Barcelona (Spain), June 2 2017

41 DIADA INTERNACIONAL

Societat Catalana d'Hematologia i Hemoteràpia

Nous Tractaments en la LLA-T
Nuevos Tratamientos de la LLA-T
New Treatments in T-ALL

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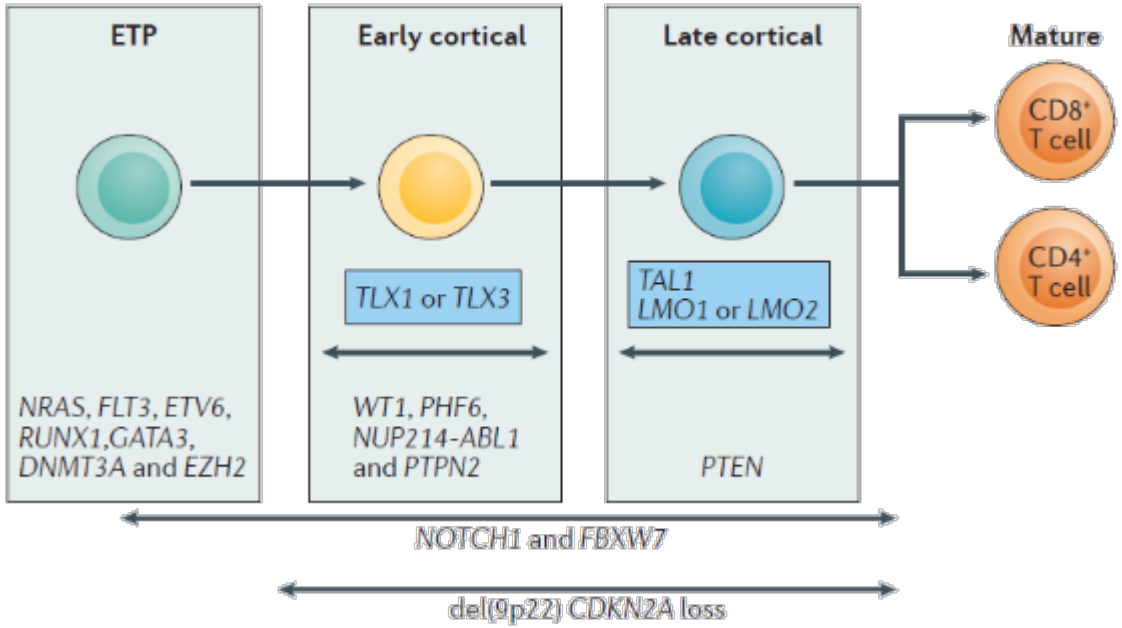
Pathogenetic role of (onco)gene expression/deregulation

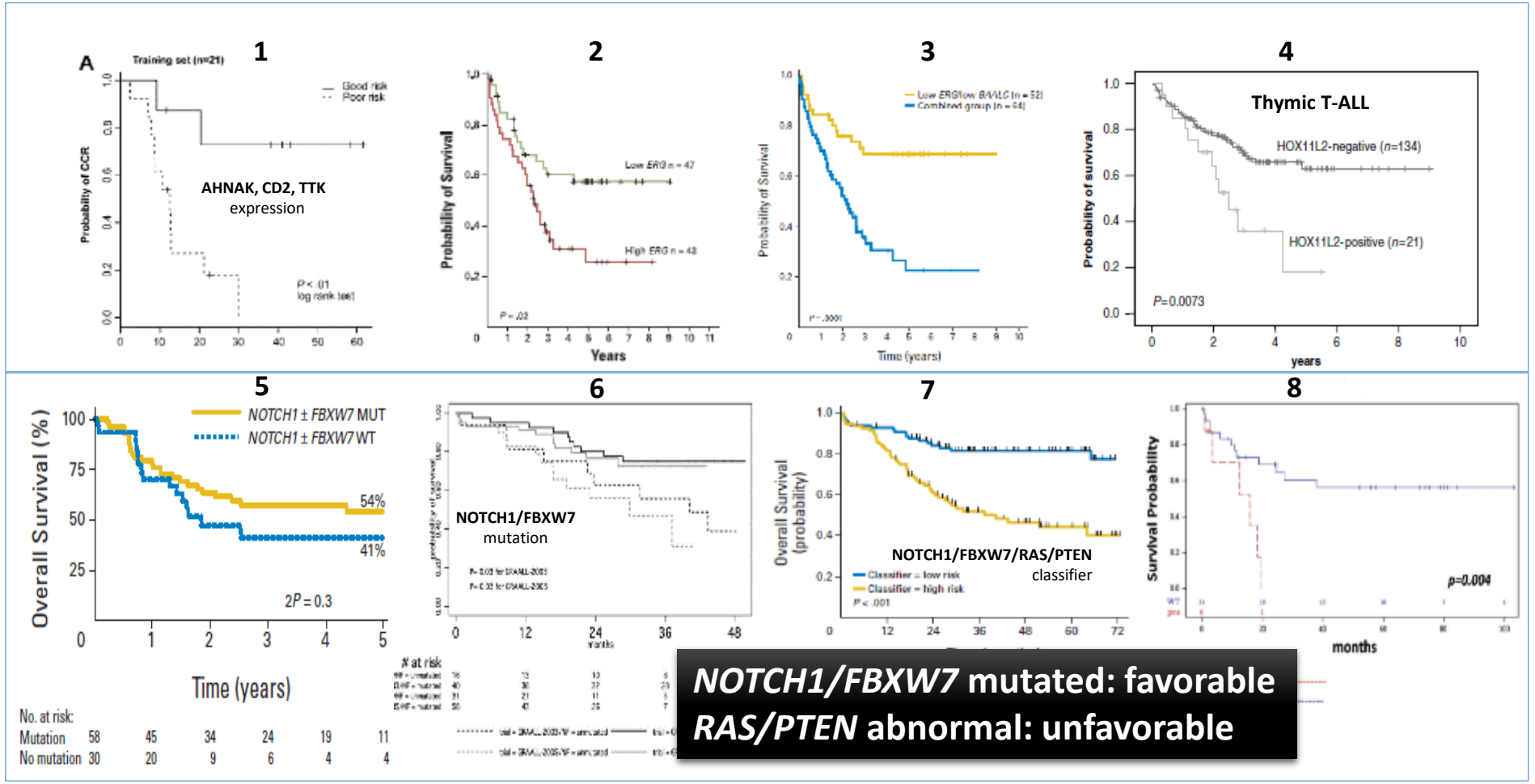
not a single-hit disease !

- **Multistep process disrupting key oncogenic, tumour suppressor and developmental pathways responsible for the normal thymocyte development, involving:**
  - **NOTCH1** (gain-of-function mutation, ≥60%)
  - **CDKN2A** (loss of activity and tumour suppressors p16/p14))
  - **Gene rearrangements** (aberrant oncogene/transcription factor expression)
    - TAL1, TAL2
    - LYL1, BHLHB1
    - LMO1, LMO2
    - TLX1, TLX3
    - NKX2-1, 2-2
    - HOXA
    - MYC
    - MIB
    - …



Belver L and Ferrando A, Nat Rev Cancer 2016;16:495–507

Prognostic role of (onco)gene expression/deregulation

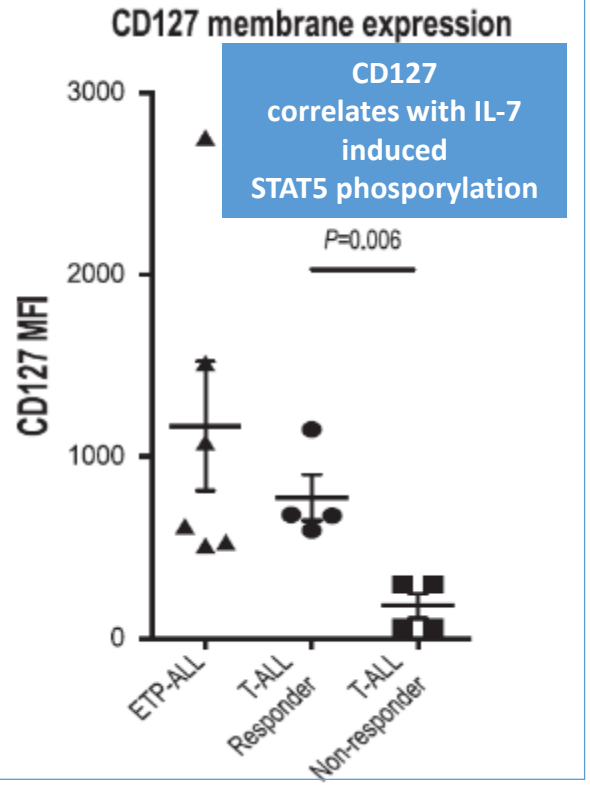


[1]Chiaretti S et al, Blood 2004;103:2771–8; [2]Baldus CD et al, J Clin Oncol 2006;24:4714–20; [3]Baldus CD et al, J Clin Oncol 2007;25:3739–45; [4]Baak U et al, Leukemia 2008;22:1154–60; [5]Mansour MR et al, J Clin Oncol 2009;27:4352–56; [6]Ben Abdelali R et al, Blood 2011;118:5099; [7]Trinquand A et al, J Clin Oncol 2013;31:4333–42; [8]Gianfelici V et al, Haematologica 2016;101:941–50

MYC+ T-ALL and JAK/STAT in ETP-ALL

- **MYC+** T-ALL[1,2]
  - MYC/TCR or MYC/other rearrangement
  - Rare (≤5%)
  - Independent of NOTCH1
  - Mainly “cortical”
  - Leukocytosis
  - High risk

- **JAK/STAT** in ETP-ALL[3]

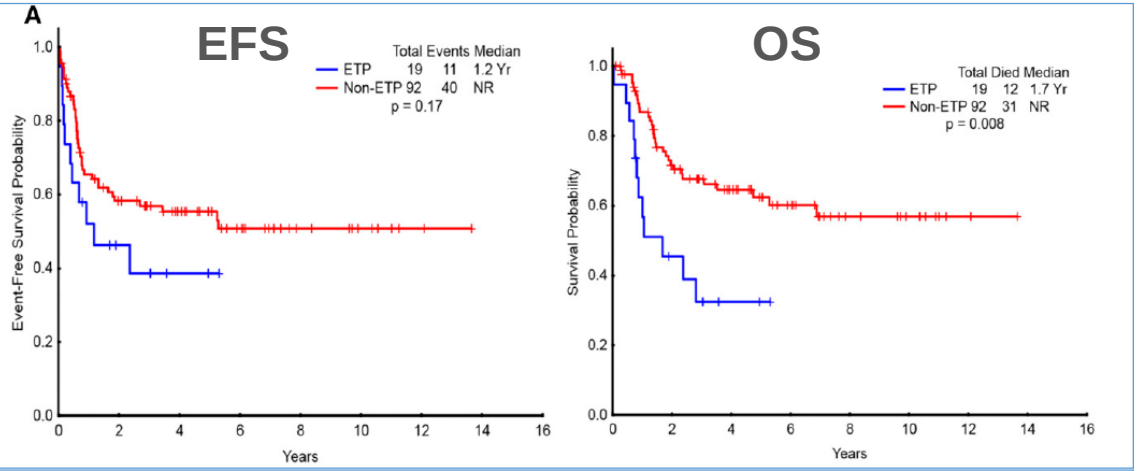


[1]La Starza R et al, Blood 2014;124;3577–82;
[2]Bonnet M et al, Blood 2011;117:6650–9; [3]Maude Sl et al,Blood 2015;125:1759–67

ETP-ALL in adults (MDACC and GRAALL)

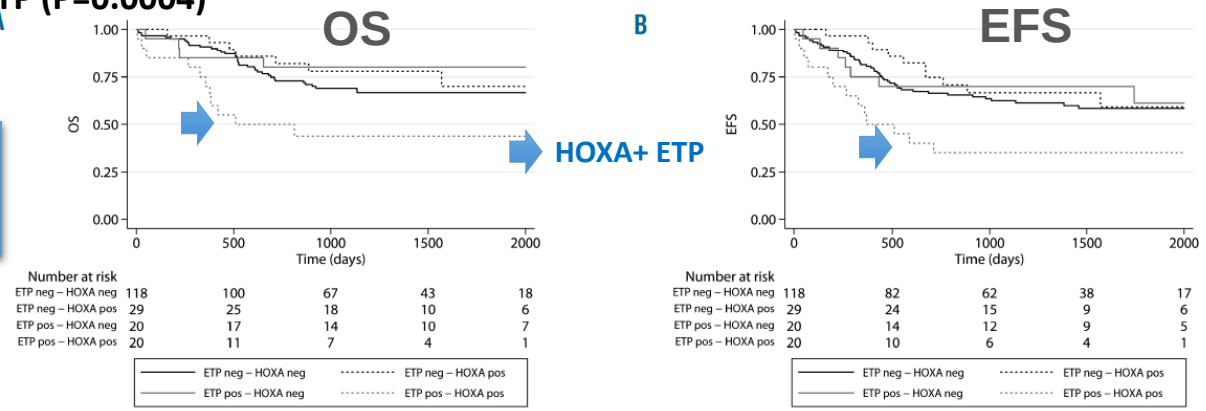
Distinct immunophenotype, early T-blasts (CD7+, CD2+, cCD3+, CD4+/-):
CD1a, CD38 neg
CD5 neg/dim (<75%)
CD11b, CD13, CD33, CD117, CD34 pos (one or more)
Distinct Gene Expression Profile (similarities to stem/myeloid cells)
Distinct molecular profile (lower incidence NOTCH1/CDKN1/2 mut; frequent FLT3/DNMT3A/RAS/IDH1/IDH2 mut)

- **N = 19/111 (17%)**[1]
- **CR 73% vs 91%** (P=0.03)



- **N = 37/209 (17.7%)**[2]
- **HOXA+ = 40.8% vs 14.5% nonETP (P=0.0004)**

HOXA mapping on chr. 7, overexpression promoting maturation arrest/leukemogeneis



[1]Jain N et al, Blood 2016;127:1863–69; [2]Bond J, Haematologica 2016;101:732–40

MYC+ T-ALL with t(8;14)(q24;q11)

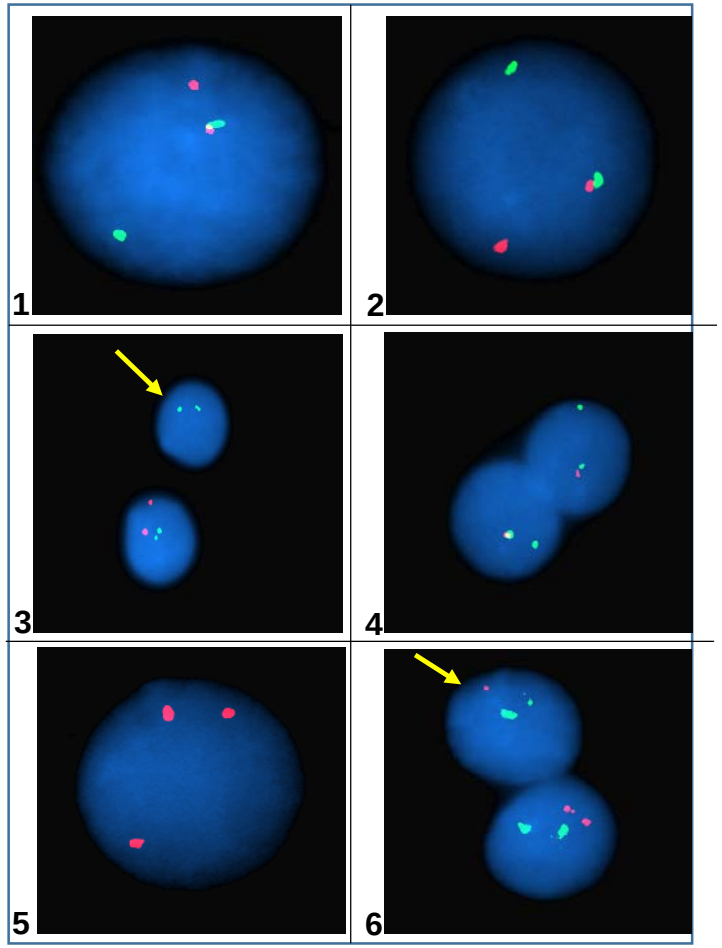
q32 in B-ALL

Combined Interphase-FISH (31 GENES)[1]

- *TCRB* (7q34)
- *WT1* (11p13)

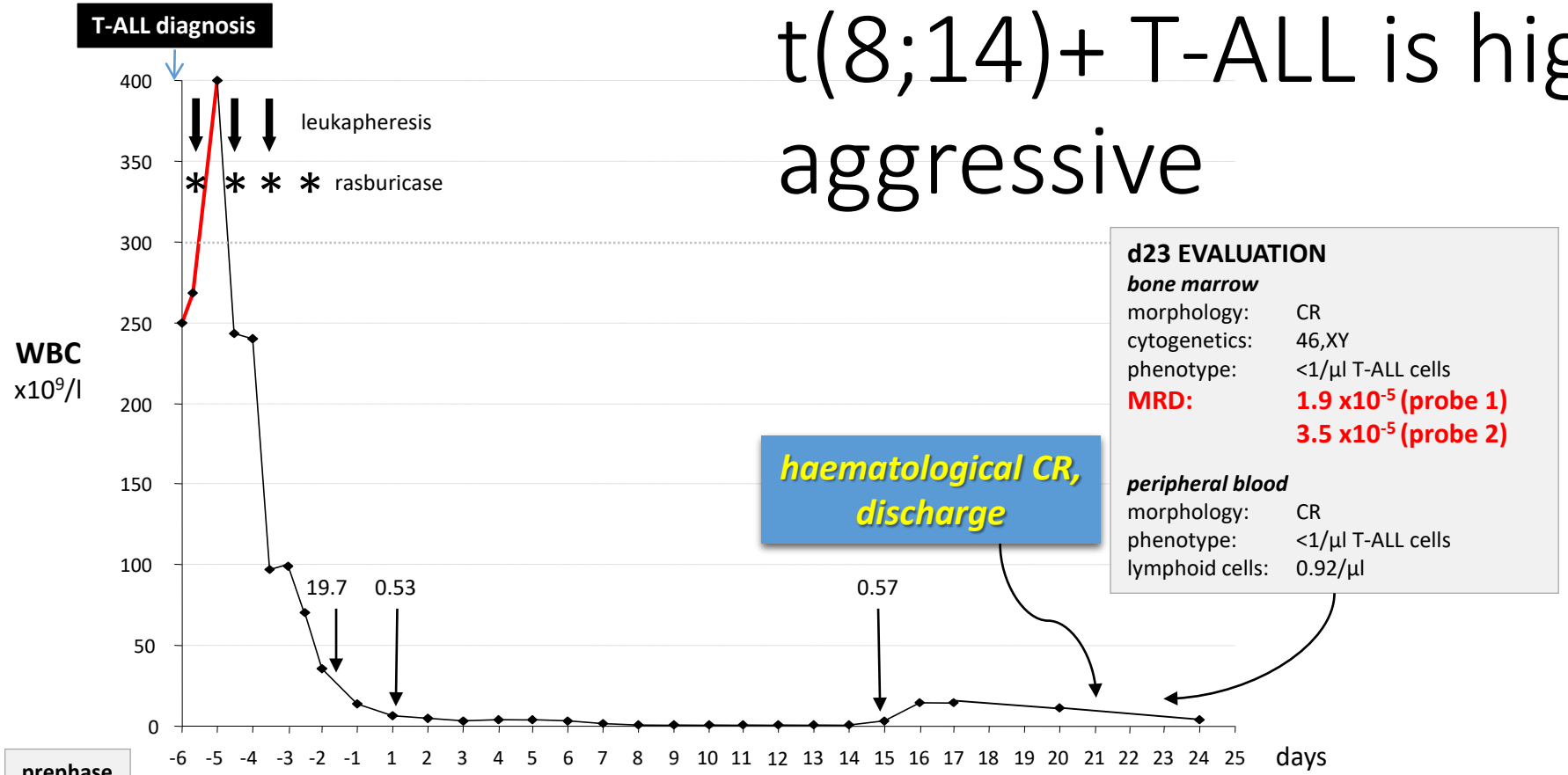
1. *TCRA/D*/14q11-translocation (98%)
2. *C-MYC*/8q24-translocation (82%)
3. biallelic del(9)(p21)/*CDKN2A/B* (88%)
4. del(1)(p32)/*SIL-TAL1* (82%)
5. gain 10p13/*AF10* (86%)
6. del(10)(q23)/*PTEN* (12%)

- *NOTCH1* (9q34)
- *PHF6* (Xp11)
- *PTEN* (10q23)



[1]Gorello P et al, Haematologica 2010;95:79–86

t(8;14)+ T-ALL is highly aggressive



prephase

CY 300 mg/m²/d

PDN 20 mg/m²/bd

cycle 1 (from d1)

IDA 12 mg/m²/d

VCR 2 mg/d

ASP 3,000 IU/m²/d

DEX 5 mg/m²/bd

Intrathecal therapy
(MTX 12.5 mg, Ara-C 50 mg, DEX 4 mg)

G-CSF

cycle 2
(from d24)

cycle 3 (HD-MTX [5 g/m²]/Ara-C
(from d46); **MRD negative d64**

cycle 4
(from d65)

Allogeneic SCT
(d99)

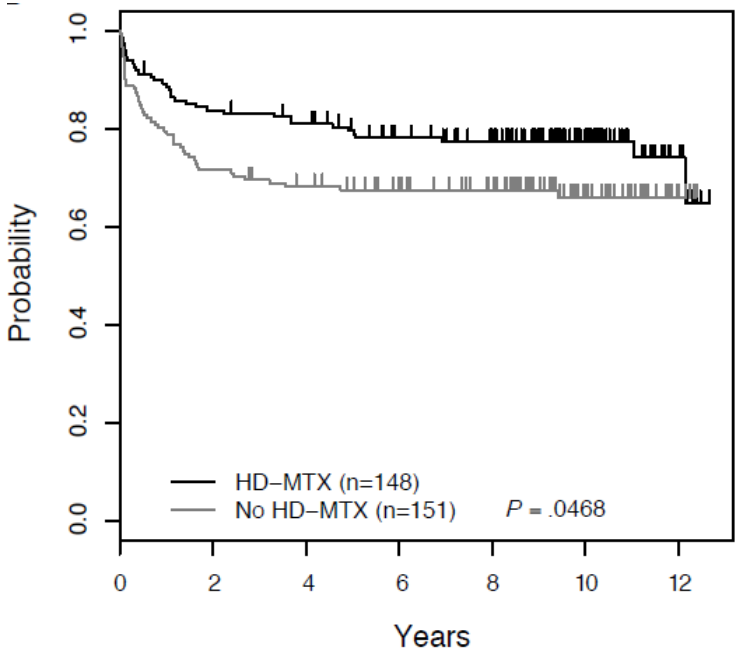
A/W
6+ years

Parolini M et al, Blood Cancer J 2014;4:e176

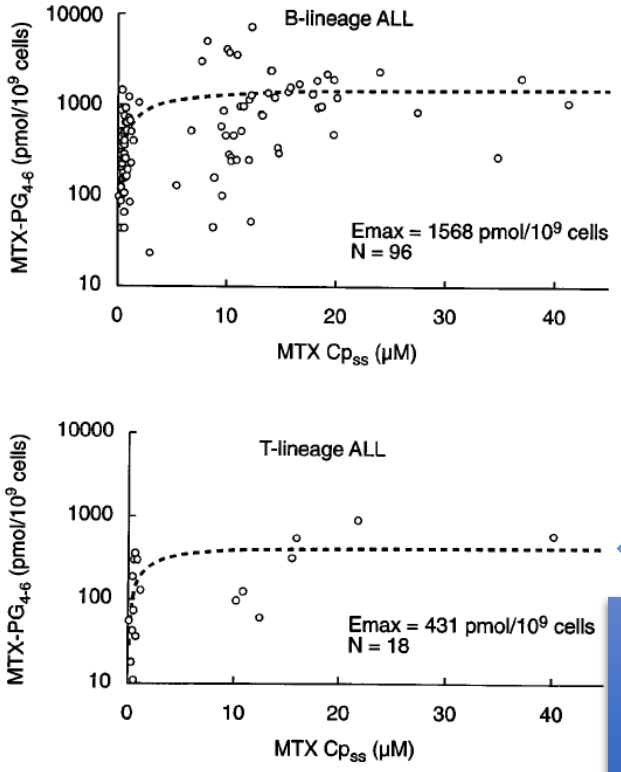
HD MTX 5g /m^2 in T-ALL

- MTX 5 g/m^2 effective in pediatric T-ALL[1], targeting MTXemia ~65 micromol/l[2,3], feasible in adults[4]

EFS by treatment[1]



Relationship between lymphoblast and plasma MTX levels[2]



Inferior accumulation of MTX polyglutamates (PG) requires higher MTX dosing to achieve therapeutic levels in T-ALL

[1]Asselin BL et al, Blood 2011;118:874–83; [2]Galpin AJ et al, Mol Pharmacol 1997;52:155–63;
[3]Masson E et al, J Clin Invest 1996;97:73–80; [4]Bassan R et al, Haematologica 2011;96(s2):238(abstr #0557)

MTX 5 g/m^2 in T-ALL

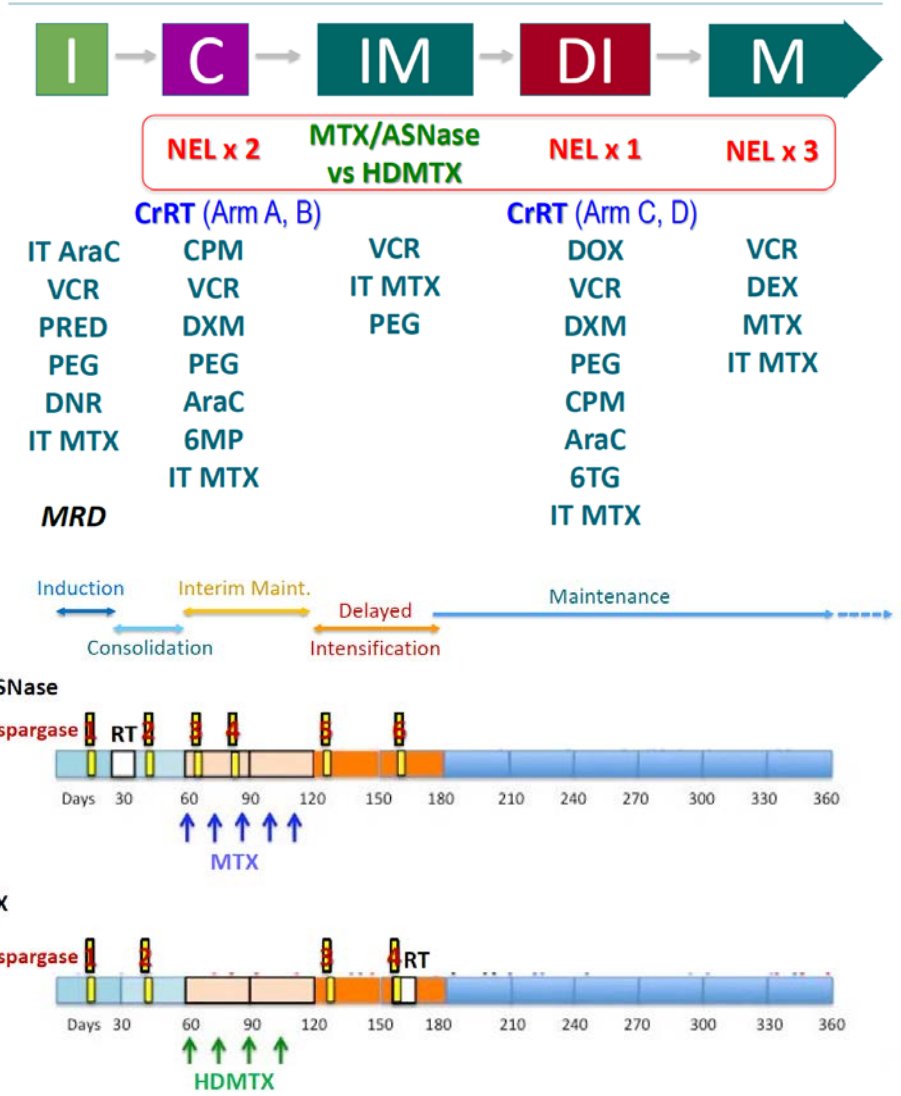
	No. (%)	Plasma MTX (micromol/l)	
		8-h	24-h (end infusion)
Patients	33		
MTX blocks	65		
MTX plasma concentration			
mean (SD)		87.7 (46.6)	66.5 (44.8)
median (range, 25th-75th percentiles)		86.0 (59-102)	69.8 (39.2-84.0)
Grade III-IV toxicity (ALL REVERSIBLE)			
patients with GIII-IV episodes	6 (18)		
MTX blocks with GIII-IV episodes	8 (12)		
GIII-IV episodes			
hepatic	3		
GI	3		
coagulation	1*		
allergy	1*		

TARGETING 65-70 micromol/l

**concomitant Asp*

COG study 0434, patient age 1-30 years[1-4]

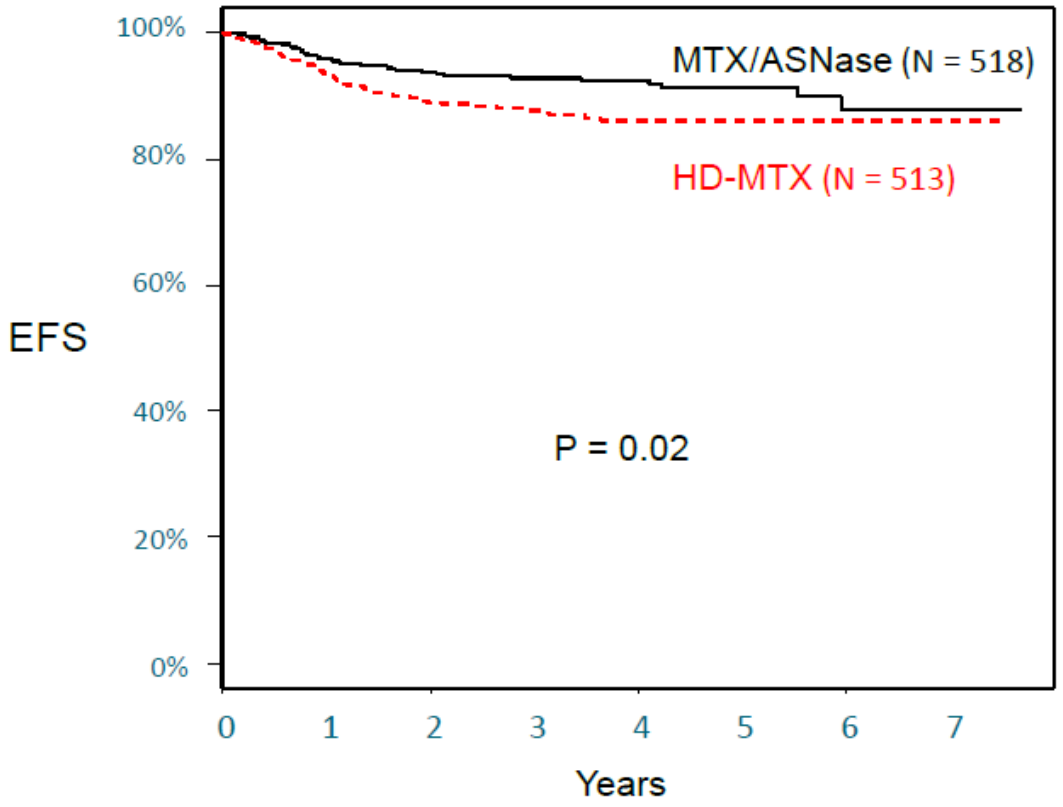
- **2 x 2 factorial design**
  - Escalating MTX (Capizzi*) *vs* HD MTX (5 g/m^2)
  - Nelarabine *vs* no Nelarabine
  - Plus Peg-ASP



*100 mg/m^2 on days 1,11,21,31,41
(with leucovorin rescue
and escalating by 50 mg/m^2 as tolerated)
[neutropenia/mucositis])

[1]Dunsmore K et al, ALL SCAG Teleconference, November 3 2015;
[2]Wood BL et al, Blood 2014;124:1 (abstr);
[3]Winter S et al, Blood 2015;126:794 (abstr);
[4]Winter S et al, Pediatr Blood Cancer 2015;62:1176-83

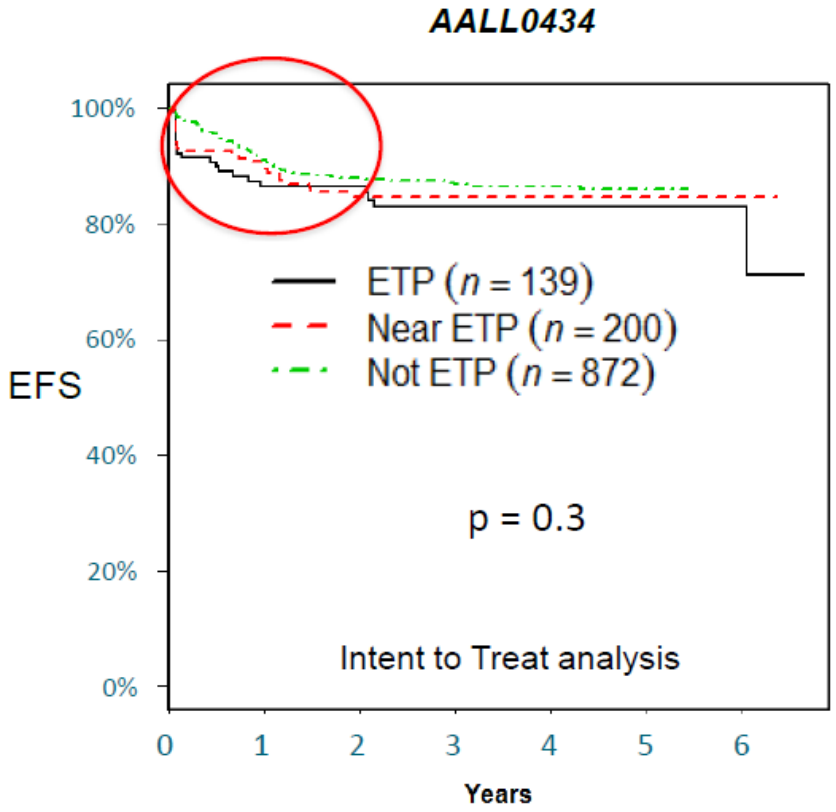
Outstanding results of COG 0434 (I): Capizzi MTX/ASP is superior to HD MTX[1-4]



	4-Year DFS (SE)	
All Patients	89.3% (1.5%)	
MTX/ASNase	92.5% (1.8%)	p=0.02
HDMTX	86.1% (2.4%)	

[1]Dunsmore K et al, ALL SCAG Teleconference, November 3 2015;
[2]Wood BL et al, Blood 2014;124:1 (abstr);
[3]Winter S et al, Blood 2015;126:794 (abstr);
[4]Winter S et al, Pediatr Blood Cancer 2015;62:1176-83

Outstanding results of COG 0434 (II): lack of significance of ETP immunophenotype[1-4]



	N	Frequency	MRD D29 <0.01% *	Induction Failure *,**	4-year EFS (% ± SE)	4-year OS (% ± SE)
ETP	130	11.3%	18.6%	7.8%	82.9 ± 6.2	91.0 ± 4.8
Near ETP	195	17.0%	35.2%	6.7%	84.7 ± 6.2	92.6 ± 4.4
Not ETP	819	71.6%	69.5%	1.1%	86.9 ± 2.5	91.5 ± 2.0

* p < 0.0001

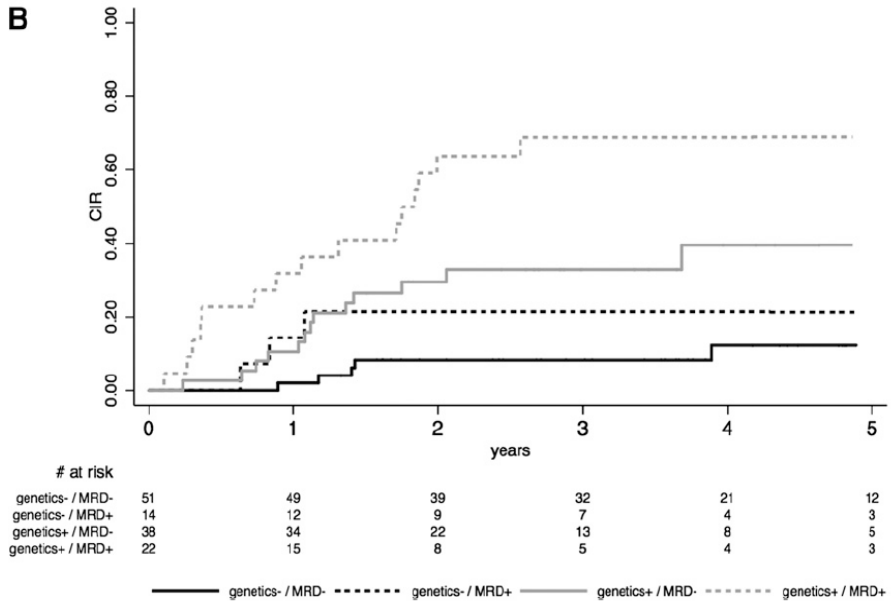
** Induction failure defined as > 25% blasts by morphology in bone marrow at Day 29

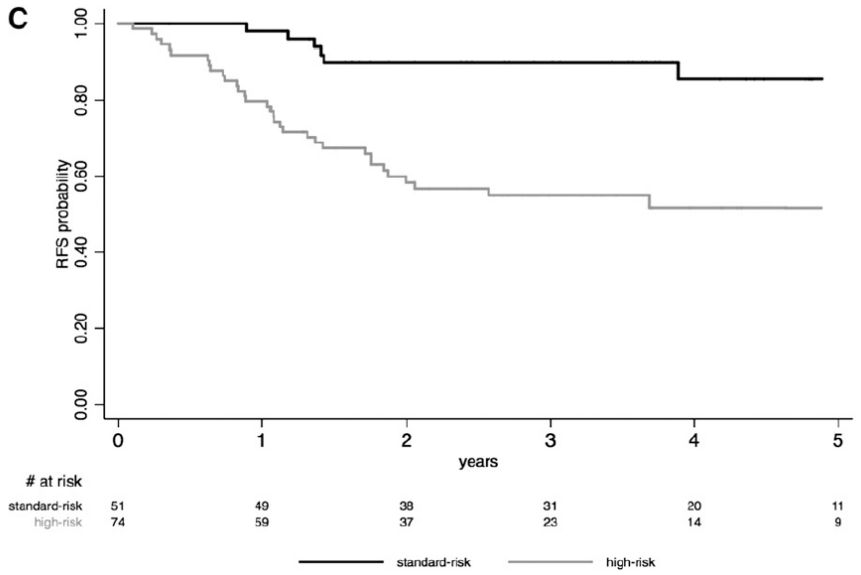
[1]Dunsmore K et al, ALL SCAG Teleconference, November 3 2015;
[2]Wood BL et al, Blood 2014;124:1 (abstr);
[3]Winter S et al, Blood 2015;126:794 (abstr);
[4]Winter S et al, Pediatr Blood Cancer 2015;62:1176-83

MRD response in adult T-ALL (I)

- **GRAALL study**

(B): **CIR by w6 MRD** (10^{-4} cut-off) **and high-risk genetics** (4 gene classifier)
(C): **RFS according to combined risk definition** (MRD and 4 gene classifier)

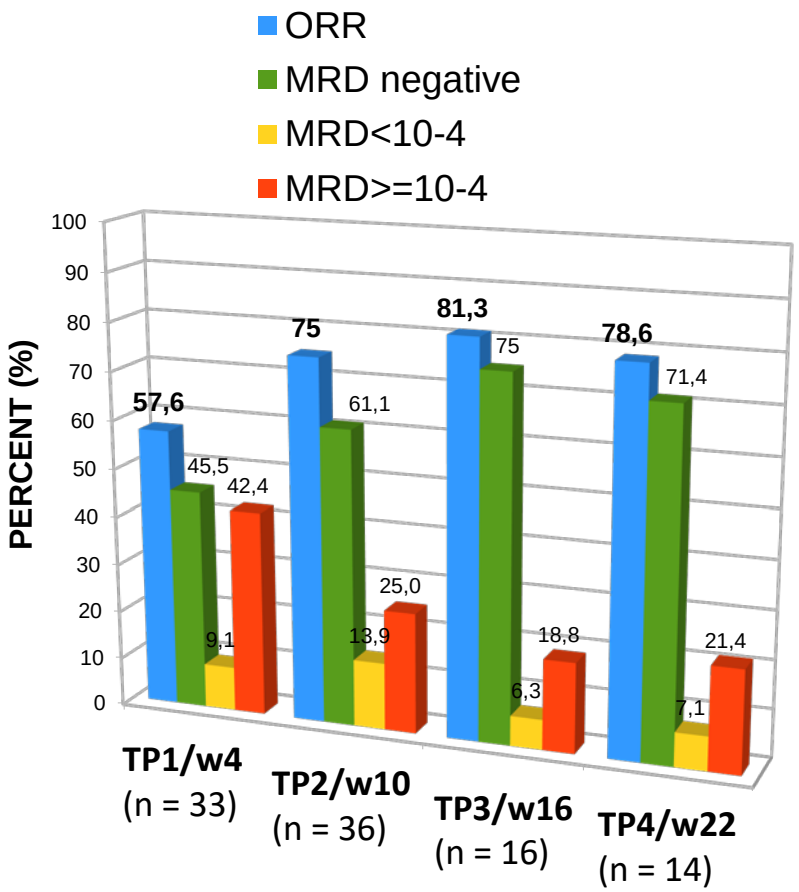


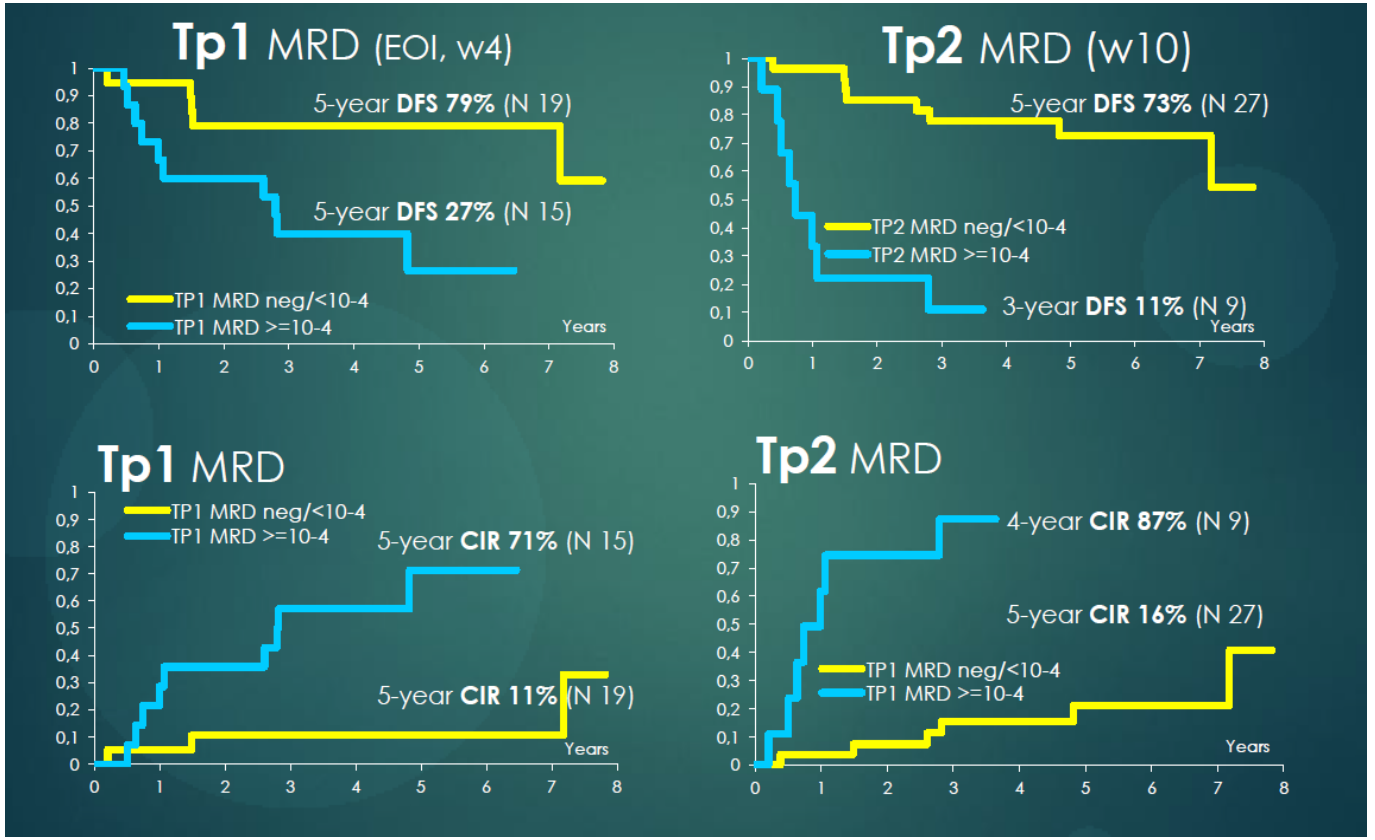


Beldjord K et al, Blood 2014;123:3739–49

MRD response in adult T-ALL (II)

- NILG study

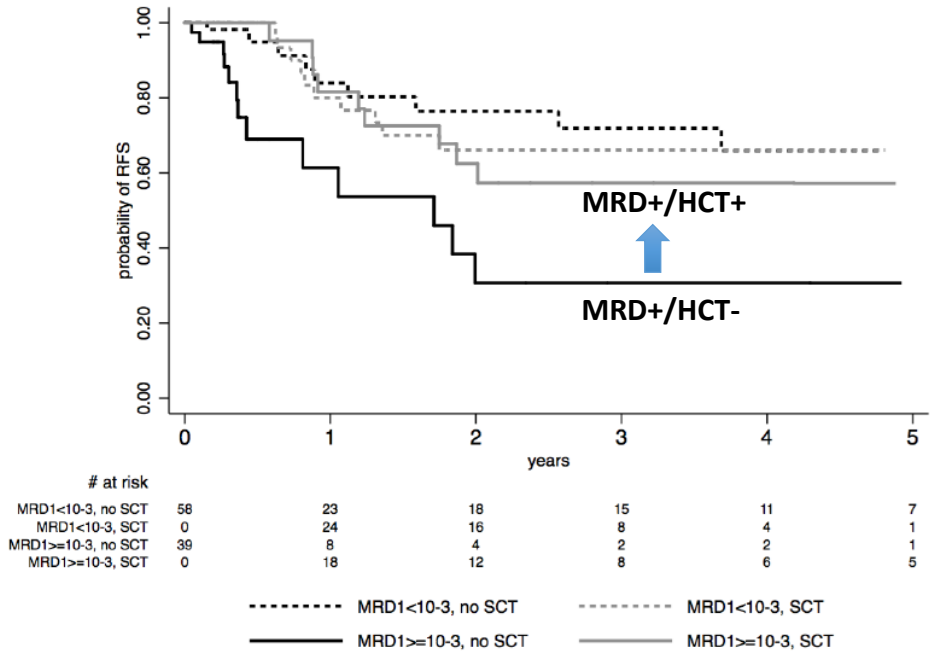




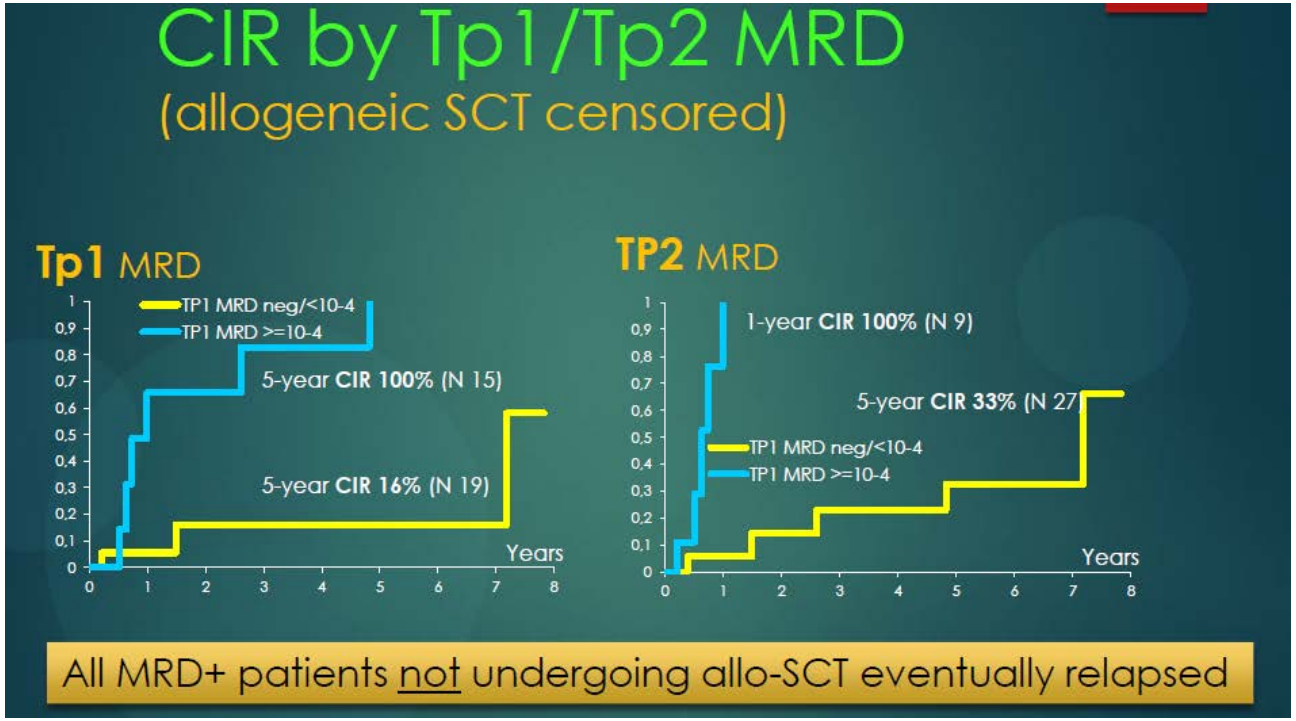
Bassan R et al, Blood 2016;128:176 (abstr)

Is allogeneic SCT helpful in MRD+ patients?

- **GRAALL study[1]**



- **NILG study[2]**



About 30% relapse rate in MRD responsive/negative patients in both studies (regardless of SCT) !

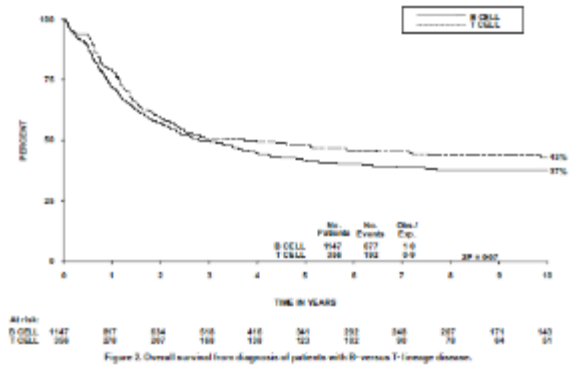
[1]Dhèdin N et al, Blood 2015;125:2486–96; [2]Bassan R et al, Blood 2016;128:176 (abstr)

High-risk T-ALL and indications for HSCT

	GMALL[1]	GRAALL[2]	NILG/GIMEMA[3]	PETHEMA[4]
WBC ($x10^9$/l)	-	-	>100	>30
Phenotype (EGIL)	Pro/pre-T Mature-T	-	Pro/pre-T Mature-T	-
Cytogenetics/ genetics	Complex	Low hypodiploidy/near triploidy, complex; *NOTCH1/FBXW7* neg, *RAS/PTEN* abn	Highly adverse	-
MRD	MRD $\geq 10^{-4}$ @ wk 10–22 (SR only)	$\geq 10^{-2}$ end of induction; $\geq 10^{-3}$ @ wk 6	$\geq 10^{-4}$ @ wk 10–16, +ve @ wk 22 (SR only)	$\geq$ 5x 10^{-4} @ wk 16-18
Miscellaneous	Late CR	CNS +ve Poor PDN and d8 BM response	-	Age 30-60 years Poor d14 BM response

[1]Hoelzer D et al, Blood 2009;114:324 (abstr); [2]Dhèdin N et al, Blood 2015;125:2486–96; [3]Bassan R et al, Blood 2016;128:176 (abstr); [4]Ribera JM et al, J Clin Oncol 2014;32:1595-604

Treatment results in adult T-ALL



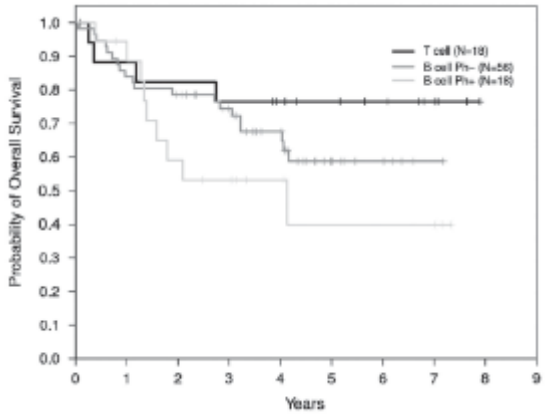
UKALL XII/ECOG[1]

N	505
(15–55 yrs)	
CR	87%
CCR	61%
OS (5-y)	56%
thymic	68% (CHT SR MRD-)
early	40% (HCT 84%)
mature	49% (HCT 68%)

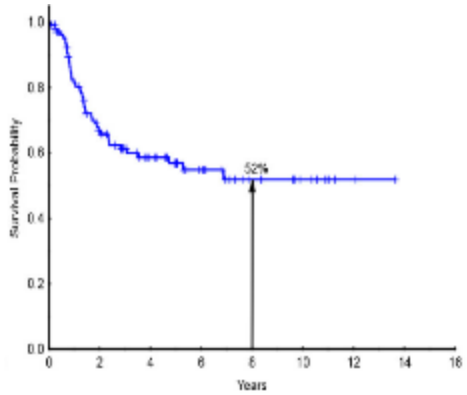
GMALL 06/99-07/03[2]

N	91
(16–56 years)	
CR	90%
(87 evaluable)	
OS (5-y)	58%
DFS	56%
CHT	55%
HCT	100%
	(6 allo, 28 BEAM/auto)

RALL[3]



DFCI[4]



MDACC (incl. 32% LBL)[5]

next 2 slides

NILG ALL 10/07[6]

[1]Marks DI et al, Blood 2009;114:5136–45; [2]Hoelzer D et al, Blood 2009;114:324 (abstr);
[3]Parovichnikova E et al, Bone Marrow Transpl 2015;50(Suppl 1):557 (abstr O098); [4]DeAngelo DJ et al, Leukemia 2015;29:526–34;
[5]Jain N et al, Blood 2016;127:1863–9; [6]Bassan R et al, Blood 2016;128:176 (abstr)

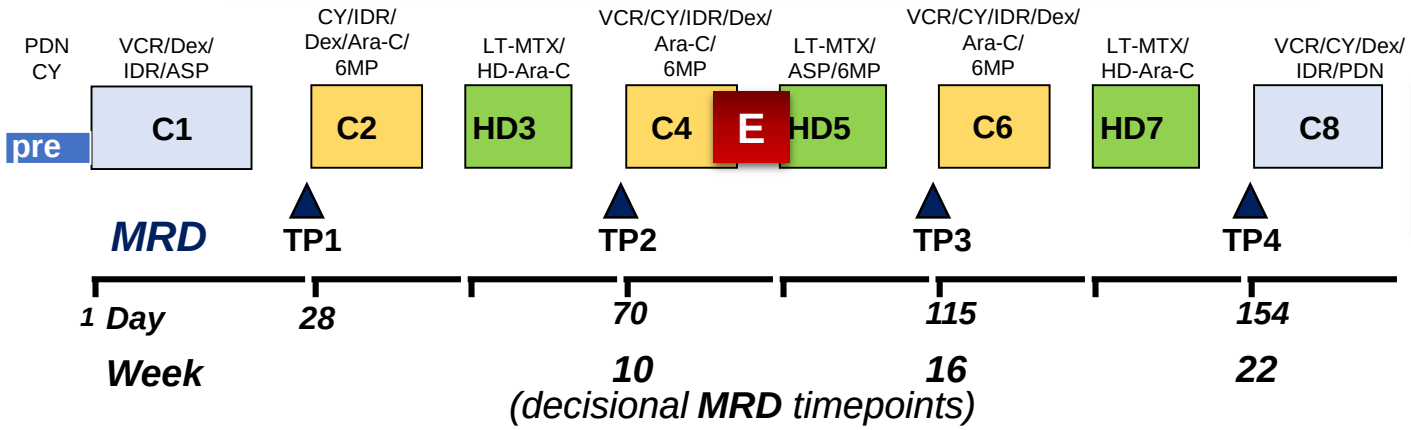
NILG 10/07 for T-ALL (subsequently modified with Peg- ASP x4 [GIMEMA LAL 1913])

SR	HR	VHR
• No risk feature	• Late CR	• WBC >100 • Early/ mature-T • Highly adverse cytogenetics*

1. Risk Stratification

* +8, -7, del6q, t(8;14), low hypodiploid/ near triploidy, complex

2. Induction/Consolidation and MRD Study



3. Risk/MRD-Specific Therapy

- **VHR** all
- **SR/HR MRD** ≥10^{-4} w10 ≥10^{-4} w16, positive w22
- **HR** **MRD** unknown

(***EARLY*** *after HD3/C4)* *(after C8)*

Allogeneic SCT (RD/URD)

Maintenance (2-Y)

(after C8)

- **SR/HR** **MRD** <10^{-4} w10-16, negative w22
- **SR** **MRD** unknown

- **HLA testing** to identify RD/URD at diagnosis
- Radiation-free, CNS prophylaxis **(triple IT vs IT liposomal cytarabine)**

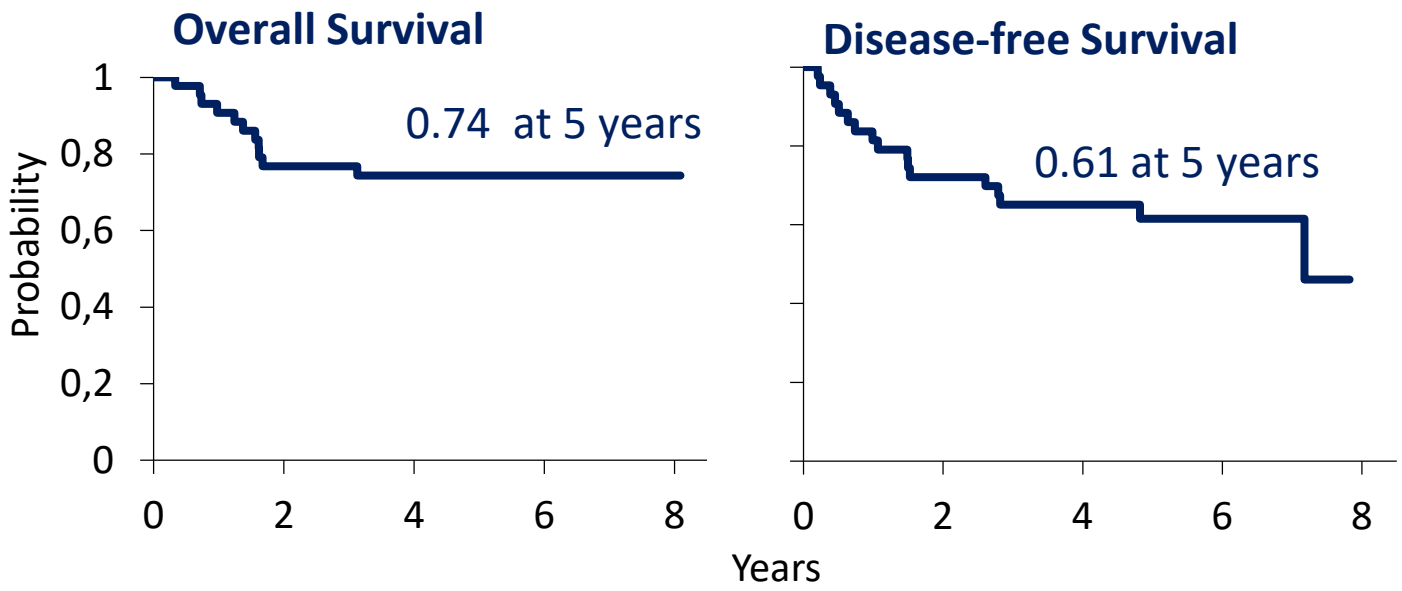
BFM-type: C2,C4,C5 **Lineage-targeted MTX**: HD3,HD5,HD7: 5 g/m^2; 1.5 g/m^2 if age >55 years

ClinicalTrials.gov NCT-00795756

Results

		TCP ALL n=44
Age (years)	Median (range)	38 (17 - 65)
<=60	N (%)	43 (97.7)
Gender (M)	N (%)	28 (63.6)
WBC (10^9/l)	Median (range)	16.7 (1.0 - 281.2)
>100	N (%)	10 (22.7)
CNS involvement	N (%)	2 (4.5)
Cytogenetics/genetics	N (%)	
Normal		26 (59.1)
Adverse		9 (20.5)
Non-adverse		4 (9.1)
Unknown		5 (11.4)
Risk stratification	N (%)	
Standard-risk		11 (25.0)
High-risk		0 (0.0)
Very high risk		33 (75.0)

CR	**43 (98%)**
NR	1 (2%)
ED	0

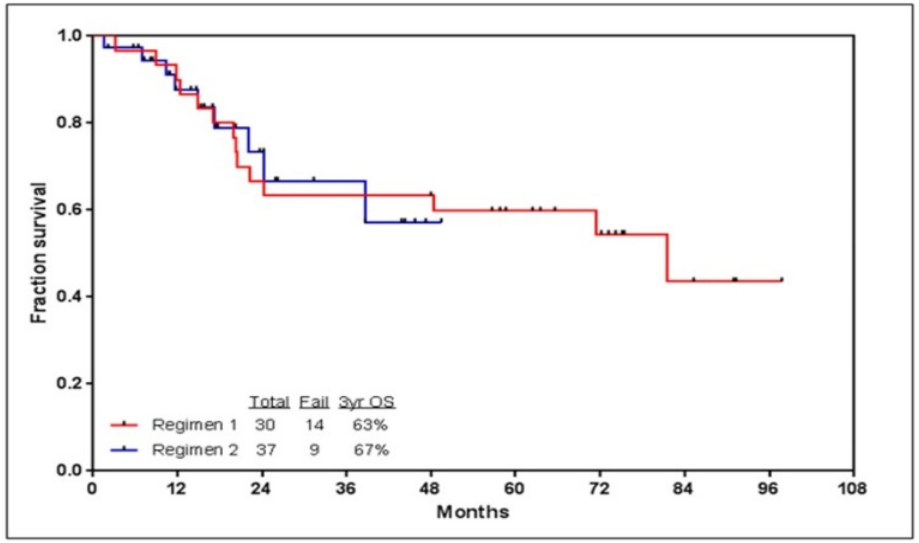


Any news with chemotherapy? Nelarabine?

- **"Effective" in relapsed/refractory**
  - CALGB study[1]
    - **Nel**: 12/39 CR/CRi (**31%**)
  - GMALL study[2]
    - **Nel**: 45/126 CR (**36%**)
    - CR "thymic" **56%** vs other **30%** (P=0.03)
    - 3-y RFS 37% in CR pts → HCT
  - UPenn study[3]
    - **Nel-CY-Eto**: 3/5 CR (**60%**)

- **Frontline studies initiated**
  - MRD+ T-ALL (GMALL, ongoing)
  - MDACC[4]
    - Early results: superimposable to historical cohort (N-)

Figure 1: Overall Survival (OS) by Regimen



[1]DeAngelo DJ et al, Blood 2007;109:5136–42; [2]Goekbuget N et al, Blood 2011;118:3504–11;
[3]Luskin MR et al, Br J Haematol 2016;174:332–34; [4]Abaza Y et al, Blood 2016;128:177 (abstr)

Where we are

- **The good**
  - Very high CR rate
  - High MolCR rate
  - OS and DFS at 50-60% and greater
  - Useful agents
    - Intensive, pediatric-type (MTX, Peg-ASP …)
    - SCT (when indicated)

- **The bad**
  - MolCR not totally protective against risk of relapse
  - High-risk subsets (biology and MRD)
  - High treatment toxicity/cannot increase further
  - Allogeneic SCT (TRM, morbidity)
  - Shortage of new chemo agents in decades (nelarabine)
  - Shortage of new targeted agents (compared to B-ALL)

How to move forward with targeted therapy

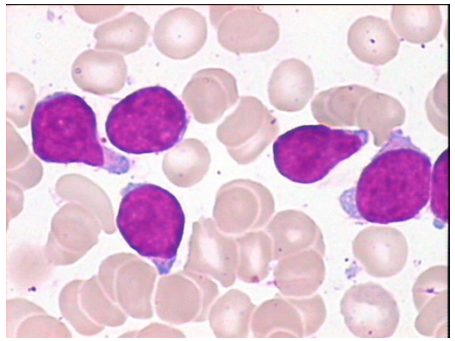
2

other membrane receptors (intracellular signaling)

Monoclonal antibodies/immunoconjugates (CD3, CD7, CD30, CD38)
CAR T cells (CD5, CD7)

1 **receptors involved in the leukemia-sustaining marrow environment**

Inhibitors
(CXCR4/CXCL)



ALL **cells**

Inhibitors
(proteasome, NOTCH/GS, BCL2/BCX, JAK/STAT, TK, HDAC, MYC, MDM2, mTOR, CK, Wnt, IRAK, hedgehog, HSP90, PTEN/AKT, LAT1 …)

Agonists
(P53, …)

signal transduction and proliferation/ apoptosis pathways **3**

New drug profiling platforms and PDX models

Integration into clinical trial or individual treatment plan
(PRECISION MEDICINE & PERSONALIZED THERAPY)

The permissive marrow niche

Targeting CXCR4/CXCRL12 reduces T-ALL burden in murine and xenograft models

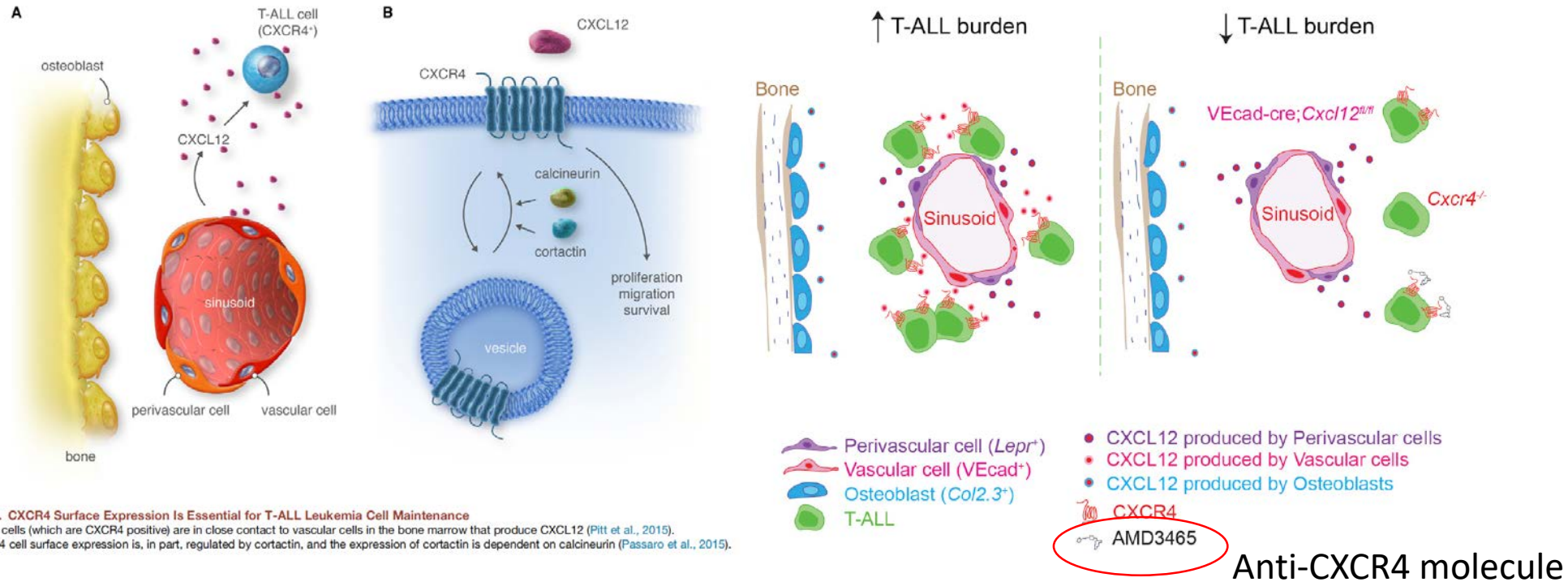


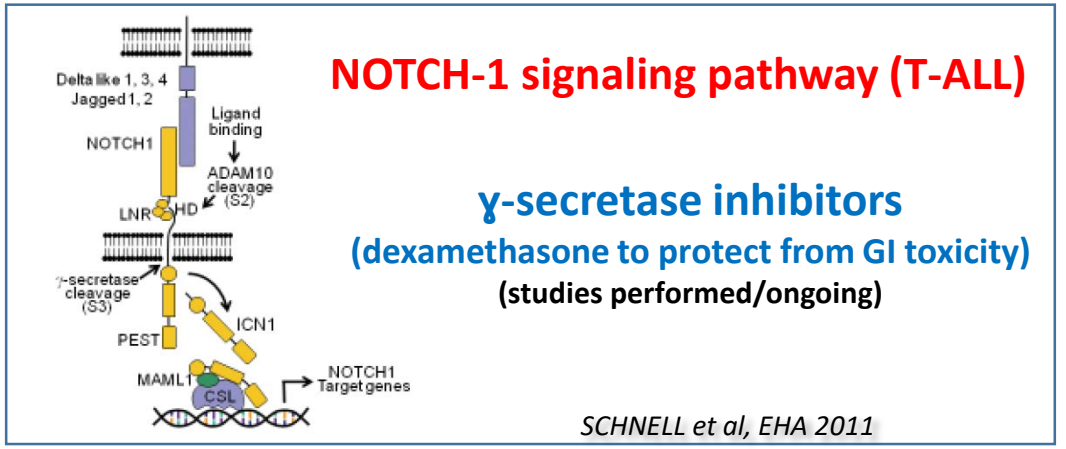
Figure 1. CXCR4 Surface Expression Is Essential for T-ALL Leukemia Cell Maintenance
(A) T-ALL cells (which are CXCR4 positive) are in close contact to vascular cells in the bone marrow that produce CXCL12 (Pitt et al., 2015).
(B) CXCR4 cell surface expression is, in part, regulated by cortactin, and the expression of cortactin is dependent on calcineurin (Passaro et al., 2015).

Anti-CXCR4 molecule

Passano et al, **Cancer Cell** 27:769;2015
Tipp LA et al, **Cancer Cell** 27:755;2015

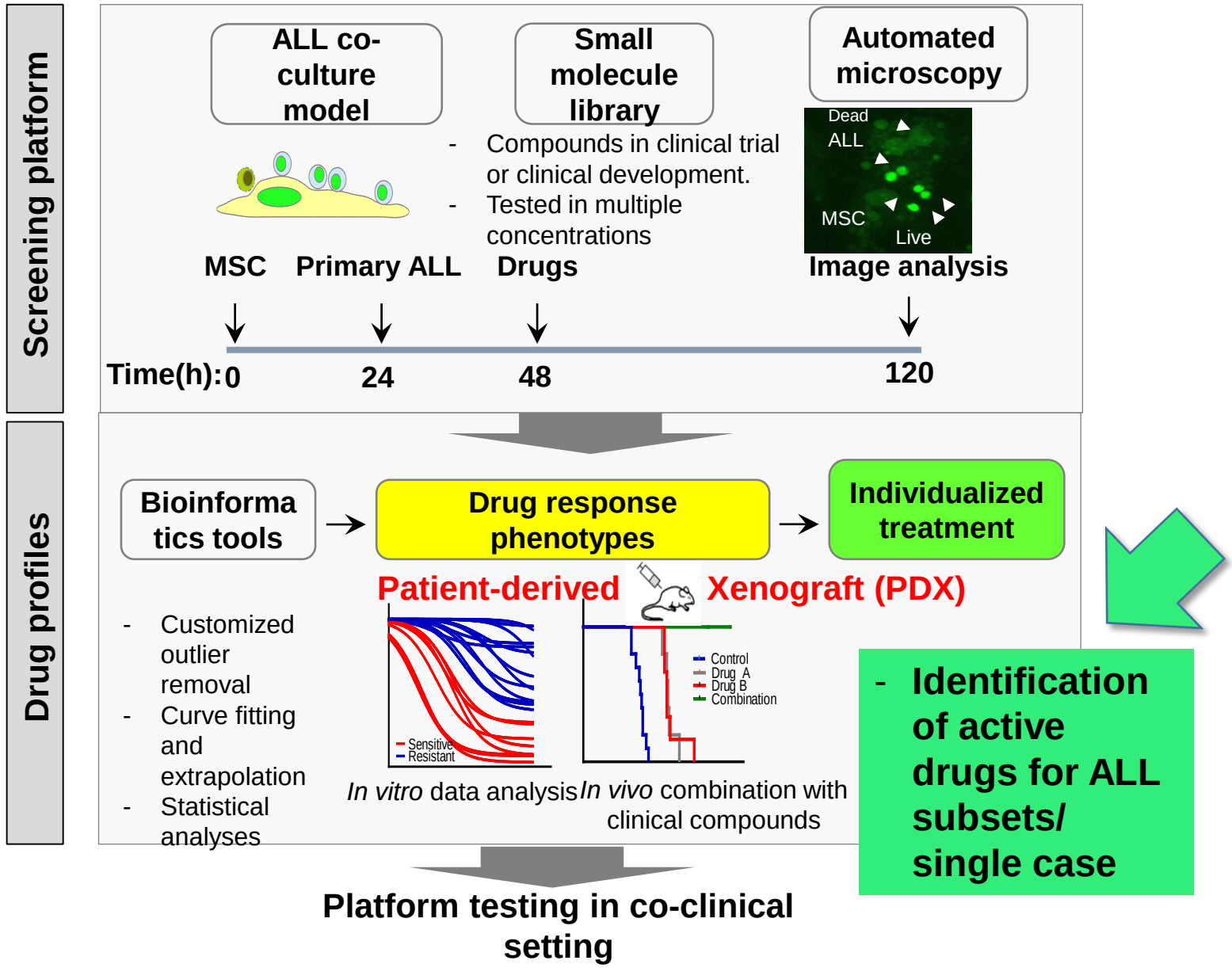
Clinical trials with NOTCH/GSI inhibitors

- **BMS-90602/GSIi (Phase I)[1]**
- N 25 adults with R/R T-ALL(LBL)
  - 8 (32%) ≥ 50% BM blasts reduction
  - CR 1 + PR 1
  - 44% drug-related diarrhea (only 1 G3)
  - 1 G3 hepatotoxicity (dose-limiting, 4 mg)

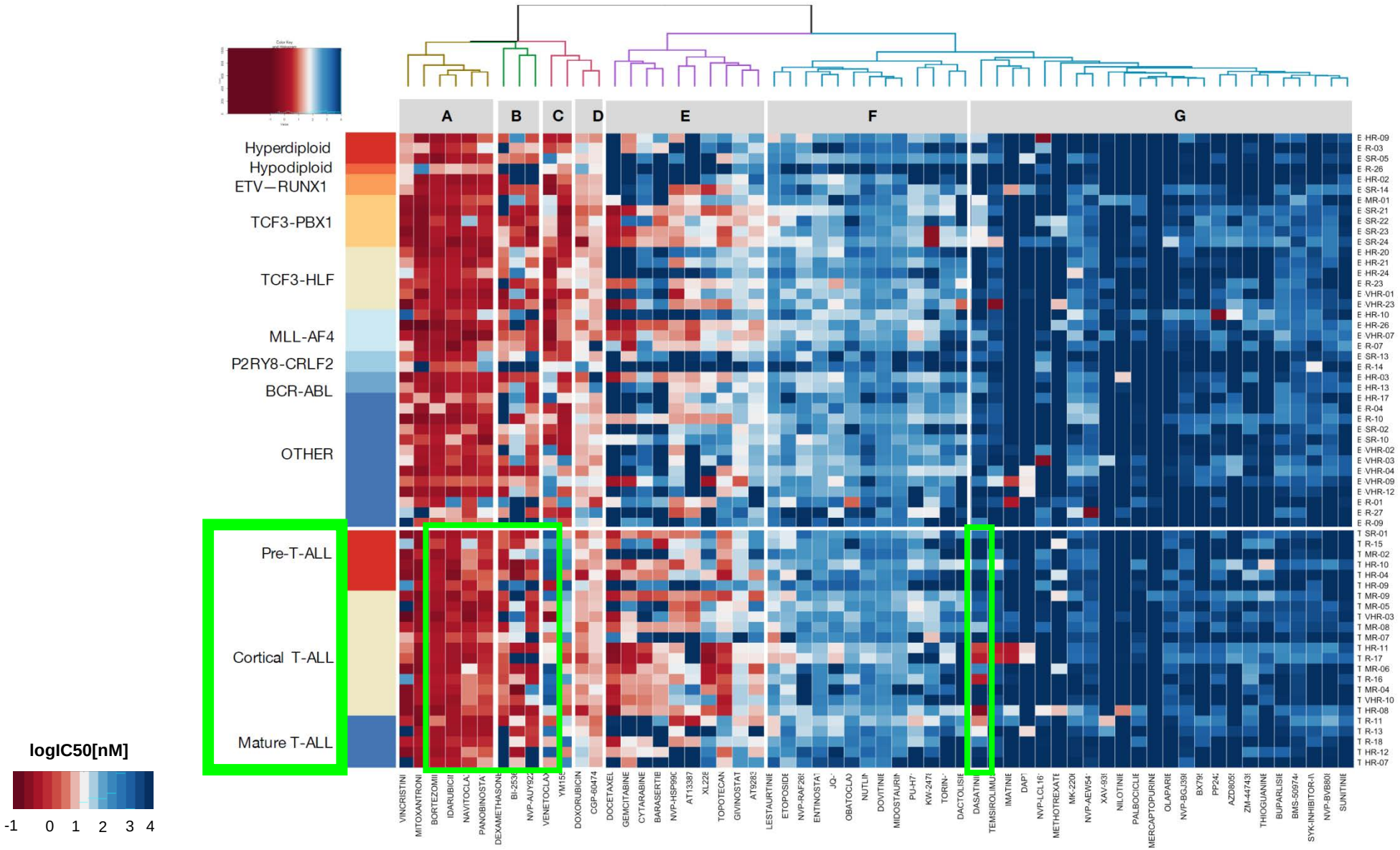


- [1]Zweidler-McKay PA et al, Blood 2014;124:968 (abstr);

Patient-derived xenografts (PDX) and new drug profiling platforms

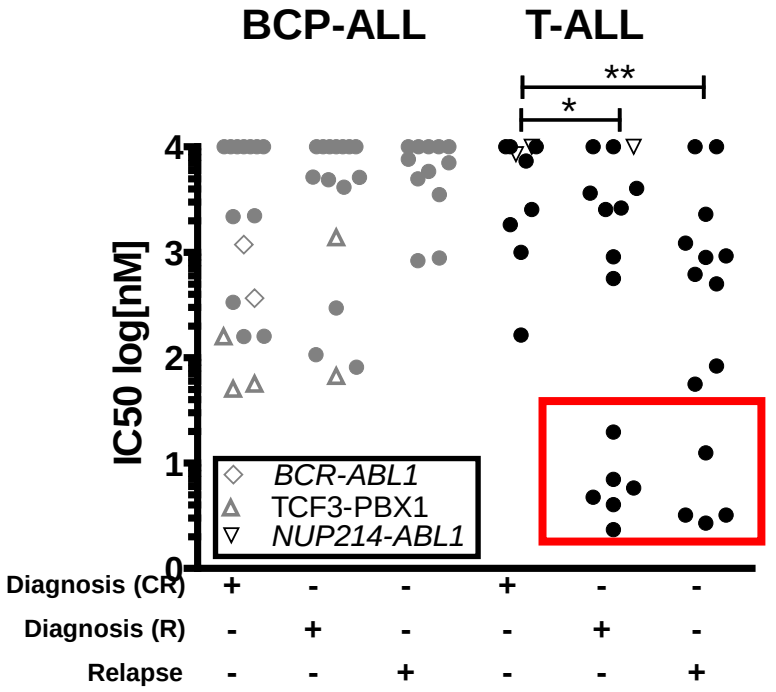


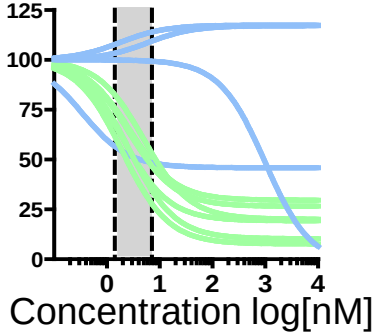
Courtesy JP Bourquin (Zurich, CH)
EHA 2016


A
B
C
D
E
F
G
Hyperdiploid
Hypodiploid
ETV—RUNX1
TCF3-PBX1
TCF3-HLF
MLL-AF4
P2RY8-CRLF2
BCR-ABL
OTHER
Pre-T-ALL
Cortical T-ALL
Mature T-ALL
logIC50[nM]
-1 0 1 2 3 4
Bortezomib
Navitoclax
Panobinostat
Venetoclax
Dasatinib

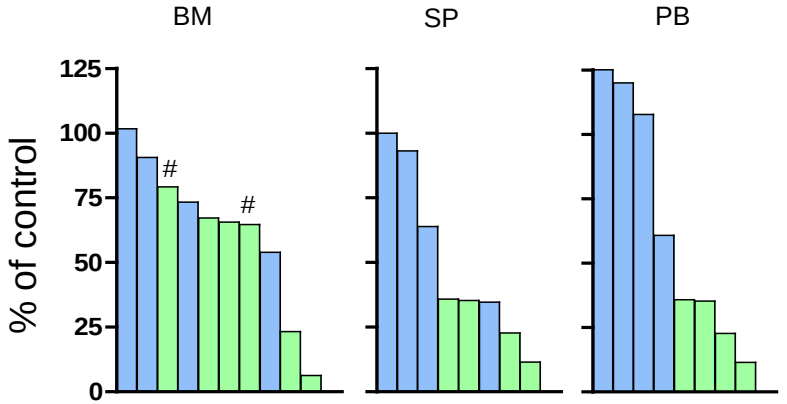
Extraordinary responses to Dasatinib in T-ALL

in vitro





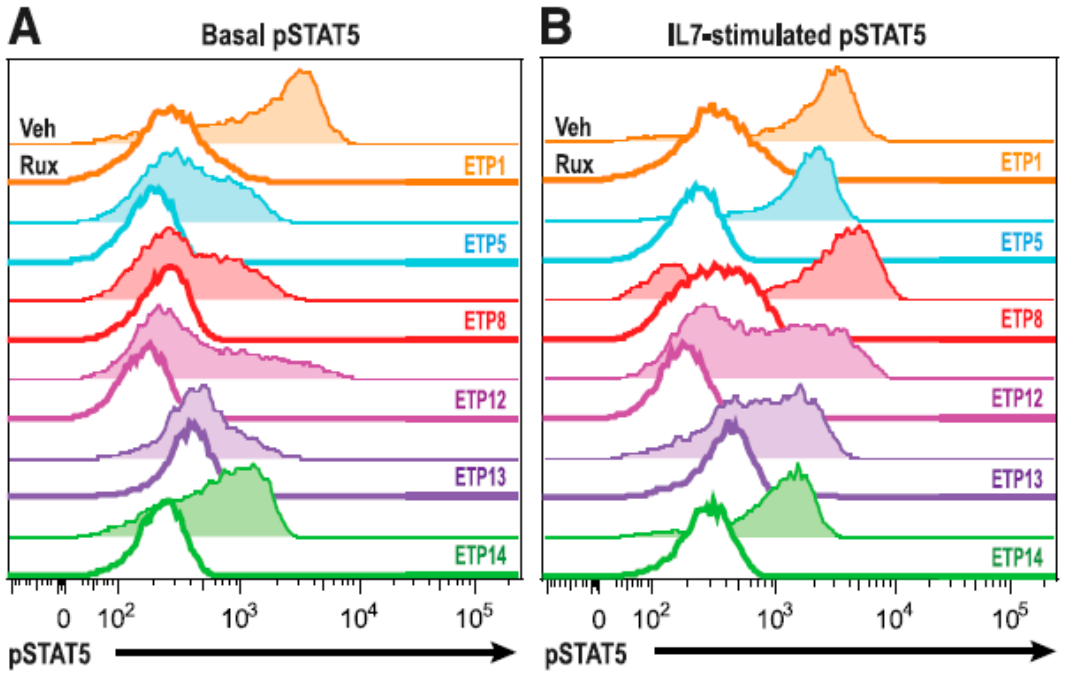
in vivo in T-ALL PDX

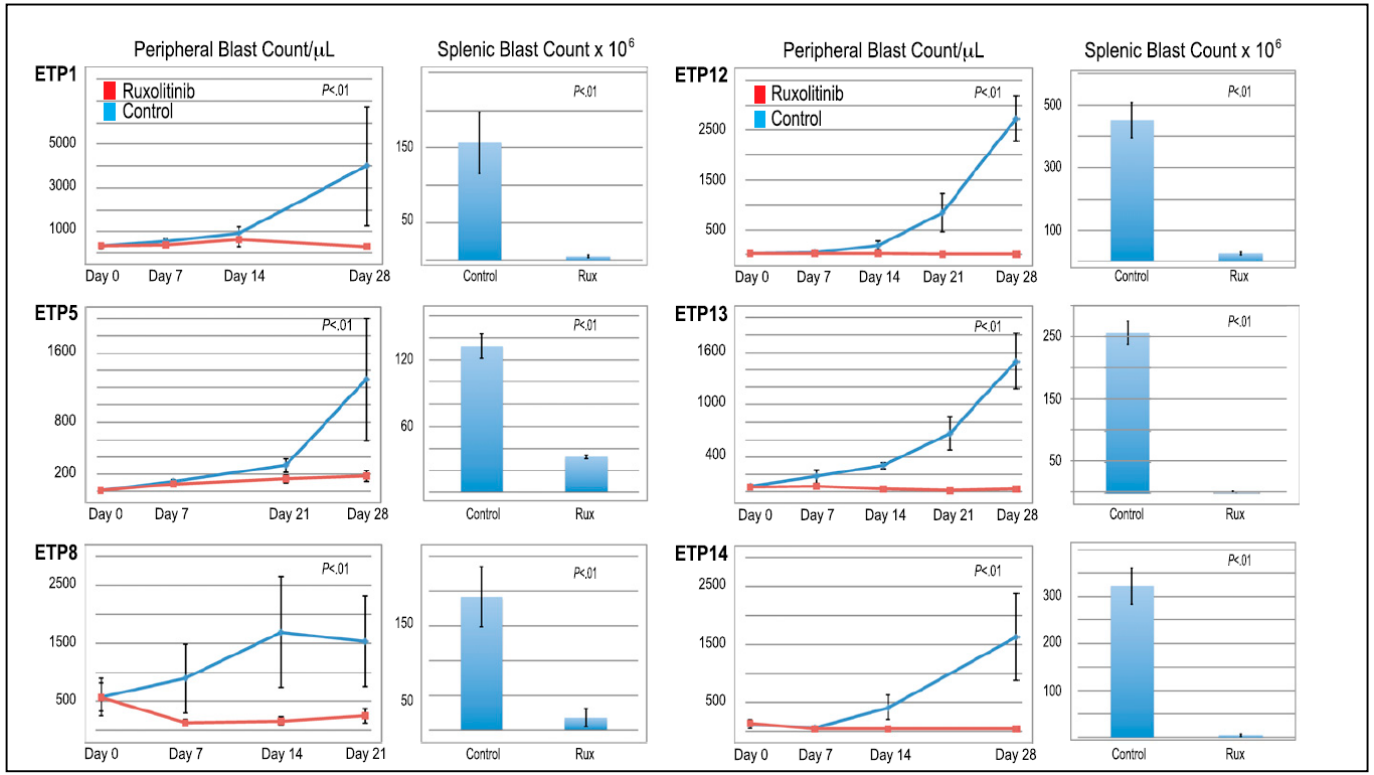


Cells detected after 5 day treatment in vivo

Efficacy of **JAK/STAT pathway inhibition** in murine xenograft models of **early T-cell precursor (ETP) ALL**

RUXOLITINIB abrogates IL7-induced STAT5 phosphorylation and inhibits ETP ALL growth in PDX model





Maude SL et al, **Blood** 2016

Ongoing registered clinical trials with exp. targeting agents in AYA/adult T-ALL (from ClinicalTrials.gov)

Institution/trial denomination	ClinicalTrials.gov identifier	Patient age (y) and no. (n)	Exp. study drug	Other drug(s)	Trial design	Primary objective/outcome measures
Relapsed/refractory						
Washington University/ 201606146	NCT02763384	18+ (n=20)	**BL-8040 (CXCR4 inhibitor)**	Nelarabine	Phase II	Safety and tolerability
Ely Lilly and Co./14548	NCT02518113	2+ (n=92, including adults)	**LY3039478 (NOTCH inhibitor)**	Dexamethasone	Phase I/II	Dose limiting toxicities/CR
Sanofi/ACT14596	NCT02999633	16+ (n=39)	**Isatuximab (CD38)**	No	Phase II	Objective response rate
Untreated						
NCI/AALL1231	NCT02112916	Age 2-30 (n=1400), including AYA	**Bortezomib**	Intensive, BFM-type chemo	Phase III	Improved event-free survival

Ongoing registered clinical trials with exp. targeting agents in AYA/adult ALL, unselected type (from ClinicalTrials.gov)

Institution/trial denomination	ClinicalTrials.gov identifier	Patient age (y) and no. (n), ALL subset	Study drug(s)	Associated chemotherapy	Trial design	Primary objective/outcome measures
Relapsed/refractory						
Children's Mercy Hospital/MERCY01	NCT02535806	1-39 (n=10), including AYA	**Bortezomib**	Yes	Phase II	Adverse events
OHSU Knight Cancer Institute/IRB00007195	NCT01620216	18+ (n=24), including non-lymphoid leukemia	**Dasatinib or Nilotinib or Sunitinib or Sorafenib or Ponatinib (based on kinase inhibition profile obtained on primary patient samples)**	No	Phase II	Clinical activity (decrease of at least 25% in bone marrow blast counts)
Daiiki Sankyo/DS3032-A-U102	NCT02319369	18+ (n=100), including non-lymphoid leukemia	**DS302-b (mdm2 inhibitor)**	No	Phase I	Maximum tolerated dose
NCI/150093	NCT02390752	3-35 (n=45), including AYA, non-lymphoid leukemia/other tumors)	**PLX3397 (multi-targeted TKI)**	No	Phase I/II	Determine phase II dose/antitumor activity
University of Washington/9226	NCT02551718	3+ (n=15), including adults, non-lymphoid leukemias, prior exhaustion of two treatment lines	**Various agents* (based on high throughput drug sensitivity assay)**	Various agents	Pilot	Feasibilty within 21 days (drug combination)

*Afatinib, arsenic trioxide, axitinib, bexarotene, bosutinib, cabazitaxel, cabozantinib, carfilzomib, ceritinib, crizotinib, dabrafenib, dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ponatinib, rapamycin, regorafenib, romidepsin, ruxolitinib, sorafenib, sunitinib, temsirolimus, trametinib, tretinoin

Conclusions

- **The management of adult T-ALL**: however difficult, things are improving and changing, justifying hope
- **New treatments** (soon) available
  - ? More effective
  - ? Less toxic
  - ? Dual, multiple TT and TT/chemo combo
  - **TT to be exploited frontline** (R/R highly disappointing) **in a patient- and subset-specific fashion**

THANK YOU