LINFOMA DI HODGKIN

Il punto di vista dell'ematologo del bambino e del giovane adulto

Dr Tommaso Casini

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prognosi

Tumore altamente curabile

DFS: 96,4% pazienti sotto i 19 anni

DFS: 89,8% pazienti 20-64 anni

Howlander et al; 2017 SEER Cancer Statistics Review

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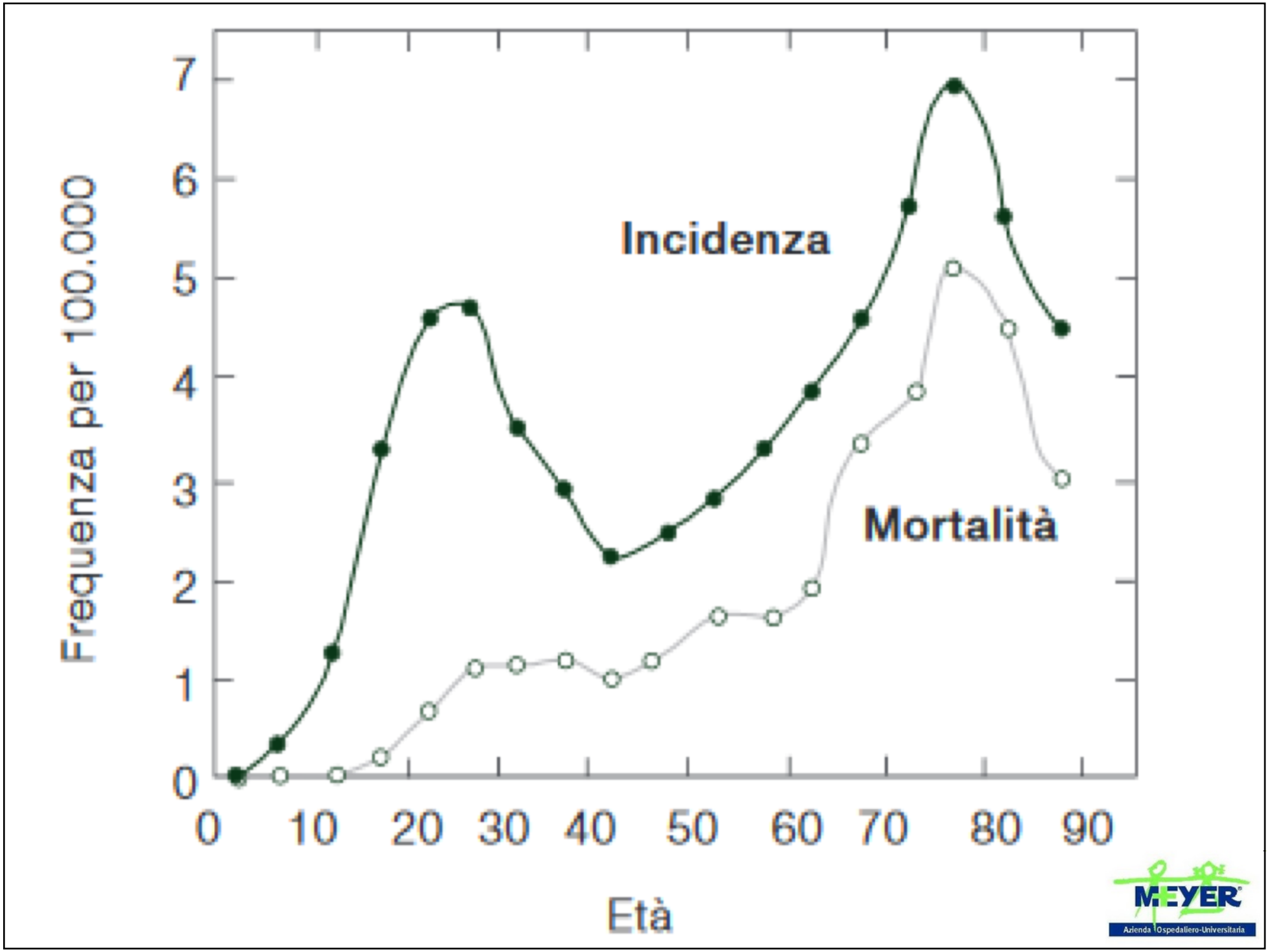
Frequenza per 100.000
0
1
2
3
4
5
6
7
0
10
20
30
40
50
60
70
80
90
Età
Incidenza
Mortalità

Cumulative Incidence of Cause-Specific Mortality

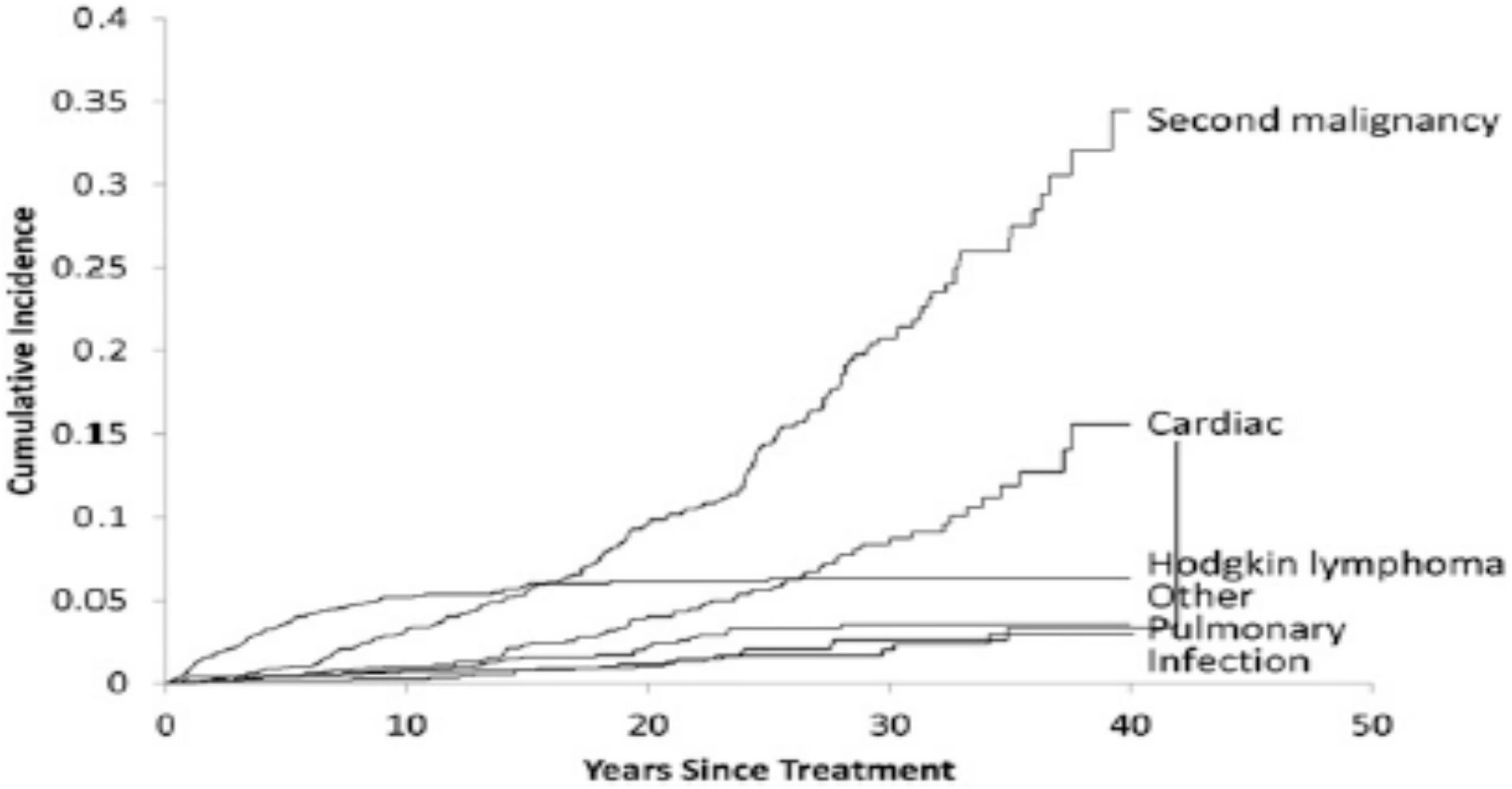

Figure 1. Cumulative incidence of cause-specific mortality of long-term HL survivors.

Blood, 2014 Andrea K

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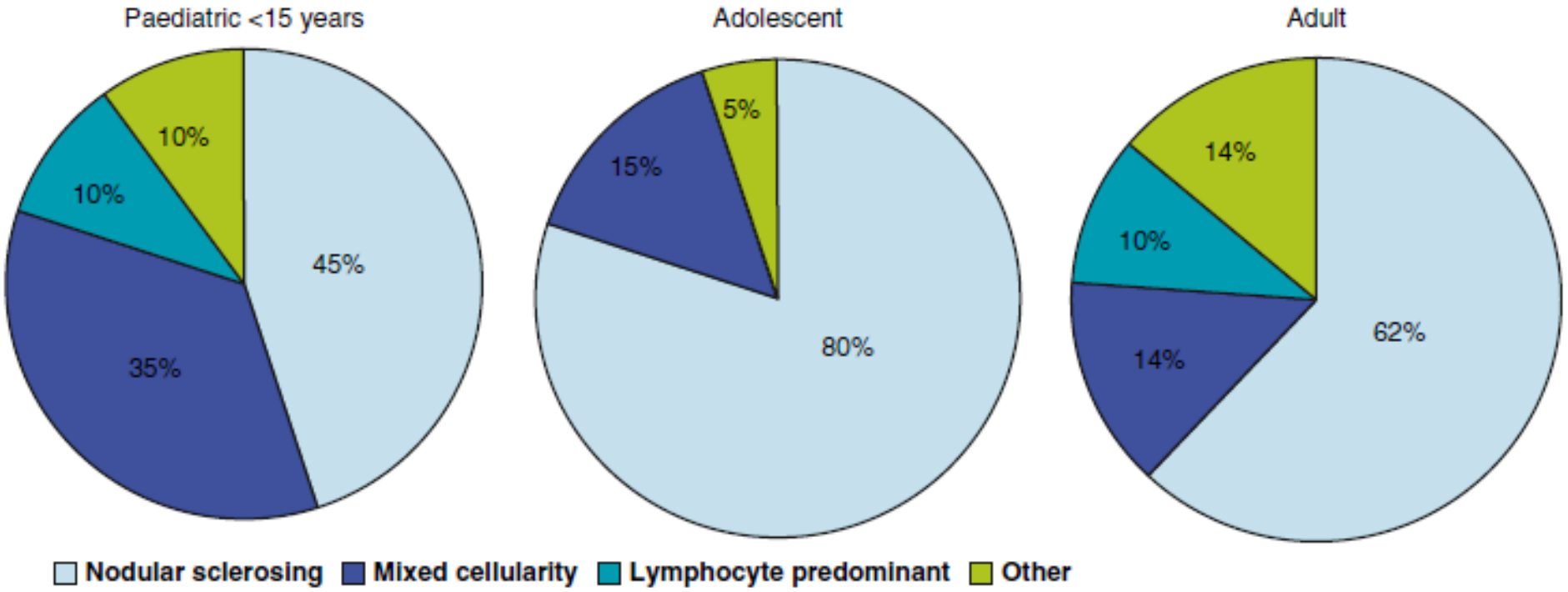

Fig 1. Distribution of HL subtypes by age. Adapted with permission from: Hochberg, J., Waxman, I.M., Kelly, K.M., Morris, E. & Cairo, M.S. (2009) Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. *Br J Haematol*, **144**, 24–40. © 2009. John Wiley & Sons, Inc.

Most common symptoms [16, 150]	Painless adenopathy involving supraclavicular or cervical area (80%)	Asymptomatic mediastinal disease	Asymptomatic lymphadenopathy (<80%), B symptoms (40%), Intermittent fever (35%)
EBV association [151]	Yes (<10yr: 80%)	No (<30%)	No (20-50 yr), Yes (>60yr; 70%)
Treatment outcome (5 yr OS[a]) [16, 149]	90-95%	90%	85.90%

[a]OS, Overall Survival

Nagpal et al, Oncotargets 2016

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LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2018.1493732

Taylor & Francis
Taylor & Francis Group

ARTICLE

Classical pediatric Hodgkin lymphoma in very young patients: the Italian experience

Piero Farruggia[a], Giuseppe Puccio[b], Francesco Locatelli[c], Mariarita Vetro[b], Marta Pillon[d], Angela Trizzino[a], Alessandra Sala[e], Salvatore Buffardi[f], Alberto Garaventa[g], Francesca Rossi[h], Maurizio Bianchi[i], Marco Zecca[j], Andrea Pession[k], Claudio Favre[l], Salvatore D'Amico[m], Massimo Provenzi[n], Giulio Andrea Zanazzo[o], Antonella Sau[p], Nicola Santoro[q], Rosamaria Mura[r], Caterina Elia[s], Tommaso Casini[t], Maurizio Mascarin[s*] and Roberta Burnelli[u*†]

Our analysis confirms the more favorable outcome among younger patients, even though age is not an independent factor, only TG and A–B symptoms being independently and significantly associated to the outcome. While our analysis certainly needs to be vali-

ORIGINAL ARTICLE

Adolescent Hodgkin Lymphoma: Are Treatment Results More Favorable With Pediatric Than With Adult Regimens?

Judit Müller, MD, PhD, Árpád Illés, MD, PhD,† Zsuzsanna Molnár, MD, PhD,‡ András Rosta, MD, PhD,‡ László Váróczy, MD, PhD,† and Gábor Kovács, MD, PhD**

Migliore EFS e OS dei pazienti adolescenti trattati con protocollo pediatrico (OPPA/COPP) rispetto a protocollo degli adulti (ABVD) : 92,8% vs 89,4% e 89,6% vs 83,1%

MEYER Azienda Ospedaliero-Universitaria

VOLUME 24 · NUMBER 16 · JUNE 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hodgkin's Lymphoma in Adolescents

Lynda M. Foltz, Kevin W. Song, and Joseph M. Connors

From the Division of Hematology, Leukemia/Bone Marrow Transplant Program of British Columbia; Division of Medical Oncology of the British Columbia Cancer Agency; and the University of British Columbia, Vancouver, British

A B S T R A C T

Purpose

To compare the clinical presentation, response to treatment, and long-term outcome of Hodgkin's lymphoma (HL) presenting in adolescents and young adults.

In conclusion, adolescents and adults with HL have similar baseline characteristics and outcomes when treated with the same adult protocols, suggesting a uniform disease biology. The overall incidence of second malignancies was also similar between the groups. We found no evidence to support the assertion that HL presenting in adolescents differs either in its basic biology or response to curative treatment when compared with the same disease presenting in adults. Overall, this study shows that adolescents with HL can be safely and effectively treated with adult treatment protocols.

From the First Medicine; Dep Oncology; Insti tics, Informatic German Hodgk sity of Cologne ment of Pathol Würzburg, Würzburg, Germany.

Study Group (GHSG).

Pediatr Blood Cancer. 2017 December ; 64(12): . doi:10.1002/pbc.26681.

Outcome of Adolescents and Young Adults Compared to Children with Hodgkin Lymphoma Treated with Response-Based Chemotherapy on Pediatric Protocols: A Children's Oncology Group Report

Karen S. Fernández, MD[1,*], Cindy L. Schwartz, MD, MPH[2], Lu Chen, PhD[3], Louis S. Constine, MD[4], Allen Chauvenet, MD[5], and Pedro A. de Alarcón, MD[6]

AYA have equivalent results to adults when they are treated with a treatment regimen commonly used to treat adult subjects with HL[5,6]. They also have similar EFS and OS to children when treated with a pediatric treatment regimen. The results obtained with either approach are excellent with OS greater than 80%. If this similarity of disease outcomes were confirmed, then the effect of different regimens in terms of quality of life and long term survival becomes the major differentiator.

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Linfoma Hodgkin pediatrico

OBIETTIVI PROTOCOLLI PEDIATRICI

Mantenere/migliorare ottime possibilità di cura

Ridurre tossicità di lungo termine e la mortalità

dosi cumulative più basse di antracicline, agenti alchilanti e bleomicina. Riduzione/omissione RTP

MOPP
ABVD

OEPA
ABVE-PC

- Nel 1978 primo trial di studio per MH pediatrico
- Da allora 8 successive generazioni di studio:

  DAL/GPOH-HD/AIEOP/EuroNet PHL

DAL-HD-78

2 cicli OPPA
- VCR
- PDN
- Procarbazina
- ADM

↓

Stadi intermedi/avanzati COPP
- CPM
- VCR
- PDN
- Procarbazina

↓

RTP **36-40 Gy** su campi interessati e 18-20 Gy su quelli adiacenti

DAL-HD-82

Numero cicli COPP in base al gruppo (0-2-4)

RTP da extended a involved field, e ridotta dose

DFS a 3,5 aa: TG-1: 99% TG-2: 96% TG-3: 87%

Sequele

- Infertilità maschile (procarbazina)
- Secondo tumore indotto da radioterapia
- Cardiopatia da antracicline e da radioterapia

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DAL-HD-90

sostituzione di procarbazina con etoposide nel TG-1 con stessa efficacia (OEPA invece OPPA)
(Schellong et al; 1999)

GPOH-HD-2002

procarbazina sostituita con dacarbazina negli altri gruppi terapeutici con stessa efficacia e minore tossicità ematologica (COPDAC anziché COPP) (Mauz-Korholz et al; 2010)

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RTP e secondi tumori

- Rischio di tumore ematologico secondario nei 15 anni dopo trattamento intorno all'1%
- Rischio di secondo tumore non ematologico del 5,7% dopo 20 anni, 11% dopo 22 anni, **25% dopo 30 anni** (Bhatia et al; 2003)
- OS a 20 anni è del 94%, ma scende all'87% dopo 24 anni

RTP e secondi tumori
response-adapted strategy

- Dallo studio GPOH-HD95 RTP omessa pazienti in CR a fine CHT (Dorffel, 2003)
- Nel TG-1 nessuna differenza tra RTP e no-RTP in termini EFS (94% vs 97%)
- Nel TG-2 e TG-3 invece 91% vs 79%

Early response assessment (ERA) FDG.PET dopo 2 cicli OEPA

EuroNet-PHL-C1

Adequate Response (AR): PET negatività e almeno remissione parziale morfologica

Nessun trattamento RTP se AR: 50% dei pazienti totali (63.2% TG-1, 50.7% TG-2, 33.3% TG-3)

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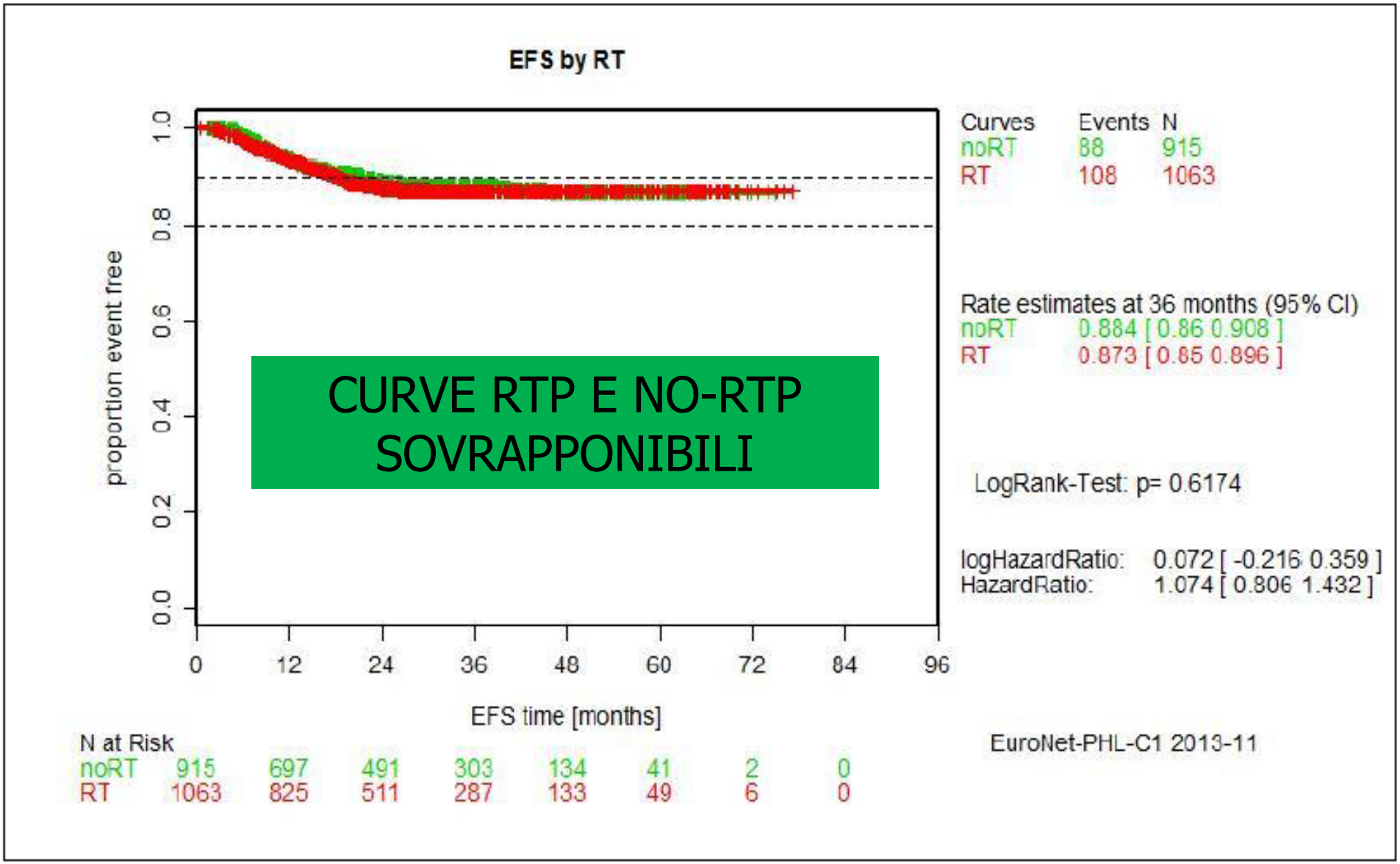


Figure 4: **Event-free Survival of Children and Adolescents with Classical Hodgkin Lymphoma Treated with/without Radiotherapy Within EuroNet-PHL-C1– Results of the Fourth Interim Analysis**

Linfoma Hodgkin pediatrico trattamento attuale

EuroNet PHL-C2 stratificazione

Risk factor	Stage (Ann Arbor) I, IIA	IIB	IIIA	IIIB, IV
No risk factor	TL-1			
ESR ≥ 30 mm/h	TL-2			
Bulk ≥ 200 ml	TL-2			TL-3
E-lesions	TL-2			TL-3

Figure 7: Treatment Stratification According to Treatment Levels (TLs) in EuroNet-PHL-C2

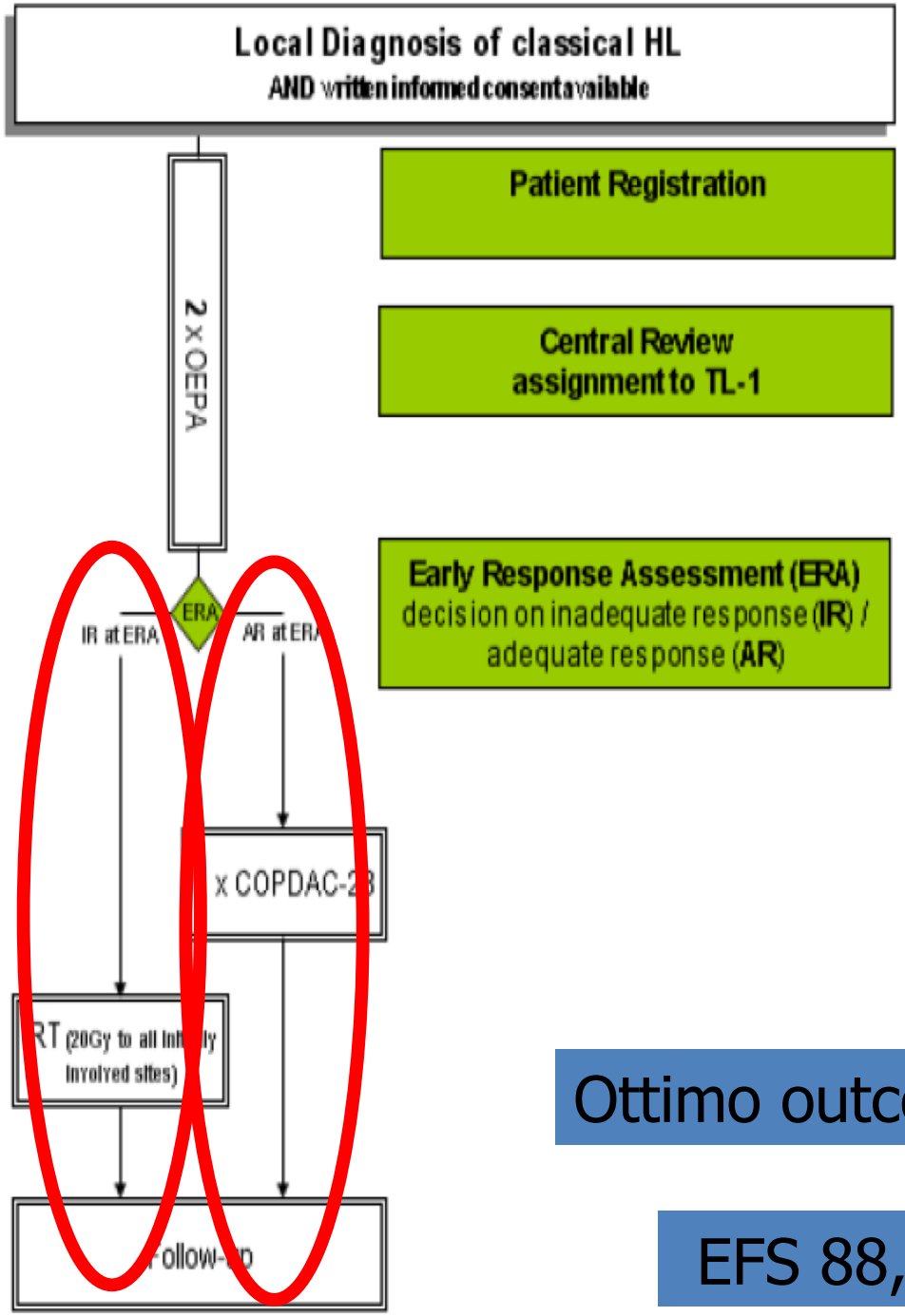
General Strategy II

Overall strategy is ***risk-stratified*** (defining chemotherapy) and ***response-adapted*** (defining radiotherapy):

- **No** Radiotherapy in patients with **negative PET** scan after 2 x OEPA.
  - •PET threshold shift from Deauville (D) 1 and 2 (= negative; C1 trial) to D 1-3 (= negative; C2 trial)
  - •Increase the number of patients without RT
- Chemotherapy Randomisation
  - •Randomisation of intermediate (TL-2) and advanced stage (TL-3) patients between standard COPDAC-28 or intensified DECOPDAC-21 consolidation.
  - •Randomisation **before** ERA to avoid delayed consolidation.
  - ***•Two randomised sub-studies based on the ERA PET response***
    - Patients with ***adequate*** **response at ERA do not** receive RT
    - Patients with ***inadequate*** **response at ERA**

DECOPDAC-21

- ✓Potenzia il ciclo classico COPDAC-28 (aumenta CPM, aggiunge doxorubicina e etoposide)
- ✓Stessa efficacia di BEACOPP
- ✓Dacarbazina al posto di procarbazina
- ✓Omessa bleomicina
- ✓Ridotta dose di doxorubicina da 35 a 25 mg/m2 per ciclo
- ✓Ridotta dose etoposide da 600 mg a 300 mg/2 per ciclo
- ✓Ridotta dose di prednisone da 600 mg/m2/ciclo a 320 mg/m2/ciclo. Fattore protettivo su osteonecrosi (Fossa et al; 2012)



TL-1

2 cicli OEPA

ERA-PET **AR** → COPDAC-28

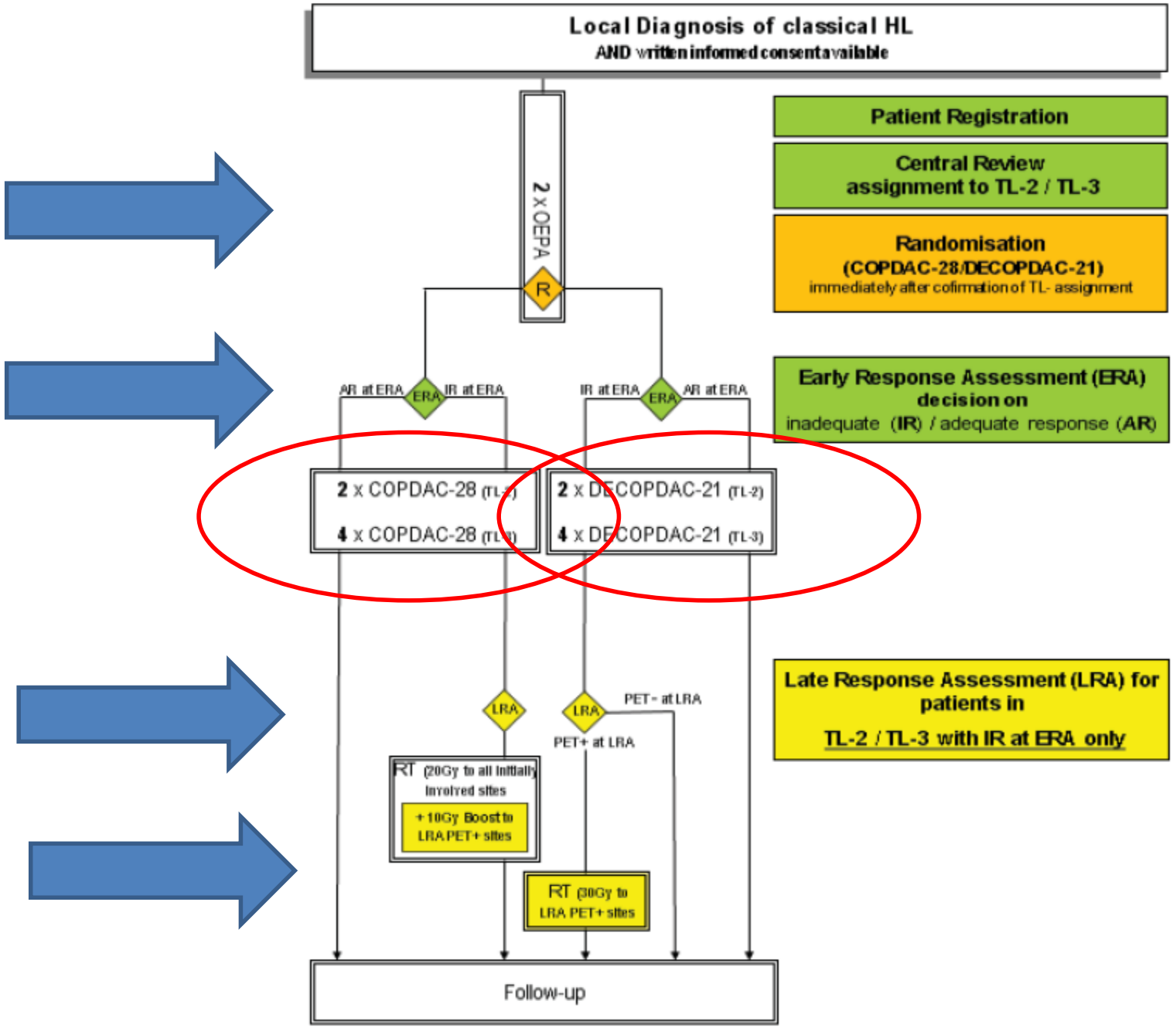
ERA-PET **IR** → RTP

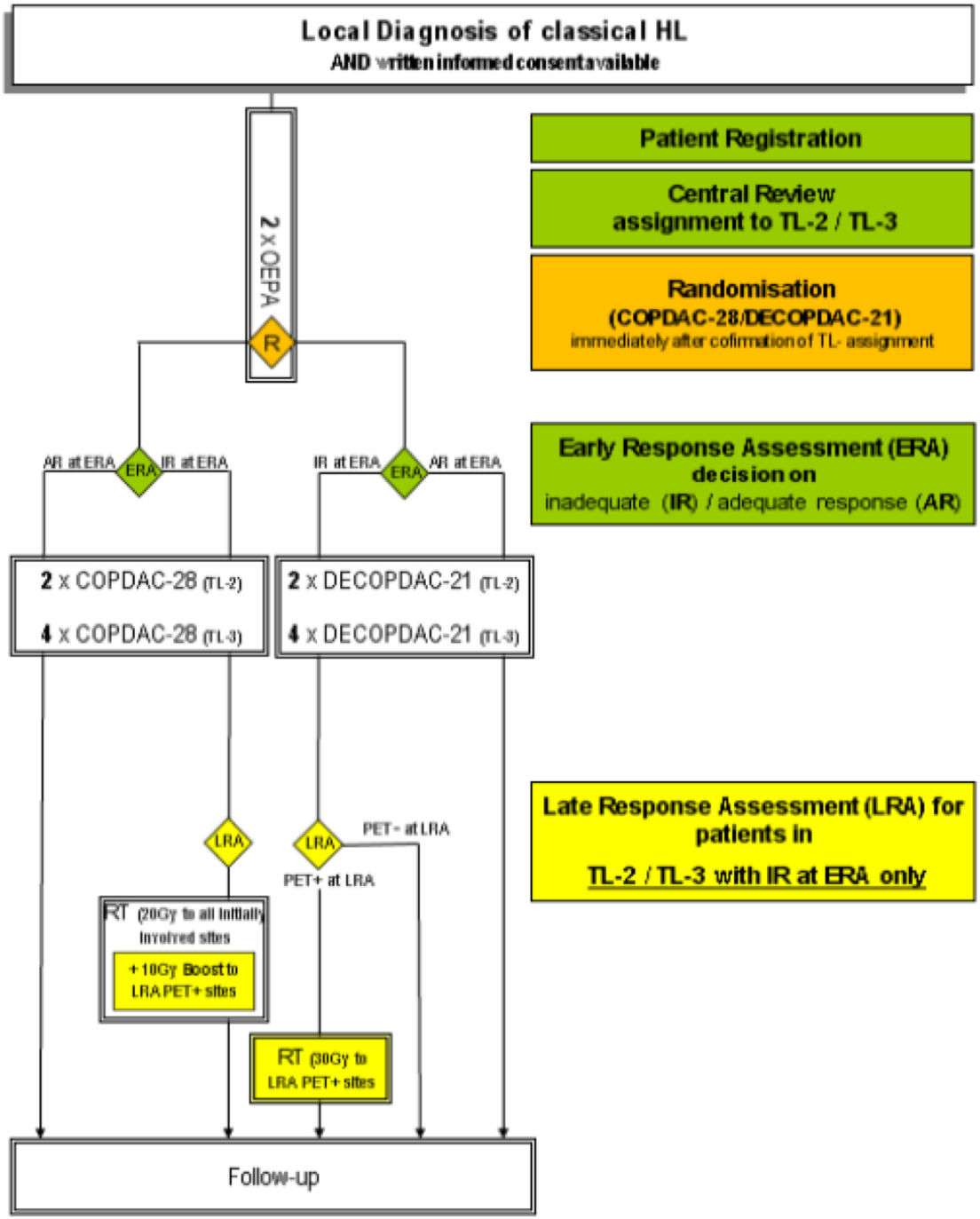
Ottimo outcome: EFS 98,3%

EFS 88,4%

EuroNetPHL-C1

Study Flow Chart TL-2&3





TL-2
EFS 3 anni
89% RTP
91% NO-RTP

EuroNetPHL-C1

TL-3
EFS 3 anni
86% RTP
87% NO-RTP

EuroNetPHL-C1

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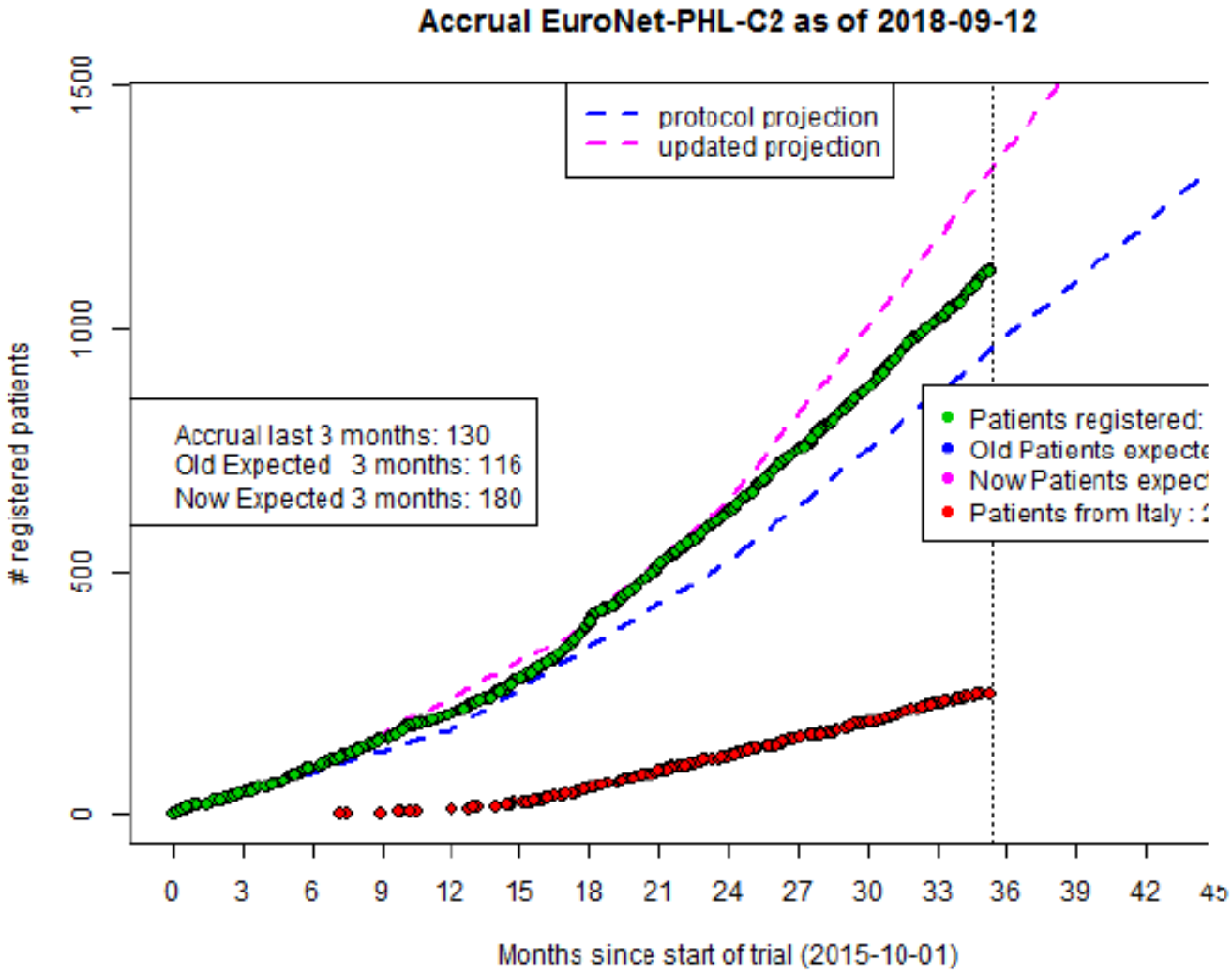
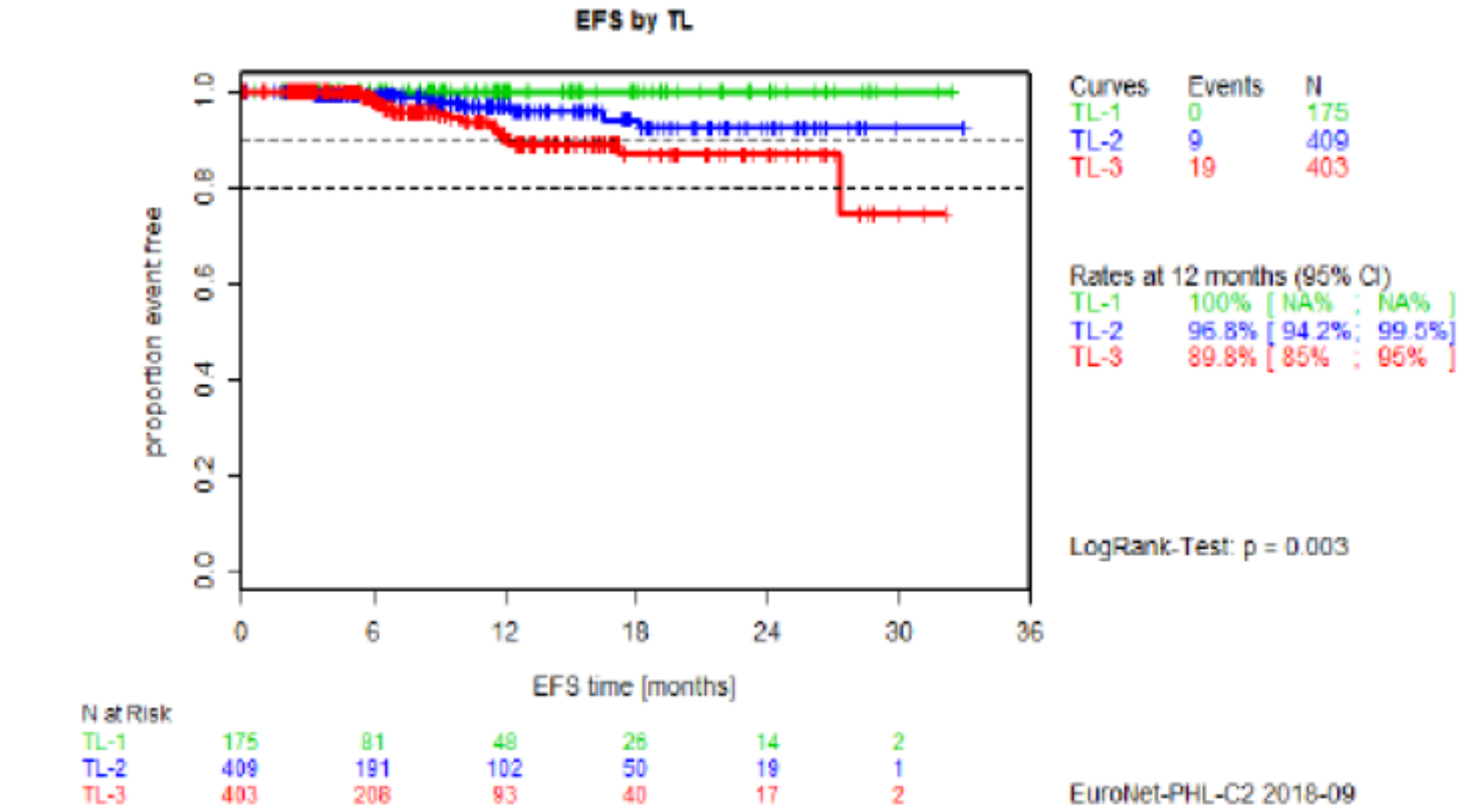
Actual accrual



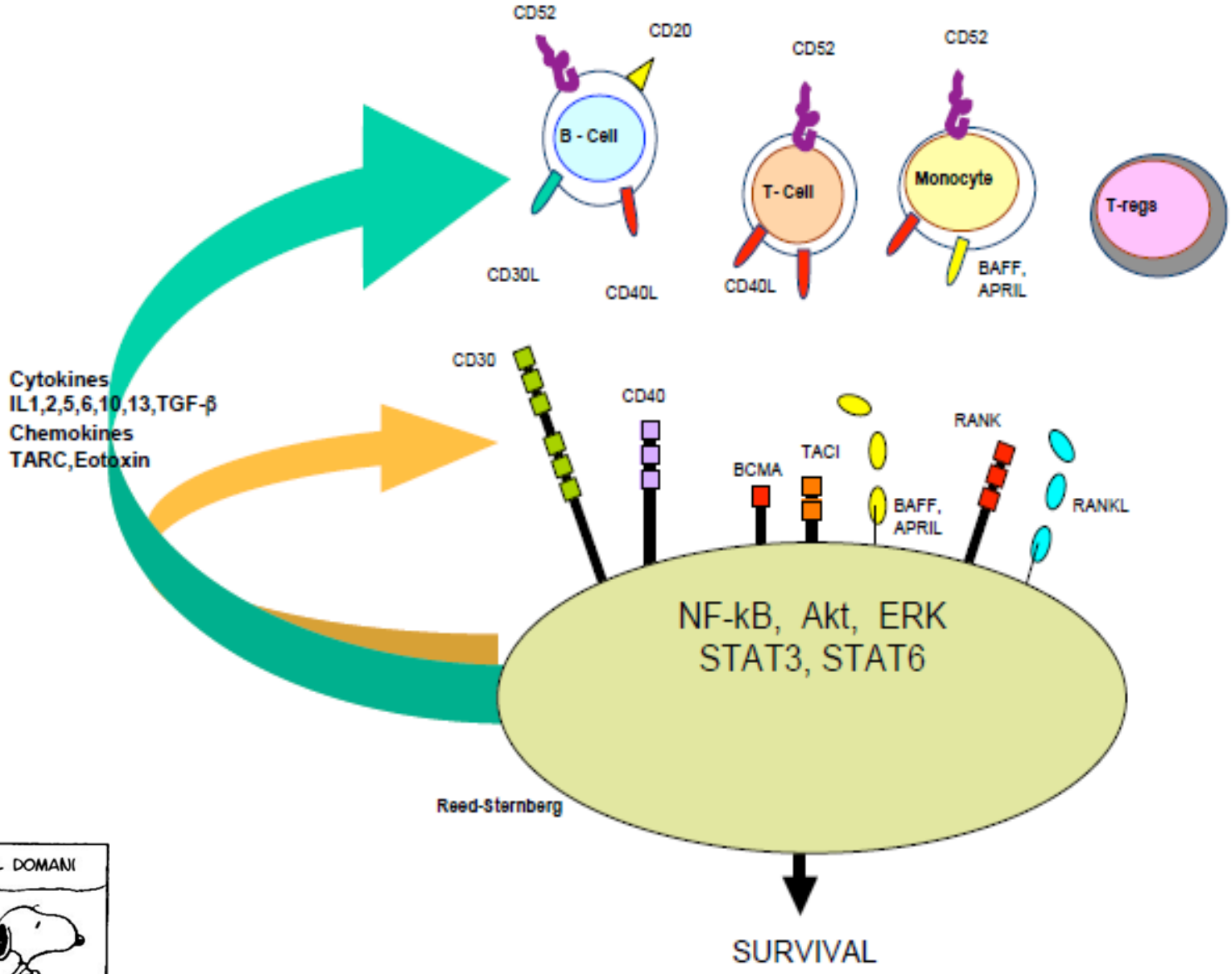
CountryLongname	Freq	Percent
Australia	36	3.2
Austria	46	4.1
Belgium	66	5.9
Czech Republic	37	3.3
Denmark	4	0.4
France	20	1.8
Germany	428	38.2
Great Britain	9	0.8
Israel	67	6
Italy	250	22.3
Netherlands	46	4.1
New Zealand	13	1.2
Norway	19	1.7
Spain	54	4.8
Switzerland	25	2.2
Sum	1120	100

EFS by Treatment-Level (TL)



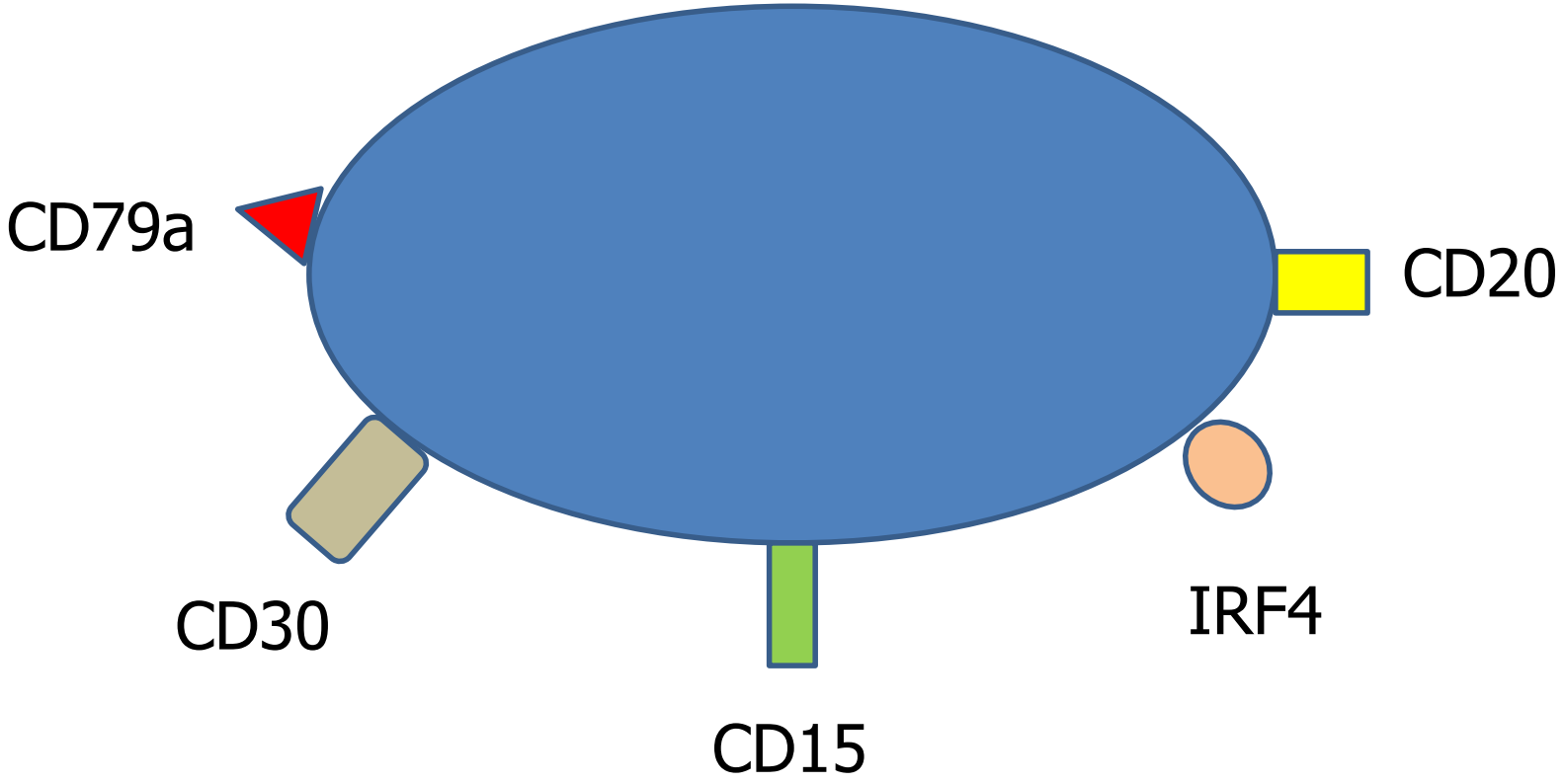
Linfoma Hodgkin pediatrico

B cells in HL microenvironment provide survival factors to HRS



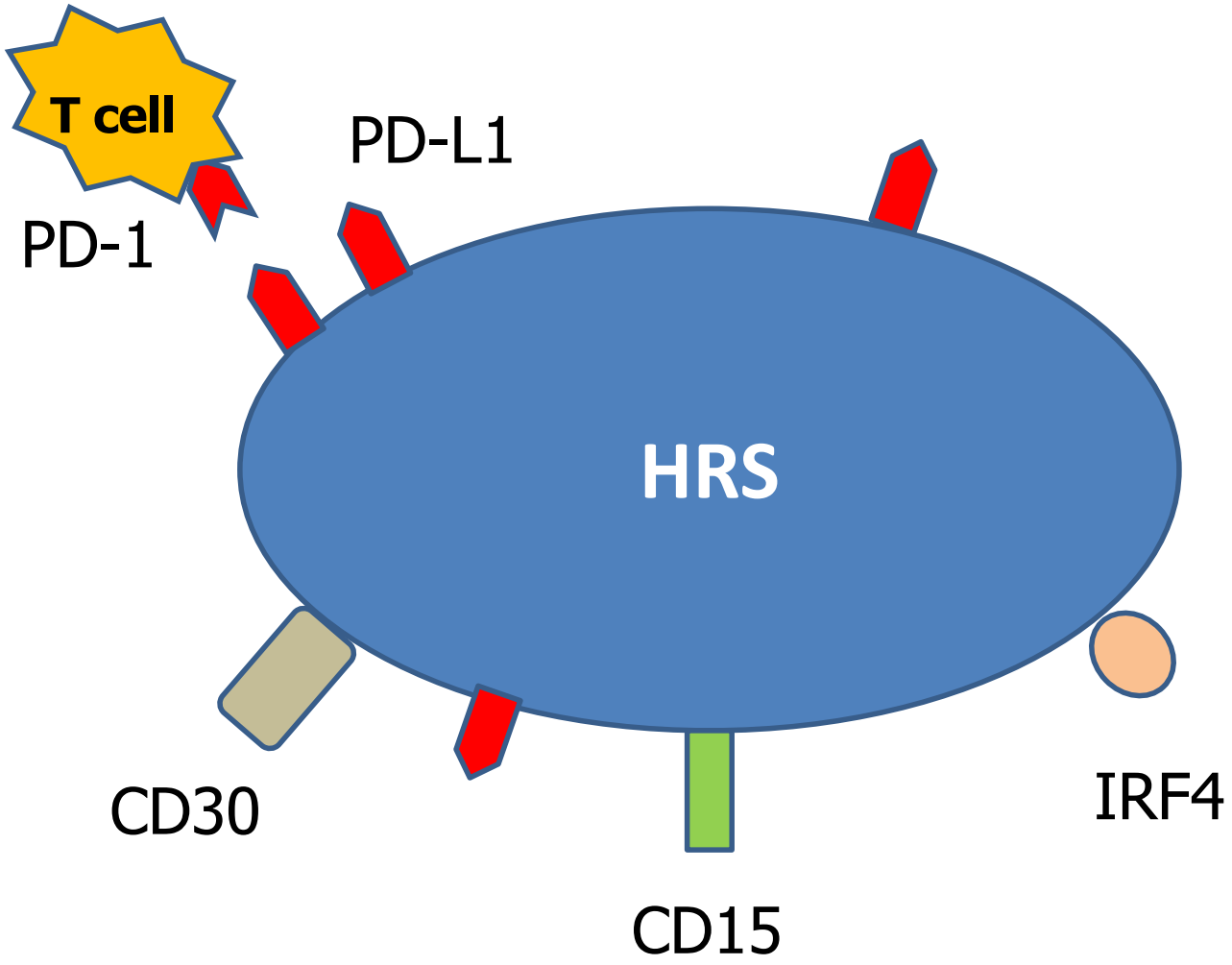
HRS

Cellula B del centro germinale



Quasi completa perdita dei marcatori linea B

Amplificazione cromosoma 9p24.1: *PD-L1, PD-L2, JAK2*



Nagel et al, 2014 Oncogene

aberrante attivazione NF-kB

aberrante attivazione JAK-STAT

aberrante attivazione PI3K-AKT

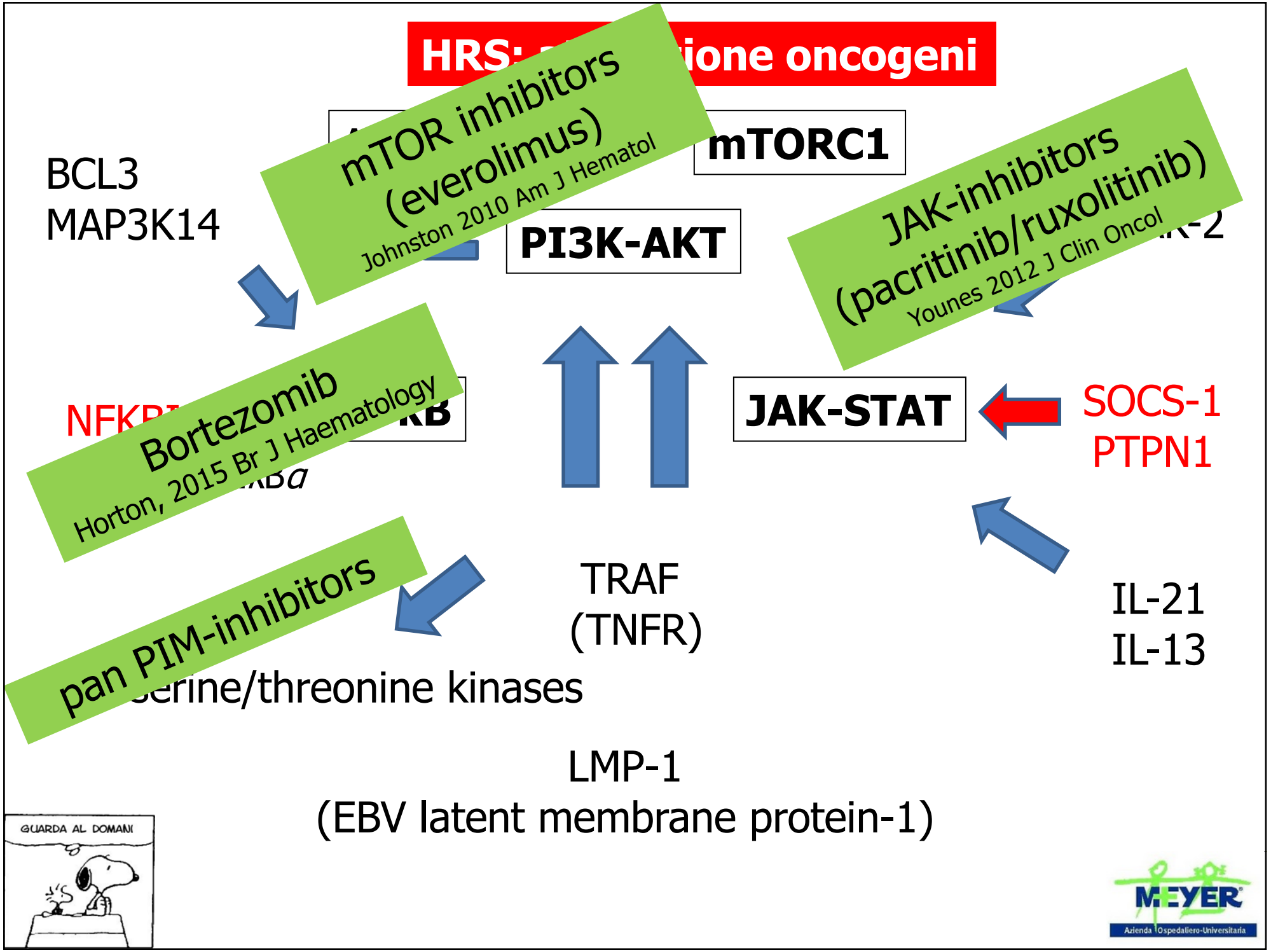
INFIAMMAZIONE

INIBIZIONE APOPTOSI

PROLIFERAZIONE

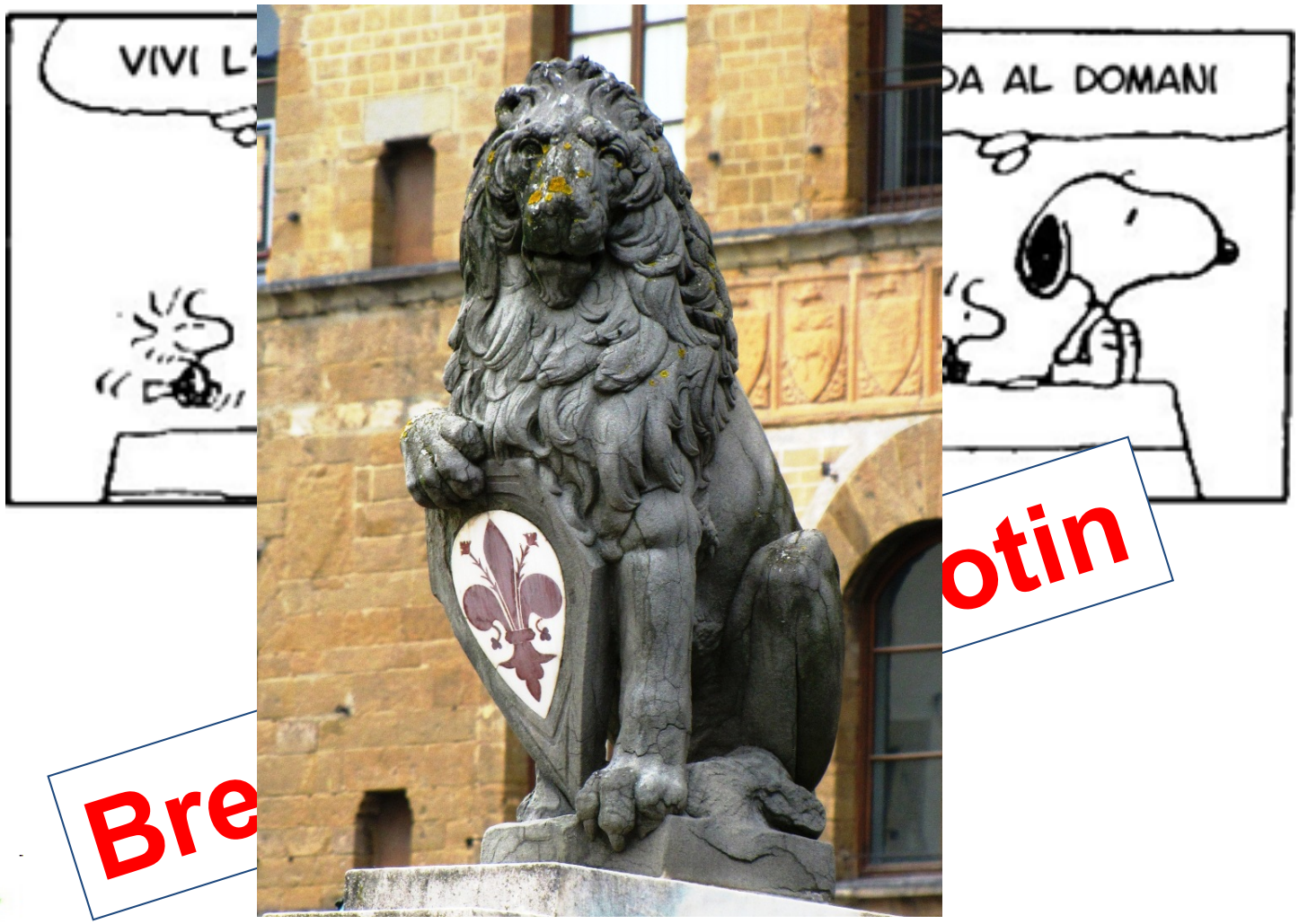
INATTIVAZIONE *TUMOR SUPPRESSOR*

Tiacci et al, 2018 Blood


HRS:
ione oncogeni
mTOR inhibitors
(everolimus)
Johnston 2010 Am J Hematol
mTORC1
BCL3
MAP3K14
PI3K-AKT
JAK-inhibitors
(pacritinib/ruxolitinib)
Younes 2012 J Clin Oncol
Bortezomib
Horton, 2015 Br J Haematology
JAK-STAT
SOCS-1
PTPN1
pan PIM-inhibitors
TRAF
(TNFR)
IL-21
IL-13
erine/threonine kinases
LMP-1
(EBV latent membrane protein-1)

GUARDA AL DOMANI

Terapia del Linfoma Hodgkin pediatrico: qualcosa di nuovo?



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Brentuximab vedotin

- Farmaco: monometil auristatin E (MMAE)

- Anticorpo monoclonale chimerico AC10 (cAC10, brentuximab), anticorpo anti CD30

- CD30 è una glicoproteina, membro della famiglia dei recettori del *tumor necrosis factor* (TNF)

- CD30 altamente espresso su cellule del linfoma Hodgkin e del linfoma anaplastico a grandi cellule (ALCL)

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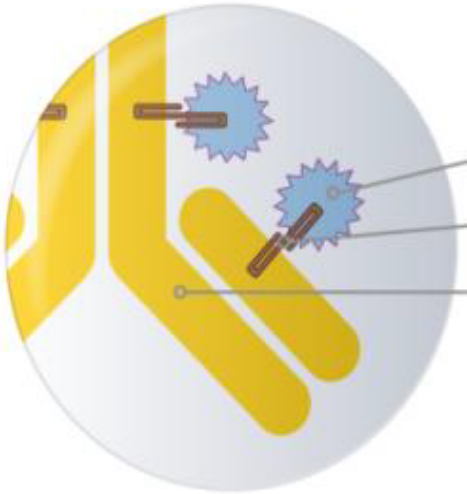
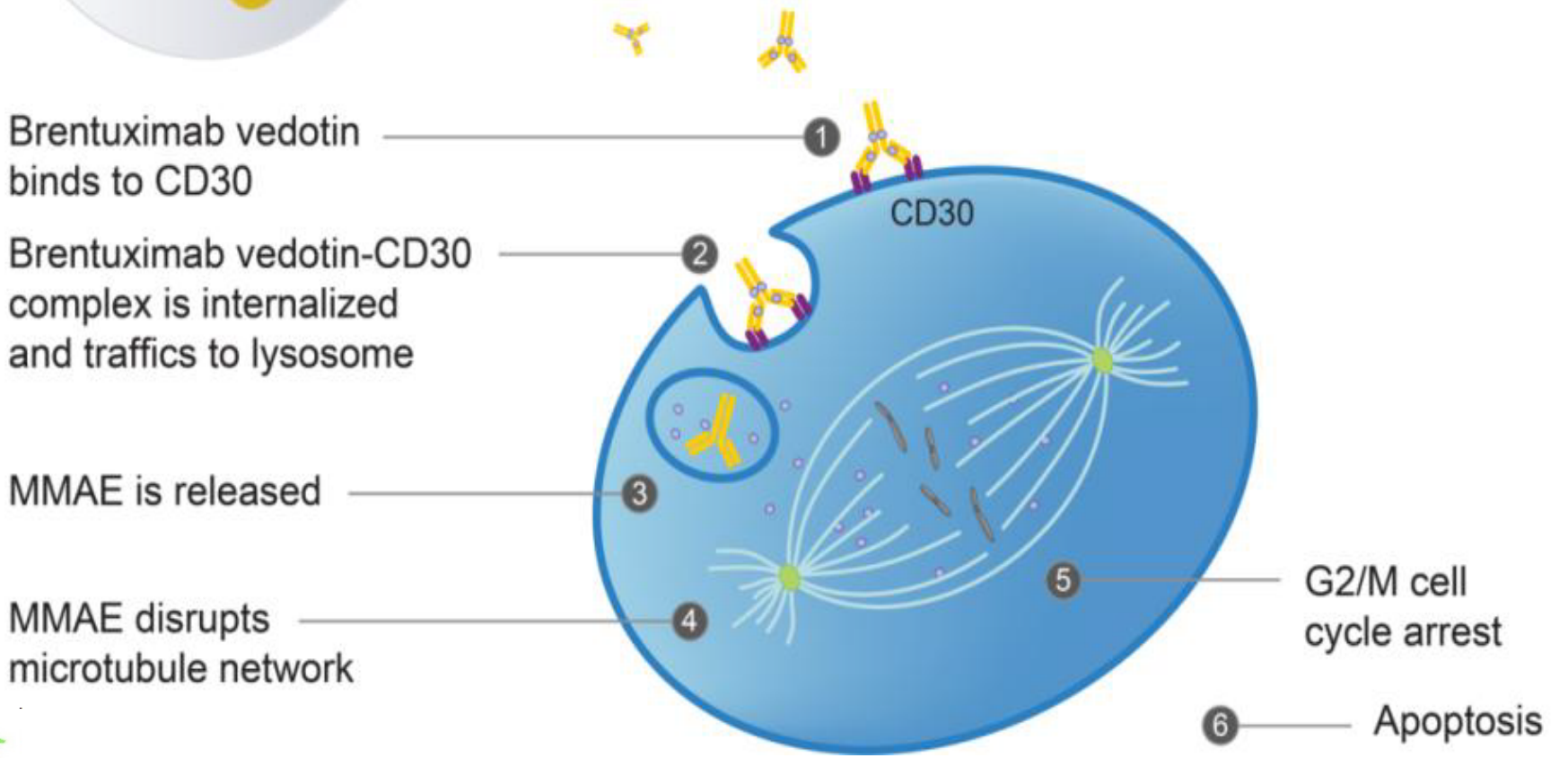
Brentuximab vedotin antibody-drug conjugate (ADC)



Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody



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Adverse Events	Grade 1-2 (>10% of pts)	Grade 3-4 (any occurrence)
Peripheral Sensory Neuropathy	42.9%	0%
Rash Acneiform	35.7%	7.1% (G3)
Rash Maculo-papular	14.3%	0%
AST elevation	28.6%	0%
Fatigue	28.6%	0%
ALT elevation	21.4%	0%
Flu like symptoms	21.4%	0%
Hypoglycemia	21.4%	0%
Nausea	21.4%	0%
Pain in extremity	21.4%	0%
Upper respiratory tract infection	21.4%	0%
Pruritis	14.3%	0%
Hyponatremia	14.3%	0%
Hypocalcemia	14.3%	0%
Generaliz		
Diarrhea		
Alk Phos		
Hypercholestrolnemia	14.3%	0%
Urinary Tract Infection	0%	7.1% (G3)

Brentuximab vedotin

- Solo rash tossicità grado 3-4
- No citopenia grado 3
- No neutropenia febbrile
- No richiesta di fattori di crescita
- No ospedalizzazione

BRENTUXIMAB IS SIGNIFICANTLY LESS TOXIC THEN CONVENTIONAL SALVAGE

NYU Cancer Institute
NYU LANGONE MEDICAL CENTER

Agosto 2011: Approvato da FDA per R/R MH dopo fallimento autotrapianto o di almeno due regimi chemioterapici se non elegibilità a trapianto

FDA Allargata indicazione al trattamento di consolidamento nei pazienti MH ad alto rischio di ricaduta o progressione dopo auto-HSCT

Study					
Younes et al. 2010 [					
Fanale et al. 2012 [12]					
Younes et al. 2012 [14–16]					R patients) Median PFS 9.3 months, median OS 40.5 months 5-year follow-up: 5-year PFS rate 22%, 5-year OS rate 41%
O'Connor et al. 2018 [19]	2	37	Relapsed or refractory	Bv 1.8 mg/kg day 1 and bendamustine 90 mg/m^2 day 1–2 Q3W for up to 6 cycles	ORR 78% (CR 43%, PR 35%) Median PFS and median OS not reached
Moskowitz et al. 2015 (AETHERA) [21]	3	329	Consolidation after ASCT	Bv 1.8 mg/kg vs placebo Q3W for 16 cycles	Bv ($n = 165$) vs placebo ($n = 164$): Median PFS 42.9 vs 24.1 months (HR = 0.57, $P = 0.0013$)
Chen et al. 2015 [22, 23]	2	37	Relapsed after or refractory to frontline therapy	Bv 1.8 mg/kg Q3W for 4 cycles	ORR 68% (CR 35%, PR 32%) 18 patients directly proceeded to ASCT; 18 patients received additional salvage chemotherapy and 15 proceeded to ASCT 18-month post-transplant PFS rate 73%
Moskowitz et al. 2015 [24]	2	45	Relapsed after or refractory to frontline therapy	Bv 1.2 mg/kg days 1, 8, 15 Q4W for 2 cycles	12 (27%) were PET negative and proceeded to ASCT; 32 received additional salvage chemotherapy and proceeded to ASCT 2-year EFS rate 80%, 2-year OS rate 95%

Wang et al. Journal of Hematology & Oncology (2018) 11:57
https://doi.org/10.1186/s13045-018-0601-9

Journal of
Hematology & Oncology

REVIEW Open Access

Advances in CD30- and PD-1-targeted therapies for classical Hodgkin lymphoma

Yucai Wang[1], Grzegorz S. Nowakowski[1], Michael L. Wang[2] and Stephen M. Ansell[1*]

These results demonstrated that brentuximab vedotin is an active first-line salvage therapy, producing 27-35% CR as a single agent. Another 30-49% of patient could achieve a CR with additional salvage therapy. The majority of patients could proceed to ASCT

20.03.18 approvato FDA insieme a chemioterapia in prima linea nei pazienti adulti stadio III-IV (dopo studio ECHELON di confronto ABVD vs AVD-Bv)

Cassada 2017 [2					ents
Garcia-S et al. 20					PR 26%)
					Projected 1-year post-transplant PFS rate 87%, OS rate 90%
LaCasce et al. 2015 [27]	1/2	53	Relapsed after or refractory to frontline therapy	Bv 1.8 mg/kg Q3W plus bendamustine 90 mg/m^2 days 1–2 Q3W for up to 6 cycles	ORR 93% (CR 74%, PR 19%) 37 had undergone ASCT Estimated 12-month PFS rate 80%
Younes et al. 2013 [29, 30]	1	51	Newly diagnosed stage IIA bulky disease or stage IIB–IV	Bv 0.6, 0.9, or 1.2 mg/kg Q2W in combination with ABVD or AVD for up to 6 cycles (28-day)	Bv+ABVD arm ($n = 25$, dose escalation): CR 95% 5-year FFS rate 79%, OS rate 92% Bv+AVD arm ($n = 26$, 1.2 mg/kg only): CR 96% 5-year FFS rate 92%, OS rate 100%
Connors et al. 2018 (ECHELON-1) [31]	3	1334	Untreated stage III or IV	Bv 1.2 mg/kg Q2W in combination with AVD vs ABVD, for up to 6 cycles (28-day)	Bv+AVD vs ABVD: ORR 86 vs 83% CR 73 vs 70% 2-year modified PFS rate 82.1 vs 77.2% (HR = 0.77, $P = 0.03$)
Abramson et al. 2015 [33]	2	34	Newly diagnosed non-bulky stage I–II	Bv 1.2 mg/kg Q2W for 1 cycle (28-day), followed by Bv+AVD for 4–6 cycles (28-day)	After first cycle of Bv: CR 53% After 2 cycles of Bv+AVD: CR 97% At the end of treatment: CR 88% PFS rate 90% and OS rate 97% (median follow-up 14 months)
Kumar et al. 2016 [34]	2	30	Newly diagnosed stage I–II with unfavorable risk factors	Bv 1.2 mg/kg Q2W in combination with AVD for 4 cycles (28-day), followed by 30 Gy ISRT if PET negative	After 2 cycles: 90% PET negative After 4 cycles: 93% PET negative 1-year PFS rate 93.3%

Brentuximab vedotin

cHL front-line stadi avanzati

cHL refrattario e recidivato (Bridge)

cHL recidivato e refrattario post ASCT

Brentuximab vedotin in età pediatrica

- ✓ Studi clinici ancora limitati, ma certo incoraggianti
- ✓ Profilo di sicurezza documentato in vari lavori (Flerlage 2016 Cancer Chemother Pharmacol)
- ✓ Ben tollerato a 1.8 mg/kg ogni 3 settimane

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Brentuximab vedotin in età pediatrica

5 pz (12-17 aa) arruolati in studio fase 2 per approvazione FDA (Fanale, 2011 Eur J Cancer)

10 pz in studio internazionale fase 1 R/R MH in monoterapia (Neville, 2013 J Clin Oncol)

COG (protocol HLHR13): brentuximab al posto di vincristina

AEPA-CAPDac anzichè OEPA-COPDac

Studio fase III Bv in combinazione con AVE-PC

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Brentuximab vedotin
studio C25004

Studio fase 1-2 multicentrico per valutare sicurezza, tollerabilità e dose raccomandata di Bv in combinazione con regime CHT multiagente (AVD) nei pazienti pediatrici con nuova diagnosi LH classico CD30+ in stadio avanzato e valutare attività antitumorale

Bv+AVD somministrati nei giorni 1-15 di ciascun ciclo di 28 giorni per massimo 6 cicli

Brentuximab vedotin

Studio fase 1-2 con gemcitabina

To conclude, brentuximab vedotin with gemcitabine is a safe combination treatment with a tolerable toxicity profile for children and young adults with primary refractory Hodgkin's lymphoma or early relapse. The preliminary activity shown is this trial along with the possibility of being administered as an outpatient salvage regimen warrants further investigation of this regimen in randomised controlled trials.

(Cole et al 2018, Lancet Oncol. Sep;19(9):1229-1238)

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Brentuximab vedotin
Quando proporlo?

Relapse disease

- Monoterapia? In associazione? Quale?
- Mantenimento per pazienti alto rischio?

Front line

- Combinato con chemioterapia?
- Combinato con altre terapie bersaglio?
- Per quali pazienti?

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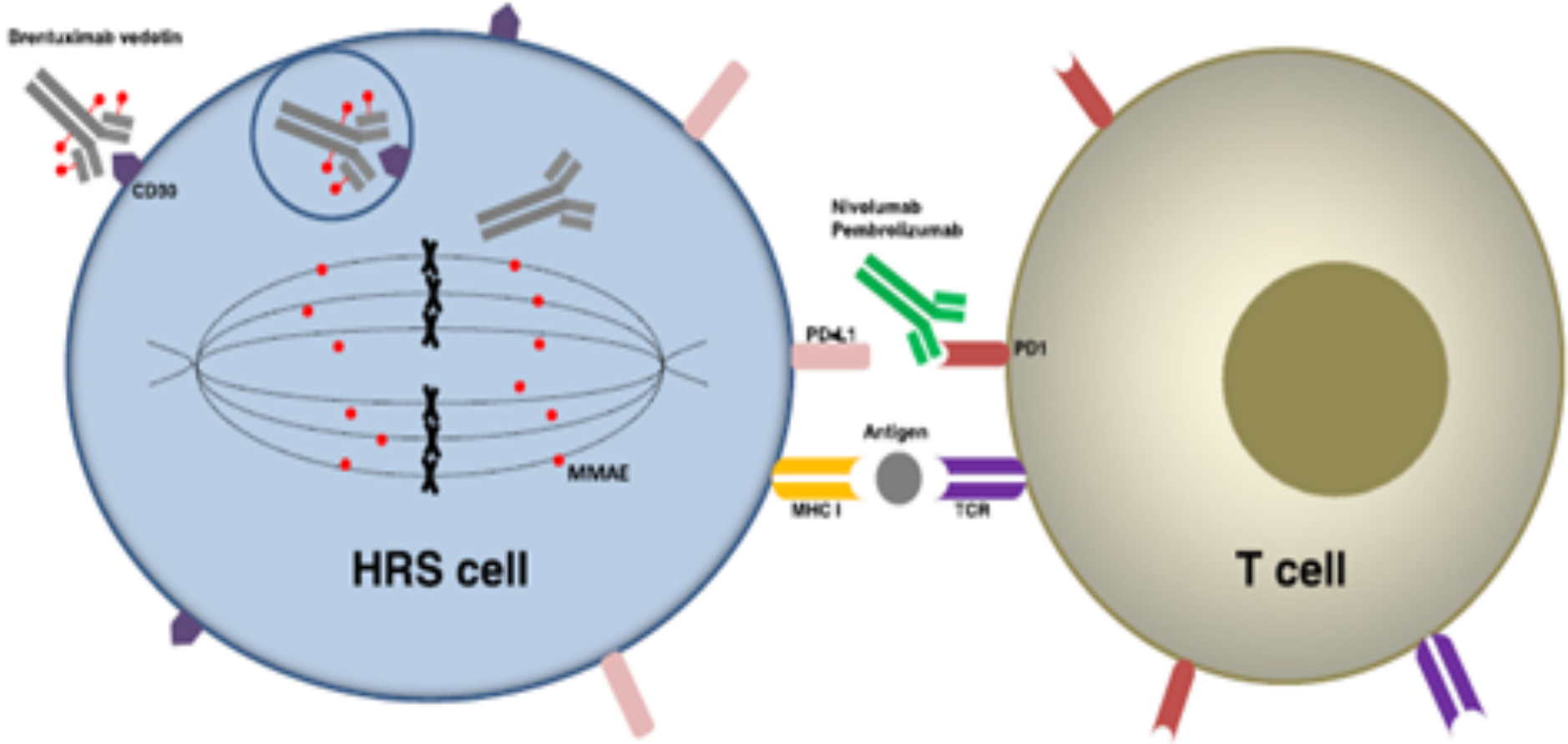
PD-1 Targeted immunotherapy



Nivolumab: in pazienti ricaduti o refrattari risposta nell'87% dei casi e 17% CR (Ansell 2015 N Engl J Med)

Silenziamento epigenetico dei sistemi regolatori B
Up-regolazione degli antagonisti trascrizionali

MOCETINOSTAT, PANOBINOSTAT, VORINOSTAT

?

Batlevi et al, 2013 Hematology Am Soc Educ Program

Nessuna pubblicazione in età pediatrica, ma studio fase 1 in corso per pazienti pediatrici affetti da malattie ematologiche R/R compreso linfoma Hodgkin

Trattamento chemo-free?

Brentuximab vedotin + nivolumab in pazienti R/R cHL

ORR 82% con 61% CR

87% avviati ad auto-trapianto, **68% direttamente ad auto-trapianto senza ulteriore chemioterapia**

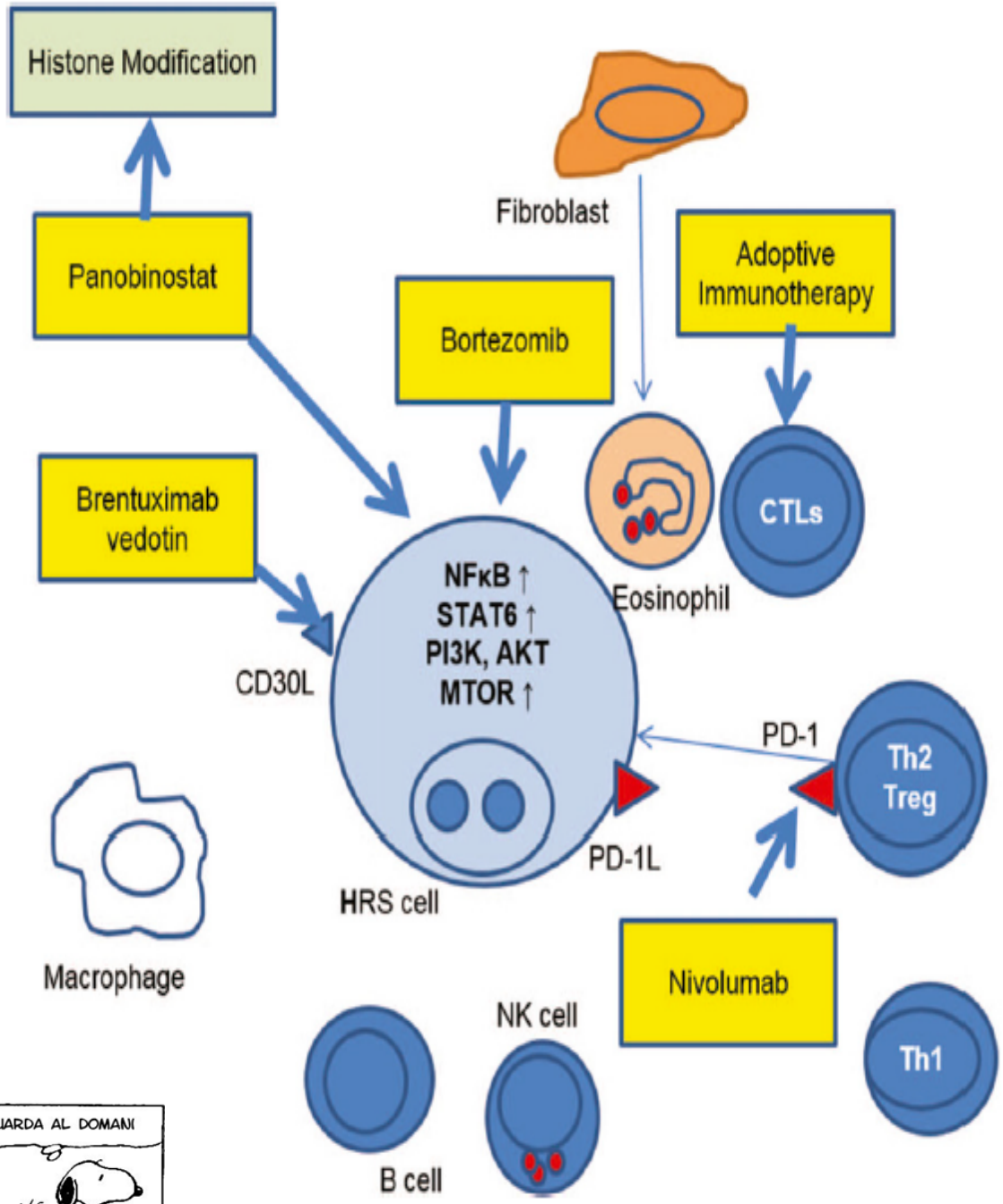
(Herrera, Blood 2018)

Nella fascia pediatrica, mancano al momento dati scientifici e esperienze significative

Trattamento chemo-free?

Terapia combinata brentuximab + bortezomib nel trattamento di pazienti pediatrici RR: effetto citotossico sinergico *in vitro*

Boll et al, Blood 2005;106:1839


Histone Modification
Panobinostat
Fibroblast
Bortezomib
Adoptive Immunotherapy
Brentuximab vedotin
CTLs
Eosinophil
NFκB ↑
STAT6 ↑
PI3K, AKT
MTOR ↑
CD30L
PD-1
Th2 Treg
PD-1L
HRS cell
Macrophage
Nivolumab
NK cell
Th1
B cell


GUARDA AL DOMANI

Childhood Hodgkin Lymphoma International Prognostic Score (CHIPS)

- Stadio IV
- Massa Bulky
- Livello albumina < 3.5 g/dL
- febbre

CHIPS was highly predictive of EFS, identifying a subset (with CHIPS 2 or 3) that comprises 27% of intermediate-risk patients who have a 4-year EFS of <80% and who may benefit from early therapeutic augmentation. Furthermore, CHIPS identified higher risk patients who were not identified by early PET or CT response. CHIPS is a robust and inexpensive approach to predicting risk in patients with intermediate-risk HL that may improve ability to tailor therapy to risk factors known at diagnosis

Pediatr Blood Cancer. 2017 Apr;64(4) 2016 Oct 27

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Esistono biomarkers prognostici in pediatria?

Bcl-2 (Barros, Leukemia & Lymphoma 2010)	Azione mediata da LMP-1
IL-10 e IL-12 (Bien, Clin Biochem 2009)	Th2, sintomi B Forme refrattarie e resistenti
sCD30 (Nadali, Blood 1998)	Stadi avanzati, masse bulky Forme refrattarie
NK CD57+ (Ortac, Anal Quant Cytol Histol 2002)	Ridotta EFS se bassi
TAMs (Barros, Leukemia & Lymphoma 2010)	Polarizzati in senso M1 se EBV+ e in senso M2 se EBV-
NF-kB (Sun, Immunol Rev 2012)	Associata a risposta lenta alla terapia
ICAM-1 (Abdelrazik, Med Princ Prac 2008)	Stadi avanzati, sintomi B, VES elevata e outcome peggiore

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Linfoma Hodgkin recidivato/refrattario (RR)
Terapie convenzionali
Terapie bersaglio

- auto/alloSCT
- IGEV
- IEP-ABVD
- ICE
- Ifosfamide/vinorelbina
- Gemcitabina/vinorelbina
- OPPA/IEP
- DHAP

- **Brentuximab vedotin**

Studio fase 1-2: 16 pazienti pediatrici
CR 21%

Studio fase 1-2: con gemcitabina

- **Bortezomib**

+ gemcitabina e vinorelbina

+ ifosfamide e vinorelbina

- **Vorinostat, panobinostat**
- **Nivolumab, pembrolizumab**

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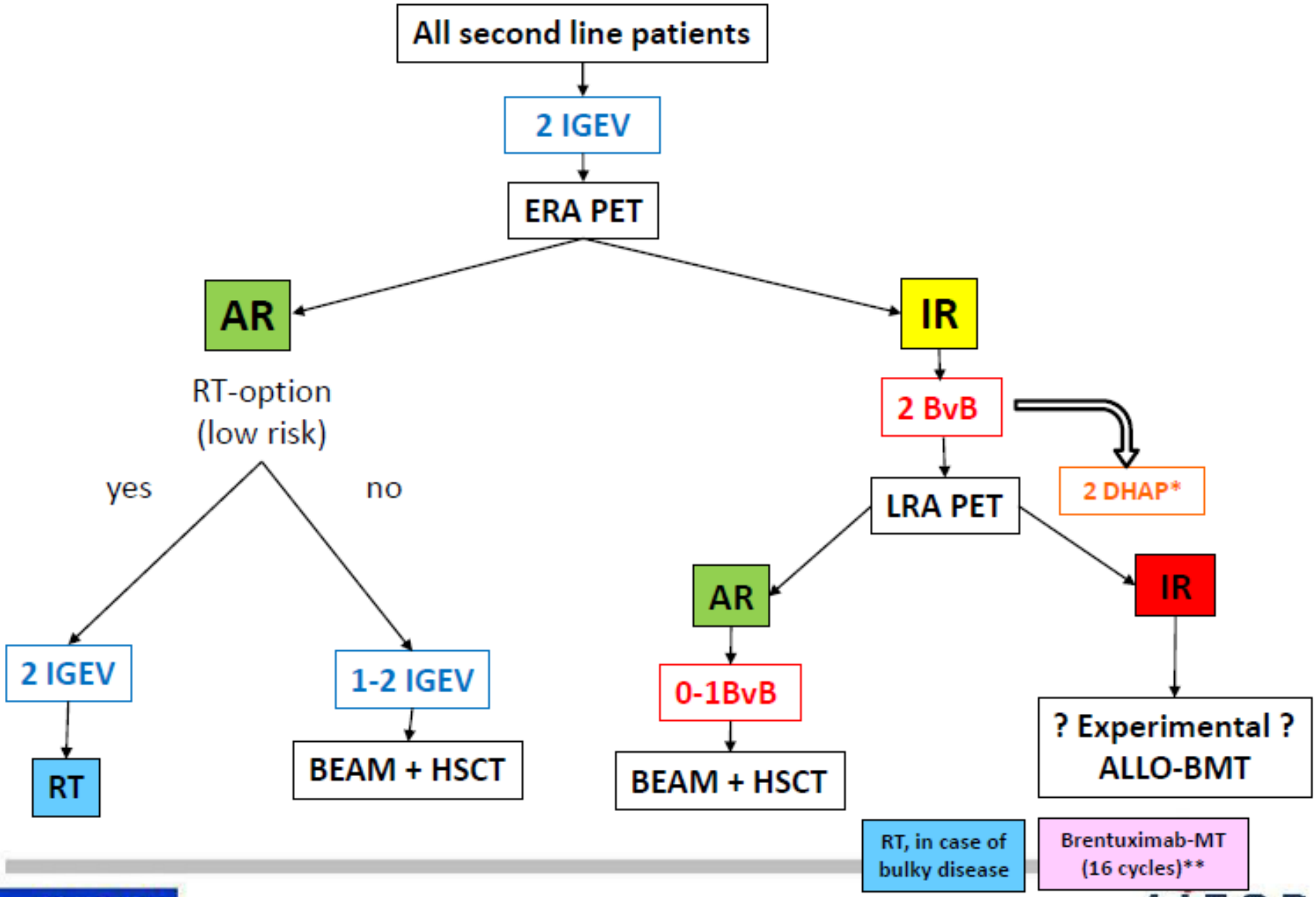
L’unico punto fermo
è
quello
INTERROGATIVO!!

Classical Hodgkin Lymphoma -First Relapse- Proposed Recommendation

Risk-based, Response-adapted



EuroNet-PHL

Stephen Daw, Thierry Leblanc x EuroNet-PHL Group

Mascarin M., Elia C., Burnelli R.

AIEOP

RELAPSED/REFRACTORY HODGKIN LYMPHOMA

CLINICAL PROTOCOL CA209744

Risk-based, response-adapted, Phase II open-label trial of **nivolumab + brentuximab vedotin (N + Bv)** for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by **brentuximab + bendamustine (Bv + B)** for participants with a suboptimal response.

Overall Design:

Risk Stratification Algorithm			
Stage at Initial Diagnosis	**Time to Relapse (from end of therapy)**	**B symptoms or extranodal disease at relapse, extensive disease where radiation therapy was contraindicated at relapse, or relapse in a prior radiation field**	**Relapse Risk Category**
IA, IIA	≥ 12 months	No	**R1 Cohort: Low Risk**
	3-12 months (≤ 3 cycles and no RT)		
IB, IIB, IIIA	> 12 months	No	
All Others			**R2 Cohort: Standard Risk**

PH Murray et al ASH 2018

Conclusioni

- MH fascia pediatrica/giovane adulti ha ottime possibilità di cura e guarigione, grazie a studi collaborativi
- Ridurre la tossicità e le complicanze tardive
- Brentuximab, checkpoint inhibitors e altre terapie bersaglio sono opzioni terapeutiche di ottime prospettive, ma che necessitano di trial clinici

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Grazie

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