Population Pharmacokinetics of Brentuximab Vedotin in Patients with CD30-Expressing Hematologic Malignancies

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Supplementary Table S1. Brentuximab Vedotin Sampling Timepoints for Studies in the Population PK Analysis

Study Description [clinicaltrials.gov no.]	Brentuximab Vedotin Dose Regimen	Patient Population	No. of Patients[a]	Brentuximab Vedotin PK Sampling Timepoints
Study 1 Phase 1 dose-ranging study [NCT00430846]	0.1 to 3.6 mg/kg IV Q3Wk (Day 1 of each 21-day cycle): 2-hr infusion	Relapsed/refractory CD30-expressing hematologic malignancies	48[b]	Cycle 1: pre-dose, 10 min, 2, 4, 8*, 12*, and 18 h* post EOI (Day 1); 24, 48*, 72, 96*, 168, 240*, and 336 h (Days 2, 3*, 4, 5*, 8, 11*, and 15) Cycle 2 & subsequent cycles: pre-dose, 10 min, 2 and 4 h post EOI (Day 1); 24, 72, 168, and 336 h (Days 2, 4, 8, and 15) Post-treatment: EOT and 28 days post EOT *Only patients enrolled in expansion cohorts
Study 2 Phase 1 dose-ranging study [NCT00649584]	0.4 to 1.4 mg/kg IV weekly (Days 1, 8, and 15 of each 28-day cycle): 2-hr or 30-min infusion[c]	Relapsed/refractory CD30-expressing hematologic malignancies	46[b]	Cycle 1: pre-dose, 10 min, 2 and 4 h post EOI (Day 1); 24 and 72 h (Days 2 and 4); pre-dose and 10 min post EOI (Days 8 and 15); and 168 h after Day 15 dose (Day 22) Cycle 2 & subsequent cycles: pre-dose and 10 min post EOI (Days 1, 8, and 15); 2 and 4 h post EOI (Day 15); 24, 72, and 168 h after Day 15 dose (Days 16, 18, and 22) Post-treatment: EOT and 28 days post EOT
Study 3 Phase 2 pivotal study in HL [NCT00848926]	1.8 mg/kg IV Q3Wk (Day 1 of each 21-day cycle): 30-min infusion	Relapsed/refractory HL; previous autologous stem cell transplant	102	Cycles 1 and 2: pre-dose and 10 min post EOI (Day 1); 24 and 336 h after dose (Days 2 and 15) Cycle 3 & subsequent cycles: pre-dose and 10 min post EOI (Day 1) Post-treatment: EOT

Study Description [clinicaltrials.gov no.]	Brentuximab Vedotin Dose Regimen	Patient Population	No. of Patients[a]	Brentuximab Vedotin PK Sampling Timepoints
Study 4 Phase 2 pivotal study in sALCL [NCT00866047]	1.8 mg/kg IV Q3Wk (Day 1 of each 21-day cycle): 30-min infusion	Relapsed/refractory sALCL; previous front-line chemotherapy	58	Cycles 1 and 2: pre-dose and 10 min post EOI (Day 1); 24 and 336 h after dose (Days 2 and 15) Cycle 3 & subsequent cycles: pre-dose and 10 min post EOI (Day 1) Post-treatment: EOT
Study 5 (Part A) Phase 1 clinical pharmacology study: drug-drug interactions[e] [NCT01026415]	1.2 mg/kg* or 1.8 mg/kg** IV Q3Wk (Day 1 of each 21-day cycle): 30-min infusion * ketoconazole arm ** midazolam and rifampin arms	Relapsed/refractory CD30-expressing hematologic malignancies	56[d]	Ketoconazole arm – Cycle 1: pre-dose and EOI post BV; 2, 4, 8, and 12 h after dose (Day 1); 24 and 36 h (Day 2); 48, 72, 96, 168, 240, 336, and 408 h (Days 3, 4, 5, 8, 11, 15, and 18) Midazolam arm – Cycle 1: pre-dose and EOI post BV (Day 1); 48 h after dose (Day 3) Rifampin arm – Cycle 1: pre-dose and EOI post BV; 2, 4, 8, and 12 h after dose (Day 1); 24 and 36 h (Day 2); 48, 72, 96, 168, and 240 h (Days 3, 4, 5, 8, and 11)
Study 5 (Part B) Phase 1 clinical pharmacology study: hepatic and renal impairment [NCT01026415]	1.2 mg/kg IV Q3Wk (Day 1 of each 21-day cycle): 30-min infusion	Relapsed/refractory CD30-expressing hematologic malignancies	4[d]	Cycle 1: pre-dose, EOI post BV, 2, 4, 8, and 12 h after dose (Day 1); 24 and 36 h (Day 2); 48, 72, 96, and 168 h (Days 3, 4, 5, and 8); and 240, 336, 408, and 504 h (Days 11, 15, 18, and 22[f]) Cycle 2: pre-dose

BV, brentuximab vedotin; EOI, end of infusion; EOT, end of treatment visit; HL, Hodgkin lymphoma; IV, intravenously; Q3Wk, every 3 weeks; sALCL, systemic anaplastic large cell lymphoma.

a Number of patients contributing to the population PK analyses.

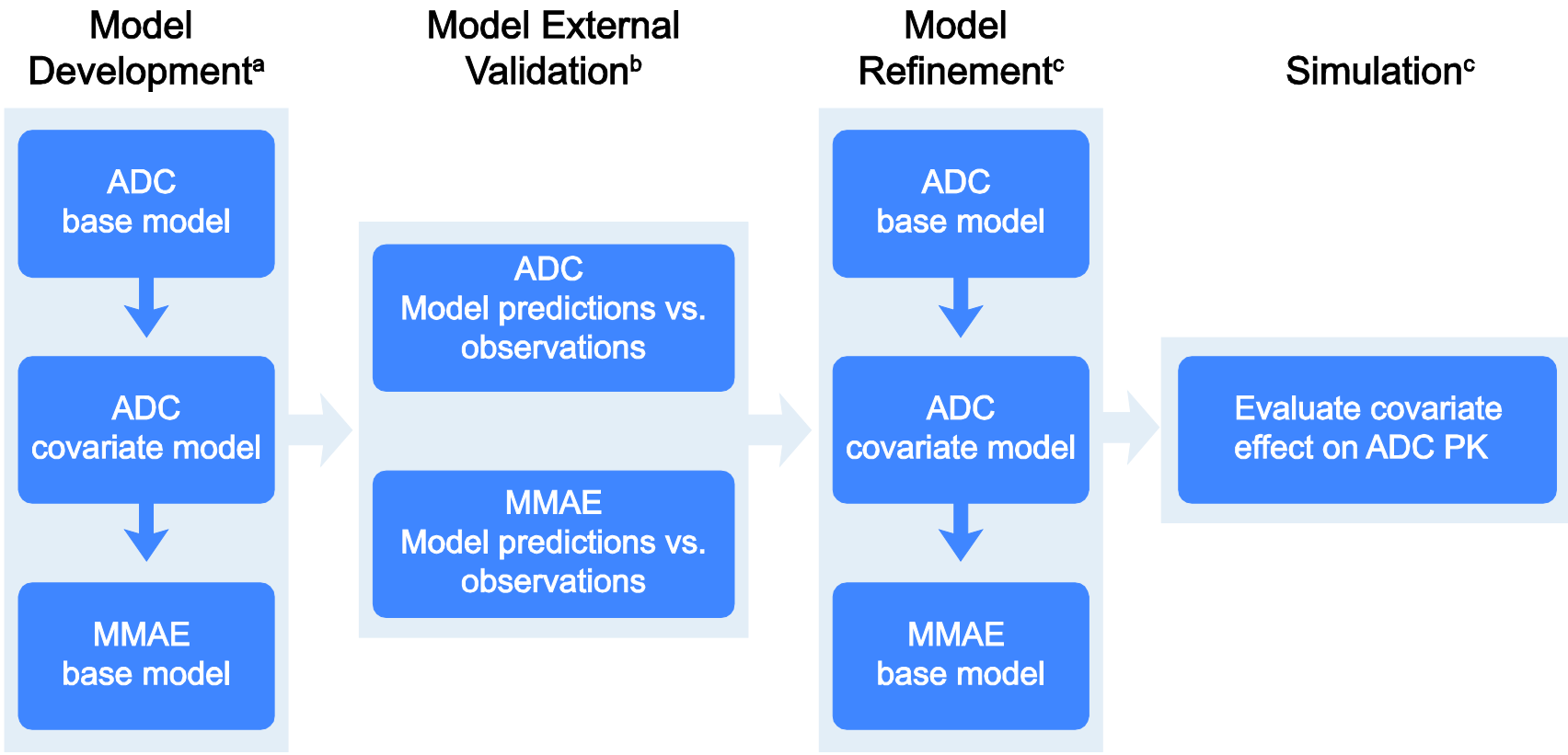
b Includes 5 patients who were re-enrolled with new patient numbers and retreated in Study 1 (n=3) or in Study 2 (n=2).

c Protocol amended to reduce infusion time.

d Study 5 included a total of 60 patients (56 patients from the drug-drug interaction portion of the study and 4 patients with renal impairment).

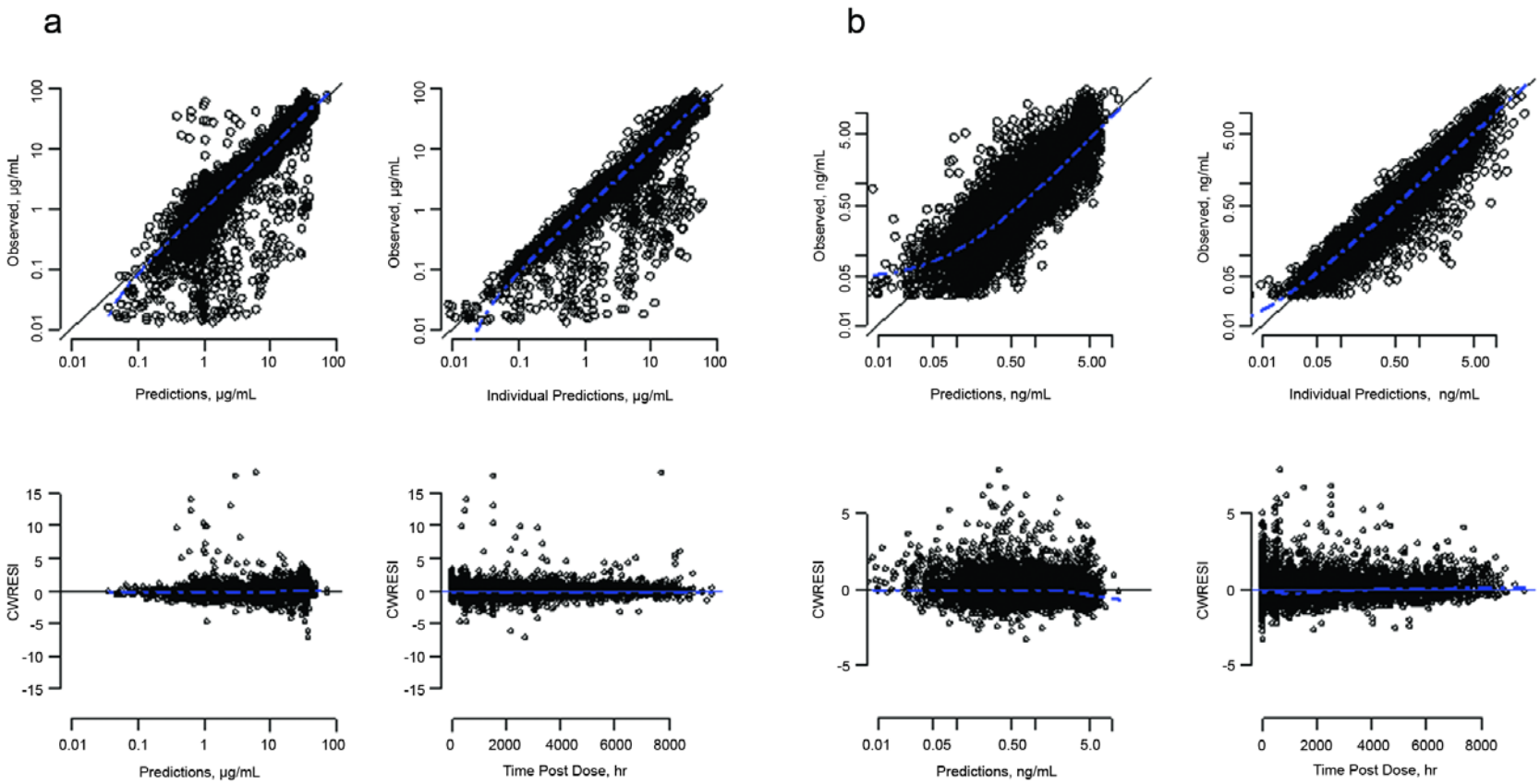
e For Study 5, concentration data that could have been affected by potential drug-drug interactions were excluded from the PopPK analysis.

f Day 22 of Cycle 1 only for patients who did not continue to Cycle 2.



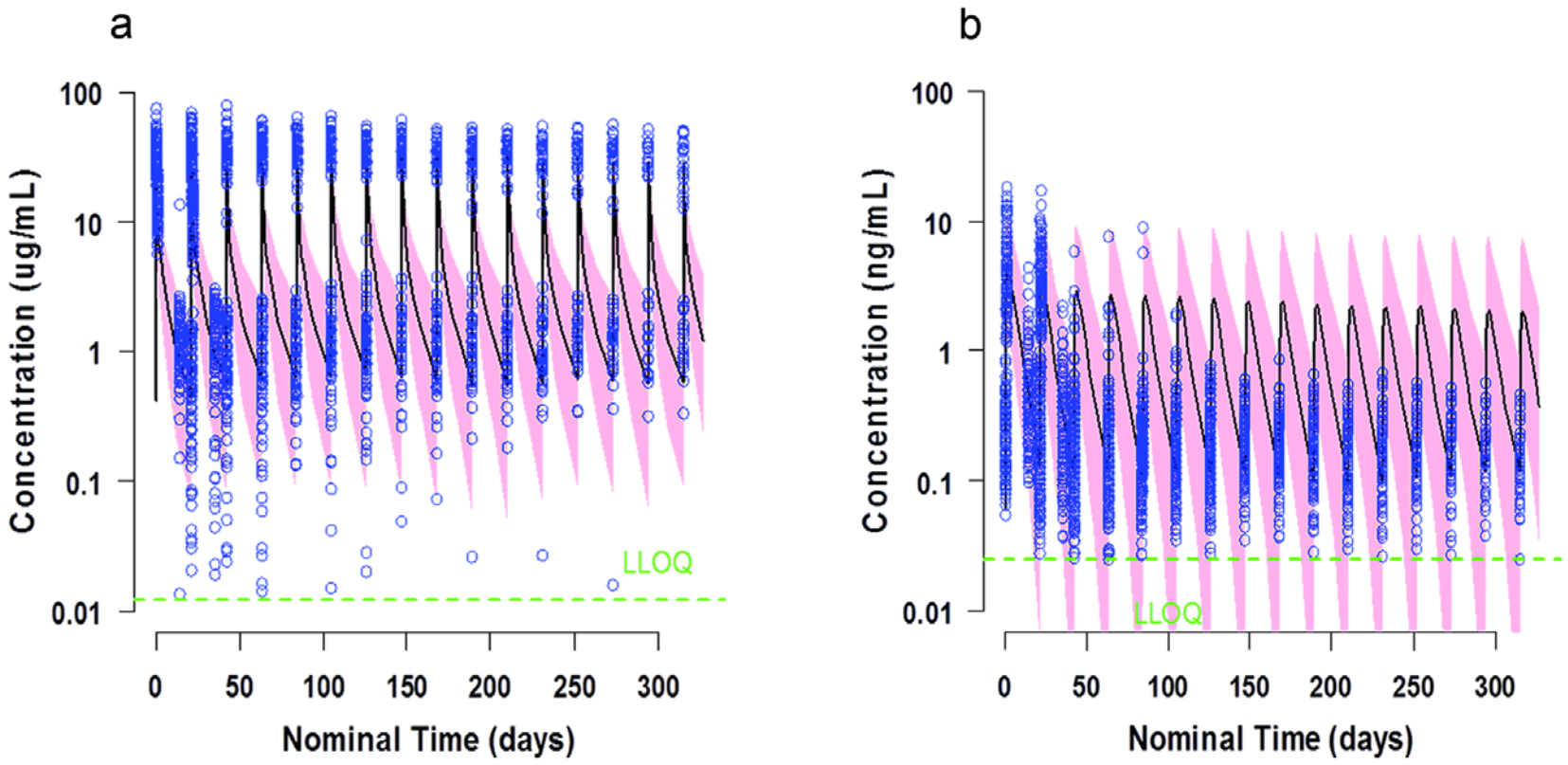
[a] Dataset for model building: Studies 1 and 2 (N=94 patients; 3677 ADC and 3796 MMAE concentrations)
[b] Dataset for model external validation: Studies 3, 4, and 5 (N=220 patients; 3404 ADC and 3656 MMAE concentrations)
[c] Dataset for model refinement and simulation: All five studies (N=314 patients; 7081 ADC and 7452 MMAE concentrations)

Supplementary Figure S1. Sequential Population PK Model Development



Supplementary Figure S2. Goodness-of-Fit Plots

Model predicted ADC (a) and MMAE (b) concentrations (population prediction and individual prediction) vs. observed concentrations for brentuximab vedotin administered IV at 1.8 mg/kg Q3Wk (Study 3); and conditionally weighted residuals with η-ε interaction (CWRESI) versus model predicted values and time postdose.



Supplementary Figure S3. Model External Validation

Model predicted ADC (a) and MMAE (b) concentrations vs. observed concentrations for brentuximab vedotin administered IV at 1.8 mg/kg Q3Wk (Study 3). Pink shaded area, 90% prediction interval; blue circles, observed data; green dotted line, lower limit of assay quantification (LLOQ).

Supplementary Material S1. NONMEM Code for the ADC and MMAE Population PK Model

```
 K10=CL/V1
 K12=Q2/V1
 K21=Q2/V2
 K13=Q3/V1
 K31=Q3/V3
 K40=CLM/V4
 K45=Q5/V4
 K54=Q5/V5

 FMC = CYCLE**FM  ;   FRACTION OF ADC CONVERTS TO MMAE BY CYCLE

$DES
 DAR=DAR0*(ALPHA + (1-ALPHA)*EXP(-BETA*(T-DTIME)))  ;
 DADT(1) = - (K10 + K12 + K13)*A(1) + K21*A(2)+ K31*A(3) ; ADC CENTRAL COMPT
 DADT(2) =   K12*A(1) - K21*A(2) ; ADC PERI COMPT -1
 DADT(3) =   K13*A(1) - K31*A(3) ; ADC PERI COMPT -2
 DADT(4) =   K10*A(1)*DAR*FMC + A(1)*(DAR-DAR0*ALPHA)*BETA-K40*A(4)-K45*A(4) + K54*A(5) ; MMAE CENTRAL COMPT
 DADT(5) =   K45*A(4) - K54*A(5)   ;MMAE PERI  COMPT

; Proteolytic pathway
 DADT(6) = K10*A(1)*DAR
; deconjugation pathway
 DADT(7) = A(1)*(DAR-DAR0*ALPHA)*BETA

$ERROR
; % contribution from deconjugation pathway
        DECON= A(7) / (A(6) + A(7)) *100
```

Supplementary Appendix S1. Clinical Study Sites and Institutional Review Boards

Principal Investigator	Study[a]	Clinical Study Site	Institutional Review Board
Advani, Ranjana	2 and 3	Stanford University Medical Center, Stanford, CA, US	Research Compliance Office, Stanford Administrative Panel on Human Subjects in Medical Research, Stanford, CA, US
Ansell, Stephen	3 and 4	Mayo Clinic, Rochester, MN, US	Mayo Clinic Institutional Review Board, Rochester, MN, US
Baccarani, Michele	3	Istituto di Ematologia ed Oncologia Medica, Bologna, Italy	Policlinico S. Orsola-Malpighi, Bologna, Italy
Bartlett, Nancy	1, 2, 3, and 4	Washington University School of Medicine, St. Louis, MO, US	Washington University School of Medicine, Human Research Protection Office, St. Louis, MO
Berryman, Robert Brian	3 and 4	Baylor University Medical Center, Dallas, TX, US	Baylor Research Institute, Dallas, TX, US
Blum, Kristie	3	James Cancer Hospital / Ohio State University, Columbus, OH, US	Western Institutional Review Board, Olympia, WA, US
Bouabdallah, Reda	3 and 4	Institut Paoli Calmettes, Marseille, France	CPP Île de France 3, Paris, France
Brice, Pauline	3 and 4	Service des Maladies du Sang / Hospital Saint Louis, Paris, France	CPP Île de France 3, Paris, France
Chen, Andy	4	Oregon Health and Science University / Center for Hematologic Malignancies, Portland, OR, US	Oregon Health & Science University Research Integrity Office, Portland, OR, US
Chen, Robert	3 and 5	City of Hope National Medical Center, Duarte, CA, US	City of Hope National Medical Center Institutional Review Board, Duarte, CA, US
Cheson, Bruce	3	Lombardi Cancer Center / Georgetown University Medical Center, Washington DC, US	MedStar Health Research Institute – Georgetown University Oncology Institutional Review Board, Washington DC, US
Cooper, Maureen	5	St. Francis Medical Group Oncology & Hematology Specialists, Indianapolis, IN, US	St. Francis Hospital and Health Center Institutional Review Board, Beech Grove, IN, US
Crump, Michael	3 and 4	University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada	University Health Network Research Ethics Board, Toronto, Ontario, Canada
de Vos, Sven	3	UCLA Medical Center / University of California at Los Angeles, Los Angeles, CA, US	UCLA Office for the Protection of Research Subjects, Los Angeles, CA, US

Principal Investigator	Study[a]	Clinical Study Site	Institutional Review Board
Elstrom, Rebecca	3 and 4	Weill Cornell Medical College, New York, NY, US	Institutional Review Board (Weill Cornell Medical College), New York, NY, US
Evens, Andrew	4	Northwestern University, Chicago, IL, US	Northwestern University Medical School - Office for the Protection of Research Subjects Institutional Review Board, Chicago, IL, US
Fanale, Michelle	2 and 4	MD Anderson Cancer Center / University of Texas, Houston, TX, US	The University of Texas, MD Anderson Cancer Center, Office of Protocol Research Houston, TX, US
Forero-Torres, Andres	1, 2, 3, and 4	University of Alabama at Birmingham, Birmingham, AL, US	Western Institutional Review Board, Olympia, WA, US
Friedberg, Jonathan	3	University of Rochester Medical Center, Rochester, NY, US	Western Institutional Review Board, Olympia, WA, US
Gopal, Ajay	3 and 5	Seattle Cancer Care Alliance / University of Washington Medical Center, Seattle, WA, US	Western Institutional Review Board, Olympia, WA, US
Goy, Andre	5	Hackensack University Medical Center, Hackensack, NJ, US	Western Institutional Review Board, Olympia, WA, US
Illidge, Tim	4	Christie Hospital NHS Foundation Trust, Manchester, United Kingdom	Central Manchester Research Ethics Committee, Manchester, United Kingdom
Leonard, John	1	Weill Cornell Medical College of Cornell University, New York, NY, US	Institutional Review Board (Weill Cornell Medical College), New York, NY, US
Link, Michael	4	Stanford Cancer Center, Palo Alto, CA, US	Research Compliance Office, Palo Alto, CA, US
Matous, Jeffrey	5	Rocky Mountain Cancer Centers, Denver, CO, US	HCA-HealthONE Institutional Review Board, Glendale, CO, US
Matous, Jeffrey	4	HCA HealthOne-Rocky Mountain Blood & Marrow Transplant Program, Denver, CO, US	Western Institutional Review Board, Olympia, WA, US
Maziarz, Richard	3	Center for Hematologic Malignancies / Oregon Health & Science University, Portland, OR, US	Oregon Health & Science University Research Integrity Office, Portland, OR, US
Moskowitz, Craig	3	Memorial Sloan Kettering Cancer Center, New York, NY, US	Institutional Review Board-Memorial Sloan Kettering Cancer Center, New York, NY, US
O'Connor, Owen	5	New York University Cancer Institute, New York, NY, US	New York University Medical Center Institutional Review Board
Oshefski, Randal Scott	4	Nationwide Children's Hospital, Columbus, OH, US	Nationwide Children's Hospital Institutional Review Board, Columbus, OH, US

Principal Investigator	Study[a]	Clinical Study Site	Institutional Review Board
Pro, Barbara	4	MD Anderson Cancer Center / University of Texas, Houston, TX, US	The University of Texas, MD Anderson Cancer Center, Office of Protocol Research Houston, TX, US
Ramchandren, Radhakrishnan	3, 4, and 5	Karmanos Cancer Institute / Wayne State, University, Detroit, MI, US	Wayne State University Human Investigation Committee, Detroit, MI, US
Rosenblatt, Joseph	3 and 4	University of Miami Hospital and Clinics, Miller School of Medicine, Miami, FL,, US	University of Miami Human Subjects Research Office, Miami, FL, US
Rosenblatt, Joseph	2	University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, US	Western Institutional Review Board, Olympia, WA, US
Savage, Kerry	3 and 4	British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, Canada	UBC BCCA Research Ethics Board, Vancouver, BC, Canada
Shustov, Andrei	4	Seattle Cancer Care Alliance / University of Washington Medical Center, Seattle, WA, US	Western Institutional Review Board, Olympia, WA, US
Smith, Scott	3	Cardinal Bernardin Cancer Center / Loyola University Medical Center, Maywood, IL, US	Loyola University Medical Center Institutional Review Board - Office of Research, Maywood, IL, US
Sweetenham, John	3	The Cleveland Clinic, Cleveland, OH, US	Case Cancer Institutional Review Board, Cleveland, OH, US
Termuhlen, Amanda	4	Nationwide Children's Hospital, Columbus, OH, US	Nationwide Children's Hospital Institutional Review Board, Columbus, OH, US
Tilly, Herve	3 and 4	Centre Henri Becquerel / Centre Regional de Lutte Contre le Cancer, Rouen, France	CPP Île de France 3, Paris, France
Trippett, Tanya	4	Memorial Sloan Kettering Cancer Center, New York, NY, US	Institutional Review Board-Memorial Sloan Kettering Cancer Center, New York, NY, US
Verhoef, Gregor	4	UZ Leuven, Leuven, Belgium	Commissie Medische Ethiek, Leuven, Belgium
Winter, Jane	4	Northwestern University, Chicago, IL, US	Northwestern University Medical School - Office for the Protection of Research Subjects Institutional Review Board, Chicago, IL, US
Younes, Anas	1 and 3	MD Anderson Cancer Center / University of Texas, Houston, TX, US	The University of Texas, MD Anderson Cancer Center, Office of Protocol Research Houston, TX, US

a Data were collected from November 2006 – July 2009 (Study 1), March 2008 – February 2010 (Study 2), February 2009 – August 2010 (Study 3), June 2009 – June 2011 (Study 4), and December 2009 – June 2010 (Study 5, Part A; Part B was ongoing at the time of the data extract).