Phase I Study of a Bispecific Ligand-Directed Toxin Targeting CD22 and CD19 (DT2219) for Refractory B-cell Malignancies

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Abstract

**Purpose:** The novel bispecific ligand-directed toxin (BLT) DT2219 consists of a recombinant fusion between the catalytic and translocation enhancing domain of diphtheria toxin (DT) and bispecific single-chain variable fragments (scFV) of antibodies targeting human CD19 and CD22. We conducted a phase I dose-escalation study to assess the safety, maximum tolerated dose, and preliminary efficacy of DT2219 in patients with relapsed/refractory B-cell lymphoma or leukemia.

**Experimental Design:** DT2219 was administered intravenously over 2 hours every other day for 4 total doses. Dose was escalated from 0.5 μg/kg/day to 80 μg/kg/day in nine dose cohorts until a dose-limiting toxicity (DLT) was observed.

**Results:** Twenty-five patients with mature or precursor B-cell lymphoid malignancies expressing CD19 and/or CD22 enrolled to the study. Patients received median 3 prior lines of chemotherapy and 8 failed hematopoietic transplantation. All patients received a single course of DT2219; one patient was retreated. The most common adverse events, including weight gain, low albumin, transaminitis, and fever were transient grade 1–2 and occurred in patients in higher dose cohorts (>40 μg/kg/day). Two subjects experienced DLT at dose levels 40 and 60 μg/kg. Durable objective responses occurred in 2 patients; one was complete remission after 2 cycles. Correlative studies showed a surprisingly low incidence of neutralizing antibody (30%).

**Conclusions:** We have determined the safety of a novel immunotoxin DT2219 and established its biologically active dose between 40 and 80 μg/kg/day × 4. A phase II study exploring repetitive courses of DT2219 is planned. *Clin Cancer Res.* 21(6); 1267–72. ©2015 AACR.

Introduction

DT2219, a recombinant fusion protein, contains the catalytic and translocation enhancing domain of diphtheria toxin (DT) and bispecific single-chain variable fragments (scFV) of antibodies targeting human CD19 and CD22 cell surface receptors (1). The protein is engineered so that the native binding region of diphtheria toxin (DT) is replaced by the more avidly bind scFV. After binding, CD19 and CD22 readily internalize (2, 3) to promote toxin entry into the cytosol, inhibition of protein synthesis, and subsequent apoptotic cell death (4). Notably, previous preclinical studies showed that the combination of two different scFVs and a toxin on the same single-chain molecule resulted in greater anticancer activity compared with monomeric anti-CD19 or anti-CD22 connected with truncated DT (5). In addition, xenograft studies demonstrated significant inhibition of CD22+CD19+ Raji tumor growth and an enhanced therapeutic effect with repetitive dosing in vivo (1).

CD19, a 95-kDa membrane glycoprotein, is ubiquitously present on the surface of all stages of B lymphocyte development and is also expressed on most B-cell mature lymphoma cells and leukemia cells (6). CD22 is a 135-kDa glycoprotein expressed on B-lineage lymphoid precursors, including precursor B acute lymphoblastic leukemia, and often is coexpressed with CD19 on mature B-cell malignancies (7). DT mediates potent cell-cycle-independent cell death and therefore can be particularly effective as an alternative therapy for chemotherapy-refractory malignancies (8). We conducted a phase I dose-escalation study to assess safety, maximum tolerated dose (MTD), and preliminary efficacy in patients with chemorefractory B-cell lymphoma or leukemia expressing CD19 and/or CD22.

Patients and Methods

**Patients**

All patients gave written informed consent to treatment on the Institutional review board (IRB)-approved treatment protocol in accordance with Declaration of Helsinki. This clinical trial was registered at clinicaltrials.gov (NCT 00889408). DT2219 was cGMP manufactured at the University of Minnesota under FDA IND-application (IND number 1000780). Inclusion criteria included: age >12 years, CD19 and/or CD22 expressing B-cell lymphoma or leukemia refractory to conventional therapy, and...
Translational Relevance

In a phase I clinical trial, we report the safety, dosing feasibility, biologic activity, and clinical efficacy of DT2219; a novel recombinant protein engineered by fusing the truncated diphtheria toxin (DT390) with bispecific single-chain variable fragments of antibodies targeting human CD19 and CD22. Bispecific immunotoxins represent a novel therapeutic strategy targeting tumor-specific antigens while limiting systemic toxicity. DT2219 will be further developed for therapy of mature or precursor B-cell lymphoid malignancies. In the future, DT2219 can be used in combination with other targeted agents providing a safer and nongenotoxic alternative to chemotherapy.

Treatment plan

In this phase I study, patients received DT2219 in a single course at doses ranging from 0.5 μg/kg/day (1/500th of the MTD in rabbits) to 80 μg/kg/day i.v. over 2 hours (4 hours for the first dose) every other day for 4 total doses (days 1, 3, 5, and 8). The dose was escalated in 9 cohorts until a dose-limiting toxicity (DLT) was observed (Table 2). The first 15 patients were treated by rapid escalation design (dose cohorts 1–3) or by standard 3+3 dose escalation design (cohorts 4–6). We applied continual reassessment method (9) to the last 10 patients (dose cohorts 8, 9) with the goal to identify the dose level that corresponds to a desired toxicity rate of 33% or less using grade 3 or greater DT2219-related toxicity except blood pressure changes and fever as the targeted toxicity [based on NCI Common Terminology Criteria for Adverse Events version (CTCAE 4)].

Statistical analysis

Patients and disease characteristics were summarized using descriptive statistics. For binary endpoints such as toxicity and clinical response, frequencies and proportions were calculated. For continuous endpoints such as area under the curve (AUC), summary statistic including median and range (minimum and maximum) were used. All statistical analyses were performed with Statistical Analysis System software version 9.3 (SAS Institute, Inc.).

Results

Patients and toxicities

We enrolled 25 patients with a median age of 55 years (range, 34–78 years). Patient and disease characteristics are detailed in Table 1. All patients were evaluable for safety and efficacy. Ten patients had pre-B acute lymphoblastic leukemia, 5 had chronic lymphocytic leukemia (CLL), and 10 had non-Hodgkin lymphoma. All patients were chemo-refractory with a median of 3 (range, 1–14) prior therapies. Most patients received prior monoclonal antibody (rituximab, ofatumumab, inotuzumab), none of the patients received blinatumomab, and eight failed prior hematopoietic cell transplantation (autologous and 3 allogeneic). All tumors were biopsy-confirmed to express CD19 and/or CD22 in at least 20% of malignant cells. Most tumors (89%) had over 60% malignant cells CD19+ and/or CD22+ and 13 expressed both CD19 and CD22 targets.

All 25 patients received a single course of therapy. One patient attained partial response after the first cycle and received an additional 4 dose course after the protocol was amended with FDA and IRB approval. Twelve patients treated at doses ranging from 0.5 μg/kg/day to 20 μg/kg/day exhibited no or minimal adverse reactions (Table 2). All 13 patients treated at dose levels ≥40 μg/kg/every other day × 4 experienced AE attributed to drug treatment. No infusion toxicity was observed. The most common transient grade 1–2 AEs included weight gain (range, 5%–14% of
underlying lymphoma or leukemia often contributed to cytopenia. Whereas lactate dehydrogenase (2–2.3-fold) transiently increased in 4 patients after the first dose, clinical tumor lysis or acute cytokine release syndrome did not occur. Most AEs were recognized during routine monitoring before the second or third dose of DT2219. All AEs were brief and resolved completely within one week. Two patients experienced DLTs: the first DLT occurred at the 40 μg/kg dose level in a 71-year-old patient with ALL who developed back pain along with acute lower extremity weakness after the third dose of study drug. While the patient had a recent history of CNS leukemia before enrollment, brain MRI and cerebrospinal fluid studies at the time of AE were negative for leukemic CNS involvement. This patient died of rapidly progressive disease. No neurologic adverse effects of any grade occurred in the next 10 patients treated at this or higher doses (40–80 μg/kg).

The second DLT event occurred at the 60 μg/kg dose level in a 55-year-old patient who developed grade 3 capillary leak and manifested as hypoxemia, hypotension, pulmonary edema, and hypoalbuminemia in combination with febrile neutropenia. The patient was hospitalized and treated with oxygen, intravenous antibiotics, hydration, and diuresis. Her symptoms improved with supportive care to grade 2 after 2–3 days and completely resolved in 10 days.

Pharmacologic and immunologic studies
At the time of enrollment, most patients exhibited low peripheral blood B-cell counts [median B-cell count 3.5% (<0.1 × 10^9 cells/μL); range, 0%–52%; n = 10] often associated with prior rituximab, corticosteroids, and chemotherapy. The effect of DT2219 on B lymphocytes in a patient with an extramedullary ALL relapse shortly after allogeneic HCT was observed with gradual decline in number of peripheral blood CD19- and CD22-expressing cells after 4 doses of DT2219 (Fig. 1A). The possibility that DT2219 may interfere with fluorochrome-labeled anti-CD19 and anti-CD22 was excluded by examining CD20^−
foid, peripheral edema, and hypoalbuminemia consistent with capillary leak syndrome, grade 1–2 fever, and fatigue (Table 2). Seven patients experienced isolated mild elevation of liver function tests (1.1–2.1 × ULN) without hyperbilirubinemia, which resolved within 3 to 7 days. Thrombocytopenia and anemia occurred in 5 patients; however, marrow involvement by

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### Table 1. Patients and disease characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of subjects (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>55 (34–78)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>13/12</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>10</td>
</tr>
<tr>
<td>CLL</td>
<td>5</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>11</td>
</tr>
<tr>
<td>Relapsed refractory</td>
<td>14</td>
</tr>
<tr>
<td>Site of disease</td>
<td></td>
</tr>
<tr>
<td>Marrow</td>
<td>13</td>
</tr>
<tr>
<td>Extramedullary ALL</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15</td>
</tr>
<tr>
<td>Extra lymphatic sites</td>
<td>3</td>
</tr>
<tr>
<td>CD19 and CD22 expression on tumor</td>
<td></td>
</tr>
<tr>
<td>CD19 only</td>
<td>11</td>
</tr>
<tr>
<td>CD22 only</td>
<td>1</td>
</tr>
<tr>
<td>CD19 and 22 both</td>
<td>13</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>Lines median (range)</td>
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<tr>
<td>Inotuzumab</td>
<td>1</td>
</tr>
<tr>
<td>Autologous hematopoietic cell transplantation</td>
<td>3</td>
</tr>
<tr>
<td>Allogeneic hematopoietic cell transplantation</td>
<td>5</td>
</tr>
</tbody>
</table>

Pharmacologic and immunologic studies
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### Table 2. Treatment detail and AEs

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Escalation detail</th>
<th>DT2219 dose μg/kg/day</th>
<th>Doses received</th>
<th>Total dose per cycle in μg</th>
<th>N</th>
<th>Drug-related AEs (CTCAE v4.03 toxicity grade)</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapid escalation</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.25</td>
<td>4</td>
<td>5</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.5</td>
<td>4</td>
<td>10</td>
<td>Grade 1 fever (n = 1)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Standard escalation</td>
<td>5.0</td>
<td>4</td>
<td>20</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>10.0</td>
<td>4</td>
<td>40</td>
<td>4*</td>
<td>None</td>
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</tr>
<tr>
<td>6</td>
<td></td>
<td>20.0</td>
<td>4</td>
<td>80</td>
<td>3</td>
<td>Grade 1 ALT elevation (n = 1) Grade 2 ALT, AST elevation (n = 1)</td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td>40.0</td>
<td>4^a</td>
<td>160</td>
<td>5</td>
<td>Grade 1 AST, Grade 2 hypoalbuminemia (n = 1)</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Continual Reassessment</td>
<td>60.0</td>
<td>4^a^d</td>
<td>240</td>
<td>5</td>
<td>Grade 2 capillary leak syndrome (n = 2) Grade 1 fatigue (n = 1) Grade 2 hypokalemia (n = 1) Grade 3 legs weakness (n = 1)</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>80.0</td>
<td>4</td>
<td>320</td>
<td>3</td>
<td>Grade 1 hypokalemia (n = 1) Grade 1-2 capillary leak syndrome (n = 2) Grade 2 anemia (n = 1) Grade 1 thrombocytopenia (n = 2) Grade 2 fever (n = 2) Grade 4 neutropenia (n = 1) Grade 3 capillary leak syndrome (n = 1) Grade 3 thrombocytopenia (n = 1) Grade 2 hearing loss (n = 1) Grade 1 hypokalemia (n = 1)</td>
<td>No</td>
</tr>
</tbody>
</table>

^aOne patient at the 10 μg/kg/day was less than 12 years old and enrolled after receiving permission from the local IRB.
^bPatient with DLT received 3 doses of DT2219.
^cOne patient at the 60 μg/kg/day was retreated 8 weeks later with second cycle at dose 40 μg/kg/day.
^dOne patient was dose reduced for fourth injection to 40 μg/kg/day due to capillary leak syndrome.

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cells, which also declined over time. The B-cell depletion was specific as CD3⁺ T-cell levels remained constant during the testing interval.

We also measured the circulating concentration of DT2219 in a functional pharmacokinetic bioassay (Fig. 1B). Patients treated at dose levels 0.5–20 μg/kg/day had no detectable drug in serum when sampled on day 1 and 8 at 15, 30, 45, 60, and 120 minutes postinfusion. All evaluable patients at the University of Minnesota treated with ≥40 μg/kg/dose (n = 10) demonstrated detectable levels of DT2219 with the exception of one (Fig. 1C) with preexisting antibodies to DT (Fig. 1D). The AUC after the first dose (4-hour infusion) was lower at a median of 285 μg/mL × minutes (range, 0–2,020; n = 8) compared with drug levels after the fourth dose (2 hours infusion; AUC median 1,249 μg/mL × minutes; range, 0–1,692; n = 7). A representative AUC is shown in Fig. 1B. The drug half-life ranged from 59 to 110 minutes (n = 4).

Because the recombinant immunotoxin contains a bacterial toxin, immunogenicity is expected and can be a major barrier to

Figure 1. Immunologic and pharmacokinetic studies. A, peripheral blood mononuclear cell (PBMC) analysis of a representative patient is shown. PBMCs were enriched from patient blood and collected at various times post-treatment. Flow cytometry was used to count cells expressing CD22, CD19, CD20, or CD3. B, a bioassay was used to determine the area under the curve (AUC) of serum DT2219 levels in serum by measuring the ability of diluted serum to inhibit proliferation of CD22⁺ CD19⁺ Raji indicator cells. Drug serum levels at various times were analyzed using prism 5.0 software to calculate AUC. A concentration-time curve is shown for our second patient at 60 μg/kg. T1/2 was 59 minutes. C–F, DT2219 serum levels and neutralizing antibodies. C, a nonresponding patient treated at the 80 μg/kg dose level showing no evidence of DT2219 in serum. D, high levels of neutralizing antibodies in this same patient at day 8 through 22. In contrast, E shows the patient that completely responded to 60 μg/kg/day DT2219 had a serum drug concentration and F shows this same patient had no detectable neutralizing antibodies. DT2219 serum levels were calculated from assays in which various serum dilutions were tested for their ability to block the killing of Raji cell proliferation. Serum collected prior to drug administration served as a negative control. Neutralization assays were performed based on the ability of undiluted patient serum samples to block the killing of a 99% inhibitory dose of DT2219. The percentage of neutralization was calculated.

A

Absence of drug in patient 7 serum: Various dilutions of serum does not inhibit Raji

B

Extrapolation of serum drug content over time for DT2219 – AUC

C

Presence of drug in patient 4 serum: Various dilutions of serum inhibit Raji cells

D

Presence of neutralizing antibody in serum of patient 7

E

Presence of drug in patient 4 serum: Various dilutions of serum inhibit Raji cells

F

Lack of neutralizing antibody in serum of patient 4

% Control response

% Positive cells by flow cytometry

Minutes

Serum dilution

% Control response

% Control response

Treatment (blocking agent)

% Control response

Treatment (blocking agent)

% Positive cells by flow cytometry

Days

Serum dilution

% Control response

% Positive cells by flow cytometry

Fig. 1.
the potential activity of bacterial toxin-based drugs. We measured serum neutralizing antibodies in all patients treated with ≥40 μg/kg/dose at days 1, 8, 15, 29, 35, and 42 (n = 9). Neutralizing antibodies developed in 3 evaluable patients (30%) at dose levels between 40 and 80 μg/kg at median of one week (range, 1–2 weeks) after the first dose of DT2219. One patient had pre-formed anti-DT antibody that we detected at screening and attributed to prior DT immunization. In some patients, the presence of neutralizing antibodies inversely correlated with the serum concentration of DT2219 (Fig. 1C); however, no consistent pattern was recognized.

Clinical responses

Twenty-five patients were evaluable for response, recognizing that only 9 patients in the highest dose cohorts had measurable drug levels. Three patients had biopsy performed at the time of progression and all 3 demonstrated persistence of one or both CD19/CD22 antigens. Treatment produced an objective tumor response in two of these patients. After a single course of DT2219 at dose level 40 μg/kg/day × 4, a 77-year-old patient with chemotherapy-refractory CD19⁺CD22⁺ CLL experienced a 40% reduction in cervical and axillary adenopathy with decrease of an abdominal tumor mass at day 28 after treatment, which was sustained for 2 months. (Fig. 2A) Patient was in continuous abdominal tumor mass at day 28 after treatment, which was sustained for 2 months. (Fig. 2A) Patient was in continuous remission after 1 cycle, an additional cycle led to complete response. In one patient who achieved partial remission after 1 cycle, an additional cycle led to complete response. One patient received a second DT2219 course at a reduced dose of 30 μg/kg/day × 4, which resulted in a complete resolution of a subcutaneous mass and pelvic lymphadenopathy (Fig. 2B). Second patient is alive and in complete remission with no neutralizing antibodies (Fig. 1F), currently at 8 months after therapy. We observed no correlation between CD19 and CD22 target expression and clinical activity in this small cohort.

Discussion

We have established the safety and dosing feasibility of a novel CD19/CD22 bispecific ligand-directed toxin DT2219. We also demonstrated that the current dosing schedule and route of administration achieves drug levels capable of biologic and clinical response against CD19/22-expressing lymphoid malignancies refractory to standard therapies with a surprisingly low incidence of neutralizing antibody responses. The current phase I study shows that although MTD was not reached, the drug can be administered safely up to 80 μg/kg/day at days 1, 3, 5, and 8 for total of 4 doses. The first dose infused over 4 hours as a safety precaution was always well tolerated. All other doses were administered over 2 hours. Interestingly, the AUC measured for the first dose was almost always lower than the AUC measured for the fourth dose suggesting the importance of shorter infusion time for immunotoxins with brief half-life. Early on-target saturation also may play a role in low AUC at the onset of therapy, yet the DT2219 dosing in 4 infusions 1 to 2 days apart resulted to adequate drug levels, biologic effectiveness, and tolerable toxicity. Although clinical responses to DT2219 were observed at doses 40 and 60 μg/kg/day, the 4 doses as administered in this trial may be inadequate to induce deeper remissions. In one patient who achieved partial remission after 1 cycle, an additional cycle led to complete tumor elimination. The rationale for improved efficacy with repetitive dosing is supported by others who are developing immunotoxin conjugates using bacterial toxins, such as the anti-CD22 monoclonal antibody pasudotox for hairy cell leukemia or SL-401, an IL3 receptor-DT fusion protein for myeloid malignancies (12–14).

In our experience, increasing the number of consecutive doses per cycle is unlikely to be tolerated; however, the treatment schedule with repetitive cycles of four every other day doses at least a week apart should be explored in future studies.

An important observation in this study is the lack of neutralizing antibodies formation in 7 of 10 of the evaluable patients treated at the 3 highest dose cohorts. In other trials involving DT-related immunotoxins in non–B-cell malignancies, neutralizing antibody responses have been frequent. One potential explanation is that prior rituximab therapy and B-cell lymphopenia contributed to a blunted humoral response that can last up to 1 year (4).

As is typical for most immunotoxins, the potential toxicity of greatest concern at higher doses was capillary leak syndrome. The underlying mechanism at least in part involves pinocytosis of the immunotoxin by endothelial cells, which is dose-dependent and thus of a particular concern at higher drug concentrations (15). Drug development strategies to engineer toxins that do not induce
capillary leak syndrome are underway (16, 17). However, despite capillary leak in many patients at the higher dose levels (40–80 μg/kg/day), this side effect was manageable and fully reversible. In contrast to recently approved anti-CD19 targeting bispecific anti-body blinatumomab, which produced neurotoxicity in 11% of patients, DT2219 therapy caused no grade 1–2 neurotoxicity and only a single grade 3 paraparesis of an uncertain drug causality. (18) Importantly, other complications inherent in the use of many experimental immunotherapeutic agents such as infusion-related reactions, pyrexia, tumor lysis, or cytokine release syndrome were not observed in this study (19).

In conclusion, we have demonstrated safety, dosing feasibility, and preliminary clinical activity of a bispecific ligand-directed toxin in chemotherapy refractory B-cell lymphoid malignancies. In contrast to cytostatic chemotherapy, DT2219-mediated tumor cell killing is cell cycle and p53 independent (8), making it a particularly attractive therapy for overcoming resistance to standard chemotherapeutics in lymphoma.

A phase I/II clinical study designed to administer sequential cycles of this unique heterodimeric bispecific antibody toxin conjugate is underway.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V. Bachanova, Q. Cao, M.R. Vernieris, H. Kantarjian, D. Weisdorf, D.A. Vallera

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Study supervision: V. Bachanova, Q. Cao, D. Lewis

Other (conducted clinical trial and wrote a protocol): V. Bachanova

Other (pathology review): B. Grzywacz

Acknowledgments

The authors thank Julie Curtisinger from University of Minnesota Cancer Center Translational Therapy Lab for assistance with blood samples retrieval and Michael Franklin for editorial assistance.

Grant Support

This work was supported U.S. Public Health Service grant R01CA36725 (to D. Vallera), the RAND Shaver Foundation, the Lion’s Children’s Cancer Fund, the William Lawrence and Blanche Hughes Fund, and by the National Center for Advancing Translational Sciences of the NIH Award Number UL1TR000114 (to V. Bachanova). This work was also supported in part by NIH P30 CA77598 utilizing the Biostatistics and informatics core, Masonic Cancer Center, University of Minnesota shared resource.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked this fact.

Received November 6, 2014; revised December 26, 2014; accepted January 19, 2015; published online March 13, 2015.

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