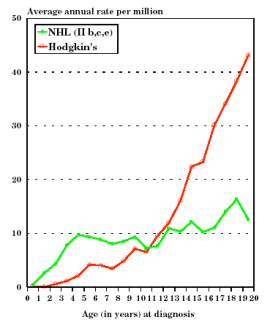
Incidence: Lymphoma

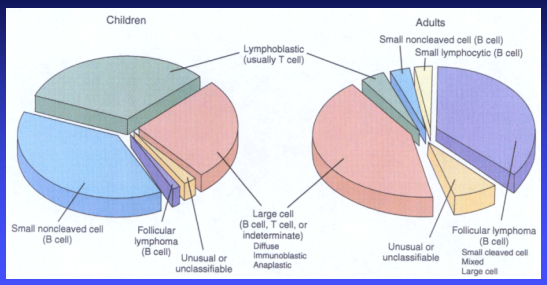


All cancers: 14/100,000

Cases/year USA (age < 16)
Total: 1,700
Hodgkin's: 850-900
NHL: 750-800

Reis et al (eds), NCI SEER Program 1975-1995, NIH Pub No 99-4649, 1999

Distribution of NHL Subtypes



Sandlund, Downing, Crist: NEJM, 1996

NHL in Childhood

- 750-800 cases/year USA (~1/100,000)
- 90% high-grade
- 2/3 advanced stage (3-4)
- Demographics
  - Males > Females (2-3:1)
  - Whites > Blacks (2:1)

Staging

Stage	Ann Arbor Staging (Hodgkins)	St. Jude (Murphy) Staging (NHL)
I	♦Single node region or extranodal site (IE)	♦Single site (excluding abdomen or mediastinum)
II	♦≥ 2 node regions, same side of diaphragm +/- • Localized contiguous extranodal site (IIE)	♦Single extranodal site with regional nodes ♦ ≥ 2 nodal sites, same side of diaphragm ♦2 extranodal sites, same side of diaphragm ♦Primary GI, completely resected (IIR)
III	♦ ≥ 2 node regions, both sides of diaphragm + • Localized contiguous extranodal site (IIIE • Spleen (IIIS) or • Both (IIIES)	♦2 extranodal sites, both sides of diaphragm ♦≥ 2 nodal sites, both sides of diaphragm ♦Primary thoracic ♦Primary GI, extensive ♦Paraspinal, epidural
IV	♦ Bone Marrow or Liver • Diffuse extranodal disease not encompass in a single radiation field.	♦ CNS and/or bone marrow (< 25%)
	♦ E: Single extranodal site contiguous with a known nodal site ♦ A: No symptoms ♦ B: Fever, weight loss, night sweats	

Burkitt's Grouping System

Group A
- Completely resected Stage I or abdominal Stage II

Group B
- Not Groups A or C

Group C
- Any CNS and/or marrow ≥ 25% blasts

NHL: Presentation

Extranodal Sites Common in Pediatrics
- 37% Abdomen
- 29% Head & Neck
- 26% Mediastinum

NHL: Presentation by Subtype

Lymphoblastic Lymphoma

- Lymphadenopathy: neck, supraclavicular, axillary
- Anterior Mediastinum
- Effusions: Pleural, Pericardial
- Liver, Spleen
- Bone Marrow
- CNS

NHL: Presentation by Subtype

Burkitt's Lymphoma

- Abdomen
- Lymphadenopathy: Mesentery, Retroperitoneum
- Intussusception
- Head & Neck
  - **Jaw**
  - **Orbit**
- Bone Marrow
- CNS

NHL: Presentation by Subtype

Large Cell Lymphoma

- Head & Neck
- Lymphadenopathy
- Mediastinum
- Soft Tissue
  - **Skin**
  - **Bone**
  - **GI**
- CNS (rare)

NHL: Presentation by Subtype

Anaplastic Large Cell Lymphoma (ALCL)

- Lymphadenopathy
- Mediastinum
- Soft Tissue
  - **Skin,** Bone, Lung
- Bone Marrow
- Systemic ("B") symptoms common
- CNS (rare)
- Age < 30 years
- M:F ratio 6.5:1

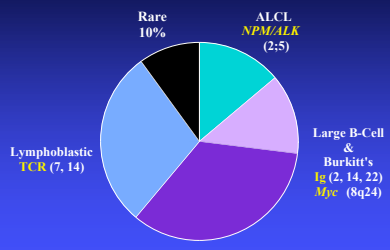
NHL: Oncologic Emergencies

- Tumor Lysis Syndrome
- Superior Vena Cava Syndrome
- Tracheal Compression
- Pericardial, Pleural Effusion
- Hyperleukocytosis
- Cytopenias
- Intussusception
- Spinal Cord Compression

Tracheal Compression

- Emergent diagnosis
  - Airway imaging: CXR, CT
  - Rapid, non-invasive tissue diagnosis if possible
    - CBC, bone marrow, thoracocentesis, node biopsy
  - Avoid intubation
- Emergent consultation
  - Surgery, Radiation Oncology, Hematology-Oncology
- Emergent intervention
  - Oxygen
  - Steroids: Dexamethasone 10mg IV, then 4mg q 6 hours
  - Radiation
  - Chemotherapy

NHL: Chromosomal Translocations



Data from Reis: NCI SEER Program, NIH, 1999

NHL: Lymphoblastic Lymphoma

- T-cell phenotype
- TdT +
- TCR translocations (30-50%)
  - 14q11 TCR-α/γ
  - 7q34-q36 TCR-β

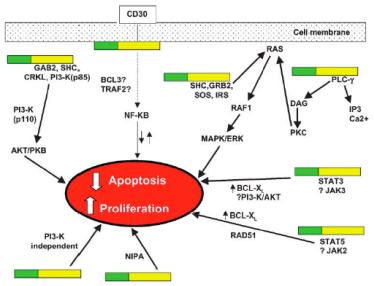
NHL: Burkitt & B-Large Cell Lymphoma

- B-cell phenotype
- s-IgM +
- Immunoglobulin gene/c- *myc* translocations
  - c-*myc* (8q24)
  - IgH (14q32)
  - Igκ (2p11)
  - Igλ (22q11)
  - t(8;14)(q24;q32) **80%**
  - t(8;22)(q24;q11)
  - t(2;8)(p11;q24)

NHL: Anaplastic Large Cell Lymphoma

- T-cell phenotype
- CD30 + (Ki-1)
- t(2;5)(p23;q35) → *NPM/ALK*
  - *NPM*: nucleophosmin
  - *ALK*: anaplastic lymphoma kinase
  - *NPM/ALK* cytoplasmic localization

NPM-ALK ( ) Signaling Pathways



NHL: Pathogenesis

Infection
- EBV
- HTLV

Acquired Immunodeficiency
- HIV
- Post-Transplant

Congenital immunodeficiency & lymphoproliferative syndromes

Hodgkin's Disease, post-treatment

Radiation

Toxic
- Organic solvents
- Insecticides

Immunodeficiency Cancer Registry

	Tumors	NHL	Hodgkin's
Ataxia-Telangiectasia	145	67 (46%)	15 (10%)
Common Variable ID	116	54 (47%)	9 (8%)
Hyper-IgM	17	10 (59%)	4 (24 %)
Hypogammaglobulinemia	21	7 (33%)	3 (14 %)
IgA Deficiency	37	6 (16%)	3 (8%)
Severe Combined ID	42	31 (74%)	4 (10%)
Wiskott-Aldrich	79	59 (75%)	3 (4%)
Other	24	11 (46%)	1 (4 %)
TOTAL	481	245 (51%)	42 (9%)

Filipovich AH et al: Am J Pediatr Hematol Oncol. 1987 9(2):183-4

NHL: Immunodeficiency Cancer Registry

NHL Risk	up to 100-fold
NHL Incidence	15-25% (WAS, AT, CVID)
Age at Diagnosis	7 years (1 - 23)
Histology	Large cell, Burkitt's
Phenotype	B > T

Primary Sites

- 8% CNS
- 9% GI
- 10% Lymph Nodes
- 22% Multiple

NHL: HIV-Associated

NHL Risk	up to 200-fold
NHL Incidence	~3%
Phenotype	>90% B-lineage
Histology	Burkitt 40%, Large cell 30%
	Immunonoblastic 30%

Pathobiology

HIV DNA not directly incorporated into tumor genome

Indirect contribution postulated via

- cytokine dysregulation
- chronic B-cell stimulation/proliferation
- impaired immune surveillance

EBV, esp in primary CNS lymphoma

HHV-8, esp in primary effusion lymphoma

Autoimmune Lymphoproliferative Syndrome (ALPS): *Lymphoma Risk*
NIH ALPS Database

Non-Hodgkin's
- 5/130 cases
- *RR 14* [95% CI 5 – 33] p<0.001

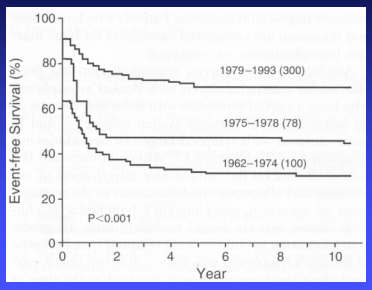
Hodgkin's
- 5/130 cases
- *RR 51* [95% CI 17 – 119] p<0.001

From Straus et al: Blood 2001;98:194-200

ALPS & Lymphoma

Consider ALPS with lymphoma and
- Young age
- Autoimmunity
- Cytopenias
- Splenomegaly
- Immunodeficiency
- + Family history

Survival of Children with NHL
St. Jude Children's Research Hospital, 1962-1993



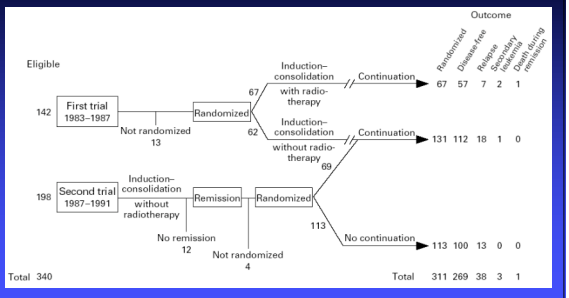
Sandlund, Downing, Crist: NEJM, 1996

NHL: Treatment

	COMP *vs.*	LSA_2L_2
Burkitt's	*better*	*worse*
Lymphoblastic	*worse*	*better*
Large Cell	*no difference*	

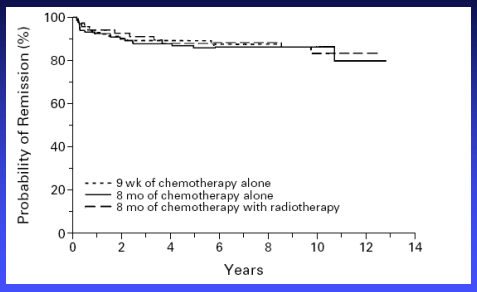
CCSG: NEJM, 1983

NHL: Treatment of Low Stage Disease



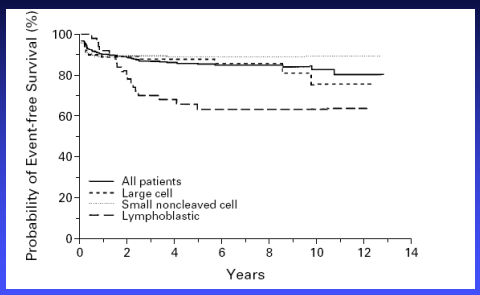
Link et al: NEJM, 1997

NHL: Treatment of Low Stage Disease



Link et al: NEJM, 1997

NHL: Treatment of Low Stage Disease

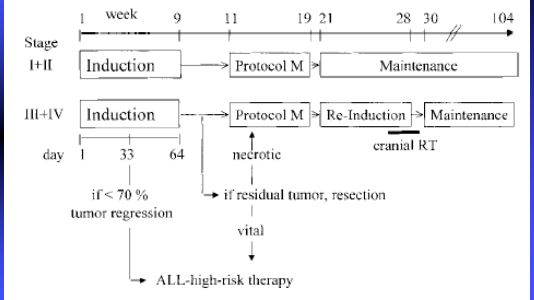


Link et al: NEJM, 1997

Lymphoblastic Lymphoma: Treatment Results

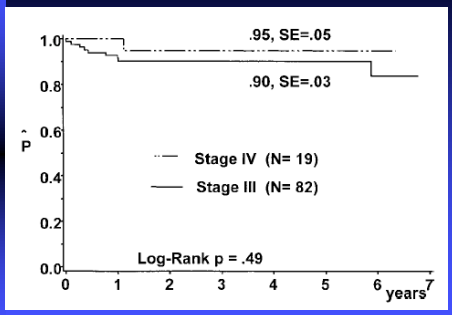
Regimen	Treatment	No. of Patients	Stage				
			All	I/II	III/IV	III	IV
BFM 90	7-drug induction, consolidation, re-induction, maintenance; 24 months	109	90% (5yr)		90% (5yr)	90% (5yr)	95% (5yr)
BFM 95	7-drug induction, consolidation, re-induction, maintenance; 24 months	156			82% (5yr)		
DFCI 87/91/95	4-5-drug induction, consolidation, maintenance; 24 months	15			87% (5yr)		
EORTC 58881	4-drug induction, consolidation, re-induction, maintenance; 24 months	60			76% (6yr)		
LMT 81	5-drug induction, consolidation, maintenance; 24 months	82	75% (5yr)	73% (5yr)		79% (5yr)	72% (5yr)
LSA_2L_2	4-drug induction, consolidation, maintenance; 24-36 months	68	75% (5yr)	88% (5yr)		85% (5yr)	74% (5yr)

T-NHL: Treatment BFM-90



Reiter: Blood, 2000

T-NHL: Treatment BFM-90

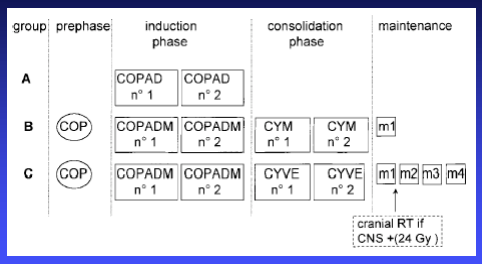


Reiter: Blood, 2000

B-NHL: Treatment Results

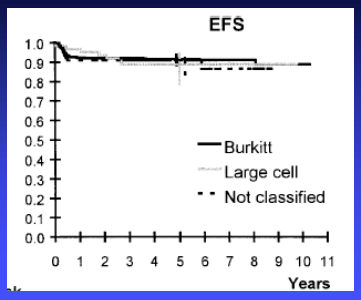
Regimen	No. of Patients	Histology (No.)	Stage (%)	CR (%)	EFS (%)	OS (%)
LMB 89	561 (peds)	Burkitt L3 ALL (420)	III-IV 79%	97%	92% (5 yrs)	92% (5 yrs)
Modified LMB	72 (adults)	Burkitt L3 ALL	III-IV 67%	72%	65% (2 yrs)	70% (2 yrs)
GMALL B-NHL 86	35	L3 ALL	N/A	74%	71% (4 yrs DFS)	51% (4 yrs)
BFM 90	413	Burkitt L3 ALL (322)	III-IV 60%	N/A	89% (6 yrs)	14 deaths
NCI 89-41 CODOX-M / IVAC	21 peds 20 adult	Burkitt	III-IV 78%	95%	85% (peds) 100% (adults) (2 yrs)	2 deaths
CODOX-M / IVAC	52	Burkitt	III-IV 61%	77%	65% (2 yrs)	73% (2 yrs)
Hyper-CVAD	26	L3 ALL	N/A	81%	61% (3 yrs DFS)	49% (3 yrs)

B-NHL: Treatment SFOP LMB89



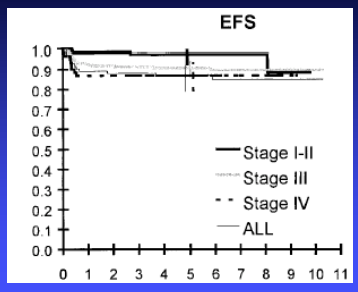
Patte: Blood, 2001

B-NHL: Treatment SFOP LMB89



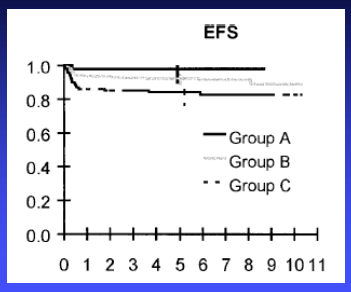
Patte: Blood, 2001

B-NHL: Treatment SFOP LMB89



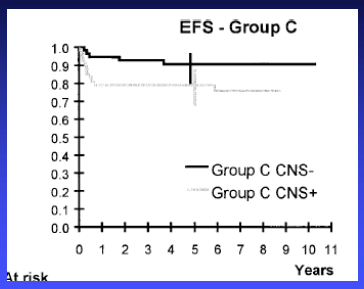
Patte: Blood, 2001

B-NHL: Treatment SFOP LMB89



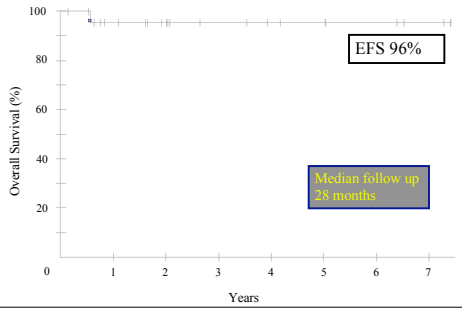
Patte: Blood, 2001

B-NHL: Treatment SFOP LMB89

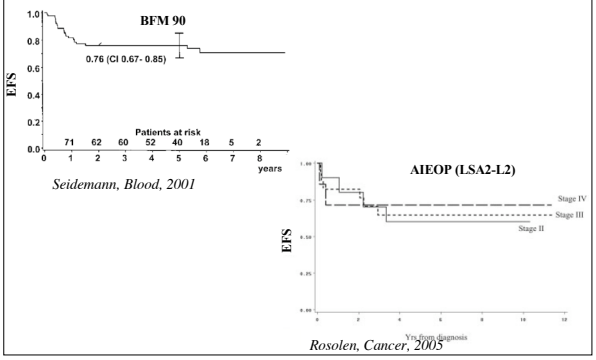


Patte: Blood, 2001

Burkitt NHL
EPOCH-R Pilot



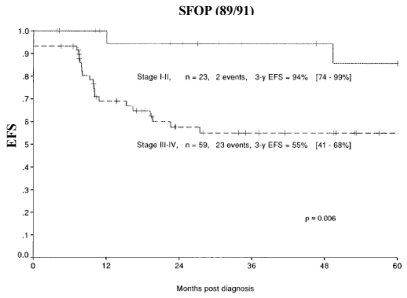
ALCL: Treatment



Seidemann, Blood, 2001

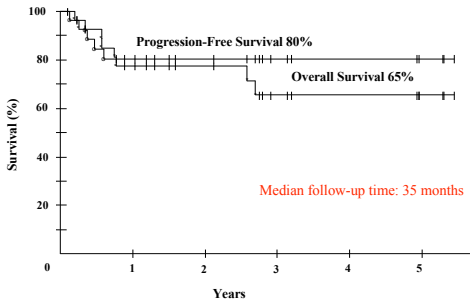
Rosolen, Cancer, 2005

ALCL: Treatment



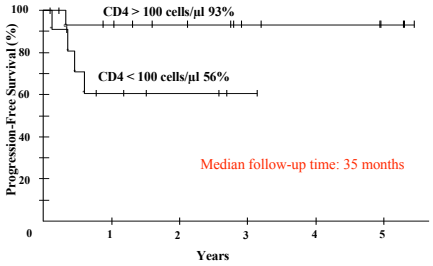
Brugieres, Blood, 1998

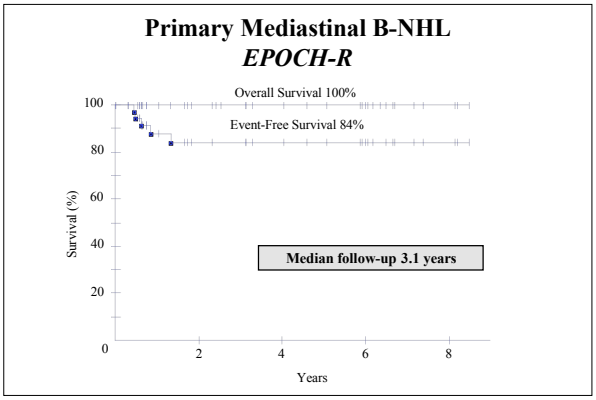
HIV-Associated B-NHL
EPOCH-R



HIV-Associated B-NHL
EPOCH-R

Progression-Free Survival by CD4 count at diagnosis





NHL: Treatment

Chemotherapy

Lymphoblastic

ALL-like, CNS prophylaxis

Burkitt & Large B-Cell

Short, intensive, CNS prophylaxis

Anaplastic Large Cell

? Optimal, ? CNS prophylaxis

Radiation therapy

Limited role: CNS involvement, ? Prophylaxis

NHL: CNS involvement

	Burkitt	Lympho	Large cell
SJCRC	13%	7%	1%
BFM	9%	3-5%	3%
CCG	4%	3%	6%

Sandlund, J Clin Oncol 2000
Salzburg, J Clin Oncol 2007

CNS Sterilization (*aka* "Prophylaxis")

- HD methotrexate + IT methotrexate
- Dexamethasone (vs. prednisone)
- CNS irradiation

CNS Treatment: Lymphoblastic Lymphoma

BFM-90 *includes* cranial XRT

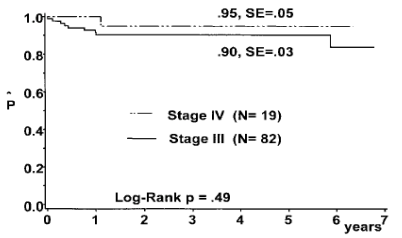


Figure 3. Probability of duration of event-free survival for patients with stage III disease and stage IV disease.

Reiter et al, Blood, 2000

CNS Treatment: Lymphoblastic Lymphoma

BFM-90 *without* cranial XRT (EORTC 58881)

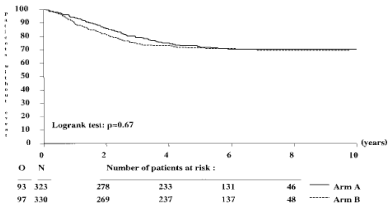


Fig 1. Disease-free survival according to arm A or arm B. Abbreviations: O, observed number of events (relapses or deaths in CR); N, number of patients at risk.

Millot et al., JCO, 2001.

CNS Treatment: Lymphoblastic Lymphoma

BFM-90 *without* cranial XRT (EORTC 58881)

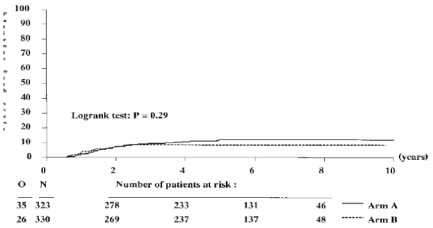


Fig 2. Cumulative risk of CNS relapse according to arm A or arm B. Abbreviations: O, observed number of events (CNS relapse, either isolated or combined with other sites); N, number of patients at risk.

Millot et al., JCO, 2001.

CNS Treatment: Lymphoblastic Lymphoma

BFM-95 *without* (*vs*. BFM-86 & BFM-90 *with*) cranial XRT

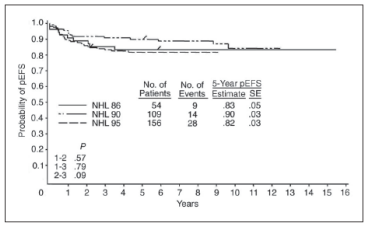


Fig 3. Event-free survival at 5 years in target patients of Non-Hodgkin's Lymphoma (NHL) –Berlin-Frankfurt-Munster (BFM) 95 trial (stage III or IV, CNS negative, sufficient response at induction day 33, and no prophylactic cranial radiotherapy) compared with the historical controls of NHL-BFM90 and NHL-BFM86 separately.

Burkhardt, J Clin Oncol, 2006

NHL: Poor Prognostic Risk Factors

- ↑ LDH
- Bone Marrow involvement
- CNS Involvement
- Slow Initial Response
- *Relapse*