EVENTO REL
Rete Ematologica Lombarda

Immunoterapia nel Mieloma Multiplo e nel Linfoma di Hodgkin

MILANO
9 Novembre 2017

Linfoma di Hodgkin
Trattamento dei pazienti ricaduti

ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

Simonetta Viviani

SC Ematologia e Trapianto di Midollo osseo

Dichiarazione

Relatore: Simonetta Viviani

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Takeda)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Italfarmaco, Takeda International)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro: contributo per partecipazione a congressi (Teva, Takeda)

Background

- 1.584 new cases/year in Italy :

- 1 st line therapy: 90- 75% Cure, 10%-25% relapsed/refractory after ABVD

  - 2 nd line therapy: CR: 25-35%, ORR 70-80%

    - CR-----Auto-SCT: 45-50% Cure– Majority of pts will relapse in the first year after ASCT

  - ≥ 3 rd line therapy---Auto/Allo-SCT: 30-40% Cure

    - 70% PD/Relapse---Clinical Trial/ Allo-SCT/ BSC

- 422 deaths/year in Italy

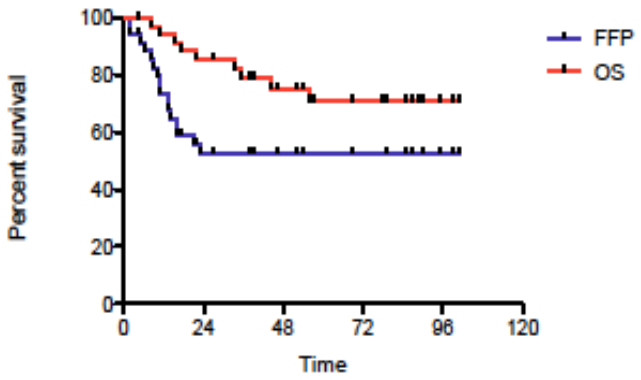
Risk factors for ASCT outcome

Primary refractory

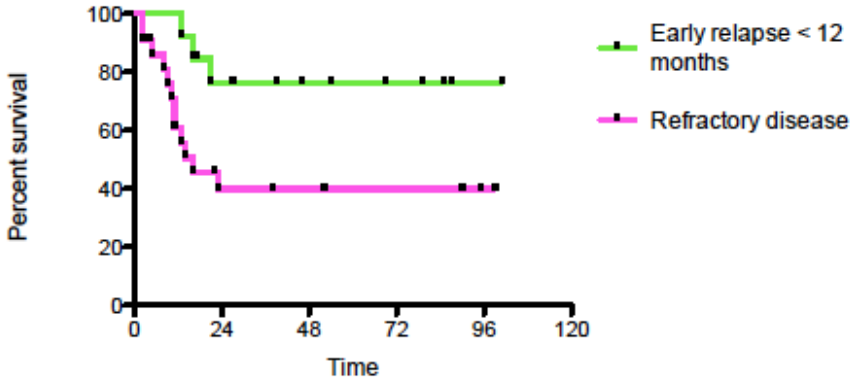
Early Relapse

TTFR ≤ 3 months

Outcome of R/R HL after IGEV + ASCT at Istituto dei Tumori Milano



3-year FFP and OS



3-year FFP in early relapse vs refractory

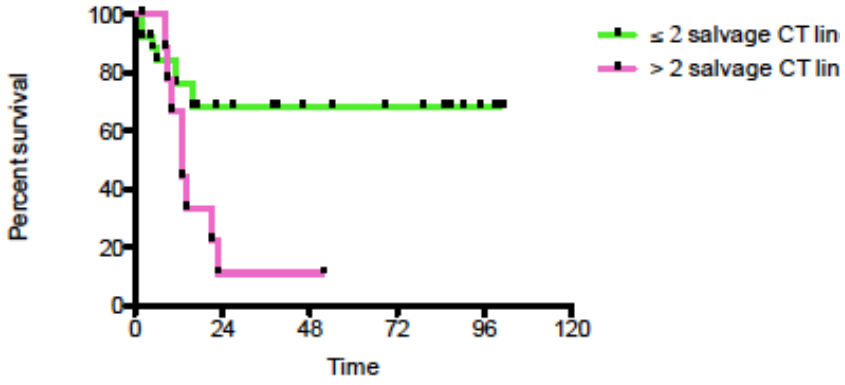
Viviani S, unpublished data

Risk factors for ASCT outcome

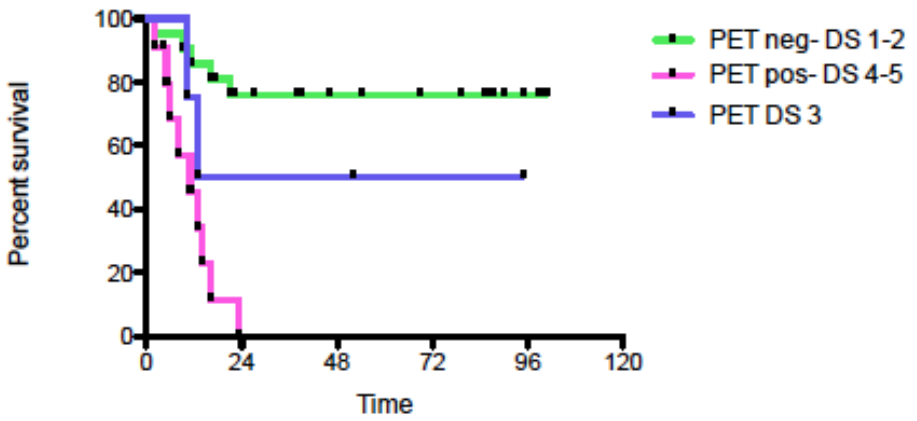
Chemorefractory to pre-ASCT salvage therapy

- **≥ 2 prior salvage regimens**
- **Residual disease at ASCT (PET positive or < PR by CT)**

3-yr FFS according number of salvage CT lines : > 2 vs ≤ 2



3-Year FFS according to PET pre-ASCT



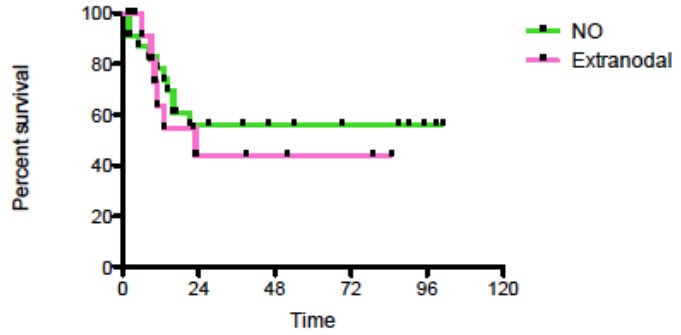
Viviani S, unpublished data

Risk factors for ASCT outcome

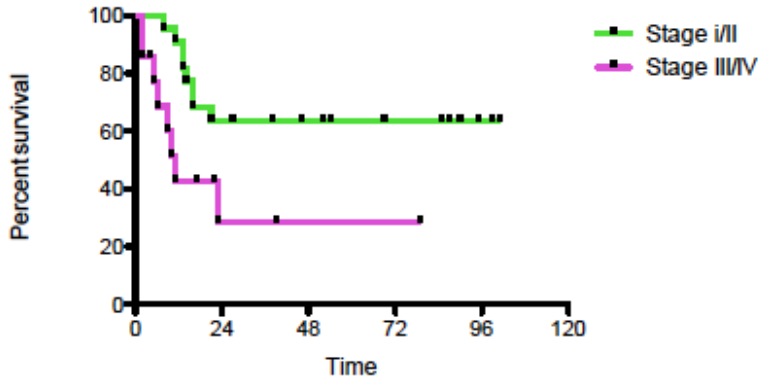
At PD/Relapse: Bulky ≥ 5cm ;

Extranodal disease, Stage IV;
ECOG ≥ 1; B Symptoms,

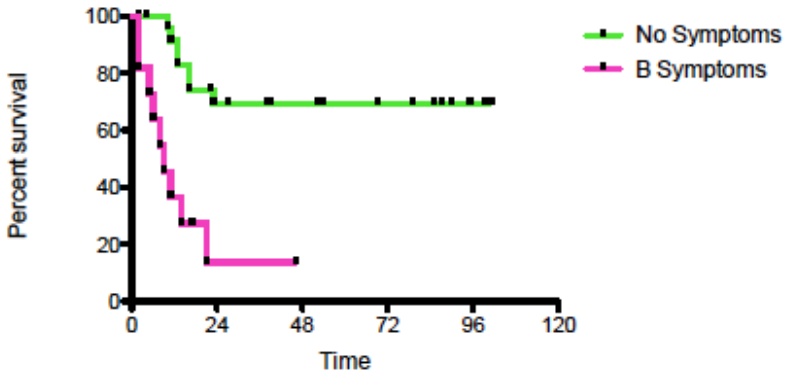
3-year FFS according to extranodal vs nodal only disease



3-Year FFP according to Stage III/IV versus I/II

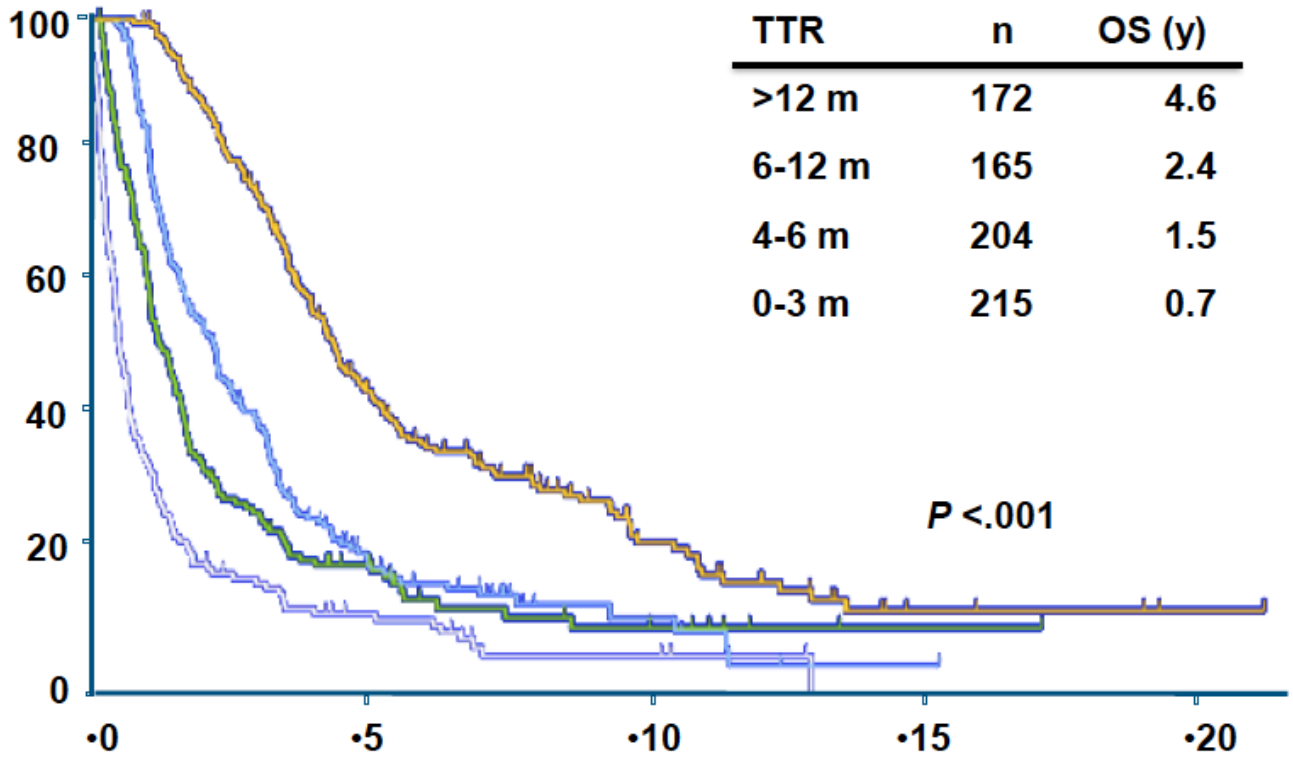


3-Year FFS according to B symptoms at relapse/progression



Viviani S, unpublished data

Survival after autoSCT fialure
(before introduction of Brentuximab Vedotin and/or checkpoint inhibitors)



TTR, time to relapse; OS, overall survival

Arai S, et al.Leukemia Lymphoma 2013; 54:2531-3

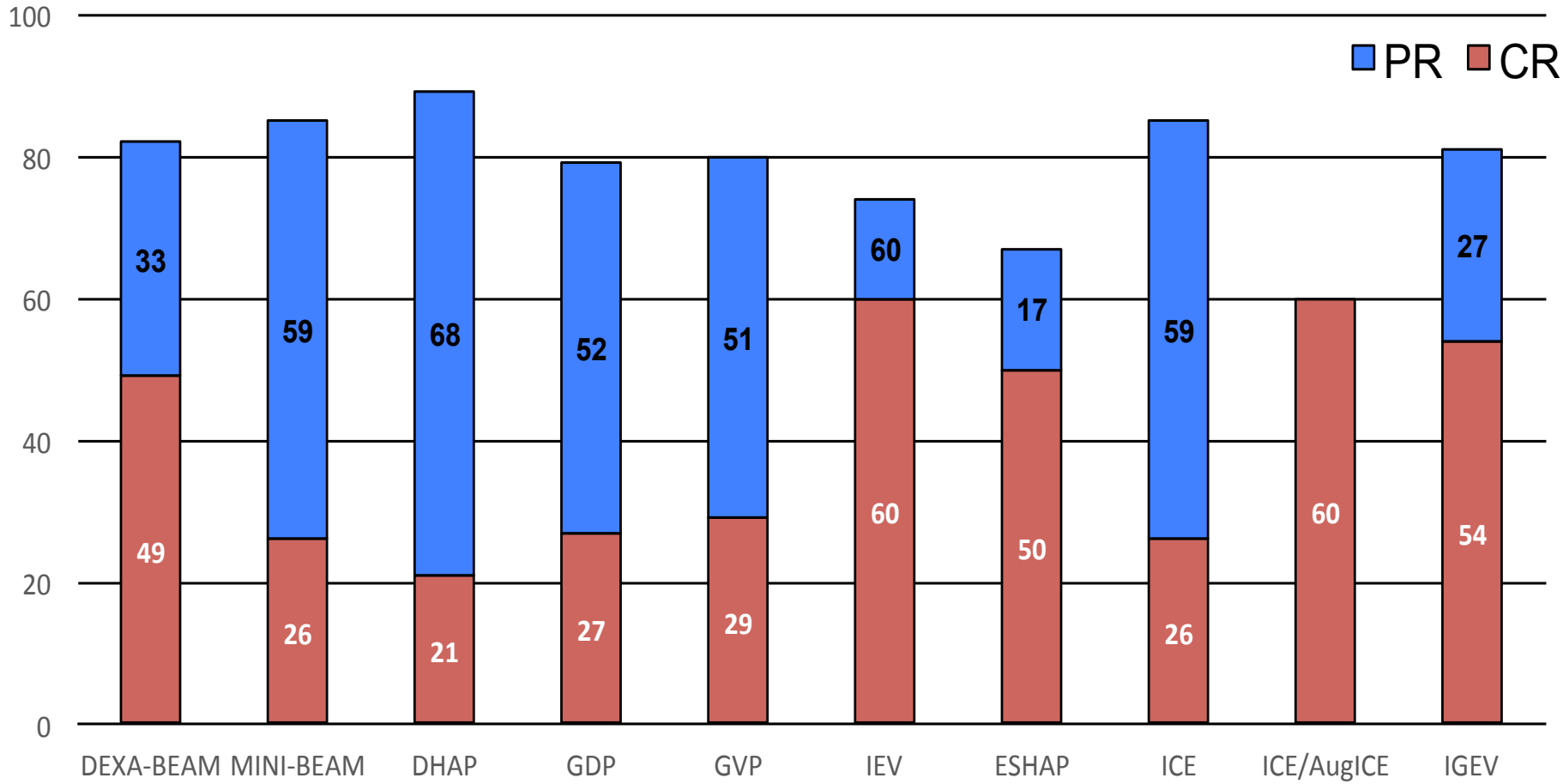
How can we improve ASCT outcome ?

- ❑ Better first salvage therapy
- ❑ New drugs-combinations including new drugs
- ❑ Post-ASCT maintenance therapy
- ❑ RT consolidation
- ❑ Tandem autologous transplant

Induction chemotherapy prior to transplant in R/R HL

Goals:

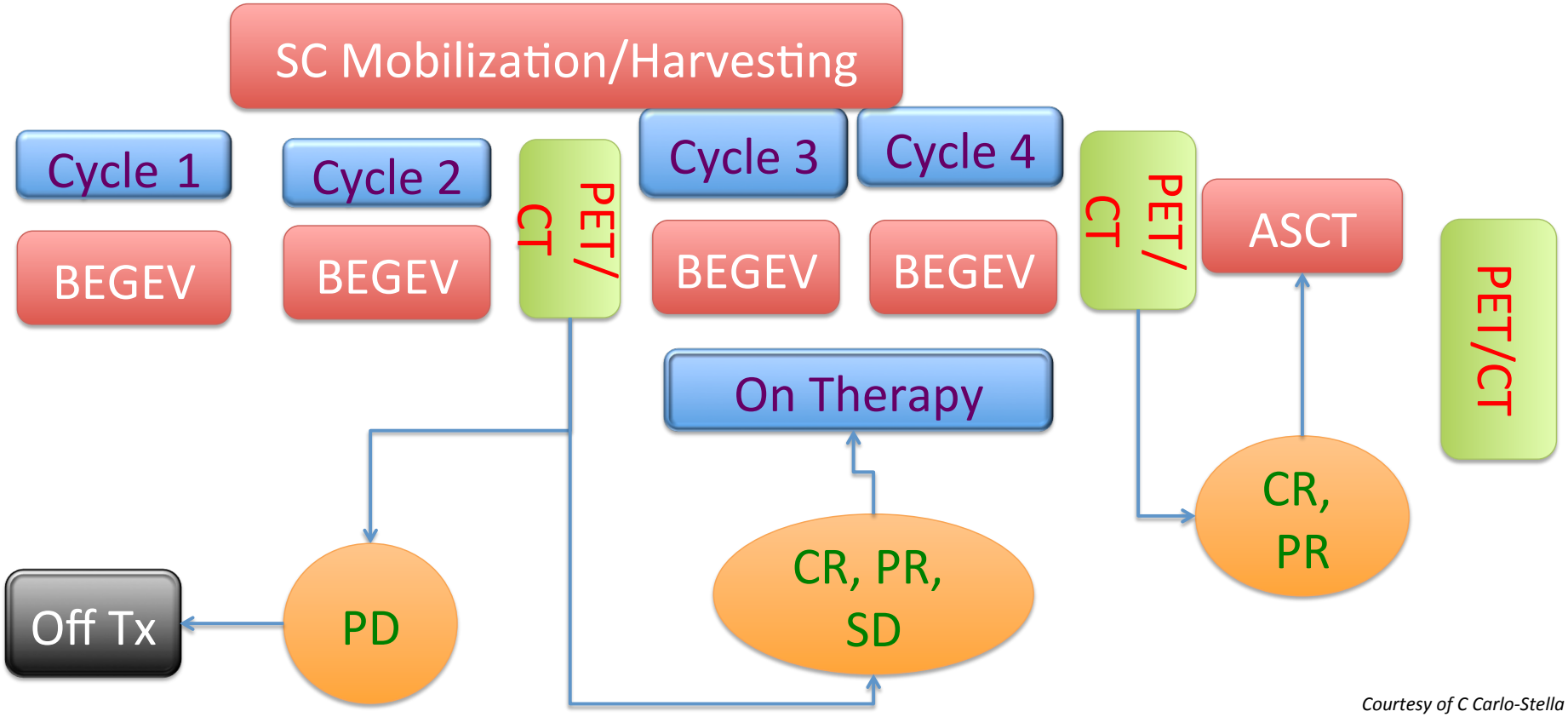
- Achieve CR= negative pre-ASCT PET;
- Mobilize PBSC
- Minimize toxicity



BeGEV chemotherapy before ASCT in R/R HL

Day	Medication	Dose
1 + 4	Gemcitabine	800 mg/sqm
1	Vinorelbine	20 mg/sqm
2 + 3	Bendamustine	90 mg/sqm

Cycles every 21 days



Courtesy of C Carlo-Stella

Patient demographic and clinical characteristics (n = 59)

Characteristic	No.	%
Age, years		
Median	33	
Range	18-68	
Sex		
Male	31	53
Female	28	48
Response to primary therapy		
Relapsed disease	32	54
CR < 1 year	22	37
CR ≥ 1 year	10	17
Primary refractory	27	46
Extranodal sites of disease		
Yes	24	41
No	35	59
Prior radiotherapy		
Yes	9	15
No	50	85
Prior chemotherapy		
ABVD	56	95
BEACOPP	3	5

Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

Clinical responses to BeGEV regimen according to ITT and disease status at entry

Parameter	No. of Patients	CR		PR	
		No.	%	No.	%
Response by ITT	59	43	73	6	10
Disease status at study entry					
Relapsed	32	27	84*	3	9
Refractory	27	16	59*	3	11

Parameter	No. of Patients	SD		PD		NE	
		No.	%	No.	%	No.	%
Response by ITT	59	1	2	8	14	1	2
Disease status at study entry							
Relapsed	32	1	3	0	0	1	3
Refractory	27	0	0	8	30	0	0

Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

Adverse events

Table 3

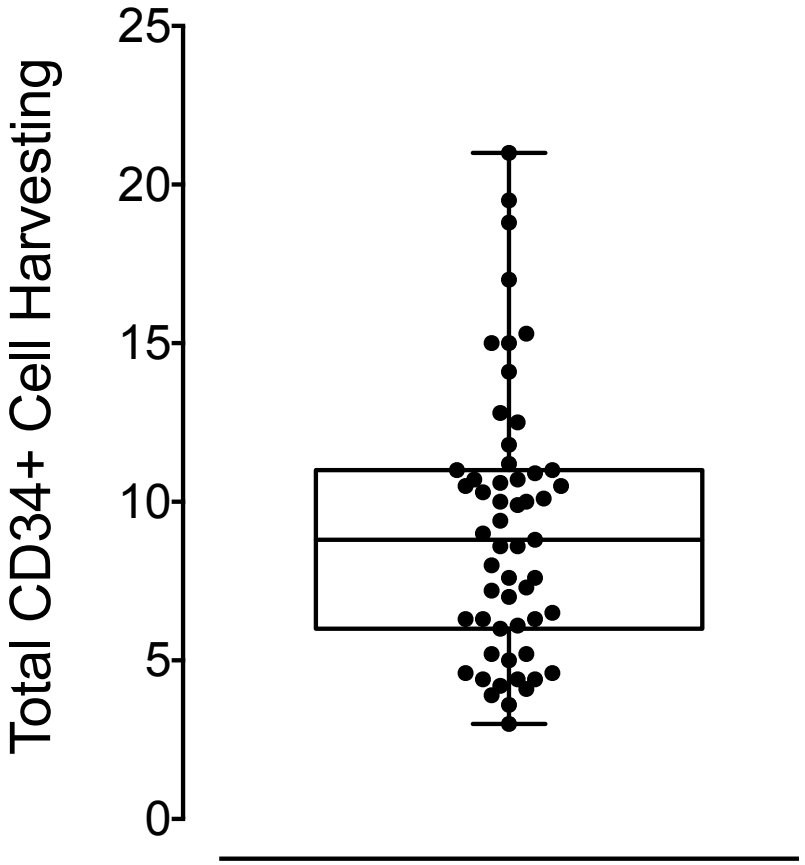
Toxicity	No. of Patients (%)	
	Grade 1 and 2	Grade 3 and 4
Anemia	3 (5)	2 (3)
Neutropenia	1 (2)	8 (14)
Thrombocytopenia	0 (0)	8 (14)
Febrile neutropenia	5 (8)	7 (12)
Infection	9 (15)	4 (7)
Nausea	10 (17)	4 (7)
Fatigue	5 (8)	0 (0)
Skin rash	6 (10)	0 (0)
AST/ALT increase	7 (12)	2 (3)

RBC transfusions were required by 14% (n = 8) and platelet transfusions by 5% of patients (n = 3), respectively.

Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

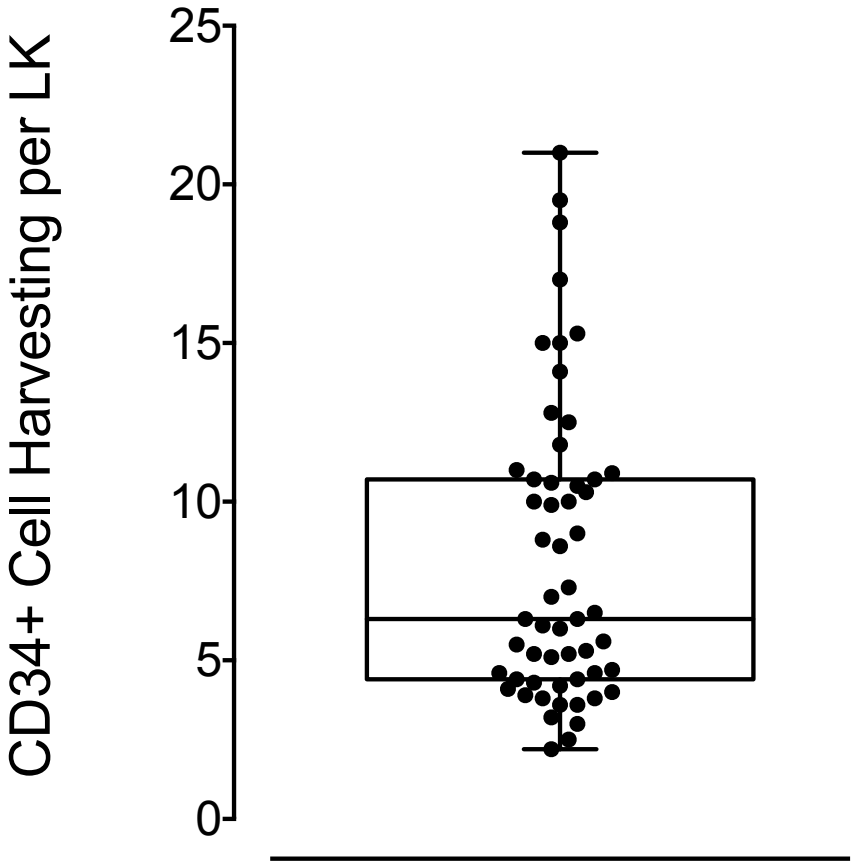
Stem cell harvest

Total CD34+ Cells



Median CD34+ cells/kg 8.8 x 10^6

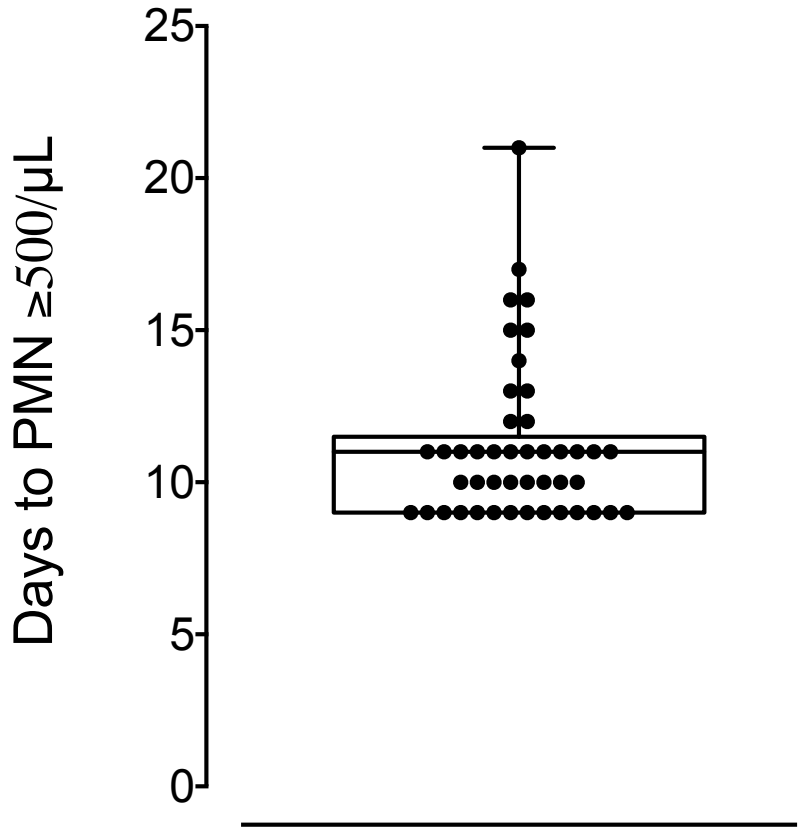
CD34+ Cells by LK



Median CD34+ cells/kg/LK 6.3 x 10^6

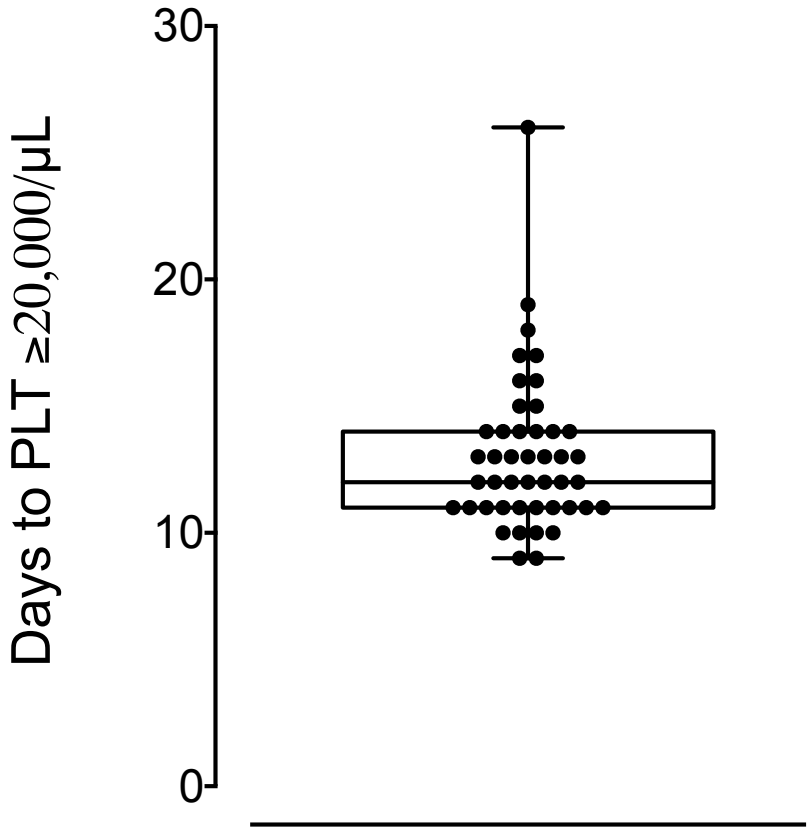
Engraftment

Days to ANC ≥500/μL



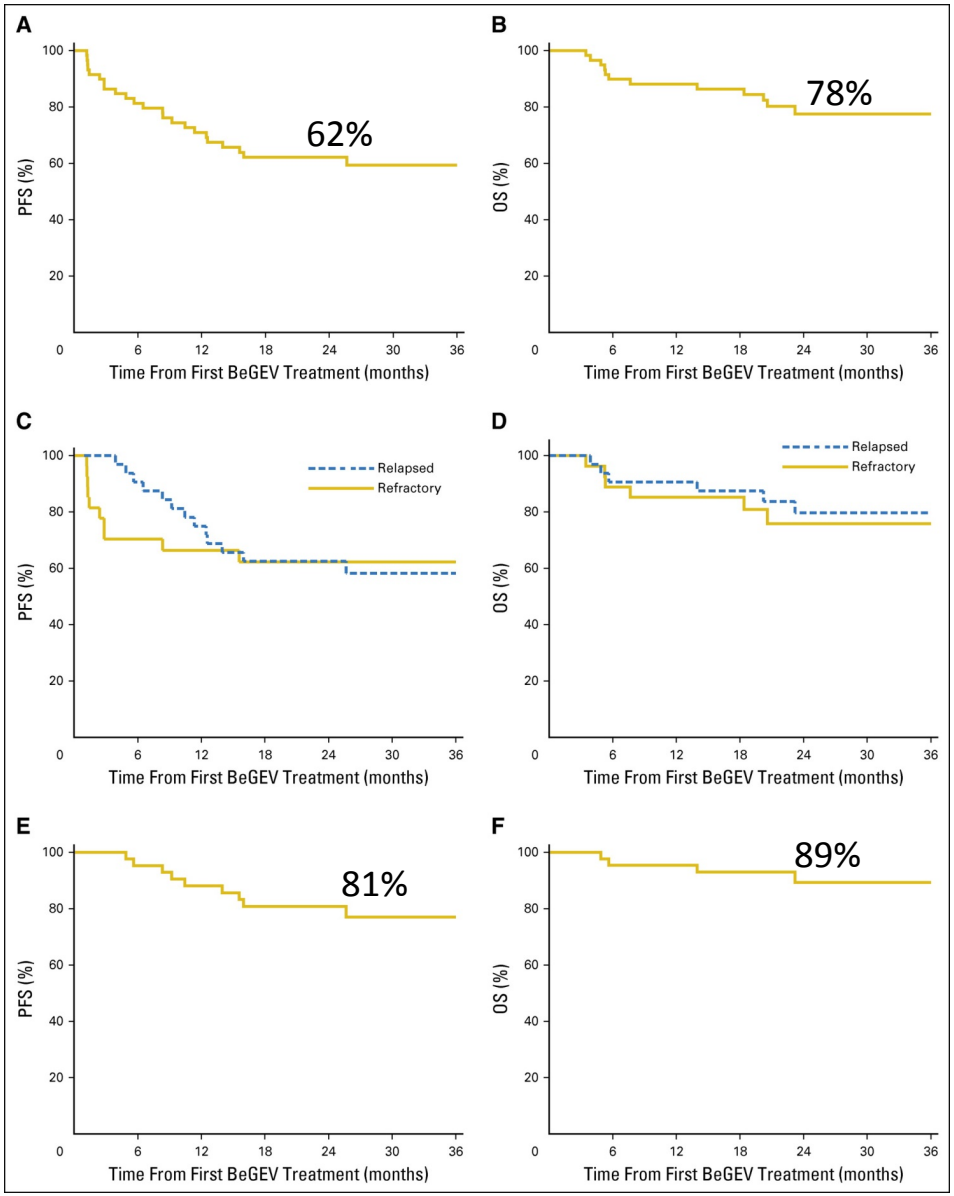
median 11 days (9 – 21)

Days to PLT ≥20,000/μL



median 12 days (9 – 26)

PFS and OS after BEGEV and ASCT



PFS and OS of the overall population

PFS and OS of patients with relapsed or refractory disease before BEGEV

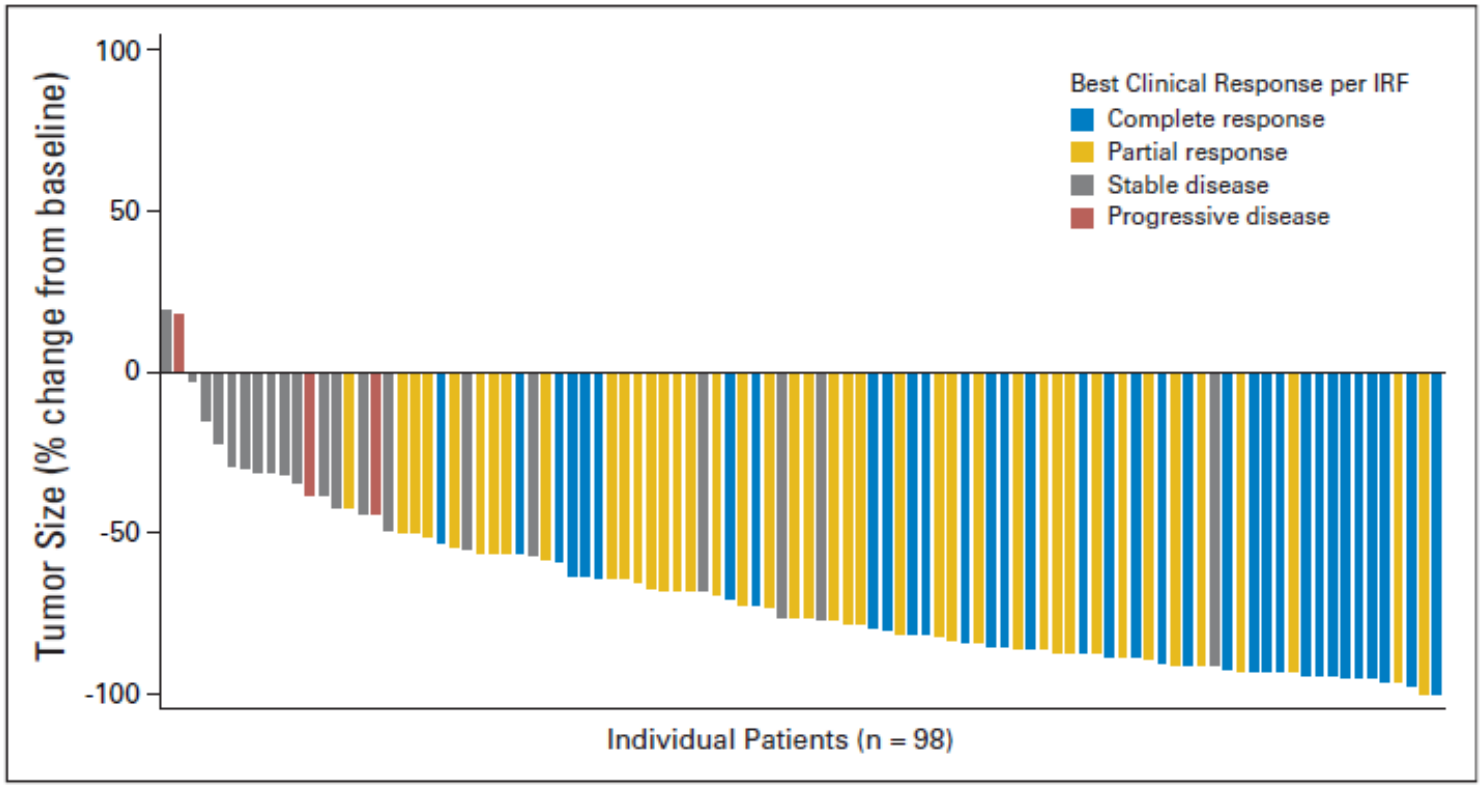
PFS and OS of patients who achieved CR and underwent ASCT

Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

How can we improve ASCT outcome ?

- ❑ Better first salvage therapy
- ❑ New drugs-combinations including new drugs
- ❑ Post-ASCT maintenance therapy
- ❑ RT consolidation
- ❑ Tandem autologous transplant

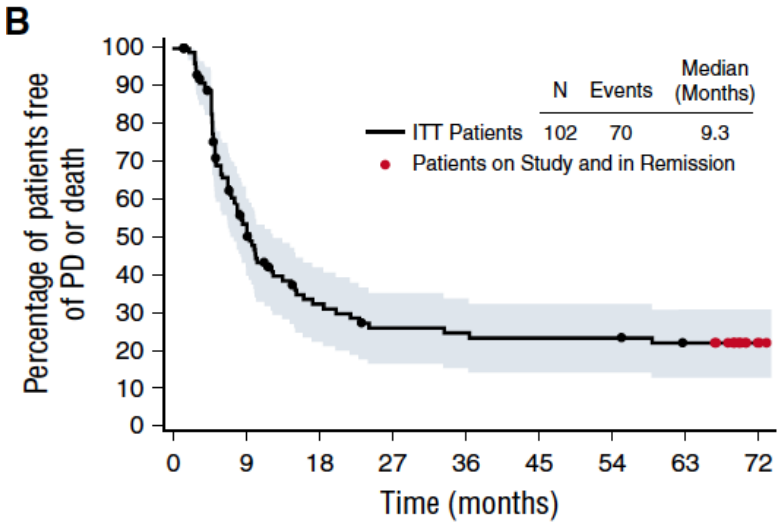
Brentuximab Vedotin in R/R HL after ASCT

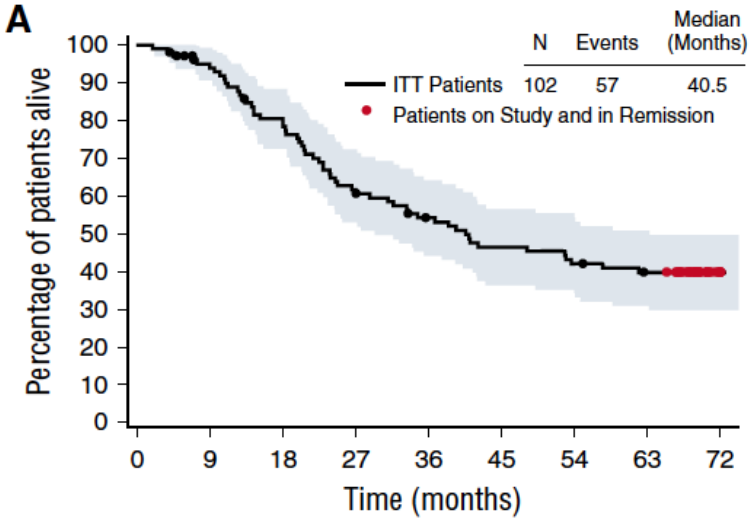


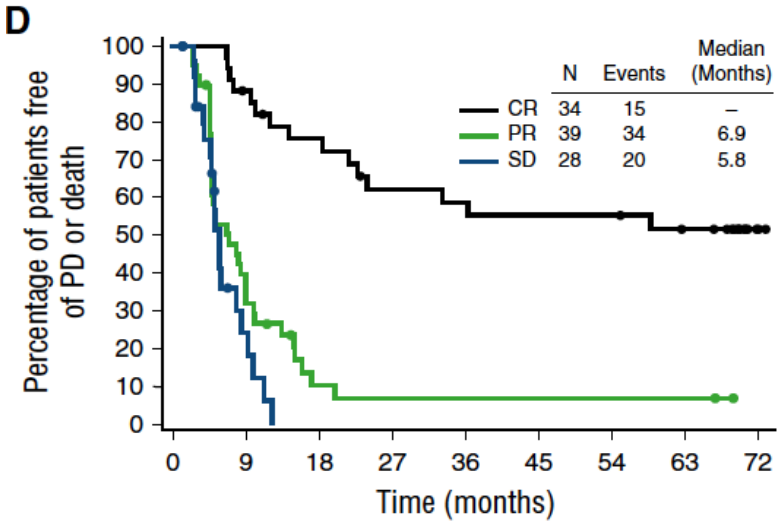
- **# patients: 102 relapsed/refractory, median 6.7 months after ASCT**
- **BV dosage: 1.8 mg/m² every 3 weeks (up to 16 cycles)**
- **ORR (CR): 75% (34%)** (per central review)

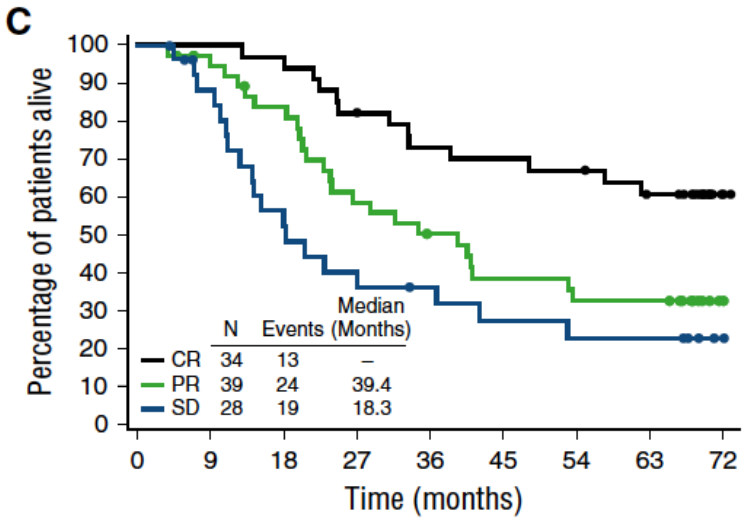
Younes A, et al. J Clin Oncol 2012; 30: 2183-89

Brentuximab Vedotin in R/R HL after ASCT









Chen R et al. Blood 2016; 128: 1562-66

Brentuximab Vedotin as second line therapy

Brentuximab Vedotin Before Auto-SCT

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma

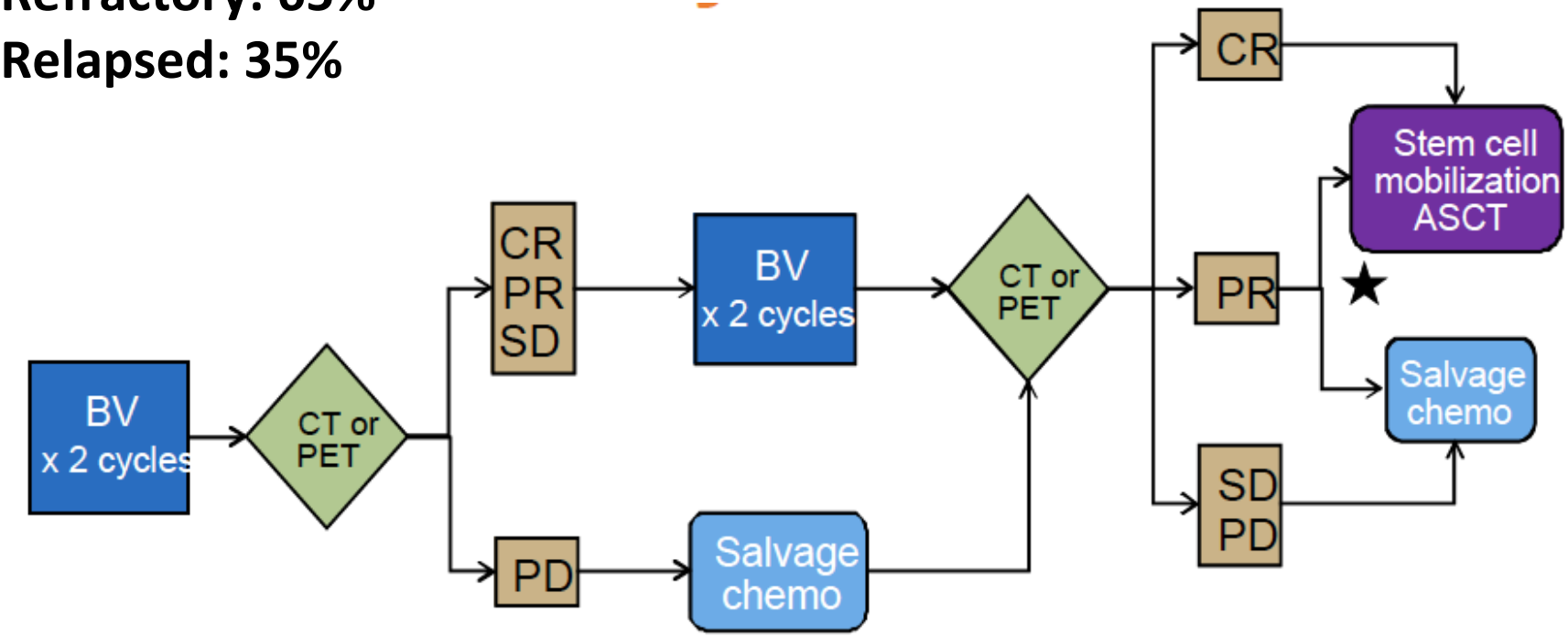
Robert Chen [1,*], Joycelynne M. Palmer [2], Peter Martin [3], Nicole Tsai [2], Young Kim [4], Bihong T. Chen [5], Leslie Popplewell [1], Tanya Siddiqi [1], Sandra H. Thomas [1], Michelle Mott [1], Firoozeh Sahebi [6], Saro Armenian [7], John Leonard [3], Auayporn Nademanee [1], Stephen J. Forman [1]

[1] *Department of Hematology/Hematopoietic Cell Transplantation, City of Hope, Duarte, California*
[2] *Department of Information Sciences, Division of Biostatistics, City of Hope, Duarte, California*
[3] *Department of Hematology/Oncology, Weill Cornell Medical College, New York, New York*
[4] *Department Pathology, City of Hope, Duarte, California*
[5] *Department Diagnostic Radiology, City of Hope, Duarte, California*
[6] *Department of Hematology/Hematopoietic Cell Transplantation, City of Hope, and Kaiser Permanente, Los Angeles, California*
[7] *Department of Population Sciences, City of Hope, Duarte, California*

Chen R, et al. Biol Blood Marrow Transolant 2015 ; 21: 2136-40

Study Design

Refractory: 65%
Relapsed: 35%



Brentuximab vedotin: 1.8 mg/kg IV every 3 weeks up to 4 cycles
Stem cell mobilization: G-CSF ± cyclophosphamide (1.5 g/m^2) ± plerixafor
ASCT conditioning: BEAM, CBV, ^{90}Y-anti-CD25 + BEAM

★ For patients in PR at this point, treatment decision (ASCT or salvage chemotherapy) is at discretion of treating physician

Response to treatment

Safety: peripheral neuropathy : grade 1: 49%, grade 2: 3%

	Best Response to BV (N = 37)	Response to Combo Therapy (ICE/DICE/IGEV/GND) After BV (N = 18)	Best Reponse at Time of ASCT (N = 33)
ORR	25/37 (68%)	16/18 (89%)	
CR	13/37 (35%)	11/18 (61%)	24/33 (73%)
PR	12/37 (32%)	5/18 (28%)	9/33 (27%)
SD	10/37 (27%)	1/18 (6%)	1/33 (3%)
PD	2/37 (5%)	1/18 (6%)	

DICE, dexamethasone, ifosfamide, cisplatin, etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine, prednisone; GND, gemcitabine, vinorelbine, doxorubicin

Stem Cell Mobilization/Harvest and Engraftment

Characteristics	N (%) or median (range)
Cell count	5.97 x 10^6 $CD34^+$/kg (2.64-34.45)
Days required for collection	2 (1-6)
Plerixafor usage	9 (27%)
ANC engraftment	11 (10-12)
Platelet engraftment	13 (9-23)

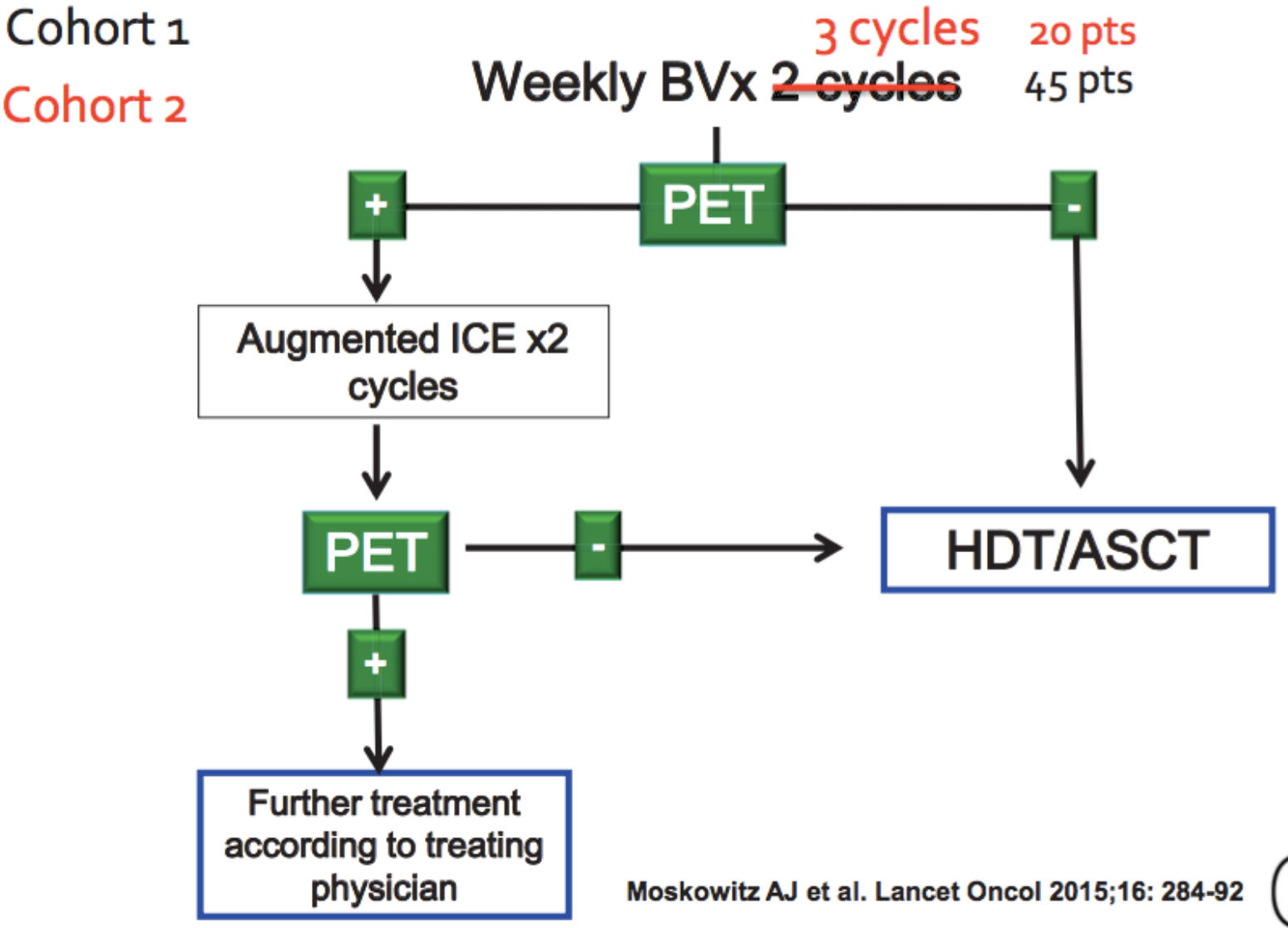
Priming with G-CSF or CTX ± plerixafor

PET-adapted Sequential Salvage Therapy with BV and augmented ICE

Qwk x 3 followed by 1 wk rest
Qwk x 3 followed by 1 wk rest
Qwek x 3 followed by 1 wk rest

Cohort 1
Cohort 2

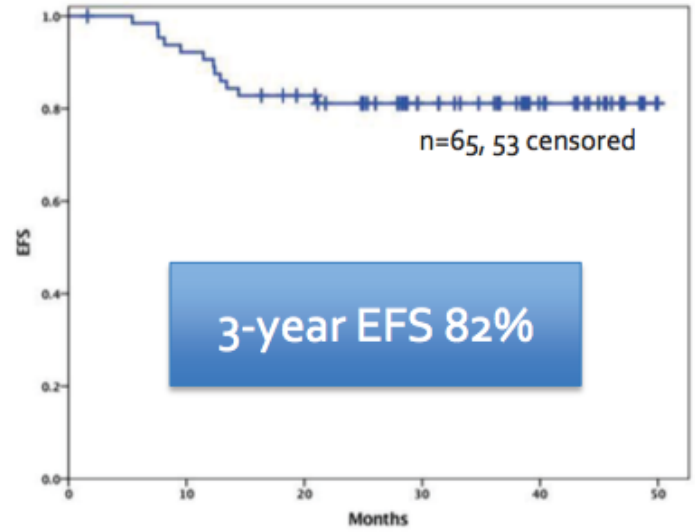
3 cycles 20 pts
45 pts

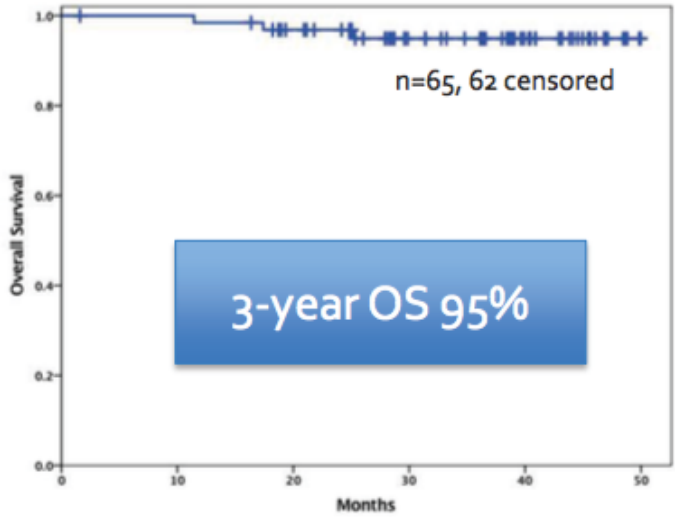


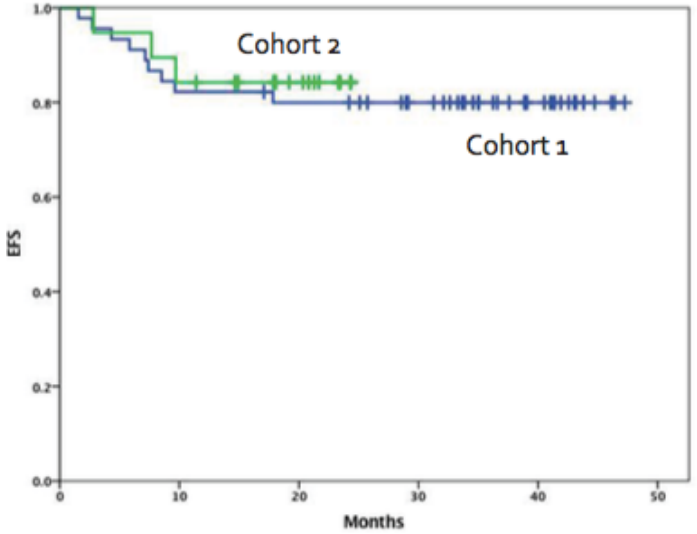
Moskowitz AJ et al. Lancet Oncol 2015;16: 284-92

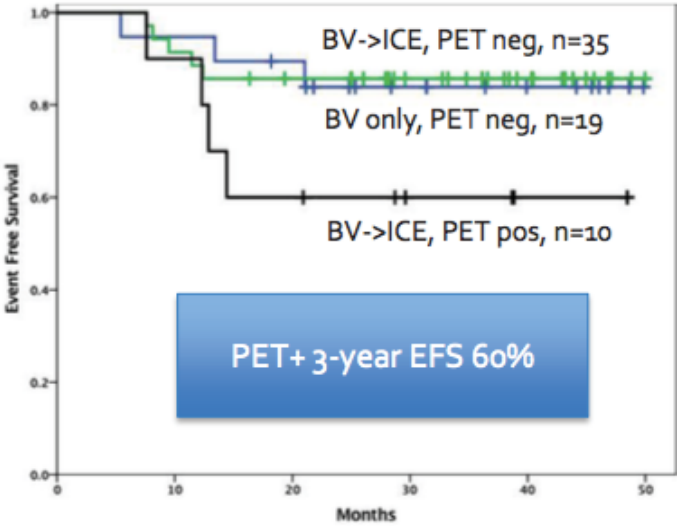
Memorial Sloan Kettering Cancer Center

PET-adapted salvage therapy with BV and augmented ICE: Outcomes









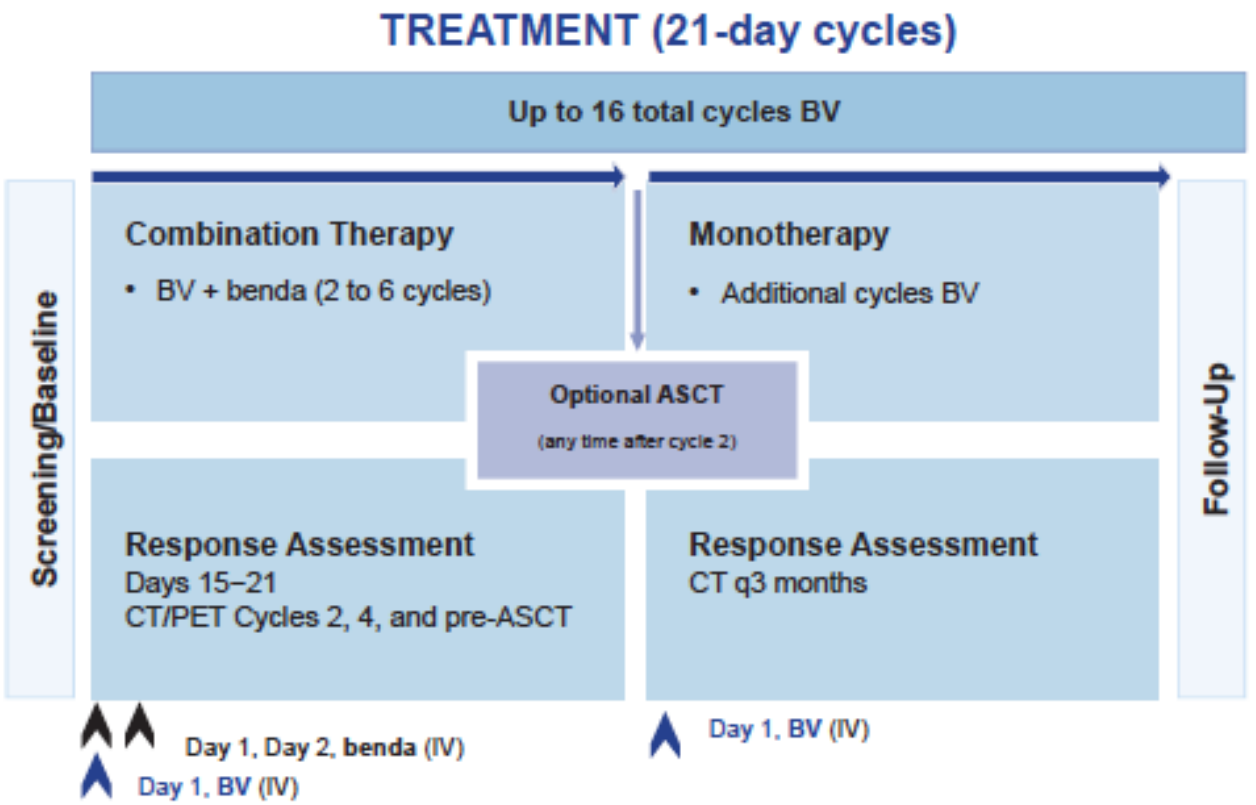
Moskowitz A et al ISHL 2017, Abstract 18

How can we improve ASCT outcome ?

- ❑ Better first salvage therapy
- ❑ New drugs-combinations including new drugs
- ❑ Post-ASCT maintenance therapy
- ❑ RT consolidation
- ❑ Tandem autologous transplant

Brentuximab Vedotin+Bendamustine

Bendamustine 90 mg/mq d 1+2 + BV: 1,8 mg/kg d 1



LaCasce et al. ISHL 2016; Abstract 0020

Patient demographic and clinical characteristics (n = 55)

	N=55
Median age, (range)	36 years (19–79)
Gender (% female/male)	56/44
ECOG status, n (%)	
0	36 (65)
1	18 (33)
2	1 (2)
Median time since HL diagnosis, (range)	13.8 months (3–98
Stage III/IV at diagnosis, n (%)	29 (53)
Baseline disease status, n (%)	
Primary refractory	28 (51)
Relapsed	27 (49)
No. of pts with remission duration ≤ 1 yr	10 (18)
B symptoms, n (%)	12 (22)
Bulky disease, n (%)	5 (9)
Extranodal disease, n (%)	17 (31)
Bone marrow involvement, n (%)	9 (16)
PET	8 (15)
Bone marrow biopsy	3 (15)[a]
Median International Prognostic Score (IPS[b]), (range)	2 (0-5)

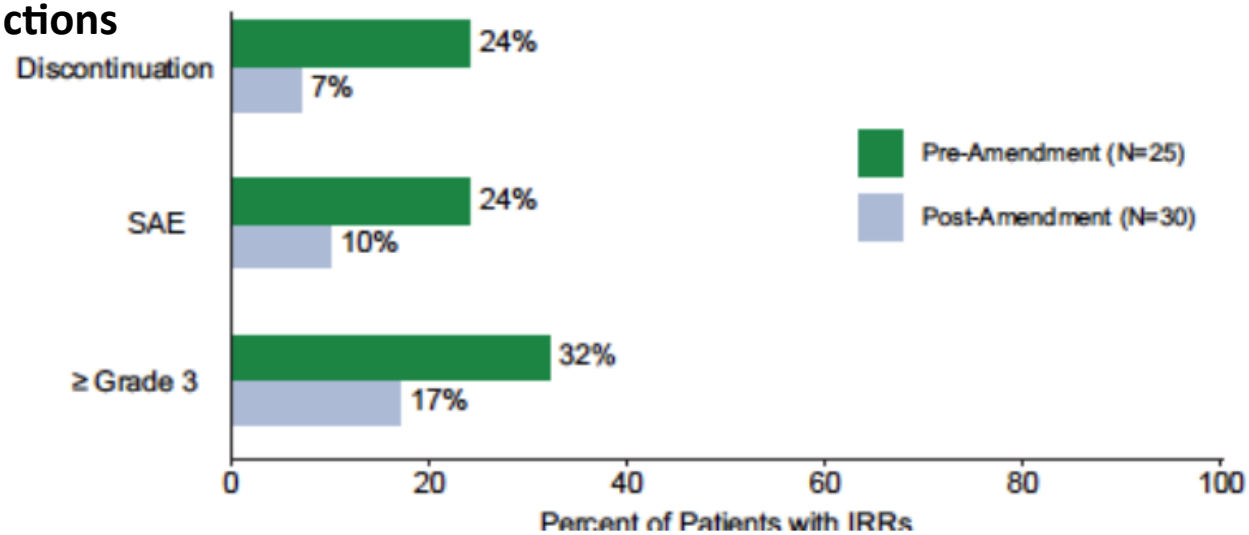
Response to treatment

Best clinical response	(n= 53) %	BeGEV (n=59) %
CR	**74**	73
Refractory	64	59
Relapsed	84	84
PR	**19**	10
SD	6	2
PD	2	14
ORR	**93**	83

LaCasce et al. ISHL 2016; Abstract 0020
Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

Adverse effects & Stem Cell Mobilization

Infusion-Related Reactions



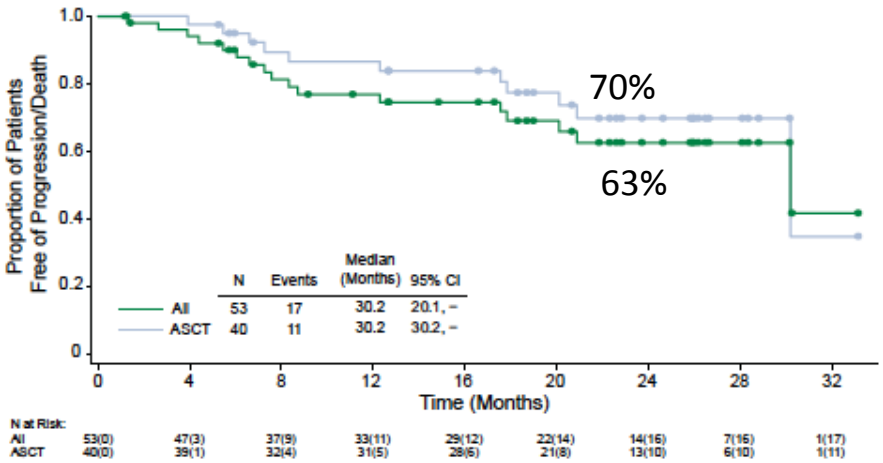
Stem Cell Harvest and Marrow Engraftment

	N = 41
Median number of apheresis session	2 (1-5)
Median number of CD34+ cells (cells/kg) harvested (range)	4.2 x 10^6 (1.7-11.8)
Plerixafor required after failure to collect CD34+ cells with first-line agents	1
Median number of cycles before mobilization (range)	2 (2-6)
Median time (days) to neutrophil engraftment (range)	12 (10-22)
Median time (days) to platelet engraftment (range)	14 (10-44)

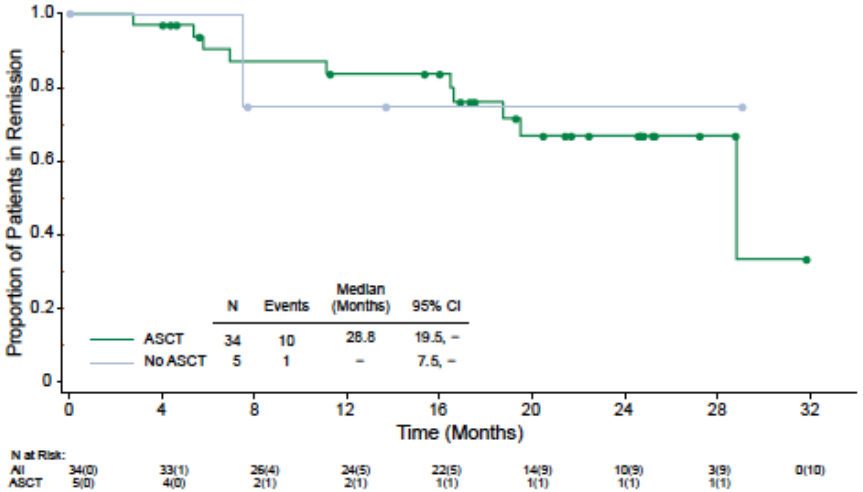
LaCasce et al. ISHL 2016; Abstract 0020

Survival after B-BV autoSCT +/- BV

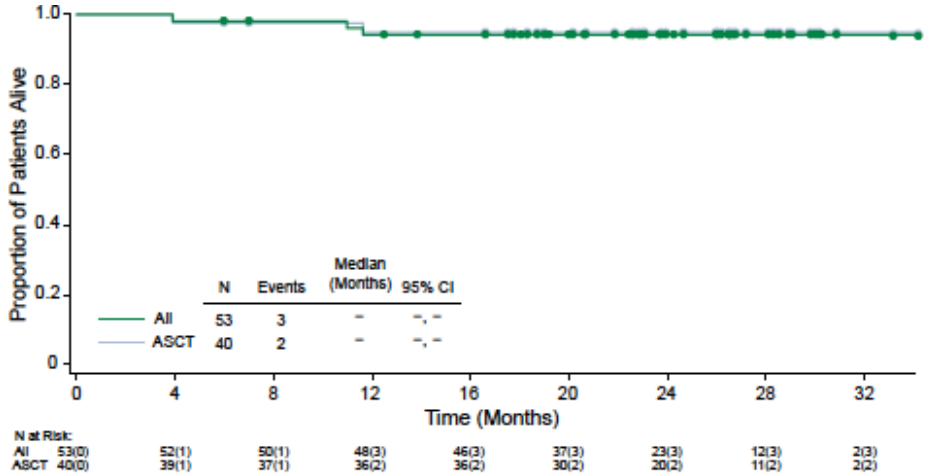
PFS all patients and ASCT subset



Duration of remission in pts in CR ± ASCT

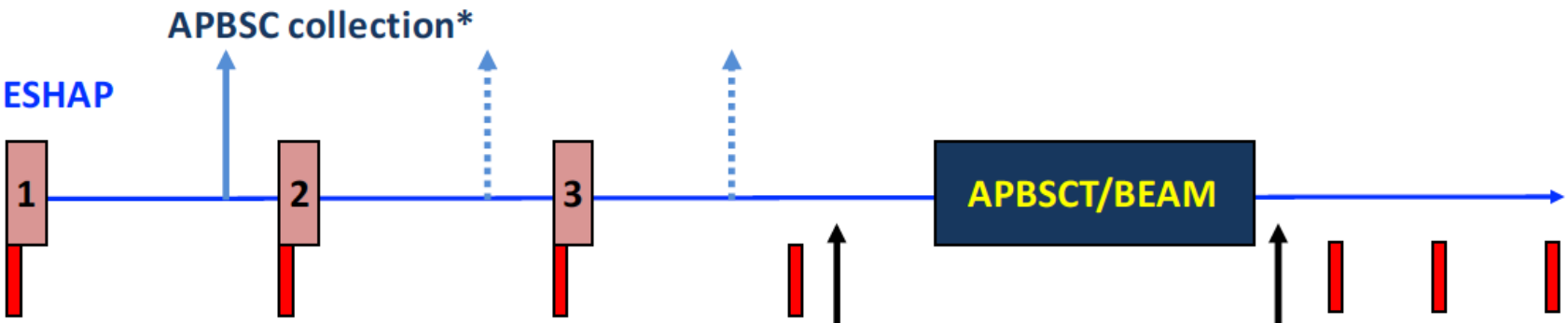


Overall Survival



LaCasce et al. ISHL 2016; Abstract 0020

BRESHAP



BV: 0,9-1.8 mg/Kg, day 1 of each course, & at 21 days post 3th ESHAP.

BRESHAP: every 21 - 28 days

BV post-APBSCT: from day +28 to +56, 3 doses, every 21 days

*CD34+ quantification: ≥ 2 x 10^6/kg CD34+ cells
G-CSF (± Plerixafor)
Prophylaxis for neutropenia: G-CSF mandatory from day+7, Peg-Filgastrim recommended

Garcia-Sanz R et al. Blood 2016; Abstract 1109

BRESHAP: Results

Primary refractory: n= 40

Early relapse: n= 16

Late relapse: n= 10

Pre-transplant Response (ITT)	**Pts (n=66)**
ORR	**94%**
mCR	**70%**
PR	24%

Safety: All pts have completed pre-transplant therapy, 263 cycles administered

22 SAE in 15 pts (fever n=13, neutropenic fever n = 7)

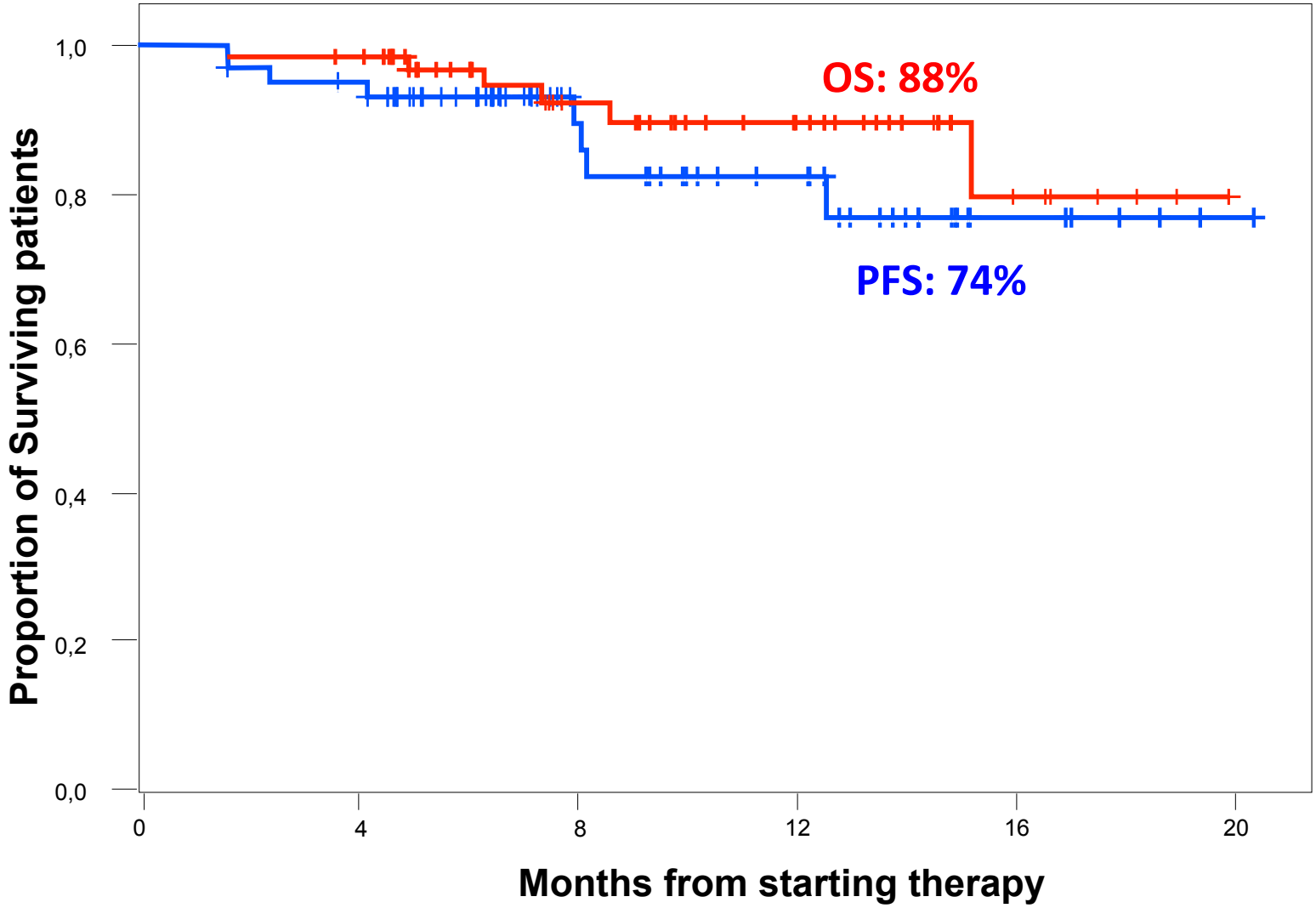
2 Toxic Deaths (non-neutropenic abdominal sepsis and pulmonary embolism)

Stem Cell Harvest and Marrow Engraftment

	N = 64
1 apheresis session	74% (80% after 1st or 2 nd cycle)
Median number of CD34+ cells (cells/kg) harvested	8.24 x 10^6 (1.78-33.47)
Time (days) to neutrophil engraftment	11.5 (9-15)
Time (days) to platelet engraftment	16 (12-20)

Garcia-Sanz R et al. Blood 2016; Abstract 1109

Survival after BRESHAP + ASCT



Garcia-Sanz R et al. Blood 2016; Abstract 1109

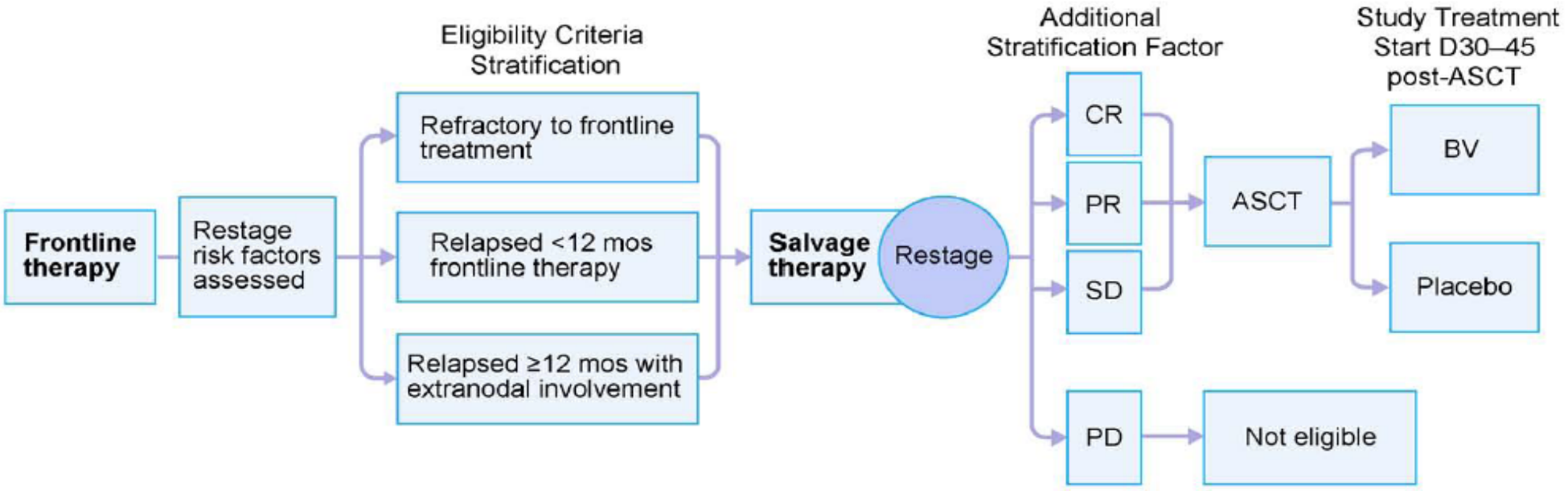
How can we improve ASCT outcome ?

- ❑ Better first salvage therapy
- ❑ New drugs-combinations including new drugs
- ❑ Post-ASCT maintenance therapy
- ❑ RT consolidation
- ❑ Tandem autologous transplant

Post-ASCT maintenance therapy : AETHERA Trial
Placebo-controlled Phase 3 study

Study Design and Key Eligibility Criteria

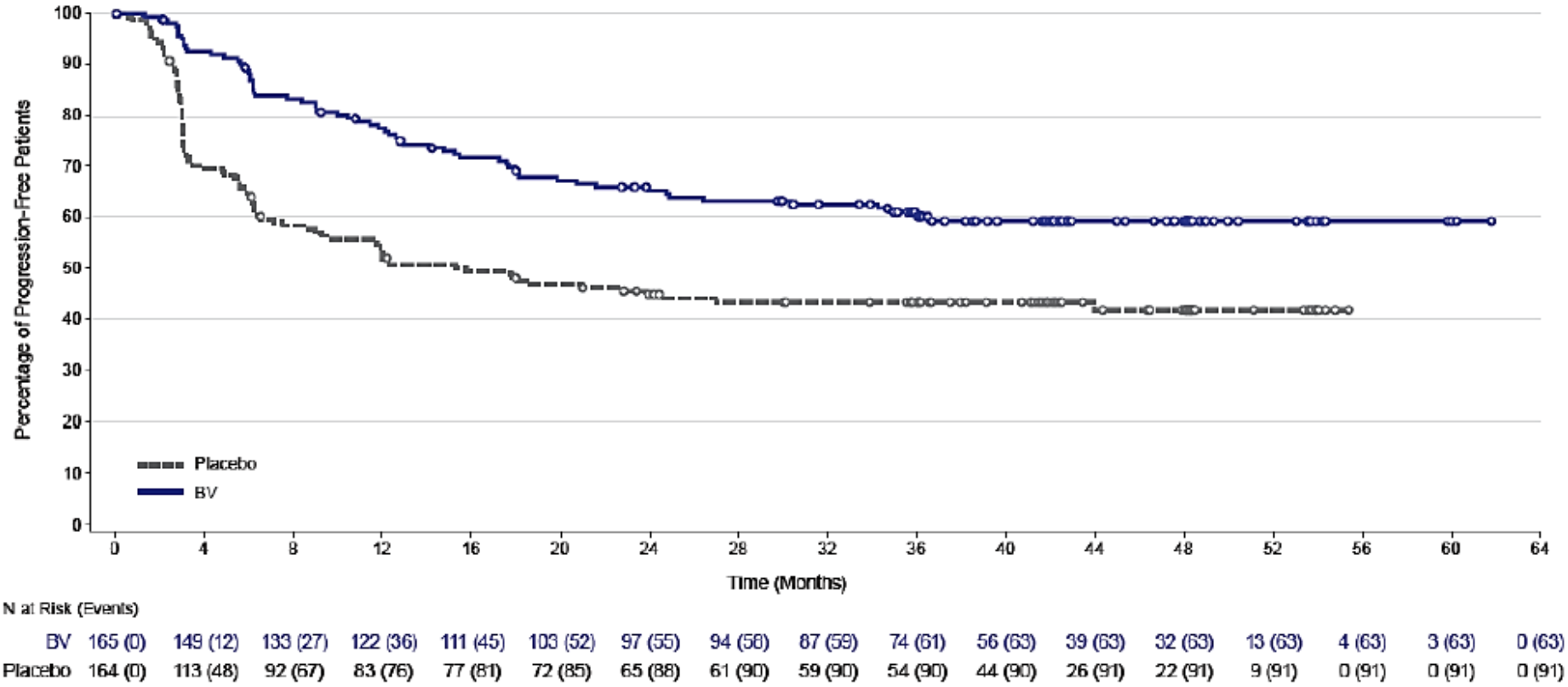
- 329 patients were randomized at 78 sites in North America and Europe



Moskowitz C, ISHL 2016; Abstract 0044

AETHERA: Updated PFS

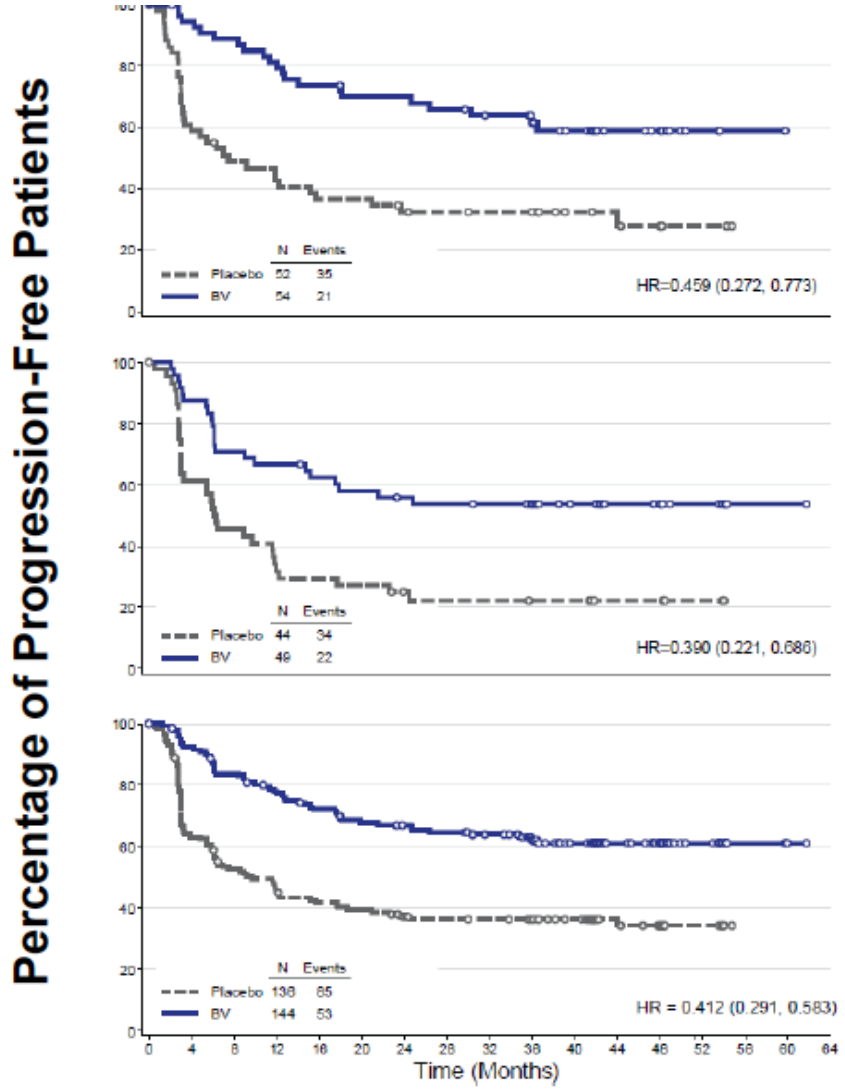
PFS* per Investigator – 3 Years Since Last Patient Randomized



	Treatment cycles (median)	Events	PFS Rate, % (95% CI)		Median PFS (mos)	Hazard ratio
			24 months	36 months		
BV (N=165)	15	63	65 (57, 72)	61 (53, 68)	–	0.52
Placebo (N=164)	15	91	45 (37, 52)	43 (36, 51)	15.8	

Moskowitz C, ISHL 2016; Abstract 0044

AETHERA: Pre-ASCT Subgroup Analysis



Pre-ASCT Partial Response

Pre-ASCT Stable Disease

Pre-ASCT ≥2 Risk Factors

Risk factors:

Relapse < 12 months

Best response PR or SD to most recent salvage treat

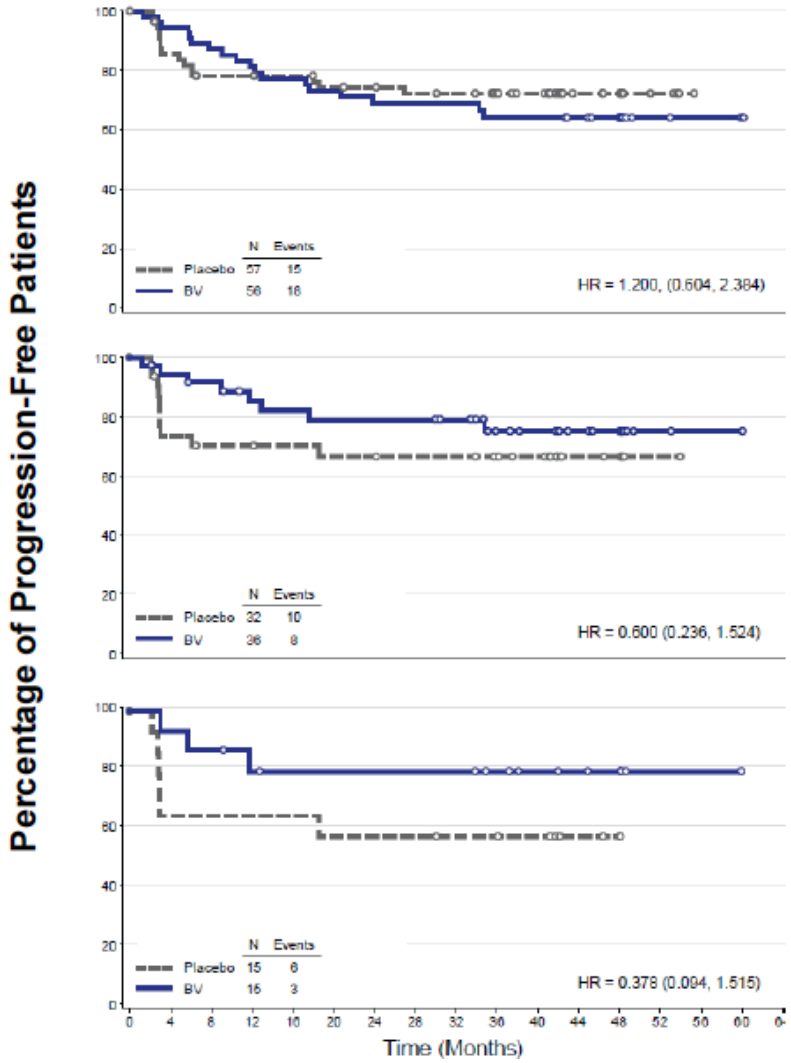
Extranodal disease at pre-ASCT relapse

B symptoms at pre-ASCT relapse

≥ 2 prior salvage therapies

SweetenhamJ et al. Blood 2015; 126: Abstract 3172

AETHERA: Pre-ASCT PET-negative : subgroup analysis



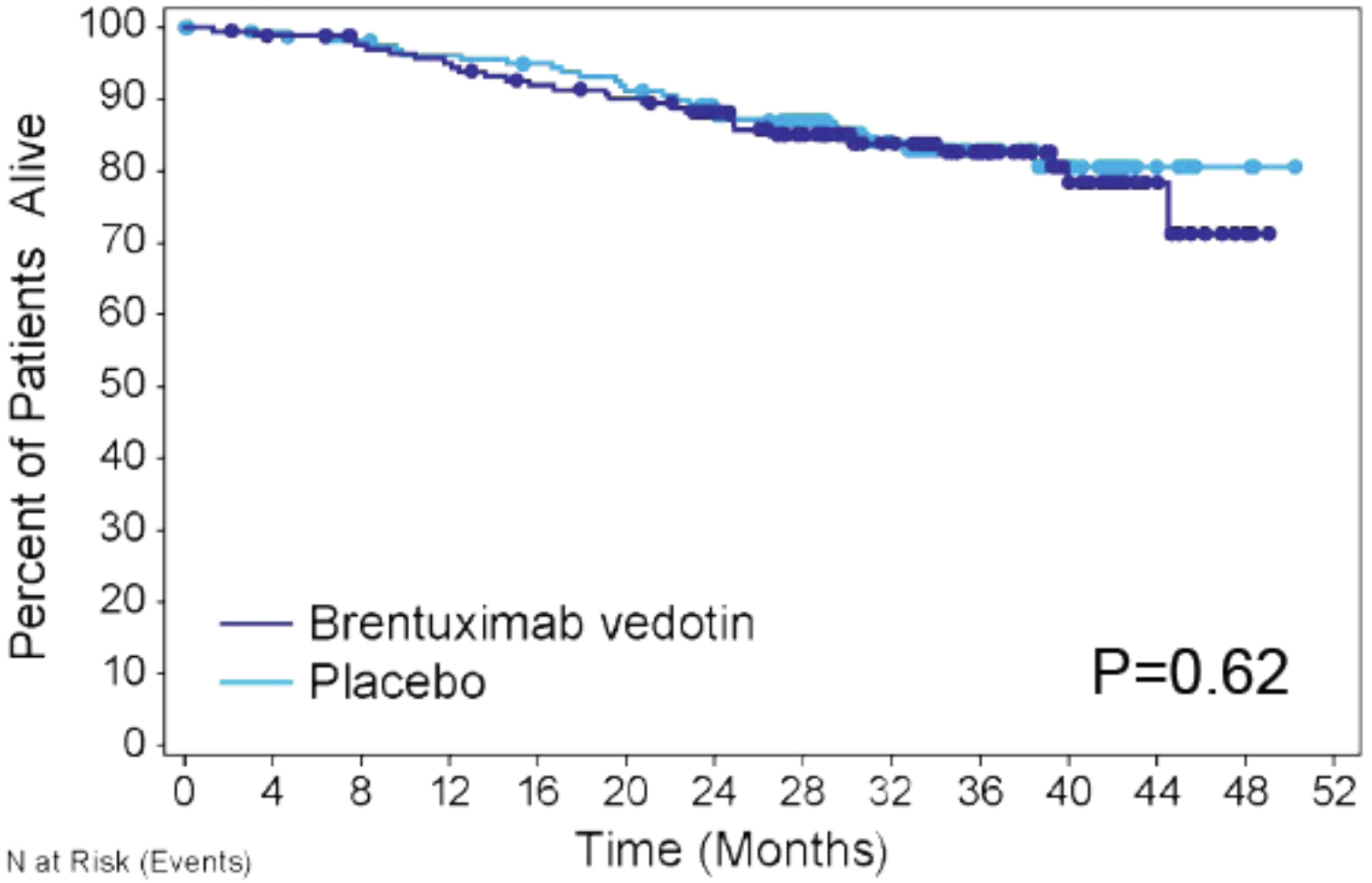
All

≥2 Risk Factors

Extranodal Disease at Relapse

SweetenhamJ et al. Blood 2015; 126: Abstract 3172

AETHERA Study: Overall Survival



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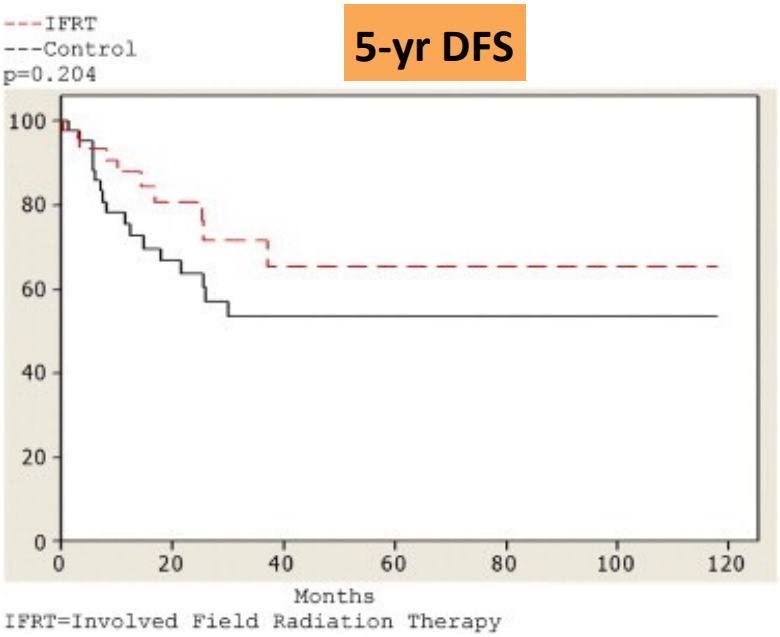
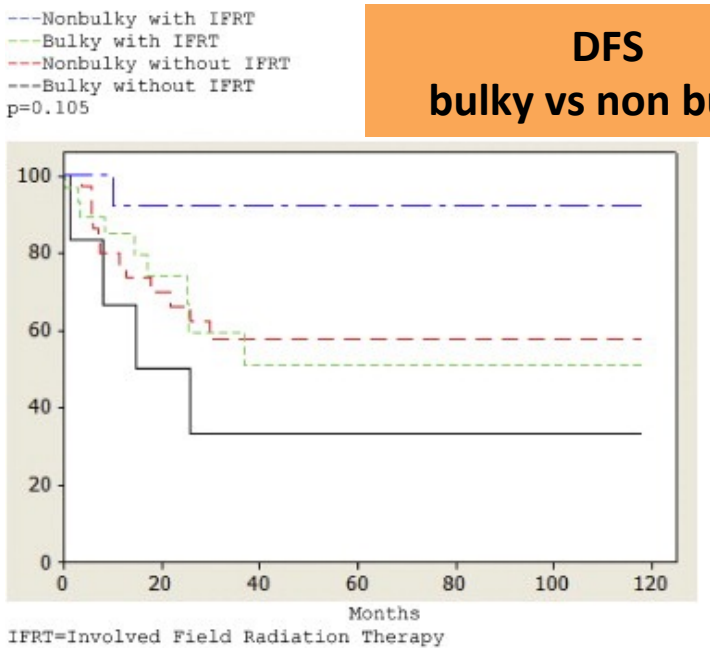
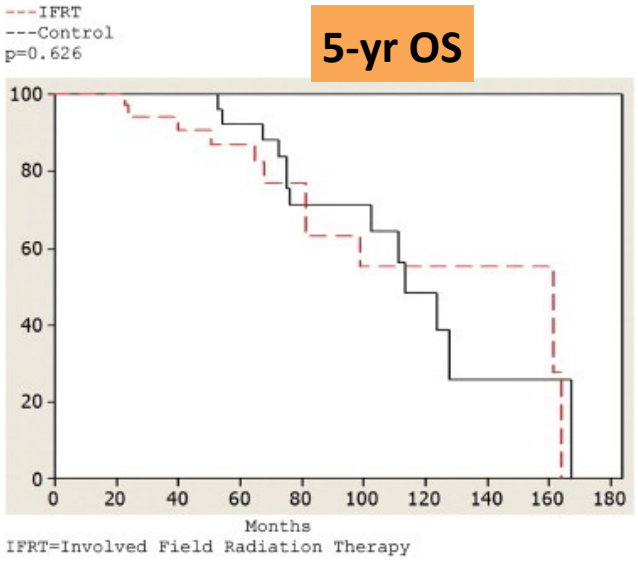
Any benefit from IFRT consolidation after ASCT?







Kahn S, et al. Int J Radiat OncolBiol Phys2011;81:175-80

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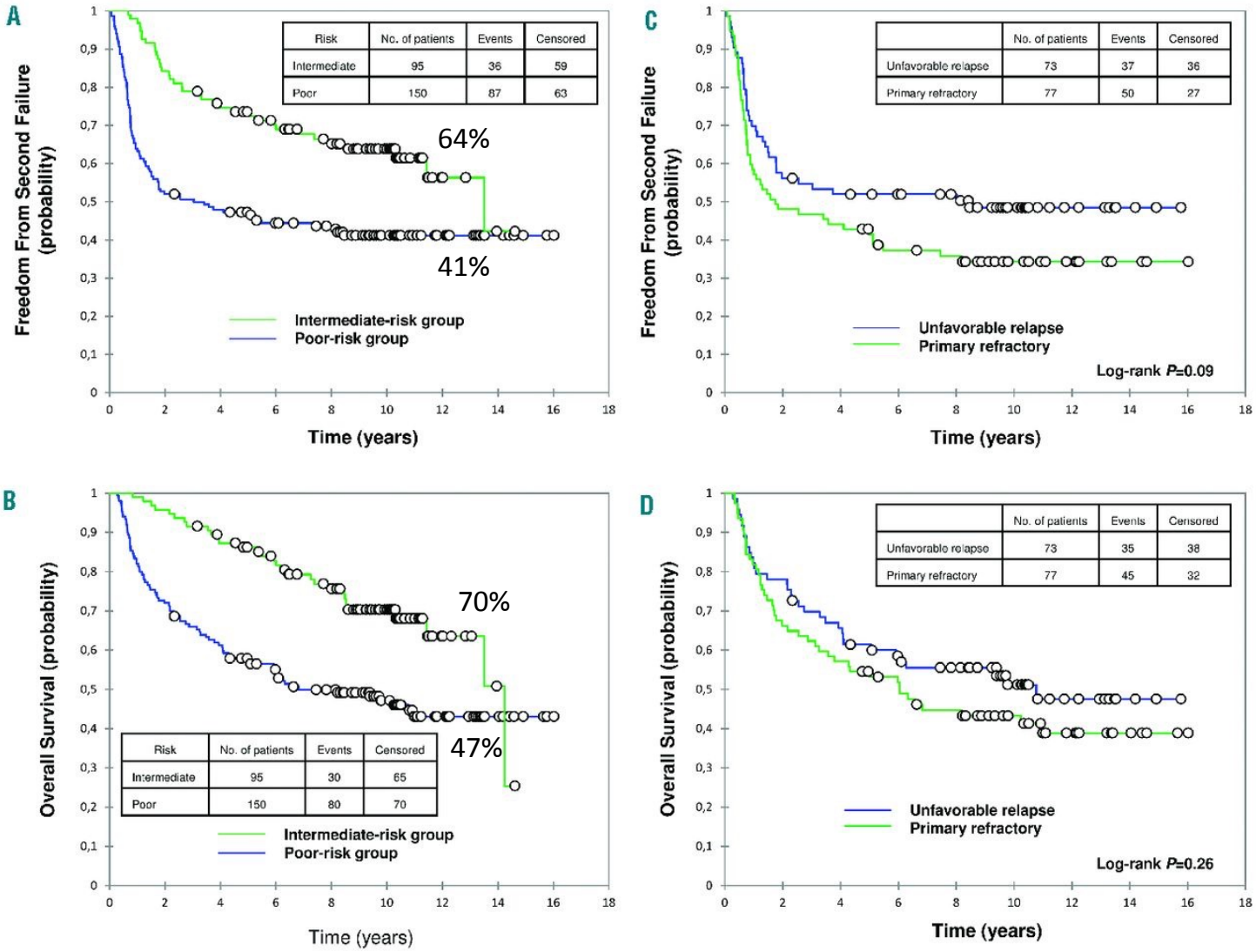
Tandem autologous transplant: 10-year results



Sibon D , et al. Haematologica 2016; 101: 474-81.

Conclusions

- ✓ First salvage therapy
  - ✓ Combinations including new drugs
- ✓ Post-ASCT maintenance therapy
  - ✓ Residual disease prior to ASCT or risk factors
- ✓ RT consolidation
  - ✓ On bulky disease ≥ 5 cm at relapse/progression
- ✓ Tandem autologous transplant
  - ✓ Feasible, no randomized studies

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

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