NUOVI FARMACI E TRAPIANTO

Udine 21-22 gennaio 2016

Integrazione dei nuovi farmaci nel programma trapiantologico della leucemia linfoblastica acuta: UN CASO CLINICO…PEDIATRICO

"Which ALL" is eligible for HSCT?

- 10% of children with very high risk ALL in CR1
- all S3/S4 CR2 (early medullary relapses)
- S2 CR2 with high MRD after induction

are eligible for allogeneic stem cell transplantation

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Ospedale San Gerardo, Monza

FONDAZIONE MONZA E BRIANZA
PER IL BAMBINO E LA SUA MAMMA

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4 standard approaches

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

PEDIATRIC ALL "MOLECULAR RELAPSING" AFTER TRANSPLANT

PEDIATRIC ALL HIGH MOLECULAR MRD LEVEL BEFORE TRANSPLANT

PEDIATRIC ALL
RELAPSING AFTER TRANSPLANT

Relapse after HCT in pediatric ALL in CR1 & CR2 EBMT Results – Myriam Labopin

3628 pediatric ALL in CR1 (45%) & CR2 (55%) reported to the EBMT in 10ys

23% out of 3628 relapse at a median of 6.5 ms (range 1-67; 25th: 4; 75th: 12 ms)

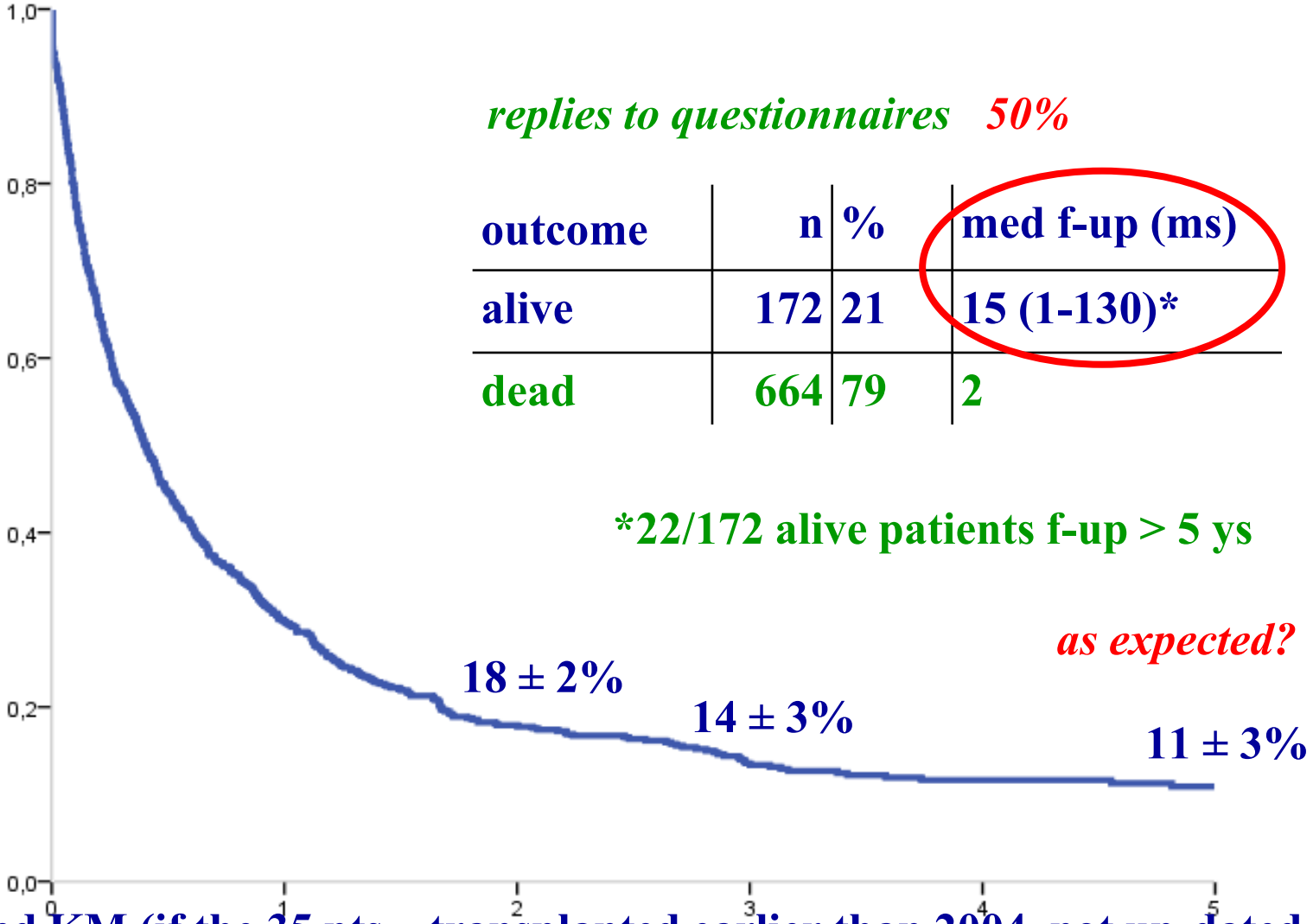
2 yr cumulative incidence of relapse after HCT 25% (SE 1)

incidence of relapse in CR1 21% and CR2 26%

enrolment n = 836 (M 66%, median 9 ys)

Relapse after HCT in pediatric ALL in CR1 & CR2 - Results

Overall Survival



replies to questionnaires 50%

outcome	n	%	med f-up (ms)
alive	172	21	15 (1-130)*
dead	664	79	2

*22/172 alive patients f-up > 5 ys

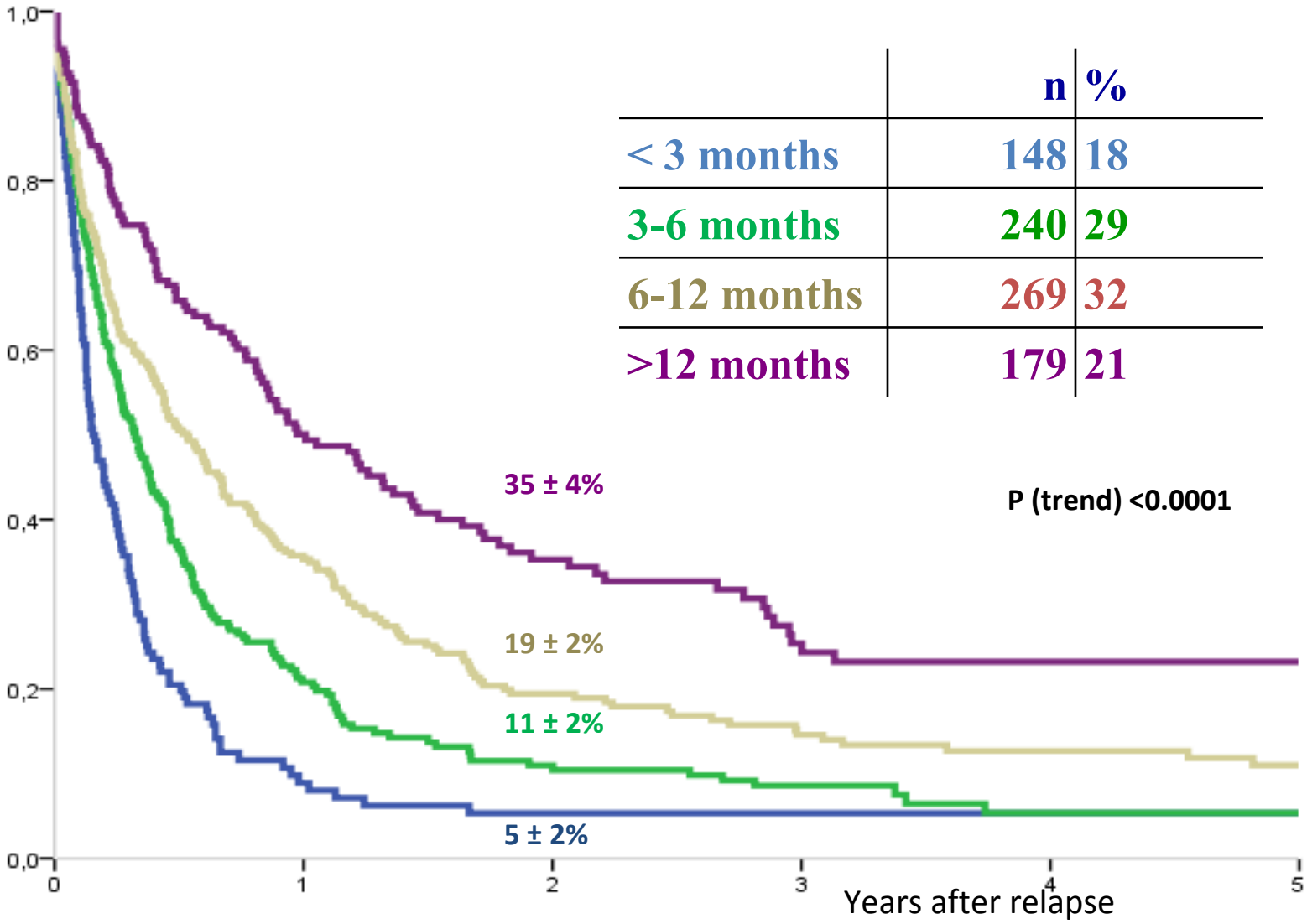
as expected?

§ simulated KM (if the 35 pts – transplanted earlier than 2004, not up-dated after 2005 – all died soon after relapse) OS at 2 years would decrease from 18 to 10%

Relapse after HCT in ALL in pediatric CR1 & CR2 - Results

Survival according to interval from HCT to relapse

	n	%
< 3 months	148	18
3-6 months	240	29
6-12 months	269	32
>12 months	179	21

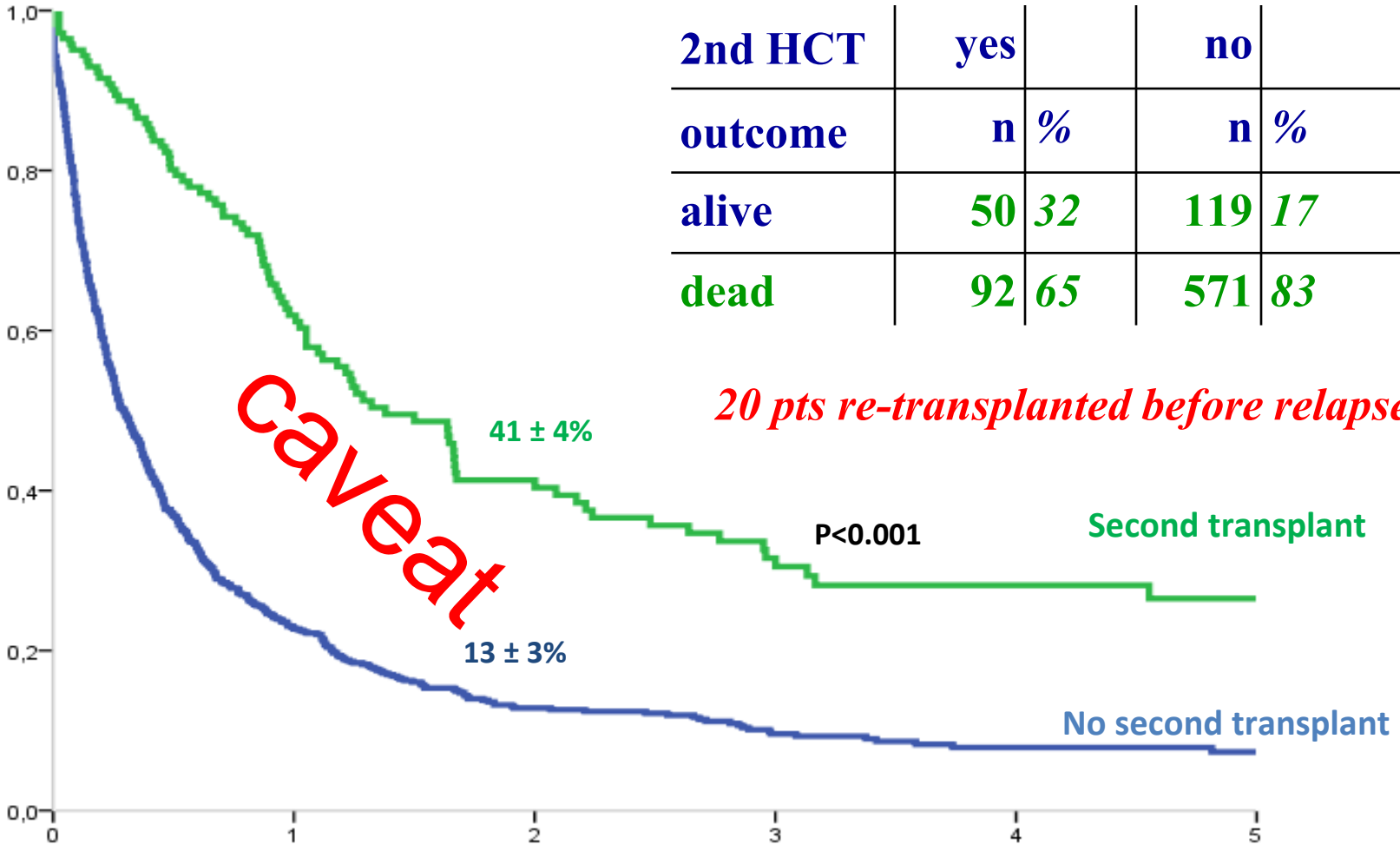


Relapse after HCT in ALL in pediatric CR1 & CR2 - Results

Outcome after second HCT (n=156)

2nd HCT	yes		no	
outcome	n	%	n	%
alive	50	*32*	119	*17*
dead	92	*65*	571	*83*

20 pts re-transplanted before relapse…



preliminary multivariate analysis for 2nd HCT
HR 1.32 (0.98-1.78) p-value 0.072

Relapse after HCT in pediatric ALL in CR1 & CR2 - Results

Multivariate analysis

variable		HR	95% CI		p-value
			lower	upper	
second HCT		*0.76*	0.56	1.02	0.072
interval (ms)	< 3	3.31	2.42	4.52	<0.0001
HCT-relapse	3-6	2.10	1.60	2.77	<0.0001
(vs > 12 ms)	6-12	0.59	1.30	2.23	<0.0001
CR2 vs CR1		*0.73*	1.14	1.67	0.001
T vs B-lineage		*1.69*	1.33	2.13	<0.0001
HLA ident vs other donors		*0.89*	0.93	1.35	0.24

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
1st of 4 approaches

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

- 8 months old
- ALL B-I, MLL germline
- frontline Interfant 06

INTERFANT PROTOCOL

Interfant	I-06 (HR only)				I-99 (HR according to I-06 only)			
	CCR	Rel	TRM	tot	CCR	Rel	TRM	tot
MSD	2	0	1	3	1	4	0	5
MD	12	1	8	21	4	2	1	7
MMD	1	2	2	5	3	1	0	4
tot	15	3	11	29	8	7	1	16

Balduzzi, Udine 21 gennaio 2016

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
1st of 4 approaches

- **8 months old (Dec 2012); ALL B-I, MLL germline→ frontline Interfant 06**
- **17 months after diagnosis: relapse ALL B-II (WBC 60x10^3/mm3; Hb 10,3 g/dl; PTL 77000/mm3; blasts 85%)→ AIEOP REC03**
- **HSCT MUD in 2° CR (5 months after relapse), HLA 10/10; source BM; NCT: $5x10^8$/kg, $CD34^+$ $7x10^6$/Kg; conditioning Bu, Flu, TT; GvHD prophylaxis: CyA, MTX, ATG**
- **aGvHD skin, grade 3, stage II→ mPDN 1mg/Kg (discontinued day +76);**
- **EBV positivity→ 3 Rituximab**

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
1st of 4 approaches

- **8 months old (Dec 2012); ALL B-I, MLL germline→ frontline Interfant 06**
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- **aGvHD skin, grade 3, stage II→ mPDN 1mg/Kg (discontinued day +76);**
- **EBV positivity→ 3 Rituximab**
- **MRD positivity 0,8%→ IS discontinued day +110 → 3 weeks later: mixed chimerism (PB 10% recipient) and morphological relapse (BM blasts 70%) at 4 months after transplant**
- **palliation, as per parental decision**

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
1st of 4 approaches: PALLIATION

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

Case 1 - 2014 palliation

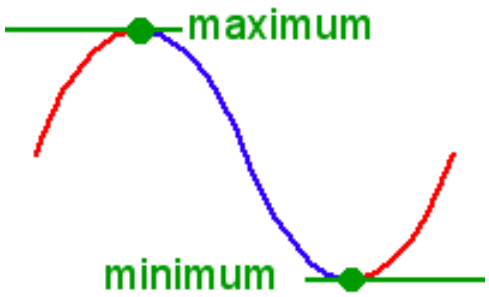
Case 2 - 2014 ?

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches

- **LLA common, SNC neg, trasl neg→ AIEOP BFM ALL 2009, SER→ HR; OT;**
- **+32 ms: isol BM relapse → AIEOP REC 2003.**
- **+5 ms post relapse:**
- **HSCT MSD BM; conditioning TBI, VP16; GvHD prophylaxis: CyA (MTX not given, high risk of relapse)**
- **MRD at transplant 1.2x10^-3**

MINIMAL residual disease & transplantation: *explained to high school students…and husband*

- **Philosophy – Blaise Pascal: "*Infiniment petits*"**
- **Math**



The derivative of f(x) at the point x is equal to the slope of the tangent to y = f(x) at x

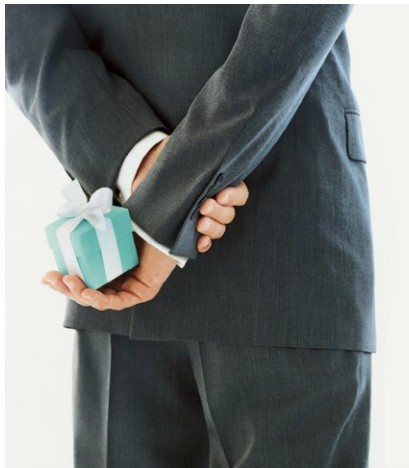
local minimum **where the graph changes from decreasing to increasing: at this point the tangent has** ***zero slope***

- $\lim_{x \to c} f(x) = L$

- **Everyday life**

A man decided to buy a diamond:

"I wonder how such a small thing can cost so much…"

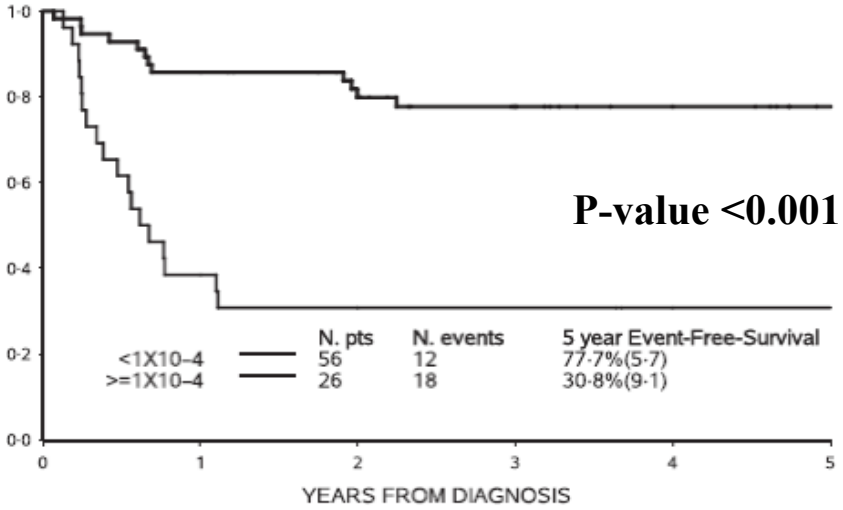


MRD in HCT for ALL – Results

MRD at transplantation: 56 (68%) neg or <1x10^{-4} vs 26 (32%) ≥1x10^{-4}

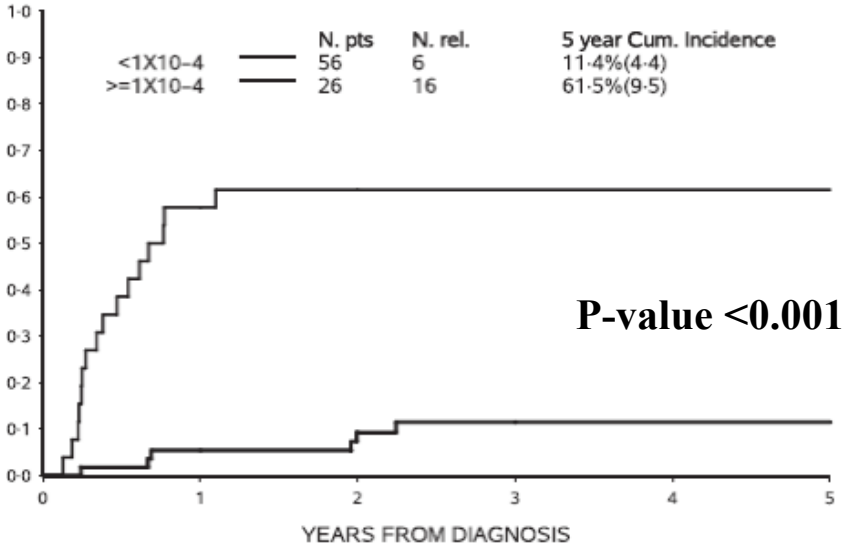
Outcome according to MRD level at transplantation:

EFS



P-value <0.001

CI Relapse



P-value <0.001

bjh research paper

Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention?

Adriana Balduzzi,[1] Lucia Di Maio,[1] Daniela Silvestri,[1,2] Simona Songia,[1] Sonia Bonanomi,[1] Attilio Rovelli,[1] Valentino Conter,[1] Andrea Biondi,[1,3] Giovanni Cazzaniga[3]* and Maria G. Valsecchi[2]*

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Summary

Eighty-two children and adolescents who underwent allogeneic transplantation for acute lymphoblastic leukaemia in remission (period 2001–2011, median follow-up 4·9 years) had been assessed for minimal residual disease (MRD) by real-time quantitative polymerase chain reaction before and at 1, 3, 6, 9 and 12 months after transplantation. Five-year event-free survival (EFS) and cumulative incidence of relapse were 77·7% [standard error (SE) 5·7] and 11·4% (SE 4·4), respectively, for patients with pre-transplant MRD $<1 \times 10^{-4}$ (68%), *versus* 30·8% (SE 9·1; $P < 0·001$) and 61·5% (SE 9·5; $P < 0·001$), respectively, for those with MRD $\geq 1 \times 10^{-4}$ (32%). Pre-transplant MRD $\geq 1 \times 10^{-3}$ was associated with a 9·2-fold risk of relapse [95% confidence interval (CI) 3·54–23·88; $P < 0·001$] compared with patients with MRD $<1 \times 10^{-4}$. Patients who received additional chemotherapy pre-transplant to reduce MRD had a fivefold reduction of risk of failure (hazard ratio 0·19, CI 0·05–0·70, $P = 0·01$). Patients who experienced MRD positivity post-transplant did not necessarily relapse (5-year EFS 40·3%, SE 9·3), but had a 2·5-fold risk of failure (CI 1·05–5·75; $P = 0·04$) if any MRD was detected in the first 100 d, which increased to 7·8-fold (CI 2·2–27·78; $P = 0·002$) if detected after 6 months. Anticipated immunosuppression-tapering according to MRD may have improved outcome, nevertheless all patients with post-transplant MRD $\geq 1 \times 10^{-3}$ ultimately relapsed, regardless of immunosuppression discontinuation or donor-lymphocyte-infusion. In conclusion, MRD before transplantation had the strongest impact on relapse and MRD positivity after transplantation, mostly if detected early and at low levels, did not necessarily imply relapse. Additional intensified chemotherapy and modulation of immunosuppression may reduce relapse risk and improve ultimate outcome.

Keywords: acute lymphoblastic leukaemia, childhood, minimal residual disease, allogeneic transplantation, relapse.

Most children affected with acute lymphoblastic leukaemia (ALL) are potentially cured by conventional chemotherapy as frontline treatment (Conter *et al*, 2010; Schrappe *et al*, 2011; Hunger *et al*, 2012; Pui *et al*, 2012). Even at relapse, approximately one-third of patients can be successfully treated with salvage chemotherapy and radiotherapy (Parker *et al*, 2010; Tallen *et al*, 2010; Freyer *et al*, 2011). Allogeneic haematopoietic stem cell transplantation (HSCT) is considered of benefit for approximately 10% of the patients who are at very-high risk at frontline therapy and for the majority of patients after relapse (Borgmann *et al*, 2003; Balduzzi *et al*, 2005; Oliansky *et al*, 2012; Zhang *et al*, 2012). Nevertheless, relapse remains the most frequent cause of treatment failure after transplantation (Balduzzi *et al*, 2005). During the last decade, the prognostic role of minimal residual disease (MRD) has been shown in both frontline and relapse protocols, even when MRD was used to stratify patients and tailor risk-adapted therapy (Eckert *et al*, 2001, 2012; Conter *et al*, 2010; Hunger *et al*, 2012). Since 1998, MRD has also been identified as a relevant prognostic factor in the

doi:10.1111/bjh.12639

MRD in HCT for ALL – Results

Multivariate analysis
MRD at transplantation

	Hazard ratio	95% CI	p-value
Any event			
MRD at transplant ≥1x10^{-4} vs Negative or <1x10^{-4}	**5.5**	**2.58-11.52**	**<0.001**
Disease Phase at transplant CR2 or CR3 vs CR1	2.3	0.97-5.35	0.06
Acute GVHD Max Grade II-IV vs 0-I	0.8	0.39-1.70	0.59
Relapse			
MRD at transplant ≥1x10^{-4} vs Negative or <1x10^{-4}	**9.2**	**3.54-23.88**	**<0.001**
Disease Phase at transplant CR2 or CR3 vs CR1	2.5	0.91-6.80	0.07
Acute GVHD Max Grade II-IV vs 0-I	0.5	0.19-1.24	0.13

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches

- LLA common, SNC neg, trasl neg→ AIEOP BFM ALL 2009, SER→ HR; OT;
- +32 ms: isol BM relapse → AIEOP REC 2003.
- +5 ms post relapse:
- HSCT MSD BM; conditioning TBI, VP16; GvHD prophylaxis: CyA (MTX not given, high risk of relapse)
- MRD at transplant 1.2x10^-3
- GvHD skin+liver grade II→ mPDN 87 days; stop IS Feb '15
- +6 ms post HSCT: MRD pos, < 1x10^-4
- +6 1/2 ms post HSCT: MRD neg
- +7 ms post HSCT: MRD pos, < 1x10^-4
- +7 1/2 ms post HSCT: 1.6x10^-4
- +9 ms post HSCT 9.5x10^-4

FONDAZIONE Monza e Brianza per il BAMBINO e la sua MAMMA

MRD in HCT for ALL –Results

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

MRD after transplantation-multivariate analyses

	Hazard ratio	95% CI	p-value
Early post transplant MRD			
MRD 1-3 ms after HCT – pos vs neg	2.5	1.05-5.75	0.04
Disease Phase at HCT - CR2/CR3 vs CR1	2.3	0.93-5.73	0.07
MRD at HCT - $\geq 10^{-4}$ vs Neg/$<10^{-4}$	5	2.13-11.73	<0.001
Acute GVHD - II-IV vs 0-I	0.7	0.32-1.69	0.46
Late post transplant MRD			
MRD 6-12 ms after HCT – pos vs neg	7.28	2.20-27.28	0.002
Disease Phase at HCT - CR2/CR3 vs CR1	1.9	1.51-7.28	0.34
MRD at HCT - $\geq 10^{-4}$ vs Neg/$<10^{-4}$	3.5	1.04-11.50	0.04
Acute GVHD - II-IV vs 0-I	3.2	0.98-10.48	0.06

bjh research paper

Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention?

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches

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- GvHD skin+liver grade II→ mPDN 87 days; stop IS Feb '15
- +6 ms post HSCT: MRD pos 1.6x10^-4
- +9 ms post HSCT 9.5x10^-4

+10 ms after 1st transplant —> haplo HSCT (mother, BM)
conditioning: TT, Treo, Flu;
GvHD prophylaxis: CyA, MMF, CY (50 mg/kg day +3, +4)

"Cy post"

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches
HAPLOIDENTICAL TRANSPLANTATION
WITH POST TRANSPLANT CYCLOPHOSPHAMIDE

Post transplantation immunologic cyclophosphamide (50 mg/Kg days +2, +3): —> hypothesis:

- **selectively depletes alloreactive T-cells**

(= creates immunogenic tolerance by specific clonal killing of activated mature T-cells)

- **from the donor responsible for GVHD and**
- **from recipient responsible for rejection**
- **preserves resting memory T-cells essential for immune reconstitution**
- **no other IS before transplant which would prevent clonal expansion after antigenic stimulation by the graft and killing**

Non-myeloablative conditioning regimen

- **highly immune-suppressive but moderately myelo-suppressive**
- **immunosuppression should be sufficient to allow donor engraftment**
- **a high dose of donor cells increases the probability of engraftment**
- **immunologic recovery may be faster**
- **initial mixed chimerism protective against GVHD by promoting immune tolerance**

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches CY POST HAPLO

"CY post" haplo in pediatrics

- **Yesilipek, Turkey, Pediatr Transplant. 2015 Dec 28**
- **Haploidentical hematopoietic stem cell transplantation with post-transplant high-dose cyclophosphamide in high-risk children: A single-center study**

- **15 pts, 16 SCTs**
- **CY +3, +5; TAC + MMF / PDN**
- **6 aGVHD, 2 cGVHD**
- **2 TRM**
- **12 CCR: OS 75 ± 10.8% and DFS 68.8 ± 11.6%**

… Survey to circulate within EBMT centers

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
2nd of 4 approaches: “CY POST” HAPLO

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

Case 1 - 2014
palliation

Case 2 - 2015
2nd transplant, haploidentical CY post

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
3rd of 4 approaches

- **ALL B-I → AIEOP R2006;**
- **+ 33 ms: relapse (BM + right testis) →AIEOP LLA REC 2003+orchiectomy; HSCT MD; GvHD gut+liver**
- **+12 ms after SCT: 2° relapse (left testis + BM MRD positivity)**
- **3 ms later: 3° relapse (BM 19% blasts)→ chemotherapy (steroid, vincristine, FLAG-D, FLA-G)**
- **5 ms later: 4° relapse (BM blasts 41%)→ 1 blinatumomab → morphological remission (MRD pre-HSCT 7x10-3)**
- **3 ms later: haplo (father; BM); conditioning: TT+ Treo+Flu; GvHD prophylaxis: CyA, MMF, CY post**
- **Nov '15: MRD positivity (<1x10-4)→ DLI+CIK**

Blinatumomab

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
3rd of 4 approaches: BLINATUMOMAB

- **Blinatumomab is a bispecific T-cell engager (BiTE) antibody derived from a B-lineage specific antitumor mouse monoclonal antibody**
- **Blinatumomab is a CD19/CD3 bispecific T-cell engaging (BiTE) antibody that binds to $CD3^+$ T-cells and co-localizes them with $CD19^+$ B-cells, thereby activates the T-cells and induces perforin-mediated death of the targeted B-cells**
- **Ongoing randomized COG phase III study for pre-B ALL children in first relapse is scheduled to open in late 2014, combining blinatumomab with UKALLR3 reinduction chemotherapy**

MRD in HCT for ALL – Results - 7
Interventions according to MRD

4 levels of INTERVENTION:

I. CHEMO INTENSIFICATION and HCT postponement
Pre-transplant intervention - based on MRD at the time when HCT was due (pre-pre MRD) (after 2007)

34 pts MRD ≥1x10^{-4} (15 after 2007)

- 13 FLA±D
  - 8 MRD neg or <1x10^{-4} → 0/8 rel
  - 5 MRD positive → 3/5 rel
- 21 no additional treatment → 10/21 rel

Administration of FLA-D was associated with a five-fold reduction of the hazard of failure (hazard ratio (HR) 0.19, 95% CI 0.05- 0.70, p-value 0.01)

II. EARLY IMMUNOSUPPRESSION TAPERING
Post HCT intervention – based on MRD at transplant (after 2004)

26 pts MRD ≥1x10^{-4}

- 19 no GvHD
  - 11 ↓IS → 5/11 rel
  - 8 no ↓IS → 5/8 rel
- 7 GvHD→ no ↓IS

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
3rd of 4 approaches: blinatumomab

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

2014
palliation

2015
2nd transplant, haploidentical CY post

2015
blinatumomab,
2nd transplant, haploidentical, “CY post”

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4th of 4 approaches

- **Thalassemia major** → Sept '09 **HSCT MSD** (donor: HLA-identical sister, source: BM); condizioning: TT-Treo-Flu; GVHD prophylaxis CyA, MTX;
- Decreasing donor chimerism and rejection despite 7 DLI; Dec '09: full autologous reconstitution.
- Apr '11: **Diagnosis of t(9;22) ALL** → EsPhALL (induction + block HR-1), morphological CR, molecular persistence of disease (Aug '11: BCR/Abl: 178 copies/10^4 abl copies; MRD <5x10-^{4})
- Sept '11: **2nd HSCT MSD** (donor: HLA-identical brother, source BM); condizioning: TT, Treo, Flu; GVHD prophylaxis CyA, MTX; full three-lineage engraftment, full donor chimerism, post-HSCT course uneventful.
- Imatinib since the 2nd month post HSCT, continued due to persistent t(9;22) positivity on PB and BM, despite MRD TCR/Ig negativity.
- Nov '13: relapse as **Bi-phenotipic t(9;22) ALL** in varicella (BM blasts 90%);
- Jan '14: phase I study **nilotinib** enrollment (blasts 50%) → Feb '14: **CR2**, BM blasts 3%; BCR-ABL 400/10.000 copies;
- May '14: **Stop nilotinib**
- Enrollment in **CD19TPALL trial** prophylactic arm: CHILDHOPE, P. Amrolia UCL
- Jun '14: **3rd HSCT MSD (donor:** same HLA-identical brother as for her second transplant, source BM); conditioning: TT, Treo, Flu; GVHD prophylaxis: CyA), MTX);
- **Post transplant treatment** (Oct- Dec '15): Lymphodepletion with Fludarabin 30mg/m^2; transfusion of cytotoxic T-cells (CD19-zeta EBV-CTLs); BLCL-Vaccination (Irradiated donor-derived B Lymphoblastoid Cell Line, BLCL);
- **Jan '15: molecular Relapse → May '15 Morphological relapse**

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4th of 4 approaches

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Enrollment in CD19TPALL trial prophylactic arm: CHILDHOPE, P. Amrolia UCL

From hope to reality!

The New York Times

December 9, 2012

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY

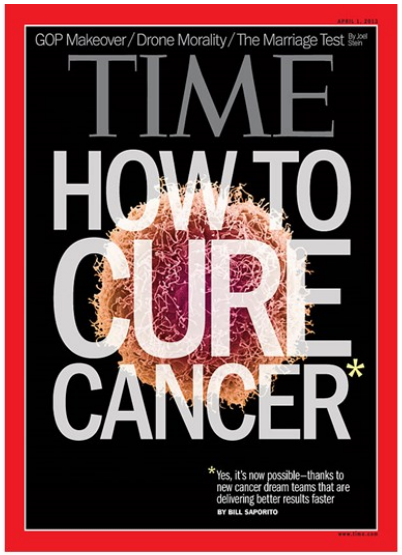
PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that make her parents wince.

It is hard to believe, but last spring Emma, then 6, was near death from leukemia. She had relapsed twice after chemotherapy, and doctors had run out of options.

The treatment very nearly killed her. But she emerged from it cancer-free, and about seven months later is still in complete remission. She is the first child and one of the first humans ever in whom new techniques have achieved a long-sought goal — giving a patient's own immune system the lasting ability to fight cancer.

How to cure cancer: a new path...

Emma Whitehead: the 1st ALL child cured by CAR




The New York Times

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MONDAY, DECEMBER 10, 2012

In Girl's Last Hope, Altered Cells Beat Leukemia

By DENISE GRADY

PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that make her parents wince.

It is hard to believe, but last spring Emma, then 5, was near death from leukemia. She had relapsed twice after chemotherapy, and doctors had run out of options.

Desperate to save her, her parents sought an experimental treatment at the Children's Hospital of Philadelphia, one that had never before been tried in a child, or in anyone with the type of leukemia Emma had. The experiment, in April, used a disabled form of the virus that causes AIDS to reprogram Emma's immune system genetically to kill cancer cells.

The treatment very nearly killed her. But she emerged from it cancer-free, and about seven months later is still in complete remission. She is the first child and one of the first humans ever in whom new techniques have achieved a long-sought goal — giving a patient's own immune system the lasting ability to fight cancer.

Emma had been ill with acute lymphoblastic leukemia since 2010, when she was 3, also her parents, Kari and Tom. She is their only child.

She is among just a dozen patients with advanced leukemia to have received the experimental treatment, which was developed at the University of Pennsylvania. Similar approaches are also being tried at other centers, including the National Cancer Institute and Memorial Sloan-Kettering Cancer Center in New York.

"Our goal is to have a cure, but we can't say that word," said Dr. Carl June, who leads the research team at the University of Pennsylvania. He hopes the new treatment will eventually replace bone marrow transplantation, an even more arduous, risky and expensive procedure that is now the last hope when other treatments fail in leukemia and related diseases.

Three adults with chronic leukemia treated at the University of Pennsylvania have also had

Continued on Page A16

Emma Whitehead, with her mother, Kari, is now cancer-free.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

RESEARCH ARTICLE

CANCER IMMUNOTHERAPY

CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia

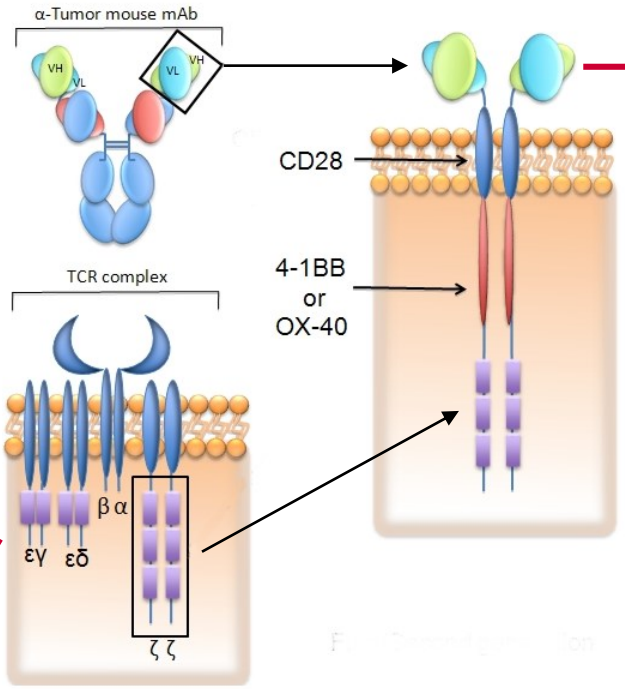
Renier J. Brentjens,[1,2,3*†] Marco L. Davila,[1†] Isabelle Riviere,[1,2,3,4†] Jae Park,[1] Xiuyan Wang,[3,4] Lindsay G. Cowell,[5] Shirley Bartido,[4] Jolanta Stefanski,[4] Clare Taylor,[4] Malgorzata Olszewska,[4] Oriana Borquez-Ojeda,[4] Jinrong Qu,[4] Teresa Wasielewska,[4] Qing He,[4] Yvette Bernal,[1] Ivelise V. Rijo,[6] Cyrus Hedvat,[6] Rachel Kobos,[7] Kevin Curran,[7] Peter Steinherz,[7] Joseph Jurcic,[1] Todd Rosenblat,[1] Peter Maslak,[1] Mark Frattini,[1] Michel Sadelain[1,2,3*]

PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4th of 4 approaches

Chimeric Receptors for Immunotherapy of Acute Leukemias

CHIMERIC ANTIGEN RECEPTORS

CARs



An extracellular domain recognizing tumor-associated antigens derived from mAb

An intracellular signaling domain triggering T cell activation

modified from Chekmasova AA, Brentjens RJ (2010), *Discov Med,* 9(44):62-70

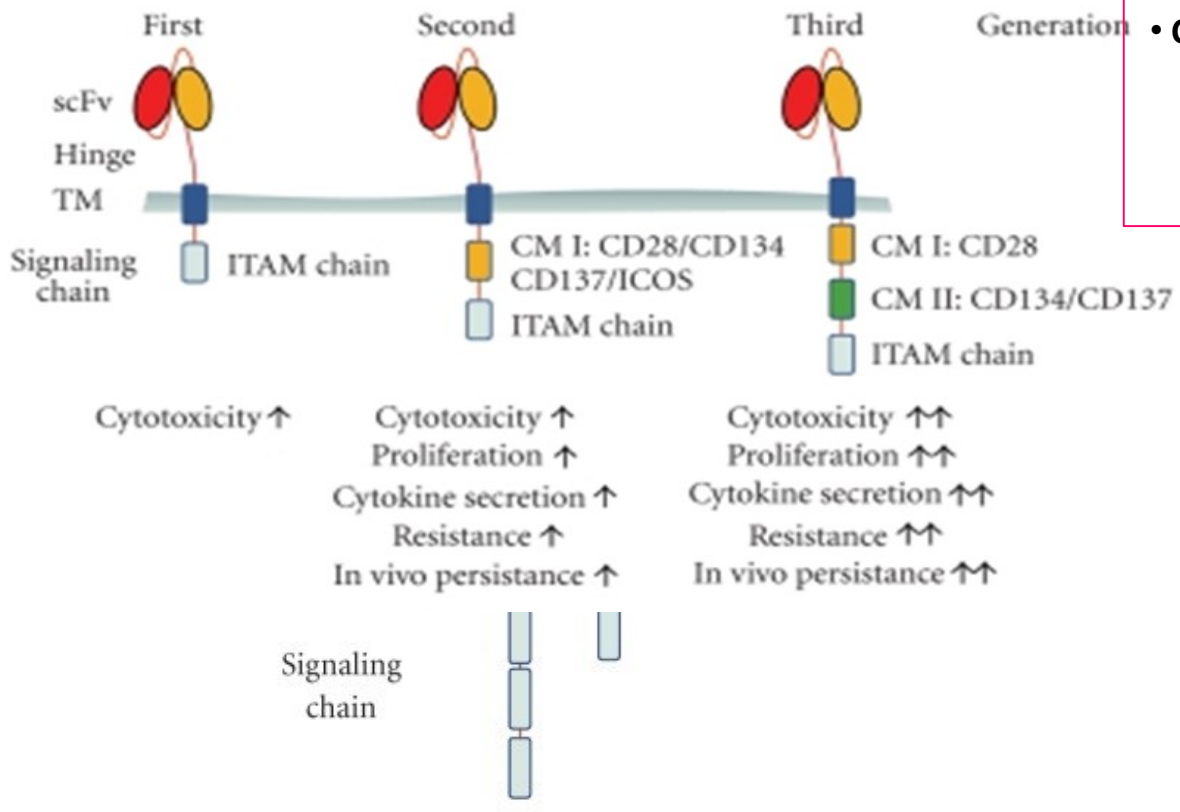
PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4th of 4 approaches

CARs T

- **Chimeric antigen receptor-modified T-cells (CAR T-cells) with CD19 specificity (adoptive transfer of CD19ζ chimaeric receptor transduced donor-derived EBV-specific cytotoxic T-lymphocytes (EBV-CTL)) are generating excitement as a novel therapy for high-risk or relapsed B cell precursor ALL after allogeneic Haematopoietic Stem Cell Transplantation (HSCT).**
- **CAR T cells are patient-derived T-cells, transduced to express a chimeric antigen receptor, which includes an anti-CD19 antibody fragment fused to a T-cell intracellular signaling domain**
- **Second-generation CAR T cells also encode for a costimulatory domain, such as CD28 or members of the tumor necrosis factor receptor family such as CD27, CD137 (4-1BB) and CD134 (OX40). The costimulatory domains activate the CAR T-cells, allowing for targeting and lysis of $CD19^+$ cells.**

Chimeric Antigen Receptors (CD19, CD20, CD30, CD33)

ANTIGEN-BINDING PROPERTY OF ANTIBODIES

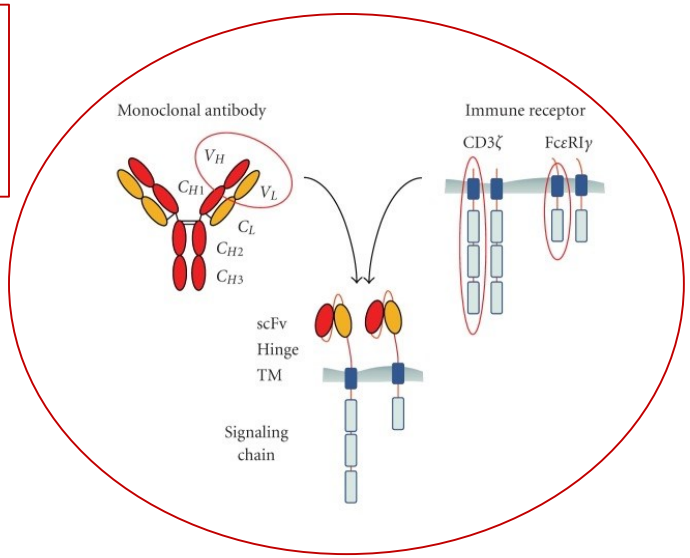


TCR-TRIGGERING DOMAIN:
- **T-cells activation**
- **Cytokines secretion**
- **Cytotoxicity**
- **Homing**

Schmidt et al., 2010
Journal of Biomed and Biotechnology

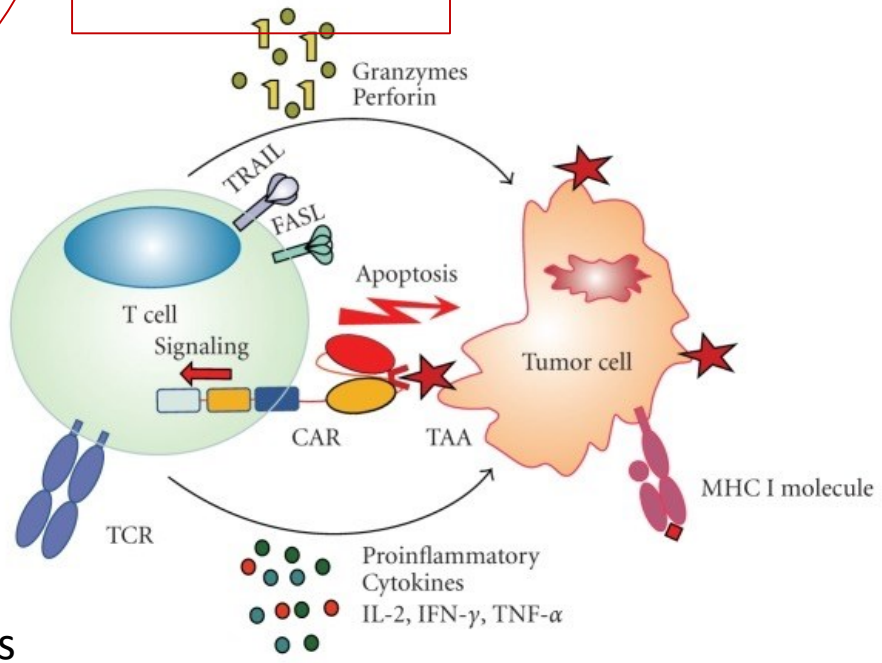
Redirecting T cell activity with Chimeric Antigen Receptors (CARs)

ANTIGEN-BINDING PROPERTY OF ANTIBODIES



TCR-TRIGGERING DOMAIN:

- **T-cell activation**
- **Cytokines secretion**
- **Cytotoxicity**
- **Persistence**
- **Homing**



Curtellieri et al., 2010

ADVANTAGES OF CARs

- HLA- independent antigen recognition
- Active in both CD4+ and CD8+ T cells
- Target antigens include proteins, carbohydrates and glycolipids
- Immunological memory
- Better biodistribution compared to mAbs

CD19 CARS AND CLINICAL APPLICATION

Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg

Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation

James N. Kochenderfer,[1] Mark E. Dudley,[2] Robert O. Carpenter,[1] Sadik H. Kassim,[2] Jeremy J. Rose,[1] William G. Telford,[1] Frances T. Hakim,[1] David C. Halverson,[1] Daniel H. Fowler,[1] Nancy M. Hardy,[1] Anthony R. Mato,[3] Dennis D. Hickstein,[1] Juan C. Gea-Banacloche,[1] Steven Z. Pavletic,[1] Claude Sportes,[1] Irina Maric,[4] Steven A. Feldman,[2] Brenna G. Hansen,[1] Jennifer S. Wilder,[5] Bazetta Blacklock-Schuver,[1] Bipulendu Jena,[6] Michael R. Bishop,[7] Ronald E. Gress,[1] and Steven A. Rosenberg[2]

B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells

James N. Kochenderfer,[1] Mark E. Dudley,[2] Steven A. Feldman,[2] Wyndham H. Wilson,[3] David E. Spaner,[4] Irina Maric,[5] Maryalice Stetler-Stevenson,[6] Giao Q. Phan,[2] Marybeth S. Hughes,[2] Richard M. Sherry,[2] James C. Yang,[2] Udai S. Kammula,[2] Laura Devillier,[2] Robert Carpenter,[1] Debbie-Ann N. Nathan,[2] Richard A. Morgan,[2] Carolyn Laurencot,[2] and Steven A. Rosenberg[2]

Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study

Conrad Russell Y. Cruz,[1] Kenneth P. Micklethwaite,[1] Barbara Savoldo,[1] Carlos A. Ramos,[1] Sharon Lam,[1] Stephanie Ku,[1] Oumar Diouf,[1] Enli Liu,[1] A. John Barrett,[2] Sawa Ito,[2] Elizabeth J. Shpall,[3] Robert A. Krance,[1,4] Rammurti T. Kamble,[1,4] George Carrum,[1,4] Chitra M. Hosing,[3] Adrian P. Gee,[1] Zhuyong Mei,[1] Bambi J. Grilley,[1] Helen E. Heslop,[1,4] Cliona M. Rooney,[1] Malcolm K. Brenner,[1,4] Catherine M. Bollard,[1,4] and Gianpietro Dotti[1]

Infusing CD19-Directed T Cells to Augment Disease Control in Patients Undergoing Autologous Hematopoietic Stem-Cell Transplantation for Advanced B-Lymphoid Malignancies

Partow Kebriaei,[1] Helen Huls,[2] Bipulendu Jena,[2] Mark Munsell,[1] Rineka Jackson,[2] Dean A. Lee,[2,3] Perry B. Hackett,[4] Gabriela Rondon,[1] Elizabeth Shpall,[1] Richard E. Champlin,[1] and Laurence J.N. Cooper[2,3]

Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia

Marco L. Davila[1], Isabelle Riviere[1,2,3,4], Xiuyan Wang[4], Shirley Bartido[4], Jae Park[1], Kevin Curran[5], Stephen S. Chung[1], Jolanta Stefanski[4], Oriana Borquez-Ojeda[4], Malgorzata Olszewska[4], Jinrong Qu[4], Teresa Wasielewska[4], Qing He[4], Mitsu Fink[4], Himaly Shinglot[4], Maher Youssif[4], Mark Satter[4], Yongzeng Wang[4], James Hosey[4], Hilda Quintanilla[1], Elizabeth Halton[1], Yvette Bernal[1], Diana C. G. Bouhassira[2], Maria E. Arcila[6], Mithat Gonen[7], Gail J. Roboz[8], Peter Maslak[1], Dan Douer[1], Mark G. Frattini[9], Sergio Giralt[1,2], Michel Sadelain[1,2,3,*] and Renier Brentjens[1,2,3,*]

Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias

*Renier J. Brentjens,[1-3] *Isabelle Rivière,[1-4] Jae H. Park,[1,2] Marco L. Davila,[1,2] Xiuyan Wang,[2-4] Jolanta Stefanski,[2-4] Clare Taylor,[2-4] Raymond Yeh,[1,2] Shirley Bartido,[2,3] Oriana Borquez-Ojeda,[2-4] Malgorzata Olszewska,[2-4] Yvette Bernal,[1] Hollie Pegram,[1,2] Mark Przybylowski,[2-4] Daniel Hollyman,[2-4] Yelena Usachenko,[1,2] Domenick Pirraglia,[2-4] James Hosey,[2-4] Elmer Santos,[3,5] Elizabeth Halton,[1] Peter Maslak,[1] David Scheinberg,[1-3] Joseph Jurcic,[1] Mark Heaney,[1] Glenn Heller,[6] Mark Frattini,[1] and Michel Sadelain[1-3]

CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia

Renier Brentjens[*,†,1,2,3], Marco L Davila[†,1], Isabelle Riviere[†,1,2,3,4], Jae Park[1], Xiuyan Wang[3,4], Lindsay G Cowell[7], Shirley Bartido[4], Jolanta Stefanski[4], Clare Taylor[4], Malgorzata Olszewska[4], Oriana Borquez-Ojeda[4], Jinrong Qu[4], Teresa Wasielewska[4], Qing He[4], Yvette Bernal[1], Ivelise V Rijo[5], Cyrus Hedvat[5], Rachel Kobos[6], Kevin Curran[6], Peter Steinherz[6], Joseph Jurcic[1], Todd Rosenblat[1], Peter Maslak[1], Mark Frattini[1], and Michel Sadelain[*,1,2,3]

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PEDIATRIC ALL RELAPSING AFTER TRANSPLANT
4 approaches

> 1985
Palliative care
Chemotherapy
DLI
Second transplant

2014
palliation

2015
2nd transplant, haploidentical CY post

2015
blinatumomab,
2nd transplant, haploidentical, “CY post”

2014
2nd transplant, CAR

NUOVI FARMACI E TRAPIANTO: LLA

What's crucial in pediatric transplantation in ALL

"Standard" innovative transplantation:

- patient selection
- reduce mortality
- reduce long-term sequelae

… and what's next…

FORUM STUDY

For omitting Radiation Under Majority Age

Innovative strategies:

Blinatumomab

Post-Cy Haplo

CAR