Extranodal NK/T-Cell Lymphoma NCCN 2015 Guidelines

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Stanford University

NCCN Guidelines Version 1.2015
Extranodal NK/T-Cell Lymphoma, nasal type

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Discussion

DIAGNOSIS[a]

ESSENTIAL:

- Hematopathology review of all slides with a least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not suitable for the initial diagnosis of lymphoma.[b]
- In certain circumstances, when tissue is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for antigen receptor rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC panel: For high clinical suspicion of NKTL, first panel should include: cCD3ε, CD56, EBER-ISH[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: TCR gene rearrangement
- IHC panel:
  - B-cell lineage: CD20
  - T-cell lineage: CD2, CD7, CD8, CD4, CD5
  - Other: CD30, Ki-67

SUBTYPES

Subtypes included:

- Extranodal NK/T-cell, nasal type

Subtypes *not* included:

- NK-cell leukemias
- Precursor NK-cell neoplasm

WORKUP

ESSENTIAL:

- Physical exam: attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles, and skin
- Performance status
- B symptoms
- CBC, differential platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate[f]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of NK/T-cell PI[g]
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenedione
- EBV viral load[h]
- Concurrent referral to RT for pre-treatment evaluation

USEFUL IN SELECTED CASES:

- Pregnancy testing in women of child-bearing age
- Discussion of fertility and sperm banking
- HIV

See Induction Therapy (NKTL-2)

[a] It is preferred that treatment occur at centers with expertise in the management of this disease.

[b] Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.

[c] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d] Typical NK-cell immunophenotype: CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, T-cell receptor (TCR)αβ-, TCRγδ-, EBV-EBER+. TCR and Ig genes are germline (NK lineage). Cytotoxic granule proteins (TIA1, Perforin, Granzyme B) are usually expressed. Typical T-cell immunophenotype: CD2+ sCD3+ cCD3e+, CD4,5,7,8 variable, CD56+/- EBV-EBER+ TCRαβ or γδ+, cytotoxic granule proteins +. TCR genes are clonally rearranged.

[e] Negative result should prompt pathology review for alternative diagnosis.

[f] BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemophagocytosis may be present.

[g] See NK/T-cell Lymphoma Prognostic Index (NKTL-A).

[h] EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines 2015: Diagnosis

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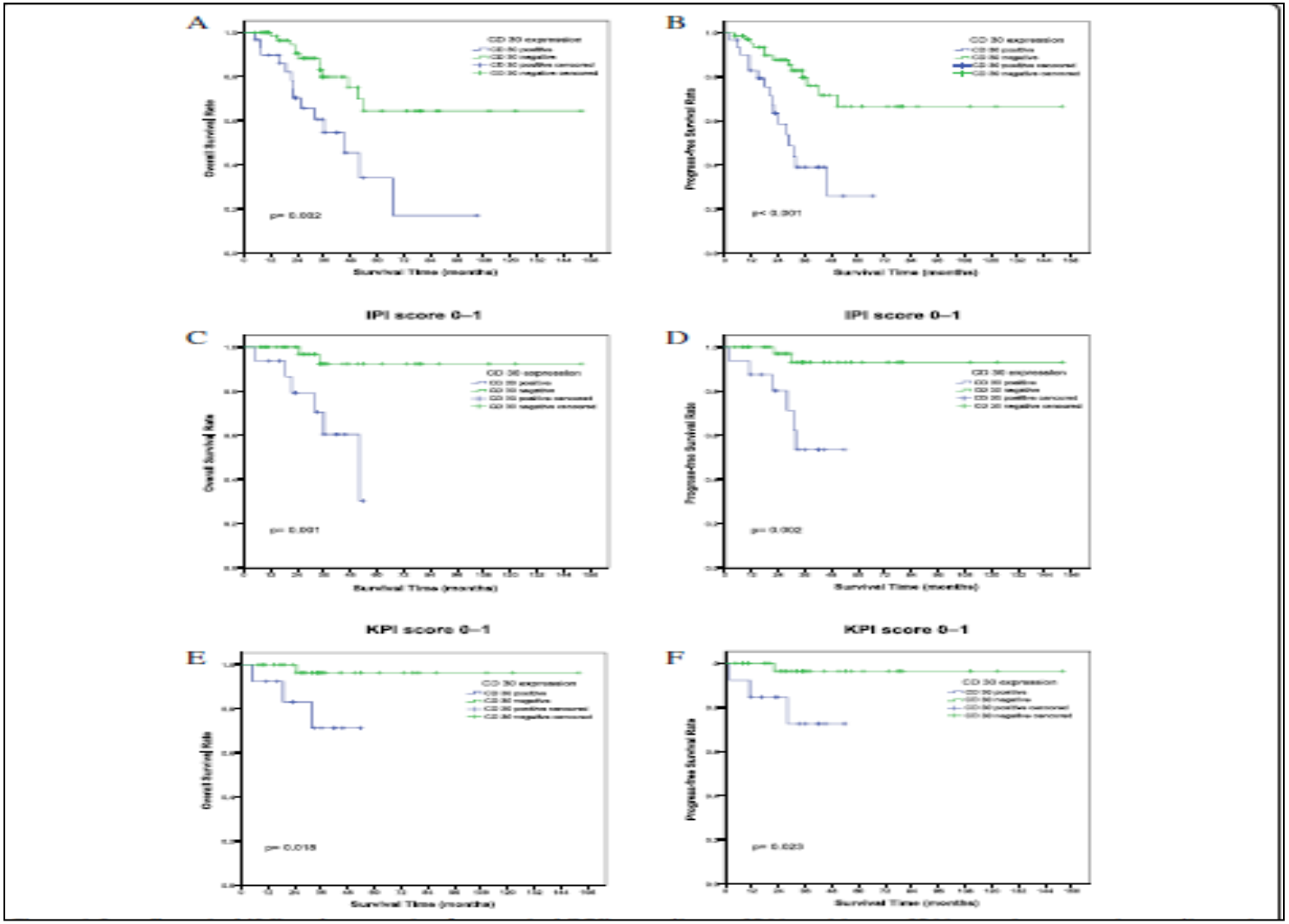
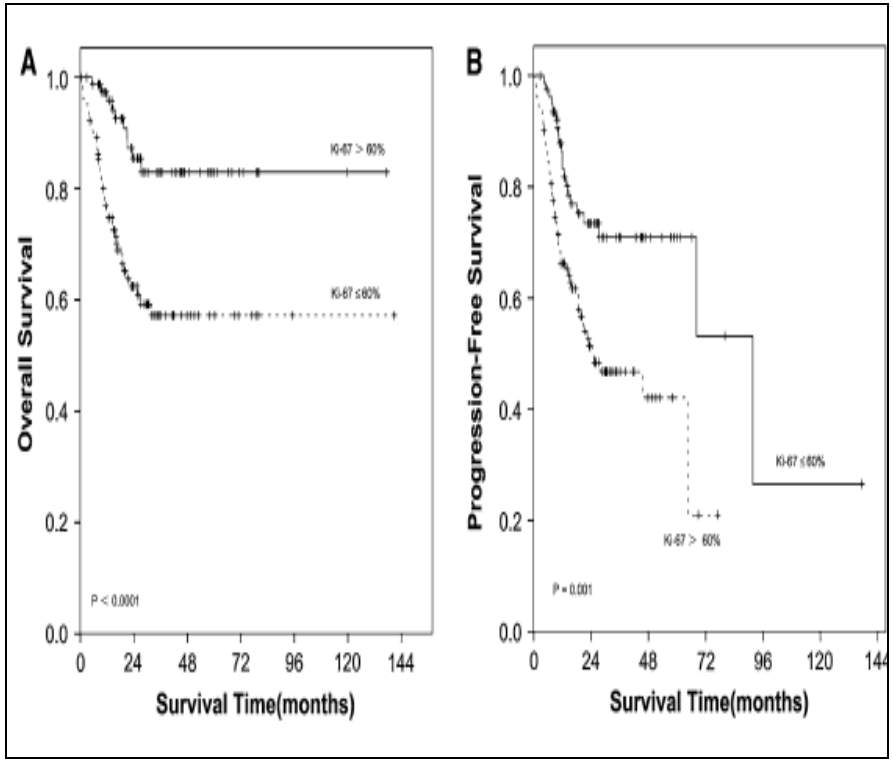
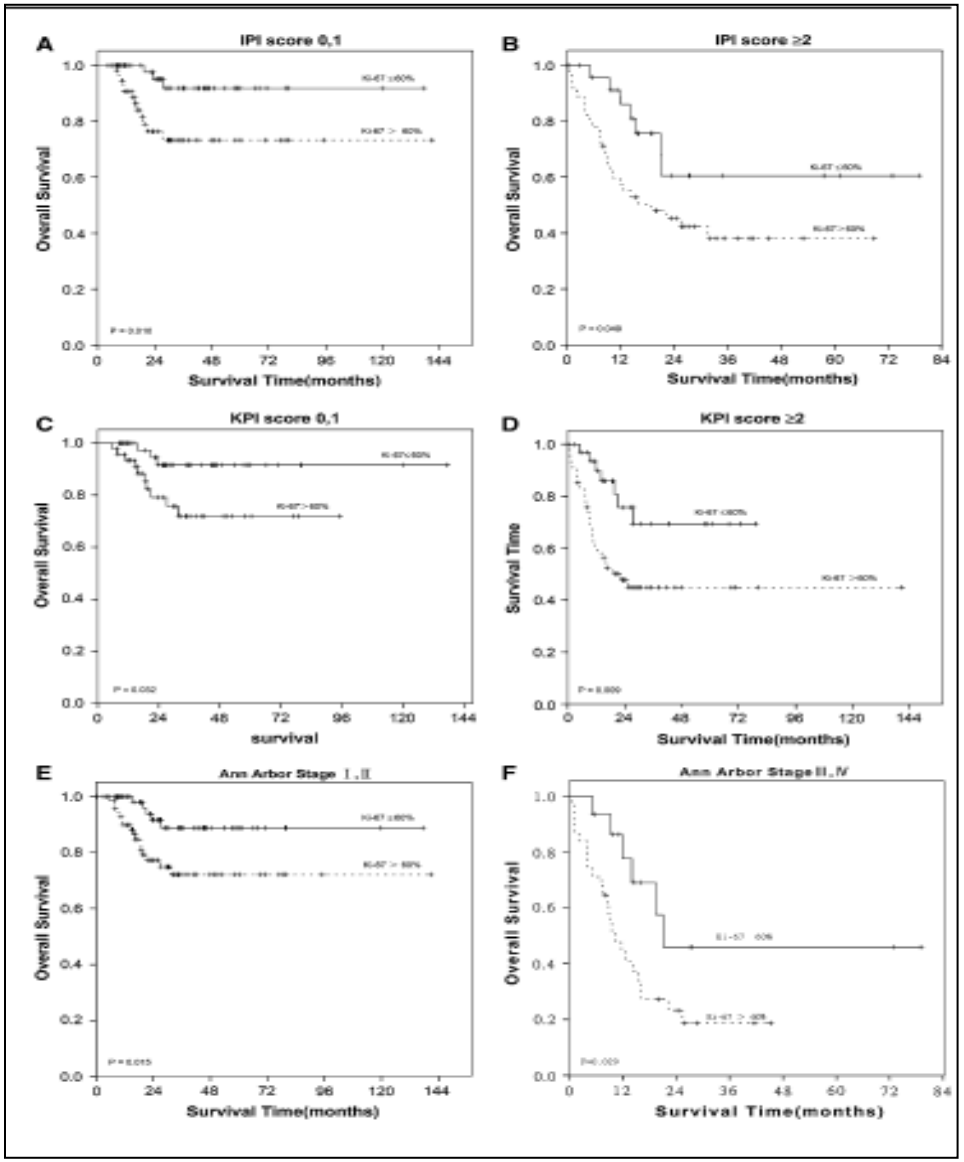
CD 30 status and outcomes



Li et al BMC Cancer 2014

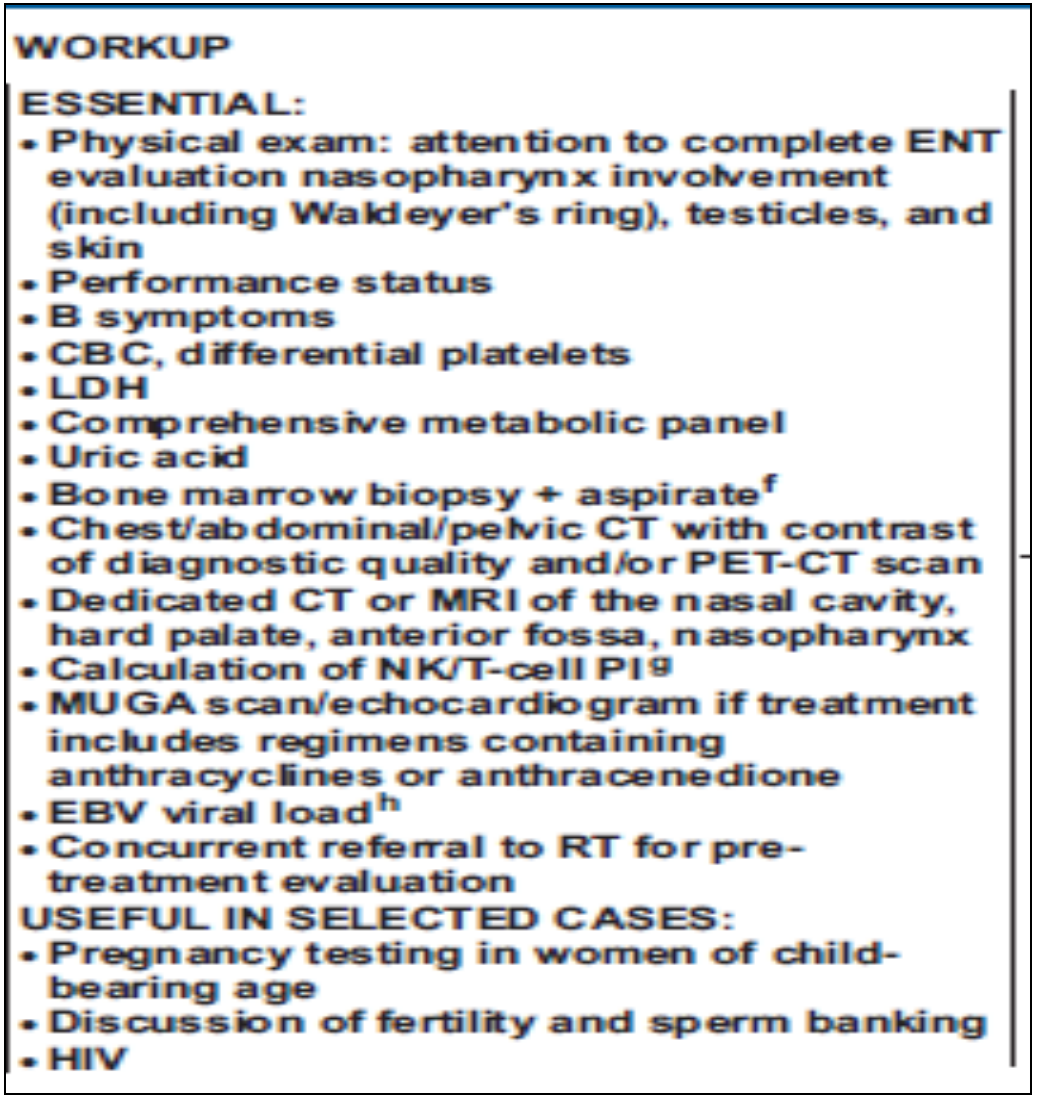
Ki 67 and Prognosis





Jiang et al Med Oncol 2014

NCCN Guidelines: Workup



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BM aspirate:

- Lymphoid aggregates are rare and are considered involved if EBER-1 positive.
- Hemophagocytosis maybe present

EBV viral load:

Important in diagnosis

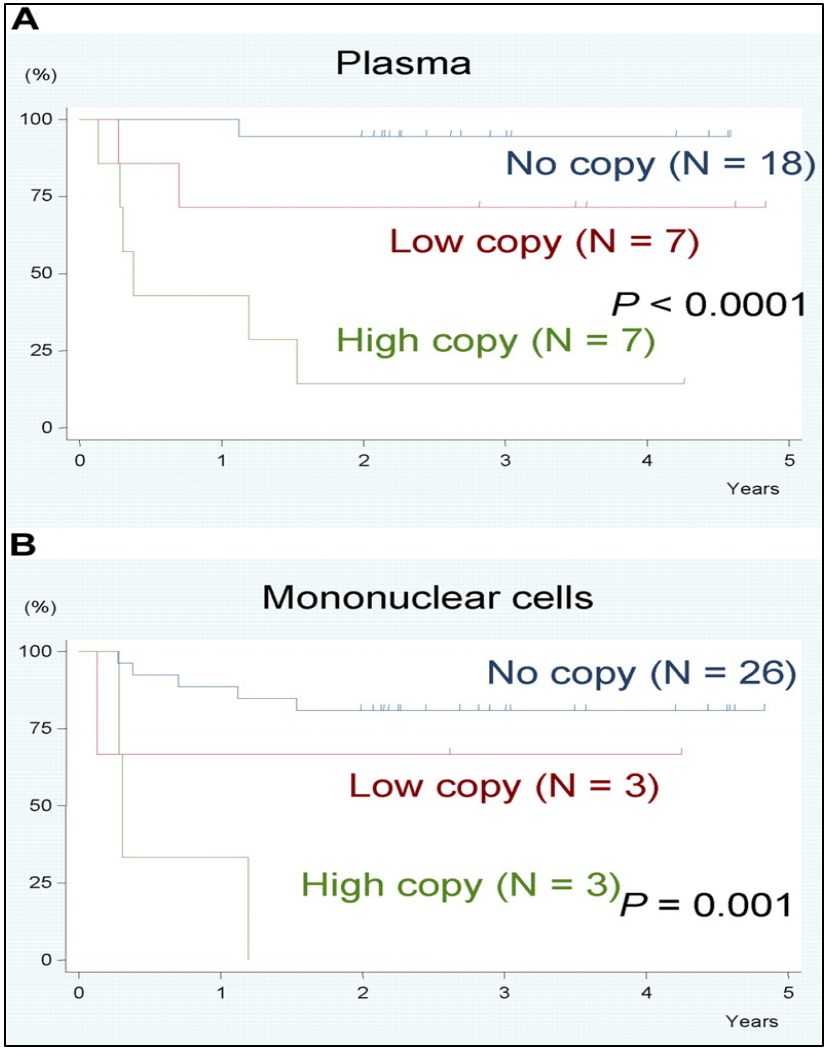
- Positive result is consistent with NK/T ell, nasal type

Monitoring of disease

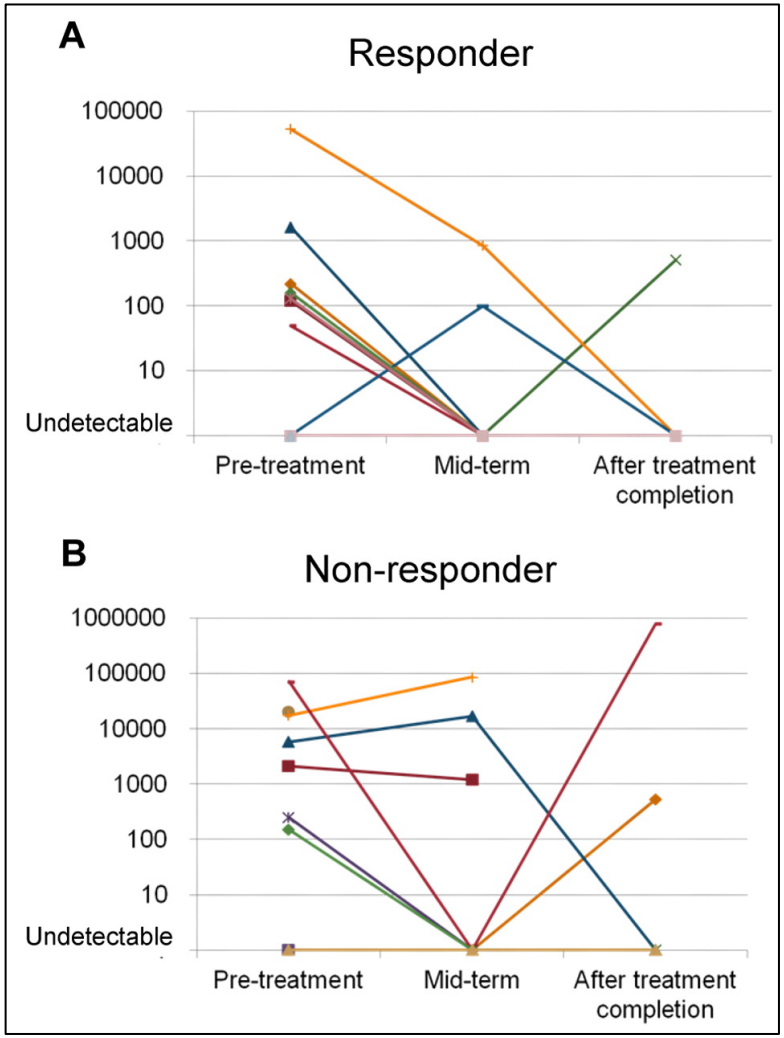
- Lack of normalization of viremia considered indirect evidence of persistent disease.

ENKT cell lymphoma: EBV

Survival by pre rx EBV-DNA.



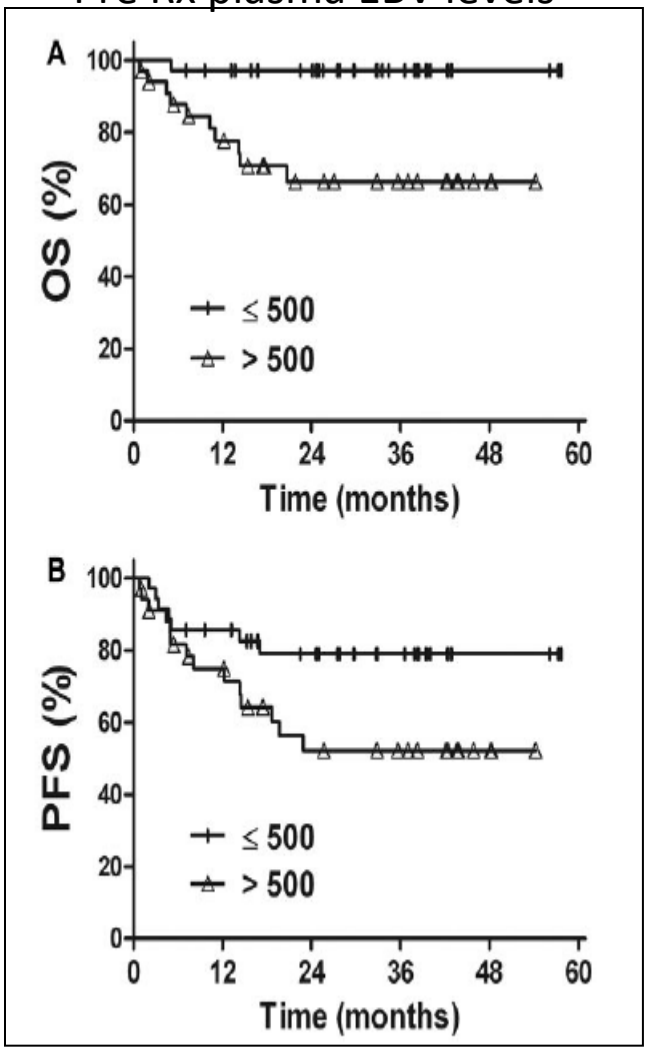
Change of plasma EBV-DNA during Rx



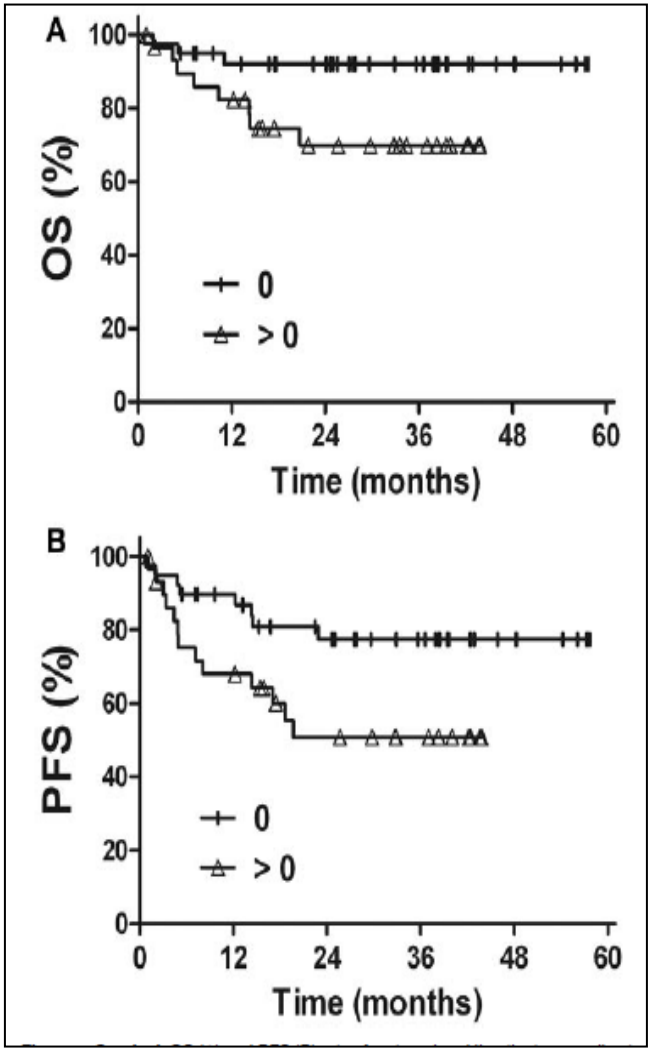
Suzuki et al. Blood 2011

EBV DNA levels prognostic in Early Stage NK/T cell Lymphoma

Pre Rx plasma EBV levels



Post Rx plasma EBV levels

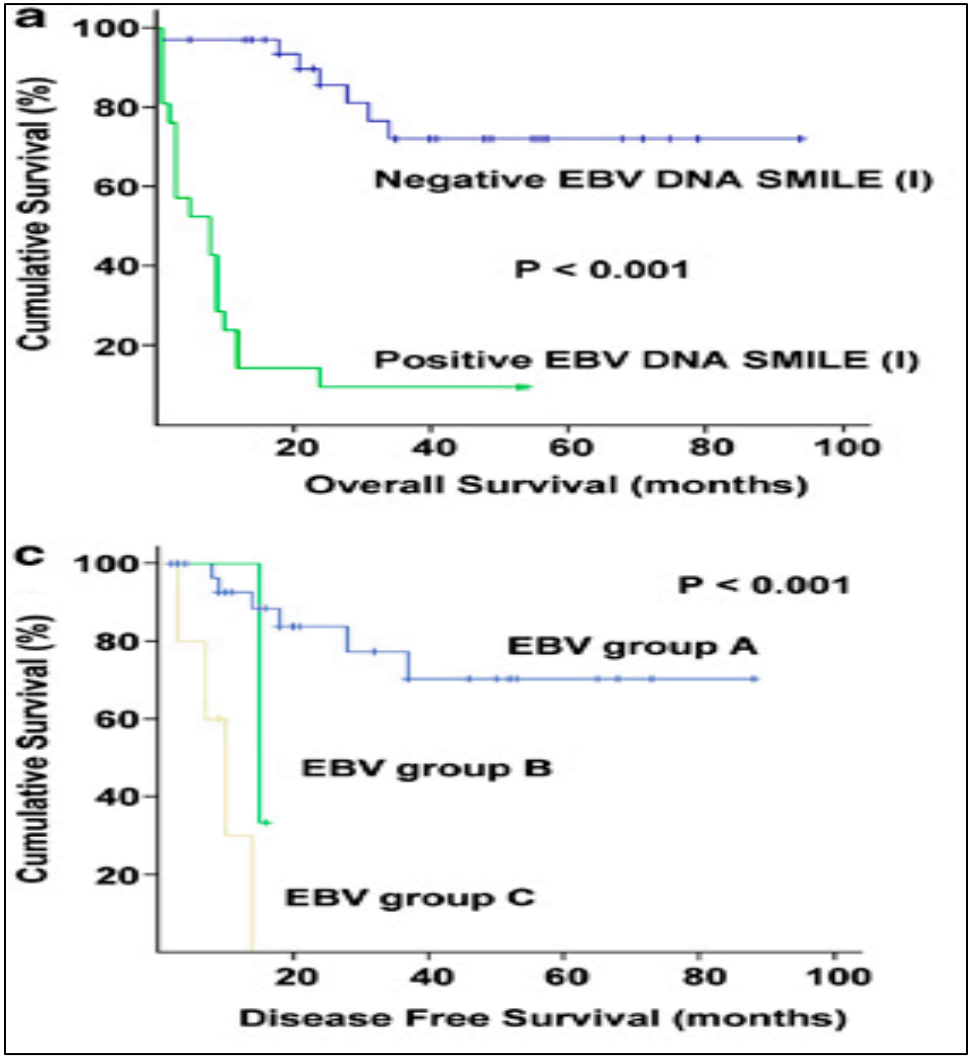


Wang et al Blood 2012

EBV DNA levels prognostic in Advanced Stage NK/T cell Lymphoma

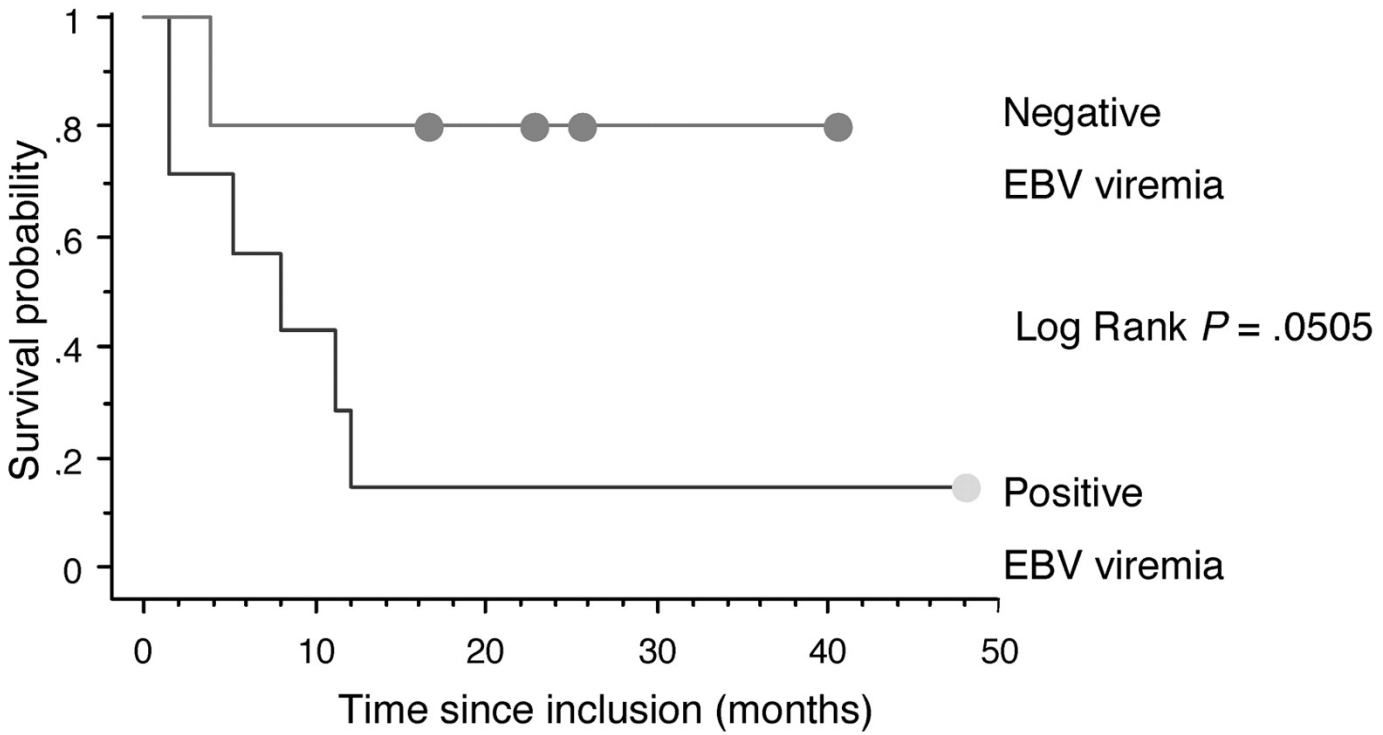
Neg EBV DNA post cycle 1

Quantifiable EBV DNA at presentation



Kwong et al Leukemia 2014

EBV DNA levels prognostic in Relapsed NK/T cell Lymphoma



Number at risk

EBV -	5	4	3	1	
EBV +	7	3	1	1	1

● Censoring time

Jaccard et al. Blood 2011

Risk Factors

- Age > 60 years
- B symptoms
- ECOG PS >/=2
- Elevated LDH
- Regional LN involvement
- Local tumor invasion
- Bone, skin involvement
- High Ki 67 staining
- EBV viral load >/= 6.1×10^{7} copies/ml

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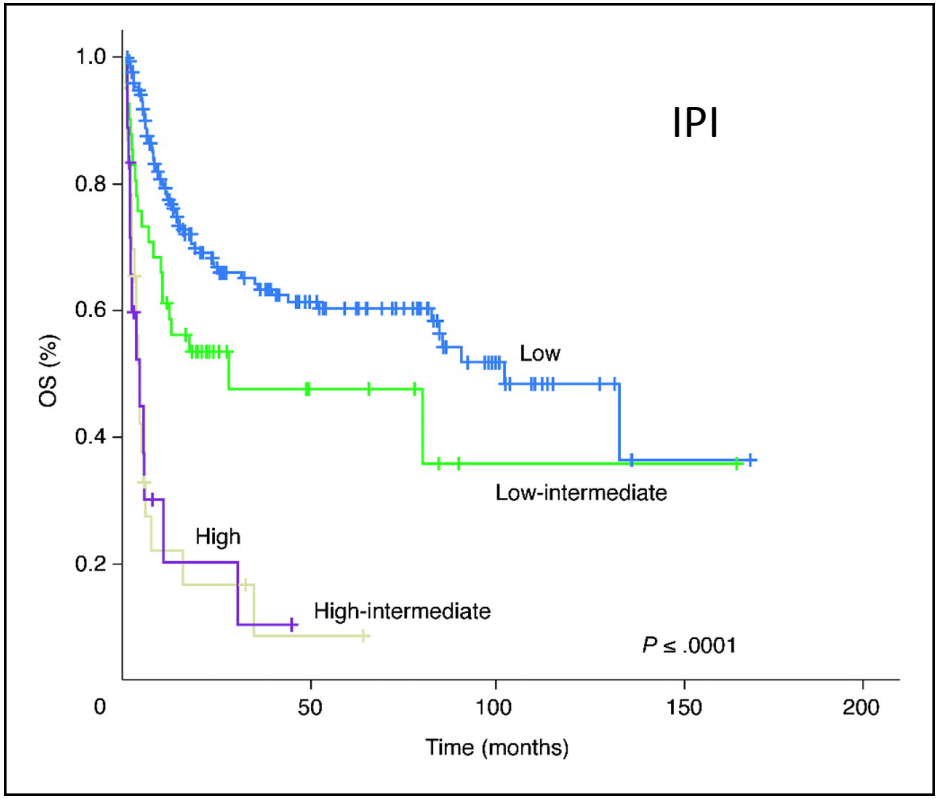
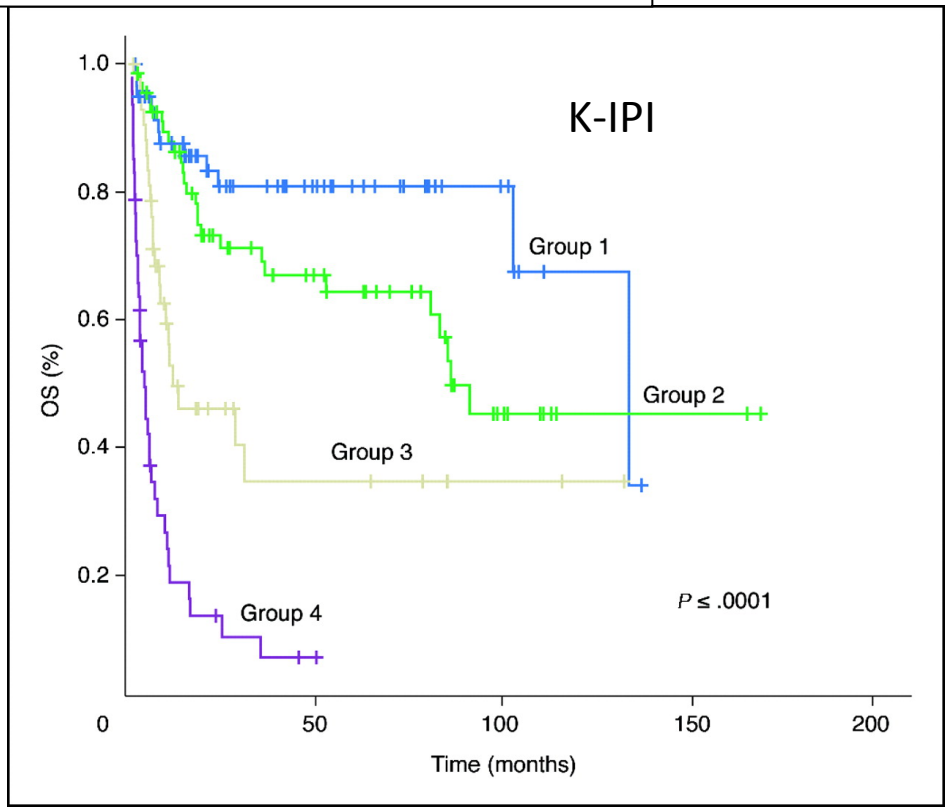
NK/T-CELL LYMPHOMA PROGNOSTIC INDEX[a]

ALL PATIENTS

Serum LDH > normal
B symptoms
Lymph nodes, N1 to N3, not M1
Ann Arbor Stage IV

	Number of risk factors
Low	0
Low intermediate	1
High intermediate	2
High	3 or 4





Lee et al. JCO 2006

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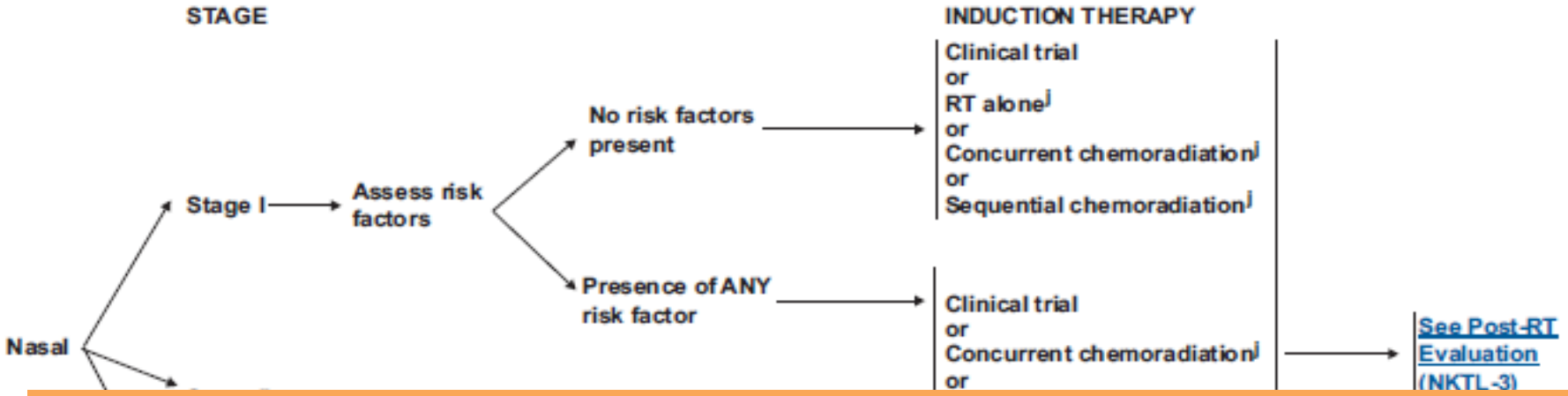


Preferred that rx occur at centers with expertise in management of this disease

All recommendations Category 2A unless otherwise indicated

Clinical trial participation preferred approach

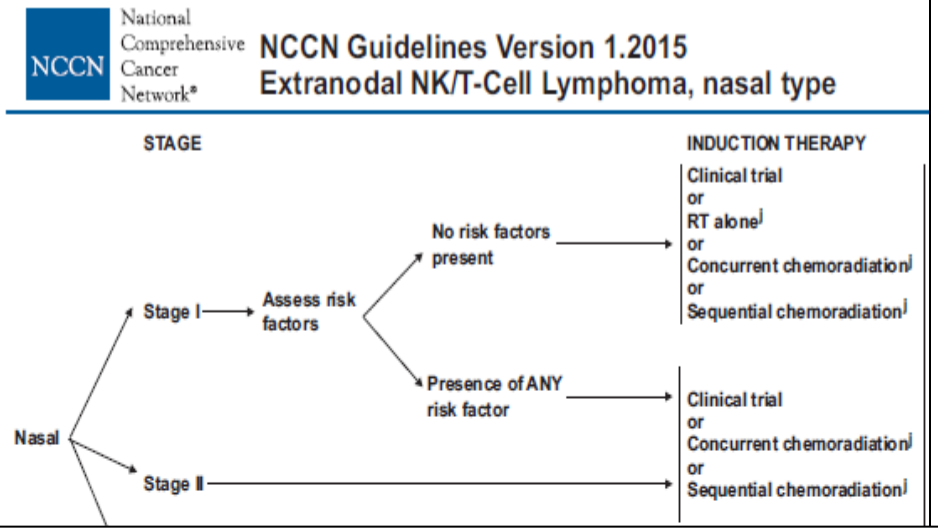
Available at: http://informahealthcare.com/doi/abs/10.1586/era.10.130.

- ECOG PS ≥2
- Elevated LDH
- Regional node involvement
- Histologic evidence of high Ki-67 staining
- EBV DNA titer ≥6.1 x 10^7 copies/mL

[i] In rare circumstances of stage I_E extranasal disease, IFRT for single skin lesions can be considered.

[j] See Suggested Treatment Regimens (NKTL-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (pegaspargase-based)
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen.)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide)

Concurrent chemoradiation therapy (CCRT)
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40–52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- SMILE followed by RT 45–50.4 Gy
- VIPD followed by RT 45–50.4 Gy

Radiation therapy alone
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with stage I disease.

Stage 2 CMT vs Single Modality

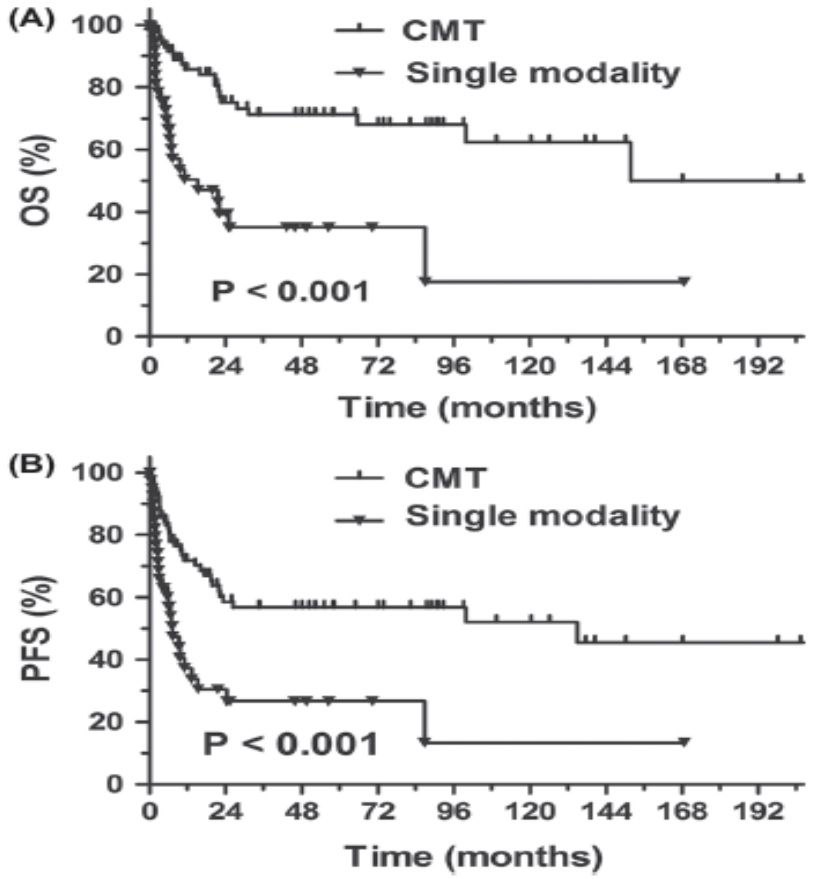


Figure 4. Overall survival (OS, A) rates and progression-free survival (PFS, B) rates for 124 patients with stage II NK/T-cell lymphoma of the upper aerodigestive tract who received either combined modality therapy (CMT) or single modality therapy.

Fang et al Leukemia Lymphoma 2014

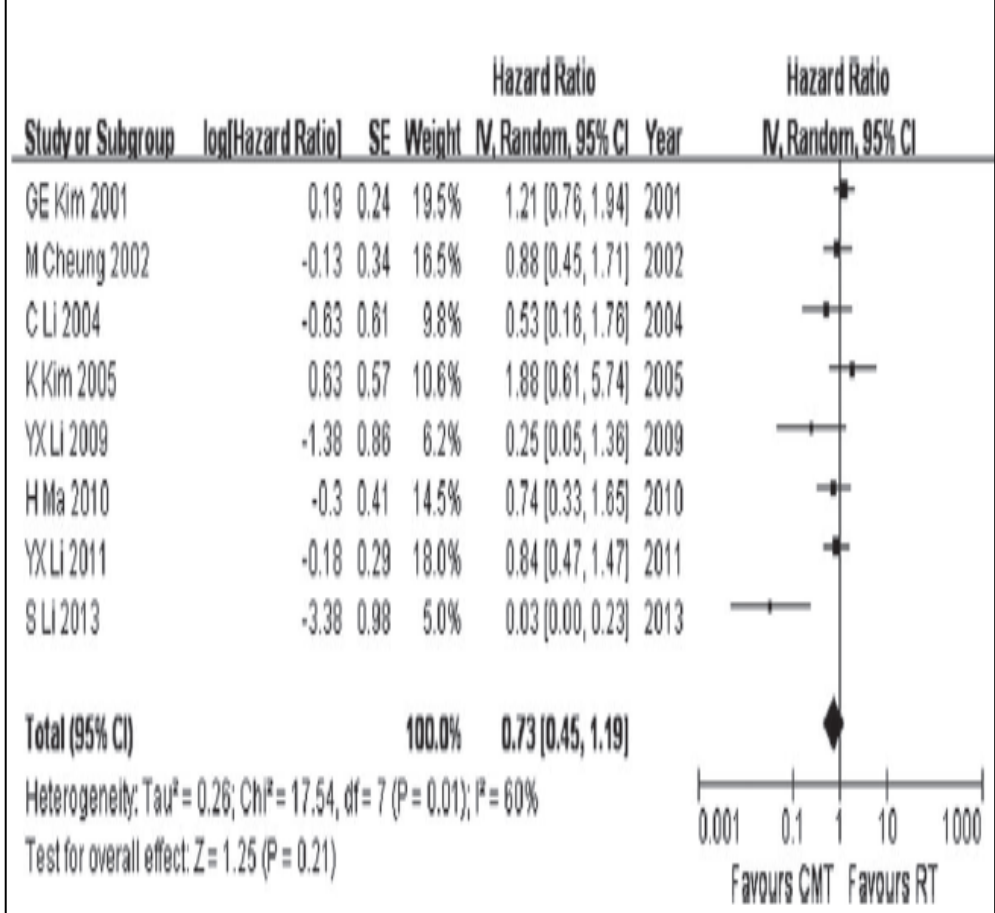
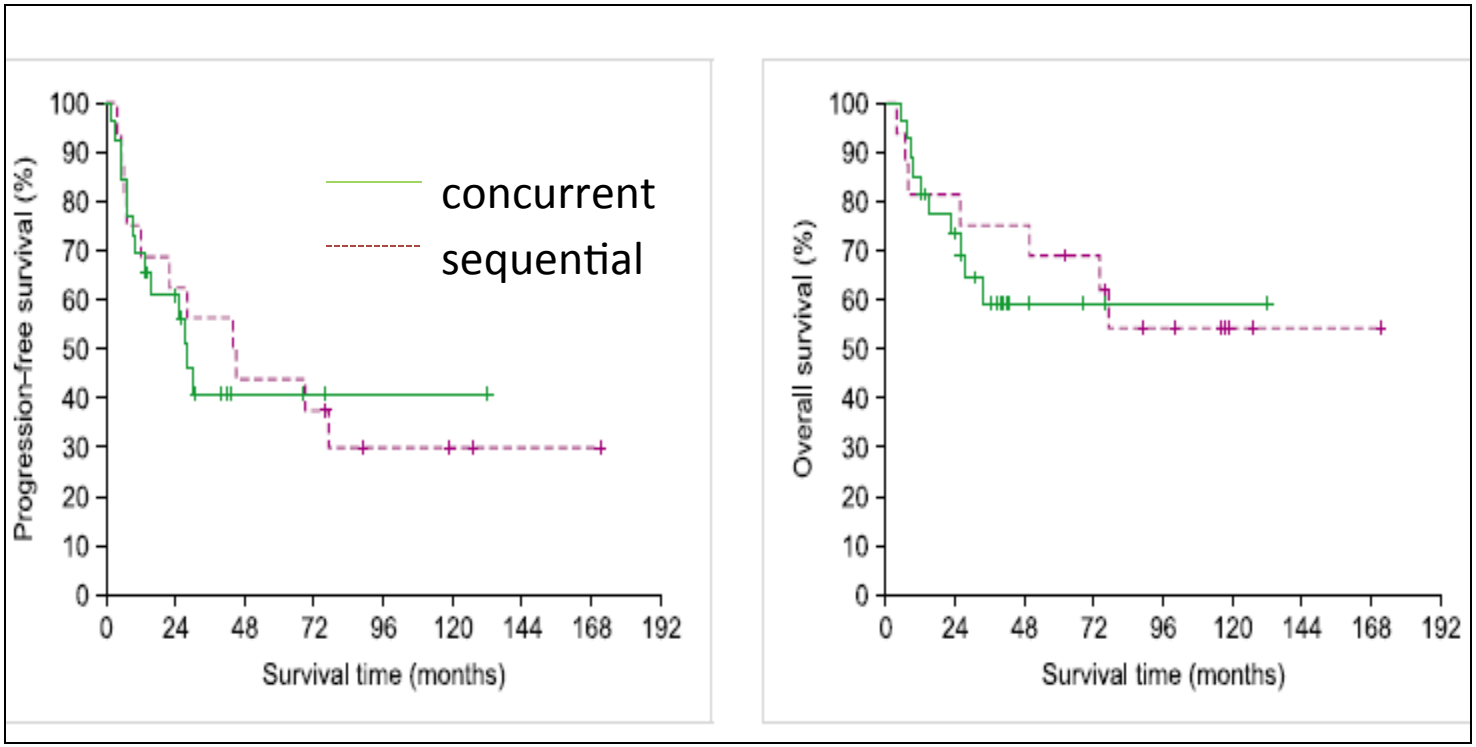


Figure 1. Risk of 5-year OS comparing CMT with RT.

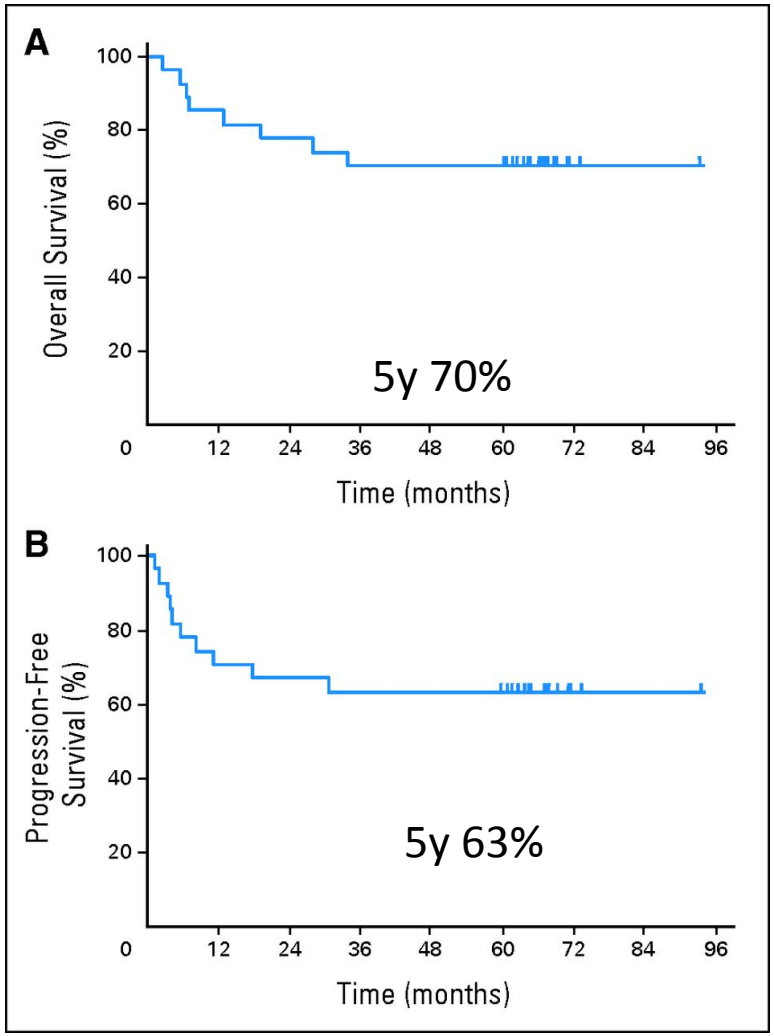
Jiang Leuk Ly 2014

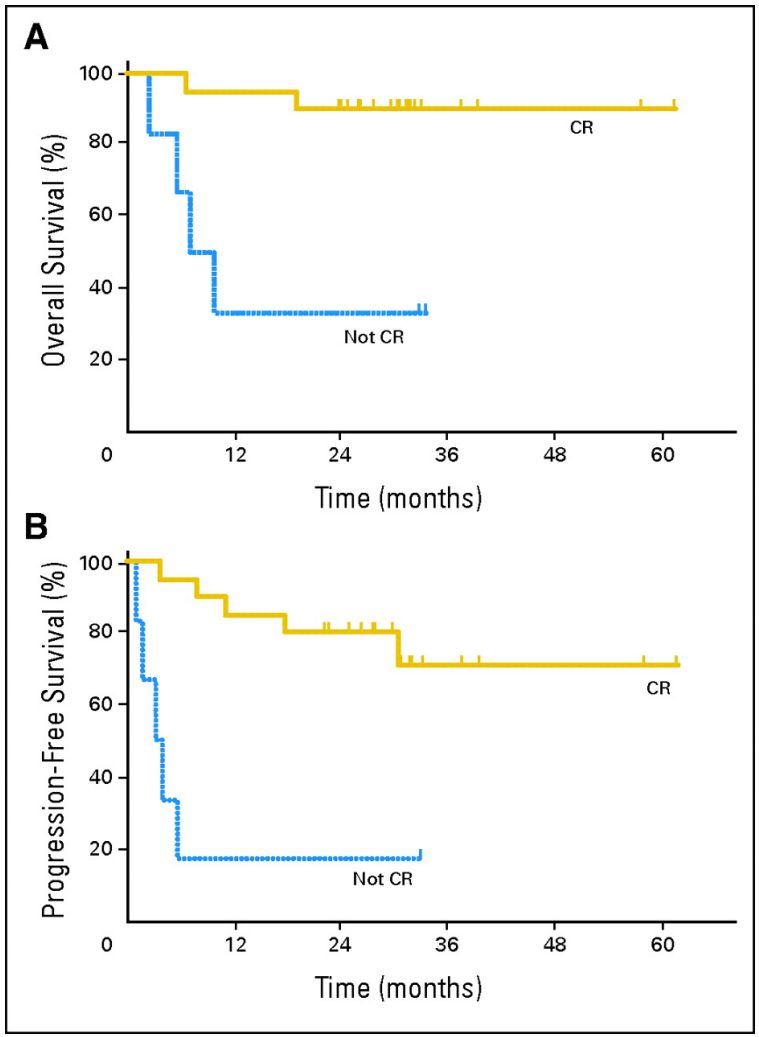
Stage I-II ENKL
Concurrent vs Sequential CMT



Lee et al: Blood Res 2013

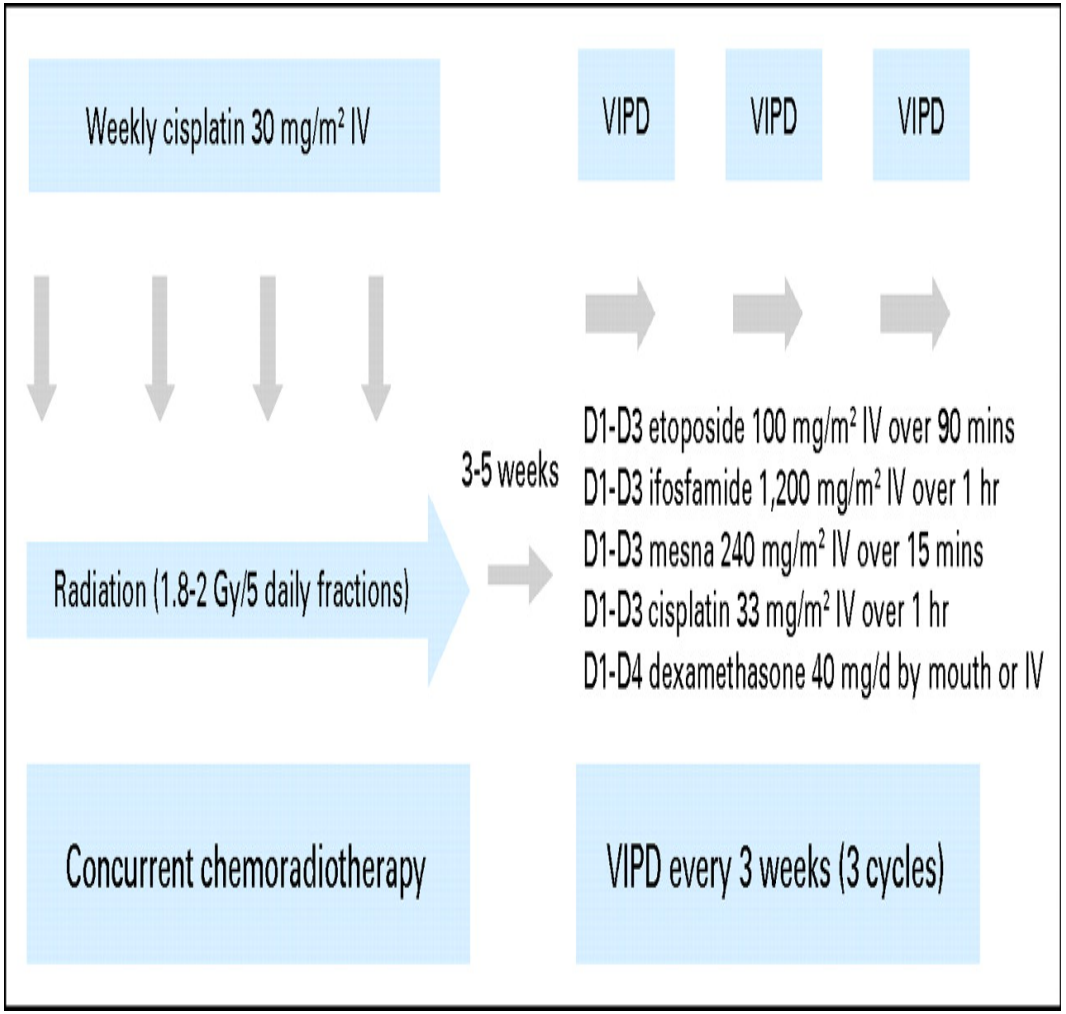
DeVIC Regimen

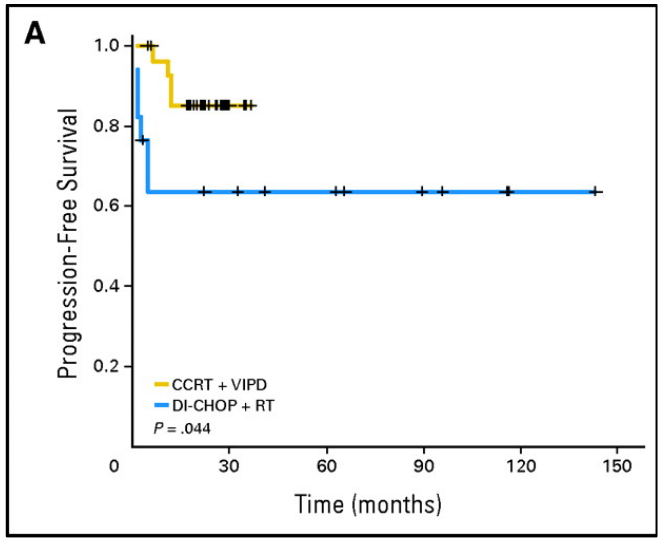


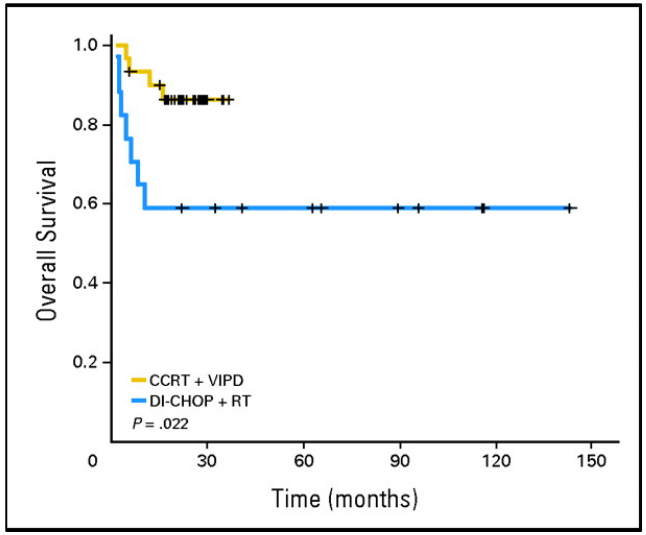


Yamaguchi et al. JCO 2012

VIPD Regimen







Seok Jin Kim et al. JCO 2009

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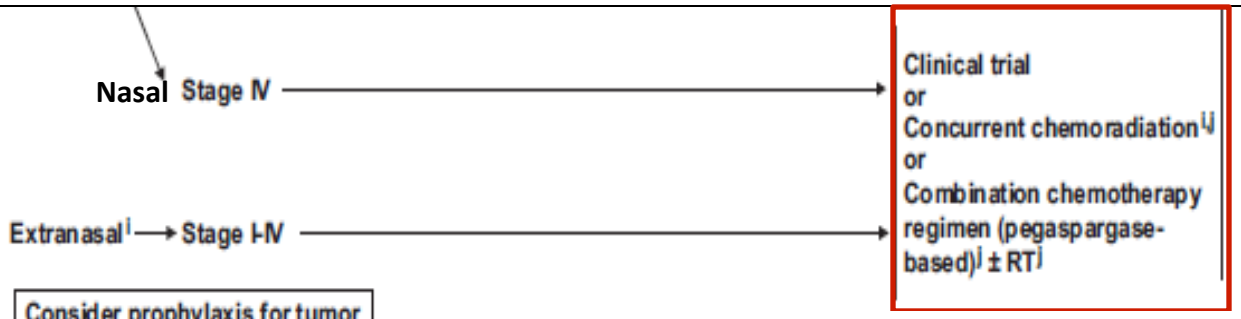

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405 Available at: http://informahealthcare.com/doi/abs/10.1586/era.10.130.

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SMILE for NK/T cell Lymphoma

Table 1. SMILE Chemotherapy

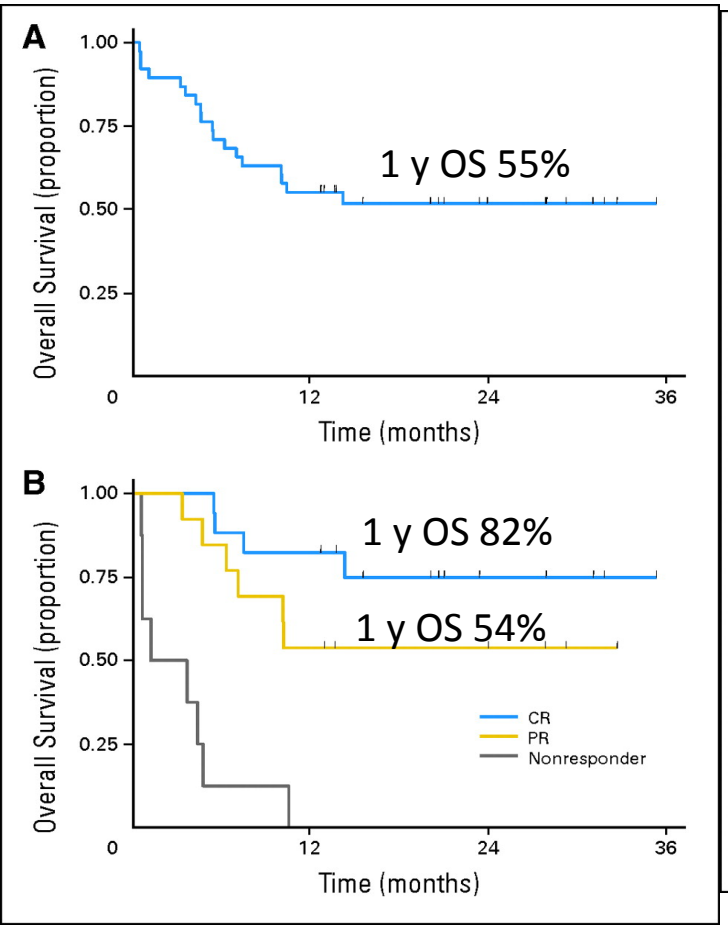
Agent	Dose/d	Route	Day
Methotrexate	2 g/m^2*	IV (6 hours)	1
Leucovorin	15 mg × 4	IV or PO	2, 3, 4
Ifosfamide	1,500 mg/m^2	IV	2, 3, 4
Mesna	300 mg/m^2 × 3	IV	2, 3, 4
Dexamethasone	40 mg/d	IV or PO	2, 3, 4
Etoposide	100 mg/m^2*	IV	2, 3, 4
L-asparaginase (*Escherichia coli*)	6,000 U/m^2	IV	8, 10, 12, 14, 16, 18, 20
G-CSF		SC or IV	Day 6 to WBC > 5,000/μL

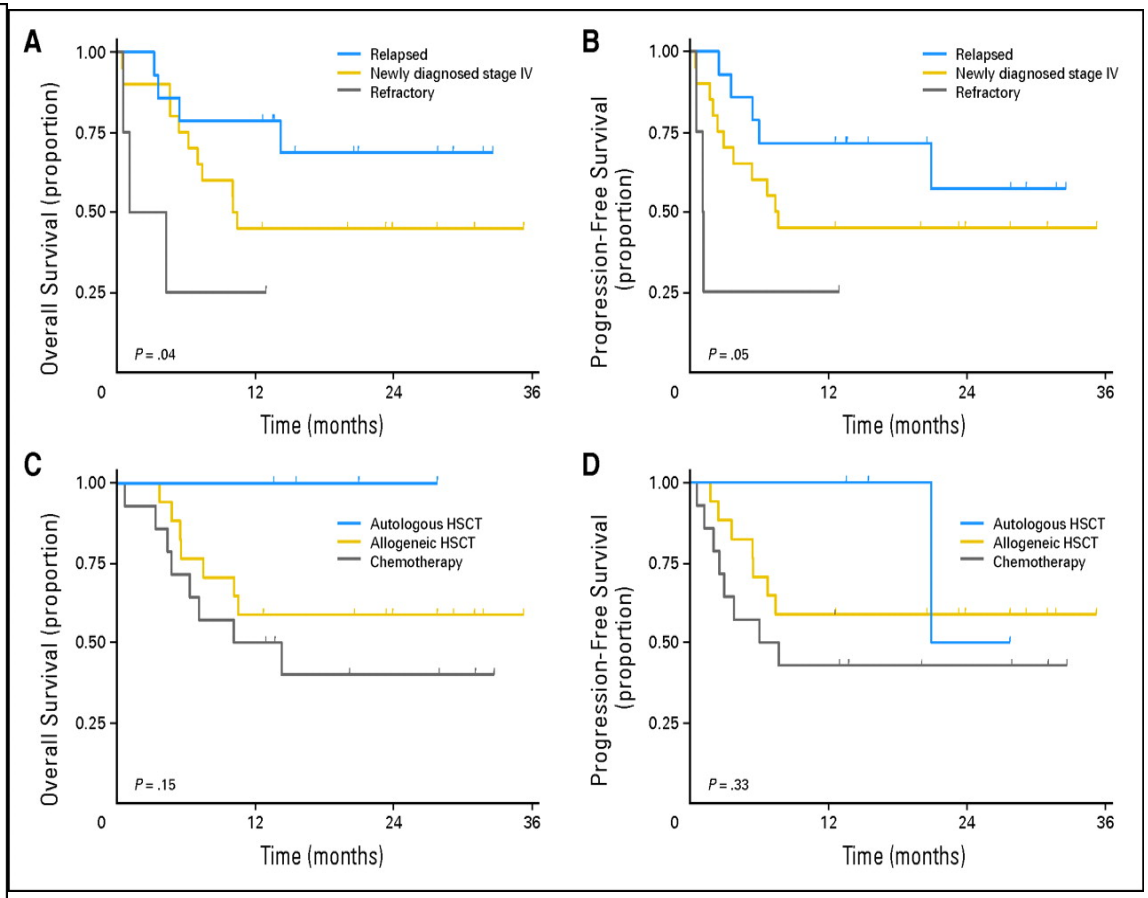
NOTE. Cycles were repeated every 28 days. Two courses were planned as the protocol treatment.
Abbreviations: G-CSF, granulocyte-colony stimulating factor; IV, intravenously; PO, orally; SC, subcutaneous injection; SMILE, steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.
*The recommended dose was determined in the preceding phase I study.

Supportive Care Important
92 % Grade 4 ANC, 40 % grade 4 thrombocytopenia

Yamaguchi JCO 2011

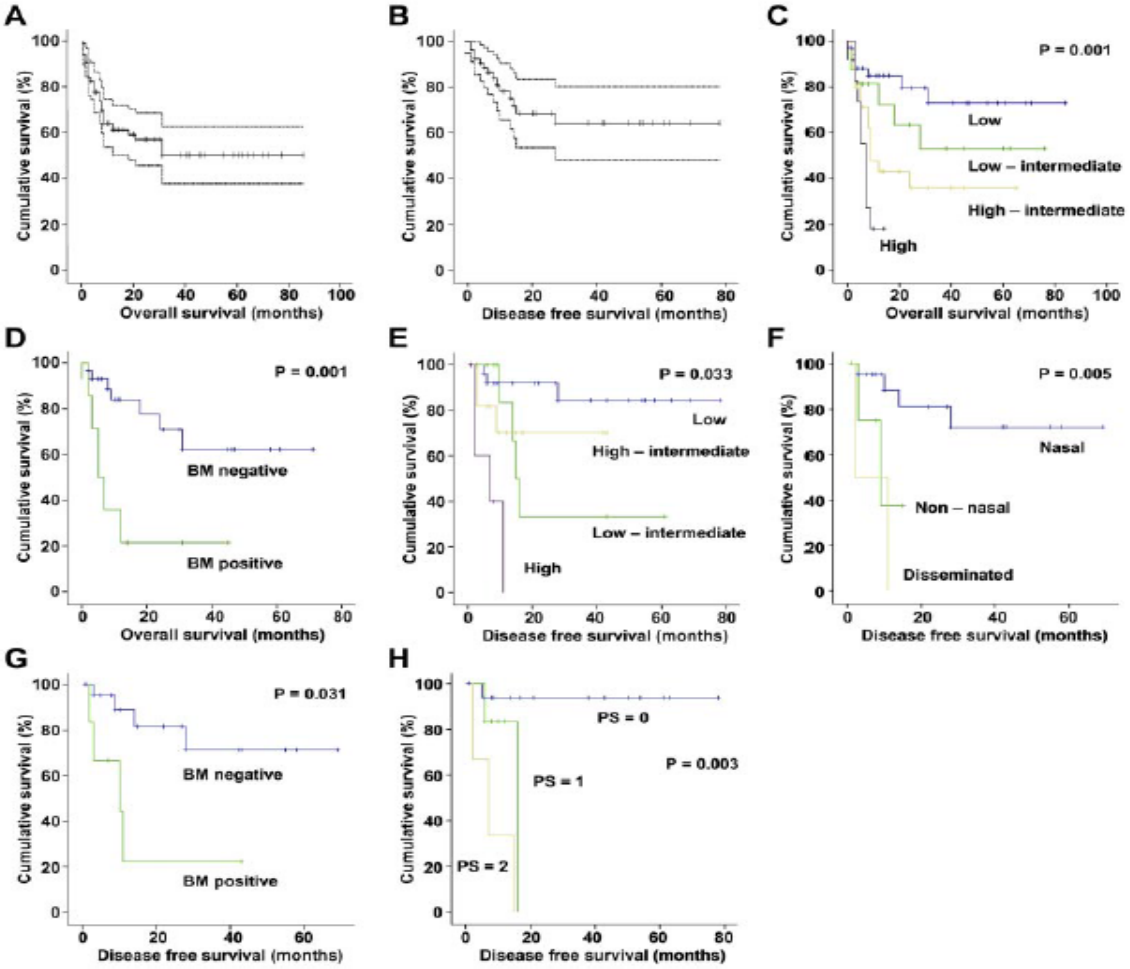
SMILE: Stage IV or Relapsed/Refractory ENKL





Yamaguchi JCO 2011

SMILE for NK/T-cell lymphoma: safety and efficacy from the Asia Lymphoma Study Group



N = 87
~ 50% frontline
~ 50% Stage III-IV
Outcomes similar for frontline vs relapsed/refractory

Median f/u:
31 mo (1-84 mo)
5-y OS 50%
4-y DFS 64%.

Kwong et al Blood 2012

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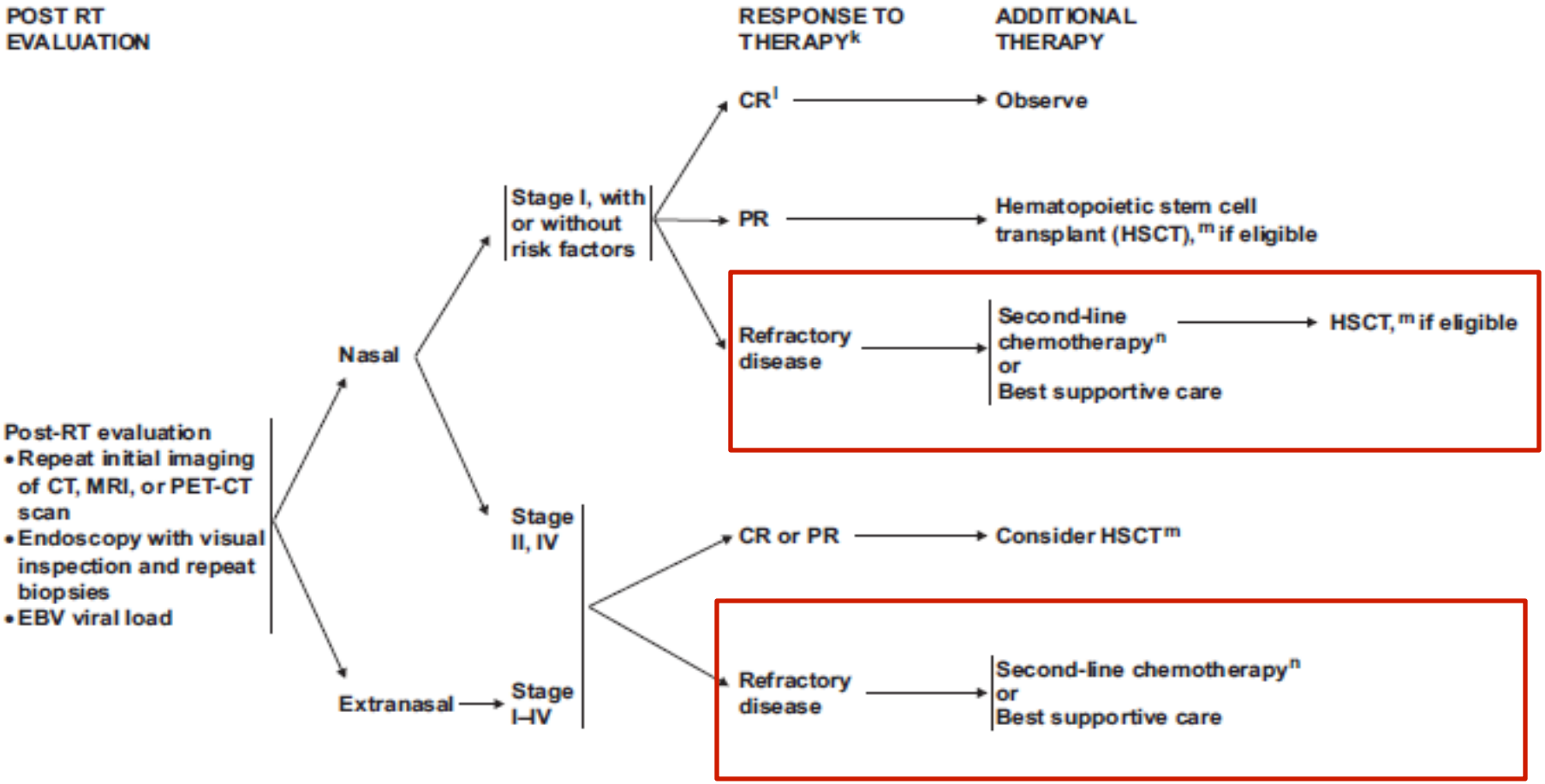

[k] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[l] Includes a negative ENT evaluation.

[m] Allogeneic preferred, if matched donor available.

[n] Combination chemotherapy regimen (pegaspargase-based), see Suggested Treatment Regimens (NKTL-B).

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.

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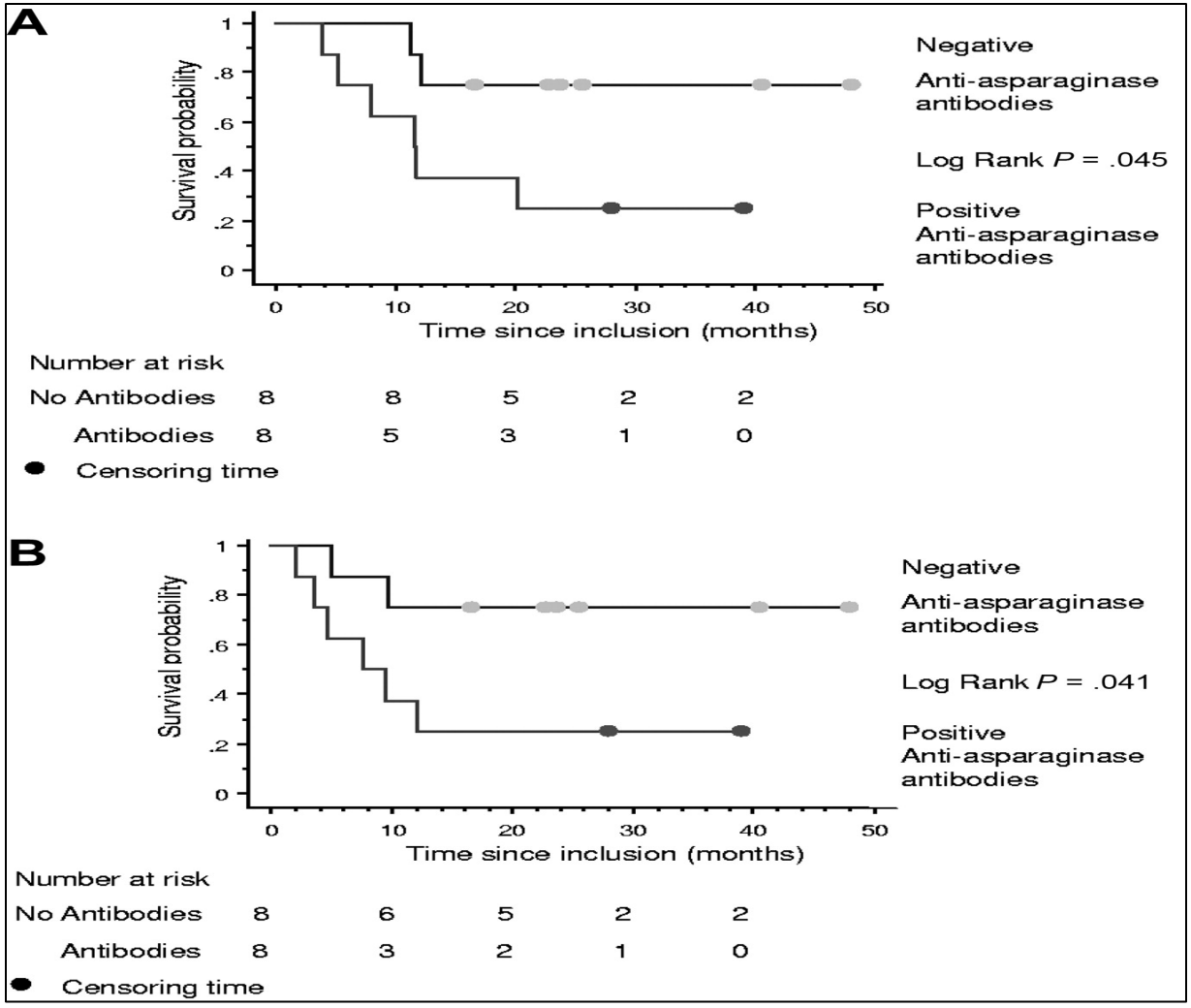
Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study

Outcomes according to anti asparaginase antibody status.



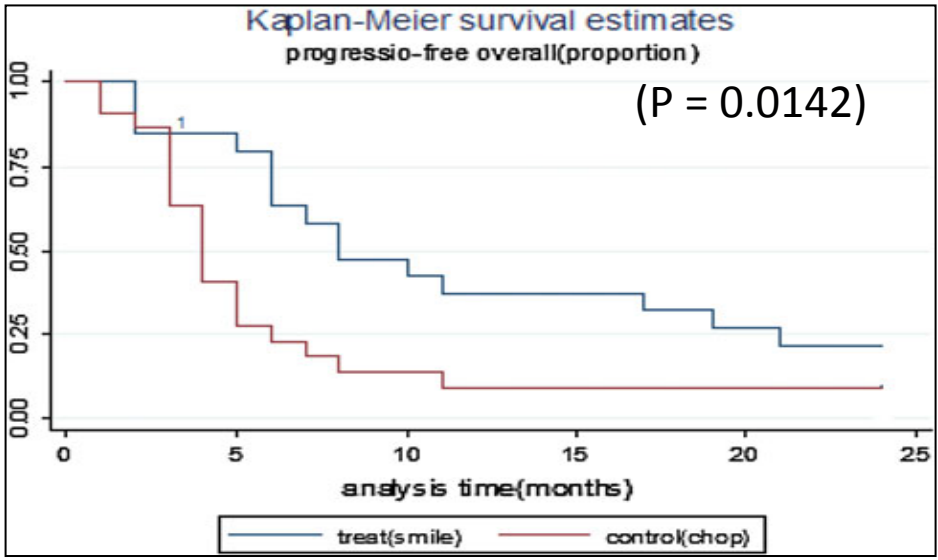
Jaccard et al. Blood 2011

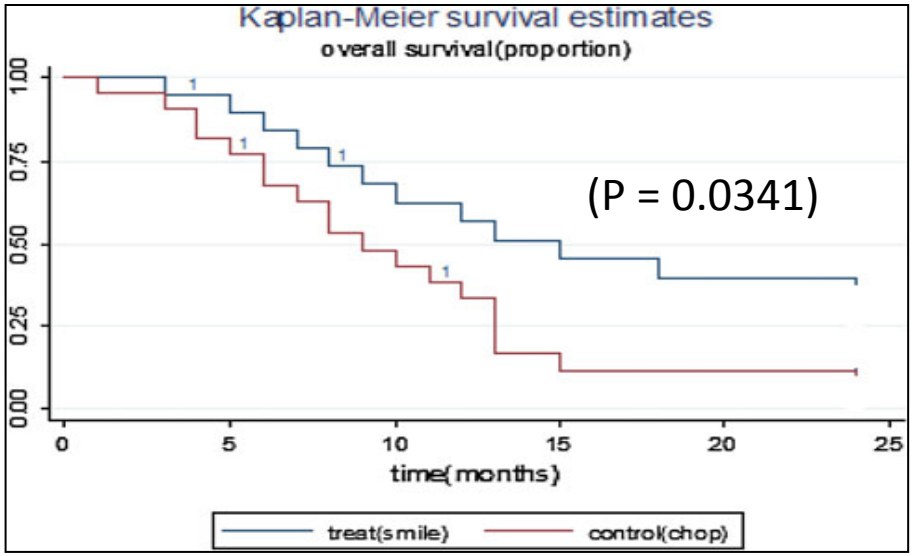
Relapsed/refractory advanced stage ENKL
Modified SMILE vs CHOP

Table 2 Chemotherapy protocols

Modified SMILE regimen

Agent	Dose/d	Route	Days
Ifosfamide	1.2 g/m^2	iv	d1–d3
Mesna	300 mg/m^2	iv	q8 h, d1–d3
Etoposide	60 mg/m^2	iv	d1–d5
Dexamethasone[a]	15 mg/m^2	iv or po	d1–d5
Pegaspargase	2,500 u/m^2	im	d8
Methotrexate	1.5 g/m^2	iv	2nd course -d1
Leucovorin	20 mg/m^2	im x 6	2nd course d1–d2





Yang et al Med Oncol (2013)

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Extranodal NK/T-Cell Lymphoma, nasal type

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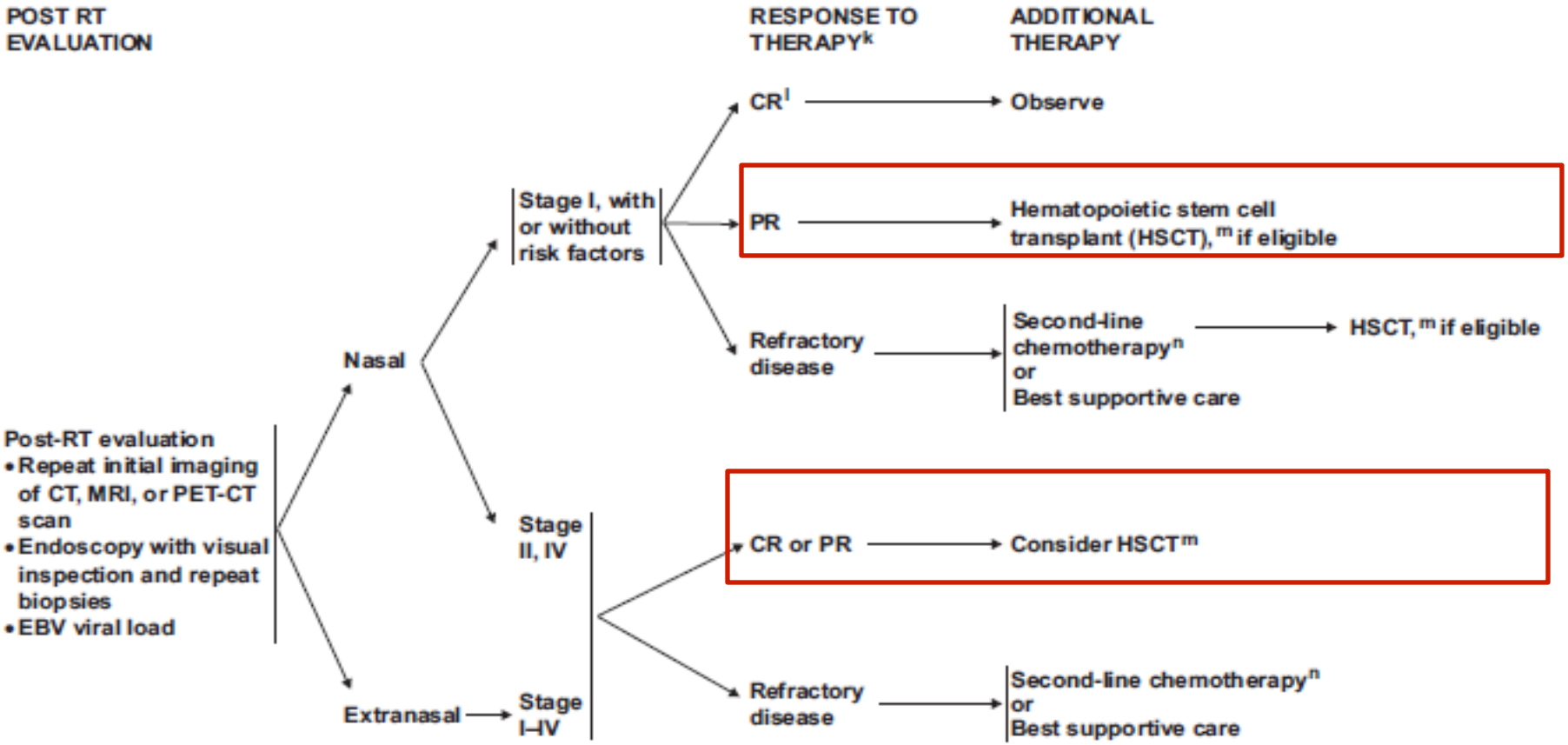


[k] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[l] Includes a negative ENT evaluation.

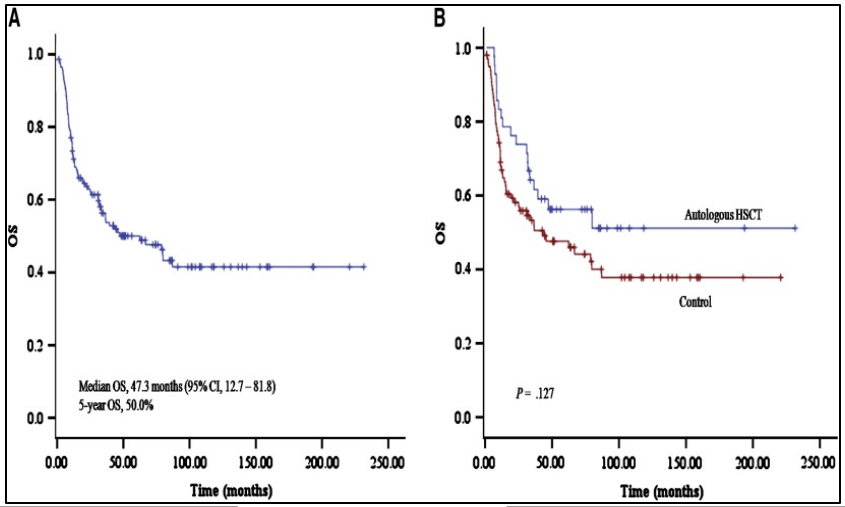
[m] Allogeneic preferred, if matched donor available.

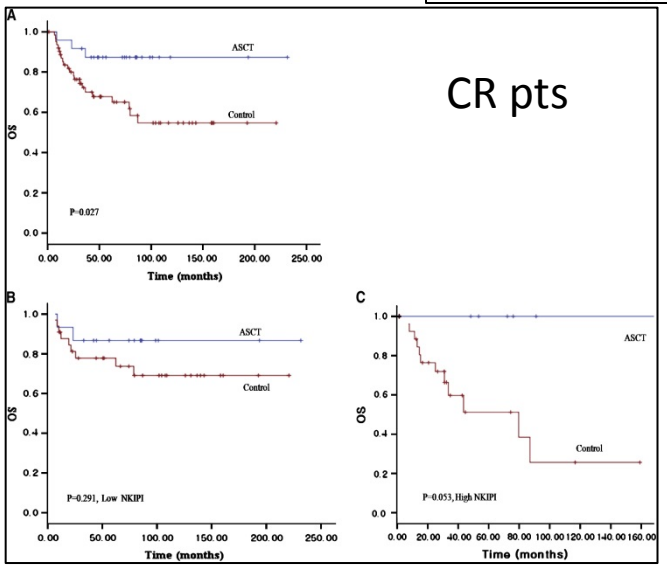
[n] Combination chemotherapy regimen (pegaspargase-based), see Suggested Treatment Regimens (NKTL-B).

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.

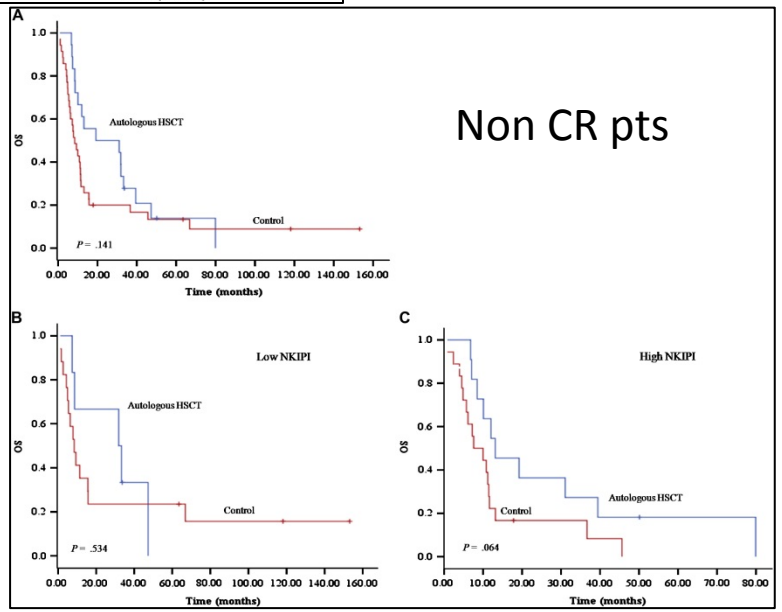
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ASCT in NK/T- cell lymphoma
A Multinational, Multicenter, Matched Controlled Study





CR pts



Non CR pts

Li et al Biology of Blood and Marrow Transplant 2008

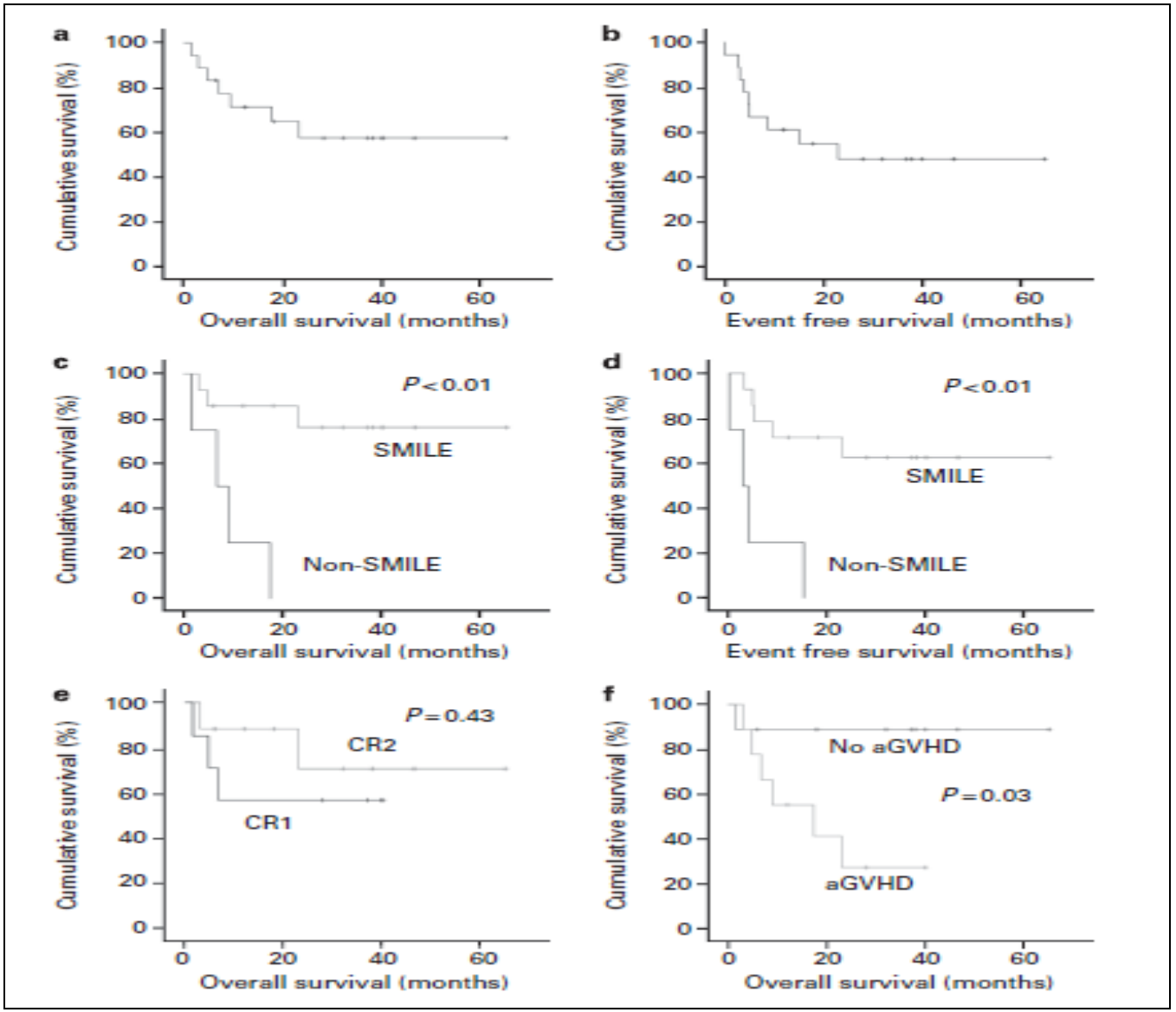
Allogenic HSCT in NK/T- cell lymphoma

Table 2. Selected studies on allogeneic HSCT in patients with natural killer/T-cell lymphomas

Study	*No.*	*Age*	*Stage*	*Status*	*Chemotherapy*	*Conditioning*	*OS*	*PFS*	*TRM (%)*
Tse *et al.* (present study)	18	40.5	I/II = 5 III/IV = 13	CR = 16 PR = 1 PD = 1	L-asp = 14 Others = 4	MAC = 14 RIC = 4	5 years, 57%	5-year 51%	22
Ennishi *et al.*[13]	12	28	I/II = 4 III/IV = 8	CR = 4 PR = 4 PD = 4	L-asp = 5 Others = 7	MAC = 9 RIC = 3	3 years, 55%	3-year 53%	8.3
Yokoyama *et al.*[12]	5	30	I/II = 3 III/IV = 2	CR = 3 PR = 0 PD = 2	L-asp = 4 Others = 1	MAC = 5 RIC = 0	ND	ND	0
Susuki *et al.*[14]	6	28	I/II = 2 III/IV = 4	CR = 1 PR = 0 PD = 5	L-asp = ND Others = ND	MAC = 6 RIC = 0	ND	ND	16.6
Murashige *et al.*[11]	22	38[a]	I/II = 1[a] III/IV = 19[a]	CR = 8[a] PR = ND PD = ND	L-asp = ND Others = ND	MAC = 17 RIC = 5	2 years[a], 40%	2 years[a], 34%	28.5[a]

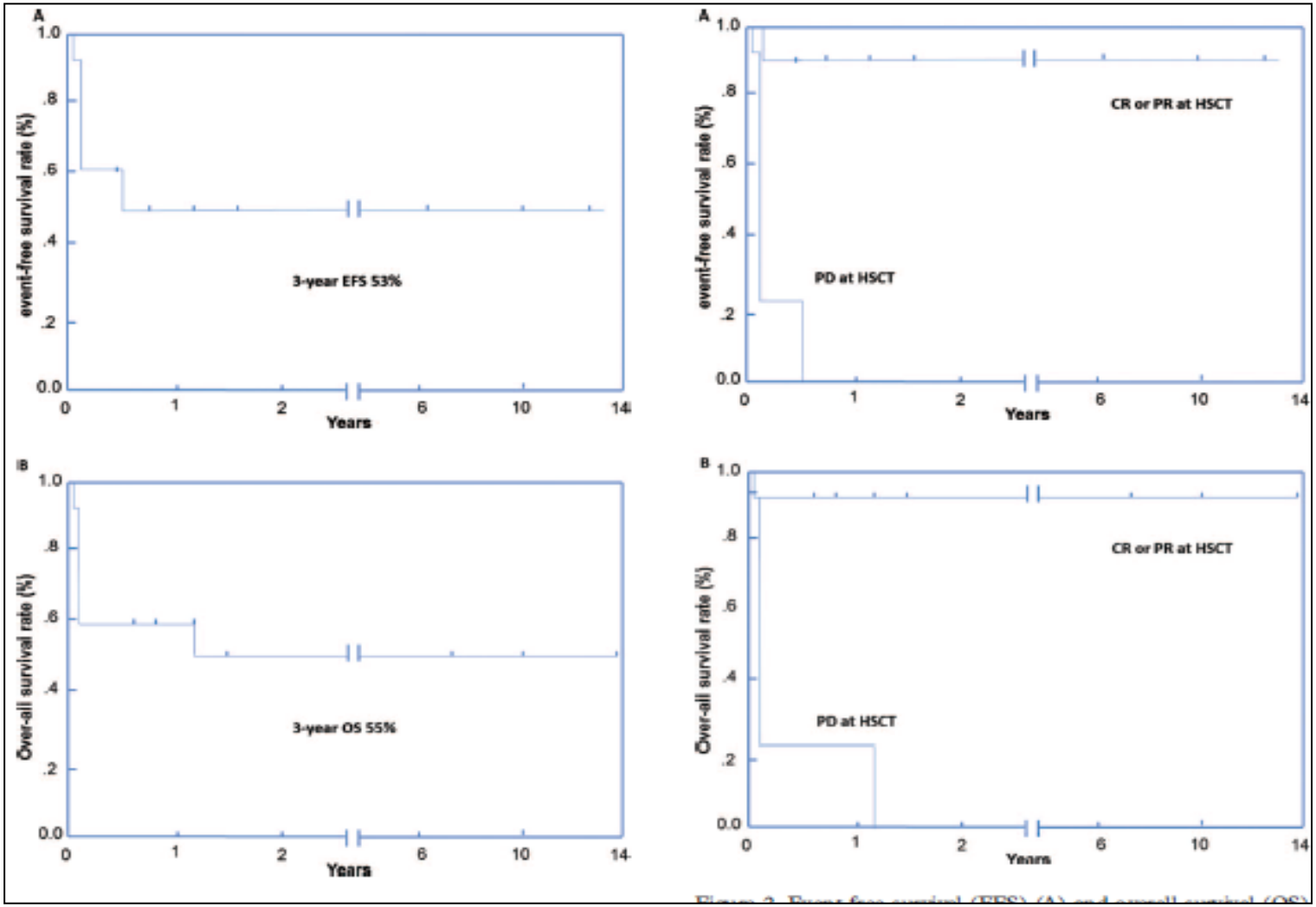
Tse et al BMT 2014

Allogenic Transplant in NK/T-cell Lymphoma



Tse et al BMT 2014

Allogenic Transplant in NK/T-cell Lymphoma



Ennishi et al Leuk Lymphoma 2011

NCCN Guidelines Version 1.2015 Panel Members
Non-Hodgkin's Lymphomas

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ξ Bone marrow transplantation
≠ Pathology
Þ Internal medicine
ϖ Dermatology
¥ Patient advocacy
* Writing Committee Member

NCCN Guidelines Panel Disclosures