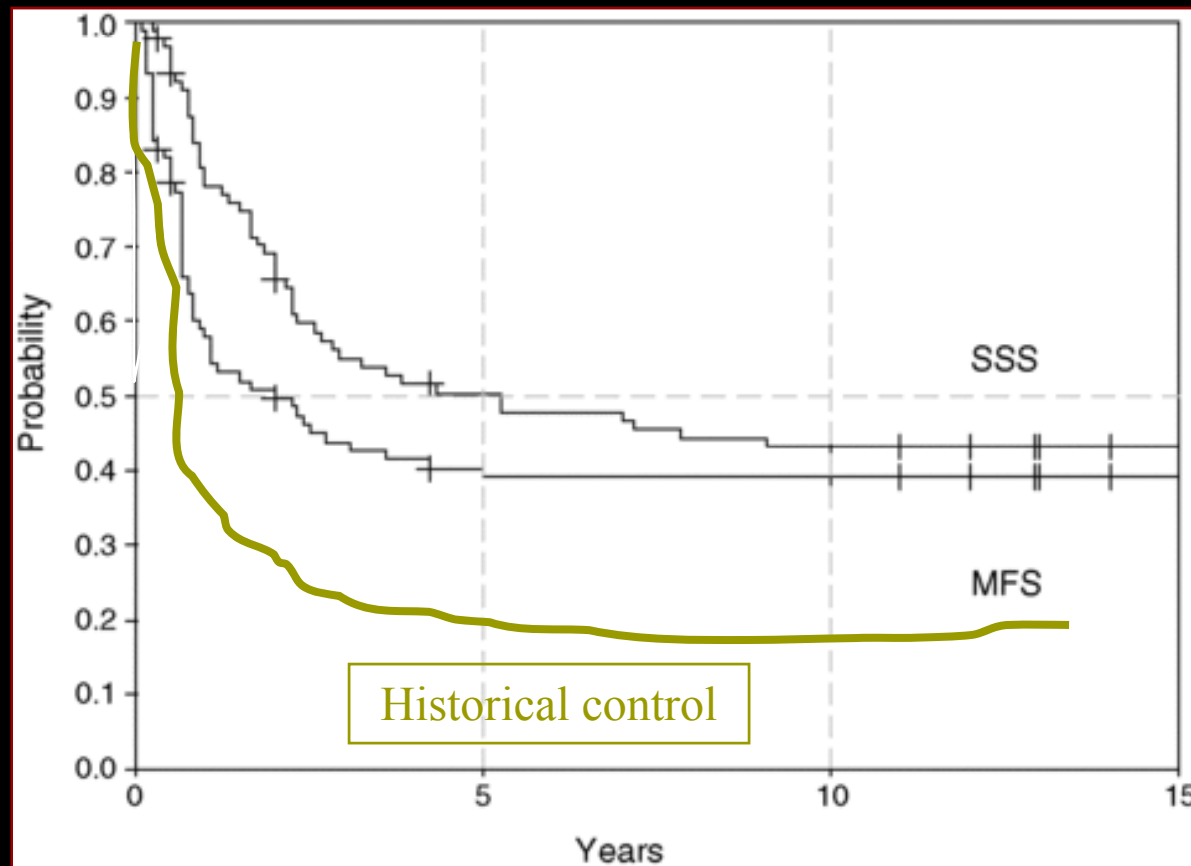
MTP-PE - synthetic analog of BCG cell: no difference



P=0.08

N = 662

Interferon- α as the only adjuvant treatment in high-grade osteosarcoma



39%

N=89

Therapeutic Strategy:
Altering Therapy in Response
to % Necrosis +
Immunotherapy



*Participating
Organization*

EURAMOS 1

ISRCTN67813327

EudraCT no. 2004-000242-20

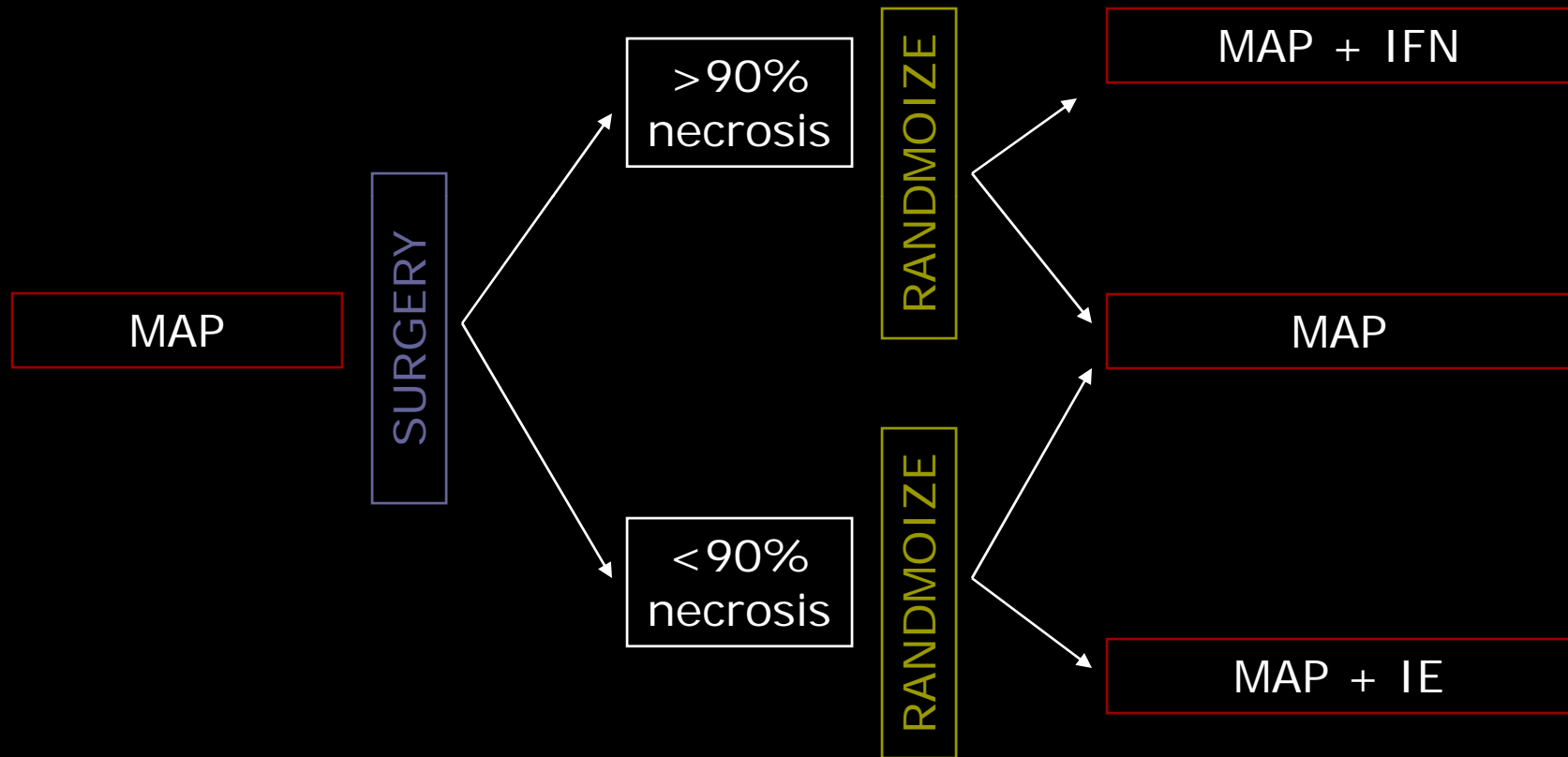
A randomized trial of the
European and American Osteosarcoma Study Group
to optimize treatment strategies for resectable
osteosarcoma based on histological response to
pre-operative chemotherapy

Clinical trial protocol

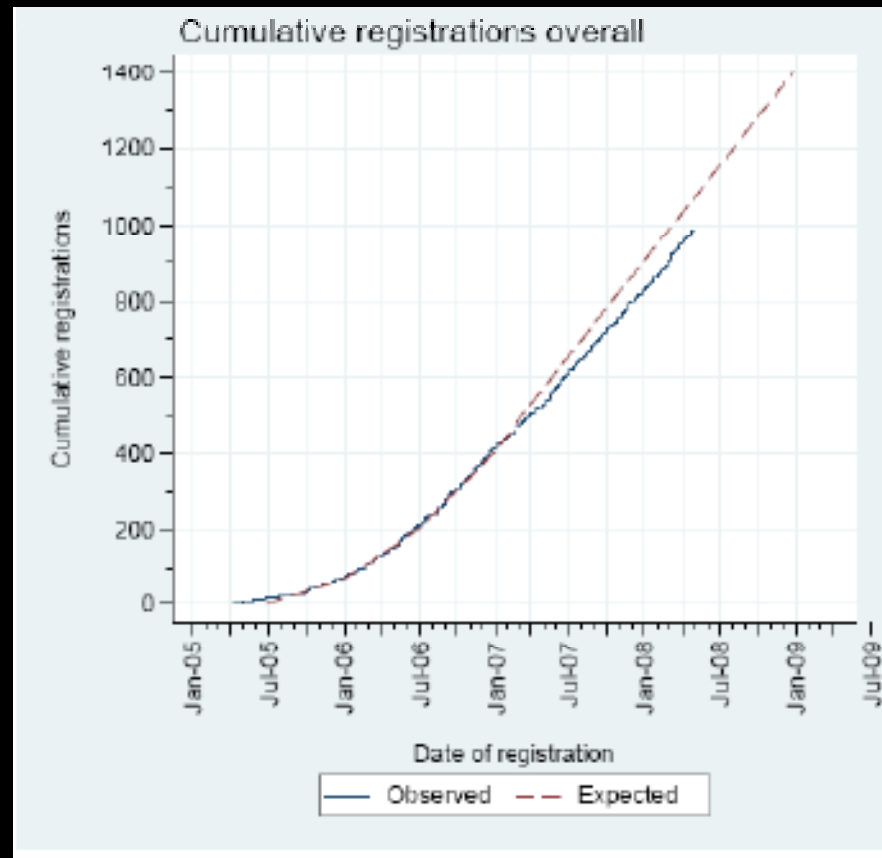
Version: 1.2

Date: 30 March 2007

A Randomized Trial to Optimize Treatment Strategies Based on Histological Response to Pre-Operative Chemotherapy



EURAMOS – current status



Novel Therapeutics

Bone tumours and IGF-IR

- Peak incidence of bone tumours in adolescence/young adults
- IGF pathway important in bone growth
- High circulating levels of IGF

Special Story: Ewing's and IGF-IR

- IGF receptors are expressed in sarcoma

Andrulis 1995

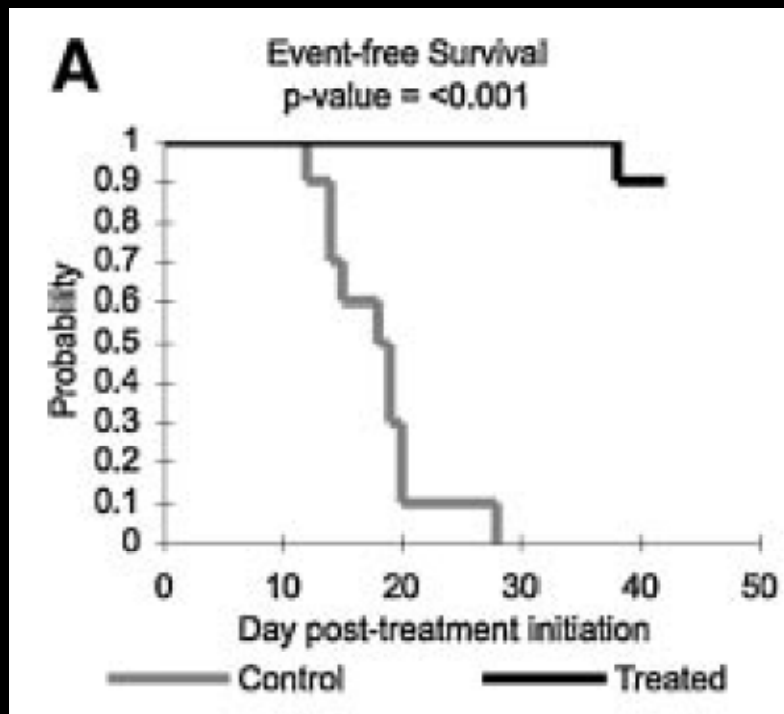
- IGF-IR is required for EWS-FLI1 mediated transformation of fibroblasts

Hellman 1997

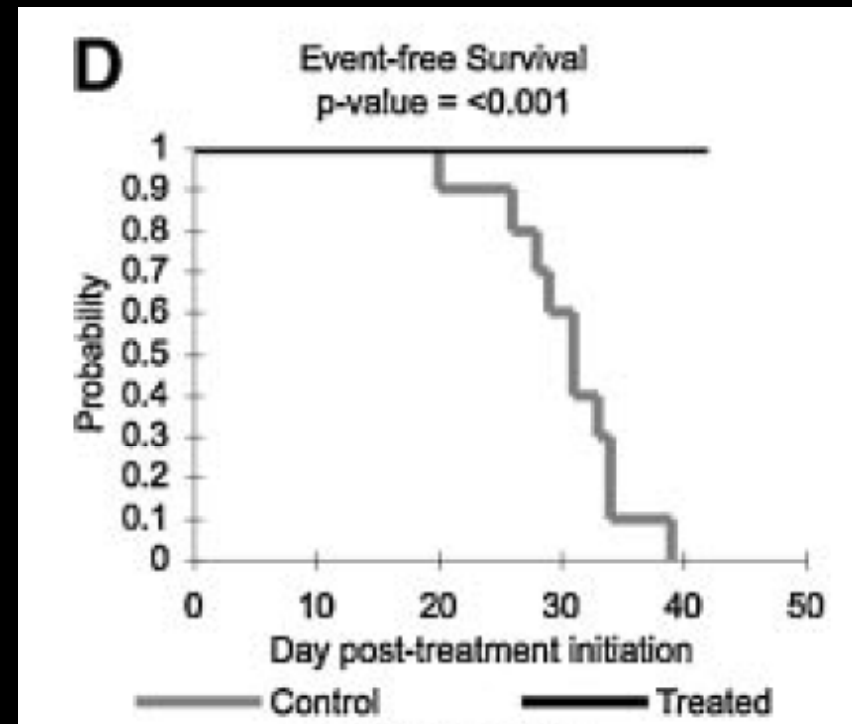
- EWS-FLI1 represses transcription of IGFBP3 - leading to constitutive activation of IGF pathway

Delattre 2004

Monoclonal Antibody Against IGF-IR Receptor in Mouse Tumour Xenografts



Ewing's Sarcoma

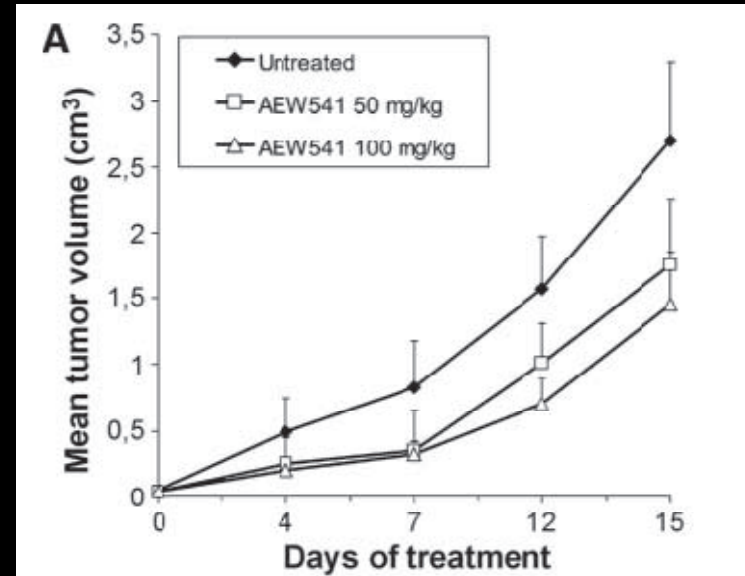
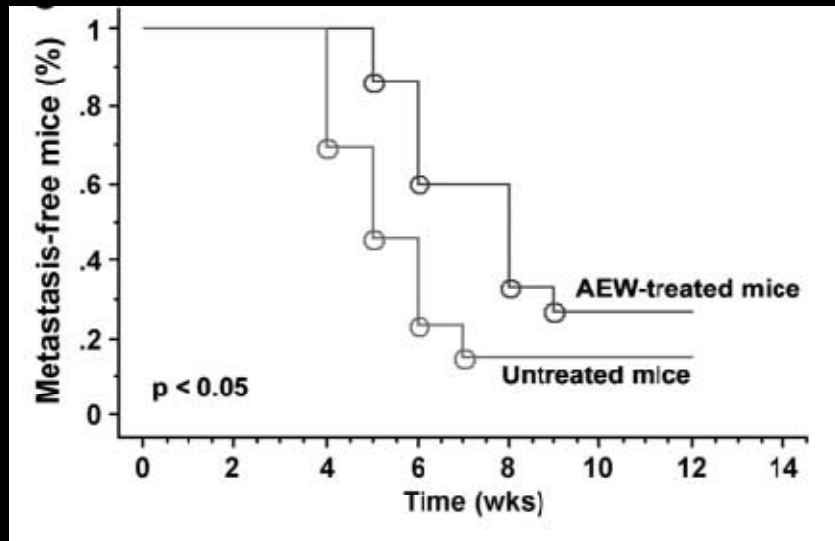


Osteosarcoma

0.5 mg/mouse twice weekly x 4 weeks

Kolb 2008

Small Molecule Inhibitor of IGF-IR in Ewing's Sarcoma



Phase II Trials IGF-IR Antibody

- Coming soon

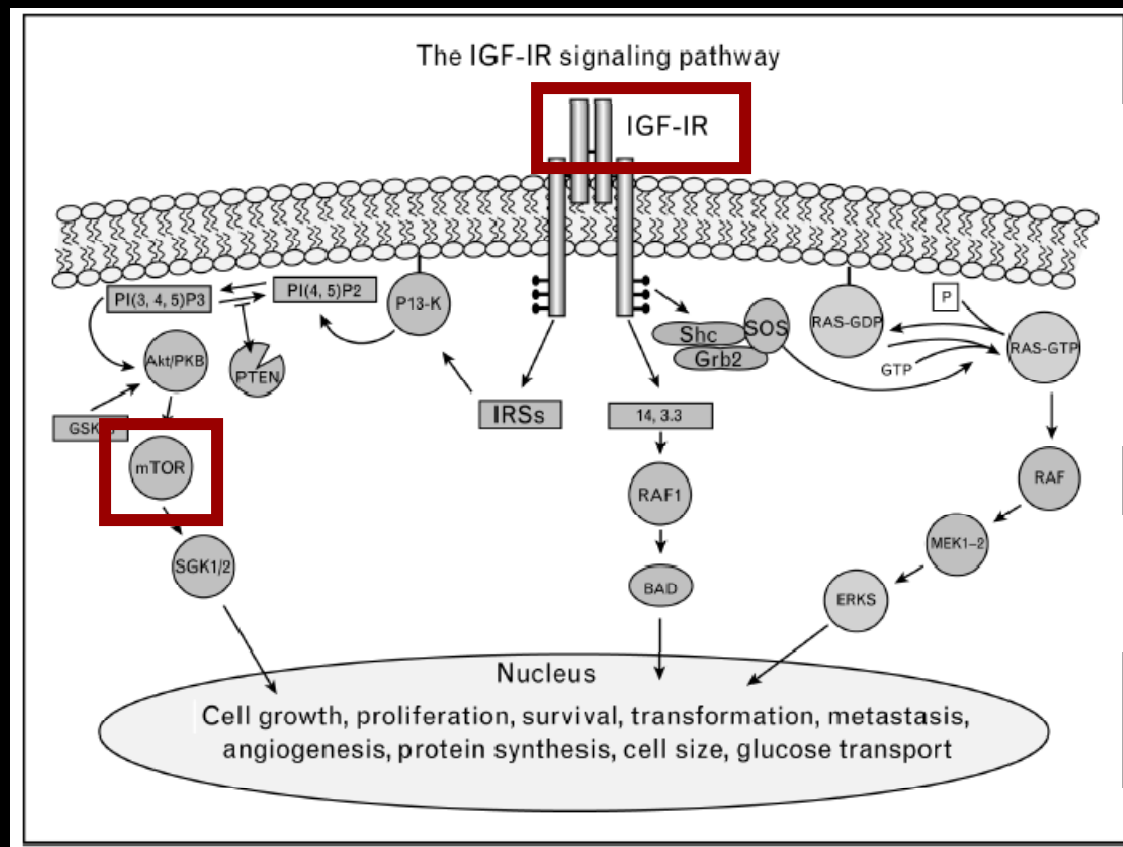
mTOR Inhibition

Rapamycin induces the fusion-type independent downregulation of the EWS/FLI-1 proteins and inhibits Ewing's sarcoma cell Proliferation

Mateo-Lozano 2003

ARIAD - A Pivotal Trial to Determine the Efficacy and Safety of AP23573 When Administered as Maintenance Therapy to Patients With Metastatic Soft Tissue or Bone Sarcomas

mTOR + IGF-RI



Relapsed Disease

- Novel agents on the horizon
- Combination therapy
- Maintenance therapy

Currently, there are no clinical trials available in Canada for newly diagnosed patients > 18 yrs of age with Ewing's or Osteosarcoma.

Unclear whether data obtained from pediatric studies are directly applicable to young adult patients.