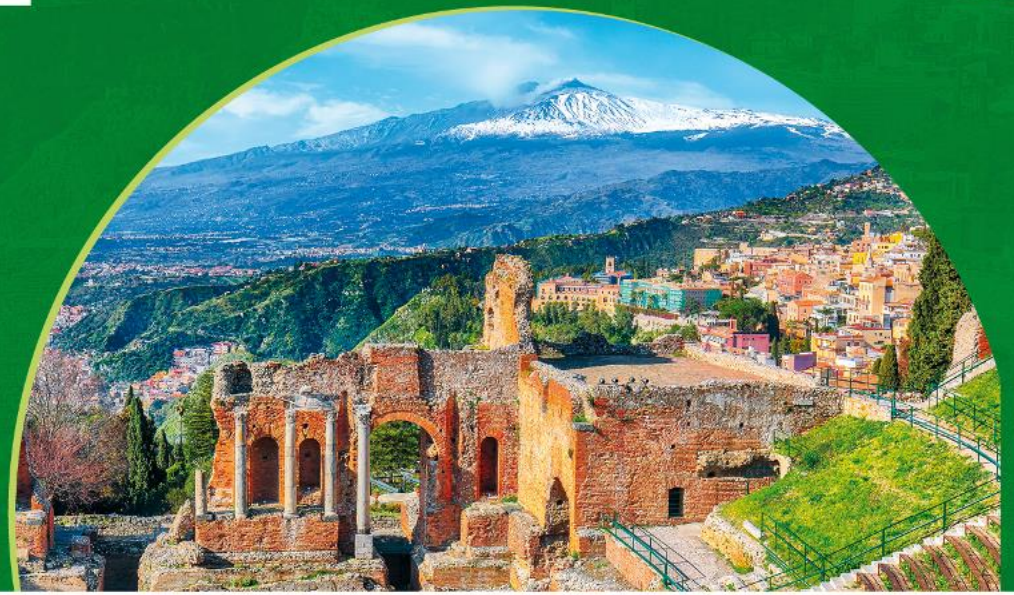
CORSO EDUCAZIONALE COMMISSIONE ANZIANI

XIII EDIZIONE

Giardini Naxos - Marriott Delta Hotels
17-18 aprile 2026

FONDAZIONE ITALIANA LINFOMI



Terapia dei linfomi T sistemici nel paziente anziano

Cinzia Pellegrini
IRCSS Policlinico S.Orsola-Malpighi Bologna

Disclosure Cinzia Pellegrini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche							**x**
Gilead							**x**
Takeda						**x**	
Janssen-Cilag						**x**	
Abbvie							**x**
Be-One							**x**

PTCL – Background – Focus on Elderly population

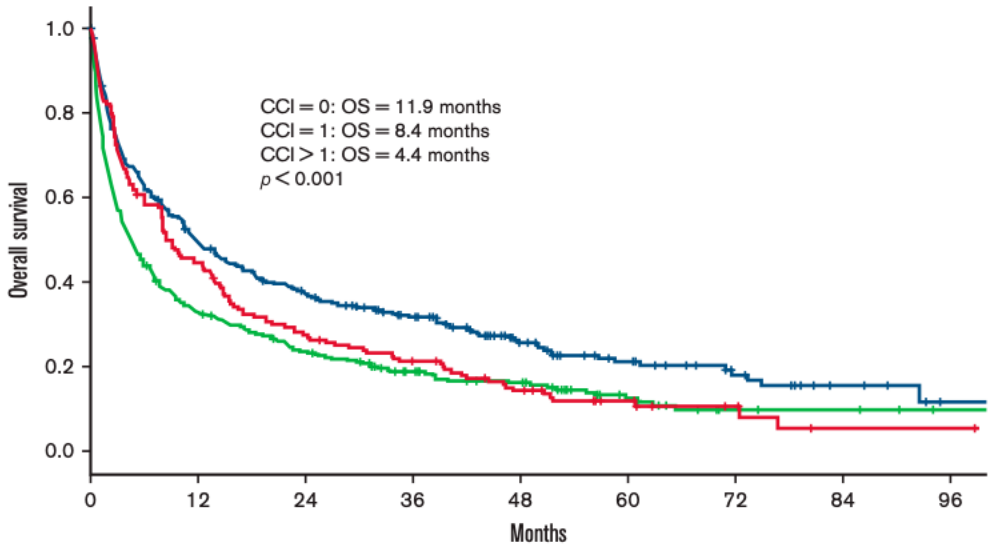
- PTCLs are **rare** and very **heterogenous** lymphoproliferative disorders accounting for 15% of all NHLs

- There are more than 30 different subtypes of PTCLS (WHO 2022; ICC 2022). **In elderly patients PTCL-NOS ~50%; AITL ~25%; ALCL ~14%;**

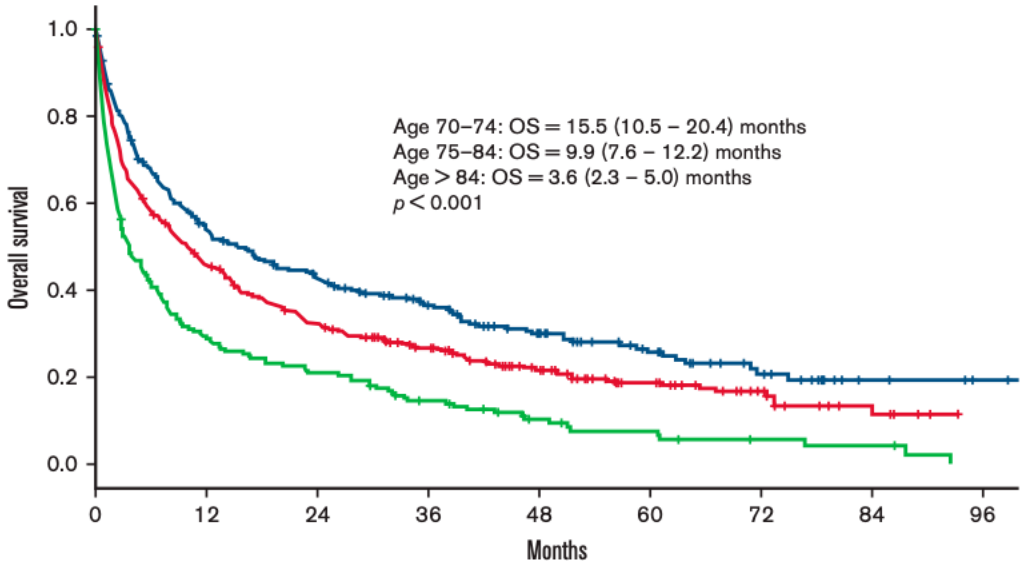
- Impact of **comorbidity** in older patients with peripheral T-cell lymphoma impact OS;

Mead et al, Blood Advances 2022

Impact of comorbidity in older patients with peripheral T-cell lymphoma: an international retrospective analysis of 891 patients



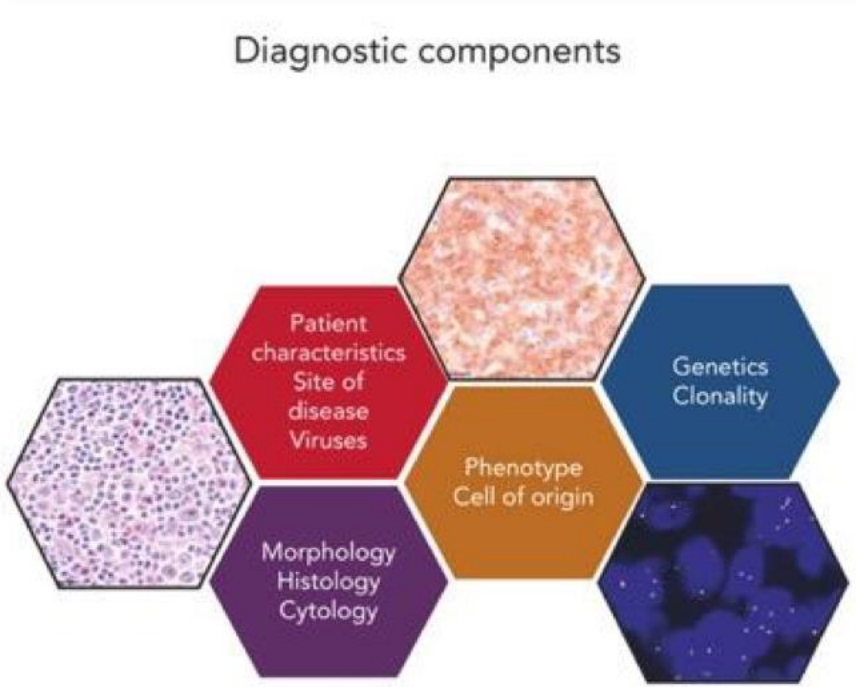
OS in PTCL according to CCI group

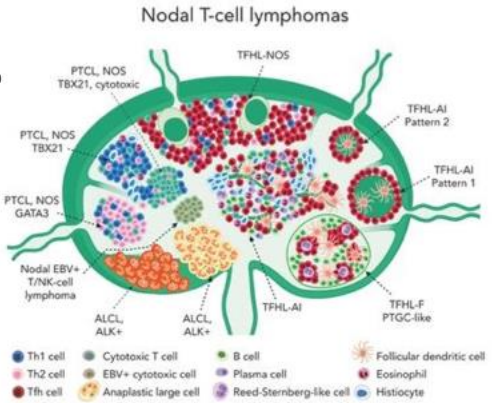


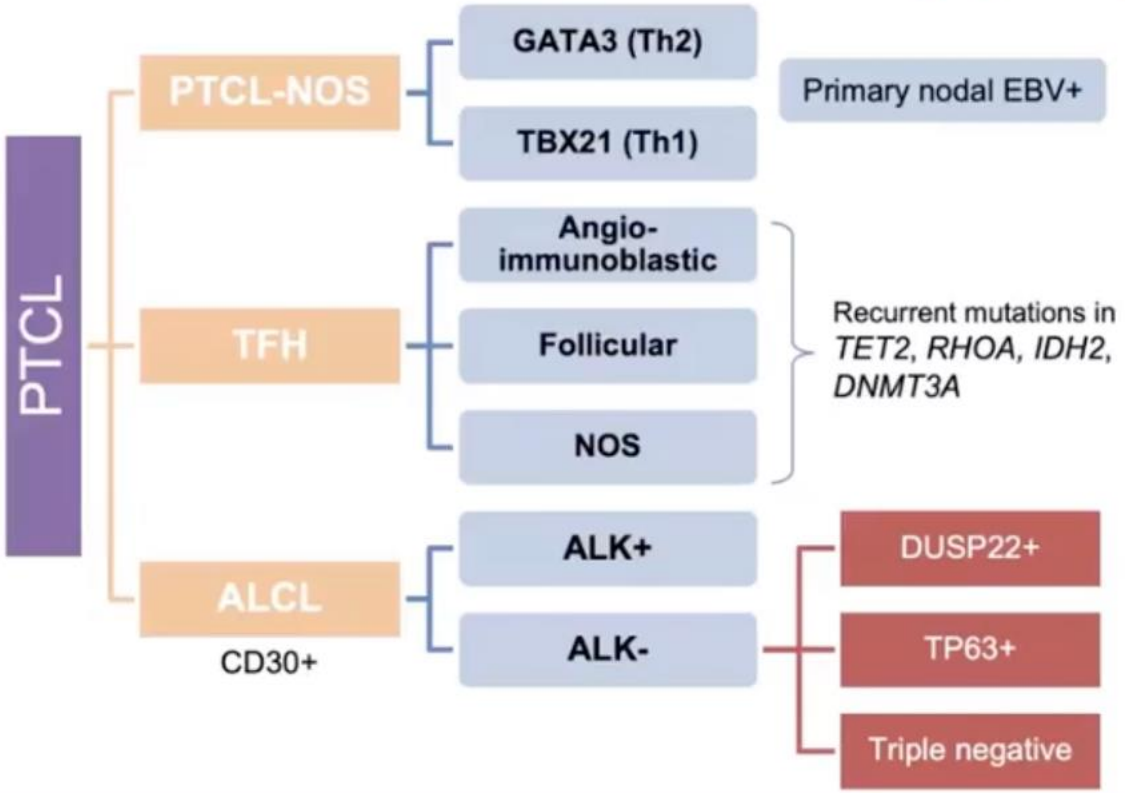
OS in patients with PTCL according to age

Mead et al, Blood Advances 2022

Diagnosis and classification of Nodal TCL







Leval L. et al. Blood 2024

ECHELON-2 Study Design (NCT01777152)

Double-blind, double-dummy, randomized, placebo-controlled, active-comparator Phase 3 study[1]

Key Eligibility Criteria

- Age ≥18 years
- CD30-expression (≥10% cells)
- Previously-untreated PTCL:
  - Systemic ALCL (sALCL)* including ALK+ sALCL with IPI ≥2, ALK– sALCL
  - PTCL-NOS, AITL, ATLL, EATL, HSTL

Stratification Factors

- IPI score (0–1 vs 2–3 vs 4–5)
- Histologic subtype (ALK+ sALCL vs all other histologies)

R (1:1)

n=226

A+CHP
(A) BV 1.8 mg/kg +
(C) cyclophosphamide 750 mg/m² +
(H) doxorubicin 50 mg/m² +
(P) prednisone 100 mg (Days 1–5)
Q3W for 6 to 8 cycles

n=226

CHOP
(C) cyclophosphamide 750 mg/m² +
(H) doxorubicin 50 mg/m² +
(O) vincristine 1.4 mg/m² +
(P) prednisone 100 mg (Days 1–5)
Q3W for 6 to 8 cycles

EOT PET

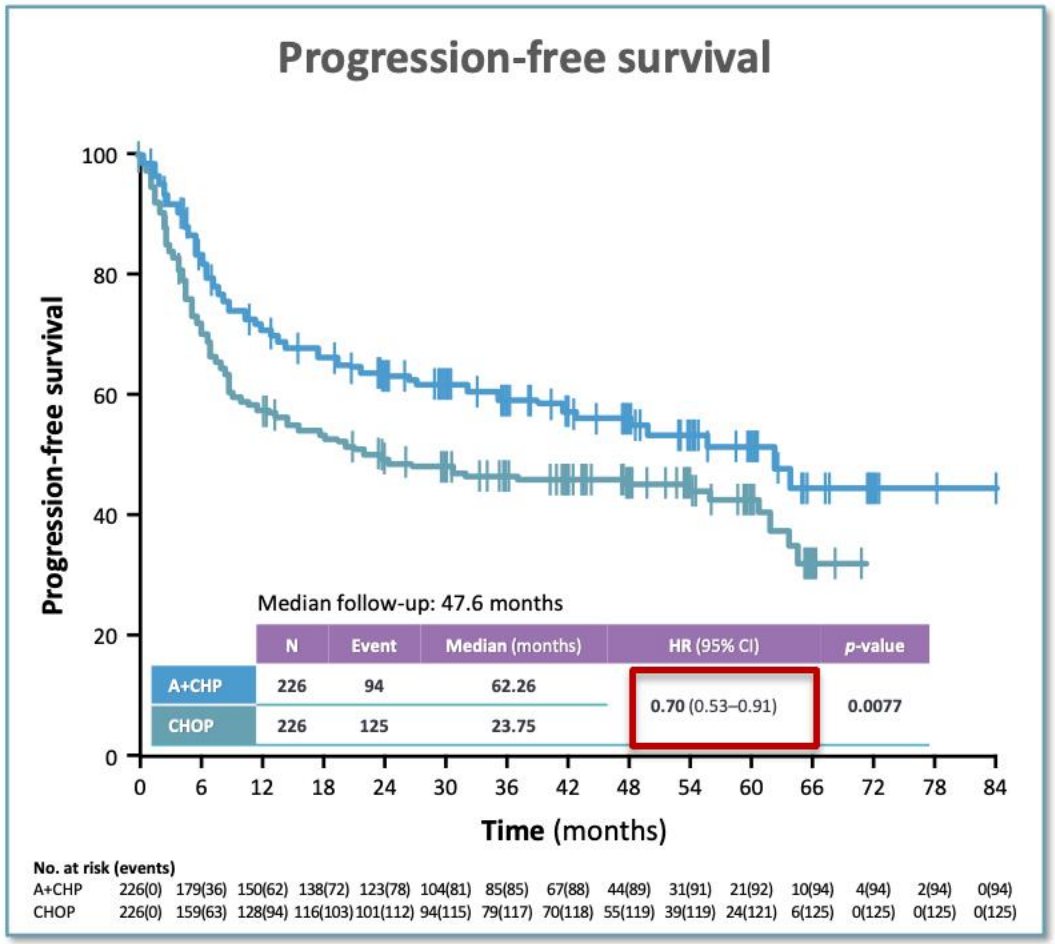
Enrollment: Jan 2013–Nov 2017; Data cutoff: 15 Aug 2018

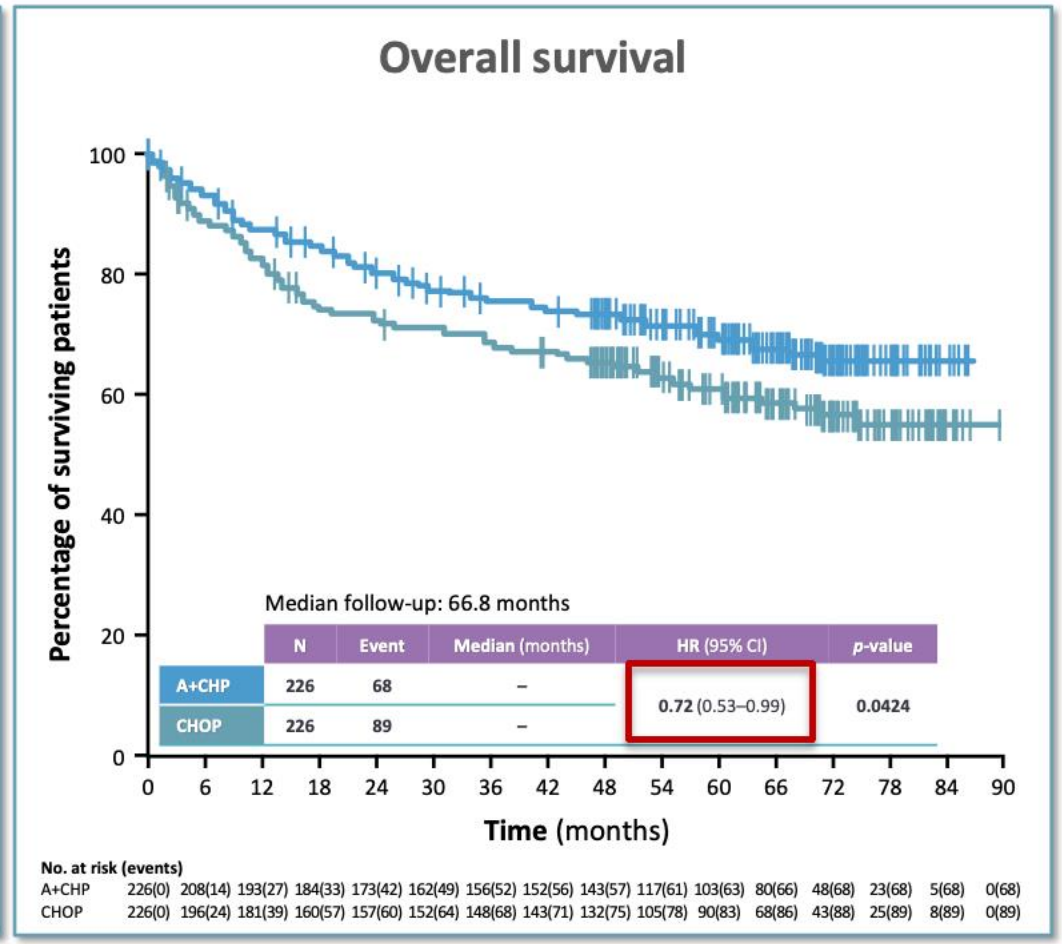
*targeting 75% (±5%) ALCL

A+CHP, brentuximab vedotin + cyclophosphamide doxorubicin prednisone; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukaemia/lymphoma; BV, brentuximab vedotin; CD30, cluster of differentiation 30; CHOP, cyclophosphamide doxorubicin vincristine prednisone; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; HSTL, hepatosplenic T-cell lymphoma; IPI, International Prognostic Index.

Horwitz S. et al Lancet 2019

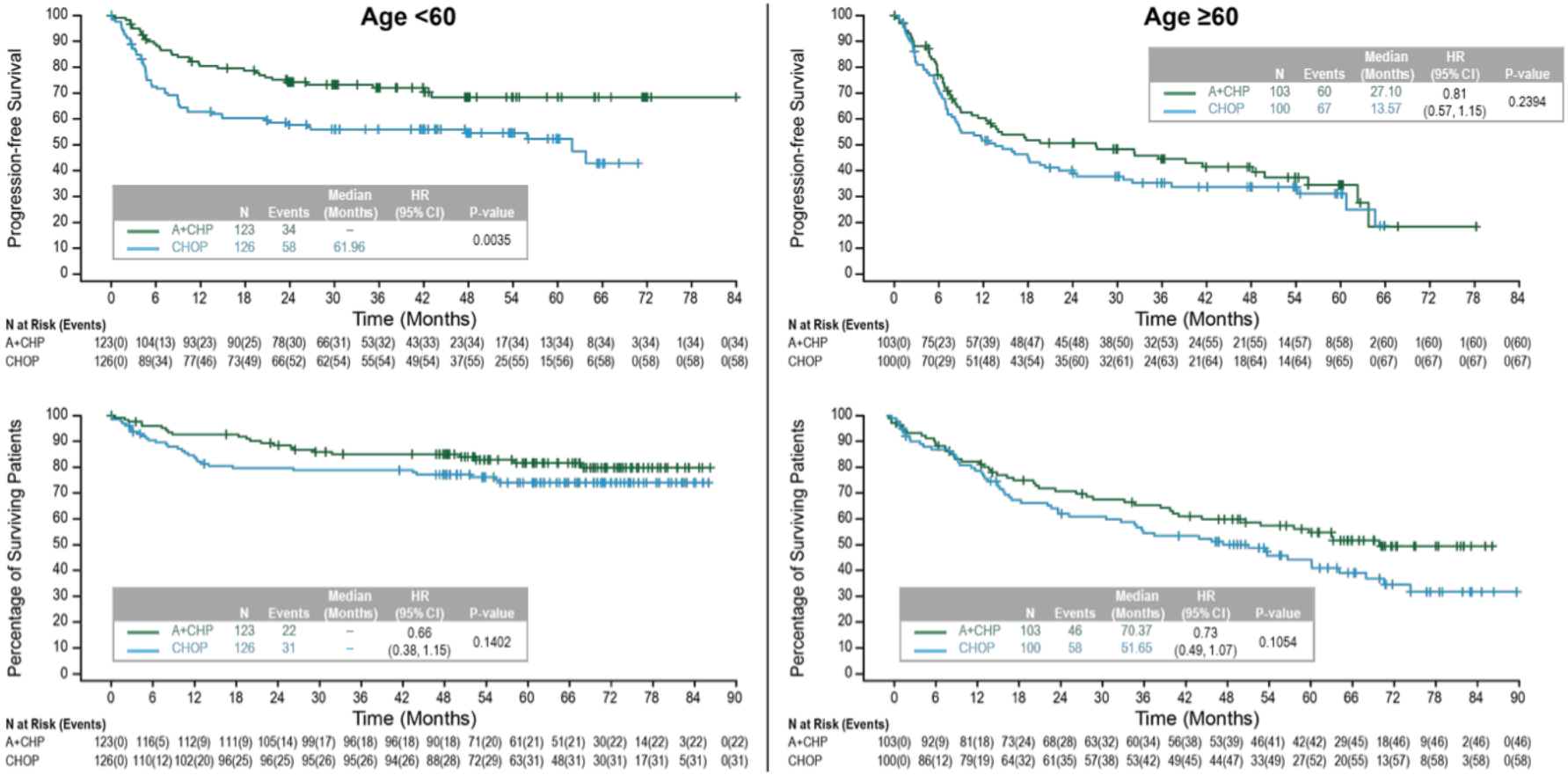
PFS and OS - 5-Year Results





Horwitz S. et al Annals of Oncology 2021

Summary of OS and PFS per Investigator (by age within arm)



Horwitz S. et al. Oral Presentation # 135 ASH 2021

In sALCL patients, A+CHP safety profile was comparable to or better than CHOP, regardless of age

	A+CHP, n (%)		CHOP, n (%)	
Patients by age	**Grade ≥3**	**Fatal**	**Grade ≥3**	**Fatal**
All patients[3] (A+CHP n=160, CHOP n=154)	**94** (59)	**4** (3)	**98** (64)	**15** (10)
Patients <60 years[2] (A+CHP n=99, CHOP n=100)	**54** (55)	**1** (1)	**60** (60)	**7** (7)
Patients ≥60 years[2] (A+CHP n=61, CHOP n=54)	**40** (66)	**3** (5)	**38** (70)	**8** (15)

Febrile neutropenia occurred more often in older patients in both treatment arms and was successfully mitigated with G-CSF primary prophylaxis[1,2]

Aes by age

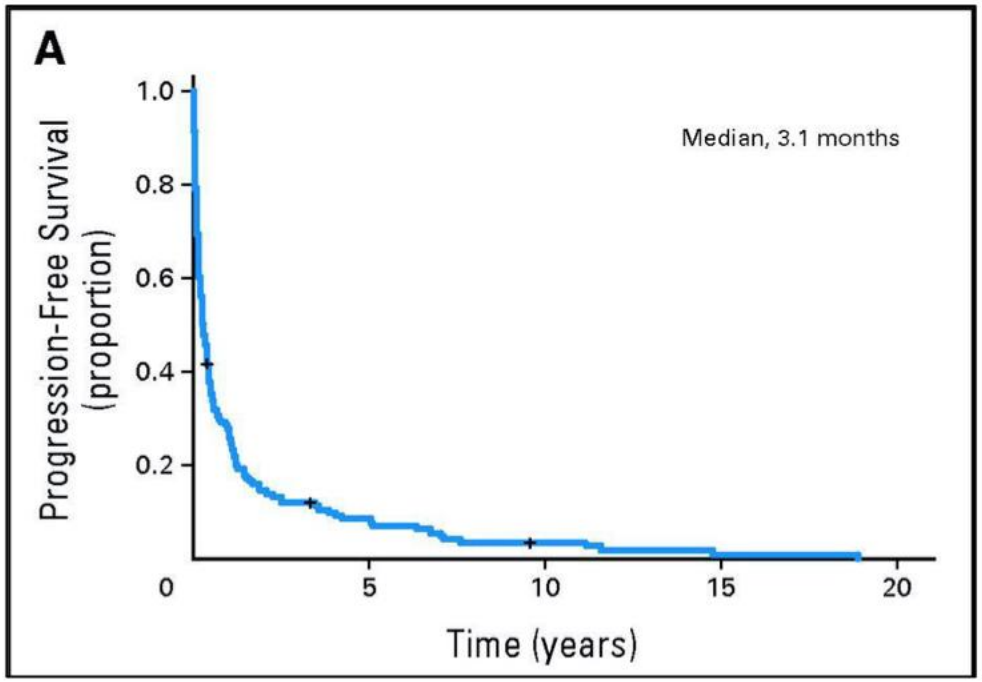
	Aged <60 years		Aged ≥60 years	
	BV + CHP (n=120)	CHOP (n=126)	BV + CHP (n=103)	CHOP (n=100)
Pre-existing PN, n (%)	8 (7)	8 (6)	16 (16)	16 (16)
Treatment-emergent PN, n (%)	63 (53)	68 (54)	54 (52)	56 (56)
Grade 2	14 (12)	8 (6)	19 (18)	18 (18)
Grade 3	4 (3)	8 (6)	4 (4)	2 (2)
Grade 4	0	0	1 (1)	0
Complete resolution of PN*, n (%)	47 (75)	48 (71)	24 (44)	34 (61)
Improvement of PN†, n (%)	3 (5)	8 (12)	10 (19)	7 (13)
Neutropenia	50 (42)	46 (37)	35 (34)	39 (39)
Febrile neutropenia	11 (9)	11 (9)	30 (29)	22 (22)

*Resolution was defined as resolved/recovered with or without sequelae, or return to baseline or lower severity as of the latest assessment for pre-existing events.
†Improvement was defined as decrease by ≥1 grade from the worst grade, with no higher grade thereafter. Patients with improvement in any event at least by one event and the date of improvement was before last follow-up date. Subjects with all events resolved were excluded.

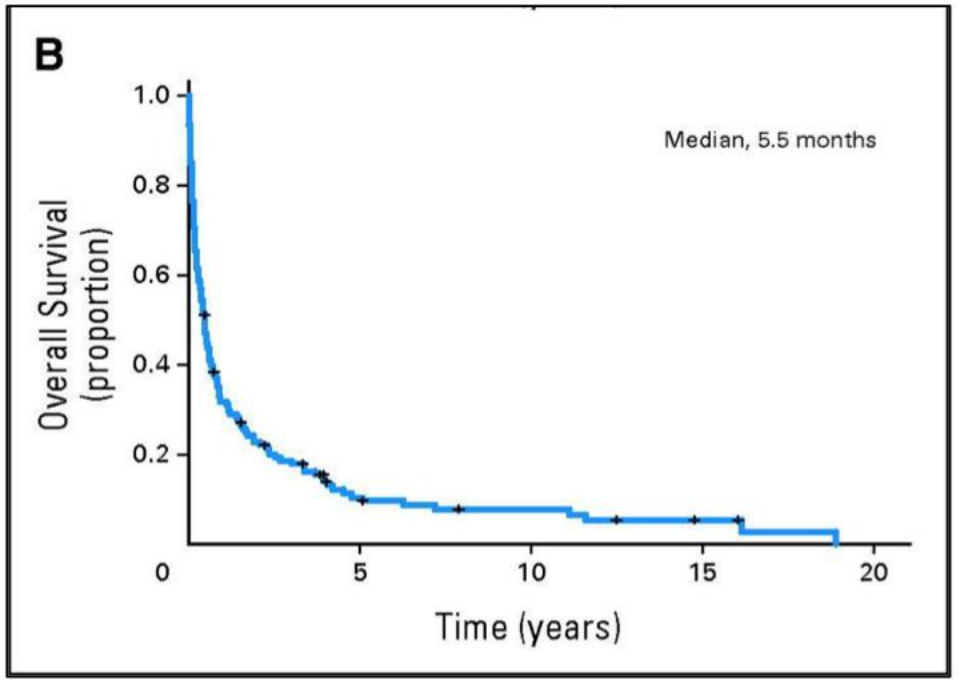
Horwitz S. et al. Oral Presentation # 135 ASH 2021

Relapsed/refractory

Patients With Relapsed or Refractory Disease Have an Especially Poor Prognosis



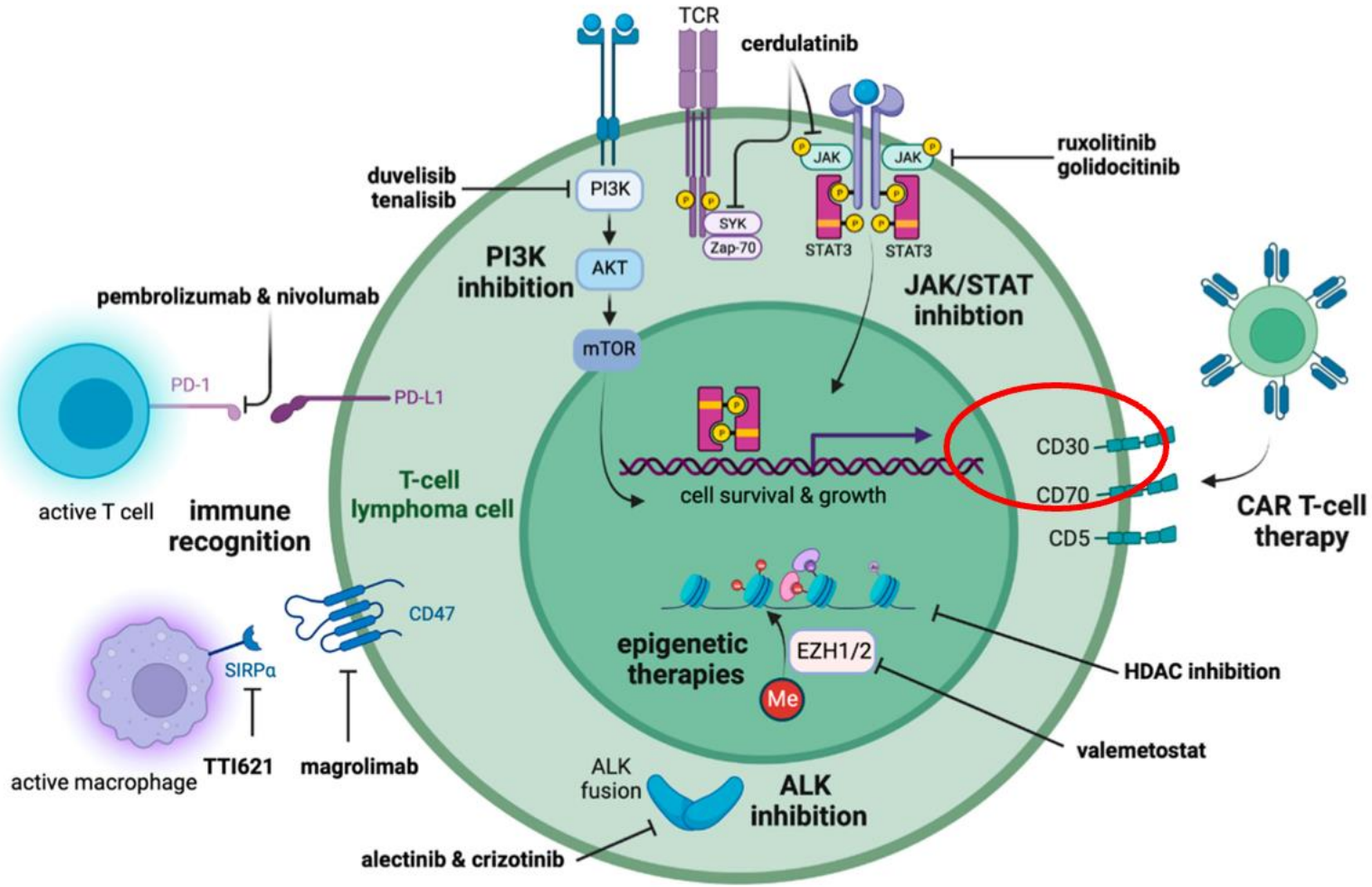
PFS at First Relapse:
3.1 Months



OS at First Relapse:
5.5 Months

Mak et al. 2013

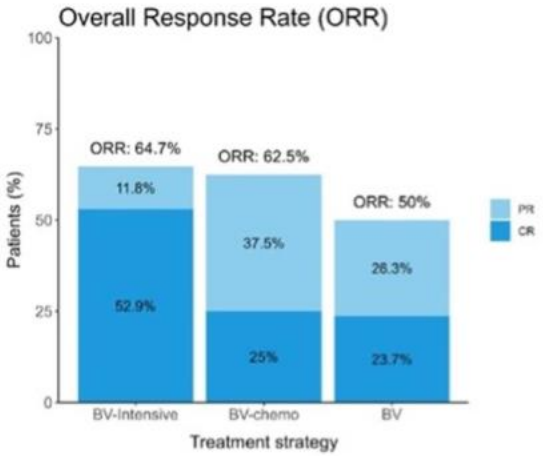
Targhets from biology to therapy

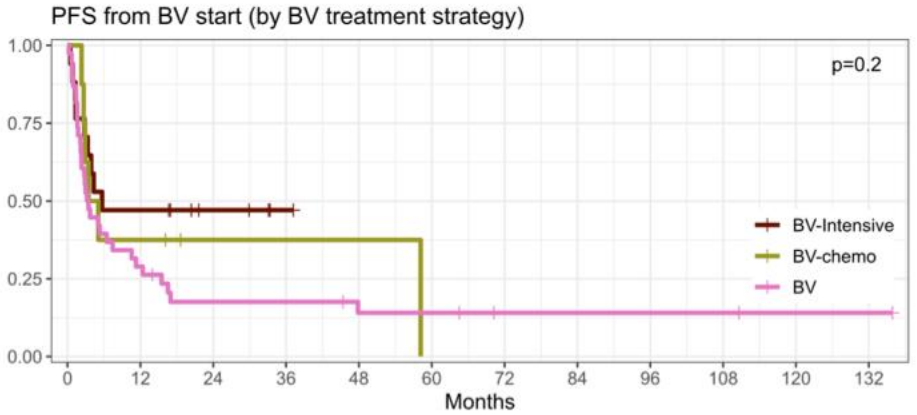


Robert Stuver and Alison J. Moskowitz Cancers 2023, 15, 589

Brentuximab vedotin (BV) in Relapsed/Refractory Peripheral T-cell Lymphomas (r/r PTCL): a multicenter retrospective study

Characteristic	BV N = 38	BV-chemo N = 8	BV-Intensive N = 17
Median age	56 (30 - 77)	57 (41 - 69)	50 (19 - 71)
Male Gender	19 (50%)	5 (63%)	13 (76%)
Stage III/IV	32 (84%)	8 (100%)	15 (88%)
IPI ≥ 3	14 (38%)	6 (75%)	6 (35%)
Subtype			
AITL/TFH	14 (37%)	7 (88%)	8 (47%)
ALCL	15 (39%)	1 (13%)	6 (35%)
PTCL, NOS	9 (24%)	0 (0%)	3 (18%)
CR after 1° line	19 (50%)	3 (38%)	2 (12%)
Median BV cycles	4.0 (1.0 - 18.0)	5.0 (1.0 - 19.0)	4.0 (1.0 - 4.0)
Best response to BV			
CR	9 (24%)	2 (25%)	9 (53%)
PR	10 (26%)	3 (38%)	2 (12%)
PD	19 (50%)	3 (38%)	6 (35%)





- 47% of patients able to proceed to ASCT in BV-intensive cohort

Ivan Dlouhy, et al. Abstract PS1935. Presented at the 2025 European Hematology Association Annual Meeting | June 12-15, 2025 | Milan, Italy

BV plus Bendamustine in r/r PTCL: a multicenter retrospective study

- A total of 81 patients were assessable for response (1 patient was lost to follow-up).
- The median number of cycles was **4** (range, 1-7).
- 27 patients received <3 cycles (32.9%), mainly owing to disease progression (21 patients, 77.8%), transplantation (2 patients, 7.4%), toxicity (2 patients, 7.4%), and loss of follow-up (2 patients, 7.4%).
- **22 patients ≤70 years (30%) received SCT** after BBv (16 allogeneic and 6 autologous).

Best Response	Pts (n = 81)	%
ORR	55	**68**
CR	40	49
PR	15	19
SD	2	2
PD	24	30
DoR (months)		
Median	15.4	
Range	0.6-50.2	

Best Response by subtype

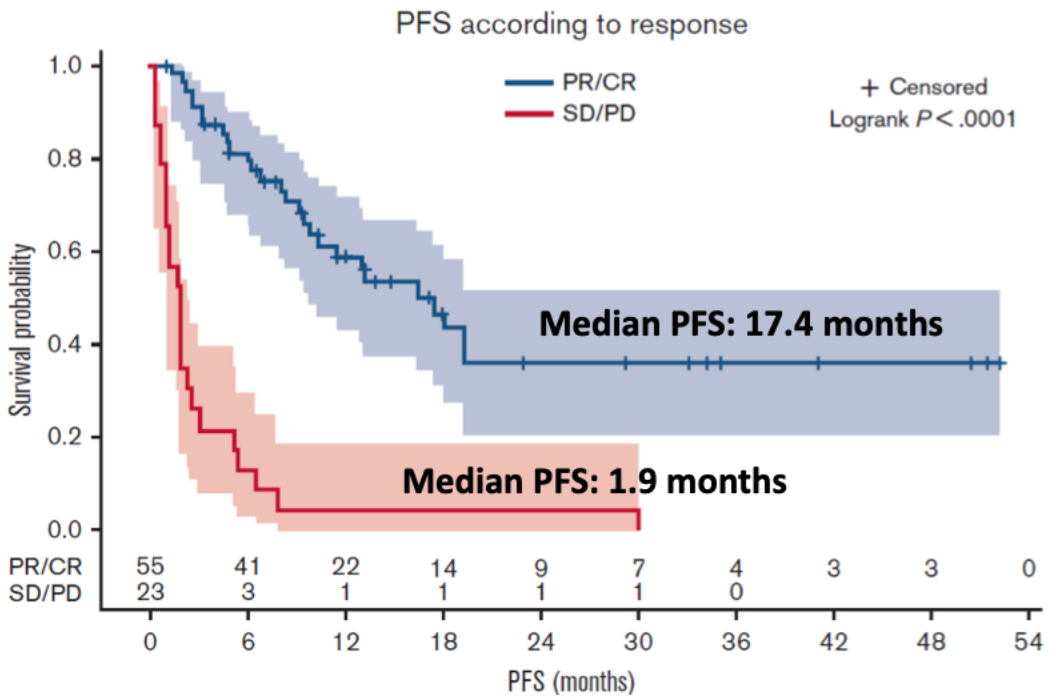
- ALCL: ORR=82% with CR=64%
- TFH: ORR=67% with CR=50%
- PTCL NOS/other subgroups: ORR=53% with CR=29%

difference was not statistically significant

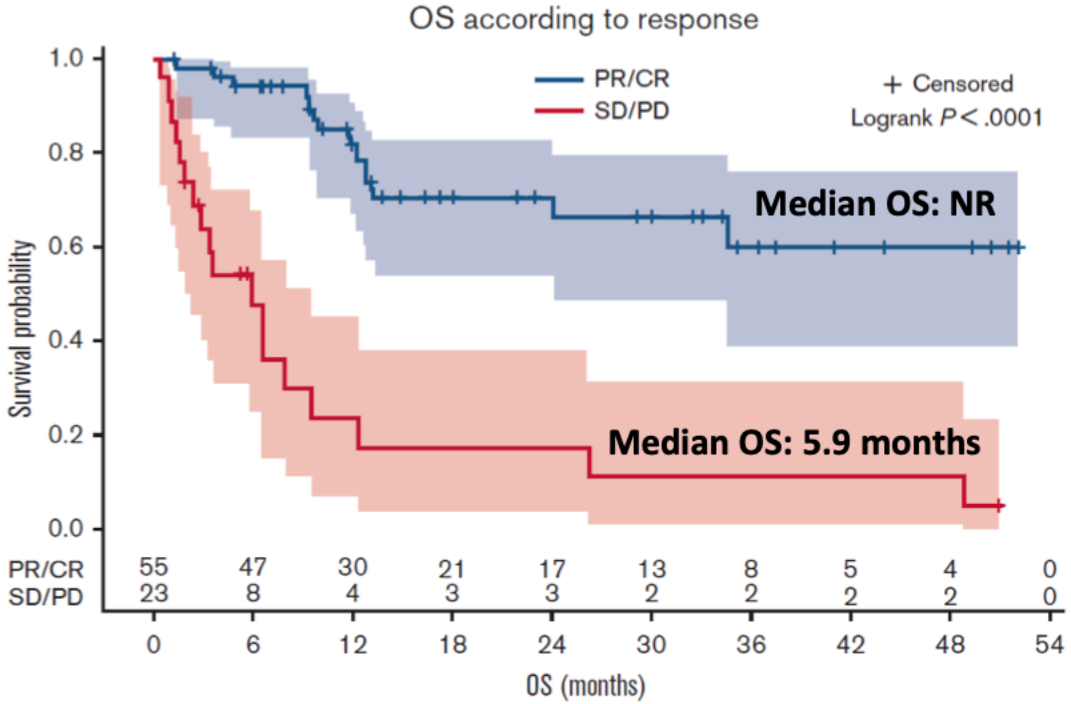
Previous treatment with BV doesn't seem to reduce the efficacy of BBv:
9 patients previously treated with BV monotherapy/association with chemotherapy (gemcitabine and vinorelbine), 5 patients responded, with 4 of them achieving a CR. Of note, 2 of them were initially refractory to BV.

Aubrais R. et al., Blood Adv, December 2022

PFS and OS according to response



P < .0001



P < .0001

PFS was significantly longer for patients in CR than in PR: 19.3 vs 7.2 months (HR = 2.65; 95% CI, 1.2-5.7; P = .013), but not OS (HR = 2.51; 95% CI, 0.9-7.2; P = .0895).

Aubrais R. et al., Blood Adv, December 2022

Epigenetic Therapy in PTCL

Epigenetic modifiers are among the most studied and used therapies in TCL

- HDACs
- Inhibitors of DNA methyltransferase

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

Table 2. Response to romidepsin as single agent or combinations in TFH vs non-TFH phenotype relapsed/refractory PTCL

	TFH (n = 76)		Non-TFH (n = 51)		
Response	**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
Single agent (n = 97)	32/59 (54.2)	15/59 (25.4)	12/38 (31.5)	8/38 (21.0)	.0371
Combinations (n = 30)	11/18 (61.1)	7/18 (38.8)	3/12 (25.0)	2/12 (16.6)	.0717

**P* values have been calculated with the Fisher's exact test.

Typical AITL/TH 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

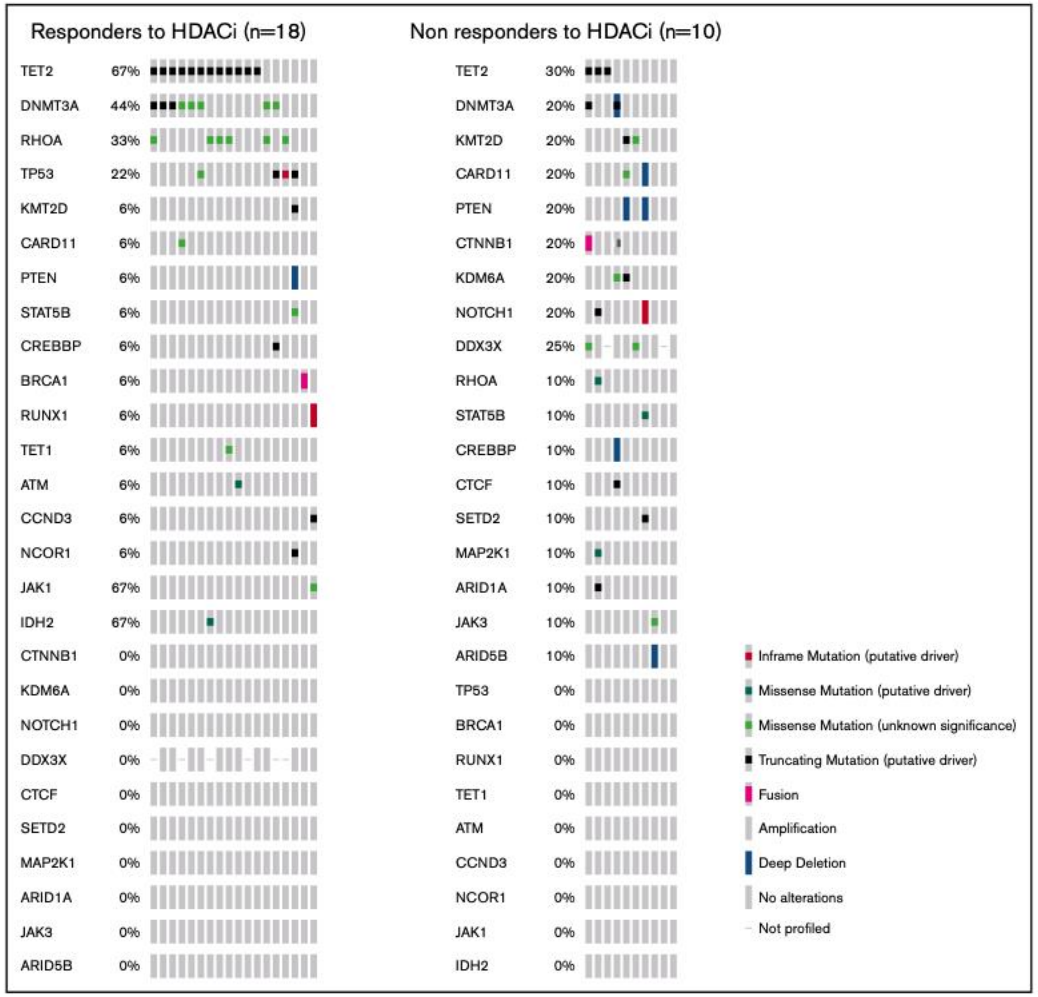
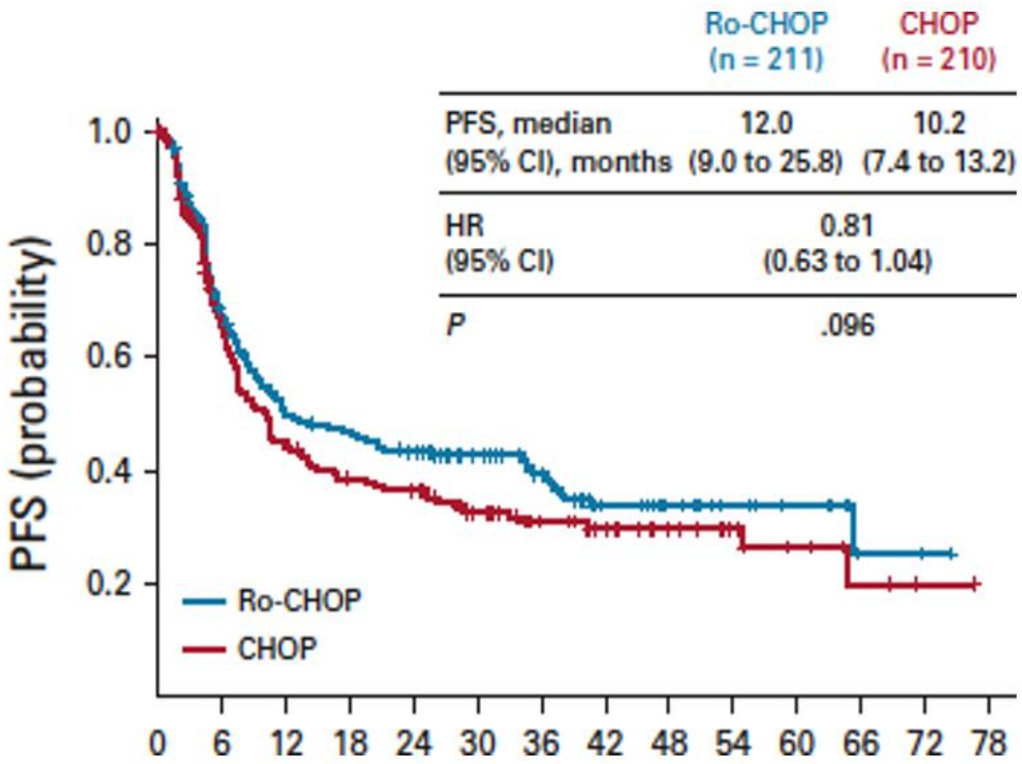


Figure 4. Detail of all more frequent mutations found on targeted sequence IMPACT heme panel performed at time of relapse/refractoriness in 28 patients receiving HDACi.

What hasn't worked? Ro-CHOP versus CHOP negative Phase 3 trial

LYSA All ages Median 65 y No

Primary end point: PFS

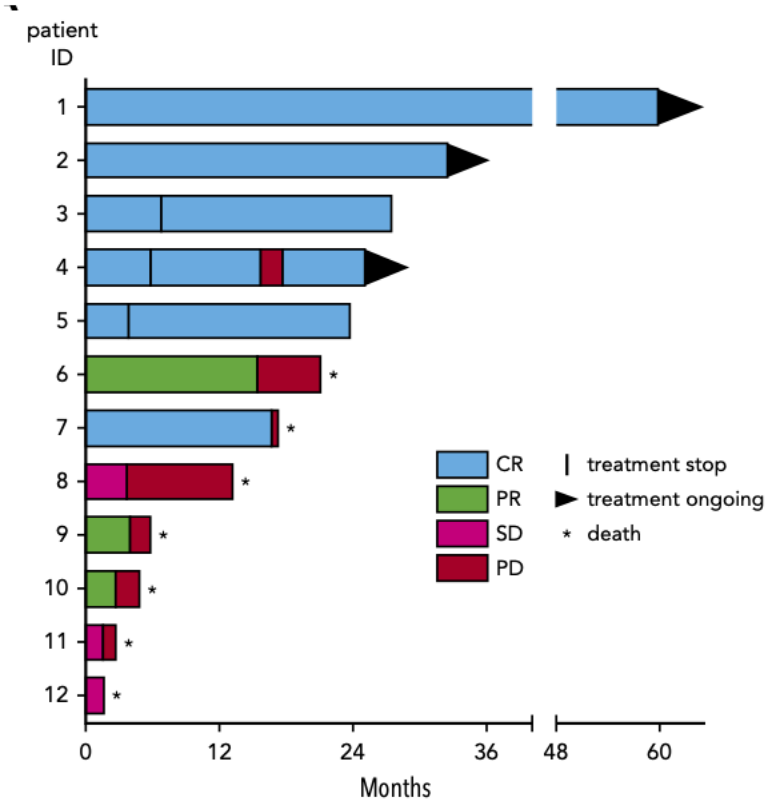


CHOP +/- Romidepsin Update 5 years

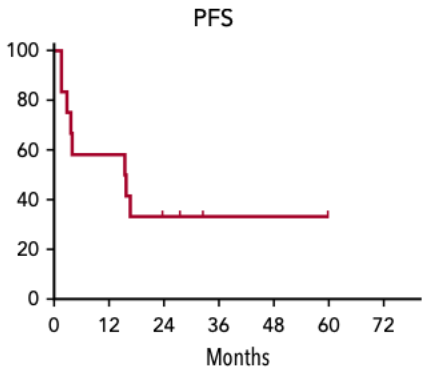
Regimen	No.	PFS	PFS by Subtype
Ro-CHOP[7,12]	421		
Ro-CHOP	211	Median PFS—12.0 months	Median PFS TFH—19.5 months Non-TFH—8.7 months Median OS TFH—65 months PTCL-NOS—25.8 months
CHOP	210	Median PFS—10.2 months	Median PFS TFH—10.6 months Non-TFH—9 months

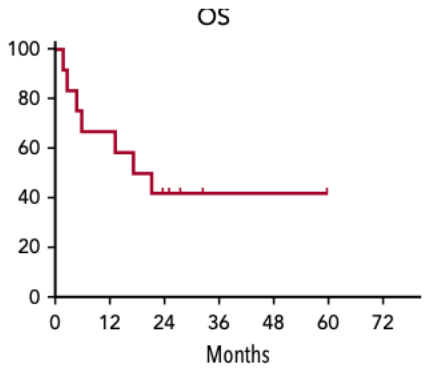
Bachy et al. JCO 2022; Camus et al. JCO 2024

Targeting the nucleosides (hypometilating agents)



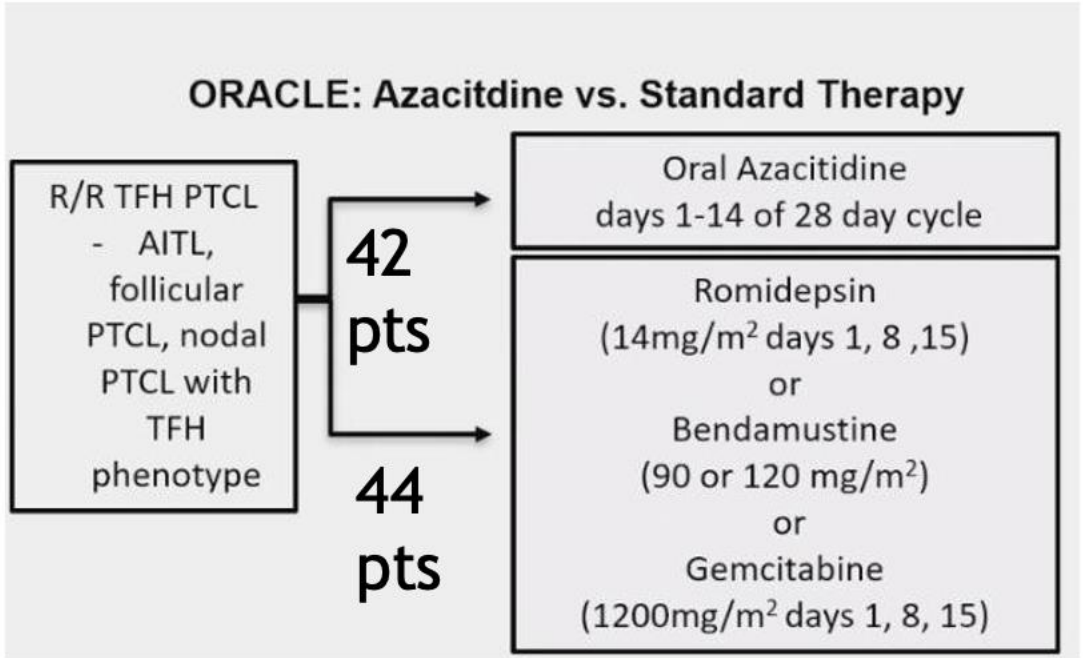
ORR: 75%
CR:50%
Median PFS: 15 months
Median OS: 21 months

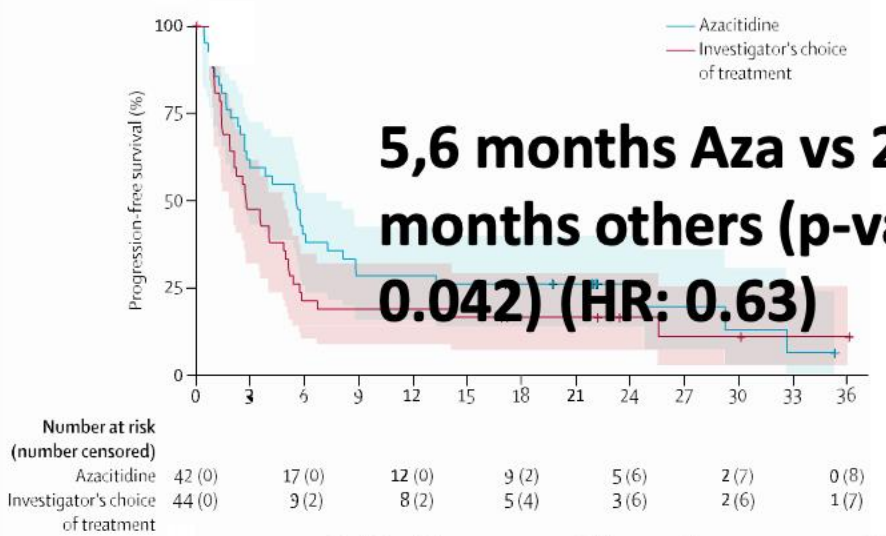




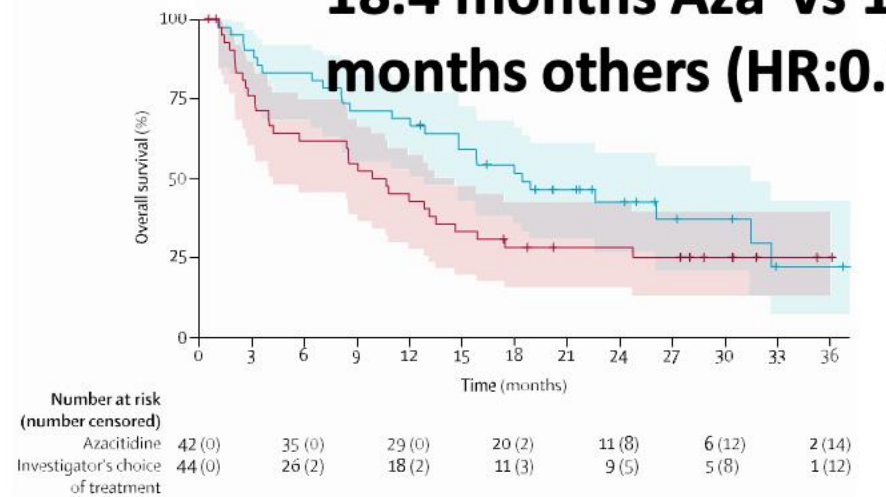
Lemonnier F. et al. Blood 2018

ORACLE STUDY: Aza versus Investigator choice in R/R THF PTCL





5,6 months Aza vs 2,8 months others (p-value: 0.042) (HR: 0.63)



18.4 months Aza vs 10,3 months others (HR:0.56)

CR RATE: 12% Aza vs 23% other therapies
Median Duration of Response: 10,4 months versus 3,4 months

The primary endpoint, PFS advantage, was not met (p-value <0.025)

Depuis J, Lancet Hematology 2024

Azacitidine + CHOP: Phase II Study

Key Eligibility

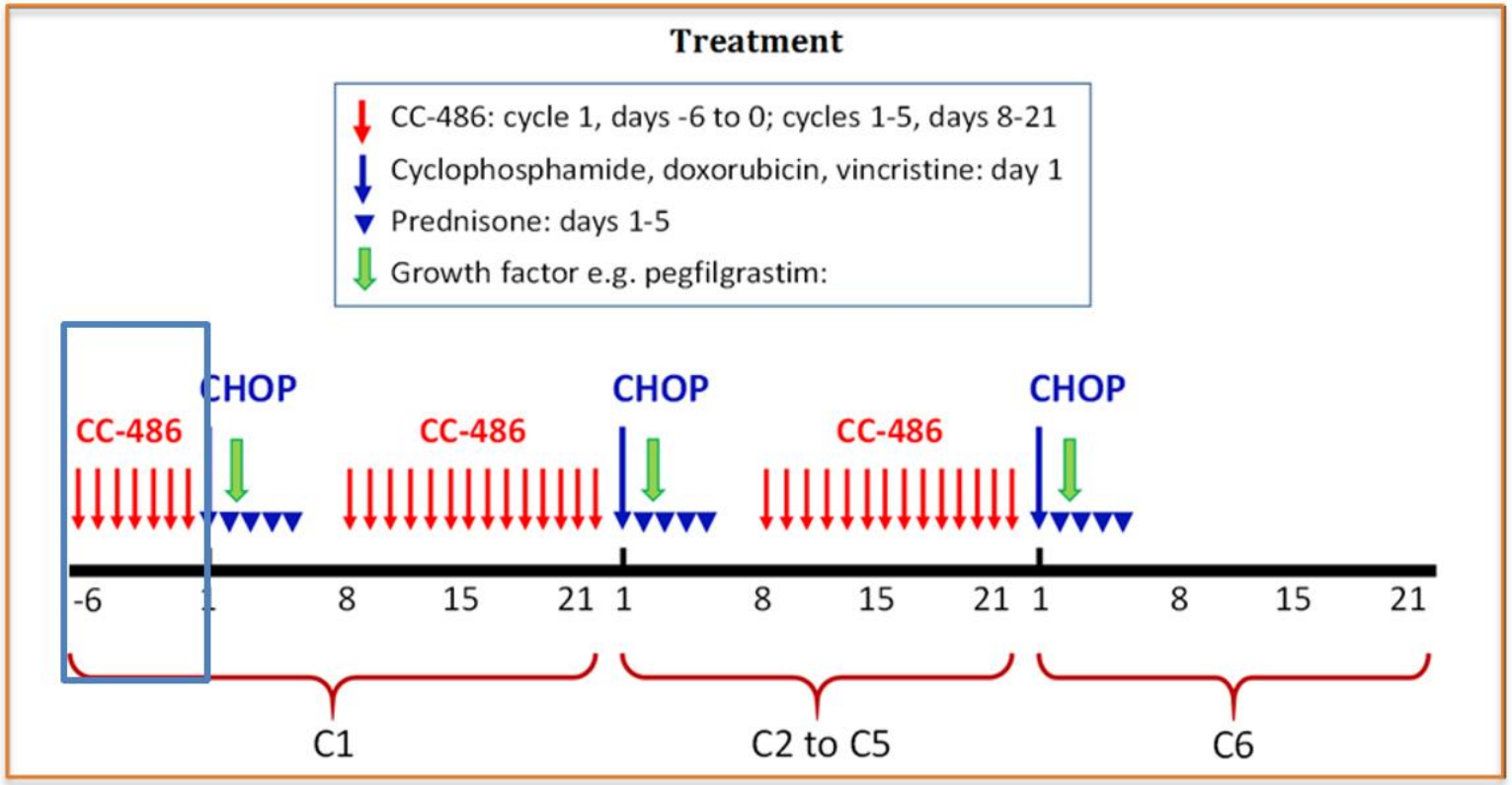
- Untreated PTCL
  - Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (WHO 2016 classification)
    - Angioimmunoblastic T-cell lymphoma
    - Follicular T-cell lymphoma
    - PTCL/NOS, T-follicular helper (TFH) variant
  - PTCL-NOS
  - Anaplastic large cell lymphoma, ALK negative
  - Anaplastic large cell lymphoma, ALK positive with IPI >2
  - Adult T-cell leukemia / lymphoma

Objectives

1st – CRR; 2nd – ORR, safety and survival
Exploratory genomic, transcriptomic and methylomic biomarkers

Sample Size = 20

Simon's two-stage design (alpha=10%, power=80%)



17/20 THF

Frontline Therapy

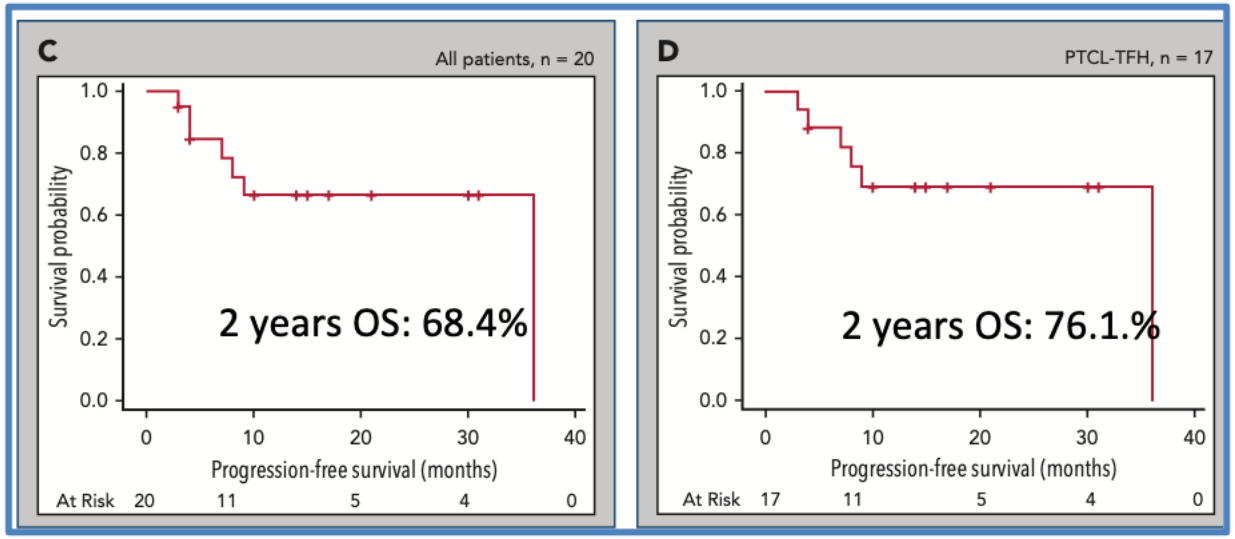
- CC486 at 300 mg daily from day -6 to day 0 for cycle 1 priming, and on days 8-21 following cycles 1-5.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative HSCT.

Ruan et al.Blood Adv. 2023

Azacitidine + CHOP: Phase II Study

- All population ORR (n=20): 75% (75% CR)
- PTCL-THF ORR (N=17): **88%** **(88% CR)**

Overall Survival

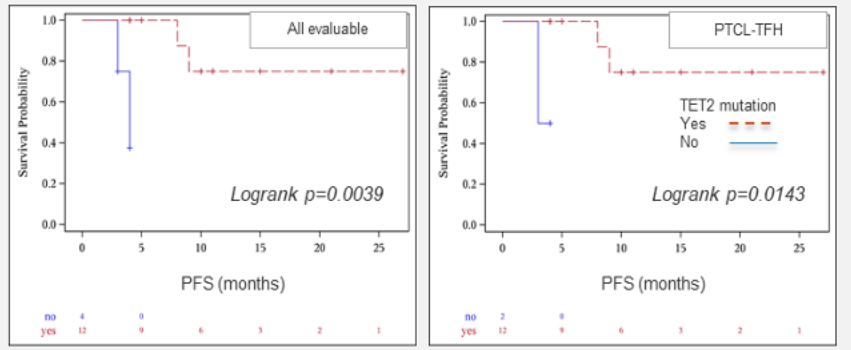


50% received Auto-Transplant

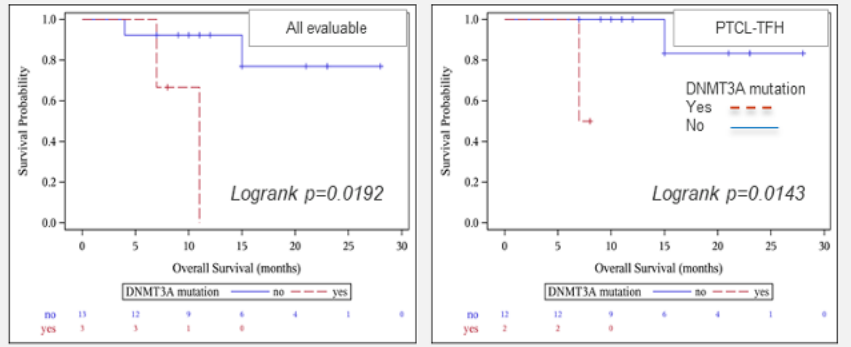
Frontline Therapy

TET2 mutations associated with CR and favorable PFS

TET2 mutations correlate with favorable PFS

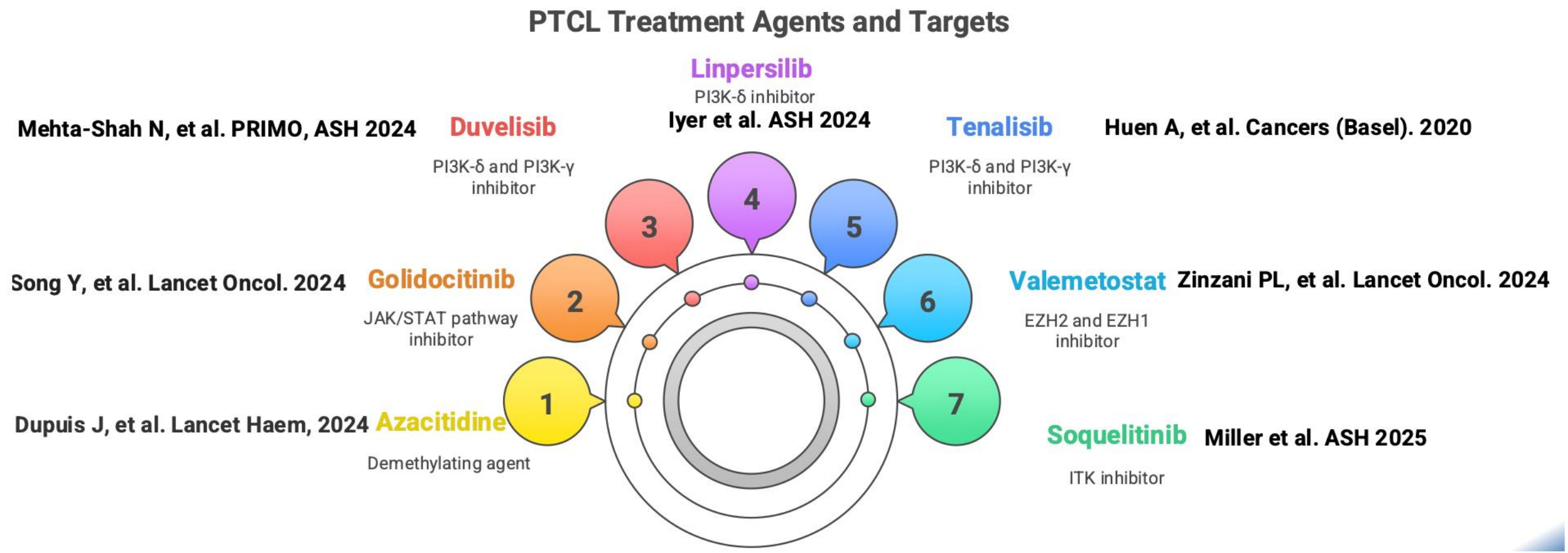


DNMT3A mutations correlate with adverse OS



Ruan et al. Blood Advances 2023

Targeting dysregulated pathways



Efficacy of novel agents

Name of Agent	Target / Pathway	N (Patients)	Median Prior Lines (Range)	ORR (Best Overall Response)	CR (Complete Response)	Median F/U	PFS (if available)	Author / Study Reference
Golidocitinib	JAK / STAT pathway (JAK1 selective inhibitor)	104 (Enrolled) / 88 (Efficacy)	2 (1–3)	44.3% (IRC-assessed)	23.9% (IRC-assessed)	NA (Data cut-off Aug 31, 2023)	NA (PFS secondary endpoint)	Song Y, et al. Lancet Oncol. 2024
Duvelisib	Dual PI3K inhibitor (PI3K-δ / PI3K-γ)	123 (All PTCL)	2 (1–9)	48.0% (IRC-assessed)	33.3%	Median PFS: 6.24 months	3.45 months (95% CI: 1.84–3.94)	Mehta-Shah N, et al. PRIMO, ASH 2024
Linperlisib (YY-20394)	PI3K-δ inhibitor	35 (PTCL FAS)	≥1 prior therapy	45.7% (Investigator-assessed)	31.4%	≥6 months follow-up	6-month PFS rate: 40.4% (95% CI: 23.5–56.8)	Iyer et al. ASH 2024
Valemetostat	Dual EZH2 / EZH1 inhibitor	133 (Enrolled) / 119 (Efficacy)	2.0 (1–12)	52.1% (BICR, CT-based)	14.3% (PET-CT based)	NA	NA	Zinzani PL, et al. Lancet Oncol. 2024
Soquelitinib (CPI-818)	ITK inhibitor	19 (Dose-escalation total)	1–18 (range across cohorts)	37%	16%	NA	NA (PFS primary endpoint in Phase 3)	Phase 1 Dose Escalation

Responses in AITL

Name of Agent	Target / Pathway	N (AITL / TfH Subtype)	Subtype Context / Cohort	Median Prior Lines (Range)	ORR	CR
Valemetostat	Dual EZH2 / EZH1 inhibitor	53 (AITL: 42; Nodal PTCL-TfH: 8; FTL: 3)	ORR 52.1% overall in efficacy-evaluable (N=119);	≥1	52.1%	—
Golidocitinib	JAK / STAT pathway (JAK1 selective inhibitor)	16 (AITL)	15.4% of cohort were AITL; overall ORR 44.3%,	≥1	44.3%)	—
Soquelitinib (CPI-818)	ITK inhibitor	7 (AITL)**	AITL & TFH-NOS eligible in Phase 3; enrolled in dose-escalation; no subtype-specific ORR reported	≥1		—
Linperlisib (YY-20394)	PI3K-δ inhibitor	Not specified for AITL subset*	Conducted in PTCL (including AITL); follow-up ≥6 months	≥1	65%	48%
Duvelisib	Dual PI3K inhibitor (PI3K-δ / PI3K-γ)	37			62.2%	51.4%

Adverse events of Novel agents

Name of Agent	Grade 3/4 Adverse Events (≥10%)	Special AEs / Key Toxicities	Discontinuation Due to AEs	Related Deaths
Golidocitinib(N = 104)	Any TRAE ≥ Grade 3: 59.6%.Most common: ↓ platelets, ↓ WBC, ↓ neutrophils, ↓ lymphocytes.	TRAE 24.0%; primarily hematologic toxicities.	8.7%	1.0% (1 patient)
Duvelisib(Phase 2 PRIMO, N = 123)	ALT ↑ (21.1%), neutrophils ↓ (17.9%), AST ↑ (17.1%).	Transaminase elevation (ALT/AST) most common special AE; Grade ≥ 3 diarrhea 9.8%.	Not explicitly stated (intolerance criteria).	Cryptococcosis (1), EBV-LPD (1), pneumonitis (1), sepsis (1).
Linperlisib(Phase 2 US & EU, N = 98)	Neutropenia (32%), pneumonia (14%), leukopenia (10%).	Pneumonia (11%) most frequent drug-related SAE; immune-related ≥ G3 TRAEs (ALT/AST ↑, diarrhea, colitis, rash) < 5%.	9.2% (9 patients); dose reductions 22.4%.	Not detailed for N = 98 cohort.
Valemetostat(N = 133)	Thrombocytopenia (23.3%).	Cytopenias common; thrombocytopenia most frequent any grade (49.6%) and G3+ TEAE; 2 secondary AML cases.	9.8% (due to any TEAE).	2 patients with secondary AML (discontinued).
Soquelitinib (CPI-818)(Phase 1 Dose Escalation, N = 45 safety pop.)	Any TEAE ≥ G3: 53.3%. Most common TRAE ≥ G3: neutropenia (11.1%).	Serious TRAE 8.9%; non-hematologic G3+ TRAEs included pneumonia (4.4%) and rash (4.4%).	Not stated.	No treatment-related deaths.

DR-01 Targets Cytotoxic Lymphomas (CTLs): Rare

CTLs

- Group of rare lymphoma subtypes (3%–6% of non-Hodgkin lymphoma)[1]
- Characterized by cytotoxic cells expressing CD94
- Few CTL patients are represented in randomized studies

Outcomes are poor

- Median overall survival (mOS) < 1 year in newly diagnosed HSTCL, EATL, and ENKTL patients[2]
- mOS of only ~3 months in R/R ENKTL[3]

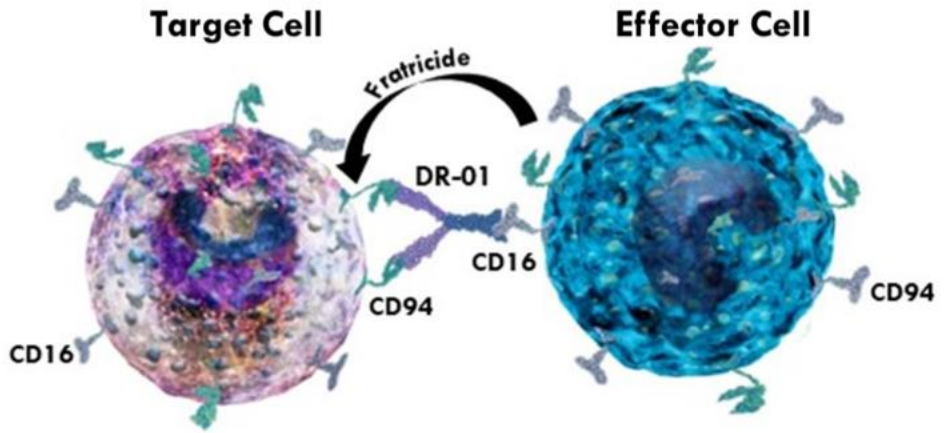
DR-01 (non-fucosylated antibody)

- Engages Fc-γ receptors, such as CD16a
- Triggers antibody-dependent cellular cytotoxicity (ADCC) by effector cells or fratricide, resulting in target cell depletion

Cytotoxic Lymphoma Histologies

ENKTL, nasal type	ET-CTCL
EATL	ANKL
MEITL	HVLPD
HSTCL	PTCL-NOS*
SPTCL	Cutaneous PTCL-NOS*
PCγδTCL	

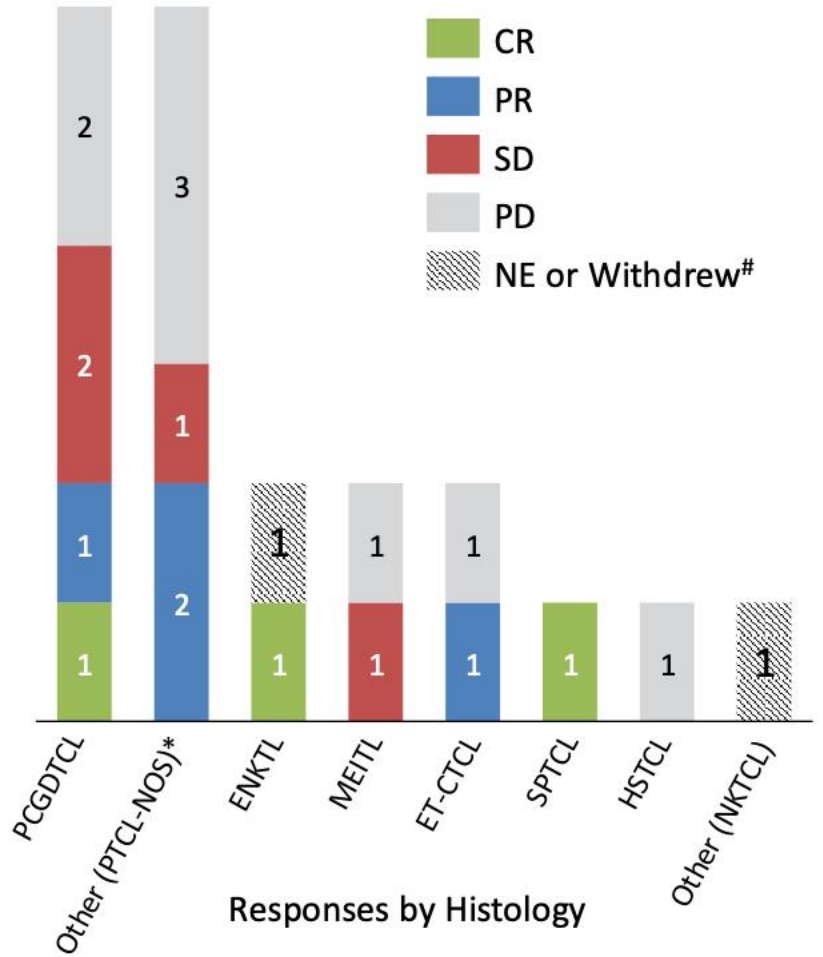
**Selected patients with a cytotoxic phenotype*



[1]*Leukemia and Lymphoma Society 2024;* [2]*Vose et al. JCO 2008 ;* [3]*Bellei M et al. Haematologica 2018*

Promising Response Rate, including CRs, in CTL Patients During Dose Escalation in Majority of Histologies

	Dose Level (mg/kg)					
	0.3 (N=1)	1 (N=6)	3 (N=4)	6 (N=5)	10 (N=3)	Total (N=19)#
ORR, n (%)	0	4 (67)	1 (25)	2 (40)	9	7 (37)
CR	0	3 (50)	0	0	0	3 (16)
PR	0	1 (17)	1 (25)	2 (40)	0	4 (21)
SD	0	0	1 (25)	2 (40)	1 (33)	4 (21)
PD	1 (100)	2 (33)	2 (50)	1 (20)	2 (67)	8 (42)



One unrelated AE withdrawal and one PI withdrawal without assessment
*Includes cutaneous subtypes

Zain J, Iyer S et al. Abstract 980: DR-01 in R/R Cytotoxic Lymphomas

Conclusioni

There is no specific focus on elderly or unfit patients in the current treatment strategies

- First-line strategy with new drugs does not fully explore the elderly population, often due to the use of CHOP as the backbone and ASCT being considered for high-risk consolidation

- In the relapsed/refractory (R/R) setting, there is a lack of long-term follow-up data on the efficacy and toxicity of new drugs, as most patients achieving complete remission (CR) and fit for treatment are consolidated with allogeneic transplant (Allo)

- In the R/R setting, the preference is towards Allo as long as possible. For elderly patients, a maintenance strategy should be considered.