10th POSTGRADUATE
Lymphoma
Conference

The vision of diversified first-line therapy in PTCL

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Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

President:
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Disclosures

Disclosures of Kerry Savage

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Seagen/Pfizer			X				
BMS	X						
Roche			X				
Coruvs							X
Regeneron							X

Mature T/NK-cell neoplasm WHO 5th (or ICC) 2022 - > 30 entries

Leukemic

- T-cell PLL
- T-large granular lymphocytic leukemia
- NK-large granular lymphocytic leukemia
- EBV-positive T andNK-cell LPDs of childhood (4)
- Adult T-cell leukemia/lymphoma

Primarily extranodal

- Extranodal NK/T-cell lymphoma
- Aggressive NK-cell leukemia
- Intestinal T-cell lymphoma, NOS
- Enteropathy-associated TCL (type 1)
- Monomorphic epitheliotropic ITCL
- Indolent T-cell LPD of the GIT
- Indolent NK-cell LPD of the GIT
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like TCL*

≈ 60% of all PTCLs

*often lumped with cutaneous TCL

Cutaneous

- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30+ T-cell LPD
  - Lymphomatoid papulosis
  - Primary cutaneous ALCL

Primary cutaneous PTCL, rare subtypes

- Primary cutaneous gamma delta TCL
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
- Primary cutaneous acral CD8+ TCL
- Primary cutaneous CD4+ sm/med T-cell LPD
- Primary cutaneous PTCL- NOS

Primarily Nodal

- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma & other nodal lymphoma of TFH-origin
- ALCL, ALK positive
- ALCL, ALK negative
- Breast-implant associated ALCL (exception=EN)
- EBV+ nodal T and NK-cell lymphoma

Therapy for nodal PTCLs: What have we learned over the past 20 years?

- Splitting is better than lumping
- Pathobiology and genetics can inform therapy
  - Subtype specific and biology driven drug sensitivities
- Collaboration is key

Diversified therapy in the front-line treatment of PTCL is already here

- **CHOP is no longer standard in:**
  - **Extranodal NK/T-cell lymphoma**

    Advanced stage – Asp-based regimens (GEMOX-P/SMILE)

    Early stage – Cisplatin-based; Asp-based 'sandwich' RT

    PD1/PDL inhibitor therapies under investigation

  - **Hepatosplenic T-cell lymphoma**

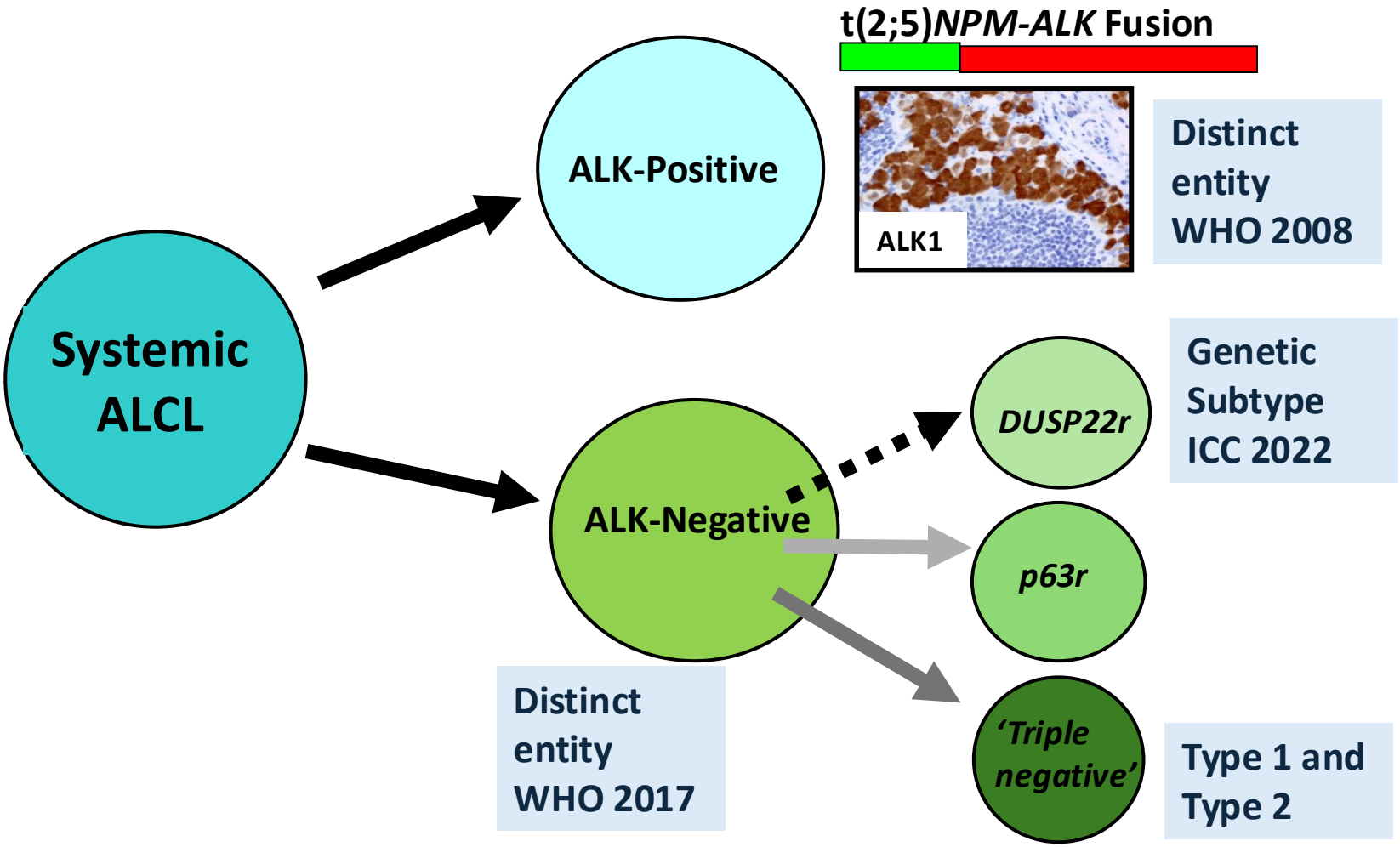
    Non-CHOP regimen (eg ICE, GDP) + allo-SCT favoured

- **CHP-BV CD30+ is new standard in:**
  - ALCL (yes)
  - Non-ALCL (maybe, maybe not)

- **Moving beyond CHOP in CD30- PTCLs:** Is CHOP still the right backbone? Should we abandon CHOP for rationale novel therapy combinations?

Splitting nodal PTCLs further can translate into further treatment precision

Anaplastic Large cell lymphomas



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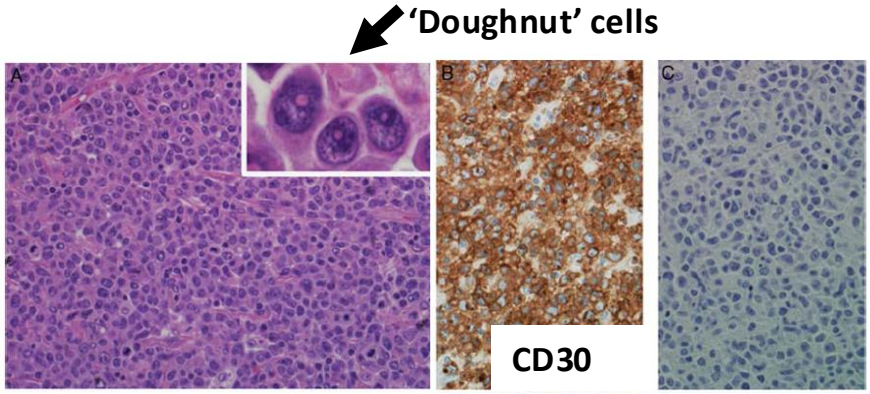
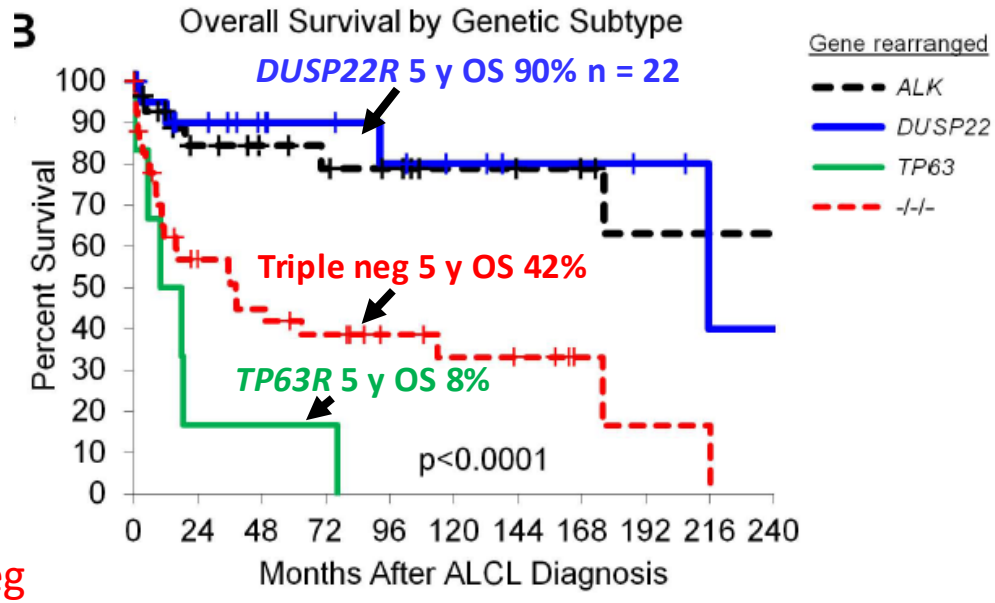
Genetic heterogeneity of ALK-Neg ALCL





***DUSP22* rearrangement (*DUSP22R*)**

ALK-neg ALCL: Key features

- 20% to 30% of all ALK-neg ALCL
- Hallmark cells; doughnut cells (inset)
- Cytotoxic marker neg; pSTAT3 neg; PDL neg
- High expression of cancer testis antigen (CTA); DNA hypomethylation
- MSC^{E116K} mutation

Parrilla Castellar, et al. Blood. 2014; Pedersen MB, et al. Blood. 2017; Luchtel RA, et al. Blood. 2018; King et al. Am J Surg Pathol. 2017 Luchtel et al. Blood 2019.

Is there High(er) risk *DUSP22R* ALK-Neg ALCL?

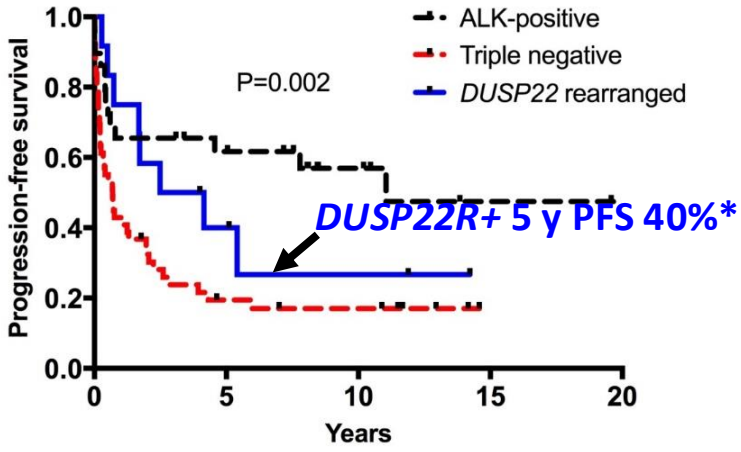
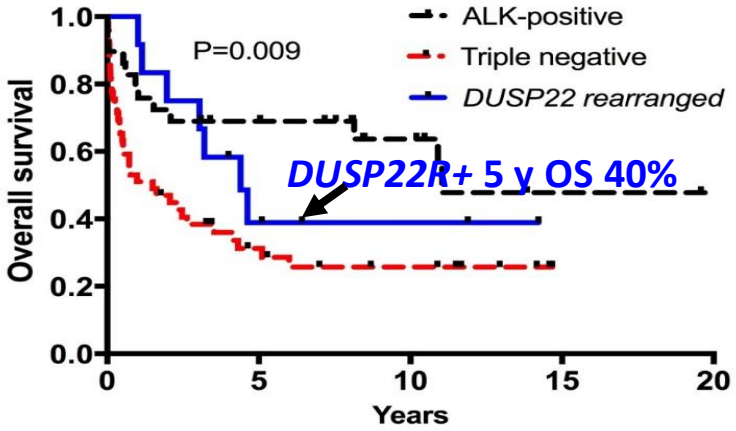
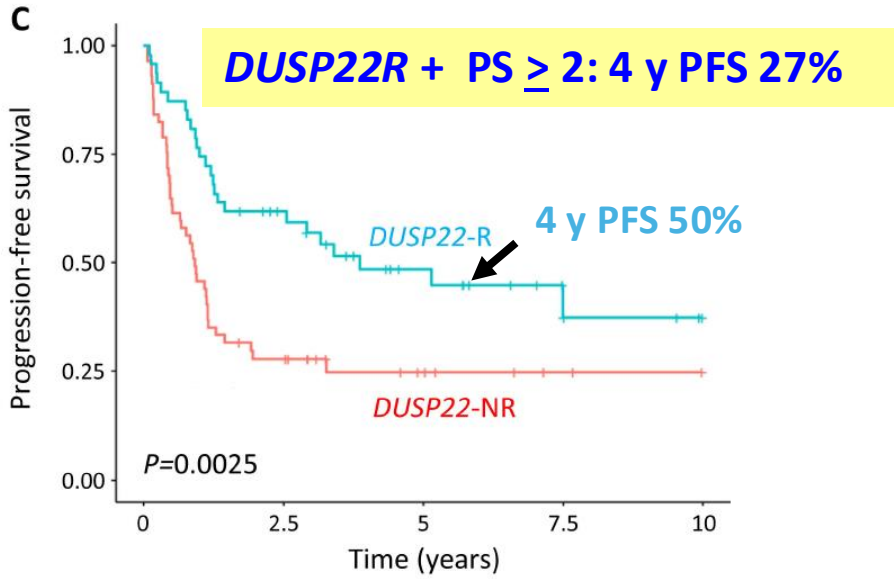
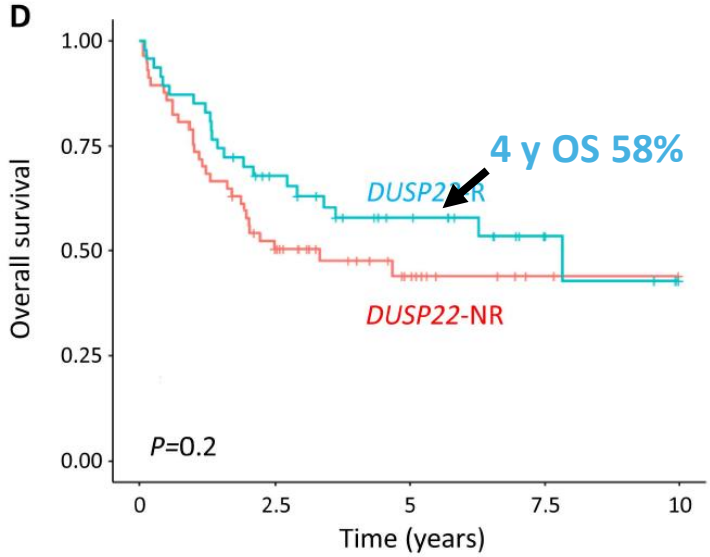


Figure 1A.

*1case DUSP22*R* CNS relapse

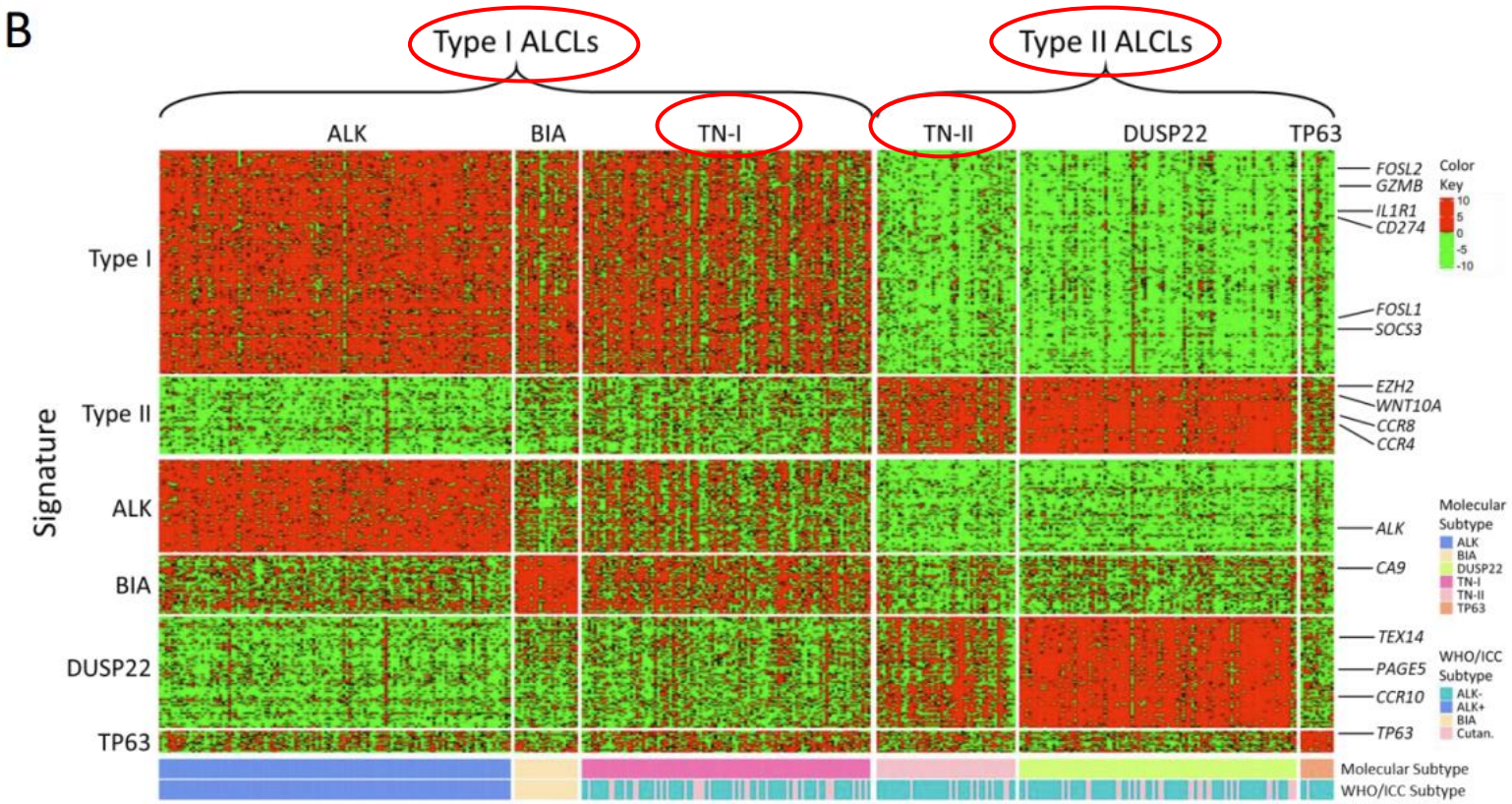






Hapgood G, et al. Br J Haematol. 2019; Adapted from Sibon D, et al. Haematologica 2022

‘Triple negative’ ALK-negative ALCL is two diseases



‘Type 1’ – **JAK-STAT3 signaling pathway** activation **(pSTAT3 positive by IHC)**
- Also includes ALK-pos, BIA-ALCL

‘Type 2’ – **Epigenetic pathway enrichment**
- Also includes *DUSP22R* (and *P63R*) cases

Feldman/LLMPP Epub Blood 2025

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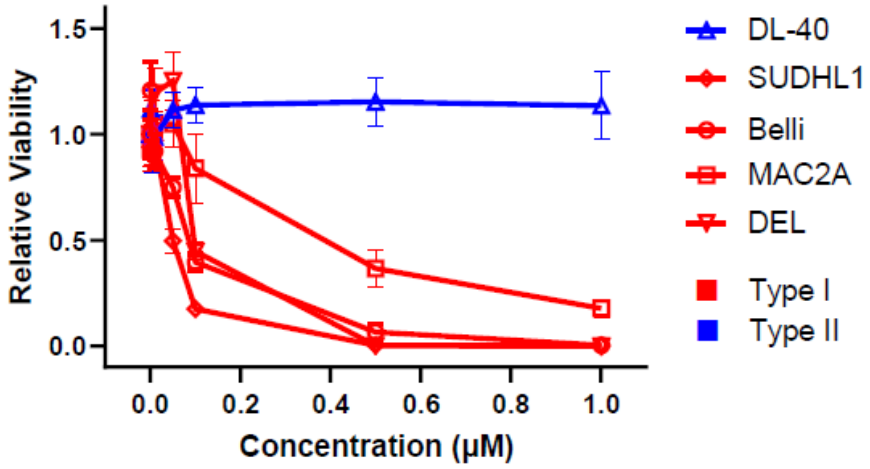
Proof in principle: Targeting STAT3 (type 1) and EZH1/2 (type 2) in ALCL cell lines

C



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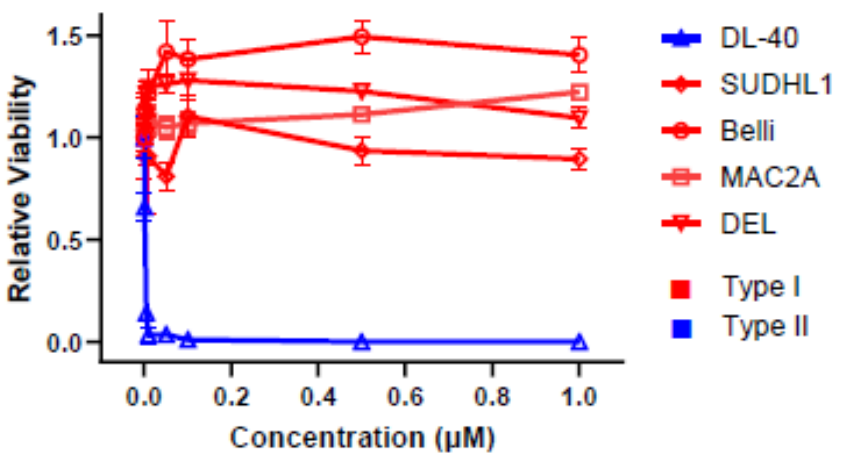

Feldman/LLMPP Epub Blood 2025

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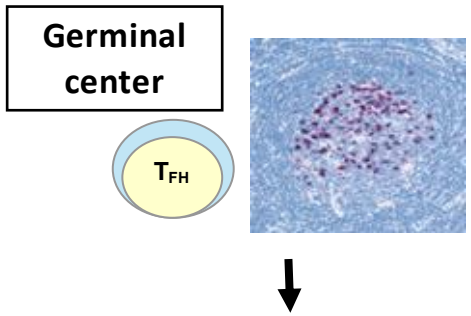
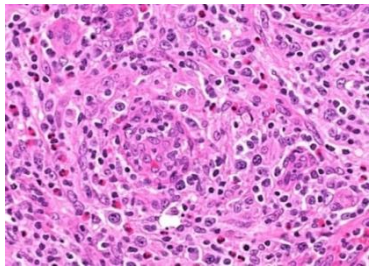
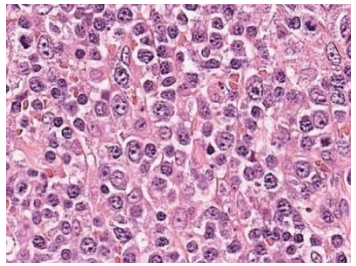
TFH (nodal) T-cell lymphoma: Disease spectrum recognised in WHO 2017 (4thR)



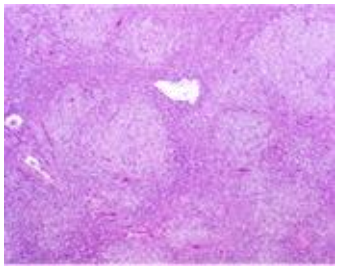
CD4 + and 2 ('preferably 3') +
for: <u>TFH markers</u>
CD10 (specific)
CXCL13 (specific)
PD1 (sensitive)
ICOS (sensitive)
BCL6 (less sensitive)



Angioimmunoblastic type



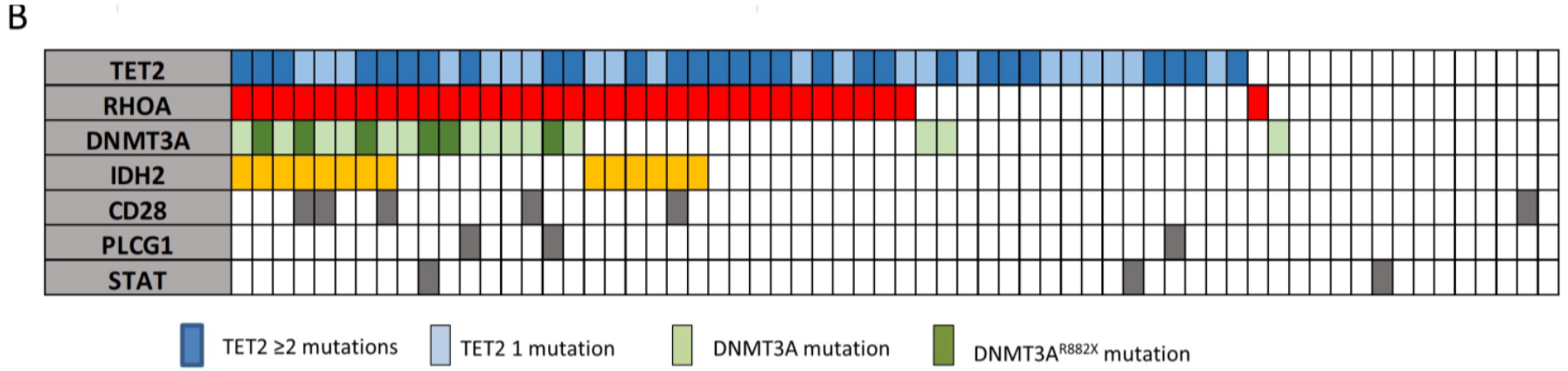
NOS



Follicular type

Microenvironment differences

TFH TCL: Poster child for personalized therapy



Lemonnier et al Blood Adv 2021

Unique mutational landscape

Epigenetic regulators

-TET2 (50-75%)

-IDH2 R172 (hotspot) (24-45% AITL)

-DNMT3 (20-30%)

Signaling pathways

-SYK-ITK (rare F-PTCL)

-RhoA G17V (hotspot) (50-70%)

-TCR signaling (e.g. CD28, PLCG1)

Sensitivity to epigenetic/immunomodulatory drugs

Epigenetic

HDAC inhibitors - romidepsin, belinostat, chidamide

Hypomethylating agents - 5-azacitadine, decitabine

EZH2 inhibitors - valometostat, SHR2554

Immunomodulatory – prednisone, lenalidomide, cyclosporine, duvelisib (also cell signalling)

Cell signalling - duvelisib (PI3K), golicitinib (JAK1)

Personalized therapy is already standard in TFH T-cell lymphomas

Agents Study	Target	Phase	PTCL subtype (N)	ORR/CR %	Median DoR in months	Median PFS in months
Alisertib[69] *vs.* Investigators' choice[a] Lumiere	Aurora kinase	III	PTCL (271 total)[c]	33/18 45/27	7.4 5.6	3.8 3.5
Lenalidomide[82]	Immunomodulatory Anti-angiogenic	II	PTCL (54) AITL (26)	22/11 31/15	3.6 3.5	2.5 4.6
Duvelisib[89]	PI3K γδ	II	PTCL (78) AITL (21)	50/32 67/48	7.8 NR	3.6 NR
Cerdulatinib[91]	Dual JAK/SYK	II	PTCL (65) TFHL (29)	35 52	NR 12.9	NR 4.6
Ruxolitinib[49]	JAK1/2	II	PTCL (53) Cohort 1 *JAK/STAT*+ Cohort 2 pSTAT3+ Cohort 3 unselected	25 33 29 12	8.4 7.5 14.7 Not reached	2.8 NR NR NR
Golidocitinib JAKPOT8[92]	JAK1	I/II	PTCL (51) AITL (20)	43/22 60	Not reached	NR
Tipifarnib[90]	Farnesyltransferase	II	CXCL12 3'UTR (12) AITL (11)[d]	42/25 45/27	NR NR	NR
Azacitidine[76] *vs.* Investigators' choice[b] ORACLE	DNMT1	III	TFHL (86 total)	33/12 43/23	NR NR	5.6* 2.8
Valemetostat[78]	EZH2	I	PTCL (45) AITL	56/24 70.6	NR NR	NR NR
Combination therapies						
Romidepsin + azacitidine[95]	HDAC + DNMT1	II TN/RR	PTCL (25) TFHL (15)	61/43 80/60	20.3 NR	8.0 8.9
Romidepsin + duvelisib[53]	HDAC + PI3K γδ	I	PTCL (55) TFHL (19)	58/42 68/58	8.1 NR	6.9 NR
Romidepsin + pralatrexate[115]	HDAC + DHFR	I	PTCL (14)	71/29	NR	NR

AITL/TFHTCL
Single agent
ORR 31%-71%
CR 15-48%

AITL/TFHTCL
Combination
ORR 70-80%
CR 60%

Ngu and Savage
Haematologica 2023

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PTCL-NOS: The ‘Wastebasket’ Diagnosis

Mature Lymphoma with T-cell phenotype

↓

Features not consistent with ‘specified’ PTCL subtype as defined by the WHO

↓

PTCL-NOS

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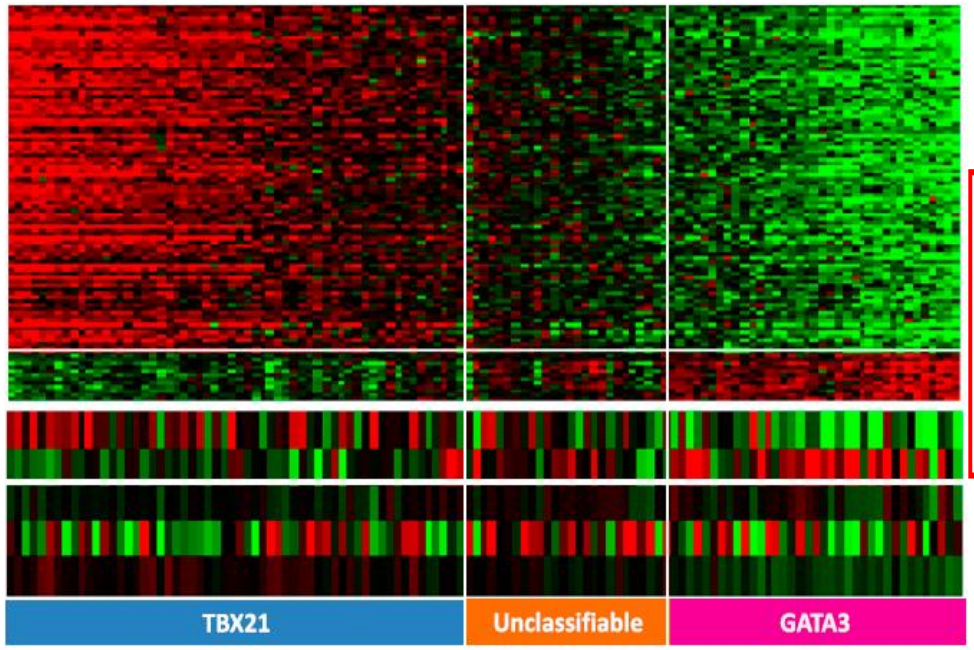
Molecular subclassification of PTCL-NOS: TBX21 vs GATA3

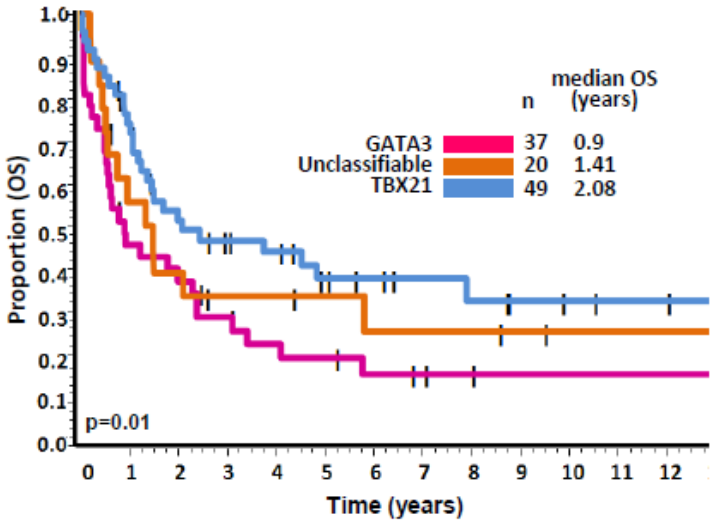
NFKB gene signature

TBX21 (T-bet) ***and EOMES and targets: CXCR3, IL2RB, CCL3, IFNγ***



GATA3 ***and targets: CCR4, IL18RA, CXCR7, IK***

MYC, MTOR, PI3K



'GATA3' inferior OS vs 'TBX21'

20% unclassified

Iqbal et al. Blood 2014

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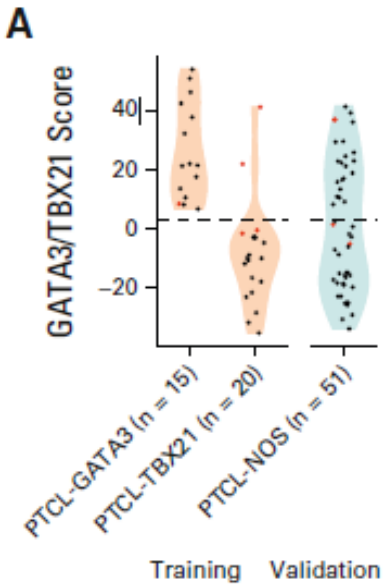
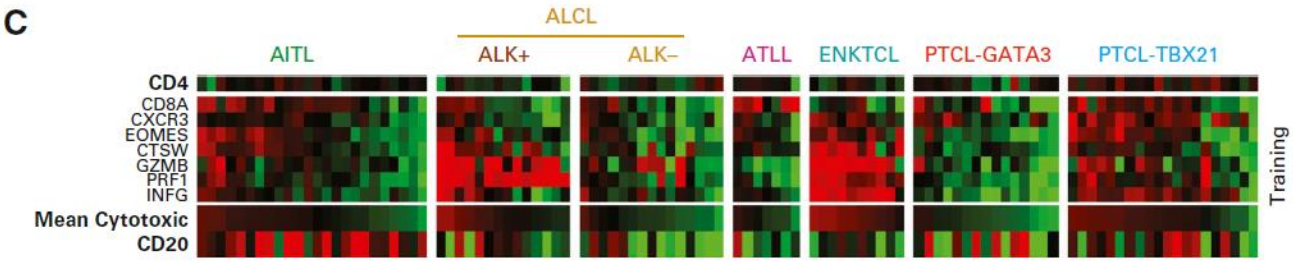
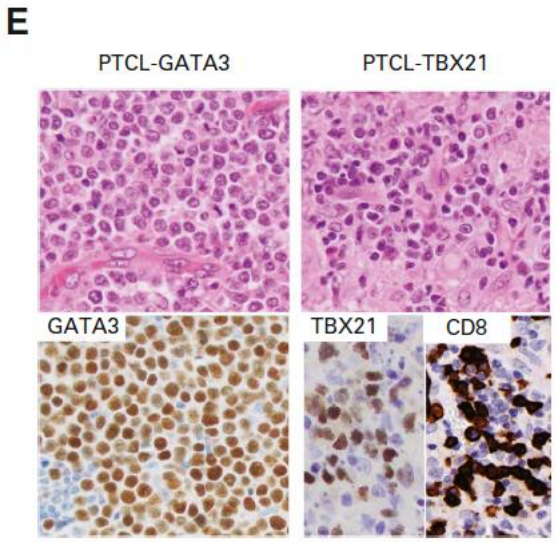
Translating molecular subtypes into clinical practice: GATA3 vs TBX21 PTCL-NOS using FFPE and nCounter assay







PTCL-GATA3 classification scores on nCounter

Molecular assay using nanoString (or RNAseq) holds potential to integrate into trials with rationale drugs

Amador et al JCO 2022

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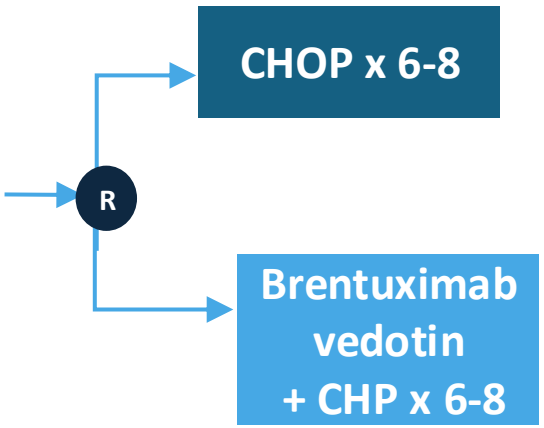
2026: Progress in diversified therapy in PTCLs and future directions

ECHELON2: Biggest breakthrough in the front-line treatment of PTCLs (CD30+): Brentuximab-vedotin (BV)-CHP

Eligibility
- Treatment naïve
- CD30+ PTCL* (≥10% cells)
- Targeting 75% ALCL** (ALK+ IPI ≥ 2)



CHP–BV vs CHOP
- ✓ Improved ORR/CR
- ✓ Improved PFS*
- ✓ Improved OS
- ✓ Comparable toxicity
- ✓ Rapid FDA approval 2018

* WHO 2008 Eligible subtypes: ALCL, PTCL-NOS, AITL, ATLL, EATL, HSTCL

**Regulatory requirement[19]

Total 552	BV+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)

ALCL →70% of enrolled patients

*Primary endpoint

Horwitz et al. Lancet Oncology 2019

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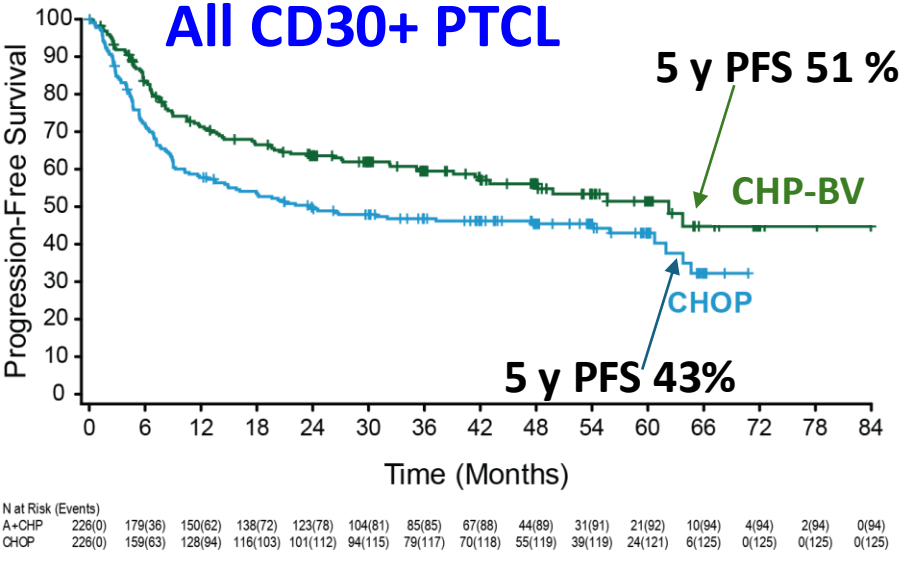
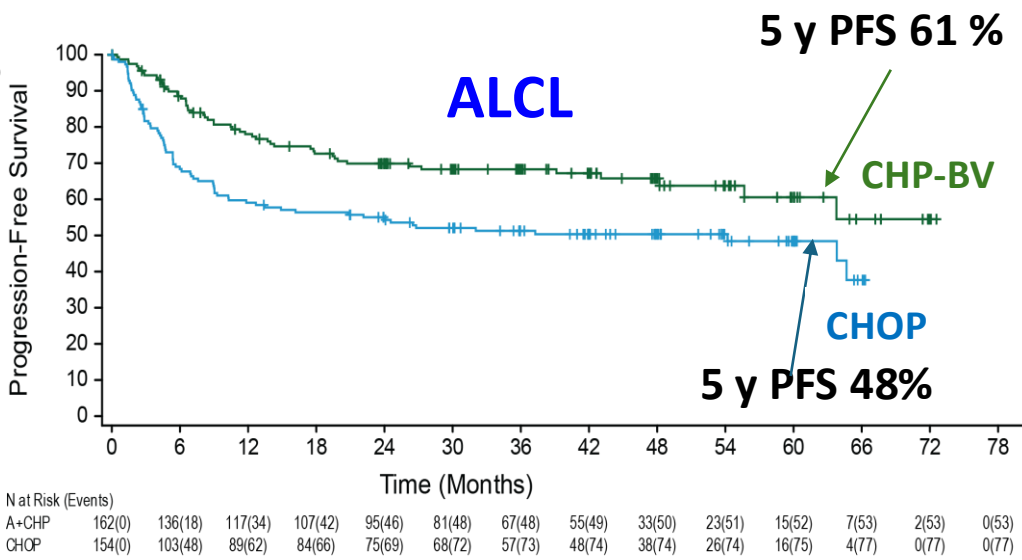
CHP-BV in CD30+ PTCLs: 5 year follow-up

All CD30+ PTCL



	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		

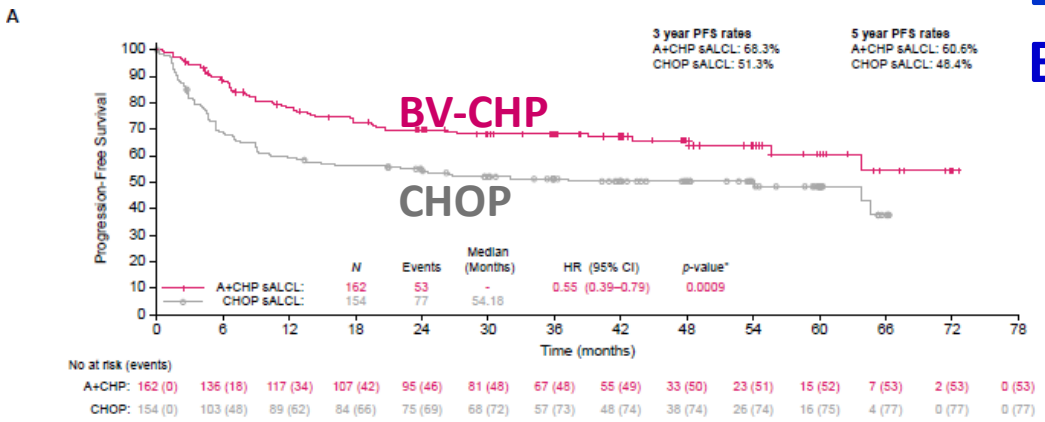
ALCL



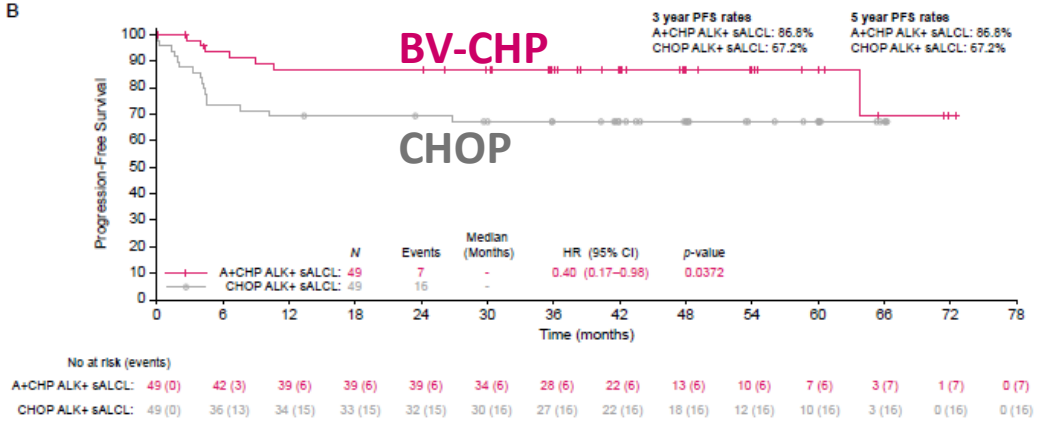
	N	Events	Medians (Months)	HR (95% CI)	p-value*
A+CHP	162	53	–	0.55 (0.39, 0.79)	0.0009
CHOP	154	77	54.18		

Horwitz et al Ann Onc 2021

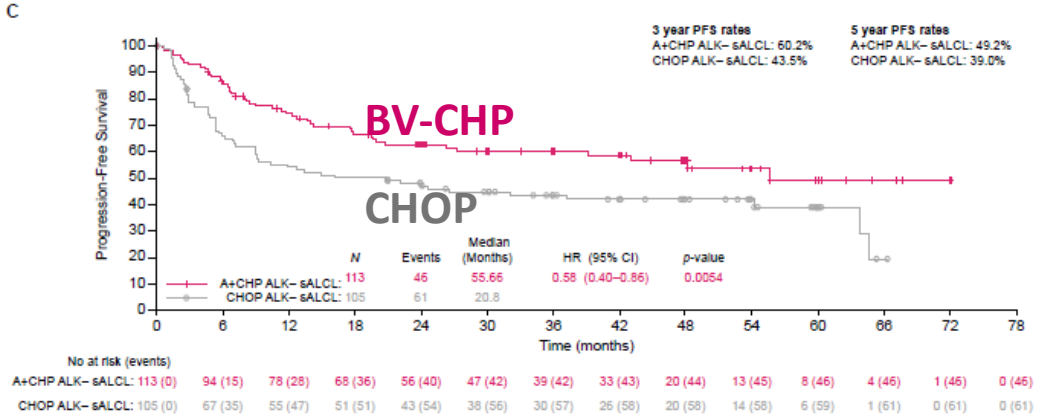
Echelon 2: ALCL subgroup 5 y f/u
BV-CHP vs CHOP



All ALCL: 5 y PFS
60.6% vs 48.4%



ALK-pos: 5 y PFS
86.8% vs 67.2%



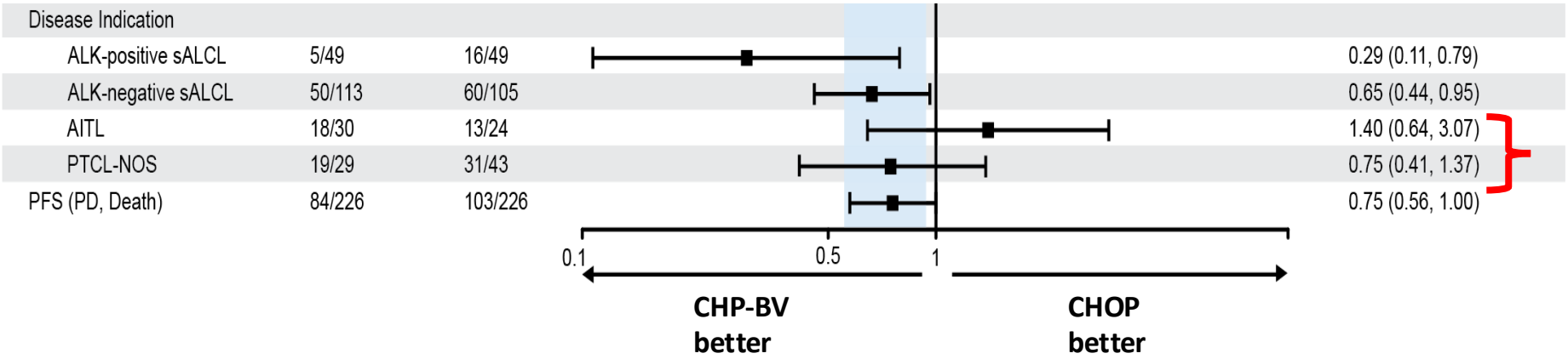
ALK-neg: 5 y PFS
49.2% vs 39%

? Outcome with BV-CHP in ALK-neg subtypes

Domingo-Domenech et al. Blood Cancer J. 2025

What about CHP-BV in CD30+ non-ALCL PTCLs?

CHP-BV vs CHOP subgroup analyses



Challenges: 1) Unplanned subgroup analysis

2) Small patient numbers

- Whole study: AITL n=54; PTCL-NOS n=72

3) Has led to regulatory approval differences

Horwitz et al. Lancet Oncology, 2019

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Current guidelines for the treatment of nodal PTCLs

	BC Cancer	NCCN 2026	UK 2022	ESMO 2025
ALCL	**CHP-BV** + consider ASCT (ALK-neg)	**CHP-BV** + consider **ASCT** (ALK-neg and high risk IPI ALK-pos if CR)	**CHP-BV** + consider **ASCT** (ALK-neg ALCL and high risk ALK-pos (age > 40, IPI ≥ 2)	**CHP-BV** + **ASCT** (ALK-neg if CR)
PTCL-NOS and TFH TCL	**CHOP, CHOP, CHP-BV** (CD30+ PTCL-NOS, AITL) + consider **ASCT** (if CR)	**CHOEP, CHOP, CHP-BV** (CD30+) + **ASCT** (if CR)	**CHOP + ASCT** (if CR)	**CHOEP + ASCT** (if CR)

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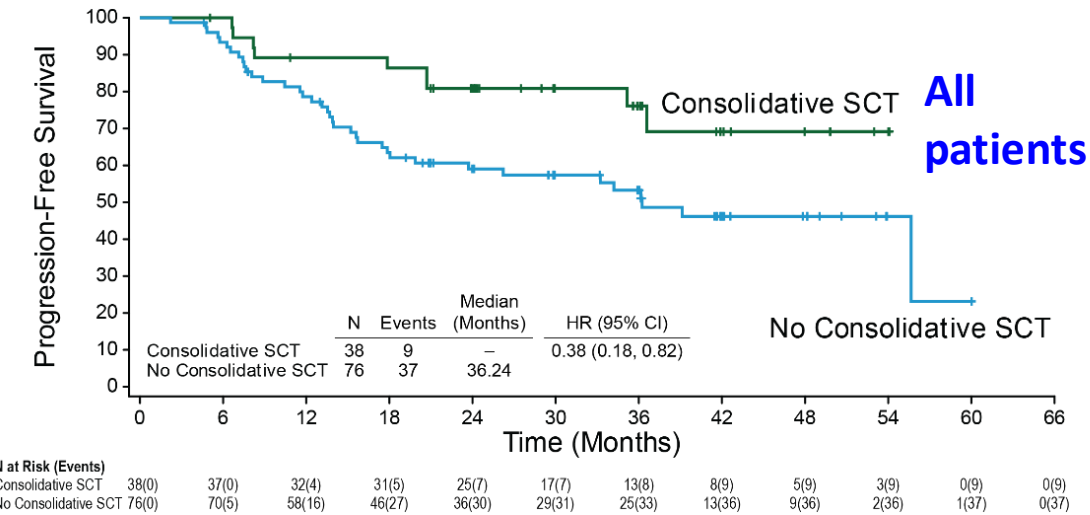
Can we forgo consolidative auto-SCT post CHP-BV? Not yet

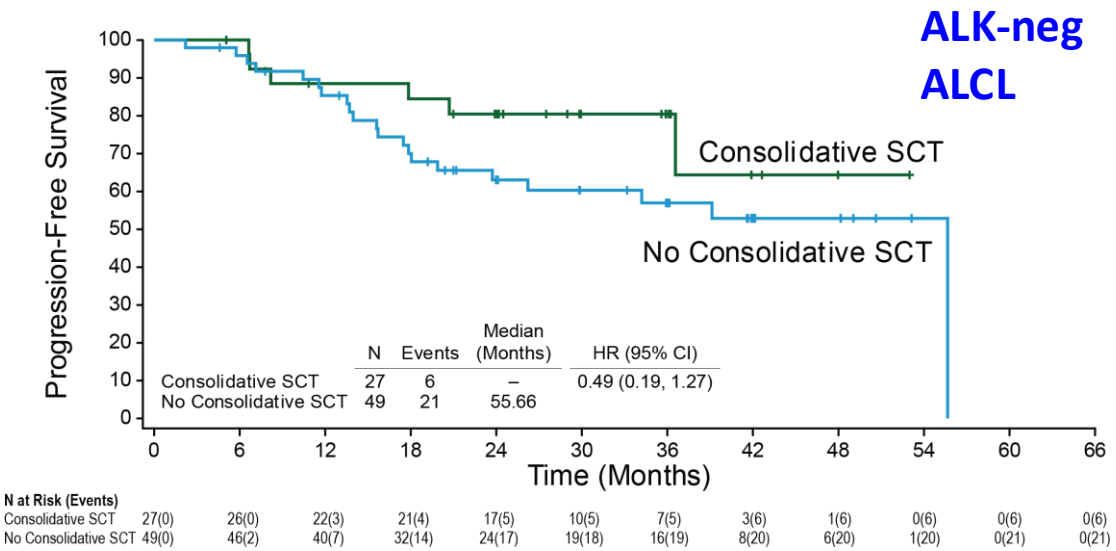
Echelon 2 subgroup analysis

- **CR patients post CHP-BV**
  →Is there a PFS benefit with SCT

- **Bottom line**: Patients who underwent consolidative ASCT had an improved PFS
  -Less clear in ALK-neg ALCL

- **Knowledge gaps:** Who can forgo ASCT (?DUSP22R, low risk IPI)





Savage et al. Blood Advances 2022

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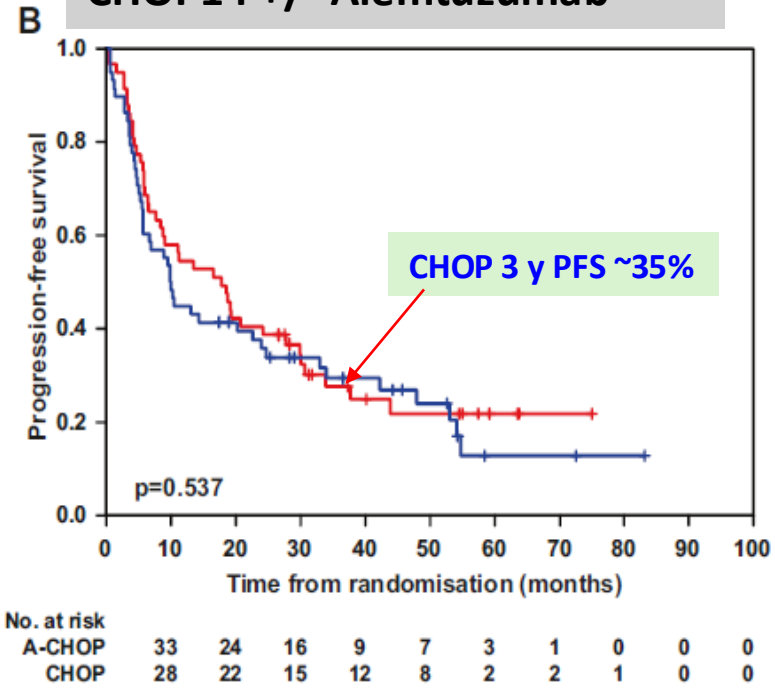
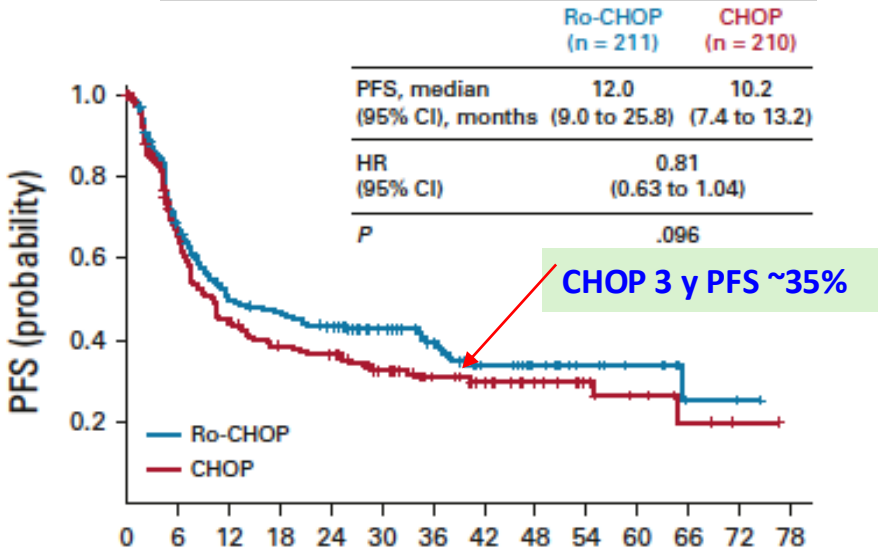
What hasn't worked? CHOP + X negative Ph 3 trials

CHOP14 +/- Alemtuzumab



Act 2 DSHNHL > 61-80 y
Median 69 y
CHOP14 vs
CHOP14-**Alemtuzumab**

CHOP +/- Romidepsin



LYSA All ages Median 65 y
CHOP vs
CHOP + **Romidepsin**
No consolidative auto-SCT allowed per protocol

Lessons learned: It's not easy to combine drugs with CHOP and challenges with disease heterogeneity

Wulf et al. Leukemia 2021; Bachy et al. JCO 2022

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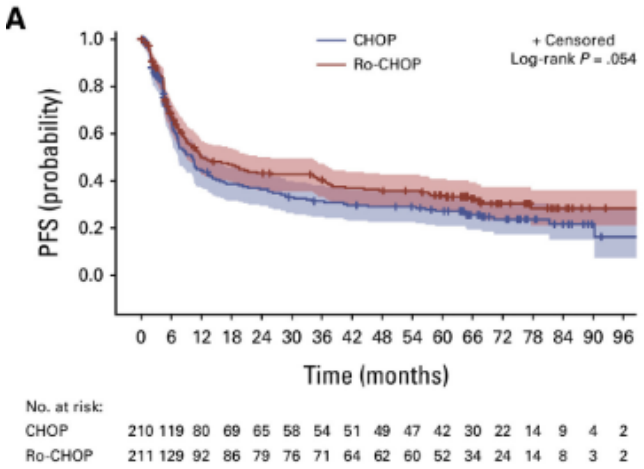
Ro-CHOP study lessons: Thou shalt not lump PTCL subtypes

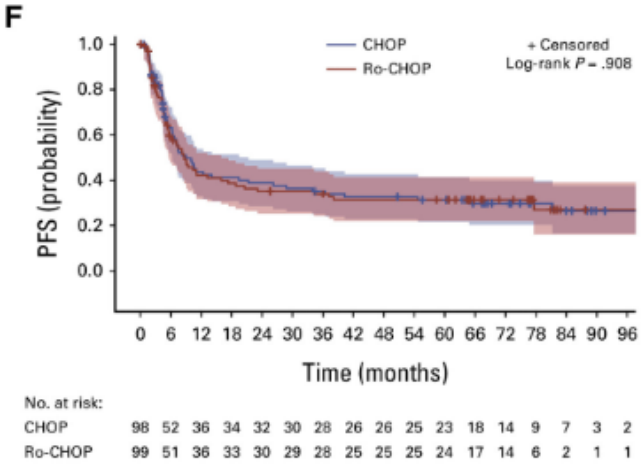
Median follow-up 72 months

All patients



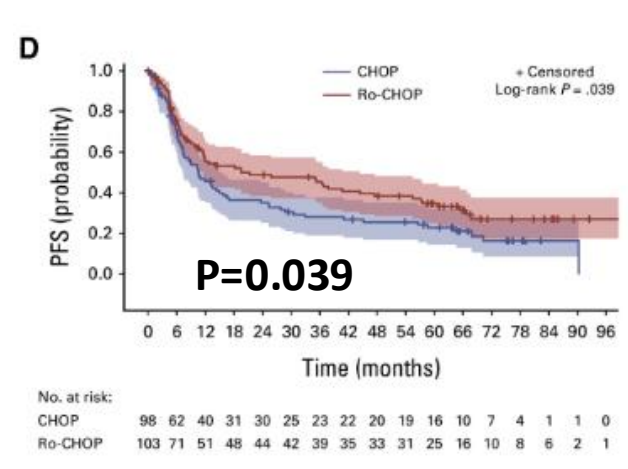
5 year PFS ≈ 40% vs 34%

Non-TFH-TCL



5 year PFS ≈ 37% for both

TFH-TCL



5 year PFS ≈ 40% vs 30%

What if the Ro-CHOP study was performed only in TFH TCLs ?

Camus et al. JCO 2024

K. Savage, Post-graduate Lymphoma Conference

Clinical trial approaches in newly diagnosed PTCL

Approach 1: CHOP + novel agent ('X')

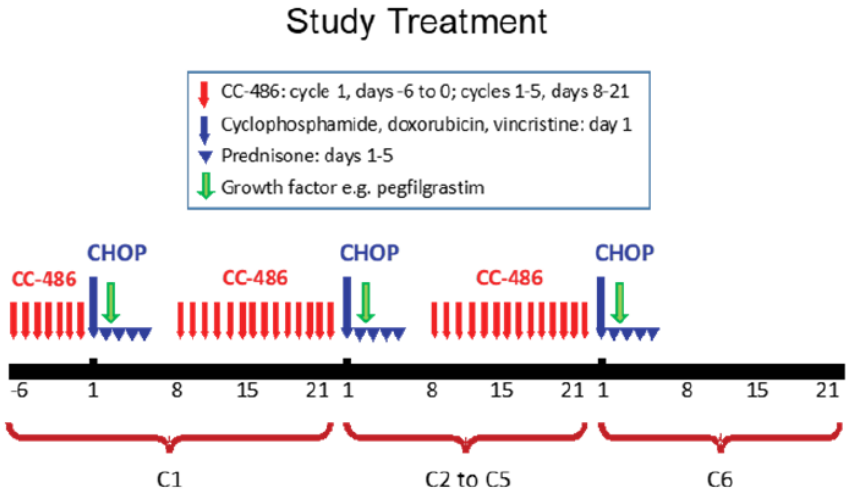
Approach 2: Novel agent combinations

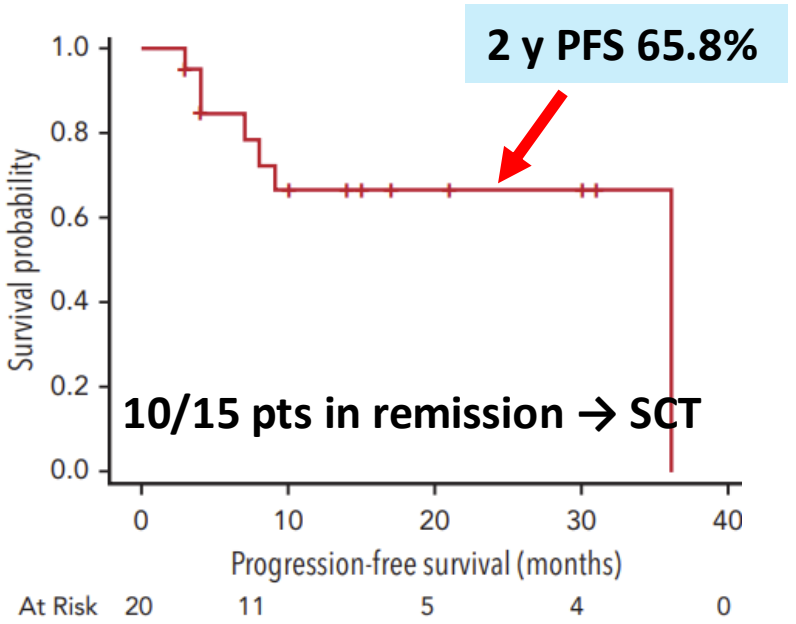
Approach 1: Phase 2 CHOP-azacitidine (enriched for TFHL)

Key eligibility
Treatment naive
-Nodal T-cell lymphoma with TFH phenotype (WHO 2016)
-PTCL-NOS
-ALCL, ALK-neg
-ALCL, ALK-pos with IPI > 2
-ATLL

- **Median age 66 y (22 – 77y)**

	ORR	CR
All n=20	75%	75%
TFHL n=17	88%	88%



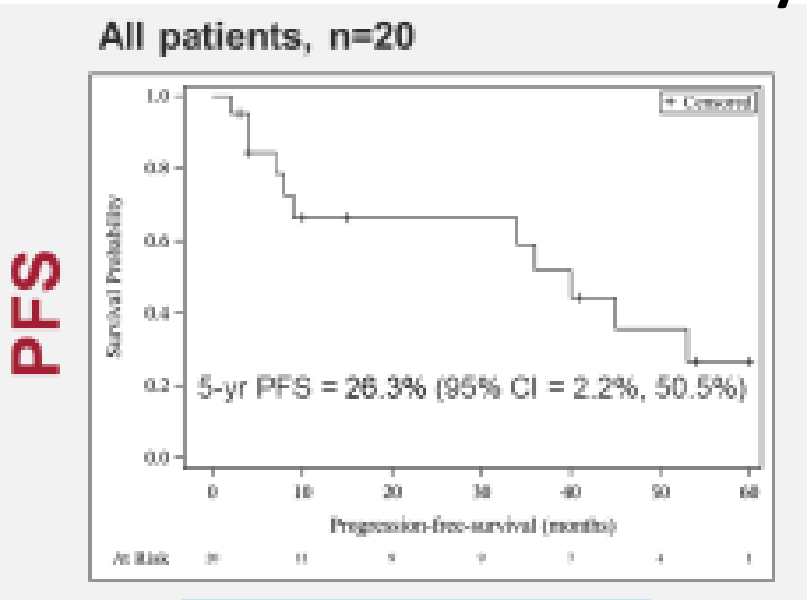


Adapted from Ruan et al Blood 2023

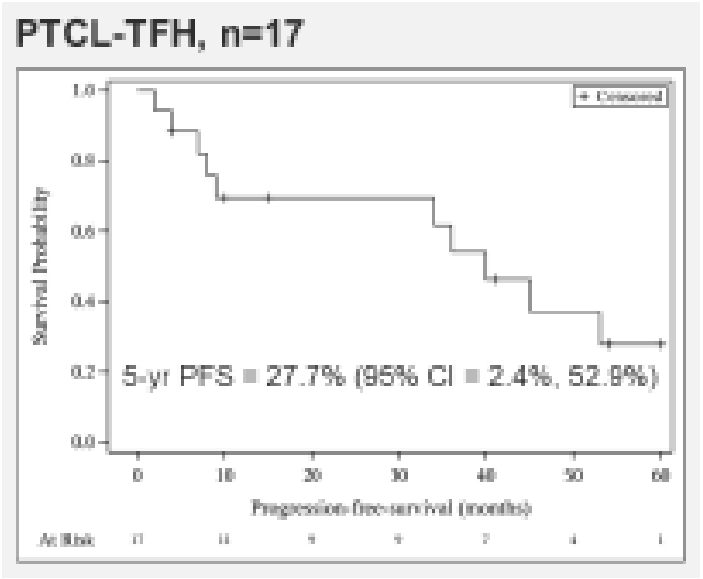
Lessons from Phase 2 CHOP-aza: Long term follow-up essential - do we need a maintenance approach?

5 year f/u

PFS



5 y PFS 26.3%!



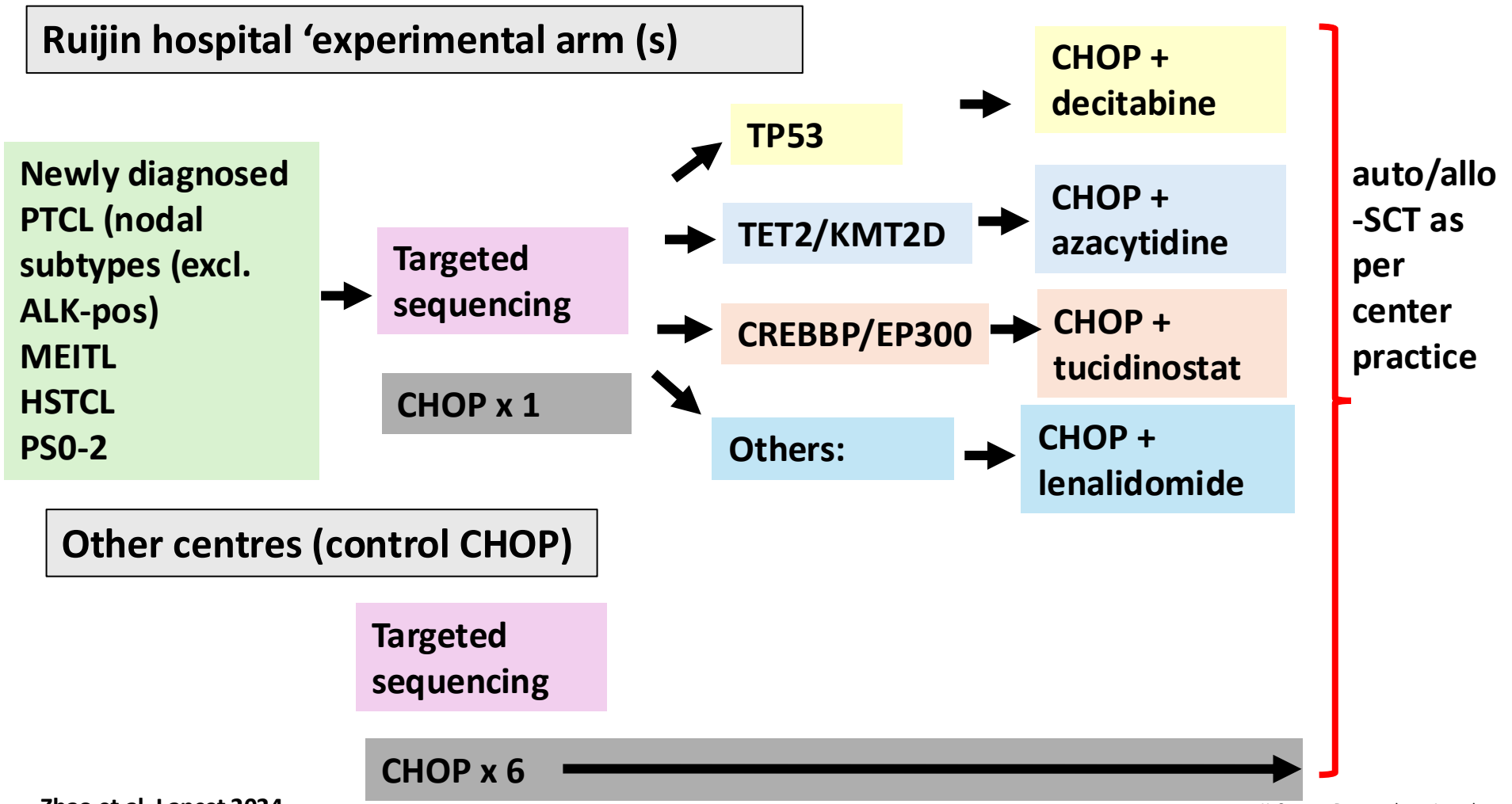
5 y PFS 27.7%!

ACANTUS (Korea) phase 1 study CHOP-Aza in nodal TFH TCL
-CHOP-aza x 6 cycles <u>maintenance</u> x 12 cycles
Kim ASH 2024 (study ongoing dose aza 75 mg/m2)
NCT05230680

Courtesy of Ruan et. al ASH 2024

Approach 1: CHOP + 'X' GUIDANCE-03 (molecularly informed)

Non-randomized phase 2 (7 hospitals)

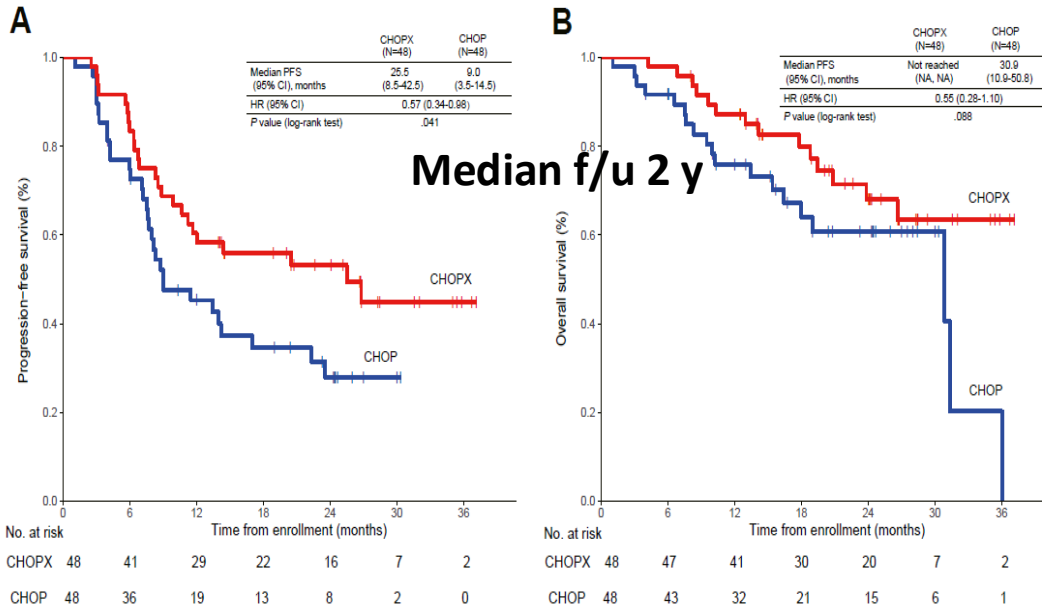


Zhao et al. Lancet 2024

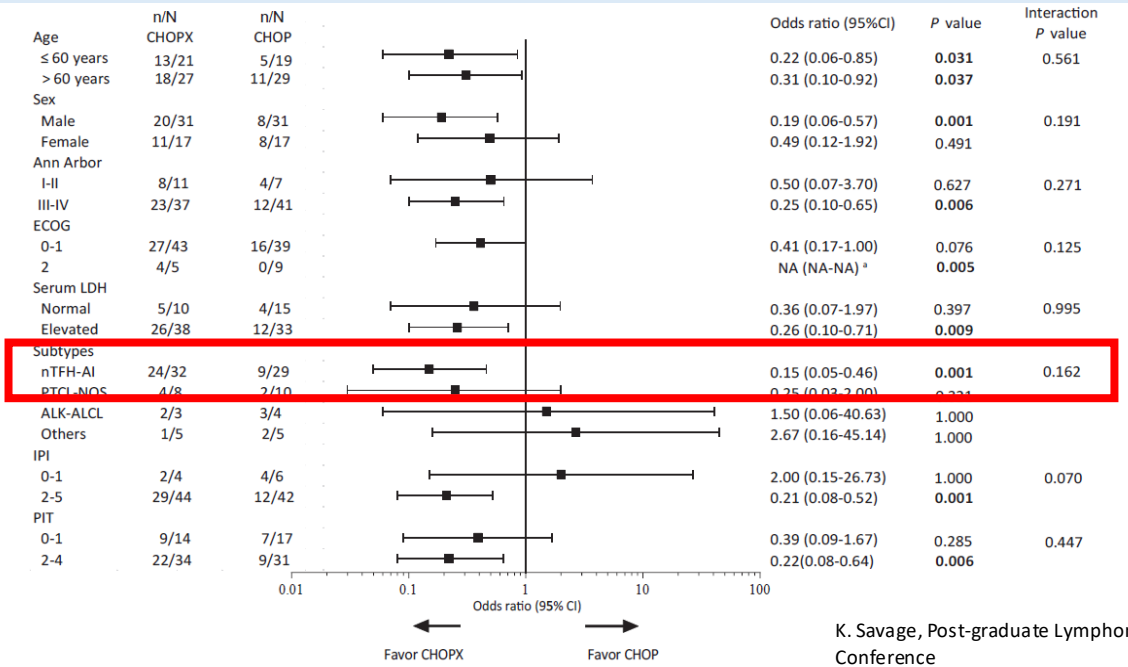
K. Savage, Post-graduate Lymphoma Conference

Comments

- Proof of concept; potential bias with design
- CHOP + X vs CHOP:
  → Improved PFS (trend OS)
- 2/3 had AITL
- Toxicity surprisingly similar



No diff in baseline factors; transplant rate = (12.5% v 10.4%)



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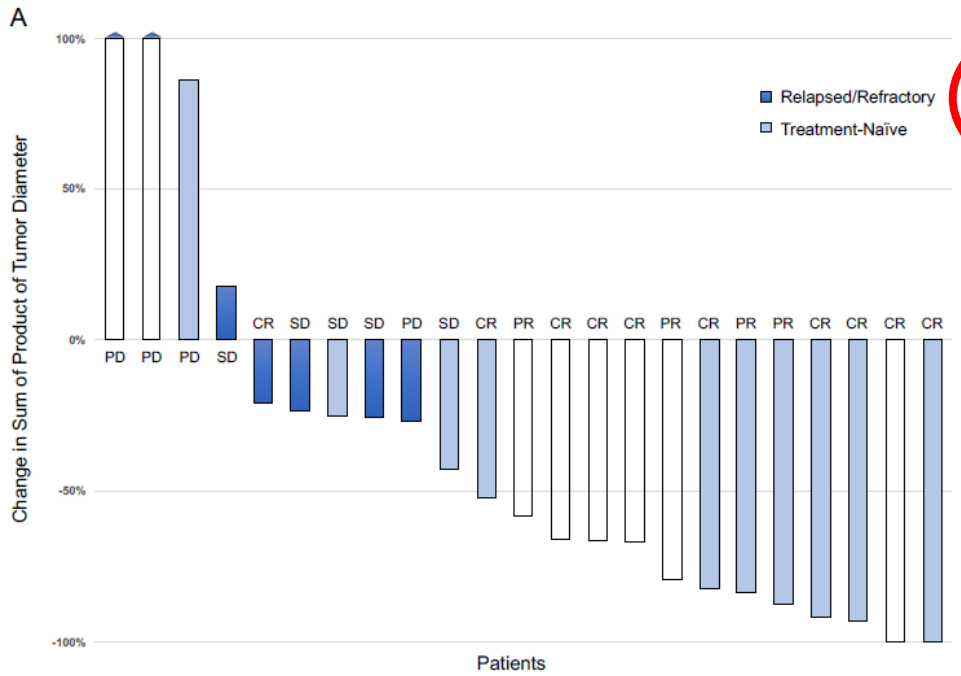
Approach 2: Romidepsin + 5-azacitidine in treatment naïve PTCL



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

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

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

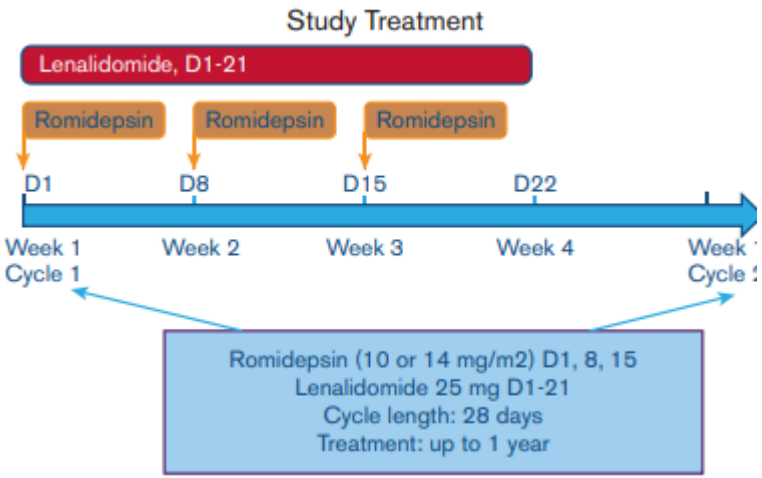
TFH PTCL n=17
ORR 80% CR 60%

2 pts excluded from response analysis (1 each TN and RR): rectal bleed (rectal cancer) + fatal sepsis

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

Falchi et al. Blood 2021; O'Connor et al. Blood 2019

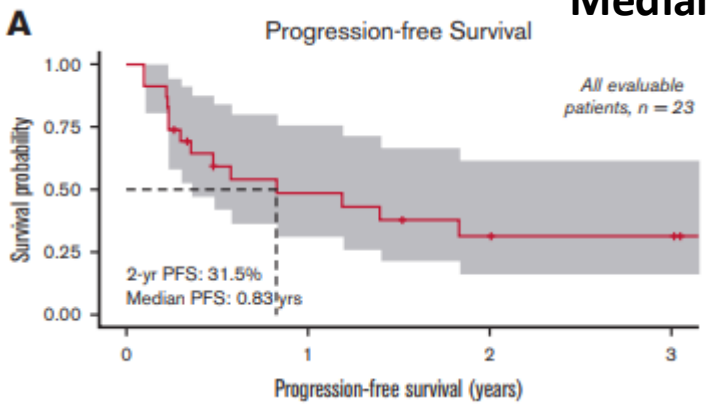
Approach 2: Romidepsin + lenalidomide in treatment naïve PTCL



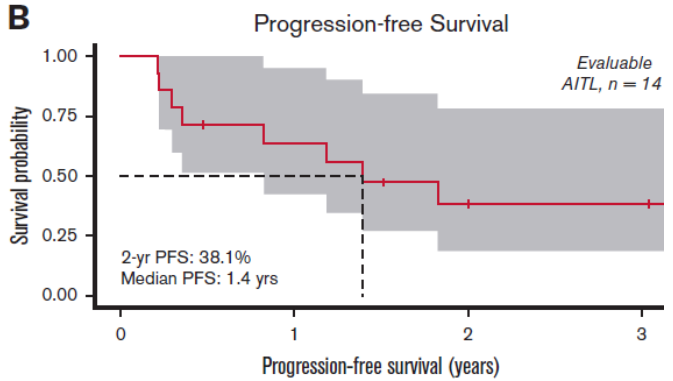
Enrolled all subtypes
-N=29 (55% AITL) > 60 y or 'not candidates for chemotherapy'
-Total n=29, 23 'evaluable'
-ORR 65.2% (CR 26.1%)
-Evaluable **AITL ORR 78.6% (CR 35.7%)**

45% grade 3 + neutropenia
34% grade 3+ thrombocytopenia

Median f/u 15.7 m



All pts 2 y PFS 31.5%

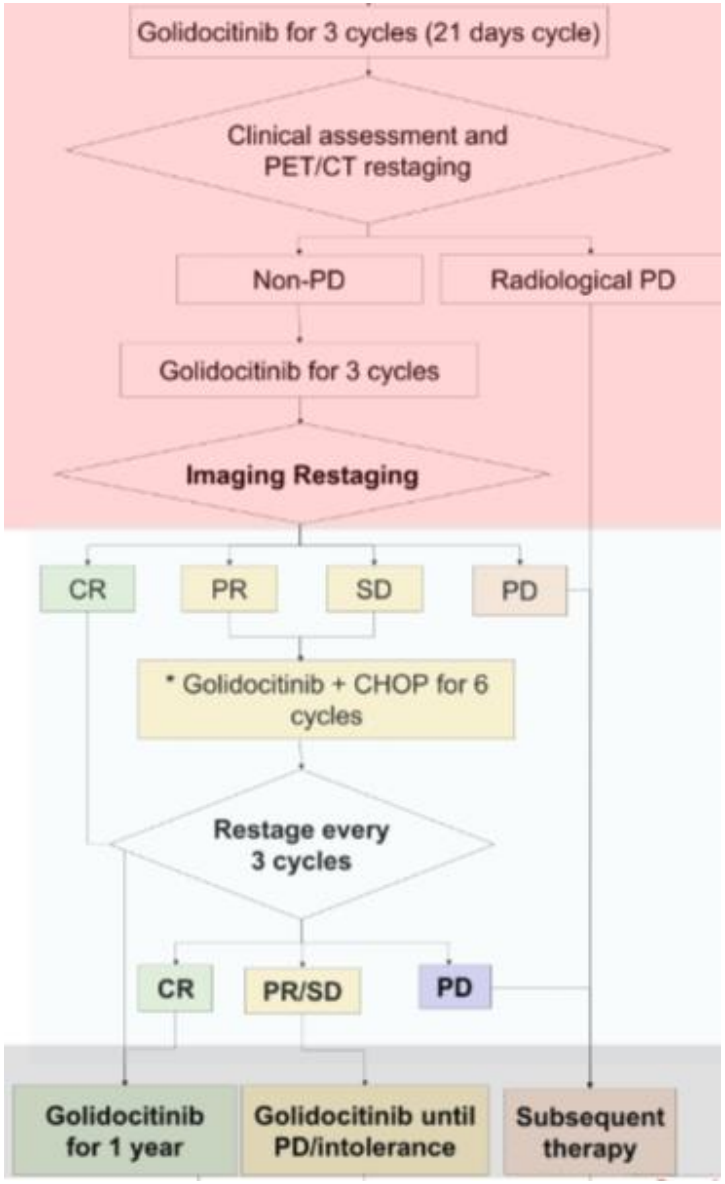


AITL 2 y PFS 38.1%

Ruan et. al Blood Advances 2023

K. Savage, Post-graduate Lymphoma Conference

Approach 2 (modified): Golidocitinib (JAK1 inhibitor) alone in newly diagnosed PTCL (ongoing)



IIT MDACC
Target 70% TFH PTCL
Patients in CR after golicidocitinib x 3 cycles continue for 1 year

Edelman Saul et al ASH 2025

K. Savage, Post-graduate Lymphoma Conference

Approach 1: Some ongoing studies of CHOP + X

Country	Phase	PTCL	CHOP/ CHOEP	+ Drug 'X'	Comparator
Acrotech Global	1 →3 (1:1:1) SPI-Bel-301	Excl ALK+	CHOP	Belinostat or Pralatrexate	CHOP
China	3(non-randomized)	All	CHOEP	Chidamide	CHOEP
China	2	TFH TCL	CHOP	Chidamide	None
US Alliance	2 (1:1:1)	CD30<10% Excl ALCL NK/TCL, HSTCL	CHOP >60y CHOEP ≤60y	Duvelisib Azacitidine	CHOP or CHOEP
China	1/2	All	CHOP/CHOEP	SHR2554	None
China	1/2	Excl ALCL, NK/TCL	CHOP	Liperlisib	None
China	1/2	All	CHOP	Golidocitinib	None
China	3	TFH TCL	CHOP	Azacitidine + Chidamide	CHOP
US	1	TFH TCL	CHOP	Ruxolitinib (+ main)	None

Front line therapy of nodal PTCLs: 2026 and beyond

Classification

- **Harmonized WHO 6th edition coming soon**

Primary therapy

- CHP-BV in CD30+ PTCLs (ALCL > non-ALCL; ALK-pos > ALK-neg) – still work to do
- CD30- PTCL(and non-ALCL CD30+) – Room for creative trial designs
- Consolidative auto-SCT? Reasonable (especially AITL)?

Relapsed/refractory PTCL

- Diversified approach is here for nodal TFH PTCLs and on the cusp in PTCL-NOS and ALK-neg ALCL