Agresif T hücreli Lenfomalar

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ASH sonrası lenfoma güncelleme toplantısı, 8 Ocak 2022

PTCL Entities: WHO 2017

Leukemic

- T-cell PLL
- T-cell LGL leukemia
- Chronic LPDs of NK cells
- Aggressive NK-cell leukemia
- ATLL
- Systemic EBV + T-cell lymphoma of childhood
- Hydroa vacciniformelike lymphoproliferative

Nodal

- PTCL-NOS
- AITL
- Follicular TCL
- Nodal PTCL with TFH phenotype
- ALCL, ALK+
- ALCL, ALK-

Cutaneous

- MF and SS
- Primary cutaneous CD30+ LPD
- Primary cutaneous γδ TCL
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
- Primary cutaneous acral CD8+ TCL
- Primary cutaneous CD4+ small/medium

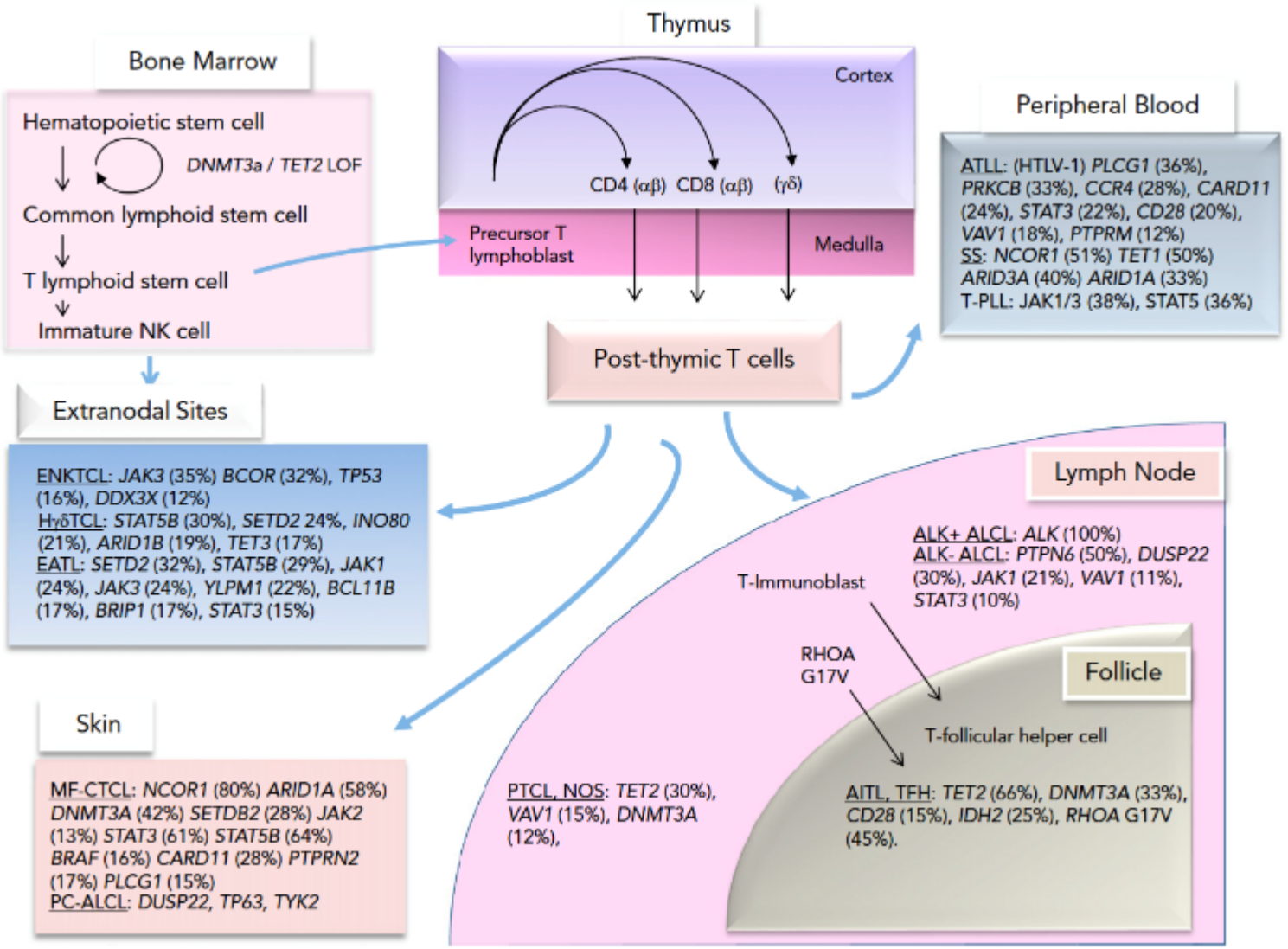
Extranodal

- Extranodal NK/TCL, nasal type
- Enteropathy-associated TCL
- MEITL
- Indolent T-cell proliferative disorder of the GI tract
- SC panniculitislike TCL
- Hepatosplenic TCL

Most common

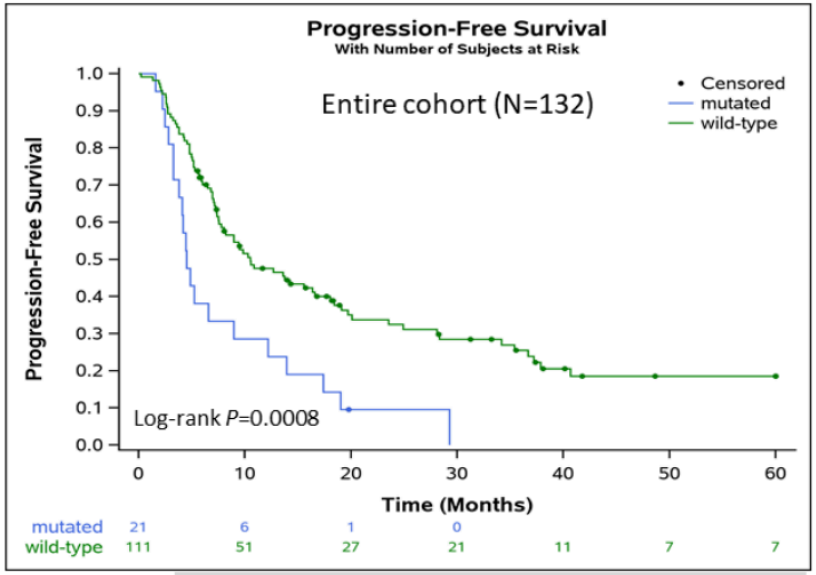
Rare/provisional

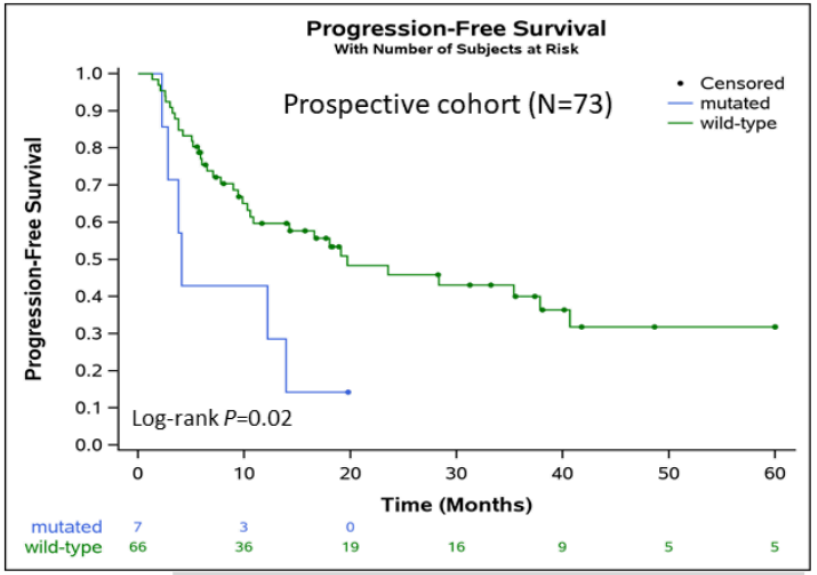
Jiang. ExpertRev Hematol. 2017;10:239.



John S. Van Arnam, Blood. 2018; 131(21):2320-2330)

TP53 Mutations Identify High-Risk PTCL Patients Treated with CHOP-Based Chemotherapy (1367)(MSKCC)





	Entire cohort (N=132)				
	n (events)	Median PFS (95% CI)	Hazard Ratio (95% CI)	Median OS (95% CI)	Hazard Ratio (95% CI)
TP53 mutated	21 (20)	4.5 (3.8-13.9)	**2.3 (1.4-3.8)**	43.1 (14.4-NR)	1.3 (0.7-2.4)
TP53 wild-type	111 (82)	10.5 (7.8-18.1)	1	42.2 (37.4-54.7)	1
Log-rank		**0.0008**	p=0.001 (for hazard)	0.4	
Total	132 (102)	9.4 (7.3-13.9)		53.2 (42.5-70.7)	

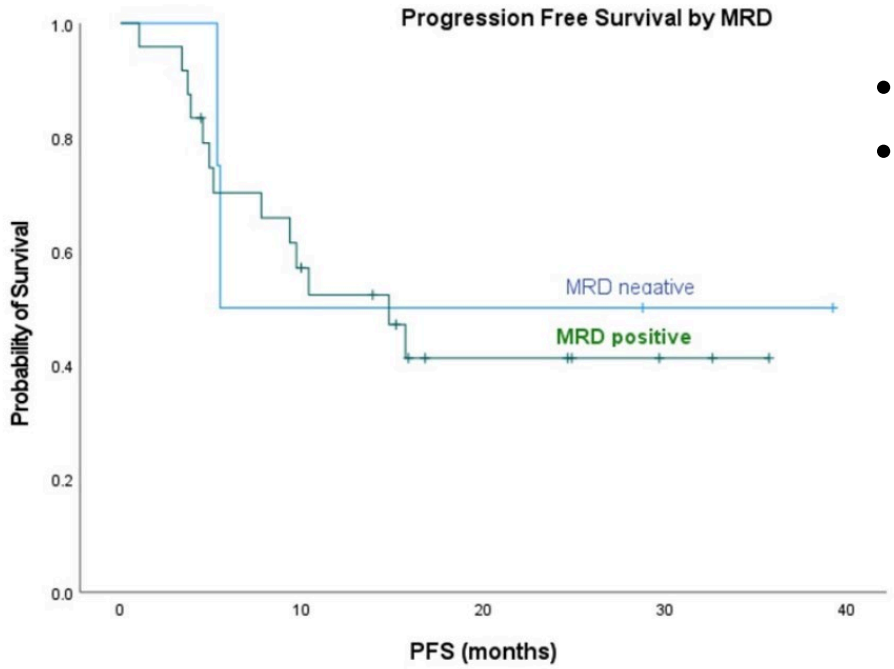
	Prospective cohort (N=73)				
	n (events)	Median PFS (95% CI)	Hazard Ratio (95% CI)	Median OS (95% CI)	Hazard Ratio (95% CI)
TP53 mutated	7 (6)	4.1 (2.8-NR)	**2.7 (1.1-6.6)**	31.4 (14.5-NR)	1.1 (0.5-2.6)
TP53 wild-type	66 (37)	19.7 (10.8-NR)	1	33.2 (19.2-41.7)	1
Log-rank		**0.02**	p=0.03 (for hazard)		
Total	73 (43)	18.1 (10.6-75.5)		58.7 (45.9-NR)	

lower rates of CR, higher rates of relapse, and shorter PFS

OS was not different compared to TP53 WT tumors.

William T. Johnson

End of Treatment **Peripheral Blood TCR Evaluation for MRD** Evaluation in PTCL (3506)



- median follow up of 20.7 mo.,
- PFS and OS at 18 months did **not differ** between TCR MRD positive or negative at EOT
  - OS 64% vs 67% p=0.63;
  - PFS 41% vs 50% p=0.40.

- prospective multi-institutional study (N=43)
- TCR by NGS in quantifying MRD in PTCL (at the end of CHOP-based therapy)
- Detectable TCR at the end of treatment correlates with **lack of CR**.

A Clinical **Prognostic Index** for AITL in an Asian Multi-Centre Study (2453)

Figure 1. Overall survival of AITL patients stratified into patients with POD24 or without POD24

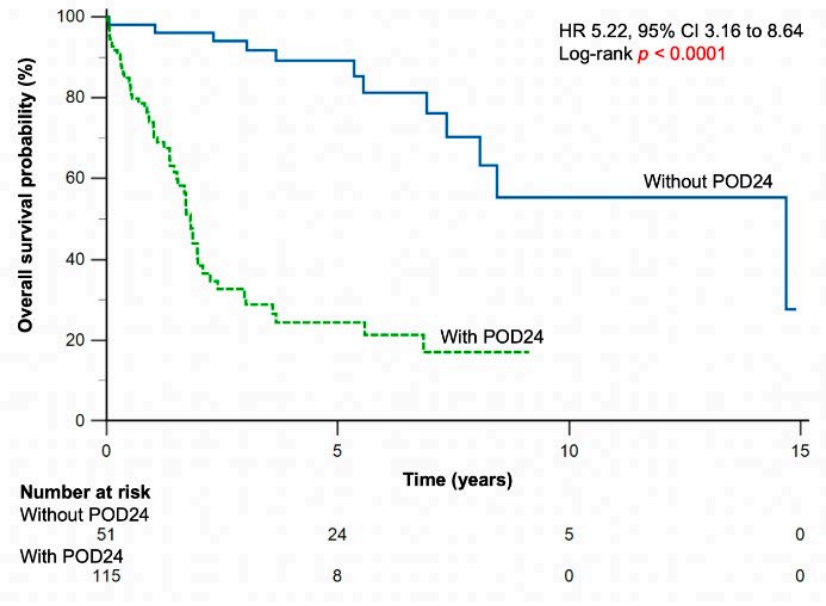
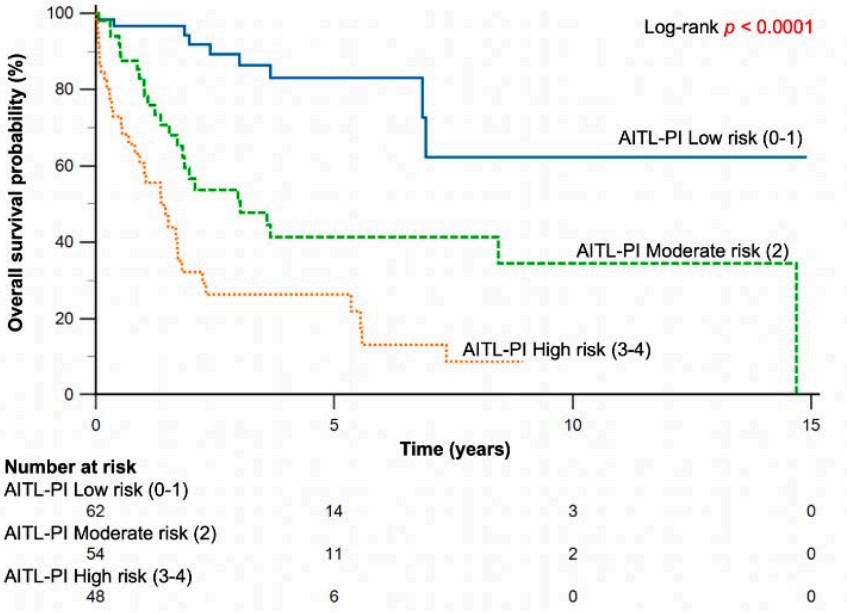


Figure 2. Overall survival of AITL patients stratified by the AITL prognostic index risk group



POD24: 5-year OS of 24%,
without POD24: 5-year OS of 90% (p<0.0001).

novel AITL score:

- age
- ECOG
- serum CRP level
- serum B2-microglobulin level

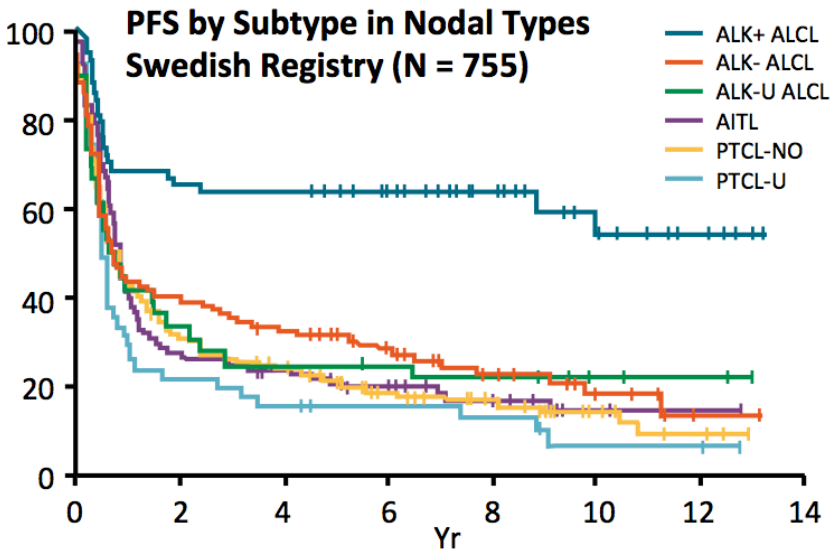
Esther Chang

PTCL: Frontline Treatment

PTCL-NOS
AITL
ALK- ALCL
ALK+ ALCL

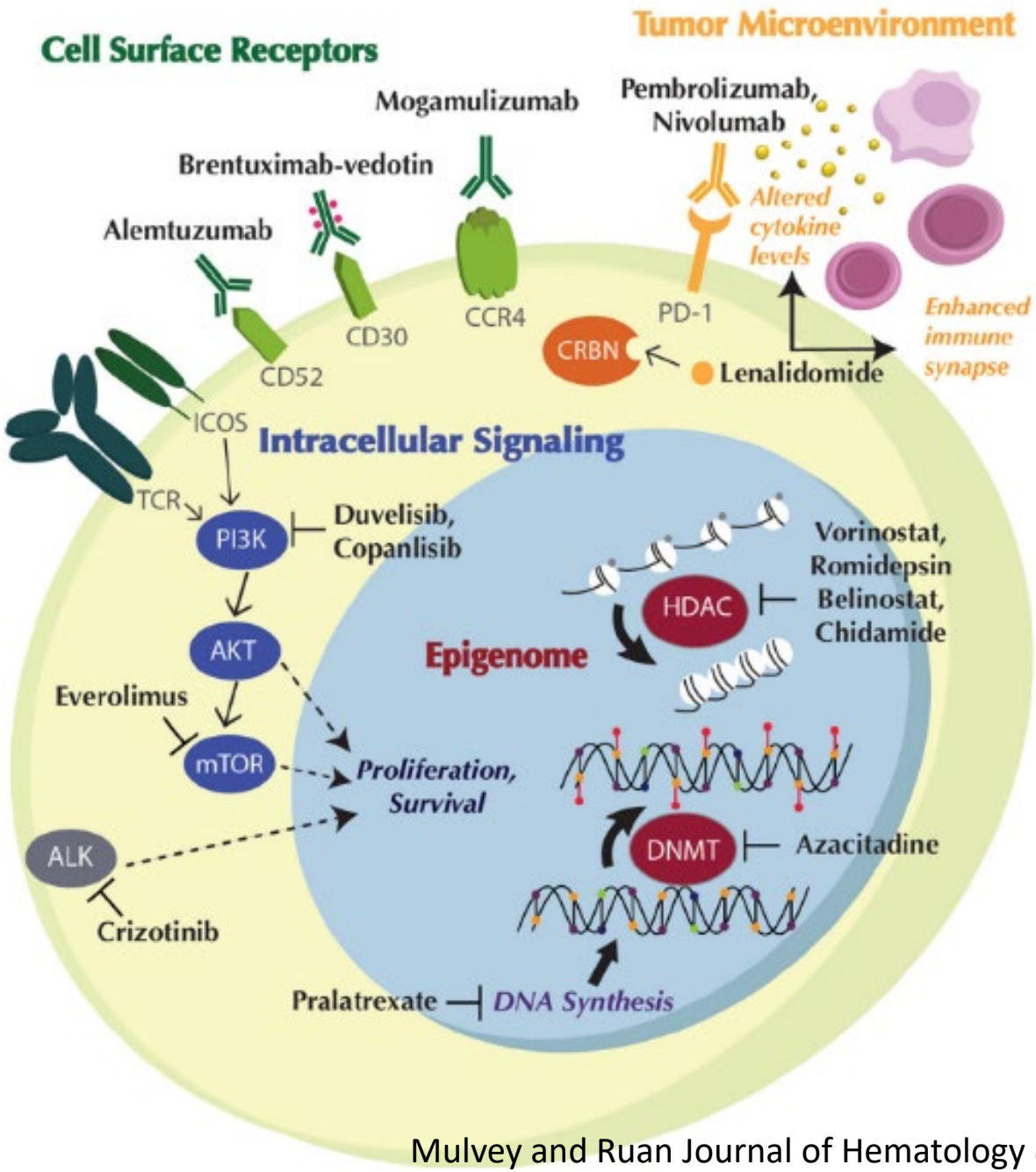
→ CHOP/CHOP-like → CR or PR → ASCT

Low-risk ALK+ ALCL → observe



	ASCT	Non-ASCT	CHOEP	CHOP
	(n = 128)	(n = 124)	(n = 145)	(n = 107)
5-yr OS, %	48	26	47	30
5-yr PFS, %	41	20	40	23

Ellin. Blood. 2014;124:1570.

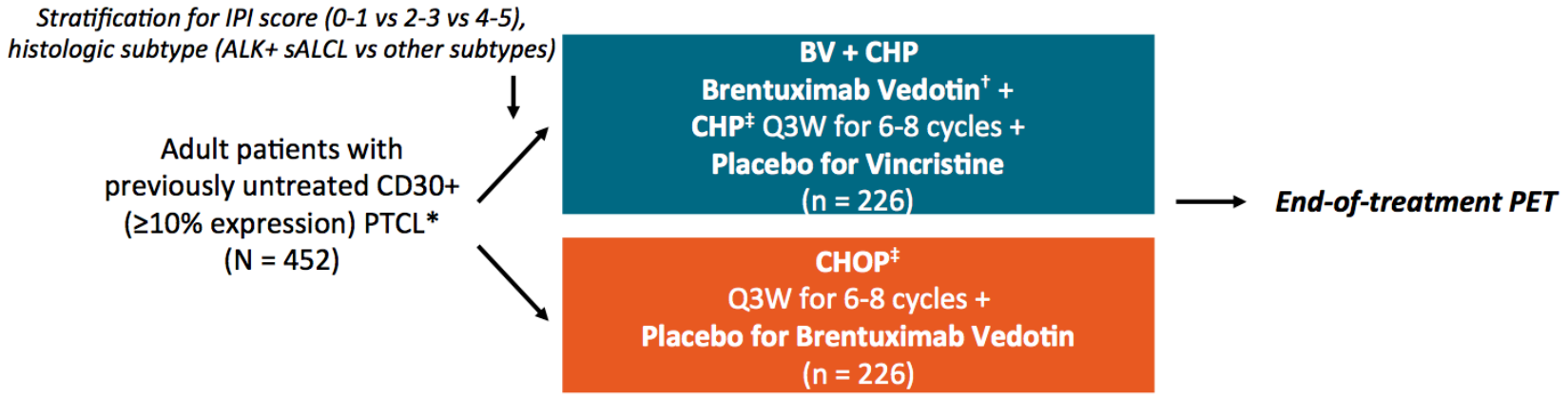


Mulvey and Ruan Journal of Hematology & Oncology (2020)

T/NK Cell Lymphoma **Frontline** Clinical Trials

The **Echelon-2 Trial**: 5-Year Exploratory Subgroup Analyses of a Randomized, Double-Blind, Phase 3 Study of (**A+CHP**) vs **CHOP** in Frontline Treatment of Pts with CD30-Positive PTCL (135)

- Multicenter, randomized, double-blind, double-dummy, active-controlled phase III trial

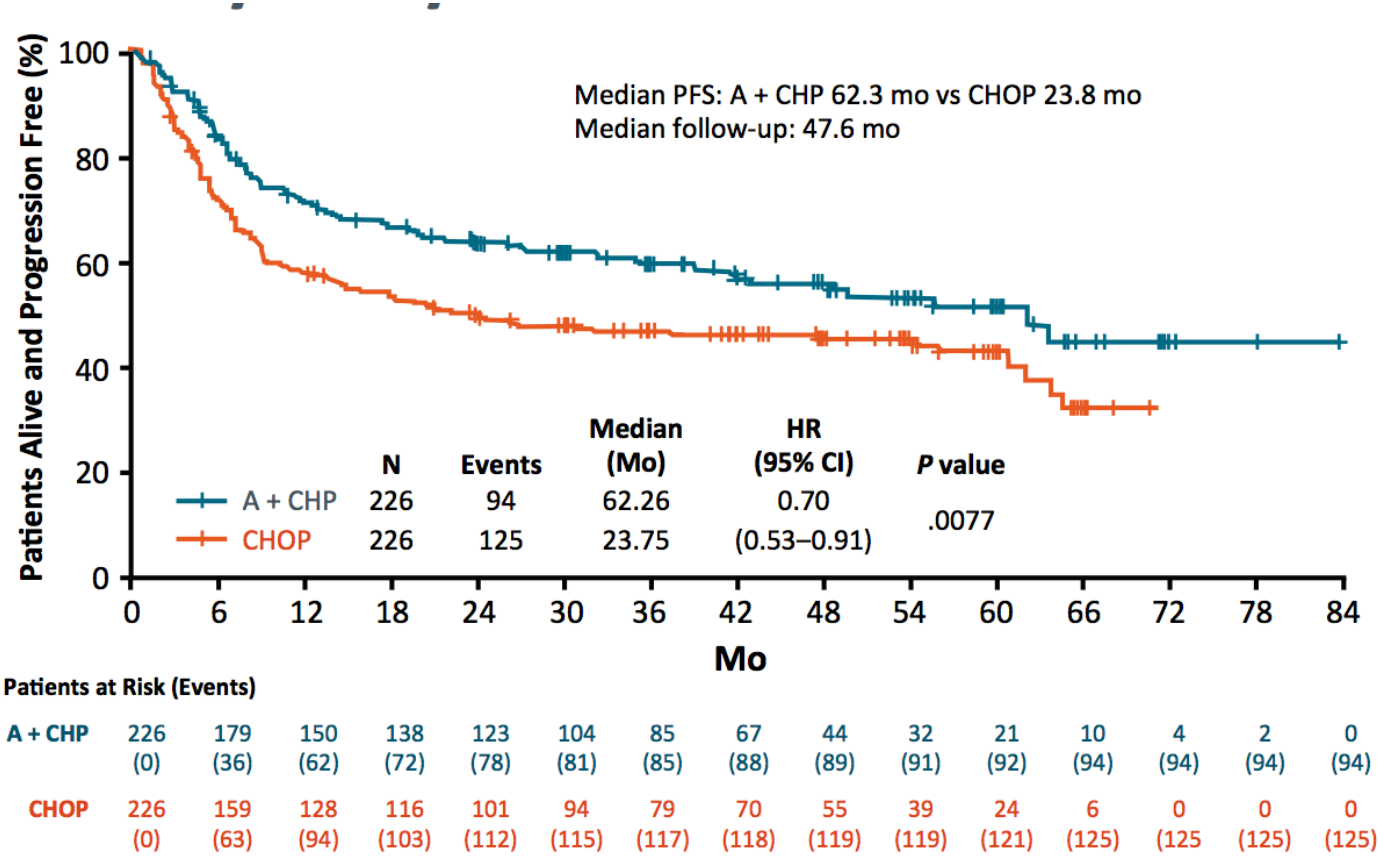


*PTCL includes sALCL (including ALK+ sALCL with IPI ≥2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

The **Echelon-2 Trial**: 5-Year Exploratory Subgroup Analyses of a Randomized, Double-Blind, Phase 3 Study of (**A+CHP**) vs **CHOP** in Frontline Treatment of Pts with CD30-Positive PTCL (135)

- BV+CHP reduced risk of progression, death, or subsequent anticancer therapy by 30% vs CHOP (investigator assessment)



The **Echelon-2 Trial**: 5-Year Exploratory Subgroup Analyses (135)

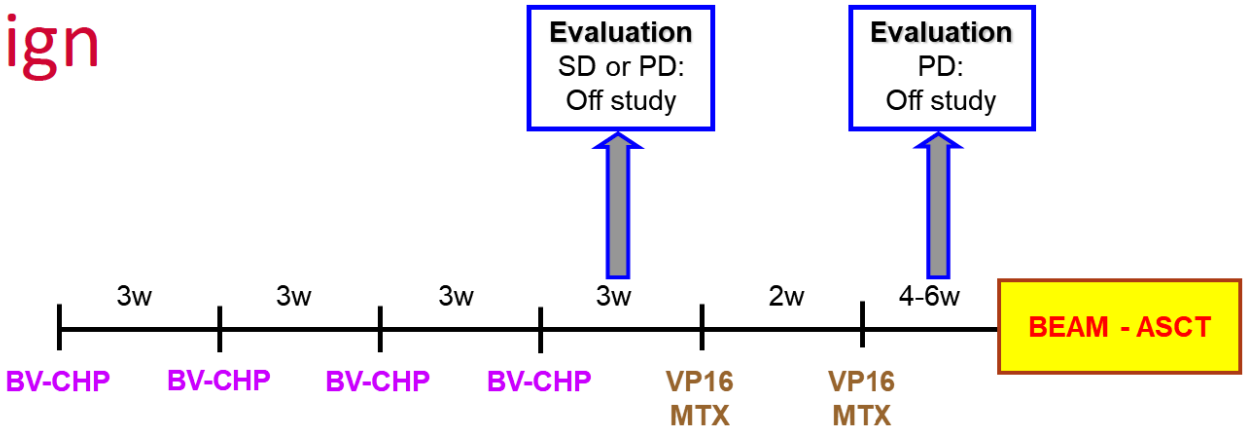
Subgroup	Estimated 5-year PFS rate		HR (95% CI)	P-value	Estimated 5-year OS rate		HR (95% CI)	P-value
	A+CHP	CHOP			A+CHP	CHOP		
ITT	51.4% (n=226)	43.0% (n=226)	0.70 (0.53, 0.91)	0.0077	70.1% (n=226)	61.0% (n=226)	0.72 (0.53, 0.99)	0.0424
Age								
<60 years	68.4% (n=123)	52.3% (n=126)	0.54 (0.35, 0.82)	0.0035	81.6% (n=123)	74.0% (n=126)	0.66 (0.38, 1.15)	0.1402
≥60 years	34.4% (n=103)	31.1% (n=100)	0.81 (0.57, 1.15)	0.2394	56.1% (n=103)	44.1% (n=100)	0.73 (0.49, 1.07)	0.1054
Gender								
Male	47.6% (n=133)	46.4% (n=151)	0.84 (0.60, 1.17)	0.2947	69.0% (n=133)	60.8% (n=151)	0.73 (0.49, 1.08)	0.1148
Female	57.0% (n=93)	35.8% (n=75)	0.44 (0.28, 0.69)	0.0003	71.8% (n=93)	61.2% (n=75)	0.68 (0.40, 1.16)	0.1597
PTCL subtype								
PTCL-NOS	26.5% (n=29)	25.7% (n=43)	0.79 (0.43, 1.43)	0.4290	46.2% (n=29)	35.9% (n=43)	0.75 (0.37, 1.48)	0.4003
AITL	26.6% (n=30)	48.1% (n=24)	1.41 (0.64, 3.11)	0.3958	67.8% (n=30)	62.5% (n=24)	1.01 (0.40, 2.55)	0.9855
sALCL								
Overall	60.6% (n=162)	48.4% (n=154)	0.55 (0.39, 0.79)	0.0009	75.8% (n=162)	68.7% (n=154)	0.66 (0.43, 1.01)	0.0529
IPI score								
0–1	59.5% (n=41)	47.6% (n=32)	0.42 (0.18, 0.94)	0.0301	87.0% (n=41)	86.2% (n=32)	0.73 (0.20, 2.73)	0.6411
2–3	68.5% (n=95)	50.9% (n=100)	0.57 (0.35, 0.90)	0.0158	80.6% (n=95)	68.7% (n=100)	0.57 (0.32, 1.01)	0.0496
4–5	27.2% (n=26)	36.4% (n=22)	0.73 (0.35, 1.50)	0.3839	38.0% (n=26)	43.2% (n=22)	0.89 (0.42, 1.89)	0.7606

The **Echelon-2 Trial**: 5-Year Exploratory Subgroup Analyses (135)

Treatment Arm	Subgroup	Estimated 5-year PFS rate	HR (95% CI)	P-value	Subgroup	Estimated 5-year OS rate	HR (95% CI)	P-value
	Age				Age			
	<60 years	≥60 years			<60 years	≥60 years		
A+CHP	68.4% (n=123)	34.4% (n=103)	0.60 (0.38, 0.94)	0.0232	81.6% (n=123)	56.1% (n=103)	0.54 (0.31, 0.93)	0.0252
CHOP	52.3% (n=126)	31.1% (n=100)	0.68 (0.46, 1.01)	0.0521	74.0% (n=126)	44.1% (n=100)	0.44 (0.27, 0.72)	0.0008
	Gender				Gender			
	Female	Male			Female	Male		
A+CHP	57.0% (n=93)	47.6% (n=133)	0.77 (0.50, 1.18)	0.2259	71.8% (n=93	69.0% (n=133)	1.00 (0.61, 1.64)	0.9966
CHOP	35.8% (n=75)	46.4% (n=151)	1.36 (0.94, 1.97)	0.1044	61.2% (n=75)	44.1% (n=151)	1.03 (0.66, 1.60)	0.9054

The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

Study design



- Primary endpoint: 2-y PFS (per INV)
- Key secondary endpoints: ORR, OS
- Key inclusion criteria:
  - Pathologically confirmed newly diagnosed EATL (WHO 2016)
  - CD30+ (≥10% of neoplastic cells by central review)
  - 18-65 years
  - PS 0-3

David Sibon

The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

Baseline characteristics

n	**14 (enrolled in 3 years)**
Median age (range), years	54 (34-65)
Surgery as initial intervention (obstruction/perforation)	11 (79%) (6/5)
Celiac disease Prior to EATL Concomitant with EATL	14 (100%) 4 (29%) 10 (71%)
RCD 2 Prior to EATL Concomitant with EATL	9 (64%) 4 (28%) 5 (36%)
CD30 % (range)	10%-100% (9 cases having 100%)
High risk of malnutrition (NRI<83.5)	8 (57%)
PS 2-3	8 (57%) (PS 2, 43% - PS 3, 14%)
EPI Low risk Intermediate risk High risk	 2 (14%) 6 (43%) 6 (43%)

David Sibon

The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

Response (Lugano 2014 criteria)

Response	After 4 BV-CHP	After 2 VP16-MTX (pre-transplantation)
ORR	11/14 (79%)	11/14 (79%)
CR	9/14 (64%)	10/14 (71%)
PR	2/14 (14%)	1/14 (7%)

3/14 (21%) cases of primary progressive EATL

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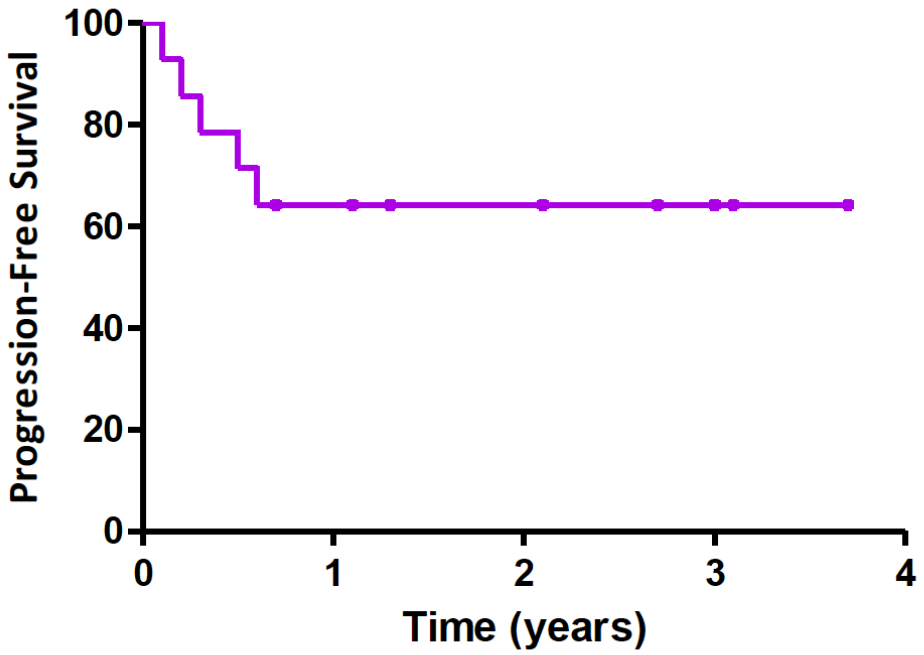
The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

PFS



Median FU: 2.7 years

2-y PFS 64%

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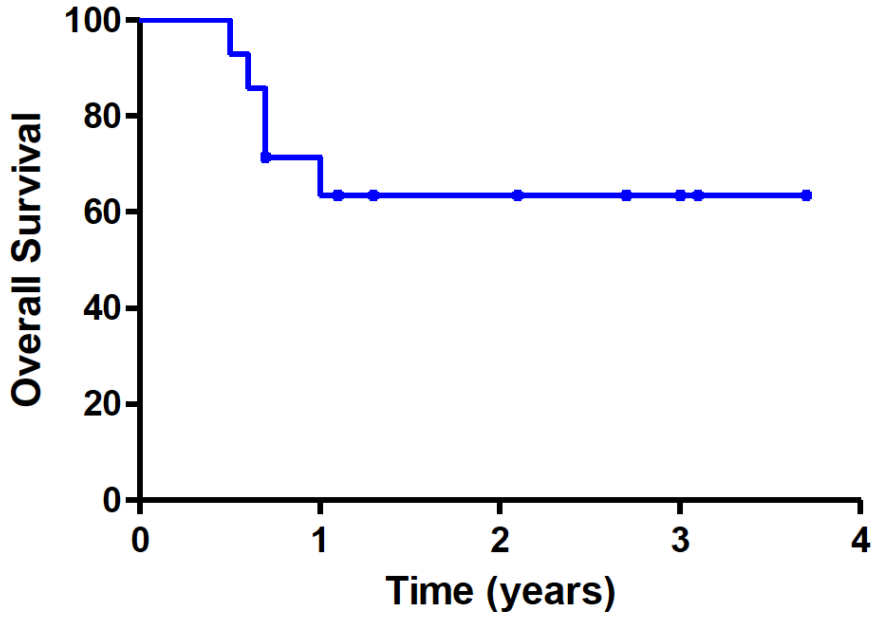
The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

OS



Median FU: 2.7 years

2-y OS 64%

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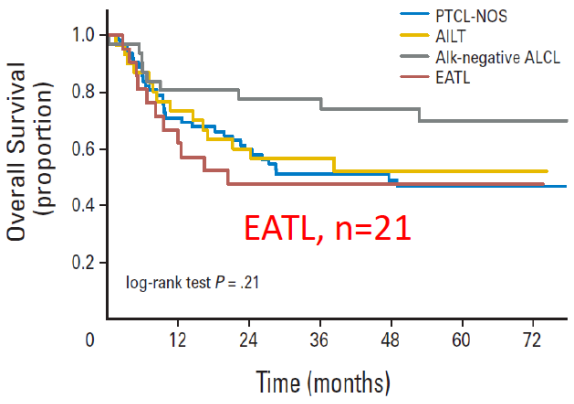
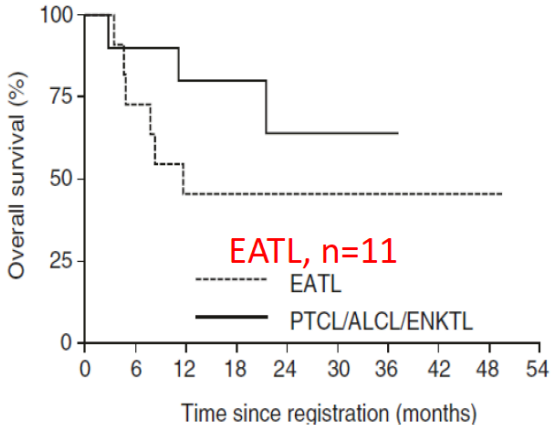
The **Eatl-001 Trial**: Results of a Phase 2 Study of **BV and CHP** Followed By **Consolidation with HDT-ASCT** in the Frontline Treatment of Patients with EATL (136)

Comparison with other prospective studies



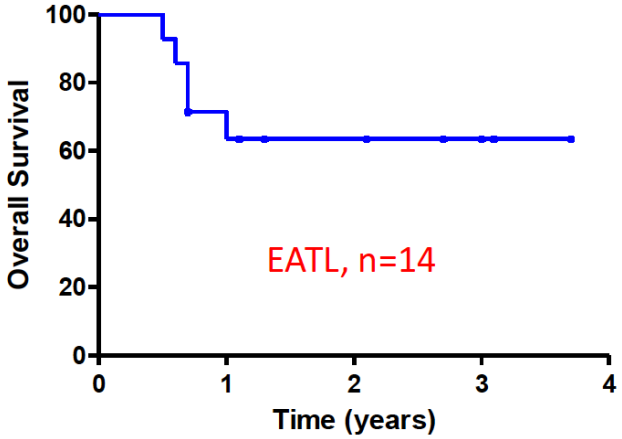
CHOEP-14 x6 + ASCT
2-y OS 48%

d'Amore F, JCO 2012



IVE-MTX x3 + ASCT
2-y OS 45%

Phillips EH, BMT 2019



EATL-001
2-y OS 64%

David Sibon

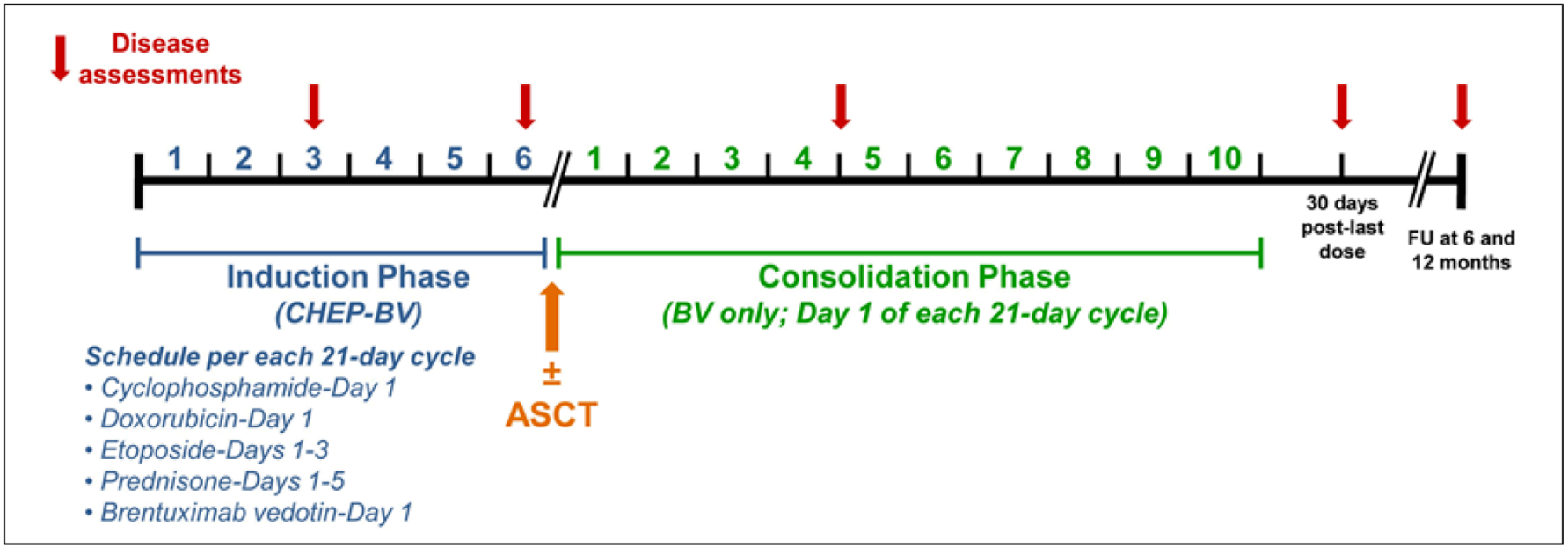
CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Rationale

- There is room for improvement with BV+CHP in CD30+ PTCLs (5y PFS 51%)[1]
  - Limited information about outcomes in PTCL with < 10% CD30 expression
- Etoposide is commonly added to CHOP (CHOEP) for 1L PTCL tx
  - Retrospective studies suggest improved outcomes, particularly in younger pts[2, 3]
- BV consolidation after ASCT improves PFS for high-risk relapsed/refractory Hodgkin lymphoma[4]
  - Ph 1 BV-CHP study in CD30+ PTCL included prolonged BV course w/excellent outcomes[5]
- Hypothesis:
  - Etoposide added to BV-CHP (CHEP-BV) +/- ASCT followed by BV consolidation is safe and effective tx for CD30+ PTCL

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Study Schema



- Response assessment by investigators: 2014 Lugano classification

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Baseline Characteristics

Variable	N (%)
Total	48 (100)
PTCL Subtype	
AITL	18 (37.5)
ALCL	16 (33)
ALK-	13 (27)
ALK+	3 (6)
PTCL NOS	11 (23)
TFH PTCL	2 (4)
ATLL	1 (2)
Male gender	30 (62.5)
Age, median in years	56 (24–79)
CD30 expression	
1-9%	16 (33)
10% or greater	32 (67)
Stage I-II	5 (10)
Stage III-IV	43 (90)
Bone marrow involvement	15 (31)

Variable	N (%)
B symptoms	31 (65)
Elevated LDH	27 (56)
Extranodal involvement	31 (65)
ECOG ≥2	7 (15)
IPI score	
0-1	10 (21)
2	19 (40)
3	14 (29)
4-5	5 (10)
Missing	1 (2)
Prior SOC chemotherapy	
No	30 (62.5)
Yes	18 (37.5)
CHOP	8 (17)
CHOEP	4 (8)
EPOCH	1 (2)
BV-CHP	5 (10)

Alex F. Herrera

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Treatment Disposition

Status	N (%)
Completed CHEP-BV	**43 (90%)**
D/c due to PD	2
D/c at MD discretion	1
Death due to COVID-19	1
Receiving CHEP-BV at data cut	1
Proceeded to ASCT	**24 (50%)**
Received BV consolidation (median 8 cycles, 1-10)	**33 (74%)**
After ASCT	20
After CHEP-BV	13
Completed consolidation	**13 of 33 (39%)**
D/c due to AE **(n=10 PN, n=1 PN+infection, n=1 pulmonary)**	12 (36%)
D/c due to PD	5
D/c due to patient/physician choice	2

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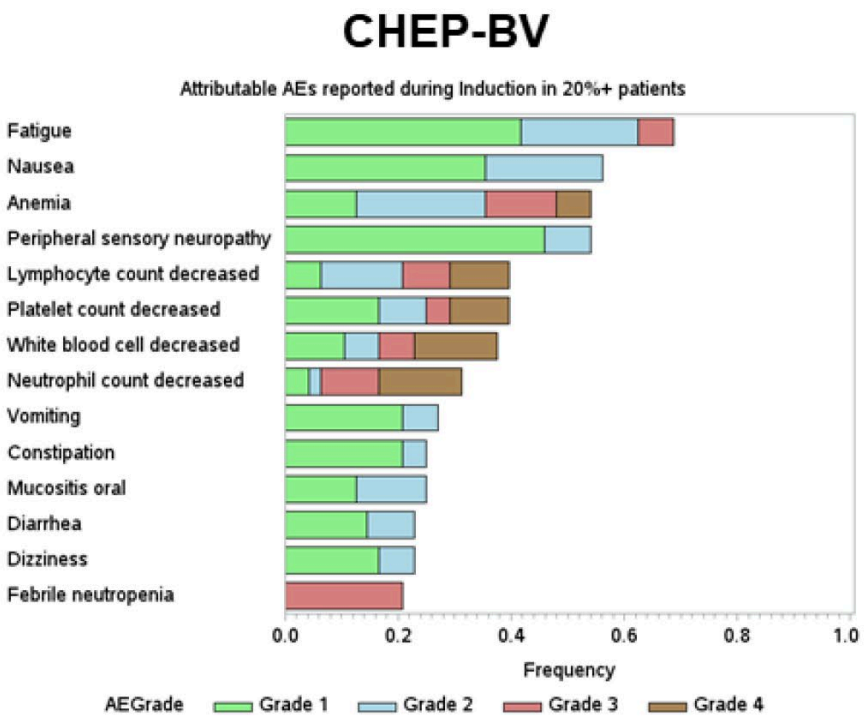
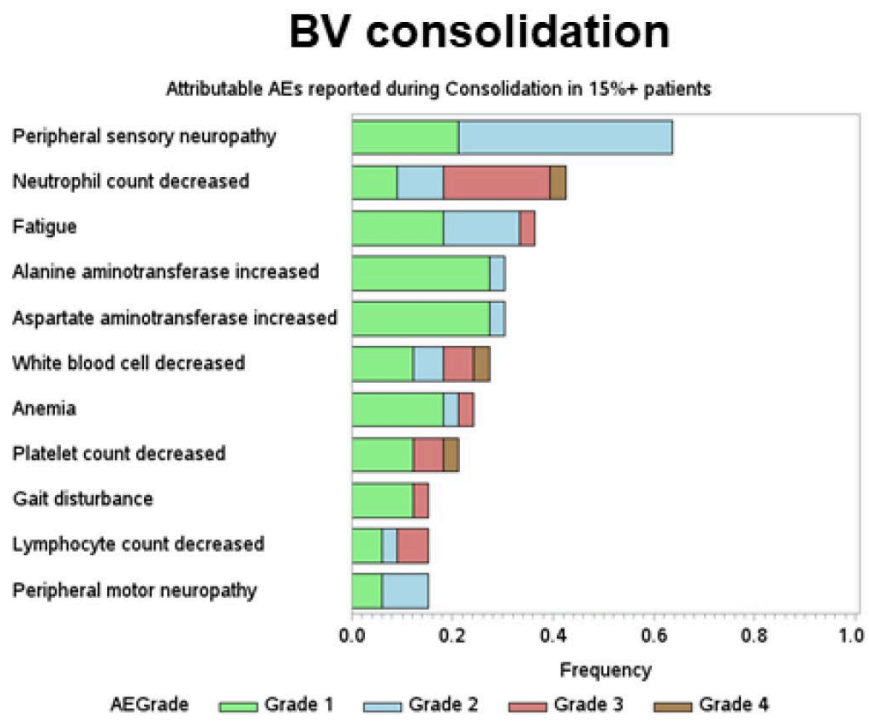
CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Most Common Adverse Events





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CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Gr ≥ 3 AEs During CHEP-BV

Most common Grade ≥ 3 AE	Grade 3	Grade 4	Total (%)
Neutropenia	5 (10%)	7 (15%)	**12 (25%)**
Febrile neutropenia	10 (21%)	0	**10 (21%)**
Leukopenia	3 (6%)	7 (15%)	**10 (21%)**
Lymphopenia	4 (8%)	5 (10%)	**9 (19%)**
Anemia	6 (13%)	3 (6%)	**9 (19%)**
Thrombocytopenia	2 (4%)	5 (10%)	**7 (15%)**
Fatigue	3 (6%)	0	**3 (6%)**
Upper respiratory infection	2 (4%)	0	**2 (4%)**

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Response to CHEP-BV

	All Patients (n=46)	
Response	**Interim**	**End of CHEP-BV**
Overall response (ORR)	**44 (96%)**	**42 (91%)**
Complete response (CR)	**27 (59%)**	**37 (80%)**
Partial response (PR)	17	5
Stable disease (SD)	1	0
Progressive disease (PD)	1	4

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

End of CHEP-BV Response: PTCL Subtypes

Response	ALCL (n=16)	Non-ALCL (n=30)	AITL (n=17)	PTCL NOS (n=11)	PTCL TFH (n=2)
Overall response (ORR)	15 (94%)	27 (90%)	16 (94%)	9 (82%)	2 (100%)
Complete response (CR)	15 (94%)	22 (73%)	14 (82%)	6 (55%)	2 (100%)
Partial response (PR)	0	5	2	3	0
Stable disease (SD)	0	0	0	0	0
Progressive disease (PD)	1	3	1	2	0

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CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

End of CHEP-BV Response: CD30%

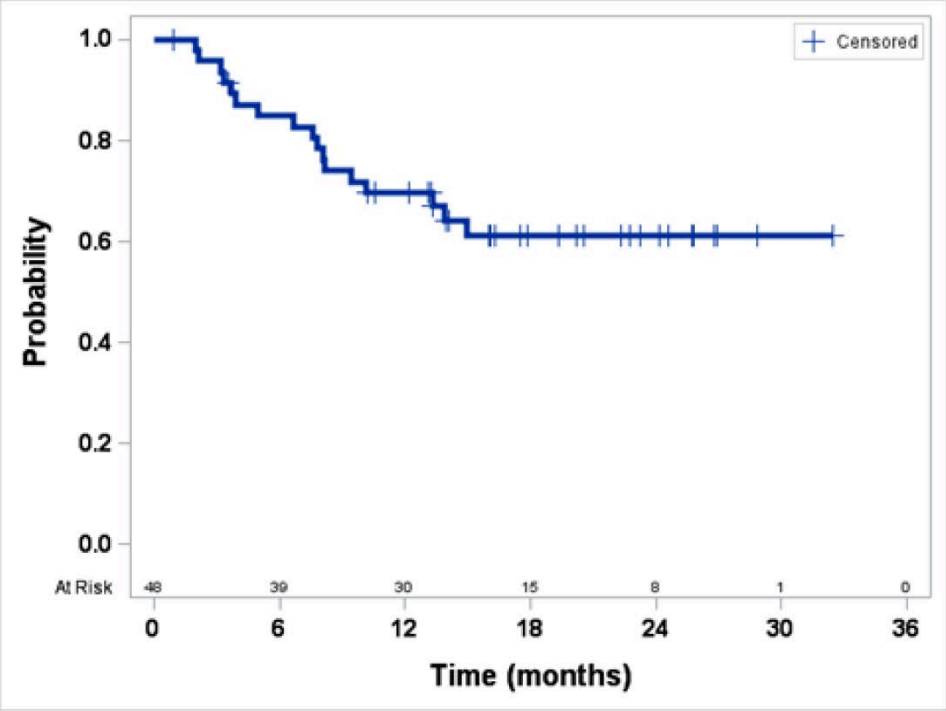
Response	Non-ALCL (n=30)	CD30 1-9% (n=14)	CD30 ≥ 10% (n=16)
Overall response (ORR)	**27 (90%)**	**13 (93%)**	**14 (88%)**
Complete response (CR)	**22 (73%)**	**9 (64%)**	**13 (81%)**
Partial response (PR)	5	4	1
Stable disease (SD)	0	0	0
Progressive disease (PD)	3	1	2

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Progression-Free Survival (all patients)

Median FU in survivors is 16.1 mo (range, 0.9-32.5)

- 18-month PFS 61%
  (95% CI 45%-74%)

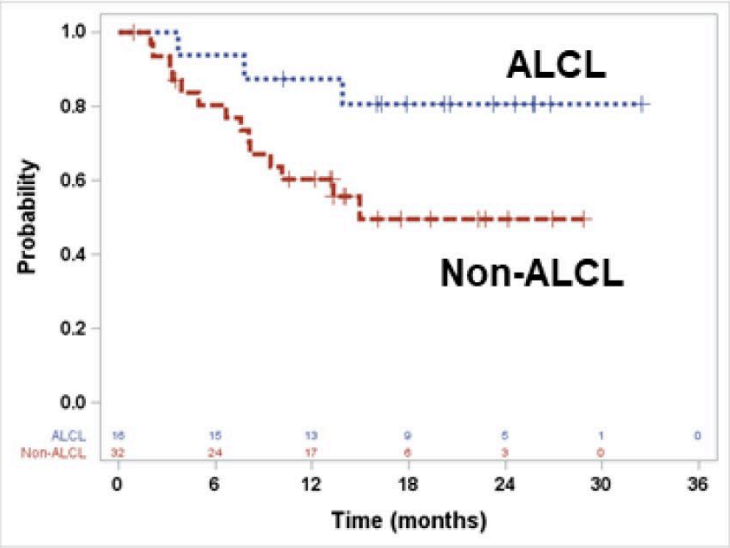


Alex F. Herrera

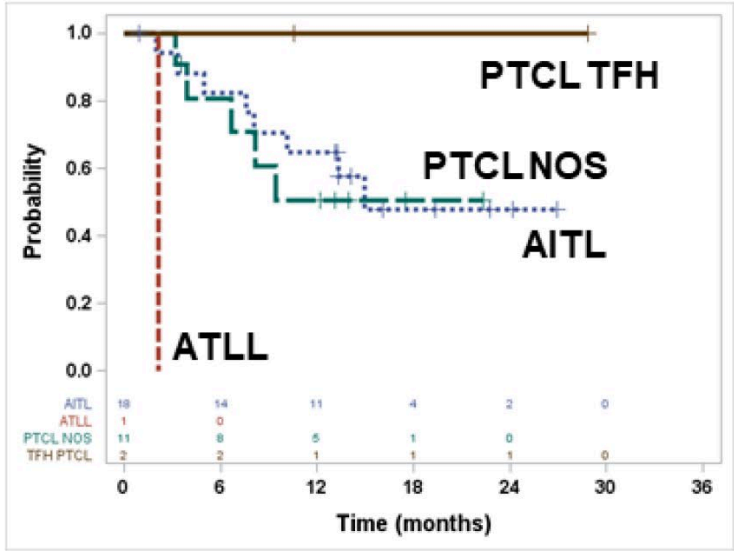
CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

PFS from treatment start in subgroups

- **18mo PFS: ALCL 81% vs non-ALCL 49%**
  - ALCL (n=16): ASCT 7 vs no 9
  - Non-ALCL (n=32): ASCT 17 vs no 15



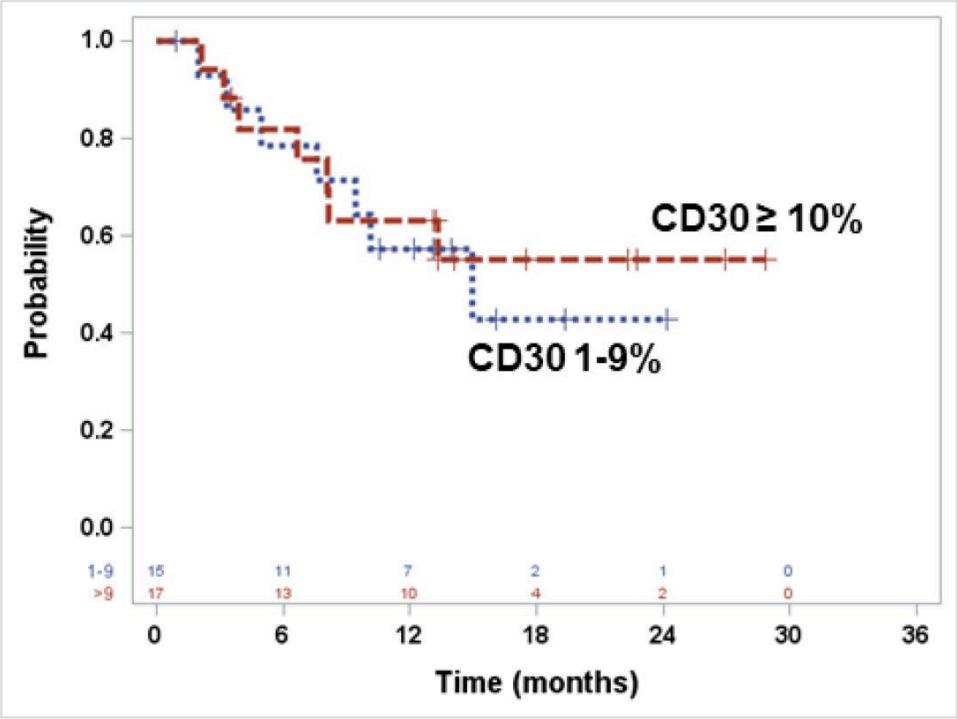
- **18mo PFS: AITL 48%, PTCL NOS 51%**
  - AITL (n=18): ASCT 12 vs no 6
  - PTCL NOS (n=11): ASCT 4 vs no 7



CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

PFS from treatment start by CD30%

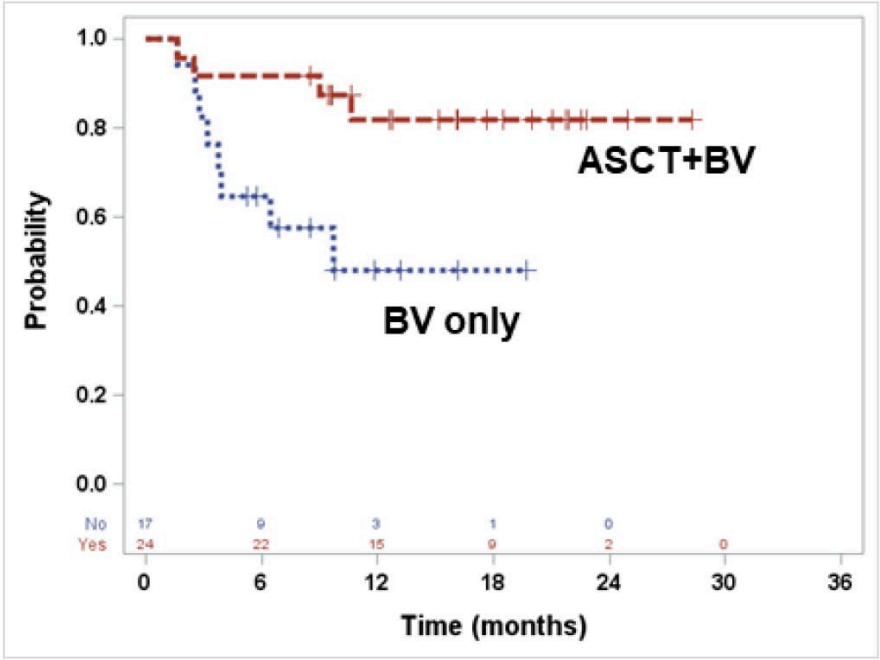
- **18mo PFS by CD30% (non-ALCL)**
  - **CD30 1-9% (n=15): 43%**
  - **CD30 ≥ 10% (n=17): 55%**



CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

PFS in transplanted vs non-transplanted pts

- **Landmark 1y PFS from end of CHEP-BV (n=41 responders with follow-up data)**
  - **ASCT+BV consolidation (n=24): 82%**
    - **22 CR, 2 PR**
  - **BV consolidation only (n=17): 48%**
    - **15 CR, 3 PR**

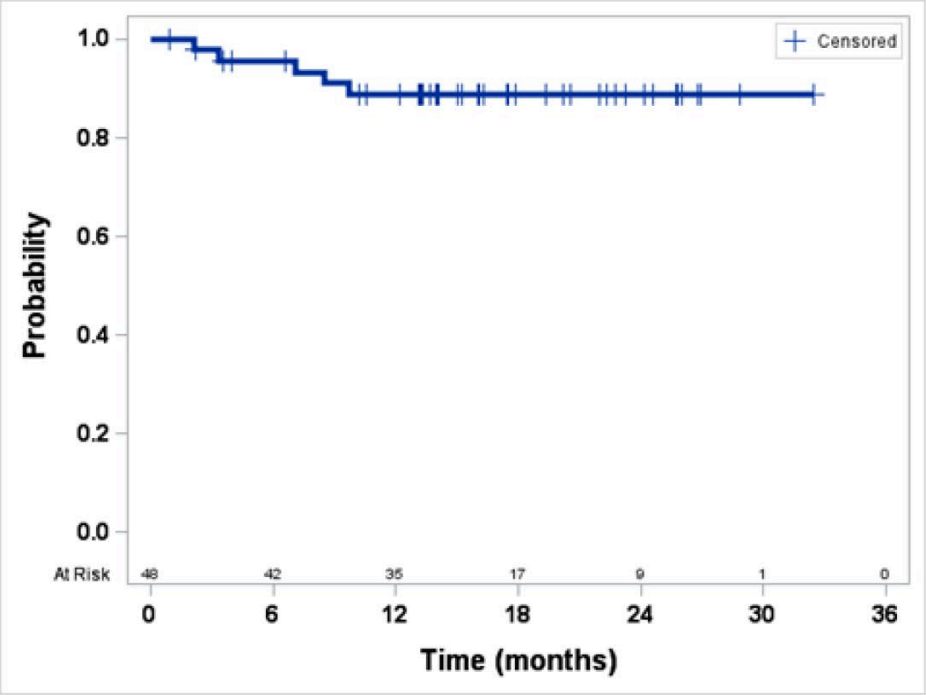


CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Overall Survival (all patients)

Median FU in survivors is 16.1mo (range, 0.9-32.5)

- 18-month OS 89%
  (95% CI: 75%-95%)



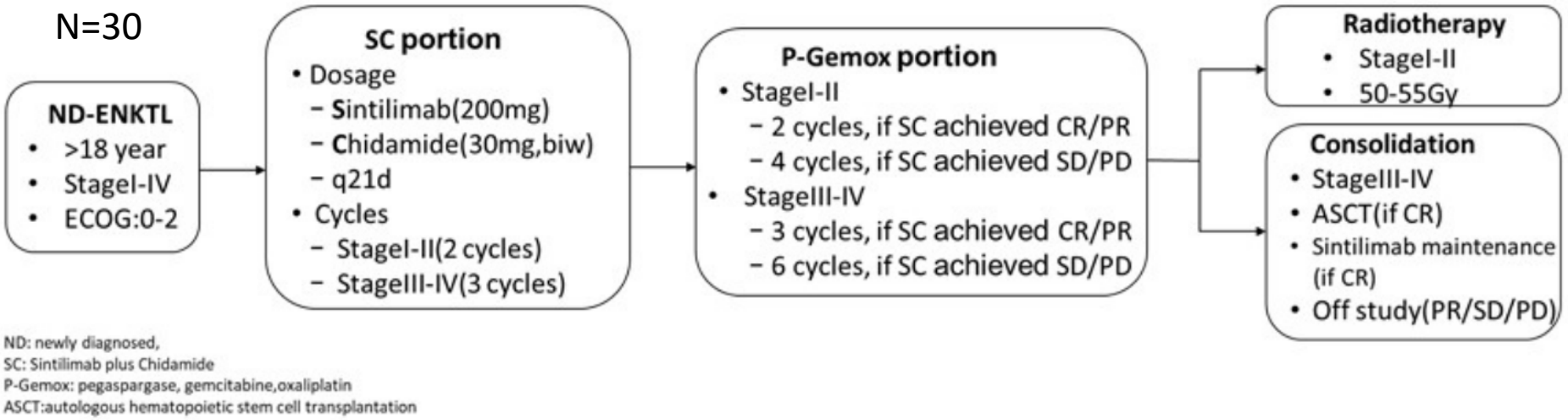
Alex F. Herrera

CHEP-BV Followed By **BV Consolidation** in Patients with CD30-Expressing PTCLs (133)

Conclusions

- CHEP-BV was tolerable and led to high CR rate
  - Similar febrile neutropenia rate to BV-CHP
- 74% received BV consolidation (median 8 cycles) most did not complete due to neuropathy
- CHEP-BV (+/- ASCT) and BV consolidation was effective
  - PFS in ALCL > non-ALCL subgroup
  - Unclear impact of % CD30 in non-ALCL pts (similar PFS, higher CR in 10+%)
  - CHEP-BV + ASCT + BV consolidation associated with excellent PFS
- CHEP-BV and BV consolidation in CD30+ PTCL merits further study

Novel Induction Therapy for Newly Diagnosed ENKTL Lymphoma Treated By **Anti-PD-1 Antibody** Plus **Histone Deacetylase Inhibitor** Followed By **P-GemOx** Regimen (137)

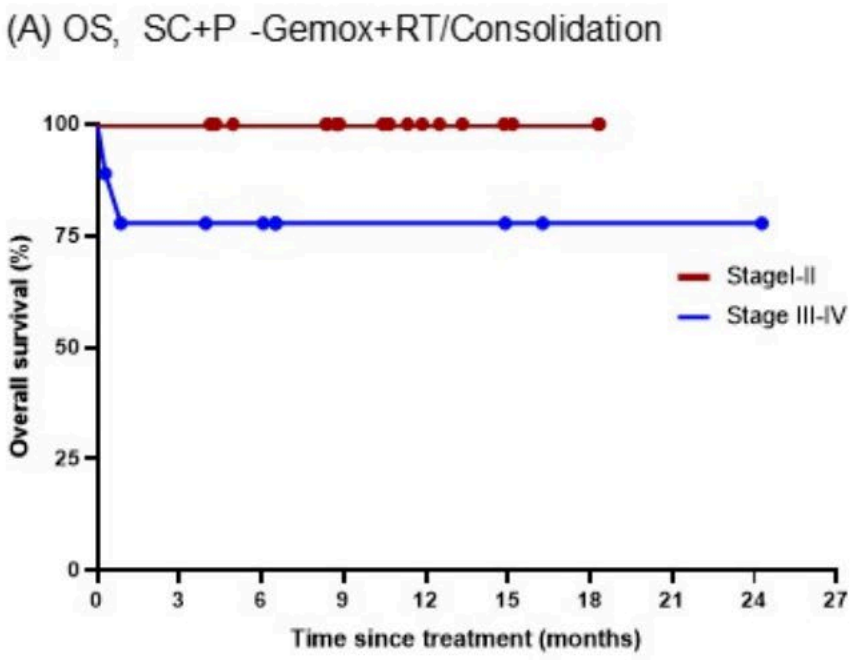


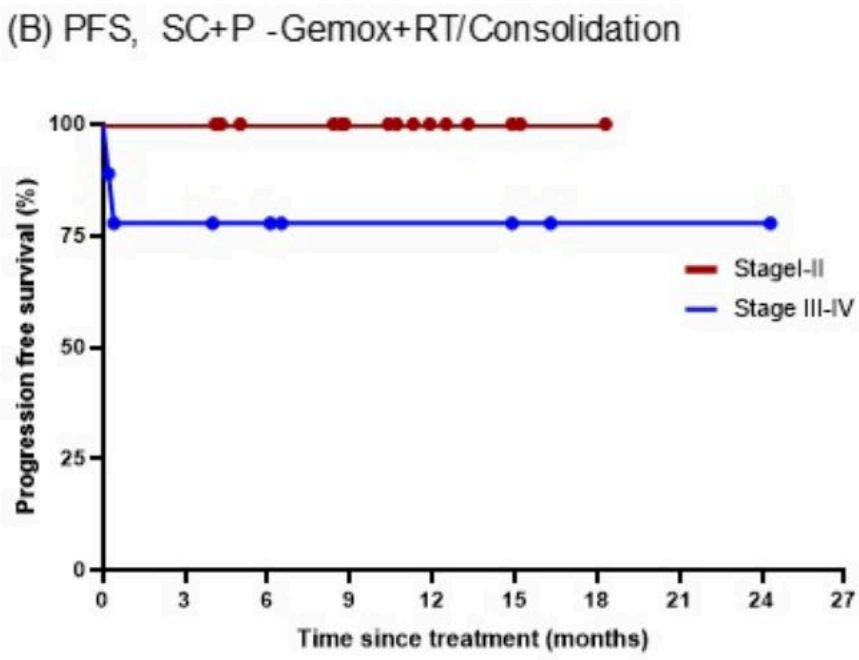
ND: newly diagnosed,
SC: Sintilimab plus Chidamide
P-Gemox: pegaspargase, gemcitabine,oxaliplatin
ASCT:autologous hematopoietic stem cell transplantation

Gao Yan

Novel Induction Therapy for Newly Diagnosed ENKTL Lymphoma Treated By **Anti-PD-1 Antibody** Plus **Histone Deacetylase Inhibitor** Followed By **P-GemOx** Regimen (137)

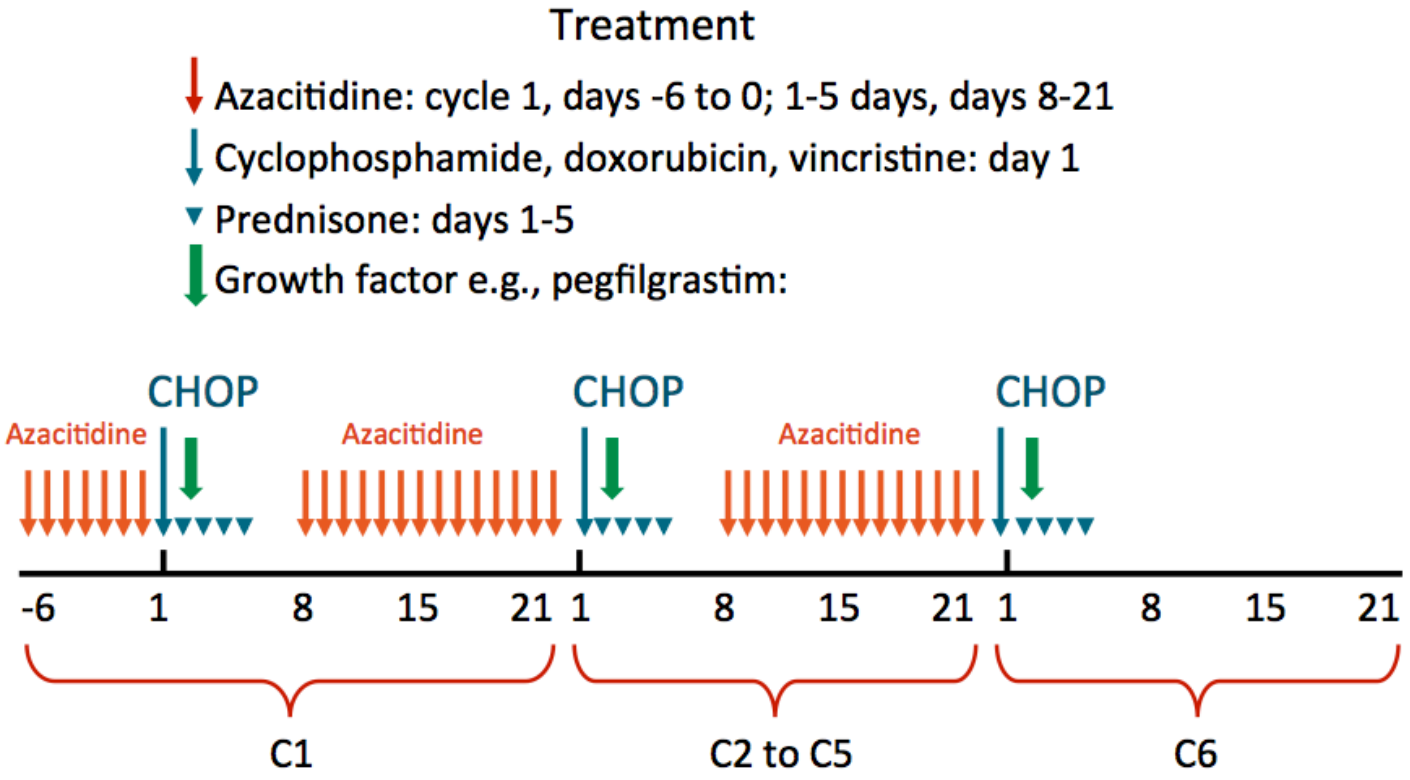
Figure 3. Survival of whole cohort





Gao Yan

High Rates of Remission with the Initial Treatment of **Oral Azacitidine Plus CHOP** for PTCL: Clinical Outcomes and Biomarker Analysis of a Multi-Center Phase II Study (138)

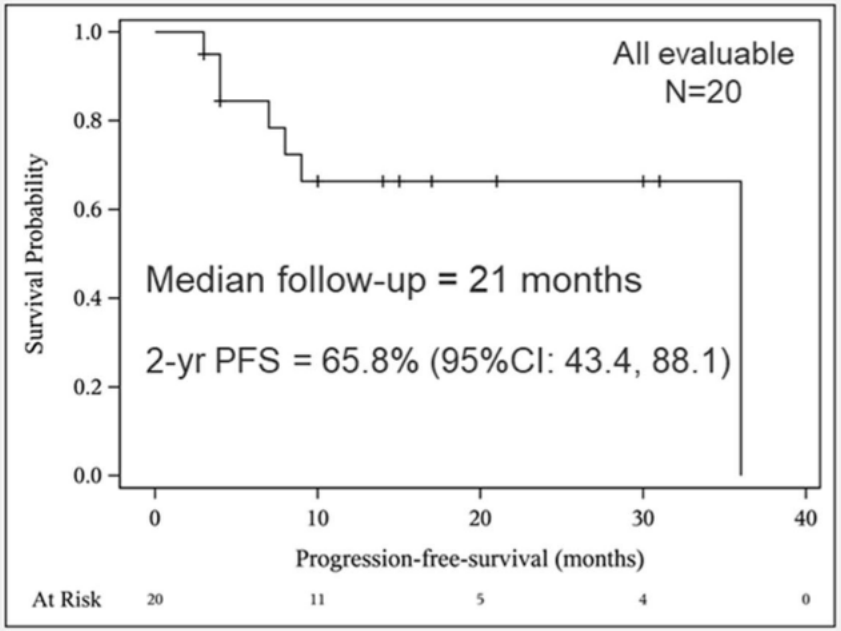


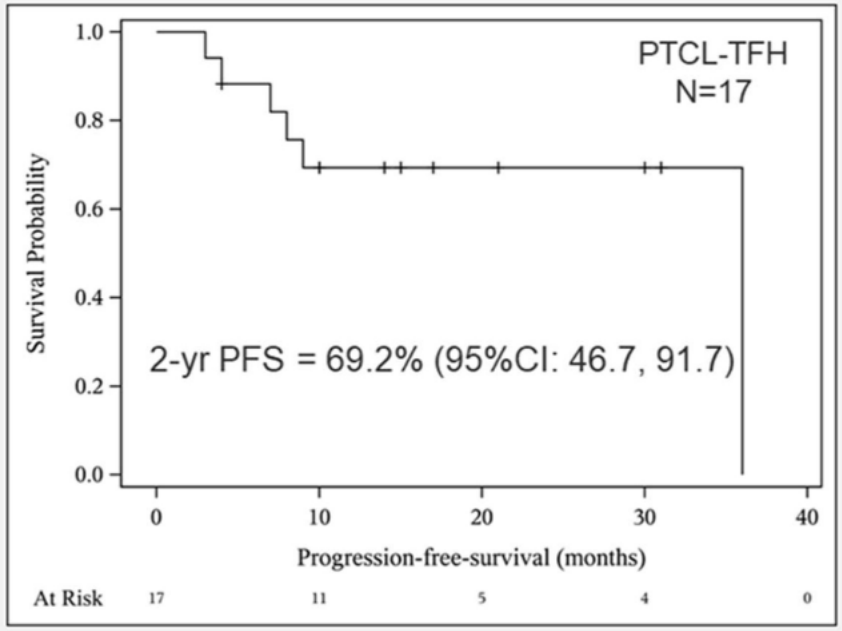
- Azacitidine dosing: 300 mg/day, d-6 to 0, then D8-21 in Cycles 1-5
- Patients in CR/PR after 6 cycles can receive consolidative HSCT

Jia Ruan

High Rates of Remission with the Initial Treatment of **Oral Azacitidine Plus CHOP** for PTCL: Clinical Outcomes and Biomarker Analysis of a Multi-Center Phase II Study (138)

Progression-free Survival





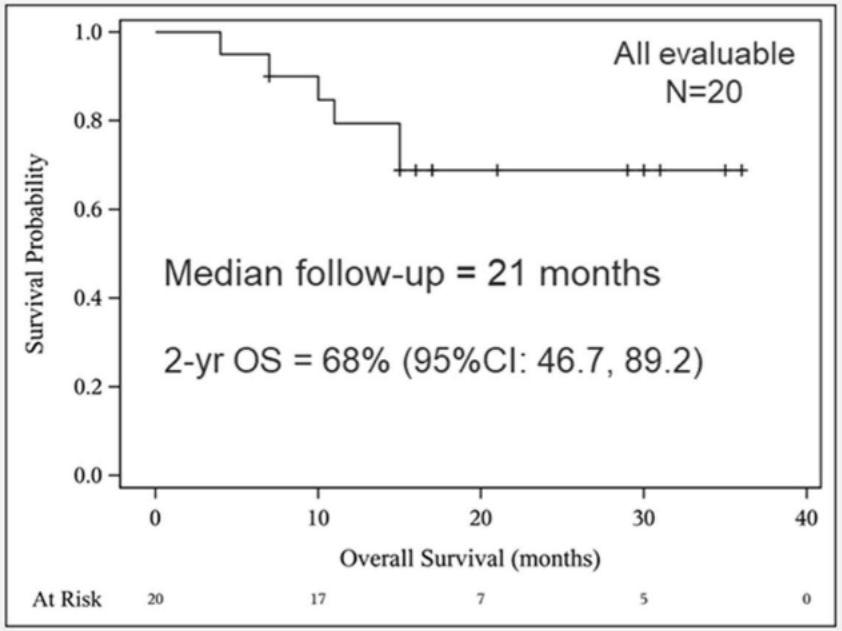
- CR : 75%
- TET2 mut : associated with CR and favorable PFS
- DNMT3A mut: adverse PFS

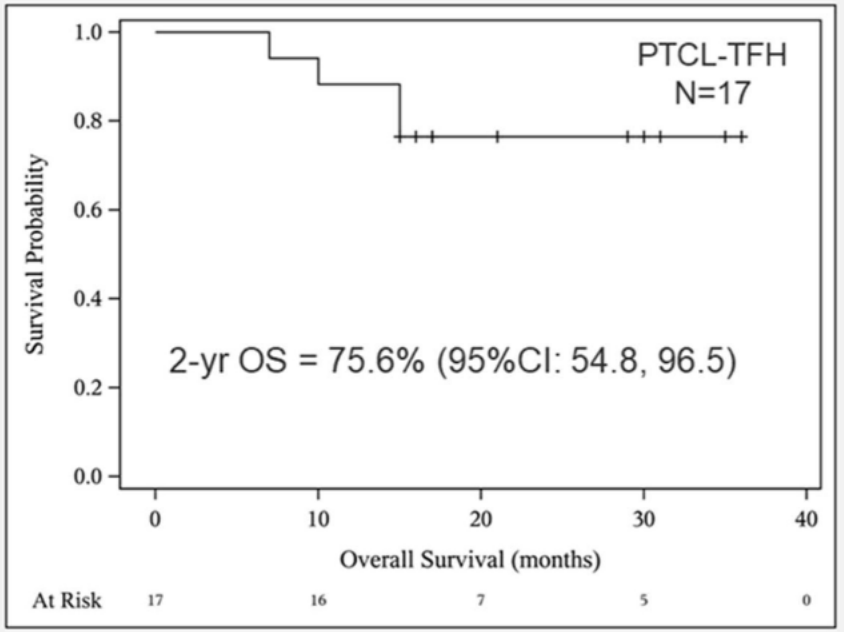
- CR : 88.2%
- TET2 mutations: favorable PFS

Jia Ruan

High Rates of Remission with the Initial Treatment of **Oral Azacitidine Plus CHOP** for PTCL: Clinical Outcomes and Biomarker Analysis of a Multi-Center Phase II Study (138)

Overall Survival





- TET2 mut : favorable OS

- Gene expression-based cell subtype deconvolution revealed a decreasing trend in TFH lymphoma cells, proliferation rate, as well as TCRB clonality in response to aza treatment

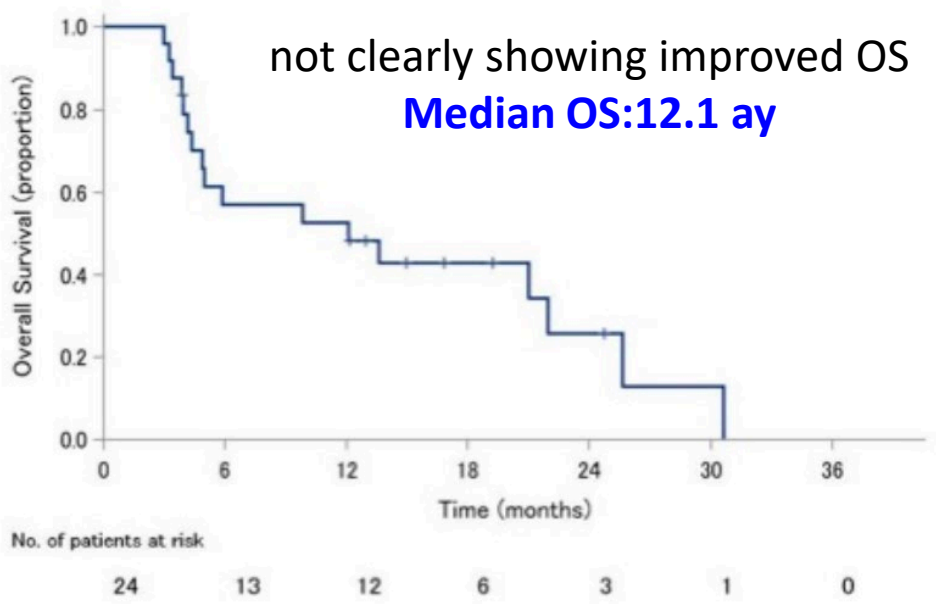
Jia Ruan

Adding **Romidepsin to CHOEP** in First Line Treatment of PTCLs Does Not Improve the Response Rate: Final Analysis of Phase II PTCL13 Study (134)

- primary objective of the study :
  - 15% increase in 18-months PFS for the combination Ro-CHOEP plus HSCT (from 55% to 70%, planned sample size=110),
  - compared to the previous Italian trial (Corradini P et al, Leukemia 2014).
  - 18-months PFS of 48%. (n=86)
- the enrollment of the **trial was stopped** due to **inefficacy of the experimental combination.**

CHOP Plus Sequential **Mogamulizumab** As First-Line Therapy for Untreated ATLL (1393)

- New-onset treatment-naive ATLL
- not eligible to HSCT
- 3 X CHOP > mogamulizumab
- primary endpoint : OS at months 12
- 24 patients
- median age was 75.5 years
- median follow-up period was 11.0 months.
- **ORR was 87.5%.**



not clearly showing improved OS

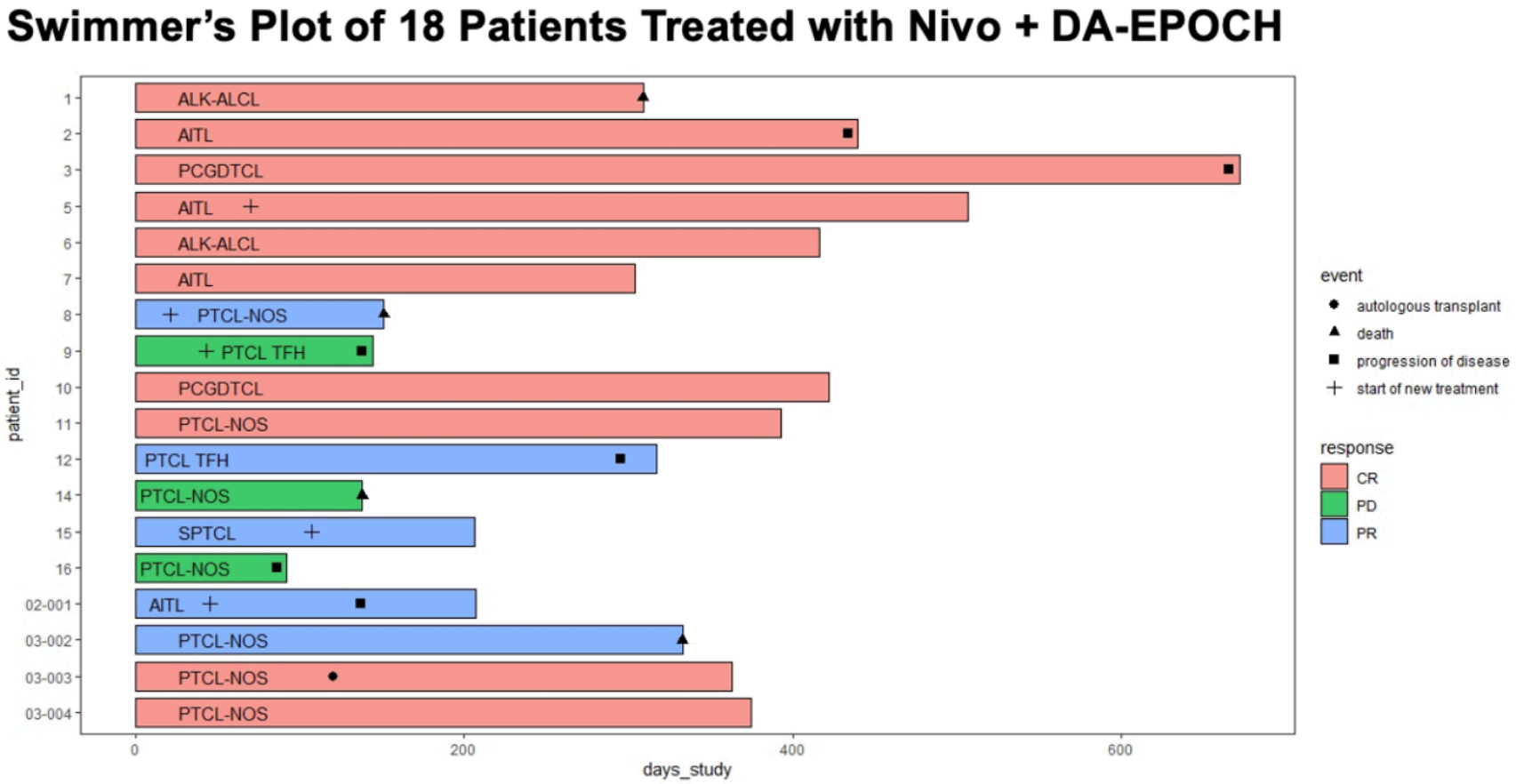
Median OS:12.1 ay

immunological consolidation therapy following chemotherapy

"mogamulizumab may unlock the tumor immune evasion mechanism by removing regulatory T cells and exert an immunological effect like GvATL"

Kazuki Tanimoto

A Pilot Study Using **Nivolumab** in Combination **with SOC CT** in Newly Diagnosed PTCLs (2444)



Brad Haverkos

T/NK Cell Lymphoma **Frontline** Clinical Trials (ASH2021)

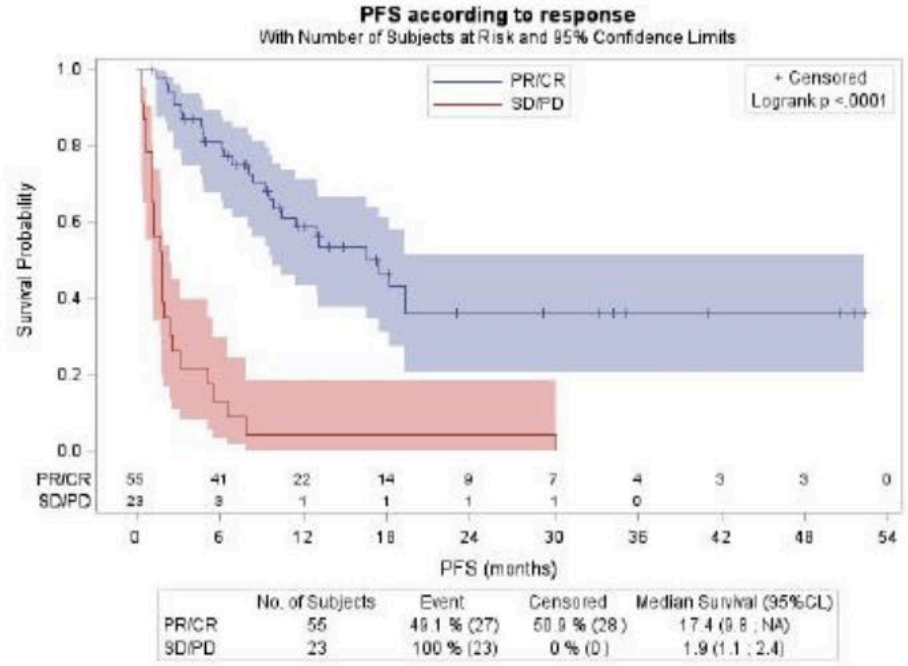
	N	FAZ	RESULTS	PFS	OS
A+CHP vs CHOP	452	3	ORR/CR: %59/38 vs %50/30	Median PFS: 62.3 mo vs 23.8 mo	5 Y :%70.1 vs %61
CHEP-BV > BV Consolidation	48	2	**ORR:%91 CR:%80**	18-mo :% 61	18-mo : %89
Oral Azacitidine + CHOP	20	2	CR: %75	2 Y : % 65.8	2 Y : % 68
Romidepsin + CHOEP	86	2		18-mo: % 48	
CHOP> Mogamulizumab	24	?	ORR:%87.5		Median OS: 12.1 ay

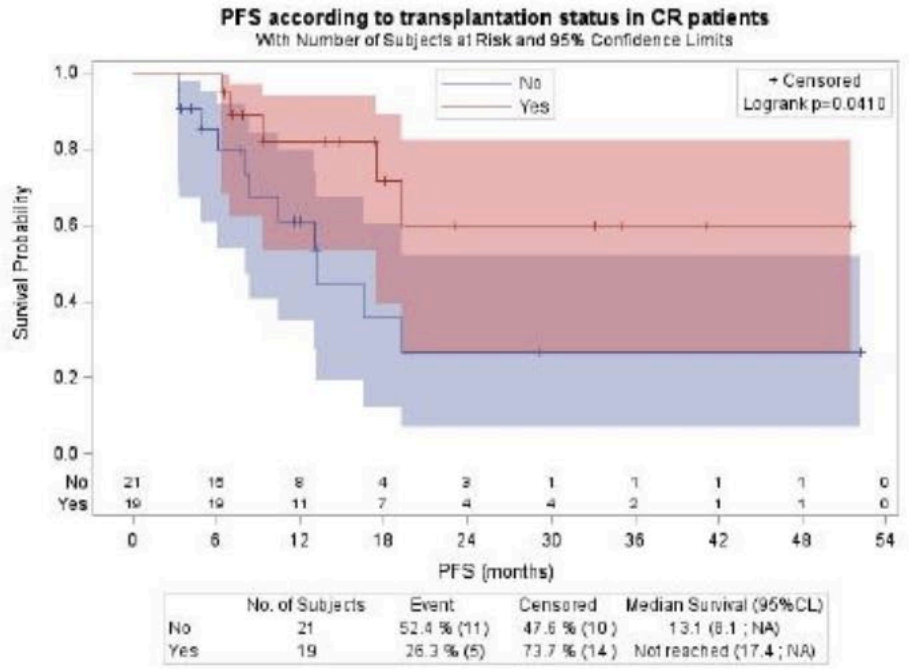
T/NK Cell Lymphoma **R/R** Therapy

Median OS : < 6 months
Current FDA approved therapies : ORR < 30%

Salvage Therapy with **BV** and **Bendamustine** for Patients with R/R PTCL. a Multicenter and Retrospective Study (620)

non-cutaneous R/R PTCL among 21 LYSA centers in France and Belgium

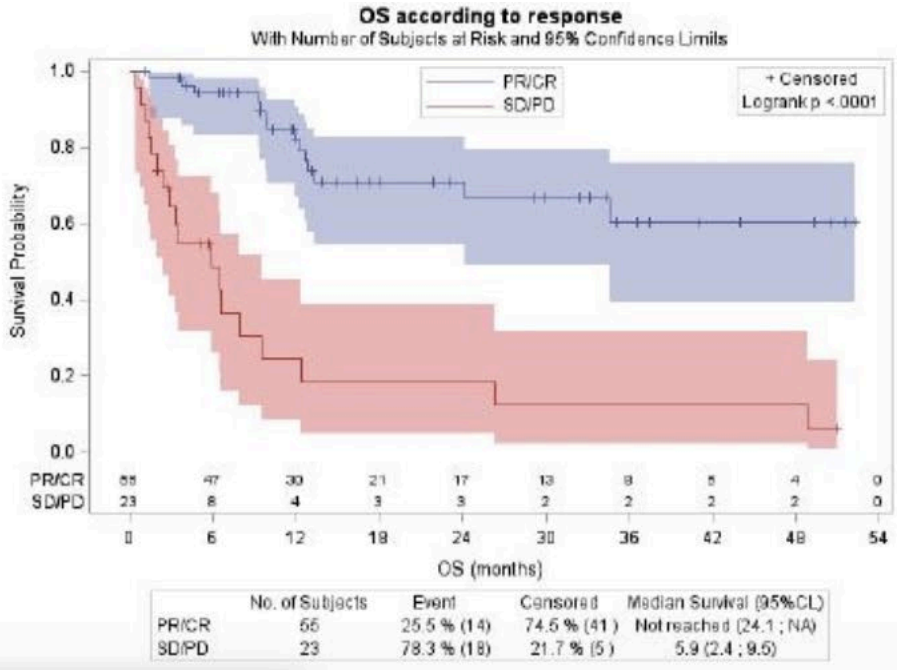


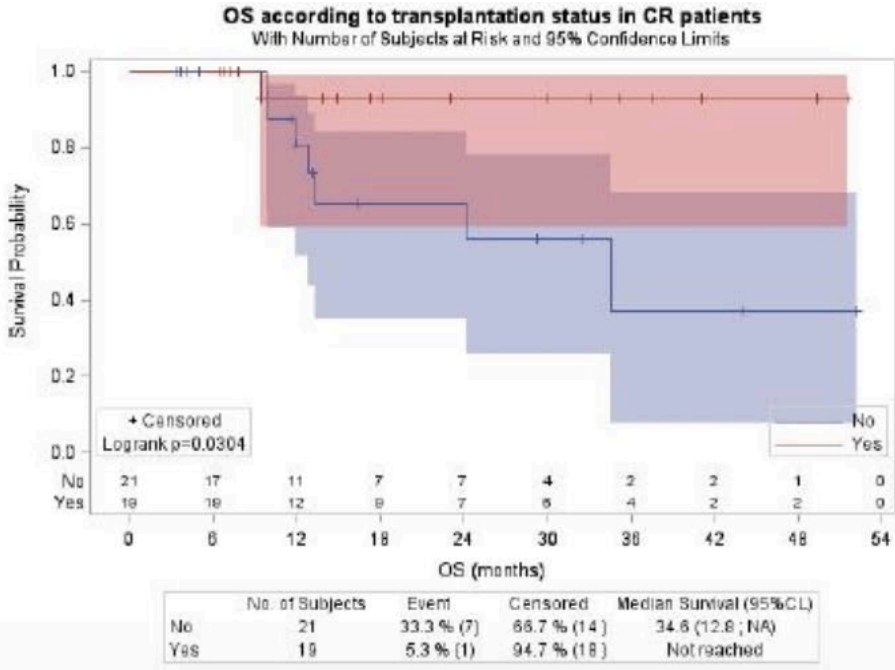


- N=82, median age : 60 years,
- advanced stage (88%) , IPI ≥ 2 (79%).
- Half of patients : refractory to last treatment.
- Median number of prior regimens : 1 (1-6).

best ORR:71%,(51% CR)

Salvage Therapy with **BV** and **Bendamustine** for Patients with R/R PTCL. a Multicenter and Retrospective Study (620)





median OS: Not Reached vs 5,9 mo, p<.0001)

median OS: Not Reached vs 34,6 mo; p=.0304)

Krimo Bouabdallah

Outcome of R/R PTCL with **Intention** for Curative Therapy Incorporating **HDC/SCT** (624)

BC Cancer Lymphoid Cancer Database

Table 1: Patient Characteristic at time of relapse/progression (n=114)		
Median age, years		53 (18-69)
Male sex, n (%)		73 (64)
Stage, n (%)	I/II	18 (16)
	III/IV	96 (84)
Secondary IPI, n (%)	0-1	41 (36)
	2	39 (34)
	3	25 (22)
	4-5	4 (4)
	Not Available	5 (4)
Performance Status, n (%)	0-1	73 (64)
	≥2	30 (26)
	Not Available	11 (10)
Elevated LDH n, (%)	No	57 (50)
	Yes	45 (40)
	Not Available	11 (10)
PTCL Subtype n, (%)	ALK- ALCL	29 (25)
	ALK+ ALCL	12 (10)
	AITL	17 (15)
	PTCL, NOS	56 (60)
Remission status, n (%)	Refractory	68 (60)
	Relapsed	46 (40)
Second-line therapy, n (%)	High dose cyclophosphamide	10 (9)
	Multiagent chemotherapy	83 (73)
	- GDP	59 (52)
	- Other	24 (21)
	Novel agents	15 (13)
	- Brentuximab Vedotin	12 (11)
	- Romidepsin	2 (2)
	- Pralatrexate	1 (1)
	No second-line therapy	6 (5)

- ORR to GDP: 61% (17% CR)
- relapsed vs refractory 81% vs. 41%,)
- ORR to BV: 75% (25% CR)

Henry S. Ngu

Outcome of R/R PTCL with **Intention** for Curative Therapy Incorporating **HDC/SCT** (624)

median follow up : 6.8 years (0.3 to 30.7)

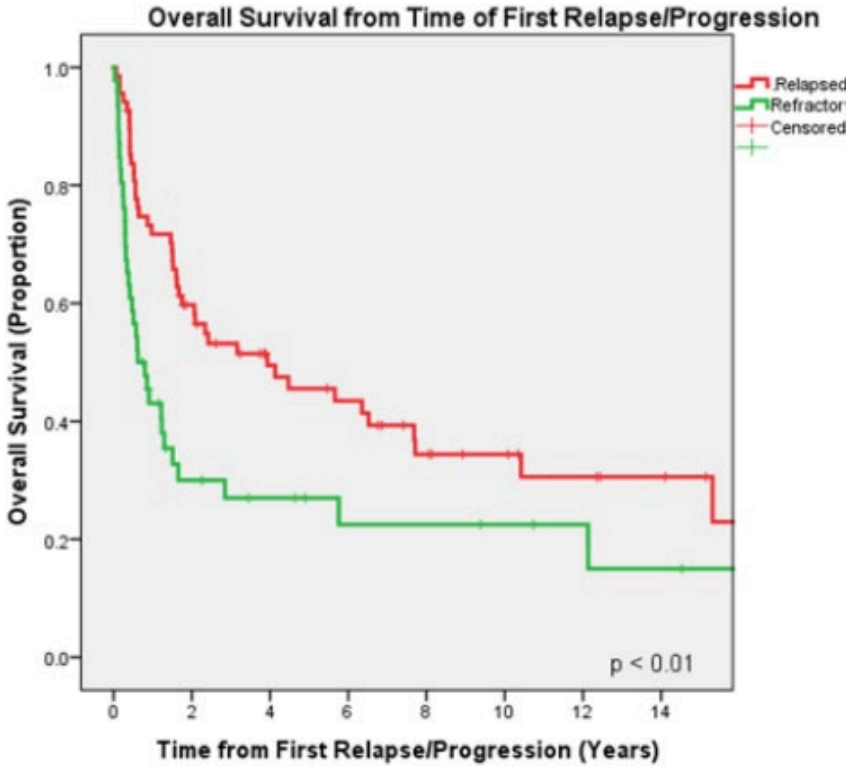
Table 2: Progression Free Survival and Overall Survival

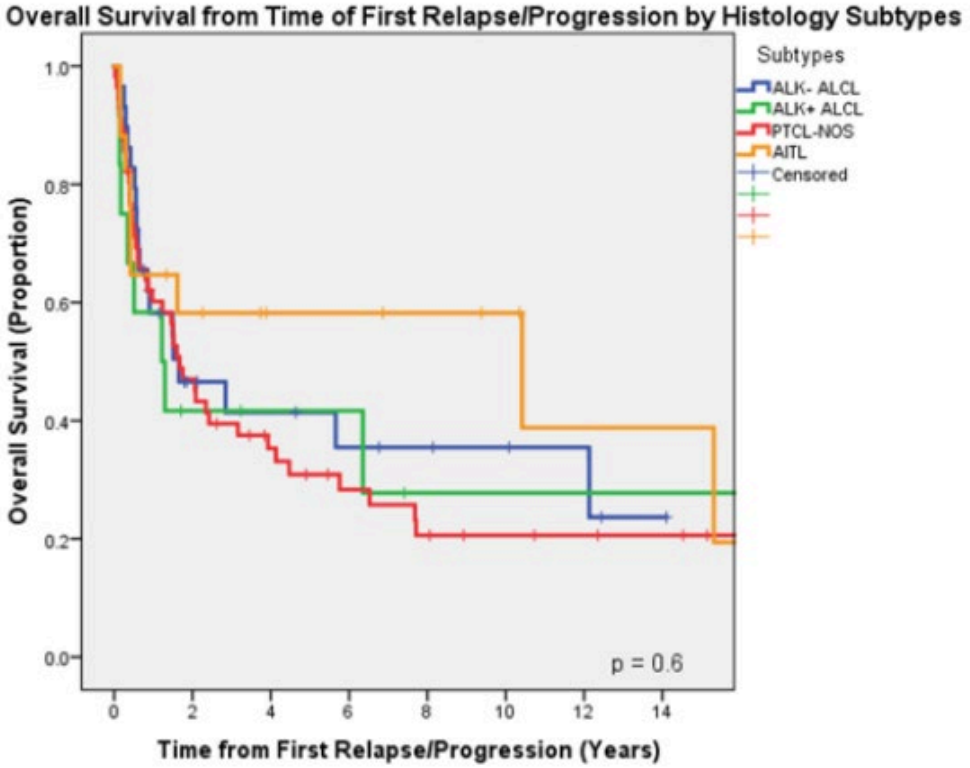
	Post Relapse/Progression					Post HDC/SCT				
	n	2 Year PFS	5 Year PFS	2 Year OS	5 Year OS	n	2 Year PFS	5 Year PFS	2 Year OS	5 Year OS
Entire Cohort	114	34%	28%	48%	38%	73	48%	45%	62%	54%
Relapsed	68	42%	32%	60%	46%	50	47%	42%	65%	56%
Refractory	46	23%	23%	30%	27%	23	53%	53%	55%	50%
		(p = 0.01)		*(p <0.01)*			*(p = 0.6)*		*(p = 0.8)*	
Autologous	39	40%	37%	58%	43%	39	42%	37%	58%	44%
Allogeneic	34	57%	47%	72%	63%	34	55%	55%	67%	67%
		(p = 0.2)		*(p = 0.4)*			*(p = 0.3)*		*(p = 0.5)*	
GDP Regimen	59	28%	21%	44%	35%	35	42%	39%	60%	48%
Subtype										
ALK- ALCL	29	32%	26%	47%	41%	21	37%	31%	58%	45%
ALK+ ALCL	12	39%	39%	42%	42%	9	52%	52%	56%	56%
AITL	17	49%	49%	58%	58%	14	64%	64%	71%	71%
PTCL NOS	56	30%	22%	47%	31%	29	46%	43%	64%	52%
		P = 0.7		*P = 0.6*			*P = 0.6*		*P = 0.6*	

outcomes in the ITT R/R PTCLs remain suboptimal with long-term survival in about only 1/3 of pts, but over half are alive at 5 years if they are able to receive a SCT

Henry S. Ngu

Outcome of R/R PTCL with Intention for Curative Therapy Incorporating **HDC/SCT** (624)





Henry S. Ngu

T/NK Cell Lymphoma R/R Therapy
Chemo-free Approaches

Phase 2a Study of the **Dual SYK/JAK Inhibitor Cerdulatinib** (ALXN2075) As Monotherapy in Patients with R/R PTCL (622)

Table 1. Tumor response to cerdulatinib monotherapy in patients with PTCL (efficacy-evaluable population[a])

	AITL/TFH (N=27)	PTCL NOS (N=9)	Other[b] (N=22)	Total PTCL (N=58)
ORR, n (%)	14 (51.9)	0	7 (31.8)	21 (36.2)
CR, n (%)	10 (37.0)	0	2 (9.1)	12 (20.7)
PR, n (%)	4 (14.8)	0	5 (22.7)	9 (15.5)
SD, n (%)	3 (11.1)	2 (22.2)	9 (40.9)	14 (24.1)
PD, n (%)	10 (37.0)	7 (77.8)	6 (27.3)	23 (39.7)
TTR, months, median (range)[c]	1.9 (1.5–16.5)	NR	1.9 (1.7–4.4)	1.9 (1.5–16.5)
DoR, months, median (range)[c]	12.9 (0–35.5)	NR	5.3 (1.0–26.2)	8.3 (0–35.5)

- oral cerdulatinib 30 mg twice daily, 28-day cycles, until disease prog or unaccep toxicity.
- median prior regimens 2 (1–10);
- 49.2% refractory to last treatment; 18 patients (27.7%) had prior stem cell transplant.
- increases in amylase-lipase: transient, reversible, not associated with clinical pancreatitis.

Final Results from a Phase 2 Study of **Tipifarnib** in Subjects with R/R PTCL (621)

- CXCL12 : essential for T-cell homing and for the maintenance of immune cell progenitors via its receptor CXCR4
- Tipifarnib inhibits farnesylation of key regulatory proteins involved in CXCL12 production
- AITL is associated with high levels of CXCL12 expression,
- tipifarnib 300 mg orally twice daily on Days 1-21 of 28-day treatment cycles until progression of disease or unacceptable toxicity
- 38 AITL, 14 PTCL-NOS, 11 PTCL-CXCL12+, 2 other.
- median of 3 prior regimens (1-8).
- ORR : 39.7%, ORR (AITL): 56.3%
- median OS (AITL): 32.8 months,
- median OS (PTCL-CXCL12+) :not reached

Thomas E. Witzig

Duvelisib in Patients with R/R PTCL from the Phase 2 Primo Trial: Results of an Interim Analysis (2456)

Table 1. Response Rates

	ORR n (%)	CR* n (%)	Time to Response (days)	mDOR (days)	mPFS (days)
	Expansion Phase, n=78				
IRC Assessment Range 95% CI	39 (50.0%)	25 (32.1%)	53 15-114 N/A	233 1+, 420+ 90, NC	107 1+, 469+ 57, 188
Subtypes (n, %)					
PTCL NOS (42, 53.8%)	22 (52.4%)	12 (28.6%)			
ALCL (11, 14.1%)	1 (9.1%)*	1 (9.1%)			
AITL (21, 26.9%)	14 (66.7%)	10 (47.6%)			
Other (4, 0.5%)	2 (50%)	2 (50%)			

- DUV at 75 mg BID for 2 cycles to maximize rapid tumor control, followed by 25 mg BID to maintain long-term disease control and mitigate late toxicities, until progressive disease (PD) or unacceptable toxicity.
- median age: 66.5 years (21-92 years)
- median of 3 prior lines of therapy (1-7)

Duvelisib in Patients with R/R PTCL from the Phase 2 Primo Trial: Results of an Interim Analysis (2456)

Table 2. Selected ≥ Grade 3 Adverse Events (n=78)

Subjects with any TEAE resulting in treatment discontinuation	14 (17.9%)
Adverse Event	**Patients Number (%)**
Neutropenia	30 (38.5%)
ALT/AST	19 (24.4%) / 17 (21.8%)
Rash	6 (7.7%)
Lymphocyte count decreased	6 (7.7%)
Sepsis	5 (6.4%)

- 3 deaths related or possibly related to duvelisib:
- pneumonitis,
- Epstein-Barr associated lymphoproliferative disorder, and
- sepsis.

Pivotal Phase 2 Study of the EZH1 and EZH2 Inhibitor **Valemetostat Tosylate (DS-3201b)** in Patients with R/R **ATLL** (303)

Parameter	Efficacy per centrally assessed EAC				Efficacy per INV
	All ATL (N=25)	ATL subtype			All ATL (N=25)
		Acute (n=16)	Lymphoma (n=6)	Unfavorable chronic type (n=3)	
Best response, n (%)					
CR	5 (20.0)	5 (31.3)	0	0	6 (24.0)
CRu	0	0	0	0	1 (4.0)
PR	7 (28.0)	5 (31.3)	1 (16.7)	1 (33.3)	7 (28.0)
SD	10 (40.0)	4 (25.0)	5 (83.3)	1 (33.3)	6 (24.0)
RD/PD	3 (12.0)	2 (12.5)	0	1 (33.3)	5 (20.0)
ORR, n (%) (95% CI)	12 (48.0) (27.8-68.7)	10 (62.5) (35.4-84.8)	1 (16.7) (0.4-64.1)	1 (33.3) (0.8-90.6)	14 (56.0) (34.9-75.6)
Median DOR, weeks (95% CI)	NR (8.14-NR)	NA	NA	NA	36.14 (12.00-NR)
Median TTR, weeks (range)	6.21 (4.1-24.1)	NA	NA	NA	4.14 (4.1-24.1)
Median PFS, weeks (95% CI)	32.14 (13.14-NR)	NA	NA	NA	32.14 (13.14-NR)

altered EZH2 expression has been implicated in the development and progression of ATLL

Makoto Yoshimitsu

The Combination of **Duvelisib** and **Romidepsin** (DR) Is Highly Active Against R/R PTCL with Low Rates of Transaminitis: Final Results and Biomarker Analysis (619)

Histology	Treated	Evaluable	ORR N (%)	CR N (%)	Bridged to Allo SCT N (%)
PTCL	**55**	**53**	**31 (58)**	**22 (42)**	**15 (28)**
PTCL NOS	20	19	10 (53)	6 (32)	3 (16)
AITL/TFH	19	19	13 (68)	11 (58)	7 (37)
PC γδ	3	3	1 (33)	1 (33)	1 (33)
ALCL	3	3	3 (100)	2 (67)	2 (66)
HSTCL	2	2	1 (50)	0	1 (50)
Aggr epidermotropic CD8+	2	2	1 (50)	1 (50)	0
Other TCL	6	5	2 (40)	1 (20)	1 (20)
CTCL	**11**	**11**	**4 (36)**	**0**	**0**
MF	7	7	2 (29)	0	0
LCT	*3*	*3*	*0*	*0*	*0*
SS	4	4	2 (50)	0	0
LCT	*1*	*1*	*0*	*0*	*0*
Overall	**66**	**64**	**35 (55)**	**22 (34)**	**15 (23)**

TET2 mutations : significantly associated with response

TP53 mutations : associated with non-response.

Safety and Efficacy of **Tenalisib** Given in Combination with **Romidepsin** in Patients with R/R TCL: Final Results from a Phase I/II Open Label Multi-Center Study (1365)

- Tenalisib (RP6530), a highly selective PI3K δ/γ and SIK3 inhibitor
- Tenalisib 400-800 mg BID (fasting), orally
- Romidepsin 12-14 mg/m2, iV, Days 1,8 and 15 of a 28-day cycle.
- 64% : refractory to their last therapy.
- median number of prior therapies : 3

Table 1: Efficacy of tenalisib and romidepsin in patients with TCL (n=27)

Response	Subtypes of PTCL				PTCL All (n=12)	Subtypes of CTCL		CTCL All (n=15)
	PTCL -NOS (N=5)	PTCL -AITL (n=5)	PTCL -TFH (n=1)	PTCL-ALCL (n=1)		MF (n=10)	Sezary syndrome (n=5)	
Complete Response (CR), n	2	4	-	-	6	-	1	1
Partial Response (PR), n	2	-	1	-	3	5	2	7
Stable disease (SD) n	1	-	-	1	2	4	1	5
Progressive disease (PD), n	-	1	-	-	1	1	1	2
Overall Response Rate (ORR), (%)	80	80	100	0	75	50	60	53

Swaminathan PIyer

Early Signals of Anti-Tumor Efficacy and Safety with Autologous **CD5.CAR T-Cells** in Patients with R/R TCL (654)

- N=14
- Median number of prior lines: 5 (2-18)
- 5 patients had relapsed after autologous (n=3) or allogeneic HSCT (n=2)
- CD5.CAR T-cells as a bridging therapy to alloHSCT
- 44% ORR (4/9)
- 3 patient proceed to alloHSCT.
- CR: 2 patient Complete responses

Figure 1. CAR transgene in peripheral blood

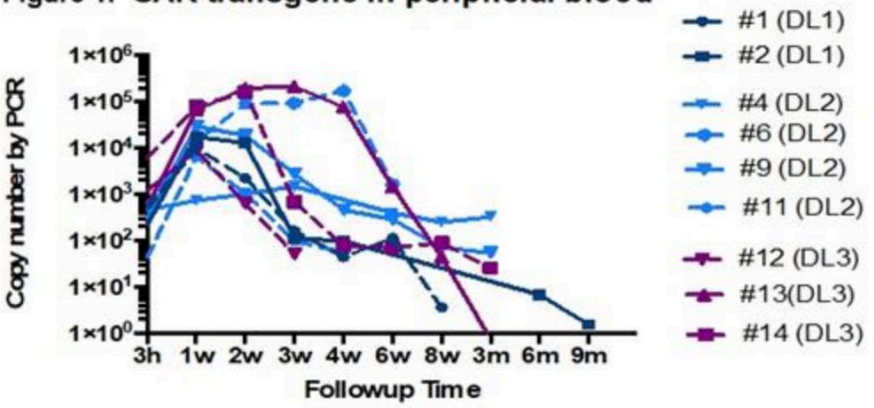
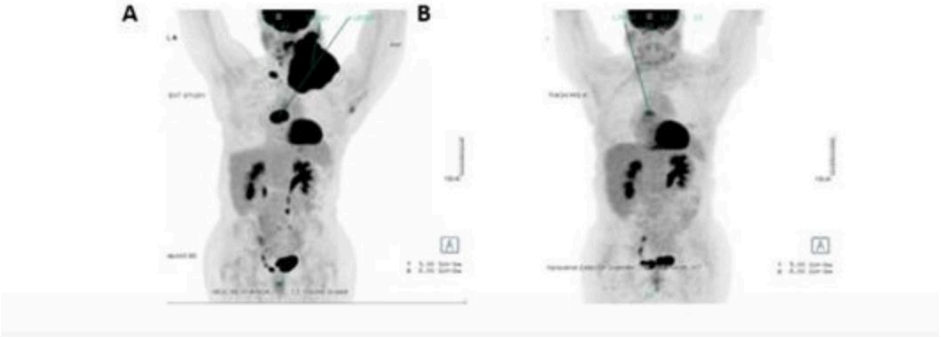


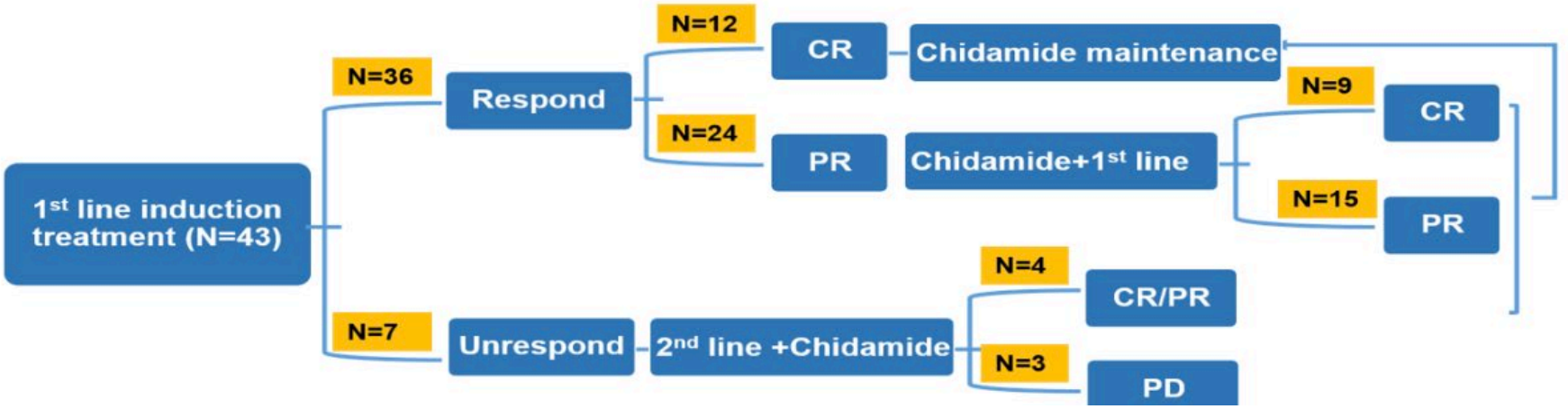
Figure 2. Pre- (A) and post- (B) treatment PET/CT for patient with ATLL treated on DL3



Rayne H. Rouce

T/NK Cell Lymphoma **Maintenance** Therapy

Chidamide Maintenance Therapy after Induction or Salvage Treatment in Patients with PTCL **Ineligible for Autologous SCT** (2442)



- Chidamide, a novel benzamide class of HDAC inhibitor
- prospective, single-center, single-arm study, n=43
  - (AITL) (44.2%),
  - (ALCL, ALK−) (11.6%),
  - (PTCL-NOS) (14.0%), extranodal
  - (NKT) (16.3%), and
  - other PTCL subtypes (14.0%),

CR: 44.2%
ORR: 79.1%

Chidamide Maintenance Therapy after Induction or Salvage Treatment in Patients with PTCL **Ineligible for Autologous SCT** (2442)

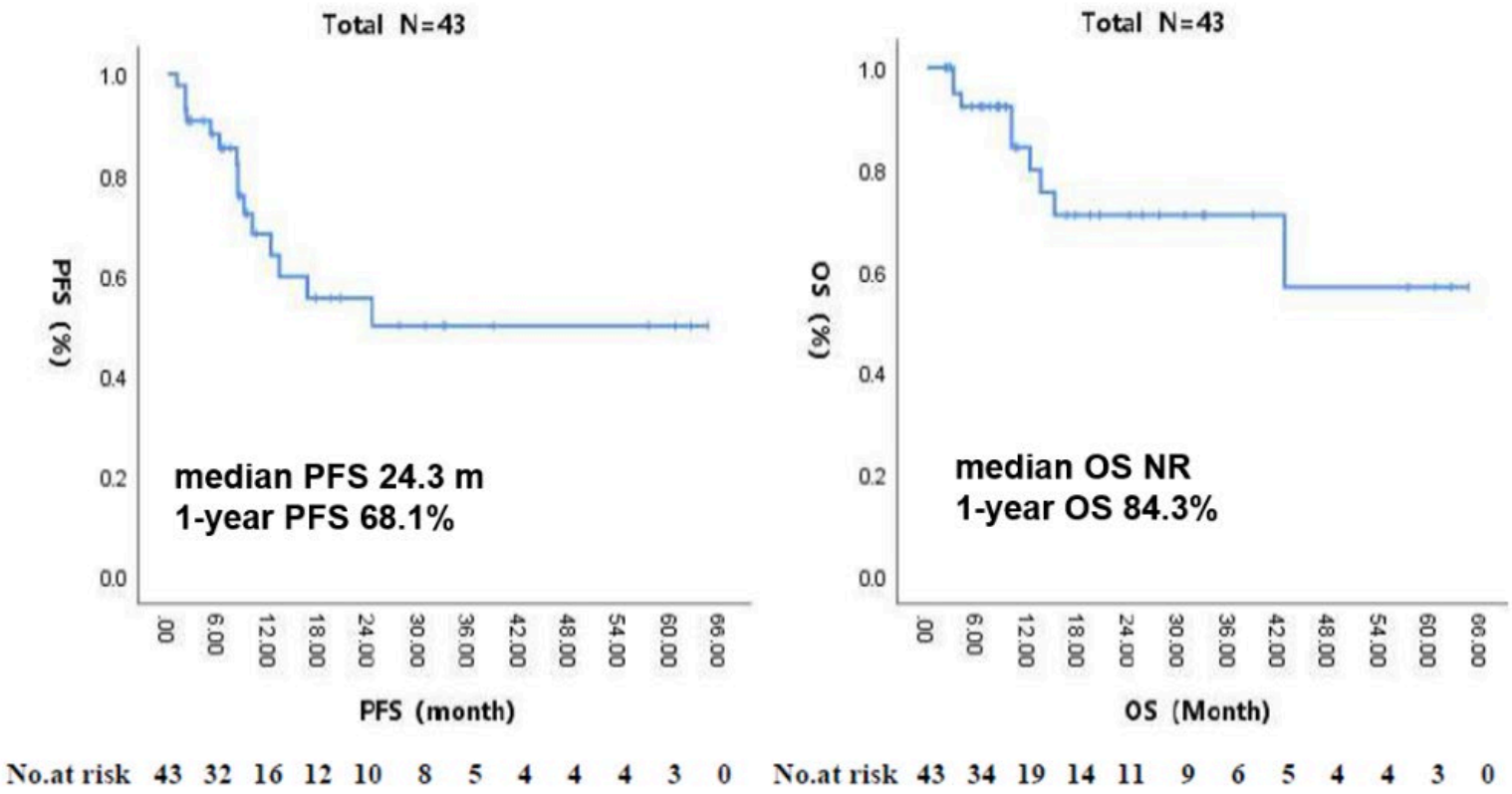
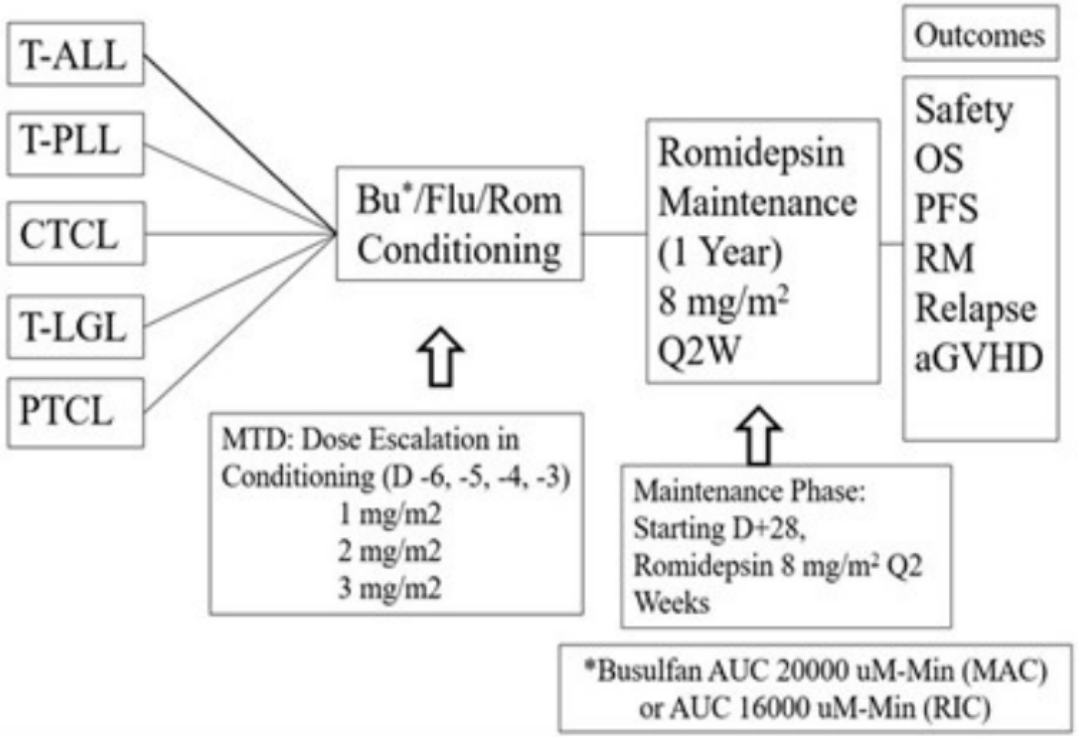


Figure 2. PFS and OS of the 43 cases (median follow-up time was 10.1 m (2–64.5))

Wei Guo

Romidepsin in **Conditioning** and **Maintenance** Mitigates Relapse Risk and Enhances NK-Cell Cytotoxicity in Patients Receiving **AlloSCT** for Aggressive T-Cell Malignancies: Results of a Phase I/II Clinical Trial (553)



- median follow-up: 10.1 m
- median OS :NR
- **1 and 3-year OS probability: 62.8% & 55.8%.**
- median PFS is 28.2 mo
- **1 and 3 year PFS : 57% & 30.4%**
- CI of NRM at day 100 and 1 year: 14.8% and 20%.
- **CI of grade II-IV aGHVD and extensive cGVHD: 47.6% and 18.5%.**
- The CIR: 22.8% at 1 year

Chitra Hosing,

T/NK Cell Lymphoma **Meta-analysis**

Novel Single Agents Are Equivalent to Conventional Chemotherapy Inpatients with R/R Mature TCLs: A Meta-Analysis (1431)

- **Novel** : antifolates, (HDACi), ab-drug conjugates, therapeutic antibodies, HMAs, cereblon modulators, inhibitors of PI3K/AKT/mTOR, JAK/STAT, aurora kinase, farnesyl transferase and proteosome pathways, and CD4 CAR T- cells.
- **Conventional :** ifosfamide-, gemcitabine-, anthracycline-, and platinum-based treatments
- 128 studies: 35 phase I , 70 phase II, 13 phase III, and 10 combination
  - R/R (n=100) : novel SA (n=84) and conv CT(n=16).
- ORR for novel agents :**37%** (95% [CI]: 34, 41)
- ORR for standard CT agents : **55%** (95% CI: 40, 69) (p=0.02).
- PTCL-NOS (n=751) had **comparable ORR** to novel agents (31%; 95%) and conventional CT (40%; 95%; p=0.08).
- Similar results were seen with patients with AITL (n=296) who achieved **equivocal ORR** to single agents (45%; 95%) when contrasted with conventional chemotherapy (55%; 95% p=0.52).

Nazila Shafagati

T/NK Cell Lymphoma **R/R** Therapy (ASH2021)

	N	FAZ	RESULTS	PFS	OS
BV + Benda	82	Retrospek.	**ORR/CR:%71/51**	Median PFS: 8.3 m	Median POS: 26.3
Cerdulatinib	58	2	ORR/CR:%36.2/20.7		
Tipifarnib	65	2	ORR : 39.7%, ORR (AITL): 56.3%		median OS(AITL): 32.8 m median OS (PTCLCXCL12+) :nr
Duvelisib	78	2	ORR/CR: %50/32.1	Median PFS: 107 day	
Valemetostat Tosylate	25	2	ORR/CR:%48/20	Median PFS: 32 week	
Duvelisib + Romidepsin	20	2	ORR/CR: %58/42		
Tenalisib + Romidepsin	12	1/2	**ORR/CR: %75/50**		
CD5.CAR T-Cells	14	?	ORR:%44		

PTHL-ASH2021-Özet

- CD30'u, epigenomu, proliferatif sinyal yollarını ve tümör mikroçevresini hedef alan yeni ajanlar ve bunların kombinasyonları ön plana çıkmış durumda.

Nanatinostat (Nstat) and **Valganciclovir** (VGCV) in R/R EBV+ Lymphomas: Final Results from the Phase 1b/2 VT3996-201 Study (623)

- EBV can be associated with 30-100% in PTCL
  - adverse impact on outcomes
- Nanatinostat is a Class-I selective oral HDAC inhibitor that induces the expression of the lytic BGLF4 EBV protein kinase in EBV+ tumor cells, activating ganciclovir (GCV) via phosphorylation.
- This results in GCV-induced inhibition of viral and cellular DNA synthesis and apoptosis.
- N=43
- ORR: 40%
- CR 19%
- T/NK-NHL (n=15; all refractory to their last therapy)
  - ORR: 60%, CR: 27%