

**MA-SPORE ALL 2003
PROTOCOL PROGRESS REPORT**

GROUP NAME: Malaysia-Singapore (Ma-Spore) Study Group

**PROTOCOL TITLE:
Malaysia-Singapore Childhood Acute Lymphoblastic Leukemia 2003
(Ma-Spore ALL 2003)**

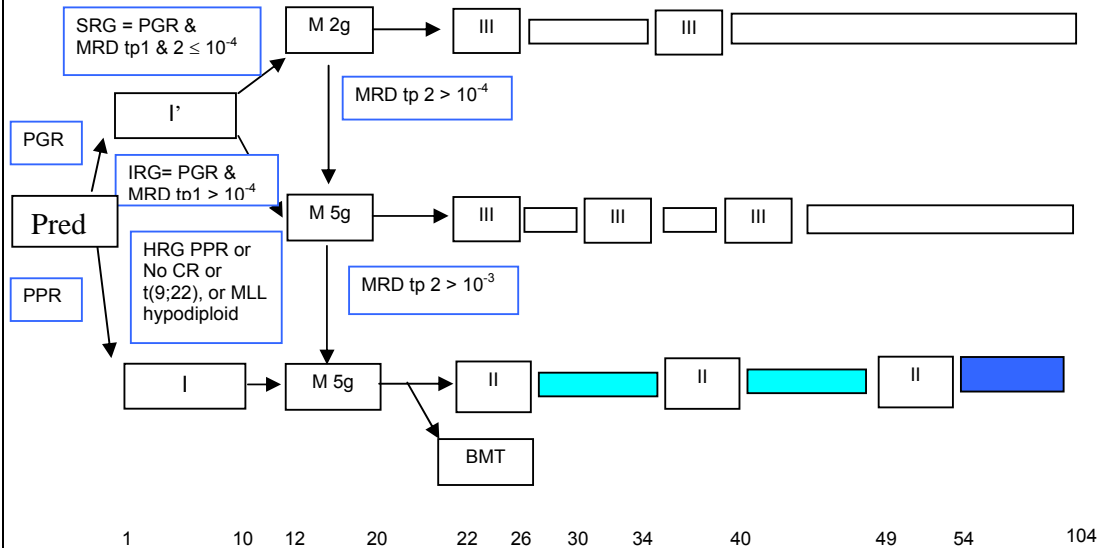
**PROTOCOL COORDINATORS: A/Prof Allen Yeoh, NUHS, Singapore
A/Prof Hany Ariffin, University Malaya, Malaysia
Prof Lin Hai Peng, Subang Jaya Medical Centre, Malaysia
Clin A/Prof Tan Ah Moy, KK Women's and Children's Hospital, Singapore**

**DATA CENTER: NATIONAL UNIVERSITY HEALTH SYSTEM NUHS
NATIONAL UNIVERSITY OF SINGAPORE**

STATISTICIAN: Dr Chan Yiong Huak, NUHS

**PROTOCOL SPONSOR:
Singapore Cancer Syndicate/Agency for Science, Technology And Research
National Medical Research Council (Singapore)**

PROTOCOL OUTLINE



PROTOCOL PROGRESS AT:**STATUS OF PROTOCOL: ENROLLMENT ONGOING****DATE PROTOCOL OPENED: 12/07/2002****END OF RECRUITMENT: Still ongoing****OBJECTIVES:**

1. Can an early treatment-response based risk stratification using very sensitive minimal residual disease (MRD) markers allow optimal decision for treatment intensity?
2. Is a simplified PCR-based MRD system using *at least one MRD* marker feasible and has comparable accuracy to the AIEOP-BFM-ALL 2000 stratification using 2 markers?
3. For standard risk patients as defined by a rapid early response, can a reduction in the intensity of therapy be associated with equal EFS?
4. For intermediate risk patients, can EFS be improved by using a three blocks of shortened delayed intensification (BFM ALL 2000 Protocol III) with similar total cumulative doses of drugs?
5. For high risk patients - as defined by slow early response to therapy and certain cytogenetic and molecular subgroups - can EFS be improved with the hybrid of augmented BFM-like regimen from CCG with additional HDMTX?

PROTOCOL DESIGN:**DEFINITION:****RANDOM: NIL****PATIENT ELIGIBILITY CRITERIA FOR INCLUSION:**

All patients are eligible who have non-B ALL and:

- Age < 18 years (up to 17 years and 364 days). Infant are enrolled in this study.

Patients with the following characteristics are not eligible for the study:

- Age ≥ 18 years
- Pretreatment with cytotoxic agents or high-dose steroids ≥ 14 days
- Acute undifferentiated leukemia
- ALL as secondary malignancy
- Abnormal renal function (Urea and Creatinine levels > 2X normal for age)
- Moribund patients
- Unable to complete planned therapy because of costs or compliance issues

CENTRALLY REVIEWED:

BM slides at diagnosis, day 8, day 15 and week 5

Minimal Residual Disease measurement

Oncogene fusion screening

STUDY OBJECTIVES:

Therapeutic Aims:

1. To estimate the overall EFS of children of all age groups (<18 yrs old) presenting with non-B-cell ALL treated with a primarily MRD risk-stratified multi-agent intensive chemotherapy regimen, based on the highly successful BFM-ALL backbone regimen.
2. To risk stratify childhood ALL patients based primarily on the early response to therapy using Day 8 prednisolone response, Day 33 and Week 12 level of minimal residual disease based on at *least one PCR* MRD marker of sensitivity $\geq 10^{-4}$.
3. To determine whether further reduction in the intensity of induction using a 3-drug induction and 2 blocks of shortened delayed intensification phase of ALL-BFM-2000 protocol (new Protocol III) in MA-SPORE ALL 2003 standard-risk patients is associated with equivalent EFS compared to our recent AIEOP-BFM-ALL-95 standard risk group.
4. To determine whether intensified therapy using the a hybrid of the BFM and the CCG augmented BFM regimen for treatment of high-risk patients results in improvement in the EFS compared to our recent AIEOP-BFM-ALL-95 high risk protocol.
5. To determine if a 3-drug induction and replacement of the delayed intensification (Protocol II) with 3 blocks of shortened delayed intensification therapy (Protocol III) in intermediate-risk patients results in improvement in EFS compared to our recent AIEOP-BFM-ALL-95 medium-risk group.

Biological Aims:

6. To correlate the various known prognostic factors of age, WBC count at diagnosis, recurrent genetic translocation and immunophenotype with the kinetics of leukaemia cell kill using MRD detection.

Risk groups definition:

HR is defined as any of the following criteria:

- Poor prednisolone responder (absolute blast count $\geq 1000/\mu\text{L}$) at day 8
- No complete remission at Day 33 by morphology
- MRD $\geq 10^{-3}$ at week 12 of therapy
- t(9;22)/BCR-ABL or MLL rearrangement or hypodiploid

BMT in first CR is indicated for patients who are very high risk of relapse i.e. any of,

- Persistently high MRD levels
- t(9;22)/BCR-ABL positive
- MLL rearrangement in infants
- Hypodiploid ALL (<45 chromosomes)

SR must have all of the following features:

- good prednisolone responder and
- MRD at day 33 and week 12 $\leq 10^{-4}$ and
- CNS I status

IR is the entry point for all patients and when they fulfil the SR or HR criteria, they are restratified accordingly. These include those without sensitive MRD markers

SURVIVAL*No. of Pts. 324 Minimum follow up: 3.6 months Median Follow-up: 28.2 months

		Global	By Treatment Arm		
			SR	IR	HR
SUR: % (\pm SE)	at 24 months	88.9 (85.2 – 92.6)	93.5 (88.4–98.6)	93.4 (89.3–97.5)	72.2 (60.4–84.0)
	at 36 months	88.3 (84.4 – 92.2)	93.5 (88.4–98.6)	93.4 (89.3–97.5)	69.8 (57.6–82.0)
	at 60 months	87.4 (83.1 – 91.7)	93.5 (88.4–98.6)	93.4 (89.3–97.5)	65.5 (51.4–79.6)

EVENT FREE SURVIVAL:*No. of Pts. 324

		Global	By Treatment Arm		
			SR	IR	HR
EFS: % (\pm SE)	at 24 months	80.3 (75.8 – 84.8)	87.4 (80.5–94.3)	86.6 (80.7–92.5)	54.7 (42.3–67.0)
	at 36 months	79.0 (74.1 – 83.9)	84.7 (76.3–93.1)	84.9 (78.2–91.6)	51.9 (39.0–64.8)
	at 60 months	76.4 (70.9 – 81.9)	84.7 (76.3–93.1)	81.2 (73.2–89.2)	51.9 (39.0–64.8)

LEUKAEMIA FREE SURVIVAL:*No. of Pts. 324

		Global	By Treatment Arm		
			SR	IR	HR
EFS: % (\pm SE)	at 24 months	89.9 (86.2 – 93.6)	94.7 (89.6–99.8)	95.3 (91.4–99.2)	69.5 (57.3–81.6)
	at 36 months	88.4 (84.3 – 92.5)	94.7 (89.6–99.8)	93.5 (88.2–98.8)	66.0 (52.8–79.3)
	at 60 months	85.5 (80.2 – 90.8)	91.8 (84.4–99.2)	93.5 (88.2–98.8)	66.0 (52.8–79.3)

* Note: Patients who absconded are censored at the time of abscondment.

Ma-Spore ALL-2003 Study

Treatment overview

1. Induction (Protocol I) – 10 weeks

Prednisolone 60 mg/m²/day p.o. from day 1 -7
IT MTX

1a' (for SR and IR group)

Dexamethasone 6mg/m²/day from day 8 to 35
IV Vincristine 1.5mg/m²/dose weekly for week 2,3,4,5
IM L-asparaginase 7,500 U/m²/dose from day 8 twice a week for 8 doses (4 weeks)
If allergic to E coli L-asp, switch to PEG L-asp 2,500U/m²/dose weekly. X 4 weeks. If this is too costly, drug is omitted.
IT MTX at day 8, d15, d33

1a (for HR group – prednisolone poor responders only)

Dexamethasone 6mg/m²/day from day 8 to 35
IV Vincristine 1.5mg/m²/dose weekly for week 2,3,4,5
IV Daunorubicin 25 mg/m²/dose weekly for week 2,3,4,5
IM L-asparaginase 7,500 U/m² from day 8 twice a week for 8 doses (4 weeks)
If allergic to E coli L-asp, switch to PEG L-asp 2,500U/m²/dose weekly. X 4 weeks. If this is too costly, drug is omitted.
IT MTX at day 8, d15, d33

1b (all groups)

IV cyclophosphamide 1000mg/m² day 36 and 64
Mercaptopurine p.o. 50mg/m²/day ON
IV or S/c cytarabine 75mg/m² for 4 days block X 4 blocks
IT MTX at day 45, 59 (beginning of the 2nd and 4th block of cytarabine)

2. Protocol M'/M (8 weeks)**Protocol M' for SR group**

IV HDMTX 2000mg/m² every 2 weeks with folinic rescue X 4 weeks
IV folinic acid 15mg/m²/dose at 42, 48, 54 hours from start of IV MTX
Mercaptopurine p.o. 25mg/m²/day ON
IT MTXwith each HDMTX

Protocol M for IR/HR

IV HDMTX 5000mg/m² every 2 weeks with folinic rescue X 4 weeks
IV folinic acid 15mg/m²/dose at 42, 48, 54 hours from start of IV MTX
Mercaptopurine p.o. 25mg/m²/day ON
IT MTXwith each HDMTX

3. Protocol III (4 weeks) – SR and IR

Dexamethasone p.o. 10mg/m²/day for 14 days,
 IV Vincristine 1.5 mg/m²/dose week on days 0, 7
 IV doxorubicin 30 mg/m²/dose every week on days 0, 7
 IM L-Asparaginase 10,000U/m²/day twice a week from day 3 for 4 doses
 If allergic to E coli L-asp, switch to PEG L-asp 2,500U/m²/dose weekly. X 4 weeks. If this is too costly, drug is omitted.

IV cyclophosphamide 500mg/m² on day 15
 IV or S/c cytarabine 75 mg/m²/dose for 4 days blocks X 2 blocks
 Thioguanine 50mg/m²/day ON for 2 weeks from day 14-28
 IT MTX on start of every cytarabine block (total of 2 IT)

4. Protocol II' (5 weeks) - HR

Dexamethasone 10mg/m²/day p.o. for 21 days
 IV Vincristine 1.5mg/m² on days 0, 7, 14
 IV doxorubicin 25mg/m² on days 0, 7, 14
 IM L-asparaginase 10,000U/m²/dose twice weekly from day 3 for 2 wks
 If allergic to E coli L-asp, switch to PEG L-asp 2,500U/m²/dose weekly. X 4 weeks. If this is too costly, drug is omitted.

IV Cyclophosphamide 1000mg/m² on day 21
 Thioguanine p.o. 50mg/m² ON
 IV cytarabine 75mg/m²/dose for 4 days block X 2 blocks
 IT MTX on start of every cytarabine block (total of 2 IT)

5. Interim maintenance HR

IV vincristine 1.5 mg/m² per week for 8 weeks
 IV methotrexate 100mg/m²/dose wkly
 IM L-asparaginase 15,000U/m² every week for 8 weeks
 If allergic to E coli L-asp, switch to PEG L-asp 2,500U/m²/dose weekly. If this is too costly, drug is omitted and switch to IR interim maintenance.
 IT MTX every fortnight X 4 doses

6. HR maintenance (12 weeks cycles till 2 years)

IV vincristine 1.5 mg/m² every 4 wks
 Dexamethasone p.o. 10mg/m²/day for 7 days every 4 weeks
 Mercaptopurine p.o. **75mg/m²/day** ON
 Methotrexate p.o. 20mg/m²/dose weekly ON
 IT MTX on week 1 of cycle

7. Interim maintenance SR or IR

Mercaptopurine p.o. 50 mg/m²/day ON

Methotrexate 20mg/m² weekly ON

IT triple every 8 weeks

8. SR and IR maintenance (12 weeks cycles till 2 years)

Mercaptopurine p.o. 50mg/m²/day ON

Methotrexate 20mg/m²/dose weekly ON

IV vincristine 1.5 mg/m²/dose at week 11 and 12

Dexamethasone 6mg/m²/day for 7 days at week 11

IT MTX at week 11 and 12

Cranial radiotherapy only for patients with CNS leukaemia or WBC > 100,000/uL at presentation. After RT, no IT after that.

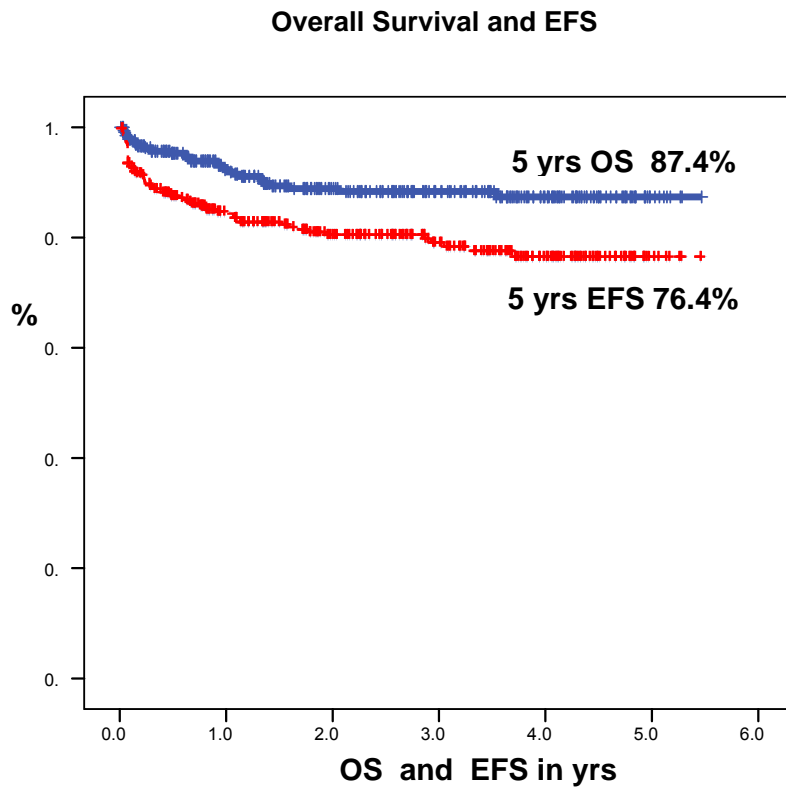


Figure 1. EFS (Red) and Overall Survival (Blue) of Ma-Spore ALL 2003. The 5-years EFS for Ma-Spore ALL 2003 is 76.4% and 4-years overall survival is 87.4%.

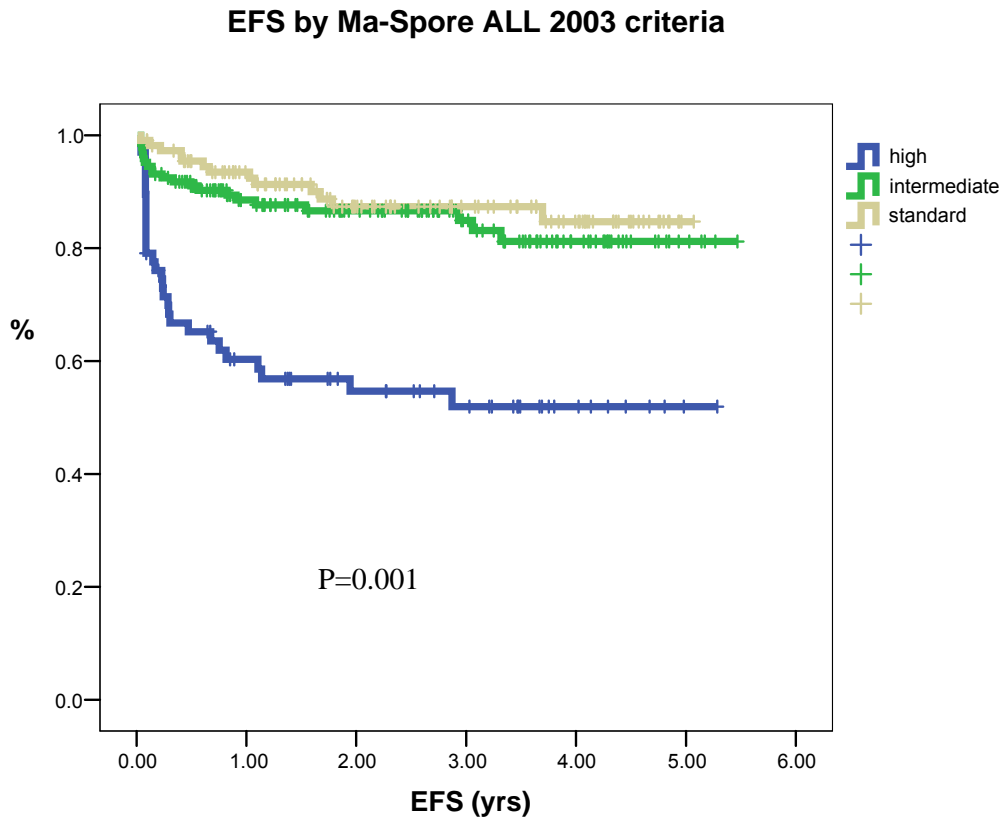


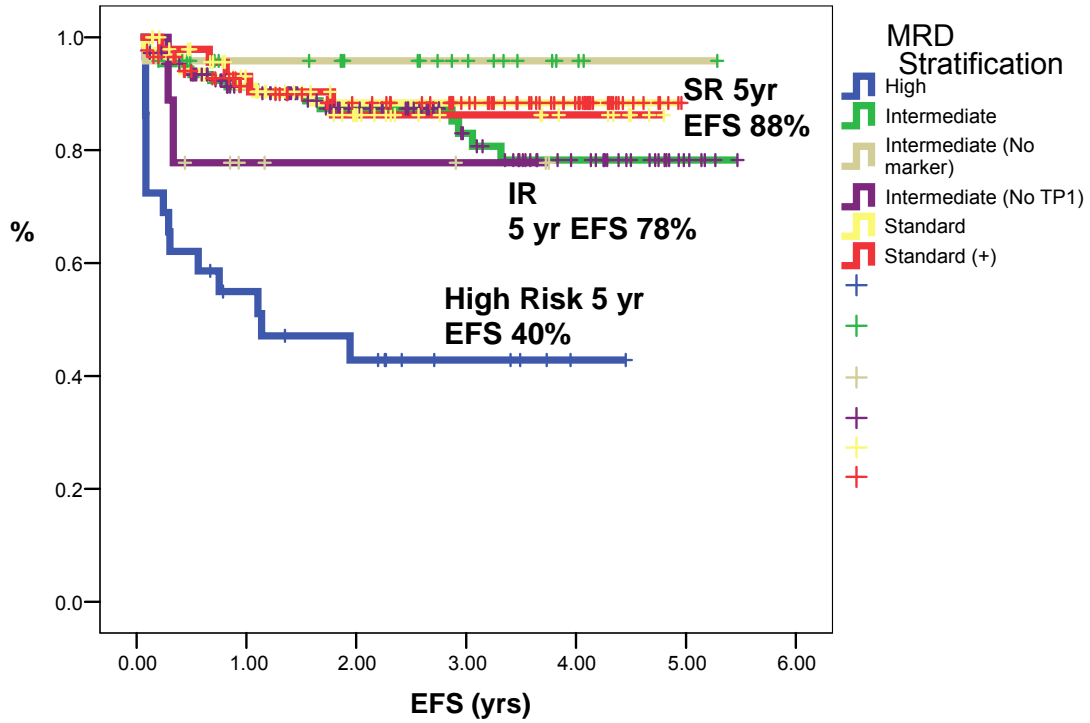
Figure 2. The EFS by Ma-Spore ALL 2003 risk stratification criteria (see text above). The 5-years EFS for

Standard Risk is 84.7% (76.3 – 93.1) n=112
 Intermediate Risk is 81.2% (73.2 – 89.2) n = 146
 HR is 51.9% (39.0 – 64.8) n= 67

Summary

final_risk	Total N	N of Events	N
high	67	30	37
intermediate	146	21	125
standard	112	13	99
Overall	325	64	261

MRD Risk stratification



P=0.001

Figure 3. MRD high risk group (5-year EFS 40%) has poorer event free survival despite intensified therapy. Standard risk patients (5-year EFS 88%) do not have increased risk of relapse despite reduction in chemotherapy compared to intermediate risk (5-year EFS 78%).

Figure 4. EFS based on NCI criteria.

NCI standard risk is defined as Age 1-9 years old and WBC <50,000/uL.

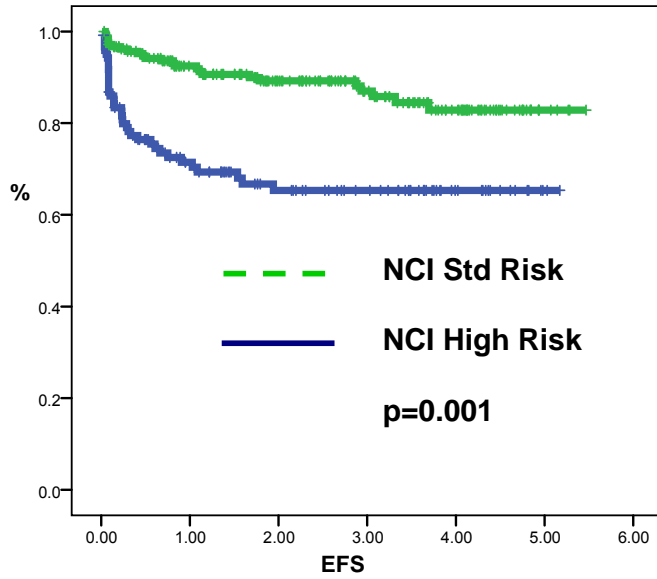
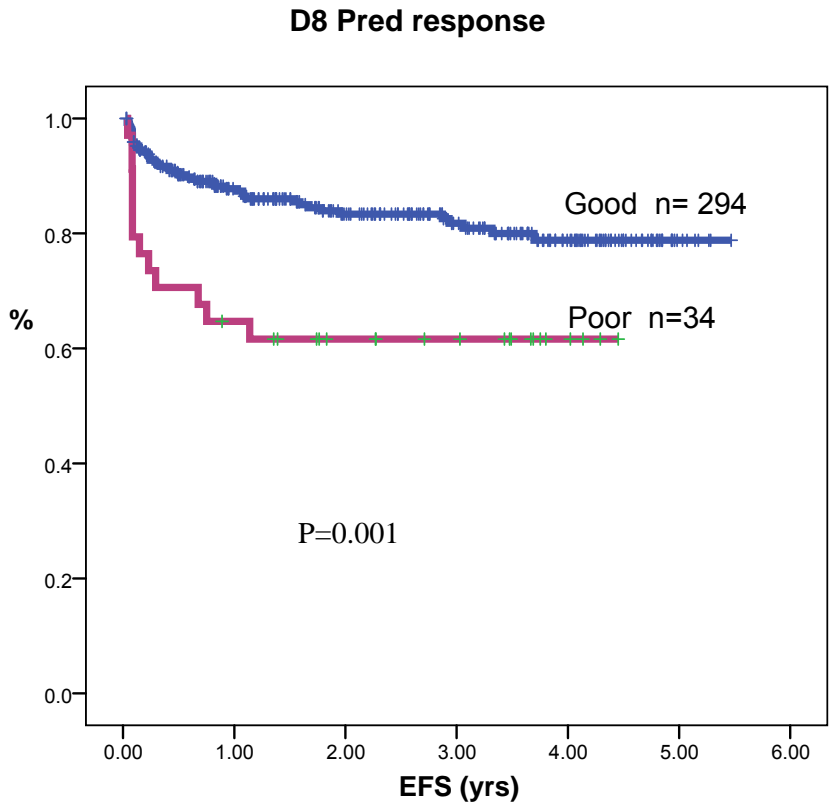


Figure 5. EFS by BFM Day 8 Prednisolone response criteria. Prednisolone poor response in 11% of patients have significantly poorer EFS.



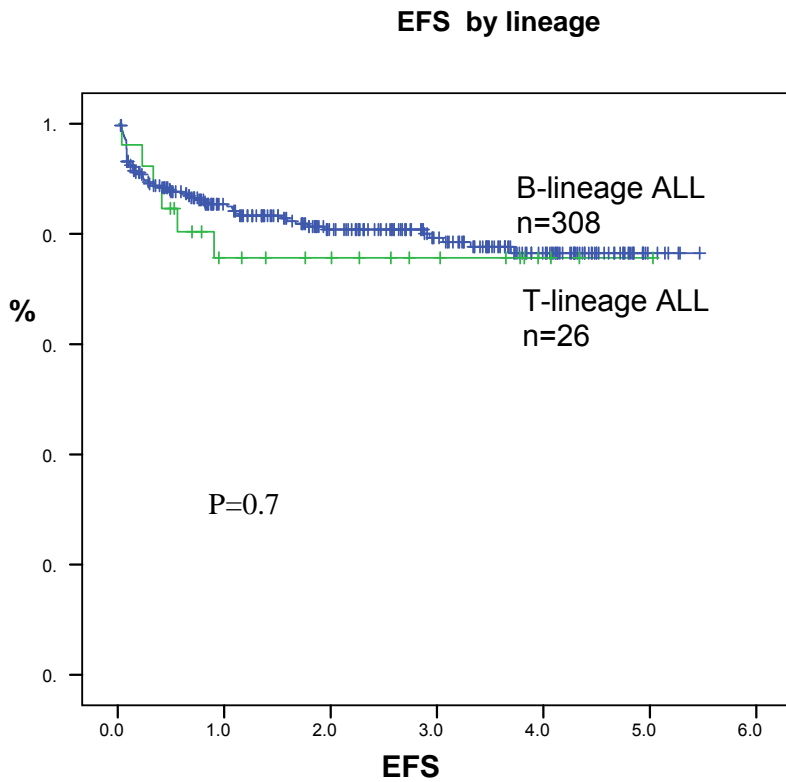


Figure 6. There is no difference in EFS between T or B-lineage

Figure 7. Infants and children more than 9 years old do significantly poorer.

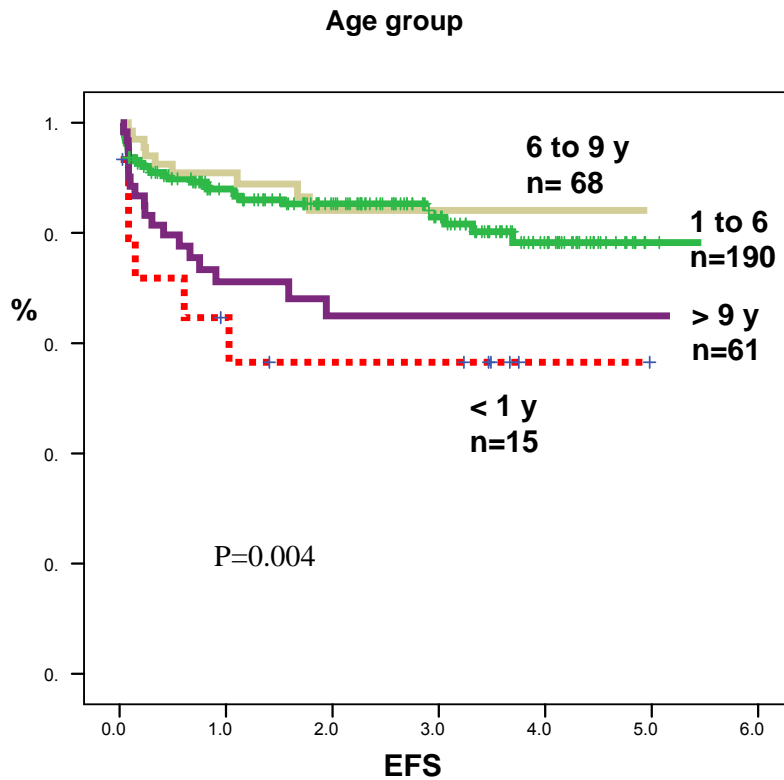
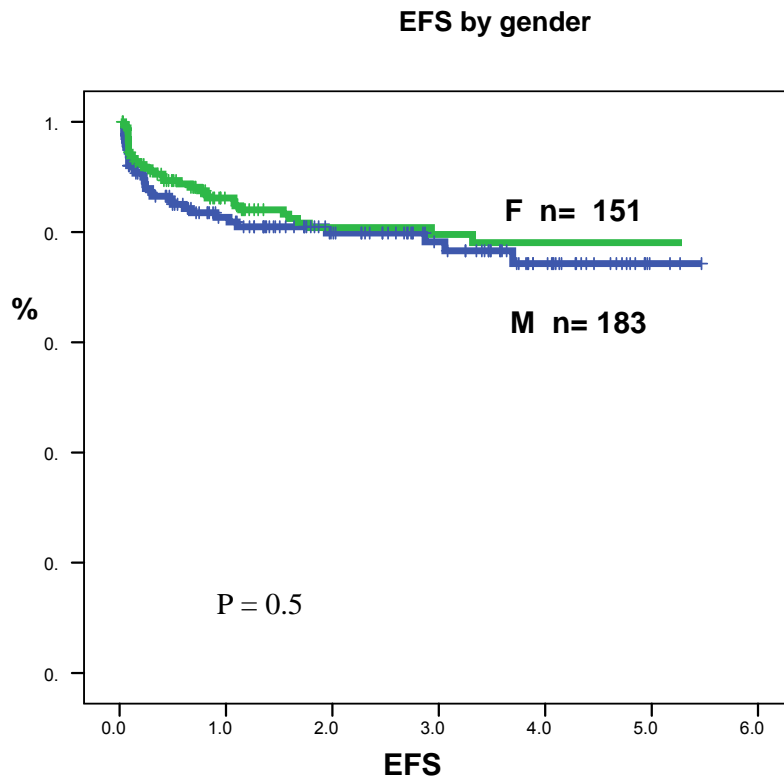


Figure 8. Females do as well as males in Ma-Spore ALL 2003



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