AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

Presidente
A. Mastronuzzi

Segreteria Scientifica
A. Colombini, T. Perillo, A. Zibaldo

Giornate AIEOP

BOLOGNA
Zanhotel Europa

14-15 Aprile 2025

Linfomi non Hodgkin

Marta Pillon
Azienda Ospedaliera Università di Padova

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda					X		
Jazz Pharma					X	X	
Pierre Fabre					X		

Resoconto attività 2024-25

- Gruppo europeo EICNHL (SIOPE), Milano Maggio 2024

- Congresso AIEOP, Bologna Ottobre 2024

- GdL LNH 11.10.2024 - Virtual

- Gruppo europeo EICNHL, Barcellona Novembre 2024

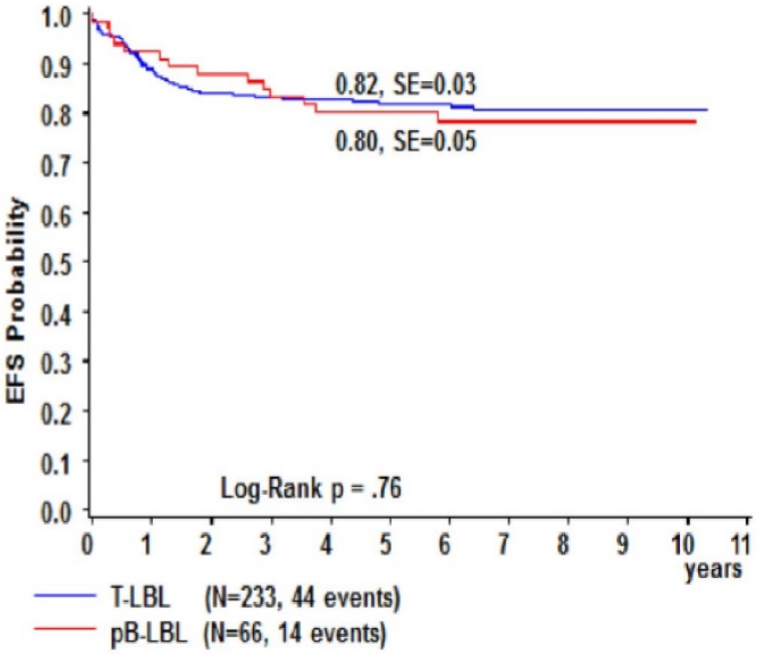
- GdL LNH allargato 04.02.2025 – Virtual

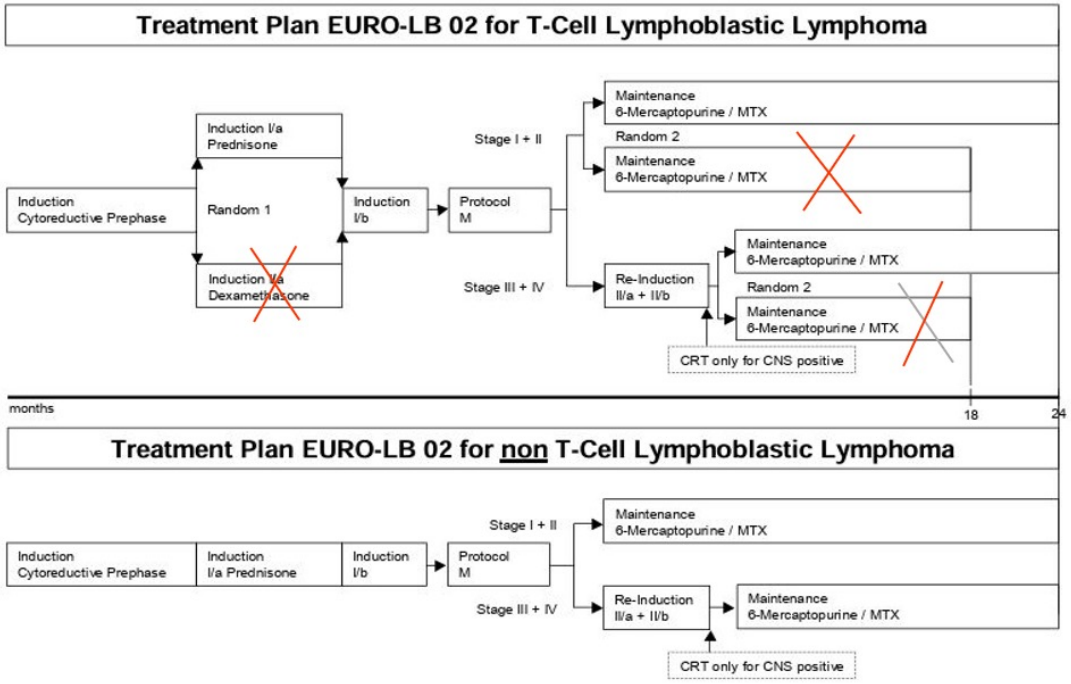
- Riunioni del gruppo EICNHL ristretto

Componenti: Teresa Battaglia, Salvatore Buffardi, Luca Lo Nigro, Rossella Mura, Lara Mussolin, Matilde Piglione, Alessandra Sala, Elisabetta Schiavello, Annalisa Tondo, Luciana Vinti

Linfoma Linfoblastico

Protocollo EURO-LB02 (no random)





Landmann E, Haematologica 2017
(Stop random 2008)

Linfoma Linfoblastico

LBL 2018

International cooperative treatment protocol for children and adolescents with lymphoblastic lymphoma

EudraCT-Nr.: 2017-001691-39
(EU-CT Nr.: 2023-508101-24-00)

Sponsor:
Universitätsklinikum Münster
Albert-Schweitzer-Campus 1

LBL 2018: Participating study groups
(status October 2023)

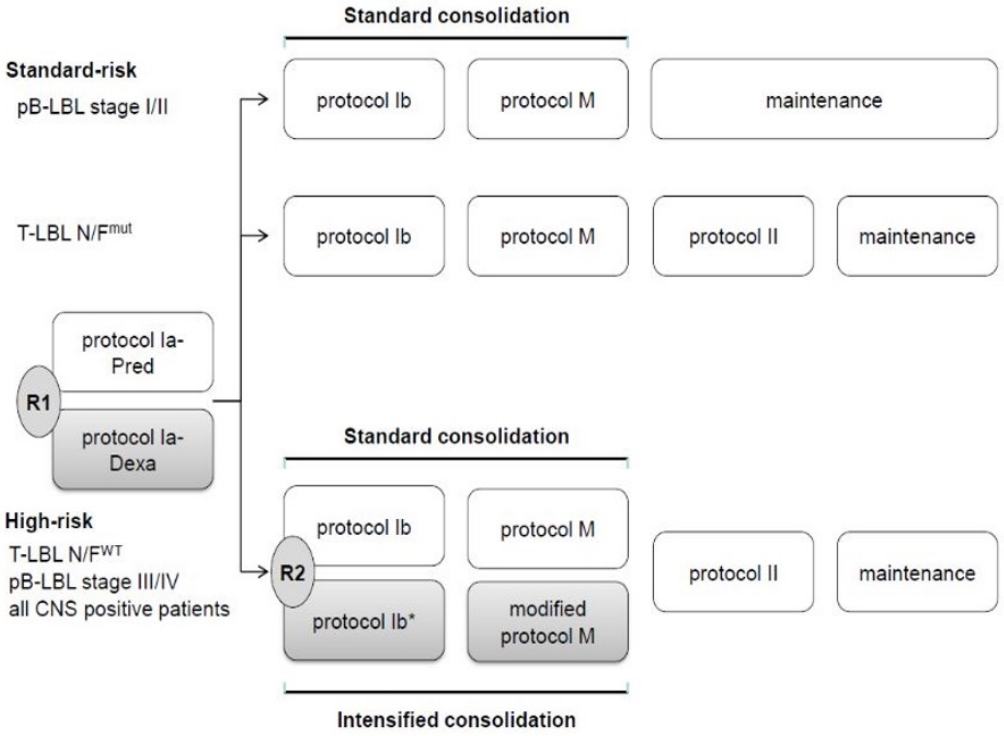
core study cohort

AIEOP	Italy
BFM	Austria, Czech Republic, Germany, Switzerland
BSPHO	Belgium
CoALL	Germany
DCOG	The Netherlands
NOPHO	Denmark, Finland, Norway, Sweden
PPLSG	Poland
SEHOP	Spain
SFCE	France
HKPHOSG	Hong Kong

extended study cohort

HPOG	Hungary
ISPHO	Israel
NSPHO	Moscow
SHOP	Portugal
SPS	Slovak Republic

LBL 2018 – Treatment plan



Apertura ufficiale del primo centro AIEOP giugno 2023

Al 30/03/2025:

20 pazienti arruolati

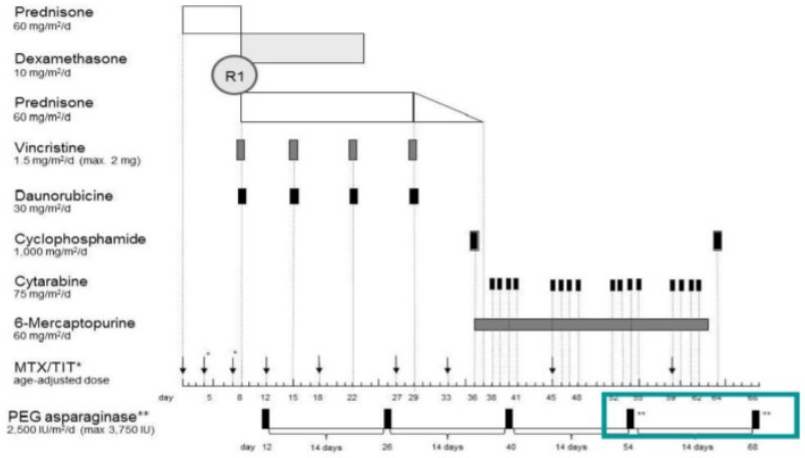
21/28 centri aperti all'arruolamento (75%), 3 centri in fase di attivazione

21 Site Initiation Visits

10 Monitoring Visits

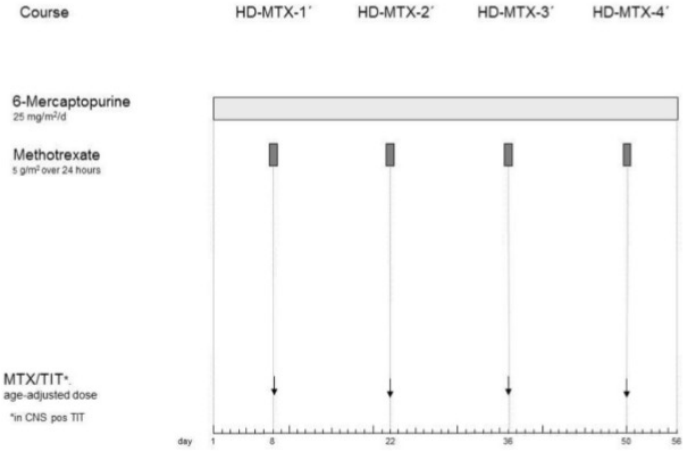
16.4 Schema of induction protocol I

R2 intensified arm



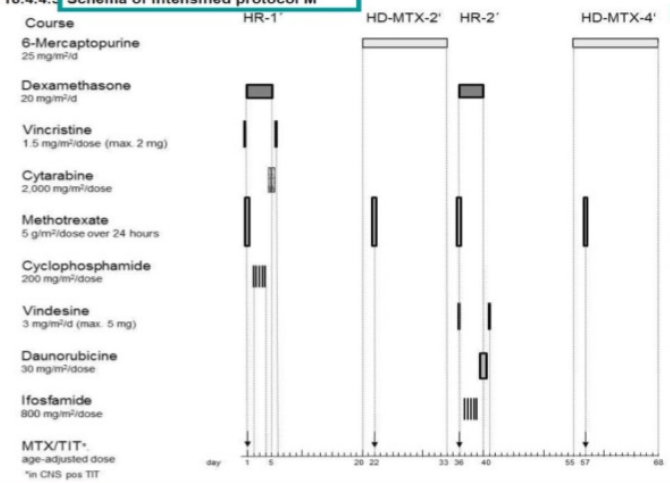
*in CNS pos pts twice weekly until clearance of blasts, 1st dose MTX IT, then TIT; **please strictly adhere to 14-day interval

16.4.4.4 Schema of protocol M

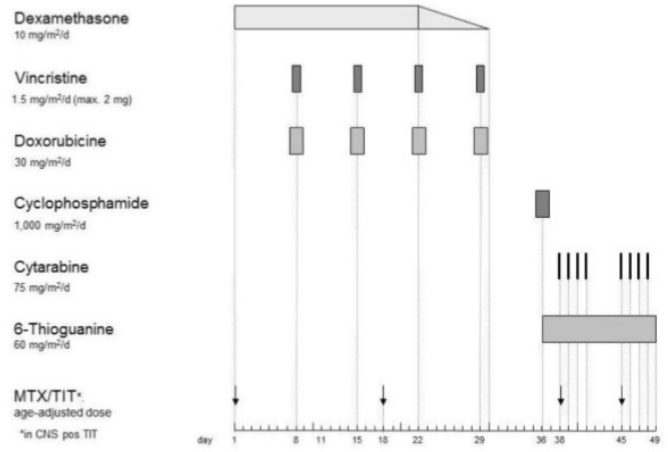


16.4.4.5 Schema of intensified protocol M

R2 intensified arm



16.4.5 Schema of reintensification phase - Protocol II



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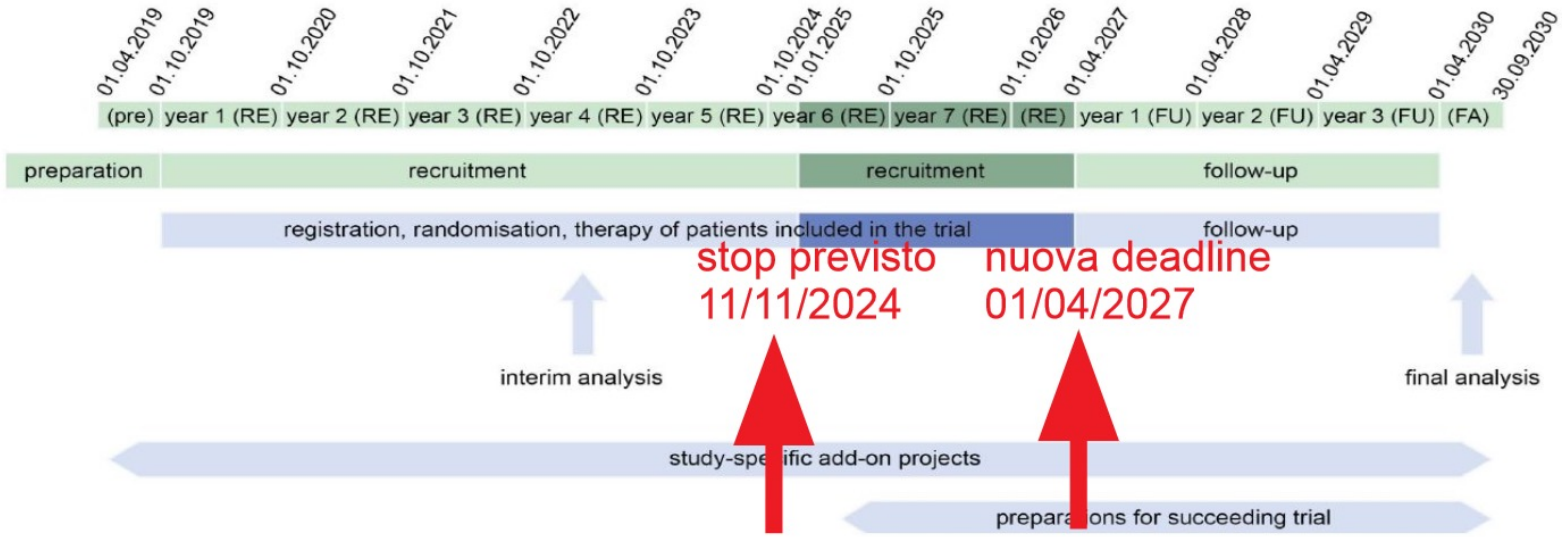
LBL 2018: Extension of recruitment period

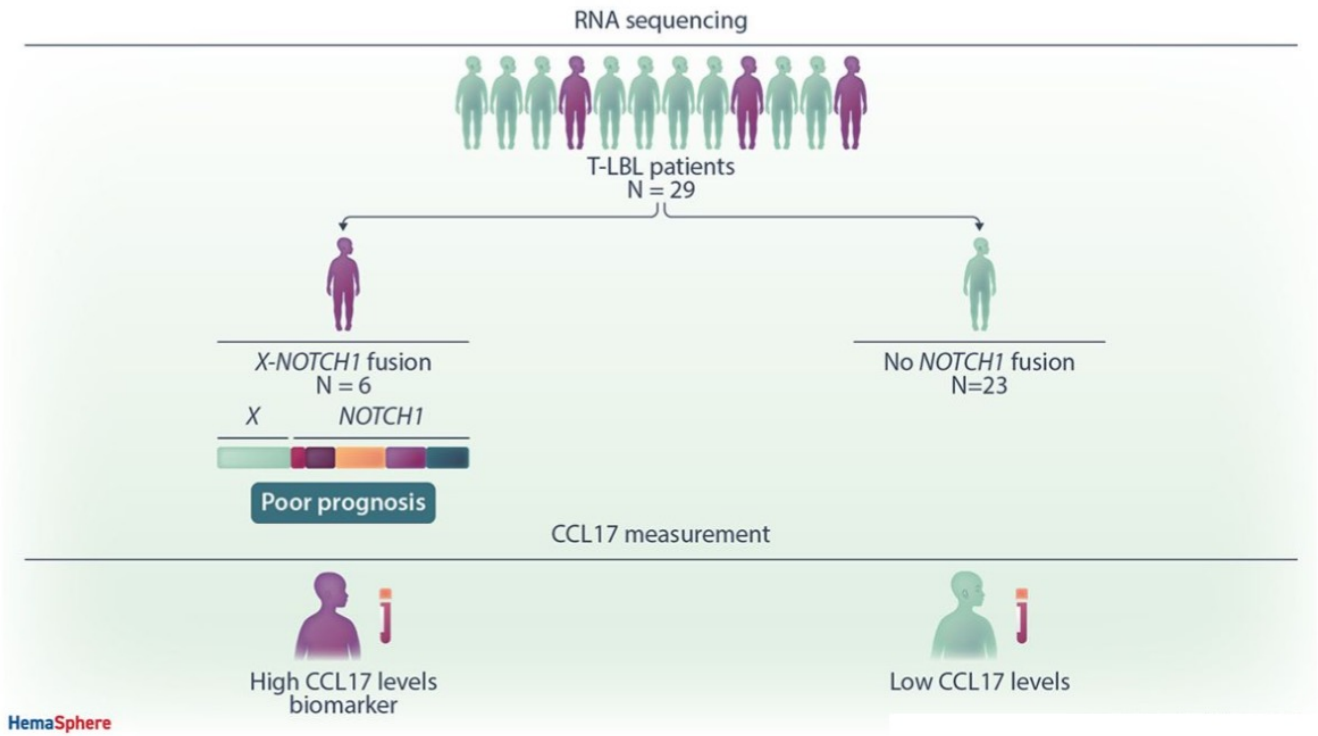


- Extension of recruitment period is necessary to answer study questions
- Interim analysis was conducted in May 2023 and reported to the DSMC
- Support and recommendation of the DSMC for continuation of the trial until required sample size for both randomizations has been reached

Emendamento sostanziale in CTIS → Febbraio 2025 (protocollo V. 2.0)

è necessario mantenere un certificato GCP (R3) aggiornato!

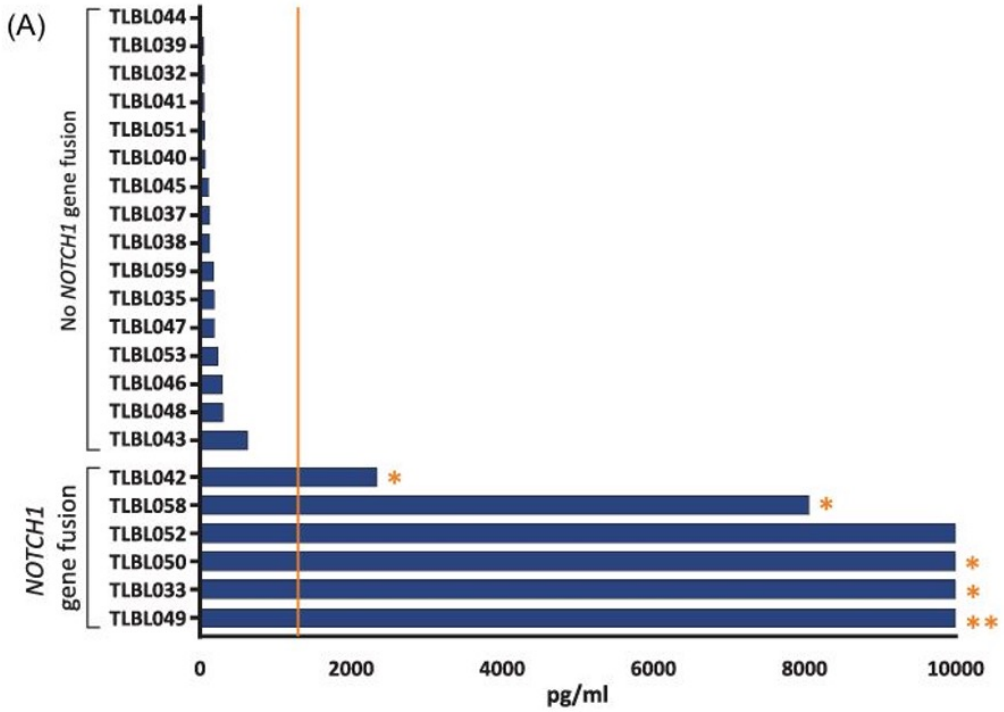
A high-risk subgroup of pediatric T-LBL with high CCL17 levels and NOTCH1 gene fusions

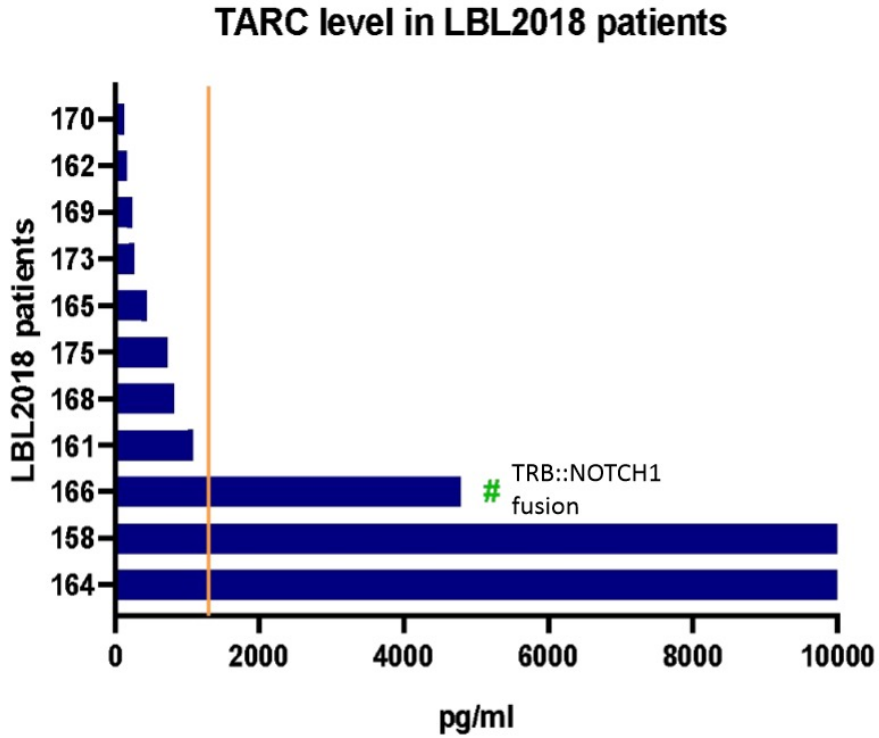


The occurrence of NOTCH1 fusions seems to correlate with a significant **increase in CCL17** (TARC) expression in the blood of the patients, so that this high-risk subcohort can possibly also be identified with a corresponding approach.

Kroeze E et al, Hemasphere 2024

Elevated TARC levels in X::NOTCH1 positive T-LBL patients





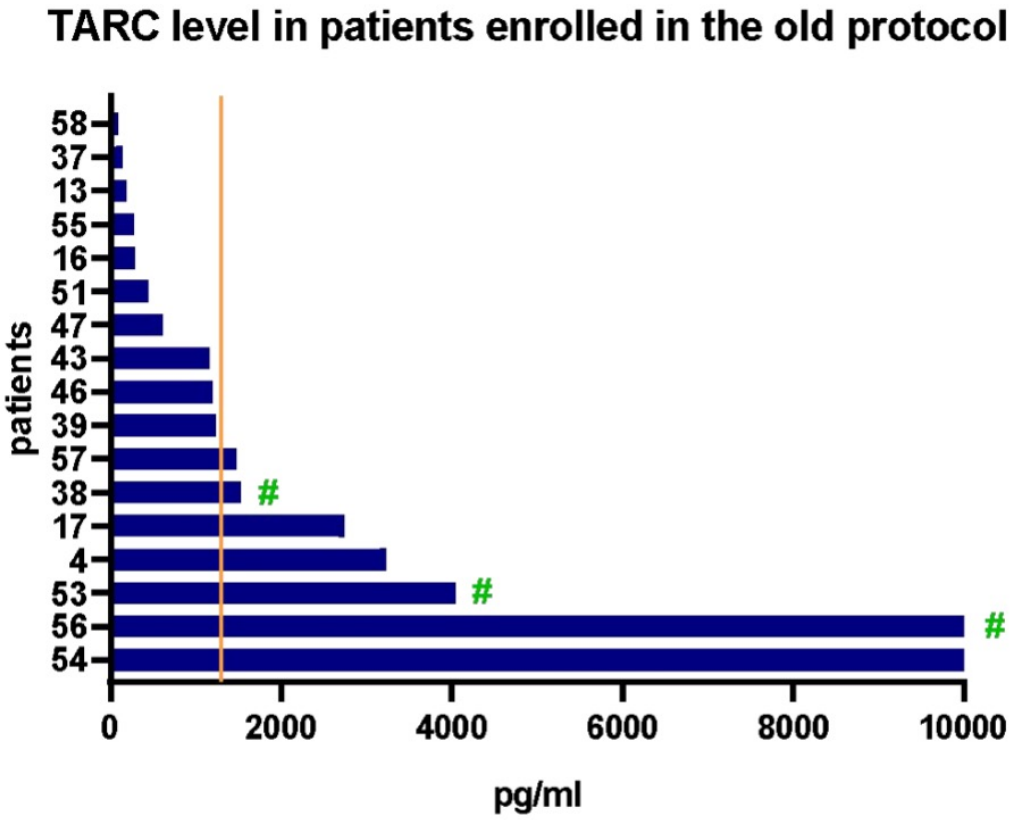
Patients 158 and 164 (HIGH TARC) may have another NOTCH1 gene fusion

Kroeze et al, HemaSphere 2024

data not published

Analysis of TARC levels in Italian patients (Euro LB02 protocol)

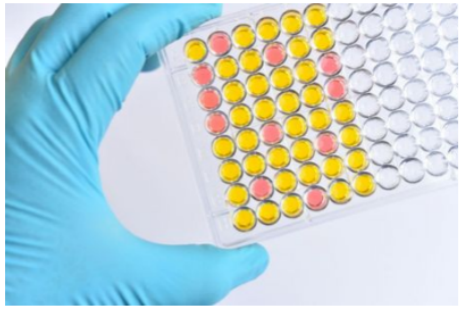
code	event	NOTCH1 mutational status	TRB::NOTCH1 fusion	TARC level pg/ml
54	no	wt	neg	22929
56	si	wt	POS	13250
53	no	wt	POS	4049
4	no	wt	neg	3235
17	no	wt	neg	2748
38	si	wt	POS	1533
57	no	wt	neg	1482
39	no	wt	neg	1239
46	no	wt	neg	1201
43	si	wt	neg	1156
47	no	wt	neg	622
51	no	wt	neg	449
16	no	wt	neg	286
55	no	wt	neg	272
13	si	wt	neg	197
37	no	wt	neg	143
58	no	wt	neg	95



work in progress

TARC levels as a non-invasive diagnostic biomarker

CCL17 measurements at diagnosis can be performed by ELISA assay using 100µl of serum or plasma.



- **Potential of TARC levels as a non-invasive diagnostic biomarker for identifying «very high-risk» T-LBL patients**

Upcoming Steps & Objectives

- Analyze a larger cohort of pediatric T-LBL patients to validate NOTCH1 gene fusions and TARC level results

Studi clinici di 2^ linea per r/r T-LNH

HEM-iSMART: International proof of concept therapeutic Stratification trial of Molecular Anomalies in Relapsed or Refractory HEMatological malignancies in children

- Pazienti < 18 years at first diagnosis with molecularly profiled R/R ALL/LBL

- Sponsor: Princess Máxima Center for Pediatric Oncology in collaboration with three pharmaceutical companies (Janssen, Novartis and ABBVIE).

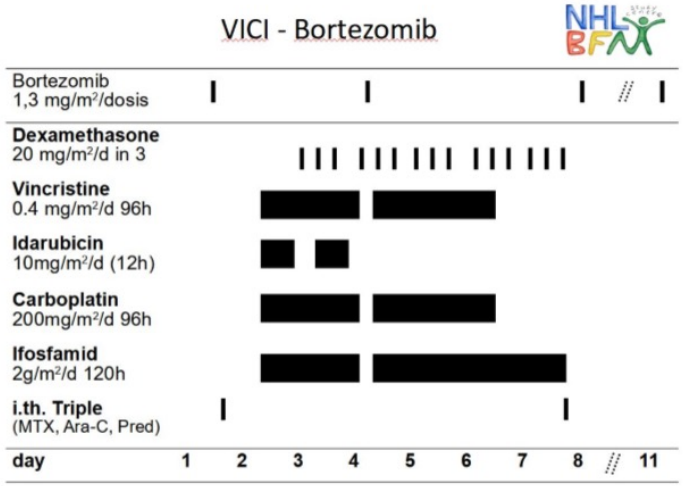
- Master Protocol and 4 Sub-Protocols, each of which consists of a Phase I and a Phase II part.
The sub-protocols will be running independently. The study will be open in around 36 sites in 15 countries.

~~- Sub protocol A: combinazione di decitabina, venetoclax e navitoclax in r/r T-ALL/LBL in pazienti apparentemente privi di alterazioni molecolari target.~~

- Sub protocol B: combinazione di dasatinib, venetoclax, desametasone, ciclofosfamide e citarabina in pazienti con alterazioni nella via Mitogen Activated Protein Kinase (MAPK)-SRC (**open**)

- Sub protocol C: combinazione di ruxolitinib, venetoclax, desametasone, ciclofosfamide e citarabina in pazienti con alterazioni della via IL7-R/JAKSTAT (Janus kinase (JAK)/signal transducer and activator of transcription) (**open**)

- Sub protocol D: combinazione di trametinib, desametasone, ciclofosfamide e citarabina in pazienti con alterazioni della via RAS-RAF-MAPK (**open**)

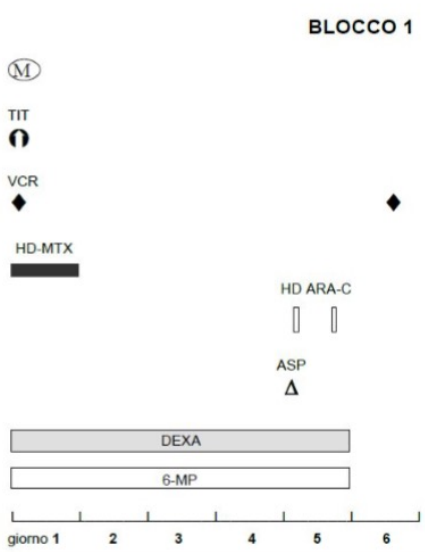


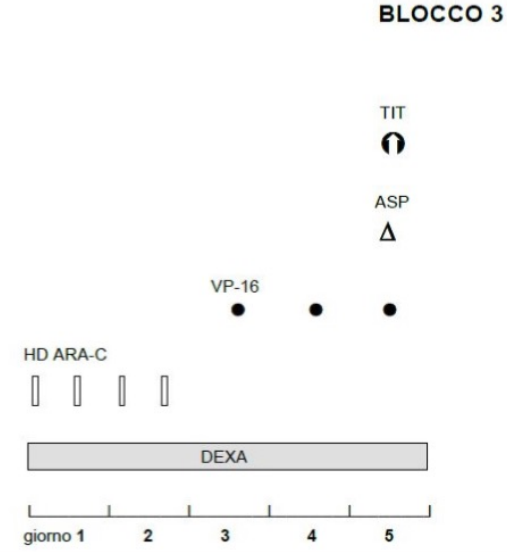
NECTAR:

NEL 650 mg/m^2, CPM 440 mg/m^2 and ETOP 100 mg/m^2, each given daily for 5 days

CAR-T anti CD7

BFM-REC

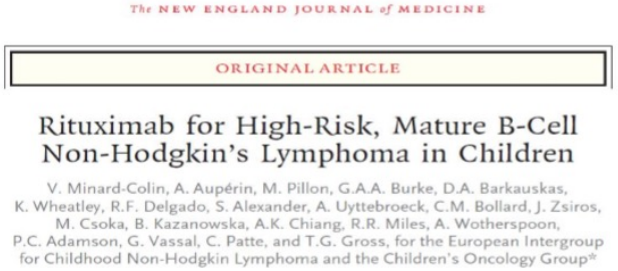




LNH-B

PROTOCOLLI NAZIONALI ED INTERNAZIONALI IN USO:

- Protocollo **AIEOP LNH97+/- Rituximab**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children

V. Minard-Colin, A. Aupérin, M. Pillon, G.A.A. Burke, D.A. Barkauskas, K. Wheatley, R.F. Delgado, S. Alexander, A. Uyttebroeck, C.M. Bollard, J. Zsiros, M. Csoka, B. Kazanowska, A.K. Chiang, R.R. Miles, A. Wotherspoon, P.C. Adamson, G. Vassal, C. Patte, and T.G. Gross, for the European Intergroup for Childhood Non-Hodgkin Lymphoma and the Children's Oncology Group*

- Protocollo **Inter B-NHL Ritux 2010**
  (2ys EFS: 93,9% Ritux vs 82,3% no Ritux)

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- Protocollo **NHL 2013** (BFM e NOPHO), in corso

NHL BFM Study Centre

NOPHO

B-NHL 2025 - Treatment protocol for mature B-cell lymphoma and leukemia in children and adolescents

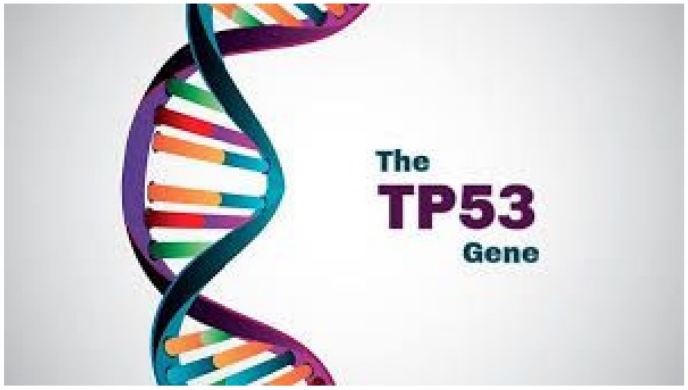
- 5 anni di arruolamento + 2 follow-up
- 185 pazienti/anno, totale 925 pazienti
- Paesi coinvolti/numero pazienti attesi/anno: AIEOP; NHL-BFM; NOPHO; PPLLSG; SEHOP.
- Pazienti eleggibili: pazienti <18 aa con diagnosi di LNH-B/LLA-B (no PMLBL)

- Braccio W&W per linfomi rari
- Ridefinizione dei gruppi di rischio

→ **possibile apertura inizio 2026**

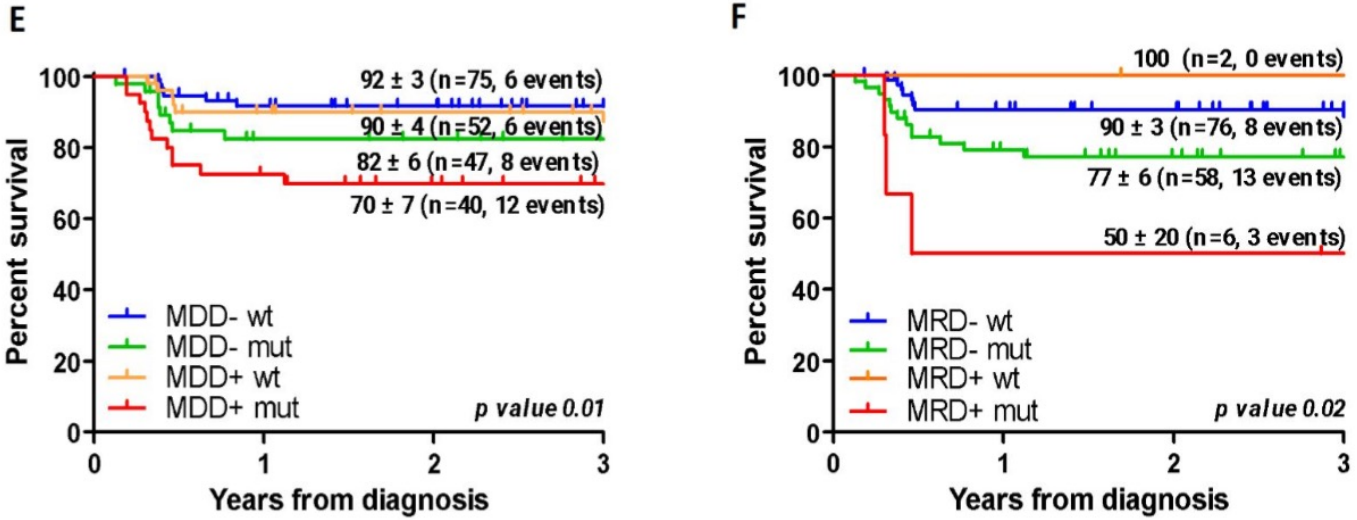
Stratification

risk group (RG)	stage and initial serum LDH level
RGw&w	pMZL and pFL
RG1	stage I + II, complete resection
RG2 low	stage I + II, incomplete resection
RG2 high	stage III and LDH < 2 x ULN (upper normal limit of local reference value for adults)
RG3	all stages, CNS-, LDH ≥ 2 x ULN but < 4 x ULN and all DLBCL stage III/IV with LDH < 4 x ULN
RG4	all stages, LDH ≥ 4 x ULN
RG5	RG3 and RG4 with *TP53*$^{mut\ (w/o\ R248Q)}$, MRD^{pos}



il nuovo marcatore molecolare per la stratificazione dei pazienti pediatrici affetti da linfoma di Burkitt e DLBCL

PATIENTS STRATIFICATION ACCORDING TO TP53 MUTATIONAL STATUS AND DISEASE DISSEMINATION



Martire G et al, Haematologica 2024

UNIVARIATE AND MULTIVARIATE ANALYSIS BASED ON CLINICAL AND BIOLOGICAL CHARACTERISTICS

Patient characteristics		# Patients	# Events	3-y PFS % (SE%)	Univariate p-Value	Multivariate p-Value	Hazard Ratio (95% CI)
Gender	Male	180	24	86 (3)	0.088	n.s.	
	Female	34	8	76 (7)			
Median age (years)	<7,7	111	14	87 (3)	0.293	n.s.	
	≥7,7	103	18	85 (3)			
BM involvement*	No	188	27	80 (8)	0.518		
	Yes	26	5	77 (10)			
CNS involvement	No	200	30	84 (3)	0.968		
	Yes	14	2	85 (10)			
Risk group#	1-2-3 and B	45	1	98 (2)	0.01	n.s.	
	4 and C	166	30	81 (3)			
Stage°	1-2	38	1	97 (3)	0.0259	n.s.	
	3-4	176	31	82 (3)			
MDD	Neg	122	14	88 (3)	0.109	n.s.	
	Pos	92	18	80 (4)			
Rituximab	No	147	26	82 (3)	0.092	0.0318	0.4 (0.1-0.9)
	Yes	66	6	90 (4)			
TP53	WT	127	12	90 (3)	0.0055	0.0247	2.3 (1.1-4.9)
	Mut	87	20	77 (5)			

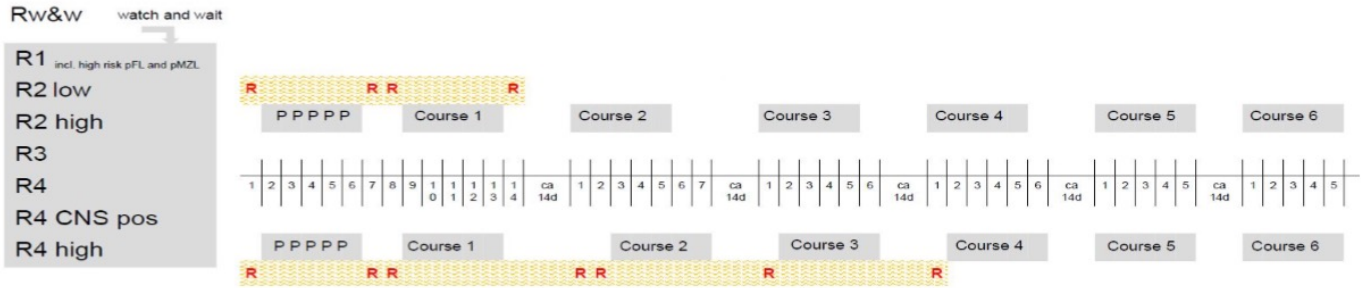
TP53 DNA binding domain mutational status and rituximab-based treatment are independent prognostic factors for pediatric Burkitt lymphoma patients stratification.

Martire G. et al, Haematologica 2024

B-NHL 2025 - Treatment protocol for mature B-cell lymphoma and leukemia in children and adolescents

Obiettivi:

- Ottimizzazione dell'**utilizzo di rituximab** (randomizzazione 4 rituximab vs 7 rituximab per tutti)
- **Riduzione della chemioterapia** classica (randomizzazione 2 e 3 secondo nuovi GR)
- Introdurre **intensificazione terapeutica** con nuovi farmaci per pazienti ad altissimo rischio



Endpoint primari:

- EFS
- QoL
- Tasso di non aderenza alla strategia W&W

Endpoint secondari:

- OS
- Frequenza tossicità e mortalità protocol related
- CIR
- Ricostituzione immunologica
- Biomarkers per predisposizione, risposta, rischio di ricaduta o tossicità

B-NHL 2025 - Treatment protocol for mature B-cell lymphoma and leukemia in children and adolescents

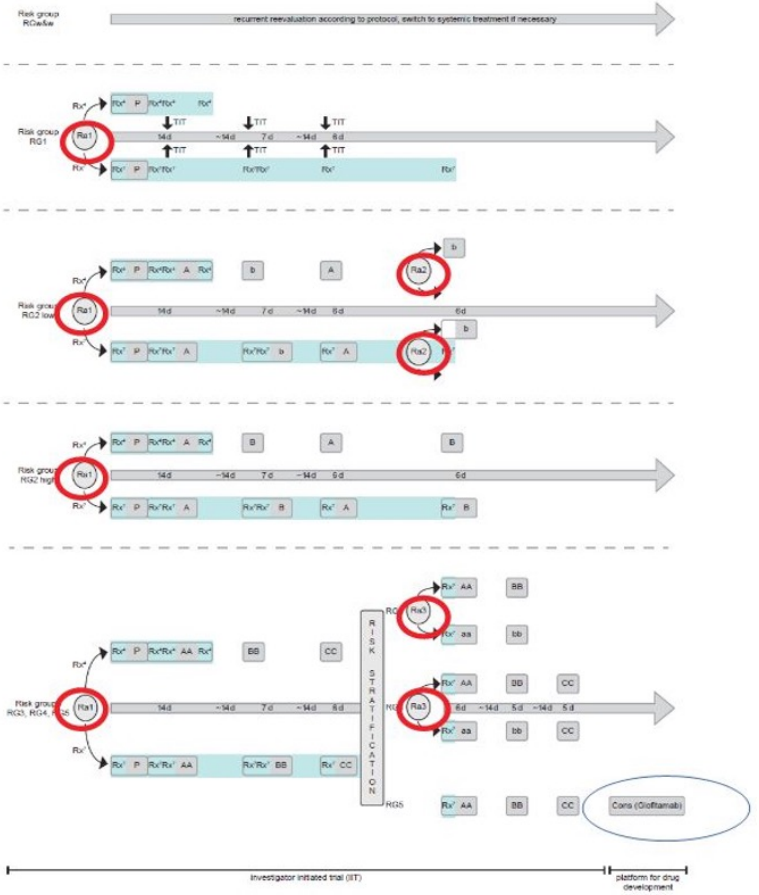
Protocollo prevederà 3 randomizzazioni:

- numero rituximab
- riduzione antracicline
- intensificazione con anticorpo monoclonale bispecifico per very high risk

Stato di avanzamento:

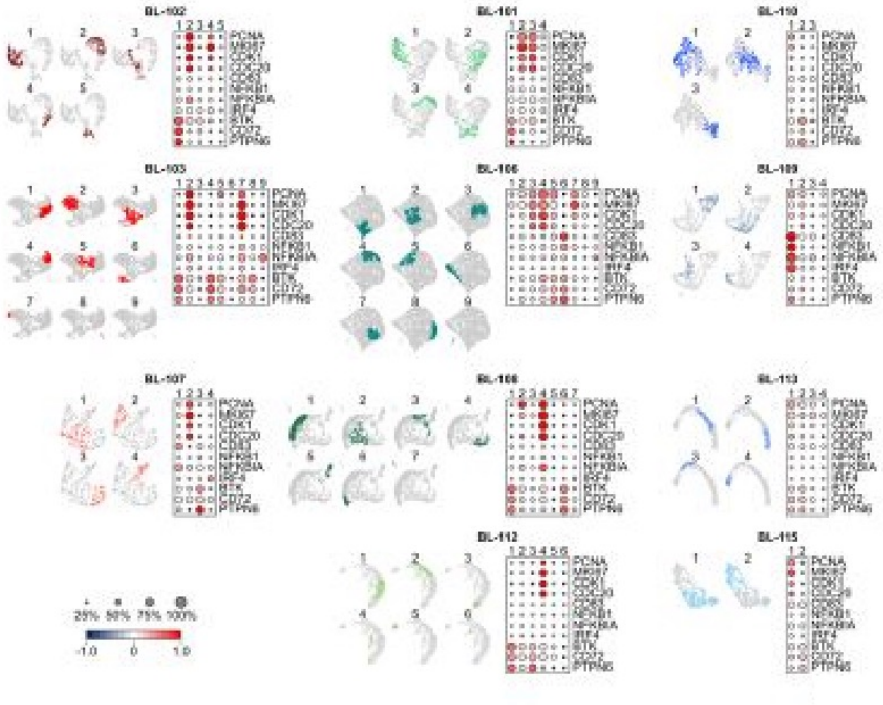
- in lettura ai centri coordinatori partecipanti
- contatto con le aziende farmaceutiche per nuovi farmaci
- definizione di progetti ancillari

Avvio delle procedure di start-up



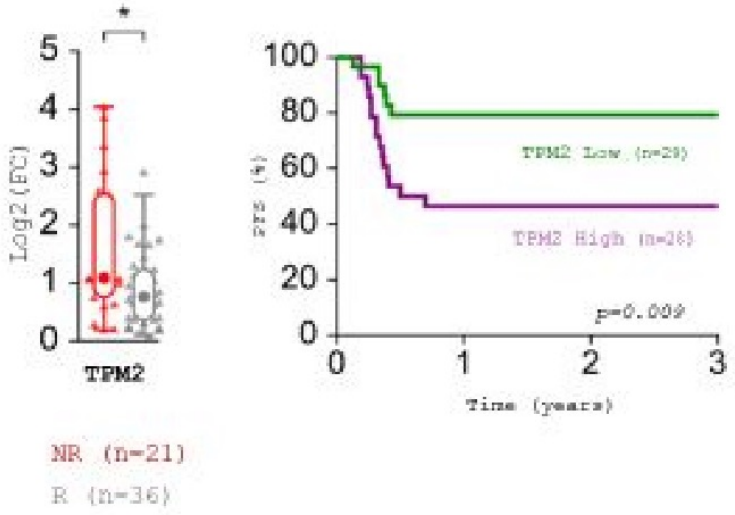
Single-cell transcriptomics of pediatric Burkitt lymphoma reveals intra-tumor heterogeneity and markers of therapy resistance

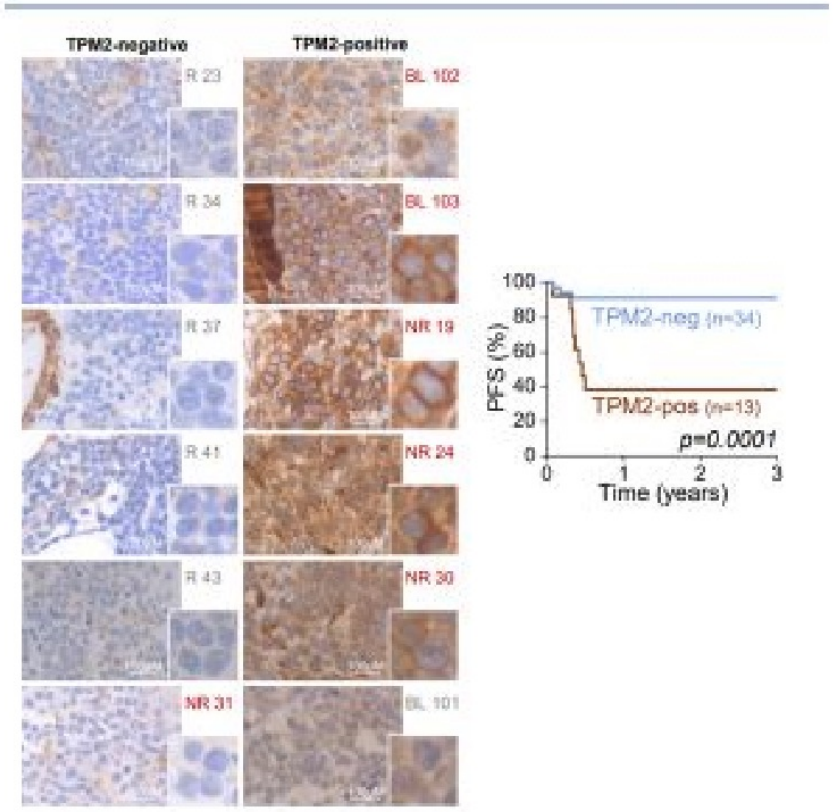
BL tumor cells display heterogeneous transcriptome



Corinaldesi C et al, Leukemia 2025

TPM2 is associated with refractory disease





Corinaldesi C et al, Leukemia 2025

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Therapy in Primary Mediastinal B-Cell Lymphoma

TO THE EDITOR: Dunleavy et al. (April 11 issue)[1] had exceptional survival rates when treating adults with primary mediastinal large-B-cell lymphoma with dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R), without radiotherapy. The biologic characteristics of the disease in children are similar to those of the disease in adults.[2] Regimens (without rituximab) that have been effective in the treatment of children with other mature B-cell non-Hodgkin's lymphomas have had limited efficacy in the treatment of children with primary mediastinal large-B-cell lymphoma.[3,4] Consequently, the Non-Hodgkin's Lymphoma Berlin–Frankfurt–Münster (NHL-BFM) study committee recommended DA-EPOCH-R[5] for children and adolescents with primary mediastinal large-B-cell lymphoma as the best available clinical practice, and this treatment

more efficient in terms of both timing and the methods used.

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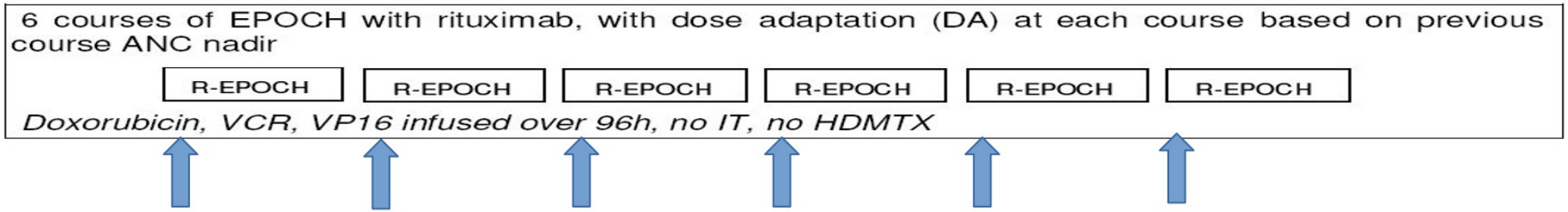
Birgit Burkhardt, M.D., Ph.D.
Westfälische Wilhelms-Universität
Muenster, Germany

for the NHL-BFM Study Group

No potential conflict of interest relevant to this letter was reported.

1. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH–rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-16.
2. Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 2011;96:262-8.

R-DA-EPOCH + rachicentesi

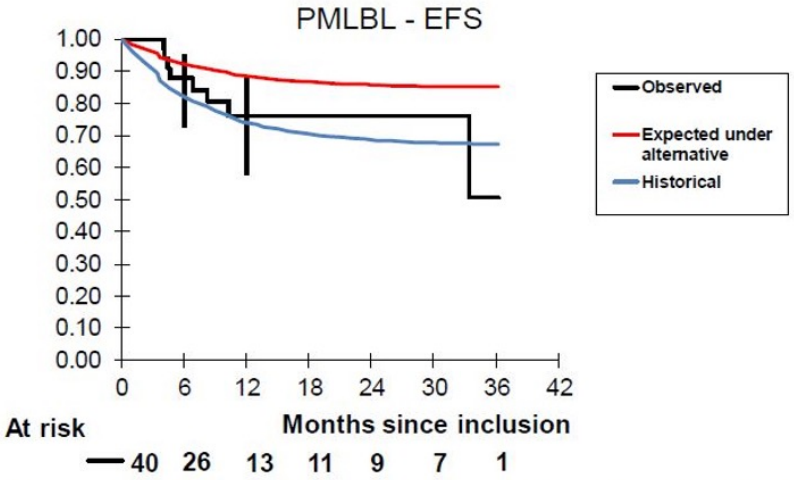


Woessmann W, NEJM 2013

Fase II

EFS rates:

	Observed rate (95%CI)	Expected rate under alternative $[0.67 + 0.33\{\exp(-1.5t)\}]^{0.406}$	Historical rate $0.67 + 0.33\{\exp(-1.5t)\}$
At 6 months	87.8% (72.6%-95.2%)	92.5%	82.6%
At 12 months	76.2% (57.9%-88.1%)	88.7%	74.4%



Phase 2 (DA-REPOCH) closed in April 2016

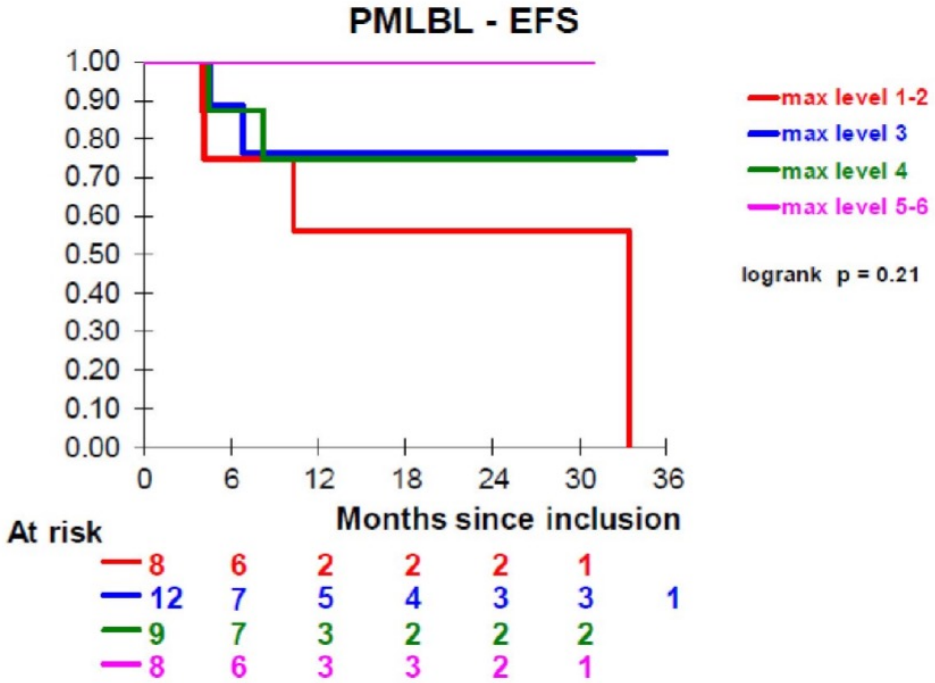
47 patients

Final analysis in April 2017 – abstract ASH 2017

Good tolerance profile

10 events

2 intracerebral relapses



Burke A et al, JCO 2021

inseriti nella lista 648/96 di AIFA:«Nivolumab» e «Brentuximab Vedotin»

- per il trattamento di pazienti affetti da linfoma primitivo del mediastino (PMBCL) e linfoma della zona grigia (GZL),
- refrattari alla prima linea di chemioimmunoterapia contenente anticorpo monoclonale anti-CD20 e chemioterapia contenente antracicline
- per pazienti >= 18 anni

Schema posologico: «Nivolumab» 240 mg (dose flat), ogni 3 settimane e «Brentuximab Vedotin» 1.8 mg/kg (dose massima 180 mg), ogni 3 settimane.

da Marzo 2025

Studi clinici di 2^ linea per r/r B-LNH

RECRUITING

A Study to Evaluate Glofitamab Monotherapy and Glofitamab + Chemoimmunotherapy in Pediatric and Young Adult Participants With Relapsed/Refractory Mature B-Cell Non-Hodgkin Lymphoma (iMATRIX GLO)

Roma BG, Torino

ClinicalTrials.gov ID NCT05533775

RECRUITING

A Study to Evaluate the Safety, Tolerability, Drug Levels, and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adults With Hodgkin and Non-Hodgkin Lymphoma (RELATIVITY-069)

ClinicalTrials.gov ID NCT05255601

Roma BG, Torino, Bologna, Firenze, Milano INT, Monza, Padova

RECRUITING

A Single Arm, Open-Label, Phase 1b Trial of Epcoritamab (bispecific antibody anti CD3-CD20) in Pediatric Patients With Relapsed/Refractory Aggressive Mature B-cell Neoplasms

Roma BG, Firenze

Studi clinici di 2^ linea per r/r B-LNH

Glo-BNHL- prioritisation

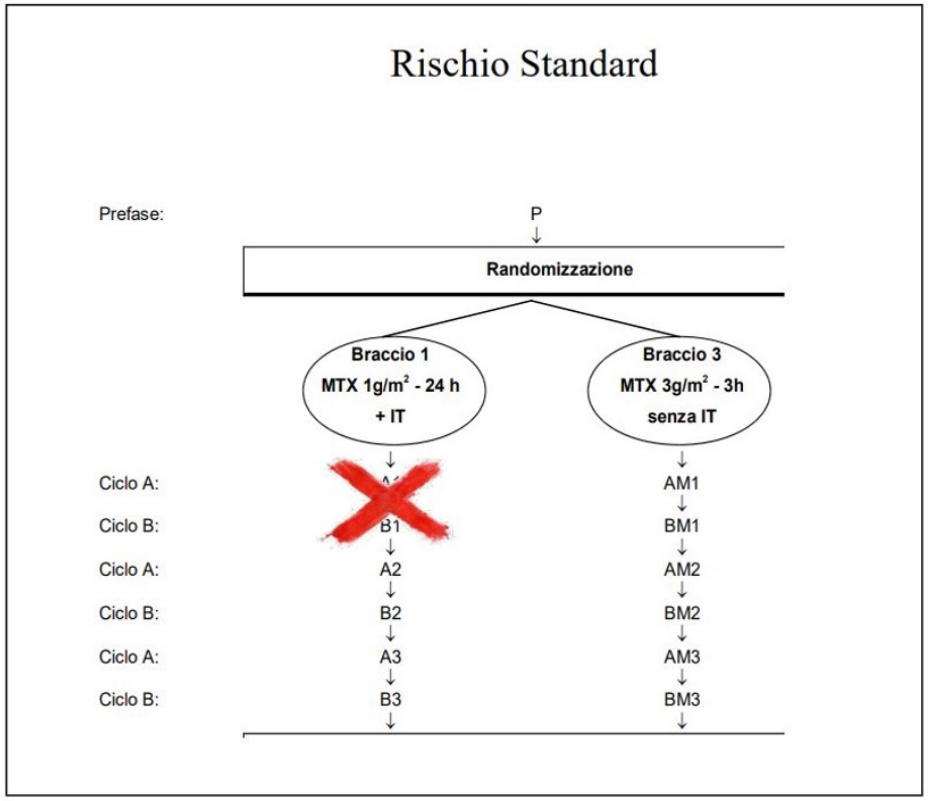
- Cohort 1: bispecific T-cell engager (BiTE)
- Cohort 2: antibody-drug conjugate (ADC) with standard chemotherapy
- Cohort 3: chimeric antigen receptor (CAR) T-cells (or haematopoietic stem cell transplant (HSCT))

In Italia è in corso la negoziazione del contratto con lo Sponsor
(UK recruiting)

Linfoma anaplastico

"INTERNATIONAL TRIAL ALCL 99"

PER IL TRATTAMENTO DEGLI ALCL – SENZA RANDOM



Linfoma anaplastico

cancers

MDPI

Article

Prognostic Factors in Childhood Anaplastic Large Cell Lymphoma: Long Term Results of the International ALCL99 Trial

Lara Mussolin [1,2,*,†], Marié-Cecilé Le Deley [3,†], Elisa Carraro [1], Christine Damm-Welk [4], Andishe Attarbaschi [5], Denise Williams [6], Amos Burke [6], Keizo Horibe [7], Atsuko Nakazawa [8], Grazyna Wrobel [9], Georg Mann [5], Monika Csóka [10], Anne Uyttebroeck [11], Rafael Fernández-Delgado Cerdá [12], Auke Beishuizen [13], Karin Mellgren [14], Birgit Burkhardt [15], Wolfram Klapper [16], Suzanne D. Turner [17,18], Emanuele S.G. d'Amore [19], Laurence Lamant [20], Alfred Reiter [21], Wilhelm Woessmann [4], Laurence Brugières [22,‡], Marta Pillon [23,‡] and on behalf of the European Inter-Group for Childhood Non-Hodgkin lymphoma (EICNHL) [§]

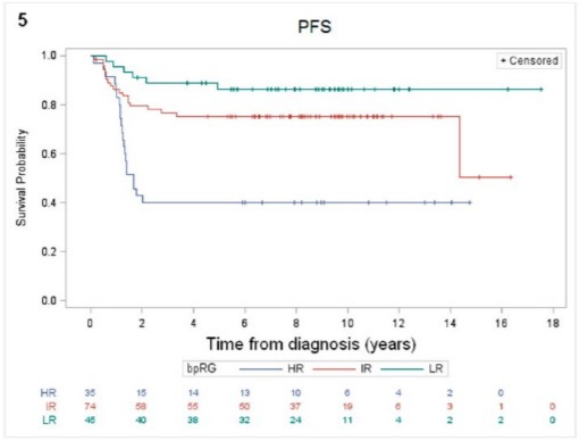
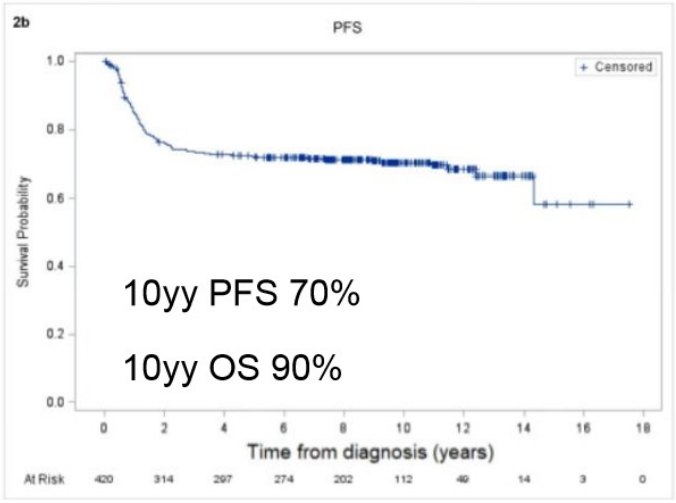
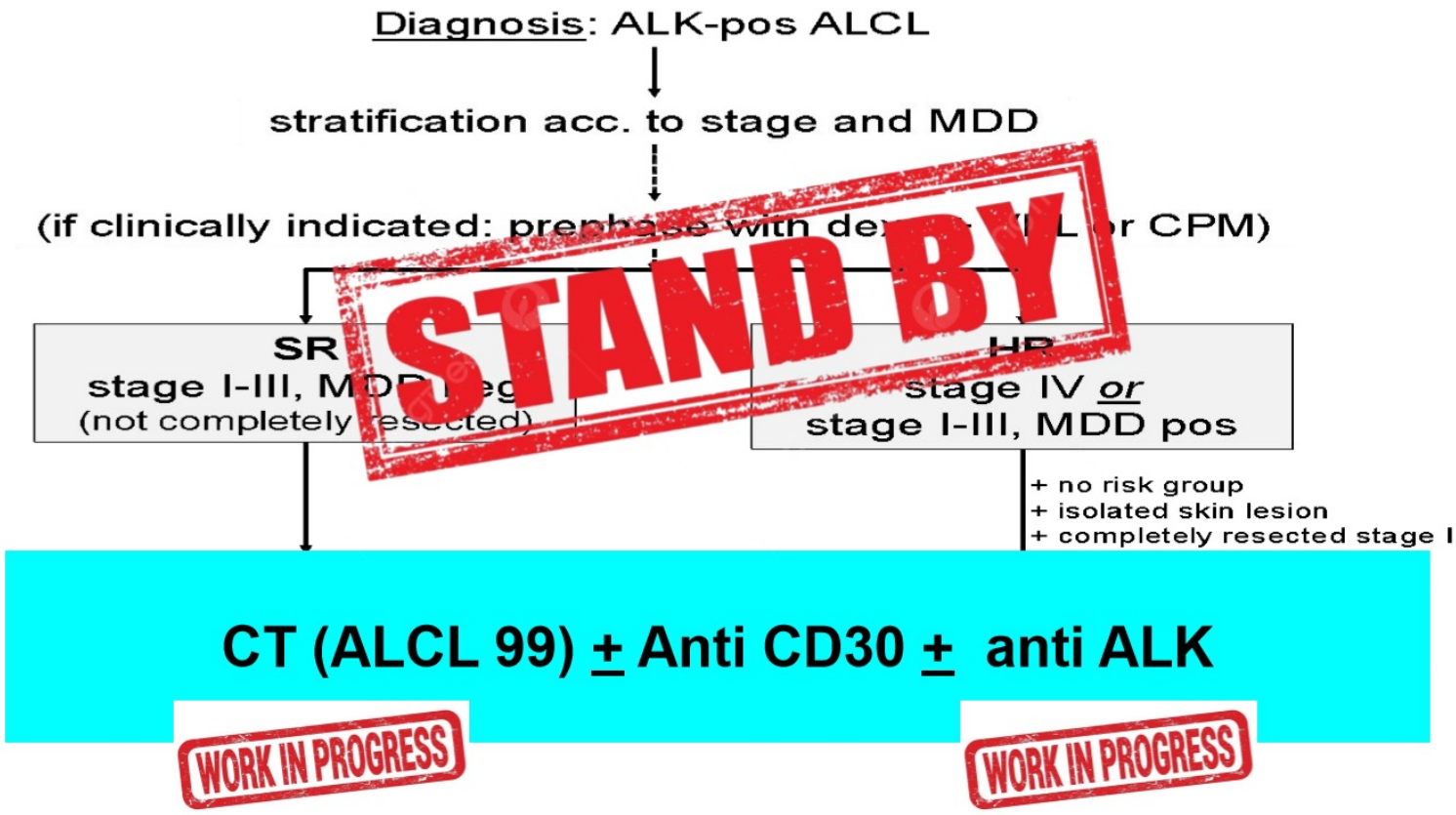


Figure 5. The 10-year PFS was 40% (SE ± 8%), 75% (SE ± 5%) and 86% (SE ± 5%) for bpHR (n = 35), bpIR (n = 74) and bpLR (n = 45), respectively (p < 0.0001).



Histological subtype SC/LH (8 mv)	No	95	19	81 (4)	0.0006	0.009	2.4 (1.23–4.66)
	Yes	59	27	53 (7)			
MDD	Neg	75	12	83 (4)	0.001	0.038	2.15 (1.04–4.64)
	Pos	87	34	62 (5)			

Mussolin L et al, Cancers 2020



Contatto con le aziende farmaceutiche per nuovi farmaci

CHILDREN'S ONCOLOGY GROUP

Crizotinib in Combination With Chemotherapy for Pediatric Patients With ALK+ Anaplastic Large-Cell Lymphoma: The Results of Children's Oncology Group Trial ANHL12P1

Eric J. Lowe, MD[1]; Anne F. Reilly, MD, MPH[2]; Megan S. Lim, MD, PhD[3]; Thomas G. Gross, MD, PhD[4]; Lauren Saguilig, MS[5]; Donald A. Barkauskas, PhD[6]; Rui Wu, MD, PhD[3]; Sarah Alexander, MD[7]; and Catherine M. Bollard, MD[8]

TABLE 1. Chemotherapy Schedule

Course	Drug	Dose per Day	Schedule
Prophase (days 1-5)	Cyclophosphamide	200 mg/m^2 once a day	Days 1, 2
	Dexamethasone	5 mg/m^2 once a day 10 mg/m^2 divided twice per day	Days 1, 2 Days 3-5
	Triple intrathecal	Age-based	Day 1
Cycles 1, 3, 5	CZ	165 mg/m^2/dose twice a day	Day 1-21
	Methotrexate	3 g/m^2 over 3 hours	Day 1
	Dexamethasone	10 mg/m^2 divided twice per day	Days 1-5
	Ifosfamide	800 mg/m^2 once a day	Days 1-5
	Etoposide	100 mg/m^2 once a day	Days 4, 5
	Cytarabine	150 mg/m^2 twice per day	Days 4, 5
Cycles 2, 4, 6	CZ	165 mg/m^2/dose twice a day	Day 1-21
	Methotrexate	3 g/m^2 over 3 hours	Day 1
	Dexamethasone	10 mg/m^2 divided twice per day	Days 1-5
	Cyclophosphamide	200 mg/m^2 once per day	Day 1-5
	Doxorubicin	25 mg/m^2 once per day	Days 4, 5

Brentuximab vedotin in combination with chemotherapy for pediatric patients with ALK$^+$ ALCL: results of COG trial ANHL12P1

Eric J. Lowe,[1] Anne F. Reilly,[2] Megan S. Lim,[3] Thomas G. Gross,[4] Lauren Saguilig,[5] Donald A. Barkauskas,[6] Rui Wu,[3] Sarah Alexander,[7] and Catherine M. Bollard[8]

Table 2. Chemotherapy schedule

Course	Drug	Daily dose	Schedule
Prophase (days 1-5)	Cyclophosphamide Dexamethasone Triple intrathecal	200 mg/m^2 5 mg/m^2 10 mg/m^2 Age based	Days 1 and 2 Days 1 and 2 Days 3-5 Day 1
Cycles 1, 3, and 5	Brentuximab vedotin* Methotrexate Dexamethasone Ifosfamide Etoposide Cytarabine	1.8 mg/kg 3 g/m^2 over 3 h 10 mg/m^2 800 mg/m^2 100 mg/m^2 150 mg/m^2 × 2	Day 1 Day 1 Days 1-5 Days 1-5 Days 4 and 5 Days 4 and 5
Cycles 2, 4, and 6	Brentuximab vedotin* Methotrexate Dexamethasone Cyclophosphamide Doxorubicin	1.8 mg/kg 3 g/m^2 over 3 h 10 mg/m^2 200 mg/m^2 25 mg/m^2	Day 1 Day 1 Days 1-5 Day 1-5 Days 4 and 5

*Brentuximab vedotin was given prior to any other chemotherapy on day 1.

ANHL12P1 trial: studio randomizzato di fase 2.

Obiettivo primario: determinare efficacia e tossicità di **BV (EFS 79,1% - OS 97%)** e **Crizotinib (EFS 76,8% - OS 95,2%)** in bambini con nuova diagnosi di ALCL CD30+

Conclusioni:

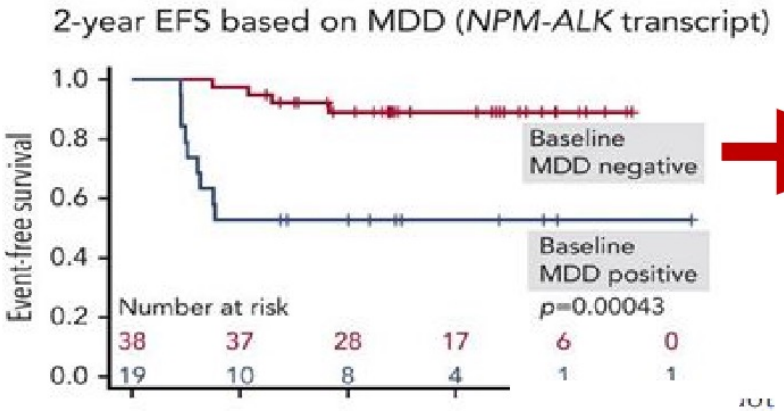
-Previene ricadute durante il trattamento

-Risultati di EFS/OS sovrapponibili allo storico - >> eventi tromboembolici per Crizotinib

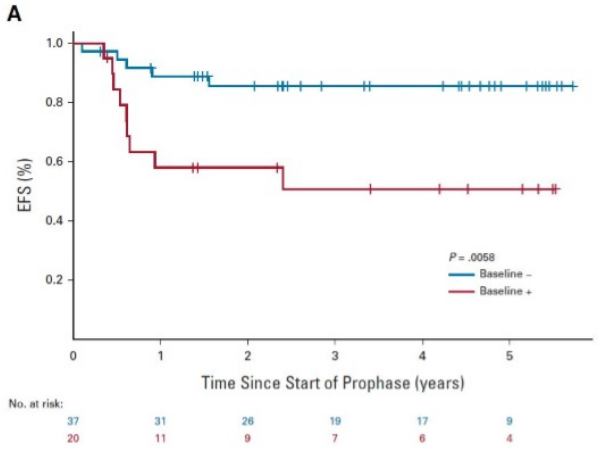
Lowe E, Blood 2021;
Lowe E, JCO 2022

ALCL and MDD

BV



CRIZO



CHILDREN'S ONCOLOGY GROUP

Lowe E, Blood 2021 e JCO 2022

CLINICAL TRIALS AND OBSERVATIONS

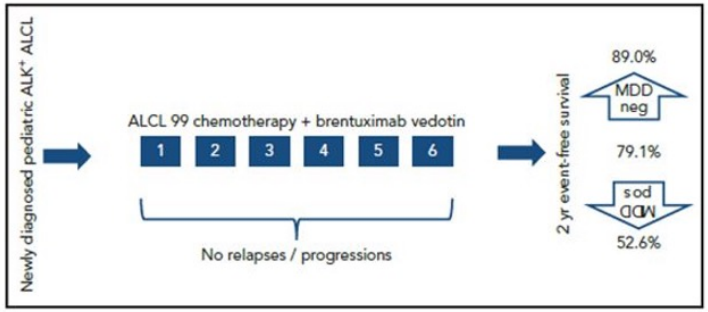
Comment on Lowe et al, page 3595

Brentuximab vedotin: frontline help in ALCL

G. A. Amos Burke | Cambridge University Hospitals NHS Foundation Trust

In this issue of *Blood*, Lowe et al present results of a phase 2 study combining brentuximab vedotin (BV) with standard chemotherapy in the treatment of newly diagnosed pediatric anaplastic lymphoma kinase–positive (ALK$^+$) anaplastic large-cell lymphoma (ALCL) and observe that it eliminated almost all relapses while receiving therapy, a significant breakthrough in the management of this disease.[1]

Burke G.A., Blood 2021



- Importante ridurre le r/r in terapia vista la peggior prognosi
- BV può essere utilizzato in prima linea in associazione alle terapie standard o come singolo agente con l'obiettivo di ridurre la tossicità e aumentare l'efficacia
- Limite attuale: il BV non previene le ricadute SNC

Studi clinici di 2^ linea per r/r ALCL

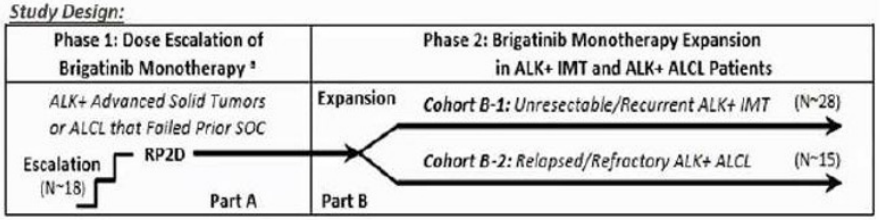
BrigaPED

Takeda Brigatinib-1002 (monotherapy)

Study population:

Patients aged ≥1 year (including pediatric and young adult patients) with relapsed/refractory ALK+ ALCL or relapsed/refractory ALK + solid tumors including unresectable/recurrent ALK+ IMT

Study Design:

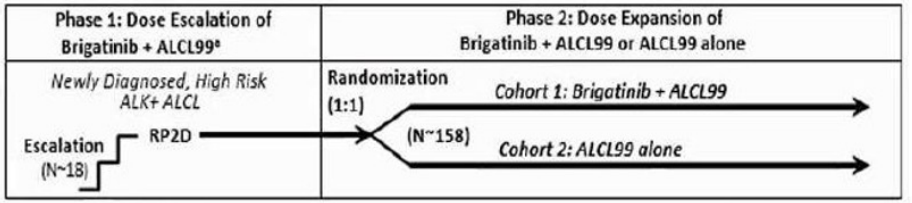


Brigatinib-1003 (brigatinib+ALCL99 vs. ALCL99)

Study population:

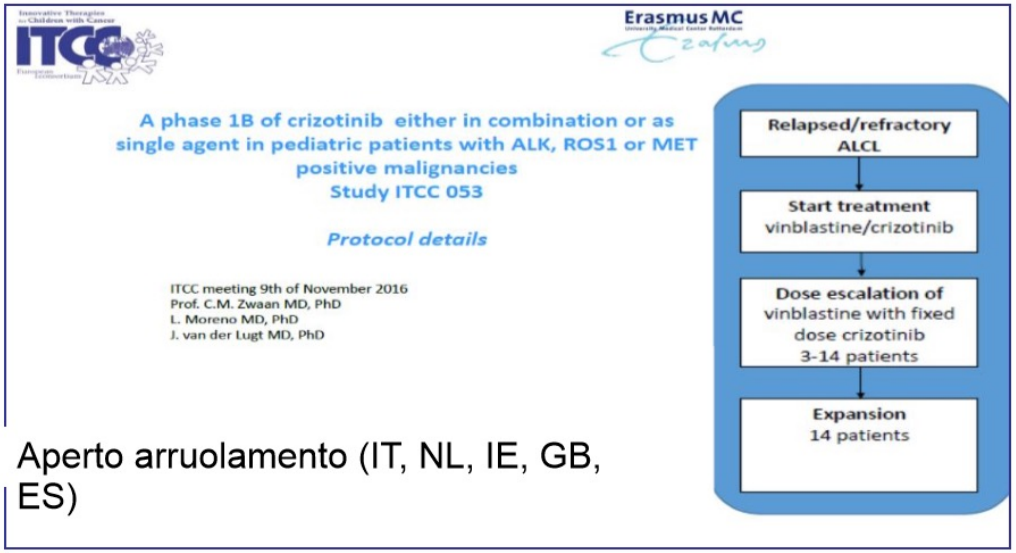
Patients aged ≥1 year (including pediatric and young adult patients) with newly-diagnosed, high risk ALK+ ALCL

Study Design:



inclusi pazienti MRD pos dopo 1°ciclo

Studi clinici di 2^ linea per r/r ALCL



Aperto arruolamento (IT, NL, IE, GB, ES)

Efficacy analysis of crizotinib at 165 mg/m2 BID in paediatric patients CRISP (ITCC-053) is scheduled to be provided to the EMA by 31 August 2027

<u>Altre terapie di seconda linea:</u>

- BV (*Locatelli F et al, Haematologica 2018*)
- BV + Bendamustina (*Vinti L et al, abs*)
- VBL (*Knorr F et al, JCO 2020*)
- allo TCSE (*Knorr F et al, JCO 2020*)
- CAR-T anti CD30+

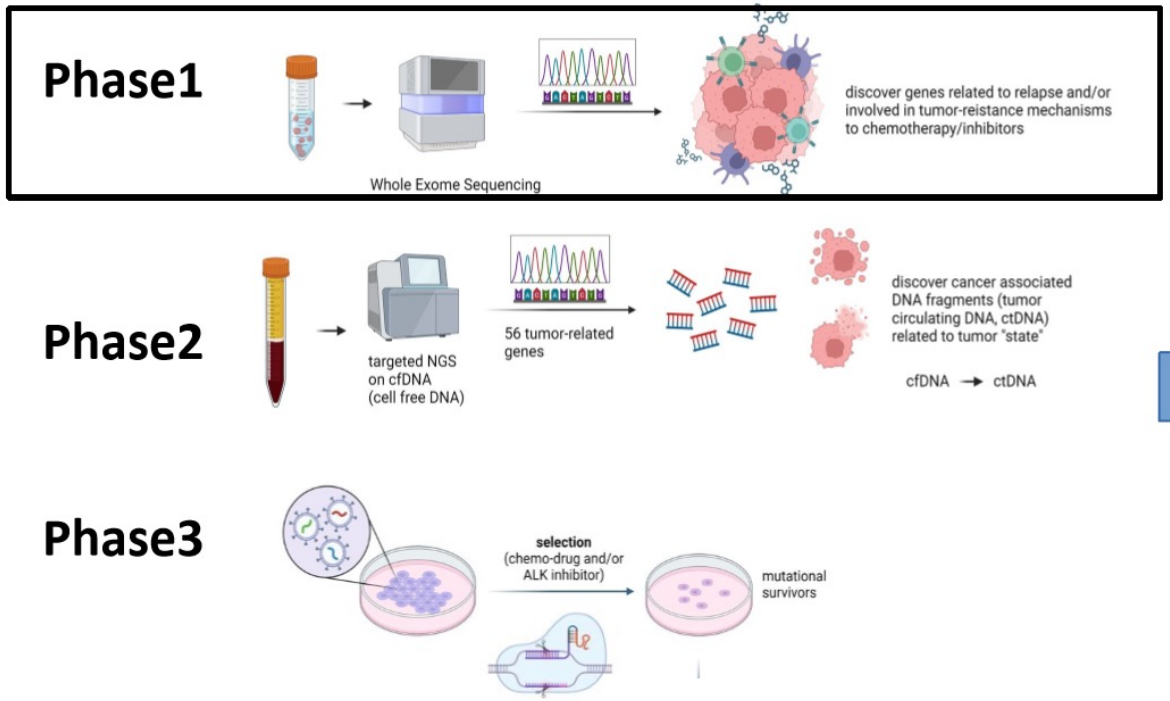
Dal 25/03/2025

Nuove Indicazioni Terapeutiche rimborsate: Xalkori (crizotinib) è indicato per il

- *Il trattamento di pazienti pediatrici (da ≥6 a < 18 anni) con tumore miofibroblastico infiammatorio (Inflammatory Myofibroblastic Tumour, IMT) non resecabile, recidivante o refrattario, positivo per ALK (chinasi del linfoma anaplastico);*
- *Il trattamento di pazienti pediatrici (da ≥6 a < 18 anni) con linfoma anaplastico a grandi cellule (Anaplastic Large Cell Lymphoma, ALCL) di tipo sistemico recidivante o refrattario, positivo per ALK (chinasi del linfoma anaplastico.*

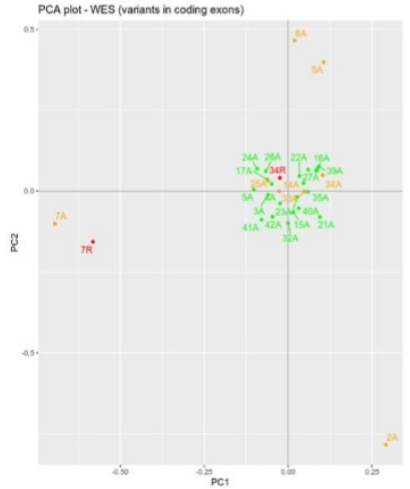
Overcoming treatment resistance mechanisms in ALK-driven cancers

- Whole Exome Sequencing (WES) performed in 38 ALCL cases, (tumor DNA and matched PB)
- 27 at diagnosis from no-relapsed patients, 11 at diagnosis from relapsed patients + 3 at relapse



work in progress

Principal Component Analysis reveals that 4/38 ALCL patients cluster separately from the main group



Samples at diagnosis (REL)

Samples at relapse time

Samples at diagnosis (CR)

Certificazione di quality control per ALCL (MMD/MRD) per il gruppo EICNHL

Certificate for the participation and performance of the quality control rounds for NPM1::ALK and 3' ALK MDD/MRD measurement:

1 Method

Method	Year	Q1	Q2	Q3	Q4
RT-PCR NPM1::ALK				X	

2 Results:

Laboratory: PHO-Diagnostic laboratories; NHL-BFM lab.		Name: L. Duscher	Date: 26.09.2024	
Sample Name	RT-PCR result NPM1::ALK	RT-PCR result ABL 1	„Diagnostic Finding"	Remarks
QCII-2024 cDNA1	negative	positive	NPM1::ALK MDD/MRD negative	
QCII-2024 cDNA2	positive	positive	NPM1::ALK MDD/MRD positive	
QCII-2024 cDNA3	positive	positive	NPM1::ALK MDD/MRD positive	
QCII-2024 cDNA4	positive	positive	NPM1::ALK MDD/MRD positive	
QCII-2024 cDNA5	negative	positive	NPM1::ALK MDD/MRD negative	
QCII-2024 cDNA6	negative	positive	NPM1::ALK MDD/MRD negative	

3 Performance

Sample Name	Expected result	Maximum deviation (%)*	Passed	Not Passed
QCII-2024 cDNA1	negative	-	x	
QCII-2024 cDNA2	positive	-	x	
QCII-2024 cDNA3	positive	-	x	
QCII-2024 cDNA4	positive	-	x	
QCII-2024 cDNA5	negative	-	x	
QCII-2024 cDNA6	negative	-	x	

*not applicable for RT-PCR; Maximum deviation for dPCR 30%

4 Total Score

A total score of 80% is required to pass the Quality control round

Passed /Number	Not Passed/Number	Total Score/Number	Total Score %
6	0	6	6

Herein we confirm that the laboratory participated the QC II2024 for ☒NPM1::ALK RT-PCR ☐ NPM1::ALK dPCR ☐ 3'ALK dPCR measurement and ☐passed/☐did not passed the quality control round with a Score of _____

09.12.2024 L. Mussolin
Lara Mussolin (PhD)

09.12.2024 C. Damm-Welk
Christine Damm-Welk(PhD)

Page - 1 - of 1

Giornate AIEOP

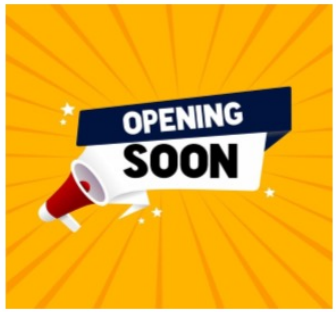
BOLOGNA 14-15 APRILE 2025

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP LNH-2024
Studio Multicentrico Nazionale sul Linfoma non Hodgkin del bambino, adolescente e giovane adulto

Studio osservazionale retrospettivo e prospettico

in arrivo richiesta di adesione ai centri AIEOP



Titolo	AIEOP LNH-2024: Studio Multicentrico Nazionale sul Linfoma non Hodgkin (LNH) del bambino, adolescente e giovane adulto (AYA). Studio osservazionale retrospettivo e prospettico
Pazienti	Pazienti di età < 18 anni con diagnosi istologica di LNH. Il limite di età può essere elevato fino ai 25 anni, per pazienti trattati all'interno di specifiche unità per AYA con diagnosi di LNH.
Obiettivo primario dello studio	Descrizione delle caratteristiche cliniche, ematochimiche, biologiche e istopatologiche all'esordio, delle terapie applicate e dell'outcome
Obiettivi secondari dello studio	- Valutare la Sopravvivenza libera da eventi (EFS) - Valutare la Sopravvivenza globale (OS) - Valutare la Sopravvivenza libera da progressione (PFS) - Valutare la Sopravvivenza Libera da Malattia (DFS) - Studiare i fattori prognostici e le caratteristiche epidemiologiche della malattia, considerando le diverse fasce di età, le sedi di insorgenza, il sottotipo istologico della variante classica, l'estensione di malattia all'esordio. - Descrivere i trattamenti somministrati, le deviazioni dai protocolli standard e le eventuali tossicità - Correlare i dati clinici con i dati biologici/ematochimici/istopatologici e con l'outcome
Disegno dello Studio	Studio osservazionale multicentrico, retrospettivo e prospettico
Popolazione in Studio	Si stimano circa 100 pazienti all'anno a livello nazionale.
Centri Partecipanti allo Studio	Centri di cura della Associazione Italiana di Ematologia-Oncologia Pediatrica (AIEOP)
Durata dello studio	10 anni. Inizio arruolamento previsto per il 01.06.2025

REDCap
Research Electronic Data Capture

Prospective Observational International Registry and biobank of Children, Adolescents and Young Adults (CAYA) with Newly Diagnosed Rare non-Hodgkin Lymphoma (NHL) sec. WHO 2022

PI: Prof. A. Attarbaschi

In female/male participants younger than 26 years of age with newly diagnosed rare forms of NHL as specified below:

Objectives and Endpoints:
Primary
• To establish a prospective collection of data and biospecimens to allow validated information on CAYA rare NHL
• To prospectively characterize the pathology, biology, clinical features, treatment patterns, response and outcomes for rare NHL in CAYA
Secondary
• To investigate the molecular-genetic landscape of rare NHL in CAYA on an international scale
• To determine associations between clinicopathological features, disease biology, and treatment outcomes for specific lymphoma histologies
• To bank biology samples from pathology tissues in a federated manner, and make them available for biology studies aimed at identifying new molecular therapeutic targets

eicnhl

incluso in AIEOP LNH-2024

Pubblicazioni 2024-oggi

Single-cell transcriptomics of pediatric Burkitt lymphoma reveals intra-tumor heterogeneity and markers of therapy resistance. Corinaldesi C, Holmes AB, Martire G, Tosato A, Rizzato D, Lovisa F, Gallingani I, Shen Q, Ferrone L, Harris M, Davies K, Molinaro L, Mortara U, Dei Tos AP, Ofori K, D'Amore ESG, Chiarle R, Ngan B, Carraro E, Pillon M, Hussein S, Bhagat G, Pizzi M, Mussolin L, Basso K. Leukemia. 2025 Jan

TP53 DNA binding domain mutational status and rituximab-based treatment are independent prognostic factors for pediatric Burkitt lymphoma patients stratification. Martire G, Lovisa F, Carraro E, Rizzato D, Cesaro S, Mura RM, Tondo A, Bertolin C, Boaretto F, Salviati L, Biffi A, Pillon M, Mussolin L. Haematologica. 2024 Feb 22.

Large B-cell lymphoma-IRF4+ in children and young people: time to reduce chemotherapy in a rare malignant mature B-cell neoplasm? Huibers M, Abla O, Andrés M, Balagué O, Beishuizen A, Carraro E, Chiang A, Csóka M, David BA, de Ville de Goyet M, Gilad G, Hori D, Kotecha RS, Kabickova E, Klapper W, Miakova N, Minard-Colin V, Nakazawa A, Pillon M, Rigaud C, Salaverria I, Tölle I, Verdú-Amorós J, von Mersi H, Wössmann W, Burkhardt B, Attarbaschi A. Blood Adv. 2024 Mar 26;8(6):1509-1514.

Large B-cell lymphoma with IRF4 rearrangement: a multi-centric study with focus on potential misleading phenotypes. Pizzi M, Bongiovanni L, Lorenzi L, Righi S, Scarmozzino F, Balzarini P, Santoro L, Mussolin L, Carraro E, Pillon M, Bonaldi L, Vianello F, Agostinelli C, Ponzoni M, Dei Tos AP, Sabattini E. Virchows Arch. 2023 Nov 14.

Quantitative assessment of minimal residual disease for monitoring of paediatric patients with relapsed/refractory anaplastic large-cell lymphoma treated with brentuximab vedotin: A case series. Contarini G, Carraro E, Lovisa F, Martire G, Lo Nigro L, Sala A, Pillon M, Mussolin L. Br J Haematol. 2024 Jan;204(1):352-355.

Cost-effectiveness analysis alongside the inter-B-NHL ritux 2010 trial: rituximab in children and adolescents with B cell non-Hodgkin's lymphoma. Lueza B, Aupérin A, Rigaud C, Gross TG, Pillon M, Delgado RF, Uyttebroeck A, Amos Burke GA, Zsíros J, Csóka M, Simonin M, Patte C, Minard-Colin V, Bonastre J. Eur J Health Econ. 2024 Mar;25(2):307-317.

Giornate AIEOP

BOLOGNA 14-15 APRILE 2025

Prossimi appuntamenti

Next EICNHL meetings: Budapest, 11 Maggio 2025

Padova, novembre-dicembre 2025

Grazie per l'attenzione!

GdL LNH

Lab Diagnostica molecolare LNH
L. Mussolin

D. Rizzato
G. Martire
C. Damanti
A. Danieli
M. Marzi
R. Salzmann
E. Tosato

E. Carraro
T. Cincotti
M. Pizzi

K.Basso

Lab Oncoematologia Pediatrica di Padova
B. Buldini

A. Biffi

GdL AIEOP

Centri AIEOP

Pazienti e le loro famiglie

Associazioni e Fondazioni