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Phase I Study of the Anti-CD22 Antibody–Drug Conjugate Pinatuzumab Vedotin with/without Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma

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Abstract

Purpose: Pinatuzumab vedotin is an antibody–drug conjugate with the potent antimicrotubule agent monomethyl auristatin E (MMAE) conjugated to an anti-CD22 antibody via a protease-cleavable linker. This phase I study determined its recommended phase II dose (RP2D) and evaluated its safety, tolerability, and antitumor activity alone and with rituximab in relapsed/refractory (r/r) non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL).

Experimental Design: Patients received escalating doses of pinatuzumab vedotin every 21 days. Clinical activity at the RP2D alone or with rituximab was evaluated in r/r diffuse large B-cell lymphoma (DLBCL) and r/r indolent NHL (iNHL) patients.

Results: Seventy-five patients received single-agent pinatuzumab vedotin. The RP2D was 2.4 mg/kg, based on dose-limiting toxicities (DLT) of grade 4 neutropenia >7 days in 1 of 3 patients and grade 4 neutropenia <7 days in 2 of 3 patients treated at 3.2 mg/kg (maximum assessed dose). No DLTs occurred at 2.4 mg/kg. At the RP2D, neutropenia was the most common grade $\geq$3 adverse event. Peripheral neuropathy–related grade $\geq$2 adverse events most frequently resulted in treatment discontinuation. Rituximab cotreatment did not impact safety, tolerability, or pharmacokinetics of pinatuzumab vedotin. Unconjugated MMAE exposure was much lower than antibody-conjugated MMAE exposure, without accumulation with repeat dosing. At the RP2D, objective responses were observed in DLBCL (9/25) and iNHL (7/14) patients; 2 of 8 patients treated with pinatuzumab vedotin (RP2D) and rituximab had complete responses. CLL patients showed no objective responses.

Conclusions: The RP2D of pinatuzumab vedotin alone and with rituximab was 2.4 mg/kg, which was well tolerated, with encouraging clinical activity in r/r NHL. *Clin Cancer Res; 23(5); 1167–76. ©2016 AACR.*

Introduction

Despite improvements in outcomes of patients with B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL), many patients experience disease recurrence or progression. Such patients have incurable disease requiring repeated courses of treatment, with survival ranging from less than 1 year for diffuse large B-cell lymphoma (DLBCL; ref. 1) to several years for indolent NHL (iNHL; refs. 2, 3). Treatments that significantly extend disease-free intervals and overall survival with minimal treatment-associated toxicity continue to be an unmet need.

Antibody–drug conjugates (ADC) directed against tumor-associated surface antigens provide targeted delivery of chemotherapy, with the goal of improving potency while reducing systemic cytotoxic effects.

CD22 is an accessory molecule that plays a role in B-cell antigen receptor signaling and is expressed on mature B cells, more than 95% of B-cell NHL, as well as in CLL (ref. 4; Genentech, data on file). The lineage specificity of CD22 makes it an attractive target for antibody-based therapeutics. Epratuzumab, a mAb targeting CD22, relies on antibody-dependent cellular cytotoxicity (ADCC) for antitumor activity, similar to rituximab. It has been tested clinically, has an acceptable safety profile and single-agent activity in patients with DLBCL and iNHL (5, 6), and is combinable with standard anti-lymphoma treatment regimens (7).

ADCs targeting CD22 internalize upon binding to the target, which is considered essential for ADC activity, and have demonstrated preclinical antitumor activity (8). Pinatuzumab vedotin

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Translational Relevance

Pinatuzumab vedotin is an antibody–drug conjugate targeting CD22 on B cells and containing the potent antimicrotubule agent MMAE. In this phase I study, clinical activity of pinatuzumab vedotin was observed in heavily pretreated patients with advanced non-Hodgkin lymphoma (NHL). In addition, evaluating the combination of pinatuzumab vedotin with rituximab administered at standard doses and schedules was feasible. Overall, this study demonstrates the feasibility of antibody–drug conjugates to deliver cytotoxic chemotherapy to tumors and further validates CD22 as a target suitable for an antibody–drug conjugate. The safety, tolerability, and clinical activity of pinatuzumab vedotin with rituximab has important implications for the ability of antibody–drug conjugates to be combined with standard anticancer treatment regimens in B-cell malignancies, and support further clinical investigation of these novel therapeutic combinations.

is an ADC consisting of the microtubule-disrupting agent, monomethyl auristatin E (MMAE), conjugated to an anti-CD22 mAb via the protease-cleavable peptide linker maleimidocaproylvaline-citrulline(vc)-p-aminobenzoyloxycarbonyl (9–11). MMAE has a mode of action similar to vincristine, which is commonly used to treat NHL and is the cytotoxic component of the anti-CD30–targeting ADC, brentuximab vedotin, which is approved for the treatment of Hodgkin lymphoma and systemic anaplastic large-cell lymphoma (12). While the unconjugated antibody of pinatuzumab vedotin demonstrated modest activity against tumor xenografts in mouse models of NHL, suggestive of some level of ADCC and/or complement-dependent cytotoxicity, tumor regression was significantly more pronounced with treatment with the ADC format (13). Together, these data supported the clinical feasibility of a CD22-directed ADC for the treatment of B-cell malignancies.

The goals of this multicenter, open-label phase I study were to identify the recommended phase II dose (RP2D) and investigate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of pinatuzumab vedotin in patients with NHL and CLL.

Materials and Methods

Study design and patients

This phase I, multicenter, open-label study employed a 3 + 3 dose-escalation design to determine the MTD. Eight centers enrolled patients with relapsed/refractory (r/r) diffuse DLBCL, iNHL (including follicular lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma), mantle cell lymphoma (MCL), and CLL, and for whom no suitable therapy of curative intent or higher priority existed. Demonstration of tumor CD22 expression was not required. Eligibility criteria included: age $\geq$18 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; measurable disease; adequate end-organ function as assessed by standard laboratory chemistries and hematology tests; no prior antibody or ADC within 4 weeks; no radiotherapy, chemotherapy, or investigational treatment within two weeks prior to the first dose of pinatuzumab vedotin; no prior allogeneic stem cell transplant; no autologous stem cell transplant within 100 days of first study treatment administration; no history of central nervous system lymphoma; grade $\leq$1 peripheral neuropathy.

The protocol was approved by institutional review boards prior to patient recruitment and was conducted in accordance with International Conference on Harmonization (ICH) E6 Guidelines for Good Clinical Practice. All patients signed an informed consent prior to enrollment. This study is registered on ClinicalTrials.gov as NCT01209130.

Procedures

Pinatuzumab vedotin (Genentech, Inc.) was administered intravenously over 30–90 minutes in 21-day cycles, with the starting dose of 0.1 mg/kg based on preclinical toxicology and pharmacokinetic data of pinatuzumab vedotin in cynomolgus monkeys (Genentech, Inc.; data on file). Patients were monitored during the first cycle for dose-limiting toxicities (DLT) defined as: grade $\geq$3 nonhematologic toxicity, excluding nausea or vomiting in the absence of premedication or that could be medically managed; febrile neutropenia; grade $\geq$3 neutropenia without recovery by at least one grade/week in the absence of growth factor support (growth factor support was permitted beyond the first cycle); grade $\geq$3 thrombocytopenia without recovery by at least one grade/week in the absence of bleeding, associated with bleeding, or requirement for platelet transfusion. The highest dose where <33% of a minimum of 6 patients experienced a DLT was designated as the MTD. The RP2D was determined on the totality of the data observed in the dose-escalation cohorts, including pharmacokinetics, DLTs, safety, and tolerability. Decisions regarding dose escalation were not made until all patients enrolled in the dose-escalation cohort, regardless of number, were evaluated through the DLT observation period. In the absence of toxicities, intrapatient dose escalation to the highest cleared dose level was permitted.

Indication-specific expansion cohorts (r/r DLBCL and r/r iNHL) were enrolled to further assess the safety and tolerability and to preliminarily assess efficacy of pinatuzumab vedotin at the RP2D. An additional cohort was enrolled to receive pinatuzumab vedotin at the RP2D combined with rituximab (375 mg/m^2) every 21 days.

Study treatment (single-agent pinatuzumab vedotin or pinatuzumab vedotin plus rituximab) was continued until progression of disease, unacceptable toxicity, or patient or physician decision. Following documented disease progression, patients were followed until resolution or stabilization of treatment-emergent adverse events (AE). Patients who discontinued study treatment for reasons other than progression of disease were followed for response and survival for up to one year. For patients with treatment-emergent grade 3–4 non-neuropathic AEs and grade 2–3 peripheral sensory neuropathy AEs, treatment delays of up to two weeks were permitted. Patients were permitted to resume treatment at the end of two weeks upon resolution of the AE(s). In these cases, patient doses were reduced to a previously established dose level. Rituximab dose modifications were not permitted.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE 2014). Adverse events were coded to preferred terms as defined by the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory monitoring (hematology and serum chemistries) was conducted at least weekly for the first four cycles,

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then on day 1 and day 15 of each cycle thereafter. Investigator-based assessments of antitumor activity using CT, CT-positron emission tomography (PET), or MRI scans, in accordance with standard response criteria for NHL (14) or CLL (15), were conducted every three months, independently of treatment schedule.

The pharmacokinetic profile of pinatuzumab vedotin was characterized by analysis of serum total antibody (TAb; including conjugated and deconjugated antibody) and rituximab, as measured by a validated ELISA (Genentech, Inc.; data on file); and plasma conjugate [antibody-conjugated MMAE (acMMAE)] and unconjugated MMAE as measured by validated LC/MS-MS (Genentech, Inc.; data on file). Pharmacokinetic parameters were derived using noncompartmental analysis (WinNonlin, Version 5.2.1; Pharsight). Antitherapeutic antibodies (ATA) were measured in serum by validated ELISA (Genentech, Inc.; data on file) and further characterized by competitive binding with unconjugated anti-CD22 antibody to determine whether responses were primarily directed against the antibody or the linker-drug portion of the ADC.

Outcomes

The primary objectives were to evaluate the safety and tolerability of pinatuzumab vedotin administered every 21 days in patients with r/r NHL and CLL, determine the MTD and DLTs of pinatuzumab vedotin, identify an RP2D for pinatuzumab vedotin, and assess the safety and tolerability of pinatuzumab vedotin combined with rituximab in patients with r/r NHL. Secondary objectives were to characterize the pharmacokinetics of pinatuzumab vedotin, determine the incidence of ATAs, and preliminarily evaluate antitumor activity per standard response criteria (14, 15).

Statistical analysis

Sample-size determinations were not based on explicit power and type I error assumptions, but rather to obtain sufficient safety, antitumor activity, and pharmacokinetic data to inform subsequent clinical testing of pinatuzumab vedotin. Planned enrollment of 30–50 patients during dose escalation was based upon the assumption that 5–8 cohorts containing 3–6 patients each would be enrolled, with allowances for patient replacement. An objective response rate (ORR) $\geq$30% with single-agent pinatuzumab vedotin would be viewed as encouraging. For an ORR $\geq$30%, the probability of observing $\geq$2 responses among 10 patients is $\geq$85% and the probability of observing $\geq$4 responses among 20 patients is $\geq$89%. Together, the total planned sample size for escalation and expansion was 80–100 patients.

Patients who received any amount of pinatuzumab vedotin were evaluable for safety analyses. Patients with baseline measurable disease and at least one post-baseline tumor assessment following pinatuzumab vedotin treatment were evaluable for efficacy analyses. Progression-free survival (PFS) and duration of response (DOR) were analyzed by the Kaplan–Meier method and were defined as the time from the first day of study treatment and response, respectively, to disease progression or death. In the absence of progressive disease, death, or loss to follow-up, PFS and DOR were censored for survival analysis at the day of the last tumor assessment.

Statistical analyses were conducted using SAS, version 9.2 (SAS Institute).

Results

Patient enrollment, treatment, and DLT determination

Between October 26, 2010 and December 12, 2012, 91 patients were enrolled into the study (Supplementary Fig. S1; Supplementary Table S1). Seventy-five patients were treated with single-agent pinatuzumab vedotin and 16 patients were treated with pinatuzumab vedotin combined with rituximab. Patient baseline and disease characteristics are shown in Table 1.

Thirty-two NHL patients were treated with single-agent pinatuzumab vedotin at dose levels of 0.1, 0.25, 0.5, 1.0, 1.8, 2.4, and 3.2 mg/kg. One DLT of grade 4 neutropenia with delayed recovery was observed among 3 evaluable patients treated at the 3.2-mg/kg dose level. The other two patients treated at the 3.2-mg/kg dose level experienced grade 4 neutropenia with recovery occurring in fewer than 7 days. On the basis of these observations, while 3.2 mg/kg did not exceed the protocol-defined MTD, no further dose escalation was tested. None of the 6 patients treated in the 2.4 mg/kg dose escalation cohort experienced a DLT. Consequently, 2.4 mg/kg every 21 days was designated the RP2D in r/r NHL. Thirty-nine NHL patients were treated with single-agent

Table 1. Baseline demographics and disease characteristics

Demographics (N = 91 patients)	DLBCL (n = 47)	iNHL (n = 31)	MCL (n = 3)	CLL (n = 10)
Median age (years)	66.0 (30–89)	64.0 (35–87)	72.0 (50–73)	72.5 (63–81)
Sex				
Female	23 (48.9%)	15 (48.4%)	0	2 (20.0%)
Male	24 (51.1%)	16 (51.6%)	3 (100.0%)	8 (80.0%)
ECOG performance status				
0	15 (31.9%)	17 (54.8%)		3 (30.0%)
1	29 (61.7%)	12 (38.7%)	2 (66.7%)	5 (50.0%)
2	3 (6.4%)	2 (6.5%)	1 (33.3%)	2 (20.0%)
Number of previous systemic therapies				
1	7 (14.9%)	3 (9.7%)	0	1 (10.0%)
2	11 (23.4%)	3 (9.7%)	0	0
$\geq$3	29 (61.7%)	25 (80.6%)	3 (100.0%)	9 (90.0%)
Previous stem-cell transplantation	5 (10.6%)	5 (16.1%)	0	0
Refractory to last therapy[a]	34 (82.9%)	21 (77.8%)	2 (100.0%)	4 (57.1%)
Previous radiotherapy	15 (31.9%)	9 (29.0%)	1 (33.3%)	0
Previous rituximab therapy (at any timepoint)	47 (100.0%)	31 (100.0%)	3 (100.0%)	10 (100.0%)

NOTE: Data are median (range) or n (%).

[a]Defined as progression on or within six months of last dose of last previous therapy.

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pinatuzumab vedotin at the RP2D, including 25 with DLBCL and 14 with iNHL (including one patient with transformed follicular lymphoma), with a median of 5 cycles (range 1–19) for DLBCL patients and a median of 5 cycles (range 1–27) for iNHL patients.

A total of 16 patients received pinatuzumab vedotin in combination with rituximab; 5 patients received pinatuzumab vedotin at 1.8 mg/kg and 11 received pinatuzumab vedotin at 2.4 mg/kg. No DLTs were observed in any patient; 2 patients who were enrolled to receive pinatuzumab vedotin at 2.4 mg/kg were not evaluable for DLTs because of clinical disease progression during the DLT observation period. Patients receiving the combination received a median of 5.5 cycles (range 1–24).

Ten patients with CLL were treated with pinatuzumab vedotin at 1.0, 1.8, and 2.4 mg/kg. No DLTs were observed. Because enrollment of CLL patients was terminated by the sponsor, the MTD was not formally determined.

Safety

Treatment-emergent AEs with single-agent pinatuzumab vedotin by assigned dose level and histology and grade 3–5 treatment-emergent AEs with single-agent pinatuzumab vedotin across all dose levels and histologies (NHL and CLL), regardless of attribution to the study drug by the treating physician, are shown in Supplementary Table S2.

Most AEs reported in the 39 NHL patients treated at the RP2D (2.4 mg/kg) were grade 1–2 in severity (Fig. 1). Twenty-seven (69%) patients reported grade 3–4 adverse events; the most common in ≥2 patients included neutropenia, fatigue, peripheral sensory neuropathy, hyperglycemia, and anemia. Grade 3 febrile neutropenia was reported in one patient. Serious AEs were reported in 13 (33%) NHL patients. Pyrexia was reported in 3 patients and dyspnea in 2 patients; otherwise, no single serious AE was reported in ≥2 patients. Thirteen (33%) patients discontinued pinatuzumab vedotin treatment due to an AE. Peripheral neuropathy–related AEs led to treatment discontinuation in 11 patients (peripheral sensory neuropathy in 7 patients, peripheral motor neuropathy in 2 patients, peripheral sensorimotor neuropathy and undefined in one patient each); no other AE led to treatment discontinuation in >1 patient. Sixteen (41%) patients had at least one dose delay due to an adverse event. Nine patients had a dose reduction to 1.8 mg/kg: 6 for peripheral neuropathy and 1 each for neutropenia, pancreatitis, and fatigue.

Among the 10 patients with CLL who were treated with pinatuzumab vedotin across all assessed dose levels, 3 patients had a grade 3 event, one patient had a grade 4 event and one patient had a grade 5 event of progressive disease. No single grade 3–5 event was reported in more than one patient. With the exception of the patient who discontinued due to grade 5 progressive disease, no

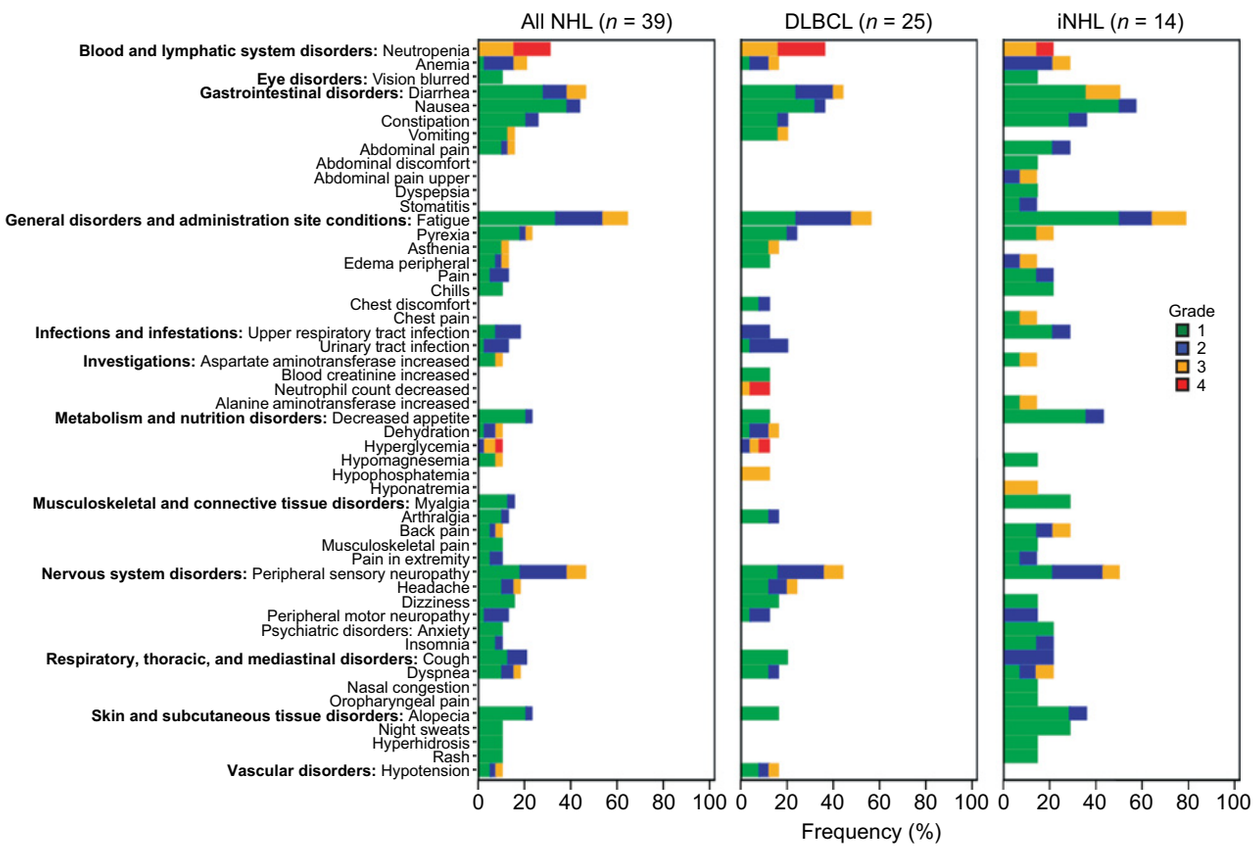

Figure 1.

Incidence of >10% of all treatment-emergent AEs in patients receiving single-agent pinatuzumab vedotin (2.4 mg/kg): iNHL versus DLBCL.

dose reductions or treatment discontinuations for adverse events were reported.

Among the 16 patients treated with pinatuzumab vedotin (both 1.8 mg/kg and 2.4 mg/kg dose levels) combined with rituximab, the most common treatment-emergent AEs in ≥4 patients were fatigue ($n = 8$), neutropenia ($n = 6$), diarrhea ($n = 5$), peripheral sensory neuropathy ($n = 5$), nausea ($n = 4$), and constipation ($n = 4$; Supplementary Table S2). Ten patients experienced a grade 3–4 AE: neutropenia ($n = 4$), peripheral sensory neuropathy ($n = 2$), and hyperglycemia ($n = 2$). Four patients discontinued study treatment for an AE: peripheral sensory neuropathy ($n = 2$); increased blood creatinine phosphokinase; and clear-cell renal cell carcinoma ($n = 1$ each). Five patients had at least one dose delay for AEs and three had a dose reduction for AEs ($n = 2$ peripheral neuropathy and $n = 1$ neutropenia).

A total of six deaths [DLBCL ($n = 4$), MCL ($n = 1$), and CLL ($n = 1$)] were reported 23–55 days after the last dose of pinatuzumab vedotin. Four deaths were reported following single-agent pinatuzumab vedotin (progressive disease, $n = 3$; failure to thrive, $n = 1$) and 2 following pinatuzumab vedotin combined with rituximab due to disease progression. None of the deaths were attributed to pinatuzumab vedotin by the treating investigator.

AEs associated with peripheral neuropathy, as defined by the MedDRA Standardized Query, were reported in 23 of 39 (59%) NHL patients treated with single-agent pinatuzumab vedotin at the RP2D, and in 7 of 16 patients (44%) treated in combination with rituximab, and were grade ≤2 in 19 of 23 (83%) and 12 of 16 (75%), respectively. The median time to onset of the first peripheral neuropathy event was 2.8 months following a median of 2 cycles. The median time to develop a grade ≥2 peripheral neuropathy was 6.2 months of treatment or a median of 7 cycles. Fifteen patients discontinued study treatment due to a peripheral neuropathy-related AE. No differences in time-to-onset were observed based on disease histology. The majority of study treatment discontinuations occurred with grade 2 events at a median of 7.4 months [interquartile range (IQR) 5.1–10.3 months]. Among 33 peripheral neuropathy events that resulted in treatment delays, dose reductions, or treatment discontinuations, complete resolution of the peripheral neuropathy event was reported in 10 (30%). Prior history of peripheral neuropathy and/or prior treatment with vinca alkaloids, which were reported in 29 of 91 (32%) and 72 of 91 (79%) of all treated patients, respectively, were not associated with a higher incidence of peripheral neuropathy resulting from pinatuzumab vedotin treatment. The incidence of new or worsening peripheral neuropathy during pinatuzumab vedotin treatment was generally similar to that among patients who lacked either or both of these baseline factors (Supplementary Table S3).

Pharmacokinetics

Pharmacokinetic parameters for acMMAE, TAb, and unconjugated MMAE in NHL patients are summarized in Table 2. Concentration–time pharmacokinetic profiles are illustrated in Supplementary Fig. S2. Maximal concentrations (C_{max}) for acMMAE and TAb were observed at the end of infusion. At the RP2D, mean half-life ($t_{1/2}$) and clearance (CL) values for acMMAE and TAb were similar, with volumes of distribution for both largely approaching plasma volume. These parameters were not affected by rituximab coadministration. Unconjugated MMAE C_{max} was observed 2–4 days after pinatuzumab vedotin administration (Supplementary Fig. S2). Unconjugated MMAE C_{max} and exposure (AUC_{inf}, area under the concentration–time curve from time 0 extrapolated to infinity) were much lower than those of acMMAE. At 2.4 mg/kg, there was an approximate 124- to 165-fold difference for C_{max} and an approximate 42- to 70-fold difference for AUC_{inf} between acMMAE and unconjugated MMAE, respectively. No unconjugated MMAE accumulation was observed with repeat dosing.

The pharmacokinetics of pinatuzumab vedotin in CLL patients was notable for faster acMMAE and TAb clearance compared with that observed in NHL patients at each corresponding dose level (Supplementary Table S4).

For patients treated with single-agent pinatuzumab vedotin, 1 of 72 ATA-evaluable patients (1.4%) tested positive for ATAs. For patients treated in combination with rituximab, none of 15 evaluable patients tested positive for ATAs. Together, the overall treatment-emergent ATA incidence was 1.1% (1/87). Characterization by competitive binding indicated that the antibody response was directed primarily to the antibody portion of pinatuzumab vedotin (Genentech, data on file).

Antitumor activity

The median duration of follow-up of all efficacy-evaluable patients across all dose levels was 3.8 months (range 0.07–27.6+ months, IQR 1.4–7.6 months). Objective responses are summarized in Table 3. Tumor reductions were mostly observed at pinatuzumab vedotin doses ≥1.8 mg/kg (Fig. 2). Objective responses at the single-agent RP2D included 5 of 20 (25%) patients with refractory DLBCL [2 complete responses, 3 partial responses (PR)]; 1 PR was observed among the 6 DLBCL patients treated with pinatuzumab vedotin combined with rituximab. Objective responses were observed in 5 of 12 (42%) patients with refractory iNHL treated with single-agent pinatuzumab vedotin (3 complete responses, 2 PRs) and 1 PR of 3 patients treated with pinatuzumab vedotin plus rituximab.

In DLBCL patients treated with single-agent pinatuzumab vedotin at the RP2D, the median PFS was 4.0 months [95% confidence interval (CI) 2.3–5.5 months, IQR 2.1–17 months; Fig. 3A]; the median DOR was 3.0 months (95% CI, 1 month–not reached, IQR 2.8–13.1 months). In iNHL patients (Fig. 3B), the median PFS was 7.6 months (95% CI, 1.3–15.2 months, IQR 6.7–15.2 months); the median DOR was 4.2 months (95% CI, 1.2–20.7 months, IQR 2.8–6.9 months). The median PFS for patients treated with pinatuzumab vedotin plus rituximab was 5.8 months (95% CI, 1.2 months–not reached, IQR 1.3 months–not reached); the median DOR was not reached (IQR 4.9 months–not reached). In MCL patients treated with pinatuzumab vedotin at doses ≥1.8 mg/kg alone or combined with rituximab, the PFS ranged from 0.4 to 9.2 months. No clear correlations between PFS outcomes and baseline characteristics were identified (Supplementary Table S5).

None of the 10 CLL patients treated with pinatuzumab vedotin achieved an objective response (Table 3).

Discussion

Results from this study established pinatuzumab vedotin at 2.4 mg/kg every 21 days as the RP2D in r/r NHL. Neutropenia and peripheral neuropathy were the principal treatment-emergent toxicities. Neutropenia was expected on the basis of preclinical

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Table 2. Selected mean (SD) pharmacokinetic parameters for antibody-conjugated MMAE, total antibody, and unconjugated MMAE after cycle 1 of pinatuzumab vedotin in pharmacokinetic-evaluable[a] NHL patients

Conjugate (evaluated as acMMAE)						
Dose (mg/kg)	**No. of patients[a]**	**C_{max} (ng/mL)**	**AUC_{inf} (ng/mL) * day**	**$t_{1/2}$ (day)**	**V_{ss} (mL/kg)**	**CL (mL/kg per day)**
0.1	3	41.4 (14.2)	65.6 (16.6)	3.59 (1.96)	83.1 (29.7)	28.6 (8.44)
0.25	4	62 (16.1)	117 (46.9)	4.29 (4.12)	133 (72.2)	42.8 (19.2)
0.5	6	164 (41.2)	335 (155)	6.36 (5.45)	123 (80.4)	30.6 (12.1)
1	3	414 (139)	895 (274)	4.42 (1.12)	78 (22.1)	21.0 (5.75)
1.8	7	588 (124)	1,710 (482)	6.69 (0.99)	117 (26.5)	19.5 (4.84)
2.4	6	834 (206)	2,440 (964)	8.18 (2.08)	111 (31.6)	25.7 (25.8)
3.2	3	1,060 (216)	3,400 (1,070)	8.44 (3.62)	120 (46)	17.9 (6.48)
2.4 (DLBCL expansion)	22	884 (225)	2,420 (661)	6.36 (2.75)	102 (31.6)	19.5 (9.48)
2.4 (iNHL expansion)	11	890 (302)	2,130 (1,010)	4.72 (2.14)	99.5 (38.9)	24.3 (11.2)
1.8 (combination with rituximab)	5	548 (160)	1,360 (552)	6.68 (2.59)	156 (93.6)	27.7 (12.4)
2.4 (combination with rituximab)	11	886 (236)	2,890 (1,110)	5.17 (1.9)	79.7 (12.8)	19.2 (17.2)
Total antibody						
Dose (mg/kg)	**No. of patients[a]**	**C_{max} (ng/mL)**	**AUC_{inf} (ng/mL) * day**	**$t_{1/2}$ (day)**	**V_{ss} (mL/kg)**	**CL (mL/kg per day)**
0.1	3	1,920 (496)	5,790 (1,660)	4.48 (2.21)	96.4 (31.2)	18.5 (5.36)
0.25	4	3,840 (851)	12,600 (7,120)	4.99 (4.24)	112 (33.9)	26.1 (16.6)
0.5	6	6,920 (1,920)	30,800 (20,000)	8.37 (7.44)	152 (69.8)	24.1 (16.3)
1	3	17,800 (8,790)	63,000 (13,500)	5.91 (1.6)	122 (21.6)	16.6 (3.64)
1.8	7	28,000 (5,660)	180,000 (51,000)	11.9 (3.93)	153 (34.7)	10.6 (2.8)
2.4	6	39,100 (11,800)	247,000 (109,000)	11.6 (5.59)	145 (36)	20.8 (30.7)
3.2	3	50,900 (19,600)	316,000 (109,000)	11.1 (8.2)	163 (128)	10.8 (3.12)
2.4 (DLBCL expansion)	21	41,600 (11,300)	276,000 (103,000)	12.2 (6.49)	131 (39.2)	11.4 (9.85)
2.4 (iNHL expansion)	11	45,400 (17,000)	219,000 (106,000)	7.39 (4.04)	113 (43.5)	14.2 (8.35)
1.8 (combination with rituximab)	5	26,000 (7,360)	154,000 (78,500)	12.3 (6.85)	191 (131)	14.1 (5.62)
2.4 (combination with rituximab)	11	41,300 (14,500)	308,000 (95,800)	9.24 (3.11)	94.2 (18.5)	7.57 (1.79)
Unconjugated MMAE[b]						
Dose (mg/kg)	**No. of patients[a]**	**C_{max} (ng/mL)**	**AUC_{inf} (ng/mL) * day**	**$t_{1/2}$ (day)**	**t_{max} (day)**	
0.1	3	0.32 (0.2)	4.15	2.67	1.72 (1.17)	
0.25	4	0.37 (0.16)	2.88 (1.57)	3.75 (0.63)	1.53 (0.95)	
0.5	6	0.86 (0.95)	6.74 (8.29)	3.11 (0.41)	2.14 (1.28)	
1	3	1.82 (0.84)	14.6 (6.93)	2.94 (0.36)	3.29 (0.49)	
1.8	7	2.92 (1.49)	30.1 (14.7)	4.08 (0.93)	3.55 (0.58)	
2.4	6	5.55 (3.26)	43 (16.7)	3.46 (0.63)	3.54 (1.97)	
3.2	3	9.83 (5.01)	104 (50.9)	4.07 (1.43)	4.28 (3.05)	
2.4 (DLBCL expansion)	22	7.15 (5.95)	54.1 (38.2)	3.85 (1)	3.99 (1.41)	
2.4 (iNHL expansion)	11	5.62 (2.39)	50.9 (29.9)	3.39 (0.75)	2.87 (1.33)	
1.8 (combination with rituximab)	5	4.10 (2.2)	37.0 (29.0)	4.52 (1.36)	3.17 (1.73)	
2.4 (combination with rituximab)	11	5.36 (4.24)	41.5 (30.9)	3.91 (0.33)	4.1 (1.52)	

NOTE: Data are mean (SD). Table shows data for pharmacokinetic-evaluable patients with NHL (i.e., those with at least one pharmacokinetic parameter estimated). Clearance refers to dose divided by area under the concentration–time curve.

Abbreviations: AUC_{inf}, area under the concentration–time curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; CL, clearance; $t_{1/2}$, terminal half-life; t_{max}, time to reach maximum concentration; V_{ss}, volume of distribution at steady state.

[a]Number of patients with at least one pharmacokinetic parameter estimated.

[b]Clearance and V_{ss} values are not estimated because the fraction of conversion of pinatuzumab vedotin to the unconjugated MMAE metabolite is unknown.

toxicology observations (Genentech, Inc.; data on file) and clinical experience with brentuximab vedotin and polatuzumab vedotin, both of which contain the same linker-MMAE construct as pinatuzumab vedotin (12, 16). Neutropenia mostly manifested as laboratory abnormalities and, in most cases, did not lead to study treatment discontinuation. Clinical sequelae of neutropenia, including febrile neutropenia and severe infections, were uncommon. Administration of growth factors in accordance

Table 3. Best overall response in relapsed/refractory indolent B-cell lymphoma and DLBCL for single-agent pinatuzumab vedotin

	Indolent B-cell lymphoma[a]			**DLBCL**				**CLL**		
	<1.8 mg/kg ($n = 8$)	**1.8 mg/kg ($n = 3$)**	**2.4 mg/kg ($n = 14$)**	**<1.8 mg/kg ($n = 8$)**	**1.8 mg/kg ($n = 4$)**	**2.4 mg/kg ($n = 25$)**	**3.2 mg/kg ($n = 1$)**	**<1.8 mg/kg ($n = 6$)**	**1.8 mg/kg ($n = 3$)**	**2.4 mg/kg ($n = 1$)**
Complete response	0	0	3 (21.4%)	2 (25.0%)	1 (25.0%)	4 (16.0%)	0	0	0	0
Partial response	0	1 (33.3%)	4 (28.6%)	1 (12.5%)	1 (25.0%)	5 (20.0%)	1 (50.0%)	0	0	0
Stable disease	4 (50.0%)	2 (66.7%)	2 (14.3%)	1 (12.5%)	0 (0.0%)	4 (16.0%)	0	1 (16.7%)	1 (33.3%)	0
Progressive disease	4 (50.0%)	(0.0%)	3 (21.4%)	4 (50.0%)	1 (25.0%)	11 (44.0%)	0	2 (33.3%)	2 (66.7%)	0
Unable to evaluate[b]	0	0	0	0	0	1 (4.0%)	0	0	0	0
Missing[c]	0	0	2 (14.3%)	0	1 (25.0%)	0	0	3 (50.0%)	0	1 (100.0%)

[a]Includes follicular lymphoma, marginal zone lymphoma and small lymphocytic lymphoma. No patients with indolent B-cell lymphoma received pinatuzumab vedotin at 1.8 mg/kg.

[b]Scan was done but response could not be determined.

[c]Early discontinuation prior to scheduled tumor assessment or assessment visit was not reached at the time of data cutoff.

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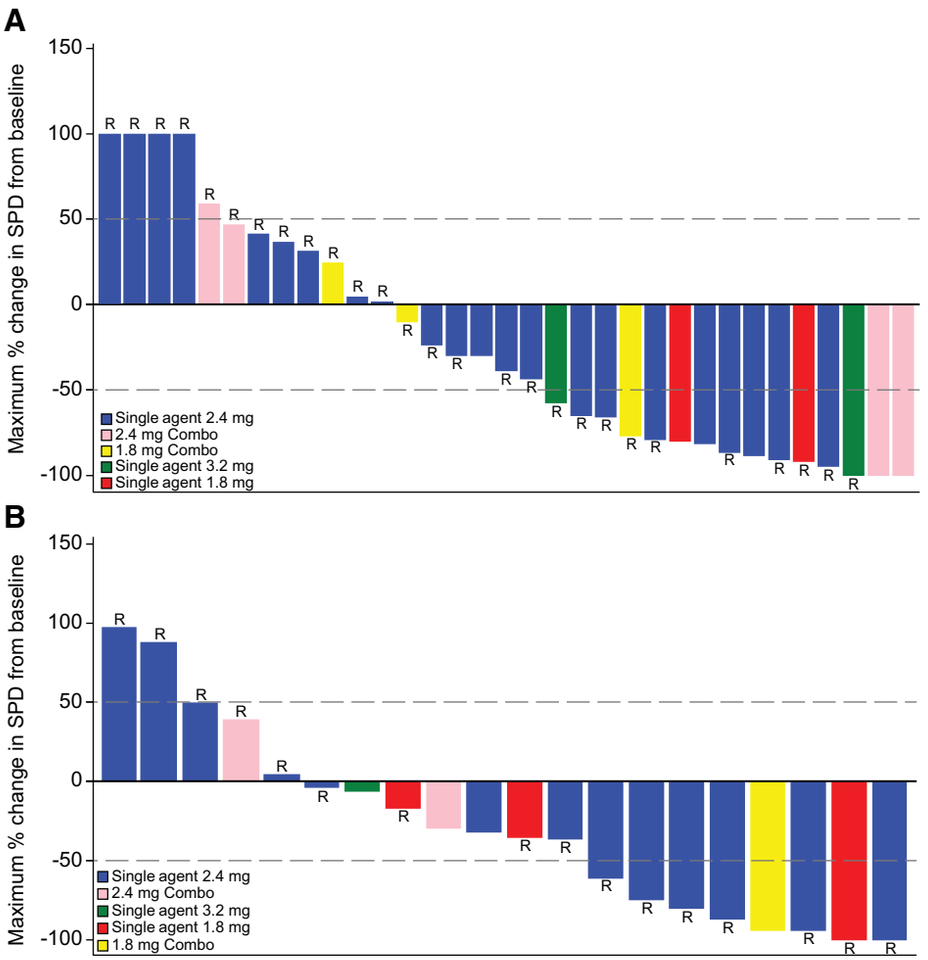

Figure 2.
Observed antitumor responses in DLBCL patients (**A**) and iNHL patients (**B**). Dashed lines indicate 50% increases and 50% decreases in SPD from baseline. R, refractory; SPD, sum of the product of the diameters.

with published guidelines (17) and increasing the cycle duration to 28 days facilitated neutrophil count recovery and enabled continued treatment.

Peripheral neuropathy is consistent with the mechanism of action of MMAE and is considered to be an effect of this class of drugs. The frequency and severity of peripheral neuropathy events observed with pinatuzumab vedotin were generally similar to that observed in r/r HL patients treated with brentuximab vedotin (18), despite differences in dose (2.4 mg/kg vs. 1.8 mg/kg), and were similar to that observed with polatuzumab vedotin in r/r NHL (16). Most events were sensory; however, peripheral motor neuropathy and combined peripheral sensorimotor neuropathy were also observed. Patients who experienced peripheral neuropathy underwent dose delays until resolution before resuming treatment at a reduced dose, but the full impact of these measures on peripheral neuropathy reversibility requires further study. While the majority of patients who were enrolled into the study received prior treatment with neurotoxic therapies, neither this nor a prior history of peripheral neuropathy was associated with a substantially increased risk of treatment-emergent peripheral neuropathy. Identifying additional factors (e.g., age, pre-existing neuropathic conditions, or other comorbidities that result in a higher predisposition to peripheral neuropathy with vc-MMAE–based ADCs) and assessing the relationship between peripheral neuropathy and pinatuzumab vedotin pharmacokinetics requires additional study.

The pharmacokinetic properties of pinatuzumab vedotin are largely consistent with reports of other MMAE ADCs (12, 16). The levels of unconjugated MMAE were consistently much lower than those of the conjugate (acMMAE). The overall pharmacokinetic profile of pinatuzumab vedotin appeared largely driven by the antibody component, given the similarities between total antibody and conjugate (acMMAE) pharmacokinetics.

Response rates, PFS, and DOR with pinatuzumab vedotin treatment in NHL were encouraging given the heavily pretreated patient population with advanced disease. Antitumor responses were observed at doses $\geq$1.8 mg/kg, suggesting that patients who require dose reductions from the RP2D for treatment-emergent toxicity may also receive continued clinical benefit with longer treatment durations. Interestingly, in 5 patients, pinatuzumab vedotin treatment resulted in responses sufficient to enable subsequent allogeneic stem cell transplantation (data not shown). Additional studies will be required to assess the potential of pinatuzumab vedotin as a bridge to allogeneic transplantation in previously transplant-ineligible patients.

Unlike NHL, there was no early evidence of clinical benefit of pinatuzumab vedotin in CLL patients. Recognizing that treatment-emergent toxicities may differ between NHL and CLL due to

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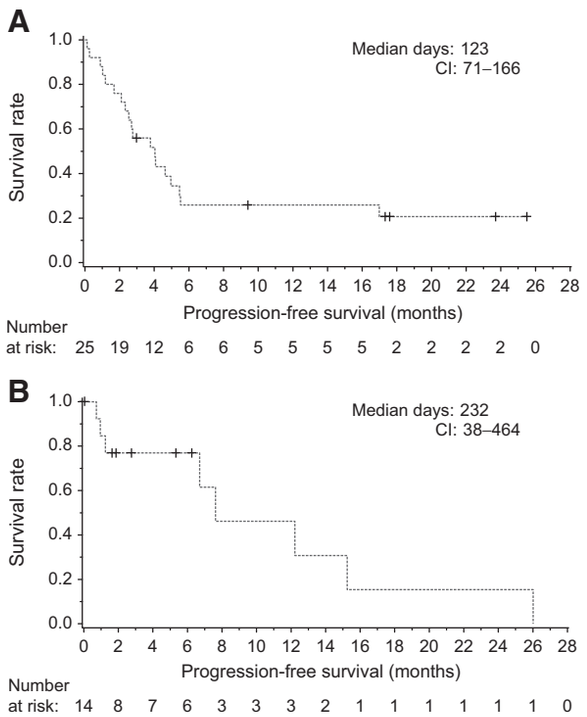

Figure 3.

Progression-free survival. Kaplan–Meier curves of progression-free survival in DLBCL patients (**A**) or iNHL patients (**B**) receiving single-agent pinatuzumab vedotin (2.4 mg/kg).

underlying differences in clinical characteristics and natural history, separate pinatuzumab vedotin dose escalations were conducted for each. Given the decision to terminate enrollment of CLL patients into the study, the MTD of pinatuzumab vedotin was not determined, and direct comparison of treatment-emergent safety data between NHL and CLL patients is therefore not possible. In CLL patients who were treated with pinatuzumab vedotin, no objective responses were observed. Pinatuzumab vedotin pharmacokinetics indicated lower exposure and faster clearance for TAb and acMMAE in CLL compared with NHL patients, presumably due to the greater number of circulating B cells in CLL patients, resulting in significant target-mediated clearance of pinatuzumab vedotin. This profile is similar to what was observed with polatuzumab vedotin treatment in CLL patients (16). Whether this and other factors may have ultimately affected the antitumor activity of pinatuzumab vedotin in CLL requires further study.

Overall, the clinical activity of pinatuzumab vedotin treatment supports the therapeutic potential of ADCs targeting CD22 in patients with B-cell NHL. The risk–benefit profile of pinatuzumab vedotin appears distinct from its individual components. For example, the response rates of 2.4 mg/kg pinatuzumab vedotin in r/r DLBCL [9/25 (36%)] and r/r iNHL [7/14 (50%)] compare favorably to those of the monoclonal anti-CD22 antibody epratuzumab, which has single-agent objective response rates of 15% in DLBCL (6) and 18% in iNHL (5). In addition, the tolerability profile of epratuzumab is similar to that of other unconjugated mAbs, without the toxicities (neutropenia or peripheral neuropathy) observed with pinatuzumab vedotin treatment. Pinatuzumab vedotin also compares favorably to vincristine and liposomal vincristine, the latter of which had an objective response rate of 25% in aggressive NHL and was associated with considerably worse neurotoxicity (29% grade 3, 3% grade 4 vs. 17% grade 3, no grade 4 events for pinatuzumab vedotin observed in this study; ref. 19). Finally, the clinical activity of pinatuzumab vedotin compares favorably with other ADCs targeting B-cell antigens (20); the response rate of pinatuzumab vedotin in r/r DLBCL is comparable with those observed with the CD22-targeted calicheamicin ADC, inotuzumab ozogamicin (15%), the CD79b-targeted polatuzumab vedotin (52%), the CD19-targeted maytansinoid ADC SAR3419 (33%), and brentuximab vedotin in $CD30^+$ DLBCL (44%; refs. 16, 21–23). While the antitumor activity is generally similar, it is important to note that each ADC has a distinct toxicity profile based largely on the mechanism of action of the cytotoxic agent: neutropenia and peripheral neuropathy for pinatuzumab vedotin, polatuzumab vedotin, and brentuximab vedotin, thrombocytopenia for inotuzumab ozogamicin, and ocular toxicities for SAR3419. Consequently, maximizing the risk–benefit profile of ADCs (e.g., through alternate doses and schedules to minimize the frequency and severity of peripheral neuropathy) is an important issue that requires further investigation.

To realize the full therapeutic potential of ADCs, it is crucial to demonstrate the ability of ADCs to combine with or replace agents that constitute current standards of care. In this regard, demonstrating the combinability of pinatuzumab vedotin with rituximab is important given the effectiveness of rituximab-containing regimens in NHL (24, 25). Clinical data with other rituximab-ADC combinations have demonstrated additive clinical activity over either agent alone; the addition of rituximab to inotuzumab ozogamicin resulted in higher objective response and complete response rates over inotuzumab ozogamicin alone (21, 26). Furthermore, the ability of combining CD22- and CD20-directed antibodies was demonstrated in a phase II study of epratuzumab and rituximab in previously untreated follicular lymphoma, with evidence of clinical activity comparable with standard chemotherapy and nonchemotherapy-based regimens (27). Preliminary results in this study suggest that the toxicity profiles between combined pinatuzumab vedotin and rituximab and single-agent pinatuzumab vedotin are similar. Pinatuzumab vedotin pharmacokinetics was unaffected by rituximab coadministration and vice versa (data not shown). While durable responses with the combination were observed, the individual contributions of each agent to overall antitumor activity could not be determined due to the small number of patients treated. Further assessment of the pinatuzumab vedotin/rituximab combination is ongoing in a phase II randomized study (ROMULUS, NCT01691898) comparing the clinical activity of two MMAE ADCs, pinatuzumab vedotin and polatuzumab vedotin, each in combination with rituximab. Preliminary results indicate no unexpected safety findings and greater clinical activity compared with either ADC alone (28). In patients with relapsed or refractory DLBCL, for example, objective and complete response (CR) rates of pinatuzumab vedotin combined with rituximab were greater than those of the single-agent pinatuzumab vedotin (ORR, 57% vs. 36%; CR, 24% vs. 16%, for combination vs. single-agent, respectively). Beyond combinations with rituximab, early data from ongoing clinical studies indicate the ability of ADCs, including

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polatuzumab vedotin and brentuximab vedotin, to combine with systemic chemotherapy used in current anti-lymphoma immunochemotherapy regimens (29, 30).

In summary, results of this phase I study of pinatuzumab vedotin demonstrate clinical activity of CD22-directed ADCs that warrants further clinical investigation of this class of molecules in B-cell malignancies. Given the emerging biologic heterogeneity and complexity of B-cell leukemias and lymphomas, correlative analyses to identify predictive and prognostic biomarkers will be important to identify patients most likely to benefit from pinatuzumab vedotin treatment. Finally, results from this study further substantiate CD22 as a clinically validated ADC target and opens up the possibility of developing ADCs targeting CD22 that contain different classes of cytotoxic agents, ultimately leading to ADC combinations that target multiple B-cell lineage antigens to deliver multiple cytotoxic agents more effectively than systemic multi-agent chemotherapy.

Disclosure of Potential Conflicts of Interest

R.H. Advani, A. Chen, and B.D. Cheson are consultant/advisory board members for Genentech. M. Brunvand reports receiving speakers bureau honoraria from Genentech. A. Goy reports receiving other commercial research support from Celgene, Genentech, and Pharmacyclics/J&J; speakers bureau honoraria from and is a consultant/advisory board member for Acerta, Celgene, Pharmacyclics/J&J, and Takeda. Y.-W. Chu holds ownership interest (including patents) in Roche. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

Phase I Study of the Anti-CD22 Antibody–Drug Conjugate Pinatuzumab Vedotin with/without Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma

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