Torino, 25 novembre 2016

Aggiornamento Protocolli FIL

Linfoma di Hodgkin

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FRONTLINE ADVANCED

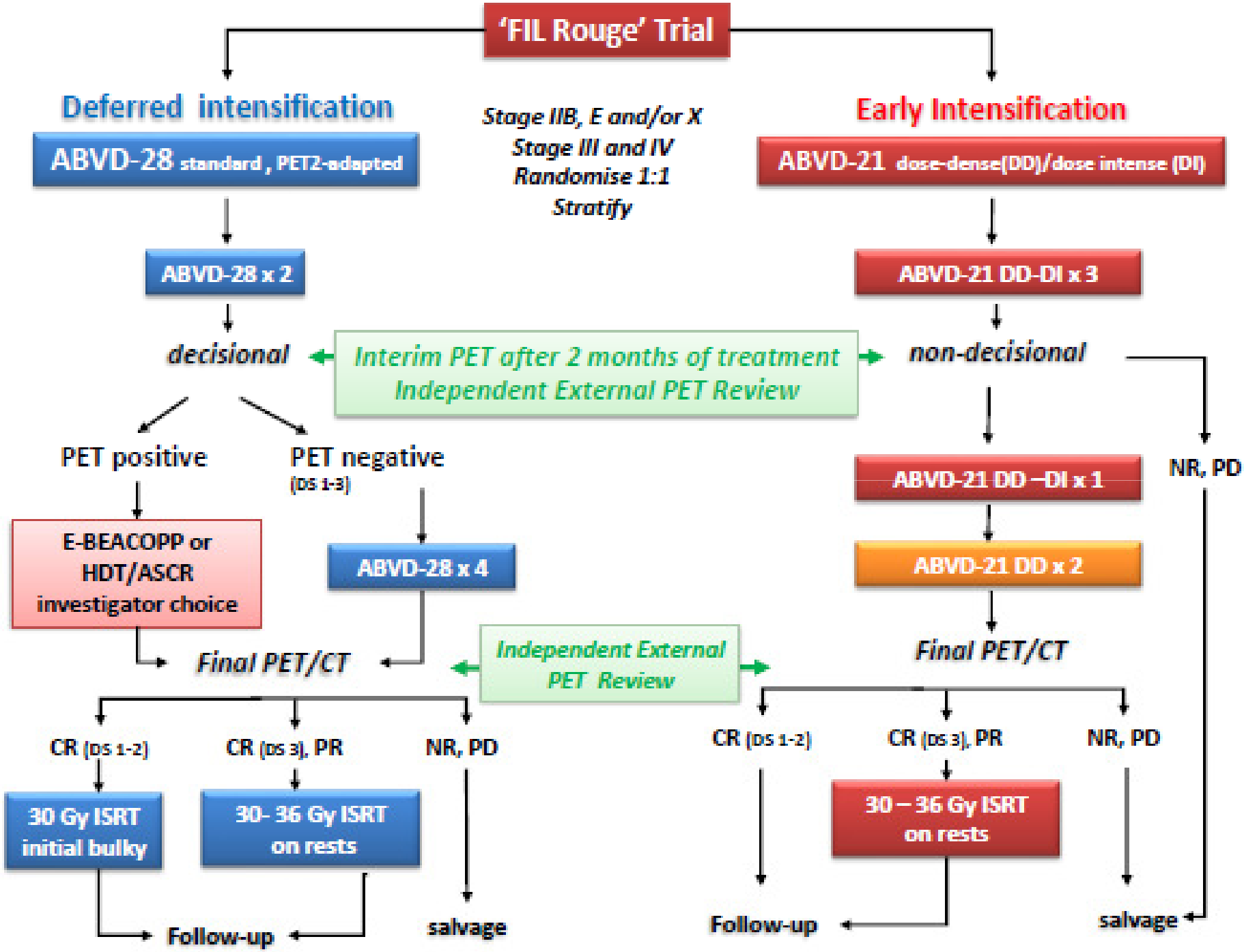
FONDAZIONE FIL ITALIANA LINFOMI

Clinical Protocol

A randomized, open-label, multicenter, phase III, 2-arm study comparing efficacy and tolerability of the intensified variant 'dose-dense/dose-intense ABVD' (ABVD DD-DI) with an interim PET response-adapted ABVD program as upfront therapy in advanced-stage classical Hodgkin Lymphoma (HL).

ID Study: **FIL-Rouge**

EudraCT number: 2016-002509-21


'FIL Rouge' Trial
Deferred intensification
ABVD-28 standard , PET2-adapted
Stage IIB, E and/or X
Stage III and IV
Randomise 1:1
Stratify
Early Intensification
ABVD-21 dose-dense(DD)/dose intense (DI)
ABVD-28 x 2
ABVD-21 DD-DI x 3
decisional
Interim PET after 2 months of treatment
Independent External PET Review
non-decisional
PET positive
PET negative
(DS 1-3)
NR, PD
ABVD-21 DD –DI x 1
E-BEACOPP or
HDT/ASCR
investigator choice
ABVD-28 x 4
ABVD-21 DD x 2
Final PET/CT
Independent External
PET Review
Final PET/CT
CR (DS 1-2)
CR (DS 3), PR
NR, PD
CR (DS 1-2)
CR (DS 3), PR
NR, PD
30 Gy ISRT
initial bulky
30- 36 Gy ISRT
on rests
30 – 36 Gy ISRT
on rests
Follow-up
salvage
Follow-up
salvage

bjh BRITISH JOURNAL OF HAEMATOLOGY

A phase II study of dose-dense and dose-intense ABVD ($ABVD_{DD-DI}$) without consolidation radiotherapy in patients with advanced Hodgkin lymphoma

Filippo Russo,[1]* Gaetano Corazzelli,[1]* Ferdinando Frigeri,[1] Gaetana Capobianco,[1] Luigi Aloj,[2] Francesco Volzone,[1] Annarosaria De Chiara,[3] Annamaria Bonelli,[4] Tindaro Gatani,[5] Gianpaolo Marcacci,[1] Daniela Donnarumma,[1] Cristina Becchimanzi,[1] Elisabetta de Lutio,[6] Franco Ionna,[7] Rosaria De Filippi,[8] Secondo Lastoria[2] and Antonello Pinto[1]

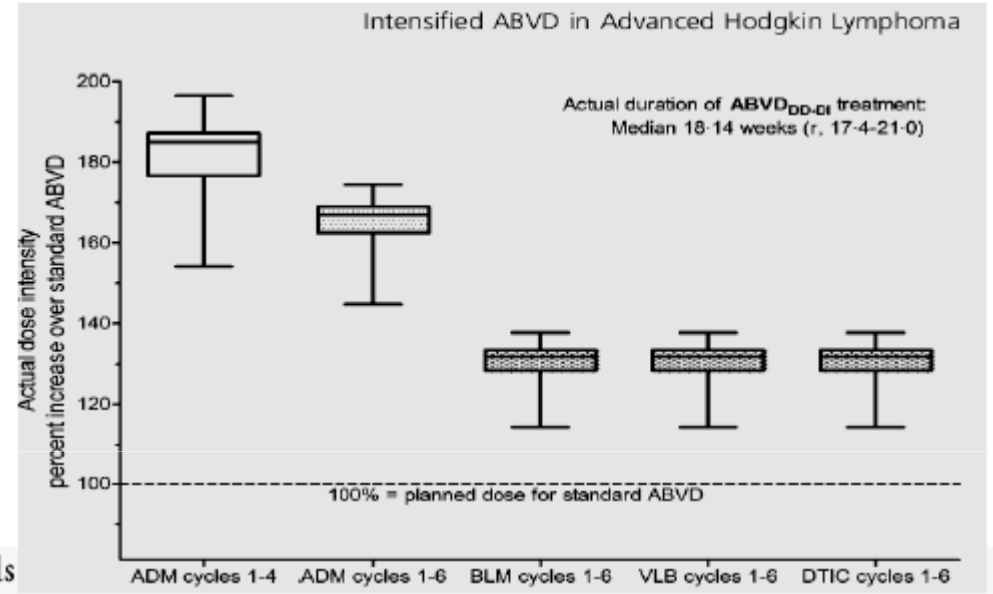


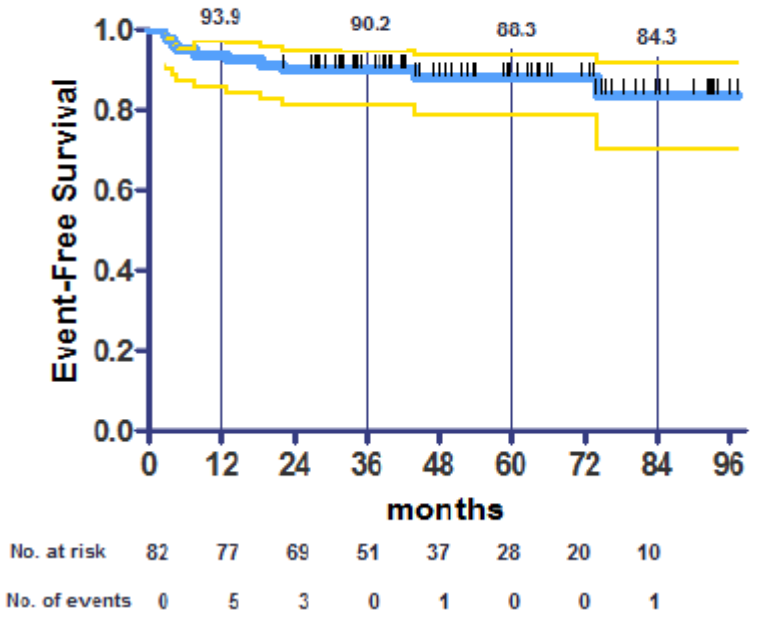
Table I. Drug doses, schedule and treatment administration details

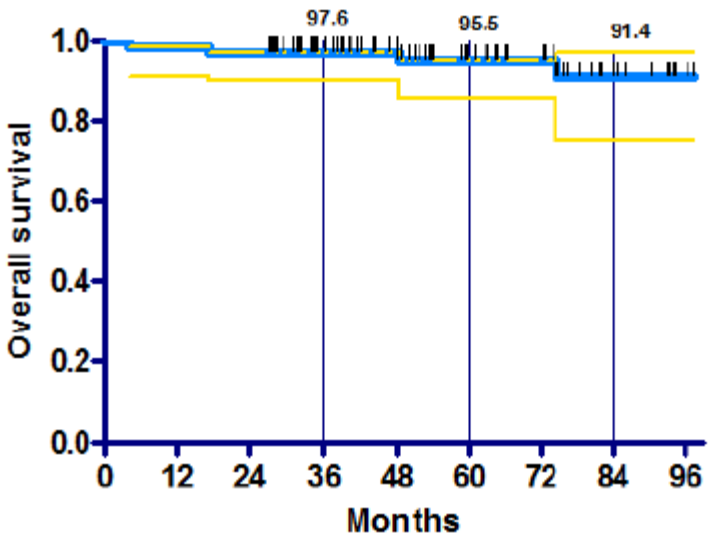
Drug	Dose (mg/m^2)	Route	Days	Cycles 1	2	3	4	5	6
Doxorubicin	35	IV	1, 11	↓	↓	↓	↓		
Doxorubicin	25	IV	1, 11					↓	↓
Bleomycin	10	IV	1, 11	↓	↓	↓	↓	↓	↓
Vinblastine	6	IV	1, 11	↓	↓	↓	↓	↓	↓
Dacarbazine	375	IV	1, 11	↓	↓	↓	↓	↓	↓
Lenograstim (G-CSF)	263 μg/d*	SC	6→8	↔	↔	↔	↔	↔	↔
Lenograstim (G-CSF)	263 μg/d*	SC	17→19	↔	↔	↔	↔	↔	↔

Median observation time for event-free survival was 57 months (range, 27–97 months).

Table IV. Treatment response, events and survival outcomes.

Outcome	*n*	%	95% CI
Final treatment response	82		
Complete remission	78	95·1	87·7–98·5
Partial remission	2	2·4	
Progression	1	1·2	
Unknown*	1	1·2	
Cycle 2 PET	82		
Negative	72	87·8	78·8–93·4
Positive	10	12·2	
Cycle 4 PET	10		
Negative	8		
Positive	2		
Cycle 6 PET	79		
Negative	78		
Positive	1		
Events	10	12·2	6·6–21·2
<Complete remission	2		
Progression	1		
Early relapse (3–12 months)	2		
Late relapse (>12 months)	2		
Secondary tumour	2		
Death from acute toxicity	1		
5-year			
Event-free survival		88·3	78·5–93·8
Disease-free survival		93·7	85·5–97·3
Overall survival		95·5	86·2–98·6





THE IMPLEMENTATION OF ABVD PLATFORM

TIME AND DOSE INTENSIFICATION

Chemotherapy	Cumulative dose		Dose density per week		
	ABVD	ABVD DD-DI	ABVD	ABVD DD-DI	Increase in dose intensity
Doxorubicin mg/mq	300	380	12.5	21.1	69%
Bleomycin units/mq	120	120	5	6.6	33%
Vinblastine mg/mq	72	72	3	4	33%
Dacarbazine mg/mq	4500	4500	188	250	33%

ENDPOINTS

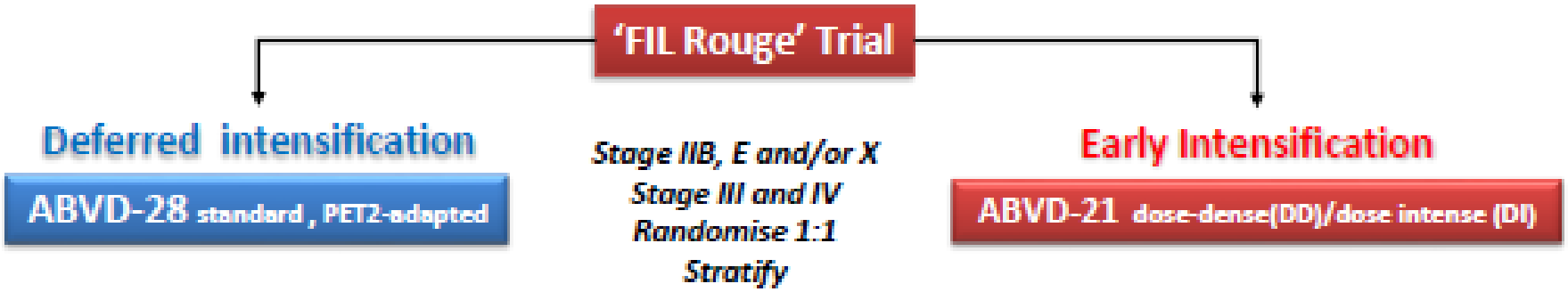
PRIMARY

Progression-Free-Survival (PFS)defined as the time from randomization until lymphoma progression or death as a result of any cause (with at least 3 years of follow-up).

SECONDARY

- CR rate
- **disease-free survival** (DFS)
- **event-free survival** (EFS)
- **overall survival** (OS)
- acute and delayed pulmonary and cardiac **toxicity**
- quality of Life (**QoL**)
- Cost-effectiveness

This sample size will also ensure to detect similar differences between arms for most of the secondary objectives with acceptable statistical power

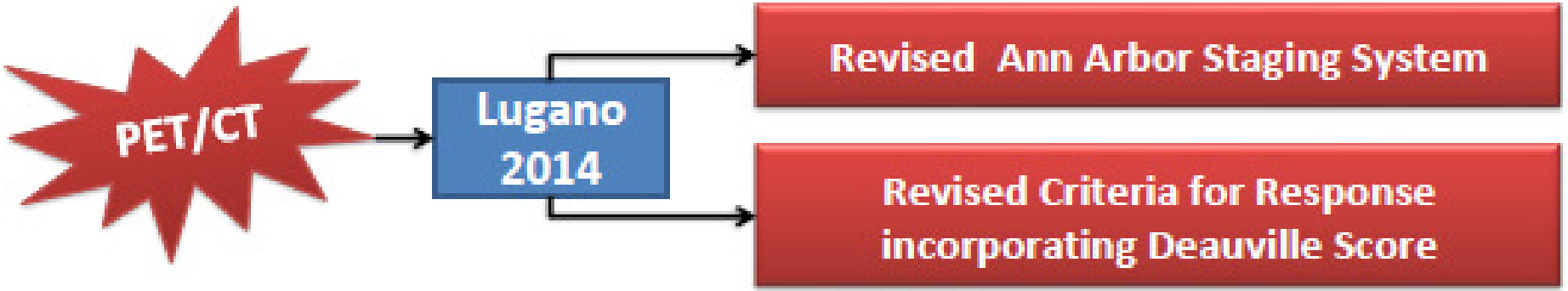


WEB-based allocation procedure

- tumor stage
- bulky disease
- age (<45 years vs. ≥45 years)
- International Prognostic Score (IPS, 0-2 vs ≥3)

Absolute 3 years PFS difference Δ (P0=75%)	α error (two-tails)	β error	Patients x arm and total
10%	0.05	0.10	250x2 =500

Staging and Response assessment



ROADMAP

FEB '17

Start up

JAN '17

Richiesta di adesione ai Centri

DEC '16

Presentazione
Comitati Etici

RELAPSED
REFRACTORY

A phase II study with bendamustine plus brentuximab vedotin in Hodgkin's lymphoma and CD30^{+} peripheral T-cell lymphoma in first salvage setting: the BBV regimen.

Study ID: FIL-BBV

EudraCT n. 2014-005382-79

Coorte linfoma di Hodgkin

BACKGROUND (1)

- Una terapia di salvataggio non *cross*-resistente con la prima linea di trattamento (± trapianto autologo) rappresenta lo standard terapeutico nei pazienti con linfoma di Hodgkin non responsivi o con malattia in ricaduta.

- I regimi di salvataggio attualmente impiegati (ifosfamide, platino) mostrano elevati tassi di risposta ma sono gravati da una marcata tossicità ematologica ed extraematologica.

Salvage regimen	N	RR (%)	CR (%)	Grade III/IV AEs
ICE	65	88%	26%	Thrombocytopenia - 29% Febrile neutropenia - 13% Mobilization failures - 14% PRBC transfusions - 60% Platelet transfusions - 30%
DHAP	99	87%	21%	
GVD	91	70%	19%	
GDP	34	62%	9%	

ABVD, adriamycin, bleomycin, vincristine, dacarbazine; ICE, ifosfamide, carboplatin, etoposide; DHAP, dexamethasone, high dose cytarabine, cisplatinum; GVD, gemcitabine, vinorelbine, doxorubicin; GDP, gemcitabine, dexamethasone, cisplatin; PRBC, packed red blood cells; RR, response rate; CR, complete response; AEs, adverse events

Moskowitz CH. *Blood*, 2001; 97: 616-623
Josting A. Ann Oncol, 2005; 16: 116-123
Kuruvilla J. *Cancer*, 2006; 106: 353-360
Bartlett NL. *Ann Oncol*, 2007; 18: 1071-1079

BACKGROUND (2)

- Brentuximab vedotin e bendamustina sono farmaci dotati di un ruolo rilevante nella terapia di salvataggio dei pazienti con linfoma di Hodgkin:
  - sono entrambi attivi come agenti singoli;
  - tasso di risposte complete con brentuximab: 34%

    Younes A. *J Clin Oncol*, 2012; 30: 2183-2189

  - tasso di risposte complete con bendamustina: 29-33%

    Anastasia A. *Blood (ASH annual meeting abstr)*, 2012; 120: 3652a
    Corazzelli G. *Br J Haematol*, 2013; 160: 207-215
    Moskowitz AJ. *J Clin Oncol*, 2013; 31: 456-460

  - hanno meccanismi d'azione differenti;
  - mostrano un favorevole profilo di tossicità.

Lacasce aggiungere

Bendamustina-Brentuximab

Phase I: Safety (n = 10)
- **Bendamustine IV, 90 mg/m^2 d1,2**
- **B-vedotin IV, d1, 1.8 mg/kg q3wk up to 6 cycles**

Phase II: Expansion (n = 40)
- **Bendamustine IV at selected dose**
- **B-vedotin, 1.8 mg/kg**

Best response	**n = 48**
Objective response rate	46 (96%)
Complete remission	40 (83%)
Partial remission	6 (13%)
Stable disease	1 (2%)

- Majority of complete remissions (34/40) achieved at Cycle 2 restage
- Stem cell mobilization and collection (n = 33)
  - Median CD34+ cell yield (cells/kg): 4.0 x 10^6 (range 1.7-11.8) in a median of 2 apheresis sessions (range 1-5)
  - Median time to platelet and neutrophil engraftment <2 weeks

* De-escalated if ≥4/10 patients had dose-limiting toxicity during cycle 1

LaCasce A et al. *Proc ASH* 2014;Abstract 293.

OBIETTIVI DELLO STUDIO

- **Obiettivo primario**: effetto antitumorale della combinazione bendamustina + brentuximab vedotin (BBV) in termini di risposta globale, quando applicata come terapia di primo salvataggio nei pazienti con linfoma di Hodgkin (o linfoma a cellule T periferiche), $CD30^+$.

- **Obiettivi secondari**: sicurezza e tollerabilità del regime BBV; sopravvivenza dei pazienti e miglioramento clinico (riduzione della sintomatologia linfoma-correlata).

- ***Endpoint* primario**: tasso globale di risposta (*overall response rate*, ORR) .

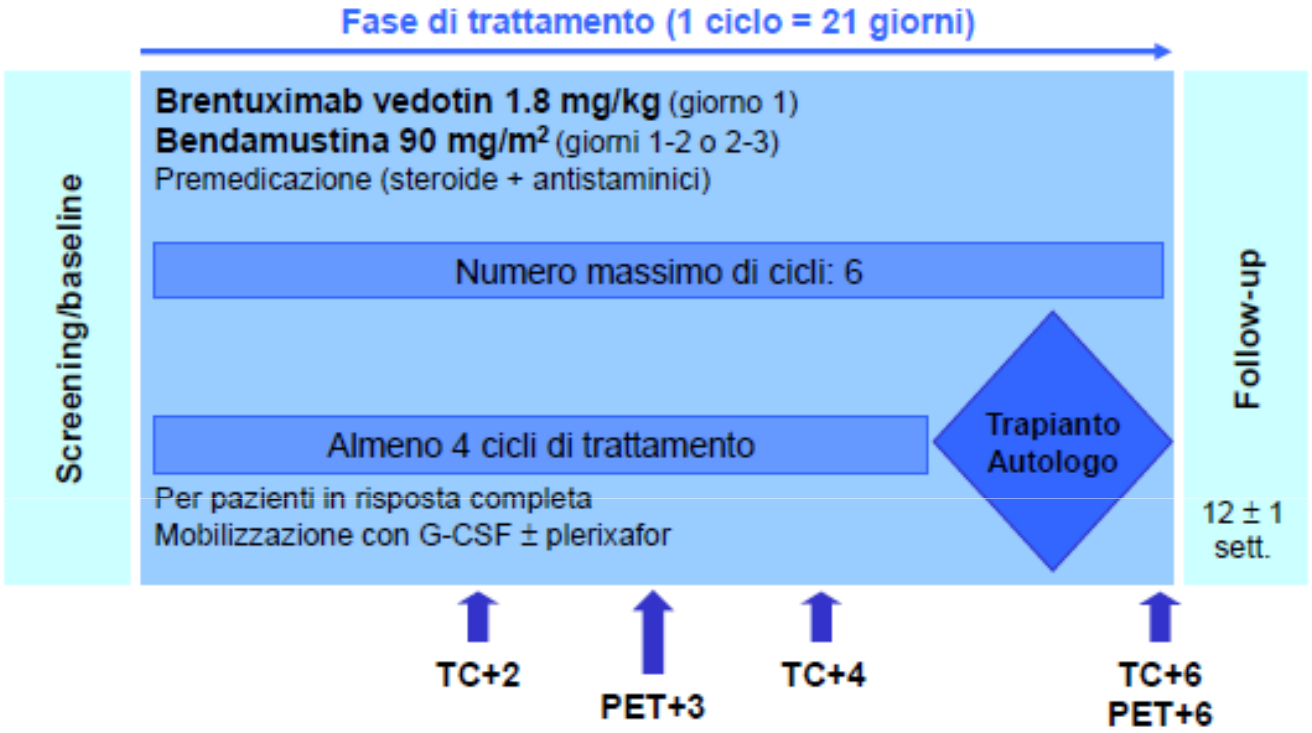
- ***Endpoints* secondari**: durata di risposta (DOR), tasso di risposta completa (CR rate), sopravvivenza globale (*overall survival*, OS) e sopravvivenza libera da progressione (*progression-free survival*, PFS) a 1 anno.

CRITERI DI INCLUSIONE

- Diagnosi di linfoma di Hodgkin, in prima ricaduta o refrattario ad una sola precedente linea di trattamento.
- Malattia $CD30^+$.
- Età compresa tra 18 e 60 anni (*).
- Malattia misurabile in TC (linfonodi: Ø massimo > 1,5 cm oppure asse lungo compreso tra 1,1 e 1,5 cm e asse corto > 1 cm) e FDG-PET-positiva.
- ECOG ≤ 1.
- Laboratorio: neutrofili ≥ 1.500/mmc, piastrine ≥ 75.000/mmc, bilirubina e creatinina sieriche ≤ 1,5 × ULN, AST/ALT ≤ 2,5 × ULN, albumina ≥ 3 g/dL.
- Adeguate misure contraccettive.

(*) Emendamento n° 1, v. 05/01/2016

PROTOCOLLO DI TRATTAMENTO



Problematiche

- Rash cutaneo
  Premedicazione obbligatoria (steroide+antistaminici).
  Infusione separata

- Mobilizzazione cellule staminali periferiche

STATUS ARRUOLAMENTO

Centro	Attivazione	Linfoma di Hodgkin	Pazienti totali (*)
Bologna	Sì	5 (+1 out)	7
Brescia	Sì	6	6
Milano (INT)	Sì	5	6
Napoli (Pascale)	Sì	3	4
Torino	Sì	9	9
Niguarda	Sì	0	0
Rozzano	Sì	0	0
TOTALE		**28**	**32**
Previsti		**40**	**40 + 25**

(*) Comprende i pazienti con linfoma a cellule T periferiche

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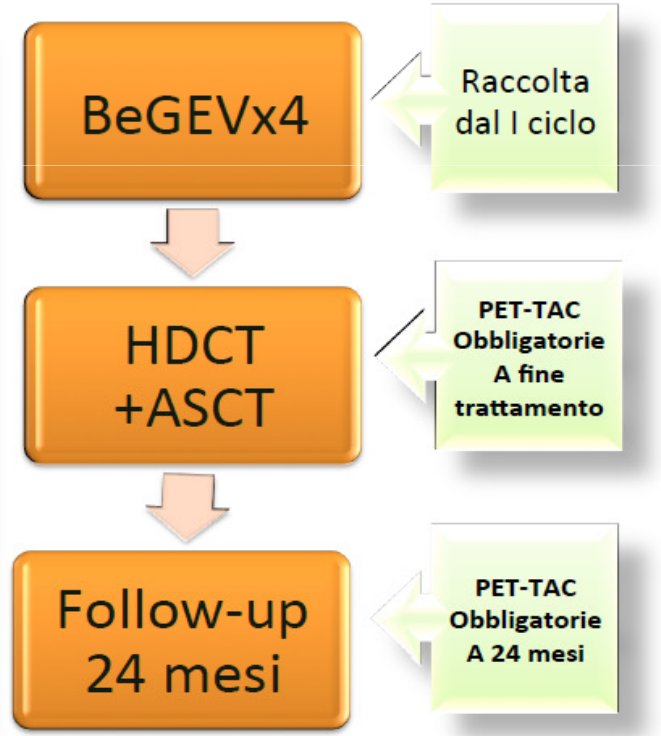
BeGEV x 4 cicli ogni 21 giorni

G. 1: Gemcitabina 800mg/mq, Vinorelbina 20mg/mq

G. 2: Bendamustina 90mg/mq

G. 3: Bendamustina 90mg/mq

G. 4: Gemcitabina 800mg/mq



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	N° (59 total)	%
Median age	33 (18-68)	
Male	31	53
Relapse		
< 1 year	22	37
>1 year	10	17
Refractory	27	46
ABVD	56	95
BEACOPP	3	5
Extranodal	24	41
RT	9	15

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	CR		PR		SD/PG		NE	
Relapse	27	84%	3	9%	1	3%	1	3%
Refractory	16	59%	3	11%	8	30%	0	0%
Total	43	**73%**	6	**10%**	9	16%	1	1%

ORR 83%

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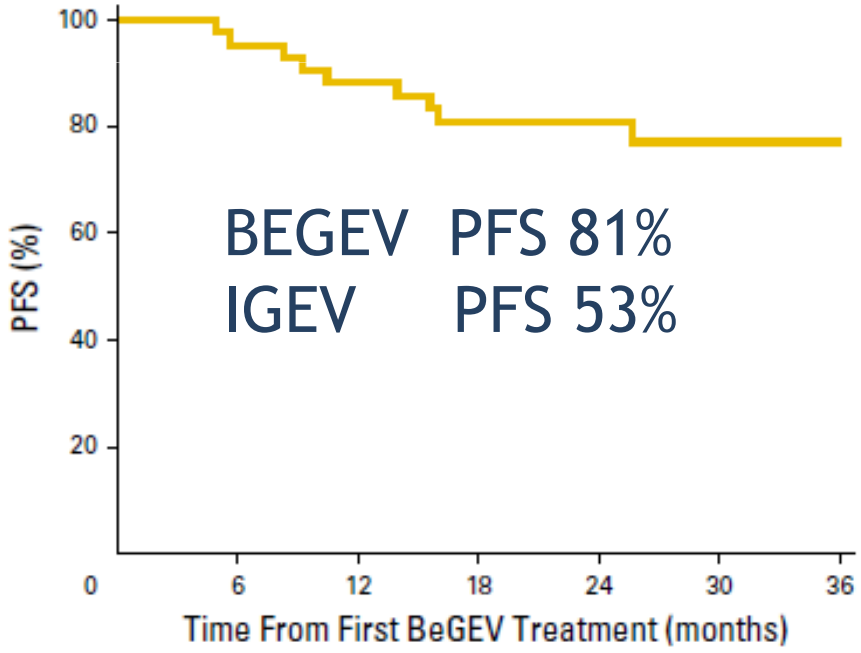

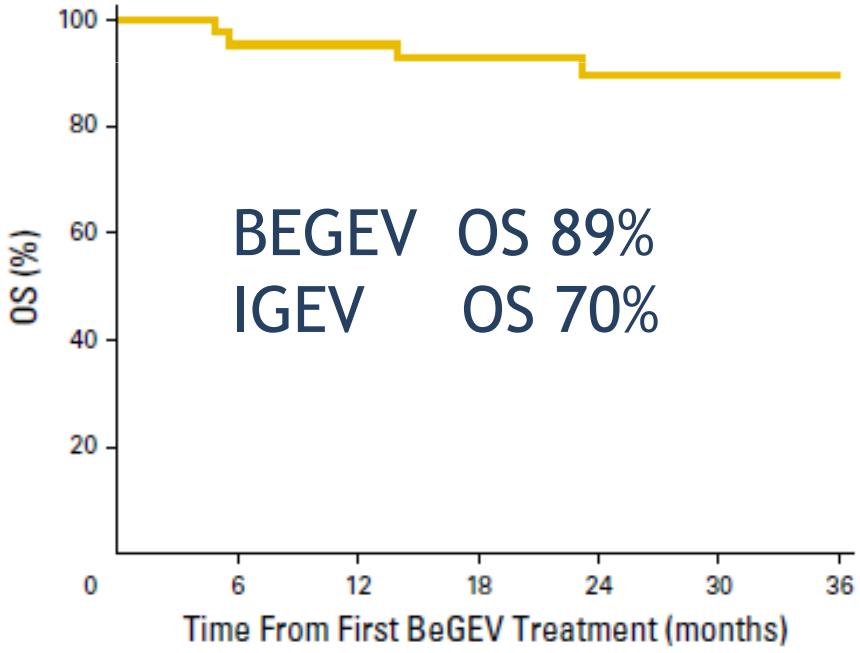

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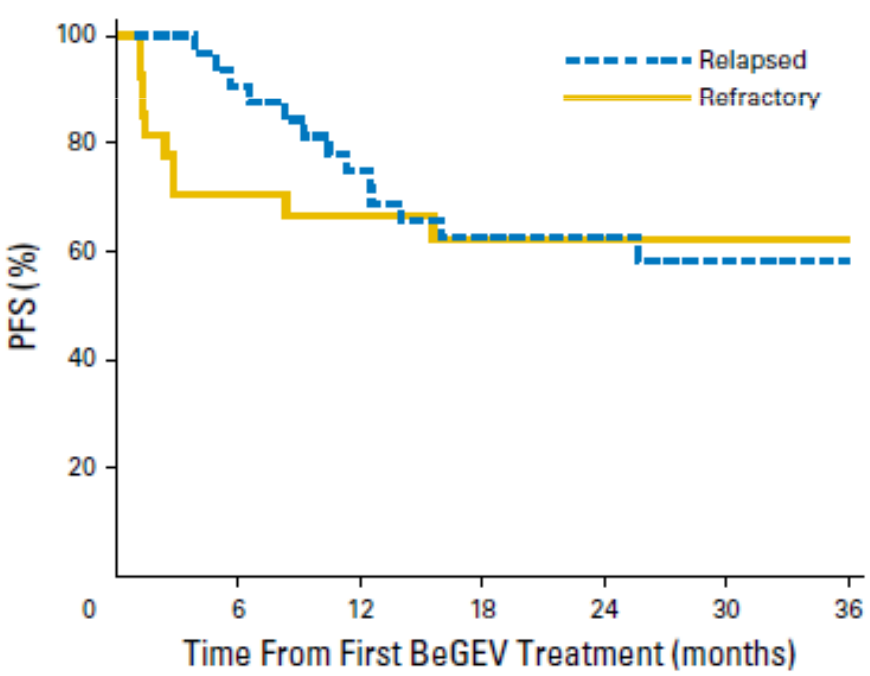

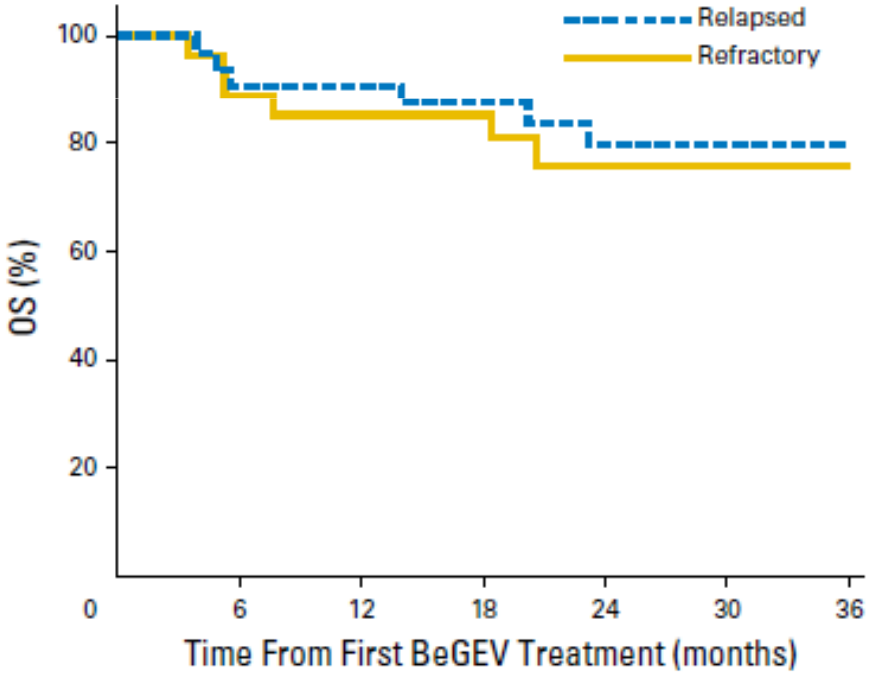

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	Grade III-IV	%
Anemia	2	3
Neutropenia	8	14
Thrombocitopenia	8	14
Transaminitis	2	3
Febrile neutropenia	7	12
Infections	4	7

Santoro et al, J Clin Oncol 2016

A Phase III, Randomized, Open-Label, Clinical Trial to compare Pembrolizumab (MK-3475) with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin's Lymphoma (KEYNOTE 204)

Have relapsed or refractory (failure to achieve CR or PR to most recent therapy) classical HL *and meet **one of the following criteria**:*

a. Have failed to achieve a response or progressed after auto-SCT. Subjects must not have had previous treatments with brentuximab vedotin.

b. Are not auto-SCT candidates due to chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy), advanced age, or comorbidities. Subjects must have received at least 2 prior multi-agent chemotherapy regimens that did not include brentuximab vedotin.

Subjects who have had a transplant greater than 5 years ago are eligible as long as no symptoms of graft-versus-host disease (GVHD).

A Phase III, Randomized, Open-Label, Clinical Trial to compare Pembrolizumab (MK-3475) with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin's Lymphoma (KEYNOTE 204)

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period
Pembrolizumab	200 mg	1 dose on Day 1 of every 3 weeks = 1 cycle	Intravenous infusion	Up to 35 cycles per subject
Brentuximab vedotin	1.8 mg/kg (maximum 180 mg per dose)	1 dose on Day 1 of every 3 weeks = 1 cycle	Intravenous infusion	Up to 35 cycles per subject