Pediatric Radiotherapy:

Soft tissue and Bone Sarcomas, Hodgkin Lymphoma in Children and AYA

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No disclosures for this presentation

Soft Tissue Sarcomas (RMS)

disegno di Caterina Santambrogio

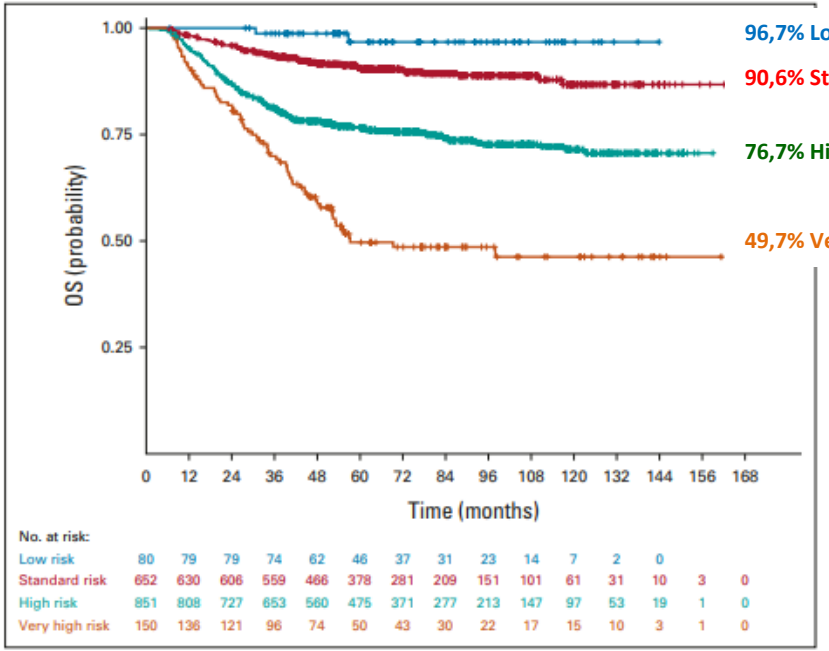
Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study

Bisogno G et al. J Clin Oncol 41:2342-2349; 2023

	Total (N = 1,733), No. (%)
Age, years	
≤1	108 (6.2)
1-9	1,177 (67.9)
10-17	389 (22.5)
≥18	59 (3.4)

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low risk	A	Negative	I	Any	N0	Both Favourable
Standard risk	B	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High risk	D	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

EpSSG 2005: Risk group 5-year OS



*__Fusion status:__ The majority (70-80%) of Alveolar RMS cases have translocations resulting in fusion PAX-FOX01

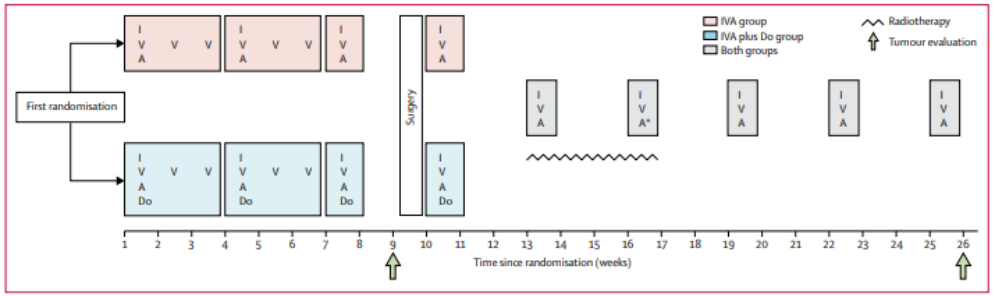
__Site:__ Favourable sites are: GU including bladder-prostate, head & neck non-parameningeal, orbit and biliary primaries . Unfavourable sites are: all other sites.

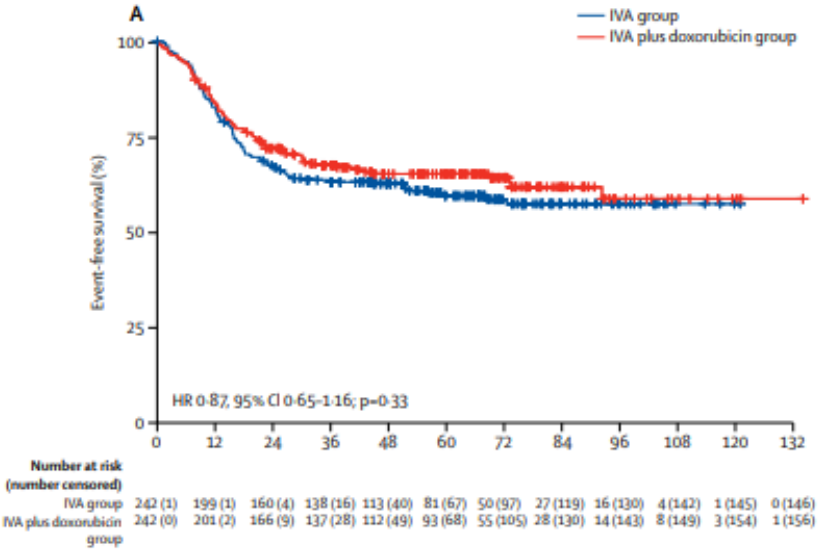
Age: Favourable is defined as age over 1 and under 10 years of age at diagnosis

__Size__: Favourable primary tumour is ≤5 cm in longest diameter

Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial

Bisogno G et al. Lancet Oncol 2018





Doxorubicin (added to standard IVA -> IVADo), **any survival benefit**,.

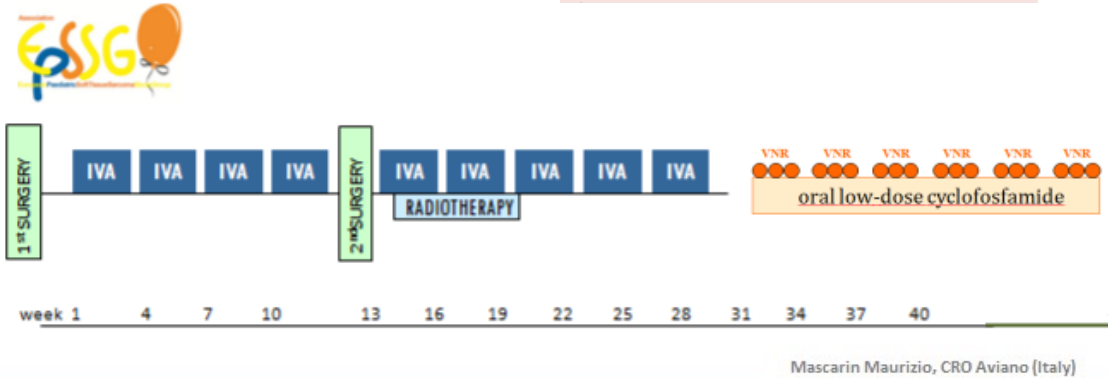
Adverse events were more severe in IVADo.

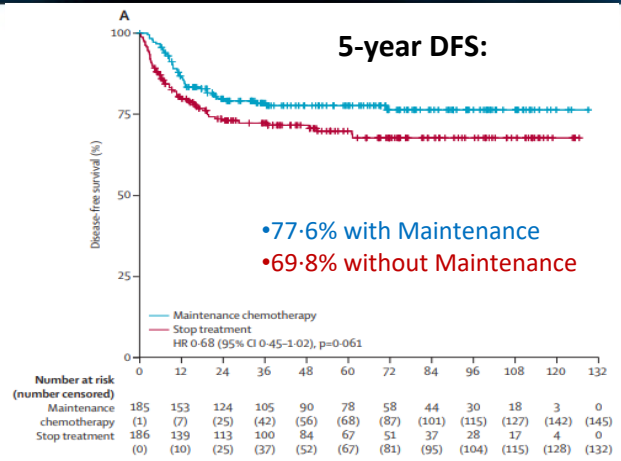
Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial

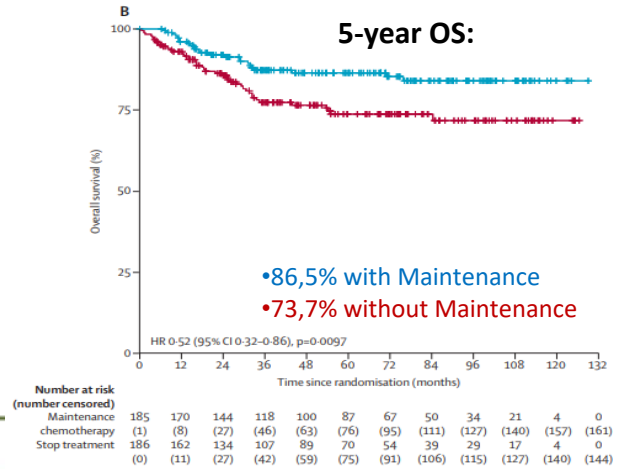
Lancet Oncol 2019; 20: 1566–75

Gianni Bisogno, Gian Luca De Salvo, Christophe Bergeron, Soledad Gallego Melcón, Johannes H Merks, Anna Kelsey, Helene Martelli, Veronique Minard-Colin, Daniel Orbach, Heidi Glosli, Julia Chisholm, Michela Casanova, Ilaria Zanetti, Christine Devalck, Myriam Ben-Arush, Peter Mudry, Sima Ferman, Meriel Jenney, Andrea Ferrari*, for the European paediatric Soft tissue sarcoma Study Group*

	Stop treatment group (n=186)	Maintenance chemotherapy group (n=185)
Age at diagnosis, years		
≤1 year	2 (1%)	11 (6%)
>1–9 years	143 (77%)	136 (74%)
10–17 years	36 (19%)	34 (18%)
≥18 years	5 (3%)	4 (2%)







FaR-RMS

Radiotherapy Questions:

- ? **pre-op or standard post-op RT** is better for pts with **resectable disease** (RT1A);
- ? **dose escalation RT** improves the outcome in patients with a **higher local failure risk** (RT1B/C);
- ? **RT of all sites of disease**, including **metastatic sites**, (RT2)

Maintenance Chemotherapy Questions:

- ? **12 + 12 cycles of Vn/C** to standard 12 cycles of maintenance **in VHR** disease at diagnosis (CT2A);
- **? 6 + 6 cycles of Vn/C** to the standard 6 cycles of mantenance **in localized HR** disease at diagnosis (CT2B)

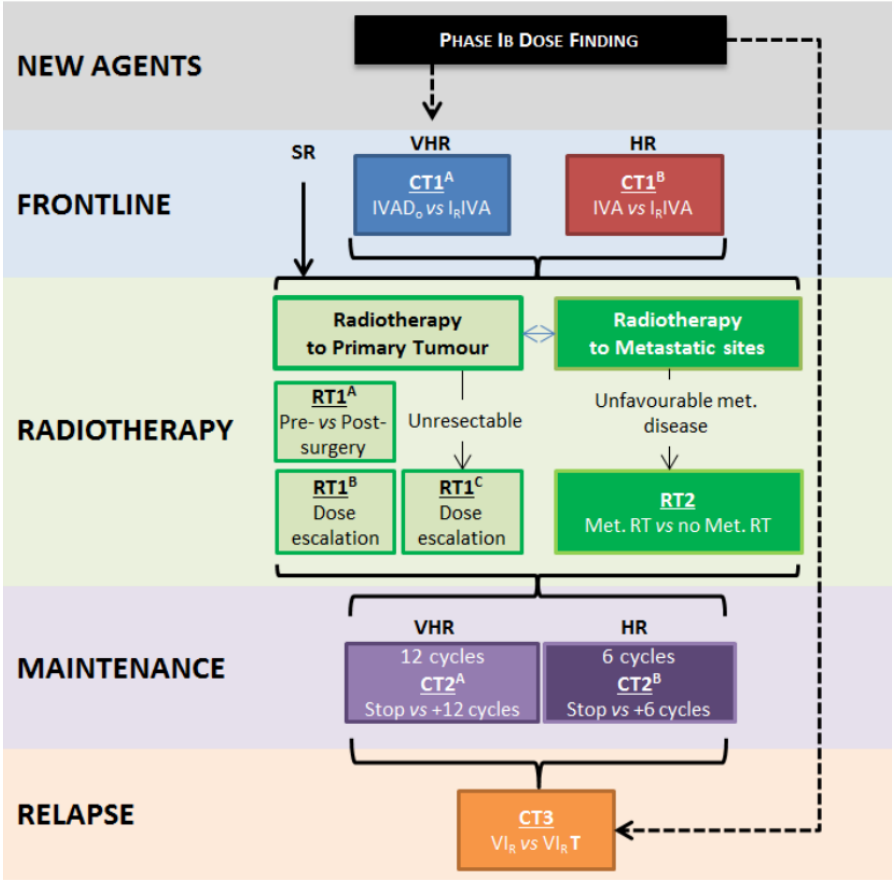


Figure 11: Radiotherapy to the primary tumour schema

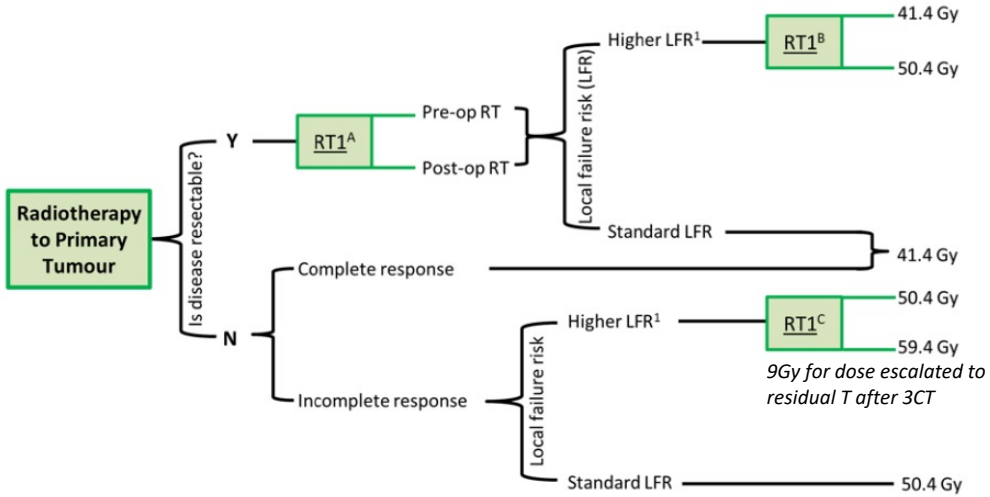
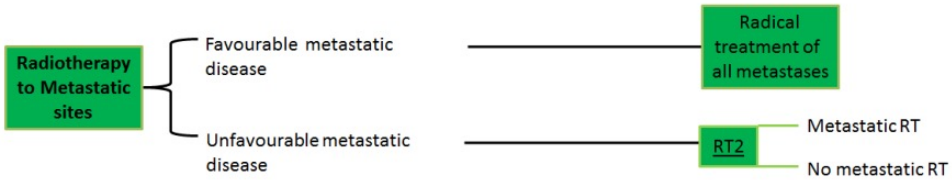


Figure 12: Radiotherapy to metastatic sites



FaR-RMS radiotherapy

RT to primary site is indicated for:
HR and **VHR**, and the **majority of SR (Group C)**

1. **HLFR:** Unfavourable site &/ or age ≥ 18yr
2. **Favourable metastatic disease**: Modified Oberlin Prognostic Score of ≤1
3. **Unfavourable metastatic disease:** Modified Oberlin Prognostic Score of ≥2

Modified Oberlin Prognostic Score (1 point for each adverse factor):

- Age ≥10y
- Extremity, Other, Unidentified Primary Site
- Bone and/ or Bone Marrow involvement
- ≥3 metastatic sites

○ Unfavourable metastatic disease: 2- 4 adverse factors
○ Favourable metastatic disease: 0-1 adverse factors

TIME: The decision to proceed to local therapy **(surgery and/or radiotherapy)** should be made **after 3 cycles of induction chemotherapy** (or after 6 cycles for patients with metastatic disease).
Preoperative, or definitive, RT for localized disease should be delivered **after 4th cycle of chemotherapy** (week 13), or **after 7th cycle of chemotherapy for metastatic disease** (week 22)

Ewing Sarcoma

disegno di Caterina Santambrogio

Effect of Radiotherapy Dose on Outcome in Nonmetastatic Ewing Sarcoma

Kersting J et al. Advances in Radiation Oncology (2023)

advances in radiation oncology
www.advancesradonc.org

The effect of different RT doses on EFS and S:
≤53Gy, 54-58Gy, ≥59 Gy

Ewing 2008: 1421 pts

- Surgery (S&RT group, 332 pts) and/or
- RT (RT alone group, 145 pts).

	Definitive RT (n = 158)		Surgery and RT (n = 370)	
Variable	No.	%	No.	%
RT dose				
≤53 Gy	17	10.8	192	51.9
54-58 Gy	64	40.5	118	31.9
≥59 Gy	64	40.5	22	5.9

- **54.0 Gy pre-op RT**,
- up to **54 Gy post-op RT in intralesional/marginal surgery**, with **poor HR** (≥10% residual tumor cells).
- **45 Gy post-op RT in marginal surgery, good HR** (<10% residual tumor cells)
- **45 Gy in wide resection with poor HR** (≥10% residual tumor cells).
- **definitive RT 54.0 Gy**

Mascarin Maurizio, CRO Aviano (Italy)

Kersting J et al. Advances in Radiation Oncology (2023)

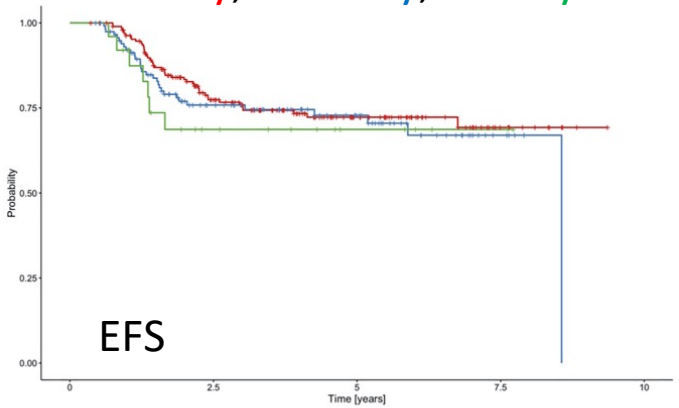
Table 2 HRs of multivariable analysis (EFS and OS) for patients treated with surgery and radiation therapy

			95% CI	
EFS	***P* value**	**HR**	**Lower**	**Upper**
Age	<.001	2.68	1.63	4.38
Sex	.959	1.01	0.63	1.62
Surgical margins	.032	1.76	1.05	2.93
Histologic response	.068	1.60	0.97	2.64
Tumor volume	.497	1.18	0.73	1.90
≤53 Gy	.098			
54-58 Gy	.782	1.08	0.63	1.84
≥59 Gy	.032	2.61	1.08	6.27
			95% CI	
OS	***P* value**	**HR**	**Lower**	**Upper**
Age	.011	2.31	1.21	4.42
Sex	.774	1.10	0.59	2.05
Surgical margins	.004	2.58	1.35	4.93
Histologic response	.182	1.59	0.81	3.12
Tumor volume	.150	1.60	0.85	3.01
≤53 Gy	.281			
54-58 Gy	.414	1.34	0.66	2.70
≥59 Gy	.121	2.39	0.80	7.15

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival.

Surgery & RT

≤53Gy, 54-58Gy, ≥59 Gy



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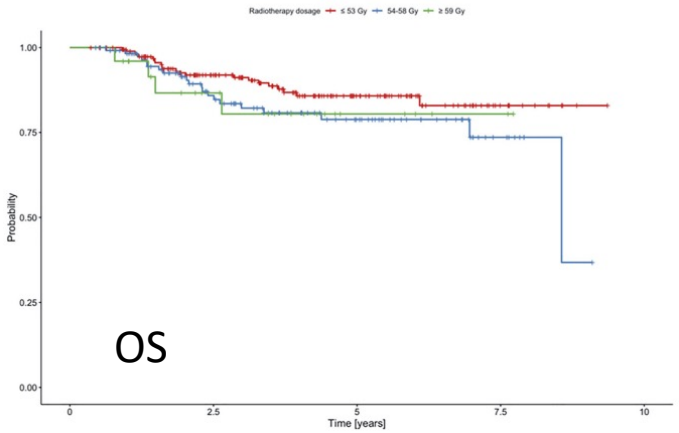


Kersting J et al. Advances in Radiation Oncology (2023)

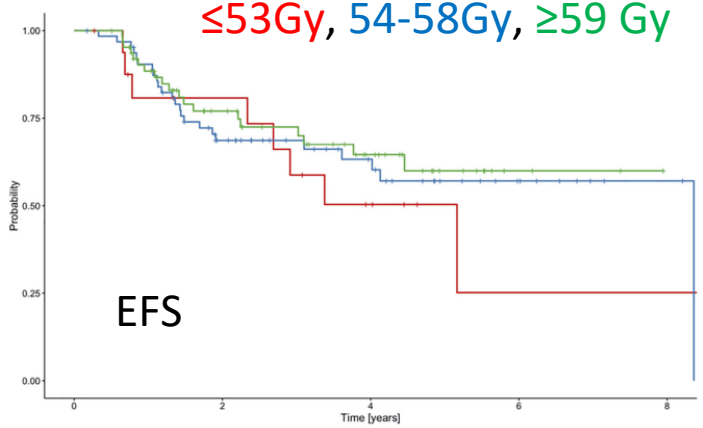
Table 3 HRs of multivariable analysis (EFS and OS) for patients treated with definitive radiation therapy

			95% CI	
EFS	***P* value**	**HR**	**Lower**	**Upper**
Age	.077	1.68	0.95	2.97
Sex	.401	1.28	0.72	2.26
Tumor volume	.009	2.20	1.21	4.00
≤53 Gy	.146			
54-58 Gy	.307	0.65	0.28	1.49
≥59 Gy	.060	0.42	0.17	1.04
			95% CI	
OS	***P* value**	**HR**	**Lower**	**Upper**
Age	.520	1.28	0.60	2.73
Sex	.766	1.12	0.52	2.41
Tumor volume	.022	2.52	1.14	5.55
≤53 Gy	.100			
54-58 Gy	.091	0.42	0.15	1.15
≥59 Gy	.035	0.32	0.11	0.92

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival.

Definitive RT

≤53Gy, 54-58Gy, ≥59 Gy



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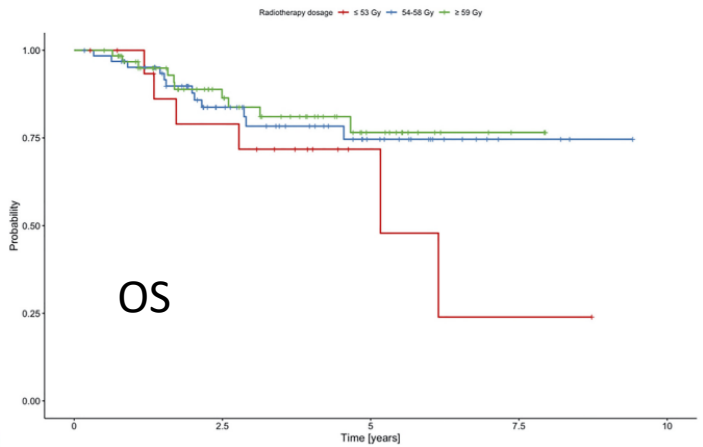
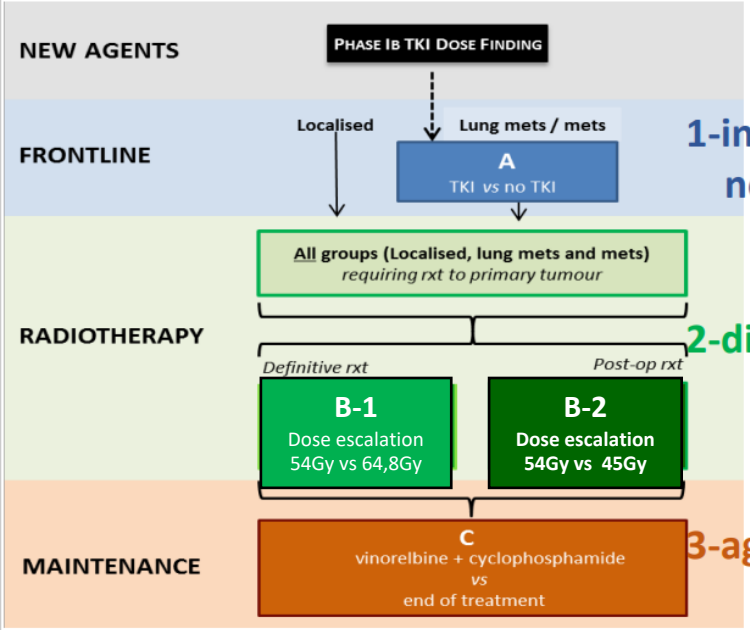


Treatment with higher RT dose had an effect on EFS, whereas higher dose of radiation when treated with **definitive RT** was associated with an increased OS

Inter-Ewing 1 Protocol

INTER-EWING-1

EURO EWING Consortium EEC



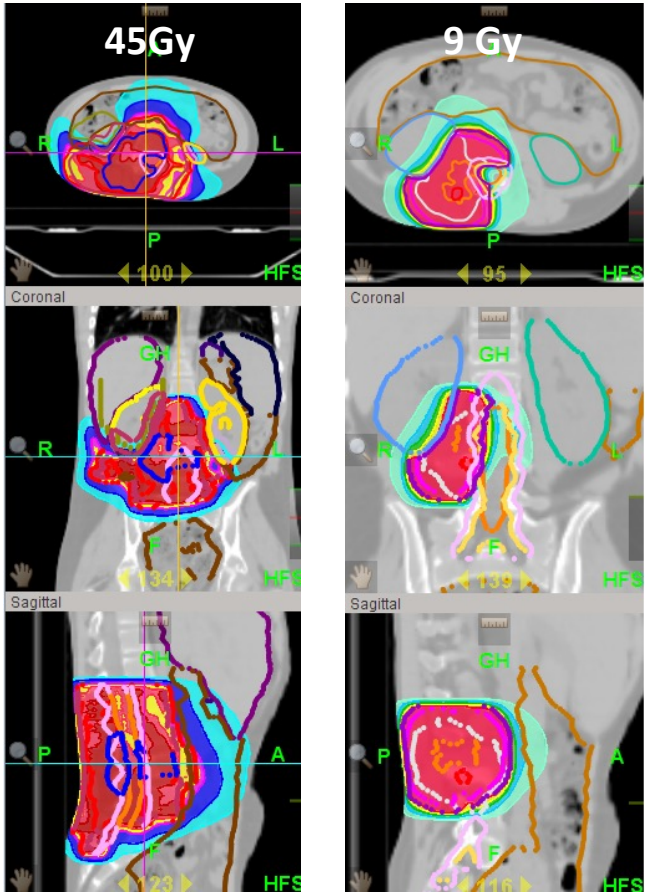
Verrà testata in forma randomizzata la efficacia di :

1-inibitori di Tirosin-chinasi associate alla chemioterapia nella malattia metastatica

2-differenti dosi di Radioterapia : Definitive RT - Post-op RT

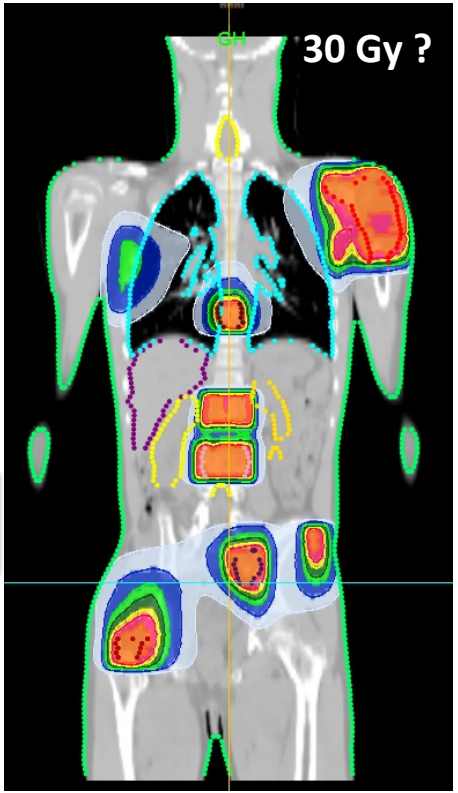
3-aggiunta di una terapia metronomica di mantenimento

Inter Ewing 1



move to higher RT
Dose: 64,8Gy

move to RT
treatment of
all mestastatic
sites



Kelly SM. European Journal of Cancer 172 (2022) 209e220

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER

Current Perspective

QUARTET: A SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer

Sarah M. Kelly [a,b,c,*], Rachel Effeney [a,b,2], Mark N. Gaze [d], Valérie Bernier-Chastagner [e], Anne Blondeel [a], Enrico Clementel [b], Coreen Corning [b], Karin Dieckmann [f,g], Samira Essiaf [a], Lorenza Gandola [h], Geert O. Janssens [i,j], Pamela R. Kearns [a,k], Denis Lacombe [b], Yasmin Lassen-Ramshad [l], Hans Merks [j], Elizabeth Miles [m], Laetitia Padovani [n], Giovanni Scarzello [o], Rudolf Schwarz [p], Beate Timmermann [q,r], Rick R. van Rijn [s], Gilles Vassal [a,t], Tom Boterberg [u,l], Henry C. Mandeville [v,l] on behalf of the QUARTET Project and the SIOPE Radiation Oncology Working Group

Establish	Establish standards for plan quality control
Improve	Improve access to high quality radiotherapy for children across Europe
Facilitate	Facilitate prospective RTQA of plans
Evaluate	Evaluate the role of RTQA
Support	Support imaging collection & evaluation

A collaborative initiative, QUARTET combines
the ped onc expertise of **SIOPE** with the experience and infrastructure of the **EORTC**
to deliver a centralised, prospective, interventional **RTQA programme** for ped international clinical trials.

Radiotherapy quality assurance in paediatric clinical trials: first report from six QUARTET-affiliated trials

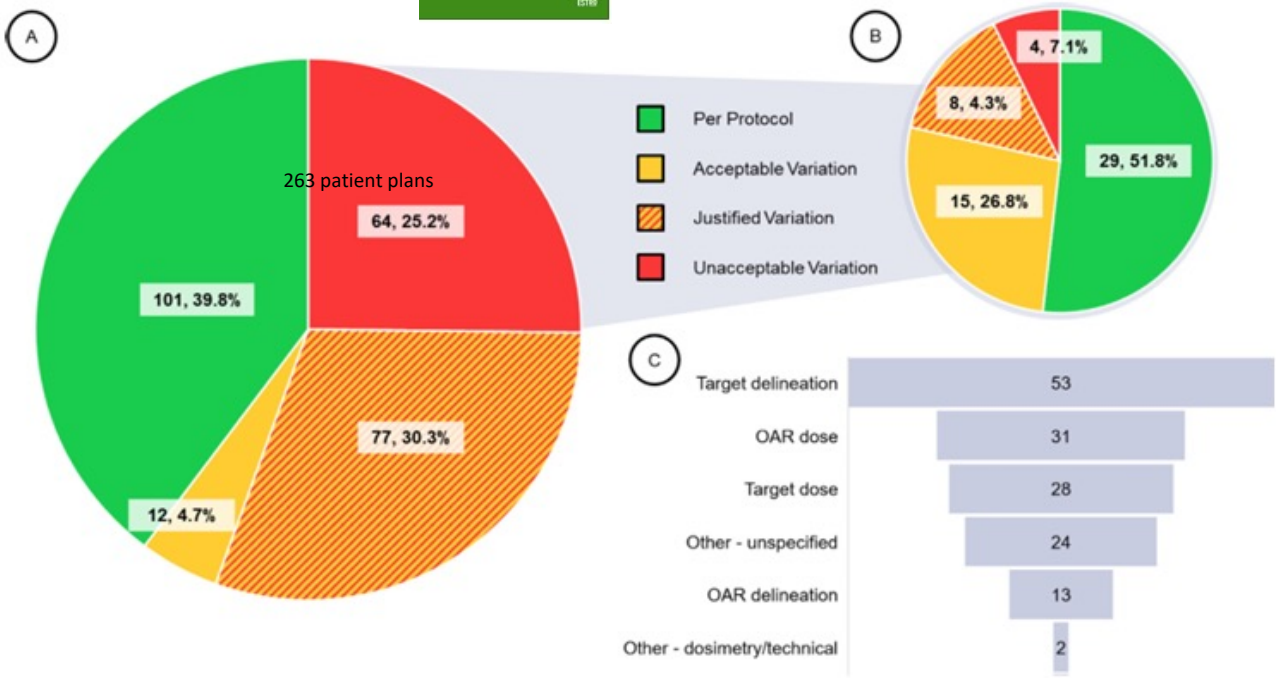
Sarah M Kelly [a,b,c,*,1], Andrada Turcas [a,b,d,1], Coreen Corning [b], Simon Bailey [e], Adela Cañete [f], Enrico Clementel [b], Andrea di Cataldo [g], Karin Dieckmann [h,i], Mark N Gaze [j], Gail Horan [k], Meriel Jenney [l], Ruth Ladenstein [h], Laetitia Padovani [m], Dominique Valteau-Couanet [n], Tom Boterberg [o], Henry Mandeville [a,p]

Radiotherapy and Oncology,182 (2023)

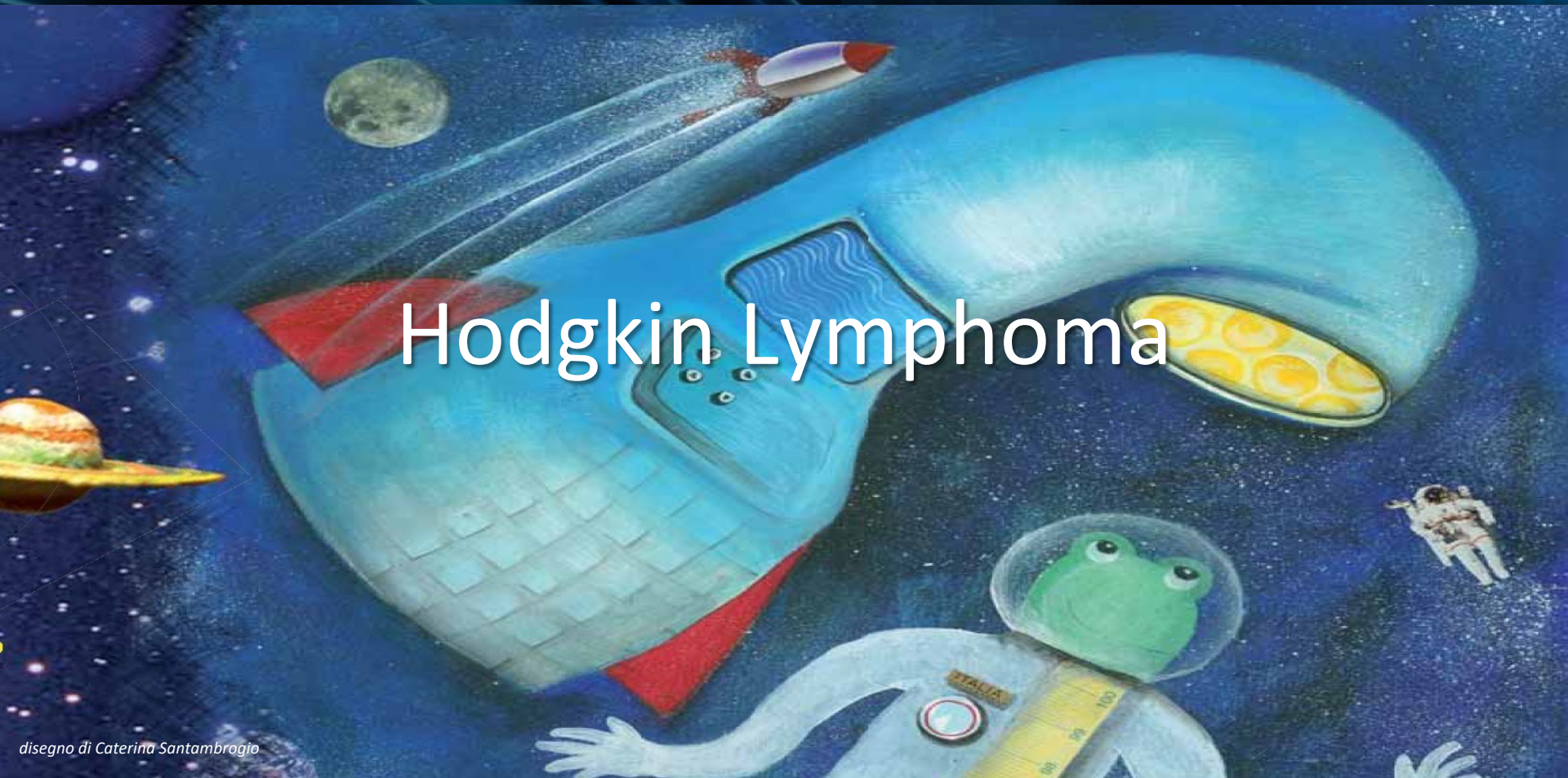
263 patient plans.

Trials included are: SIOPEN

HR-NBL1, SIOPEN-LINES, SIOPEN-VERITAS, SIOP-BTG HRMB, EpSSG-FaR-RMS, and SIOPEN HR-NBL2.

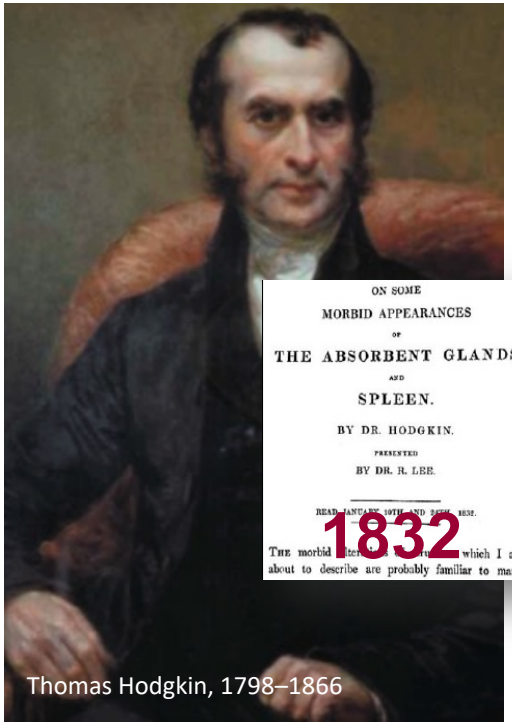


Hodgkin Lymphoma



disegno di Caterina Santambrogio

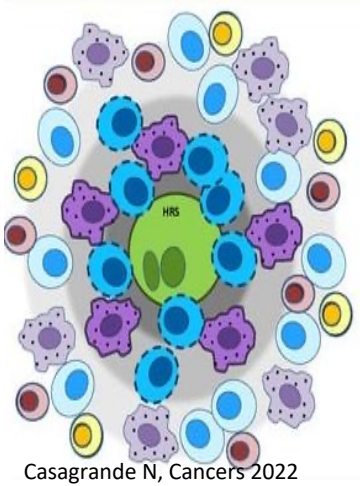
«The first thing I would tell to a patient is that we get 2 good chances to cure cHL, actually we have at least 3 good chances for cure» *(Alison Moskowitz)*



Thomas Hodgkin, 1798–1866

Chemotherapy & Radiotherapy

hd-CT & ASCT



Casagrande N, Cancers 2022

New drugs

Historical and current approach to Hodgkin Lymphoma

EuroNet-PHL-C1 study, **early stages**

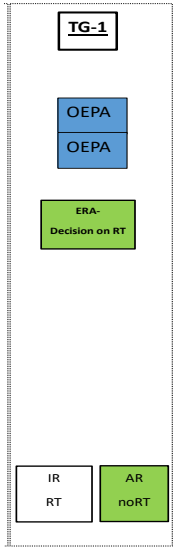
Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study

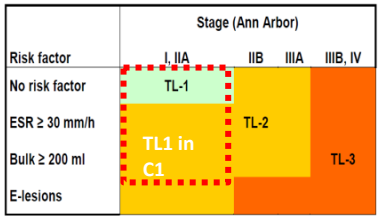
Christine Mauz-Körholz, Judith Landman-Parker*, Ana Fernández-Teijeiro*, Andishe Attarbaschi, Walentyna Balwierz, Jörg M Bartelt, Auke Beishuizen, Sabah Boudjemaa, Michaela Cepelova, Francesco Ceppi, Alexander Claviez, Stephen Daw, Karin Dieckmann, Alexander Fossà, Stefan Gattenlöhner, Thomas Georgi, Lisa L Hjalgrim, Andrea Hraskova, Jonas Karlén, Lars Kurch, Thierry Leblanc, Georg Mann, Francoise Montravers, Jane Pears, Tanja Pelz, Vladan Rajić, Alan D Ramsay, Dietrich Stoevesandt, Anne Uyttebroeck, Dirk Vordermark, Dieter Körholz†, Dirk Hasenclever†, William H Wallace†, Regine Kluge†*

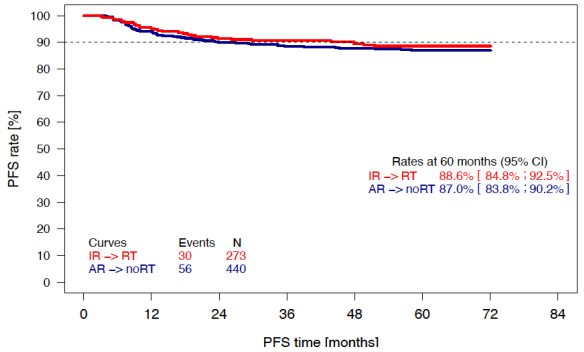
The Lancet Oncology Vol 24 March 2023

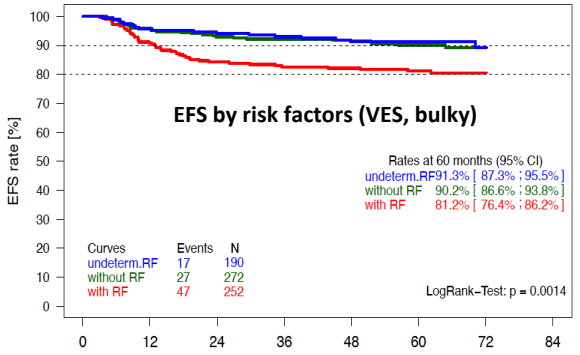
714 pts group 1 (TG1 early-stage disease)

Age, years	
≥13 years	477 (67%)
<13 years	236 (33%)
Median	14·6 (12·0–16·0)









62% TG1 with ERA-PET2 AR, no RT

EuroNet-PHL-C1 study, **intermediate advanced stages**

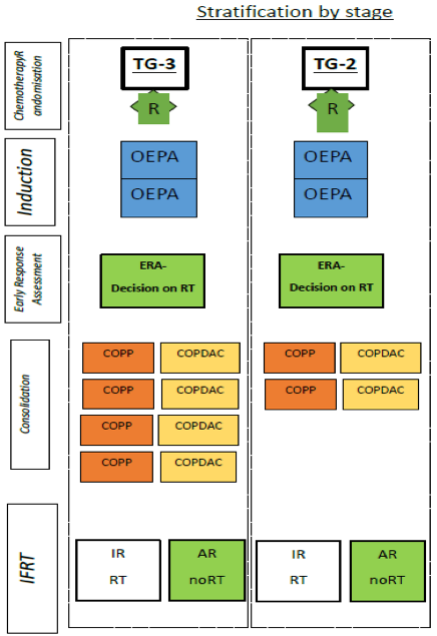
Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial

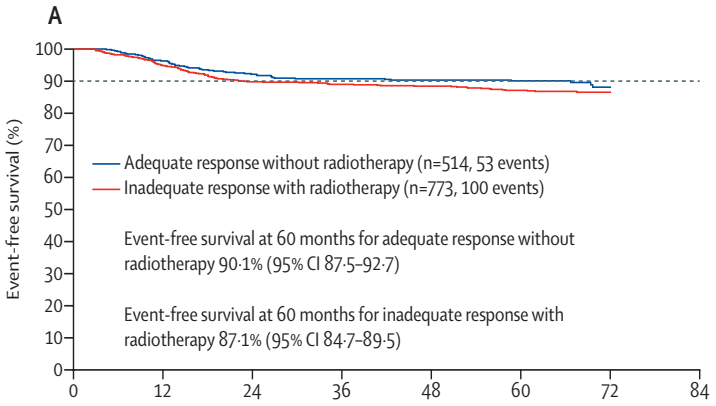
Christine Mauz-Körholz*, Judith Landman-Parker*, Walentyna Balwierz*, Roland A Ammann, Richard A Anderson, Andische Attarbaschi, Jörg M Bartelt, Auke Beishuizen, Sabah Boudjemaa, Michaela Cepelova, Alexander Claviez, Stephen Daw, Karin Dieckmann, Ana Fernández-Teijeiro, Alexander Fosså, Stefan Gattenlöhner, Thomas Georgi, Lisa L Hjalgrim, Andrea Hraskova, Jonas Karlén, Regine Kluge, Lars Kurch, Thiery Leblanc, Georg Mann, Francoise Montravers, Jean Pears, Tanja Petz, Vladan Rajić, Alan D Ramsay, Dietrich Stoevesandt, Anne Uyttebroeck, Dirk Vordermark, Dieter Körholz†, Dirk Hasenclever†, William Hamish Wallace†

The Lancet Oncology Vol 23 January 2022

Jan 31, 2007, and Jan 30, 2013, **2102 pts** (**1287 pts TG2-TG3**)

	Patients in the titration study (n=1287)
Age, years	
≥13 years	934 (73%)
<13 years	353 (27%)
Median (IQR)	14·8 (12·8–16·2)





40% TG2 & TG3 with ERA-PET2 AR, no RT

EuroNet-PHL-C2

EuroNet-Paediatric Hodgkin's Lymphoma Group

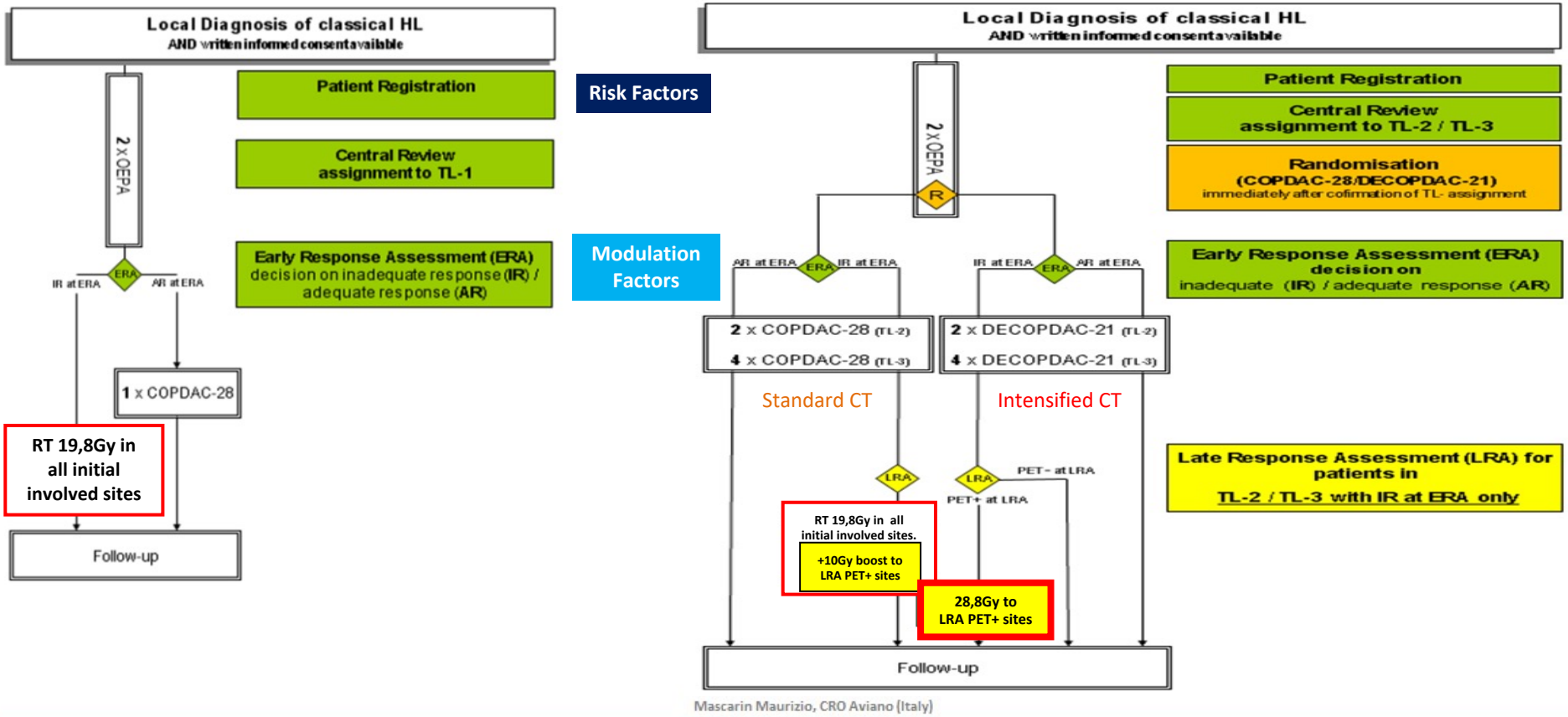
Second International Inter-Group Study for Classical Hodgkin's Lymphoma in Children and Adolescents

EudraCT-Number: 2012-004053-88

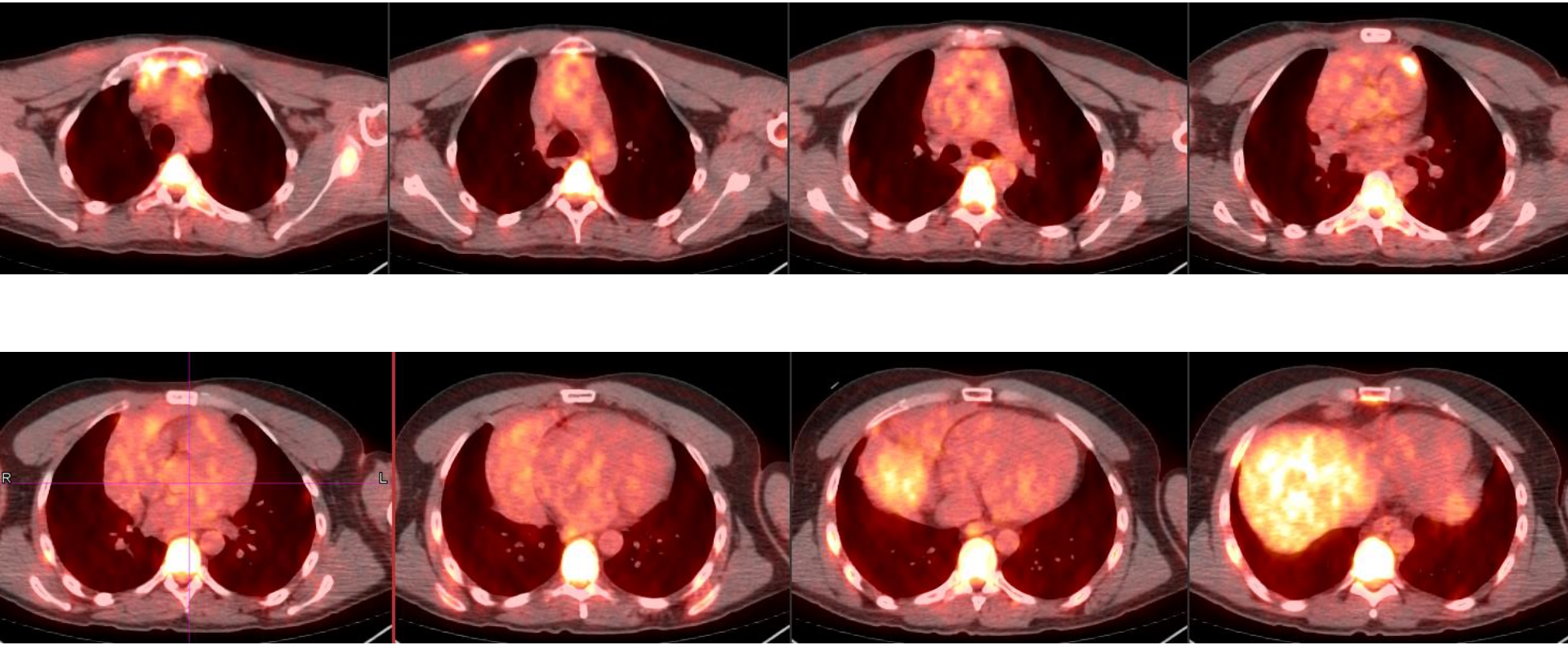
Prof. Dr. Dieter Körholz and Prof. Dr. Christine Mauz-Körholz
for the EuroNet-PHL study group

Comprehensive treatment strategy
for all first line classical Hodgkin lymphoma patients
under 18 years (under 25 years in UK, Italy and France)

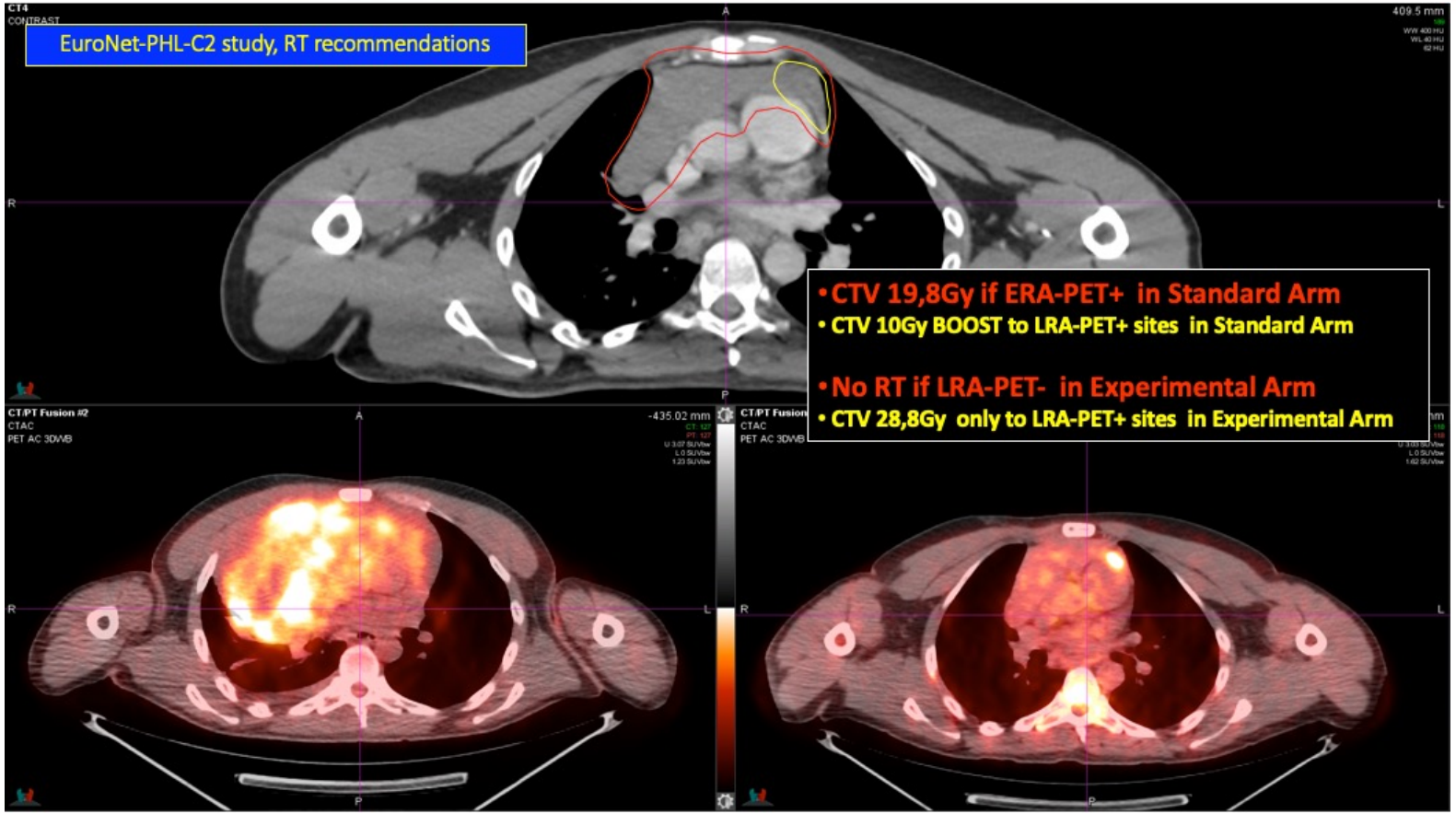
Strategy of EuroNet-PHL-C2 study



Stage IIA bulky HL



Hoppe B-Dierkman K –Hodgson D –Krasin M-Mascarin M_ISCAYAHL 2020 Berlin


EuroNet-PHL-C2 study, RT recommendations
•CTV 19,8Gy if ERA-PET+ in Standard Arm
• CTV 10Gy BOOST to LRA-PET+ sites in Standard Arm
•No RT if LRA-PET- in Experimental Arm
• CTV 28,8Gy only to LRA-PET+ sites in Experimental Arm

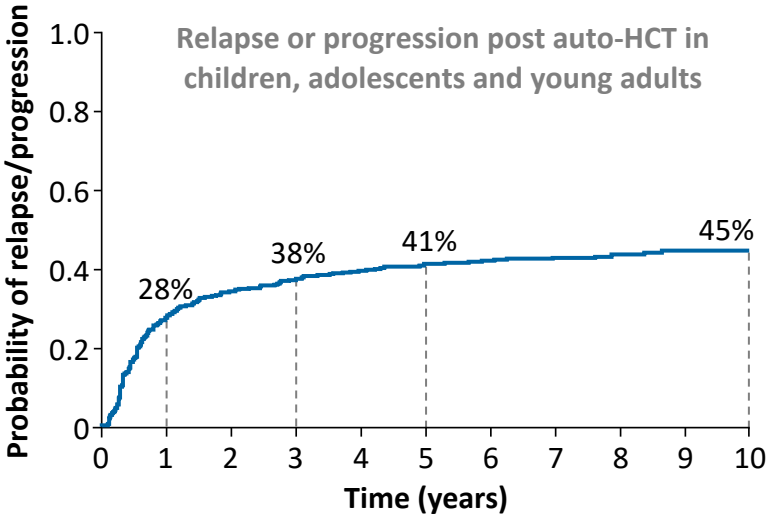
Result of autoHCT and implication in **relapsed cHL**

ORIGINAL ARTICLE

A prognostic model predicting autologous transplantation outcomes in children, adolescents and young adults with Hodgkin lymphoma

Satwani P et al. Bone Marrow Transplant 2015;50:1416–1423

- **606 CAYA pts** treated with AHCT for cHL (1995 and 2010)
- **median age** 23 years (3–29 years)



Original Article

Long-Term Outcomes Among 2-Year Survivors of Autologous Hematopoietic Cell Transplantation for Hodgkin and Diffuse Large B-Cell Lymphoma

Regina Meyers et al. Cancer February 15, 2018

- **836 pts** who survived progression-free for >2 years after AHCT for cHL (1990 and 2008).
- **median age** 33 years (range 15-77).
- 44% received RT before ASCT.

- The **risk of late mortality not related to HL** was **9.6-fold higher** for patients with HL in comparison with the general population.

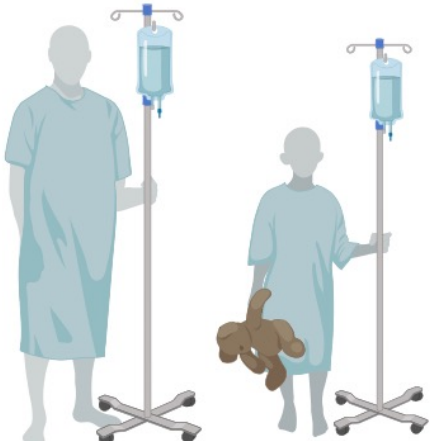
- **44 SNMs in the cHL group (5%)**
- predictors of SMNs: **older age** (P < .001) **higher number of CT lines.**

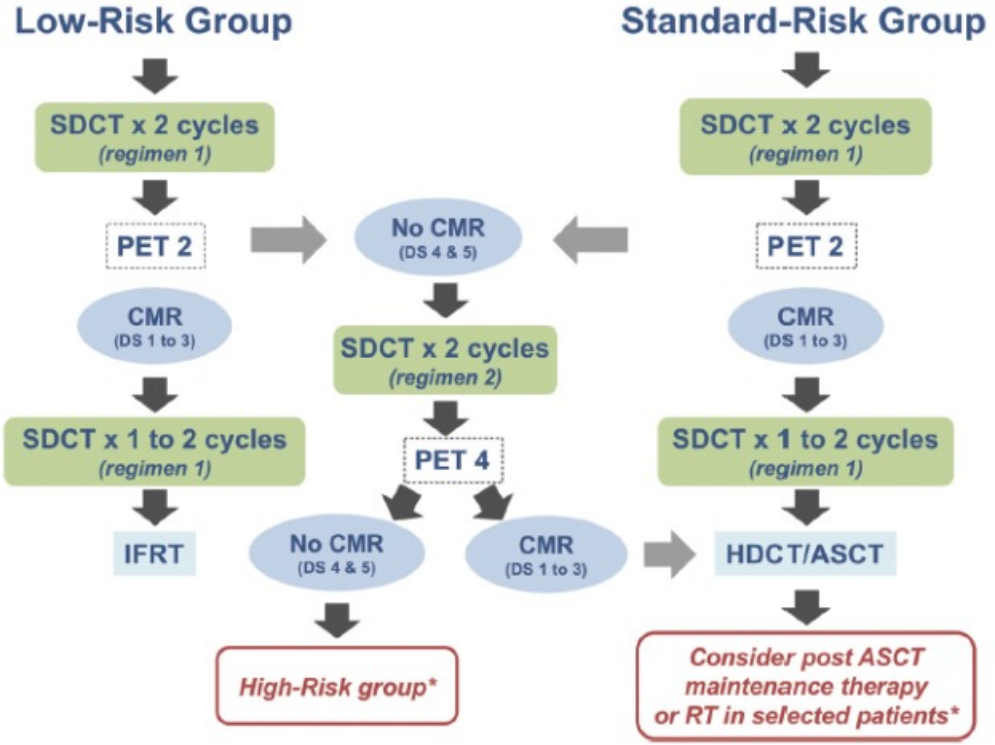
Relapsed/Refractory Ped-AYA cHL EuroNet recommendations

Risk and Response Adapted Treatment Guidelines for Managing First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group

Stephen Daw[1], Dirk Hasenclever[2], Maurizio Mascarin[3], Ana Fernández-Teijeiro[4], Walentyna Balwierz[5], Auke Beishuizen[6], Roberta Burnelli[7], Michaela Cepelova[8], Alexander Claviez[9], Karin Dieckmann[10], Judith Landman-Parker[11], Regine Kluge[12], Dieter Körholz[13], Christine Mauz-Körholz[13], W. Hamish Wallace[14], Thierry Leblanc[15], on behalf of the EuroNet Paediatric Hodgkin Lymphoma Group

HemaSphere Powered by EHA 2020



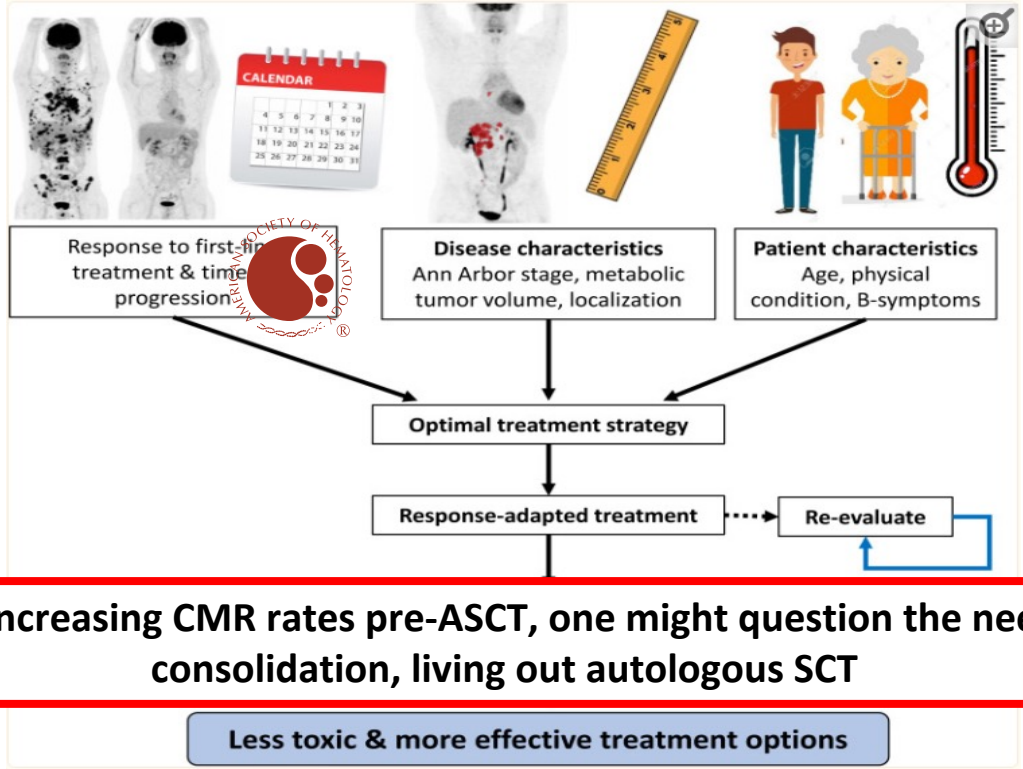


(I) Time to relapse, (II) Prior treatment in first line, (III) Stage at relapse and … (IV) Chemo-sensitivity

Systemic consolidation in relapsed and refractory cHL in CAYA

How to choose first salvage therapy in Hodgkin lymphoma: traditional chemotherapy vs novel agents

Driessen J et al, Hematology 2021, ASH

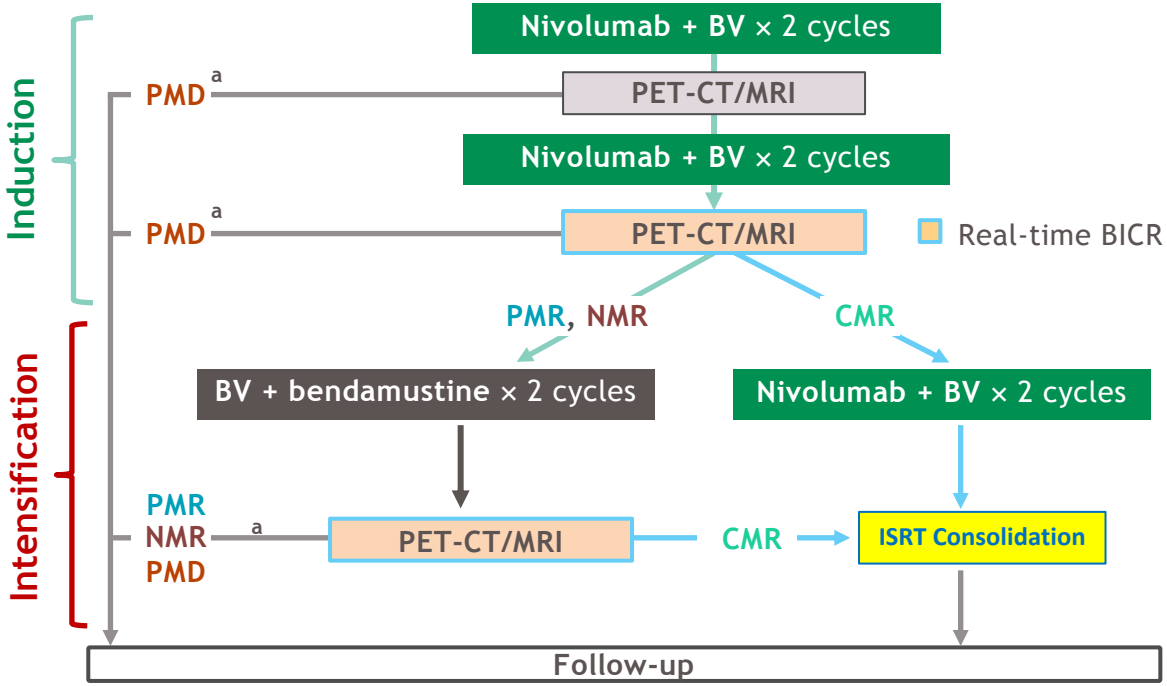


With increasing CMR rates pre-ASCT, one might question the need for consolidation, living out autologous SCT

Less toxic & more effective treatment options

Nivo & Bv in Relapsed/Refractory Ped-AYA cHL (Low risk R1 Cohort CA 209-744)

P Harker Murray et al. ASCO 2023 Annual Meeting
B Hoppe, ASTRO 2023 Annual Meeting



R1 Cohort:

- IA, IIA relapse ≥ 12 months
- IA, IIA relapse 3-12 months (≤ 3 cycles and no RT)
- IB, IIB, IIIA relapse >12 m
- No B symptoms or Extra Nodal D
- No extended RT fields required

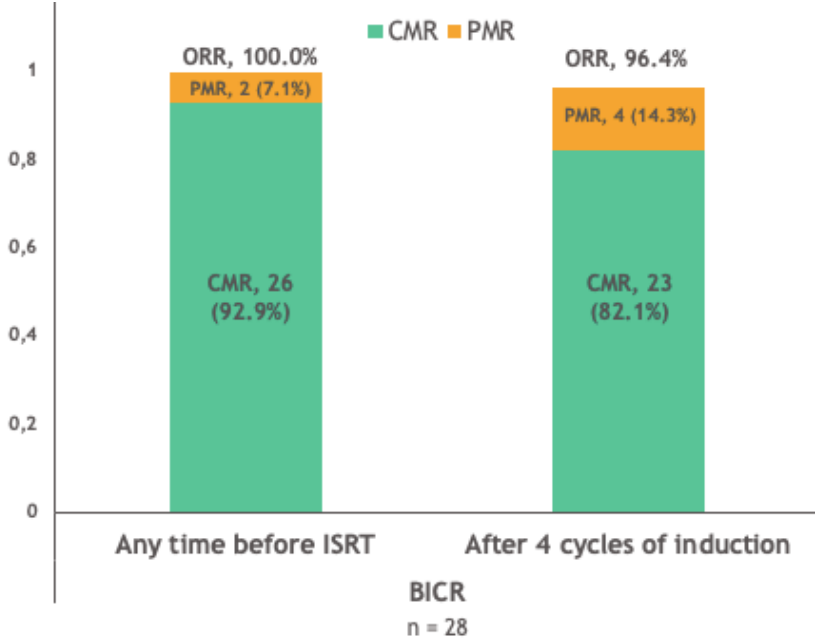
CMR defined as Deauville score ≤ 3 per Lugano 2014 criteria

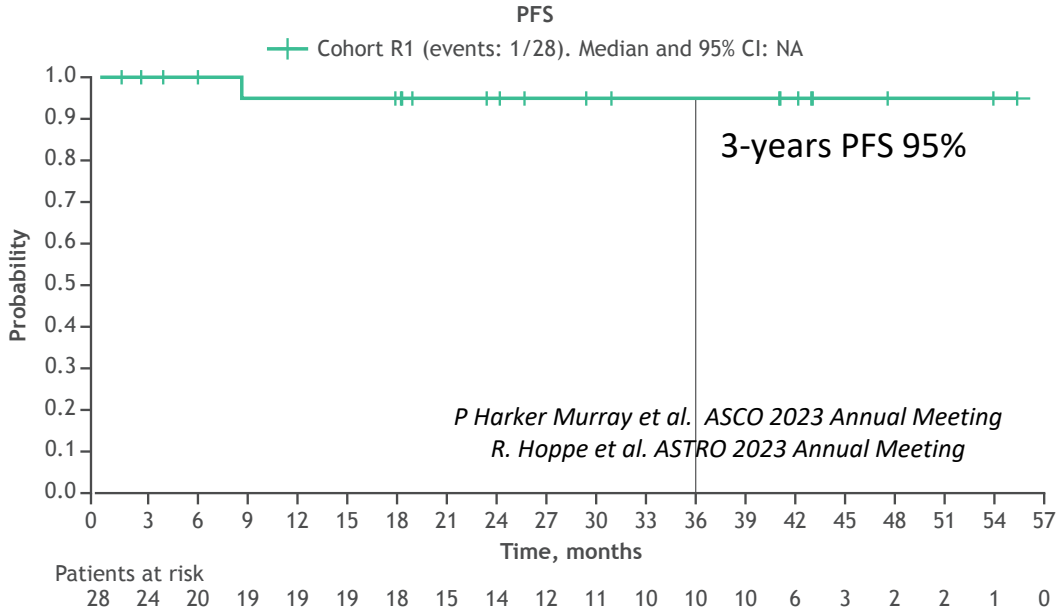
Nivolumab 3 mg/kg (day 8 cycle 1; day 1 for others)
BV 1.8 mg/kg (day 1 of every cycle)
Bendamustine 90 mg/m^2 (days 1 and 2)

ISRT Consolidation

- **Dose 30 Gy (1.5 Gy per day) or 30.6 Gy (1.8 Gy per day)**
- Treatment given 5 days per week over 17–20 sessions, no later than 6 weeks from start of last chemotherapy cycle

Nivo & Bv plus RT in Relapsed/Refractory Ped-AYA cHL (R1 Cohort)



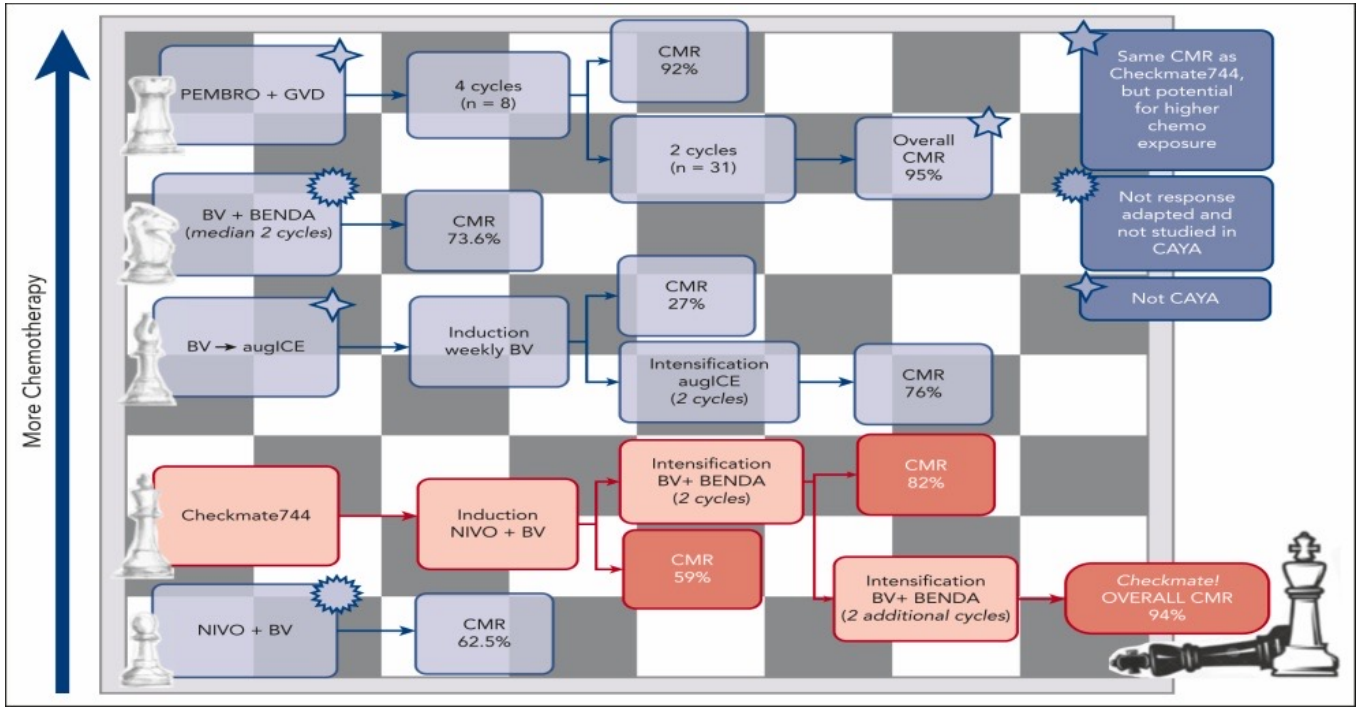


P Harker Murray et al. ASCO 2023 Annual Meeting
R. Hoppe et al. ASTRO 2023 Annual Meeting

R1 Cohort:
- IA, IIA relapse ≥ 12 months
- IA, IIA relapse 3-12 months (≤ 3 cycles and no RT)
- IB, IIB, IIIA relapse >12 m
- No B symptoms or Extra Nodal D
- No extended RT fields required

CAYA with low-risk relapsed cHL can be salvaged with **low-toxicity chemoimmunotherapy** and **consolidation with 30Gy ISRT**, and **do not require HDCT/auto-HCT for cure.**

Checkmate 744 gives Queen's gambit, in CAYA with r/r cHL

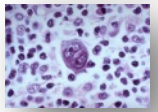
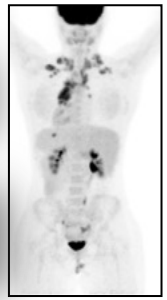


Seda S. Tolu,Jennifer E. Amengual, Queen's gambit: response-adapted win in CAYA with cHL, Blood, 2023

Conclusions: to build a best treatment selection model

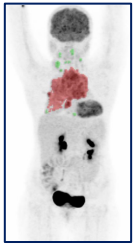
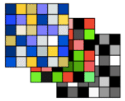
STEP 1

- Clinical data
- Pathology data
- Traditional imaging data

STEP 2

- Volumetric / Texture - data
- Radiomic data
- Age specific analysis (CAYA)

STEP 3

- Biomarkers

STEP 4

- Treatment adjusted on "*modulation factors*" and personalized choice


"the RT renaissance goes through different views of the same problem"