Acute Lymphoblastic Leukaemia (ALL) in Children: Improvement without new drugs

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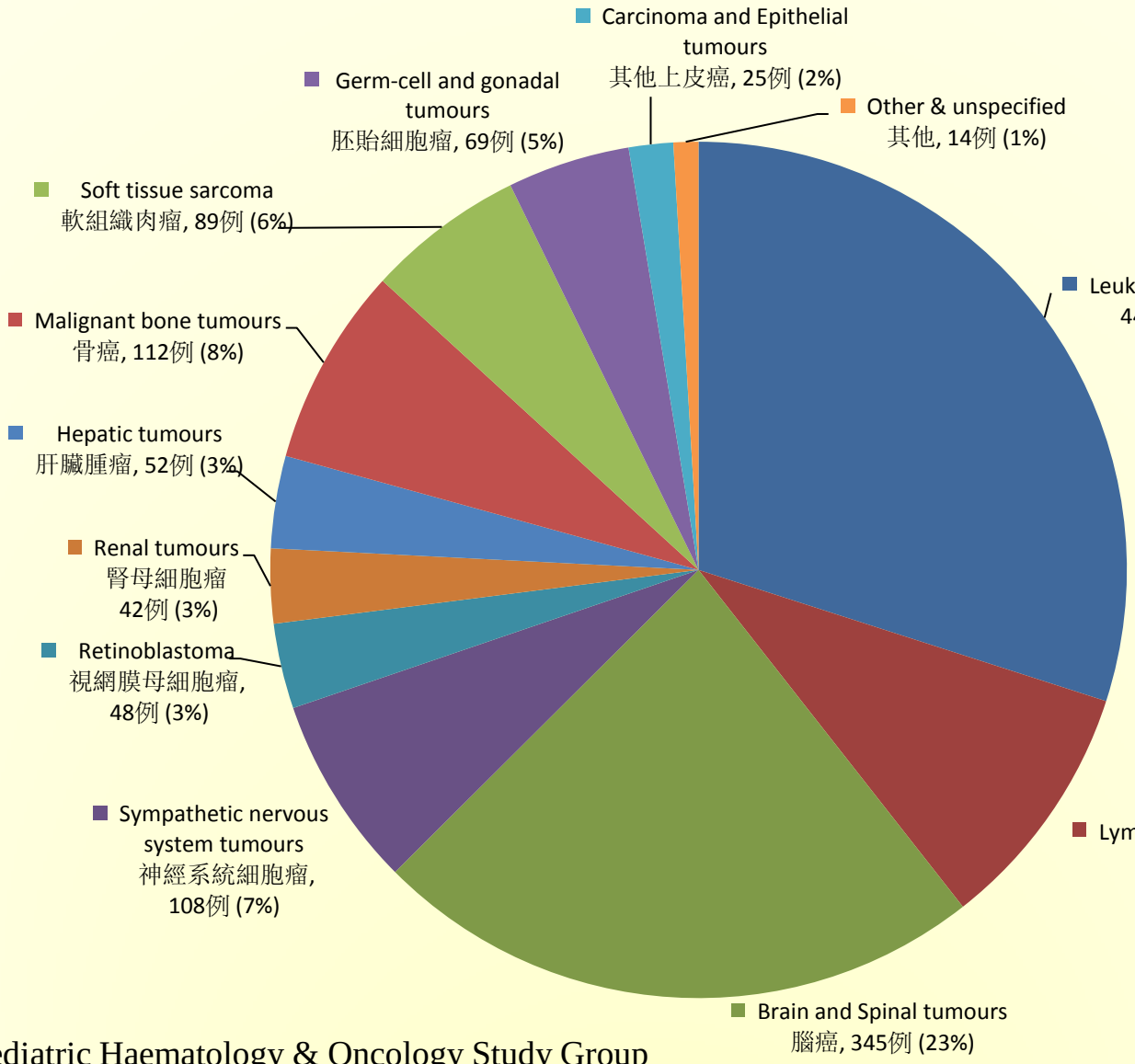
Trends in New Cases of Cancer among Children and Adolescents (0-18 years), 2001-2010



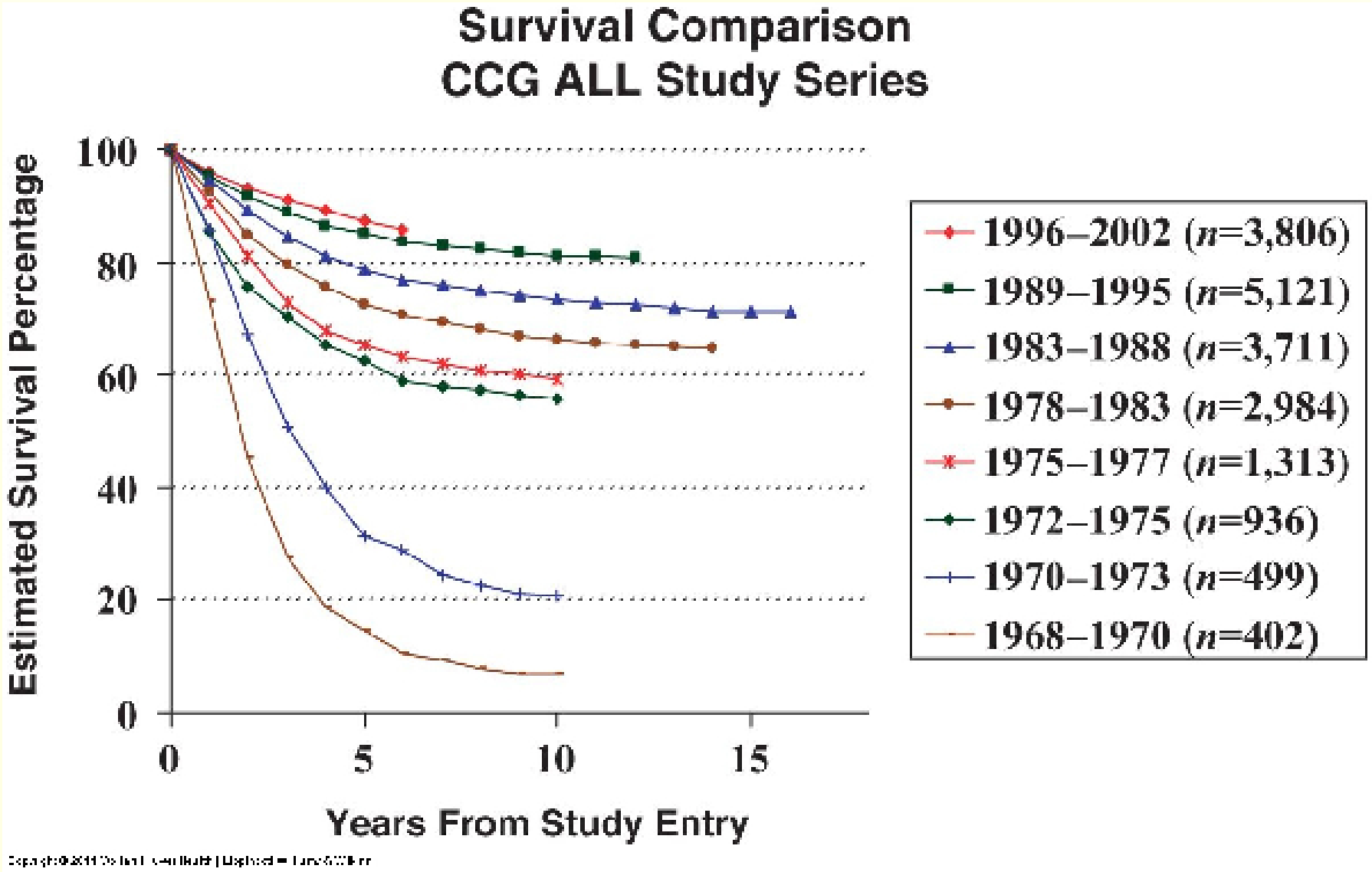
Hospital Authority:

5 Designated Children Cancer Unit

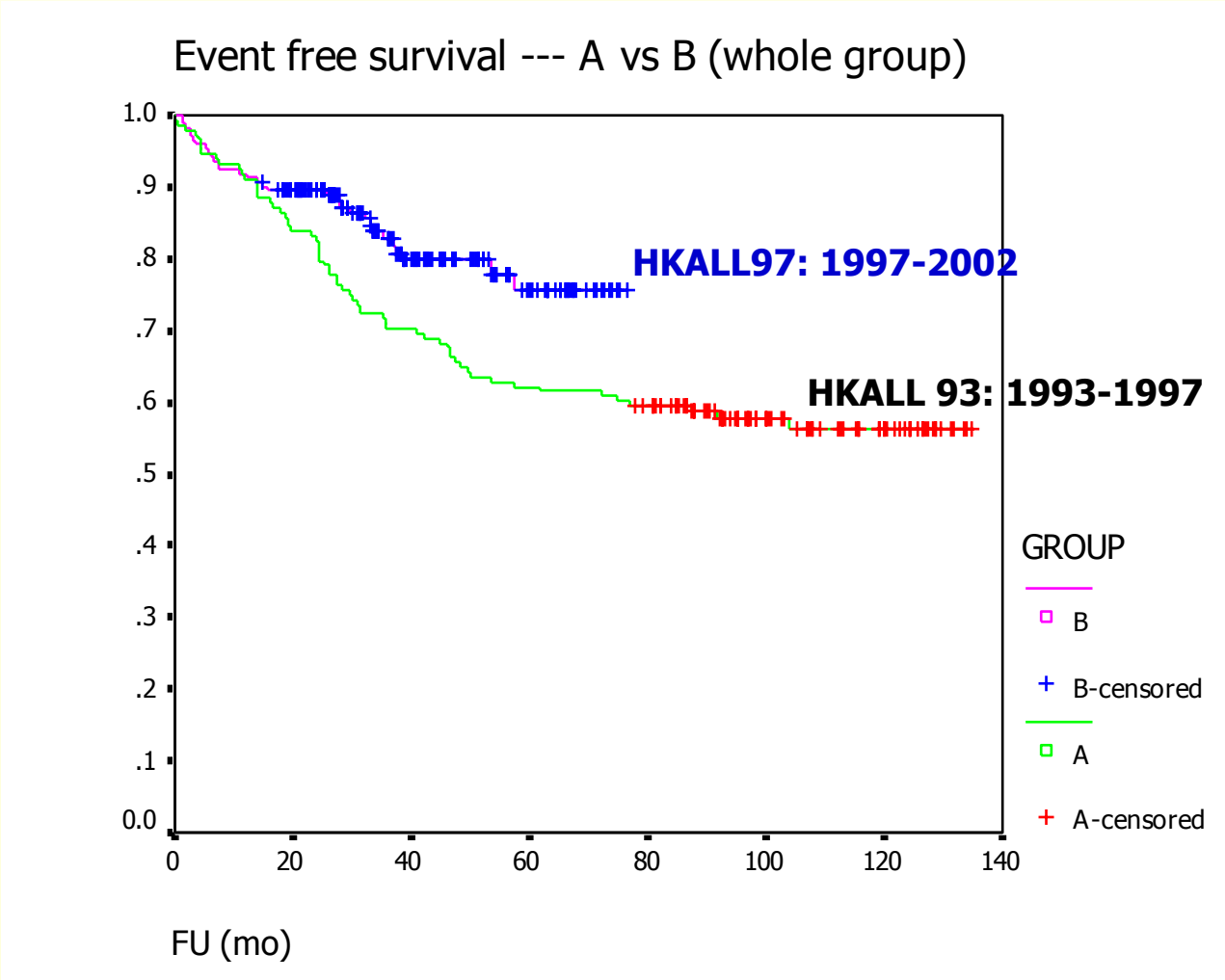
Hong Kong Paediatric Haematology & Oncology Study Group

Paediatric ALL

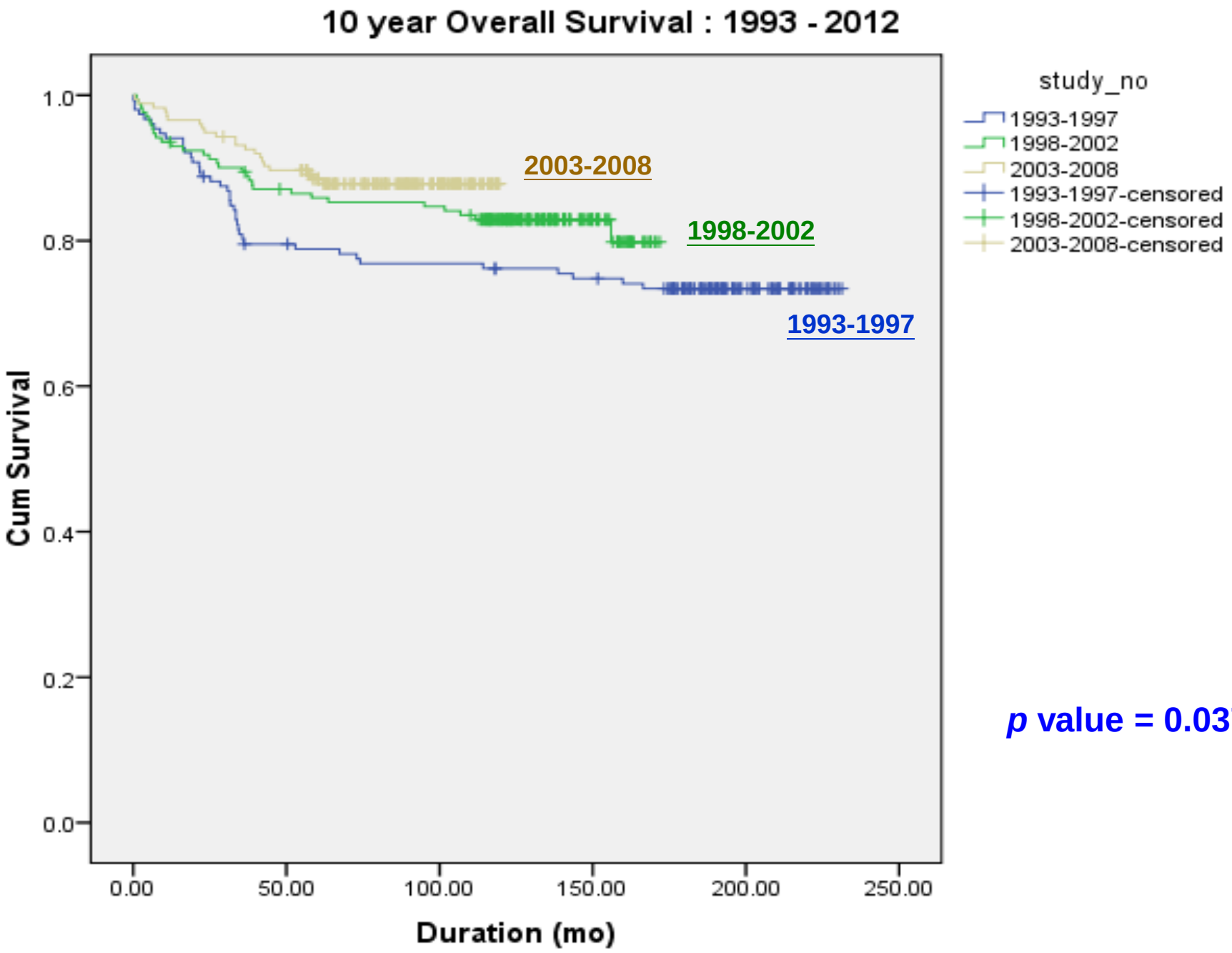
- Commonest childhood malignancy
- 25% of all childhood cancer
- Incidence: 3-4 cases per 100,000 children
- 30-40 new cases per year in Hong Kong
- 6,600 – 8,800 new cases per year in China (222 million children <15 yr)


Survival Comparison
CCG ALL Study Series
Estimated Survival Percentage
100
80
60
40
20
0
0
5
10
15
Years From Study Entry
1996–2002 (n=3,806)
1989–1995 (n=5,121)
1983–1988 (n=3,711)
1978–1983 (n=2,984)
1975–1977 (n=1,313)
1972–1975 (n=936)
1970–1973 (n=499)
1968–1970 (n=402)

Improvement of Event free survival by chemo: HKALL 93 (UK based) vs HKALL 97 (BFM based)



Li CK et al. Hong Kong Med J. 2006 Feb;12(1):33-9, Li CK et al: Hematol Oncol 2003; 21:1-9


10 year Overall Survival : 1993 - 2012
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
50.00
100.00
150.00
200.00
250.00
Duration (mo)
2003-2008
1998-2002
1993-1997
study_no
1993-1997
1998-2002
2003-2008
1993-1997-censored
1998-2002-censored
2003-2008-censored

***p* value = 0.037**

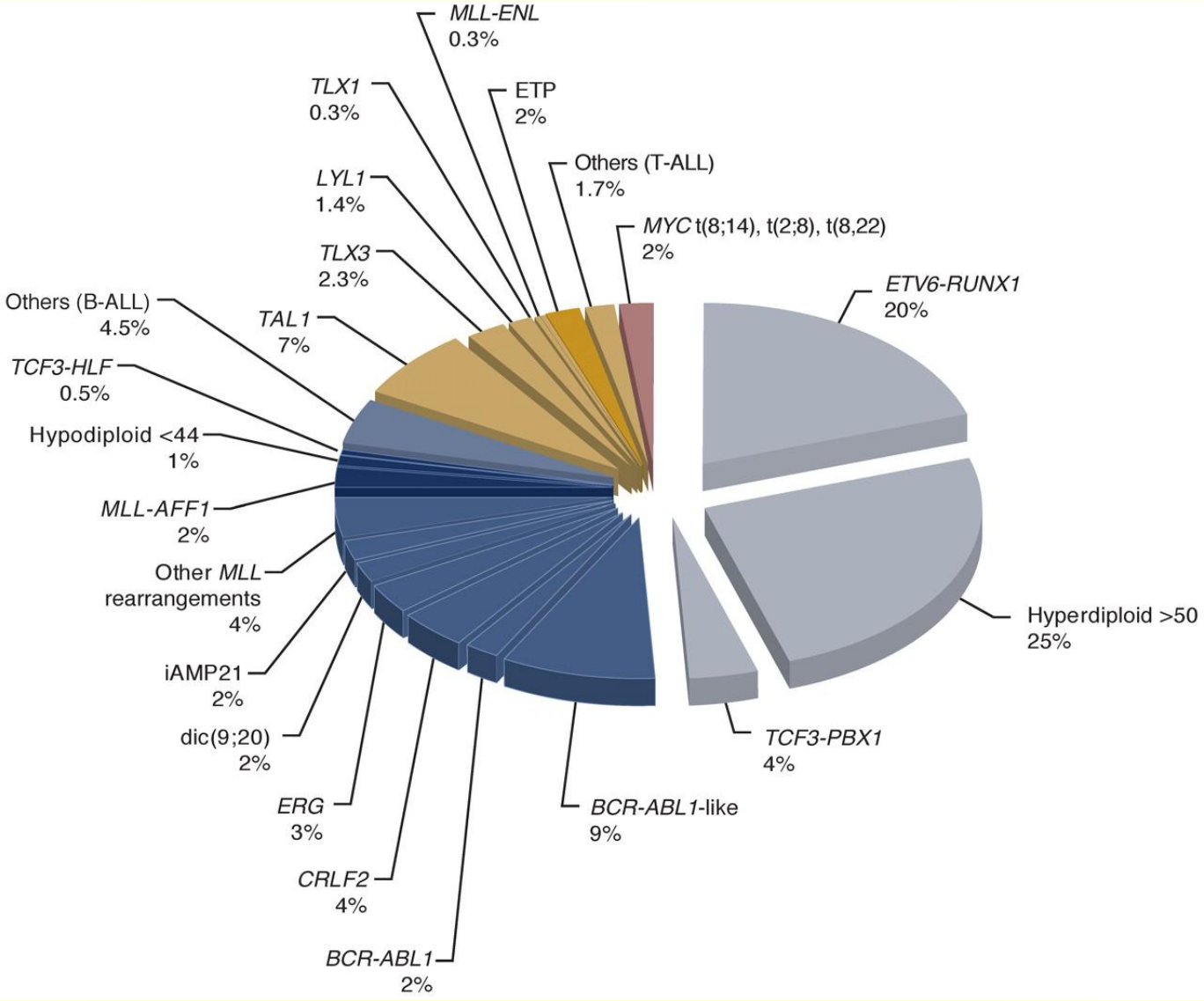
How to improve the cure rate?

1. Understand the genetic basis of ALL,
2. Discover effective anti-leukaemia agents
3. Learn to use the anti-leukaemia drugs properly and wisely through large scale randomized studies
4. Avoid agents/therapy with significant late complications
5. Tailor the treatment intensity best suit the patient (individualized treatment)

Genetic basis

* ALL is NOT a single disease
* Heterogeneity in genetic basis with great variability in prognosis, treatment response
* Large clinical trials define the importance of various genetic basis

Estimated frequency of specific genotypes in childhood ALL.



Pui C et al. Blood 2012;120:1165-1174

Characteristics and Clinical Outcomes of Selected Subtypes of Childhood ALL: Treatment implications

Subtype	Frequency (%)	Clinical Implication	Estimated 5-Year Event-Free Survival (%)
B-Cell precursor			
Hyperdiploidy >50	20 – 30	Excellent prognosis with antimetabolite-based therapy	85 – 95
t(12;21)(p13;q22) *ETV6-RUNX1*	15 – 25	Expression of myeloid-associated antigens CD13 and CD33; excellent prognosis with intensive asparaginase therapy	80 – 95
Trisomies 4 and 10	20 – 25	Excellent prognosis with antimetabolite therapy	85 – 90
t(1;19)(q23;p13) *TCF3-PBX1*	2 – 6	Increased incidence in blacks; excellent prognosis with high-dose methotrexate treatment; increased risk of CNS relapse in some studies	80 – 85
Intrachromosomal amplification of chromosome 21	2 – 3	More common in older children and adolescents; poor prognosis; benefit from intensive induction and early re-intensification therapy	30 – 40
t(4;11)(q21;q23) *MLL-AF4*	1 – 2	Poor prognosis and predominance in infancy, especially those <6 months of age; overexpression of *FLT3*	30 – 40
t(9;22)(q34;q11.2) *BCR-ABL1*	2 – 4	Imatinib plus intensive chemotherapy improve early treatment outcome	80 -90 at 3 years
t(8;14)(q23;q32.3)	2	Favourable prognosis with short-term intensive therapy with high-dose methotrexate, cytarabine, and cyclophosphamide	75 – 85
Hypodiploidy <44 chomosomes	1 -2	Poor prognosis	35 – 40
CRLF2 overexpression	6 – 7	Poor prognosis, common in patients with Down syndrome (55%)	?

Effective Anti-Leukaemia Agents

Temporary remission in acute leukaemia in children produced by folinic acid antagonist, 4-aminopteroyl-glutamic acid (Aminopterin)

Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA

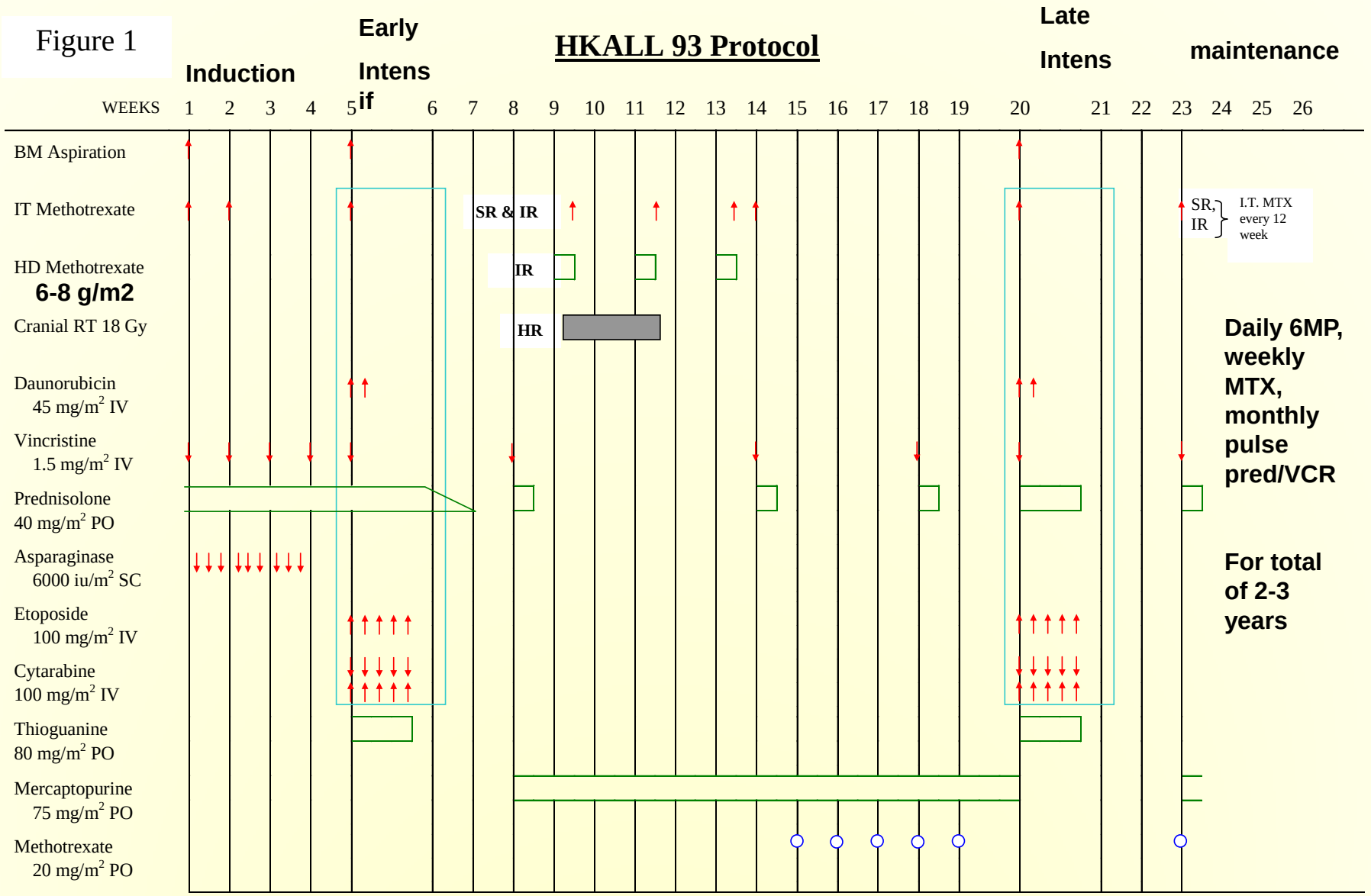
New England J Medicine 1948, 238:787.

5-year survival

* < 10% in the 1960s
* 20% in early 1970s to 60% in late 70s
* Further improve to 77% in 1985 -1994
* ~90% in 2000s

* New anti-leukaemia drugs introduced in 1970s

Figure 1



IT: intrathecal, HD: high dose, IV: intravenous, SC: subcutaneous, po: oral,
SR: standard Risk, IR: intermediate risk, HR: high risk.

Chemotherapy in 80s, 90s, 2000s: No new drugs!

Years	Induction:	Consolidation:	Maintenance:	EFS and OS
1980s	Prednisone, Vincristine, L-asparaginase +/- daunorubicin	Cyclophosphamide, Cytarabine, Methotrexate, Mercaptopurine, thioguanine +/- Re-induction	Mercaptopurine, Methotrexate, +/- Vincristine, Prednisone	Event-Free Survival 60-70% , Overall survival : 70-80%
1990s	Prednisone, Vincristine, L-asparaginase +/- daunorubicin	Cyclophosphamide Cytarabine, Methotrexate, Mercaptopurine, thioguanine Re-induction	Mercaptopurine, Methotrexate, +/- Vincristine, Prednisone	EFS 70-80%, Overall survival : 80-85%
2000s	Prednisone Vincristine, L-asparaginase (PEG-aspar) +/- daunorubicin	Cyclophosphamide ,Cytarabine, Methotrexate, Mercaptopurine thioguanine Re-induction	Mercaptopurine, Methotrexate, +/- Vincristine, Prednisone	EFS 80-90%, Overall survival : 85->90%

Basically no new drugs in past 3 decades

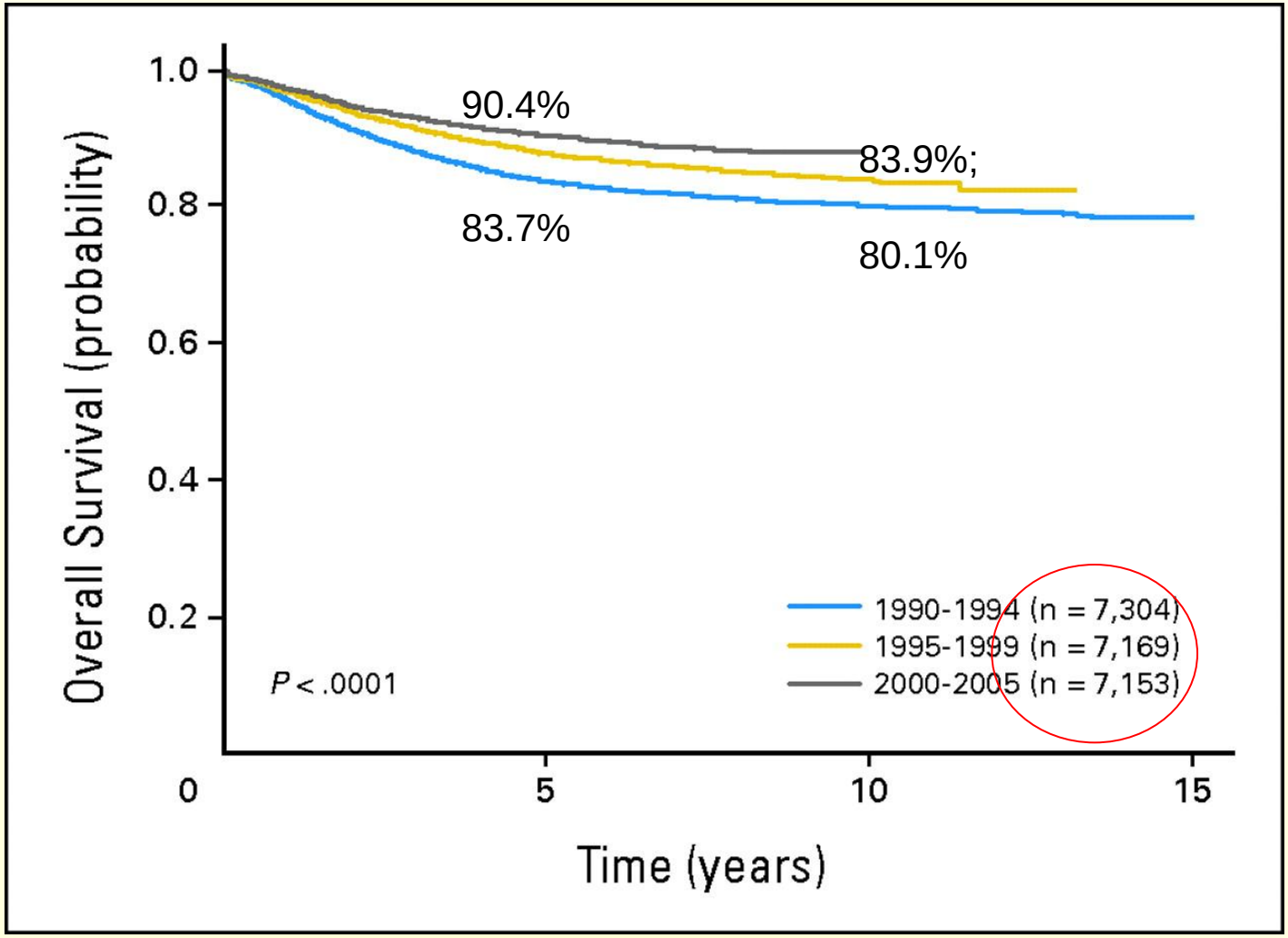
Why is there significant improvement in survival?

Proper use of chemotherapy

- Multi-center large scale clinical trials
- Randomised studies to test hypothesis
- Applying drugs
  - of different combination
  - at different dosage
  - at different timing
  - According to patient biological characteristics and initial response to treatment

Overall survival probability by treatment era for patients enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

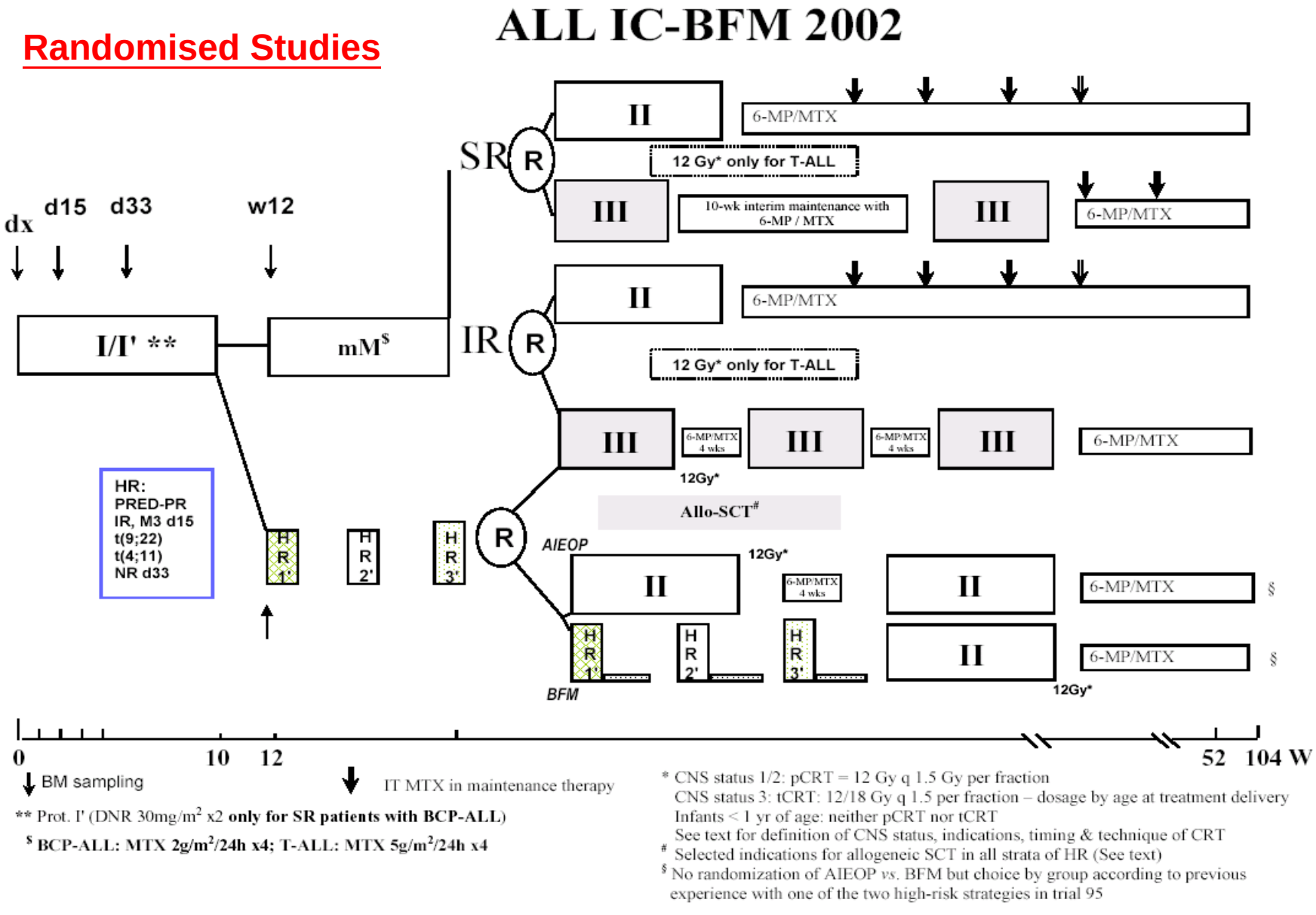
COG



1990 to 1999, 84% of death occurred within 5 year of diagnosis, only 1% > 10 year

Hunger S P et al. JCO 2012;30:1663-1669

Randomised Studies



** Prot. I' (DNR 30mg/m^2 x2 **only for SR patients with BCP-ALL)**

$ **BCP-ALL: MTX 2g/m^2/24h x4; T-ALL: MTX 5g/m^2/24h x4**

* CNS status 1/2: pCRT = 12 Gy q 1.5 Gy per fraction
CNS status 3: tCRT: 12/18 Gy q 1.5 per fraction – dosage by age at treatment delivery
Infants < 1 yr of age: neither pCRT nor tCRT
See text for definition of CNS status, indications, timing & technique of CRT

\# Selected indications for allogeneic SCT in all strata of HR (See text)

$ No randomization of AIEOP *vs.* BFM but choice by group according to previous experience with one of the two high-risk strategies in trial 95

Randomized studies with sig results

- **CCG-105:** Intermediate Risk (<10 years)
  - ***Delayed intensification*** (DI) vs no DI,
  - 625 p'ts recruited,
  - DI showed sig survival benefit:
    10-year EFS 74% vs 60%
- **UKALL 97:**
  - Induction **: *Dexamethasone 6.5mg vs Prednisone 40 mg*** (same steroid during maintenance)
  - 1621 p'ts recruited
  - Dexamethasone reduced CNS relapse, 2.5% vs 5.0% (p=0.007)
  - EFS also improved 84.2% vs 75.6% (p=0.0007)

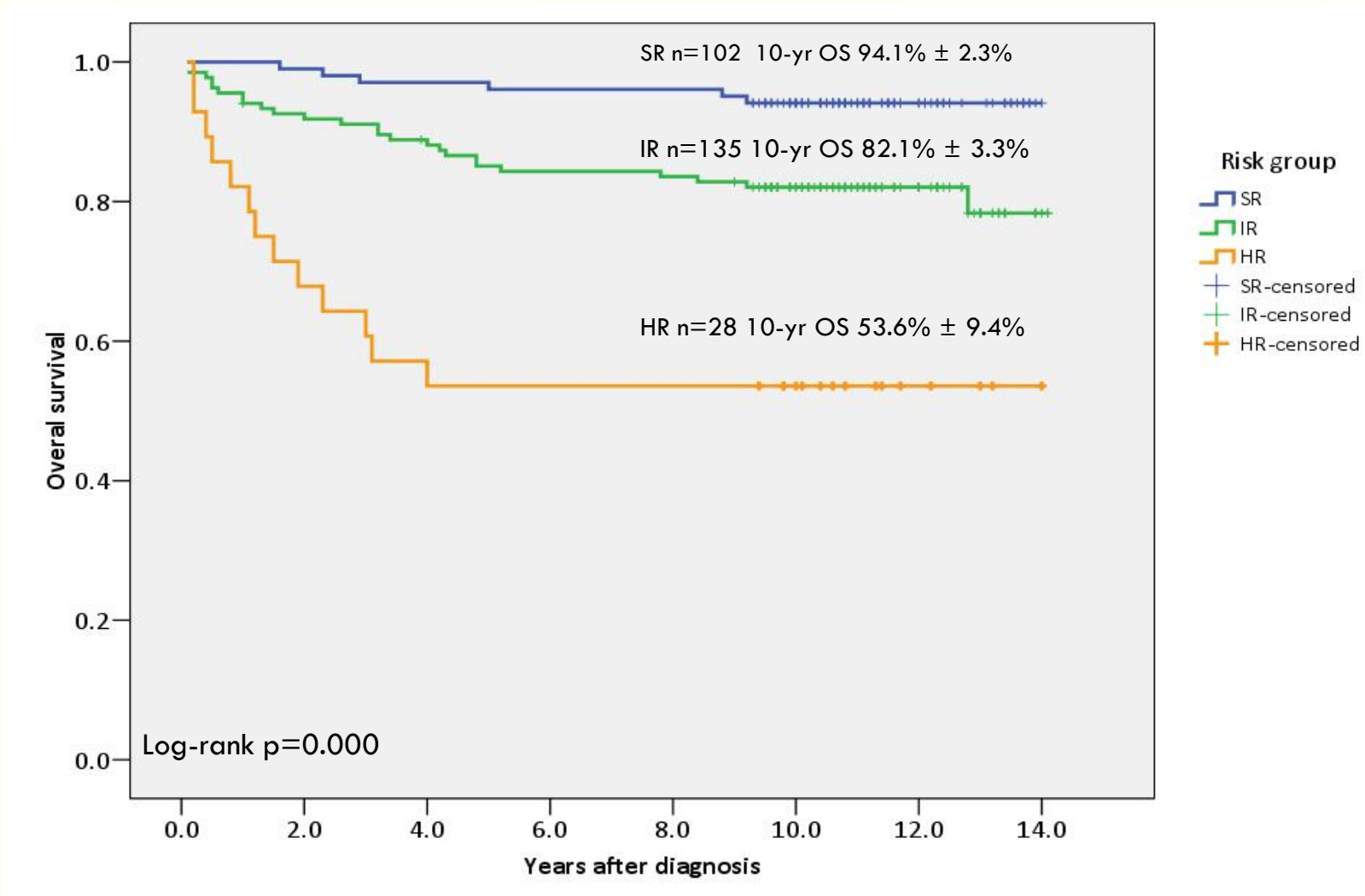
CCG Studies

	Research Question	EFS	Conclusion
CCG1881 (1988-92)	+/ - DI : delayed intensification	83% vs 77%	Confirm value of DI
CCG1891 (1990-93)	2 DI vs 1DI (prednisone)	83% vs 76%	Confirm value of two DI
CCG1922 (1993-95)	Dexa vs Prednisone (1X DI)	85% vs 77%	Confirm value of Dexamethasone
CCG1991 (2000-05)	2 DI vs 1DI (Dexamethasone)	88.1% vs 88.3%	Dexa based, 1x DI sufficient
POG9904	NCI SR + t(12,21) or hyperdiploid +4+10, (MRD <0.01% -ve)	D8, 29 MRD -ve : 97%, (43% patients) D29 MRD -ve 92%	Favorable cytogenetics and good early response with best outcome

Treatment intensity according to biological characteristics and early treatment response

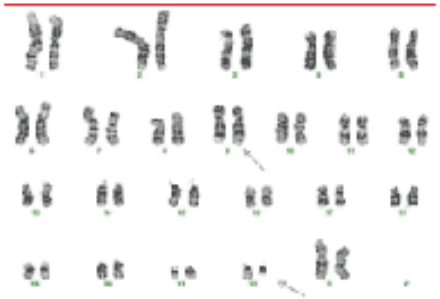
- Precise stratification: age, WBC, genetics
- Early treatment response: (in-vivo drug response)
  - 7 days steroid response
  - Bone marrow blast % : Day 7, Day 15, Day 30 by morphology
  - Detection of very low level residual leukaemia cells in first 3 months:
    - Minimal Residual Disease monitoring (1 in 10,000-100,000)

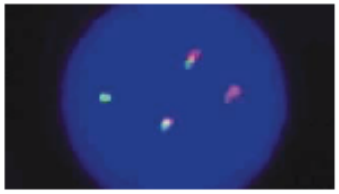
HK-SG 97:Overall Survival of SR, IR, HR

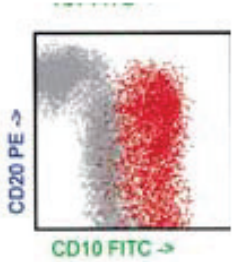


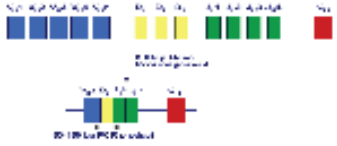
Sensitivity of techniques in detecting MRD

Technique	Sensitivity
Morphology	1-5%
Cytogenetics	1/100
FISH	1/1000
Flow cytometry	1/10000
Quantitative PCR	1/100000



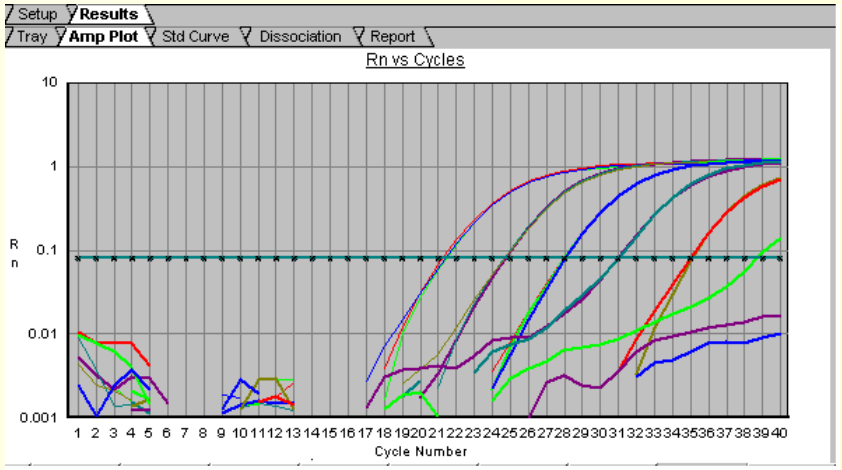


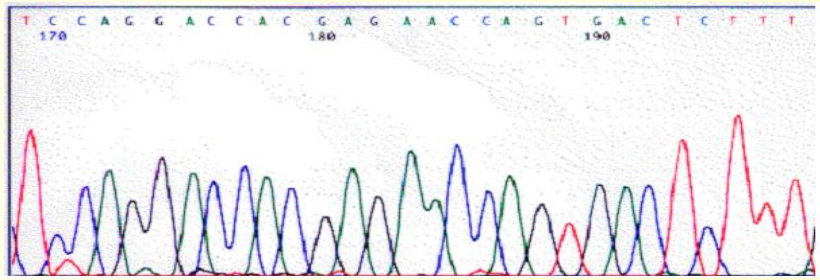


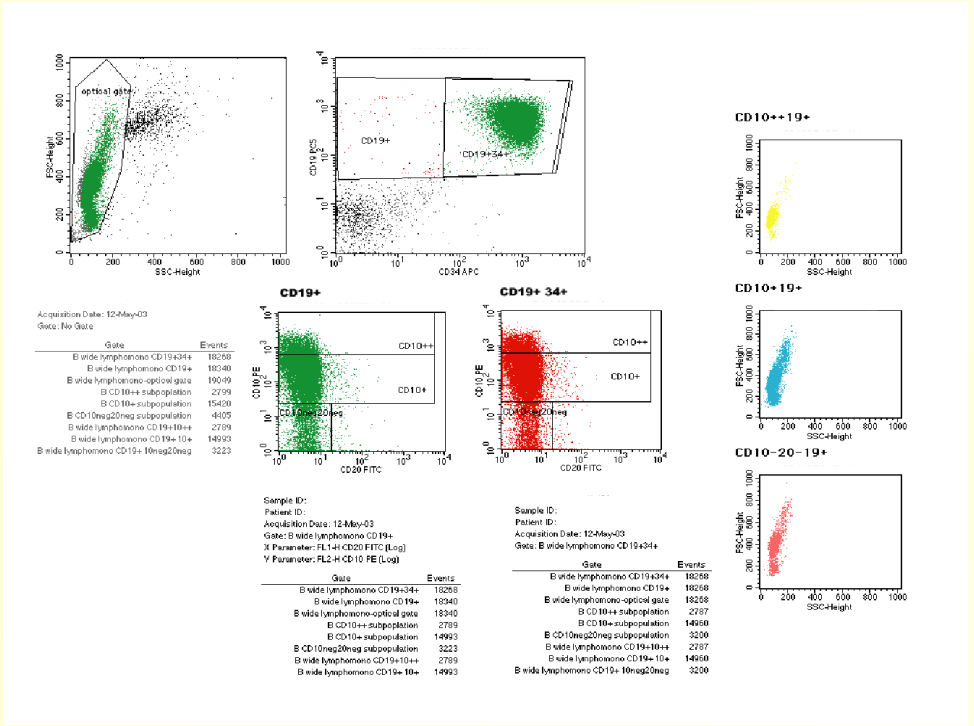


Minimal Residual Disease detection in paed ALL: Real-time Quantitative PCR, or Flow cytometry

Patient-specific Leukaemia marker:
either genetic mutation or Leukaemic-associated antigens



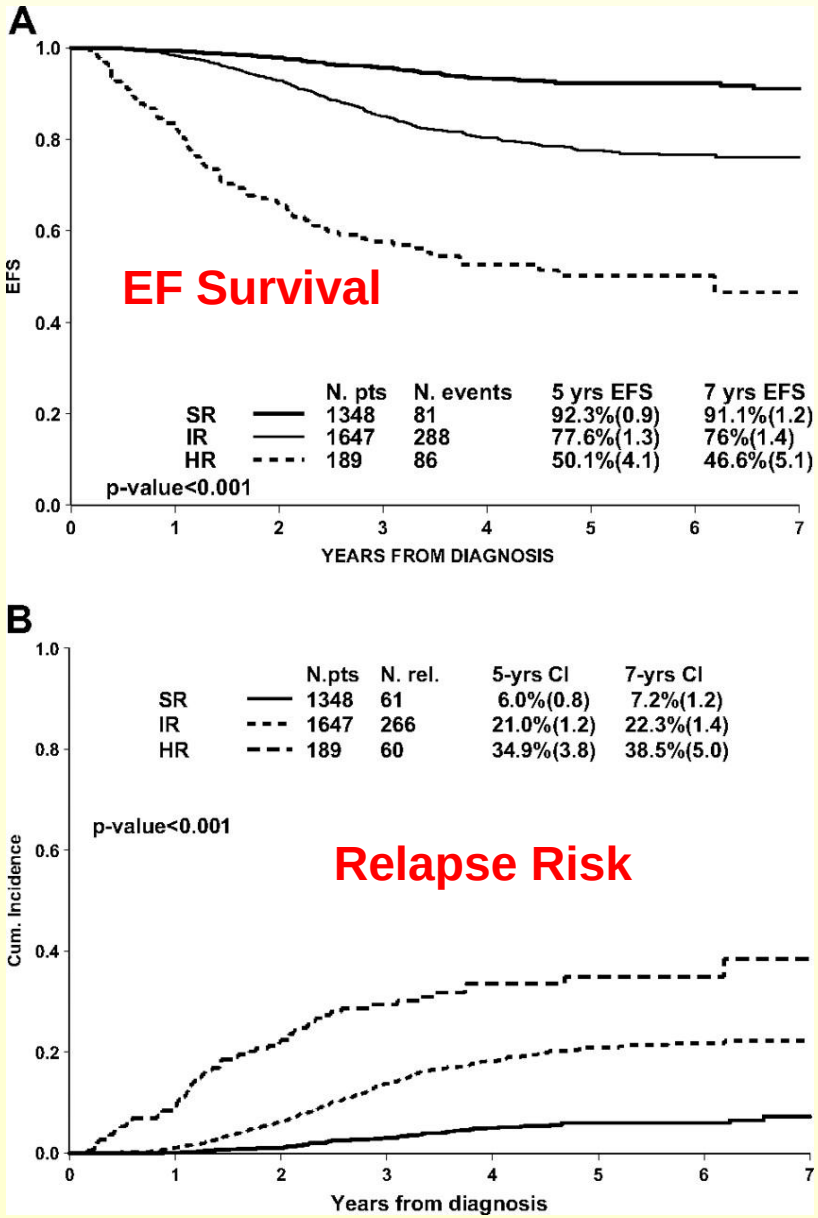




Event-free survival (A) and cumulative incidence of relapse (B) according to PCR-MRD classification in pB-ALL patients

3184 patients treated in the AIEOP-BFM-ALL 2000 trial.

Stratified into 3 risk groups according to MRD on day 33 and 84 marrow as detected by q-PCR



Standard Risk

Intermediate risk

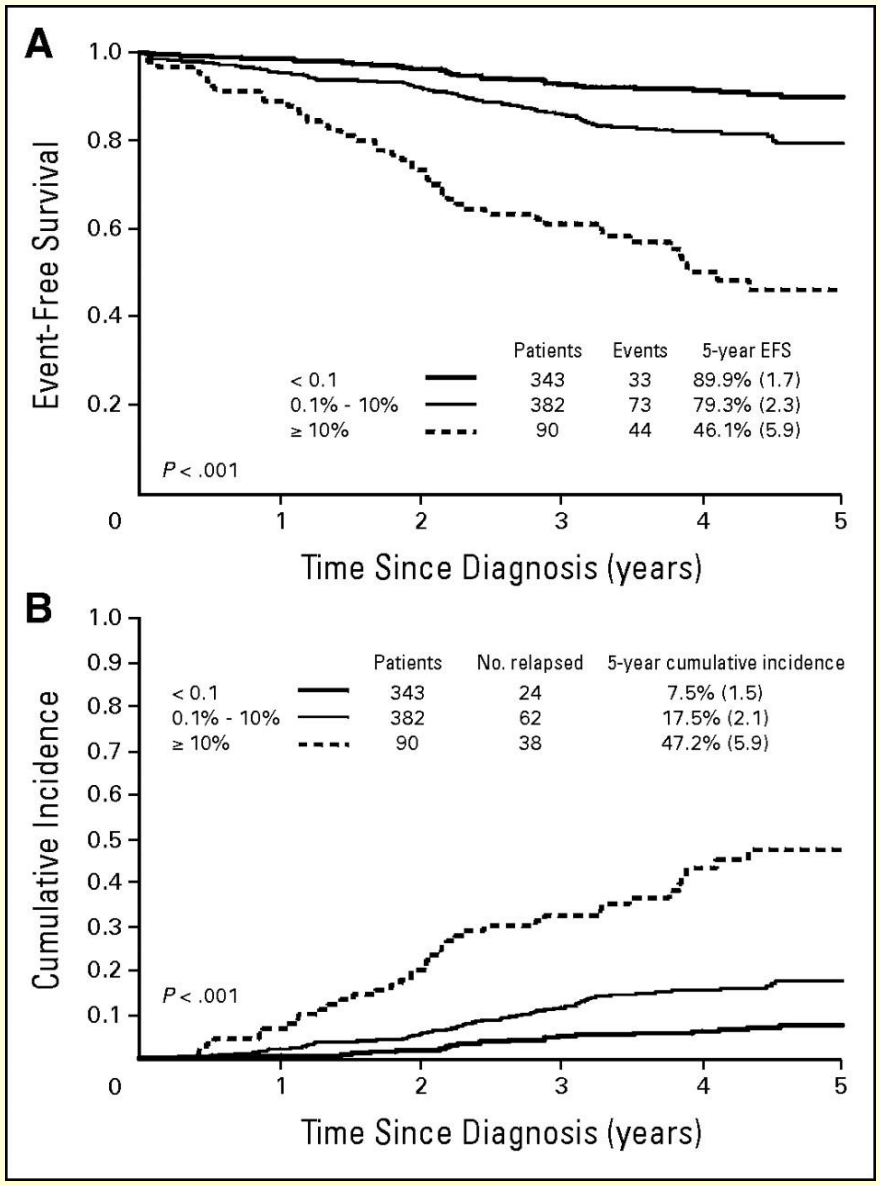
High Risk

Conter, V. et al. Blood 2010;115:3206-3214

(A) Event-free survival (EFS) and (B) cumulative incidence of relapse

815 patients treated in the AIEOP-BFM-ALL 2000 trial.

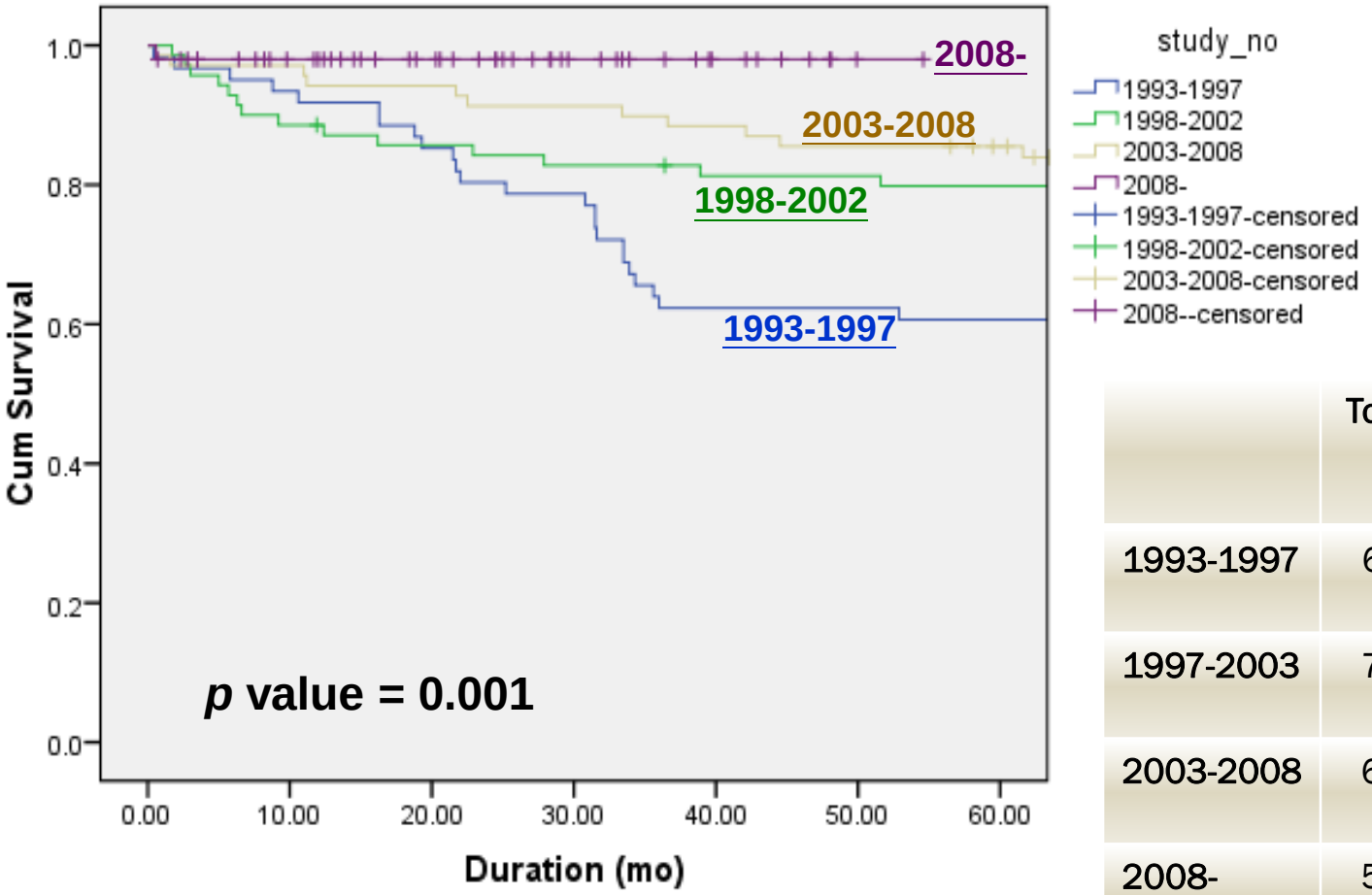
Stratified into 3 risk groups according to MRD on day 15 marrow as detected by flow cytometry



Basso, G. et al. J Clin Oncol; 2009, 27:5168-5174

5 year Overall Survival : 1993 - 2012

HIGH RISK GROUPS



	Total N	N of Deaths at 5yr	% of OS at 5yr
1993-1997	61	24	60.7 (6)
1997-2003	70	14	79.8 (14)
2003-2008	69	10	85.5 (4)
2008-	50	1	98.0 (2)

Avoid late sequelae

- High chance of long term survival
- Avoid agents predispose to second malignancy:
  - Etoposide not used in non-High Risk patients
  - Cranial irradiation for CNS prophylaxis nearly stopped for all patients (decresed from 24.3% to 14.3%, now < 5%)
  - Limit dose of anthracycline to prevent late cardiac toxicity

New Drugs

- For very resistant diseases
- Difficulty to conduct clinical trials:
  - Small number of patients
  - Need multi-national collaboration study
  - Pharmaceutical industry may not be interested
  - National grant or NGO sponsors

Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study

Andrea Biondi, Martin Schrappe, Paola De Lorenzo, Anders Castor, Giovanna Lucchini, Virginie Gandemer, Rob Pieters, Jan Stary, Gabriele Escherich, Myriam Campbell, Chi-Kong Li, Ajay Vora, Maurizio Arico, Stija Rottgers, Vaskar Saha, Maria Grazia Valsecchi

Summary

Background Trials of imatinib have provided evidence of activity in adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (ALL), but the drug's role when given with multidrug chemotherapy to children is unknown. This study assesses the safety and efficacy of oral imatinib in association with a Berlin–Frankfurt–Munster intensive chemotherapy regimen and allogeneic stem-cell transplantation for paediatric patients with Philadelphia-chromosome-positive ALL.

Methods Patients aged 1–18 years recruited to national trials of front-line treatment for ALL were eligible if they had t(9;22)(q34;q11). Patients with abnormal renal or hepatic function, or an active systemic infection, were ineligible. Patients were enrolled by ten study groups between 2004 and 2009, and were classified as good risk or poor risk according to early response to induction treatment. Good-risk patients were randomly assigned by a web-based system with permuted blocks (size four) to receive post-induction imatinib with chemotherapy or chemotherapy only in a 1:1 ratio, while all poor-risk patients received post-induction imatinib with chemotherapy. Patients were stratified by

(2004-001647-30) and ClinicalTrials.gov, number NCT00287105.

Findings Between Jan 1, 2004, and Dec 31, 2009, we screened 229 patients and enrolled 178: 108 were good risk and 70 poor risk. 46 good-risk patients were assigned to receive imatinib and 44 to receive no imatinib. Median follow-up was 3·1 years (IQR 2·0–4·6). 4-year disease-free survival was 72·9% (95% CI 56·1–84·1) in the good-risk, imatinib

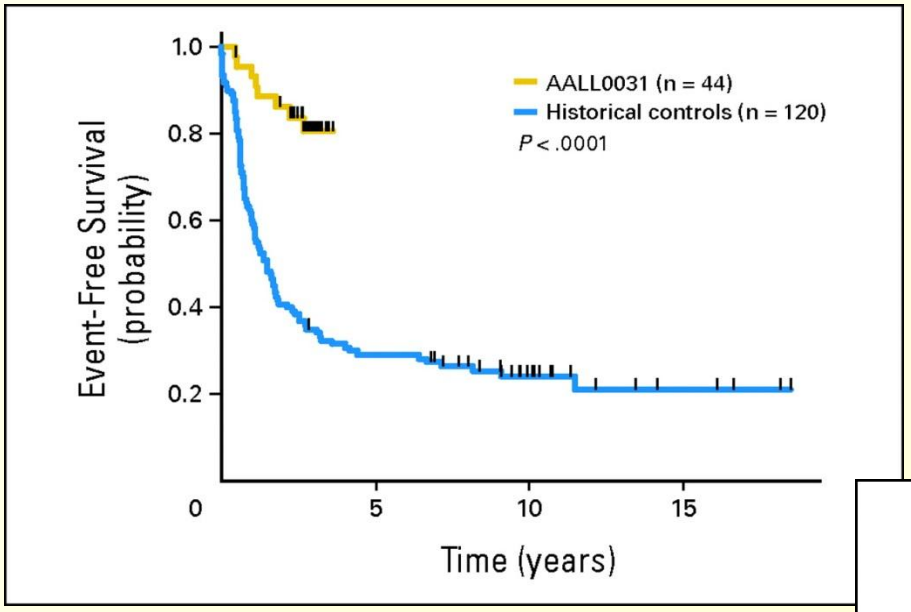
Published Online August 14, 2012 http://dx.doi.org/10.1016/S1470-2045(12)70377-7

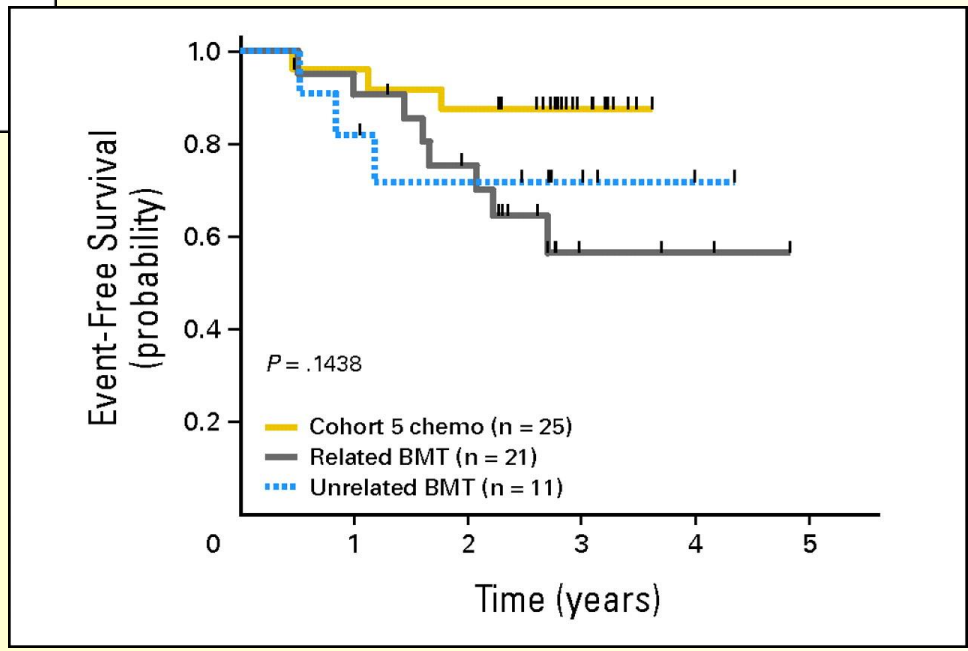
Department of Paediatrics (Prof A Biondi MD, P De Lorenzo PhD, G Lucchini MD), Department of Clinical and Preventive Medicine and EsPhALL Trial Data Centre (P De Lorenzo, Prof M G Valsecchi PhD), University of Milano-Bicocca, Monza, Italy; Department of

Oncology, Lund University Hospital, Lund, Sweden (A Castor PhD); Department of Paediatric Haematology Oncology, CHU Hôpital Sud, Rennes, France (V Gandemer MD); Erasmus

www.thelancet.com/oncology **Published online August 14, 2012**
http://dx.doi.org/10.1016/S1470-2045(12)70377-7

EFS in Philadelphia chromosome-positive ALL patients treated with imatinib





Schultz, K. R. et al. J Clin Oncol; 27:5175-5181 2009

Chinese Childhood Leukemia Group (CCLG): 17 hospitals from 8 cities

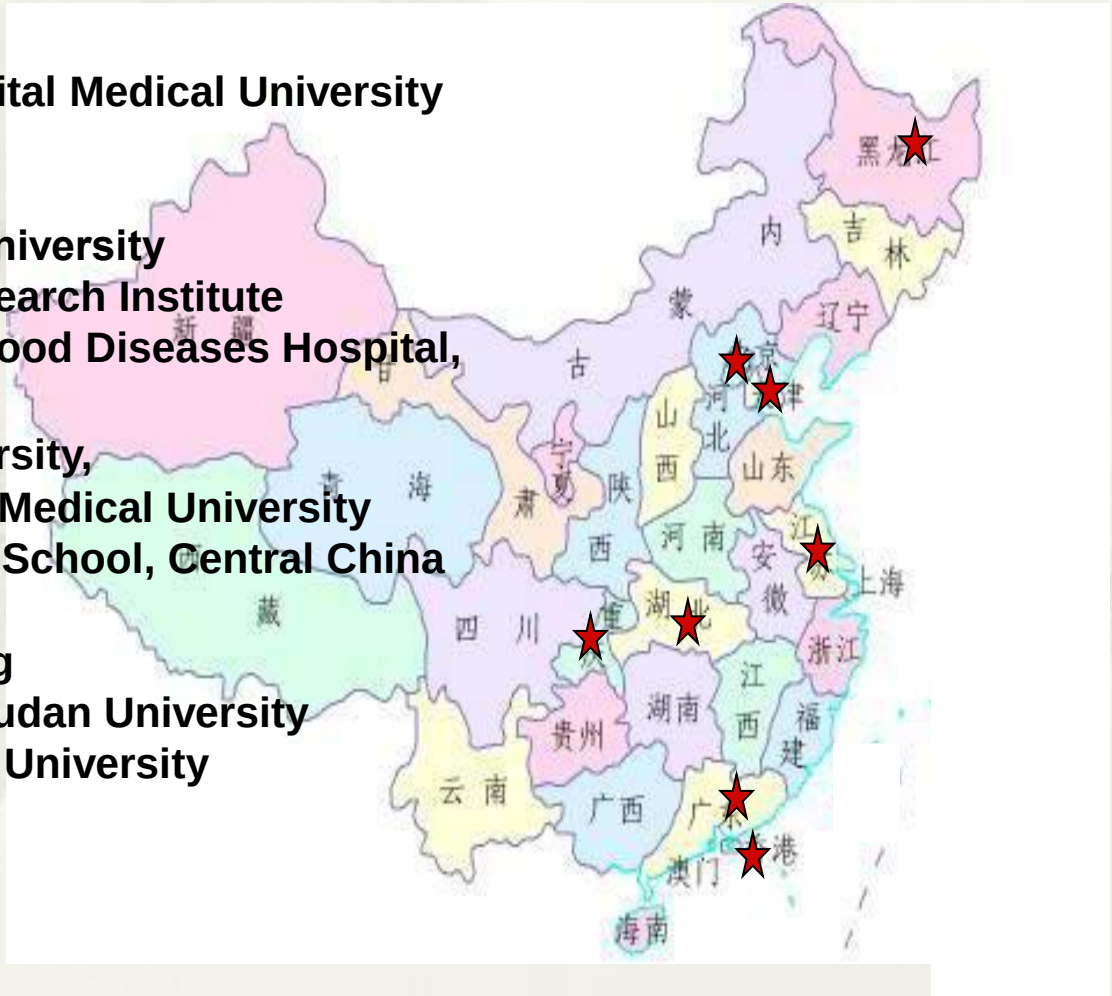
From 2008: 1989 patients recruited in this CCLG 2008 Study

Coordinating hospital：

Beijing Children Hospital, Capital Medical University

Participating hospitals：

Hong Kong (5 hospitals)
Children's Hospital, Suzhou University
Children Hospital, Capital Research Institute
Institute of hematology and Blood Diseases Hospital, CAMS , Tianjin
People Hospital, Peking University,
Children Hospital, Chongqing Medical University
Union Hospital Tongji Medical School, Central China
PLA General Hospital, Beijing
Naval General Hospital, Beijing
Shanghai Children Hospital, Fudan University
Children Hospital, West China University



Success of ALL treatment

- > 90% patients recruited into clinical studies
- Multi-centre studies, national or international, to have large sample size to test treatment hypothesis,
- New intervention arm always based on the best treatment arm of earlier study as control
- Randomised studies as gold standard
- Scientifically study the genetic basis and pharmacogenetics, and introduction of target therapy
- Individualised treatment to ‘optimal’ intensity