2015…2018
T-Cell Lymphomas: We are close to the finalization

NK/T-cell lymphoma: SMILE and other "asparaginase" containing regimens Experience in Japan

Motoko Yamaguchi
Department of Hematology and Oncology
Mie University Graduate School of Medicine
Tsu, Japan

May 8, 2018
Royal Hotel Carlton, Bologna, Italy

2015... 2018
T-Cell Lymphomas:
we are close to the
finalization

Bologna
ROYAL HOTEL CARLTON
May 7-9, 2018

President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Disclosures of MOTOKO YAMAGUCHI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Chugai Pharma, Eisai, Takeda Phamaceuticals, Nippon Shinyaku, Kyowa Hakko Kirin, Bristol-Myers Squibb, Teijin Pharma, Meiji Seika Pharma, Celgene							Honoraria
Erytech						X	

NK/T-cell lymphoma: SMILE and other “asparaginase” containing regimens - Experience in Japan

- L-asparaginase in the management of NK/T-cell lymphoma

  in Japan

- Unmet medical needs in the treatment of NK/T-cell lymphoma

  in Japan

NK/T-cell lymphoma (NKTCL) in Japan

- Incidence: 1.0 - 2.6% of ML

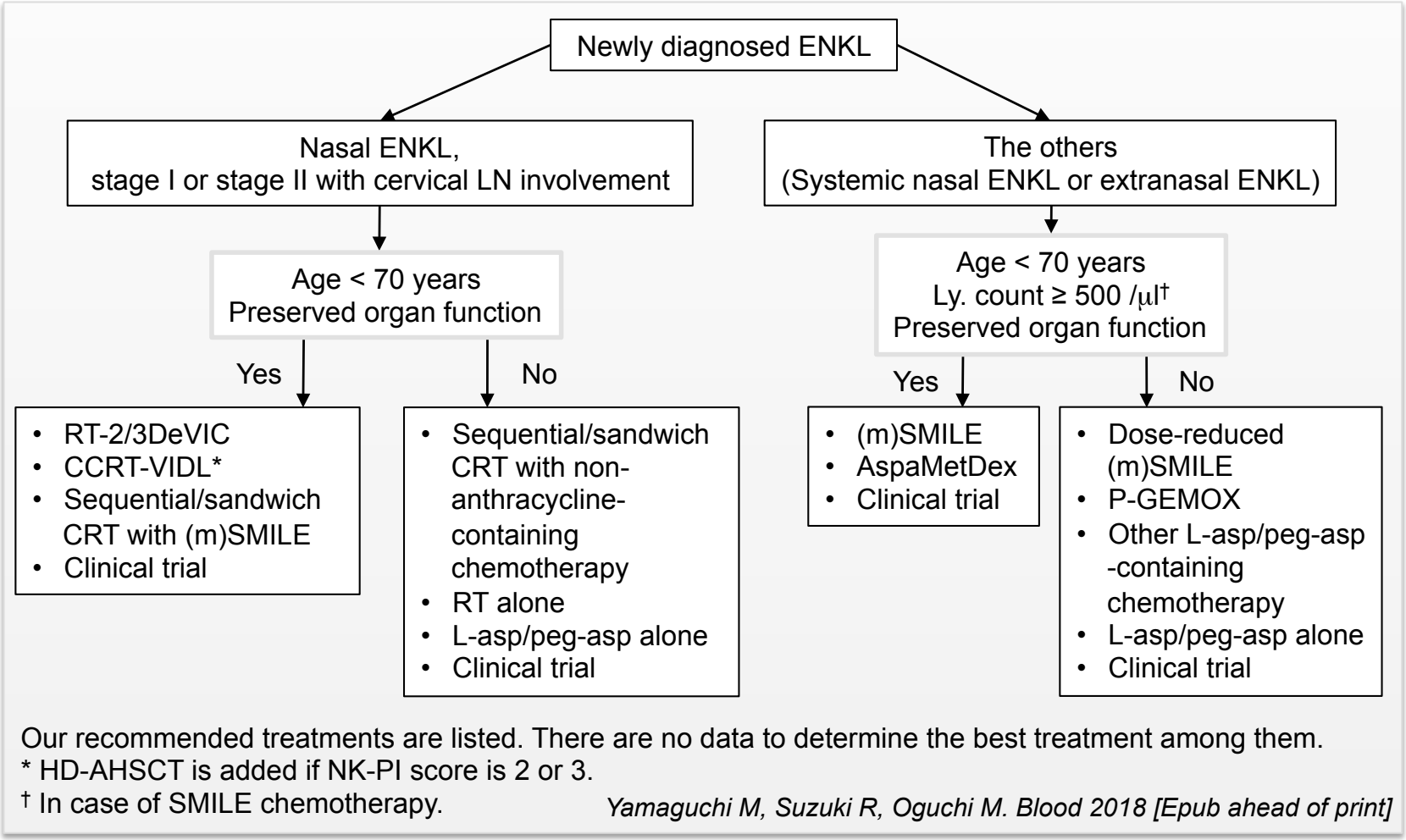
  Lymphoma Study Group of Japanese Pathologists. Pathol Int 2000
  Chihara D, et al. Br J Haematol 2014

- Median age at diagnosis: 58 years

	Study (group)	N	Median age at diagnosis	Age > 60 y	Reference
International	IPTCLP	136	49	-	*Au WY, et al. Blood 2009*
	PINK	527	-	31%	*Kim SJ, et al. Lancet Oncol 2016*
Korea	NK-PI	262	-	21%	*Lee J, et al. JCO 2006*
China	RT *	1,273	43	14%	*Yang Y, et al. Blood 2015*
Europe	GELA	48	46	-	*Bossard C, et al. Blood 2007*
	AspaMetDex †	19	60	-	*Jaccard A, et al. Blood 2011*
US	NCDB *	642	-	34%	*Vargo JA, et al. Cancer 2017*
Japan	NKEA	358	58	43%	*Yamaguchi M, et al. JCO 2017*

*, Localized NKTCL; †, Relapsed NKTCL.

Recommended first-line therapy for NKTCL



Our recommended treatments are listed. There are no data to determine the best treatment among them.
* HD-AHSCT is added if NK-PI score is 2 or 3.
† In case of SMILE chemotherapy.

Yamaguchi M, Suzuki R, Oguchi M. Blood 2018 [Epub ahead of print]

- Multiple recommended regimens are listed
  - Differences in preference and logistics of RT; availability of key agents
  - No standard therapy based on RCT

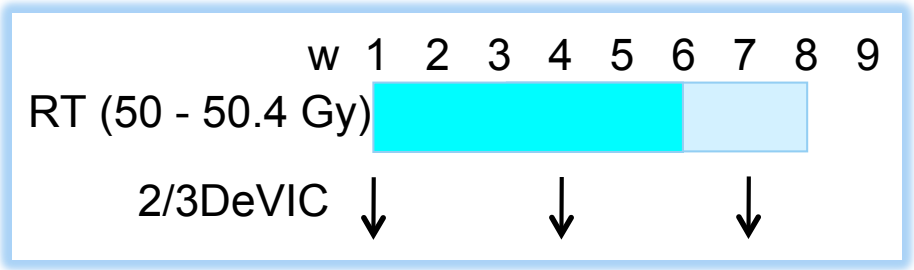
Standard of care for newly diagnosed NKTCL in Japan

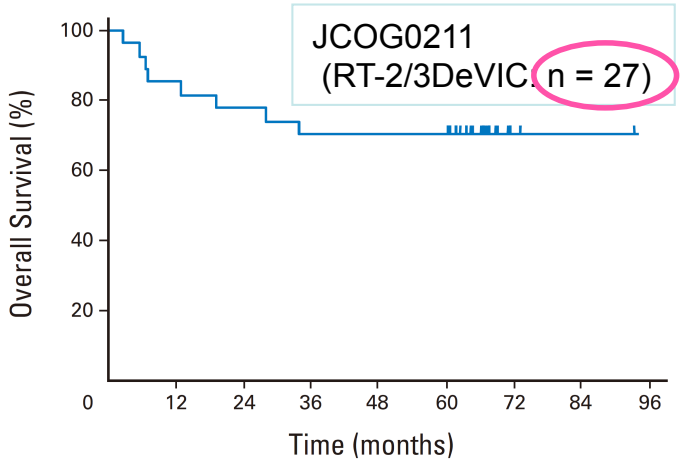
- JSH guidelines (2013)

Localized, nasal,

stage IE or contiguous stage IIE

→ RT-2/3DeVIC





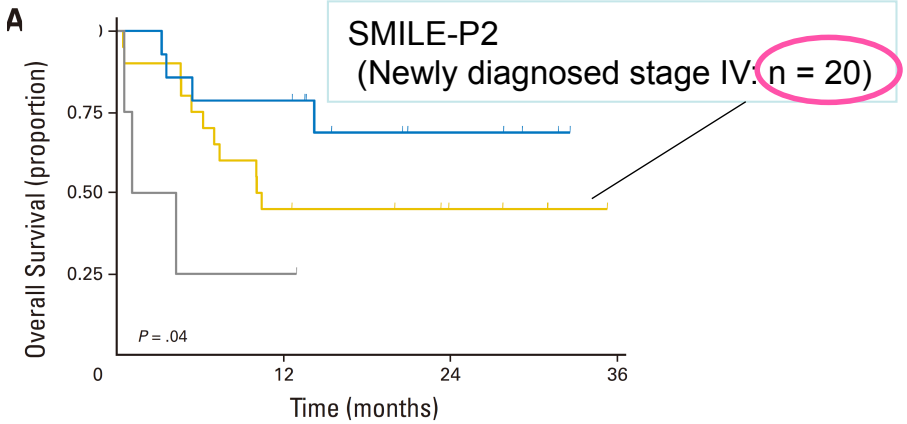
Yamaguchi M, Tobinai K, Oguchi M, et al. JCO 2012

The others

→ SMILE x 2-6

or other L-asp-containing regimens

Drug	Dose (/day)	Route	Day
MTX	2 g/m^2	IV (6h)	1
Leucovorin	15 mg x 4	IV or PO	2, 3, 4
IFM	1,500 mg/m^2	IV	2, 3, 4
Mesna	300 mg/m^2 x3	IV	2, 3, 4
DMS	40 mg/day	IV or PO	2, 3, 4
ETP	100 mg/m^2	IV	2, 3, 4
L-asp	6,000 U/m^2	IV	8, 10, 12, 14, 16, 18, 20
G-CSF		SC or IV	6 - WBC > 5,000/mm^3



Yamaguchi M, Kwong YL, Kim WS, et al. JCO 2011

NKEA project (Next-Generation Therapy for NK/T-cell lymphoma in East Asia)

- Part A

Objectives:

- To clarify the current situation of the treatment for NKTCL in Japan

Study design:

• Multicenter, retrospective study

Eligibility Criteria:

(1) Biopsy-proven NKTCL (WHO 2008)

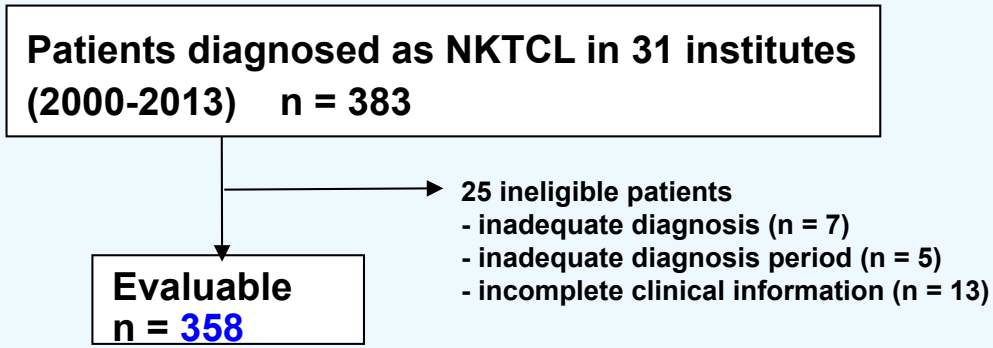
(2) Diagnosed between 2000 and 2013

(3) No restriction of availability of clinical information

Endpoints:

• Baseline clinical characteristics
• Response
• Survival
• Toxicity
• Prognostic factors

Patients selection



Collaborators:

• Japanese Radiation Oncology Study Group

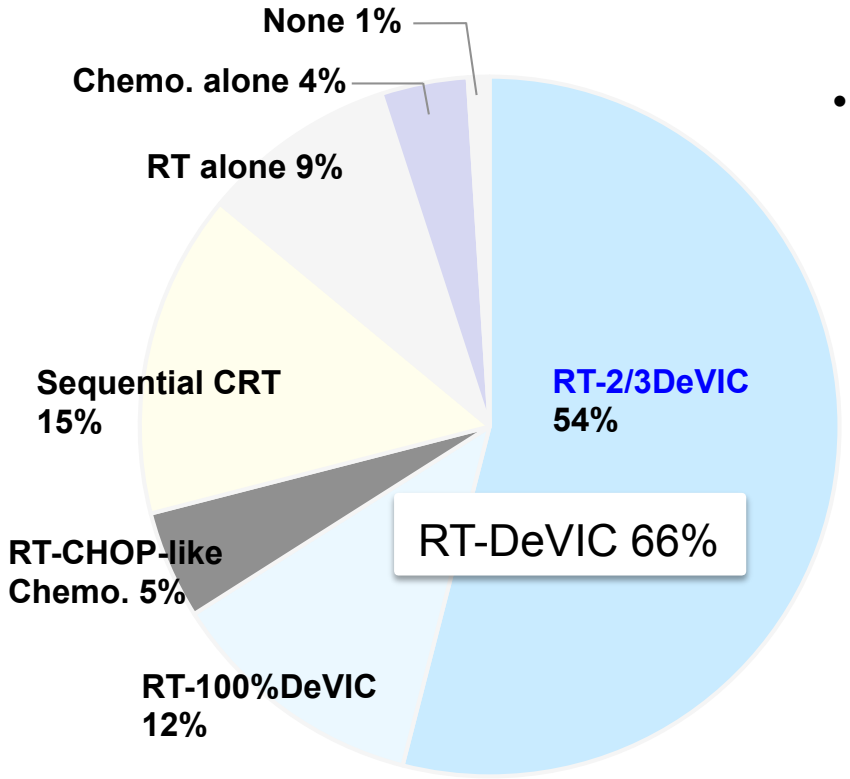
JROSG Japanese Radiation Oncology Study Group

NKEA

UMIN-CTR ID: UMIN000015491

Yamaguchi M, Suzuki R, Oguchi M, et al. JCO 2017

First-line therapy in patients with localized NKTCL in 31 institutes in Japan (2000-2013, n = 257)



J Clin Oncol 2017

- L-asparaginase-containing chemotherapy (n = 5)
  - SMILE (n = 3)
  - SMILE(-like) chemo → RT (n = 2)

- JSH Guidelines
- RT-2/3DeVIC: only 9 weeks

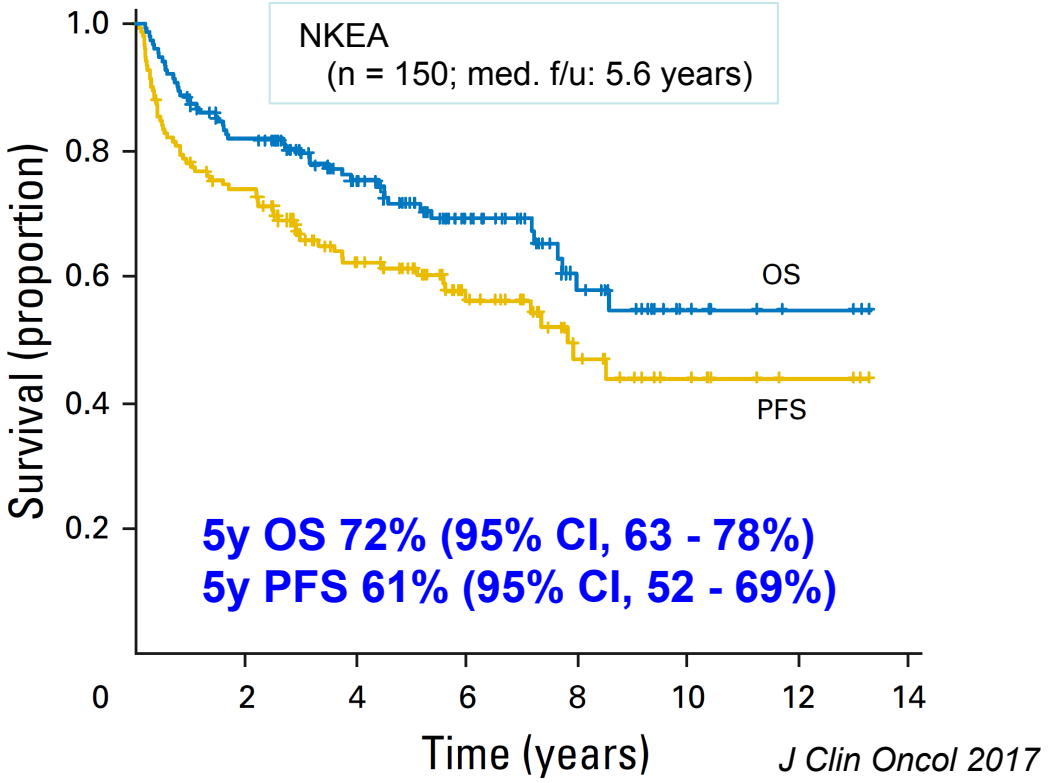
Fig: Yamaguchi M & Miyazaki K. J Clin Exp Hematop 2017

Treatment period	2000 - 2004	2005 - 2009	2010 - 2013
RT-DeVIC	32%	65%	82%

Efficacy of RT-DeVIC in clinical practice

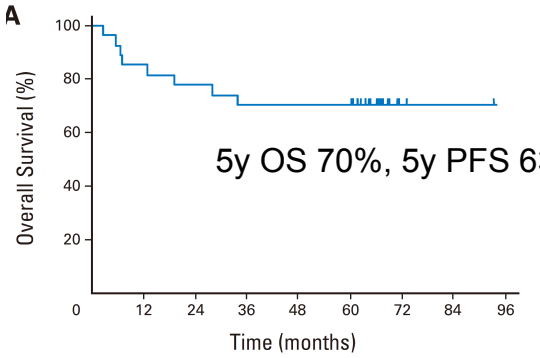
- Baseline clinical characteristics

	NKEA (n = 150) %	JCOG0211 (n = 33) %
Median age, y (range)	56 (16 - 83)	54 (21-68)
Age > 60 y	37	21
Male sex	74	58
Elevated LDH	28	21
ECOG PS > 1	5	6
B symptom (+)	35	36
Reg. LN invol.	19	33
Hb < 11 g/dL	11	18
PLT < 150 x $10^3/\mu L$	11	3
Elevated CRP	58	55
Elevated sIL-2R	42	37
%CR	82	75
ORR	89	78



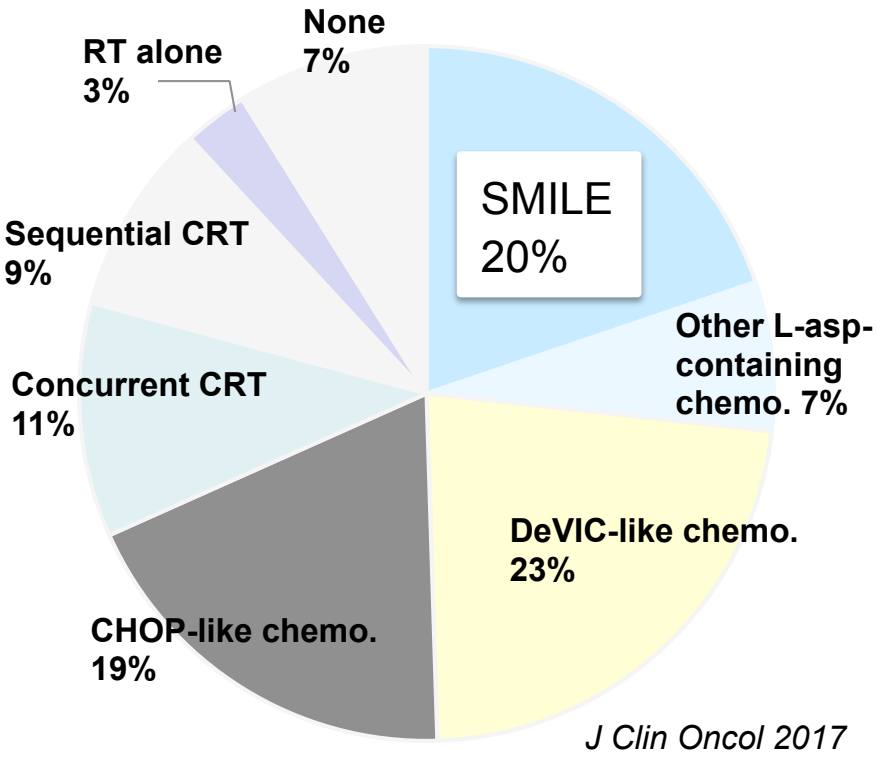
J Clin Oncol 2017

JCOG0211
(RT-2/3DeVIC: n = 27)



J Clin Oncol 2012

First-line therapy in patients with systemic NKTCL in 31 institutes in Japan (2000-2013, n = 101)



J Clin Oncol 2017

Fig: Yamaguchi M & Miyazaki K. J Clin Exp Hematop 2017

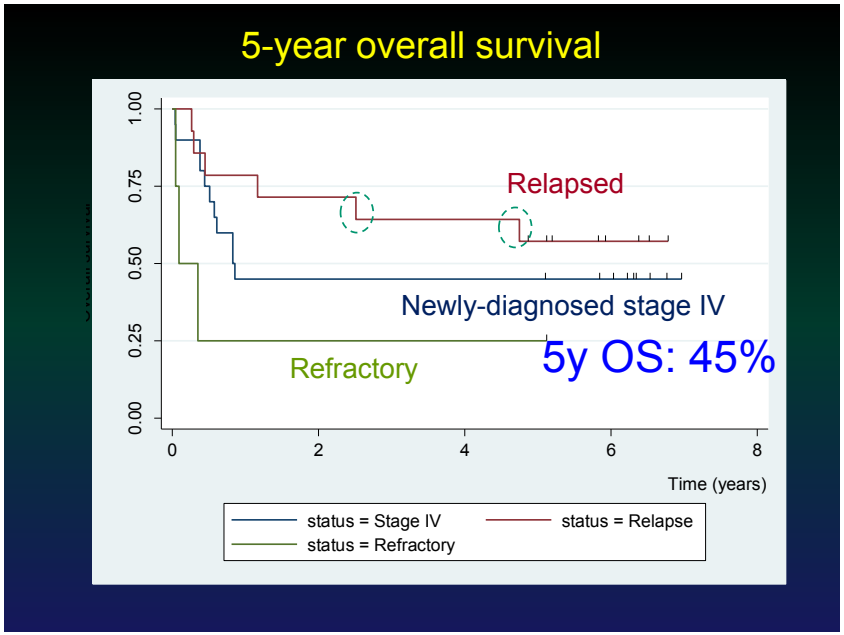
- L-asparaginase-containing chemotherapy (n = 30)
  - SMILE (n = 20)
  - Other L-asp+ chemo (n = 7) (MIPEL, HyperMAIL)
  - SMILE(-like) chemo → RT (n = 2)
  - CCRT with SMILE (n = 1)

Treatment period	2000 - 2004	2005 - 2009	2010 - 2013
L-asp-containing chemo.	17%	18%	32%

cf. SMILE-P2 *J Clin Oncol 2011*

SMILE chemotherapy for newly diagnosed stage IV disease

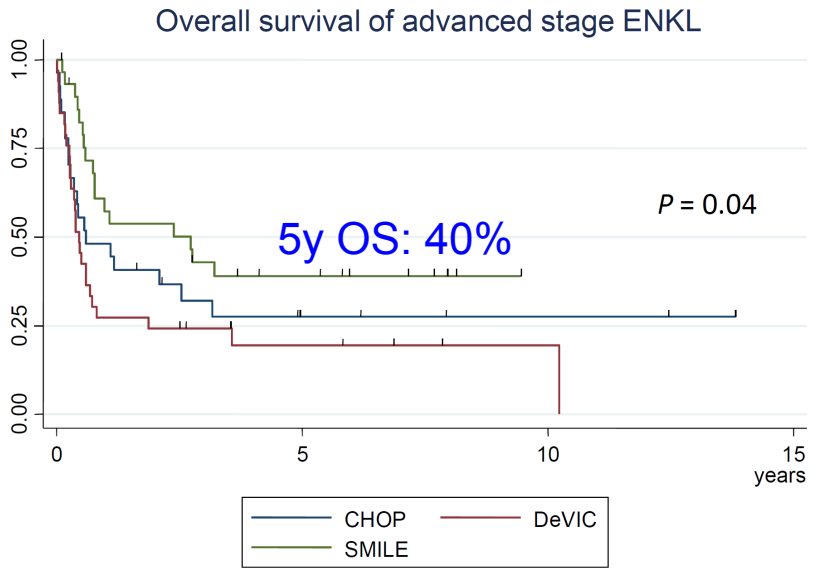
SMILE-P2



Suzuki R, et al. 13-ICML, 2015

- n = 20
- Protocol treatment: 2 cycles
- G3/4 infection 61%
- G3/4 abnormal liver test 58%
- TRD (n = 2) infection

NKEA Part A



Suzuki R, et al. EHA2016

- n = 13
- Median No. of cycles: 2
- G3/4 abnormal liver test 46%
- Febrile neutropenia 15%
- TRD (n = 1) pancreatitis

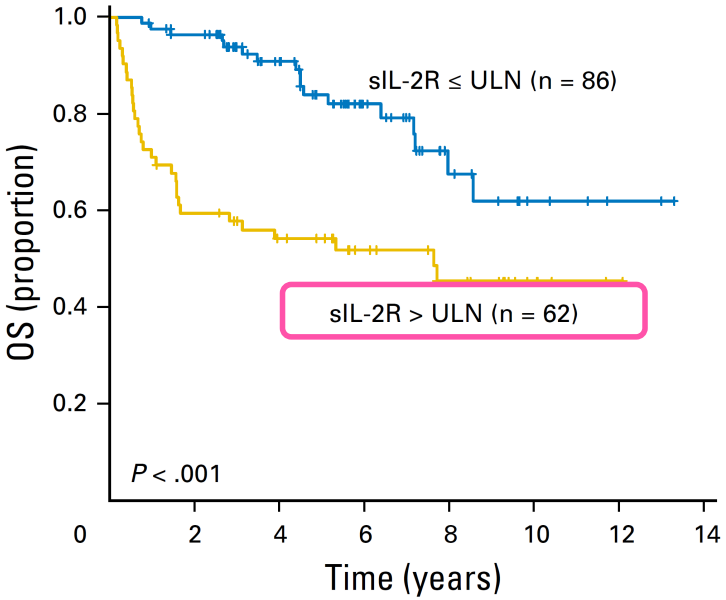
NK/T-cell lymphoma: SMILE and other “asparaginase” containing regimens - Experience in Japan

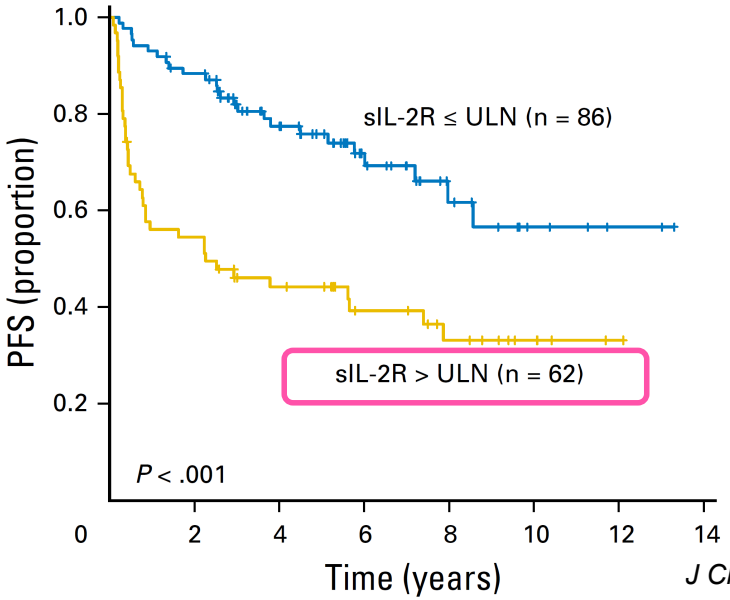
- L-asparaginase in the management of NK/T-cell lymphoma in Japan

- **Unmet medical needs in the treatment of NK/T-cell lymphoma in Japan**

Multivariate analysis of factors affect on survival (RT-DeVIC, n = 145)

Variable	OS						PFS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
LDH > ULN	1.47	0.80 - 2.72	0.22	-	-	-	1.65	0.97 - 2.80	0.063	1.21	0.70 - 2.11	0.49
ECOG PS >1	3.86	1.80 - 8.29	< 0.001	2.24	0.99 - 5.07	0.052	3.03	1.43 - 6.40	0.0037	1.86	0.83 - 4.16	0.13
Regional LN invol.	2.02	1.10 - 3.69	0.023	1.81	0.99 - 3.33	0.055	1.54	0.88 - 2.70	0.13	-	-	-
Hb < 11 g/dL	2.83	1.40 - 5.70	0.0037	2.05	0.98 - 4.29	0.057	2.14	1.11 - 4.11	0.023	1.49	0.74 - 2.99	0.26
CRP > ULN	2.09	1.13 - 3.87	0.019	1.39	0.71 - 2.72	0.34	1.71	1.01 - 2.89	0.044	1.12	0.63 - 2.00	0.69
sIL-2R > ULN	2.99	1.65 - 5.44	< 0.001	2.28	1.24 - 4.23	0.008	2.95	1.76 - 4.94	< 0.001	2.46	1.42 - 4.28	0.0014





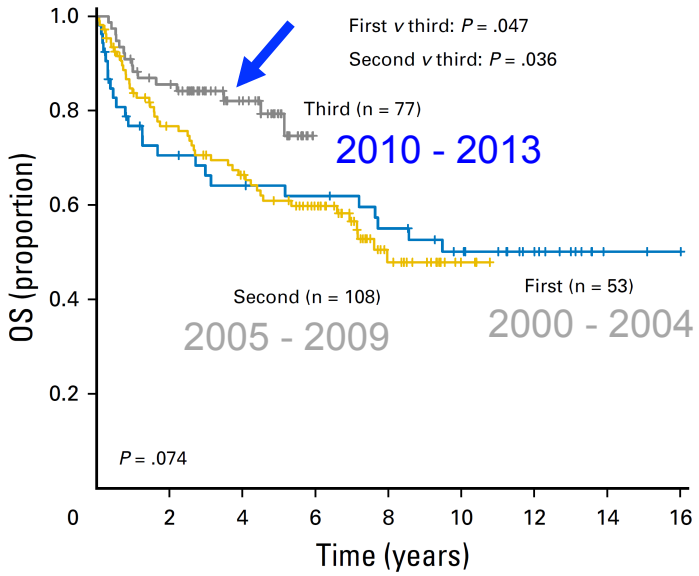
J Clin Oncol 2017

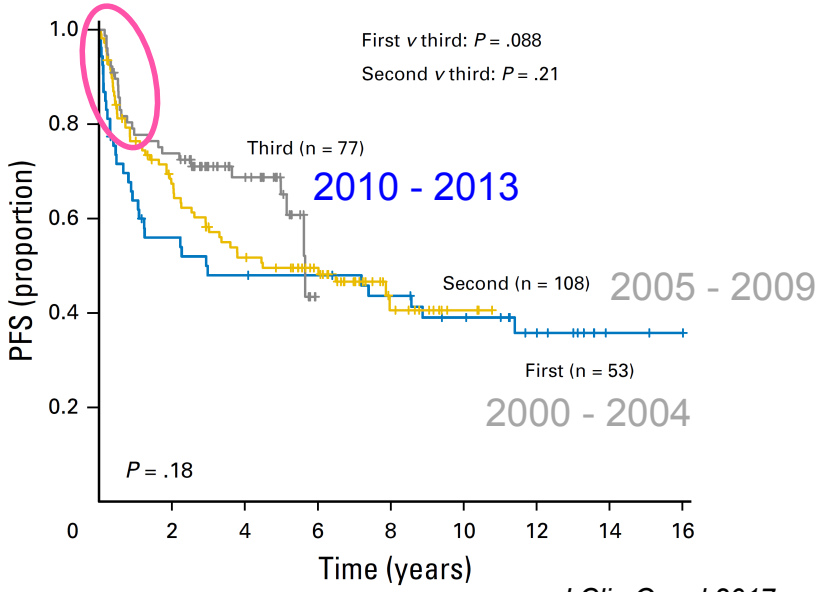
Elevated sIL-2R identify patients who have unmet medical needs.

Survival of patients with NKTCL in clinical practice

- Med. f/u in the third era: 4.3 years

Localized NKTCL (n = 238)

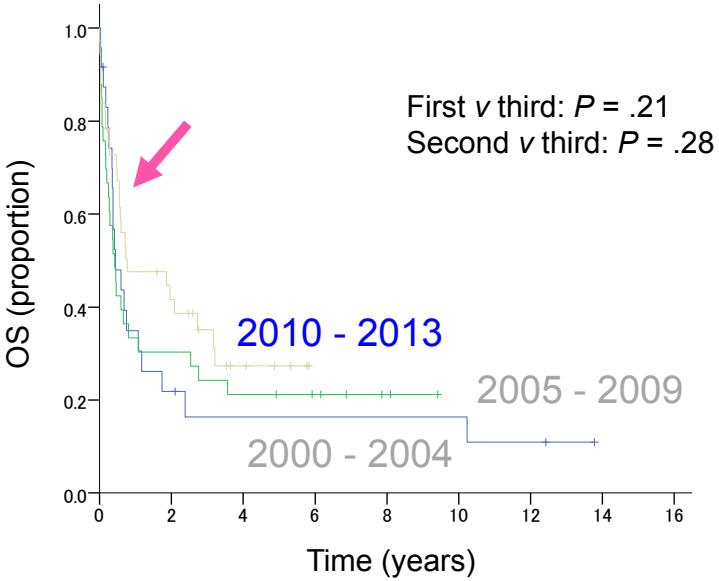


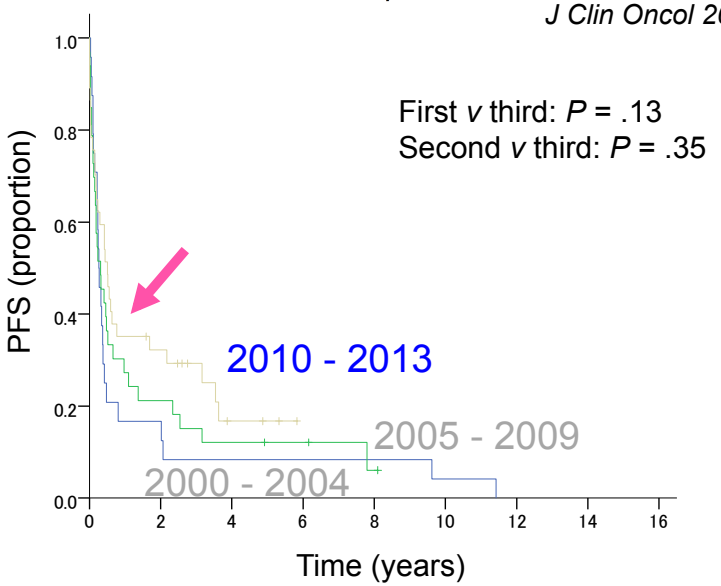


J Clin Oncol 2017

Advanced NKTCL (n = 94)

Unmet medical needs





NKEA "Part B & C"

Objectives:

- To elucidate clinical features of patients with newly diagnosed localized nasal NKTCL who experienced early disease progression after receiving CCRT

Eligibility Criteria (NKEA Part A):

(1) Biopsy-proven NKTCL (WHO 2008)

(2) Diagnosed between 2000 and 2013

(3) No restriction of availability of clinical information

Eligibility Criteria (This Study):

1. Nasal NKTCL

2. Stage IE or contiguous stage IIE (No distant LN involvement)

3. Patients received CCRT as first-line therapy

Definition of Early Disease Progression:

- Progression of disease within 2 years after diagnosis (POD24)

  National LymphoCare Study. Casulo C, et al. JCO 2015

- Patients who were lost to follow-up or dead without POD24 were excluded.

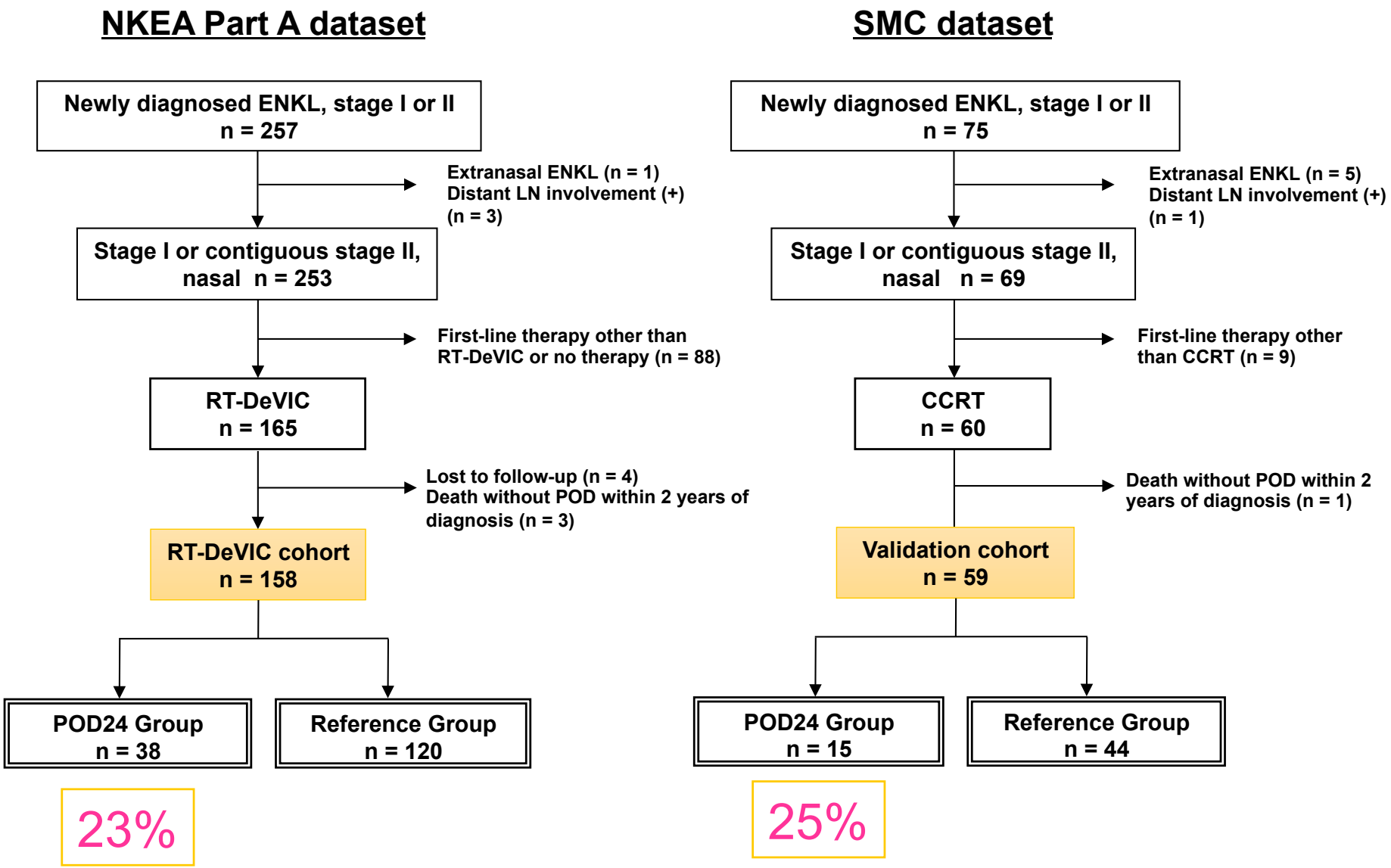
Collaborators:

- JROSG
- Samsung Medical Center (Part C)

SAMSUNG MEDICAL CENTER

✓ CCRT
✓ Long-term follow-up

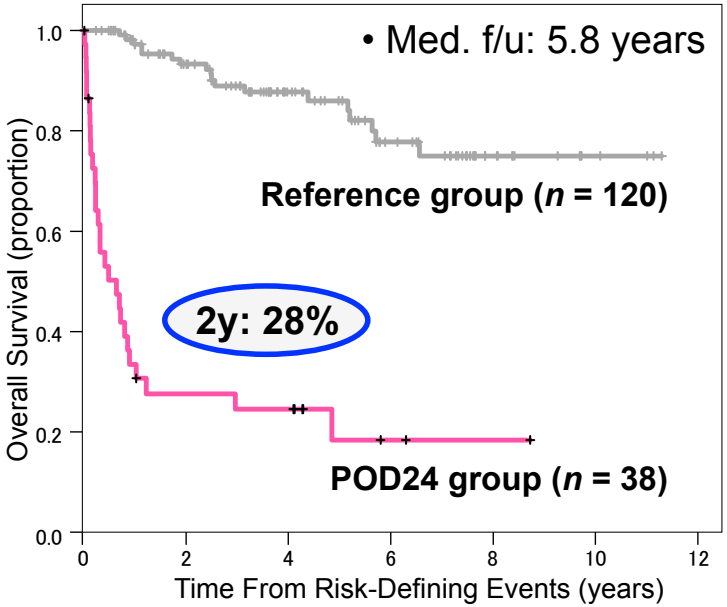
Consort diagrams



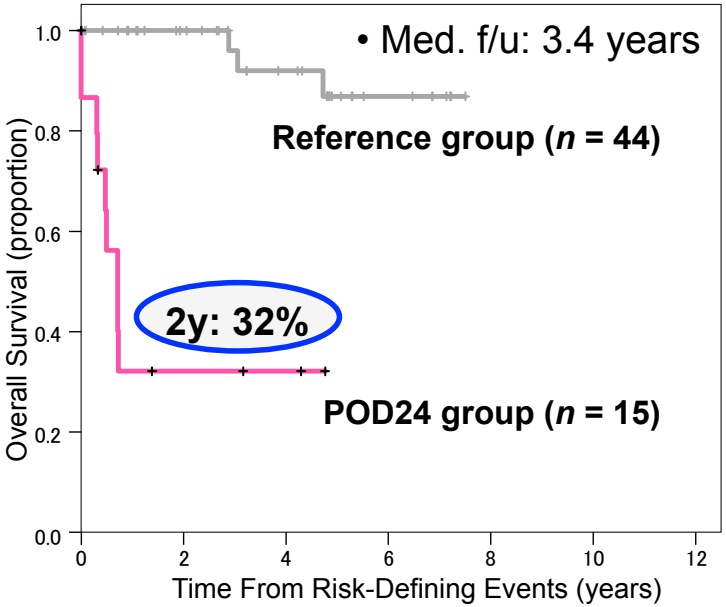
Yamaguchi M, Suzuki R, Kim SJ, et al. Cancer Sci 2018

Impact of early disease progression on subsequent OS

RT-DeVIC cohort



Validation cohort (SMC)



POD24 was associated with markedly reduced subsequent OS compared with the reference group.

Patients who experienced POD24 have great unmet needs in the treatment of NKTCL.

Yamaguchi M, Suzuki R, Kim SJ, et al. Cancer Sci 2018

Patients' fitness for SMILE chemotherapy

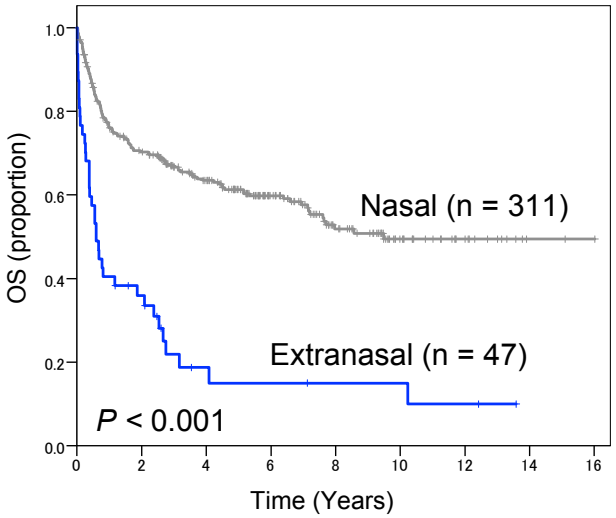
- Major inclusion criteria of SMILE-P2
  - Age: 15 - 69 years
  - ECOG PS: 0 - 2
  - WBC ≥ 3,000 /μL, Ly count ≥ 500 /μL, PLT ≥ 75 x 10^9 /L
    (or ≥ 50 x 10^9 /L in patients with BM involvement and/or HPS)
  - No serious complications

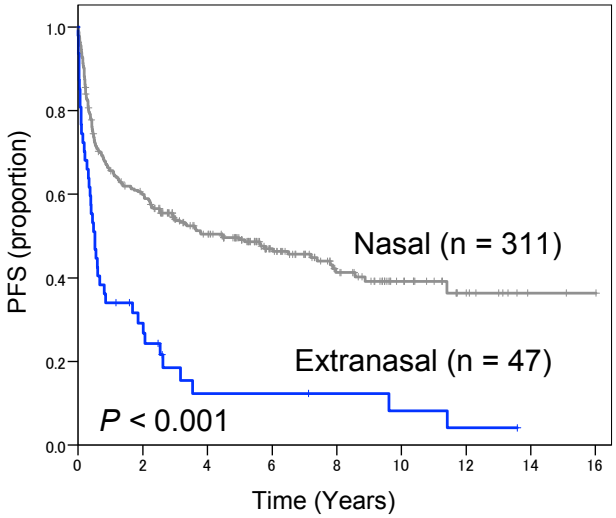
- Analysis using the NKEA Part A dataset

Subgroup	Fit	Unfit	*P* (vs. extranasal NKTCL)
	No. (%)	No. (%)	
Nasal NKTCL (n = 311)	188 (60)	123 (40)	< 0.001
Advanced nasal NKTCL (n = 60)	23 (38)	37 (62)	0.091
Extranasal NKTCL (n = 47)	10 (21)	37 (79)	-

Yamaguchi M, et al. ASH2017, #1518

No improvement of prognosis in extranasal NKTCL



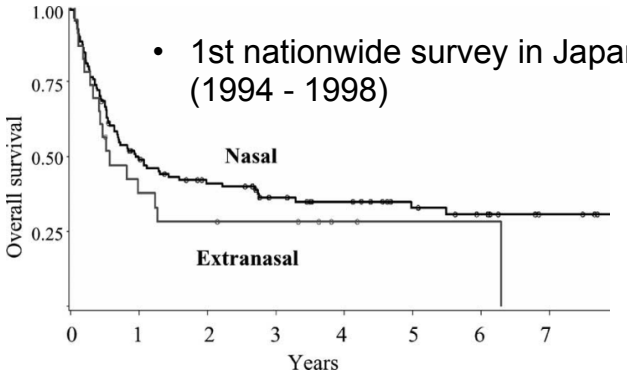


- Median follow-up: 5.8 years

- 2-year OS
  - Nasal NKTCL: 70% (95% CI, 65 - 75%) > H_0 (< 50%)
  - Extranasal NKTCL: 36% (95% CI, 23 - 49%) *cf.* H_0 : < 30%

Patients with extranasal NKTCL have great unmet medical needs.

Yamaguchi M, et al. ASH2017, #1518



- 1st nationwide survey in Japan (1994 - 1998)

Oshimi K, et al. Hematology 2005

NK/T-cell lymphoma: SMILE and other "asparaginase" containing regimens - Experience in Japan - Summary -

- L-asparaginase in the treatment of NKTCL in Japan
  - Usually used as a component of SMILE chemotherapy
  - SMILE chemotherapy → manageable toxicity in fit patients

- Prognosis of patients with localized NKTCL: improved

- NKEA study revealed unmet medical needs in the treatment of NKTCL
  - Advanced NKTCL, extranasal NKTCL
  - Localized NKTCL, RT-DeVIC: elevated sIL-2R, POD24
  - (a risk of CNS relapse)

    → May be candidates for a clinical trial of a new agent

- International cooperation utilizing the advantages of each country/region will advance the development of new treatments for NKTCL

NKEA

Ritsuro Suzuki
Masahiko Oguchi
Naoko Asano
Kana Miyazaki
Naoyuki Katayama

Seok Jin Kim
Young-Hyeh Ko
Won Seog Kim

SAMSUNG MEDICAL CENTER

JROSG
Japanese Radiation Oncology Study Group

Tohoku University, Akita University, Gunma University, Saitama Cancer Center,
International Medical Center-Saitama Medical University, National Cancer Center Hospital,
Showa University, Cancer Institute Hospital, Yokohama City University Hospital,
Kanagawa Cancer Center, Tokai University, Niigata University, Kanazawa Medical University,
Shinshu University, Nagaoka Red Cross Hospital, Nagoya University, Nagoya City University,
Toyota Kosei Hospital, Mie University, Shiga Medical Center for Adults,
Kyoto Daini Red Cross Hospital, Kobe University, Hyogo Cancer Center, Nara Medical University,
Tottori Prefectural Central Hospital, Shimane University, Kurashiki Central Hospital,
Kawasaki Medical University, Kyushu Cancer Center, Saga University, Kumamoto City Hospital,
and Samsung Medical Center

JCOG-LSG

JCOG
Japan Clinical Oncology Group

NK-cell Tumor Study Group

NKTSG
NK-cell Tumor Study Group

Department of Hematology and Oncology
Mie University Graduate School of Medicine