



*Standard care Extranodal  
NK/T-cell lymphoma*

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**Won Seog Kim**

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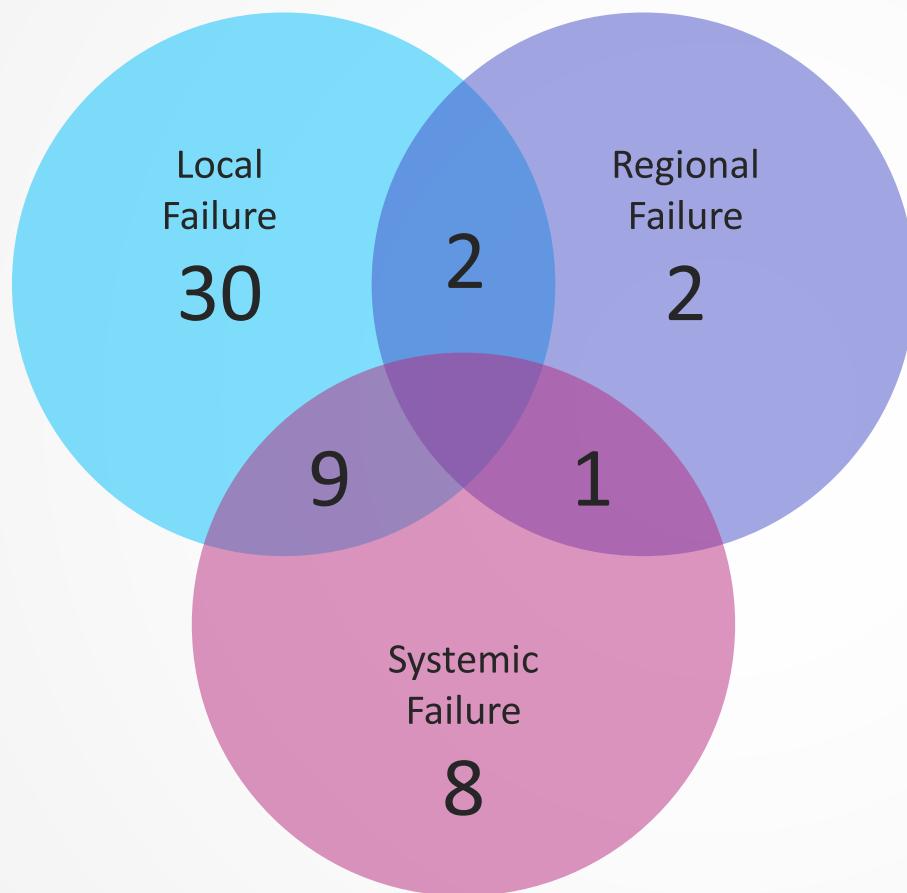
**SAMSUNG MEDICAL CENTER**

SEOUL, KOREA

## *Optimal Treatment of localized Disease*

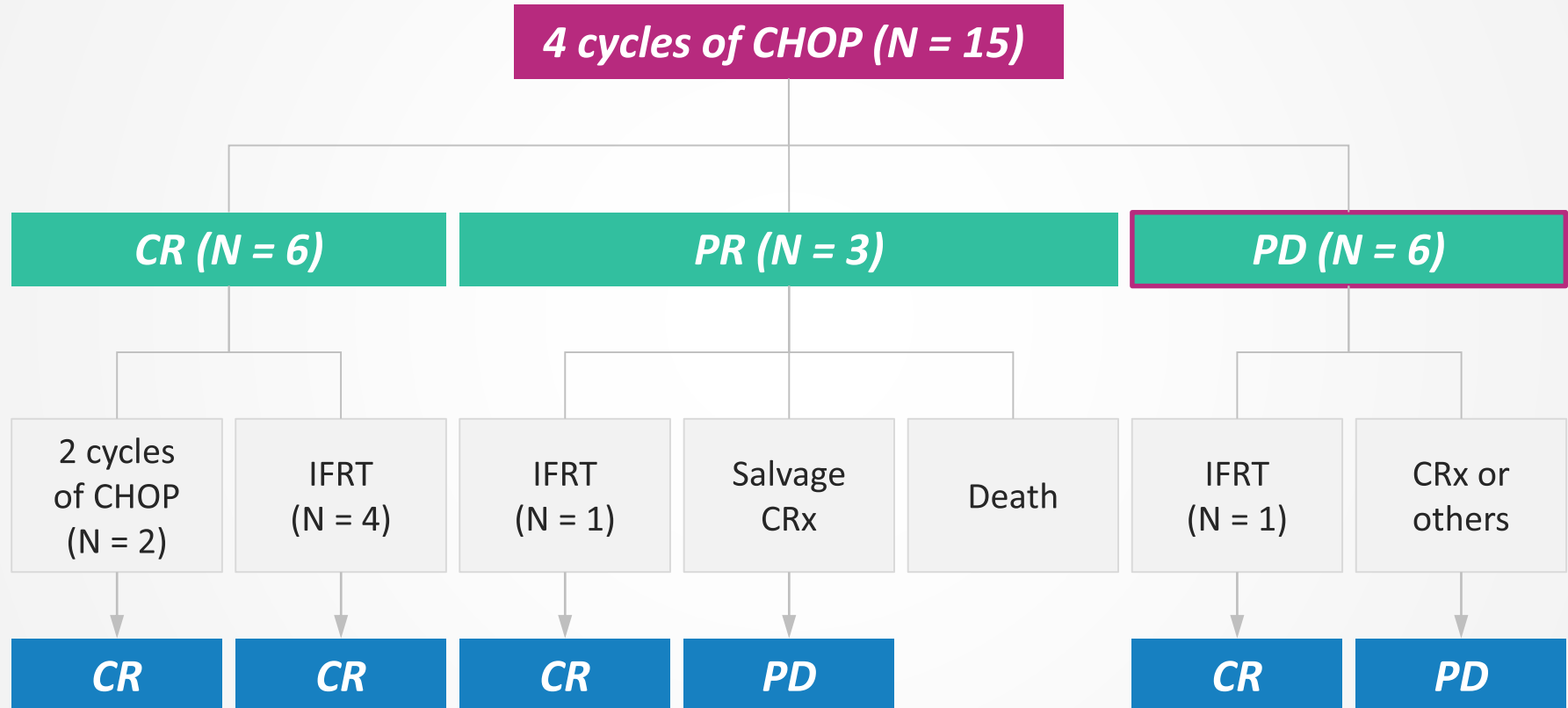


# Failure pattern after radiation: *Stage IE/II E NKTL*



- ◆ N = 92,
- ◆ 1976-1994
- ◆ 5-yr OS 40.1%
- ◆ 5-yr DFS 37.8%

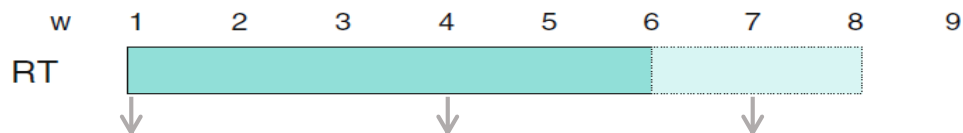
# Treatment of Localized ENKTL





# Treatment of Localized ENKTL

## RT-2/3 DeVIC



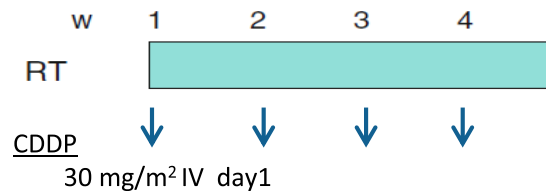
### 2/3 DeVIC

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)

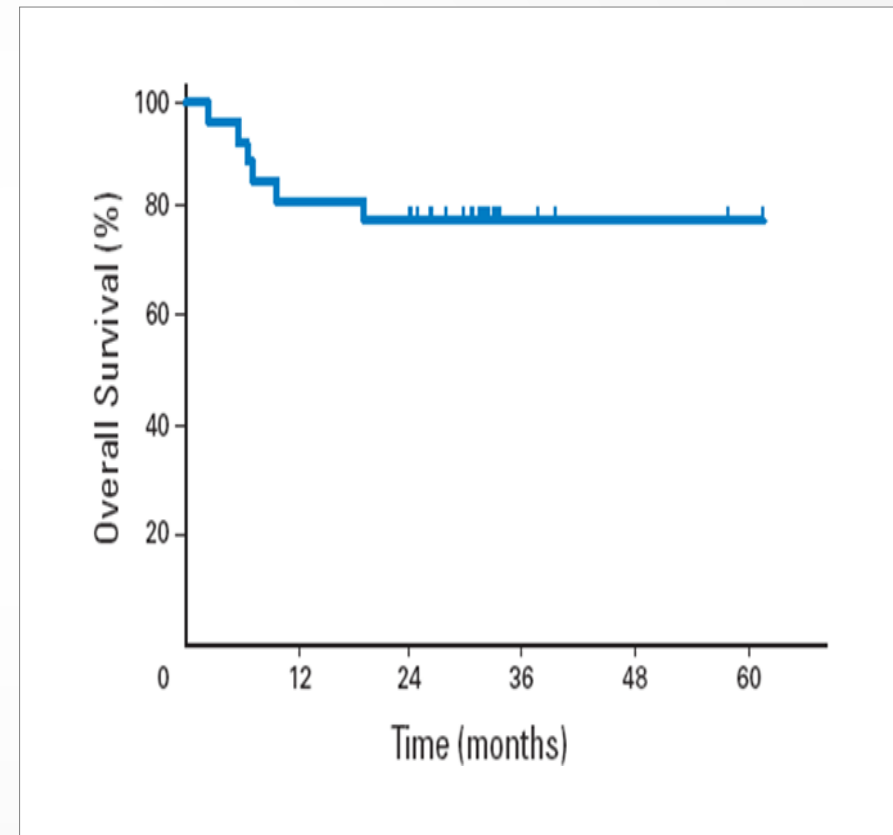
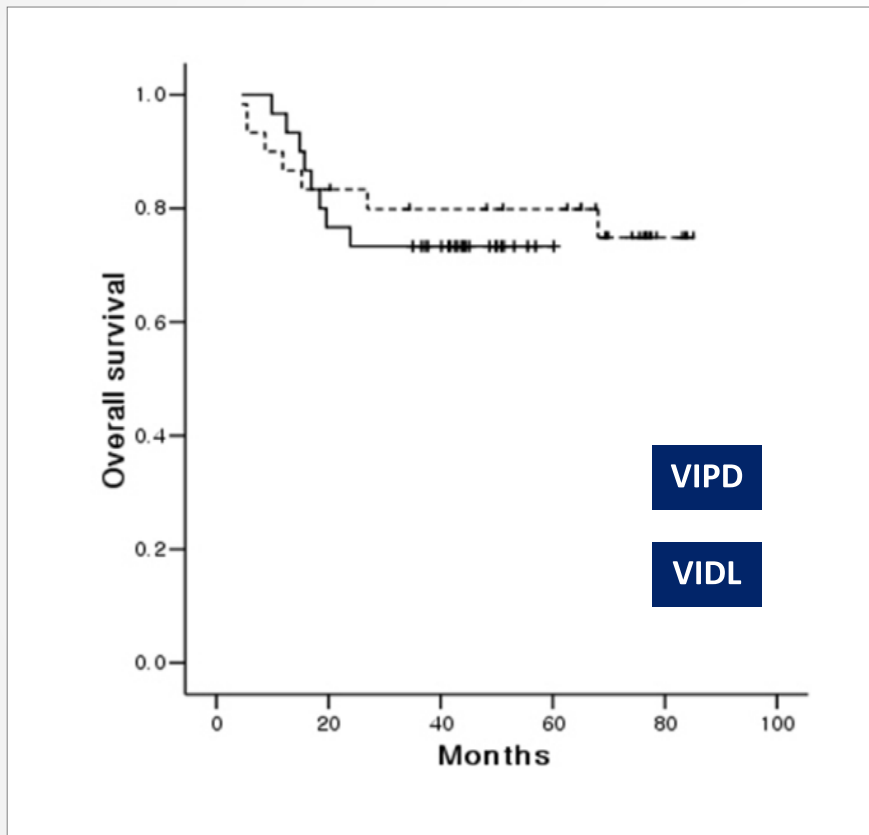
ETP	100 mg/m <sup>2</sup> IV	days 1-3
IFM	1,200 mg/m <sup>2</sup> IV	days 1-3
CDDP	33 mg/m <sup>2</sup> IV	days 1-3
DMS	40 mg/day PO/IV	days 1-4

3-5  
weeks

### 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



## *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?*

# GELOX followed by IFRT for stage I/II ENKL

Type of ASP

Response Rate  
After 2 Cycles  
of CT, %

$P^a$

Response Rate  
at the End of  
Treatment, %

$P^a$

L-ASP, n = 20

CR 50/PR 40

.785

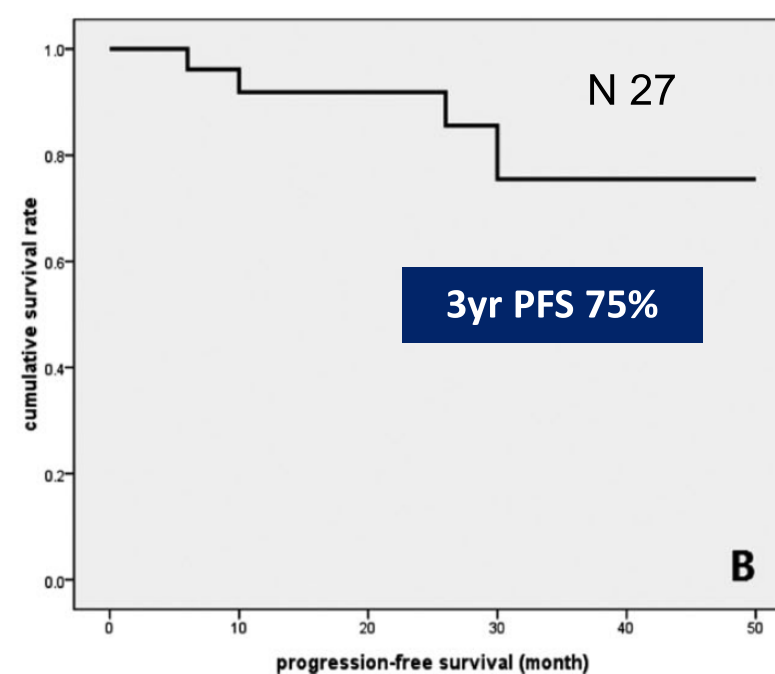
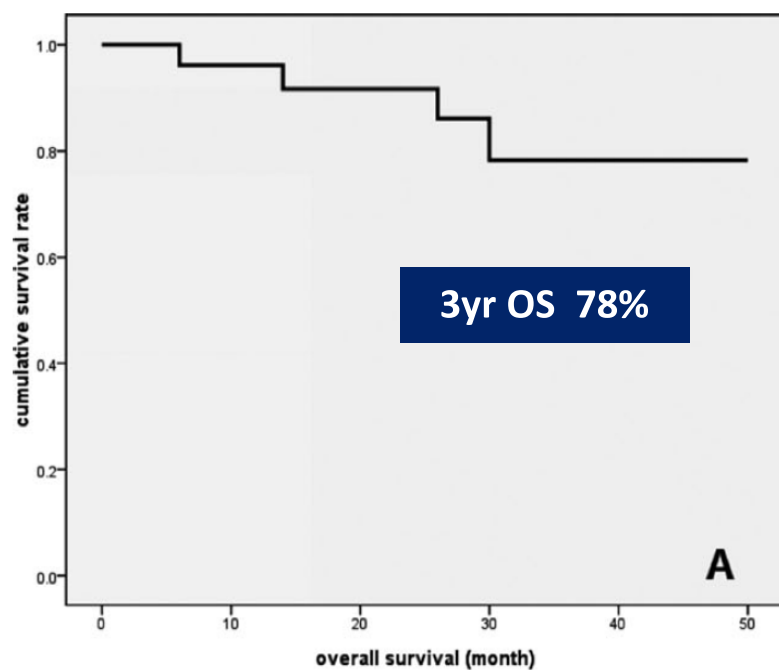
CR 65/PR 30

.242

Pegaspargase, n = 7

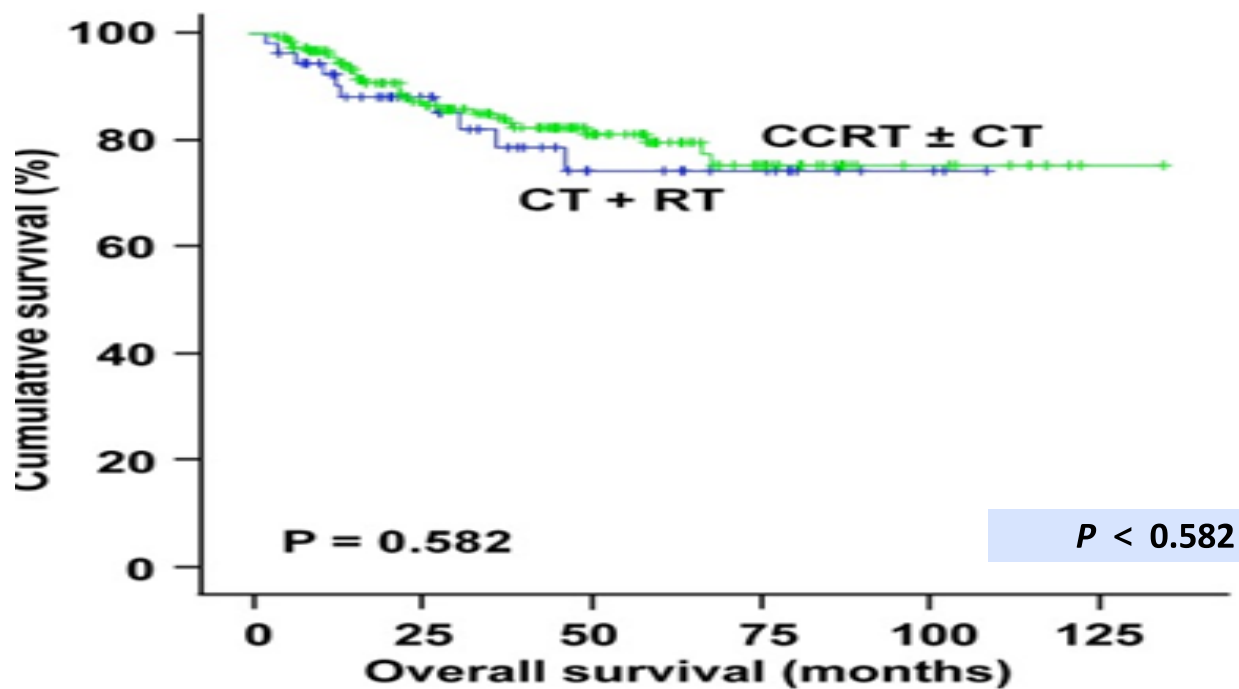
CR 71.4/PR 28.6

CR 100

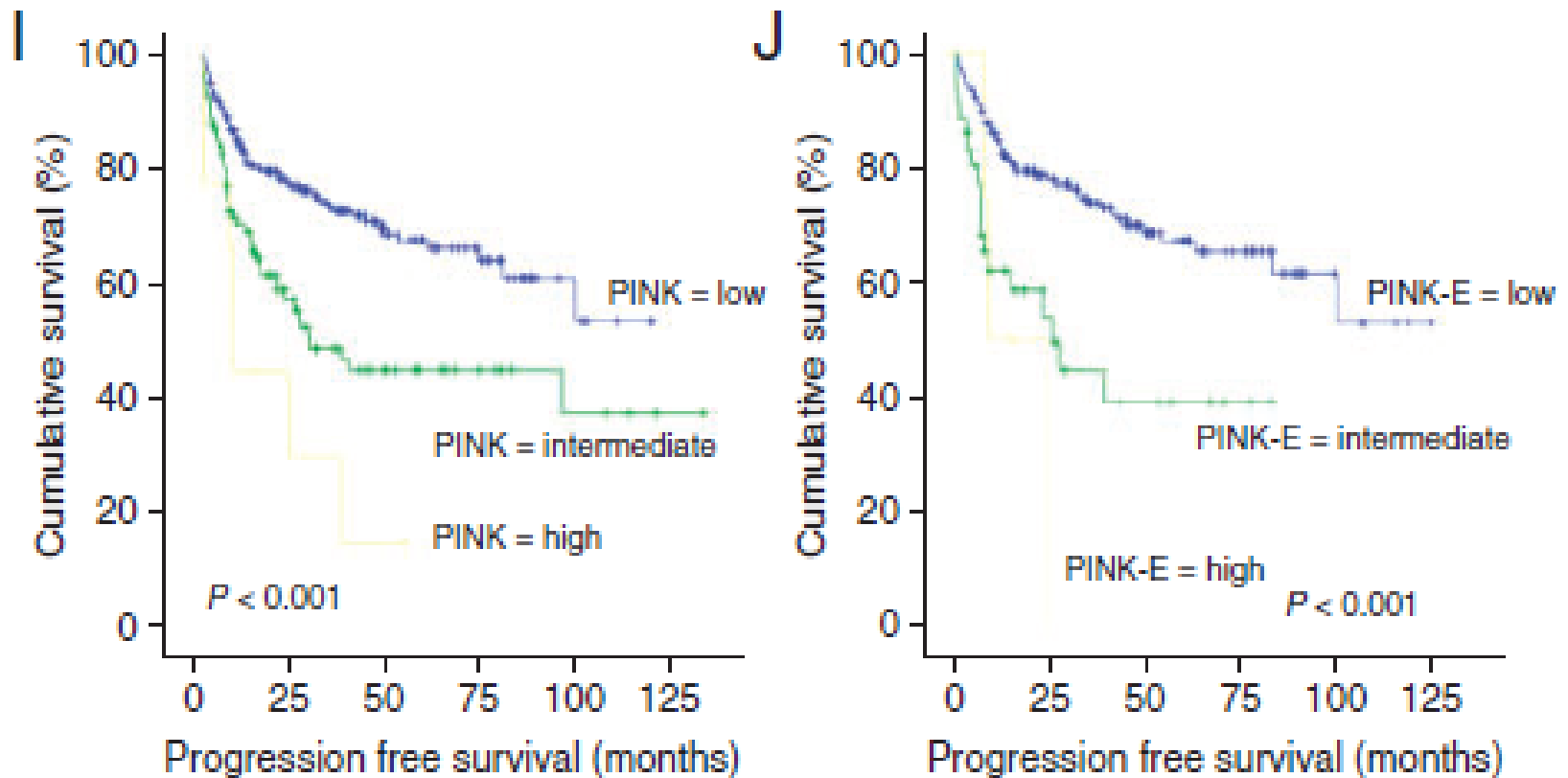




## Early RT vs late RT



# Outcome of localized ENKL according to PINK

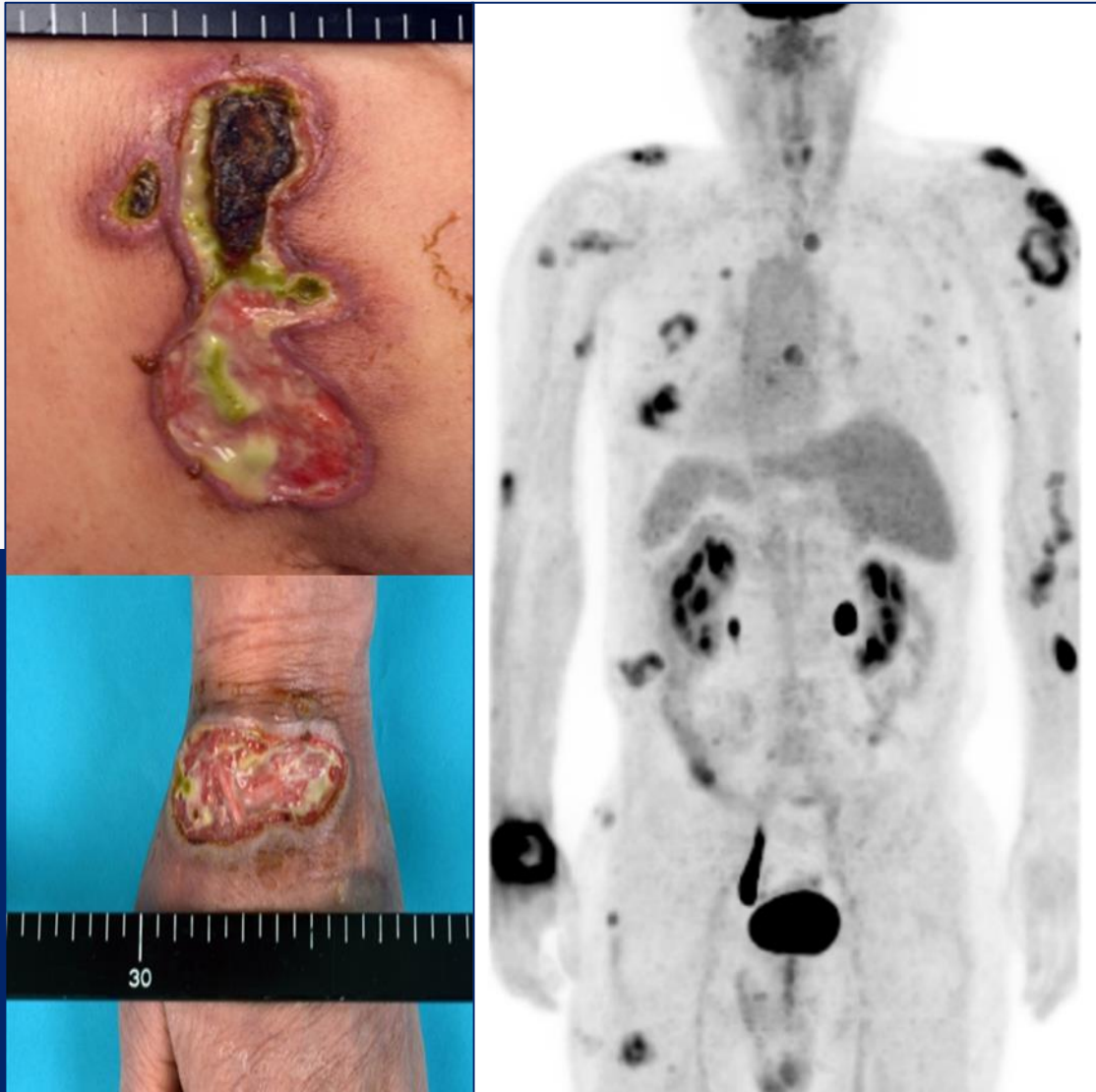


# *Unanswered questions in mx of localized ENKTL*

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?



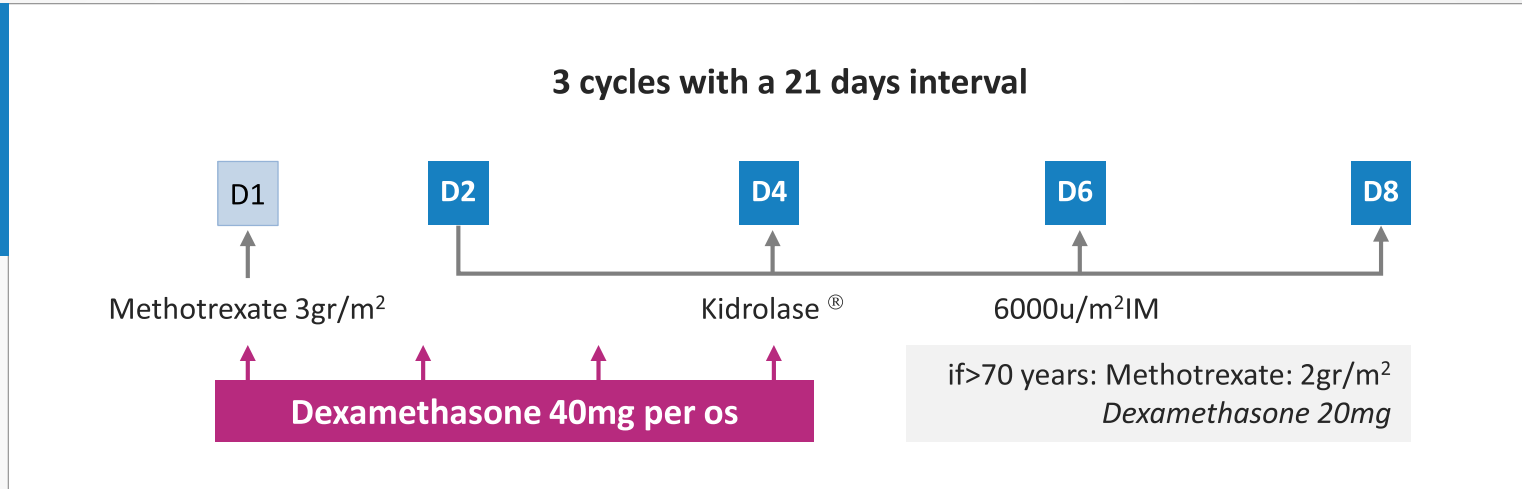
# *Optimal Treatment of advanced Disease*





# L-asparaginase containing regimens regimens

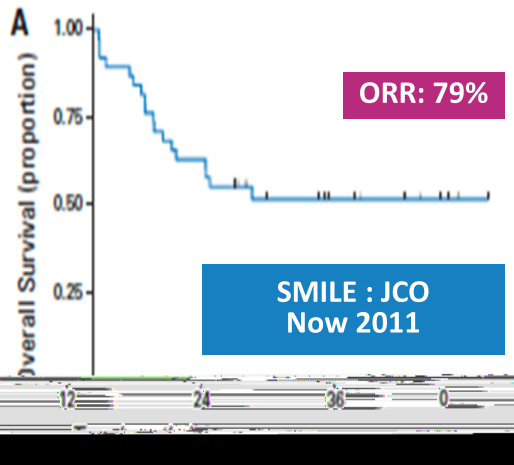
## Aspa-Met-Dex



## SMILE

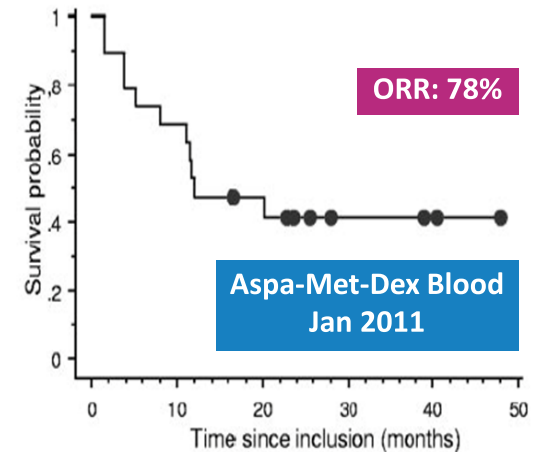
Agent	Dose(/day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	20	21	MTX	2 g/m <sup>2</sup>
Methotrexate(MTX)	* Ag/m <sup>2</sup>	●																							ETP	100 mg/m <sup>2</sup>
Leucovorin	15mgx4		●	●	●																					
Ifosfamide (IFM)	1,500 mg.m <sup>2</sup>		●	●	●																					
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 : Blood  
Aug 2012

ORR: 81%

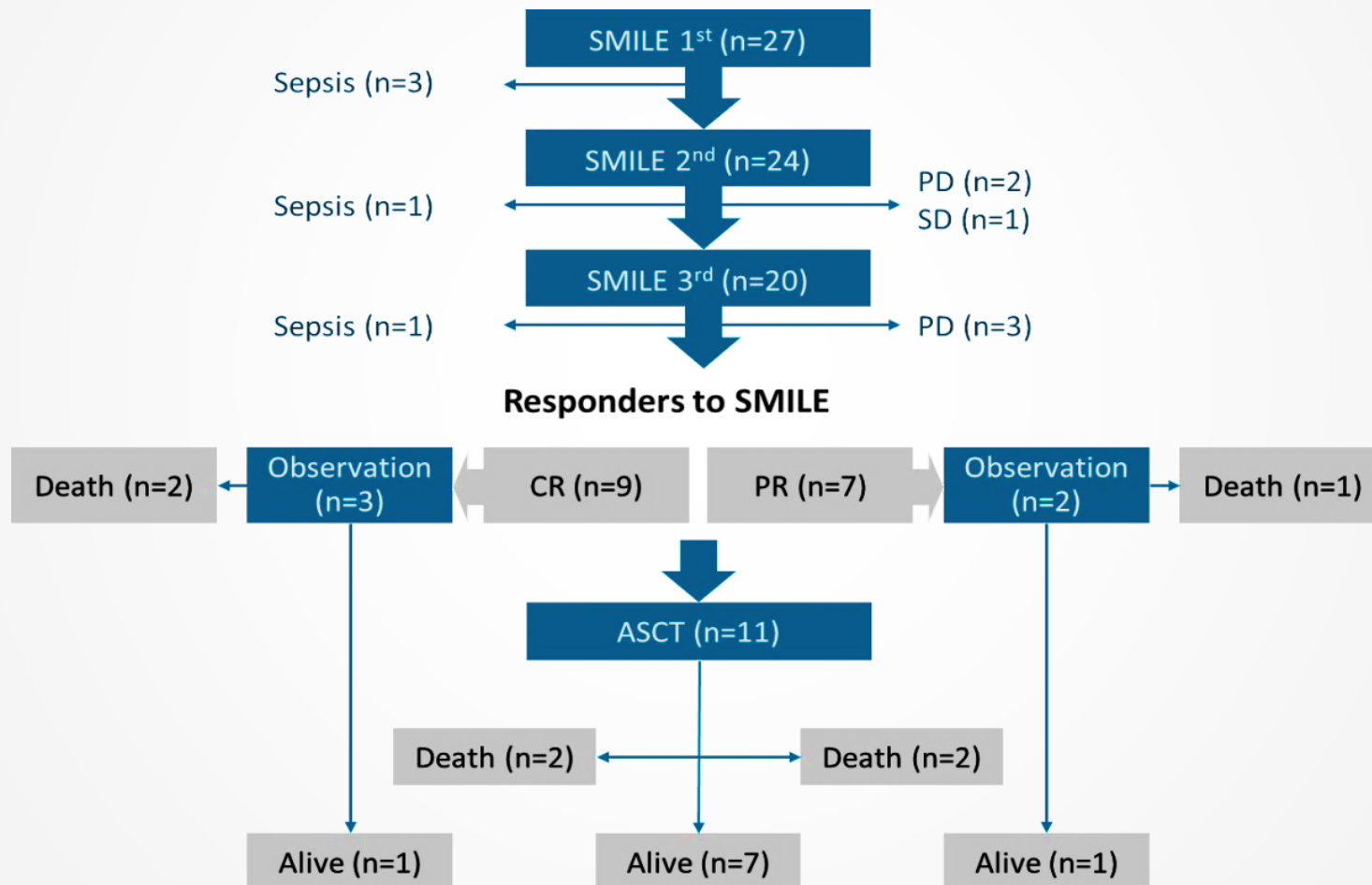


# Patient characteristics of advanced ENKL with SMILE followed by auto-HSCT in advanced stage ENKL

(N=27)

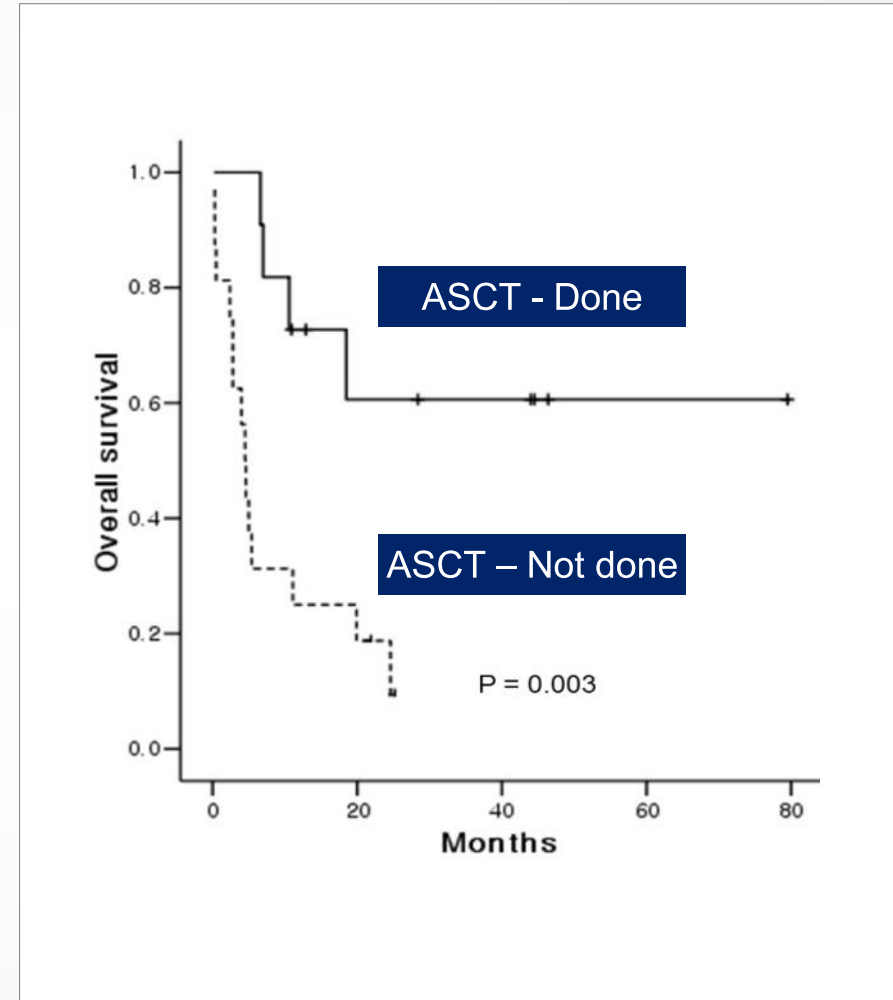
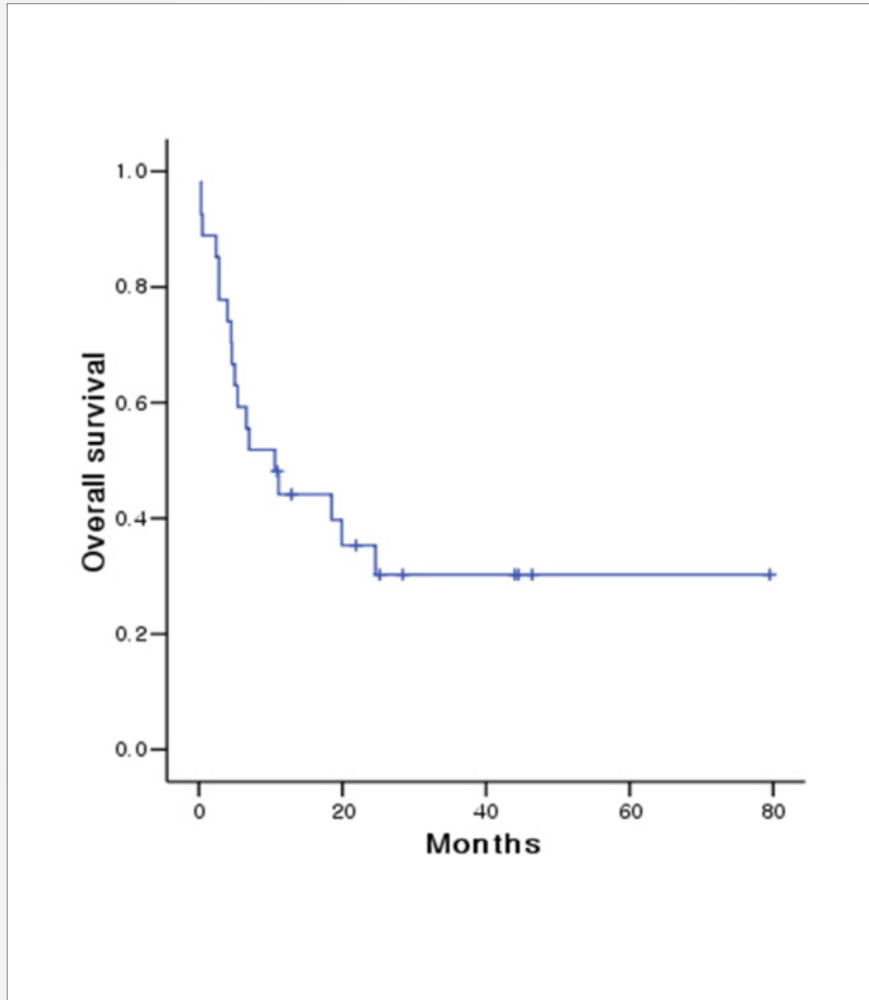
ECOG $\geq 2$	7 (26%)
BSx+	23 (85%)
BM+	13 (48%)
Hemophagocytic syndrome	5 (19%)
H/Hi in IPI	22 (81%)
Group 3-4 in KPI	27 (100%)

# SMILE followed by auto-HSCT





# Outcome of SMILE followed by auto-HSCT in ENKL

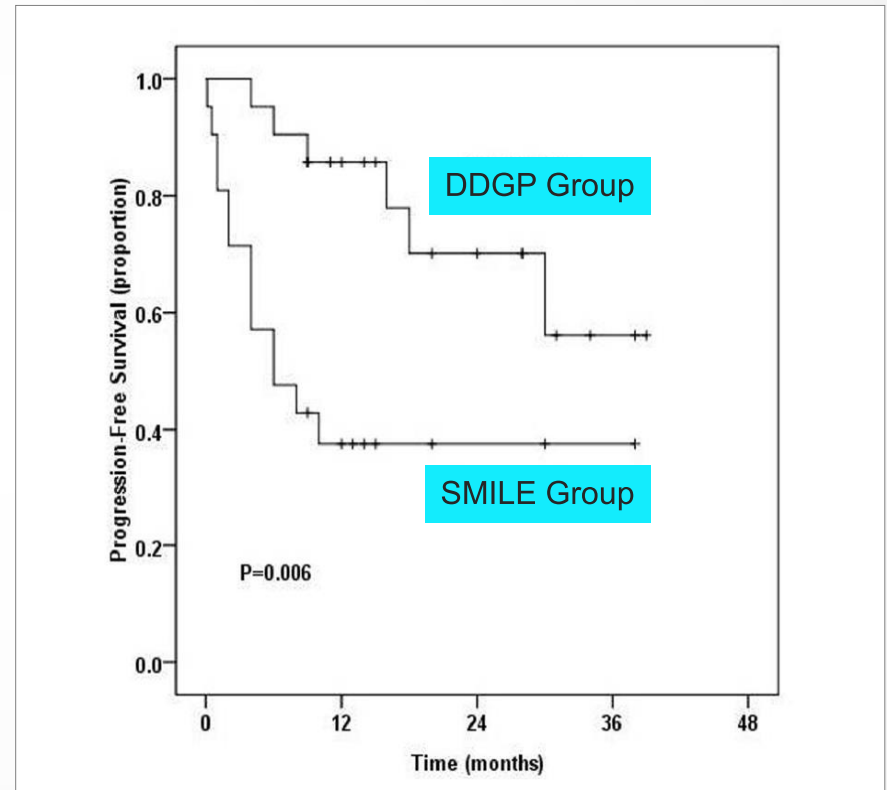


## DDGP vs SMILE

Agents	Dose	Route	Timing of treatment
DDGP			
PEF-Asp	2500 IU/m <sup>2</sup>	IM	Day 1
Gemcitabine	800 mg/m <sup>2</sup>	IV	Day 1 and day 8
Cisplatin	20 mg/m <sup>2</sup>	IV	Day 1-4
Dexamethasone	15 mg/m <sup>2</sup>	IV	Day 1-5
SMILE			
Methotrexate	2 g/m <sup>2</sup>	IV (6 hours)	Day 1
Dexamethasone	40 mg/m <sup>2</sup>	IV	Day 2-4
Ifosfamide	1500 mg/m <sup>2</sup>	IV	Day 2-4
Mesna	300 mg/m <sup>2</sup>	IV	Day 2-4
Etoposide	100 mg/m <sup>2</sup>	IV	Day 2-4
L-Asp	6000 U/m <sup>2</sup>	IV	Day 3-9

# DDGP vs SMILE

Response	Number of patients(%)		
	DDGP	SMILE	Pvalue
	N=21	N=21	
CR	15 (71)	6 (29)	0.005
PR	5 (24)	8 (38)	-
SD	0 (0)	0 (0)	-
PD	1 (5)	3 (14)	-
ORR	20 (95)	14 (67)	0.018



# *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?





## *CNS prophylaxis Necessary?*

- Most of the disease occur in nasal and paranasal area

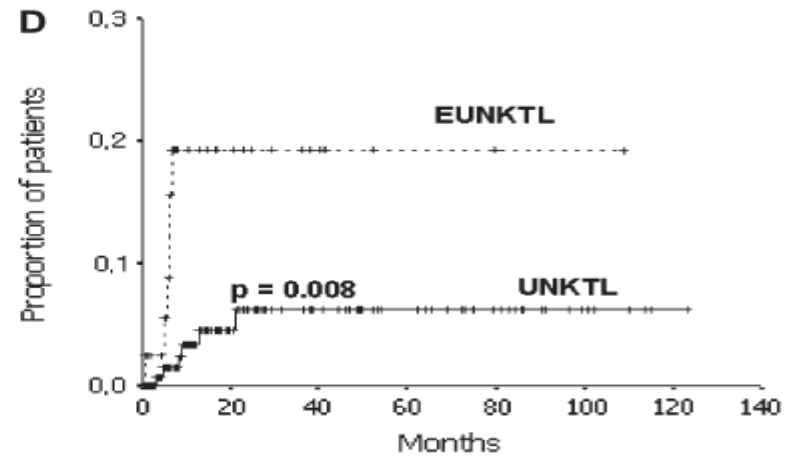
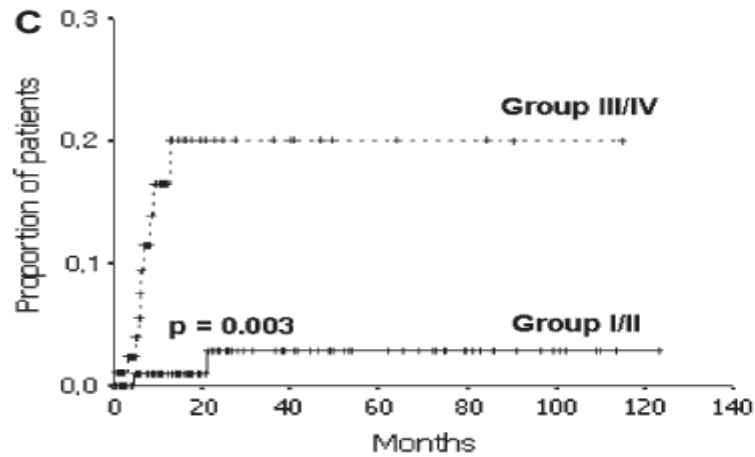
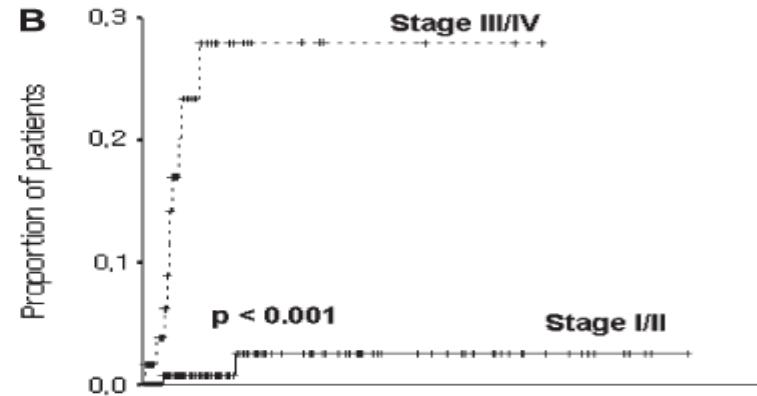
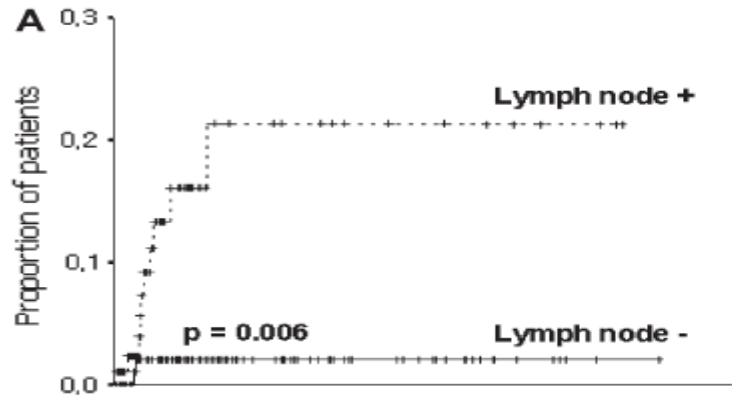
# CNS events

N 12/208( 5.75%)

Clinical features of patients before CNS relapse							Characteristics of CNS relapse					
Sex	Age (years)	Stage	IPI	NKPI	Sites of involvement	Response to the first-line treatment	Pattern	Manifestation	Time to CNS relapse (months)	Response to CNS-directed therapy	Status after CNS relapse	Survival time after CNS relapse (months)
Patients with CNS relapse during follow-up after the first-line treatment												
M	40	IIE	LI	I	Nasal cavity, orbit, LN	CR to IMVP-16	Leptomeningeal	Lower extremity weakness	4.63	CR	PD	5.57
M	22	IV	LI	IV	Skin	CR to CHOP	Parenchymal	No symptom	5.63	CR	2nd CNS relapse with PD	19.63
M	35	IV	LI	IV	Nasal cavity, bone marrow	CR to VIPD with ASCT	Parenchymal	Right motor weakness	9.03	PD	PD	2.53
M	48	IV	LI	III	Nasal cavity, liver, LN	CR to CHOP	Leptomeningeal	Lower extremity weakness	6.03	PD	PD	0.80
Patients with CNS relapse during the first-line treatment												
M	52	IV	LI	III	Lung	PR to CHOP	Parenchymal	Headache	0.67	PR	PD	6.63
F	63	IV	HI	III	Liver, rectum, bone marrow	PR to CHOP	Leptomeningeal	Lower extremity weakness	5.07	CR	PD	3.47
M	33	IV	H	IV	Oral cavity, skin, LN	PR to VIPD	Leptomeningeal	Blurred vision	6.80	NE	PD	2.20
F	59	IIIE	LI	III	Nasal cavity, LN	PR to CHOP	Leptomeningeal	Headache	3.13	CR	Follow-up loss	2.53
Patients with CNS relapse during salvage chemotherapy after systemic disease progression or relapse												
M	39	IV	HI	IV	Larynx, jejunum, LN	PD to CHOP	Leptomeningeal	Seizure	6.10	NE	PD	1.17
M	51	IIIE	LI	III	Nasal cavity, LN	CR to CHOP	Parenchymal	Ptosis	12.73	NE	PD	5.37
F	51	IIIE	HI	IV	Nasal cavity, LN	CR to VIPD with ASCT	Parenchymal	Disorientation	8.23	NE	PD	0.13
M	51	IIE	L	IIE	Oropharynx, LN	CR to VIPD with RTx	Parenchymal	Lower extremity weakness	20.97	NE	PD	1.33

# CNS events

N 12/208 (5.75%)



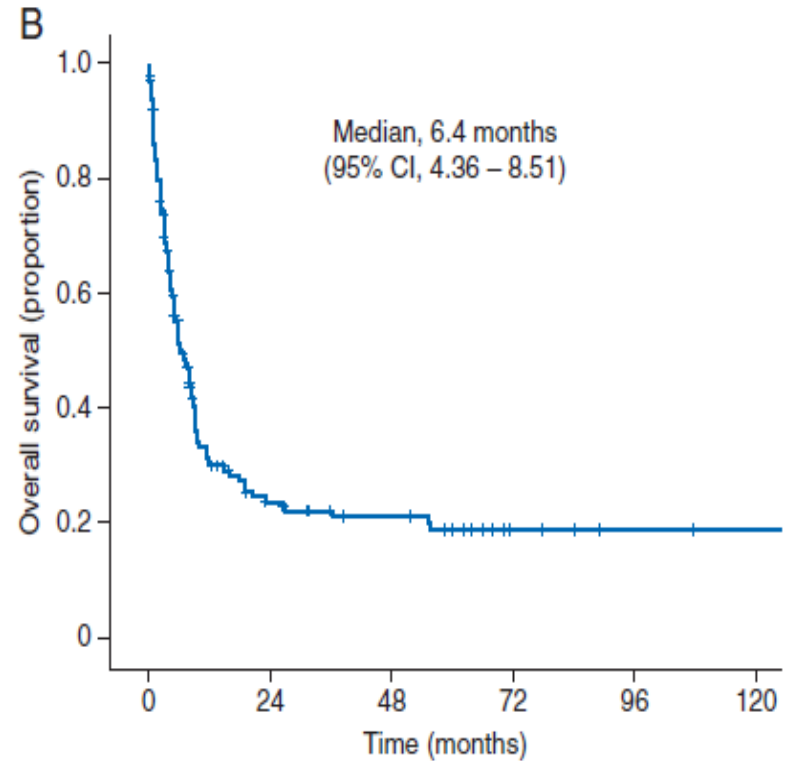
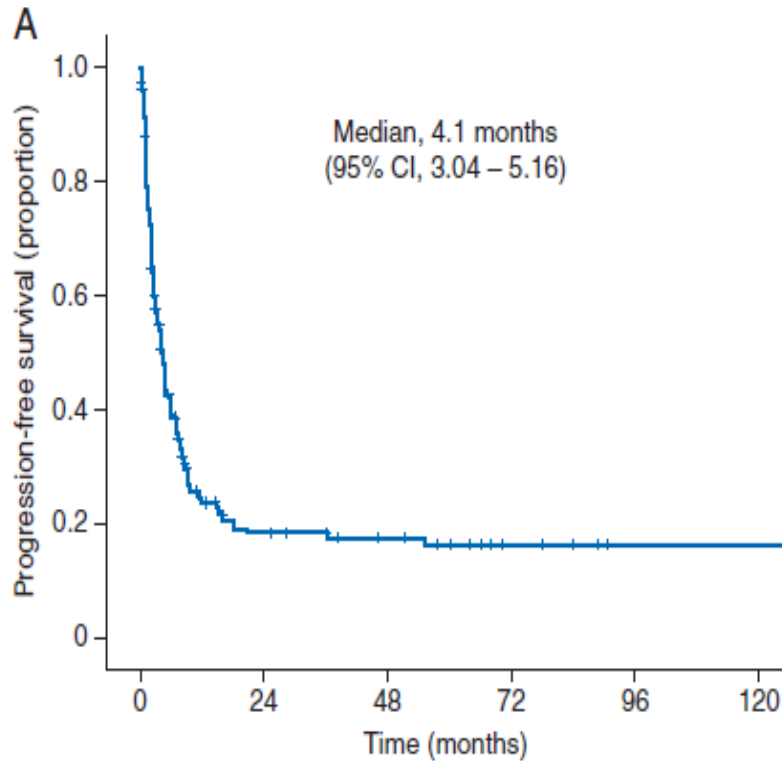
# CNS prophylaxis Necessary?

1. For localized ENKL, CNS prophylaxis seems not to be necessary
2. CNS prophylaxis can be necessary
  - Advanced stage disease
  - High risk patients by PINK /PINK-E

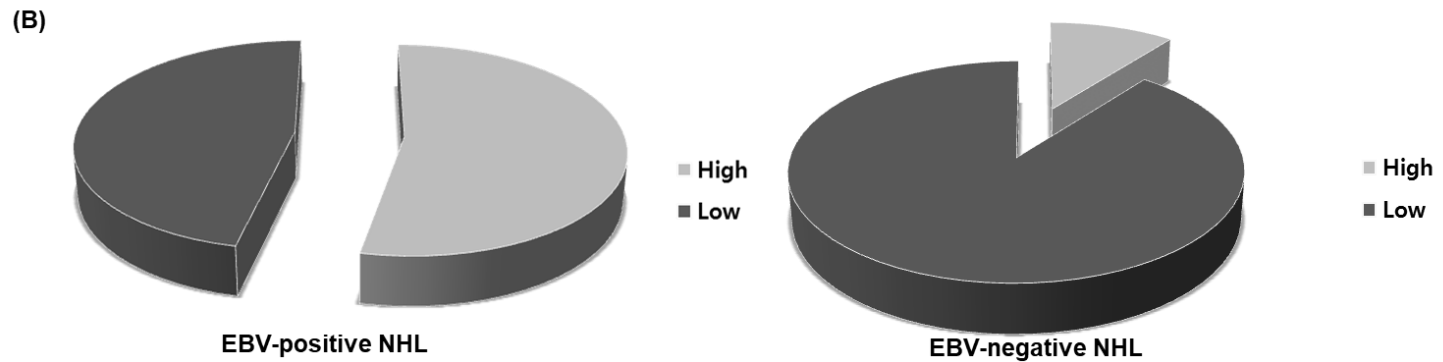
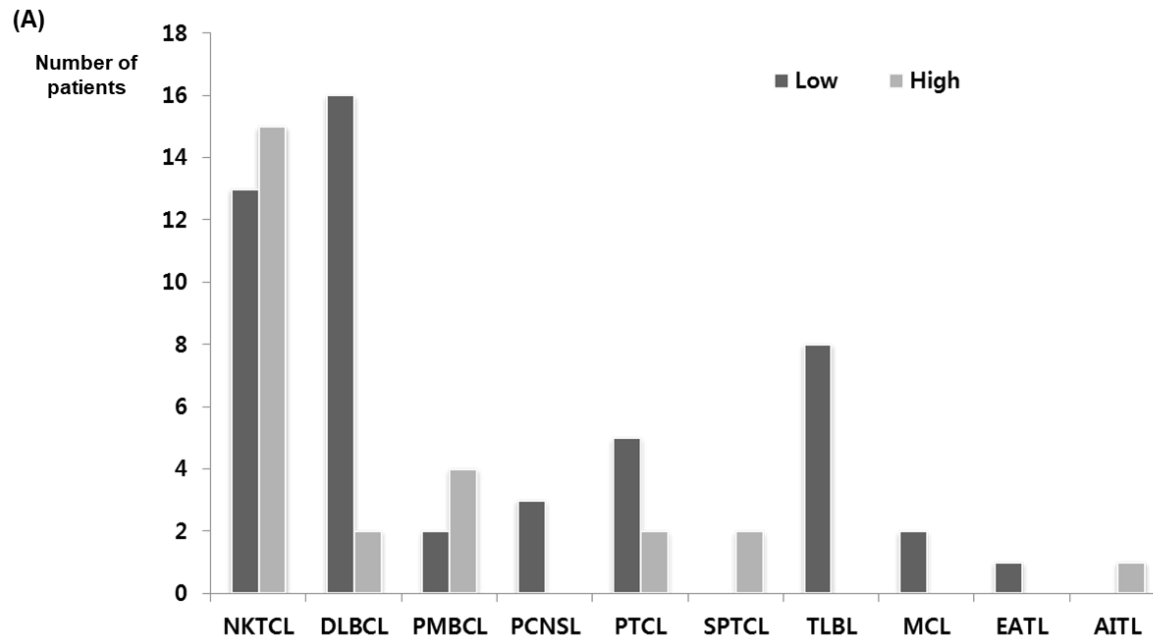
***SMILE and AspMetDex are already including MTX***



## Beyond failure of standard care



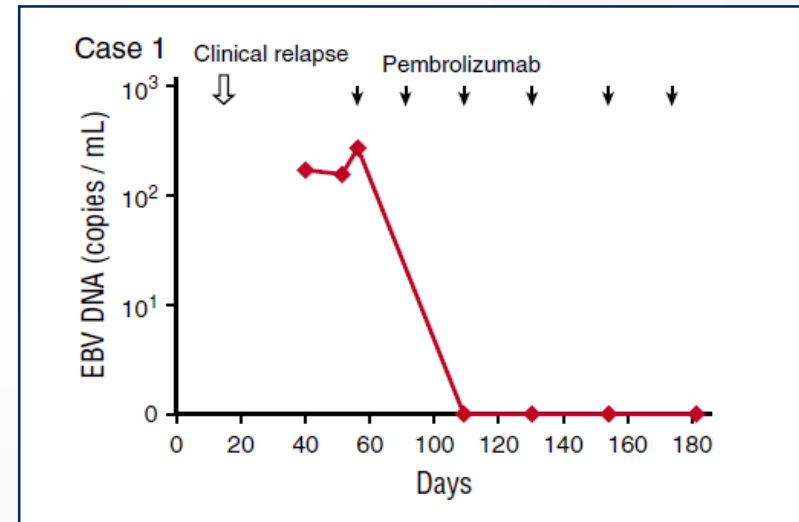
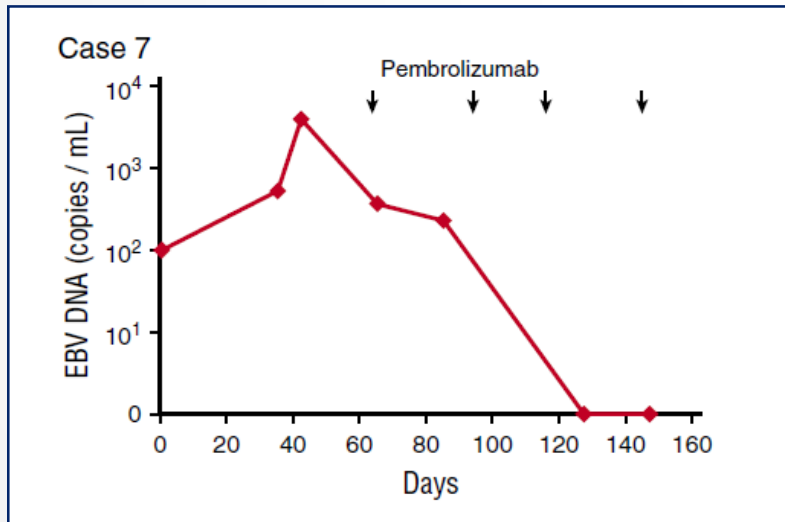
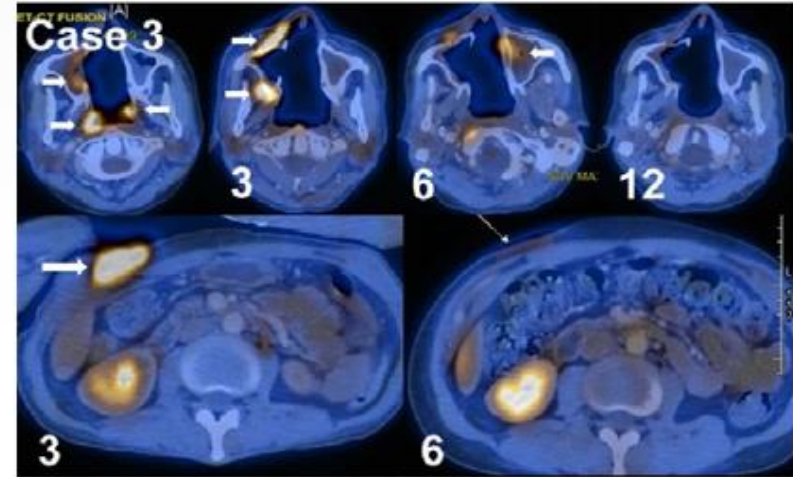
# PDL1 expression in SMC



# ICI in r/r ENKTL

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

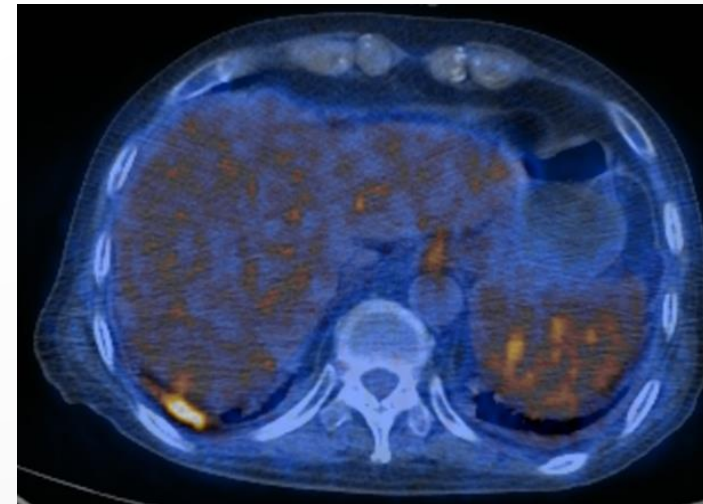
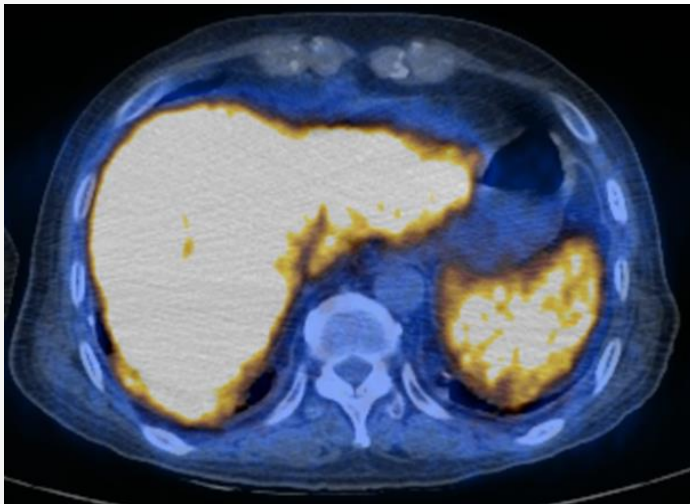
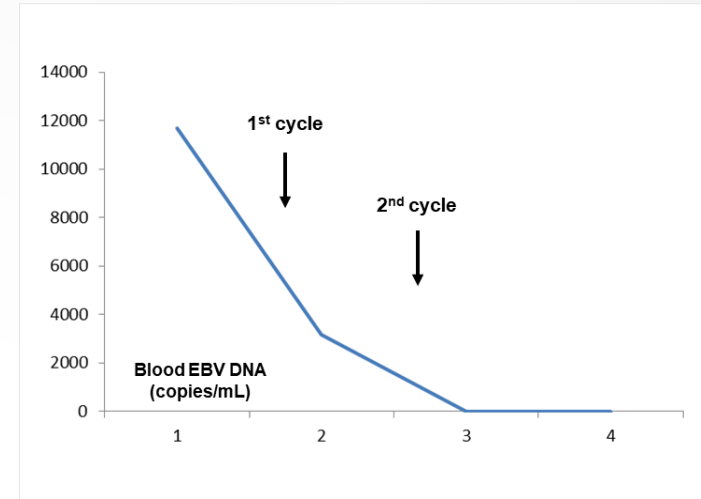
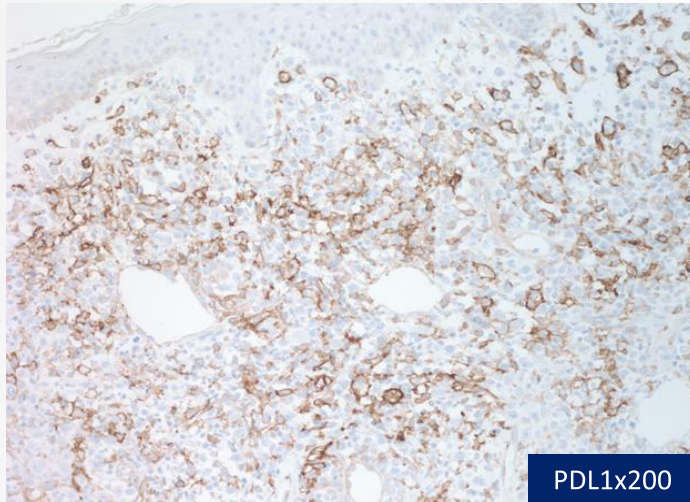
Case	Sex	Age, y	Primary sites	Marrow	Stage
1	M	68	Skin of lower limbs, nasal cavities	Negative	IV
2	M	49	Nasal cavities, lymph nodes, liver, spleen, bone	Negative	IV
3	M	38	Nasopharynx	Negative	I <sub>E</sub>
4	M	50	Liver	Positive	IV
5	M	31	Nasal cavity, nasopharynx, masseter muscle, bone	Negative	IV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



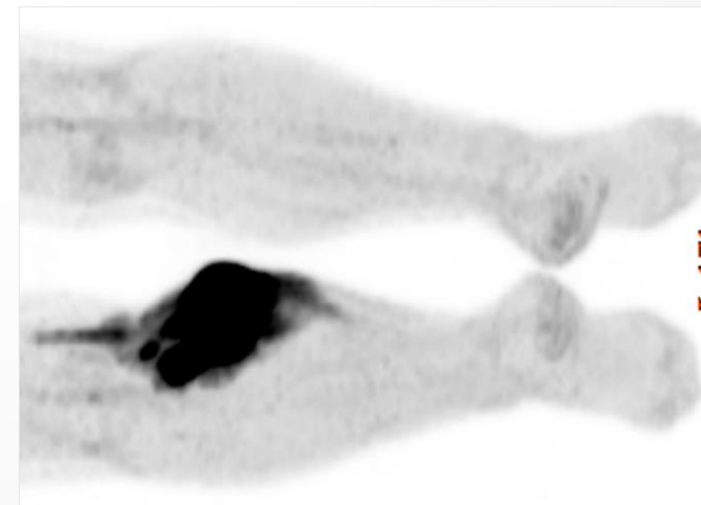
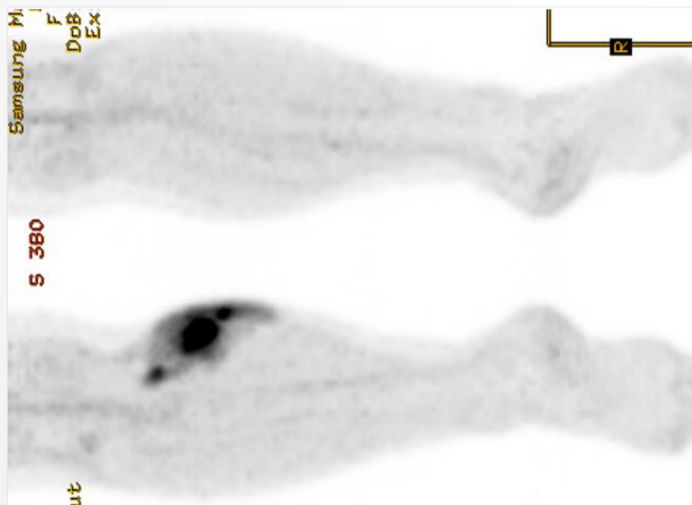
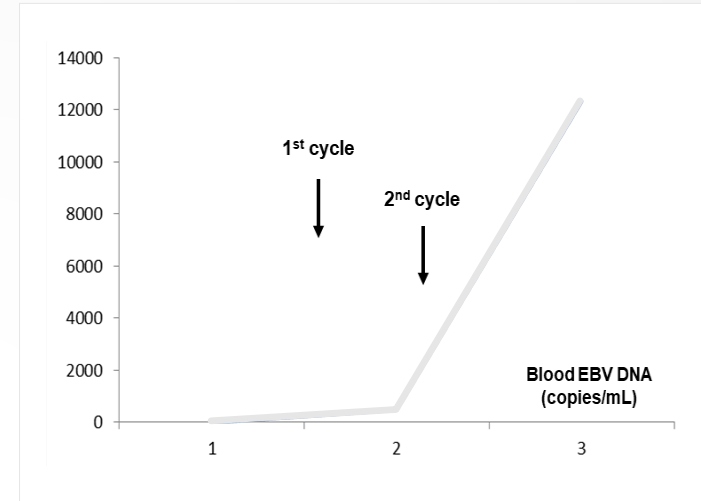
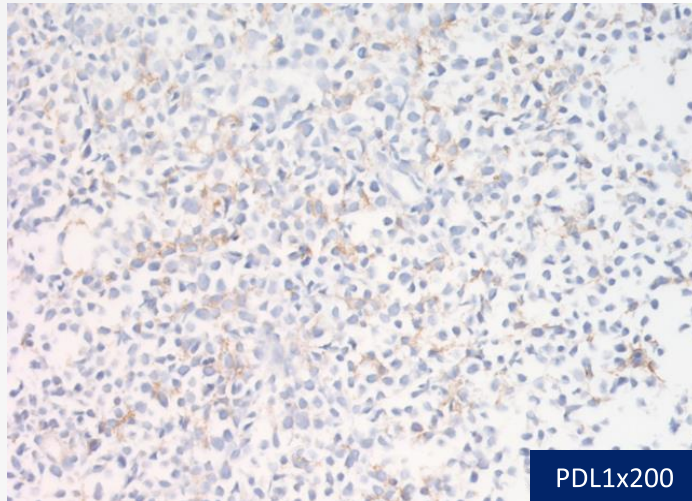




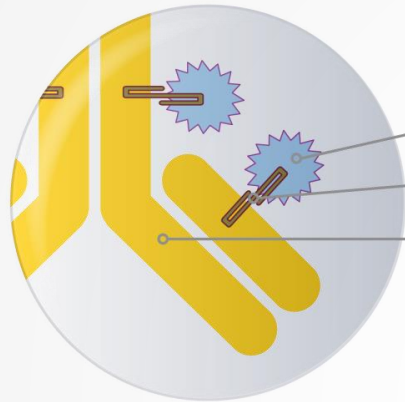
# Pembrolizumab in SMC



# Pembrolizumab in SMC



# Brentuximab Vedotin MOA

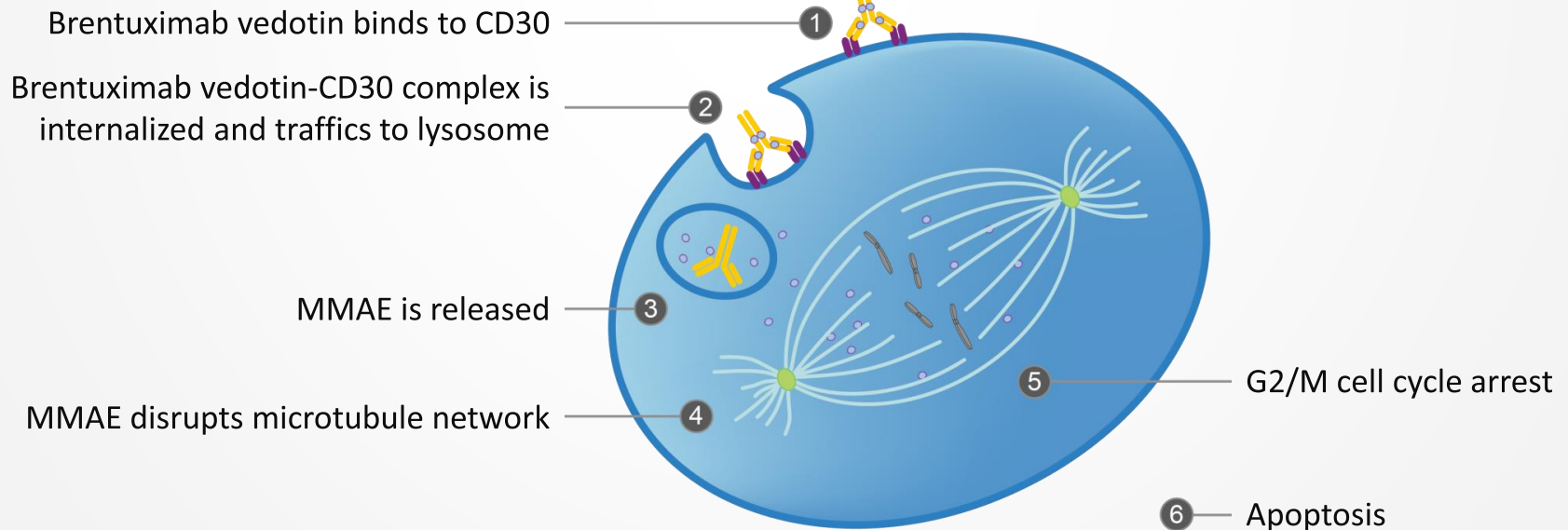


## Brentuximab Vedotin Antibody-Drug Conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent

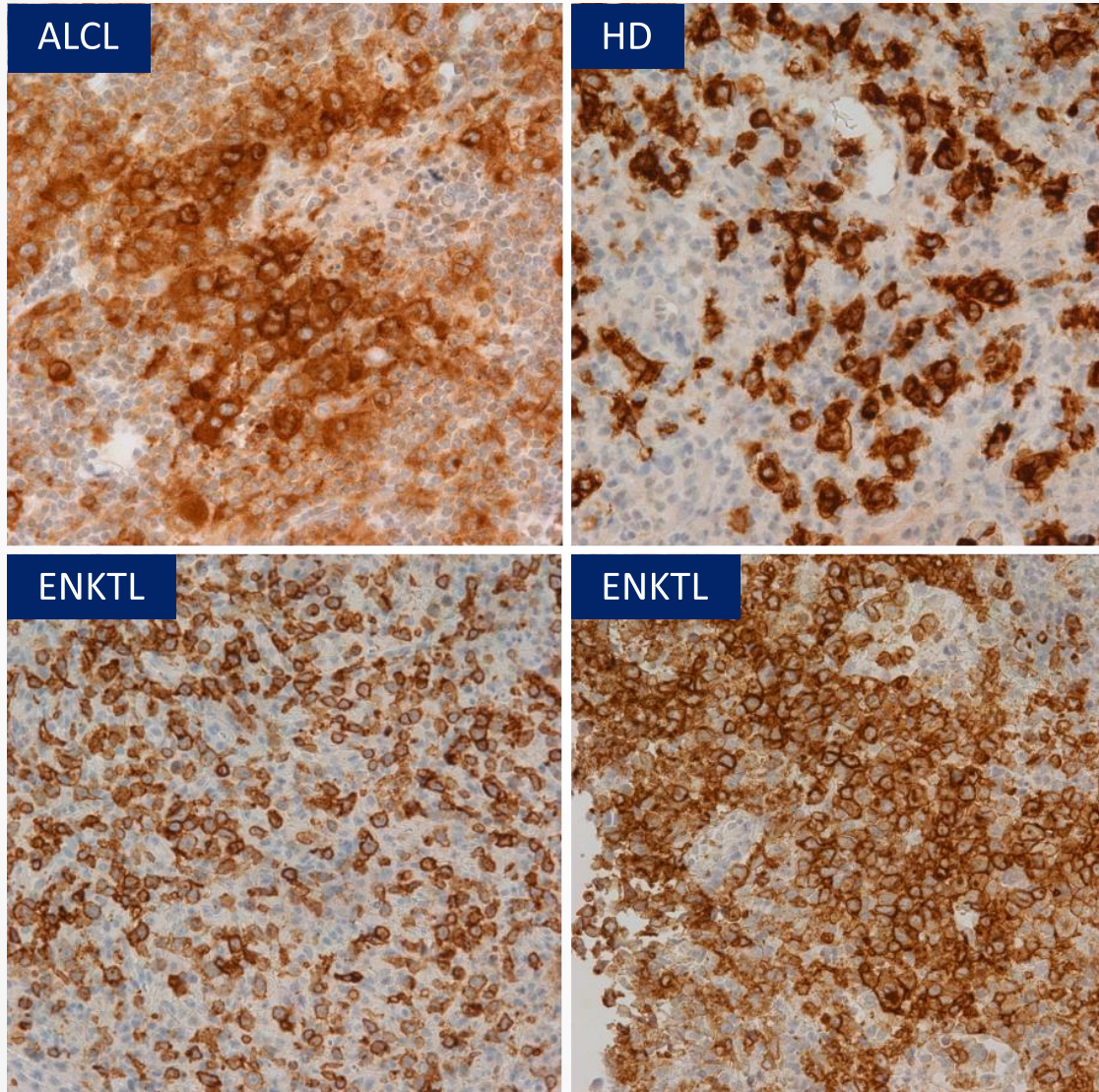
Protease-cleavable linker

Anti-CD30 monoclonal antibody





# *CD30 Expression*



# Case 1

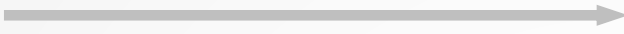
## M/63 Extranodal NK/T-cell lymphoma

- s/p CHOP #3 (2011.6.2-7.19) → PD
- s/p IMEP/L-aspa (2011.8.11-9.1) → PD : orbital involve
- s/p R-dmCODOX-MIAC#1 (2011.9.29) → PD
- s/p GEM-Dex: #1(2011.10.26) → PD

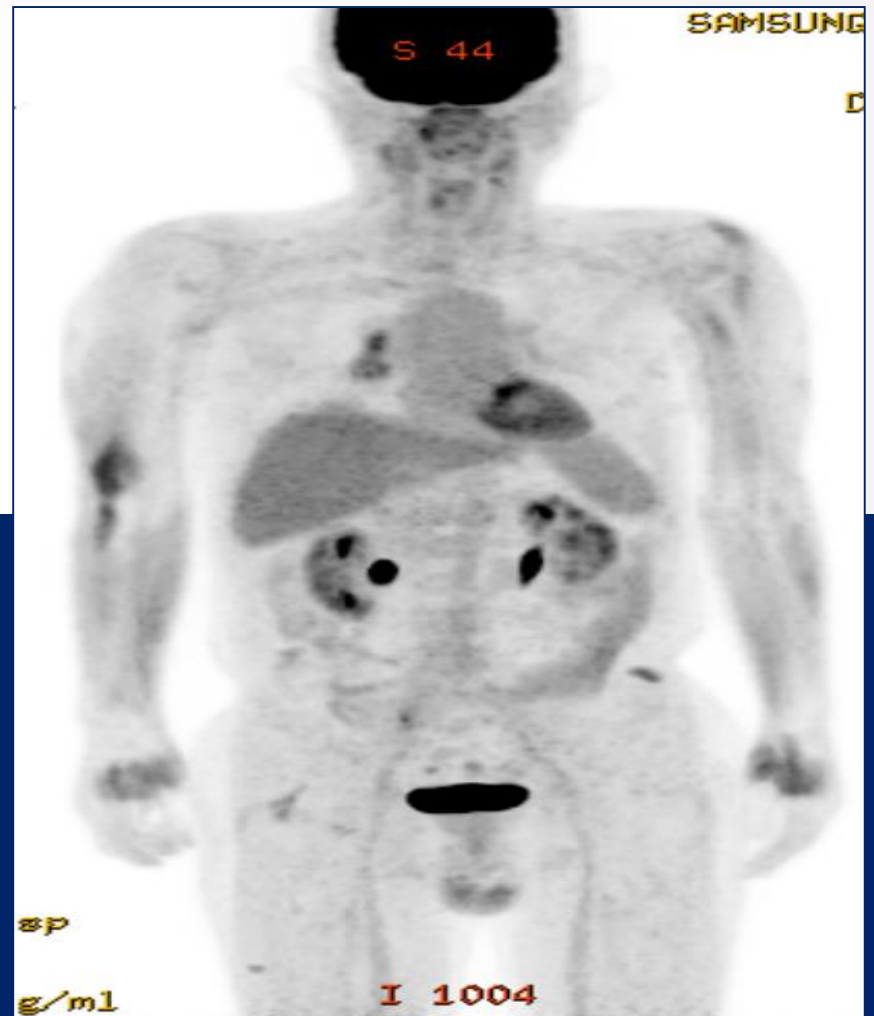
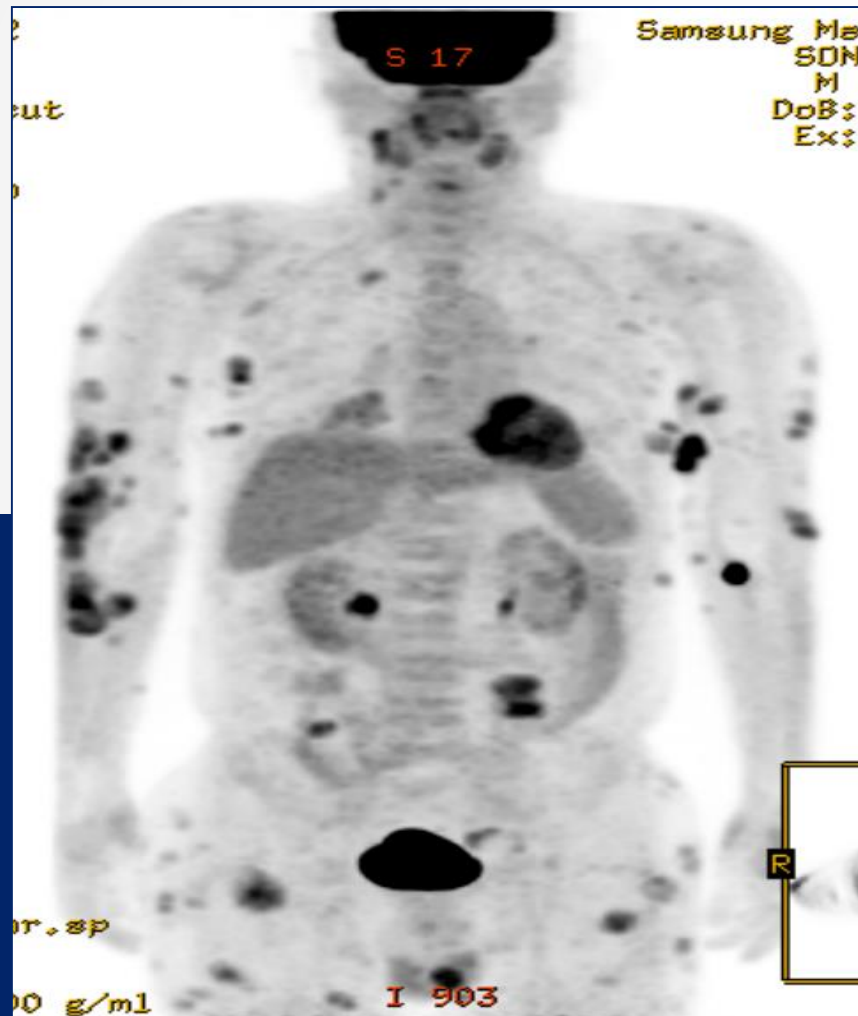


# Brentuximab after 4 cycles

2013.12.05

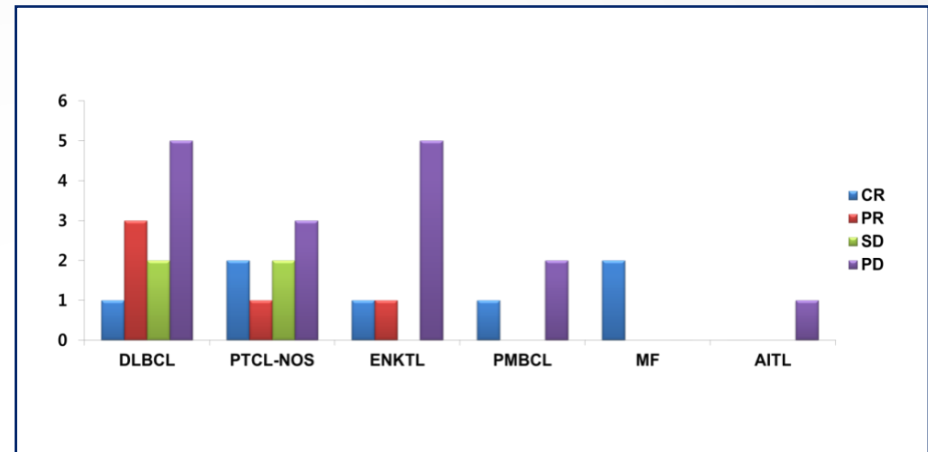
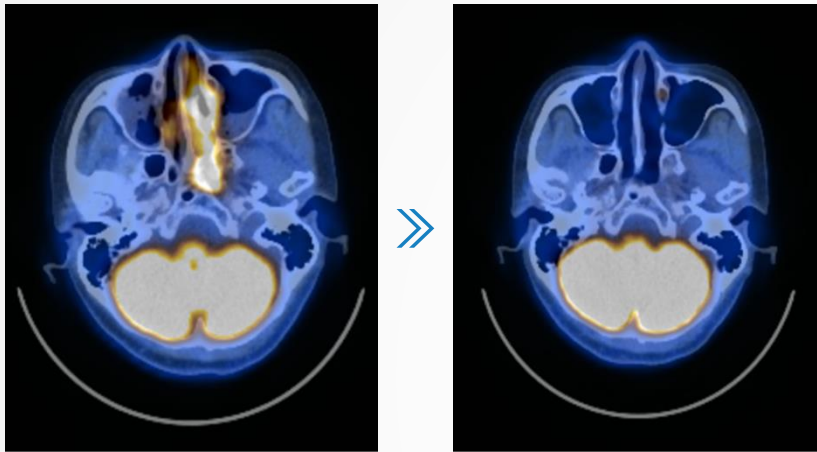


2013.03.18





# A Phase II Study of BV for R/R CD30-Positive NHL Other Than ALCL



F/53, Refractory ENKTL, CD30 90%

## DLBCL

1CR, 3PR, 2SD; 6/11, 55%

## PTCL-NOS

2CR, 1PR, 2SD, 5/8, 63%

## ENKTL

1CR, 1PR, 2/7, 29%

## PMBCL

1CR, 1/3, 33%

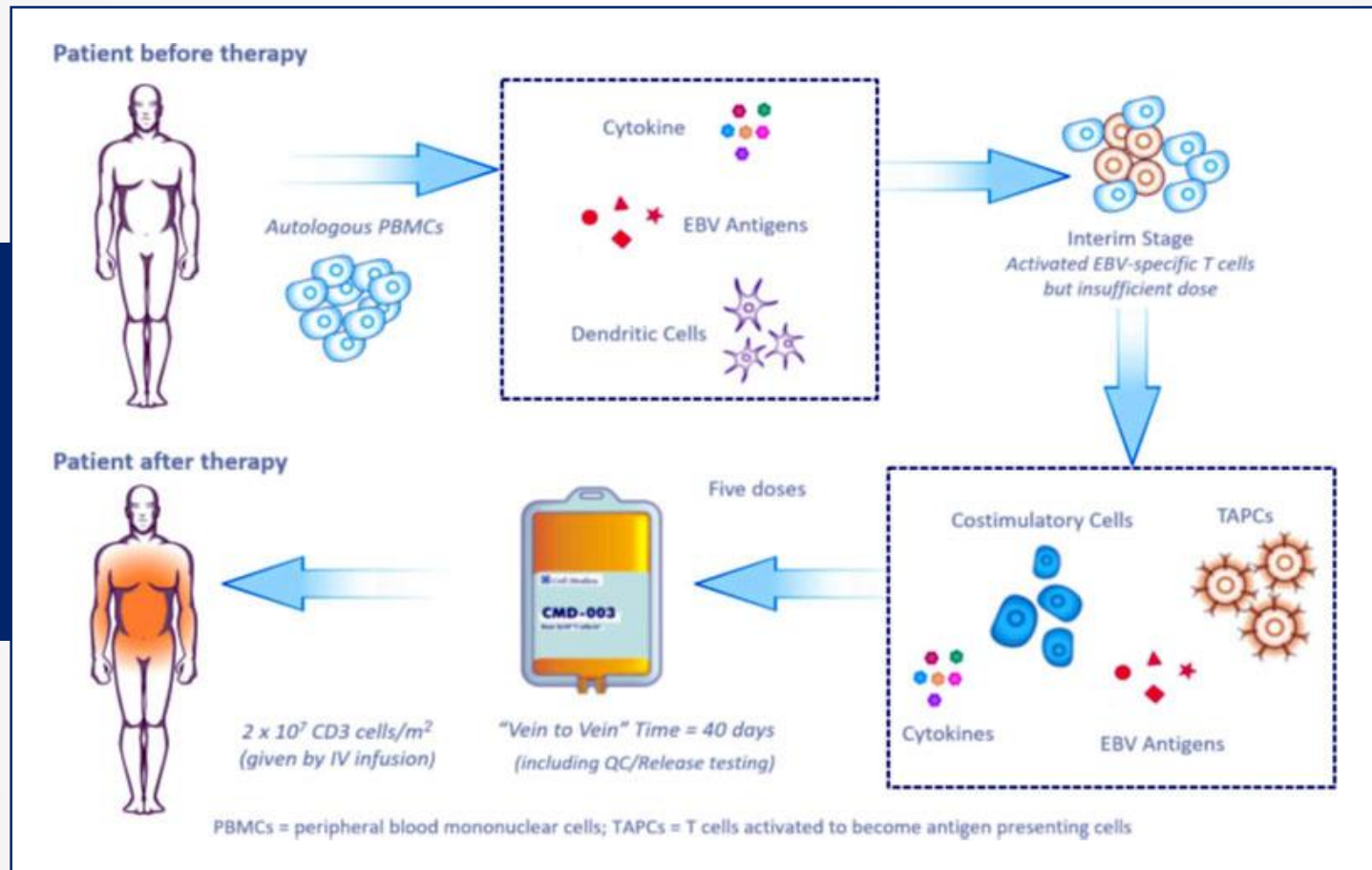
## MF

2PR, 2/2, 100%

## AITL

0/1, 0%

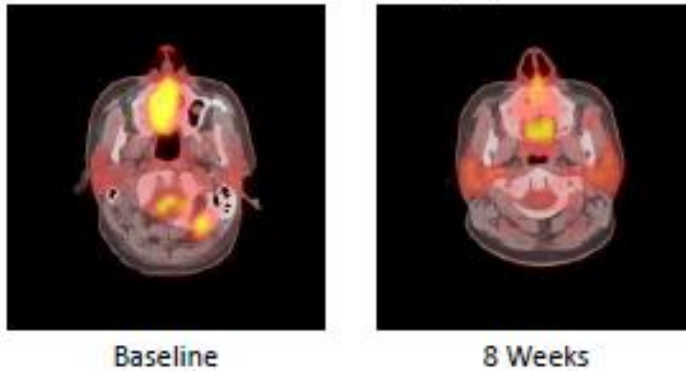
# Autologous EBV-Specific T Cells (CMD-003): Early Results from a Multicenter, Multinational Phase 2 Trial



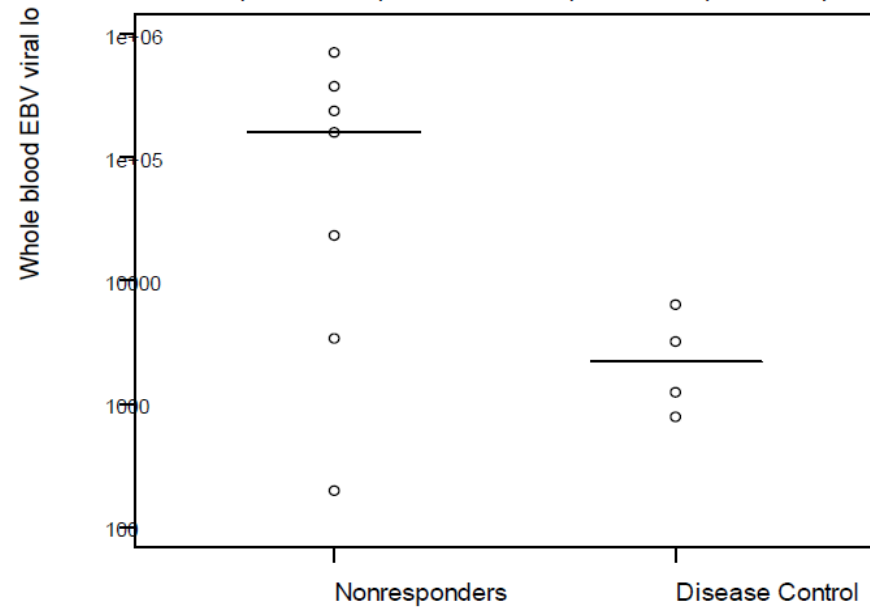


# Treatment Responses

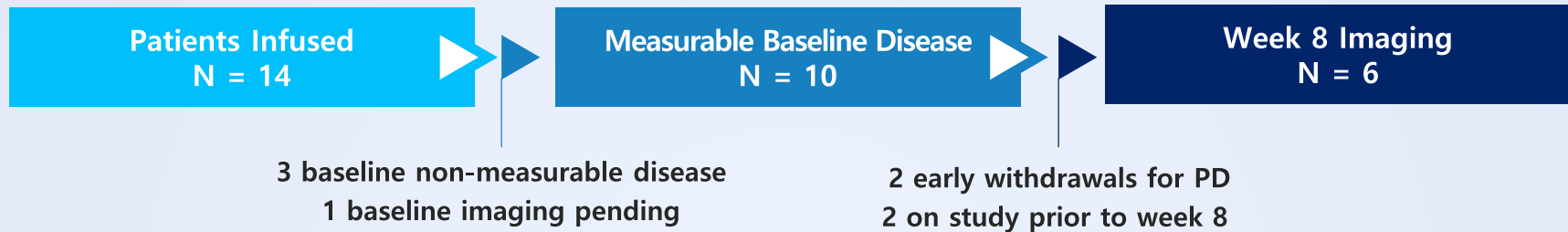
PR in a Patient with NKT Lymphoma



Maximum post baseline EBV levels were greater in nonresponders (Welsh 2 sample t test  $p=0.043$ )



# CITADEL Results as of 2018

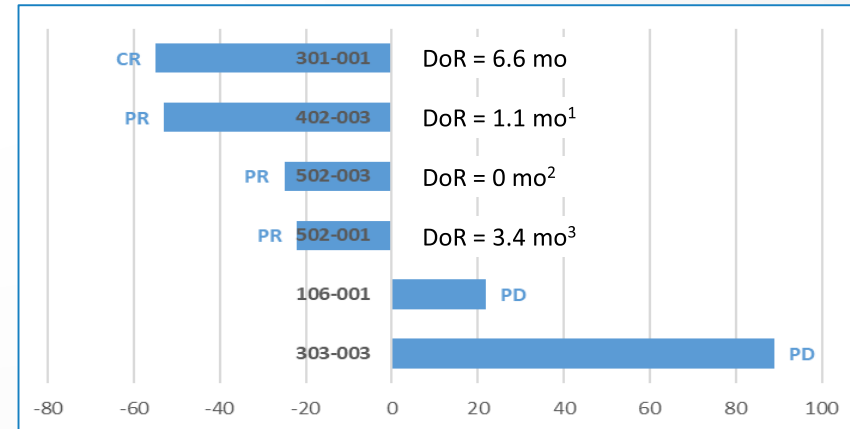


## Primary endpoint: Overall Response Rate

Patient Responses	Full Analysis Set(N = 6)	Per Protocol (N = 5)
CR	1	1
PR	3	3
Stable Disease	0	0
Progression	2	1
ORR (prespecified evaluable)	4/6	4/5
ORR (including early withdrawals)	4/8	4/7

Responses based on independent radiology review

## Percent change in lymphoma SUV



<sup>1</sup> Withdrew to receive HSC transplant

<sup>2</sup> Ongoing response

<sup>3</sup> Withdrew to receive chemotherapy

Agent	Study design	Treatment	No. of patients	Disease state	Outcome	Reference
Immune checkpoint inhibitors						
Pembrolizumab	Retrospective	Single agent	7	Relapsed or refractory after SMILE-like therapy	CR, n=5; PR, n=2 ORR 100%	Kwong et al. (2017) <sup>6</sup>
	Retrospective	Single agent	1	Refractory	CR	Lai et al. (2017) <sup>89</sup>
	Retrospective	Single agent	7	Relapsed or refractory	CR, n=2; PR, n=2 ORR 57%	Li et al. (2018) <sup>90</sup>
Nivolumab	Retrospective	Single agent, low dose	3	Relapsed or refractory after SMILE-like therapy	CR, n=2; SD, n=1	Chan et al. (2017) <sup>91</sup>
Other "new" agents*						
Alemtuzumab	Phase II, Multi-center	Combined with CHOP	3	Newly diagnosed	CR, n=1; SD, n=1; PD, n=1	Kim et al. (2007) <sup>94</sup>
	Phase II, multi-center	Combined with DHAP	8	Relapsed or refractory after first-line therapy	PR, n=1; PD, n=7	Kim et al. (2012) <sup>95</sup>
Thalidomide	Prospective, single center	Combined with CHOP and RT, GELOX, and others	12	Newly diagnosed (n=9), relapsed (n=3)	CR, n=8; PR, n=1; PD, n=3	Wu et al. (2014) <sup>102</sup>
Romidepsin	Phase II	Single agent	1	Refractory	ORR 0%	Coiffier et al. (2012) <sup>107</sup>
	Pilot study	Single agent	5	Relapsed or refractory	NE, n=4; SD, n=1 EBV reactivation (n=3)	Kim et al. (2016) <sup>108</sup>

# *Answered questions in relapsed ENKTL*

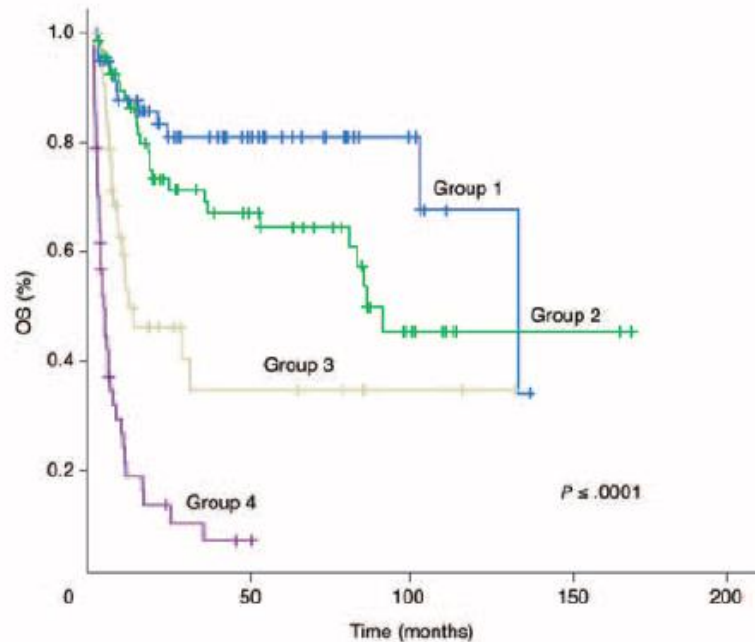
# *Special thanks*

- CISL members
- Lymphoma team members in SMC
- Asia lymphoma study group members
- Investigators joined to PINK project

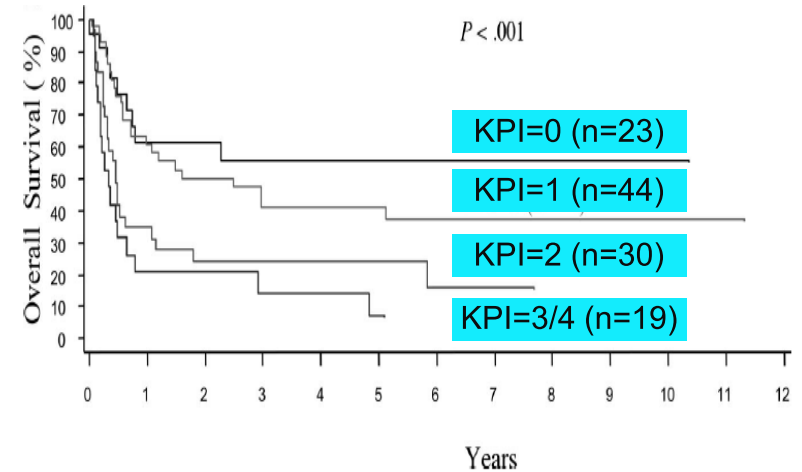


*Can we predict the outcome?*

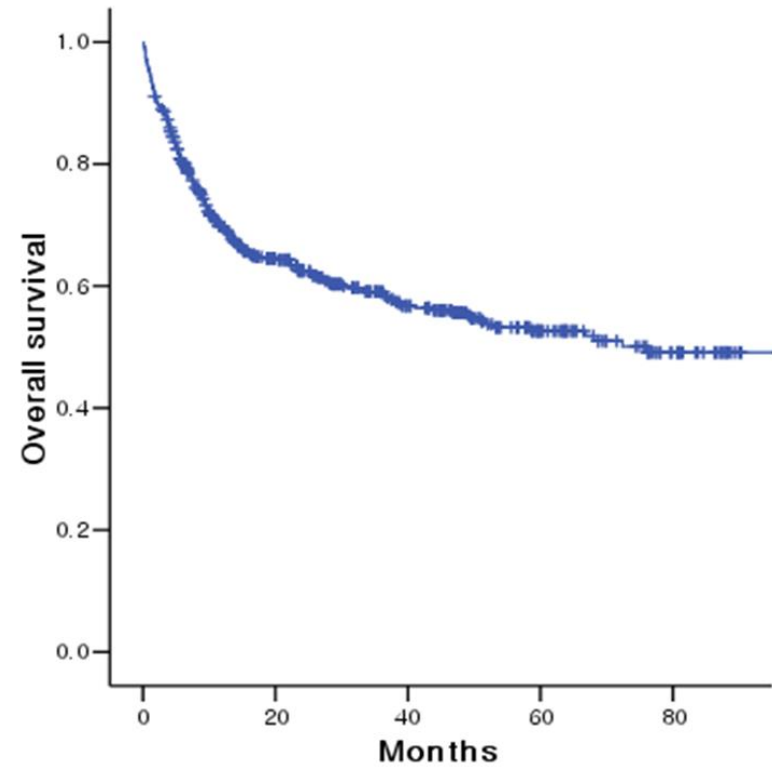
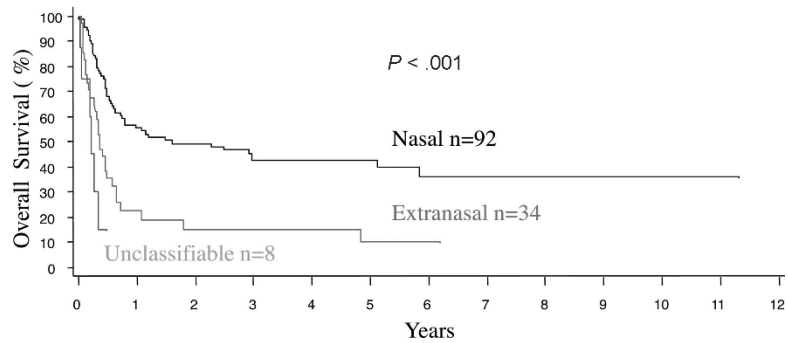
# Survival improvement since new treatment



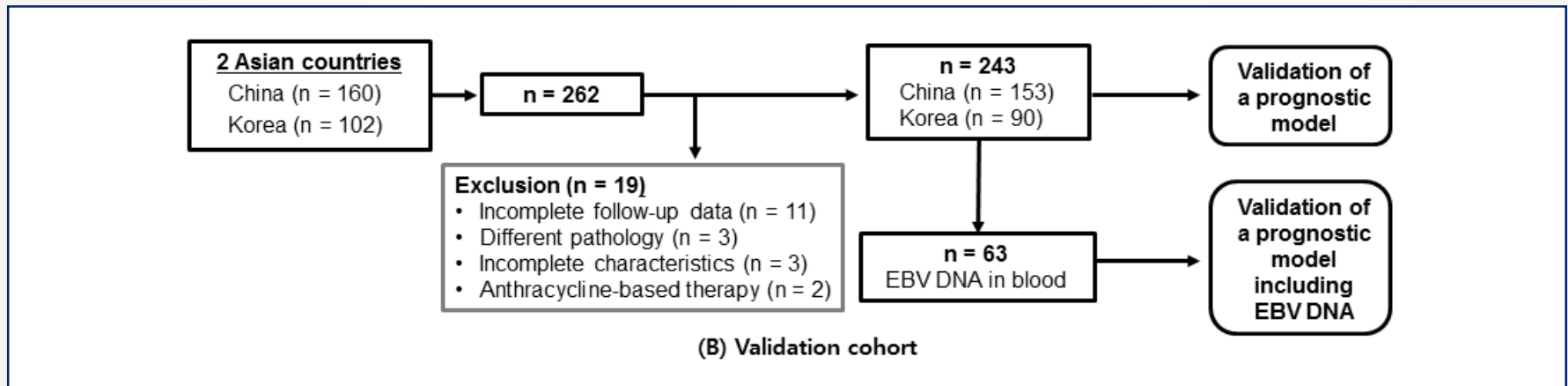
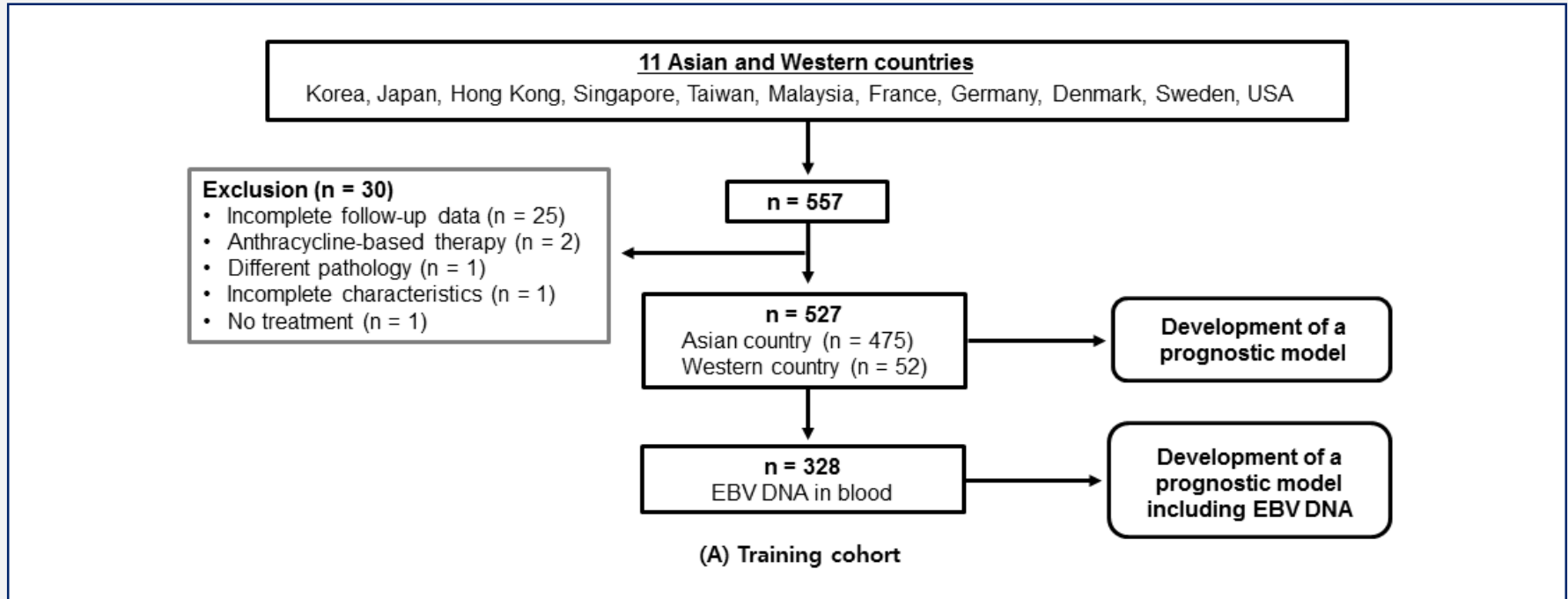
**Fig 3.** Survival according to the new prognostic index. Group 1, n=60(27%); group2, n=68(31%); group3, n=44 (20%); group4, n=47 (22%). OS, overall survival



# NK/T-cell lymphoma





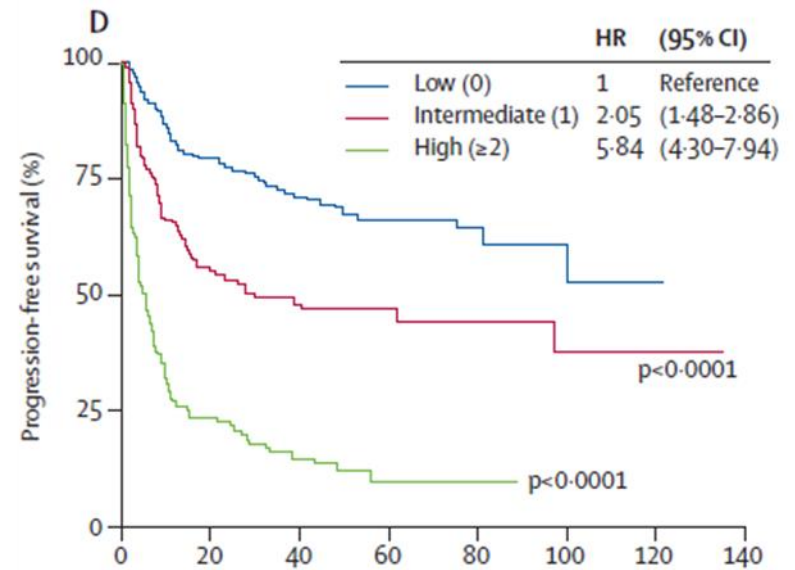
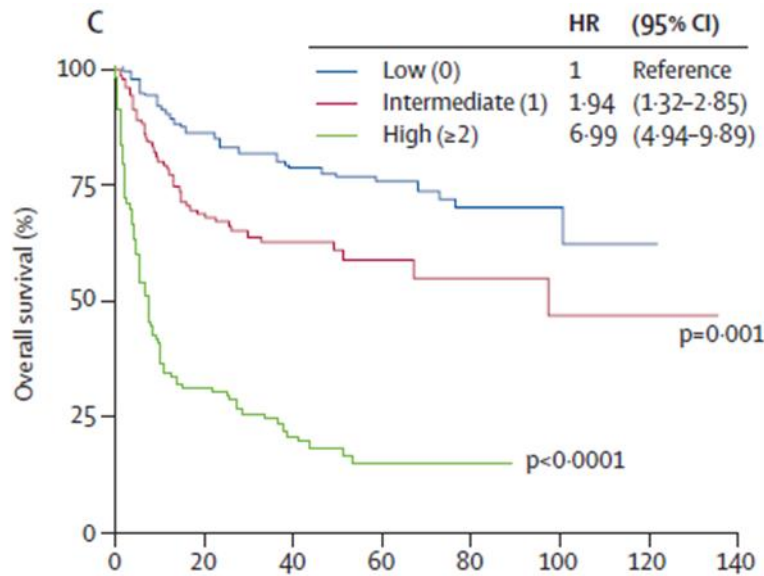


# Survival improvement since new treatment

	All patients (n=527)						Patients with data for Epstein-Barr virus in DNA (n=328)					
	Overall survival			Progression-free survival			Overall survival			Progression-free survival		
	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio	Parameter estimate	p	Hazard ratio
Age > 60years	0.774	<0.0001	2.168	0.760	<0.0001	2.138	0.820	<0.0001	2.271	0.762	<0.0001	2.142
ECOG performance status $\geq 2$	0.527	0.003	1.694	..	..	..				0.583	0.004	1.792
Stage III-IV	0.942	<0.0001	2.565	0.722	<0.0001	2.058	0.906	<0.0001	2.475	0.839	<0.0001	2.315
Non-nasal type	0.662	<0.0001	1.939	0.692	<0.0001	1.998	0.495	0.018	1.640	0.536	0.005	1.709
Distant lymph-node involvement	0.547	0.002	1.727	0.527	0.002	1.693	0.845	<0.0001	2.329	0.507	0.024	1.660
Serum albumin $\leq 35$ g/L	0.530	0.001	1.699	0.400	0.006	1.492	..	..	..	..	..	..
Platelet $\leq 75$ 000 mm <sup>3</sup>	0.562	0.006	1.754	0.490	0.016	1.632	..	..	..	..	..	..
Lymphocyte $\leq 3.5$ g/dL	..	..	..	0.312	0.032	1.366	..	..	..	..	..	..
Haemoglobin $\leq 100$ g/L	..	..	..	..	..	..	0.672	0.004	1.958	..	..	..
Detectable Epstein-Barr virus DAN	..	..	..	..	..	..	0.516	0.011	1.675	0.538	0.002	1.712

Parameter estimates are regression estimates that are used to calculate a risk score for patients. ECOG=Eastern Cooperative Oncology Group.

# PINK

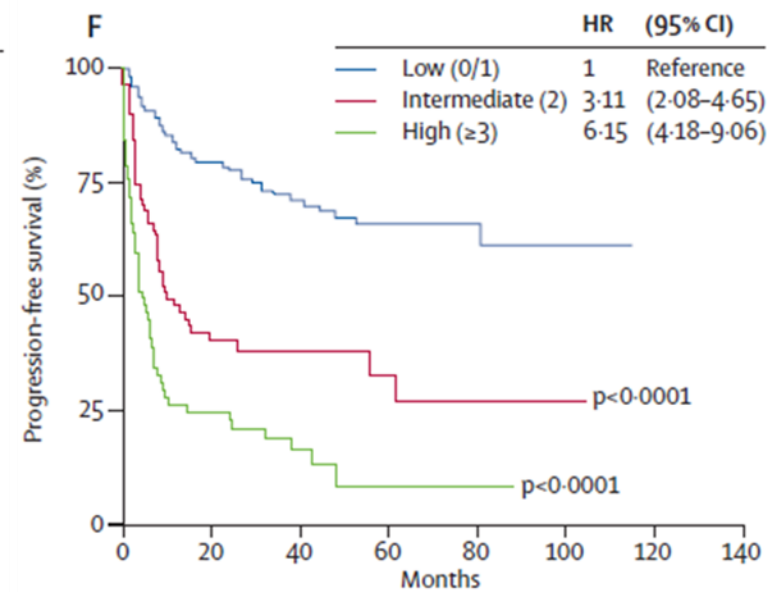
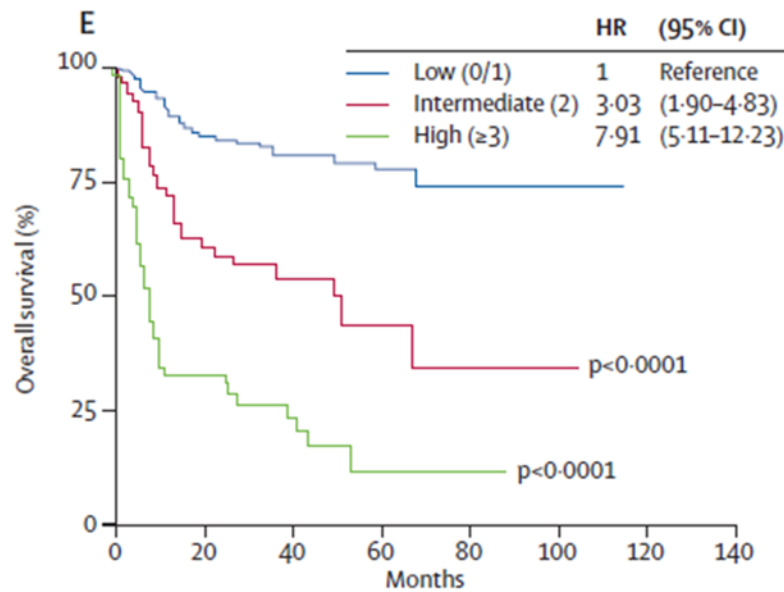


### Number at risk

Low risk	211	143	99	56	28	9	2	0
Intermediate risk	162	82	46	21	10	6	2	0
High risk	153	37	17	5	1	0	0	0

	211	132	89	49	25	7	2	0
	162	69	38	19	9	6	2	0
	153	29	14	4	1	0	0	0

# PINK

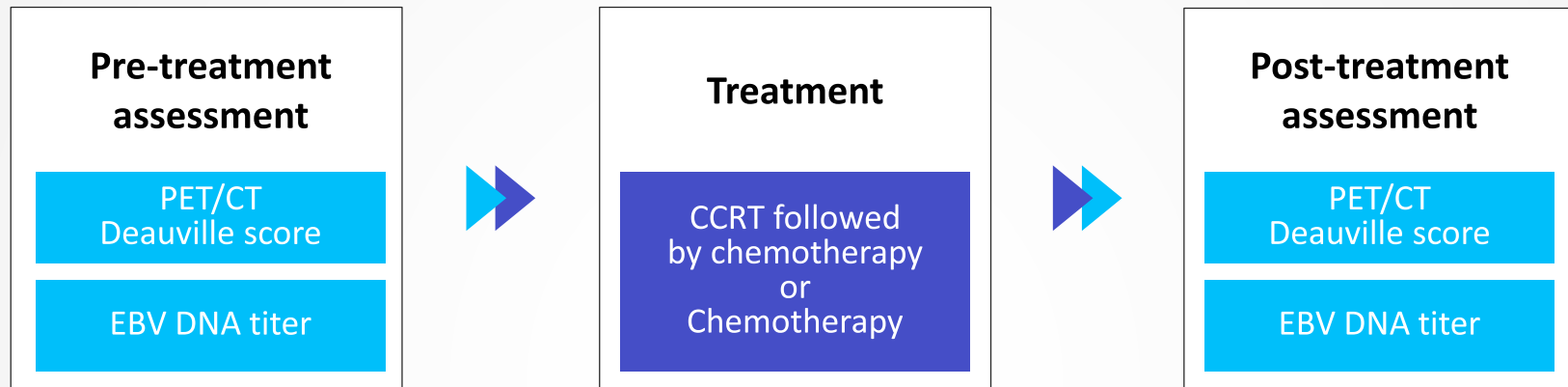


Number at risk		0	20	40	60	80	100	120	140
Low risk	108	110	74	37	18	4	0	0	
Intermediate risk	78	35	18	7	3	1	0	0	
High risk	70	17	8	1	1	0	0	0	

	180	105	67	33	17	4	0	0
	78	25	14	6	2	1	0	0
	70	14	7	1	1	0	0	0

# Response evaluation based in PET/CT and EBV DNA

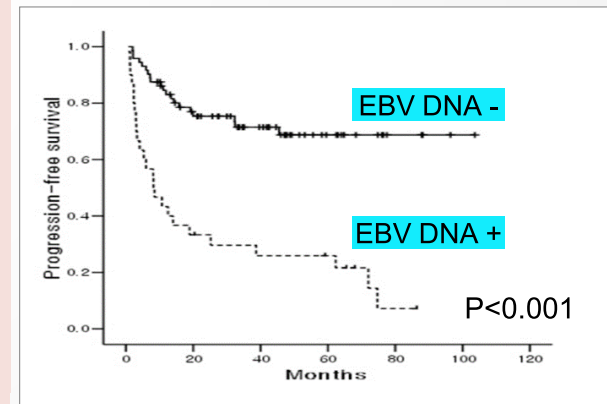
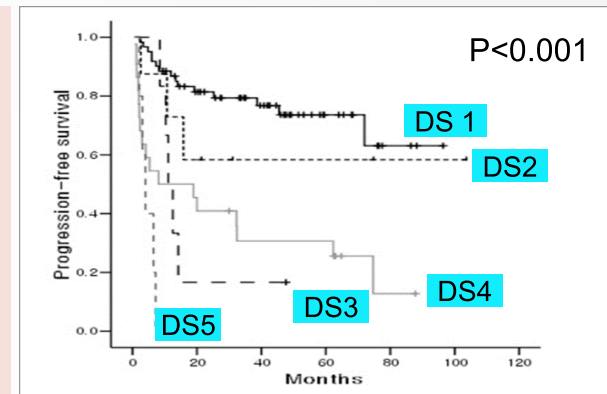
N 102



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

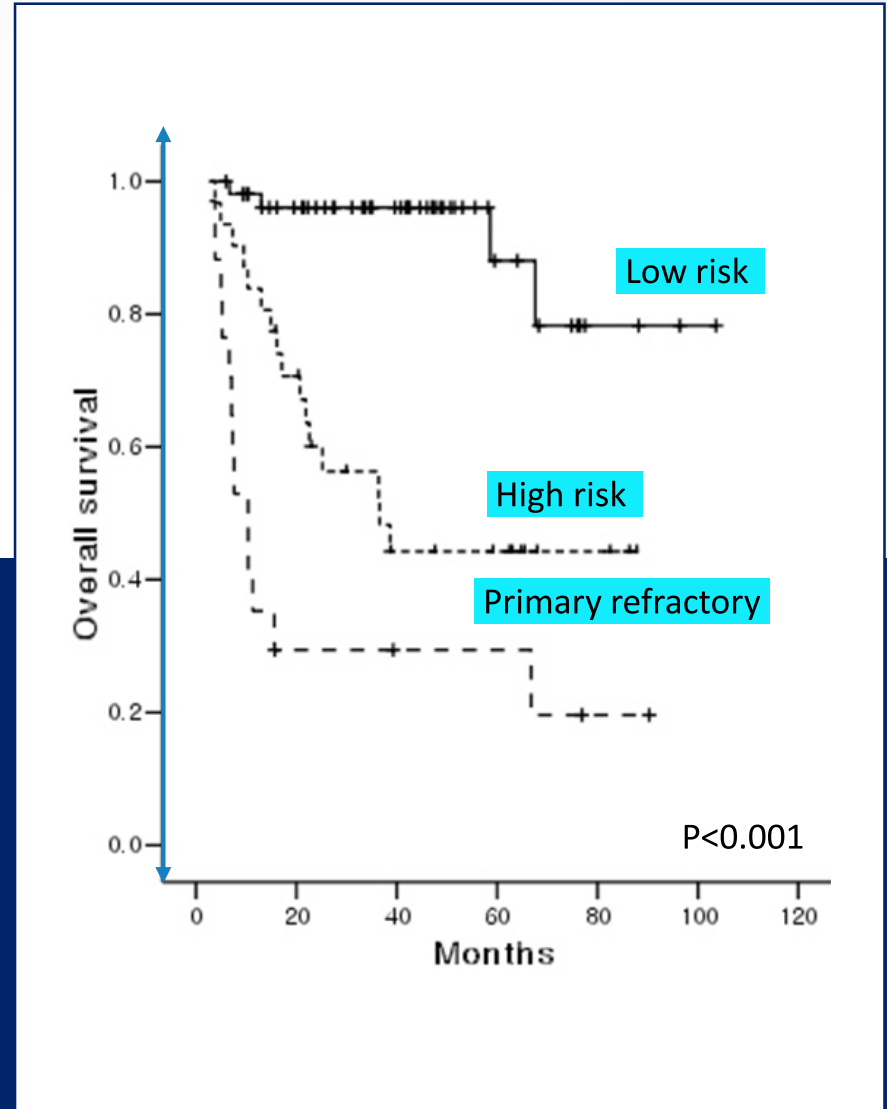
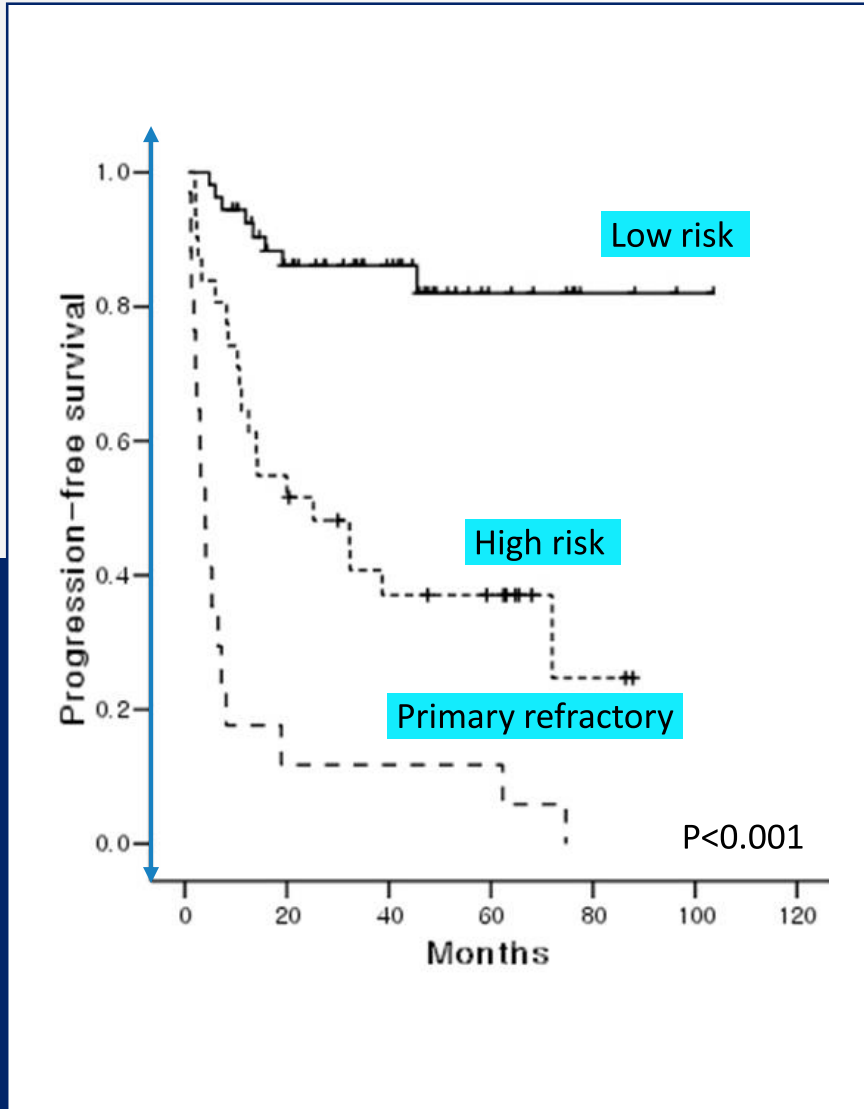
	Pre-treatment		Post-treatment	
	Number of patients	Treatment failure	Number of patients	Treatment failure
<b>Deauville score</b>				
1	2	1 (50%)	61	15 (25%)
2	2	1 (50%)	8	3 (38%)
3	3	0	6	5 (83%)
4	25	12 (48%)	22	17 (77%)
5	70	31 (44%)	5	5 (100%)
<b>Epstein-Barr virus DNA</b>				
Negative	54	21 (39%)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

## Relapse rate based on EOT





# Treatment recommendation according to EOT response criteria

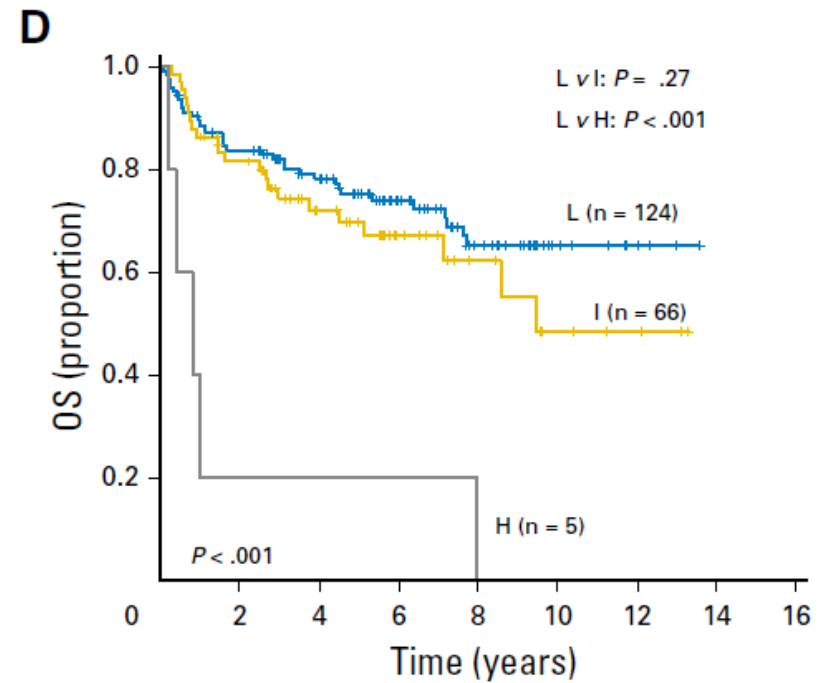
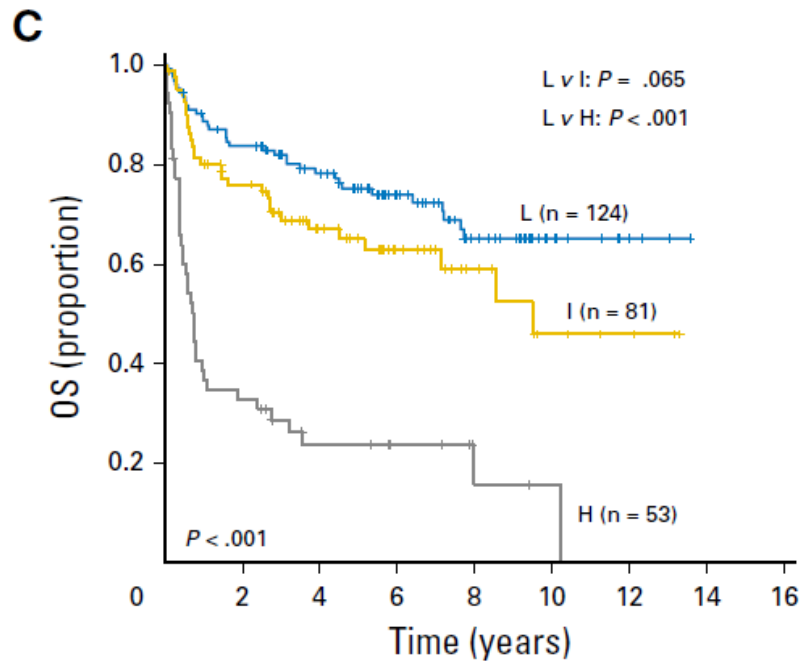
		Post-treatment Deauville score				
		1	2	3	4	5
Post-treatment Epstein-Barr virus	Negative	Observation after primary treatment		Additional treatment to achieve Deauville score 1-2		
	Positive		Additional treatment to achieve Epstein-Barr virus negativity		Salvage treatment or clinical trial	

- Low risk
- High risk
- Failure

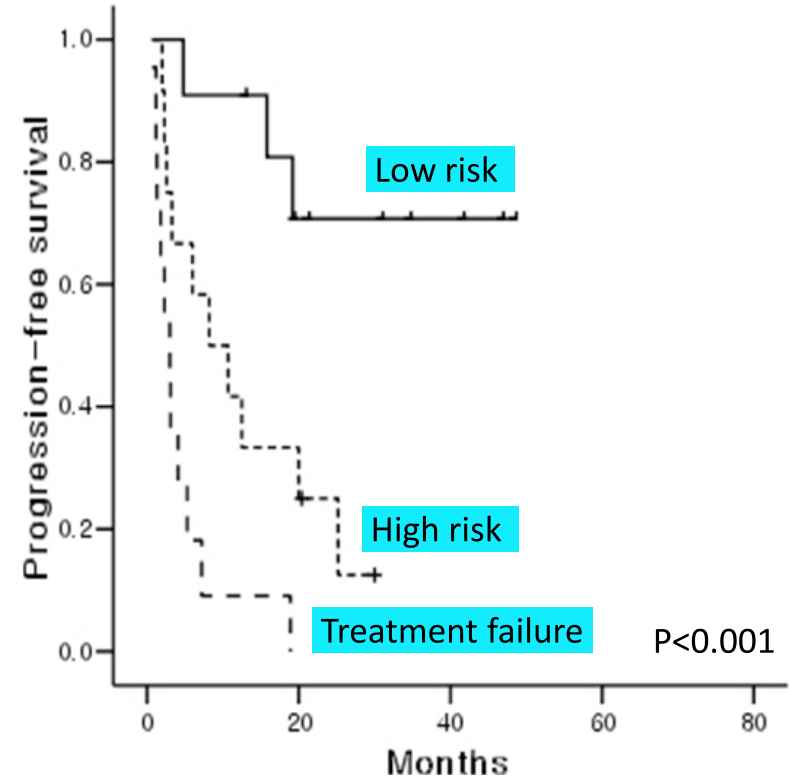
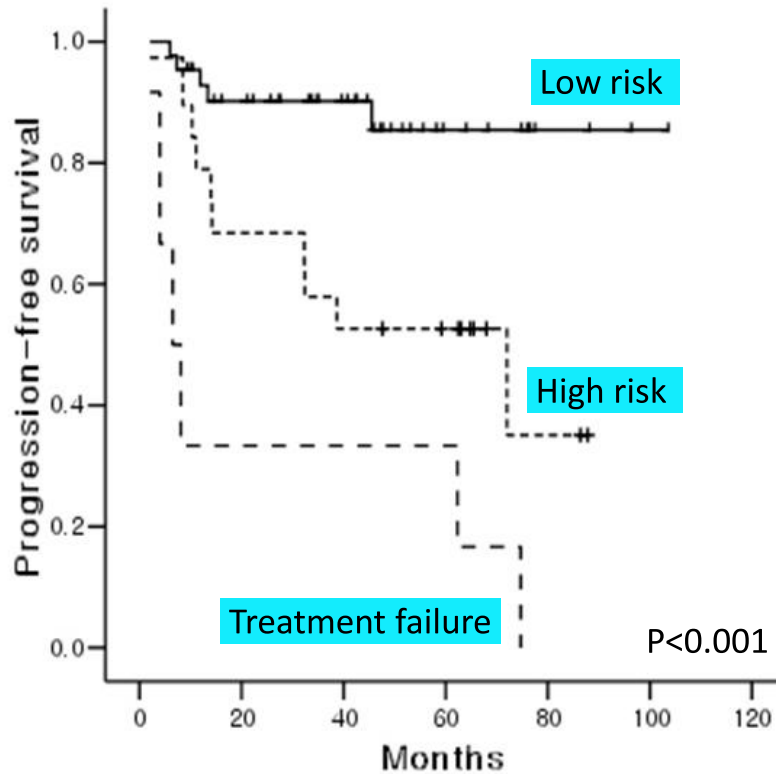
# Still long way to go

▶ <b>Optimal chemotherapy regimens</b>	▶ <b>Role of transplantation</b>	▶ <b>Risk-adapted</b>
SMILE ?	Whom and When	
New combination : PD1/PDL1 inhibitor, new Antibody	Auto vs Allo	Low risk vs high risk

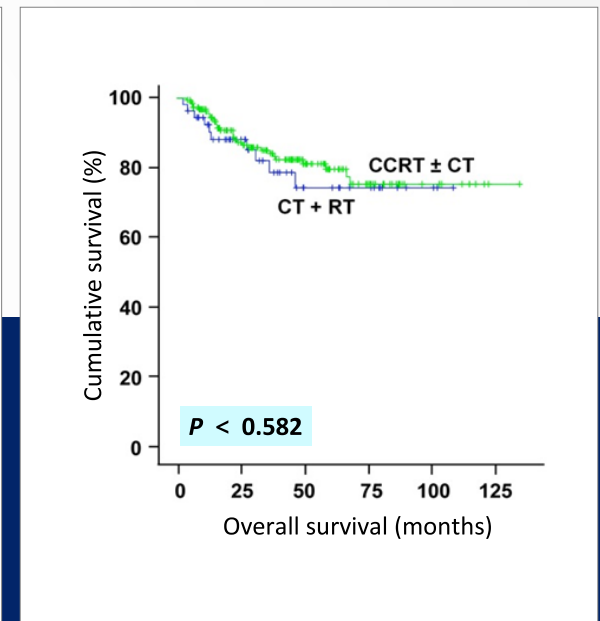
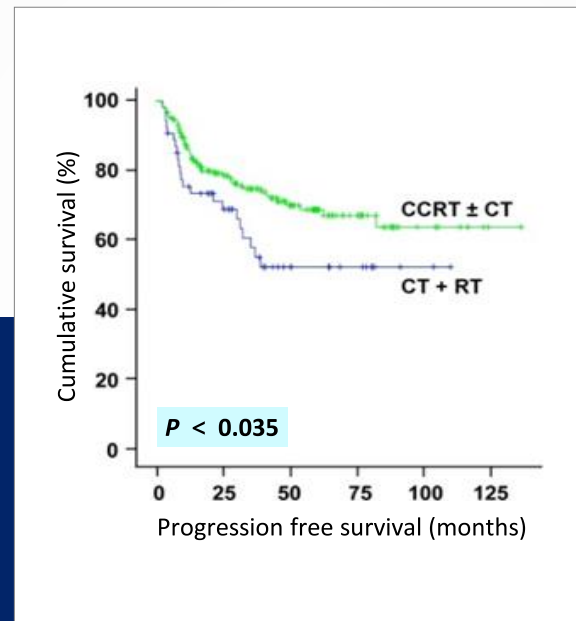
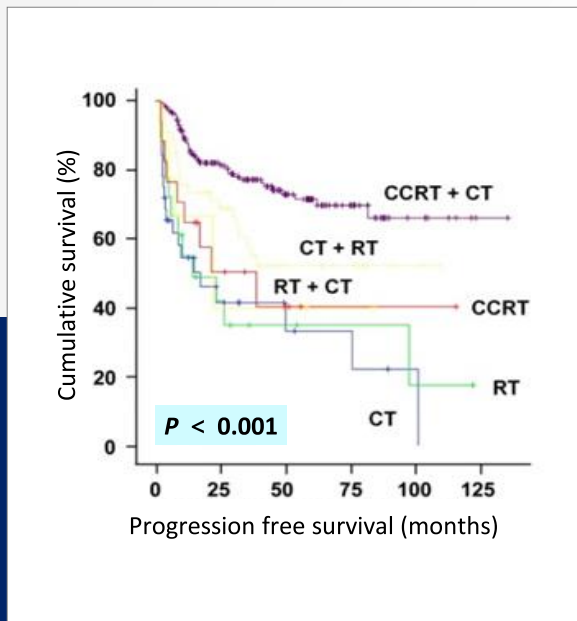
# Japan experience



## *PFS based on PET/CT and EBV DNA*



# Early RT vs late RT





***Thank you***  
*- For your attention -*

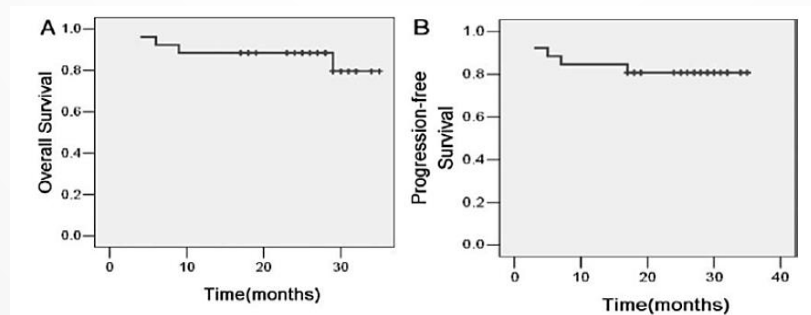
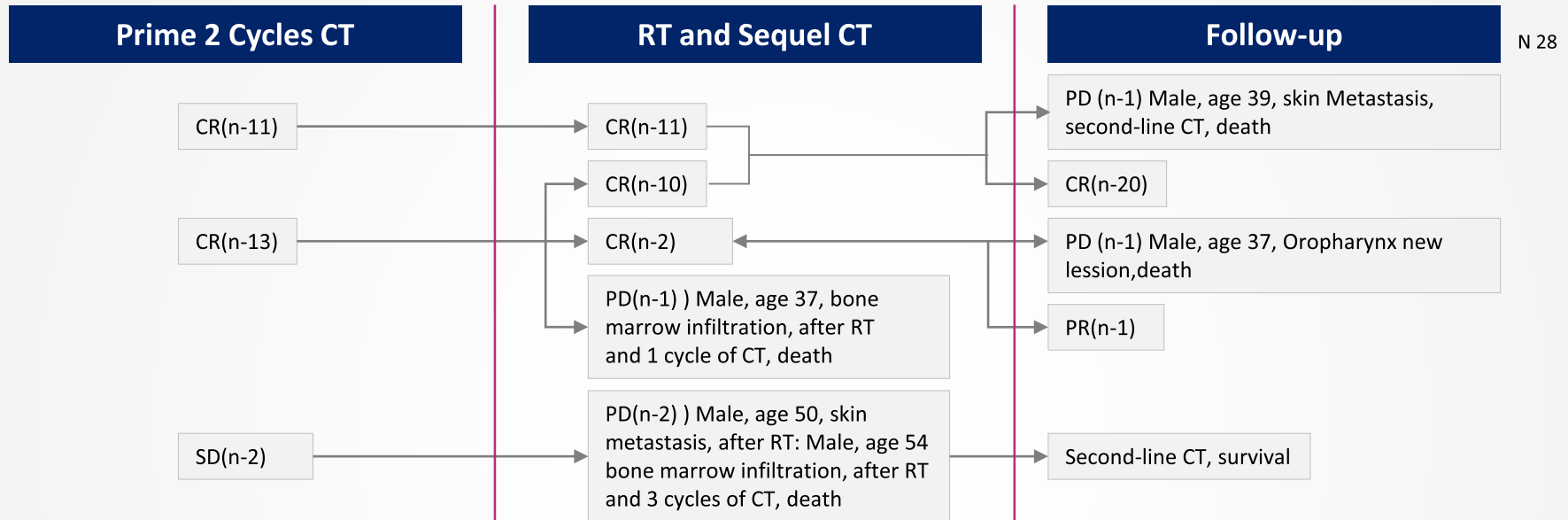
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**Won Seog Kim**

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**SAMSUNG MEDICAL CENTER**  
SEOUL, KOREA

# Sandwich LVP with RT for stage I/II ENKL





## *Conclusions*

*Optimal treatment after 1<sup>st</sup> failure is not determined yet.*

*Immunotherapy can be promising.*

*The efficacies of novel agents should be explored.*

# Outcome after failure of 1<sup>st</sup> line treatment

		Gemcitabine-based chemotherapy (N=29)	L-asparaginase-based chemotherapy (N=63)		
Time of relapse	< 6 months	17 (59%)	18 (29%)		
	≥ 6 months	12 (41%)	45 (71%)		
IPI*	Low/Low-intermediate	12 (44%)	38 (64%)		
	High-intermediate/High	15 (56%)	21 (36%)		
NKPI <sup>&amp;</sup>	Group I/II	9 (33%)	20 (35%)		
	Group III/IV	18 (67%)	37 (65%)		
PINK**	Low	4 (15%)	20 (33%)		
	Intermediate	5 (18%)	12 (20%)		
	High	18 (67%)	28 (47%)		
PINK-E <sup>\$</sup>	Low	6 (29%)	25 (57%)		
	Intermediate	3 (14%)	8 (18%)		
	High	12 (57%)	11 (25%)		
Time of relapse		< 6months N=17	≥ 6 months N=12	< 6 months N=18	≥ 6 months N=45
Primary treatment	CCRT+/- chemotherapy	1 (6%)	5 (42%)	7 (39%)	28 (62%)
	Chemotherapy	16 (94%)	7 (58%)	11 (61%)	17 (38%)
Response to salvage treatment	CR	3	4	6	18
	PR	2	4	2	11
	PD	11	4	8	10
	NE	1	-	2	6
	ORR	29.4%	66.7%	44.4%	64.4%

		Rechallenge of L-asparaginase (N=32)	First use of L-asparaginase (N=31)		P value
Time of relapse	< 6 months	4 (12.5%)	14 (45.2%)		0.005
	≥ 6 months	28 (87.5%)	17 (54.8%)		
Initial treatment	CCRT +/- chemotherapy	17 (53.1%)	18 (58.1%)		0.801
	Chemotherapy	15 (46.9%)	13 (41.9%)		
IPI*	Low/Low-intermediate	21 (72.4%)	17 (56.7%)		0.279
	High-intermediate/High	8 (27.6%)	13 (43.3%)		
NKPI&	Group I/II	9 (34.6%)	11 (35.5%)		1.000
	Group III/IV	17 (65.4%)	20 (64.5%)		
PINK**	Low	8 (27.6%)	12 (38.7%)		0.229
	Intermediate	4 (13.8%)	8 (25.8%)		
	High	17 (58.6%)	11 (35.5%)		
PINK-E <sup>§</sup>	Low	11 (57.9%)	14 (56.0%)		0.462
	Intermediate	2 (10.5%)	6 (24%)		
	High	6 (31.6%)	5 (20%)		
Response	CR	7	17		0.042
	PR	7	6		
	PD	12	6		
	NE	6	2		
ORR		43.7%	74.2%		
Time of relapse		< 6months	≥ 6 months	< 6 months	≥ 6 months
		N=4	N=28	N=14	N=17
Response	CR	-	7	6	11
	PR	-	7	2	4
	PD	3	9	5	1
	NE	1	5	1	1
ORR		0%	50.0%	57.1%	88.2%

Reference	Study design	Treatment	RT delivery Median dose (range)	No. of patients	CR, %	Median follow-up, mo (range)	OS, %	PFS, %	Leukopenia Grade 3, %/ Grade 4, %	Mucositis <sup>†</sup> Grade 3, %/ Grade 4, %
Simultaneous initiation of RT and chemotherapy										
Yamaguchi et al. (2009, 2012) <sup>29,47</sup>	Phase I/II	RT-2/3DeVIC: RT+ 2/3DeVIC x 3	3D-CRT 50 Gy (50-50.4)	27	77	67 (61-94)	70 (5 y)	63 (5 y)	85/15 *	30/0
Tsai et al. (2015) <sup>41</sup>	Phase II	DEP-CCRT/DVIP: RT + DEP x 2 → DVIP x 2	NA 50.4 Gy	33	63	59 (16-79)	66 (5 y)	60 (5 y)	35/48 *	30/0
Michot et al. (2015) <sup>42</sup>	Retrospective	RT + modified ESHAP x 2 → modified ESHAP x 2	3D-CRT (n=9), IMRT (n=3) 40 Gy (40-52.2)	13	92	38 (NA)	72 (2 y)	90 (2 y, FFP)	31/62 †	23/23
CCRT with weekly cisplatin followed by non-anthracycline chemotherapy										
Kim et al. (2009) <sup>43</sup>	Phase II	CCRT-VIPD: RT + wCDDP → VIPD x 3	3D-CRT 40 Gy (40-52.8)	30	80	24 (17-37)	86 (3 y)	85 (3 y)	20/27 *	0/0 §
Kim et al. (2014) <sup>30</sup>	Phase II	CCRT-VIDL: RT + wCDDP → VIDL x 2 (→ HD-AHSCT if NK-PI score 2-3)	NA 40 Gy (40-50)	30	87	44 (95% CI, 41-47)	73 (5 y)	60 (5 y)	20/60 *	13/3 §
Yoon et al. (2016) <sup>44</sup>	Phase II	CCRT-MIDLE: RT + wCDDP + tri-weekly L-asparaginase → MIDLE x 2	3D-CRT or IMRT NA (36-44)	28	82	46 (95% CI, 39-47)	82 (3 y)	74 (3 y)	9/83 †* (n=23)	4/0 §

Reference	Study design	Treatment	RT delivery Median dose (range)	No. of patients	CR, %	Median follow-up, mo (range)	OS, %	PFS, %
Kwong et al. (2012) <sup>53</sup>	Prospective	SMILE	NA	17 (stage I/II)	82	NA	NA	NA
Qi et al. (2016) <sup>3</sup>	Retrospective	Modified SMILE x 2-3 → RT	IMRT or 3D-CRT 45 Gy (45-54)	11	NA	24 (1-43)	100 (2 y)	83 (2 y)
Jiang et al. (2012) <sup>54</sup> Zhang et al. (2016) <sup>55</sup>	Phase II	LVP → RT → LVP	NA 56 Gy	26	81	67 (4-78) (n=25)	64 (5 y)	64 (5 y)
Jiang et al. (2017) <sup>56</sup>	Phase II	LVDP x 2 → RT + wCDDP → LVDP x 2	IMRT or 3D-CRT NA	66	83	24 (12-51)	70 (3 y)	67 (3 y)
Huang et al. (2017) <sup>31</sup>	Phase II	IMRT → GDP x 4	IMRT 51.5 Gy (50-56)	44	89	38 (6-90)	85 (3 y)	77 (3 y)

NA indicates not available.