Antibody-Drug Conjugates for the Treatment of Non–Hodgkin’s Lymphoma: Target and Linker-Drug Selection


Genentech, Inc., South San Francisco, California

Abstract

Antibody-drug conjugates (ADCs), potent cytotoxic drugs covalently linked to antibodies via chemical linkers, provide a means to increase the effectiveness of chemotherapy by targeting the drug to neoplastic cells while reducing side effects. Here, we systematically examine the potential targets and linker-drug combinations that could provide an optimal ADC for the treatment of non–Hodgkin’s lymphoma. We identified seven antigens (CD19, CD20, CD21, CD22, CD72, CD79b, and CD180) for potential treatment of non–Hodgkin’s lymphoma with ADCs. ADCs with cleavable linkers mediated in vivo efficacy via all these targets; ADCs with uncleavable linkers were only effective when targeted to CD22 and CD79b. In target-independent safety studies in rats, the uncleavable linker ADCs showed reduced toxicity, presumably due to the reduced release of free drug or other toxic metabolites into the circulation. Thus, our data suggest that ADCs with cleavable linkers work on a broad range of targets, and for specific targets, ADCs with uncleavable linkers provide a promising opportunity to improve the therapeutic window for ADCs in humans. [Cancer Res 2009;69(6):2358–64]

Introduction

Antibody-drug conjugates (ADCs), cytotoxic drugs linked to antibodies through specialized chemical linkers, provide a method to target cytotoxic drugs to a tumor and minimize normal tissue damage, thereby increasing the effectiveness and reducing the toxicity of chemotherapy. The design of an ideal ADC is a dichotomy requiring tight linkage between the cytotoxic drug and the antibody to prevent nonspecific drug release while the agent is in circulation, yet appropriate release of the drug when the ADC reaches the tumor. The specific release of the cytotoxic drug is critical to the safety of the ADCs because the cytotoxic drug must be hundreds-fold more potent than the drugs used in typical systemic chemotherapy to be effective in the context of an ADC (1–3). To accomplish this specificity, specialized linkers between the antibody and drug have been designed that are cleaved only in a specific microenvironment found in or on the target tumor cell. Examples include linkers that are cleaved by acidic conditions, reducing conditions, or proteases (4–6). Another option is to have stable linkers that are not cleaved, but rather, coupled to antibodies against tumor antigens that are internalized and then degraded, releasing the drug attached to the conjugating amino acid within cells (7, 8). Thus, the active metabolite(s) and amounts of active drug released should be substantially different for the cleavable linker ADC and this could affect the safety and efficacy of the ADCs.

Another factor that has been less explored is the interaction of the linker type and the target. In vitro data suggest that the biology of the target, in particular, the extent of trafficking to the lysosomal compartment, will influence the effectiveness of the ADC (7–10). In vivo, the situation is even more complex; the extracellular microenvironment, and the intracellular trafficking of the target, the longer exposure times (weeks instead of days), in combination with the linker-drug used, will determine where, to what extent, and in what form the cytotoxic drug is released and thus which linker-drug combinations are both effective and safe.

This work focuses on four linker-drug combinations that all result in the release of cytotoxic metabolites that inhibit microtubule polymerization. We used two maytansinoid linker-drugs consisting of N(2’)-deacetyl-N(2’)-(3-mercaptop-1-oxopropyl)-maytansine (DM1) with one of two different linkers that are conjugated to the antibody through lysines; the disulfide linker N-succinimidyl 4-(2-pyrydldithio)-pentanoate (SPP), which releases drug through the reduction of a disulfide bond (11); or the thioether linker succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (MCC), which is uncleavable such that the antibody must be degraded to release the active drug lysine-MCC DM1 (8). The other two ADCs are based on auristatins, which are mitotic inhibitors derived from dolastatin 10: monomethylauristatin E, linked to antibody cysteines by maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB-MMAE); and monomethylauristatin F, linked to antibody cysteines by maleimidocaproyl (MC-MMAF). MC-vc-PAB-MMAE ADCs release free, membrane-permeable MMAE when cleaved by proteases such as cathepsin B (12). In contrast, MC-MMAF ADCs are uncleavable, like MCC-DM1, and must be internalized and degraded within a cell, releasing cysteine-MC-MMAF as the active drug (7).

The development of ADCs for the treatment of non–Hodgkin’s lymphoma (NHL) provides a unique opportunity to develop ADC treatments for an important unmet medical need and as a model system to understand ADCs. NHL is responsive to chemotherapy, unconjugated antibody therapies, and radioconjugate therapies,
suggesting that these tumors are accessible by antibody-based therapies and would be responsive to cytotoxics delivered by an ADC. Furthermore, clinical experience with rituximab (chimeric IgG1 anti-CD20), which greatly reduces the number of normal as well as malignant B cells without serious side effects, suggests that expression of an ADC target on normal B-cells and the consequent elimination of normal B cells is not a major safety concern (13). There are a number of potential ADC targets whose expression is limited to the B-cell compartment and that are expressed on NHLs. This abundance of targets with appropriate expression patterns allow for a unique opportunity to study the effect of the target on ADCs. We identified seven potential antigens with the appropriate B cell–specific expression patterns and tested the efficacy and safety of four different linker-drug formats. This combinatorial approach allowed us to elucidate some general principles for the development of ADCs, as well as identifying two targets that are responsive to ADCs with a wide range of linker-drugs and therefore hold the most promise for the treatment of NHL with ADCs.

Materials and Methods

Antibodies and ADCs. Anti-CD19 (B96, mlgG1; Biomedia), anti-CD22 (RF64; Leinco), and anti-CD180 (MHR73-11, mlgG1; from Ebioscience) were purchased and further purified on protein A-Sepharose and MonoQ resins to reduce endotoxin levels. The anti-CD21 (THB-5, mlgG1) hybridoma was obtained from American Type Culture Collection and anti-CD79a (SNK, mlgG1) hybridoma was obtained from Ben Seon (Roswell Park Cancer Institute), and the antibodies from these were produced and purified as described below. Anti-CD22 (10Fv4 /3, hu IgG1), anti-CD72 (10D6.8.1, mlgG1), anti-gp120 (mlgG1), and trastuzumab (hu IgG1) were generated at Genentech, Inc, using previously described methods (14–16). Hybridoma supernatants were harvested and purified by affinity chromatography (fast protein liquid chromatography; Pharmacia) as previously described (17). Purified antibodies were sterile-filtered (0.2 μm pore size; Nalgene) and stored at 4°C in PBS, MCC-DM1, MC-MMAF, and MC-vc-PAB-MMAF ADCs were made as previously described (12, 18). The SPP conjugates were prepared the same as the previously described for the MCC conjugates except that the purified antibody was buffer-exchanged into a solution containing 50 mmol/L of potassium phosphate and 2 mmol/L of EDTA (pH 6.0). SPP was dissolved in 100% ethanol and added to the antibody solution to make a final SPP/antibody molar ratio of 8:1, resulting in final DM1/antibody ratios of 3:1 to 4:1.

 Xenograft models. All animal studies were performed in compliance with NIH guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Care and Use Committee at Genentech. Cells for implantation were washed and suspended in HBSS (Hyclone) and inoculated subcutaneously into the flanks of female CB17 ICR severe combined immunodeficiency mice (7–16 weeks of age from Charles Rivers Laboratories), in a volume of 0.2 mL/mouse. When mean tumor size reached the desired volume, the mice were divided into groups of 8 to 10 mice with the same mean tumor size and doses intravenously via the tail vein with ADCs or antibodies. ADC doses were either measured as the mass of the conjugated cytotoxic small molecule drug per surface area of 8 to 10 mice with the same mean tumor size and dosed intravenously via the tail vein with ADCs or antibodies. ADC doses were either measured as the mass of the conjugated cytotoxic small molecule drug per surface area of the mouse (e.g., 300 μg antibody-linked DM1/m2 of mouse), or as a constant mass of ADC per mass of the mouse (e.g., 5 mg of ADC/kg mouse). In general, the drug loads on the antibodies in any given experiment were similar (three to four drug molecules per antibody), so these two measures could be considered equivalent.

Antibody internalization studies. B-cell lines were incubated for 3 or 20 h at 37°C with 1 μg/mL test antibody, along with FcR block (Miltenyi), and 25 μg/mL of Alexa 647-transferase (Invitrogen), the latter to label the recycling compartment and confirm cell viability. The incubations were carried out in RPMI culture medium, 10% heat-inactivated fetal bovine serum (Hyclone), 1% t-glutamine (Invitrogen) in the presence of 10 μg/mL leupeptin (Roche), and 5 μmol/L of pepstatin (Roche) to inhibit lysosomal degradation. Primary antibodies were then detected postfixation using Cy3 anti-mouse secondary antibodies (Jackson), and processed and photographed as previously described (18).

Rat safety and pharmacokinetic studies. Rat studies were conducted at Genentech in compliance with NIH guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Care and Use Committee. Female Sprague-Dawley rats weighing 75 to 80 g were randomized on the basis of weight into groups of six animals each. On study day 1, animals were given a single intravenous dose of vehicle or anti-CD22-MC-vc-PAB-MMAF, anti-CD22-SPP-DM1, anti-CD22-MCC-DM1, or anti-CD22-MC-MMAF at 2,000 μg/kg conjugated cytotoxin (~20 mg/kg ADC), which was the highest tolerated dose for anti-CD22-SPP-DM1. This dose was chosen for all compounds in order to assess relative toxicities. The dose of the cytotoxin, 2,000 μg/kg, based on body surface area was about 7-fold higher than the dose used in the efficacy studies in mice. Serum chemistry and hematology variables were measured pre-dose, on day 5, and on day 12, and included alanine aminotransferase (ALT), amylase, alkaline phosphatase (ALP), aspartate aminotransferase (AST), creatine kinase (CK), γ-glutamyl transferase, lactate dehydrogenase, sodium, potassium, chloride, calcium, inorganic phosphorous, blood urea nitrogen, creatinine, glucose, total protein, albumin, cholesterol, triglycerides, total bilirubin, WBC count, RBC count, hemoglobin, mean corpuscular volume, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC distribution width, mean platelet volume, platelet count (PLT), absolute segmented neutrophils (NEUT), absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. Clinical observations and body weights were also monitored throughout the study.

For pharmacokinetic studies, Sprague-Dawley rats weighing 225 to 250 g were randomized into groups of four animals each. Rats were dosed with 10 mg/kg of anti-CD22-SPP-DM1 or anti-CD22-MCC-DM1 via the jugular vein catheter. Blood samples (300 μL) were collected for pharmacokinetic analysis at 0 (pre-dose) and 3 min; 1, 6, and 24 h; and 2, 3, 4, 7, 10, 15, 21, 28, and 35 days post-dose. Serum samples were analyzed for total antibody and ADC concentration via ELISA. Pharmacokinetic variables were calculated with WinNonlin (version 5.0.1, Pharsight Corporation).

Results

Efficacy of uncleavable linker ADCs shows more target dependence than cleavable linker ADCs. We identified seven antigens, CD19, CD20, CD21, CD22, CD72, CD79b, and CD180 the expression of which is largely restricted to the B-cell compartment and are expressed in the majority of NHLs (Table 1; data not shown; refs. 19–24). Antibodies were identified that were reported, or found by ourselves (data not shown), to bind cognate antigen in flow cytometry assays. Using these antibodies, we identified cell lines that expressed each target and grew reliably with high take rates in mouse xenograft models. The models shown were not selected to be responsive to the test agents.

We made SPP-DM1 and MCC-DM1 conjugates of all the antibodies and tested their efficacy in vivo. We found that all of the SPP-DM1 (cleavable linker) conjugates (red lines, Figs. 1 and 2) were effective in the relevant xenograft models as compared with a control ADC (trastuzumab or anti–gp120, black lines) that did not bind the cell line of interest (Figs. 1 and 2). The absence of activity with control conjugates indicates that the activity seen with the targeted conjugates is specific, for example, it is not due to systemic release of free drug. In several cases, tumors were not only inhibited, but also completely regressed by certain ADCs. These data indicate that all of these surface antigens are potentially effective targets for ADCs. The cleavable SPP-DM1 conjugates worked even with antibodies against targets that are very poorly internalized such as CD20, CD21, and CD72 (Fig. 3), suggesting that SPP-DM1 ADCs have broad efficacy and are relatively
Insensitive to the target biology compared with MCC-DM1 ADCs. By contrast, only the ADCs targeted to CD79b and CD22 were effective with the uncleavable linker MCC-DM1 conjugates (blue lines, Figs. 1D and 2B).

In light of the relative specificity for the MCC-DM1 ADCs observed for CD22 and CD79, we decided to further explore these two antigens as targets. We tested anti-CD22 and anti-CD79b MC-vc-PAB-MMAE and MC-MMAF conjugates in relevant xenograft...
models and found that all four ADCs were able to regress or eliminate the tumors (Fig. 4).

CD79b and CD22 are expressed only in the B-cell compartment and are both expressed on the surface of most NHL cells (21, 23). Furthermore, ADCs targeted against CD22 or CD79b worked with all linker-drug combinations tested, suggesting that these two antigens are particularly robust and attractive targets.

ADCs with uncleavable linkers exhibit reduced toxicity in rats when compared with cleavable linkers. ADCs with uncleavable linkers might be expected to be better tolerated than ADCs with cleavable linkers, as they should release less drug into systemic circulation, reducing the risk of toxicity (7, 8). However, this may not necessarily be the case, as even uncleavable linker ADCs are metabolized and may result in bioconcentration of the cytotoxin or its metabolites. We therefore evaluated the toxicity of ADCs with uncleavable and cleavable linker-drug combinations in rats. We used anti-CD22 conjugated to the maytansinoids, SPP-DM1 (cleavable) and MCC-DM1 (uncleavable); and the auristatins, MC-vc-PAB-MMAE (cleavable) and MC-MMAF (uncleavable), as these linker-drug combinations are already in or likely to soon enter the clinic for indications other than NHL (25). The anti-CD22 antibody does not bind rat CD22 (data not shown), so the results should reflect the systemic toxicity of ADCs in general, rather than the effects of targeting the ADC to specific tissues. Rats were chosen for these safety studies instead of mice, as it has been shown that mice are unusually tolerant of some small molecule tubulin inhibitors (26), and indeed, we observed no weight loss or other adverse effects of ADC dosing in our mouse models. Rats were given a single intravenous dose of each ADC at 2,000 μg conjugated cytotoxic drug/mouse (20 mg ADC/kg) and were observed for 12 days. Only anti–CD22-SPP-DM1 had a negative effect on body weights (Fig. 5A), indicative of toxicity. Hematology and serum chemistry, evaluated 5 and 12 days post-dosing, identified hepatic and hematologic toxicities in the two cleavable linker groups, anti–CD22-SPP-DM1 and anti–CD22-MC-vc-PAB-MMAE. Specifically, serum liver enzymes, ALT and AST, and cholesterol (data not shown) levels were mildly and transiently increased 5 days post-dosing in these cleavable linker groups. By contrast, no elevations were seen over baseline or over historical reference ranges for the groups given anti–CD22-MCC-DM1 and anti–CD22-MC-MMAF (Fig. 5B; Table S1). In addition, γ-glutamyl transferase and total bilirubin were elevated in the group given...
anti–CD22-SPP-DM1 (data not shown). The two groups given the cleavable linkers also developed decreases in WBC and absolute neutrophil counts on day 5 (Fig. 5B; Table S1) and decreases in RBC mass, hemoglobin, and hematocrit on day 12 (data not shown). Decreases in platelet counts were observed 5 days post-dosing in the group given anti–CD22-SPP-DM1 and 12 days post-dosing in the group given anti–CD22-MC-vc-PAB-MMAE (Fig. 5B; Table S1). In contrast, the ADCs with uncleavable linkers, MCC-DM1 and MC-MMAF, caused no significant hematologic effects compared with the control group, suggesting that they are much better tolerated than ADCs with cleavable linkers. All other clinical pathology variables (see Materials and Methods) in the ADC-dosed groups were no different from the vehicle-dosed control group.

**Pharmacokinetics of cleavable and uncleavable linker ADCs.** We hypothesized that the ADCs with uncleavable linkers, anti–CD22-MCC-DM1 and anti–CD22-MC-MMAF, were better tolerated because they released smaller amounts of free drug or small molecule metabolites. Another possible reason is that the uncleavable linker ADCs were cleared faster resulting in less exposure to the ADC and metabolites. To test these ideas, we performed pharmacokinetic assays on the four ADCs, measuring total antibody (which includes both the ADC and the unconjugated antibody) and drug-conjugated antibody. We found that the total antibody clearance was similar for both cleavable and uncleavable conjugates, suggesting that the type of linker has a minimal effect on the metabolism of the antibody (Fig. 5C and D). However, whereas the (drug-loaded) uncleavable linker conjugates cleared with similar kinetics as the total antibody, the cleavable linker conjugates lost drug more quickly, particularly SPP-DM1. This suggests that the cleavable linker ADCs release more free cytotoxic drug (or metabolites thereof) into the circulation. The correlation of drug loss from the antibody to hepatic and hematologic toxicities with the cleavable linker ADCs suggests that the reason that the uncleavable linkers are better tolerated than their cleavable counterparts is their decreased systemic release of free drug.

**Discussion**

We examined seven potential ADC targets for the treatment of NHL, and in all cases, the cleavable-linker ADC SPP-DM1 was...
effective in xenograft models. Our observation that SPP-DM1 ADCs have activity even when the antibodies to the targets are poorly internalized seems to be a general characteristic of cleavable-linker ADCs with membrane-permeable drugs. For example, CD21 is poorly internalized (Supplemental Fig. S1; Fig. 3), yet anti–CD21-MC-vc-PAB-MMAE was effective in our model. Similarly, others have shown an anti–CD20-AcBut-calicheamicin, which also recognizes a poorly internalized target (Fig. 3) and uses an acid-cleavable linker, is effective in a xenograft model, whereas anti–CD20-amide-calicheamicin with an uncleavable linker is not (27). A likely mechanism that would explain why cleavable linkers are broadly effective and less sensitive to the biology, particularly the trafficking, of the target, is that following antibody binding, the linker is cleaved in the extracellular space and free drug subsequently permeates the cell to reach its target. One line of evidence for this mechanism is shown in Supplemental Fig. S1; anti–CD21-MC-vc-PAB-MMAE is efficacious, but substitution of MMAF for MMAE on this conjugate results in an inactive ADC. MMAF is a more potent drug than MMAE, but is charged and relatively membrane-impermeable (7); thus, the efficacy of the MMAE conjugate in this experiment must be due to extracellular cleavage of the linker followed by cell permeation of the liberated drug. Although the data presented suggest that cleavable linkers are broadly active, our data also show that the cleavable linkers are a double-edged sword; such ADCs are more toxic in an acute setting. Still, cleavable-linker ADCs are likely to be the format of choice for many targets, particularly those with less internalization, lower copy number, or heterogeneous tumor expression (5). Indeed, the only marketed ADC, gemtuzumab ozogamicin, has an acid-cleavable linker (28).

Figure 5. Safety assessment of uncleavable linker (blue) and cleavable-linker (red) ADCs in rats. Rats were dosed on day 1 with a single dose of anti–CD22-MC-MMAF, anti–CD22-MCC-DM1, anti–CD22-MC-vc-PAB-MMAE, or anti–CD22-SPP-DM1, at 0 (vehicle) or 2,000 μg/m2 conjugated cytotoxin (n = 6 animals/group). Body weight was monitored daily (A) and clinical chemistry and hematology variables were measured pre-dose, on day 5, and on day 12 (B). The data points of the individual animals for these times are shown by lines connecting them. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelets; and Neut, neutrophils. Neutrophils, AST, and ALT are on log scale; WBC and PLT are on their original scale. Dotted lines, historical levels (mean ± 3 SDs) from many toxicology experiments. Median percent change of day 5 from day 0, median [100% × (Xday5 − Xday0) / Xday0]. Statistical analysis in Table S1. C, pharmacokinetic comparison of anti–CD22-MCC-DM1 and anti–CD22-SPP-DM1 in rats. The cleavable linker ADC anti–CD22-SPP-DM1 cleared faster than the uncleavable linker ADC anti–CD22-MCC-DM1 (ADC, 66.5 mL/d/kg; total antibody, 13.2 mL/d/kg anti–CD22-SPP-DM1 vs. ADC, 18.0 mL/d/kg; total antibody, 11 mL/d/kg for anti–CD22-MCC-DM1). D, pharmacokinetic comparison of anti–CD22-MC-MMAF and anti–CD22-MC-vc-PAB-MMAE in rats. The cleavable linker ADC anti–CD22-MC-vc-PAB-MMAE cleared faster than the uncleavable linker anti–CD22-MC-MMAF (ADC, 89.6 mL/d/kg; total antibody, 23.9 mL/d/kg for anti–CD22-MC-vc-PAB-MMAE vs. ADC, 29 mL/d/kg; total antibody, 11 mL/d/kg for anti–CD22-MC-MMAF).
We and others (7) have hypothesized that uncleavable linker ADCs would be safer than ADCs with cleavable linkers. We tested this in a general way by using a rat model system in which the antibody was not targeted to any rat antigen, and found that, indeed, the uncleavable linker ADCs showed reduced toxicity compared with their cleavable counterparts. The faster decrease in the amount of cleavable linker ADC compared with the total antibody suggests that this is due to the release of free drug or linker-drug metabolite(s). In the context of safety, it is also important to note that there are differences in the metabolites that arise from cleavable and uncleavable linkers. For example, the reported metabolite of Ab-MCC-DM1 is lysine-MCC-DM1, a charged molecule that is relatively impermeant to cells (8). If released into the circulation, this molecule would presumably permeate normal tissues to a lesser extent than free DM1, for example. Thus, the increased safety of uncleavable linkers observed in this study could be a combination of both reduced drug release as well as differing properties of the metabolites.

Although cleavable SPP-DM1 resulted in efficacy in vivo when conjugated to antibodies to all seven NHL targets, uncleavable linker MCC-DM1 ADCs were only effective when targeted to two of them, CD22 and CD79b. These data suggest that ADCs targeted to CD22 and CD79b would be effective with a wide range of linker-drugs. However, it remains possible that the other antigens we tested could also be effective targets for uncleavable linker ADCs because different antibodies to the same target can sometimes lead to different efficacies (18), and other linker-drug combinations could result in greater efficacies than MCC-DM1. Thus, the right combination of antibody, linker, and drug could lead to an efficacious uncleavable ADC directed to one of the other antigens. CD19 and CD180, which are highly internalized, would seem to be the most promising antigens in this regard.

The work presented here suggests that anti–CD22-MCC-DM1, anti–CD22-MC-MMAF, anti–CD79b-MCC-DM1, and anti–CD79b-MC-MMAF are excellent candidates for the treatment for NHL. We have recently detailed the efficacy of anti–CD79b-MCC-DM1 and anti–CD79b-MC-MMAF (18) and found that these ADCs have significant efficacy in xenograft models of NHL. Our data also show that anti-CD22 and anti-CD79b ADCs with uncleavable linkers have potent efficacy and acceptable safety profiles in animal studies, and suggest that for specific targets, uncleavable linkers provide an opportunity to improve the therapeutic index of ADCs. It will be important to assess if the differences reported here are supported by additional future toxicology studies in a binding species and for extended dosing periods as anticipated for clinical use.

**Disclosure of Potential Conflicts of Interest**

All authors are employees of and have ownership interest in Genentech.

**Acknowledgments**

Received 6/13/2008; revised 12/24/2008; accepted 12/30/2008; published OnlineFirst 3/3/2009.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank Ben Seon (Roswell Park Cancer Institute, Buffalo, NY) for the SN8 hybridoma, Peter Senter and Dannon Meyer (Seattle Genetics, Inc., Bothell, WA) for auristatin antibody conjugations, David Xie and Rong Deng for help with the pharmacokinetic analysis, Klara Totpal and Lynne Giere for cell line production, Craig Crowley and Victoria Smith for helpful advice, Archana Upadhy and Elmer Wu for project or study management and reagent inventories, Daniel Coleman for help with the statistical analysis, and Vanitha Ramakrishnan for helpful comments on the manuscript.

**References**


Antibody-Drug Conjugates for the Treatment of Non-Hodgkin’s Lymphoma: Target and Linker-Drug Selection

Andrew G. Polson, Jill Calemine-Fenaux, Pamela Chan, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-08-2250

Supplementary Material
Access the most recent supplemental material at:
http://cancerres.aacrjournals.org/content/suppl/2009/03/02/0008-5472.CAN-08-2250.DC1

Cited articles
This article cites 27 articles, 8 of which you can access for free at:
http://cancerres.aacrjournals.org/content/69/6/2358.full#ref-list-1

Citing articles
This article has been cited by 24 HighWire-hosted articles. Access the articles at:
http://cancerres.aacrjournals.org/content/69/6/2358.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.