9th POSTGRADUATE

Lymphoma Conference

Barbara Pro, MD

Columbia University

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Hotel Brunelleschi

President:
P.L. Zinzani

Disclosures

Disclosures of Barbara Pro

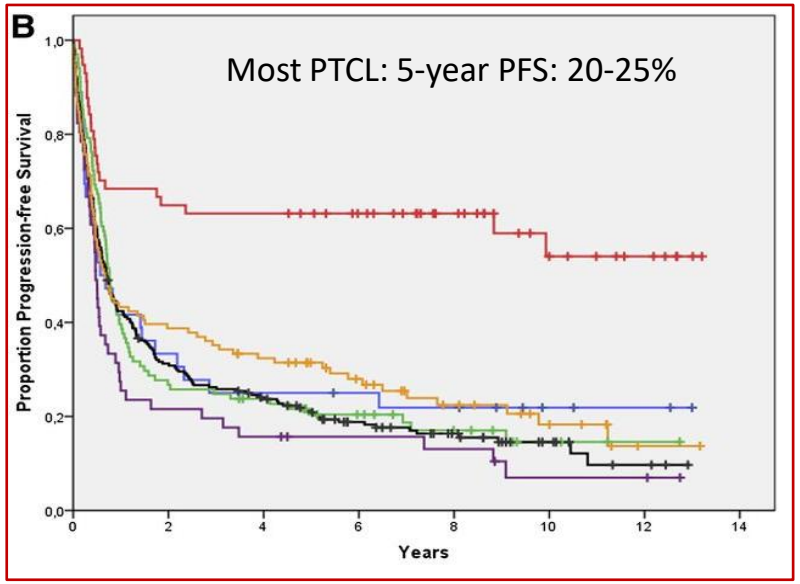
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Secura Bio						X	
SciTech	X						
Ono Pharma	X						

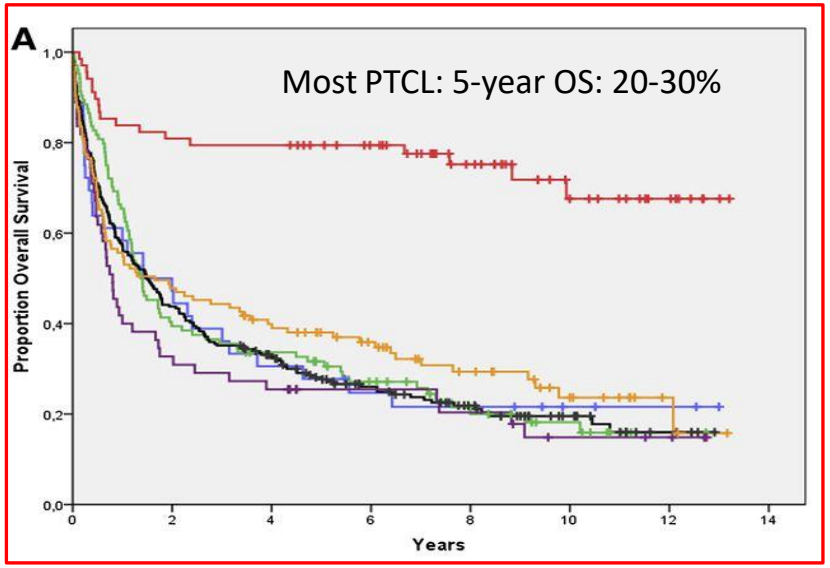
The Potential Frontline Therapies in PTCL

Barbara Pro, MD
Professor of Medicine
Director of Lymphoma Program
Columbia University

Introduction

- PTCL are a group of mature, postthymic, T-cell, and NK-cell lymphoproliferative disorders
  - 15% to 20% of aggressive lymphomas and 10% of NHLs
- Clinical and biological diversity with over 30 different subtypes
- Molecular characterization has led to identification of specific subtypes and has contributed to discovery of novel pathway-directed therapies
- Poor outcomes with standard treatments
  - 25% of patients refractory to 1L therapy





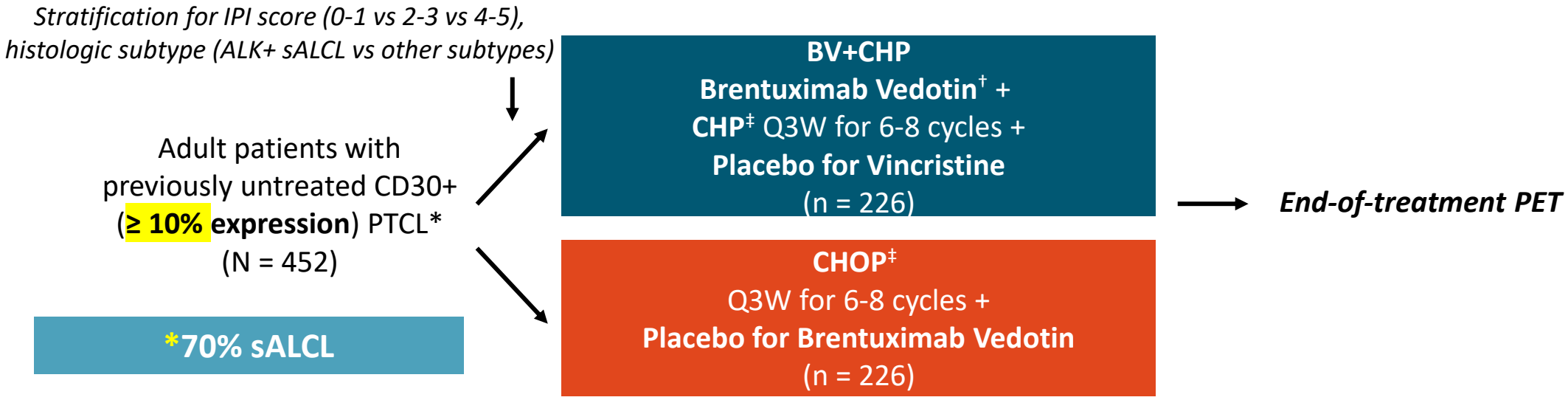
Ellin et al. Blood 2014;124:1570-1577

PTCL: Historical SOC for common nodal subtypes

* Not recommended in patients with ALK pos. ALCL low IPI

Targeted Therapy in PTCL-CD30
ECHELON-2: Brentuximab Vedotin + CHP vs CHOP

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



*PTCL includes sALCL (including ALK+ sALCL with IPI ≥ 2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin: 1.8 mg/kg. ‡Cyclophosphamide 750 mg/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.

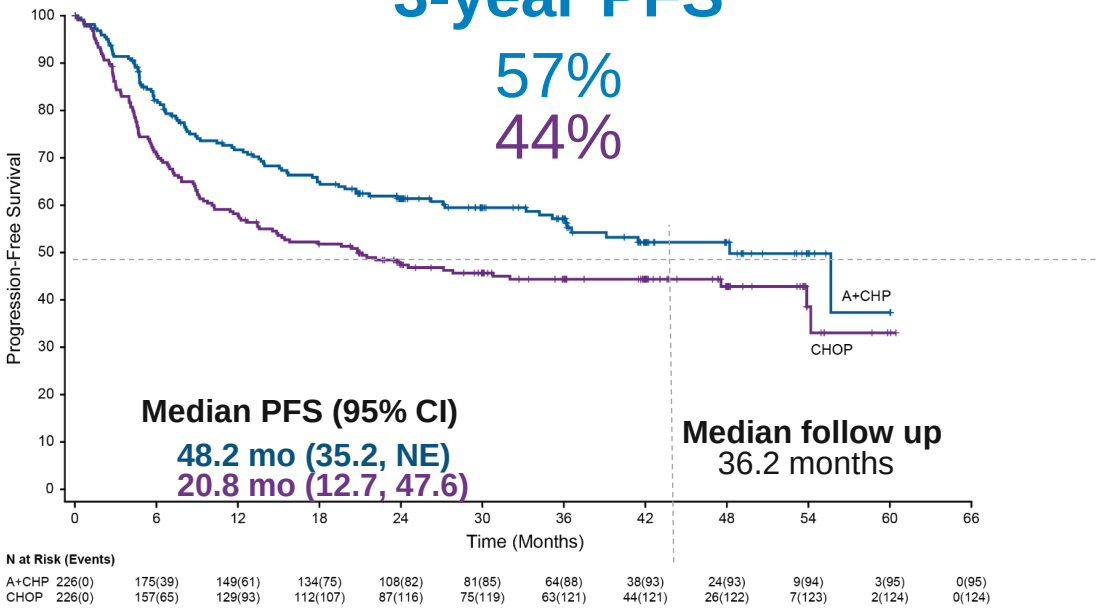
- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz et al. Lancet. 2019;393:229.

ECHELON-2: PFS and OS

3-year PFS

57%
44%



- ***ALCL***
  - ***OS benefit***
  - ***SOC***
- ***PTCL-NOS, AITL***
  - ***Smaller subsets- unclear benefit***

5-Year OS by Histology

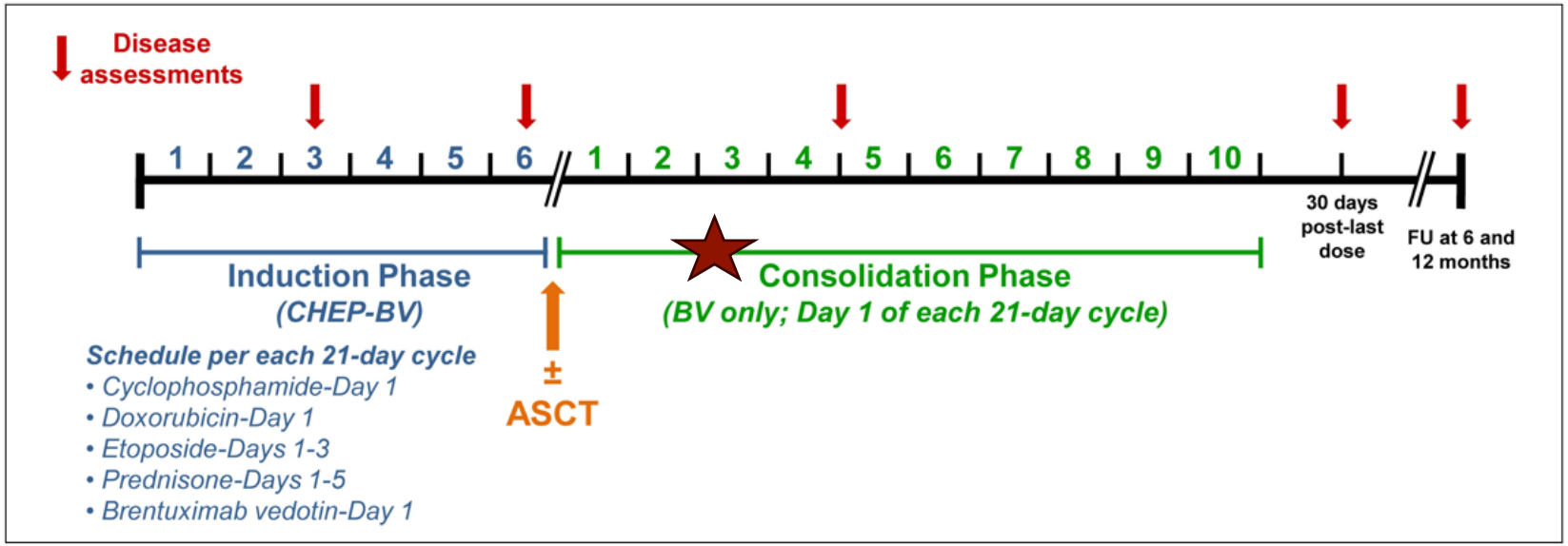
	BV-CHP	CHOP
ALCL (n=316)	75.8%	68.7%
AITL (n=54)	62.5%	67.8%
PTCL-NOS (n=72)	46.2%	35.9%

Horwitz et al. Lancet. 2019;393:229

Can we improve BV–CHP?

Etoposide addition and brentuximab vedotin consolidation in first-line treatment of CD30-positive peripheral T-cell lymphoma

-CD30 cutoff set at 1%



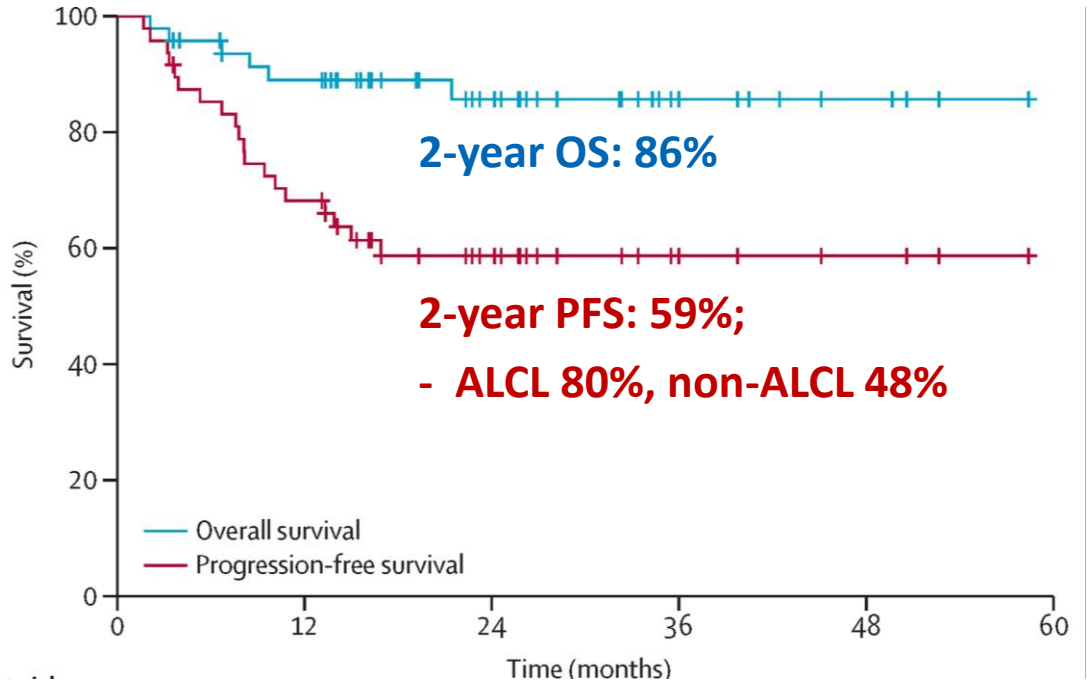
- Response assessment by investigators: 2014 Lugano classification

Herrera et al. Lancel Hematol 2024

Frontline Therapy with BV-CHEP + BV Maintenance (n=47)

Response by Histology

Response	All (n=47)	ALCL (n=15)	Non-ALCL (n=32)	AITL (n=19)	PTCL NOS (n=11)	PTCL TFH (n=2)
ORR	**43 (91%)**	14 (93%)	29 (91%)	18 (95%)	9 (82%)	2 (100%)
CR	**37 (79%)**	13 (87%)	24 (75%)	15 (79%)	7 (64%)	2 (100%)
PR	**6 (13%)**	1 (7%%)	5 (16%)	3 (16%)	2 (18%)	0

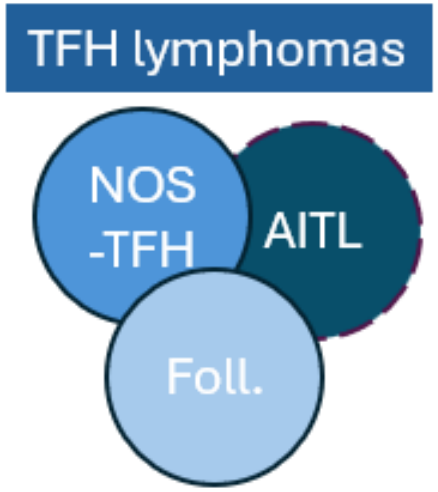


Median Follow-up 25 months

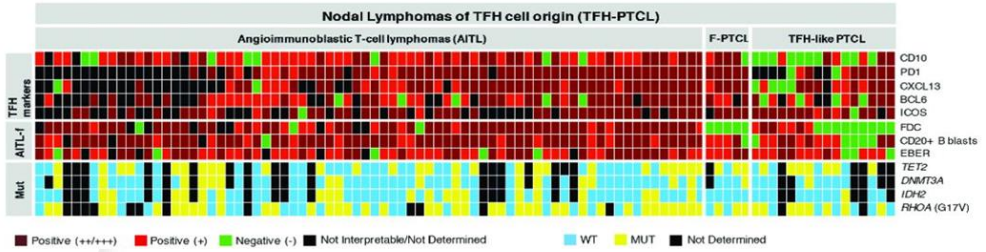
2-yr PFS of 80% in patients who received ASCT and BV consolidation

Herrera et al. Lancel Hematol 2024

T-Follicular Helper Lymphomas and Role of Epigenetic Modifiers



-Recurrent mutations in TET2, RHOA, IDH2, DNMT3A

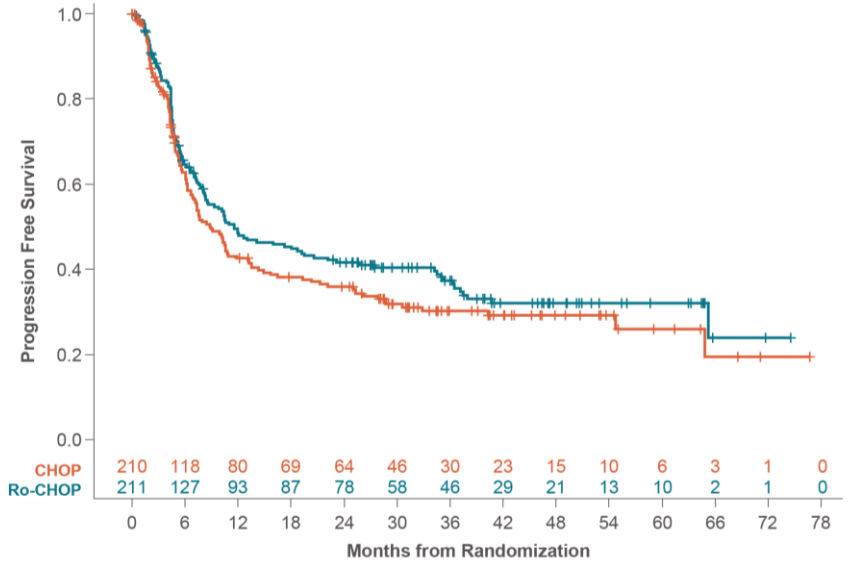


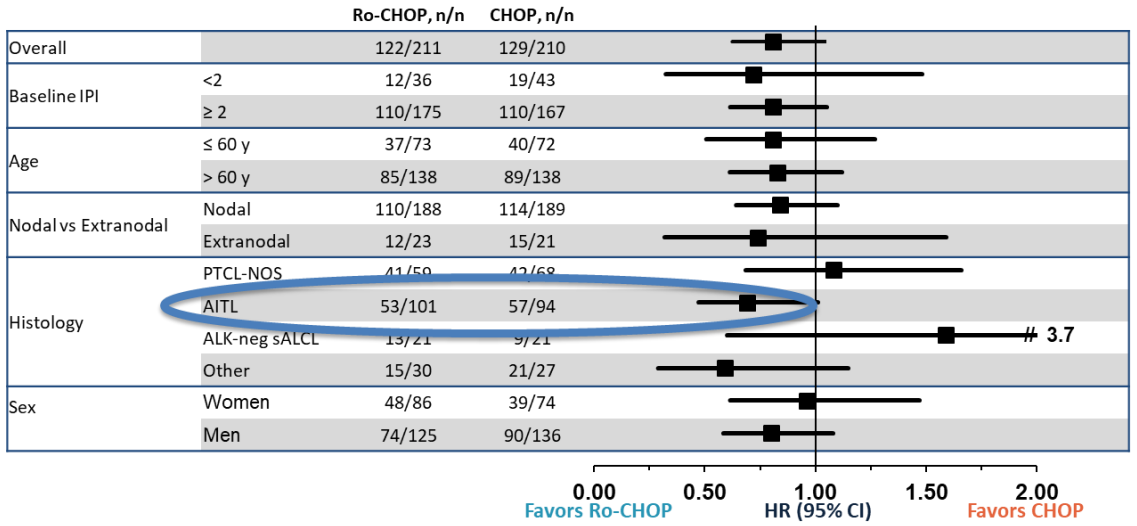
Romidepsin CHOP vs. CHOP

Key Inclusion Criteria
- Aged 18-80 y
- PTCL-NOS, AITL, ALK-neg ALCL, EATCL, HSTCL, SPTCL
- ECOG PS 0-2

→ CHOP X 6 cycles

→ Ro-CHOP X 6 cycles
- Romidepsin 12 mg/m2 days 1-8





→ **Phase II FIL-PTCL13 Study- addition of etoposide to CHOP-Romidepsin did not improve outcome**

Bachy JCO 2022
Chiappella Blood 2022

Azacitidine + CHOP: Phase II Study

Key Eligibility

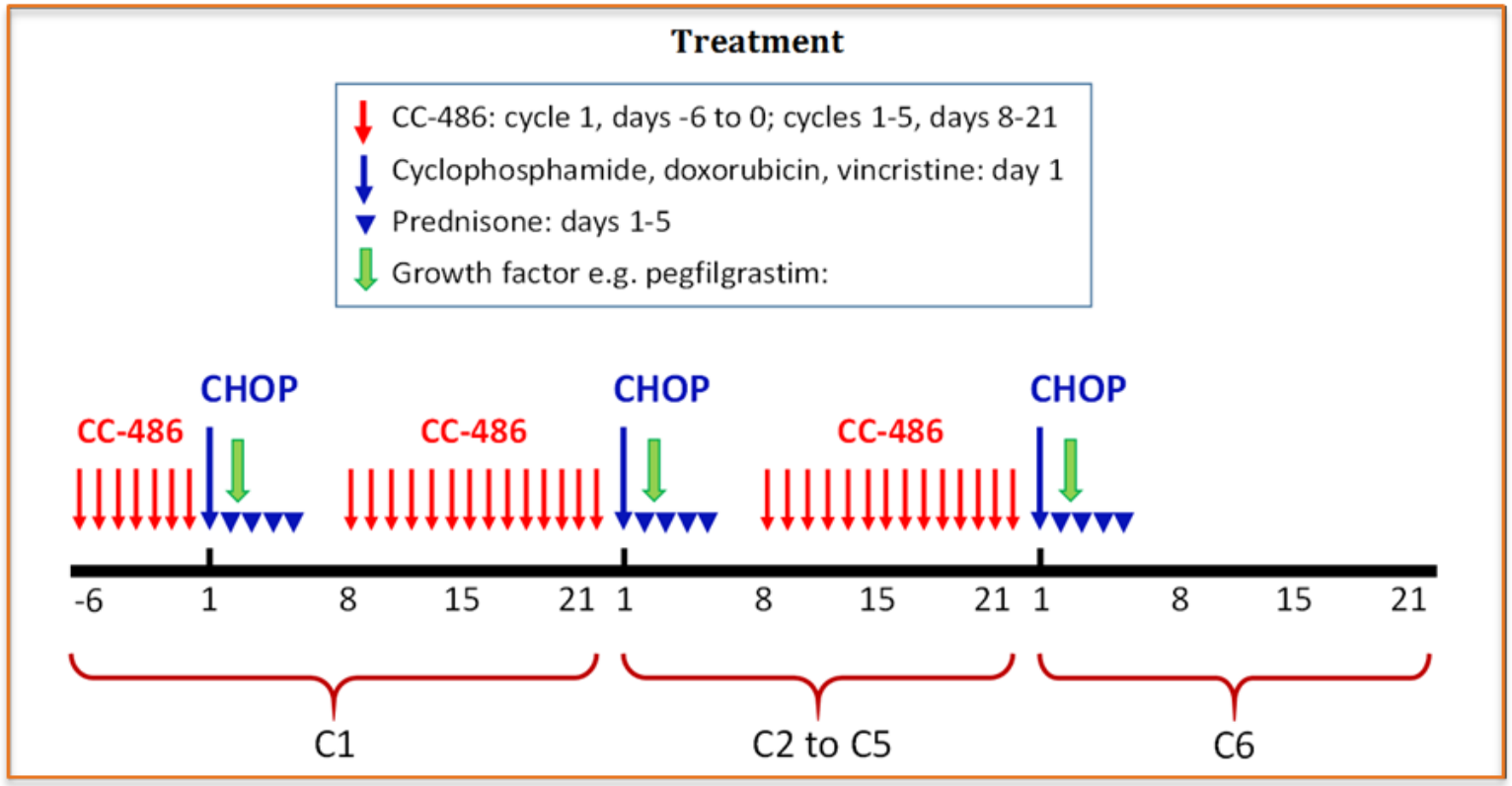
- Untreated PTCL
  - Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (WHO 2016 classification)
    - Angioimmunoblastic T-cell lymphoma
    - Follicular T-cell lymphoma
    - PTCL/NOS, T-follicular helper (TFH) variant
  - PTCL-NOS
  - Anaplastic large cell lymphoma, ALK negative
  - Anaplastic 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%)



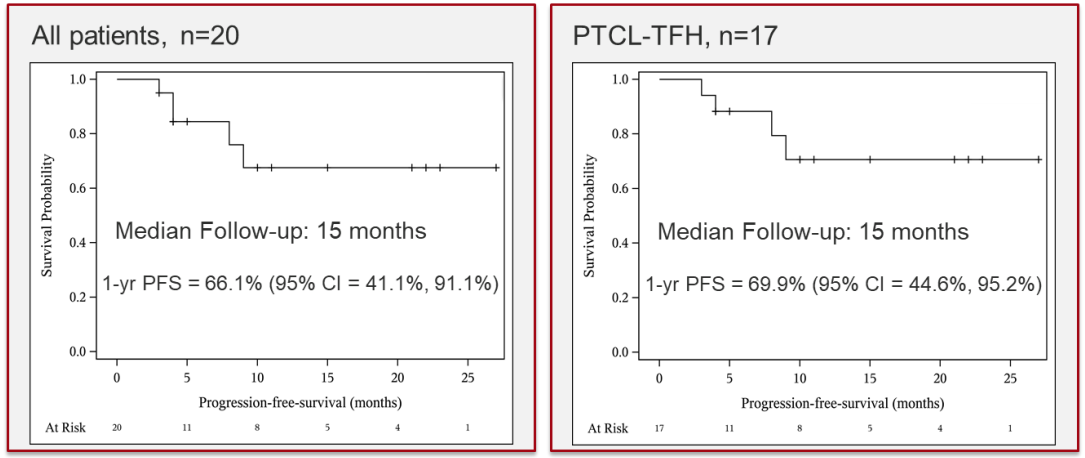
- CC486 at 300 mg daily from day -6 to day 0 for cycle 1 priming, and on days 8-21 following cycles 1-5.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative HSCT.

Ruan et al. ASH 2020

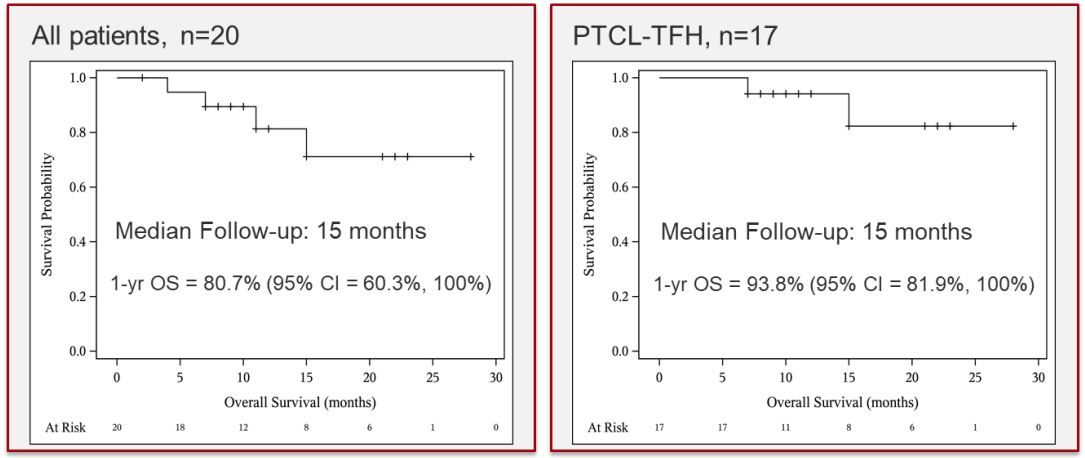
Azacitidine + CHOP: Phase II Study

- ORR (n=20): 85% (55% CR)
- At EOT, ORR: 75% (75% CR)

Progression-free Survival

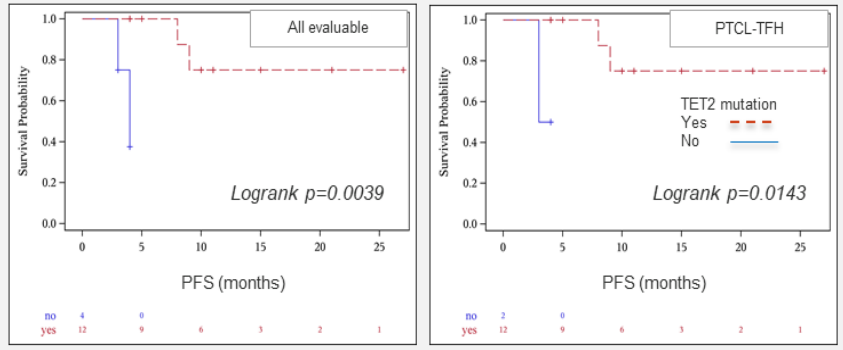


Overall Survival

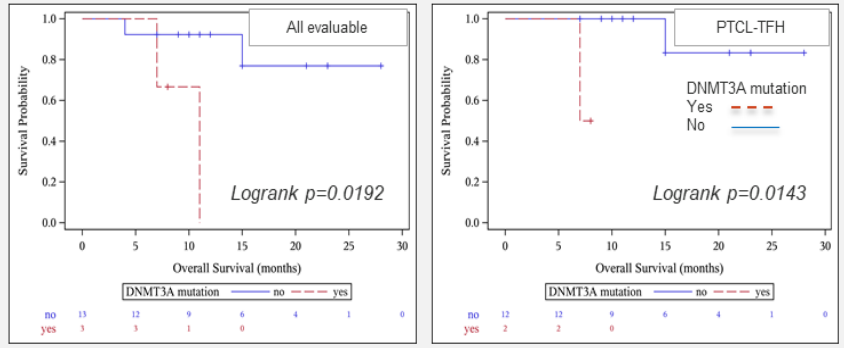


TET2 mutations associated with CR and favorable PFS

TET2 mutations correlate with favorable PFS

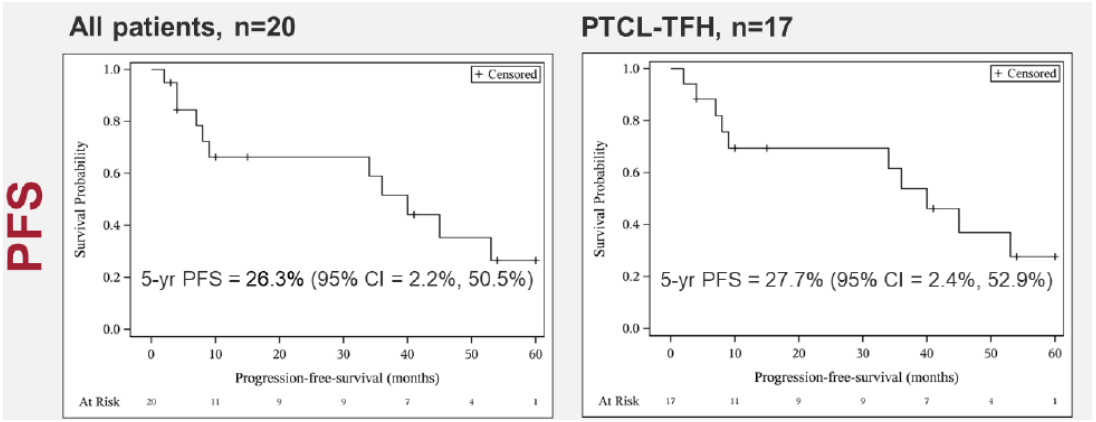


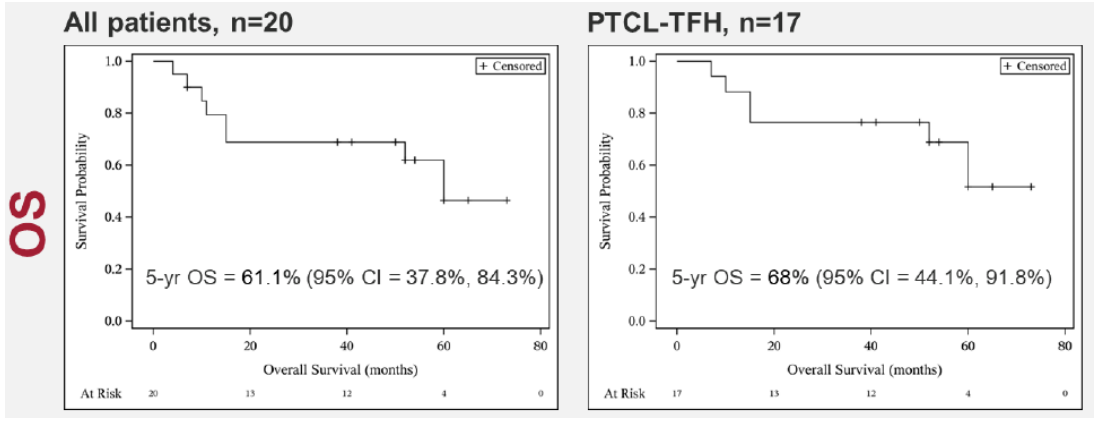
DNMT3A mutations correlate with adverse OS



Ruan et al. ASH 2020

Phase II Study of Oral Azacitidine + CHOP
5-year Follow Up

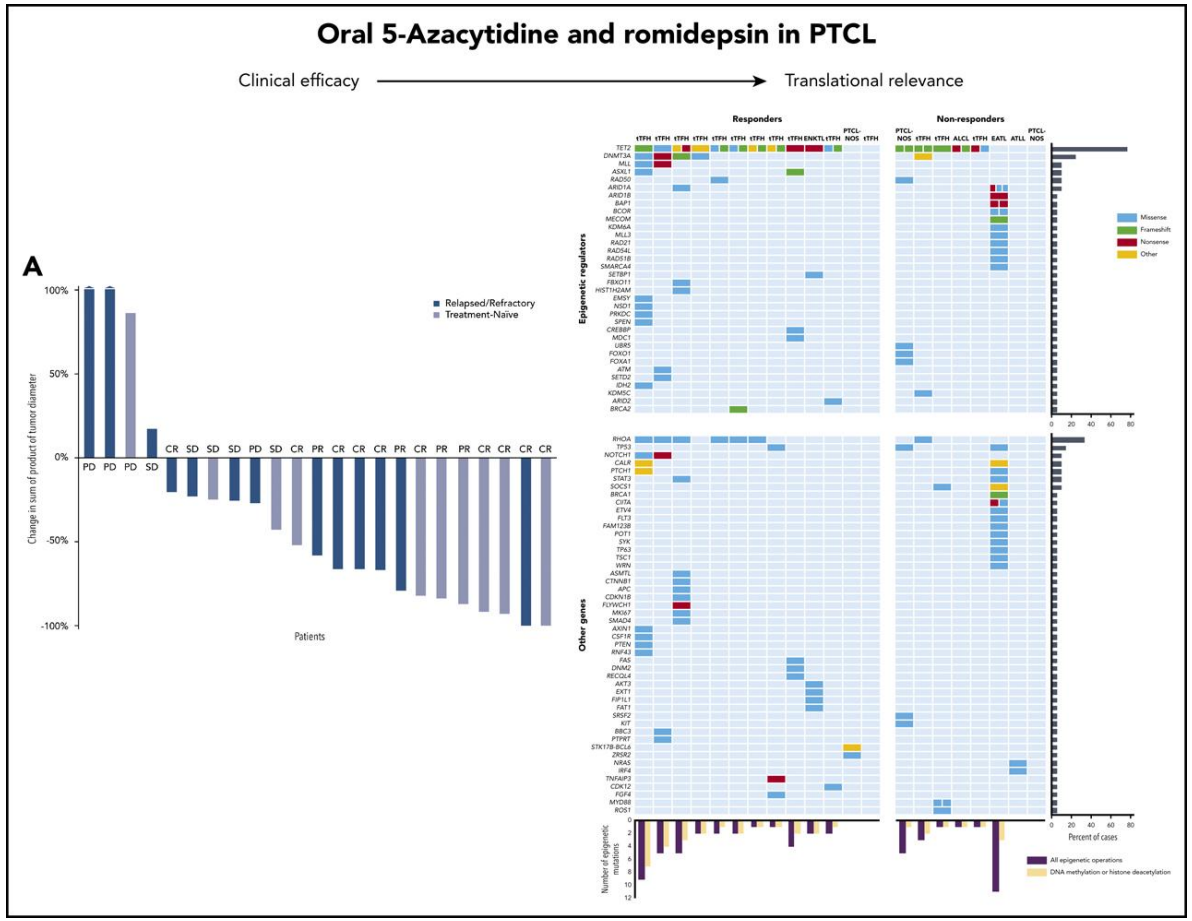




Biomarker analysis confirmed that TET2 mutations were associated with favorable PFS and OS, while *DNMT3A* mutations and elevated LDH were associated with adverse PFS.

Ruan et al. ASH 2024

Non-CHOP Approaches



Phase 2 study n=25 relapsed/refractory AND treatment naïve PTCLs

→ **Treatment naïve n=11 (TFH/AITL n=8)**
ORR 70% CR 50% (n=10 evaluable)

→ **Relapsed/refractory n=14***
ORR 54% CR 38% (13 evaluable)
*includes 5 pts from expansion ph 1

TFH PTCL n=17
ORR 80% CR 60%

Grade 3/4
Thrombocytopenia 48%
Neutropenia 40%
Febrile neutropenia 12%

Falchi et al. Blood 2021

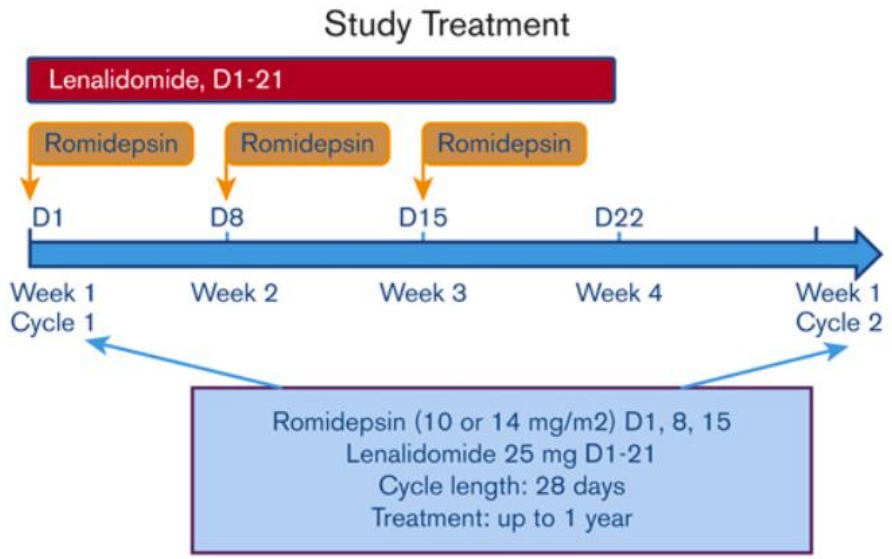
Phase II Study of Romidepsin + Lenalidomide

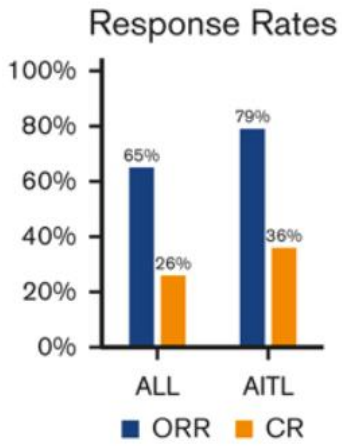
Key Eligibility
(N = 20)

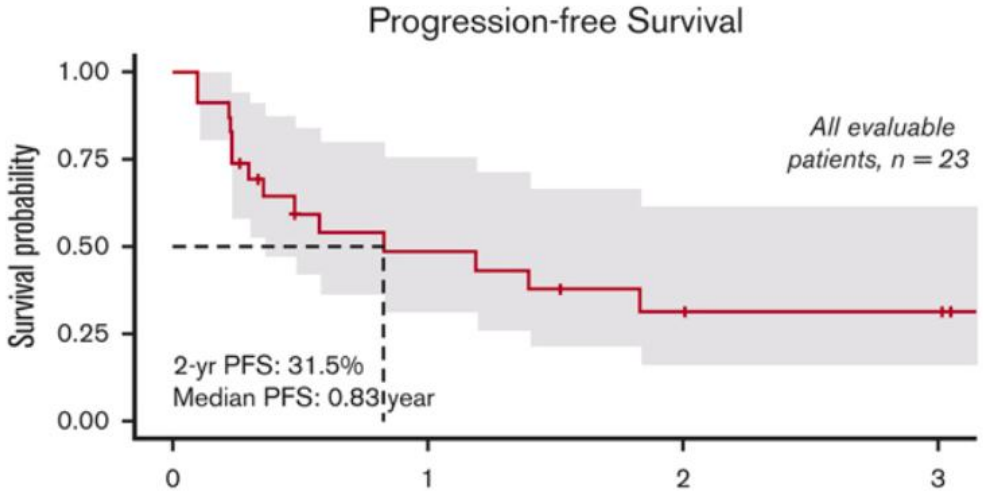
- Untreated PTCL
- Measurable disease
- Age ≥ 60 or noncandidate for chemo

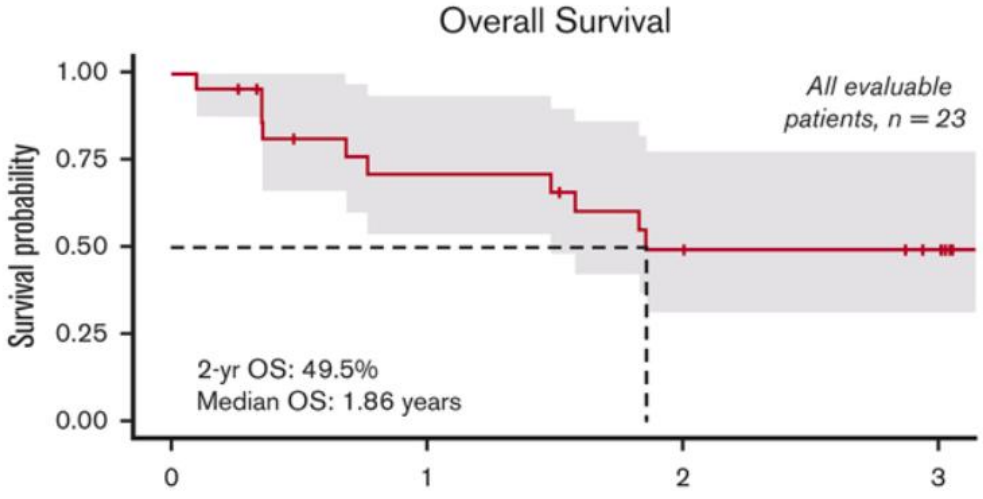
Outcome

- 1st Endpoint
  - ORR
- 2nd Endpoint
  - Safety
  - Survival









Ruan, Pro Blood Adv 2023

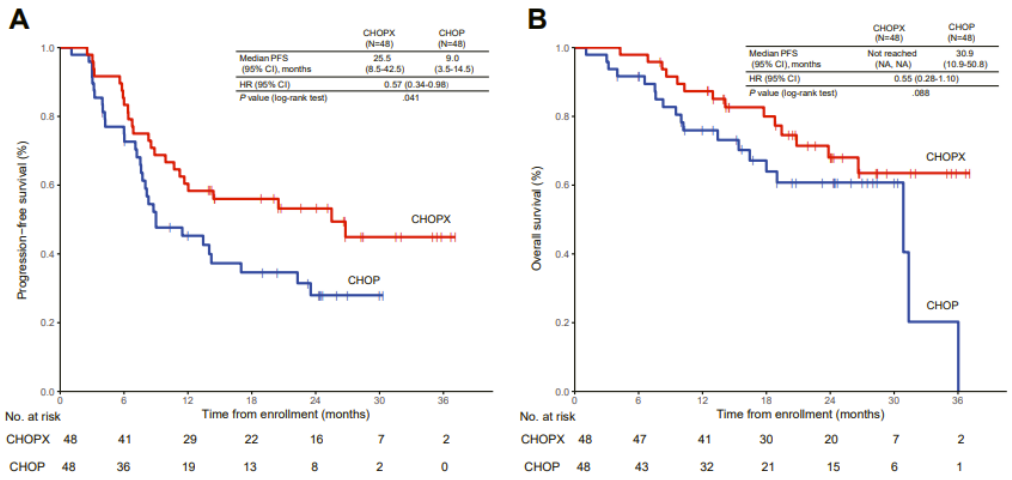
Targeted agents plus CHOP compared with CHOP as the first-line treatment for newly diagnosed patients with peripheral T-cell lymphoma (GUIDANCE-03): an open-label, multicentre phase 2 clinical trial

Ming-Ci Cai,[a,j] Shu Cheng,[a,j] Hong-Mei Jing,[b,j] Yan Liu,[a,j] Guo-Hui Cui,[c] Ting Niu,[d] Jian-Zhen Shen,[e,i] Liang Huang,[f] Xin Wang,[g] Yao-Hui Huang,[a] Li Wang,[a,h] Peng-Peng Xu,[a] and Wei-Li Zhao[a,h,*]

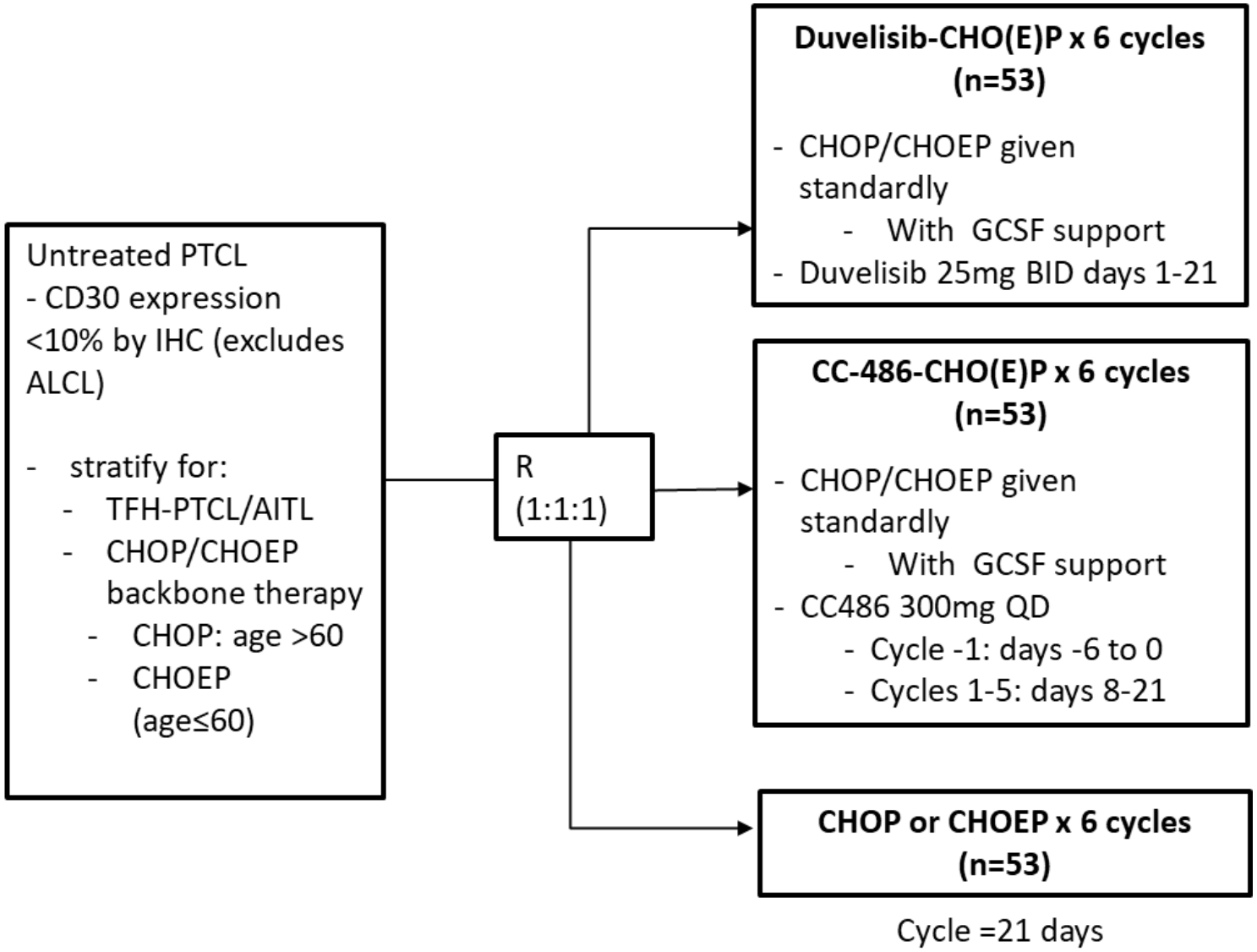
The Lancet Regional Health - Western Pacific
2024;50: 101160

CHOP X 1 Cycle → **CHOP X** X 5 Cycles

CHOP **X**
-P53^{mut}- decitabine
-TET2/KMT2D ^{mut} azacytidine
-CREBBP/EP300 ^{mut} tucidinostat
-Lenalidomide



A051902: A randomized phase II study of duvelisib or 5-azacitidine in addition to CHOP or CHOEP in comparison to CHOP/CHOEP



- Primary Objective:
  - To compare the PET CR rate of duvelisib or 5-azacitidine in combination with CHOP/CHOEP compared to CHOP/CHOEP
- Primary Endpoint:
  - **25% difference PET CR rate**
- Correlative Studies:
  - Monitoring MRD
  - Gene Expression Profiling and Custom Capture Sequencing
  - Patient Reported Outcomes
  - PET/CT Evaluation

NCT04803201

Conclusions

- Advances in understanding the biology and molecular mechanisms of PTCL have led to improved classification and treatment strategies.
- Treatment approaches have become more targeted, offering the potential for better patient outcomes
- BV-CHP has changed the treatment landscape in ALCL
  - Intensification regimens-safe and effective
- Recent studies highlight the sensitivity of TFHL to epigenetic therapies
- Future research should prioritize evaluating new treatments for specific subtypes or molecularly defined subgroups

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