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Response to brentuximab vedotin plus CHP according to CD30 expression in the ECHELON-2 trial

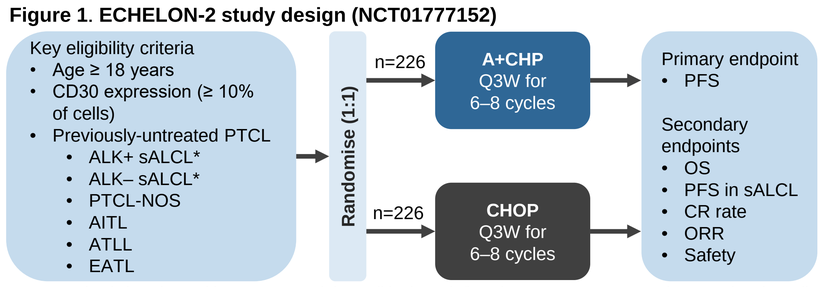
T. ILLIDGE[1], S. HORWITZ[2], S. IYER[3], N. BARTLETT[4], W. S. KIM[5], D. BELADA[6], T. FELDMAN[7], Á. ILLÉS[8], E. JACOBSEN[9], A. HÜTTMANN[10], P. L. ZINZANI[11], O. A. O'CONNOR[12], P. MCKAY[13], W. TREPICCHIO[14], H. MIAO[14], K. FENTON[15], M. ONSUM[15], T. MANLEY[15] and R. ADVANI[16]

1 Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, National Institutes of Health and Research Biomedical Research Centre, Manchester Academic Health Sciences Centre, Christie Hospital National Health Service Foundation Trust, Manchester, UK; 2 Memorial Sloan Kettering Cancer Center, New York, USA; 3 University of Texas MD Anderson Cancer Center, Houston, USA; 4 Washington University School of Medicine, Saint Louis, USA, 5 Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 6 Charles University, Hospital and Faculty of Medicine, Hrádéc Kralove, Czech Republic; 7 Hackensack University Medical,Center, Hackensack, USA; 8 University of Debrecen, Faculty of Medicine, Department of Hematology, Debrecen, Hungary; 9 Dana-Farber Cancer Institute, Boston, USA; 10 Universitatsklinikum Essen, Essen, Nordrhein-Westfalen, , Germany; 11 Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; 12 Columbia University Medical Center, New York, USA; 13 Beatson West of Scotland Cancer Centre, Glasgow, UK; 14 Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; 15 Seattle Genetics, Inc., Bothell, USA; 16 Stanford Cancer Institute, Stanford, USA

INTRODUCTION

- Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of lymphoid malignancies.
- Approximately 50% of PTCLs express CD30.
  - Systemic anaplastic large cell lymphomas (sALCL) high uniform expression of CD30.
  - CD30 expression levels vary among other PTCL subtypes.[1,2]
- Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved in the USA, EU and Japan for relapsed/refractory sALCL.
- The ECHELON-2 trial (Figure 1) compared brentuximab vedotin + cyclophosphamide, doxorubicin and prednisone (A+CHP) to CHP with vincristine (CHOP) in patients with previously untreated CD30-expressing (≥ 10% of cells) PTCL. The trial met all endpoints with significance.[3]
  - Progression-free survival (PFS) (hazard ratio=0.71; P=0.0110).
  - Overall survival (OS) (hazard ratio=0.66; P=0.0244).
  - Complete remission (CR) rate (A+CHP 68% vs CHOP 56%; P=0.0066).
  - Objective response rate (ORR) (A+CHP 83% vs CHOP 72%; P=0.0032).
- A+CHP has a manageable safety profile similar to CHOP.
- ECHELON-2 was the first prospective randomised trial in PTCL to show overall survival benefit over CHOP.
- A+CHP is approved in the USA for adults with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma (AITL) and PTCL-not otherwise specified (NOS).

Figure 1. ECHELON-2 study design (NCT01777152)



ALK, anaplastic lymphoma kinase; ATLL, adult T cell leukaemia/lymphoma; EATL, enteropathy-associated T cell lymphoma; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; Q3W, every 3 weeks
*Targeting 75% (±5%) patients

- While delivery of monomethyl auristatin E (MMAE) is the primary mechanism of action of brentuximab vedotin[4], antibody-dependent cellular phagocytosis, immunogenic cell death and the bystander effect are additional proposed mechanisms of tumour killing that may contribute to clinical activity.[5-11]
  - Intrinsic sensitivity of the tumour cells to MMAE may also influence response to brentuximab vedotin.
- Several factors could affect the relationship between CD30 expression level, as measured by IHC, and tumour response to brentuximab vedotin, including:
  - Intrapatient heterogeneity of CD30 expression in lymphoma tumour tissues
  - Technical limitations of detecting low levels of cell surface markers with standard IHC
  - The dynamic nature of CD30 expression in the tumour microenvironment
  - The additional mechanisms of action of brentuximab vedotin that do not require the expression of CD30 on every tumour cell.

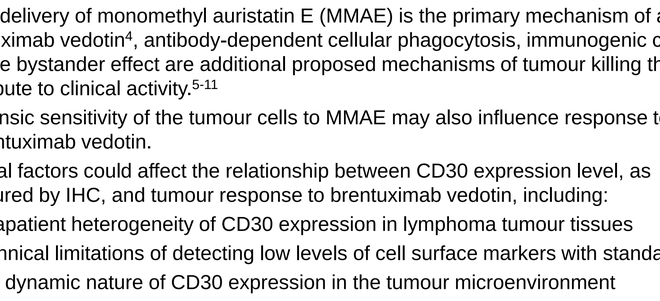
AIM

- The relationship between CD30 expression level and tumour response to brentuximab vedotin has not been fully established for patients with PTCL.
- As ORR is a direct measure of antitumour activity, we examined response to A+CHP by CD30 expression in patients with AITL and PTCL-NOS treated with A+CHP in the ECHELON-2 study.

METHODS

- CD30 expression was assessed by immunohistochemistry (IHC) in local laboratories using the Ber H2 antibody (Figure 2).
- In cases where enumeration of neoplastic cells was not possible, total lymphocytes were used.
  - For AITL, expression levels were reported as percent of lymphoma cells for 34 patients (65%) and percent of total lymphocytes for 18 patients (35%).
  - For PTCL-NOS, expression levels were reported as percent of lymphoma cells for 52 patients (72%) and percent of total lymphocytes for 20 patients (28%).

Figure 2. CD30 IHC assay scoring guidelines for peripheral T-cell lymphomas



C, cytoplasmic; G, golgi; M, membrane

- Median CD30 expression values were calculated for patients with AITL and PTCL-NOS in the A+CHP treatment arm. For patients with CD30 above vs below the median:
  - CR rates were compared using a Cochran-Mantel-Haenzel test and 2-sided P values were reported
  - Duration of complete response (DOCR) was compared using a log-rank test and 2-sided P values were reported.

RESULTS

STUDY POPULATION

- Demographics, exposure to investigational products, and disease characteristics (Table 1) in the CD30 subgroups were consistent with the intent-to-treat population of the study.

Table 1: Disease characteristics of AITL or PTCL-NOS patients in the A+CHP arm

		AITL		PTCL-NOS	
		CD30 expression > median n=14*	CD30 expression ≤ median n=15	CD30 expression > median n=14	CD30 expression ≤ median n=14
Median time from diagnosis to first dose, months		0.8	0.7	0.6	1.2
Disease staging at diagnosis, n (%)	Stage I	0	0	0	0
	Stage II	2 (14)	1 (7)	1 (7)	3 (21)
	Stage III	7 (50)	5 (33)	9 (64)	5 (36)
	Stage IV	5 (36)	9 (60)	4 (29)	6 (43)
Baseline International Prognostic Index score, n (%)	0	1 (7)	0	0	0
	1	3 (21)	2 (13)	2 (14)	2 (14)
	2	5 (36)	5 (33)	4 (29)	2 (14)
	3	4 (29)	5 (33)	7 (50)	8 (57)
	4	1 (7)	3 (20)	1 (7)	2 (14)
	5	0	0	0	0
Extranodal disease involvement, n (%)	≤1 site	13 (93)	10 (67)	11 (79)	9 (64)
	>1 site	1 (7)	5 (33)	3 (21)	5 (36)

*One patient with AITL in the CD30 above the median subgroup was randomised to A+CHP but did not undergo treatment.

CD30 EXPRESSION AND RESPONSE

- Most (26/29, 90%) AITL patients had CD30 expression between 10% and 30% (Figure 3).
  - AITL CD30 expression: median=18%, mean=20%.
- PTCL-NOS patients were more distributed across levels of CD30 expression ranging from 10% to 100% (Figure 4).
  - PTCL-NOS CD30 expression: median=25%, mean =41%.
- CD30 expression levels were similar across response types (Figure 3 and Figure 4).

Figure 3: CD30 expression by response in patients with AITL in the A+CHP treatment arm

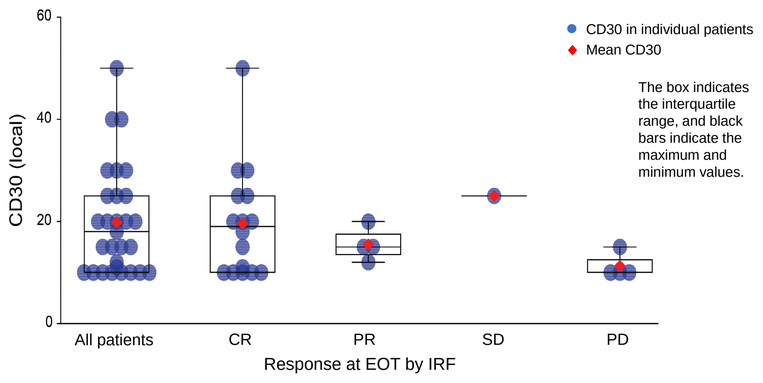
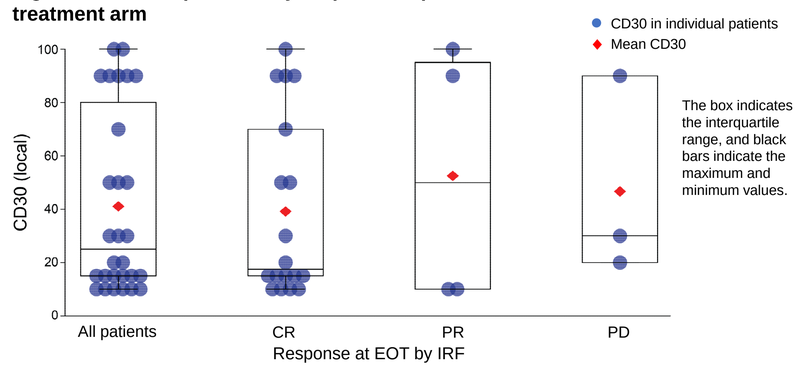


Figure 4: CD30 expression by response in patients with PTCL-NOS in the A+CHP treatment arm



- CR rates in patients with AITL (P=0.84) and PTCL-NOS (P=0.44) were independent of the level of CD30 expression (above vs below the median) (Table 2).
- CRs and PRs were observed across the range of CD30 expression, including CD30=10%.

Table 2: CR and PR rates across CD30 subgroups in patients with AITL or PTCL-NOS

	CD30	Patients, n	CR, n (%)	PR, n (%)	P value*
AITL	CD30 > median	14	8 (57)	1 (7)	0.84
	CD30 ≤ median†	15	8 (53)	3 (20)	
	CD30=10%	8	5 (63)	0	
PTCL-NOS	CD30 > median	14	8 (57)	2 (14)	0.44
	CD30 ≤ median	14	10 (71)	2 (14)	
	CD30=10%	6	4 (67)	2 (33)	

*Cochran-Mantel-Haenzel test comparing CR rates in patients with CD30 above vs below median.
†Patients with CD30=10% were included in the category CD30 ≤ median.

CD30 EXPRESSION AND RESPONSE DURATION

- DOCR in patients with AITL (P=0.30) and PTCL-NOS (P=0.90) was independent of the level of CD30 expression (above vs below the median) (Figure 5 and Figure 6).

Figure 5: DOCR in each patient with AITL in the A+CHP treatment arm

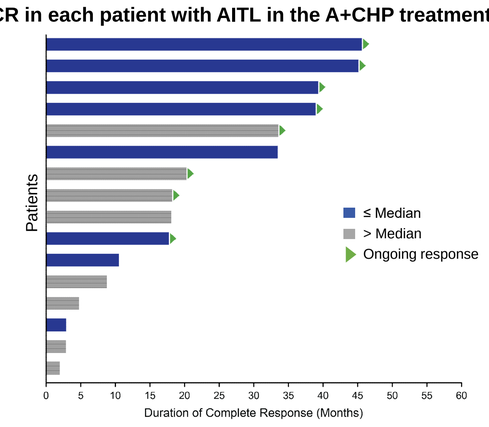
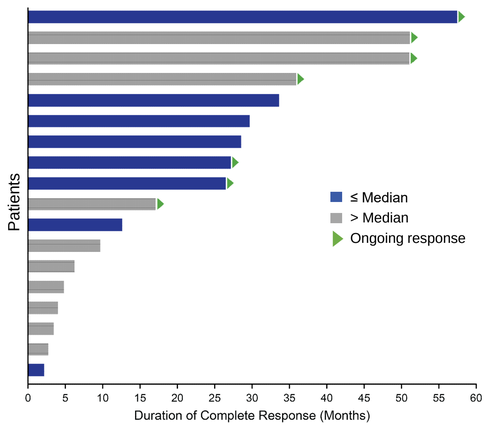


Figure 6: DOCR in each patient with PTCL-NOS in the A+CHP treatment arm



CONCLUSIONS

- **Among AITL and PTCL-NOS patients in ECHELON-2, response rate and durability of response were independent of CD30 expression above vs below the median, and responses were observed among patients with the lowest CD30 expression level: CD30=10%.**
- **The degree of CD30 expression alone, as measured by IHC, does not predict benefit from A+CHP.**
- **Further evaluation of the expression-response relationship in PTCL patients with CD30 < 10% is warranted.**

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CONTACT INFORMATION

tim.illidge@manchester.ac.uk