Θεραπεία 1ης γραμμής στο Λέμφωμα Hodgkin στην εποχή των νέων παραγόντων.

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Αιματολόγος
Αιματολογική και Λεμφωμάτων Κλινική
Γ.Ν.Α 'Ο ΕΥΑΓΓΕΛΙΣΜΟΣ'

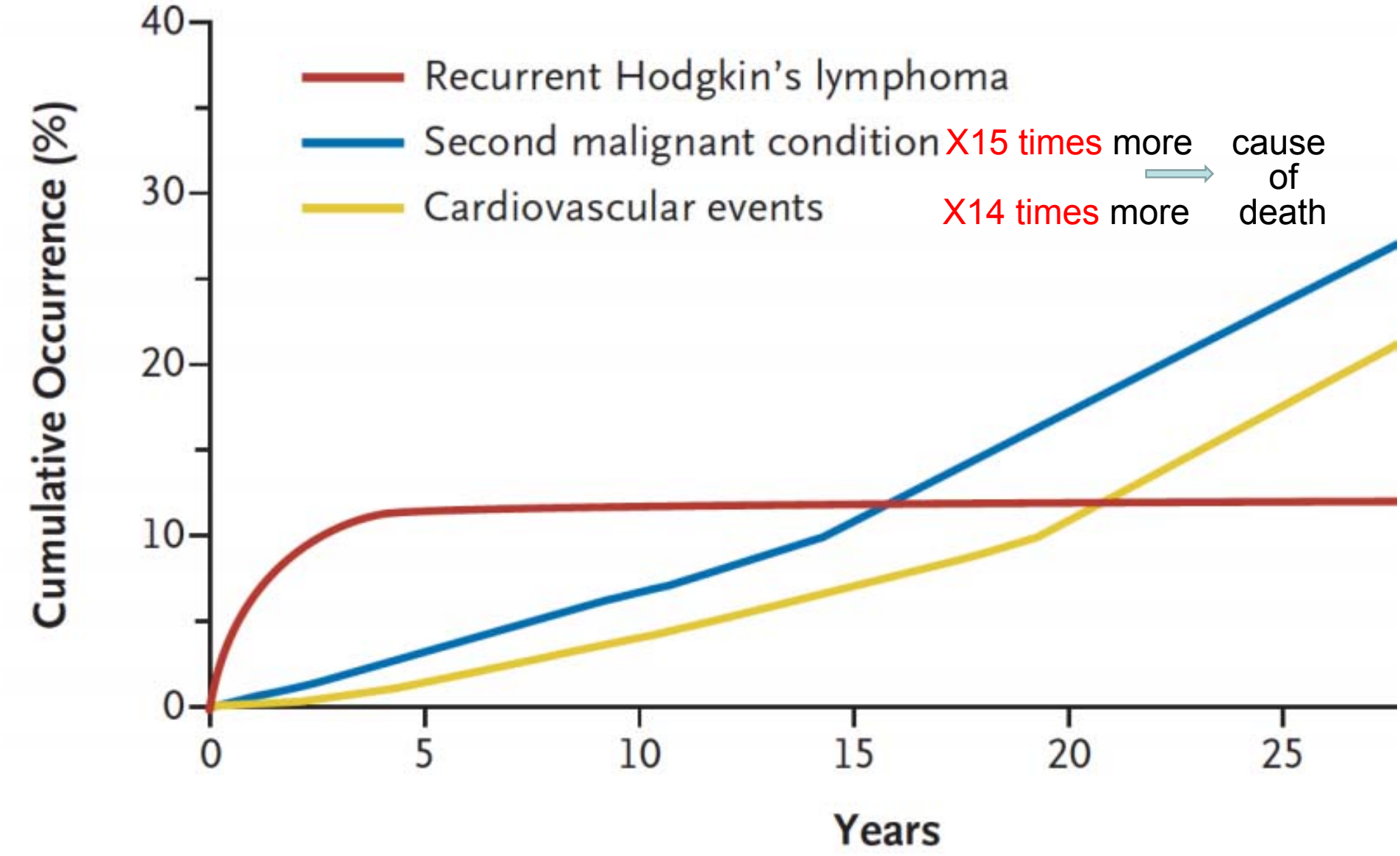
23° Ετήσιο Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης Νοσοκομείου «Ο Ευαγγελισμός»

Αθήνα, 26 Φεβρουαρίου – 2 Μαρτίου 2018

Δεν υπάρχει σύγκρουση συμφερόντων με τις παρακάτω χορηγούς εταιρείες:

NOVARTIS, JANSSEN ONCOLOGY, ABBVIE, BRISTOL-MYERS SQUIBB, MEDTRONIC, TAKEDA, GENESIS, MSD, PFIZER, AMGEN, ASTELLAS, GILEAD, AENORASIS, BAXTER, BIANEΞ, WINMEDICA, ABBOTT, BIOΣΕΡ, SANOFI, ANGELINI, DEMO, ELPEN, EDWARDS, ROCHE, RONTIS, SPECIFAR, UCB, ΥΓΕΙΟΔΥΝΑΜΙΚΗ, MAVROGENIS

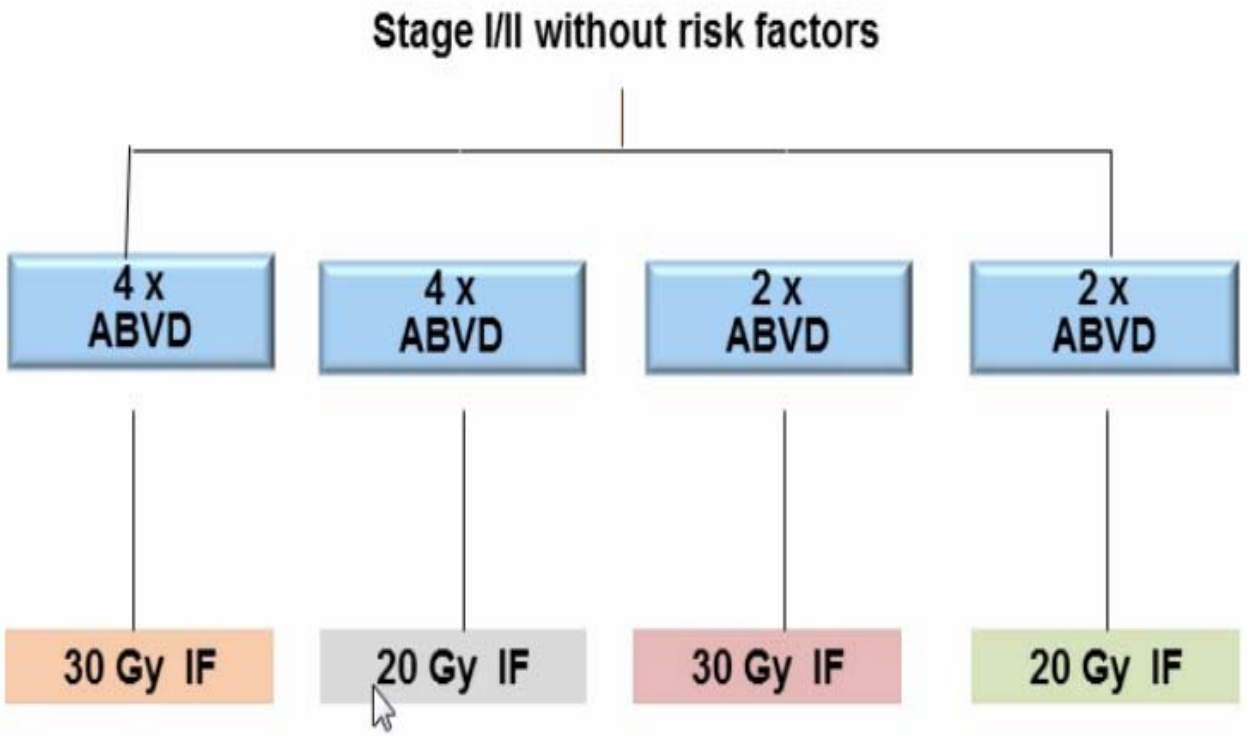
Λέμφωμα Hodgkin: Ιάσιμο Νόσημα?



Λέμφωμα Hodgkin το Τίμημα της Επιτυχίας

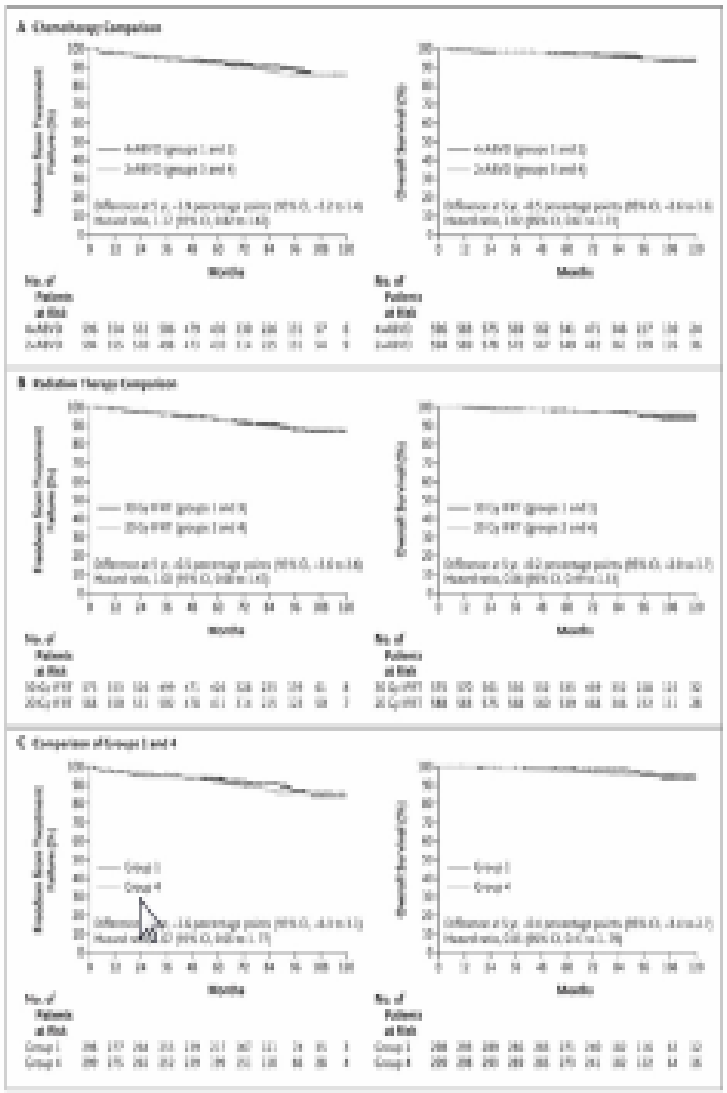
	Απώτερες	Επιπλοκές
Δευτεροπαθείς Κακοήθειες	ΟΜΛ	← Αλκυλιούντες
	Συμπαγείς Όγκοι	← Χ/Θ +Α/Θ
Βλάβες Οργάνων	Πνεύμονες	← Bleomycin +Α/Θ
	Καρδιά	← Ανθρακ/νες+Α/Θ
	Θυρεοειδής	← Α/Θ
Άλλες	Στειρότητα	→ MOPP>BEACOPP>ABVD

Early Stage Favorable HL
HD10 Study
(n = 1190)



Engert A, et al. *N Engl J Med*. 2010;363(7):640-652.

Early Stage Favorable HL: HD10 Study

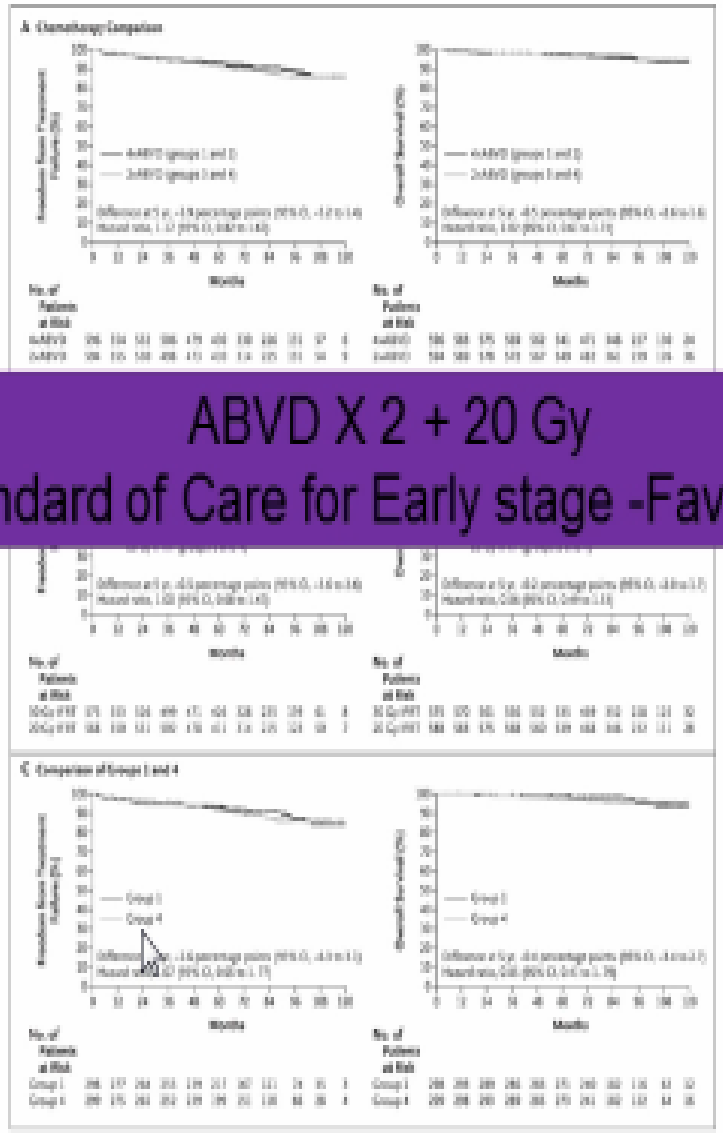


Chemo comparison
4 vs 2 ABVD

Radiation therapy comparison
30 vs 20 Gy

Group 1 and 4 comparison
ABVD x 4 + 30 Gy
vs
ABVD x 2 + 20 Gy

Early Stage Favorable HL: HD10 Study



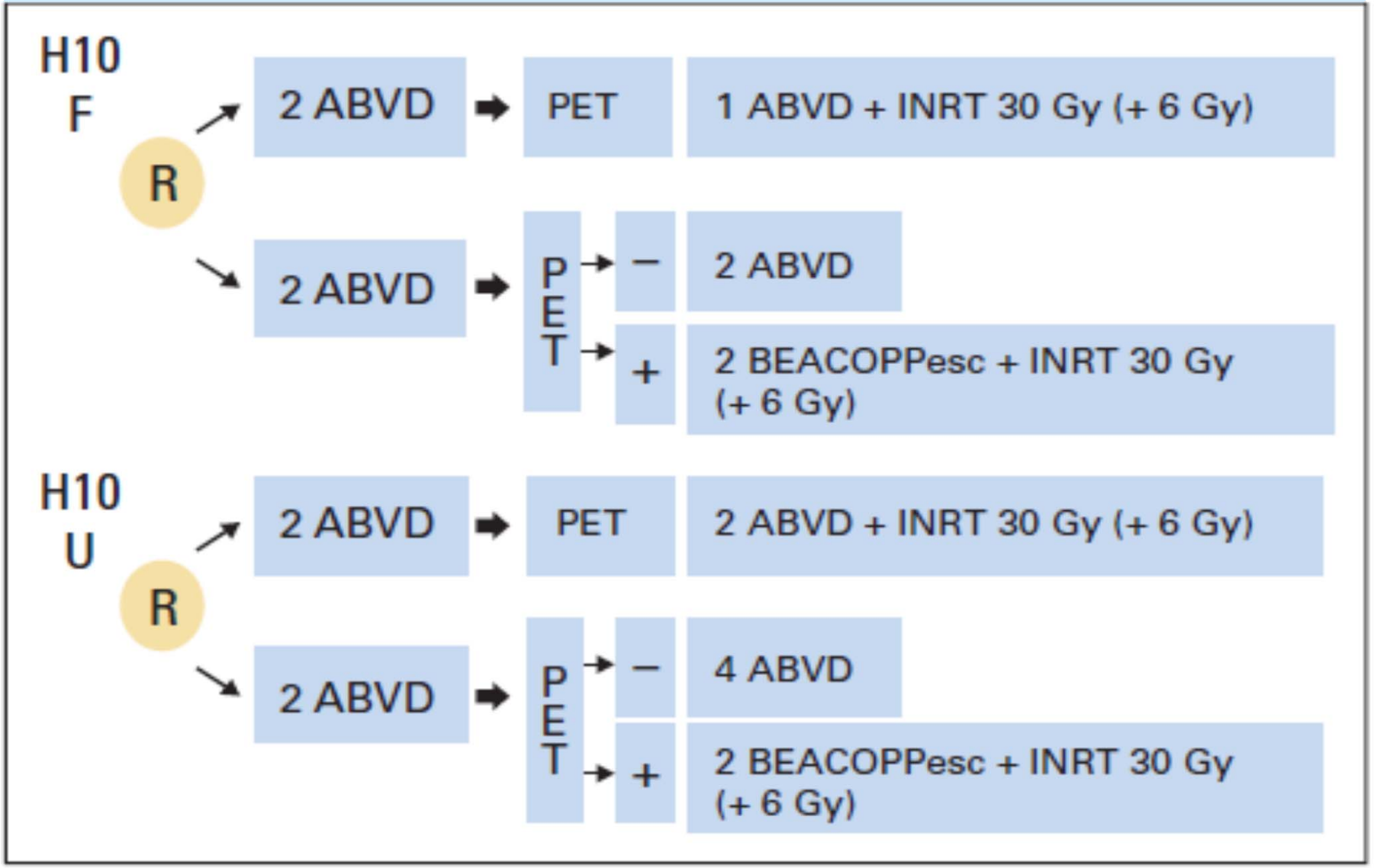
ABVD X 2 + 20 Gy
Standard of Care for Early stage -Favorable

Chemo comparison
4 vs 2 ABVD

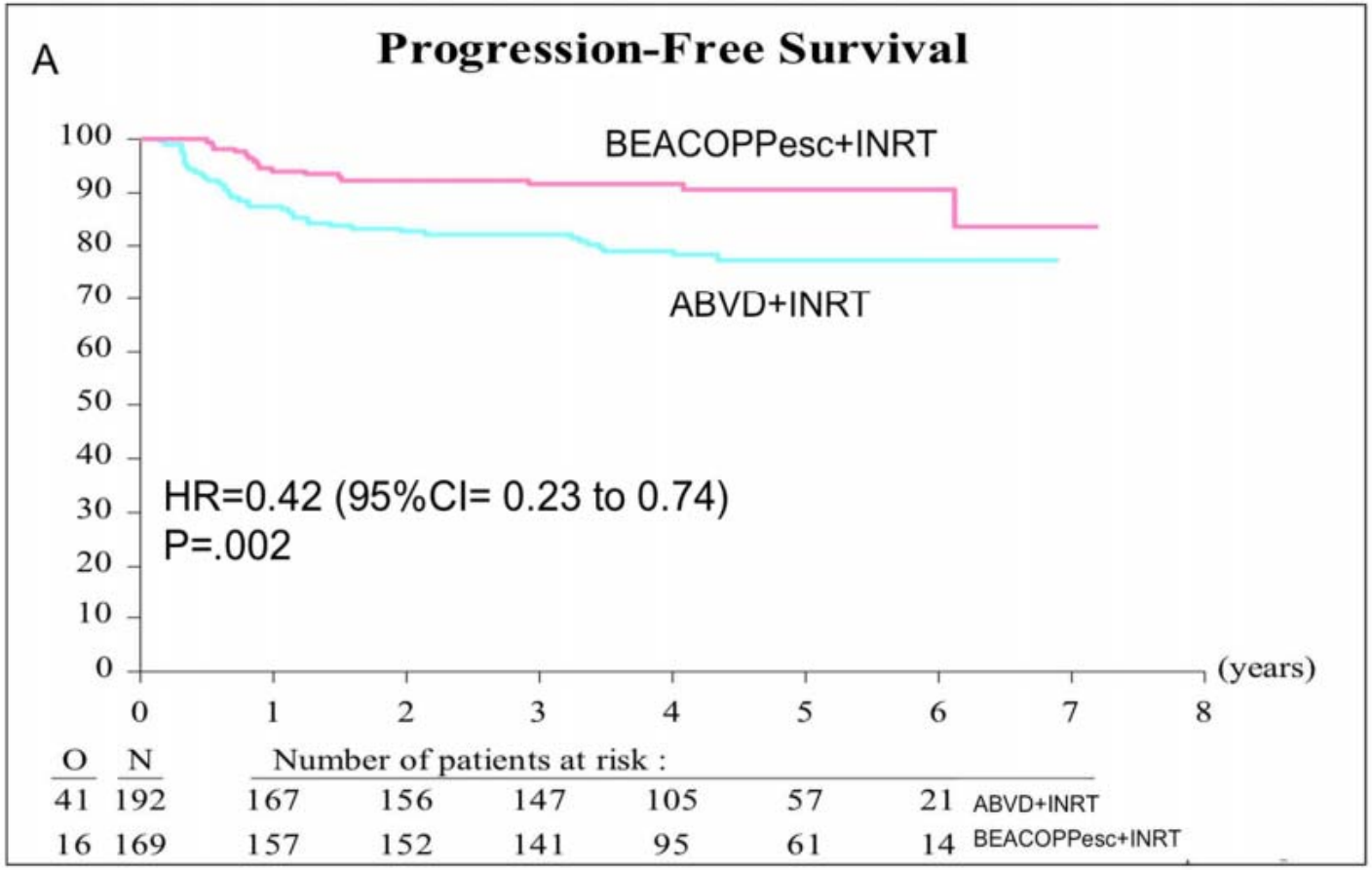
…apy
…comparison
30 vs 20 Gy

Group 1 and 4 comparison
ABVD x 4 + 30 Gy
vs
ABVD x 2 + 20 Gy

EORTC/GELA IIL H10 study

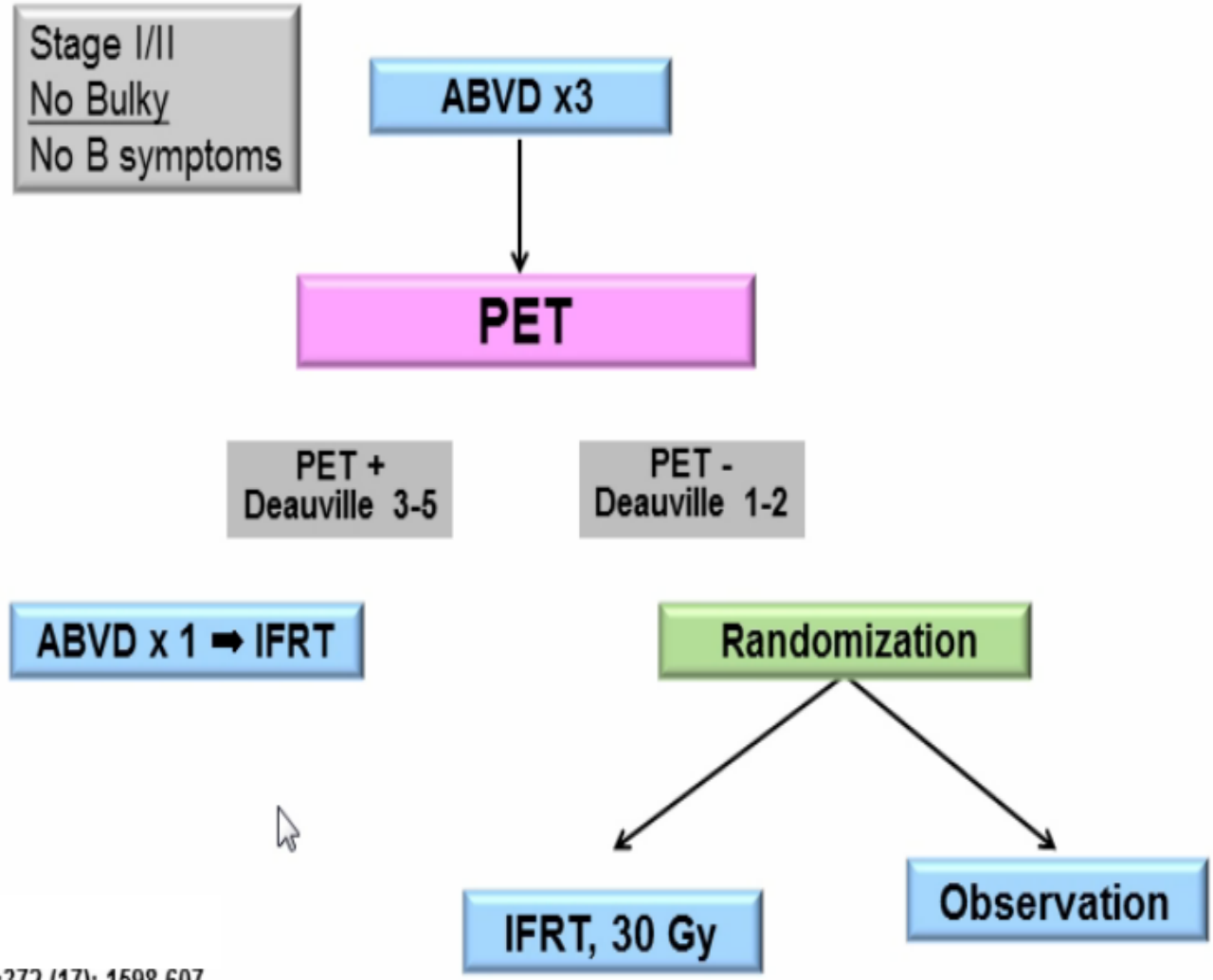


H10: PET positive



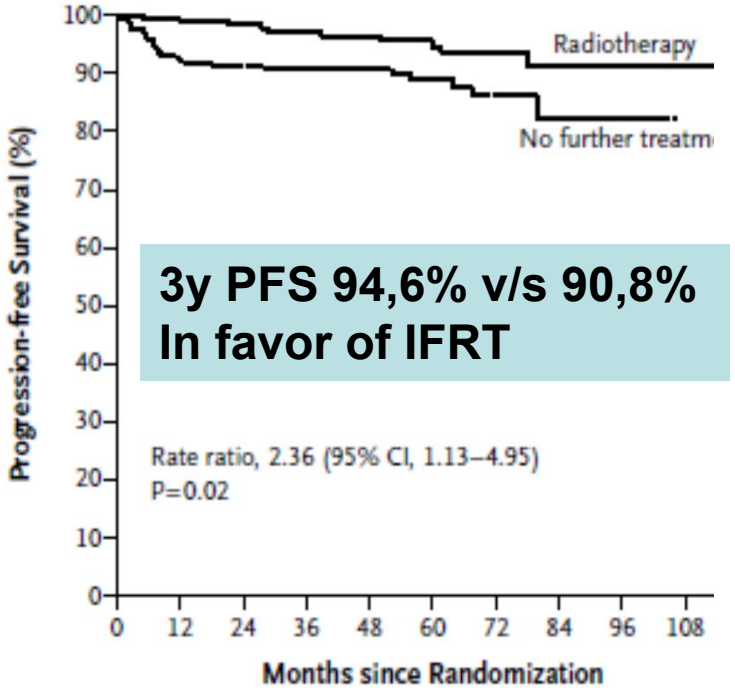
HR: Hazard Ratio BEACOPPesc *vs.* ABVD

Rapid Trial

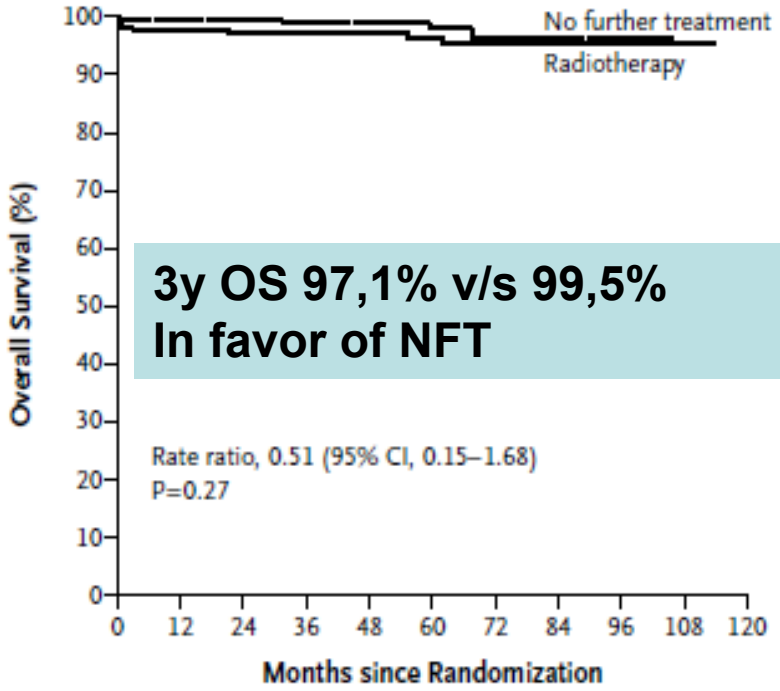


l. N Engl J Med 2015;372 (17): 1598-607.

Rapid Trial



3y PFS 94,6% v/s 90,8%
In favor of IFRT



3y OS 97,1% v/s 99,5%
In favor of NFT

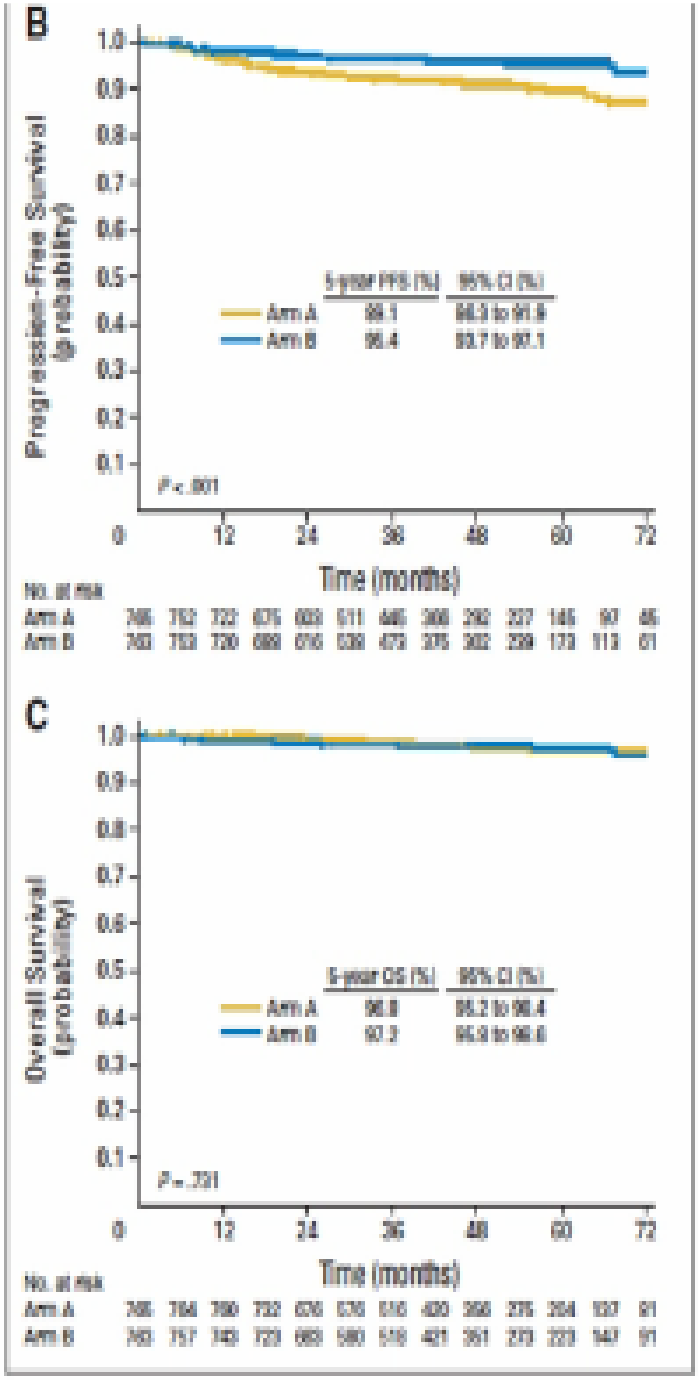
NEJM 2015

Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin study group HD14 trial.

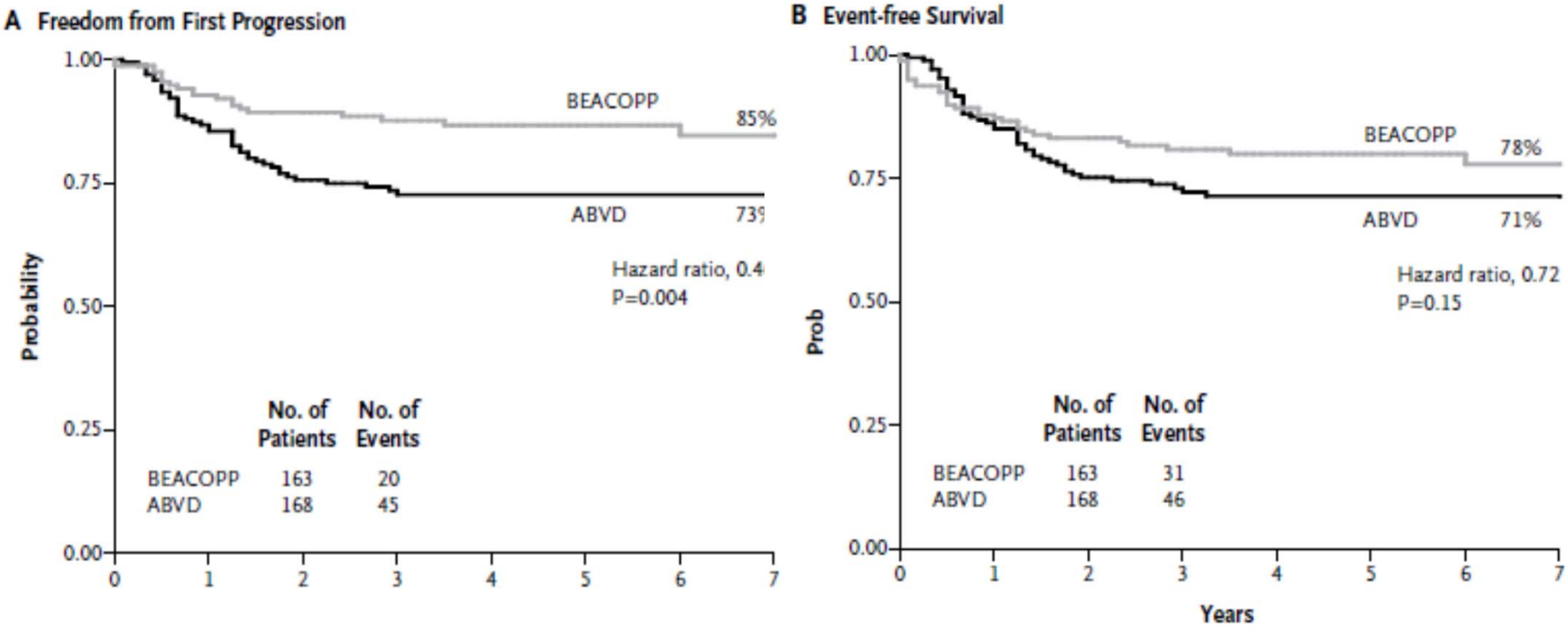
Von Tresckow et al. J Clin Oncol. 2012; 30:907-13.

BEACOPP x 2 plus ABVD x 2 (B)
Vs ABVD x 4 (A)

All got 30Gy IFRT



BEACOPP v/r ABVD for Advanced Hodgkin's Lymphoma



NEJM 2011

VOLUME 34 · NUMBER 11 · APRIL 10, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Results of the HD2000 Trial Comparing ABVI Versus BEACOPP Versus COPP-EBV-CAD in Untreated Patients With Advanced Hodgkin Lymphoma: A Study by Fondazione Italiana Linfomi

Francesco Merli, Stefano Luminari, Paolo G. Gobbi, Nicola Cascavilla, Caterina Mammi, Fiorella Ilariucci, Caterina Stelitano, Maurizio Musso, Luca Baldini, Sara Galimberti, Francesco Angrilli, Giuseppe Polimeno

10y PFS 69% ABVD
75% BEACOPP

VOLUME 34 · NUMBER 12 · APRIL 20, 2016

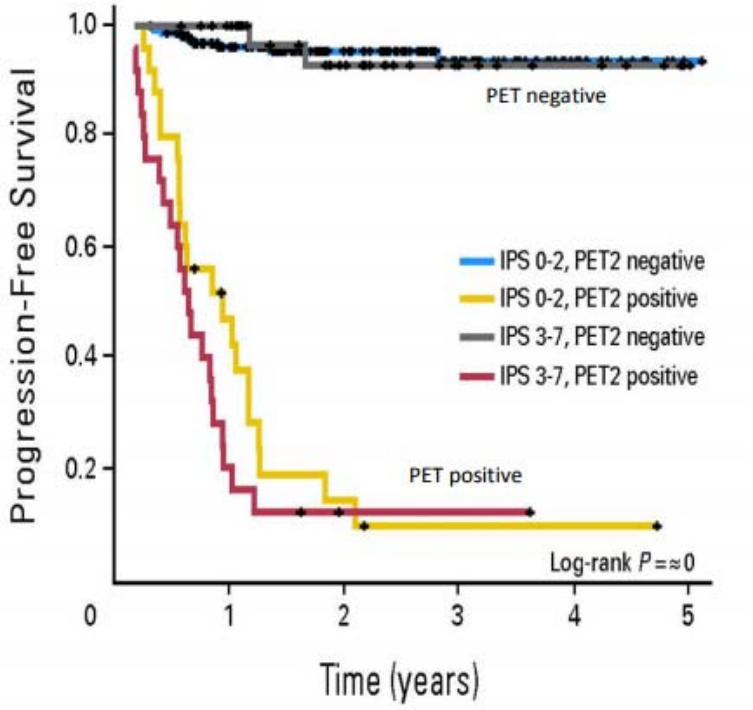
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

25% PET2+

Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

Pier Luigi Zinzani, Alessandro Broccoli, Daniela Maria Gioia, Antonio Castagnoli, Giovannino Ciccone, Andrea Evangelista, Armando Santoro, Umberto Ricardi, Maurizio Bonfichi, Ercole Brusamolino,† Giuseppe Rossi, Antonella Anastasia, Francesco Zaja, Umberto Vitolo, Vincenzo Pavone, Alessandro Pulsoni, Luigi Rigacci,

Λ.Hodgkin:PET-2 + ve Δυσμενής Προγνωστικός Δείκτης



Gallamini, A. et al. J Clin Oncol, 2007

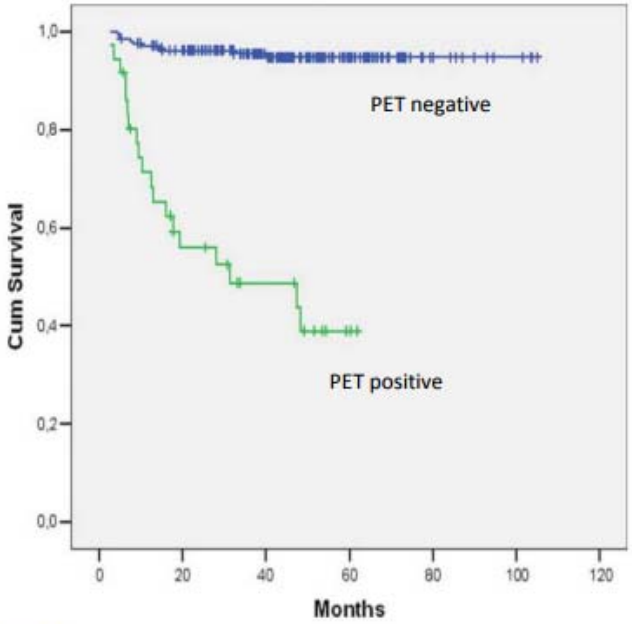


Figure 2. Progression-free survival according to interim-PET results using IHP criteria. Upper line negative interim-PET, lower line positive interim-PET. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Rigacci L. et al. Am. J. Hematol, 2015

GHSG Risk Allocation for HL

<table>
<tr><th></th><th colspan="4">Stage (Ann Arbor)</th></tr>
<tr><td>Risk factors</td><td>IA, IB, IIA</td><td>IIB</td><td>IIIA, IIIB</td><td>IVA, IVB</td></tr>
<tr><td>None</td><td colspan="2">Early favorable</td><td colspan="2" rowspan="5">Advanced</td></tr>
<tr><td>≥ 3 LK- Areas</td><td colspan="2" rowspan="4">Early unfavor-able</td></tr>
<tr><td>Elevated ESR</td></tr>
<tr><td>Large Med Mass</td></tr>
<tr><td>Extranodal disease</td></tr>
</table>

Βιολογικοί Προγνωστικοί Παράγοντες και Μοριακά Μονοπάτια στο Λέμφωμα Hodgkin

Θεραπευτικοί Στόχοι	→	Νέοι Παράγοντες
IL-10		Μονοκλωνικά Αντισώματα
CD30		***Brentuximab Vedotin***
BCL2		Αντινοηματικά Ολιγονουκλεοτίδια
NFK-B		Bortezomib
PD-1		***Nivolumab , Pebrolizumab***
CD20		Rituximab

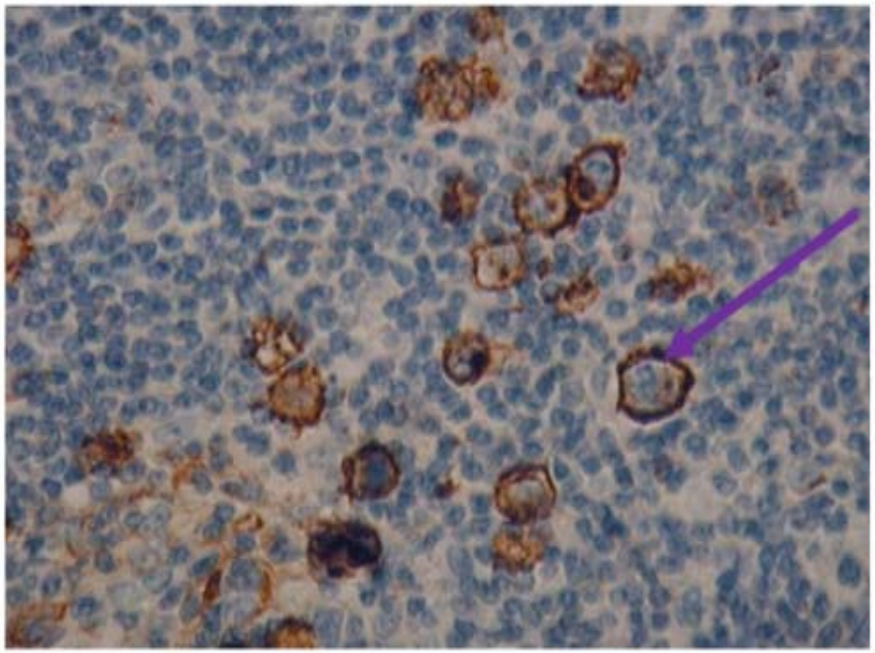
Διαθέσιμοι Νέοι Παράγοντες για τη Θεραπεία του Λεμφώματος Hodgkin.

Brentuximab Vedotin: 2012 2ης γραμμής

Nivolumab : 2015>3ης γραμμής

Pebrolizumab : 2016>3ης γραμμής

CD30: A Rational Target in HL



Hodgkin Reed-Sternberg (HRS) cell

- Very low expression on normal cells[2]
- In healthy tissue, limited to small numbers of activated B and T lymphocytes and natural killer cells[2]

Stein H, *Blood* 1985;66:848-858
2. Durkop H, *J Pathol* 2000;190:613-618

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody

ADC binds to CD30 — 1

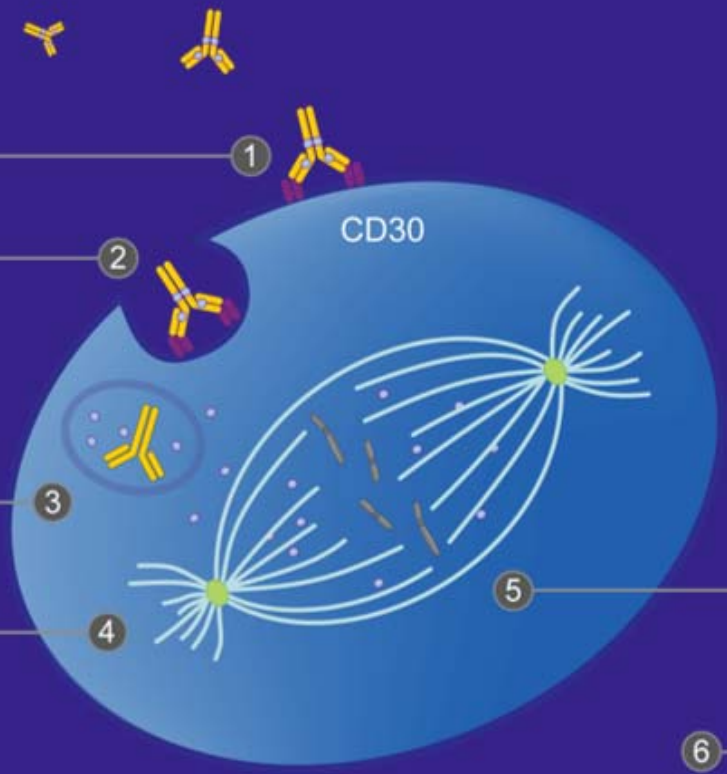
ADC-CD30 complex traffics to lysosome — 2

MMAE is released — 3

MMAE disrupts microtubule network — 4

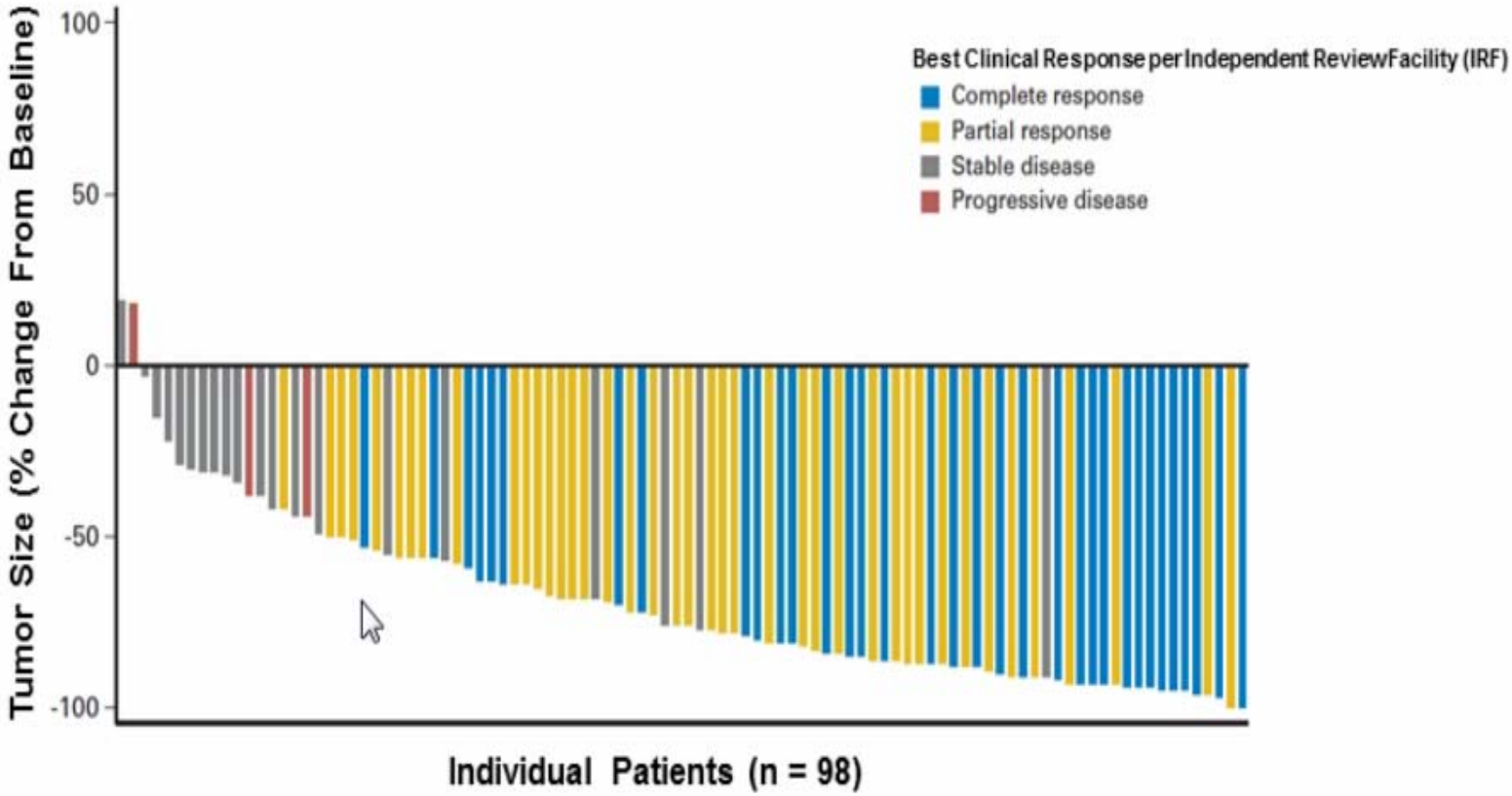
G2/M cell cycle arrest — 5

Apoptosis — 6



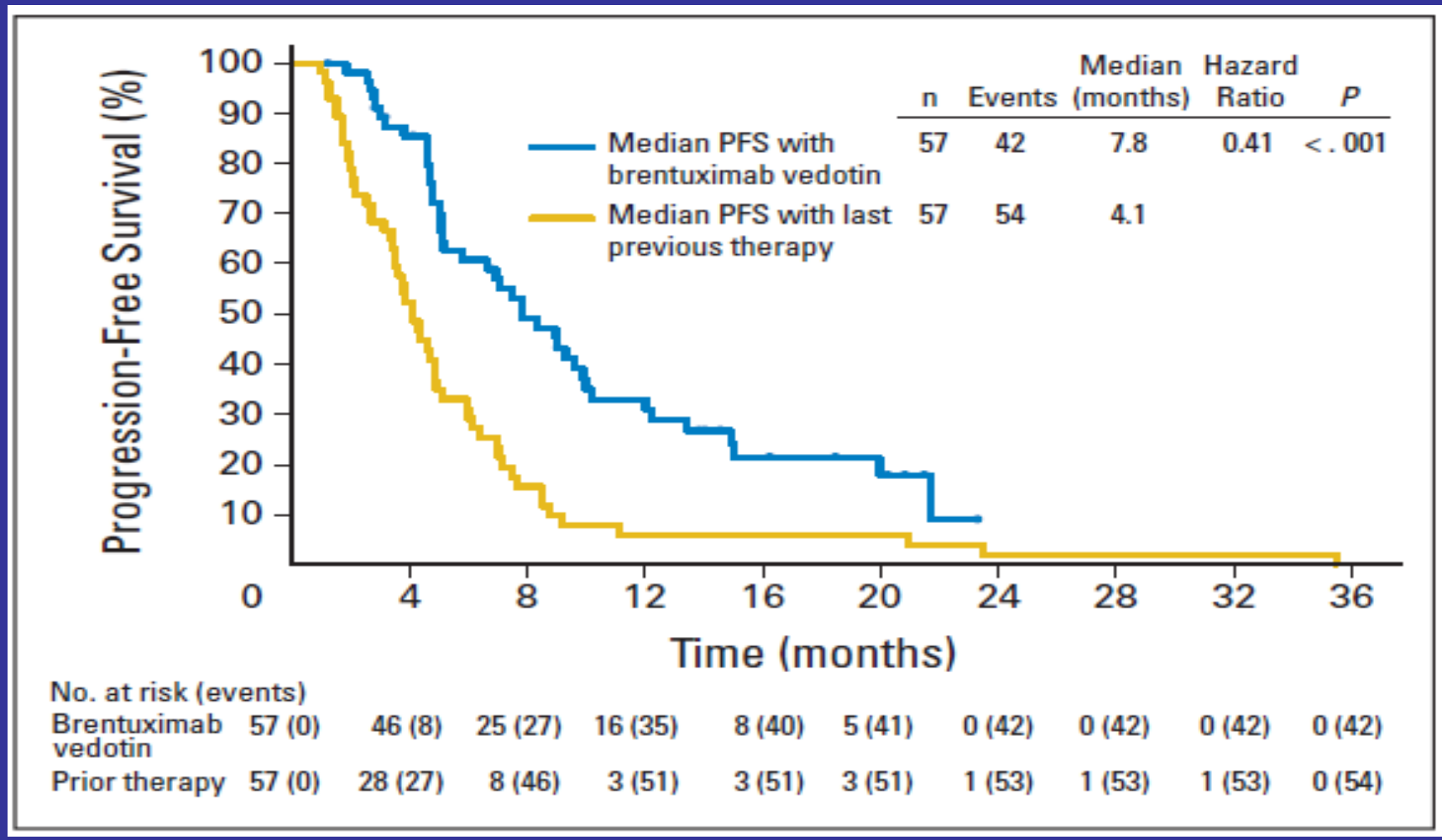
Brentuximab Vedotin in Relapsed/Refractory HL

- Pivotal study in 102 patients with relapsed/refractory HL after ASCT
- 75% objective response rate with brentuximab vedotin
- 34% complete response rate

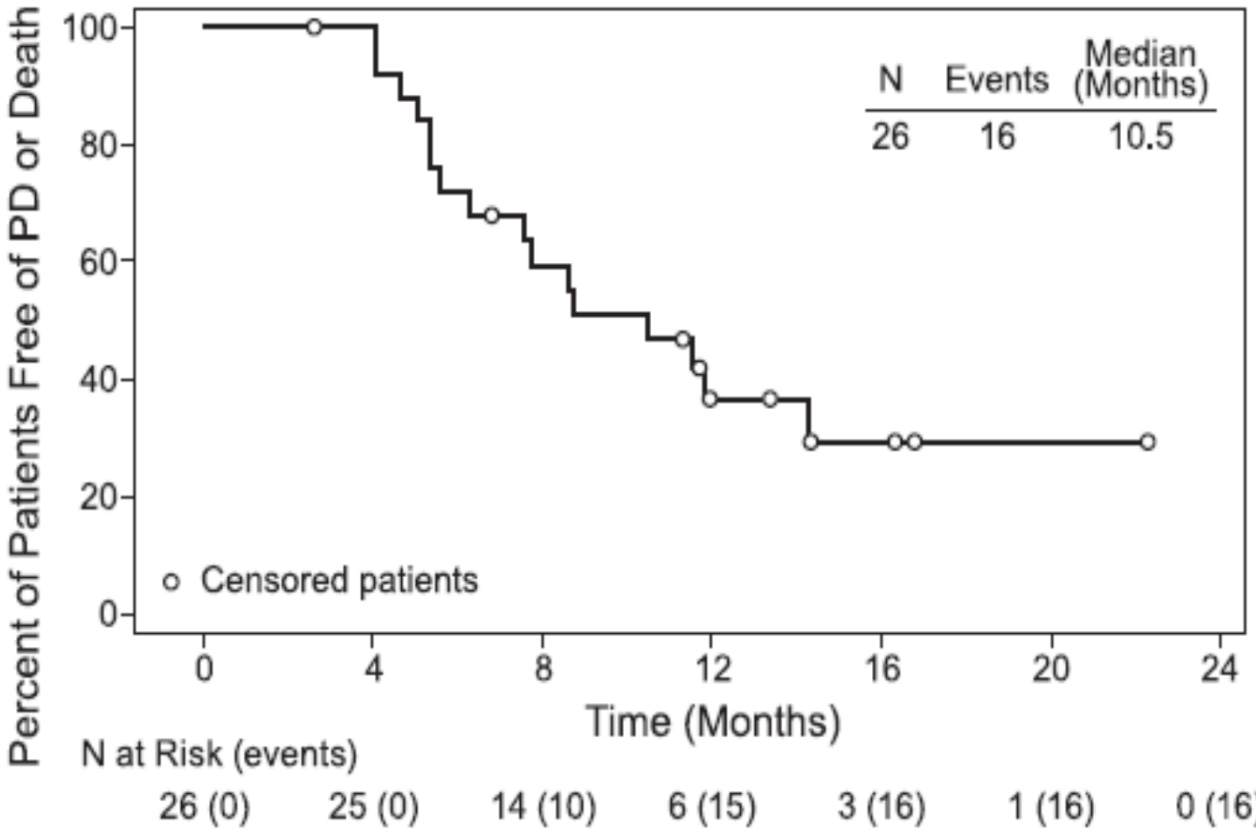


Younes A, et al. *J Clin Oncol.* 2012;30(18):2183-2189.

Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma



Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older

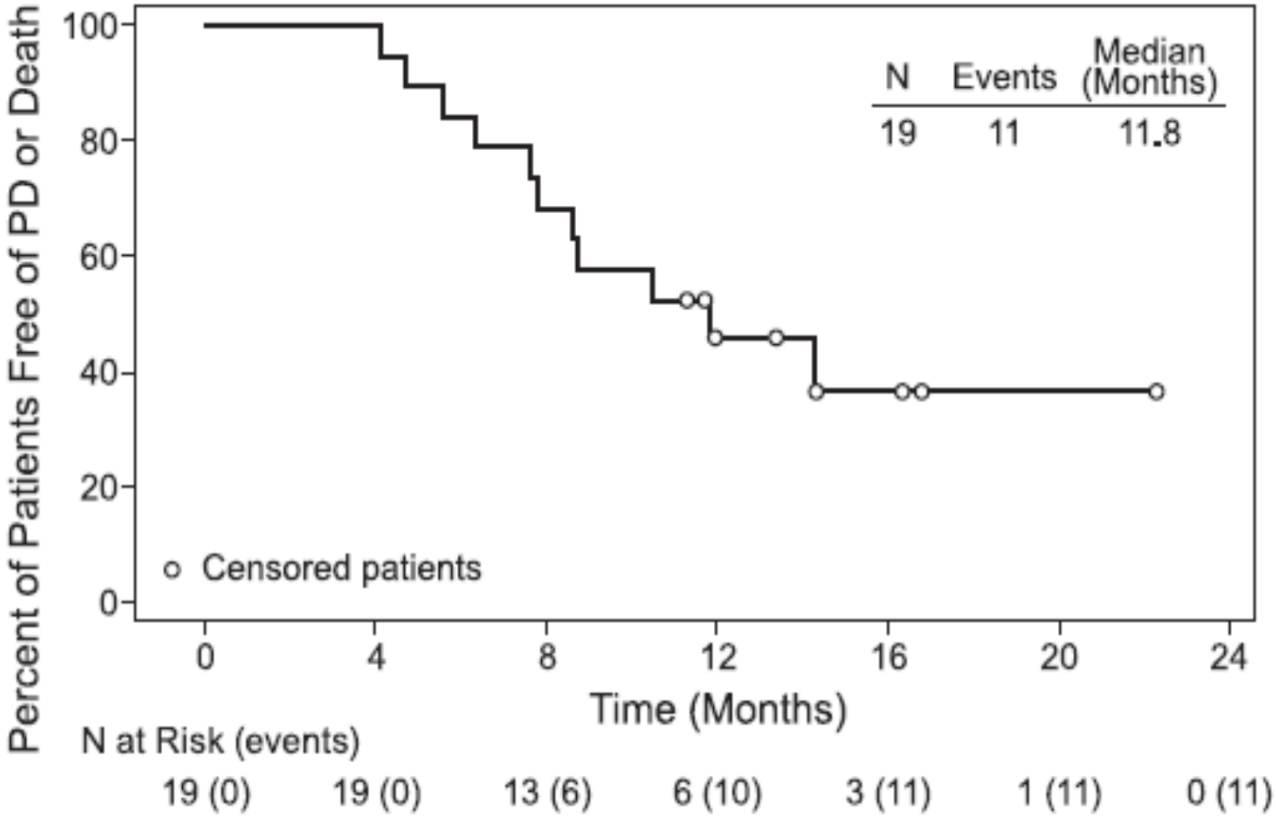


Key Points

- Frontline brentuximab vedotin monotherapy provided a 92% ORR and was generally well tolerated in elderly HL patients.

A.F. TORRES ***Blood.* 2015**

Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older



A.F. TORRES Blood 2015

Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older

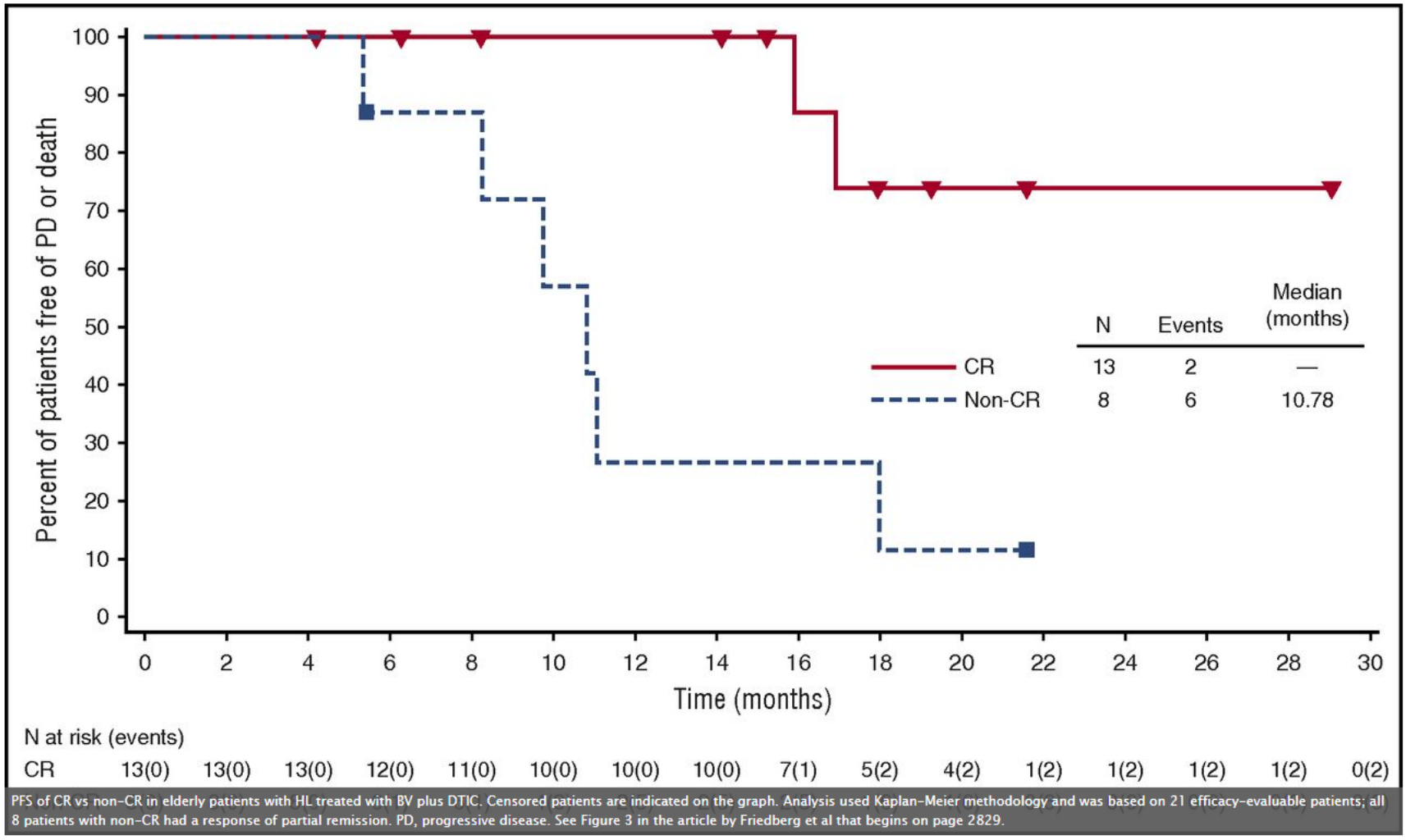
Table 5. Treatment-emergent AEs occurring in at least 15% of patients treated with frontline brentuximab vedotin monotherapy

	N = 27		
Event*	Grade 1/2 n (%)	Grade 3† n (%)	Total n (%)
Peripheral sensory neuropathy	14 (52)	7 (26)	21 (78)
Fatigue	12 (44)	0	12 (44)
Nausea	12 (44)	0	12 (44)
Peripheral edema	10 (37)	0	10 (37)
Diarrhea	9 (33)	0	9 (33)
Decreased appetite	8 (30)	0	8 (30)
Constipation	7 (26)	0	7 (26)
Alopecia	5 (19)	0	5 (19)
Cough	5 (19)	0	5 (19)
Muscular weakness	5 (19)	0	5 (19)
Pruritus	5 (19)	0	5 (19)
Rash	3 (11)	2 (7)	5 (19)
Urinary tract infection	4 (15)	1 (4)	5 (19)
Vomiting	5 (19)	0	5 (19)
Deep vein thrombosis	4 (15)	0	4 (15)
Dizziness	4 (15)	0	4 (15)
Maculopapular rash	3 (11)	1 (4)	4 (15)
Weight decreased	4 (15)	0	4 (15)

*AEs were summarized using MedDRA version 15.1 and graded using the NIH National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
†No grade 4 events were reported for these AE terms.

A.F. TORRES Blood 2015

Initial Hodgkin treatment of the frail elderly with Brentuximab & DTIC



PFS of CR vs non-CR in elderly patients with HL treated with BV plus DTIC. Censored patients are indicated on the graph. Analysis used Kaplan-Meier methodology and was based on 21 efficacy-evaluable patients; all 8 patients with non-CR had a response of partial remission. PD, progressive disease. See Figure 3 in the article by Friedberg et al that begins on page 2829.

D.Straus blood 2017

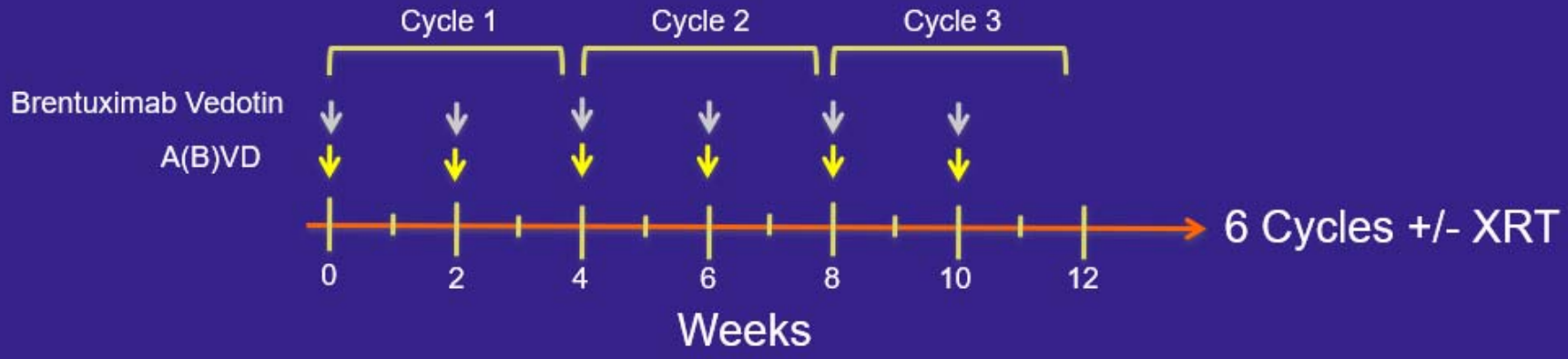
Frontline Therapy With Brentuximab Vedotin Combined with ABVD or AVD in patients with Newly Diagnosed Advanced-Stage Hodgkin Lymphoma

Abstract 798 ASH 2012

Ansell SM

Study Design

- Phase I, multicenter, dose-escalation study
- Major eligibility criteria
  - Treatment-naïve HL patients
  - Age ≥18 to ≤60 years
  - Stage IIA bulky disease or Stage IIB-IV disease
- Treatment design
  - 28-day cycles (up to 6 cycles) with dosing on Days 1 and 15
  - Dose escalation cohorts – I-6, II-13, III-6, IV-6, expansion-20



Ansell SM, et al. *Blood.* 2012;120: Abstract 798.

Response Results at End of Front-Line Therapy

Response per Investigator[a]	ABVD with brentuximab vedotin N = 22	AVD with brentuximab vedotin N = 25
Response at end of front-line therapy, n (%)		
Complete remission	21 (95)	24 (96)
Progressive disease	0	1 (4)
Not evaluable due to AEs	1[b] (5)	0

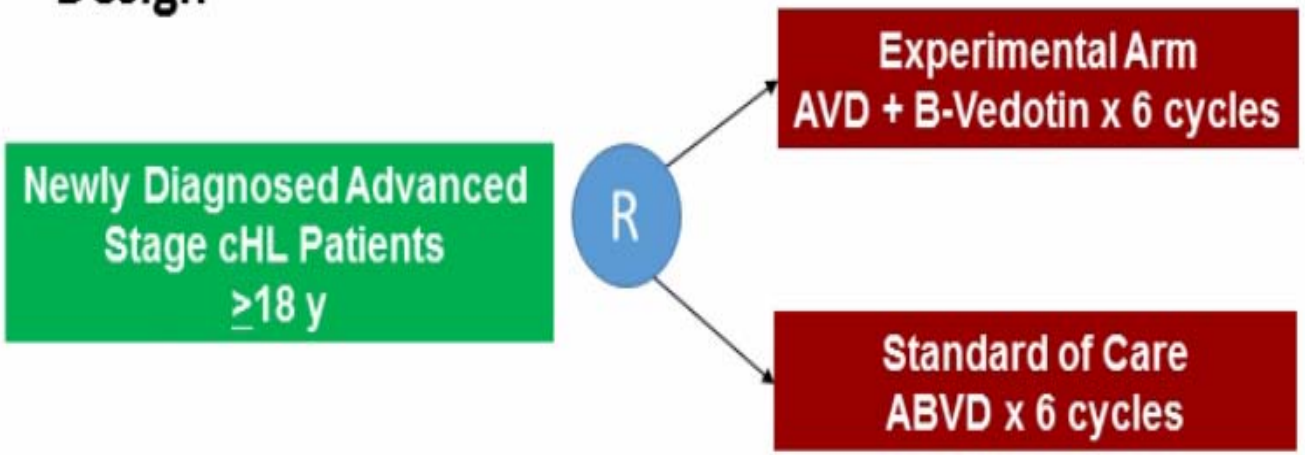
a Assessed using Cheson 2007
b Patient had a Grade 5 event of pulmonary toxicity prior to the end of front-line therapy

- Response results at end of front-line therapy:
  - ABVD cohorts: 21 of 22 CR (95%)
  - AVD cohorts: 24 of 25 CR (96%)
- In addition, 1 patient withdrew consent and 3 patients were lost to follow-up prior to completion of front-line therapy and were not evaluable for response

Ansell SM, et al. *Blood.* 2012;120: Abstract 798.

Phase III Frontline HL (ECHELON-1)

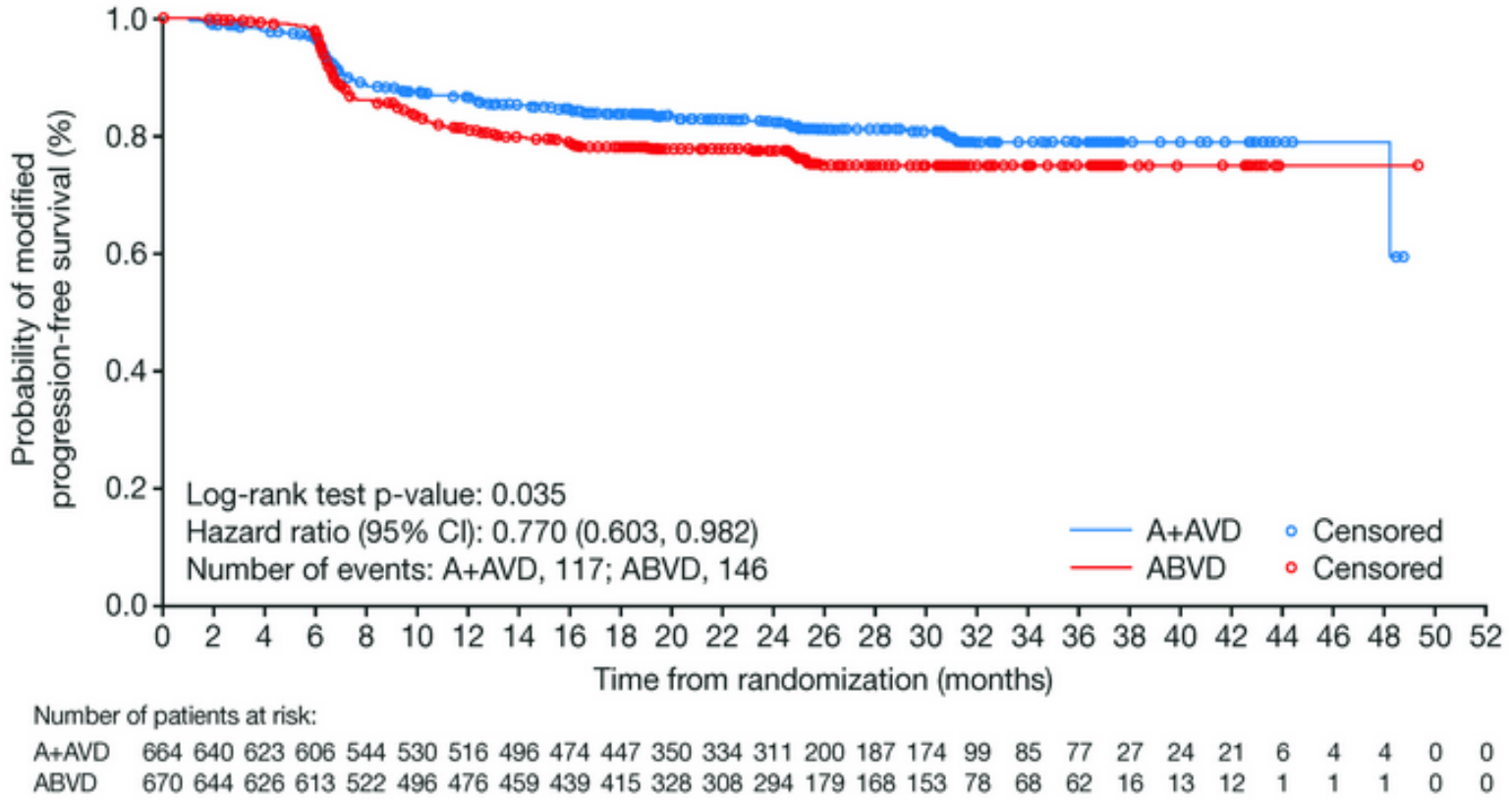
- **Design**



- Target n = 1040
- Primary outcome measure: PFS

Frontline HL : Phase III (ECHELON-1) Trial

Conclusions: Compared with standard ABVD, A+AVD as frontline therapy improves outcome for patients with advanced HL including a 23% risk reduction in progression, death, or need for additional anticancer therapy. This establishes A+AVD as a new frontline option for patients with advanced-stage HL.

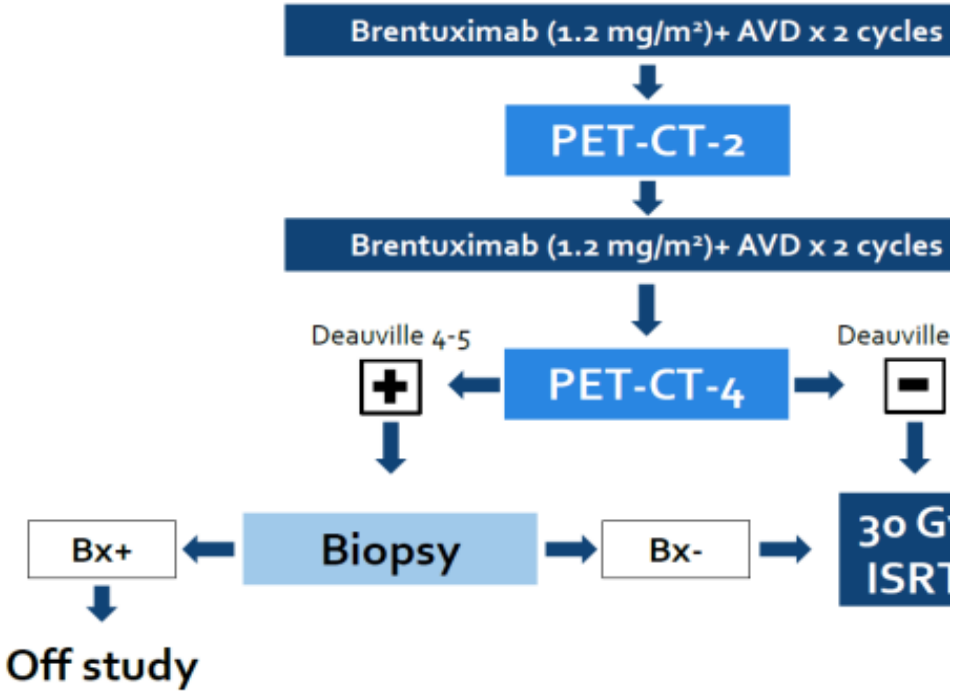


ASH 2017

Pilot study of brentuximab vedotin plus AVD/ISRT in previously untreated early-stage, unfavorable-risk HL

Objectives: *Primary:* safety, pulmonary toxicity; *Secondary:* prognostic significance of interim PET (Deauville criteria), preliminary efficacy

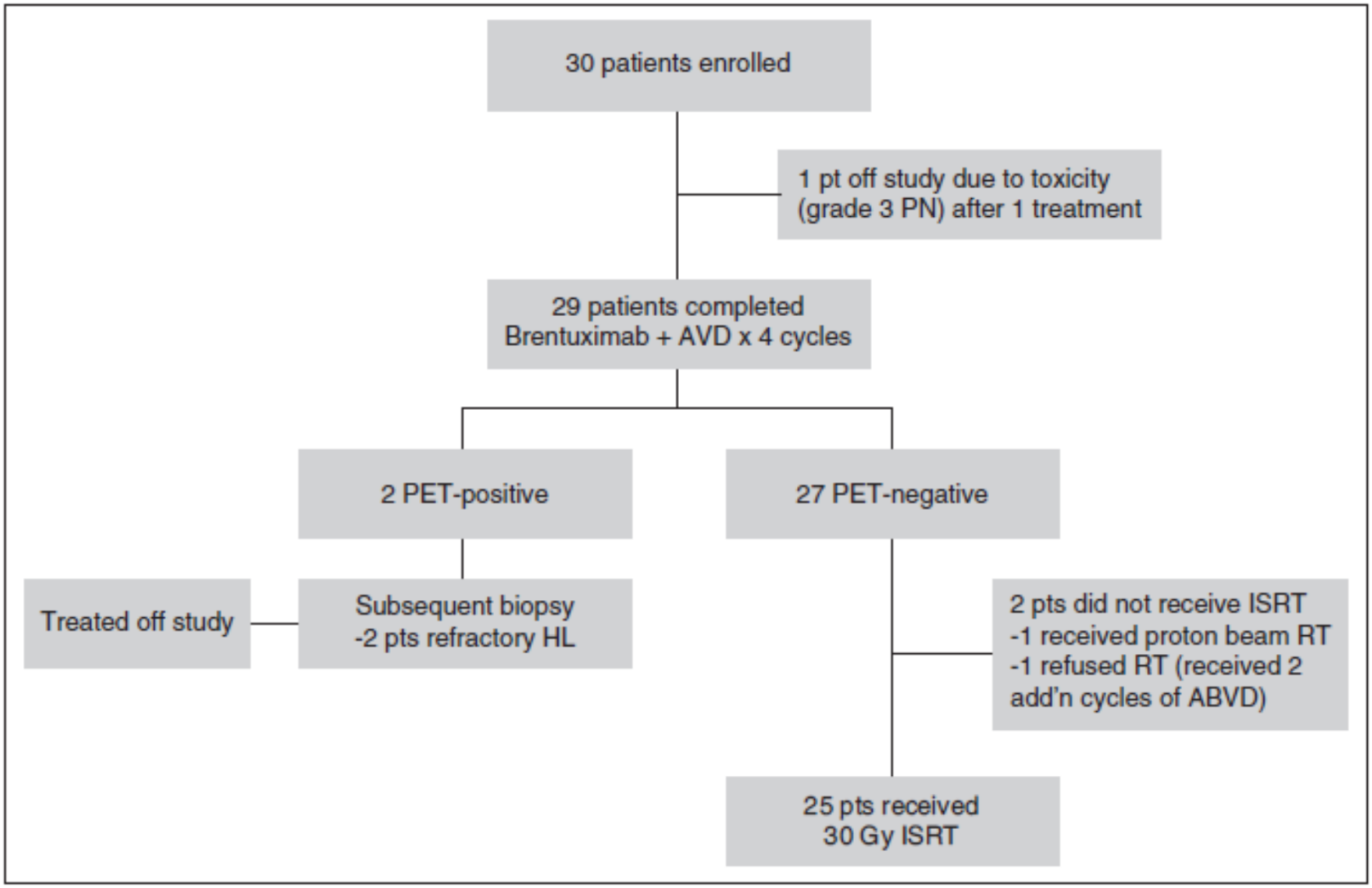
Pt Characteristics, N=30	
Median age, yrs (range)	31 (18–59)
CD30+ HL, %	100
CD20+	13
EBV +, n=27	11
Stage II, %	100
Unfavorable risk features, ≥1 (%)	100
B symptoms, %	47
ESR >50 or ESR >39 with B-symptoms, %	67
Nodal sites >2, %	67
Extranodal involvement, %	47
Bulk ≥10 cm, %	47
Anterior mediastinal mass >10 cm, n=14; median size, cm (range)	13 (10–16.9)
Bulky by MSK definition*, n=28 (%)	86



* >7 cm in MTD or >7 cm in MCD

Kumar A et al. ICML 2015, Oral presentation from Abstract #88

Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma



Kumar 2015

Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma

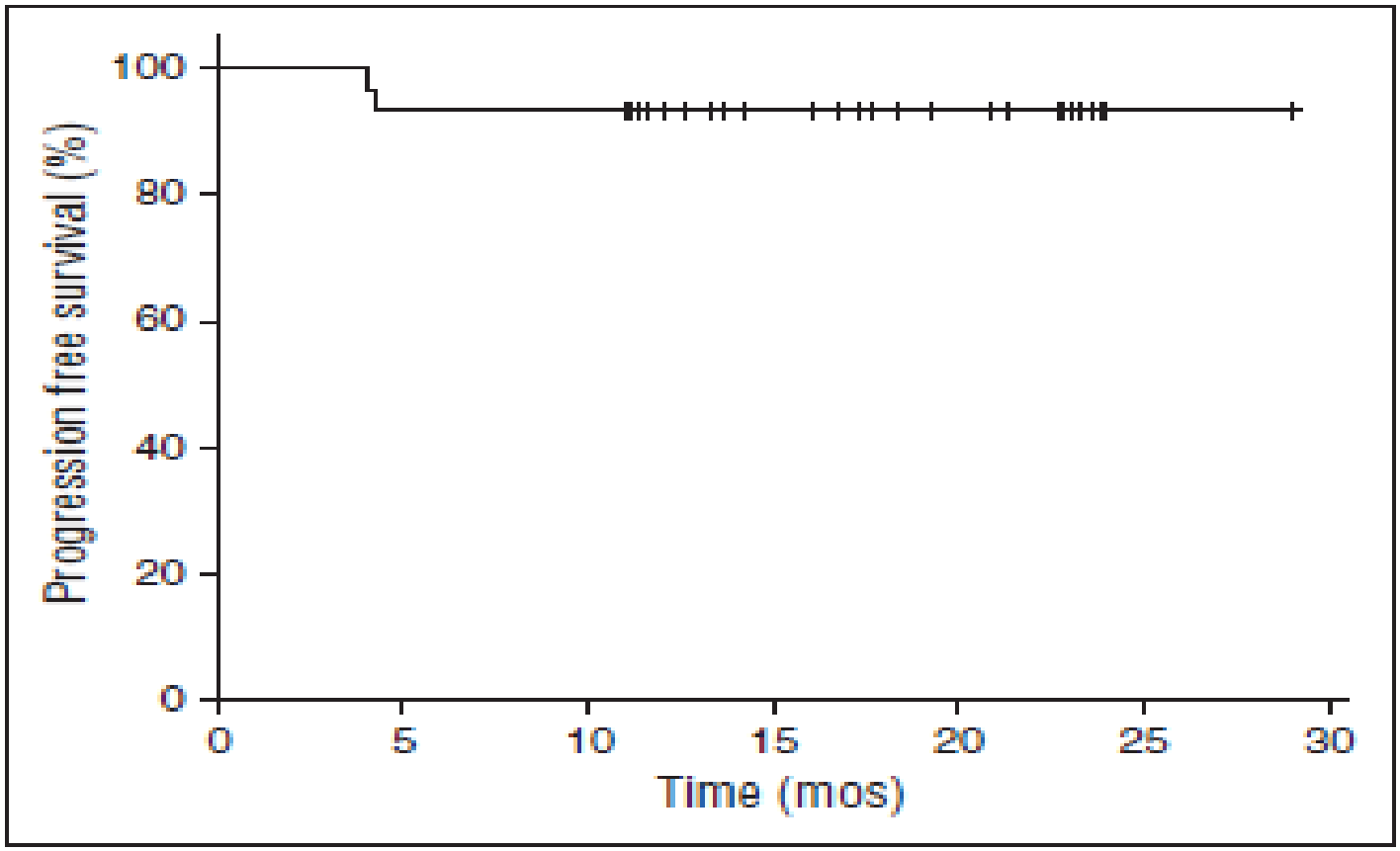


Figure 4. PFS by intent to treat (N = 30) with median follow up of 18.8 months.

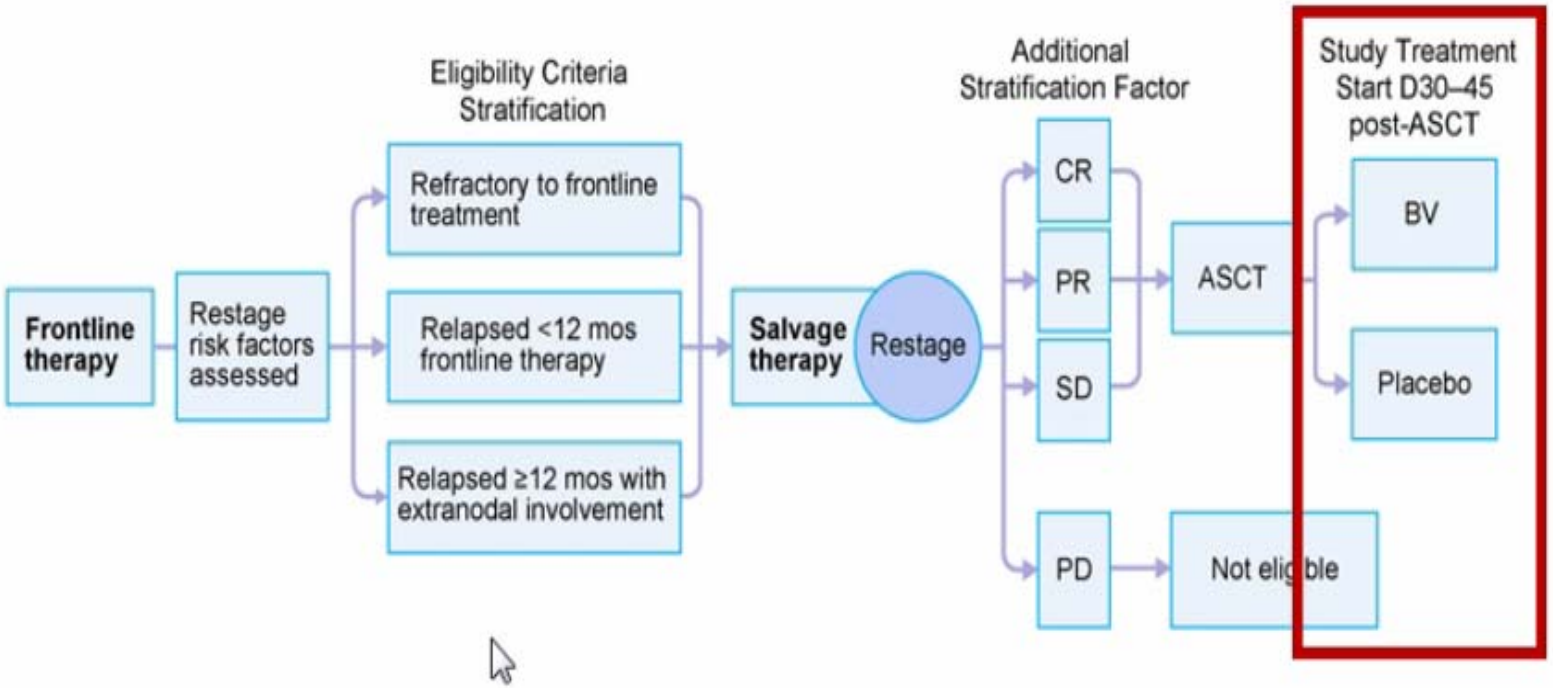
Kumar 2015

734 A Pilot Study of Brentuximab Vedotin and AVD Chemotherapy Followed By 20 Gy Involved-Site Radiotherapy in Early Stage, Unfavorable Risk Hodgkin Lymphoma

Conclusion: BV+AVD x 4 cycles followed by 20Gy ISRT is an effective treatment program for early stage, unfavorable risk HL, including a high proportion of patients with bulky disease. As with 4 cycles of escalated BEACOPP tested in the GHSG HD11 clinical trial, 20Gy ISRT appears to be adequate consolidation after BV+AVD x 4 cycles. A third cohort of this pilot study is currently accruing in which patients receive BV+AVD x 4 cycles followed by 30Gy consolidation volume radiation. There is also a planned 4th cohort with no radiotherapy for PET-negative patients after 4 cycles of BV+AVD. After completion of the 4 cohorts, we plan to recommend the therapeutic strategy with the greatest efficacy and least toxicity to be further studied in a larger, randomized prospective study for early stage, bulky HL. Updated response data for all patients will be presented at the meeting.

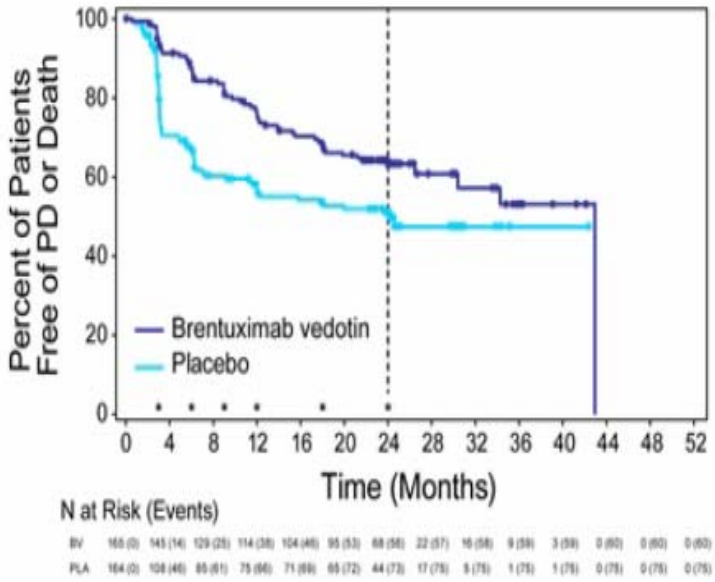
A. KUMAR ASH 2017

BV after ABMT
Study Design and Key Eligibility Criteria



Progression-Free Survival

PFS per IRF

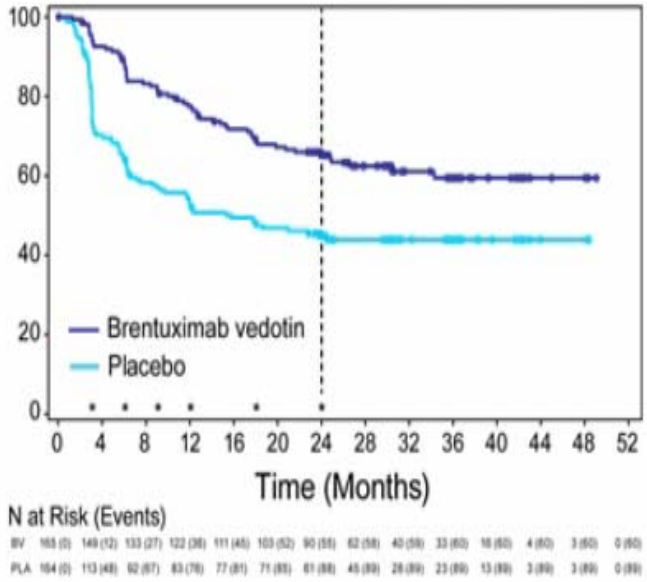


N at Risk (Events)

BV	165 (0)	145 (14)	129 (25)	114 (38)	104 (46)	95 (53)	68 (56)	22 (57)	16 (58)	9 (59)	3 (59)	0 (60)	0 (60)	0 (60)	
PLA	164 (0)	108 (46)	85 (61)	75 (66)	71 (69)	65 (72)	44 (73)	17 (75)	5 (75)	1 (75)	1 (75)	0 (75)	0 (75)	0 (75)	

	BV (N = 165)	Placebo (N = 164)
Hazard Ratio (95% CI)	0.57 (0.40–0.81, P = .001)	
Events	60	75
Median PFS (months)	43	24
2-year PFS rate	63%	51%

PFS per Investigator†



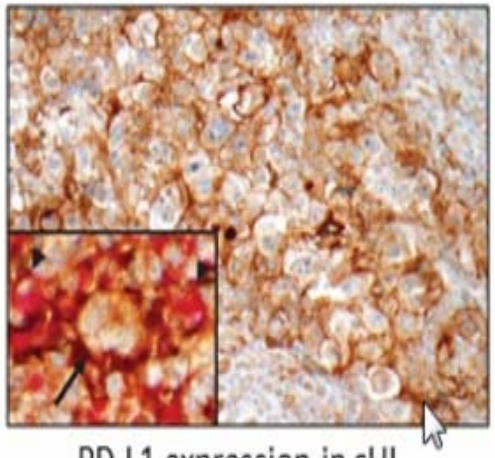
N at Risk (Events)

BV	165 (0)	149 (12)	133 (27)	122 (38)	111 (45)	103 (52)	90 (55)	62 (58)	40 (59)	33 (60)	16 (60)	4 (60)	3 (60)	0 (60)	
PLA	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	71 (85)	61 (88)	45 (89)	28 (89)	23 (89)	13 (89)	3 (89)	3 (89)	0 (89)	

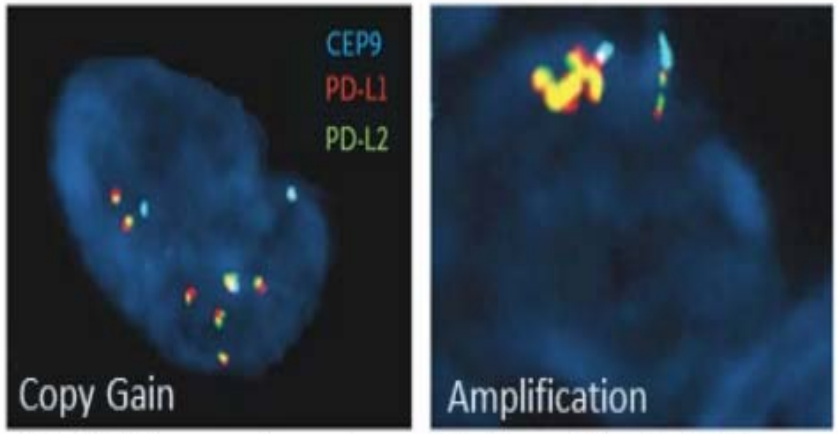
	BV (N = 165)	Placebo (N = 164)
Hazard Ratio (95% CI)	0.50 (0.36–0.70)	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

PD-1 Immune Checkpoint Pathway

- Classical Hodgkin lymphoma (cHL) is characterized by expression of PD-L1 and PD-L2 on malignant Reed–Sternberg cells and on inflammatory cells in the tumor microenvironment
- PD-L1 expression in cHL frequently occurs in the setting of genetic amplification of the 9p24.1 locus



PD-L1 expression in cHL

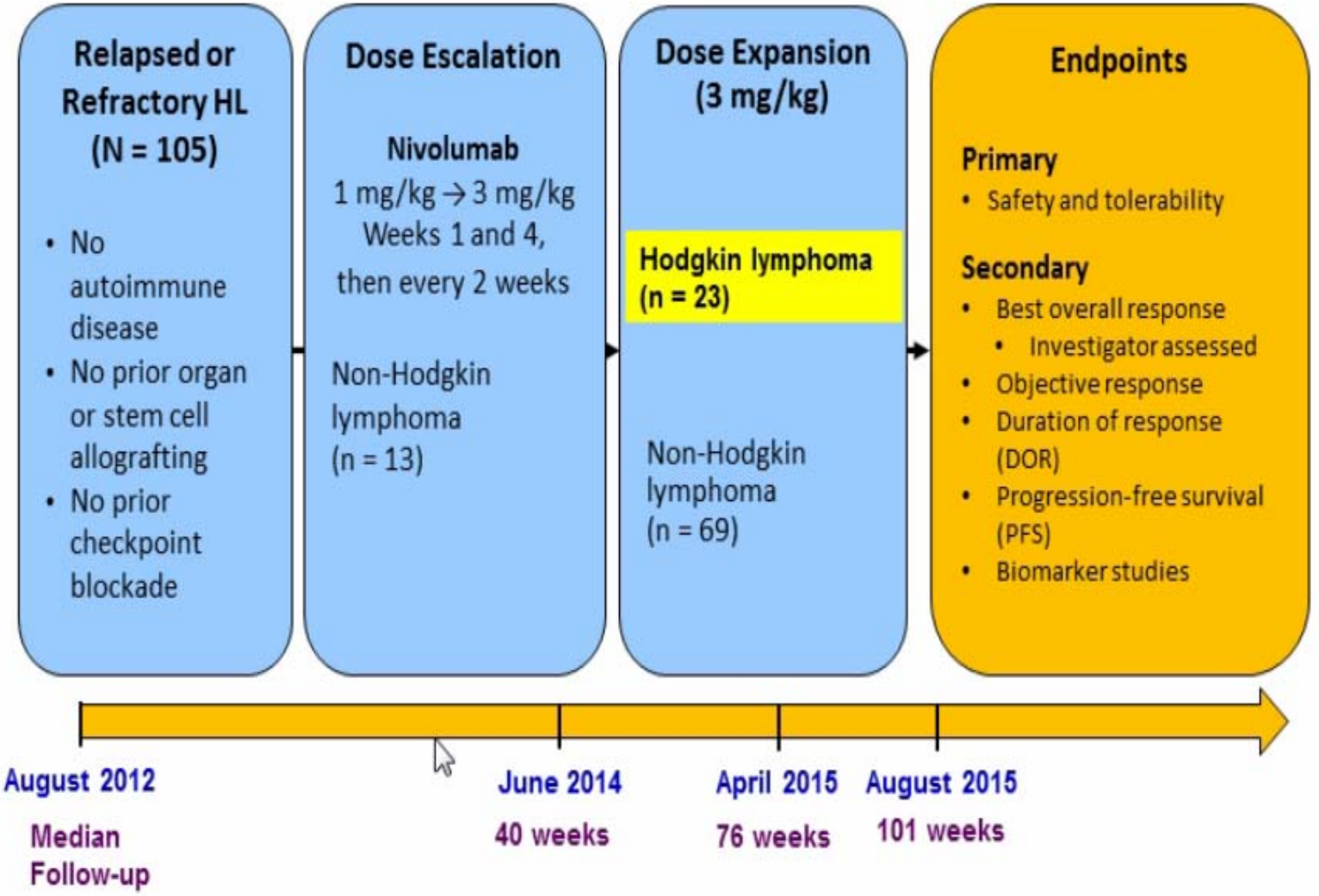


PD-L1/L2 copy gains and amplification visible by FISH

Chen BJ, et al. *Clin Cancer Res*. 2013;19(13):3462-3473. Ansell SM, et al. *N Engl J Med*. 2015;372(4):311-319.

Ansell SM, et al. *Blood*. 2015;126: Abstract 583.

Study Design



Ansell SM, et al. *Blood*. 2015;126: Abstract 583.

Results

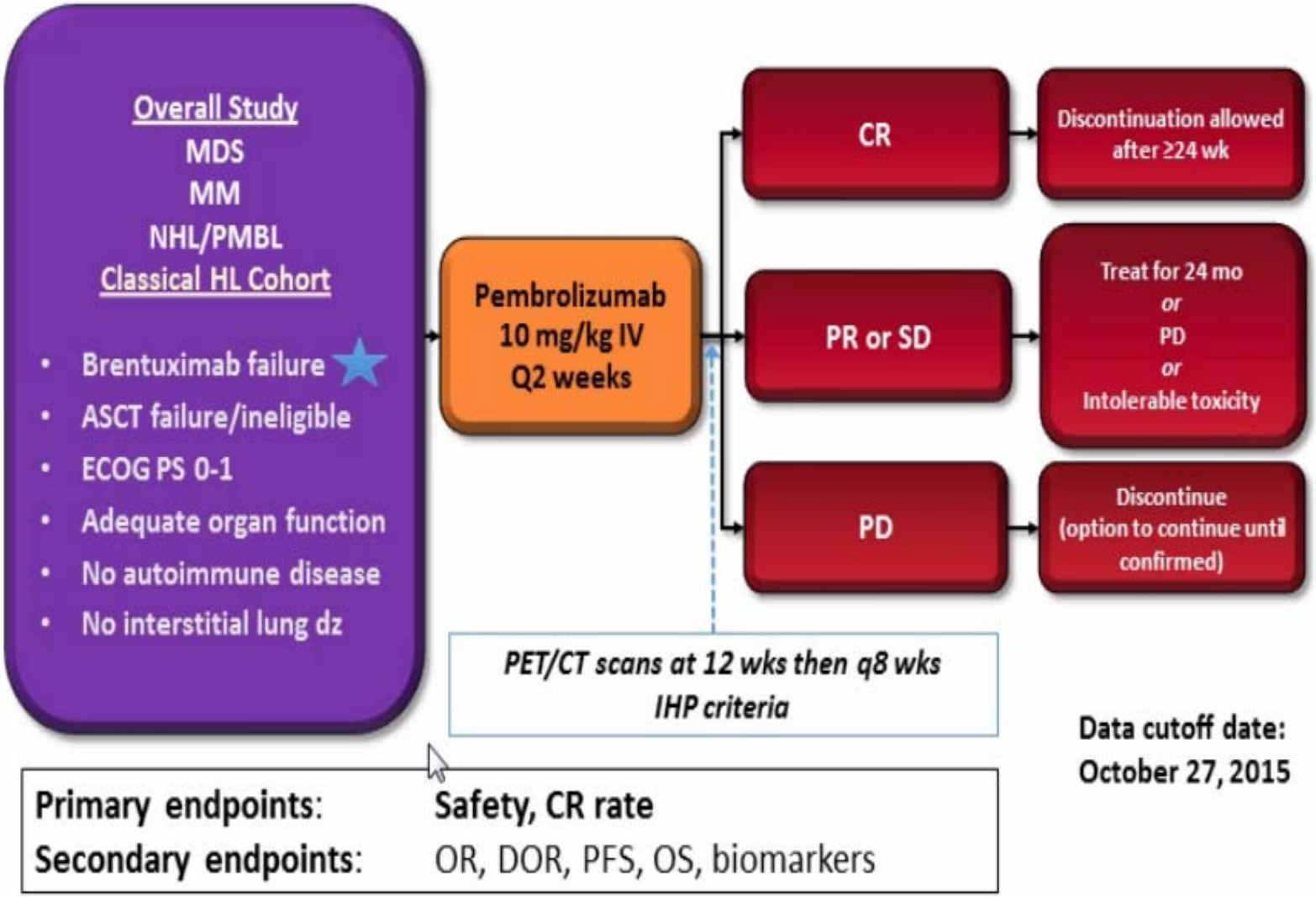
Prior Autotransplant, n (%)	18 (78)
Prior BV, n (%)	18 (78)
Number of prior therapies, median (range)	5 (2-15)

	cHL (n = 23)
Overall response, n (%)	**20 (87)**
24-week PFS, %	**86%**
Median duration of response, weeks (range)	**NR (18-82+)**

NR, not reached

Ansell SM, et al. *Blood*. 2015;126: Abstract 583.
Ansell SM , et al. N Engl J Med 2015

KEYNOTE-013 Study



Data cutoff date:
October 27, 2015

KEYNOTE -013 Study

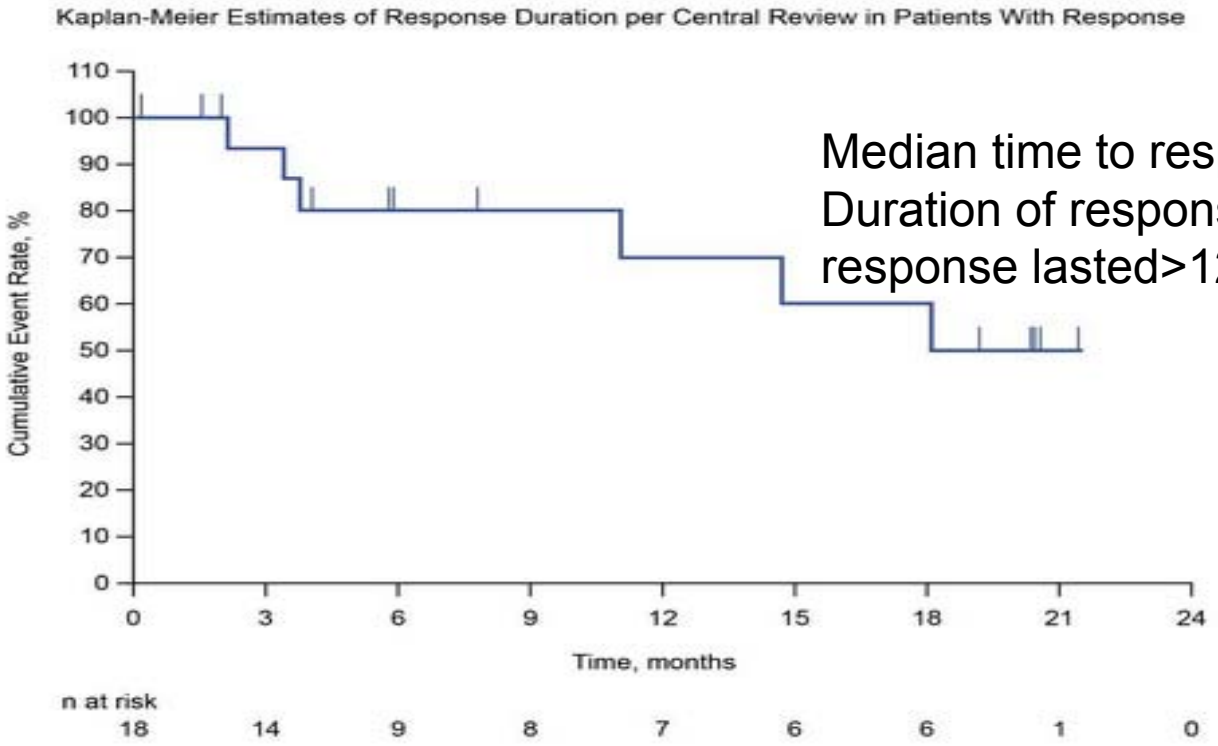
Best Overall Response

	All Patients N = 31	
	Blinded Independent Central Review	
	n (%)	95% CI
ORR	18 (58%)	39-76
CR	6 (19%)	8-38
PR	12 (39%)	22-58
SD	7 (23%)	10-41
PD	6 (19%)	8-38

P. ARMAD ASH 2016

KEYNOTE- 013 Study

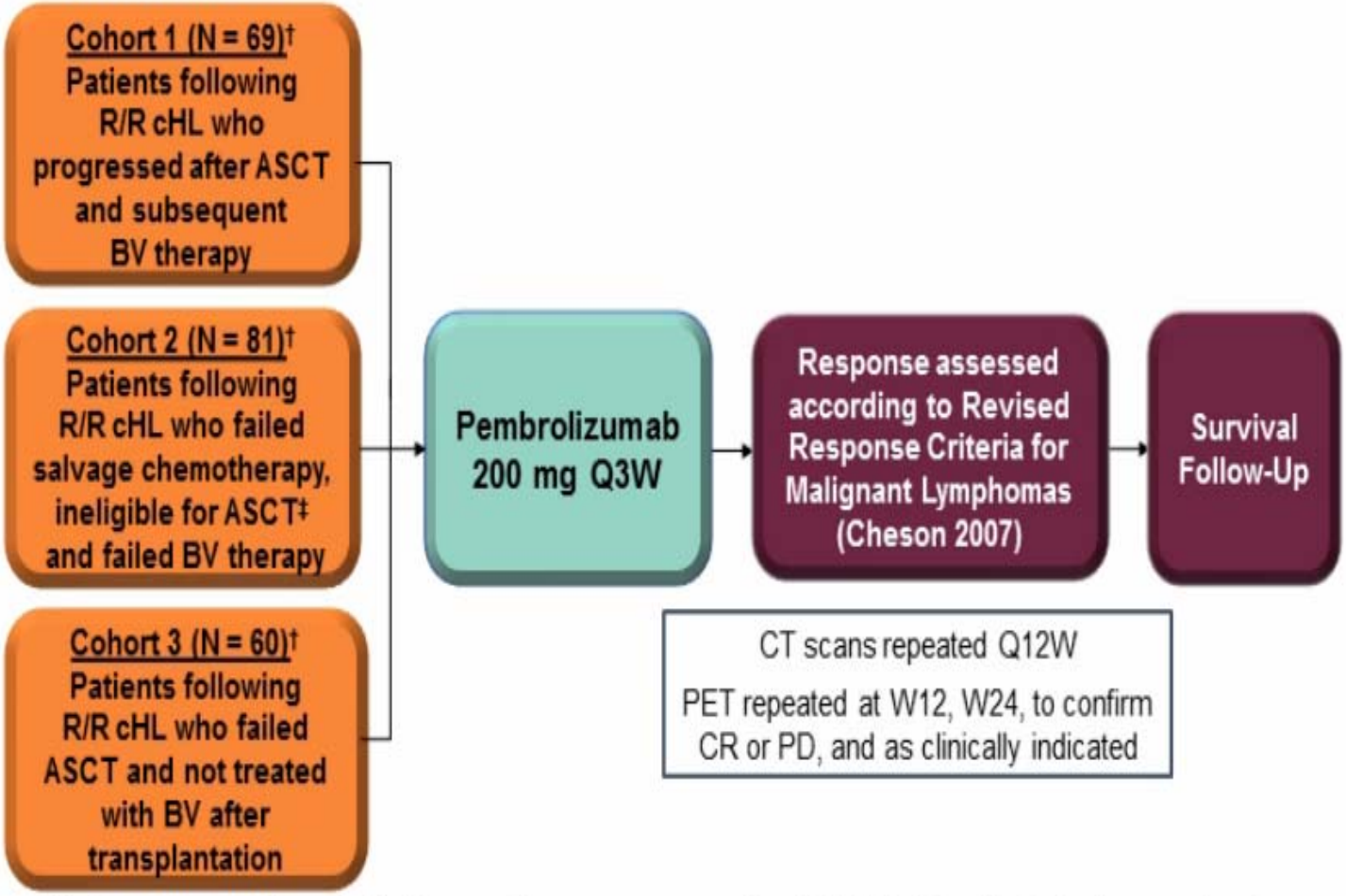
Conclusions: With nearly 2.5 years of median follow-up, the present results demonstrate that a subset of heavily pretreated patients who failed BV therapy can achieve a long-term response with single-agent pembrolizumab, without consolidative therapy. PD-1 blockade may offer a new treatment paradigm for patients with relapsed/refractory cHL, supporting the hypothesis that this tumor has a genetic dependence on the PD-1 pathway.



Median time to response 2,8mo
Duration of response: 70% of response lasted>12mo

P. ARMAD ASH 2016

KEYNOTE-087: Study Design

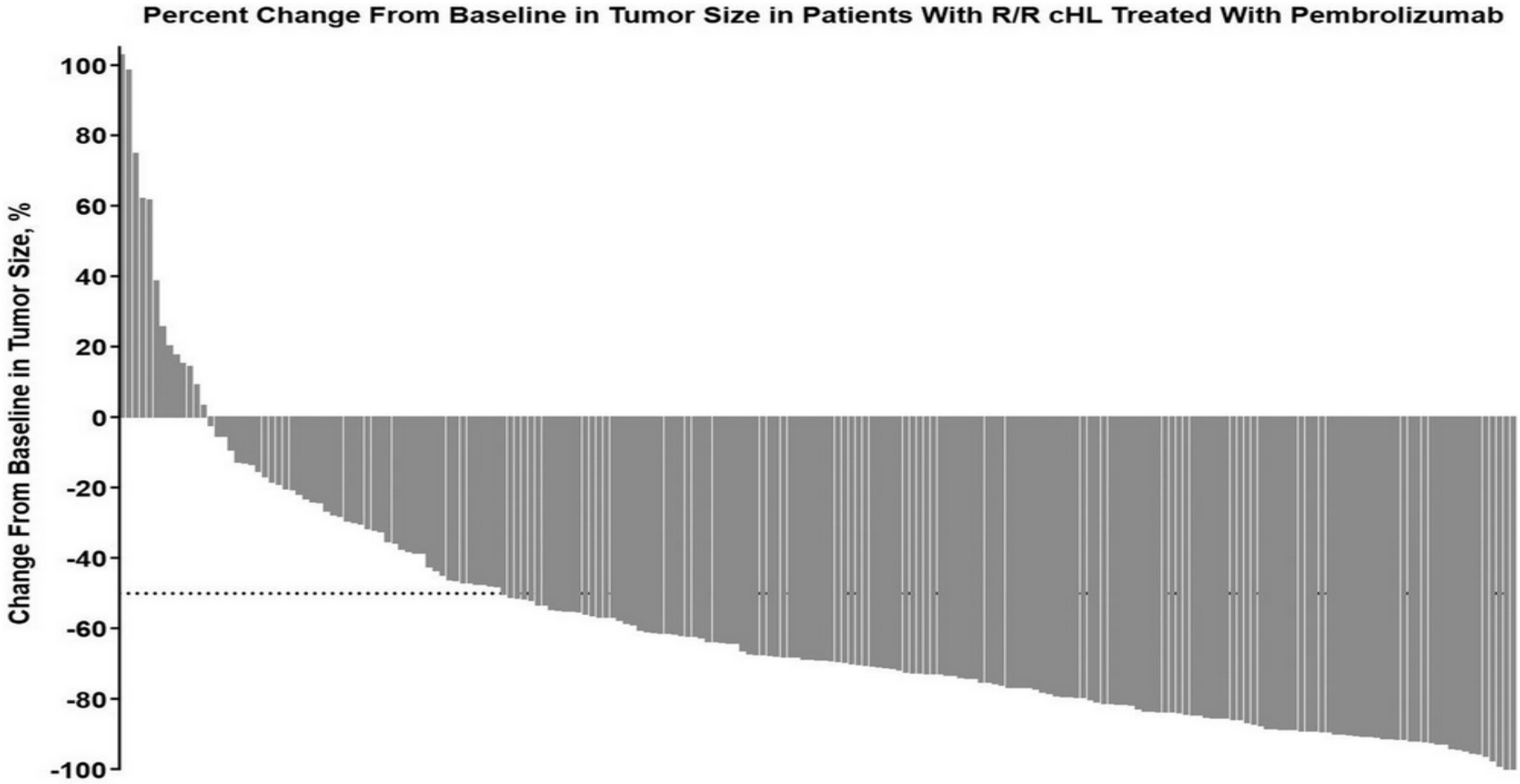


- **Primary end point:** Overall response rate (ORR; blinded independent central review)
- **Secondary end points:** ORR (investigator review), DOR, PFS, OS

†Patients in all cohorts had to have ECOG PS 0-1
‡Unable to achieve a CR or PR to salvage chemotherapy

ClinicalTrials.gov registration number: NCT02453594

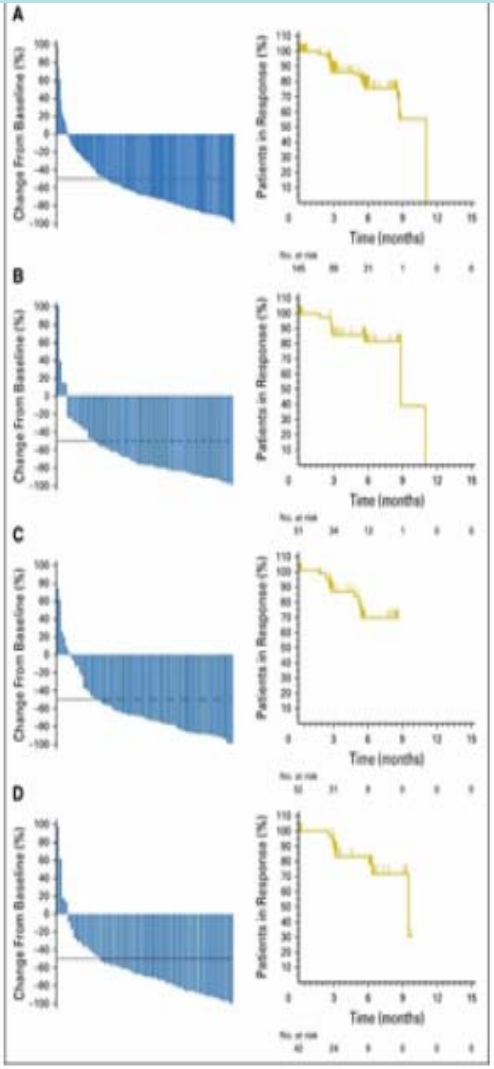
KEYNOTE -087 study



C. Moskowitz ASH 2016

KEYTONE – 087 STUDY

	By Blinded Independent Central Review (BCIR) All Patients N = 210		By Investigator Review All Patients N = 210	
	n (%)	95% CI†	n (%)	95% CI†
ORR	**145 (69.0)**	**62.3-75.2**	143 (68.1)	61.3-74.3
Complete remission‡	47 (22.4)	16.9-28.6	63 (30.0)	23.9-36.7
Partial remission	98 (46.7)	39.8-53.7	80 (38.1)	31.5-45.0
Stable disease	31 (14.8)	10.3-20.3	40 (19.0)	14.0-25.0
Progressive disease	30 (14.3)	9.9-19.8	23 (11.0)	7.1-16.0
Unable to determine	4 (1.9)	0.5-4.8	4 (1.9)	0.5-4.8



Chen R., J Clinic Oncol 2017

Συμπεράσματα Ι

- Στο **Λέμφωμα Hodgkin** η εφαρμογή του PET-CT και οι νέοι παράγοντες θα καθορίσουν την νέα εποχή των θεραπειών με λιγότερες επιπλοκές → **ιάσιμη νεοπλασία**.

Σε περιορισμένου σταδίου ,ευνοϊκής πρόγνωσης νόσο, ο μικρός αριθμός(2-4) κύκλων του συνδυασμού ABVD+/- IFRT (20Gy) παραμένει θεραπεία εκλογής.

ΣΥΜΠΕΡΑΣΜΑΤΑ II

Σε περιορισμένα στάδια με δυσμενή πρόγνωση όπως και σε προχωρημένα ο συνδυασμός **Brentuximab+AVD** ως θεραπεία 1ης γραμμής υπόσχεται:

- υψηλά ποσοστά υφέσεων PET- ve
- μείωση συχνότητας των υποτροπών
- περιορισμό της ανάγκης χορηγησης θεραπείας διάσωσης.

Brentuximab:is it time for a new "B" in ABVD?

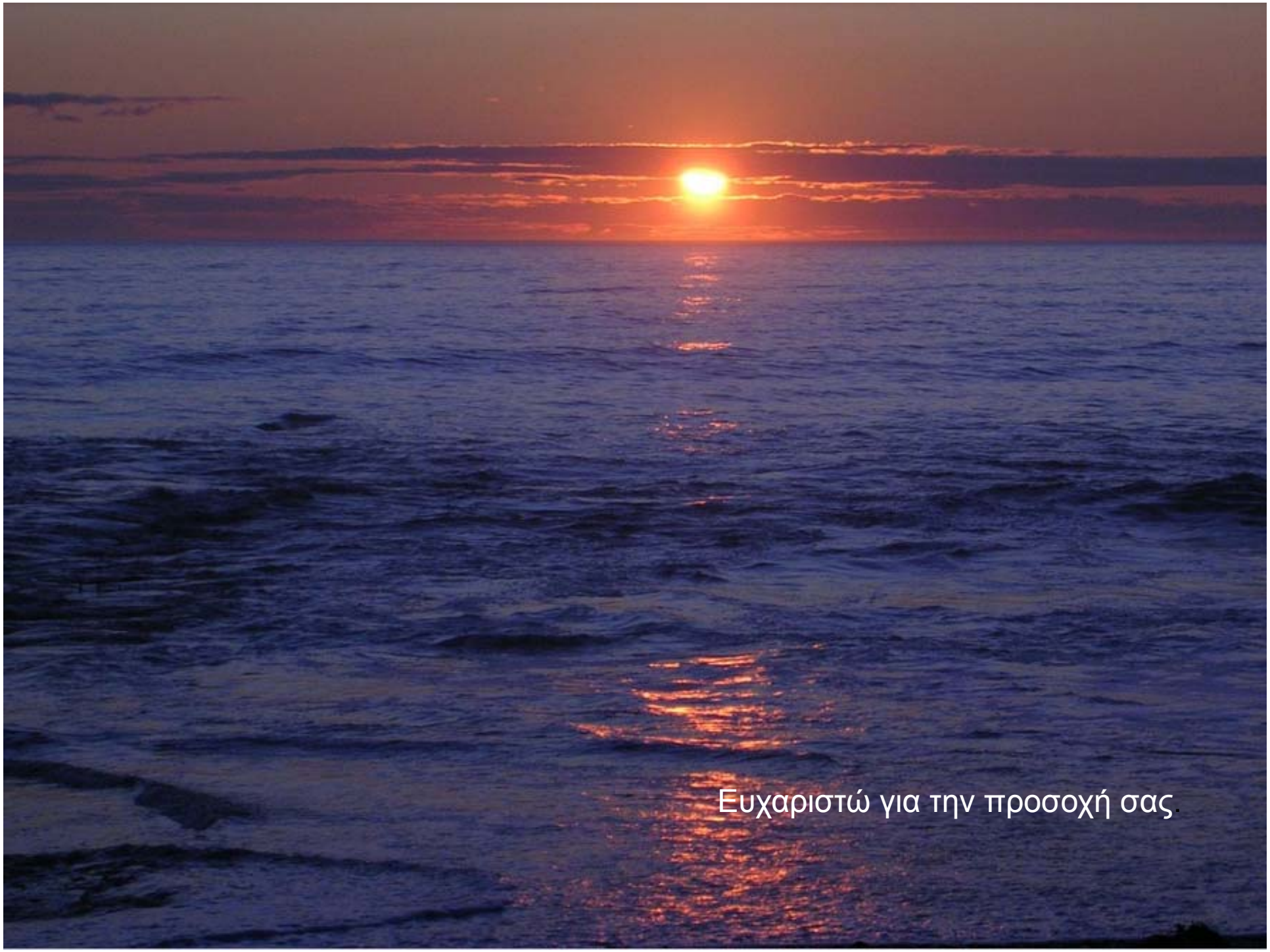
D.M. Stephens Blood 2017

IT IS TIME

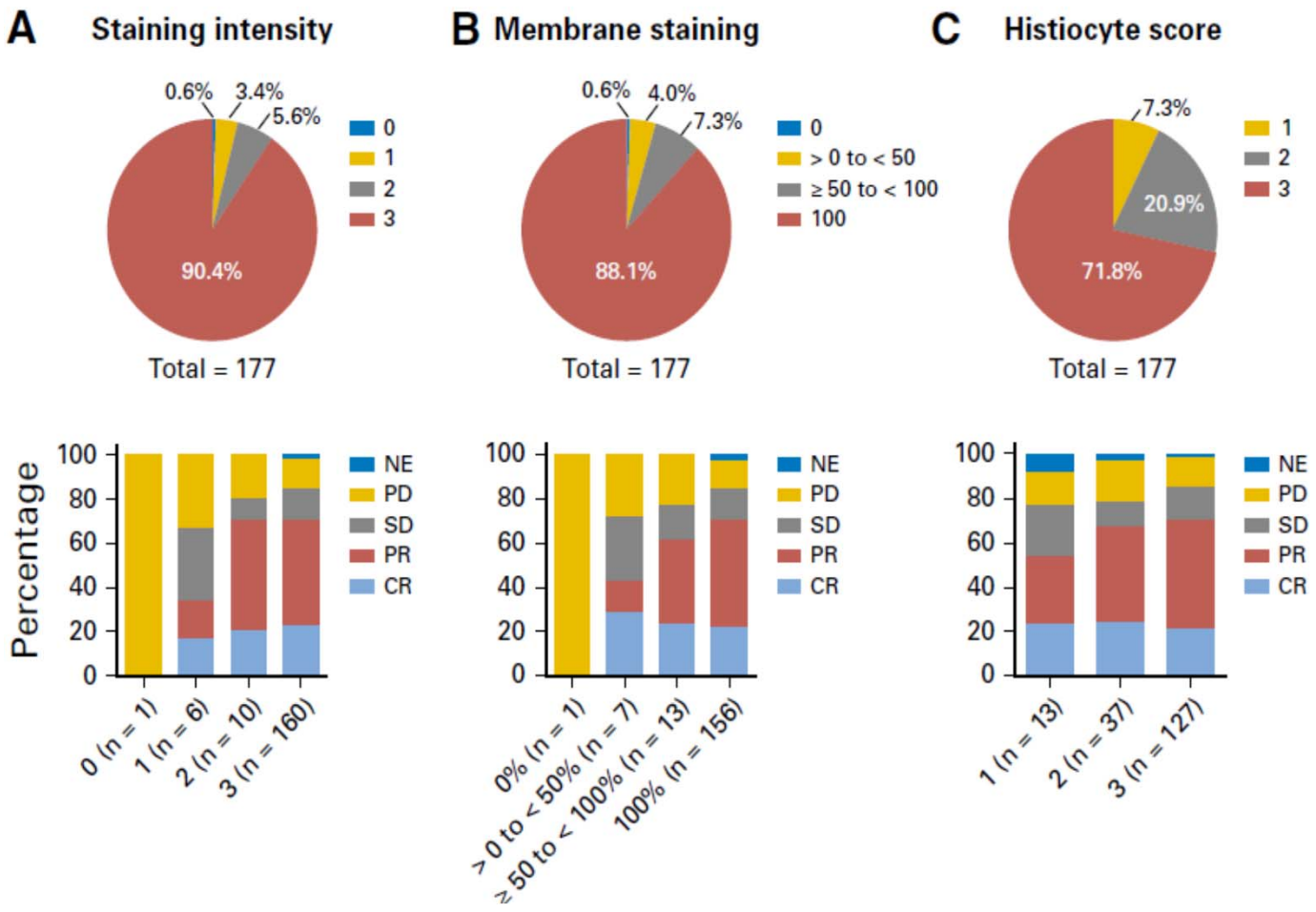
Συμπεράσματα III

Σε ασθενείς>65 ετών οι συνδυασμοί με Brentuximab είναι καλά ανεκτοί ,εξαιρετικά αποτελεσματικοί (Brentuximab+DTIC) και ελκυστικοί ως θεραπεία 1ης γραμμής.

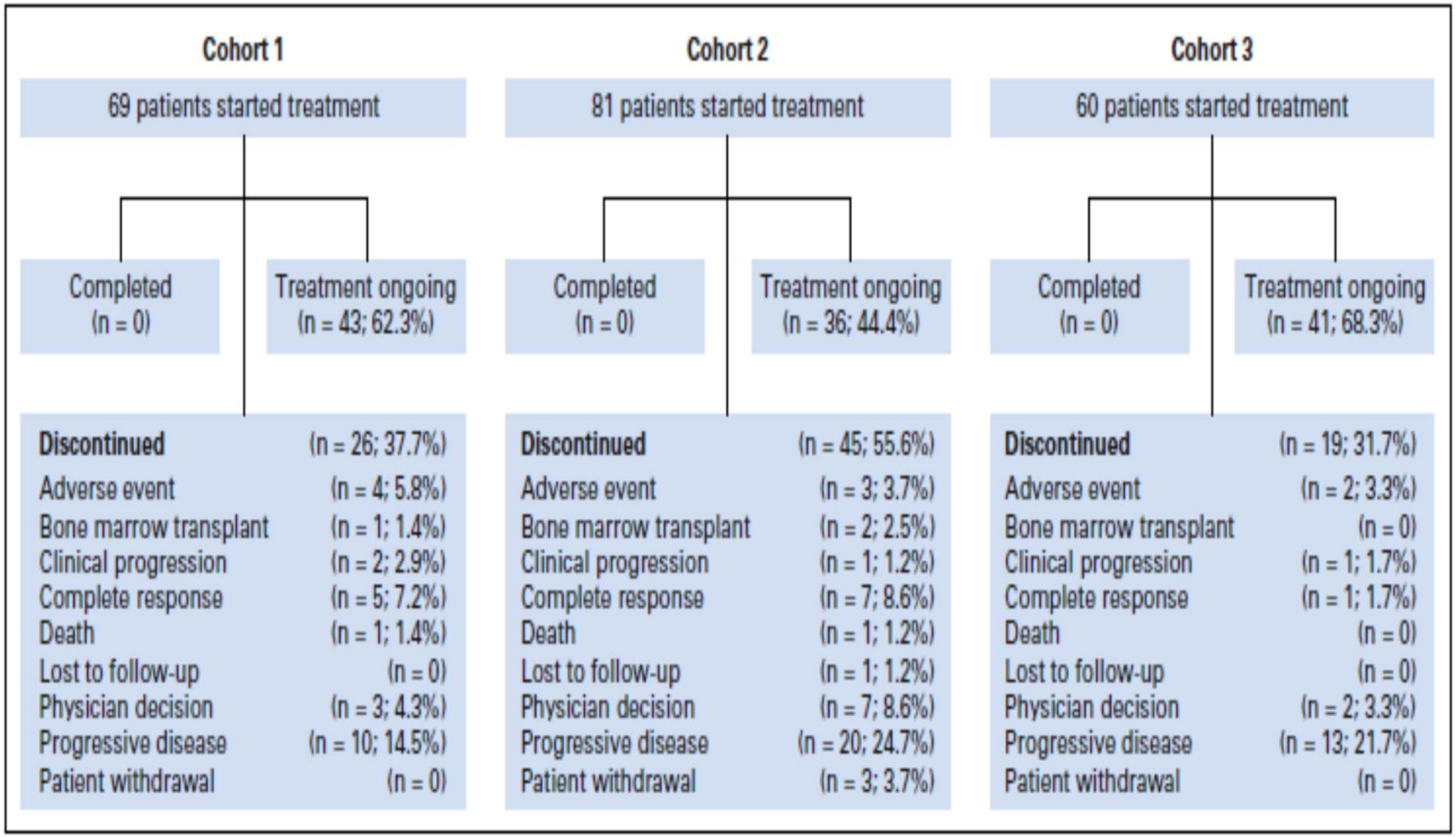
Η θέση των αναστολέων του PD-1 σε νεοδιαγνωσθέντες ασθενείς εξετάζεται σε κλινικές μελέτες ,ως μονοθεραπεία (Pebrotuzomab) και σε συνδυασμό με Χ/Θ (Nivolumab+AVD).


Ευχαριστώ για την προσοχή σας.

Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma



Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma



736 PET-Based Response after 2 Cycles of Brentuximab Vedotin in Combination with AVD for First-Line Treatment of Unfavorable Early-Stage Hodgkin Lymphoma: First Analysis of the Primary Endpoint of Breach, a Randomized Phase II Trial of Lysa-FIL-EORTC Intergroup

serious AEs (SAEs) were documented in 19% of the patients in the experimental arm (treatment-related SAEs in 17%) and 7% in the standard arm. SAEs have led to permanent BV discontinuation in 7/113 (6%) patients during the first 2 cycles. Reasons for permanent BV discontinuation were loss of weight, hyponatremia, febrile neutropenia, epileptic seizure, peripheral neuropathy, hepatitis and cutaneous rash.

Conclusion: This randomized, multicentric, open-label phase II trial aimed to evaluate the efficacy of BV in combination with AVD chemotherapy based on PET response after 2 cycles for previously untreated, unfavorable early-stage HL. The primary objective was met with an improvement of the negative-PET rate with BV-AVD regimen. This first analysis highlighted an increased toxicity with BV-AVD regimen compared to ABVD, with a higher rate of grade 3-4 AEs and SAEs during the first 2 cycles of treatment.

L.M. FORNECKER ASH 2017