HOW I TREAT T-Prolymphocytic Leukemia

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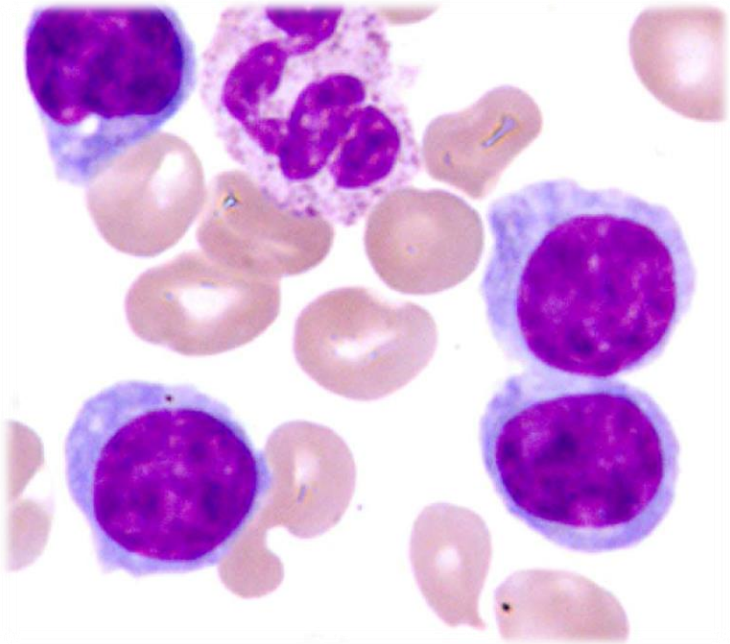
Medizin ist unsere Berufung.



PROLYMPHOCYTIC LEUKÆMIA OF B AND T CELL TYPE

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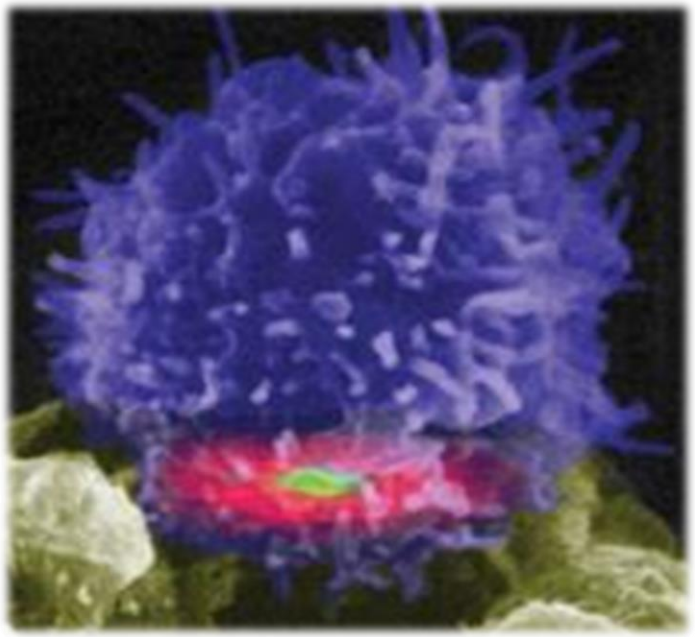
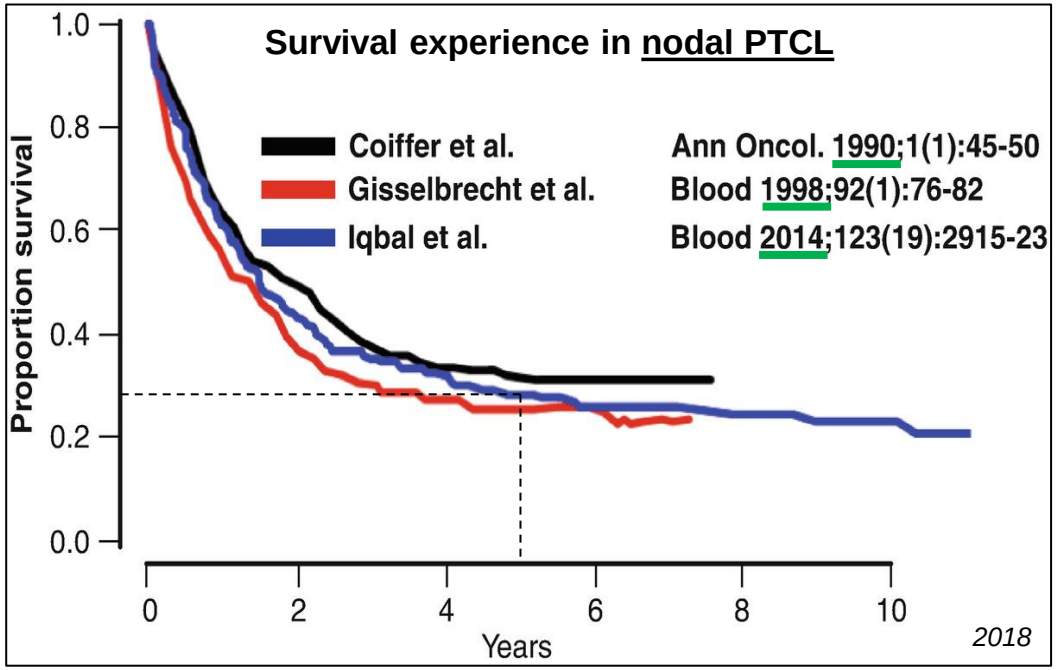
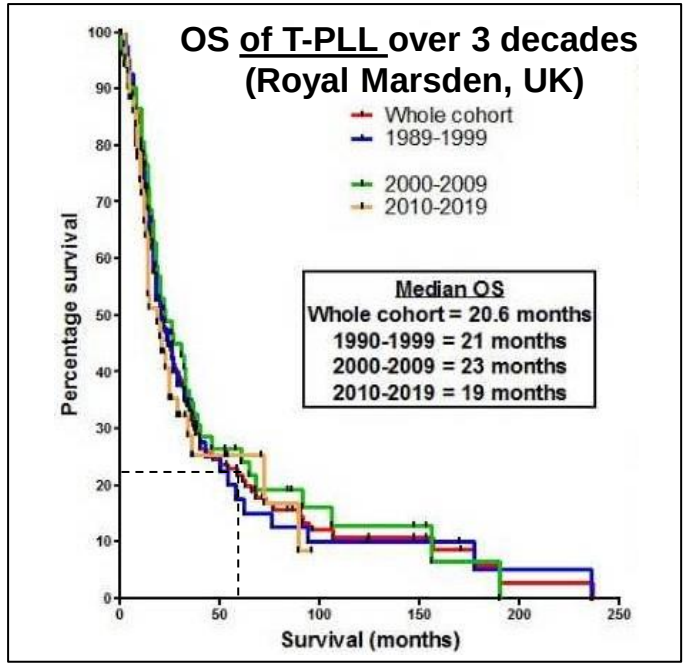
Summary B and T cell markers were studied in four patients with prolymphocytic leukæmia. Three patients demonstrated B-lymphocyte features: a high proportion of cells with surface immunoglobulins and C3 receptors but a low proportion of cells forming rosettes with sheep red blood-cells. The fourth patient had distinct T-lymphocyte characteristics: negative surface immunoglobulins, low proportion of cells with C3 receptors, and more than half of the neoplastic prolymphocytes forming rosettes with sheep red blood-cells. There were no clinical or hæmatological differences among these cases. This is the second unequivocal report of a lymphoproliferative disease of the T-cell type in man and the first of a T prolymphocytic leukæmia.



The poor prognosis of most T-cell neoplasms – a lasting paradigm ?





Cross et al
https://doi.org/10.1182/blood-2019-122094

Retrospective and prospective data

CONTINUE to show a

5-year overall survival of <30%

for most PTCL - with T-PLL being no exception !

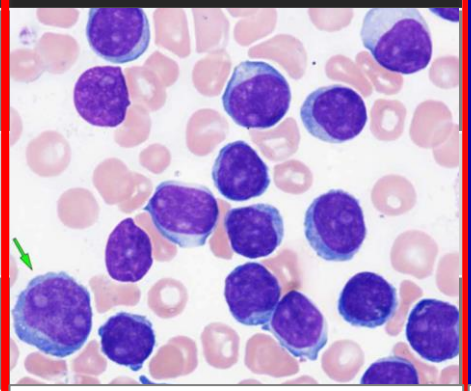
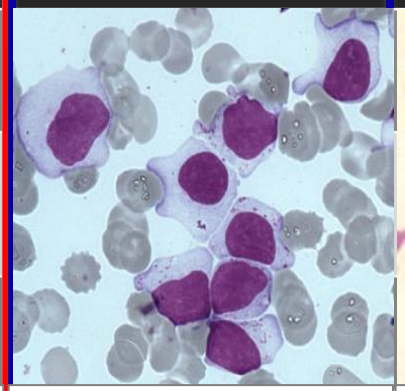
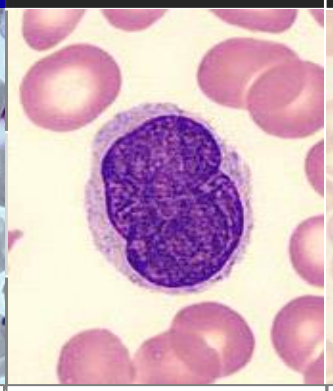
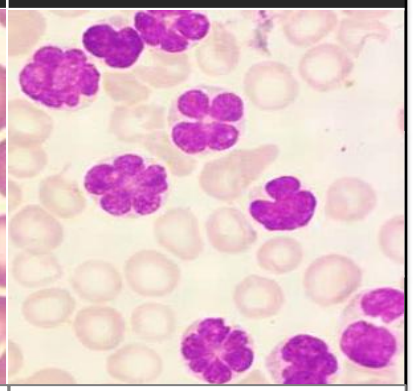
The importance of an accurate differential diagnosis of leukemic mature T-cell neoplasms

Mature T-cell leukemias in a nutshell

	T-PLL	T-LGL	Sézary S.	ATLL
Morphology	60-70% prolymphocytoid	80% LGL	40% small cerebriform	size variation; polylobated nuclei
Phenotype	62% CD4+8-; 35% 4+8+ CD7+	CD8+4-5^{dim}, CD57+, (CD16+); rare CD4+, rare γδ, rare NK	CD4+8- CD7 loss	CD4+8- CD25++
Mol. marker	inv(14) / t(14;14) / t(X;14) -11q23; Chr.8 gain; *ATM*^{mut}	*STAT3*^{mut} (50%) *STAT5B*^{mut} (5%)	-	HTLV+
WBC	hyperlymphocytosis, exponential rise	neutropenia, anemia, rarely hyper-proliferat.	mild, eosinophilia	moderate in acute and chronic phase
HS-megaly	80%	53%	rare	frequent in lymphoma phase
Skin	20-30%	27% (vaskulitis)	100%	50% (in smold. phase)
Specific presentation	late symptoms, BM failure, effusions	assoc. with RA, AIHA, PNH, MDS, AA/PRA	erythroderma	hypercalcemia / osteolytic lesions
Natural Hx	aggressive at Dx	indolent, but symptomatic	chronic and symptomatic	very aggressive (stages)
Treatment	single or combinations of alemtuzumab (RR 90%); cures after allo-SCT ?	MTX, cyclophospha-mide, CSA; improving cytopenias	systemic / multimodal / escalating	Zidov./IFNa, Mogamu., experimental allo-SCT in young pts.

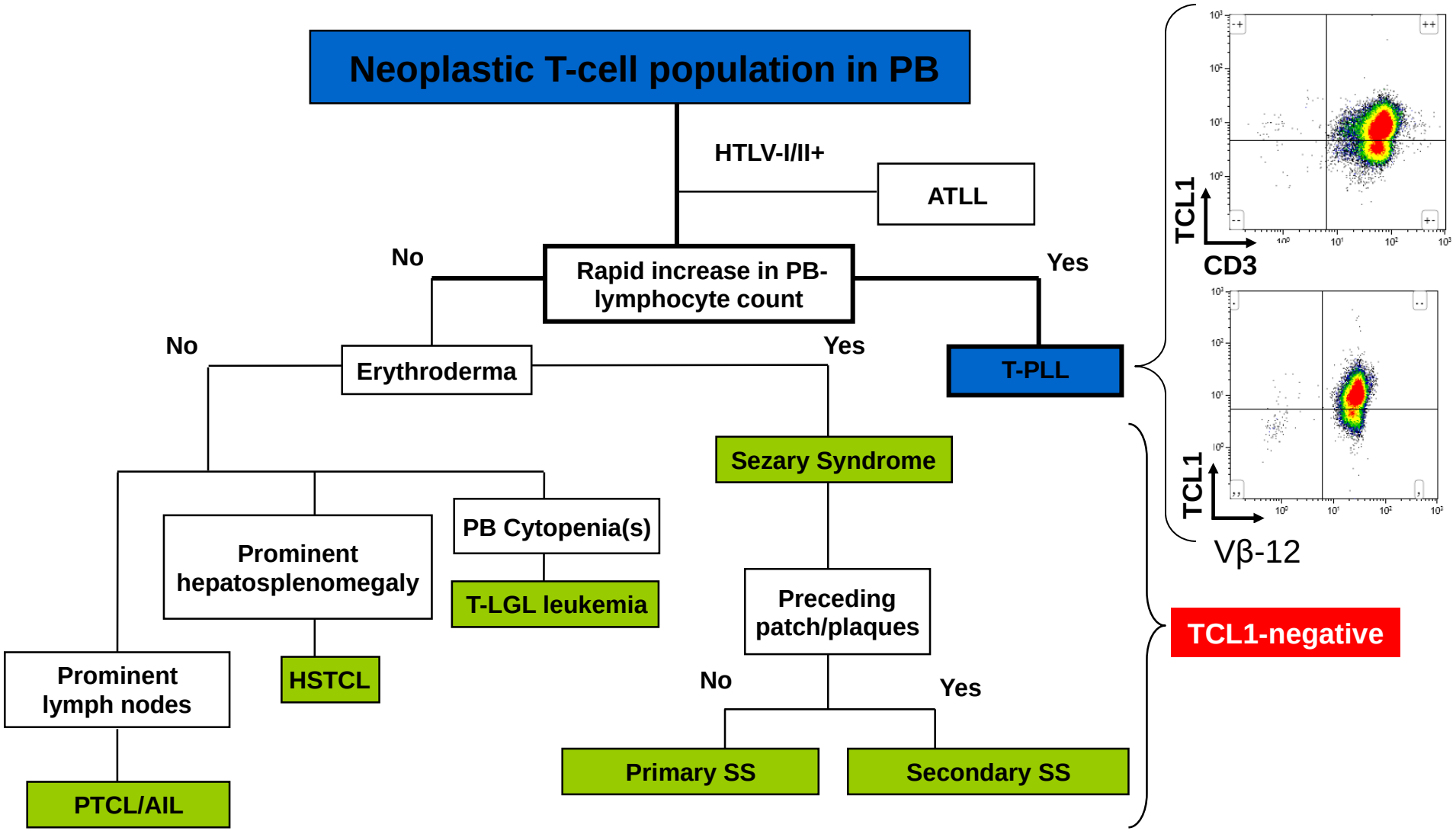
Herling et al, Blood 2004
Herling et al, Blood 2008

Mature T-cell leukemias in a nutshell

	T-PLL	T-LGL	Sézary S.	ATLL
Morphology				
Phenotype				
Mol. marker				
WBC	median OS	median OS	median OS	median OS
HS-megaly	1-2 years	10 yrs.	4 yrs.	2 years
Skin				
Specific presentation	**central-memory T-cell**	**cytotoxic autoreac-tive T-cell**	**TH2 cell**	**regulatory T-cell**
Natural Hx				
Treatment	single or combinations of alemtuzumab (RR 90%); cures after allo-SCT ?	MTX, cyclophospha-mide, CSA; improving cytopenias	systemic / multimodal / escalating	Zidov./IFNa, Mogamul., experimental allo-SCT in young pts.

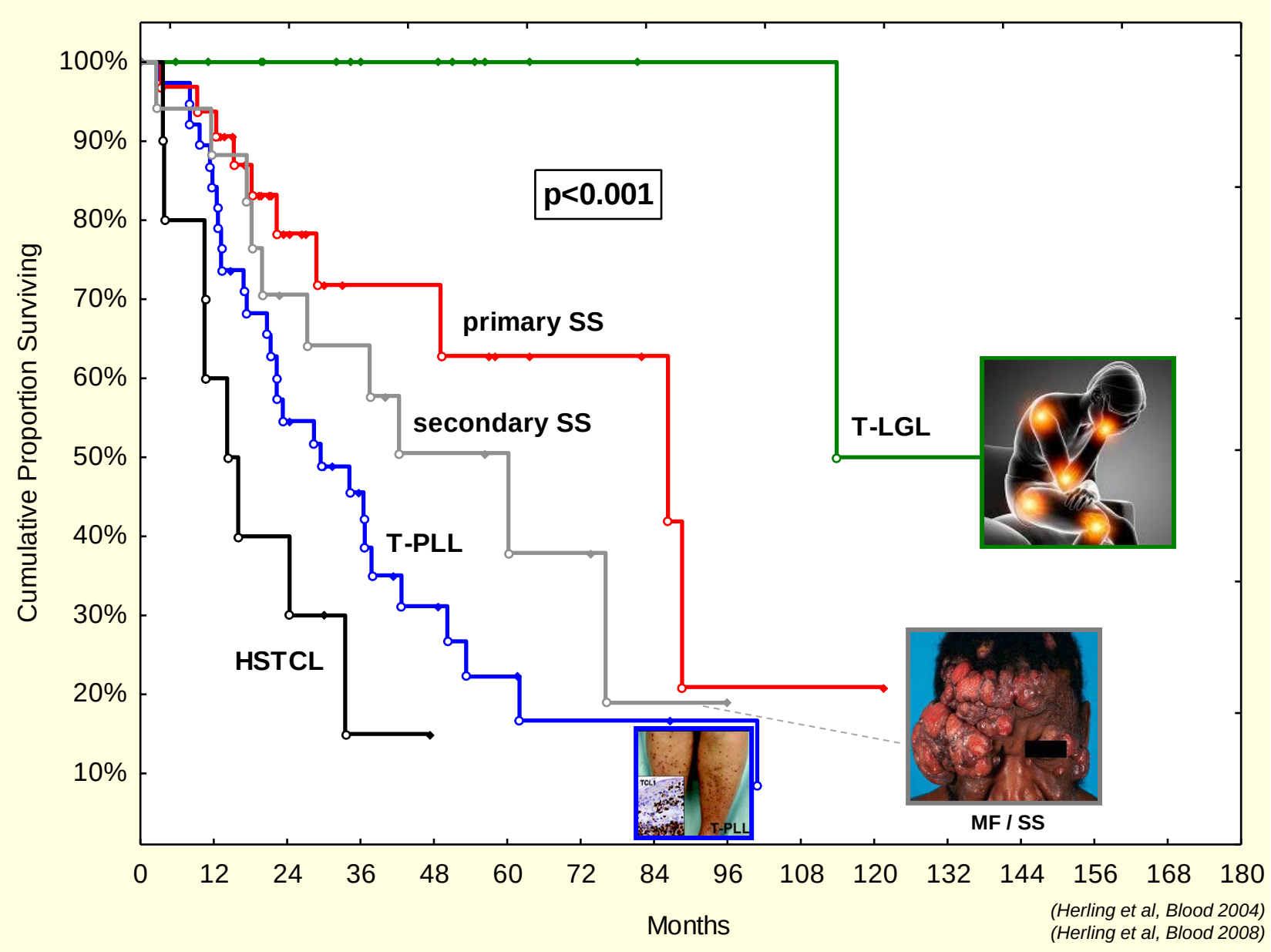
Herling et al, Blood 2004
Herling et al, Blood 2008

Diagnostic algorithm for leukemic T-cell lymphomas



(Herling et al Blood 2004)

An ‘indolent’ course does not mean ‘asymptomatic’ !



(Herling et al, Blood 2004)
(Herling et al, Blood 2008)

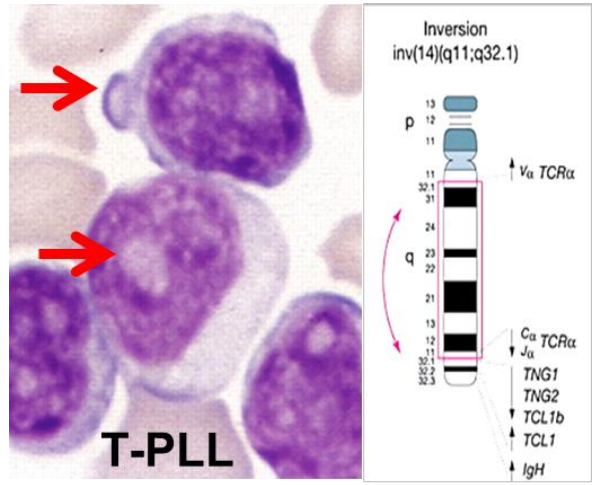
Presenting features of T-PLL

- med. age 63 yrs. (30s - 9th decade); M : F = 1.3
- 1-2 / 1 Mio. in EU
- incidental diagnosis and indolent initial course in 15-20% (inactive disease), but **inevitable aggressive progress** within 1-2 years after Dx (active disease)
- **CD4+/8-** (62%), CD4+/8+ (35%)
- CD7 (95%), **CD52 (>95%)**
- **TCL1 family (95%)**
- ***Prognostic factors ?***

  (WBC, TCL1 protein, complex karyotype, miR-patterns, …) ?

Clinical Feature	Frequency
Splenomegaly	**79%**
Lymphadenopathy (small nodes)	46%
Hepatomegaly	39%
Skin lesions	23%
Effusions	12%
White blood cell count (>100 x 10^9/L)	**72%**
Platelets (<100 x 10^9/L)	44%
Hemoglobin (<100 g/L)	25%

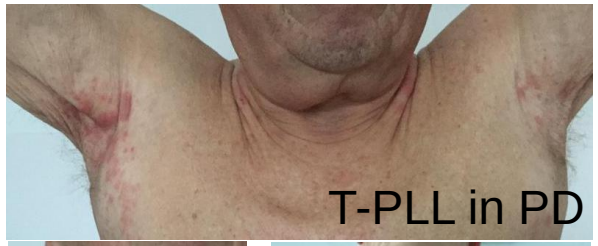
updated Royal Marsden series (Dearden 2006; 135 pts)

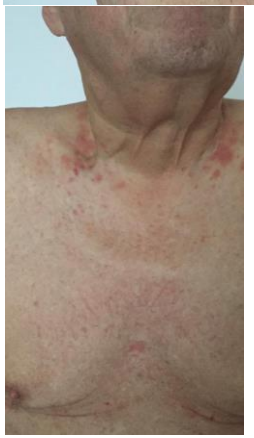


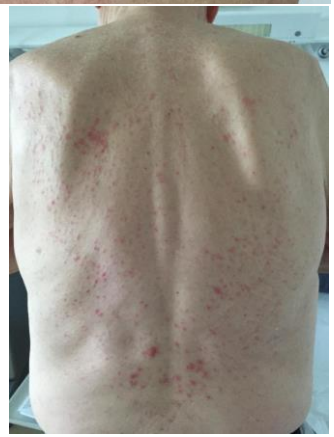
Complex karyotypes in 71% of cases
- 14q (80-90%)
- 8p+ (60%)
- 11q- (40-50%)
- …

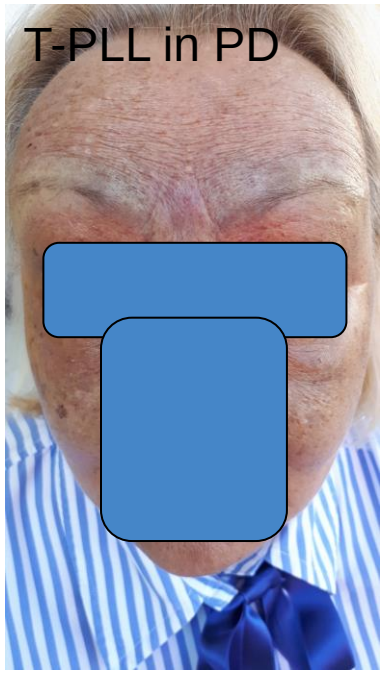
(Hu et al, AJH 2017; MDACC series)

The various faces of skin manifestations in T-PLL





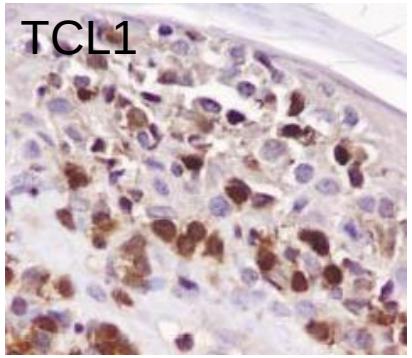




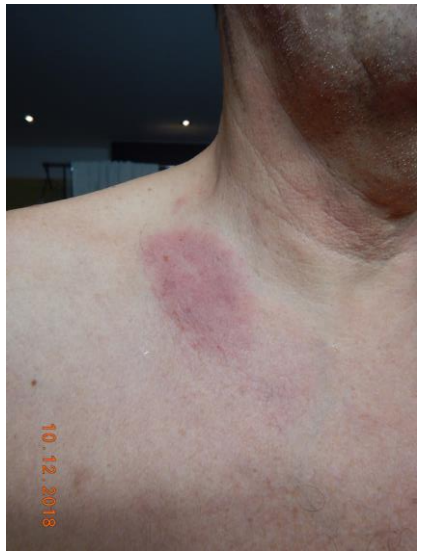
Cologne cohort (n=120)

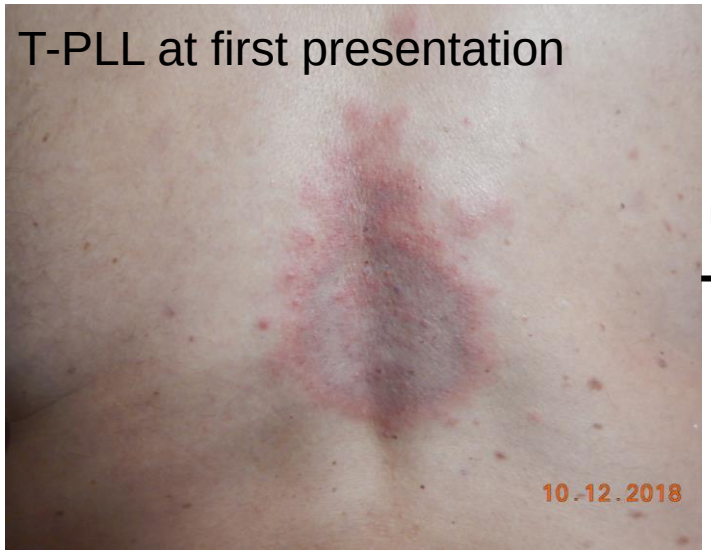
Skin manifestations in 35 pt. (29.2%)
- at initial Dx in 77.4%
- face and conjunctivae 55.2%
- trunk 48.3%
- extremities 34.5%

maculo-papular rash, indurated, purpura, palmoplantar hyperkeratosis, erythroderma

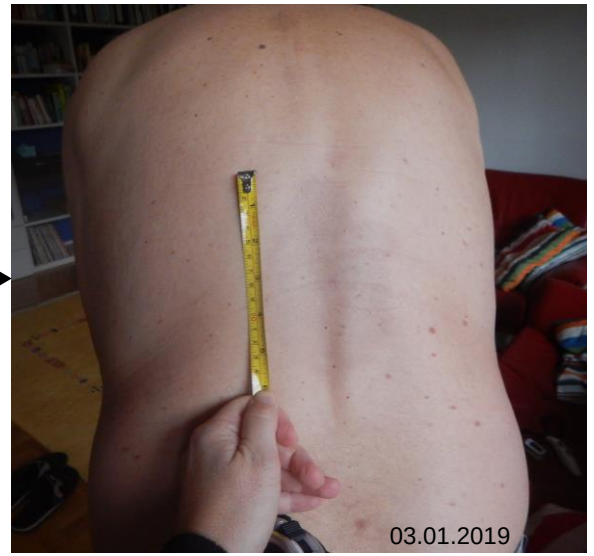


focal epidermotropism; TCL1 immunohistochemistry





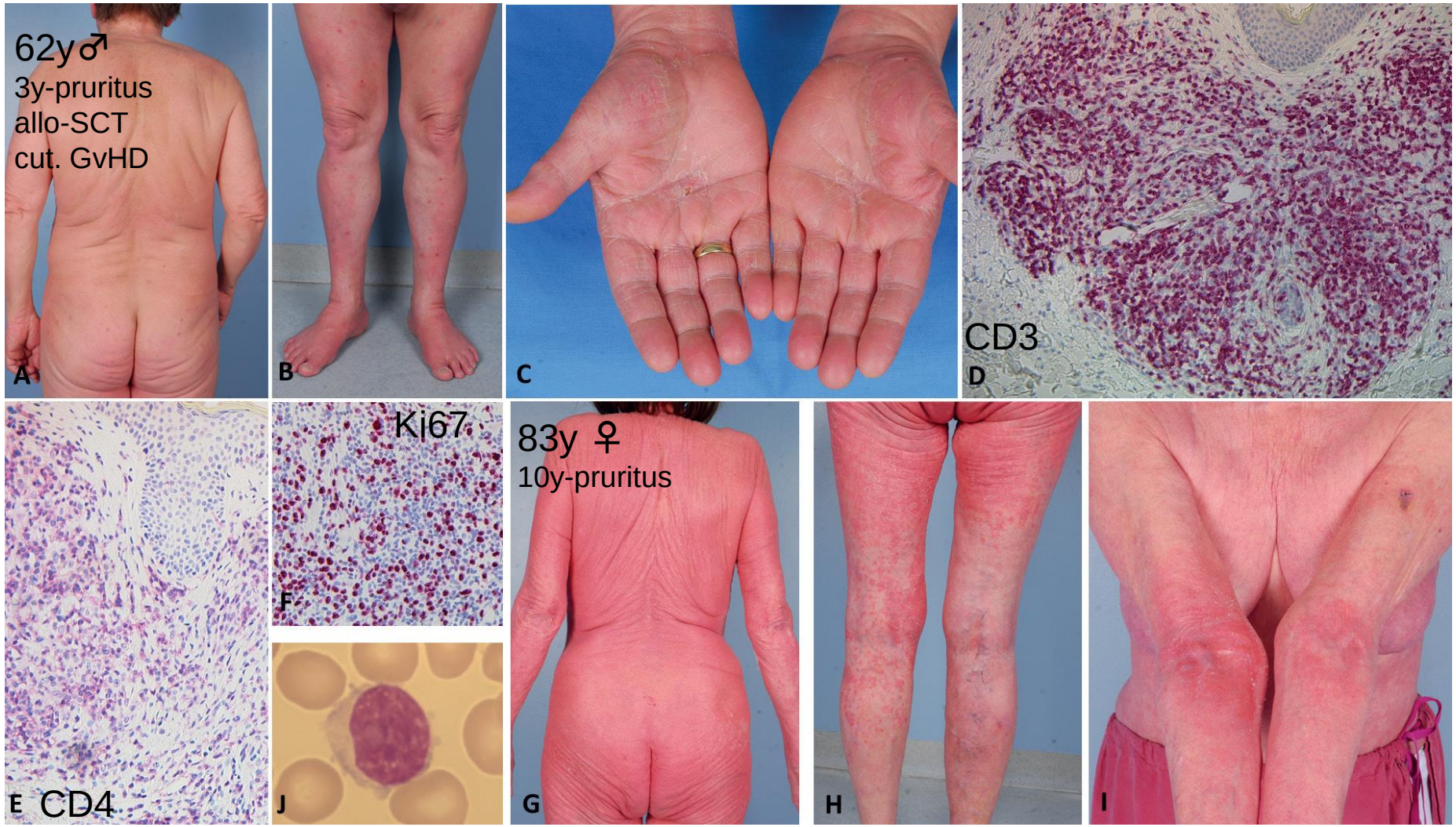
100mg/qm
AraC
+
Prednisolon



skin manifestation
- **no genetic or phenotypic subset**
- **no prognostic relevance**

The various faces of skin manifestations in T-PLL

prodromial phases (e.g. pruritus with palmo-plantar hyperkeratosis)

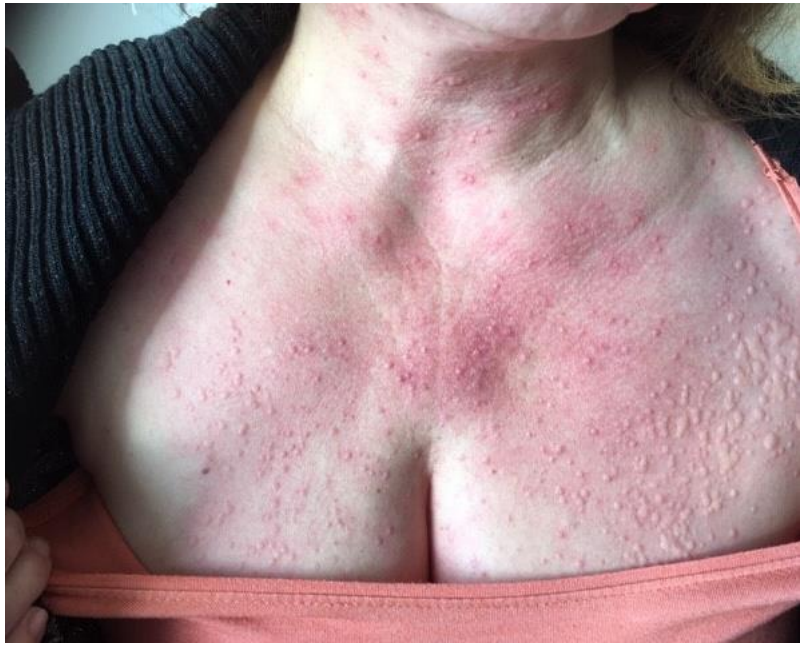


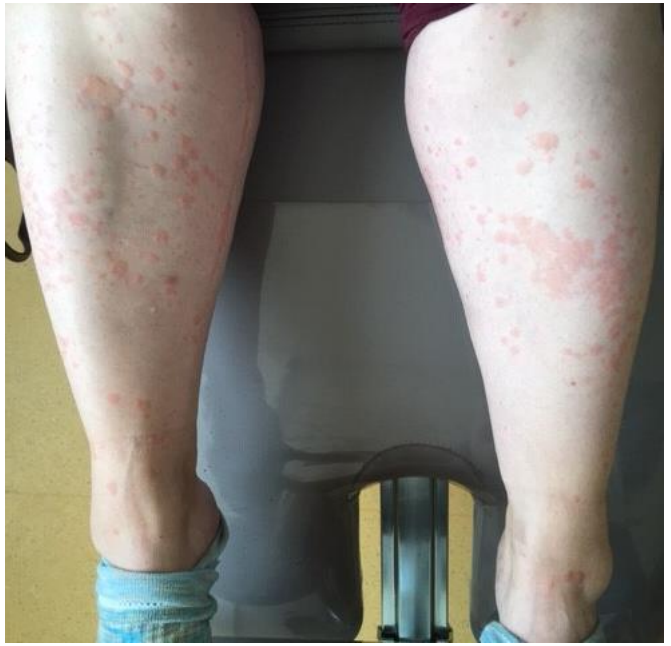
Hoffmann et al, Severely Itching Dermatitis and Palmoplantar Keratoderma as First Manifestation of T-cell Prolymphocytic Leukaemia. Acta Derm Venereol 2019

The various faces of skin manifestations in T-PLL

Important differentials:

- VZV under T-lymphopenia
- Bacterial skin infections
- GvHD after allo HSCT
- allergic reactions (Cotrim, Alemtuzumab, etc)

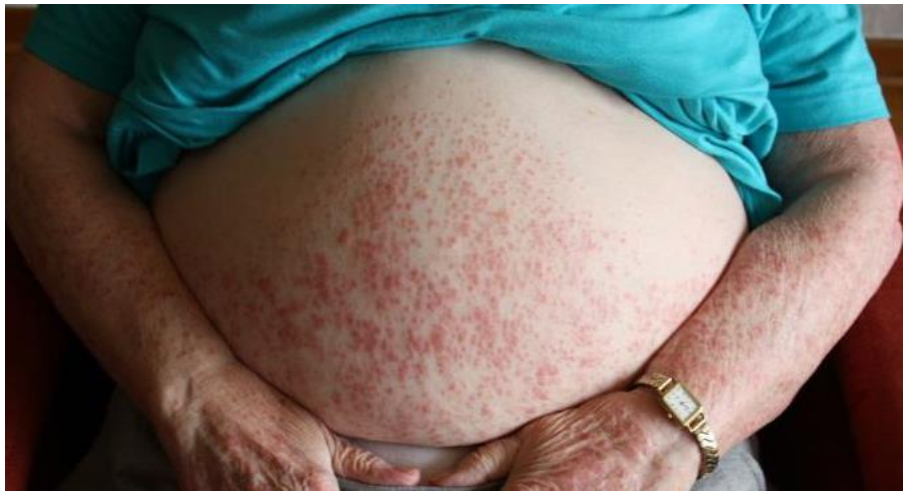


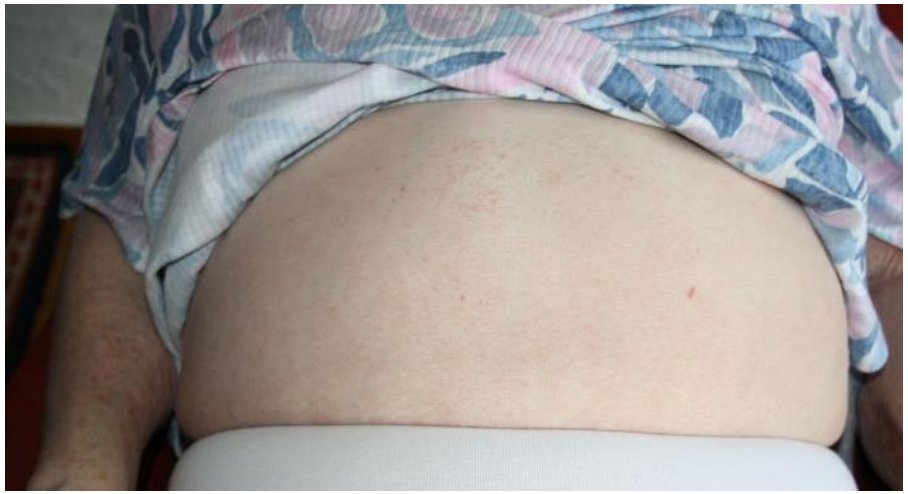


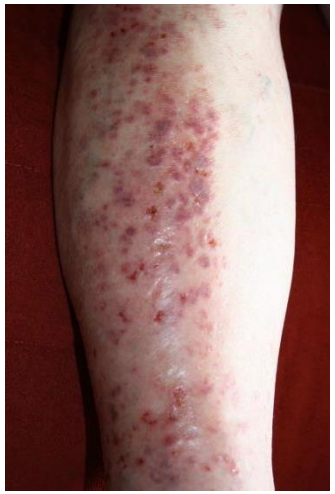
Urticaria under first Alemtuzumab infusions

(*later tolerance, but initial need of prophylactic H1/2 blocker, prednisolone, PCM, montelukast)*

Case …T-PLL, general condition did not allow systemic therapy



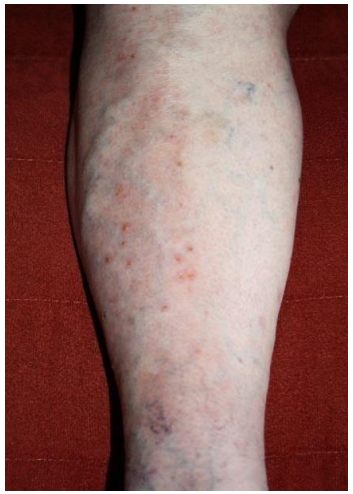




12.04.2015

- UVA therapy -

30.04.2015



Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia

Philipp B. Staber,[1] Marco Herling,[2-4] Mar Bellido,[5] Eric D. Jacobsen,[6] Matthew S. Davids,[7] Tapan Mahendra Kadia,[8] Andrei Shustov,[9] Olivier Tournilhac,[10] Emmanuel Bachy,[11] Francesco Zaja,[12] Kimmo Porkka,[13] Gregor Hoermann,[14,15] Ingrid Simonitsch,[16] Claudia Haferlach,[17] Stefan Kubicek,[18,19] Marius Mayerhoefer,[20,21] Georg Hopfinger,[22] Ulrich Jaeger,[1] and Claire Dearden[23]

Blood 2019

All 3 major need to be fulfilled

If criterion 3 is not met, then at least one minor needs to be present

Major criteria	Minor criteria
• >5 × 10⁹/L cells of T-PLL phenotype in peripheral blood or bone marrow	• Abnormalities involving chromosome 11 (11q22.3; *ATM*)
• T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)	• Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
• Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1**	• Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
	• Involvement of T-PLL specific site (eg, splenomegaly, effusions)

*Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.

At presentation

- **20% inactive**
- **80% active**

(dynamic classification likely to change in the future)

Staging: at least 1 criterion defines active T-PLL (= indication for treatment)		
Disease-related constitutional symptoms	Significant fatigue: ECOG ≥2	
	Unintentional weight loss of >10% of normal body weight in ≤6 mo	
	Drenching night sweats, without evidence of infection	
	Fever greater than 38°C, without evidence of infection	
Symptomatic bone marrow failure	Hemoglobin	<10 g/dL
	Platelet count	<100 × 10⁹/L
Rapidly enlarging lymph nodes, spleen, and liver	>50% in 2 mo; diameter doubling <6 mo	
	Symptomatic enlarged lymph node, spleen, or liver	
Increasing lymphocytosis	If >30 × 10⁹/L: >50% in 2 mo; lymphocyte doubling time <6 mo	
Extranodal involvement	Organ infiltration; peritoneal or pleural effusion, central nervous system involvement	

Evolution of treatment approaches

(Alemtuzumab i.v. remains 'standard' 1L therapy)

Systematic treatment evaluations in T-PLL

Summary of most relevant clinical studies on chemo-/immunotherapy in T-PLL

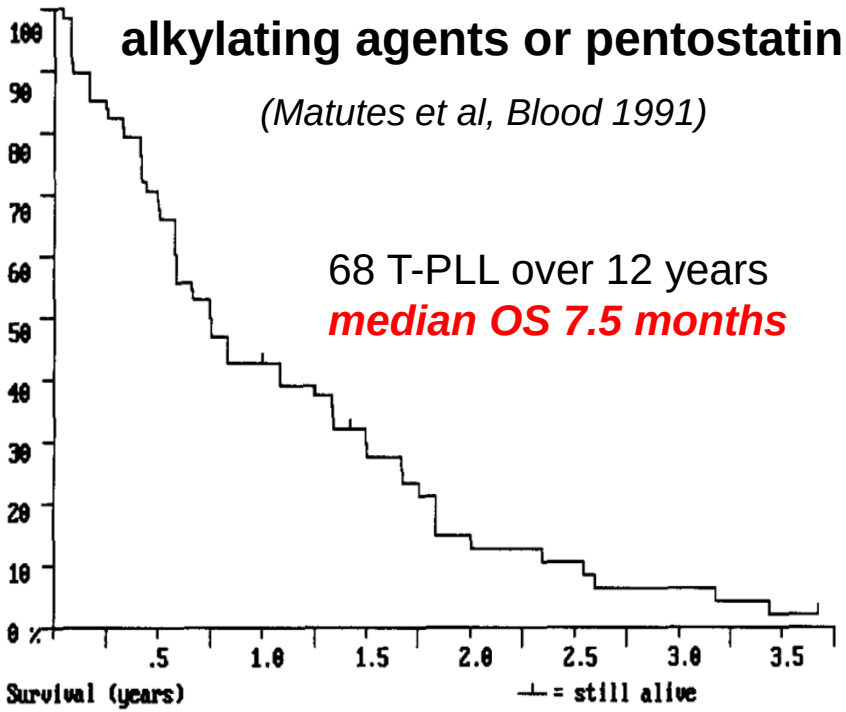
Regime	Study design	Treatment status	*n*	ORR [%]	CR [%]	PR [%]	PFS [mo]	OS [mo]	Reference
Pentostatin	Single center, retrospective	Pretreated	56	45	9	36	6	9	Mercieca J et al 1994
Alemtuzumab, iv	Single center, retrospective	Pretreated	15	73	60	13	6	8	Pawson R et al 1997
Alemtuzumab, iv	Multicenter, prospective	Pretreated	39	76	60	16	7	10	Dearden et al 2001
Alemtuzumab, iv	Multicenter, retrospective	Untreated	4	75	75	0	5	8.7	Keating et al 2002
		Pretreated	72	50	37.5	12.5	4.5	7.5	
Pentostatin + alemtuzumab, iv	Single center, prospective	Pretreated	13	69	62	8	7.8	10.2	Ravandi et al 2009
Alemtuzumab, iv	Single center, prospective	Untreated	32	91	81	10	12	48	Dearden et al 2010
		Pretreated	45	74	60	14	12	48	
Alemtuzumab, sc		Untreated	9	33	33	0	12	48	
FMC + alemtuzumab, iv	Multicenter, prospective	Untreated	16	92	48	44	11.5	17.1	Hopfinger et al 2013
		Pretreated	9						
Bendamustine	Multicenter, retrospective	Untreated	6	55.3	20	33.3	5	8.7	Herbeaux et al 2015
		Pretreated	9						
Alemtuzumab, iv	Single center, retrospective	Untreated	13	n.a.	n.a.	n.a.	n.a.	40.5	Damlaj et al 2015
Alemtuzumab, sc	Single center, retrospective	Pretreated	5	n.a.	n.a.	n.a.	n.a.	13.7	Damlaj et al 2015
Alemtuzumab, iv + cladribine +/− HDAC inhibition	Single center, retrospective	Untreated	4	100	75	25	6.3	14.8	Hasanali et al 2015
		Pretreated	4	100	100	0	11.35	23.7	
Alemtuzumab, iv	Single center, retrospective	Untreated	42	81	61	20	11	15	Jain et al 2017
		Pretreated	15	46	46	0	3	15	
Alemtuzumab, iv + pentostatin		Untreated	13	82	73	9	4.3	10.4	
		Pretreated	5	75	50	25	2.6	2.6	
FMC + alemtuzumab, sc	Multicenter, prospective	Untreated	13	68.7	32.1	36.6	7.5	11.5	Pflug et al 2019
		Pretreated	5						

iv intravenous, *sc* subcutaneous, *FMC* fludarabine, mitoxantrone, cyclophosphamide, *HDAC* histone deacetylase

use i.v. route of Alemtuzumab !

(mod. from Braun et al, Curr Hematol Malig Rep 2020)

Milestone: Alemtuzumab as the single most efficient agent markedly improved outcome

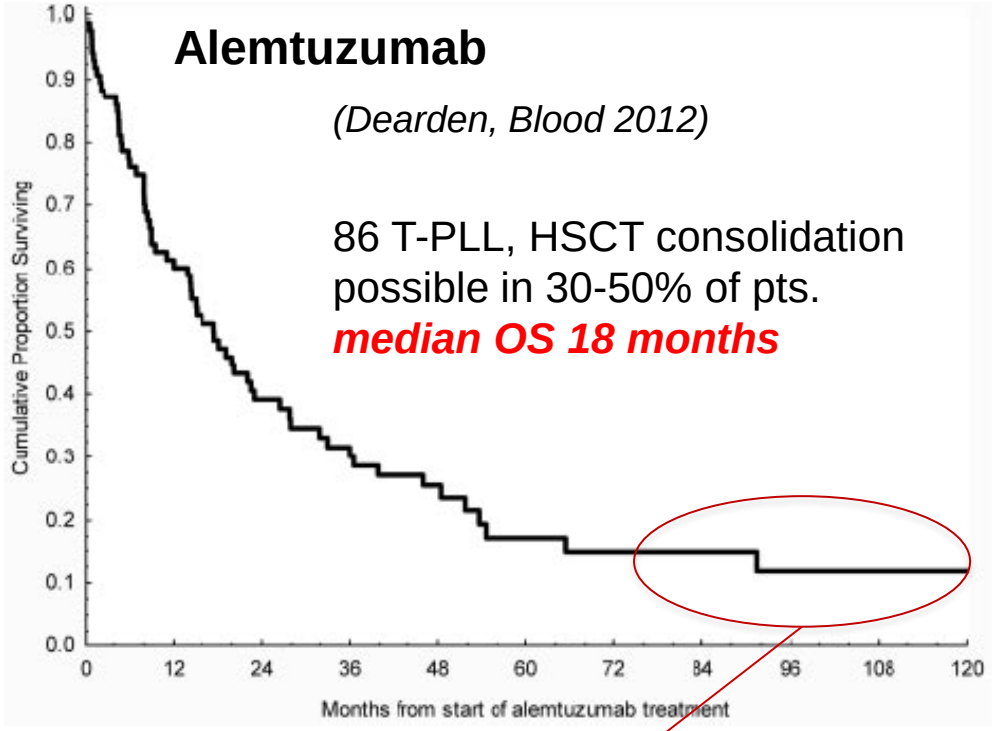


alkylating agents or pentostatin

(Matutes et al, Blood 1991)

68 T-PLL over 12 years

median OS 7.5 months



Alemtuzumab

(Dearden, Blood 2012)

86 T-PLL, HSCT consolidation possible in 30-50% of pts.

median OS 18 months

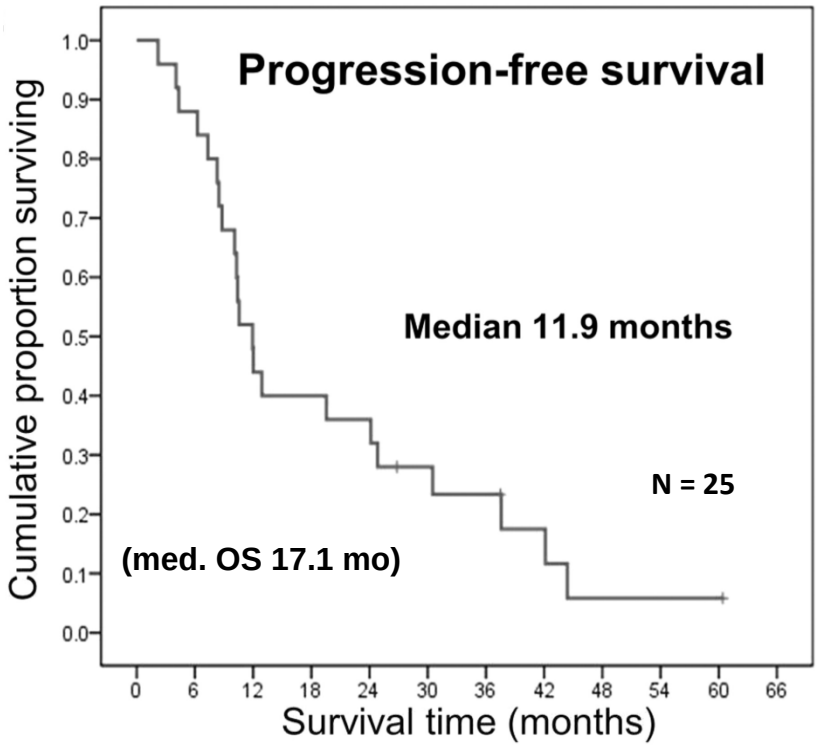
- subsequent monocentric series (UK)
- both included naïve and pre-treated pts.
- survivors >72 months were all after HSCT

BUT: median response duration after Alemtuzumab with or w/o chemotherapy is around / less than 1 year and relapse rate is 100% !

Disease control in T-PLL after Alemtuzumab induction is not profound

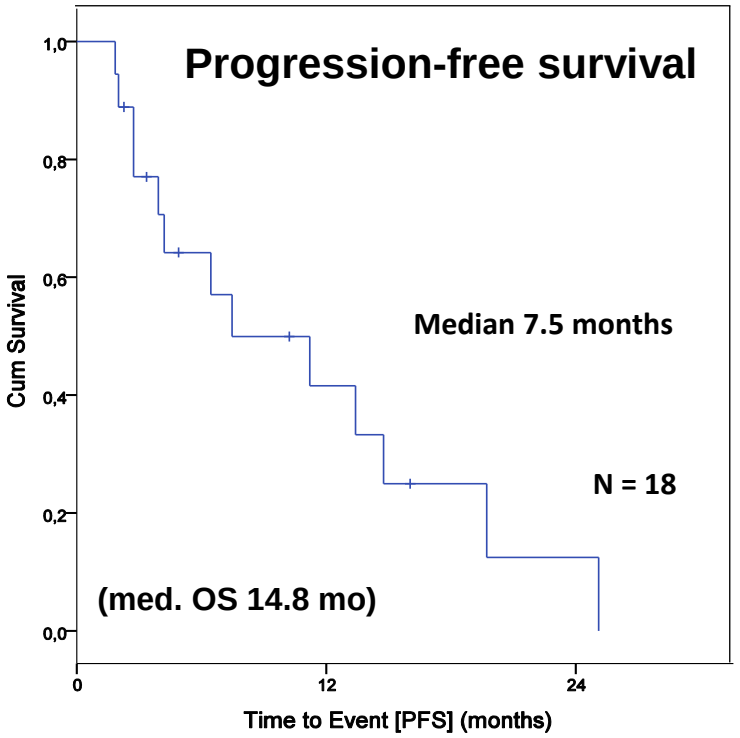
DCLLSG 'TPLL1' *(Hopfinger et al, Cancer 2013)*

FMC followed by Alemtuzumab i.v.



'TPLL2' *(Pflug et al, Leuk Lymph 2019)*

FMC with simult. Alemtuzumab s.c. + mainten.



HOWEVER: remissions after Alemtuzumab alone or with chemotherapy last at median no longer than 1 year !

Abbr.:
FMC (Fludarabine – Mitoxantron – Cyclophosphamide)

Are we improving the outcome by allo-SCT ?

Study design	*n*	Age [years]	Relapse rate [%]	TRM [%]	Pre-HSCT CR [%]	Post-HSCT CR [%]	PFS [mo]	OS	Reference
Summary of clinical studies on auto-HSCT in T-PLL									
Multi-center, retrospective	15	58	60	7	87	100	n.a.	52 mo	Krishnan B et al 2010
Summary of clinical studies on allo-HSCT in T-PLL									
Multicenter, retrospective	13	51	33	31	69	92	n.a.	33mo	Krishnan B et al 2010
CIBMTR registry, retrospective	21	54	39*	28*	n.a.	n.a.	5.1	11.2mo	Kalaycio ME et al 2010
EBMT registry, retrospective	41	51	41**	41**	27	n.a.	10	21%**	Wiktor-Jedrzejczak W et al 2012
Multicenter, prospective	5	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	24.8mo	Hopfinger et al 2013
French Society of SCT, retrospective	27	53	47	31**	52	78	26**	36%**	Guillaume T et al 2015
Single-center, retrospective	11	56	21***	34***	91	91	15	56mo	Dholaria BR et al 2018
EBMT registry, prospective (a)	37	56	38***	32***	62	n.a.	30***	42%***	Wiktor-Jedrzejczak W et al 2019
TRUMP registry, retrospective	20	54	69.6**	20.9*	30	n.a.	33.5%**	40%**	Yamasaki S et al 2019

(a) Patients < 65 years, with progressive disease, with a mismatched unrelated donor or with cord blood were excluded

*at one year

**at three years

***at four years

EBMT: European Society for Blood and Marrow Transplantation; CIBMTR: Center for International Blood and Marrow Transplant Research; TRUMP: Transplant Registry Unified Management Program, Japan

(mod. from Braun et al, Curr Hematol Malig Rep 2020)

Essence

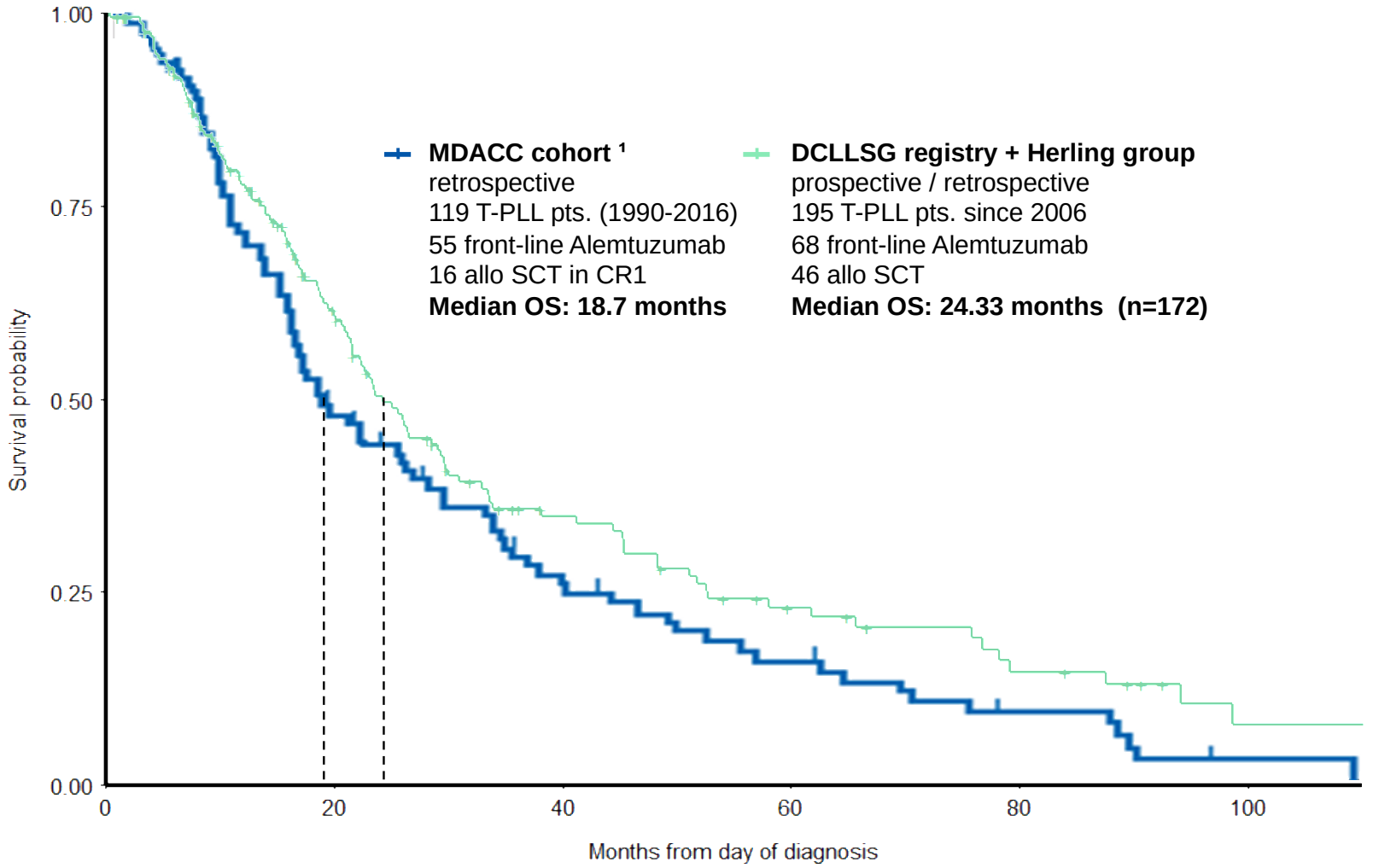
- 30-50% are SCT-eligible !
- 3-yr. NRM 30-40%
- 3-yr PFS / OS 20-30%
- benefit to undefined patient subset
- most post-transplant relapses within 1st year
- predictors for better outcome: TBI 8-12Gy, (time-to-transplant <1yr)

Suggested strategy

- Alemtuzumab i.v. 12-16 wks. as 1L > 1st best response → allo-SCT / W&W
- “debulk” by cyclophosphamide if needed
- add purine (Cladribine) or switch to FMC when Alemtuzumab intolerance or no CR by week 8
- 6 wks. pre-SCT Alemtuzumab wash-out; ‘chemo-bridging’ if needed
- conditioning: Fludarabine / 8 Gy TBI / (ATG) / post-allo Cy + Everolimus
- Relapse: Cladri., Benda., FMC, experimental (synergies), trial

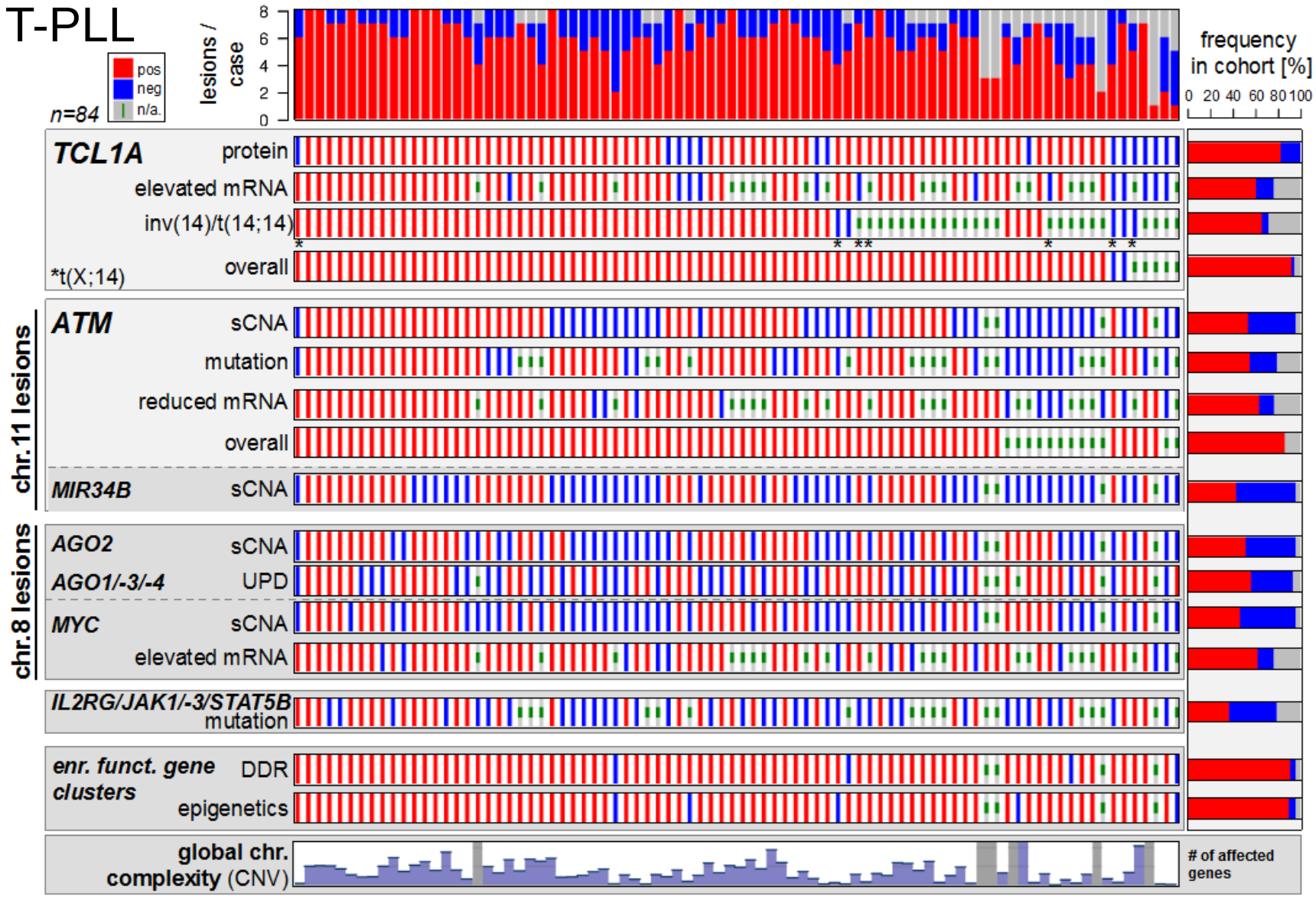
Can we derive novel strategies that target non-conventional lesions?

The asset of prospectively collected data and biomaterial



¹ Jain, P. et al. Characteristics, outcomes, prognostic factors and treatment of patients with T-PLL. Ann. Oncol. 28, 1554–1559 (2017)

How to exploit the hallmark of a defective DNA damage response?



95% *TCL1A* (or *MTCP1*)

86% *ATM* (del / mut)

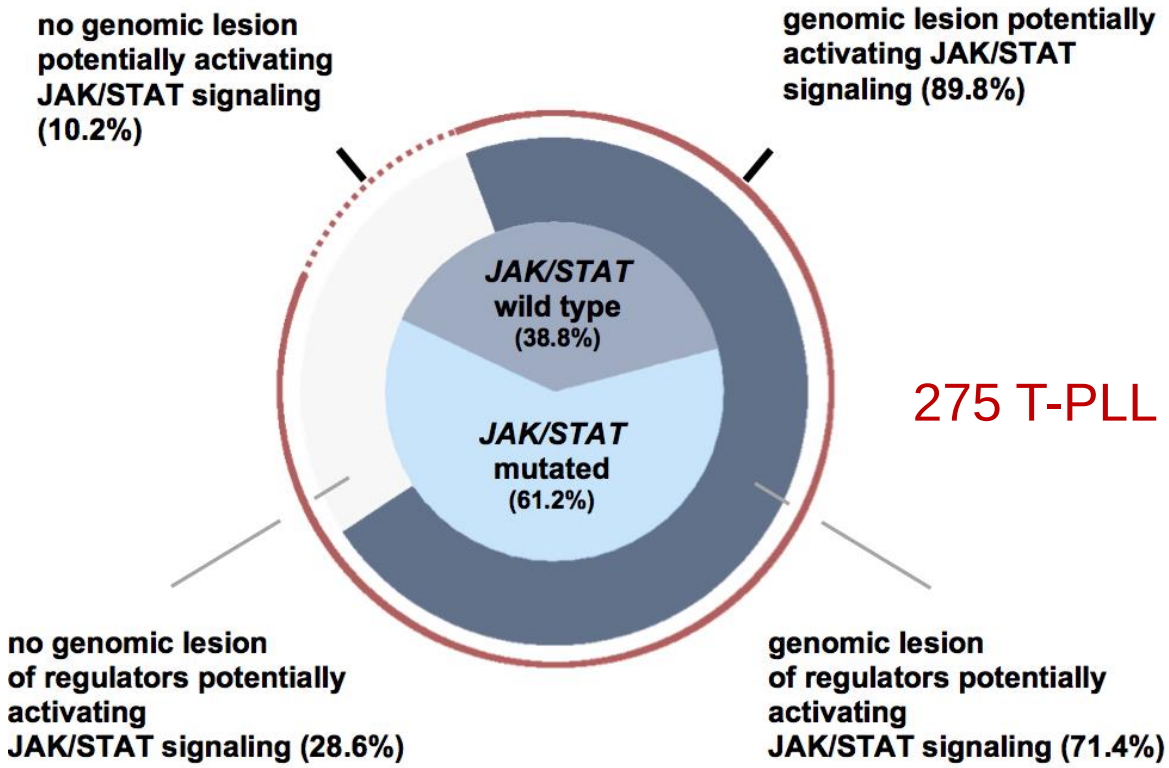
42% Chr.8 CN gains

65% *JAK1/3/STAT5B* GOF mut

Schrader et al, Nat Commun 2018

The true incidence of JAK / STAT alterations

- meta-analysis of comprehensive NGS and CNA data
- **89.8%** carry genomic lesions involving JAK / STAT signal elements
- **>90% with** baseline and/or cytokine-mediated pSTAT3/5 higher than in normal T-cells

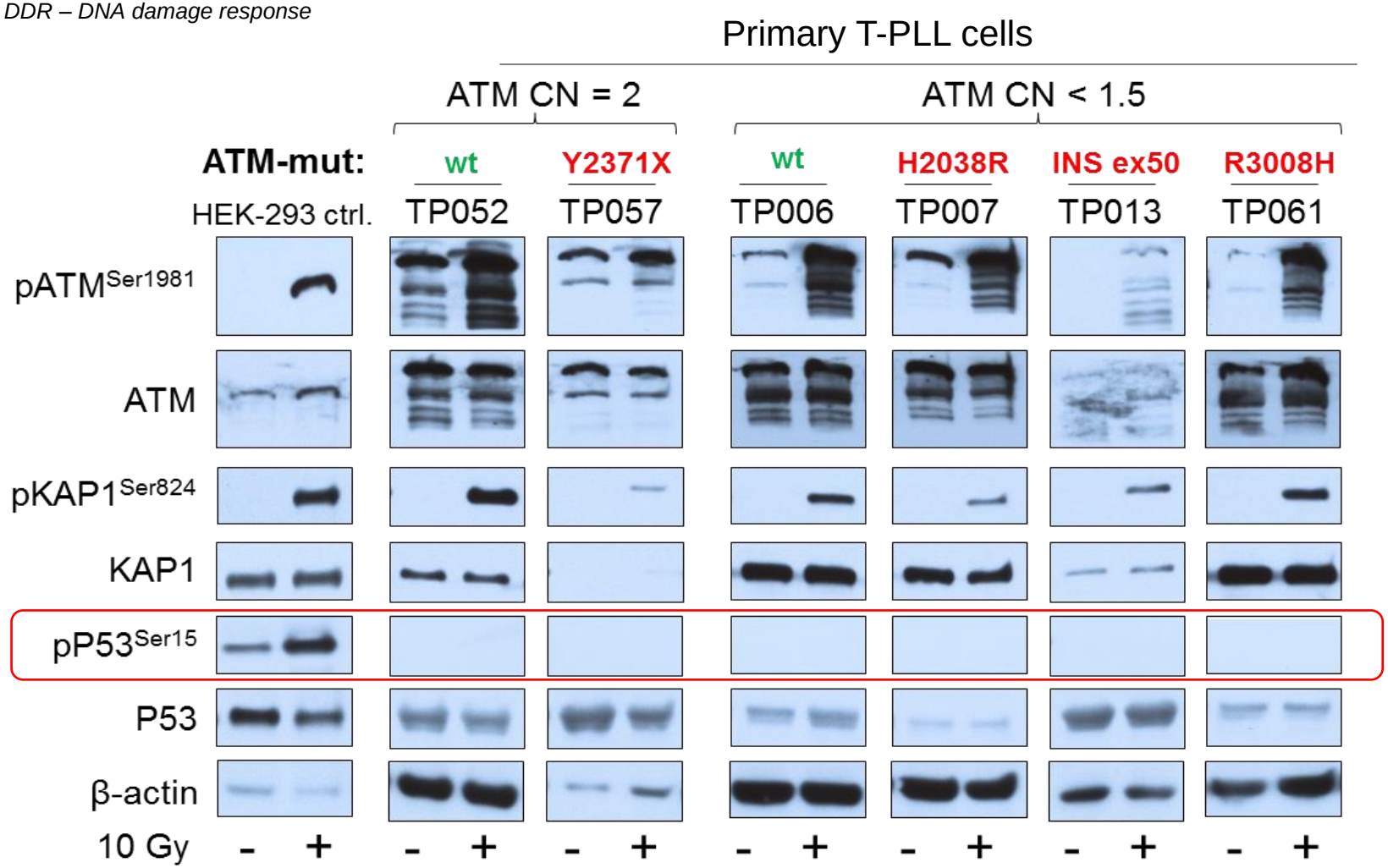


275 T-PLL

(Wahnschaffe et al, Cancers 2019)

Functionally hypomorphic ATM and absence of p53 induction characterize the DDR of T-PLL cells

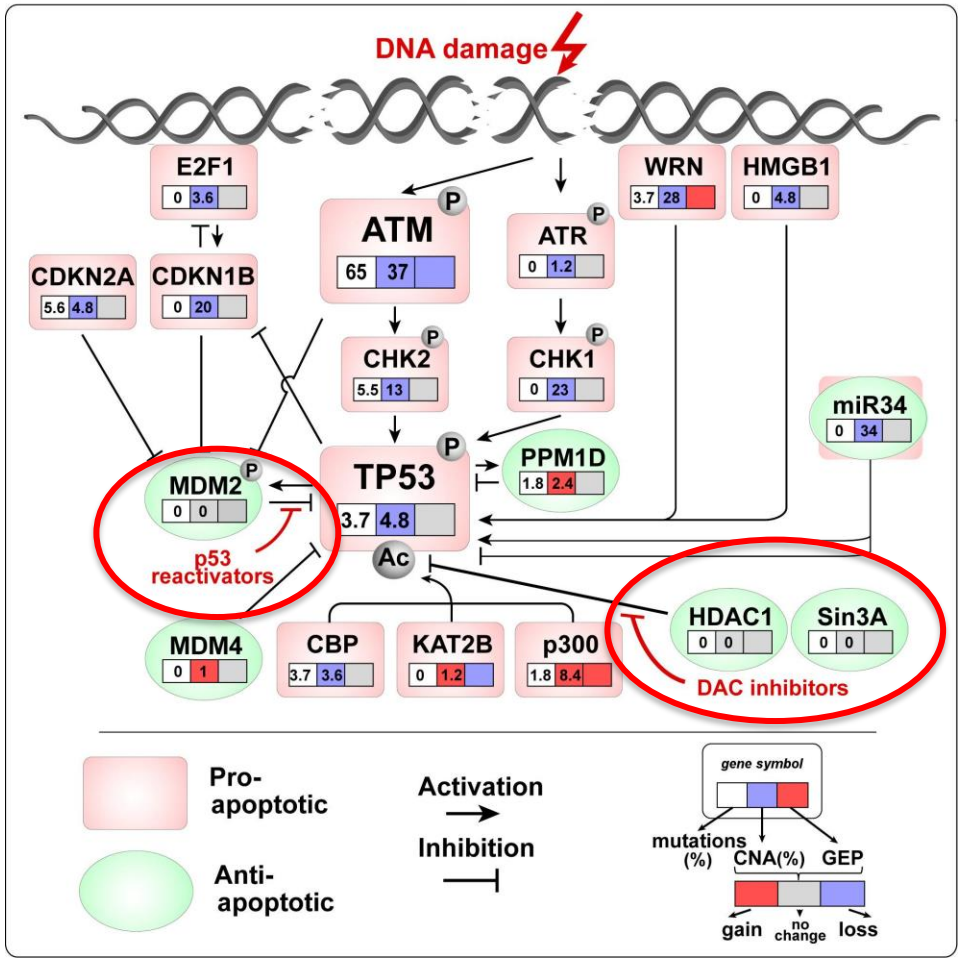
DDR – DNA damage response



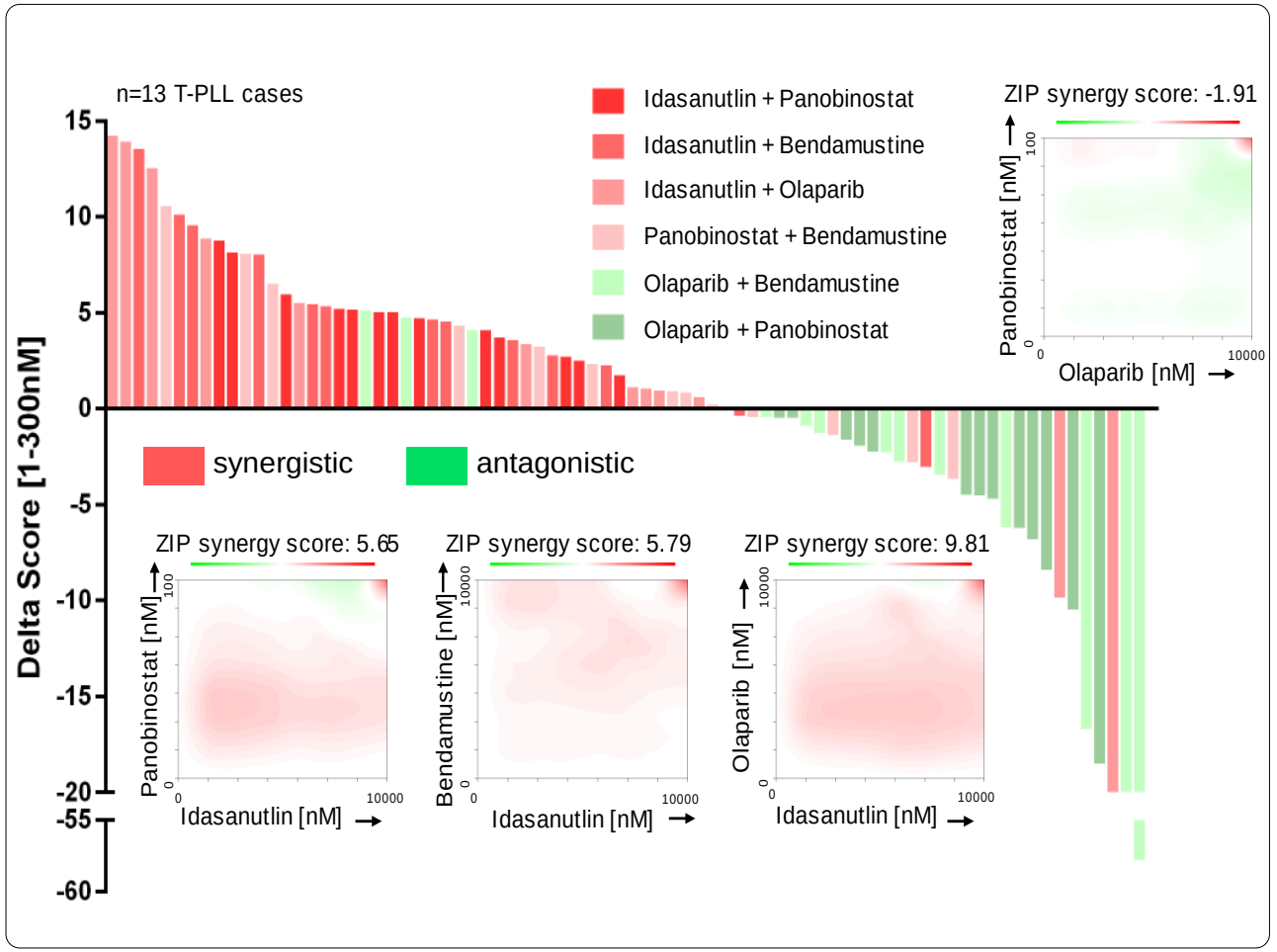
Schrader et al, Nat Commun 2018

The deficient ATM/CHK2 axis represents a vulnerability that is amenable to pharmacologic TP53 de-repression

Lesions in the ATM / p53 pathway in 85 T-PLL

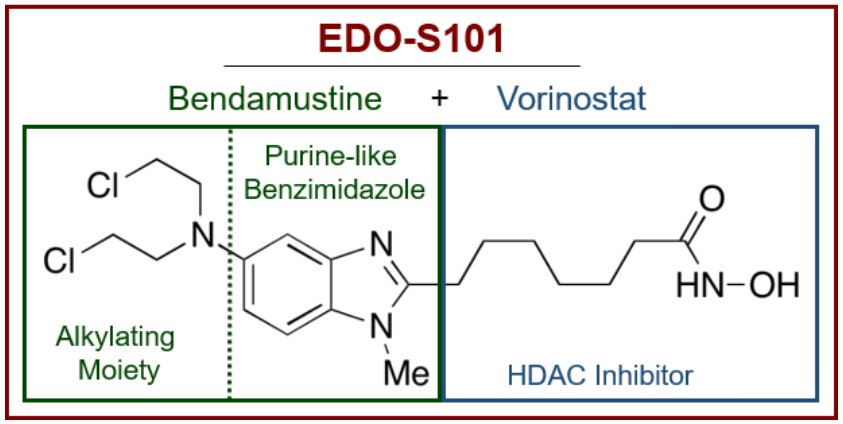


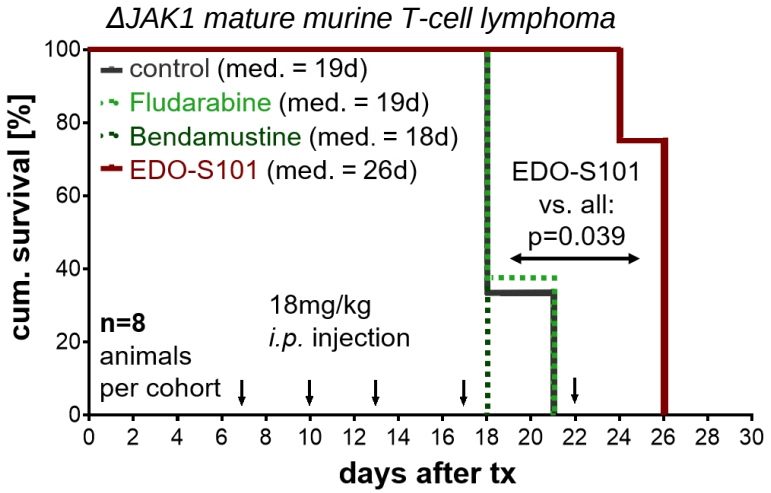
Highly synergistic relationships based on MDM2-inhibition by Idasanutlin

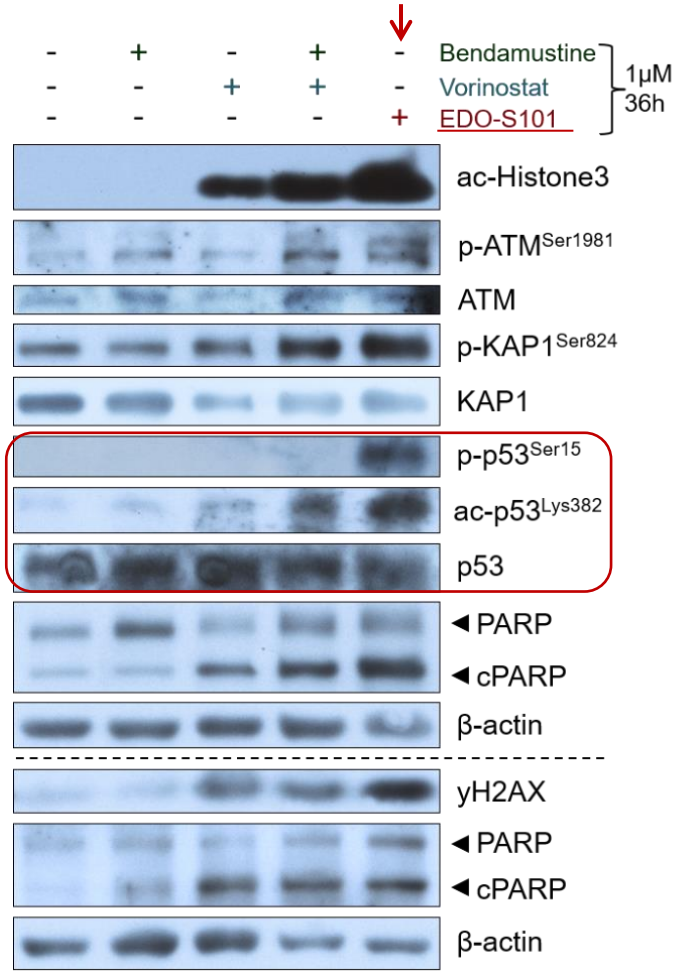


Schrader et al, Nat Commun 2018

Mechanism-driven application of a novel dual alkylating (H)DAC-inhibitor EDO-S101 (*Tinostamustine*)







T-PLL cells

Pützer et al, Leukemia 2020

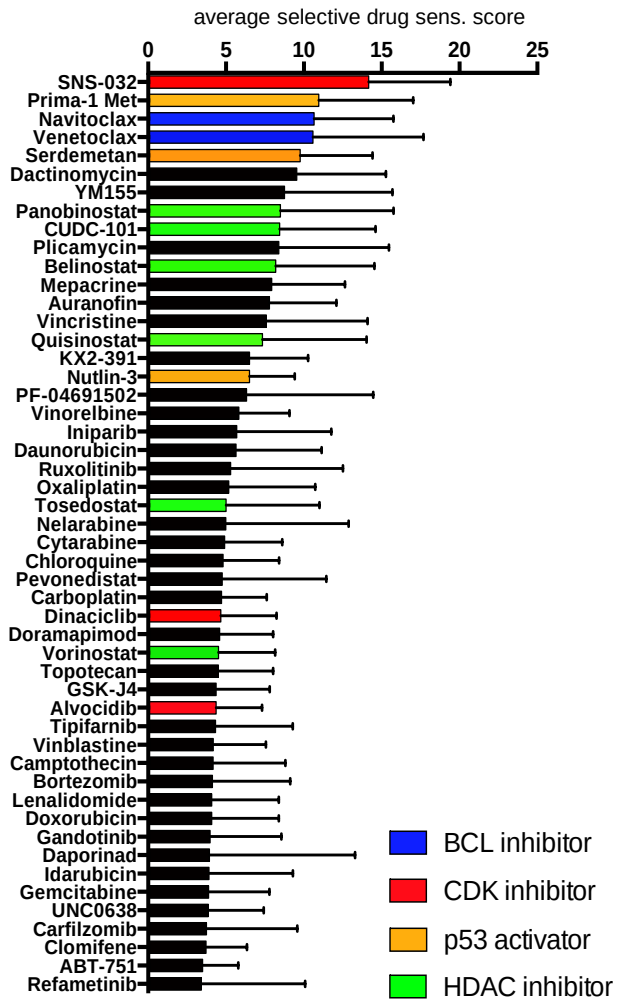
>> 2019 FDA / 2020 EMA orphan drug designation for T-PLL

>> ***ClinicalTrials.gov*** **NCT02576496**

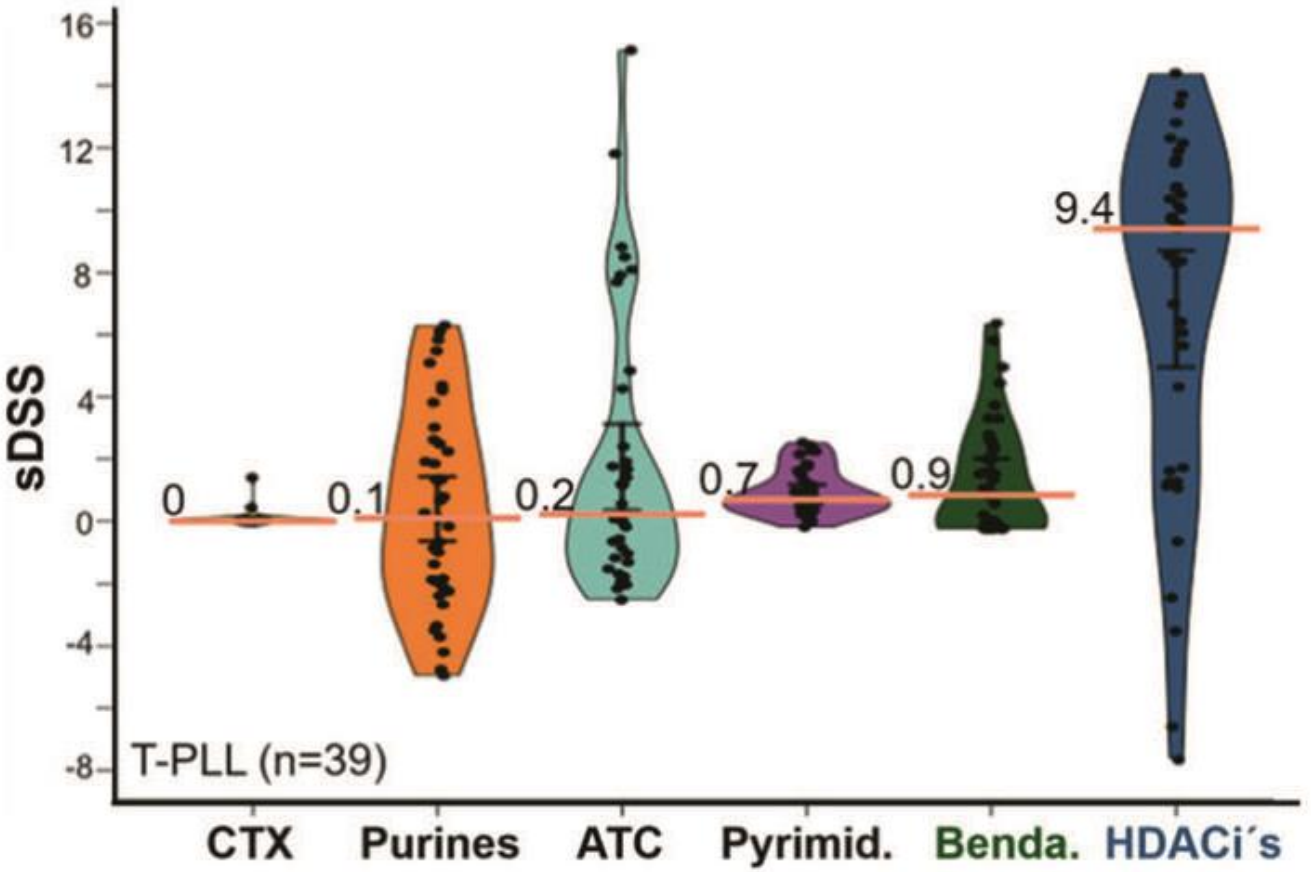
The promise by single agent sensitivity screens

compound library screen in 39 T-PLL

(integrated with NGS profiling)

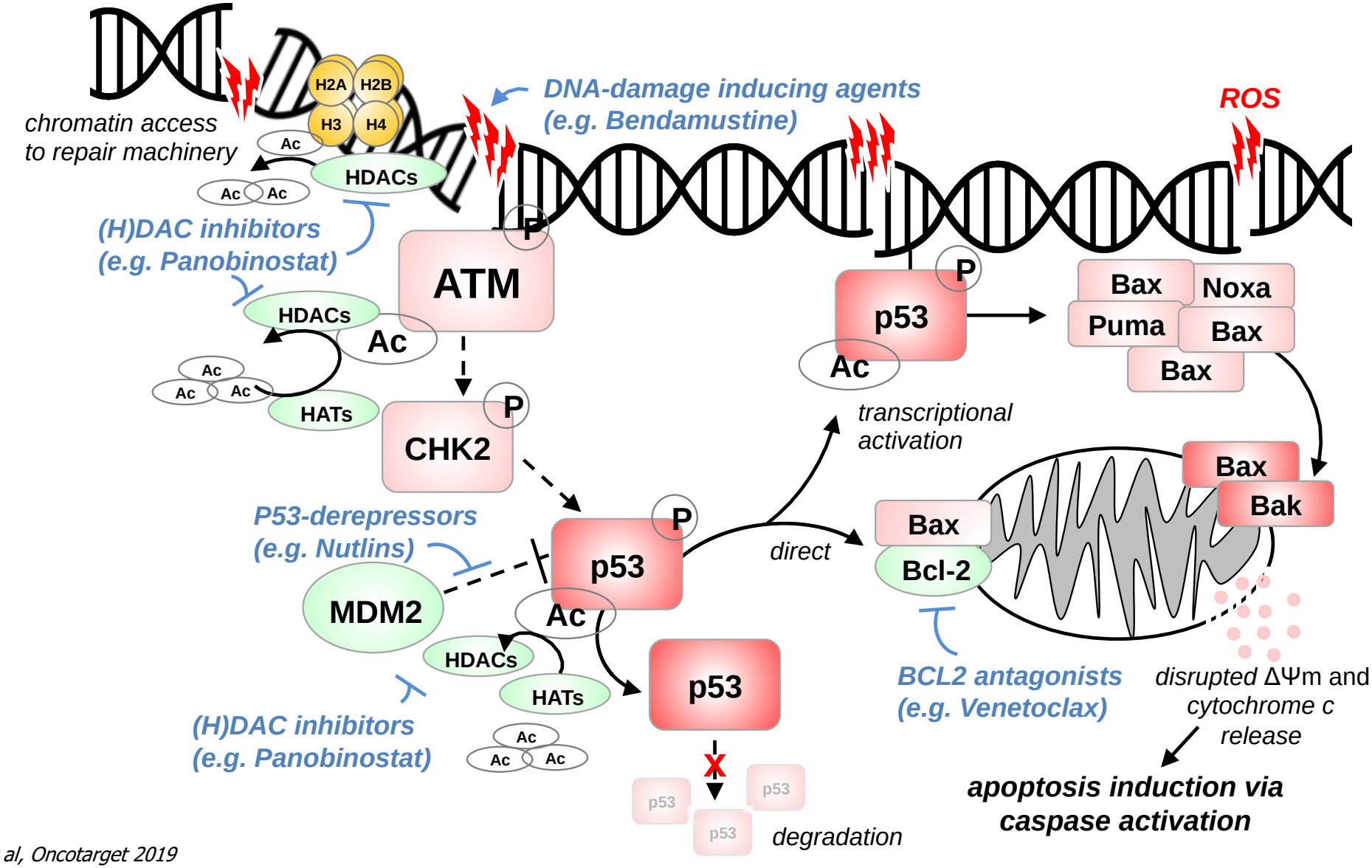


Andersson et al, Leukemia 2017



Pützer et al, Leukemia 2020

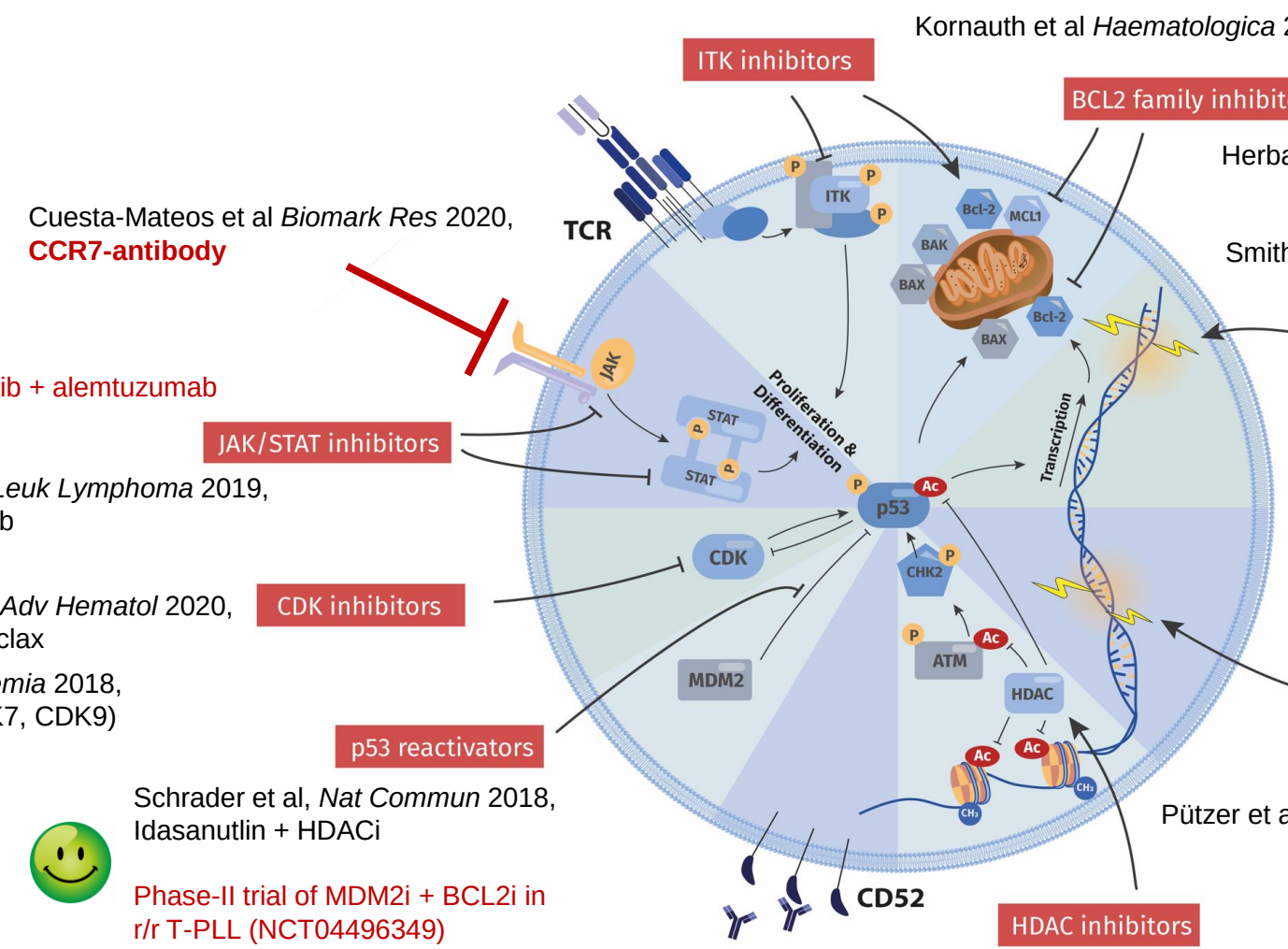
Promising synergistic combinatorial approaches in T-PLL



Schrader et al, Oncotarget 2019

anti-apoptotic pro-apoptotic post-transcriptional modification

A new era in devising therapies for T-PLL
Ongoing search for promising synergisms



Kornauth et al *Haematologica* 2021, Venetoclax + Ibrutinib AND NCT03873493

Herbaux et al *Blood* 2021, Venetoclax + Ruxolitinib
Venetoclax + Belinostat

Smith et al *Blood Adv* 2020, Venetoclax + MCL1i

Alkylating agents

Cuesta-Mateos et al *Biomark Res* 2020,
CCR7-antibody

NCT03989466: itacitinib + alemtuzumab

JAK/STAT inhibitors

Gomez-Arteaga et al *Leuk Lymphoma* 2019,
Ruxolitinib + Tofacitinib

Johansson et al, *Ther Adv Hematol* 2020,
CDK9-inhib. + Venetoclax

CDK inhibitors

Andersson et al *Leukemia* 2018,
SNS-032 (CDK2, CDK7, CDK9)

Alfayez et al *Leuk Lymphoma* 2020,
Venetoclax + Pentostatin

Purine analogues

p53 reactivators

Schrader et al, *Nat Commun* 2018,
Idasanutlin + HDACi

Phase-II trial of MDM2i + BCL2i in
r/r T-PLL (NCT04496349)

Pützer et al *Leukemia* 2020, Tinostamustine (SAHA+Benda)
AND NCT02576496

HDAC inhibitors

Alemtuzumab

Hasanali et al *Sci Transl Med* 2015, Cladribine + HDACi + alemtuzumab

(Fig. mod. from Braun et al, Curr Hematol Malig Rep 2020)

10 THINGS TO REMEMBER ABOUT T-PLL

1. Don't call it "T-CLL"; it erroneously communicates "indolent course" !
2. Multi-disciplinary integrative diagnostics (hematologist; clinical, cytology, FACS, cytogenetics, clonality, > 95% can be assigned a rearrangement of a TCL1 family member) !
3. First-line: single-alemtuzumab i.v., treat early; if transplant is no option, may be later !
4. Priming (debulking) with Cyclophosphamide (or Cladribine)
5. Non-consolidated relapse rate after alemtuzumab-induced CR is 100% !
6. Campath works also at 2nd line (check CD52 by FACS not BM histochemistry) !
7. Perform allo-SCT in eligible pts. in 1st best response rather early (<1yr) than late !
8. Campath alternatives / bridging: purines (CDA, DCF), F(MC), or Benda. !
9. Explore options at relapse at large academic center (novel synergisms, trial) !
10. Novel molecular insights reveal new vulnerabilities;

    - but T-PLL is not CLL (e.g. Ibru/Ven) !

    - limitations of in-vitro sensitivity

Multi-center efforts - (International T-PLL Study Group) !

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Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

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