Title:

Five-year survival data from a pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma

Authors:

Pro B et al.

Journal:

ASH conference 2016

Five-Year Survival Data from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Barbara Pro[1], Ranjana Advani[2], Pauline Brice[3], Nancy L. Bartlett[4], Joseph D. Rosenblatt[5], Tim Illidge[6], Jeffrey Matous[7], Radhakrishnan Ramchandren[8], Michelle Fanale[9], Joseph M. Connors[10], Keenan Fenton[11], Dirk Huebner[12], Juan M. Pinelli[11], and Andrei Shustov[13]

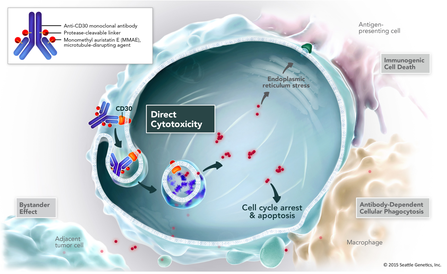
[1]Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [2]Stanford University Medical Center, Palo Alto, CA, USA; [3]Hospital Saint Louis, Paris, France; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL, USA; [6]Christie Hospital NHS, Manchester, UK; [7]Colorado Blood Cancer Institute, Denver, CO, USA; [8]Karmanos Cancer Institute, Detroit, MI, USA; [9]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]BC Cancer Agency Centre for Lymphoid Cancer, Vancouver, Canada; [11]Seattle Genetics, Inc., Bothell, WA, USA; [12]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceuticals Limited; [13]University of Washington Medical Center, Seattle, WA, USA

Background

- Systemic anaplastic large cell lymphoma (ALCL) is a CD30-expressing aggressive subtype of peripheral T-cell lymphoma (PTCL)
- Approximately 40% to 65% of systemic ALCL patients (pts) will develop recurrent disease after frontline treatment, with median progression-free survival (PFS) and overall survival (OS) after relapse of 3.1 and 5.5 months, respectively[a, b]
- A pivotal phase 2 study evaluated brentuximab vedotin (ADCETRIS®), a CD30-directed antibody-drug conjugate, in pts with relapsed or refractory (R/R) systemic ALCL (NCT00866047)
- The phase 2 study is now closed. After a 5-year follow-up period, the final end-of-study results are presented.

[a] Savage KJ. Hematology Am Soc Hematol Educ Program: 280-288; 2008
[b] Mak et al., J Clin Oncol 31: 1970-1976; 2013

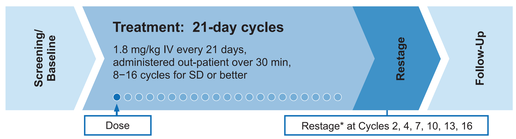
Primary Brentuximab Vedotin Mechanism of Action and Proposed Secondary Effects



Study Design

Eligibility

- Relapsed or refractory CD30+ sALCL
- Age ≥12 years
- Measurable disease ≥1.5 cm and FDG-avid
- ECOG 0–1



* Revised Response Criteria for Malignant Lymphoma (Cheson 2007), postbaseline PET scans obtained in Cycles 4 and 7 only

A phase 2, multicenter, open-label study of brentuximab vedotin in pts with R/R systemic ALCL

- The first pt was enrolled June 2009
- All pts completed treatment June 2011 and were followed for progression and survival until the end of study

Study Endpoints

- Primary: Overall objective response rate (ORR) by independent review facility (IRF)
- Secondary: Overall survival
- Additional (pre-specified): ORR and PFS by investigator

Results

Patient Baseline Characteristics (N=58)

Age, median (range)	52 yrs (14–76)
Gender (n)	33 M / 25 F
ECOG status, n (%)	
0	19 (33)
1	38 (66)
2	1 (2)
ALK negative, n (%)	42 (72)
Refractory to frontline therapy, n (%)	36 (62)
Refractory to most recent treatment, n (%)	29 (50)
Prior autologous stem cell transplant (SCT), n (%)	15 (26)

Efficacy (N=58)

	IRF*	Investigator
Objective response rate, n (%)	50 (86)	50 (86)
Complete remission (CR) rate, n (%)	34 (59)	38 (66)

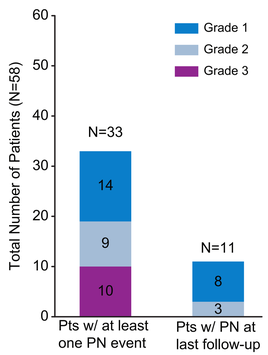
* Pro et al., J Clin Oncol 30: 2190–2196; 2012

Safety

- The most common (≥20%) treatment-emergent adverse events were peripheral neuropathy (PN), nausea, fatigue, pyrexia, diarrhea, rash, constipation, and neutropenia
- Adverse events of Grade 3 or higher that occurred in ≥5% of pts were neutropenia (21%), PN (17%), thrombocytopenia (14%), anemia (7%), fatigue (5%), and recurrent ALCL (5%)

Resolution of Peripheral Neuropathy

- 33 of 58 pts (57%) experienced PN[a], the majority of whom had symptoms ≤ Grade 2
  - 30/33 pts (91%) experienced complete resolution or some improvement of PN symptoms at last follow-up
    - 22/33 pts (67%) had complete resolution[b]
    - No Grade 3 PN events were observed at last follow-up
- The majority of pts with ongoing PN (8/11) had a maximum severity of Grade 1 at last follow-up
- For those PN events that resolved, the median time from onset to resolution was 14 weeks

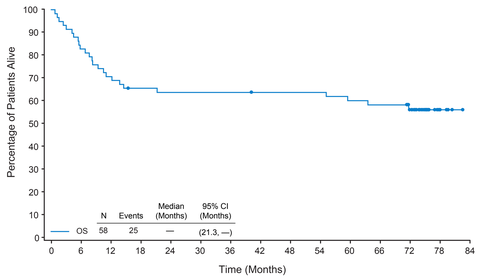


[a] Standardized MedDRA query (SMQ) analysis
[b] Resolution is defined as event status of resolved/recovered or resolved/recovered with sequelae; or return to baseline or lower severity as of the last follow-up

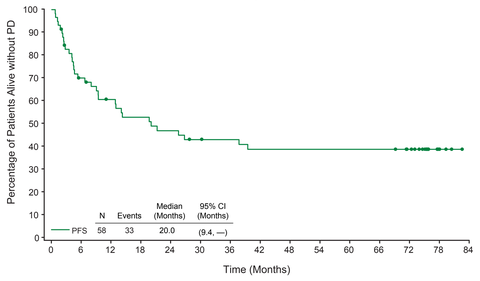
Long-Term Survival and Durability

- At study closure, which occurred approximately 5 years after the last pt's end-of-treatment visit, the median observation time for all enrolled pts was 71.4 months from first dose (range, 0.8 to 82.4)
- The estimated 5-year overall survival (OS) rate was 60% (95% CI: 47, 73), and the median OS was not estimable (95% CI: 21.3, –; range, 0.8 to 82.4+ months)
- The median progression-free survival (PFS) was 20.0 months (95% CI: 9.4, –)
- Of the 58 enrolled pts, 42 (72%) had ALK-negative disease
  - The estimated 5-year OS rate was 61% (95% CI: 47, 76) for ALK-negative pts and 56% (95% CI: 32, 81) for ALK-positive pts
  - Median PFS for ALK-negative and ALK-positive ALCL was 20 months (95% CI: 6.7, –) and 25.5 months (95% CI: 8.0, –), respectively, with the median OS not reached for each

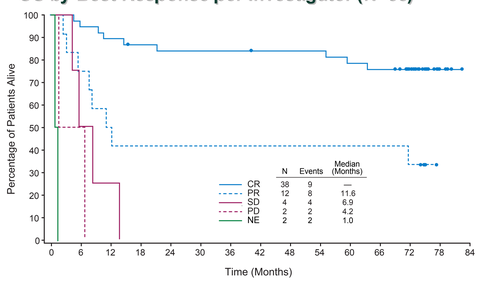
Overall Survival (N=58)



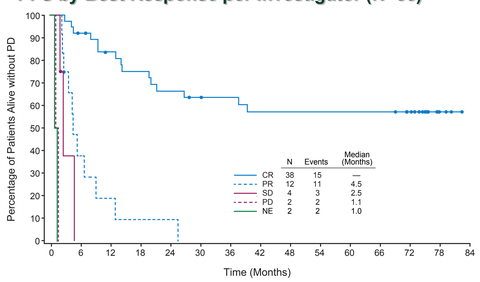
Progression-Free Survival (N=58)



OS by Best Response per Investigator (N=58)



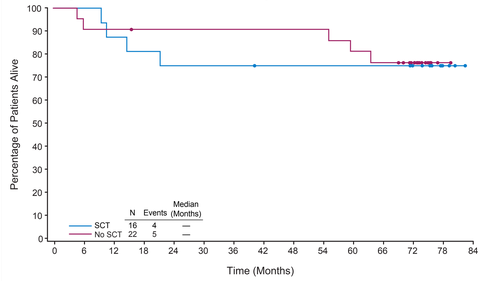
PFS by Best Response per Investigator (N=58)



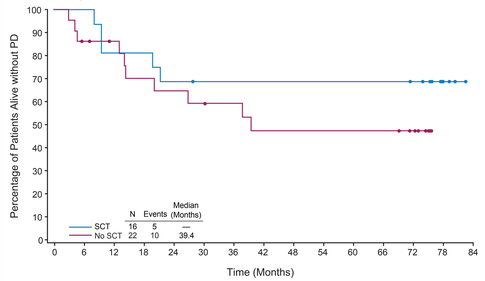
Patients Who Achieved CR Following Treatment with Brentuximab Vedotin (N=38)

- In the 38 pts who achieved CR with brentuximab vedotin, the median response duration was not reached (95% CI: 20.0, –) and ranged from 0.9 to 79.7+ months
- Of the 38 CR pts, 16 underwent consolidative SCT (8 allogeneic, 8 autologous) as the next therapy after brentuximab vedotin
  - Median OS and PFS were not reached in these pts who underwent subsequent SCT
- In the 22 pts with CR who did not receive SCT as consolidation, the median OS was not reached, and the median PFS was 39.4 months (95% CI: 14.3, –)

OS by Consolidative Transplant

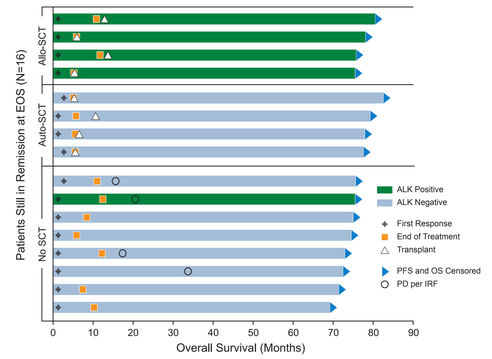


PFS by Consolidative Transplant



Patients in Follow-Up and in Remission at End of Study (N=16)

- Of the 38 pts who achieved CR, 16 pts (42%) were still on study and in remission at study closure without the start of new anticancer therapy, other than SCT
- The median observation time for the 16 pts still on study and in remission was 75.4 months (range, 69 to 82.4)



Baseline Characteristics of Patients with Best Response of CR

	CR and in remission at EOS (N=16)	All other CR (N=22)
Median age in years (range)	56 (14, 76)	50 (17, 74)
Female, n (%)	4 (25)	13 (59)
ECOG status, n (%)		
0	4 (25)	11 (50)
1	12 (75)	11 (50)
ALK negative, n (%)	11 (69)	17 (77)
Median time from initial diagnosis, months (range)	22 (6.2, 113.2)	20 (4.4, 186.5)
Stage III/IV at initial diagnosis, n (%)	6 (37)	10 (46)
Refractory to frontline therapy, n (%)	7 (44)	16 (73)
Refractory to most recent treatment, n (%)	5 (31)	11 (50)
Median baseline SPD, cm² (range)	14 (3.2, 76.8)	12 (2.0, 51.3)
Baseline bone marrow involvement, n (%)	0	2 (9)

SPD = sum of the product of diameters

Summary and Conclusions

- These end-of-study results, presenting over 5 years of follow-up data, demonstrate that among pts with R/R systemic ALCL, the majority of pts have achieved clinically significant durable remissions, and a subset may have been potentially cured with single-agent brentuximab vedotin
- Furthermore, associated toxicities are manageable, with high rates of improvement or resolution for peripheral neuropathy associated with brentuximab vedotin
- A randomized phase 3 trial (ECHELON-2) is ongoing to evaluate the combination of brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone for frontline treatment of CD30-expressing peripheral T-cell lymphomas, including systemic ALCL (NCT01777152)

Direct funding for this research was issued by Seattle Genetics, Inc. through the joint financial support of Seattle Genetics, Inc. and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals Limited. Seattle Genetics, Inc. provided research funding to the institutions of BP, RA, PB, NLB, JDR, TI, JM, RR, MF, JMC, and AS. BP, TI, and MF have acted as consultants for Seattle Genetics, Inc.; and MF has received honoraria from Seattle Genetics, Inc. JM and RR have participated in a Seattle Genetics, Inc. speakers' bureaus; and BP and MF have received travel expenses from Seattle Genetics, Inc. JP and KF are employees of and have equity ownership in Seattle Genetics, Inc. Takeda Pharmaceuticals Limited has provided research funding to the institution of PB. JM has participated in a speakers' bureau for Takeda Pharmaceuticals Limited, and TI has acted as a consultant for and received honoraria from Takeda Pharmaceuticals Limited. BP and PB have received honoraria from Takeda Pharmaceuticals Limited. BP has received travel expenses from Takeda Pharmaceuticals Limited. DH is an employee and has equity ownership in Takeda Pharmaceuticals Limited.

Abstract No. 4144
American Society of Hematology; December 3–6, 2016; San Diego, CA