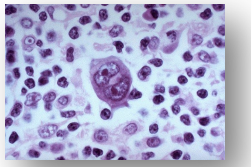
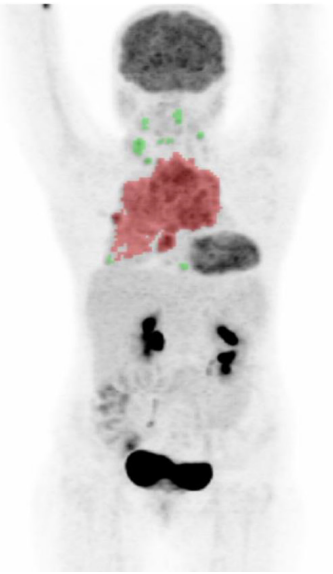
GdL Linfoma di Hodgkin

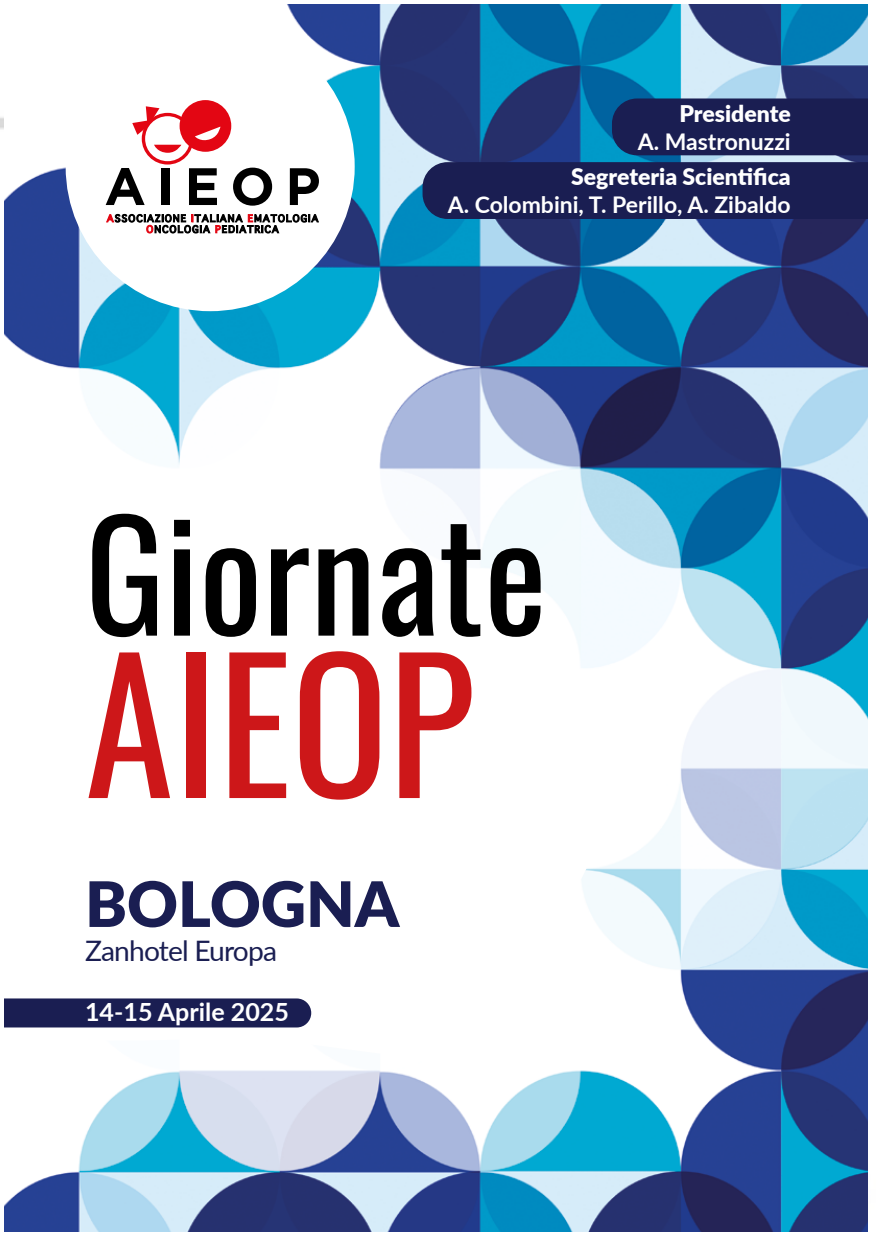




Maurizio Mascarin

CRO - Centro di Riferimento Oncologico, Aviano (PN), Italy

mascarin@cro.it



Il sottoscritto Mascarin Maurizio
in qualità di relatore,

ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 Febbraio 2017

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

«SAC» Scientific Advisor Committee member, supporting the program MK-3475 KN 667 for pediatric and adolescent Hodgkin lymphoma. Speaker bureau with Takeda and Menarini.
Co-authors disclosed relationships with the AIEOP, AIOM, Bristol Myers Squibb, EuroNet-PHL..

AIEOP

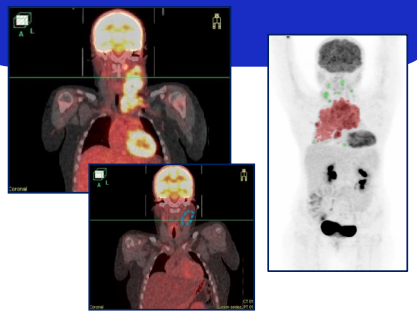
To build a best treatment selection model

CHEMO TOXICITIES

- Reduce dose of Antracyclines
- Reduce Dacarbazine
- Avoid Bleomicine
- Fertility (Dacarbazine replace Procarbazine)

RADIOTHERAPY

- PET based-modulation
  - Indication to RT
  - RT Fields
  - RT Doses



BMT

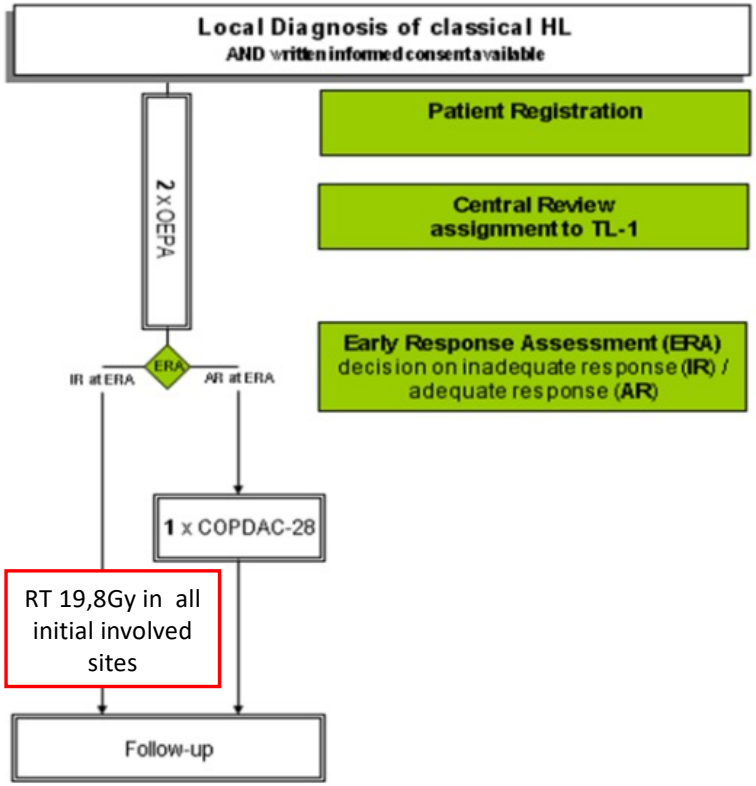
- Less indications in relapsed HL

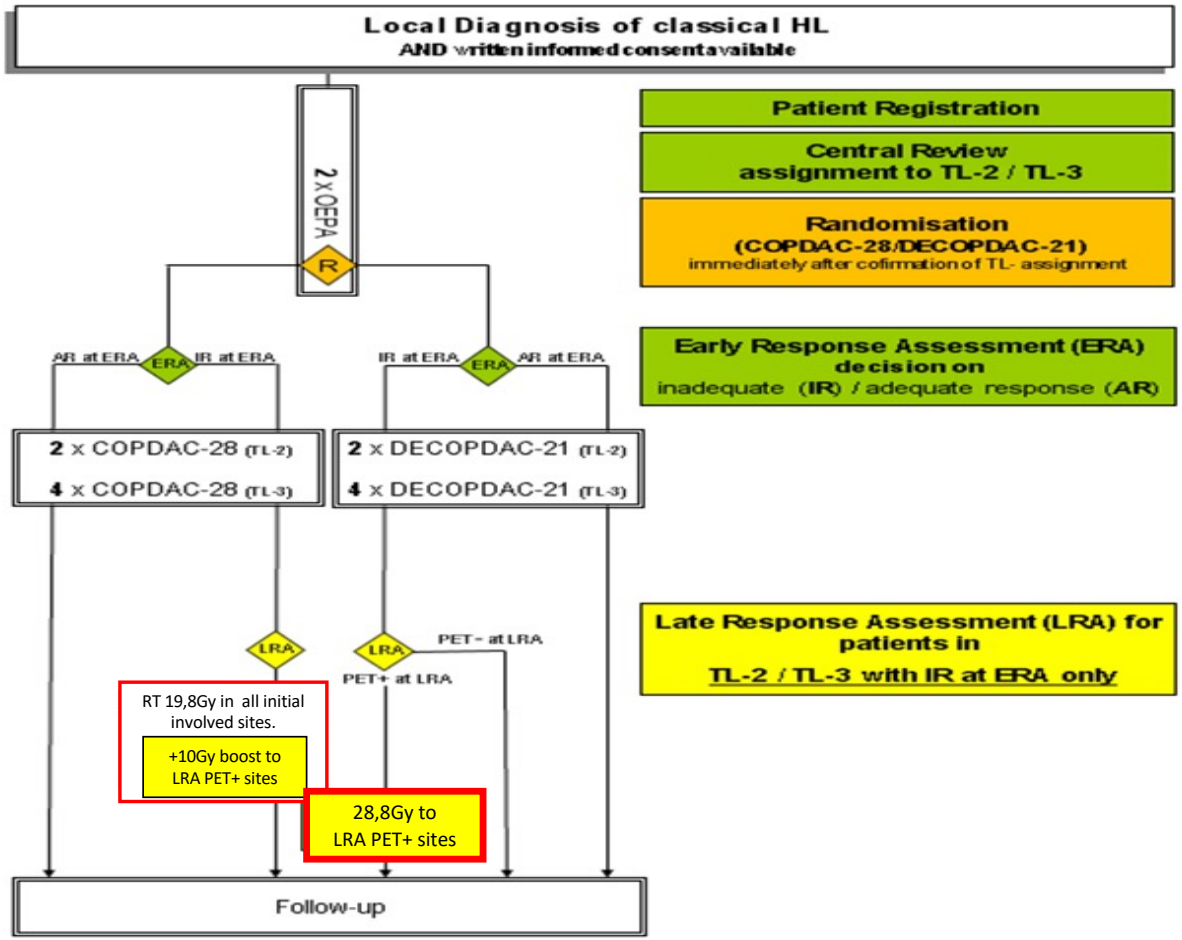
NEW DRUGS

- EMA vs FDA

"multiple views on the same problem"

EuroNet-PHL-C2 study

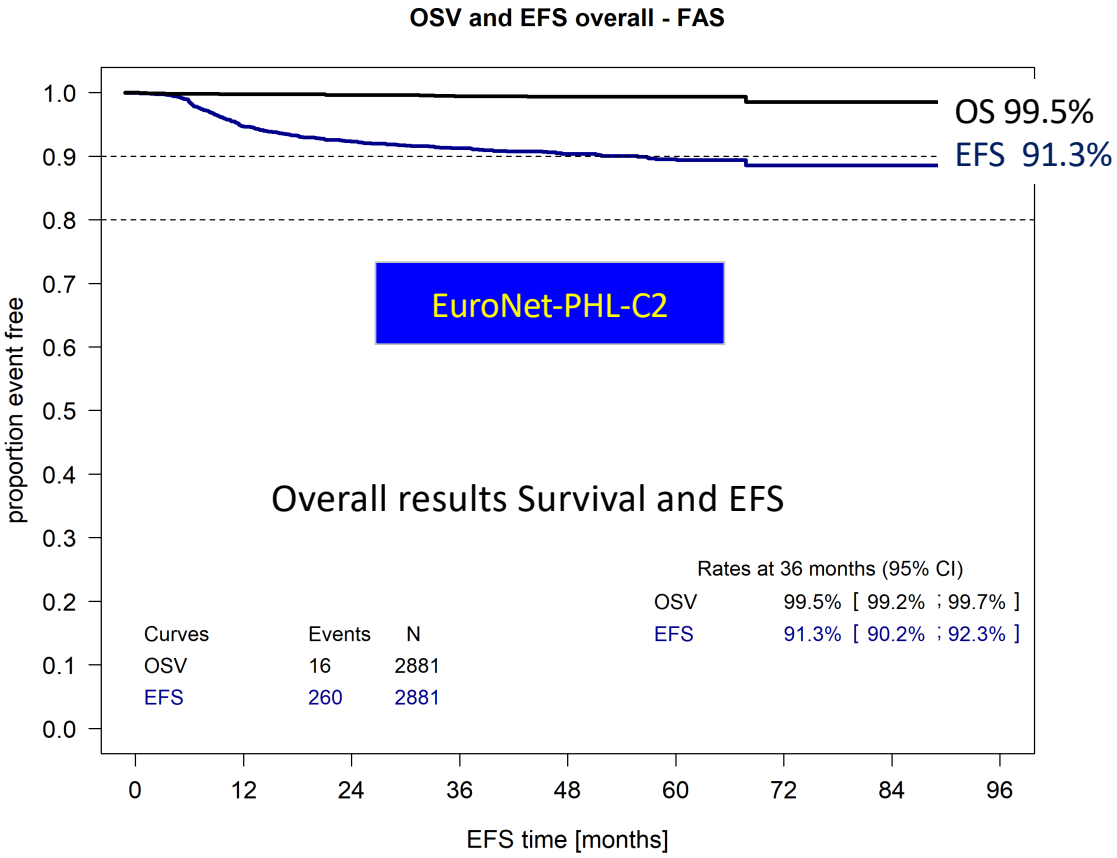


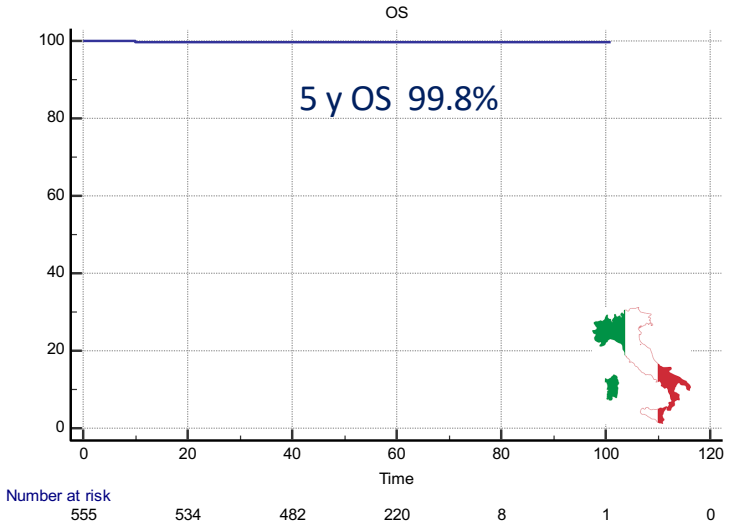


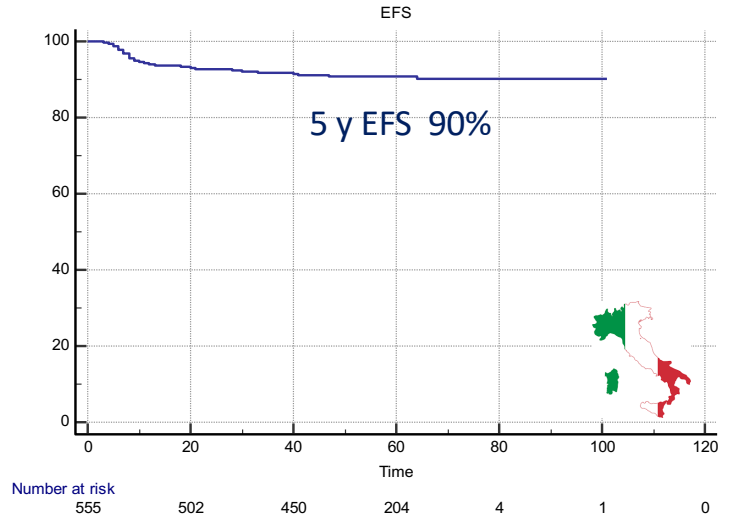
AIEOP

PHL-C2 preliminary data: OS and EFS (EU vs Italy)

- 2921 total C2 pts
- 562 pts Italy (19,2%)

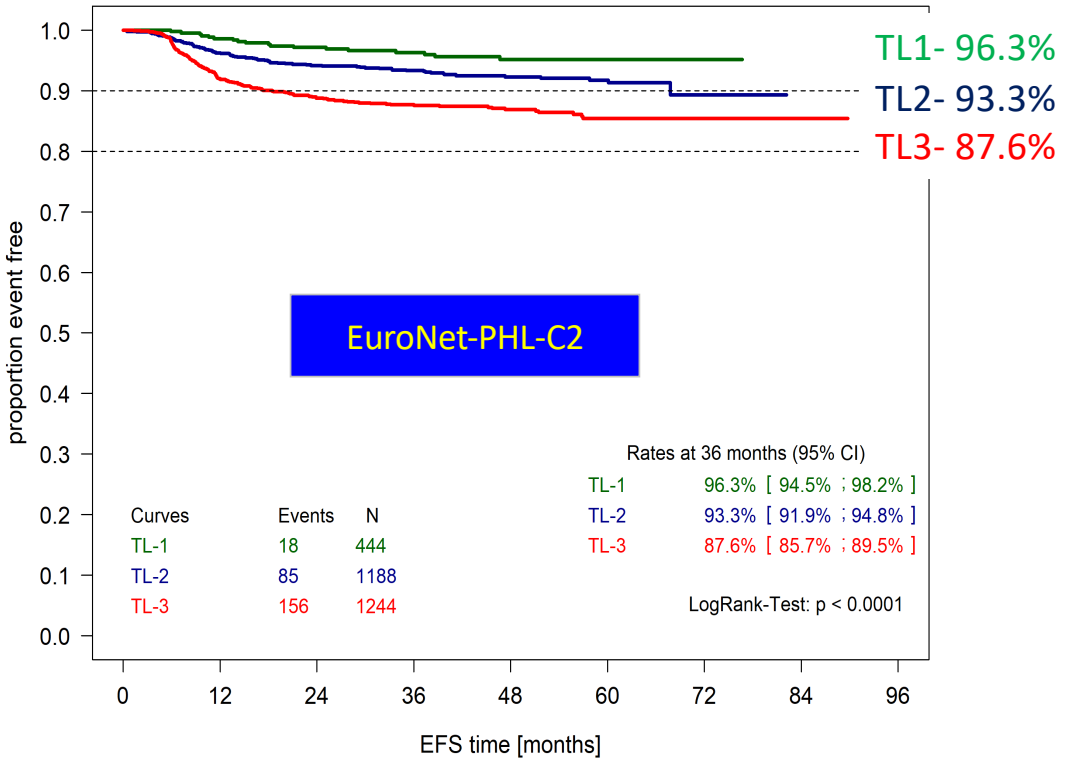


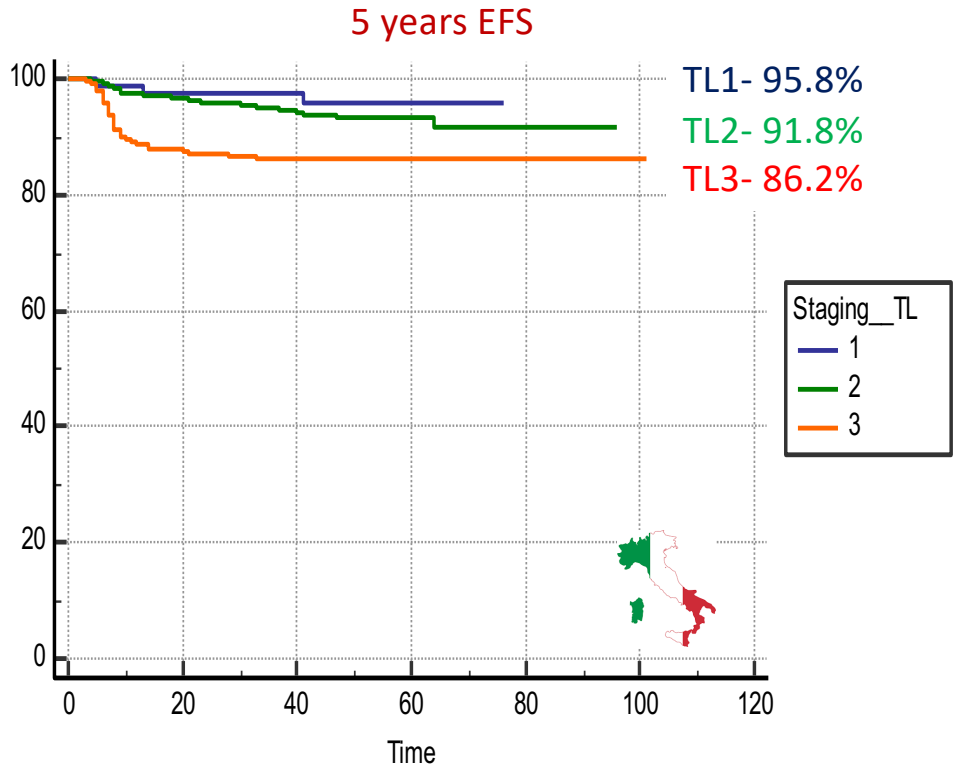




CM Koerholz, D Hasenclever: CONFIDENTIAL 7th Formal interim analysis data as of 2024-02-19

PHL-C2 preliminary data: EFS by TL (EU vs Italy)



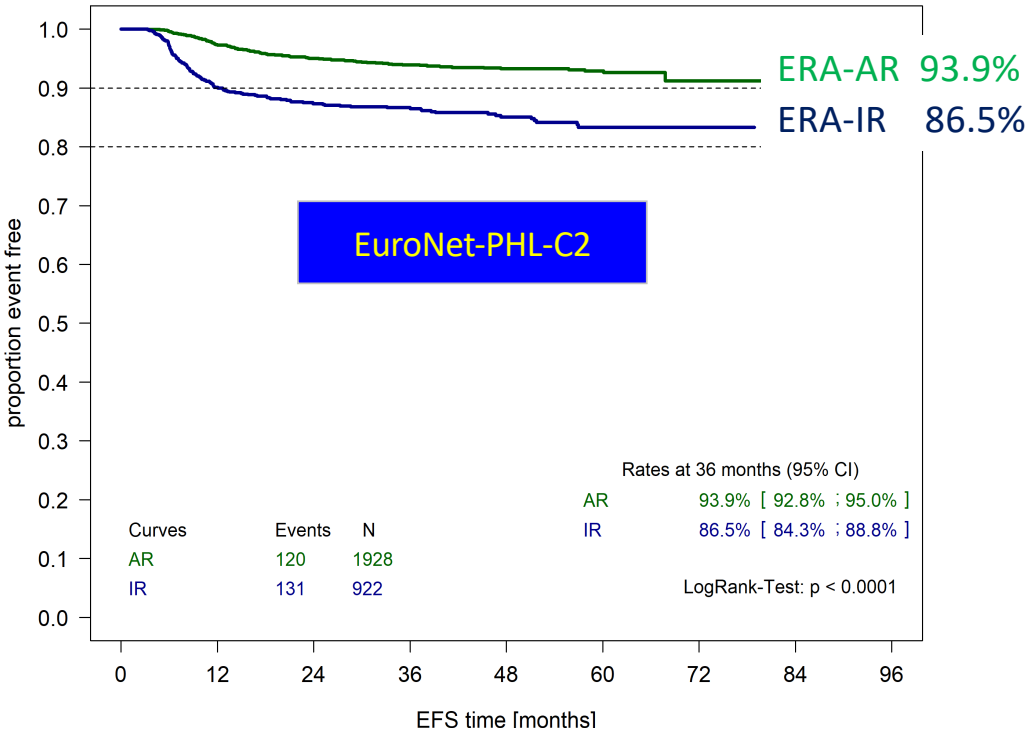


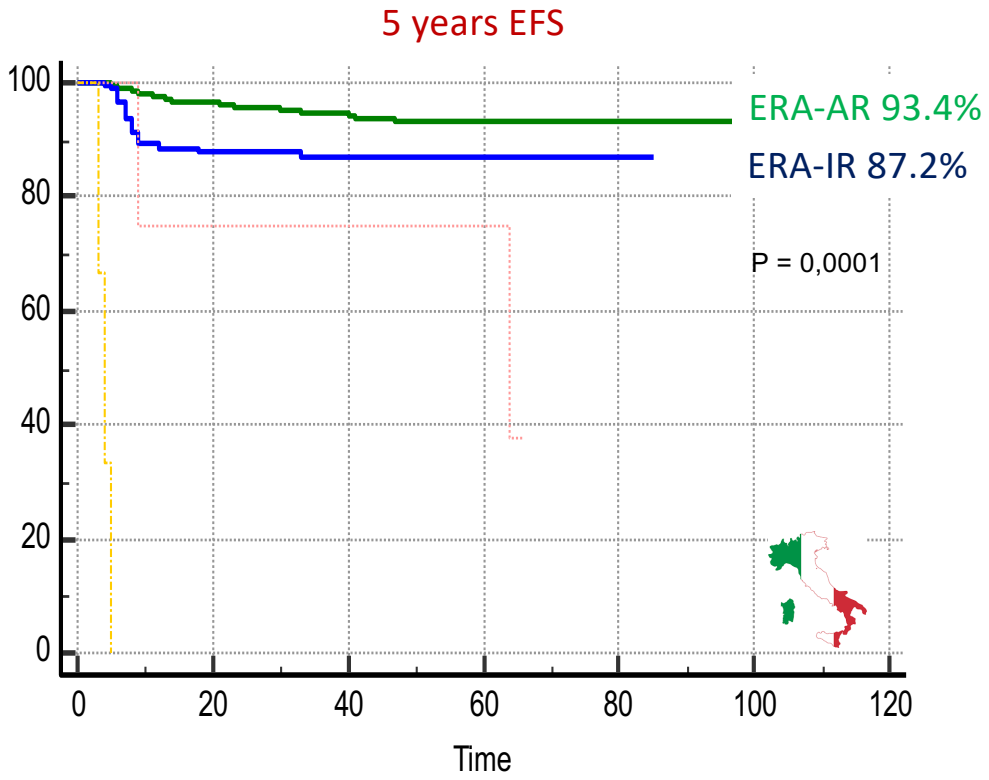
Number at risk

Group: 1							
	77	70	66	30	0	0	0
Group: 2							
	260	247	215	103	2	0	0
Group: 3							
	218	185	169	71	2	1	0

CM Koerholz, D Hasenclever:CONFIDENTIAL 7th Formal interim analysis data as of 2024-02-19

PHL-C2 preliminary data: ERA AR vs IR





2 ricadute su 4 pts con ERA non disponibile

CM Koerholz, D Hasenclever:CONFIDENTIAL 7th Formal interim analysis data as of 2024-02-19

pediatrici

AIEOP

PHL-C2 preliminary data: ERA AR rates by TL

EuroNet-PHL-C2

			TL2-		TL2-		TL3-		TL3-			
Ntotal=2689	TL1	%col.1	C	%col.2	D	%col.3	C	%col.4	D	%col.5	All	%All
noRT	387	87.4	412	75.2	492	88.6	310	54.1	489	85.8	2090	77.7
RT	56	12.6	136	24.8	63	11.4	263	45.9	81	14.2	599	22.3
Nvalid	443	100	548	100	555	100	573	100	570	100	2689	100

As expected, the RT indication rate increases with more advanced disease and is reduced with the DECOPDAC. COPDAC probably is not adeguate to avoid RT in high stage disease.

CM Koerholz, D Hasenclever:**CONFIDENTIAL** 7th Formal interim analysis data as of 2024-01-17

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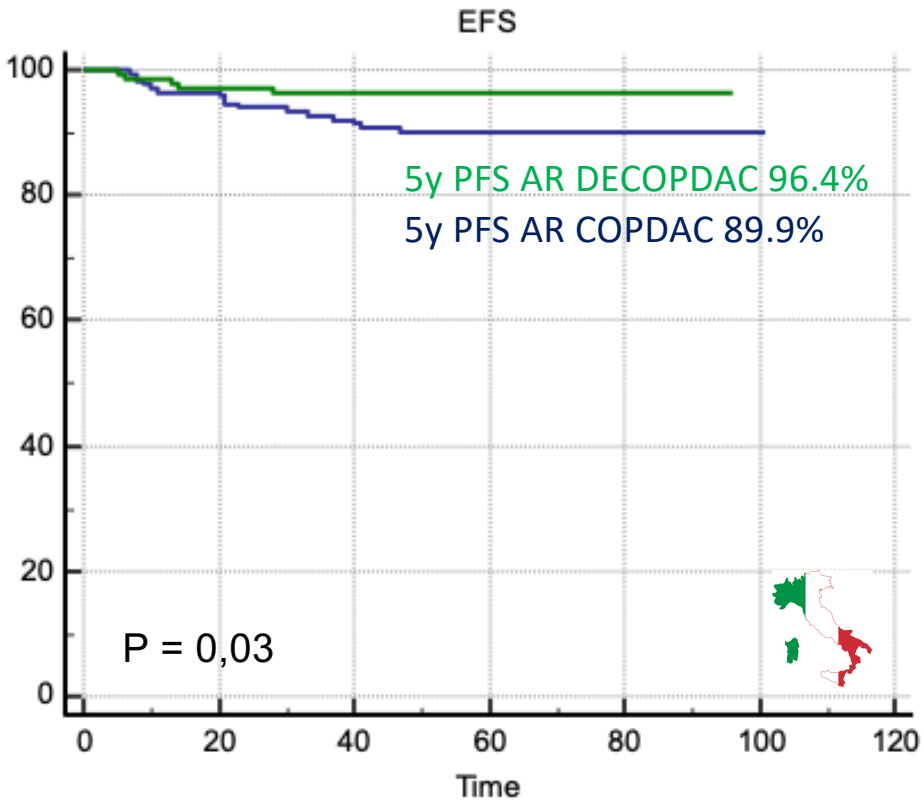
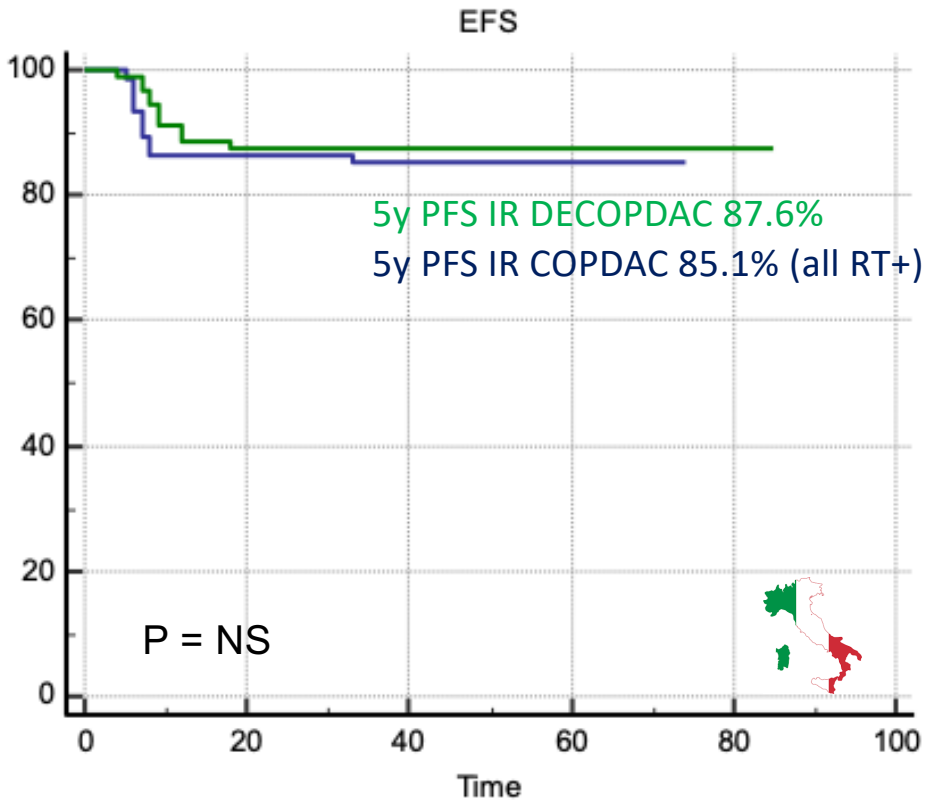
PHL-C2 preliminary data: ERA-PET AR and IR by random

AR TL2, TL3 cohort (all no RT)



IR TL2, TL3 cohort



2 SNM: 1 Ca tiroide (+66 mesi) TL3 COPDAC + RT (+boost); **1 Ca tiroide** (+72 mesi) TL3 COPDAC, recidiva -> TMO

Phl.italy: **CONFIDENTIAL** interim analysis data as of 2025-03-30

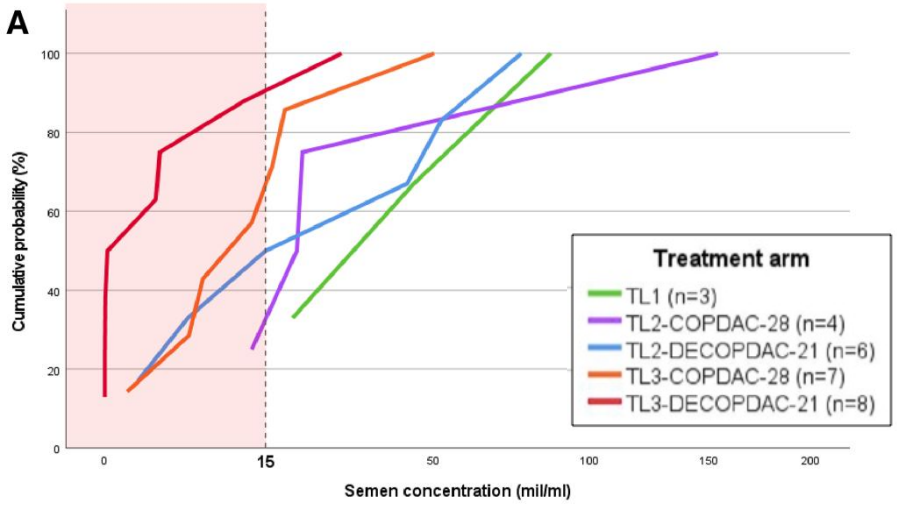
AIEOP

Late effects in PEDIATRIC HODGKIN LYMPHOMA

Semen analysis and reproductive hormones in boys with classical Hodgkin lymphoma treated according to the EuroNet-PHL-C2 protocol

K.C.E. Drechsel[1,2,3,*], S.L. Broer[4], H.M.K. van Breda[5], F.S. Stoutjesdijk[1], E. van Dulmen-den Broeder[1], A. Beishuizen[2,6], W.H. Wallace[7], D. Körholz[8], C. Mauz-Körholz[8], D. Hasenclever[9], M. Cepelova[10], A. Uyttebroeck[11], L. Ronceray[12], J.W.R. Twisk[13], G.J.L. Kaspers[1,3], and M.A. Veening[1,3]

Human Reproduction, 2024, 00(0), 1-12

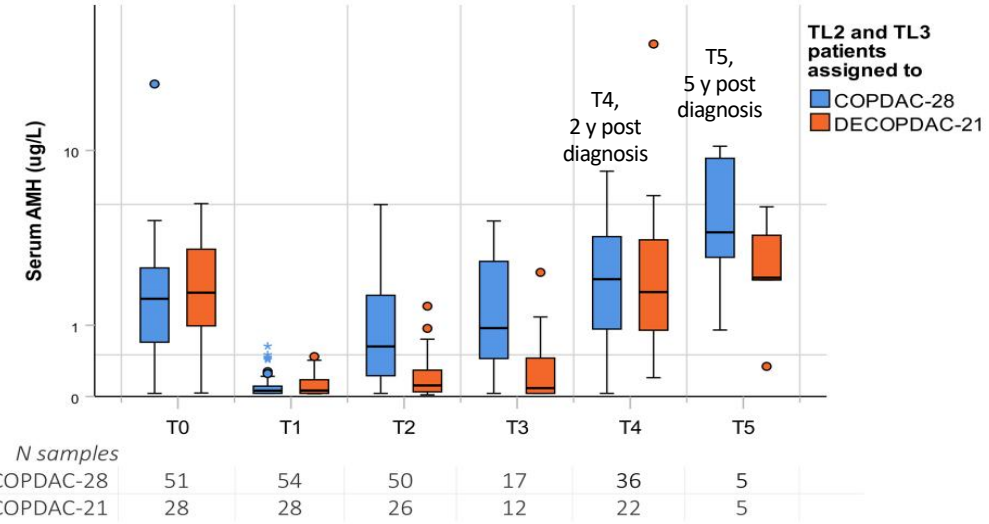


More than half of the patients (52%) had oligozoospermia or azoospermia at 2 years from cHL diagnosis (particularly boys treated for advanced-stage cHL).

The impact of treatment for childhood classical Hodgkin lymphoma according to the EuroNet-PHL-C2 protocol on serum anti-Müllerian Hormone

K.C.E. Drechsel[1,2,3,*], S.L. Broer[4], F.S. Stoutjesdijk[1], E. van Dulmen-den Broeder[1], A. Beishuizen[2,5], W.H. Wallace[6], D. Körholz[7], C. Mauz-Körholz[7,8], D. Hasenclever[9], M. Cepelova[10], A. Uyttebroeck[11], L. Ronceray[12], J.W.R. Twisk[13], G.J.L. Kaspers[1,2], and M.A. Veening[1,2]

Human Reproduction, 2024, 39(8), 1701–1711



N samples	T0	T1	T2	T3	T4	T5
COPDAC-28	51	54	50	17	36	5
DECOPDAC-21	28	28	26	12	22	5

Serum AMH levels decreased after induction chemotherapy and increased during subsequent treatment and 2 years of follow-up, with lowest levels in patients treated for advanced stage cHL.

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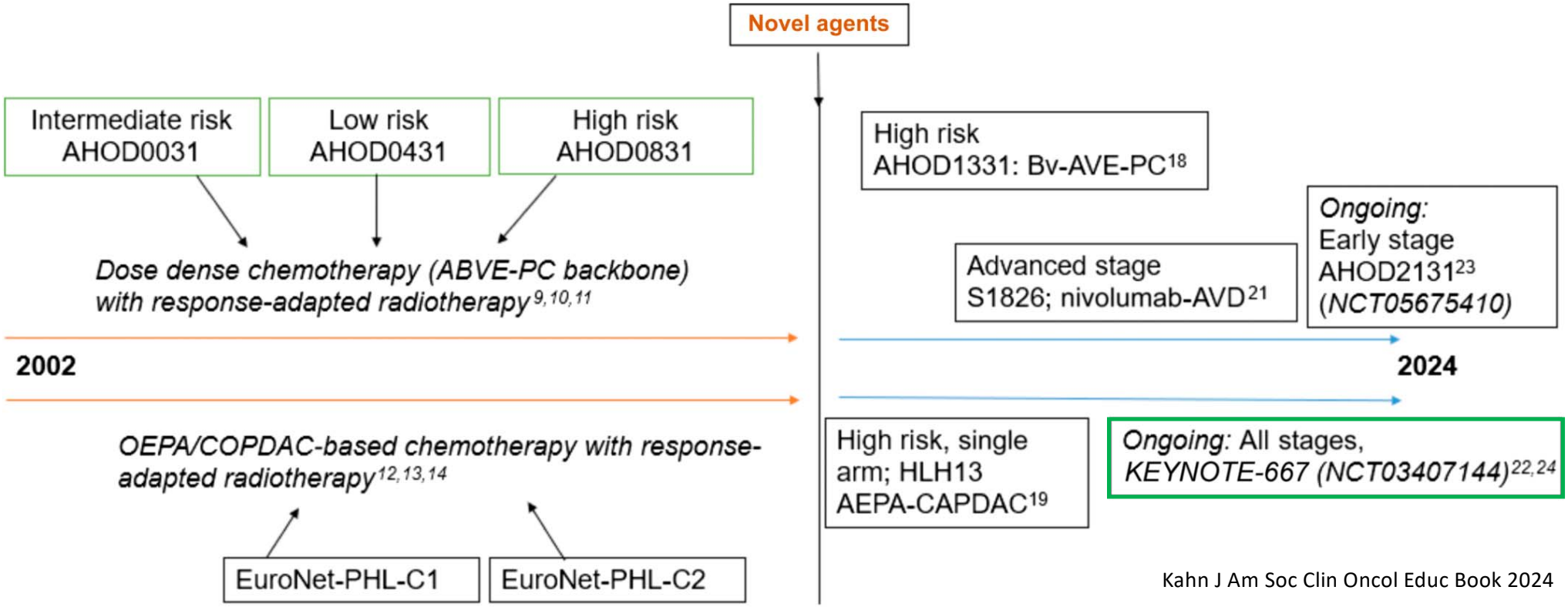
Frontline clinical trials design for ped AYA cHL before and after the introduction of novel IT agents



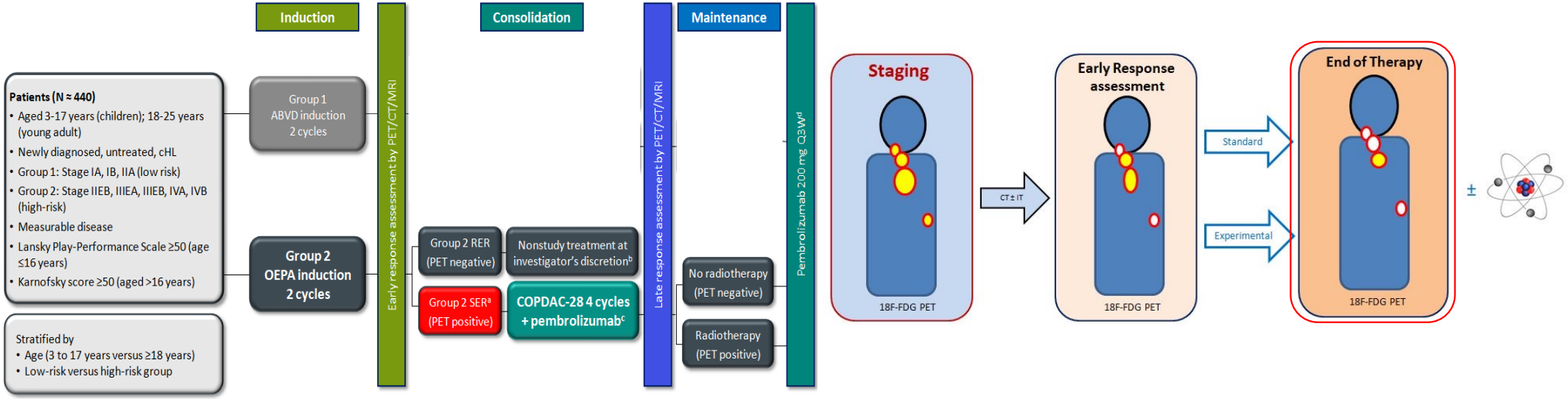
Kahn J Am Soc Clin Oncol Educ Book 2024

AIEOP

New drugs in 1^ line PEDIATRIC HL: AHOD1331

New drugs (Pembro) in 1^ line PED cHL combine with standard CT, to better spare RT

KEYNOTE-667 Study Design (NCT03407144) Group 2



Courtesy L Vinti, KM Koerholz

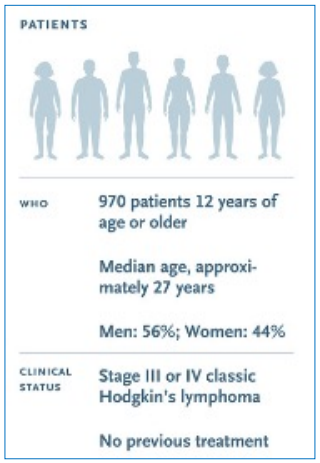
- modified involved-site RT to late PET-positive residual nodes
- 66 % of SER patients had a PET-negative response at end of chemotherapy and spared RT.
- In EuroNet-C2 trial, 55% TL3 pts treated with COPDAC and ERA-AR spared RT.

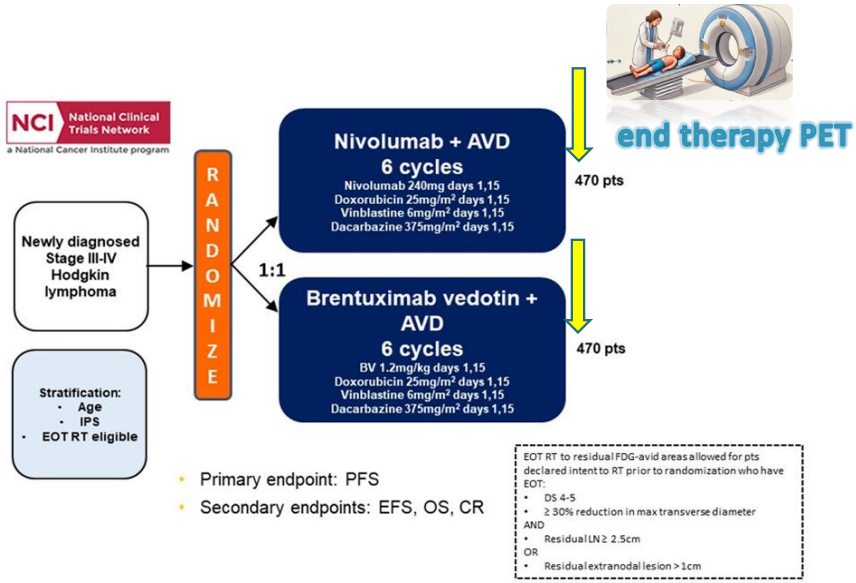
New drugs in 1^ line PEDIATRIC HL: SWOG S1826

Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma

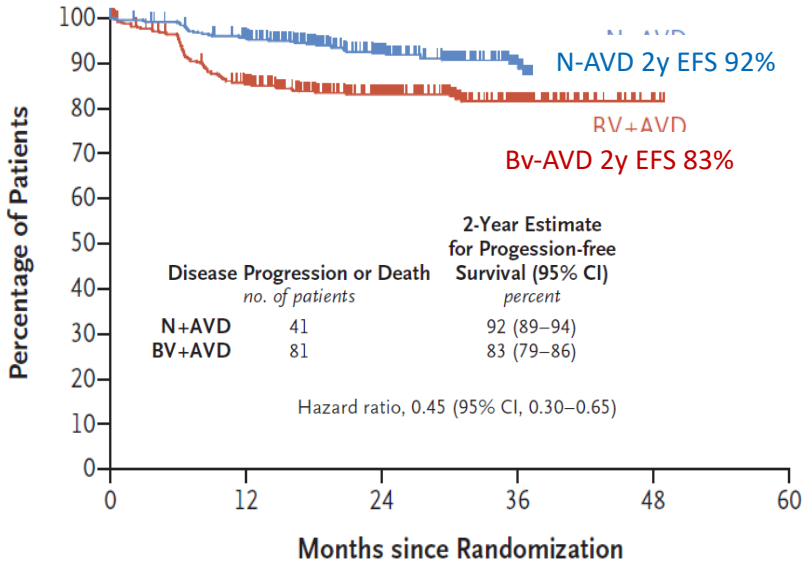
A.F. Herrera, M. LeBlanc, S.M. Castellino, H. Li, S.C. Rutherford, et al. NEJM 391, 15, October 17, 2024

The NEW ENGLAND JOURNAL of MEDICINE





2 years EFS



Key Points:

- < 1% of patients in the trial received end-of-treatment radiotherapy.
- Zero steroid or cyclophosphamide, … but Doxorubicin dose 300mg/mq.
- Nivo and Bv eliminated the predictive value of the interim PET.

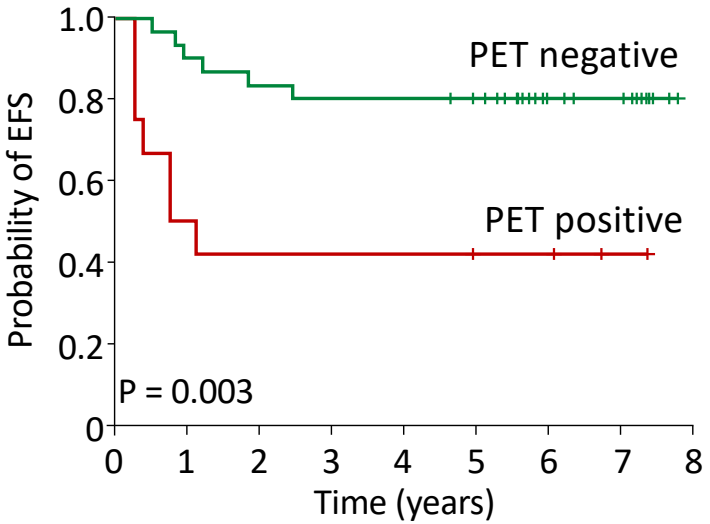
AIEOP

Relapsed/Refractory Ped-AYA cHL: disease status pre auto-HCT

Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma

Alison J. Moskowitz,[1] Joachim Yahalom,[1] Tarun Kewalramani,[2] Jocelyn C. Maragulia,[1] Jill M. Vanak,[1] Andrew D. Zelenetz,[1] and Craig H. Moskowitz[1]

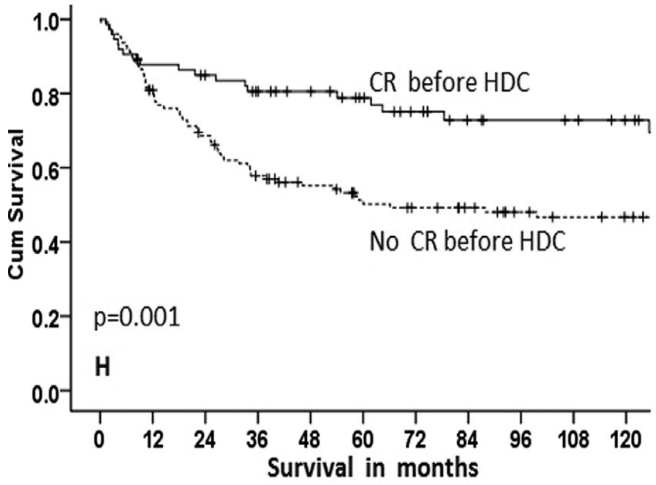
Blood 2010;116:4934–4937.



Impact of Risk Factors and Long Term Survival Analysis of Patients With Primary Refractory Hodgkin Lymphoma Who Underwent High Dose Chemotherapy and Autologous Stem Cell Transplant

Saad Akhtar[1,2,*], M. Shahzad Rauf[1], Tusneem Ahmed M. Elhassan[1], Zubair Ali Khan[3], Mahmoud A. Elshenawy[1,4], Irfan Maghfoor[1]

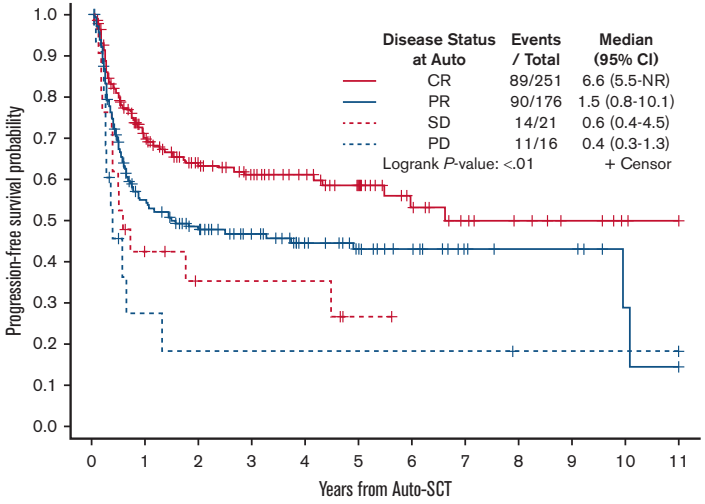
Transplantation and Cellular Therapy 29 (2023)



Evaluation of prognostic factors in patients with high-risk classical Hodgkin lymphoma undergoing autologous transplantation

Narendranath Epperla,[1,2] Ying Huang,[1] Amanda F. Cashen,[3] John L. Vaughn,[1,4] Walter Hanel,[1] Talha Badar,[5,6] Stefan K. Barta,[7,8] Paolo F. Caimi,[9,10] Tarsheen K. Sethi,[4,11] Nishitha Reddy,[11] Reem Karmali,[12] Celeste Bello,[13] Julio C. Chavez,[13] Shalin K. Kothari,[4,14] Francisco J. Hernandez-Ilizaliturri,[14] Jakub Svoboda,[8] Frederick Lansigan,[15] Martha J. Glenn,[2] Jonathon B. Cohen,[16] Caryn Sorge,[17] Beth Christian,[1] Alex F. Herrera,[18] Mehdi Hamadani,[5] Luciano J. Costa,[19] and Ana C. Xavier[20]

bloodadvances.2024



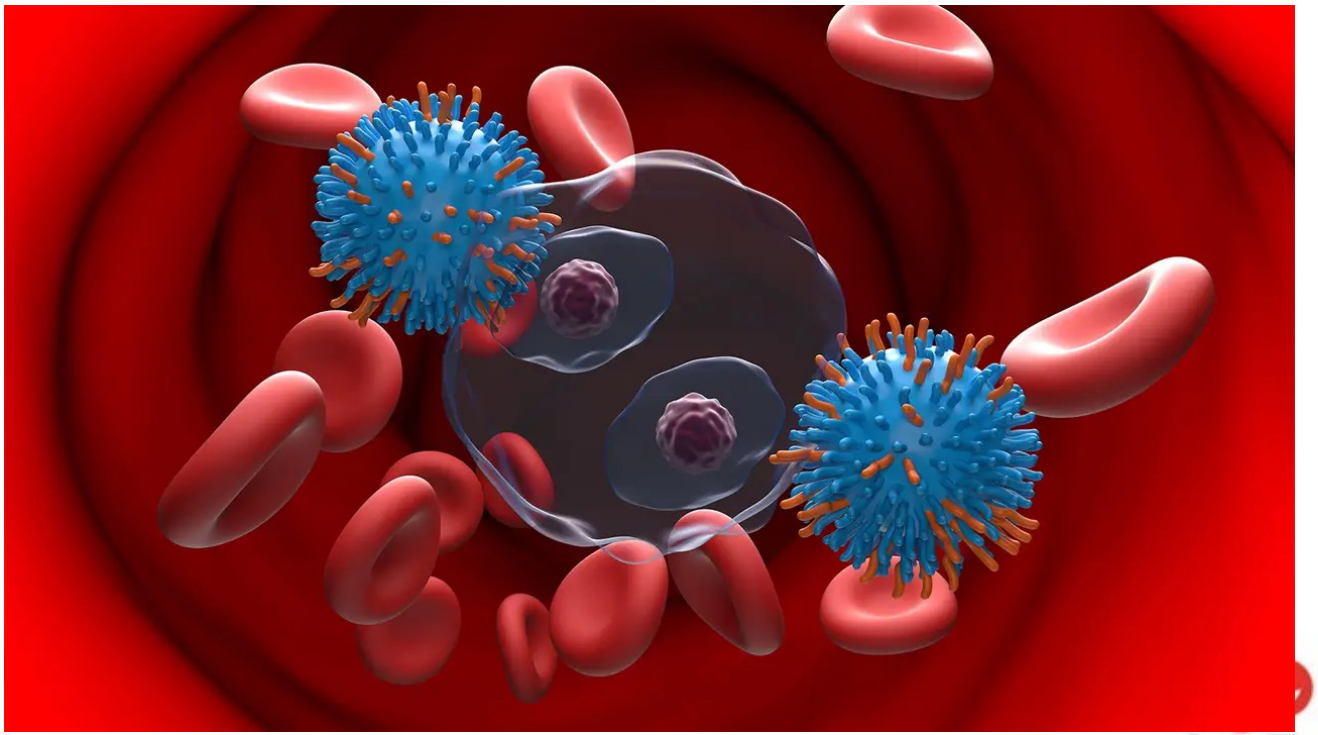
Response prior to auto-HCT in pediatric adolescent pts is a strong predictor of favorable outcomes

Adult patients who are PET negative prior to auto-HCT have better outcomes

AIEOP

Enthusiasm for Transplant-Free Strategies for Low-Risk Relapsed Hodgkin Lymphoma

MEDPAGETODAY 2025



Relapsed Ped-AYA cHL (R1 cohort)

JAMA Oncology | Original Investigation

Transplant-Free Approach in Relapsed Hodgkin Lymphoma in Children, Adolescents, and Young Adults

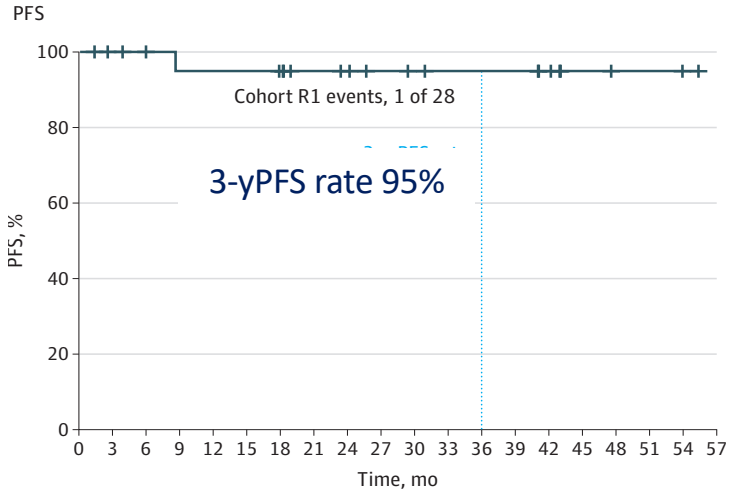
A Nonrandomized Clinical Trial

CheckMate 744

Stephen Daw, MD; Peter D. Cole, MD; Bradford S. Hoppe, MD, MPH; David Hodgson, MPH; Auke Beishuizen, MD; Nathalie Garnier, MD; Salvatore Buffardi, MD; Maurizio Mascarin, MD; Andrej Lissat, MD; Christine Mauz-Körholz, MD; Jennifer Krajewski, MD; Alev Akyol, MD; Russell Crowe, MA; Bailey Anderson, MPH; Yan Xu, MS; Richard A. Drachtman, MD; Kara M. Kelly, MD; Thierry Leblanc, MD; Paul Harker-Murray, MD, PhD

AMA Oncol.,January 2, 2025

28 relapsed R1 pts (0-27y, 36%> 18 y)



R1:

- Stage IA/IIA
- Time 3-12 m, < 3 cycles
- >12 m IB/IIB/IIIB
- No B symptoms;
- No E disease
- No extensive RT.

A total of 5 patients (18%) had 1 or more serious TRAEs during induction, including grade 3 or 4 rash, urticaria, and febrile neutropenia (1 each)

JAMA Oncology | Original Investigation

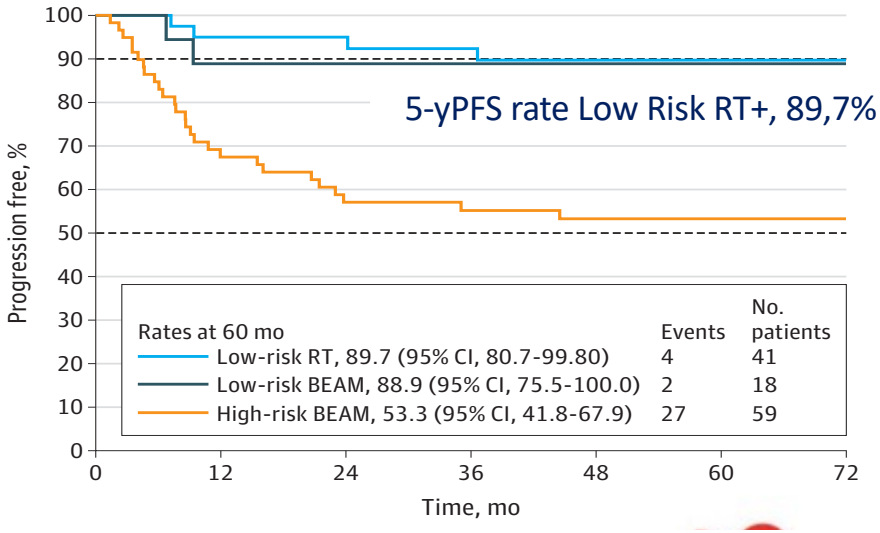
Transplant and Nontransplant Salvage Therapy in Pediatric Relapsed or Refractory Hodgkin Lymphoma

The EuroNet-PHL-R1 Phase 3 Nonrandomized Clinical Trial

Stephen Daw, MD; Alexander Claviez, MD; Lars Kurch, MD; Dietrich Stoevesandt, MD; Andishe Attarbaschi, MD; Walentyna Balwierz, MD; Auke Beishuizen, MD; Michaela Cepelova, MD; Francesco Ceppi, MD; Ana Fernandez-Teijeiro, MD; Alexander Fosså, MD; Thomas W. Georgi, MD; Lisa Lyngsie Hjalgrim, PhD; Andrea Hraskova, MD; Thierry Leblanc, MD; Maurizio Mascarin, MD; Jane Pears, MD; Judith Landman-Parker, MD; Tomaž Prelog, MD; Wolfram Klapper, MD; Alan Ramsay, DM; Regine Kluge, MD; Karin Dieckmann, MD; Tanja Pelz, MD; Dirk Vordermark, MD; Dieter Körholz, MD; Dirk Hasenclever, PhD; Christine Mauz-Körholz, MD

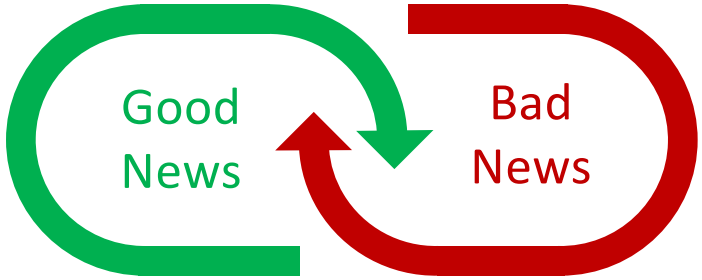
AMA Oncol.,January 2, 2025

118 relapsed pts (0-18 y, 86%> 13 y)



PFS analysis: 27/33 second relapses occurred in 55 patients with ERA IR, and all received HDCT/ aSCT.

Good News and Bad News



C1 an C2 trial

A subgroup of DS1 and D2 pts at ERA, who do extremely well: de-escalation is feasible

Modulation factors

The effect of CT can be largely view at ERA

Radiotherapy

In C2 trial the indication to RT has been reduced to combination to 22% of pts.

COPDAC

Easy to administer; but steroid doses are high.

Combination IT+CT

The combination of Bv and Nivo + CT is highly effective in HL

DS5 at ERA and at LRA

There are "BAD PLAYERS" and "BAD of BAD PLAYERS"

Modulation factors

The effect of IT and IT+CT cannot be view at ERA, but at the end of therapy. CPI based strategy is efficacy only if applied to all pts.

Radiotherapy

RT is still necessary in some patients. The results of ERA-IR pts treated with COPDAC+RT are slightly better than DECOPDAC alone.

DECOPDAC

The hospitalization rate is generally considered high for pts with HL.
The cumulative dose of Doxo and Eto are not-negligible.

Combination IT+CT

The combination of IT+CT is better than IT alone.
IT alone is not probably the definitive solution.

AIEOP

AIEOP PHL-2021 Osservazionale

41 Centri hanno aderito (tutti i centri EuroNet + INTMi

Registrati 88 pazienti in 4 anni !!

Inviate schede di registrazione da 17 centri:
Ancona, **Aviano*,** Bergamo, Bologna, Firenze, **Genova*,** INT Milano, **Modena*, Napoli UNI*, Parma*,** Pavia, **Pisa*,** Reggio Calabria, Rimini, Taranto, Torino, **Verona*.**

***anche terapia e FUP**

AIEOP

Linfoma di Hodgkin a Prevalenza Linfocitaria:

studio osservazionale “LH-PL rev AIEOP-2004”

PI e Coordinatore Nazionale: dott.ssa Elena SABATTINI (IRCCS-Bologna)

Co-PI: dott.ssa Simona RINIERI (Oncoematol Ped - Ferrara)

titolo dello studio: “Studio retrospettivo sul linfoma di Hodgkin a predominanza linfocitaria (LHPL) in età pediatrica completamento della revisione dello studio AIEOP LH-2004

CHIUSURA DELLO STUDIO 01.01.2025

“Studio AIEOP LHPL – 2019” (studio attivo, in corso)

PI e Coordinatore Nazionale: dott.ssa Paola MUGGEO (Bari)

Studio AIEOP – LHPL – 2019

Coordinatore: dott.ssa Paola Muggeo

ATTIVITA' in corso

1. analisi dei dati raccolti fino al marzo 2024 con stesura del manoscritto

2. collaborazione con **IFOM** (Istituto Fondazione di Oncologia Molecolare) di Milano, dott. Claudio Tripodo per studio di **PROTEOMICA SPAZIALE** (tecnologia che permette di studiare contemporaneamente un numero elevato di espressioni proteiche con elaborazione ed interpretazione informatica digitale) con tecnica di **MICROARRAY** per il quale sarà inviato **emendamento** al protocollo

3. collaborazione con **FIL** (dott. Manuel Gotti, PAVIA) per analisi dei dati FIL-AIEOP

4. proposta ad AIFA per inserimento del **RITUXIMAB** in **648/1996** per la rimborsabilità nel paz pediatrico con LHPL (come già possibile nel paz adulto)

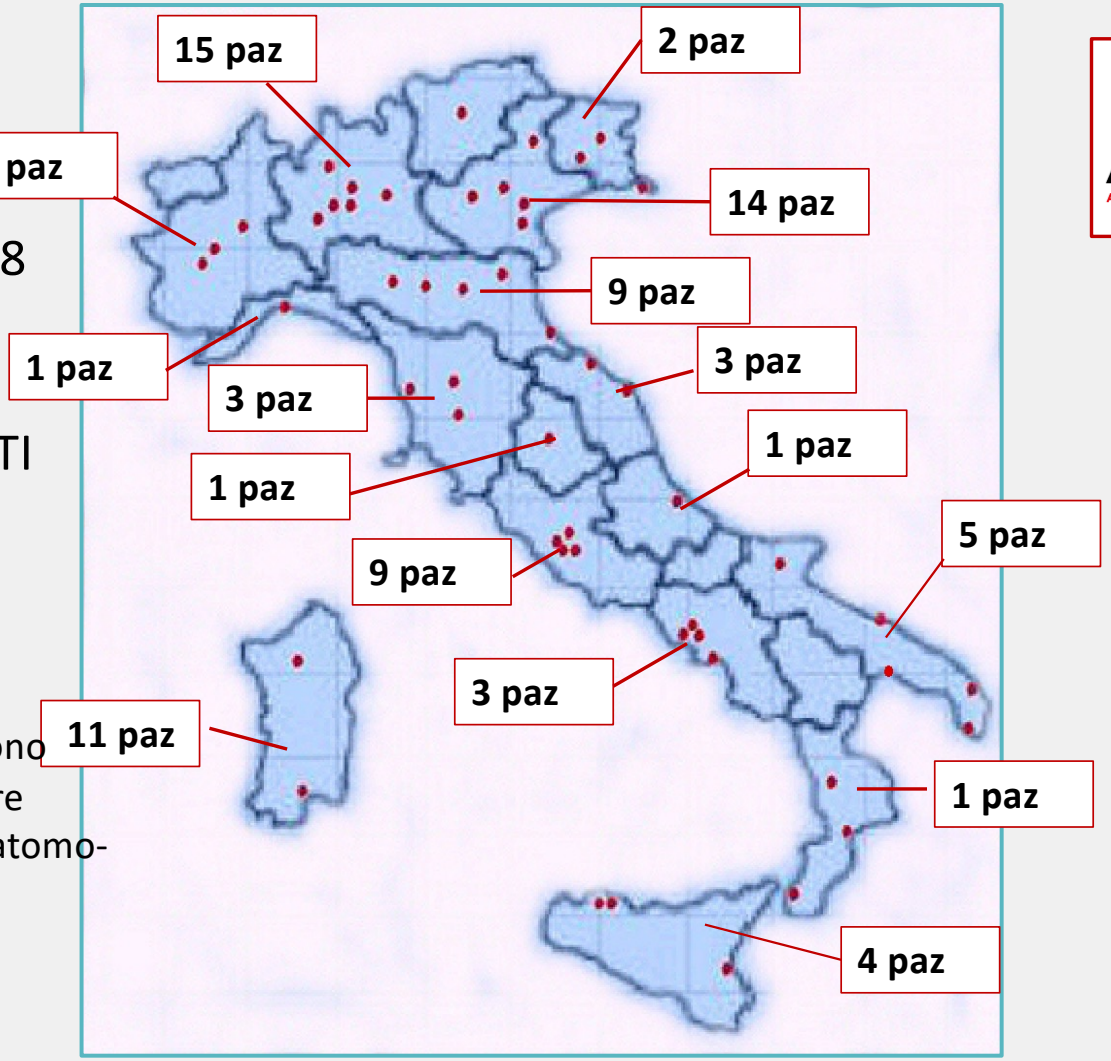
5. richiesta **report a Studi Clinici AIEOP** per nuovi pazienti registrati nello studio Mod. 1.01 dal 2024 ad oggi.

Linfoma di Hodgkin Prevalenza Linfocitaria: "Studio AIEOP – LHPL – 2019"

PROTOCOLLO APERTO IN 28 CENTRI

DIAGNOSTICATI 90 PAZIENTI
(7 da aprile 2024 ad oggi)
in 28 CENTRI da 16 Regioni

Dei 7 pazienti del 2024-25 solo 3 sono stati segnalati al centro coordinatore tutti inviati per centralizzazione anatomo-patologica.
altri pazienti non ancora segnalati?



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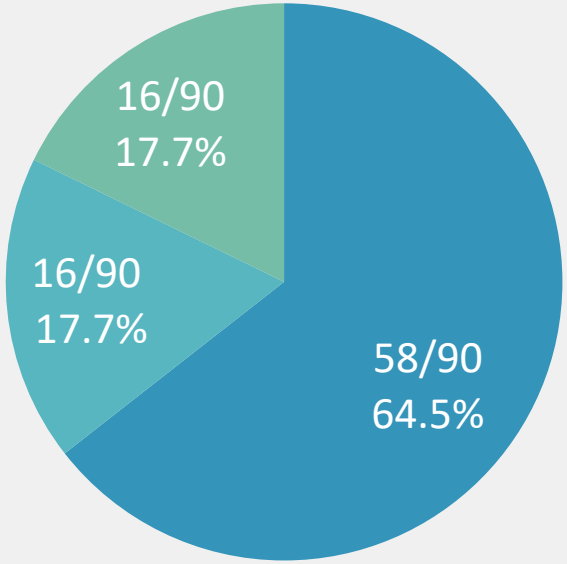
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

CENTRALIZZAZIONE ANATOMIA PATOLOGICA
dott.ssa Elena SABATTINI emolinfopatologia IRCCS Bologna



58/90 casi centralizzati a dott.ssa Sabattini (Bologna)
16/90 casi riferiti al dott. D'Amore (Vicenza)
16/90 casi non centralizzati

centralizzati per revisione 82.2%

Concludendo:

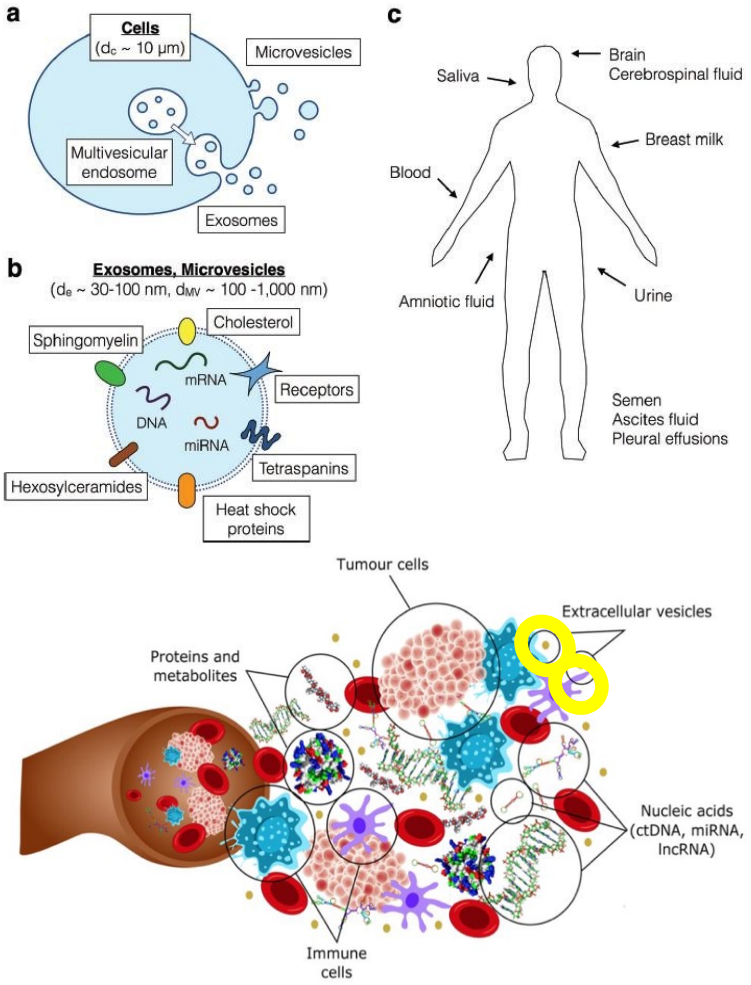
- **casistica attuale rilevante: 90 paz diagnosticati, il reclutamento continua**
- le caratteristiche cliniche confermano la prevalenza di **stadi I-IIA (80%),** del **sesso maschile (81.2% M), dell'età adolescenziale (80% >10aa)**
- possibile risparmio di terapia in stadi senza fattori di rischio, probabilmente allungando i tempi di terapia

- **alla diagnosi inviare CRF per registrazione del paziente o segnalare tramite mail/wa**
  alla mail LHPL.AIEOP@gmail.com

- **inviare il caso per revisione centralizzata anatomo-patologica**
  alla dott.ssa Sabattini **- *Bologna* al seguente indirizzo:**
  SD di Emolinfopatologia
  IRCCS - Azienda Ospedaliero-Universitaria di Bologna,
  Via Massarenti 9, 40138 Bologna
  tel 0039 51 214 4562

per qualsiasi dubbio o comunicazione, contattateci!

Biology: Exosomes



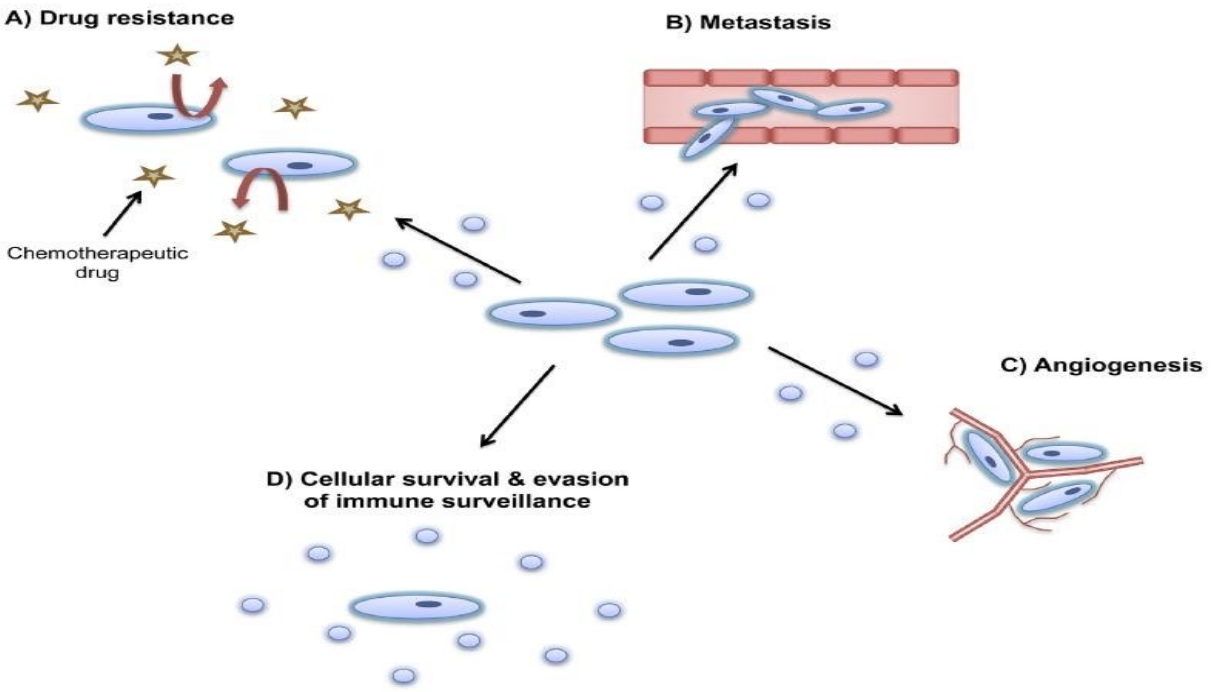
Cell Death and Differentiation (2015) 22, 34–45

www.nature.com/cdd

Review

Exosomes as divine messengers: are they the Hermes of modern molecular oncology?

C Braicu[1,9], C Tomuleasa[1,2,9], P Monroig[3,4], A Cucuianu[2,5], I Berindan-Neagoe*[,1,6,7] and GA Calin*[,3,8]



Molecular Cancer, 2018

Courtesy: L Mussolin

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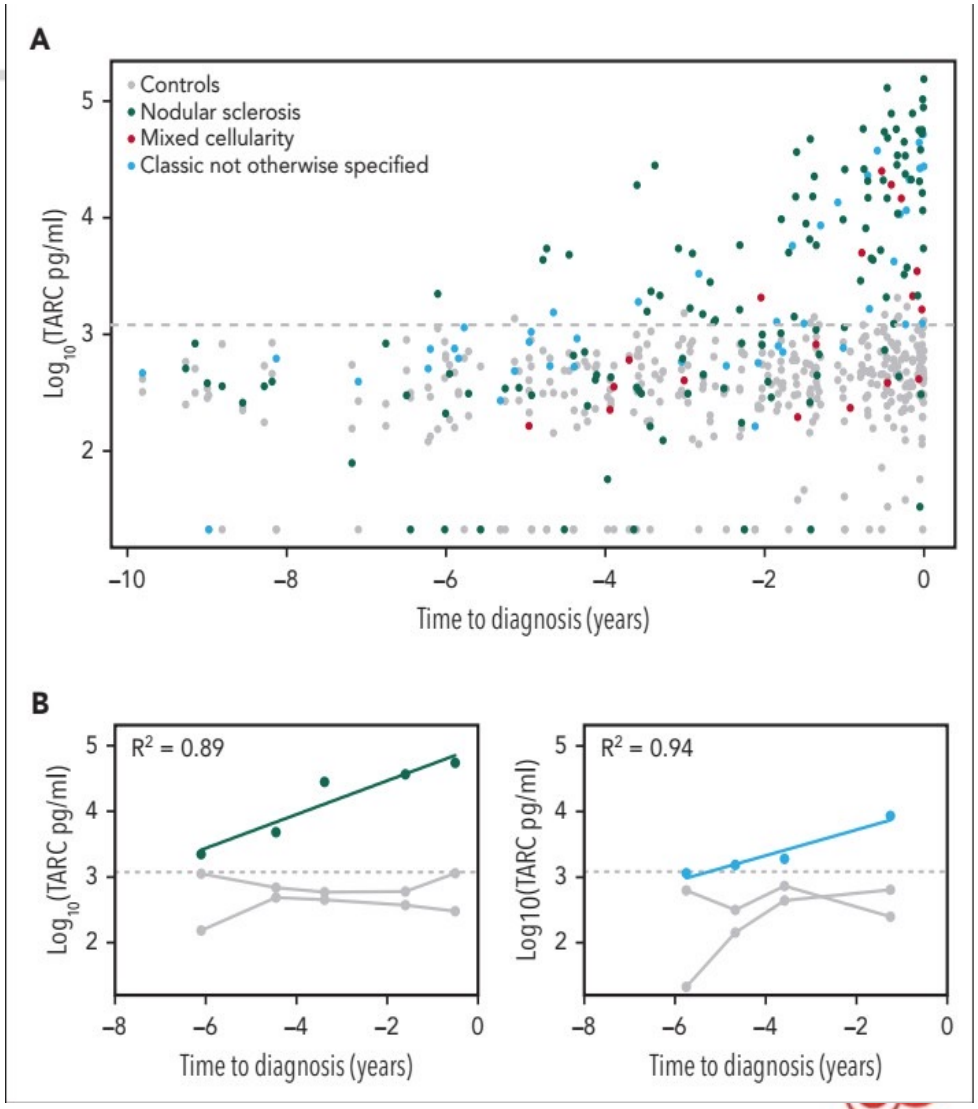
blood
Letters to *Blood*

TO THE EDITOR:

Elevated serum TARC levels precede classic Hodgkin lymphoma diagnosis by several years

Arjan Diepstra,[1] Ilja M. Nolte,[2] Anke van den Berg,[1] Larry I. Magpantay,[3] Otoniel Martínez-Maza,[3] and Lynn I. Levin[4]



Courtesy: L Mussolin

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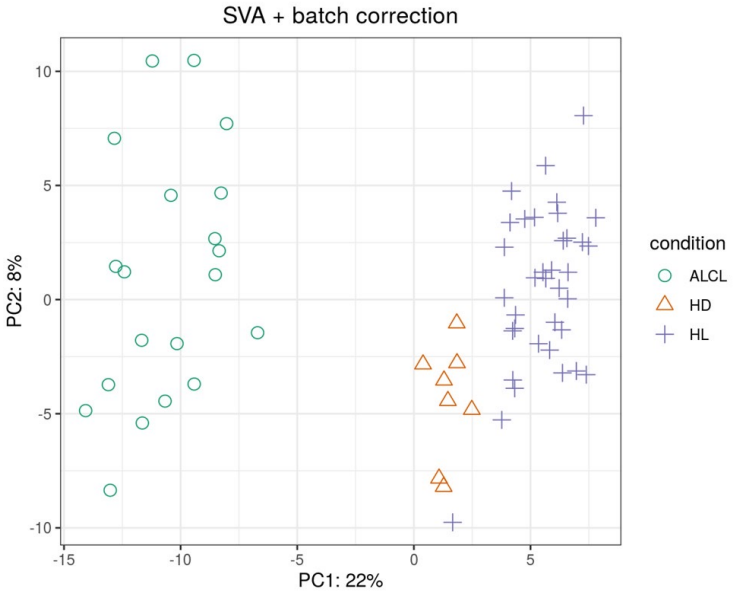
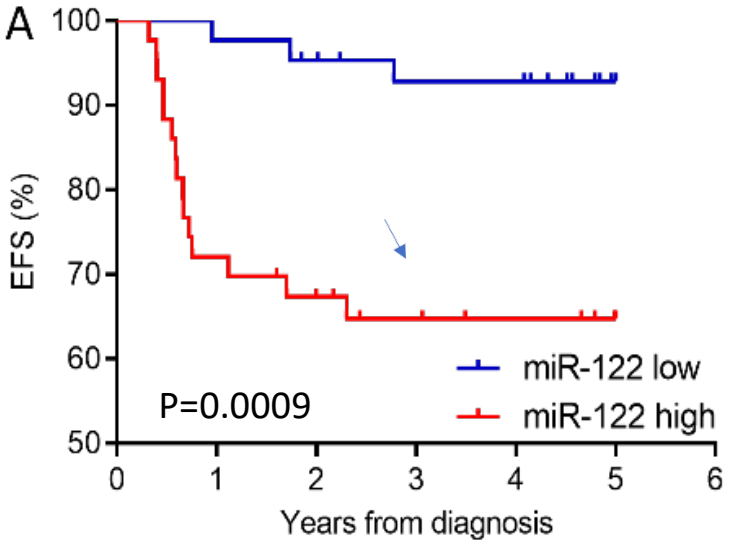
Biology: extracellular vesicle miR-122-5p in cHL

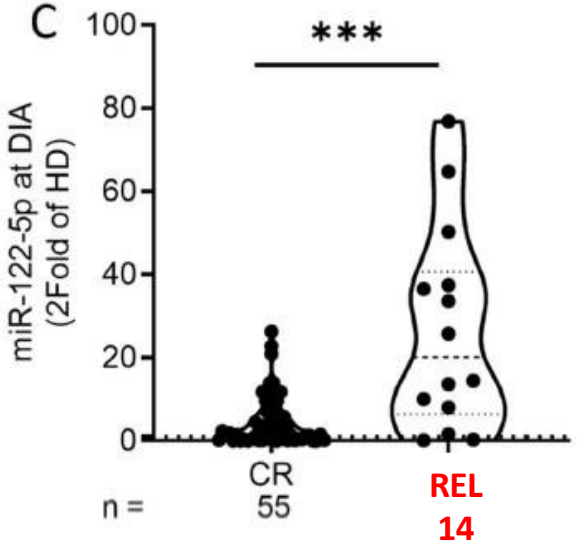
miR-122-5p has a prognostic potential, based on into miR-122 low and miR-122 high (median expression values).
miR-122-5p targets are involved in Tyrosine kinase receptors signaling

Small-RNAseq analysis was conducted on:

- **7 Healthy donors (HD)**
- **36 pediatric Hodgkin lymphomas (HL)**







p-value: 0.0002, AOC=0.8065

Courtesy: L Mussolin

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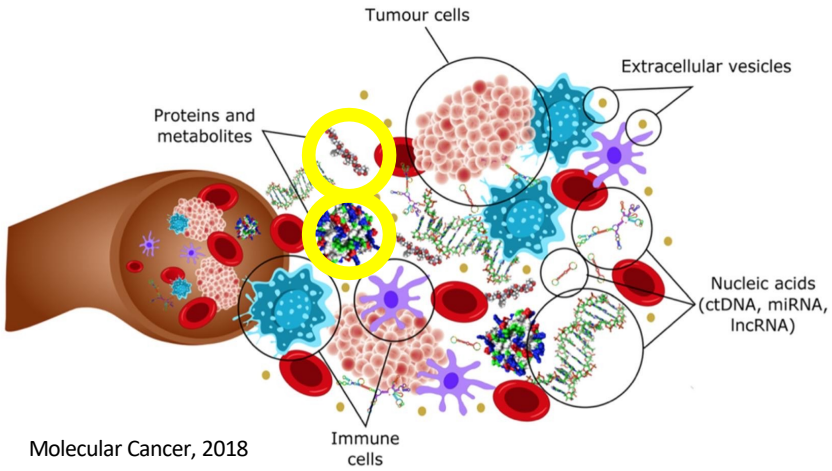
Thymus and activation Regulated chemokine (TARC)/CCL17 in ped HL

Produced by HRS cells and antigen presenting cells

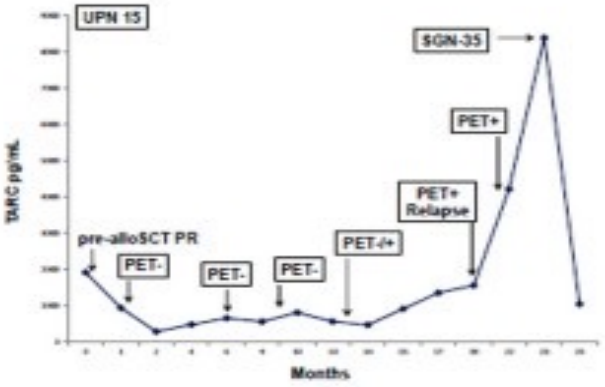
Attracts T-helper type 2 cells



Molecular Cancer, 2018

In adult higher TARC levels correlate with :

- ✓ the extent of the disease
- ✓ higher disease stage
- ✓ presence of B-symptoms
- ✓ bulky disease
- ✓ metabolic tumor volume
- ✓ treatment response.



TARC levels increased progressively even before PET became positive at relapse.

Farina L, et al; Clinical Res 2015

-8 ml of peripheral blood in Na-citrate at diagnosis.

-4 ml of peripheral blood in Na-citrate at end of therapy (aemendament proposal).

Courtesy: L Mussolin

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Attività formative

11 aprile 2024

11-12 novembre 2024

27 febbraio 2025

25 marzo 2025

GdL Linfomi Hodgkin pediatrici

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GdL Linfoma di Hodgkin

GdL AIEOP linfoma di Hodgkin:

Bianchi Maurizio

Buffardi Salvatore

Farruggia Piero

Garaventa Alberto

Sala Alessandra

Vinti Luciana

Muggeo Paola (protocollo NLPHL)

Lopci Egesta (Medicina Nucleare)

Mussolin Lara (Biologia)

Bianchi Simona (Discovery)

Thank you

and to all members of the "AIEOP ped-HL centers"

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Christine Mautz Koerholz (C2)
Dirk Hasenclever (Data management C2)
Stephen Daw (Relapse strategy)
Tierry Leblanc (Relapse strategy)

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Elena Sabattini, Clara Bertuzzi (Anatomia Patologica NLPHL)

Marco Pizzi (Anatomia Patologica cHL)

Caterina Elia (Data management)

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