3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:
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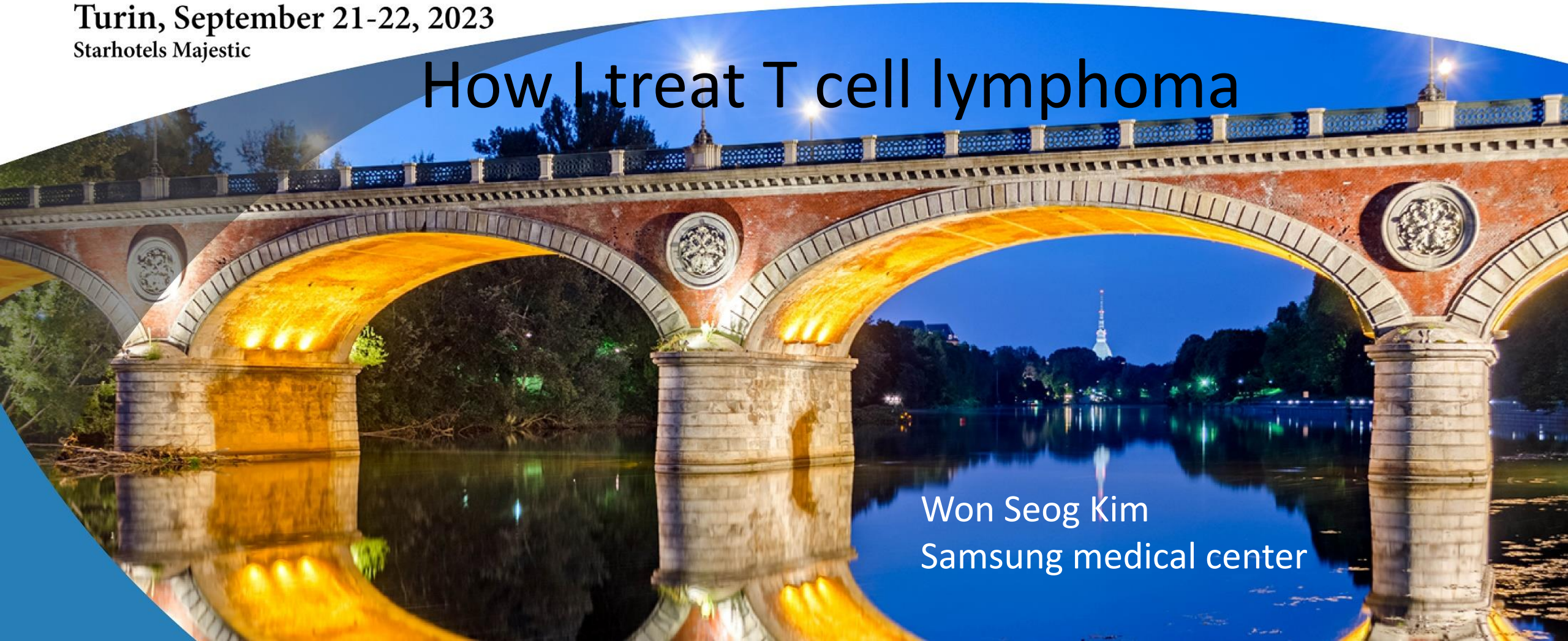

How I treat T cell lymphoma

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Disclosure

- **Grant/Research support from: Sanofi, Beigene, Boryong, Roche, Kyowa-Kirin, Donga**

CHOP as a standard

1002 THE NEW ENGLAND JOURNAL OF MEDICINE April 8, 1993

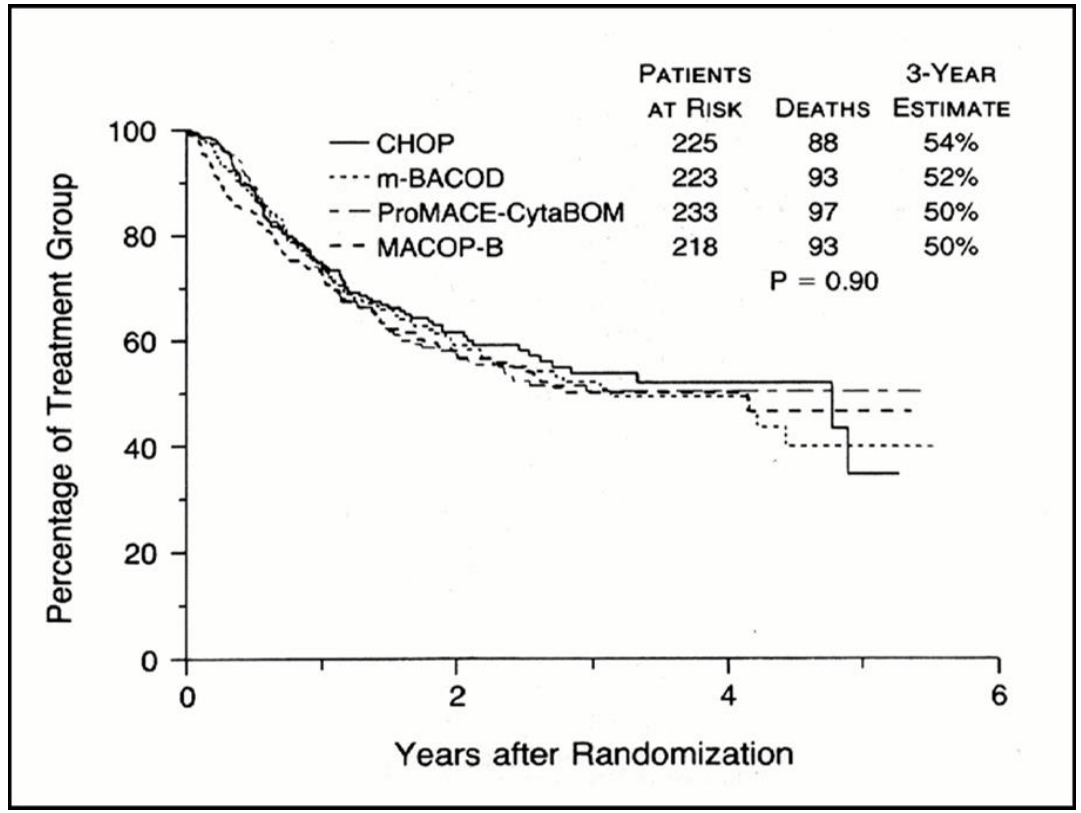
COMPARISON OF A STANDARD REGIMEN (CHOP) WITH THREE INTENSIVE CHEMOTHERAPY REGIMENS FOR ADVANCED NON-HODGKIN'S LYMPHOMA

RICHARD I. FISHER, M.D., ELLEN R. GAYNOR, M.D., STEVE DAHLBERG, M.S., MARTIN M. OKEN, M.D., THOMAS M. GROGAN, M.D., EVONNE M. MIZE, JOHN H. GLICK, M.D., CHARLES A. COLTMAN, JR., M.D., AND THOMAS P. MILLER, M.D.

CHARACTERISTIC	CHOP (N = 225)	m-BACOD (N = 223)	ProMACE-CytaBOM (N = 233)	MACOP-B (N = 218)
Age				
Median (yr)	56	57	54	57
Range (yr)	15–79	18–81	17–81	19–79
≥65 yr (%)	26	25	27	24
Marrow involvement (%)	25	26	27	27
Bulky disease (%)	40	41	41	40
LDH >250 U/liter (%)*	45	43	42	43
Working formulation group (%)†				
D or E	14	15	15	14
F, G, or H	81	82	81	82
J	5	4	4	4

*LDH denotes lactate dehydrogenase.

†These groups were defined according to the system of the Non-Hodgkin's Lymphoma Pathologic Classification Project.[10]



CHOP as a standard

The Working Formulation

Low Grade	Intermediate Grade	High Grade
Small lymphocytic (A)	Follicular large cell (D)	Large cell immunoblastic (H)
Follicular small cleaved cell (B)	Diffuse small cleaved cell (E)	Lymphoblastic (I)
Follicular small cleaved and la rge cell (C)	Diffuse mixed and small and l arge cell (F)	Small non-cleaved cell (Burkit t and non-Burkitt type) (J)
	Diffuse large cell (G)	

Dilemma in CHOP era

ENKTL can not be a candidate for CHOP treatment.

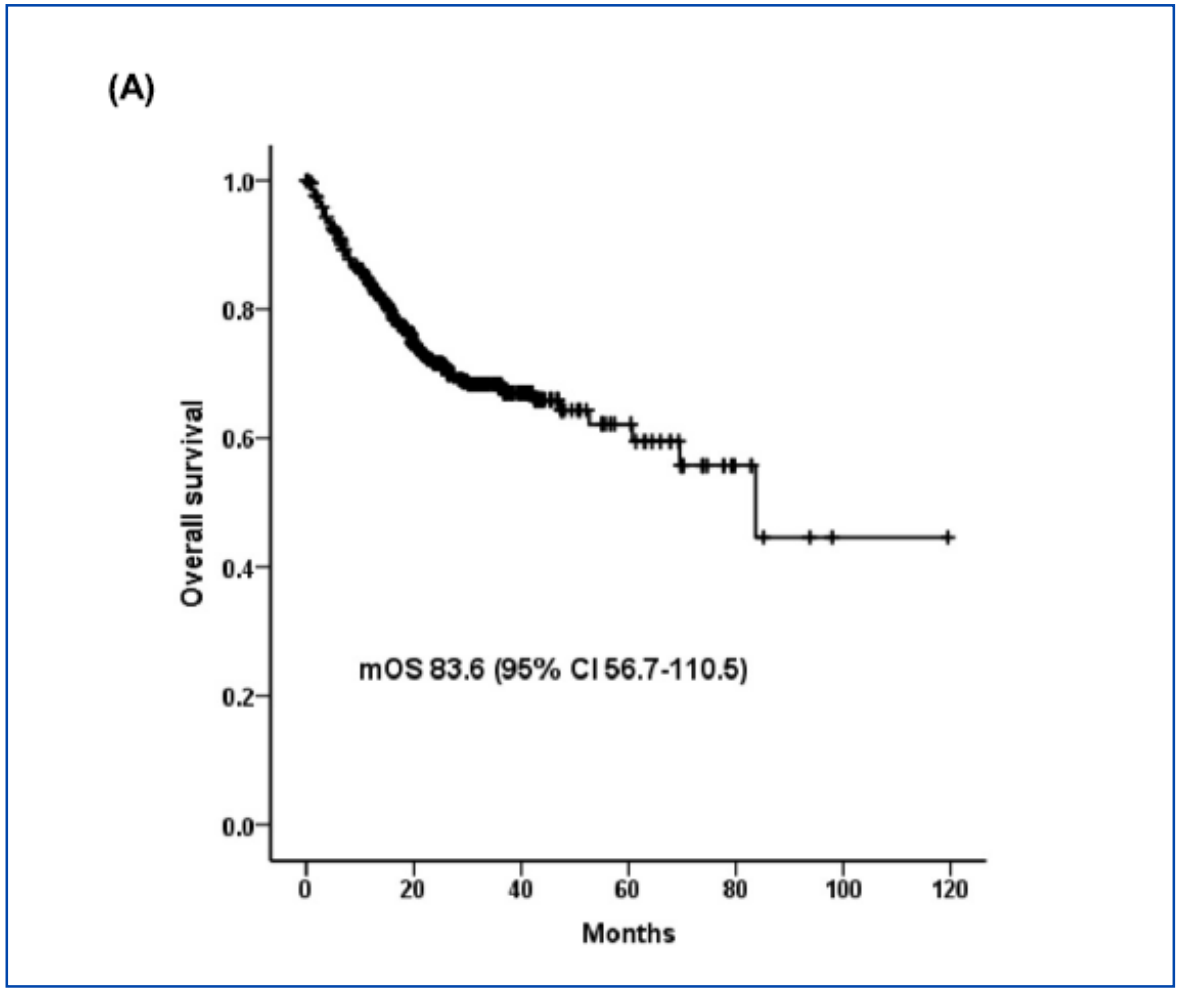
CHOP : is it a standard induction regimen?

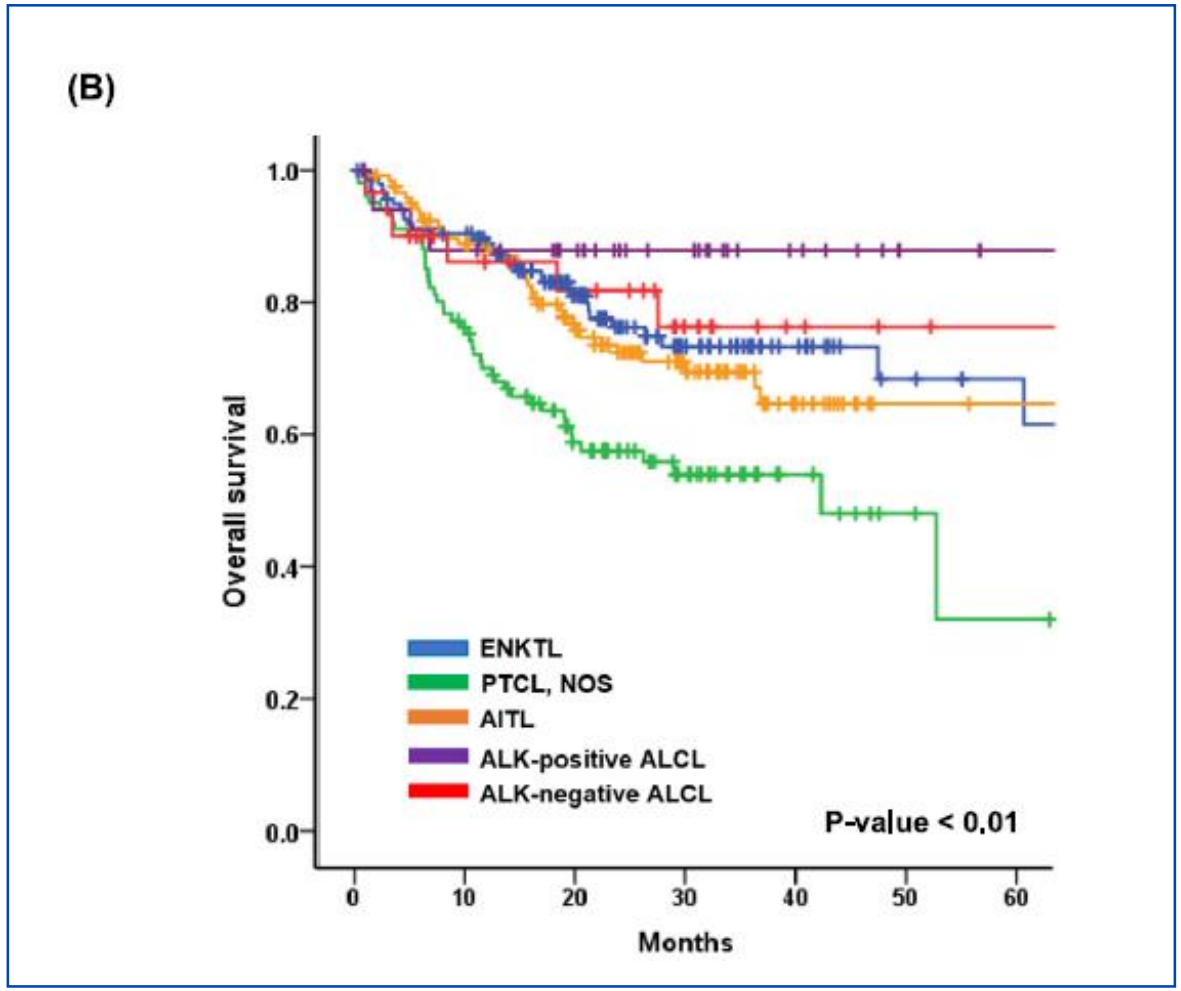
CHOP is not inferior/superior to other combination chemo-therapies

If CHOP is standard, still different biology under same treatment

Upfront auto-HSCT : for every young and fit PTCL patients?

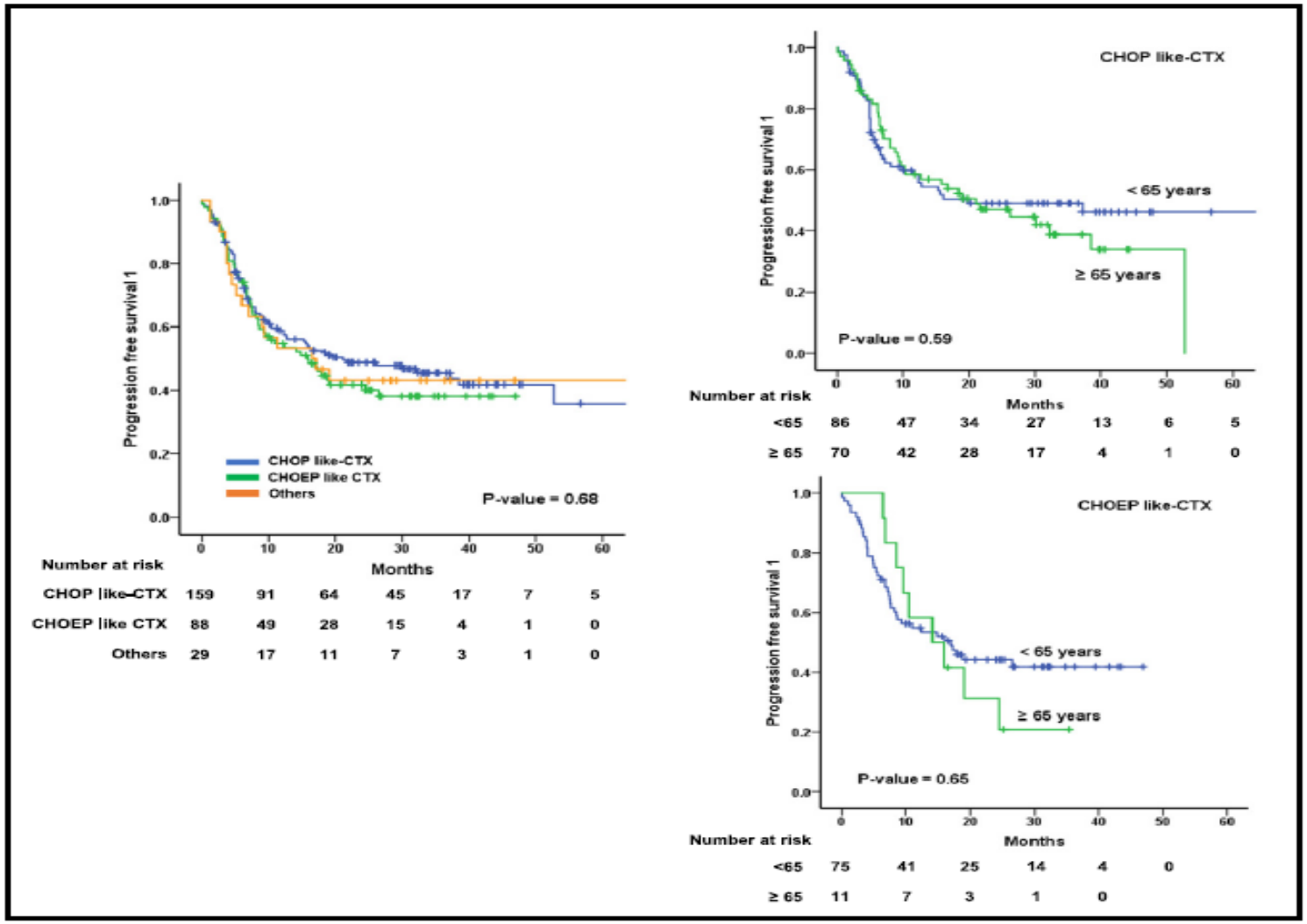
Current practice in Asia

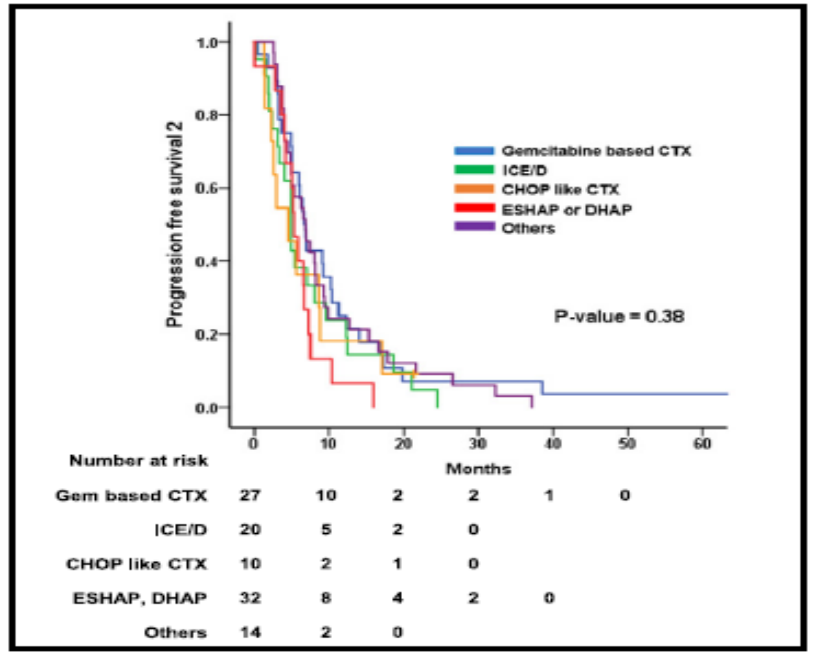




Yoon SE et al . Lancet regional med 2021

Current practice in Asia





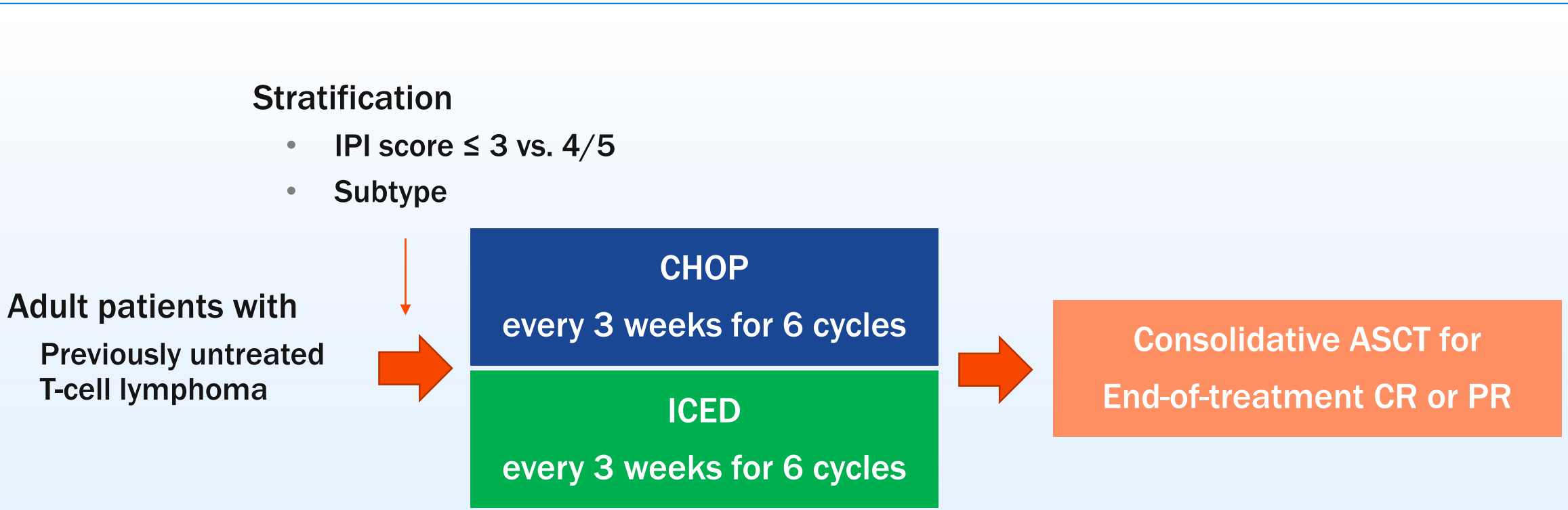
Yoon SE et al . Lancet regional med 2021

CHOP+X for PTCLs

	Alemtuzumab	Bortezomib	Bevacizumab	Denileukin	Everolimus
N	20	46	39	49	30
Median age	50 years	51 years	60 years	52 years	54 years
% ≥ 6 cycle	85	63	72	59	67
ORR/CRR %	90/65	76/65	90/49	65/55	90/57
Median PFS	10 months	9 months	8 months	12 months	11 months
2-year PFS	27%	37% (2-year)	25% (2-year)	43%	33%
Median OS	27 months	27 months	22 months	Not reached	Not reached
2-year OS	55%	52%	42%	65%	70%

CHOP+X = CHOP

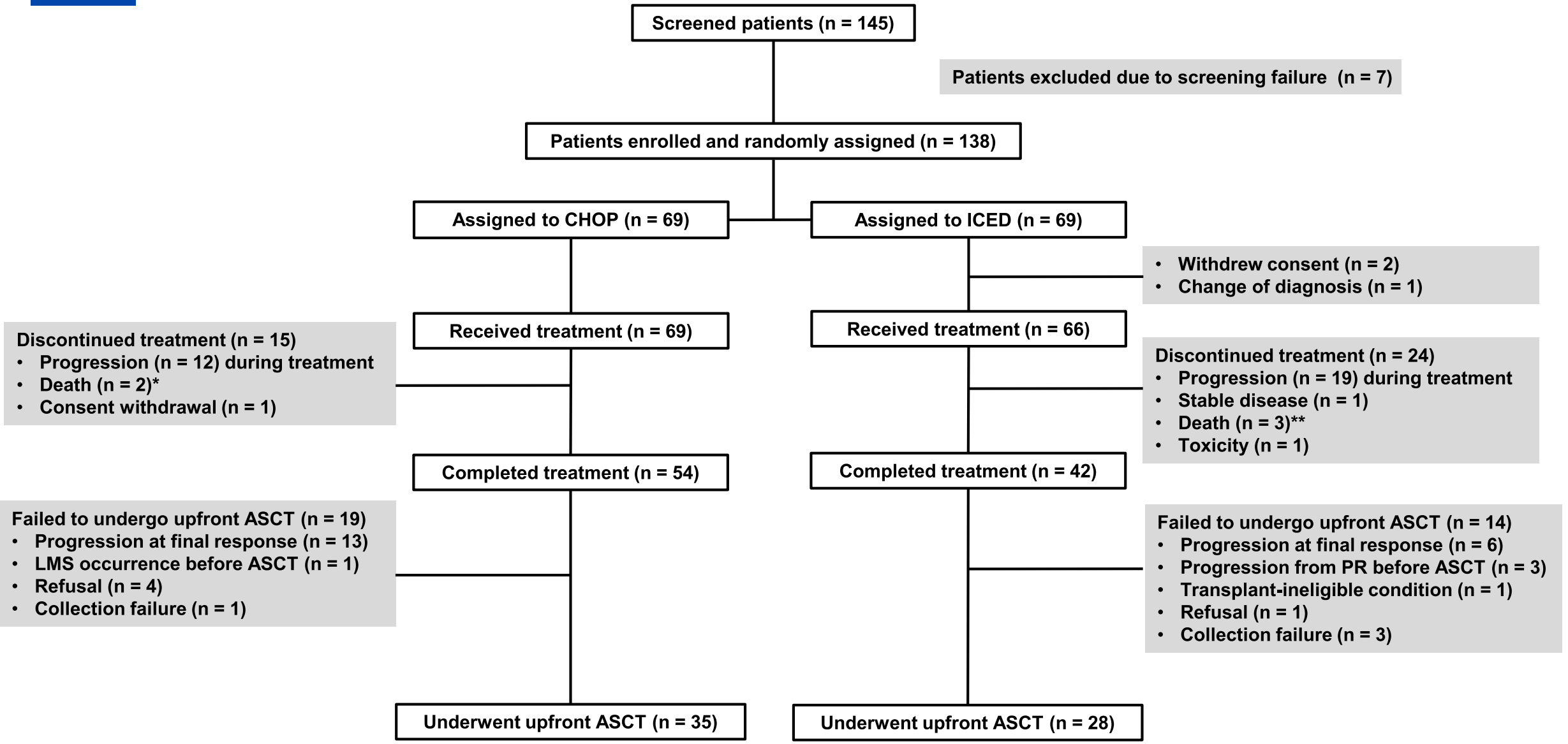
Study Scheme of ROSE trial



- Primary endpoint: Progression-free survival
- Secondary endpoints: Response rate, Overall survival, Safety (ClinicalTrials.gov: NCT02445404)

Yoo K et al ICML 2023

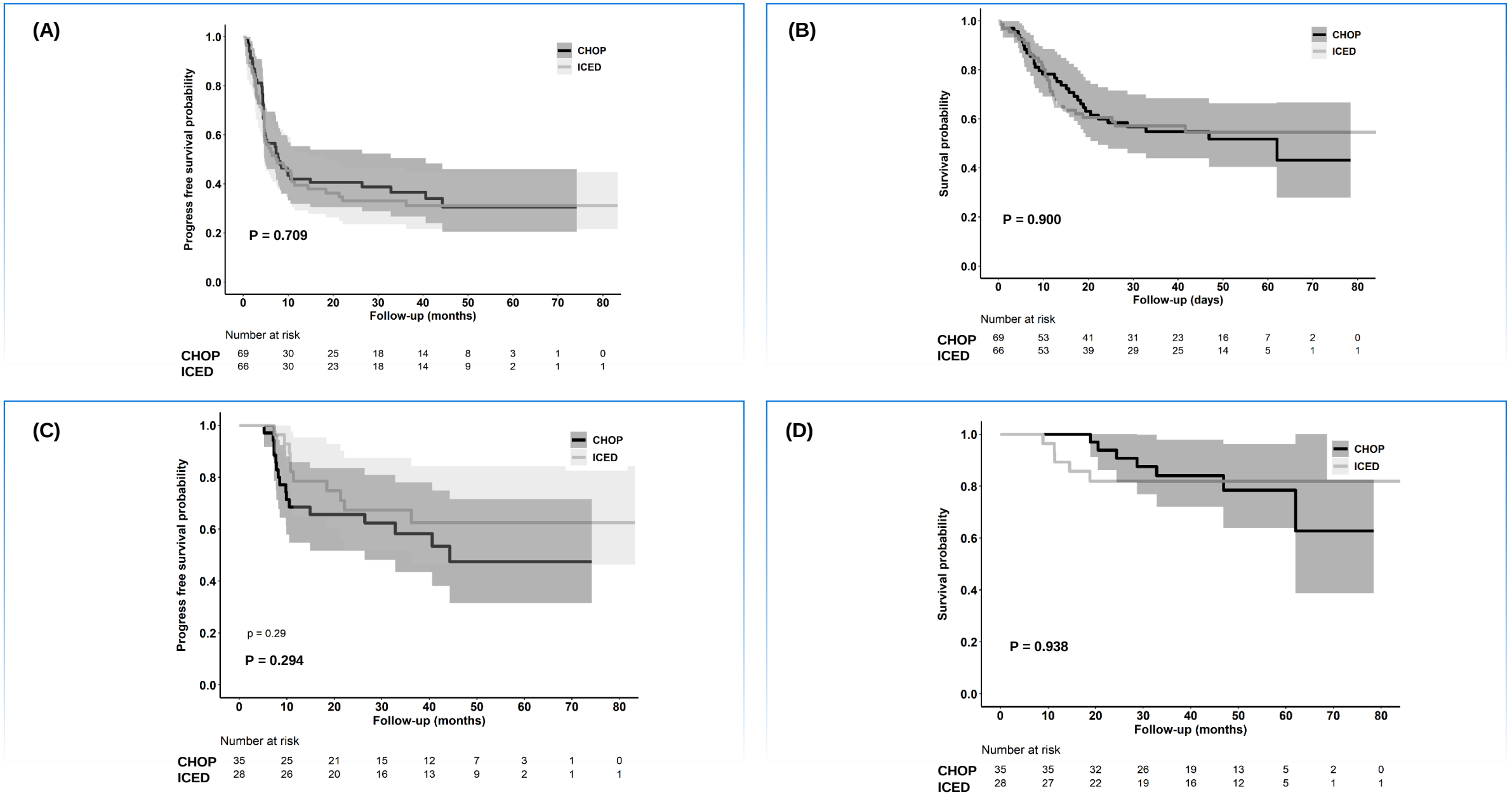
Figure 1



Air embolism after 1st, Perforation after 1st (n = 2)*

AMI after 1st, Sepsis after 1st, Unknown cause after 3rd (n = 3)**

Figure 3


(A)
Progress free survival probability
1.0
0.8
0.6
0.4
0.2
0.0
CHOP
ICED
P = 0.709
0 10 20 30 40 50 60 70 80
Follow-up (months)
Number at risk
CHOP 69 30 25 18 14 8 3 1 0
ICED 66 30 23 18 14 9 2 1 1
(B)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
CHOP
ICED
P = 0.900
0 10 20 30 40 50 60 70 80
Follow-up (days)
Number at risk
CHOP 69 53 41 31 23 16 7 2 0
ICED 66 53 39 29 25 14 5 1 1
(C)
Progress free survival probability
1.0
0.8
0.6
0.4
0.2
0.0
CHOP
ICED
p = 0.29
P = 0.294
0 10 20 30 40 50 60 70 80
Follow-up (months)
Number at risk
CHOP 35 25 21 15 12 7 3 1 0
ICED 28 26 20 16 13 9 2 1 1
(D)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
CHOP
ICED
P = 0.938
0 10 20 30 40 50 60 70 80
Follow-up (months)
Number at risk
CHOP 35 35 32 26 19 13 5 2 0
ICED 28 27 22 19 16 12 5 1 1

CHOP vs. GEM-P : CHEMO-T Phase 2, Randomized Trial

CHOP arm

- CHOP every 3 weeks for six cycles

GEM-P arm

- Gemcitabine 1000 mg/m² on days 1, 8, and 15
- Cisplatin 100 mg/m² on day 15
- Methylprednisolone PO or IV 1000 mg on days 1–5 every 4 weeks for four cycles

Front-line therapy in previously untreated patients

UK and Australia

- Between June 2012 and Nov 2016

Characteristic	CHOP (n = 43)	GEM-P (n = 44)
Median age (Years, IQR)	64 (54-69)	61 (50-70)
Stage III/IV, n (%)	34 (79)	41 (93)
IPI score, n (%) ▪ 0-1 ▪ 2-3 ▪ 4-5	 9 (21) 26 (60) 8 (19)	 8 (18) 25 (57) 11 (25)
Diagnosis, n (%) ▪ PTCL-NOS ▪ ALK-, ALCL ▪ AITL ▪ EATL	 19 (44) 6 (14) 17 (40) 1 (2)	 18 (41) 8 (18) 17 (39) 1 (2)

Gleeson M, et al. Lancet Haematol. 2018 May;5(5):e190-e200.

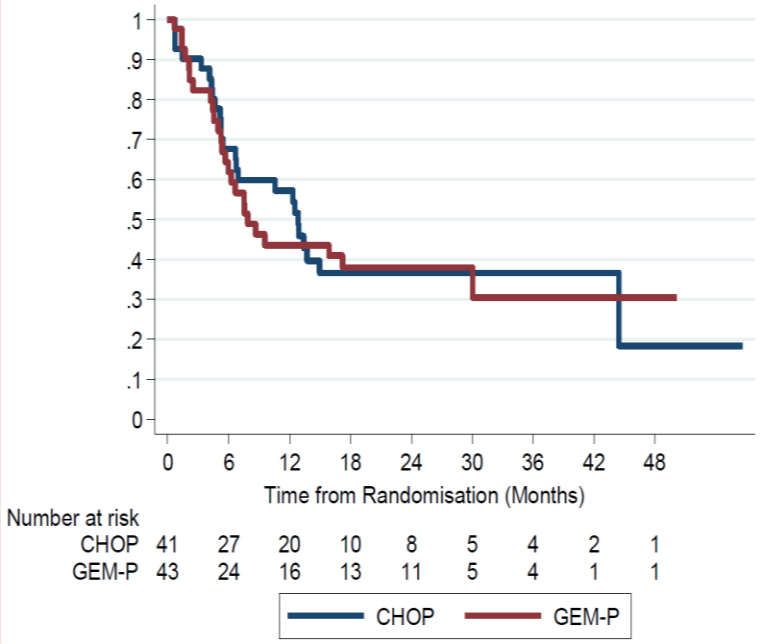
CHOP vs. GEM-P : No difference of outcome, early closed

	CHOP				GEM-P		
	Cyclophosphamide	Doxorubicin	Vincristine	Prednisolone	Gemcitabine	Cisplatin	Methylprednisolone
Total dose received (mg)	7960 (5080–8760)	540 (342–588)	12 (7–12)	2400 (1500–3000)	18262·5 (7060–21900)	361·5 (201·5–707·5)	20 000 (7500–20 000)
Relative dose intensity	98·1 (90·5–100)	97·9 (91·9–100·0)	99·2 (85·7–100·0)	97·0 (89·7–100·0)	86·5 (69·2–95·9)	82·2 (41·6–97·4)	98·1 (83·3–100·0)

Data are median (IQR).

	CHOP (six cycles; n=43)	GEM-P (four cycles; n=44)
Overall response	28 (75·7)	25 (67·6)
Complete response or unconfirmed complete response*	23 (62·2)	17 (45·9)
Partial response	5 (13·5)	8 (21·6)
Stable disease	2 (5·4)	3 (8·1)
Progressive disease	4 (10·8)	6 (16·2)
Progressive disease assessed clinically	3 (8·1)	3 (8·1)
Not done or not assessable	6	7

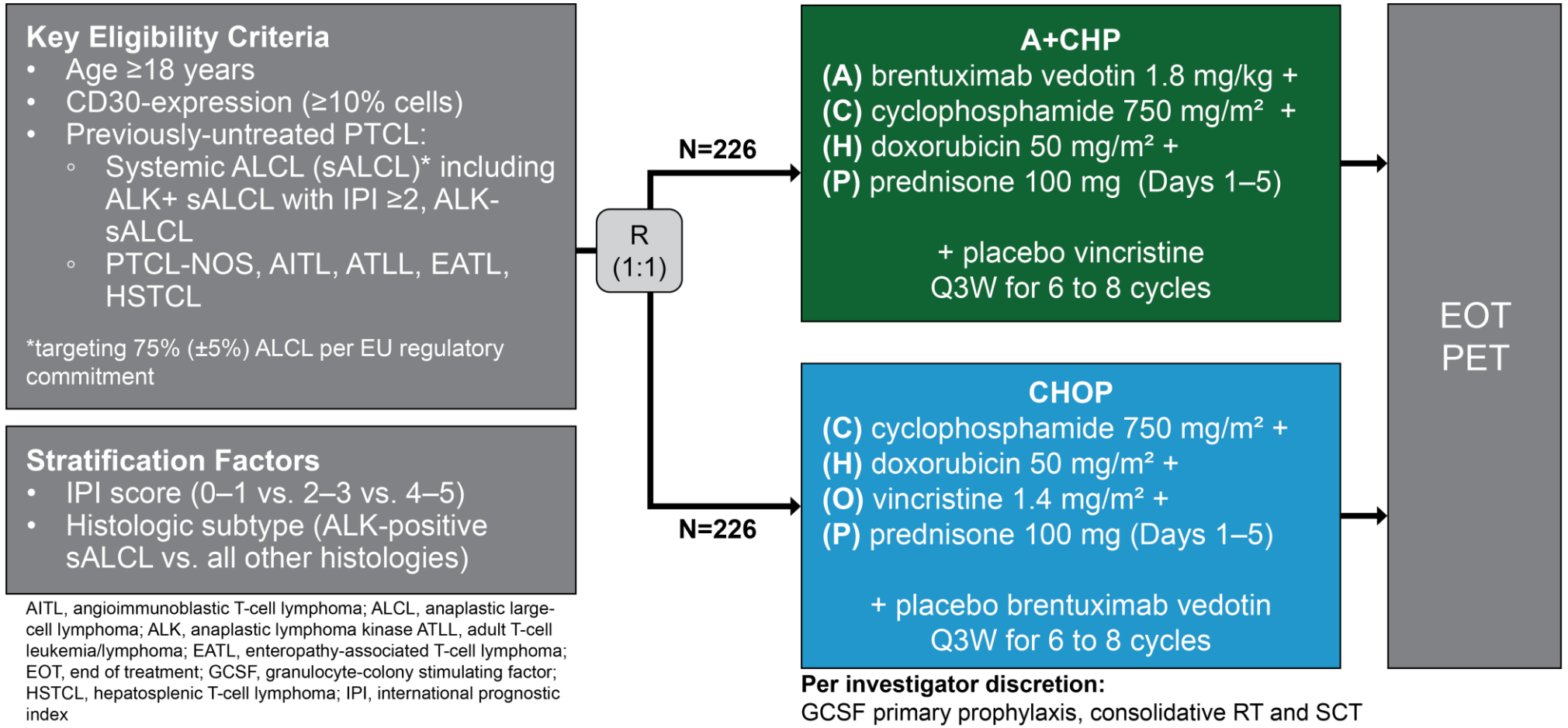
Data are n (%) of those who had an assessment. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone. GEM-P=gemcitabine, cisplatin, and methylprednisolone. *p=0·164.



Gleeson M, et al. Lancet Haematol. 2018 May;5(5):e190-e200.

ECHELON-2 : Study design

- ECHELON-2 is a phase 3, randomized, double-blind, double-dummy, placebo-controlled, active-comparator, multicenter study.



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

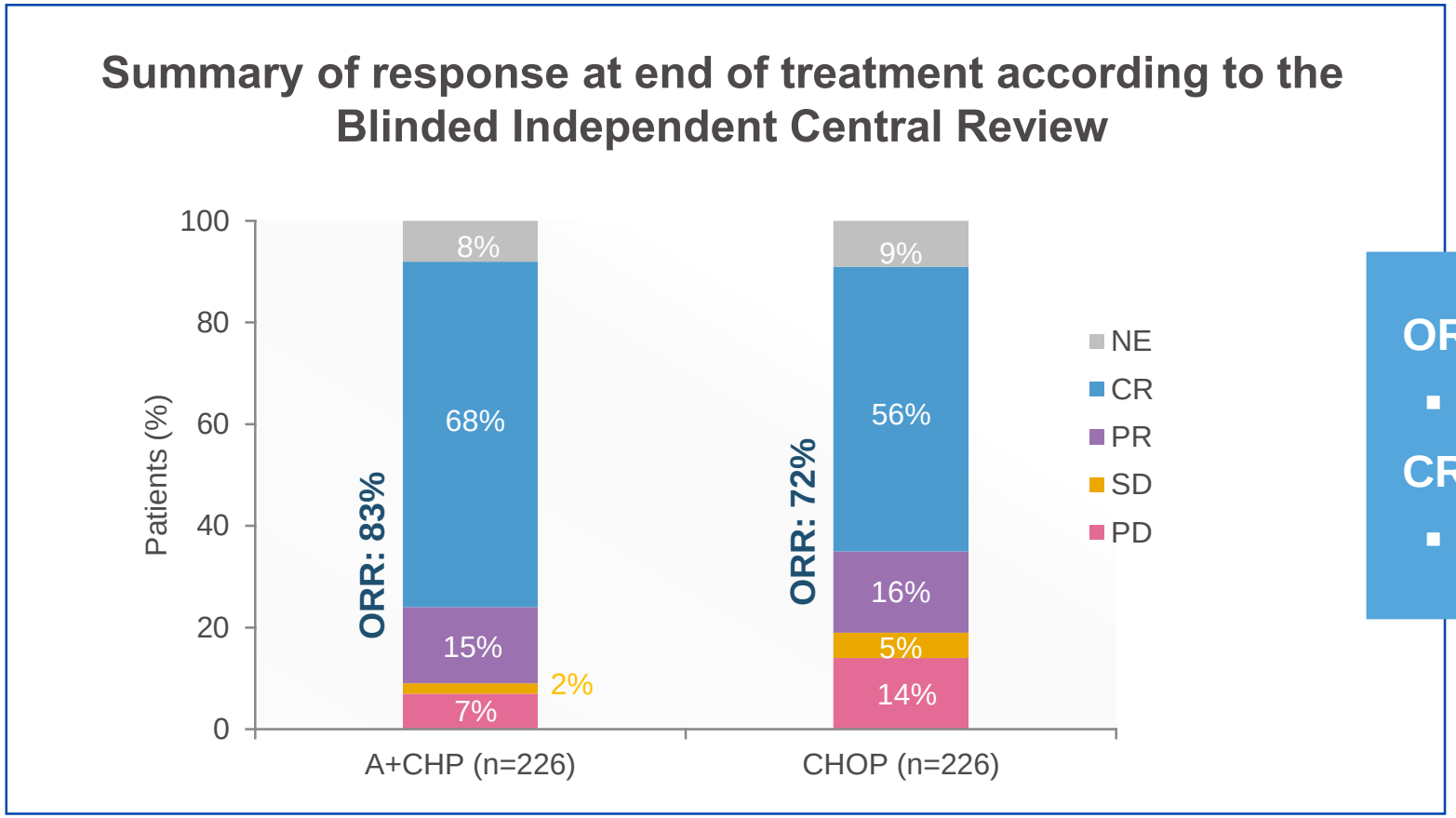
ECHELON-2: Baseline Characteristics

Characteristic	BV + CHP (n = 226)	CHOP (n = 226)
Male, n (%)	133 (59)	151 (67)
Median age, yrs (IQR)	58 (45-67)	58 (44-67)
Disease stage III/IV, n (%)	184 (81)	180 (80)
IPI score, n (%)		
• 0-1	53 (23)	48 (21)
• 2-3	140 (62)	144 (64)
• 4-5	33 (15)	34 (15)
Disease diagnosis, n (%)		
• sALCL	162 (72)	154 (68)
• ALK+ sALCL	49 (22)	49 (22)
• ALK- sALCL	113 (50)	105 (46)
• AITL	30 (13)	24 (11)
• PTCL-NOS	29 (13)	43 (19)
• ATLL	4 (2)	3 (1)
• EATL	1 (0)	2 (1)

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

Slide credit: clinicaloptions.com

Statistically significant and clinically meaningful differences favoring A+CHP were observed in both CR rate and ORR in ITT population



ORR:

- 83% vs 72% (p=0.0032)

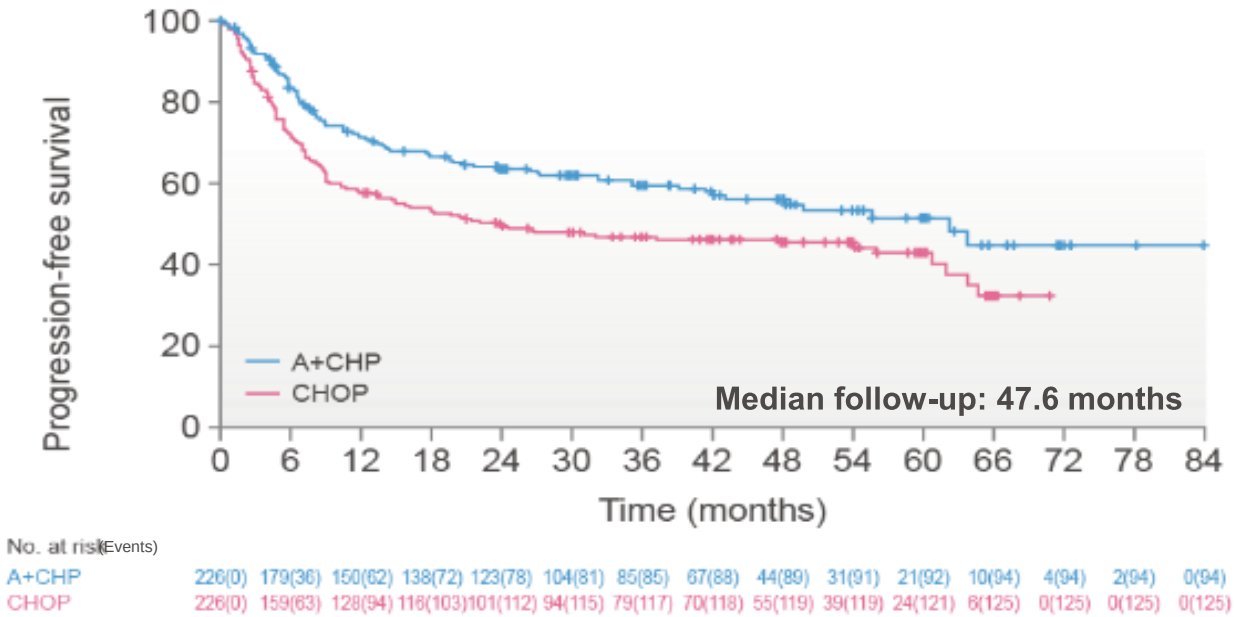
CR rate:

- 68% vs 56% (p=0.0066)

A, brentuximab vedotin; CH(O)P, cyclophosphamide doxorubicin (vincristine) prednisone; CR, complete response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Horwitz S, et al. Lancet 2019;393:229–40

Long-term follow-up in ECHELON-2 shows sustained efficacy with A+CHP *(5-year PFS analyses)*



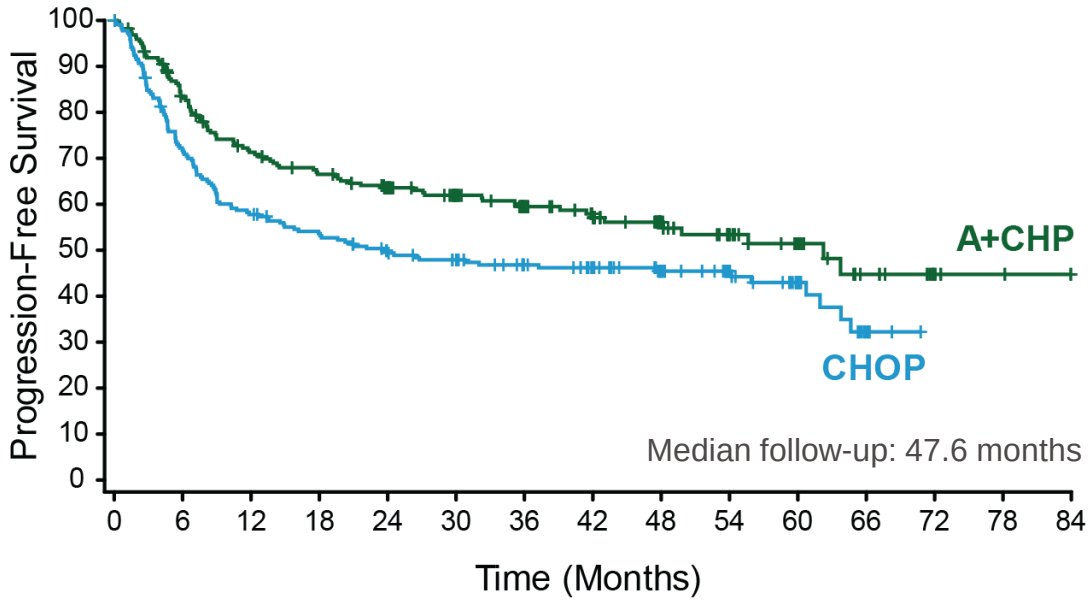
	A+CHP (N=226)	CHOP (N=226)
3-Year results (primary analysis): PFS rate (95% CI) per BICR Median follow-up: 36.2 months	57.1% (49.9, 63.7)	44.4% (37.6, 50.9)
HR (95% CI); P-value	0.71 (0.54–0.93); P=0.0110	
5-Year results: PFS rate (95% CI) per INV assessment Median follow-up: 47.6 months	51.4% (42.8, 59.4)	43.0% (35.8, 50.0)
HR (95% CI); P-value	0.70 (0.53–0.91); P=0.0077	

A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell lymphoma; BICR, blinded independent central review; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; INV, investigator; PFS, progression-free survival; PTCL(-NOS), peripheral T-cell lymphoma (-not otherwise specified); sALCL, systemic anaplastic large-cell lymphoma.

Horwitz SM, et al. Presented at the 62nd American Society of Hematology Virtual Annual Meeting, December 2020, Poster #1150

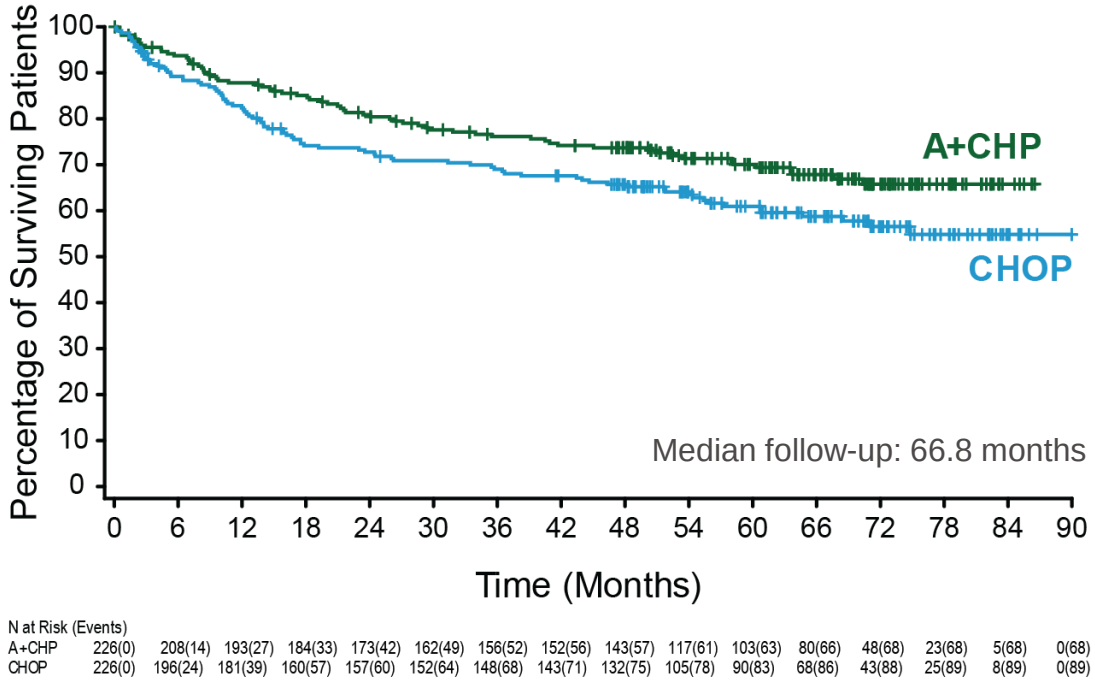
PFS (INV Assessment) and OS *(5-year follow-up)*

PFS



	N	Events	Medians (Months)	HR (95% CI)	p-value*
A+CHP	226	94	62.26	0.70 (0.53, 0.91)	0.0077
CHOP	226	125	23.75		

OS

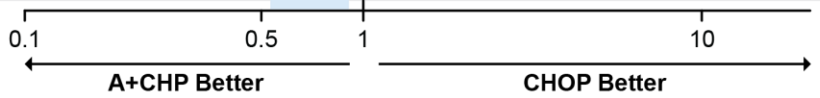


	N	Events	Medians (Months)	HR (95% CI)	p-value*
A+CHP	226	68	–	0.72 (0.53, 0.99)	0.0424
CHOP	226	89	–		

Horwitz SM, et al. Presented at the 62nd American Society of Hematology Virtual Annual Meeting, December 2020, Poster #1150

Prespecified Subset Analyses: PFS *(5-year follow-up)*

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
PFS per Investigator	94/226	125/226	0.70 (0.53, 0.91)
IPI Score			
0–1	14/52	27/48	0.42 (0.22, 0.81)
2–3	59/141	79/145	0.72 (0.51, 1.01)
4–5	21/33	19/33	1.14 (0.61, 2.15)
Age			
<65	51/157	74/156	0.64 (0.45, 0.92)
≥65	43/69	51/70	0.68 (0.45, 1.04)
Sex			
Male	60/133	79/151	0.84 (0.60, 1.17)
Female	34/93	46/75	0.44 (0.28, 0.69)
Baseline ECOG Status			
0	36/84	56/93	0.63 (0.41, 0.96)
1	38/90	50/86	0.61 (0.40, 0.93)
2	20/51	19/47	0.99 (0.52, 1.88)
Disease Stage			
I	3/12	2/9	2.15 (0.22, 20.88)
II	12/30	18/37	0.93 (0.43, 1.99)
III	26/57	36/67	0.63 (0.37, 1.05)
IV	53/127	69/113	0.66 (0.46, 0.95)
Disease Indication			
ALK-positive sALCL	7/49	16/49	0.40 (0.17, 0.98)
ALK-negative sALCL	46/113	61/105	0.58 (0.40, 0.86)
ATLL	2/4	2/3	0.69 (0.10, 4.94)
AITL	19/30	12/24	1.41 (0.64, 3.11)
EATL	1/1	2/2	not estimable
PTCL-NOS	19/29	32/43	0.79 (0.43, 1.43)
sALCL	53/162	77/154	0.55 (0.39, 0.79)
non sALCL	41/64	48/72	0.96 (0.63, 1.47)



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Dilemma in CHOP era

ENKTL can not be a candidate for CHOP treatment.

CHOP : is it a standard induction regimen?

- CHOP is superior to other combination chemo-therapy
- If CHOP is standard, still different biology under same treatment

Upfront auto-HSCT : for every young and fit PTCL patients?

Upfront auto or not?

No Randomized trial yet.

- **Therefore, we should do that.**
- **Therefore, we should not do that .**

Auto vs Non-Auto HSCT in CR with nodal PTCL (Transcript)

- 18-69 y
- Fit enough for ASCT
- PTCL-NOS
- TFH TCLs
- ALK-negative ALCL
- PS 0-2

→ CHOP
CHOEP
CHP-BV*

*ALK-neg ALCL only

→ CHOP
CHOEP
CHP-BV* } + ASCT (if CR)

- Enrollment goal n= 204
- Primary endpoint PFS in CR patients
- August 2022 activated (NCT05444712)
- Dr. Bachy PI (France)

Dilemma in CHOP era

ENKTL can not be a candidate for CHOP treatment.

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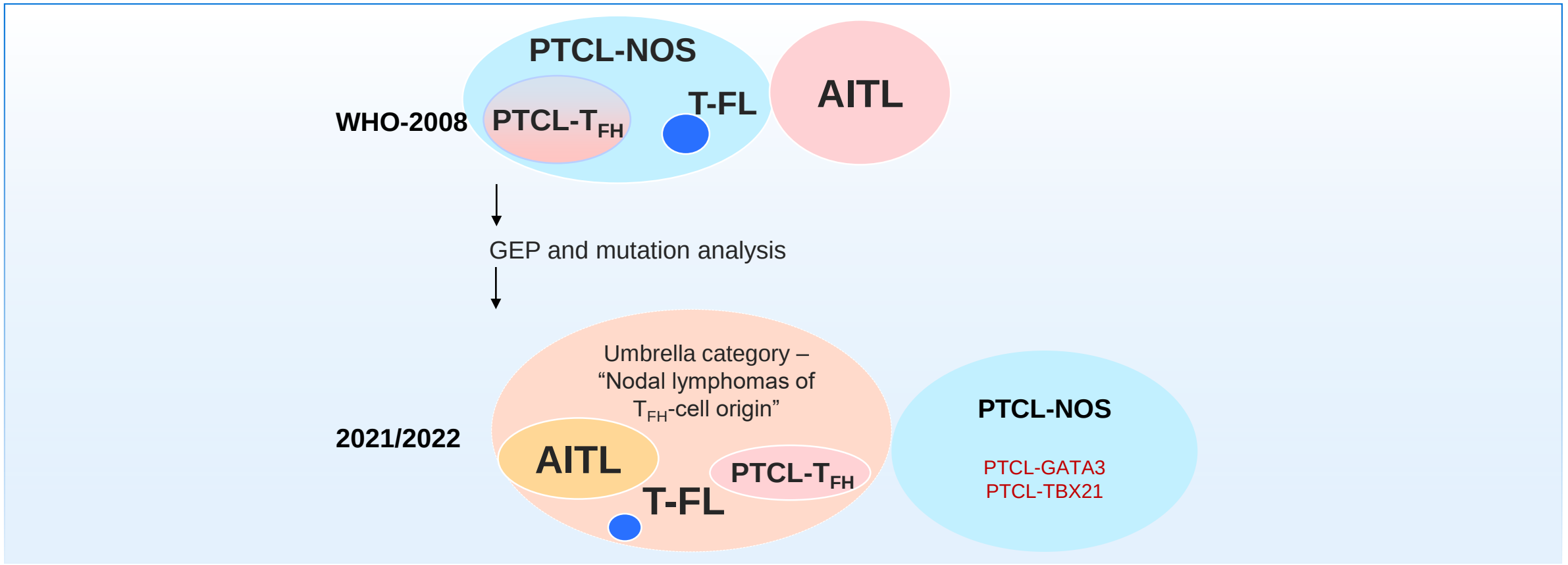
If CHOP is standard, still different biology under same treatment

Upfront auto-HSCT : for every young and fit PTCL patients?

T_{FH} lymphomas: revised version: spectrum of single disease

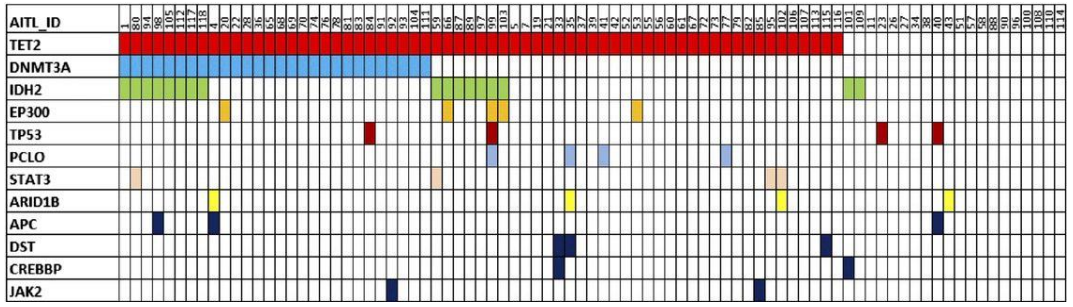


WHO 4th 2017	ICC 2022	WHO 5th 2022
Nodal lymphomas of T follicular helper	Follicular helper T-cell lymphoma	Nodal T follicular helper cell lymphoma
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma, angioimmunoblastic type	Nodal TFH lymphoma, angioimmunoblastic-type
Follicular T-Cell lymphoma	Follicular helper T-cell lymphoma, follicular type	Nodal TFH lymphoma, follicular-type
Nodal peripheral T-Cell lymphoma with T FH phenotype	Follicular helper T-cell lymphoma, NOS	Nodal TFH lymphoma, NOS

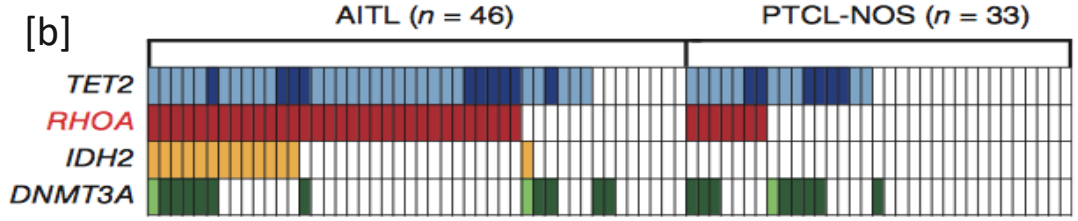
Genetic Drivers in Subtypes and Subgroups of PTCL

AITL and TFH subtypes of PTCL enriched for mutations in epigenetic modifiers:
TET2, DNMT3A, RHOA, IDH2

[a]



[b]



[c]

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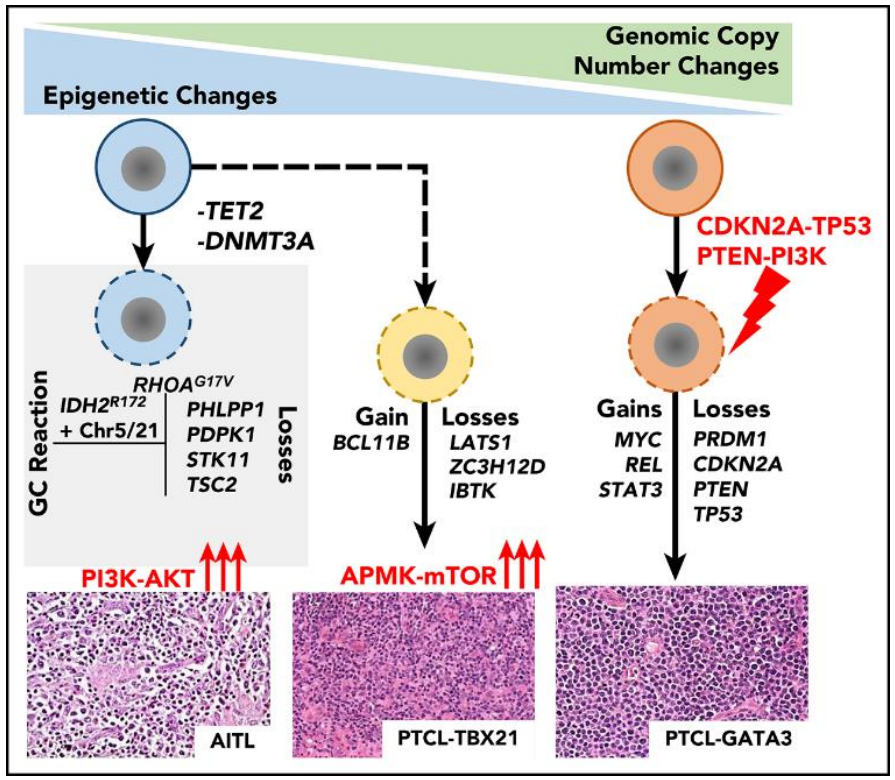

- a. Odejide O, et al. *Blood.* 2014;123:1293-1296; b. Sakata-Yanagimoto M, et al. *Nat Genet.* 2014;46:171-175.
- c. Palomero et al. *Nat Genet.* 2014;46:166-170; d. Heavican TB, et al. *Blood.* 2019;133:1664-1676.

Tucidinostat in R/R PTCLs : PIIb

Characteristics	Total N=55
Sex, N (%)	
Male	35 (64)
Female	20 (36)
Age (years), median (min, max)	71 (38, 87)
Ethnicity, N (%)	
Japanese	39 (71)
South Korean	16 (29)
ECOG Performance Status, N (%)	
0	28 (51)
1	25 (46)
2	2 (4)
Diagnosis (confirmed by CPR), N (%)	
PTCL	52 (95)
PTCL-NOS	37 (67)
AITL	10 (18)
ALCL, ALK-negative	3 (5)
EATL	2 (4)
Non-PTCL	2 (4)
DLBCL	1 (2)
NLPHL	1 (2)
Unknown	1 (2)
Duration since initial diagnosis in years, median, range	1.339 (0.06-12.88)
PTCL subset, N (%)	
Relapsed (CR, CRu, PR)	32 (58)
Refractory (SD, PD)	23 (42)

Characteristics	Total N=55
Type of previous cancer therapy, N (%)	
Chemotherapy	55 (100)
Other anticancer therapy	16 (29)
Brentuximab vedotin	2 (4)
Darinaparsin	8 (15)
Denileukin Diftitox	2 (4)
Forodesine	6 (11)
Mogamulizumab	1 (2)
Pralatrexate	3 (5)
Rituximab	2 (4)
Romidepsin	4 (7)
Radiotherapy	6 (11)
Autologous stem cell transplantation	6 (11)
Other	2 (4)
N of prior systemic therapies including targeted therapies, median (min, max)	2 (1, 9)
N of regimens received (%)	
1 regimen	20 (36)
2 regimens	17 (31)
3 regimens	8 (15)
4 regimens	5 (9)
5 or more regimens	5 (9)
N of days from end of last immediate previous therapy, median (min, max)	97 (29, 3,861)

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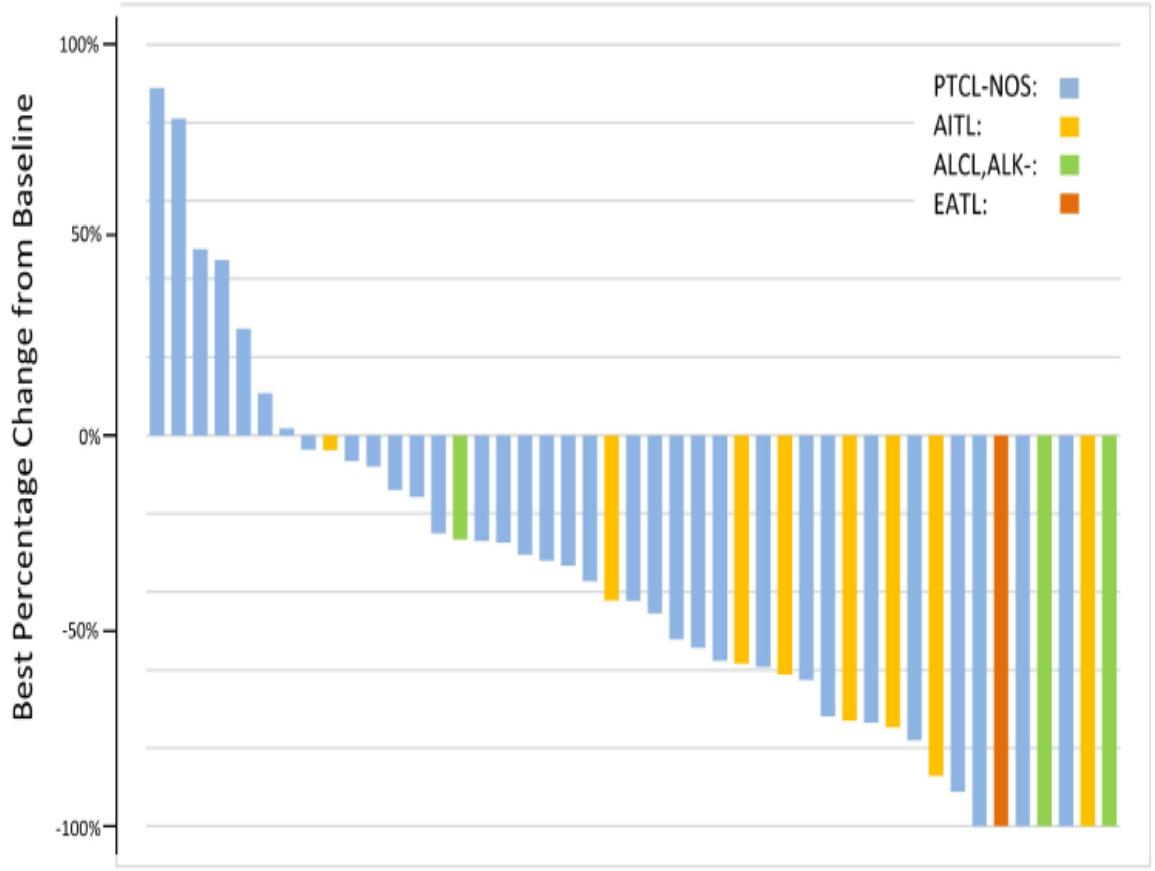
Tucidinostat in R/R PTCLs : PIIb



		Total N=46	
	Response	N (%)	95% CI
Objective response	CR or PR	21 (46)	30.9-61.0
Best response	CR	5 (11)	
	PR	16 (35)	
	SD	12 (26)	
	PD	13 (28)	
ORR by PTCL subtype	PTCL-NOS	12/34 (35)	19.7-53.5
	AITL	7/8 (88)	47.3-99.7
	ALCL, ALK-negative	1/3 (33)	0.8-90.6
	EATL	1/1 (100)	2.5-100

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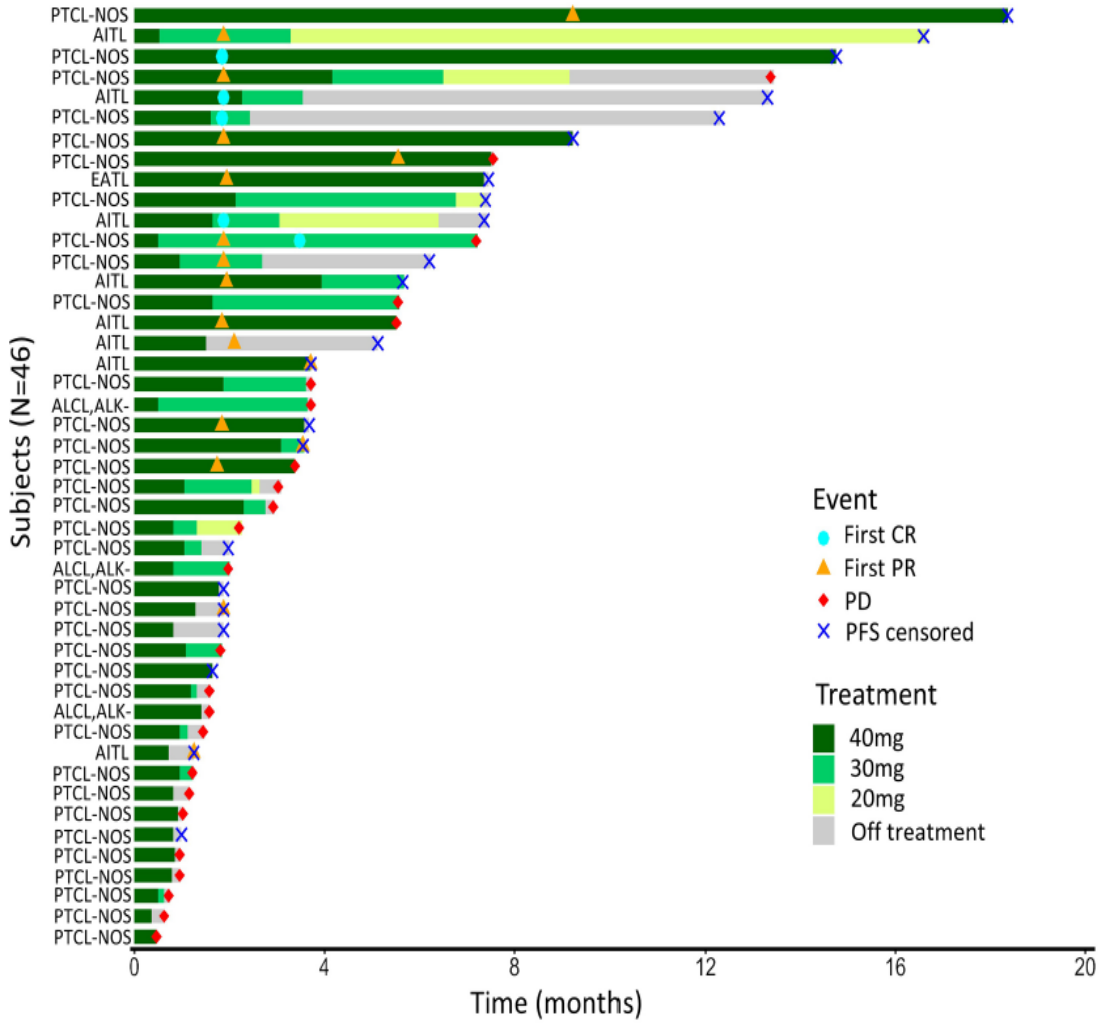
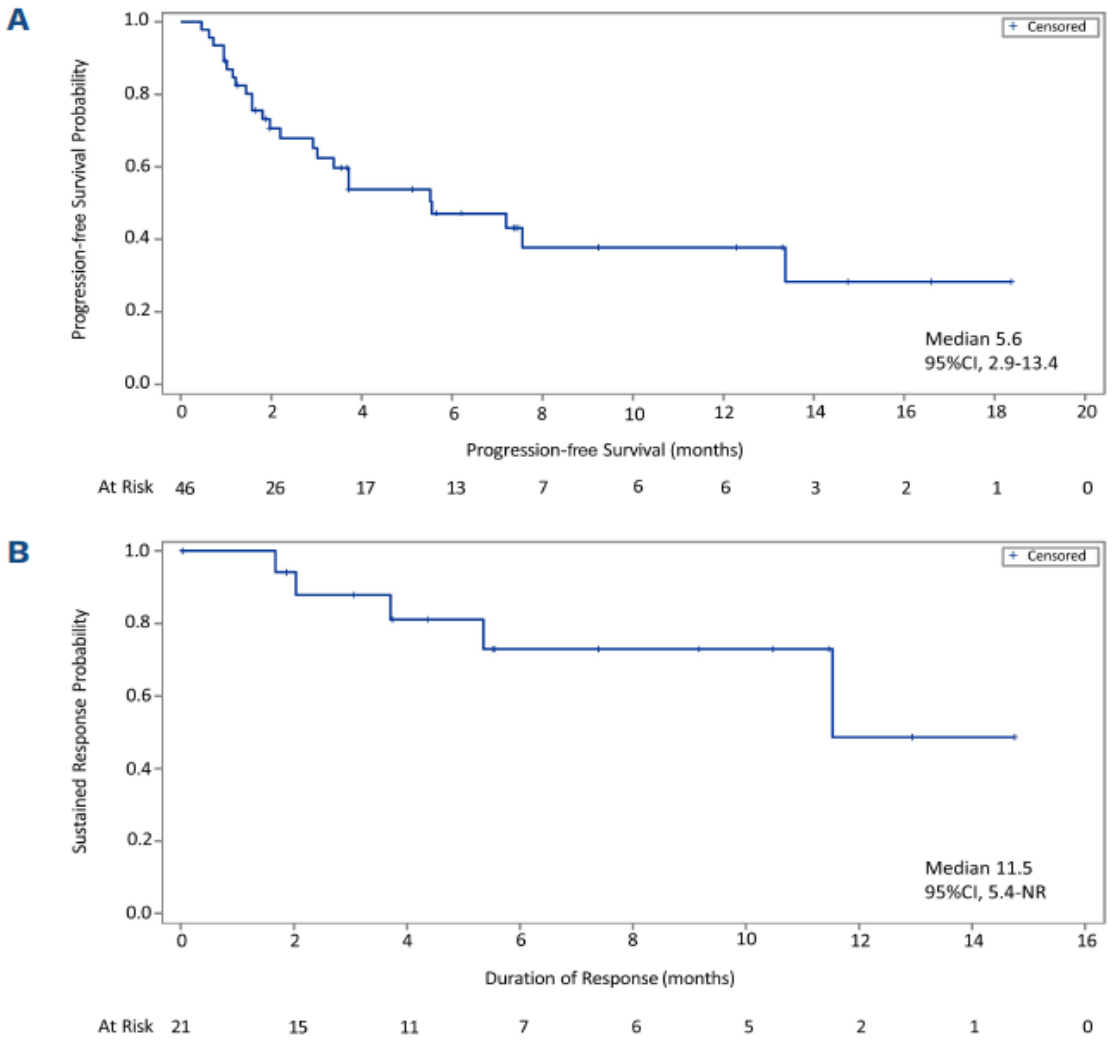
Tucidinostat in R/R PTCLs : PIIb





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ORACLE

Abstract #959: Oral Azacitidine in Patients with Relapsed/Refractory Angioimmunoblastic T-Cell Lymphoma: Final Analysis of the Oracle Phase III Study

Jehan Dupuis, Kunihiro Tsukasaki, Emmanuel Bachy, Franck Morschhauser, Guillaume Cartron, Noriko Fukuhara, Nicolas Daguindau, René-Olivier Casasnovas, Sylvia Snauwaert, Rémy Gressin, Christopher P. Fox, Francesco Annibale d'Amore, Philipp B. Staber, Argyrios Gkasiamis, Mitsufumi Nishio, Luc-Matthieu Fornecker, Marie-Helene Delfau, Nouhoum Sako, Sebastien Mule, Laurence De Leval, Philippe Gaulard, and **François Lemonnier**

ASH 2022

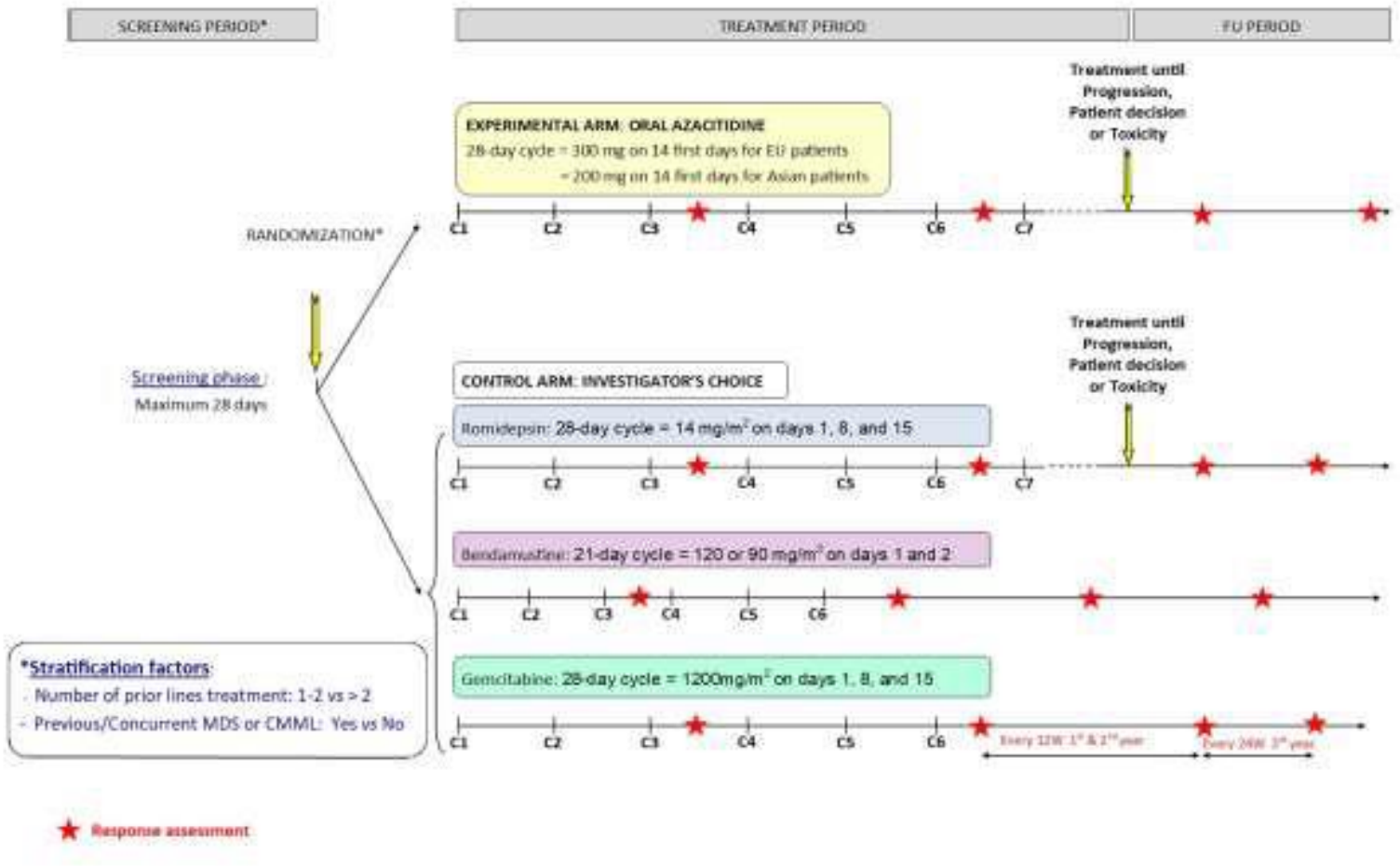
OEACLE

➢ **Key inclusion criteria**

- Aged ≥18y
- TFH PTCL (WHO 2016):
  - AITL
  - Follicular PTCL
  - Nodal PTCL with TFH phenotype
- ECOG 0-3
- **Relapsed/refractory lymphoma after≥ 1 previous line**
- Adequate hematopoietic function

➢ **Key exclusion criteria**

- CNS or meningeal involvement
- Candidate for stem cell transplantation
- Steroid use except if stable or decreasing dose for ≥ 1week before ICF signature
- Impaired renal or hepatic functions
- Previous exposure to hypomethylating agent or investigator's choice therapy



Endpoints and statistics

Primary endpoint: PFS based on local assessment using CT based IWG 2014

Key secondary endpoint: OS

Secondary endpoints:

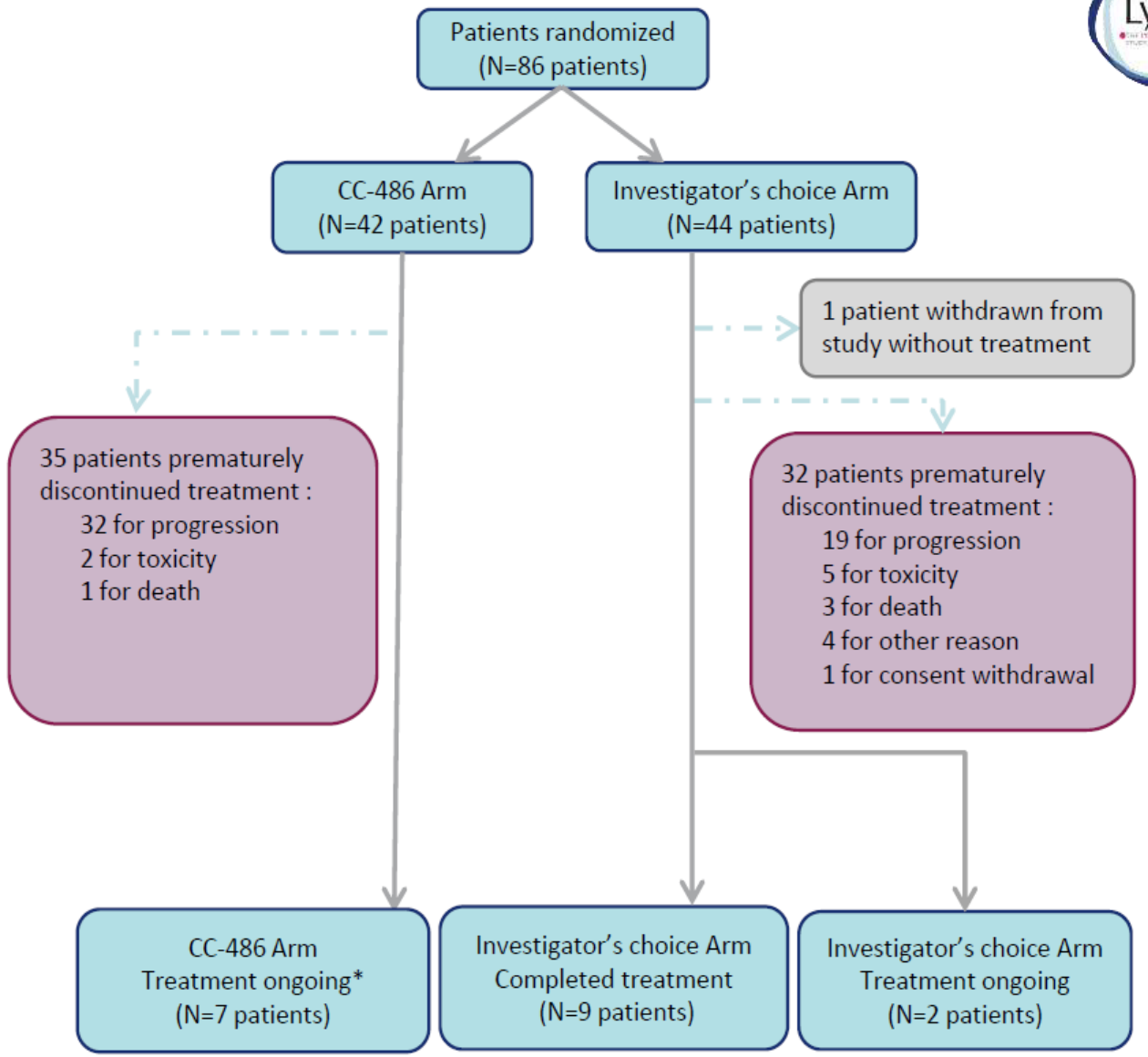
- PFS by the IRC
- Overall response rate (ORR)
- Complete response rate (CRR)
- Duration of response
- Time to response
- PFS2 using local assessment
- HRQOL endpoints EORTC QLQ-C30
- safety

Assumptions

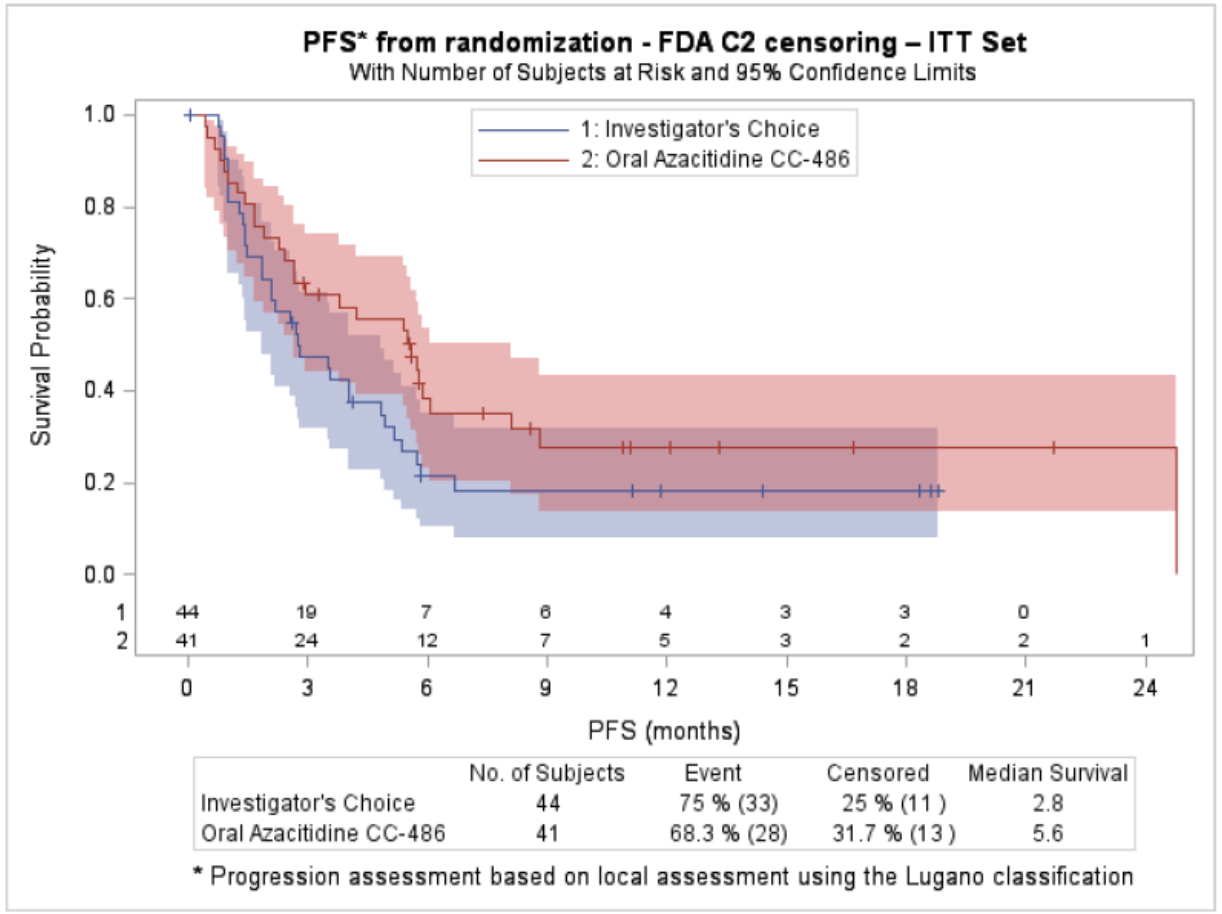
- **PFS**
  - PFS improvement from 5 (ICT) to 12 (CC-486) months
  - HR=0.417, power 90%, one sided α risk= 2.5%
  - **Superiority claimed if p-value from a stratified log rank test is < 0.025**
  - Analysis after 61 events
- **OS**
  - OS improvement from 7 (ICT) to 16.8 (CC-486) months
  - power 90%, one sided α risk= 2.5%
  - **Superiority claimed if p-value from a stratified log rank test is < 0.02**

Patient disposition

- 86 patients were included in the study from 09 Nov 2018 to 22 Feb 2021
- 87 opened sites
  - ✓ France: 57
  - ✓ Japan: 15
  - ✓ Belgium: 6
  - ✓ UK: 5
  - ✓ Denmark: 2
  - ✓ Austria: 1
  - ✓ South Korea: 1
- Median follow-up is 27.4 months (0.5-39.5)
- Central pathological review confirmed the diagnosis of AITL and TFH PTCL in 69 and 9 cases.



Primary endpoint: PFS based on local assessment

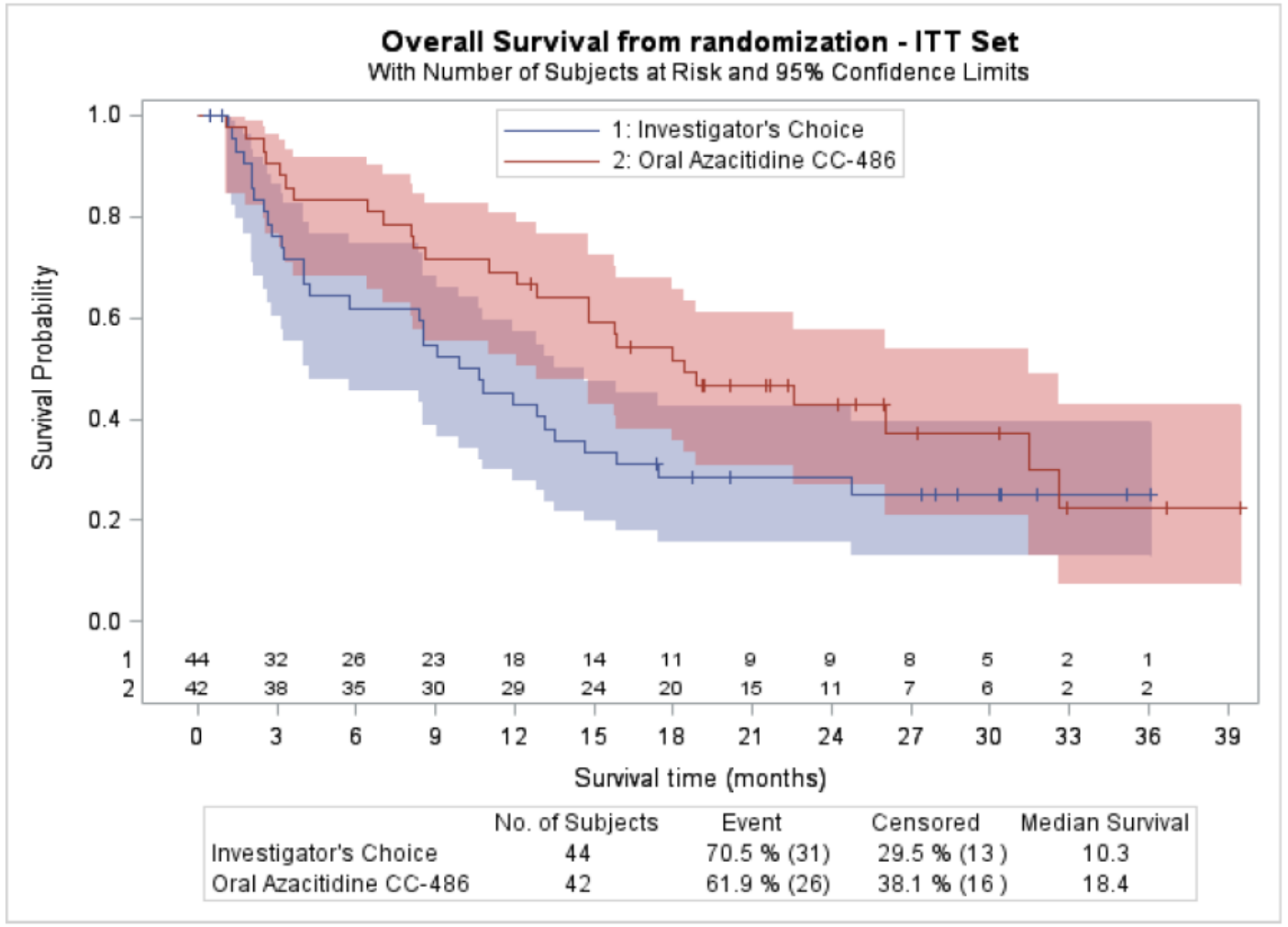


	Investigator's choice	CC-486
median	2.8 months	5.6 months
95% CI	1.9 - 4.8 months	2.7 - 8.1 months

P=0.0421

prespecified p=0.025

Key secondary endpoint: Overall survival



	Investigator's choice	CC-486
median	10.3 months	18.4 months
95% CI	4.2 – 13.5 months	12.9 – 31.5 months

P=0.0166*

* Descriptive p value

ORACLE: Response rate

	CC-486 N=42	Investigator's choice N=44	
3 months (or PTD cycle 1-3)			
Overall response rate	**14 (33%)** [19.6%-49.5%]	**19 (43.2%)** [28.3%-59%]	p =0.33
Complete response rate	**5 (11.9%)** [4%-25.6%]	**10 (22.7%)** [11.5%-37.8%]	p =0.18
6 months (or PTD cycle 4-6)			
Overall response rate	**13 (31%)** [17.6-47.1%]	**10 (22.7%)** [11.5%-37.8%]	p =0.40
Complete response rate	**5 (11.9%)** [4%-25.6%]	**7 (15.9%)** [6.6%-30.1%]	p =0.56

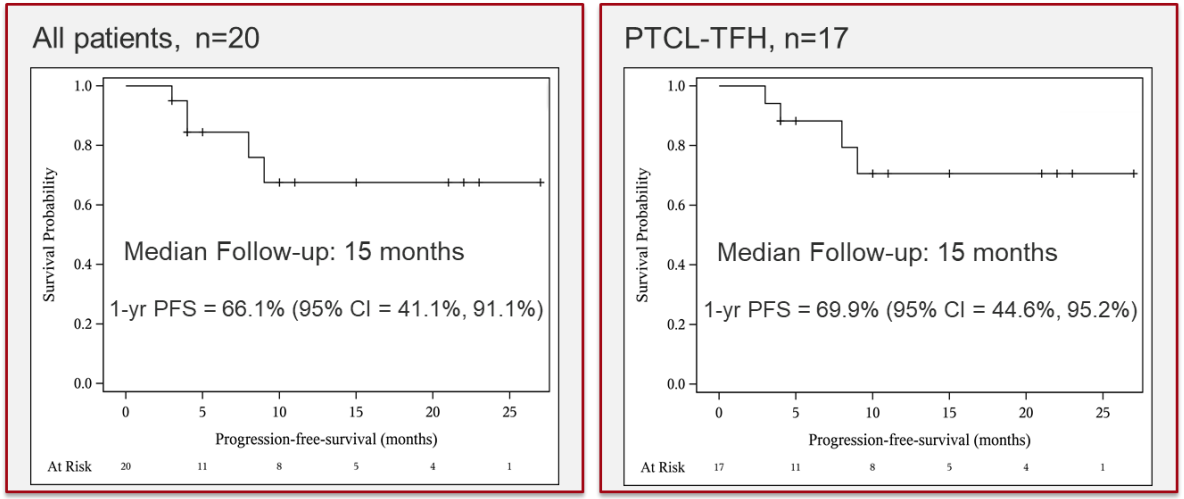
Oral Azacitidine (CC486) Plus CHOP
Efficacy and Safety

Objective Responses

Response	Interim*			EOT*		
	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)
ORR	17	85%	94%	15	75%	88%
CR	11	55%	59%	15	**75%**	**88%**
PR	6	30%	35%	0	0	0
SD	2	10%	0	1	5%	0
PD	1	5%	6%	2	10%	6%
Discontinuation	0	0	0	2	10%	6%
Median follow-up		15 months (range 9-23)				

"*": Interim – following 3 cycles of treatment; EOT following 6 cycles of treatment.
"#": Dicontinuation due to 1) disease progression; 2) strongyloides infection.

Progression-Free Survival



- Grade 3-4 toxicities in > 10% :
  - Neutropenia 71% (N =15)
  - Febrile Neutropenia 14% (N = 3)
  - Anemia 14% (N = 3)
  - Thrombocytopenia 10% (N = 2)
  - Fatigue 14% (N = 3)
  - Hyponatremia 14% (N = 3)

Ruan J, et al. ASH 2020. Abstract 40.

Dilemma in CHOP era

ENKTL can not be a candidate for CHOP treatment.

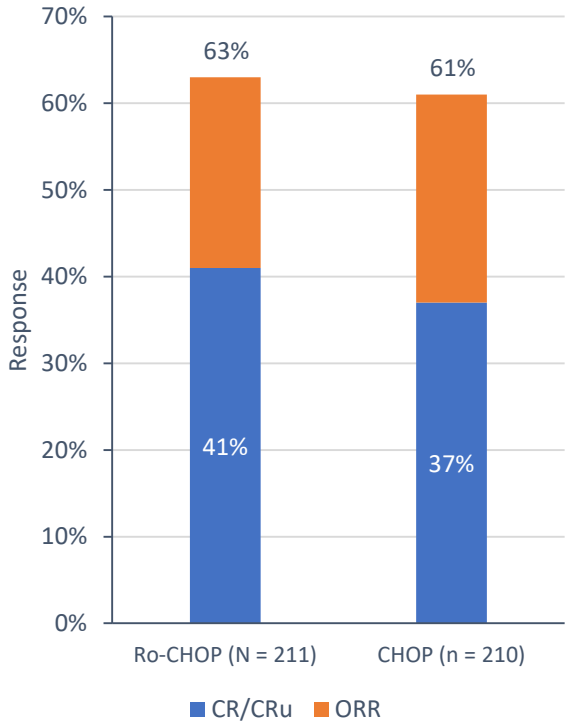
CHOP : is it a standard induction regimen?

- CHOP is superior to other combination chemo-therapy
- If CHOP is standard, still different biology under same treatment

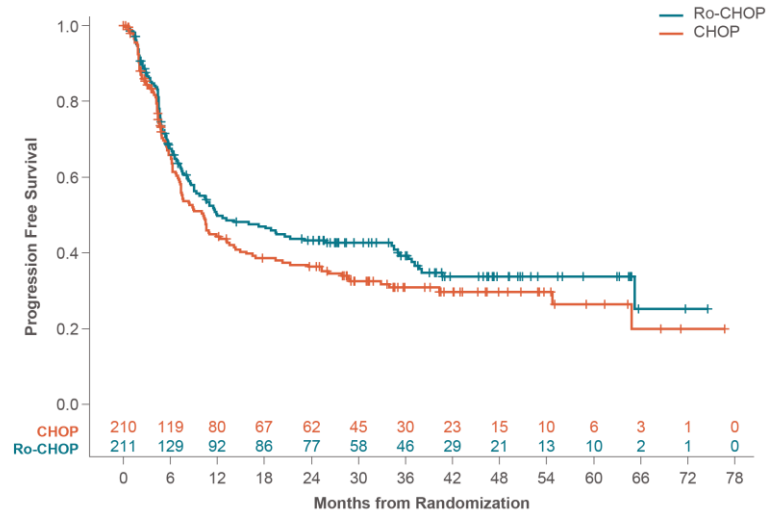
Upfront auto-HSCT : for every young and fit PTCL patients?

Ro-CHOP Efficacy

Ro-CHOP: Response at End of Treatment

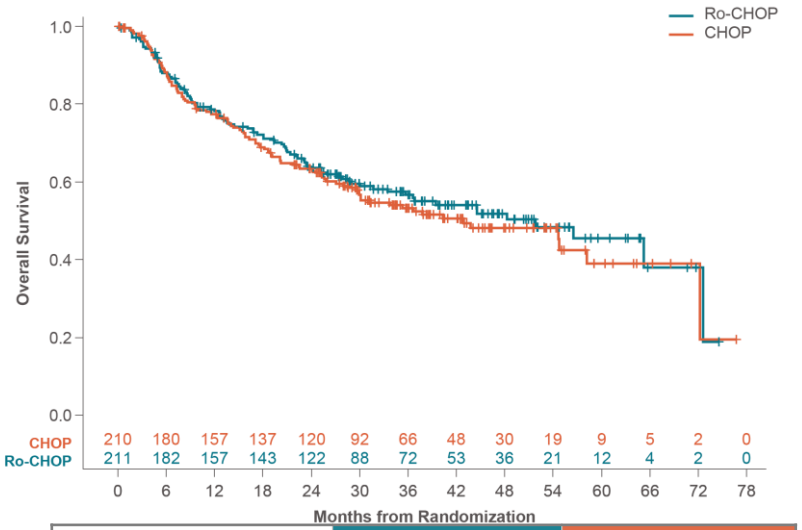


Ro-CHOP: PFS by independent RAC (ITT Population)*



	Ro-CHOP (n = 211)	CHOP (n = 210)
PFS, median (95% CI), mo	12.0 (9.0-25.8)	10.2 (7.4-13.2)
HR (95% CI)	0.81 (0.63-1.04)	
P value	0.096	

Ro-CHOP: OS (ITT Population)



	Ro-CHOP (n = 211)	CHOP (n = 210)
OS, median (95% CI), mo	51.8 (35.7-72.6)	42.9 (29.9-NR)
HR (95% CI)	0.90 (0.68-1.20)	
P value	0.477	

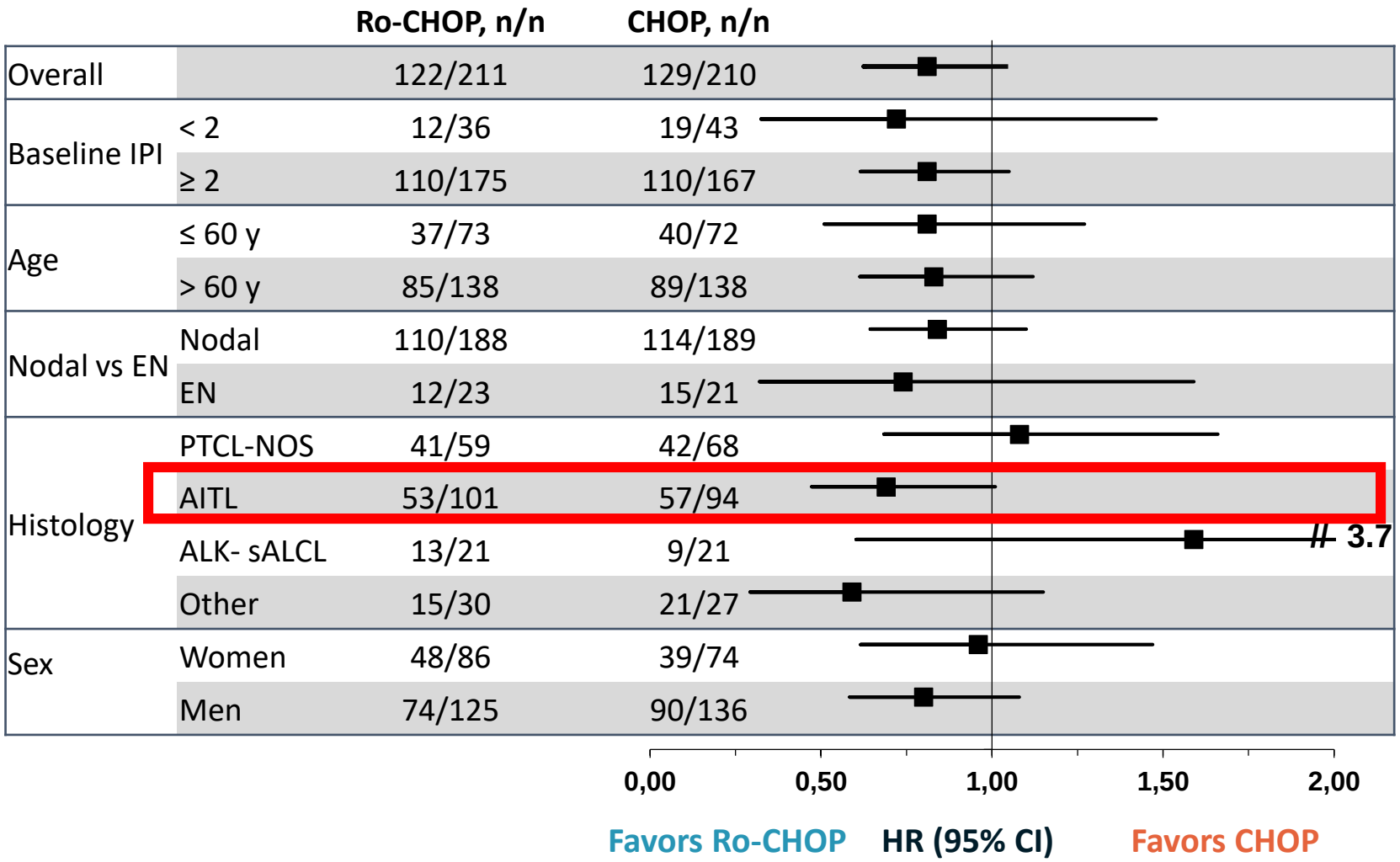
- Bachy E, et al. ASH 2020. Abstract 39.

Ro-CHOP
*Subgroup Analysis of PFS (ITT Population)- **outcomes in AITL***

Dose Reductions and Interruptions

≥ 1 TEAE Dose Modification, n (%)	Ro-CHOP (n = 210)	CHOP (n = 208)
Romi red	77 (37)	NA
Romi interrupt	132 (63)	NA
Romi DC	17 (8)	NA
CHOP red	54 (26)	31 (15)
CHOP interrupt	75 (36)	42 (20)

Completed All 6 Cycles w/o R ed or Inter, n (%)	Ro-CHOP (n = 210)	CHOP (n = 208)
Romi	62 (30)	NA
CHOP	112 (53)	125 (60)



- Bachy E, et al. ASH 2020. Abstract 39.

CHOP+X = CHOP

Drug (n)	Dose as Single Agent	Daily DI as Single Agent (mg/kg/day)	Dose in Combination	Daily DI with CHOP (mg/kg/day)	% Dose Intensity	Reference
Romidepsin	14 mg/kg D 1, 8 and 15 Q28 day	1.5 mg/kg/day	12 mg/kg D 1 and 8	1.1 mg/kg/day	28% Reduction in DI	Bachy et al., 2021
Brentuximab vedotin	1.8 mg/kg Q21 days	0.9 mg/kg/day	1.8 mg/kg D 1	0.9 mg/kg/day	100% of planned DI	Horwitz et al. 2019 & 2022
Vorinotstat	400 mg PO QD	400 mg/day	300 mg PO tid days x 5 days	214 mg/day	47% Reduction in DI	Oki et al. 2013
Everolimus	10 mg PO QD	10 mg/day	5 mg D 1-14 Q 21 D	3.3 mg/day	66% Reduction in DI	Kim et al. 2013
Denilukein difitox	18 mcg/kg/day x 5 day Q21 D	2.1 mcg/kg/day (or 4.2 mcg/kg/day)	18 mcg/kg D 1 and 2 Q 21D	1.7 mcg/kg/day	80% of planned DI	Foss et al. 2013
Bortezomib	1.3 mg/m2 Days 1, 4, 8 and 11 Q 21 D	0.25mg/kg/day	1.6 mg/m2 Days 1 & 8	0.15 mg/kg/day	40% Reduction in DI	Lee et al., 2008
Chidamide	50 mg TIW x 3 wks Q21 D	9.5 mg/day	30 mg Days 1, 4 and 8 Q 21 days	4.3 mg/day	55% Reduction in DI	Lu et al. 2016

- **Courtesy of Owen O'Connor**

CHOP : is it a standard?

Dose Level	CHOP	Dose Changes	'Plus' Drug	Dose Changes
Dose Level 1	CTX 750 Dox 50 VCN 2 Pred 100 QD x 5	Fixed Dosing	1x	Escalated
Dose Level 2	CTX 750 Dox 50 VCN 2 Pred 100 QD x 5		2x	
Dose Level 3	CTX 750 Dox 50 VCN 2 Pred 100 QD x 5		3x	
Dose Level 4	CTX 750 Dox 50 VCN 2 Pred 100 QD x 5		4x	
Dose Level 5	CTX 750 Dox 50 VCN 2 Pred 100 QD x 5		Single Agent MTD/OBD	

Dose Level	CHOP	Dose Changes	'Plus' Drug	Dose Changes
Dose Level 1	CTX **X** Dox **X** VCN **X** Pred 100 QD x 5	Escalated	OBD / MTD Dose = X	Fixed Dosing
Dose Level 2	CTX **2X** Dox **2X** VCN **2X** Pred 100 QD x 5		OBD / MTD Dose = X	
Dose Level 3	CTX **3X** Dox **3X** VCN **3X** Pred 100 QD x 5		OBD / MTD Dose = X	
Dose Level 4	CTX **4X** Dox **4X** VCN **4X** Pred 100 QD x 5		OBD / MTD Dose = X	
Dose Level 5	CTX **5X** Dox **5X** VCN **5X** Pred 100 QD x 5		OBD / MTD Dose = X	

- **Courtesy of Owen O'Connor**

Recent advances in T/NK cell lymphoma

More biologic /genomic data based classification

CHOP is standard ?

- ALCL : BV congaing should be recommended
  - CD30+PTCL other than ALCL : recommended in US / not in EU
- COO : FHT subtypes –epigenetics based
- Cytotoxic T-cell lymphoma : ?
- Gamma/delta T-cell lymphoma : ?
- ENKTL : immuno-oncology based

SAMSUNG MEDICAL CENTER

THANK-YOU