POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

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Leucemia acuta linfoblastica

Felicetto Ferrara

DICHIARAZIONE

Felicetto Ferrara

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(ABBVIE, GLAXO, NOVARTIS, JAZZ, JANNSENN, ASTELLAS, PFIZER)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

Educational Program ASH 2022

New developments in ALL in AYA

Nicolas Boissel

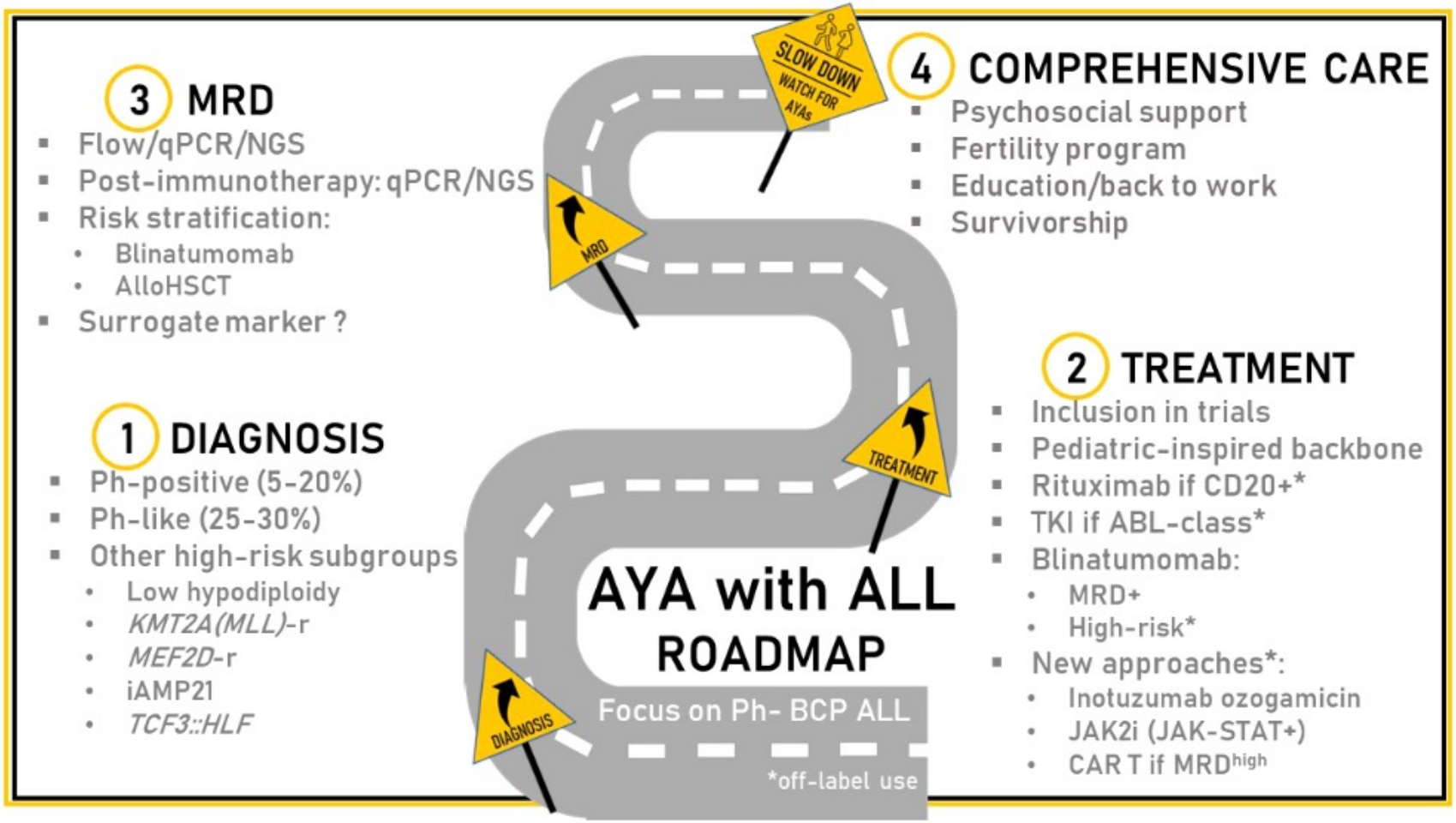
Optimal approach to T-cell ALL

Kristen M. O ' Dwyer

Ph+ ALL in 2022: is there an optimal approach ?

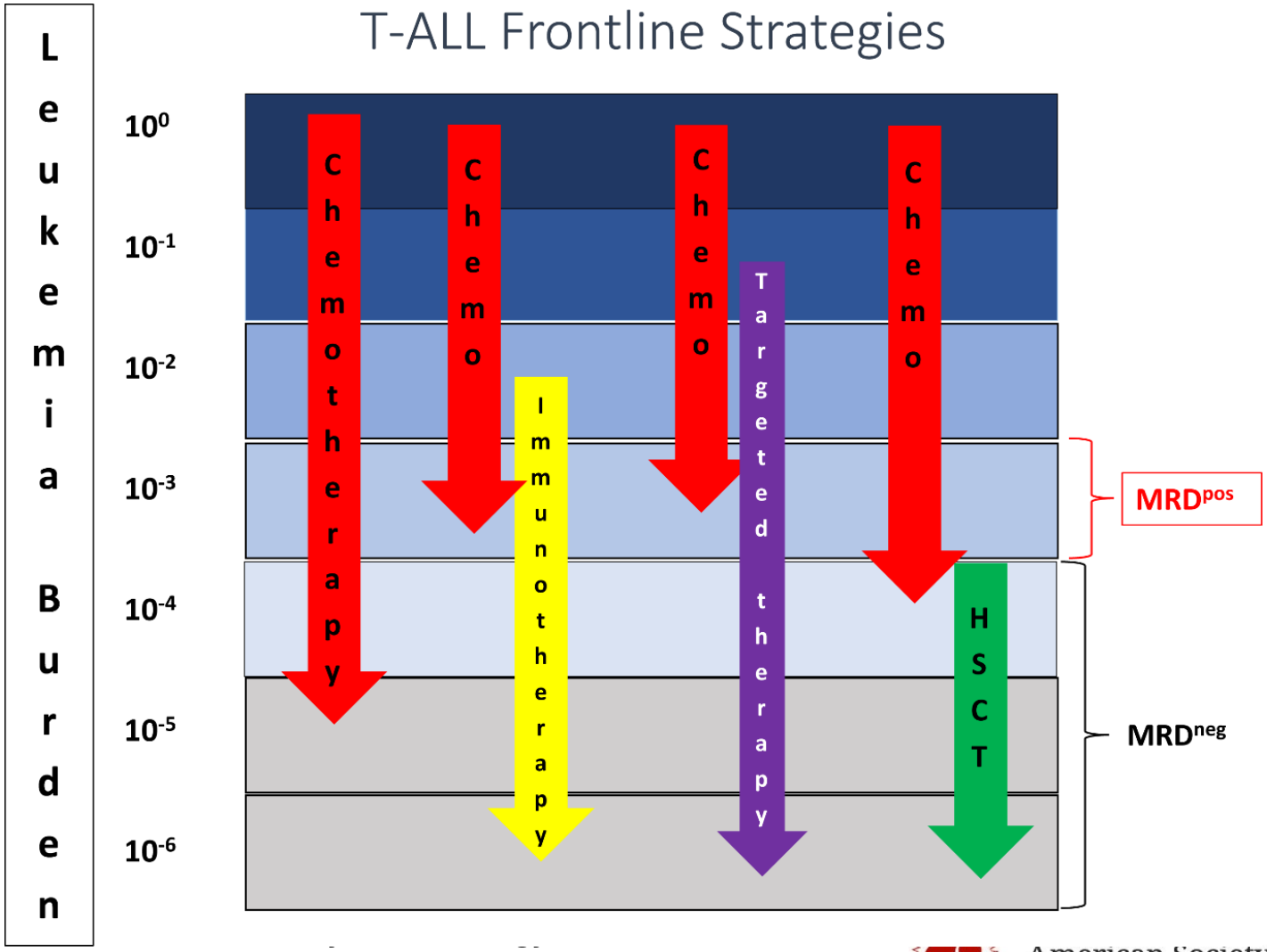
Matthew J. Wieduwilt

New developments in ALL in AYA

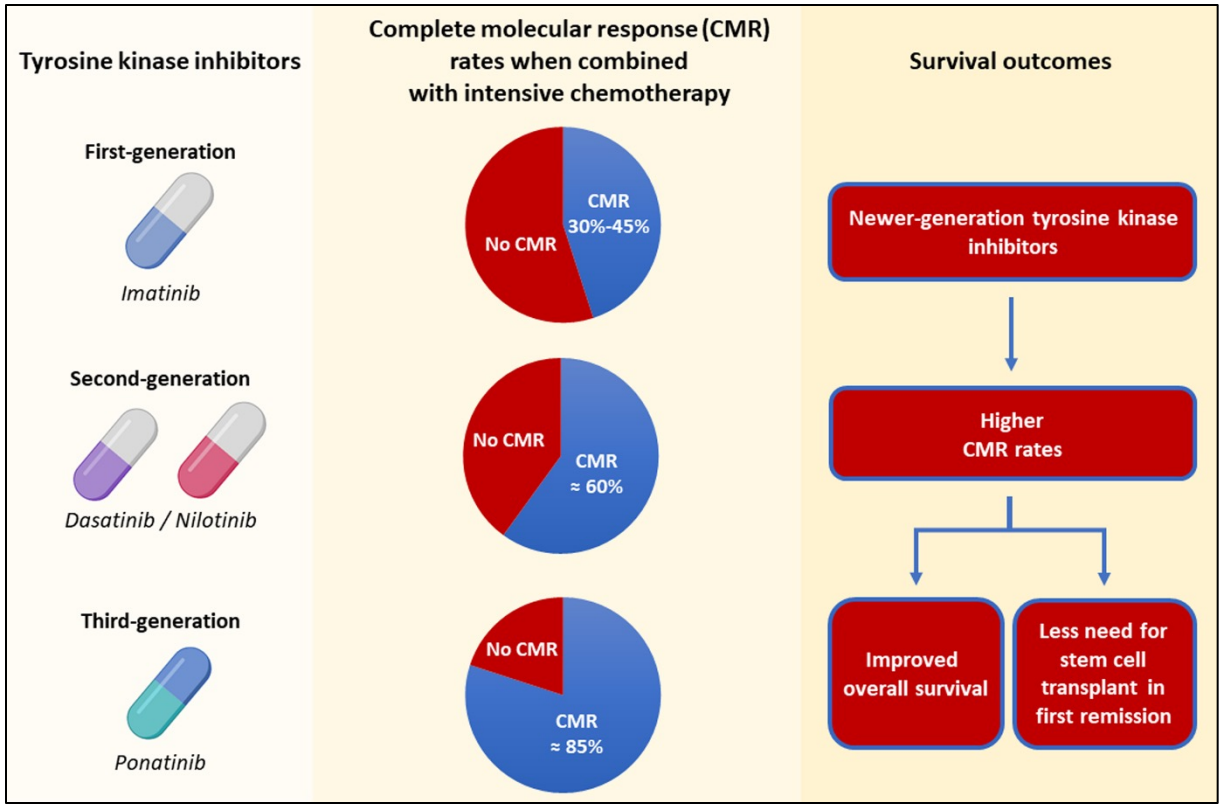


Nicolas Boissel, Hematol Educ Program, 2022,

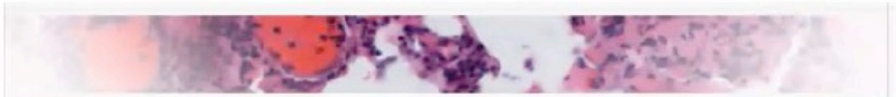
Optimal approach to T-cell ALL



Evidence-Based Minireview: What is the optimal tyrosine kinase inhibitor for adults with newly diagnosed Philadelphia chromosome–positive acute lymphoblastic leukemia?



Fadi G. Haddad, Nicholas J. Short, Hematology Am Soc Hematol Educ Program, 2022,



Inotuzumab Ozogamicin induction followed by standard chemotherapy yields high remission rates and promising survival in older (>55 years) patients with de novo B-lymphoblastic leukemia (GMALL-Initial1 Trial)

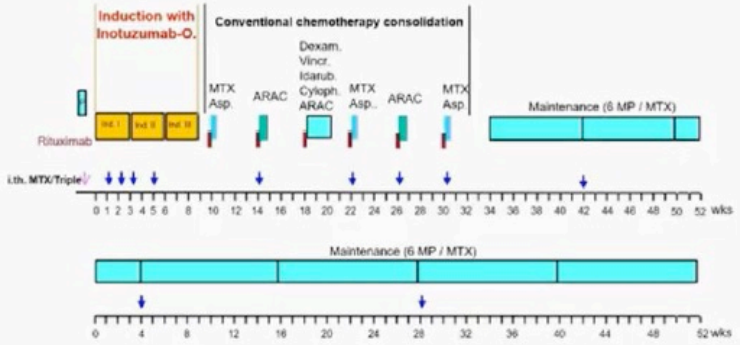
Matthias Stelljes
University of Münster / Germany
for the GMALL study group

INITIAL-1: Phase II Study to Evaluate the Efficacy and Safety of Inotuzumab for ALL Induction Therapy

- **Front line induction treatment with 3 cycles of inotuzumab monotherapy** followed by conventional consolidation for patients >55 years of age
- **Primary objective:** To evaluate the efficacy of an inotuzumab induction therapy, defined as the number of patients being alive in first remission one year after start of induction therapy.
- **Secondary objective:** To evaluate the safety of an inotuzumab ozogamicin induction therapy.

INITIAL-1 Trial: Treatment Schedule

An open label phase II study to evaluate the efficacy and safety of **In**otuzumab Ozogamicin for **I**nduction **T**herapy followed by a conventional chemotherapy-based consolidation and maintenance therapy **In** patients aged 55 years and older with **A**cute **L**ymphoblastic leukemia (ALL)



Stelljes. ASH 2022. Abstr 212.

INITIAL-1: Phase II Study to Evaluate the Efficacy and Safety of Inotuzumab for ALL Induction Therapy

- **Primary endpoint**: Event free survival (EFS) at 12-months follow-up.
  An event is any of the following: persisting bone marrow blasts after two cycles of inotuzumab, relapse or death.
- **Secondary endpoints:** Remission rate and rate of MRD neg. remission after induction treatment; RFS and OS after two years; rate of deaths during induction and / or deaths in CR; proportion of patients with molecular relapse.
- **Hypothesis:** An event rate of ≤40% at 12 months follow-up is considered to qualify the experimental treatment as very promising for additional testing.
- **42 evaluable patients** needed for primary endpoint analysis (type I error probability of α=0.05 and power of 0.80 was chosen).

INITIAL-1 Trial: Patients Characteristics

	n=43
Median age (range), years	64 (56-80)
≥65 years	20 pts
≥70 years	12 pts
Female / male, n	20 pts / 23 pts
Commom ALL / pro B-ALL, n	38 pts / 5 pts
Blasts ≥20% positive for CD20, n	17 pts
Median CD22 expression (range)	69% (21-99%)
Blasts ≥20-40% positive for CD22, n	5 pts
Blasts >40-60% positive for CD22, n	10 pts
Blasts >60% positive for CD22, n	28 pts

INITIAL-1: Main Inclusion and Exclusion Criteria

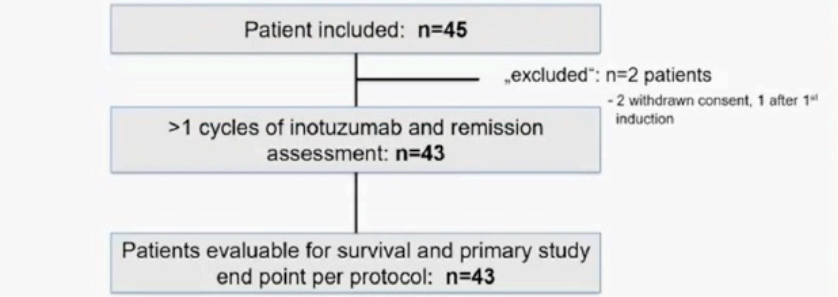
Main inclusion criteria

1. Male or female patients, > 55 years of age and fit for therapy
2. CD22-positive acute lymphoblastic
3. No previous ALL-specific treatment with the exception of a pre-phase
4. With or without documented CNS involvement

Main exclusion criteria

1. Philadelphia-chromosome or BCR-ABL positive ALL
2. Burkitt's or mixed phenotype acute leukemia based on the WHO 2008 criteria
3. Peripheral absolute lymphoblast count >10 /nl before start of study medication

INITIAL-1 Trial: Consort diagram



13 study sites in Germany, first / last patient included: June 2018 / April 2021

Stelljes. ASH 2022. Abstr 212.

GMALL-INITIAL1: Study Design

- **Single-arm, open-label phase II trial**

Patients aged >55 yr with untreated CD22+, Ph- ALL considered fit for therapy ± documented CNS involvement (N = 45)

Induction (up to 3 cycles)	Consolidation	Maintenance	
Inotuzumab Ozogamicin 0.5 mg/m^2 D1, 8, 15 each cycle*†	**Conventional Chemotherapy**	**6-Mercaptopurine/ Methotrexate**	*2 yr*

***Cycle 1, D1 dose 0.8 mg/m^2. †In combination with 10 mg/m^2 dexamethasone D7, 8 and D14, 17 plus MTX, AraC, Dex.**

- **Primary endpoint:** 12-mo EFS
- **Secondary endpoints:** CR rate, MRD negativity after induction, 2-yr RFS, 2-yr OS, deaths during induction or CR, molecular relapse, safety

Stelljes. ASH 2022. Abstr 212.

INITIAL-1 Trial: Response rates

Evaluable for hematological remission, n=43	
CR / CRi after 2 induction cycles	43 pts (100%)
Patients receiving 3 cycles inotuzumab	42 pts (94%)*
Early deaths within the first 6 months	0
Evaluable for MRD (by PCR), n=43	
MRD negative after after the 2nd induction cycle	23/43 pts (53%)
MRD negative after after three induction cycles	31/42 pts (74%)
Time between 1st - 2nd induction, median (range)	21 days (21-31)
Time between 2nd - 3rd induction, median (range)	28 days (27-33)
Time between 3rd induction - 1st consolidation, median (range)	30 days (26-42)

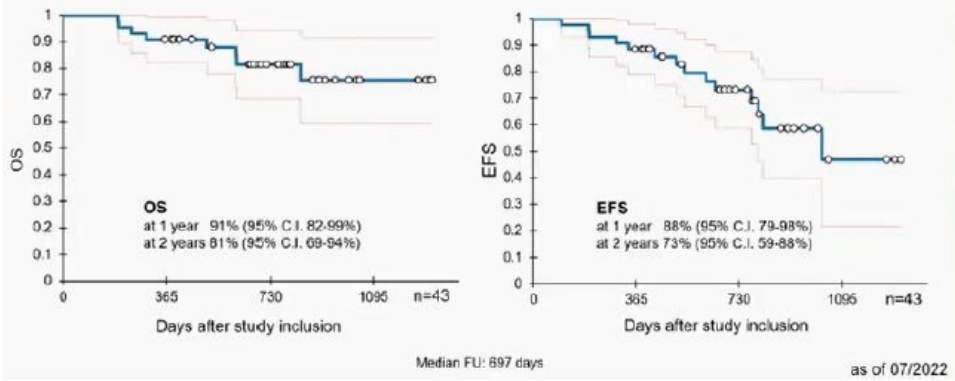
* 1 pts. received only 2 induction cycle (died in mol. CR)

INITIAL-1 Trial: Events; subsequent treatment for measurable residual disease / relapse

Events within the 1st year	
Persisting disease / relapse / death in CR, 1st year, n	**0 / 2 / 3 (event rate 12 %)**
Subsequent treatment	
- with blinatumomab, n#	7 (5 relapse / 2 MRD)
- with inotuzumab, n#	3 (relapse)
- with CAR-T cells, n#	1 (relapse)
- Allogeneic HCT, n#	10 (4 in 1st CR / 6 after relapse)*

as of 07/2022
* 7 alive after allo SCT at last FU

INITIAL-1 Trial: Overall survival and Event Free Survival



INITIAL-1 Trial: Adverse Events

AEs >5% (CTC 3-4; CTCAE 4.0)	Induction 1 (n=43)	Induction 2 (n=43)	Induction 3 (n=42)*
Leukocytopenia, %	74	19	2
Anemia, %	37	5	0
Thrombocytopenia, %	49	7	2
Elevation of GOT / GPT, %	14	0	0
Elevation of bilirubin, %	2	0	0
Hyperglycemia, %	12	5	2
Febrile neutropenia, %	5	0	0
veno occlusive disease, %	0	2 (1 pts.)	0

* one patient has been reported with suspected veno occlusive disease (after 2nd induction therapy)

Stelljes. ASH 2022. Abstr 212.

GMALL-INITIAL1: Investigators' Conclusions

- Inotuzumab ozogamicin monotherapy appeared to be highly effective as frontline induction therapy for patients >55 yr of age with newly diagnosed CD22+ B-lymphoblastic leukemia
  - MRD-negative CR after 3 induction cycles: 74%
  - OS after 2 yr (following conventional consolidation and maintenance): 81%
- Toxicity acceptable with no early deaths within first 6 mo
- Investigators suggested that inotuzumab induction therapy be evaluated in prospective trials for possible integration with other regimens

Stelljes. ASH 2022. Abstr 212.

ECOG-ACRIN E1910: Background

- Adults with newly diagnosed ALL who achieve CR with conventional chemotherapy often relapse, even if MRD is negative after induction, leading to suboptimal survival outcomes
- Blinatumomab: bispecific T-cell engager that binds to both CD19 and CD3
  - FDA approved for treatment of CD19+ B-ALL in first or second CR with MRD ≥0.1% and for treatment of R/R CD19+ B-ALL
- E1910-ACRIN E1910 NCTN phase III trial investigated consolidation chemotherapy ± blinatumomab to determine if addition of blinatumomab improved outcomes for patients who become MRD negative (<0.01%) after induction chemotherapy
  - Current analysis reflects median follow-up of 3.6 yr (43 mo)

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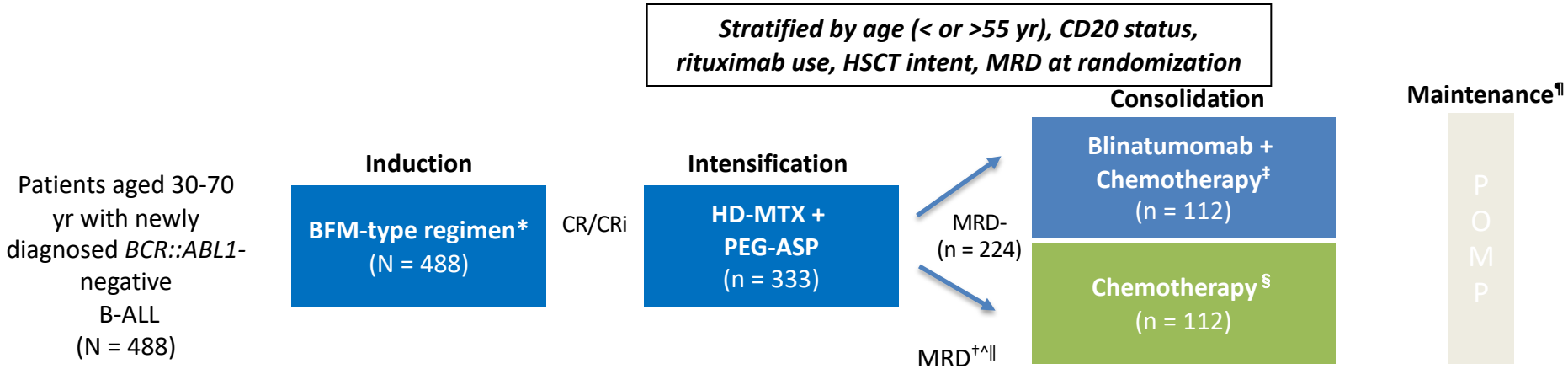
ECOG-ACRIN E1910: Study Design

- **Multicenter, randomized, open-label phase III trial**



- **Regimen adapted from E2993/UKALLXII trial, including extended remission induction, addition of PEG-ASP for patients <55 yr of age, and addition of rituximab for CD20+ disease.** †
- **<u>MRD assessed centrally by 6-color flow cytometry, with cutoff of ≤0.01% for MRD negativity</u>.** ^

- **Primary endpoint:** OS in MRD^{neg} patients
- **Key secondary endpoints:** MRD status, RFS

Litzow. ASH 2022. Abstr LBA1.

STUDY FLOW

- **286 patients underwent MRD assessment, with 224 being negative and 62 being positive.**
- **After blinatumomab regulatory approval in March 2018 for MRD^{pos} *BCR::*$ABL1^{neg}$ B-ALL, MRD^{pos} patients were assigned to Blina arm and no longer randomized. .**

- **2.5 yr of maintenance POMP timed from start of intensification.**
- **Patients could undergo alloHSCT at discretion of treating physician, ideally after first 2 cycles of Blina in experimental arm or at any time following intensification in control arm.**

Litzow. ASH 2022. Abstr LBA1.

ECOG-ACRIN E1910: Patient Characteristics

- **Postinduction CR/CRi rate: 81% (395/488)**
  - **CR rate: 75% (364/488)**
  - **CRi rate: 6% (31/488)**
- **MRD status after intensification**
  - **MRD^{neg}: 78% (224/286)**
  - **MRD^{pos}: 22% (62/286)**
- **At third interim analysis, 80% of patients assigned to experimental arm received ≥2 cycles of blinatumomab**

- Baseline characteristics well balanced between arms

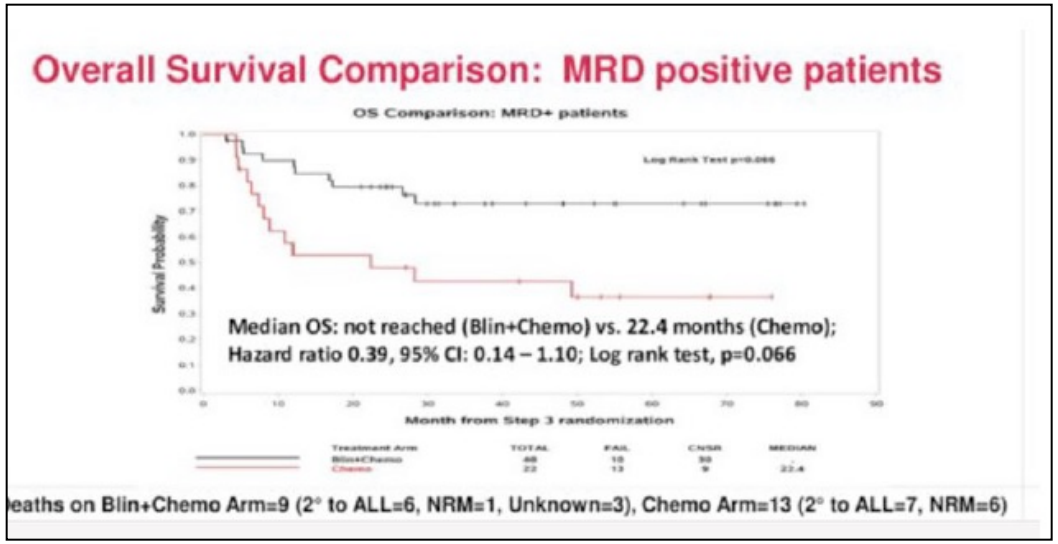
Characteristic	Blinatumomab + Chemotherapy (n = 152)	Chemotherapy (n = 134)
Median age, yr (range)	51 (30-70)	
MRD^{neg}, n	**112**	**112**
▪ Proceeded to HSCT, n	**22**	**22**
MRD^{pos}, n	40	22

Litzow. ASH 2022. Abstr LBA1.

ECOG-ACRIN E1910: OS in MRD^{pos} Disease

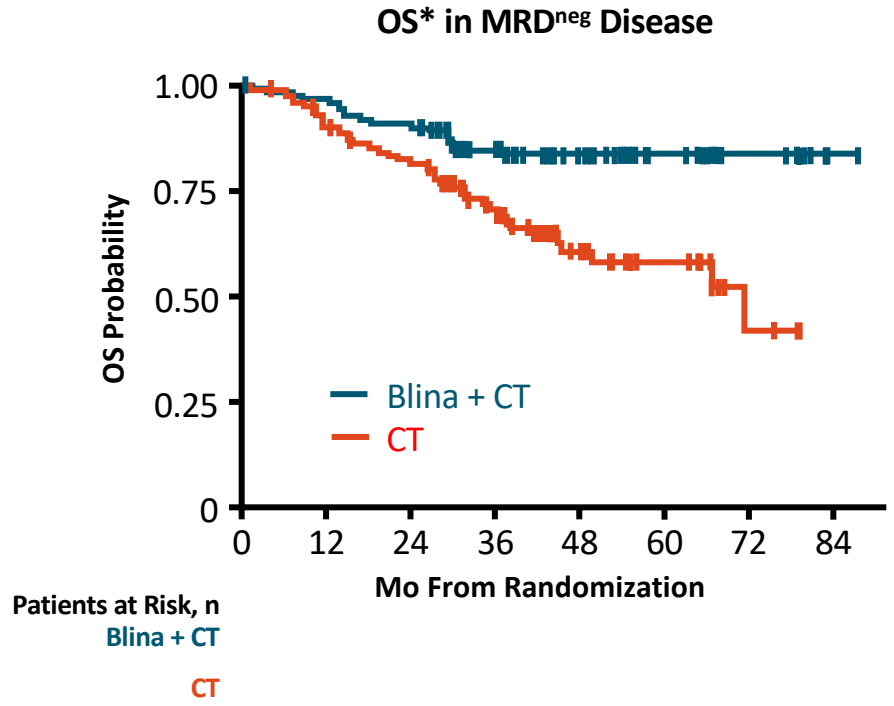
Efficacy Outcome	Blinatumomab + Chemotherapy (n = 40)	Chemotherapy (n = 22)	HR (95% CI)	*P* Value
Median OS, mo	Not reached	22.4	0.39 (0.14-1.10)	.066
▪ Deaths, n	9	13	--	--

- Blinatumomab demonstrated benefit in MRD^{pos} patients



Litzow. ASH 2022. Abstr LBA1.

ECOG-ACRIN E1910: Survival in MRD^{neg} Disease



	Blina + CT (n = 112)	CT (n = 112)	HR (95% CI)	*P*
mOS,* mo	NR	71.4	0.42 (0.24-0.75)	.003
▪ 3.6-yr OS, %	83	65		
▪ Deaths, n	17†	39‡		
mRFS, mo	NR	22.4	0.46 (0.27-0.78)	.004

*Primary endpoint. †n = 8 secondary to ALL, n = 9 NRM.
‡n = 20 secondary to ALL, n = 17 NRM, n = 2 unknown.

- At third interim efficacy analysis, ECOG-ACRIN DSMB recommended releasing results due to benefit observed with blinatumomab in MRD^{neg} disease

Litzow. ASH 2022. Abstr LBA1.

ECOG-ACRIN E1910: Investigators' Conclusions

- Results from this randomized phase III trial demonstrated **significant OS benefit with addition of blinatumomab to chemotherapy as consolidation therapy in adult patients with MRD-negative *BCR::ABL1*-negative B-ALL**
- Blina + CHT was well tolerated, and no new safety signals were observed
- Investigators concluded that addition of Blina to consolidation chemotherapy **represents new standard of care for patients with MRD-negative *BCR::ABL1*-negative B-ALL**

Litzow. ASH 2022. Abstr LBA1.

Novità dal Meeting della Società Americana di Ematologia

Poster 2727

Safety and Pharmacokinetics of Subcutaneous (SC) Blinatumomab for the Treatment of Adults With Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (R/R B-ALL): Results From a Phase 1b Study

Pilar Martínez-Sánchez[1], Gerhard Zugmaier[2], Paul Gordon[3], Elias Jabbour[4], José Juan Rifón[5], Stefan Schwartz[6], Erika Borlenghi[7], Francoise Huguet[8], Jesús María Hernández Rivas[9], Federico Lussana[10], Céline Berthon[11], Priti Kadu[12], Hansen Wong[13], Ana Markovic[3], Yuliya Katlinskaya[13], Alessandro Rambaldi[14,15]

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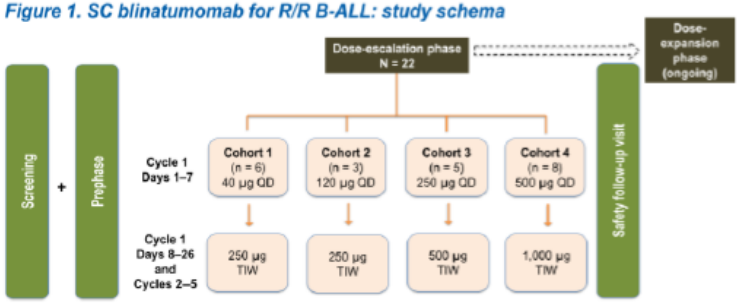
22 patients, median age: 50 years (19-83)

METHODS

Study Design

Figure 1. SC blinatumomab for R/R B-ALL: study schema



Bone marrow evaluation was performed on day 27 of each cycle and additionally on day 12 of cycle 1 in cohorts 3 and 4.
QD, once daily; R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; SC, subcutaneous; TIW, three times weekly.

Pharmacokinetic and pharmacodynamic assessments

- Blinatumomab serum concentrations, lymphocyte numbers, and serum cytokine concentrations were assessed predose and/or postdose for select doses in treatment cycles 1 and 2 per protocol.

Safety assessments

- Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

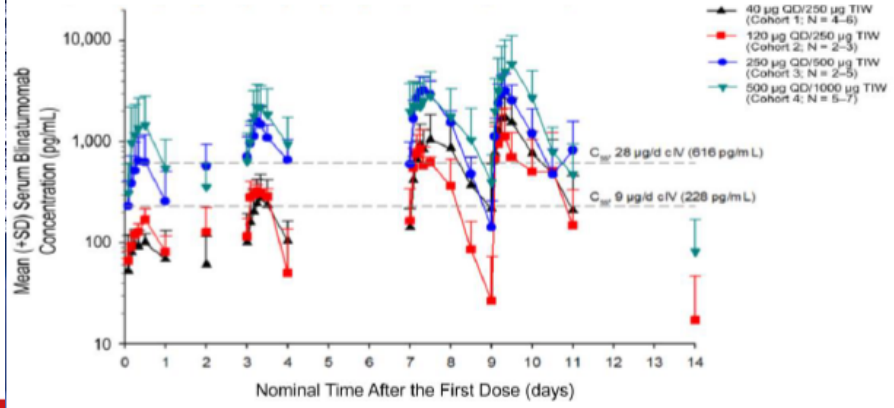
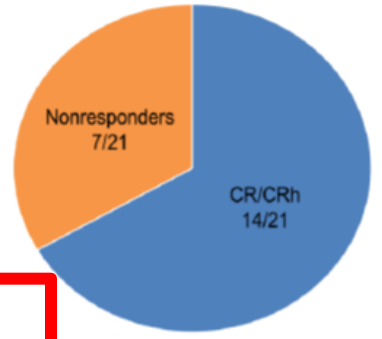


Table 2. Summary of treatment-emergent adverse events

	Total (N = 22)	Cohort 1 (n = 6)	Cohort 2 (n = 3)	Cohort 3 (n = 5)	Cohort 4 (n = 8)
TEAEs (any grade)	22 (100.0)	6 (100.0)	3 (100.0)	5 (100.0)	8 (100.0)
Grade ≥ 3 TEAEs	19 (86.4)	6 (100.0)	2 (66.7)	4 (80.0)	7 (87.5)
Serious TEAEs	18 (81.8)	4 (66.7)	2 (66.7)	5 (100.0)	7 (87.5)
Serious TEAEs leading to discontinuation of SC blinatumomab (excluding disease progression)	3 (13.6)	1 (16.7)	0 (0.0)	1 (20.0)	1 (12.5)
Fatal adverse events	3 (13.6)	1[a] (16.7)	0 (0.0)	1[b] (20.0)	1[c] (12.5)
Grade ≥ 3 TEAEs of interest					
Cytokine release syndrome	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2[b] (25.0)
Blinatumomab-associated neurotoxicity[e]	6 (27.3)	1 (16.7)	0 (0.0)	1 (20.0)	4[f] (50.0)
Transient liver enzyme elevation	2 (9.1)	0 (0.0)	0 (0.0)	1 (20.0)	1 (12.5)

[a]Grade 5 herpes encephalitis unrelated to SC blinatumomab. [b]Progressive disease. [c]Refractory bleeding event unrelated to SC blinatumomab and disease progression. [d]Each event resolved within 48 h and subsequent cycle 1 dose was restarted. [e]At week 1 of treatment with SC blinatumomab. [f]Two patients with neurotoxicity in week 1 and two patients in week 4, one associated with nonresponse and the other with the concomitant use of psychotropic (antipsychotic) medications.
SC, subcutaneous; TEAE, treatment-emergent adverse event.

- Response evaluation was available for only 21[a] of 22 patients.
- Fourteen of 21 (66.7%) evaluable patients achieved CR/CRh within one cycle of SC blinatumomab
  - Cohort 1, 3/6 (50.0%)
  - Cohort 2, 2/3 (66.7%)
  - Cohort 3, 4/5 (80.0%)
  - Cohort 4, 5/7 (71.4%)
    - Two patients who did not respond were underexposed to SC blinatumomab based on serum levels of blinatumomab.
- Thirteen of 14 patients with CR/CRh were MRD-negative after cycle 1 of SC blinatumomab
  - Eight of 14 patients underwent bone marrow evaluation at day 12, of which 100% of patients were MRD-negative on day 12



Investigators' Conclusions

- **In this ongoing phase 1b dose-escalation study, SC Blina demonstrated an acceptable safety profile and anti-leukemia activity in heavily pretreated pts with R/R B-ALL.**
- **No dose-limiting toxicities were reported in any cohort.**
- **PK exposures and PD profiles were consistent with those reported for the cIV regimen of blinatumomab, supporting the use of SC dosing of blinatumomab in this pt population.**

Pilar Martínez Sánchez et al, PO 2727

51 Results of the Risk-Adapted, MRD-Stratified GMALL Trial 08/2013 in 281 T-ALL / T-Lbl Patients: Excellent Outcome of Standard Risk Thymic T-ALL

Different Strategies to Classify T-ALL

EGIL	GMALL		GRAALL
Pro (T-I) Pre (T-II) Cortial (T-III) Mature (T-IV) α/ß (group a) γ/δ (group b)	Early Thymic Mature	ETP Near ETP ETP-like non ETP? Immature (IM0, IMδ, IMγ) Mature α/ß Mature γ/δ	NOTCH1/FBXW7 RAS/PTEN International Consensus Classification ETP with BCL11B ETP NOS T-ALL NOS provisional (N=8)

Coustan-Smith et al 2009; Kim et al, 2019; Bond et al, 2016
Bene Leukemia 1995; Trinquand et al, 2013; Arber 2022.
Pölönen et al, ASH 2022 ,#718 Meyer et al, ASH 2022, #716

GMALL Approach: Immunologic Subtypes in ALL

Todorova et al, DGHO 2021

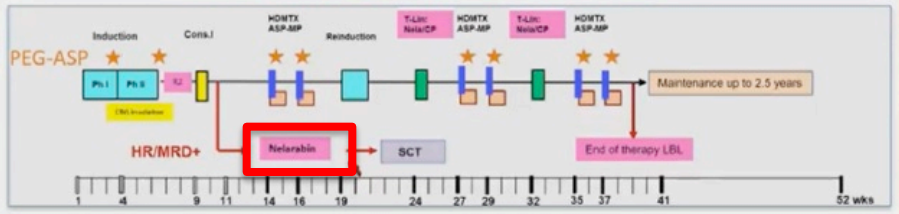
All: CD7+, cyCD3+

	Group	Subtype	Immunophenotype
High Risk	Early T	Pre-T (CD2-)	CD2-, CD1a-
		Pre-T (CD2+, CD5-)	CD2+, CD1a-, CD5-, sCD3-, CD4-, CD8-
Standard Risk	Thymic T	Thymic T	CD1a+
	Mature T	Mature T (sCD3+)	CD2+, CD1a-, sCD3+
High Risk		Mature T (sCD3-)	CD2+, CD1a-, sCD3-, CD5+

- Pre-T largely includes ETP ALL
- Large discrepancy between EGIL pre-T and GMALL early T

GMALL 11/2022

GMALL Trial 08/2013: Flow Sheet for T-ALL



- BFM-based ‚pediatric' regimen
- Dexa during induction/consolidation I
- 9 x PEG-asparaginase (2000 - 1000 – 500 U/m²)
- 7x HDMTX (1.5 g/m²)
- Reinduction
- Risk-adapted SCT indication
- Randomization 2 for HR pts with MolCR before Cons I: SCT vs Chemo

Risk stratification for T-ALL: HR: >= 1 risk factor
- early / mature T
- No CR after induction I
+ Molecular Failure after Consolidation I

Final Total Recruitment: 1023
Recruitment Duration: 6 years

GMALL 11/2022

GMALL Trial 08/2013: T-ALL and T-LBL Patient Characteristics: Age 18-55 yrs

Between 8/2017-3/2022 pts from 78 centers

	Total	T-ALL	T-LBL	Thymic	Early	Mature
Number	281	208	73	95	78	35
Median age	30	29	31	29	30	28
Gender (female)	22%	22%	25%	23%	24%	11%
Mediastinal tumor	58%	52%	75%	65%	37%	49%
CNS involvement	8%	10%	3%	8%	9%	14%
WBC (median)	13.119	23.380	8.200	27.500	14.740	42.600
WBC>100.000	12%	16%	0	15%	10%	34%
Subtype (available)		208 (100%)	46 (63%)	-	-	-
Early		78 (37%)	14 (30%)	-	-	-
Mature		35 (17%)	3 (6%)	-	-	-
Thymic		95 (46%)	29 (63%)	-	-	-

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GMALL Trial 08/2013: T-ALL and T-LBL
Hematologic Reponse to Induction and Consolidation I

	Total	T-ALL	T-LBL	Thymic	Early	Mature
Evaluable	268	200	68	93	73	35
CR/CRu	84%	87%	74%	88%	88%	80%
Early death	4%	5%	1%	4%	5%	6%
PR	10%	7%	21%	8%	5%	9%
Failure	2%	1%	4%	0%	1%	3%

- Similar CR rates in all ALL subtypes
- Early death rates constant over decades:
- ED Causes: Mostly infections
- PR/Failure mainly extramedullary

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GMALL Trial 08/2013
Response Assessment in T-LBL (including PET)

Conventional \ PET	Negative	Positive
CRu (N = 14)	12 (86%)	2 (14%)
PR (N = 14)	7 (50%)	7 (50%)

1 Relapse
1 Extramedullary

2 Relapses
1 Mediastinum
1 Bone marrow

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GMALL Trial 08/2013: T-ALL and T-LBL
Molecular Reponse after Consolidation I

	Total	T-ALL	T-LBL	Thymic	Early	Mature
No MRD Marker (clonal Ig/TCR rearrangements)	26%	15% (3% no test)	63% (84% no test)	1%	34%	14%

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GMALL Trial 08/2013: T-ALL and T-LBL
Molecular Reponse to Induction and Consolidation I

	Total	T-ALL	T-LBL	Thymic	Early	Mature
Evaluable	174	156	18	84	44	28
Molecular CR	70%	69%	78%	82%	48%	64%
Molecular Failure	10%	11%	6%	2%	27%	11%
Molecular Intermediate	20%	20%	17%	15%	25%	25%

Pts with evaluable MRD test after consolidation I; calculated in relation to CR pts; Molecular CR (MolCR): MRD negative with sensitivity of at least 0.01%; Molecular Failure (MolFail): MRD positive above 0.01%; Molecular Intermediate (MolIMR): MRD positive below 0.01%.

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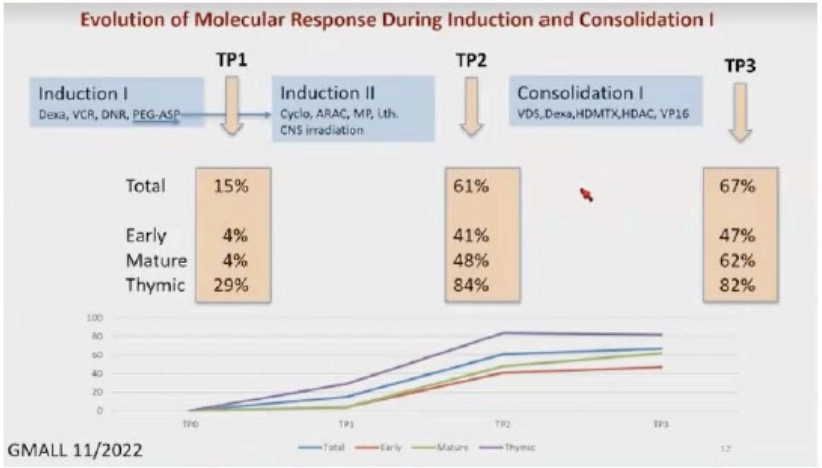

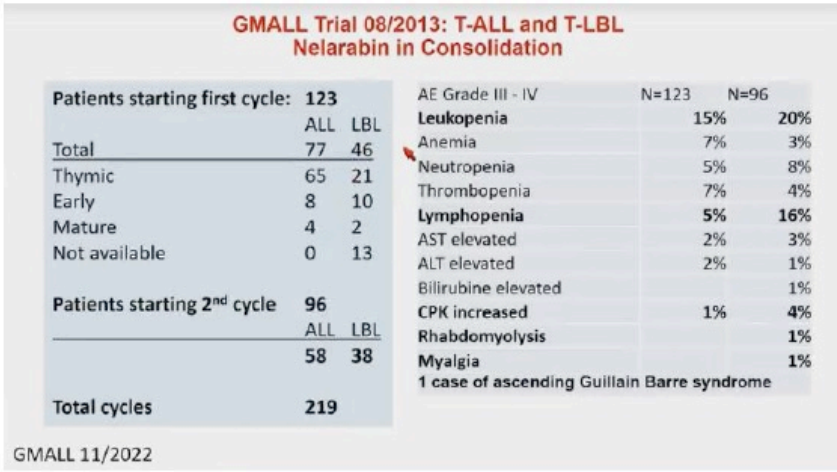

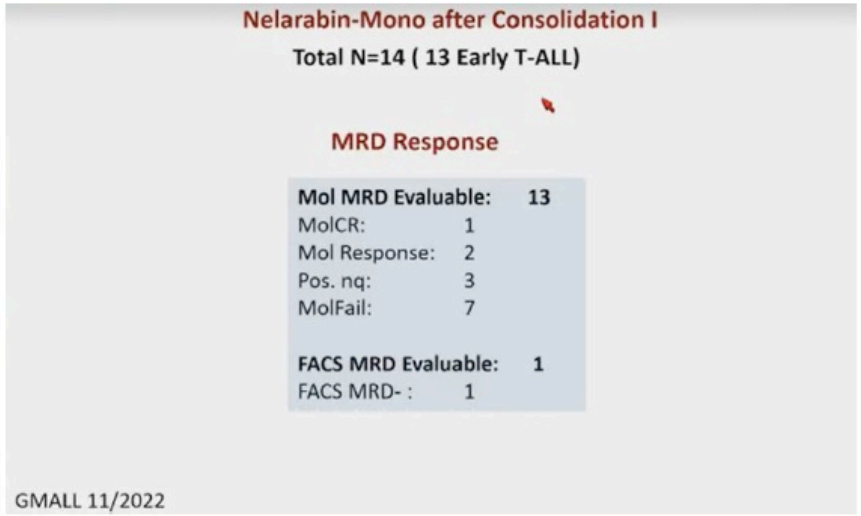

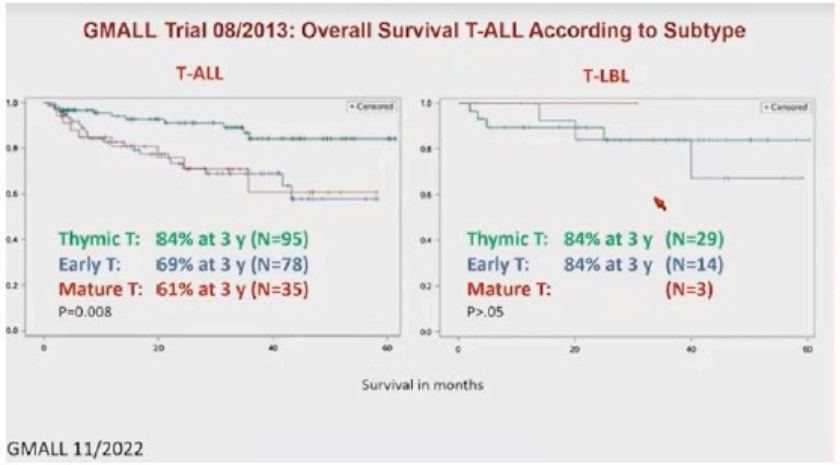

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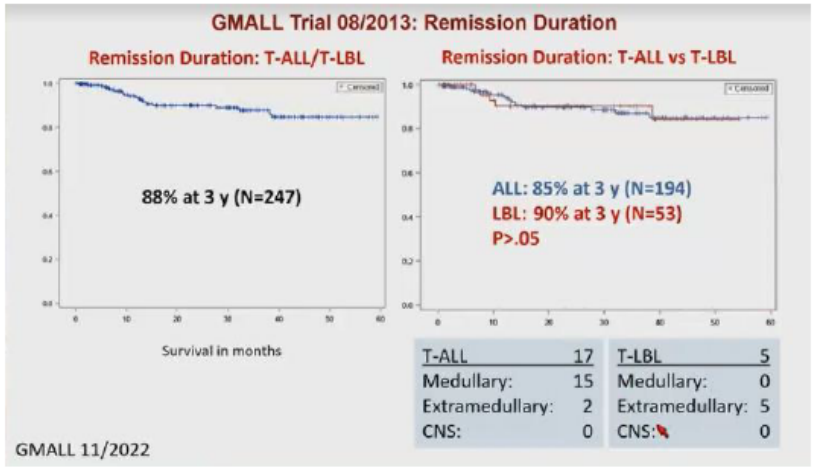

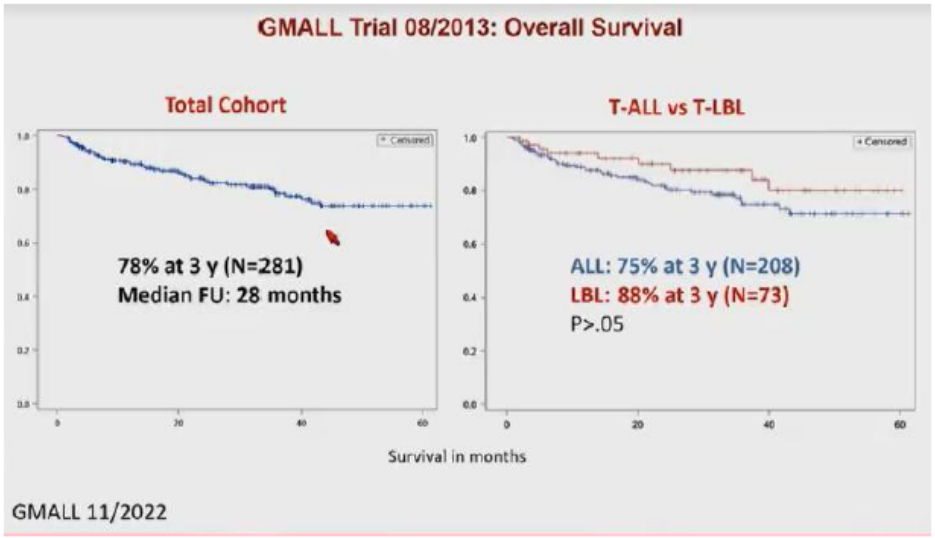

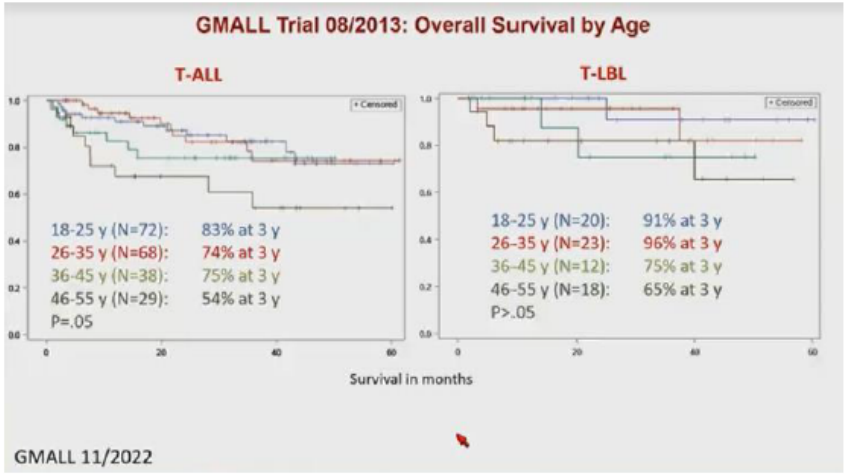

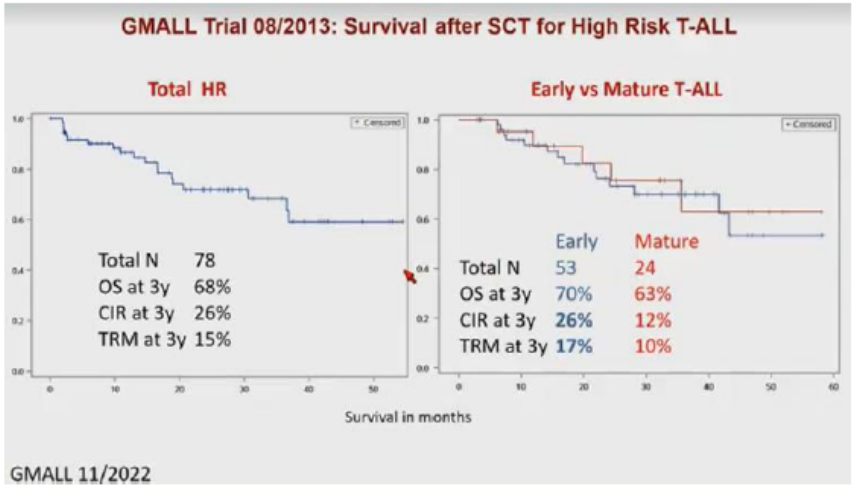

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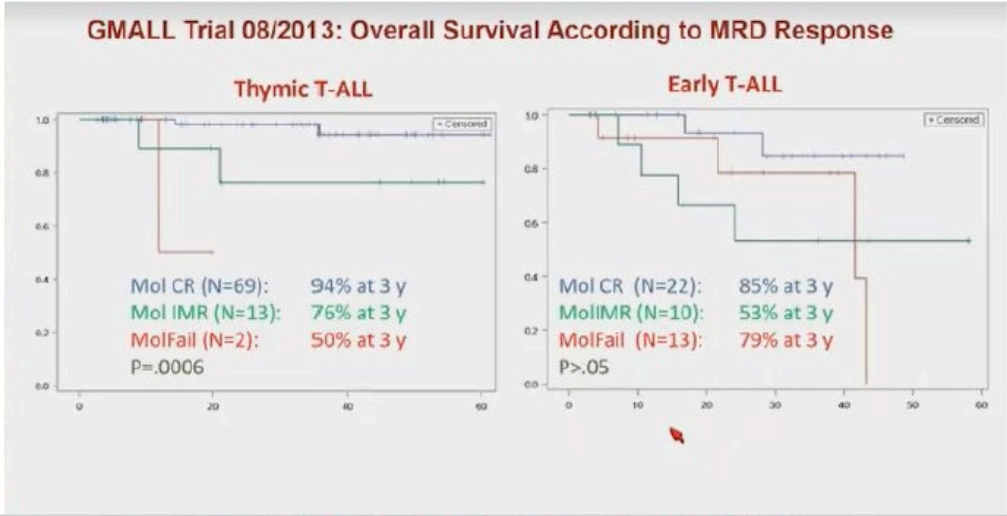

GMALL Trial 08/2013: Conclusions for T-ALL

- **Pediatric-based regimen feasible and effective up to 55 yrs**
- **Intensive / individualized ASP therapy feasible in a large multicenter setting**
- **Excellent results in T-LBL; no prognostic indicator; no clear impact of PET**
- **High CNS efficacy (zero CNS relapses)**
- **Simple risk stratification of T-ALL based on CD1a expression**
  - Not part of International Consensus / WHO classification
  - No international harmonization of classifications
- **Excellent response and survival of thymic T-ALL**
  - Further molecular stratification within thymic T-ALL helpful?
  - Higher risk: WBC >100.000? **MRD intermediate?**
  - Impact of Nelarabin consolidation probable but remains to be analyzed
- **Improved outcome of early T-ALL (role of SCT) but still non-satisfactory**
  - Poor MRD response and higher relapse rate
  - Higher mortality after SCT
  - Alternative MRD markers required
  - Nelarabine for MRD eradication ineffective
  - New compounds for MRD persistence needed: Bortezomib, Venetoclax, CD38-AB?

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