NK/T cell lymphoma
Hong Kong Experience with
L-Asparaginase containing regimens

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Management of NK cell malignancies

Principles

1. **Accurate staging is needed for NK/T-cell at all anatomical locations**

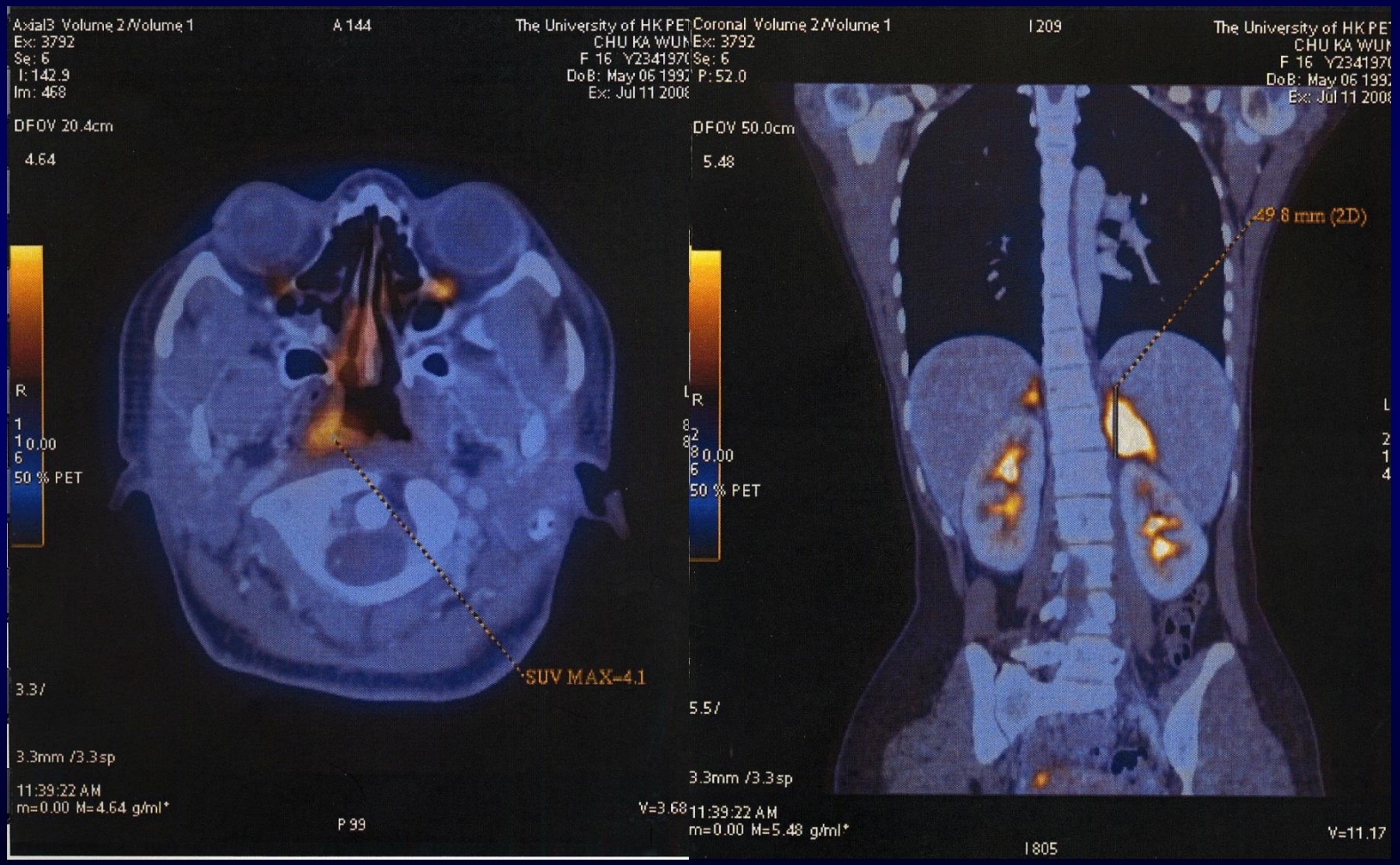
2. **“Non-nasal” NK/T-cell lymphomas may have occult nasal involvement, and hence are disseminated “nasal” lymphomas**

3. **NK/T-cell lymphomas of all stages require chemotherapy**

4. **Radiotherapy alone should not be used**

Cutaneous NK cell lymphoma, nasal type

Cutaneous NK/T cell lymphoma, nasal type
Disseminated NK cell lymphoma



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L-asparaginase containing regimens

Table 1. Novel chemotherapeutic regimens for NK/T-cell lymphomas

Regimen	Protocol	Reference
AspaMetDex	*Escherichia coli* L-asparaginase: 6000 U/m^2 IM, days 2, 4, 6, and 8 Methotrexate: 3000 mg/m^2 IV, day 1 Dexamethasone: 40 mg orally, days 1-4	16
LVP	L-asparaginase: 6000 IU/m^2 IV, days 1-5 Vincristine: 1.4/m^2 IV, day 1 Prednisolone: 100 mg orally, days 1-5	59
GELOX	Gemcitabine: 1000 mg/m^2 IV, days 1 and 8 *E. coli* L-asparaginase: 6000 units/m^2 IM, days 1-7 Oxaliplatin: 130 mg/m^2 IV, day 1	60
SMILE	Dexamethasone: 40 mg IV or orally, days 2-4 Methotrexate: 2000 mg/m^2 IV, day 1 Ifosfamide: 1500 mg/m^2 IV, days 2-4 *E. coli* L-asparaginase: 6000 U/m^2 IV, days 8, 10, 12, 14, 16, 18, and 20 Etoposide: 100 mg/m^2 IV, days 2-4	62

IM, intramuscularly.

L-asparaginase containing regimens

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IM, intramuscularly.

Rationale for the SMILE protocol

SMILE

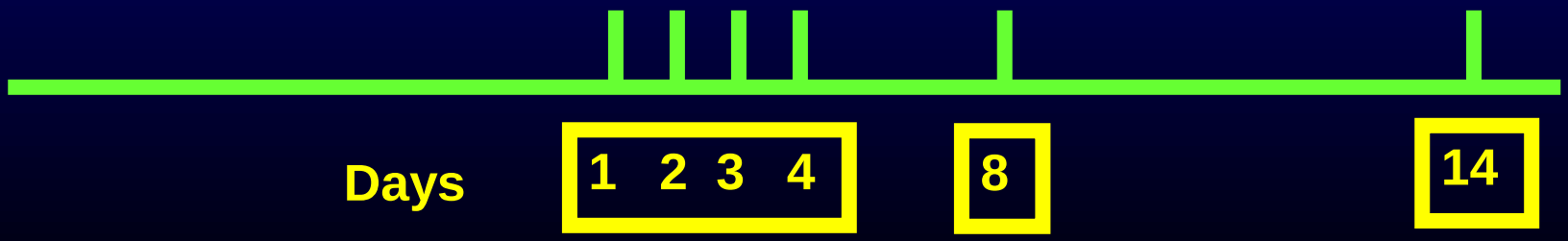
1. Non-MDR dependent drugs: dexamethasone, ifosfamide, methotrexate

2. L-asparaginase: effective as a single agent

3. Etoposide (MDR-dependent): effective for CAEBV and other EBV related lymphoproliferation

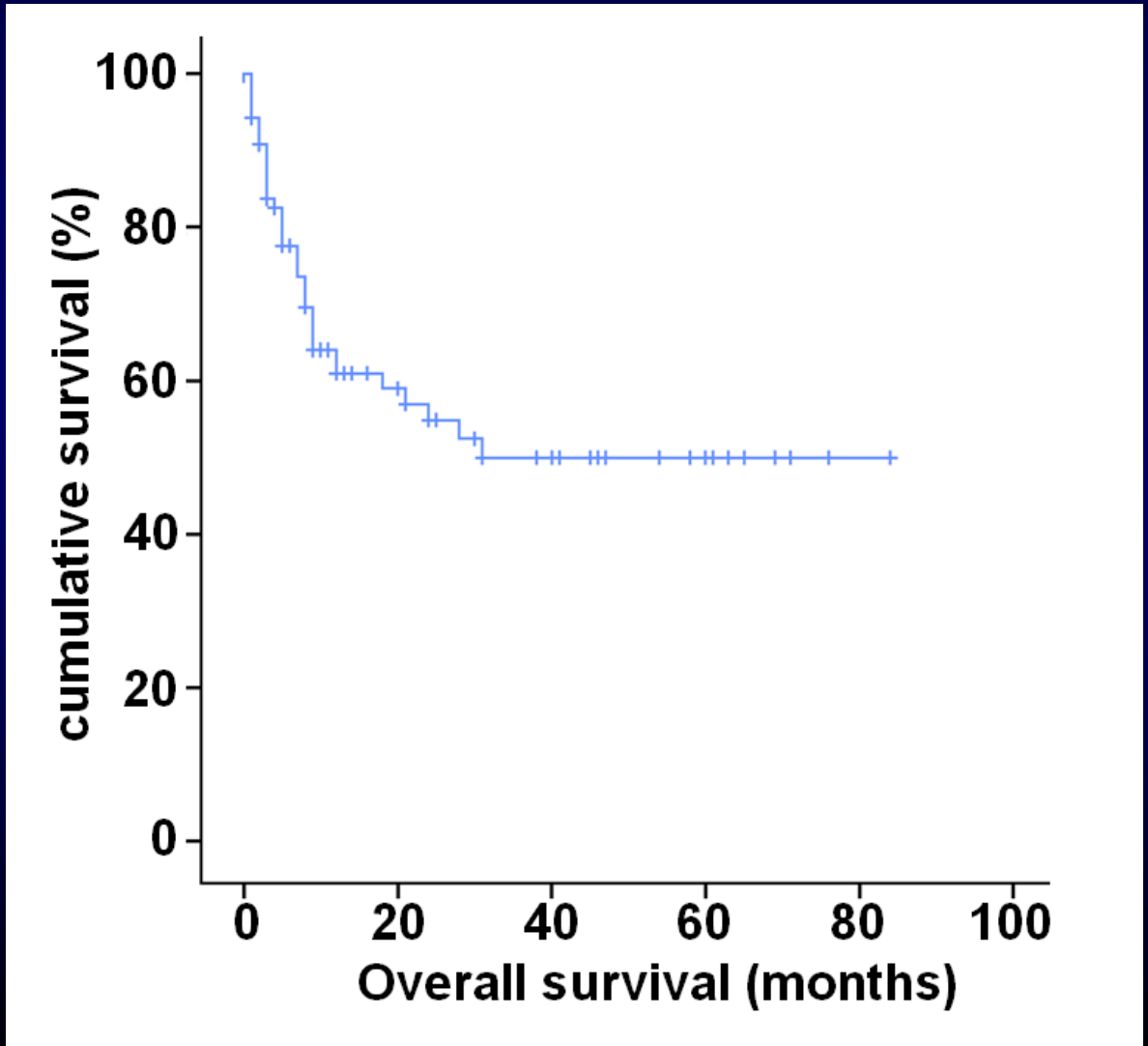
SMILE protocol for NK cell lymphomas (K. Oshimi)

2 g/m^2	Methotrexate Folinic acid	√
		Daily MTX level
1.5g/m^2	Ifosphamide mesna	√ √ √
40mg/d	Dexamethasone	√ √ √
100mg/m^2	etoposide	√ √ √
6000u/m^2/d	L-asparaginase	
	G-CSF	



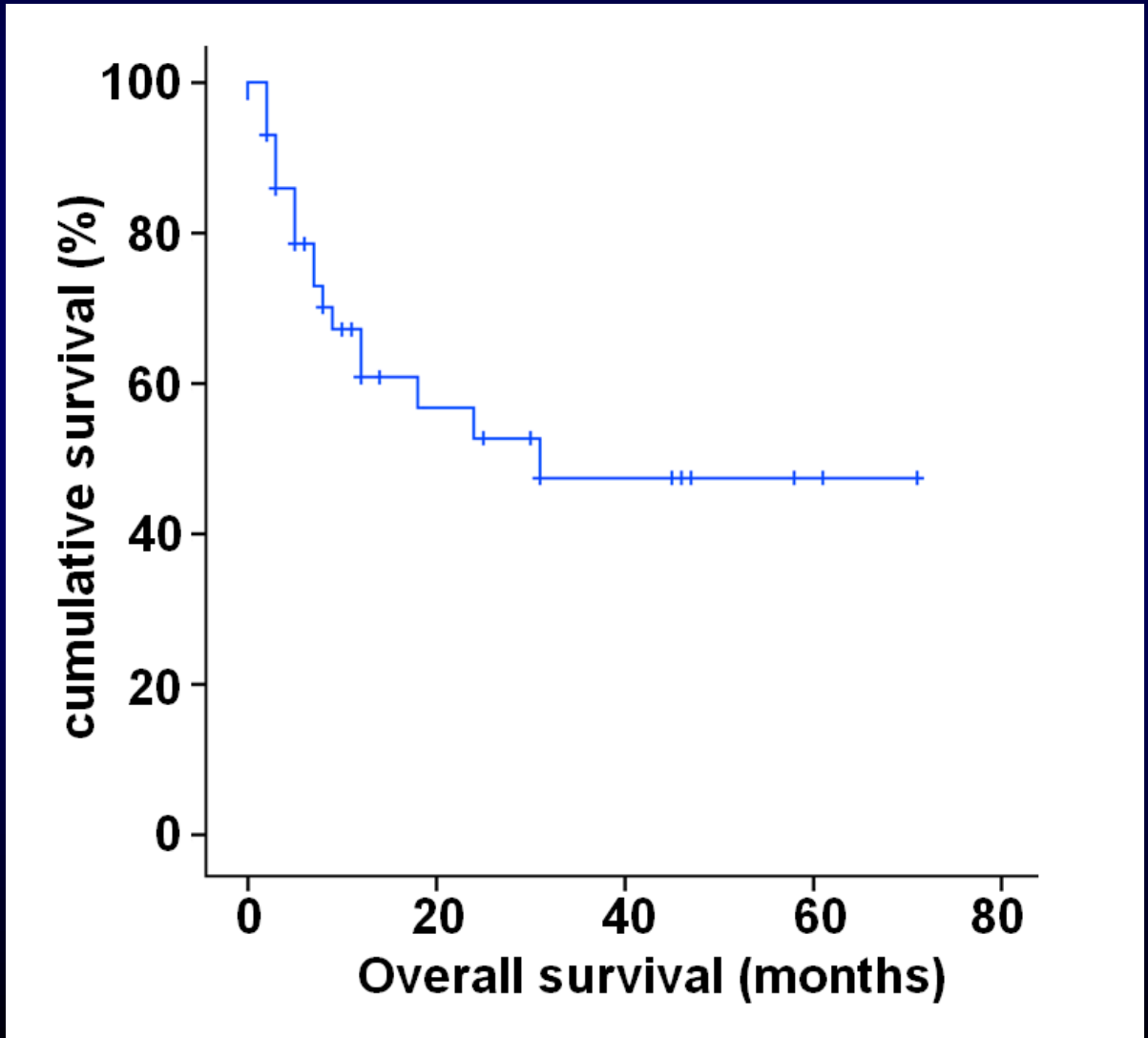
SMILE in 87 cases of NK/T-cell lymphomas

Overall survival



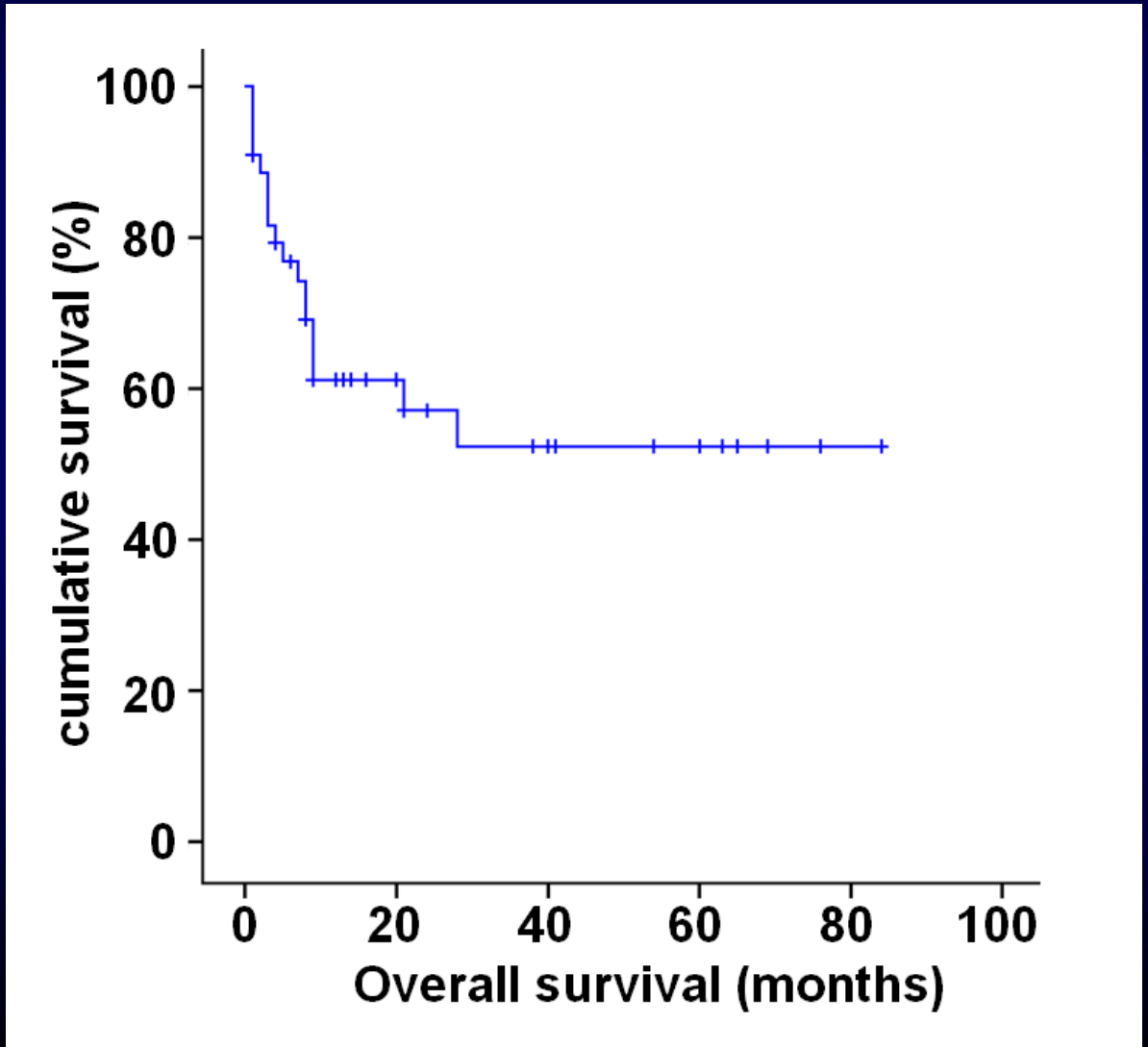
SMILE in 87 cases of NK/T-cell lymphomas

Overall survival: newly-diagnosed



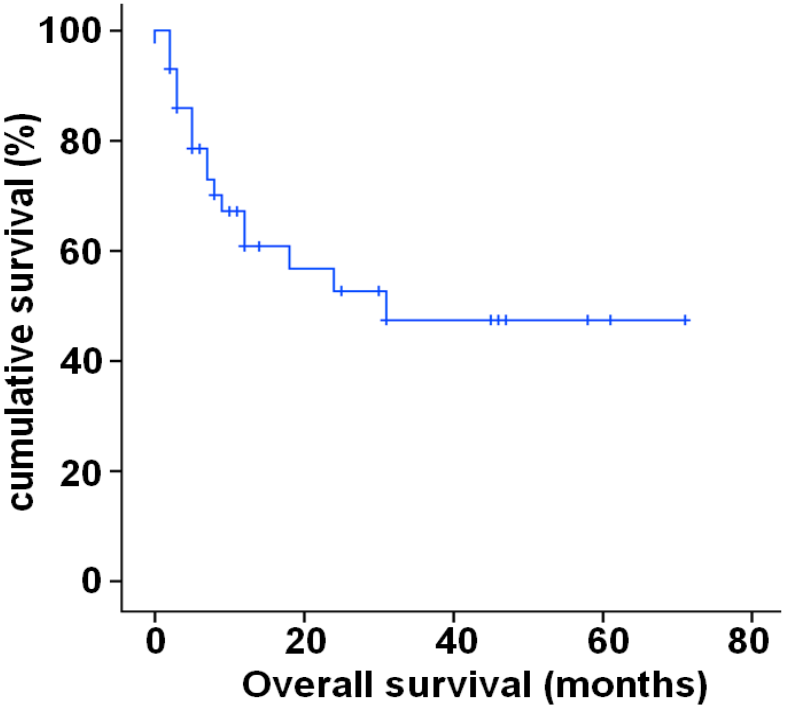
SMILE in 87 cases of NK/T-cell lymphomas

Overall survival: relapsed / refractory

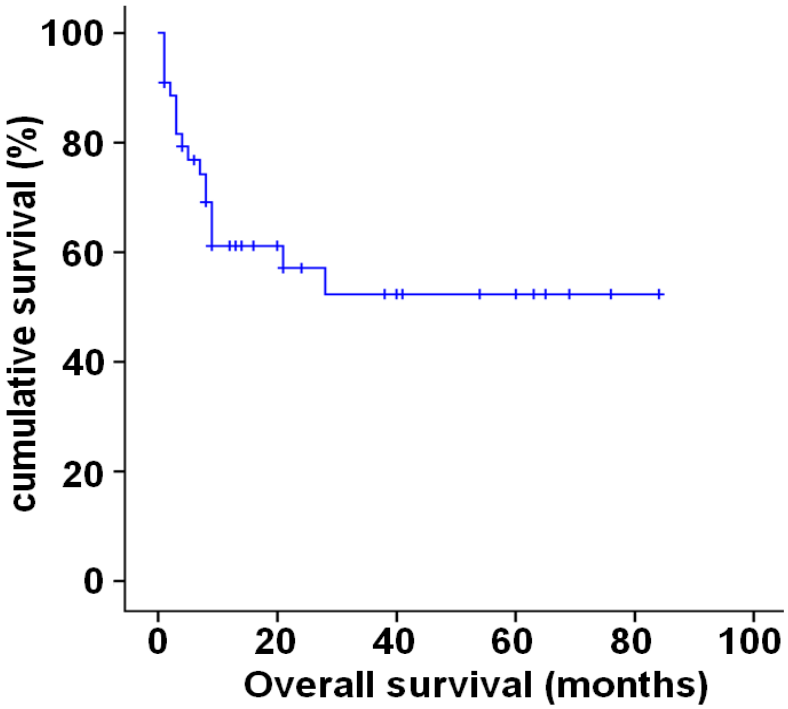


SMILE in 87 cases of NK/T-cell lymphomas

Similar OS for newly-diagnosed and relapsed / refractory cases



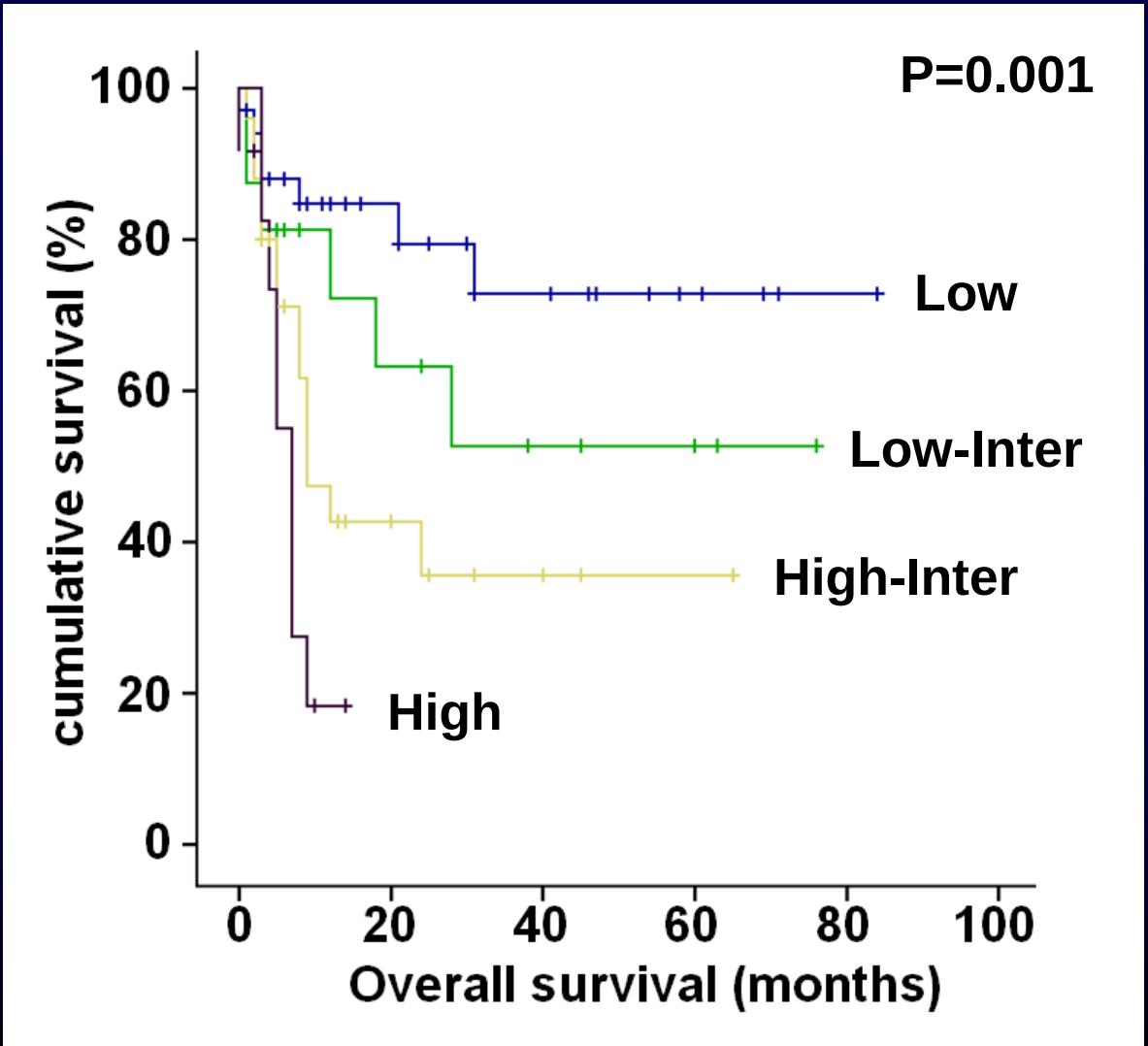
Newly diagnosed



Relapsed / refractory

SMILE in 87 cases of NK/T-cell lymphomas

Overall survival: IPI for prognostication



Non MDR related chemotherapy

Promace-CytaBOM (III)
DHAP (I)

SMILE (II)

Non MDR related chemotherapy

Promace-CytaBOM (III) + RT

SMILE (II)

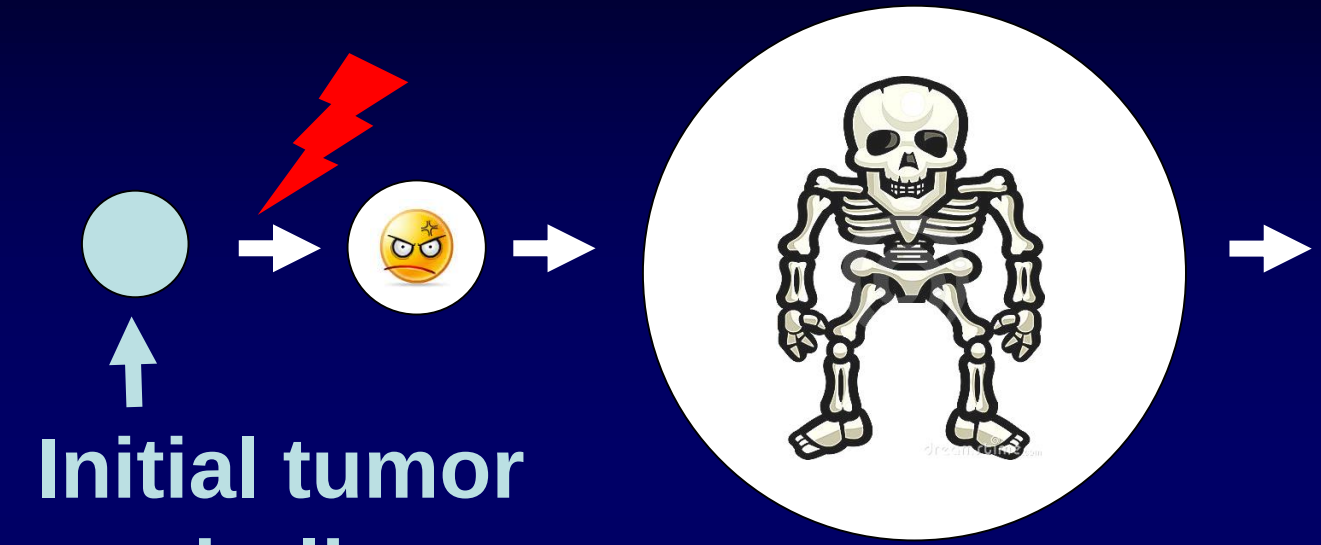
Prognostication of NK/T-cell lymphoma treated by SMILE

Current prognostic models rely on constitutional features of the patients and lymphoma load

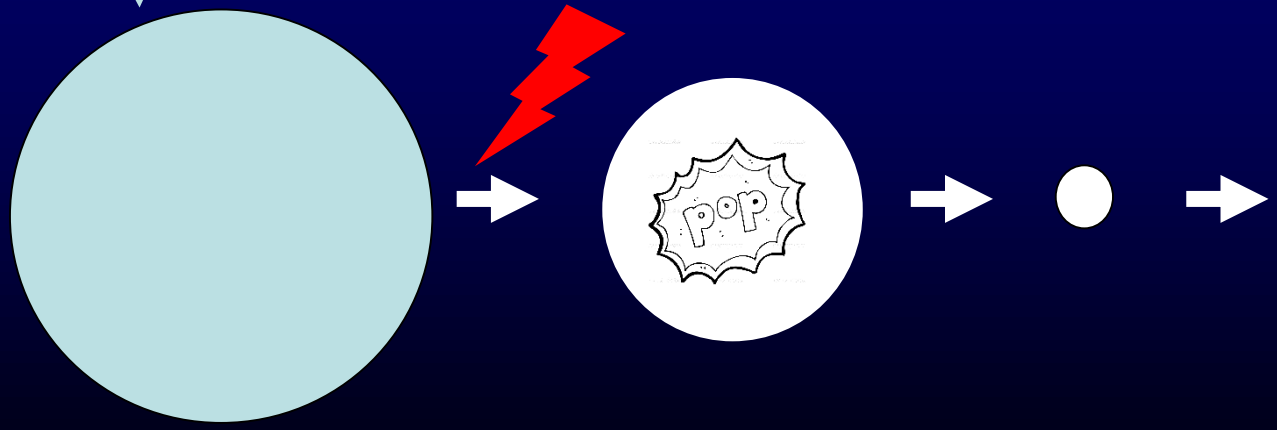
Hypothesis

Sensitivity of lymphoma cells to chemotherapy is a more important indicator of outcome

Lymphoma sensitivity to treatment



Initial tumor bulk



NK/T-cell lymphoma
Monitoring of response to SMILE

1. EBV DNA
2. PET/CT scan

NK/T-cell lymphoma
Monitoring of response to SMILE

1. **EBV DNA**
2. **PET/CT scan**

Prognostic factors for SMILE

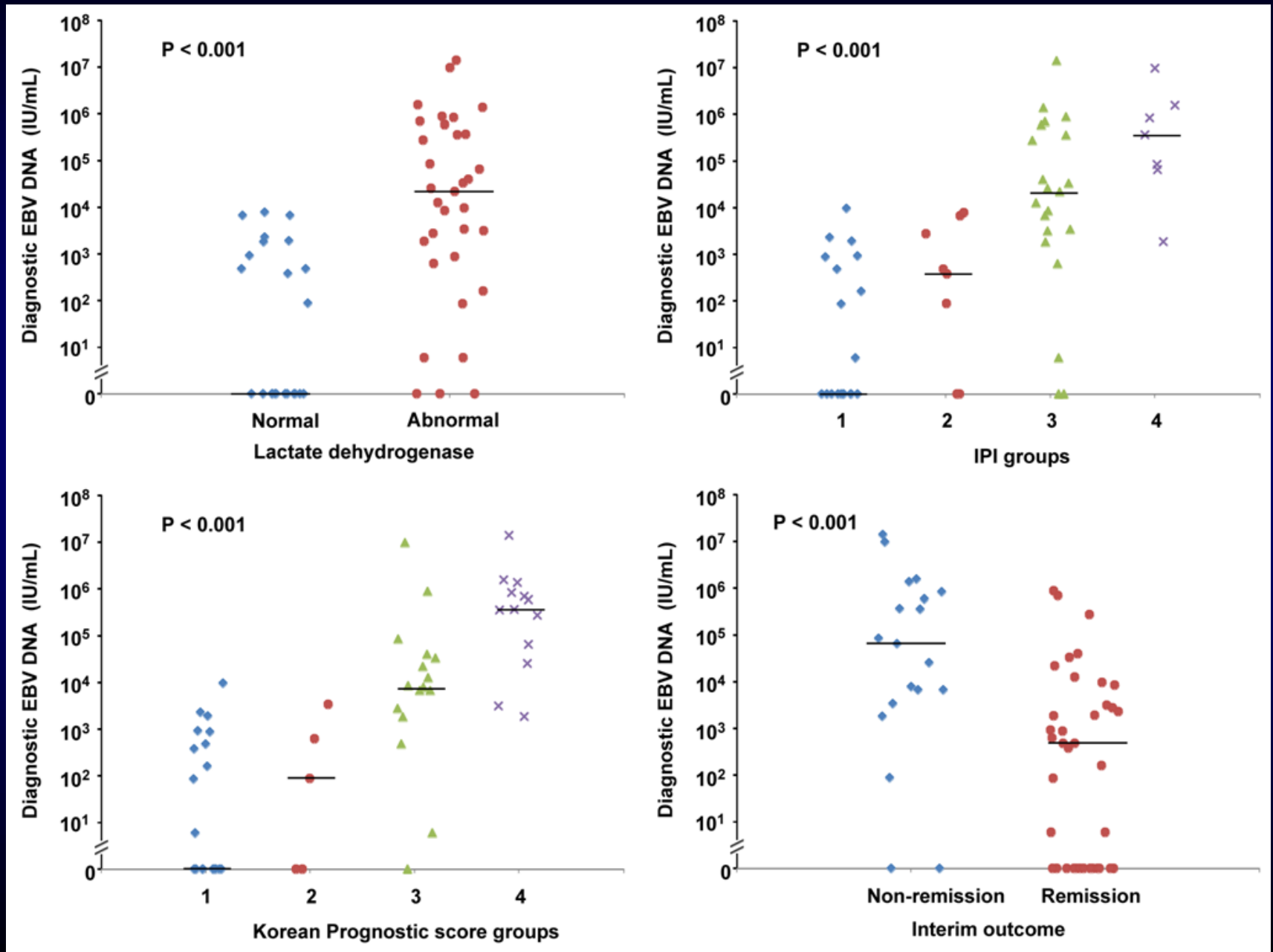
Prospective evaluation of

1. **Presentation EBV DNA**

2. **Non-detectable EBV DNA after SMILE**

3. **Dynamic patterns**
    - **A. persistent non-detectable**
    - **B. detectable, but < presentation**
    - **C. detectable, but > presentation**

Presentation EBV DNA for SMILE treated NK/T-cell lymphoma



Presentation plasma EBV DNA

1. Correlated very well with conventional parameters of tumor load, including LDH, IPI, KIPI, and remission

2. Did not correlate with overall survival or disease free survival

3. Implications: EBV DNA reflects tumor load, but tumor load is not the only factor that impacts on survival

Dynamic changes of EBV DNA

1. Reduction of EBV DNA after SMILE

2. Levels of EBV DNA during SMILE therapy
   A. non-detectable
   B. detectable, but < presentation
   C. detectable, but > presentation

Dynamic changes reflect tumor sensitivity to SMILE therapy

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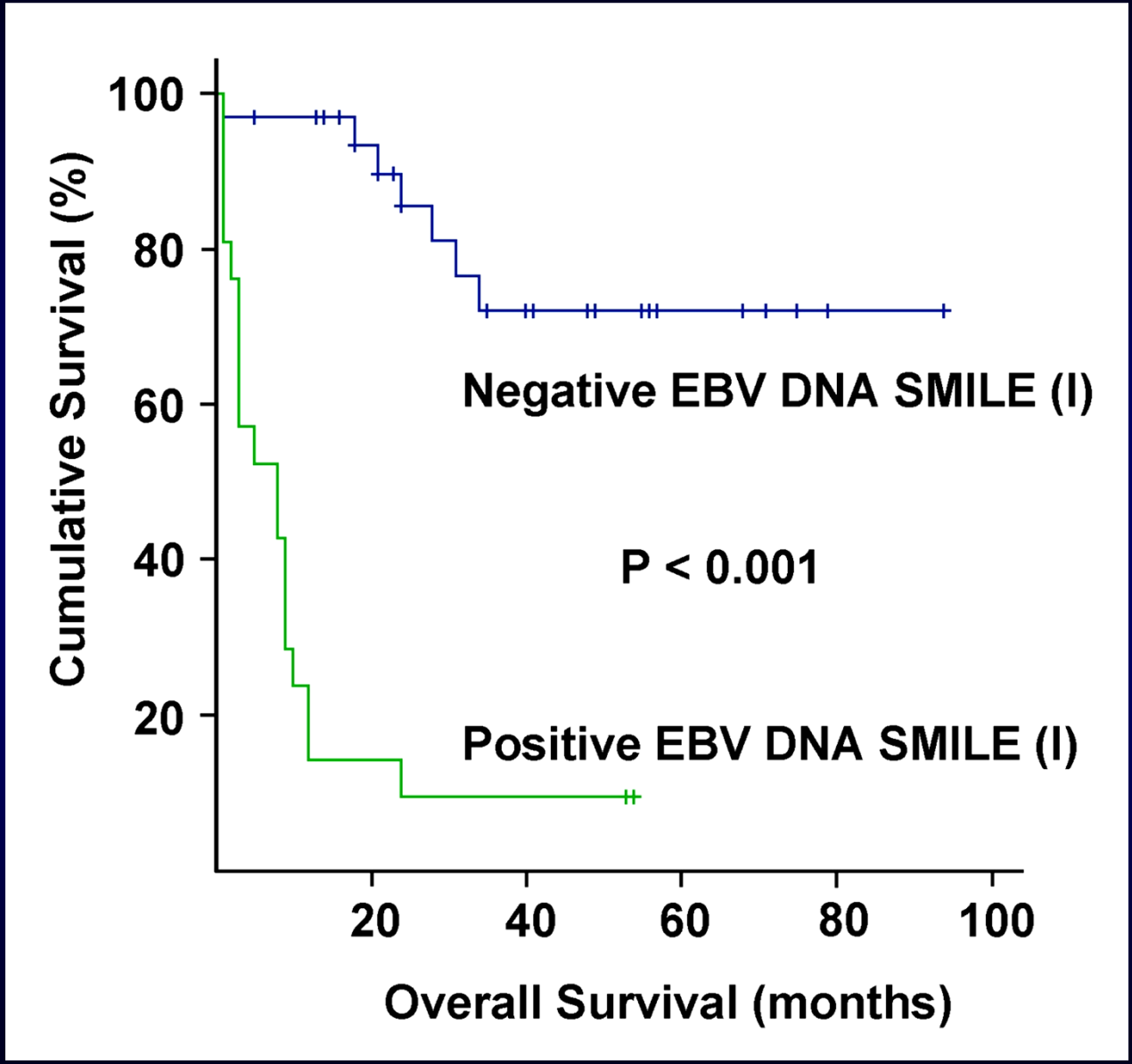
Dynamic changes reflect tumor sensitivity to SMILE therapy

Impact of negative EBV DNA after SMILE (I) on OS



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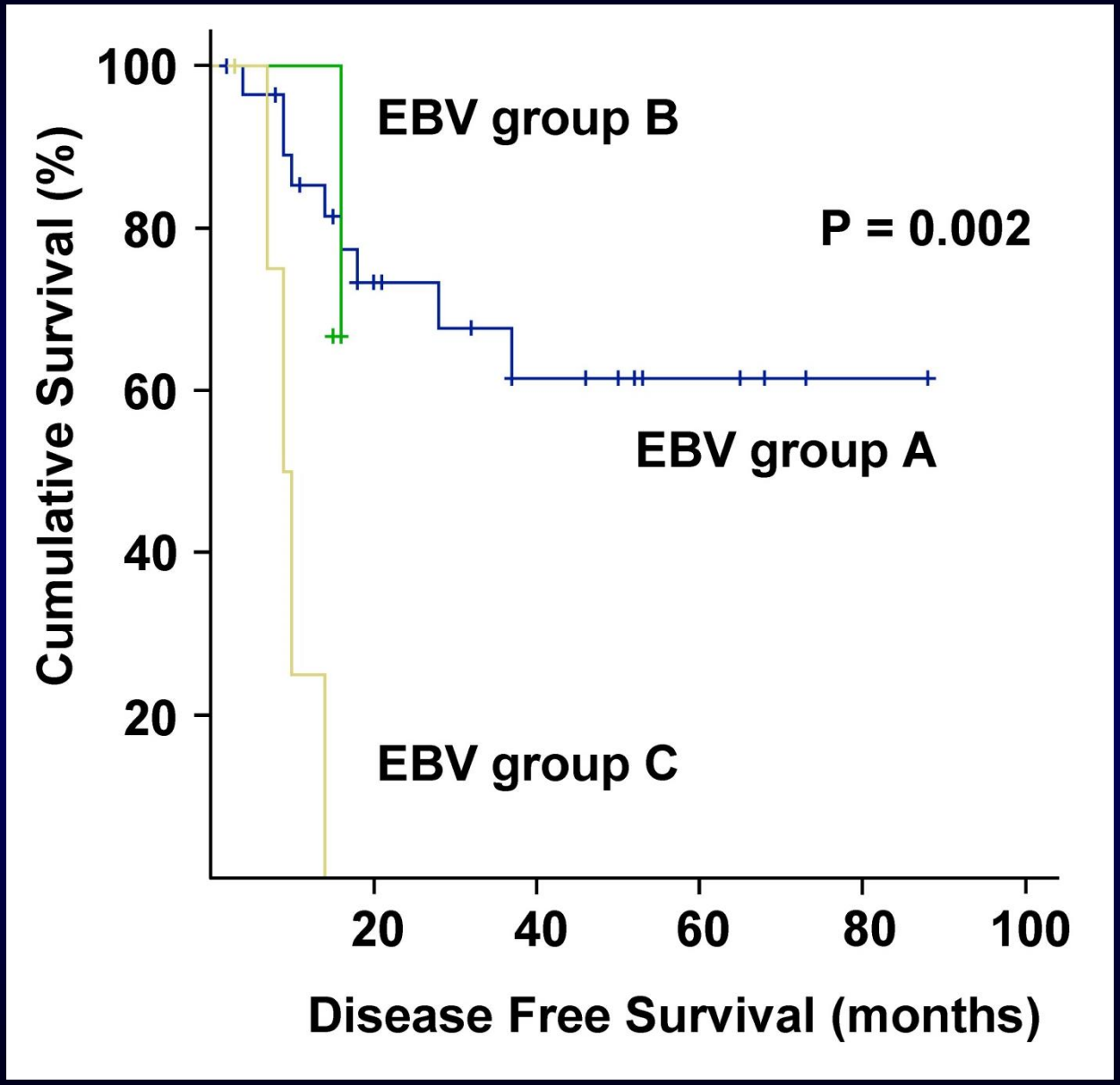
Impact of dynamic EBV DNA changes on DFS



Prognostic factors for SMILE treated NK/T-cell lymphoma

Table 4. Multivariate analysis of prognostic factors for survivals after SMILE therapy

Significant factors	P value	Hazard ratio	95% confidence interval
Whole cohort			
Overall survival			
Albumin	0.005	3.589	1.458 – 8.831
Negative EBV DNA after SMILE (I)	< 0.001	12.883	4.759 – 34.876
Disease free survival			
Age	0.015	1.078	1.014 – 1.145
Dynamic EBV change grouping	0.002	4.072	1.676 – 9.890
Patients with quantifiable EBV DNA at presentation			
Overall survival			
Albumin	0.002	5.764	1.896 – 17.516
Negative EBV DNA after SMILE (I)	< 0.001	19.887	5.331 – 74.104
Disease free survival			
Age	0.047	1.067	1.001 – 1.137
Dynamic EBV change grouping	0.036	2.849	1.070 – 7.587

Conclusions

1. Presentation EBV DNA reflects tumor load, but does not impact on survivals

2. Negative EBV DNA after SMILE (I) reflects superior response to chemotherapy, and therefore impacts on OS

3. For patients already in CR, non-detectable EBV DNA means optimal suppression of tumor cells, and therefore impacts on DFS

NK/T-cell lymphoma
Monitoring of response to SMILE

1. EBV DNA
2. PET/CT scan

Role of interim PET/CT scan in SMILE

Design

1. **Baseline PET/CT**
2. **Interim PET/CT after 2 – 3 cycles**
3. **End-treatment PET/CT**

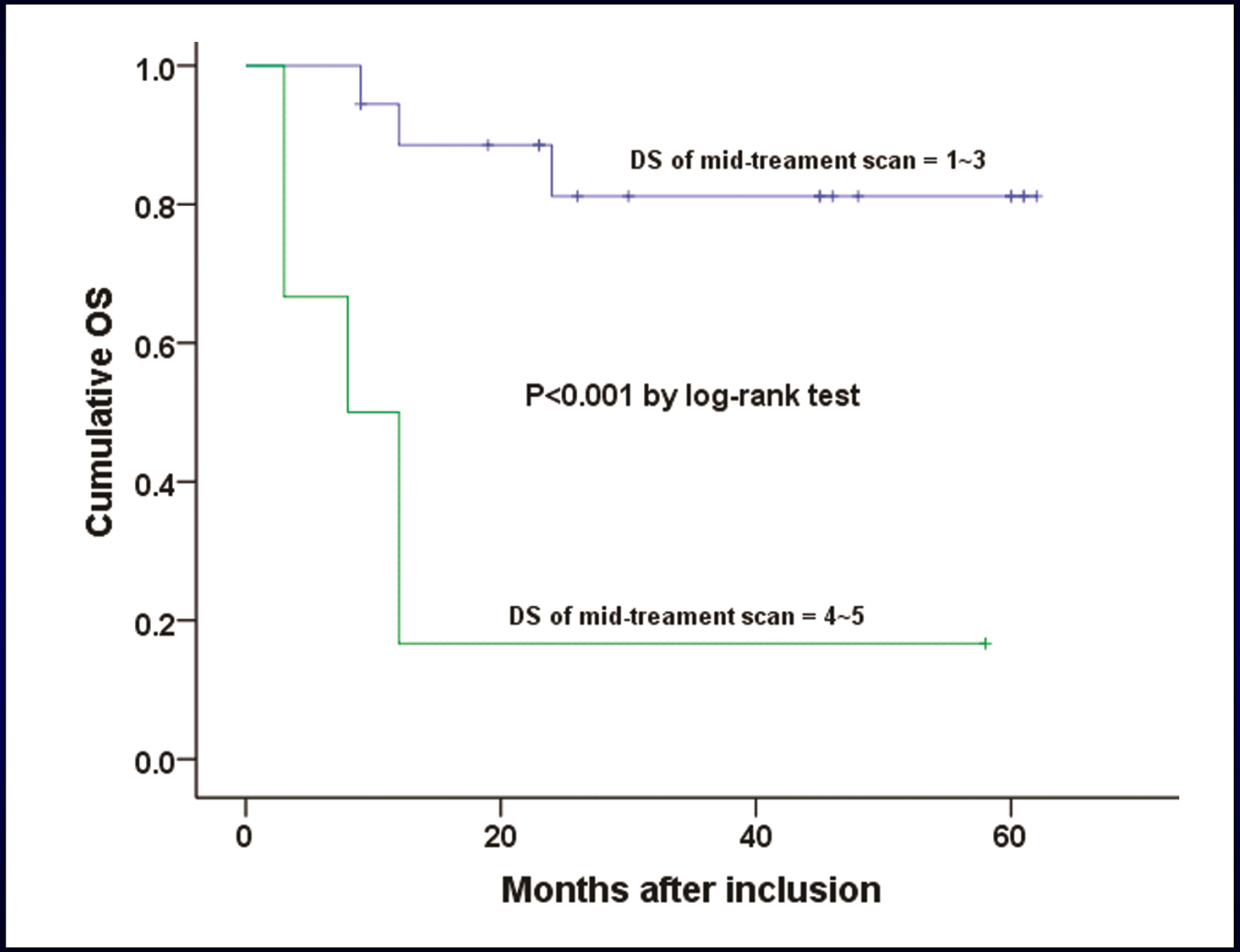
Parameters

SUVmax, ΔSUVmax, tumor volume, 5-point Deauville score

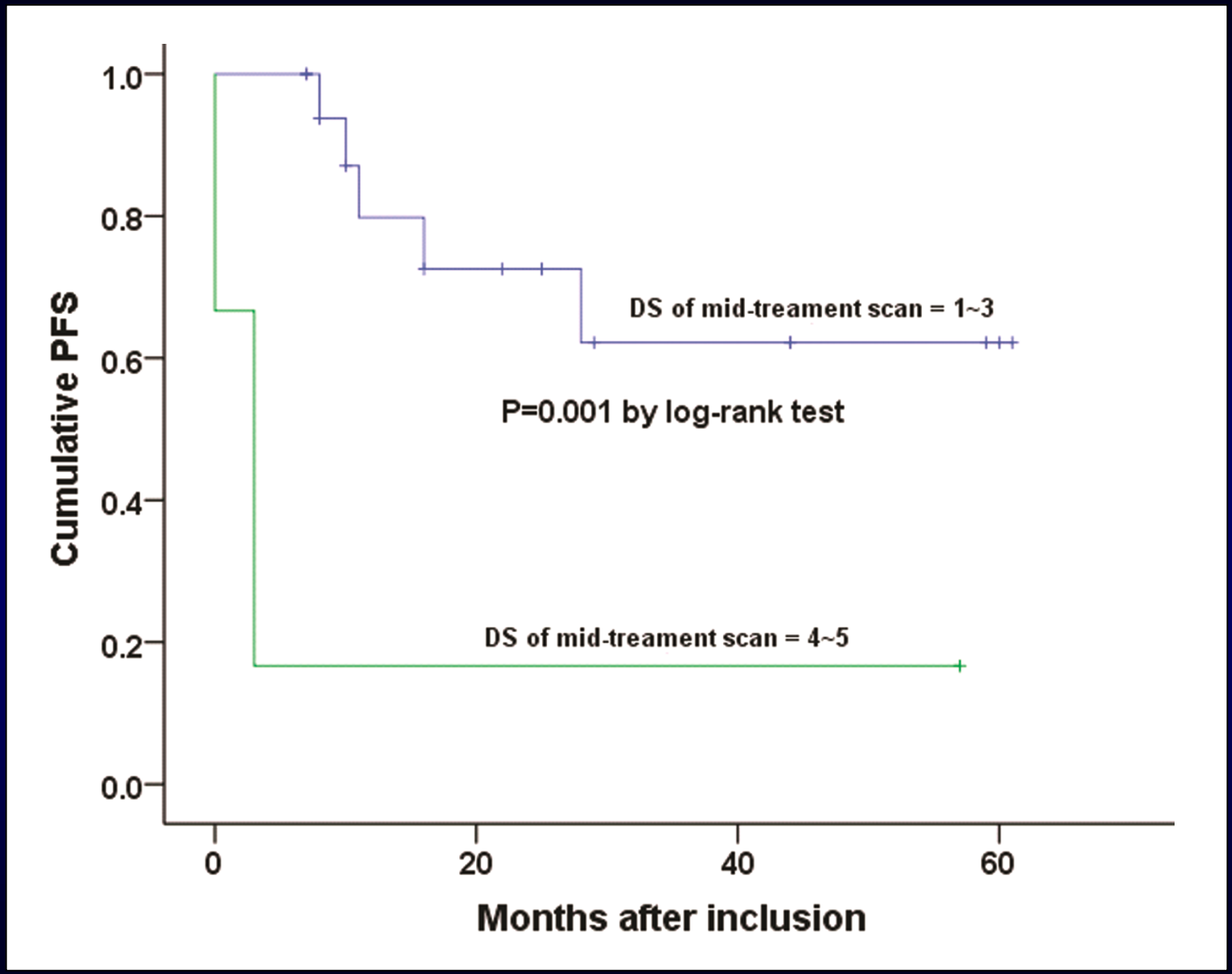
Role of interim PET/CT in SMILE therapy

Multivariate analysis	**OS**
Deauville 5-point score	**P < 0.001**
Multivariate analysis	**PFS**
Deauville 5-point score	**P < 0.001**

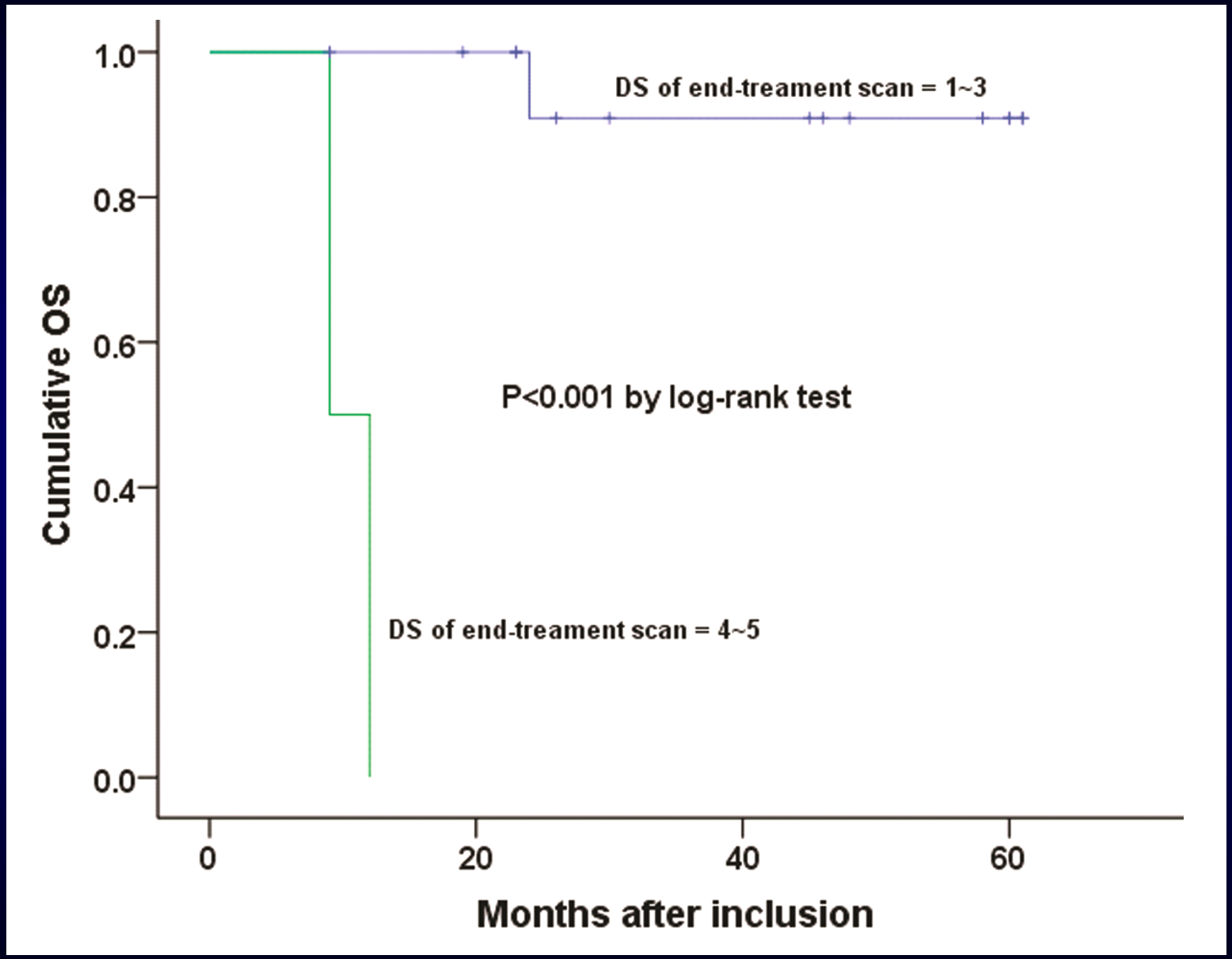
Impact of mid-treatment PET/CT on OS



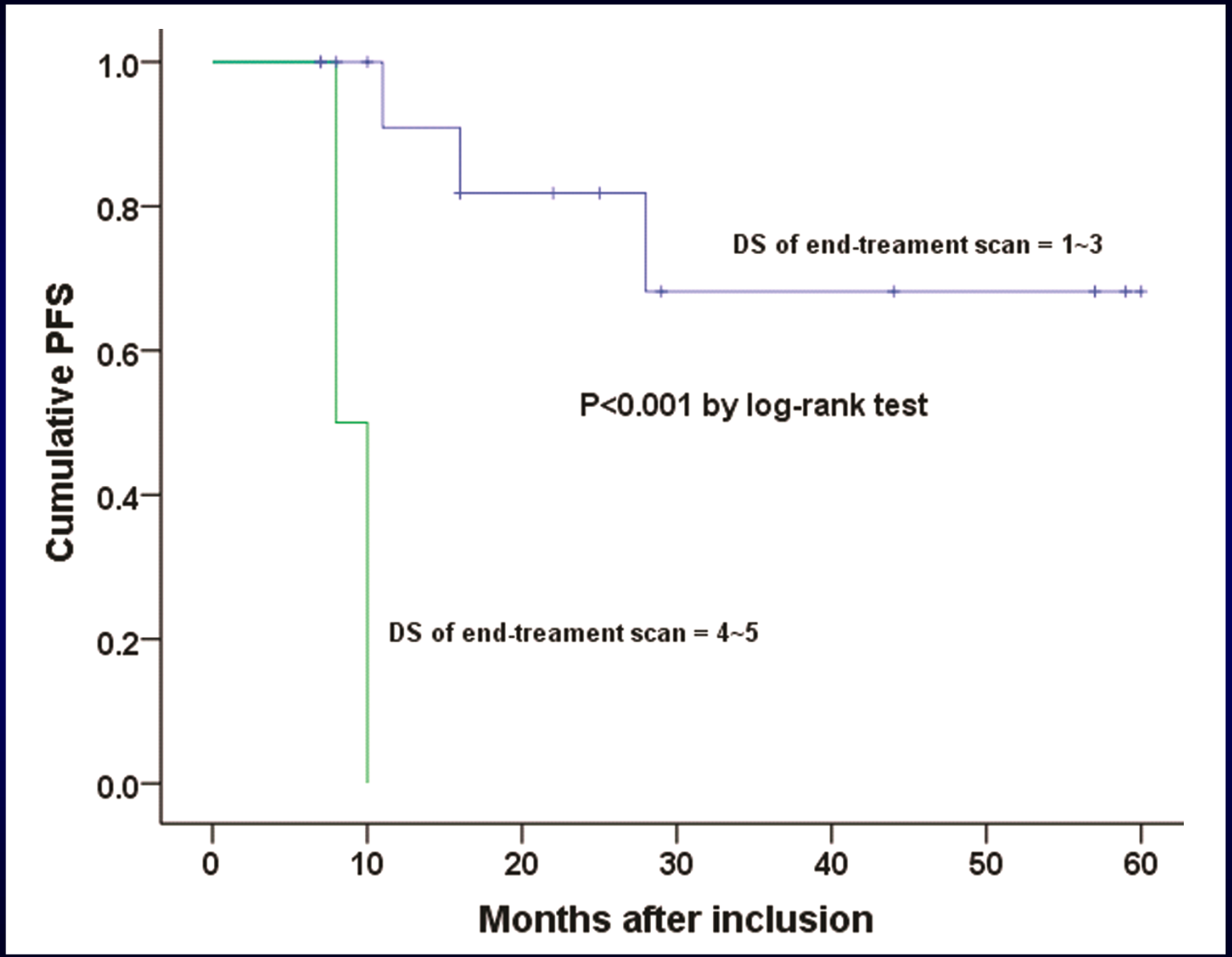
Impact of mid-treatment PET/CT on PFS



Impact of end-of-treatment PET/CT on OS



Impact of end-of-treatment PET/CT on PFS



Role of interim PET/CT in SMILE therapy

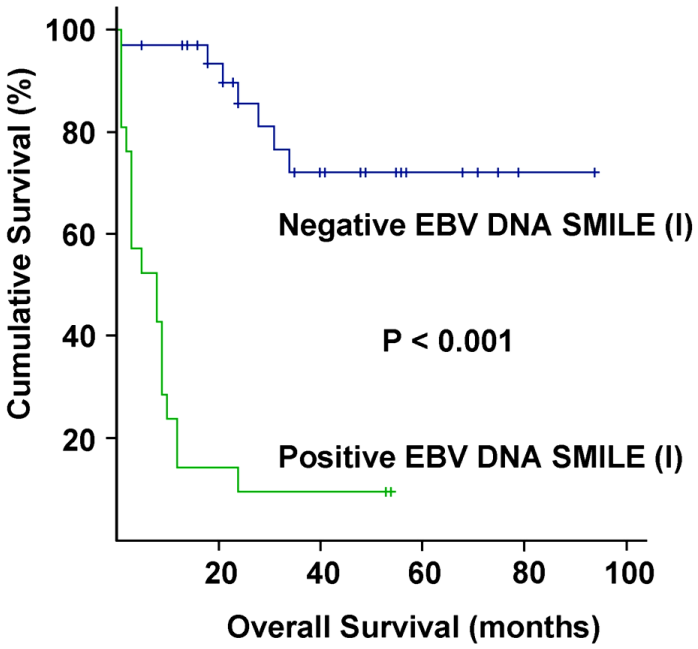
- Should aim at achieving a negative PET/CT scan after 2 – 3 cycles of SMILE

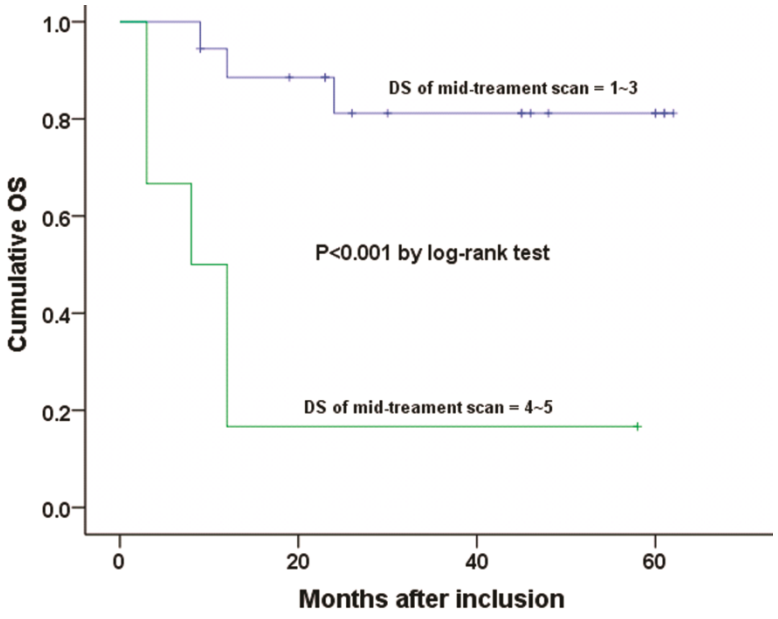
- Patients with a Deauville score of 4 – 5 at interim scan will not do well, and may require additional therapy to achieve durable remission

Which is more prognostic

EBV DNA or PET/CT scan

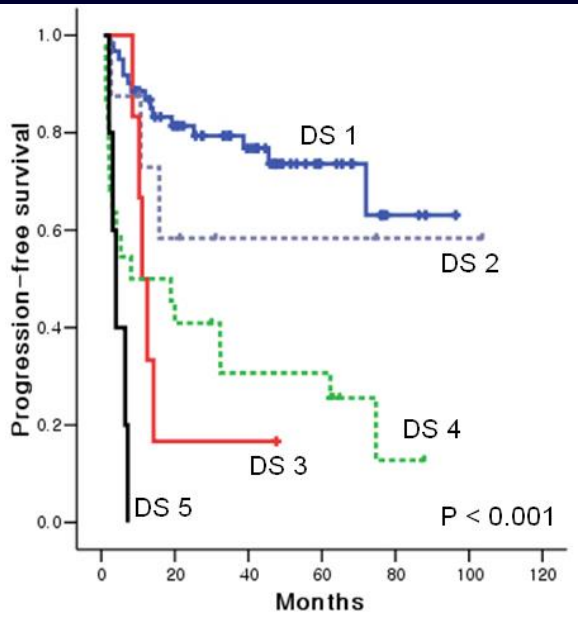
Interim assessments



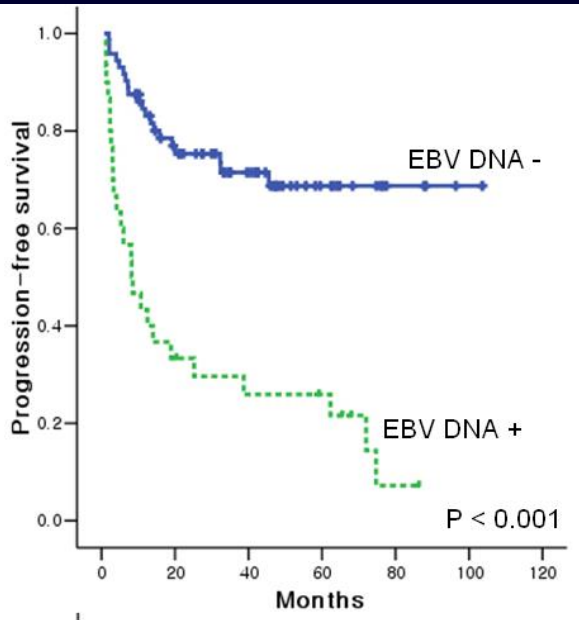


Combined EBV DNA and PET/CT at end of treatment
Prognostic impact

(A)



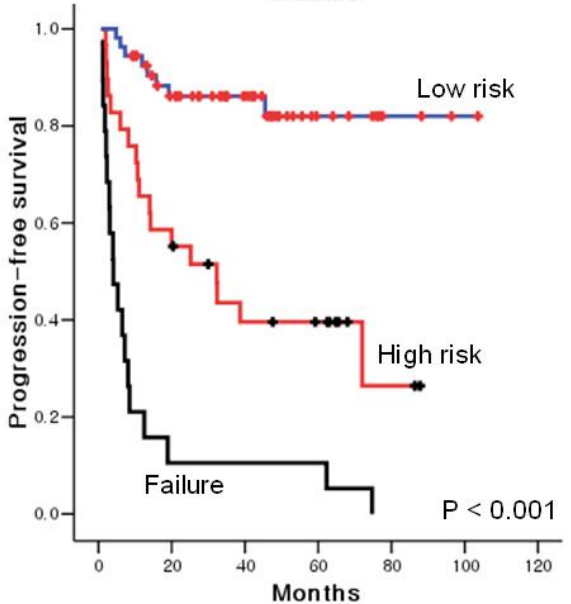
(B)



(C)

	EBV-negative (n = 72)	EBV-positive (n = 30)
DS 1/2 (n = 69)	8/54 (15%)	8/15 (53%)
DS 3/4 (n = 28)	8/14 (57%)	14/14 (100%)
DS 5 (n = 5)	4/4 (100%)	1/1 (100%)

(D)



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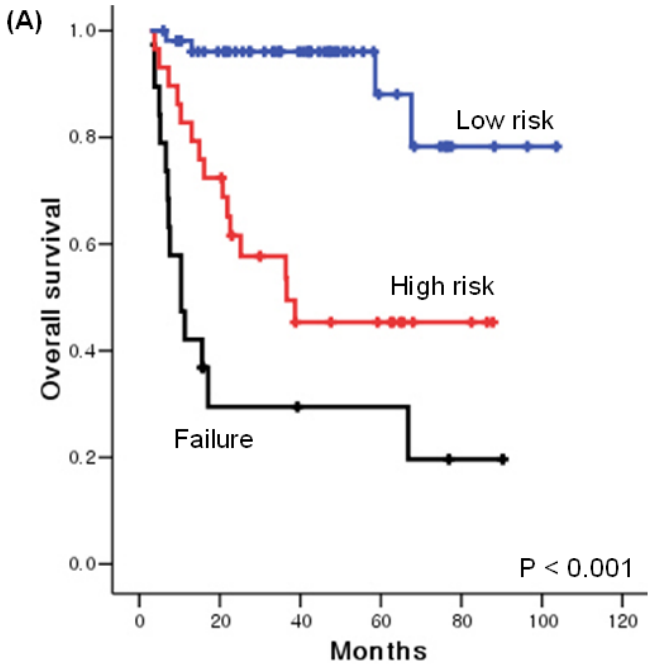
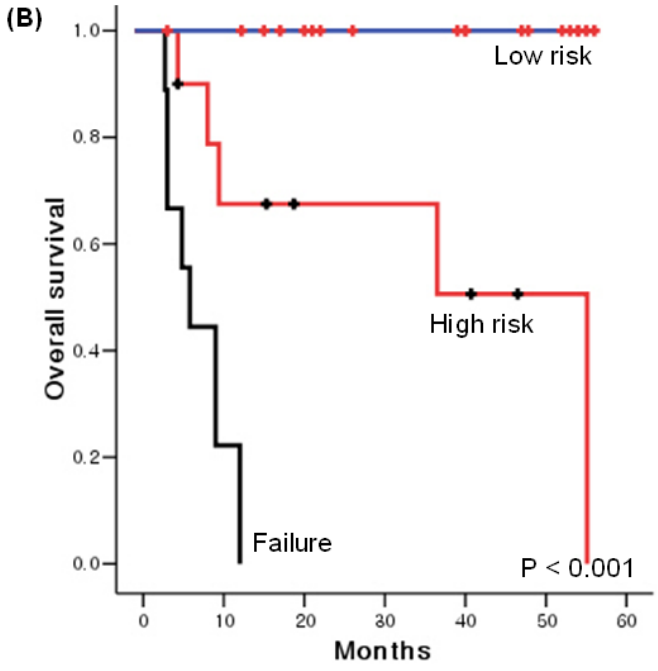
Prognostic impact





(C)

	DS 1	DS 2	DS 3	DS 4	DS 5
EBV-negative	Low-risk group : Observation		High-risk group : Intensified treatment		
EBV-positive	High-risk group : Intensified treatment		Failure group : Salvage treatment		

Incorporation of presentation EBV DNA in prognostication

Age
Stage
Nasal / non-nasal
Nodal involvement
EBV DNA (detectable / non-detectable)

Other L-asparaginase containing regimens

Acknowledgement

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