P-Gemox and Beyond

Longterm outcomt of Newly diagosed and relaposed/refratory NKTCL

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Background

1. NK/TCL is the most common ,aggressive subtype T cell lymphoma in China, account for 6% among NHLs
2. Radiotherapy (extensive involved field radiotherapy) is major effective approach for stage I/II NKTCL , While approximately 25-40% patients fail locally or systemically treated by RT alone
3. Chemotherapy may improve efficacy of RT for NK/TCL. Concurrent or sequential CT and RT is frequently administered.
4. SMILE , AspaMetDex and P-Gemox are most effective and frequently administered combination recommended by NCCN guidedline. Long term surivival is still poor.
5. ASCT consolidation may be benefficial for advanced or chemosensitive relapsed cases
6. Novel agents is urgently needed.

1.Ishida F, et al. Expert Rev Hematol, 2010,3(5). 2.Kluin PM, et al. Histopathology. 2001 Mar. 3.Chim CS, et al. Blood 2004;103. 4.Kwong YL,et al. J cline EXP hematop, 2011, 51(1). 5.Tse E,et al. Blood. 2013 Jun 20

Contents

1. Longterm results of NKTCL treated by P-Gemox, real world data，from 10 Chinese hospital

2. Phase II trial of Chidamide monotherapy for relpased or refractory NKTCL

Clinical Characteristics, n=216

	No. of Patients	Percent
No. of Patients	216	
Sex		
Male	147	68.1%
Female	69	31.9%
Age, years		
Median	41	
Range	17-79	
<60y	191	88.4%
⩾60y	25	11.6%
Baseline chemotherapy status		
Newly diagnosed	167	77.8%
Refractory†	28	13.0%
Relapsed‡	21	9.7%
Median time from last therapy to initiation of this trial (m)	7.0(1.1-68.8)	
Response to last chemotherapy		
CR		
PR		
SD		
PD		
ECOG Performance Status		
0-1	213	98.6%
>1	3	1.4%
B symptom		
Absent	95	44.0%
Present	115	53.2%
Unknown	6	2.8%
Ann Arbor Stage		
I	89	41.2%
II	59	27.3%
III-IV	68	31.5%
Primary lesion		
UAT-NKTCL	141	65.3%
NUAT-NKTCL	75	34.7%

Serum LDH		
Normal	137	63.4%
Elevated	77	35.6%
Unknown	2	0.09%
Bone Marrow Involvement		
Yes	16	7.4%
No	200	92.6%
Local lymph node invasion		
Yes	101	46.8%
No	14	53.2%
Ki67%		
<50%	68	31.5%
⩾50%	130	60.2%
Unknown	18	8.3%
Distant lymph node invasion		
Yes	39	18.1%
No	177	81.9%
Bulky disease		
Yes	7	3.2%
No	209	96.8%
Serum Epstein-Barr virus DNA		
Positive€	129	59.7%
Negative	59	27.3%
Unknown	28	13.0%
C reactive protein level		
Normal	128	59.3%
Elevated	86	39.8%
Unknown	2	0.09%

Clinical Characteristics, n=216

PINK risk category		
Low risk (0-1)	148	68.6%
Intermediate risk (2)	27	12.5%
High risk (3)	41	29%
PINK-E risk category		
Low risk (0-1)	121	56.0%
Intermediate risk (2)	17	7.9%
High risk (3-4)	52	24.1%
Unknown	25	13.0%
Treatment		
Chemo→radio	86	39.8%
Concurrent	1	0.05%
Sandwich	36	16.7%
Radio→chemo	2	0.09%
No radio	91	42.1%
Treatment Regimens		
Initial therapy		
Asparaginase-contained regimen		
Median number of regimen		
Radiotherapy		
ASCT in CR1		
ASCT in CR2		

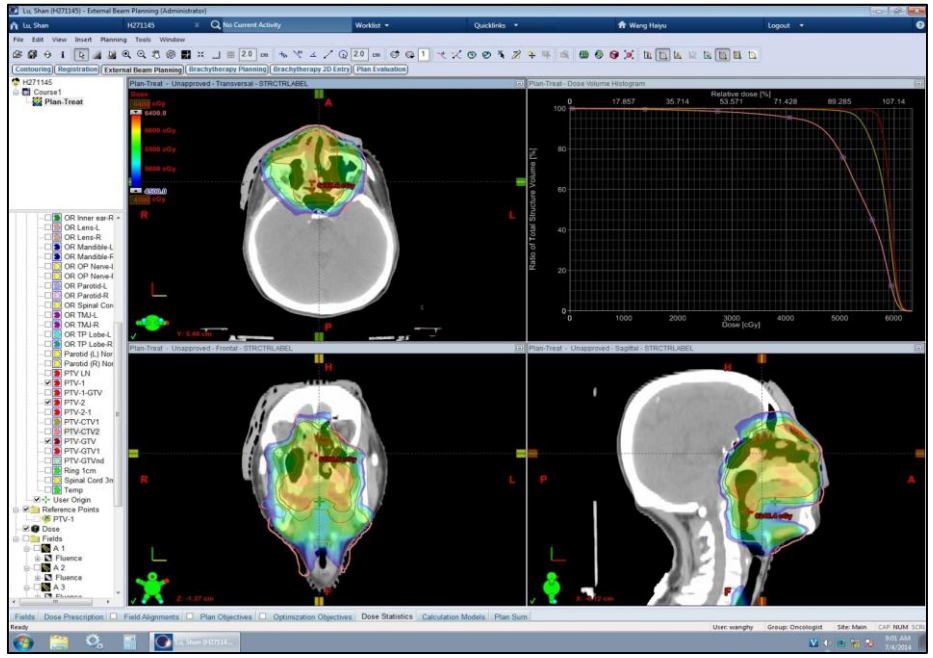
P-Gemox and EIFRT

P-Gemox

- Gemcitabine 1000 mg/m^2 , d1,8,
- Oxaliplatin 130 mg/m^2 , d1,8
- Pegaspargase 2000U/m^2 im d1

1. Pegaspargase and Oxaliplatin: Jiangsu HengRui Medicine Co.LTD
2. Gemcitabine: Hanson Pharmaceutical Co.ltd

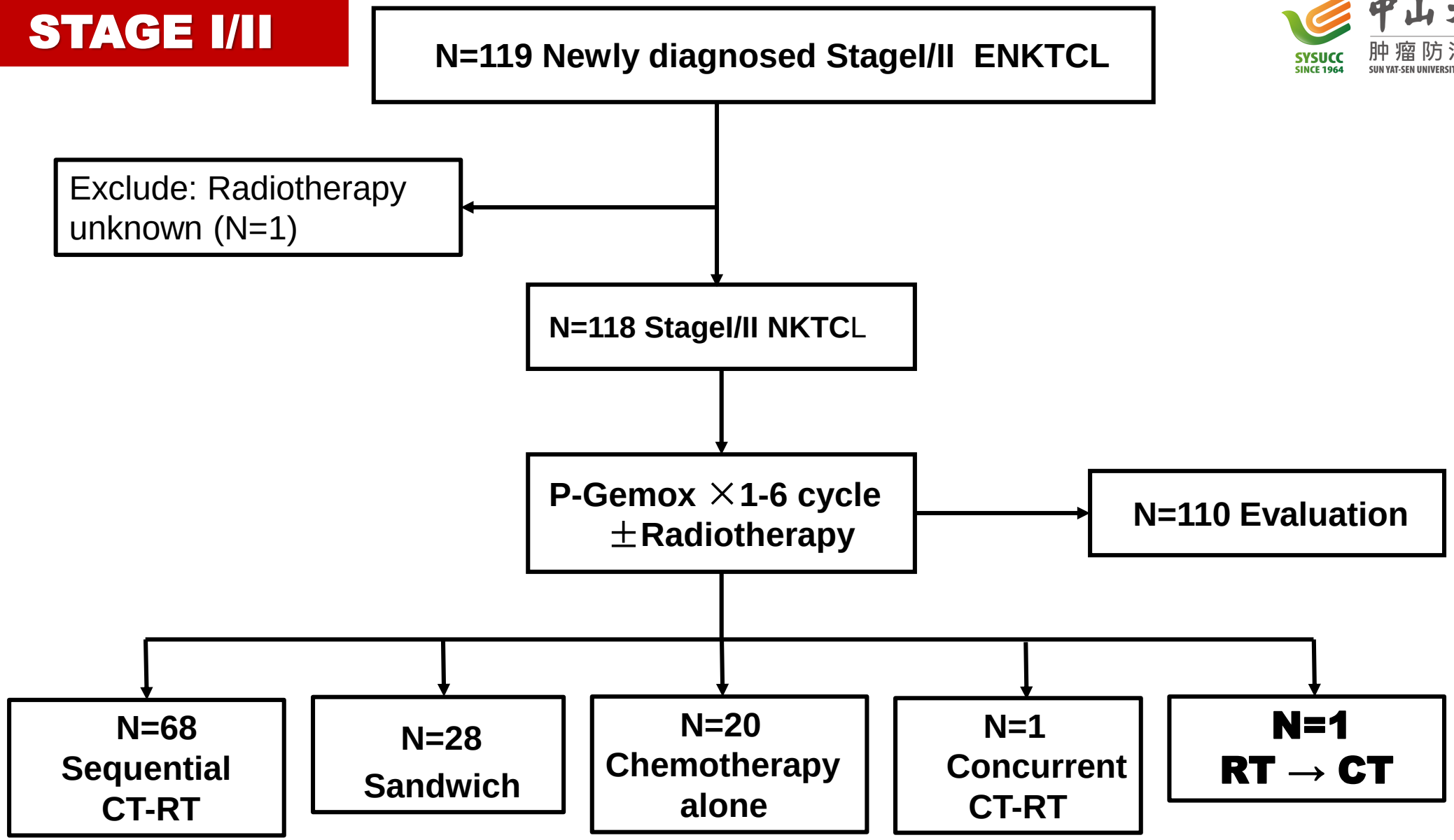
Extensive involved-field Radiotherapy for NK/TCL , EIFRT, RT> 50 Gy

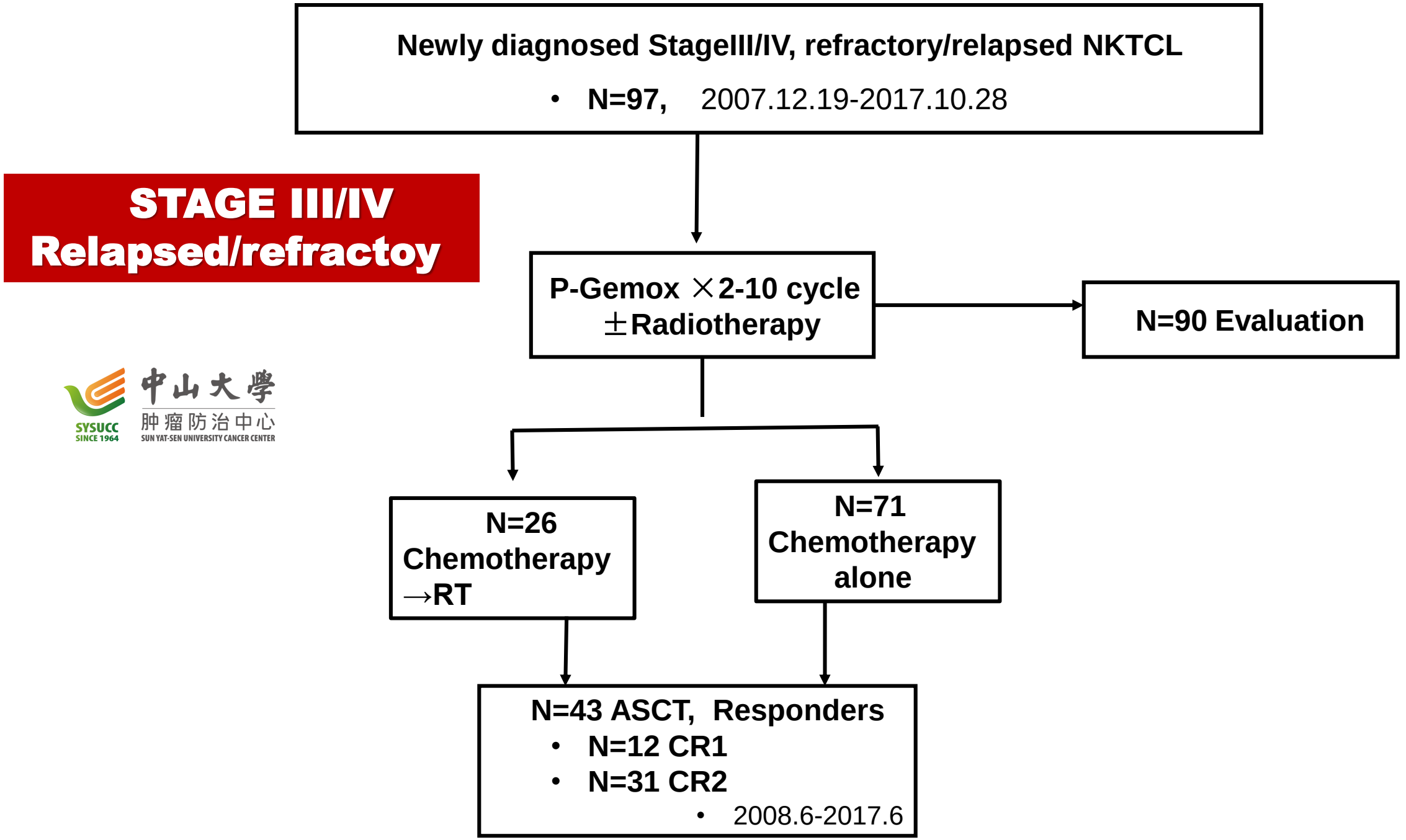


EIFRT Alone for stage I

1. without B Symtom
2. without local extention
3. EBV-DAN negative

STAGE I/II


N=119 Newly diagnosed StageI/II ENKTCL
Exclude: Radiotherapy unknown (N=1)
N=118 StageI/II NKTCL
P-Gemox ×1-6 cycle ±Radiotherapy
N=110 Evaluation
N=68 Sequential CT-RT
N=28 Sandwich
N=20 Chemotherapy alone
N=1 Concurrent CT-RT
N=1 RT → CT


Newly diagnosed StageIII/IV, refractory/relapsed NKTCL
• N=97, 2007.12.19-2017.10.28
STAGE III/IV
Relapsed/refractoy
P-Gemox ×2-10 cycle
±Radiotherapy
N=90 Evaluation
N=26
Chemotherapy
→RT
N=71
Chemotherapy
alone
N=43 ASCT, Responders
• N=12 CR1
• N=31 CR2
• 2008.6-2017.6

Objective Response rate, P-Gemox

（ N=216, 201 evaluable ）

	CR+PR	CR	SD	PD	NA
Newly diagnosed (n=167)	89.8%（150）	61.1%(102)	2.4%(4)	2.4%(4)	5.4%(9)
Refractory (n=28)	50%（14）	25.0%(7)	17.9%(5)	10.7%(3)	21.4%(6)
Relapsed (n=21)	71.4% (15)	61.9%(13)	0	28.6%(6)	0

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Objective Response rate, P-Gemox

（Newly diagnosed NKTCL, n=167， 158 evaluable）

	CR+PR	CR	SD	PD	NA
Stage I,(n=68)	86.8%(59)	70.6%(48)	0(0)	2.9%(2)	10.3%(7)
Stage II, (n=51)	92.1% (47)	58.8%(30)	3.9%(2)	2.0%(1)	2.0%(1)
Stage III/IV, (n=48)	91.7%(44)	50.0%(24)	4.2%(2)	2.1%(1)	2.1%(1)

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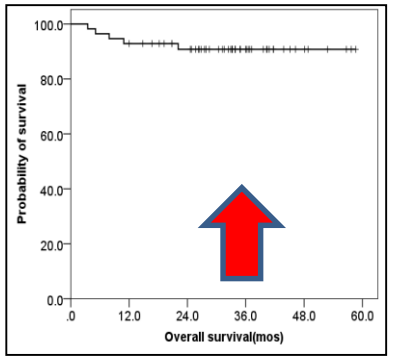
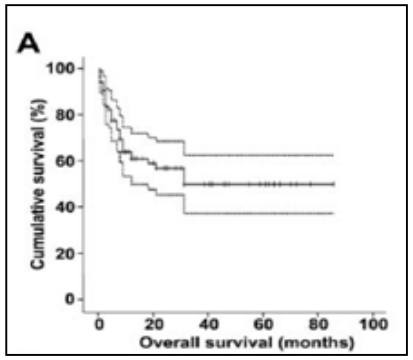
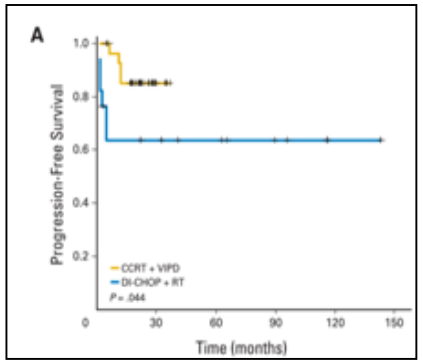
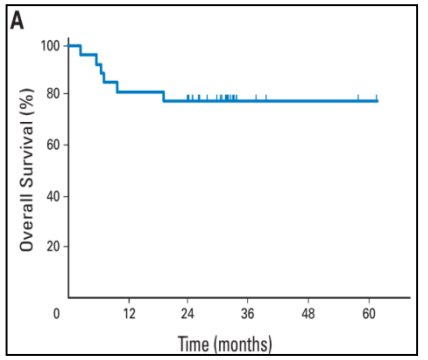
stage I/II NKTCL :
systemic chemotherapy and radiotherapy， OS









sequential CT-RT

Concurrent CT-RT

P-GEMOX

N= 56

4y OS:

90.7±4.0%

SMILE

N=87

5y OS

47.4±18.4%

VIPD-RT

N= 30

2 y OS 86.3%

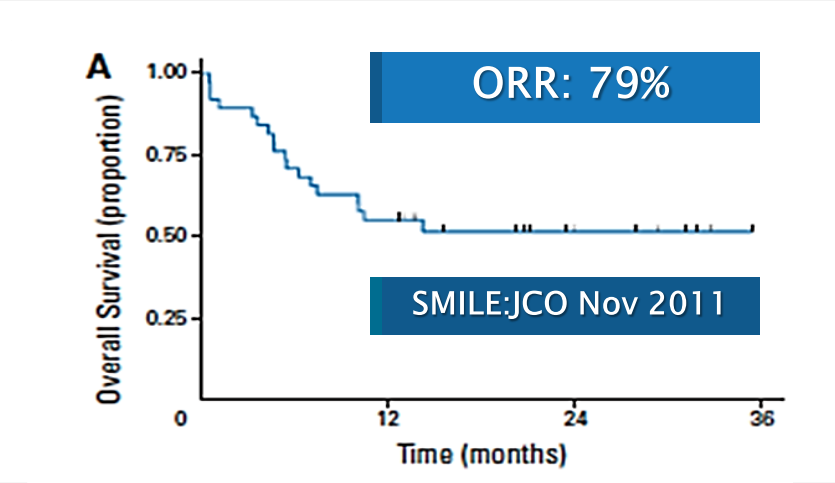
DeVIC-RT

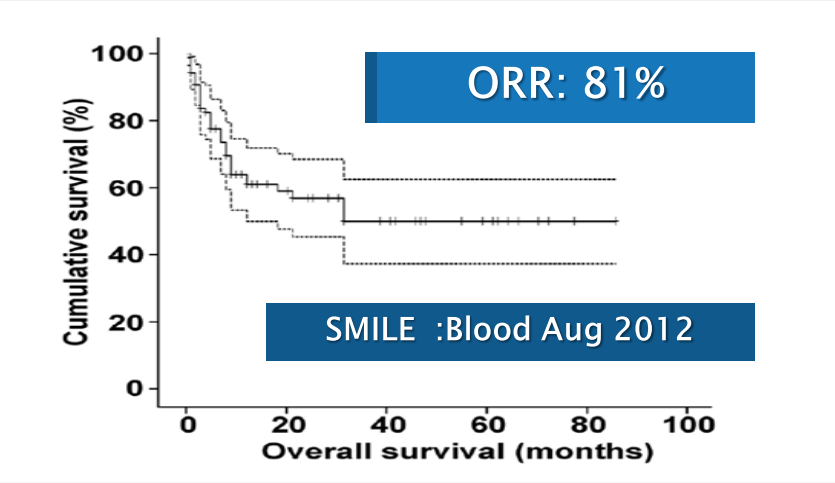
N= 27

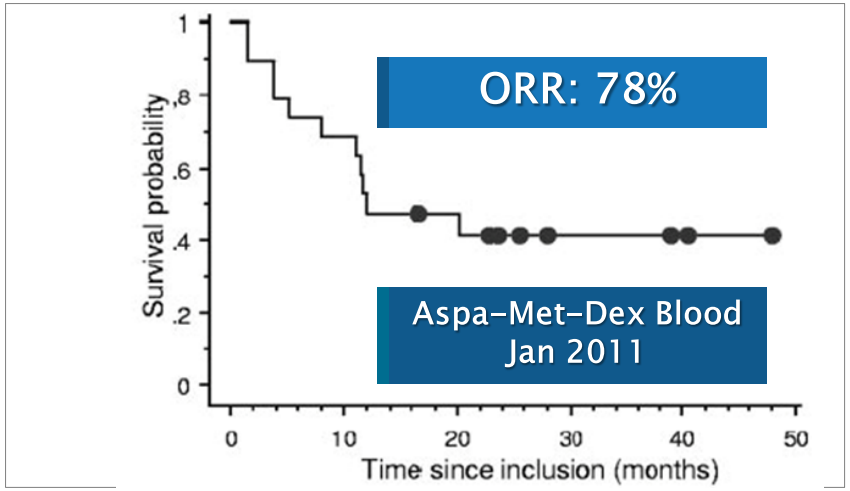
2y OS 78%

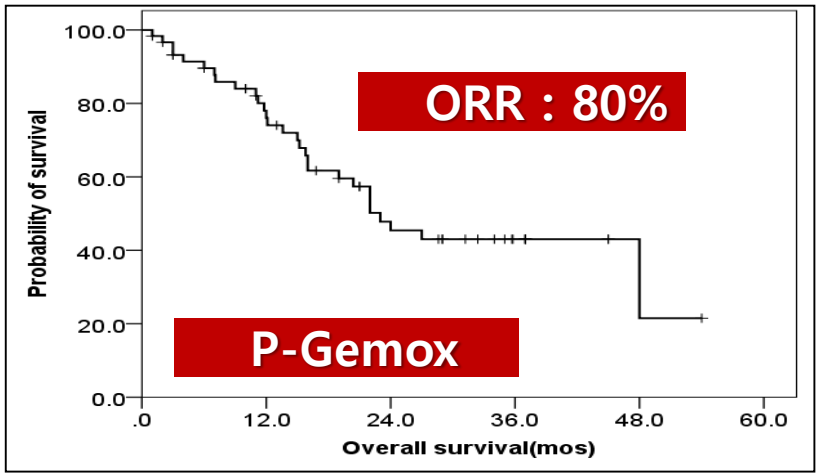
1.M Jiang,et al. Cancer. 2012 Jul 1;118. 2.YL Kwong,et al. Blood. 2012 Oct 11. 3.SJ Kim,et al. J Clin Oncol. 2009 Dec 10. 4.M Yamaguchi,et al. J Clin Oncol. 2009 Nov 20. 5.Nj Lin,et al. J Hematol Oncol. 2013 Jul 1.6.L Wang,et al. Cancer. 2013 Jan 15

Stage III/IV,relpased NK/TCL : Chemotherapy alone,OS



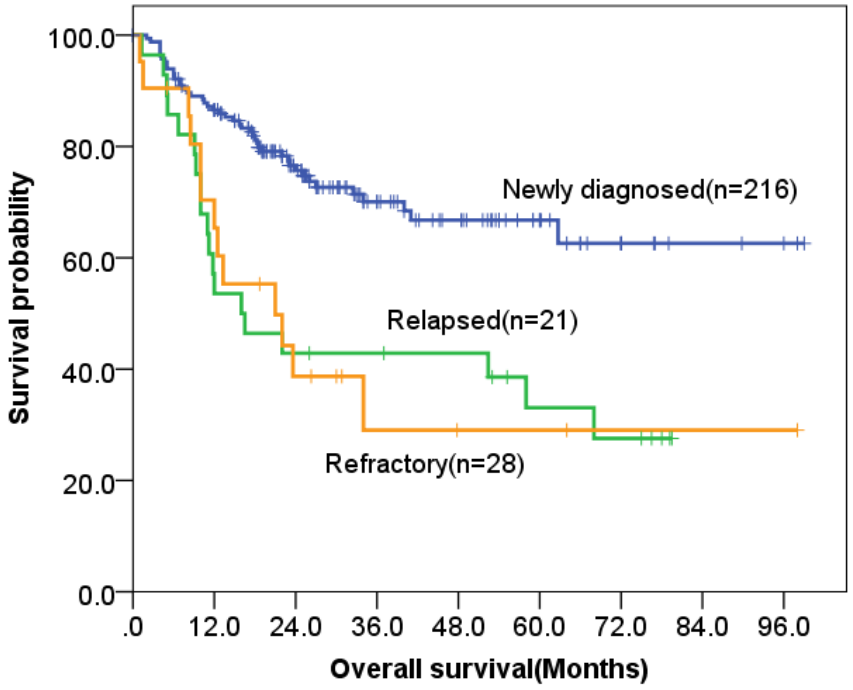






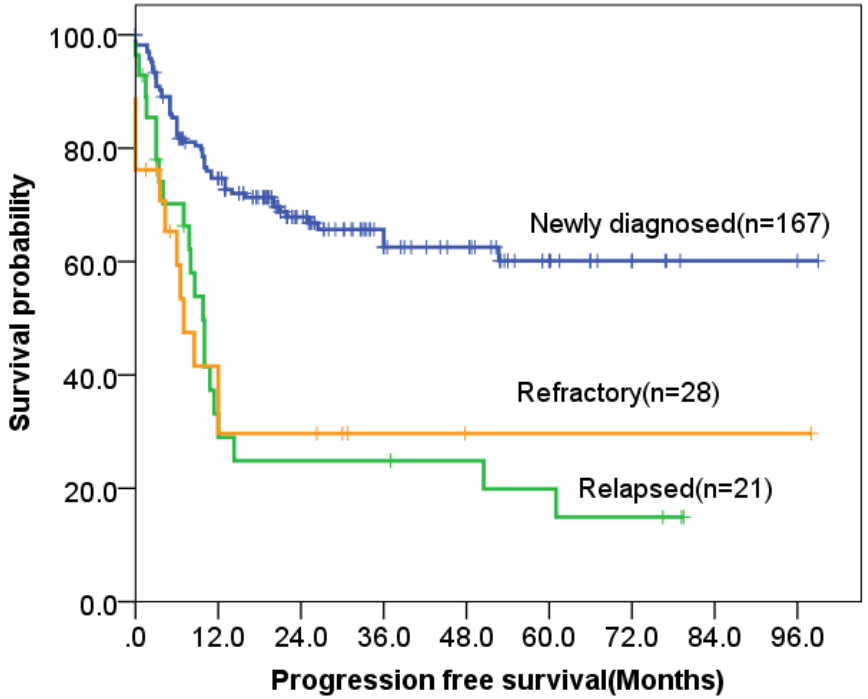
Courtesy by Jaccard A

Survival , P-Gemox



OS

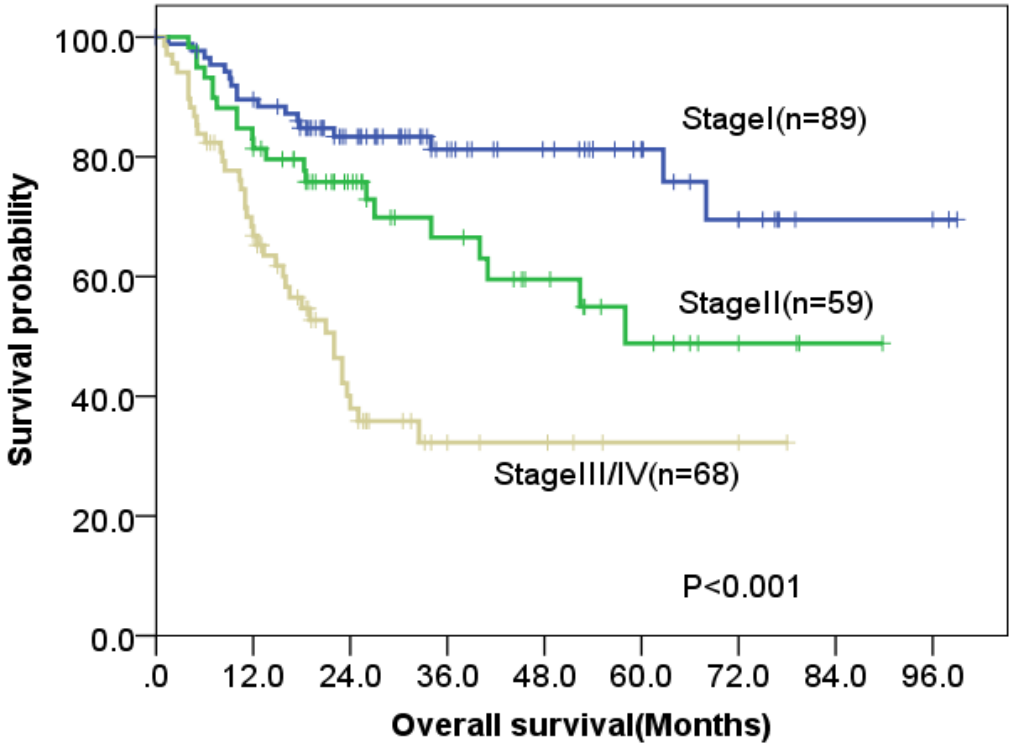
Newly diagnosed (n=167) : not reached
Refactory (n= 21): 16m
Relapsed (n= 28): 21m



PFS

Newly diagnosed: not reached
Refactory: 9.8m
Relapsed: 7m

Survival , different stage, P-Gemox

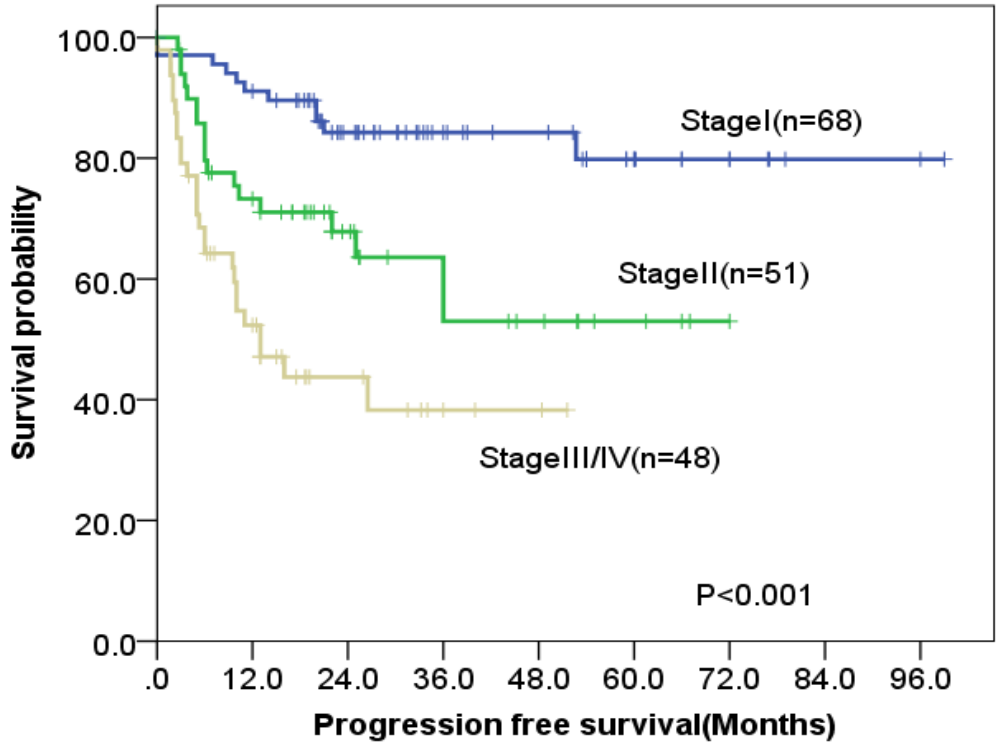


OS

StageI: not reached

StageII: 58m

StageIII/IV: 22m



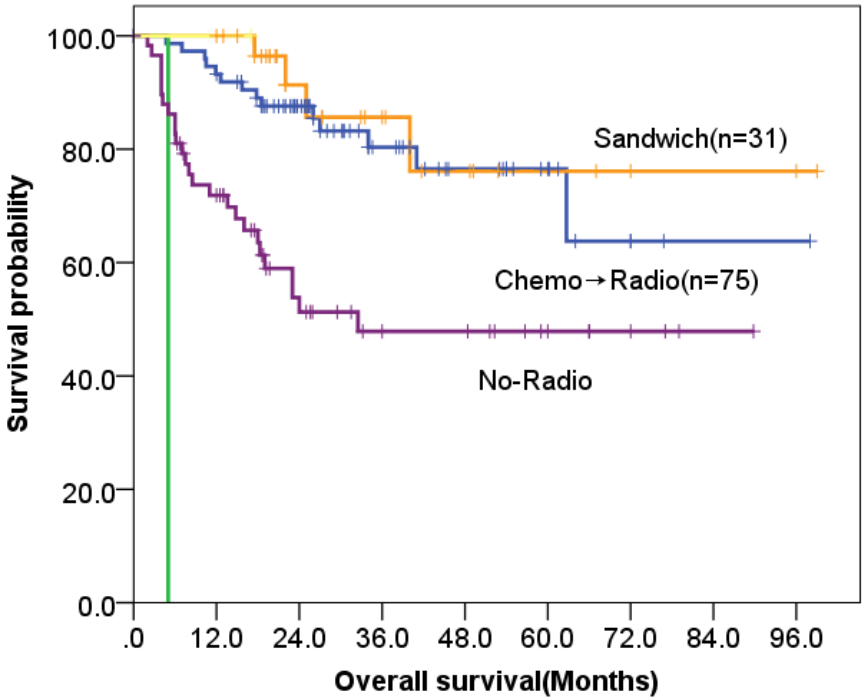
PFS,

StageI: not reached

StageII: 45.4

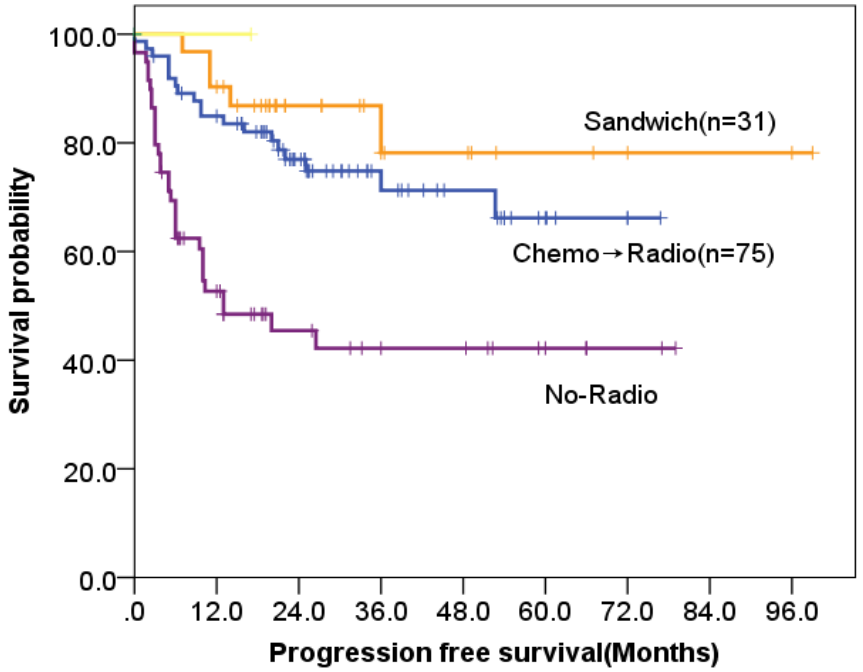
StageIII/IV: 12.4m

Survival , different sequence CT-RT , P-Gemox



OS

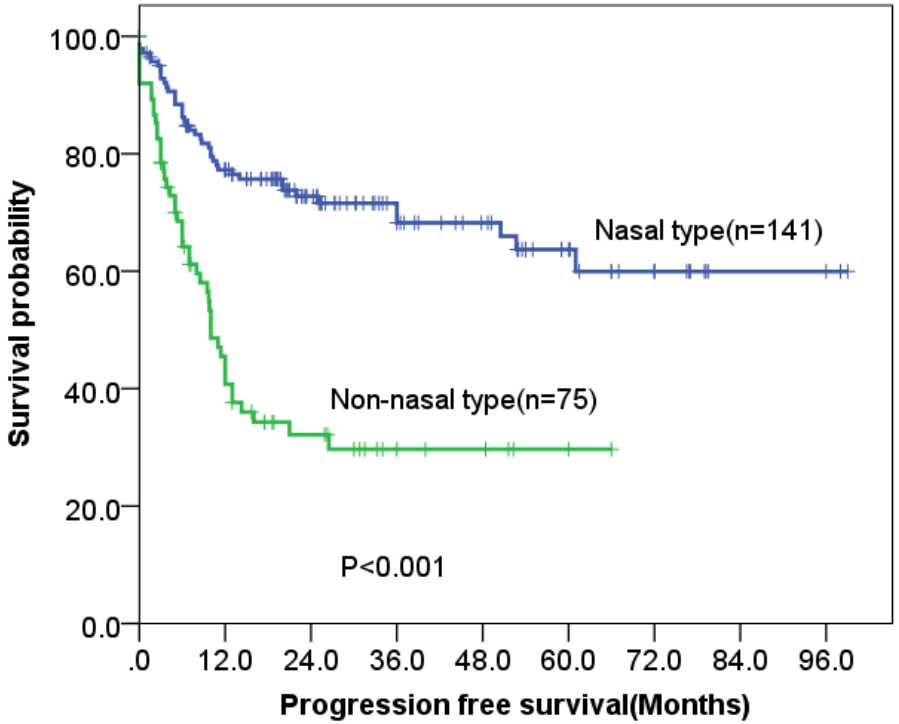
1. treatment-naive stage1/2, different CT-RT
2. P= 0.496（Sandwich vs. Chemo→Radio)

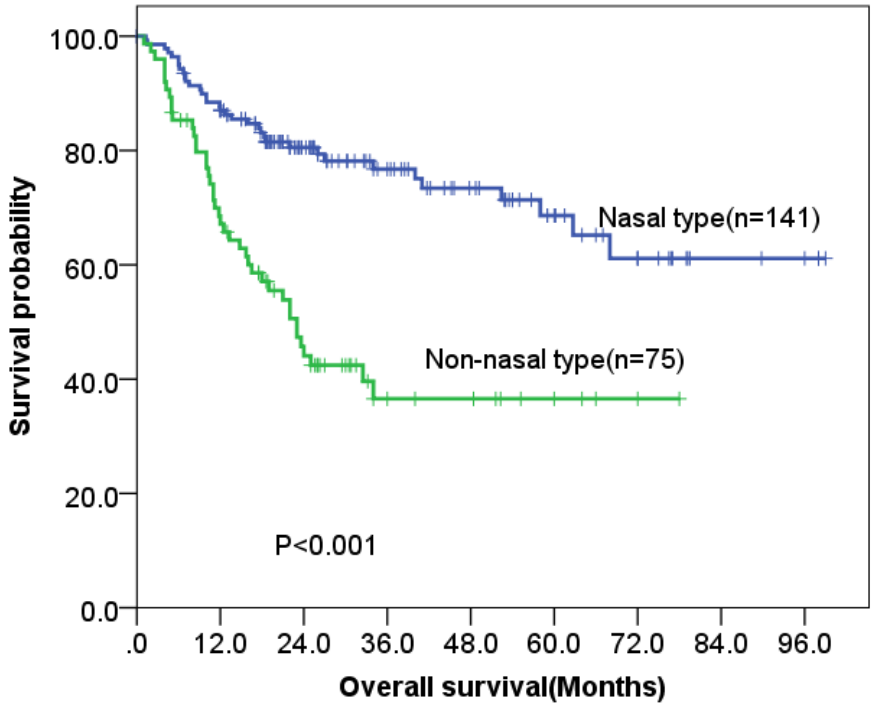


PFS

1. treatment-naive stage1/2, different CT-RT
2. P=0.307（Sandwich vs. Chemo→Radio)

Survival of Nasal type was superior to non-nasal type ,NKTCL





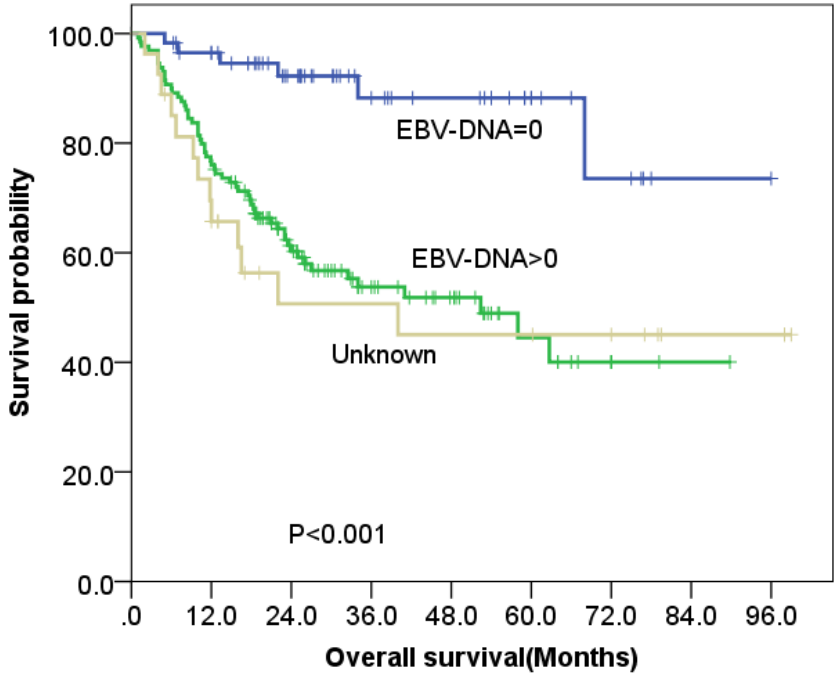
PFS

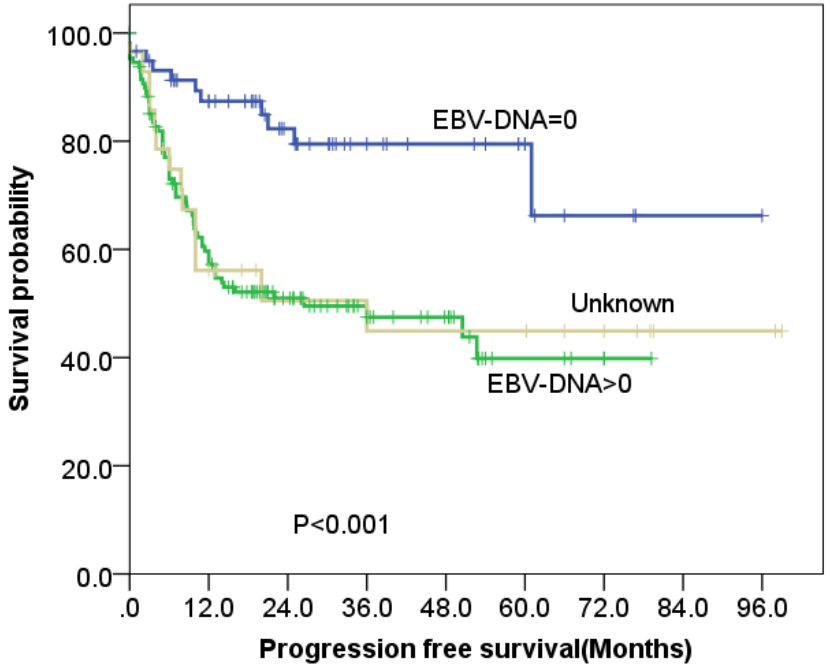
Nasal ,not reached vs. Non-nasal ,10.0 m

OS

Nasal ,not reached vs.Non-nasal 23.0m

Baseline EBV-DAN is a predicter for Survival, NKTCL





OS

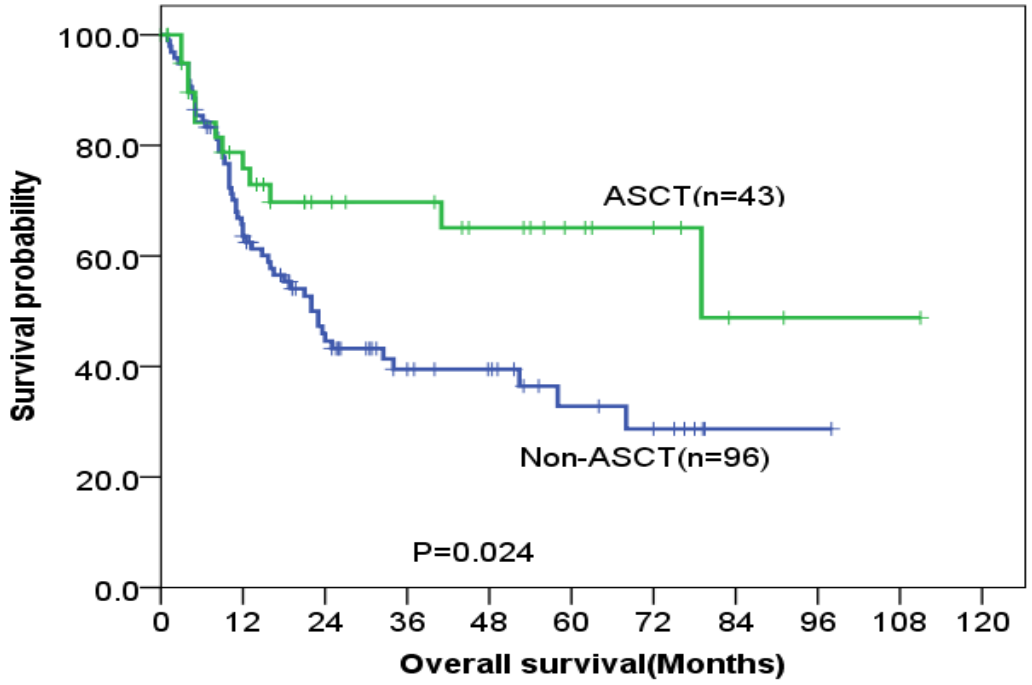
EBV-DNA=0, not reached vs.52.4 m（ EBV-DNA>0 ）VS .40.0 m (Unknown)

PFS

Not reached（EBV-DNA=0）vs.26.5m（ EBV-DNA>0 ）VS.36.0m (Unknown)

OS : ASCT consolidation

Newly diagnosed stage 3/4 and relapased and refractory NKTCL



OS：79 vs 23m

How to improve longterm outcome

Survival for the advanced and relpased is still poor !

Possible Therapeutic Option:

1. checkpoint inhibitors: PD-1
2. HDACi： Chidamide ,oral selective HDACi
3. IMIDs
4. other asparaginase-containing regimen ?

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Exporatory trial to Compare two Chidamide dosing schedule for lymphoma patients in Therapeutic Efficacy, Pharmacokinetics, Pharmacodynamics and EB Virus Reactivation

NCT 02878278

Sun Yat-sen University Cancer Center
Department of Medical Oncology,
Lymphoma Treatment and Research Center
Huiqiang Huang

Chidamide monotherapy for refactory/relapsed lymphoma

■ Inclusion Criteria:

(1) Pathologically confirmed ENKTL;

(2) relapsed or refractory ， >/=2 line previous treatment, L-ASP -based chemotherapy (including ASCT),

(3) Age 18-75 years old,

(4) ECOG 0-2;

(5) Adequate haematologic, hepatic, renal function(Hb > 9.0 g/l, ANC> 1.5×10^9, platelets > 75×10^9,TBIL ≤ 1.5 ×ULN, AST/ALT≤ 1.5 ×ULN) CR ≤ 1.5 mg/dl, CCR≥ 50 ml/min);

(6) Normal coagulation function and ECG;

(7) Prior chemotherapy and radiotherapy should have been completed >4 weeks earlier;

(8) Estimated survival ≥ 3 months.

(9) informed consent

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1. 客观疗效， Objective Response（n=29)

	NK/TCL			PTCL			B-NHL	
	30mg biw (n=5)	10mg qd (n=6)	20mg qod (n=3)	30mg biw (n=3)	10mg qd (n=5)	20mg qod (n=3)	30mg biw (n=1)	10mg qd (n=5)
CR	60%(3)	16.7%(1)	0	0%(0)	0%(0)	0(0)	0%(0)	20%(1)
ORR	80%(4)	50%(3)	33.3%(1)	67%(2)	20%(1)	0(0)	0%(0)	40%(2)
Disease Control Rate (CR+PR+SD)	80%(4)	50%(3)	100%(3)	67%(2)	40%(2)	0(0)	0%(0)	100%(5)

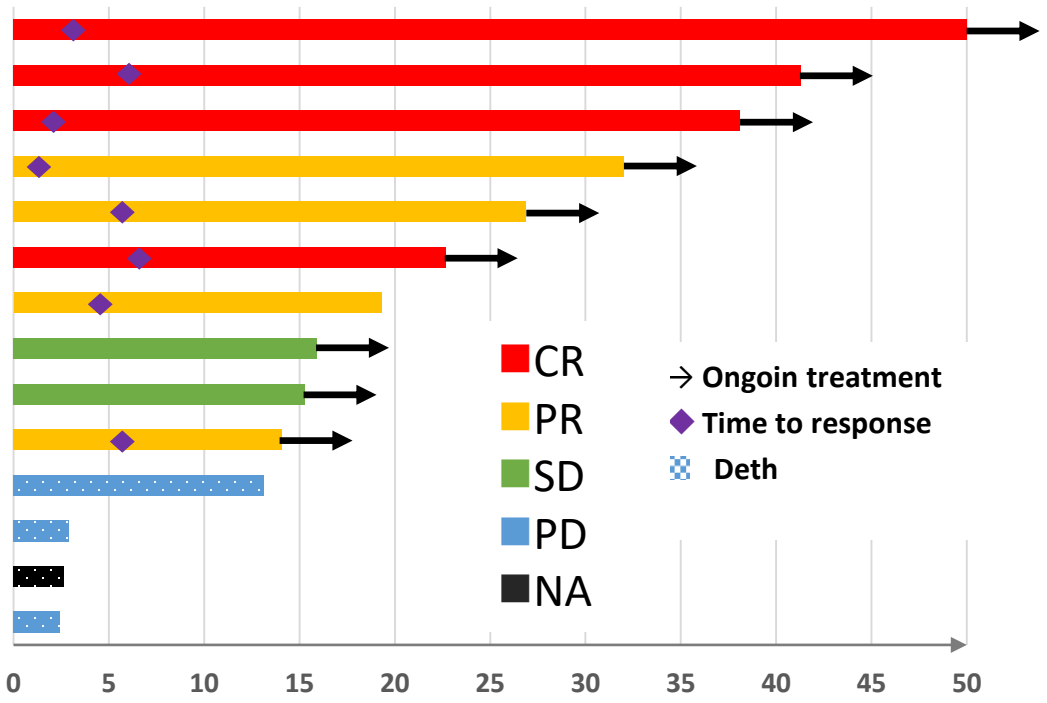
2. Objective Response（n=29)

	NK/TCL (n=14)	PTCL (n=9)	B-NHL (n=6)
CR	28.6%(4)	0%(0)	16.7%(1)
ORR	57.2%(8)	33.3%(3)	33.3%(2)
Disease Control Rate (CR+PR+SD)	71.4%(10)	44.4%(4)	83.3%(5)

- DCR: Disease Control Rate(CR+PR+SD).
- B-NHL : DLBCL3, FL1, MCL2

西达本胺，Chidamide单药

复发难治NK/T淋巴瘤(n=14)



NK/TCL (n=14)
CR 28.6%(3)
RR 57.2%(6)

Adverse Events （AEs）

	NKT(n=14)	
	I/II %(n)	III/IV %(n)
Neutropenia	42.8 (6)	50 (7)
Thrombocytopenia	50 (7)	50 (7)
Anemia	64.2 (9)	21.4 (3)
Leucopenia	50 (7)	42.8 (6)
Lymphopenia	71.4 (10)	7.1 (1)
Hypoalbuminemia	28.5 (4)	
Nasea	28.5 (4)	7.1 (1)
Vomiting	21.4 (3)	
Abdominal distension	7.1 (1)	
Loss of appetite	7.1 (1)	
Stomachache		
Diarrhea	7.1 (1)	
Inceased SGPT	50 (7)	
Increased SGOT	35.7 (5)	
Hyperbilirubinemia	7.1 (1)	
Mucositis	14.2 (2)	
Fever	7.1 (1)	7.1 (1)
Pain	7.1 (1)	
Cough	7.1 (1)	
Epistaxis	14.2 (2)	
Conspitation	7.1 (1)	
Fatigue	14.2 (2)	

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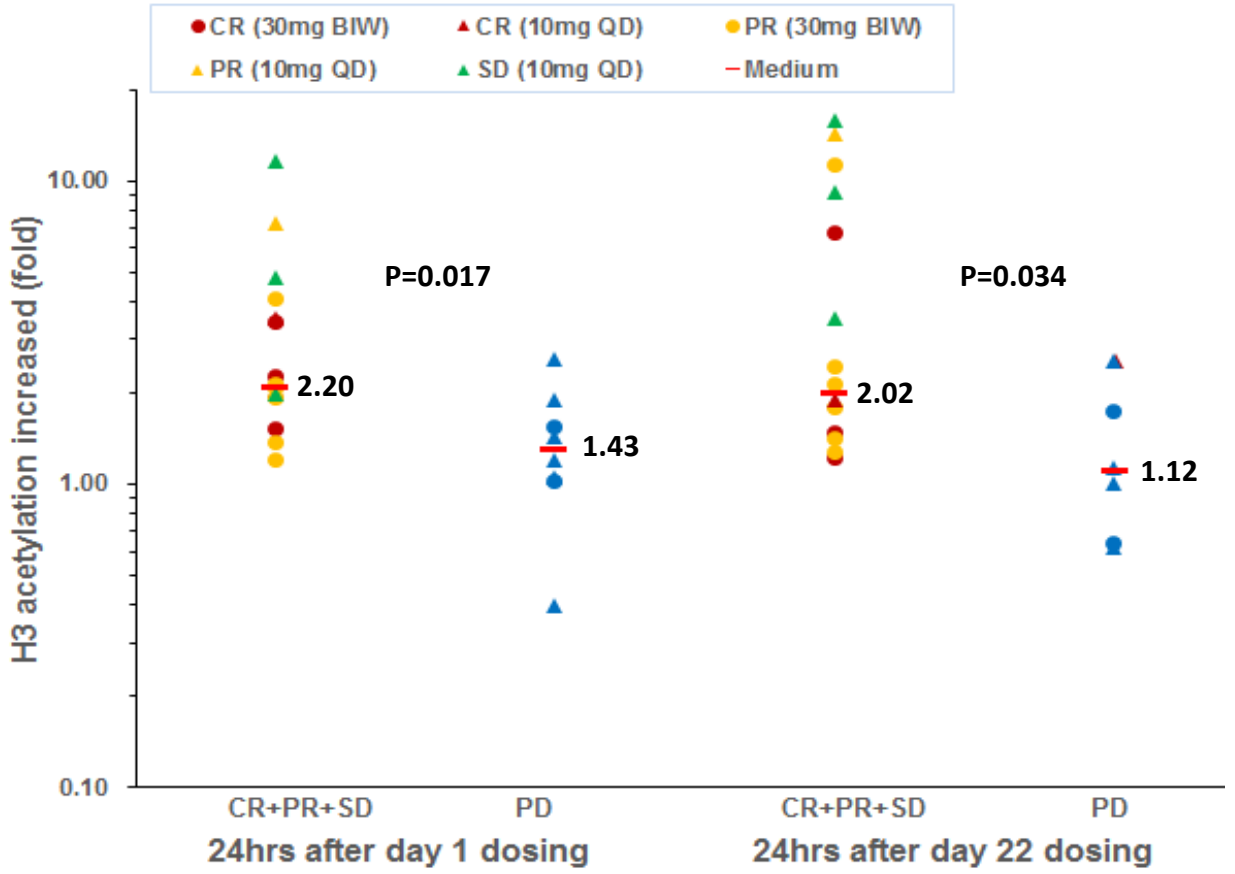
Response associated with elevated H3 acetylation level



Left 2 columns: Comparison of H3 acetylation increase after first dosing between disease controlled (CR+PR+SD, n=14) with progressed patients (PD, n=9) ;

Right 2 columns: Comparison of H3 acetylation increase after 3 weeks dosing between disease controlled (n=14) with progressed patients (n=7, 2 patients data missed).

CASE 01 ZXM， M， 27, refractory NK/TCL

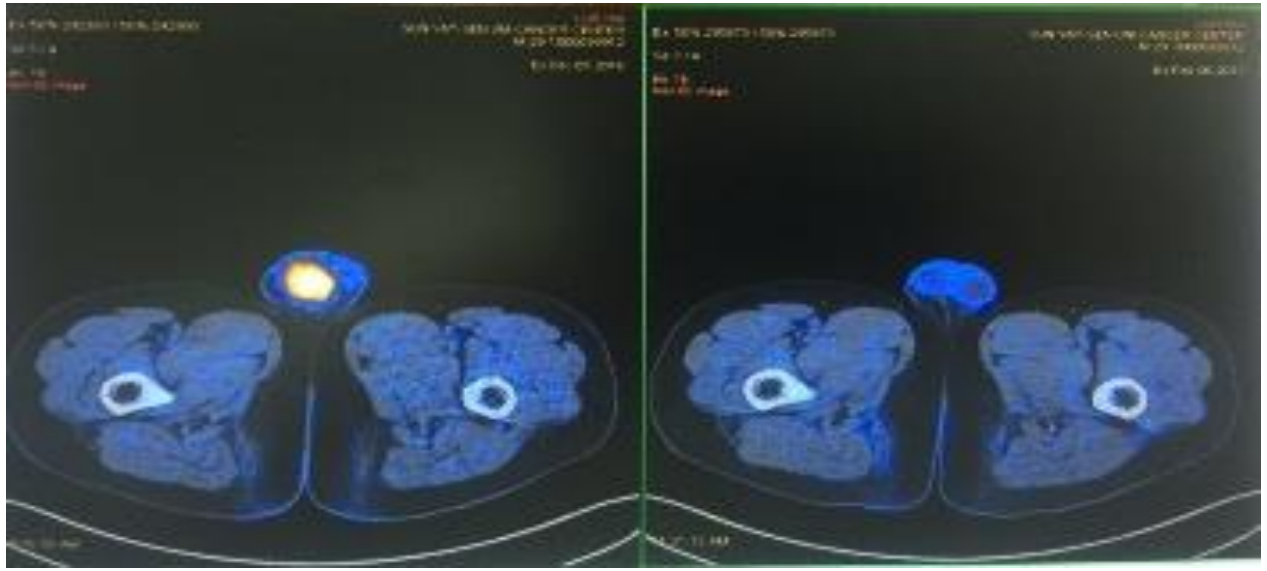
CCR 56wks ， Chidamide 30mg ,biw

Treatment recommended: local RT !!!

Previous therapy:

P-Gemox×3， ASCT ， Thalidomide maintenance 12m and AspaMetDex×6 ,

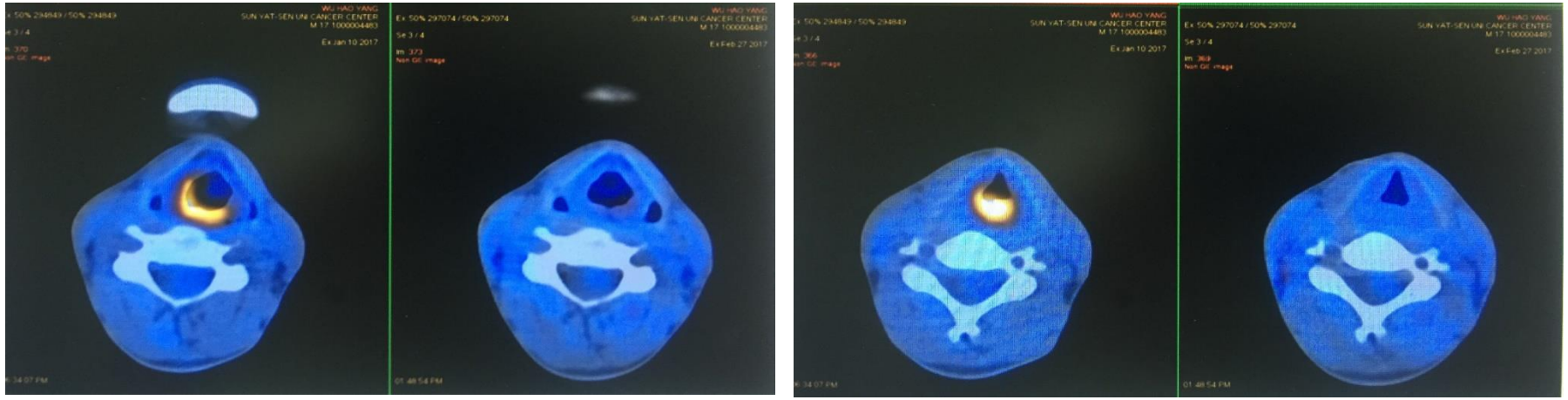
CASE 2，LH, M,32，relpased after P-Gemox X 6 ，Chidamide monotherapy ,**CR**



R.testicular SUV=15.6（baseline）　　SUV=4.7（ater +40d treatment）

1. Chidamide：30mg/d，twice/w
2. 2016-12-26至今
3. PET/CT : CR
4. Time to response：+14d（testis shrinked ）
5. Time to CR：+40d
6. major AE：G 2 leucopenia，G 2 thrombocytopenia，G1 N/W

CASE 3,WHY， m 18, Chidamide monotherapy **CR**



SUV=13.3（baseline） VS SUV first PETCT

1. previous therapy: BFM CCR 5 years， pharyngeal recurrence ,rebiopsy comfirmed
2. Chidamide：30mg， twice /w, orally
3. 2017-1-17:
4. PET/CR :CR
5. Time to response:：+21d（ improvement of speach）
6. time to CR： +40d
7. Major AE：G 2 N/W， G 2 leucopenia , G 3 ANC
8. no dose modification

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nature medicine

Recurrent *ECSIT* mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma

Haijun Wen[1–3,14], Huajuan Ma[1,4,14], Qichun Cai[1,5,6,14], Suxia Lin[1,7,14], Xinxing Lei[1,14], Bin He[1,14], Sijin Wu[8,14], Zifeng Wang[1], Yan Gao[1,6], Wensheng Liu[1], Weiping Liu[9], Qian Tao[10], Zijie Long[11], Min Yan[1], Dali Li[12], Keith W. Kelley[13], Yongliang Yang[8], Huiqiang Huang[1,6] & Quentin Liu[1,2,11]

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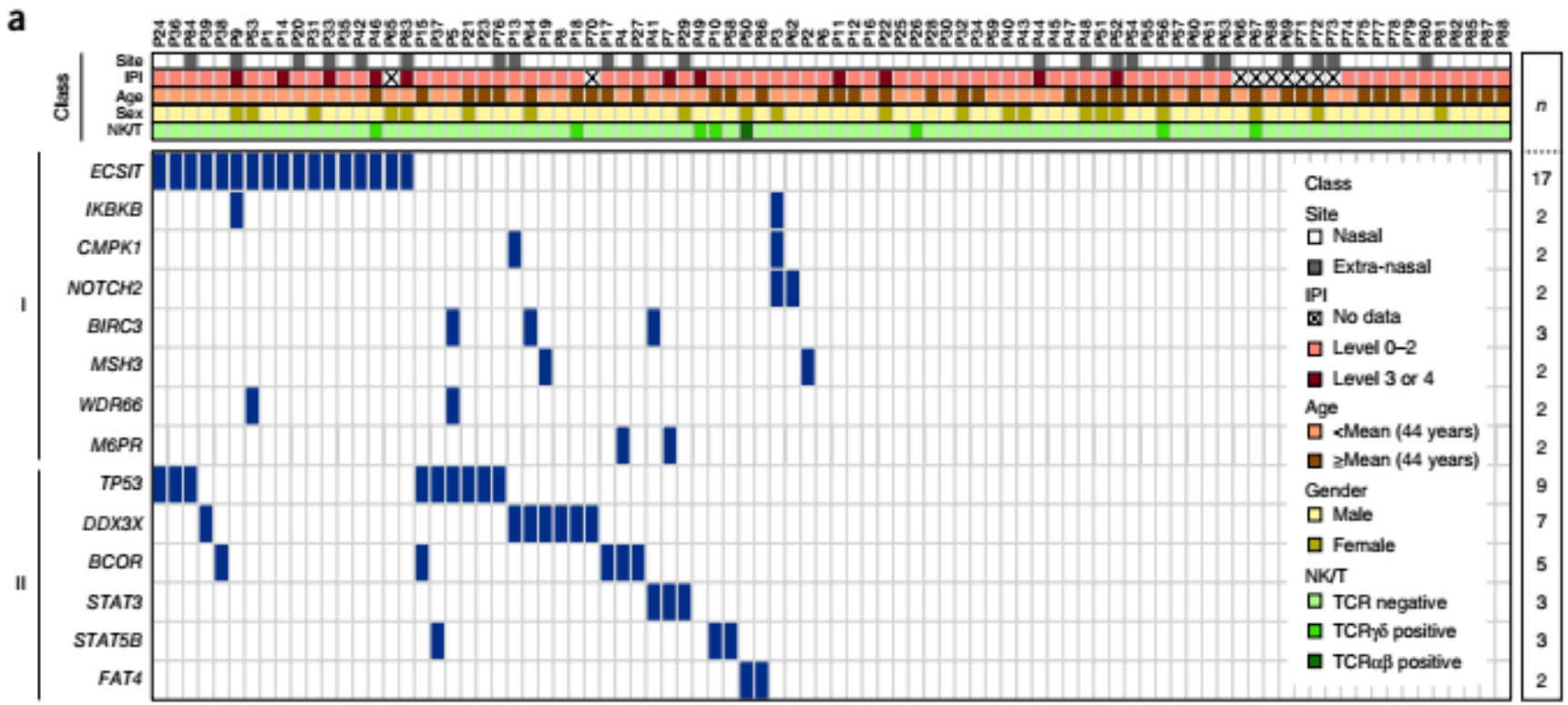
Recurrent *ECSIT* mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma



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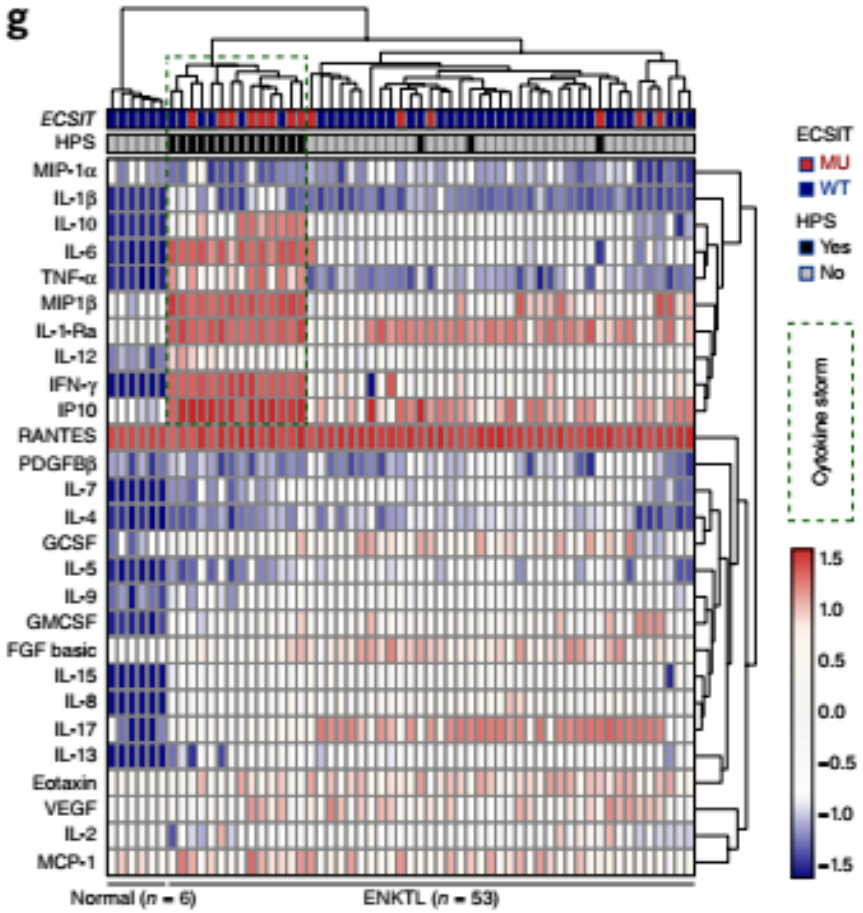

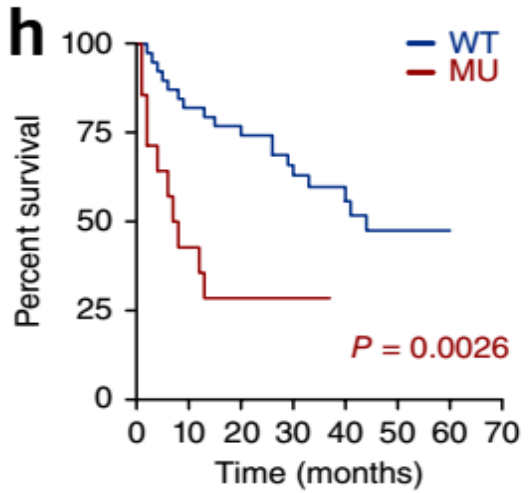

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Summary and conclusions

1. P-Gemox is one of the effective , simplified combination for newly diagnosed or relapsed NKTCL with good tolerability.
2. ASCT may improve longterm survival of advanced or relapsed NKTCL
3. Favourable response was obtained in 15 refractory NKTCL treated by ,novel selective HDAC inhibitor Chidamide monotherapy
   - previous heavily treated NK/TCL: ORR 57.2%, CR28.6%,especially CR were durable!
4. The adverse events for chidamide monotherapy were mild to moderate,well-tolerated ; Major AE N/W, leucopenia and thrombocytopenia .
5. EBV reactivation following long-term oral chidmide monotherapy in patients with NK/T lymphoma has not been comfirmed in this study.
6. Future consideration: further investigation combined with novel agents is urgently needed .

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