Adult T-cell lymphoblastic leukemia/lymphoma

Lymphoma Tumor Board

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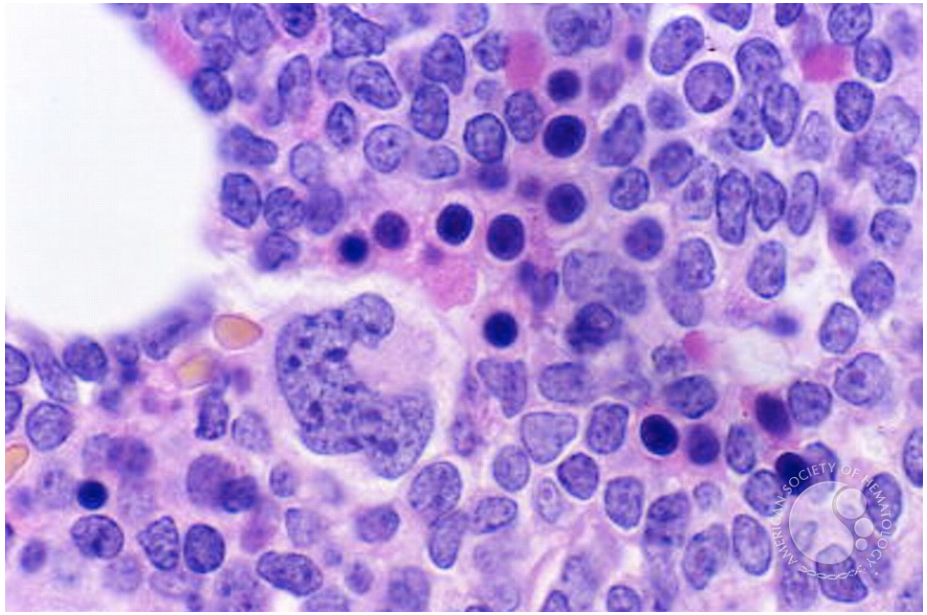
Diagnosis of T-cell lymphoblastic leukemia/lymphoma

- Lymphoblastic lymphoma (LBL) is rare
- Sub-type of lymphoma that is generally of T-cell origin
- Comprises about 2% of all NHLs in adults
- Characteristics are very similar to acute lymphoblastic leukemia (ALL)
- *Patients with predominantly nodal disease at presentation are classified as LBL, whereas those with primarily disease in the marrow or peripheral blood are classified as ALL*
- Historically, no standard of care treatment specifically designed for LBL
- Pathology – antigens usually evaluated at time of diagnosis:
  - CD45 (LCA), CD3, CD2, CD5, CD7, TdT, CD1a, CD10, CD19, CD20, CD79a, kappa/lambda, CD13, CD33, myeloperoxidase

Pathology of T-cell lymphoblastic leukemia/lymphoma

A.



B.

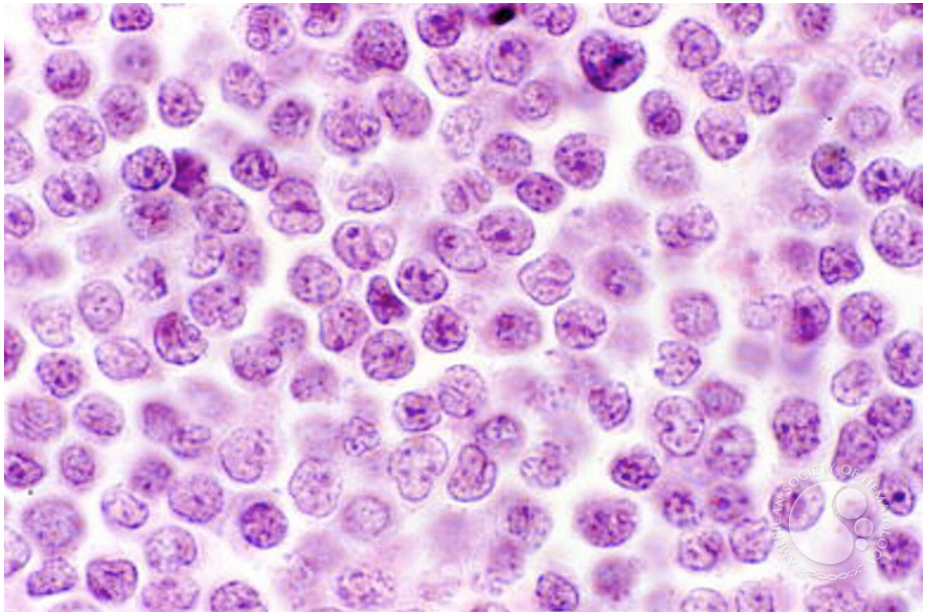


Image A. T-cell lymphoblastic lymphoma/leukemia in bone marrow biopsy. Neoplastic lymphocytes surround residual megakaryocytes and erythroid precursors. H&E section of formalin fixed tissue.

Image B. T-cell lymphoblastic lymphoma/leukemia. Cytology of lymphoblasts reveals medium sized cells with delicate unclumped chromatin, convoluted nuclear membrane and small but distinct nucleoli.

Immunophenotype of lymphoblastic T-cell leukemia/lymphoma

Table 1. T-cell CD antigen expression in pro-, pre-, cortical (thymic), and mature T-cell ALL cyCD3 indicates cytoplasmic CD3; sCD3, surface CD3

	cyCD3	CD7	CD5	CD2	CD1a	sCD3	CD34
Pro-T	+	+	—	—	—	—	±
Pre-T	+	+	+	+	—	—	±
Cortical (thymic)	+	+	±	±	+	±	—
Mature	+	+	±	+	—	+	—

Table 1 Immunophenotypes in T-ALL

Disease Subtype	Immunophenotype
T-Lineage	TdT+, cyCD3+, CD7+
Early	CD2–, sCD3–, CD1a–
Thymic	sCD3±, CD1a+
Mature	sCD3+, CD1a–

Table 2 Clinical Features in Adult T-ALL/T-LBL (GMALL Results)

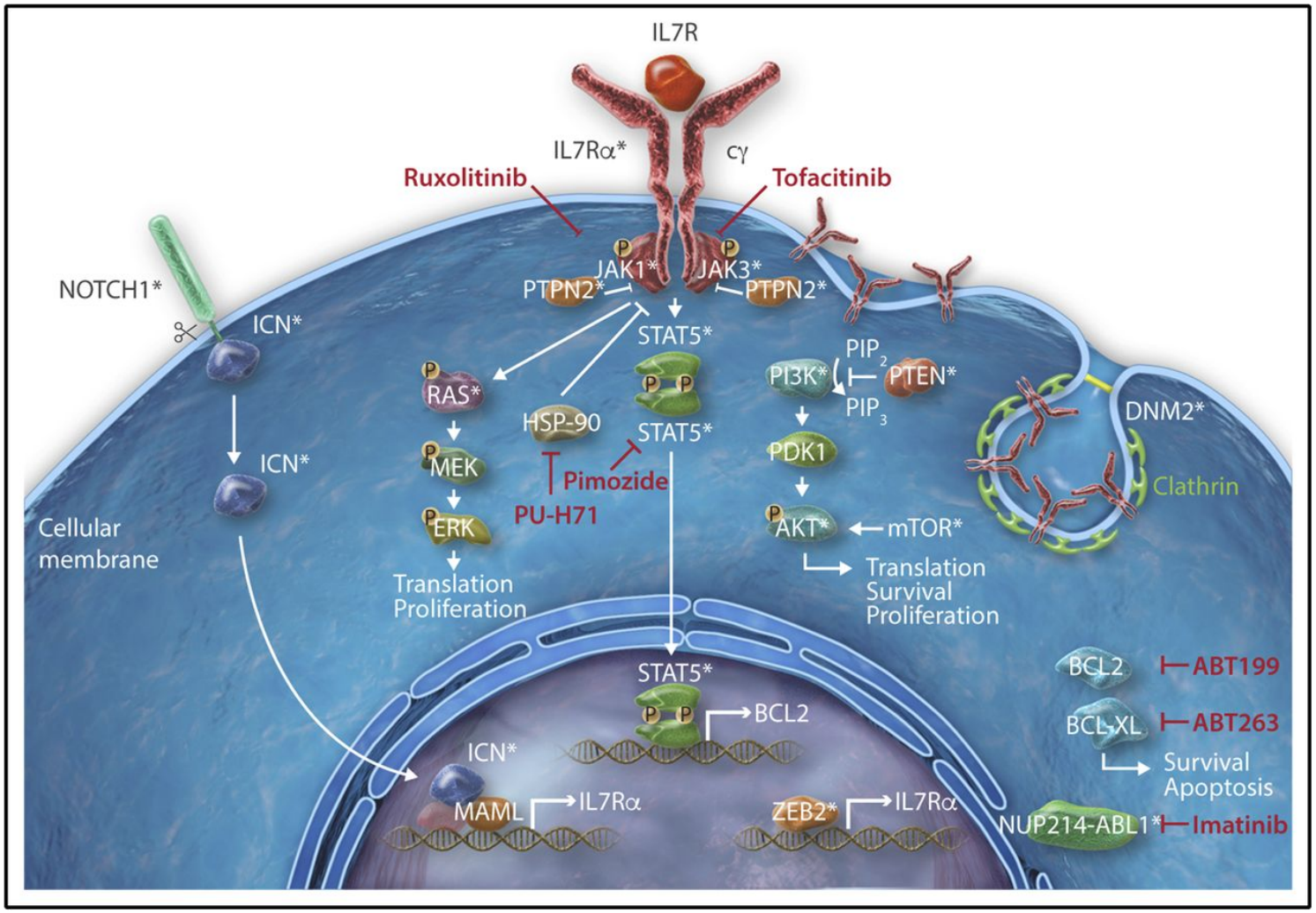
Characteristic	T-ALL (N = 506)	T-LBL (N = 101)
Median Age, Years	30	25
Male Sex, %	70	73
Mediastinal Tumor, %	66	91
Pleural Effusion, %	1	40
CNS, %	7	0-10
BM Involvement, %	100	0-23

Abbreviation: BM = bone marrow; CNS = central nervous system; GMALL = German Multicenter Study Group for Adult ALL

The landscape of genetic alterations in T-ALL

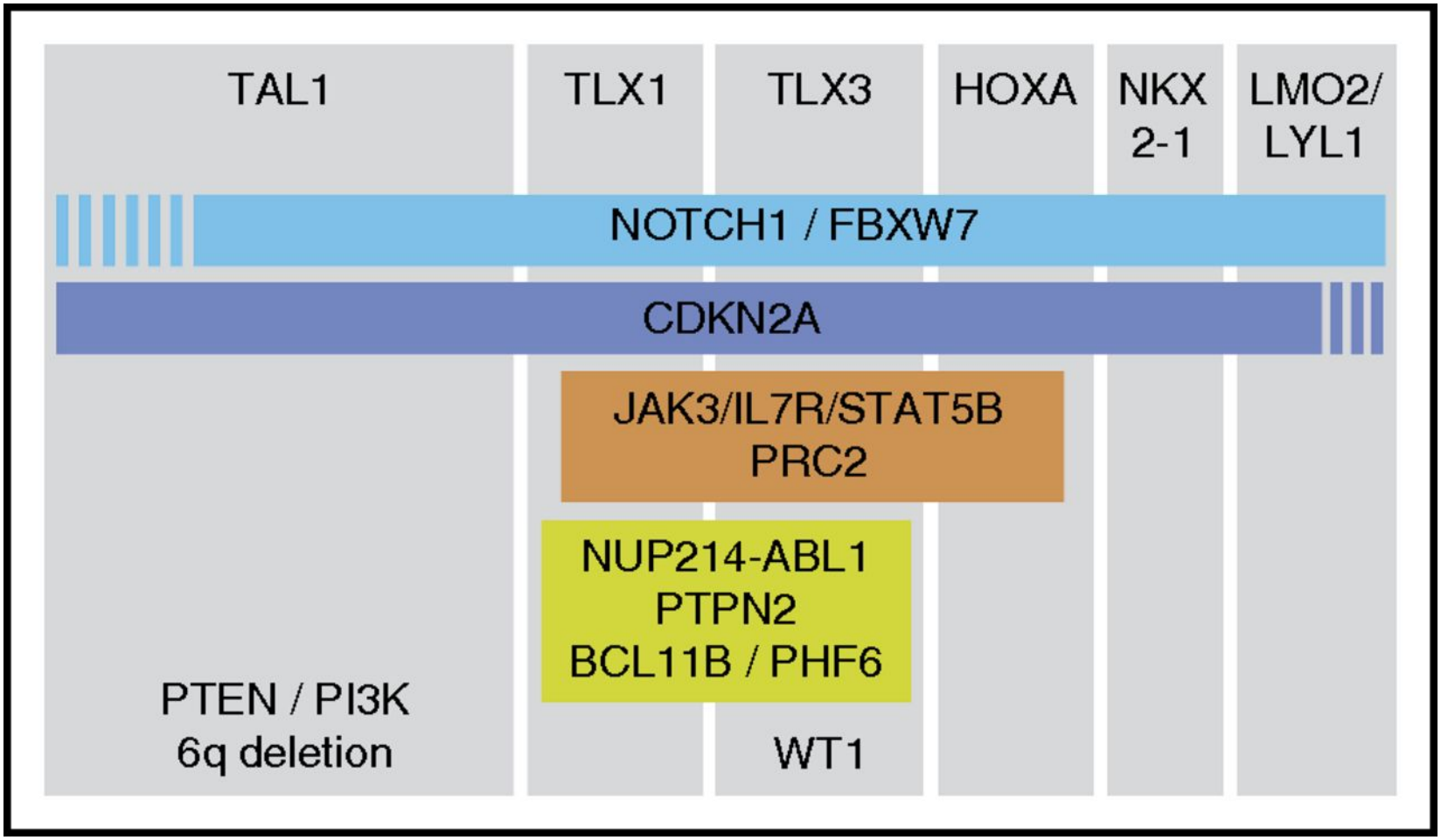
Mark R. Litzow, and Adolfo A. Ferrando Blood 2015;126:833-841

Deregulation of the JAK-STAT signaling cascade in T-ALL



Tiziana Girardi et al. Blood 2017;129:1113-1123

Representation of the cooperation of oncogenic events

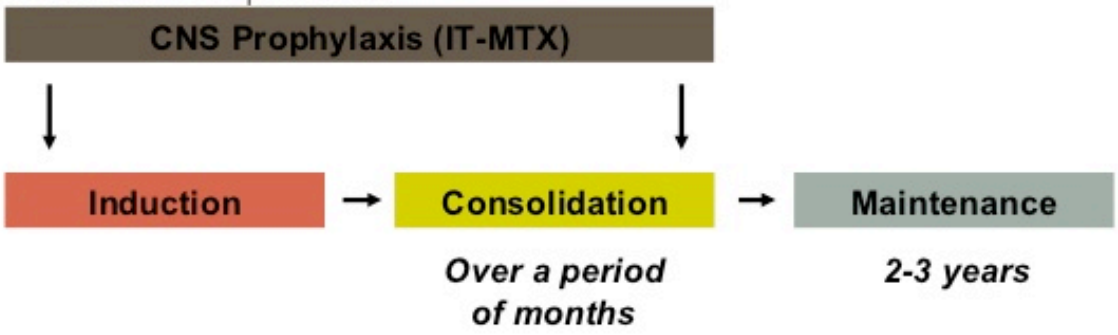


Tiziana Girardi et al. Blood 2017;129:1113-1123

Treatment of ALL - general principles

ALL: TYPICAL TREATMENT

- Primary objective : to achieve and maintain a complete remission (CR)
- Induction, consolidation, maintenance phases
  - CNS prophylaxis with IT-MTX during induction and consolidation phases



Treatment of T-cell lymphoblastic leukemia/lymphoma

- Adaptation of pediatric protocols of intensive chemotherapy and CNS prophylaxis has led to marked improvements in outcomes in adults
- Numerous chemotherapy/radiotherapy regimens are similar in dose and schedule to ALL regimens
- Common features of these regimens include:
  - Induction therapy
  - CNS prophylaxis
  - Consolidation therapy
  - Subsequent maintenance therapy for 12 to 18 months
- Long-term disease-free survival rates between 40-70%

Table 3 Cumulative Treatment Results in Adult Patients With Lymphoblastic Lymphoma[8]

Study Result	No. of Studies	No. of Patients	Median Age, Years	CR, % (Range)	DFS, % (Range)
Conventional NHL	5	114	28-45	58 (53-71)	36 (23-53)
Modified NHL	5	112	14-22	92 (79-100)	49 (23-56)
High-Grade NHL	4	64	25-34	67 (57-84)	51 (35-75)
ALL Protocols	9	282	22-37	80 (55-100)	56 (45-67)

Abbreviations: ALL = acute lymphoblastic leukemia; DFS = disease-free survival; NHL = non-Hodgkin lymphoma

Table 4 Recent Results of ALL-Type Regimens in Adult Patients With Acute Lymphoblastic Lymphoma

Study	Year	Number of Patients	Median Age, Years	Induction	CNS Prophylactic	CR, %	DFS, %
Hoelzer et al[6]	2002	45	25	GMALL 04/89 + 05/93	Intrathecal, CRT	93%	62%
Thomas et al[18]	2004	33	28	fC, V, DX, HDM, HDAC repeated	Intrathecal	91%	70%
Song et al[19]	2007	34	26	ALL-type induction + autoSCT	Intrathecal ± TBI	NR	72%

Abbreviations: autoSCT = autologous stem cell transplantation; CRT = cranial radiation therapy; DX = doxorubicin; fC = fractionated cyclophosphamide; GMALL = German Multicenter Study Group for Adult ALL; HDAC = high-dose cytosine arabinoside; HDM = high-dose methotrexate; NR = not reported; TBI = total-body irradiation; V = vincristine

Intensive induction regimens for ALL

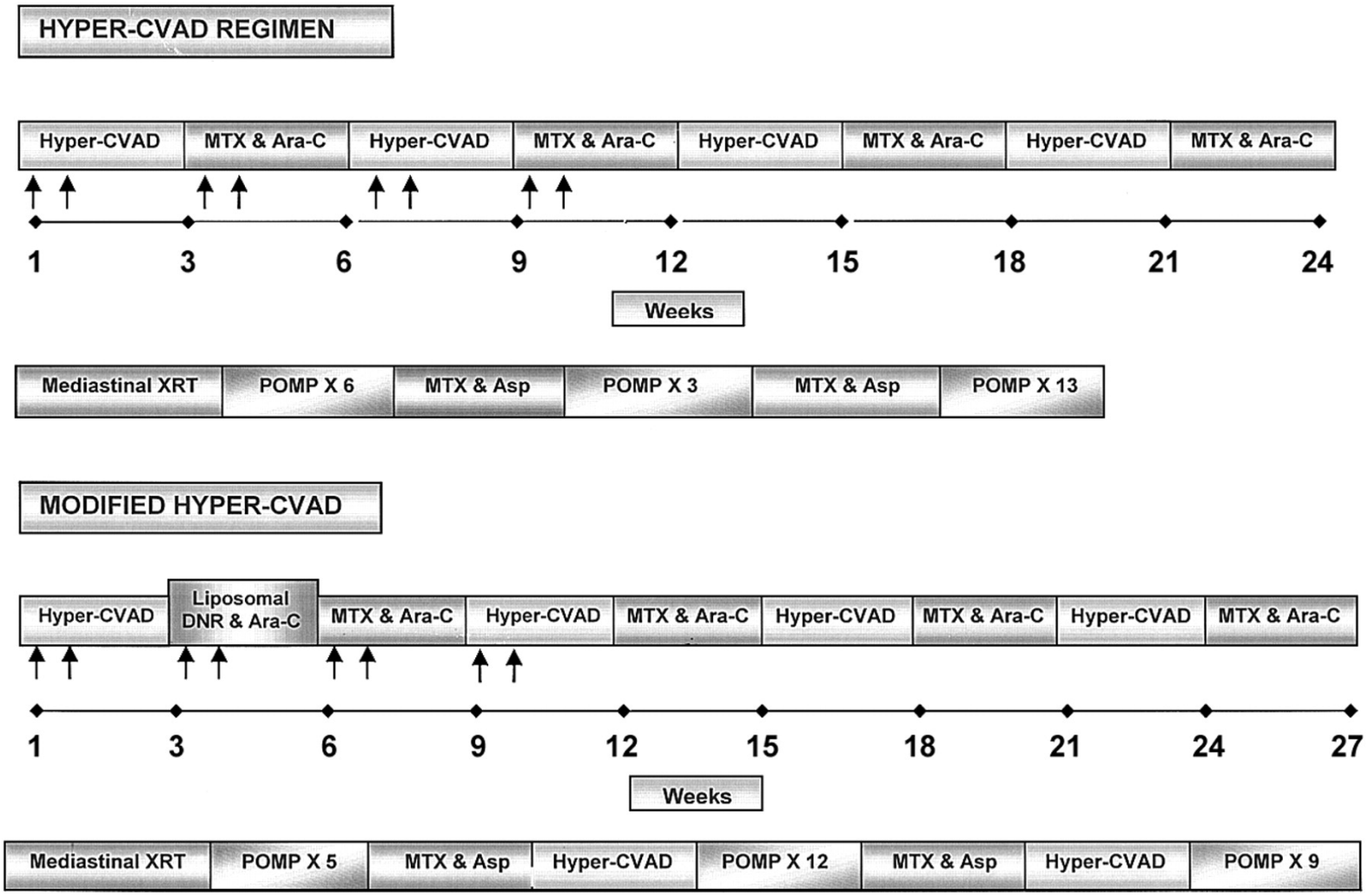
Table 1

Intensive Induction Regimens for Adult Lymphoblastic Lymphoma

Author	Regimen	N	Response Rate	Failure-Free Survival/ Relapse-Free Survival	Overall Survival
Coleman et al [11]	Two ALL-type protocols with intensified CNS	44	100%	3-yr FFS = 56%	NA
Slater et al [12]	Various ALL protocols	51	80% CR for "nonleukemic"; 77% CR for leukemic	NA	5-yr actuarial OS = 45%
Bernasconi et al [13]	Various ALL protocols	31	77% OR	3-yr RFS = 45%	3-yr OS = 59%
Levine et al [16]	Modified LSA_2L_2	15	73% CR; 27% PR	5-yr actuarial FFS = 35%	5-yr actuarial OS = 40%
Weinstein et al [17]	APO	21	95% CR	3-yr actuarial FFS = 58%	5-yr actuarial OS = 69%
Hoelzer et al [18]	Two ALL-type protocols, both including CNS and	45	93% CR	7-yr actuarial DFS = 62%	7-yr actuarial OS = 51%
Thomas et al [19]	HyperCVAD	33	91%	3-yr PFS = 66%	3-yr OS = 70%
Jabbour et al [20]	LMT-89 (ALL-type induction regimen derived	27	85% OR	5-yr FFP = 44%	5-yr OS = 63%
Song	"Hybrid" NHL/ALL regimen	34	100% OR	4-yr EFS = 68%	4-yr OS = 72%

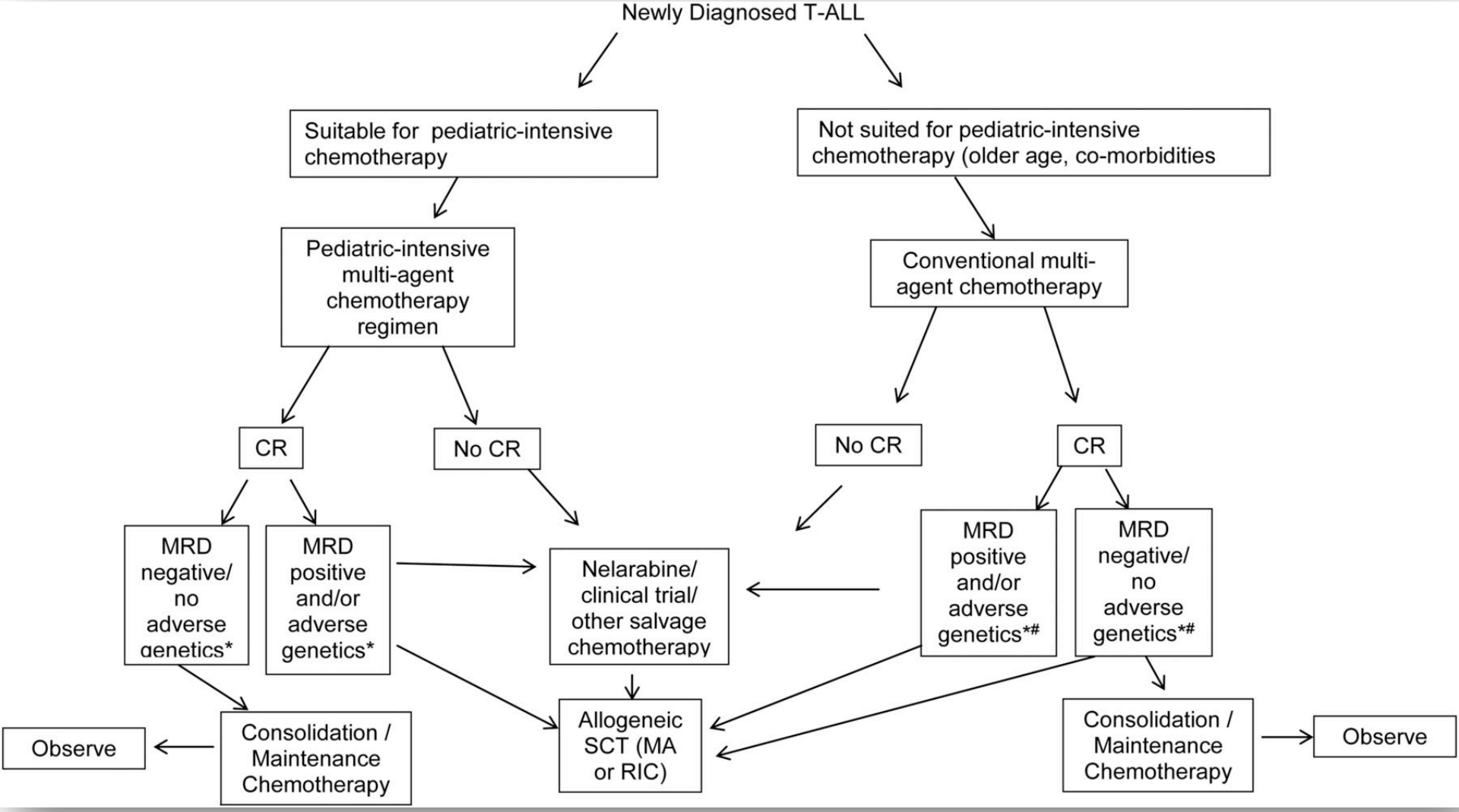
ALL = acute lymphoblastic leukemia; APO = doxorubicin (Adriamycin), prednisone, vincristine (Oncovin); CHOP = cyclophosphamide, hydroxydaunomycin, vincristine, prednisone; CNS = central nervous system; CR = complete response; DFS = disease-free survival; EFS = event-free survival; FFP = freedom from progression; FFS = failure-free survival; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate; IPI = International Prognostic Index; NA = not available; NHL = non-Hodgkin lymphoma; OR = overall response; PR = partial response; RFS = relapse-free survival; SCT = stem cell transplantation.

Schema for the hyper-CVAD and modified hyper-CVAD regimens



Deborah A. Thomas et al. Blood 2004;104:1624-1630

Treatment of T-ALL



Mark R. Litzow, and Adolfo A. Ferrando Blood 2015;126:833-841

Supportive care - ALL

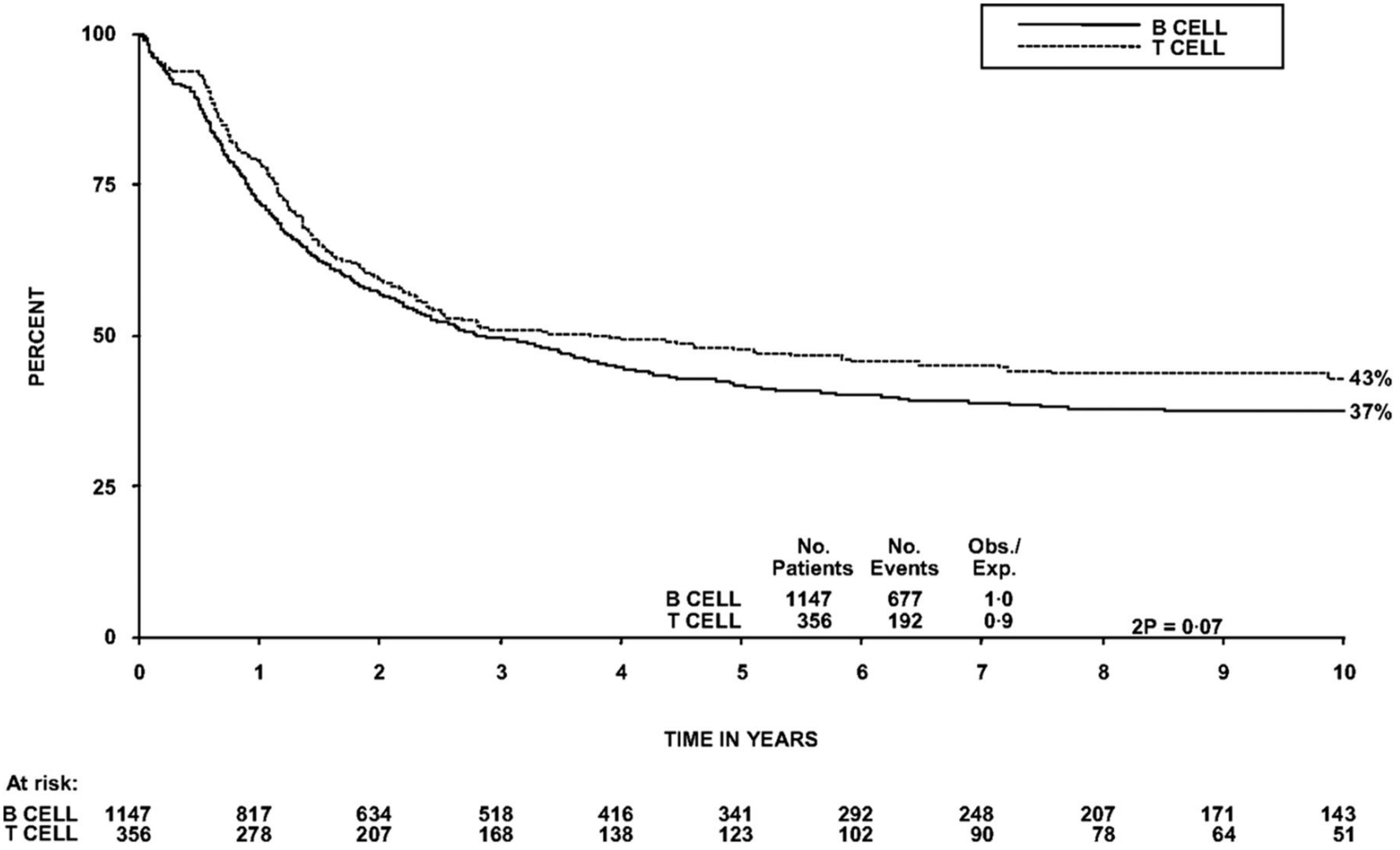
- Allopurinol is recommended for the first 10 days of induction therapy to prevent hyperuricemia.

- Antimicrobial prophylaxis, antiviral and *Pneumocystis jiroveci* pneumonia prophylaxis throughout treatment.

- Fungal prophylaxis should include mould coverage throughout induction therapy.
  - Broader spectrum azole antifungals should be used with caution when using vincristine.

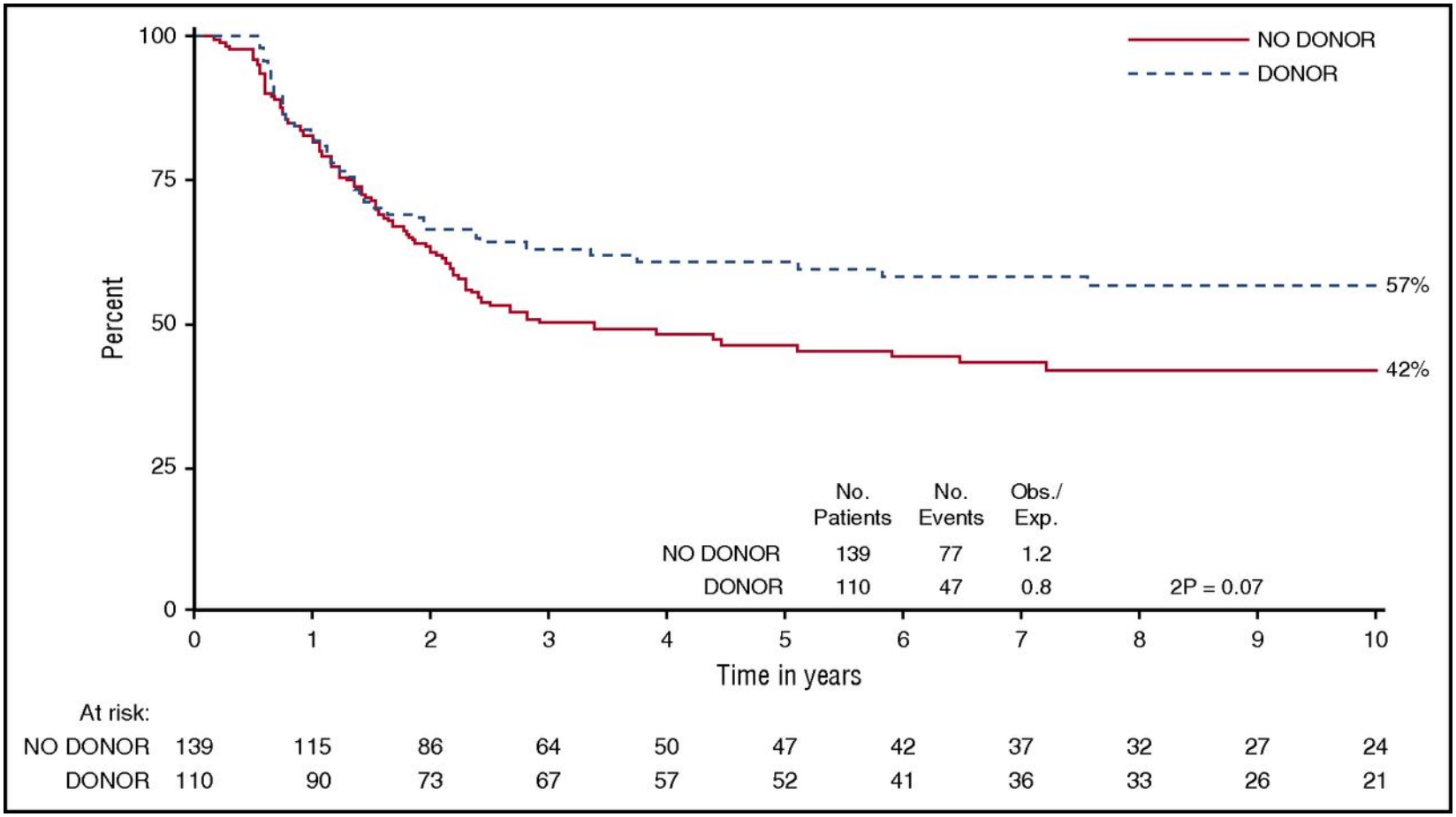
- Asparaginase-related toxicities (used for B-ALL)
  - Asparaginase-related hypersensitivity reactions can occur in 20% of children and adults.

OS from the diagnosis of patients with B- vs T-ALL in the UKALLXII/E2993 trial



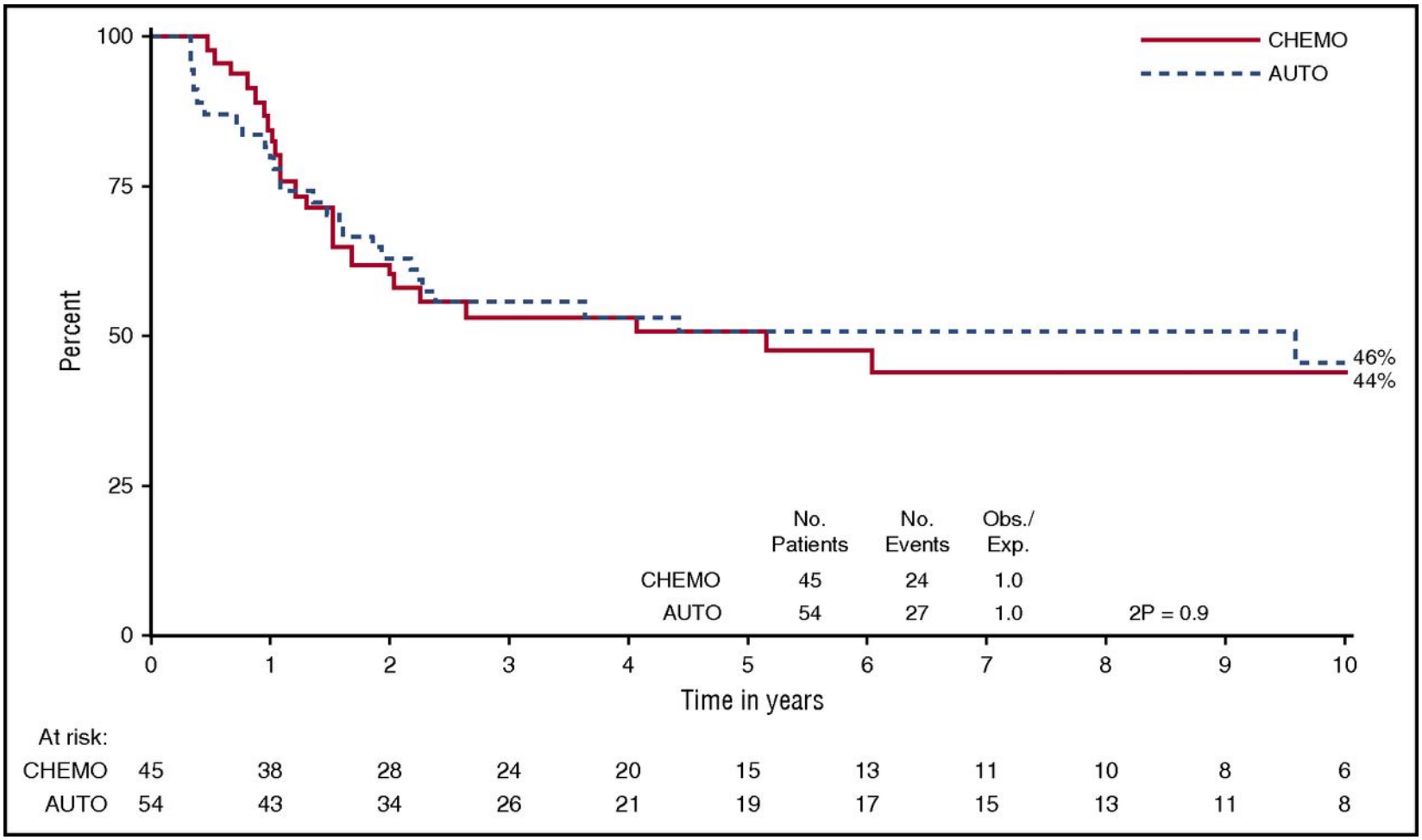
Mark R. Litzow, and Adolfo A. Ferrando Blood 2015;126:833-841

Comparison of OS in patients with T-cell ALL who had a matched sibling donor vs. those without a donor within the UKALL XII/E2993 trial



David I. Marks, and Clare Rowntree Blood 2017;129:1134-1142

Comparison of OS in patients with T-cell ALL treated with autologous stem cell transplantation (auto) or chemotherapy (chemo) within the UKALL XII/E2993



David I. Marks, and Clare Rowntree Blood 2017;129:1134-1142

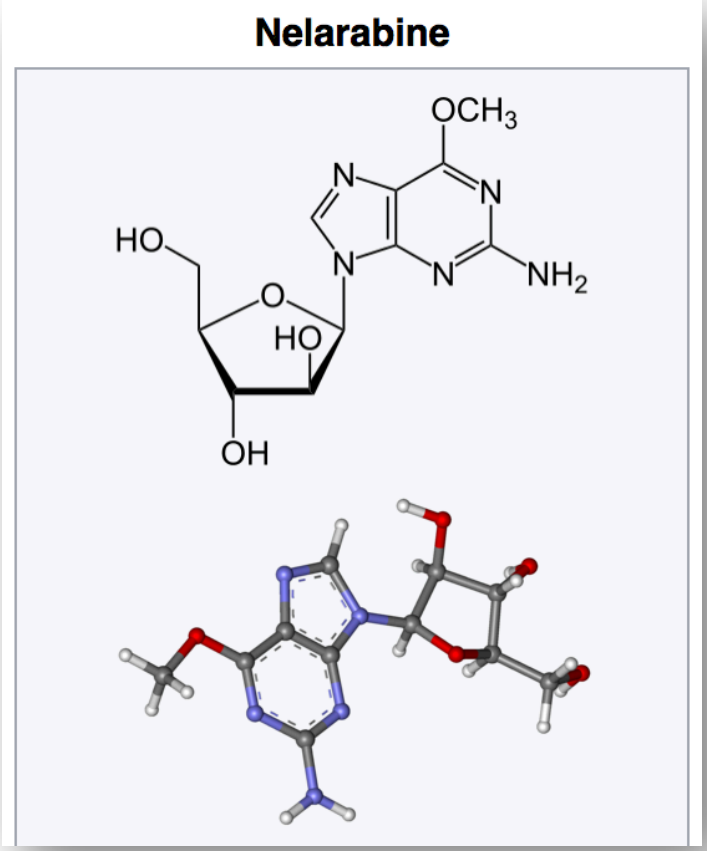
Table 7 Results of SCT in adult B/T-LBL[8]

Treatment Result	N	DFS, % (Range)
Auto CR1	241	61 (31-77)
Auto > CR1	15	47 (43-50)
Allo CR1	30	74 (59-91)
Allo > CR1	32	16 (14-17)

Results of most of the studies were not separated by B- or T-LBL.
Abbreviations: allo = allogeneic; auto = autologous; CR1 = first complete remission; DFS = disease-free survival; SCT = stem cell transplantation

Nelarabine

- Arabinonucleoside antimetabolite with antineoplastic activity
- Metabolized to ara-G; inhibits DNA synthesis, leads to apoptosis
- Approved by US FDA in October of 2005 for ALL and T-cell lymphoblastic lymphoma that has not responded to treatment
- Also approved by the EU in October of 2005
- Complete responses have been achieved with Nelarabine



bjh research paper

Safety and efficacy of nelarabine in children and young adults with relapsed or refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of a phase 4 study

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Summary

Nelarabine is an antineoplastic agent approved for the treatment of relapsed/refractory T-lineage acute lymphoblastic leukaemia (T-ALL) or T-lineage acute lymphoblastic lymphoma (T-LBL). The purpose of this phase 4, multicentre, single-arm, observational, open-label trial was to provide additional data on the safety and efficacy of nelarabine under licensed conditions of use in children and young adults ≤21 years of age. Patients ($N = 28$) had a mean ± standard deviation age of 11·5 ± 4·6 years; 71% were male and 61% had a diagnosis of T-ALL. Adverse events (AEs) and treatment-related AEs were experienced by 46% and 21%, respectively, and included few haematological AEs and no haematological serious AEs. Neurological AEs from one of four predefined categories (peripheral and central nervous systems, mental status change and uncategorized) were reported in four patients. There were no AE-related treatment discontinuations/withdrawals. The overall response rate was 39.3%: complete response (CR), 35.7%; CR without full haematological recovery (CR*), 3.6%. Post-treatment stem cell transplantation was performed for 46% of the cohort. Median overall survival (OS) was 3·35 months for non-responders and not reached for responders (CR + CR*). The response rate, median OS, and safety profile of nelarabine in this disease setting and population were consistent with those reported previously.

Keywords: nelarabine, paediatric, acute lymphoblastic leukaemia, acute lymphoblastic lymphoma, T-lineage.

Efficacy of Nelarabine in a phase 4 trial

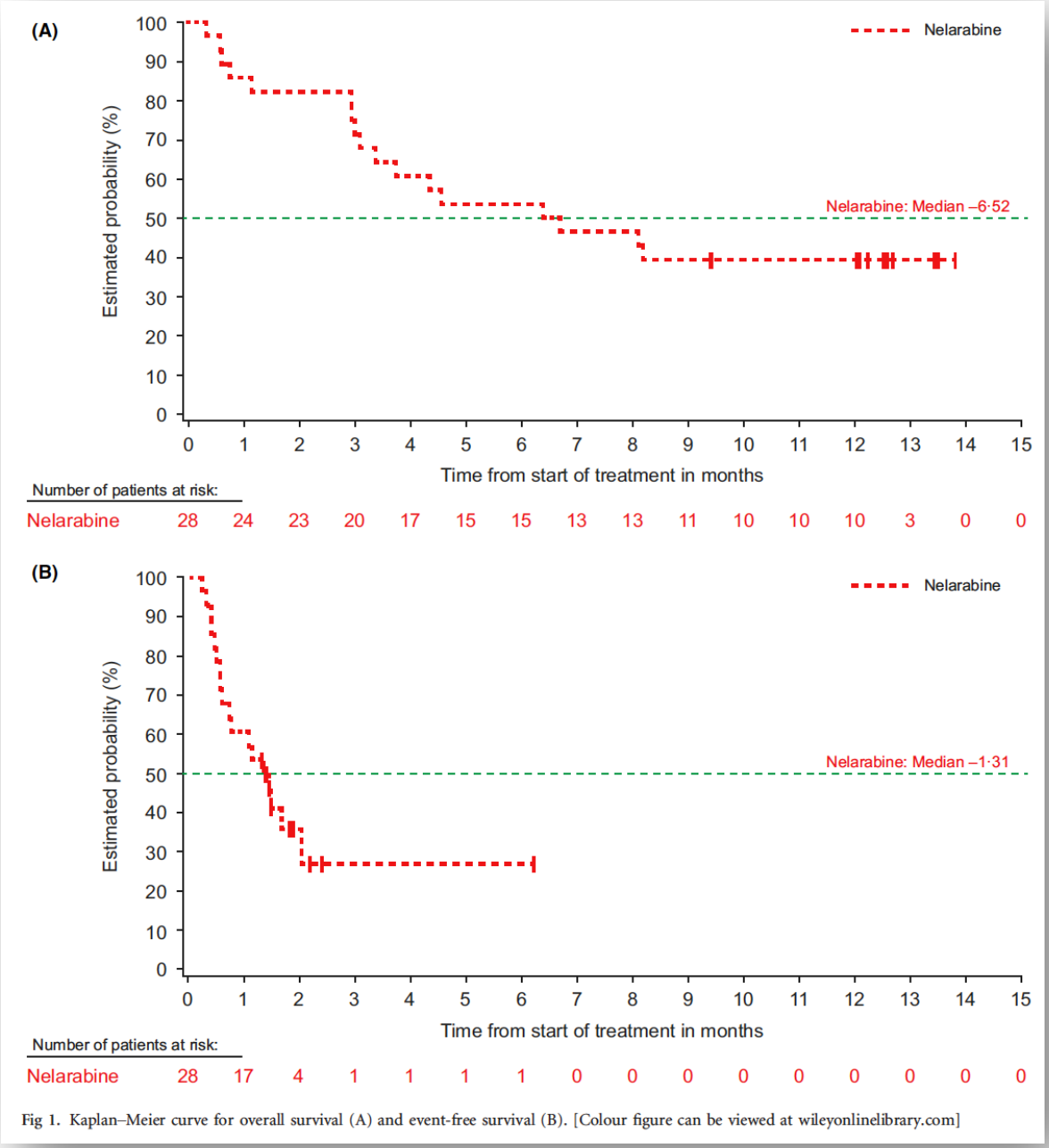

Fig 1. Kaplan–Meier curve for overall survival (A) and event-free survival (B). [Colour figure can be viewed at wileyonlinelibrary.com]

Efficacy of Nelarabine in a phase 4 trial

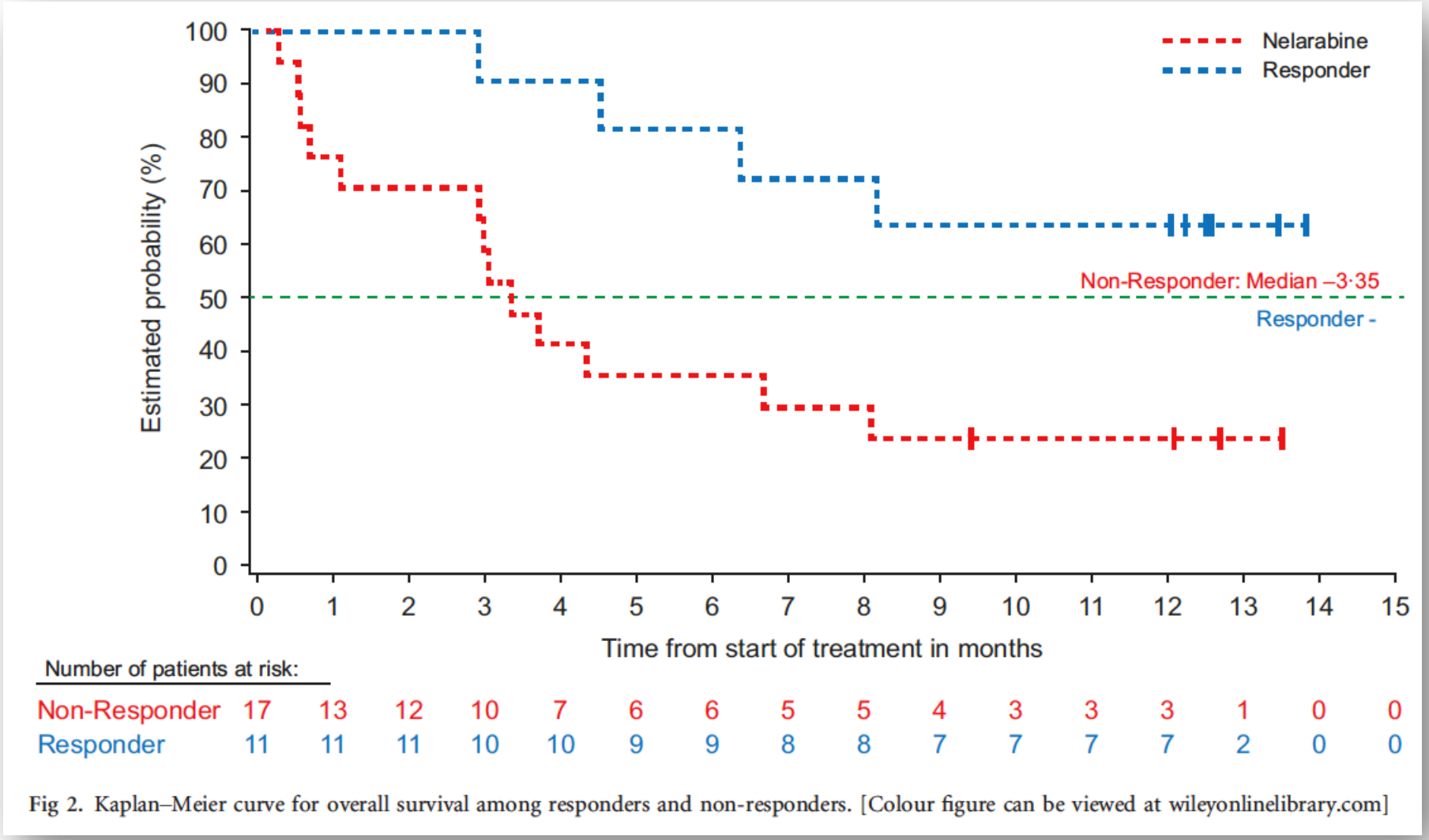

Fig 2. Kaplan–Meier curve for overall survival among responders and non-responders. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 5 Mediastinal Relapses in Adult T-ALL/T-LBL (GMALL Results)

Study Proposal	T-ALL		T-LBL	
	Prophylactic, All Patients	Therapeutic Only if Residual Mediastinal Tumor	Therapeutic, All Patients	Therapeutic, All Patients
Mediastinal Radiation Dose	24 Gy	24 Gy	24 Gy	36 Gy
Relapses				
Total	61	251	15	10
Mediastinal	1 (~1%)	9 (3%)	7 (47%)	3 (30%)

Abbreviations: GMALL = German Multicenter Study Group for Adult ALL; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma

Table 6 Potential Adverse Prognostic Factors in Adult ALL

Prognostic Factor at Diagnosis	All	B-Precursor	T-ALL
High WBC	–	> 30,000/µL	> 100,000/µL ±
Immunophenotype	–	pro-B, CD10 neg pre-B	Early T, Mature T, CD56
Cytogenetics/Molecular Genetics	Complex karyotype, Dic (9), High hyperdiploid	t(9;22)/BCR-ABL, t(4;11)/ALL1-AF4 (pro-B), t(1;19)/PBX-E2A, t(12;21)/TEL-AML1	ERG, BAALC, SIL-TAL1, HOX11L2, NUP214-ABL, HOX11

Abbreviations: ALL = acute lymphoblastic leukemia; WBC = white blood cell count

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