Extra nodal NK/T cell lymphoma (ENKTL)

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Today`s TOPIC

- Background
- Prognostic Factor
- 1st line treatment
    - Limited stage with case presentation
    - Advanced stage with case presentation
- Role of stem cell transplantation
- Novel treatment

Extra nodal NK/T cell lymphoma (ENKTL)

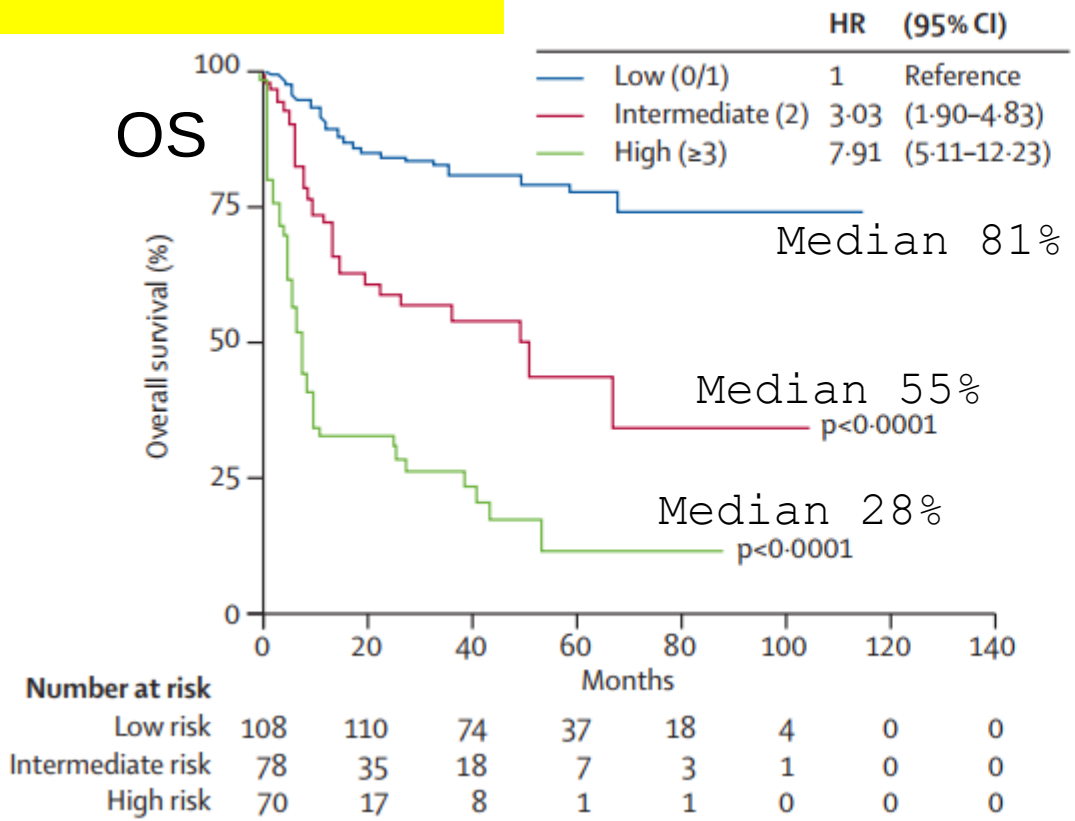
- More common in East Asia and Latin America
- Median age at diagnosis: 40-60
- Associated with Epstein-Barr virus (EBV)
- Predominantly extranodal disease, especially nasal lesion (around 90%)
- OS < 50% for pts treated with CHOP followed by radiation therapy (RT)
- No Phase 3 clinical trials` based evidence due to the rarity of the disease (Less than 1% of lymphoma)

Prognostic Index for Natural killer lymphoma (PINK-E)

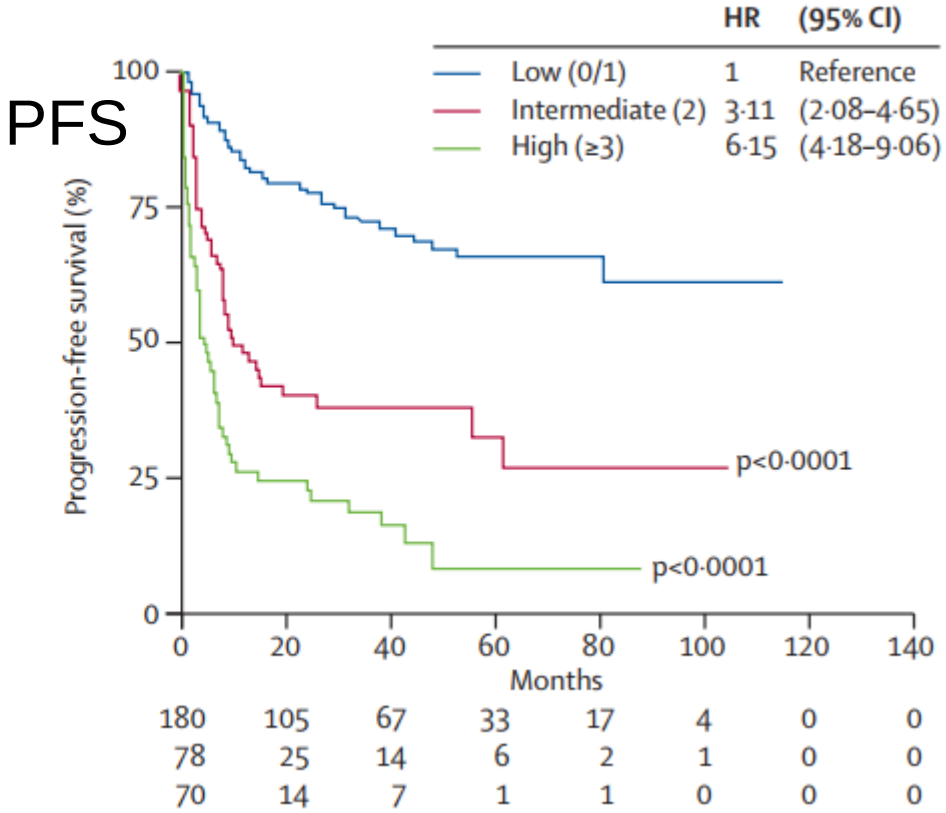
Risk Factors
- Age > 60
- Stage III/IV
- Distant Lymph-node involvement
- Non-nasal type disease
- EBV-DNA

N = 527 from 11 countries
Median Follow-up:44.9 Mo

OS



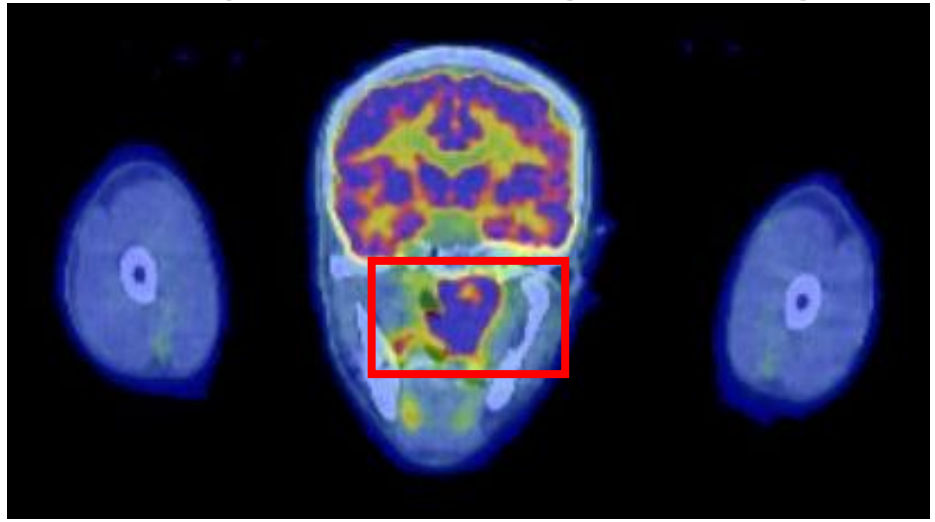
PFS



Kim et al, Lancet Oncol 2016:17:389-400

Limited Stage: Case#1

- 58 y.o. Male
- Developed fever, nasal congestion, difficulty breathing through the nose, and throat pain
- No major comorbidity
- Stage 2E
- EBV-DNA:1.5 x 10*3
- PINK-E: Low (1)



A large mass (6.9 x 4.0 x 7.2 cm)
- posterior nasopharynx left of midline
- with extension into the left nasal cavity
- involvement into the left skull base

No other systemic disease

Which Treatment option you would choose?

1. Radiation only
2. CHOP+ Radiation therapy (RT)
3. Co-current cisplatin/radiation followed by VIPD
4. Co-current DeVIC and radiation
5. (Modified) SMILE followed by radiation therapy
6. DDGP followed by radiation therapy
7. GELAD-IMRT-GELAD
8. Others

Treatment options for limited stage ENKTL

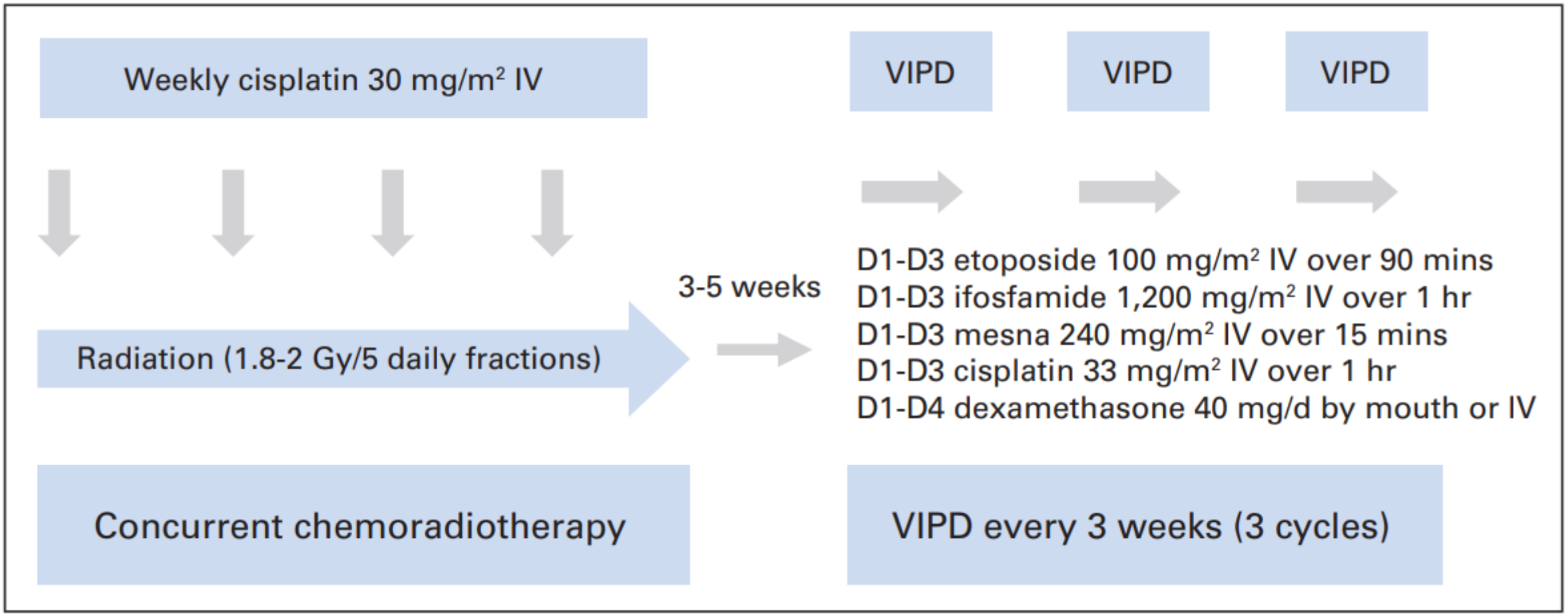
Treatment	N	RT	CR (%)	Median Follow-up	OS (%)	PFS (%)	Design
CCRT-2/3DeVIC	27	50 Gy	77	67 Mo	70 (5 yr)	63 (5 yr)	P1/2
CCRT+CDDP- VIPD x3	30	40 Gy	80	24 Mo	86 (3 yr)	85 (3 yr)	P2
CCRT+CDDP- VIDL +- ASCT	30	40 Gy	87	44 Mo	73 (5 yr)	60 (5 yr)	P2
Sandwitch RT GELAD-IMRT-GELAD	52	50-60Gy	92.3	32 Mo	94.2 (3 yr)	90.4 (3 yr)	P2
M-SMILE x 2 Followed by RT	11	45 Gy	100	24 Mo	100 (2 yr)	83 (2 yr)	Retro
DDGP x 2 Followed by RT	11	45 Gy	100	24 Mo	100 (2 yr)	83 (2 yr)	Retro
P-GEMOX x4 Followed by IMRT	202	54.6 Gy	83.2	44 Mo	85.2 (3 yr)	74.6 (3 yr)	Retro

CCRT or Peg-Asp combined regimen are recommended at NCCN guideline

The benefit of L-Asp for limited stage ENKT was not confirmed due to severe toxicity

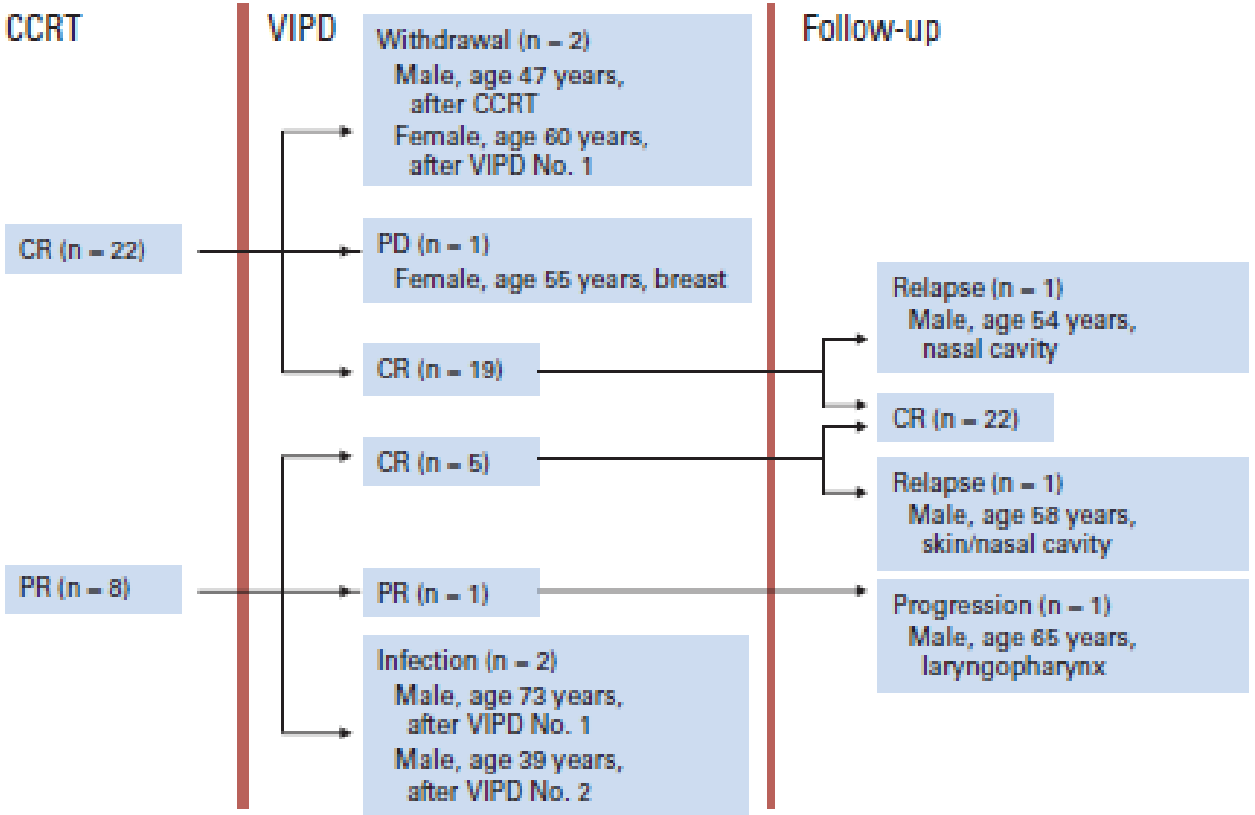
Yamaguchi et al, JCO 2009, 27(33):5594-5600
Kim et al, JCO, 2009;27(35):6027-6032
Kim et al Annals of Hematology 2014;93(11):1895-1901
Zhu et al, Br J Hematol 2022;196:939-946.
Qi et al, Leuk Lymphoma. 2016 November ; 57(11): 2575–2583
Zhang et al Am J Hematol. 2021;96:1481–1490
Zhang et al Leukemia Research. 2022;118:106881
Yamaguchi et al, Blood 2018;131(23):2528-2540

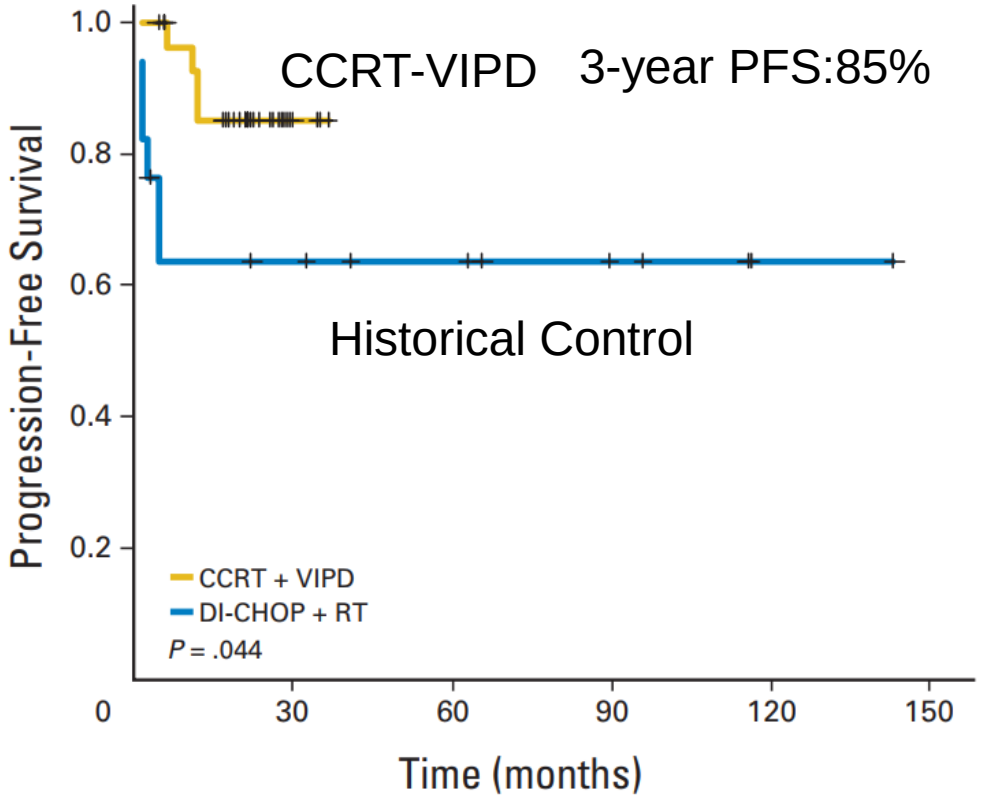
Case #1: On CCRT followed by VIPD



Kim et al, JCO, 2009;27(35):6027-6032

Clinical outcome: CCRT-VIPD





Response Rate:
After CCRT:
CR 73%, ORR100%
After VIPD:
CR 80%, ORR100%

Relapse:
13% (4/30) vs 29.4% (5/17)

Kim et al, JCO, 2009;27(35):6027-6032

Toxicity: CCRT-VIPD

Table 2. Toxicity Profiles

	Adverse Event by Treatment Group and Event Grade							
	CCRT				VIPD			
Toxicity	1	2	3	4	1	2	3	4
Hematologic								
Anemia	10				4	11	7	1
Leukopenia	2	5			5	4	6	8
Thrombocytopenia						5	7	
Febrile neutropenia							15	3
Nonhematologic								
Nausea	13	10	1		10	7	1	
Vomiting	6	3			3	4	1	
Diarrhea	2				2			
Anorexia	5	1			5			
Constipation	2	1			4			
Stomatitis	7	4			5	1		
Azotemia						3		
Gastritis					1			
Neuropathy	6				6	1		

Abbreviations: CCRT, concurrent chemoradiotherapy; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone.

CCRT

- 23% G1/2 hematological toxicity
- One G3 nausea

VIPD

- G3/4 hematologic toxicities were frequent
- 1 death due to PD/Sepsis

Summary: Limited stage ENKTL

– CCRT approach might be preferred considering prospective P2 evidence with good outcome

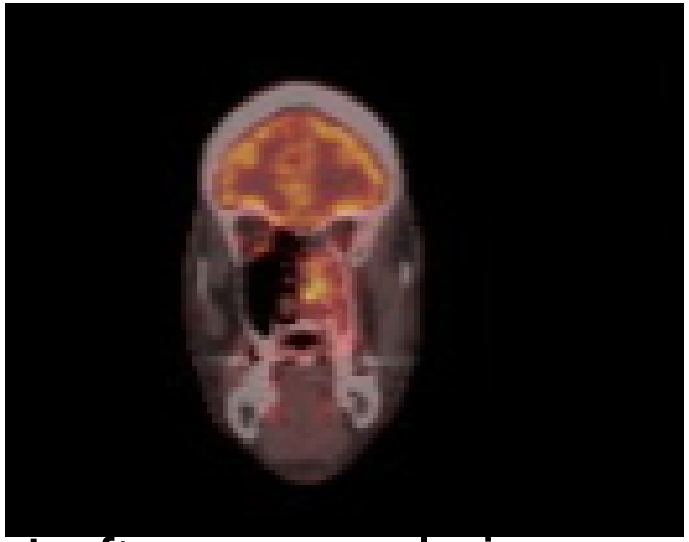
- Sandwich (GELAD) approach can be another reasonable option to be considered.

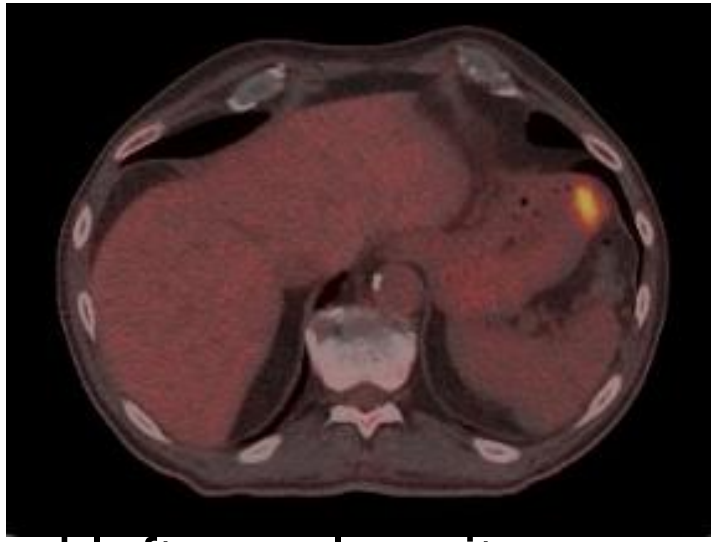
- Retrospective data of other P-Asp based regimen showed encouraging outcome and further evaluation with prospective trial is warranted.

- Careful assessment and communication between hematologists and radiation-oncologists is critical

Advanced Stage: Case Presentation

- 66 y.o. Male
- Developed sinusitis with GI issue on his gastric involvement.
- No major comorbidity
- Stage IV
- EBV-DNA:+
- PINK-E:4, High risk





Left paranasal sinuses and left nasal cavity, Stomach, colon, nodal (left submandibular region) and peripheral nerve (left C7 exiting nerve root)

Which Treatment option you would choose?

1. CHOP
2. Co-current cisplatin/radiation followed by VIPD
3. Co-current DeVIC and radiation
4. (Modified) SMILE
5. DDGP
6. P-GEMOX
7. Others

Treatment option for Advanced stage or relapsed/refractory ENKTL

Treatment	N	ORR	CR	Median Follow-up	OS (%)	PFS (%)	Design
SMILE x 2	38	73 %	45 %	24 Mo	55 (1 yr)	53 (1 yr)	P1/2
P-GEMOX x 5	30	94%	26%	28 Mo	65 (2 yr)	39 (2 yr)	Retro Single center
DDGPx6	40	90%	67.5%	41.5 Mo	74.3 (Median)	56.6 (Median)	Randomized P2
M-SMILE	9	78%	100	8.5 Mo	56 (6 Mo)	56 (6Mo)	Retro

- L-asparaginase is the key drug
- ORR by CHOP is between 10-36%
- Original SMILE demonstrated severe toxicity

- modified-SMILE or dose-reduction are recommended

Suzuki et al, JCO 2009, 27(33):5594-5600
Wang et al Oncotarget 2016;7(20):29092-29101. DDGP
Qi et al, Leuk Lymphoma. 2016 November ; 57(11): 2575–2583
Wang er al JAMA Oncology 2022
Yamaguchi et al, Blood 2018;131(23):2528-2540

Efficacy and Toxicity: DDGP/SMILE

Response	No. (%) DDGP Group (n = 40)	No. (%) SMILE Group (n = 40)	*P* value[a]
CR			
Yes	27 (67.5)	19 (47.5)	.07
No	13 (32.5)	21 (52.5)	
ORR (CR + PR)			
Yes	36 (90.0)	24 (60.0)	.002
No	4 (10.0)	16 (40.0)	

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response.

[a] χ^2 test.

Hematological Toxicity

- G3/4 neutropenia

  85% (SMILE) VS 65% (DDGP)

Treatment-related death

- 17.5% (SMILE) VS 2.5% (DDGP)

Mainly infection, but

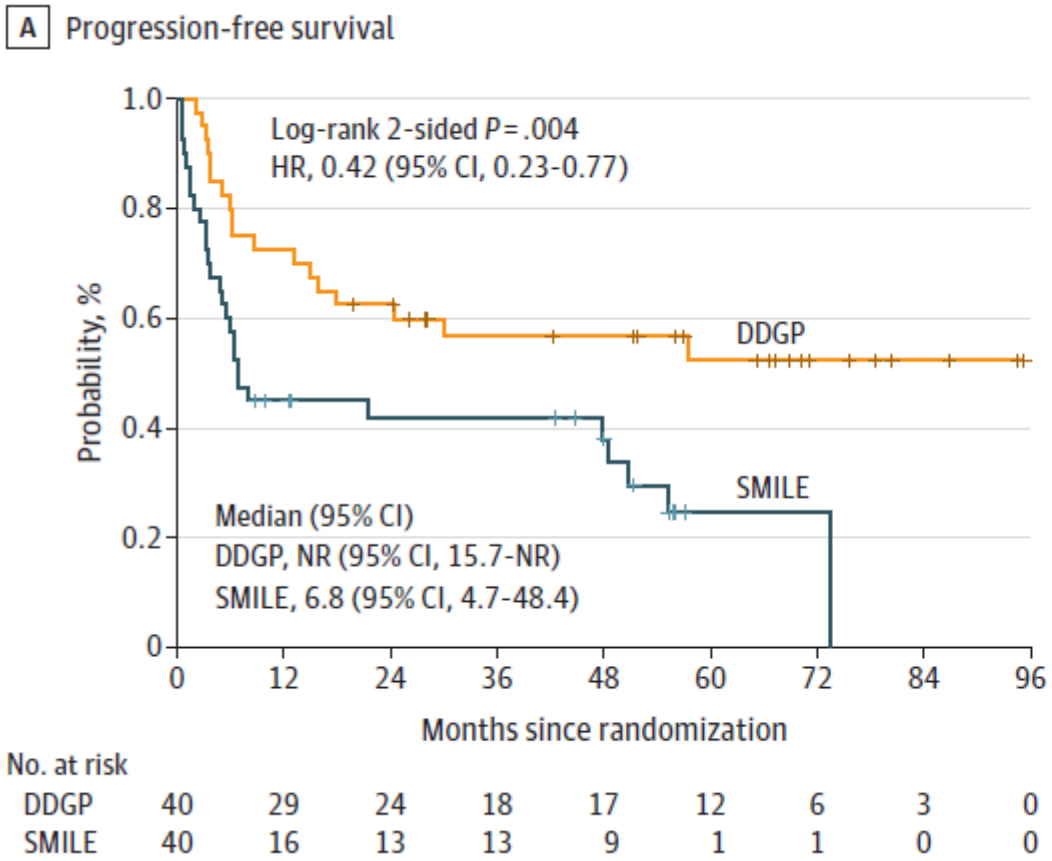
infection events were not reported

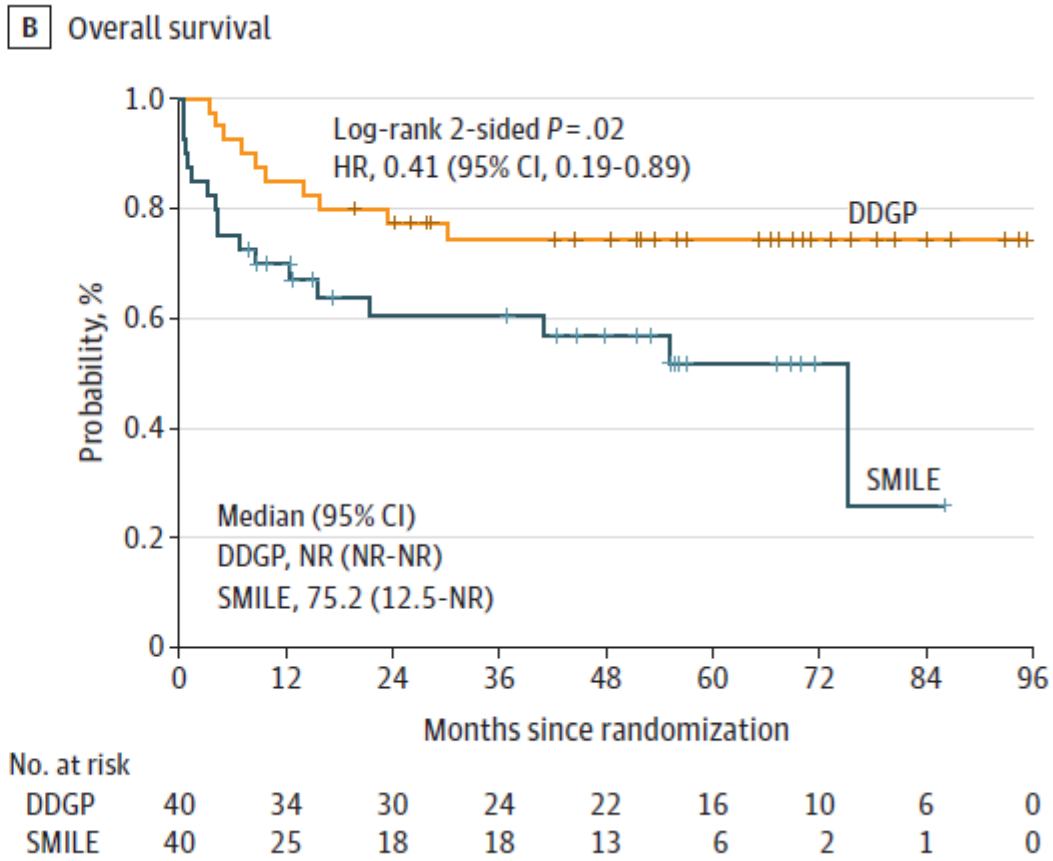
in the study

⋆This is not original SMILE as reported P2 study (4 weeks cycles), but 3 weeks cycle

Wang er al JAMA Oncology 2022

Survival analyses: DDGP vs SMILE





*Stem cell transplantation information is not available.

Summary: Advanced stage ENKTL

- L-asparaginase is the key drug with prospective study evidence

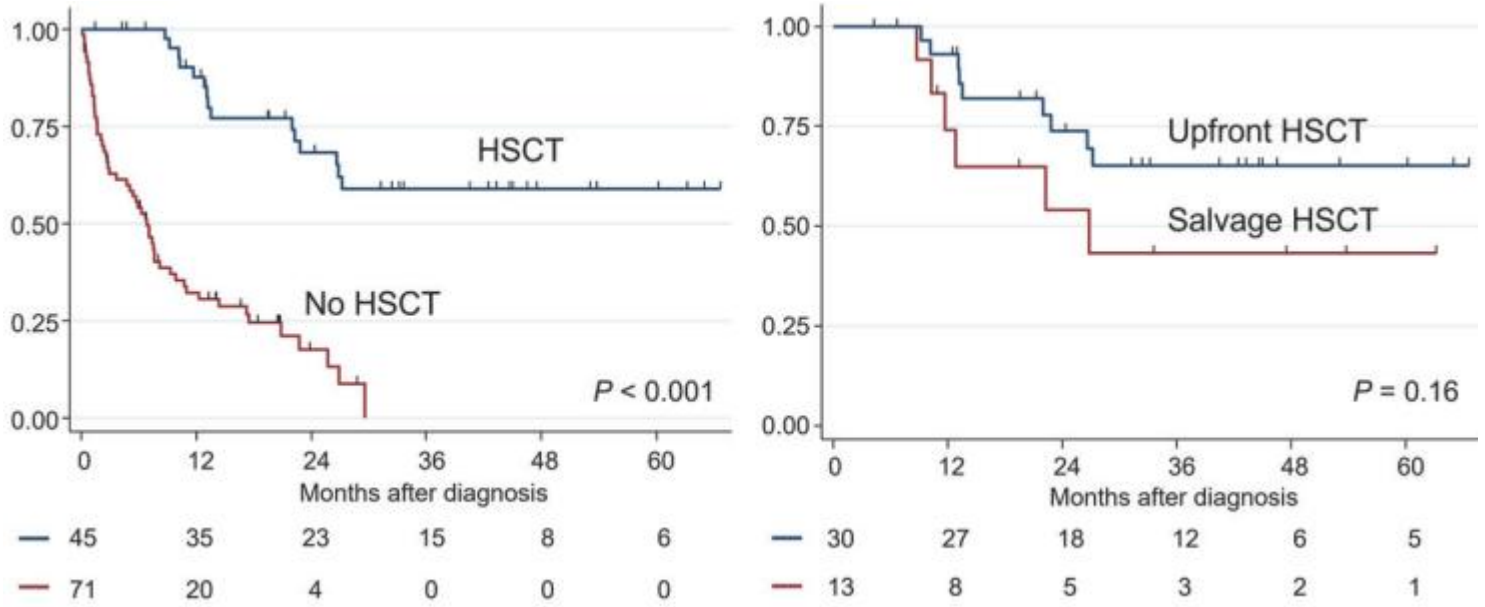
- SMILE (every 3 weeks) might be too toxic

- DDGP and/or mSMILE could be reasonable option.

- Might require consolidative stem cell transplantation

Stem cell transplantation: Limited evidence

- No clear evidence of benefit of ASCT or allo-SCT in limited stage ENKTL
- For advanced stage, retrospective study (real world data from Japan) indicated the benefit of consolidative allo-SCT after L-Asp based induction (2 year OS> 70%)
- Could be a reasonable option for high-risk Advanced stage or relapsed setting
- Role of Auto-SCT is uncertain due to small sample size in the studies



Fujimoto et al, Leukemia 2025;39:909-915

High efficacy of PD-1/PD-L1 targeted treatment

Treatment	N	ORR	CR	Median Follow-up	OS (%)	PFS (%)	Design
Pembrolizumab	7	100 %	71 %	6 Mo	NA	NA	Retro
Sugemalimab (PD-L1)	80	44.9%	28%	18.7 Mo	67.5 (1 yr)	NA	P2
Avelumab (PD-L1)	21	38%	24%	15.7 Mo	NA	NA	P2
Cemiplimab (PD-1) + Isatuximab (CD38)	37	65%	51%	30.2 Mo	NR (Median)	9.5Mo	P2
Sintilimab+P-GEMOX	34	100%	85%	21 Mo	76% (3 yrs)	64% (2 yrs)	P2
PD-1+P-GEMOX	135	89.6	77	40.7Mo	91.5% (3 yrs)	79.5% (3 yrs)	Retro

Potential Biomarker: 3'-UTR Structure variant of PD-L1 and PD-L1 expression

Kwong et al, Blood, 2017; 129(17):2437-2442
Huang et al, J Clin Oncol, 2023; 41:3032-3041
Kim et al, Blood. 2020;136(24):2754-2763
Kim et al, Blood 2025; 146 (2): 155–166.
Tian et al, Lancet Hematology 2024;11: 336-344
Zou et al, Blood Cancer Journal 2026, E-pub

Summary

Newly diagnosed ENKTL
- Prognostic Index: PINK(-E)

EBV-DNA measurement

Limited Stage

- RT-2/3 DeVIC
- CCRT-VIPD
- Sandwich RT with GELAD
- mSMILE followed by RT
- Clinical Trial

Advanced Stage

- (modified)-SMILE
- DDGP
- P-GEMOX
- Consolidative allo-SCT
- Clinical Trial

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Thank you!

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