Treatment approaches in NK/T cell lymphoma nasal type

Dr Dima El-Sharkawi

Haematology Consultant

The Royal Marsden Hospital,

London, UK

Disclosures

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Summary

- ENKTCL is rare and aggressive with geographic variations in incidence
- Optimal treatment not defined but in limited stage combination chemotherapy and radiotherapy optimal and advanced stage asparginase containing regimens are optimal
- CHOP insufficient (MDR associated protein on ENKTL)
- PD1 inhibition is a promising strategy for management

Background

- NK cells traditionally thought to be part of the innate immune system
- Reside and mature in non-nodal sites including extranodal sites
- No “unique” rearrangements in contrast to B and T lymphocytes
- Express CD2, CD3ε, CD16, CD56, CD94 and KIR receptors

Differential Diagnosis

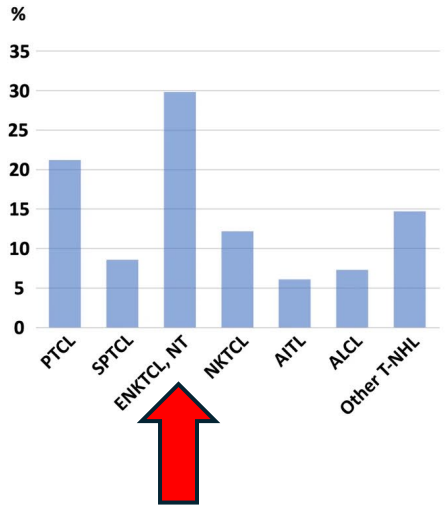
- Aggressive NK cell leukaemia

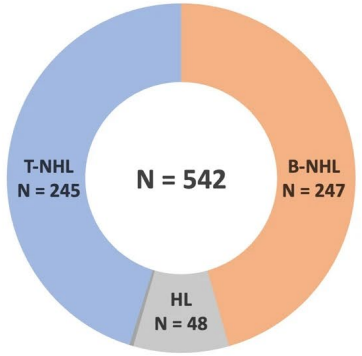
- EBV positive nodal T and NK cell lymphomas
  - EBV positive nodal T and NK cell lymphoma
  - Extranodal NK/T cell lymphoma
    - Nasal or non-nasal

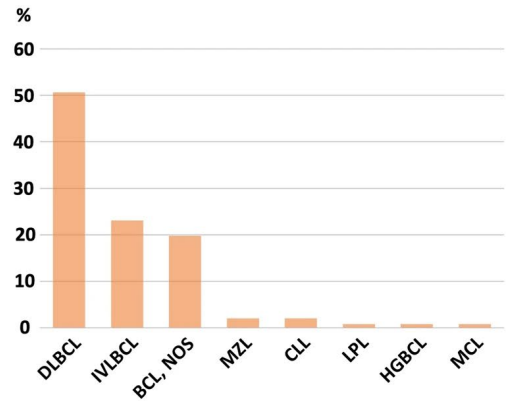
WHO 2022

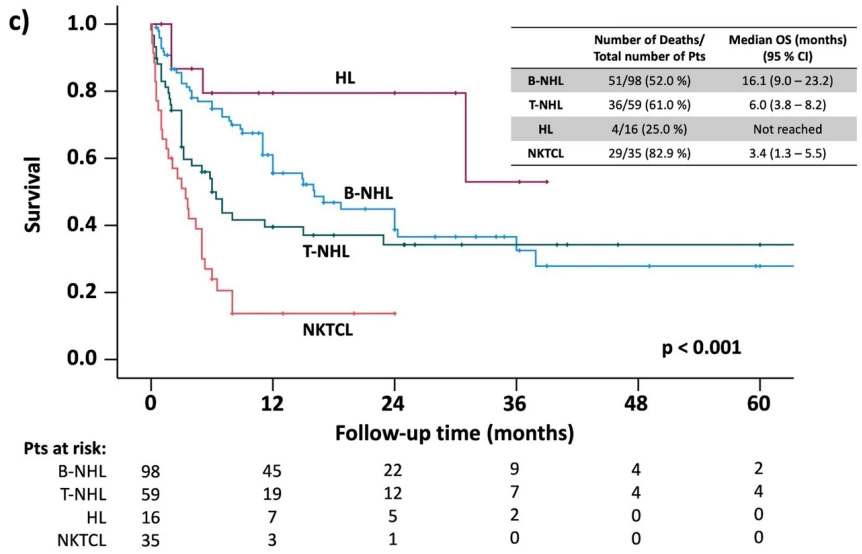
Haemophagocytic lymphohistiocytosis HLH

- Pathologic activation cytotoxic T lymphocytes and macrophages
- Fever cytopenia splenomegaly









- Etoposide containing regimens required?
- Case reports with PD1 inhibition

Leukemia 2024 38: 235-249
J Hematol 2024 13(1-2):46-51
Clin Onc 2021 147: 863-869

Comparison of differential diagnoses

	Aggressive NK cell leukaemia	EBV positive nodal T and NK cell lymphoma	Extranodal NK T cell lymphoma
Geographical distribution	Asia	E Asia	E Asia C and S America
Most common demographics	Young to middle aged adults Strong ass with EBV	Older males RF: autoimmune history/DM	Adults male predilection Ass with certain HLA subtypes? IS?
Presenting features	B symptoms HLH	Lymphadenopathy B symptoms Thrombocytopenia	Nasal blockage, sinus, orbital involvement Advanced stages: B symptoms, marrow infiltration HLH
Disease distribution	PB, marrow, liver spleen	Nodal	Nasal type 80% upper aerodigestive tract involvement
Mutations	Del6(q21q25) i7(q10) and 11q del Losses of 7p and 17p gains in 1q TET2 mutation CREBBP KMT2D DDX3X PDL1 TP53 STAT3 STAT5	TET2 64% PIK3CD 33% DDX3X 20% STAT3 19% Recurrent losses of 14q11.2 Gains of 6p22.1 14q32.33	Loss of 6q STAT3 JAK3 STAT5B Epigenetic regulators Tumour suppressor DDX3X BCOR
IHC	CD2+ CD3ε+ CD5- CD7+ CD16+ CD56+ and cytotoxic molecules	Pan T cell marker expression and cytotoxic molecules (20% NK) EBER+ve	
Prognosis	3 months	2.5-8 months	26-76 months

Different molecular subtypes

- Multi-omics approach on 128 samples defined patients into 3 subgroups with differing cell of origin, EBV expression, transcriptional profiles and response to asparaginase therapies

- TSIM subtype: activation of JAK STAT (3yr OS 92%)

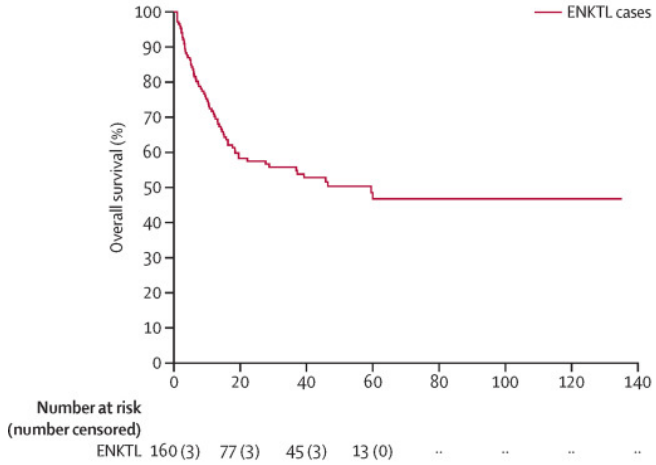
- MB subtype: MYC overexpression (3yr OS 38.5%)

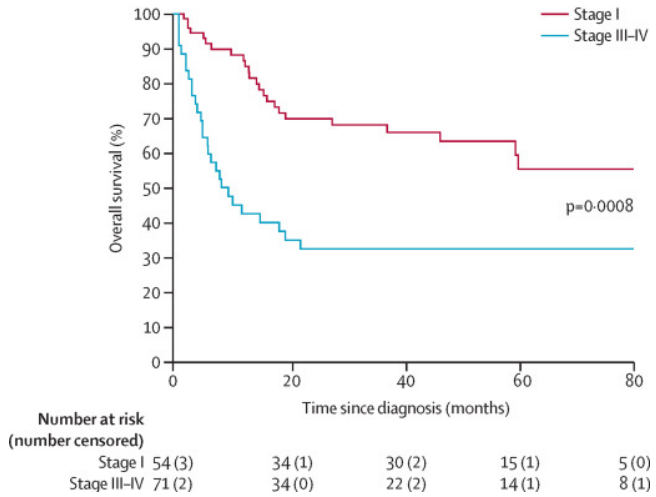
- HEA subtype: overexpression of histone chaperone DAXX (3yr OS 79%)

Cancer Cell 2020 37(3): 403-419

Prognosis

			Number of pt	OS	Reference
SEER	2001-2014	Routinely collected statistics	797	mOS 20m	Clin Lymph Myel Leuk 2018 18(7):475-479
Japan	2000-2013	Retrospective study	358	5yr OS 68% limited stage 24% advanced stage	JCO 2017 35(1):32-39
International T cell project	2007-2017	Prospective cohort study	106	5yr OS 54%	Lancet Haematol 2020 7(4): e284-294





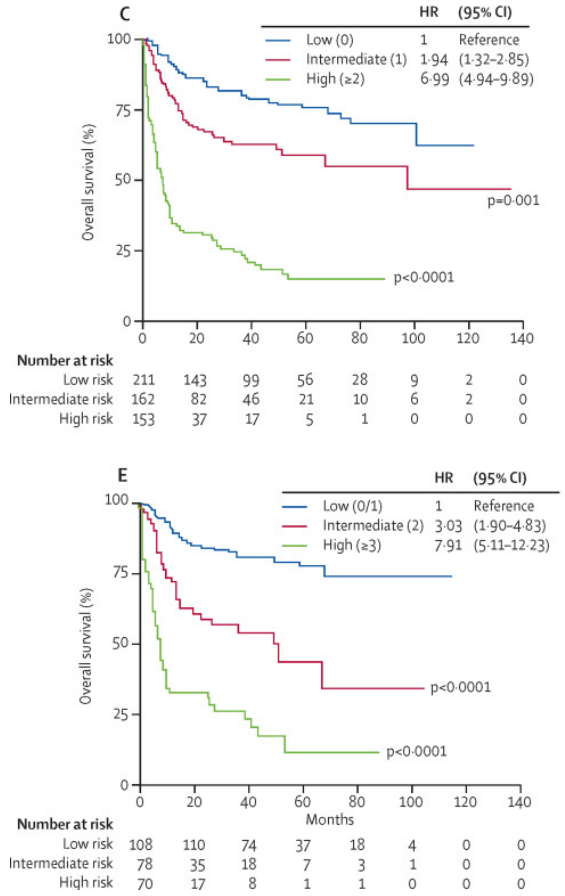
Lancet Haematol 2020 7(4): e284-294

Prognostic indices

- IPI
- Korean Prognostic Index
- PINK Prognostic index of natural Killer lymphoma
  - Age >60; stage 3 or 4; non-nasal type; distal LN involvement
- Nomogram revised Risk index NRI
- CA system

- EBV-DNA in plasma ass with poor prognosis
- Persistence of EBV positivity ass with poor prognosis

PINK
PINK-E IPI



JCO 2006 24:612-618
Lancet Oncol 2016 17:389-400
Leukemia 2020 34(8):2243-2248
Leukemia 2021 35(1):130-142
Blood 2011 118(23):6018-6022

Treatment approaches

- Anthracycline containing regimens are ineffective
- L-asparginase containing regimens

- Radiotherapy in localised disease or nasal site

- ?PDL1 inhibition

Frontline therapy- limited stage disease

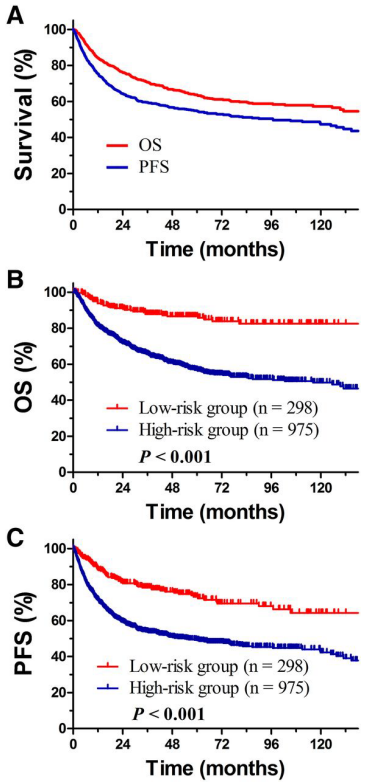
- Combined modality treatment (chemotherapy and radiotherapy) is standard of care in many countries although some consider radiotherapy only as initial studies didn't indicate added benefit of chemotherapy.

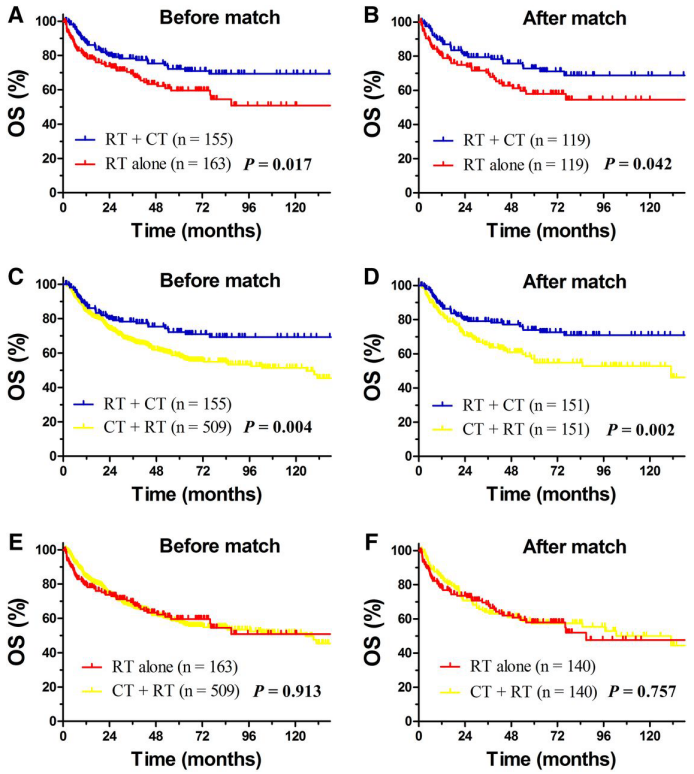
- Optimal chemotherapy regimen or whether radiation should be concurrent or "sandwich" is unknown

- VIDL/ LVP/ GELOX/ SMILE/MESA chemo regimens.
- 40-50Gy Radiotherapy

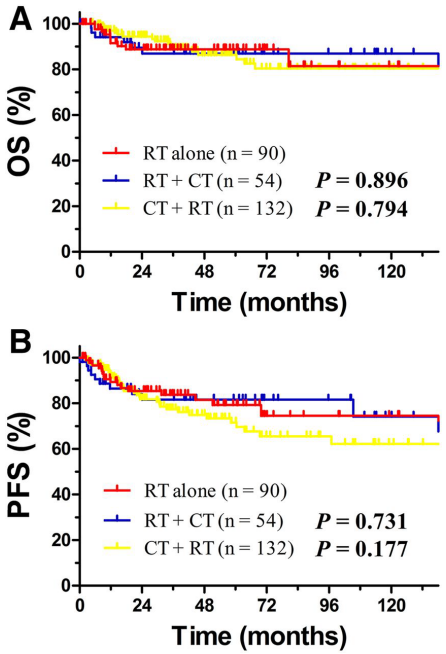
Journal Hem Onc 2018 11:140

- Retrospective analysis of 1273 patients with propensity score matched analyses





High risk patients



Low risk patients

Blood 2015 126(12):1424-1432

Frontline therapy- advanced stage disease

- SMILE chemotherapy:

  Steroid, Methotrexate, Ifosfamide, L-asparaginase, Etoposide

- DDGP chemotherapy

  Dexamethasone, gemcitabine, Cisplatin, peg-Aspariginase

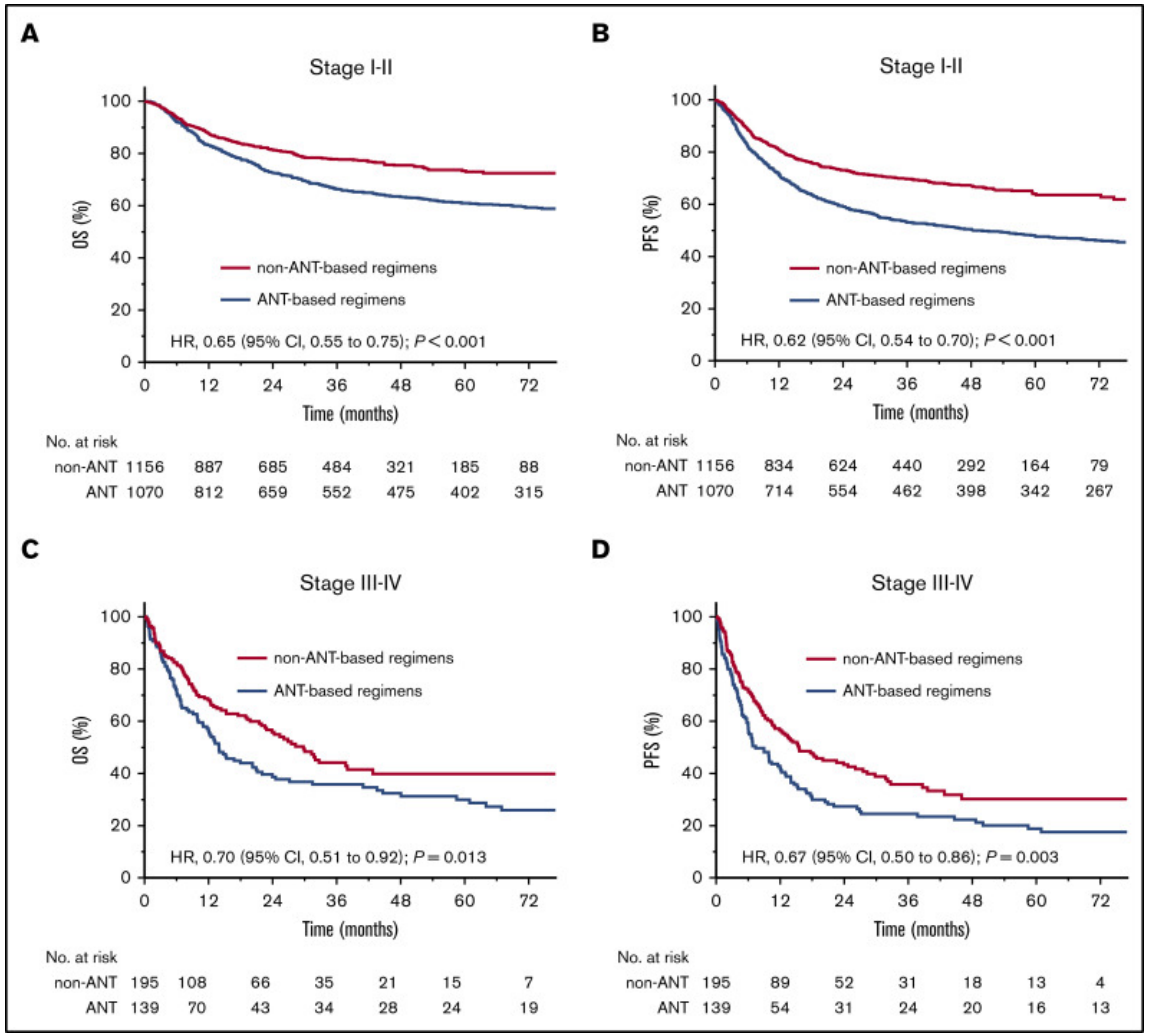
- AspaMetDex

Evidence to not use anthracycline based chemotherapy regimens

Chinese retrospective series of 2560 patients from 2000-2015

5y OS 69% (non-anthracycline)

5yr OS 58% (ANT)



Blood Adv 2020 4(13): 3141-3153

SMILE chemotherapy

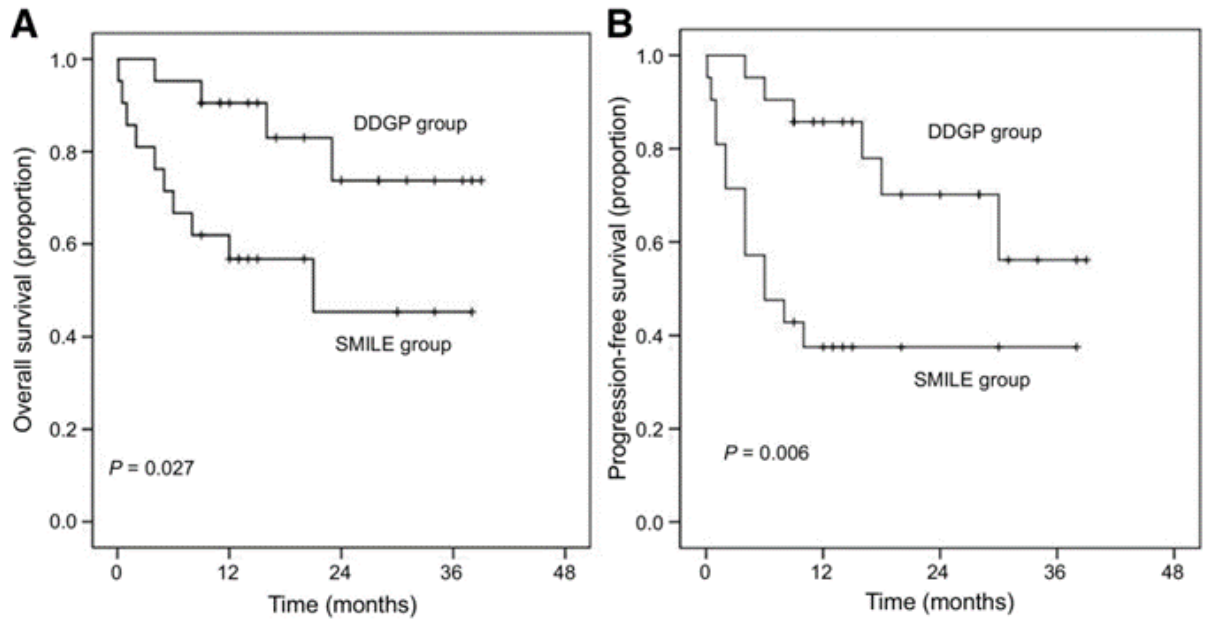
			ORR	CR	OS		
SMILE	Phase 2 1st line and RR	38	79%	45%	1yr 55%		JCO 2011 29(33):4410-4416
	retrospective	87 26	81%	66% 54%	5yr 50% 47%	43 1st line 26 stage IV patients	Blood 2012 120(15): 2973-2980
	retrospective R/R	23	61%	31%		compared to DDGP	Clin Transl Sci 2021 14(1):405-411
	Prospective Phase III	21	67%	29%	2yr 45%	Randomised to DDGP	Clin Cancer Res 2016 22(21):5223-5228

Median number of cycles across studies = 2-3

Cytopenias, infection, hepatotoxicity common
10% rate of ITU admission, treatment related deaths.

DDGP versus SMILE chemotherapy

	ORR	CR
DDGP	95%	71%
SMILE	67%	29%



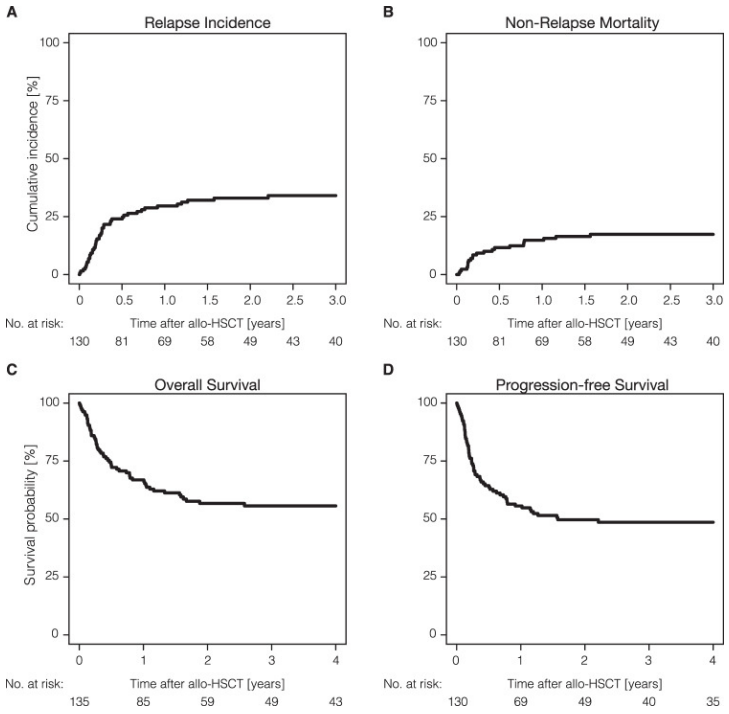
Clin Cancer Res 2016 22(21):5223-5228

Assessing interim and EOT response

- Mid treatment PET predictive during SMILE chemotherapy
- EBV DNA response predictive during and at end of treatment

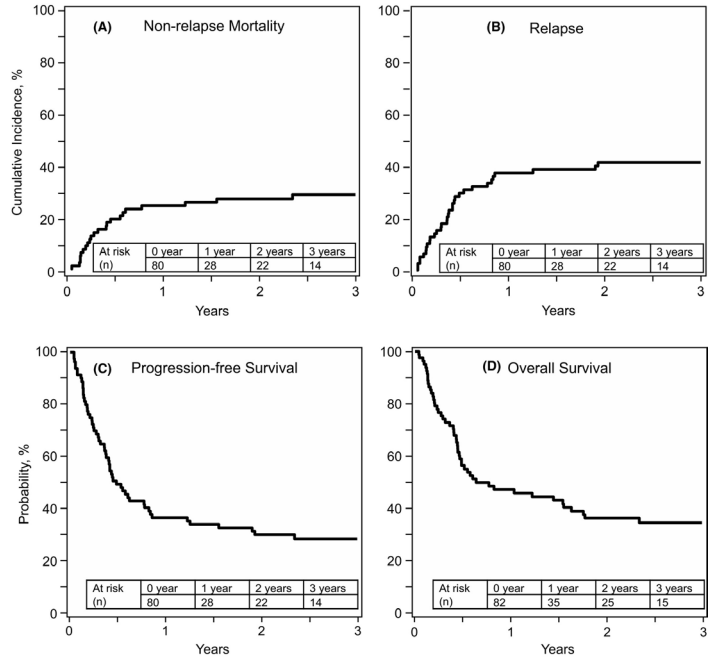
Blood 2011 118(23):6018-6022
Blood 2004 104(1):243-249
Leukemia 2014 28(4):865-70
J Nucl Med 2014 55(6):911-916

Role of transplant: allogeneic transplant



Outcomes 135 patients between 2010 and 2020 from EBMT registry and Asian centres

Leukemia 2023: 37(7): 1511-1520



CIBMTR outcomes 82 patients between 2000 and 2014

BJHaem 2018 182(6):916-920

Role of transplant unclear

- Role of autologous transplant very unclear
- Matched controlled study indicated perhaps a benefit, but retrospective analysis.

- Consider allogeneic transplant in those with advanced stage or R/R disease, and who achieve remission.

Relapsed/ refractory disease

PD1/ PDL1 inhibition in NK/T cell lymphoma

	Trial type	Inhibitor	Number of patients	ORR	CRR	Notes
Annals of Hem 2024 epub	Retrospective	Pembrolizumab	58	39%	32%	
Leukemia 2020 34:3413-3419	Retrospective	Pembrolizumab	19	47%	36%	Long term clinical benefit in those with CR 28m Cryptic rearrangements of PDL1 were strong predictor of response
Blood 2017 129:2437-2442	Retrospective	Pembrolizumab	7	100%	5/7 71%	All 5 in durable remission at 6m
J Hematol oncol 2018 11:15	Retrospective	Pembrolizumab	7	57%	2/7 29%	
Cancer Res Treat 2019 51(2): 611-622	Retrospective	Pembrolizumab	14	44%	5 36%	Included some of the pt in ref 1
Ann Hematol 2018 97:193-6	Retrospective	Nivolumab	3	100%	2/3	1 died from infection Low dose nivolumab given
Blood 2020 136(24):2754-2763	Phase 2	Avelumab	21	38%	24%	PD1 exp predictive Those with CR had durable response
Blood 2020 136 S1 P39 Signal Transduction and targeted therapy 2024 epub	Phase 2 SCENT	Sintilimab + HDACi chidamide	38	60%	49%	mDOR 25m EBV DNA prognostic

Also some trials using sintilimab plus chemo and CS-001

Other therapies

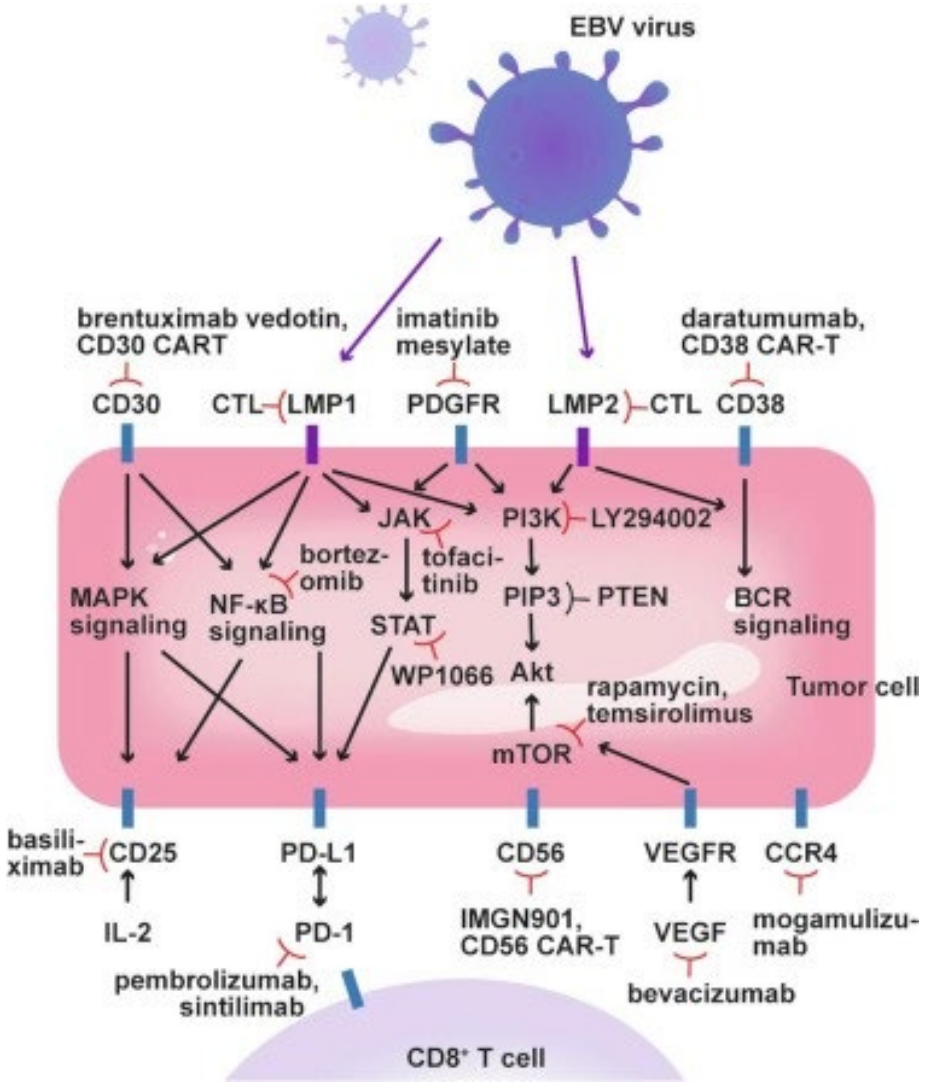
- Anti-CD38 monoclonal antibody (daratumumab)
  - Expressed on NK cells and upregulated in ENKTCL
  - Phase 2 study in 32 patients ORR 25% DoR 55 days

- Anti-CD30 Brentuximab
  - Case reports
  - 7 patients included in trial for CD30+ve NHL ORR 29% (1 PR 1CR) durable> 1 year

Journal Hematol and Oncol 2021 14(25)
Cancer Res Treat 2020 52(2):374-387

Other potential targets

- CD25 – denileukin
- CD56
- JAK inhibitors
- PI3Kinase inhibitors
- Proteasome inhibitors
- HDAC inhibitors
- IMiDs
- EBV-CTLs



Cancer Treatment Reviews 2020 89: 102065

Summary

- ENKTCL is rare and aggressive with geographic variations in incidence
- Optimal treatment not defined but in limited stage combination chemotherapy and radiotherapy optimal and advanced stage asparginase containing regimens are optimal
- CHOP insufficient
- PD1 inhibition is a promising strategy for management