Meldola 24 settembre 2016

Nuovi obiettivi clinici nell'impiego del Brentuximab-Vedotin: I linfomi diffusi a grandi cellule

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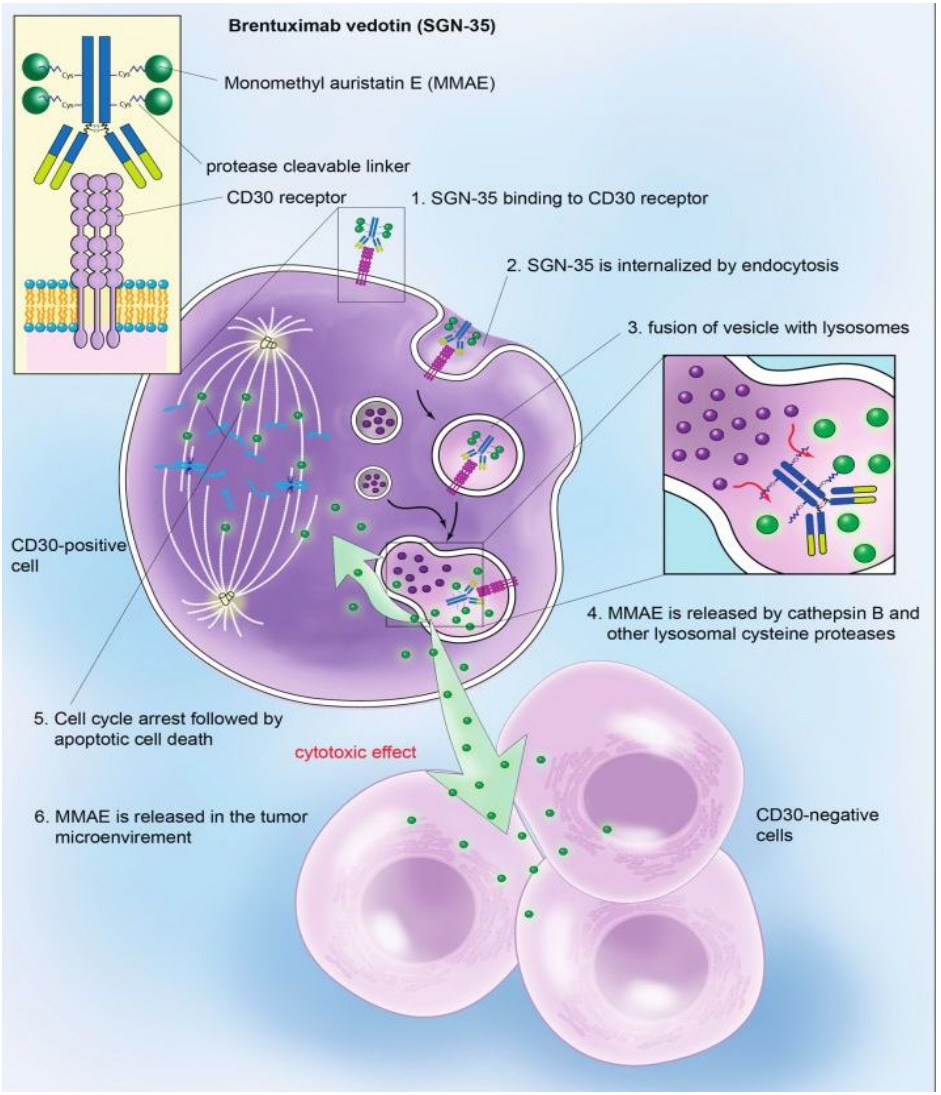
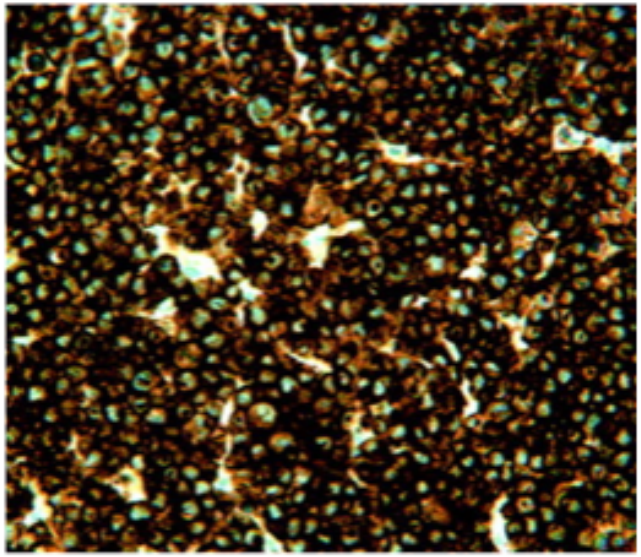
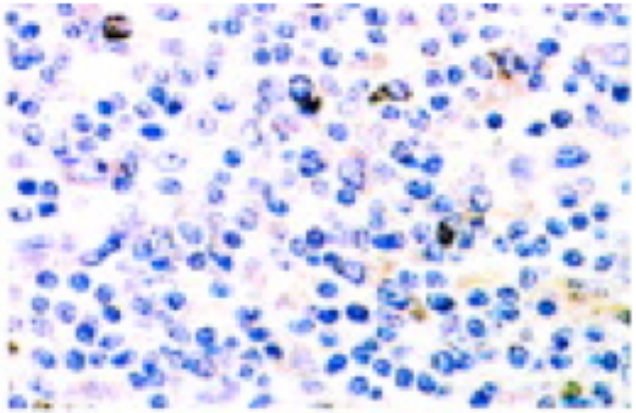
Brentuximab Vedotin in DLBCL

- ✓ What is the single agent activity with BV?
- ✓ What are the results in combination with other agents?
- ✓ What's its role in DLBCL?

Brentuximab vedotin – Mechanisms of action







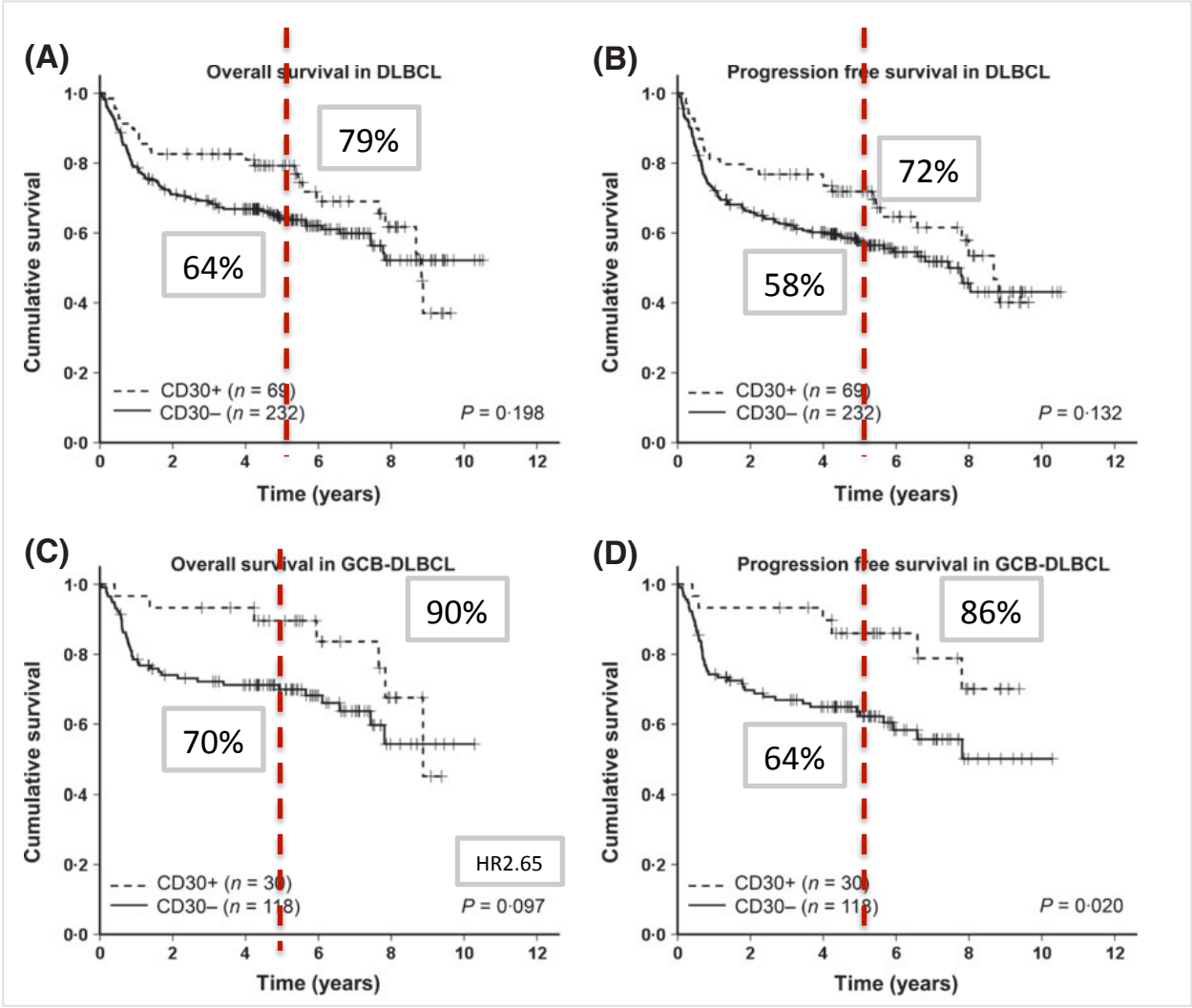
Vaklavas et al. Ther Adv Hem. 2012;3(4):209-225.
Brown et al. Immunotherapy. 2014 Apr;6(4):371-5.

Brentuximab and DLBCL: background

- ✓ High response rates in HL and ALCL in phase 2 studies
  - HL: 75% ORR (34% CR)
  - ALCL: 86% ORR (57% CR)
- ✓ Response rate independent of maximal CD30 TLI by routine IHC
- ✓ Clinical response observed in subjects with non-detectable CD30 via routine IHC

CD30 expressed in 14% to 25% of de novo DLBCL cases
Cutoff for CD30 positivity varies (e.g., >0% and ≥20%)

CD30 expression in *de novo* diffuse large B-cell lymphoma



Slack et al. Br J Haematol. 2014 Dec;167(5):608-17

Brentuximab monotherapy in relapsed/ refractory DLBCL

Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/ refractory DLBCL with variable CD30 expression.

Eric D. Jacobsen et al. Blood Volume 125(9):1394-1402 February 26, 2015

Brentuximab vedotin demonstrates antitumor activity in CD30 + DLBCL.

Smith M.R. et al ICML 2015 Abstract #091

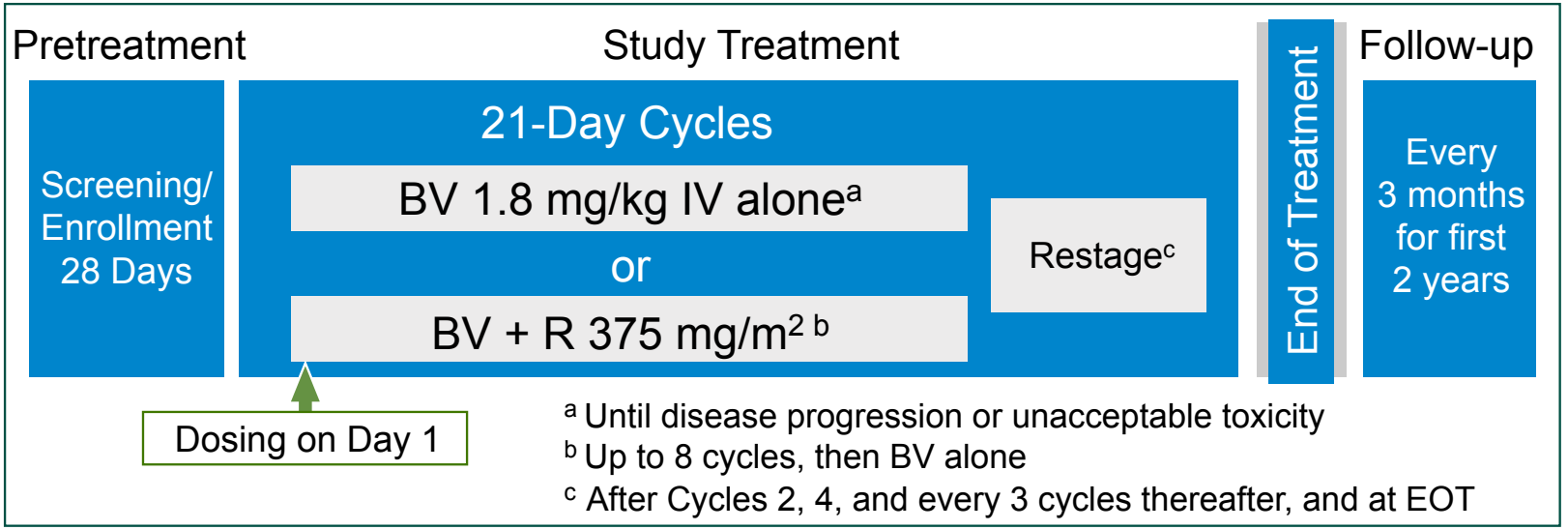
Phase 2 Study to Assess Brentuximab Vedotin Activity in DLBCL With Variable CD30 Expression

Primary Endpoints

- BV monotherapy – ORR (CR + PR)
- BV + Rituximab (R) – safety and tolerability

Eligibility Criteria

- Relapsed/refractory DLBCL, CD30+ or undetectable CD30 (CD30u) by local lab visual assessment of routine IHC using BerH2 antibody
- Age ≥12 years
- ECOG ≤2



ClinicalTrials.gov #NCT01421667

Eric D. Jacobsen et al. Blood 2015;125:1394-1402

Baseline Characteristics

Patient Characteristics	CD30+		CD30u
	Brentuximab vedotin + rituximab (n=16)	Brentuximab vedotin (n=49)	Brentuximab vedotin (n=53)
Median age, yrs (range)	62 (22-78)	62 (17-85)	65 (21-91)
Median prior therapies, n (range)	2 (1-3)	2 (1-6)	2 (1-4)
Prior ASCT, %	25	20	21
Refractory to most recent therapy, %	56	84	70
Refractory to frontline therapy, %	63	69	66
Median baseline sCD30,[†] ng/mL (range)	ND	206 (36–9429)	140 (53-1696)
Median CD30 expression,[‡] % (range)	ND	36 (0.1-95)	2 (0-54)

a Enrollment in study arms based on CD30 positivity per local laboratory visual assessment of routine IHC
b Combination studied for assessment of safety and tolerability

Smith MR, et al. ICML 2015, Presentation from Abstract #91

Antitumor Activity: Interim Response and PFS

Outcome	CD30+		CD30u
	Brentuximab vedotin + rituximab (n=13)	Brentuximab vedotin (n=48)	Brentuximab vedotin (n=51)
ORR, %	46	44	31
CR, %	15	19	12
PR, %	31	25	20
DOR, mos (range)	2.1 (1.4–10.7+)	4.7 (0+–22.7+)	4.7 (0+–11.6)
CR duration	NR (7.1–10.7+)	16.6 (2.7–22.7+)	11.6 (2.9+–11.6)
Median PFS, mos (range)	2.8 (1.2–12+)	4 (0.6+–24+)	1.4 (0.4–15.6)

Smith MR, et al. ICML 2015, Presentation from Abstract #91

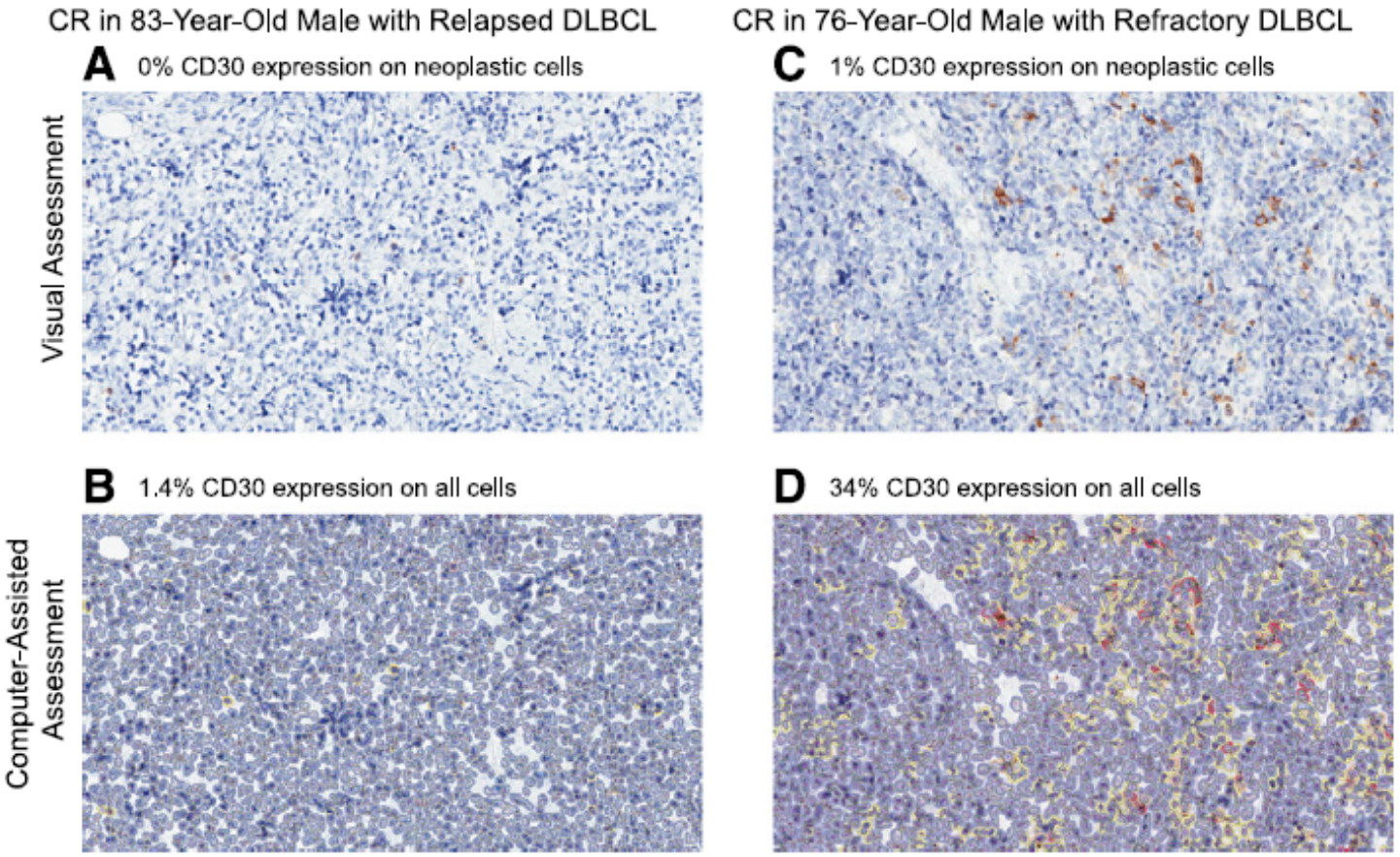
Antitumor Activity: Interim Response and PFS

Outcomes by CD30 expression*	CD30 <1% (n=24)	CD30 ≥1% (n=69)	CD30 ≥20% (n=30)
ORR, %	21	45	53
CR, %	8	19	23
Median PFS, mos (range)	1.25 (0.4–0.6)	4 (0.4–24+)	5.1 (0.5–24+)

- *CD30 expression per computer-assisted IHC

Smith MR, et al. ICML 2015, Presentation from Abstract #91

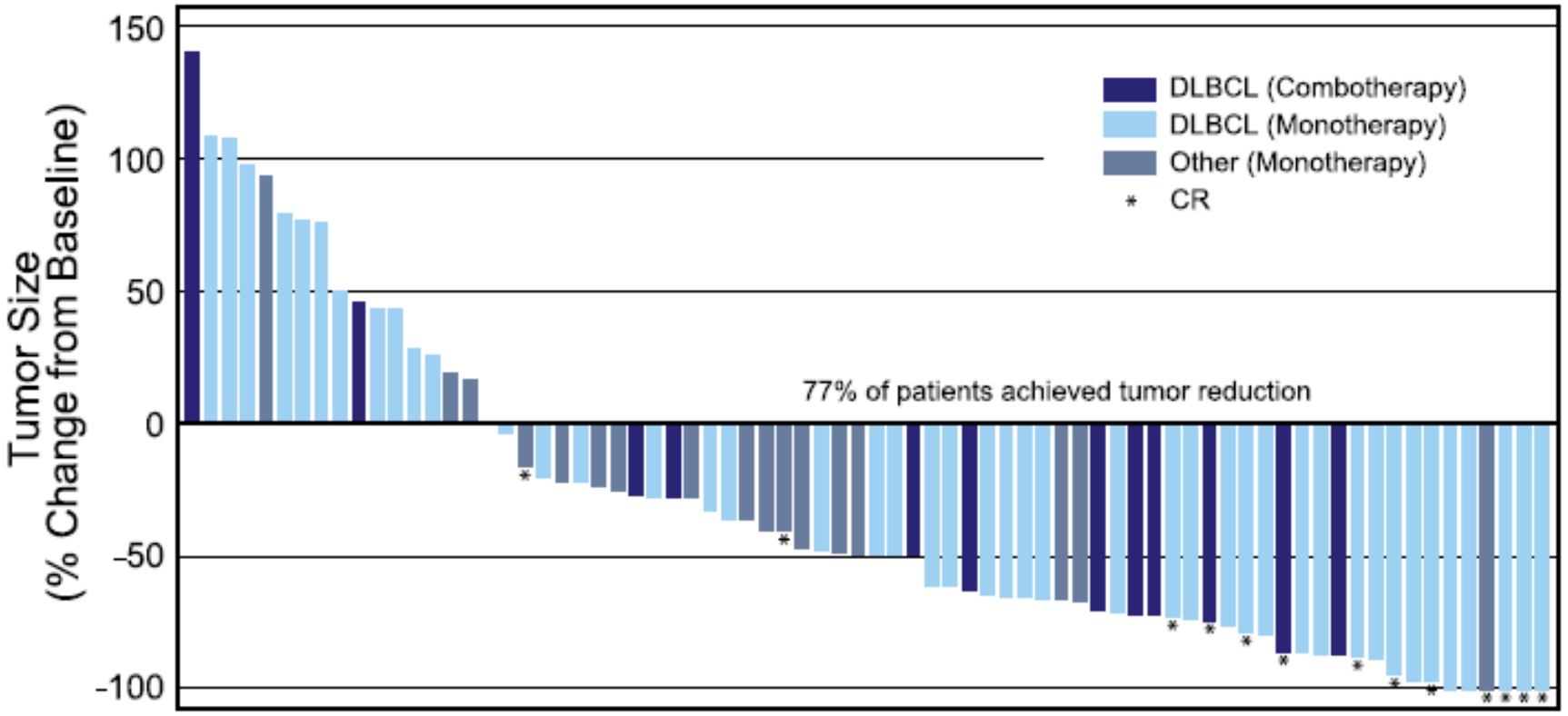
CD30 expression assessed by IHC and computer assisted methods



Computer-assisted IHC detected CD30 expression in ~50% of tumors classified as negative by visual assessment

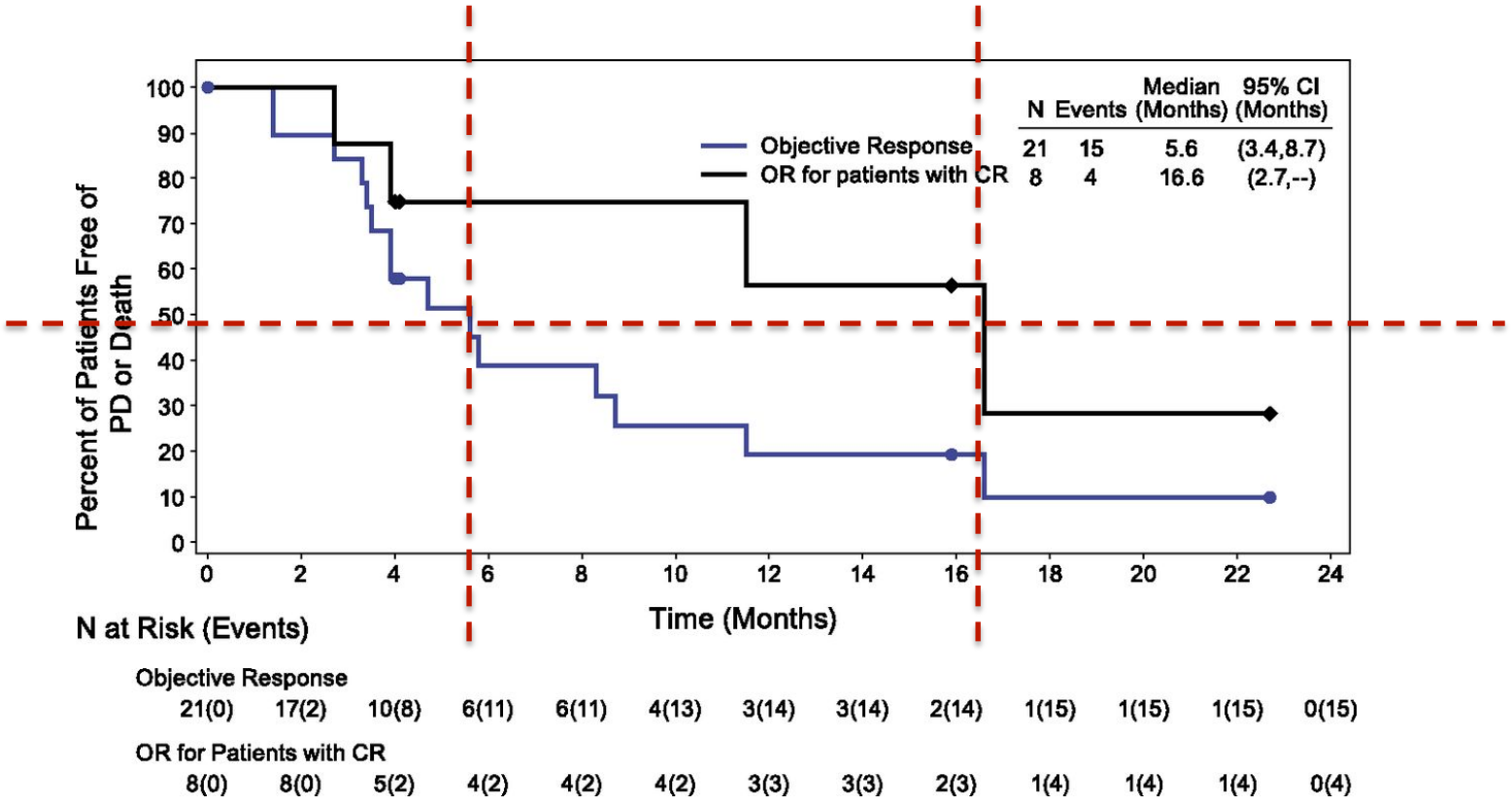
Eric D. Jacobsen et al. Blood 2015;125:1394-1402

Maximum tumor size reduction



Eric D. Jacobsen et al. Blood 2015;125:1394-1402

Duration of objective response (OR) and CR in DLBCL patients.



Eric D. Jacobsen et al. Blood 2015;125:1394-1402

Safety

- ✓ Neutropenia was the most frequent related ≥ G3 AE regardless of treatment ***(BV alone 28%; BV+R 13%)*** or CD30 expression

- ✓ Peripheral neuropathy
  - ***BV alone: 26% PSN*** (3% Grade 3); 7% PMN (3% Grade 3)
  - ***BV+R: 38% PSN;*** 0% PMN; No Grade 3
  - No Grade 4 PSN or PMN on study

- ✓ PSN (3%) and PMN (2%) were the only AEs leading to treatment discontinuation in more than 1 patient on BV alone (BV+R 0%)

- ✓ Ten deaths occurred ≤30 days post-treatment
  - Two due to AEs: treatment-related toxic epidermal necrolysis (BV+R) and unrelated cardiac arrest (CD30u)
  - Eight disease related

Smith MR, et al. ICML 2015, Presentation from Abstract #91

Conclusion (1)

- ✓ Single agent Brentuximab(BV) showed antitumor activityin CD30+ R/R DLBCL (***ORR 44%,CRs 17%).***
- ✓ The response rate was not different in relapsed or refractory DLBCL
- ✓ All responding patients have quantifiable level of CD30 expression by computer assisted methods even if negative to visual IHC

Conclusion (2)

- ✓ BV clinical activity is lower for DLBCL-CD30u:
  - ORR 31% vs 44%, median PFS 1,4 vs 4.0 months

- ✓ Safety profile of BV consistent with labeled indications and no added toxicity in combination with Rituximab

- ✓ Future studies on biomarker status should better support the BV action in DLBCL .

- Brentuximab in combination with Lenalidomide in relapsed/refractory DLBCL

A Phase I Trial of Brentuximab Vedotin in Combination with Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Jeffrey P. Ward, et al.

Abstract # 3988# Poster ASH Meeting Orlando 2015

Phase I study: brentuximab vedotin plus lenalidomide in R/R DLBCL

Endpoints: *Primary*: Safety, MTD; Secondary: ORR, PFS, DOR, efficacy in non-GCB vs GCB subsets, association between CD30 expression and efficacy; *Other:* correlative studies

Patients: 22 pts with R/R DLBCL, previously received or ineligible for ASCT; median age 61 yrs (51-79), 23%/45%/32% IPI score 0–1/2/3–5, 32%/68% CD30+/CD30-, 55%/45% GCB/non-GCB, 32%/9% prior ASCT/allo-SCT, 5%/32%/64% with 1/2/>2 prior therapies

Dose and schedule: Brentuximab vedotin 1.2 or 1.8 mg/kg + lenalidomide 20 or 25 mg/day continuously in 21 day cycles

DLT: table 1

MTD: Brentuximab vedotin 1.2 mg/kg Q3wk; lenalidomide 20 mg/day continuously

# of pts	Brentuximab vedotin dose, mg/kg	Lenalidomide dose, mg	Number of DLT	DLT
9	1.2	20	1	Neutropenia
6	1.2	25	2	Neutropenia, DVT
3	1.8	25	2	Fatigue, neutropenia

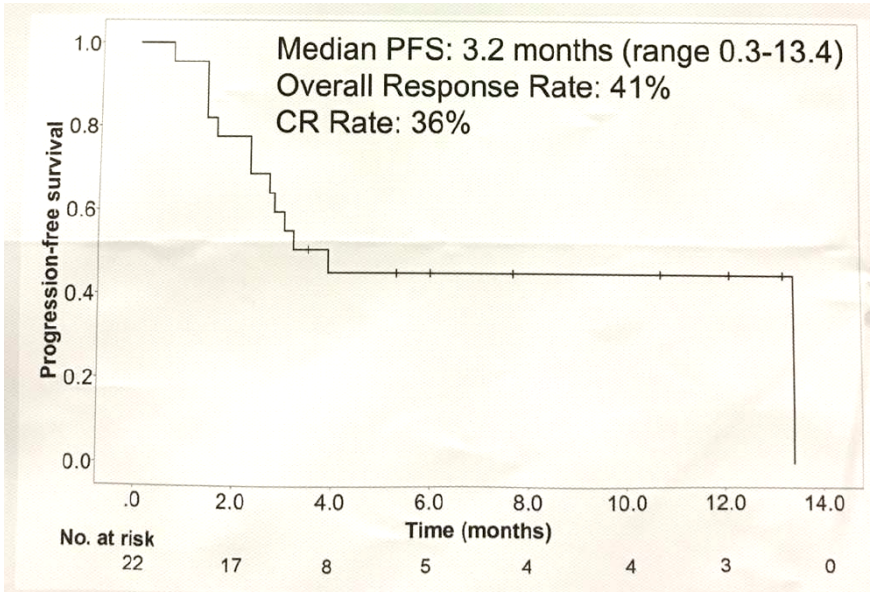
Ward JP, et al. ASH 2015, Poster presentation from Abstract #3988

Phase I study: brentuximab vedotin plus lenalidomide in R/R DLBCL
Preliminary results

Efficacy: Responses: 8 CR, 2 PR

- **ORR: 86%** (4 CR, 2 PR) in 7 CD30+ pts,
  27% (4 CR) in 15 CD30- pts
- **ORR: 25%** (3 CR) in 12 GCB pts,
  70% (5 CR, 2 PR) in 10 non-GCB pts
- DOR was 1.4–11+ mos and median PFS was 3.2 mos (0.3–13.4)

PFS:



SAFETY:

Gr ≥3 drug-related AE	%
Neutropenia	68
Anemia	32
Thrombocytopenia	27
Maculo-popular rash	14
Febrile neutropenia	9
Fatigue	9
Hypoalbuminemia	9
Hypokalemia	9
Diarrhea	5
Nausea	5
Hypocalcemia	5

Ward JP, et al. ASH 2015, Poster presentation from Abstract #3988

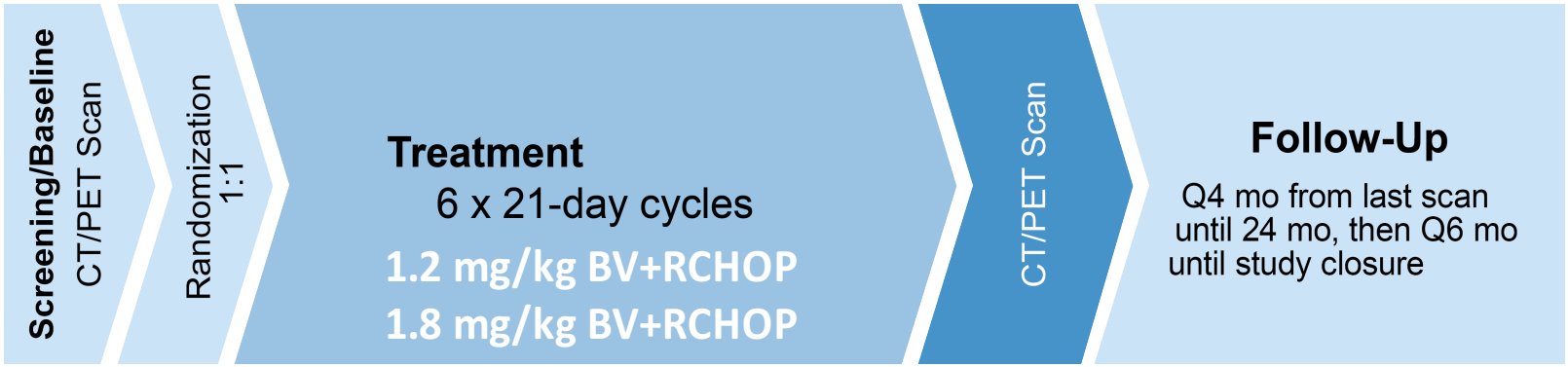
- Brentuximab combined with R CHOP as a first line therapy

Brentuximab Vedotin with R-CHOP As Frontline Therapy in Patients with High-Intermediate/High-RiskDiffuse Large B Cell Lymphoma (DLBCL): Results from an Ongoing Phase 2 Study

Christopher A. Yasenchak, et al.

Astract # Oral comunication ASH Meeting Orlando 2015

Brentuximab vedotin plus R-CHOP in DLBCL



Key eligibility criteria included:

- **CD30-unselected high-intermediate or high-risk untreated DLBCL**
- **High-intermediate or high risk**
  - **Standard IPI score 3–5 (>60 years) or**
  - **Age-adjusted IPI [aaIPI] score 2–3 (≤60 years)**
- **ECOG performance status ≤2**

Ansell S. M. et al. Hematol Oncol.2015 149: abs 92

Baseline Characteristics

	DLBCL (N: 51)
Median age	66 (21-81)
High/Int risk (IPI:3 aaIPI: 2)	63%
High risk (IPI:4-5 aaIPI: 3)	37%

Due to an increased rate of G3 neuropathy seen early in the 1.8 mg/kg BV+R-CHOP arm (**30% vs 8**%), after **10** patients in each arm had completed the ET visit, SMC recommended treatment continues at 1.2 mg/kg BV+R-CHOP

Yasenchak et al ASH 2015 #814

Antitumor Activity: Dose Cohort

	1.2 mg/kg BV+RCHOP N=29	1.8 mg/kg BV+RCHOP N=22	Total N=51
ORR, % (n) [95% CI]	79% (23) [60.3, 92.0]	82% (18) [59.7, 94.8]	80% (41) [66.9, 90.2]
CR, % (n) [95% CI]	66% (19) [45.7, 82.1]	68% (15) [45.1, 86.1]	69% (34) [52.1, 79.2]
PR, % (n)	14% (4)	14% (3)	14% (7)
PD, % (n)	7% (2)	14% (3)	10% (5)

The CR rate was comparable between the ABC subtype and the GCB subtype (69% versus 65%)

Yasenchak et al ASH 2015 #814

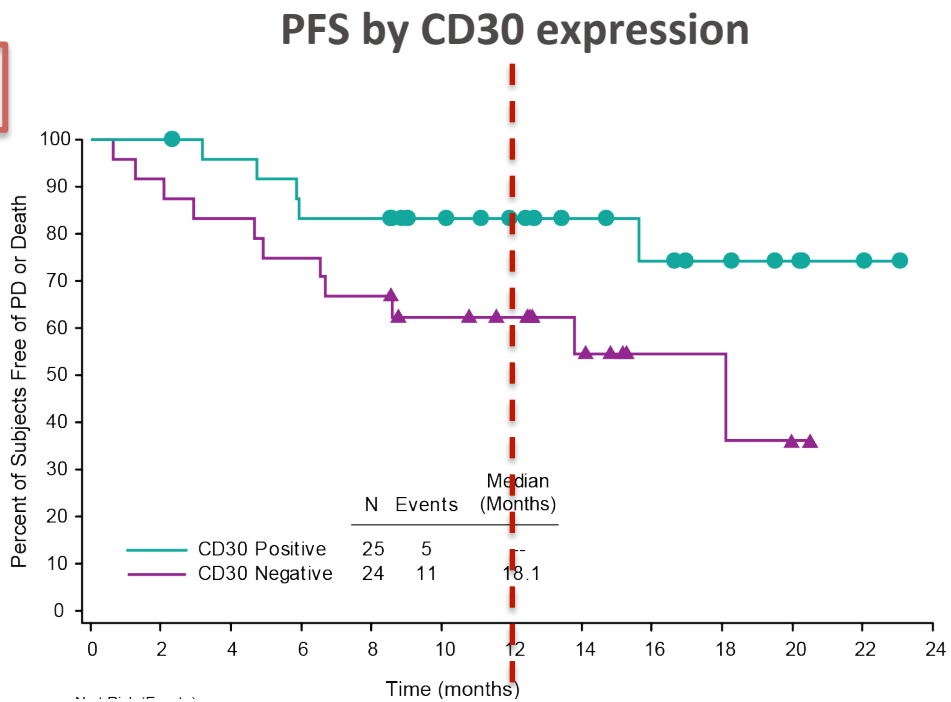
Antitumor Activity: CD30 Status

	CD30-positive N=25	CD30-negative N=23
ORR, % (n) [95% CI]	84% (21) [44.4, 98.3]	83% (19) [61.2, 95.0]
CR, % (n) [95% CI]	76% (19) [54.9, 90.6]	63% (14) [38.5, 80.3]
PR, % (n)	8% (2)	21% (5)
PD, % (n)	8% (2)	4% (1)

Yasenchak et al ASH 2015 #814

Progression-Free Survival: CD30 Status

	CD30-positive N=25	CD30-negative N=23
Patients with PD or death, n (%)	4 (16)	9 (39)
Estimated progression-free rate at:		
6 months (95% CI) 26 patients at risk	86% (62, 95)	81% (56, 92)
12 months (95% CI) 12 patients at risk	82% (62, 95)	56% (30, 78)
Median follow-up time (months)	8.7	6.8



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Phase II trial of brentuximab vedotin plus R-CHOP in previously untreated DLBCL: updated interim results (NCT01925612)

Efficacy: Median follow up from first dose was 12.5 months

Cell of origin by CD expression per IHC and response at EOT[a,b]	CD30-negative (n=24)		CD30-positive (n=25)	
	GCB (n=14)	ABC (n=5)	GCB (n=9)	ABC (n=11)
ORR (CR + PR), n (%)	11 (79)	4 (80)	**8 (89)**	8 (73)
CR	9 (64)	3 (60)	6 (67)	8 (73)
PR	2 (4)	1 (20)	2 (22)	0
95% CI for ORR rate	49. 93	28, 99	52, 100	39, 94
95% CI for CR rate	35, 87	15, 95	30, 92	39, 94

- a,b2 pts did not have CD30 status and 8 pts did not have cell of origin subtype assessed at baseline

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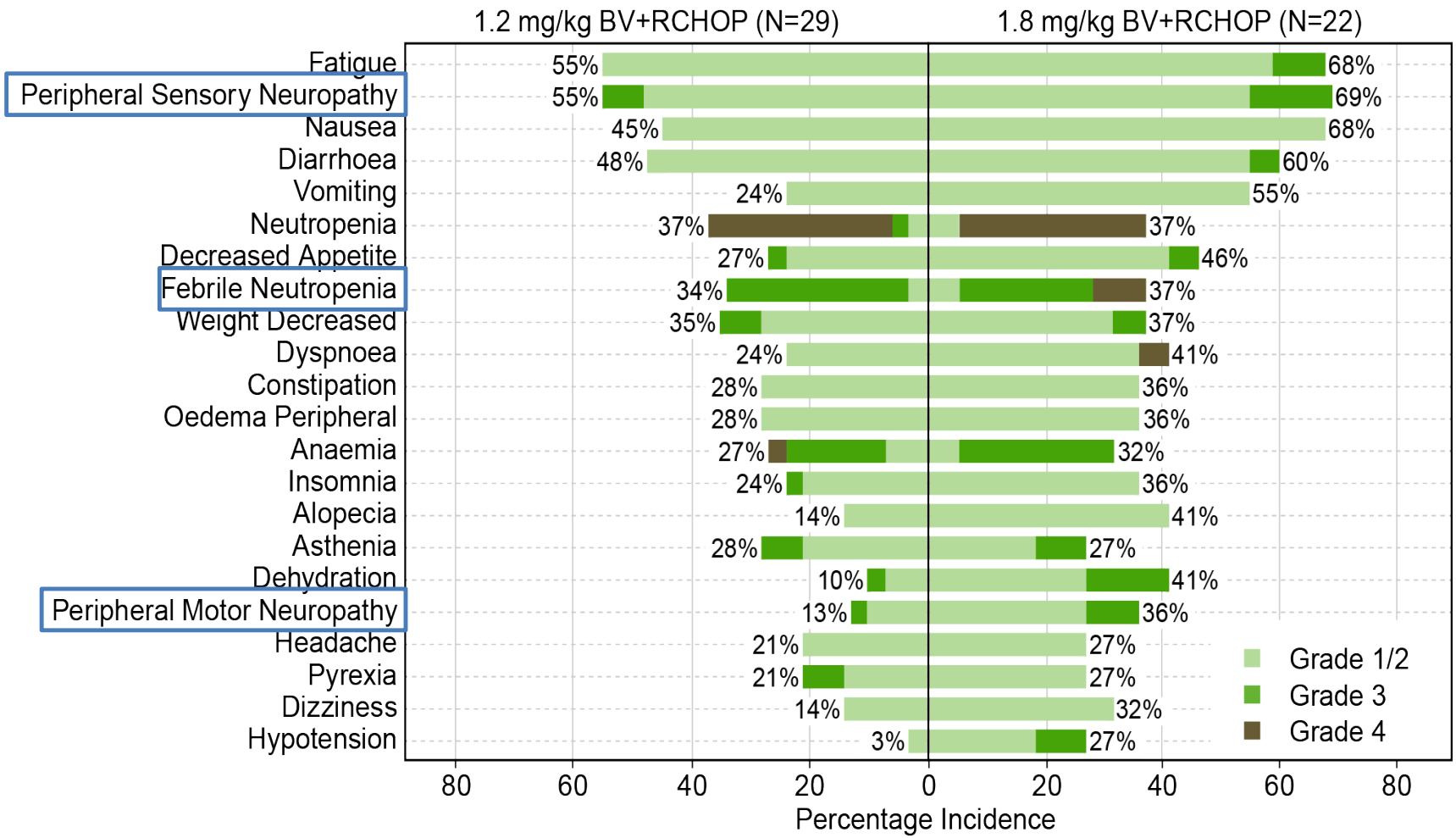
Treatment-Emergent Adverse Events Grades1–4



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Conclusions

- ✓ BV+ R-CHOP has encouraging activity in frontline high risk DLBCL
- ✓ CR rate is higher in CD30+ patients
- ✓ BV in combination with R-CHOP is better tolerated at dose 1.2 mg/kg
- ✓ Evaluation of tumor microenviroment showed that highter frequencies of infiltrating CD3+ cell observed in the CR group, suggesting possible immunologic correlates of response.
- ✓ The protocol was amended to assess the activity of BV+ R-CHOP only in **DLBCL CD30+**

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Brentuximab in DLBCL: conclusions and exploratory work

- BV single agent activity observed in DLBCL
- The results of BV are comparable to other agents studied in relapsed/refractory DLBCL (lenalidomide, ibrutinib, R-benda)
- Antitumor activity is associated with CD30 expression
- Exploratory work ongoing:
  - quantification of CD30 by methods other than standard IHC - additional combination studies should be considered for the treatment of R/R DLBCL

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