PCN472

PATIENT REPORTED HEALTH STATE UTILITIES IN CUTANEOUS T-CELL LYMPHOMA (CTCL) - AN ANALYSIS OF EQ-5D AND SKINDEX-29 DATA COLLECTED FROM THE ALCANZA TRIAL

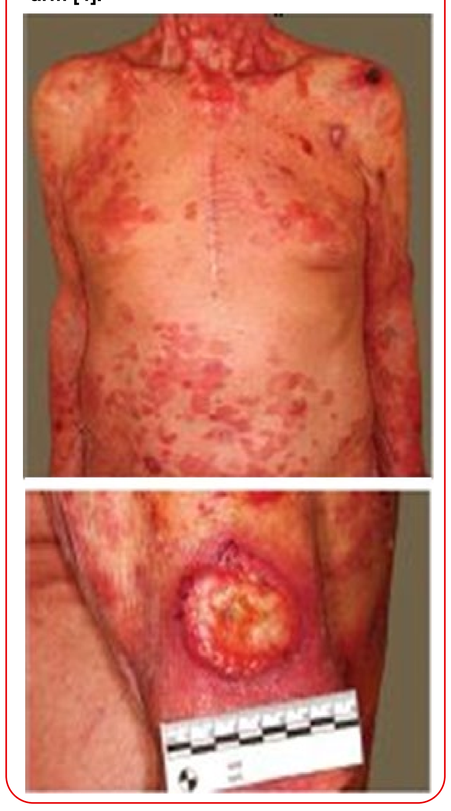
Podkonjak T[1], McCarthy G[2], Cranmer H[3], Birnie R[2]

[1]Takeda UK Ltd, Wooburn Green, UK
[2]BresMed Health Solutions Ltd, Sheffield, UK
[3]Takeda UK Limited, High Wycombe , BKM, UK

Background

- Cutaneous T-Cell Lymphomas (CTCLs) are a rare group of clinically heterogenous non-Hodgkin lymphomas, of which the most common form is mycosis fungoides (MF).[1] The primary manifestation of CTCL is in the skin.
- In early stage disease, skin directed therapies often control symptoms. However, treatment options for advanced stage disease are limited and patients suffer symptoms including painful and disfiguring cutaneous tumours (Figure 1), pruritus, insomnia and recurrent infections.[2]
- As a consequence of this devastating condition, patients with advanced stage disease suffer impaired health-related quality of life (HRQL). While overall survival for patients with advanced stage disease is shortened relative to early stage CTCL, patients with the condition can live for many years.[2]
  - MF Stage IIB median survival = 4.7 years [3]
- The pivotal Phase III (ALCANZA) clinical trial demonstrated superior efficacy of brentuximab vedotin versus physician's choice (PC) as well as collecting HRQL data.
  - EQ-5D-3L and Skindex-29 were used to measure patients' HRQL. Skindex-29 is a skin specific measurement of HRQL.
  - No algorithm exists to map from Skindex-29 to EQ-5D utility
- Brentuximab vedotin was recently recommended by NICE (TA577) as a treatment option for CD30-positive CTCL after at least 1 systemic therapy in adults with MF stage IIB or over, pcALCL or SS [5]

Figure 1. Patient with MF stage IIB, including ulcerative tumour on the left arm [4].



Objectives

- To predict health state utilities in patients with advanced CTCL, adjusting for disease progression and skin-specific Skindex-29 scores.
- To explore the relationship between EQ-5D utility and Skindex-29 scores

Study design

- The pivotal international, open-label, phase III, randomised ALCANZA trial investigated treatment of 128 adult patients with CD30-positive CTCL using either brentuximab vedotin or physician's choice (PC).[2]
  - Brentuximab vedotin was administered at 1·8 mg/kg once every 3-weeks, for up to 16 3-week cycles
  - PC included treatment with either oral methotrexate (5-50mg once per week) or oral bexarotene (300mg/m^2) once daily.
  - An advanced subgroup of patients were investigated within these analyses including MF stage IIB-IVB and pcALCL (n = 92, Table 1). Within TA577, clinical experts advised NICE that this advanced population was where brentuximab vedotin was most likely to be used in the NHS.[5]
- Patient reported HRQL data were collected using the EQ-5D and Skindex-29 measures.
  - The EQ-5D measure is a generic preference-based instrument which assesses HRQL across five domains – mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
  - Skindex-29 is a dermatology-specific non preference-based measure comprised of questions across three domains – symptoms, emotions and functioning. Skindex-29 is measured on a scale from 0-100 with 100 being the most severe impact
- Questionnaires were completed on Day 1 of Cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16, at end of treatment, and during post-treatment follow-up.

Methods

- UK tariff reported by Dolan was applied to EQ-5D-3L data collected in ALCANZA to derive utility values [6].
- Exploratory univariate analyses were conducted to identify covariates predicting EQ-5D utility including age, response status, progression status, CTCL subtype, study treatment, Skindex-29 total score
- Linear mixed effects regression models were fitted to the available data, accounting for repeated measures from individual patients
- A stepwise backwards selection process using AIC was used to identify a final multivariate model to predict health state utilities for an accompanying economic evaluation presented to NICE.

Table 1. ALCANZA baseline patient characteristics – advanced CTCL

Characteristic	Brentuximab vedotin (N=49)	Physician's choice (PC) (N=46)
Treatment breakdown of PC, n (%)		
MTX	NA	21 (45.65%)
BEX	NA	25 (54.35%)
Sex, n (%)		
Male	25 (51.02%)	24 (52.17%)
Female	24 (48.98%)	22 (47.83%)
Age		
Mean ± sd	59.1 ± 13	54.9 ± 14.4
Median	62	54
Min, max	31, 82	25, 83
ECOG performance status, n (%)		
0	34 (69.69%)	31 (67.39%)
1	12 (24.49%)	13 (28.26%)
2	3 (6.12%)	2 (4.35%)
MF stage, n (%)		
IIB	19 (57.58%)	19 (61.29%)
IIIA	4 (12.12%)	2 (6.45%)
IIIB	0 (0%)	0 (0%)
IVA$_1$	0 (0%)	1 (3.23%)
IVA$_2$	2 (6.06%)	8 (25.81%)
IVB	7 (21.21%)	0 (0%)
Unknown	1 (3.03%)	1 (3.23%)
Prior therapy		
Median	4	3
Min, max	0, 13	1, 15
Prior systemic therapy		
Median	2	2
Min, max	0, 11	1, 8

Results

- A total of 713 observations from 92 patients with advanced CTCL were used to inform these analyses.
- Patients with advanced CTCL often suffered from impaired HRQL. Of patients with available EQ-5D observations, 14 (15%) had EQ-5D utility less than 0, indicating HRQL worse than death.
- Poor correlation between the two instruments was observed; some patients with Skindex-29 scores close to 100 (worst symptoms) scored close to 1.0 (perfect health) on EQ-5D (Figure 2).
- Following stepwise selection, the final regression model was:

$$Utility = Intercept + progression\ status + Skindex{-}29\ total\ score$$

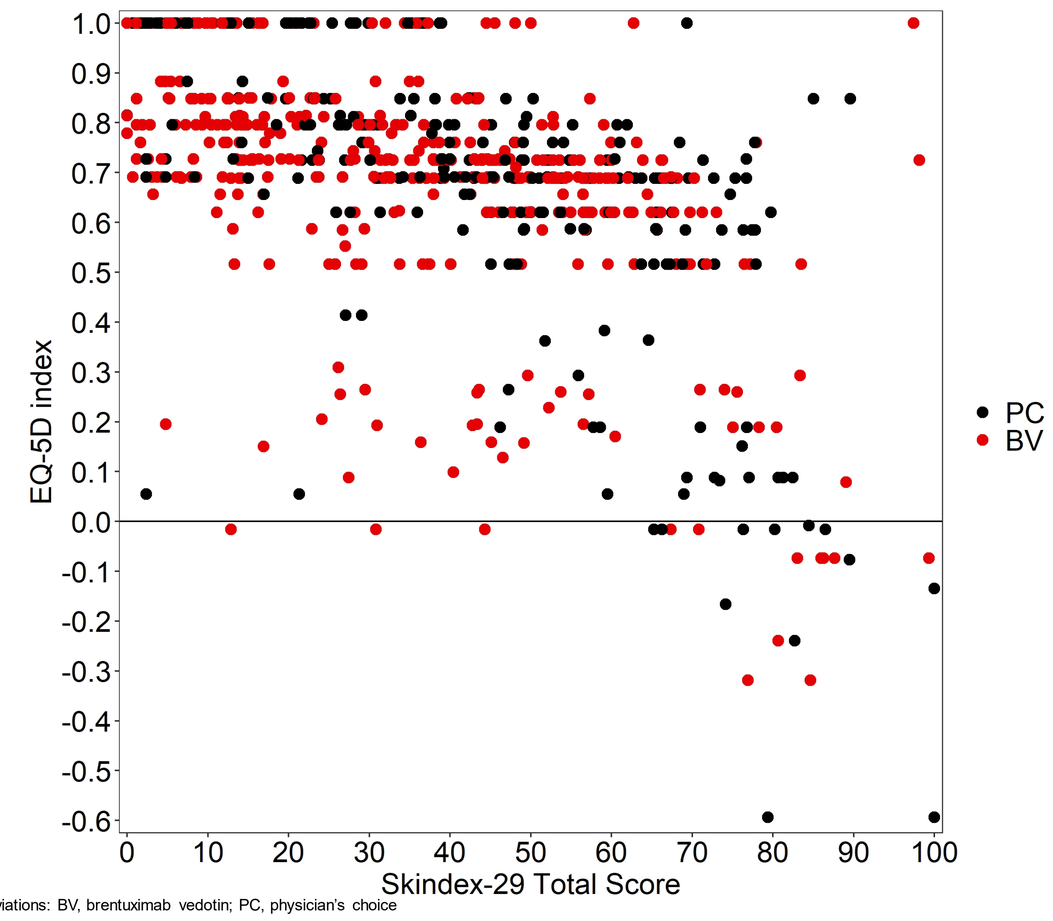
- The final multivariate model coefficients indicated a utility decrement of 0.05 for a 10-point increase in Skindex-29 total score and a utility decrement of 0.03 for disease progression (Table 3).

Table 2. Observed utility by health state and treatment arm

Health state	Treatment	Patients	Observations	EQ-5D - Mean	EQ-5D - SD	Skindex-29 Total score - Mean	Skindex-29 Total score - SD
Pre-progression	All	91	540	0.69	0.25	35.79	23.19
	BV	48	389	0.70	0.24	33.79	23.12
	PC	43	151	0.68	0.27	41.07	22.62
Post-progression	All	46	173	0.64	0.32	41.33	25.36
	BV	22	59	0.63	0.28	37.39	22.17
	PC	24	114	0.64	0.34	43.37	26.73

Abbreviations: BV, brentuximab vedotin; PC, physician's choice; SD, standard deviation

Figure 2. Correlation of Skindex-29 total score with EQ-5D utility



Abbreviations: BV, brentuximab vedotin; PC, physician's choice

Table 3. Final regression model

Covariate	Coefficient	Standard Error	P value	Variance covariance matrix		
				Intercept	Progression	Skindex-29 total score
Intercept	0.847	0.029	0.000	8.57E-04	-6.22E-05	-8.81E-06
Progression	-0.034	0.019	0.072	-6.22E-05	3.57E-04	-3.36E-07
Skindex-29 total score	-0.005	0.000	0.000	-8.81E-06	-3.36E-07	2.09E-07

Conclusions

- Overall, models fitted to the available data indicated both a higher Skindex-29 total score and disease progression predicted worse EQ-5D utility
  - Applying a mean of covariates approach resulted in pre-progression health state utility values of 0.68 for brentuximab vedotin and 0.64 for PC. The post-progression health state utility was 0.61.
- Figure 2 showed that there was a poor correlation between Skindex-29 total score and EQ-5D utility, with severely symptomatic patients observed to have EQ-5D utility of almost 1. The same relationship was shown for the individual Skindex-29 domains (symptoms, emotion, functioning) compared to EQ-5D (data not shown).
- A lack of correlation between the two measures suggests that the EQ-5D instrument was not sensitive to changes in HRQL captured by Skindex-29. Development of a mapping algorithm predicting EQ-5D utility from Skindex-29 scores may not be appropriate as this could lead to over estimation of utilities.
- The limited number of observations and follow-up post-progression may also have resulted in an underestimate of the true impact of progression on patient utility.
- Within the NICE technology appraisal for brentuximab vedotin, the Committee acknowledged the limitations of EQ-5D for measuring HRQL in advanced CTCL because "it may not be sensitive to skin-related diseases, but noted that it should capture depression and pain described by patients in consultation responses" [5].
  - The clinical experts in TA577 explained that neither tool fully [EQ-5D or Skindex-29] captures all skin-related and physiological symptoms of CTCL and emphasized the importance of symptom improvement to HRQL for patients with CTCL.[5]
  - The Committee concluded that CTCL significantly reduces patients' HRQL and agreed that better measures to capture CTCL-specific HRQL are required. [5]
  - The Committee concluded that brentuximab vedotin appears to improve HRQL, but the size of the effect captured in ALCANZA is unclear, at least partly due to the tools available. [5]
- Development of a preference based CTCL-specific measure may better capture changes in patient HRQL and more appropriately support economic evaluations of new and existing therapies.

References

1. Duvic M, Tetzlaff MT, Gangar P, et al. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis. J Clin Oncol. 2015; 33(32):3759-65.
2. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017; 390(10094):555-66.
3. Agar NS, Wedgeworth E, Crichton S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. Journal of Clinical Oncology. 2010; 28(31):4730-9.
4. Kim YH, Tavallaee M, Sundram U, et al. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sezary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project. J Clin Oncol. 2015; 33(32):3750-8.
5. National Institute for Health and Care Excellence (NICE). TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. 2019. (Updated: 24 April 2019) Available at: https://www.nice.org.uk/guidance/ta577. Accessed: 21 August 2019.
6. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997; 35(11):1095-108.

Abbreviations

AIC, Akaike information criterion; BEX, bexarotene; BV, brentuximab vedotin; CTCL, Cutaneous T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; EQ-5D-3L, European Quality of Life 5-Dimension 3 Level Version; HRQL, health-related quality of life; MF, Mycosis fungoides; MTX, methotrexate; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PC, Physician's choice; pcALCL, Primary cutaneous anaplastic large T-cell lymphoma; SD, standard deviation; SE, standard error; SS, Sézary syndrome.

ISPOR Europe 2019, 2-6 November 2019, Copenhagen, Denmark