

# How I treat Extranodal NK/T-cell lymphoma

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# Conflict of Interest Disclosure

- I hereby declare the following potential conflicts of interest concerning my presentation: no
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- Honoraria: takeda

# Extranodal NK/T-cell lymphoma, nasal type

## What do we know ?

More common in far eastern Asia and some area of south America

More common in male

Mostly presented stage I or II

PINK/PINK-E is prognostic model

Refractory to anthracycline based chemotherapy

Sensitive to L-asparaginase

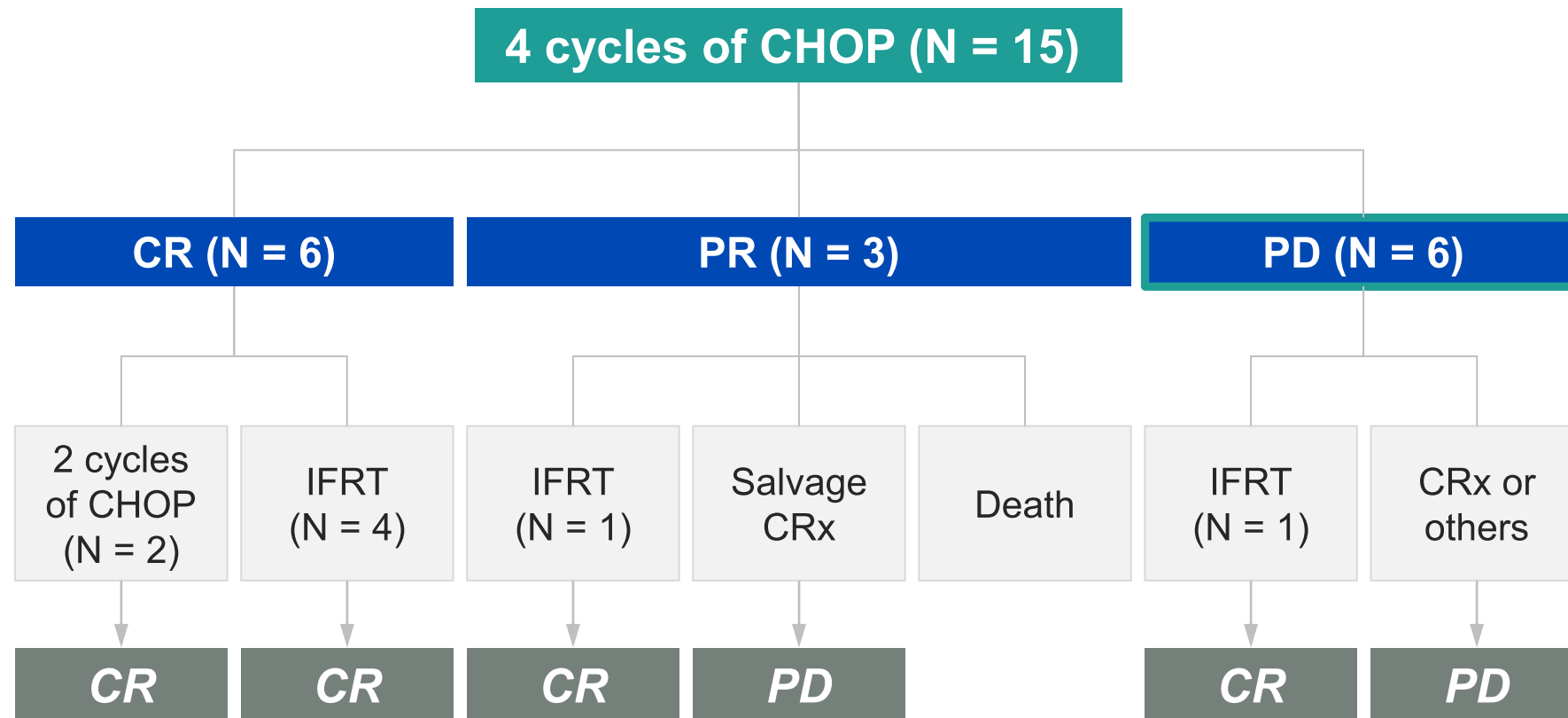
Sensitive to radiation



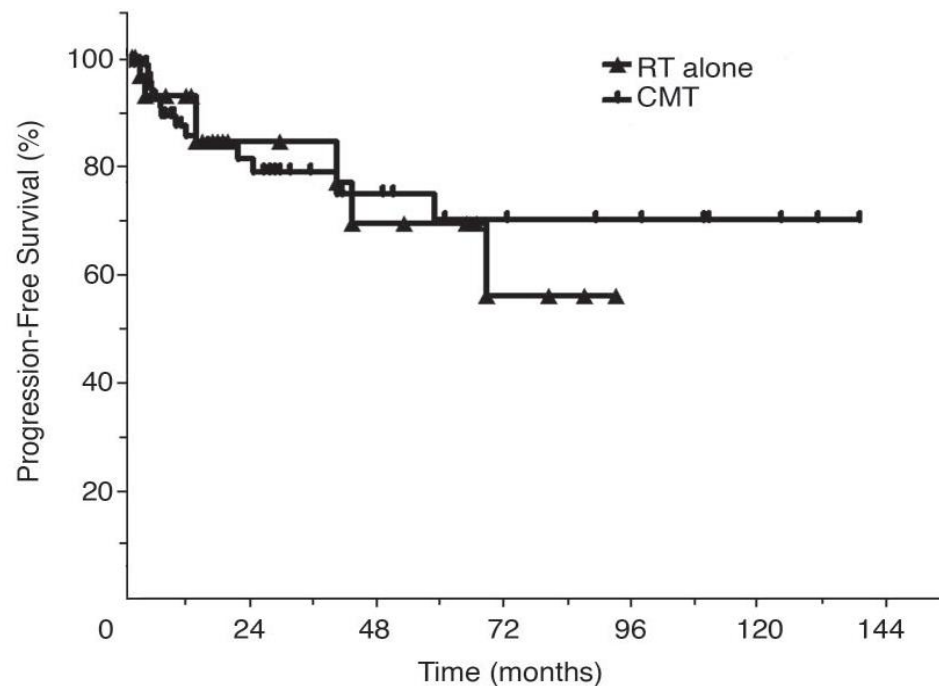
# Treatment of localized Disease



# Treatment of Localized ENKTL

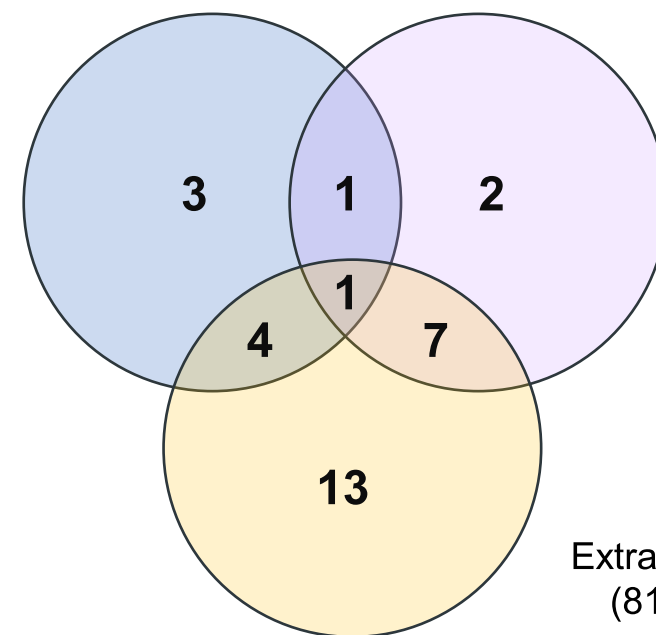


# Radiation alone in stage I/II ENKTL



**CRx (74) : CHOP(64)/ COBVP-16  
(9)/COPP(1)**

Local  
(29%)



**Distant extranodal dissemination :  
primary patterns of failure.**

# Basic strategies from CHOP failure

**1. Radiation alone is similar to radiation and chemo-combination.**

**2. Why chemotherapy is not so successful? P-glycoprotein**

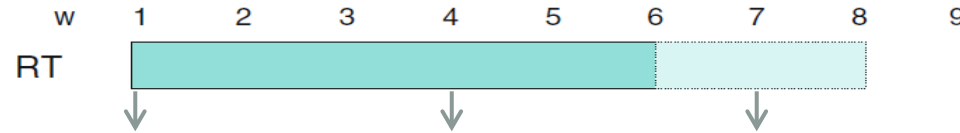
**3. Distant dissemination is the major pattern of failure**

## CHOP-resistant disease /radiosensitive

- Combination with radiation and chemotherapy
- start radiation ASAP
- Select chemotherapy agents not affected by p-glycoprotein

# Treatment of Localized ENKTL

## RT-2/3 DeVIC



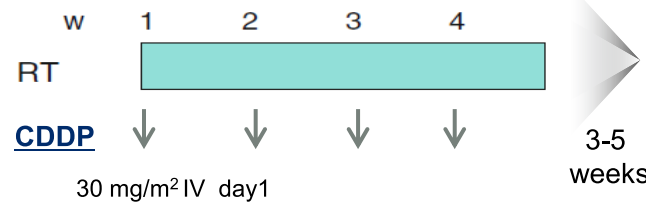
### 2/3 DeVIC

CBDCA	200 mg/m <sup>2</sup> IV	day 1
ETP	67 mg/m <sup>2</sup> IV	days 1-3
IFM	1.0 g/m <sup>2</sup> IV	days 1-3
DMS	40 mg/day IV	days 1-3

RT (50-50.4 Gy; 1.8-2.0 Gy /fraction)

- CT-based 3 dimensional RT planning
- Clinical target volume for stage IE : the entire nasal cavity nasopharynx, and the volume +  $\geq 2$ cm to gross tumor
- Clinical target volume for stage IIE : included the cervical node area
- Planning target volume : clinical target volume + 5mm
- Incorporated an intraoral spacer and 2-step cone done technique
- Supported by an RT quality assurance program

## CCRT-VIPD



### VIPD x3 (9 weeks)

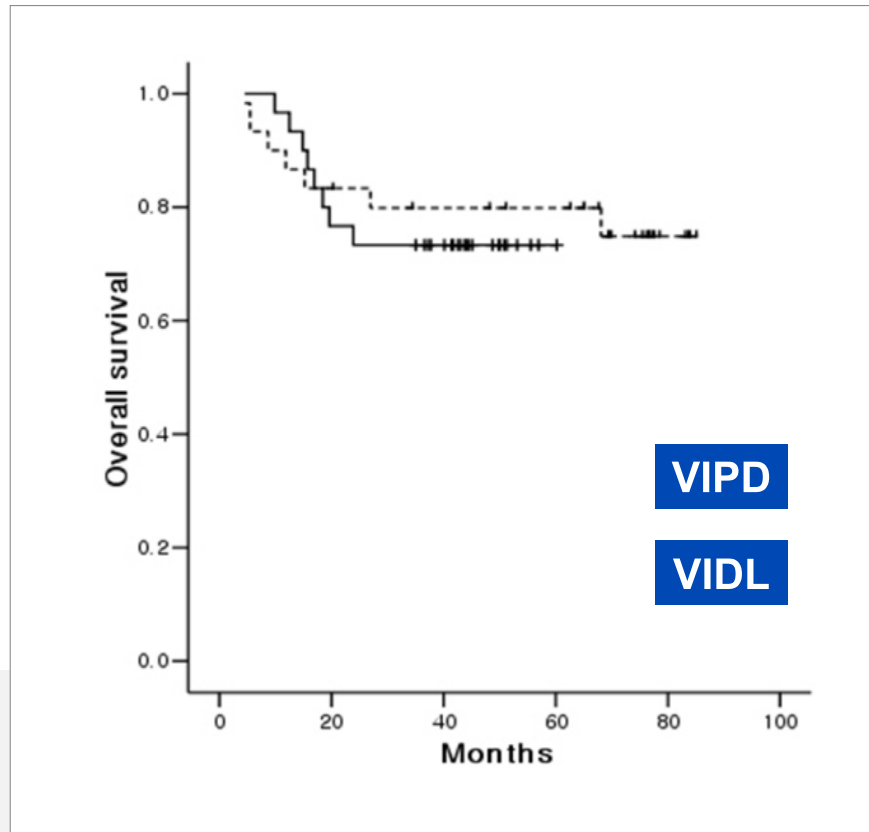
ETP	100 mg/m <sup>2</sup> IV	days 1-3
IFM	1,200 mg/m <sup>2</sup> IV	days 1-3
CDDP	33 mg/m <sup>2</sup> IV	days 1-3
DMS	40 mg/day PO/IV	days 1-4

RT (median dose 40 Gy; 1.8-2.0 Gy / fraction)

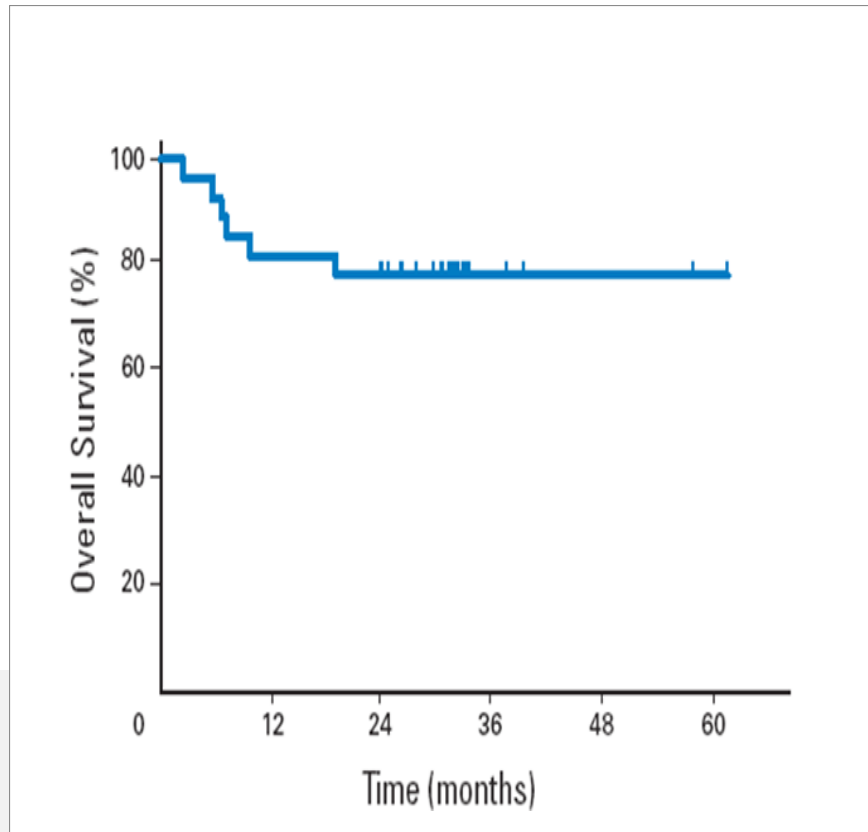
- CT-based 3 dimensional RT planning
- Target volume : the gross clinical lesions + adequate margins



# Outcome of localized ENKL with CCRT come of localized ENKL with CCRT

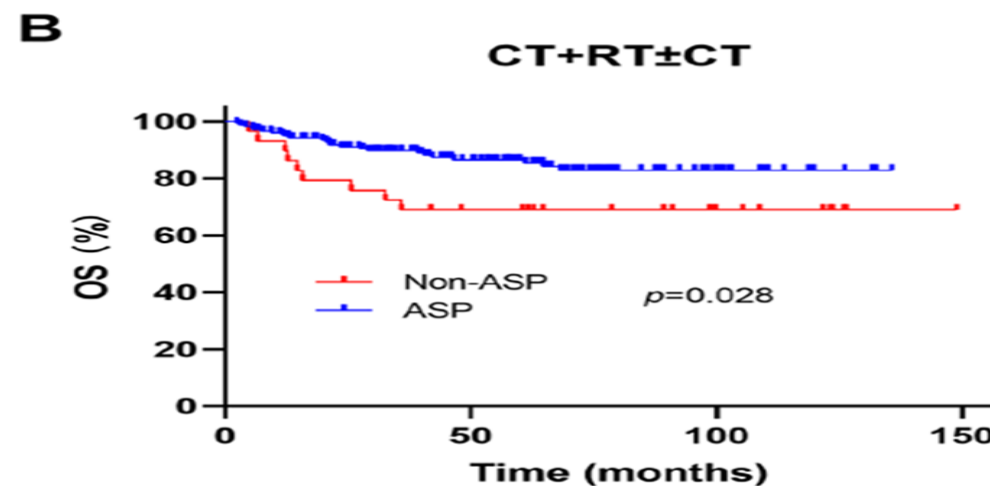
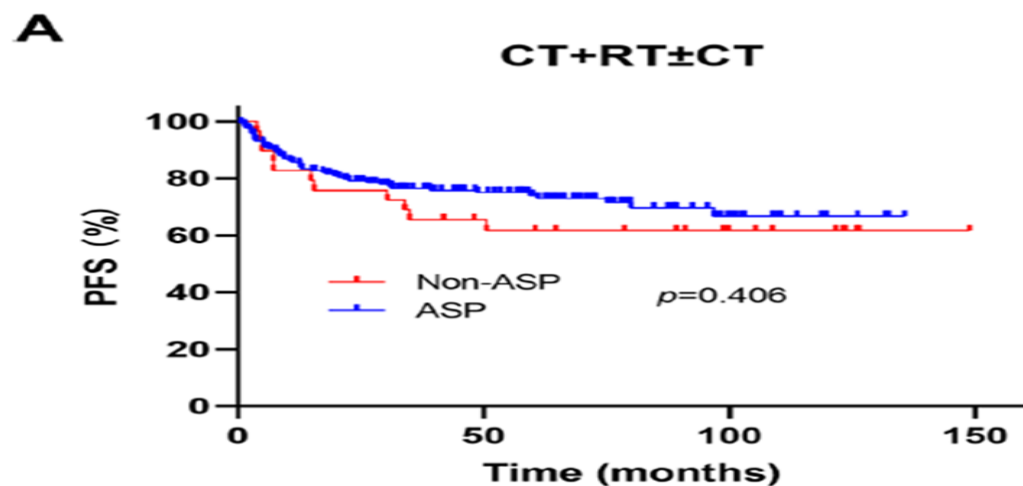
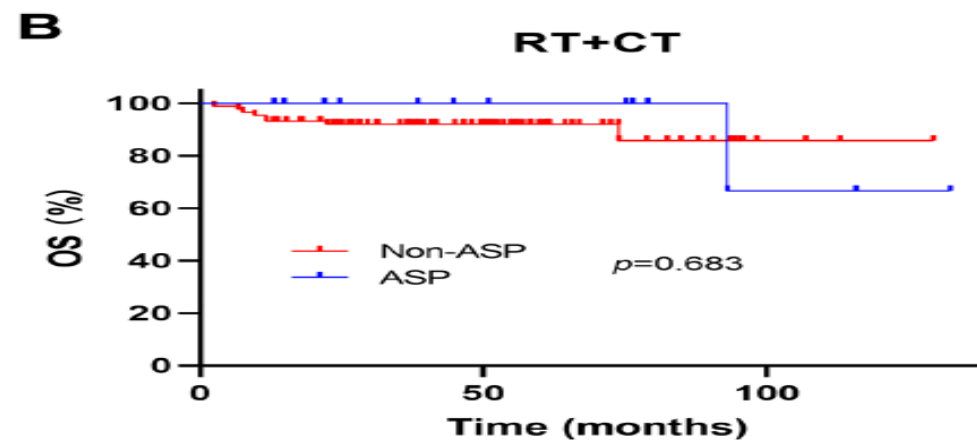
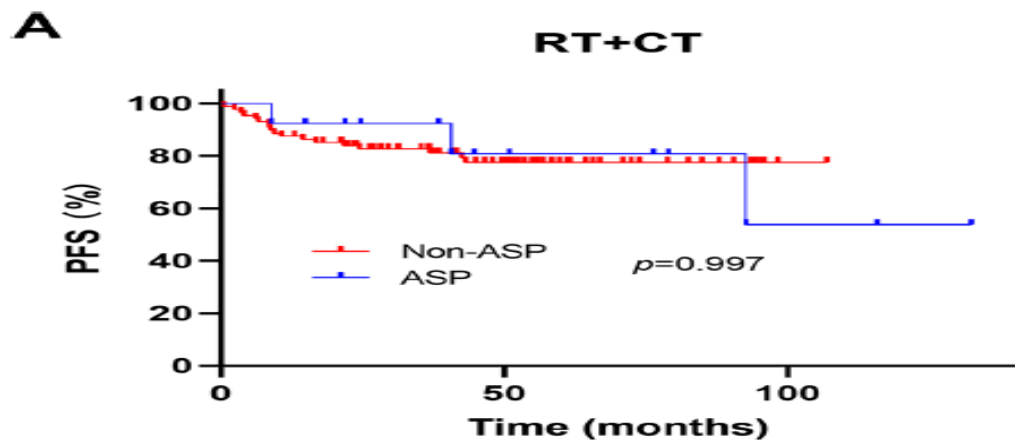


Kim SJ et al ASH 2011



Yamaguchi M, et al. JCO 2009

# L-asp containing, is it essential?



# Radiation: the earlier the better?



**Radiation  
the earlier the better**

Is it real?

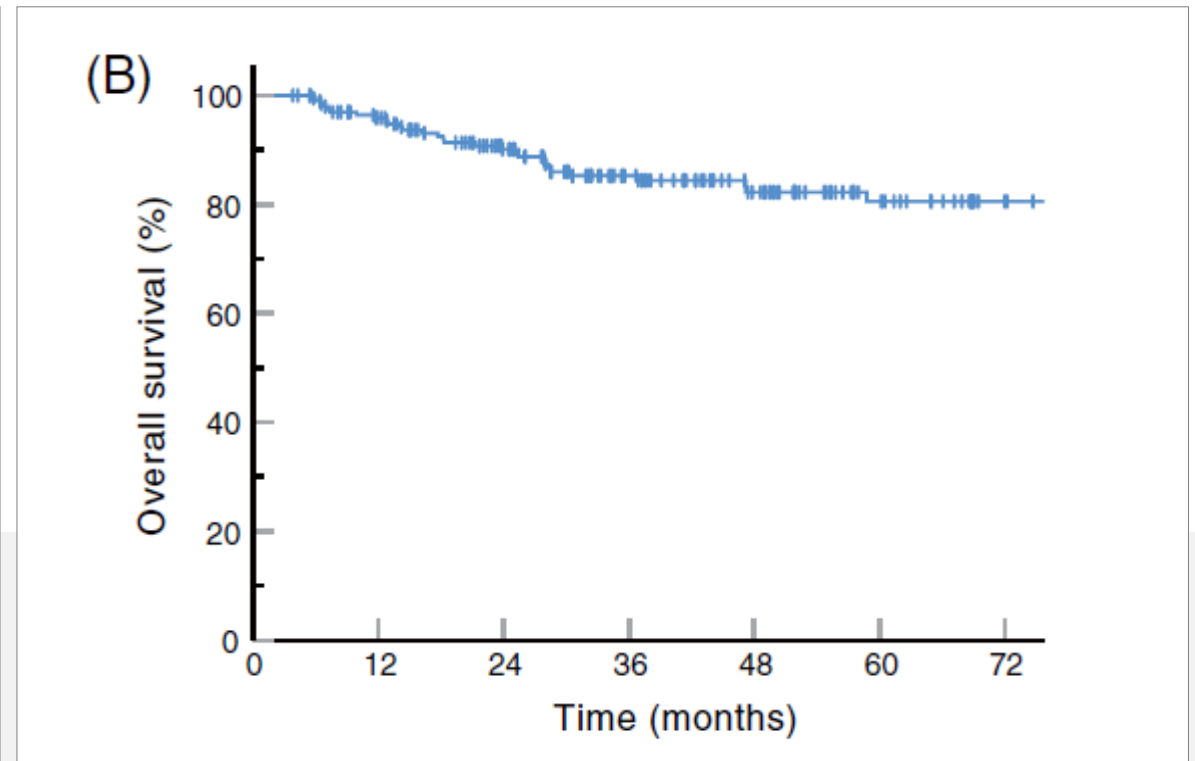
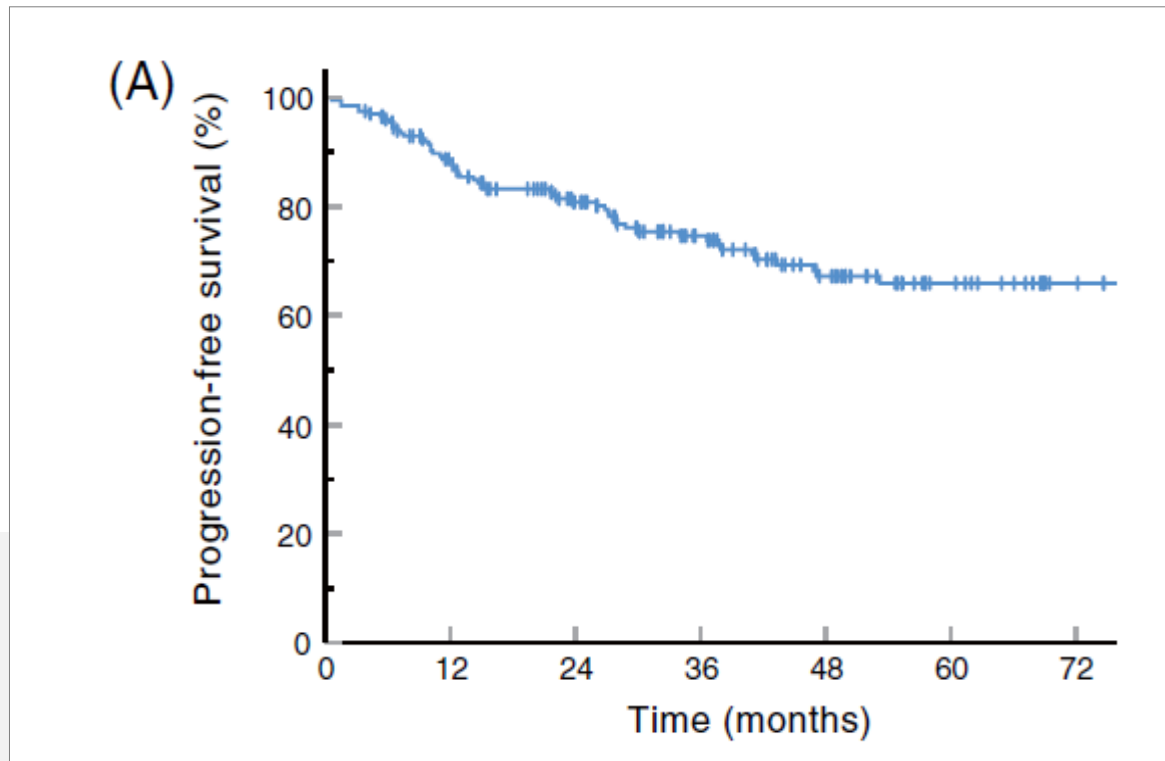
CHOP followed by RT

*Did we treat patients with inefficient chemotherapy like CHOP?*

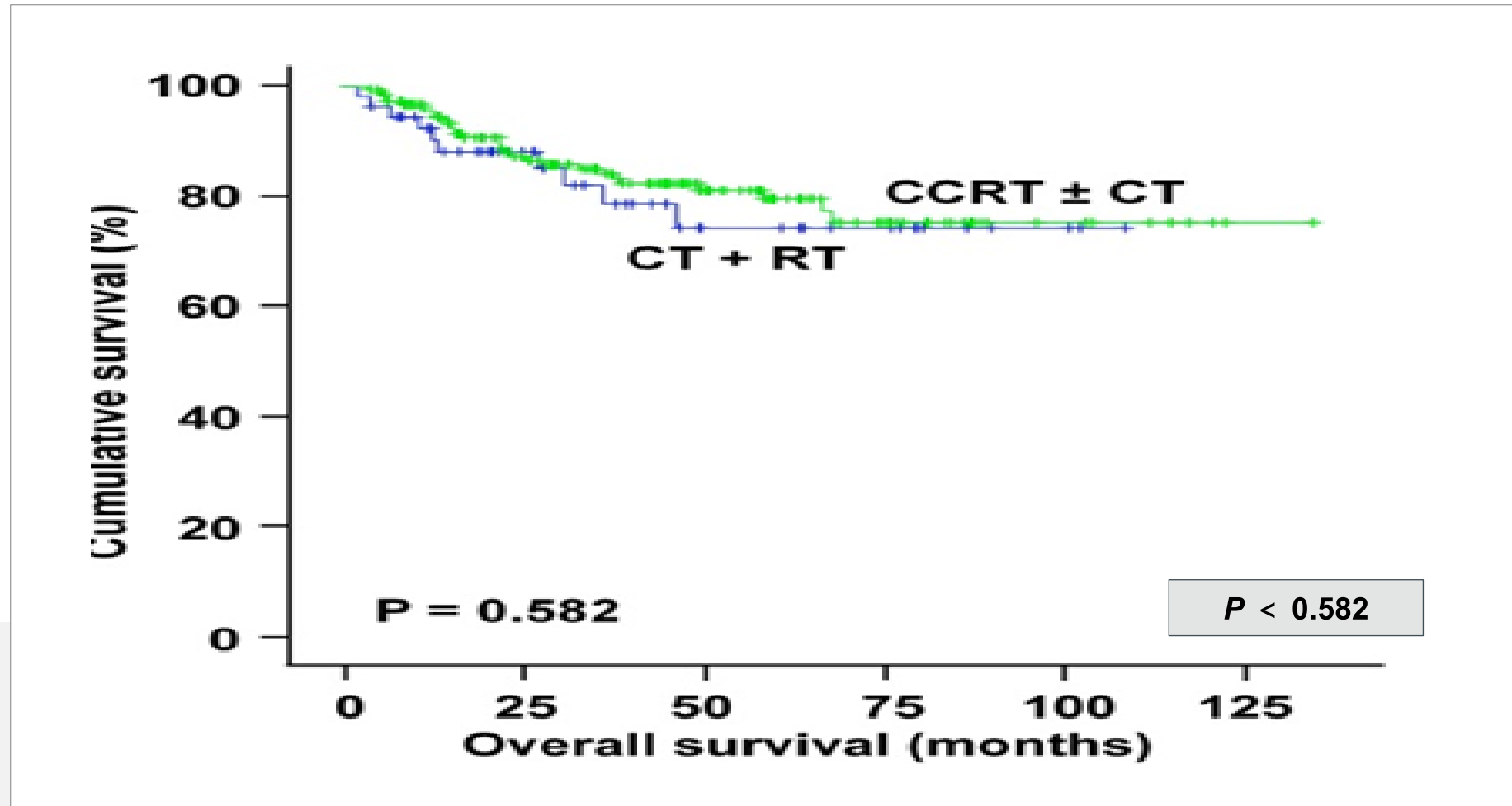
*How about sequential treatment efficient chemotherapy followed by radiation?*

# Sequential P-GEMOX and radiotherapy

**P-GEMOX :** pegaspargase 2000 IU/m<sup>2</sup> IM D1  
gemcitabine 1000 mg/m<sup>2</sup> D1&8  
oxaliplatin 130 mg/m<sup>2</sup> D1



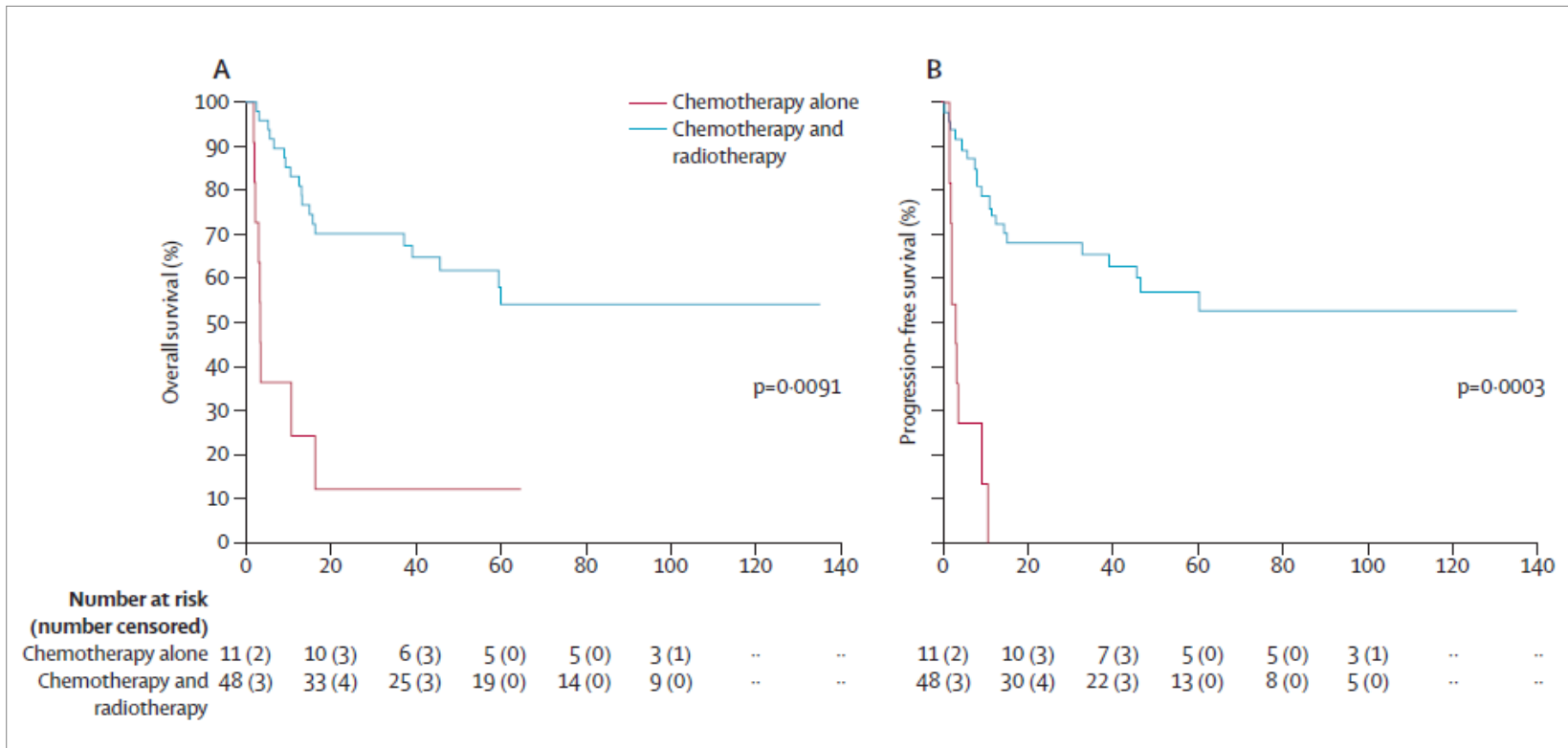
# Early RT vs late RT



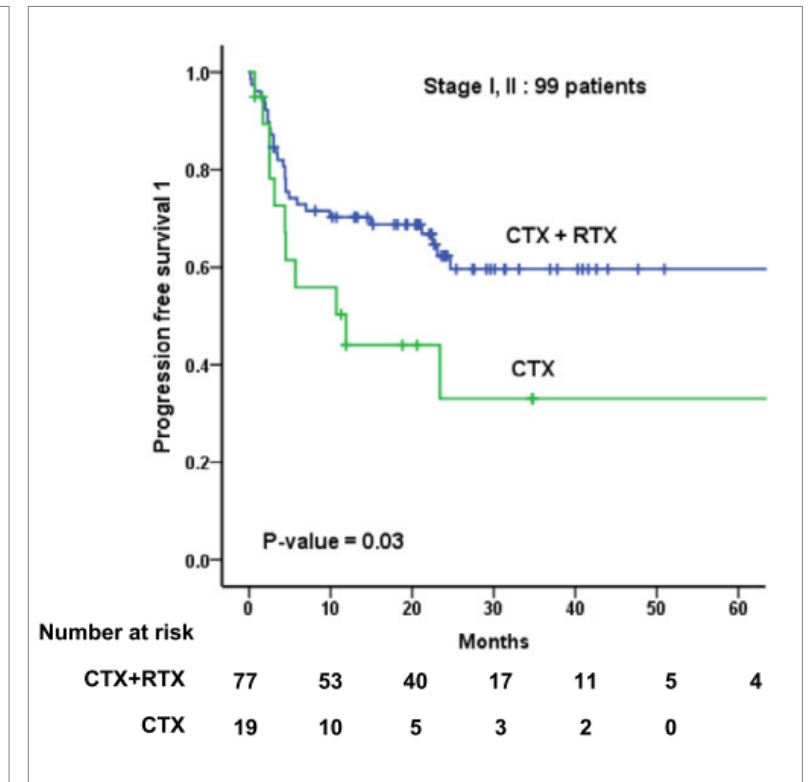
# ENKTL treated with asparaginase-containing regimens

Regimens	Status	Stage	ORR	CR (%)	PFS	OS
VIDL + RT	Newly diagnosed	I/II	90%	87	5 year: 60%	5 year: 73%
LVP + RT	Newly diagnosed	I/II	89%	81	5 year: 64%	5 year: 64%
GELOX + RT	Newly diagnosed	I/II	96%	74	5 year: 74%	5 year: 85%
P-GEMOX [+ RT for stage I/II]	Newly diagnosed	I/II	94%	80	2 year: 77%	2 year: 83%
	Newly diagnosed	I/II	94%	64	3 year: 66%	3 year: 81%
	Relapsed/refractory		81%	52	3 year: 24%	3 year: 58%
DICE-L-asp	Newly diagnosed	I/II	100%	91	5 year: 82%	5 year: 89%
MESA	New diagnosed	I/II	92%	89	2 year: 89%	2 year: 92%
SMILE [+ RT for stage I/II]	Newly diagnosed	I/II	90%	69	Not reported	
		III/IV	Not reported	54	4 year: 60%	5 year: 47%
	Relapsed/refractory		77%	66	4 year: 68%	5 year: 52%
DDGP	Newly diagnosed	III/IV	95%	71	1 year: 86%	1 year: 90%
AspaMetDex	Relapsed/refractory		78%	61	2 year: 40%	2 year: 40%
MEDA	Relapsed/refractory		77%	61	1 year: 62%	1 year: 69%
GELAD	Newly diagnosed	I/II	94%	92	2 year: 90%	2 year: 94%

# Chemo alone vs Chemo-RT in early stage disease

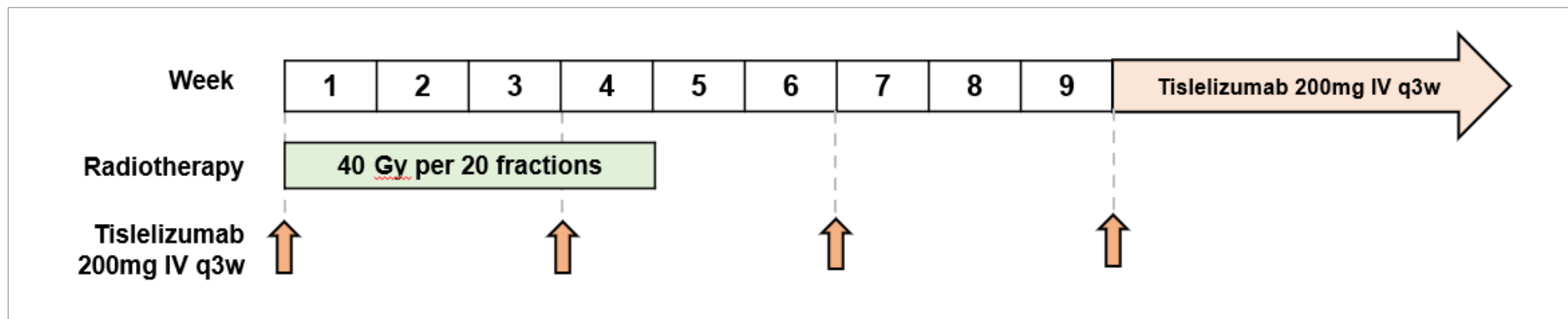


Fox CP et al. Lancet Haematol 2020



Yoon SE et al Lancet Reg Heath 2021

# Ongoing trial



Stage IE/II E (nasal) with PINK, PINK-E risk score: 0-1

## CCRT

- 1) Tislelizumab: 200mg IV, q 3wks
- 2) Radiotherapy 40Gy/20 fractions

## Maintenance

- 1) Tislelizumab: 200mg IV, q 3 wks for 2yrs

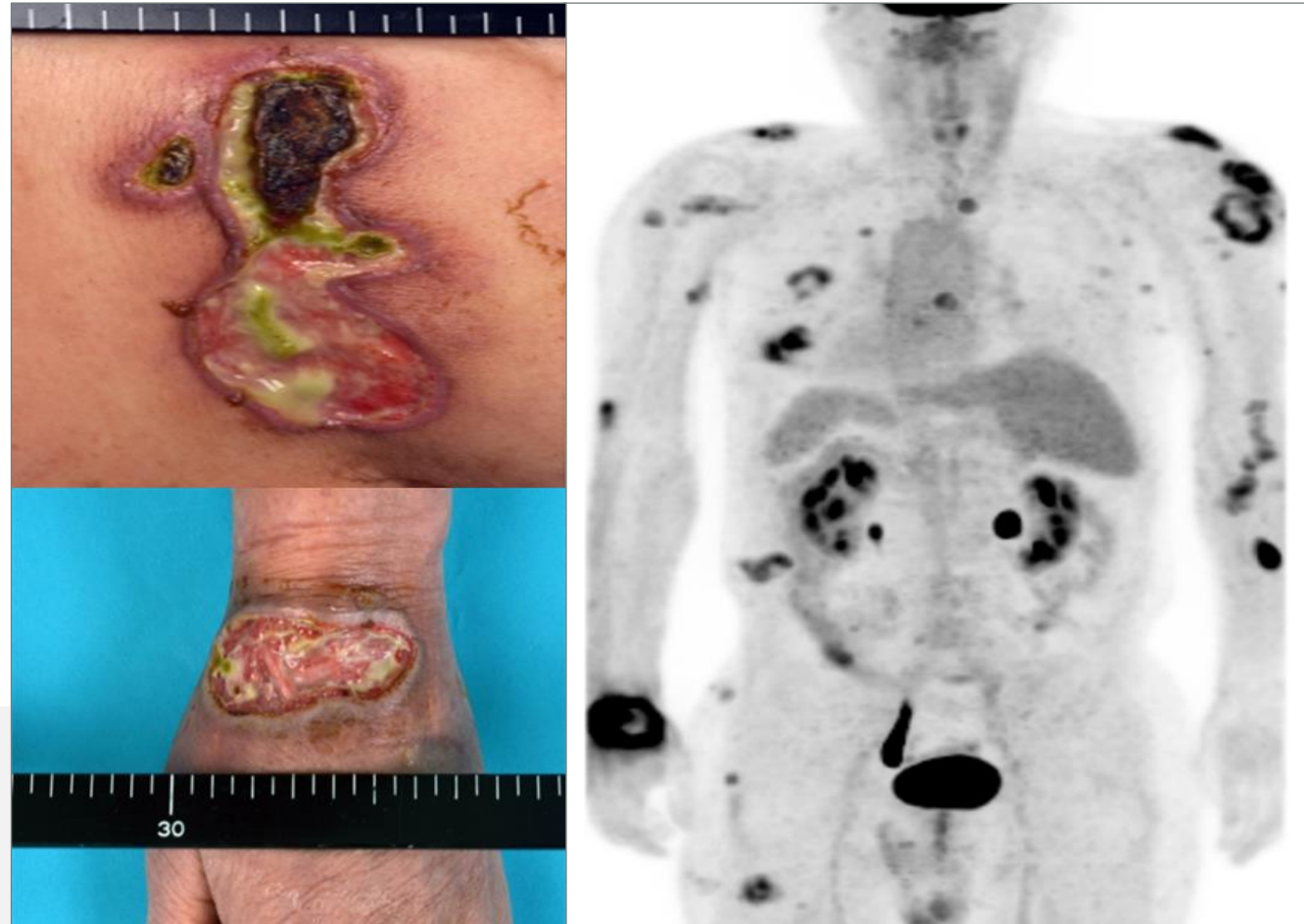


# Unanswered questions in mx of localized ENKTL

1. Do we need L-asparaginase in frontline treatment?
2. Do we need chemotherapy for all patients?
3. Do we need radiation for the patients who received standard chemotherapy?
4. What is the optimal dose of radiation?
5. Do we need more treatment for high risk patients?

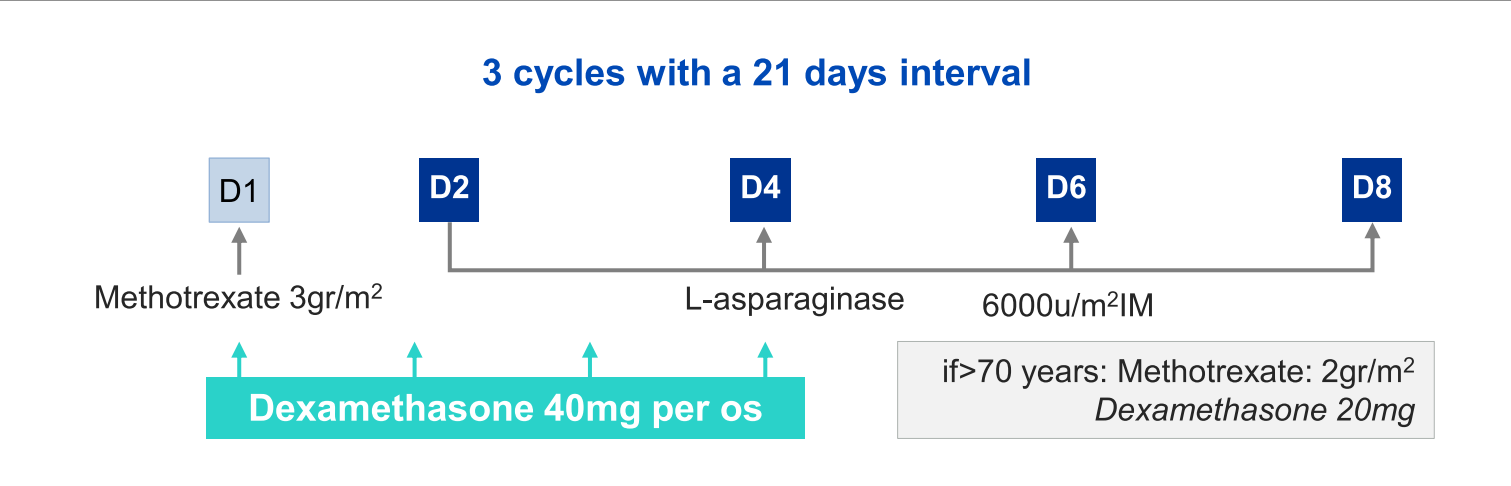


# Optimal Treatment of advanced Disease



# L-asparaginase containing regimens

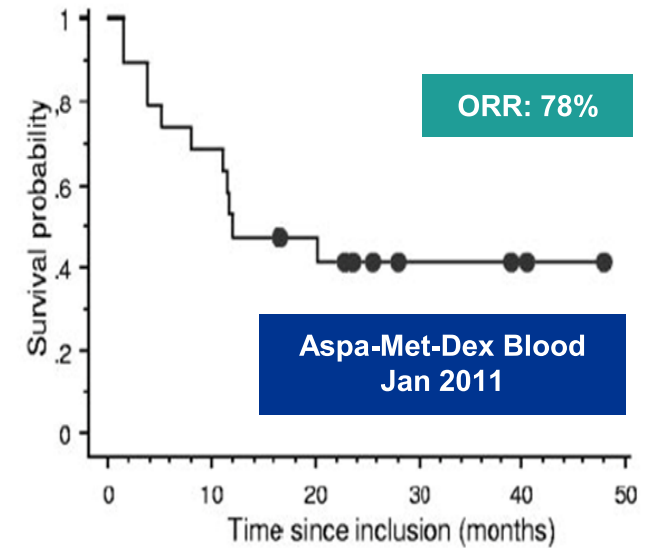
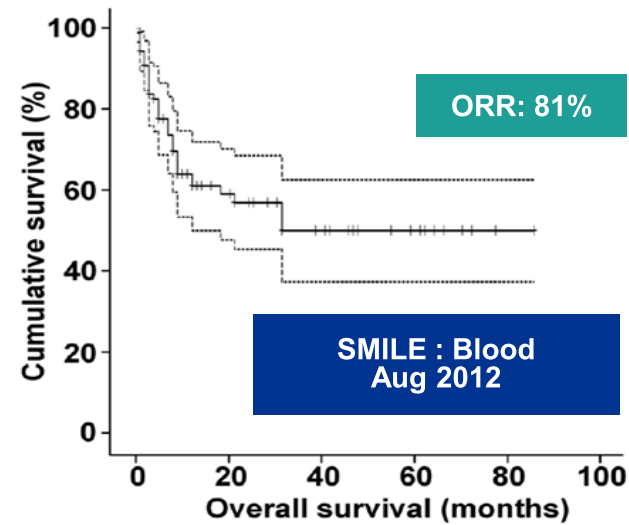
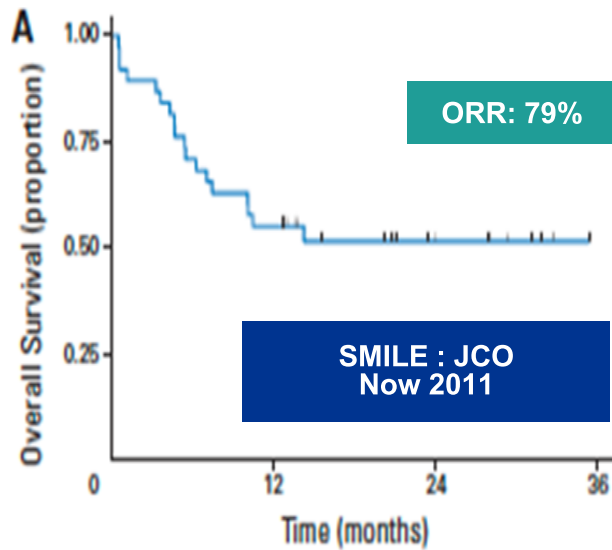
## Aspa-Met-Dex



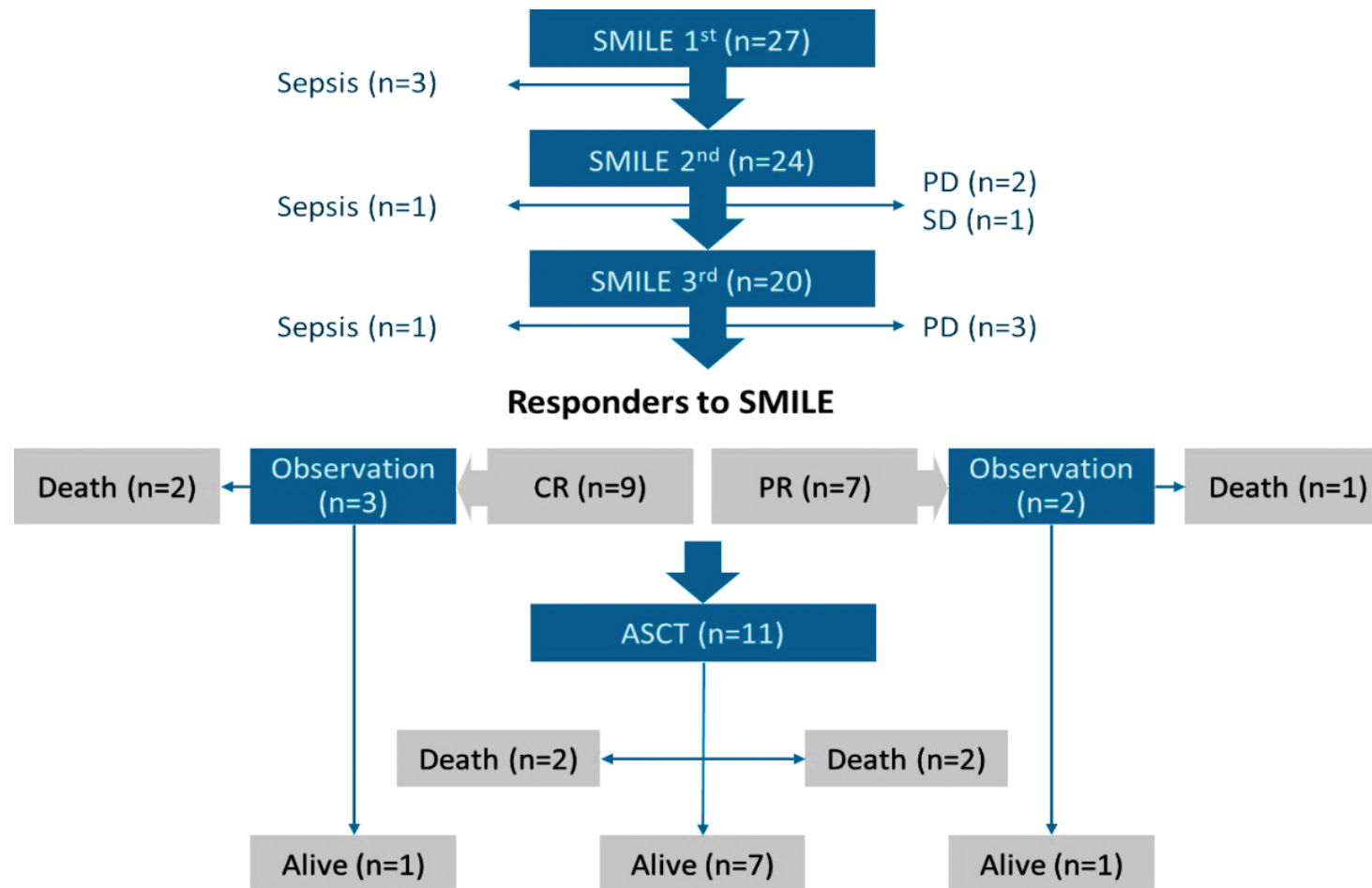
## SMILE

Agent	Dose(/day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	20	21	MTX	2 g/m <sup>2</sup>
Methortexate(MTX) * Ag/m <sup>2</sup>		●																							ETP	100 mg/m <sup>2</sup>
Leucovorin	15mgx4		●	●	●																					
Ifosfamide (IFM)	1,500 mg.m <sup>2</sup>		●	●	●																					
Mesna	900 mg/m <sup>2</sup>		●	●	●																					
Etoposide (ETP) *B mg/m <sup>2</sup>			●	●	●																					
Dexamethasone (DMS)	40 mg/body		●	●	●																					
L-asparaginase (L-asp)	6,000 U/m <sup>2</sup>								●		●		●		●		●		●		●		●			
G-CSF							●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	..

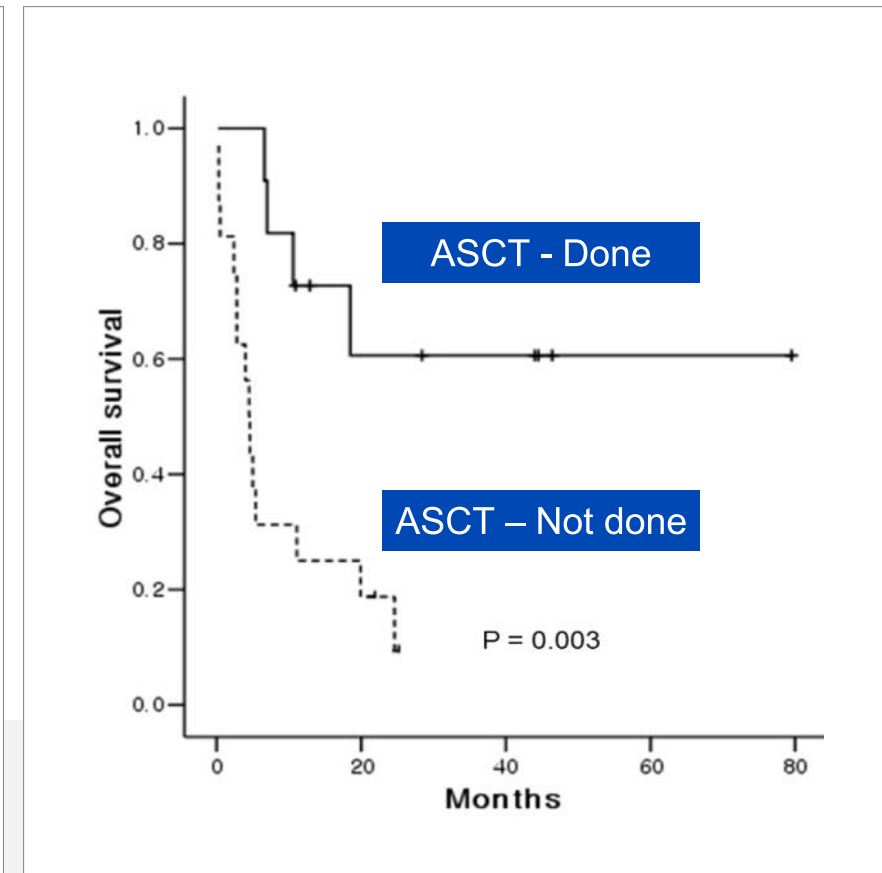
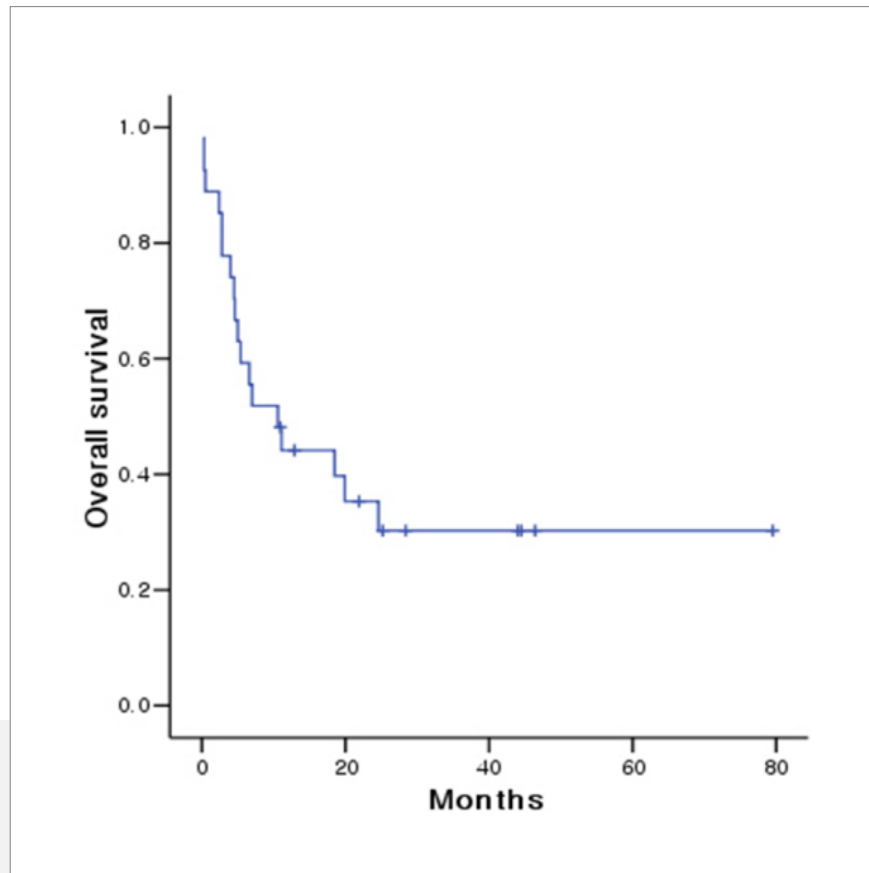
# Outcome of advanced stage ENKL after L-asparaginase containing regimen



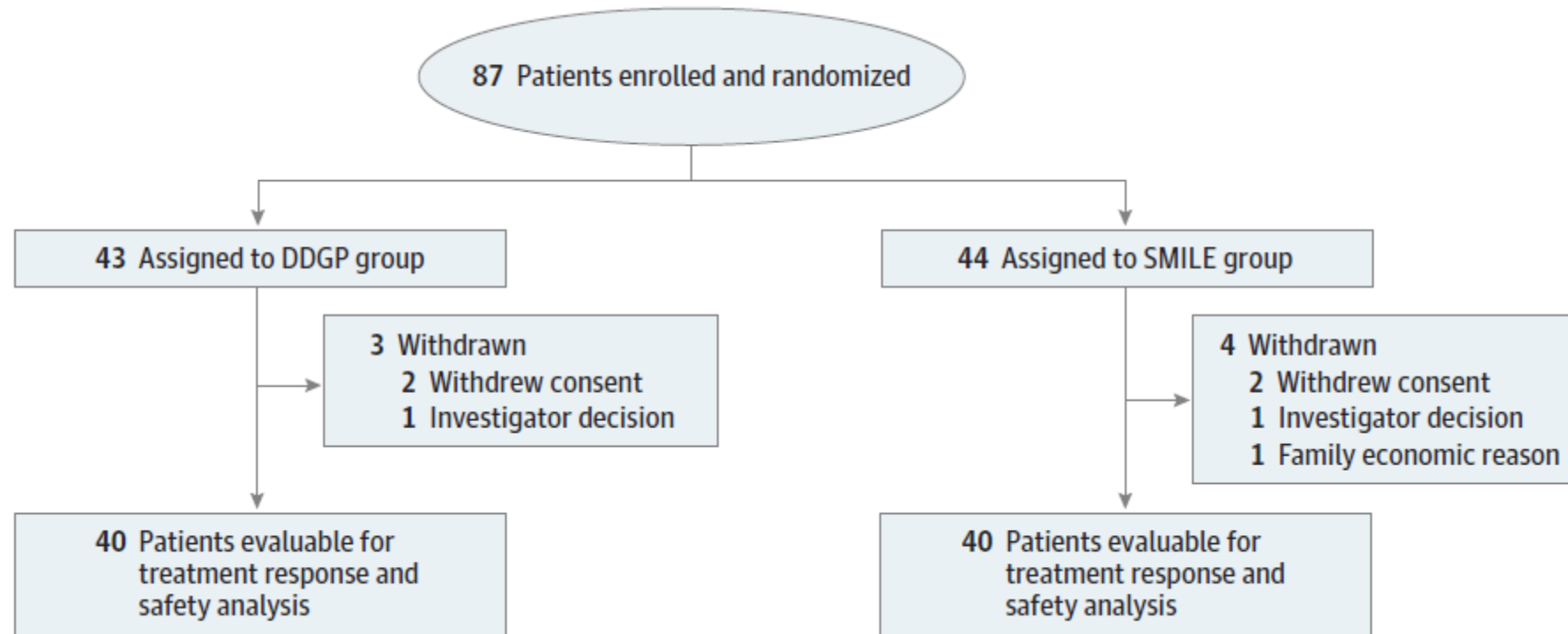
# SMILE followed by auto-HSCT



# Outcome of SMILE followed by auto-HSCT in ENKL



# SMILE vs DDGP



# SMILE vs DDGP

Response	No. (%)		P value <sup>a</sup>
	DDGP Group (n = 40)	SMILE Group (n = 40)	
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)	

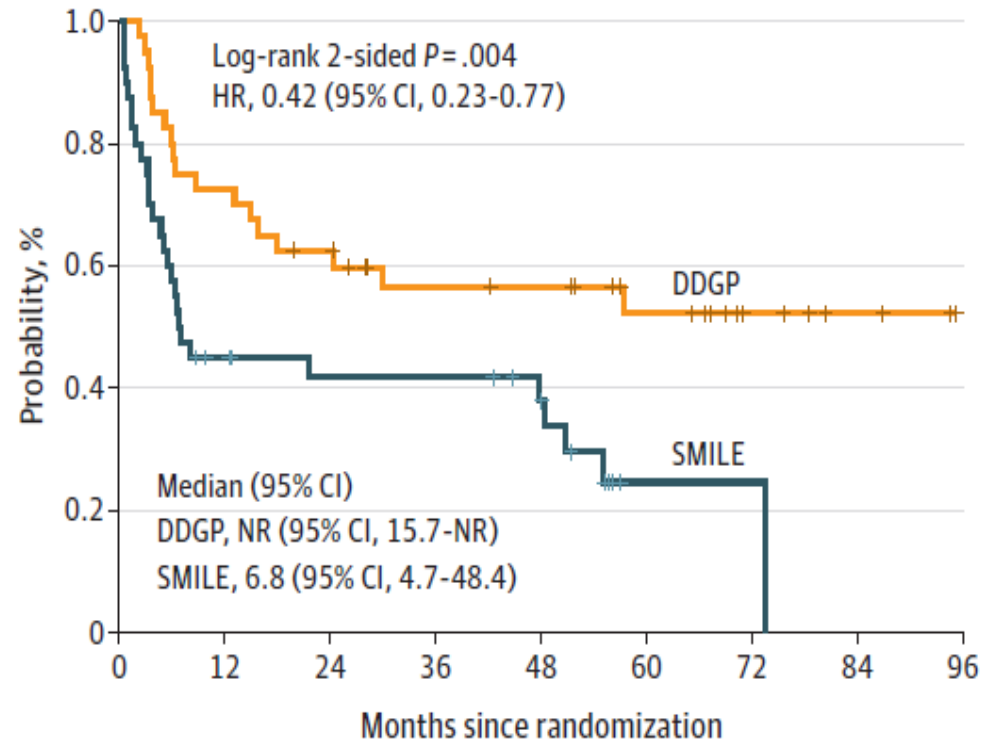
Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response.

<sup>a</sup>  $\chi^2$  test.



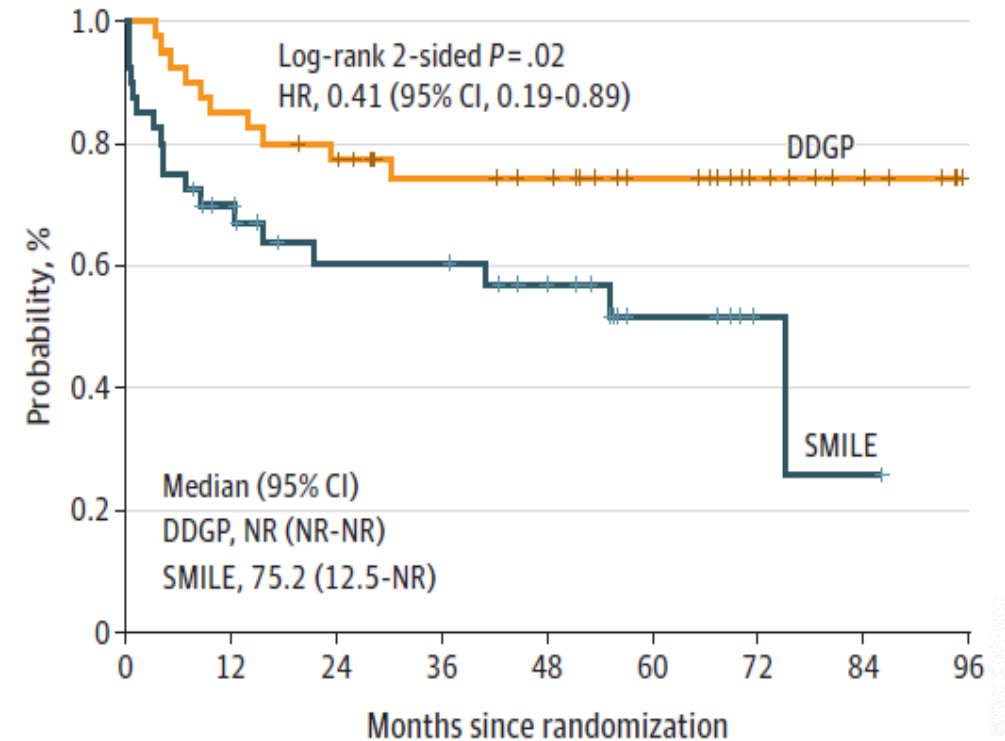
# SMILE vs DDGP

**A** Progression-free survival



No. at risk	0	12	24	36	48	60	72	84	96
DDGP	40	29	24	18	17	12	6	3	0
SMILE	40	16	13	13	9	1	1	0	0

**B** Overall survival

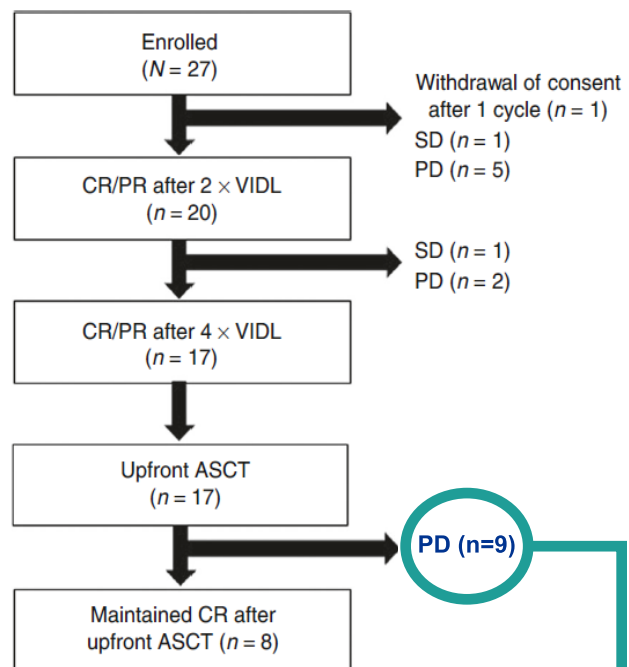


No. at risk	0	12	24	36	48	60	72	84	96
DDGP	40	34	30	24	22	16	10	6	0
SMILE	40	25	18	18	13	6	2	1	0

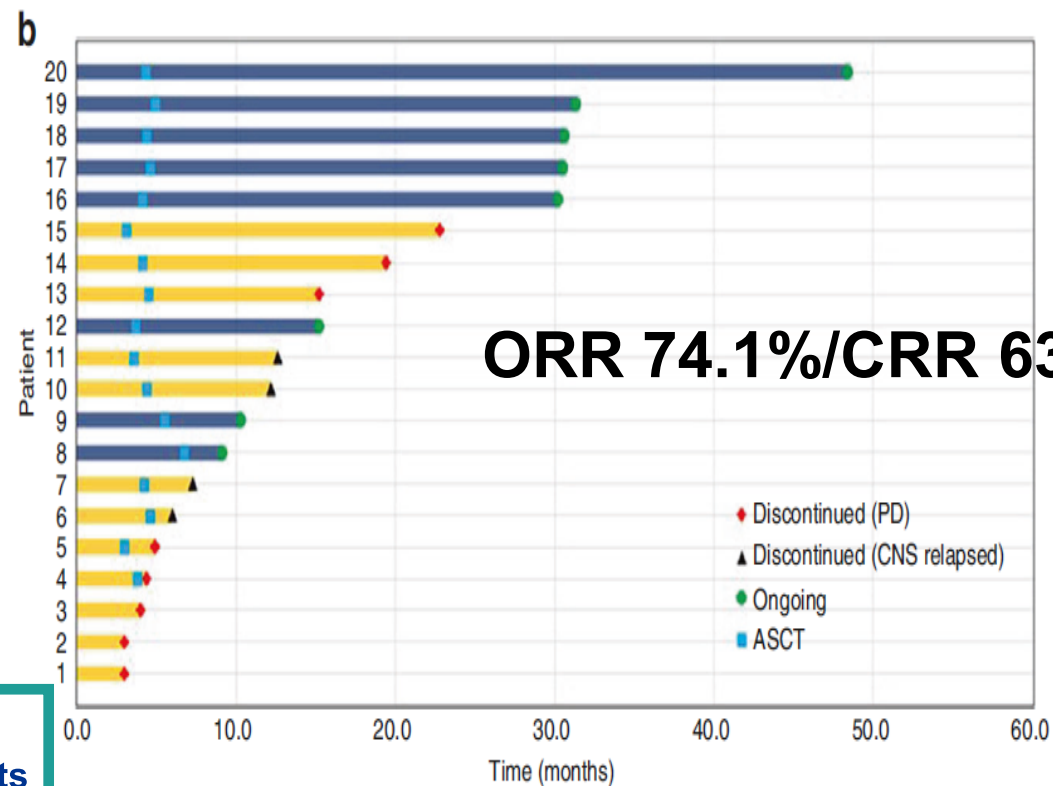
# Treatment outcome of advanced ENKTL

Chemotherapy	No.	Response, % (CR+PR)	Grade 3/4 AE	PFS	OS
SMILE	38	79% (17 CR+13 PR)	Leucopenia: 100%	1-year PFS: 53%	1-year OS: 55%
SMILE	43	84% (28 CR+8 PR)	Neutropenia: 45%, TRM: 7%	4-year DFS: 60%±22.9%	5-year OS: 49.9%±12.5%
SMILE	27	59% (9 CR+7 PR)	Cytopenia: 9.3%, TRM: 12%	Median PFS: 5.1 months	Median OS: 10.6 months
Asp-MTX-Dex	19	78% (11 CR+3 PR)	Leucopenia: 44%	2-year PFS: 40%	2-year OS: 40%
DDGP	28	89.3% (17 CR+8 PR)	NA	2-year PFS: 68.4%	2-year OS: 84.5%
SMILE vs. DDGP	40 vs. 40	90% vs. 60% (27 CR+9 PR) vs. (19 CR+5 PR)	Leucopenia: 62.5% vs. 85%, mucositis: 0% vs. 7.5%, TRM: 0% vs. 17.5%	3-year PFS: 56.6% vs. 41.8%	5-year OS: 74.3% vs. 51.7%

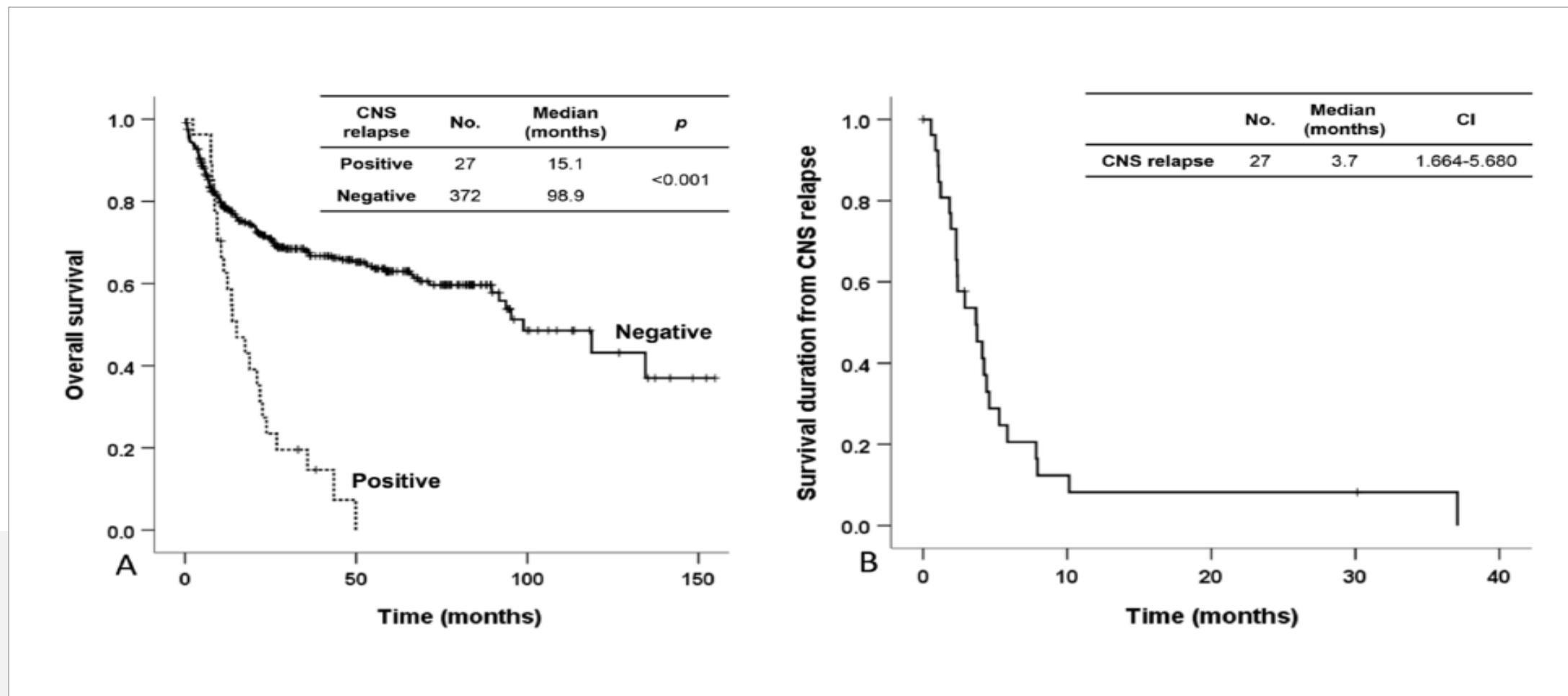
# VIDL followed by auto-HSCT for advanced ENKTL



4 CNS relapse  
5 no CNS events



# Outcome of ENKTL with CNS event

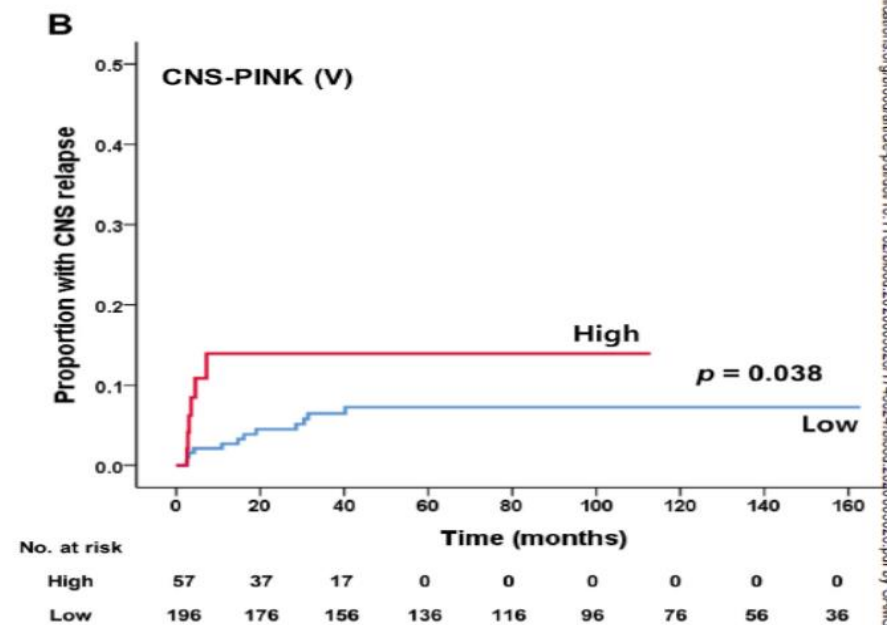
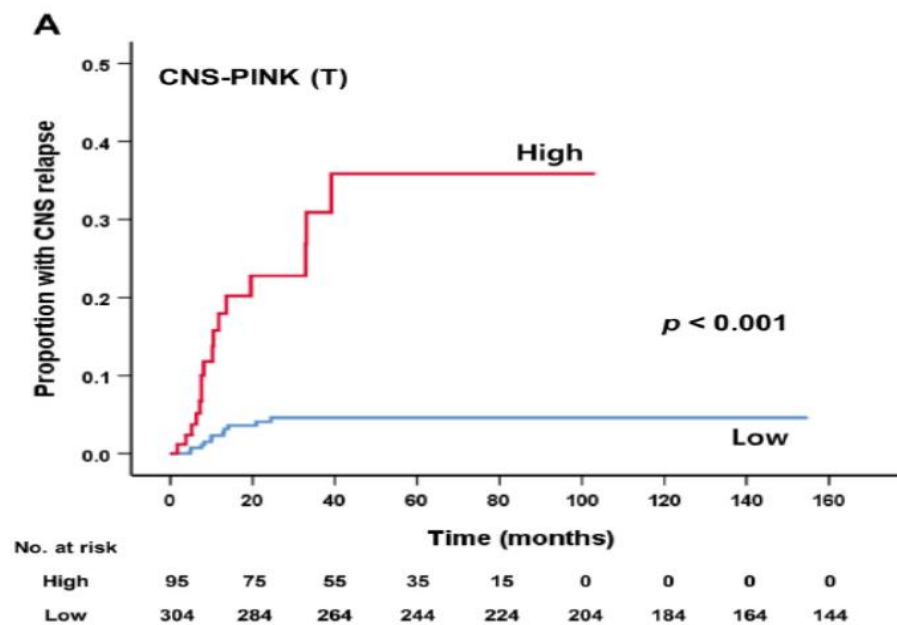


# Risk factors for CNS relapse

Univariate analysis	HR (95% CI)	P-value
Age > 60 years	1.130 (0.477–2.675)	.781
LDH	2.762 (1.279–5.962)	.010
EBV DNA	3.199 (1.282–7.982)	.013
Extranodal involvement $\geq 2$	7.123 (3.246–15.629)	.000
Distant LN involvement	4.413 (2.040–9.549)	.000
Ann Arbor stage III/IV	6.665 (2.977–14.924)	.000
<b>PINK</b>		
Intermediate vs. low	3.717 (1.268-10.897)	.071
High vs. low	7.288 (2.553-20.807)	.000
High vs. intermediate	1.932 (0.832-4.484)	.125
intermediate/high vs. low	5.056 (1.908–13.397)	.001
Multivariate analysis	HR (95% CI)	P-value
Extranodal involvement $\geq 2$	4.628 (1.974-10.852)	.000
PINK intermediate/high	2.677 (0.936-7.652)	.066

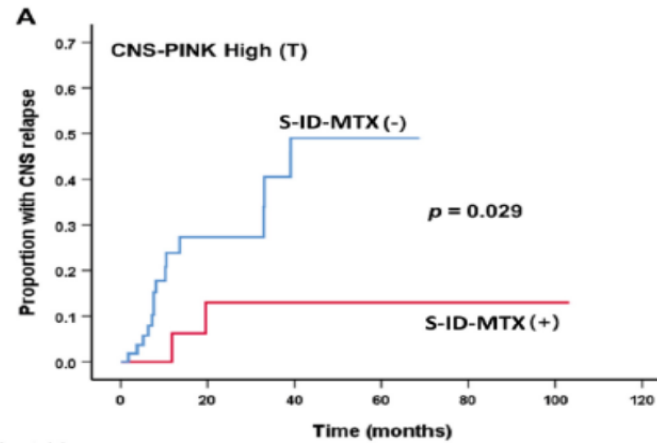
# CNS-PINK

Factors	CNS-PINK scoring criteria	
	0	1
Extranodal involvement	0 - 1	$\geq 2$
PINK	low	intermediate/high
<b>Sum</b>	Low-risk	0 - 1
	High-risk	2

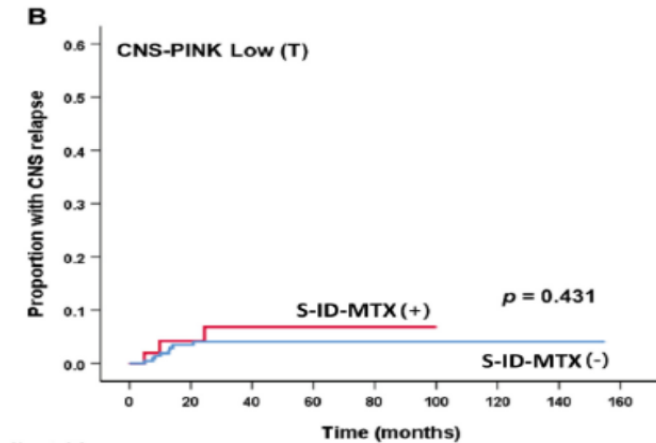


publications.org/doi/10.1182/blood-2020-05-5028174624/blood-2020-05-502817

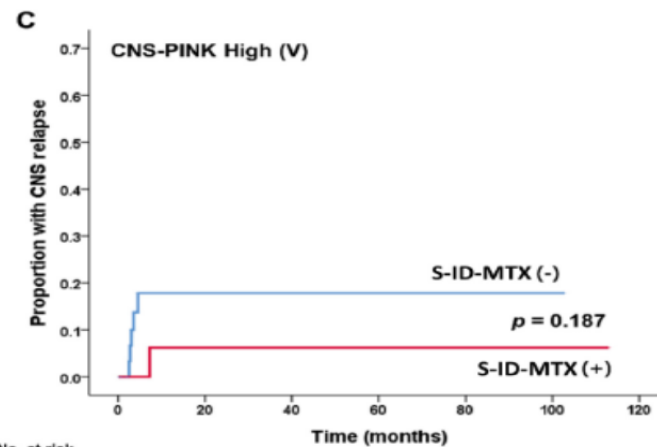
# Role of MTX in prevention of CNS relapse



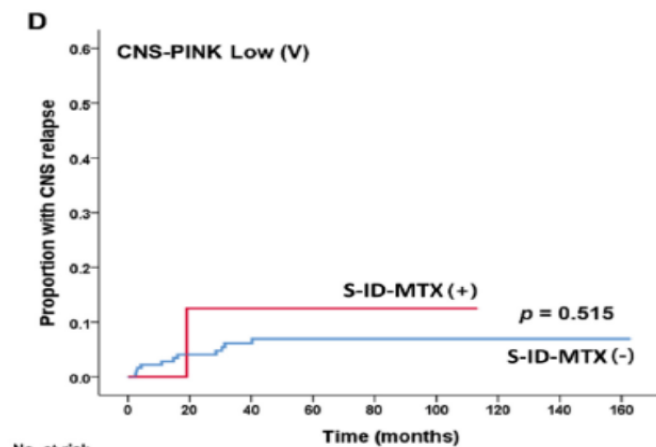
No. at risk	0	20	40	60	80	100	120
HD-MTX(-)	62	42	22	2	0	0	0
HD-MTX(+)	33	13	0	0	0	0	0



No. at risk	0	20	40	60	80	100	120	140	160
HD-MTX(-)	237	217	197	177	157	137	117	97	77
HD-MTX(+)	67	47	27	7	0	0	0	0	0



No. at risk	0	20	40	60	80	100	120
HD-MTX(-)	37	17	0	0	0	0	0
HD-MTX(+)	20	0	0	0	0	0	0



No. at risk	0	20	40	60	80	100	120	140	160
HD-MTX(-)	187	167	147	127	107	87	67	47	27
HD-MTX(+)	9	0	0	0	0	0	0	0	0

# Unanswered questions in mx of advanced ENKTL

1. What is optimal induction regimen?

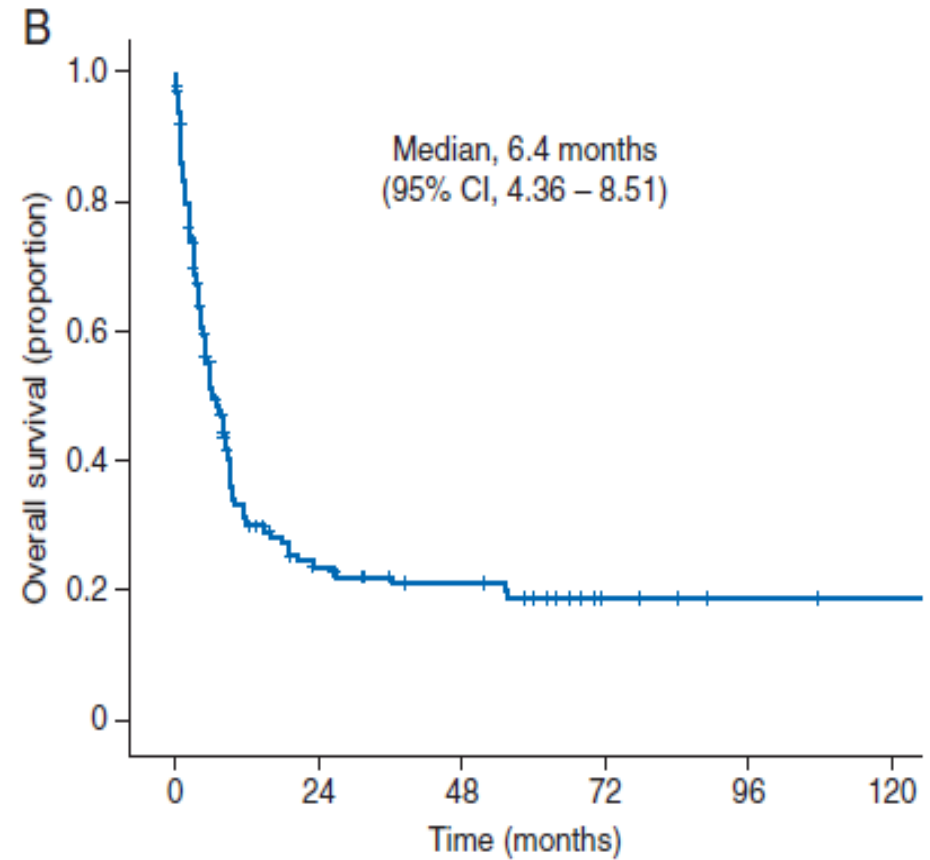
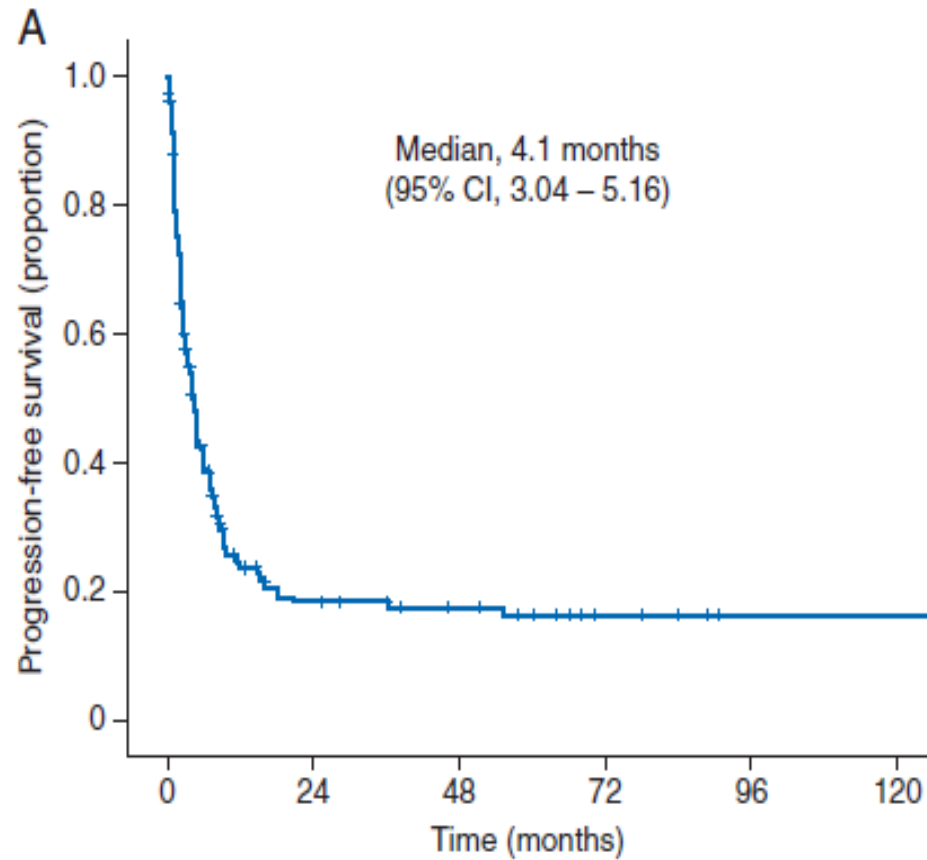
1. What is the role of HSCT?

1. Allo- or auto HSCT, when and whom?





# Beyond failure of standard care

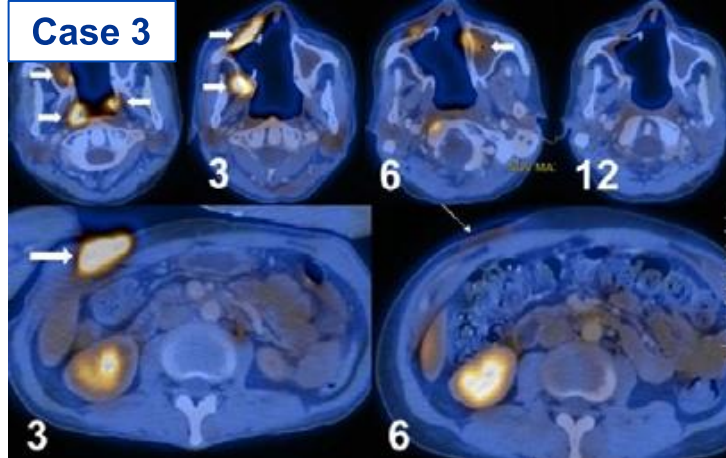


# ICI in r/r ENKTL

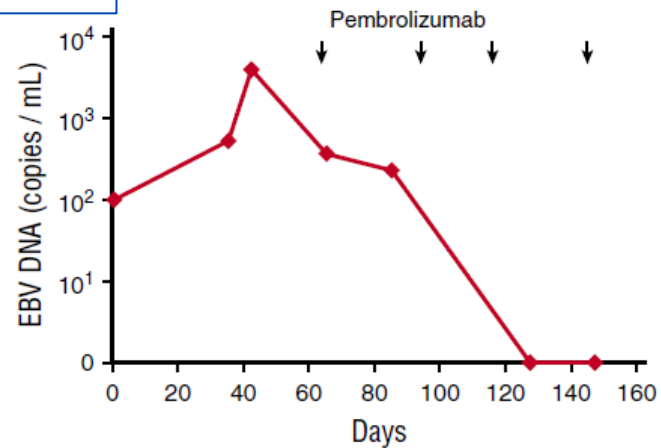
Off-label use: 100mg of pembrolizumab  
HK, Singapore, Korea

Case	Sex	Age, y	Primary sites	Marrow	Stage
1	M	68	Skin of lower limbs, nasal cavities	Negative	IV
2	M	49	Nasal cavities, lymph nodes, liver, spleen, bone	Negative	IV
3	M	38	Nasopharynx	Negative	I <sub>E</sub>
4	M	50	Liver	Positive	IV
5	M	31	Nasal cavity, nasopharynx, masseter muscle, bone	Negative	IV
6	M	35	Nasal cavity	Negative	I <sub>E</sub>
7	M	51	Liver, spleen	Positive	IV

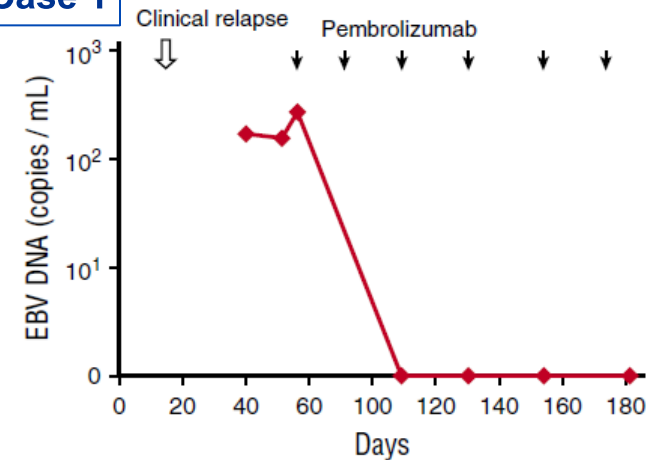
Case 3



Case 7



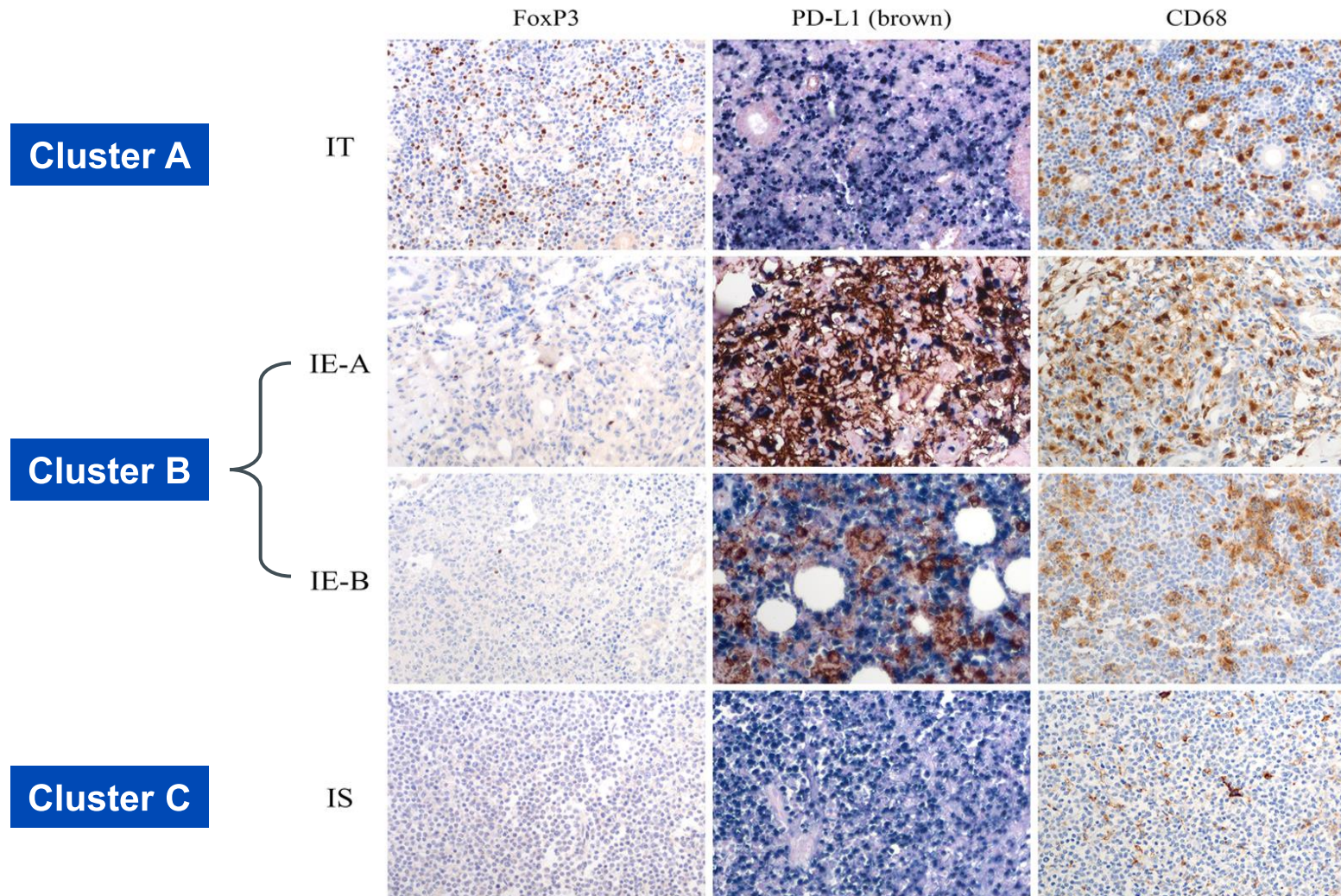
Case 1



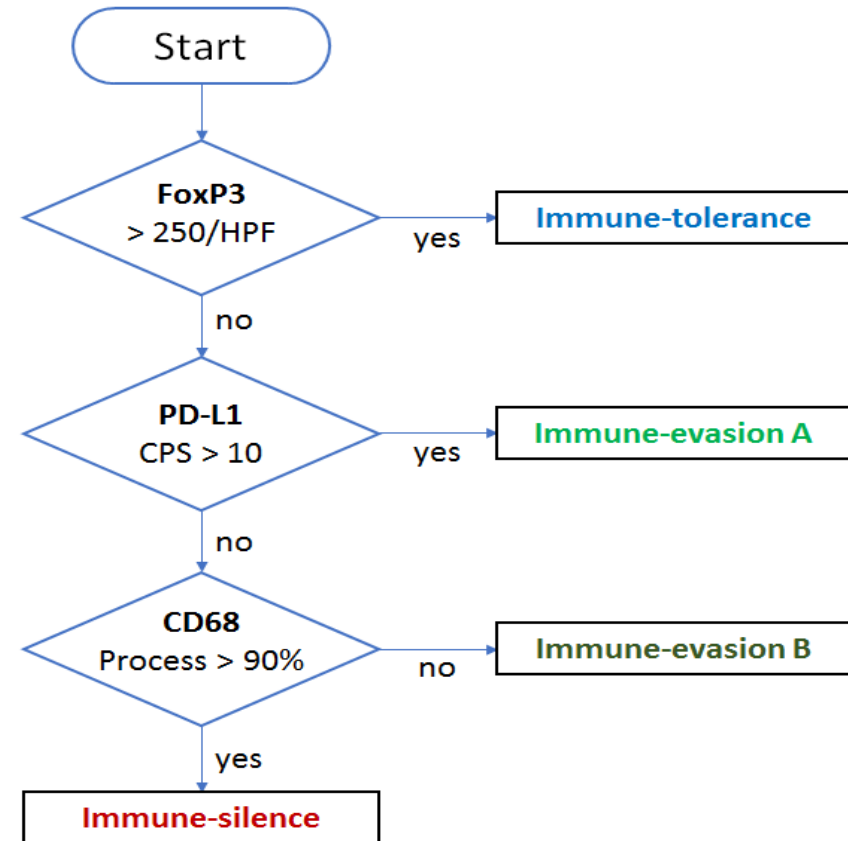
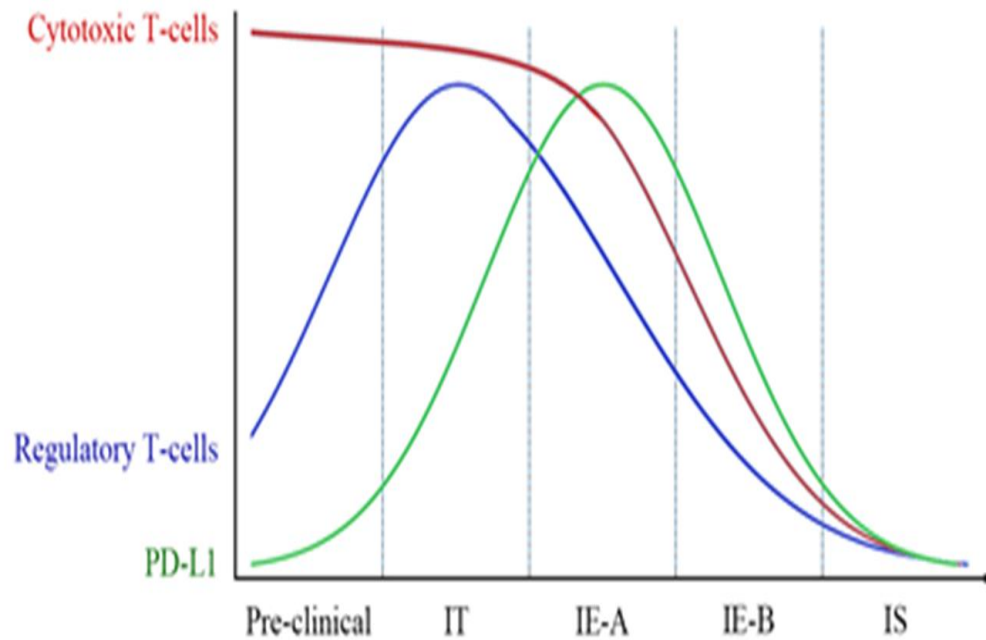
# PD1 or PDL1 inhibitors in ENKTL

Chemotherapy	No.	Dose	Number of previous chemotherapy cycles, median (range)	Response, %	Common AE	Biomarker to predict response	Survival outcome	Ref
Pembrolizumab	7	2 mg/kg, Q3W	7(2-13)	100% (7/7)	Grade 2 rash 100%	Strong PD-L1 expression	NA	[10]
Pembrolizumab	7	NA	4 (2-18)	57.1% (4/7)	All-grade AEs 71.4%	Not correlated with PD-L1 expression	NA	[57]
Pembrolizumab	14	Fixed-dose 100 mg, Q3W	2 (1-19)	44% (6/14)	NA	High PD-L1 expression	NA	[46]
Nivolumab	3	40 mg, Q2W	1	100% (3/3)	NA	NA	NA	[47]
Sintilimab	28	200 mg, Q3w	3 (1-13)	68%(19/28)	Lymphopenia: 46.4%	NA	1-year OS : 82.1%	[48]
Avelumab	21	10 mg/kg, Q4W	NA	38% (8/21)	NA	Expression of PD-L1 by tumor tissue	NA	[12]
CS1001	29	NR	2 lines: 8 (27.6%) ≥3 lines: 6 (20.7%)	40.9% (9/22)	Pyrexia : 20.7% Elevated TSH: 13.8%	NA	NR	[11]

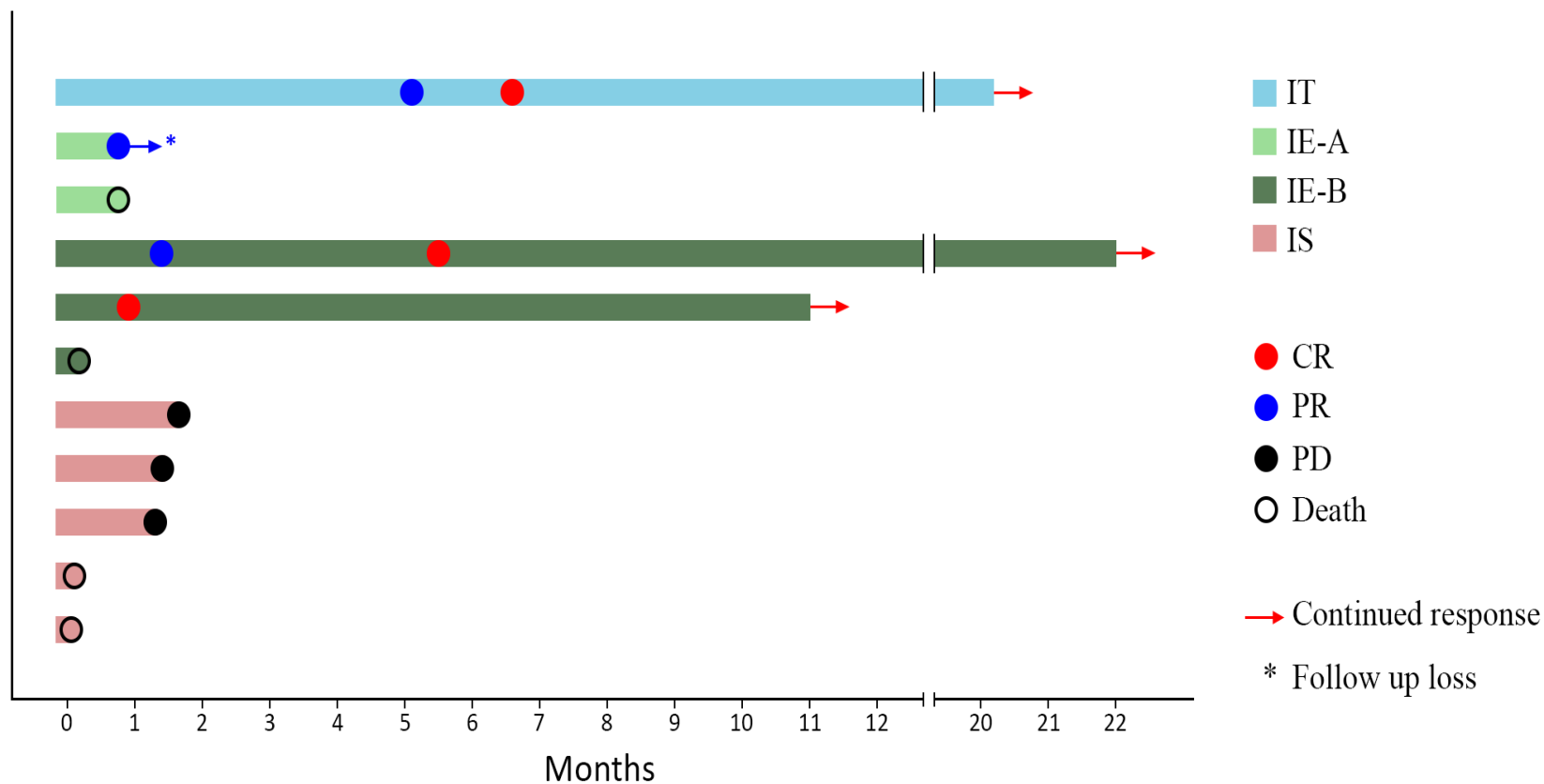
# Histologic features



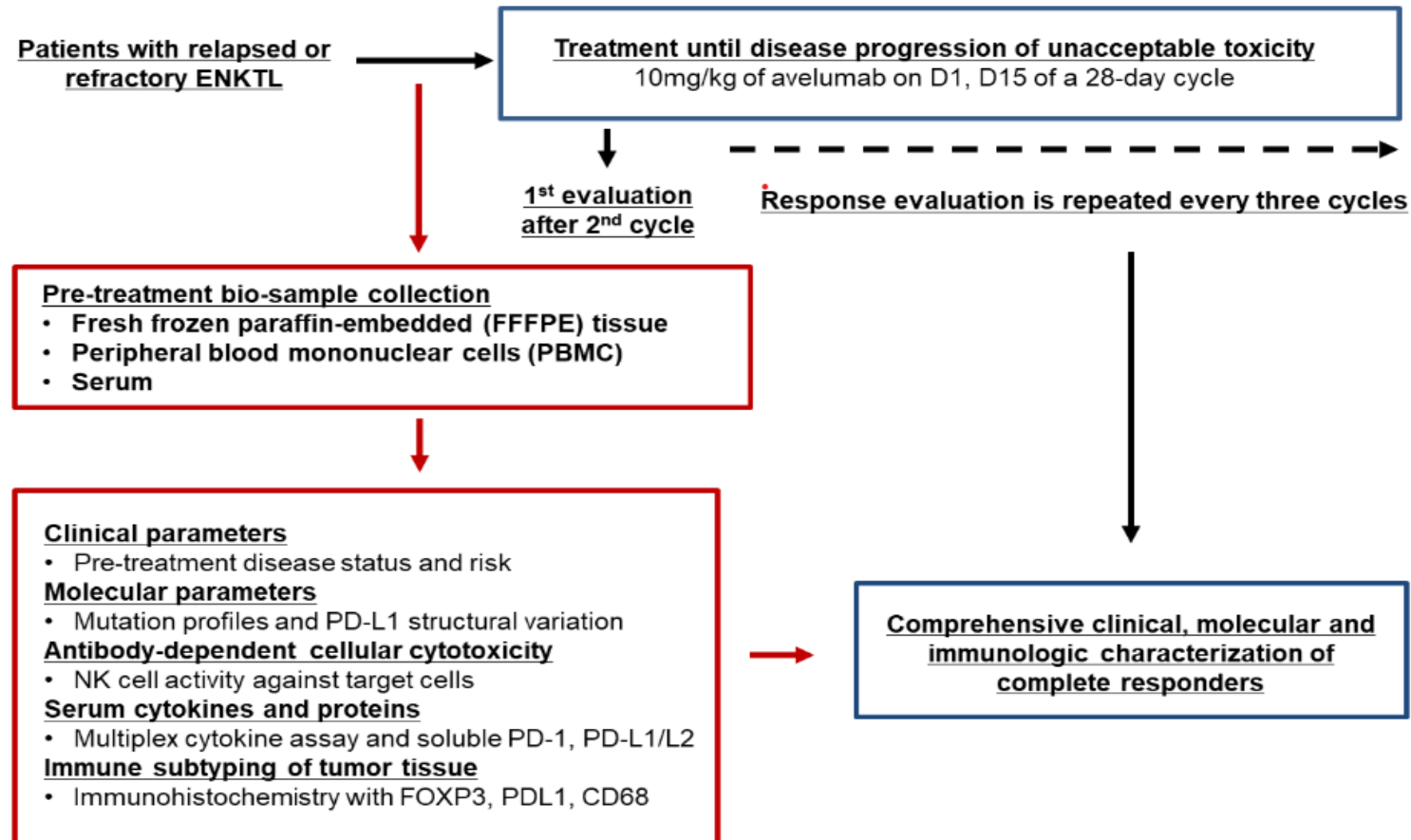
# Algorithm of immuno-subtypes based on histology



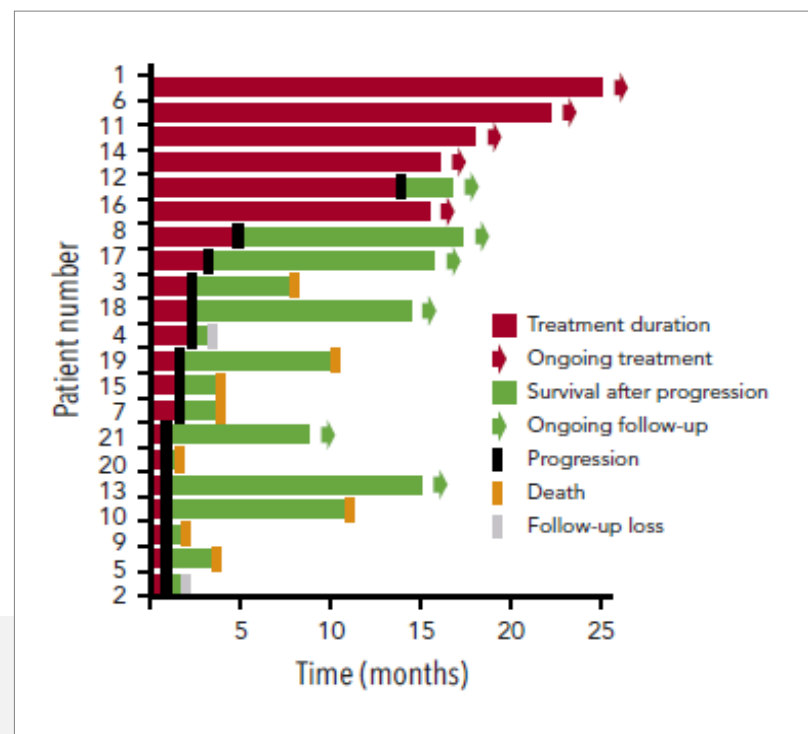
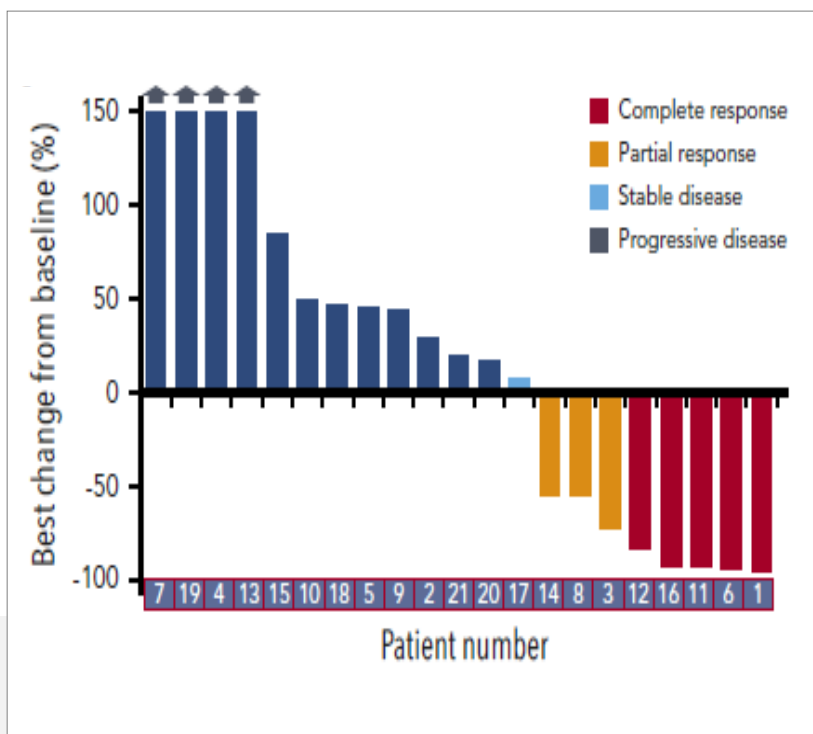
# Responses to Pembrolizumab according to immuno-subtype



# PD-L1 inhibitor in R/R ENKTL

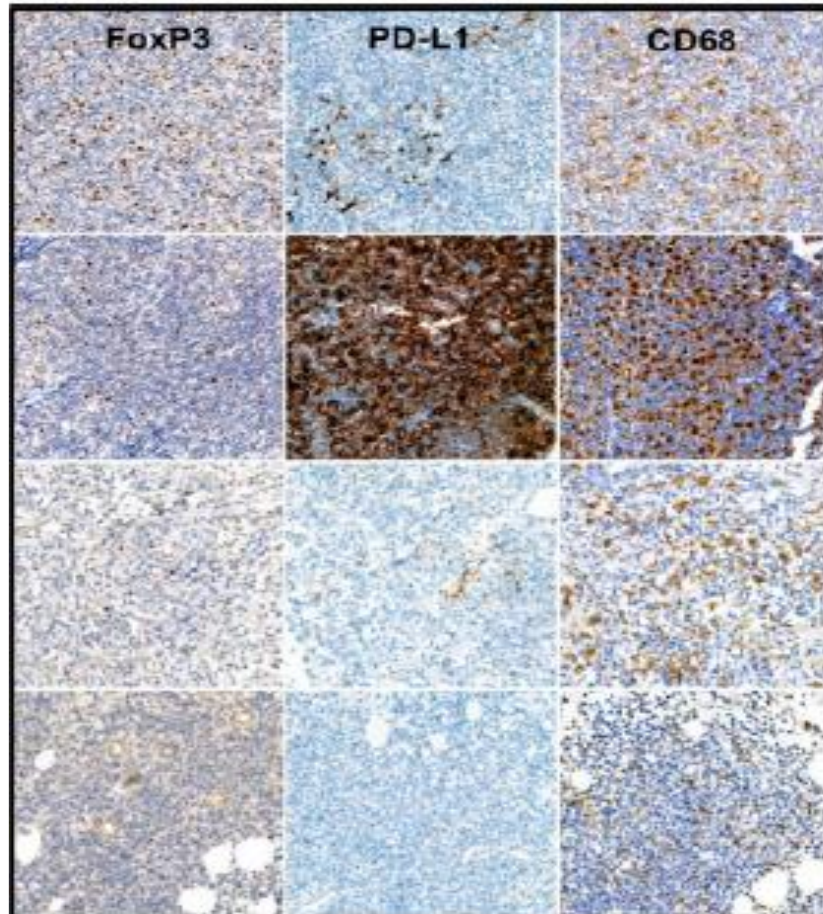


# PD-L1 inhibitor in R/R ENKTL





# PD-L1 inhibitor in R/R ENKTL

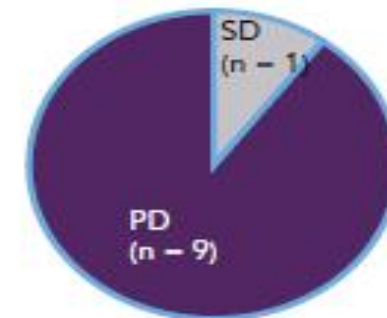
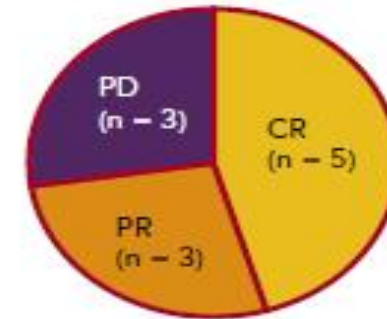


Immune Tolerance (n = 1) → 1 PR

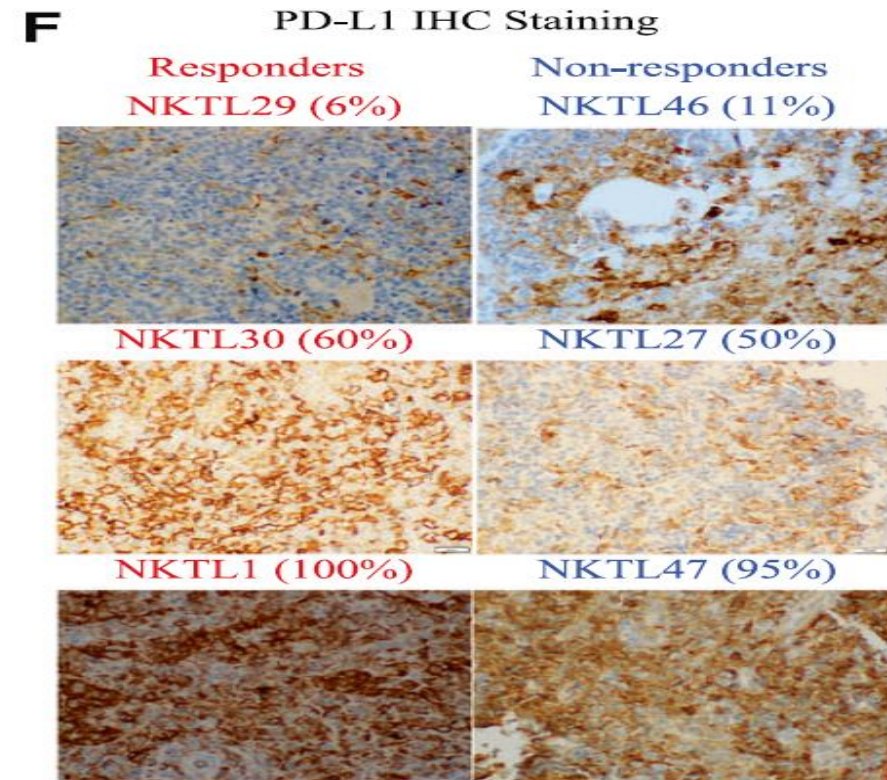
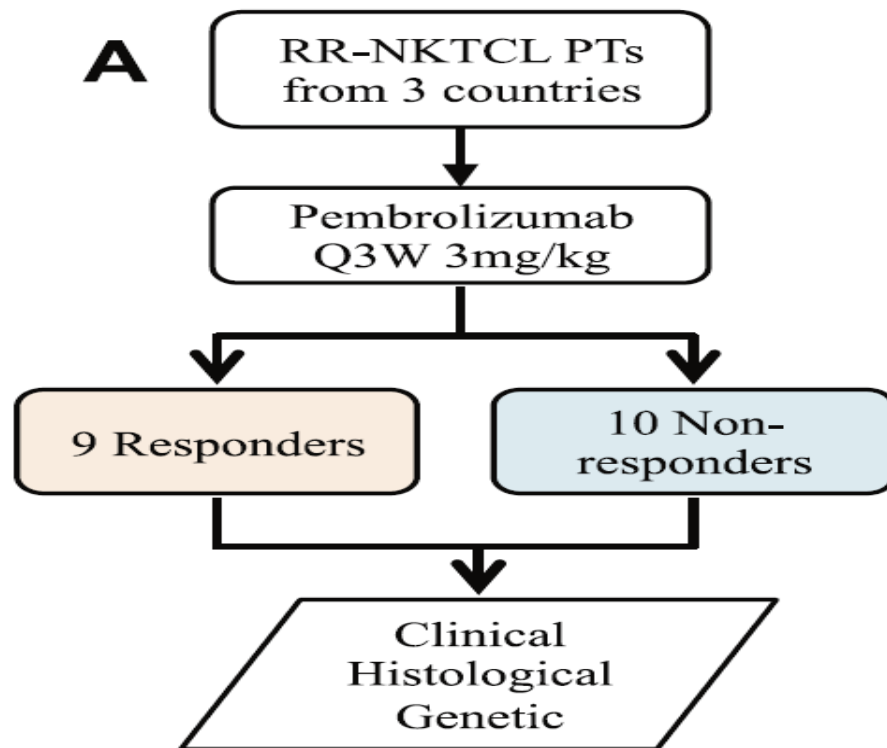
Immune Evasion-A (n = 10) → 5 CR  
2 PR  
3 PD

Immune Evasion-B (n = 5) → 5 PD

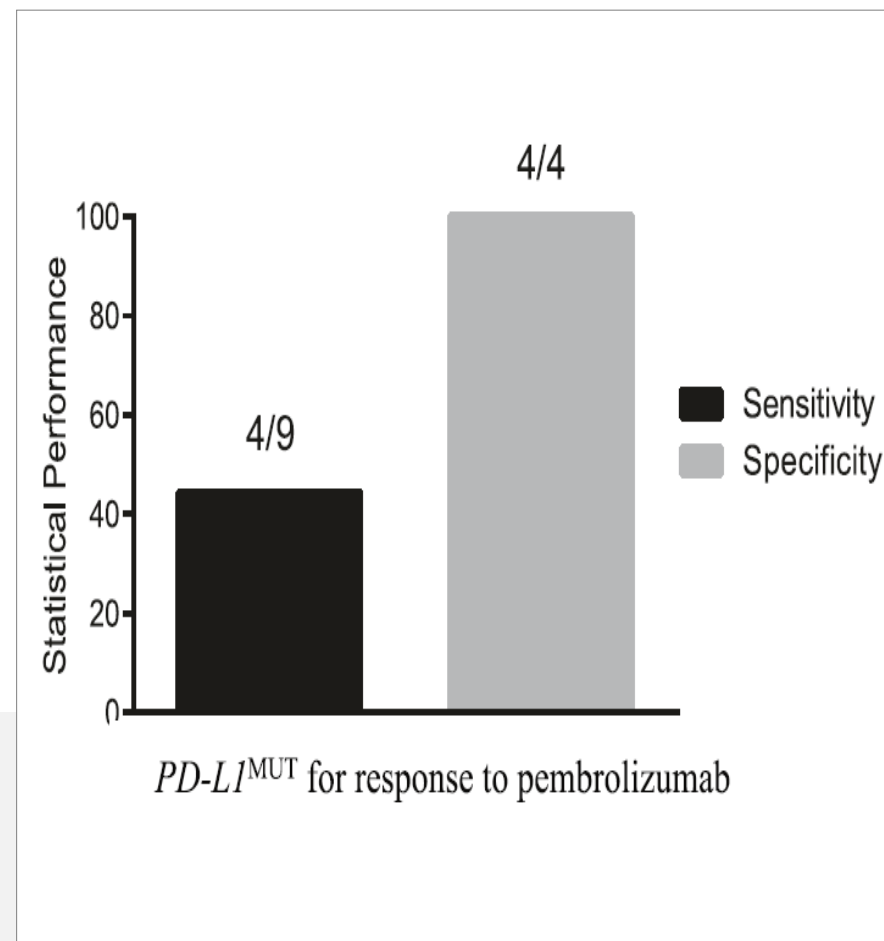
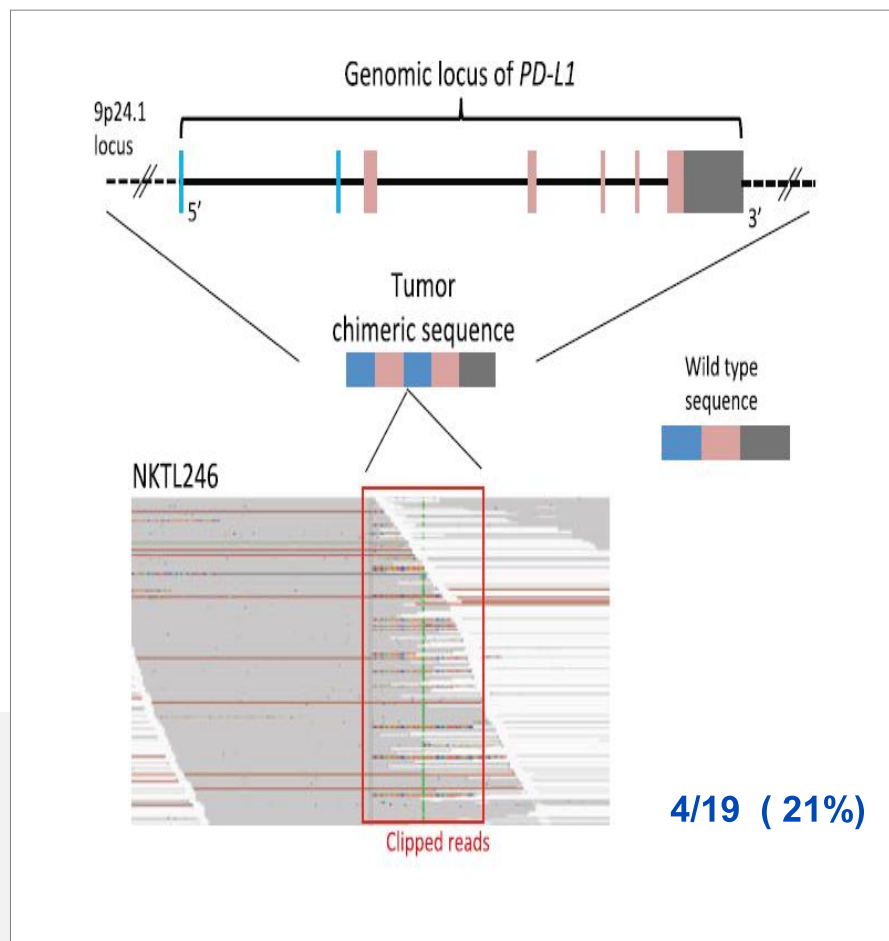
Immune Silenced (n = 5) → 1 SD  
4 PD



# Whole genome sequencing identifies responders to pembrolizumab



# Whole genome sequencing identifies responders to pembrolizuman



# A phase II study of Isatuximab / Cemiplimab in R/R ENKTL

**Isatuximab (SAR650984) – anti-CD38 antibody**

**1st cycle: 10mg/kg IV every week (Day 2, 9, 16, and 23)**

**2nd – 6th cycle: 10mg/kg every 2 weeks (Day 2 and 16)**

**7th cycle and beyond: 10mg/kg IV every 3 weeks (Day 2)**

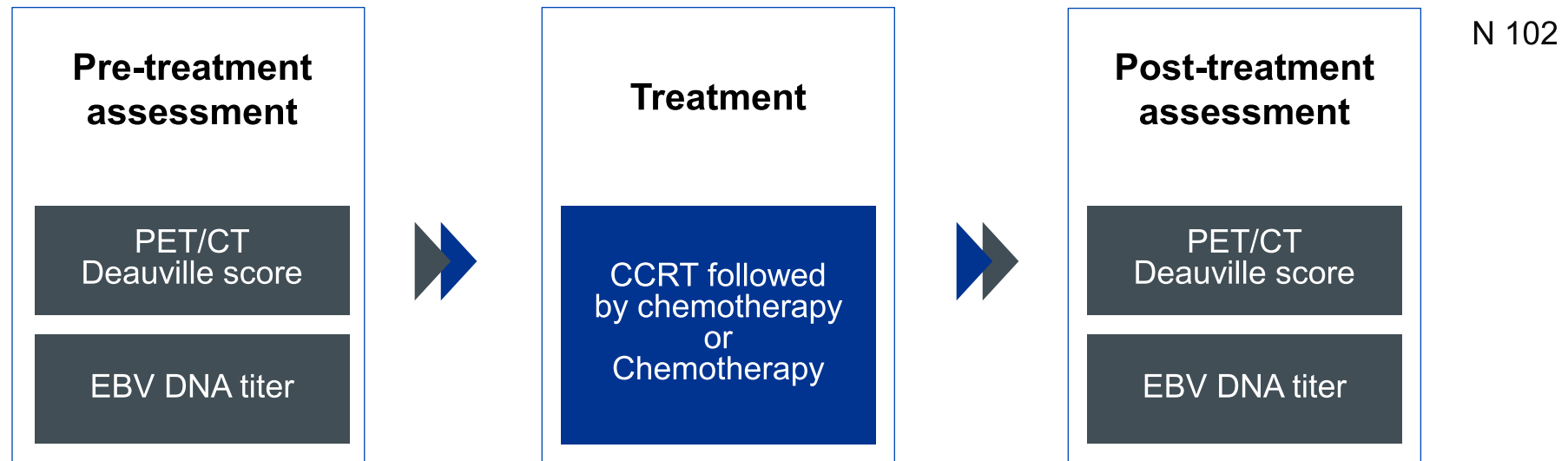
**Cemiplimab (REGN2810) – anti-PD1 antibody**

**1st – 6th cycle: 250mg IV every 2 weeks (Day 1 and 15)**

**7th cycle and beyond: 350mg every 3 weeks (Day 1)**

.

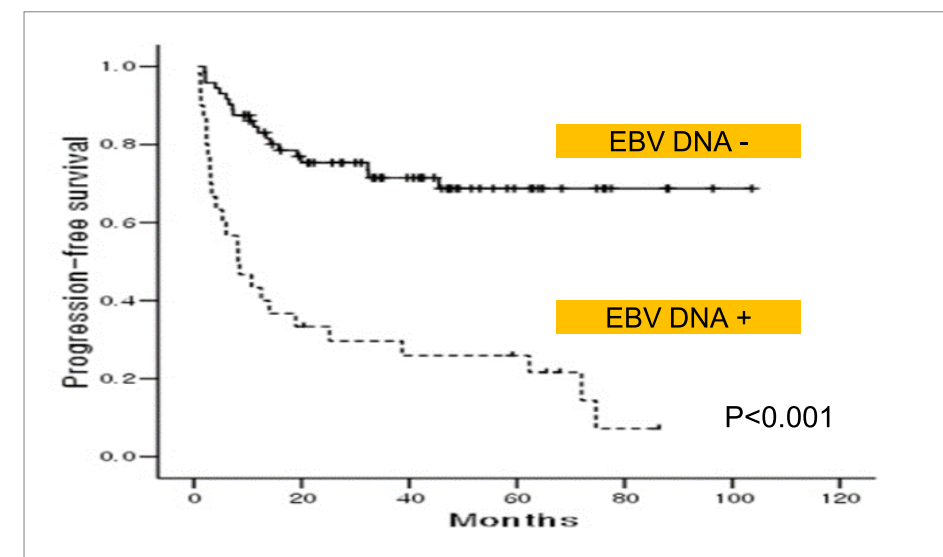
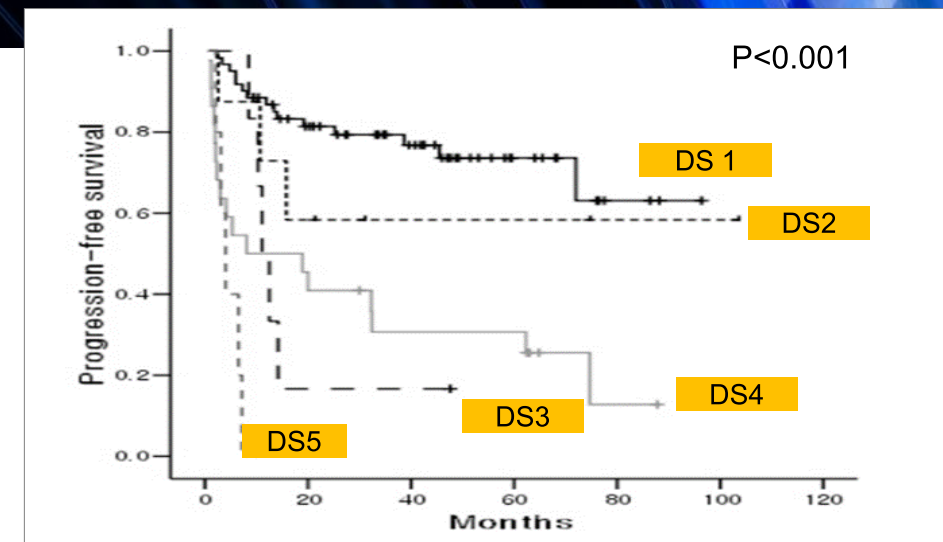
# Response evaluation based in PET/CT and EBV DNA



Stage I-II / III-IV	68/34
EBV DNA - /+	54/48
CCRT+Chemo	56
CCRT	5
Chemo	41

# PFS based on DS and EBV DNA

	Pre-treatment		Post-treatment	
	Number of patients	Treatment failure	Number of patients	Treatment failure
<b>Deauville score</b>				
1	2	1 (50%)	61	15 (25%)
2	2	1 (50%)	8	3 (38%)
3	3	0	6	5 (83%)
4	25	12 (48%)	22	17 (77%)
5	70	31 (44%)	5	5 (100%)
<b>Epstein-Barr virus DNA</b>				
Negative	54	21 (39%)	72	20 (28%)
Positive	48	24 (50%)	30	25 (83%)



# Relapse rate based on EOT

	Epstein–Barr virus negative (n=72)	Epstein–Barr virus positive (n=30)
Deauville score 1-2 (n=69)	8/54 (15%)	10/15 (67%)
Deauville score 3-4 (n=28)	8/14 (57%)	14/14 (100%)
Deauville score 5 (n=5)	4/4 (100%)	1/1 (100%)

# Treatment recommendation according to EOT response criteria

		Post-treatment Deauville score				
		1	2	3	4	5
Post-treatment Epstein-Barr virus	Negative	Low risk Observation after primary treatment	High risk Additional treatment to achieve Deauville score 1-2	Failure		
	Positive	High risk Additional treatment to achieve Epstein-Barr virus negativity	Failure Salvage treatment or clinical trial			



**There have been great progress in treatment of ENKTL during last 2 decades.**

## **Questions not answered**

- What can be the best induction regimen
- CNS event
- What can be the positioning of ICI
- Molecular classification

# Acknowledgement

- **Samsung medical center. lymphoma center:** *Kim SJ, Yoon SE, Kim H, Cho J, Ko YH*
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- **NCC Singapore:** *Lim ST, Ong CK*
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- **PINK /PINK-E project investigators**