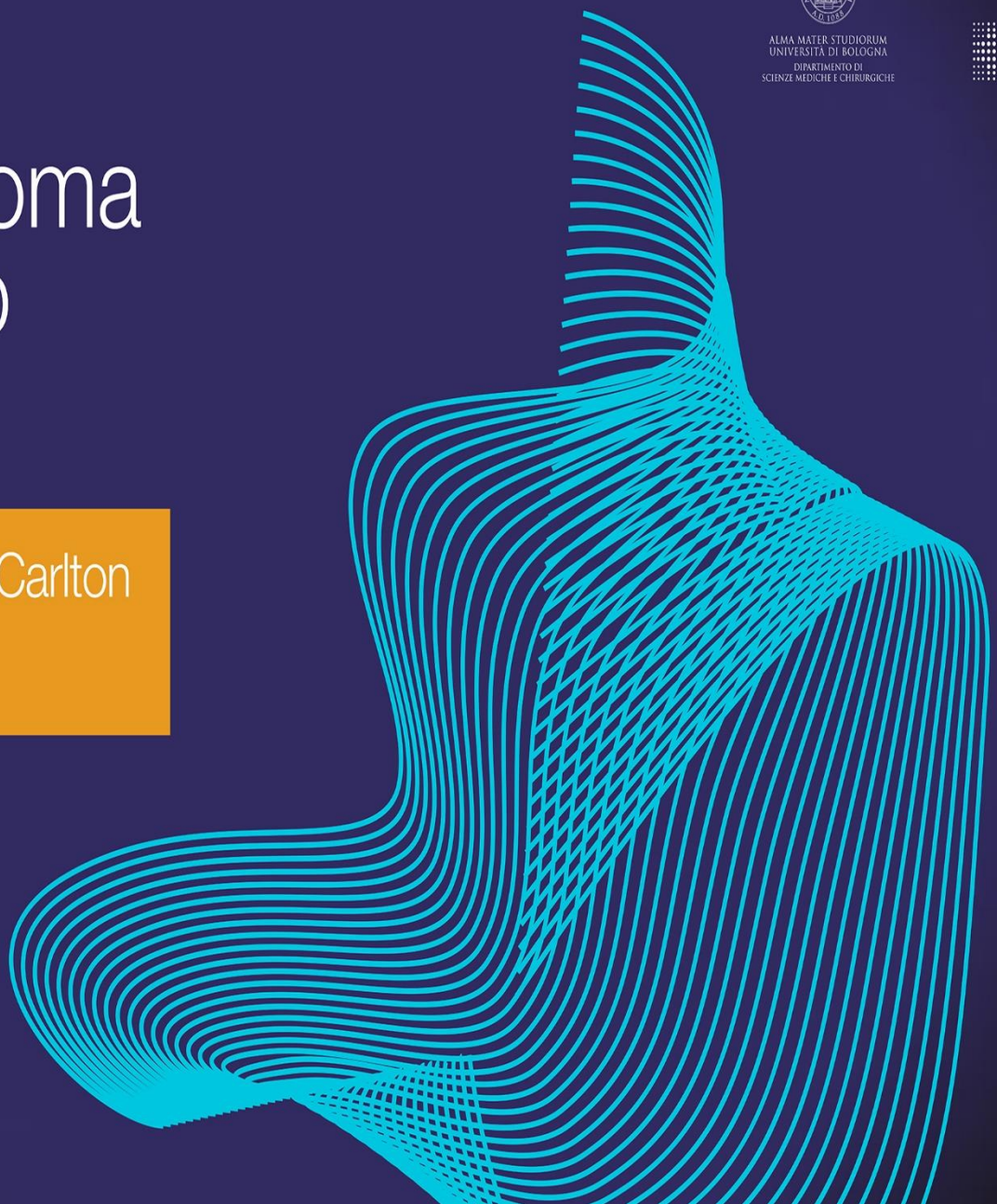
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

Update of PTCL in 2023: Focus on 'nodal' subtypes

Kerry J. Savage MD MSc FRCP(C)
Medical Oncologist, BC Cancer
Professor of Medicine, University of British Columbia
May 9, 2023

Disclosures

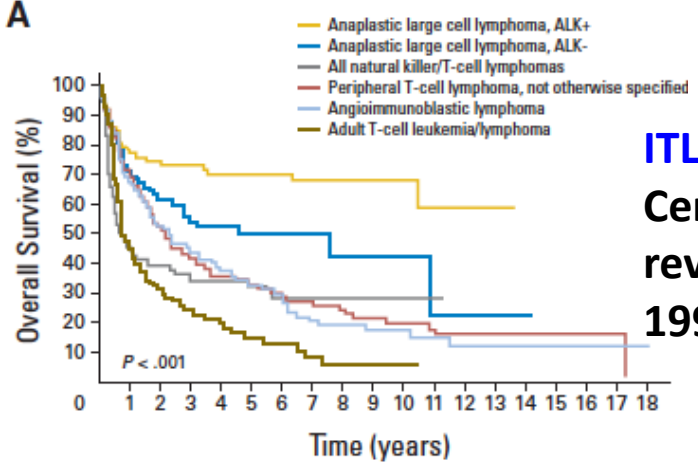
- Honoraria/consulting: BMS, Merck, Seagen, Janssen
- Steering committee: Beigene
- Research funding: BMS
- Institutional research funding: Roche
- DSMC: Regeneron

Nodal PTCL classification updates

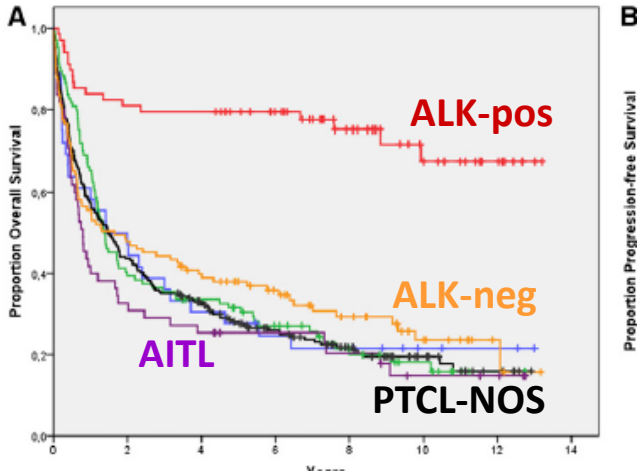
2017 WHO 4th Edition	2022 International Consensus Classification (ICC)	2022 WHO 5th Edition
PTCL-NOS	PTCL-NOS	PTCL-NOS
Not listed as entity, included with PTCL-NOS	*Primary nodal EBV+ T/NK-cell lymphoma*	EBV+ nodal T-and NK-cell lymphoma
ALK-positive, ALCL	ALK-positive, ALCL	ALK-positive, ALCL
ALK-negative, ALCL	ALK-negative ALCL *DUSP22R+* genetic entity	ALK-negative ALCL
Nodal lymphomas of T-follicular origin Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma angioimmunoblastic type (angioimmunoblastic T-cell lymphoma)	Nodal TFH cell lymphoma, angioimmunoblastic-type
Nodal PTCL with TFH phenotype	NOS	NOS
Follicular T-cell lymphoma	follicular type	follicular type

Alaggio et al. Leukemia 2022; de Leval Blood 2022

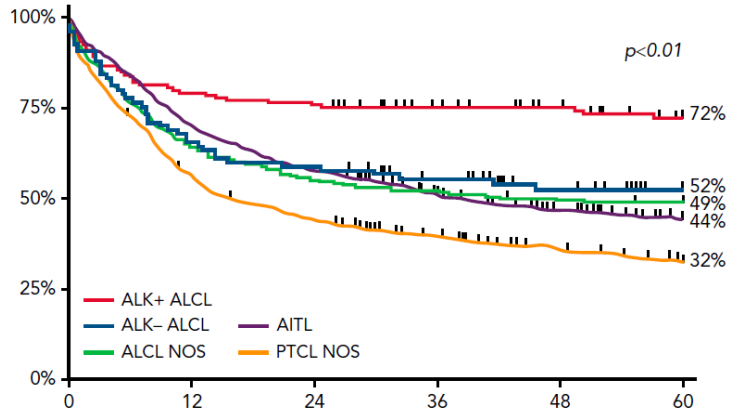
Outcome of nodal PTCL in large retrospective studies



ITLP n=1153
Central path review
1990-2002



Swedish registry
n=755
2000-2009



Netherlands registry
n=1424
1989-2018

Progression-free survival (5-year)

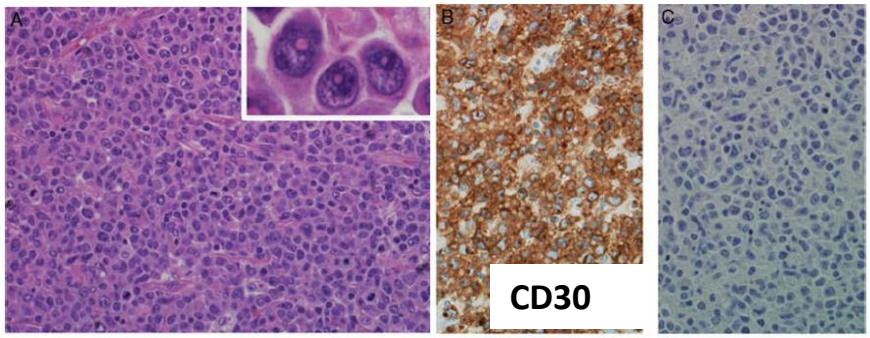
Subtype	ITLP	Swedish	Netherlands
ALK +	60%	63%	-
ALK -	36%	31%	-
PTCL-NOS	20%	21%	-
AITL	18%	20%	-

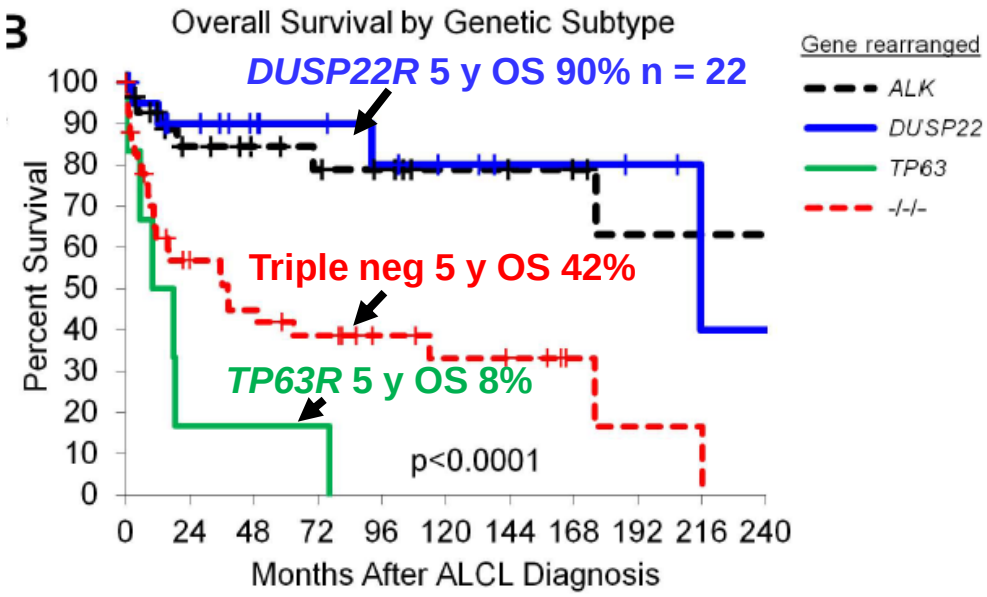
Overall survival (5-year)

Subtype	ITLP	Swedish	Netherlands
ALK +	70%	79%	72%
ALK -	49%	38%	52%
PTCL-NOS	32%	28%	32%
AITL	32%	31%	44%

Vose et al. JCO 2012; Ellin et al. Blood 2014; Brink et al. Blood 2022

Genetic heterogeneity of ALK-Neg ALCL





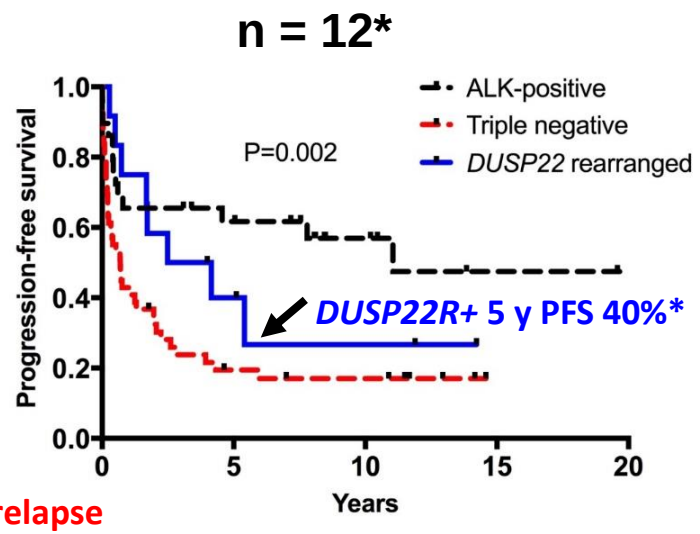
***DUSP22* rearrangement (*DUSP22R*)**

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

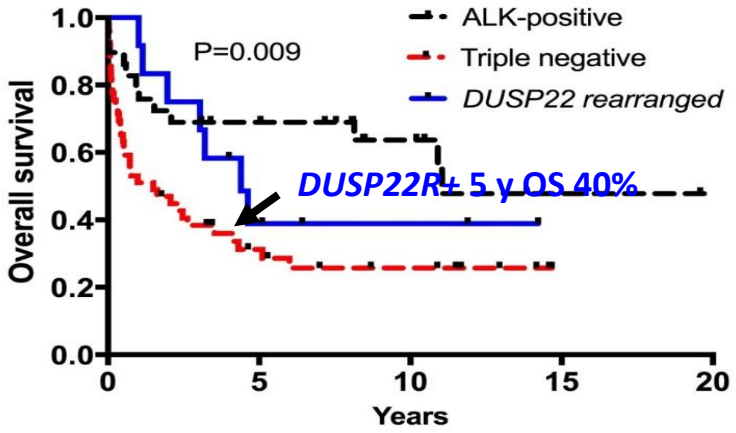
Parrilla Castellar ER, et al. Blood. 2014;124:1473-80; b. Pedersen MB, et al. Blood. 2017;130:554-557; c. Luchtel RA, et al. Blood. 2018;132:1386-1398.; d. King et al. Am J Surg Pathol. 2017;40:36-43; Luchtel et al. Blood 2019.

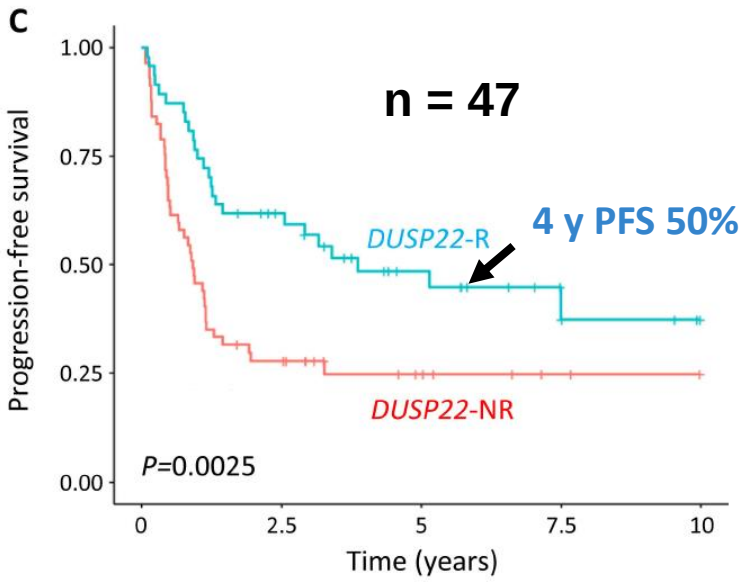
Is there High(er) risk *DUSP22R* ALK-Neg ALCL?

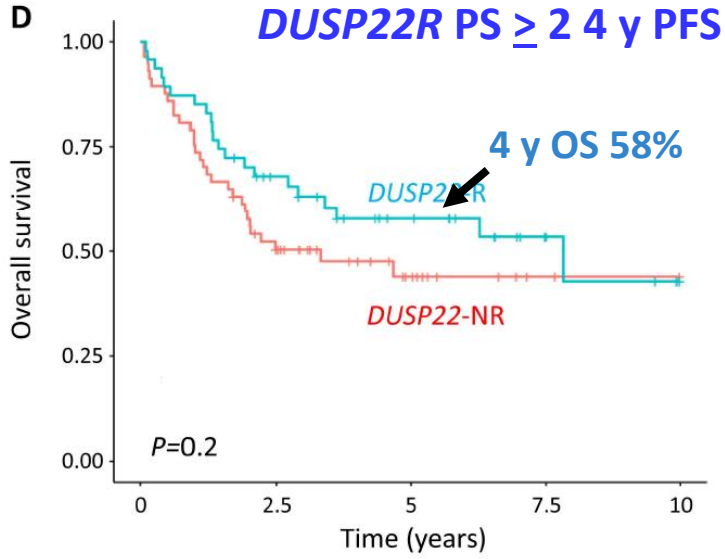


*CNS relapse n=1

Figure 1A.







Hapgood G, et al. Br J Haematol. 2019;186:e28-e31; Adapted from Sibon D, et al. Haematologica 2022

Past strategies to improve upon CHOP in PTCLs

Was the therapeutic bar moved?

- **Add consolidative ASCT**

Maybe (?) – no RCT

- Dose intensity maybe important in a minority

-?Subtype specific differences

- Benefit may be limited to those in a CR

- **Add etoposide (CHOEP)**

Unknown (?) – no RCT

-Primary benefit from retrospective studies ALK-pos and patients < 60 y

-More toxic

- **Build a new chemotherapy backbone – gemcitabine based**

No

SWOG PEGS (2 y PFS 12%)

UK RPh2 (CHOP vs **GEM-P**) Negative study

-?Importance of alkylators or anthracyclines (mixed results)

- **Add drug 'X' to CHOP**

No and Yes

Improving upon CHOP in PTCLs

Was the therapeutic bar moved?

- **Most popular trial design →Add novel agent 'drug X' to CH(O)P backbone**

-No: CHOP +

Alemtuzumab – Ph 3 trial negative **3 y PFS 28%,** toxic

Romidepsin - Ph 3 negative **3 y PFS ~ 39%**

Denileukin deftitox – Ph 2: **2 y 42.9%**

Bevicuzumab – Ph 2 **1 y PFS 44%,** cardiotoxic

Everolimus – Ph2 **- 2 y PFS 33%**

Bortezomib – Ph1/2 ORR 76%(CR 65%) – **3 y PFS 35%**

Pralatrexate – Ph 2 CR 66%; PFS Not reported

Pralatrexate(+CEOP) Ph 2 CR 66%; **2 y PFS 39%**

Lenalidomide (AITL elderly) ORR 54% **2 y PFS 42.3%**

Lenalidomide (+ CHOEP) – Ph 1/2 CR 48%; **1 y PFS 68%;** (Gr 5 n=5)

-Work in progress: CHOP +

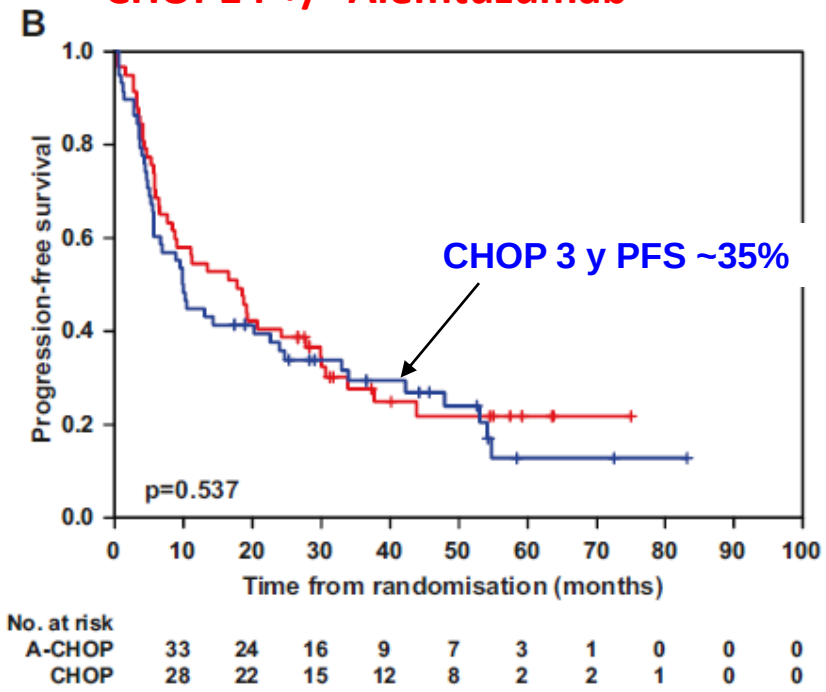
Belinostat – CR 67% Ph 1

5-Azacitadine – Ph 1 –CR 75% **1 y PFS 66.1%**

-Yes: CHP + Brentuximab vedotin (CD30 +PTCLs) (Ph 3)

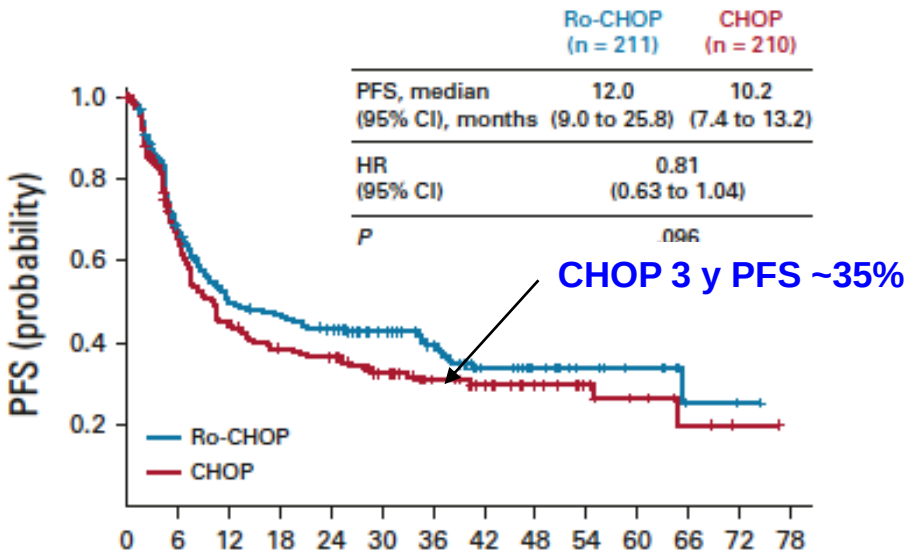
What hasn't worked? CHOP + novel agent negative Ph 3 trials

CHOP14 +/- Alemtuzumab



Act 2 DSHNHL > 61-80 y
Median 69 y
(Act 1 ≤ 60 y also negative)

CHOP +/- Romidepsin



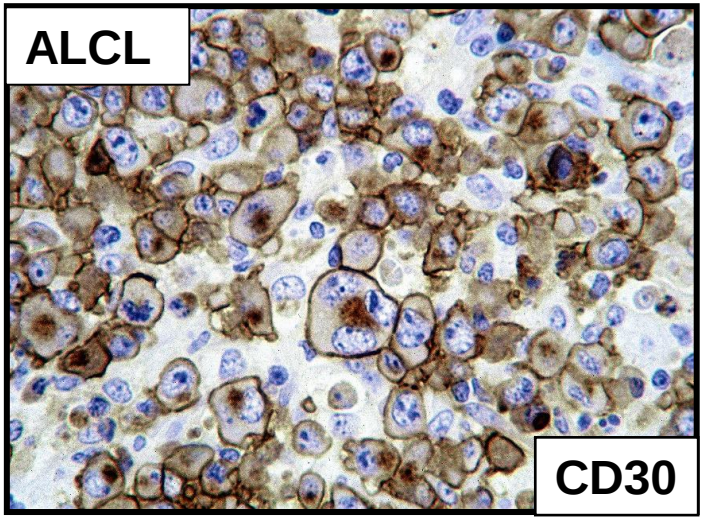
LYSA All ages
Median 65 y
No ASCT

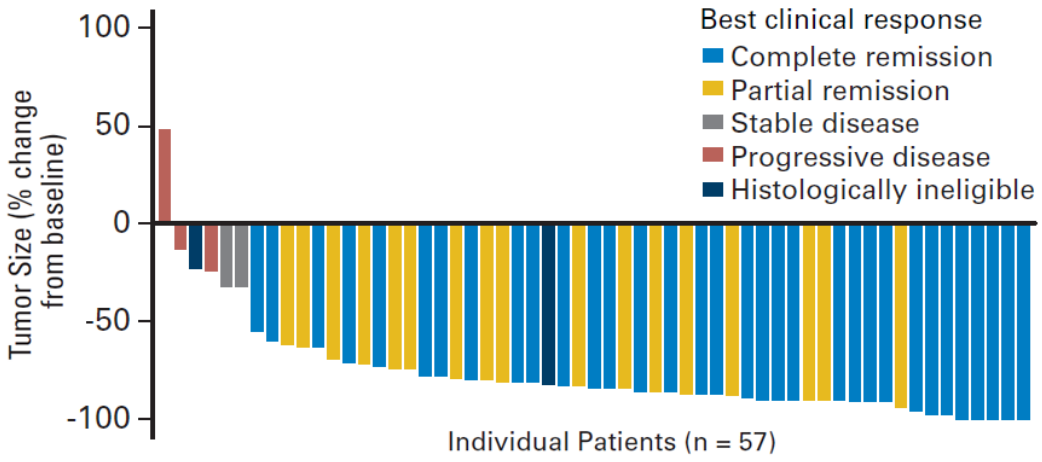
Lessons learned: It's not easy to combine drugs with CHOP and ongoing challenges with disease heterogeneity

Wulf et al. Leukemia 2021; Bachy et al. ASH 2021

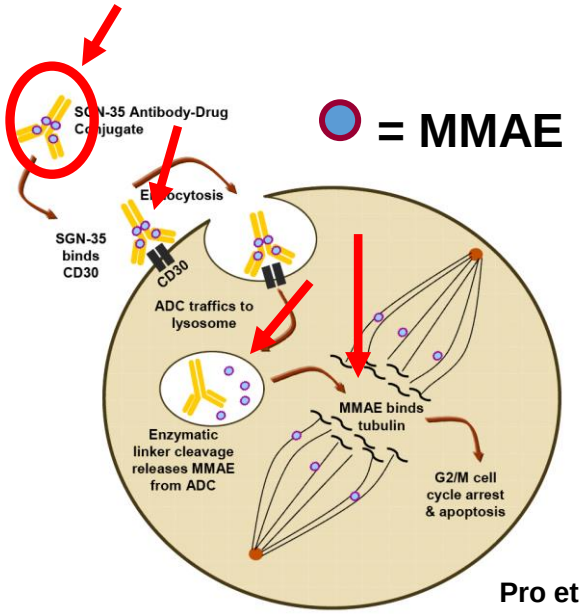
Picking the right novel agent and right disease: CHP-BV in CD30+PTCLs

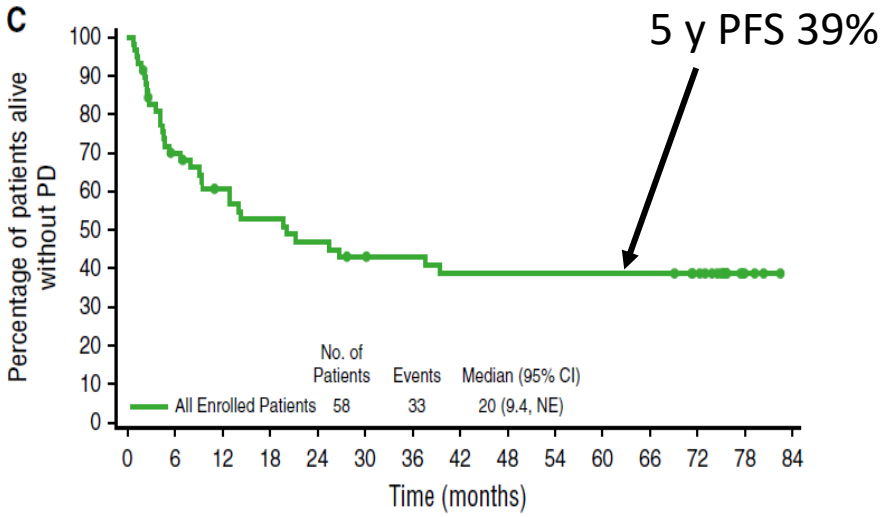
Brentuximab Vedotin (BV): Antibody-Drug Conjugate





Brentuximab Vedotin





Pro et al. JCO 2012; Pro et al. Blood 2018

5 year follow-up pivotal trial ALCL

Phase 3 ECHELON-2 CHP-BV vs CHOP in CD30+ PTCLs

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

R

CHOP x 6-8

Brentuximab vedotin + CHP x 6-8

CHP–BV vs CHOP
Improved PFS √
Improved OS √
Comparable toxicity √
Rapid FDA approval 2018 √

Primary endpoint: PFS =PD, death, subsequent therapy to treat residual or PD)

***Events do not include consolidative RT/SCT**

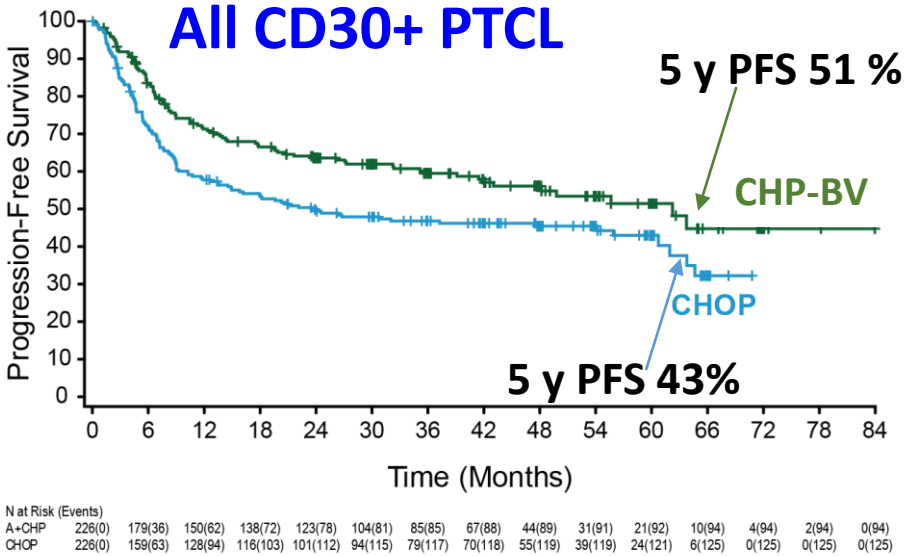
Total 552	A+CHP (N=226)	CHOP (N=226)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

ALCL represents 70% of enrolled patients

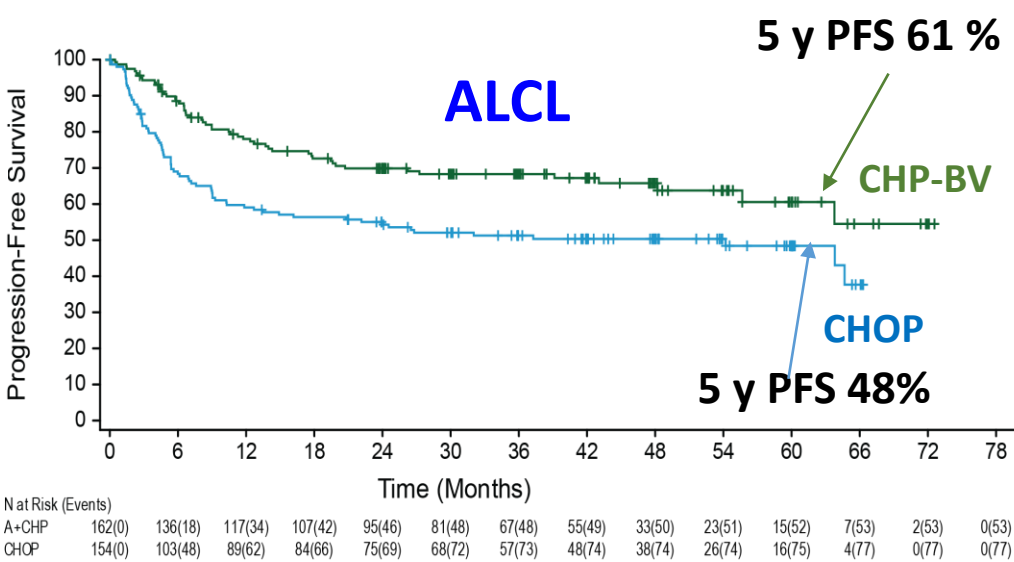
PTCL-NOS n=72 (13%)
AITL n=54 (~10%)

Horwitz et al. ASH 2018; Horwitz et al. Lancet Oncology 2019

CHP-BV in CD30+ PTCLs: 5 year results



	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		



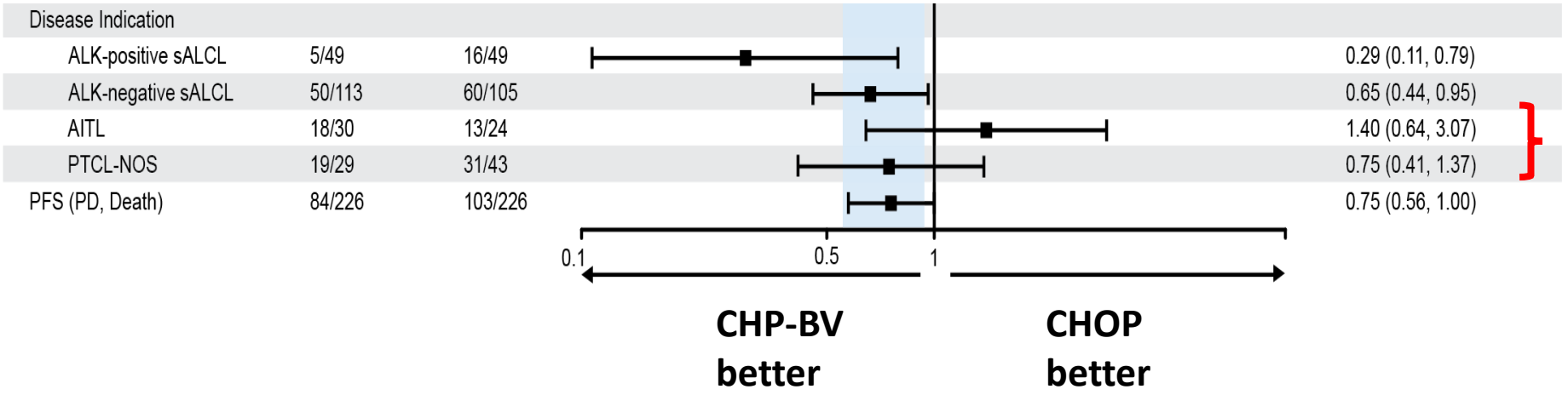
	N	Events	Medians (Months)	HR (95% CI)	p-value*
A+CHP	162	53	–	0.55 (0.39, 0.79)	0.0009
CHOP	154	77	54.18		

	5 y PFS CHP-BV	5 y PFS CHOP
ALK-negative	49%	39%
ALK- positive	87%	67%

Adapted from: Horwitz et al Ann Onc 2021; Horwitz et al ASH 2021

What is the evidence for CHP-BV in CD30+ non-ALCL PTCLs?

CHP-BV vs CHOP subgroup analyses



Challenges: 1) Unplanned subgroup analysis

2) Small patient numbers

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

3) Definition of CD30 + was ≥ 10%

Horwitz et al Lancet Oncology, 2019

Some differences in the regulatory approval of CHP-BV in newly diagnosed CD30+ PTCLs

Regulatory body	Date of approval	Approval specifics	Funding
FDA	November 2018	**Broad** All CD30+ PTCLs by eligibility Systemic ALCL *or* other CD30 expressing PTCL including AITL and PTCL-NOS	Yes
Health Canada	November 2019	**Somewhat restricted** Systemic ALCL, PTCL-NOS or AITL whose tumors express CD30	Yes
EMA	May 2020	**Restricted** Systemic ALCL	Yes

***Grastofil recommended with CHP-BV**

Cautionary notes about consolidative auto-SCT in PTCL

1) There are no RCT demonstrating that consolidative auto-SCT improves outcome in PTCL

2) There is retrospective evidence 'for' and 'against'

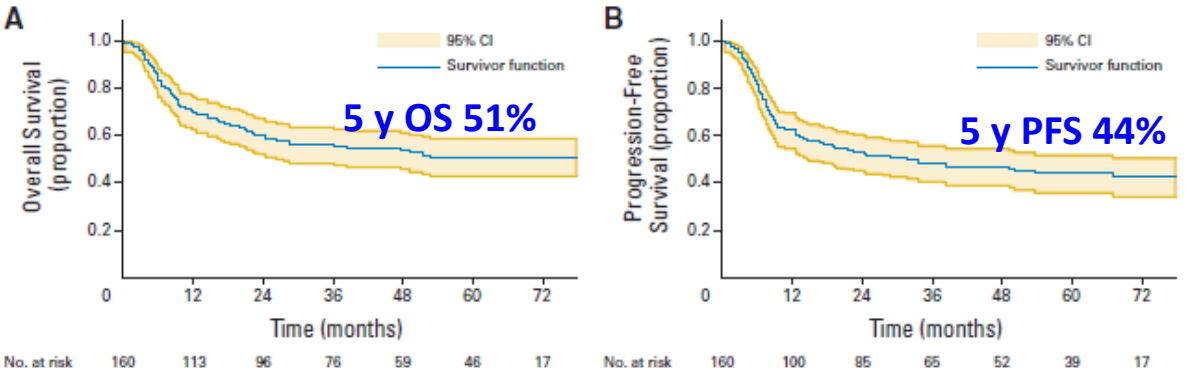
3) There are few prospective trials – diverse subtype inclusion

however,

4) The relapse risk remains high with CHOP(like) chemotherapy alone thus, it is 'considered' in most subtypes (exception ALK-pos ALCL)

Upfront transplant in PTCL: Nordic NLG-T-01 Phase 2 study

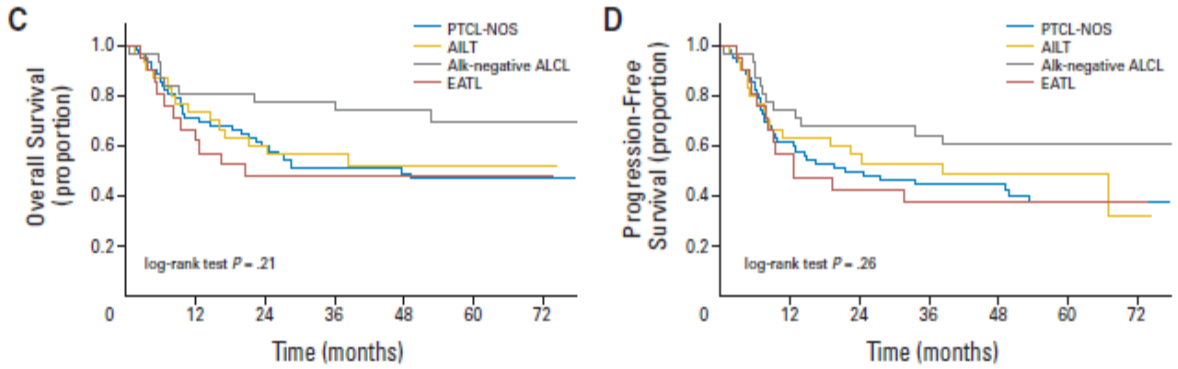
n=160 (PTCL-NOS n=62, 39%)



All patients

d' Amore JCO 2012

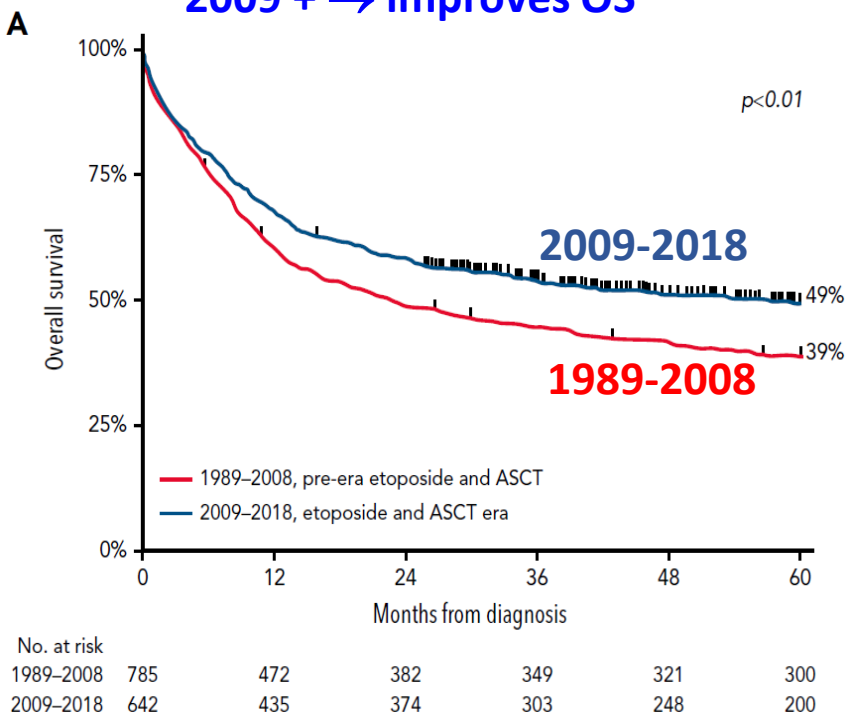
5 y OS by Subtype
ALK- 70%
AITL 52%
NOS 47%
ETTL 48%



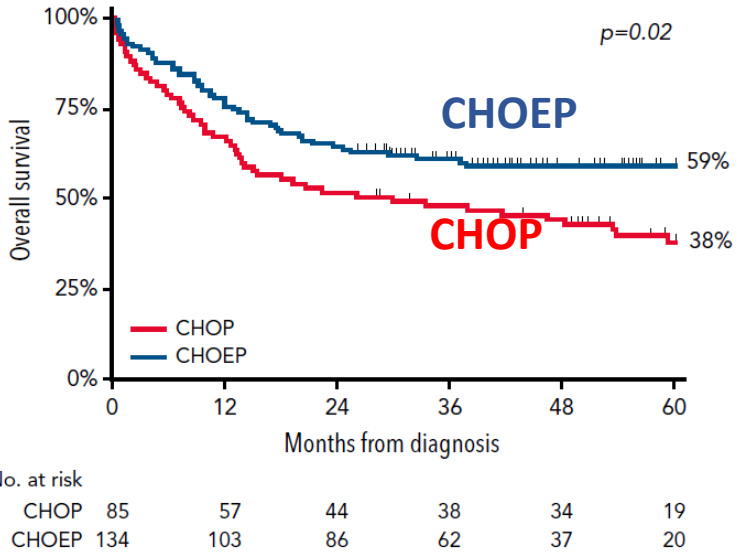
5 y PFS by Subtype
ALK- 61%
AITL 49%
NOS 38%
ETTL 38%

Impact of etoposide and ASCT: nodal PTCL < 65 y Netherlands Cancer Registry (NCR) n=1427

2009 + → improves OS

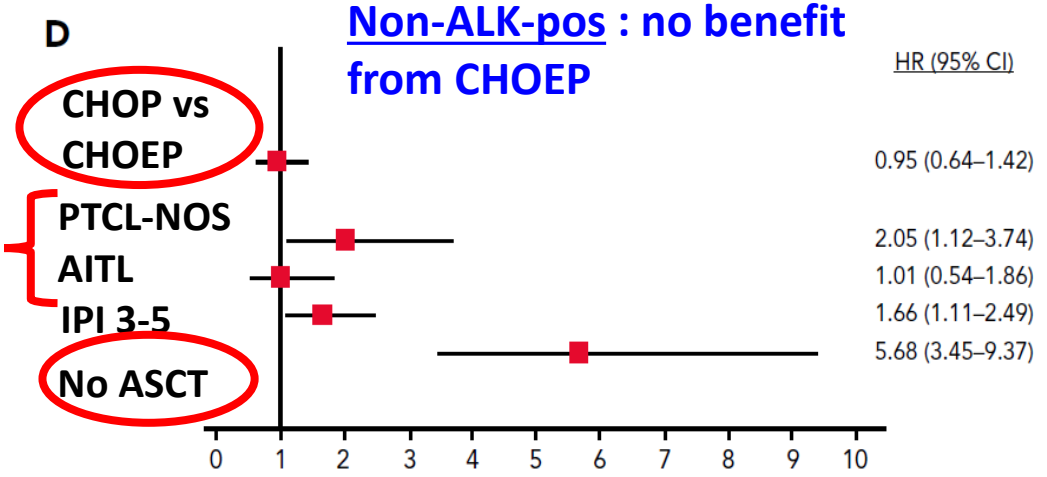


ALK-pos: CHOEP → improves OS



?Due to CHOEP vs ASCT vs other

Non-ALK-pos : no benefit from CHOEP

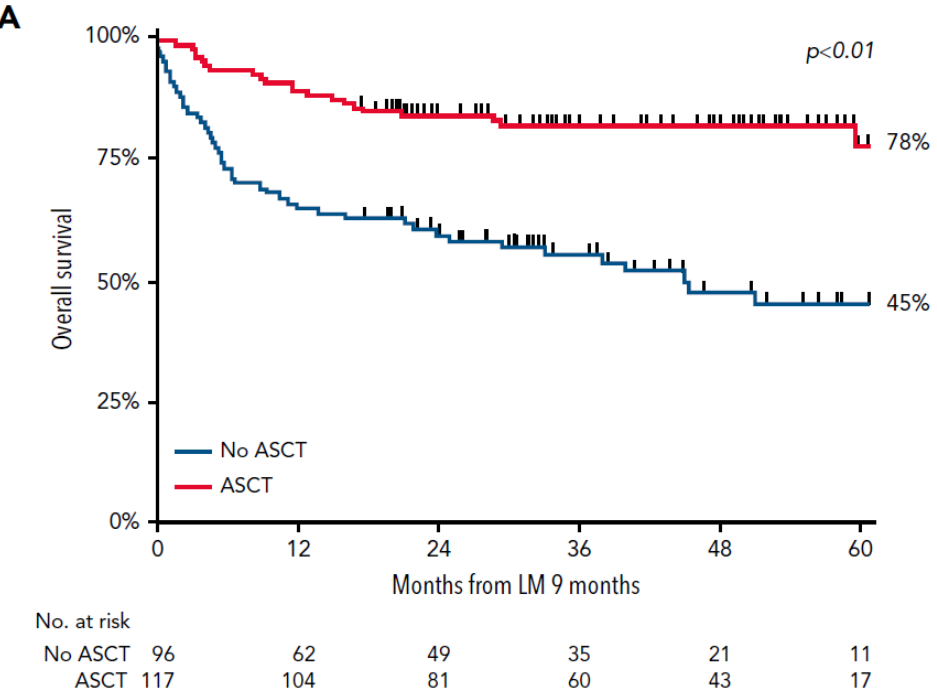


Brink et al. Blood 2022

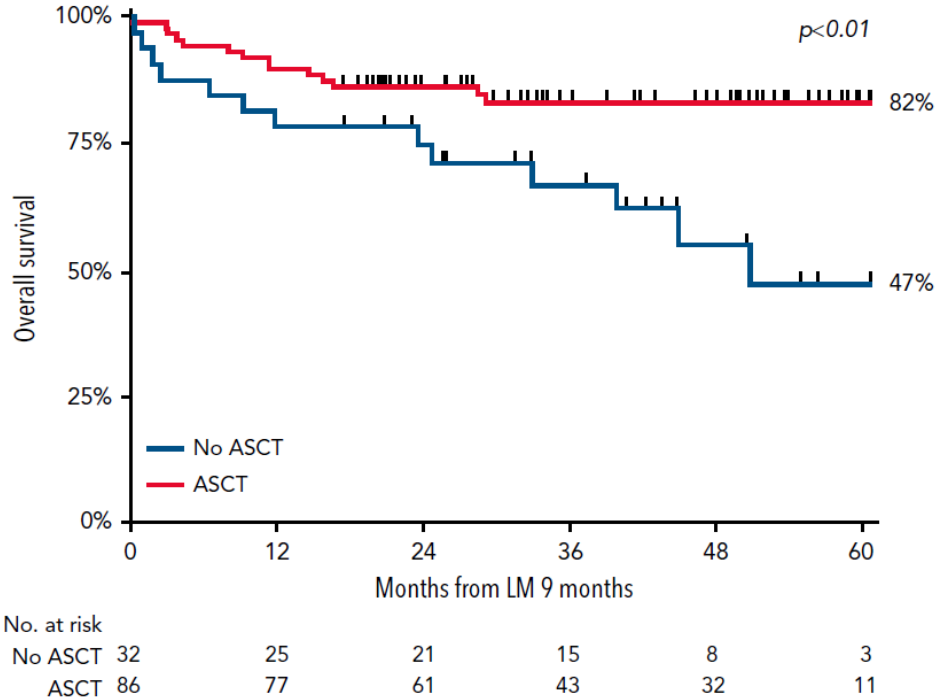
Non ALK-pos ↓ OS with: no ASCT, High IPI, PTCL-NOS subtype

What is the supportive evidence for up-front ASCT? PTCL diagnosed 2014-2108 from the NCR

Landmark analysis (9 m)



Nodal PTCLs in CR: ASCT vs no ASCT



Brink et al. Blood 2022

What is the role of auto-SCT post CHP-BV in CD30+ PTCLs?

- Overall, only 16% of all patients in E2 had consolidative ASCT (CHP-BV n=98, 22%; CHOP n=50, 17%)

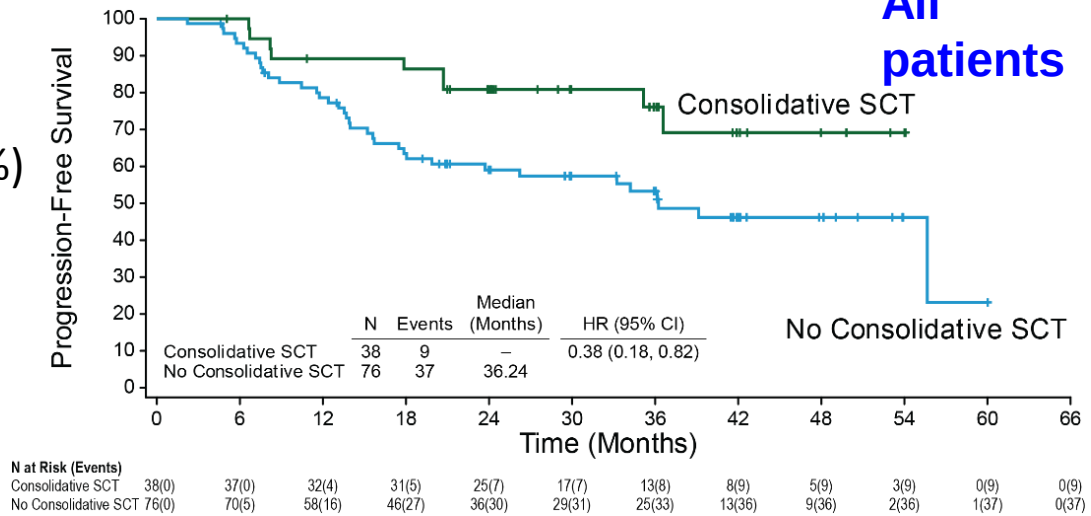
Echelon 2 subgroup analysis

- <u>CR patients post CHP-BV</u> evaluated PFS +/- consolidative ASCT

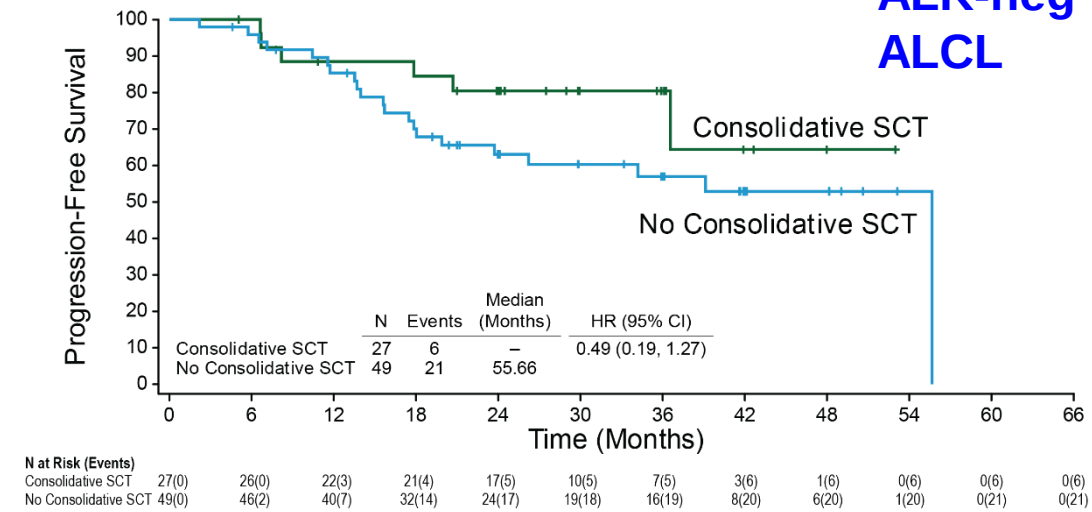
- **Bottom line**: Limited analysis *but* ASCT post CHP-BV improved PFS

- **Knowledge gaps**: Are there low risk groups (esp ALCL) that can forgo ASCT?

All patients



ALK-neg ALCL



Savage et al. ASH 2019/Savage et al. Blood Advances 2022

Randomized study of auto-SCT post CR in nodal PTCLs (TRANSCRIPT)

- 18-69 y
- Fit enough for ASCT
- PTCL-NOS
- TFH TCLs
- ALK-negative ALCL
- PS 0-2

→ CHOP
CHOEP
CHP-BV*

*ALK-neg ALCL only

→ CHOP
CHOEP
CHP-BV* } + ASCT (if CR)

- Enrollment goal n= 204
- Primary endpoint PFS in CR patients
- August 2022 activated (NCT05444712)
- Dr. Bachy PI (France)

Moving away from ’one size fits’ all: Subtype or biologically drive therapy

Lessons from relapsed/refractory studies

Global differences in approval of drugs for R/R PTCL

	U.S.(FDA)	Canada (HC)	Europe (EMA)
Pralatrexate (Folotyn)	Approved 2009	Approved 2018	Not approved for marketing
Romidepsin	Approved 2012 (withdrawn)*	Approved 2013 (withdrawn)*	Not approved for marketing
Brentuximab Vedotin	Approved 2011 (relapsed ALCL)	Approved 2013 (relapsed ALCL)	Approved 2011 (relapsed ALCL)
Belinostat	Approved July 2014	Withdrawn	Not approved for marketing
Crizotinib	Approved Jan 2021 (ALK-pos, 1-≤21 y)	Not approved	Not approved

*** Withdrawn due to negative Ro-CHOP v CHOP study**

Challenge: All are phase 2 studies
What is the comparator?

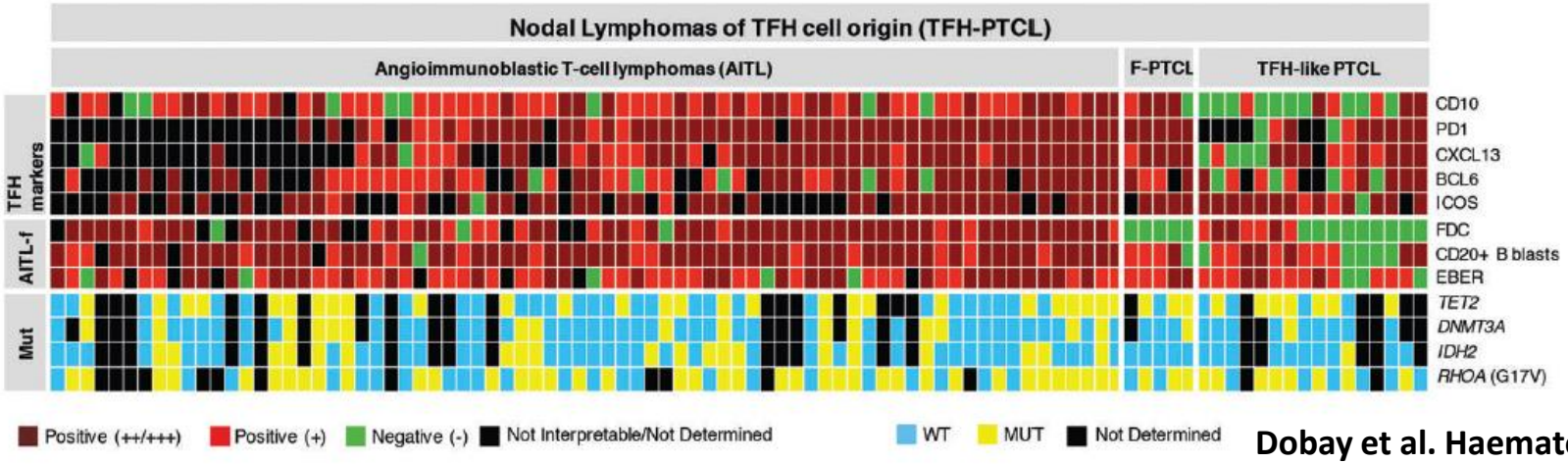
Efficacy is modest in most phase 2 studies

FDA approved drug	PTCL subtype	ORR	CR	Median DoR	Median PFS	Median OS
Pralatrexate	All PS not reported (!)	29%	11%	All 10.5 m	3.5 m	14.5 m
Romidepsin*	All PS 0/1 87%	25%	15%	All 28 m CR-not reached	4 m	11.3 m
Belinostat	All PS 0/1 78%	26%	10%	All 13.6 m	1.6 m	7.9 m
Brentuximab vedotin	ALCL PS 0/1 99%	86%	57%	All 25.6 m CR- not reached	12.6 m	All-not reached
Crizotinib	ALK+ ALCL 1- 21 y	88%	81%	-	-	-

***withdrawn in US and Canada**

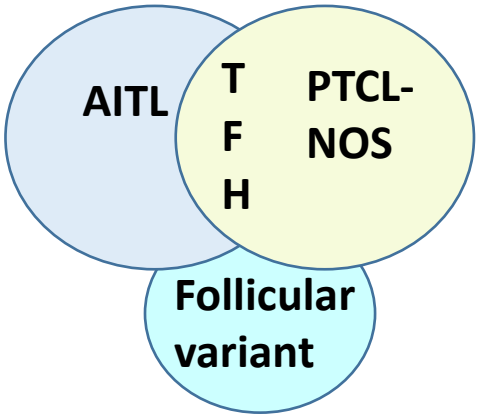
But, meaningful durable remissions seen in some patients

TFH lymphomas: Poster child for personalized therapy



Dobay et al. Haematologica 2017

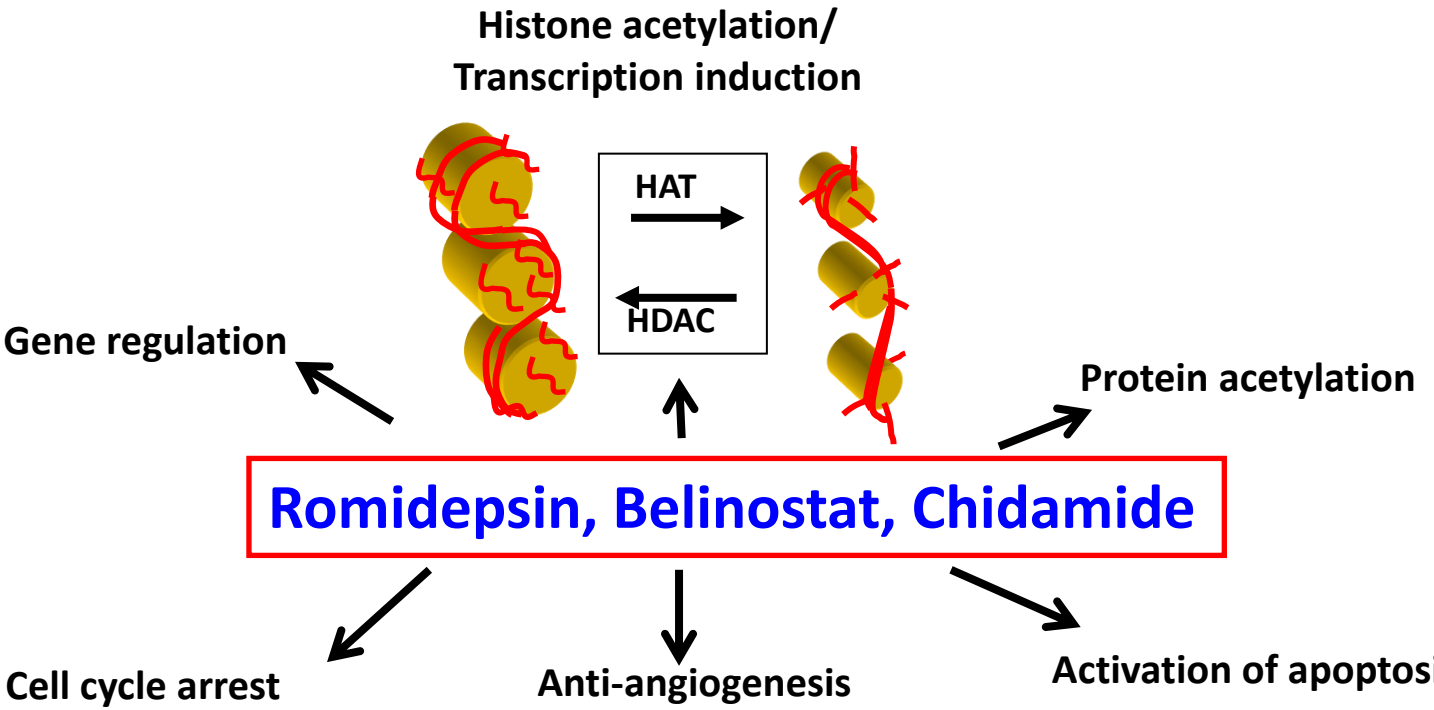
TET2 **~ 50% to 75%**
IDH2^{R172} **~ 25% to 45%**
DNMT3A **~ 20% to 30%**
RHOA^{G17V} **~ 50% to 70%**



HDAC inhibitors - romidepsin, belinostat, chidamide
Hypomethylating agents – 5-azacitadine, decitabine
EZH2 inhibitors – valemetostat
IMiDs – lenalidomide

TFH lymphomas – a disease spectrum sensitive to epigenetic therapies

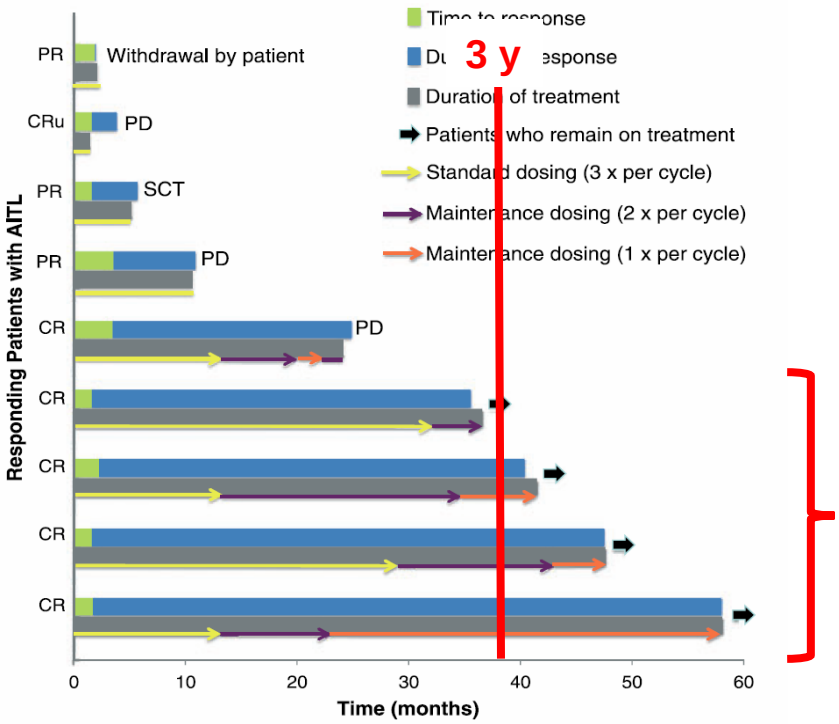
HDAC inhibitors in AITL and other TFH lymphomas



	ORR(CR) of HDAC Inhibitors in Phase II trials		
	Romidepsin %	Belinostat %	Chidamide % (China)
All PTCL	25(15)	26(11)	28(14)
PTCL-NOS	29(14)	23.3	22(7)
AITL	30(19)	45.5	50(40)
ALK-neg ALCL	24(19)	15	45(36)

Coiffier JCO 2012; O'Connor et al. JCO 2015; Shi et al. Ann Onc 2015

Some very durable remissions with romidepsin in AITL



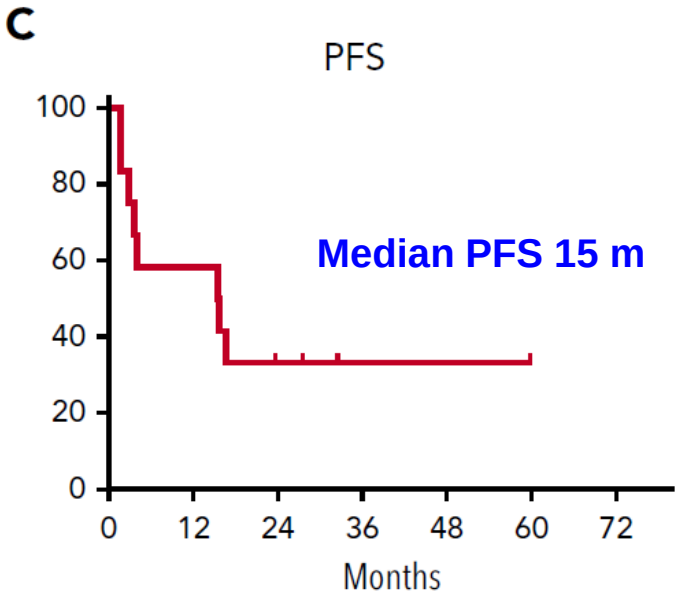
- **Update of Pivotal Phase 2 study**
- **N=27 AITL** median age 62 y (47- 76), **PS 0/1 81%**
- ORR 33%(CR 22%)
- Median time to response 52 days
- Median DoR not reach (1-56 months)

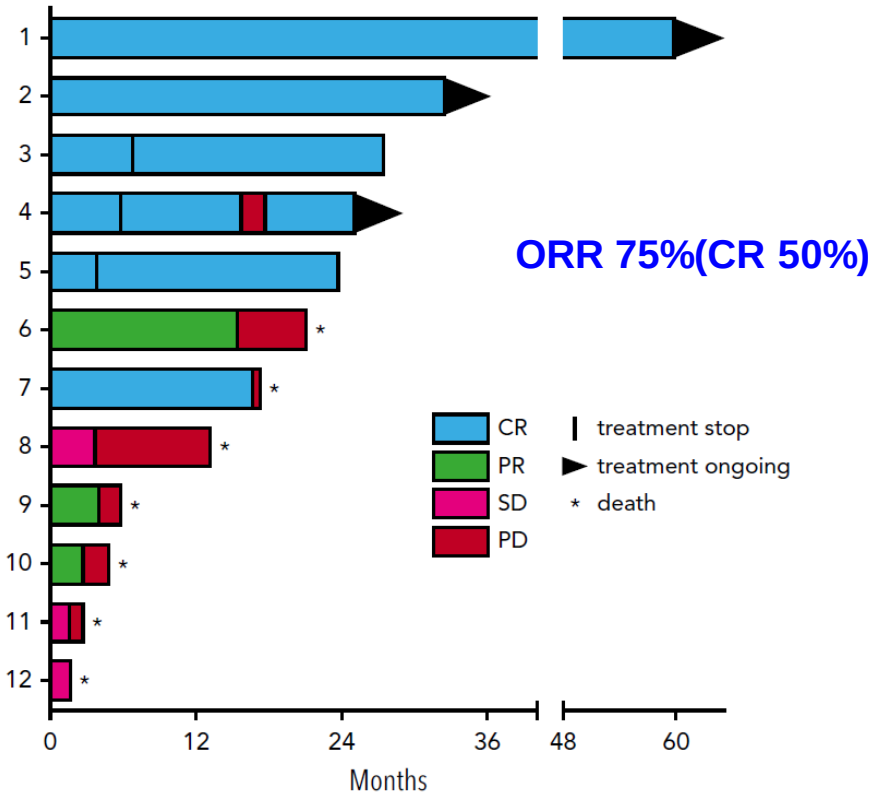
4 (15%) remain in CR > 3 y

Pro et al. Hematological Oncology 2017

Hypomethylating agents: Sustained responses with 5-azacitidine in R/R AITL

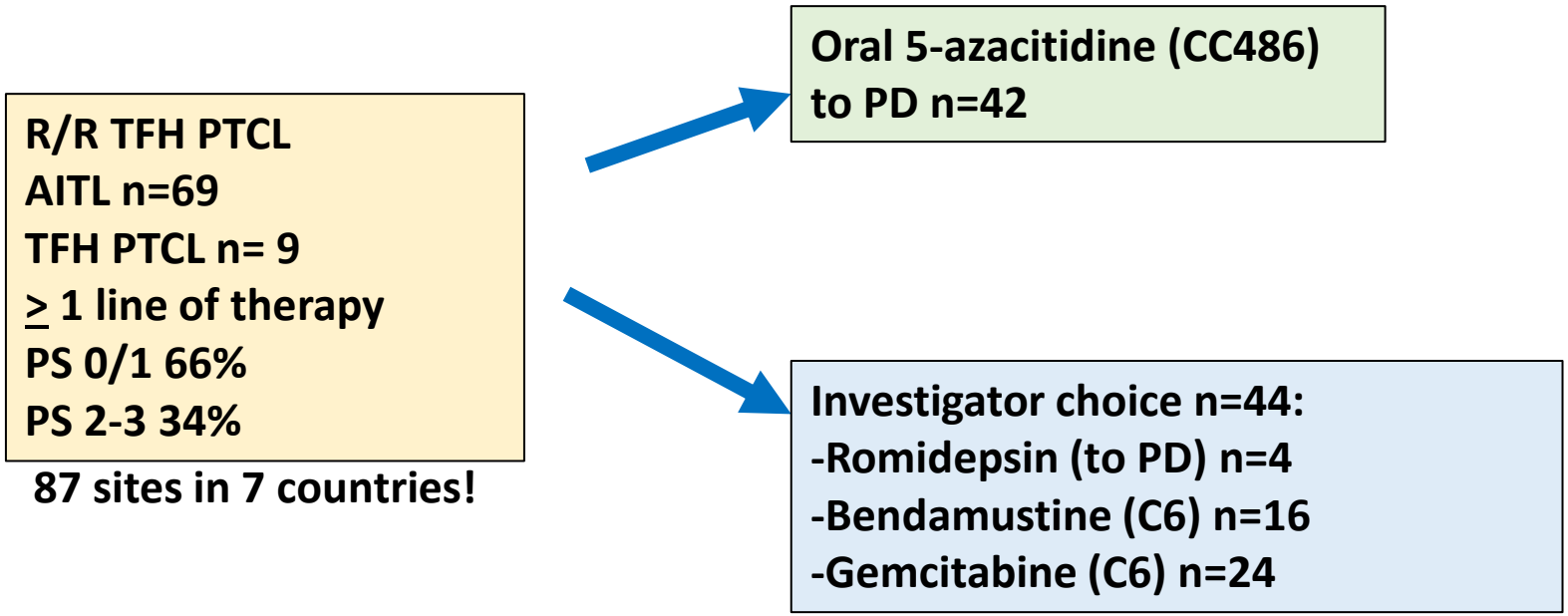
- **Recurrent mutations in genes involved in methylation → strong rationale to evaluate 5-aza**
- **12 patients with AITL treated with 5-Aza (+/- concurrent myeloid neoplasms)**



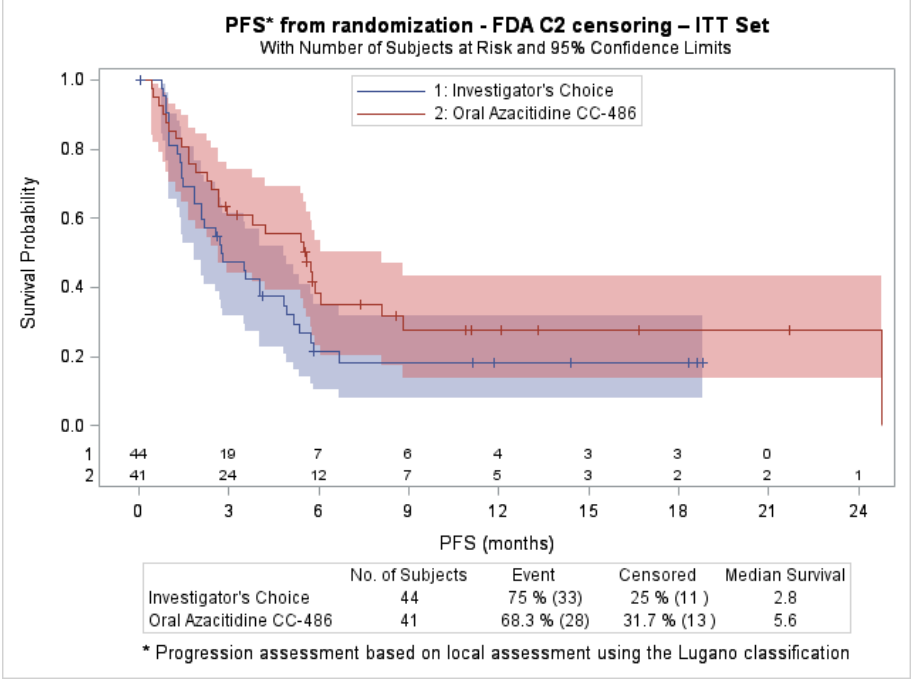


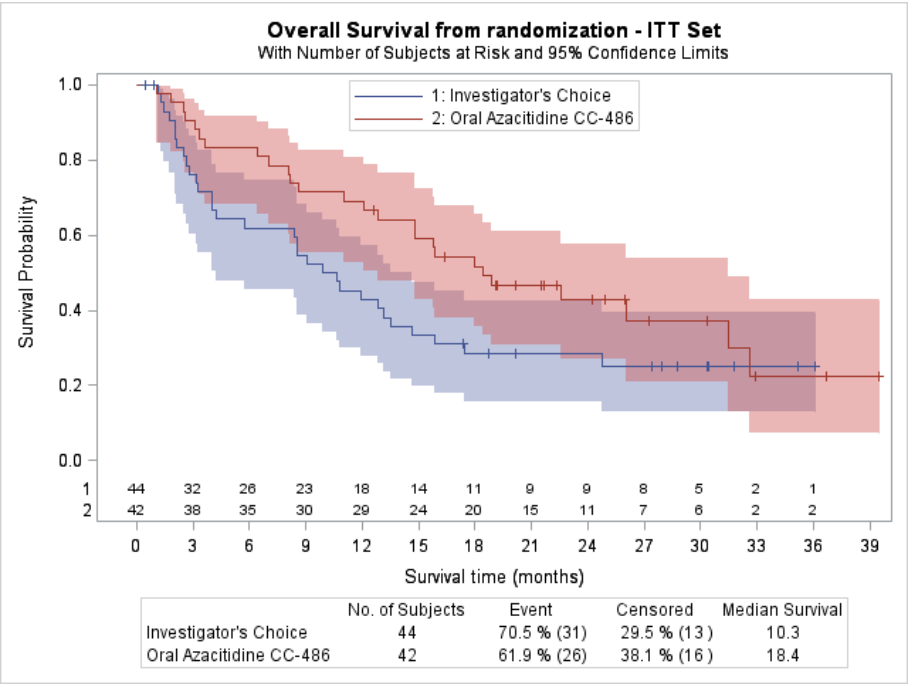
Lemonnier et al. Blood 2018

Oracle Phase 3 study: 5-aza vs investigator choice in TFHLs



Primary endpoint: PFS by investigator using CT (Cheson 2014)
Power calculation: PFS improvement 5 to 12 months
Superiority if p value < 0.025





Progression-free survival

	Median PFS	95% CI
5-aza	5.6 m	2.7-8.1 m
Inv choice	2.8 m	1.9-4.8 m
	p=0.0412	

Primary endpoint for significance (p<0.025)

Overall survival

	Median OS	95% CI
5-aza	18.4 m	12.9-31.5m
Inv choice	10.3 m	4.2-13.5 m
	P=0.0166*	

***descriptive**

ORR(CR at 6 m) 31% (12%) vs 23% (16%) (p=0.40 for ORR)

Adapated, Lemonnier, et al. ASH 2022 [Abstract #959]

Valemetostat (EZH1/2 inhibitor) Phase 1/2 PTCL expansion cohort

- **Selective dual inhibitor of EZH1 and EZH2 → prevents trimethylation of H3K27**

Subtype n	ORR(CR) %	DoR (m)	PFS
All PTCL 44	54(27)	14 m	12 m
AITL 17	64(47)	Not reached	12 m
PTCL-NOS 20	50(20)	14 m	16 m
ALCL 2	50(0)	Not evaluable	Not evaluable
TCL 'other' 5	40(0)	Not evaluable	4
ATLL 14	57(29)	Not reached	Not reached

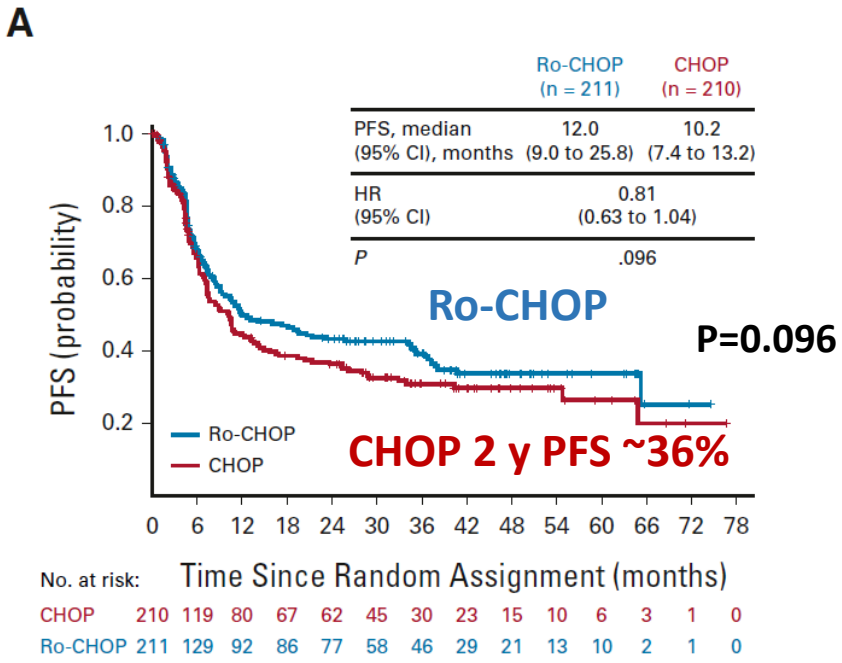
Phase 2 VALENTINE-PTCL01 study has completed accrual (NCT04703192)

What about epigenetic modifiers in the front-line therapy of AITL (and other TFHLs ?

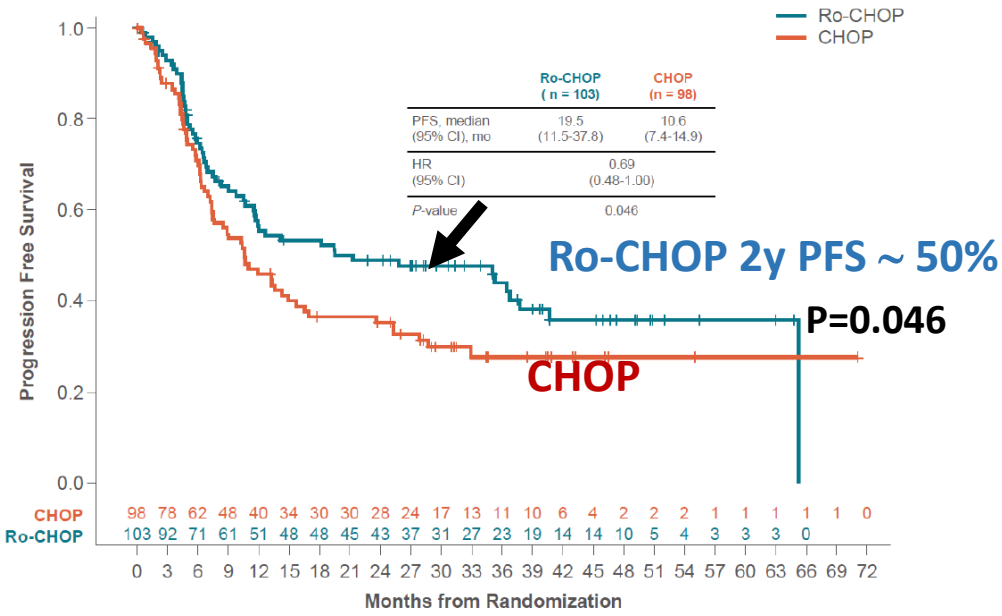
Adapted from: EHA and ICML 2021 Ishitsuka et al.

Lessons from the Phase 3 study Ro-CHOP vs CHOP study

Intention to treat: All PTCLs



TFH lymphoma Subgroup



Bachy et al. JCO 2022

Clinical trial approaches in newly diagnosed PTCL

Approach 1: CHOP (or CHP) + novel agent

Approach 2: Novel agent combinations

Approach 1: Phase 1 CHOP-aza in treatment naïve PTCL (enriched for TFHL)

Key eligibility

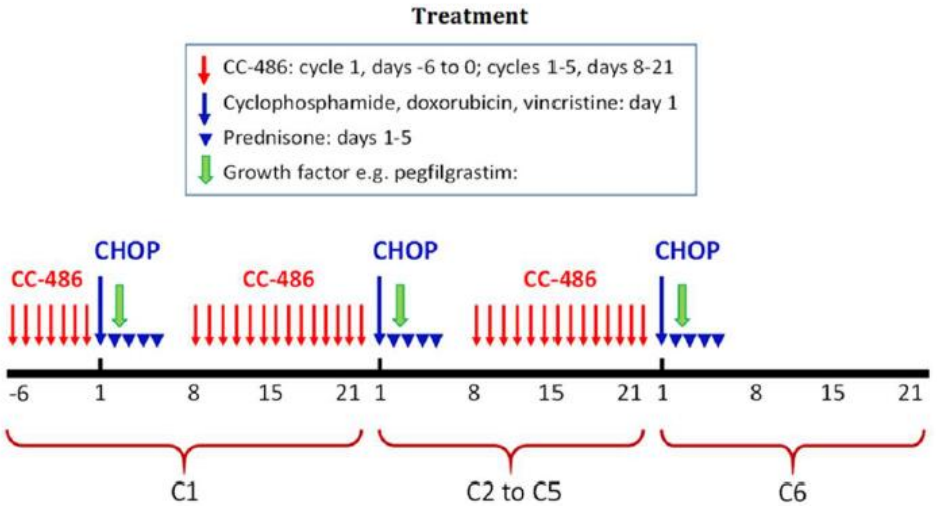
-Nodal T-cell lymphoma with TFH phenotype (WHO 2016)

-PTCL-NOS

-ALCL, ALK-neg

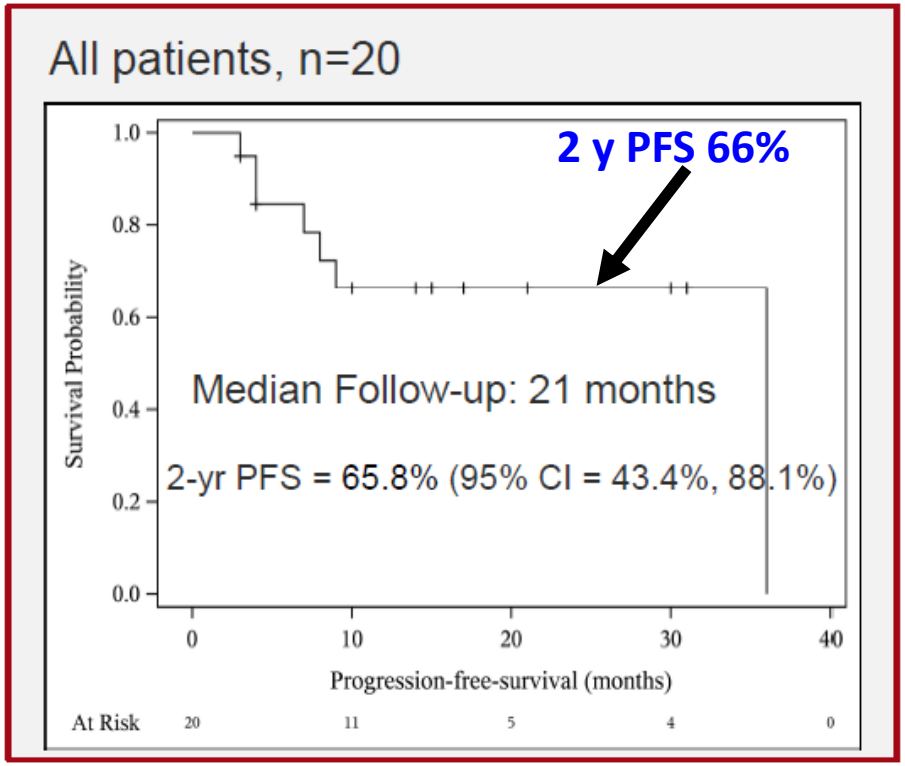
-ALCL, ALK-pos with IPI > 2

-ATLL



- **Median age 66 y (22 – 77y)**

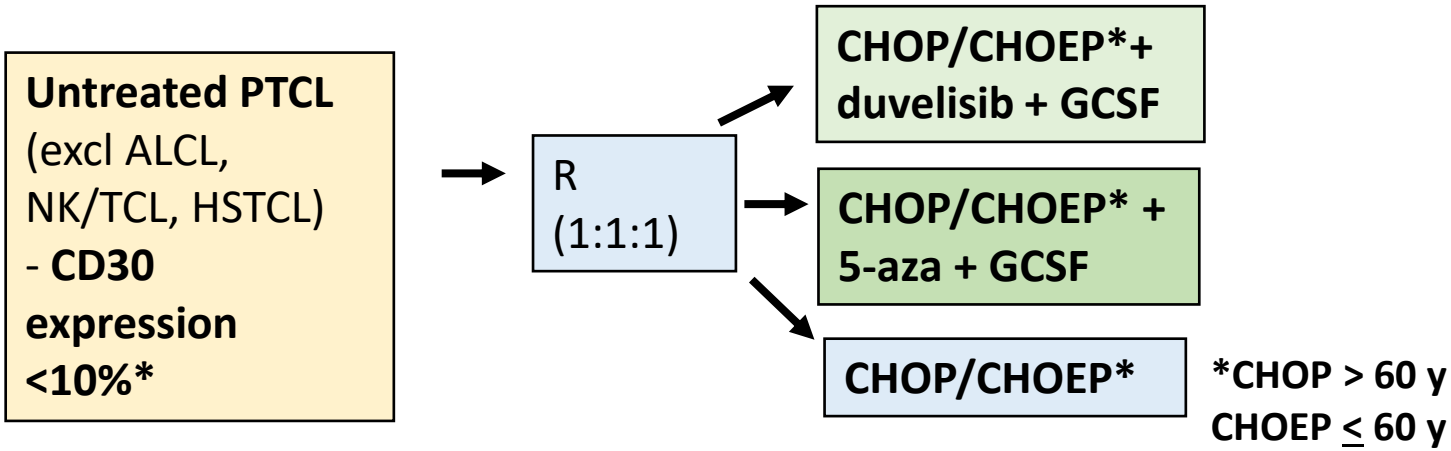
	ORR	CR
All n=21	75%	75%
TFHL n=17	88%	88%



Adapted from Ruan et al ASH 2021

Approach 1 CHO(E)P +/- duvelisib or 5-aza in treatment naïve PTCL

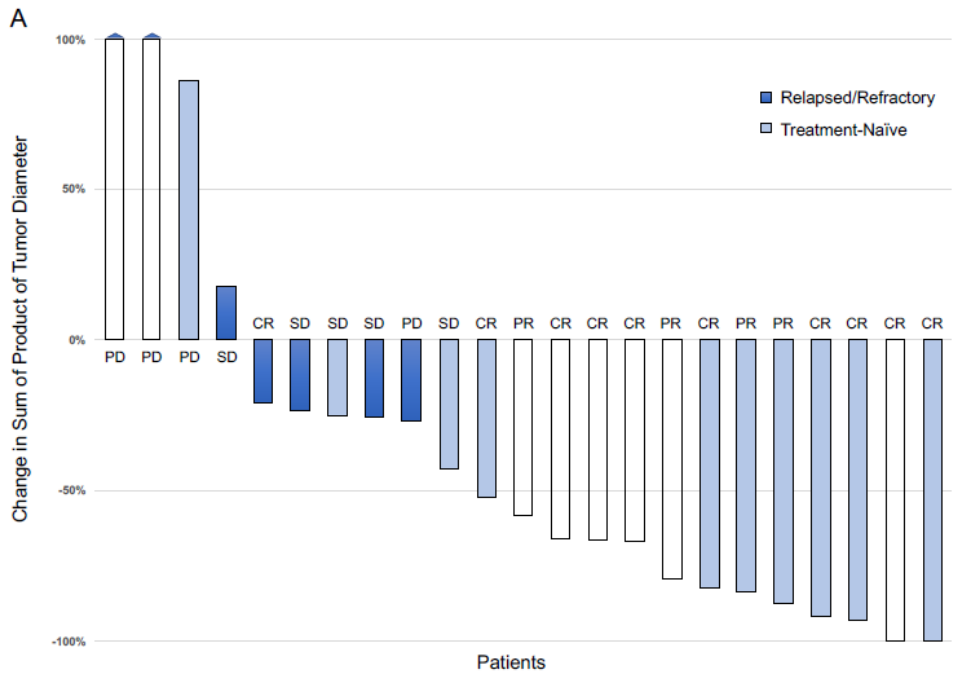
Alliance Randomized Phase 2 (activated NCT04803201)



PI N Mehta-Shah

Primary endpoint PET CR

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)**
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

Other therapies under investigation in R/R PTCL

Targeted therapy	Class	Subtype	ORR/CR
Duvelisib PRIMO	PI3$\gamma\delta$ inhibitor	All	50%/32%
Cerdulatinib	Pan JAK/SYK inhibitor	ALL(+++TFHPTCL)	All 35% TFHL 52%
Tipifarnib	Farnesyltransferase inhibitor	ALL(+++TFHPTCL)	CXCL12 3'UTR 42/25% AITL 45/27%
Ruxolitinib	JAK 1/2 inhibitor	++ JAK/STAT mutations or pSTAT3	25 (JAK/STAT 44%) TFH 33%
Golidocitinib JACKPOT8	JAK1 inhibitor	All	43%/22% (preliminary) (look for ASCO 2023 update)

Summary PTCL in 2023

Primary therapy

- New treatment paradigm: CHP-BV in CD30+ PTCLs

  - CD30+ non-ALCL? Other CD30+ PTCL not well represented (ETTL separate Ph2)

- CD30 - PTCL - Optimal trial design?: CHOP + X *vs* novel agent combinations (what is the curative potential?)

- Consolidative auto-SCT ? forgo in low risk patients (IPI and 'classic' *DUSP22R*)
  ?Role of PET + cfDNA for MRD

Relapsed/refractory PTCL

- Personalized approach is here for TFH PTCLs
  - - additional studies needed of 'typical' mutation profile and response
- Combination therapies – induce deeper responses, watch for toxicities
- In all trials, integration of rich correlative studies