Conclusiones de
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Leucemia aguda linfoblástica

JM Ribera
ICO-Hospital Germans Trias i Pujol
Badalona

Main issues

- ✓ **Minimal residual disease**
- ✓ Ph+ ALL
- ✓ ALL in adolescents and young adults
- ✓ ALL in elderly patients
- ✓ Burkitt ALL
- ✓ T-ALL
- ✓ Hematopoietic stem cell transplantation
- ✓ New drugs

Response to therapy according to MRD in adult ALL

Updated NILG data. Bassan et al, #2493

MRD^{pos} : level (PCR) of 10^{-4} or greater at week, 10, 16 or 22

Groups:

- MRD^{neg}: always MRD^{neg}
- MRD^{pos1} less than 10^{-4}
- MRD^{pos2} 10^{-4} and greater but less than 10^{-3}
- MRD^{pos3} 10^{-3} and greater

Patients: 304 registered, 136 with data at the 3 time points

	MRD^{neg}	MRD^{pos1}	MRD^{pos2}	MRD^{pos3}
OS (6yr), %	72	56	48	23
DFS (6yr), %	64	57	46	15
RR (6yr), %	36	32	50	76
DFS, Allo SCT%		60		18

- With long f-u, level of MRD retains the prognostic influence
- Poor results after Allo HSCT in patients with the highest MRD+ level

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Ph+ ALL. “More imatinib, less chemotherapy”

Randomized study from GRAALL (Chalandon et al, #138)

	I-800 VD	I-800 HCVAD	p
N	133	132	
Induction mortality	1	9	0.01
CR	98%	89%	0.003
MRD <0.1% end induction	44%	46%	0.79
MRD neg. end induction	10%	10%	
MRD <0.1% end consolidation	68%	63.5%	0.56
MRD neg end consolidation	28%	22%	0.33
EFS at 3 yr.	46%	38%	0.25
OS at 3 yr.	53%	49%	0.61
Allo HSCT	80	77	
Auto HSCT	17	17	
OS after allo in MRD <0.01% post-cons.	58%		0.08
OS after auto MRD <0.01% after cons.	69%		

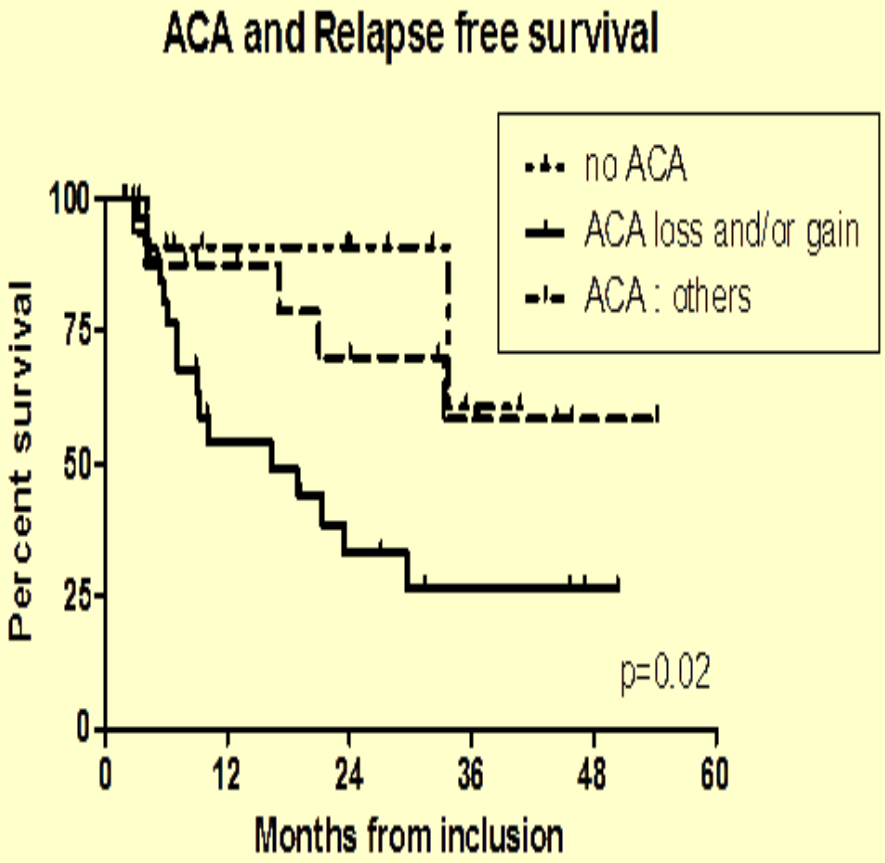
- Chemotherapy intensity may be safely reduced when associated with high-dose IM

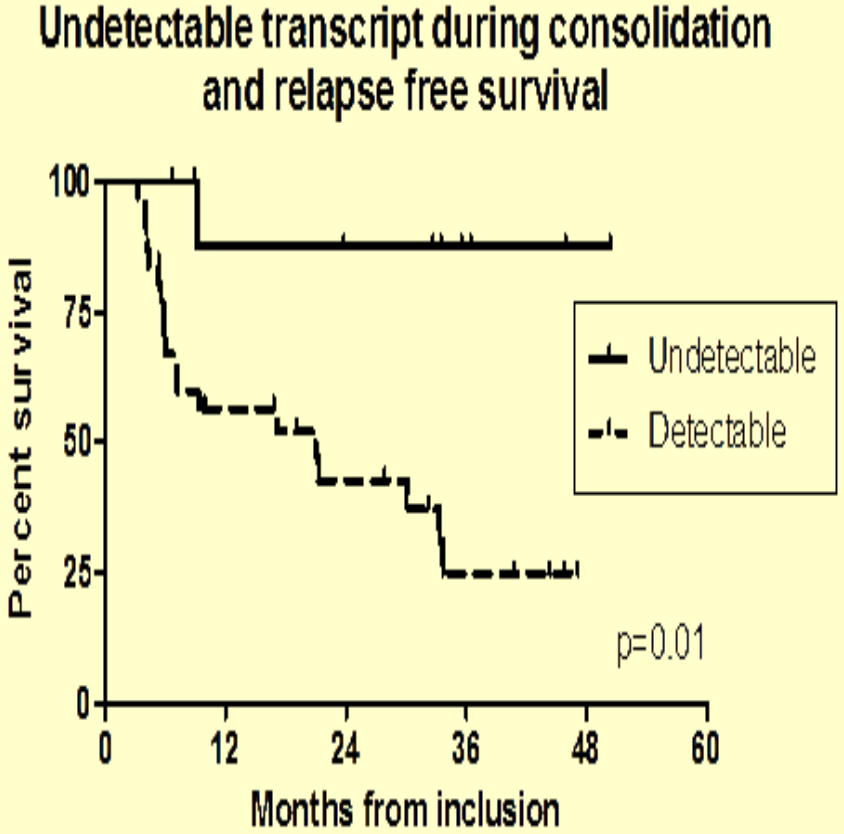
Dasatinib + low-intensity chemotherapy in elderly Ph+ ALL

EWALL-Ph-01 Phase II study, final results. Rousselot P, et al, #666

	Patients (n=71), median f-u 3.3 yr
Median age, yr	69 (58-83)
ACA	75%
Death in induction	3
CHR	67 (94%)
MMR / CMR	54% / 22%
Relapses, n, median	29, 9 mo. (3-34)
RFS / OS (95%CI)	43% (27%-58%) / 45% (32%-57%)
ABL mutations, %, T315I ,%	89%, T315I 63%

- Relapses associated with T315I mutation in most cases
- Kinetics of the T315I signal predicted relapse 3-6 months later
- ACA and BCR-ABL level at maintenance predicted RFS


ACA and Relapse free survival
no ACA
ACA loss and/or gain
ACA : others
Percent survival
100
75
50
25
0
0
12
24
36
48
60
Months from inclusion
p=0.02


Undetectable transcript during consolidation and relapse free survival
Undetectable
Detectable
Percent survival
100
75
50
25
0
0
12
24
36
48
60
Months from inclusion
p=0.01

3rd generation TKI inhibitors in Ph+ ALL. Ponatinib

PACE Trial, Phase 2, open-label clinical trial in Ph+ leukemia. 12 mo. f-u
Kantarjian et al, #915

Pts resistant or intolerant (R/I) to dasatinib or nilotinib,or T315I mutation at baseline

	AP-CML		BP-CML		Ph+ ALL	
	R/I N=65	**T315I** N=18	**R/I** N=38	**T315I** N=24	**R/I** N=10	**T315I** N=22
MaHR	58%	50%	32%	29%	50%	36%
MCyR	34%	56%	18%	29%	60%	41%
CCyR	22%	33%	16%	21%	50%	32%
PFS in MaHR (median)			4.5 mo.			
OS in MaHR (median)			7.5 mo.			

Treatment-related AE: thrombocytopenia (29%), rash (25%), neutropenia (22%).
SAE: thrombocytopenia (3%) and pancreatitis (3%).

Accelerated FDA approval of Ponatinib

On December 14, 2012, the U.S. Food and Drug Administration granted accelerated approval to ponatinib (Iclusig™ tablets, ARIAD Pharmaceuticals, Inc.) for the treatment of adult patients with

- Chronic myeloid leukemia in
  - Chronic phase
  - Accelerated phase
  - Blast phase

  that is resistant or intolerant to prior tyrosine kinase inhibitor therapy

- **Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)** that is resistant or intolerant to prior tyrosine kinase inhibitor therapy

FDA required that the sponsor commit to submit 24-month follow-up data for all patients as a condition for the accelerated approval.

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Moderately intensive chemotherapy in elderly ALL

GMALL study. Goekbuget, et al, #1493, n= 268 Ph- ALL)

Group 1: Standard CHT + rituximab (CD20+)
Grroup 2: Modified CNS prophylaxis (Depocyte, ↑MTX), *E coli* ASP
Group 3: Standard CNS prophylaxis. PEG-ASP

	Overall (n=268)	Group 1 (n=180)	Group 2 (n=43)	Group 3 (n=45)
CR, %	76	72	86	82
ED, %	14	18	0	11
Failure, %	10	10	14	7
OS, %	23 (5yr)	33 (2yr)	52 (2yr)	Too early
Death in CR, %	6			
Withdrawn in CR, %	15			
CCR probability, %	32 (5yr)	42 (2yr)	43 (2yr)	Too early

- Good CR with low ED, esp. in the CNS Depocyte prophylaxis group (lower ED)
- Moderate intensive consolidation feasible. ASP, and PEG-ASP, well tolerated.
- Age correlated with outcome and 75 yrs. is the upper limit for this regimen

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Burkitt's leukemia/lymphoma
Rituximab + specific intensive chemotherapy

GMA LL (Hoelzer, #667) and NILG (Intermesoli T, #1494)

	GMALL		NILG	
	B-NHL(n=229)	B-L (n=134)	B-NHL (n=55)	B-L (n=50)
Stage III-IV	53%	100%	53%	100%
CR	182 (91%)	162 (86%)	79%	
OS	88% (7yr)	90%/71%/46%	67%	
PFS	83% (7yr)		75% (DFS, 3-yr)	
Prognostic factors	aaIPI	Age, Plts <25000/µL	Age, PS	

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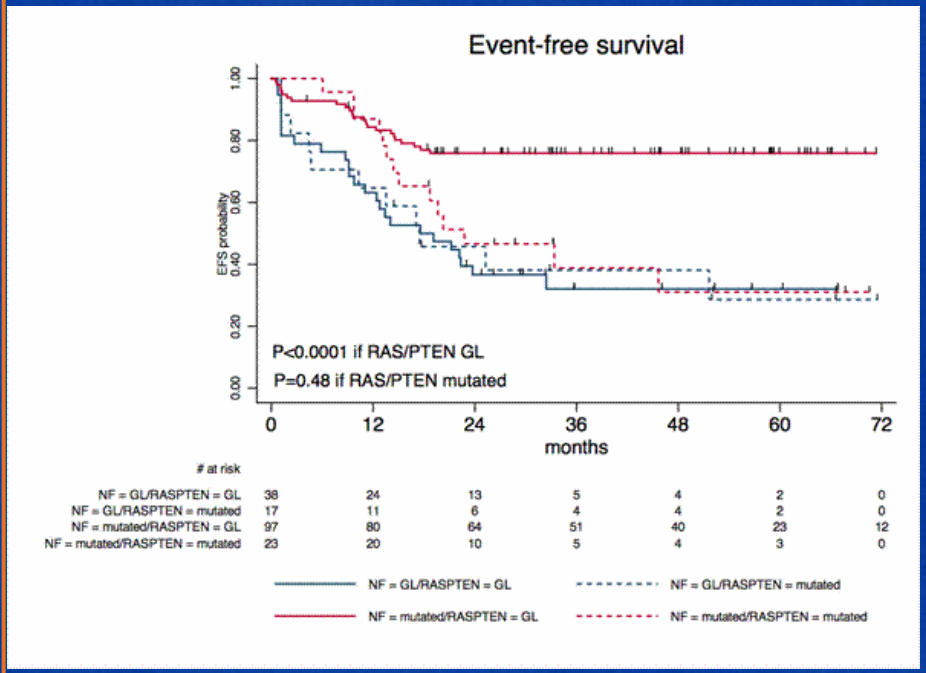
Oncogenetic risk classification in T-ALL

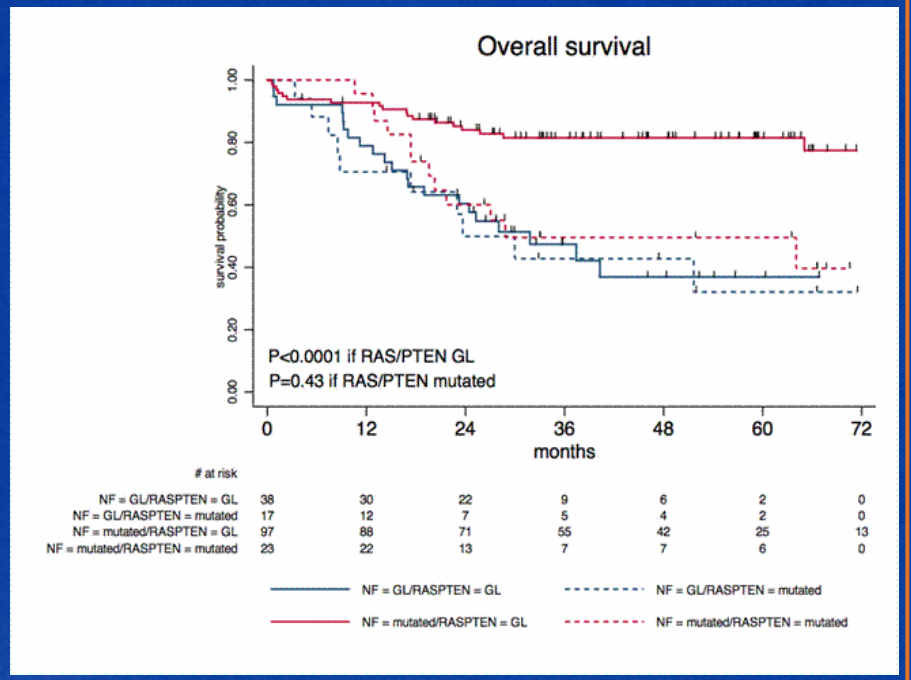
GRAALL 2003 and 2005 studies. Trinquand A, et al. # 881

Mutated genes	Frequency (n=198)
NOTCH1/*FBXW7* (N/F)	143/198 (67%)
N-RAS	3/191 (1.6%)
K-RAS	17/191 (8.9%)
PTEN	17/175(9.7%)

Risk category	Feature	Frequency
Low	N/F mutation and no *RAS*/*PTEN* mutation	97/189 (51%)
High	Remaining	92/189 (49%)

- Detection of *RAS* and *PTEN* mutations add significant prognostic value to the assessment of the *NOTCH1*/*FBXW7* status
- 50% of adults with T-ALL have good prognosis according to this genetic risk classification
- This oncogenetic classification remained the only prognostic factor


Event-free survival
EFS probability
0.00
0.20
0.40
0.60
0.80
1.00
P<0.0001 if RAS/PTEN GL
P=0.48 if RAS/PTEN mutated
0
12
24
36
48
60
72
months
# at risk
NF = GL/RASPTEN = GL 38 24 13 5 4 2 0
NF = GL/RASPTEN = mutated 17 11 6 4 4 2 0
NF = mutated/RASPTEN = GL 97 80 64 51 40 23 12
NF = mutated/RASPTEN = mutated 23 20 10 5 4 3 0
NF = GL/RASPTEN = GL
NF = GL/RASPTEN = mutated
NF = mutated/RASPTEN = GL
NF = mutated/RASPTEN = mutated


Overall survival
survival probability
0.00
0.20
0.40
0.60
0.80
1.00
P<0.0001 if RAS/PTEN GL
P=0.43 if RAS/PTEN mutated
0
12
24
36
48
60
72
months
# at risk
NF = GL/RASPTEN = GL 38 30 22 9 6 2 0
NF = GL/RASPTEN = mutated 17 12 7 5 4 2 0
NF = mutated/RASPTEN = GL 97 88 71 55 42 25 13
NF = mutated/RASPTEN = mutated 23 22 13 7 7 6 0
NF = GL/RASPTEN = GL
NF = GL/RASPTEN = mutated
NF = mutated/RASPTEN = GL
NF = mutated/RASPTEN = mutated

Genetic profiling and prognosis in T-ALL in adults

ECOG E2993 protocol. Van Vlierberghe P et al, #294

N= 53,T-ALL treated according to ECOG E2993 protocol
T oncogenes: *NOTCH1*, *IL7R*, *FLT3*, *NRAS*
Tumor suppressor genes: *FBXW7*, *PTEN*, *DNM2*, *PHF6*, *BCL11B*, *WT1*, *EZH2*, *ETV6*, *IDH1*, *IDH2*, *DNMT3A*, *GATA3* and *RUNX1*

Unsupervised analysis: 2 signatures
- Early T (n=28, stem cell and myeloid markers, poor prognosis, esp. CD13)
- Cortical/mature (n=25, better prognosis)

Array CGH analysis
- Absence of biallelic deletion TCRγ (n=27, early T (22/27), poor prognosis
- del p17 (*TP53*): poor prognosis
- Homozygous del p19 (*CDKN2A/CDKN2B*): good prognosis in cortical/mature

Mutation analysis
Good prognosis: Mutations in *NOTCH1* and/or *FBXW7,* heterozygous inactivating mutations or deletions in the *BCL11B* tumor suppressor gene
Poor prognosis: somatic mutations in *DNMT3A* and *IDH1/2.*

Multivariate analysis
Good prognosis: *NOTCH1* and/or *FBXW7* mutations
Poor prognosis:*TP53* deletions and *DNMT3A* mutations
Cortical/mature: *CDKN2A/CDKN2B* deletions good. CD13: poor
Early T: *DNMT3A* mutation, poor

Nelarabine in 1st-line therapy of T-ALL and LL

Phase II study from MDACC. Jain P et al, #1501

HCVAD
Nelarabine 650 mg/m^2/d x 5d, 2 cycles during consolidation, 2 in maintenance

	Patients (n=36)
T-ALL / T-LL	21 (58%)/ 15(42%)
CR	33 (92%)
MRD neg in CR (T-ALL) (FCM)	8/15 (53%)
CR duration (3-yr)	66%
OS (3-yr)	62%
G 1-2 Peripheral neuropathy	16 (44%)
At least 1grade ≥3 infection	30/36 (83%)
Thrombosis	6 (17%)
Nelarabine dose reduction/withdrawal	2 / 1

- Nelarabine can be safely combined with HCVAD
- Nelarabine + HCVAD is active and can achieve MRD-negative CR
- Up to now, no difference in survival vs. HCVAD alone

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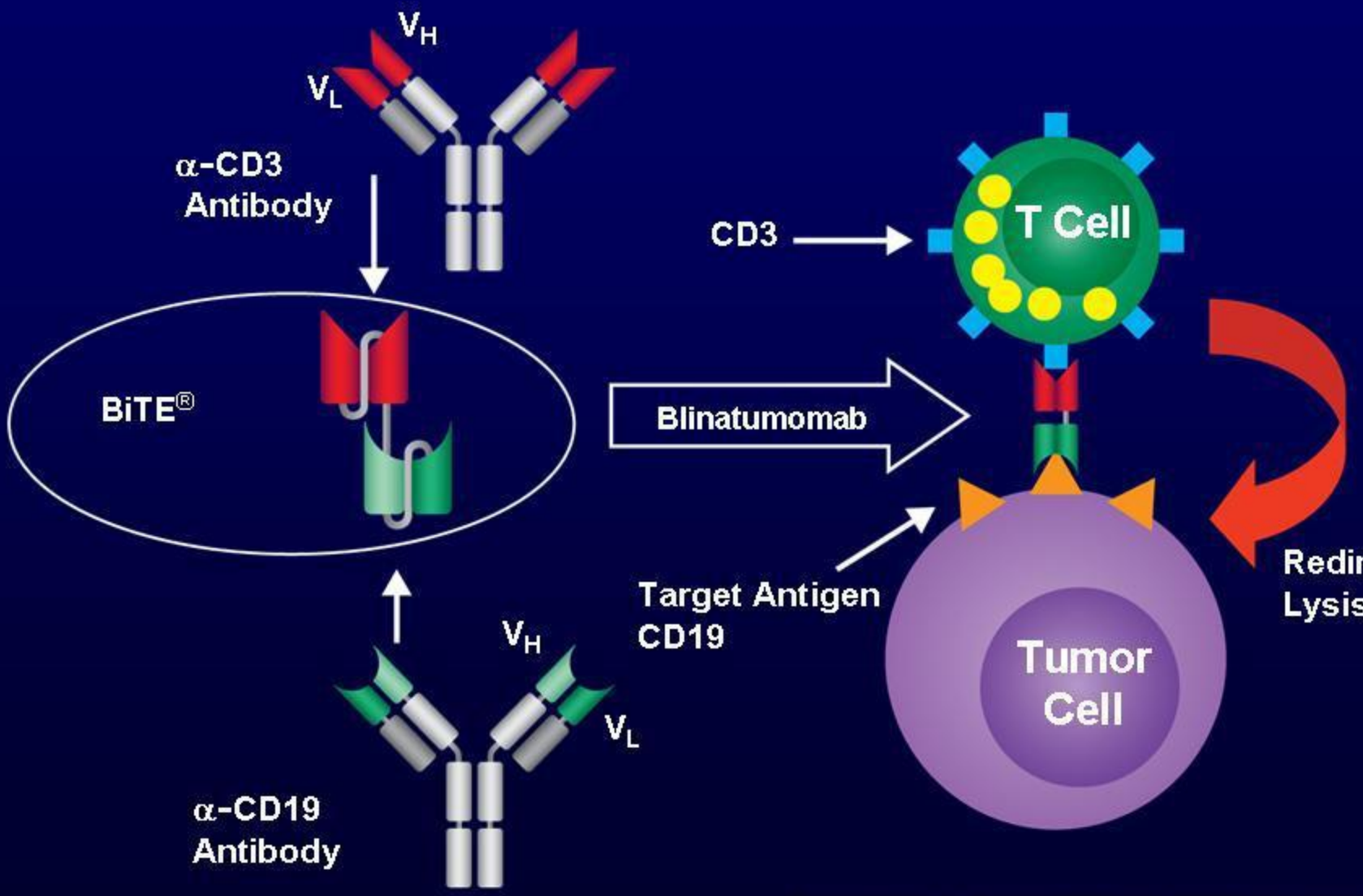
New drugs

- Clofarabine combined with MoAb (#2603)
- L-ASP-loaded red blood cells (#1473)
- PEG *Erwinia*-derived L-ASP (#2571)
- Monoclonal antibodies
  - Unconjugated: Rituximab in B-precursor ALL (#3572)
  - Bispecific: Blinatumomab (#670)
  - Conjugated with immunotoxoins. Inotuzumab ozogamycin (#671, #2612)
- mTOR inhibitors: Everolimus (#3567)
- Bruton tyrosine kinase inhibitors: Ibrutinib (#2569)
- Proteasome inhibitors: bortezomib (Education session)
- Aurora kinases A and B (#1465)
- Survivin blockers: EZN3042 (Education session)
- Epigenetic therapy: vorinostat, decytabine, vorinostat+decytabine (Education session)
- Autologous T cells engineered to express CD19-directed chimeric T-cell receptor (CART19)(Education session, #3566)

Blinatumomab (MT103), a Bispecific T Cell Engaging BiTE® Antibody



Topp MS, et al. *Blood*. 2010;116(21):79-80 [abstract 174].

Blinatumomab

Phase II study on Blinatumomab in R/R ALL. Topp MS, et al, #670

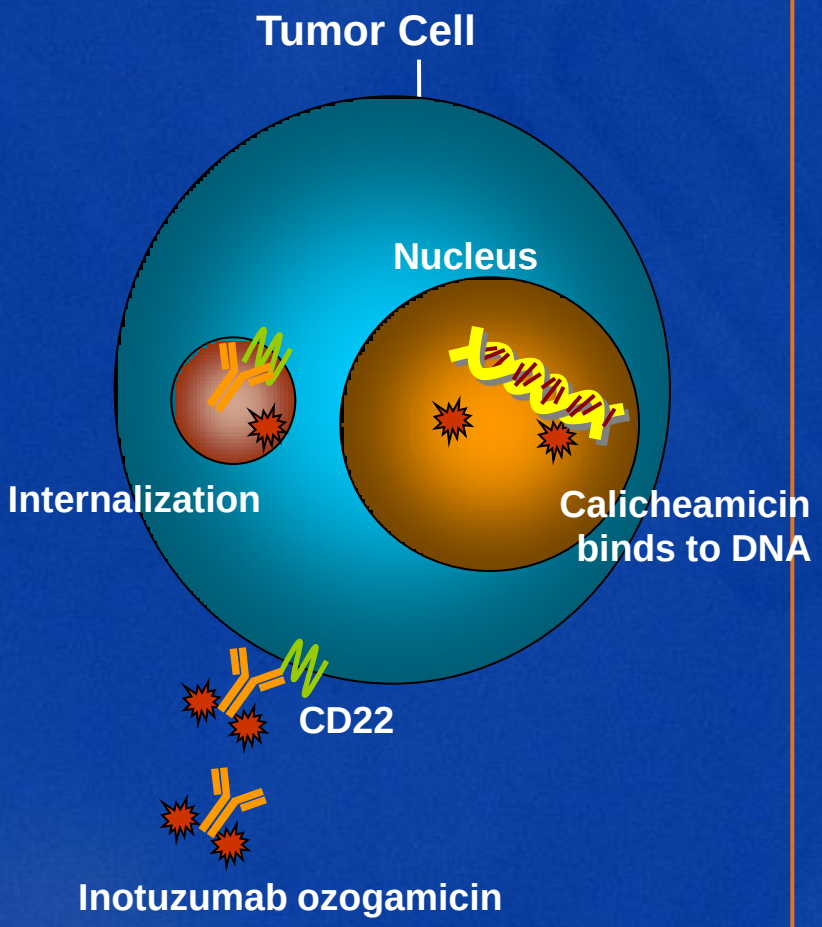
- Continuous IV infusion for 28 d followed by a 14-d treatment-free interval.
- Responding pts had the option to receive 3 additional cycles of treatment or alloHSCT.

	Patients (N=36)
ORR (CR/CRh)	26/36, 72% (62%/38%)
MRD<10^{-4} within 2 cycles	24/26 (92% of responders)
ORR pts 1st relapse	20/21 (95%)
ORR pts > 1st relapse	6/15 (40%)
AlloHSCT in CR/CRh	13 → 1 relapse (CD19-)
No AlloHSCT	13 → 8 relapses (3 extram., 2 CD19-)
Median OS, overall/ CR / NR	9 / 14 / 6 months
Optimal dose regimen	5 µg/m²/d in wk 1, 15 µg/m²/d for the remaining treatment (80%ORR)

- The final dosing regimen produced high CHR / MolR rates and was well-tolerated
- A global phase II study to confirm these data is being conducted

Inotuzumab in ALL. Mechanisms of Action

- Antibody-antigen complex rapidly internalized upon binding to CD22
- Calicheamicin released inside the tumor cell; more potent than other cytotoxic chemoRx agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- Development of DNA breaks followed by apoptosis of tumor cell



Inotuzumab ozogamycin

MDACC. Comparison of efficacy and toxicity of two schedules. O'Brien S, #671

	1.3-1.8 mg/m2 q3-4 wk	0.8 mg/m2 d1, 0.5 mg/m2 d 8, 15 q3-4 wk
N pts.	49	34
ORR	28/49 (57%)	18/34 (53%)
ORR salvage 1 vs. other **Ph+, t(4,11) vs. other**	71% vs. 49% 39% vs.62%	
Cytog. response in ORR pts	25/28 (89%)	
MRD neg (FCM) in ORR pts	28/44 (64%)	
Median OS	5.0 mo	6.3 mo.
G 1-2/3-4 bilirubin ↑	24% / 4%	3% / 0%
G 1-2/3-4 liver enzymes ↑	55% / 2%	21% / 6%
HSCT	22/49 (49%)	9/34 (26%)(ongoing f-u)
VOD	5/22 (23%)	1/9 (11%)

- Inotzumab highly active in R/R ALL
- Weekly dose appears to be equally effective and less toxic than single dose

Autologous T cells engineered to express CD19-directed chimeric T-cell receptor (CART19)

Principle: Use of gene transfer technology to introduce genes encoding chimeric antigen receptors (CAR) anti CD19 attached to the TCR in T-cells. These effector cells are redirected to target Ags expressed by leukemic cells (i.e, CD19).

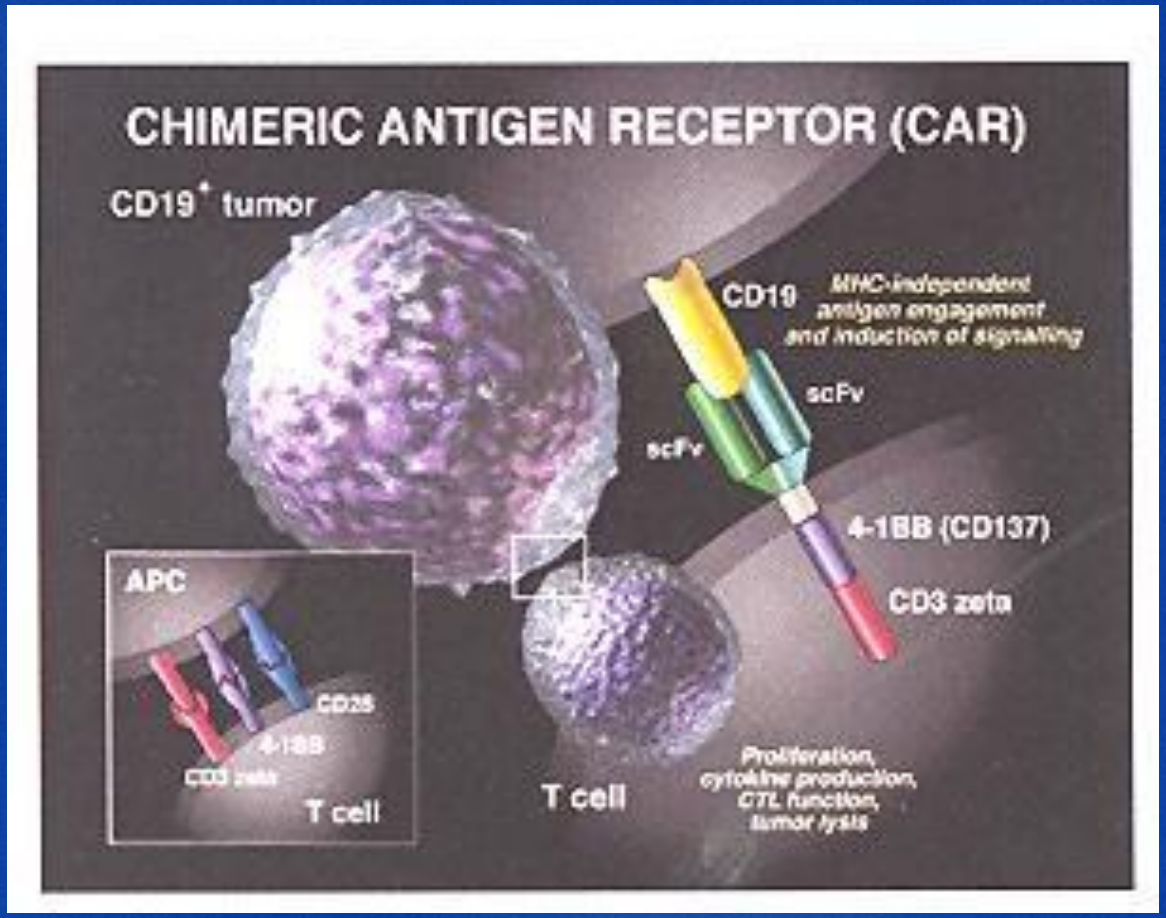
Composition of 2nd generation CARTs: Ag-specific binding domain (signal 1 reaction) + transmembrane domain + cytoplasmic signaling domains

Types according to the effector cells: Autologous T-cell CART, Allogeneic T-Cell CART, Haploidentical NK CART.

Current status: Variability in gene transfer methods, CART design, prior conditioning chemotherapy, cytokine support after CART

Trials with CARTs: ALL(#3566), CLL, NHL

CART19


CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent antigen engagement and induction of signaling
scFv
scFv
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation, cytokine production, CTL function, tumor lysis