Peripheral T-Cell Lymphoma: Incorporating Novel Therapies

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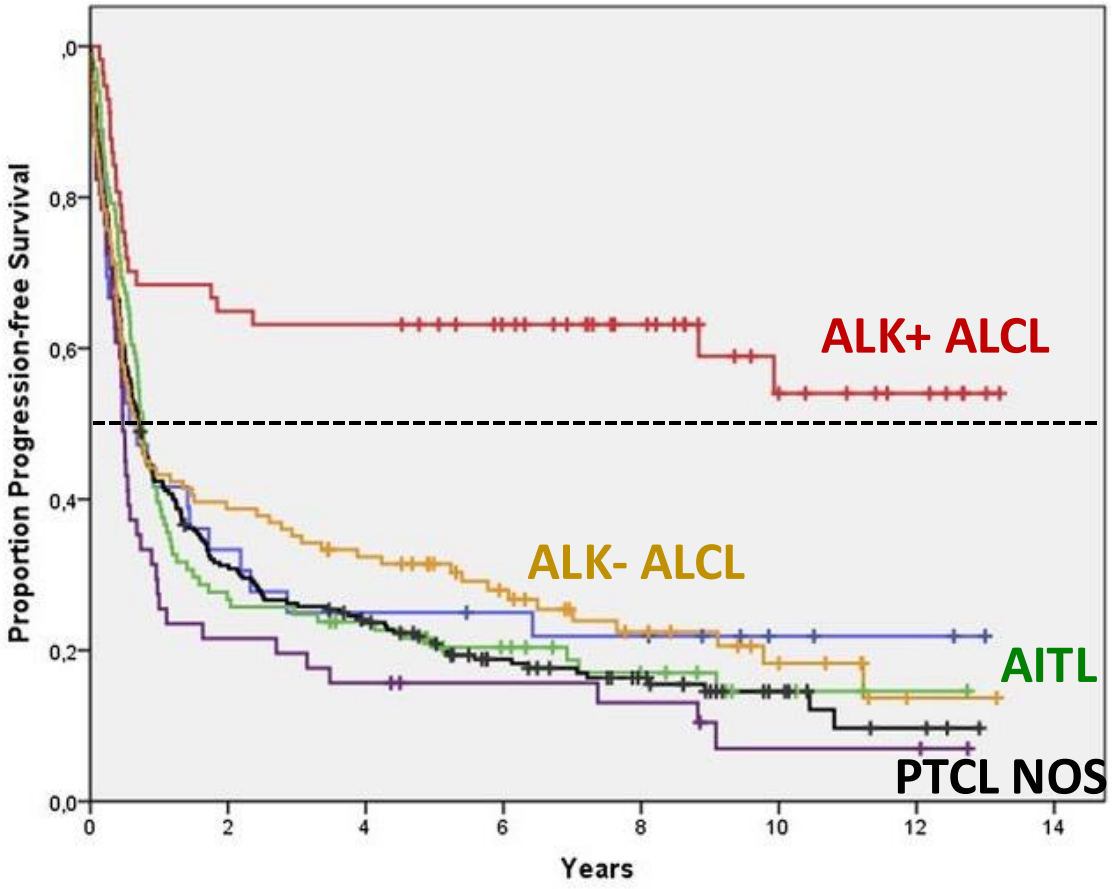
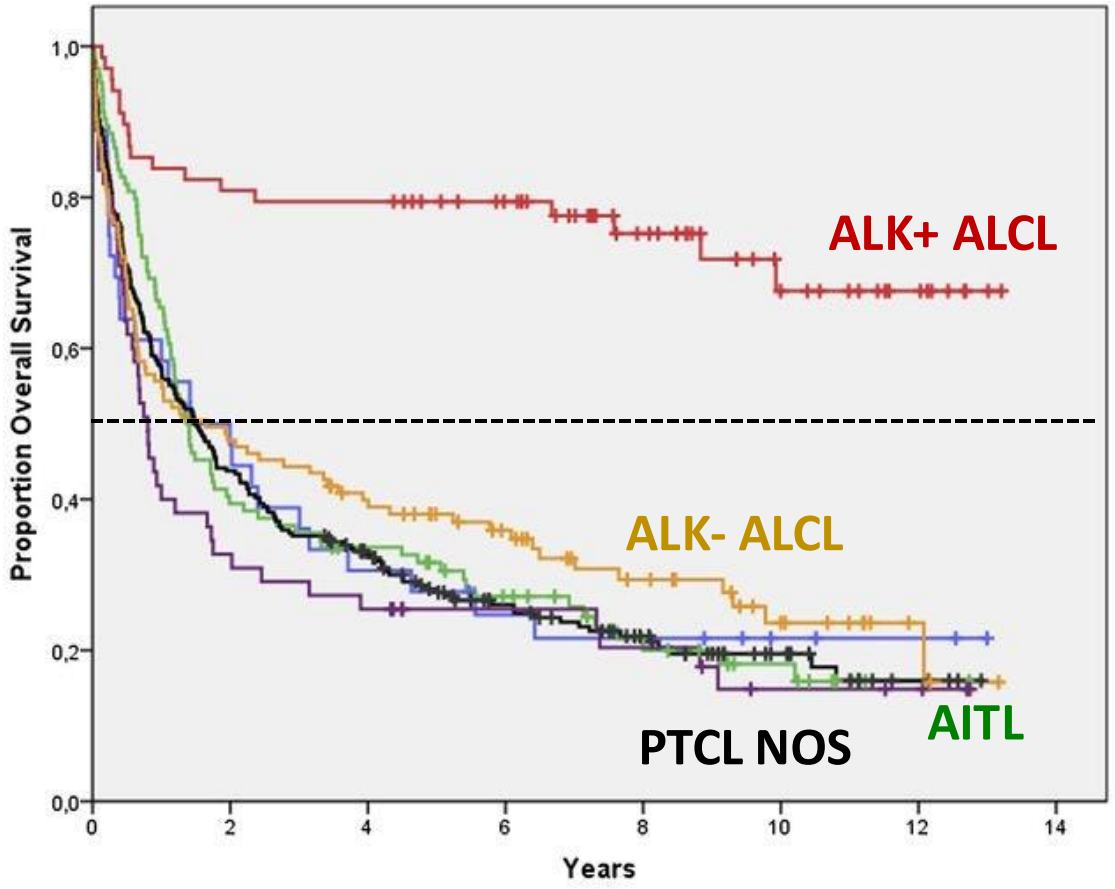
Population Outcomes in PTCL: Swedish National Registry

PFS



OS



Overall survival mirrors PFS-lack of effective second line+ therapy

Fredrik Ellin et al. Blood 2014;124:1570-1577

PTCL Genetics and Molecular Pathogenesis

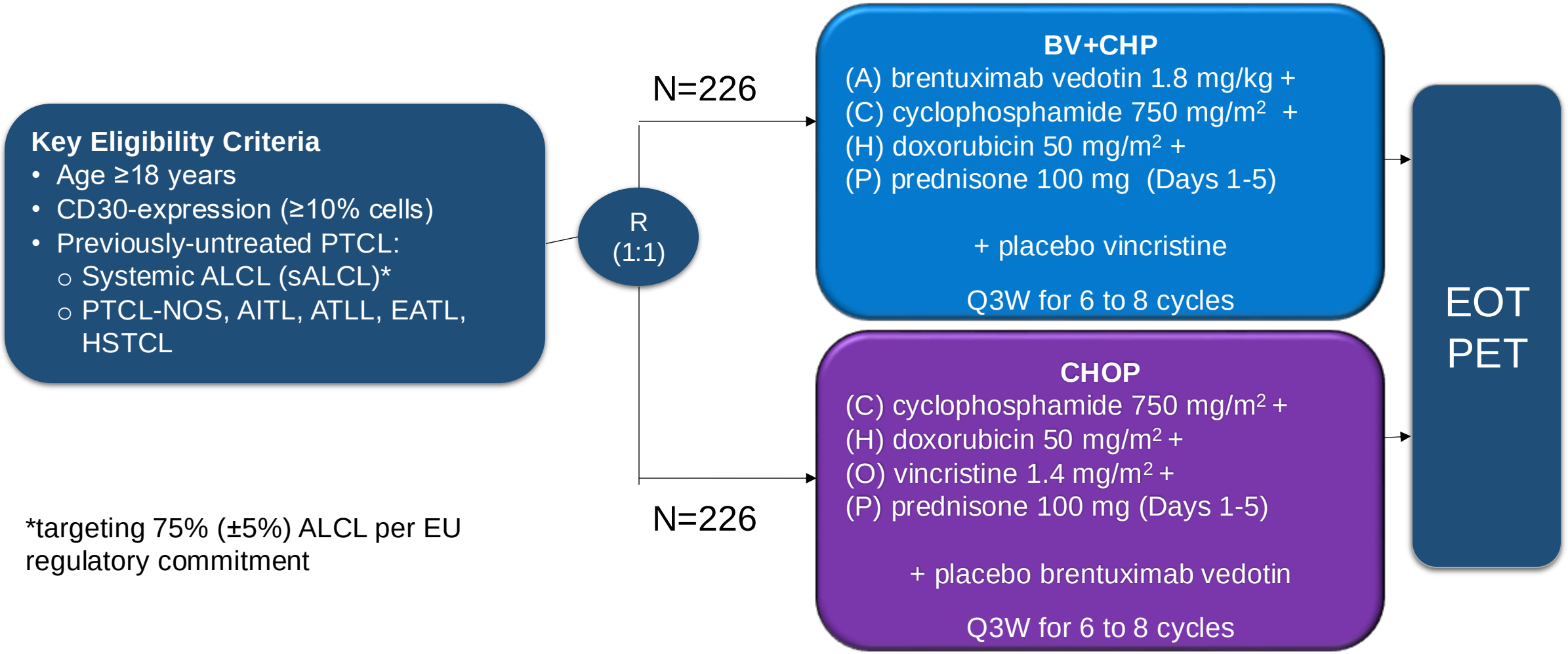
Increasing understanding of biology of T-cell Lymphomas

- AITL and TFH (T-Follicular Helper PTCL) develop on a background of epigenic dysregulation
  - TET2, DMNT3A, IDH2, CHiP
- Aberrant TCR signaling is common
  - RHOA, VAV1, SYK
- Other signaling pathways are frequently dysregulated
  - PI3K, JAK/STAT
- Alterations in Tumor suppressor genes are *common*
- Subtype Specific or Subtype Independent
- Aberrant signaling in pathways may converge or be present simultaneously

Adding to a CHOP Backbone in a Targeted or Selective Way

Brentuximab vedotin in PTCL

ECHELON-2 Study Design (NCT01777152)



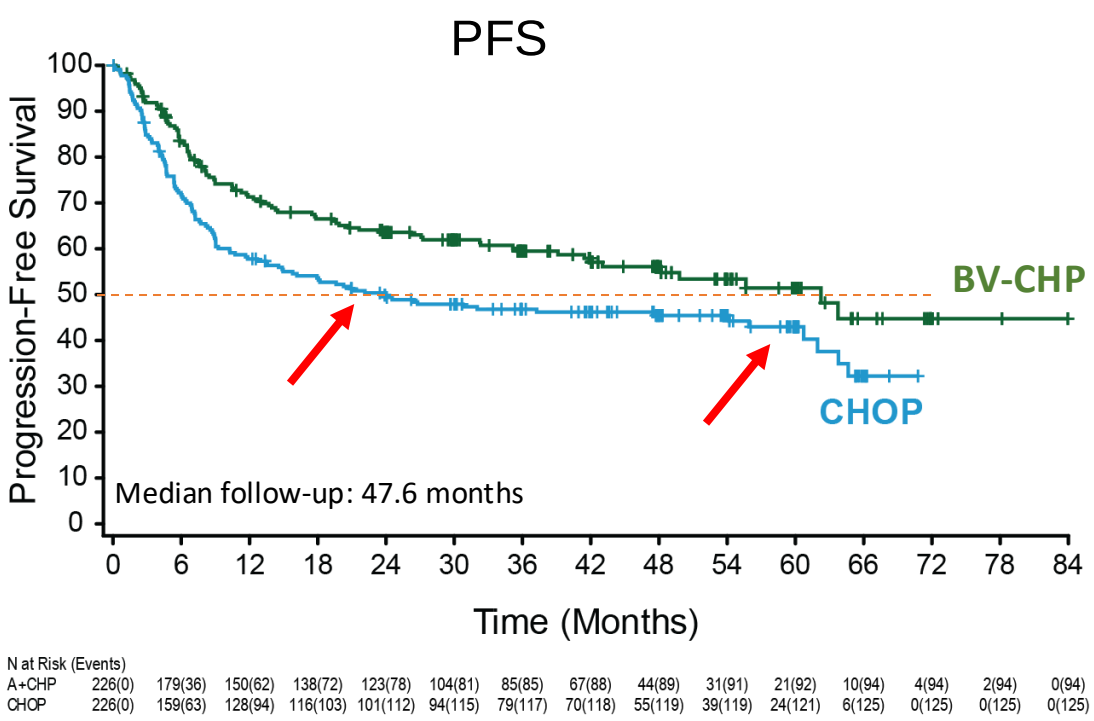
*targeting 75% (±5%) ALCL per EU regulatory commitment

Primary Endpoint

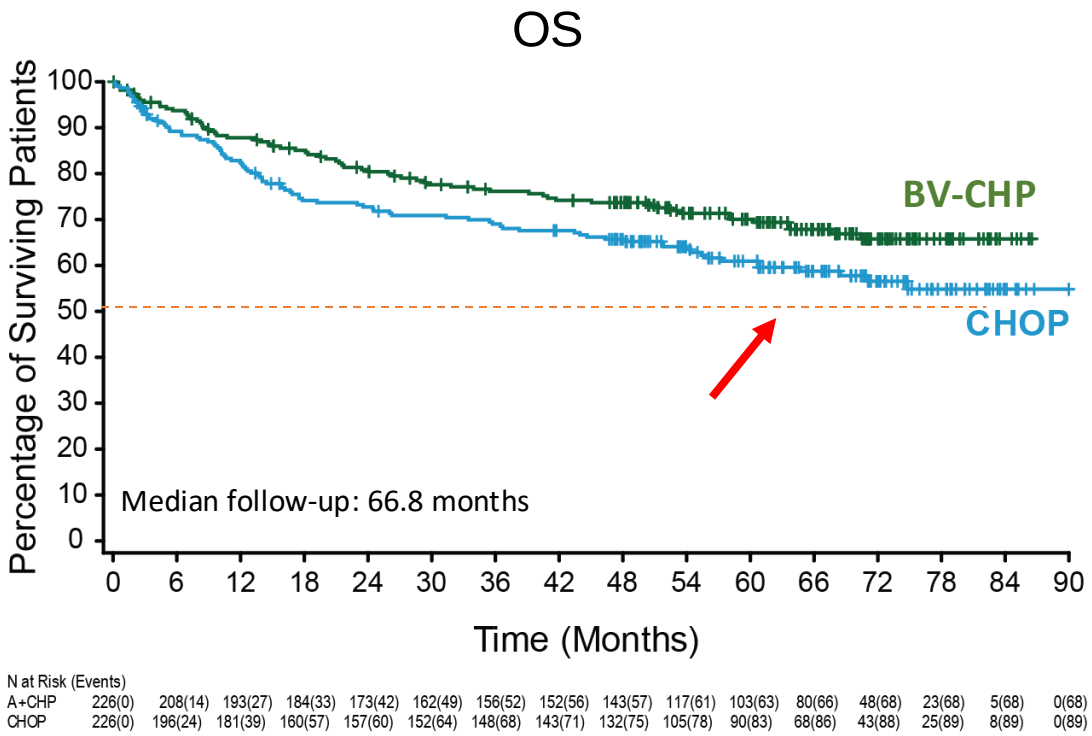
PFS per BICR, ASCT or RT consolidation not an event

Horwitz S et al. *Lancet.* 2019; 393:229-240.

Echelon-2 Trial 5-Year Results: PFS (INV Assessment) and OS



	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		



	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 S et al. *Lancet.* 2019; 393:229-240.

Updated in Horwitz S et al. Ann Oncol 2022 33: 288-298

Adding to a CHOP backbone-BV in untreated PTCL

- ALCL
  - BV-CHP-Overall survival benefit
  - *standard of care*

- CD30 expressing PTCL-NOS, AITL
  - Part of ITT
  - Smaller subset size precludes statistical conclusions-but unclear *benefit*

- BV-CHEP-ASCT (T-MAX; Herrera et al. ASH 2021)
- EATL-BV-CHP-ASCT (EATL-001 Trial; Sibon et al. ASH 2021)

Adding to a CHOP Backbone in a Targeted or Selective Way

Epigenetic Therapies

TFH Phenotype Predicts Response to HDAC Inhibitors in Relapsed/Refractory PTCL

Response	TFH (n = 76)		Non-TFH (n = 51)		
	ORR, n/total (%)	CR, n/total (%)	ORR, n/total (%)	CR, n/total (%)	*P**
Overall (n = 127)	43/76 (56.5)	22/76 (28.9)	15/51 (29.4)	10/51 (19.6)	.0035

- Ghione P, et al. *Blood Adv.* 2020;4:4640-4647.

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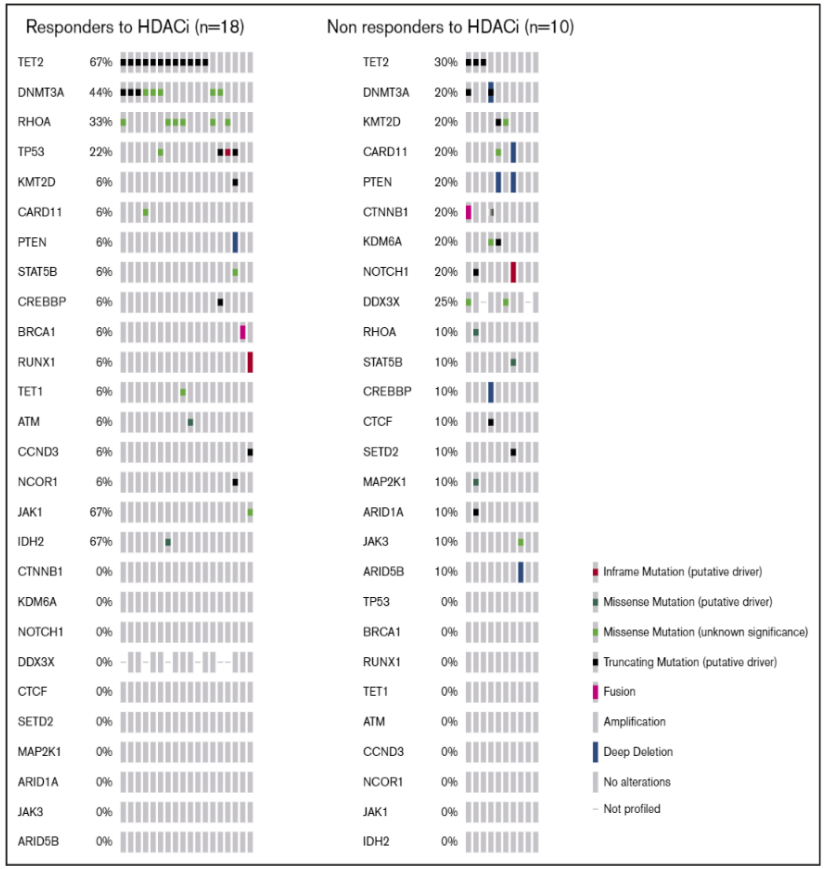
Typical AITL/TFH mutations in *TET2*, and/or *DNMT3A*, and/or *RHOA* present in

- Responders 15/18 (83%)
- Non-responders 4/10 (40% (*P* = .034)

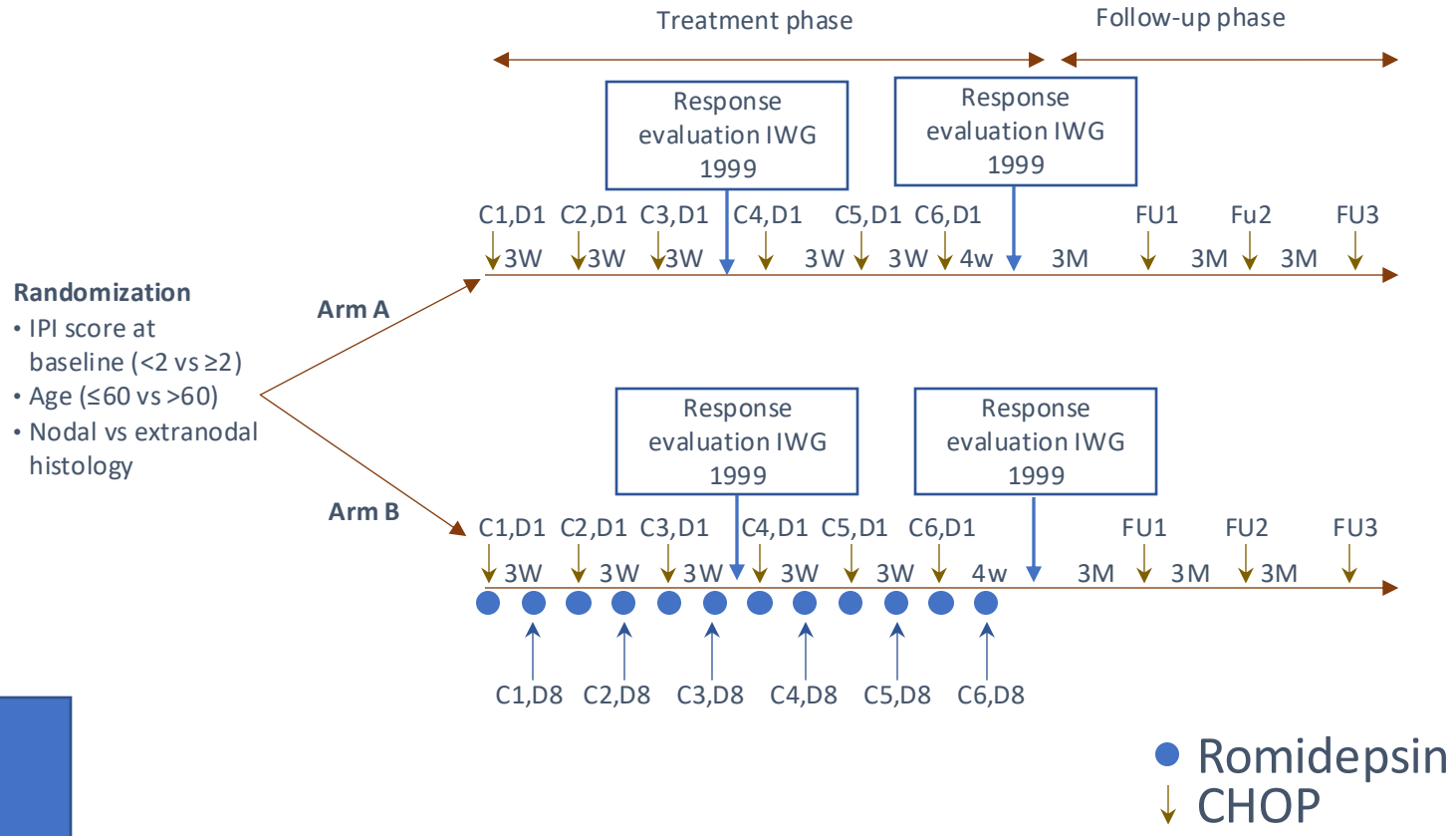


- Ghione P, et al. *Blood Adv.* 2020;4:4640-4647.

Ro-CHOP: Study Design

Key Inclusion Criteria
- Aged 18-80 y
- Histologically proven PTCL according to WHO classification: PTCL-NOS, AITL, ALK-neg ALCL, EATCL, HSTCL, SPTCL

Key Exclusion Criteria
- Autologous or allogeneic transplant planned as consolidation



Primary end point: PFS by RAC assessment according to IWG 1999
- Median PFS of 12 mo (control) vs 16.8 mo

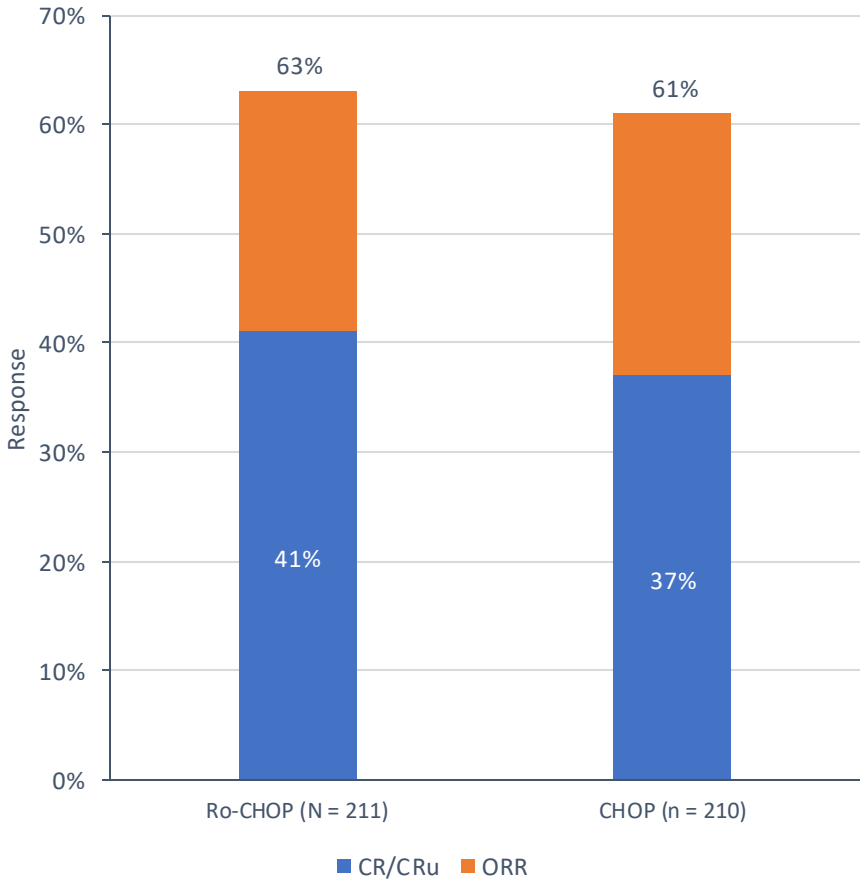
Secondary end points: OS, response rate, DOR, TTP, TTF, safety, QOL

Bachy E, et al. ASH 2020. Abstract 39./JCO 2022

Romidepsin Plus CHOP vs CHOP in Previously Untreated PTCL

Efficacy

Ro-CHOP: Response at End of Treatment



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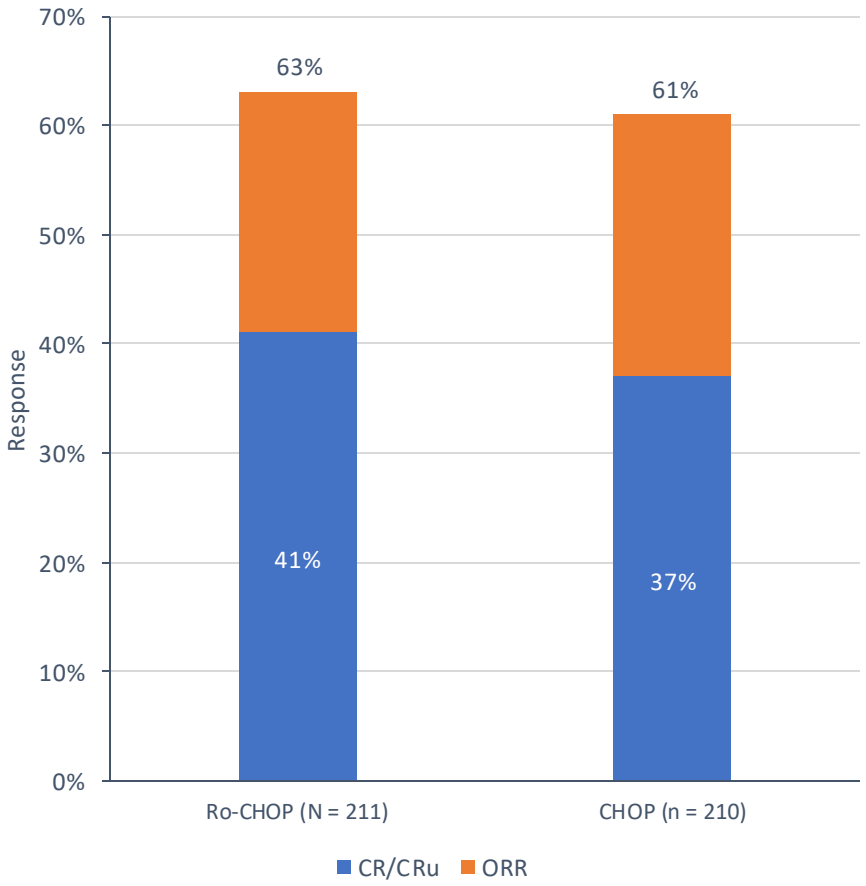


Dose Reductions and Interruptions

≥ 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)

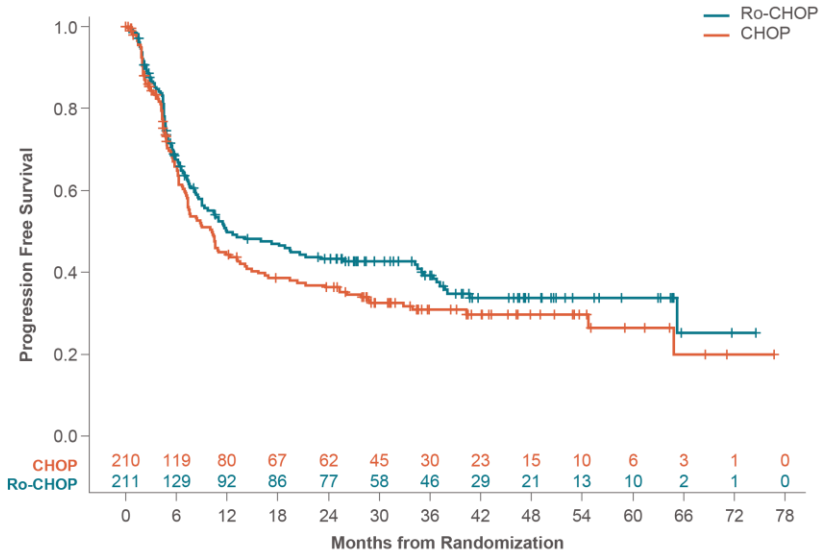
Completed All 6 Cycles w/o Red or Inter, n (%)	Ro-CHOP (n = 210)	CHOP (n = 208)
Romi	**62 (30)**	NA
CHOP	112 (53)	125 (60)

Bachy E, et al. ASH 2020. Abstract 39./JCO 2022

Romidepsin Plus CHOP vs CHOP in Previously Untreated PTCL

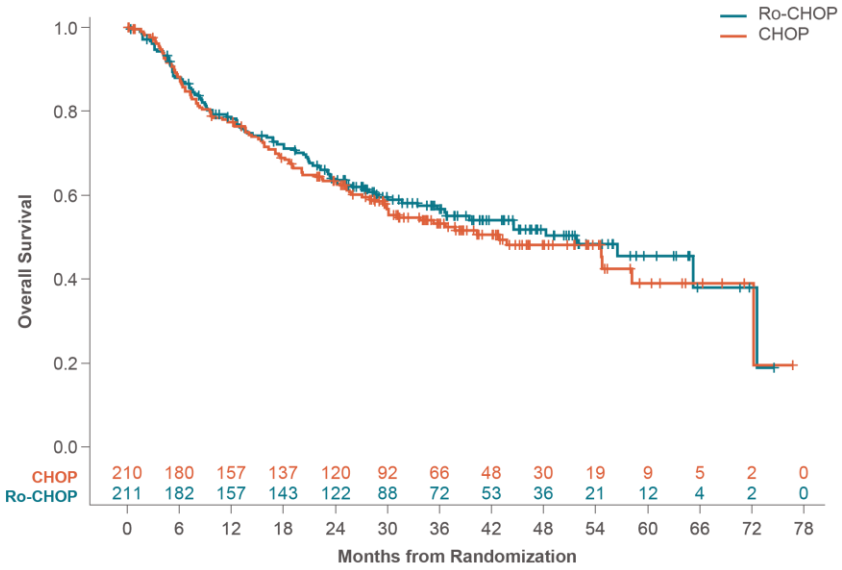
Efficacy

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)

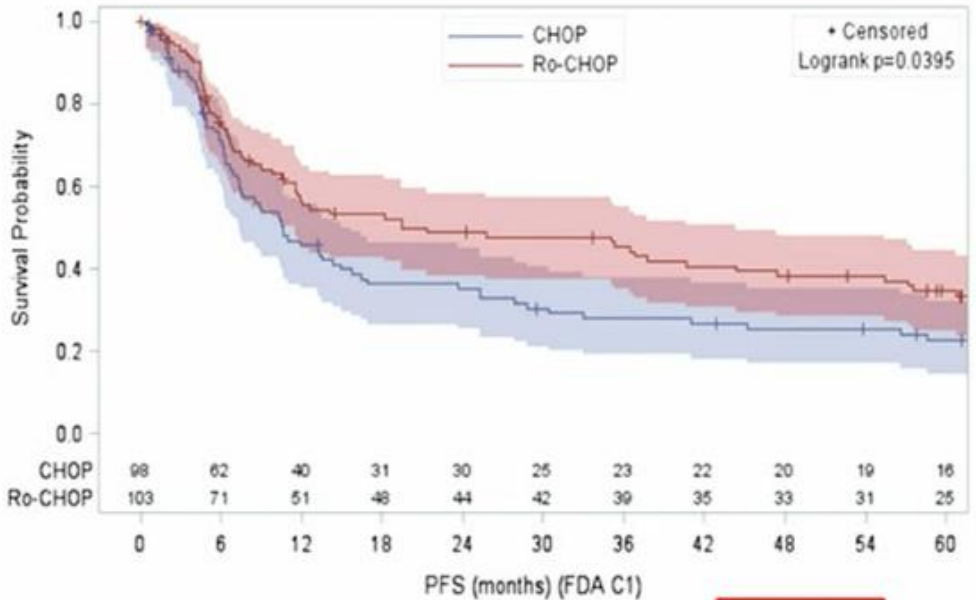


	Ro-CHOP (n = 211)	CHOP (n = 210)
OS, median (95% CI), mo	51.8 (35.7-72.6)	42.9 (29.9-NR)
HR (95% CI)	0.90 (0.68-1.20)	
P value	0.477	

Bachy E, et al. ASH 2020. Abstract 39./JCO 2022

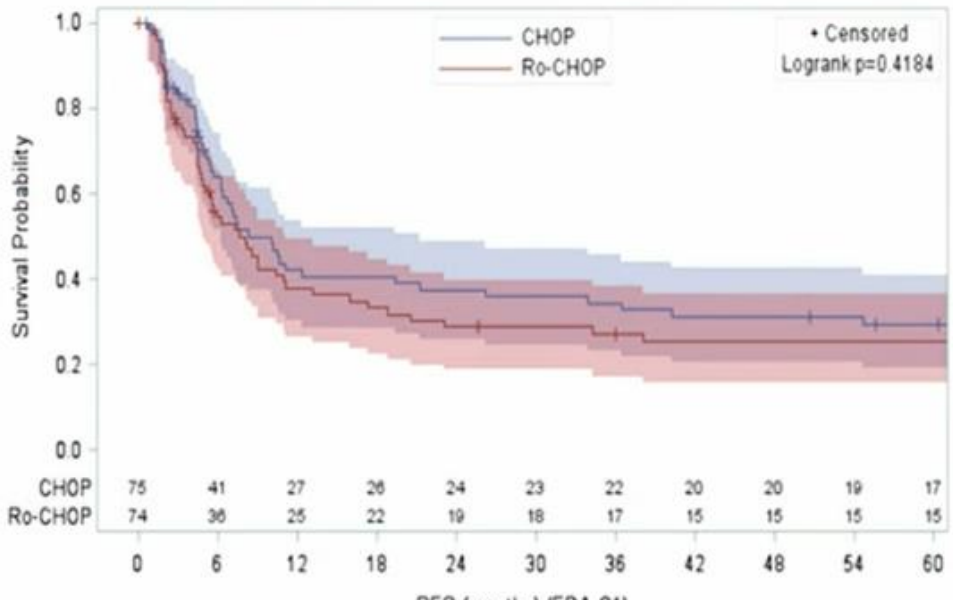
PFS in patients with PTCL-TFH (centrally reviewed) and patients with confirmed non-TFH diagnosis

PTCL-TFH



	No. of Subjects	Event	Censored	Median Survival
CHOP	98	72.4 % (71)	27.6 % (27)	10.6 (7.4 ; 14.9)
Ro-CHOP	103	63.1 % (65)	36.9 % (38)	19.5 (11.5 ; 44.4)

PTCL non-TFH



	No. of Subjects	Event	Censored	Median Survival
CHOP	75	64 % (48)	36 % (27)	8.3 (6.2 ; 21.3)
Ro-CHOP	74	70.3 % (52)	29.7 % (22)	8.1 (4.8 ; 11)

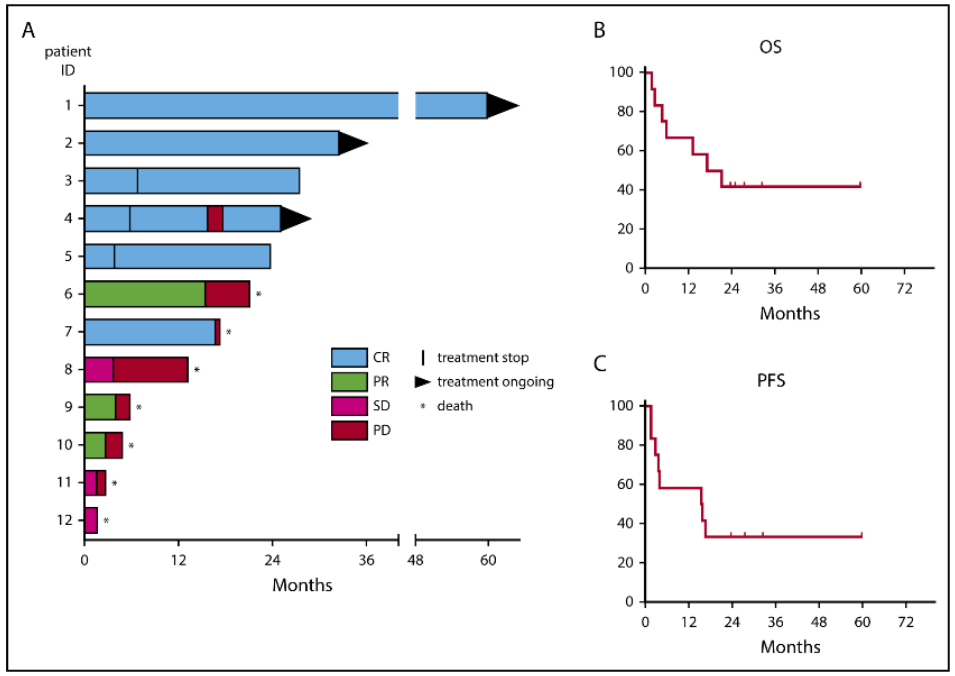
Other therapies in PTCL

- Hypomethylating agents
- EZH inhibitors
- Jak/STAT
- Pi3K

5-Azacitidine in T-Cell Lymphoma

- Treatment with 5-azacytidine induces a sustained response in patients with AITL

	N	CR	PR	ORR
PTCL	7	0	1	1/7 (14%)
AITL*	12	5	4	9/12 (75%)



- Lemonnier F, et al. *Blood.* 2018;132:2305-2309;

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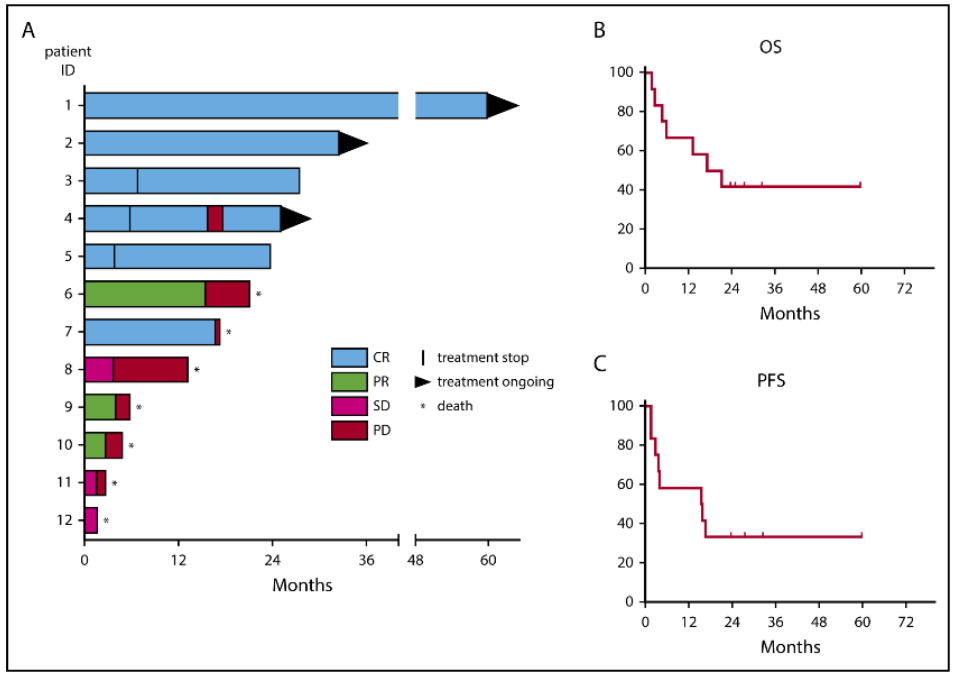

Oracle Study Oral AZA vs Investigators Choice

	CC-486 N=42
3 months (or PTD cycle 1-3)	
Overall response rate	**14 (33%)** [19.6%-49.5%]
Complete response rate	**5 (11.9%)** [4%-25.6%]
6 months (or PTD cycle 4-6)	
Overall response rate	**13 (31%)** [17.6-47.1%]
Complete response rate	**5 (11.9%)** [4%-25.6%]

- Lemonnier F, et al. *Blood.* 2018;132:2305-2309; Dupuis J, et al ASH 2022

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%

- 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 2021.

Oral Azacitidine (CC486) Plus CHOP
Efficacy and Safety

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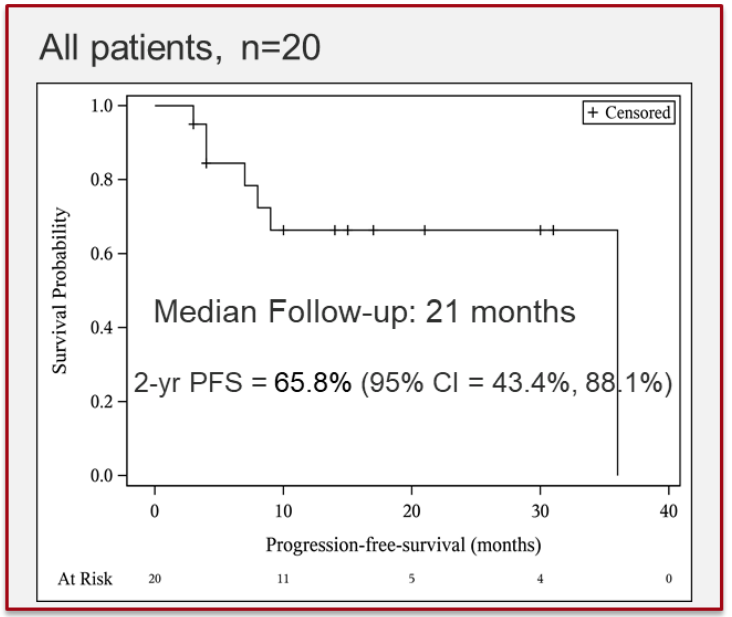
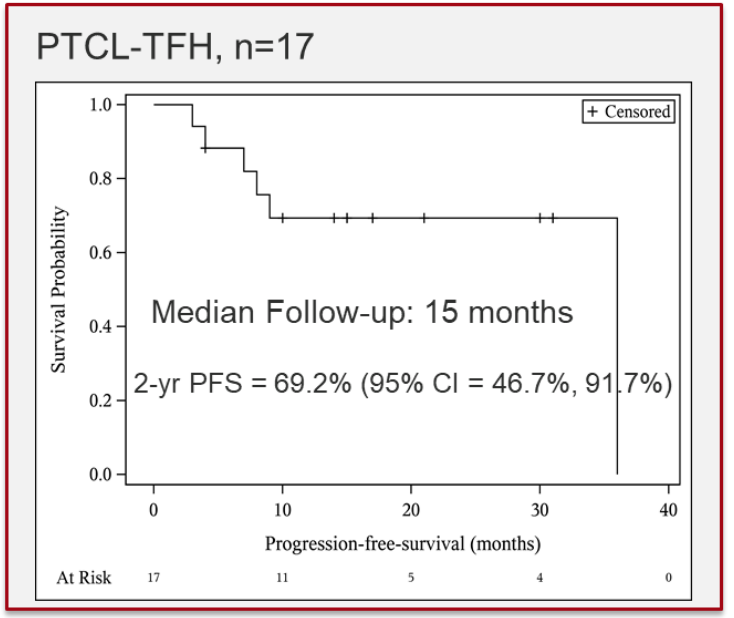
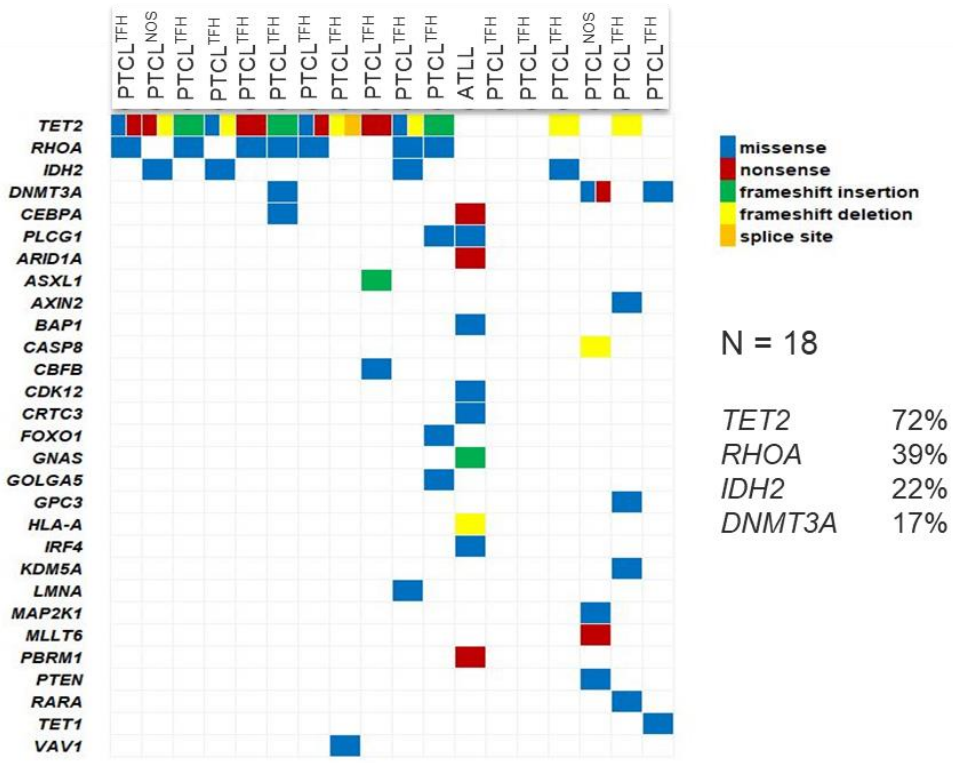




Ruan J, et al. ASH 2021.

Oral Azacitidine (CC486) Plus CHOP
Mutational Status

Genomic Mutational Analysis by NGS

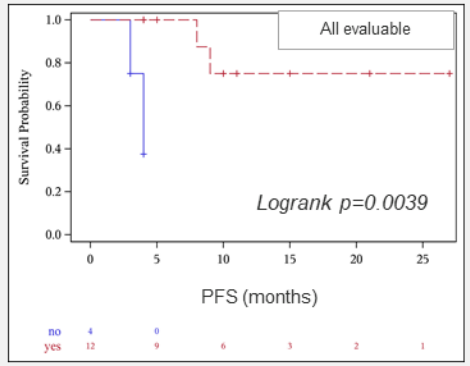


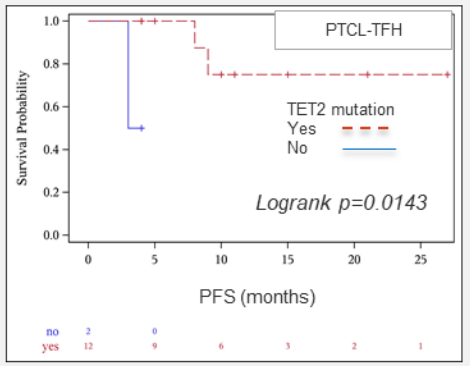
N = 18

TET2	72%
RHOA	39%
IDH2	22%
DNMT3A	17%

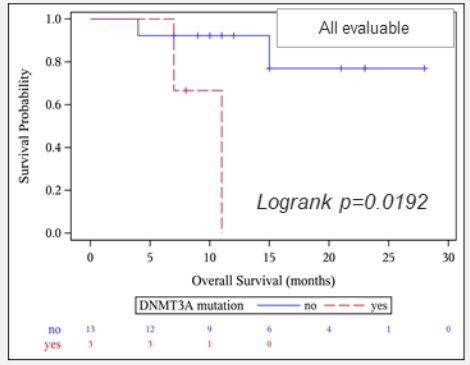
Impact of Mutational Status on Survival

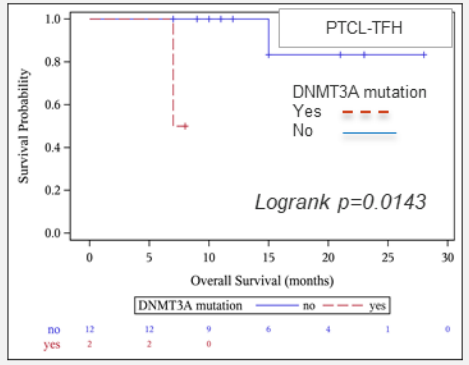
TET2 mutations correlate with favorable PFS





DNMT3A mutations correlate with adverse OS

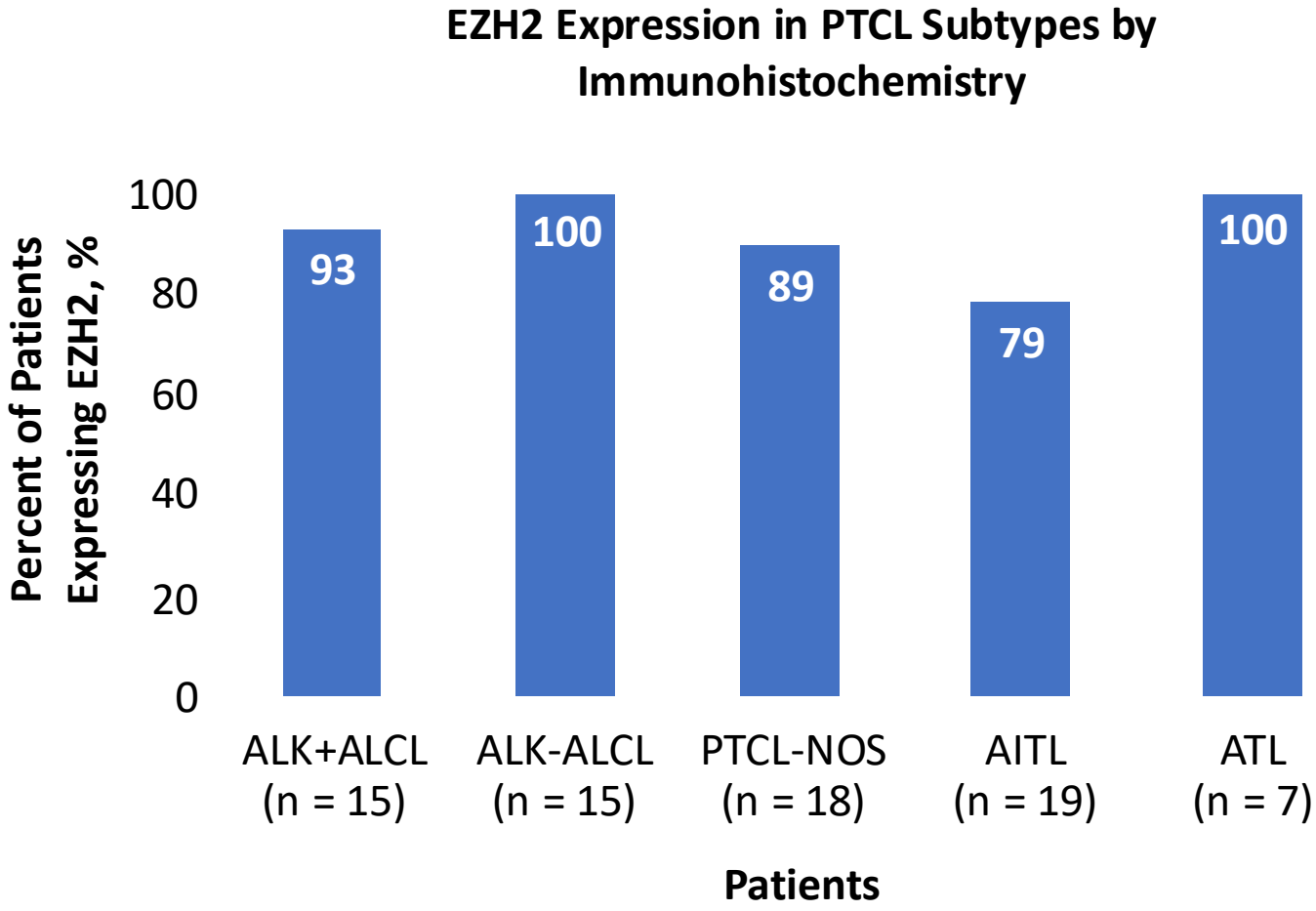




- Ruan J, et al. ASH 2020. Abstract 40.

Variation in EZH2 Expression Across PTCL Subtypes

- EZH2 is overexpressed in PTCL
- Expression of EZH2 correlates with a high tumor proliferation rate
- Can be associated with more aggressive disease and poor prognosis
- Gain if function mutations in TCL rare/not seen



Shi. Leukemia & Lymphoma. 2015;56:2087. Zhang. Oncol Letters. 2019;18:1415.

VALENTINE-PTCL01: global, multicenter, open-label, single-arm, phase 2 trial of valemetostat in R/R PTCLs

Eligibility Criteria

- ≥ 18 years
- Confirmed PTCL diagnosis (WHO 2016 classification[1])
- ECOG PS score ≤ 2
- ≥ 1 prior line of systemic therapy
  - Patients with ALCL received prior brentuximab vedotin treatment

R/R PTCL

N = 133

N = 119 with PTCL histology confirmed by central pathology

Valemetostat

200 mg/day

Continuous 28-day cycles until PD or unacceptable toxicity

Primary endpoint: ORR (CT-based BICR assessment; ≥ 10 months follow-up[b])

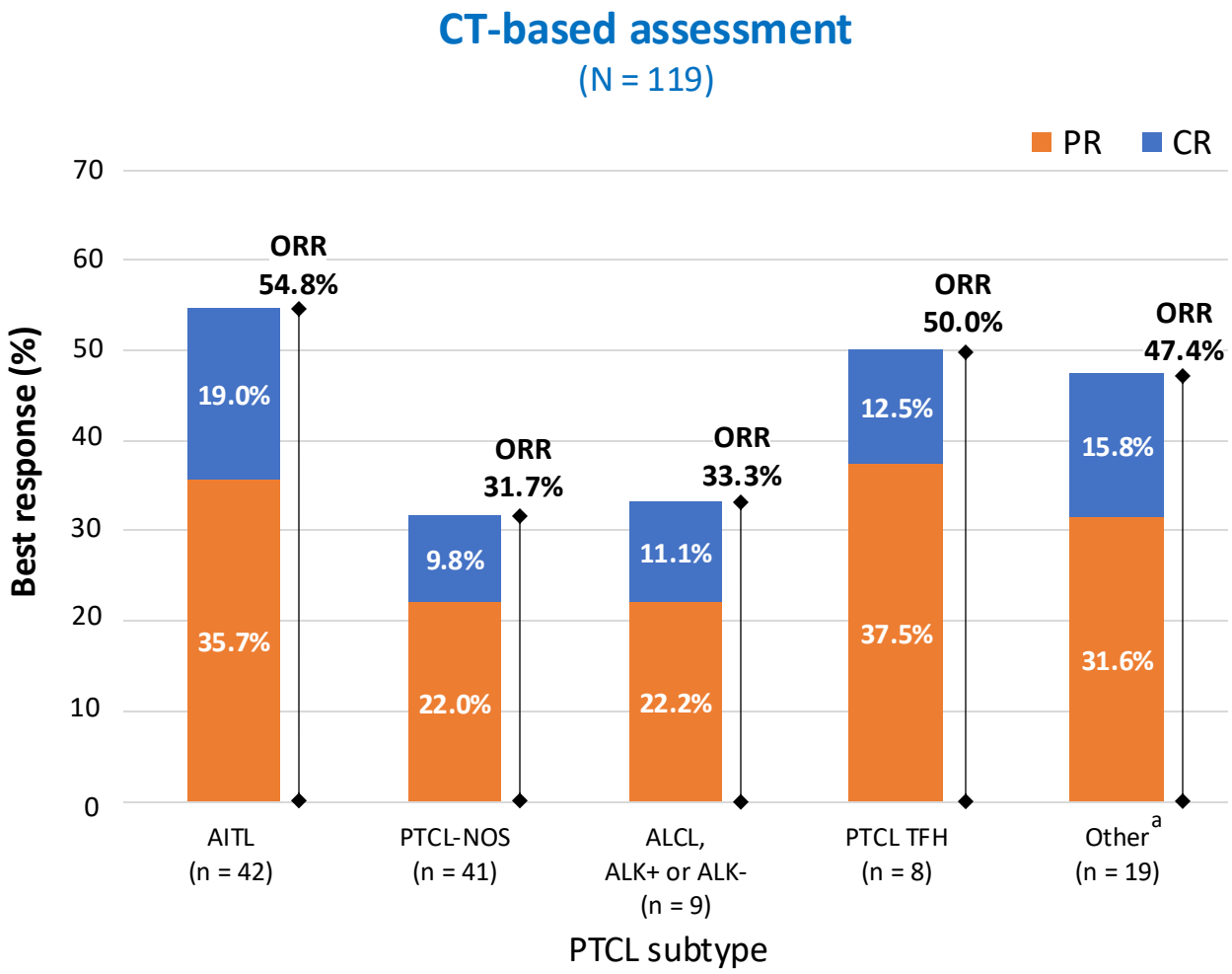
Key secondary endpoints: DOR, DOCR, CR rate, PR rate, PFS (CT-based BICR assessment and investigator assessment), OS, safety and tolerability

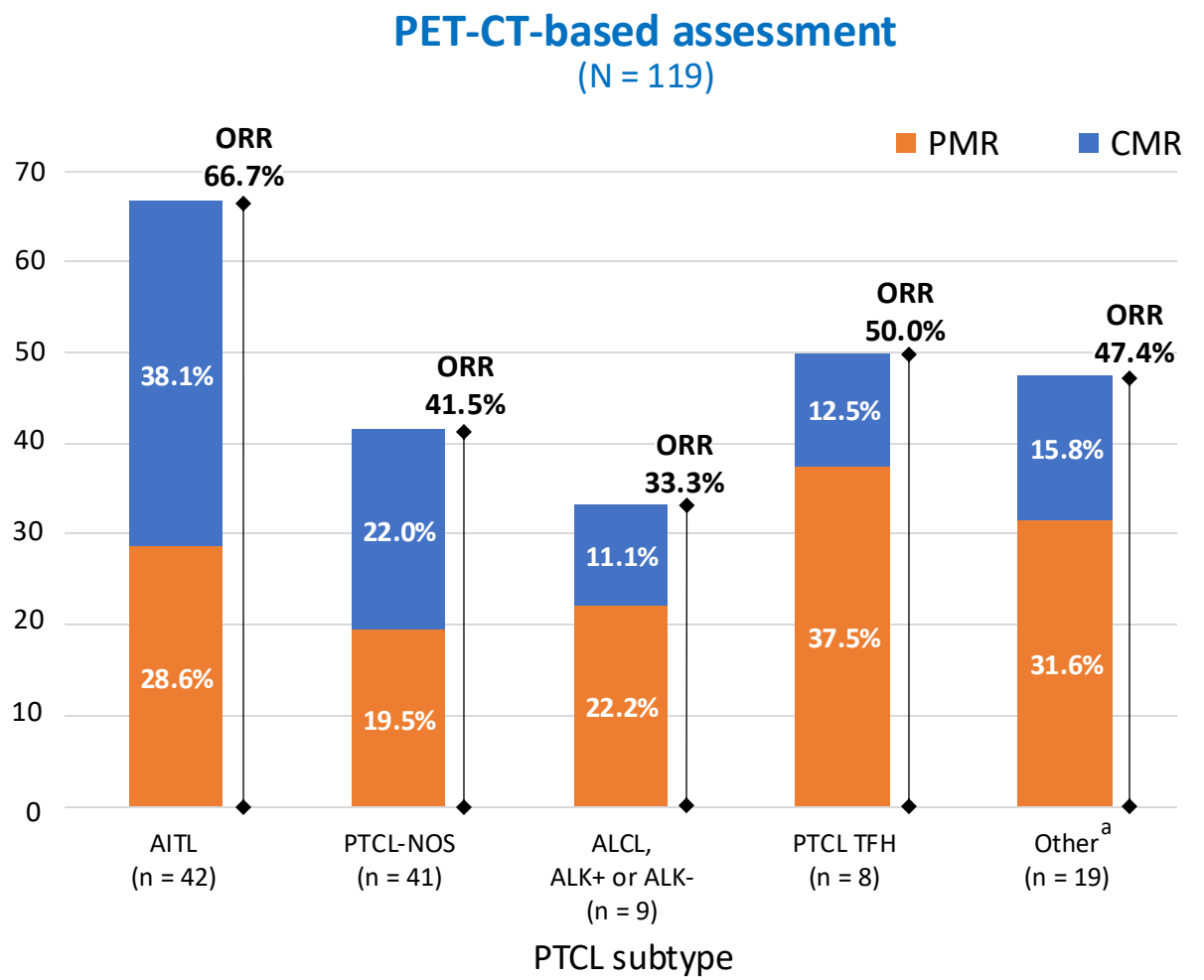
Key exploratory endpoint: PET-CT–based clinical response (BICR)

Lugano 2014 response criteria[2]

[a] PTCL subtypes included AITL, FTL, PTCL-TFH, PTCL-NOS, ALCL (ALK$^{+/-}$), EATL, MEITL, HSTL, PCGTL, or CD8^{+} PCAECyTCL; subtypes were determined prior to the initiation of study drug according to 2016 WHO classification.
[b] Primary analysis was planned at least 10 months after the first dose of the last enrolled patient.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CD, cluster of differentiation; CD8^{+} PCAECTCL, primary cutaneous CD8^{+} aggressive epidermotropic cytotoxic T-cell lymphoma; CR, complete response; CT, computed tomography; DOCR, duration of complete response; DOR, duration of response; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FTL, follicular T-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NOS, not otherwise specified; ORR, objective response rate; PCGTL, primary cutaneous gamma delta T-cell lymphoma; PD, progressive disease; PET, positron emission tomography; PR, partial response; PS, performance status; TCL, T-cell lymphoma; TFH, T follicular helper; WHO, World Health Organization.1. Swerdlow SH, et al. *Blood* 2016;127:2375–2390. *2.* Cheson BD, et al. *J Clin Oncol* 2014;32:3059–3068.

Responses were observed across all PTCL subtypes





Data cutoff: May 5, 2023.

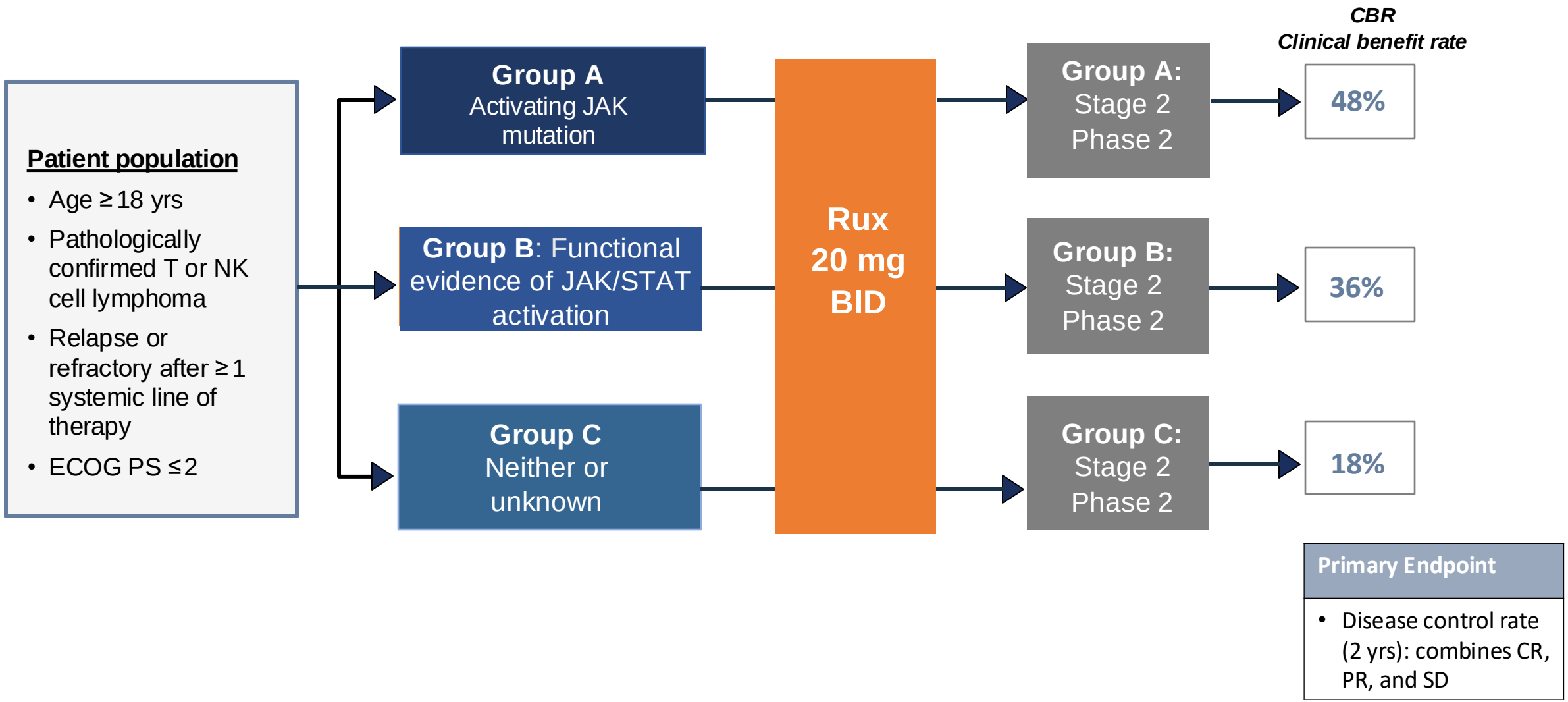
[a] Other TCLs include 3 patients with FTL, 1 with **PCGTL**, 1 with **CD8+ PCAECTCL**, 1 with MEITL, and 13 with other eligible, but undetermined PTCL subtypes.

Other therapies in PTCL

- Hypomethylating agents
- EZH inhibitors
- Jak/STAT
- Pi3K

Ruxolitinib: Phase 2 Multicenter Biomarker-Driven Study

Targeting JAK1/2 Inhibition in R/R T-Cell Lymphomas



Moskowitz AJ, et al. *Blood.* 2021;138(26):2828-2837. ClinicalTrials.gov. NCT02974647.

Ruxolitinib Efficacy: Phase 2 Multicenter Biomarker-Driven Study *Targeting JAK1/2 Inhibition in R/R T-Cell Lymphomas*

Response by Cohort

Cohorts	Total treated, n	Total evaluable for response, n	ORR n (%)	CBR n (%)
Cohort 1	21	21	**7 (33%)**	10 (48%)
Cohort 2	15	14	**4 (29%)**	5 (36%)
Cohort 3	17	17	**2 (12%)**	3 (18%)
Total	53	52	**13 (25%)**	18 (35%)
P (cohorts 1 & 2 versus 3)			***P*=0.2**	*P*=0.073

Response by Subtype

Subtype	Evaluable for response, n	ORR n (%)	CBR n (%)
PTCL-NOS	11	**2 (18%)**	2 (18%)
T-PLL	8	**3 (38%)**	4 (50%)
AITL/TFH	9	**3 (33%)**	4 (44%)
T-LGL	5	**2 (40%)**	4 (80%)
ALCL	4	**1 (25%)**	1 (25%)
ATLL	3	**0**	0
CTCL	7	**1 (14%)**	1 (14%)
G/D TCLs	4	**1 (25%)**	1 (25%)
SPTCL	1	**0**	1 (100%)

Moskowitz AJ, et al. *Blood*. 2021;138(26):2828-2837

Golidocitinib Efficacy in JAKPOT08

A Non-Randomized, Single Arm, Multinational, Phase 2 Trial for R/R PTCL

	n = 88	
Tumor response	**By IRC**	**By investigator**
ORR, n (%)	39 (44.3)	33 (37.5)
Overall response, n (%)		
Complete response	21 (23.9)	11 (12.5)
Partial response	18 (20.5)	22 (25.0)
Stable disease	17 (19.3)	17 (19.3)
Progressive disease	20 (22.7)	27 (30.7)
Not evaluable	12 (13.6)	11 (12.5)

Data cut-off date: August 31, 2023

Song Y, et al. *Lancet Oncol*. 2024;25(1):117-125.

Golidocitinib Efficacy in JAKPOT08

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Histology subtypes*	Total number of subjects, n** (%)	ORR*** n (%)	CRR*** n (%)
PTCl-NOS	50 (56.8)	23 (46.0)	14 (28.0)
AITL	16 (18.2)	9 (56.3)	4 (25.0)
ALCL	10 (11.4)	1 (10.0)	0
NKTCL	3 (3.4)	2 (66.7)	1 (33.3)
Others	9 (10.2)	4 (44.4)	2 (22.2)

Song Y, et al. *Lancet Oncol*. 2024;25(1):117-125.

Duvelisib Phase 2:

Outcome by Subtype	PRIMO-EP (N=101)*
ORR by IRC, n (%) [95% CI]	**49 (48.5) [38.8–58.3]**
PTCL, NOS	25/52 (48.1)
AITL	20/30 (66.7)
ALCL	2/15 (13.3)
Other#	2/4 (50.0)

Zinzani et al. EHA 2022

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Outcome by Subtype	PRIMO-EP (N=101)*
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PTCL, NOS	25/52 (48.1)
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Other#	2/4 (50.0)

CR by Subtype	PRIMO-EP (N=101)*
Complete response (CR)	**34 (33.7)**
PTCL, NOS	14/52 (26.9)
AITL	16/30 (53.3)
ALCL	2/15 (13.3)
Other#	2/4 (50.0)

Zinzani et al. EHA 2022

Dual-targeted therapy with ruxolitinib plus duvelisib for T cell lymphoma

Efficacy

Histology	n	ORR (n)	CRR (n)	PRR (n)
All patients	49	45% (22)	22% (11)	22% (11)
PTCL-NOS	13	31% (4)	15% (2)	15% (2)
AITL/TFH	14	79% (11)	64% (9)	14% (2)
ALK- ALCL	4	0%	-	-
ALK+ ALCL	1	0%	-	-
T-PLL	5	60% (3)	-	60% (3)
T-LGL	3	67% (2)	-	67% (2)
ATLL	1	0%	-	-
MEITL	1	0%	-	-
CTCL	7	29% (2)	-	29% (2)

Moskowitz et al ASH 2024

Ruxolitinib plus duvelisib: Efficacy by JAK/STAT activation

Cohort	n	ORR (n)	CRR (n)	PRR (n)
Cohort 1: JAK/STAT activation	32	53% (17)	25% (8)	28% (9)
Cohort 2: No JAK/STAT activation	17	29% (5)	18% (3)	12% (2)
		p=0.14		

TFH lymphomas (n=12 assessed for pSTAT3)	n	ORR (n)	CRR (n)	PRR (n)
pSTAT3 overexpression	8	100% (8)	75% (6)	25% (2)
No pSTAT3 overexpression	4	25% (1)	25% (1)	0
		p=0.02		

T-PLL (ORR 60%)

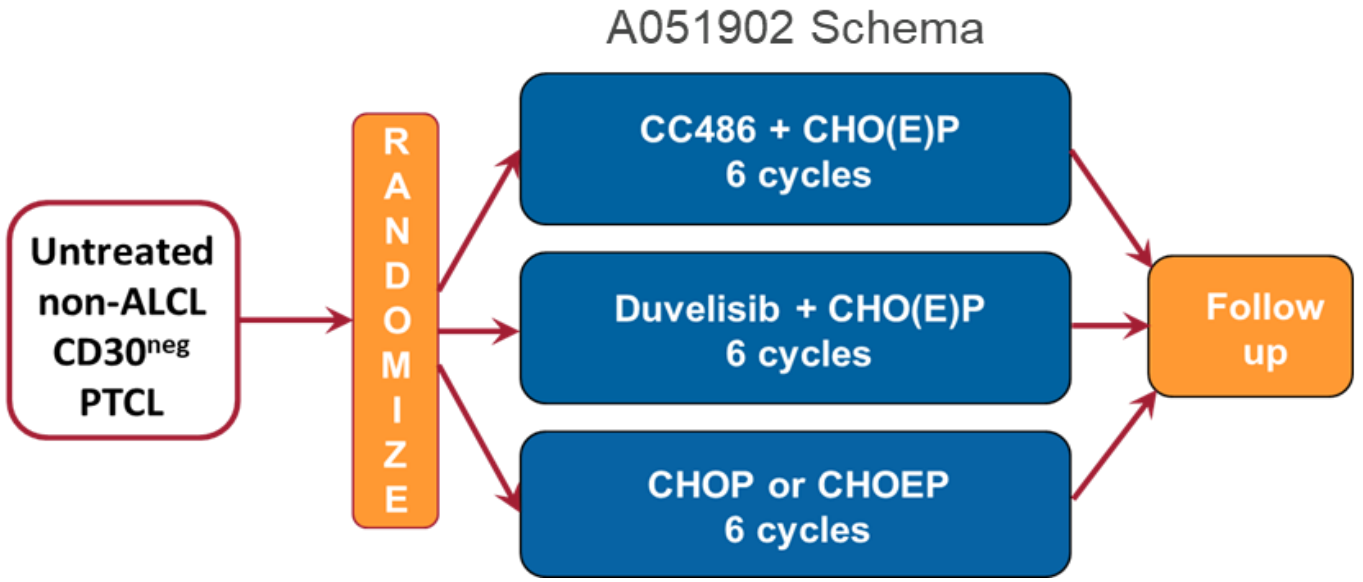
JAK3 mutations present in all 5 patients

Additionally: JAK2 fusion (n=1) and TYK2 fusion (n=1)

Incorporation into Upfront Trial

Alliance

- Phase II study of adding duvelisib or CC-486 to SOC for PTCL. NCT04803201



PI: Mehta -Shah

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Immune Therapies in PTCL

- Allogeneic SCT is potentially curative in relapsed setting
- Many strategies with safety, efficacy, role TBD
- T-cell Checkpoint inhibitors
  - Subtype specific responses
  - NK, MF/SS
  - Risk of hyper-progression and lack of predictors precludes wider use
- CD47 Strategies
  - Combination Studies ongoing (Magrolimab + Mogamulizumab in CTCL)
- CAR
  - CART-Early studies CD5, 7, 30, 37, 4, CCR4, TCRB1, others
  - ? Need for allo backup
  - Other cell types/sources
  - Allo-T, NK, Myeloid
- Bi-specifics
  - CD30, PD-1

Peripheral T-cell lymphoma

- PTCL remains heterogeneous and poor prognosis, however:
  - Cures for some with combination chemotherapy
  - Prognostic factors can impact decision making/individualizing therapy
    - Pretreatment-Subtype, Mutational profile?
    - On treatment-interim response
- Attempts to incorporate into combination/upfront/curative therapy
    - Active agents
    - Enriched population + minimize toxicity
    - Subtype specific strategies: Disease subtypes, molecular subtypes, other vulnerabilities
- Newer Approaches
  - Epigenetic therapies, signaling targets, immune therapy
  - Likely also need subtype specific approaches

Treatment of the common nodal peripheral T-cell lymphomas (PTCLs) is evolving