ABVD versus BEACOPP arguments for ABVD

Dr Pauline BRICE

Hôpital saint louis Université Paris VII PARIS

DISCLOSURES

- HONORARIAS: Takeda, roche
- GRANT RESEARCH : Millenium Takeda, AMGEN

ABVD the standard chemotherapy

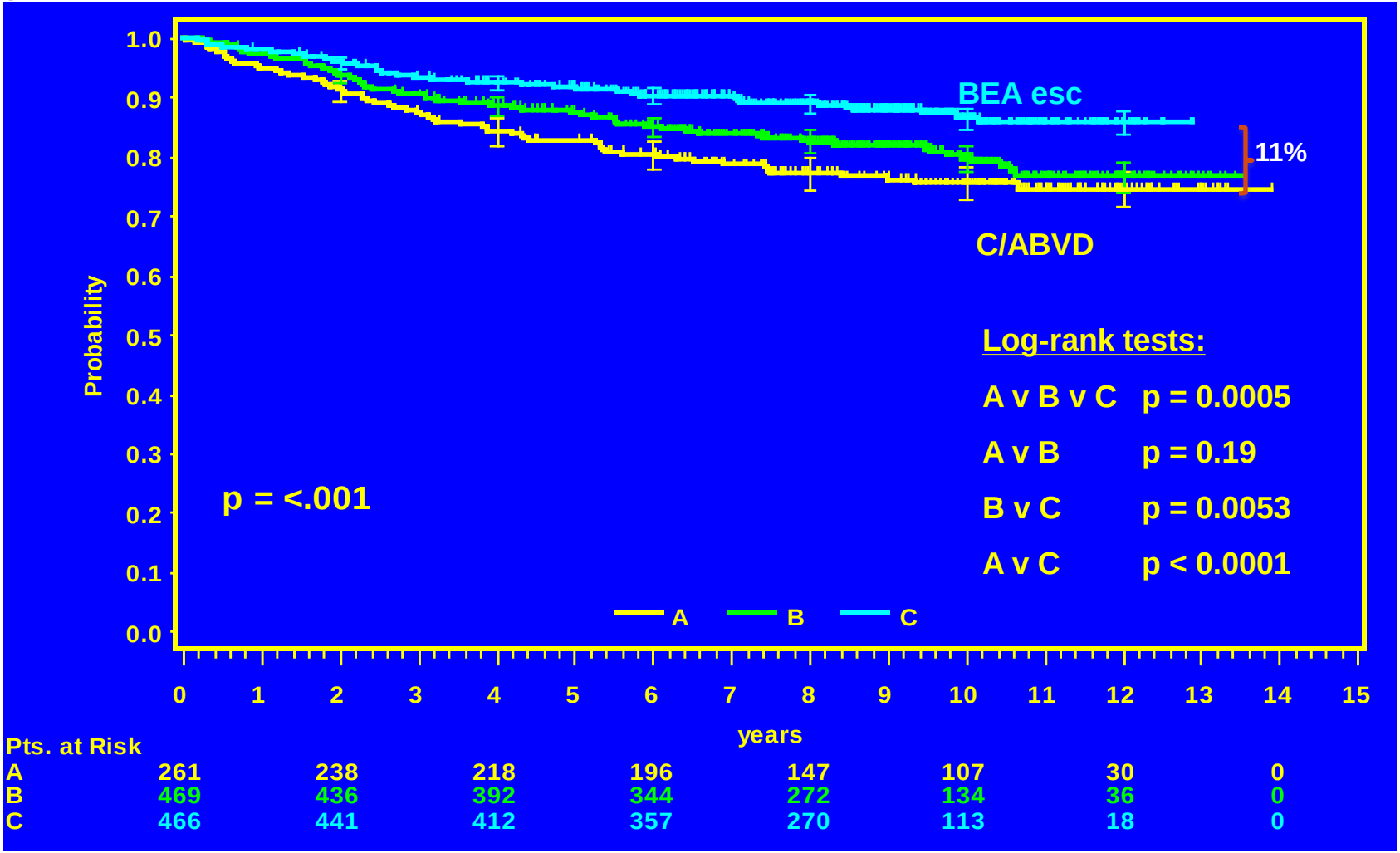
ABVD (Adriamycin, bléomycin, vinblastin, dacarbazine D1D15)

- superior to MOPP (Canellos, NEJM 1992)

- equivalent to MOPP/ABV:, **(5 years EFS and OS in both arms : 63 & 66% and 82 & 81%)**
  with less toxicity(e.g. secondary tumors) (Duggan, JCO 2003)

HD9 (Stage IIB-IV)– esc BEACOPP

10 years survival



Diehl NEJM 2003 Engert JCO 2009

HD9 : secondary tumors

	COPP/ABV n (%)	$BEACOPP_s$ n (%)	$BEACOPP_E$ n (%)
LAM/MDS	1 (0.4%)	4 (0.8%)	9 (1.9%)
LNH	7	4	5
tumeurs solides	3	8	2
au total	11 (4.2%)	16 (3.4%)	16 (3.2%)

Diehl, NEJM 2003

Hodgkin lymphoma
Stages IIB-IV ABVD vs escBEACOPP italian studies

		n	IPS		CR	3y-PFS	3y-OS
			0-2	3-7			
VIVIANI NEJM 2011	ABVD x 6-8	168	46%	54%	76%	**73%***	91%
	eBEACOPP 4+4	163	45%	55%	81%	**85%***	90%
HD2000 (Federico JCO 09)	ABVD x 6	99	70%	30%	70%	**73%****	92%
	eBEACOPP 4+2	98	57%	43%	81%	**90%****	91%

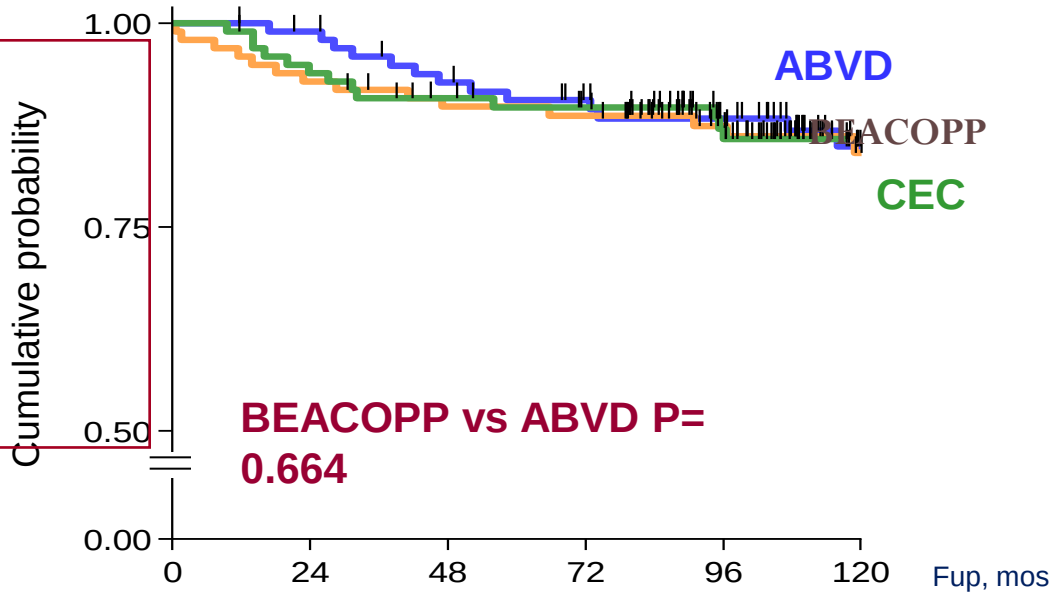
* p= .01
** p = .036

HD2000 Study Update: OS

10-yrs OS:

- **ABVD n = 103 84%**
- **BEACOPP n = 102 84%**
- **CEC n = 102 86%**

P=0.883



median fup: 119 mos (range 1-169)

Federico et al ASH 2014

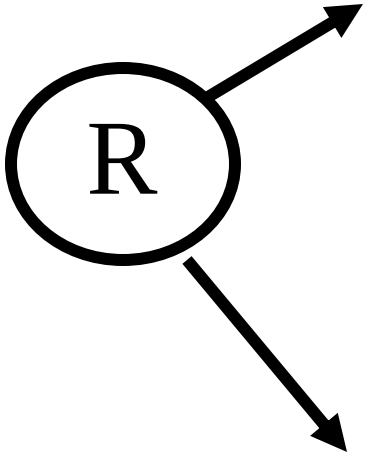
HD2000 Study Update: deaths

Cause of Death	ABVD	BEACOPP	CEC	Total
Lymphoma	11	5	8	**24**
Toxicity *(I line)*	-	2	-	**2**
Toxicity *(II line)*	2	3	2	**7**
II neoplasia	-	5	3	**8**
Unknown	-	-	1	**1**
Total	13	15	14	**42**

BEA vs ABVD P= 0.664

Fup, mos

H3-4 protocol : Intergroup study GELA/EORTC (2002-2010)



4 ABVD + 4 ABVD

8 courses without RT if a partial response >50% was observed after 4 cycles and a CR/CRu after 6 cycles

4 escBEACOPP + 4 BEACOPP

Flow of patients: stage III/IV IPS 3+

550 patients randomized

549 patients randomized with IC

275 assigned to ABVD

272 started ABVD

- **43 discontinued**
- **229 completers (84%)**

274 assigned to BEACOPP

267 started BEACOPP

- **49 discontinued**
- **218 completers (81%)**

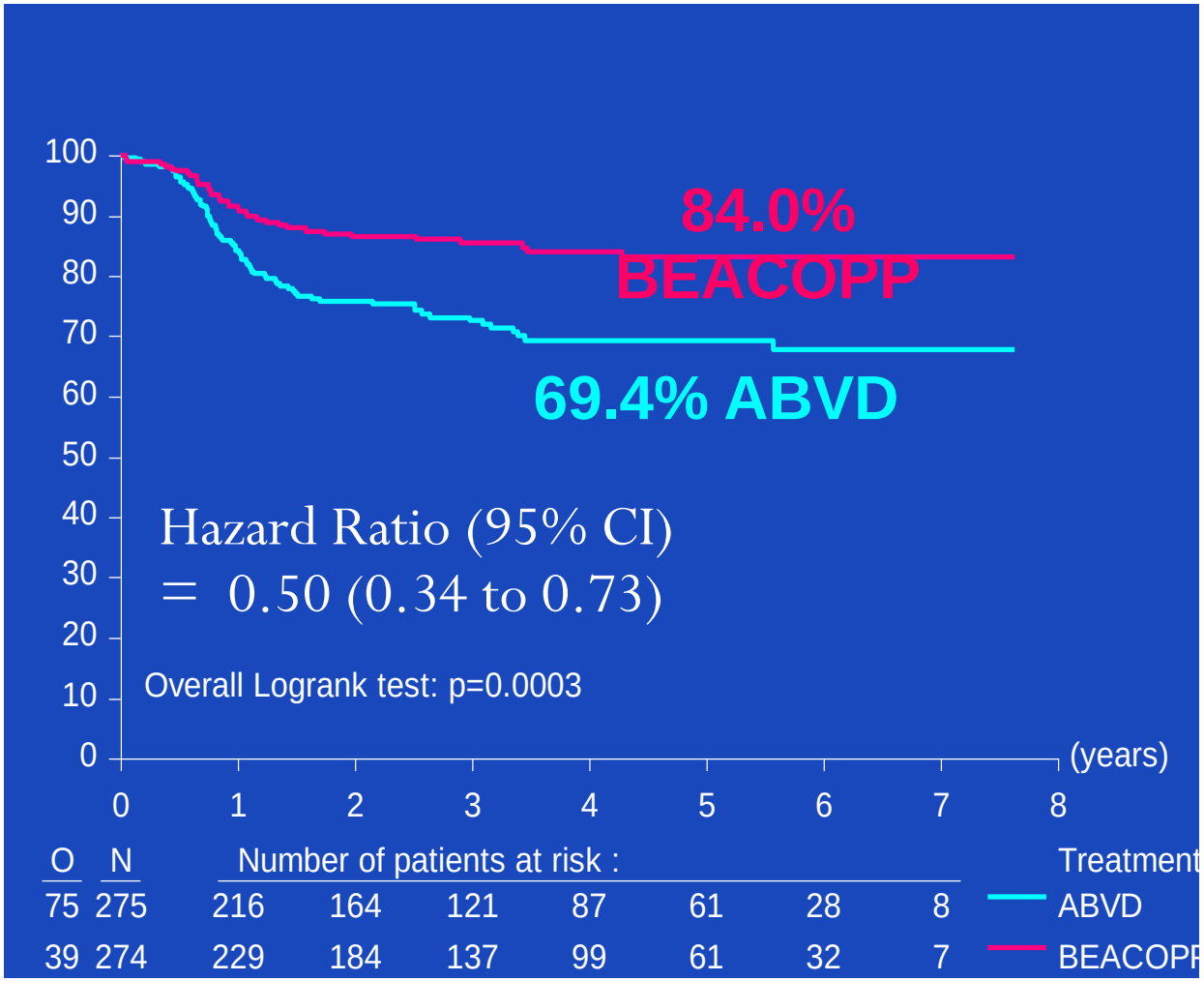
Carde et al ASCO 2012
submitted 2015

primary endpoint – Event-Free Survival

first event	ABVD (N=275) n (%)	BEACOPP (N=274) n (%)
early discontinuation	37 (13.5)	49 (17.9)
no CR/CRu after 8 cycles	39 (14.2)	38 (13.9)
progression/relapse	39 (14.2)	16 (5.8)
death	6 (2.2)	9 (3.3)

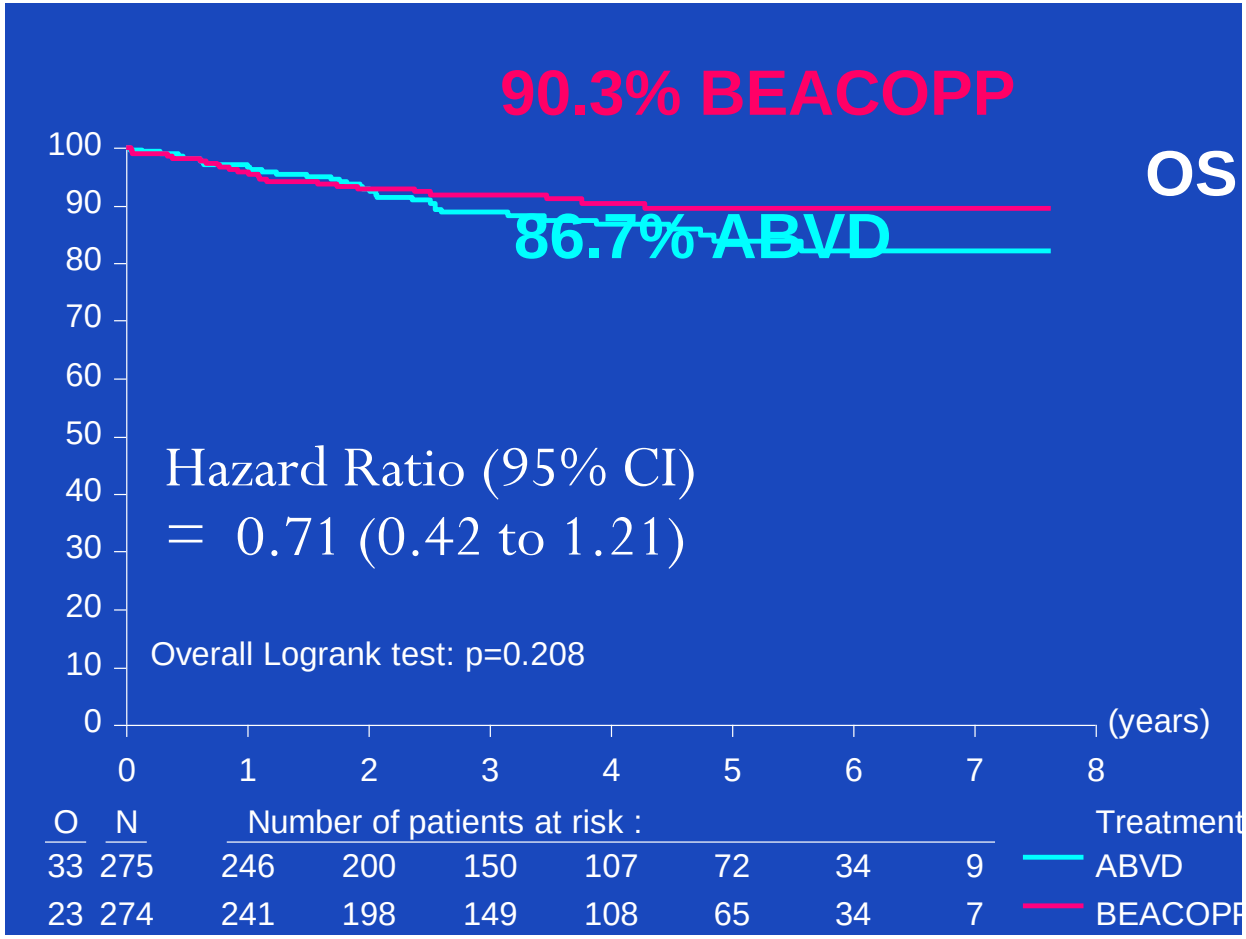
Carde et al ASCO 2012
submitted 2015

4 y Progression Free Survival IPS 3+



Carde et al ASCO 2012 submitted 2015

Overall Survival stage III/IV IPS 3+



Carde et al ASCO 2012

cause of deaths

	ABVD (N=275) n (%)	BEACOPP (N=274) n (%)
DEATHS	33 (12.0)	23 (8.4)
HL	15 (5.5)	7 (2.6)
secondary hematological or solid tumor	2 (0.7)	4 (1.5)
toxicity including toxic death*	9 (3.3)	6 (2.2)
intercurrent infectious disease	2 (0.7)	3 (1.1)
intercurrent cardiovascular disease	1 (0.4)	1 (0.4)
other	2 (0.7)	2 (0.7)
unknown	2 (0.7)	0 (0.0)

6 and 5 deaths due to toxicity occurred within treatment + 3 months

Carde et al ASCO 2012 submitted 2015

The standard treatment for advanced stages: ABVD 6 cycles is enough

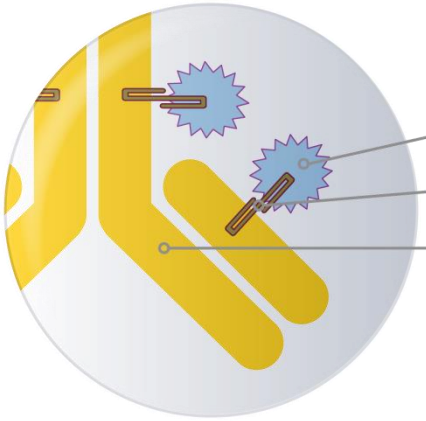
ABVD 6 cycles if a PET CR is obtained after 4 cycles (Aleman NEJM 2003) to avoid the excess of cardiopulmonary toxicity observed after 8 cycles

→ 50 % of the 30% relapsed after ABVD are cured with high dose therapy and ASCT and avoid excess of BEACOPP toxicity in 70% of patients

→ fertility is preserved in 70% of patients

HOW TO IMPROVE ABVD WITHOUT INCREASING TOXICITY ?

Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin antibody-drug conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

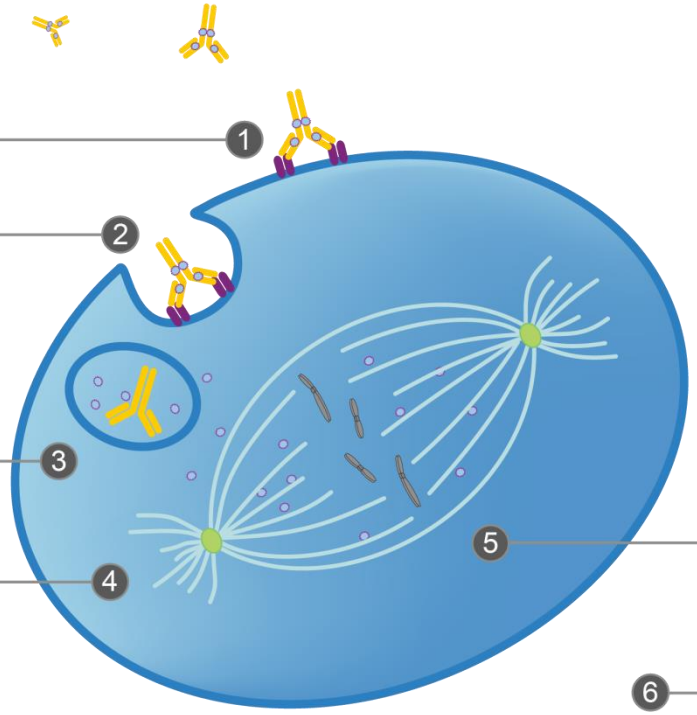
Anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex is internalized and traffics to lysosome

MMAE is released

MMAE disrupts microtubule network



G2/M cell cycle arrest

Apoptosis

PHASE I ABVD AND BV in advanced stages

dose at 0,9 than 1,2 mg/kg Bléomycin toxicity +++

	BV + ABVD n = 25	BV + AVD n = 26
Age médian	35 [19-59]	33 (18-58]
Sexe H/F	20/5	17/9
Stade IIB ou bulky III ou IV	4 21	7 16
bulky	5	12
IPS >3	7	6

Younes Lancet Oncol 2013

PHASE I ABVD AND BV

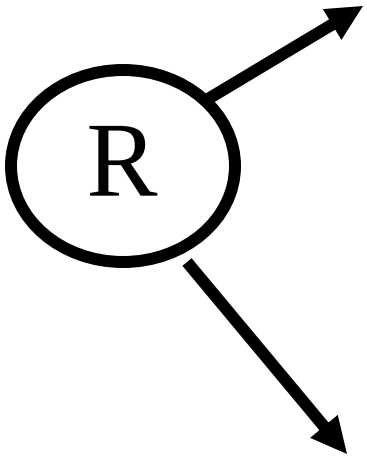
Résults & toxicity

	BV + ABVD n = 25	BV + AVD n = 26
Pulmonary toxicity	44%	0
negative PET 2	100%	92%
End of tt CR	95%	96%
failure	0	1
Toxic death relapses FFS	2 3 (9 -22 -23 mo) 79%	0 2 (7- 22 mo) 92%

Younes Lancet Oncol 2013

Connors ASH 2014

Echelon 1 Clinical Study Protocol C25003(EudraCT: 2011-005450-60) Stage III/IV Hodgkin lymphomas



2 ABVD + 4 ABVD

↑

PET at 2 cycles continue if Deauville score 1-4

↓

2 A+AVD + 4 A+AVD

A: adcetris°
brentuximab vedotin

ECHELON 1: OBJECTIVES

Primary

☐ To compare the modified progression-free survival obtained with brentuximab vedotin plus AVD (doxorubicin [Adriamycin], vinblastine, and dacarbazine; abbreviated A+AVD) versus that obtained with ABVD (doxorubicin ,Adriamycin, bleomycin, vinblastine, and dacarbazine) for the frontline treatment of advanced classical Hodgkin lymphoma (HL) (> 1000 patients to be included)

CONCLUSION: ABVD versus esc BEACOPP

- Lower initial toxicity (6 cycles)
- Preservation of fertility
- Fewer second cancer
- Survival (86%)
- Better PFS
- Less refractory
- Non significant better survival (90%)

→ Adcetris° -ABVD may have same results as escBEACOPP with less toxicity