French & German SFGM-TC Day

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Post-transplantation maintenance or donor lymphocyte infusion (DLI)

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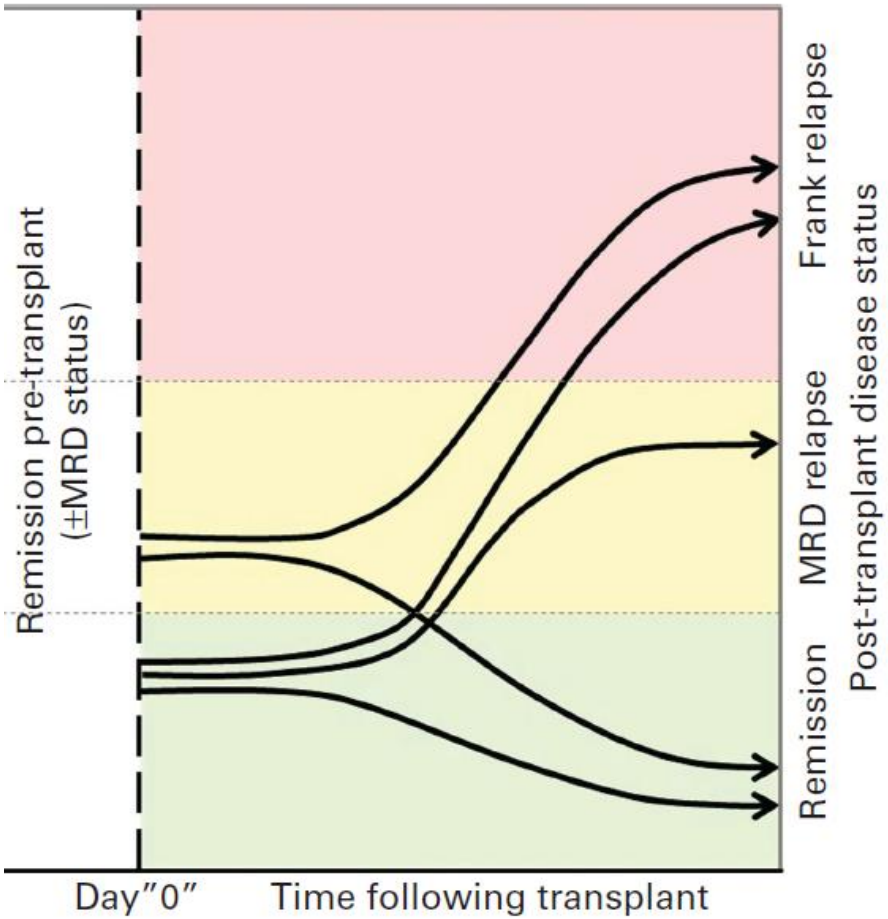
Potential conflict of interests

1. Employment or Leadership Position	none
2. Advisory Role or Expert Testimony	Celgene, CTI Life Sciences
3. Stock Ownership	none
4. Patent, Copyright, Licensing	none
5. Honoraria / Travel grants	Astellas, Celgene, Gentium, Gilead, Janssen Jazz, Neovii, Novartis, Pfizer, Sanofi
6. Financing of Scientific Research	none
7. Other Financial Relationships	none

Strategies to prevent relapse post-alloSCT in ALL

Course of disease



Type of intervention

Therapeutic
- rapid reduction of immunosuppression
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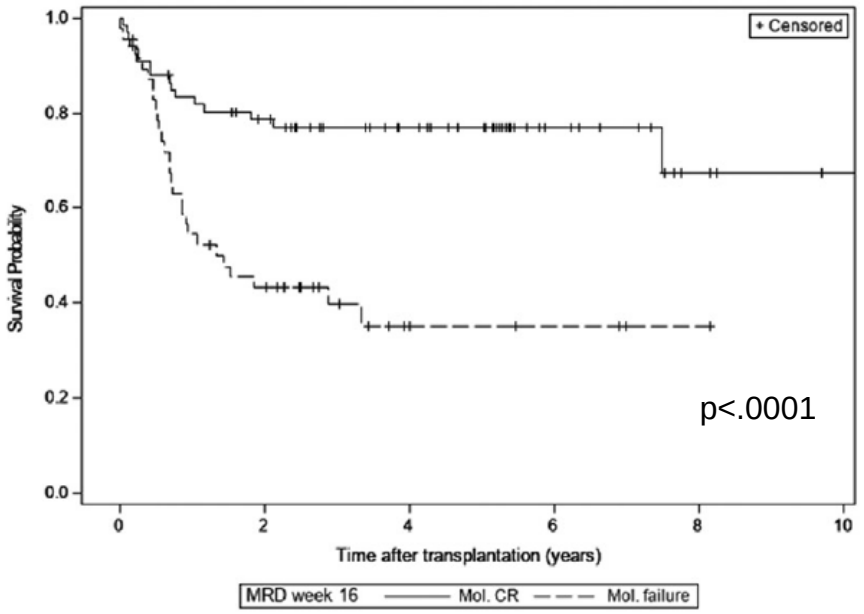
Prophylactic
- early reduction of immunosuppression
- Ph+: TKI
- antibodies, others?
- DLI
- combinations of these options?

adapted from Korn BLOOD 2017, 129:811

Pre-alloSCT factors correlate with post-alloSCT survival – rationale for prophylactic post-SCT treatment

- prospective GMALL cohort, N=542 (MRD data N=114)
- failed MRD-negative CR pre-alloSCT: strong predictor for post-alloSCT relapse

PFS



Beelen TRANSPL CELL THER 2022, 28:834

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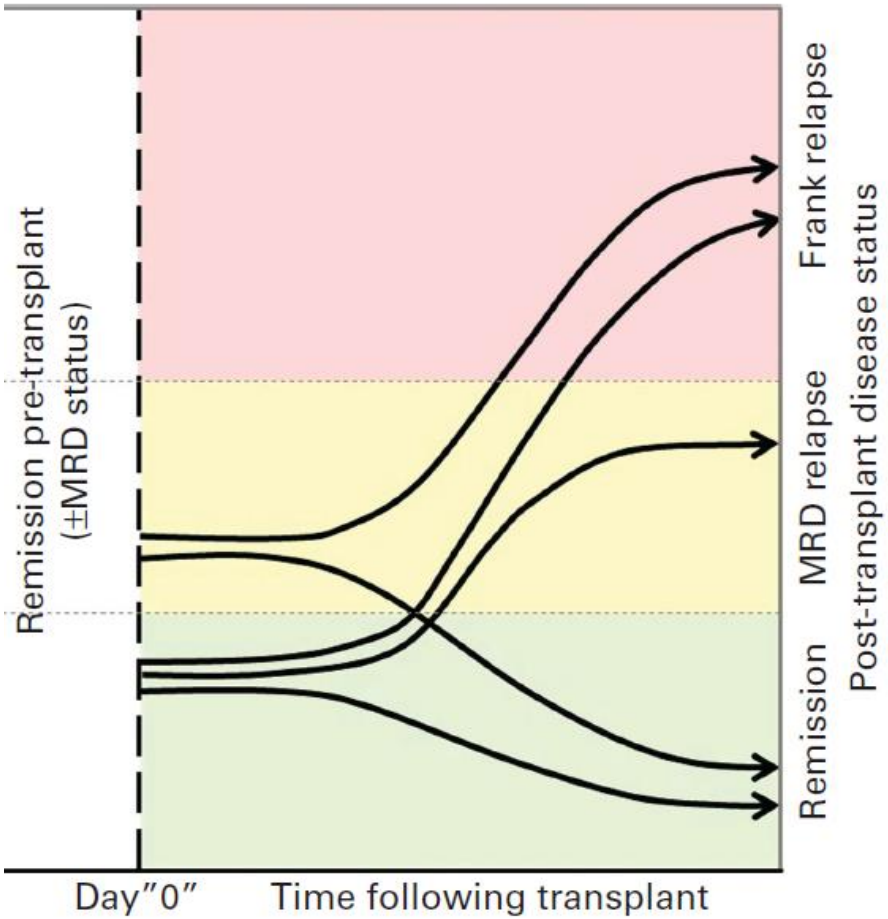

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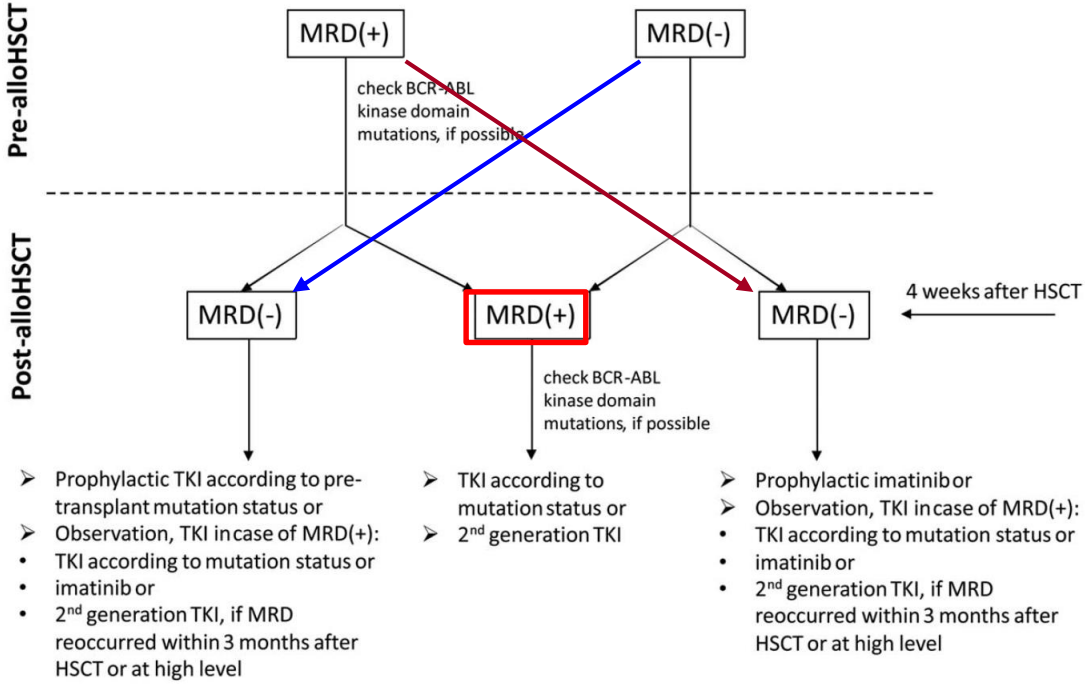
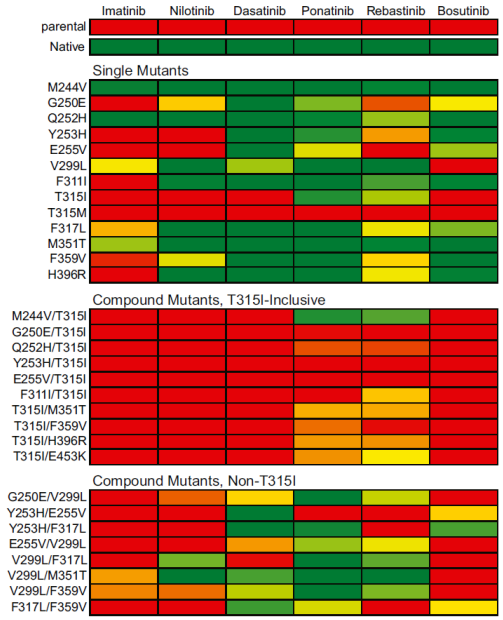
Prophylactic or preemptive TKI in Ph+ ALL?

EBMT guideline 2016 and GMALL recommendations:

- close MRD monitoring
- favouring preemptive TKI
- choice of TKI based on prior therapy and mutation status



Giebel CANCER 2016, 122:2941



Zabriskie CANCER CELL 2014, 26:428

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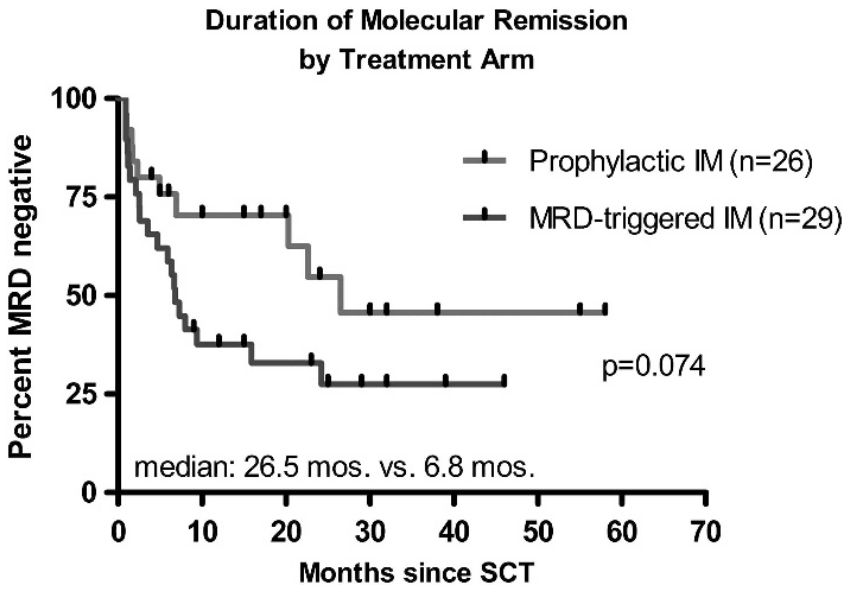
TKI maintenance in Ph+

- randomized study for imatinib in Ph+ ALL post alloSCT
- hematological toxicity with high discontinuation rate



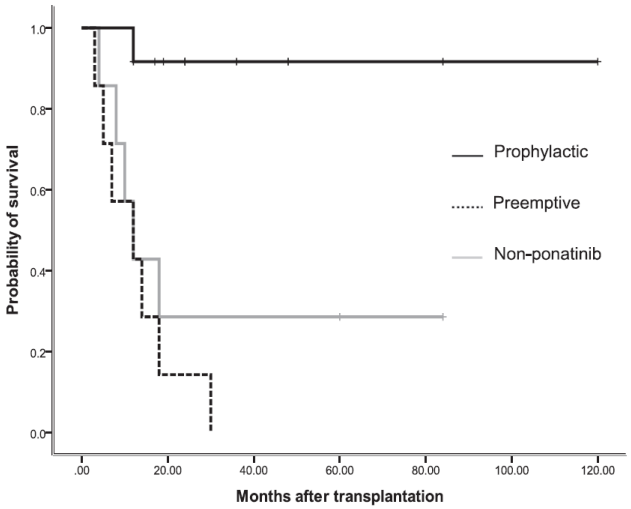
	Prophylactic IM, N = *26*	*MRD-triggered IM,* N = *29*
IM started	24 (92%)	14 (48%)
400 mg/day	18 (69%)	8 (28%)
600 mg/day	6 (23%)	6 (21%)
Never	2 (8%)	15 (52%)
Time from SCT to start of IM Median (range)	48 days (23–88)	70 days (39–567)
IM discontinued early	16 (67%)	10 (71%)
Median time from start of IM to last dose	245 days (4–927)	191 days (18–964)
Actual duration of IM administration median (range)	201 days (4–927)	127 days (18–964)

Pfeifer LEUKEMIA 2013, 27:1254

Ponatinib maintenance

- prospective, (T315I before alloSCT, incl. N=6 pediatric), 45mg/d (30mg/d in ped.), start d +45 - +120
- AE >II° in 15% with dose reduction, 5% discontinuation

OS

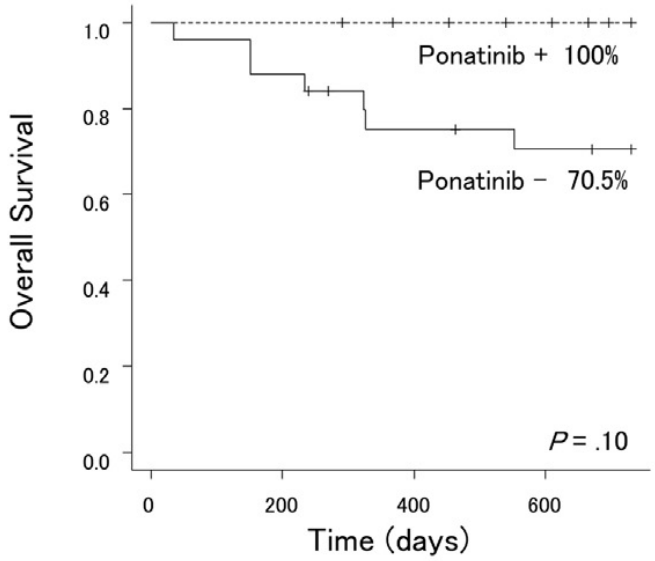


No. of risk:

Prophylactic	12	11	11	11	11	11	11
Preemptive	7	1	0				
no-ponatinib	7	2	2	2	2	2	2

Chen LEUK RES 2022, 121:106930

- retrospective, irrespective of T315I (pona N=9, no pona N=25) reduced dose 15mg/d, plasma level monitored, start d+36 - +124
- no AE>2, no AE-related discontinuation



Nanno CLIN LYM MYEL LEUK 2020, 20:813

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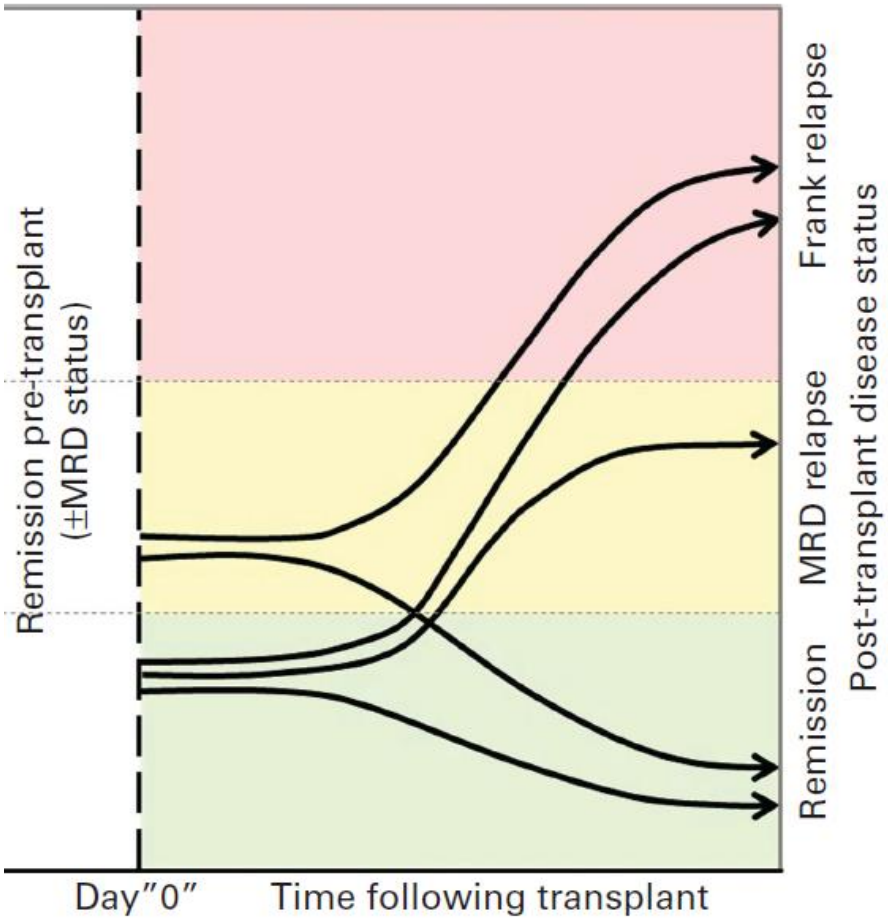

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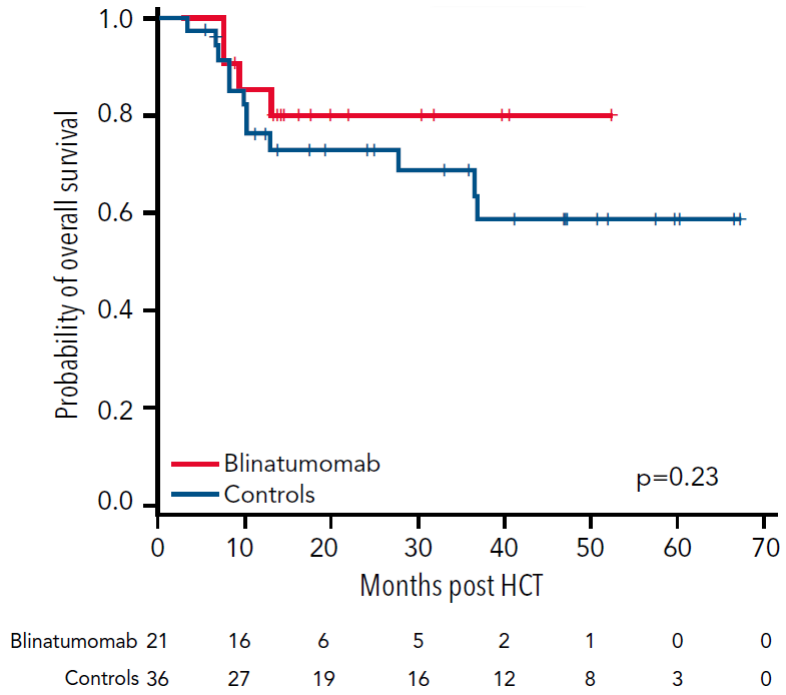
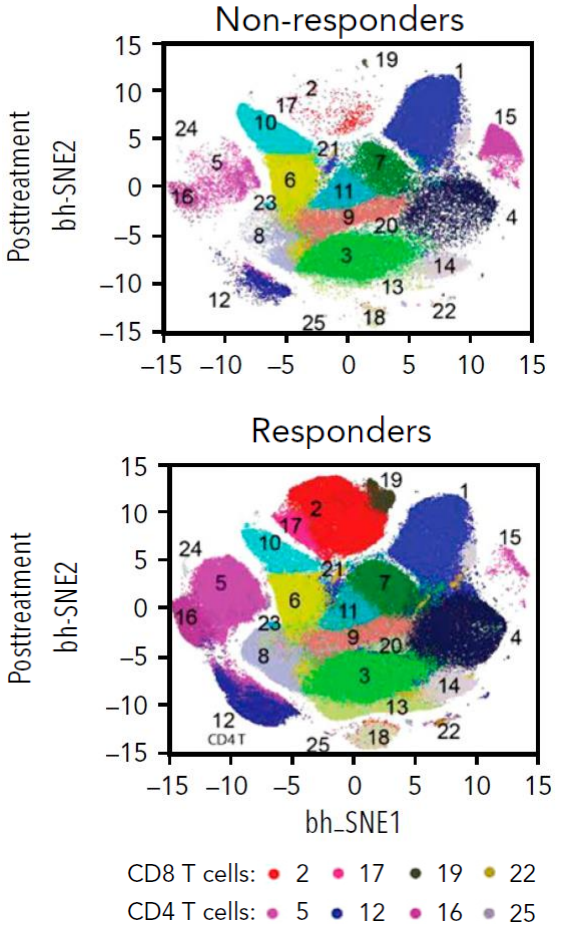
Prophylactic intervention in Ph- ALL - blinatumomab

- blinatumomab maintenance, Ph+ and Ph-, prospective phase 2 blina q3m 4x, starting >d+44
- differential T-cell composition in responders
- AE III-IV°: neutropenia 19%, rash 10%; neuro-tox.: 5% II°



Gaballa BLOOD 2022, 139:1908



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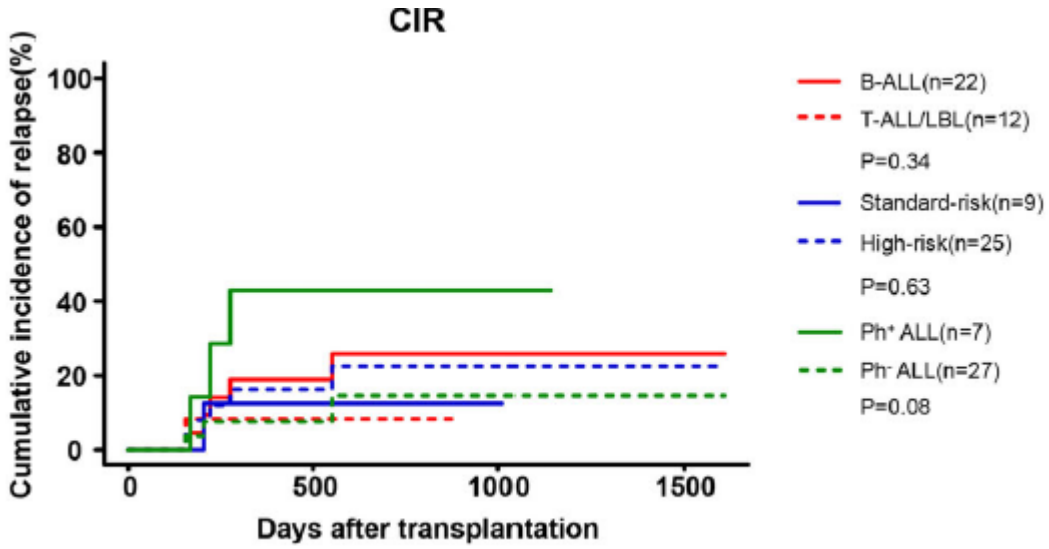
Prophylactic intervention in Ph- ALL - decitabine

- putative pro-GvL function of HMA (re-expression of MHC-genes)
- decitabine maintenance, Ph+ and Ph-, 10mg/d d1,3,5, q4w, 8x, starting >d+50
- no relapse in T-ALL – specific GvL-activation?



Liu FRONT ONCOL 2021, 11:710545

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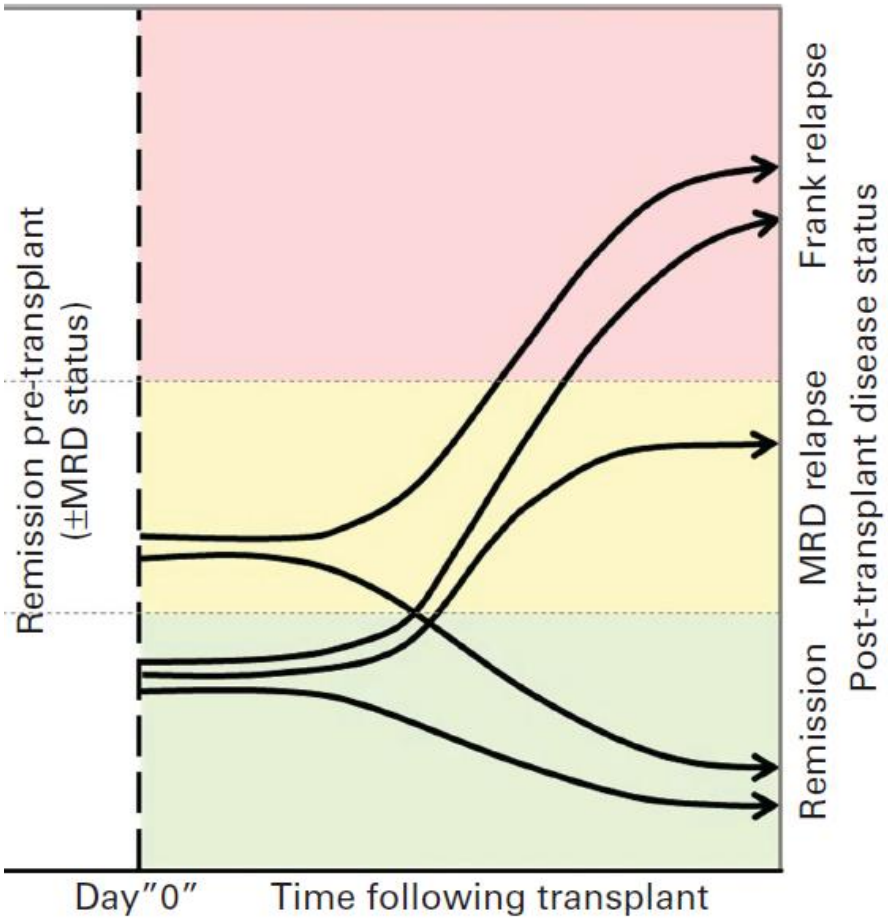

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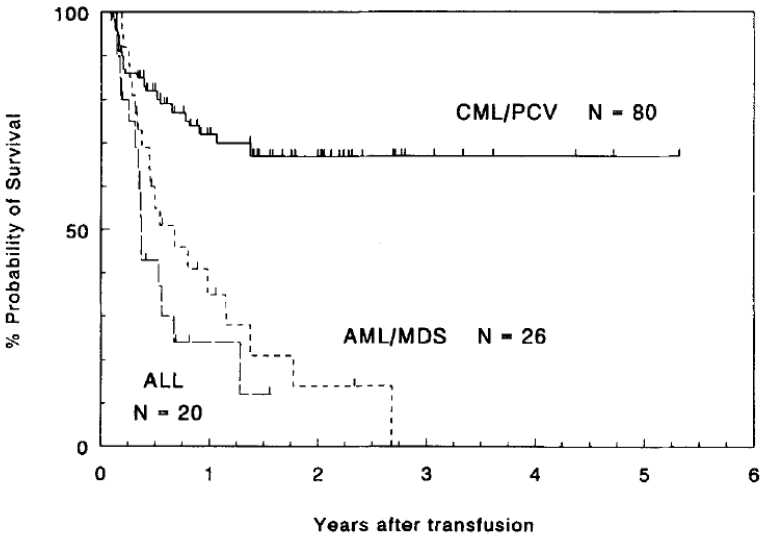
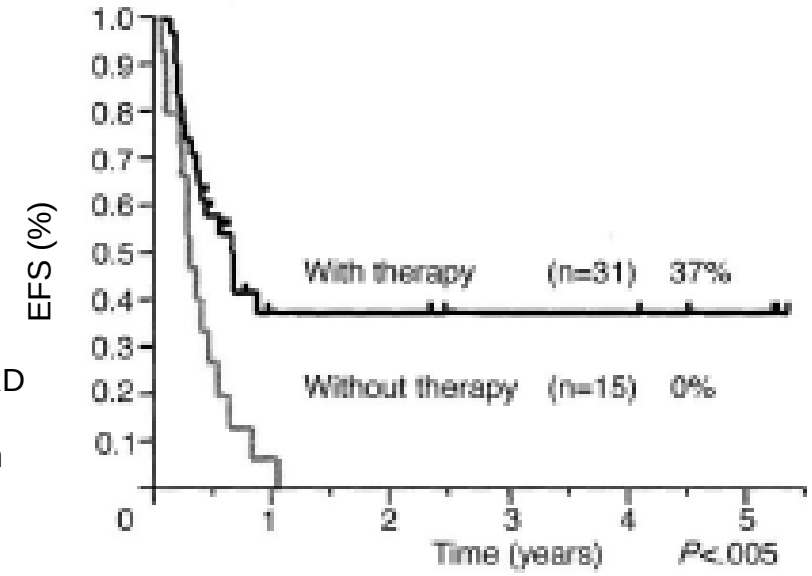
DLI – established post-SCT cellular therapy



- DLI (0.1 – 15x10^8 MNC/kg) for relapse, N=135
- +/- preceeding CTx for AML, ALL, MDS, CML AP

Kolb BLOOD 1995, 129:811



- prospective multicenter, pediatric ALL, PCR-based MRD
- increasing mixed chimerism (iMC) N=46
- stop of immunosuppression a/o DLI vs. no intervention
- 3-year EFS 37% with therapy vs. 0% without (P<.001)

Repsonse to DLI	Entity
High (40-80%)	CML, Myelofibrosis, low grade NHL
Intermediate (20-50%)	Hodgkin-Lymphoma, AML, MDS, Multiple Myeloma
Low (10-20%)	ALL, DLBCL

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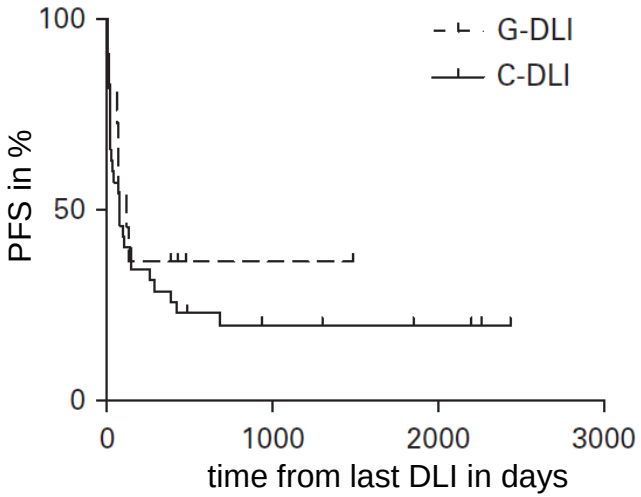
DLI – source, dosing and toxicity

- prerequsite:
  established donor chimerism
  absence of relevant GvHD (and infection)

- from stem cell product (G-CSF-stimulated)
  or 2nd apheresis (naïve)

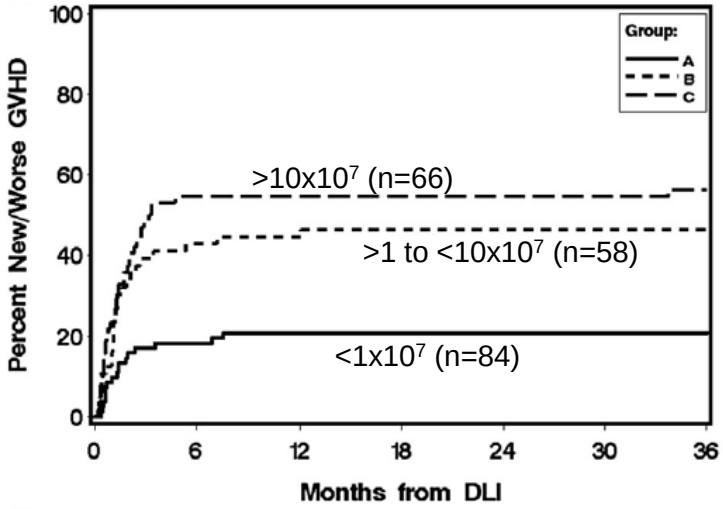
- post-DLI cumulative incidence of
  aGVHD: 40–60%; cGVHD: 30–60%
  GvHD-related deaths: 5–11%

- increase of GvHD-risk at >1x10^7 CD3$^+$/kg



- retrospective, AML / MDS relapse after SCT
- G-CSF-DLI (N=11) vs. conventional DLI (N=35)
- rate of GvHD similar

Abbi BMT 2013, 129:811



- retrospective, relapse, any malignancy post RIC / MAC; N=225
- cum. GVHD 12m after DLI 21%, 45%, 55%
- multivariate: initial DLI CD3$^+$ >10x10^7/kg assoc. with increased GvHD (P=0.03) without decreasing relapse risk

Bar BBMT 2013, 19:949

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DLI in ALL – retrospective GMALL / DRST / DAG-HSZT analysis

- retrospective multicenter

Main inclusion criteria

- age at alloSCT > 18 years
- ALL incl. Ph-positive
- alloSCT 01/2005 until 12/2017
- treatment within GMALL-registry or GMALL-trial
- treatment with DLI

Main exclusion criteria

- previous alloSCT

- entire cohort N=243; cohort with full information on DLI indication and outcome N=147

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GMALL / DRST / DAG-HSZT analysis –

Indication for DLI

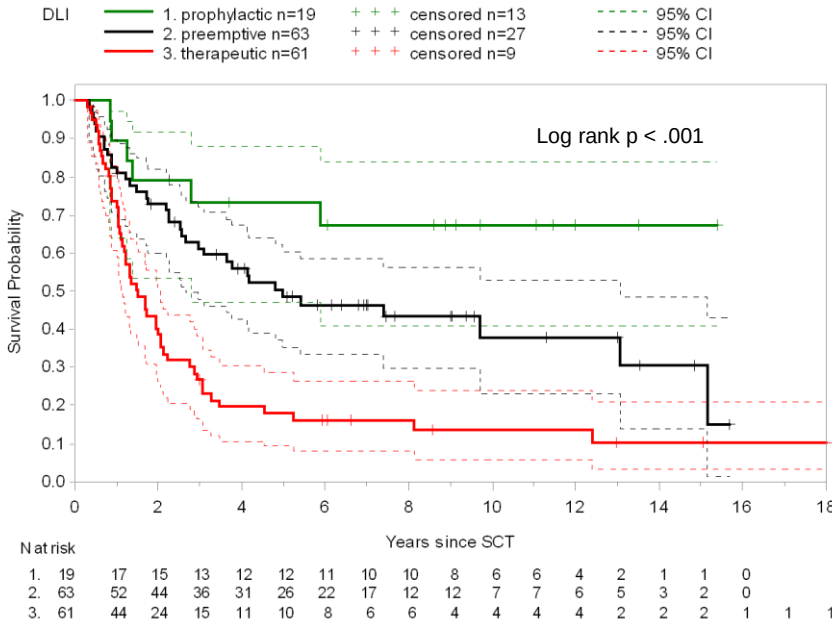
- repetitive DLI over years and changing DLI indications in 6 patients

  ⇒ definition of 1. DLI-Series: no subsequent DLI for next 6 months

Indication for first DLI	n (% of entire cohort)
Prophylactic (N=19)	
CR2 / high or very high risk ALL	13 (5.4)
MRD positivity prior to SCT	6 (2.5)
Pre-emptive (N=65)	
mixed chimerism without relapse	24 (9.9)
sustained MRD positivity after SCT	20 (8.2)
MRD relapse after SCT	21 (8.6)
Therapeutic (N=63)	
haematological relapse after SCT	50 (20.6)
extramedullary relapse after SCT	13 (5.4)
Other reasons (e.g. infectious complications, poor graft function)	11 (4.5)
Not reported / details missing	85 (35.0)
Abbreviation: MRD= minimal residual disease; SCT= stem cell transplantation	

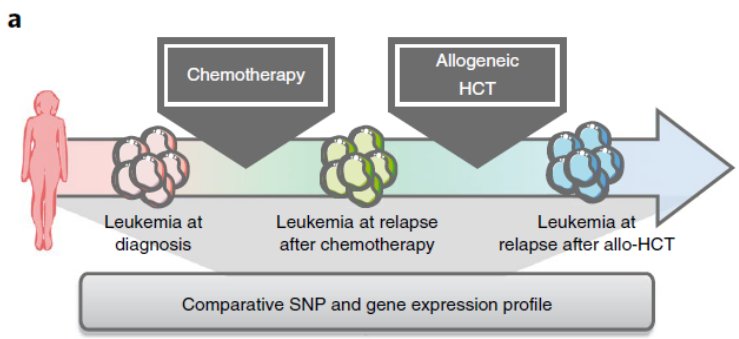
GMALL / DRST / DAG-HSZT analysis –

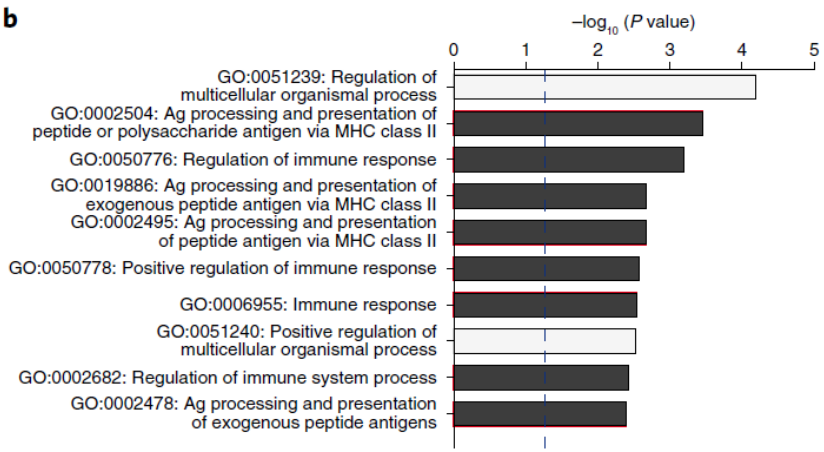
Overall survival



Reasons for failing GvL

- in AML: down-regulation of MHC / immune-response

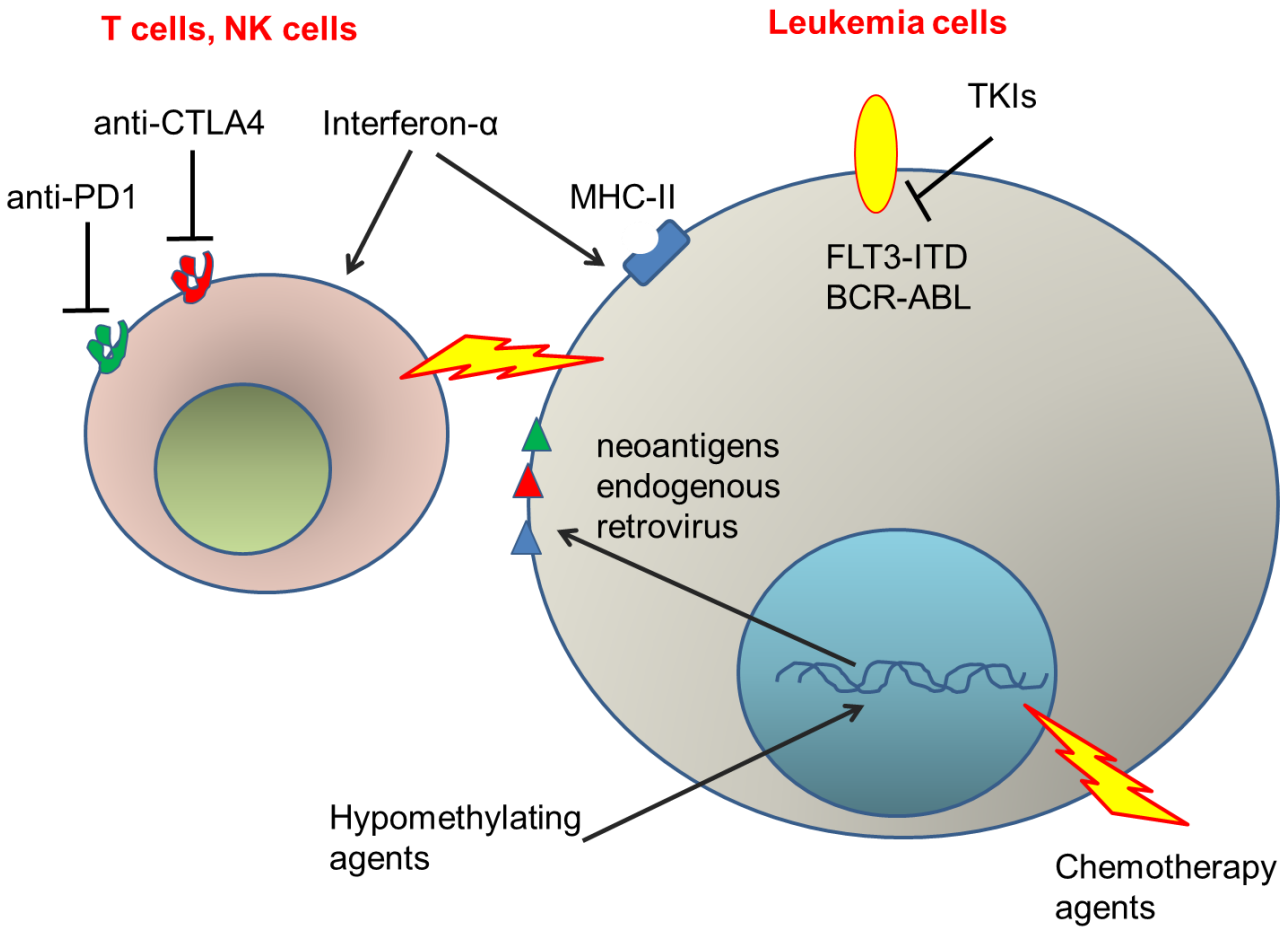




Toffalori NATURE MED 2019, 25:603

- in ALL?

Combination of DLI with other therapies



courtesy R. Zeiser

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post-alloSCT maintenance: Summary

Ph+ ALL

- TKI maintenance established
- drug, dose, starting time according to individual patient factors (BM- / cardio-toxicity)

ALL general

- maintenance not standard
- retrospective data favor prophylactic over preemptive DLI

- needed: prospective trials on risk-stratified prophylactic interventions

Merci and Danke

- Monika Brüggemann, Nicola Gökbuget - GMALL
- Helga Neidlinger - DRST
- Kooperative Transplantstudiengruppe – DAG-HSZT
- Antje Kleinbauer, Cora Gromann – University trial center, Halle

- all centers:
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  Nael Sami Alakel – Dresden
  Guido Kobbe – Düsseldorf
  Anna Brandt – Erlangen
  Dittrich Beelen – Essen
  Gesine Bug – Frankfurt
  Jürgen Finke – Freiburg
  Gerald Wulf – Göttingen
  Nadja Jäkel – Halle
  Michael Stadler – Hannover
  Nicolaus Kroeger – Hamburg
  Stefan Schoenland – Heidelberg
  Vladan Vucinic - Leipzig
  Eva Wagner-Drouet - Mainz
  Johanna Tischer – München
  Matthias Stelljes – Münster
  Daniel Wolff – Regensburg
  Wolfgang Bethge – Tübingen

- Grant support by AMGEN Inc.

DAG HSZT

DRST Deutsches Register für Stammzelltransplantationen

GMALL German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

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