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Making Cancer History®
TCLG
RAD-ONC
SCT
HEM-LYM
HEM
PATH
DERM
DERM
Studies in TCL and regulatory lessons
Dr.Swami Iyer
Professor of Lymphoma/Myeloma

Classification of Peripheral T-cell Lymphoma (PTCL)

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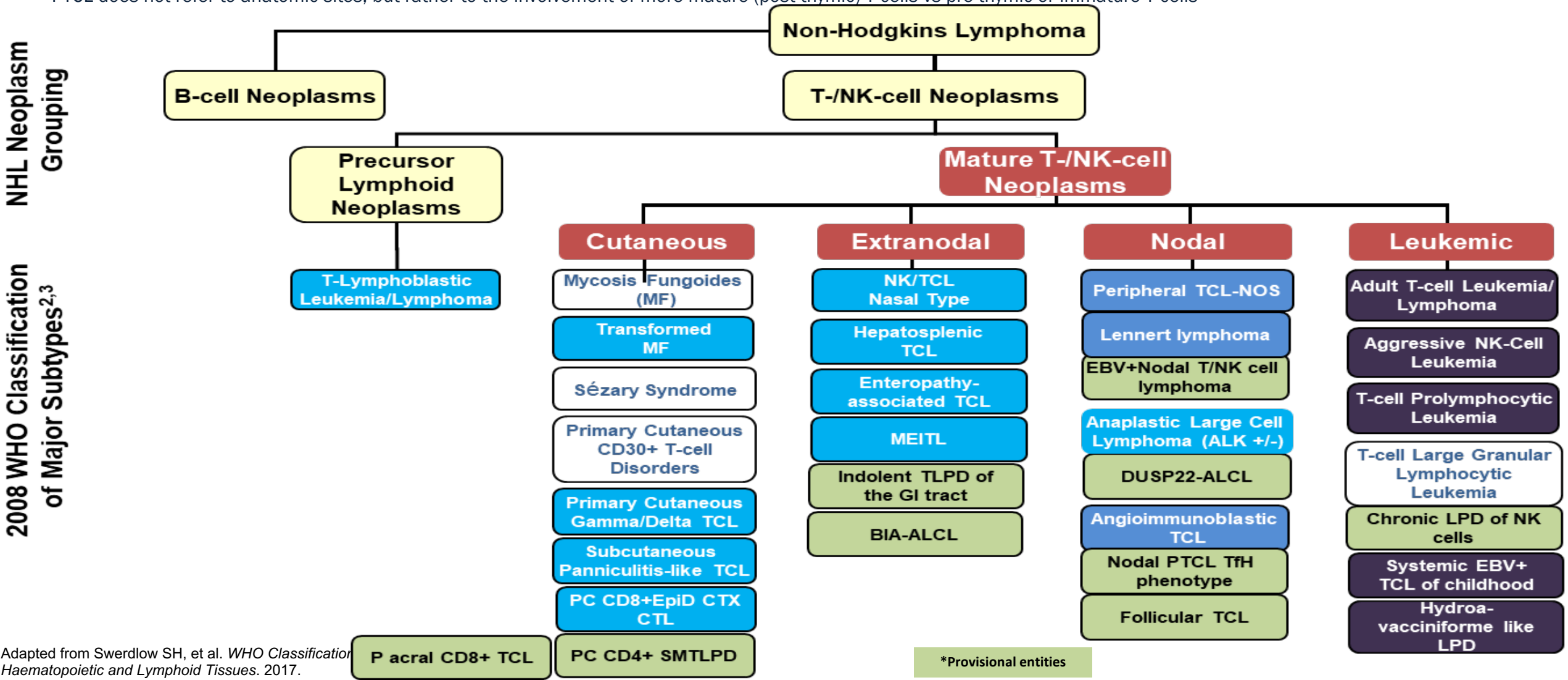
PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas

PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells[1]



Adapted from Swerdlow SH, et al. *WHO Classification of Haematopoietic and Lymphoid Tissues*. 2017.

PTCL Prognostic Characteristics

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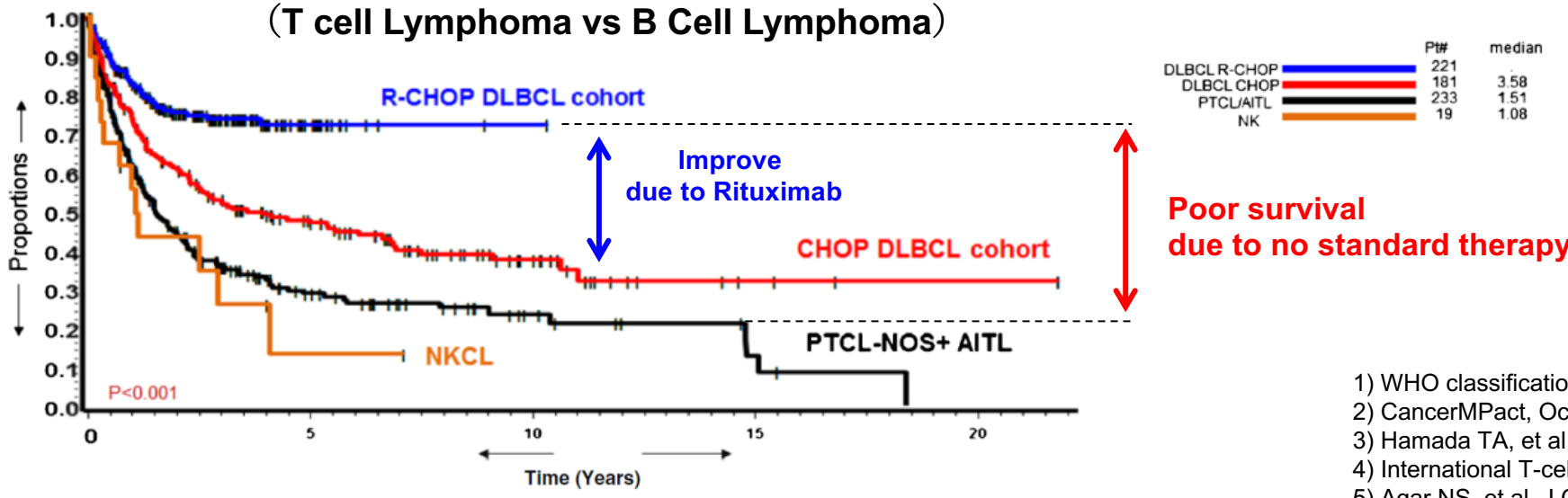
Major subtype of T-cell Lymphoma[1] (WHO classification 2008)	Number of newly diagnosed Pts in 2018 [2]			5yr OS [4) 5)] (%)
	US	EU	Japan	
PTCL (Peripheral T-cell lymphoma) **PTCL-NOS** (PTCL not otherwise specified) **AITL** (Angioimmunoblastic T-cell lymphoma) **ALK (+) ALCL** (Anaplastic large-cell lymphoma) **ALK (-) ALCL**	3,683	3,033	2,340	32 32 70 49
CTCL (Cutaneous T-cell lymphoma) **MF** (Mycosis fungoides) **SS** (Sezary syndrome)	3,466	1,798	278 [3]	18～37*

n.d.: No data * Advance stage

Overall survival
(T cell Lymphoma vs B Cell Lymphoma)



Poor survival
due to no standard therapy

1) WHO classification of haematopoietic and Lymphoid Tissues. 2008.
2) CancerMPact, Oct, 3, 2019.
3) Hamada TA, et al, Nationwide survey on cutaneous lymphomas. 2008
4) International T-cell Lymphoma project, J Clin Oncol.2008.
5) Agar NS, et al, J Clin Oncol. 2010.
6) Lone W, et al, Current Hematologic Malignancy Reports. 2018.

Advances in Lymphoma Biology

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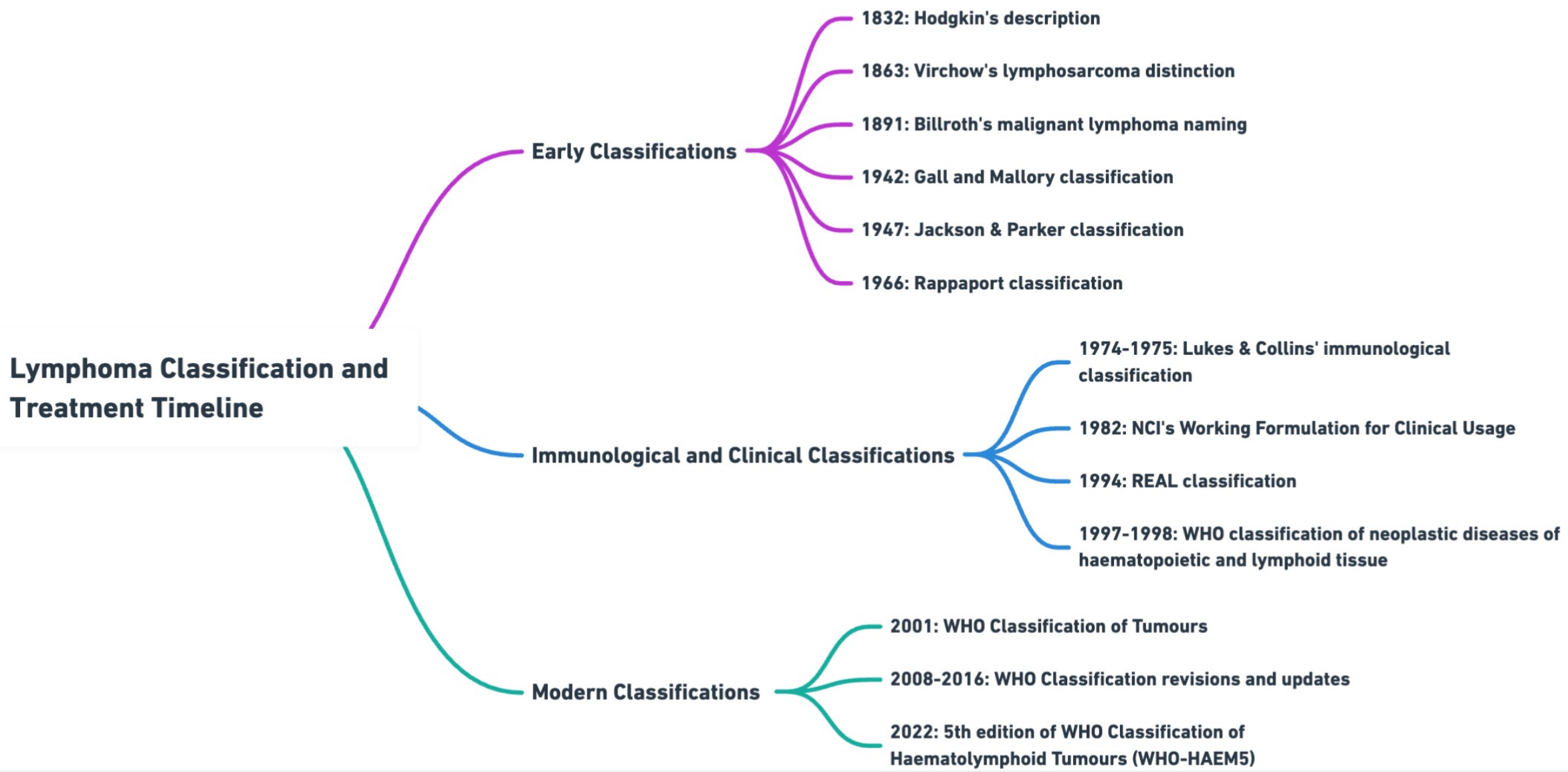

Subtype, subtype, subtype: Pathology as basis for diagnosis, prognosis in PTCL

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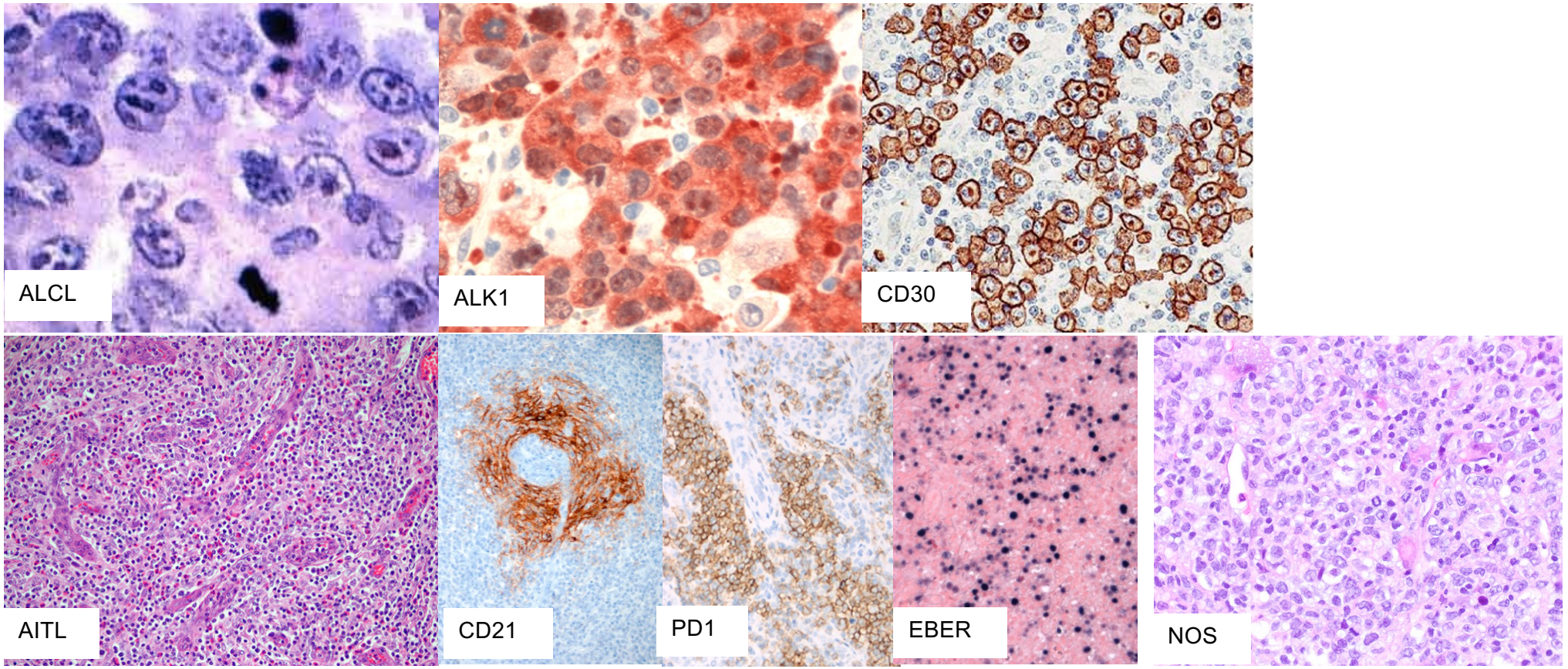
- Approximately 30-50% of PTCL cases are incorrectly diagnosed with conventional diagnostic techniques[1]
- Immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays



1. Armitage J, et al. *J Clin Oncol*. 2008;26:4124–4130.
2. Warnke RA, et al. Am J Clin Pathol. 2007;127:511–527
3. Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008
4. Kocjan G. J Clin Pathol. 2005;58:561–567.

Advances

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Treatment Advar

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T-Cell Lymphoma Subtypes Based on Utility of CHOP Treatment

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Always

- Anaplastic large-cell, ALK-1 positive

CHOP variations

- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell, ALK-1 negative
- Enteropathy-type intestinal lymphoma
- Subcutaneous panniculitis-like T cell
- Hepatosplenic T-cell lymphoma
- Adult T-cell leukemia/lymphoma

Never

- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ disorders
  - Anaplastic large-cell lymphoma
  - Lymphomatoid papulosis
- T-cell large granular lymphocytic
- Extranodal NK/T-cell lymphoma, nasal
- NK/T-cell leukemia/lymphoma
- T-cell prolymphocytic leukemia

- Is there an R-CHOP?
  - Romidepsin
  - Lenalidomide
  - Alemtuzumab
  - Brentuximab
  - Etoposide
  - Azacitidine
  - PI3Kγδ inhibitors

What is the goal? Increased efficacy with Increased toxicity?
Induction prior to consolidation (SCT): CR/safety
Increased cure rates: PFS/OS

Gallamini A, et al. Blood. 2007;110:2316-2323. Foss F, et al. 2008 ICML. Abstract.

Selected Attempts To Improve Upon CHOP for PTCL

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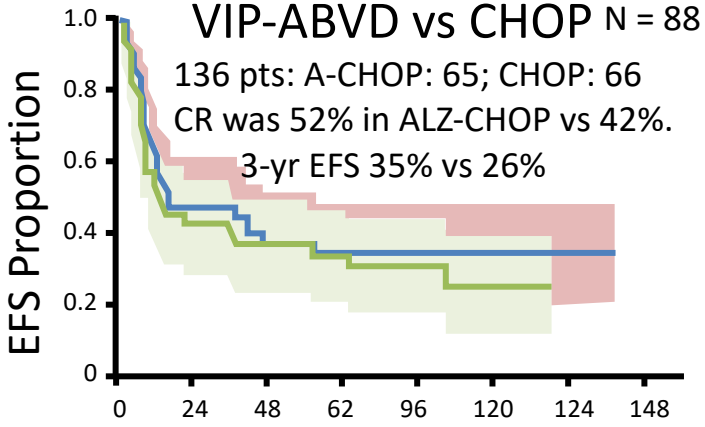
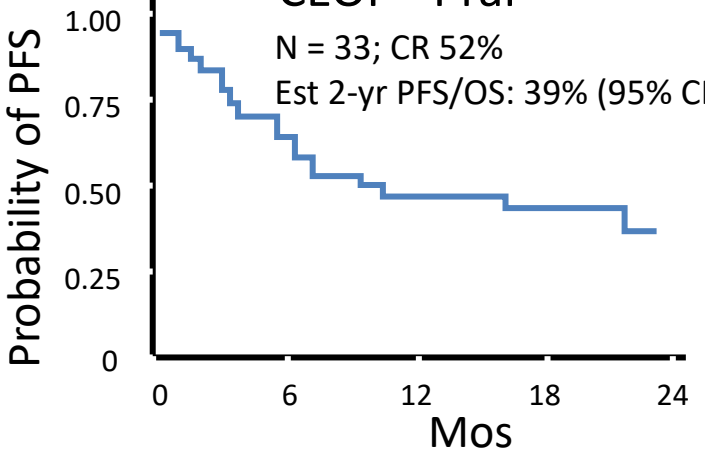
VIP-ABVD vs CHOP N = 88

136 pts: A-CHOP: 65; CHOP: 66
CR was 52% in ALZ-CHOP vs 42%.
3-yr EFS 35% vs 26%

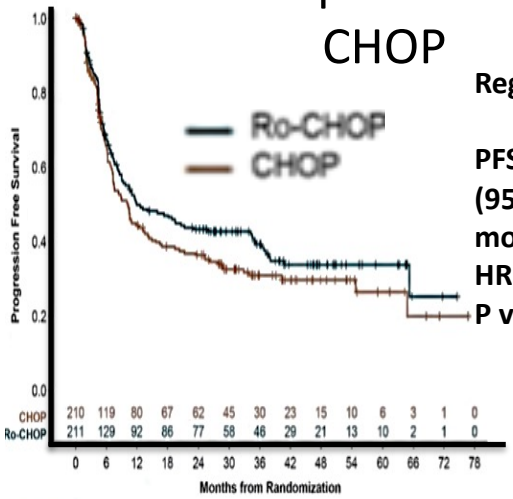


CEOP –Pral

N = 33; CR 52%
Est 2-yr PFS/OS: 39% (95% CI 21-57)

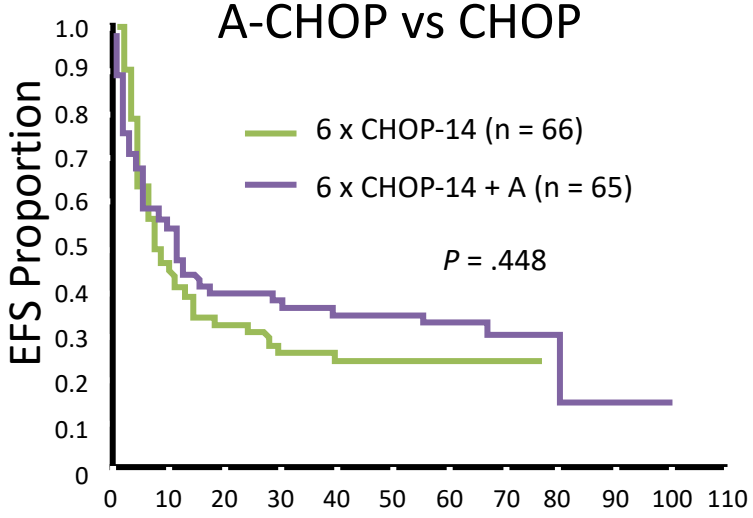


Romidepsin-CHOP vs. CHOP



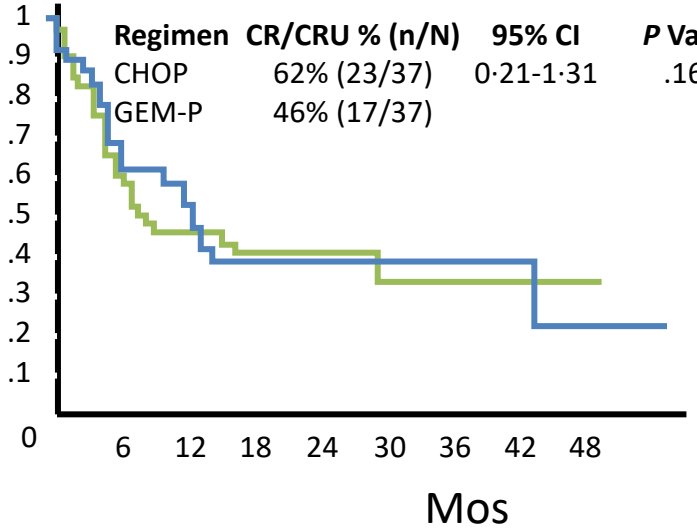
Regimen	Ro-CHOP (n=211)	CHOP (n=230)
PFS median (95% CI), mo	12.0 (9-25.8)	10.2 (7.4-13.2)
HR (95% CI)	0.81 (0.63-1.04)	
P value	0.096	

A-CHOP vs CHOP



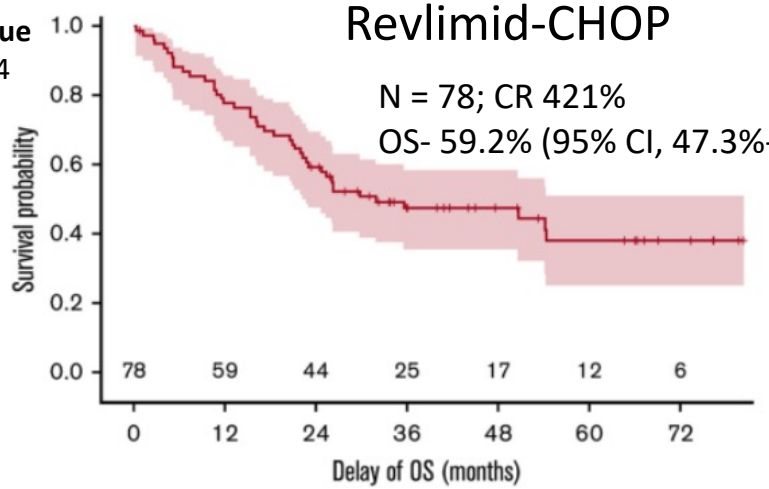
CHOP vs GEM-P

Regimen	CR/CRU % (n/N)	95% CI	*P* Value
CHOP	62% (23/37)	0·21-1·31	.164
GEM-P	46% (17/37)		



Revlimid-CHOP

N = 78; CR 421%
OS- 59.2% (95% CI, 47.3%-69.3%)



Simon. Br J Haem. 2010. d'Amore. ASH 2018. Advani. Br J Haem. 2016;172:636. Gleeson. Lancet Haem. 2018;5:E190; Bachy et al. Lancet Haem. 2021, Lemmonier et al. Blood Adv, 2021

MDACC Outcomes for PTCL

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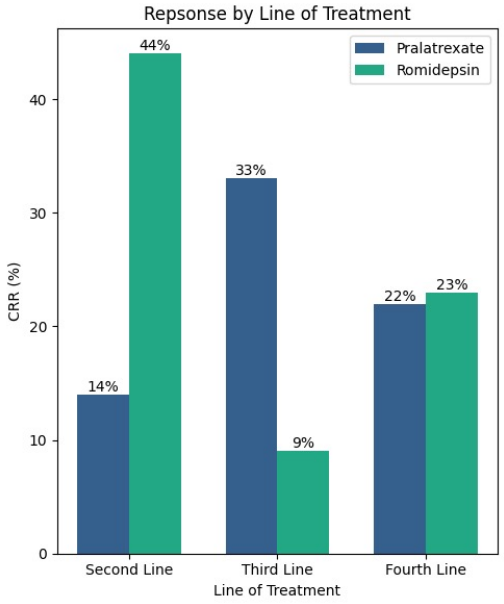
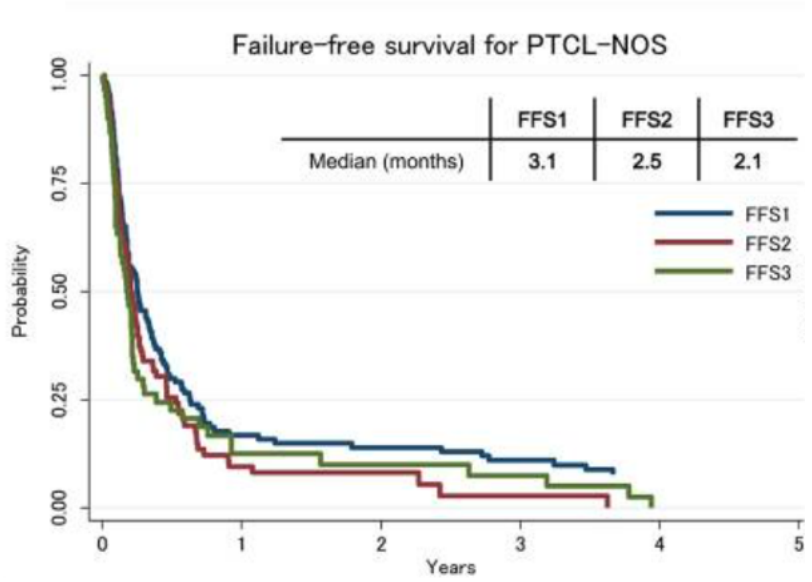
PTCL-NOS, AITL: 321 pts (180 PTCL-NOS, 141 AITL)
PFS1: PFS to front-line therapy
PFS2: PFS to 1st salvage
PFS3: PFS to 2nd salvage
Med OS1, OS2 and OS3 were 47.7, 15.1 and 8.1 mo.

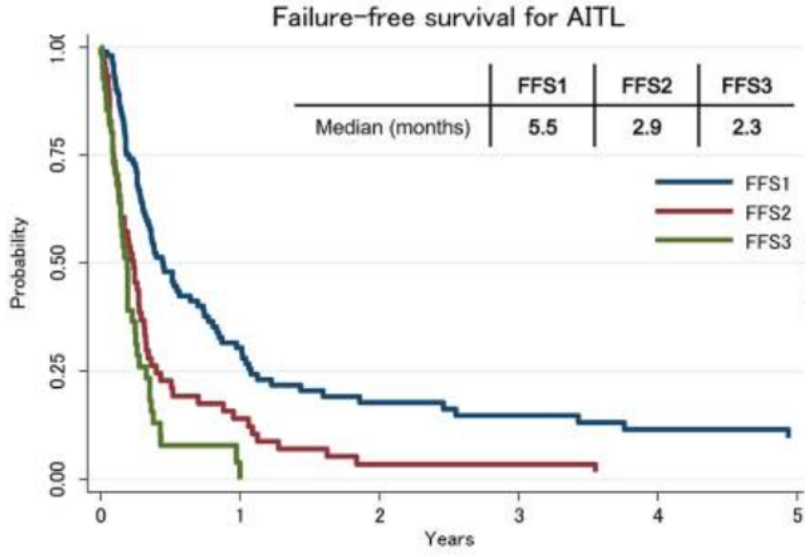
Pralatrexate or Romidepsin at 1st or 2nd salvage TX were not associated with longer PFS2 or PFS3.



	PFS1	PFS2	PFS3
All	**10.3**	**4.1**	**2.5**
PTCL	**8.4**	**3.1**	**2.5**
AITL	**13.1**	**10.9**	**2.4**

Results: Med Mo





Chihara D, et al. Br J Haematol. 2017

Intensification → ASCT in PTCL

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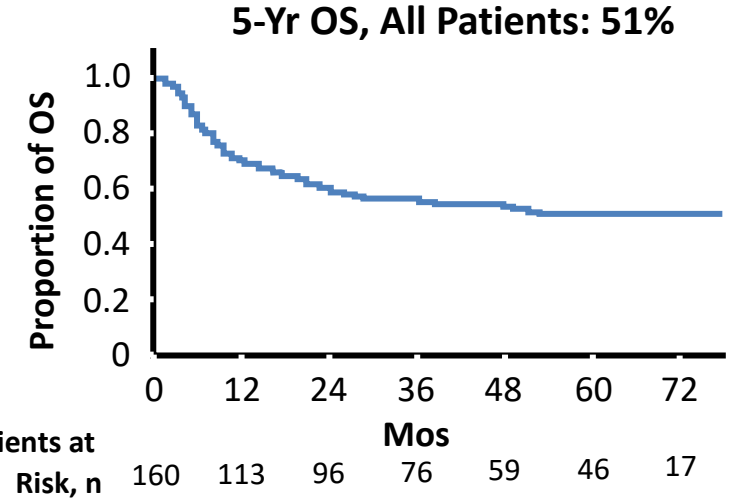
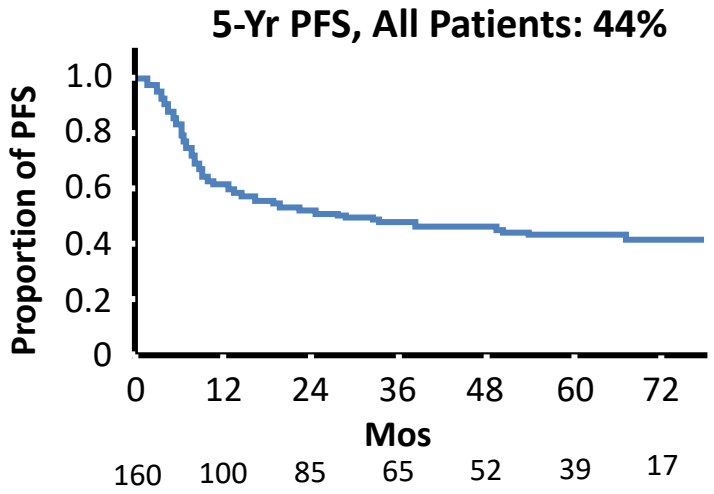
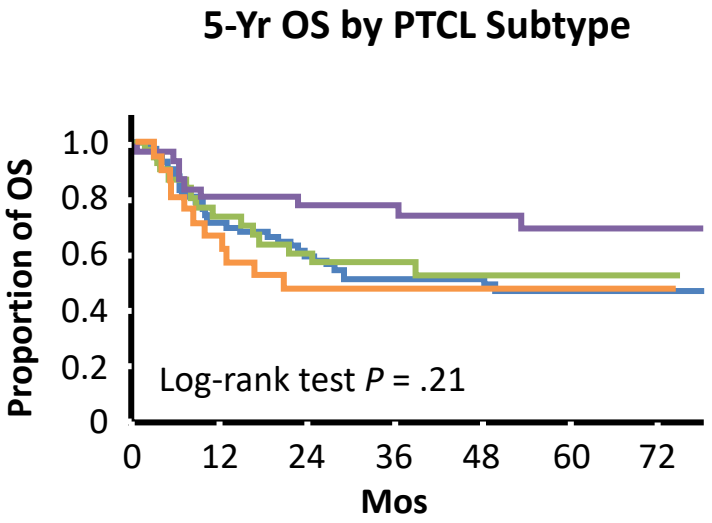
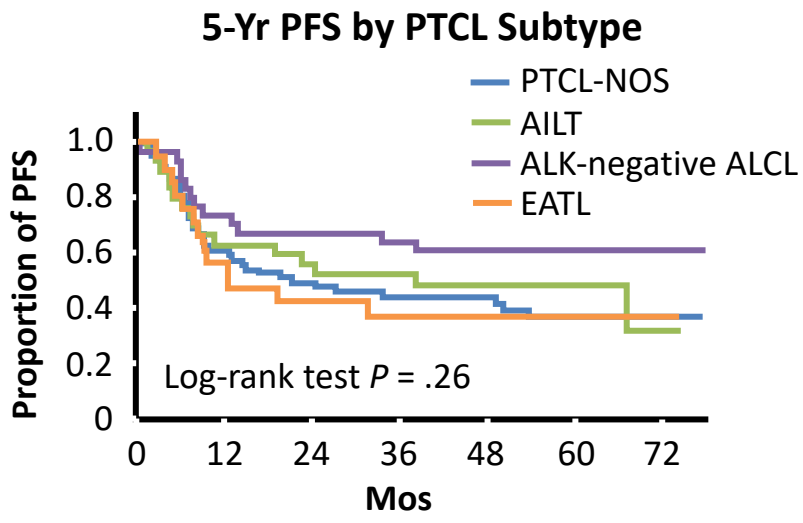
- Phase II NLG-T-01 Trial (aka The Nordic Trial)
- N = 160 patients with untreated systemic PTCL
- Treatment: CHO(E)P-14* Q2W x 6 cycles
  - ORR: 82% with CR 51%
  - BEAM or BEAC plus ASCT (n = 115; 72%)

*Etoposide omitted for patients older than 60 yrs of age.









d'Amore. J Clin Oncol. 2012;30:3093.

CD30-Targeted mAbs: In memorium Dr.Ekhard Podack

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Antibody	KA (M^-1)	KD (nM)
10C2	1.65 x 10^9	0.607
12B1	5.02 x 10^9	0.199
13H1	6.7 x 10^9	0.149
15B8	1.02 x 10^9	0.978
AC10	6.77 x 10^9	0.148
8D10	16.9 x 10^9	0.0592

Attributes	8D10F10 mAb	AC10 mAb
Location	Epitope is located in a distinct region of the CD30 protein	Epitope is located in a different region of the CD30 protein
Cluster	Binds to cluster A of CD30 epitopes	Binds to cluster C
Epitope Motifs	Recognizes epitopes with motifs EEKYEE, DFMLYD, and CEPDYYLDE	Recognizes epitopes with motifs YWKIKGLVQPTR, LYERDEGDKWRNK, TQQCPQRPTDCR, GTRLAQEAASK, and FKKRIEAIPQIDKYL

> J Immunol. 1993 Dec 1;151(11):5896-906.

Functional effects of CD30 on a large granular lymphoma cell line, YT. Inhibition of cytotoxicity, regulation of CD28 and IL-2R, and induction of homotypic aggregation

M A Bowen [1], K J Olsen, L Cheng, D Avila, E R Podack

Unconjugated Antibody	Antibody Type	Therapeutic Activity in cHL	Therapeutic Activity in sALCL
SGN-30 (cAC10)	Chimerized IgG1 (IgG1)	Minimal activity	17/41 responses
MDX-060	Fully Human	6% ORR in patients with cHL	29% ORR in patients with ALCL

Forero-Torres A. et al. Br J Haematol. (2009)
Ansell SM. et al. J Clin Oncol. (2007)

≈

CD30 as the predictive marker in TCL

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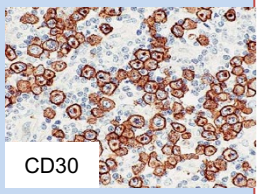
CD30+ Histologies:
PTCL-NOS
AITL (?)
ALK- ALCL
ALK + ALCL



BV + CHP

CR or PR → Complete Rx → CR or PR → ASCT

No response or PD → Rx as r/r PTCL

No response or PD → Rx as r/r PTCL

CD30

PTCL

Salvage therapy/ Clinical trials

PTCL Histologies:
PTCL-NOS
AITL (?)

CHOP

No response or PD → Rx as r/r PTCL

CR or PR → Complete Rx → No response or PD → Rx as r/r PTCL

CR or PR → ASCT

ECHELON-2: Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL

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

Stratification for IPI score (0-1 vs 2-3 vs 4-5), histologic subtype (ALK+ sALCL vs other subtypes)

Adult patients with previously untreated CD30+ (≥10% expression) PTCL* (N = 452)

BV + CHP
Brentuximab Vedotin† +
CHP‡ Q3W for 6-8 cycles +
Placebo for Vincristine
(n = 226)

Interim PET4

CHOP‡
Q3W for 6-8 cycles +
Placebo for Brentuximab Vedotin
(n = 226)

	A+CHP N=226	CHOP N=226
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK–	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

*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/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (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

Horwitz. Lancet. 2019;393:229.

ECHELON-2 Exploratory Analysis: PFS at 5 Yr

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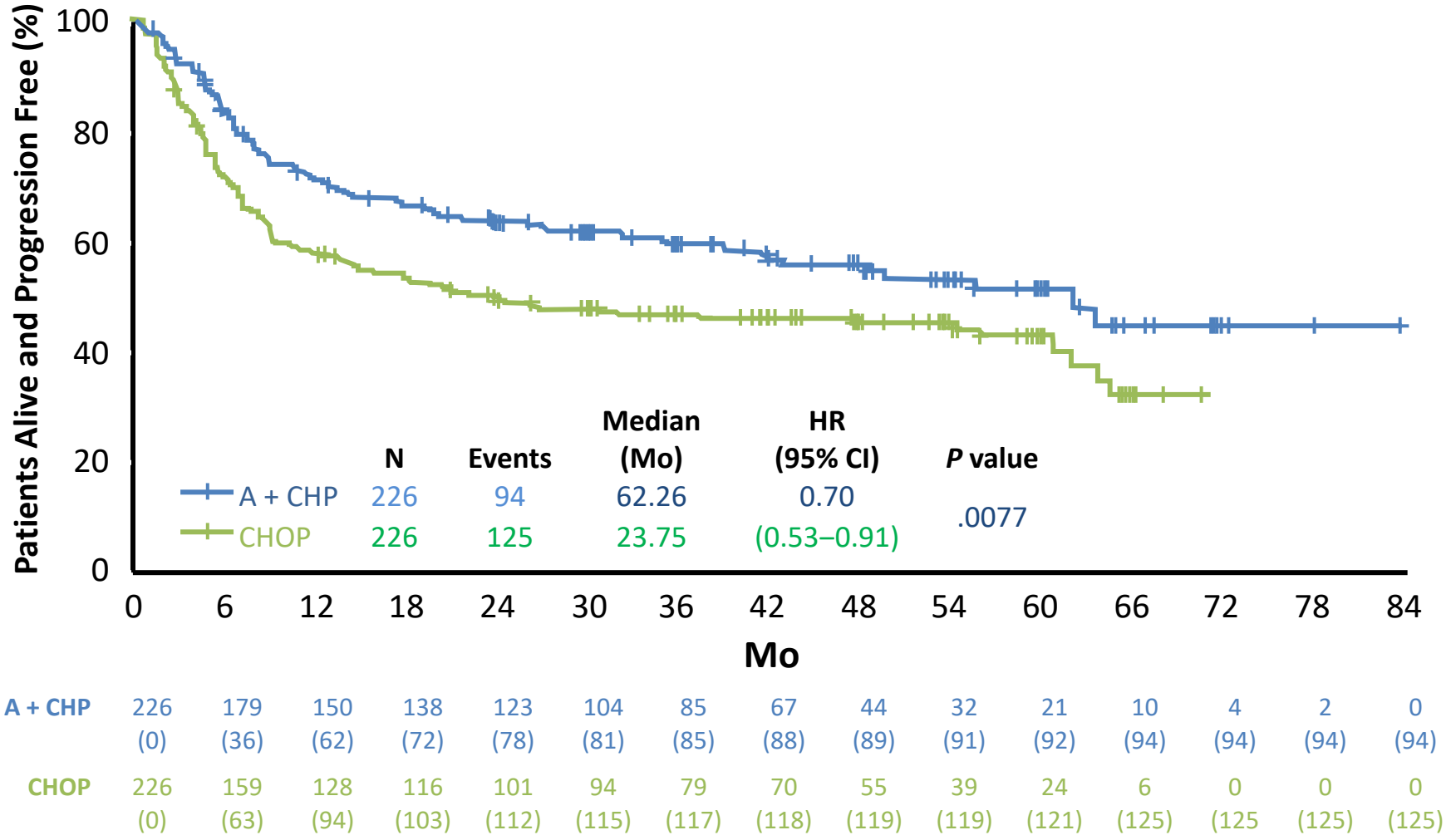
PFS: A+CHP-48.2 months [95% CI = 35.2-not estimable] vs CHOP-20.8 months [12.7-47.6]; hazard ratio [HR] = 0.70 [0.53-0.92])

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



Iyer. SOHO 2021. Abstr TCL150, Horwitz et al. Annals of Oncology

ECHELON-2 Secondary Endpoint: OS

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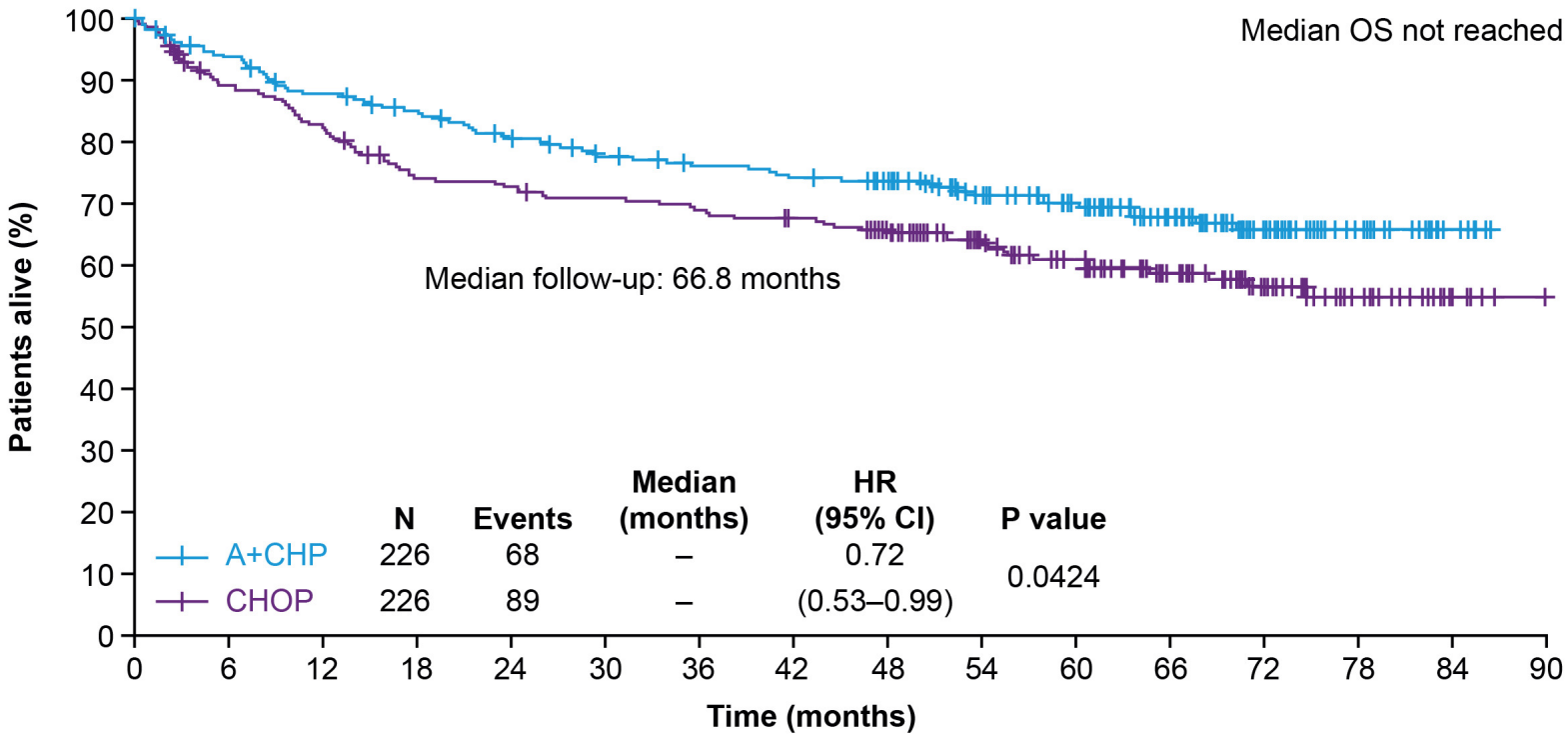
A+CHP reduced the risk of death by 28% compared with CHOP



Number of patients at risk (events)

A+CHP	226 (0)	208 (14)	193 (27)	184 (33)	173 (42)	162 (49)	156 (52)	152 (56)	143 (57)	117 (61)	103 (63)	80 (66)	48 (68)	23 (68)	5 (68)	0 (68)
CHOP	226 (0)	196 (24)	181 (39)	160 (57)	157 (60)	152 (64)	148 (68)	143 (71)	132 (75)	105 (78)	90 (83)	68 (86)	43 (88)	25 (89)	8 (89)	0 (89)

Iyer. SOHO 2021. Abstr TCL150.

PET4negative Patients Show Improved PFS and OS in the Overall Population

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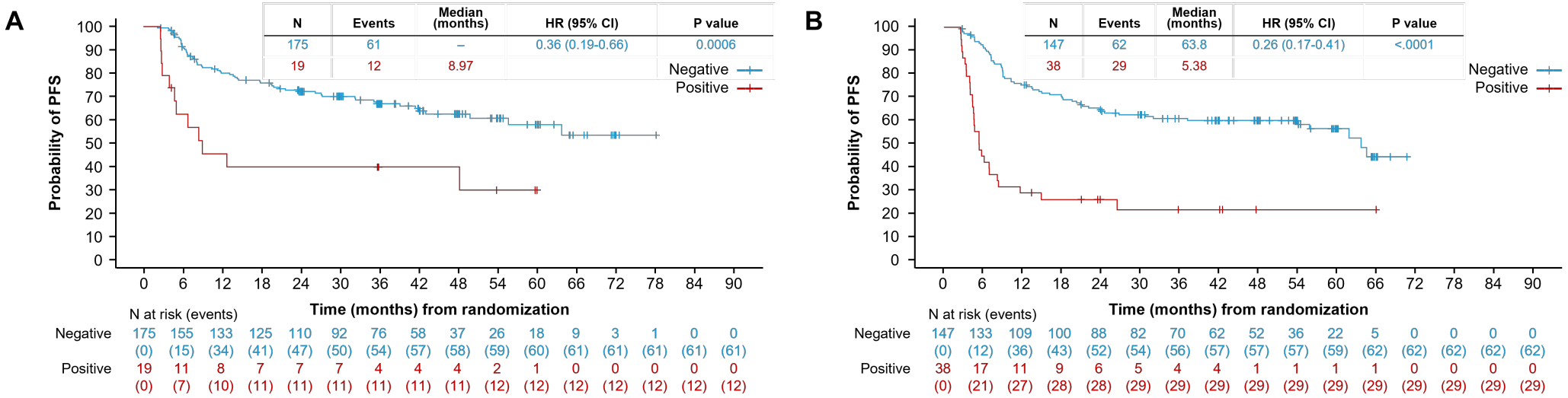
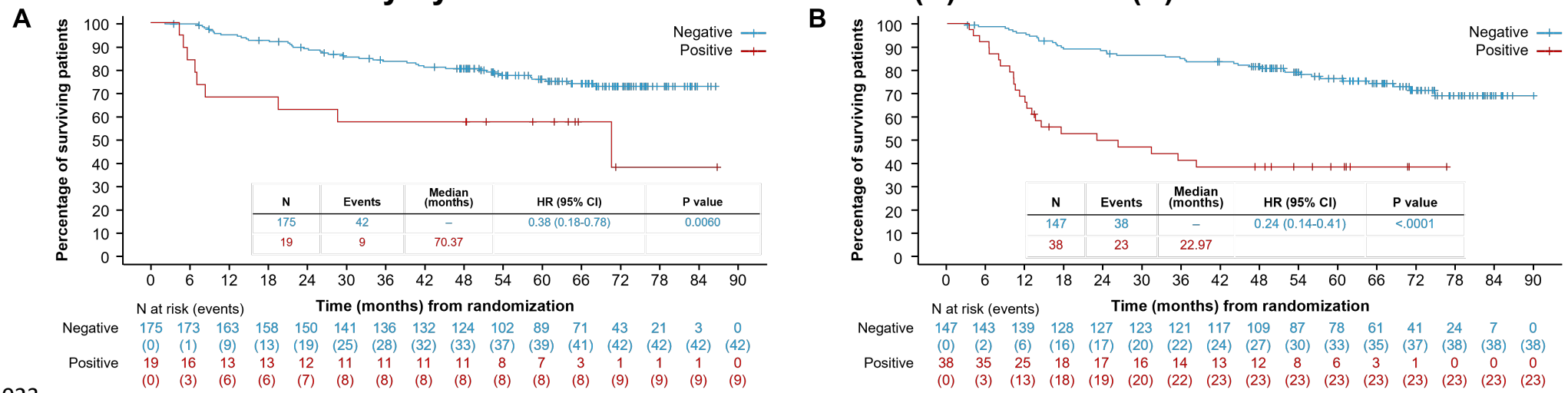
PFS by Cycle 4 PET Status in the A+CHP (A) and CHOP (B) arms



OS by Cycle 4 PET Status in the A+CHP (A) and CHOP (B) arms



Iyer S, et al. ASH 2023.

ECHELON-2 Exploratory Analysis: PFS by SCT After CR

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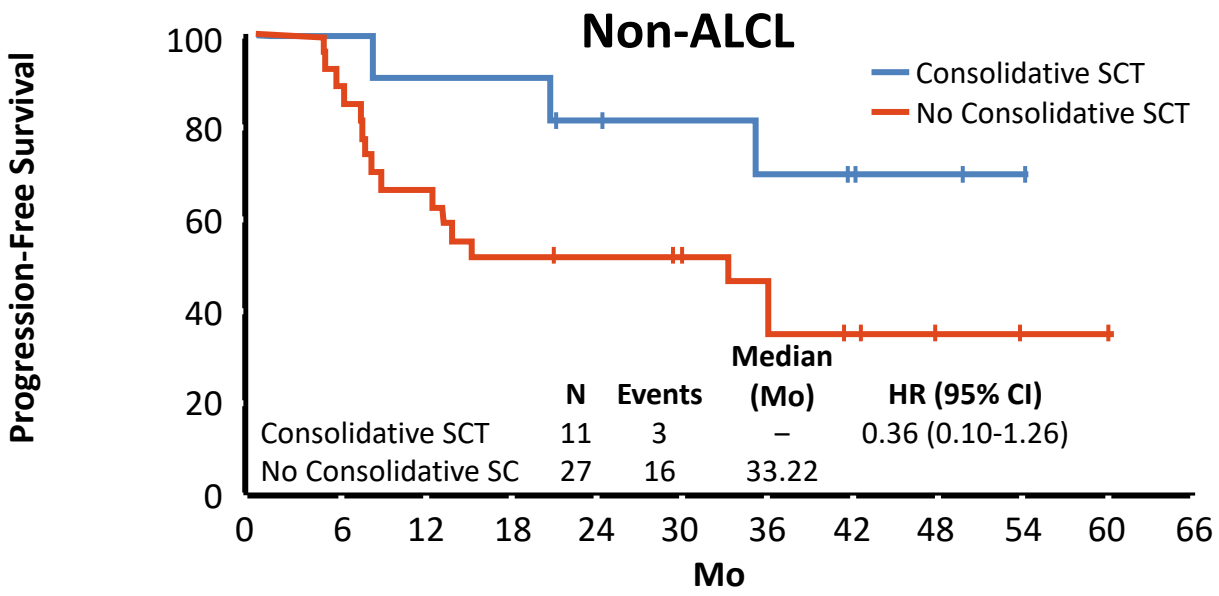
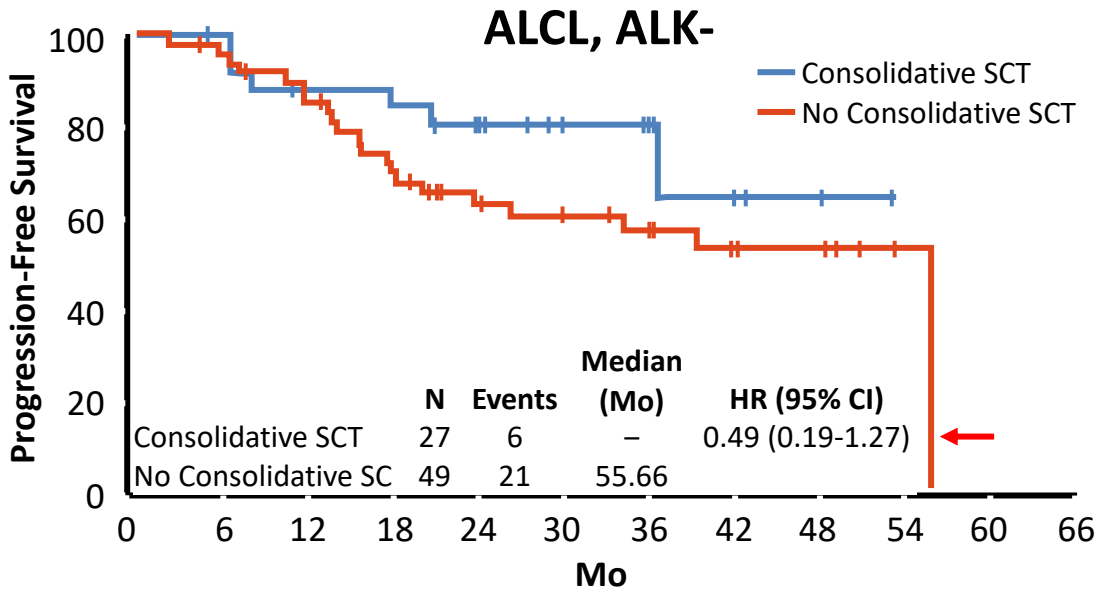
CD30 +
PTCL-NOS
AITL (?)
} CD30+
ALK- ALCL
ALK + ALCL

→ BV + CHP → CR or PR → ? → ASCT





Savage K…..Iyer S. Blood Adv. 2022, Apr 25

Response to CHEP-BV

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	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

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

Alex F. Herrera… Swaminathan P Iyer ASH 2021, Blood (2019) 134 (Supplement_1): 4023.

Summary of PFS CHP-BV (PTCL-NOS, AITL, sALCL vs. CHEP-BV)

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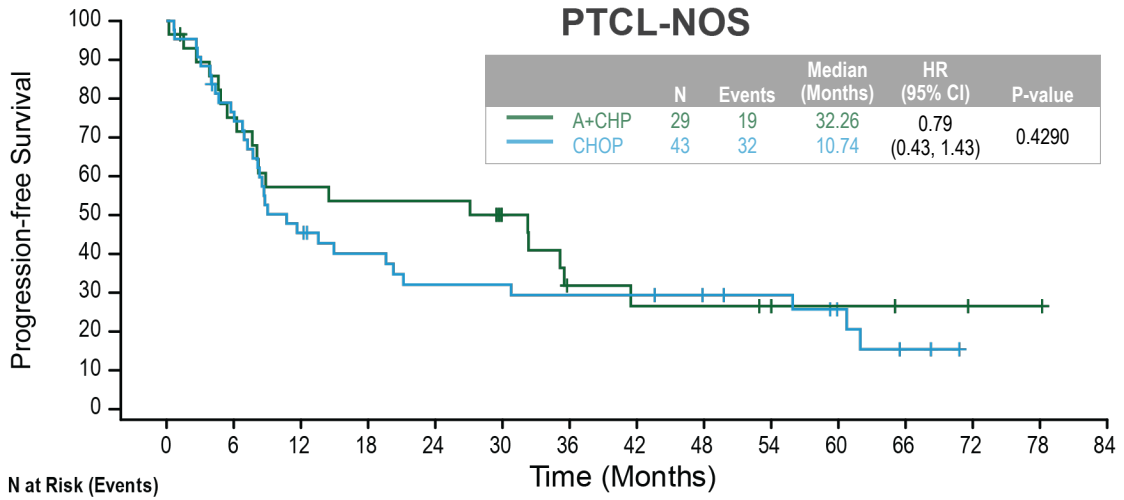
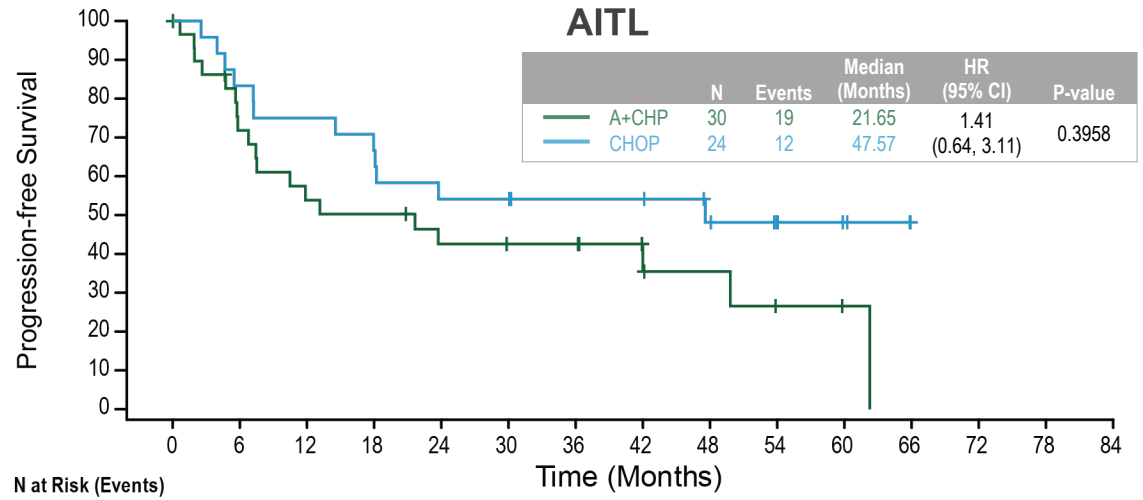
PTCL-NOS



N at Risk (Events)

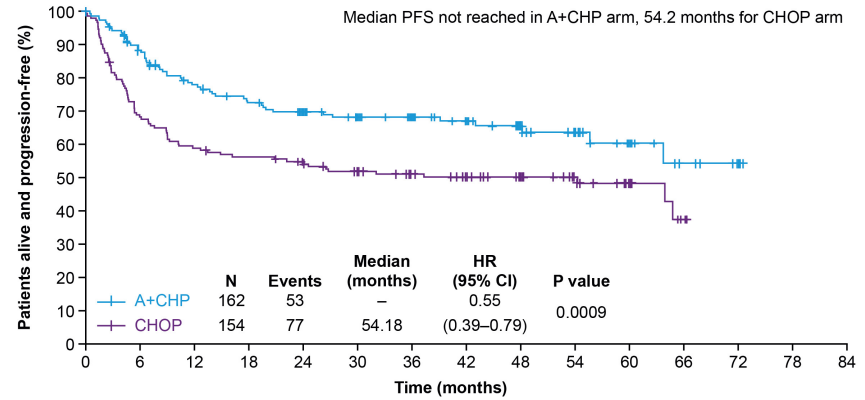
A+CHP	29(0)	21(7)	16(12)	15(13)	15(13)	11(14)	6(18)	5(19)	5(19)	4(19)	3(19)	2(19)	1(19)	1(19)	0(19)
CHOP	43(0)	32(10)	19(23)	15(25)	12(28)	12(28)	11(29)	11(29)	9(29)	8(29)	5(30)	2(32)	0(32)	0(32)	0(32)

AITL



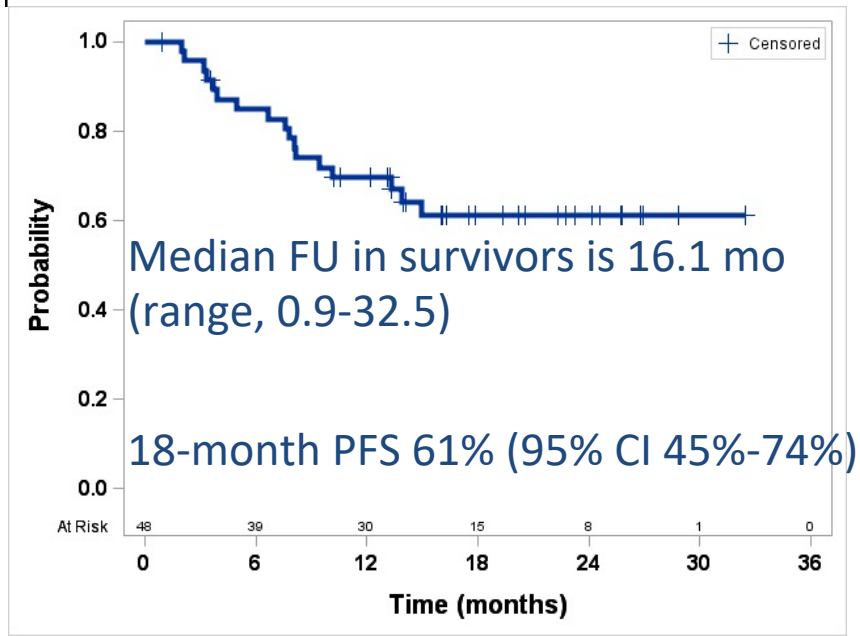
N at Risk (Events)

A+CHP	30(0)	20(8)	15(13)	14(14)	11(16)	10(16)	10(16)	5(17)	4(17)	2(18)	1(18)	0(19)	0(19)	0(19)	0(19)
CHOP	24(0)	20(4)	18(6)	16(8)	13(11)	13(11)	11(11)	11(11)	8(12)	5(12)	3(12)	0(12)	0(12)	0(12)	0(12)



Number of patients at risk (events)

A+CHP	162 (0)	136 (18)	117 (34)	107 (42)	95 (46)	81 (48)	67 (48)	55 (49)	33 (50)	23 (51)	15 (52)	7 (53)	2 (53)	0 (53)	0 (53)
CHOP	154 (0)	103 (48)	89 (62)	84 (66)	75 (69)	68 (72)	57 (73)	48 (74)	38 (74)	26 (74)	16 (75)	4 (77)	0 (77)	0 (77)	0 (77)



Alex F. Herrera… Swaminathan P Iyer ASH 2021, Blood (2019) 134 (Supplement_1): 4023.

Summary of OS CHP-BV (PTCL-NOS, AITL, sALCL vs. CHEP-BV)

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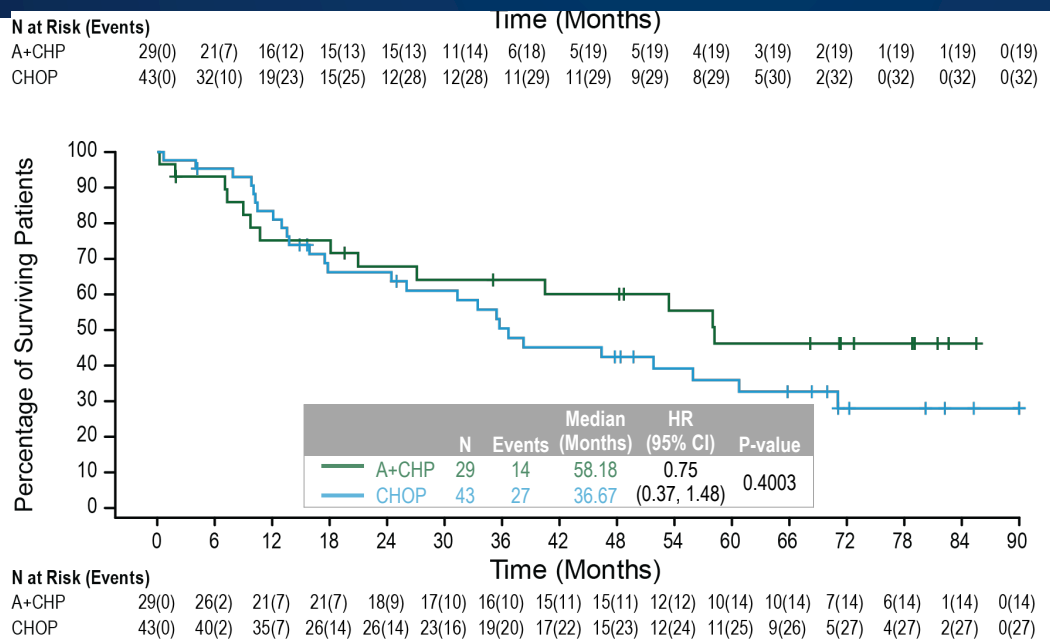

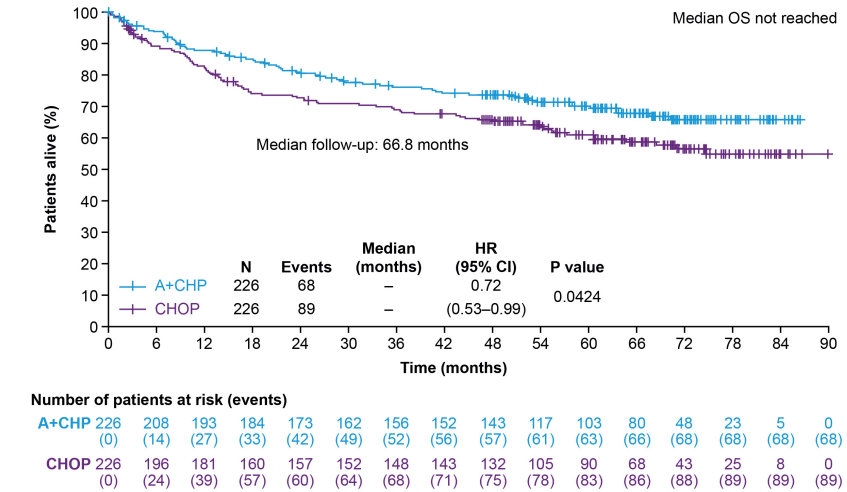

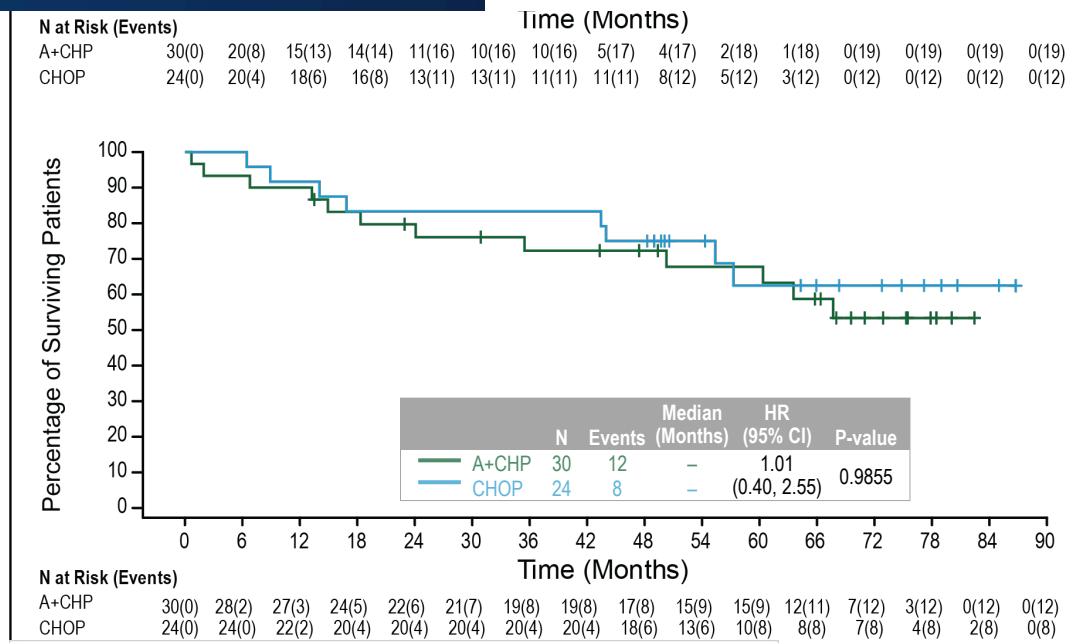

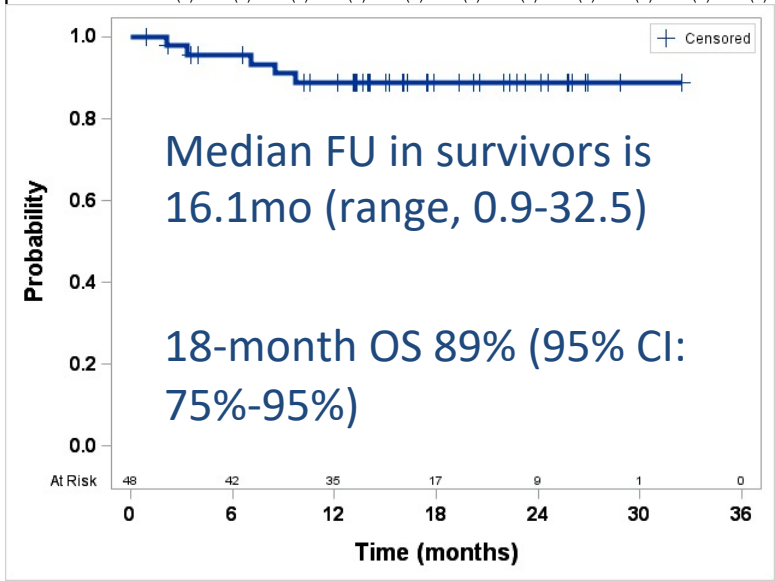

Alex F. Herrera… Swaminathan P Iyer ASH 2021, Blood (2019) 134 (Supplement_1): 4023.

CHP-BV (CD30 <1 and <10)

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Response rate by Investigators

	CD30 <1% (n = 19)	CD30 1% to <10% (n = 27)	Total (N = 46)
Best overall response[a,b], n (%)			
CR	11 (58)	16 (59)	27 (59)
PR	5 (26)	4 (15)	9 (20)
SD	1 (5)	3 (11)	4 (9)
PD	1 (5)	3 (11)	4 (9)
NE	1 (5)	1 (4)	2 (4)
CR rate[a,b]	11 (58)	16 (59)	27 (59)
95% CI[c] for CR rate	(33.5, 79.7)	(38.8, 77.6)	(43.2, 73.0)
ORR (CR+PR), n (%)	16 (84)	20 (74)	36 (78)
95% CI[c] for ORR	(60.4, 96.6)	(53.7, 88.9)	(63.6, 89.1)

- ORR per INV was 76% (61.2, 87.4) overall with 79% (54.4, 93.9) and 74% (53.7, 88.9) for CD30 <1%, CD30 1 to <10%, respectively.

Safety

Treatment-related TEAEs (>10% of total patients)	CD30 <1% (n = 23)	CD30 1% to <10% (n = 32)	Total (N = 55)
Patients with any event, n (%)	17 (74)	26 (81)	43 (78)
Diarrhea	7 (30)	9 (28)	16 (29)
Nausea	5 (22)	8 (25)	13 (24)
Peripheral sensory neuropathy	5 (22)	7 (22)	12 (22)
Anemia	5 (22)	6(19)	11 (20)
Febrile neutropenia	4 (17)	7 (22)	11 (20)
Lymphopenia	1 (4)	5 (16)	6 (11)
Stomatitis	1 (4)	5 (16)	6 (11)

- No new safety signals were observed
- Three patients (5%) discontinued study treatment due to TEAE
- Sixteen patients (29%) had BV-related TE SAEs
- One patient (2%) had a treatment-related fatal event of general physical health deterioration

Treatment-emergent SAEs (>5% of total patients)	CD30 <1% (n = 23)	CD30 1% to <10% (n = 32)	Total (N = 55)
Patients with any SAE, n (%)	8 (35)	12 (38)	20 (36)
Febrile neutropenia	4 (17)	7 (22)	11 (20)
Diarrhea	2 (9)	2 (6)	4 (7)

Grade ≥3 TEAEs (>10% of total patients)	CD30 <1% (n = 23)	CD30 1% to <10% (n = 32)	Total (N = 55)
Patients with any event, n (%)	13 (57)	16 (50)	29 (53)
Febrile neutropenia	4 (17)	6 (19)	10 (18)
Neutropenia	2 (9)	7 (22)	9 (16)
Anemia	1 (4)	6 (19)	9 (13)

Iyer S, EHA 2023.

CD30 Expression in AITL

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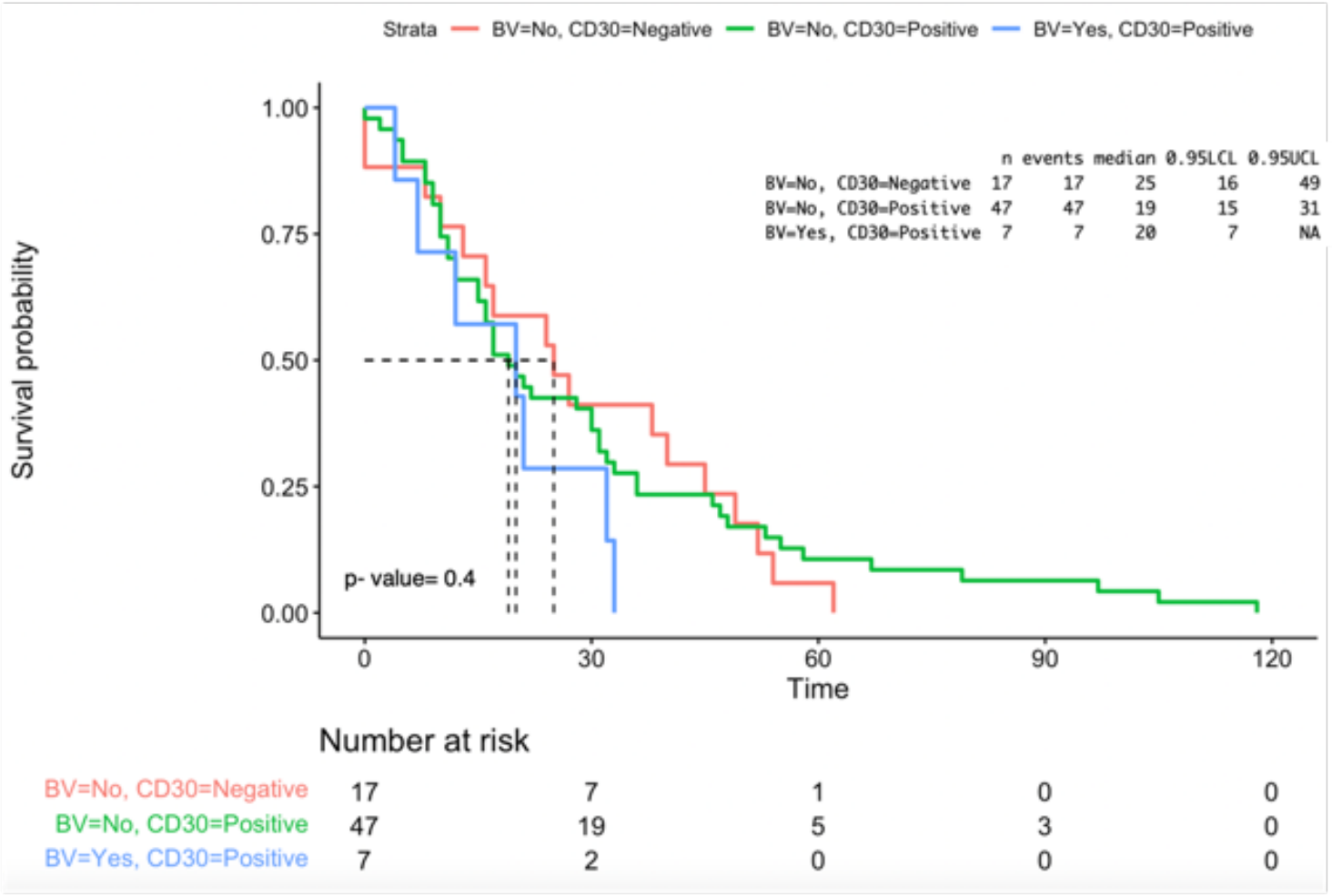
		CD 30 Expression			
Demographics	**N**	**All**, N= 237[1]	**No**, N= 55[1]	**Yes**, N= 182[1]	p[2]
Gender	237				0.3
Female		113 (48%)	23 (42%)	90 (49%)	
Male		124 (52%)	32 (58%)	92 (51%)	
Race	196				0.7
Asian		9 (4.6%)	2 (4.2%)	7 (4.7)	
Black or African American		8 (4.1%)	3 (6.3%)	5 (3.4%)	
Declined to Answer		2 (1.0%)	0 (0%)	2 (1.4%)	
Other		5 (2.6%)	2 (4.2%)	3 (2%)	
White of Caucasian		172 (88%)	41 (85%)	131 (89%)	
Unknown		41	7	34	
Stage	165				**<0.001**
I		3 (1.8%)	1 (2.3%)	2 (1.6%)	
II		9 (5.5%)	5 (12%)	4 (3.3%)	
III		71 (43%)	7 (16%)	64 (52%)	
IV		82 (50%)	30 (70%)	52 (43%)	
Unknown		72	12	60	
BM Involvement	179	72 (40%)	20 (48%)	52 (38%)	0.3
Unknown		58	13	45	
BV First Line	171	32 (19%)	3 (7%)	29 (23%)	**0.023**
Unknown		66	12	54	
Transplant	155	68 (44%)	19 (48%)	49 (43%)	0.6
Unknown		82	15	67	



Elias A,…….Iyer S, ASH 2023.

Ro-CHOP vs. CHOP in Untreated PTCL

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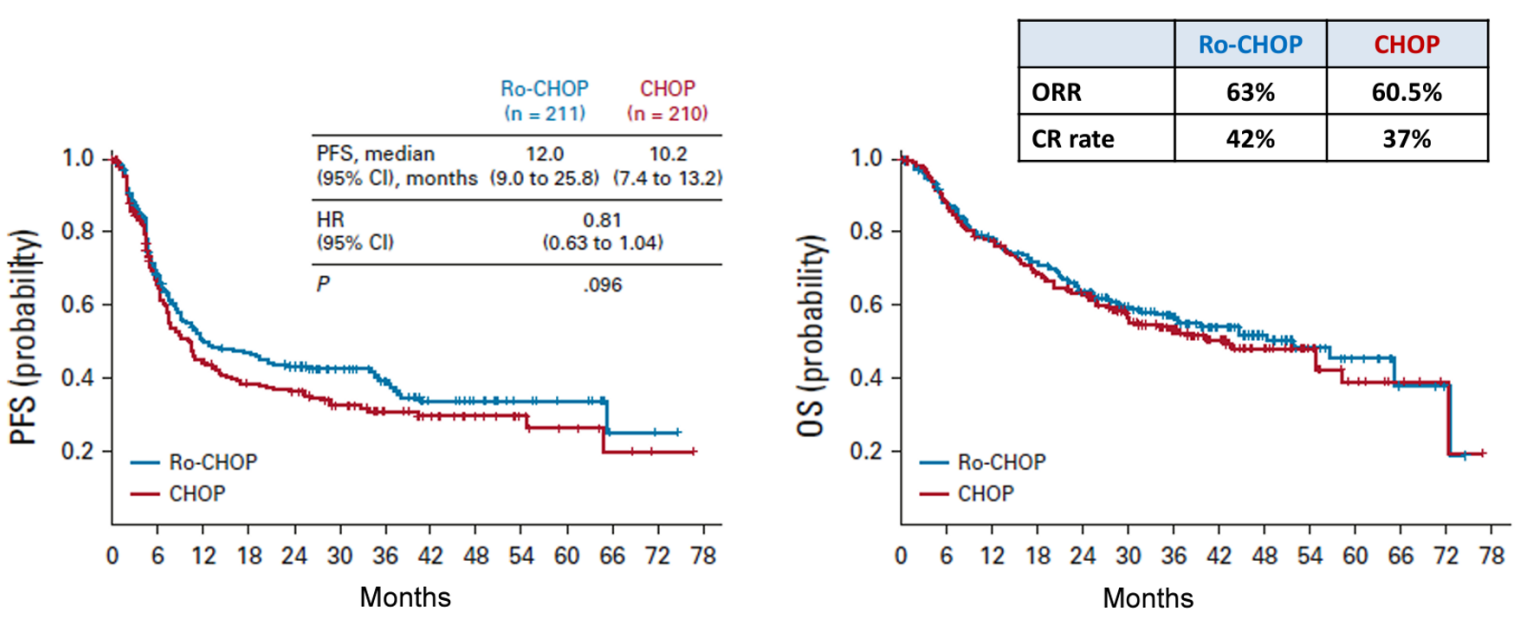

	Ro-CHOP	CHOP
ORR	63%	60.5%
CR rate	42%	37%

Outcome		Ro-CHOP (N=210)	CHOP (N=208)
Treatment-emergent AEs	Grade 3 or higher	94%	70%
	Grade 4	74%	42%
	Serious	42%	29%
Delivery of CHOP	6 cycles without dose reduction or interruption	53%	60%
	Average RDI < 90%	15%	9%

Potentially compromised delivery of CHOP backbone

- **PFS primary endpoint was not met**
- **Similar OS and response rates,**
- **Greater toxicity with**
- **Ro-CHOP**

Bachy E, et al. J Clin Oncol. 2022

Ro-CHOP Trial: 5-year update

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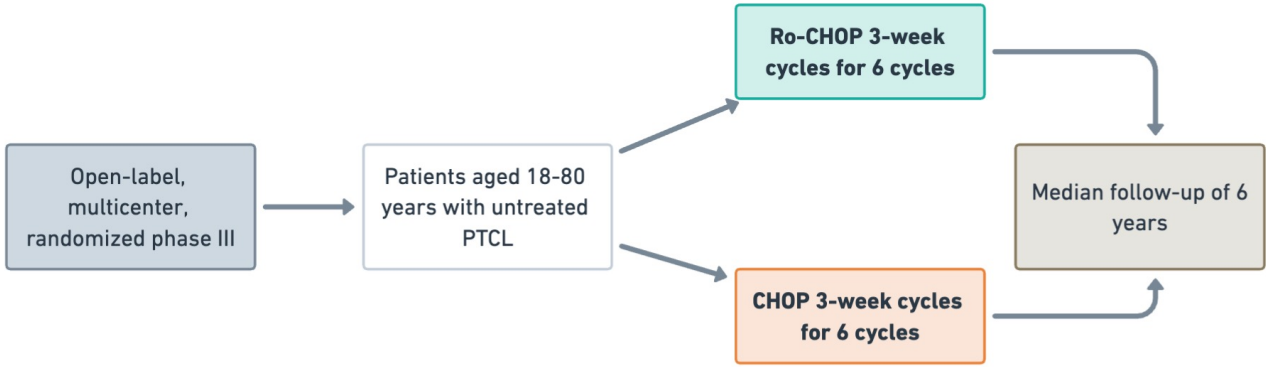

Primary Endpoint: Progression-free survival (PFS)

Key Findings

Median PFS: 12.0 months (Ro-CHOP) vs. 10.2 months (CHOP)
- Median OS: 62.2 months (Ro-CHOP) vs. 43.8 months (CHOP).
- **TfH lymphoma subgroup: Longer median PFS Ro-CHOP (19.5 vs. 10.6 months).**

Statistical Significance

PFS: HR, 0.79 (95% CI, 0.62 to 1.005); P = .054
- OS: HR, 0.88 (95% CI, 0.68 to 1.14); P = .324
- **TfH Lymphoma Subgroup: PFS HR, 0.703 (95% CI, 0.502 to 0.985); P = .039**

Camus V, et al. J Clin Oncol. 2024 Feb 16

Summary of Frontline studies in TCL:

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- CD30 targeted therapy has improved survival- at 5 years, frontline treatment with A+CHP continues to provide clinically meaningful improvement in PFS and OS versus CHOP
- Bv CHP has not demonstrated any OS benefit for non-ALCL patient eg, AITL)
- Addition of etoposide in CHEP-BV was tolerable and led to high CR rate
  - PFS in ALCL > non-ALCL subgroup
  - CHEP-BV + ASCT + BV consolidation associated with excellent PFS
- Impact of % CD30 expression: Initial findings show that A+CHP is effective for patients with non-ALCL PTCL regardless of CD30 expression by local testing supporting the proposed, multi-faceted mechanism of action of BV in combination with CHP

Overwhelming number of patients relapse – where chemotherapy is even less effective

Patients With Relapsed or Refractory Disease Have an Especially Poor Prognosis

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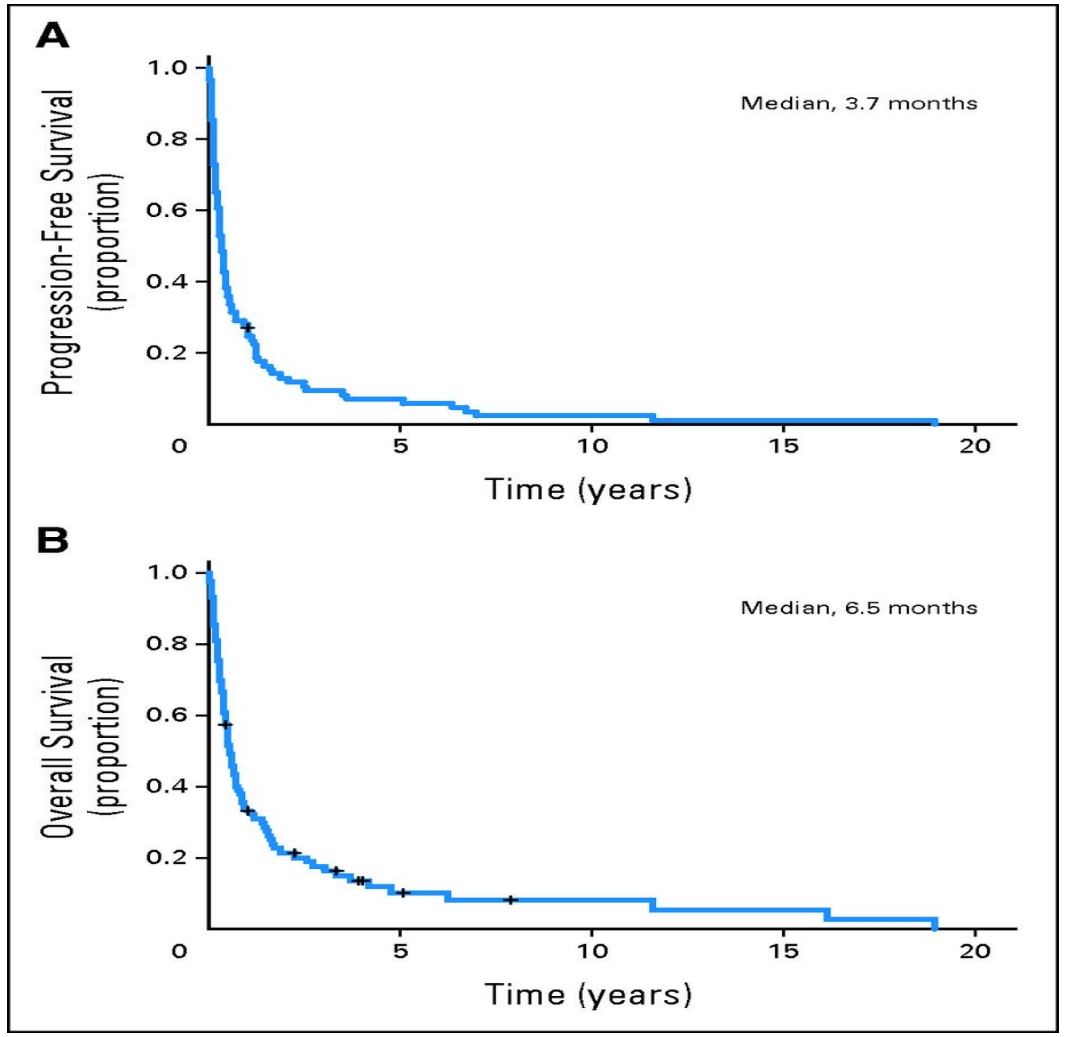

2nd PFS (median, 3.7 months) of patients treated with chemotherapy (n = 89) with R/R PTCL

2nd PFS = 3.7 months

OS (median, 6.5 months) after first relapse or progression of PTCL.

Overall Survival from 2nd Relapse = 6.5 months

Mak et al. 2013

Pralatrexate and Belinostat: Primary Efficacy Data Supporting Accelerated Approval

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	PROPEL Study Pralatrexate[1] N = 109	BELIEF Study Belinostat[2] N = 120
Overall response rate (ORR), n (%)	**32 (29%)**	**31 (26%)**
Best overall response		
Complete response (CR)	**11 (10%)**	**13 (11%)**
Complete response unconfirmed (CRu)*	**1 (1%)**	**-**
Partial response (PR)	**20 (18%)**	**18 (15%)**
Duration of response, median (95% CI)	**10.1 months** (3.4–NE)	**13.6 months** (4.5–29.4)
Progression-free survival (PFS), median (95% CI)	**3.5 months** (1.7–4.8)	**1.6** (1.4–2.7)
Overall survival (OS), median (95% CI)	**14.5 months** (10.6–22.5)	**7.9** (6.1–13.9)

1. O'Connor, 2011; 2. O'Connor, 2015

***CRu is a category between CR and PR (ie, does not strictly match either CR or PR); a CRu does not indicate a short-lasting CR**

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- HOW CAN WE HARNESS THE ADVANCES IN BIOLOGY?

Nodal T-cell lymphomas with TfH phenotype
AITL, PTCL with TfH & Follicular TCL

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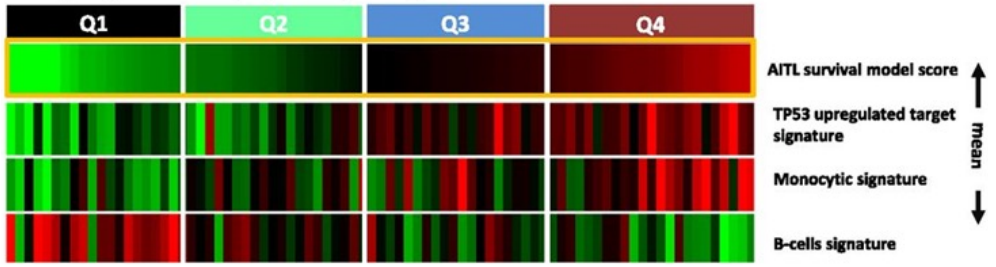
- TFH markers: PD1, ICOS, CXCL13, BCL6 & CD10
- Partial overlapping genetic landscapes

Gene	Freq.
RHOA (G17V)	50-70%
Epigenetic regulators	
TET2	47-83%
DNMT3	20-30%
IDH2 (R172)	20-45%

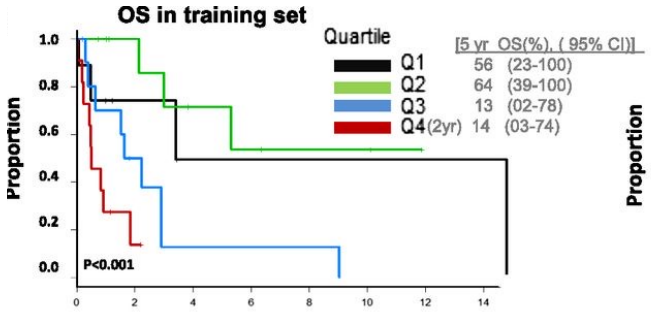
Average expression of prognostic gene signature in AITL

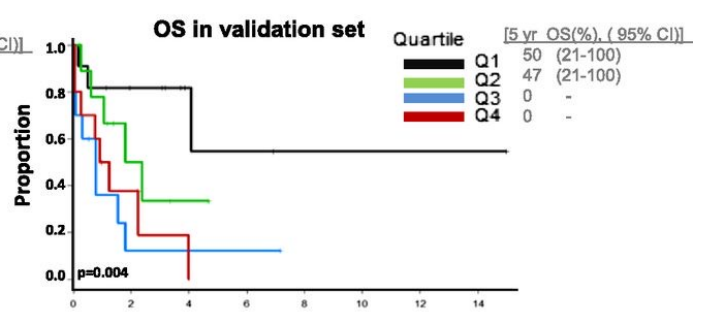


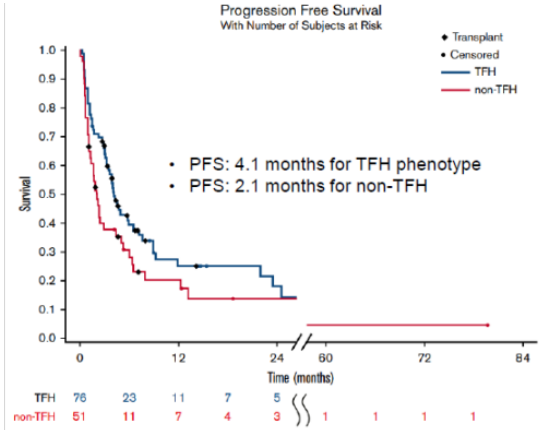
AITL with *RHOA* mutations	Classical clinicopath features
	Higher microvessels density
	More FDC proliferation
	More pronounced THF phenotype
AITL with *IDH2* mutations	Medium to large tumor cells with clear cells Strong CD10 and CXCL13 expression
	Gains of chromosomes 5 and 21

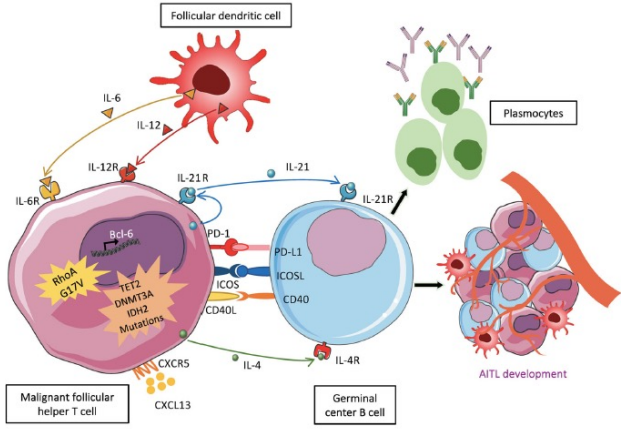
Nodal lymphomas of TFH cell origin (TFH-PTCL)

n=114	AITL	Other TFH-PTCL: TFH-like PTCL	Other TFH-PTCL: F-PTCL*	PTCL-NOS	
Mutations (%)					
TET2	31/64 (48%)	7/11 (64%)	3/4 (75%)	4/24 (17%)	p<0.001
DNMT3A	19/64 (30%)	1/10 (10%)	1/4 (25%)	1/24 (4%)	p<0.05
IDH2	22/66 (33%)	1/11 (10%)	0/5 (0%)	0/23 (0%)	p<0.001
RHOA (G17V)	42/72 (58%)	8/14 (57%)	3/5 (60%)	0/23 (0%)	p<0.001









Iqbal et al. Blood 2014; 123;2915-23, Ondrejkaet al. Am J SurgPathol2016: 40:335-41; Nagao R et al. Am J SurgPathol2016; 40:1041-50; Steinhilberet al. Mod Pathol2019; 32:1123-34

Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

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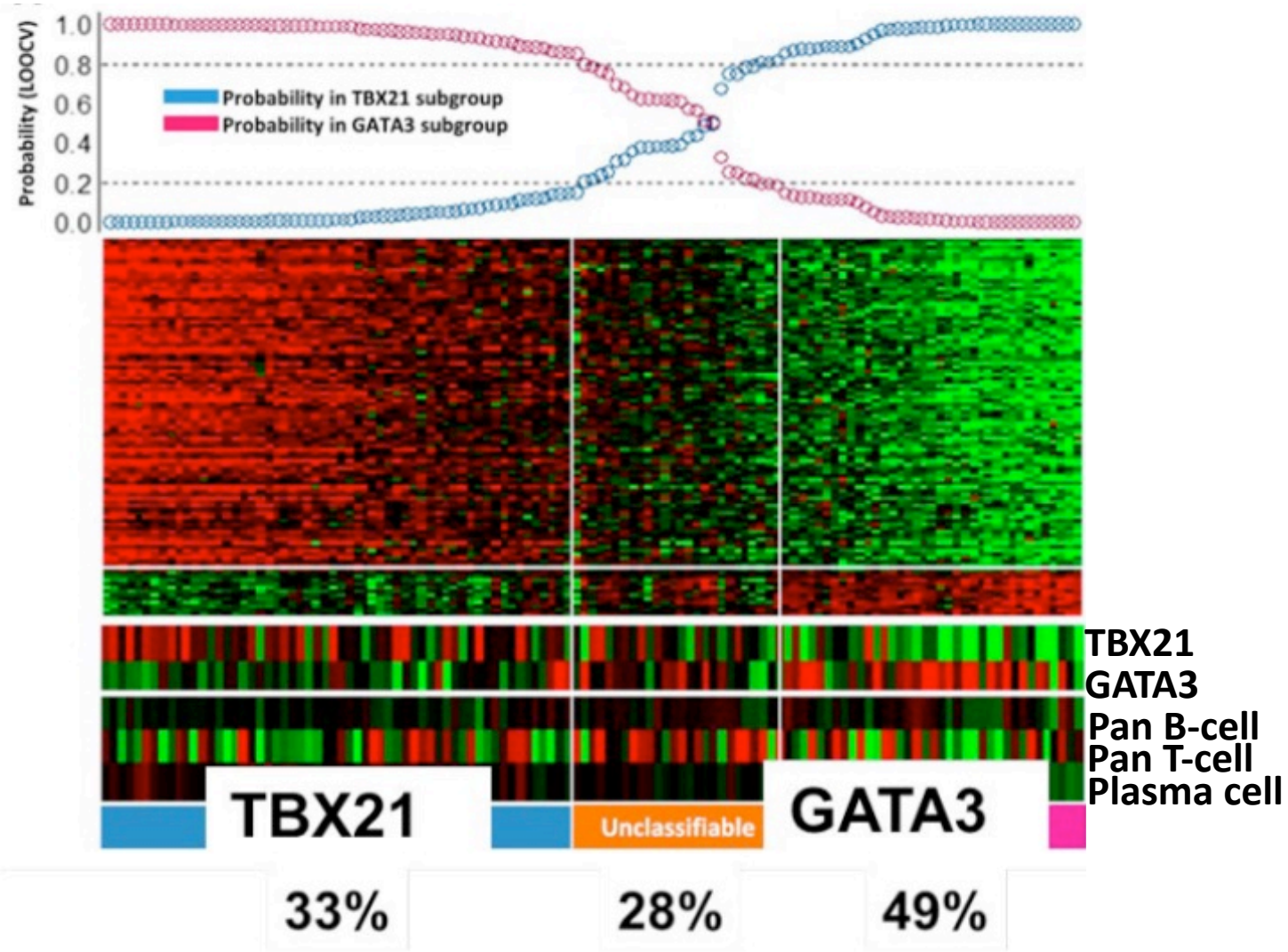

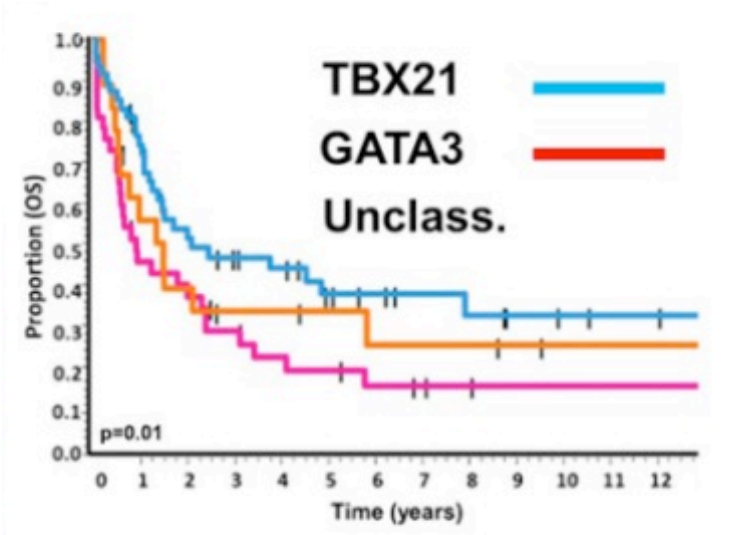

Cell of origin for PTCL-NOS

	PTCL-GATA3	PTCL-TBX21
Frequency	33%	49%
Gene expression	GATA3 and its target genes	TBX21 and its target genes
Phenotype	Th2 (IL4, IL5, IL13)	Th1 (IFNγ)
Cell Signaling	MYC and PI3K-mTOR	NF-κB
Median OS	< 1 year	> 2 years

Iqbal et al. Blood 2014; 123;2915-23

COO based Diagnosis in PTCL

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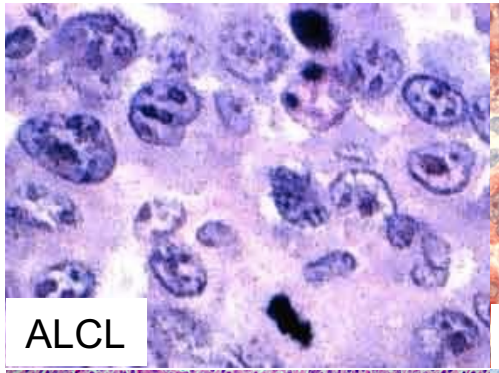
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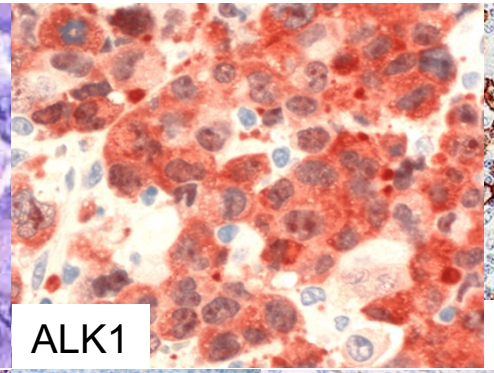
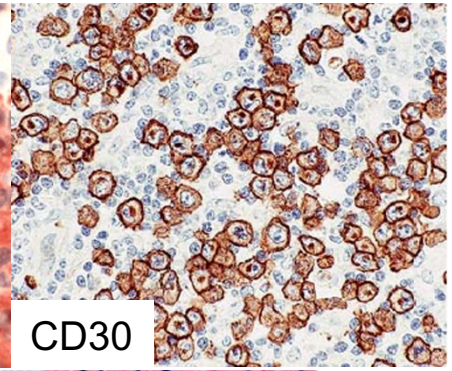
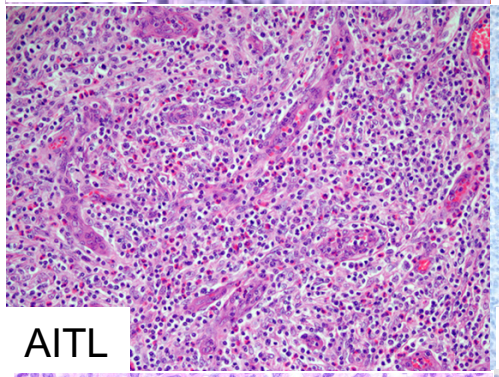
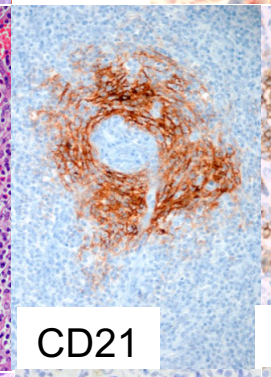

ALK1


CD30


AITL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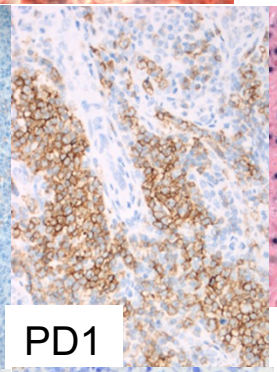
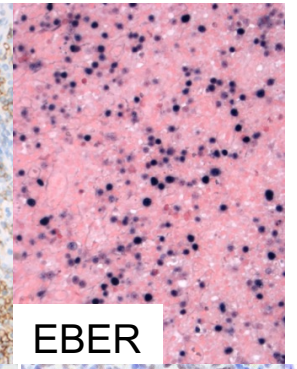

PD1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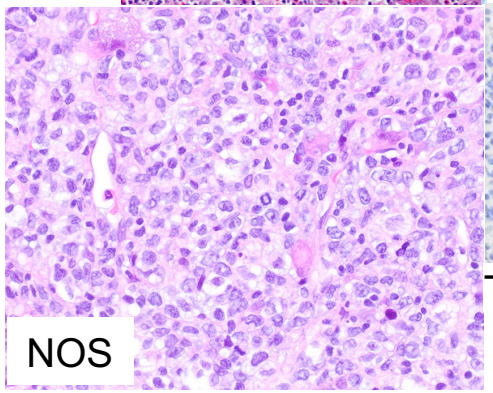
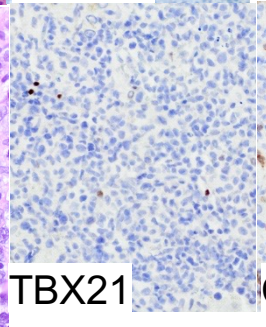

NOS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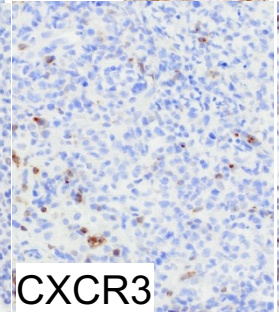
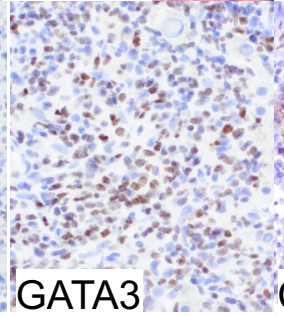
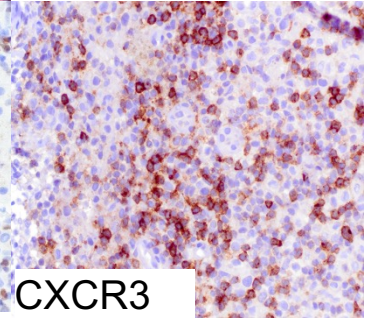
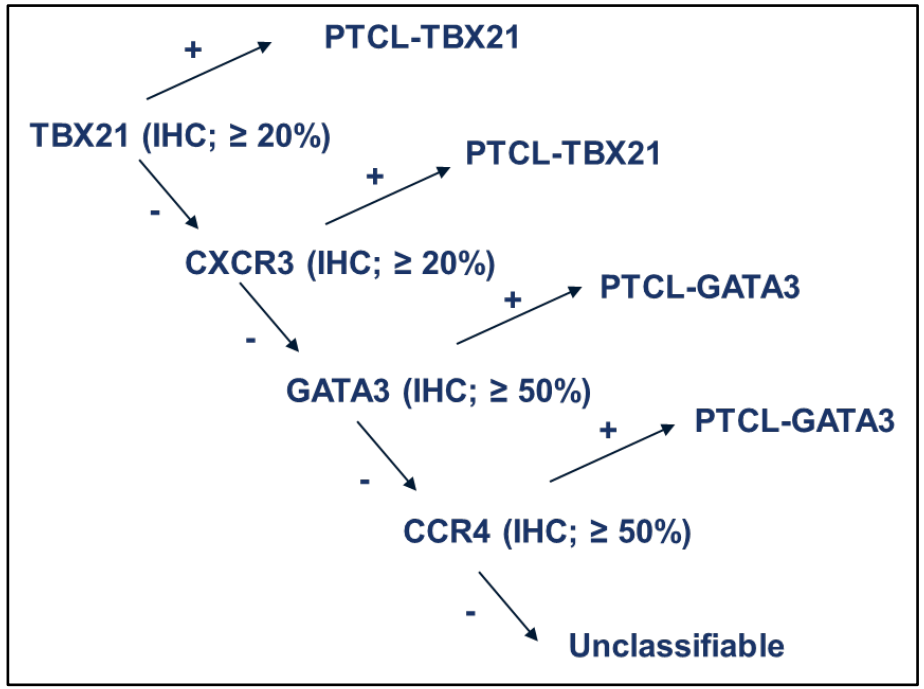

CXCR3


GATA3


CXCR3



Vega F, EXABS-TCL-052.2020

Nodal Lymphomas with TFH Phenotype: Role of Epigenetic Modifiers

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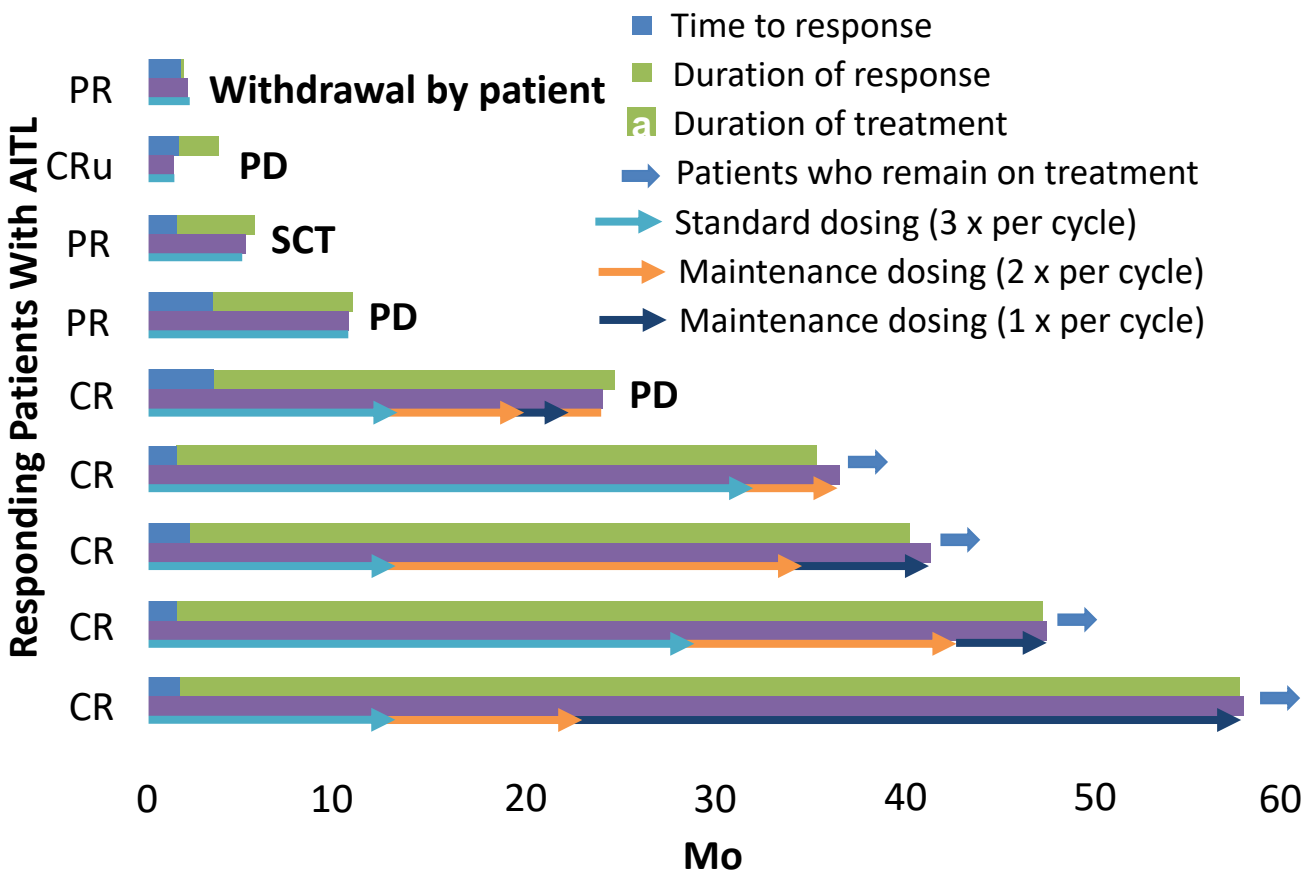
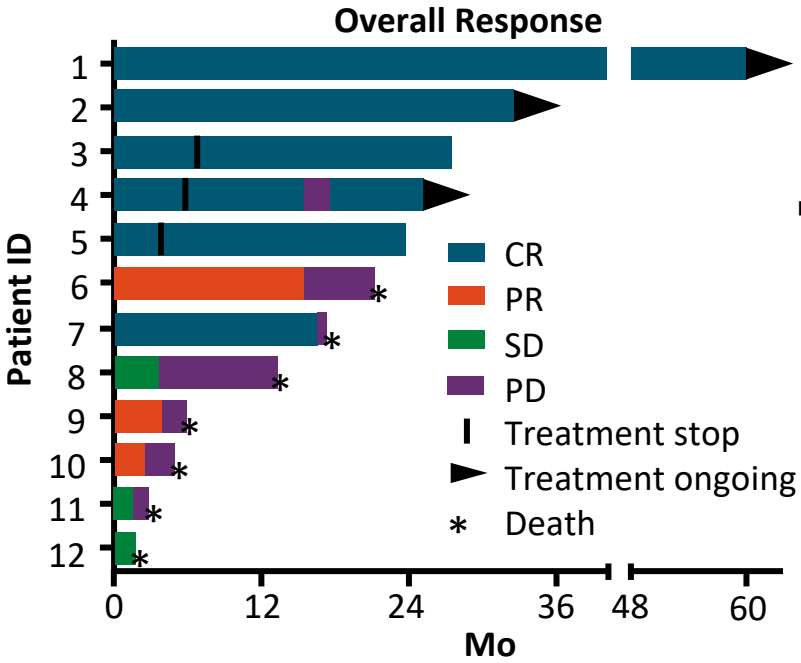
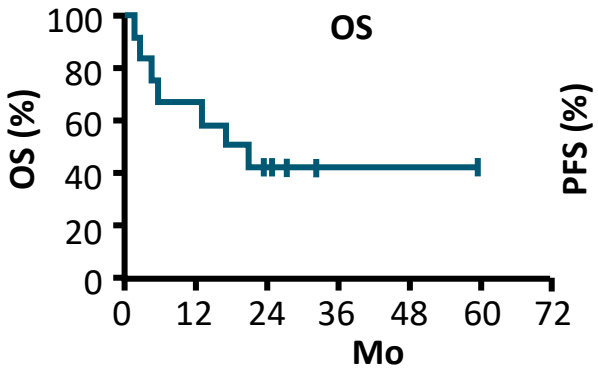
Romidepsin in AITL[1]

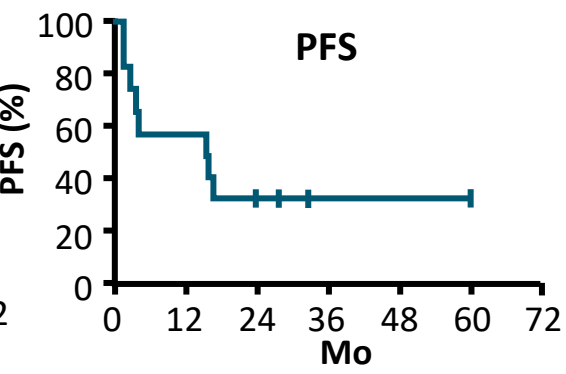


Azacitidine in AITL[2]



- ORR 75%
  - CR 6/12
  - PR 3/12
  - SD 3/12





1. Pro. Hematol Oncol. 2017;35:914. 2. Lemonnier. Blood. 2018;132:2305.

TfH as the predictive marker in TCL: Lessons from Ro-CHOP Phase III

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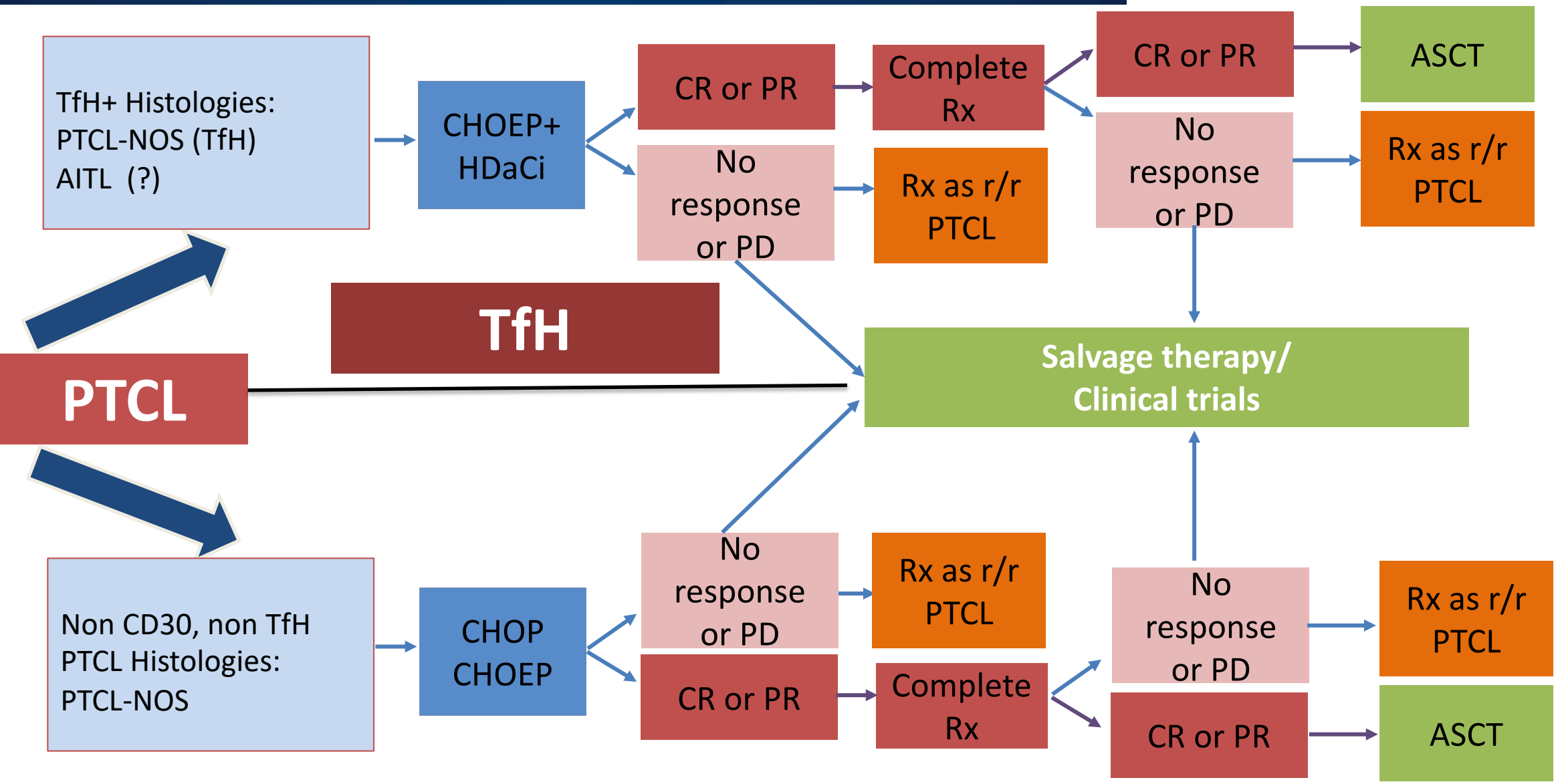

Phase II Trial: Azacitidine + CHOP as Initial Therapy for PTCL

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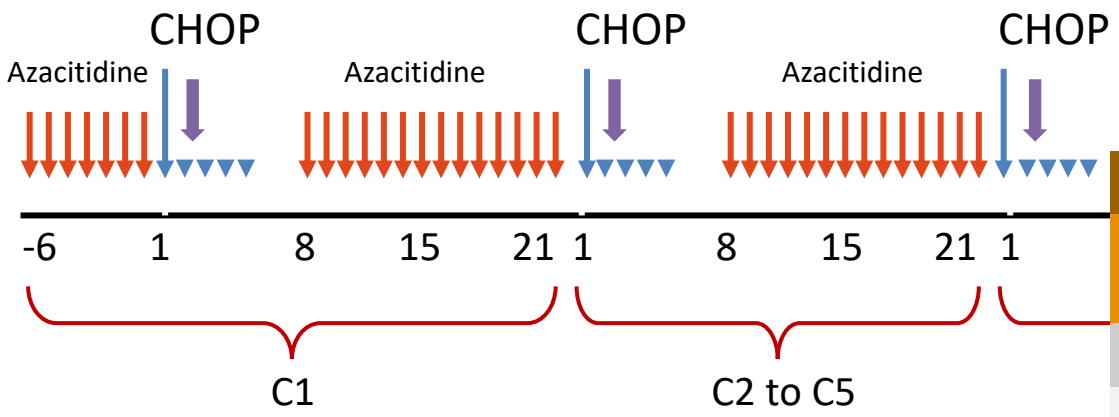
Treatment

- Azacitidine: cycle 1, days -6 to 0; 1-5 days, days 8-21
- Cyclophosphamide, doxorubicin, vincristine: day 1
- Prednisone: days 1-5
- Growth factor e.g., pegfilgrastim:



- Azacitidine dosing: 300 mg/day, d-6 to 0, then D8-2
- Patients in CR/PR after 6 cycles can receive consoli

Patients with untreated PTCL (N = 20)

- **Nodal TCL w/TFH phenotype (per WHO 2016)**
  - **AITL**
  - **Follicular TCL**
  - **PTCL-NOS, TFH variant**
- **PTCL-NOS**
- **ALCL, ALK neg**
- **ALCL, ALK pos w/IPI >2**
- **Adult T-cell lymphoma/leukemia**

Response	Interim			EOT		
	n	Evaluable, % (n = 20)	PTCL-TFH, % (n = 17)	n	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
Discontinued	0	0	0	2	10	6
Median FU, mo	15 (range: 9-23)					

Ruan. ASH 2020. Abstr 40.

SPI-BEL-301 Phase 3 PMR Study Design in Patients With Newly Diagnosed, Untreated PTCL

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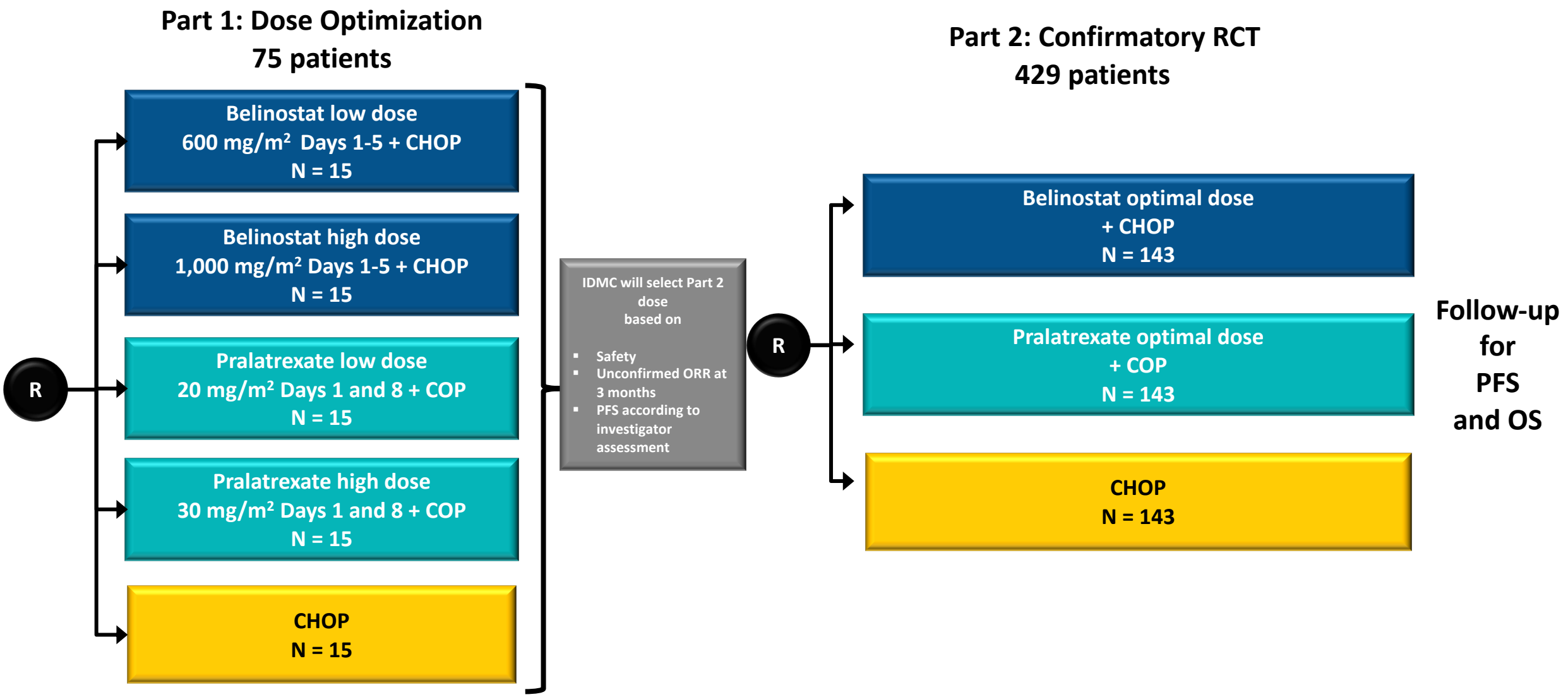

A051902 Intergroup Study

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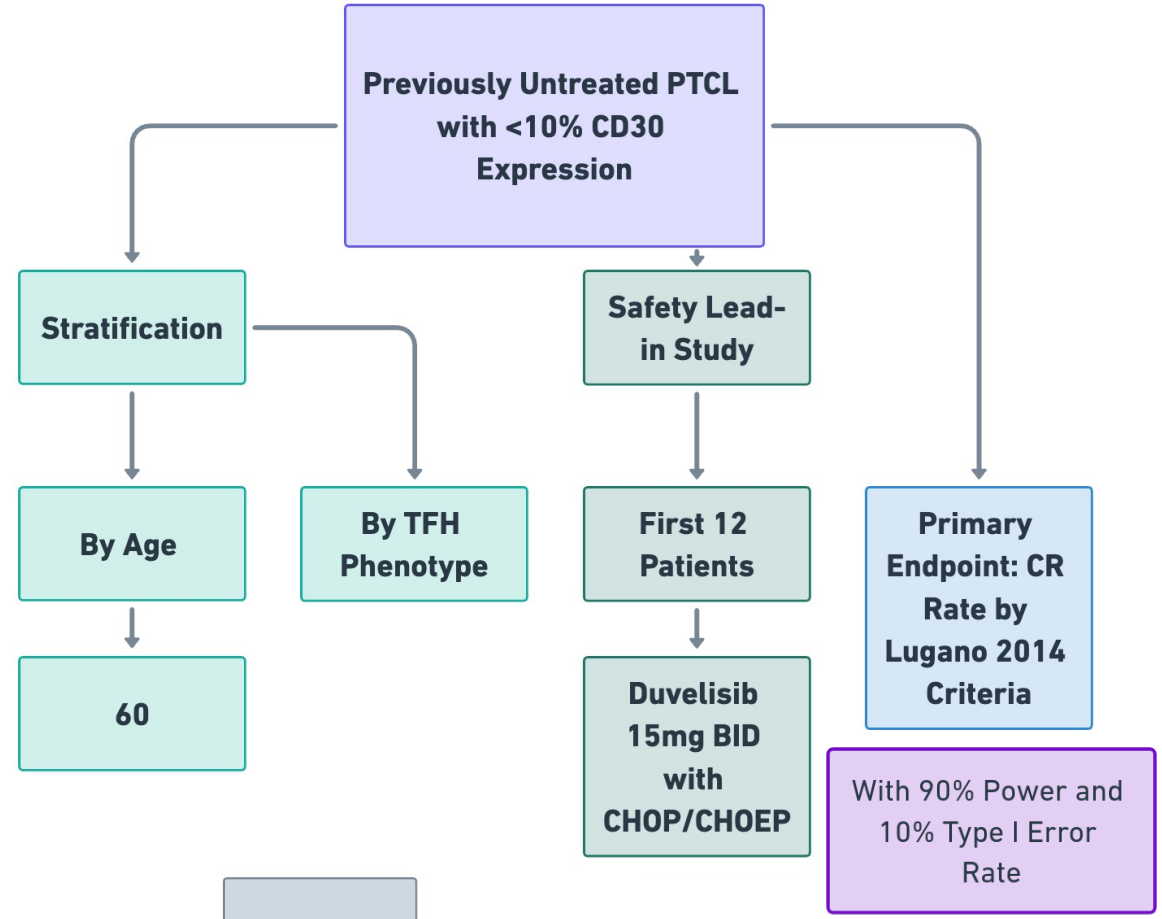
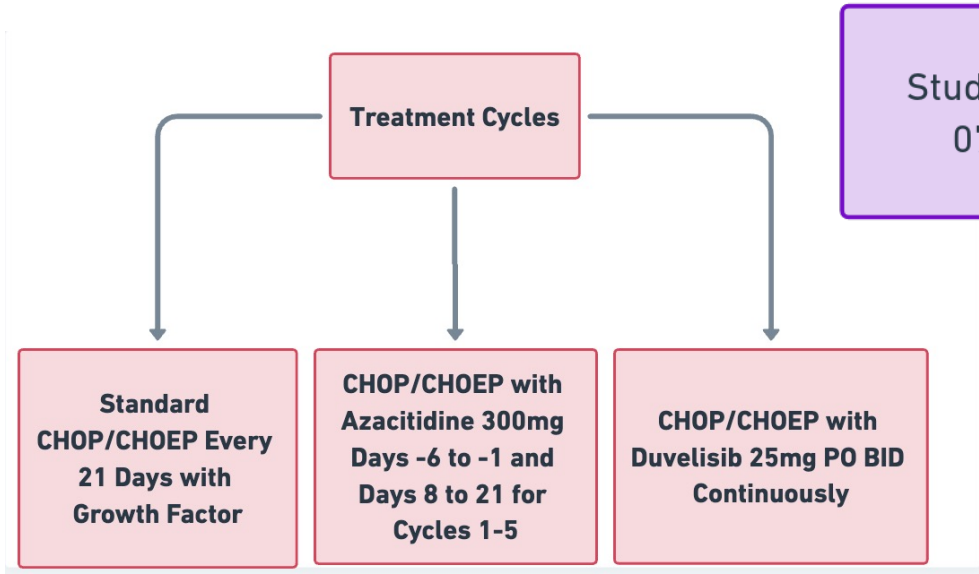
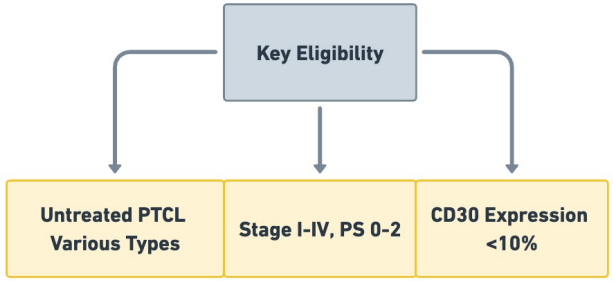
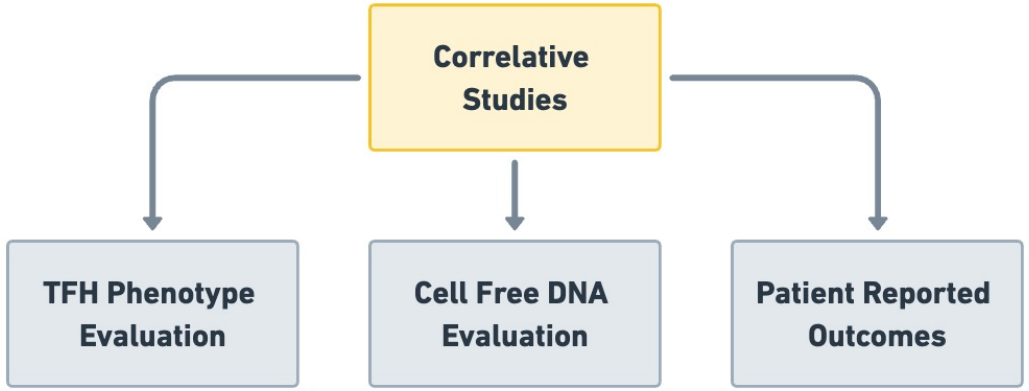




Study Activation: 07/30/2021





Neha Mehta-Shah et al. Alliance A059102: A randomized phase II U.S. intergroup study of CHO(E)P versus CC-486-CHO(E)P versus duvelisib-CHO(E)P in previously untreated, CD30-negative, peripheral T-cell lymphomas.. *JCO* **40**, TPS7593-TPS7593(2022).DOI:10.1200/JCO.2022.40.16_suppl.TPS7593

Emerging themes in T cell Lymphomas

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- Epigenetic targeting of Tfh
- Targeting dysregulated pathways: JAK/STAT, PI3K, EZH1/2
- Targeting cytotoxic, gamma-delta and NK subtypes

Golidocitinib: Demographics and Baseline Characteristics

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Demographics & Characteristics	n = 104
Median age, y (range)	58 (20 - 78)
Female/Male, n (%)	37 (35.6)/67 (64.4)
ECOG PS, n (%)	
0/≥1	46 (44.2)/58 (55.8)
Median lines of prior systemic therapies (range)	2 (1 - 3)
Types of prior systemic therapies, n (%)	
Chemotherapy	104 (100.0)
Pralatrexate	1 (1.0)
Mitoxantrone liposome	3 (2.9)
HDAC inhibitor	50 (48.1)
Brentuximab vedotin	13 (12.5)
ALK inhibitor	1 (1.0)
Prior autologous HSCT, n (%)	2 (1.9)
Bone marrow involvement at baseline, n (%)	20 (19.2)
LDH elevation at baseline, n (%)	52 (50.0)

Demographics & Characteristics	n = 104
Histology subtypes by central review, n (%)	
PTCL, NOS	51 (49.0)
AITL	16 (15.4)
ALCL	11 (10.6)
NK/TCL	4 (3.8)
Others*	9 (8.7)
Central confirmed non-PTCL	4 (3.8)
Unable to confirm	9 (8.7)

Data cut-off date: August 31, 2023

- Between Feb 26, 2021 to Oct 12, 2022, a total of 104 subjects with r/r PTCLs were enrolled.
- All subjects received at least one dose of golidocitinib at 150 mg QD.

Note: * 'Others' including 1 centrally diagnosed as T cell prolymphocytic leukemia and 8 centrally diagnosed as PTCLs with unconfirmable histology subtypes.
Abbreviations: AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HDAC, histone deacetylase; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; NK/TCL, natural-killer/T cell lymphoma; PTCL, NOS, peripheral T cell lymphoma, not otherwise specified; r/r, relapsed/refractory; QD, once daily.

Tumor Response

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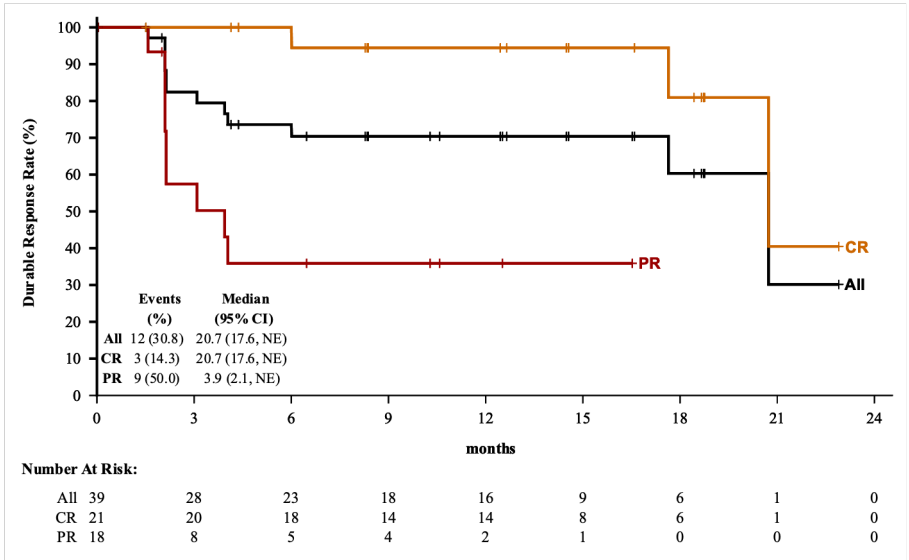
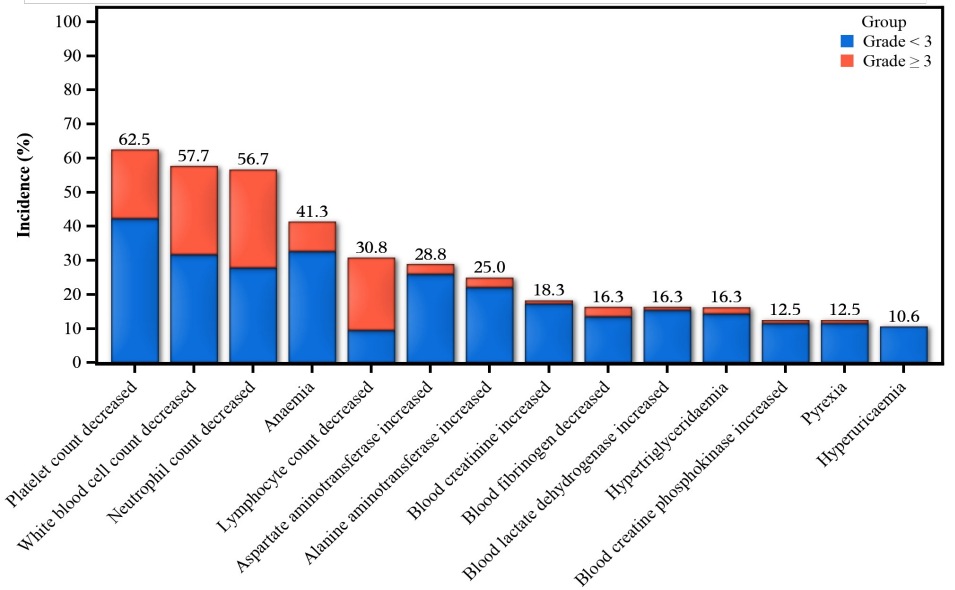
Tumor Response	n = 88	
	By IRC	By Investigator
ORR, n (%)	39 (44.3)	35 (39.8)
Overall response, n (%)		
Complete response	21 (23.9)	10 (11.4)
Partial response	18 (20.5)	25 (28.4)
Stable disease	17 (19.3)	15 (17.0)
Progressive disease	20 (22.7)	26 (29.5)
Not evaluable	12 (13.6)	12 (13.6)

The following subjects were **not** included in the efficacy analysis set: 4 confirmed as non-PTCL by central pathology review, 9 not providing sufficient tumor tissue for central pathology confirmation, and 3 no baseline measurable lesions by IRC assessment.
Abbreviations: CR, complete response; IRC, independent review committee; ORR, objective response rate; PR, partial response; PTCL, peripheral T cell lymphoma.

DOR-IRC Assessment





Linperlisib: pharmacokinetics and Efficacy

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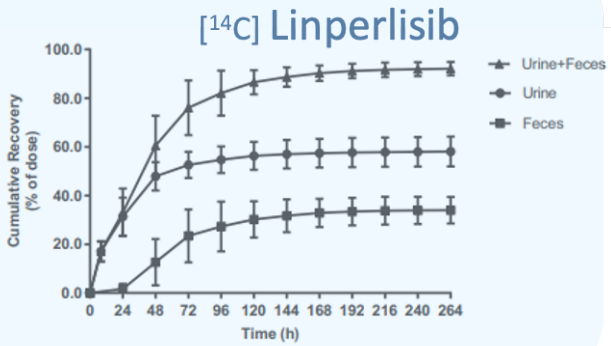
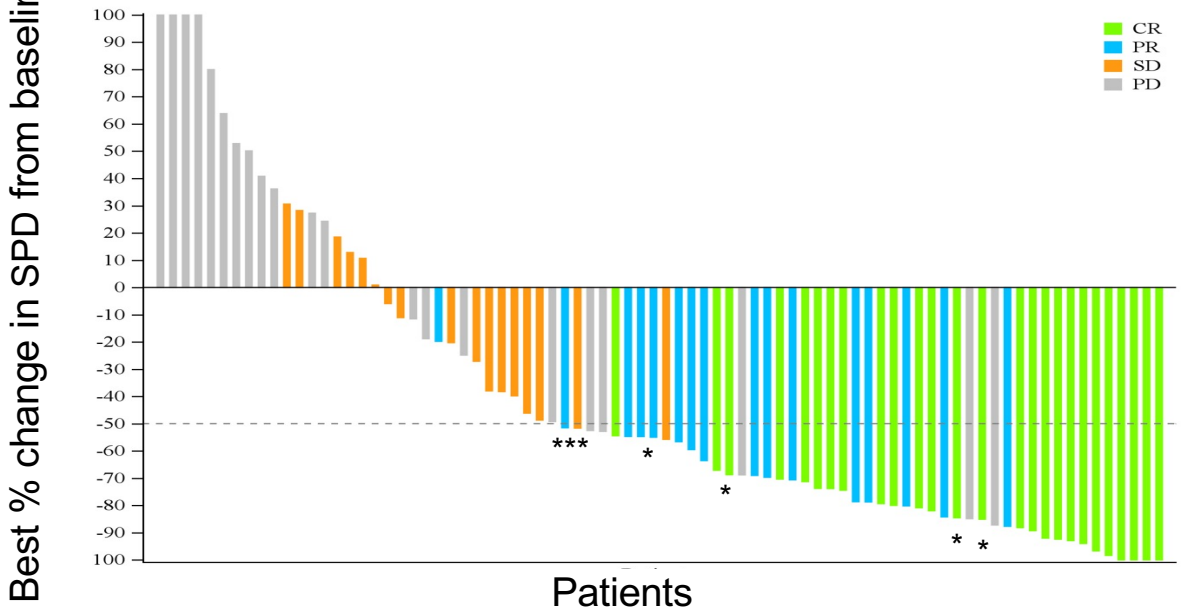


PI3K DRUG	Dose	% in Urine	% in Feces
Linperlisib	80 mg, po	58	34
Idelalisib	25 mg, po	14	78
Duvelisib	150 mg, po	14	79
Copanlisib	12 mg, iv	22	64
Umbralisib	800 mg, po	3	81

A higher urinary excretion rate of YY-20394 may lead to lower incidence of diarrhea and colitis and other AEs



* Five PD patients had new lesions appearing, even though target lesions met the response criteria

Yuqin Song, ASH 2023, #306

Response	n(%)
ORR, n(%)	42(48)
95% CI	(37, 59)
CR	**26(30)**
PR	16(18)
SD	18(21)
PD	21(24)
NE	7(8)
DCR, n(%)	60(68)
95% CI	(57, 78)

- FAS, n=88 patients
  - ✓ The study met the primary endpoint
  - ✓ CR 30%, PR 18%
- A disease control rate of 69% observed

PI3K Inhibitor	# pts	ORR	CR	Reference
Duvelisib	35	50%	19%*	Horwitz et al.
Tenalisib	35	45.7%	26%	Huen et al.
Linperlisib	48	48%	30%	Song et. al

Safety

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Any Grade TRAEs, Preferred Term	(≥10%) n (%)
Neutropenia	58 (59)
Leukopenia	46 (47)
Thrombocytopenia	31 (32)
Anemia	24 (24)
Elevated ALT	23 (23)
Elevated AST	20 (20)
Pneumonia	20 (20)
Lymphocytopenia	17 (17)
Hypertriglyceridemia	15 (15)
Fever	15 (15)
Diarrhea	14 (14)
Elevated lipase	13 (13)
Hyperuricemia	13 (13)
Rash	13 (13)
Hypercholesterolemia	12 (12)
Hyponatremia	11 (11)
Elevated lactate dehydrogenase	10 (10)
Elevated creatinine	10 (10)

SAS = 98 patients

≥Grade 3 TRAE, Preferred Term	(≥5%) n (%)
Neutropenia	31 (32)
Pneumonia	14 (14)
Leukopenia	10 (10)
Anemia	6 (6)
Thrombocytopenia	5 (5)
Upper respiratory tract infection	5 (5)
Lymphocytopenia	5 (5)

- TRAEs were observed in 94 pts (95.9%)
- The most frequent ≥Grade 3 TRAE were **neutropenia, pneumonia and leukopenia;**
- ***Immune-related ≥Grade 3 TRAEs as elevated ALT,AST, diarrhea, colitis, rash were observed at <5%;***
- The most frequent drug-related SAE was pneumonia (11%);
- Twenty-two pts (22.4%) had dose reductions, and 9 pts (9.2%) discontinued from the study due to AEs.

Yuqin Song, ASH 2023, #306

Efficacy: PTCL subtypes

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	AITL n=48	PTCL-NOS n=24	NK/T n=8	Other* n=8	Total n=88
Best Response， n (%)					
CR	23(48)	2(8)	0(0)	1(13)	26(30)
PR	8(17)	5(21)	2(25)	1(13)	16(18)
SD	8(17)	7(29)	3(38)	0(0)	18(21)
PD	6(13)	9(38)	2(25)	4(50)	21(24)
NE	3(6)	1(4)	1(13)	2(25)	7(8)
ORR, n(%)	31(65)	7(29)	2(25)	2(25)	42(48)
95% CI	(50, 78)	(13, 51)	(3, 65)	(3, 65)	(37, 59)
DCR, n(%)	39(81)	14(58)	5(63)	2(25)	60(68)
95% CI	(67, 91)	(37, 78)	(25, 92)	(3, 65)	(57, 78)

*Other, includes ALCL, MEITL, or unclassified PTCL

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Open label single arm Phase2 Study Design in r/r T-Cell Lymphoma

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- A Phase2 study (NCT05274997) opened in August 2022
  - First trial to evaluate linperlisib-treated patients in the U.S. and E.U.
  - Stage 1, interim analysis for safety,
  - Stage 2, study completion N=36 pts
- r/r T-cell lymphomas having ≥1 prior therapy
  - All PTCL subtypes enrolling, PTCL-NOS, AITL, ALCL, NKT, EATL, MEITL and CD30+ brentuximab-progressing or intolerant.
  - There is a Central Lab confirmation of diagnosis in this study
  - CTCL patients are enrolling
- Dose schedules for 28-day cycles
  - 80 mg QD (RP2D) to progression
  - 80 mg QD for 4 cycles or until response, followed by 40 mg QD
- Primary endpoint is Overall Response Rate
- Principal Investigators: Dr. Swami Iyer (Study Chair), Dr.Pierluigi Zinzani
- Study is closed

Baseline Demographics and Disease Characteristics

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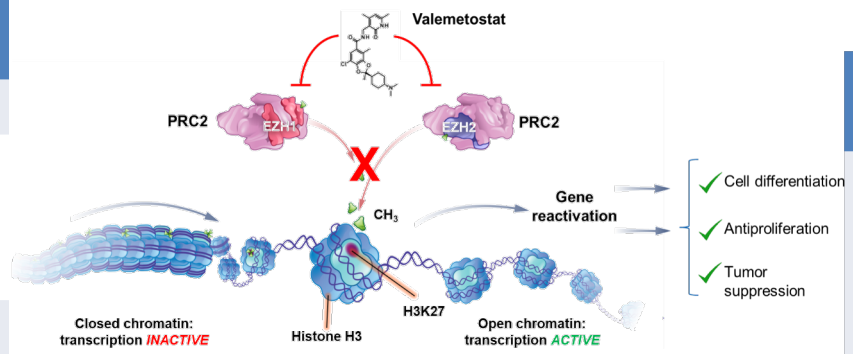
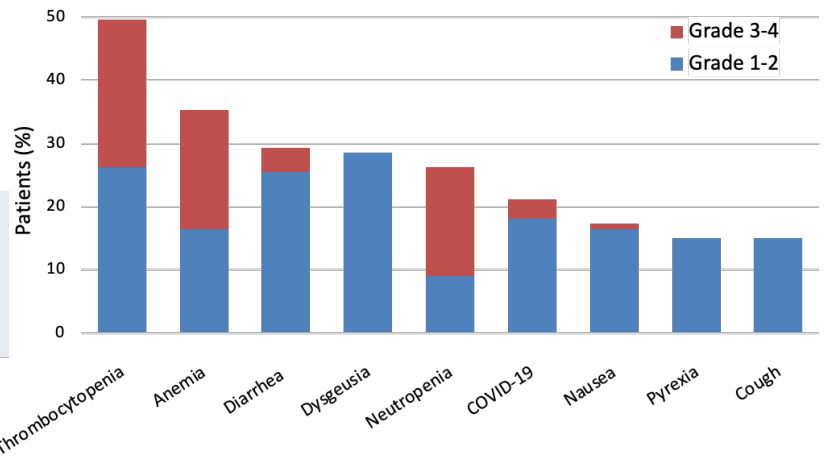
Characteristic	PTCL (N = 133)
Median age, years (range)	69.0 (22–85)
Sex, n (%)	
Male	91 (68.4)
Female	42 (31.6)
ECOG PS score, n (%)	
0	58 (43.6)
1	65 (48.9)
2	9 (6.8)
3	1 (0.8)
Median prior lines of therapy (range)	2.0 (1–12)
1	36 (27.1)
2	36 (27.1)
3	29 (21.8)
≥ 4	32 (24.1)
Prior HCT, n (%)	35 (26.3)
Autologous	32 (24.1)
Allogeneic	5 (3.8)



Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 that suppresses aberrant H3K27me3, thereby promoting antitumorigenic processes[2-4]



PTCL subtypes, n (%) (WHO 2016 classification; central review)	PTCL (N = 133)
TFH phenotype	
AITL	42 (31.6)
Nodal PTCL with TFH phenotype	8 (6.0)
FTL	3 (2.3)
PTCL-NOS	41 (30.8)
ALCL	
ALK+	7 (5.3)
ALK−	2 (1.5)
MEITL	1 (0.8)
CD8+ PCAECTCL	1 (0.8)
PCGTL	1 (0.8)
Other TCL[a]	13 (9.8)
Non-TCL or undetermined[b]	6 (4.5)
Missing[c]	8 (6.0)

Efficacy analysis set

Horwitz SM, et al. ASH 2023 #302

Clinical Response (BICR Assessment)

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CT–based assessment

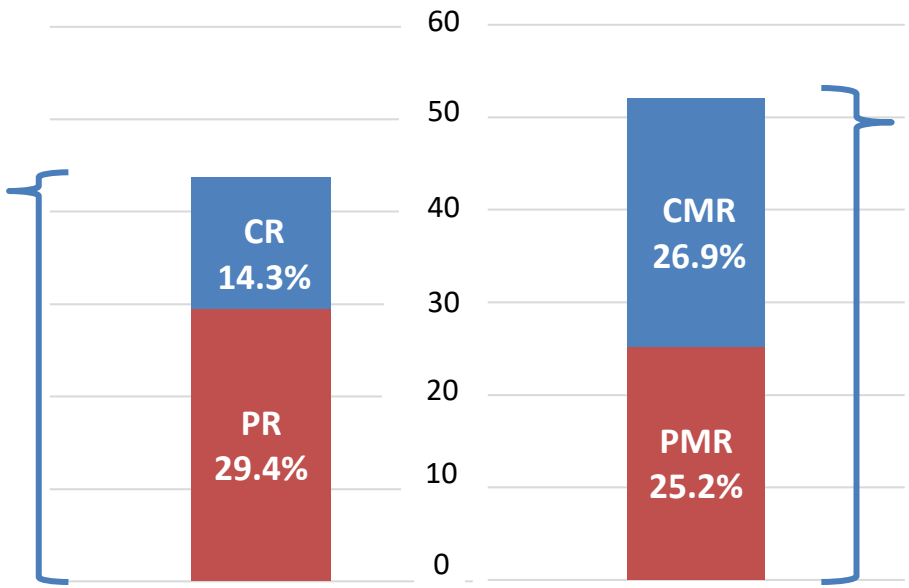
(Primary endpoint)

ORR was **43.7%**
(n = 52; 95% CI, 34.6–53.1)

17 patients **(14.3%)** achieved a **CR**

35 patients **(29.4%)** achieved a **PR**

Efficacy-evaluable population (N = 119)



PET-CT–based assessment

(Exploratory endpoint)

ORR was **52.1%**
(n = 62; 95% CI, 42.8–61.3)

32 patients **(26.9%)** achieved a **CMR**

30 patients **(25.2%)** achieved a **PMR**

- Ten (8.4%) patients treated with valemetostat proceeded to allo-HCT, including 8 patients (6.7%) with a CR[a] and 2 patients with an unknown response
  - The median time from first dose of valemetostat to subsequent allo-HCT was 6.9 months

Horwitz SM, et al. ASH 2023 #302

"Do or do not. There is no try."

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- Oh yes, the past can hurt. But the way I see it, you can either run from it or learn from it- Simba

FDA: Reliability and uncertainty of Early endpoints

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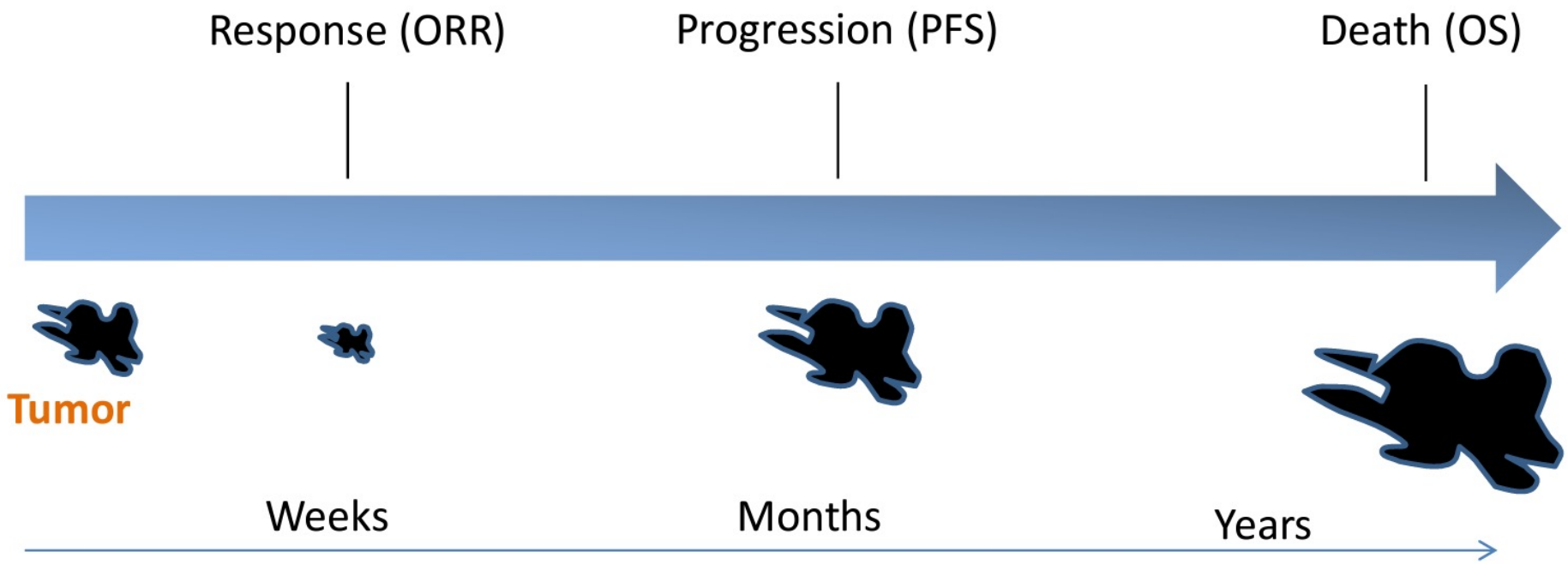
Conduct of Clinical Trials to Verify Benefit

FDA

- Early endpoints may not correlate with longer-term outcomes



Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival

FDA: Commitments for PMR to show clinical benefit (or OS)

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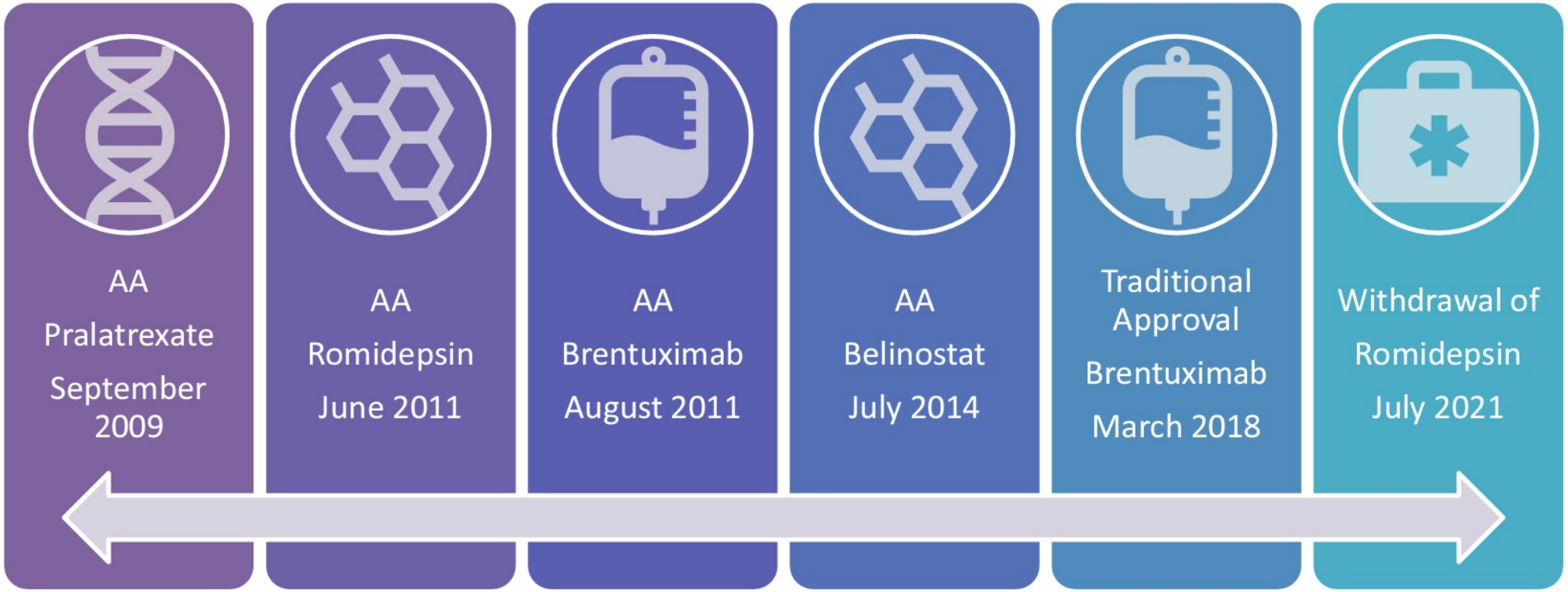
FDA

Approvals in PTCL



Abbreviations: AA, accelerated approval; PTCL, peripheral T-cell lymphoma

Is PFS the best endpoint for PTCL?

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Reasons Why PFS Is an Inappropriate Primary End Point in Most Trials Evaluating Anticancer Drugs
Improvement in PFS is **seldom a surrogate** for, nor reliably predictive of, improvement in OS
Improvement in PFS is not a surrogate for, **nor predictive of, improvement in QoL**
PFS does **not recognize** that the **balance between benefit and harm** depends not only on changes in tumor size but also on toxicity
PFS measurement and comparisons are **subject to error and bias** because of -**Timing of assessment** **-Measurement error in assessing tumor progression** **-Informative censoring because of uneven dropout between groups in an RCT**
Improvement in PFS is **widely misunderstood by patients** and the public to **imply** improvement in **survival**

Endpoint	Definition	Events Included	Clinical Implications
PFS (Progression-Free Survival)	Time from start of treatment to disease progression or death from any cause.	- Disease progression - Death from any cause	Measures the effectiveness of a treatment in delaying disease progression. Does not account for subsequent treatments.
EFS (Event-Free Survival)	Time from start of treatment to the occurrence of any predefined event.	- Disease progression - Initiation of new treatment - Death from any cause	Provides a comprehensive view of treatment failure, including disease progression, new treatment initiation, and death.
FFS (Failure-Free Survival)	Time from start of treatment to treatment failure due to disease progression or relapse.	- Disease progression - Relapse - Death related to the disease (in some definitions)	Focuses on the duration of disease control without progression or relapse, excluding deaths not directly related to the disease.

Modified from Booth CM, et al. J Clin Oncol. 2023

PFS in Pivotal studies

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Regimen	Type of Study	No. Patients	Median PFS	PFS by Subtype
Nordic CHOEP-ASCT	Retrospective	160	5-year PFS: 44%	PTCL-NOS: 38%; AITL: 49%; ALCL: 61%
Ro-CHOP	Prospective	211	Median PFS: 12.0 months	TFH: 19.5 months, Non-TFH: 8.7 months, Median OS for TFH: 65 months, PTCL-NOS: 25.8 months
CHOP		210	Median PFS: 10.2 months	TFH: 10.6 months, Non-TFH: 9 months
ECHELON-2 BV CHP	Prospective	226	Median PFS: 62.3 months; 5-year PFS: 51%	sALCL: Not Reported (NR), PTCL-NOS: 32.3 months, AITL: 21.7 months, 5-year PFS - sALCL: 60%, PTCL-NOS: 26.5%; AITL: 26.6%;
CHOP		226	Median PFS: 23.8 months; 5-year PFS: 43%	sALCL: 54.2 months, PTCL-NOS: 10.7 months, AITL: 47.6 months, 5-year PFS -sALCL: 48.4%, PTCL-NOS: 25.7%; AITL: 48.1%;

Mehta-Shah N, Horwitz SM. J Clin Oncol. 2024

Beware of PFS threshold in r/r PTCL

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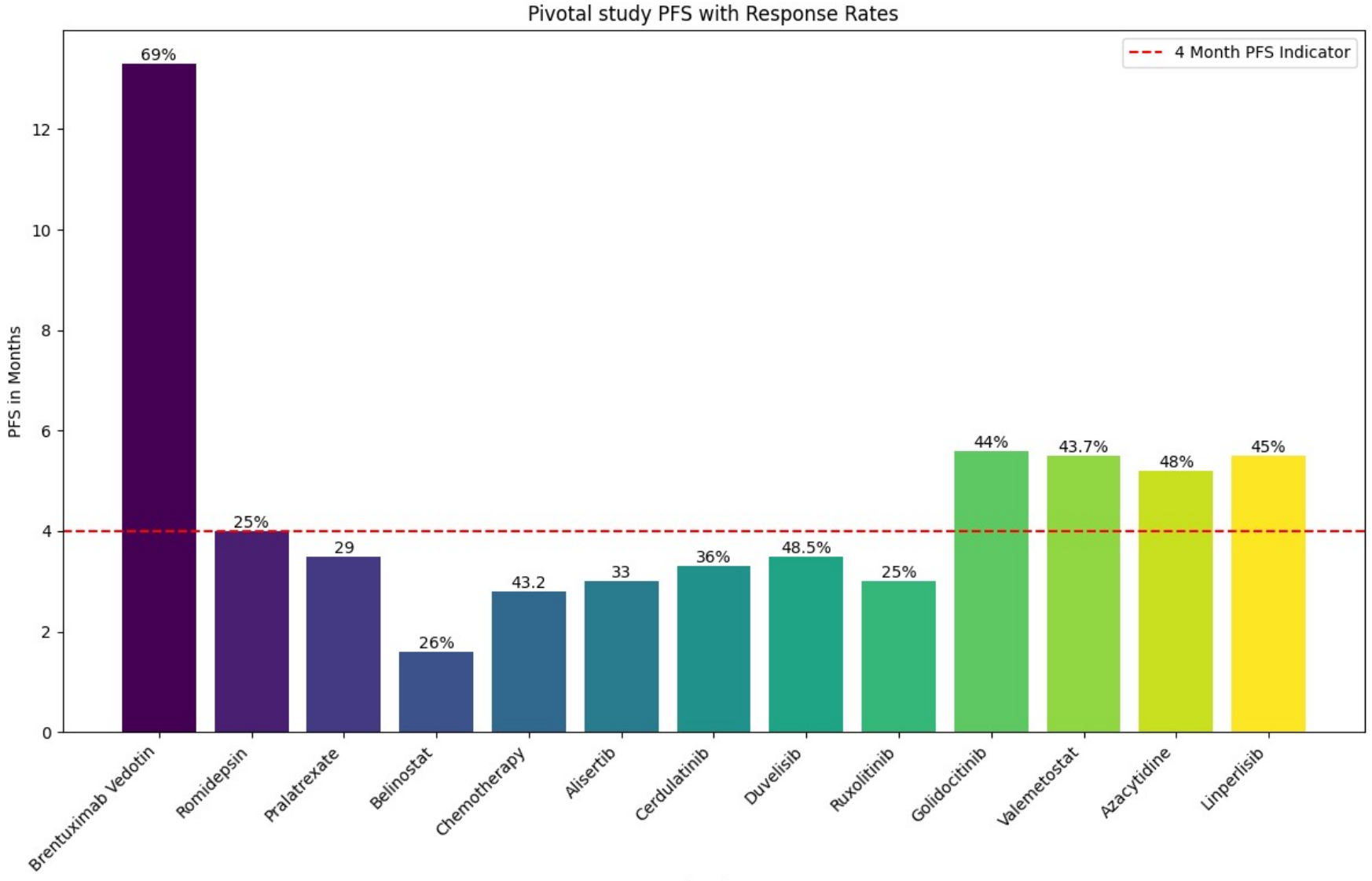

Iyer S- unpublished-Modified from pivotal studies

LUMIERE STUDY: PFS was 1/3 of proposed time

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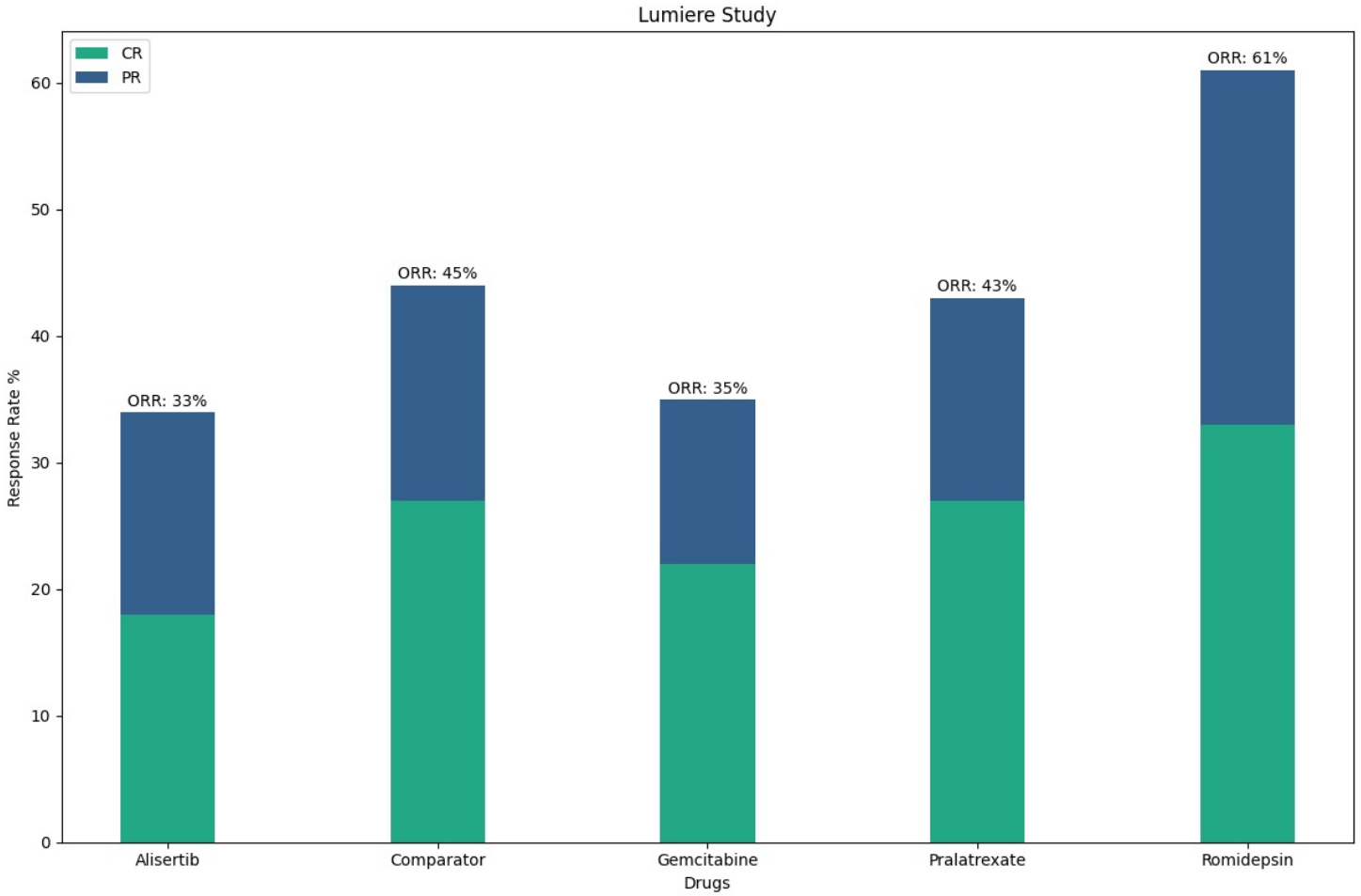

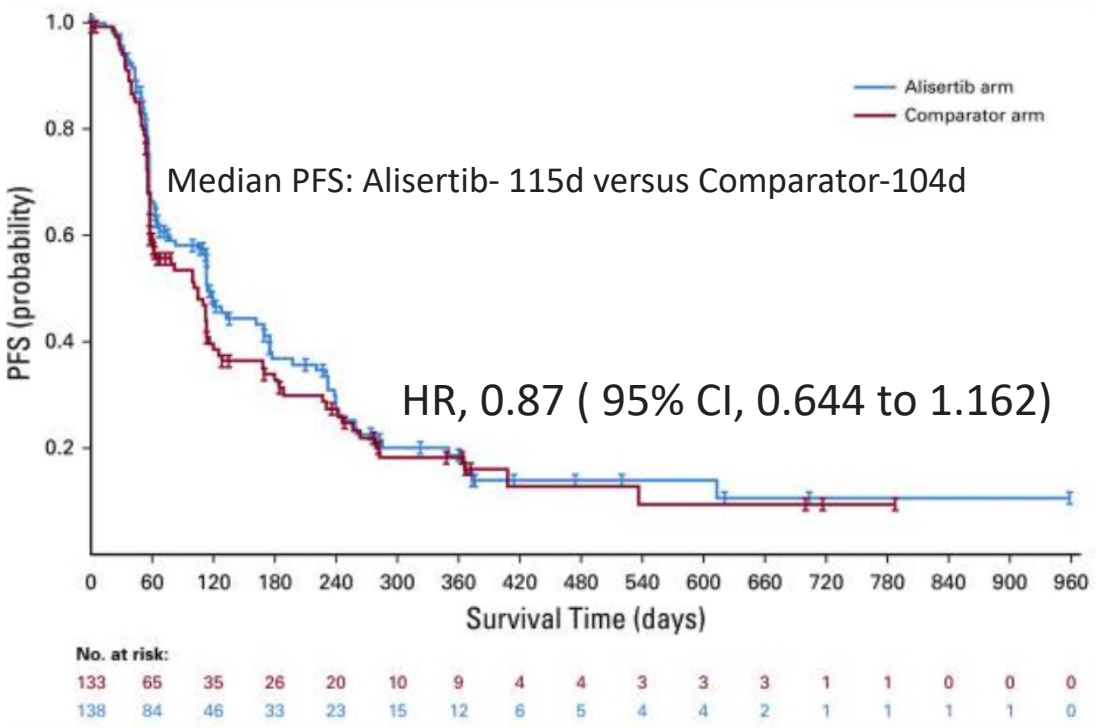

261 PFS events, to detect a difference in median PFS of 6 months in the comparator arm and 9 months in the alisertib arm (85% power; α = .0125)

Modified from O'Connor OA, et al. J Clin Oncol. 2019

ORACLE: Phase III study baseline characteristics

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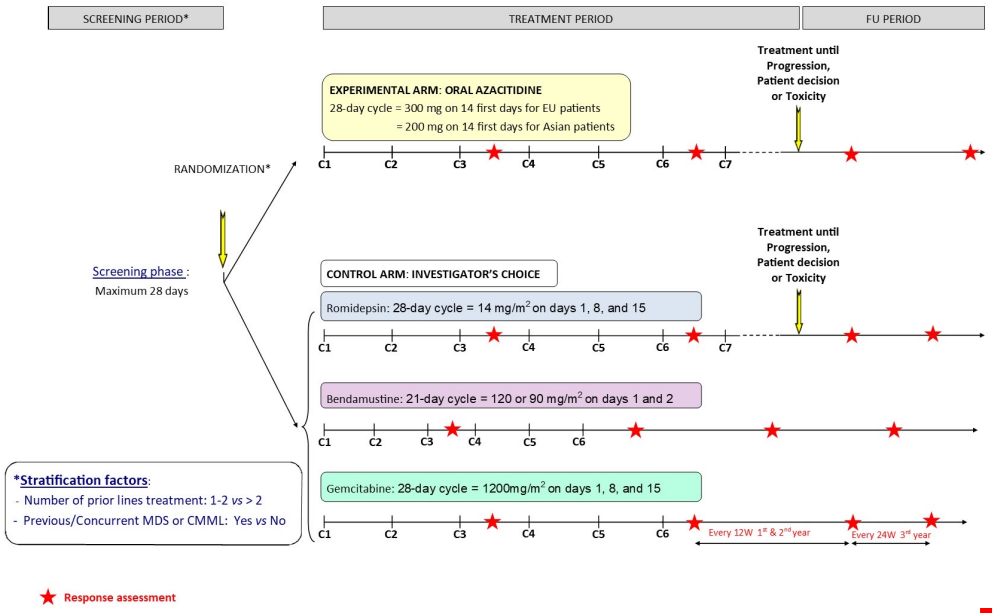

	Azacitidine CC486	Investigator treatment choice	romidepsin	Bendamustine	gemcitabine
N	42	44	4	16	24
median age (IQR)	70.5 (65-77)	68 (58.5-73.5)	68.5 (62.5-71.5)	63.5 (53-68)	72 (64-78)
Sex male	22 (52%)	28 (64%)	3 (75%)	10 (62.5%)	15 (62.5%)
ECOG 2-3	11 (26%)	9 (20%)	0 (0%)	4 (25%)	5 (20%)
Bone marrow involvement	12/37 (32%)	17/40 (42,5%)	1/4 (25%)	8/16 (50%)	8/20 (40%)
Associated MDS/CMML	0	1 (2%)	0	0	1 (4%)
IPI 4-5	13/42 (31%)	14/42 (33%)	0/4	5/15 (33%)	9/23 (39%)
Previous line number					
1-2 vs ≥3	34 (81%) vs 8 (19%)	37 (84%) vs 7(16%)	4 (100%) vs 0 (0%)	14 (88%) vs 2 (12%)	19 (79%) vs 5 (21%)
1	24 (57%)	14 (32%)	4 (100%)	3 (19%)	7 (29%)
2	10 (24%)	23 (52%)	0 (0%)	11 (69%)	12 (50%)
refractory patients	20 (48%)	28 (64%)	1 (25%)	13 (80%)	14 (58%)

Dupuis J et al, ASH 2022 #959

PFS –primary endpoint and OS

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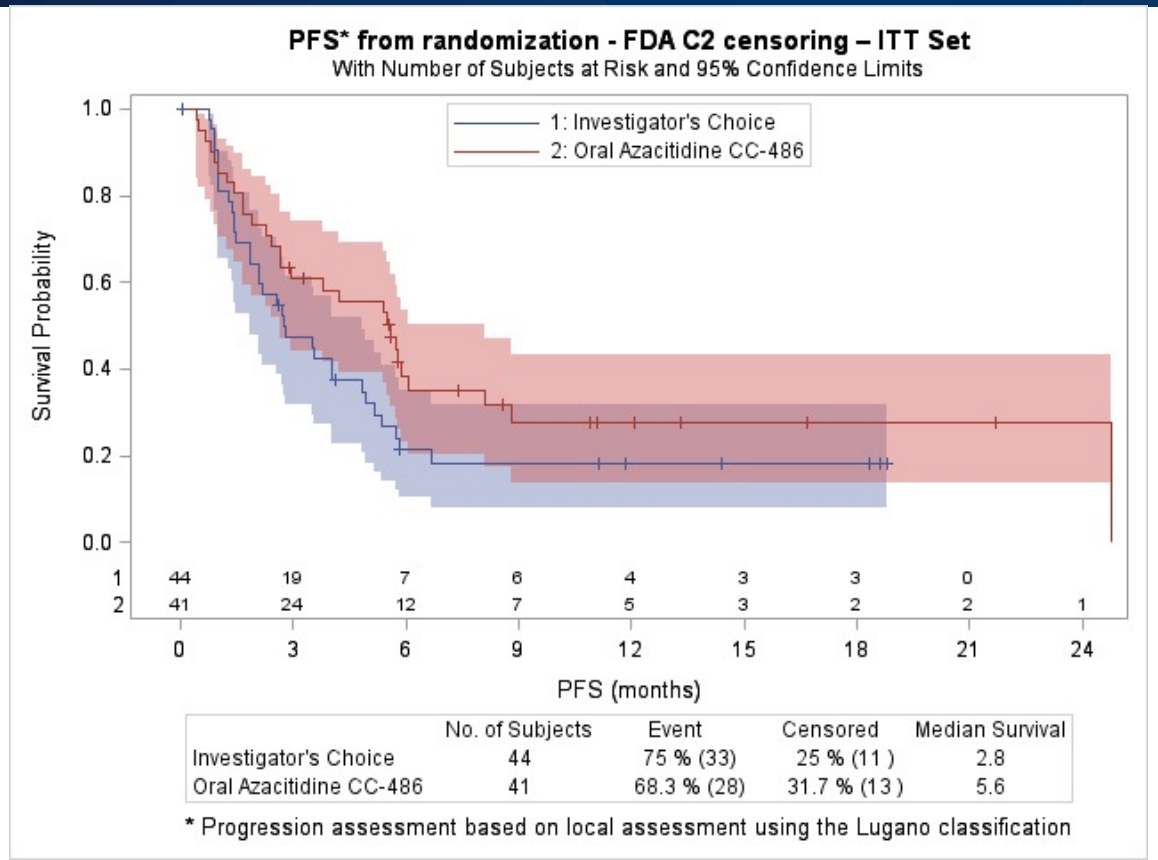

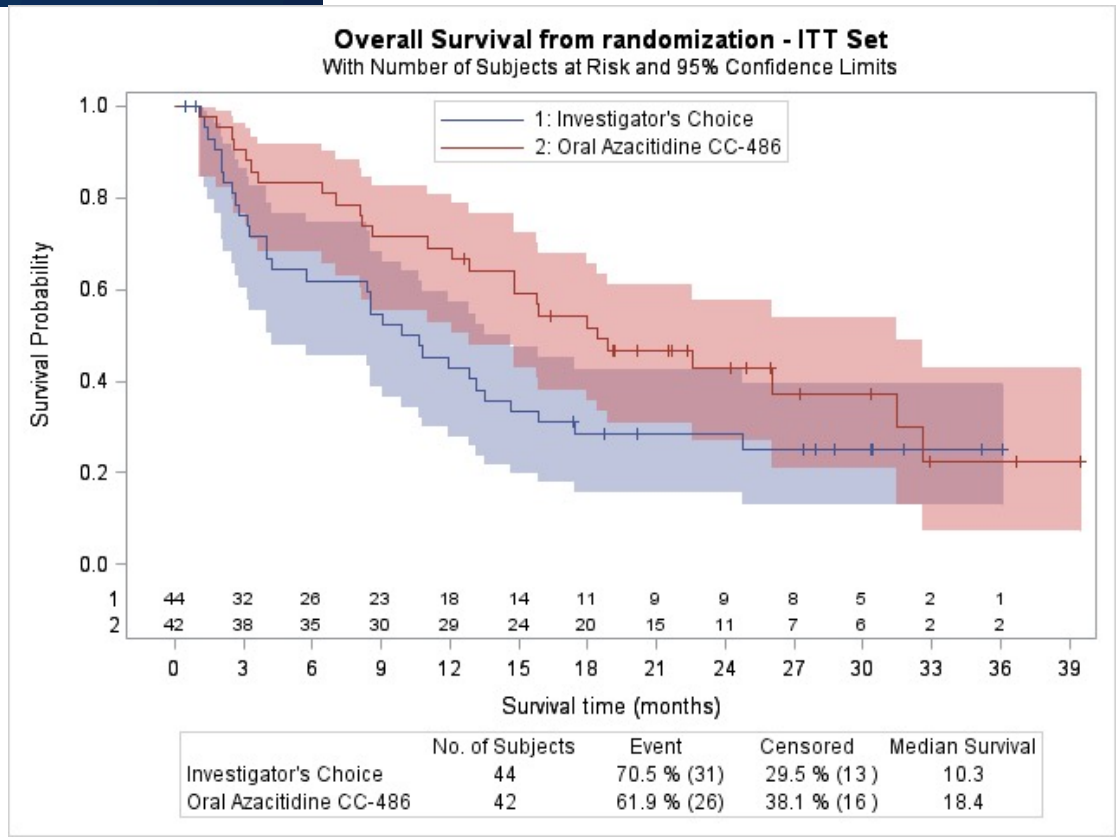

	CC-486	Investigator's choice
median	5.6 months	2.8 months
95% CI	2.7 - 8.1 months	1.9 - 4.8 months
	P=0.0421	>p=0.025

	CC-486	Investigator's choice
median	18.4 months	10.3 months
95% CI	12.9 – 31.5 months	4.2 – 13.5 months
	P=0.0166*	

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* Descriptive p value

Romidepsin pivotal study response rate by PET Status

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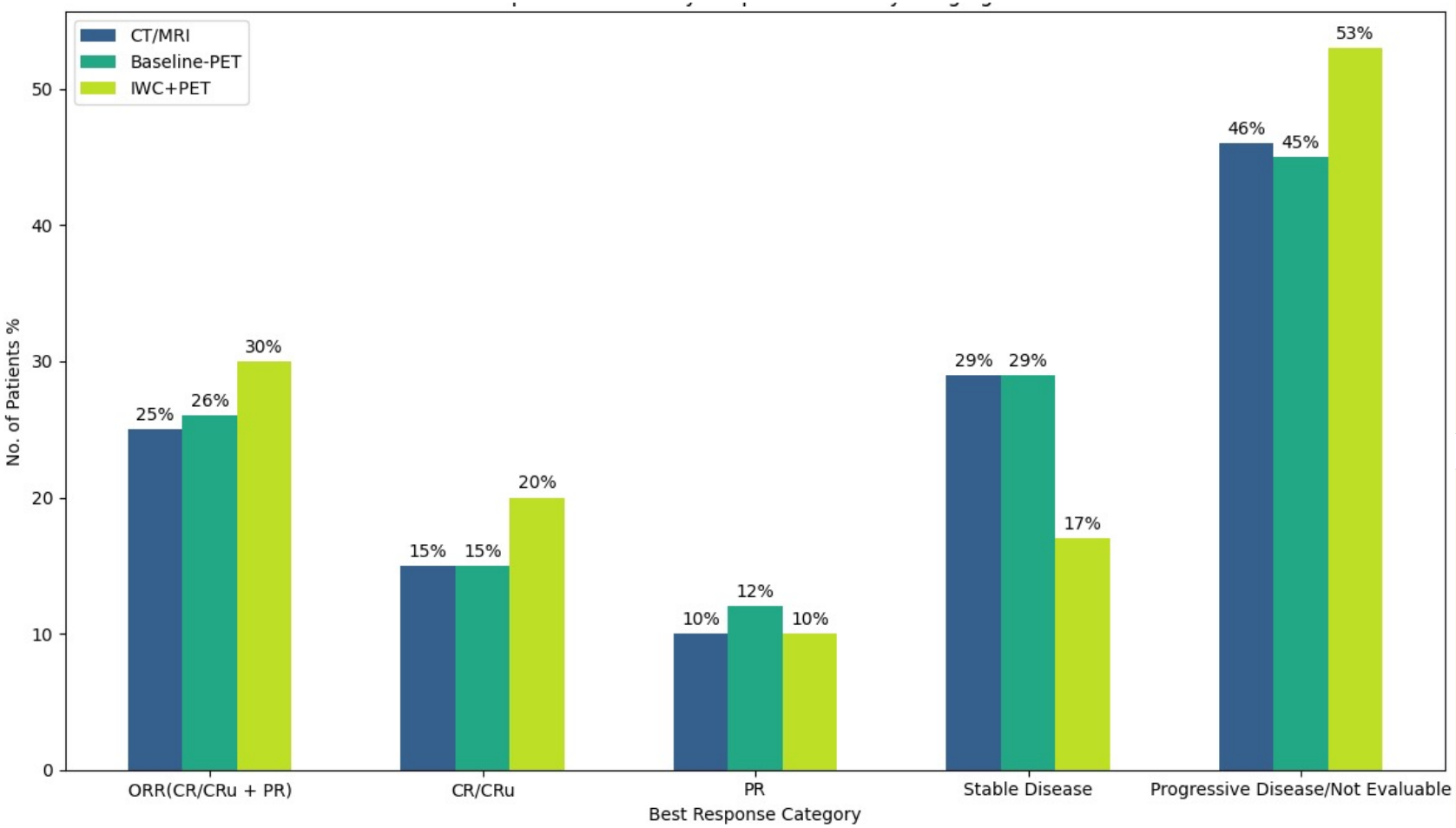

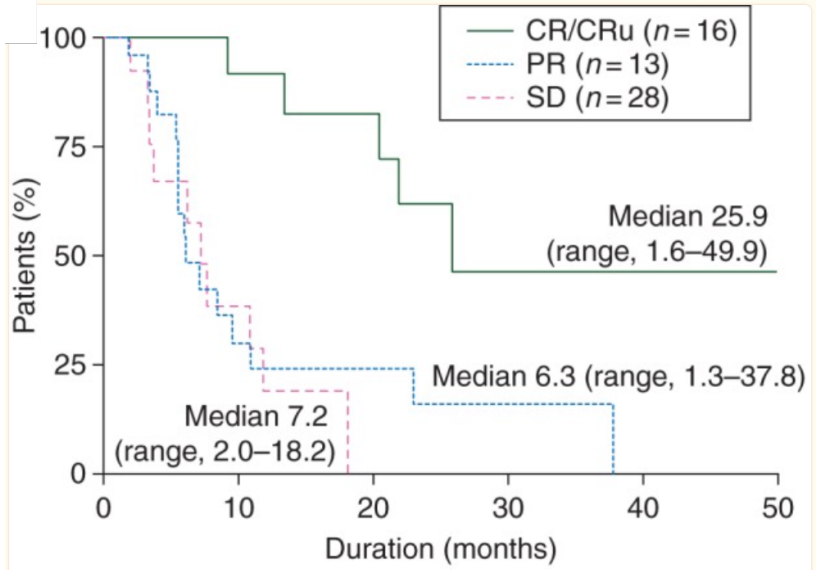

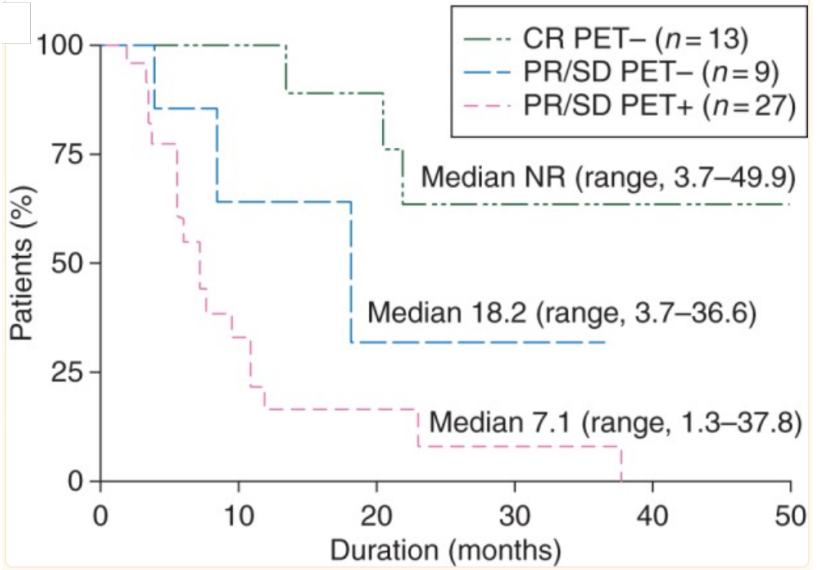

Modified from Horwitz S, et al. Ann Oncol. 2015

PFS goals for PTCL can vary: but be realistic!

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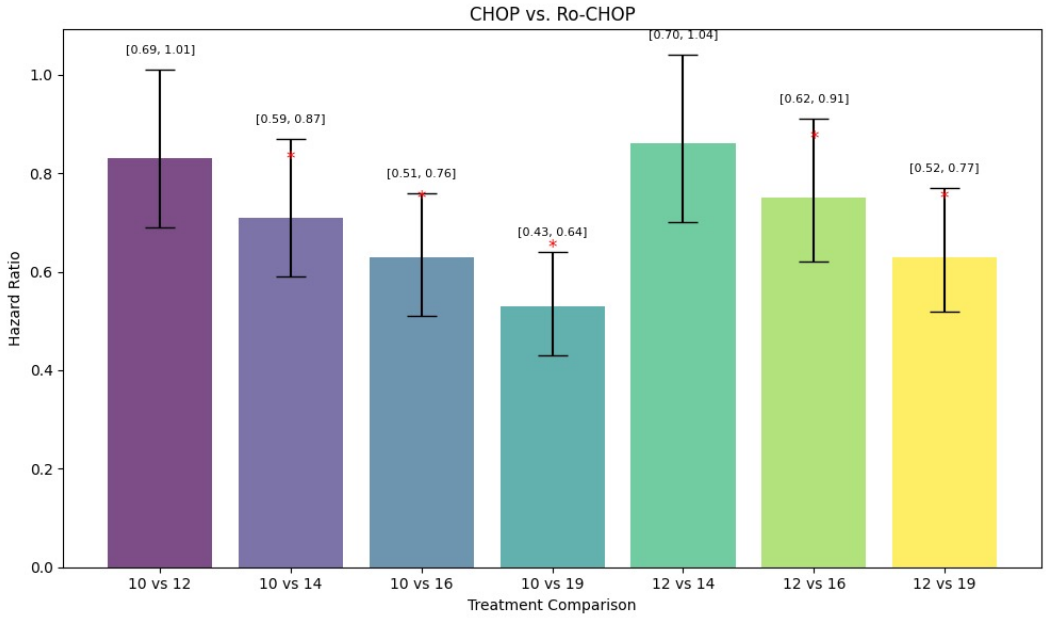
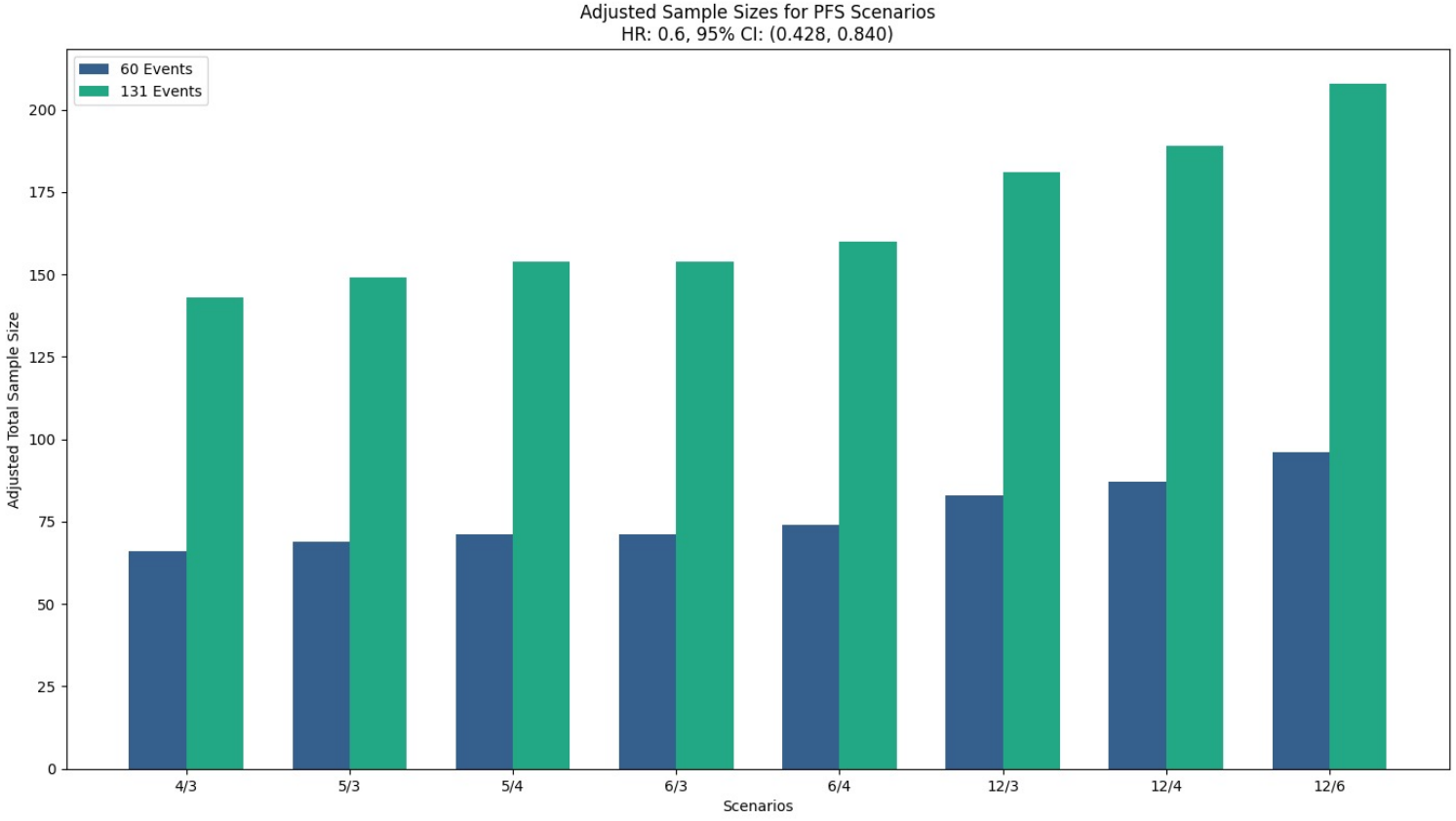
Frontline studies HR



R/r studies HR



40% improvement in median PFS (from 12 months in control to 16.8 months in testing arms)

Iyer S- unpublished-Modified from pivotal studies

Beware of PFS threshold in r/r PTCL

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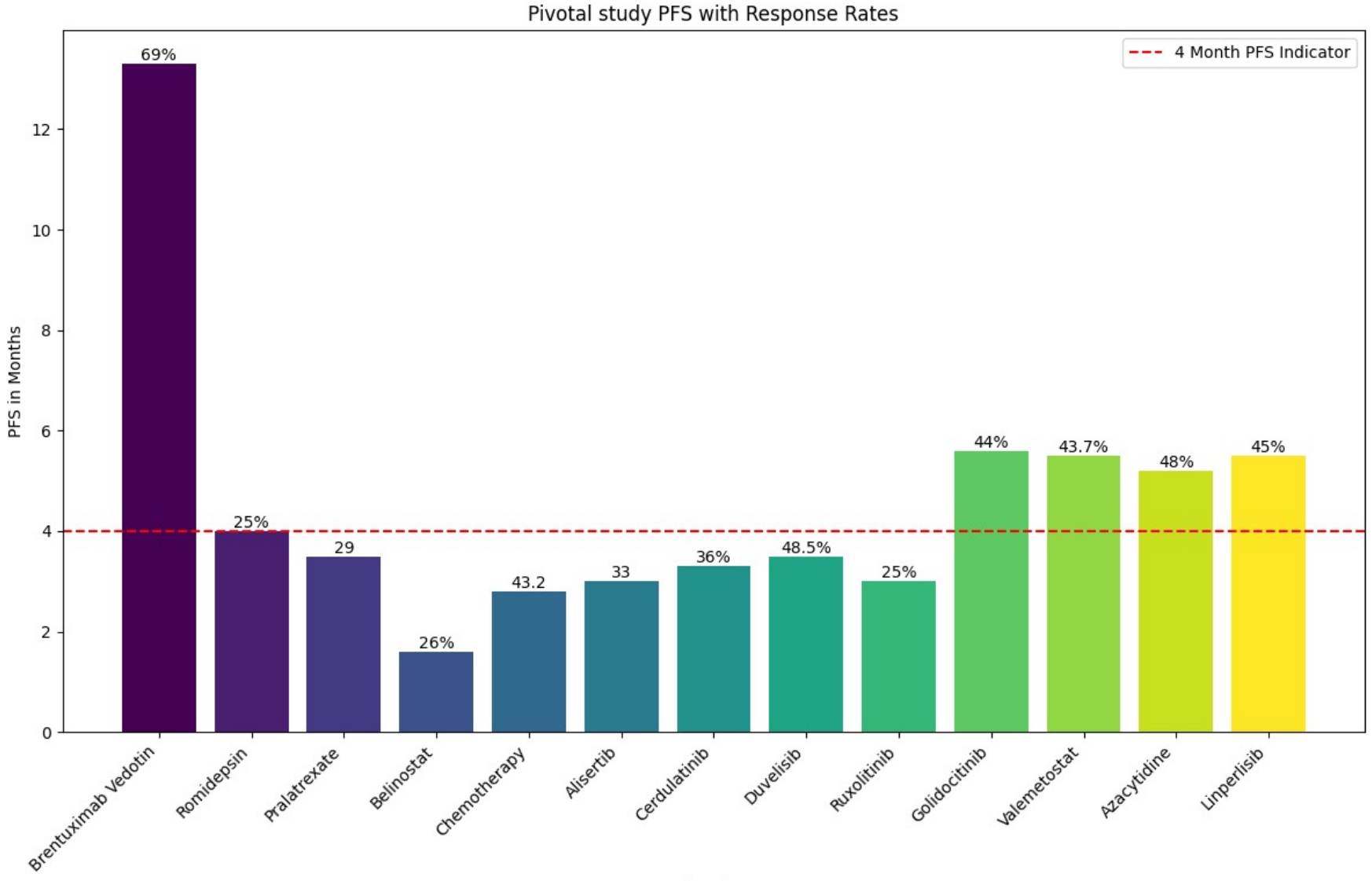

Iyer S- unpublished-Modified from pivotal studies

Conclusions

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- Impact size of treatment: higher response rate (RR) generally has higher impact- intensification is reasonable
- In newly diagnosed T-cell lymphoma (TCL), progression-free survival (PFS) is around 10 months even with 80% RR
  - ✓ Adding compound X takes into account additional benefit but is diminished by compounded toxicity
  - ✓ Benefit can vary more for one group than another
  - ✓ Tilting the efficacy/risk ratio by enriching responsive groups
  - ✓ E2 and Ro-CHOP studies have shown this is possible
- Current paradigm of single agent approval followed by combination approaches
- For rare disease and promising drug- potential benefit is assumed to exist until proven otherwise
  - Preclinical and early phase studies are promising
  - However, aim for realistic PFS in front line and relapsed/refractory settings
  - Humbling lessons point to an incremental approach that can get drugs approved (eg in Lung Cancer)
  - Targeting disease subtypes
  - Naysayers and data pundits who don't treat patients
  - They analyze data and perform a watchdog function
  - We should be given the benefit of the doubt to get drugs approved
- ODAC meeting was reality check on FDA views
  - ➢ An exceptional case was made for PTCL approval
  - ➢ This is unlikely to happen again in PTCL or other diseases

T Cell Lymphoma Group

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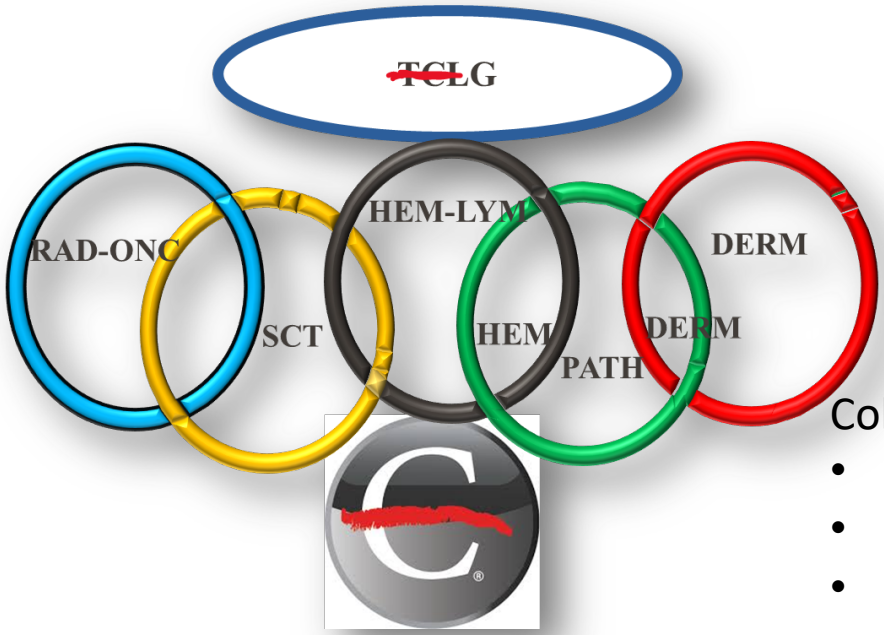

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- Div. Medicine

Collaborators:

- Statisticians

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- Dr.Pavan Bachireddy

Thank you very much!

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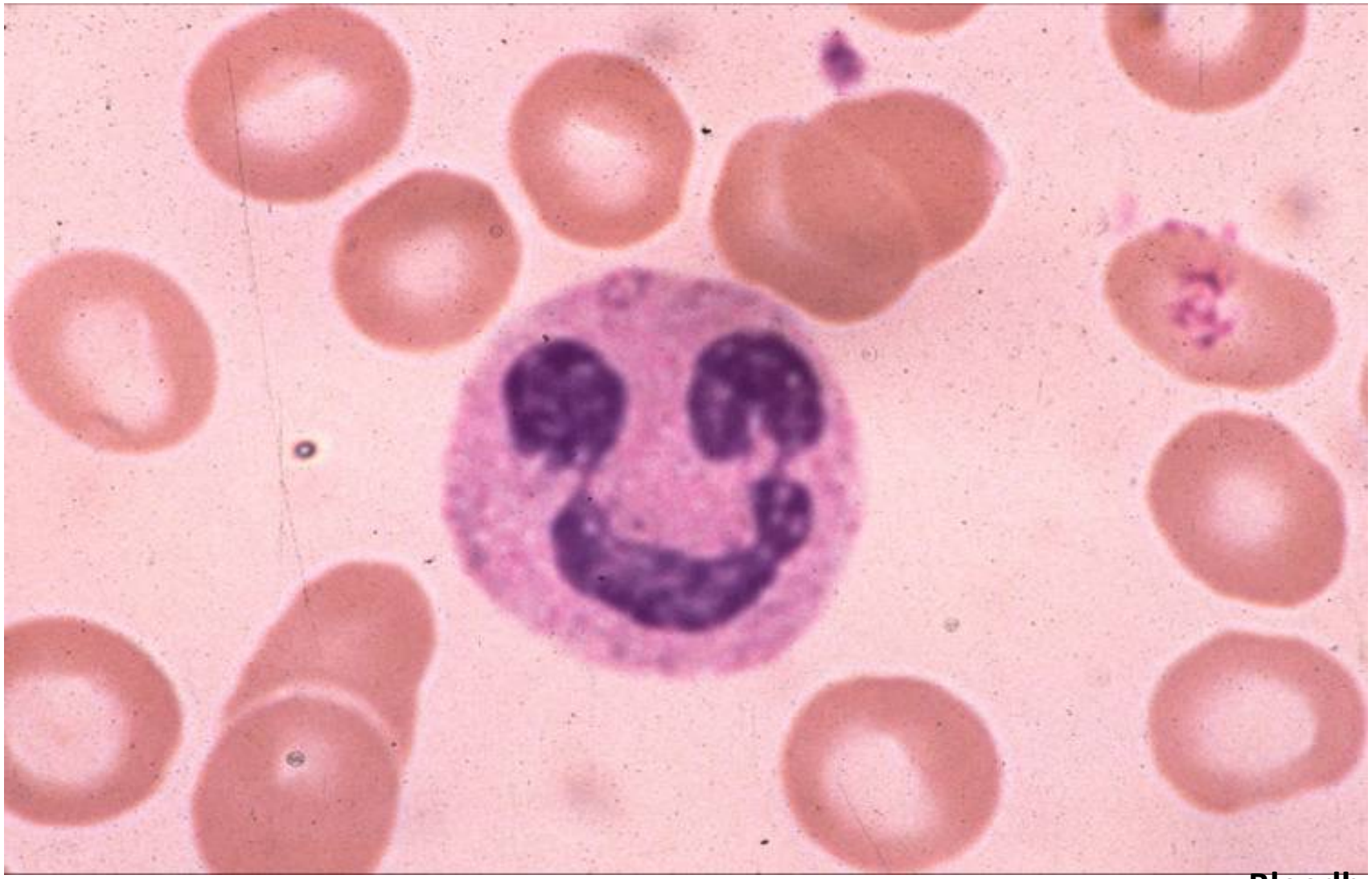

Bloodbytes @DrSwami_Iyer