Brentuximab Vedotin: …CD30…HL…and beyond...

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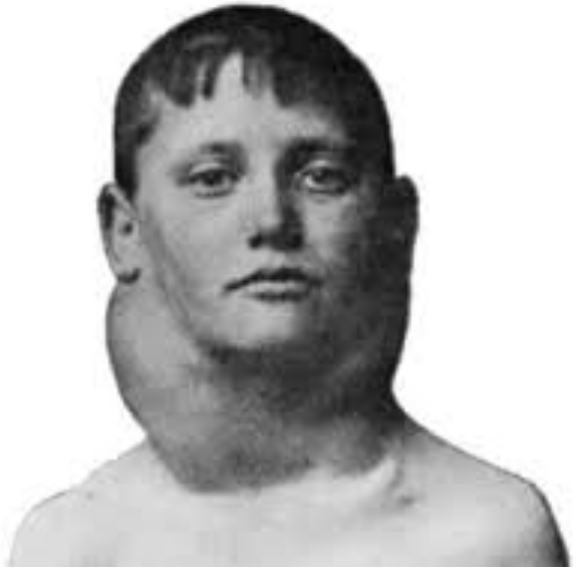
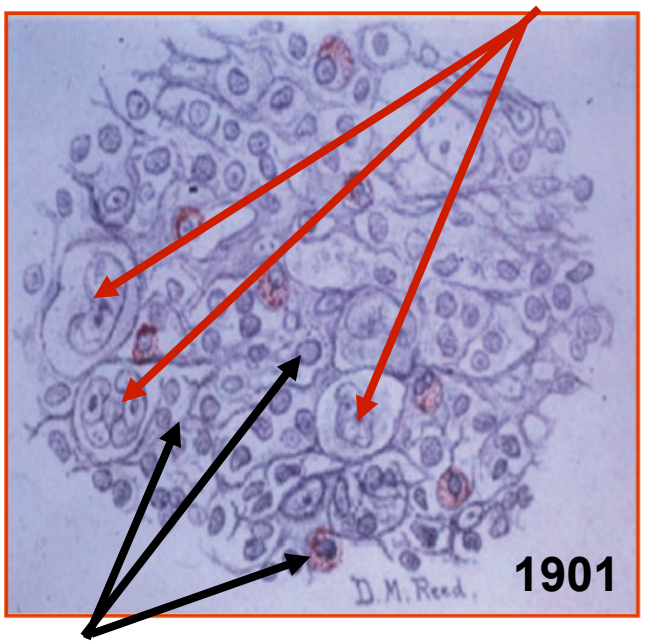
Naples, Italy

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale





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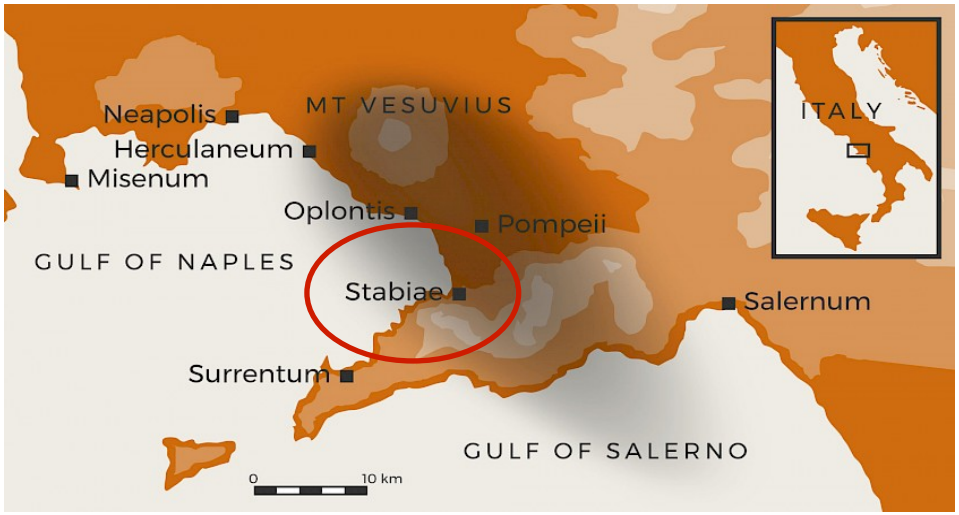

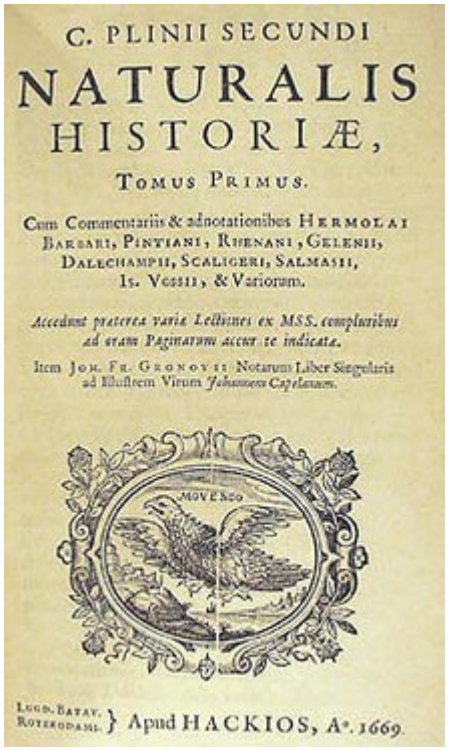
C. PLINII SECUNDI
NATURALIS HISTORIÆ,
TOMUS PRIMUS.
Cum Commentariis & adnotationibus HERMOLAI BARBARI, PINTIANI, RHENANI, GELENII, DALECHAMPII, SCALIGERI, SALMASII, Is. VOSSII, & Variorum.
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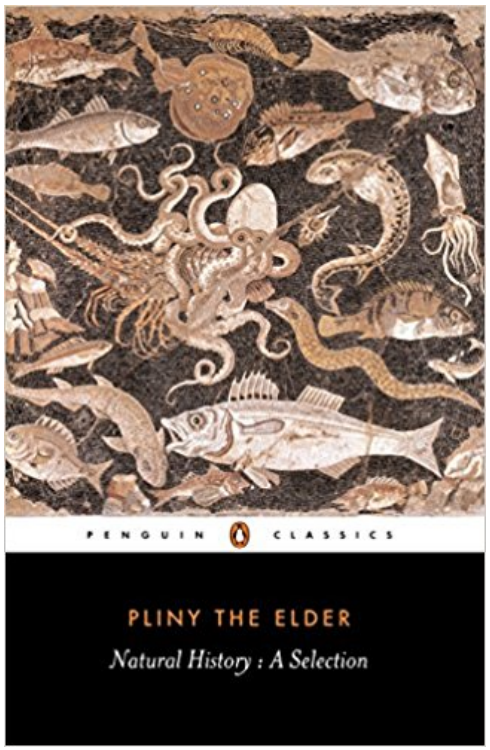
Lugd. Batav. Rotterodami } Apud HACKIOS, A°. 1669.



Como 23 DC – C. di Stabia 79 DC

Aquatilium secuntur in medicina beneficia, opifice natura ne in illis quidem cessante et per undas fluctusque…

Seguono i benefici nella medicine degli esseri acquatici, con la natura artefice… e che esercita le instancabili forze attraverso onde e flutti …. …

Brentuximab Vedotin: …CD30…HL…and beyond...

The great Roman natural scientist Gaius Plinius Secundus (Pliny the Elder) in his comprehensive study (4) of about 60 A.D. first described a most potent Indian Ocean sea hare[2] of the genus *Dolabella*. Extracts from this animal and two related *Aplysia* species from the Mediterranean were well known for their toxic properties during the reign of Nero (4, 5). By 150 A.D. Nicander (5) recognized the possibility of using such extracts for treatment of certain diseases. However, the potential of the Indian Ocean *Dolabella* with respect to modern medical problems was not recognized until we uncovered evidence for extremely active anticancer constituents in the Indian Ocean *Dolabella auricularia*[3] (3c).

We have now completed the isolation and preliminary characterization of an exceptionally promising series of cancer chemotherapeutic agents designated dolastatins 1–9 from *D. auricularia*. The dolastatins most probably correspond to the potent *D. auricularia* constituents recognized from ancient to fairly recent (7) times. Since dolastatin 1 has been shown (by the U.S. National Cancer

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[1]The present contribution is part 72 in the series Antineoplastic Agents. For part 71 refer to (1).

[2]The Romans first designated Mollusca of the family Aplysiidae in this fashion due to a similarity between the ears of a hare and the auriculate tentacles of these gastropods, consult (5).

[3]The *D. auricularia* was probably that first described by Pliny and the minor variations recorded in subsequent literature as, e.g., *D. andersoni*, *D. californica*, *D. ecaudata*, and *D. scapula* are actually one species, namely *D. auricularia*, see (6).

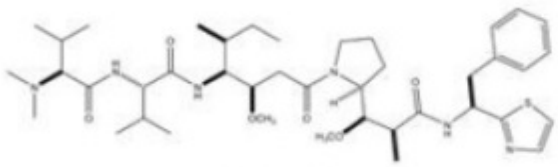
Brentuximab Vedotin: …CD30…HL…and beyond...

Auristatins
(Tubulin polymerase inhibitor)

The Auristatins

Monomethyl auristatin E (MMAE)
- Warhead of Brentuximab Vedotin
- Up to 1000x more potent than doxorubicin

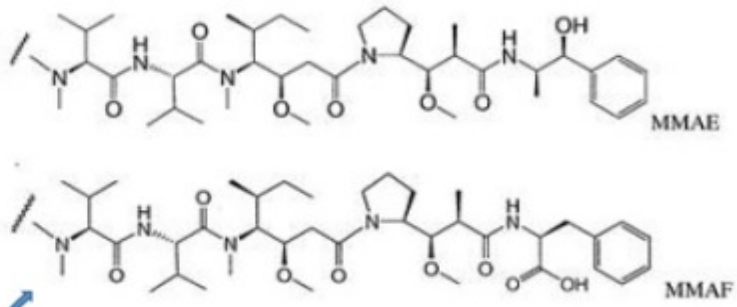
A.



Dolastatin 10

B.

C.



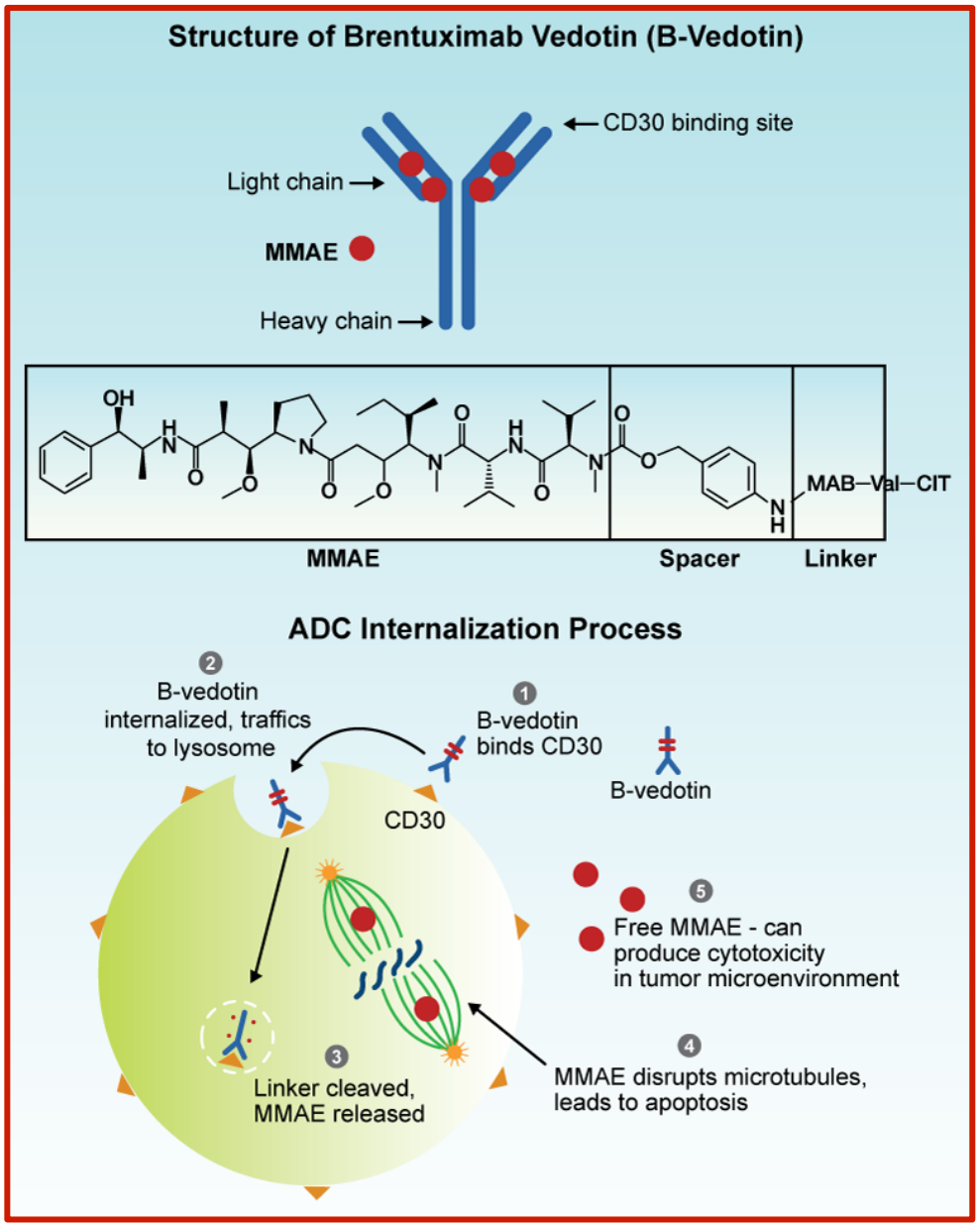
Valine

Tubulin Inhibitors

A. The parent antitubulin agent Dolastatin 10 isolated from the Indian ocean sea hare *Dolabella ariculara (*shown in B)

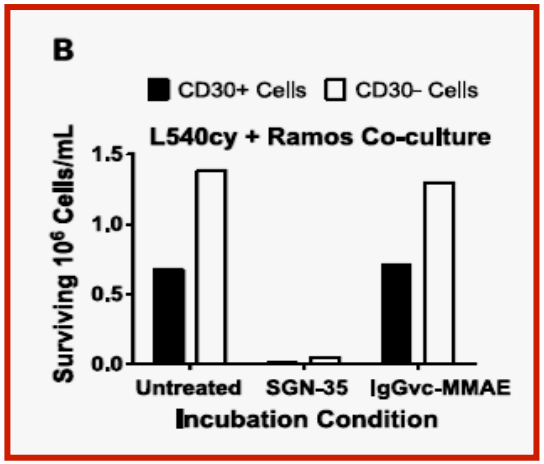
C. The synthetic Dolastatin 10 analogues monomethylauristatin E (MMAE) and monomethylauristatin F (MMAF) are used as payloads for ADCs.

Brentuximab Vedotin: …CD30…HL…and beyond...



In addition to BV's primary MOA non-clinical studies highlight other contributory mechanisms of action, including :

- Antibody dependent phagocytosis (ADCP)
- Bystander effects on nearby cells in the tumor microenvironment due to released MMAE
- Immunogenic cell death (ICD) due to endoplasmic reticulum (ER) stress that drives exposure of immune-activating molecules



Cancer Therapy: Preclinical

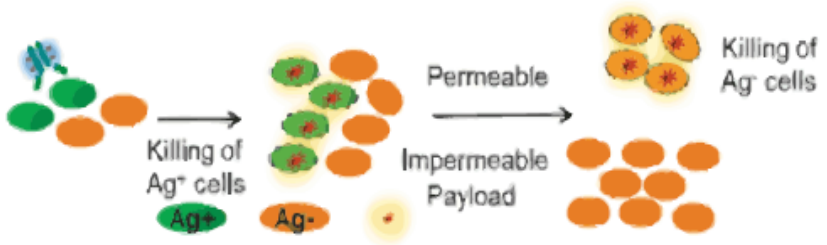
Clinical Cancer Research

Intracellular Activation of SGN-35, a Potent Anti-CD30 Antibody-Drug Conjugate

Nicole M. Okeley, Jamie B. Miyamoto, Xinqun Zhang, Russell J. Sanderson, Dennis R. Benjamin, Eric L. Sievers, Peter D. Senter, and Stephen C. Alley

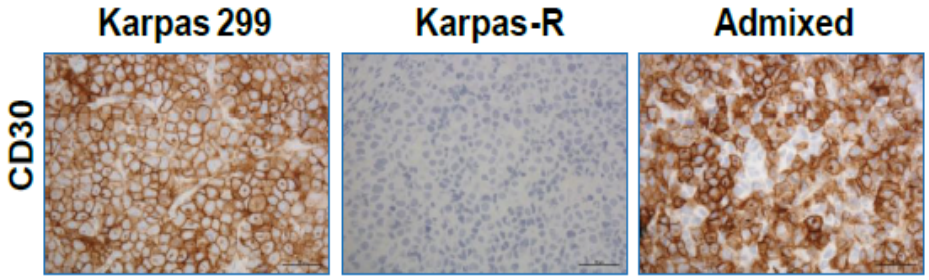
Brentuximab Vedotin: …CD30…HL…and beyond...

BV Targetting of CD30+ Tumors Mediates Bystander Killing

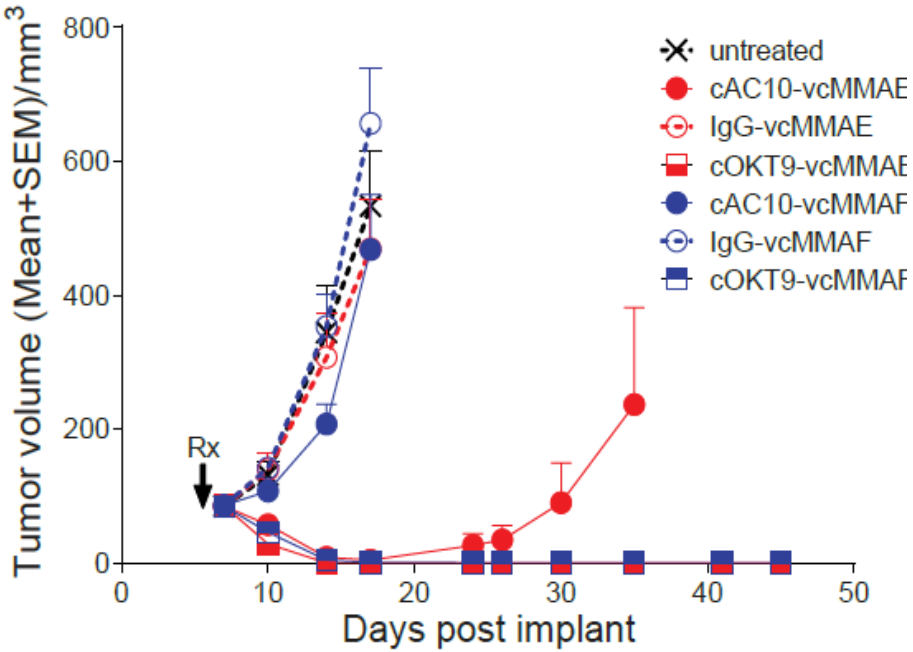


- Targetted, internalization, and trafficking of ADC-receptor complexes results in drug release in the lysosomal compartment.
- Free drug can be released into the tumor micro-environment resulting in killing of CD30+ and CD30- tumor cells.

Mixed CD30 Tumor Model To Assess In Vivo MMAE Bystander Killing



Released MMAE, but not MMAF Mediates Bystander Killing in Admixed Xenografts

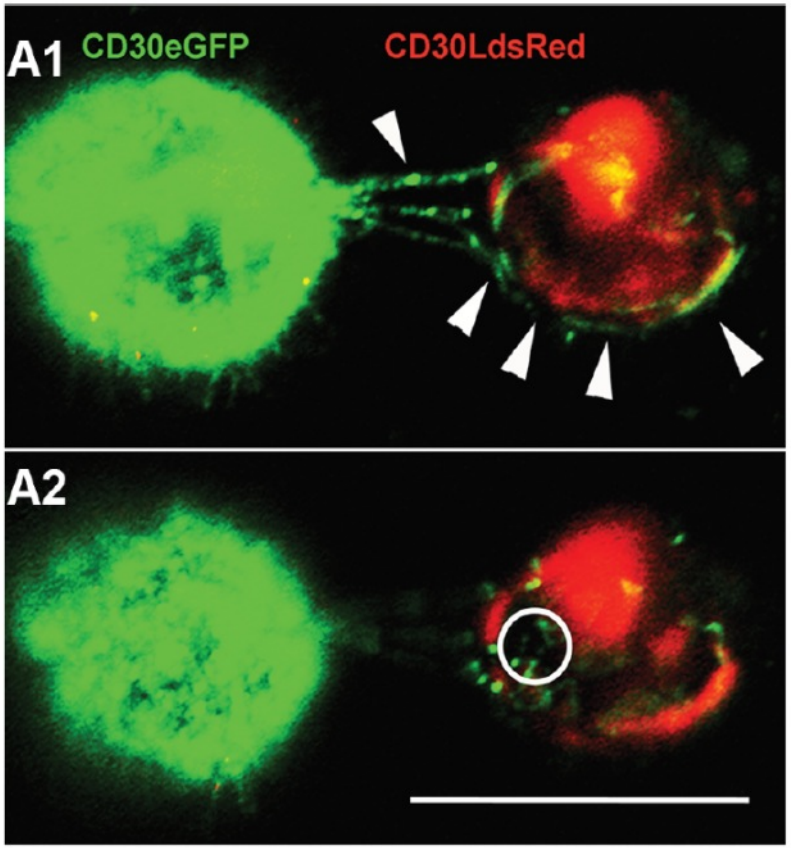


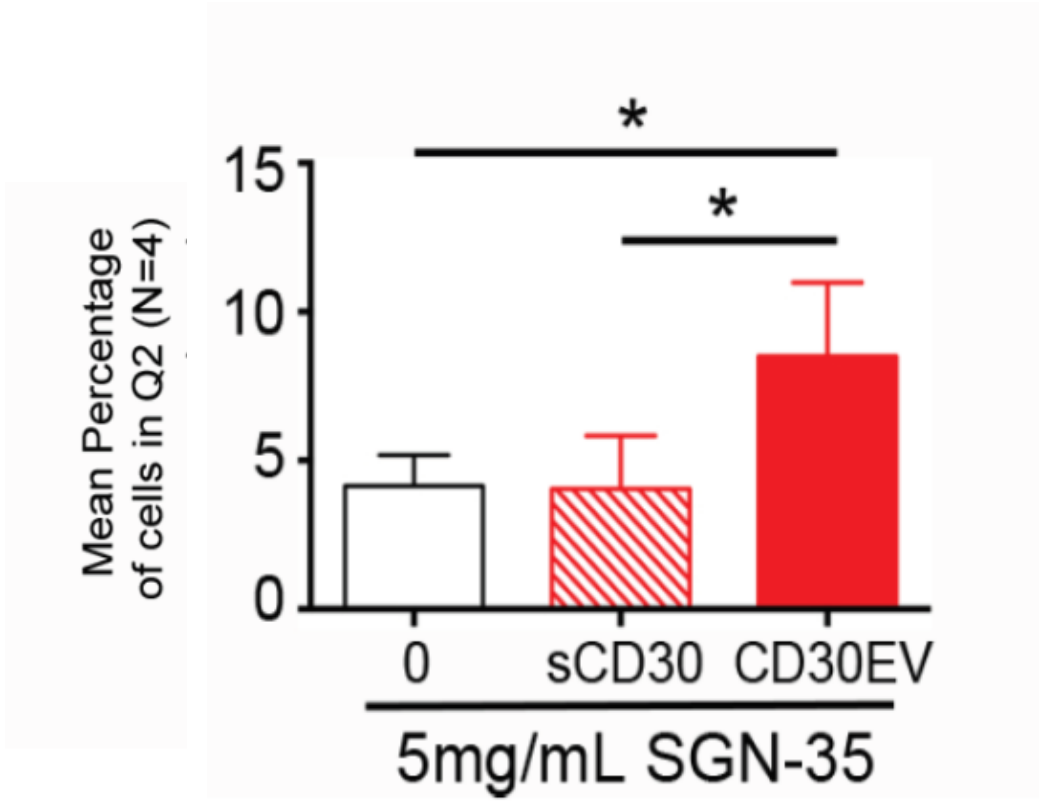
Administration of anti-CD30-vcMMAE, but not cell impermeable-vcMMAF payload, led to tumor regression. An ADC against CD71 (present on both tumor types) caused complete tumor regression.

Brentuximab Vedotin: …killing 0f CD30-negative targets

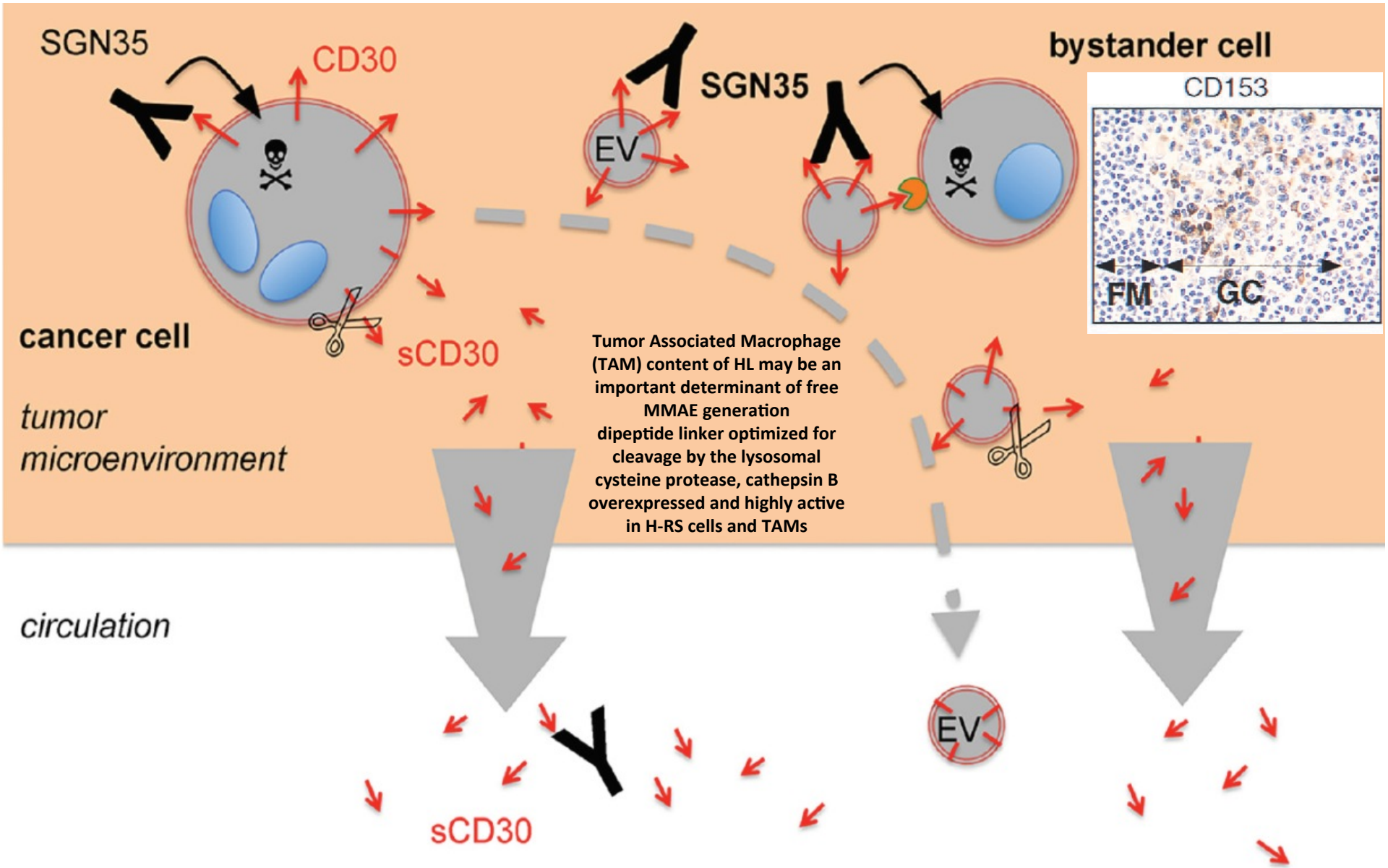
CD30 on extracellular vesicles from malignant Hodgkin cells supports damaging of CD30 ligand-expressing bystander cells with Brentuximab-Vedotin, *in vitro*

Hinrich P. Hansen[1], Ahmad Trad[2], Maria Dams[1], Paola Zigrino[3], Marcia Moss[4], Maximilian Tator[1], Gisela Schön[1], Patricia C Grenzi[1], Daniel Bachurski[1], Bruno Aquino[5], Horst Dürkop[6], Katrin S Reiners[1], Michael von Bergwelt-Baildon[1], Michael Hallek[1], Joachim Grötzinger[2], Andreas Engert[1], Adriana F Paes Leme[5], Elke Pogge von Strandmann[1]



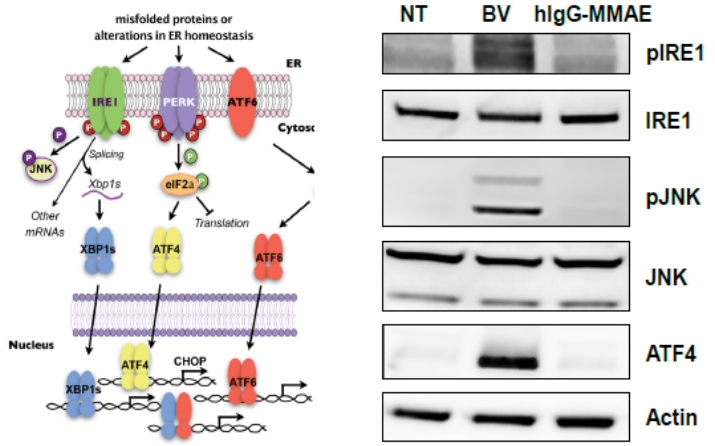


Brentuximab Vedotin: …killing 0f CD30-negative targets



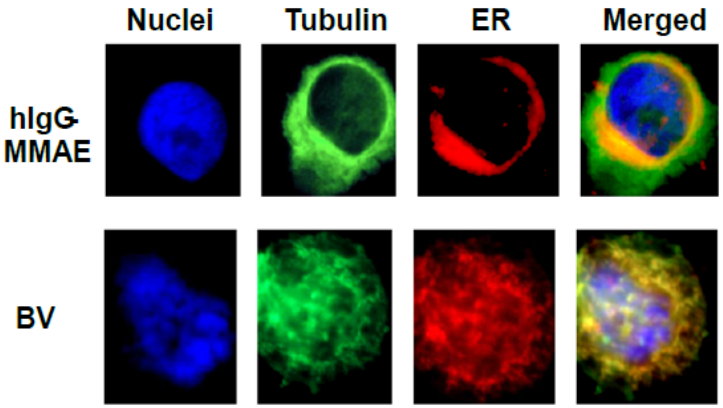
Brentuximab Vedotin: …CD30…HL…and beyond...

BV Induced ICD and ER Stress



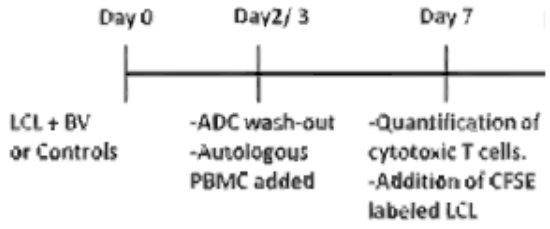
CD30 positive L540cy cells were treated with 1μg/ml of BV or control non-targeted ADC (hIgG-MMAE) and cell pellets were analyzed for ER stress response by western blot.

ER Mislocalization Following Autistatin Treatment

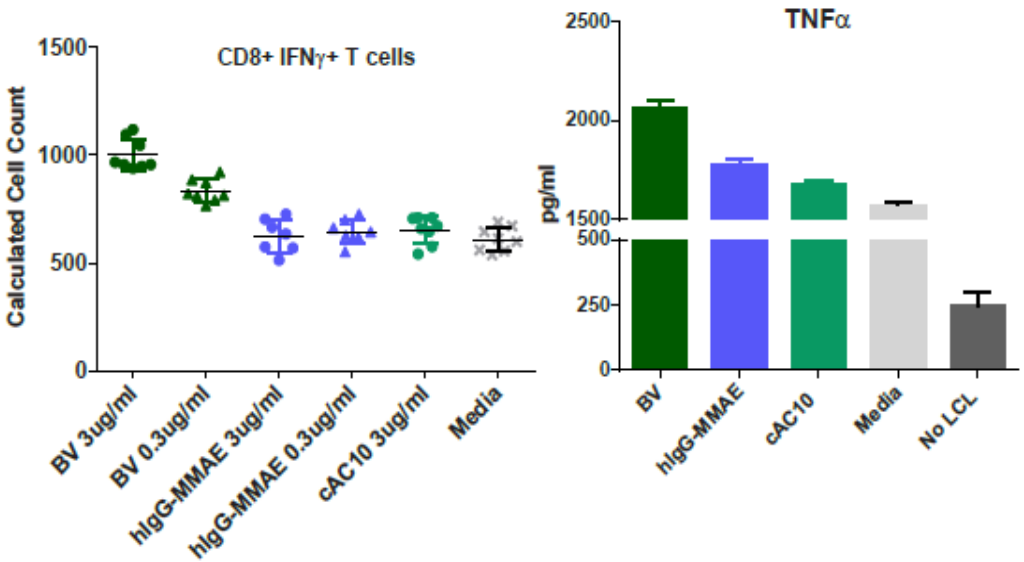


L540cy cells were treated for 16hrs and microtubules and ER were imaged. Inhibition of microtubule polymerization leads to ER mislocalization.

ICD Following BV Treatment Promotes Cytotoxic T cell Expansion



CD30+ EBV transformed cells (LCL) and autologous PBMCs were paired and the effect of BV on ICD driven cytotoxic T cell responses were investigated.



T cell responses were measured on day 7 by intracellular INFγ staining. Cell culture supernatants were measured for TNFα.

Brentuximab Vedotin: Mechanisms of resistance

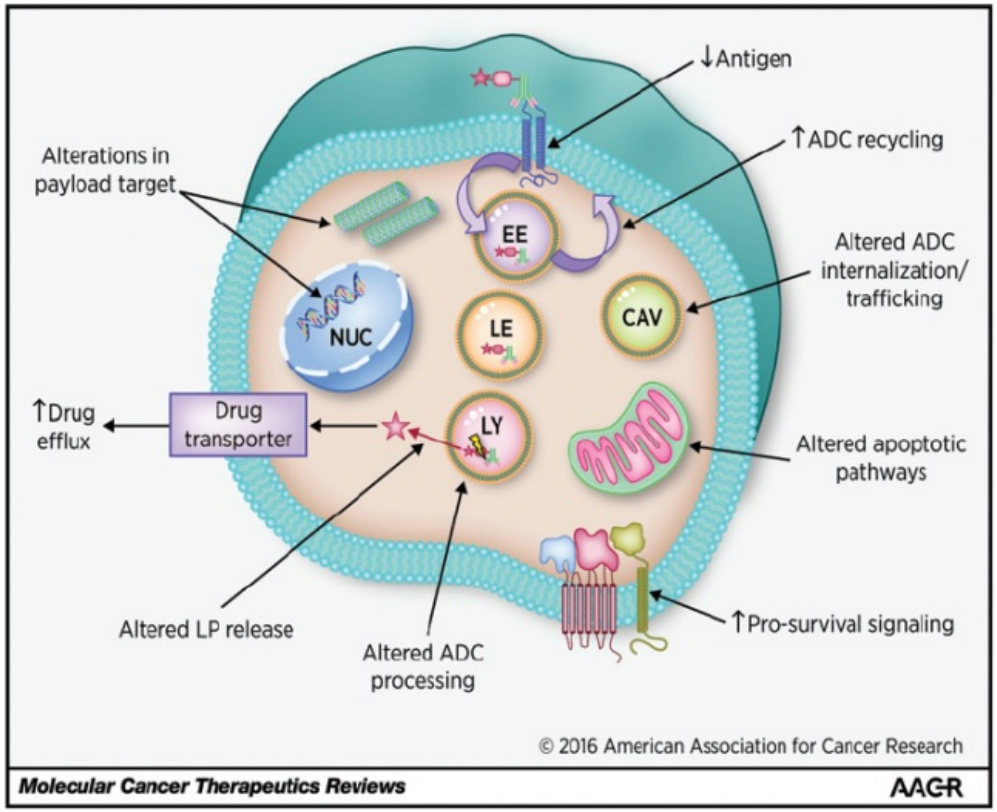


Table 1. Preclinical models of acquired ADC resistance

ADC	Cell model	Dosing approach	Fold resistance vs. parental	Mechanism of resistance (MOR)	Reference
T-DM1	KPL-4-T-DM1-R	Continuous, with increasing dose	~1,000X	HER2 reduction; MDR1 induction; EGFR and IGF1Rβ induction, altered signaling	Lewis Phillips (24)
T-DM1	BT-474-M1-T-DM1-R	Continuous, with increasing dose	~100X	PTEN and IGF1Rβ reduction; DUSP3/2 induction; MIR221 RNA induction	Lewis Phillips (24)
T-DM1	361-TM	Cyclical, with constant high dose	256X	MRP1 induction, trafficking protein modulation	Loganzo, et al. (27)
T-DM1	JIMT1-TM	Cyclical, with constant high dose	16X	HER2 reduction; trafficking protein modulation	Loganzo et al. (27)
T-DM1	HCC1954-TM, BT-474-TM	Cyclical, with constant high dose	>1,000X, ~11X	HER2 reduction	Loganzo et al. (34)
T-DM1	NB7-TM	Cyclical, with constant high dose	~100X	Trafficking or lysosomal defects; CAV1 overexpressed	Sung et al. (49)
T-DM1	BT-474, NCI-N87, SK-OV-3, MDA-MB-361	Continuous, with increasing dose	>100 to >1,000X	Not reported	Li et al. (30)
BV	Karpas-R	Continuous, at high dose	655X	CD30 downregulation	Chen et al. (26)
BV	L428-R	Cyclical, with constant high dose	8.7X	MDR1 induction	Chen et al. (26)
BV	Karpas-299-35R	Continuous, with increasing dose	>1,000X	CD30 downregulation	Lewis et al. (25)
BV	L540cy-35R	Continuous, with increasing dose	>100X	Low-level MDR1 induction	Lewis et al. (25)
BV	DEL-35R	Continuous, with increasing dose	>1,000 to >10,000X	MDR1 induction	Lewis et al. (25)
Anti–CD22-vc-MMAE	BJABLuc-22R1; WSU-DLCL2-22R1	*In vivo* xenograft; cyclical increasing dose	No response to 8–12 mg/kg αCD22-vc-MMAE *in vivo*	MDR1 induction	Yu et al. (29)
DM1/maytansine-containing ADCs	786-0 with SLC46A3 shRNA	shRNA transfection (no drug induction)	n/a	SLC46A3 knockdown	Hamblett et al. (57)

Abbreviations: T-DM1, trastuzumab emtansine; Rituxi-vc, rituximab MCC-DM1; BV, brentuximab vedotin; Karpas, anti-CD30-vcACD-vc-MMAE.

Mol Cancer Ther; 15(12); 2825–34. ©2016 AACR.

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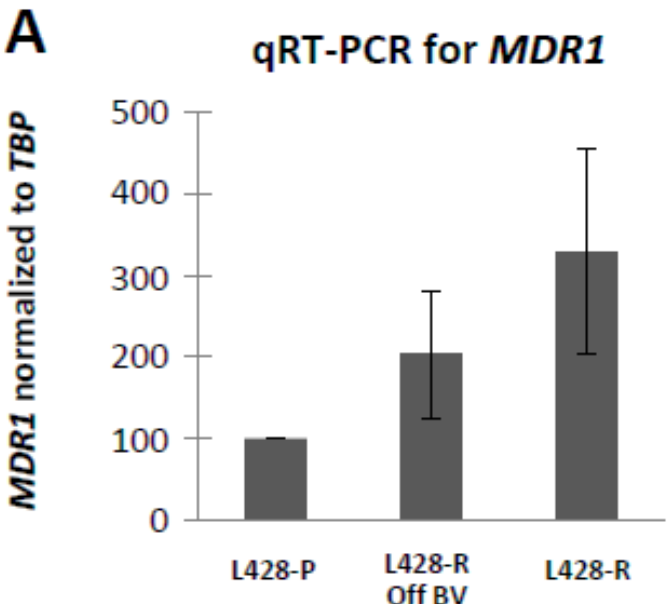
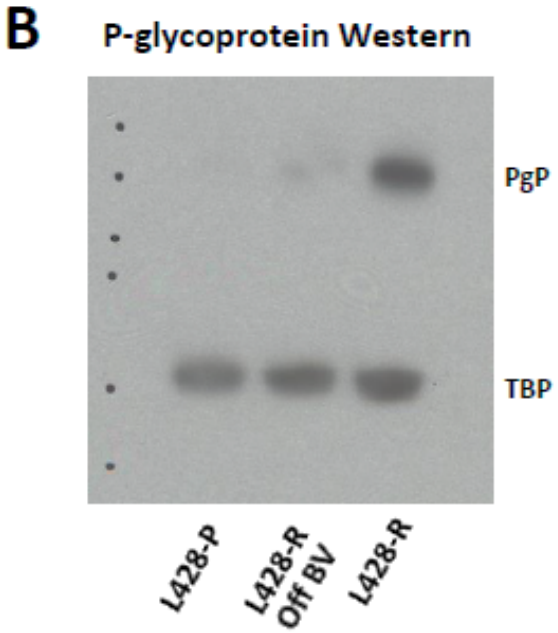
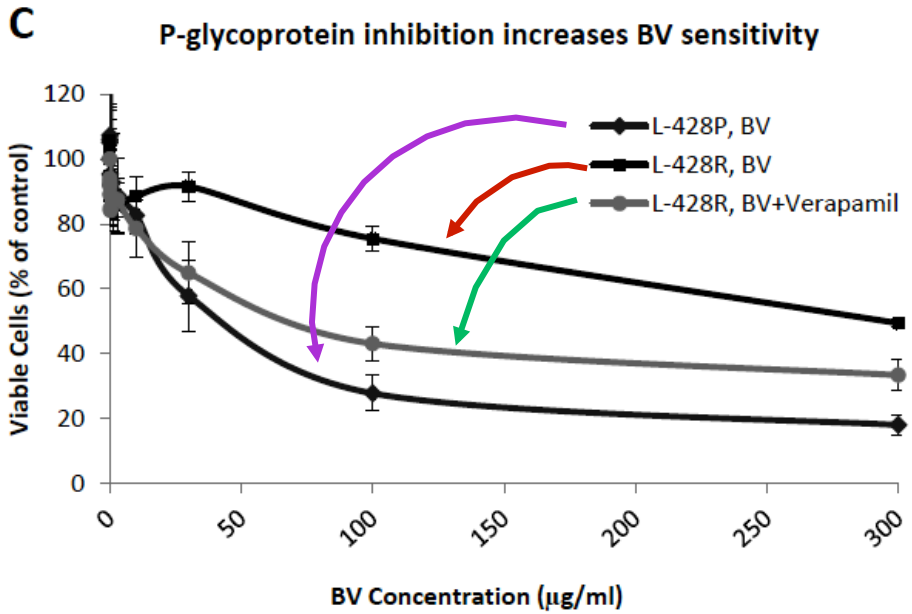




U.S. National Library of Medicine
inicalTrials.gov

Brentuximab Vedotin, Cyclosporine, and Verapamil in Treating Patients With Relapsed or Refractory Hodgkin Lymphoma

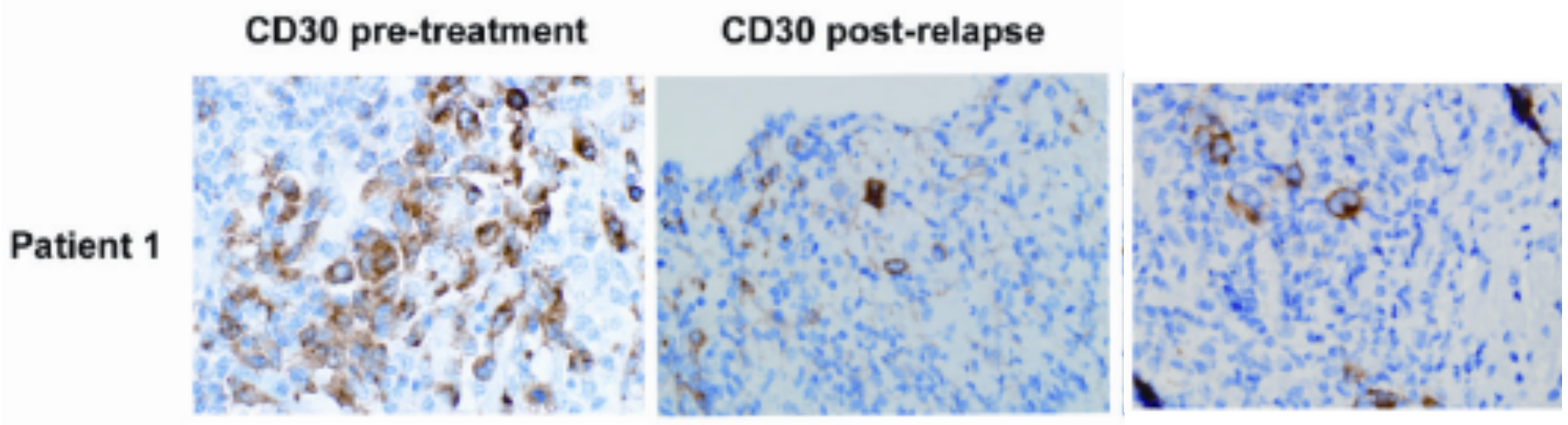
ClinicalTrials.gov Identifier: NCT03013933
Recruitment Status : Recruiting
First Posted : January 9, 2017
Last Update Posted : March 30, 2018
See Contacts and Locations



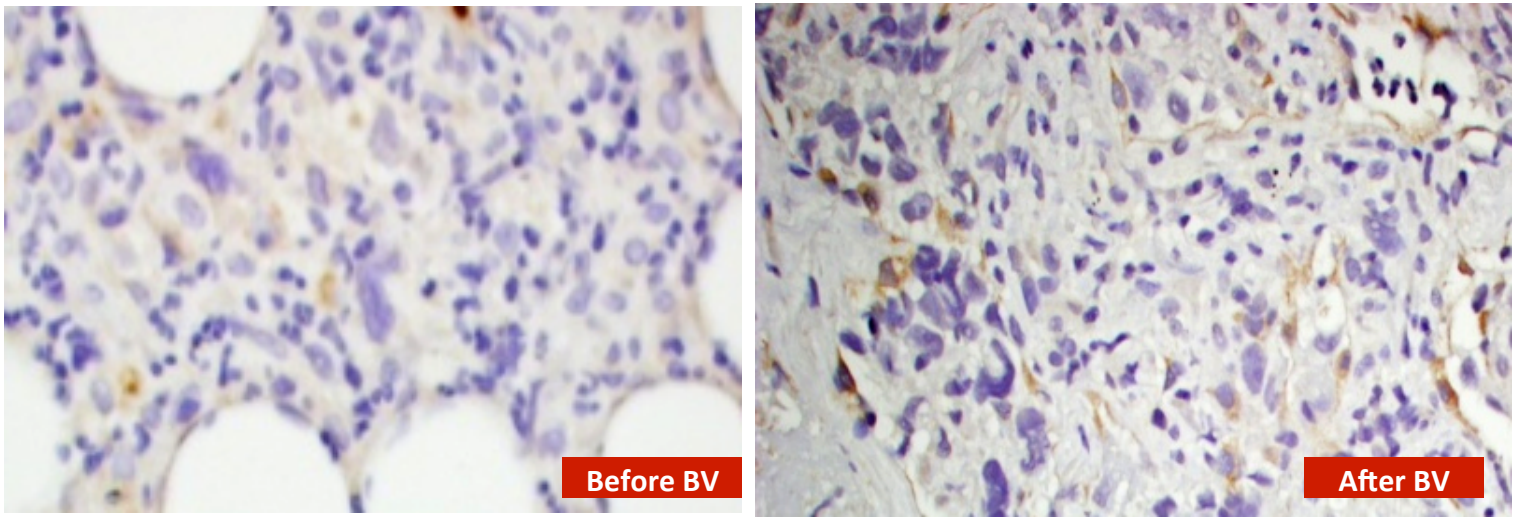
Chen R. et al. Molecular Cancer Therapeutics OnlineFirst on April 3, 2015

Brentuximab Vedotin: Mechanisms of resistance

CD30 staining in tissue from HL patients resistant to BV



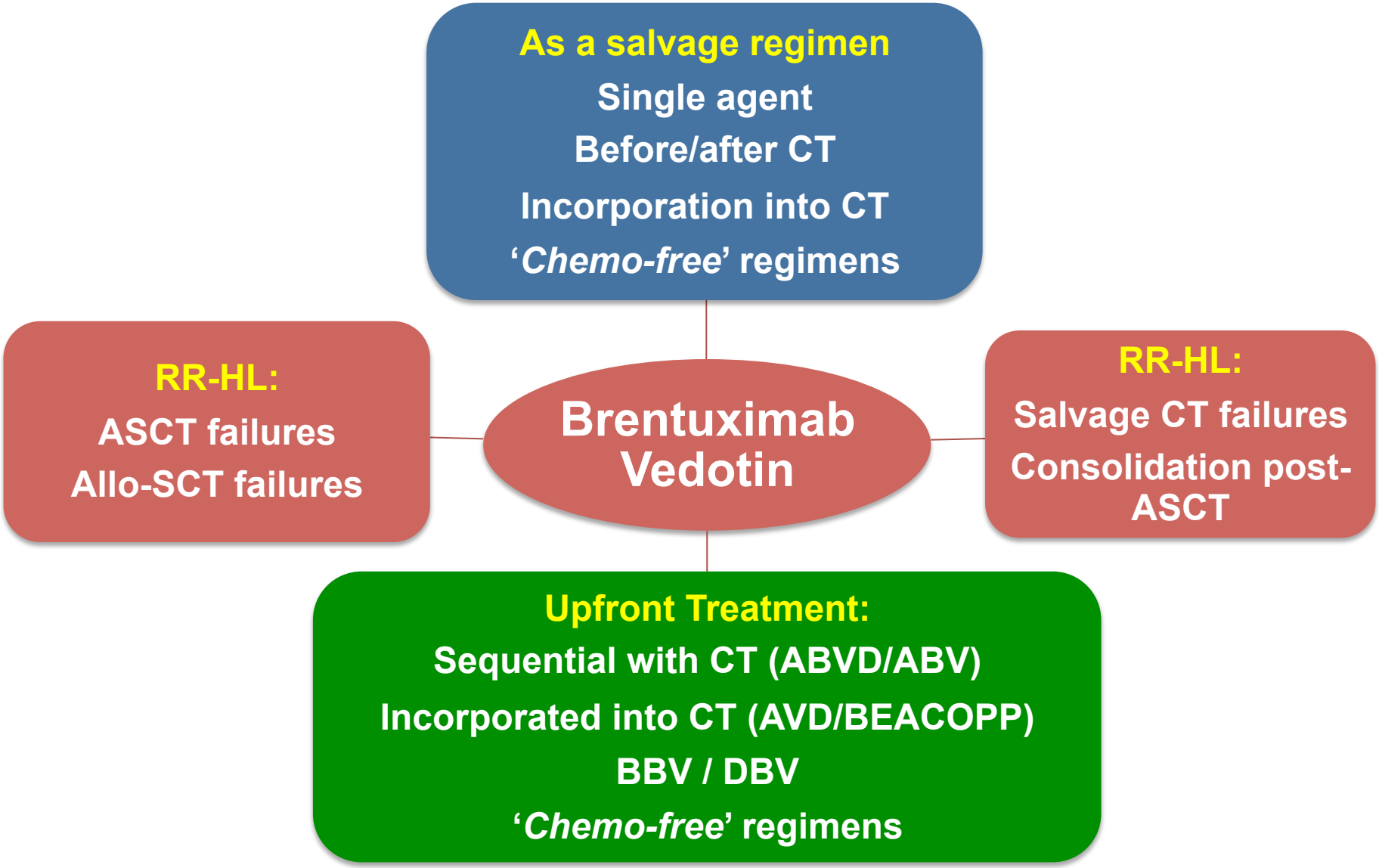
PgP Expression Acquired by HL Patient at BV Resistance



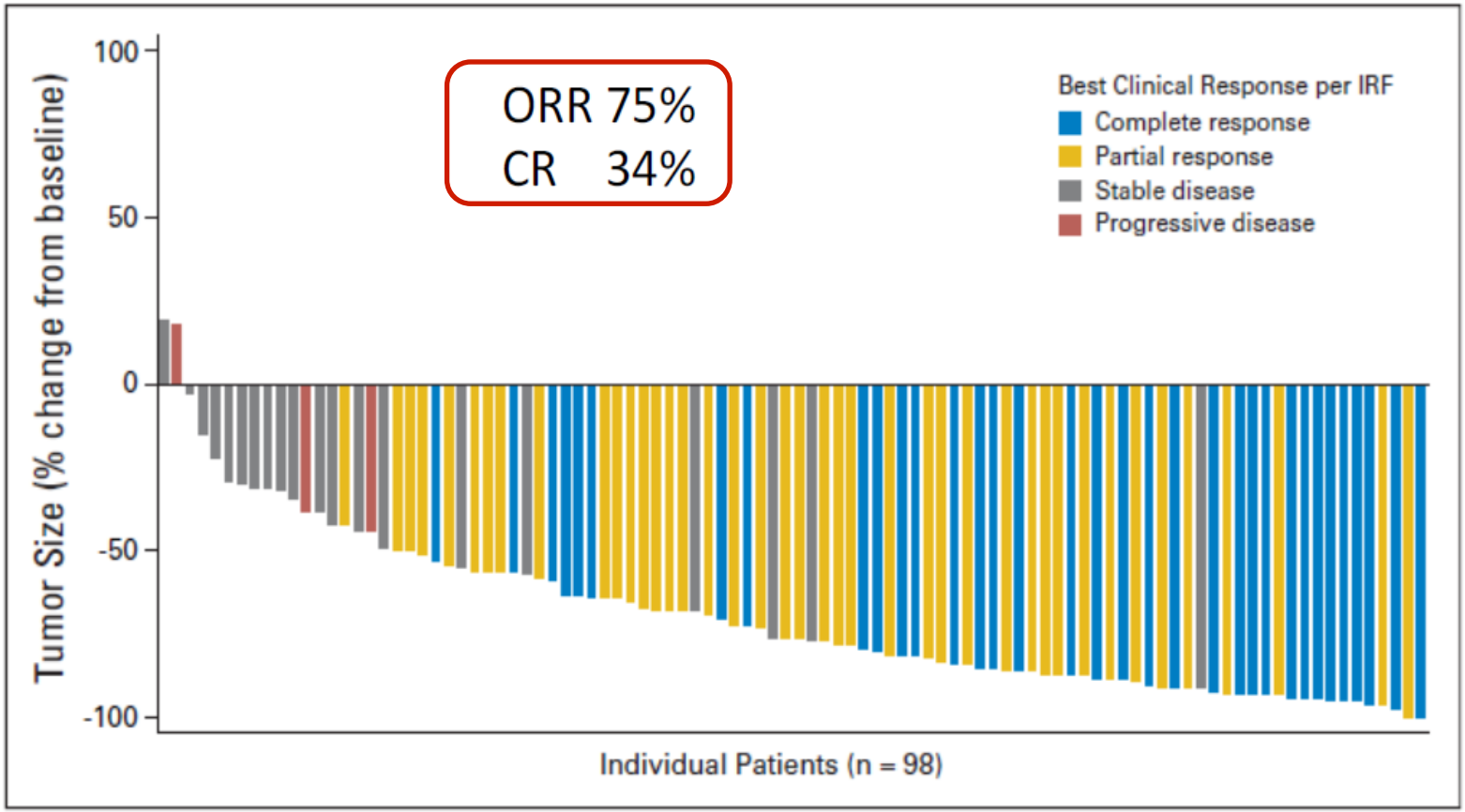
Chen R. et al. Molecular Cancer Therapeutics OnlineFirst on April 3, 2015

Nathwani N. et al. Leuk Lymphoma. 2012;53:2051-3.

Brentuximab Vedotin: …CD30…HL…and beyond…



Phase II pivotal study of brentuximab vedotin in relapsed HL post ASCT



94% patients achieved tumour reduction

IRF – independent review facility

Younes A et al. J Clin Oncol 2012;30: 2183-9.

Brief Report

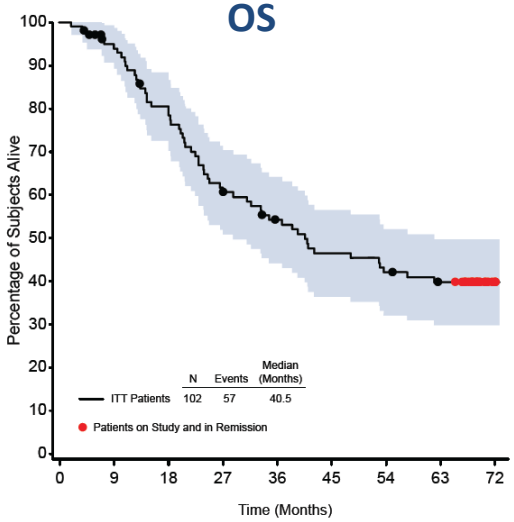
blood

CLINICAL TRIALS AND OBSERVATIONS

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

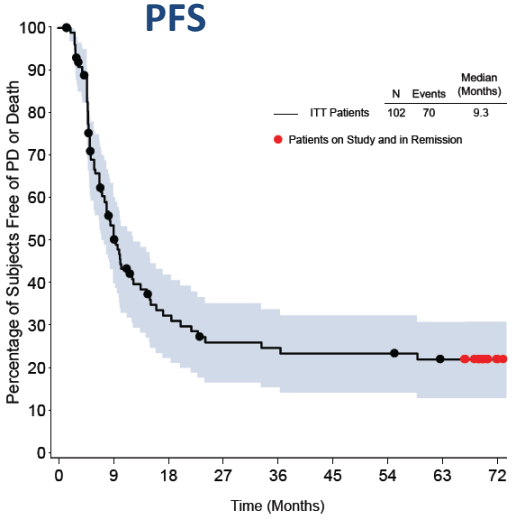
Robert Chen,[1,*] Ajay K. Gopal,[2,*] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Dirk Huebner,[9] Abraham Fong,[8] and Anas Younes[10]

OS



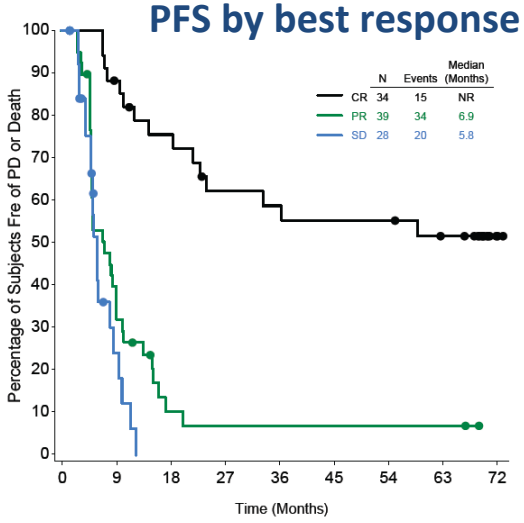
Median OS: 40.5 mos
(95% CI: 28.7, 61.9 [1.8–72.9+])
5-yr OS: 41%
(95% CI: 31-51)

PFS



Median PFS: 9.3 mos
(95% CI: 7.1, 12.2)
5-ys PFS: 22%
(95% CI: 13-31)

PFS by best response



Median OS & PFS
not reached in pts with CR

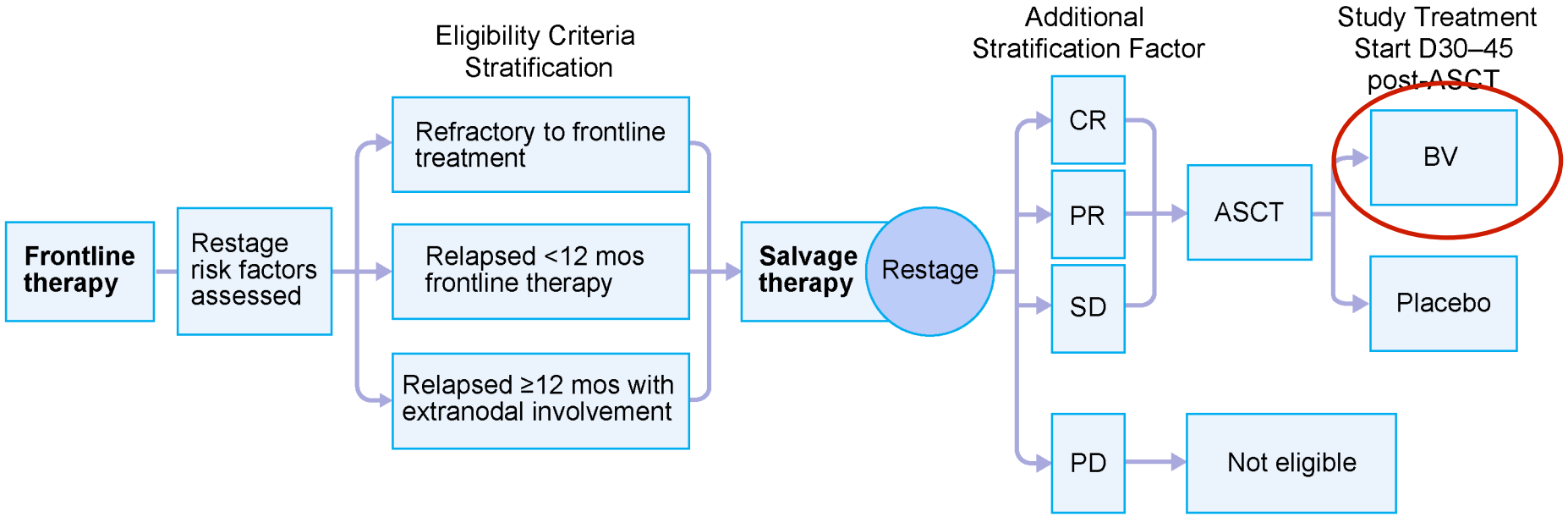
For patients in CR, the estimated 5-years OS rate was 64% and PFS was 52%

Blood , 22 September 2016

Brentuximab Vedotin in the Overall Treatment Strategy for HL

AETHERA Trial: Phase 3 randomized, double-blind, placebo-controlled, multicenter study of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of progression following ASCT(NCT01100502)

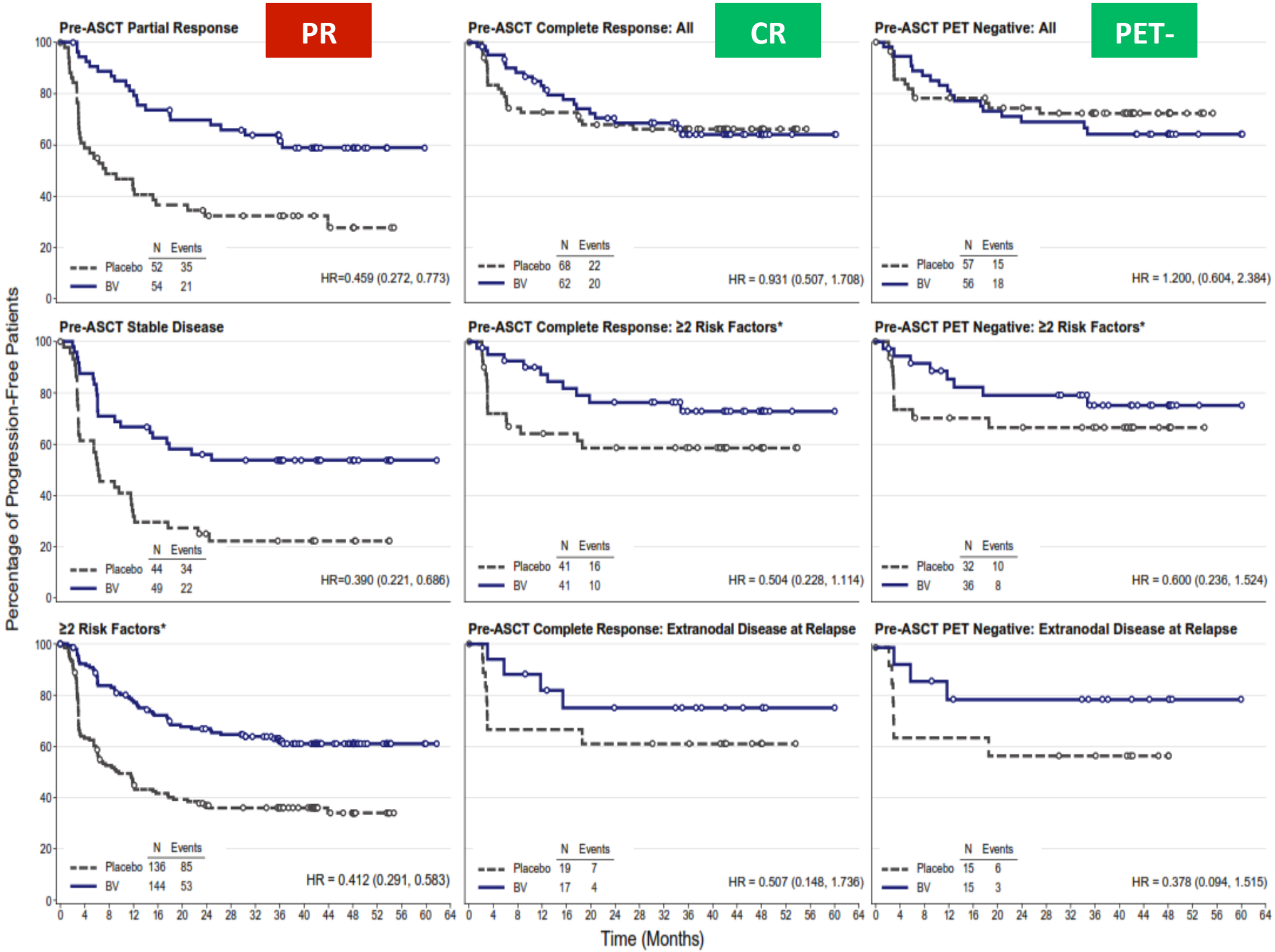
Objectives: *Primary:* PFS per IRF; *Secondary:* OS, safety/tolerability



Risk factors

- Relapsed <12 mos or refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- ≥2 prior salvage therapies

Moskowitz CH, et al. Lancet 2015;385(9980):1853-1862

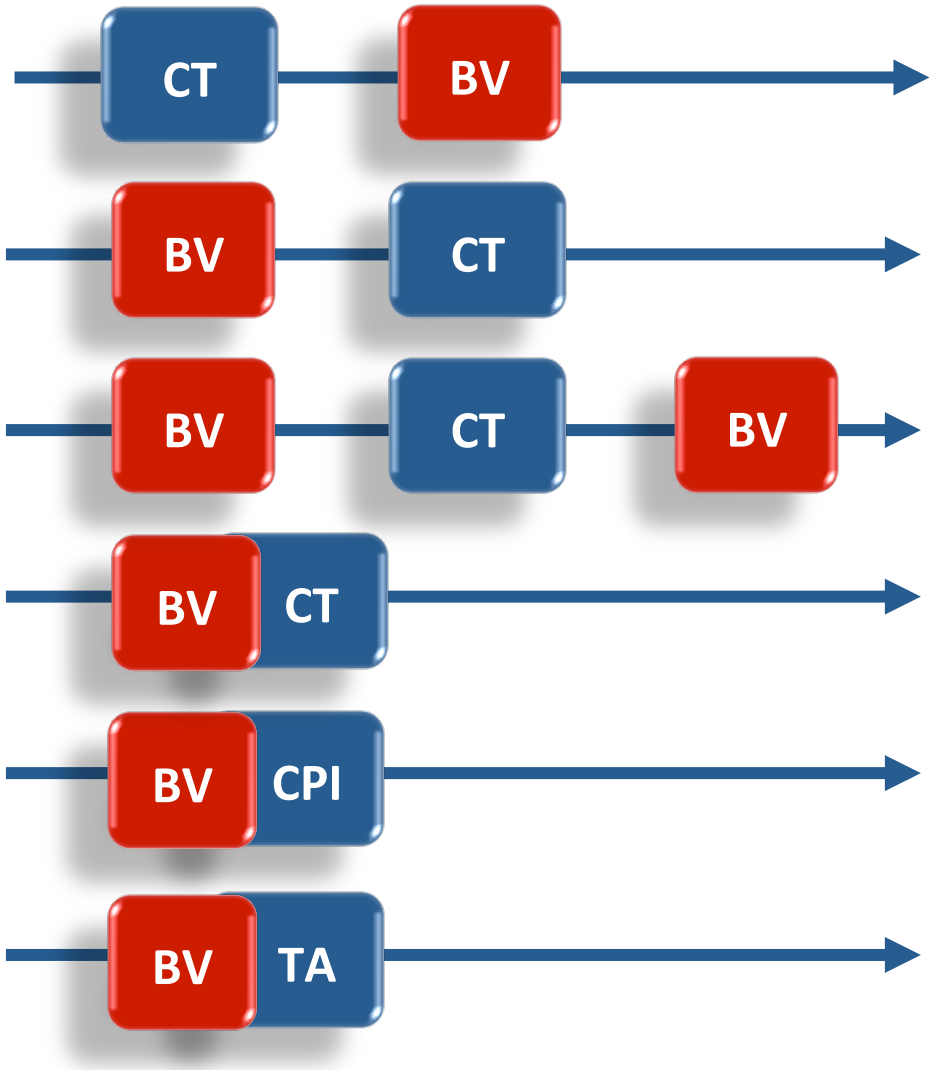

Pre-ASCT Partial Response
PR
Pre-ASCT Complete Response: All
CR
Pre-ASCT PET Negative: All
PET-
Pre-ASCT Stable Disease
Pre-ASCT Complete Response: ≥2 Risk Factors*
Pre-ASCT PET Negative: ≥2 Risk Factors*
≥2 Risk Factors*
Pre-ASCT Complete Response: Extranodal Disease at Relapse
Pre-ASCT PET Negative: Extranodal Disease at Relapse
Percentage of Progression-Free Patients
Time (Months)
N Events
Placebo 52 35
BV 54 21
HR=0.459 (0.272, 0.773)
Placebo 68 22
BV 62 20
HR = 0.931 (0.507, 1.708)
Placebo 57 15
BV 56 18
HR = 1.200, (0.604, 2.384)
Placebo 44 34
BV 49 22
HR=0.390 (0.221, 0.686)
Placebo 41 16
BV 41 10
HR = 0.504 (0.228, 1.114)
Placebo 32 10
BV 36 8
HR = 0.600 (0.236, 1.524)
Placebo 136 85
BV 144 53
HR = 0.412 (0.291, 0.583)
Placebo 19 7
BV 17 4
HR = 0.507 (0.148, 1.736)
Placebo 15 6
BV 15 3
HR = 0.378 (0.094, 1.515)

RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

Strategies to achieve a PET neg.ve status @ transplant:

- **Sequential single agent BV and chemotherapy**
  (…*if needed*…)
  - BV alone (about 30-35% of pts. achieve a metabolic CR)
  - BV <mCR: ICE, DICE, IGEV, GVD, GDP
  - BV and Bendamustine or Bendamustine and BV
- **Incorporate BV into salvage**
  - Bendamustine BV (BBV)
  - BV-DHAP (Brave)
  - BV-ESHAP (BrESHAP)
  - BV-ICE
- **Change 'conventional' salvage platform**
  - BeGEV
  - Test a 'chemo-free' strategy (BV+CPI)

Brentuximab Vedotin in the Overall Treatment Strategy for HL



Brentuximab Vedotin in the Overall Treatment Strategy for HL

Regimen	Pts. n	CR %	ORR %
ICE[a]	65	26	85
ICE/Aug ICE[b]	97	60	88
DHAP[c]	102	21	87
ESHAP[d]	82	50	67
GVD[e]	88	19	70
GDP[f]	23	17	69
IEV[g]	51	76	84
IGEV[h]	91	54	81

Regimen	Pts. n	Rel. / Ref.	PET neg CR Pre-ASCT	CD34	ASCT (%)	PFS (ITT)
BV (NCT01393717)	37	13 / 24	35 %	5.97	47	72% @ 27 mo.s
BV-ESHAP	66	26 / 40	70 %	5.75	92	Too early
Benda-BV	54	27 / 27	74 %	4	74	63% @ 3 yrs
BV-ICE	16	5 / 11	69 %	11	75	Too early
BV-DHAP	12	10 / 2	90 %	5.3	100	Too early
BV Seq. ICE	66	33 / 33	73 %	6.2	95	79% @ 3 yrs
BV Seq. salvage	37	13 / 24	73 %	5.6	89	72% @ 18 mo.s
ICE/GDV	97	56 / 41	76 %	6.3	88	68% @ 3 yrs
BeGEV	59	27 / 32	73 %	8.8	73	63% @ 2 yrs

Brentuximab Vedotin-based combinations for RR-HL

CLINICAL TRIALS AND OBSERVATIONS

Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

Alex F. Herrera,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Stephen M. Ansell,[8] Craig H. Moskowitz,[2] Keenan Fenton,[9] Carol Anne Ogden,[9] David Taft,[9] Qu Zhang,[9] Kazunobu Kato,[10] Mary Campbell,[9] and Ranjana H. Advani[11]

Methods

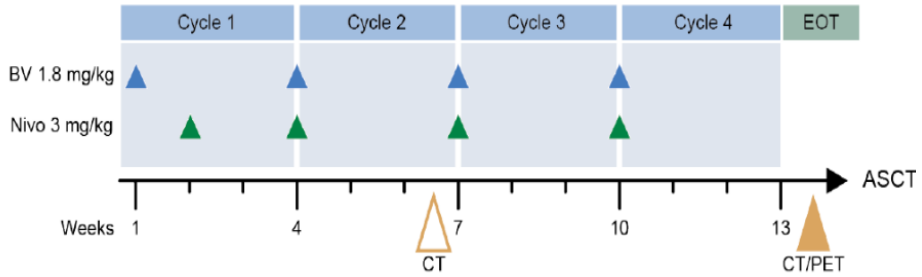
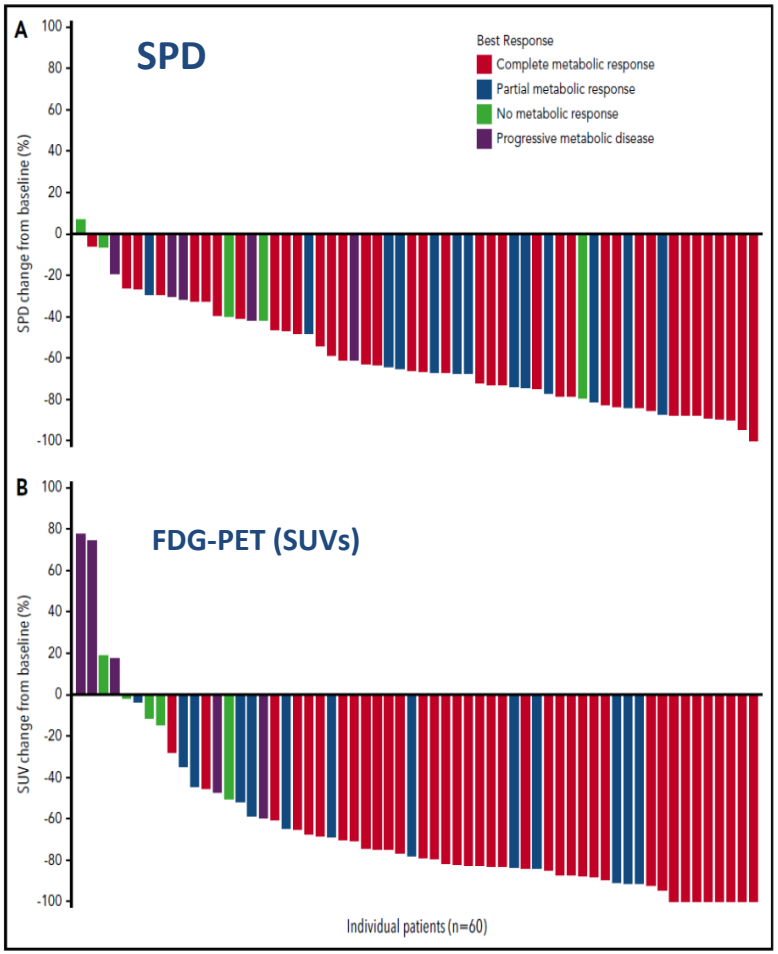


Table 1. Baseline demographics and disease characteristics

	n = 62
Age (y), median (range)	36 (18–69)
Sex, n (%)	
Male	30 (48)
Female	32 (52)
Disease stage at initial diagnosis, n (%)	
I/II	37 (60)
III/IV	24 (39)
Unknown	1 (2)



CR rate: 61%,
ORR: 82%
6-mo.s PFS: 86%

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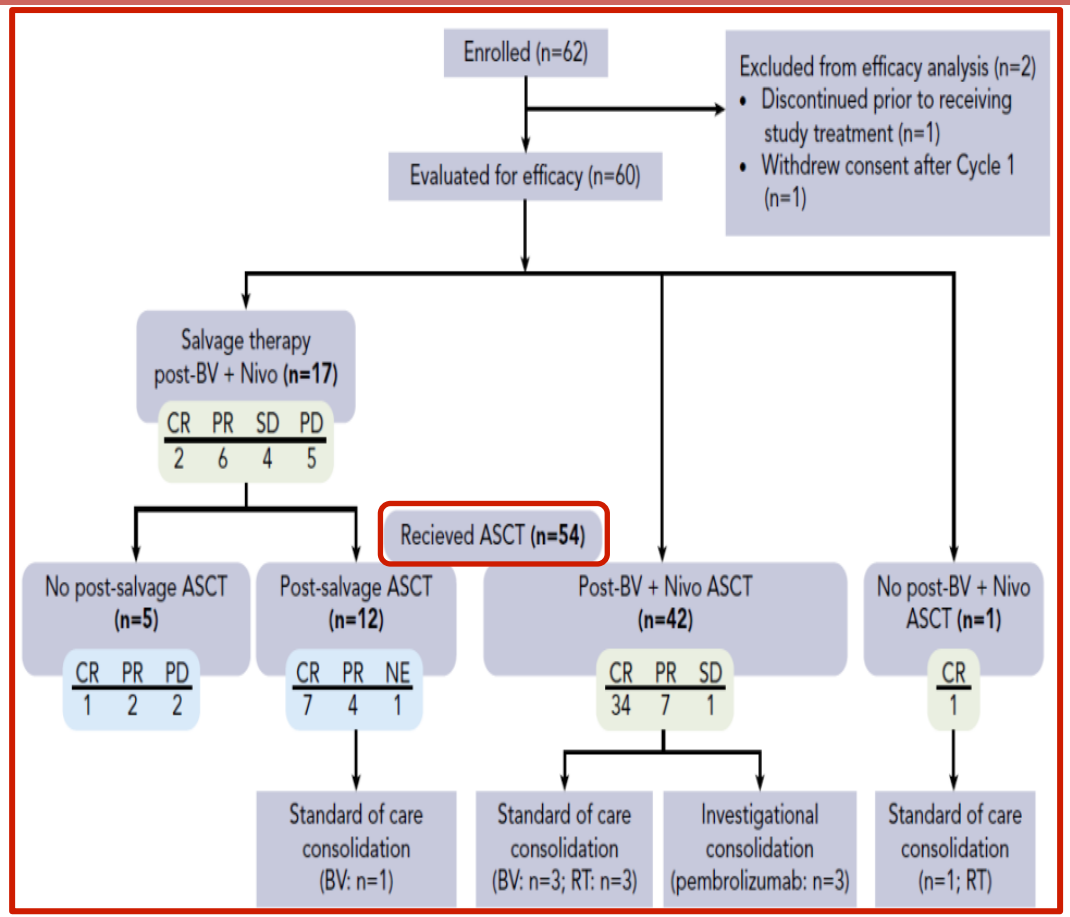
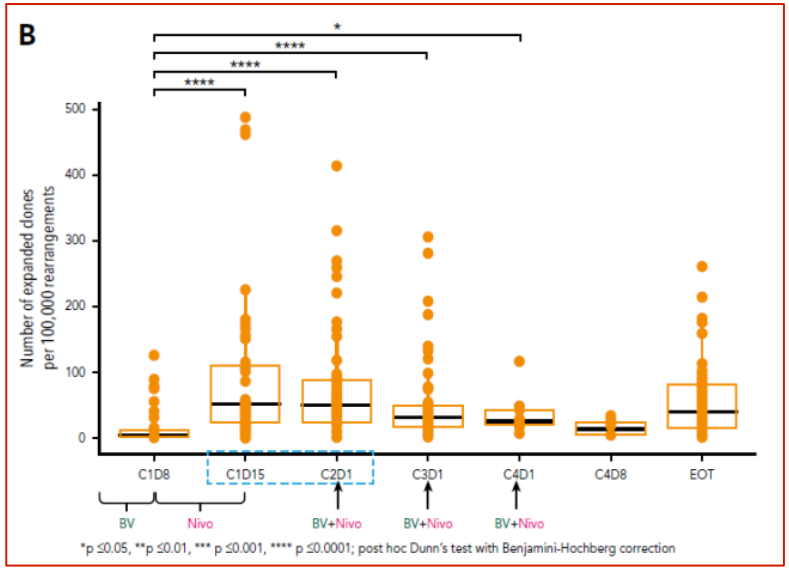
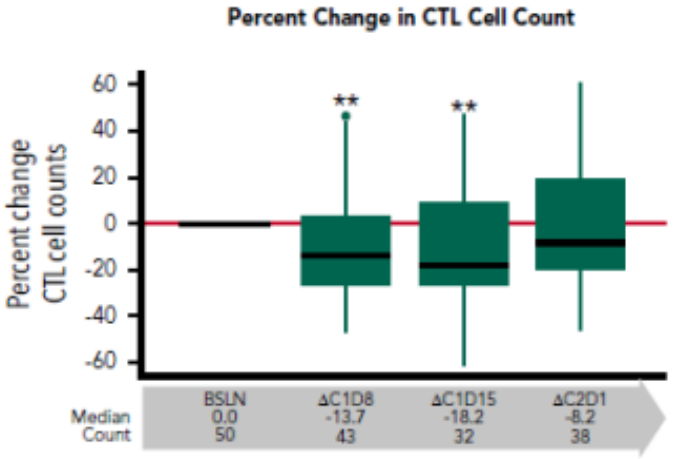
Brentuximab Vedotin-based combinations for RR-HL





Disease status relative to frontline treatment, n (%)	
Primary refractory	28 (45)
PR or SD to frontline therapy	10 (16)
PD to frontline therapy	18 (29)
Relapsed	34 (55)
Remission duration ≤1 y	19 (31)
Remission duration >1 y	15 (24)



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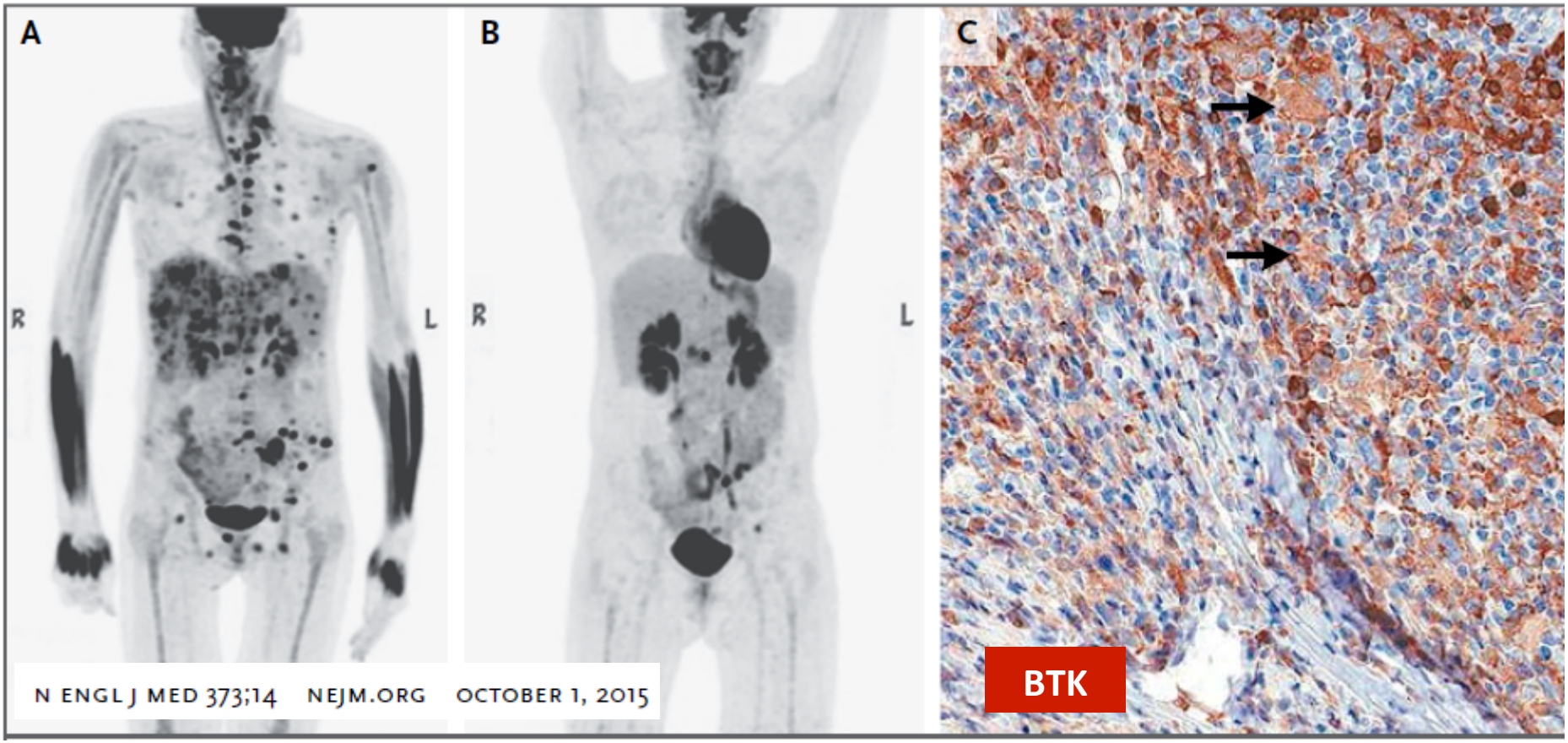
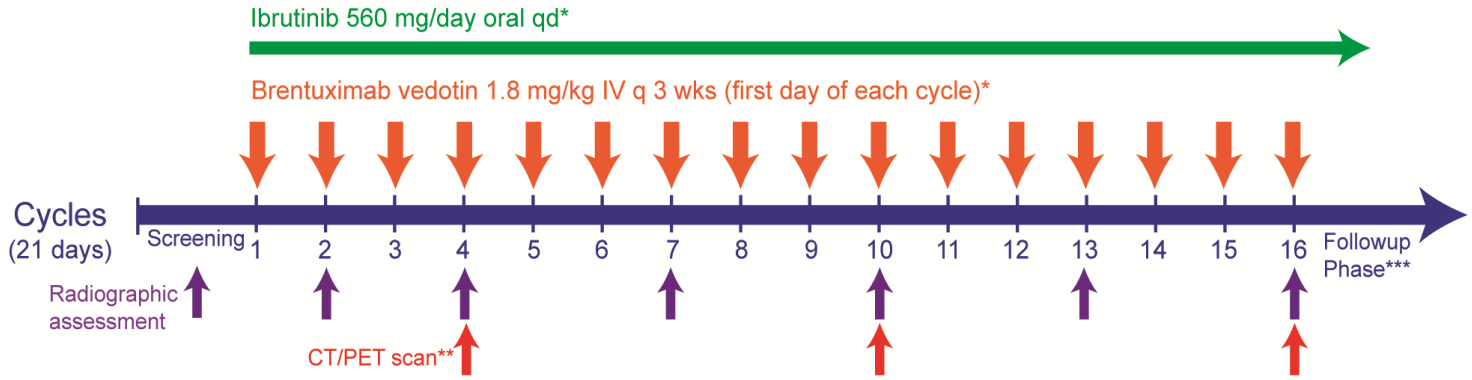
Brentuximab Vedotin in the Overall Treatment Strategy for HL

Ibrutinib in Refractory Classic Hodgkin's Lymphoma



Phase II Study of Brentuximab Vedotin Plus Ibrutinib for Patients With Relapsed/Refractory Hodgkin Lymphoma

Brentuximab Vedotin in the Overall Treatment Strategy for HL



*Patients will be treated until disease progression, unacceptable toxicity, or moving onto auto- or allo-HCT
**Once PET portion is negative, it does not need to be performed again.
***Subjects will be followed for up to two years with q3 month interval visits or telephone calls.

Characteristic, n (%)	Phase II Patients [n = 13] 560 mg Ibrutinib
Gender	
Female	5 (38)
Male	8 (62)
Age	33 (17-69)
Stage at Diagnosis	
I-II	7 (54)
III-IV	6 (46)
B symptoms (at diagnosis)	6 (46)
Prior Therapy	
ABVD	12 (92)
BEACOPP	3 (23)
R-CHOP	1 (8)
IGEV	1 (8)
BV	1 (8)
ICE	0
Clinical Trials	0
PD1 inhibitors	0
Prior Radiation	3 (23)
Status Prior to Treatment	
Progressive Disease	7 (54)
Relapsed Disease	6 (46)
Stable Disease	0
Best Response to Induction	
Refractory	5 (38)
Relapsed	8 (62)

Characteristic, n (%)	Phase II Patients [n = 13] 560 mg Ibrutinib
Median Number of Cycles	5 (2-9)
Best Response	
CR	6 (46)
PR	5 (39)
SD	2 (15)
PD	0
Response Rate (PR/CR)	84.6%

Chen R, et al. *Blood.* 2017;130: Abstract 738.

BV-based combinations for upfront treatment of HL

CLINICAL TRIALS AND OBSERVATIONS

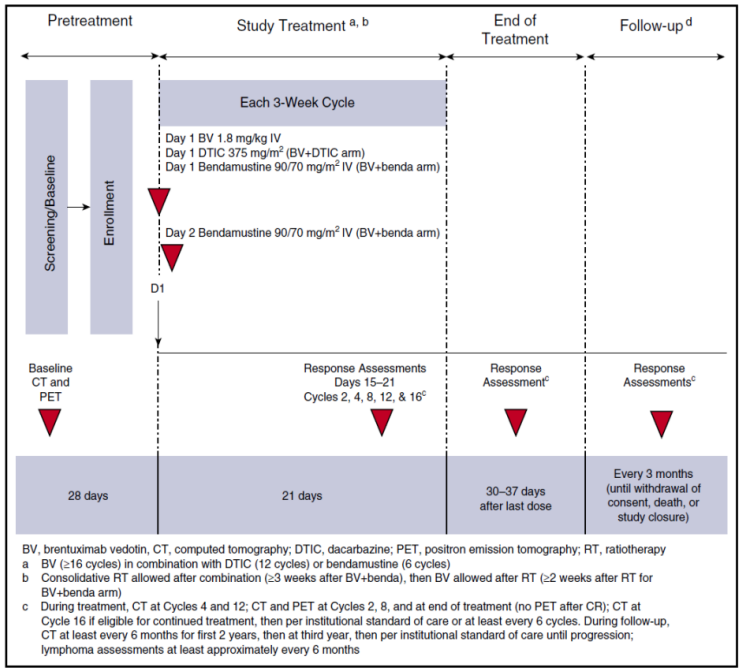
Blood. 2017;130(26):2829-2837

Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL

Jonathan W. Friedberg,[1] Andres Forero-Torres,[2] Rodolfo E. Bordoni,[3] Vivian J. M. Cline,[4] Dipti Patel Donnelly,[5] Patrick J. Flynn,[6] Gregg Olsen,[7] Robert Chen,[8] Abraham Fong,[9] Yinghui Wang,[9] and Christopher A. Yasenchak[10]

Table 3. Summary of best clinical response

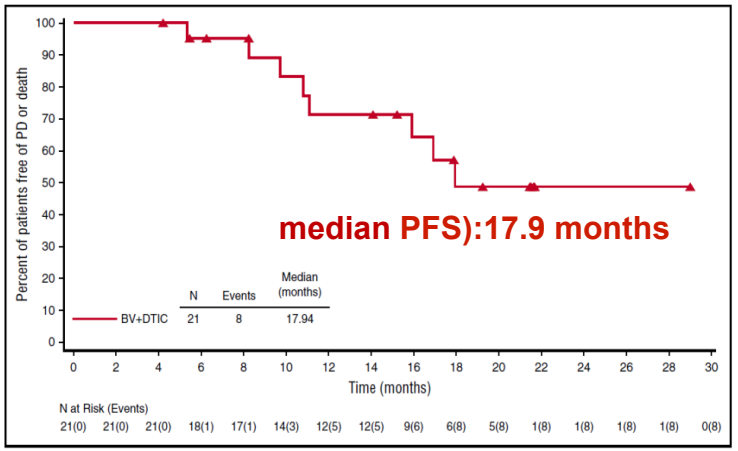
	BV+DTIC (n = 21)	BV+bendamustine (n = 17)
ORR*	21 (100)	17 (100)
95% CI†	83.9, 100	80.5, 100
Best clinical response		
CR	13 (62)	15 (88)
PR	8 (38)	2 (12)
95% CI† for CR rate	38.4, 81.9	63.6, 98.5



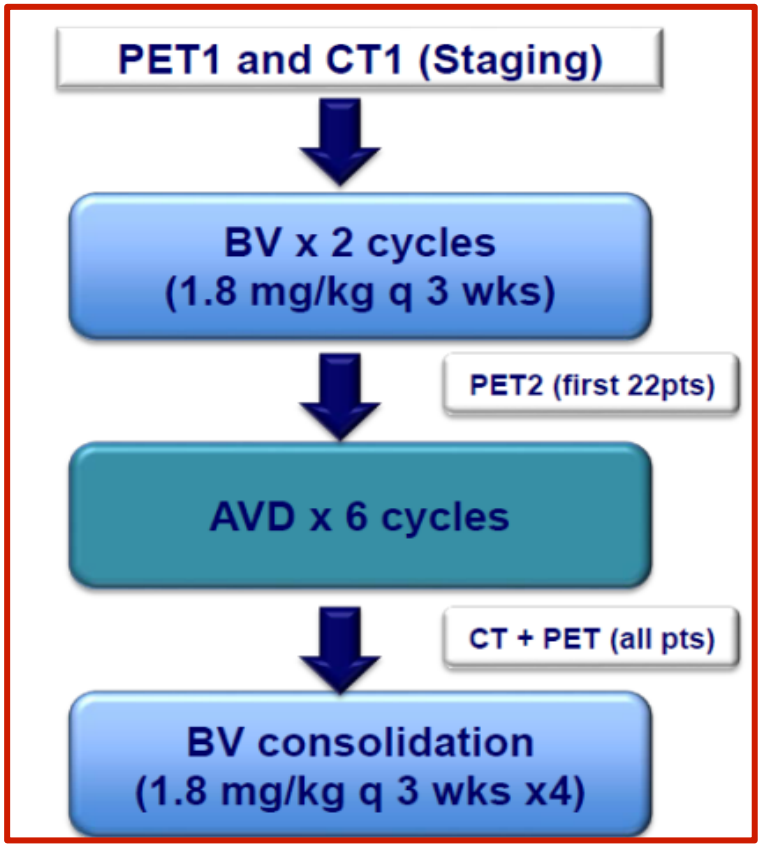
BV, brentuximab vedotin, CT, computed tomography; DTIC, dacarbazine; PET, positron emission tomography; RT, ratiotherapy
a BV (≥16 cycles) in combination with DTIC (12 cycles) or bendamustine (6 cycles)
b Consolidative RT allowed after combination (≥3 weeks after BV+benda), then BV allowed after RT (≥2 weeks after RT for BV+benda arm)
c During treatment, CT at Cycles 4 and 12; CT and PET at Cycles 2, 8, and at end of treatment (no PET after CR); CT at Cycle 16 if eligible for continued treatment, then per institutional standard of care or at least every 6 cycles. During follow-up, CT at least every 6 months for first 2 years, then at third year, then per institutional standard of care until progression; lymphoma assessments at least approximately every 6 months

Table 4. Summary of AEs

	BV+DTIC (n = 22)	BV+bendamustine (n = 20)
Any TEAE*	22 (100)	20 (100)
Treatment-related AEs	22 (100)	19 (95)
Grade ≥3 AEs	10 (45)	18 (90)
SAEs	4 (18)	13 (65)
AEs leading to treatment discontinuation	12 (55)	12 (60)
Deaths within 30 d of last dose	0	2 (10)†



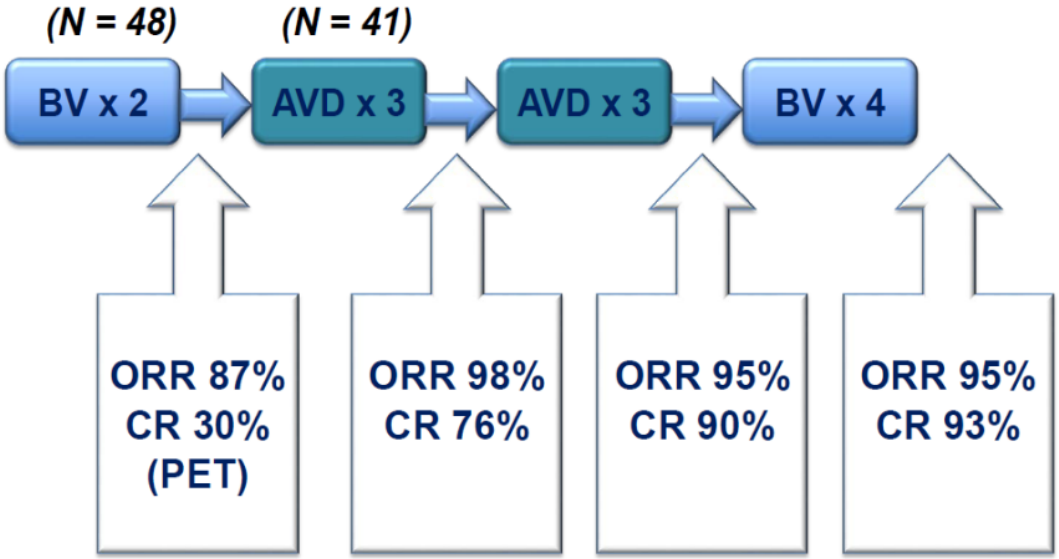
Brentuximab Vedotin: upfront treatment of HL in the elderly



- Phase II investigator-initiated study
- Untreated advanced-stage elderly HD (≥ 60 yo)
- Participating institutions: Tufts, Northwestern, Univ of Chicago, UMass, Ohio State, MDACC, Stanford, Nebraska, and MSKCC
- Window (lead-in) study with brentuximab vedotin
- CGA (CIRS-G) and HRQL assessments

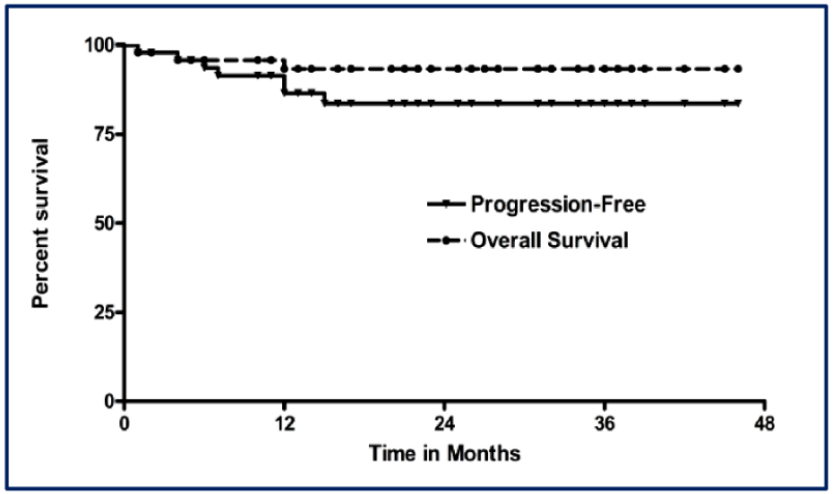
Evens AM, et al. *Blood*. 2017;130: Abstract 89.

Results: Efficacy



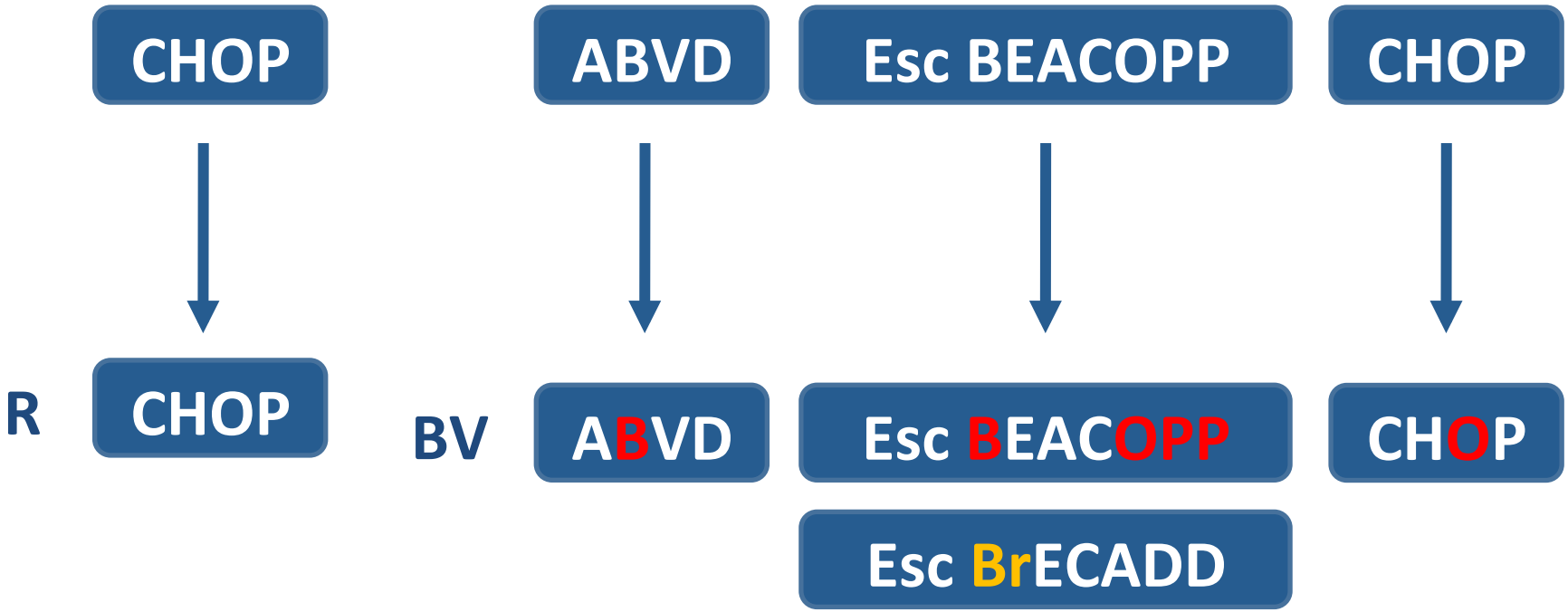
ITT (n = 48) after 6 AVD: ORR 88% and CR 81%

Survival: PFS and OS



2-Year PFS 85% and 2-year OS 94% (ITT)

Brentuximab Vedotin in the Overall Treatment Strategy for HL



Brentuximab Vedotin: upfront treatment of HL

Five-year follow-up of brentuximab vedotin combined with ABVD or AVD for advanced-stage classical Hodgkin lymphoma

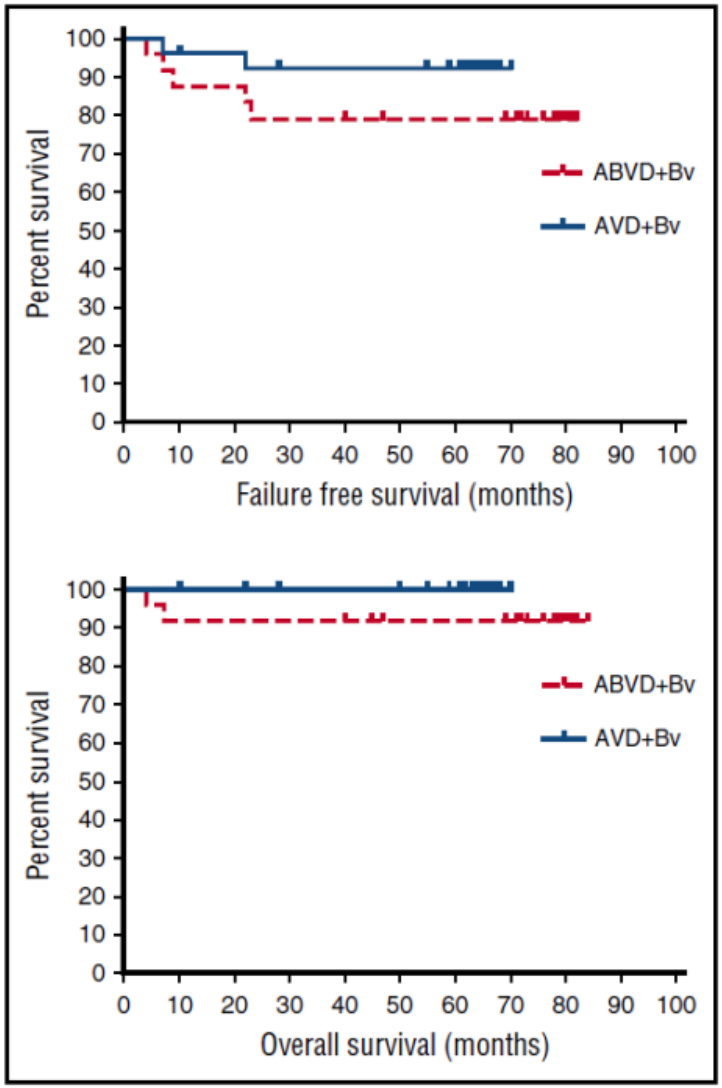
Joseph M. Connors,[1] Stephen M. Ansell,[2] Michelle Fanale,[3] Steven I. Park,[4] and Anas Younes[5]

Table 1. Patient characteristics

	ABVD + brentuximab vedotin	AVD + brentuximab vedotin
n	25	26
Age, y, median (range)	35 (19-59)	33 (18-58)
Male sex, n (%)	20 (80)	17 (65)
Performance status,* n (%)		
0	13 (52)	11 (42)
1	12 (48)	15 (58)
Stage, n (%)		
IIA bulky†	0	3 (12)
IIB	4 (16)	4 (15)
IIIA	5 (20)	3 (12)
IVA	4 (16)	5 (19)
IVB	12 (48)	11 (42)
International Prognostic Score, n (%)		
0-3	5 (20)	12 (46)
4-7	20 (80)	14 (54)

*Eastern Cooperative Oncology Group scale.
†Bulky = any mass ≥10 cm.

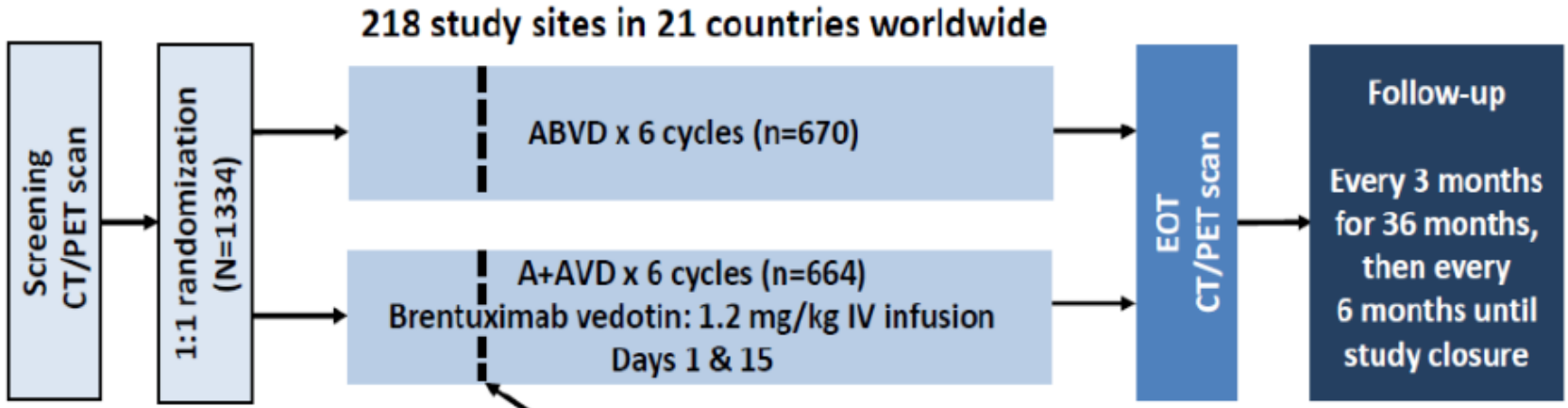
CR: 96%
5-year FFS: 92%
5-year OS: 100%



BLOOD, 14 SEPTEMBER 2017 • VOLUME 130, NUMBER 11

Brentuximab Vedotin for the upfront treatment of HL: ECHELON 1

ECHELON-1: Open-Label, Global, Randomized, Phase III Study of a+AVD Versus ABVD in Patients With Newly Diagnosed Advanced cHL



- Inclusion criteria
  - cHL stage — III or IV
  - ECOG PS — 0, 1 or 2
  - Age — ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan
- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

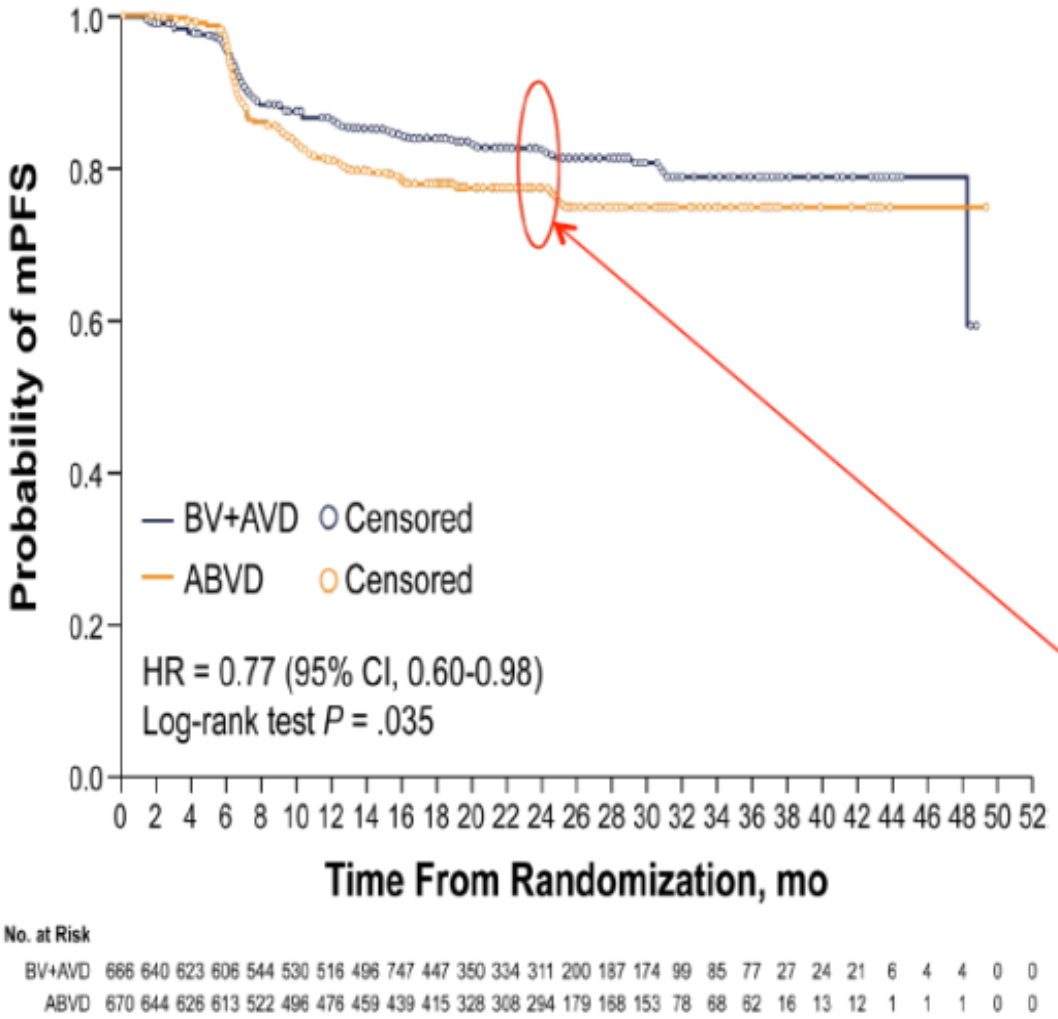
Connors J, et al. *Blood.* 2017;130: Abstract 6.

Brentuximab Vedotin for the upfront treatment of HL: ECHELON 1

END POINTS

The primary end point was modified progression-free survival, defined as time to disease progression, death, or modified progression (with the latter defined as evidence of noncomplete response after completion of frontline therapy according to review by an independent committee, followed by subsequent anticancer therapy). This end point was chosen specifically to evaluate the effectiveness of the primary chemotherapy and encompasses three possible outcomes, each of which represents a failure of the primary chemotherapy to eliminate Hodgkin's lymphoma: documented progression[20] at any time after initiation of primary chemotherapy, death from any cause, and detection of a response that was less than complete at the end of primary chemotherapy (Deauville score of 3, 4, or 5 on a PET scan), followed by the delivery of subsequent anticancer therapy. The latter outcome was considered to be an event only if noncomplete response was confirmed during review by an independent committee, whose members were unaware of group assignments, and was followed by the delivery of subsequent anticancer treatment that was not specified in the protocol. Additional justifica-

Brentuximab Vedotin for the upfront treatment of HL: ECHELON 1



Number of Events

	BV+AVD (n = 117)	ABVD (n = 146)
Progression	90	102
Death	18	22
Modified progression	9	22
• Chemotherapy	7	15
• Radiotherapy	2	7

mPFS Estimates

	BV+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7-85.0)	77.2 (73.7-80.4)

Median follow-up (range): 24.9 mo (0.0-49.3)

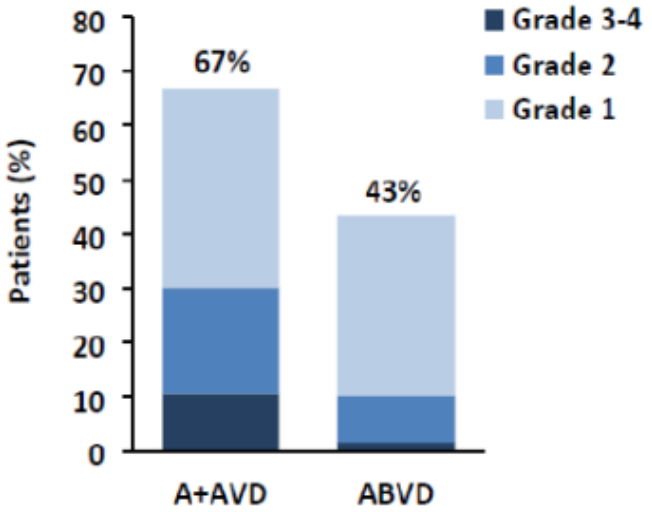
Brentuximab Vedotin for the upfront treatment of HL: ECHELON 1

	A+AVD (N=662)		ABVD (N=659)	
Common adverse events, %*	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	58	54	45	39
Constipation	42	2	37	<1
Vomiting	33	3	28	1
Fatigue	32	3	32	1
Peripheral sensory neuropathy	29	5	17	<1
Diarrhea	27	3	18	<1
Pyrexia	27	3	22	2
Peripheral neuropathy	26	4	13	<1
Abdominal pain	21	3	10	<1
Stomatitis	21	2	16	<1
Febrile neutropenia	19	19	8	8

Brentuximab Vedotin for the upfront treatment of HL: ECHELON 1

Peripheral Neuropathy and Pulmonary Events

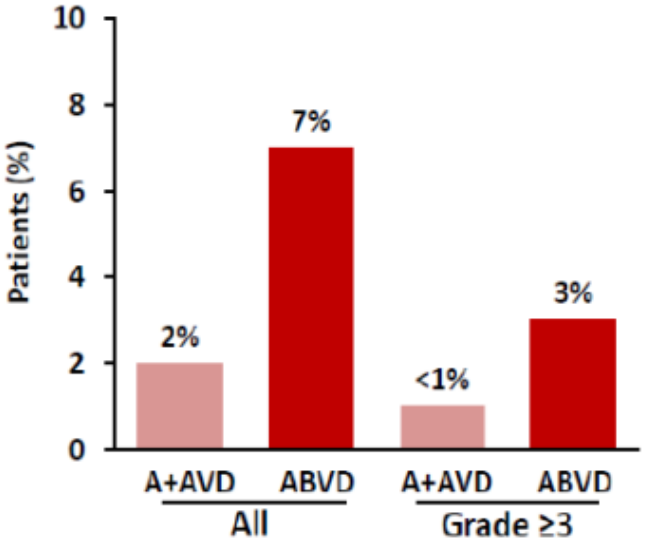
Treatment-emergent PN*



- 67% of pts with PN in the A+AVD arm had resolution or improvement by ≥1 grade at last follow-up
- Of those with ongoing PN at last follow-up:
  - Grade 1 64%
  - Grade 2 29%
  - Grade 3 7%

- Drug discontinuations due to PN:
  - A+AVD 7%
  - ABVD 2%

Interstitial lung disease†



Interstitial lung disease was more frequent and more severe in ABVD arm

*Includes the preferred terms peripheral sensory neuropathy, PN, hypoesthesia, polyneuropathy, paraesthesia, muscular weakness, peripheral motor neuropathy, peroneal nerve palsy, muscle atrophy, hypotonia, autonomic neuropathy, neuralgia, burning sensation, dysesthesia, gait disturbance, toxic neuropathy, neurotoxicity, and sensory disturbance; PN, peripheral neuropathy

†Includes the preferred terms lung infiltration, pneumonitis, interstitial lung disease, acute respiratory distress syndrome, organizing pneumonia, pulmonary fibrosis, and pulmonary toxicity

Connors J, et al. *Blood.* 2017;130: Abstract 6.

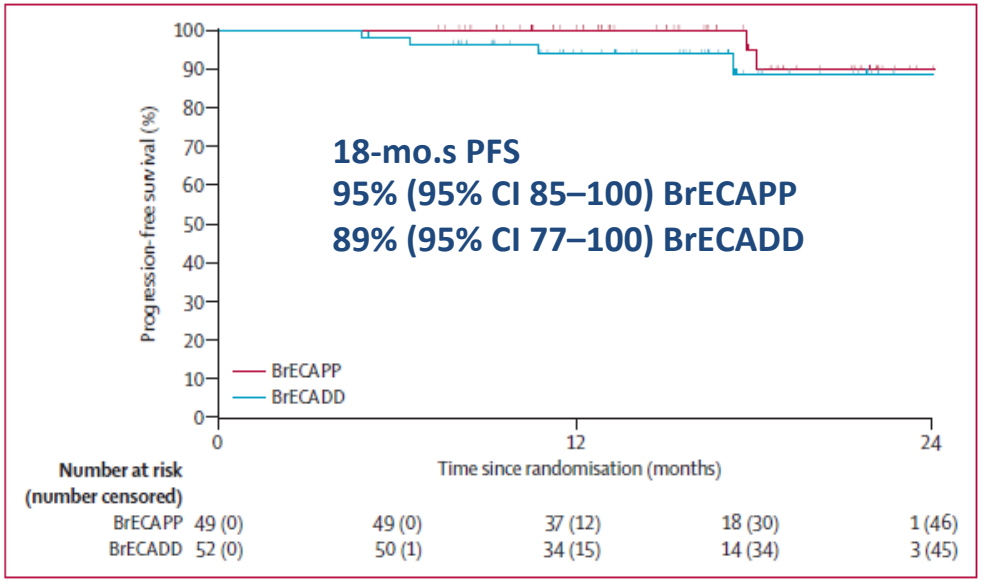
Brentuximab Vedotin in the Overall Treatment Strategy for HL

	BrECAPP	BrECADD
Restaging after two cycles*		
CR	2/50 (4%)	0/52
CRu	4/50 (8%)	6/52 (12%)
PR	40/50 (80%)	45/52 (87%)
NC	4/50 (8%)	1/52 (2%)
PET after two cycles (Deauville score)		
1	13/49 (27%)	9/52 (17%)
2	7/49 (14%)	14/52 (27%)
3	18/49 (37%)	18/52 (35%)
4–5	11/49 (22%)	11/52 (21%)
Restaging after six cycles†		
CR	4/48 (8%)	3/52 (6%)
CRu	3/48 (6%)	7/52 (13%)
PR	1/48 (2%)	2/52 (4%)
PR (residual ≥2·5 cm)	40/48 (83%)	39/52 (75%)
PD (residual ≥2·5cm)	0/48	1/52 (2%)
PET after chemotherapy (Deauville score)‡		
1	10/40 (25%)	13/40 (33%)
2	9/40 (23%)	13/40 (33%)
3	14/40 (35%)	8/40 (20%)
4–5	7/40 (18%)	6/40 (15%)
Complete response to chemotherapy		
No (further treatment recommended by CREP)	7/49 (14%)	6/52 (12%)
Yes (CR or PR <2·5 cm [local investigator] or no indication for further treatment [CREP])	42/49 (86%)	46/52 (88%)

Lancet Oncol 2017; 18: 1680–87

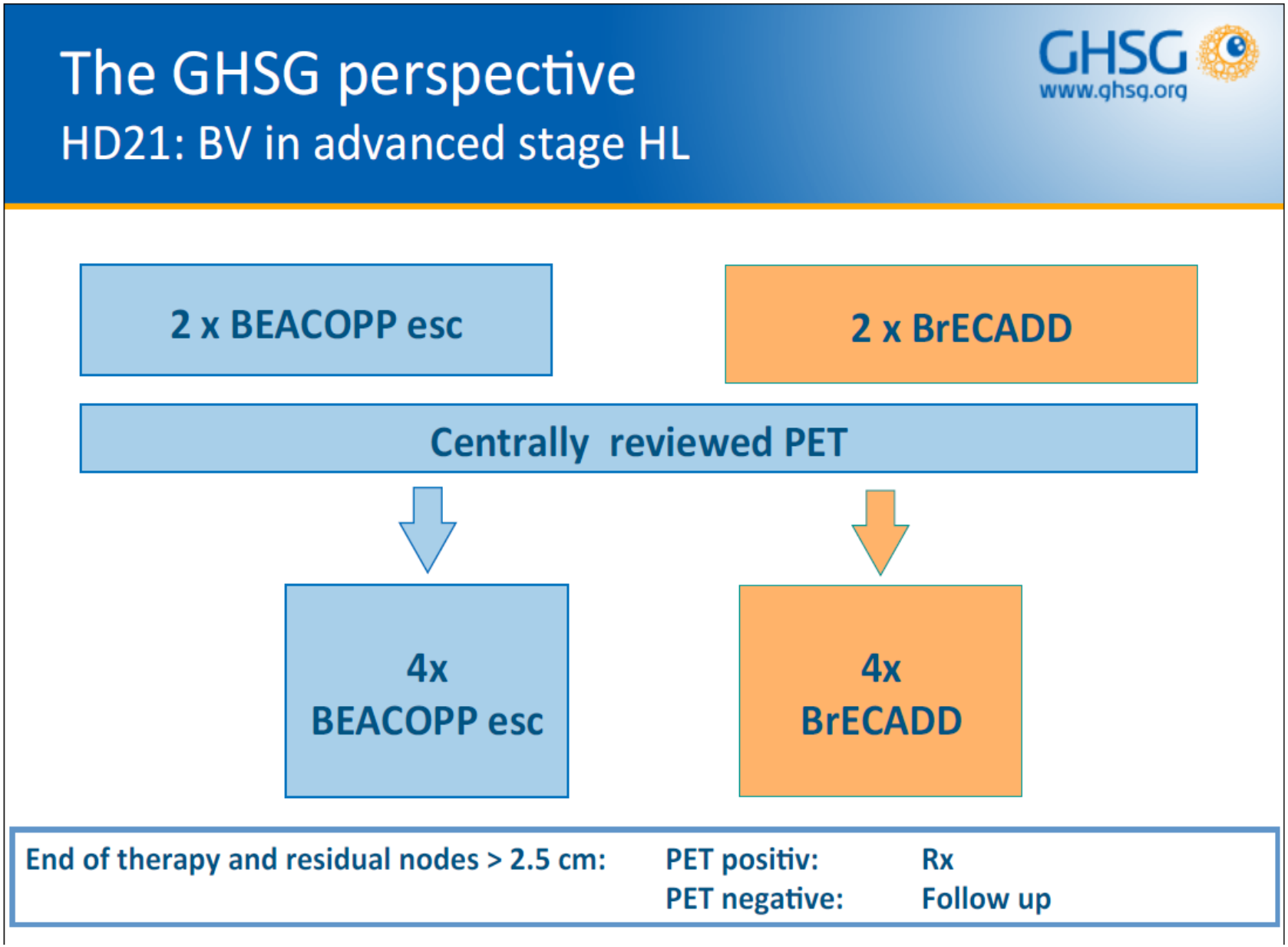
Remodeling BEACOPPesc with Brentuximab Vedotin

Drug	Day	6x BEACOPP	6x BrECADD	6x BrECAPP
Bleomycin	8	10		
Etoposide	**1-3**	**200**	**150**	**200**
Adriamycin	**1**	**35**	**40**	**35**
Cyclophosphamide	**2**	**1250**	**1250**	**1250**
Vincristine	8	1.4		
Brentuximab vedotin	**1**		**1.8**	**1.8**
Procarbazine	1-7	100		100
Prednisone	1-14	40		40
Dacarbazine	**2-3**		**250**	
Dexamethasone	**1-4**		**40**	

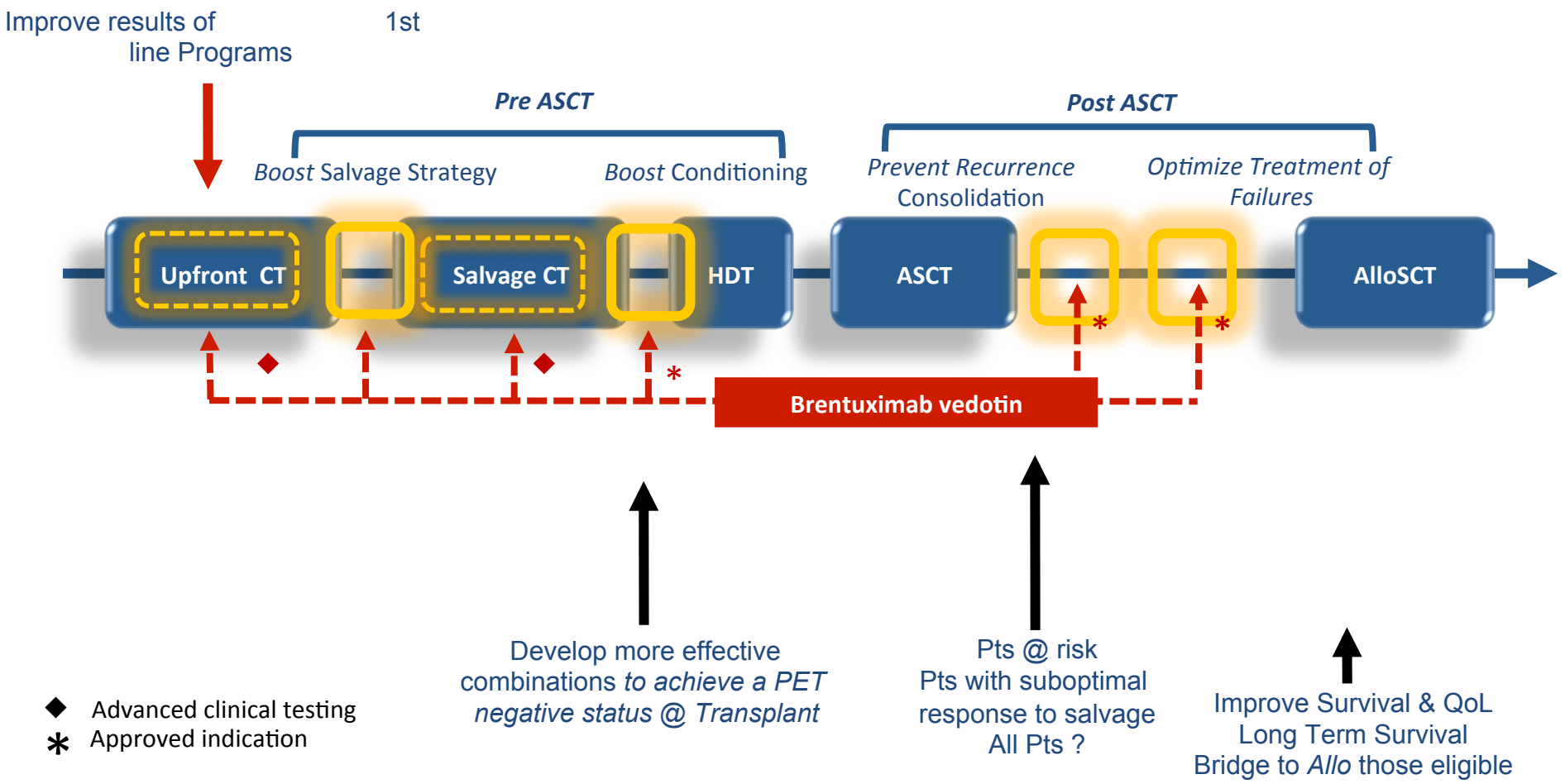


18-mo.s PFS
95% (95% CI 85–100) BrECAPP
89% (95% CI 77–100) BrECADD

Brentuximab Vedotin in the Overall Treatment Strategy for HL



Brentuximab Vedotin in the Overall Treatment Strategy for HL

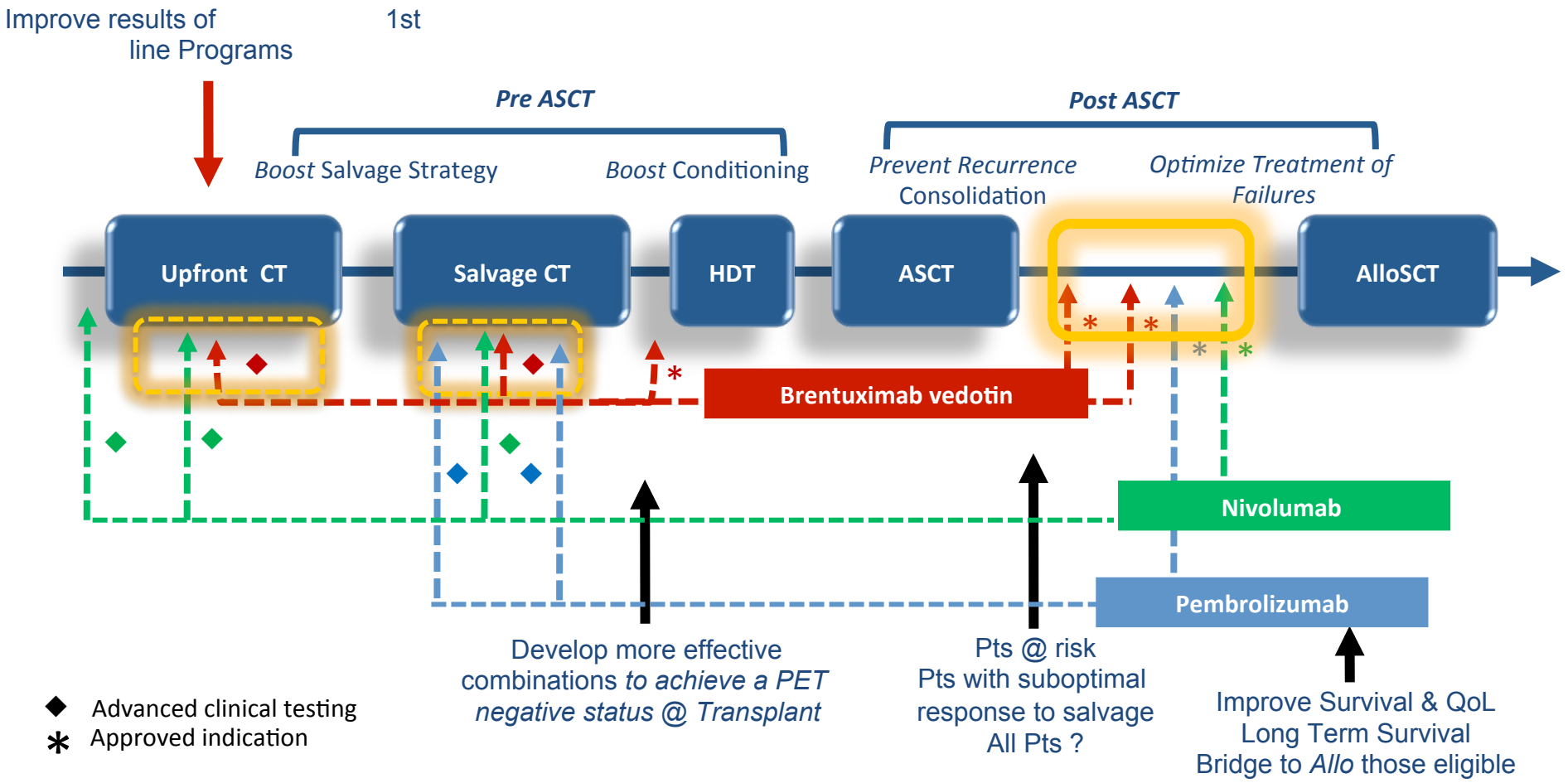


Brentuximab Vedotin: …CD30…HL…and beyond...

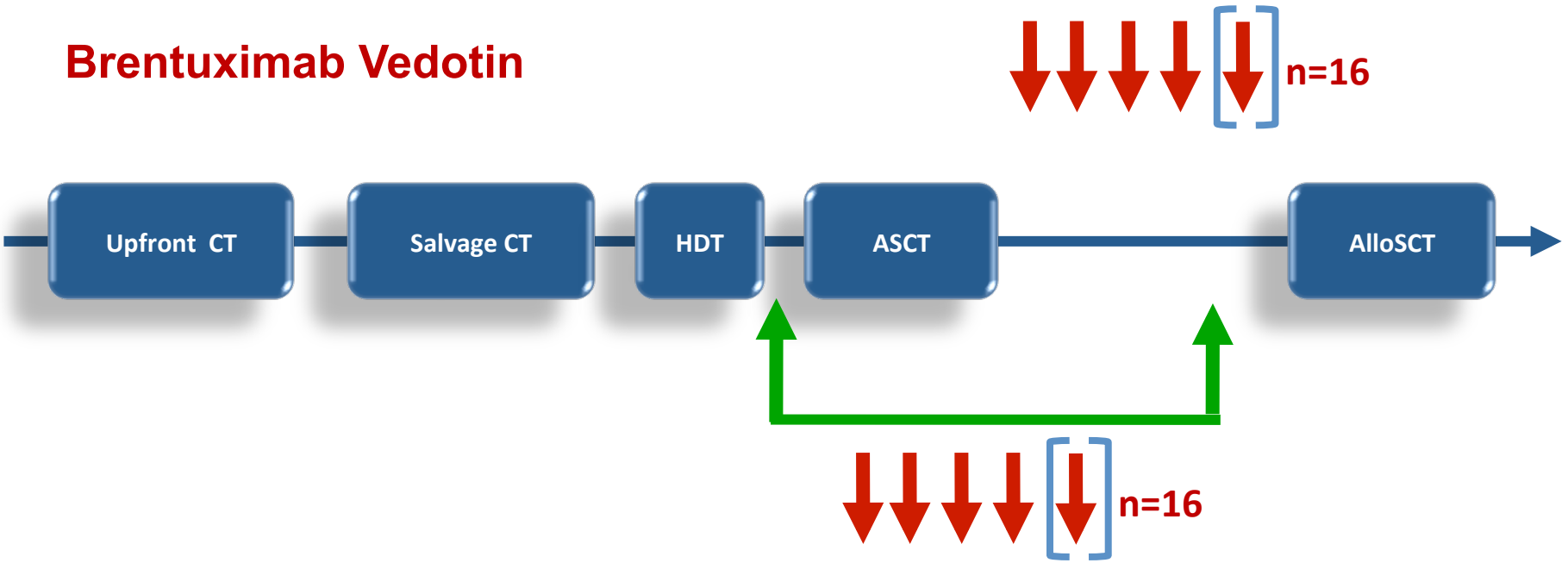
Dolabella auricularia,la miglior soluzione contro qualsiasi tipo di alga,anche quelle più ostili come l'alga briopsis.
Instancabile divoratrice di qualsiasi alga infestante possiate trovarvi in acquario.

€22.90

Brentuximab Vedotin in the Overall Treatment Strategy for HL



Brentuximab Vedotin in the Overall Treatment Strategy for HL

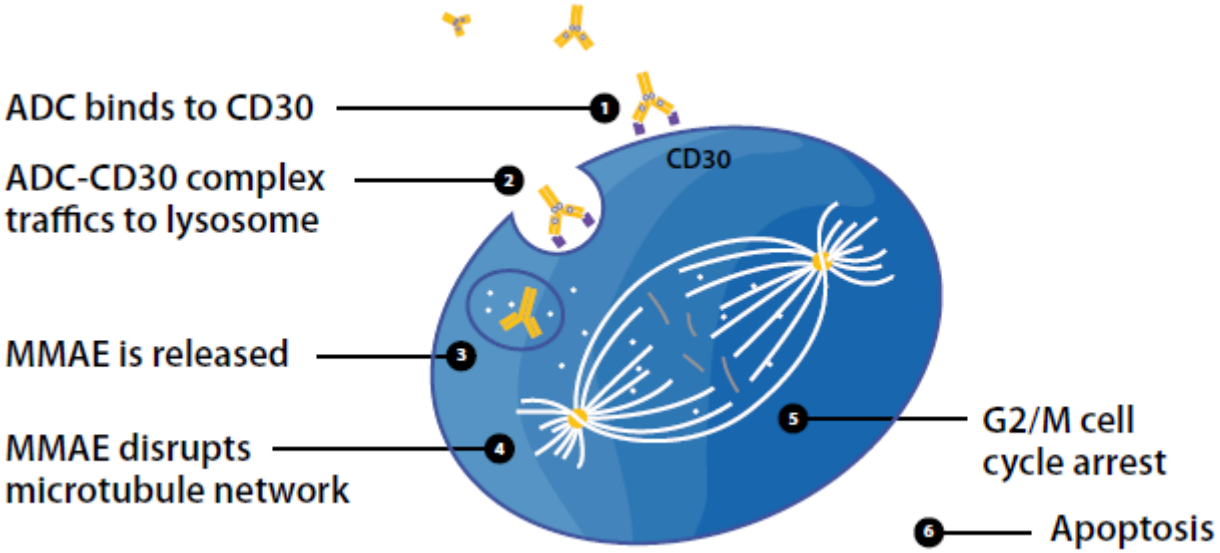


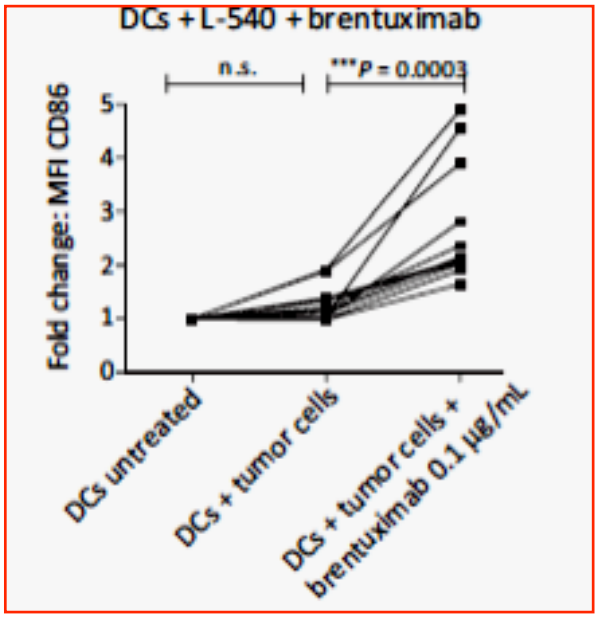
4.1 Indicazioni terapeutiche

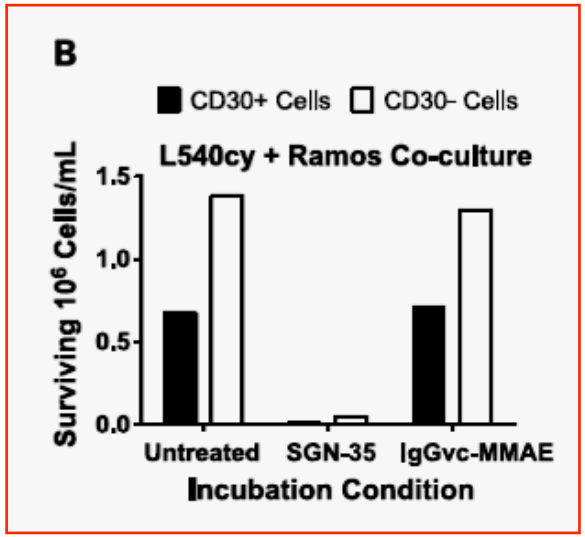
ADCETRIS è indicato per il trattamento di pazienti adulti affetti da linfoma di Hodgkin (HL) CD30+ recidivante o refrattario:

1. in seguito a trapianto autologo di cellule staminali (ASCT) oppure
2. in seguito ad almeno due precedenti regimi terapeutici, quando l'ASCT o la poli-chemioterapia non è un'opzione terapeutica.

ADCETRIS è indicato per il trattamento di pazienti adulti affetti da linfoma anaplastico a grandi cellule sistemico recidivante o refrattario.







Microtubule-Depolymerizing Agents Used in Antibody–Drug Conjugates Induce Antitumor Immunity by Stimulation of Dendritic Cells

Philipp Müller[1], Kea Martin[1], Sebastian Theurich[8], Jens Schreiner[1], Spasenija Savic[5], Grzegorz Terszowski[6], Didier Lardinois[2], Viola A. Heinzelmann-Schwarz[3], Max Schlaak[9], Hans-Michael Kvasnicka[10], Giulio Spagnoli[4], Stephan Dirnhofer[5], Daniel E. Speiser[7], Michael von Bergwelt-Baildon[8], and Alfred Zippelius[1,4]

Cancer Immunology Research

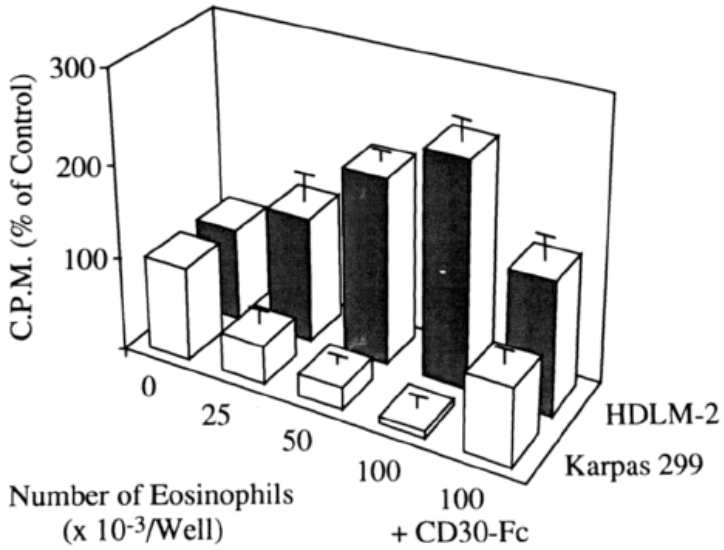
Cancer Therapy: Preclinical

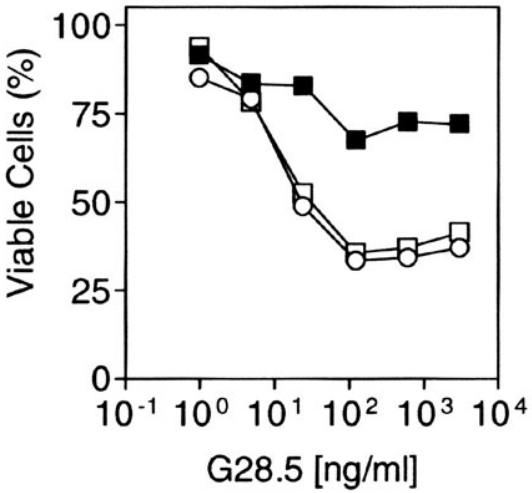
Intracellular Activation of SGN-35, a Potent Anti-CD30 Antibody-Drug Conjugate

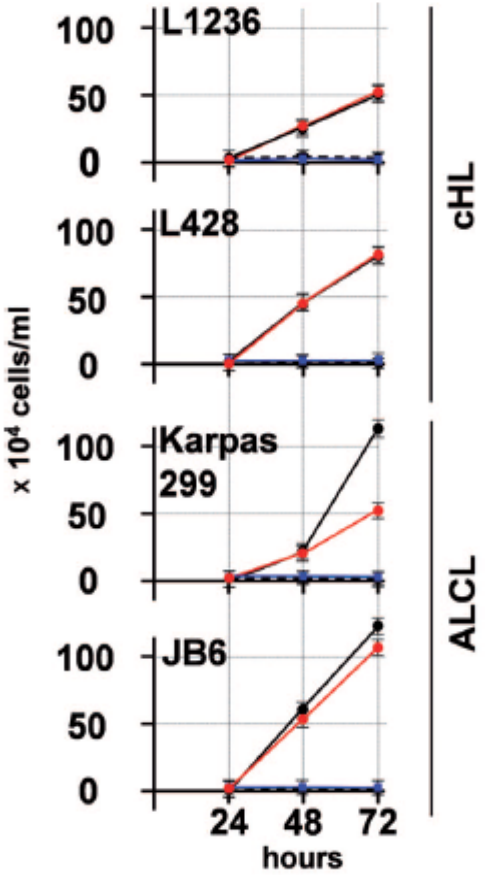
Nicole M. Okeley, Jamie B. Miyamoto, Xinqun Zhang, Russell J. Sanderson, Dennis R. Benjamin, Eric L. Sievers, Peter D. Senter, and Stephen C. Alley

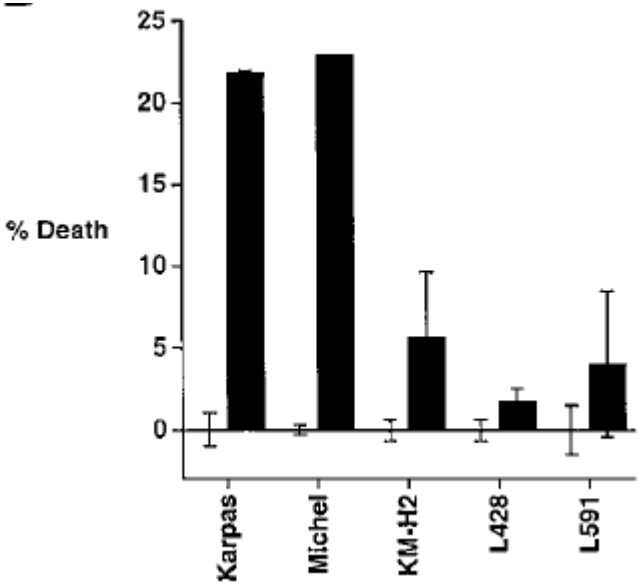
Clinical Cancer Research

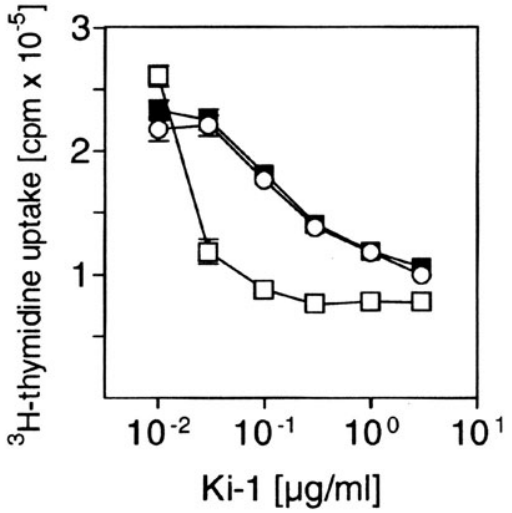
CD30 activation elicits different effects in HL and ALCL cells





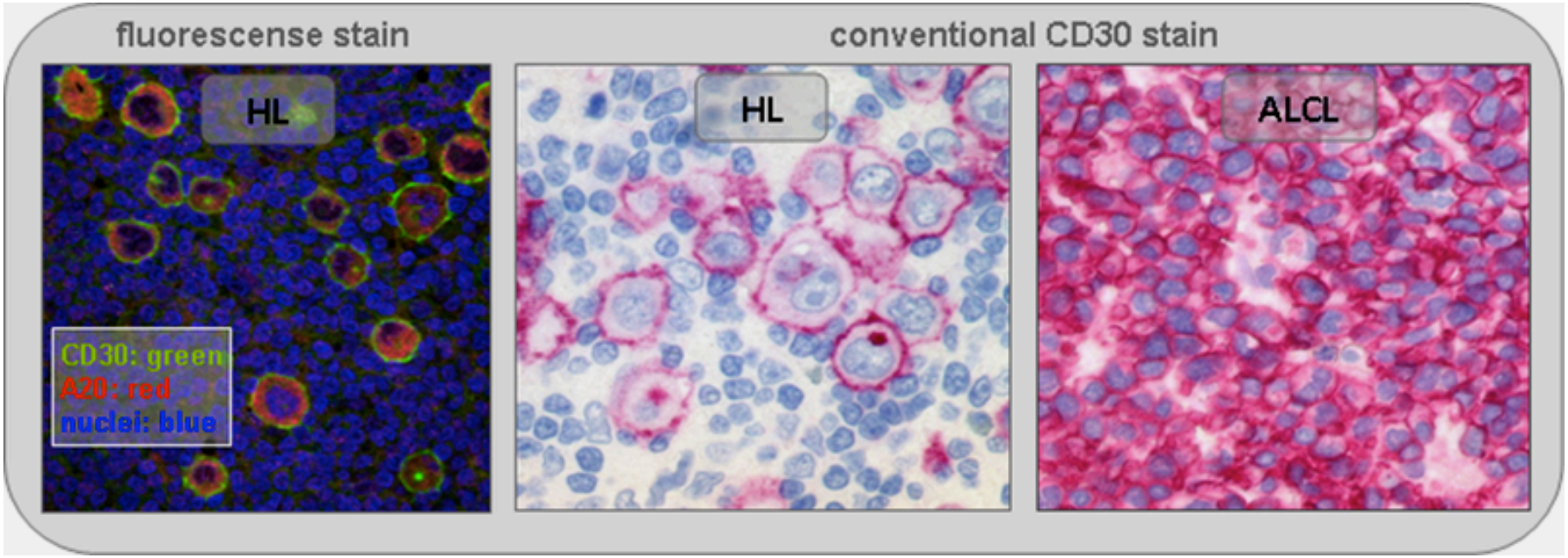


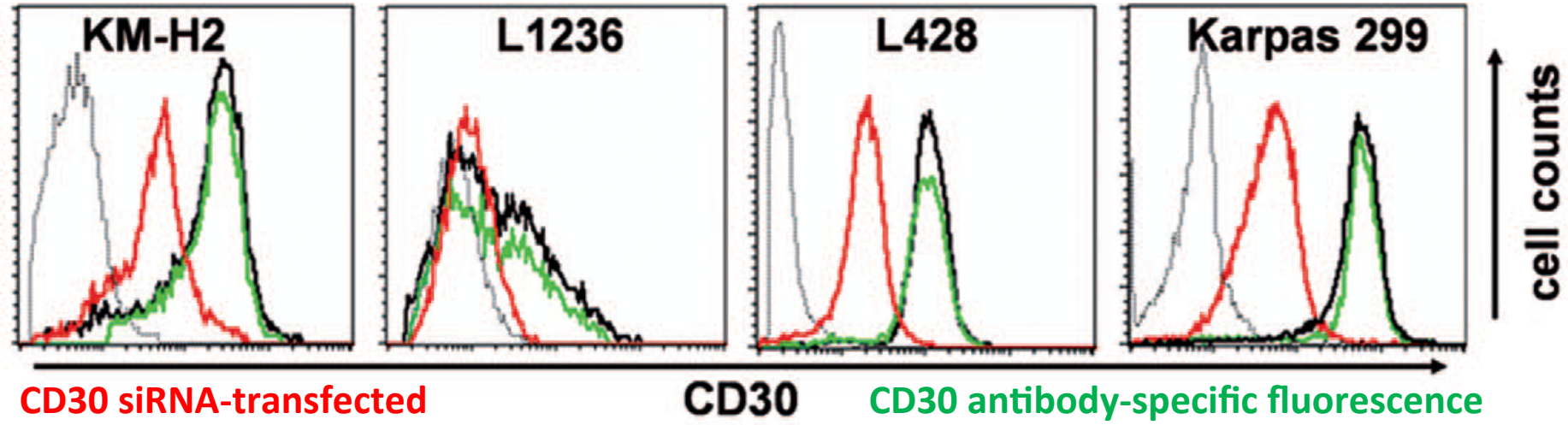




Pinto et al. Blood 1996;
Mir et al. Blood 2000;
Hirsch et al. Am J Pathol 2008;

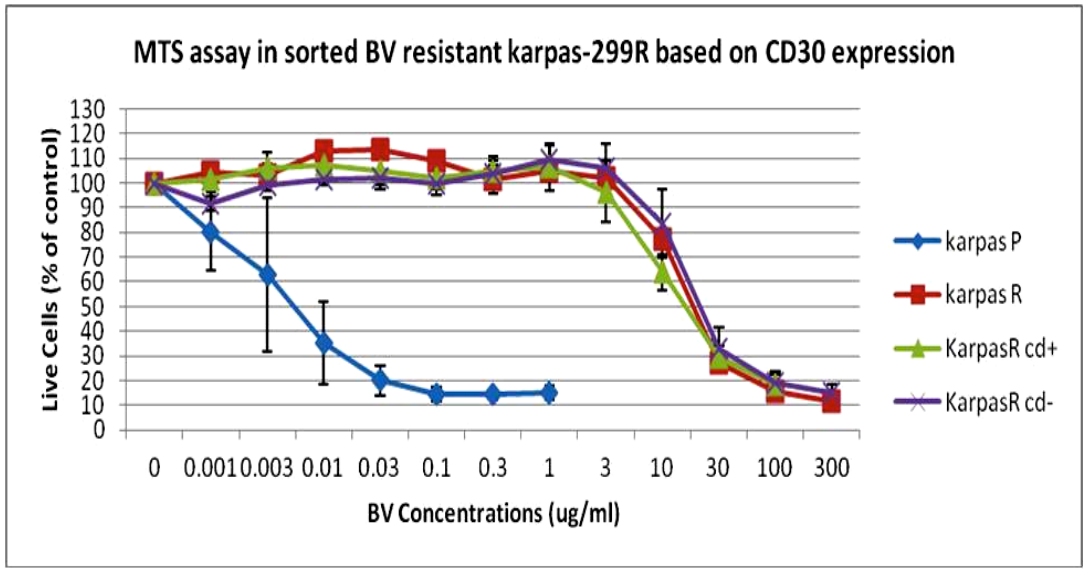
CD30 Expression in HL and ALCL

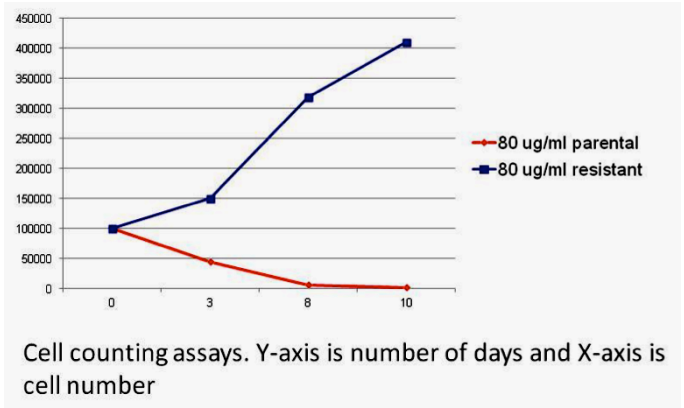




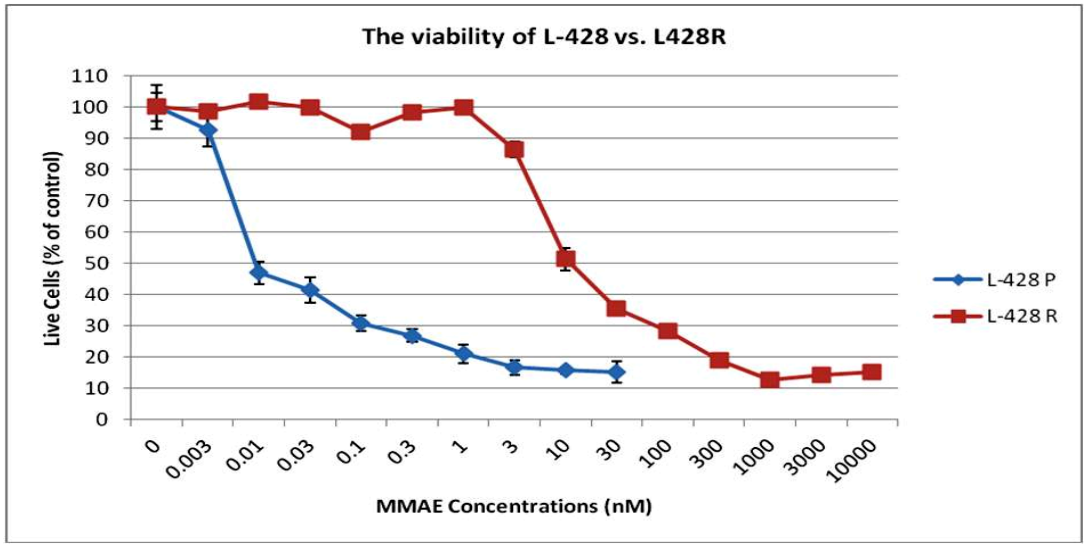
Mechanisms of reistance to Brentuximab Vedotin: Not just Surface CD30 Expression

3643 Downregulation of CD30, Resistance to MMAE, and Upregulation of MDR1 Are All Associated with Resistance to BV





Cell counting assays. Y-axis is number of days and X-axis is cell number

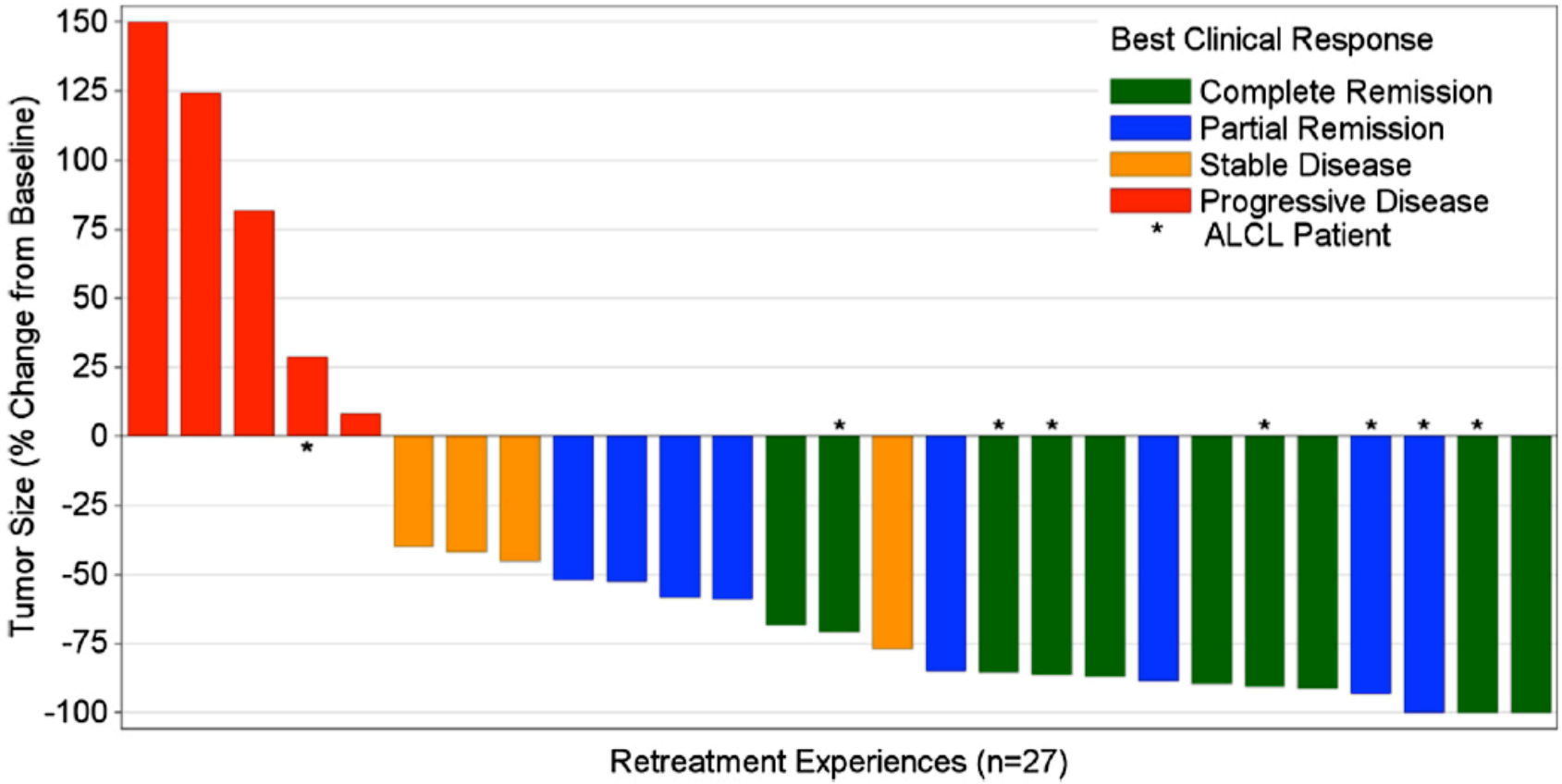


Upregulation of MDR-1 and resistance to MMAE were seen in BV-resistant HL cells, rather than downregulation of CD30.

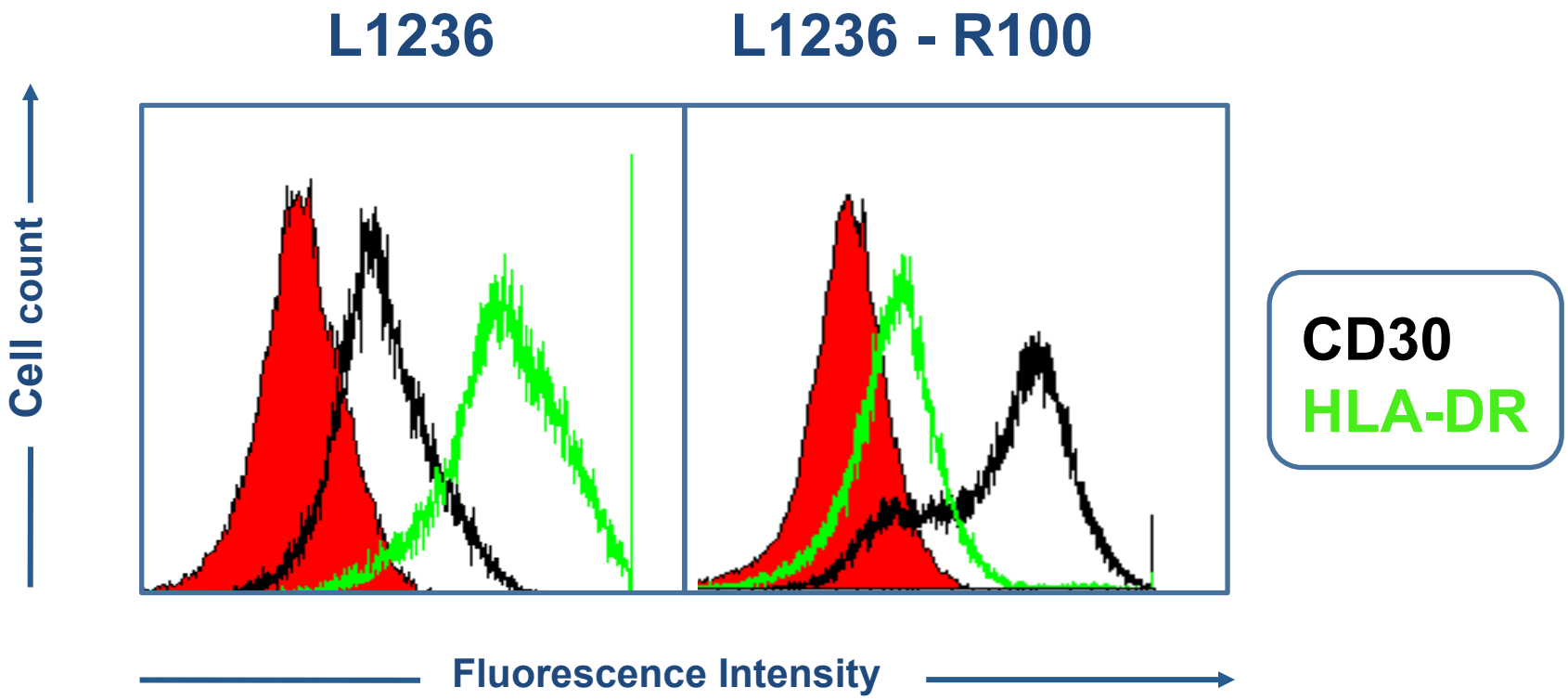
Robert Chen et al. 2014

56th ASH® Annual Meeting and Exposition
San Francisco, CA • December 6-9, 2014
ABSTRACTS & PROGRAM

doi:10.1186/1756-8722-7-24
Cite this article as: Bartlett *et al.*: Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. *Journal of Hematology & Oncology* 2014 **7**:24.

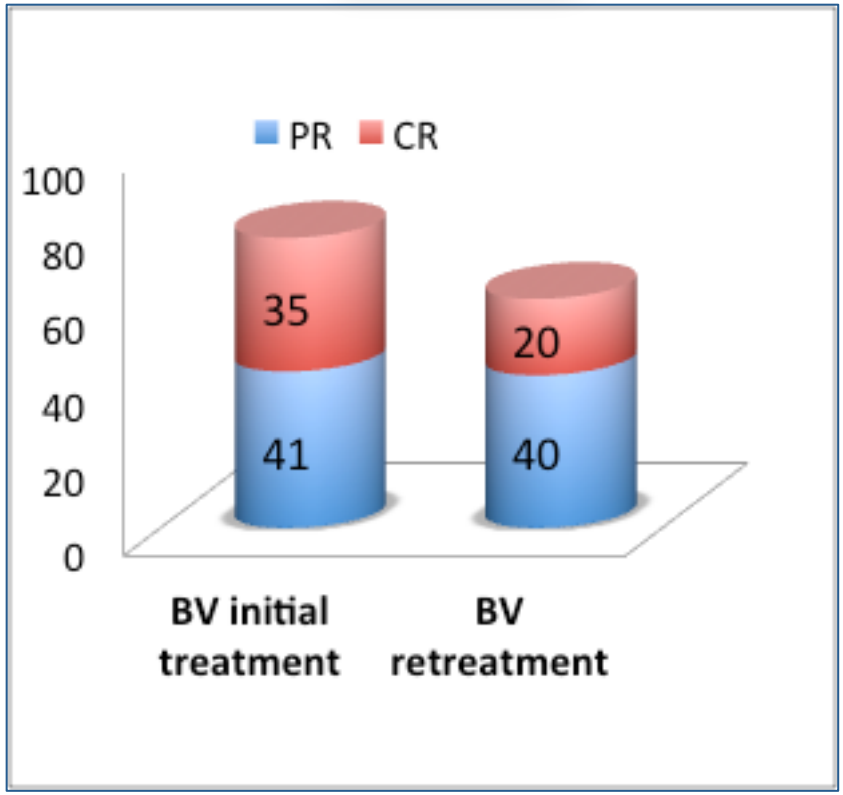


Acquired resistance to bendamustine is associated to a stable upregulation of CD30 in L1236 HL cells



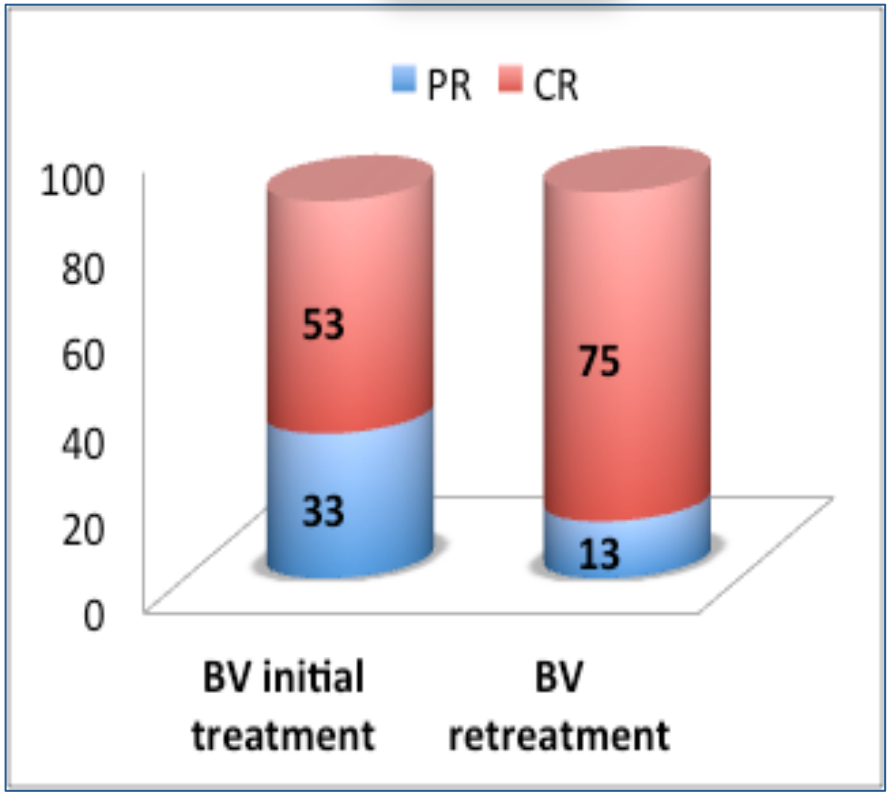
Brentuximab vedotin: initial treatment vs. retreatment

HL



N=102 N=15

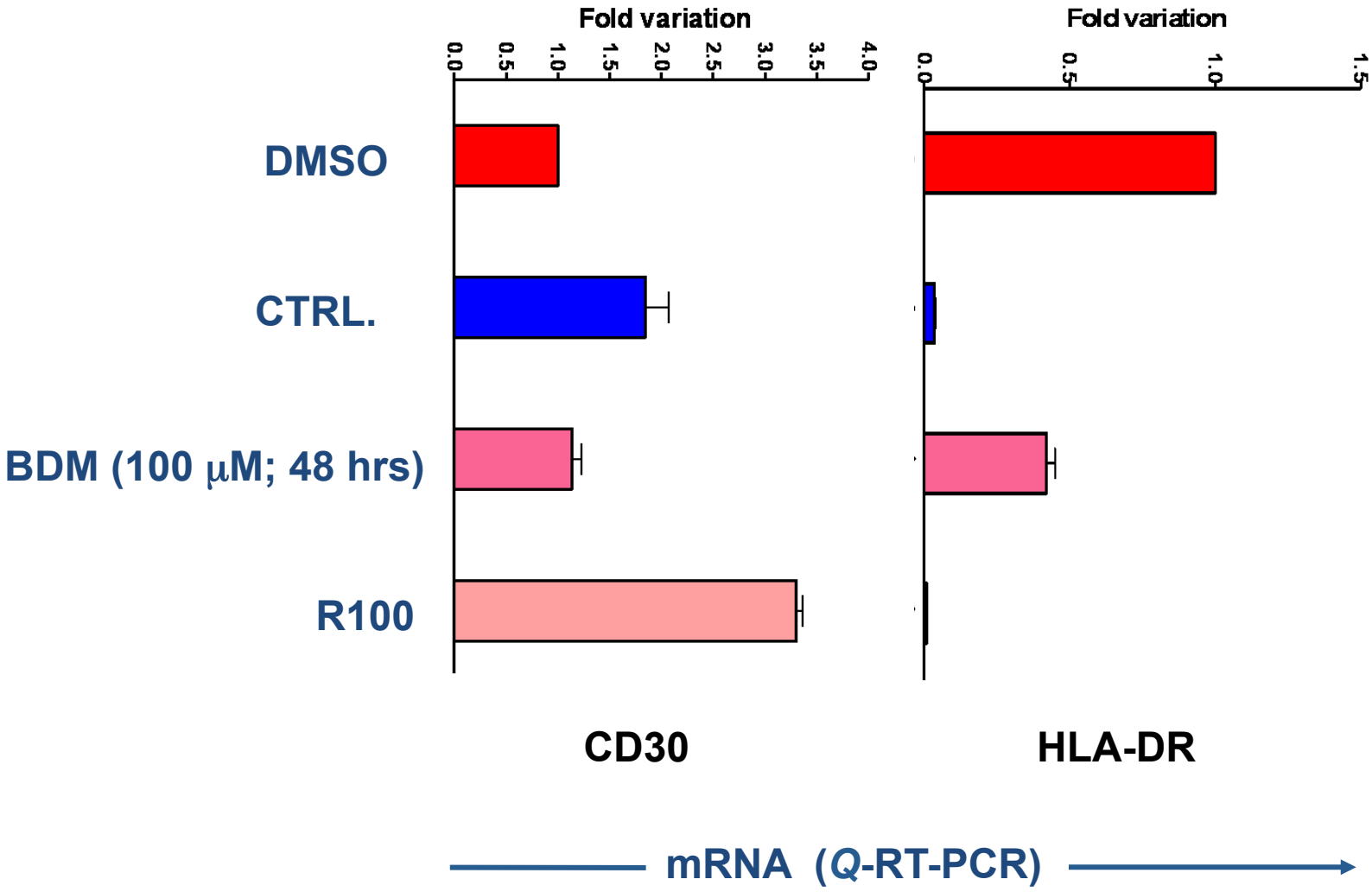
sALCL



N= 58 N=8

Bartlet et al. ASCO 2012

Acquired resistance to bendamustine is associated to a stable upregulation of CD30 in L1236 HL cells



Brentuximab Vedotin: …CD30…HL…and beyond...

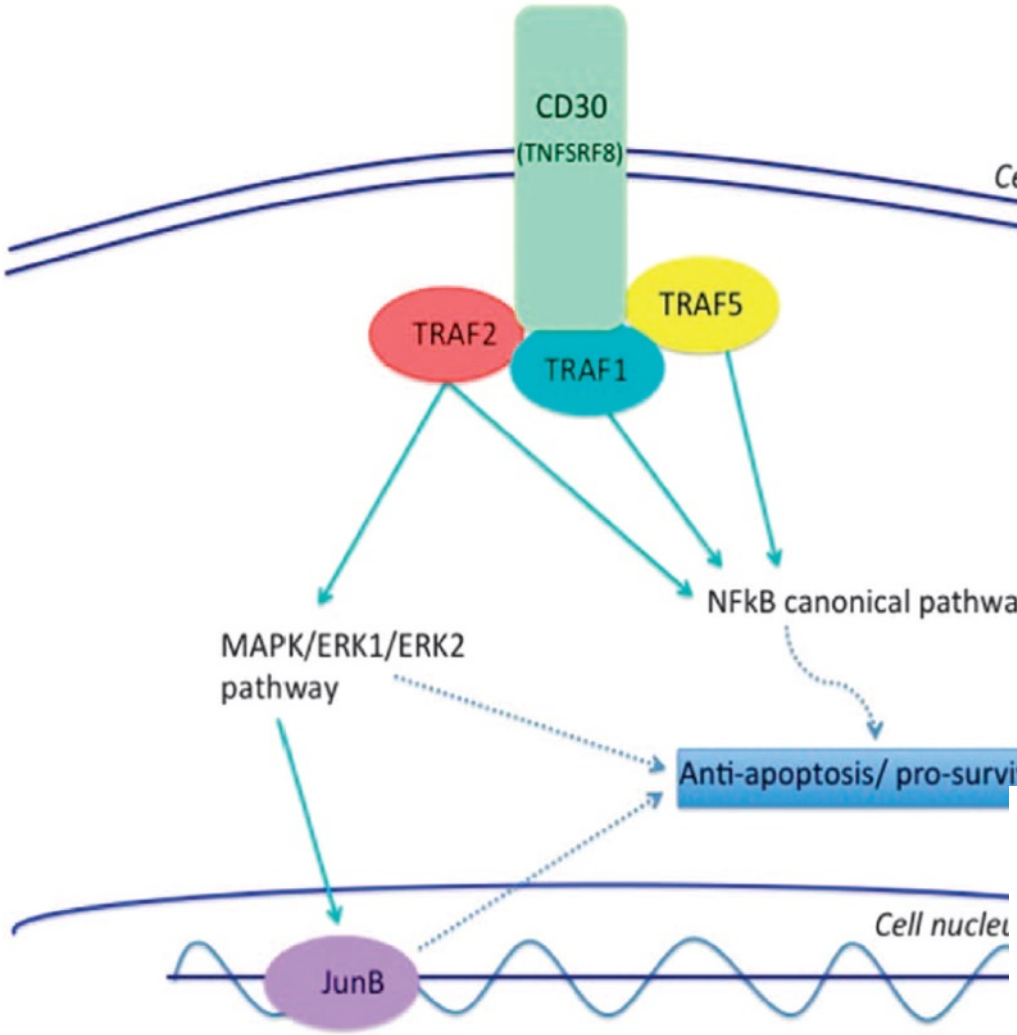


Figure 1. CD30 mediates its effects through a number of diverse signaling pathways, which in concert confer a survival benefit to the cells on which CD30 is upregulated. Stimulation of the CD30 molecule results in trimerization and signal mediation through tumor necrosis factor receptor-associated proteins (TRAF), in particular TRAF2, but also TRAF1 and TRAF5, to stimulate the nuclear factor-kappa B (NFkB) pathway. In addition to this, CD30 ligation also signals through the mitogen-activated protein kinase (MAPK) pathways, including ERK1 and ERK2, which have diverse anti-apoptotic and pro-survival benefits in the neoplastic cell. There appears to be a positive feedback loop between the MAPK/ERK pathway and the nuclear transcription factor JunB, which not only contributes to cell survival, but also upregulates CD30 expression.

Brentuximab Vedotin: …CD30…HL…and beyond...

Mol Cancer Ther; 13(12) December 2014

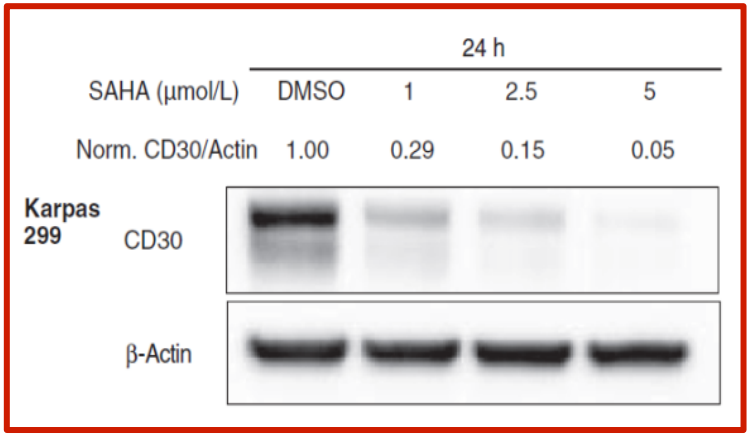
Small Molecule Therapeutics

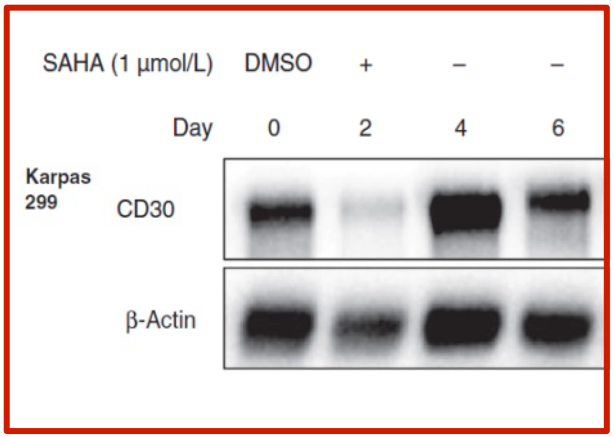
Molecular Cancer Therapeutics

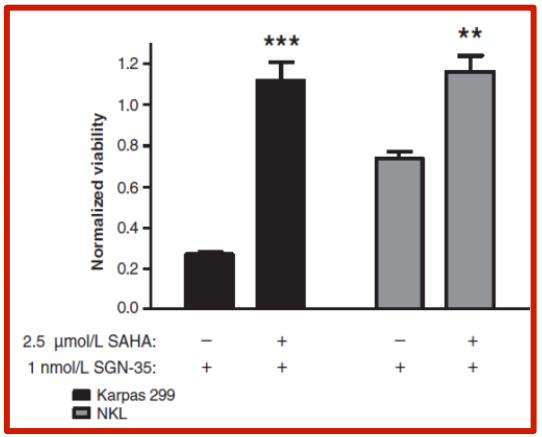
SAHA 400 mg: 0.5 – 1 µmol/L

Vorinostat Downregulates CD30 and Decreases Brentuximab Vedotin Efficacy in Human Lymphocytes

Zainul S. Hasanali[1], Elliot M. Epner[2], David J. Feith[3], Thomas P. Loughran Jr[3], and Clare E. Sample[1]







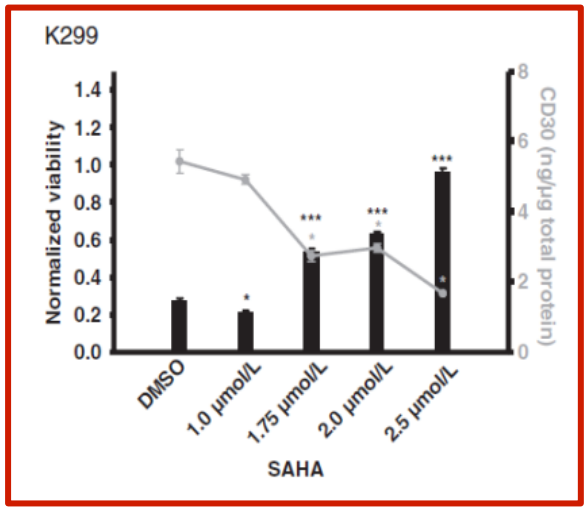
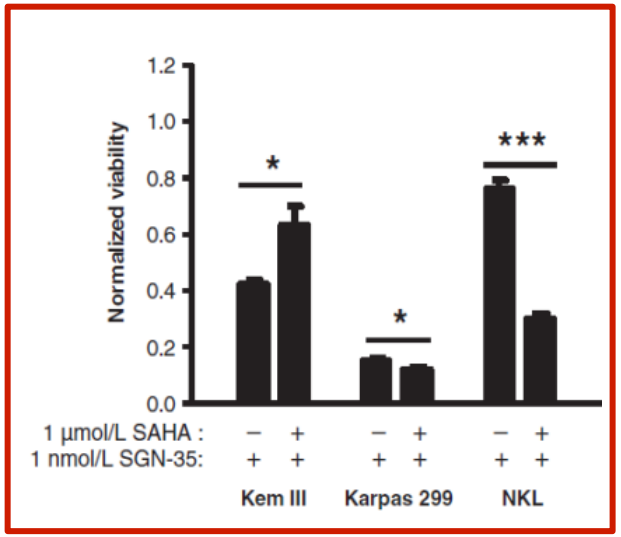


Table 1. Summary of CD30 threshold for brentuximab vedotin efficacy

	Baseline CD30	CD30 level at decreased brentuximab vedotin efficacy	Knockdown
NKL	2.41	1.32	45%
Karpas 299	5.11	2.57	50%
Kem III	1.67	1.14	32%



Protein binding

Monomethyl auristatin E has a plasma protein binding range of 68-82%. Highly-protein bound drugs are not likely to displace it.

Metabolism

Only a small fraction of monomethyl auristatin E or MMAE is metabolized primarily via oxidation by CYP3A4 and CYP3A5.

Route of elimination

Monomethyl auristatin E is eliminated by the feces (with 72% unchanged) and urine.

Half Life

The terminal half-life is 4-6 days.

Clearance

Monomethyl auristatin E is cleared by the liver but not quantitative studies have been performed.

Toxicity

The most severe toxic reaction seen in patients is progressive multifocal leukoencephalopathy. Other toxicities include bone marrow suppression, infusion reactions, peripheral neuropathy, Stevens-Johnson syndrome, and tumor lysis syndrome.

RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

Agents suitable for Salvage Strategies in RR-HL:

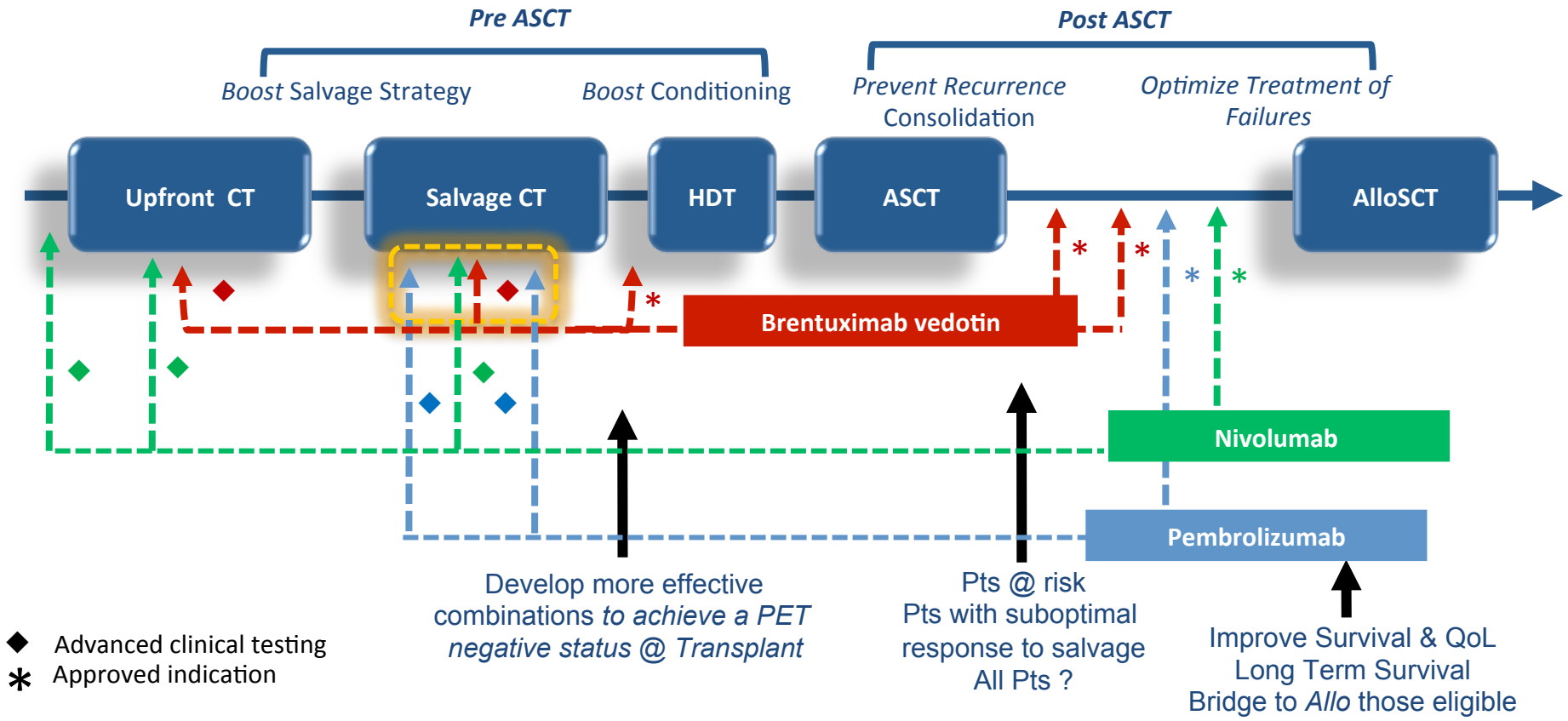
- Brentuximab vedotin
- Bendamustine & its Fusion-upgrade (EDO-S101)
- Immune Checkpoint Inhibitors (Nivolumab, Pembrolizumab)
- HDAC inhibitors & Fusion Molecules (EDO-S101)
- PI3K inhibitors
- *Newcomers*

- *…and their optimal combinations…*

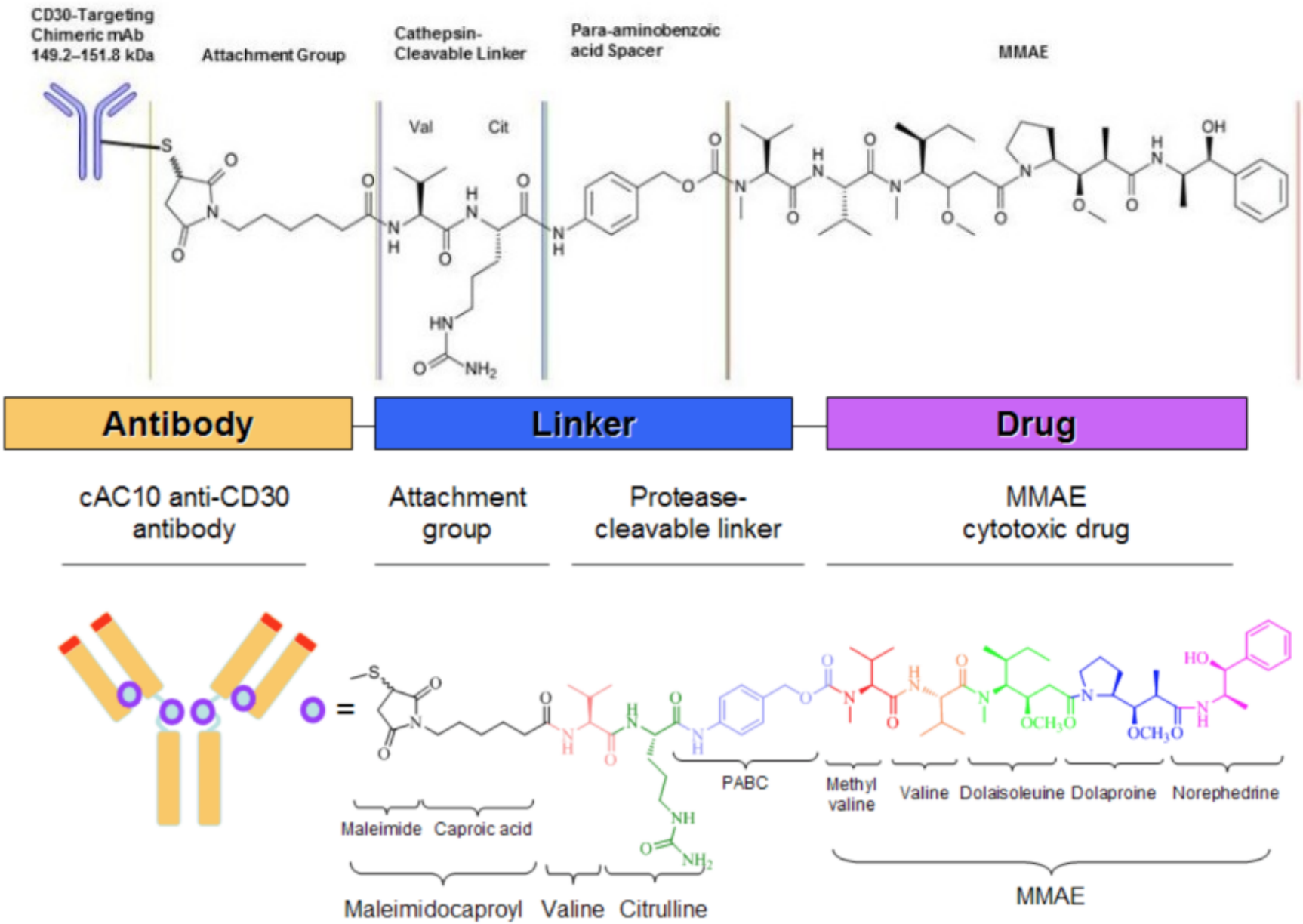
Brentuximab vedotin & RR-HL

- **Approved indications**
  - Post-ASCT recurrences
  - After 2 lines of therapy if ASCT is not a therapeutic option
- **Improving of salvage therapy before ASCT**
  - Integration with chemoterapy (BV-ICE; Bendamustine BV, BV-DHAP)
  - As a single agent before ASCT
  - As a single agent in pts. showing suboptimal response to salvage CT
- **Consolidation Rx after ASCT**
  - *Aethera trial*
- **Upfront therapy with or w/o chemotherapy**
  - A2VD (BV-AVD) [ECHELON -1]
  - BV followed by ABVD/AVD [Elderly, young early stages]

RR-HL: ….future outlooks…



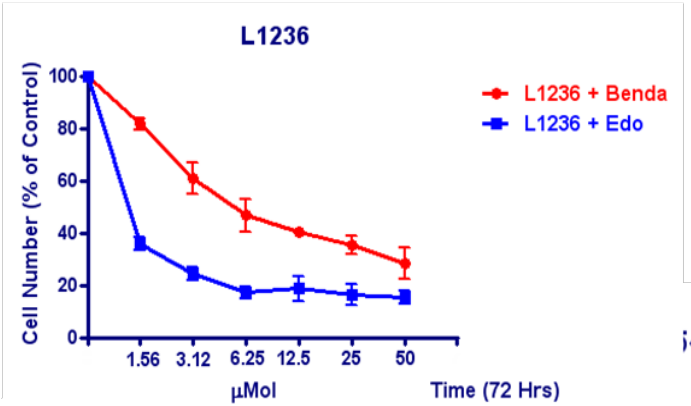
Brentuximab Vedotin: …CD30…HL…and beyond...

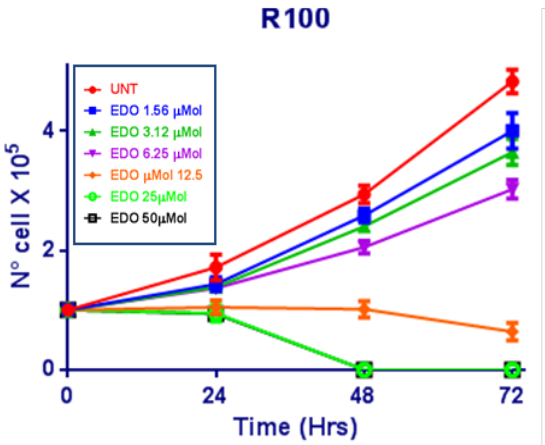


…No man is an island…

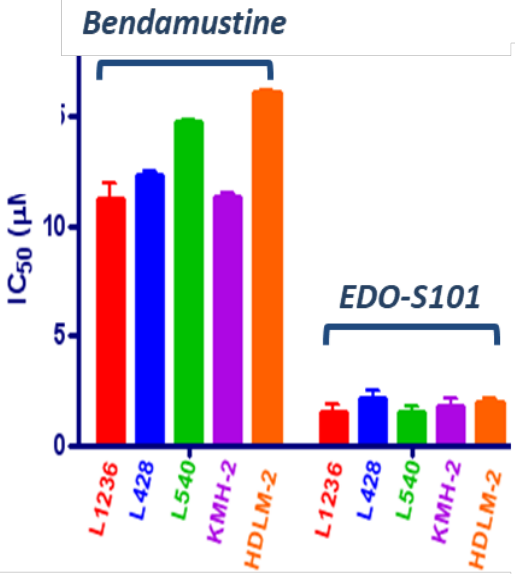
1572-1631

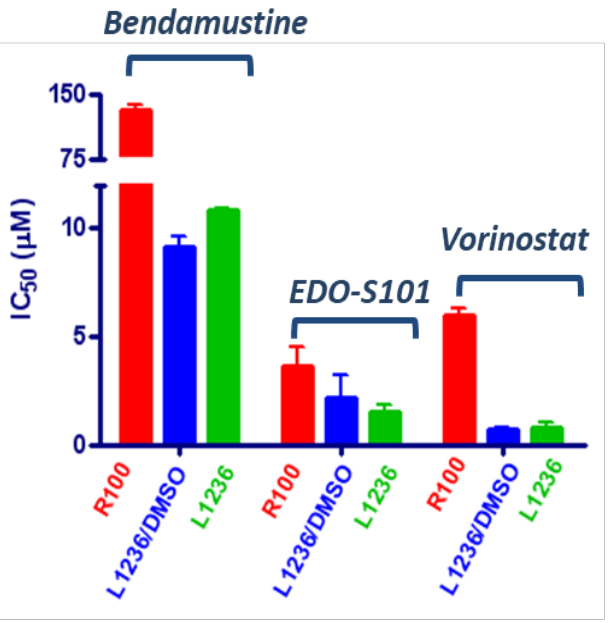
Brentuximab Vedotin: …CD30…HL…and beyond...



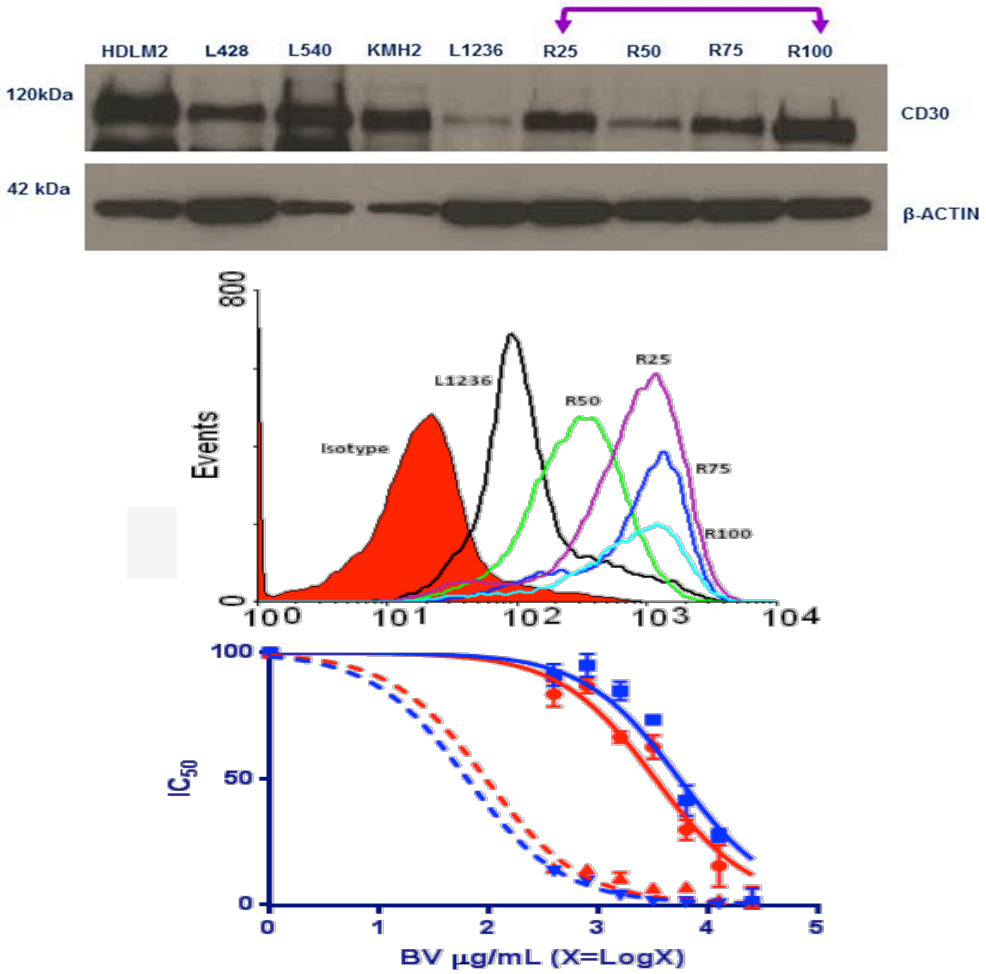


- EDO-S101 inhibits HL cells growth @ IC50s ~10-fold lower than BDM
- EDO-S101 Displays a potent anti-proliferative effects on BDM-resistant HL cells

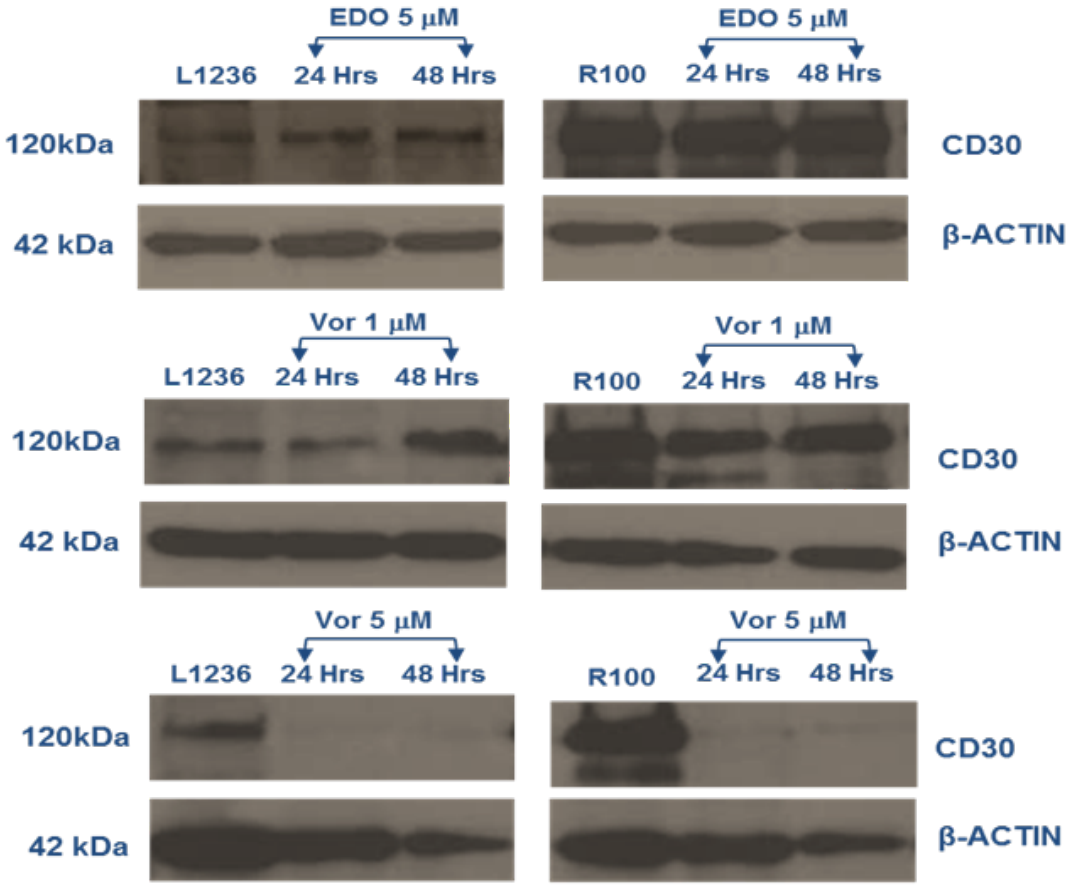




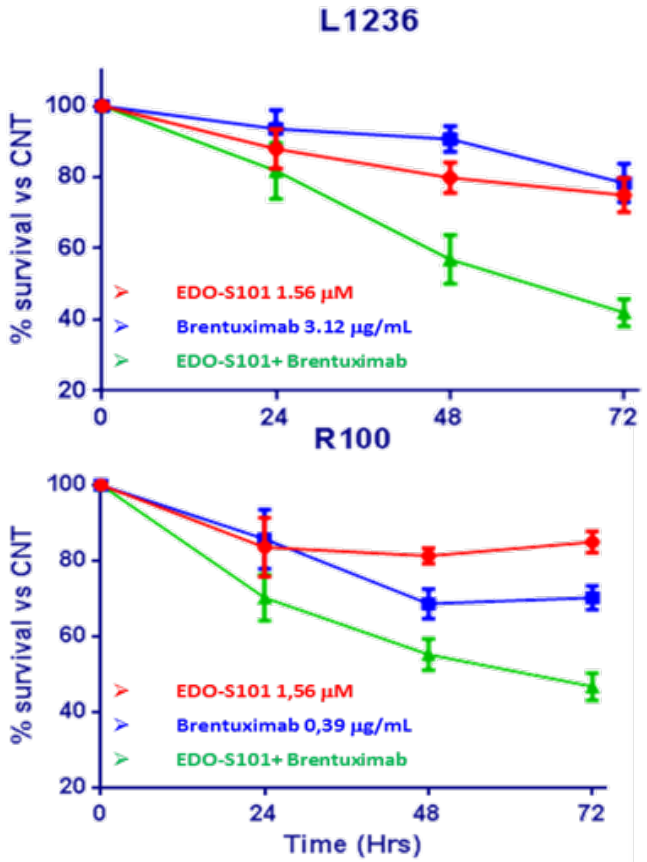
3. Synergizes with BV



Brentuximab Vedotin: …CD30…HL…and beyond...

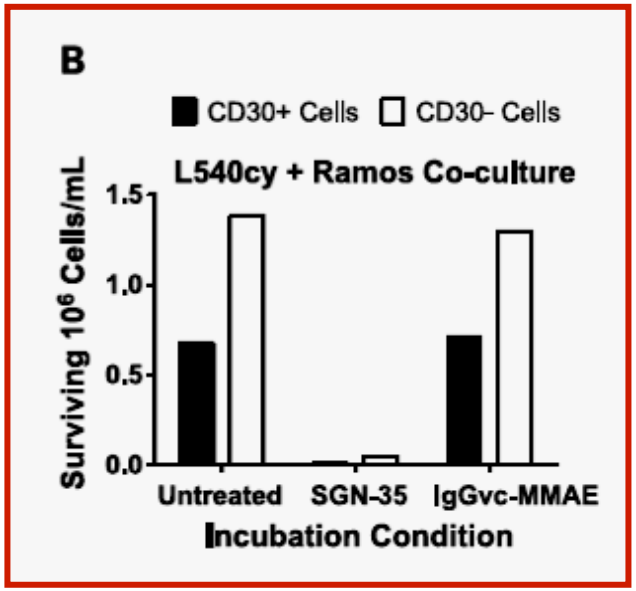


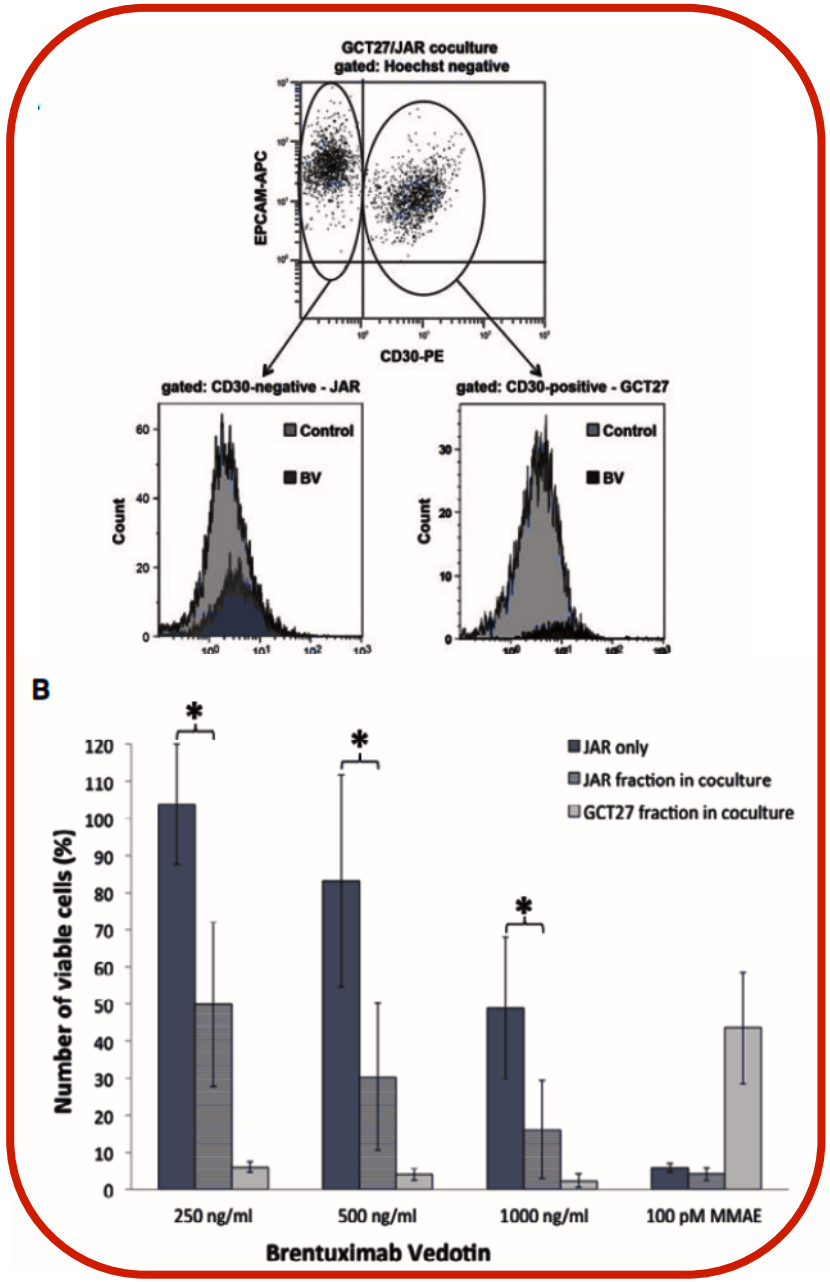
Differently from Vorinostat, EDO-S101 does not downregulate CD30



EDO-S101 is synergic with Brentuximab Vedotin at sub-IC concentrations allows low doses of Brentuximab Vedotin (10-fold lower than IC50) to exert a striking cytotoxic effect on BDM-resistant L1236 R100 cells which overexpress CD30

Brentuximab Vedotin: …killing 0f CD30-negative targets





Cancer Therapy: Preclinical

Clinical Cancer Research

Intracellular Activation of SGN-35, a Potent Anti-CD30 Antibody-Drug Conjugate

Nicole M. Okeley, Jamie B. Miyamoto, Xinqun Zhang, Russell J. Sanderson, Dennis R. Benjamin, Eric L. Sievers, Peter D. Senter, and Stephen C. Alley

Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines

Stefan Schönberger [a, *], Cornelius van Beekum [a], Barbara Götz [a], Daniel Nettersheim [b], Hubert Schorle [b], Dominik T. Schneider [c], Anna Casati [a], Rogerio B. Craveiro [a], Gabriele Calaminus [a], Dagmar Dilloo [a]

J. Cell. Mol. Med. Vol 22, No 1, 2018 pp. 568-575

Brentuximab Vedotin in the Overall Treatment Strategy for HL

Table 2. Results of BV-based combinations in patients with relapsed or refractory Hodgkin's lymphoma.

Study	Combined agents	N	CR rate (%)	ORR (%)	Stem cell collection (median)	Main toxicities
LaCasce *et al.* [76]	Bendamustine 90 mg/m^2 (D1–2)	55	74	93	Success in 93% 4.1×10^6/kg	IRR (56%), pyrexia (26%), chills (20%), dyspnea/nausea (15% each), flushing (13%), hypotension (11%).
Cassaday *et al.* [77]	Ifosfamide 5 g/m^2 (D2) Carboplatin AUC 5 (D2) Etoposide 100 mg/m^2 (D1–3)	16	88 (INV) 69 (CIR)	94	Not described	Grade 3–4 neutropenia, lymphopenia, anemia (12% each), neuropathy (31%)
Garcia-Sanz *et al.* [78]	Etoposide 40 mg/m^2 (D1–4) Solu-Medrol 250 mg (D1–4) Cytarabine 2 g/m^2 (D5) Cisplatin 25 mg/m^2 (D1–4)	66	70	96	Success in 95% 5.75×10^6/kg	Fever (20%), grade 3–4 neutropenia (27%), thrombocytopenia (18%), anemia (8%), death (3%)
Herrera *et al.* [79]	Nivolumab 3 mg/kg (D1)	25	50 (3/6)	100 (6/6)	Success in 100% (6/6) 12.9×10^6/kg	No grade 4 adverse events Fatigue (35%), nausea (26%), rash (22%), dyspnea, myalgia, pruritus (17%)
Diefenbach *et al.* [80]	Nivolumab 3 mg/kg (D1)	10	62.5 (5/8)	100 (8/8)	Not described	No grade 4 adverse events pneumonitis (N=1), rash (N=4), pruritus (N=1), transaminitis (N=9), peripheral sensory neuropathy (N=6)

Abbreviations: CIR, central independent review; CR, complete response; INV, investigator; ORR, overall response rate.

Blood Res 2017;52:243-53.