

# Recent Advances in Understanding the Clinical Responses of Brentuximab Vedotin in Lymphoma and the Correlation with CD30 Expression

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**Abstract:** Brentuximab vedotin (BV) is an antibody-drug conjugate that combines the CD30 monoclonal antibody with the microtubule-disrupting agent, monomethyl auristatin E, which induces apoptosis in the tumor cell upon its release from the conjugate. The safety and efficacy of BV have been assessed in several studies in patients with T- and B-cell lymphomas. This article reviews the currently available data on the distribution of CD30 expression in T- and B-cell lymphomas, as well as the various levels of CD30 positivity cutoff used in the literature. It also analyzes the relationship between CD30 expression levels and the clinical response to BV in clinical trials for both T- and B-cell lymphomas and investigates BV efficacy in patients with low or undetectable levels of CD30 and examines potential mechanisms by which BV exerts its effect on these patients. This review contributes to the growing evidence suggesting that CD30 expression levels do not predict the clinical benefit of BV as the drug demonstrated substantial efficacy in patients across a wide range of CD30 expression levels while suggesting that the antitumor activity was not associated with CD30 expression levels. Furthermore, the potential of BV as a targeted approach along with its mechanism of action is also summarized to explain its key role in the future treatments of lymphomas, especially for CD30-expressing lymphomas.

**Keywords:** Brentuximab vedotin, CD30 expression, non-Hodgkin lymphomas, T-cell lymphoma, B-cell lymphoma

## Introduction

CD30, a transmembrane glycoprotein receptor and the member of tumor necrosis factor receptor superfamily, is rarely expressed on normal cells and is rapidly internalized, making it an ideal therapeutic target for monoclonal antibody therapy in patients with lymphoma with positive CD30 expression. However, naked anti-CD30 antibodies and combinations with bacterial toxins and radioimmunoconjugates were found to have limited efficacy. Nevertheless, continuous innovations on developing antibody-drug conjugates (ADCs) have reignited interest in CD30 as a tumor target in non-Hodgkin's lymphoma (NHLs).<sup>1,2</sup> Brentuximab vedotin (BV) is a potent ADC that targets the CD30 antigen. BV consists of a chimeric immunoglobulin G (IgG1) monoclonal antibody, which specifically targets CD30 antigen and is conjugated to the anti-microtubule agent, monomethyl auristatin E (MMAE) payload moiety.<sup>3</sup> After binding to CD30 protein, BV is rapidly internalized and transported to lysosomes where MMAE is released and binds to tubulin, leading to cell cycle arrest and apoptosis.<sup>4</sup> In a phase I clinical trial including 45 patients with relapsed or refractory (R/R) CD30-positive lymphomas, treatment with BV as a single agent resulted in an objective response rate (ORR) of 67%.<sup>5</sup> In a phase II clinical trial for R/R systemic anaplastic large-cell lymphoma (sALCL), treatment with single-agent BV resulted in an ORR of 86% and a complete response (CR) rate of 57%.<sup>6</sup> Based on these results, BV was approved by the United States Food and Drug Administration in 2011 for the treatment of R/R Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL).<sup>7</sup>

CD30 is expressed universally in classical Hodgkin's lymphoma and sALCL, as well as primary cutaneous anaplastic large-cell lymphoma (pcALCL) and lymphomatoid papulosis.<sup>8,9</sup> Variable levels of CD30 expression have been found in other T- and B-cell malignancies, such as diffuse large B-cell lymphoma (DLBCL), primary mediastinal (thymic) large

B-cell lymphoma (PMBCL), follicular lymphoma (FL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma, extranodal natural killer/T-cell lymphoma, mycosis fungoides (MF), Sézary syndrome (SS), and primary cutaneous gamma delta T-cell lymphoma.<sup>10</sup>

Based on the available clinical data on treatment with BV in NHL, in this article we summarize the association between the CD30 expression level and the clinical response to BV in NHL reported until now.

## CD30 Expression in T- and B-Cell Lymphomas

Various cutoff values of CD30 expression levels, ranging from >0%–≥80% of tumor cells, have been reported in different studies reporting of T-cell lymphomas that reflect the lack of consensus on using a standard cutoff (Table 1). A previous study conducted in 319 patients with T-/NK-cell lymphomas showed that CD30 expression ranges from 0–64% in various types of T-cell lymphomas, including AITL and PTCL-NOS.<sup>11</sup> The positivity of CD30 expression in ALCL is generally defined as expression of tumor cell ≥75%<sup>1</sup> (Table 1).

Studies have shown that CD30 expression in DLBCL may vary from 9.5%–40%, which could be attributed to various factors such as nonstandardized immunohistochemistry (IHC) staining methods, different methods of CD30 estimation, evaluation of results, differences in demographic factors, and variations in handling strategies of the samples.<sup>12,13</sup> Table 1 displays the various cutoff values used in DLBCL, along with the corresponding percentages of patients who tested positive for CD30 expression. Furthermore, it has been demonstrated that evaluating the CD30 expression using a >0% cutoff in DLBCL cases is significantly influenced by factors within the tumor microenvironment.<sup>13</sup>

## Response to BV Treatment with CD30 Expression ≥10% in T- and B-Cell Lymphomas

In a study involving patients with MF, BV improved ORR of 57% in patients with CD30 ≥10% compared with methotrexate or bexarotene (10.3%).<sup>14</sup> In another study by Kim et al,<sup>15</sup> which explored the efficacy of BV in patients with MF and SS, patients with 10–50% and >50% of CD30 expression levels reported an ORR of 79% and 100%, respectively. In the phase III ALCANZA study, patients with R/R CTCL having CD30 expression >10% and treated with BV showed a high response rate of 56%.<sup>16</sup> Similarly, in the phase III ECHELON-2 study, patients with PTCL having CD30 expression levels ≥10% showed a prolonged progression-free survival (PFS) of 48.2 months with BV treatment combined with chemotherapy<sup>17</sup> (Table 2).

Similar results were also observed in B-cell lymphomas (Table 3). In PMBCL, a B-cell lymphoma subtype that typically expresses high levels of CD30, the response rate to BV treatment was 13%–17%.<sup>18,19</sup> In another clinical study SGN35-012, patients with B-cell NHL with CD30 expression ≥10% and treated with BV monotherapy reported an ORR of 36% (17/47; 95% confidence interval [CI], 22.7–51.5%).<sup>20</sup>

## Response to BV Treatment with Undetectable or Low CD30 Expression in T- and B-Cell Lymphomas

Several studies have shown that BV has single-agent activity in ALCL as well as NHLs with very low CD30 expression or undetectable CD30.<sup>15,18,21</sup> A phase II study by Jacobsen assessing the efficacy and safety of BV in patients with B-cell lymphomas with variable CD30 expression (≥1%) reported an ORR of 44% (including CR rate of 17%) in patients with DLBCL and an ORR of 26% in other B-cell lymphomas<sup>18</sup> (Table 3). In another study, SGN35-012, B-cell NHL treated with BV monotherapy demonstrated an ORR of 36% in patients the CD30 <10% (24/66; 95% confidence interval [CI], 24.9%–49.1%,  $p = 0.983$ ). Additionally, an ORR of 34% (17/50; 95% CI, 21.2–48.8%) was also reported in patients with B-cell NHL with an undetectable CD30 expression.<sup>20</sup> Furthermore, a phase II study by Bartlett et al has shown a response rate of 27% in patients with DLBCL with undetectable CD30 expression levels.<sup>22</sup>

In SGN35-012 study of PTCL, the ORR was reported to be 33% (4/12; 95% CI, 9.9–65.1%) in patients with CD30 <10%. In the same study, the ORR was 33% (2/6; 95% CI, 4.3–77.7%) in patients with PTCL with an undetectable CD30 expression.<sup>20</sup> The ALCANZA study reported an ORR of 43% (6/14; 95% CI, 17.7–71.1%) in patients with MF and pcALCL and CD30<sub>average</sub> (CD30<sub>avg</sub>) <10%. In addition, ORR lasting for four months was reported to be 56.3% (36/64

**Table I** CD30 Expression Rates in T-Cell Lymphomas Reported in Different Studies

T-Cells											
Study	Number of Patients	Treatment	CD30+ % Cell Cutoff Used	Percentage (%) of Patients With CD30 Positive Expression							
				PTCL-NOS	AITL	ATLL	ENKTL	ALK <sup>-</sup> ALCL	ALK <sup>+</sup> ALCL	EATL	CTCL
Kawamoto et al 2018 <sup>39</sup>	97	BV monotherapy	≥1%	–	–	–	57	–	–	–	–
			≥10%	–	–	–	55	–	–	–	–
			≥20%	–	–	–	44	–	–	–	–
Lamarque et al 2016 <sup>40</sup>	46*	BV monotherapy	<5%	10	0	100	–	0	0	0	6
			5%–24%	10	100	0	–	0	0	0	4
			25%–49%	30	0	0	–	0	20	0	6
			50%–75%	30	0	0	–	0	20	1	6
			>75%	20	0	0	–	100	60	0	24
Weisenburger et al 2011 <sup>41</sup>	217	A	>20%	32	–	–	–	–	–	–	–
Li et al 2014 <sup>42</sup>	96	EPOCH or GELOX	>10%	–	–	–	31	–	–	–	–
Karube et al 2008 <sup>11</sup>	319	–	>70%	5	0	15	0	58	–	9	–
			20%–70%	11	32	24	64	35	–	–	9
Savage et al 2008 <sup>43</sup>	490	–	>80%	4.5	–	–	–	100	100-	–	–
		–	<80%	32	–	–	–	–	–	–	–
Asano et al 2011 <sup>44</sup>	47	–	–	51	–	–	–	–	–	–	–
Sabattini et al 2013 <sup>9</sup>	192	–	0: no staining	36	51	–	20	–	–	0	41 (MF); 0 (t-MF)
			1+: >0%–<25%	13	21	–	10	–	–	0	47 (MF)
			2+: 25%–50%	21	12	–	30	–	–	22	6 (MF); 33 (t-MF)
			3+: >50%–75%	13	10	–	10	–	–	0	0 (MF); 67 (t-MF);
			4+: >75%	18	0	–	30	–	–	78	6 (MF); 0 (t-MF)

(Continued)

Table I (Continued).

Bossard et al 2014 <sup>45</sup>	376	–	0: <5%	42	37	44	54	0	0	50	–
			1+: 5%–24%	26	47	11	7	0	0	0	–
			2+: 25%–49%	9	10	33	11	0	5	0	–
			3+: 50%–75%	10	5	11	14	0	2	7	–
			4+: >75%	13	0	0	14	100	93	43	–
Wang et al 2017 <sup>46</sup>	122	–	0: no staining	–	–	–	30	–	–	–	–
			1+: >0%–<25%	–	–	–	38	–	–	–	–
			2+: 25%–50%	–	–	–	18	–	–	–	–
			3+: >50%–75%	–	–	–	10	–	–	–	–
			4+: >75%	–	–	–	5	–	–	–	–
B-Cells											
Study		Number of Patients	Treatment	CD30+ % Cell Cutoff Used	Percentage (%) of Patients With CD30 Positive Expression						
					DLBCL			Other B-cell lymphomas			
Jacobsen et al 2015 <sup>18</sup>		68	BV monotherapy	≥1%	25			48			
Malysz et al 2016 <sup>47</sup>		116	BV monotherapy	≥11%	38			DLBCL/FL grade 3, FL grade 3, PMLBCL, PTLD, LBCL: 46			
Slack et al 2014 <sup>48</sup>		308	R-CHOP	>0%	24			–			
				≥20%	11			–			
Ok et al 2014 <sup>49</sup>		732	R-CHOP	≥20%	16			–			
Ok et al 2015 <sup>50</sup>		533	R-CHOP	≥20%	14			–			
Hao et al 2015 <sup>12</sup>		146	CHOP or R-CHOP	≥20%	16			–			
Song et al 2015 <sup>51</sup>		230	EPOCH, R-CHOP, and CHOP		36 (EBV+)			–			
Gong et al 2015 <sup>52</sup>		232	R-CHOP and CHOP	>0%	12			–			
				≥20%	10			–			
Xu-Monette et al 2015 <sup>53</sup>		879	R-CHOP		17			–			

Wang et al 2016 <sup>54</sup>	98	R-CHOP R+EPOCH, and doxorubicin or hyper- CVAD	>0%	41	–
			≥20%	22	–
			≥40%	12	–
			≥85%	6	–
Hu et al 2013 <sup>55</sup>	461	R-CHOP	≥20%	14	–
Collie et al 2013 <sup>56</sup>	94	R-CHOP	≥ 20%	10	–
Xu-Monette et al 2016 <sup>57</sup>	520	R-CHOP		15	–
Xu et al 2017 <sup>58</sup>	97	R-EPOCH	>0%	25	–
			≥20%	12	–
Tracy et al 2018 <sup>59</sup>	362	R-CHOP and R-CEPP	≥20%	9	–
Gong et al 2018 <sup>60</sup>	241	CHOP; R-CHOP	>0%; ≥20%	10; 8	–
Salas et al 2020 <sup>61</sup>	216	R-CHOP	>0%	31	–
			>20%	19	–
Santoso et al 2020 <sup>13</sup>	104	–	>0%	13	–
			>20%	2	–
Al-Humood et al 2013 <sup>62</sup>	44	–		34	–
Campuzano-Zuluaga et al 2013 <sup>63</sup>	167	–	≥20%	21	–
			20%–49%	16	–
			50%–79%	32	–
			≥80%	52	–

**Note:** \*The values are presented in numbers and not in % under different subtypes.

**Abbreviations:** AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK–/+, anaplastic lymphoma kinase negative/positive; ATLL, adult T-cell leukemia/lymphoma; BV, brentuximab vedotin; CD30+, CD30 positive; CTCL, cutaneous T-cell lymphoma; CEPP, cyclophosphamide, etoposide, procarbazine, and prednisone; CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; ENKTL, extranodal natural killer/T-cell lymphoma; EPOCH, etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone; FL, follicular lymphoma; GELOX, gemcitabine, oxaliplatin, and L-asparaginase; A, anthracycline; MF, mycosis fungoides; t-MF, transformed mycosis fungoides; PTCL-NOS, peripheral T-cell lymphoma unless otherwise specified, PMBCL, primary mediastinal large B-cell lymphoma; PTLD, post-transplant lymphoproliferative disorder; R-EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-CEPP, etoposide and procarbazine substituting for doxorubicin and vincristine.

**Table 2** BV and BV Combination Treatment Responses in T-Cell Lymphomas

Study	Phase	Treatment	Line of Treatment	Disease Subtype	Patient Number	CD30+ % Cutoff Used	Response Rate (Overall)			Survival Outcomes (Overall)		% of Patients With Different CD30+ Levels	Response Rates	Survival Outcomes
Younes et al 2010 <sup>5</sup>	I	BV monotherapy	R/R	ALCL	2	–	ORR: 100%	CR: 100%		–		–	–	–
Pro et al 2017 <sup>64</sup>	2	BV monotherapy	R/R	ALCL	58	–	ORR: 86%	CR: 66%	PR: 21%	mPFS: 20 months	mOS: NR	–	–	–
Song et al 2021 <sup>65</sup>	2	BV monotherapy	R/R	sALCL	9	–	ORR: 67%	CR: 56%	PR: 11%	mOS: NR		–	–	–
Pro et al 2012 <sup>6</sup>	2	BV monotherapy	Recurrent disease	sALCL	58		ORR: 86%	CR: 57%	PR: 29%	mPFS: 13.3 months	mOS: NR	–	–	–
Ogura et al 2014 <sup>66</sup>	2	BV monotherapy	R/R	sALCL	5	–	ORR: 100%	CR: 80%	PR: 20%	mPFS: 10.8 months		–	–	–
Kim et al 2021 (ALCANZA sub analysis) <sup>14</sup>	3	BV monotherapy	R/R	MF	100	≥10%	–			–		<10%: 43%	ORR4: 41%	mPFS: 16.7 months
												≥10%: 57%	ORR4: 57%	mPFS: 15.5 months
Horwitz et al 2014 <sup>67</sup>	2	BV monotherapy	R/R	PTCL-NOS	21		ORR: 41%	CR: 24%	PR: 18%	mPFS: 1.6 months		≤15%: 74%	ORR: 33% CR: 14% PR: 19%	–
				AITL	13					mPFS: 6.7 months			ORR: 54% CR: 38% PR: 15%	
Duvic et al 2015 <sup>23</sup>	2	BV monotherapy	Refractory	MF	28	–	ORR: 54%	CR: 7%	PR: 46%	PFS: 1.1 year		≤10%: 36%	ORR: 50% (PR, n = 5)	–
												10%–50%: 43%	ORR: 58% (CR, n = 1, PR, n = 6)	
												>50%: 21%	ORR: 50% (CR, n = 1, PR, n = 2)	
				LyP	9		ORR: 100%	CR: 56%	PR: 44%	–		–	–	–
				pcALCL	2		ORR: 100%	CR: 100%				–	–	–

Kim et al 2015 <sup>15</sup>	2	BV monotherapy	Refractory or Advanced	MF and SS	32 (30 for efficacy)	–	ORR: 70%	CR: 3%	PR: 67%	mPFS: NR at 12 months	<10%: 44% 10%–50%: 44% >50%: 13%	ORR: 54% ORR: 79% ORR: 100%	
Horwitz et al, 2022 (ECHELON-2) <sup>25</sup>	3	BV + chemotherapy (A+CHP)	FL	PTCL-NOS	89	≥10%	CD30 > median (25%): CR: 57% PR: 14% CD30 ≤ median: CR: 71% PR: 14% CD30 = 10%: CR: 67% PR: 33%			mPFS: 62.3 months for A+CHP 23.8 months for CHOP mOS: not reached in either arm	>50%: 13%	ORR: 100%	
				AITL	37		CD30 > median (18%): CR: 57% PR: 7% CD30 ≤ median: CR: 53% PR: 20% CD30 = 10%: CR: 63% PR: 0%						
Horwitz et al 2019 (ECHELON-2) <sup>17</sup>	3	BV + chemotherapy (A+CHP)	FL	PTCLs	226	≥10%	ORR: 83%	CR: 68%	PR: 15%	mPFS: 48.2 months			
		chemotherapy (CHOP)			226		ORR: 72%	CR: 56%	PR: 16%	mPFS 20.8 months			
Prince et al 2017 (ALCANZA) <sup>16</sup>	3	BV or physician's choice (oral methotrexate or oral bexarotene)	R/R	MF	97	≥10%	ORR4: 50% or 10% ORR: 65% or 16% CR: 10% or 0			mPFS: 15.9 or 3.5 months			
				pcALCL	31		ORR4: 75% or 20% ORR: 75% or 33% CR: 31% or 7%			mPFS: 27.5 or 5.3 months			

**Note:** \*CD30<sub>min</sub> <10% and CD30<sub>min</sub> ≥10%.

**Abbreviations:** A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; CD30<sub>min</sub>, CD30 minimum; CD30+, CD30 positive; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; F/L, front-line; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NR, not reached; ORR, overall response rate; ORR4, objective response lasting at least 4 months; OS, overall survival; pcALCL, primary cutaneous anaplastic large-cell lymphoma; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; PR, partial response; R, rituximab; R/R, relapsed/refractory; SS, Sézary syndrome.

**Table 3** BV and BV Combination Treatment Responses in B-Cell Lymphomas

Study	Phase	Treatment	Line of Treatment	Disease Subtype	Patient Number	CD30+ % Cutoff Used	Response Rate (Overall)	Survival Outcomes (Overall)	% of Patients with Different CD30+ Levels	Response Rates	Survival Outcomes
Jacobsen et al 2015 <sup>18</sup>	2	BV monotherapy	R/R	DLBCL	49	≥1%	ORR: 44% CR: 17% PR: 27%	mPFS: 4 months			–
				Gray zone lymphoma	6		ORR: 26% CR: 16% PR: 11%	–	≥1%: 100%	ORR: 50% CR: 17% PR: 33% SD: 33%	–
				PMBL	6			–	≥1%:	ORR: 17% CR: 17% SD: 50%	–
				FL	3			–	≥1%: 100%	ORR: 0% SD: 67%	–
				PTLD	3			–	≥1%: 100%	ORR: 33% CR: 33%	–
				Plasmablastic lymphoma	1			–	–	ORR: 0%	–
Bartlett et al 2017 <sup>68</sup>	2	BV monotherapy	R/R	DLBCL	52	CD30 undetectable	ORR: 31% CR: 12% PR: 19%	mPFS: 1.4 months mOS: 7.5 months	–	–	–
Zinzani et al 2017 <sup>19</sup>	2	BV monotherapy	R/R	PMBL	15	Not mentioned, but all patients were CD30+	ORR: 13.3%	–	–	–	–
Yasenchak et al 2014 <sup>69</sup>	2	BV monotherapy	F/L	DLBCL	33	≥1%–	ORR: 92% CR: 58% PR: 33%	–	–	–	–
Gandhi et al 2014 <sup>70</sup>	I/2	BV + R	F/L	B-cell lymphoma	7		CR: 71%	–	–	–	–
Ward et al 2022 <sup>71</sup>	I	BV + L	R/R	DLBCL	37	No cutoff used	ORR: 57% CR: 35% PR: 22%	mPFS: 10.2 months mOS: 14.3 months	CD30+ >1%: 41%	ORR: 73% CR: 40%	–
Yasenchak et al 2015 <sup>24</sup>	2	BV + R-CHOP	F/L	DLBCL	51	≥1%	CR: 69%	–	<1% (CD30–)	CR: 63%	PFS rate: 56%
									≥1%	CR: 76%	PFS rate: 82%

**Abbreviations:** BV, brentuximab vedotin; CD30+, CD30 positive; CR, complete response; DLBCL, diffuse large B-cell lymphoma; F/L, front-line; L, lenalidomide; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; PTLD, Post-transplant lymphoproliferative disorder; PR, partial response; R, rituximab; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PMBL, Primary mediastinal B-cell lymphoma; FL, follicular lymphoma; mOS, median overall survival; mPFS, median progression-free survival; R/R, relapsed/refractory; SD, stable disease.



patients) in the CD30 positive patients.<sup>16</sup> In a study involving patients with CD30 positive (CD30+) CTCL and lymphoplasmacytic lymphoma treated with BV, a response rate of 50% was observed in patients with CD30 expression levels <10%.<sup>23</sup> Furthermore, a study of BV in SS and MF with variable CD30 levels showed an ORR of 54% in patients with CD30 levels <10%.<sup>15</sup> In another study, 35-IST-002, 12 patients with MF were reported to have undetectable CD30, and partial responses (PRs) were achieved in 8 patients with an ORR of 67% (95% CI, 34.9–90.1%).<sup>20</sup>

## Correlation Between BV Treatment Response and CD30 Expression in T- and B-Cell Lymphomas

Considering that CD30 is its molecular target, theoretically, the level of CD30 expression should influence the efficacy of BV. However, the published literature suggests otherwise, as evidenced from the results of various studies conducted in patients with T- and B-cell lymphomas (Tables 2 and 3).

In 2015, Jacobsen et al, investigating the efficacy and safety of BV in R/R mature T- and B-cell lymphomas with a variable CD30 expression in a phase II, open-label, multicenter study reported no correlation between the BV therapy response and level of CD30 expression in patients with R/R DLBCL. In that study, 50% (n = 8) of patients achieving CR had a low level of CD30 (<10%).<sup>18</sup> However, patients with R/R DLBCL and other B-cell lymphomas with CD30 >1% and treated with BV showed a CR of 50% and CR + PR of 21% in patients with <10% CD30 levels.<sup>18</sup> A study conducted by Yasenchak et al further supported these findings, demonstrating a CR of 63% in patients with DLBCL who had CD30 <1%.<sup>24</sup> Furthermore, a study by Jagadeesh et al, which assessed the response to BV based on the CD30 expression across 5 different clinical studies in NHL, demonstrated no significant differences in the overall response between patients with CD30 expression ≥10% and <10%, indicating that CD30 expression does not predict the clinical response to BV.<sup>20</sup> In SGN35-012 B-cell NHL, SGN35-012 PTCL, ALCANZA (avg), ALCANZA (min), 35-IST-001, 35-IST-002 (avg) and 35-IST-002 (min) treated with BV monotherapy, the ORR was 36% (17/47), 45% (10/22), 72% (26/36), 71% (20/28), 55% (11/20), 80% (8/10) and 80% (4/5) respectively in the CD30avg ≥ 10% group. Similarly, 36% (24/66), 33% (4/12), 43% (6/14), 55% (12/22), 55% (11/20), 59% (13/22) and 63% (17/27) in the CD30avg <10%. In the CD30min group, the ORR was 34% (17/50) in SGN35-012 B-cell NHL, 40% (4/10) in ALCANZA (min), and 67% (8/12) in 35-IST-002 (min) treated with BV monotherapy.

Among one of these studies, Phase III ALCANZA study involving patients with MF, characterized patients as CD30<sub>min</sub> <10% (1 biopsy with <10% CD30 expression) or CD30<sub>min</sub> ≥10% (all biopsies with ≥10% CD30 expression). Compared with the physician's choice of treatment, BV improved the ORR and PFS in both patient groups regardless of baseline CD30 expression levels, indicating no correlation between the CD30 expression level and BV treatment response.<sup>14,20</sup> Similarly, in the ECHELON-2 study in patients with PTC, no correlation was observed between the median CD30 expression level (of 18%) or above or below the median level and treatment response with BV plus cyclophosphamide, doxorubicin, and prednisone as responses were observed across CD30 expression levels. The median CD30 expression was found to be 18% in AITL and 25% in PTCL-NOS. However, there appeared to be no correlation between the level of CD30 expression, when evaluated as above or below the median for the subtype, and the probability of achieving CR in patients with either AITL or PTCL-NOS.<sup>25</sup> The ECHELON-1 Phase-III trial showed that BV in combination with chemotherapeutic is robust and durable in improving the PFS with a consistent safety profile. Treatment with BV in combination with other chemotherapeutic drugs resulted in a 5-year PFS of 82.2% (95% CI 79.0–85.0) at the follow-up period of 60.9 months with only peripheral neuropathy (19%) as major AE.<sup>26</sup>

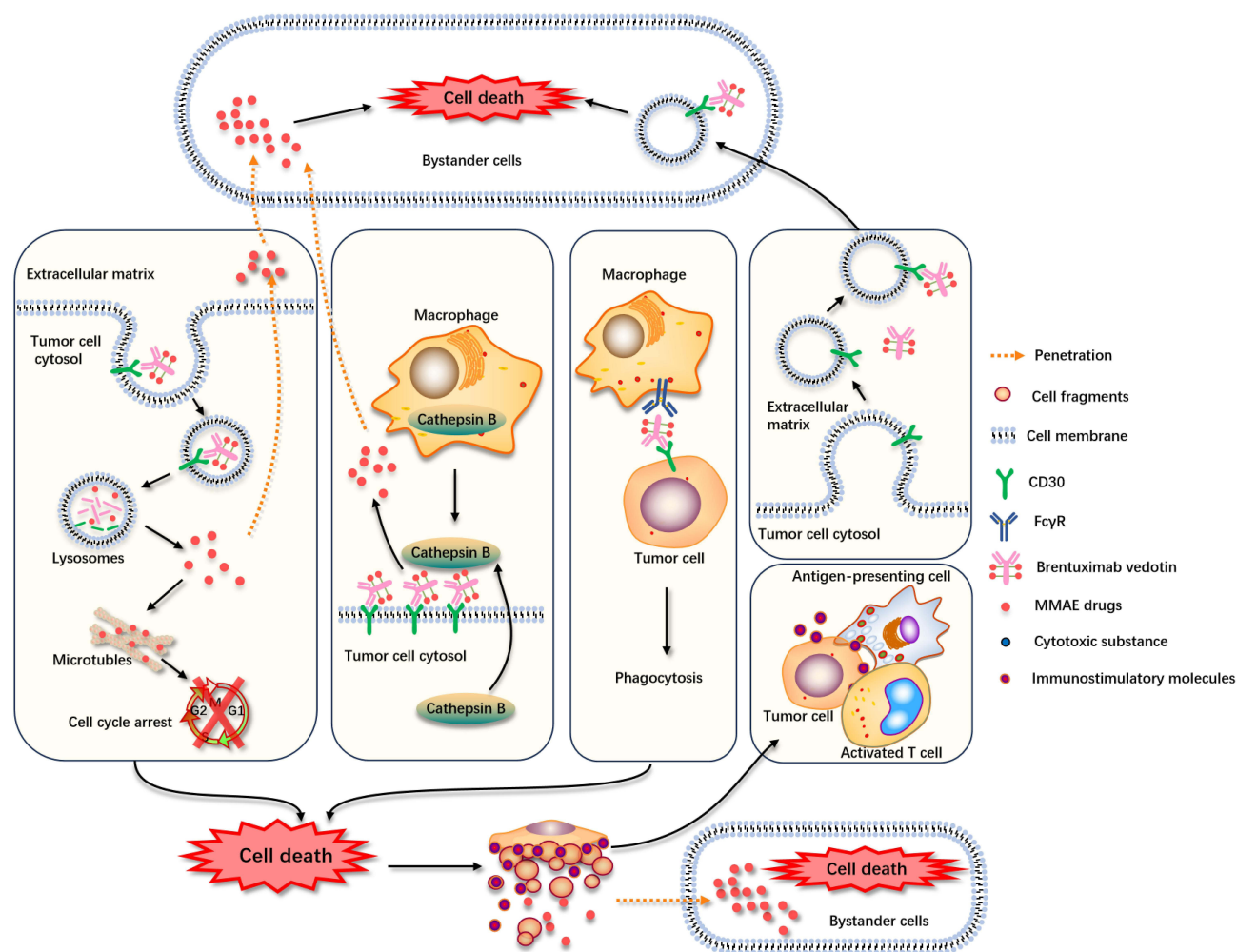
A recent long-term study demonstrated that patients with R/R PMBCL with a varied range of CD30 expression were able to achieve a CR or PR when treated with a combination of BV and nivolumab.<sup>27</sup> In addition, an ongoing recent trial has demonstrated that BV combined with cyclophosphamide, doxorubicin, and prednisone was effective in patients with PTCL regardless of CD30 expression, with an ORR of 83% in CD30 negative patients (CD30 expression <1%) and 74% in patients with low levels of CD30 (CD30 expression 1–10%).<sup>28</sup> Furthermore, a study by Duvic et al<sup>23</sup> had shown similar rates of ORR in both low and high CD30-expressing patients with MF.

Overall, the expression levels of CD30 did not appear to exert an impact on the response to the BV treatment, indicating a lack of direct correlation between the CD30 expression levels and treatment response. To better guide the clinical treatment, no threshold should be used, and pathologists should report the CD30 expression based on what is

observed at any staining intensity, estimate the percent positive expression in tumor cells or total cells, and report in number or range expression with any expression level.<sup>10</sup>

## Potential Mechanisms of Action of BV in Patients with All Levels of CD30 Expression or Not Visually Detectable CD30 Expression

Various studies have shown that the clinical responses/outcomes to the treatment with BV were not associated with CD30 expression levels in various CD30-expressing lymphomas. These findings suggest the presence of some off-target immune modulatory mechanism of BV action, other than the standard ADC internalization, and MMAE release followed by apoptosis of the tumor cells.<sup>4</sup> Several hypotheses have been proposed to explain the observable clinical response to BV, independent of the CD30 expression level. The foremost hypothesis is the bystander effect of BV where MMAE crosses the cell membrane and is released into the surrounding extracellular matrix (ECM), exerting its cytotoxic activity on adjacent tumor cells (Figure 1).<sup>29</sup> The



**Figure 1** Proposed alternative mechanisms of action for BV with all levels of CD30 expression. Binding of BV to the CD30 antigen leading to its internalization via endocytosis. BV is transferred to the lysosomes where the dissociation of the linker occurs resulting in the release of free diffusible MMAE drug. This free drug is released into the cytosol where it binds to microtubules and at the cellular level induces cell cycle arrest and ultimately leads to cell death. MMAE can penetrate surrounding bystander cells after diffusing out of the target cell and cause cell death. There is an alternative route where BV binds to CD30 but does not get internalized. Before internalization process an extracellular enzyme such as cathepsin B, released by tumor cells and tumor-associated macrophages (TAMs) leads to generate diffusible MMAE. Therefore, MMAE can penetrate surrounding bystander cells after diffusing out of the target cell and cause cell death. Also, there is another potential drug delivery path where the BV-bound target tumor cell, internalized through Fc-mediated phagocytosis which involves recognition and engulfment and upon degradation of the target tumor cell, it would lead to the release of free and diffusible drug. BV may also stimulate immune effector cell recruitment via MMAE-mediated immunogenic cell death. CD30 is also released in large EVs (l-EVs) by budding from the surface and in small EVs (s-EVs) by plasma membrane fusion of multivesicular endosomes. CD30+ EVs bind BV and target difference cells within the tumor microenvironment, such as CD30+ or CD30- DLBCL cells.

**Abbreviations:** BV, Brentuximab vedotin; MMAE, monomethyl auristatin E; TAMs, tumor associated macrophages; EV, extracellular vesicles.

bystander effect occurs when the payload is released from the cell that has been internalized and degraded the ADC.<sup>30,31</sup> Another proposed mechanism for the bystander effect of BV is the cleavage of MMAE from CD30+ bound to BV on tumor cells by extracellular enzymes such as cathepsin B released by surrounding tumor cells and tumor-associated macrophages, thereby releasing MMAE in ECM and killing the tumor cells in the vicinity. Furthermore, targeted tumor cells can undergo antibody-dependent cellular phagocytosis releasing free MMAE in ECM that can induce apoptosis in the surrounding tumor cells.<sup>29,31–33</sup> Another proposed mechanism is the depletion of regulatory T cells by BV and induction of immunogenic cell death.<sup>27,34</sup> All these alternative mechanisms of BV action do not require CD30 antigen on all targeted cells. Moreover, it has been demonstrated in vitro that CD30-negative cells cultured in isolation are not sensitive to BV. However, when they were cocultured with CD30-expressing cell lines and treated with BV, cell death was observed in the CD30-negative cells.<sup>15,20,30,31</sup> One study also suggested that CD30-based BV not only targets CD30+ tumor cells but also CD30– DLBCL cells in the presence of CD30+ extracellular vesicles (EVs). This study provides a feasible explanation for the clinical impact of BV on CD30– DLBCL and warrants confirmatory studies in animal models.<sup>35</sup>

Several factors may contribute to the observation that a response to BV can occur in patients with not visually detectable CD30 expression. The first factor involved is the standard immunohistochemistry (IHC), which is a semiquantitative assay, may exhibit a limited sensitivity, particularly for lower CD30 levels crucial for therapeutic decisions. Tests designed for diagnostic calibration may not identify clinically significant lower expression levels. Technical challenges also add complexities to the accuracy of IHC. Nevertheless, standard IHC remains to be appropriate for characterizing CD30-expressing malignancies, holding promise for optimization as a predictive biomarker to guide the treatment.<sup>36</sup> Another potentially significant factor involved is the intra- and inter-lesional heterogeneity of CD30 expression in tumor samples. CD30 expression within a single tumor can vary, and a random biopsy sample could be misrepresentative of the overall CD30 expression status of the patient's lymphoma. In the ALCANZA study, inter-lesional variability was prominent among the screened patients with MF, 44% (55 of 125) of patients had demonstrated at least 1 biopsy with low (<10%) or undetectable CD30 in lymphoid cells. This increases the possibility that these patients may not have been eligible for recruitment if only a single biopsy had been required.<sup>14,20</sup> Furthermore, another assessment revealed inter- and intra-patient variability in CD30 levels, with several patients demonstrating large differences in CD30 expression between biopsies, ranging from 0%–70%. Therefore, if the inclusion criteria for the patients are based on the results of a single biopsy, then most of the patients would be excluded from the studies and remain devoid of treatment with BV or any other CD30-targeted treatment.<sup>20</sup>

The heterogeneity observed in biopsy tissue can be influenced by the dynamic nature of CD30 expression, involving protein cleavage leading to soluble CD30 expressions in the blood.<sup>20,37,38</sup> Increased soluble CD30 levels observed in inflammatory and oncologic parameters may be associated with tumor burden. The dynamic partitioning between surface-bound and secreted CD30 forms in tumors implies that the surface levels of CD30 are not constant, complicating the assessment of CD30 expression at a single time point.<sup>20</sup>

## Future Prospects

Surface expression of CD30 receptors has been recognized as a clinically potential target to treat cancers, especially lymphomas. CD30-targeted therapies, such as BV, have demonstrated significant efficacy, highlighting the potential for personalized treatment strategies. Previously, it was considered that BV could provide clinical benefits only in NHLs with substantial CD30 expression. However, this review adds to the growing evidence that treatment with BV benefits patients with NHL, with all levels of CD30 expression or undetectable CD30 expression. For therapeutic decision-making, the protocol of CD30 tests used in clinical IHC laboratory should be optimized to guarantee that it should be capable of detecting clinically important low levels of CD30. In addition, numerous studies have used more sensitive methods than IHC to assess the CD30 expression. In several studies, computer-assisted digital image analysis revealed CD30 expression of tumors, which is classified as undetectable by IHC. Furthermore, multispectral image analysis identified CD30 expression in biopsies with negligible IHC-detected CD30 expression. With more standardization of these new methods, they can also become more widely used in the future. On the other hand, artificial intelligence-assisted interpretation software is also encouraged to be developed for better quantification of CD30 expression levels, especially at low expression levels.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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