Lead team presentation

Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma (STA)

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee C

Lead team: Iain Miller, Robert Walton, Judith Wardle

ERG: Health Economics Research Unit, University of Aberdeen

NICE technical team: Sana Khan, Nicola Hay

Company: Takeda UK

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Key issues preview – clinical management and effectiveness

- Where in the treatment pathway would brentuximab vedotin be used?
- What is the rate of stem cell transplant post brentuximab and post-chemotherapy seen in clinical practice in England?
- What treatments are given in clinical practice on disease progression?
- How many cycles of brentuximab vedotin would a patient receive in clinical practice in England?
- Which is the committee's preferred source of data to determine outcome analysis: INV or IRF?
- How effective is brentuximab vedotin?
  - Phase II Single arm trial – 58 people
  - 2 retrospective studies
  - 3 Named Patient Programmes
- Does the committee consider the unadjusted treatment comparison of brentuximab vedotin with chemotherapy to estimate overall survival appropriate?

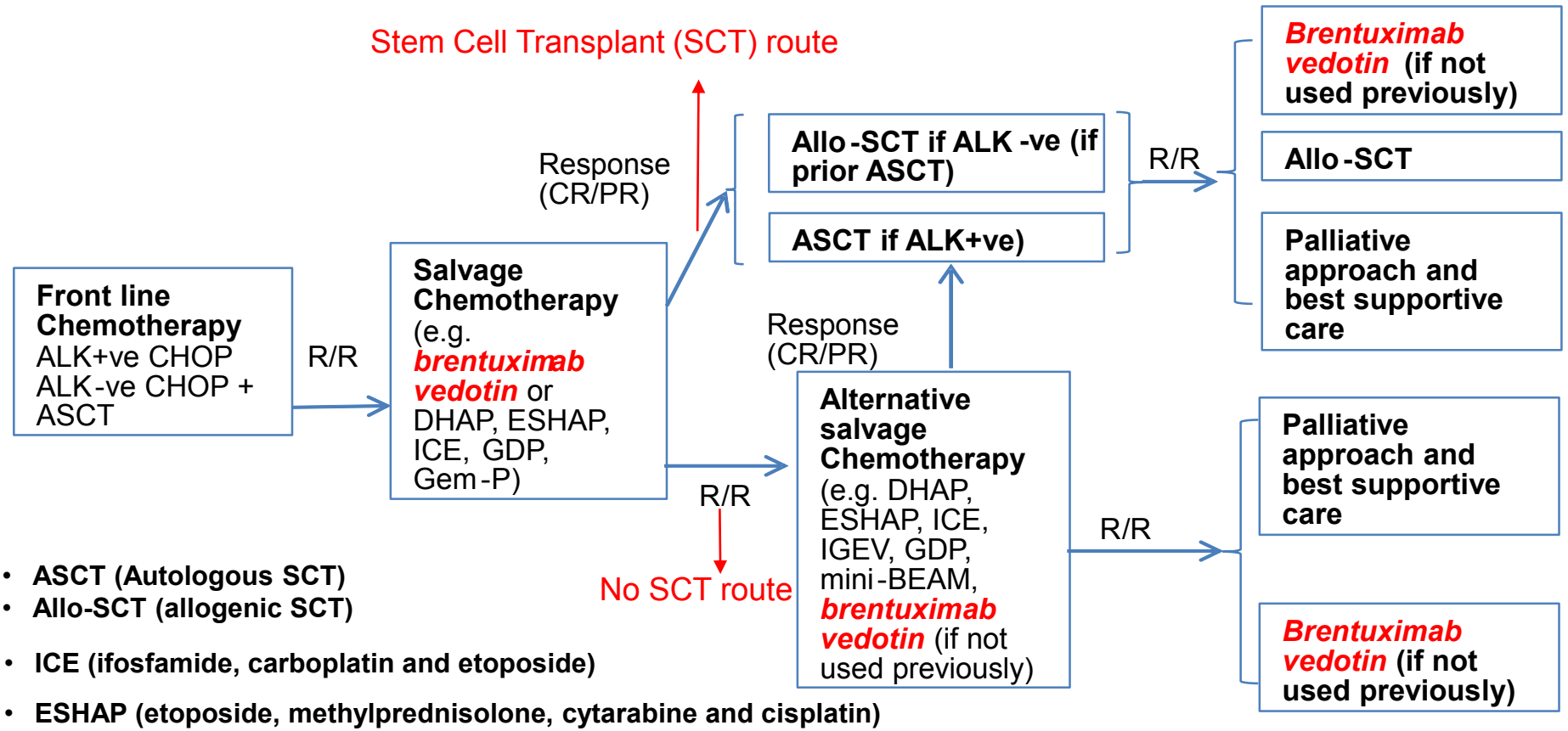
Systemic anaplastic large cell lymphoma

- Anaplastic large cell lymphoma (ALCL) is a rare disease occurring commonly in children and young people
- 2 main types of ALCL: systemic ALCL (sALCL) and primary cutaneous ALCL
- CD30+ is invariably expressed on the surface of sALCL cells
- 2 subtypes of sALCL: defined by presence or absence of anaplastic lymphoma kinase (ALK) protein expression
- sALCL is most common and aggressive form of ALCL with 40% to 65% of patients developing recurrent disease after front-line therapy and requiring further treatment
- People with ALK +ve ALCL tend to be younger than those diagnosed with ALK -ve ALCL
- Prognosis of ALK +ve ALCL is better than that of ALK-ve disease

Brentuximab vedotin (Takeda UK)

Mechanism of action	Antibody–drug conjugate comprising an anti-CD30 monoclonal antibody attached to a potent chemotherapeutic agent. The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells.
Marketing authorisation	"Brentixumab vedotin is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). Brentuximab vedotin has been available through the Cancer Drugs Fund in England since April 2013 for "relapsed or refractory systemic anaplastic large cell lymphoma". Number of patients forecast to receive it is expected to remain constant over the next five years at approximately 45 patients per year.
Administration and dose	1.8 mg/kg administered intravenously over 30 minutes every 3 weeks
Cost	List price £2,500 per vial Company has agreed a commercial access agreement with NHS England*

Company treatment pathway



- **ASCT (Autologous SCT)**
- **Allo-SCT (allogenic SCT)**
- **ICE (ifosfamide, carboplatin and etoposide)**
- **ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin)**
- **DHAP (dexamethasone, high-dose cytarabine and cisplatin)**
- **GDP (gemcitabine, dexamethasone and cisplatin)**
- **Gem-P (gemcitabine, methylprednisolone and cisplatin)**
- **IGEV (ifosfamide,gemcitabine, vinorelbine and prednisone)**
- **Mini-BEAM (carmustine, etoposide, cytarabine & melphalan)**
- **CHOP (cyclophosphamide, hydroxydaunomycin,vincristine, prednisolone)**

Current management
No standard of care, no NICE guidance

- Company pathway representative of current clinical practice. Several points at which brentuximab vedotin can be used, depending on the clinician's choice of salvage regimens and prior use of brentuximab vedotin.
- NCCN guidelines for PTCL recommend chemotherapy or an alternative salvage regimen such as brentuximab vedotin at first relapse
- Patients responding to salvage therapy then follow "SCT " route (ASCT if not received in the front-line, or allogenic SCT).
- Allogeneic transplantation may be an effective procedure for R/R ALK +ve ALCL, but value in the treatment of ALK -ve disease remains unclear.
- For patients with R/R ALCL ineligible for transplantation, or for whom second-line salvage therapy has failed (no SCT route), outcome has historically been poor

Impact on patients

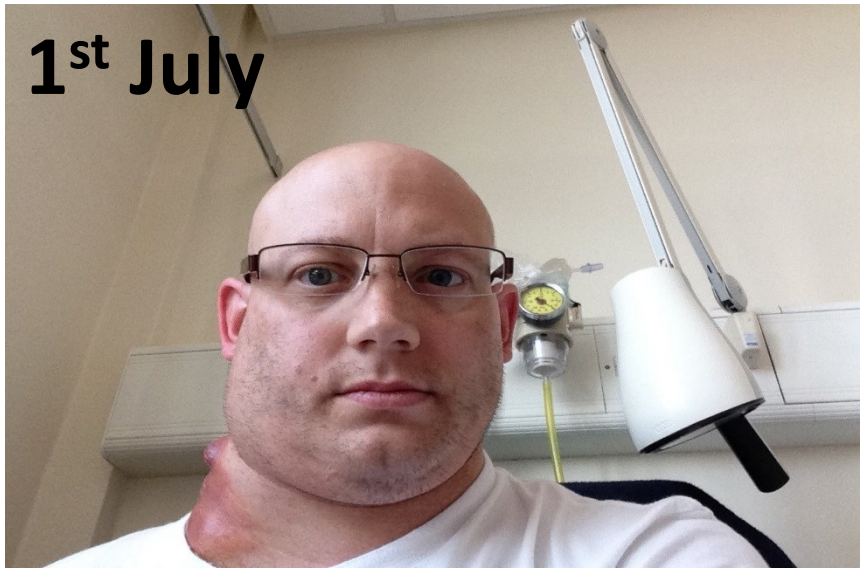
- Condition extremely painful and frightening: severe pain has major impact on quality of life and mental wellbeing
- Side effects of chemotherapy & radiotherapy very unpleasant
- Patient goals for treatment:
  - Lasting cure & QoL
  - Speed of treatment
  - Less side effects than current treatments

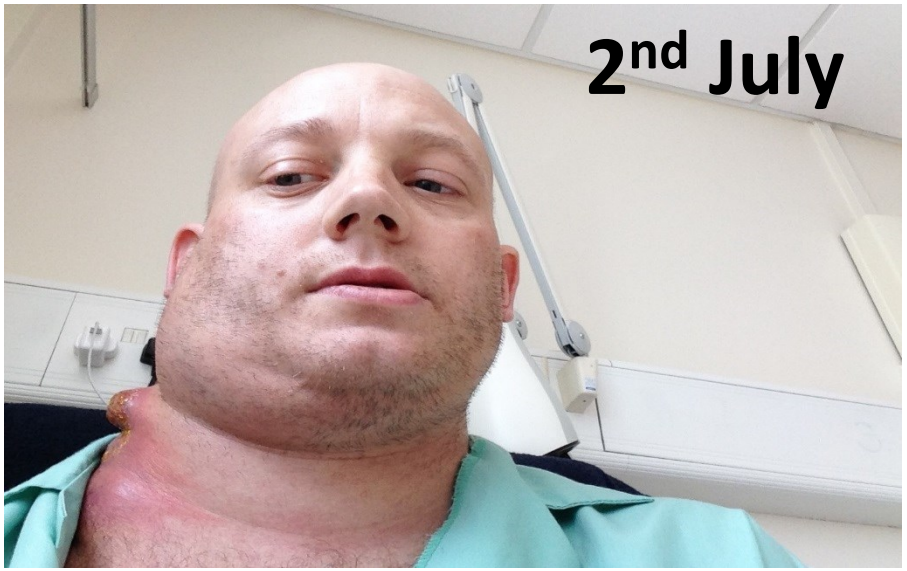
Patient views on Brentuximab

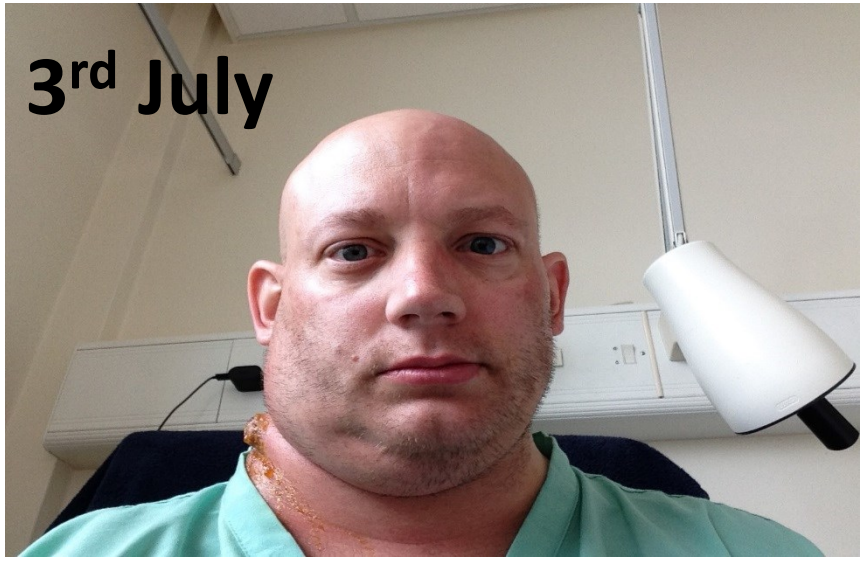
- Treatment improves mental outlook – hope for the first time
- Overall improvement in QoL
- Provides sustained pain relief – less use of medication to relieve pain
- Administered in outpatients in c. 1 hour so less time in hospital than for other treatments
- Side effects are tolerable
- Makes access to further lines of treatment possible
- Innovative

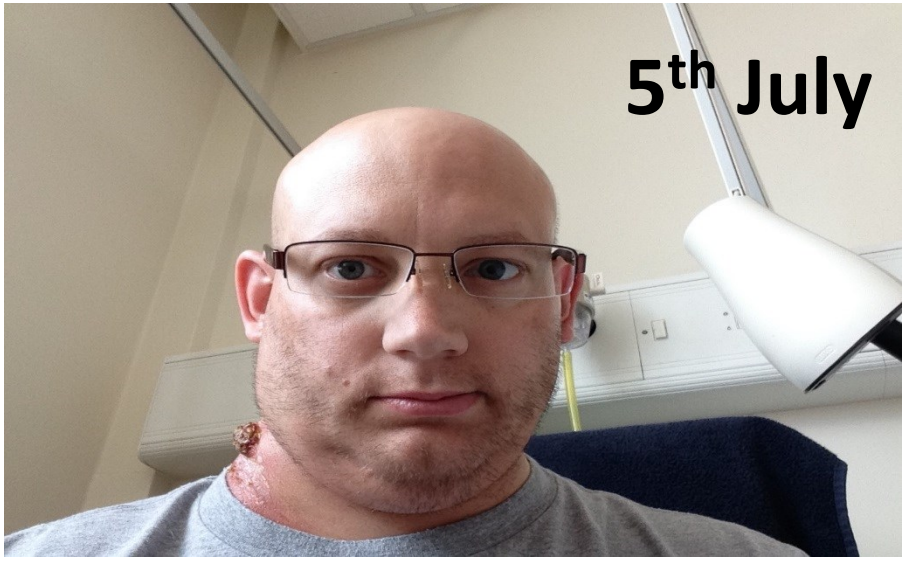
Patient photo diary

first brentuximab vedotin infusion on 1 July 2014









Clinical expert's comments

- Lack of clear consensus or strong evidence base on which to recommend second line therapies. Conventional salvage chemotherapy (e.g. ICE) is used, followed by either ASCT or allo-SCT; determined by clinician and patient preference influenced by a number of factors (e.g. patient age and fitness, nature and response to prior therapy(ies), donor availability and clinical trial options)
- Typically, patients with R/R sALCL have received treatment with brentuximab vedotin with 2 strategies in mind (according to individual patient and disease characteristics and guided by regional lymphoma MDT discussion)
  - brentuximab vedotin- first salvage therapy as a bridge to consolidation with either ASCT or allo-SCT.
  - Brentuximab vedotin- first salvage therapy without intention to consolidate with SCT but to deliver 16 cycles of brentuximab vedotin. This route supported evidence of ongoing response and tolerability.

NICE scope and decision problem compared with company submission

	NICE scope	Company submission
Population	People with relapsed or refractory systemic anaplastic large cell lymphoma	Patients with relapsed or refractory systemic anaplastic large cell lymphoma who have received at least one prior regimen with curative intent: • ALK-positive • ALK-negative *
Comparator	Established clinical management without brentuximab vedotin	Established clinical management without brentuximab vedotin
Outcomes	• Overall survival • Progression-free survival • Objective response rate • Complete response rate • Adverse effects of treatment • Health-related quality of life • Rate of stem cell transplantation	• As per NICE scope

*Marketing authorisation for brentuximab vedotin does not specify population based on ALK status

Company's clinical evidence

Company submission included:
Main evidence: SG035-0004 (prospective, single-arm, phase 2 study in patients with R/R sALCL) 5 data up-dates, 2 presented in company submission: • 16.8 months: primary end point data (Pro et al. 2012) • 71.4 months: for up to 5-years follow-up (Pro et al. 2016)
Supplementary evidence: Two retrospective case series • Gopal et al. 2014 • Chihara et al. 2015
Supplementary evidence : Three Named Patient Programme • Gibb 2013 • Lamarque 2016 • Pellegrini 2016
Mak et al. 2013 (study reporting outcomes for historical cohort of 153 patients identified in the British Columbia Cancer Agency Lymphoid Cancer database with nodal PTCLs who were R/R after primary therapy) Study used in the unadjusted indirect comparison for the economic modelling

SG035-0004 trial (Pro et al.)

Design	Multicentre, phase II, open-label, single arm 22 centres in the US, Canada and Europe (UK 1 centre, 3 participants)
Population (n=58)	Patients with relapsed or refractory sALCL after treatment failure of at least 1 prior therapy with curative intent; age ≥12 years (USA) or ≥18years (other countries)
Baseline characteristics	Median age 52 years, predominantly ALK-ve and chemo-refractory disease (72%). 50% considered refractory, 50% experienced relapse; 62% primary refractory to front-line treatment (i.e. no CR or relapse within 3 months of front-line therapy), 22% not achieved an ORR to any previous therapy. Median number of prior chemotherapy regimens excluding ASCT=2 (range 1-6 regimens); 26% had previous ASCT before study enrolment. Most recent therapy before study enrolment ASCT or multi-agent chemotherapy for 91% of patients
Intervention	Brentuximab vedotin 1.8 mg/kg every 3 weeks.
Treatment	Maximum 16 cycles (approximately 1 year) Median number of cycles 7 Among patients with an objective response, median number of cycles was 8
Outcomes	Outcomes assessed and reported by independent review facility (IRF) or investigator (INV) **Primary outcome**: ORR per independent review facility (IRF) (response criteria: Cheson 2007) **Secondary outcomes**: Duration of response per IRF, complete remission per IRF, PFS per IRF and OS
Follow-up	5 year; survival data reported at 3 and 4 year separately

SG035-0004 results: Per IRF (median follow-up 16.8 months)

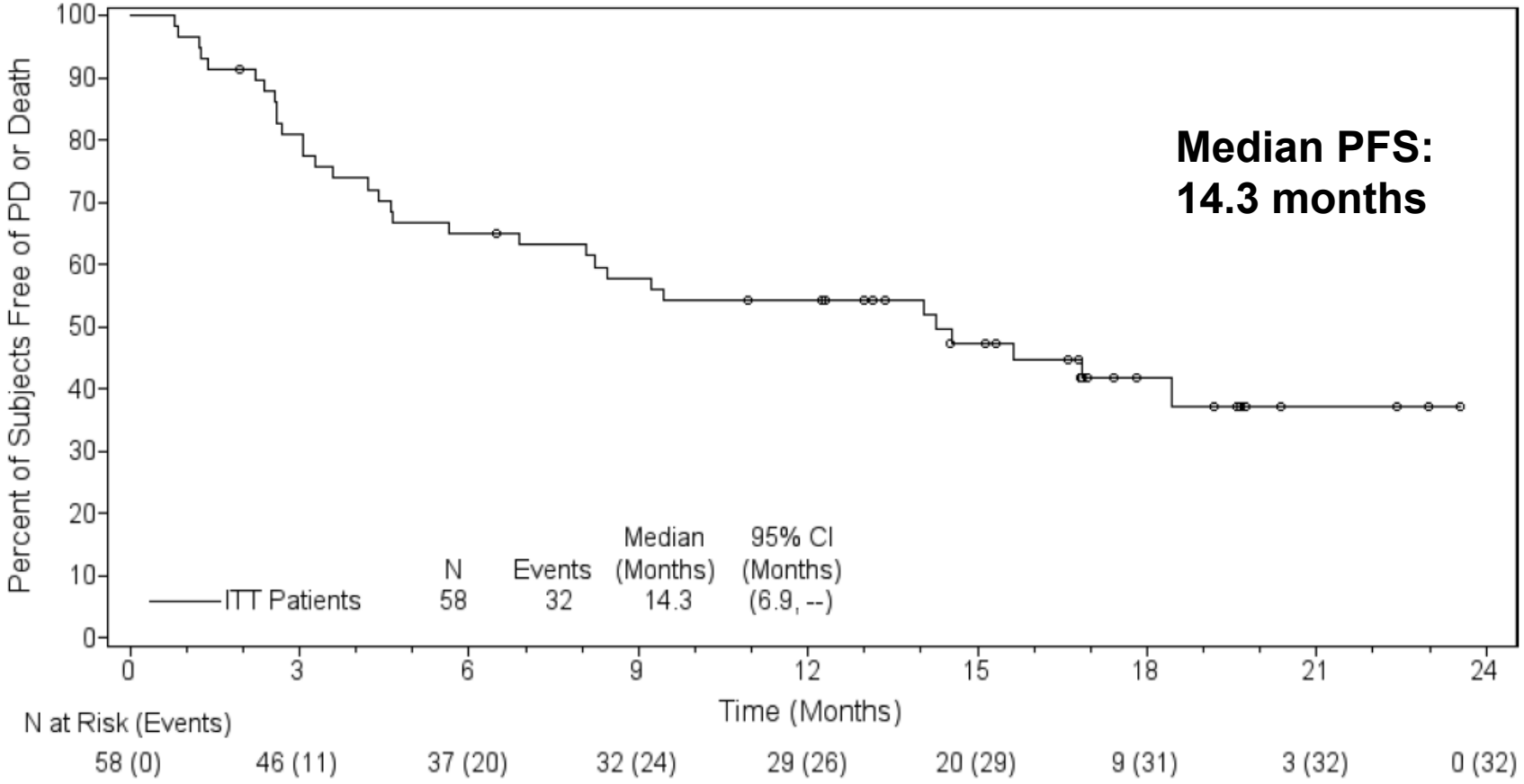
Best clinical response (N=58)	IRF N (%)	95% CI
Objective response rate (CR + PR)	50 (86)	74.6, 93.9
• Complete remission (CR)	34 (59)	44.9, 71.4
• Partial remission (PR)	16 (28)	NA
Disease control rate (CR+PR+SD)	52 (90)	78.8, 96.1
Duration of response	**Median per IRF**	**95% CI**
Objective response rate (CR + PR)*	13.2	5.7, NE
Complete remission (CR)	Not reached	13.0, NE
Overall survival	**Median**	**95% CI**
Median	Not reached**	21.3, NE

NE = Not estimable

* The range of DOR was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.

** The estimated 36 month overall survival was 63% (the median observation time (time to death or last contact) from first dose was 33.4 months

PFS: SG035-0004 (ITT set)
Per IRF (median follow-up 16.8 months)



Duration of response: SG035-0004
Per INV (median observation time 71.4 months)

ORR	86% (n=50/58)
CR	66% (38/58)
Of 38 CR patients:	
DOR	Not reached (95% CI: 20.0, -), range 0.9 to 79.7+ months
Median OS	Not reached
Median PFS	Not reached
Of 38 CR patients,16 underwent SCT after brentuximab vedotin:	
Type of SCT	8 allo SCT, 8 ASCT
Median OS	Not reached
Median PFS	Not reached
Of 38 CR patients, 22 did not receive SCT after brentuximab vedotin:	
Median OS	Not reached
Median PFS	39.4 months (95% CI: 14.3, -)
Of 38 CR patients, 16 still enrolled in trial and in remission without the start of new anticancer therapy, other than SCT	
Median observation	75.4 months (range 69 to 82.4).

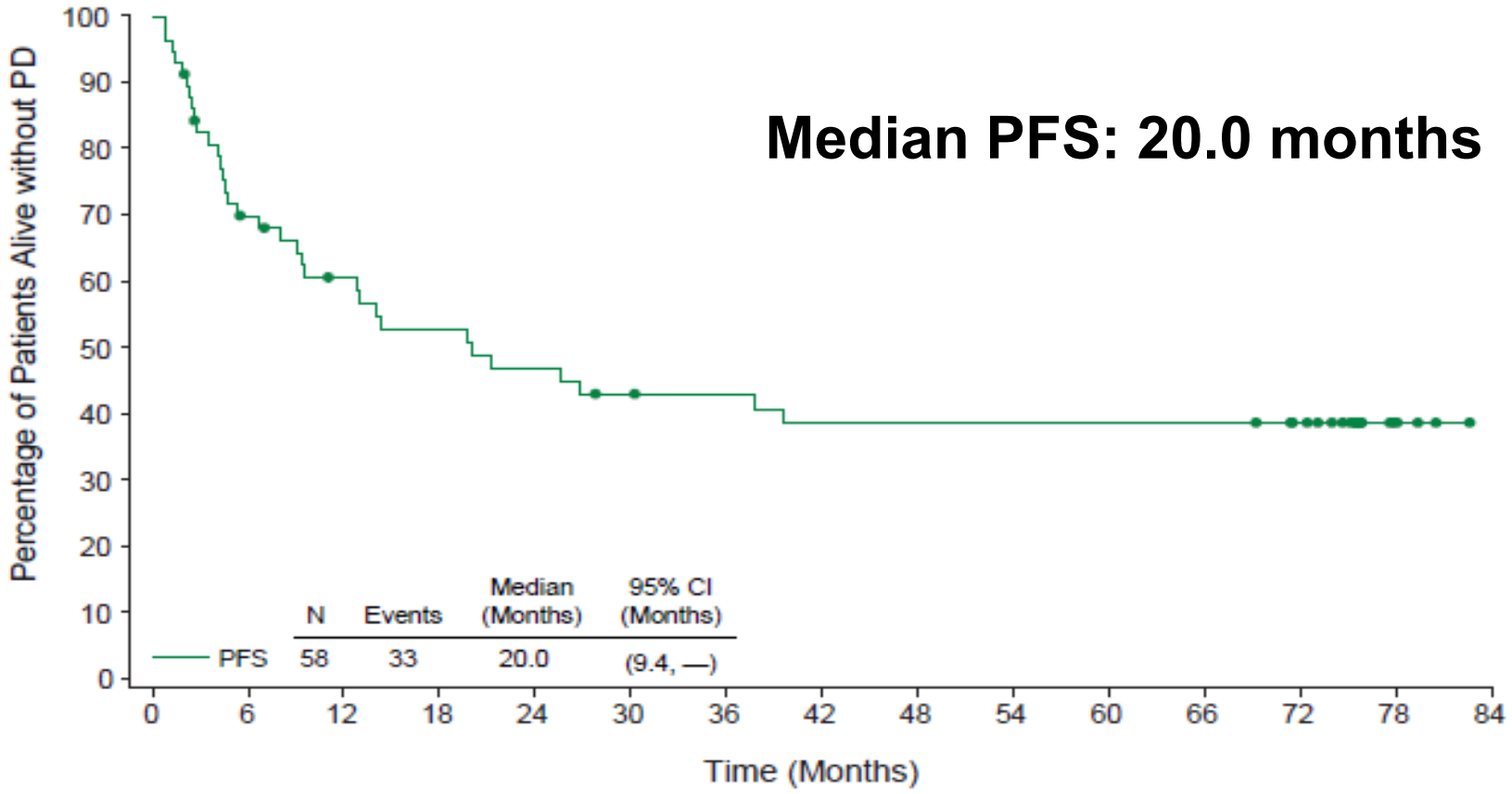
OS and PFS: SG035-0004
Per INV (all enrolled patients, median follow-up 5 years)

Overall population	
Estimated 5-year OS rate	60% (95% CI: 47, 73),
Median OS	Not estimable (95% CI: 21.3,-; range 0.8 to 82.4+ months)
Median PFS	20.0 months (95% CI: 9.4,-) *
Of 58 enrolled patients, 42 (72%) had ALK-ve disease:	
Estimated 5-year OS	61% (95% CI: 47%, 76%)
Median PFS	20 months (95% CI 6.7,-)
Median OS	Not reached**
Of 58 enrolled patients, 16 (28%) had ALK +ve disease:	
Estimated 5-year OS	56% (95% CI: 32%, 81%)
Median PFS	25.5 months (95% CI 8.0,-)
Median OS	Not reached**

* Median PFS in patients who achieved a CR has not been reached

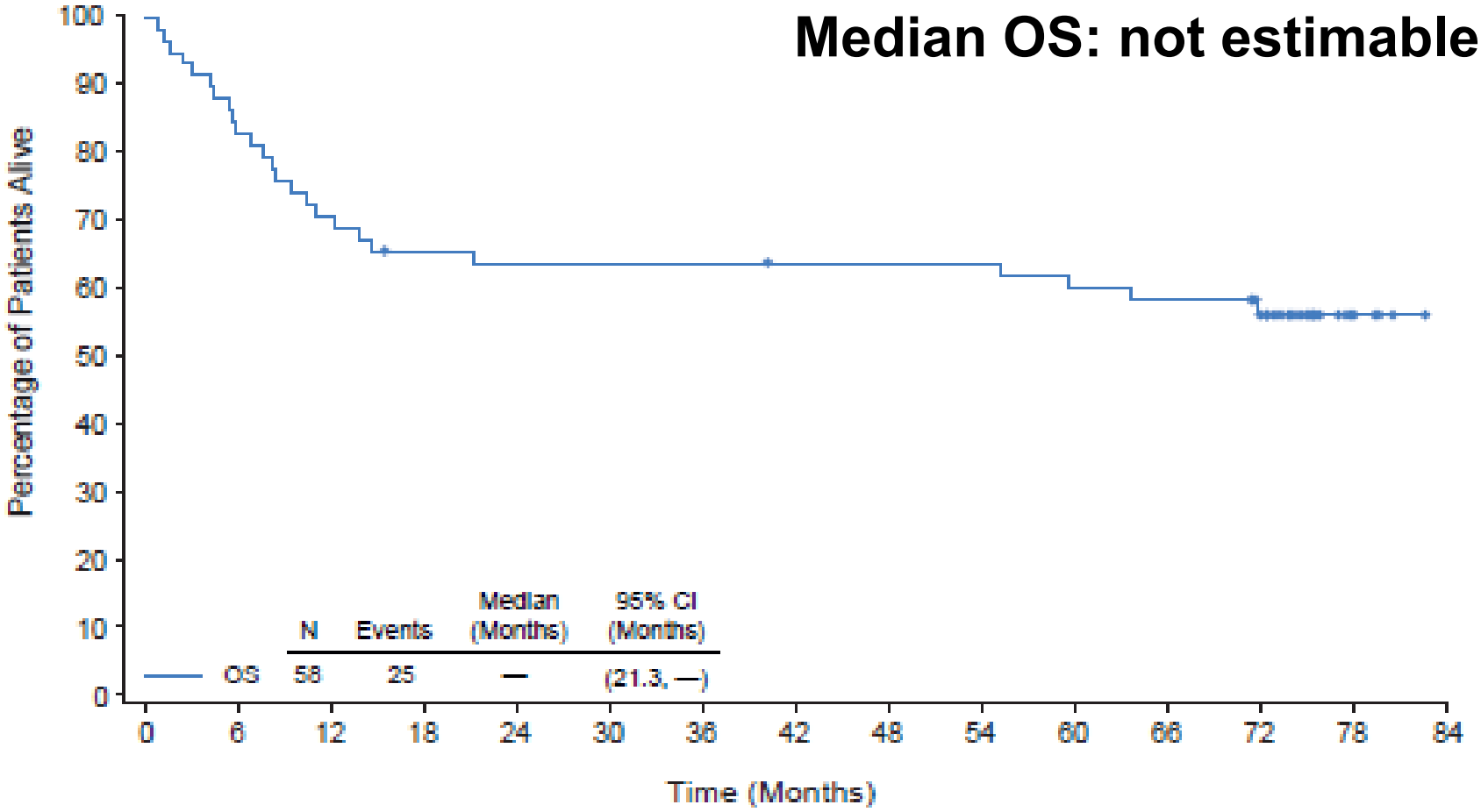
**16 patients still enrolled in study and in remission at study closure

PFS: SG035-0004
Per INV (median follow-up 5 years)

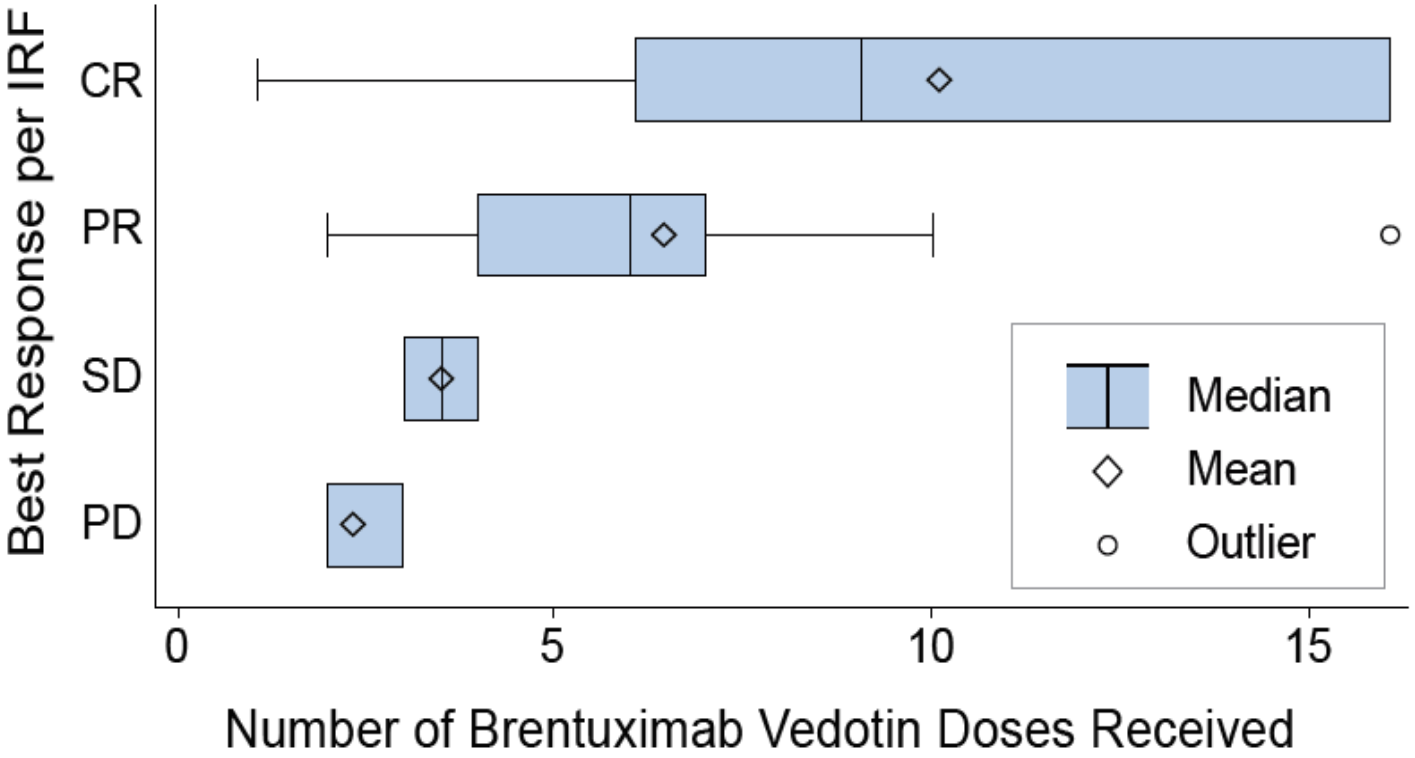


Median PFS: 20.0 months

OS: SG035-0004
Per INV (median follow-up 5 years)



Number of cycles of brentuximab vedotin: SG035-0004 Per INV (median observation time 71.4 months)



median number of brentuximab vedotin cycles administered to patients in SG035-0004 =7 (mean 8.2 cycles)

- Real word evidence from UK NPP show the number of cycles of brentuximab vedotin used in everyday clinical practice is less than in SG035-0004 trial; median of 5.5 cycles (range 1-13) for all population in the NPP

Indirect treatment comparison with chemotherapy (1)

- No data providing direct comparative evidence for brentuximab vedotin compared with chemotherapy.
- The company identified 2 studies through its systematic review; Mak et al. 2013 and Coiffier et al 2012
- The company focussed its submission on Mak et al. as the chemotherapy regimens administered were reflective of those used in clinical practice in the UK
- Mak et al. reported PFS and OS data for a historical cohort of 153 patients with PTCL on the British Colombia Cancer Agency Lymphoid Cancer database who had relapsed or experienced progressive disease
- The company focussed its analyses on a subset of Mak et al. who had received systemic chemotherapy (n=89). Median follow-up 4 years. None had received SCT

Indirect treatment comparison with chemotherapy (2)

- 2 subgroups of patients from tsubset of Mak et al. (n=89) informing PFS and OS for chemotherapy
  - ALCL (n=17)
  - PTCL and performance status <2 (n=47)
- The company undertook an unadjusted, indirect comparison of brentuximab vedotin with chemotherapy using a subgroup of patients from SG035-0004 who do not go on to receive SCT (n=41) and above subgroups from Mak et al.
  - unadjusted indirect comparison made because baseline characteristics of the subgroups in Mak et al. were not reported
- Company explored if matched adjusted indirect comparison (MAIC) between SG035-0004 and Mak et al. could be undertaken but noted the effective sample size for the MAIC would be 4.8
  - concluded it was inappropriate to undertake an MAIC.

ERG review: Indirect treatment comparison with chemotherapy

- ERG agreed that unadjusted, indirect comparison offers appropriate choice of comparison and MAIC inappropriate.
- ERG noted that while subgroup from Mak et al. with PTCL and performance status<2 not vastly different from subgroup with ALCL, it may contain a number of histologies with inherently different responses and survivals.
- ERG agreed with company that there was heterogeneity between the populations in SG035-0004 and Mak et al. particularly relating to age, stage of disease and performance status (all likely to bias in favour of brentuximab vedotin).
- However, ERG noted basing analysis on subgroup from Mak et al. with PTCL and performance status <2 (used in company's base case analysis for OS and as a sensitivity analysis for PFS), should improve comparability with SG035-0004
  - only 2% of patients in SG035-0004 had a performance status >2

NHS England (clinical lead for CDF) comments

- Main phase 2 study of brentuximab in R/R sALCL was in heavily pre-treated patients
- Complete remission rate high for brentuximab vedotin and achieved quickly, thus treatment is usually stopped after 4-6 cycles of treatment.
  - Mean number of cycles 8 in the phase II study and NHS England considers number will be less in practice in England.
- INV data more clinically relevant as assessment of response is not just on CT/PET scans but includes assessment of symptoms and findings from clinical examination. Only assessment of scans subject to IRF.
- Tail and plateauing on PFS and OS curves for brentuximab in SG035-0004 noteworthy and occur at higher survival levels than Mak et al. NHS England regards the benefits of brentuximab to be a step change in the management of R/R sALCL.
- License for brentuximab vedotin is limited to adults but R/R sALCL common in patients <18 years too. If brentuximab is recommended for sALCL within its marketing authorisation, NHS England would potentially wish to routinely commission its use in patients<18 years (subject to NHS England ascertaining the impact of such a decision on currently running clinical trials)

Key issues – clinical management and effectiveness

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