# L-asparaginase

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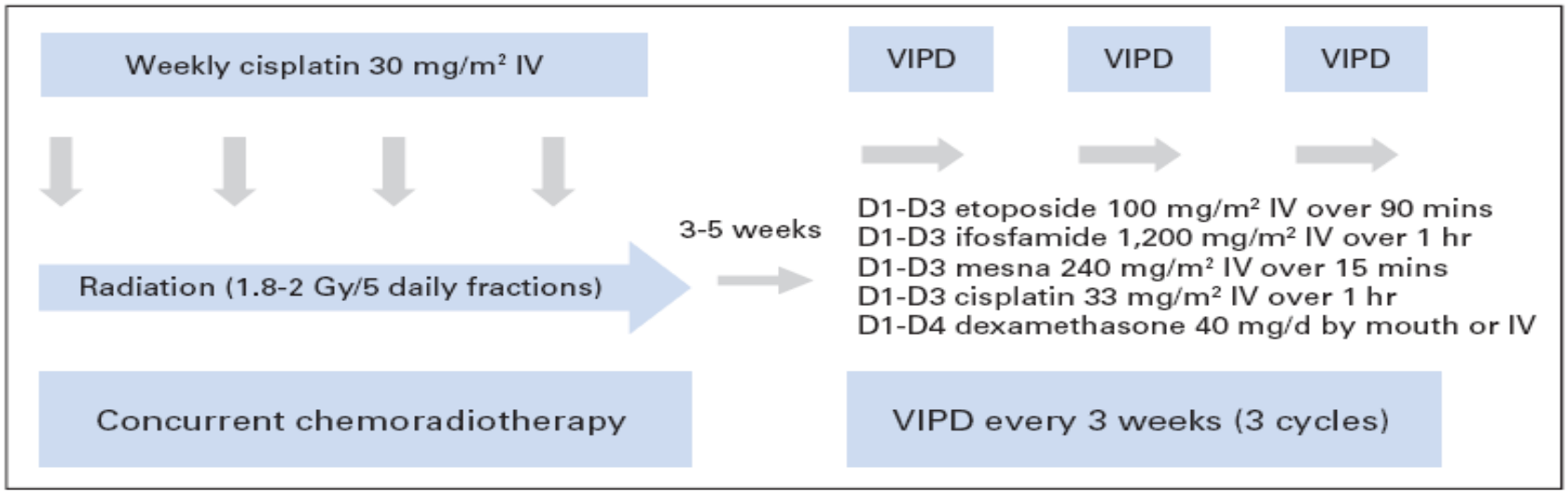
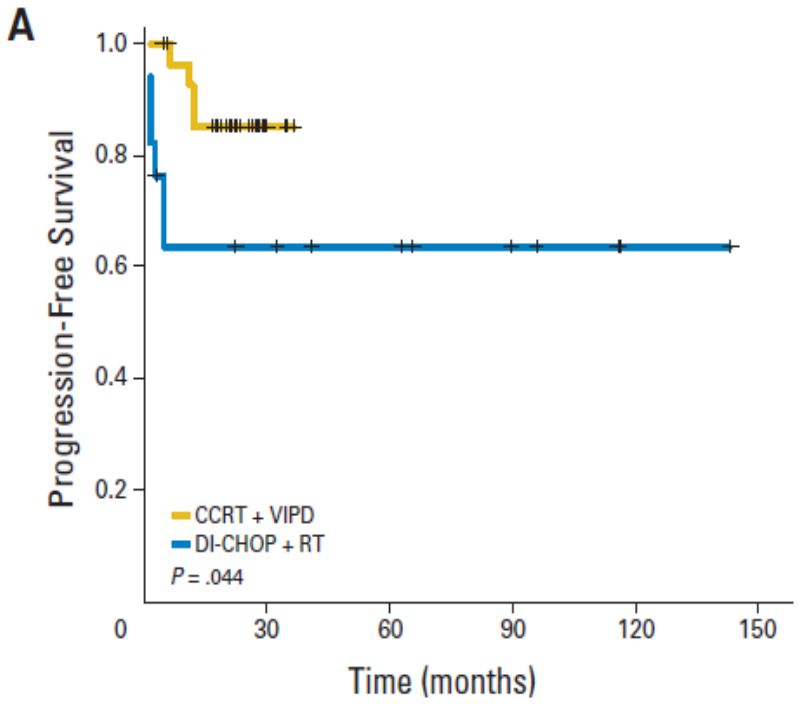
# Phase II Trial of Concurrent Radiation and Weekly Cisplatin Followed by VIPD Chemotherapy in Newly Diagnosed, Stage IE to IIE, Nasal, Extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma Study

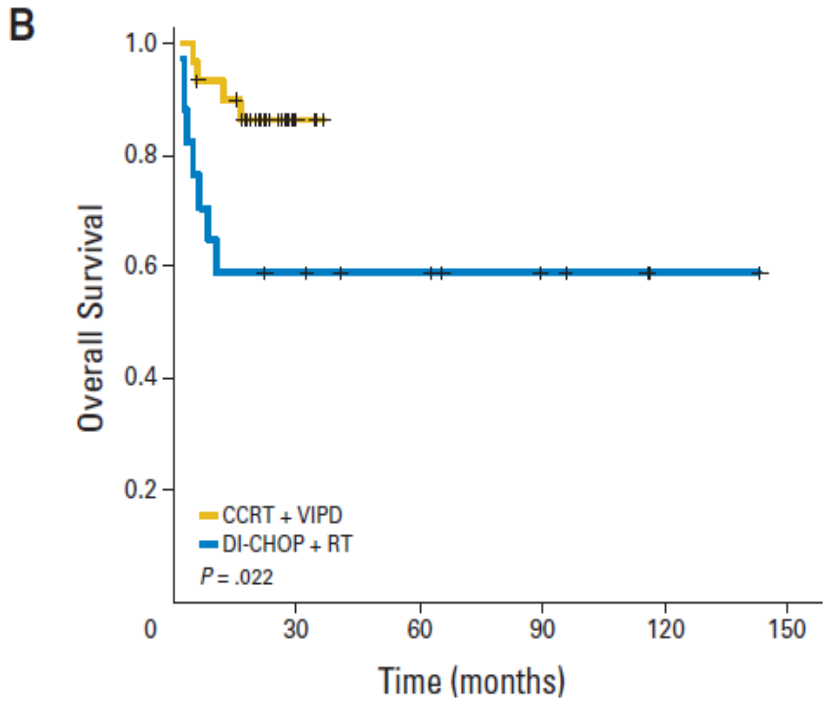
*Seok Jin Kim, Kihyun Kim, Byung Soo Kim, Chul Yong Kim, Cheolwon Suh, Jooryung Huh, Sang-Wook Lee, Jin Seok Kim, Jaeho Cho, Gyeong-Won Lee, Ki Mun Kang, Hyeon Seok Eom, Hong Ryull Pyo, Yong Chan Ahn, Young Hyeh Ko, and Won Seog Kim*




*Kim SJ, et al. JCO 2009*

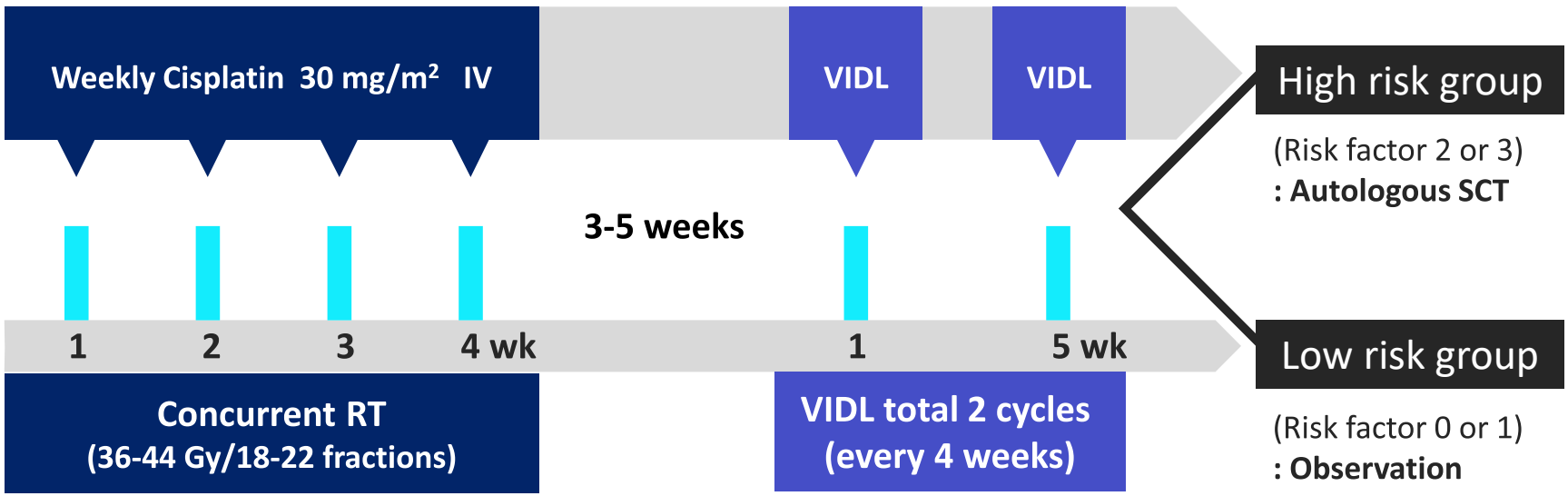
# Survival outcome




Good outcome but most efficient drug is not included

# Treatment scheme




**VIDL Chemotherapy**

**D1-D3** Etoposide **100 mg/m² IV,**

**D1-D3** Ifosfamide **1200 mg/m² IV ,**

**D1-D3** Dexamethasone **40 mg/d PO or IV,**

**D8, 10, 12, 14, 16, 18, 20** L-asparaginase **4000 IU/m² IV or IM**

# Response

| Response | After CCRT | | After VIDL (Final response) | |
|---|---|---|---|---|
| | Number | % | Number | % |
| CR | 19 | 61.3 | 25 | 80.6 |
| CRu | 3 | 9.7 | 1 | 3.2 |
| CR rate | | 71.0 | | 83.9 |
| PR | 6 | 19.4 | 1 | 3.2 |
| Overall response rate | | 90.4 | | 87.1 |
| PD | 3 | 9.7 | 4 | 12.9 |

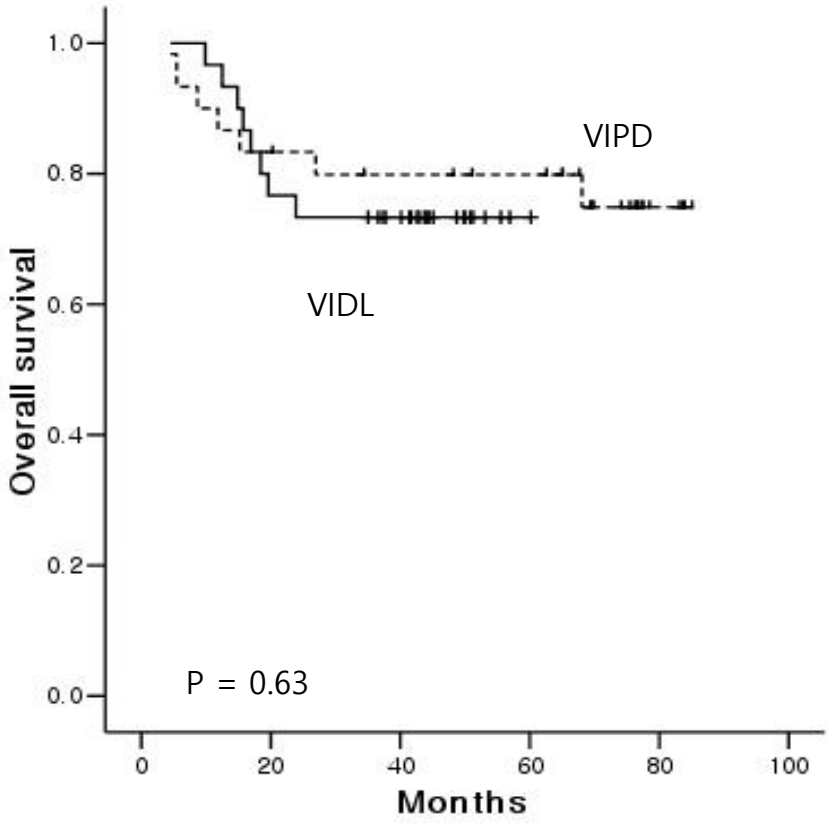
*Kim SJ et al Ann Hematol 2014*

# Toxicities

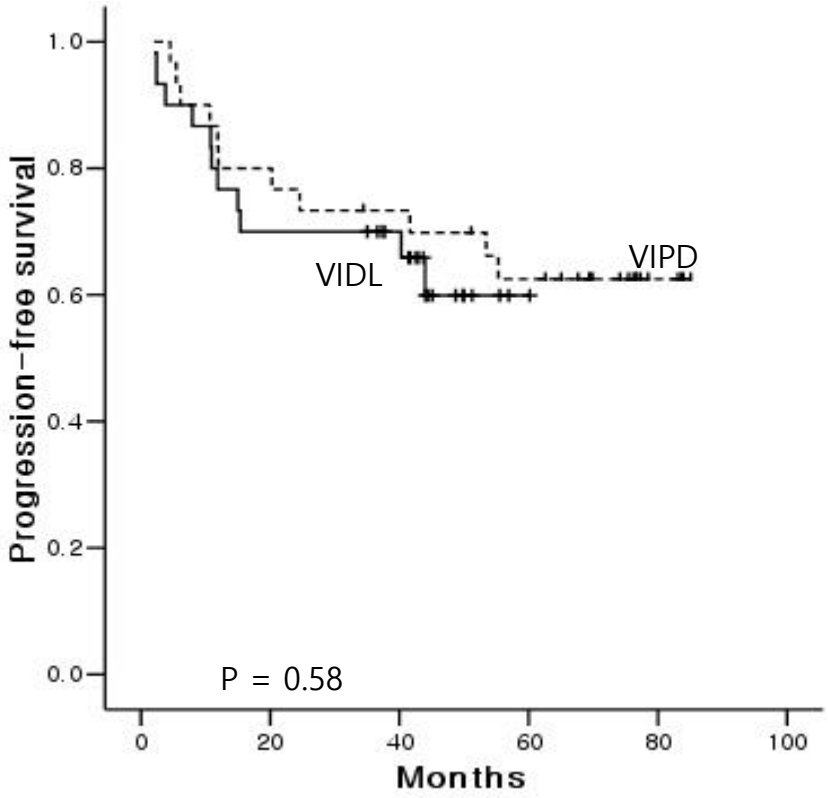
| Toxicity | Concurrent chemoradiation | | | | VIDLchemotherapy | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| Hematologic toxicity | | | | | | | | |
| Anemia | 2 | | | | 4 | 5 | 3 | |
| Leukopenia | 2 | 1 | | | 1 | 1 | 6 | 18 |
| Thrombocytopenia | 2 | | | | 7 | 3 | 3 | 1 |
| Febrile neutropenia | | | | | | | 5 | |
| Nonhematologic toxicity | | | | | | | | |
| Nausea | 12 | 3 | | | 11 | 8 | 2 | 1 |
| Vomiting | 4 | 3 | | | 8 | 5 | | |
| Diarrhea | | 2 | | | 2 | 2 | | |
| Anorexia | 8 | 2 | | | 10 | 5 | | |
| Constipation | 5 | | | | 6 | 2 | | |
| Stomatitis | 4 | 5 | 4 | 1 | 5 | 5 | 5 | 1 |
| General weakness | | | 1 | | 2 | 4 | 2 | |
| Insomnia | | | | | 3 | 2 | | |
| Edema | 2 | | | | 3 | 1 | | |
| Dizziness | 1 | | | | 2 | 1 | | |
| Myalgia | 1 | | | | 2 | | | |
| Fatigue | 1 | | | | 1 | 1 | | |
| Pain | 2 | 1 | | | | 3 | 1 | |
| Xerostomia | 1 | | | | | | | |
| Epistaxis | 2 | | | | | | | |
| Peripheral neuropathy | 1 | | | | | | | |
| Skin rash | 1 | | | | 1 | 1 | | |
| Transaminase elevation | 1 | | | | 10 | 4 | 3 | |

# Survivals

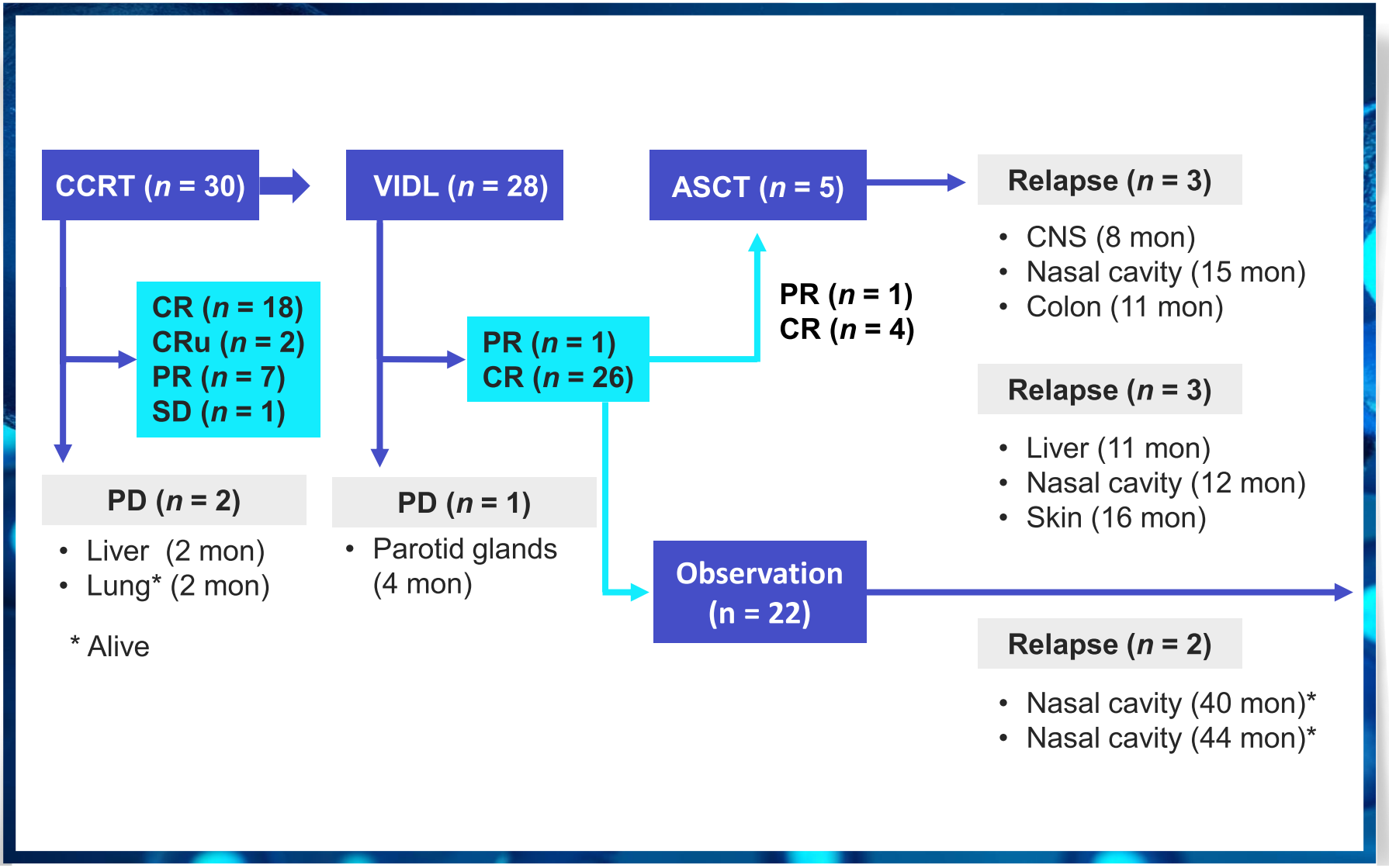
A



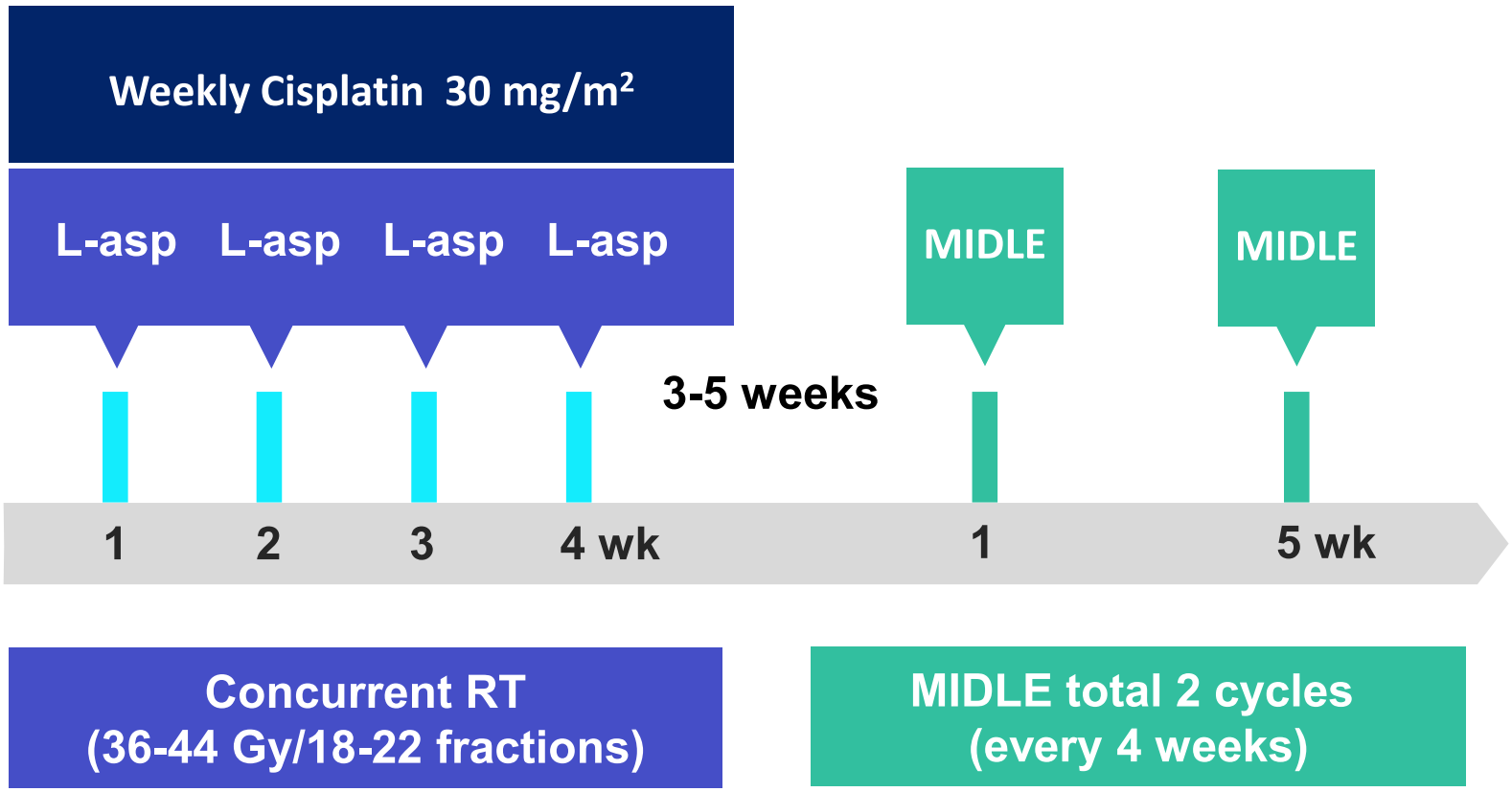

B



# Clinical course



# *Phase II study of concomitant chemo-radiotherapy followed by MIDLE chemotherapy in stage I/II Extranodal NK/T-cell Lymphoma*



# *MIDLE chemotherapy*


**Methotrexate**

3.0 g/m$^2$ I.V. **D1**

**Ifosfamide**

1000 mg/m$^2$ **D2-3**

**Dexamethasone**

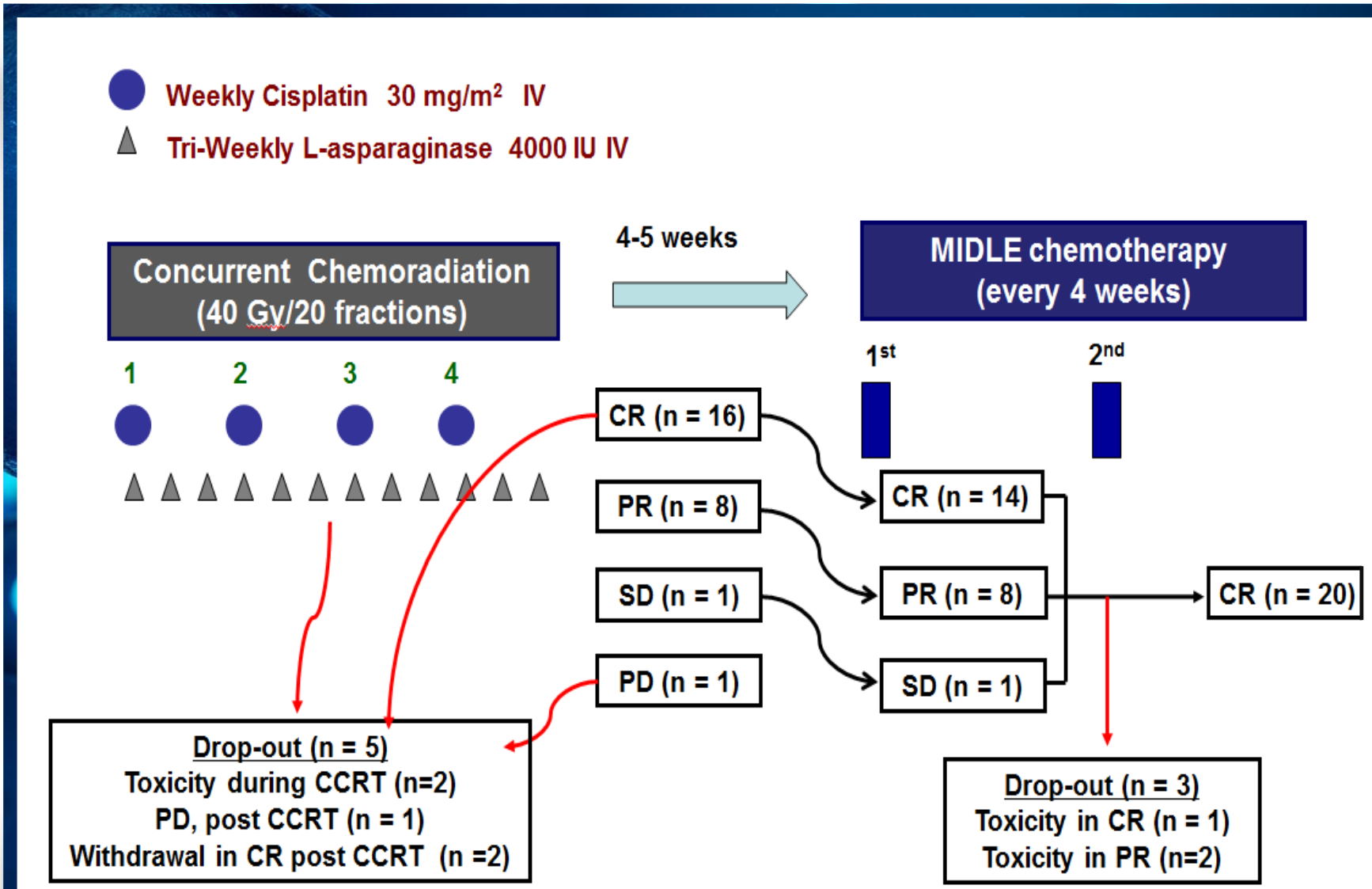
40 mg/d PO or IV **D1-4**

**Etoposide**

100 mg/m$^2$ **D2-3**

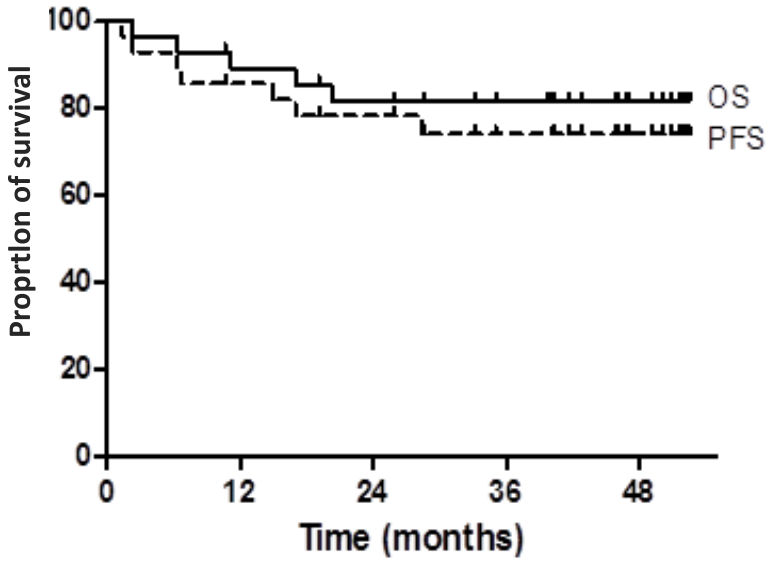

**L-asparaginase**

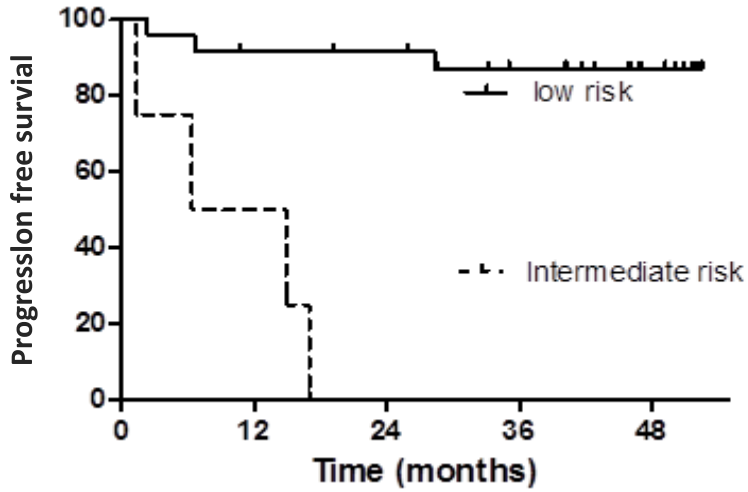
4000 IU/m$^2$ IM or IV
Repeated every 4 weeks
for 2 cycles

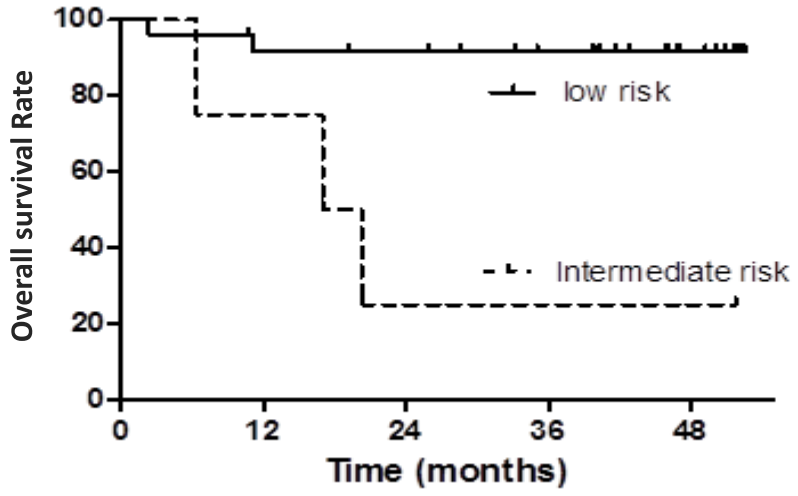

Weekly Cisplatin 30 mg/m² IV
Tri-Weekly L-asparaginase 4000 IU IV
Concurrent Chemoradiation
(40 Gy/20 fractions)
1
2
3
4
4-5 weeks
MIDLE chemotherapy
(every 4 weeks)
1st
2nd
CR (n = 16)
PR (n = 8)
SD (n = 1)
PD (n = 1)
CR (n = 14)
PR (n = 8)
SD (n = 1)
CR (n = 20)
Drop-out (n = 5)
Toxicity during CCRT (n=2)
PD, post CCRT (n = 1)
Withdrawal in CR post CCRT (n =2)
Drop-out (n = 3)
Toxicity in CR (n = 1)
Toxicity in PR (n=2)

# Survivals

PINK-E

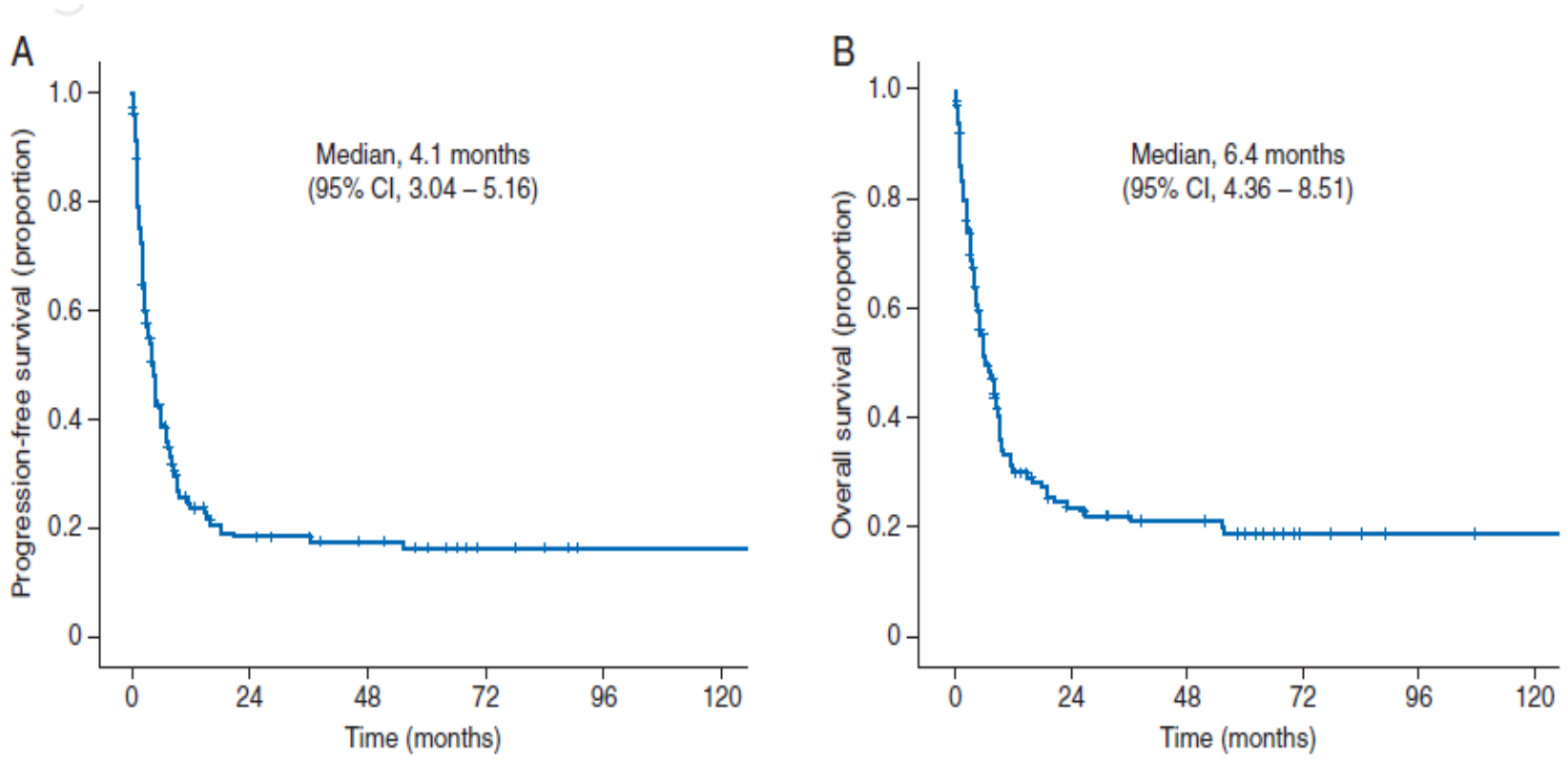


| | MIDLE (n=28) | VIPD (n=30) | VIDL (n=30) | DeVIC (n=27) |
|---|---|---|---|---|
| **regimens for** CCRT | Weekly cisplatin 30 mg/m$^2$ + triweekly L-asp 4,000 IU/m$^2$ | Weekly cisplatin 30 mg/m$^2$ | Weekly cisplatin 30 mg/m$^2$ | DeVIC |
| **Radiotherapy** | 36-44 Gy | 40-52.8 Gy | 40-44 Gy | 50 Gy |
| Chemotherapy | | | | |
| **Methotrexate** | 3 g/m$^2$ on D1 | - | - | - |
| **Epotoside** | 100 mg/m$^2$ on D2-3 | 100 mg/m$^2$ on D1-3 | 100 mg/m$^2$ on D1-3 | 67 mg/m$^2$ on D1-3 |
| **Ifosfamide** | 1,000 mg/m$^2$ on D2-3 | 1,200 mg/m$^2$ on D1-3 | 1,200 mg/m$^2$ on D1-3 | 1,000 mg/m$^2$ on D1-3 |
| **Platinum** | - | Cisplatin 33 mg/m$^2$ on D1-3 | - | Carboplatin 200 mg/m2 on D1 |
| **Dexamethasone** | 40 mg/day on D1-4 | 40 mg/day on D1-4 | 40 mg/day on D1-4 | 40 mg/day on D1-3 |
| **L-asparaginase** | 6,000 IU/m$^2$, 4 doses | | 4,000 IU/m$^2$, 7 doses | |
| CR rate | 82% | 80.0% | 87% | 77% |
| PFS | 3yr PFS, 74.1% | 3yr PFS, 85.2% | 5yr PFS, 73% | 2yr PFS, 67% |
| G3-4 neutropenia | 91.3% | 46.7% | 80% | 93% |
| G3-4 FN | 43.5% | 60% | 16.7% | 56% |
| G3-4 Mucositis | 7.1% | 0% | 20% | 30% |
| TRM | 1; AKI and pneumonia | 2; infection | 0 | 0 |

# *Beyond failure of standard care*




*Lim SH et al Ann Oncol 2017*

# Outcome after failure of 1st 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& | 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$ | Low | 6 (29%) | 25 (57%) |
| | Intermediate | 3 (14%) | 8 (18%) |
| | High | 12 (57%) | 11 (25%) |

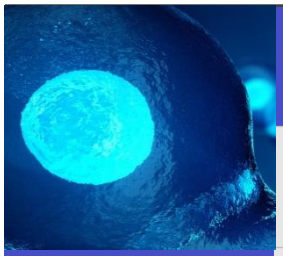
| Time of relapse | | < 6months N=17 | ≥ 6 months N=12 | < 6 months N=18 | ≥ 6 months N=45 |
|---|---|---|---|---|---|
| Primary treatment | CCRT+/- chemotherapy | 1 (6%) | 5 (42%) | 7 (39%) | 28 (62%) |
| | Chemotherapy | 16 (94%) | 7 (58%) | 11 (61%) | 17 (38%) |
| Response to salvage treatment | CR | 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% |

*Lim SH et al Ann Oncol 2017*

| | | 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%) | |
| | ≥ 6 months | 28 (87.5%) | 17 (54.8%) | 0.005 |
| Initial treatment | CCRT +/- chemotherapy | 17 (53.1%) | 18 (58.1%) | |
| | Chemotherapy | 15 (46.9%) | 13 (41.9%) | 0.801 |
| IPI* | Low/Low-intermediate | 21 (72.4%) | 17 (56.7%) | |
| | High-intermediate/High | 8 (27.6%) | 13 (43.3%) | 0.279 |
| NKPI& | Group I/II | 9 (34.6%) | 11 (35.5%) | |
| | Group III/IV | 17 (65.4%) | 20 (64.5%) | 1.000 |
| PINK** | Low | 8 (27.6%) | 12 (38.7%) | |
| | Intermediate | 4 (13.8%) | 8 (25.8%) | |
| | High | 17 (58.6%) | 11 (35.5%) | 0.229 |
| PINK-E$ | Low | 11 (57.9%) | 14 (56.0%) | |
| | Intermediate | 2 (10.5%) | 6 (24%) | |
| | High | 6 (31.6%) | 5 (20%) | 0.462 |
| Response | CR | 7 | 17 | |
| | PR | 7 | 6 | |
| | PD | 12 | 6 | |
| | NE | 6 | 2 | |
| ORR | | 43.7% | 74.2% | 0.042 |

| 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% |

# Characteristics of patients



| | | All | >60 | 60-65 | >66 |
|---|---|---|---|---|---|
| | N | 527 | 51 | 23 | 28 |
| **Sex** | Male | 64.7 | 60.8 | 73.9 | 50 |
| **ECOG PS** | ≥ 2 | 12.5 | 35.3 | 34.8 | 35.7 |
| **B Sx** | presence | 37 | 41.2 | 30.4 | 50 |
| **Serum LD** | increased | 42.1 | 60.8 | 56.5 | 64.3 |
| **Stage** | III/IV | 34.3 | 39.2 | 26.1 | 50 |

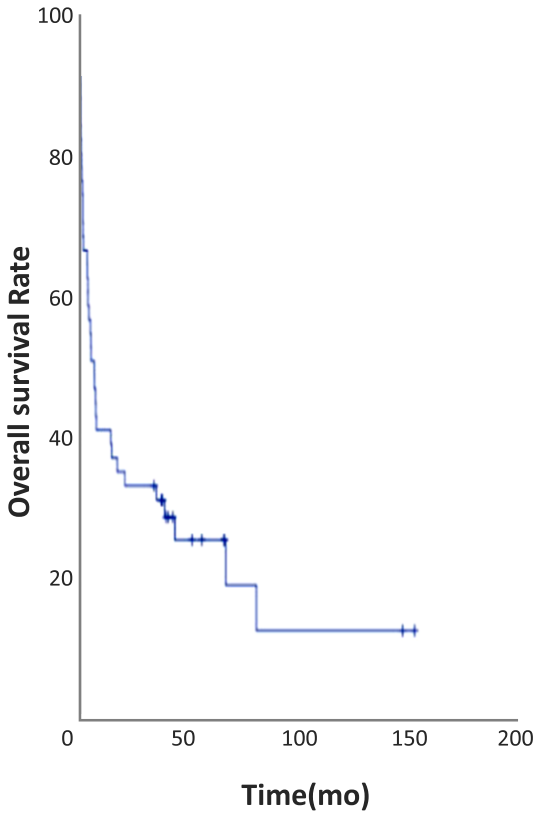
From 2 SMC lymphoma cohorts : 1998-2012

*Kim SM Ann Hematol 2016*

# Survivals from elderly ENKL

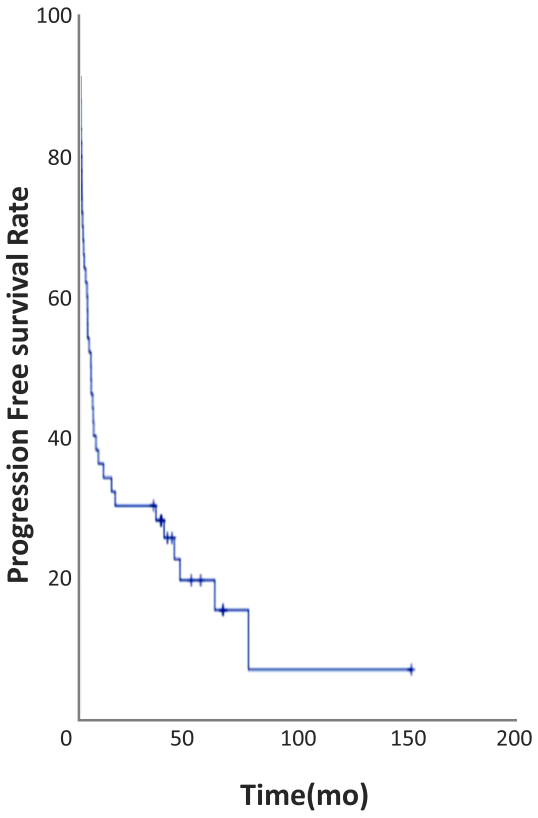
A

Median OS 6.7 mo



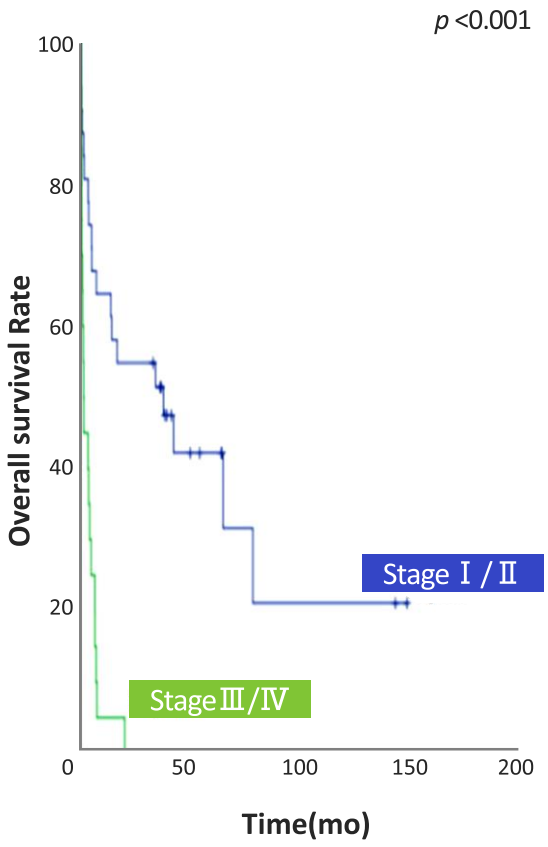

B

Median PFS 5.2 mo




C

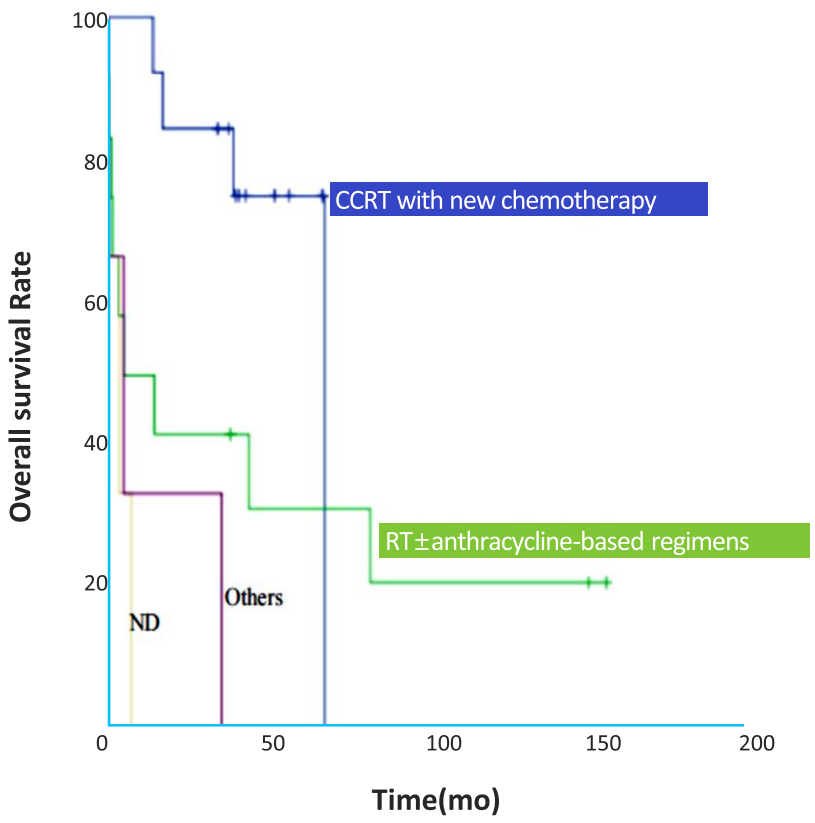
Stage Ⅰ/Ⅱ : Median OS = 38.6 mo
Stage Ⅲ/Ⅳ: Median OS = 1.6 mo



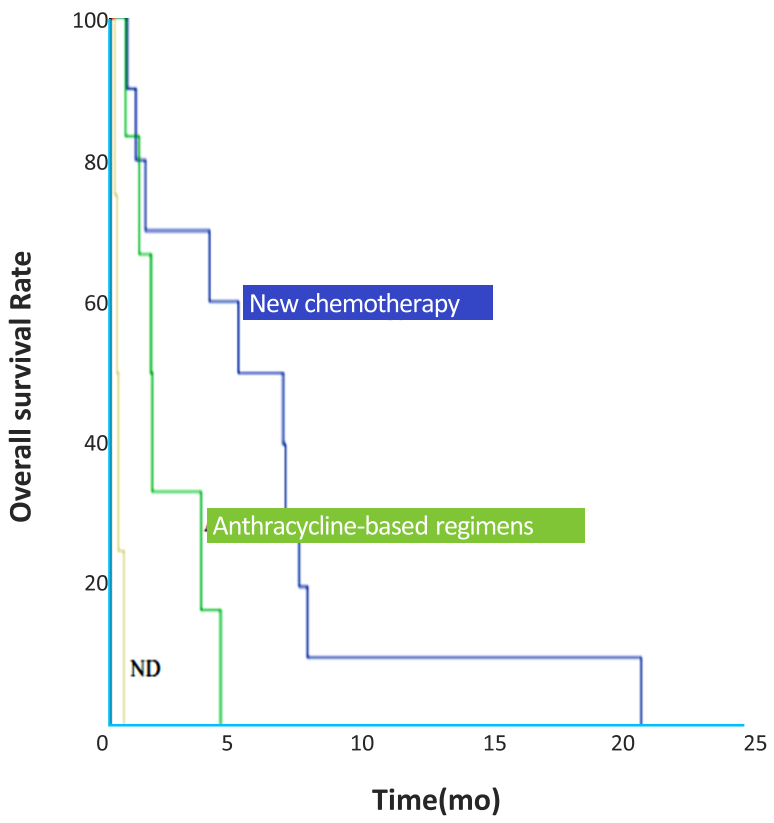

*Kim SM et al Ann Hematol 2016*

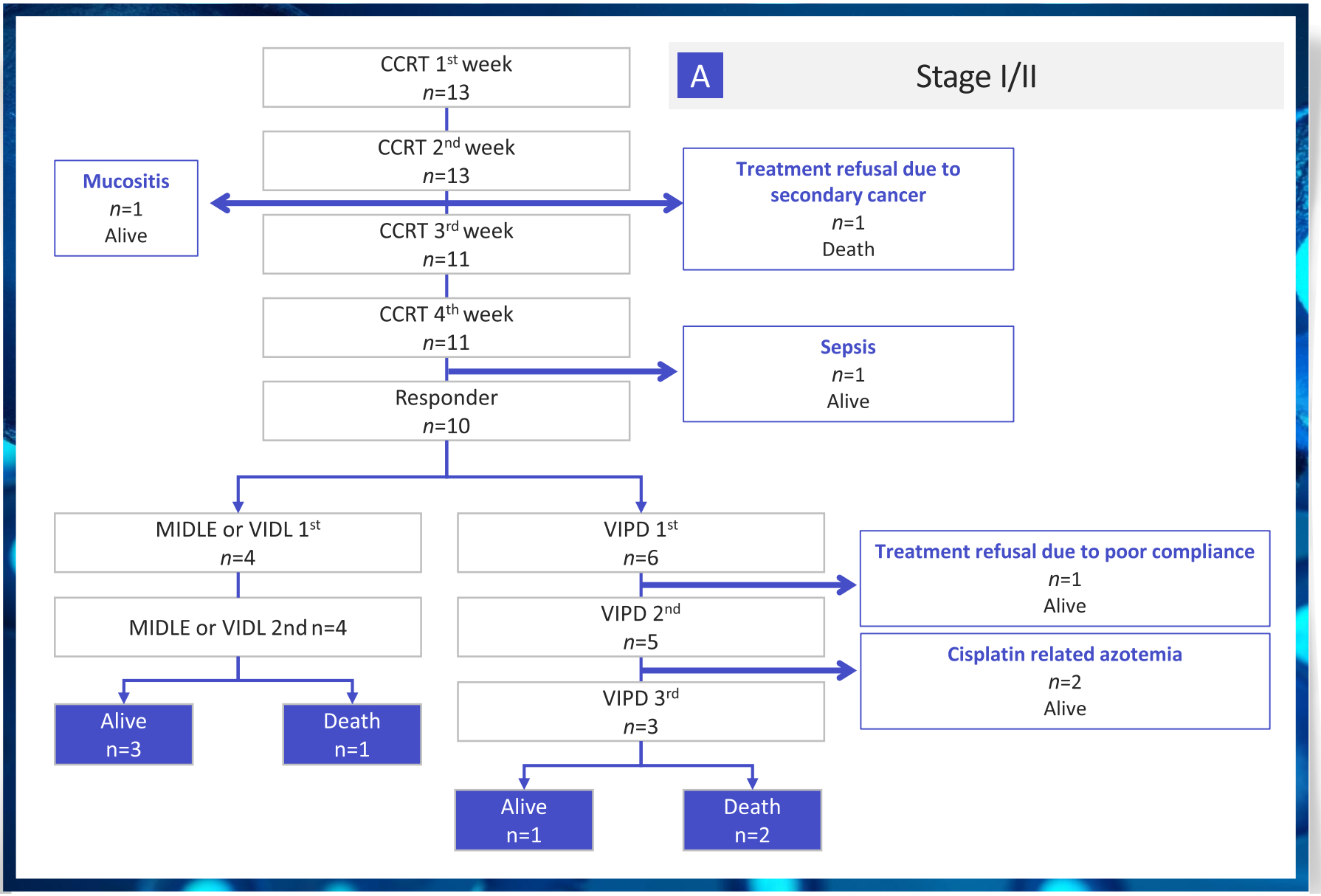
# Survivals according to treatment

A Stage I/II

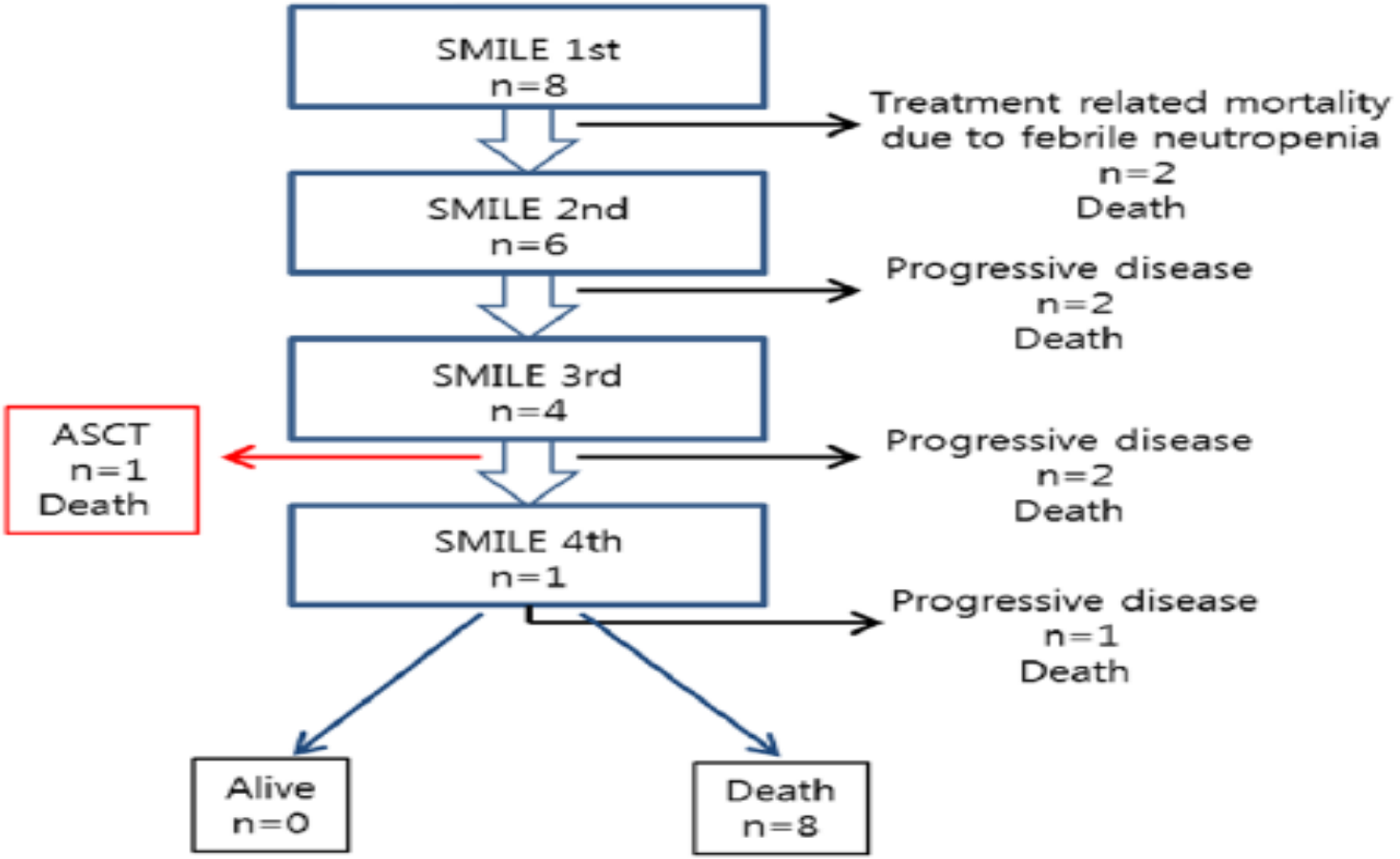



C Stage Ⅲ/Ⅳ




A
Stage I/II
CCRT 1st week
n=13
CCRT 2nd week
n=13
CCRT 3rd week
n=11
CCRT 4th week
n=11
Responder
n=10
Mucositis
n=1
Alive
Treatment refusal due to secondary cancer
n=1
Death
Sepsis
n=1
Alive
MIDLE or VIDL 1st
n=4
MIDLE or VIDL 2nd n=4
Alive
n=3
Death
n=1
VIPD 1st
n=6
VIPD 2nd
n=5
VIPD 3rd
n=3
Alive
n=1
Death
n=2
Treatment refusal due to poor compliance
n=1
Alive
Cisplatin related azotemia
n=2
Alive

# Stage III/IV


SMILE 1st
n=8
Treatment related mortality
due to febrile neutropenia
n=2
Death
SMILE 2nd
n=6
Progressive disease
n=2
Death
SMILE 3rd
n=4
ASCT
n=1
Death
Progressive disease
n=2
Death
SMILE 4th
n=1
Progressive disease
n=1
Death
Alive
n=0
Death
n=8

# *L-asparaginase based treatment*

- Optimal dose and schedule
- Difference between  formulation
- Role of retreatment

Elderly ENKTL patients

- Optimal How can we incorporate L-asparaginase  in treatment?
  - Localized disease
    - CCRT or RT  with L-asparaginase?
    - CCRT or RT followed by L-asparaginase?
  - Advanced stage disease
    - L-asparaginase alone?
    - Combination  ?

*Lim SH et al Ann Oncol 2017*

# *Thank you*

*- For your attention -*

**Won Seog Kim**

**SAMSUNG MEDICAL CENTER**

SEOUL, KOREA

| Characteristics | | Total (N = 28) | |
|---|---|---|---|
| | | Number | % |
| Age (Median 51 years, range: 30-77) | ≤ 60 | 21 | 75 |
| | > 60 | 7 | 25 |
| Sex | Male | 24 | 86 |
| | Female | 4 | 14 |
| Performance status | ECOG 0/1 | 28 | 100 |
| | ECOG 2 | 0 | 0 |
| Ann Arbor stage | IE | 22 | 79 |
| | IIE | 6 | 21 |
| Serum LDH | Normal | 25 | 89 |
| | Increase | 3 | 11 |
| B symptoms | Absence | 24 | 86 |
| | Presence | 4 | 14 |
| Regional LN involvement | Absence | 23 | 82 |
| | Presence | 5 | 18 |
| Primary site | Nasal cavity | 25 | 89 |
| | Others (pharynx or ear) | 3 | 11 |
| IPI | Low | 27 | 96 |
| | Low-Intermediate | 1 | 4 |
| NKPI* | Low (Risk factor 0/1) | 26 | 93 |
| | High (Risk factor 2/3) | 2 | 7 |
| PINK-E† | Low (Risk factor 0/1) | 24 | 86 |
| | Low-intermediate (Risk factor 2) | 4 | 14 |

*Yoon DH ASH 2015*

# Toxicities

| Toxicity | CCRT (n=28) | | | | MIDLE (n=23) | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| **Hematologic** | | | | | | | | |
| **Anemia** | 3 | 2 | | | 2 | 3 | 2 | |
| **Neutropenia** | | 1 | 2 | | | | 2 | 19 |
| Thrombocytopenia | | | | | | 3 | 1 | 2 |
| Febrile neutropenia | | | | | 1 | 1 | 10 | |
| **Nonhematologic** | | | | | | | | |
| Nausea | 4 | 3 | 11 | | 4 | 2 | 6 | |
| Vomiting | 5 | 3 | 3 | | 3 | 2 | | |
| Diarrhea | 1 | 1 | | | 1 | 3 | | |
| Anorexia | 2 | 1 | 5 | | 6 | 3 | 4 | |
| Constipation | 5 | 1 | | | 2 | 1 | | |
| Stomatitis | 4 | 8 | 1 | | 6 | 6 | 2 | |
| General weakness | 2 | | 1 | | 3 | 1 | 1 | |
| Insomnia | 1 | 1 | | | 1 | 1 | | |
| Allergic reaction | 2 | 3 | 1 | | 2 | 2 | 2 | |
| Alopecia | 3 | | | | 3 | 3 | | |
| infection | | | | | | | | 1 (G5)* |
| Creatinine elevation | | 2 | | | 1 | 1 | 1 | 1 (G5)* |
| Amylase elevation | 2 | | | | | | | |
| Transaminase elevation | 6 | 6 | 1 | | 2 | 3 | 3 | |
| Bilirubin elevation | 1 | 8 | 3 | | 1 | 3 | 1 | |

# Treatment outcome from elderly ENKL

| | CR | PR | ORR | *p* value |
|---|---|---|---|---|
| **Stage Ⅰ/Ⅱ** | | | | **0.116** |
| **New treatment** | 75.0%(12/16) | 12.5%(2/16) | 87.5%(14/16) | |
| **Anthracyclin-based treatment** | 50.0%(5/10) | 10.0%(1/10) | 60.0%(6/10) | |
| **Stage Ⅲ/Ⅳ** | | | | **0.060** |
| **New treatment** | 10.0%(1/10) | 20.0%(2/10) | 30.0%(3/10) | |
| **Anthracycline-based treatment** | 0%(0/6) | 0%(0/6) | 0%(0/6) | |
| **All Stage** | | | | **0.008** |
| **New treatment** | 50.0%(13/26) | 15.4%(4/26) | 65.4%(17/26) | |
| **Anthracycline-based treatment** | 31.3%(5/16) | 6.3%(1/16) | 37.5%(6/16) | |

CR complete response, PR partial response, OPR overall response rate

*Kim SM et al Ann Hematol 2016*