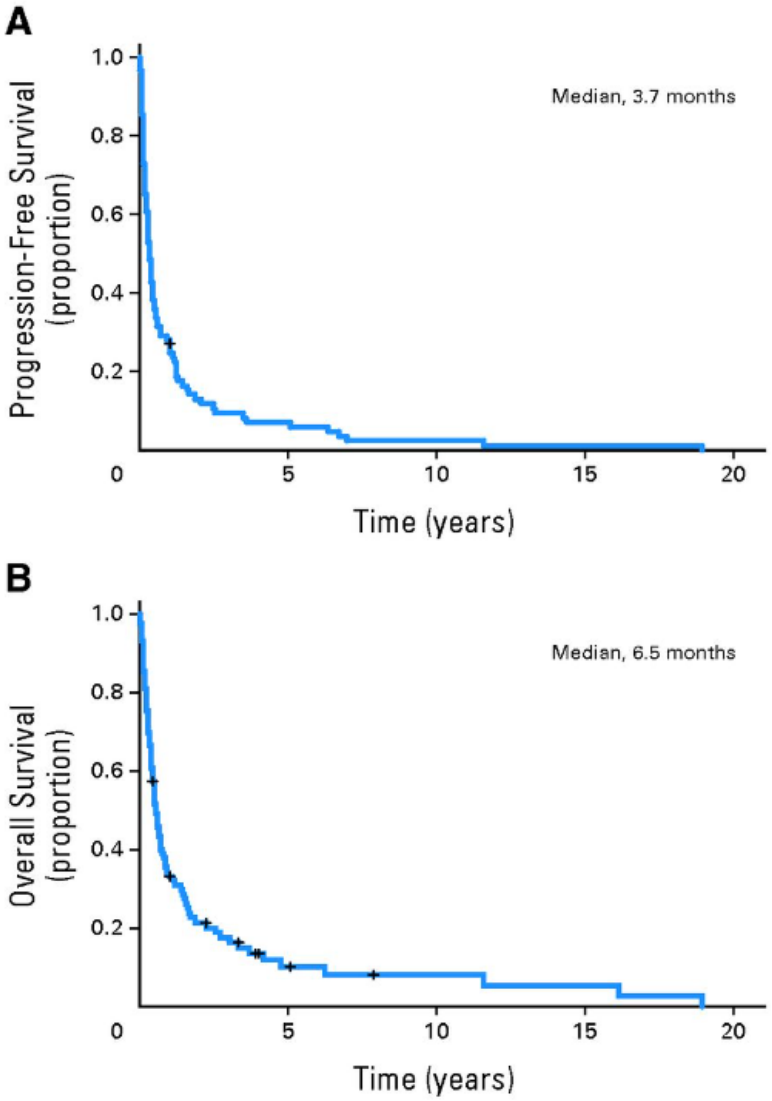
Treatment approaches in R/R PTCL

Prof Francois Lemonnier
Lymphoid Hematology Department & IMRB
Henri Mondor Hospital
Créteil, France

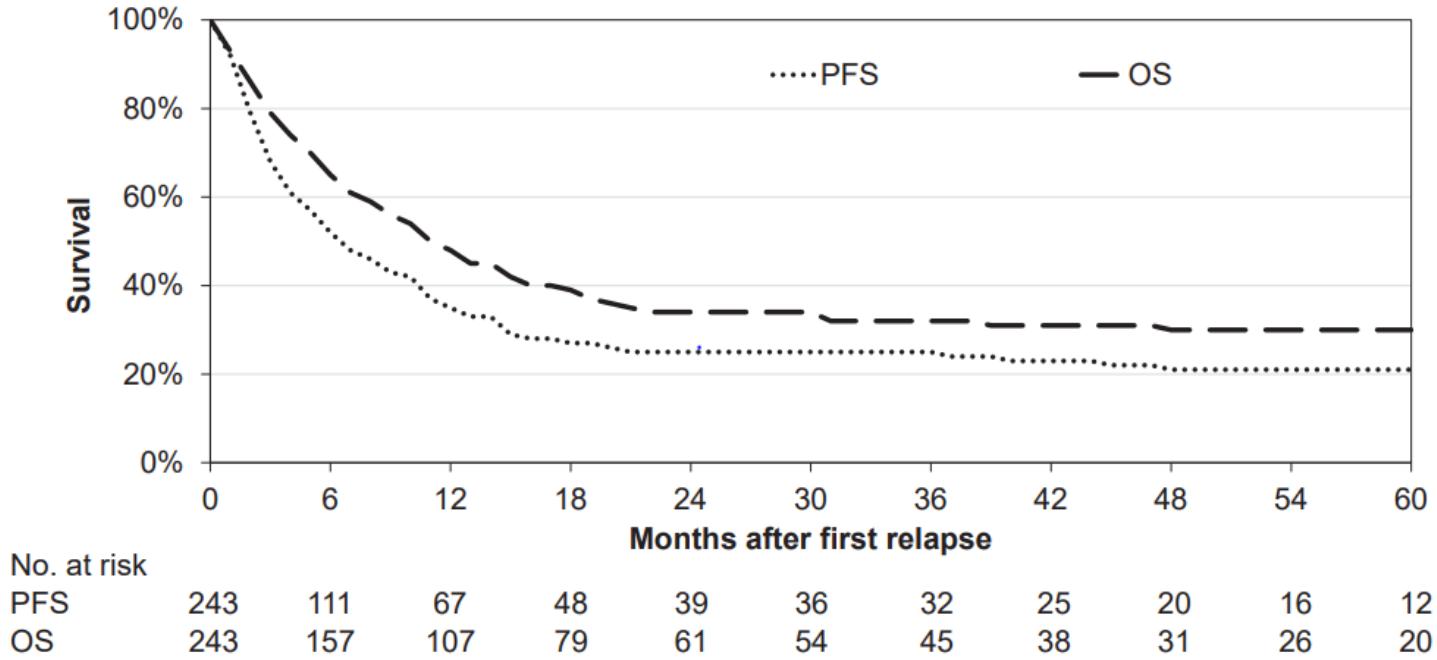
Conflict of interest

- Honoraria Takeda, Astra Zeneca
- Advisory board: Miltenyi, Kyowa kirin, BMS
- Travel: Roche, Gilead, Abbvie
- Research: BMS, Roche

R/R PTCL: an unmet medical need



Mak et al. JCO 2013



Brink et al. Blood advances 2024

Challenges in R/R PTCL

Why so few therapeutic progress compared to B-cell lymphomas?

Challenges in R/R PTCL

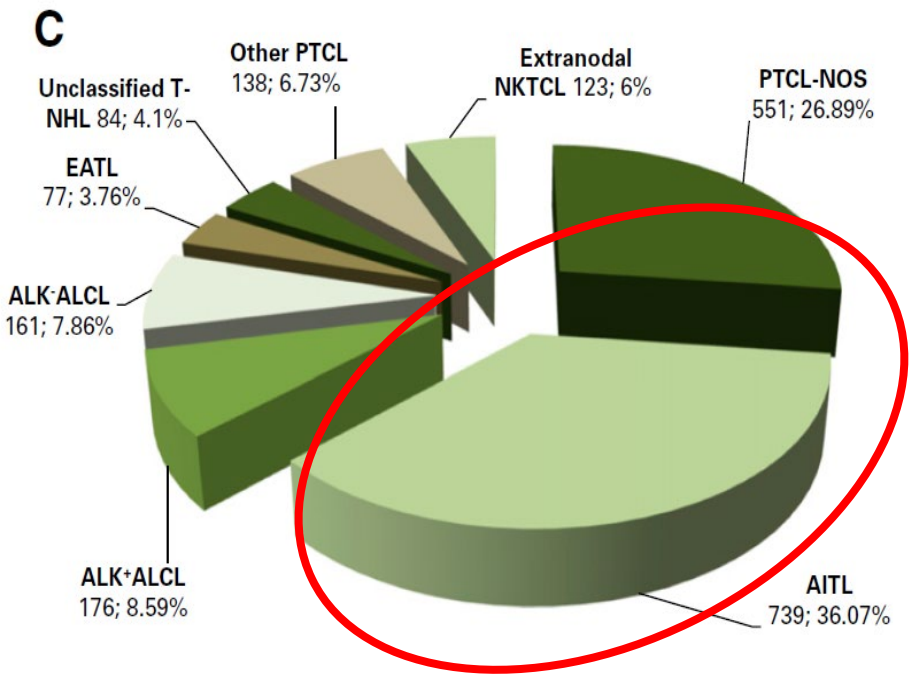
- Heterogeneity of disease

WHO-HAEM4R-2017	ICC-2022	WHO-HAEM5-2022
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukaemia	T-prolymphocytic leukemia
T-cell large granular lymphocytic leukaemia	T-cell large granular lymphocytic leukaemia	T-large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK cells	*Chronic lymphoproliferative disorder of NK cells*	NK-large granular lymphocytic leukaemia
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
EBV-positive T-cell/NK-cell lymphoproliferative disorders of childhood Hydroa vacciniforme-like lymphoproliferative disorder	EBV-positive T-cell/NK-cell lymphoproliferative disorders of childhood Hydroa vacciniforme lymphoproliferative disorder - Classic type and systemic type	EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood Hydroa vacciniforme lymphoproliferative disorder
Severe mosquito bite allergy	Severe mosquito bite allergy	Severe mosquito bite allergy
Chronic active EBV infection of T- and NK-cell type, systemic form	Chronic active EBV disease, systemic (T-cell and NK-cell phenotype)	Systemic chronic active EBV disease
Systemic EBV-positive T-cell lymphoma of childhood	Systemic EBV-positive T-cell lymphoma of childhood	Systemic EBV-positive T-cell lymphoma of childhood
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	Aggressive NK-cell leukemia
Not listed as an entity, subtype of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	*Primary nodal EBV+ T-cell/NK-cell lymphoma*	EBV+ nodal T- and NK-cell lymphoma
Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma
Not listed as an entity	Type II refractory celiac disease	Not listed as an entity
Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent T-cell lymphoma of the gastrointestinal tract
Not listed	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma
Mycosis fungoides	Mycosis fungoides	Mycosis fungoides
Sezary syndrome	Sezary syndrome	Sezary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders - Lymphomatoid papulosis - Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous CD30+ T-cell lymphoproliferative disorders - Lymphomatoid papulosis - Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous CD30+ T-cell lymphoproliferative disorder: Lymphomatoid papulosis Primary cutaneous CD30+ T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma	Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder	Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Not listed	Not listed	Primary cutaneous peripheral T-cell lymphoma, NOS
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Nodal lymphomas of T follicular helper origin	Follicular helper T-cell lymphoma	Nodal T-follicular helper (TFH) cell lymphoma
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma, angioimmunoblastic type (angioimmunoblastic T-cell lymphoma)	Nodal TFH cell lymphoma, angioimmunoblastic-type
Follicular T-cell lymphoma	Follicular helper T-cell lymphoma, follicular type	Nodal TFH cell lymphoma, follicular-type
Nodal peripheral T-cell lymphoma with T follicular helper phenotype	Follicular helper T-cell lymphoma, NOS	Nodal TFH cell lymphoma, NOS
Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma, ALK-positive	ALK-positive anaplastic large cell lymphoma
Anaplastic large cell lymphoma, ALK-negative	Anaplastic large cell lymphoma, ALK-negative	ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma

de Leval and Bisig, Pathologie 2023

Challenges in R/R PTCL

- Heterogeneity of disease



Entity oriented approach	Biomarker oriented approach
Specific treatment • ENKTCL • TFHL • ALK+ ALCL • Etc…	Targeting • cell surface receptors • Signaling pathways • Biological process • Etc…

Laurent C et al. J Clin Oncol 2017

Challenges in R/R PTCL

- Heterogeneity of disease

- Lack of relevant preclinical models

Absence of cell lines of TFHL or PTCL, NOS

→ Recent development of mice models
transgenic mice models
Patient derived xenograft

Challenges in R/R PTCL

- Heterogeneity of disease
- Lack of relevant models
- the T/NK-cell nature of the malignant cells
- The niche market reputation

Challenges in CAR-T cells or BiTE development

- Fratricide
- T cell aplasia

Challenges in R/R PTCL

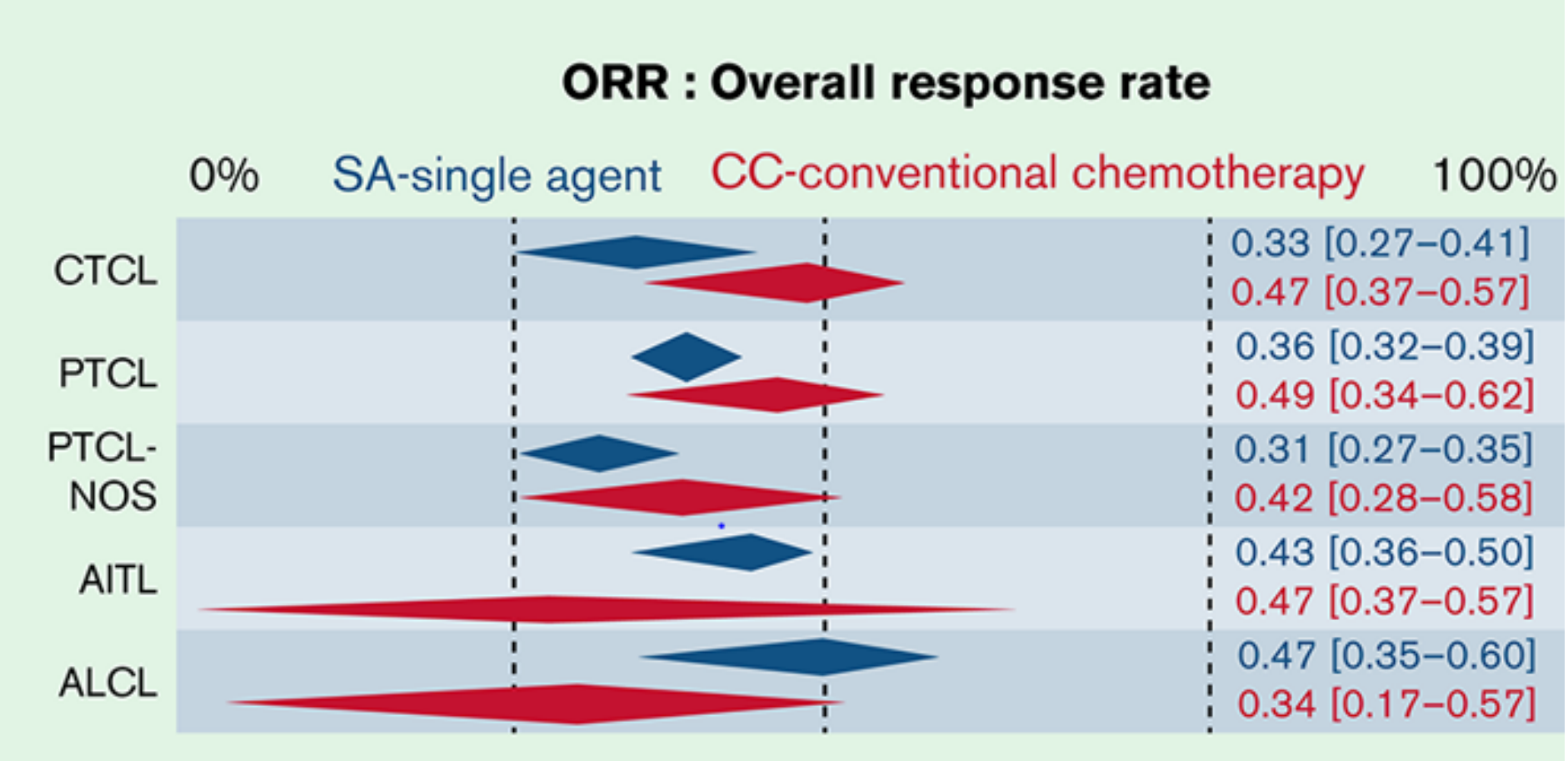
- Heterogeneity of disease
- Lack of relevant models
- the T/NK-cell nature of the malignant cells
- The niche market reputation

Urgent need to overcome these pitfalls

Limited activity of chemotherapies

chemotherapy including

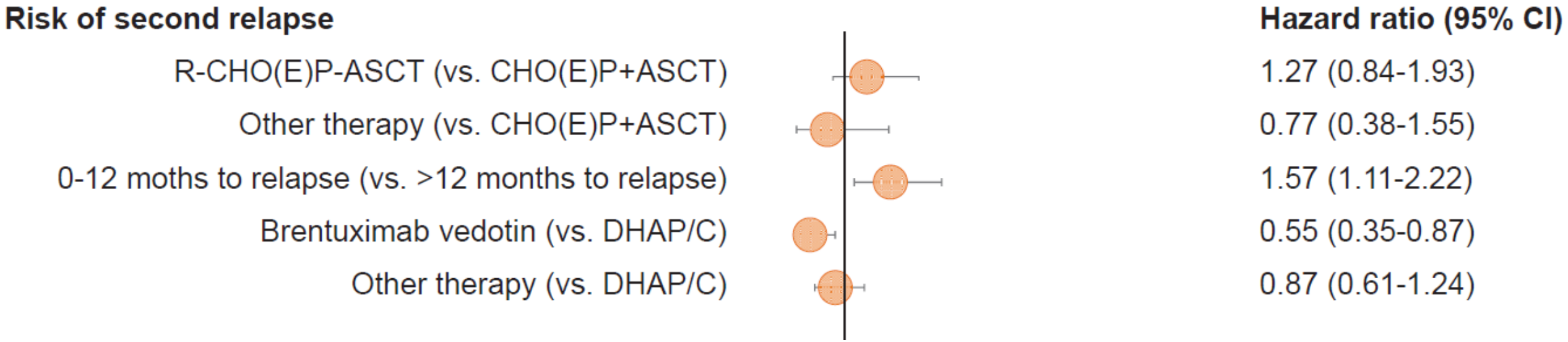
- Ifosfamide
- Gemcitabine
- Platinium based regimen
- anthracyclins



Shafagati et al. Blood advances 2022

Interest of brentuximab vedotin

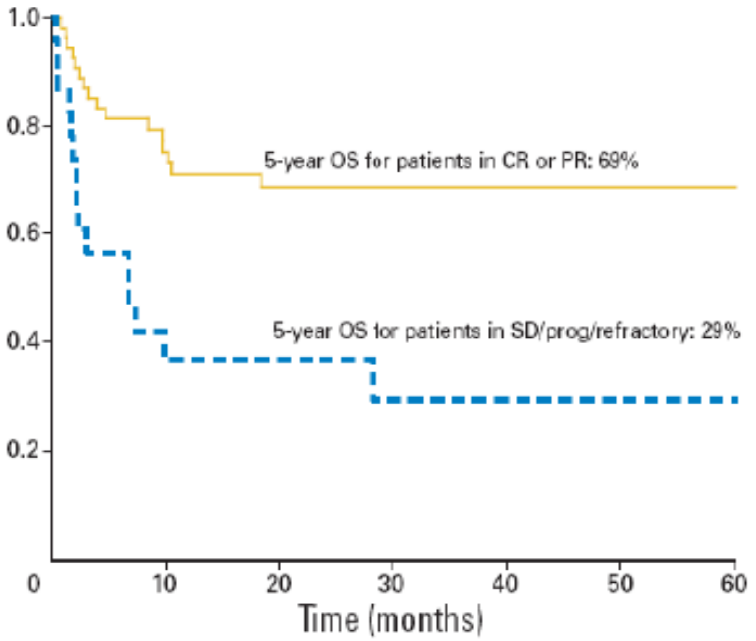
N=311 R/R patients



Brink et al. Blood advances 2024

Relapse

- **=> allogeneic stem cell transplantation**

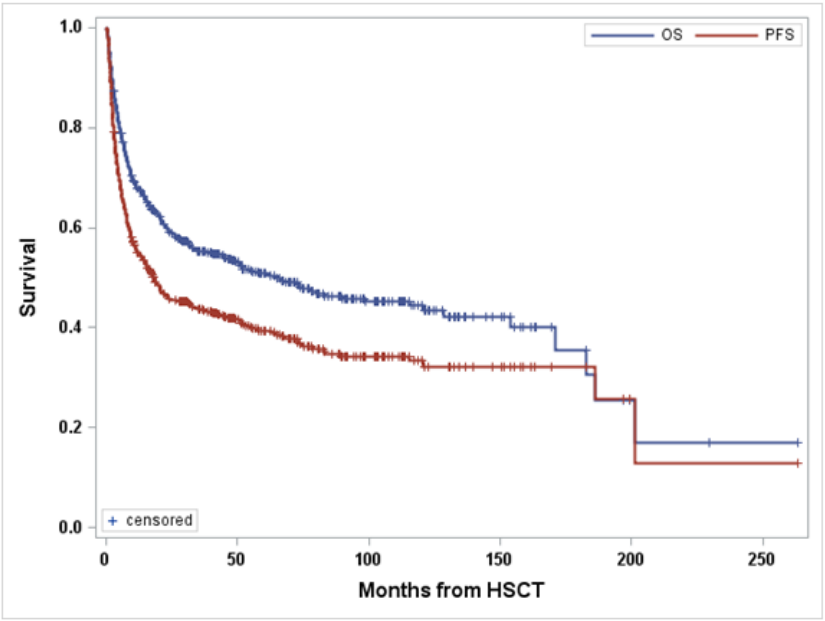


Le Gouill et at. *J Clin Oncol* 2007

Table 1: Patient characteristics and PFS by disease subtypes.

Disease Type (N)	Age at Transplant Median (range)	HCT-CI at Transplant Median (range)	IPI at Diagnosis Median (range)	Remission Status at Transplant	Conditioning Regimen Intensity	2 – yr PFS (95% CI)	5- yr PFS (95% CI)
PTCL-NOS (133)	52.1 (24-72)	1 (0-8)	2 (0-4)	60 CR 43 PR 10 SD 6 PD 14 UNK	51 MA 82 NMA/RIC	49.6% (40.5-58%)	43.9% (34.9-52.5%)
AITL (82)	52 (34-71)	2 (0-8)	2 (0-5)	45 CR 26 PR 2 SD 2 PD 7 UNK	27 MA 55 NMA/RIC	56.4% (44.7-66.6%)	47.3% (35.2-58.5%)
NK/T (20)	41 (20-62)	1 (0-5)	1 (0-4)	12 CR 4 PR 4 UNK	8 MA 12 NMA/RIC	30% (12.3-50.1%)	30% (12.3-50.1%)
Hepatosplenic (34)	33.5 (16-58)	2 (0-7)	3 (0-4)	11 CR 12 PR 4 SD 7 UNK	18 MA 16 NMA/RIC	54.7% (36.3-69.8%)	48.6% (29-65.6%)
CTCL: MF/SS (67)	51.5 (26-72)	1 (0-5)	2 (0-4)	24 CR 32 PR 3 SD 4 PD 4 UNK	11 MA 55 NMA/RIC 1 UNK	33.9% (22.6-45.5%)	18.6% (9.7-29.8%)
ALK-positive ALCL (18)	42 (19-58)	1 (0-4)	1.5 (0-3)	12 CR 3 PR 1 PD 2 UNK	9 MA 9 NMA/RIC	35.3% (14.5-57%)	35.3% (14.5-57%)
ALK-status UNK ALCL (7)	35 (23-49)	0 (0-2)	2 (1-4)	3 CR 3 PR 1 SD	6 MA 1 NMA/RIC	14.3% (0.7-46.5%)	14.3% (0.7-46.5%)
ALK-negative ALCL (26)	54 (25-69)	1 (0-5)	1.5 (0-3)	18 CR 7 PR 1 UNK	6 MA 20 NMA/RIC	34.9% (17.1-53.4%)	34.9% (17.1-53.4%)
Subcutaneous Panniculitic-like T-cell (11)	36 (26-49)	0 (0-4)	2 (2-3)	5 CR 4 PR 2 UNK	3 MA 7 NMA/RIC 1 UNK	55.6% (20.4-80.5%)	55.6% (20.4-80.5%)
Enteropathy-associated (7)	58.5 (48-69.1)	1.5 (0-6)	2 (0-4)	3 CR 2 PR 1 SD 1 UNK	1 MA 6 NMA/RIC	33.3% (4.6-67.6%)	33.3% (4.6-67.6%)
Primary Cutaneous gamma-delta TCL (6)	57 (57-57.26)	1.5 (0-9)	2 (1-5)	2 CR 4 PR	4 MA 2 NMA/RIC	33.3% (4.6-67.6%)	33.3% (4.6-67.6%)
Other (97)	51 (19-70)	1 (0-11)	3 (0-6)	50 CR 28 PR 2 SD 3 PD 14 UNK	38 MA 58 NMA/RIC 1 UNK	48.1% (37.5-57.9%)	42.2% (31.6-52.5%)

Figure 1: Overall and Progression Free Survival in patients who underwent allogeneic transplant for T-cell Lymphoma (n=508)



Key: International prognostic index (IPI), hematopoietic cell transplant comorbidity index (HCT-CI), progression free survival (PFS) Peripheral T-cell Lymphoma (PTCL), Not otherwise specified (NOS), Anaplastic Large-cell Lymphoma (ALCL), Anaplastic Lymphoma Kinase (ALK), T-cell Lymphoma (TCL), primary cutaneous gamma/delta TCL (GDTCL); Other: Adult T cell Leukemia Lymphoma (ATLL), primary cutaneous anaplastic large cell lymphoma (PCALCL) etc], Complete Remission (CR), Partial Remission (PR), Stable Disease (SD), Progressive Disease (PD), Unknown (UNK), Myeloablative (MA), Reduced-intensity Conditioning (RIC), Non-Myeloablative (NMA)

Mehta-Shah et al. ASH 2020

Back to the biology

Epigenetic regulation

DNA methylation
- *TET2*
- *IDH2*
- *DNMT3A*

Histone PTM
- *SETD2*
- *KDM2A*
- KMT2D

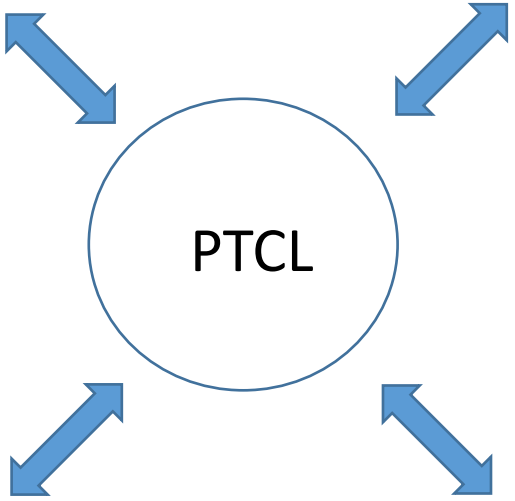
….

Others
- *ARIDIA*

TFH

MEITL
HSTL

All
PTCL



Signaling

TCR signaling
- *RHOAG17V*
- *ITK-SYK*
- *PLCG1*
- *CARD11*
- *CD28*
- Dusp22

JAK/STAT pathway

NFκB

ALK fusions

TFH
CTCL
ATLL

ALCL
LGL
HSTL
MEITL

Cell cycle/apoptosis

- *TP53* family
- *CDKN2A*
- Others

All
PTCL

Immune surveillance

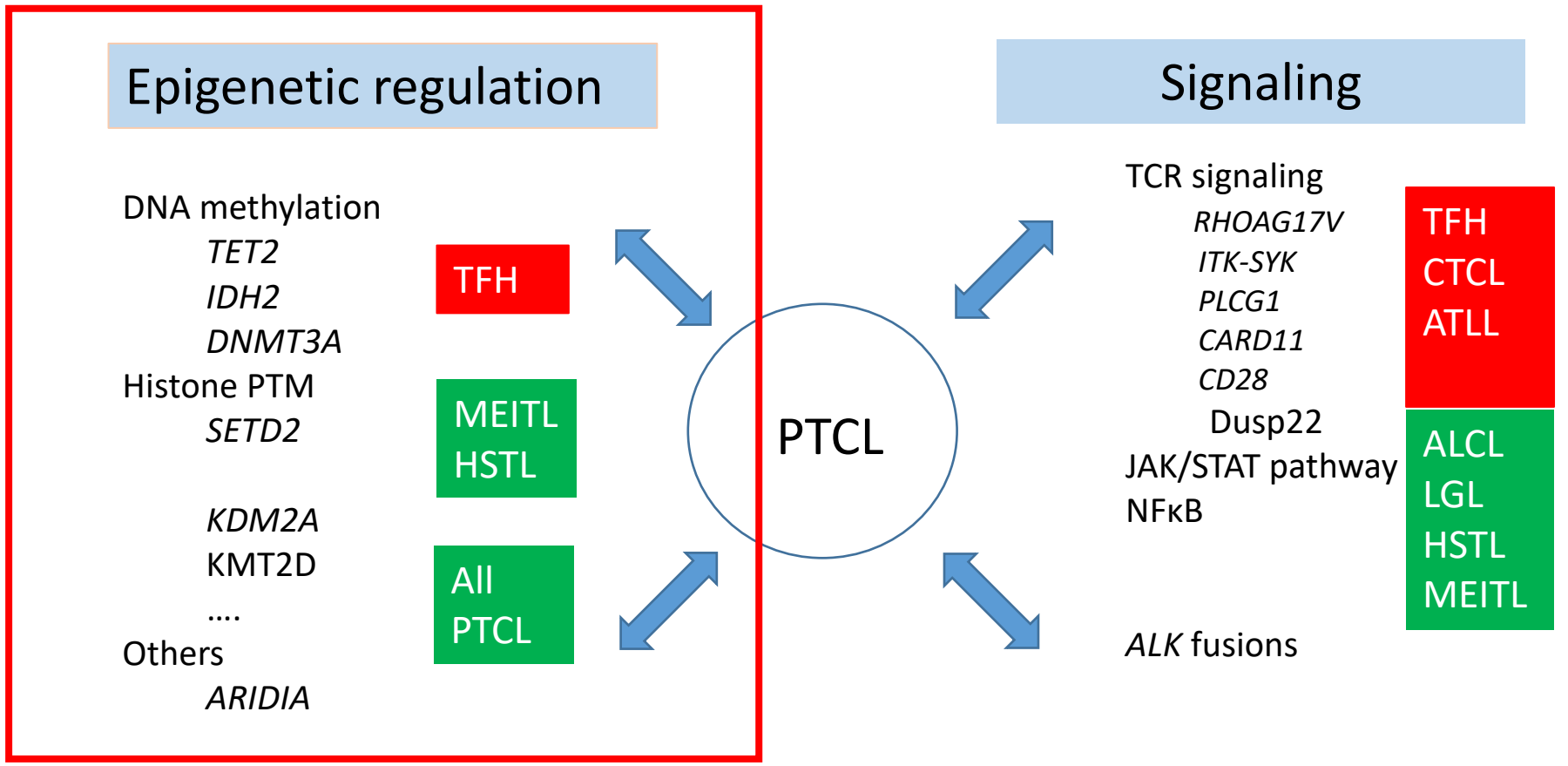
- PDL1 3’ UTR
- HLA B2M
- CD58

NKT
ATLL

Pathways involved in PTCL oncogenesis

80% TFH

90% SS



Cell cycle/apoptosis

TP53 family
CDKN2A
Others

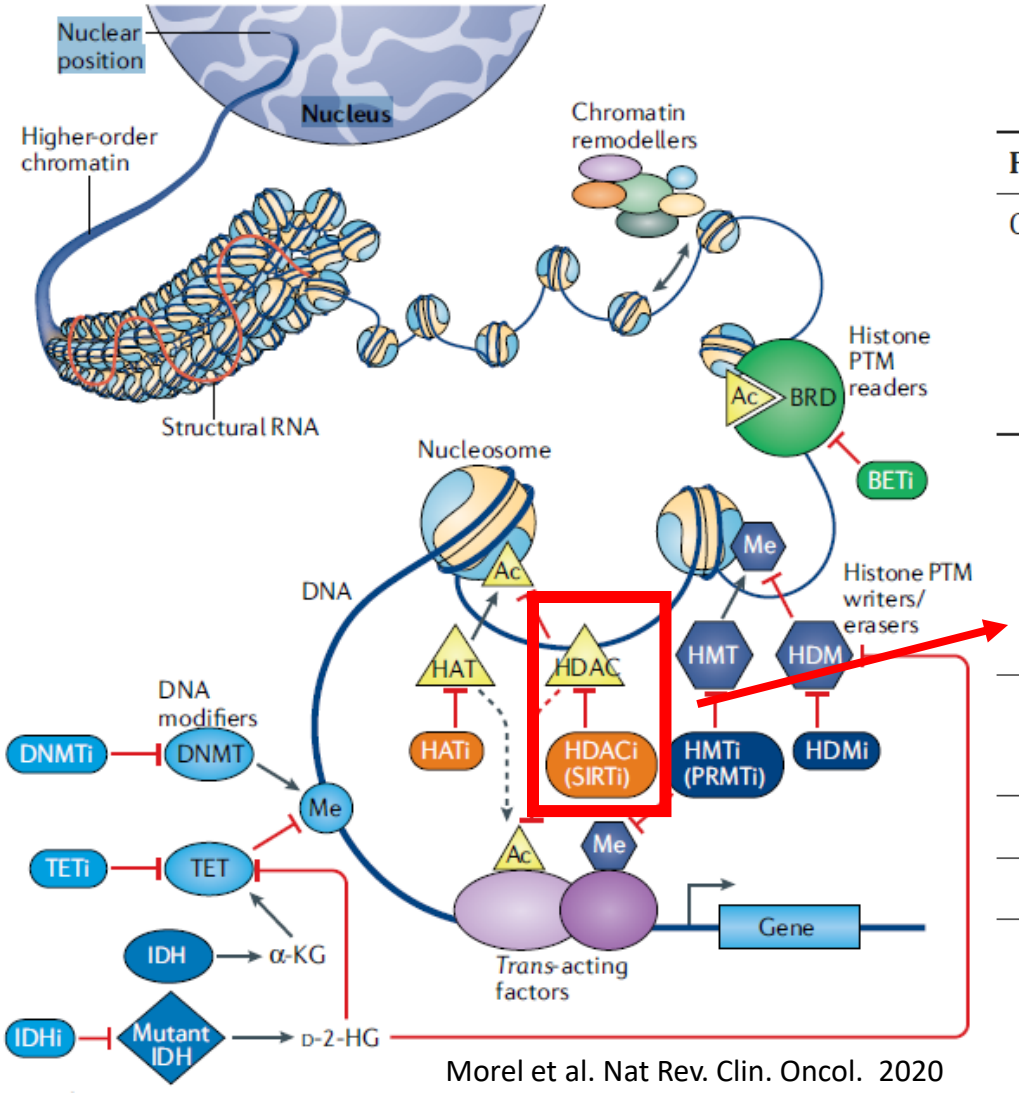
All
PTCL

Immune surveillance

PDL1 3' UTR
HLA B2M
CD58

NKT
ATLL

Histone deacetylase inhibitors



Morel et al. Nat Rev. Clin. Oncol. 2020

Family	Class (Yeast Homolog)	Subclass	Protein
Classical (Zn^{2+} dependent)	I (Rpd3)		HDAC1
			HDAC2
			HDAC3
			HDAC8
	II (Hda1)	IIa	HDAC4
			HDAC5
			HDAC7
			HDAC9
		IIb	HDAC6
			HDAC10
	IV (Rpd3, Hda1)		HDAC11
NAD dependent	III (Sir2, Hst1-4)		SIRT 1-7

Milazzo et al. Genes 2020

romidepsin

class I

belinostat

pan

vorinostat

pan

chidamide

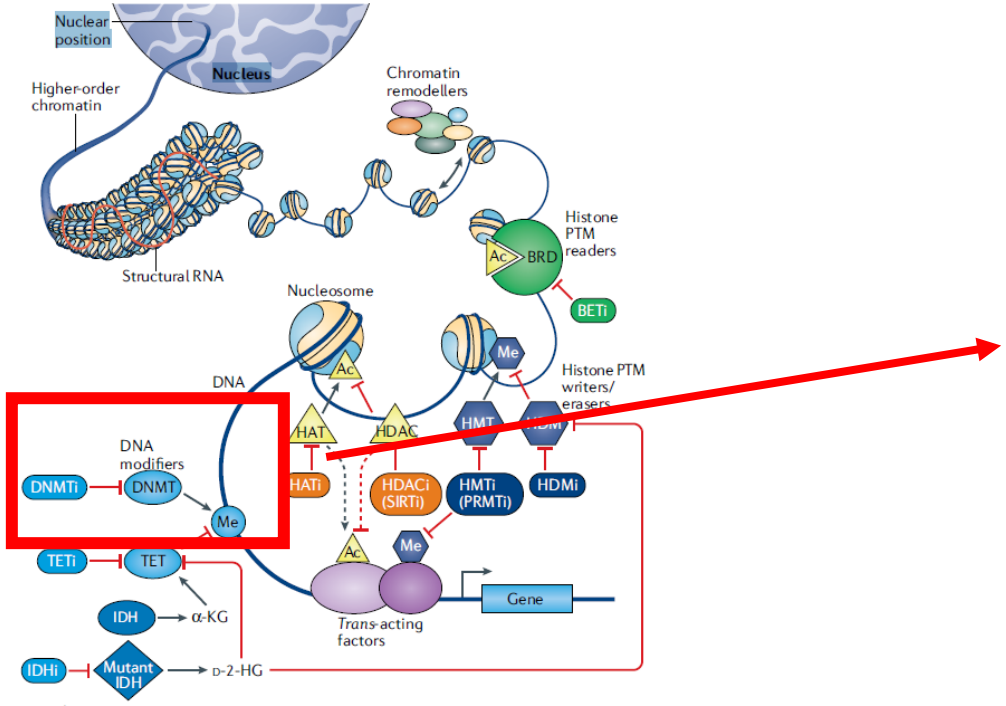
HDAC1, 2, 3 10

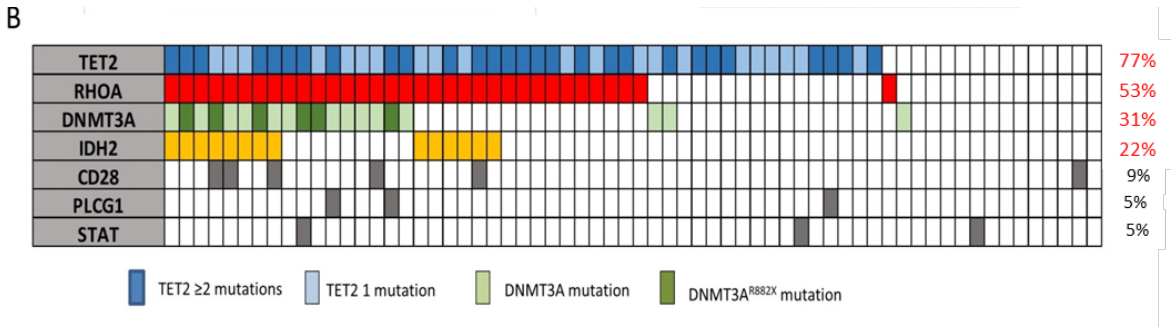
Others

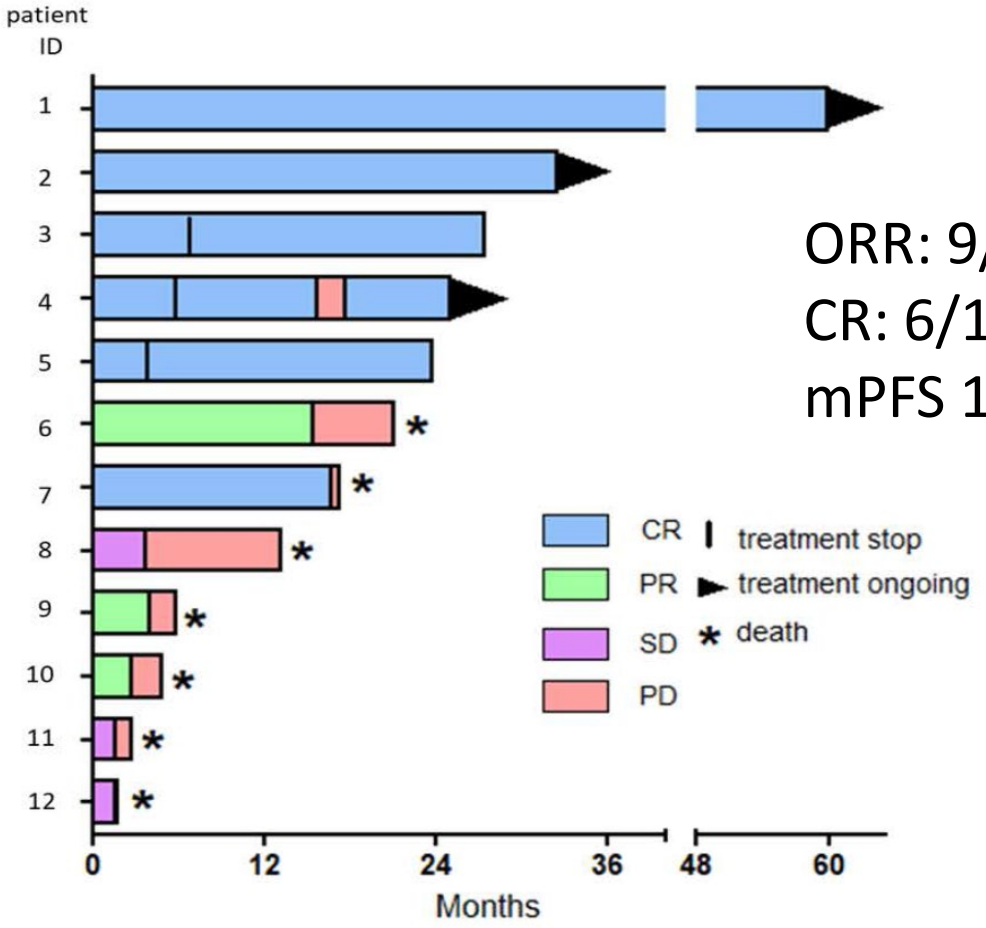
Histone deacetylase inhibitors in PTCL single agents, pivotal studies

	Approval	Pivotal Study	Patient	pathology	ORR	CR	m PFS	m DOR
Romidepsin	~~FDA~~	Coiffier et al JCO	130	PTCL	25%	15%	4 months	17 months
Belinostat	FDA	O'Connor et al JCO	120	PTCL	25.8%	10.8%	1.8 months	13.6 months
Vorinostat	FDA	Olsen et al JCO	74	CTCL	29.7%	-	NA	NR
Chidamide	China	Shi et al. Ann Oncol	83	PTCL	28%	14%	2.1 months	9.9 months

Hypomethylating agent: azacitidine



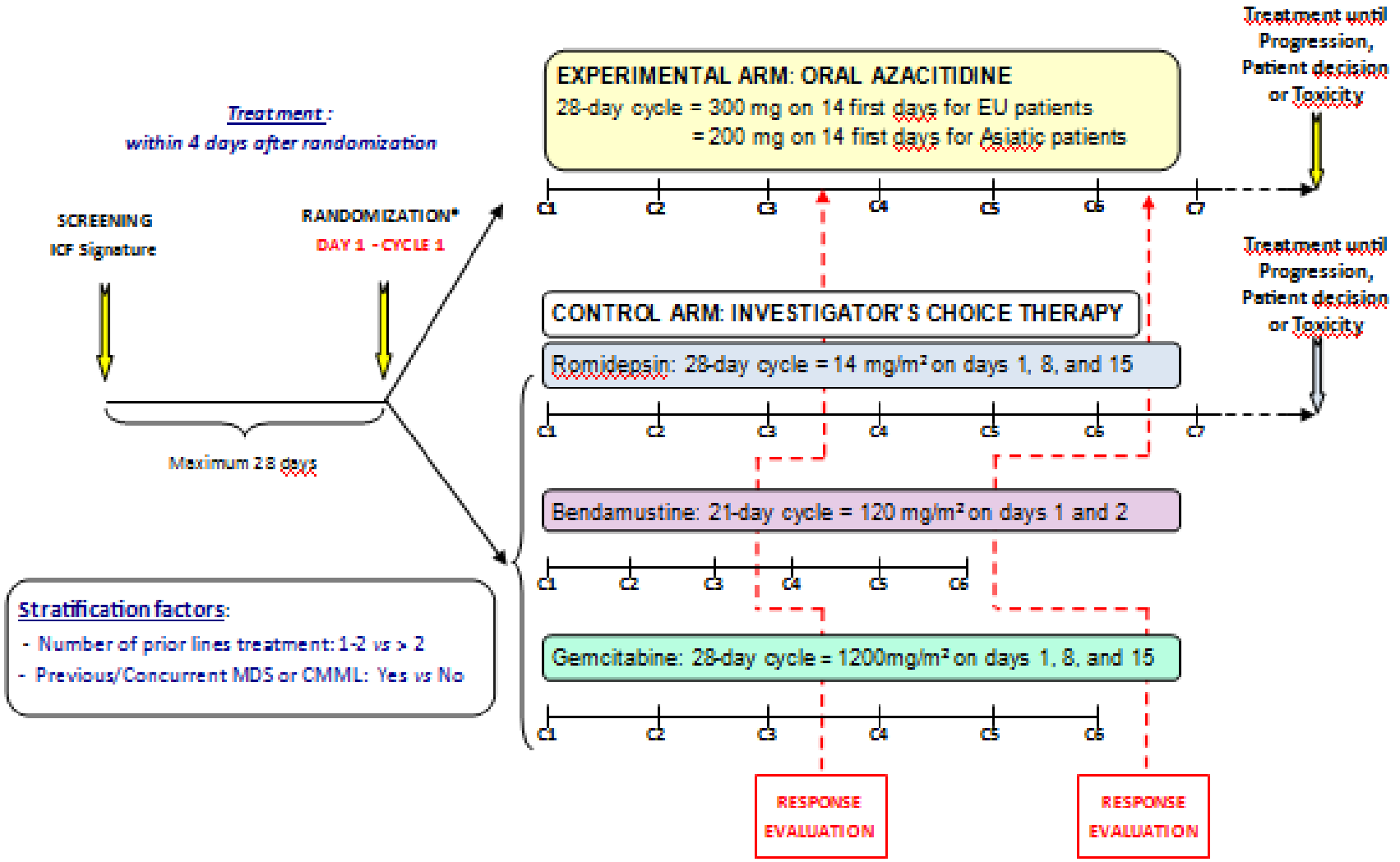




ORR: 9/12
CR: 6/12
mPFS 15 months

Lemonnier et al, Blood 2018

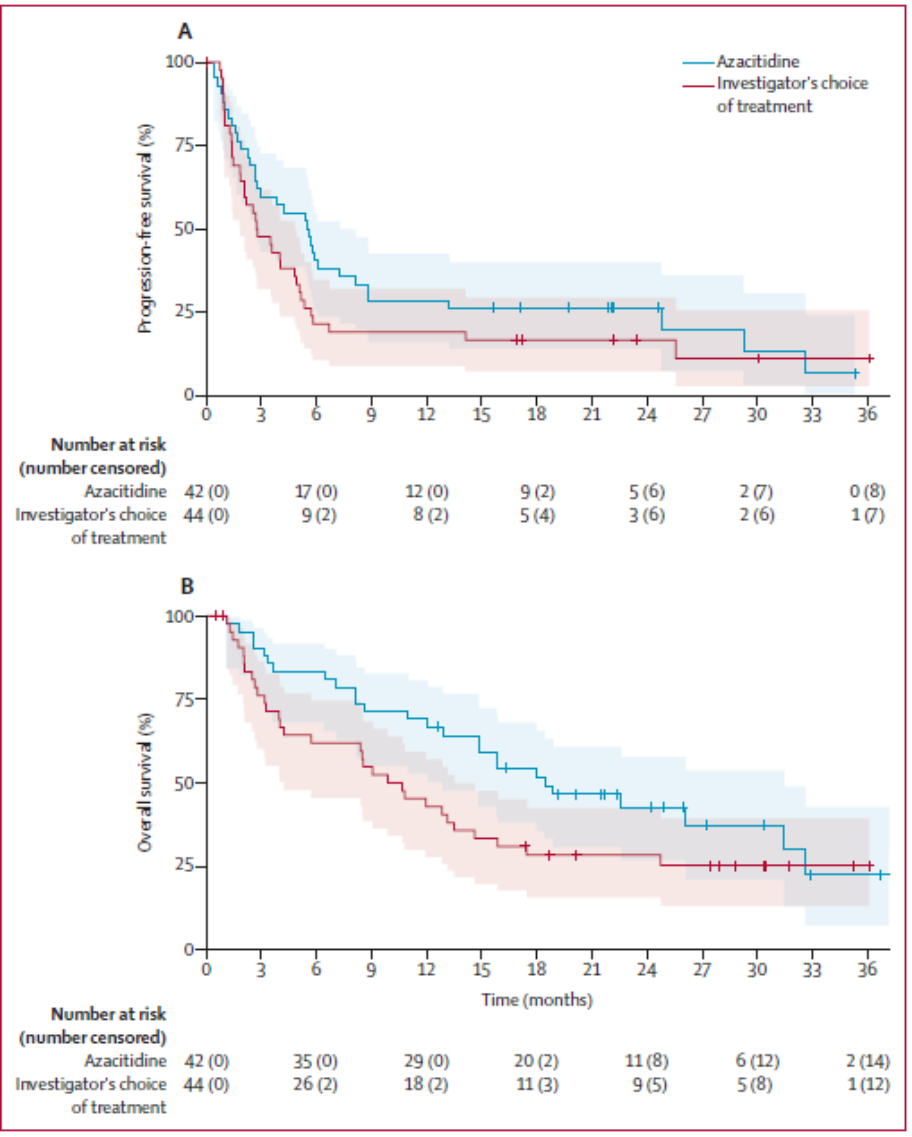
Azacitidine in R/R TFHL: ORACLE STUDY



Lysa
THE LYMPHOMA STUDY ASSOCIATION

Lysarc
THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

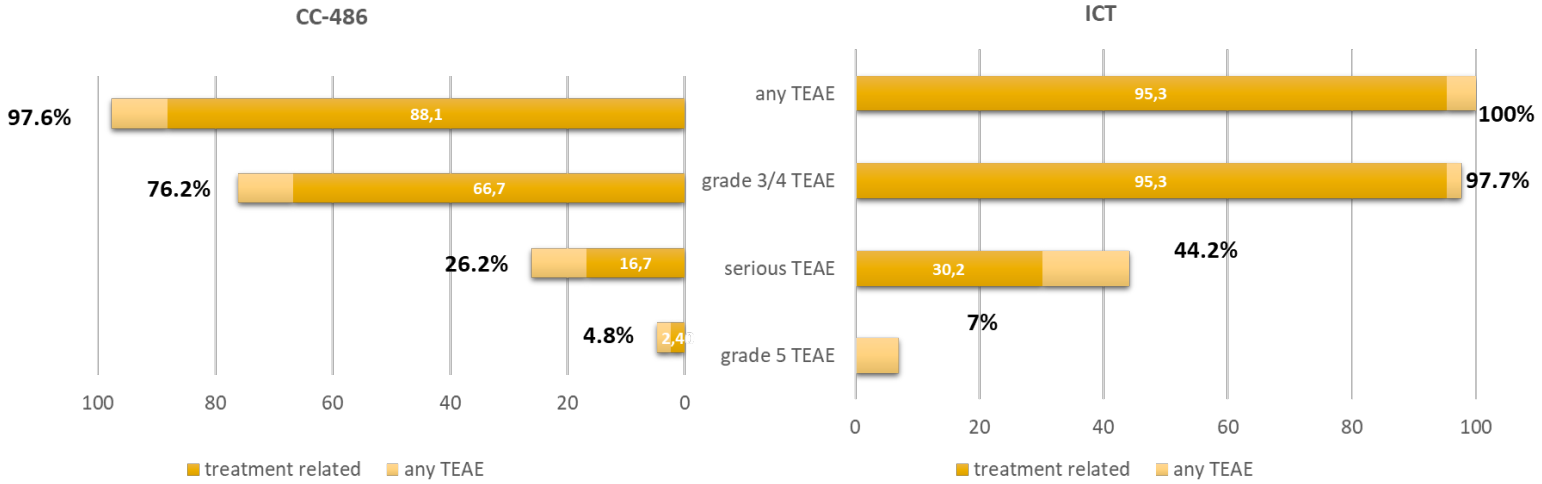
Azacitidine in R/R TFHL ORACLE study



	Oral azacitidine group (n=42)	Investigator's choice of treatment group (n=44)
3 months (or premature treatment discontinuation cycle one to three)		
Overall response rate	14 (33%, 20–50)	19 (43%, 28–59)
Complete response rate	5 (12%, 4–26)	10 (23%, 12–38)
6 months (or premature treatment discontinuation cycle four to six)		
Overall response rate	13 (31%, 18–47)	10 (23%, 12–38)
Complete response rate	5 (12%, 4–26)	7 (16%, 7–30)

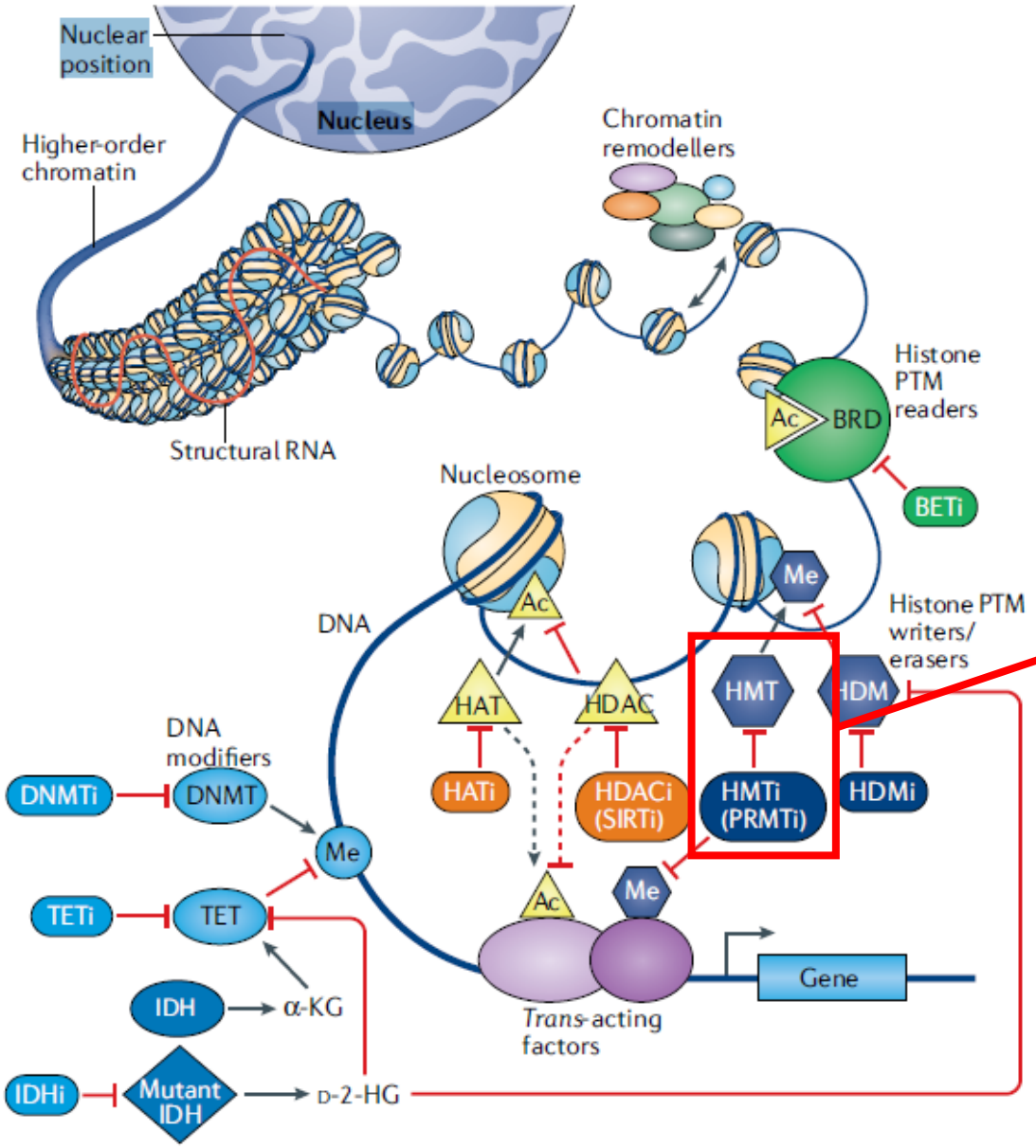
Date are n (%, 95% CI).

Table 2: Response rates at 3 and 6 months



Dupuis et al. Lancet Haematol. 2024

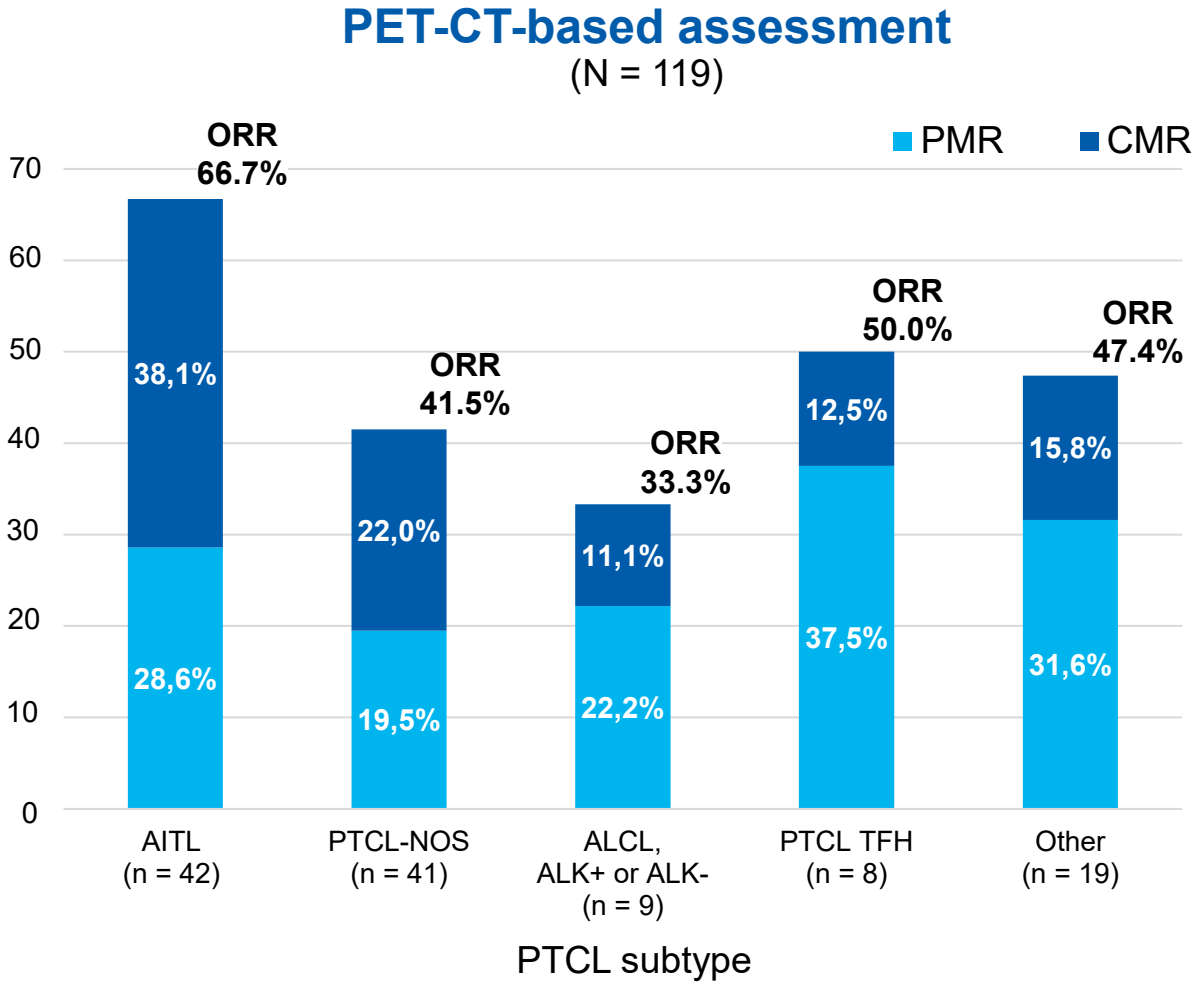
Other epigenetic targeting approach



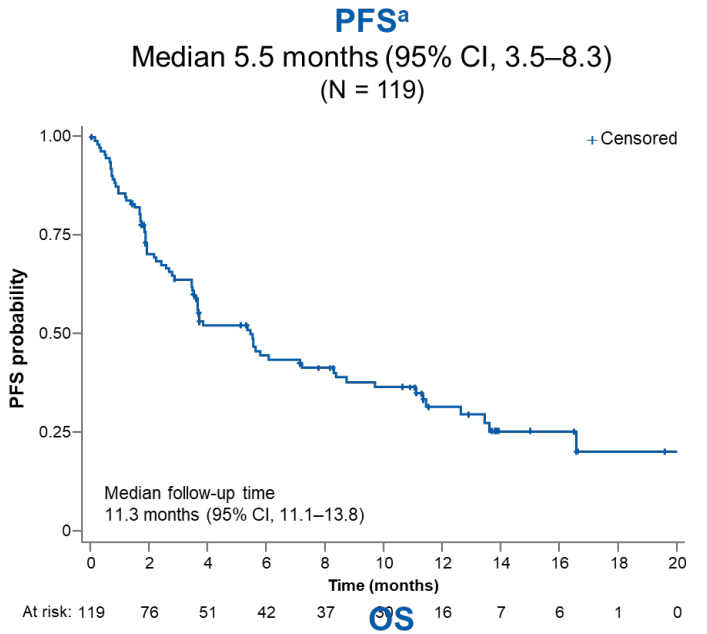
EZH1/EZH2

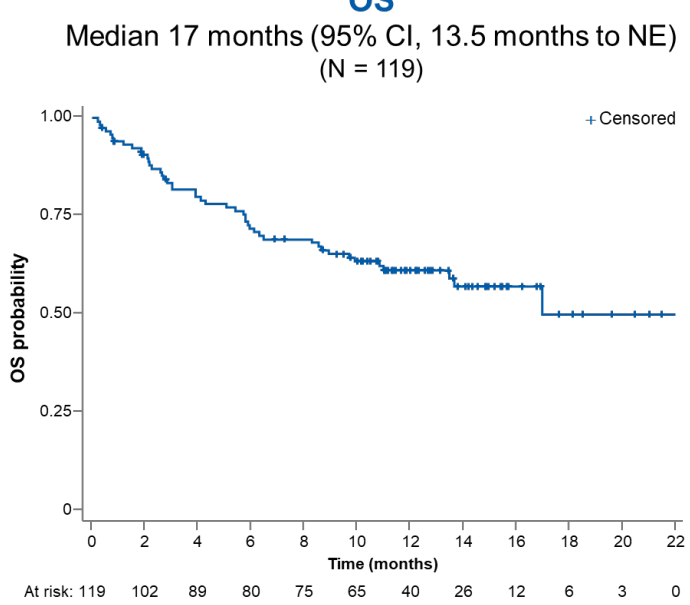
Valemetostat

Valemetostat Valentine 01 study



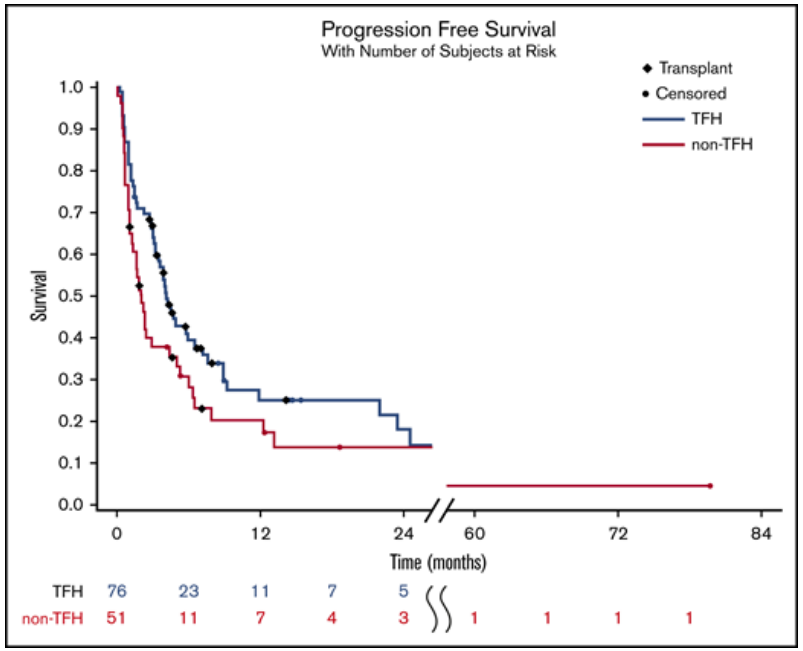
Horwitz et al. ASH 2023





TFHL have an epigenetic susceptibility

HDACi



Non-TFH vs TFH phenotype	P value
ORR to HDACi and HDACi combinations 29% (19% CR) vs 56% (29% CR)	.003
Logistic regression model TFH independent predictive factor of ORR to HDACi	.009

Ghione et al. Blood advances 2020

Response to azacitdine and romidespin

Response	All patients (n = 23)	tTFH phenotype (n = 15)	Other subtypes (n = 8)
Overall response	14 (61)	12 (80)	2 (25)
Complete response	10 (43)	9 (60)	1 (12.5)
Partial response	4 (17)	3 (20)	1 (12.5)
Stable disease	5 (22)	2 (13)	3 (37.5)
Progressive disease	4 (17)	1 (7)	3 (37.5)
Not evaluable	2	2	0

Falchi et al. Blood 2021

Pathways involved in PTCL oncogenesis

80% TFH

90% SS

Epigenetic regulation

DNA methylation
- *TET2*
- *IDH2*
- *DNMT3A*

Histone PTM
- *SETD2*
- *KDM2A*
- KMT2D
- ….

Others
- *ARIDIA*

TFH

MEITL
HSTL

All
PTCL

PTCL

Signaling

TCR signaling
- *RHOAG17V*
- *ITK-SYK*
- *PLCG1*
- *CARD11*
- *CD28*
- Dusp22

JAK/STAT pathway

NFκB

ALK fusions

TFH
CTCL
ATLL

ALCL
LGL
HSTL
MEITL

Cell cycle/apoptosis

TP53 family
CDKN2A
Others

All
PTCL

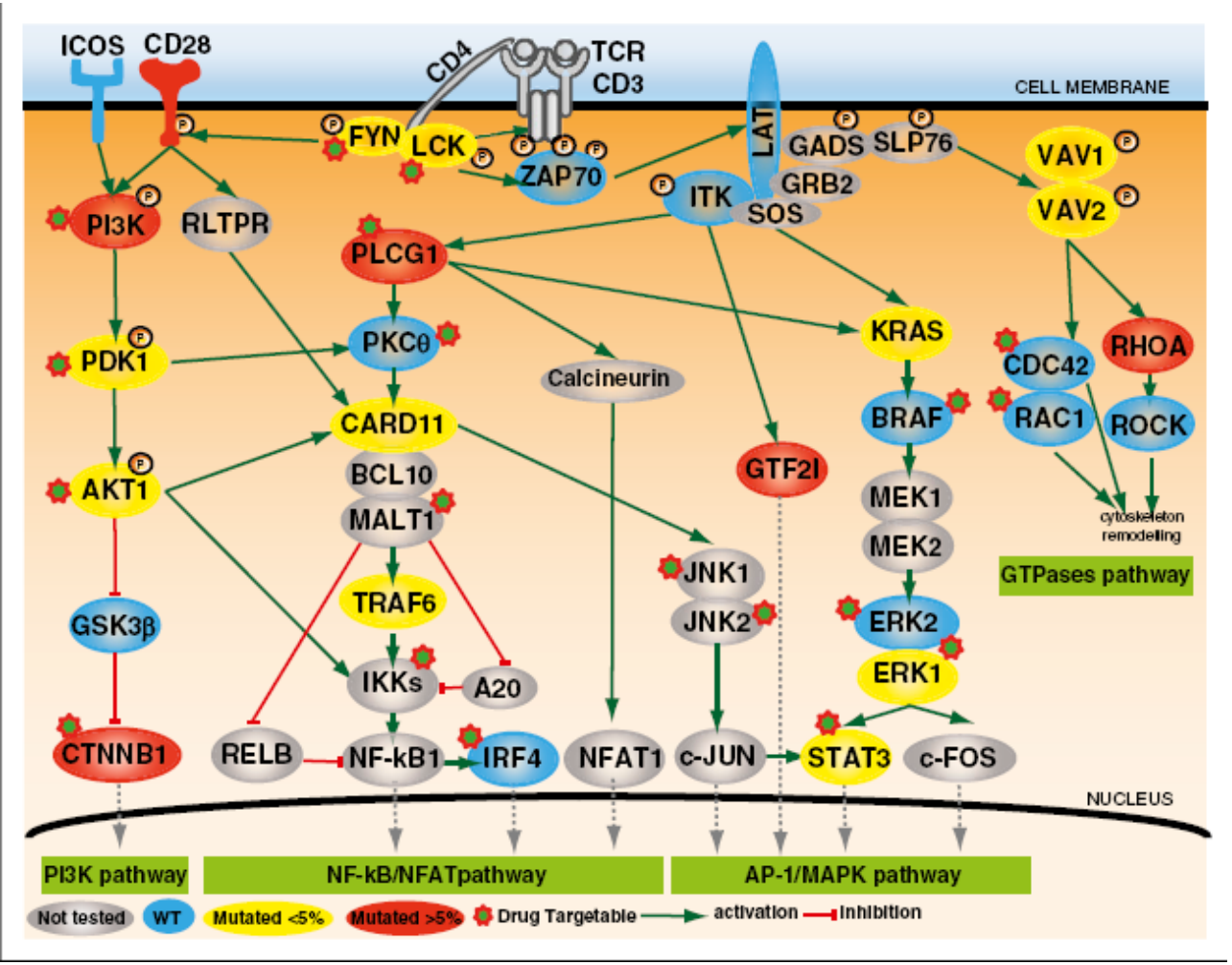
Immune surveillance

PDL1 3’ UTR
HLA B2M
CD58

NKT
ATLL

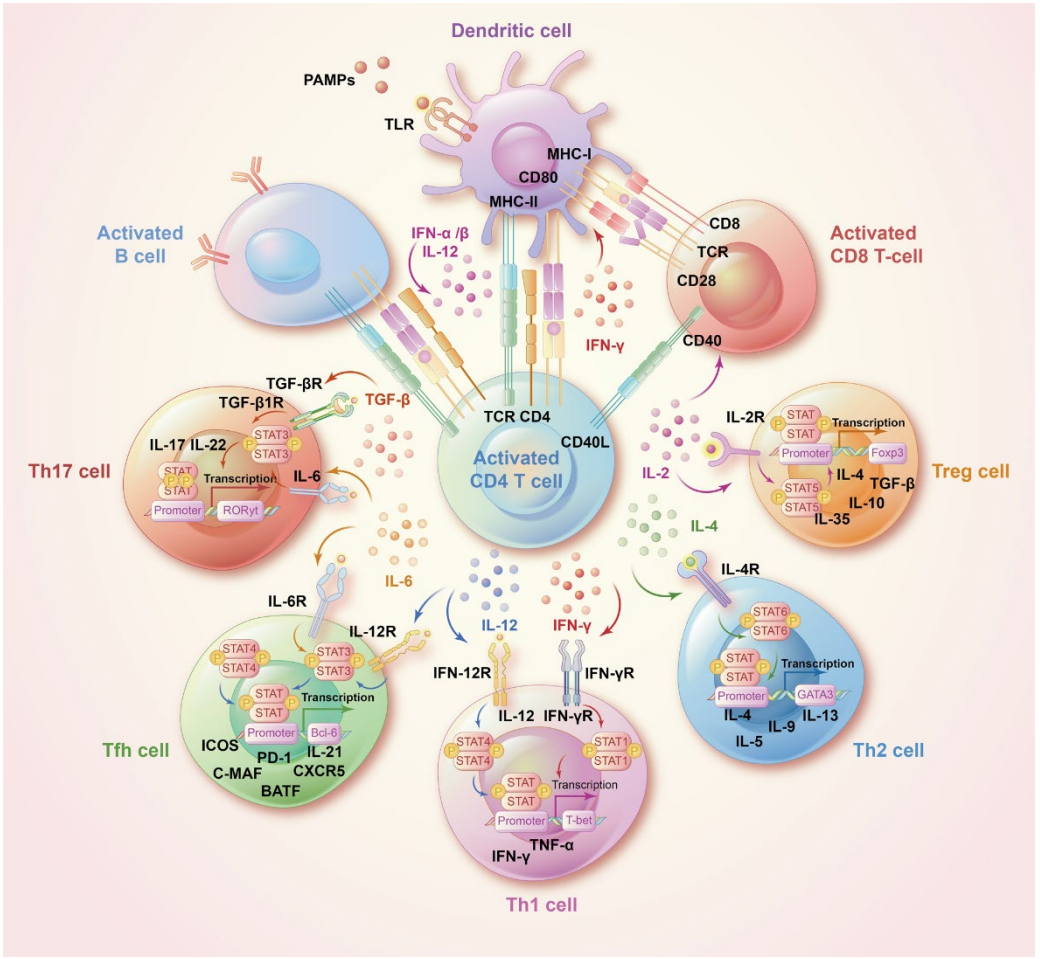
T cell signaling

TCR signaling



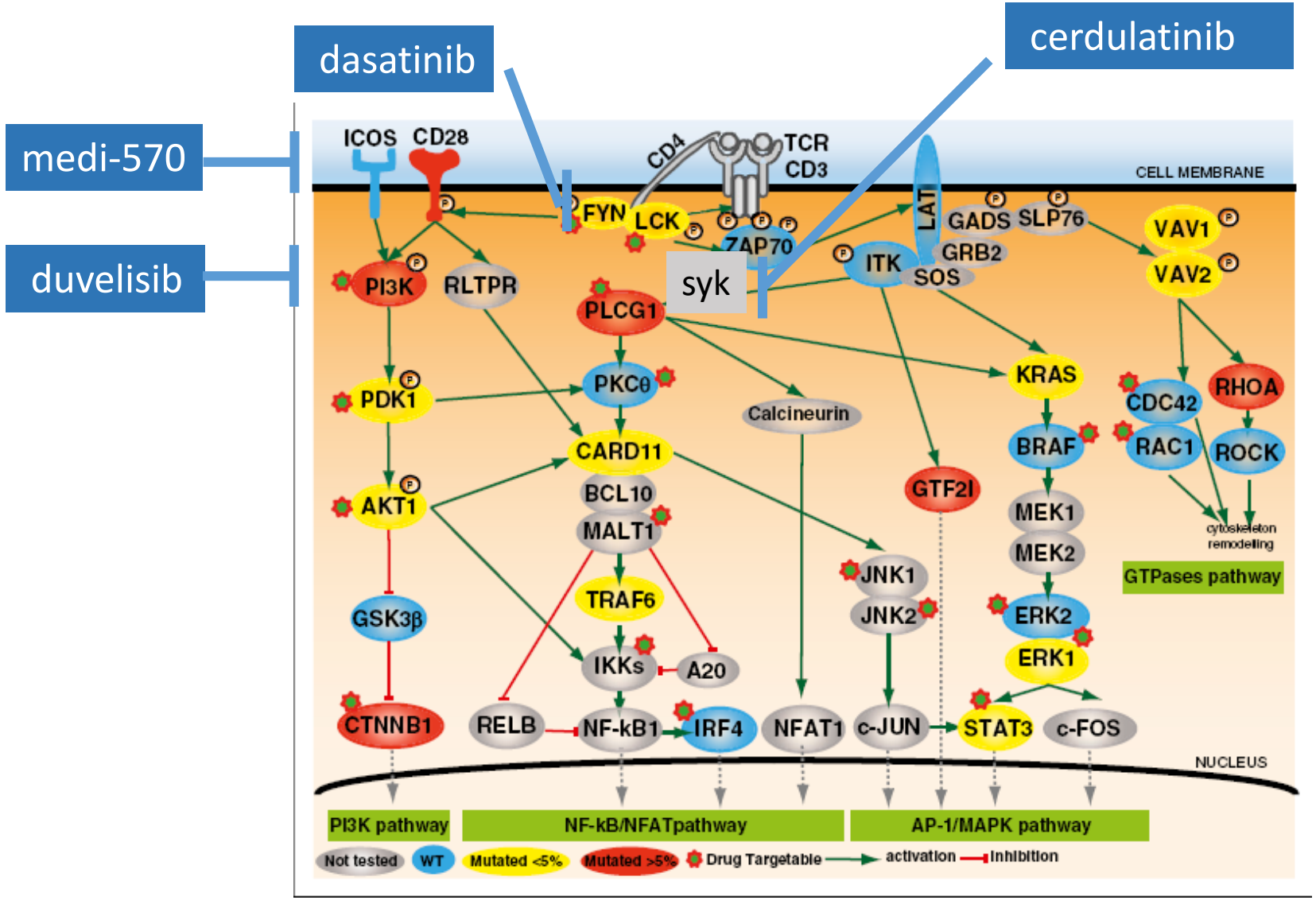
Vallois et al. Blood 2016

JAK-STAT signaling



Xue et al. Signal Transduct Target Ther 2023

TCR signaling and costimulation



Vallois et al. Blood 2016

Signaling inhibition

duvelisib, a PI3K-γ,δ inhibitor

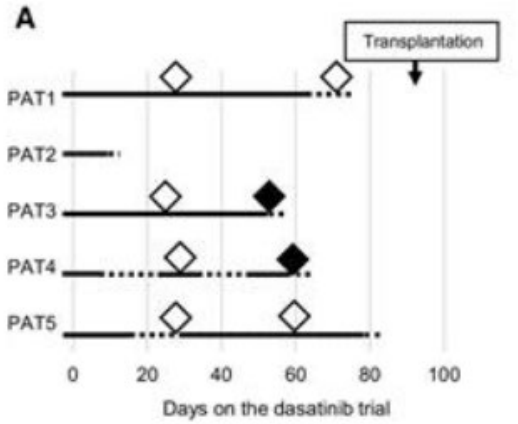
Table 1. Outcomes from the PRIMO Expansion Phase stratified by baseline histology

Outcome (n=97)*	PTCL-NOS (n=52)	AITL (n=30)	ALCL (n=15)
ORR by baseline histology, n (%)	25/52 (48.1)	20/30 (66.7)	2/15 (13.3)
Best overall response, n (%)			
Complete response (CR)	14/52 (26.9)	16/30 (53.3)	2/15 (13.3)
Partial response (PR)	11 (21.2)	4 (13.3)	0 (NC, NC)
Median PFS by IRC, months (95% CI)	3.5 (1.8, 8.1)	9.1 (6.2, NC)	1.5 (0.7, 1.7)
Median OS, months (95% CI)	10.9 (5.1, NC)	15.5 (9.5, 18.0)	4.8 (1.7, 15.7)
Median time to response (range)	1.7 (1.7, 0.5)	1.8 (1.9, 0.5)	2.6 (2.6, 1.3)
Median DOR by IRC, months (95% CI)	5.5 (2.0, 9.2)	8.8 (7.7, NC)	1.9 (1.9, 2.0)
Median DOR for patients achieving CR	7.4 (6.4, NC)	7.9 (3.3, NC)	1.9 (1.9, 2.0)

*In the current analysis (n=97), four patients discontinued prior to first scheduled scan due to progressive disease.
NC, not calculated.

Mehta Shah EHA 2023

Dasatinib (multikinase inhibitor)



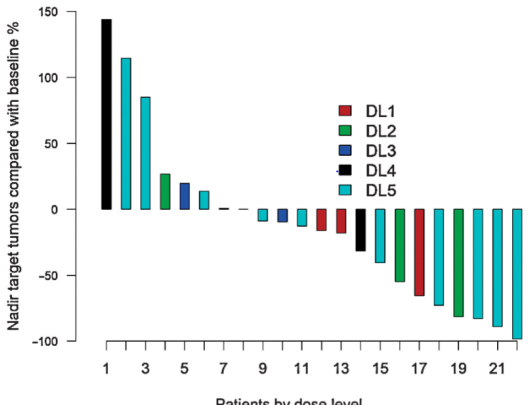
Nguyen et al. cancer research 2020

cerdulatinib, a dual SYK JAK inh in PTCL

Response	AITL / TFH	PTCL-NOS	Gamma-delta[1]	ALCL (ALK-)	ATLL	T-PLL	Total
N evaluable (%)	14	13	7	3	3	1	41
ORR	**8 (57)**	**2 (15)**	**1 (14)**	**1 (33)**	**2 (67)**	**0**	**14 (34)**
CR	7 (50)	2 (15)	1 (14)	0	1 (33)	0	11 (27)
PR	1 (7)	0	0	1 (33)	1 (33)	0	3 (7)
SD	1 (7)	3 (23)	3 (44)	1 (33)	0	1 (100)	9 (22)

Horwitz et al. ASH 2018

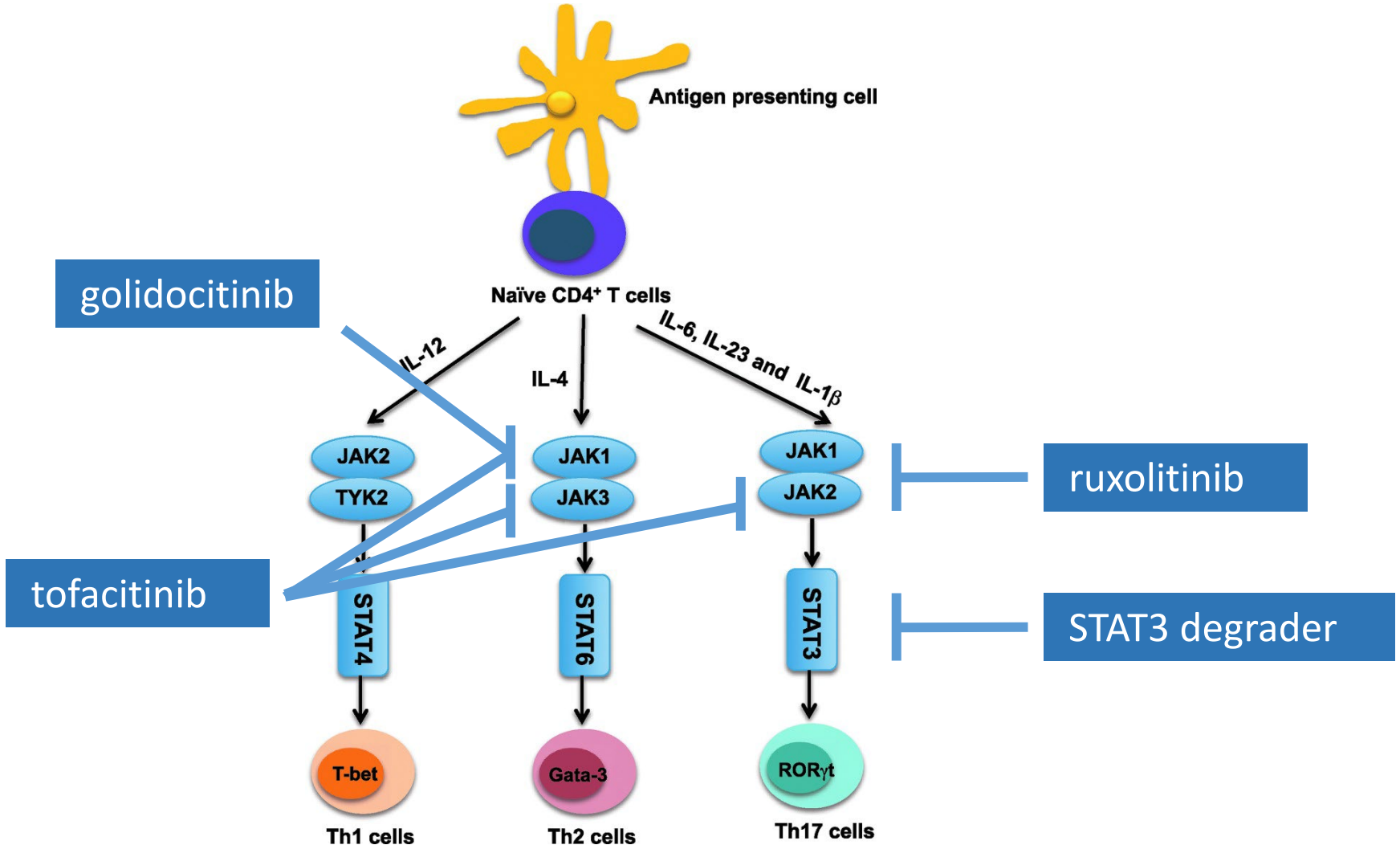
MEDI-570, an anti ICOS Ab



ORR: 7/23
CR:2/23

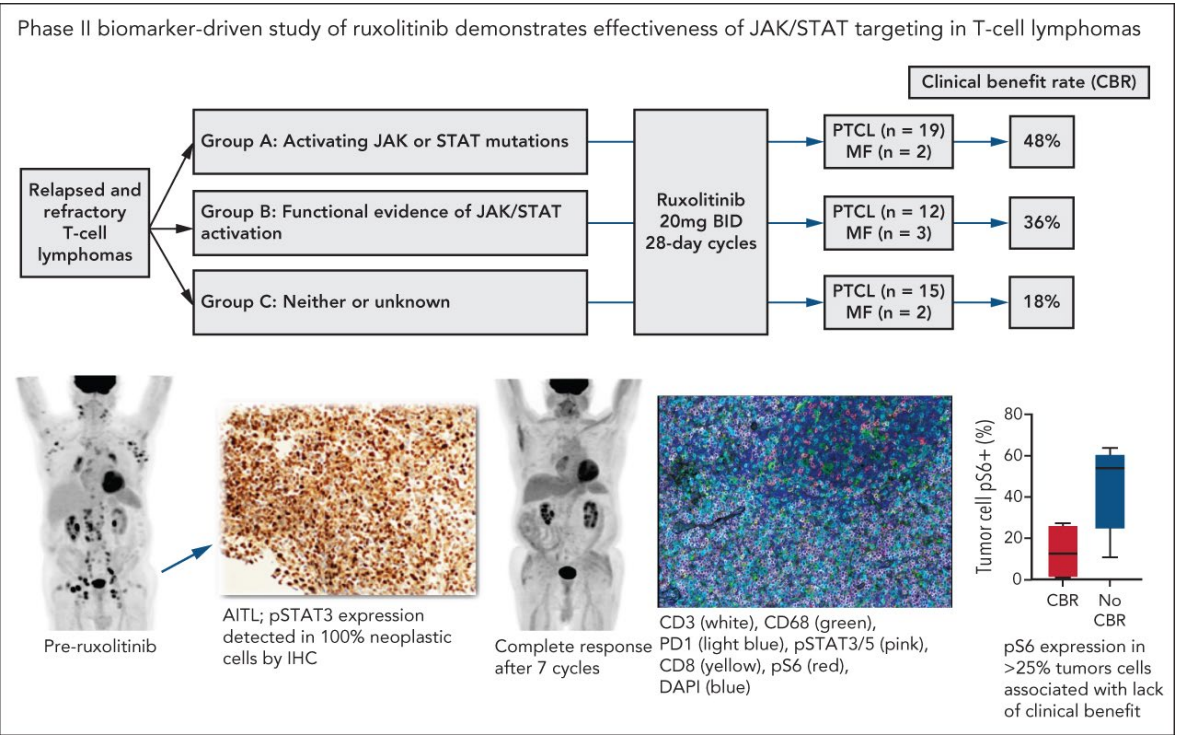
Chavez et al. ASH 2020

JAK STAT signaling



Benveniste et al. J interferon Cytok Res 2014

Jak Stat pathway: ruxolitinib



Cohorts	Total treated	Total evaluable for response	ORR	CBR	CR	PR	SD >6 mo
Cohort 1	21	21	7 (33%)	10 (48%)	1 (5%)	6 (29%)	3 (14%)
Cohort 2	15	14	4 (29%)	5 (36%)	2 (14%)	2 (14%)	1 (7%)
Cohort 3	17	17	2 (12%)	3 (18%)	0	2 (12%)	1 (6%)
Total	53	52	13 (25%)	18 (35%)	3 (6%)	10 (19%)	5 (10%)
P (cohorts 1 & 2 vs 3)			*P* = .2	*P* = .073			

Subtypes	Total treated	Total evaluable for response	ORR	CBR	CR	PR	SD >6 mo
PTCL, NOS	12	11	2 (18%)	2 (18%)	1 (9%)	1 (9%)	0
T-PLL	8	8	3 (38%)	4 (50%)	0	3 (38%)	1 (13%)
AITL/TFH	9	9	3 (33%)	4 (44%)	1 (11%)	2 (22%)	1 (11%)
T-LGL	5	5	2 (40%)	4 (80%)	0	2 (40%)	2 (40%)
ALCL	4	4	1 (25%)	1 (25%)	1 (25%)	0	0
ATLL	3	3	0	0	0	0	0
MF	7	7	1 (14%)	1 (14%)	0	1 (14%)	0
γ/δ TCLs	4	4	1 (25%)	1 (25%)	0	1 (25%)	0 (0%)
SPTCL	1	1	0	1 (100%)	0	0	1(100%)

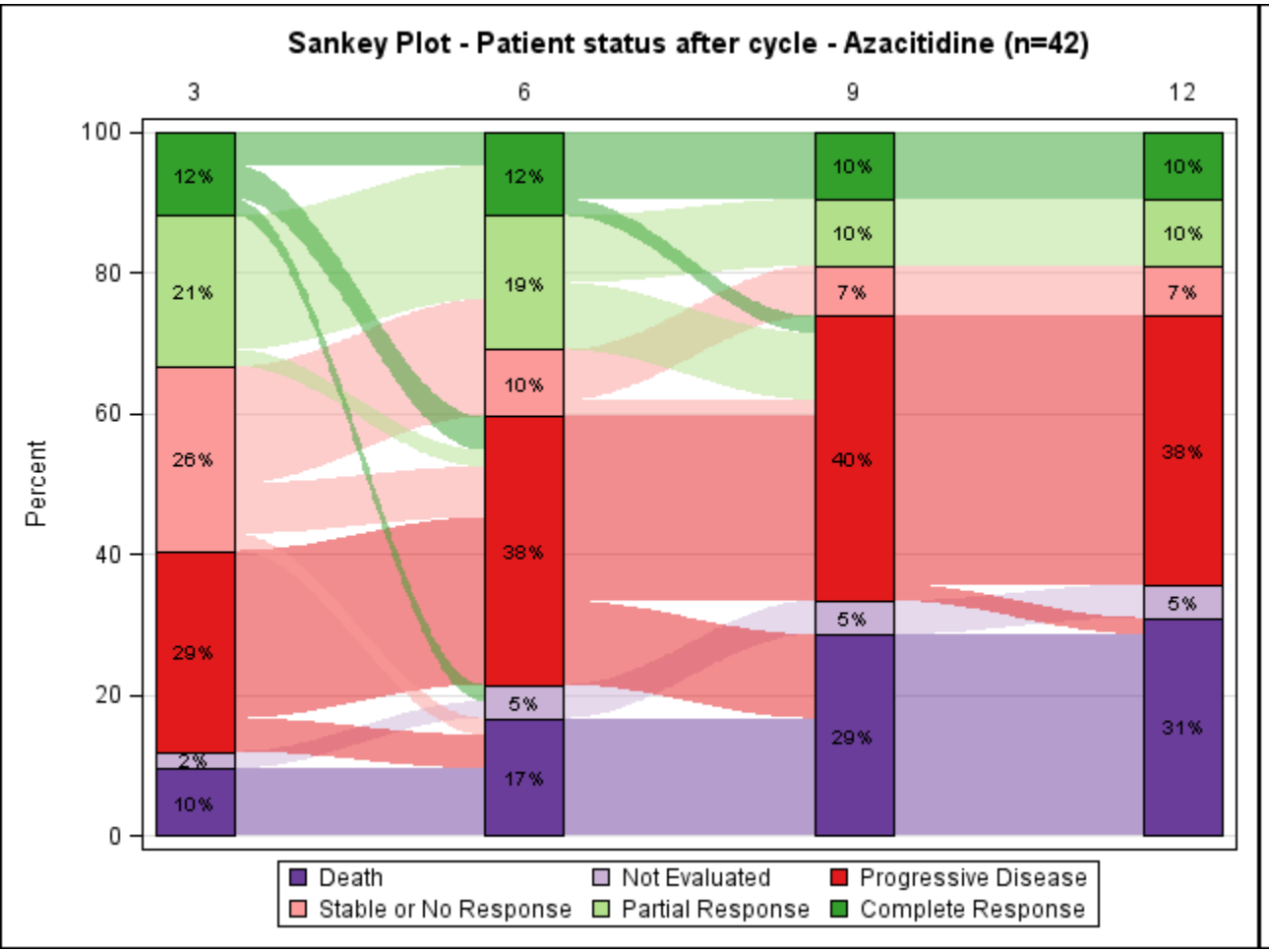
AITL/TFH, angioimmunoblastic T-cell lymphoma and other T-follicular helper lymphomas; ATLL, adult T-cell lymphoma lymphoma/leukemia; γ/δ TCL, γ/δ T-cell lymphomas; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

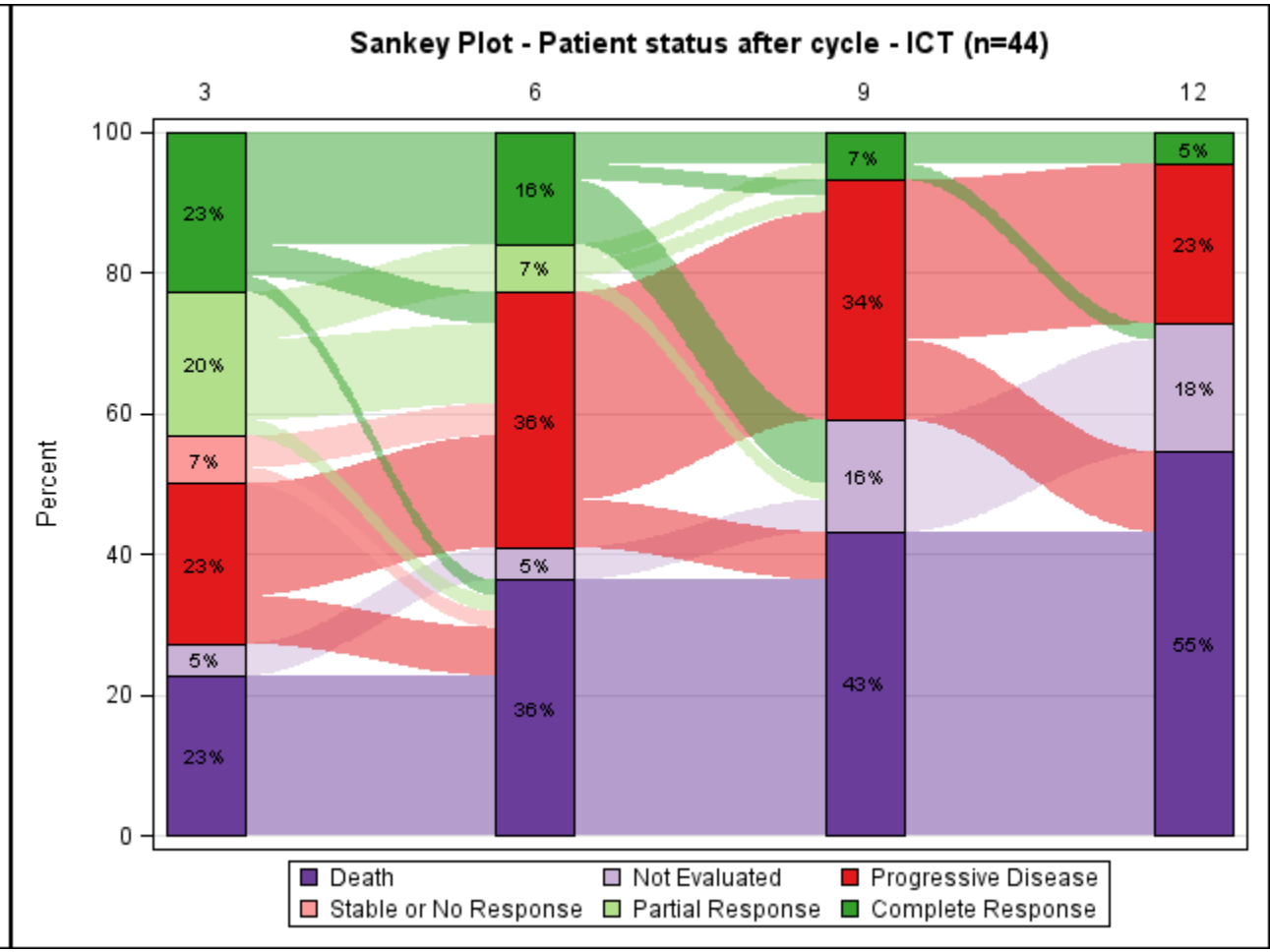
Moskowitz et al. Blood 2021

Distinct response patterns in ORACLE study

Azacitidine

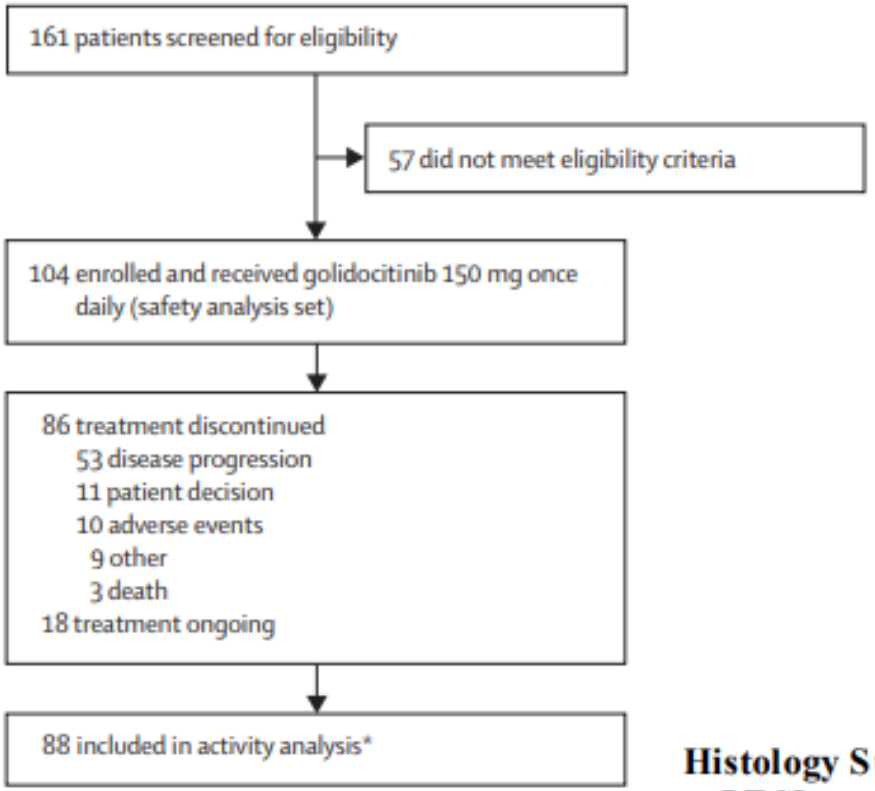
Investigator's choice therapy

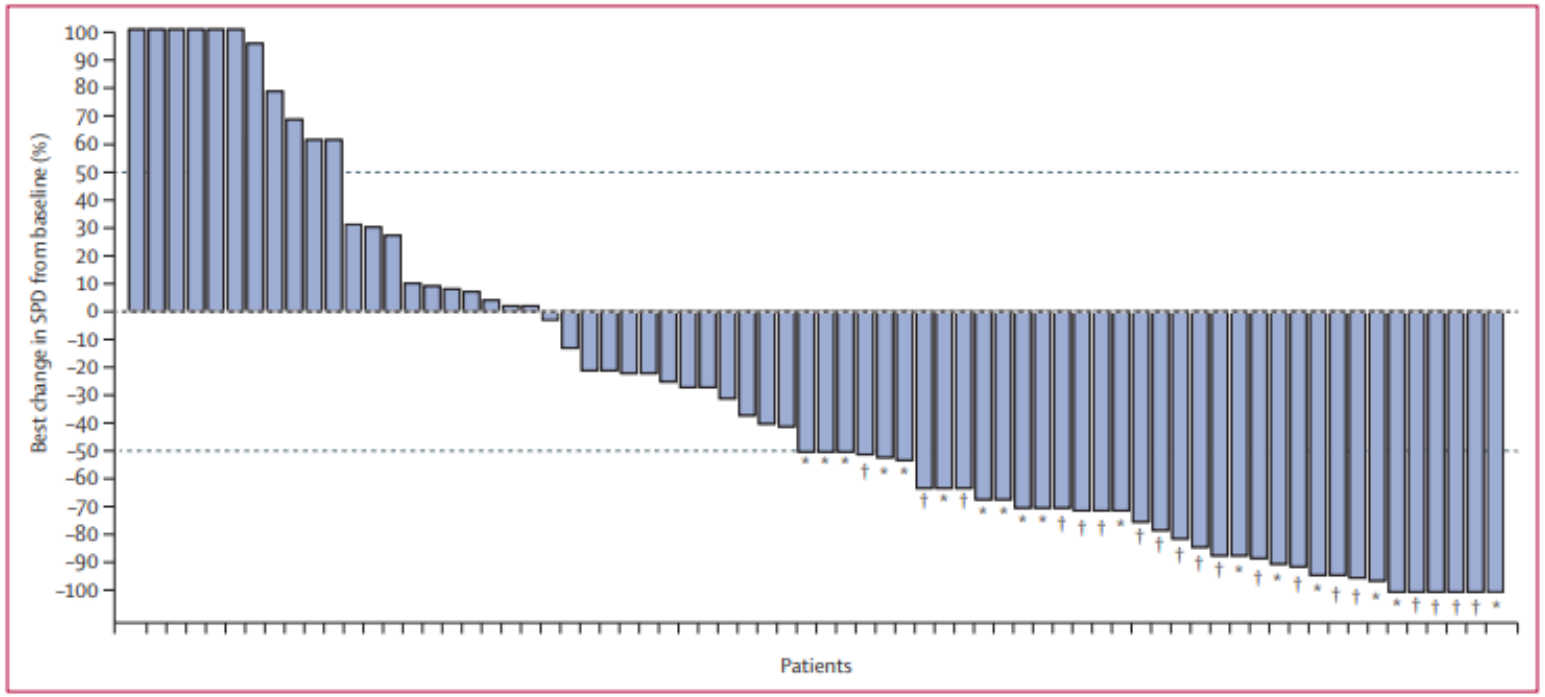




Dupuis et al. Lancet Haematol. 2024

Jak Stat pathway: golidocitinib





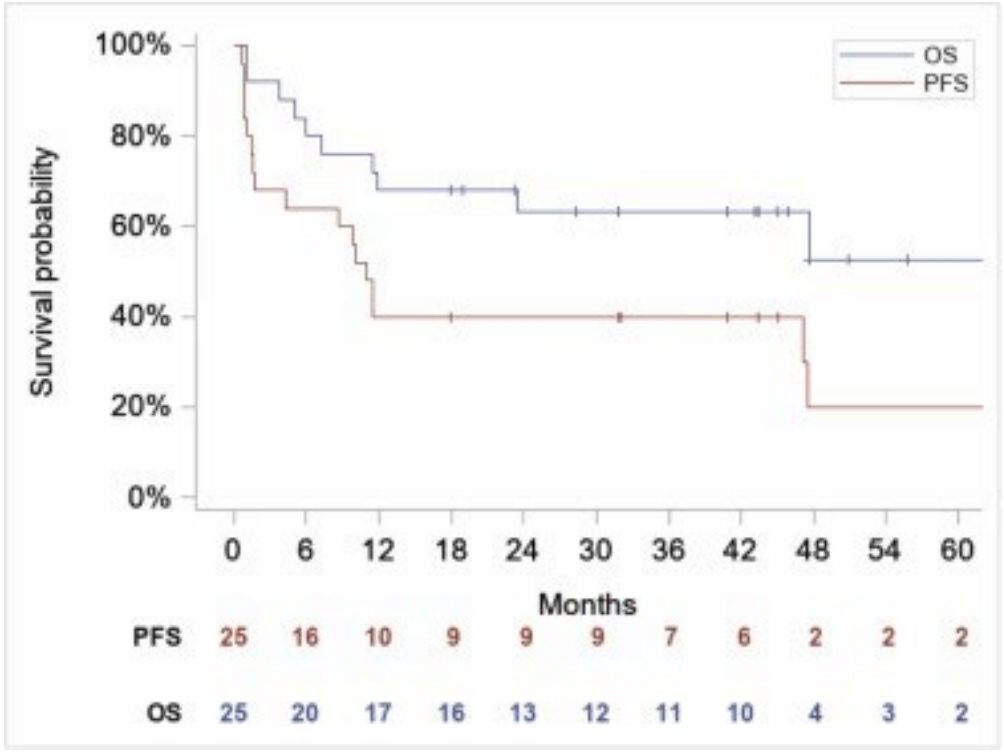
ORR:44.3%
CR:29,5%

Histology Subtype by Central Pathology Review		
PTCL-not otherwise specified (PTCL, NOS)	23/50 (46·0)	(31·8, 60·7)
Angioimmunoblastic T-cell lymphoma (AITL)	9/16 (56·3)	(29·9, 80·2)
Anaplastic large-cell lymphoma (ALCL)	1/10 (10·0)	(0·3, 44·5)
Natural killer/T-cell lymphoma (NK/TCL)	2/3 (66·7)	(9·4, 99·2)
Others	4/9 (44·4)	(13·7, 78·8)

Song et al. Lancet Oncol 2023

ALK inhibition in ALK+ ALCL

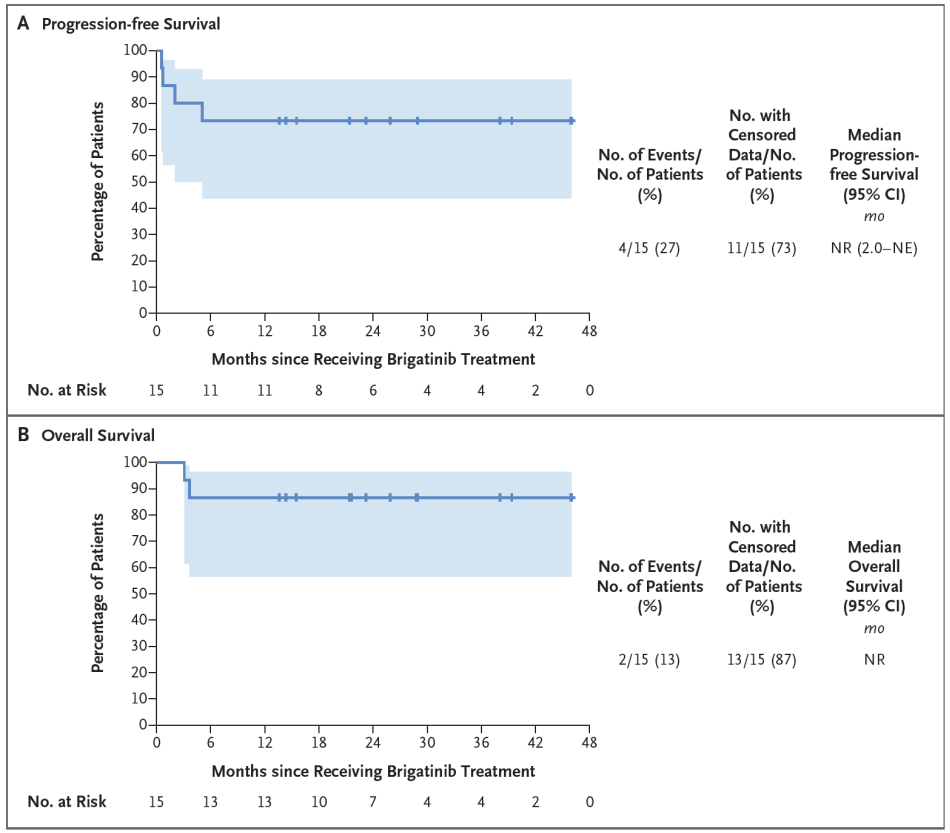
crizotinib



ORR 64%

Brugieres et al. Eur J Cancer 2023

brigatinib



ORR 92%

Veleanu, Lamant, Sibon. NEJM 2024

Pathways involved in PTCL oncogenesis

80% TFH

90% SS

Epigenetic regulation

DNA methylation
- *TET2*
- *IDH2*
- *DNMT3A*

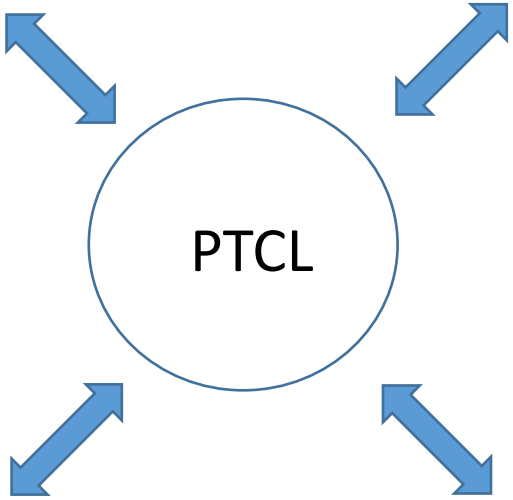
Histone PTM
- *SETD2*
- *KDM2A*
- KMT2D
- ….

Others
- *ARIDIA*

TFH

MEITL
HSTL

All
PTCL



Signaling

TCR signaling
- *RHOAG17V*
- *ITK-SYK*
- *PLCG1*
- *CARD11*
- *CD28*
- Dusp22

JAK/STAT pathway

NFκB

ALK fusions

TFH
CTCL
ATLL

ALCL
LGL
HSTL
MEITL

Cell cycle/apoptosis

TP53 family
CDKN2A
Others

All
PTCL

Immune surveillance

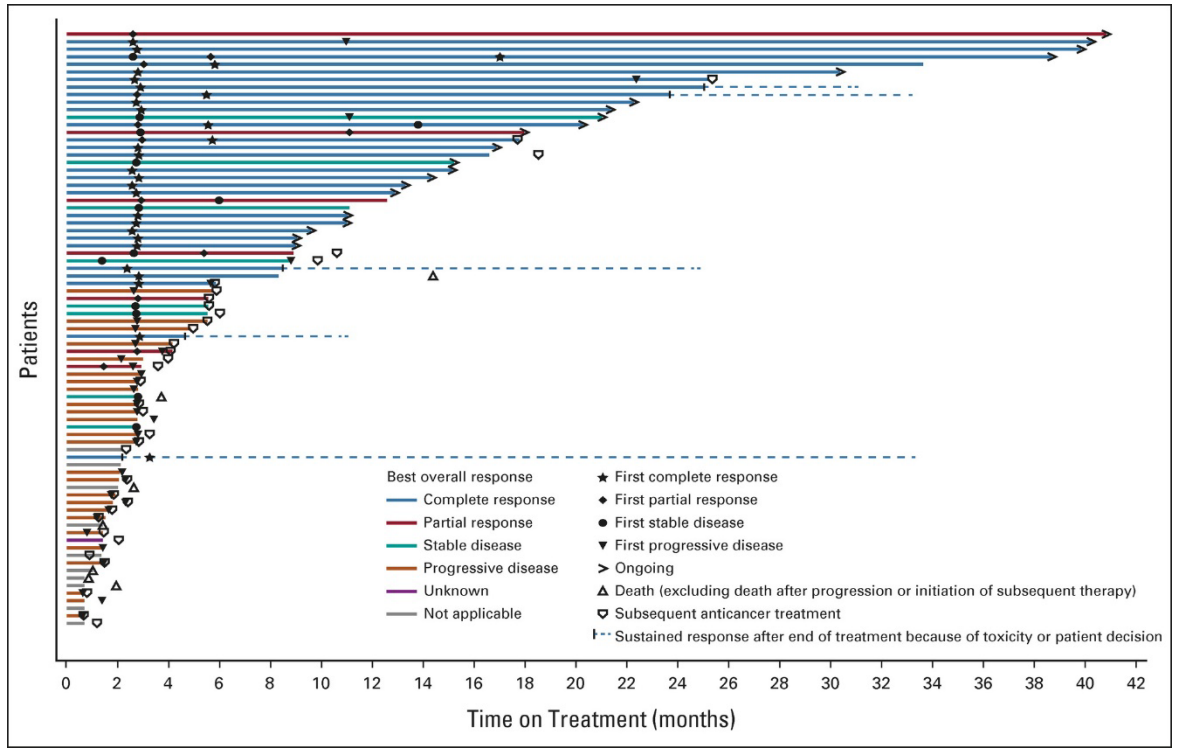
PDL1 3’ UTR
HLA B2M
CD58

NKT
ATLL

Immune check point in PTCL: anti PD1

R/R ENKTCL

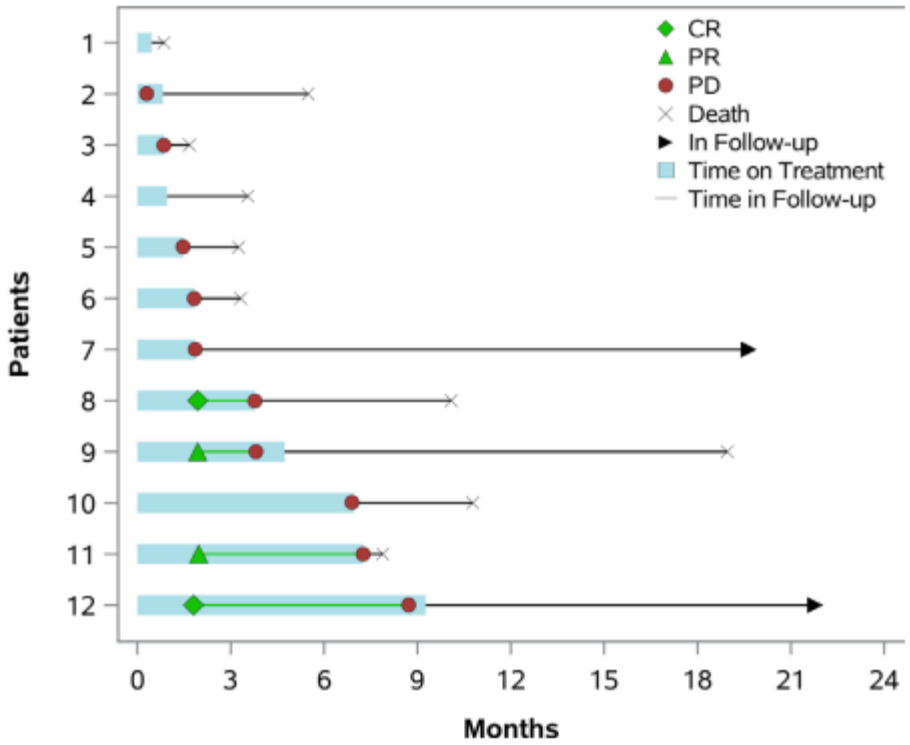
Sugemalimab in R/R ENKTCL



ORR 46%, CR: 30%

Huang et al. JCO 2023

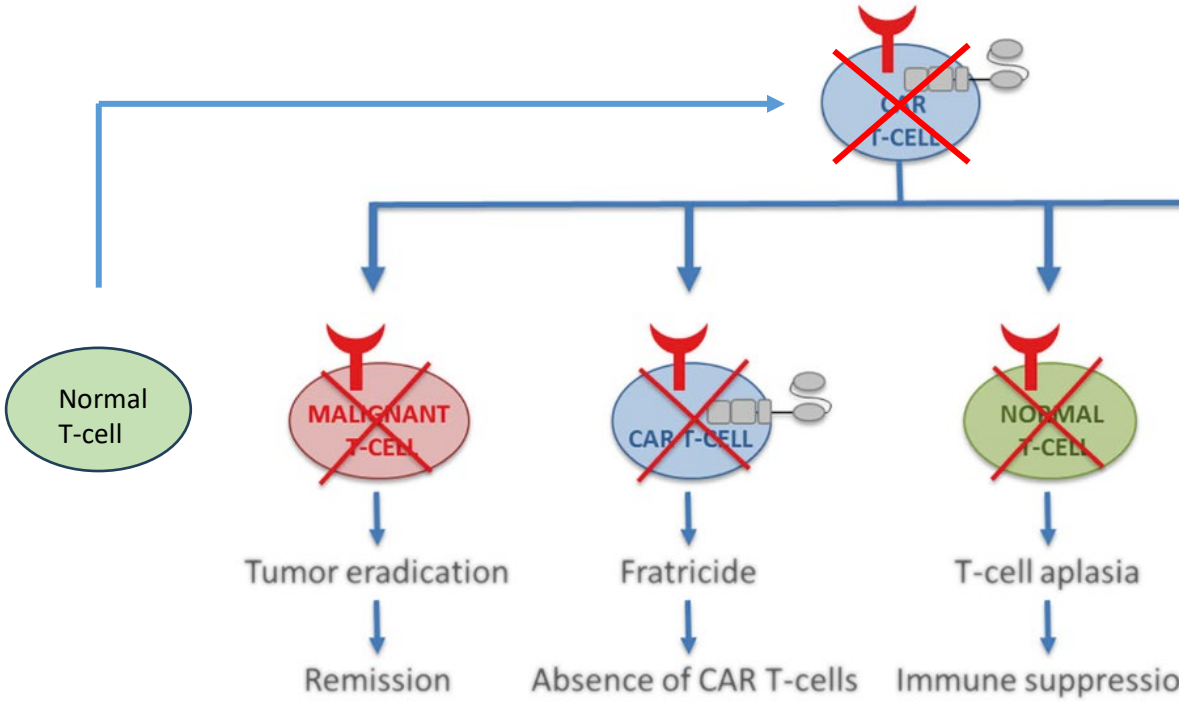
R/R PTCL



Existence of hyperprogression in PD1 positive PTCL?

Bennani, J Immunother Cancer 2022

Challenges with CAR-T cells



N=75 clinical trials (clinicaltrial.gouv)

Target	75
TCRB1	2
CD30	13
CD7	41
CD5	11
CD4	5
Others	3

N=49/75

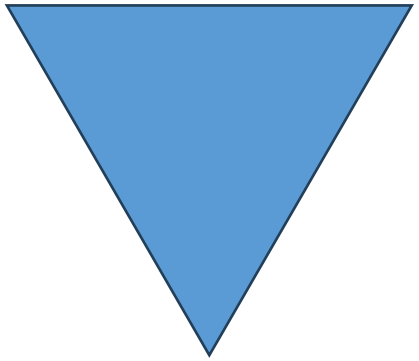
Nichakawade et al. Nature 2024

Alcantara et al. Leukemia 2018

Moving to combination

Epigenetic targeting drugs

romidepsin
azacitdine
valemetostat
belinostat
chidamide
others



Signaling targeting drugs

duvelisib
cerdulatinib
ruxolitinib
golidocitinib
others

others

cellmod
checkpoint inhibitors:anti PD1
chemotherapy
brentuximab vedotin
others

Moving to combination

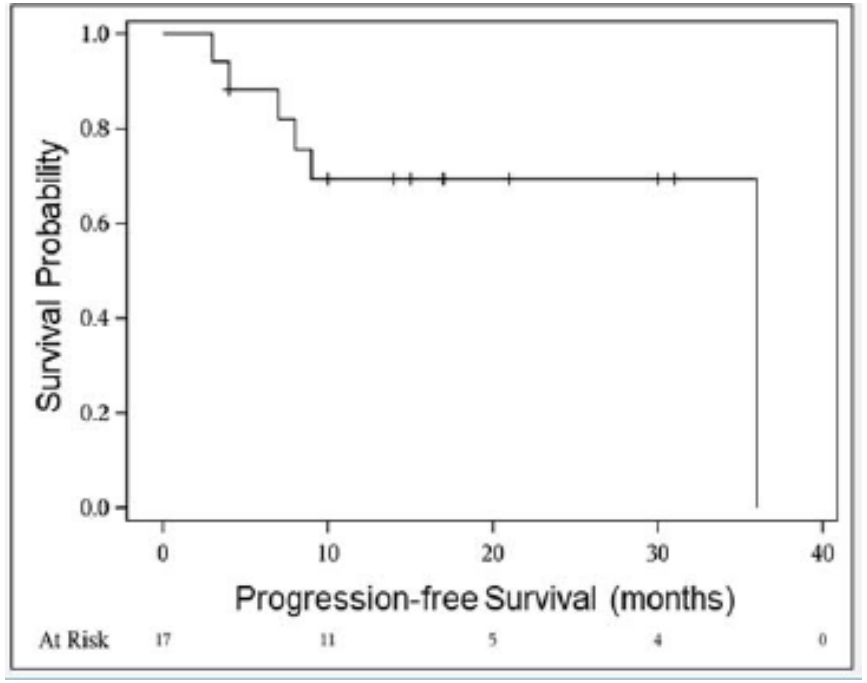
Romidepsin+ duvelisib

Histology	Treated	Evaluable	ORR N (%)	CR N (%)	Bridged to Allo SCT N (%)
PTCL	**55**	**53**	**31 (58)**	**22 (42)**	**15 (28)**
PTCL NOS	20	19	10 (53)	6 (32)	3 (16)
AITL/TFH	19	19	13 (68)	11 (58)	7 (37)
PC γδ	3	3	1 (33)	1 (33)	1 (33)
ALCL	3	3	3 (100)	2 (67)	2 (66)
HSTCL	2	2	1 (50)	0	1 (50)
Aggr epidermotropic CD8+	2	2	1 (50)	1 (50)	0
Other TCL	6	5	2 (40)	1 (20)	1 (20)

Horwitz et al. ICML 2021

Moving to combination: first line?

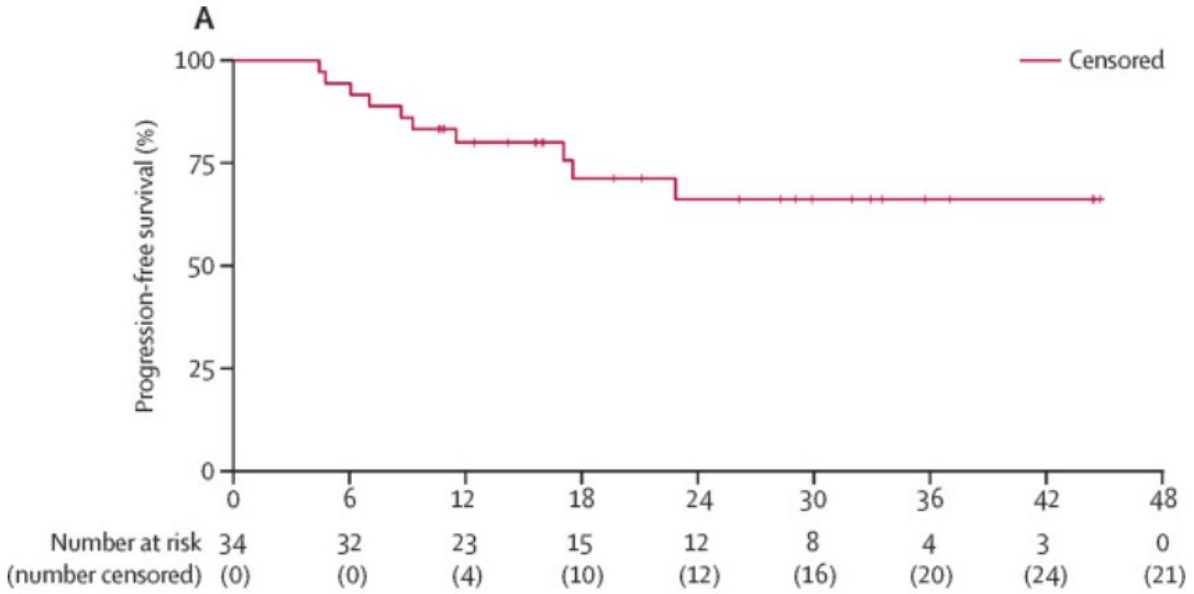
azacitidine + CHOP in TFHL



CR:88%

Ruan et al. Blood 2023

Anti PD1+ P-GMOX in ENKTCL

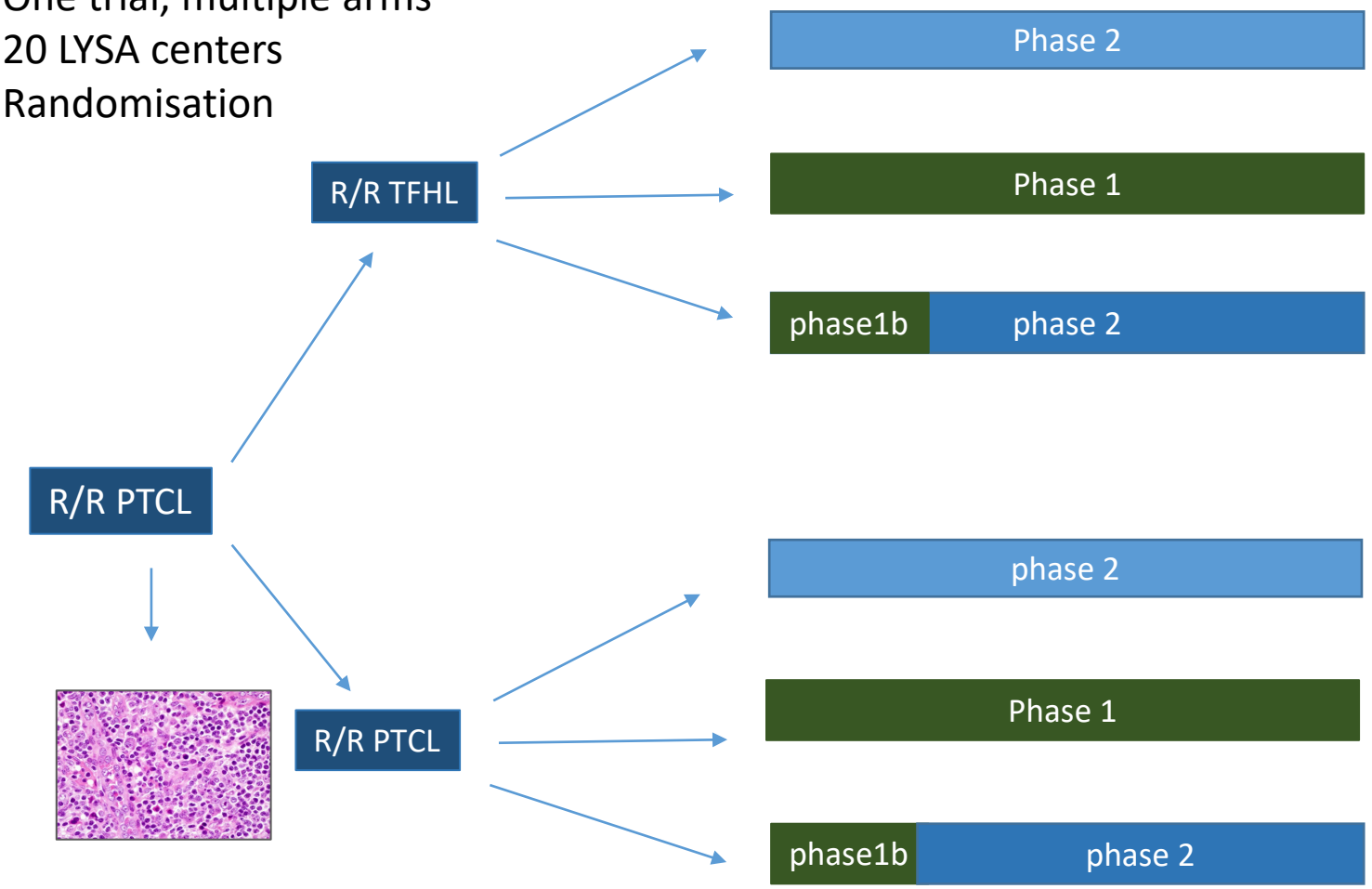


CR:85%

Tian et al. Lancet Haematol 2024

plaTform trial

One trial, multiple arms
20 LYSA centers
Randomisation



Biopsy
viable
congelation

Primary objective:
- mPFS based on investigator assessment

Secondary objectives:
- ORR
- CR
- OS
- Safety
- duration of response
- comparison with a synthetic arm

Exploratory objectives
- identification of biomarkers of response
- Comprehensive studies on PDXs
- identifying new drugs and combinations

Evaluation: Lugano 2014

Phase 2
PFS 3.7=> 7.4 months
One sided α= 0.05
Power=0.8
N=31 patients/arm

Phase 1
Boin method
target toxicity rate for the MTD is 0.3
N=18 patients

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force hemato

LEUKEMIA & LYMPHOMA SOCIETY®

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