Late-Stage Cancer Patients Remain Highly Responsive to Immune Activation by the Selective TLR8 Agonist Motolimod (VTX-2337)

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Abstract

Purpose: Immunotherapy as a treatment for cancer holds the promise of complete and durable tumor remission, yet the immunosuppressive environment created by many tumors, advanced patient age, and previous treatments with cytotoxic agents may limit the approach. The activity of motolimod (VTX-2337), a potent and selective Toll-like receptor 8 (TLR8) agonist, was therefore assessed in the context of advanced, late-stage cancer patients.

Experimental Design: The repertoire of mediators induced from human peripheral blood mononuclear cells in response to motolimod was characterized. Translational studies in cynomolgus monkeys elucidated the activity of motolimod on an intact immune system, identified biomarkers of TLR8 activation, and defined the relationship between the pharmacokinetic and pharmacodynamic (PK/PD) response. The PK/PD relationship for motolimod in cancer patients was assessed, compared with preclinical findings, and contrasted with activity in healthy volunteers.

Results: In late-stage cancer patients, plasma levels of multiple biomarkers, including IL6, G-CSF, MCP-1, and MIP1-β, increased with increasing motolimod dose. The magnitude and breadth of the biomarker response closely aligned with the response seen in preclinical studies, demonstrating that advanced cancer patients remained responsive to TLR8 activation. In addition, the PK/PD relationship in cancer patients closely aligned with the activity of motolimod seen in healthy volunteers.

Conclusions: Late-stage cancer patients are highly sensitive to TLR8 activation by motolimod. Tumor burden, advanced age, and prior treatment history with cytotoxic agents did not moderate or modify the response predicted by nonclinical studies and confirmed in healthy volunteers. Clin Cancer Res; 21(24); 5445–52. ©2015 AACR.

Introduction

Motolimod (VTX-2337) is a selective, small molecule, Toll-like receptor 8 (TLR8) agonist that is currently in clinical development as an immunotherapy for ovarian cancer and squamous cell carcinoma of the head and neck (SCCHN). Motolimod activation of TLR8 in endosomal compartments of monocytes and myeloid dendritic cells (mDC) stimulates the release of distinct inflammatory mediators, including Th1-polarizing cytokines, chemokines, and other acute phase proteins (1–4). TLR8 activation of antigen-presenting cells (APC) also increases expression of costimulatory molecules, which facilitate the development of adaptive, T-cell-mediated immune responses. In addition, TLR8 agonists can drive natural killer (NK) cell function by direct TLR8 activation, or via the induction of specific cytokine networks (5). Accordingly, antitumor responses, facilitated by monoclonal antibodies (mAb) that evoke antibody-dependent cell cytotoxicity (ADCC) or “antigenic” tumor cell death triggered by some cytotoxic agents, including anthracyclines, are enhanced by motolimod activity (5, 6). Thus, TLR8-mediated immune activation has the potential to act in concert with many existing standard-of-care cancer treatments, and is the basis for clinical trials of motolimod in combination with pegylated liposomal doxorubicin for ovarian cancer and with cetuximab for SCCHN.

Induction of a productive antitumor response through TLR8 activation is closely tied to the fitness of an individual’s immune system. One potential concern is that a cancer patient’s general health, production of immunomodulatory mediators such as VEGF, IL10, and prostaglandin E2 (PGE2) from tumors (7–9), age, and prior treatments with immunosuppressive cytotoxic agents, may blunt the activity of motolimod in these individuals. Therefore, the activity of motolimod in cancer patients has been characterized to determine whether their immune response aligns with results predicted by in vitro and translational preclinical studies. In addition, the pharmacokinetic and pharmacodynamic (PK/PD) relationship for motolimod in cancer patients is compared with that observed for healthy volunteers.
Translational Relevance

Recently, immunotherapy has been propelled into the forefront of new cancer treatments, as it holds the promise of complete and durable tumor remission. Motolimod (VTX-2337), a novel immunotherapy, activates TLR8, which drives antigen presentation, natural killer (NK) cell cytotoxicity, and induces Th1-polarizing cytokines. These activities can facilitate the development of adaptive, tumor-directed immune responses. However, the immunosuppressive environment created by many tumors, advanced patient age, and previous treatments with cytotoxic agents may temper the activity of motolimod in cancer patients. This study demonstrates that the magnitude and breadth of the biomarker response to motolimod in advanced- or late-stage cancer patients, with a life expectancy ≥16 weeks closely aligned with results from in vitro and translational preclinical studies. The pharmacokinetic and pharmacodynamic response in late-stage cancer patients also closely correlates with that in healthy volunteers, confirming that immune activation through TLR8 is not compromised in advanced cancer patients.

Materials and Methods

Motolimod

Motolimod, formerly designated as VTX-2337, is a synthetic small molecule that is a selective TLR8 agonist. The molecule is based on a 2-aminobenzazepine core, and the structure has been previously published (5). The molecule has no clinically relevant activity on any other TLR family members, and due to its non-nucleotide structure, motolimod does not interfere with purine catabolism or interact with purinergic receptors.

Measurement of immune mediators

In vitro production of immune mediators by peripheral blood leukocytes in response to motolimod activation was characterized in blood samples from 10 healthy volunteers using the TruCulture assay system (Myriad-RBM). Blood samples collected from each volunteer were incubated at 37°C in TruCulture tubes that contained either the supplied media (baseline response), or media supplemented with motolimod at concentrations of 300 and 1,000 nmol/L. Following a 24 hours activation period, media from the TruCulture tubes were assessed for levels of 96 unique analytes or biomarkers of immune activation (including cytokines, chemokines, and acute phase proteins) using the HumanMAP v1.6 inflammation panel (Myriad-RBM).

To assess motolimod activity in vivo, plasma samples were collected from treated cynomolgus monkeys, cancer patients, and healthy volunteers at various times relative to dosing (see below) and analyzed using the HumanMAP v1.6 inflammation panel. Mediators that were induced in response to increasing doses of motolimod were considered biomarkers of TLR8 activation. Although the HumanMAP v1.6 inflammation panel is optimized for quantitation of human mediators, it is able to quantify many TLR8-responsive analytes in cynomolgus monkeys.

Nonclinical studies in cynomolgus monkeys

Cynomolgus monkeys (3/dose level) were administered s.c. doses of motolimod at dose levels of 1.2, 3.6, and 12 mg/m². Plasma levels of motolimod were assessed at 1, 2, 4, 8, 12, and 24 hours after dosing using high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS), to assess the PK of the agent. Additional plasma samples were collected predose and at 6 and 12 hours after dosing to assess levels of mediators induced by TLR8 activation using the HumanMAP v1.6 inflammation panel, described above.

Studies in cynomolgus monkeys were conducted at Charles River Laboratories, Preclinical Services, in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the NIH. Study protocols were reviewed and approved by the Charles River Institutional Animal Care and Use Committee.

Clinical studies

Clinical study VRXP-A101 (NCT00688415) was a single-arm, open-label, dose-escalation, phase I study conducted at 2 study centers in the United States (November 2008–October 2010). Study subjects were adult patients diagnosed with histologically or cytologically confirmed solid tumors or lymphoma, with locally advanced or metastatic disease for which there were no further treatment options known to provide clinical benefit. Study subjects had a life expectancy of ≥16 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Thirty-three subjects were evaluated in 8 successive cohorts using a dose-ascending protocol, where motolimod was administered weekly via s.c. injection, with weekly doses ranging from 0.1 to 3.9 mg/m². Motolimod was well tolerated, with the predominant adverse events (AE) being transient grade 1 or 2 fever, chills, flu-like symptoms, and injection site reactions (10). The 3 highest motolimod dose levels: 2.0, 2.8, and 3.9 mg/m² (cohorts 6–8) administered weekly, were both active and tolerated. In addition, motolimod doses evaluated in ongoing phase II oncology trials fall within the range of 2.0 to 3.9 mg/m². The demographics of these late-stage cancer patients, including age, cancer type, and previous treatment history, are shown in Table 1.

Clinical study VRXP-A105 was a single-center, open-label, 2-period, 2-treatment, randomized, crossover, phase I study conducted in healthy male and female adult volunteers. Ten healthy volunteers (5 males and 5 females) received two motolimod doses of 2.5 mg/m² administered by the s.c. route, and separated by a 1 week washout period. This dose was considered pharmacologically active, close to dose levels being evaluated in phase II oncology trials, and well tolerated in previous clinical studies. The demographics of subjects participating in study VRXP-A105 are shown in Table 1.

Both clinical studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles based on the Declaration of Helsinki. Approval for study procedures was obtained from the institutional review boards of each study site and all subjects provided written informed consent upon study enrollment.

Pharmacokinetic and pharmacodynamic assessments in human subjects

The PD response to motolimod in human subjects was assessed using plasma samples collected predose and 8 hours following the initial dose. Analyses that showed a dose-related response in vitro and in preclinical studies were considered...
biomarkers of TLR8 activation. Changes in plasma biomarkers levels were used to gauge the extent of innate immune activation by motolimod in advanced-stage cancer patients and healthy volunteers.

For the PK evaluation of motolimod in cancer patients, blood samples were collected predose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 hours after the initial dose in clinical study VRXP-A101. For the PK evaluation in healthy volunteers (clinical study VRXP-A105), blood samples were collected predose and at 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 12, and 24 hours after the first motolimod administration. The quantitation of motolimod in the plasma from the blood samples in both studies was done using a validated HPLC/MS-MS method.

Data analysis
Following motolimod administration, clinical subjects were monitored for changes in plasma levels of mediators indicative of TLR8 activation. The magnitude of this PD response was assessed for each study subject. Fold-increase relative to baseline values were calculated for each biomarker at 8 hours, and mean fold increases from baseline values were then calculated for each dose cohort in both clinical studies. If baseline levels were below the level of quantification for the analyte, the lowest quantifiable level for the analyte provided by Myriad-RBM was used to calculate the fold increase. The fold increase in plasma concentration values was log$_2$ (base 2) transformed. Significant changes were assessed using a one-sample Wilcoxon rank sum test, testing (for each analyte) whether the mean log-fold change is different from zero. Resulting P values were corrected for multiple testing using the FDR approach of Benjamini and Hochberg (11), set at 10%. Only significant changes with a minimum fold change of 1.3 were retained. Comparison of baseline plasma mediator and blood leukocyte counts was done using a t test comparing the levels in healthy volunteers with cancer patients. Determination of the PK parameters for motolimod in cynomolgus monkeys and human subjects was done using a noncompartmental method in Phoenix WinNonlin 64, Version 6.3 (Pharsight a Certara-Company). Actual plasma sampling times and actual administered dose levels were used in the analysis. Plasma motolimod values below the limit of quantification were set to 0; single values of ‘0’ between 2 measurable concentrations were excluded from analyses, as were values occurring after 2 consecutive values of 0.

Results
Human blood leukocyte response to motolimod
The range of mediators induced by motolimod in blood collected from 10 healthy volunteers was assessed using TruCulture tubes. Of the 96 analytes measured in the culture media, 14 mediators increased in a concentration-dependent manner, shown in Fig. 1. Absolute levels of the mediators induced at the 1,000 nmol/L concentration of motolimod ranged from a median of 17 pg/mL for granulocyte-colony stimulating factor (G-CSF), up to a median of 34,050 pg/mL for macrophage inflammatory protein-1β (MIP-1β). In addition, the level of induction was more than 500-fold for multiple mediators, including IL1 receptor antagonist (IL1RA), IL6, IL8, IL10, monocyte chemotax attractant protein-1 (MCP-1), MIP-1α, MIP-1β, and TNFα. Consistent with the hypothesis that TLR8 activation can facilitate the development of tumor-directed adaptive immune responses, motolimod induced the Th1 polarizing cytokines, IL12p70, and IFNγ. Overall, these in vitro results, using a large multiplex assay system, provide a broad assessment of the mediator response to human TLR8 activation by motolimod.

Because of the high degree of similarity between humans and primate TLR8 (12), a similar evaluation was done in whole blood collected from cynomolgus monkeys. The response in cynomolgus monkey blood closely paralleled that of humans (data not shown), demonstrating that motolimod is a potent TLR8 agonist in the species. Therefore, in vivo studies of motolimod in the cynomolgus monkey offer the opportunity to translate the in vitro activity to a PD response, before the conduct of clinical studies.

Pharmacodynamic response in cynomolgus monkeys
Mediators induced by motolimod in human blood cultures represent the repertoire of cytokines and chemokines that are released from circulating peripheral blood mononuclear cells in response to TLR8 activation. However, in vivo, the production, utilization, and clearance of cytokines and chemokines is a dynamic process, and some mediators seen in vitro may not circulate in the plasma following motolimod dosing. To characterize both the mediator response and PK profile of motolimod in...
In vitro, translational studies were conducted in cynomolgus monkeys (n = 3/dose). Motolimid doses levels ranging from 1.2 to 12.0 mg/m² were administered s.c. Following dosing, plasma levels of motolimid followed a predictable and dose-related pattern. Motolimid was readily measured in the plasma within 1 hour, whereas mean maximum concentration (C_{max}) and AUC values increased with increasing dose level, as shown in Fig. 2A. Changes in plasma levels of mediators that were induced in human blood cultures served as a measure of motolimid’s PD activity over the range of doses. Mediators showing dose-related increases in plasma were many of the mediators induced to high levels in vitro, including G-CSF, IL1RA, IL6, MCP-1, and MIP-1β, as shown in Fig. 2B. The largest increases were in G-CSF and IL6, with mean log₂ increases of 6.5- and 6.7-fold, respectively, at the 12.0 mg/m² dose, and 4.1- and 3.7-fold increases, respectively, at the 3.6 mg/m² dose. Plasma levels of several chemokines induced in human blood were also highly responsive to motolimid activation of TLR8. At the 12.0 mg/m² dose, mean log₂ increases of 5.8- and 4.8-fold were seen for MCP-1 and MIP-1β, respectively, whereas increases of 2.0- and 2.8-fold, respectively, were seen at the 3.6 mg/m² dose.

Baseline mediator levels and peripheral blood leukocytes levels in clinical study subjects

Basal plasma levels of mediators known to be induced by motolimid in cynomolgus monkeys and/or in vitro studies with human blood, were compared between the late-stage cancer patients participating in study VRXP-A101 and the healthy volunteers enrolled in Study VRXP-A105 (see Fig. 3). Although mean levels trended slightly higher for cancer patients, only the difference in IL6 levels was statistically significant. Overall, baseline plasma mediator levels in the older, late-stage cancer patients were comparable with younger, healthy volunteers. A comparison of blood leukocyte counts at baseline, found no significant differences in total white cell counts, absolute neutrophil or monocyte counts between cancer patients and healthy volunteers. Levels of lymphocytes were significantly reduced in cancer patients relative to the healthy volunteers (1.03 × 10^3 ± 0.42 × 10^3 versus 1.74 × 10^3 ± 0.39 × 10^3, P < 0.01).

Pharmacodynamic responses to motolimid in clinical subjects

In late-stage cancer patients, motolimid doses between 2.0 and 3.9 mg/m² (Cohorts 6–8, n = 14), induced statistically significant, dose-related increases in plasma levels of G-CSF, IL10, IL1RA, IL6, IL8, MCP-1, MIP-1β, and matrix metalloprotease 9 (MMP9),
shown as a fold-increase (log2) in Fig. 4A. Most of these responsive
mediators had been identified as biomarkers of motolimod
activity in both peripheral blood cultures from healthy volunteers
and in the plasma of motolimod-dosed cynomolgus monkeys. At
comparable dose levels of 3.9 mg/m² for cancer patients versus 3.6
mg/m² in cynomolgus monkeys, mediator induction trended
higher for the cancer patients (Figs. 2B and 4A).

In healthy volunteers, motolimod induced significant changes
in the same array of analytes that were elevated in the plasma of
advanced-stage cancer patients. Although increases in GH
(growth hormone), VEGF, and MPO (myeloperoxidase) reached
statistical significance in healthy volunteers, but not in cancer
patients, the magnitude of these changes was similar for the two
groups (Fig. 4A). Overall, the magnitude of the increase in
mediator levels in late-stage cancer patients from cohorts 6 and
7 (2.0 and 2.8 mg/m²) was comparable with that in healthy
volunteers who received a dose of 2.5 mg/m². For cancer patients
who received the 3.9 mg/m² dose of motolimod (cohort 8), the
mediator response was considerably stronger than for healthy
volunteers dosed at 2.5 mg/m².

Mediators that showed a clear, dose-related increase in late-
stage cancer patients are shown as box plots at each motolimod
dose and compared with the response in healthy volunteers
(Fig. 4B). For each mediator, the magnitude of the response in
healthy volunteers administered 2.5 mg/m² motolimod generally
fell between responses in cancer patients administered 2.0 and 2.8 mg/m².

Pharmacokinetics of motolimod in late-stage cancer patients
and healthy volunteers
The plasma concentration time profile for motolimod at dose
levels of 2.0, 2.8, and 3.9 mg/m² in late-stage cancer patients is
shown in Fig. 5A. Subcutaneous administration of motolimod
resulted in a well-defined, dose-related, plasma concentration
time profile, with plasma levels reaching a maximum (Tmax) at
0.5 hours for all dose levels, then declining rapidly, although
quantifiable levels were found in the plasma of all subjects at
24 hours.

The plasma concentration time profile for motolimod in
healthy volunteers at a dose level of 2.5 mg/m² is also shown
in Fig. 5A. The PK profile for healthy volunteers at this dose was
highly comparable with the cancer patients at doses of 2.0 to
3.9 mg/m². Relevant PK parameters for dose levels of 2.0, 2.8
and 3.9 mg/m² in cancer patients and 2.5 mg/m² in healthy
volunteers are compared in Fig. 5B. The mean Cmax for healthy
volunteers dosed at 2.5 mg/m² of motolimod was 16.3 ± 2.8 mg/
ml, which falls between the mean Cmax values of 14.6 ± 10.3 and
19.9 ± 10.2 ng/ml observed for late-stage cancer patients dosed at
2.0 and 2.8 mg/m², respectively. Although systemic exposure or
AUC(0–last) in healthy volunteers was slightly lower than means
observed for cancer patients at dose levels of 2.0 and 2.8 mg/m²,
the difference was not statistically significant.

Discussion
An emerging paradigm in the treatment of cancer is to harness
the individual’s immune system to actively participate in the
eradication of tumor cells. When successful, the development of
an adaptive immune response to tumor-expressed antigens results
in long-term tumor cell surveillance and translates into a durable
clinical response.

One promising pathway to evoke an innate immune response is
through TLR8 activation. This pathway drives the production of
Th1-polarizing cytokines and activates mDCs and other APCs to
more effectively present tumor-expressed antigens to T cells. The
TLR8 pathway also enhances NK activity, leading to augmented
ADCC, and the production of IFNγ (5). An ideal setting for the use
of motolimod is in combination with other therapeutic agents such
as mAbs that facilitate ADCC (13), or with chemotherapies that
induce immunogenic tumor cell death (14). In both cases, the
immune system is in contact with high levels of tumor-expressed
antigens, and TLR8 stimulation should provide activating signals
that facilitate the development of tumor-specific, adaptive immune
responses.

There is the perception that cancer patients have weak
immune systems due to repeat cycles of immunosuppressive
chemotherapy (15), advanced age and/or deregulated immune
function related to the malignancy. For example, tumors can
exert negative effects on the immune system through the release
of either soluble mediators (7, 9) or expression of immuno-
modulatory cell surface antigens (8, 16). To address these
concerns, a series of investigations, including clinical studies,
have fully characterized motolimod activity in advanced-stage cancer patients.

Initial in vitro studies using whole human blood confirmed the production of a specific set of cytokines and chemokines made in response to TLR8 activation by motolimod. Activation of this response serves to recruit and activate immune cell populations that may not express TLR8 to sites of inflammation. In vivo, the production, consumption, and clearance of cytokines/chemokines made in response to TLR8 activation is a highly dynamic process. Plasma levels of induced mediators change over time, and are influenced by the magnitude of the response, clearance rates for different mediators, and even feedback pathways. To translate motolimod in vitro activity into a meaningful measure of immune activation, PK and PD assessments were done in cynomolgus monkeys administered escalating dose levels of motolimod. Study results confirm motolimod activity in young, healthy animals, elucidated the dose-response and plasma kinetics of induced mediators, and identified multiple biomarkers of immune activation for clinical studies. Generally, plasma analytes with the greatest dynamic response to increasing doses of motolimod were a subset of analytes induced at high levels when human blood was incubated with motolimod. Although strict regulation and rapid plasma elimination of some TLR8-induced mediators, such as IL12p70, VEGF, and IFNγ, probably limit their detection in plasma samples, they are assumed to be part of the overall immune signature of motolimod in vivo.

Figure 4.
The PD activity of motolimod was characterized by quantitating plasma levels of 96 distinct analytes in samples collected predose and 8 hours following dosing. Analyte levels were log2 (base 2) transformed and log-fold changes relative to baseline were calculated for each study subject. A, biomarkers showing a significant, dose-related increase in late-stage cancer patients and healthy volunteers included: GCSF, IL10, IL1ra, IL6, IL8, MCP-1, MIP-1β, and MMP9. B, in the cancer patients dosed at 2.0 and 2.8 mg/m², changes in the magnitude of plasma biomarker levels were comparable with healthy volunteers dosed at 2.5 mg/m².
Motolimod Activation of TLR8 in Late-Stage Cancer Patients

On the basis of the initial comparison with results from preclinical studies, the magnitude and repertoire of mediators induced by motolimod in late-stage cancer patients did not appear to be compromised. The PK and PD responses for cancer patients relative to healthy volunteers are comparable. In healthy volunteers, motolimod induced significant changes in the same array of biomarkers elevated in the plasma of late-stage cancer patients, who were generally older, and had been previously treated for their cancer. In addition, the magnitude of the increases seen in healthy volunteers at the 2.5 mg/m² dose was comparable with the response seen in cancer patients at doses of 2.0 and 2.8 mg/m². However, the magnitude of the increases seen in healthy volunteers at the 2.5 mg/m² dose was comparable with the response seen in cancer patients at doses of 2.0 and 2.8 mg/m². The comparison also shows that with higher motolimod doses, comparable with those used in phase II oncology studies, the magnitude of the immune response continues to increase rather than plateau.

The health and age of cancer patients could also affect the PK profile of motolimod. If the metabolism and subsequent elimination of motolimod in cancer patients is reduced, the corresponding increase in plasma levels could compensate for decreased immune responsiveness. The PK profile of motolimod was found to be comparable in the late-stage cancer patients and healthy volunteers. A PK analysis and comparison of relevant parameters found that the overall exposure or AUC for healthy volunteers at 2.5 mg/m² was in the range observed for late-stage cancer patients at doses of 2.0 and 2.8 mg/m². Thus, the similar PD responses for cancer patients relative to healthy volunteers are the result of comparable motolimod exposure.

In summary, late-stage cancer patients are highly sensitive to TLR8 activation by motolimod. As predicted by nonclinical studies and confirmed by comparison with the response in healthy volunteers, tumor burden, increased age, and prior treatment history with cytotoxic agents do not moderate the response. This demonstration of robust immune activation in cancer patients has led to the conduct of additional clinical studies designed to determine whether motolimod can augment the effectiveness of some “standard-of-care” oncology treatments. TLR8 activation is expected to enhance tumor directed immune responses to “antigenic” tumor cell death mediated by anthracyclines, which are commonly used in the treatment ovarian cancer. TLR8 activation can also augment the ADCC activity of approved mAb therapies such as cetuximab, used in the treatment of SCCHN. Thus, motolimod is being assessed in randomized, placebo controlled, phase II clinical studies of ovarian cancer and SCCHN to determine whether it increases the effectiveness of these standard treatments.
Disclosure of Potential Conflicts of Interest

T.D. Randall, K.L. Manjarrez, R.M. Hershberg, and G.N. Dietsch have ownership interests in VentiRx Pharmaceuticals. R. Gottardo is a consultant/advisory board member for VentiRx. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: G.N. Dietsch, K.L. Manjarrez, R.M. Hershberg

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G.N. Dietsch, D.W. Northfelt, R.K. Ramanathan, K.L. Manjarrez

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.N. Dietsch, T.D. Randall, R. Gottardo, D.W. Northfelt, J.K. Bryan, R.M. Hershberg


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