Understanding ETP-ALL - Biology and its implications

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- A distinct subtype of T- cell ALL
- Criteria for diagnosis
- Genetics and disease biology
- Clinical presentation
- Treatment -Pediatric and adult
- Our data

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T-cell ALL

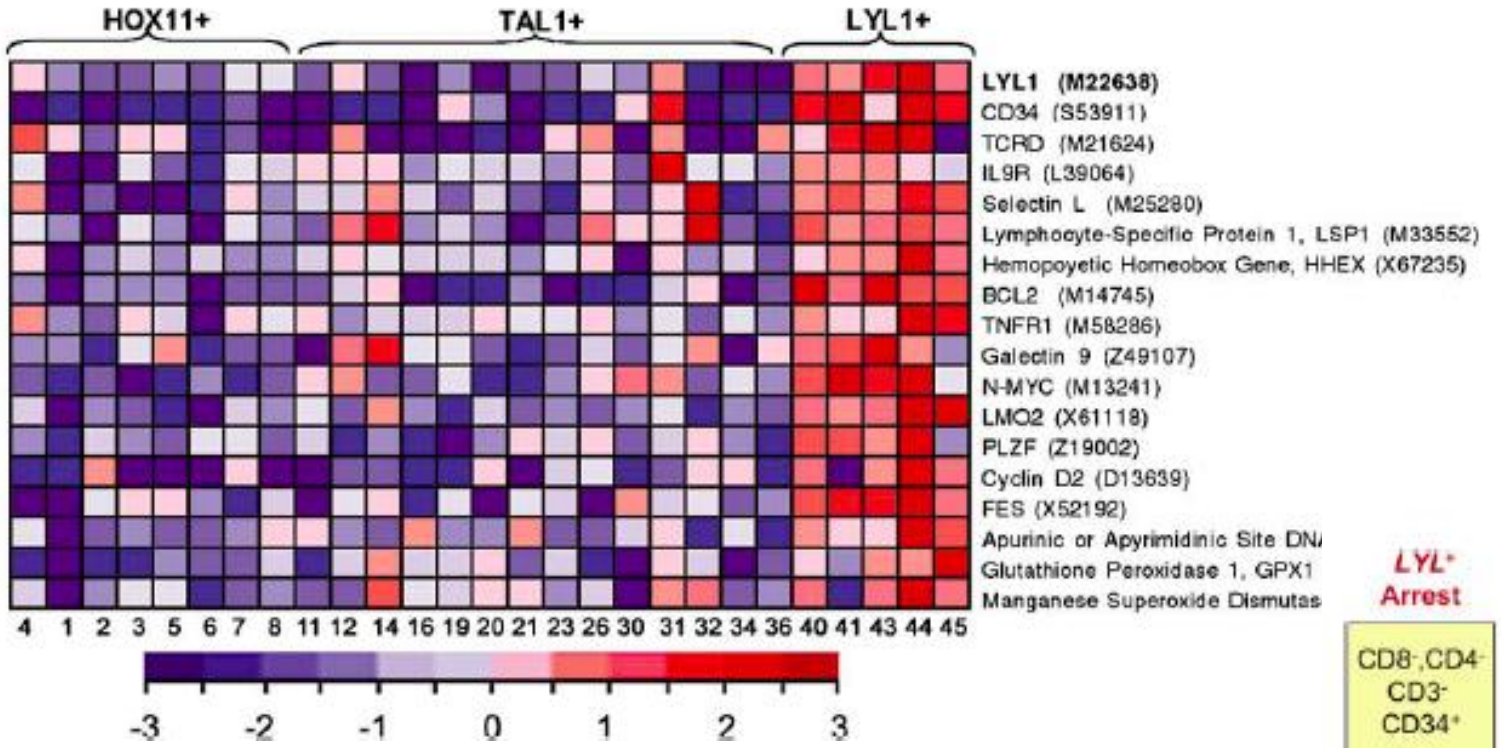
Table 1
Immunophenotype of T-ALL according to stages of thymic differentiation

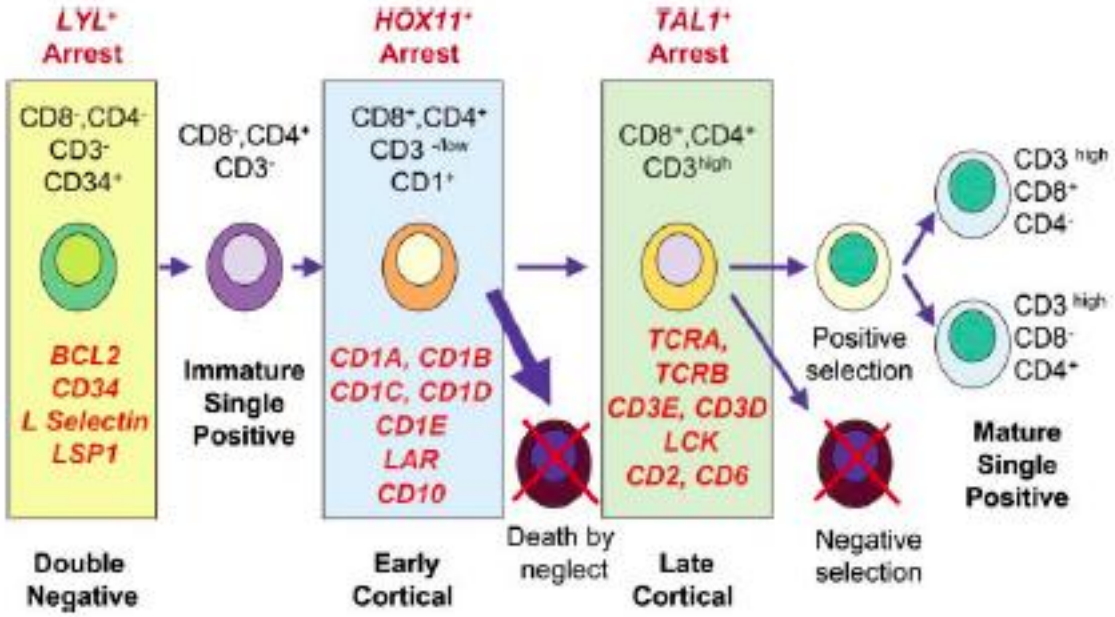
Stage of Maturation	CD1a	CD34	CD2	cCD3	sCD3	CD4	CD5	CD7	CD8
Pro-T	–	±	–	+	–	–	–	+	–
Pre-T	–	±	+	+	–	–	±	+	–
Cortical T	+	–	+	+	–	+	±	+	+
Medullary T	–	–	+	+	+	±[a]	±	+	±[a]

Surgical Pathology 6 (2013) 661–676

Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia

CANCER CELL : FEBRUARY 2002



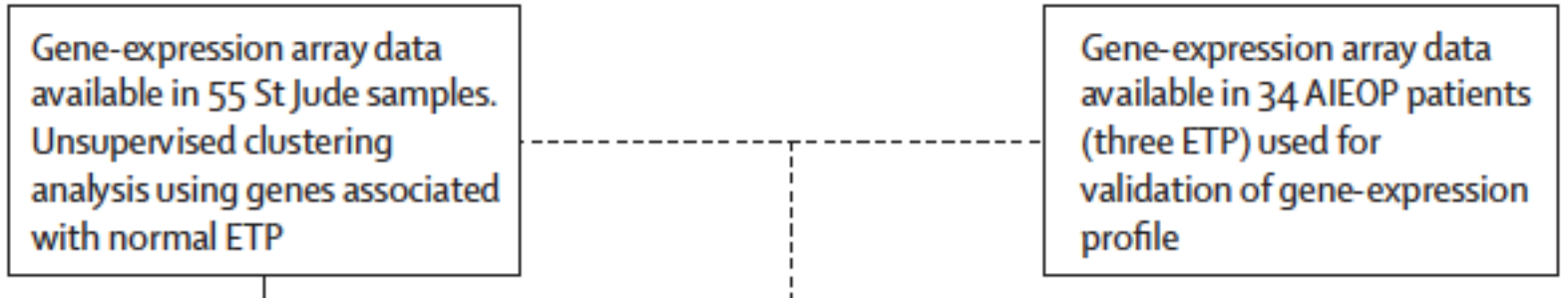


The postulation was tested

Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia

Elaine Coustan-Smith, Charles G Mullighan, Mihaela Onciu, Frederick G Behm, Susana C Raimondi, Deqing Pei, Cheng Cheng, Xiaoping Su, Jeffrey E Rubnitz, Giuseppe Basso, Andrea Biondi, Ching-Hon Pui, James R Downing, Dario Campana

Lancet Oncol 2009; 10: 147–56



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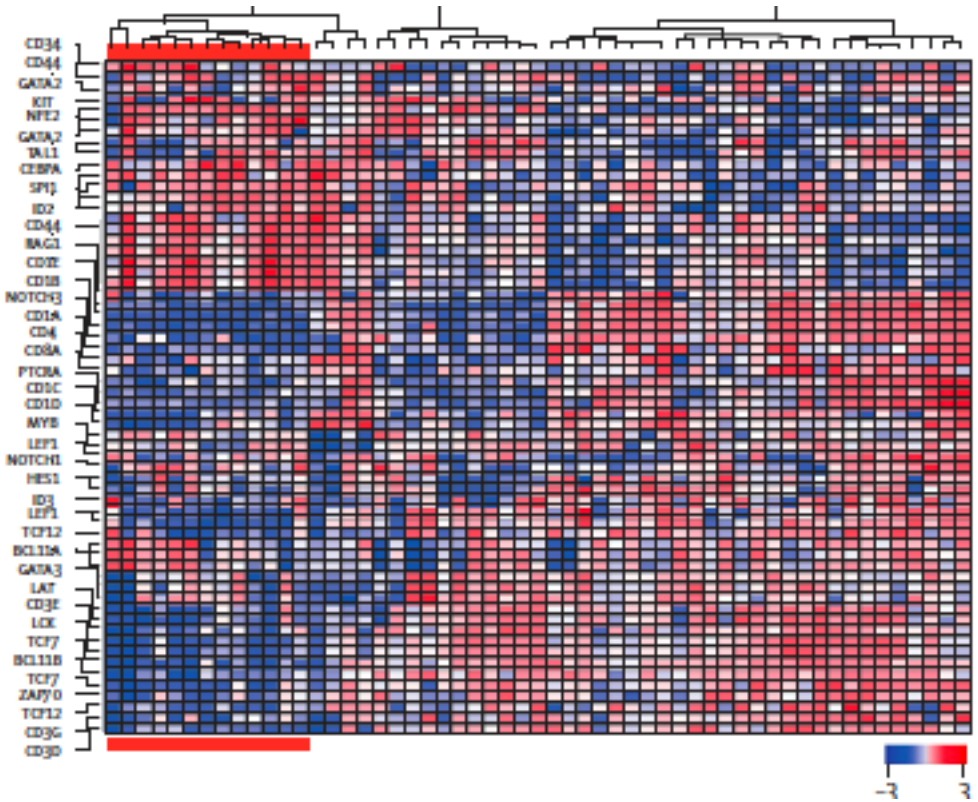

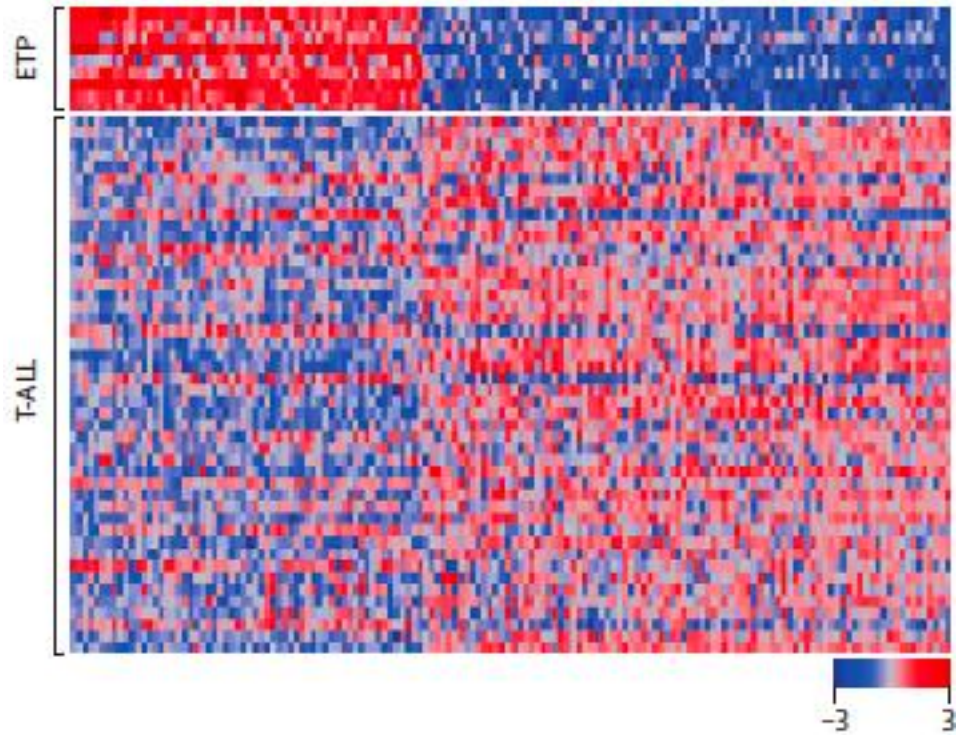

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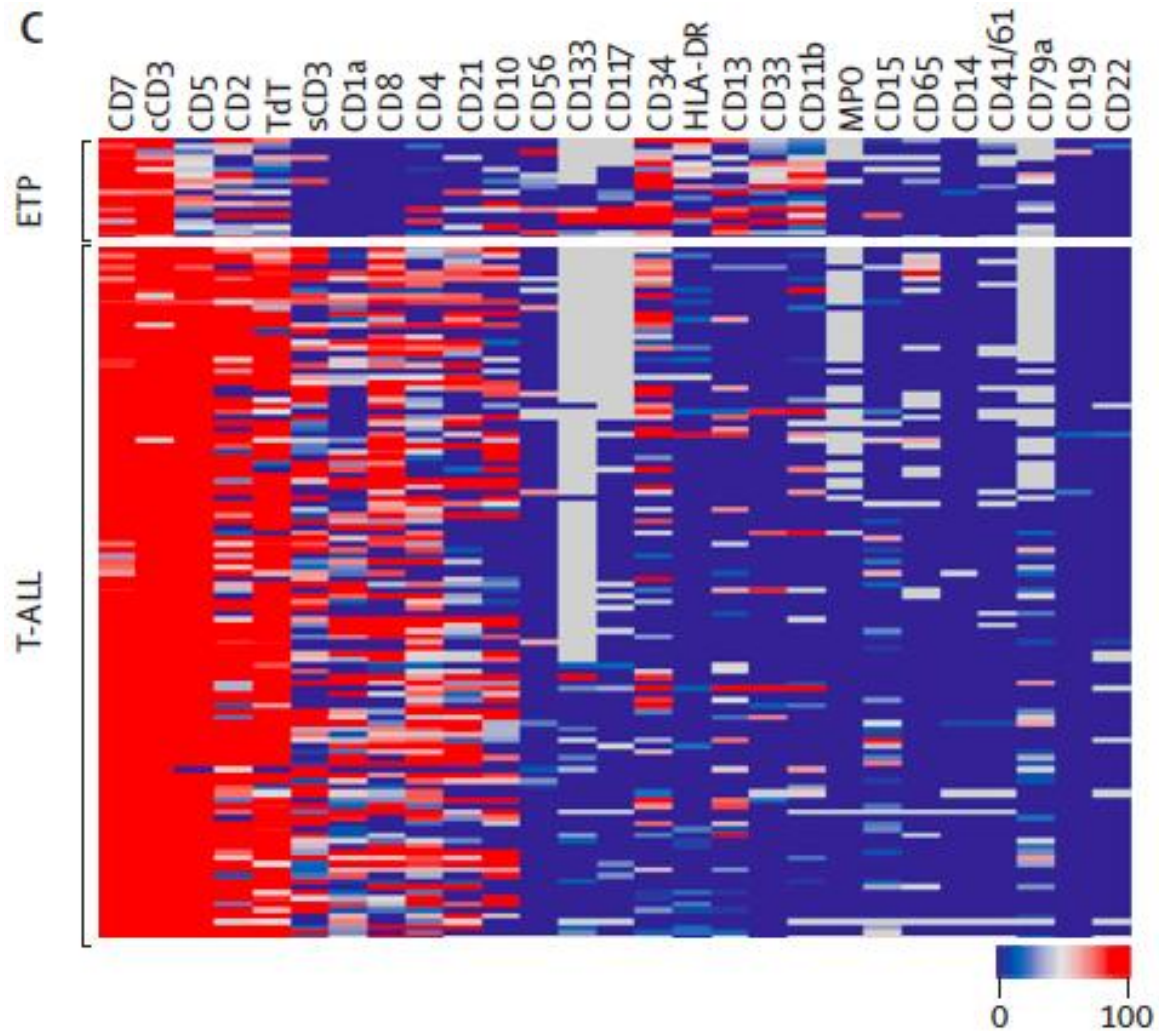
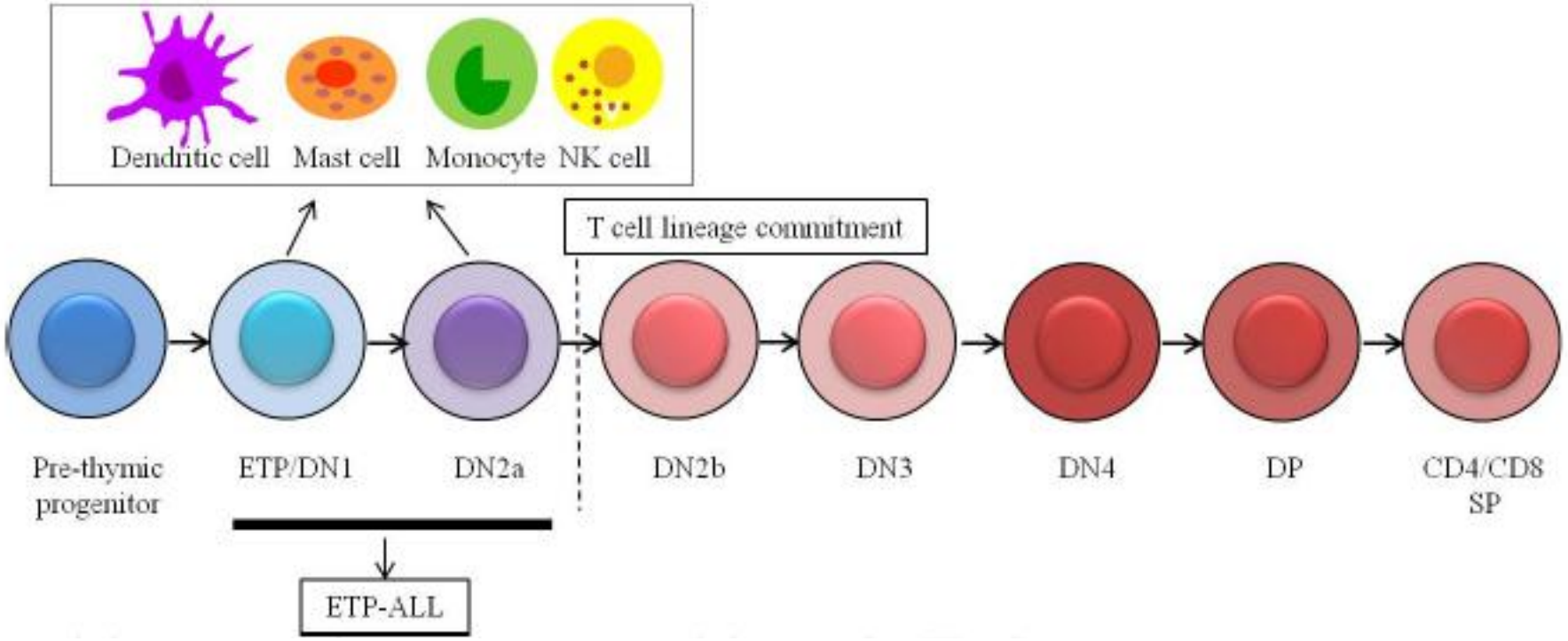


ETP-ALL – cell of origin



Early T-cell Precursor Acute Lymphoblastic Leukemia – A Characteristic Neoplasm Presenting the Phenotype of…
http://dx.doi.org/10.5772/60901

A distinct entity

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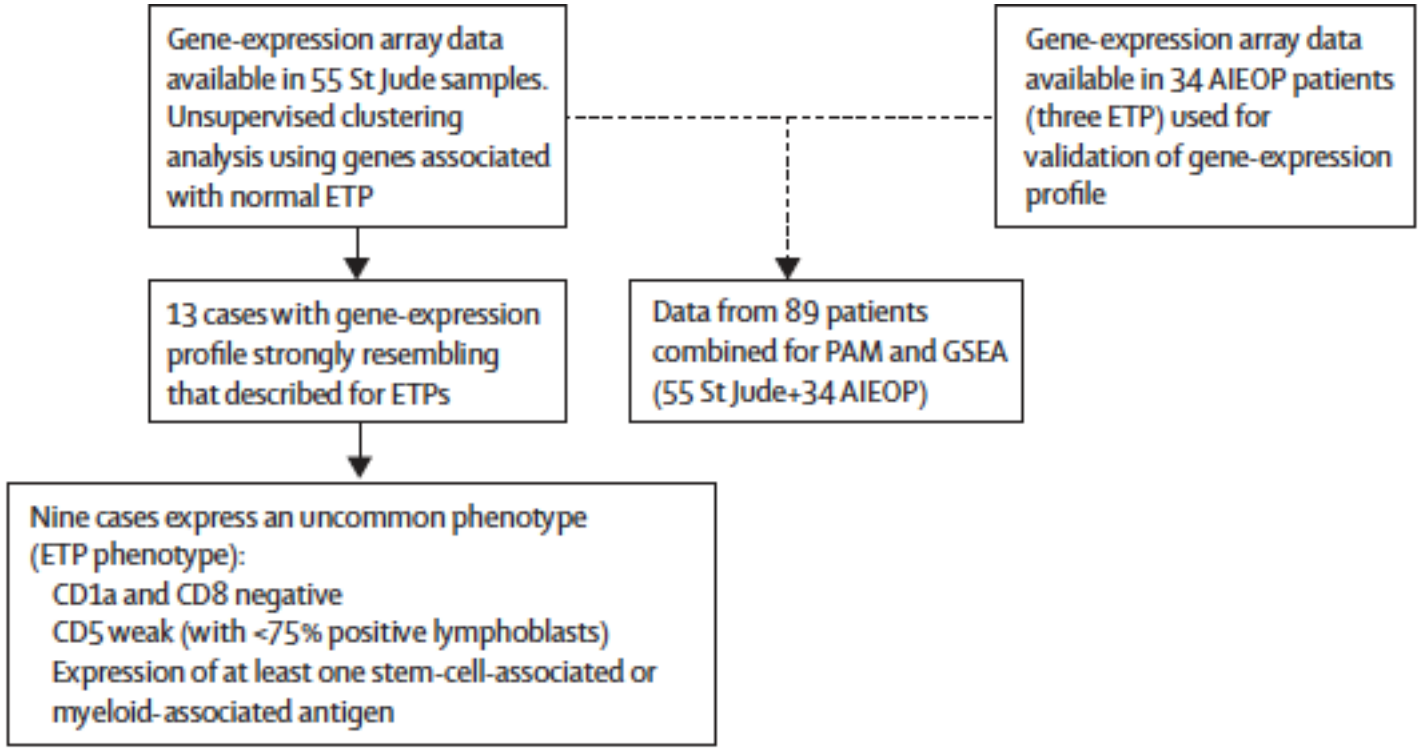

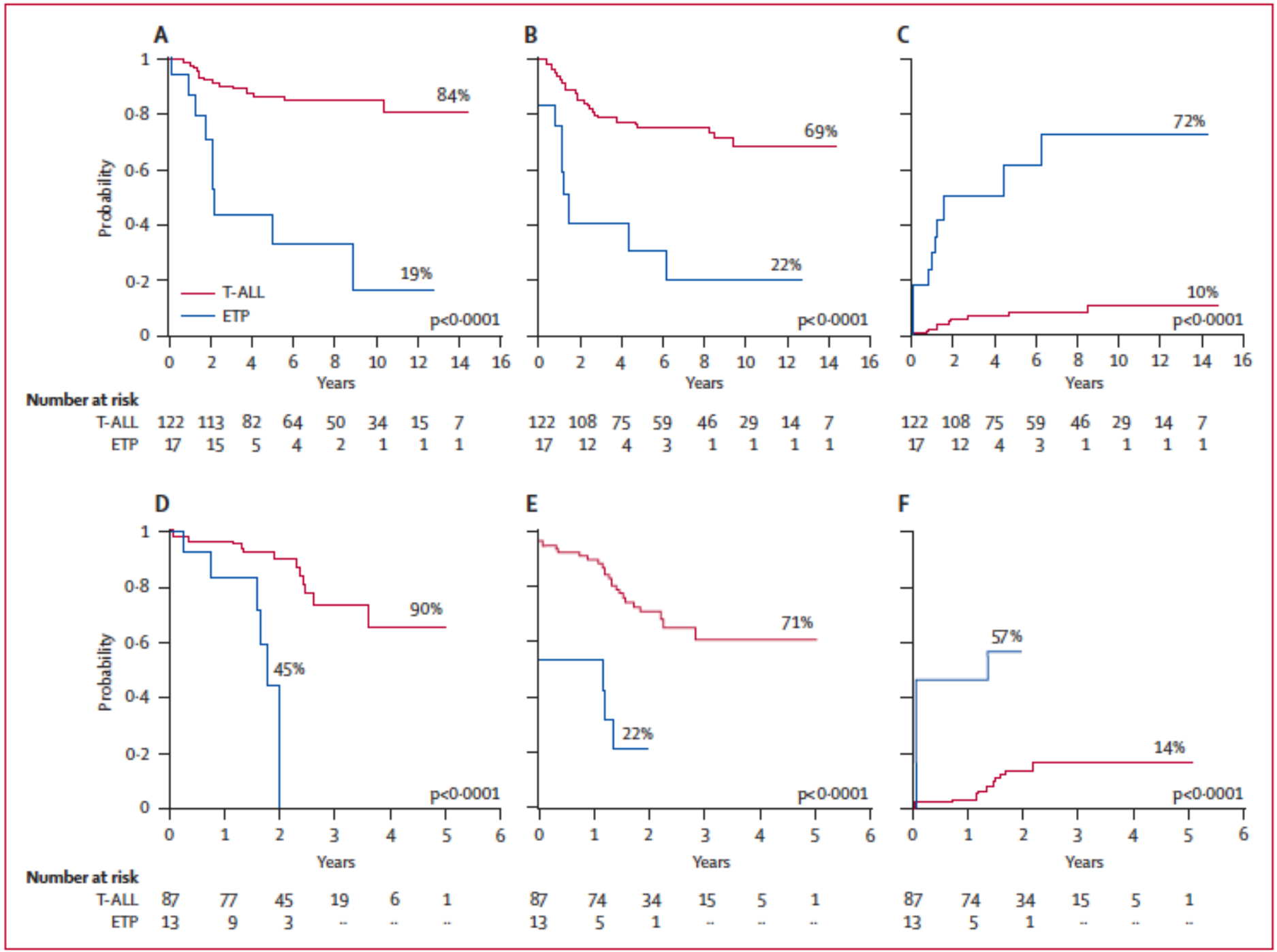
A
B
C
D
E
F
Probability
Years
T-ALL
ETP
84%
19%
69%
22%
72%
10%
90%
45%
71%
22%
57%
14%
p<0·0001
Number at risk
T-ALL 122 113 82 64 50 34 15 7
ETP 17 15 5 4 2 1 1 1
122 108 75 59 46 29 14 7
17 12 4 3 1 1 1 1
122 108 75 59 46 29 14 7
17 12 4 3 1 1 1 1
T-ALL 87 77 45 19 6 1
ETP 13 9 3 .. .. ..
87 74 34 15 5 1
13 5 1 .. .. ..
87 74 34 15 5 1
13 5 1 .. .. ..

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ETP-ALL diagnosis

Box 1
Immunophenotypic definition of ETP-ALL

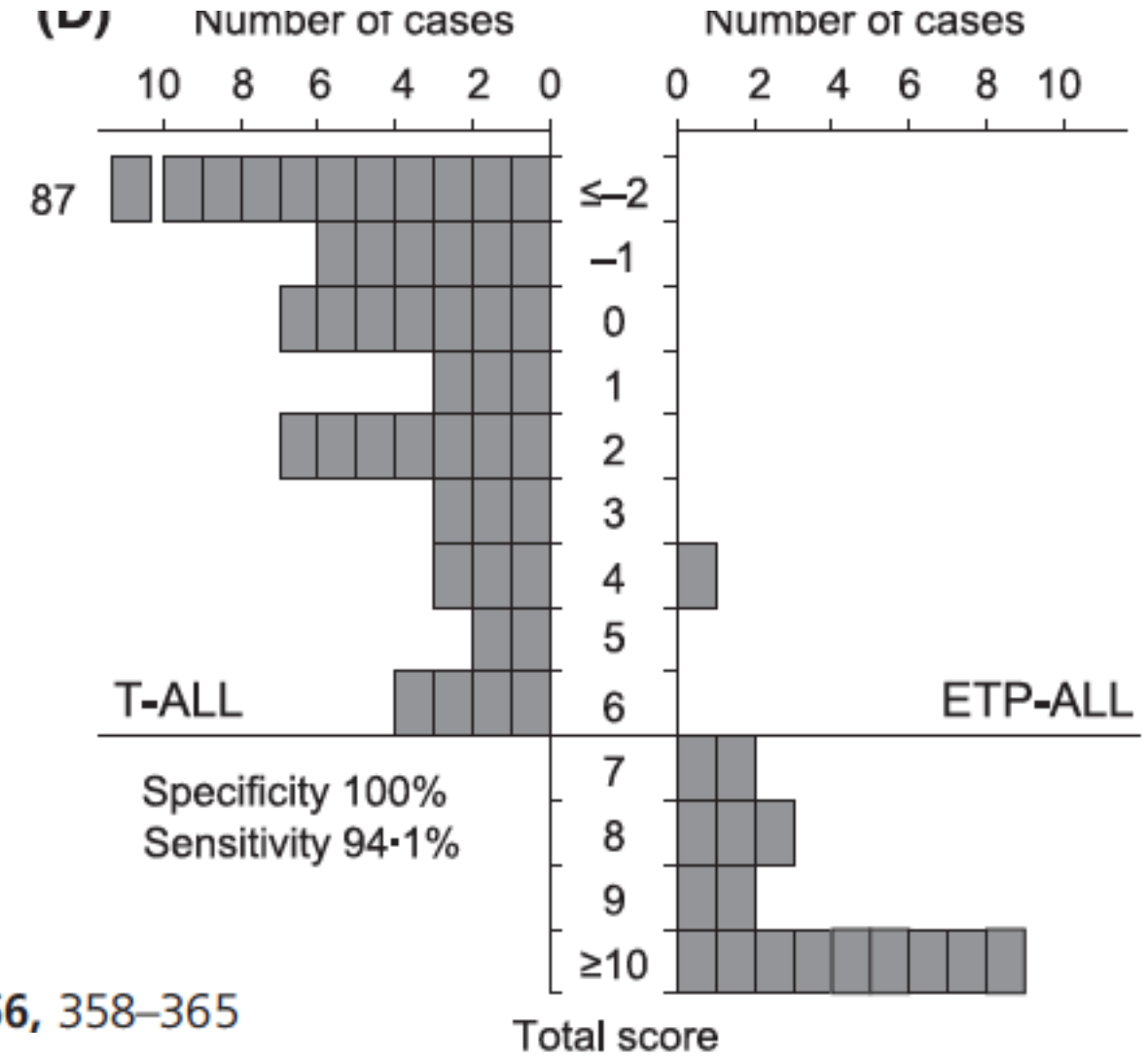
To be considered ETP-ALL, a case of T-ALL must fulfill all of the following criteria[6,a]:

- Absence of CD1a and CD8 expression
- Weak to absent CD5 expression (<75% of blasts positive)
- Expression (positive in >25% of blasts) of one or more of the following myeloid or stem cell–associated markers: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65

[a] Assuming that blasts are cCD3 positive and MPO negative.

Clinical significance of early T-cell precursor acute lymphoblastic leukaemia: results of the Tokyo Children's Cancer Study Group Study L99-15

Scoring system based on 11 marker expression				
Score	–2	–1	+1	+2
CD5	≥75%			<75%
CD8	≥5%			<5%
CD13			≥25%	≥75%
CD33			≥25%	≥75%
CD34			≥25%	≥75%
HLA-DR			≥25%	≥75%
CD2		≥75%	<20%	
CD3		≥75%	<20%	
CD4		≥75%	<20%	
CD10		≥75%	<20%	
CD56			≥20%	



British Journal of Haematology, **156**, 358–365

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

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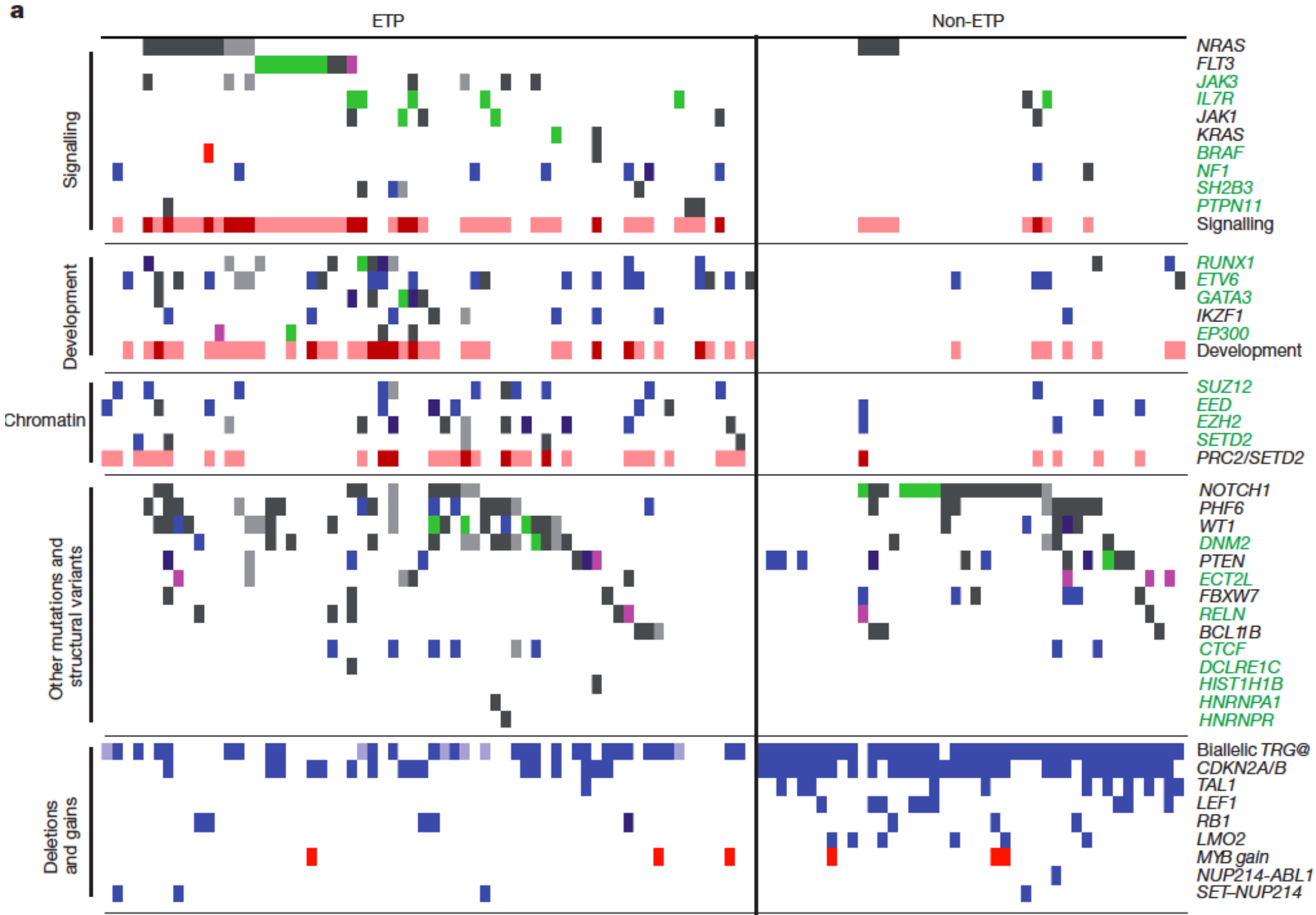
Cytogenetics

- 80% have clonal cytogenetic abnormality
- No specific recurrent abnormality
- 13 q deletion
- Chromothripsis

The genetic basis of early T-cell precursor acute lymphoblastic leukaemia

doi:10.1038/nature10725


a
ETP
Non-ETP
Signalling
Development
Chromatin
Other mutations and structural variants
Deletions and gains
NRAS
FLT3
JAK3
IL7R
JAK1
KRAS
BRAF
NF1
SH2B3
PTPN11
Signalling
RUNX1
ETV6
GATA3
IKZF1
EP300
Development
SUZ12
EED
EZH2
SETD2
PRC2/SETD2
NOTCH1
PHF6
WT1
DNM2
PTEN
ECT2L
FBXW7
RELN
BCL11B
CTCF
DCLRE1C
HIST1H1B
HNRNPA1
HNRNPR
Biallelic TRG@
CDKN2A/B
TAL1
LEF1
RB1
LMO2
MYB gain
NUP214-ABL1
SET–NUP214

Adult ETP-ALLs are different

Whole-exome sequencing in adult ETP-ALL reveals a high rate of *DNMT3A* mutations

Key Points

- Exome sequencing of adult ETP-ALL reveals new recurrent mutations; in particular, *DNMT3A* is frequently mutated in adult ETP-ALL.
- More than 60% of all adult patients with ETP-ALL harbor a mutation that could potentially be targeted by a specific therapy.

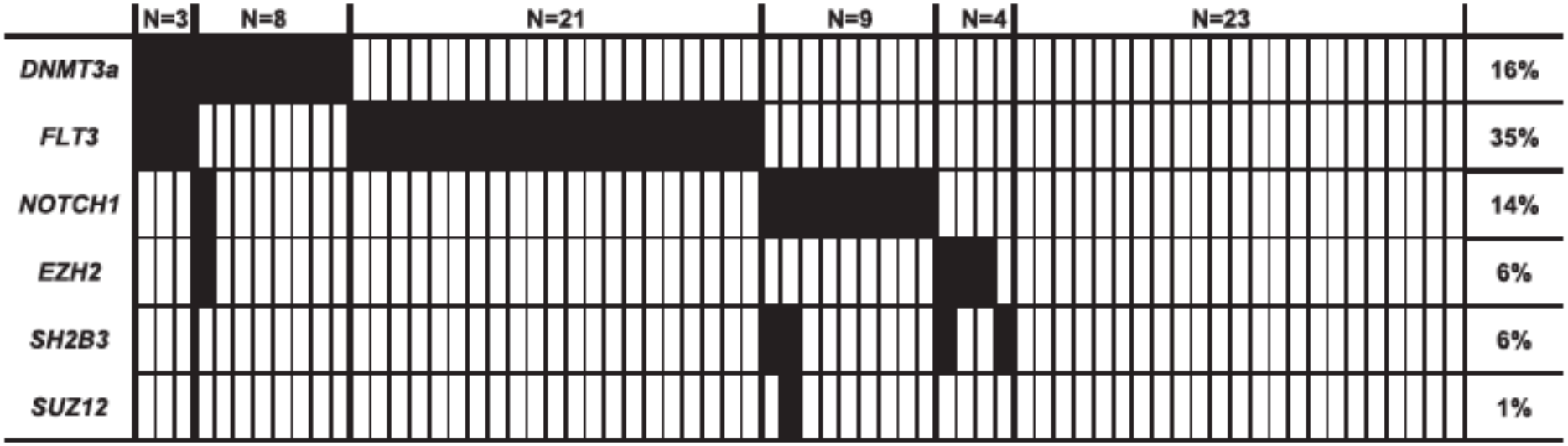


Figure 1. The spectrum of mutations in *DNMT3A*, *FLT3*, *NOTCH1*, *EZH2*, *SH2B3*, and *SUZ12* in 68 adult patients with ETP-ALL

(*Blood*. 2013;121(23):4749-4752)

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Clinical features

- 5.5-16% of all T-cell ALL
- Lower blast counts
- Lower TLC
- Lower frequency of mediastinal mass
- *Similar gender distribution (GMALL)*
- *Similar CNS involvement (MDACC)*

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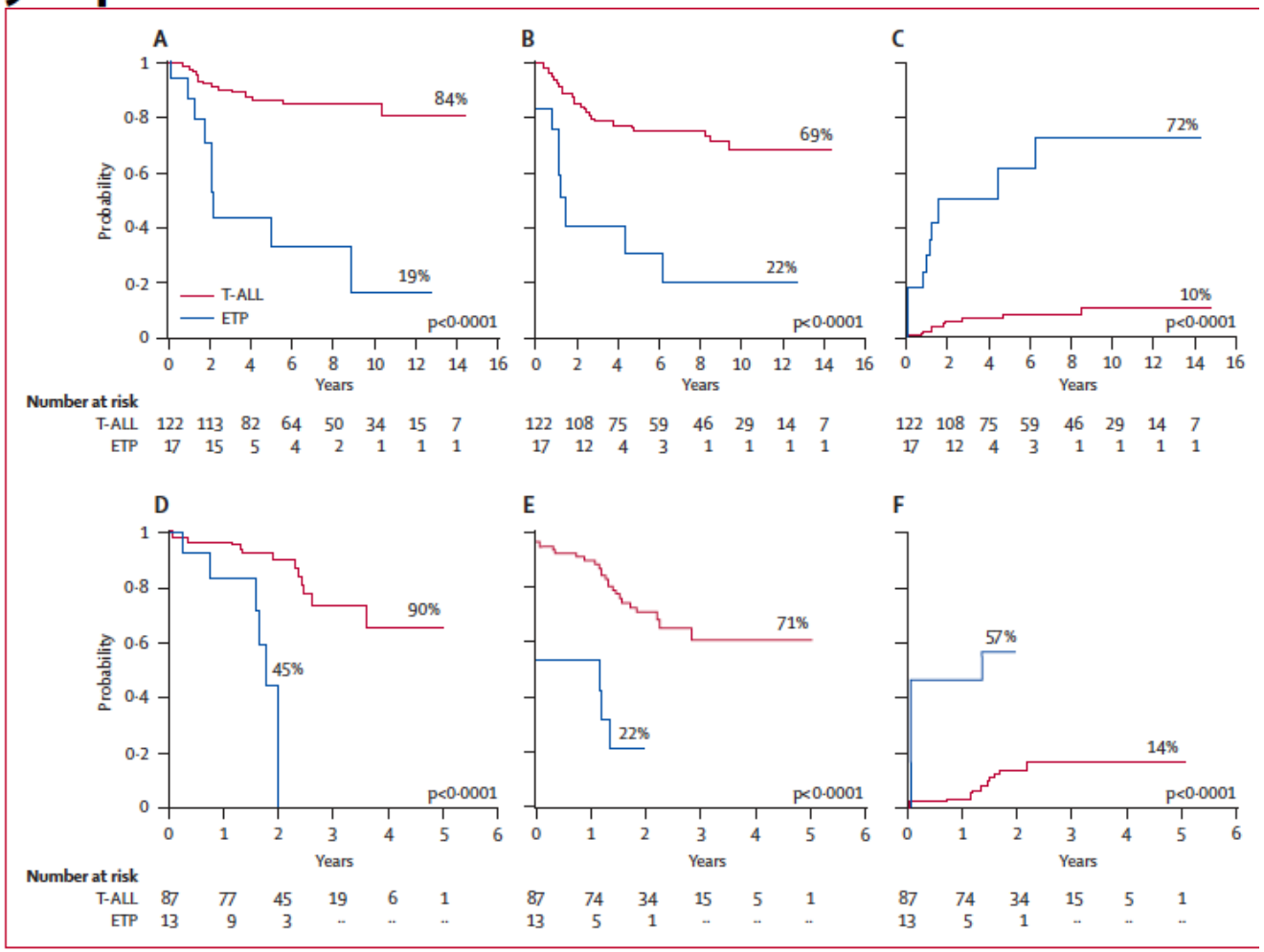
Treatment

Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia



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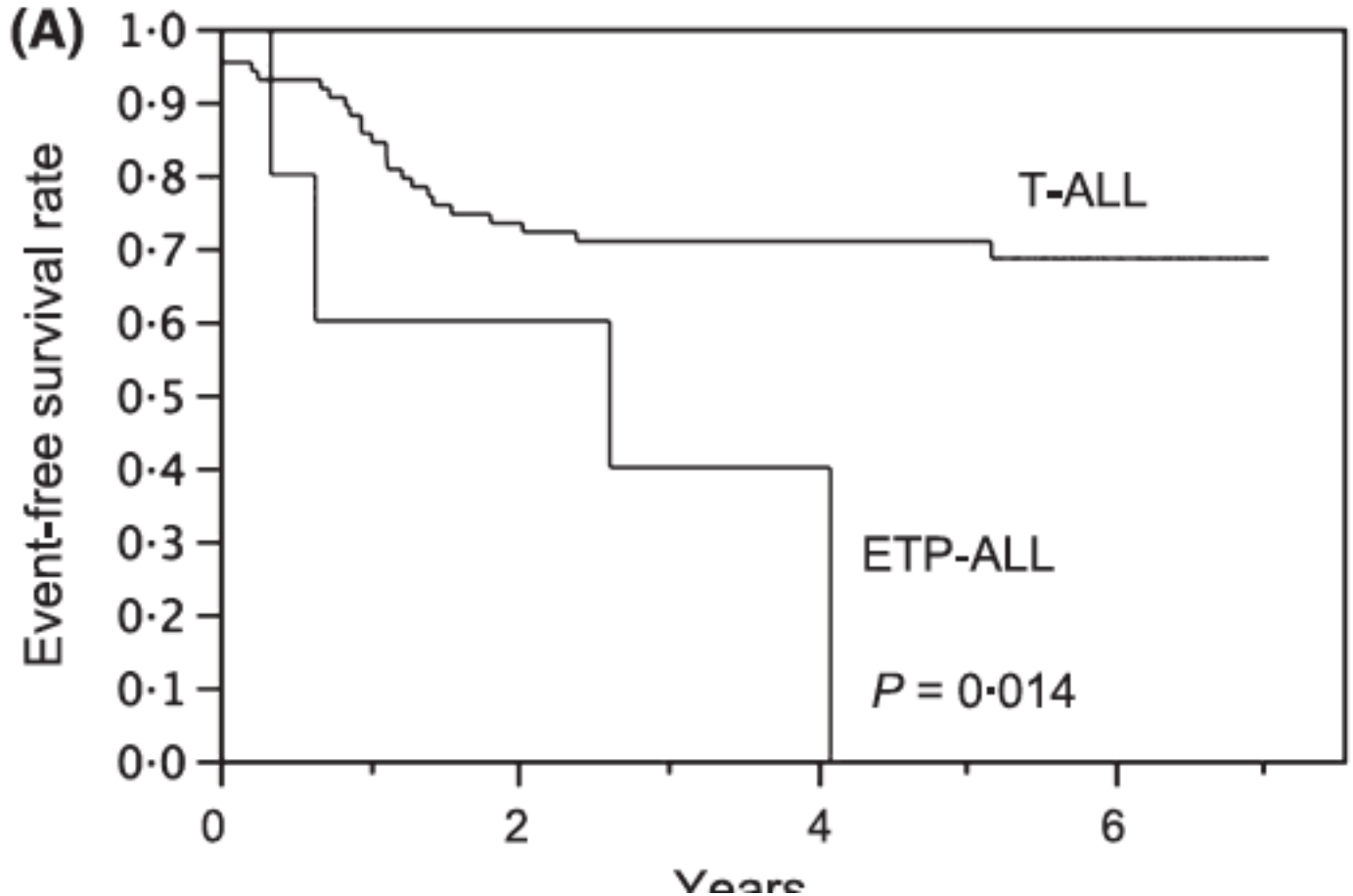

Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype

[*Blood*. 2016;127(15):1863-1869)

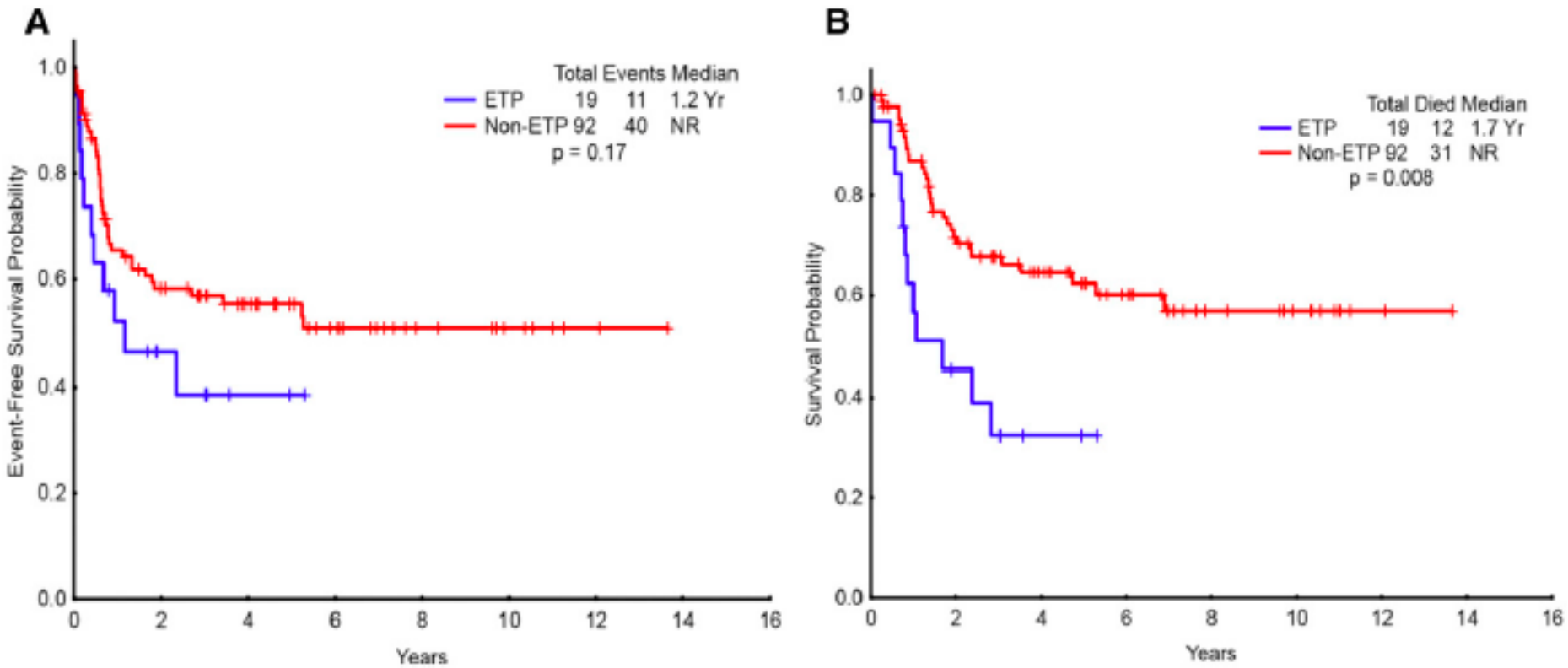

Figure 3. Survival for the entire study population categorized as ETP vs non-ETP. (A) Event-free survival and (B) overall survival of patients with ETP ALL (n = 19) compared with non-ETP ALL (n = 92). NR, not reached.

Common theme

- Poor prednisolone response
- Higher rates of failure to achieve morphological CR
- High MRD post induction – better clearance of disease post phase IB

Change

- Intensification based on the prednisone response and post induction MRD

- All in high risk group

Early T-cell precursor acute lymphoblastic leukaemia in children treated in AIEOP centres with AIEOP-BFM protocols: a retrospective analysis

Lancet Haematol 2016;
3: e80–86

treatment and stratification of T-cell acute lymphoblastic leukaemia between the two protocols were that in the 2009 protocol only, pegylated L-asparaginase was substituted for *Escherichia coli* L-asparaginase, patients with prednisone poor response received an additional dose of cyclophosphamide at day 10 of phase IA, and high minimal residual disease at day 15 assessed by flow cytometry was used as a high-risk criterion. Outcomes were assessed in terms of event-free survival, disease-free survival, and overall survival.

Interpretation Early T-cell precursor acute lymphoblastic leukaemia is characterised by poor early response to conventional induction treatment. Consolidation phase IB, based on cyclophosphamide, 6-mercaptopurine, and ara-C at conventional (non-high) doses is effective in reducing minimal residual disease. Although the number of patients and observational time are limited, patients with early T-cell precursor acute lymphoblastic leukaemia treated with current BFM stratification and treatment strategy have a favourable outcome compared with earlier reports. The role of innovative therapies and haemopoietic stem cell therapy in early T-cell precursor acute lymphoblastic leukaemia needs to be assessed.

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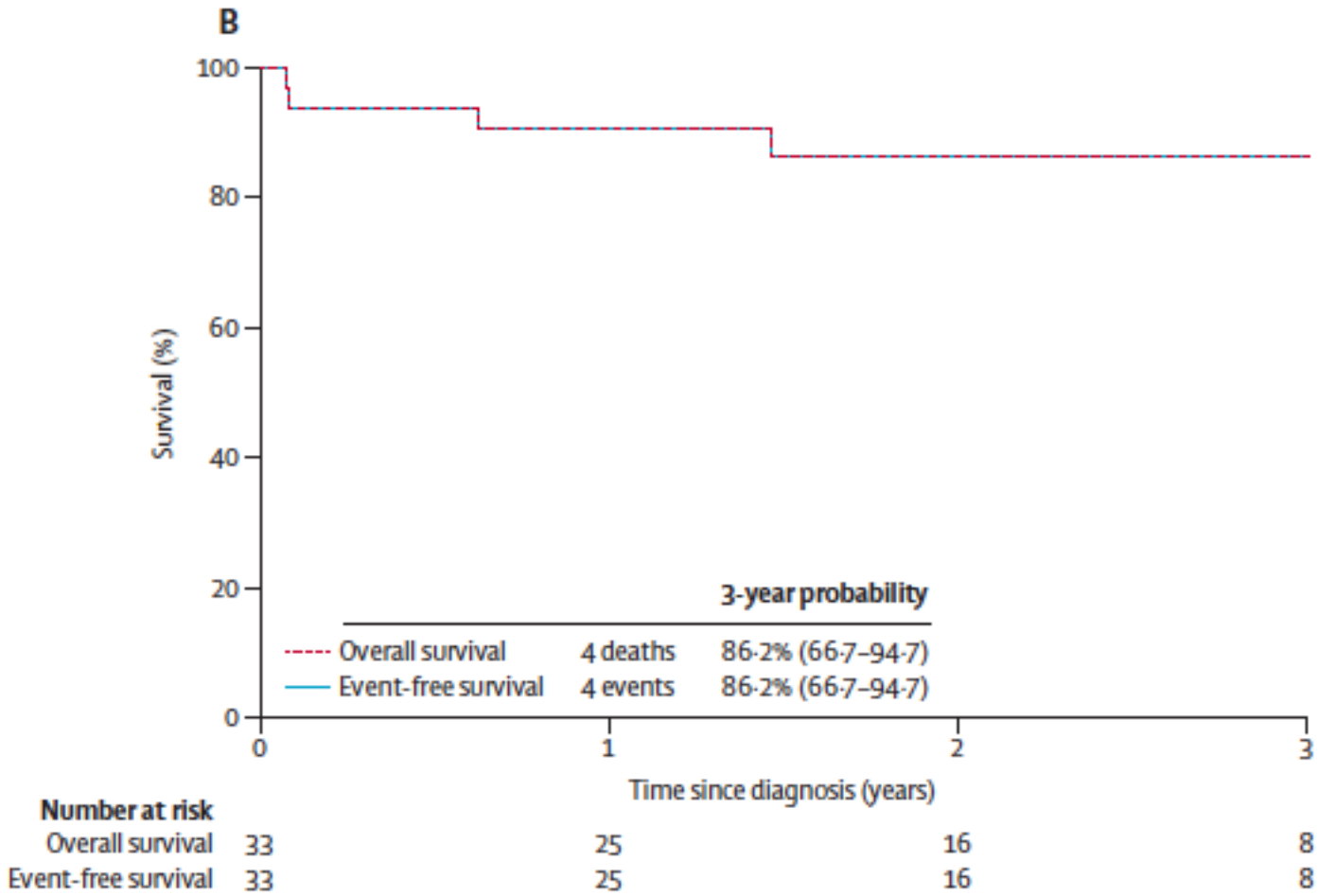
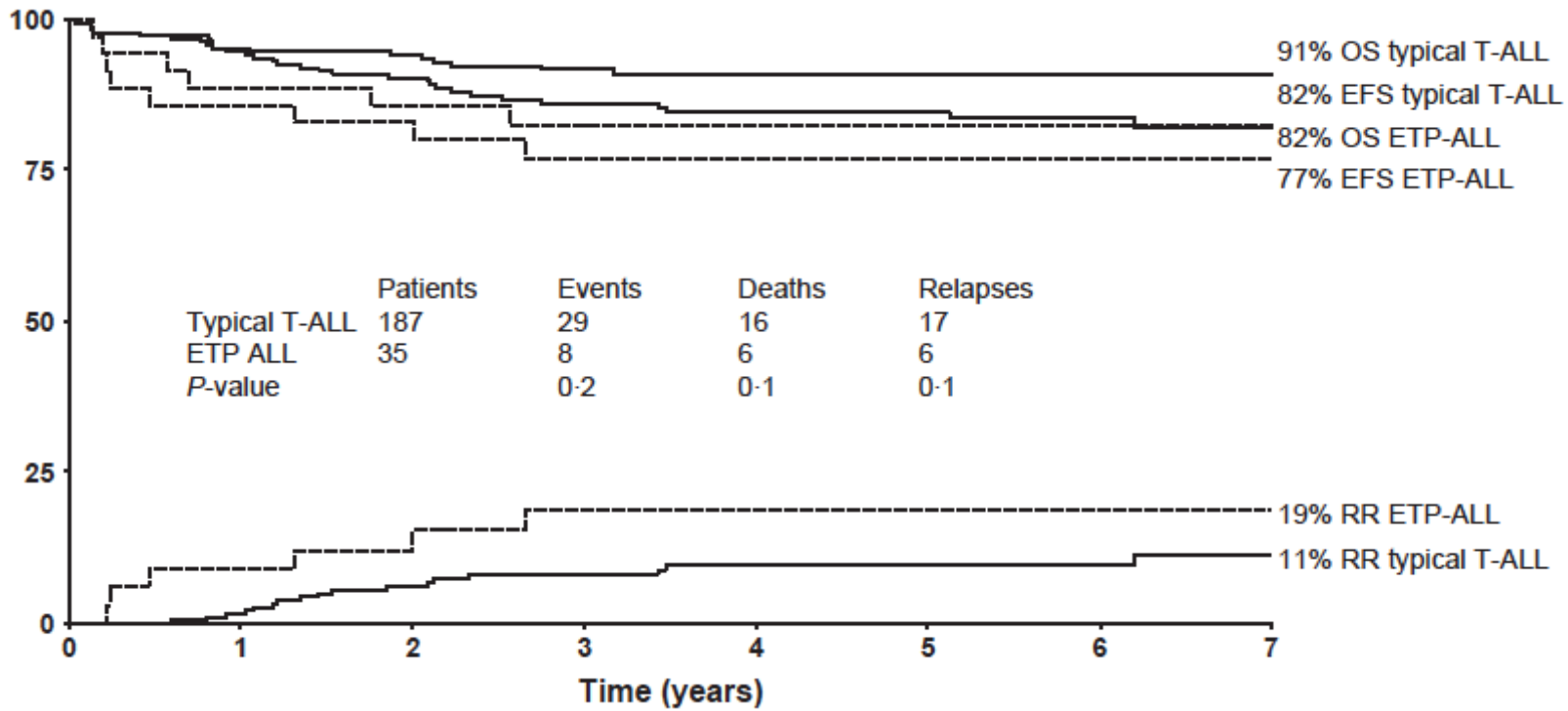


Outcome for children and young people with Early T-cell precursor acute lymphoblastic leukaemia treated on a contemporary protocol, UKALL 2003



T-Lymphoblastic Leukemia (T-ALL) Shows Excellent Outcome, Lack of Significance of the Early Thymic Precursor (ETP) Immunophenotype, and Validation of the Prognostic Value of End-Induction Minimal Residual Disease (MRD) in Children's Oncology Group (COG) Study AALL0434

Brent L. Wood, Stuart S. Winter, Kimberly P. Dunsmore, Meenakshi Devidas, Si Chen, Barbara Asselin, Natia Esiashvili, Mignon L. Loh, Naomi J. Winick, William L. Carroll, Elizabeth A. Raetz, and Stephen P. Hunger

Blood 2014 124:1;

VOLUME 35 · NUMBER 23 · AUGUST 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Response–Based Therapy Stratification Improves Survival in Adult Early Thymic Precursor Acute Lymphoblastic Leukemia: A Group for Research on Adult Acute Lymphoblastic Leukemia Study

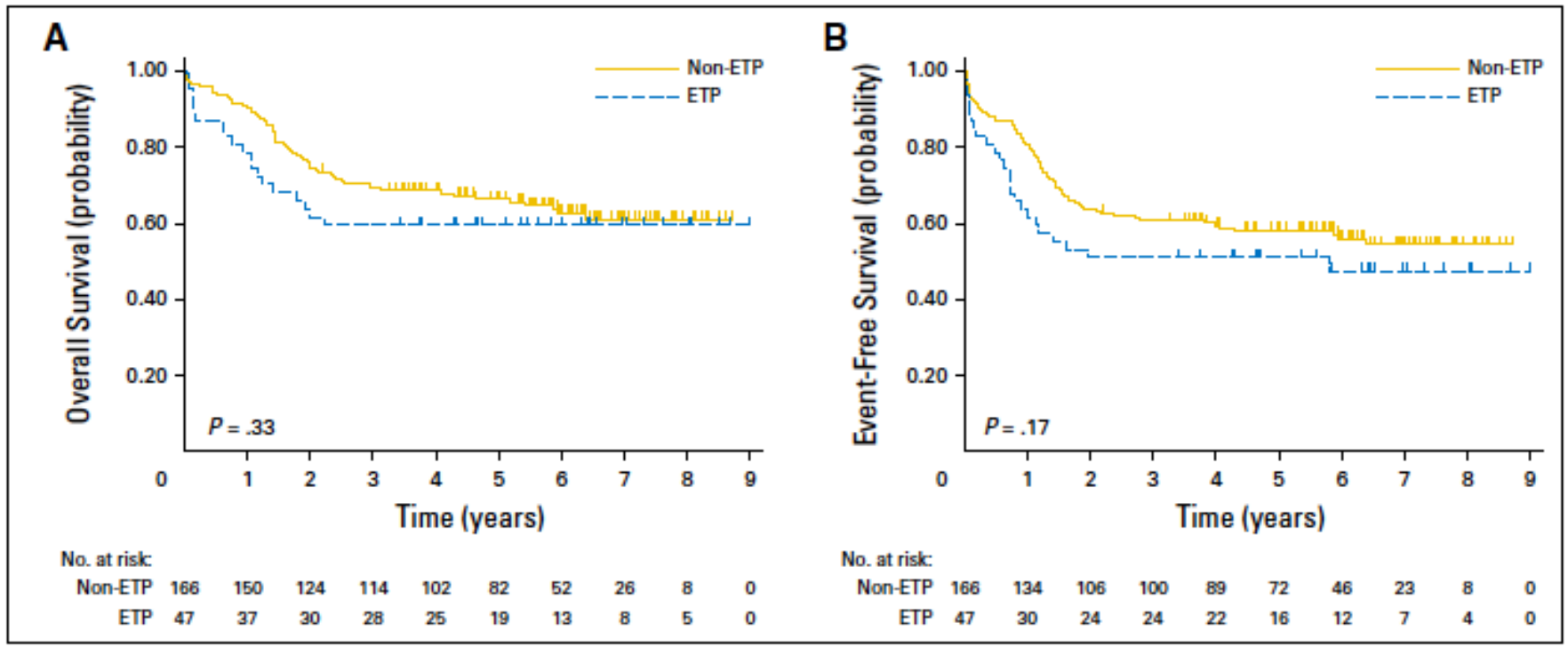


Fig3. Adult early thymic precursor (ETP) acute lymphoblastic leukemia is associated with a neutral prognosis. (A) Overall survival. The 5-year survival figures were 59.6% (95% CI, 44.2% to 72.0%) for the ETP group and 66.5% (95% CI, 58.7% to 73.2%) for the non-ETP group. (B) Event-free survival. The 5-year survival figures were 51.1% (95% CI, 36.1% to 64.2%) for the ETP group and 58.1% (95% CI, 50.2% to 65.2%) for the non-ETP group. *P* values are indicated.

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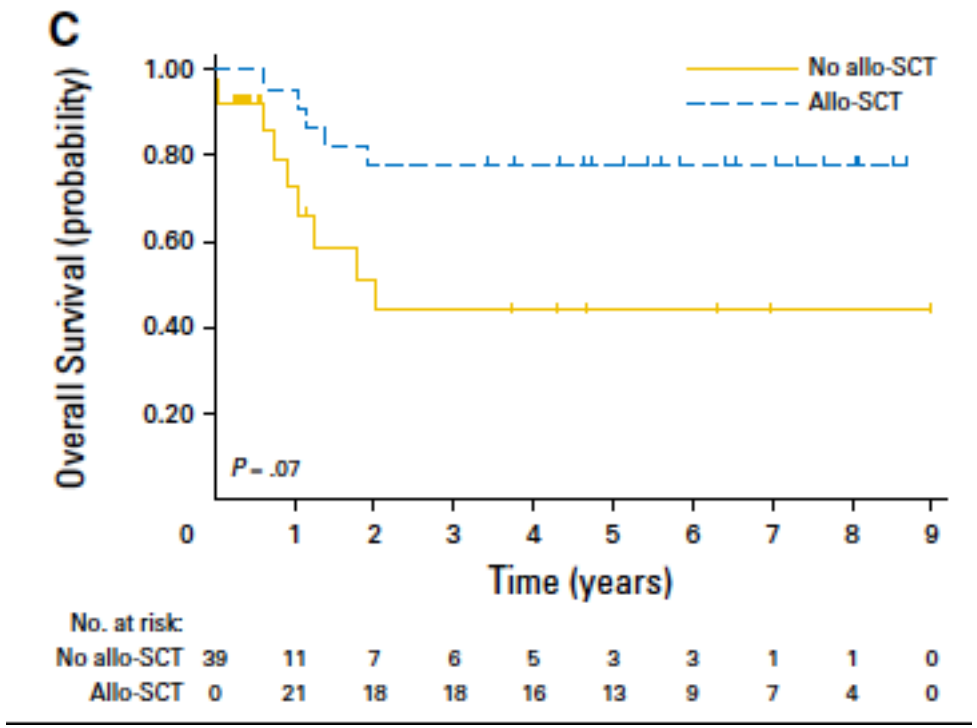

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Data from TMH

Variable	Number (total – 100) Jan 2013- Dec 2017
Age Median(range)	27 years (16-63 years)
Male:Female	77:23
Baseline TLC	Median -13000/cumm >100,000/cumm- 16
CSF involvement	8
Treated at TMH	85

No response to prednisolone - 54%

Failure to achieve CR - 60%,

Post-induction MRD + - 90%

Data from TMH- Non ETP T-ALL versus ETP-ALL

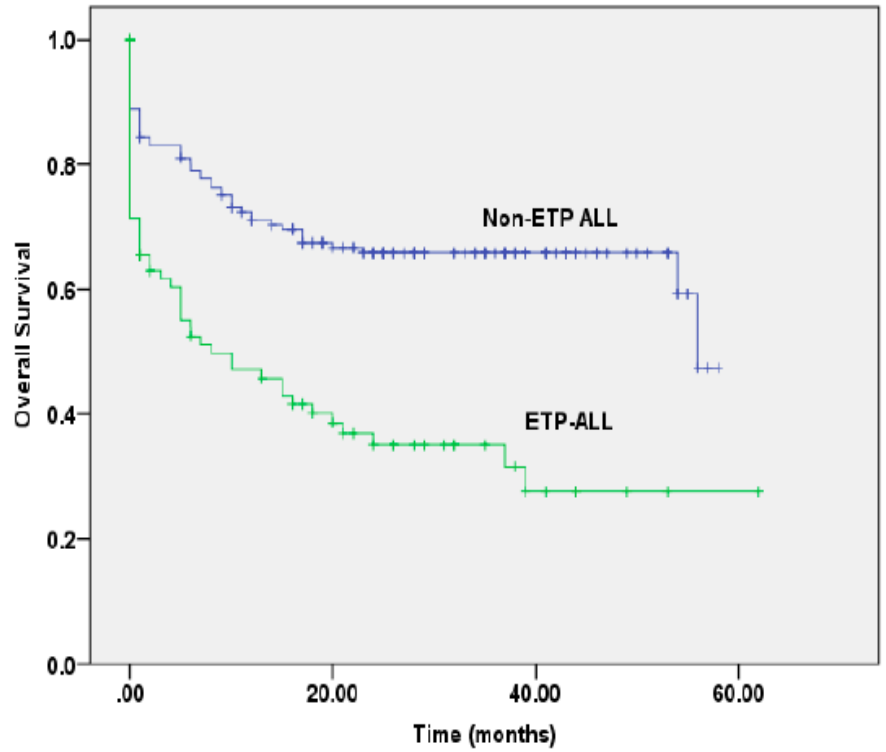


Figure 1: Comparison of overall survival between non-ETP and ETP Acute Lymphoblastic Leukemia

Cellworks

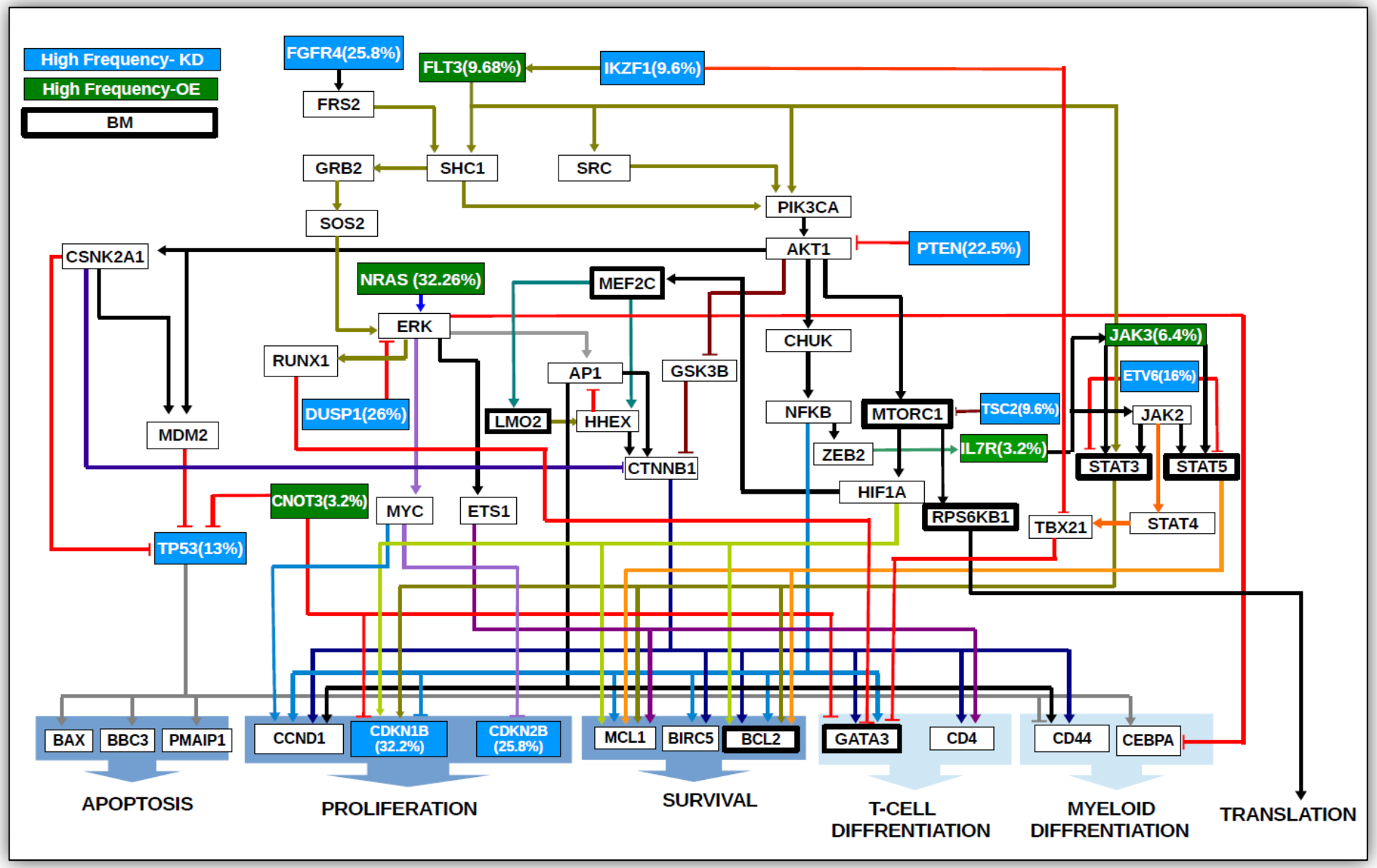
PERSONALIZED THERAPY. TRANSPARENT DESIGN.

Early T-cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) Precision Oncology Program

Computational Modeling & Validation
Cumulative Update

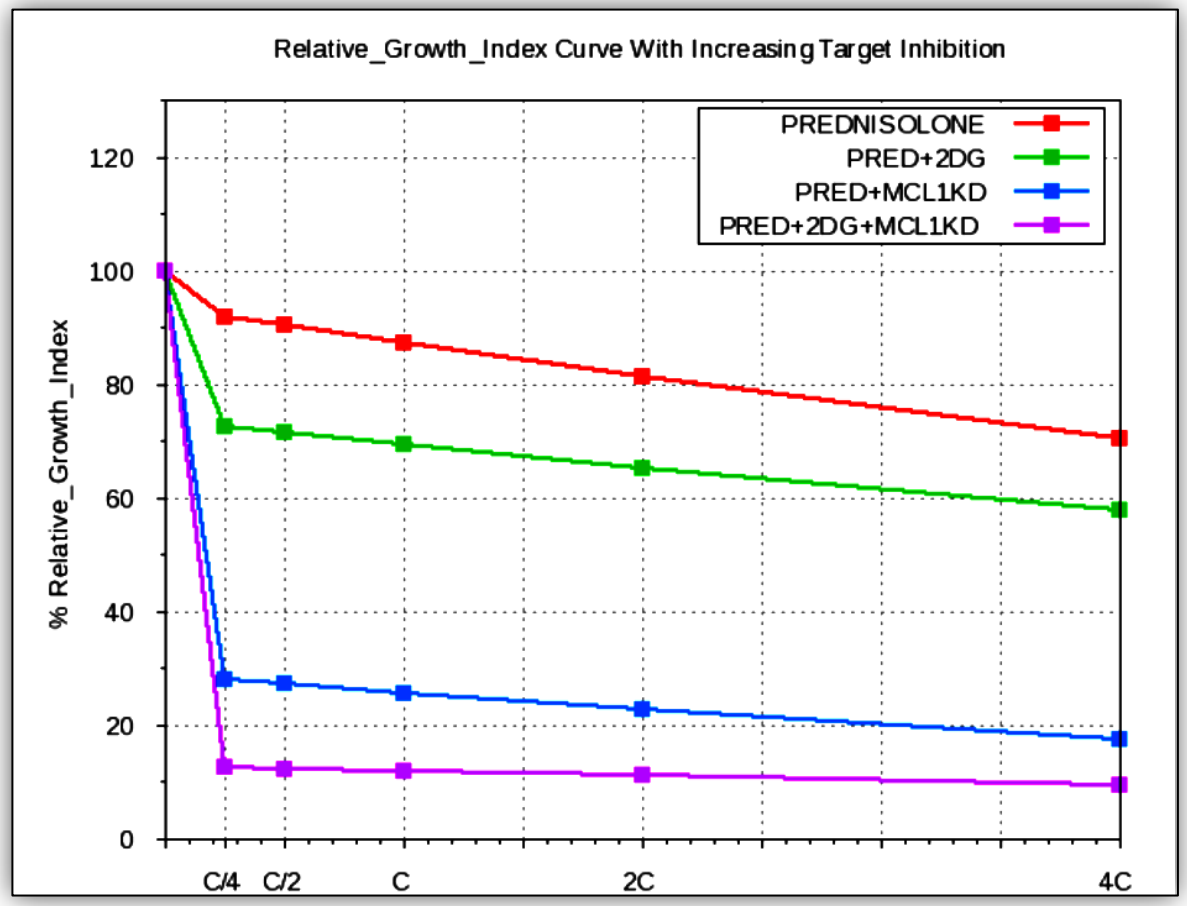
Version dated : November 11, 2017

ETP-ALL Population Level Genomic Analysis



Gene	Frequency
FGFR4 ⇩	25.80 %
FLT3 ⇧	9.68 %
IKZF1 ⇩	9.60 %
NRAS ⇧	32.26 %
PTEN ⇩	25.50 %
DUSP1 ⇩	26.00 %
TP53 ⇩	13.00 %
CDKN1B ⇩	32.20 %
CDKN2B ⇩	25.80 %
TSC2 ⇩	9.60 %
IL7R ⇧	3.20 %
ETV6 ⇩	16.00 %
JAK3 ⇧	6.40 %

⇧ - OE ⇩ - KD



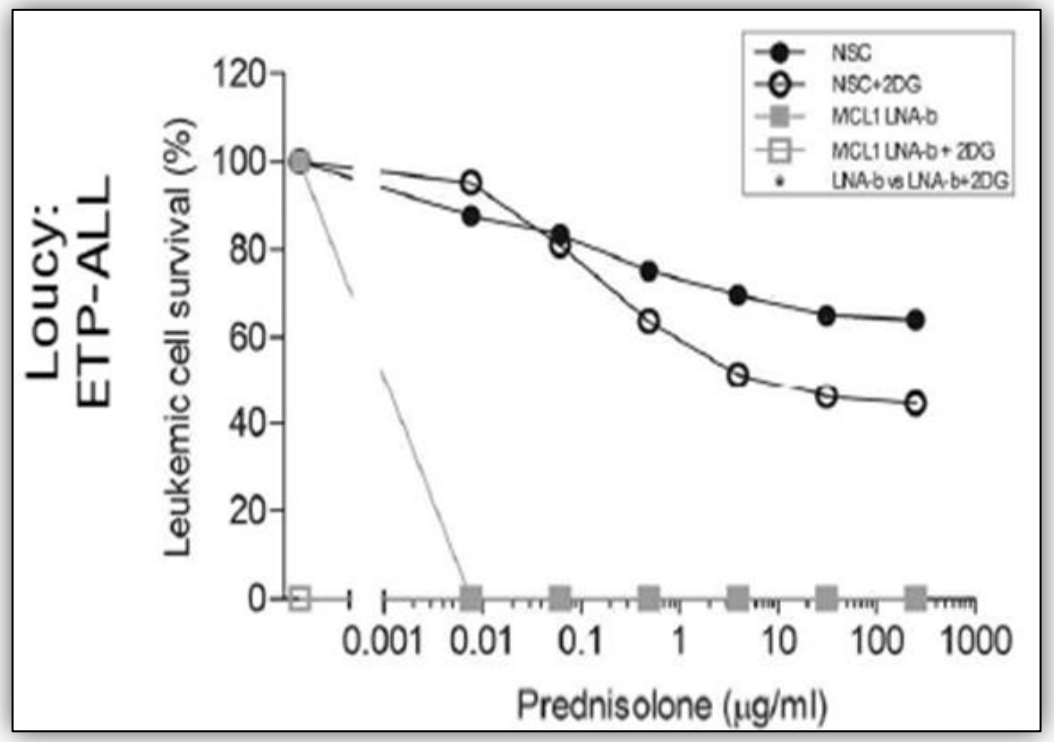
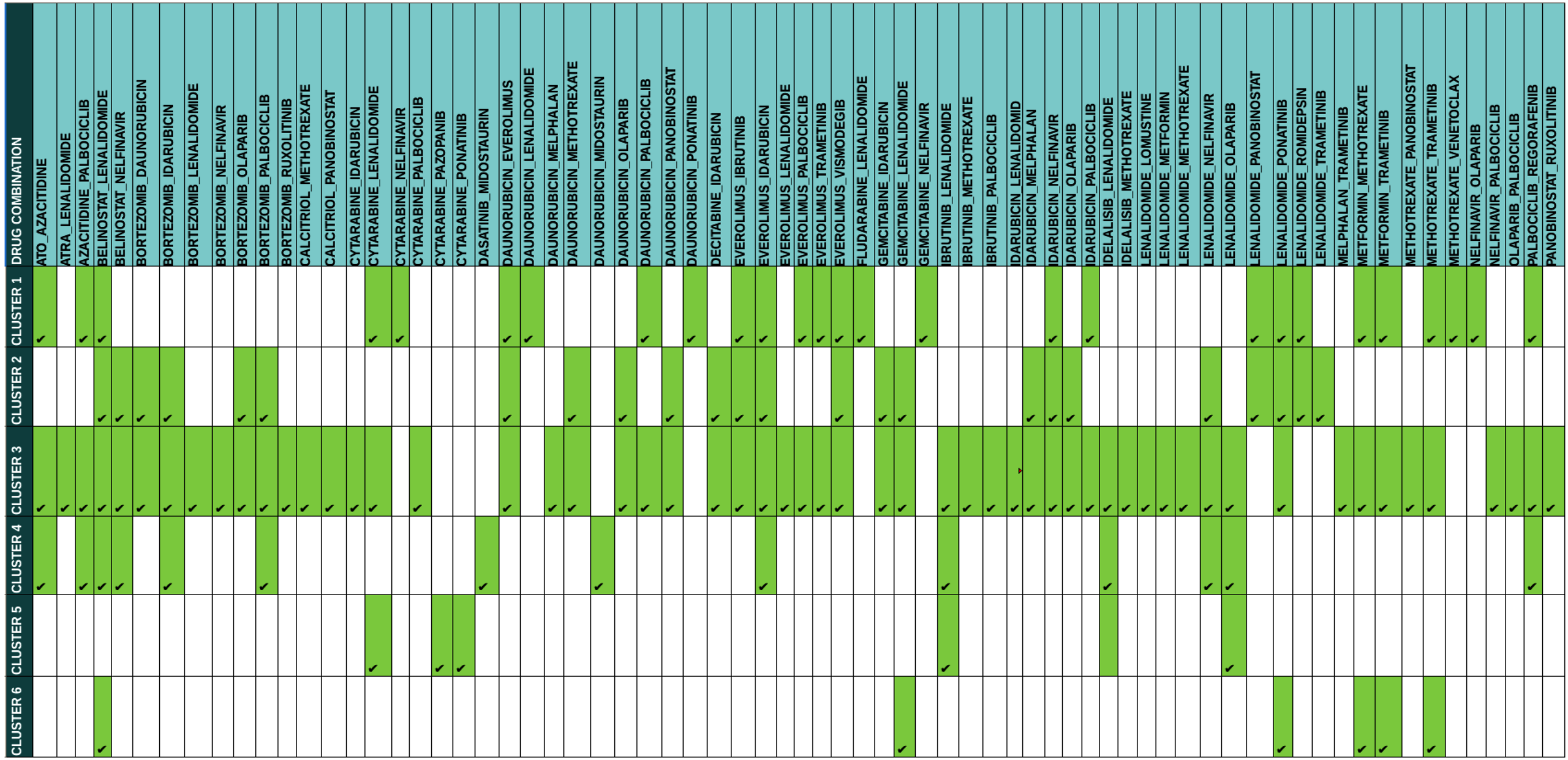


Figure 3: Prednisolone Response in presence of 2 deoxy-glucose and MCL1 silencing. A) Prediction in LOUCY CBM. B) In-vitro validation in LOUCY cell line

ETP- ALL CLUSTERS: THERAPY SELECTION



Early T-cell precursor acute lymphoblastic leukaemia: Unravelling mechanisms of resistance and development of novel therapeutic strategies

Aim: To evaluate the biological basis of differential sensitivity of ETP-ALL to prednisolone, 6-MP and other repurposed drugs to improve the outcomes in this subgroup of patients

Hypotheses

- Understanding the biological basis of differential sensitivity of ETP-ALL to prednisolone and 6-MP and translation of this knowledge in designing the induction therapy, will improve the complete remission rates
- Computational biology modelling in adult ETP-ALL can identify active drugs amongst the FDA approved drugs for other indications

Early T-cell precursor acute lymphoblastic leukaemia: Unravelling mechanisms of resistance and development of novel therapeutic strategies

- **Objective 1:** To demonstrate prednisolone resistance and its biological basis in ETP-ALL compared to non-ETP subtype of T ALL and to evaluate the impact of prednisolone exposure on the chemosensitivity to other drugs used in ALL induction therapy
- **Objective 2:** To demonstrate the exquisite sensitivity of ETP- ALL to 6-MP as compared to other ALL subtypes and its underlying biological basis
- **Objective 3:** In-vitro and in-vivo validation of sensitivity of ETP-ALL to FDA approved drugs as predicted by in-silico analysis
- **Objective 4:** To evaluate the activity of a novel “prednisolone-free” induction regimen using 6-MP in improving the complete responses

Conclusion

- Biologically different disease
- Risk stratified therapy works better
- Need to look at novel approaches