BCL-2 Antisense Oligonucleotide Genasense Is Active against Imatinib-resistant BCR-ABL-positive Cells

Tetsuzo Tauchi, Masahiko Sumi, Akihiro Nakajima, Goro Sashida, Takashi Shimamoto, and Kazuma Ohyashiki

First Department of Internal Medicine, Tokyo Medical University, Shinjuku-ku, Tokyo 160-0023, Japan

ABSTRACT

Purpose: The near-universal emergence of imatinib resistance in patients with acute forms of Philadelphia chromosome-positive leukemia highlights the need for additional therapy to control this disease. G3139 (Genasense, oblimersen; Genta Inc.), a Bcl-2 antisense oligonucleotide, has been shown to down-regulate the Bcl-2 protein and induce apoptosis in myeloid leukemia cells from treated patients. We tested G3139 for its ability to inhibit BCR-ABL-mediated transformation in mice.

Experimental Design: Nude mice (n = 5/group) were transplanted s.c. with imatinib-resistant BCR-ABL-transformed TF-1 cells (BCR-ABL-TF-1-R cells). Mice with established tumors (0.1 g) were treated for 14 days with G3139 (7 mg/kg/day i.p.), or with the reverse-sequence control oligonucleotide G3622 (7 mg/kg/day i.p.) or with imatinib (50 mg/kg/day i.p.).

Results: Mice treated with G3622 or imatinib died within 10–12 weeks. Nearly all of the mice treated with G3139 survived for >6 months and had reduced tumor volume. Three of the 5 mice showed complete tumor regression. A transient decrease in Bcl-2 protein was observed that correlated with histological evidence of apoptosis. In addition, we harvested BCR-ABL-TF-1-R tumor cells from mice treated with G3139 or control G3622 (7 mg/kg/day i.p., 7 days). Cells were then cultured with the antileukemic agents imatinib, daunorubicin, 1-β-D-arabinofuranosylcytosine, or etoposide. G3139 pretreatment resulted in enhanced induction of apoptosis by all of the agents.

Conclusion: These results suggest that G3139 is a promising candidate for treatment of patients with imatinib-resistant Ph-positive leukemia, and that combination of G3139 and imatinib may be useful to circumvent clinically acquired imatinib resistance.

INTRODUCTION

BCR-ABL is a chimeric oncogene protein generated by a reciprocal translocation between chromosomes 9 and 22 [the t (9;22) Ph+], and is implicated in the pathogenesis of Ph-positive leukemia (1). The BCR-ABL fusion protein exhibits elevated tyrosine kinase activity and transforming properties (2, 3). BCR-ABL protein protects hematopoietic progenitor cells from apoptosis induced by various stimuli, including many chemotherapeutic agents (4). The 2-phenylaminopyrimidine derivative imatinib (Gleevec, STI-571; Novartis, Inc.) is a tyrosine kinase inhibitor that competitively inhibits ATP binding in the kinase domains of both the c-ABL and BCR-ABL kinases (5). Imatinib specifically induces apoptosis both in vitro and in vivo in a variety of BCR-ABL-transformed cells (6, 7). Imatinib has shown promise in human clinical trials of Ph-positive leukemia (7). However, the emergence of imatinib resistance in patients with acute forms of Ph-positive leukemia highlights the need for combination chemotherapy to eradicate the disease (7).

The components of the apoptotic program are targets for anticancer therapy (8). Various cell death stimuli can cause mitochondrial membrane changes, resulting in release of caspase-activating factors, such as cytochrome c, into the cytosol (9). The cytochrome c is not released, even when cell death stimuli are present, thus blocking the initiation of the intrinsic apoptosis pathway. BCR-ABL induces an increase in the levels of Bcl-2 protein, which may explain its ability to block the mitochondrial release of cytochrome c and the subsequent activation of caspase 3 (14, 15).

Genasense (G3139, oblimersen; Genta Inc.) is an 18-mer phosphorothioate antisense oligonucleotide targeted to the initiation codon region of the Bcl-2 mRNA (16, 17). A therapy-enhancing strategy depends on combining G3139 with other anticancer agents to inflict more effective cellular damage (18–26). A growing body of preclinical and clinical evidence suggests that G3139 synergizes with many cytotoxic and biological/
immunotherapeutic agents against a variety of hematological malignancies and solid tumors (19, 20, 24–26).

In the present study, we investigated the activity of G3139 against imatinib-resistant BCR-ABL-transformed leukemia cells. We found that G3139 as a single agent had antitumor activity in nude mice transplanted with imatinib-resistant BCR-ABL-transformed cells. Furthermore, we observed that cells harvested from G3139-treated animals were more sensitive to subsequent treatment with the antileukemic agents imatinib, DNR, AraC, and VP-16. Given the activity of G3139 against BCR-ABL-positive leukemia, the present study points to the combined use of G3139 and imatinib as an effective therapeutic approach for Ph-positive leukemias.

MATERIALS AND METHODS

Antibodies and Reagents. Anti-ABL mAb (24–21), anti-BCR mAb (100), and anti-Bcl-2 mAb (C2) were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Imatinib was kindly provided by Novartis Inc. (Basel, Switzerland). DNR, AraC, and VP-16 were obtained from Sigma (St. Louis, MO). Bcl-2 antisense oligonucleotide (G3139), 5′-tct ccc agc ggt cgc cat-3′, was a gift from Genta Inc. (Berkeley Heights, NJ). The reverse polarity oligonucleotide 5′-tac cgc gtg cga ccc tct-3′, also provided by Genta Inc., was used as a control.

Cells and Cell Culture. BCR-ABL-TF-1 cells have been described previously (27). K562 cells were obtained from American Type Culture Collection. These cell lines were cultured in McCoy’s 5A modified medium (Life Technology, Inc.) supplemented with 10% FCS (Hyclone Laboratories, Logan, UT).

Preparation of Subcellular Fractions. Subcellular fractionation was performed as described previously (14). Cells were lysed in hypotonic buffer [5 mM Tris (pH 7.4), 5 mM KCl, 1.5 mM MgCl2, 0.1 mM EDTA (pH 8.0), 1 mM DTT, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml benzamidine, 1 mM phenylmethylsulfonyl fluoride, and 0.2 mM sodium orthovanadate] at 4°C for 30 min. After homogenization, samples were centrifuged (2,000 × g for 5 min) to remove the nuclei, and centrifuged again (10,000 × g for 10 min) to obtain the heavy membrane fraction. The supernatant was centrifuged at 150,000 × g for 1.5 h to obtain the cytosolic fraction. The heavy membrane fractions were solubilized in 1% Triton X-100, 10 mM Tris-HCl (pH 7.4), 150 mM NaCl, 5 mM EDTA, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml benzamidine, 1 mM phenylmethylsulfonyl fluoride, and 0.2 mM sodium orthovanadate, and were used as the mitochondrial fraction.

Immunoblotting and Immunoprecipitation. Immunoblotting and immunoprecipitation were performed as described previously (28).

Antitumor Effect in Vivo. We studied the antitumor effect of G3139 in mice bearing imatinib-resistant BCR-ABL-transformed cells. Tumors were observed 4 weeks after cells were injected into the back of 6-week-old female nude mice. In this study, we started to treat these animals 4 weeks after tumor inoculation, once transplantability was confirmed (tumor weight was 0.05–0.1 g). These mice were treated with G3139 (7 mg/kg i.p.), or reverse polarity oligonucleotide (7 mg/kg i.p.) or imatinib (50 mg/kg i.p.) for 14 days. Mice were observed daily, and body weight as well as signs of stress (for example, lethargy, ruffled coat, or ataxia) were used to detect possible toxicities. Caliper measurements of tumors were converted into mean tumor weight (g) with the formula: 1/2 [length (cm)] × [width (cm)]2. Average tumor weight per mouse was calculated and was used to analyze the group mean tumor weight ± SE (n = 5 mice).

Apoptosis Assay. Tumor-bearing mice were treated with G3139 (7 mg/kg/day i.p.) or reverse polarity oligonucleotide (7 mg/kg/day i.p.) for 7 days. BCR-ABL-TF-1-R cells were har-
vested and pooled. These BCR-ABL-TF-1-R cells were cultured with the indicated concentrations of imatinib, DNR, AraC, and VP-16 for 48 h. The incidence of apoptosis was determined by flow cytometric analysis with the FITC-conjugated APO2.7 mAb (clone 2.7), which was raised against the Mr 38,000 mitochondrial membrane protein (7A6 antigen) that is expressed by cells undergoing apoptosis (28).

Tumor and Tissue Processing. Tumors were collected at selected times and fixed in paraformaldehyde. Paraffin-embedded tissues were sectioned and processed for gross histopathology by H&E staining and TUNEL staining.

Statistical Analysis. Comparisons between groups were analyzed with the Mann-Whitney U test. Values of $P < 0.05$ were considered to indicate statistical significance. The statistical tests were performed using the Microsoft Word Excel (Brain Power Inc., Calabashes, CA) software package for the Macintosh personal computer.

RESULTS

Subcellular Localization of Bcl-2 Protein in Imatinib-resistant and Nonresistant Cells. We selectively generated resistant BCR-ABL-TF-1 cells and K562 cells by culture in the presence of gradually increasing concentrations of imatinib. BCR-ABL-TF-1 cells and K562 cells were cultured in the presence of 0.2 μM imatinib for 4 months, and the concentration of imatinib was gradually increased to 0.5 μM over a period of 2 months. Whereas nonresistant BCR-ABL-TF-1 cells and K562 cells die at 0.5 μM imatinib, imatinib-resistant BCR-ABL-TF-1-R cells and K562-R cells proliferate well in the presence of 0.5 μM imatinib (data not shown). To determine whether imatinib resistance was associated with alteration of BCR-ABL protein expression, as described previously (29), immunoblotting was performed on these cell lines (Fig. 1). Compared with BCR-ABL-TF-1 cells and K562 cells, BCR-ABL proteins are significantly overexpressed in BCR-ABL-TF-1-R cells and K562-R cells (Fig. 1). Previous reports indicate that BCR-ABL induces Bcl-2, which may explain its ability to block the mitochondrial release of cytochrome c (14, 15). The subcellular localization of various members of the Bcl-2 family is also important for controlling the apoptotic process. Therefore, we investigated Bcl-2 protein expression in mitochondrial fraction and cytosolic fraction from imatinib-resistant and nonresistant cell lines. To investigate the subcellular distribution of Bcl-2 protein, extracts of the indicated cell lines were fractionated and immunoblotted with anti-Bcl-2 mAb (Fig. 2). Bcl-2 was equally expressed in the cytosolic fraction from these cell lines, whereas Bcl-2 was increased in the mitochondrial fraction from imatinib-resistant BCR-ABL-TF-1-R cells and K562-R cells (Fig. 2).

Fig. 3 G3139 treatment transiently decreases Bcl-2 protein in imatinib-resistant BCR-ABL-TF-1-R cells in nude mice during drug administration. Whole cell lysates from the indicated harvested cells treated with G3139 (A) or G3622 control (B) were immunoblotted with anti-Bcl-2 mAb.

Fig. 4 G3139 treatment reduces the tumorigenicity of imatinib-resistant BCR-ABL-TF-1-R cells in nude mice. Effect of G3139 on tumor growth in nude mice bearing BCR-ABL-TF-1-R cells. Tumor-bearing mice were treated with G3139 (7 mg/kg/day i.p., 14 days, $n = 5$) or reverse polarity control (G3622; 7 mg/kg/day i.p., 14 days, $n = 5$) or imatinib (50 mg/kg/day i.p., 14 days, $n = 5$). Tumor volume in individual animals was measured and plotted versus time. G3139 induces a significant reduction in the growth rate of s.c. tumor.

Fig. 5 G3139 treatment leads to increased survival of nude mice transplanted with imatinib-resistant BCR-ABL-TF-1-R cells. Control G3622-treated mice and imatinib-treated mice died within 10 weeks and 12 weeks, respectively. Nearly all of the mice treated with G3139 survived for $>6$ months and had reduced tumor volume; 3 of 5 showed complete tumor regression.
These results suggest that imatinib resistance at least in part may be because of Bcl-2 protein.

**Growth Properties of BCR-ABL-TF-1-R Cells in Nude Mice Treated with G3139.** We tested the antitumor effects of G3139 in nude mice bearing BCR-ABL-TF-1-R cells implanted s.c. Treatment was initiated when the tumors were established to a size of 0.05–0.1 g (approximately day 28). We examined changes in Bcl-2 protein expression during the course of G3139 treatment. Implanted mice with established (0.1 g) BCR-ABL-TF-1-R tumors were treated with 7 mg/kg G3139 or reverse polarity control with a treatment schedule of daily i.p. injections for 14 days. Cell lysates of tumor (from treatment day 1 to day 15) were immunoblotted with anti-Bcl-2 mAb. Systemic administration of G3139 (7 mg/kg) caused a pronounced down-regulation of Bcl-2 protein within 5 days of G3139 treatment (Fig. 3A). No down-regulation of Bcl-2 protein was observed with reverse polarity control treatment (Fig. 3B). Despite continued administration of G3139, Bcl-2 protein levels recovered within the 14 days of treatment (Fig. 3A). Therefore, down-regulation of Bcl-2 by G3139 appears to be transient in this system. We proceeded to examine the antitumor effects of G3139. Treatment with G3139 significantly delayed tumor growth: tumor weights at 6 weeks after implantation of BCR-ABL-TF-1-R cells were 0.54 ± 0.06 g (n = 5) and 0.11 ± 0.03 g (n = 5) in the control and G3139-treated groups, respectively (Fig. 4). Complete tumor regression was observed in 3 of 5 G3139-treated mice. None of the mice treated with G3139 displayed any signs of toxicity. Treatment with imatinib (50 mg/kg i.p.; 14 days) also delayed tumor growth (tumor weight 0.29 ± 0.04 g at 6 weeks after implantation; n = 5); however, tumors grew rapidly without imatinib treatment (Fig. 4). In contrast with imatinib, the effect of G3139 on tumor growth appeared to be maintained after G3139 treatment, and G3139 could completely eliminate tumor progression (Fig. 4). As a control, administration of reverse polarity oligonucleotide (7 mg/kg i.p. for 14 days) provided no therapeutic activity (Fig. 4). G3139 treatment also leads to increased survival of nude mice transplanted with imatinib-resistant BCR-ABL-TF-1-R cells (Fig. 5). Control (G3622-treated) mice and imatinib-treated mice died within 10 weeks and 12 weeks, respectively (Fig. 5). However, nearly all of the mice treated with G3139 survived for >6 months and had reduced tumor volume.

**Detection of Apoptosis in BCR-ABL-TF-1-R Cells Grown in Nude Mice.** To evaluate whether administration of G3139 results in direct induction of apoptosis in BCR-ABL-TF-1-R cells, we examined the histology of tumors after G3139 treatment (day 15). Mice with established (0.1 g) BCR-ABL-TF-1-R tumors were given 7 mg/kg G3139 or reverse polarity oligonucleotide i.p. for 14 days. Tumors from G3139-treated mice revealed an increased fraction of dead cells, identified by their amorphous shape and condensed nuclei (Fig. 6B). Dead tumor cells and areas of degenerative tissue were observed, appearing as loosely arranged cells with the occurrence of vacuolated structures (Fig. 6B). Areas of tumor cells were heterogeneous throughout the tumor section. Features of apoptosis were observed in the tumor sections stained with TUNEL (Fig. 6D), with a high proportion of sections from G3139-treated mice showing apoptosis (58.8%) also determined by APO2.7 antibody (Fig. 6D).
Enhancement of Apoptosis in G3139-treated BCR-ABL-TF-1-R Cells by Chemotherapeutic Agents. We examined the impact of down-regulation of Bcl-2 in vivo on chemotherapeutic responses. Mechanistically distinct classes of agents were selected for analysis, including imatinib, DNR, AraC, and VP-16. To assess the effects of Bcl-2 down-regulation in modulating responses to these agents, experiments focused on BCR-ABL-TF-1-R cells harvested from mice treated with G3139 (7 mg/kg/d i.p.; 7 days) or reverse polarity oligonucleotide (7 mg/kg/d i.p.; 7 days). Pooled BCR-ABL-TF-1-R cells were cultured with the indicated concentrations of imatinib, DNR, AraC, or VP-16 for 48 h, and the incidence of apoptosis was determined by flow cytometry with APO2.7 mAb (Fig. 7, A–D). G3139-treated BCR-ABL-TF-1-R cells showed enhanced induction of apoptosis compared with control cells after exposure to imatinib, DNR, AraC, and VP-16 (Fig. 7, A–D). These results demonstrating enhanced sensitivity to some classes of chemotherapeutic agents imply cytotoxic synergy between Bcl-2 down-regulation and these agents.

DISCUSSION

The emergence of resistance to imatinib remains a major problem in the treatment of Ph-positive leukemia, although patients usually have a good initial response to imatinib (7). The Bcl-2 protein can block apoptosis induced by most chemotherapeutic agents (11–13), and has been found to be up-regulated by BCR-ABL tyrosine kinase in hematopoietic cells (14, 15). The development of a Bcl-2 antisense oligonucleotide, G3139, has led to clinical investigation of this molecule with promising early results (16–26). Combining chemotherapeutic agents with G3139 represents an additional therapeutic strategy (18–26). Because many chemotherapeutic agents exert their cytotoxic activity via apoptosis, concurrent treatment with G3139 and chemotherapeutic agents could enhance their effectiveness and provide an attractive strategy to overcome drug resistance (18–26). We selectively generated imatinib-resistant BCR-ABL-TF-1-R cells and K562-R cells by culture in the presence of gradually increasing concentrations of imatinib (Fig. 1). Imatinib-resistant BCR-ABL-TF-1-R cells and K562-R cells displayed

Fig. 7 Prior in vivo treatment with G3139 enhances apoptosis by chemotherapeutic agents in imatinib-resistant BCR-ABL-TF-1-R cells in vitro. BCR-ABL-TF-1-R tumor cells were harvested from mice treated for 7 days with G3139 or G3622 (control). Cells were then cultured with the antileukemic agents (A) imatinib, (B) AraC, (C) DNR, or (D) VP-16. The incidence of apoptosis was measured by flow cytometry with APO2.7 antibody.
increased expression of BCR-ABL protein (Fig. 1). By subcel-
lar fractionation and immunoblotting analysis, increased lev-
els of Bcl-2 protein were detected in the mitochondrial fraction
of imatinib-resistant BCR-ABL-TF-1-R cells and K562-R cells
compared with imatinib-nonresistant TF-1-BCR-ABL cells and
K562 cells (Fig. 2). Therefore, imatinib resistance in these cell
lines may be at least in part mediated by Bcl-2 protein in the
mitochondrial fraction.

In the present study, we evaluated the in vivo activity of
G3139 in nude mice bearing BCR-ABL-TF-1-R cells (Figs.
4–6). We demonstrated that treatment with G3139 (7 mg/kg/
day i.p.; 14 days; n = 5) was capable of achieving significant
down-regulation of Bcl-2 protein in BCR-ABL-TF-1-R cells,
and that this was associated with antitumor activity (Figs. 3–5).
Antitumor activity was specific for the Bcl-2 antisense oligonu-
cleotide G3139 sequence, and there was no observable activity
with the control Bcl-2 reverse polarity oligonucleotide (Figs.
4 and 5). Histological examination of these tumors by TUNEL
staining revealed significant induction of apoptosis, suggesting
that the changes in tumor volume may reflect a large population
of apoptotic cells (Fig. 6, B and C). Immunoblotting analysis of
tumor samples during the course of G3139 treatment indicated a
>90% reduction of Bcl-2 protein by day 5; however, Bcl-2
protein thereafter gradually increased up to day 15 (Fig. 3). The
observation that Bcl-2 down-regulation was transient, despite
continued G3139 treatment and complete tumor regression, is an
interesting result (Figs. 3 and 4). Although we are unable to
resolve the precise mechanism, it is clearly a feature that has
significant implications for therapeutic applications and war-
rants additional investigation.

Our observations also indicate that Bcl-2 down-regulation
may lead to chemosensitization, including to imatinib (Fig. 7,
A–D). A previous report has documented sensitization to mitox-
antrone after Bcl-2 down-regulation in a solid tumor-bearing
murine model (23). The interpretation of that study was simpli-
fied by the lack of direct cytotoxicity of Bcl-2 antisense oligo-
nucleotides on the cell line used, and consequently the obser-
vations can be considered as sound evidence for Bcl-2 antisense
oligonucleotide-related chemosensitization (23). Our study does
not unambiguously establish whether Bcl-2 down-regulation
with G3139 chemosensitizes BCR-ABL-TF-1-R cells, but this
is certainly one possible explanation of our results.

In summary, we demonstrate that the Bcl-2 antisense oli-
gonucleotide G3139 can cause effective reductions in Bcl-2
protein levels that lead to induction of antitumor activity. The
very low toxicity observed in recent clinical trials suggests the
potential for the additional development of G3139 in the treat-
ment of leukemia. These results, which should not be extrapo-
lated to other types of tumors, highlight the complexity of the
cell death process and the myriad of intracellular changes that
may be required to achieve it. This, in turn, may shed some
additional light on the cellular requirements for the development
of effective and specific therapeutic strategies.

REFERENCES


2. Konopka, J. B., Watanabe, S. M., and Witte, O. N. An alteration of
the human c-ABL protein in K562 leukemia cells unmasks associated

3. Klotetzker, W., Kurzrock, R., Smith, L., Talpaz, M., Spiller, M.,
Gutterman, J., and Arlinghaus, R. The human cellular abl gene product
in the chronic myelogenous leukemia cell line K562 has an associated

4. Thiesing, J. T., Ohno-Jones, S., Kolibaba, K. S., and Druker, B. J.
Efficacy of STI571, an abl tyrosine kinase inhibitor, in conjunction with
other antileukemic agents against bcr-abl-positive cells. Blood, 96:

5. Druker, B. J., Tamura, S., Buchdunger, E., Ohno, S., Segal, G. M.,
Fanning, S., Zimmermann, J., and Lydon, N. B. Effects of a selective
inhibitor of the Abl tyrosine kinase on the growth of BCR-ABL positive

6. Nakajima, A., Tauchi, T., and Ohyashiki, K. ABL-specific tyrosine
kinase inhibitor, STI571 in vitro, affects Ph-positive acute lymphoblas-
tic leukemia and chronic myelogenous leukemia in blastic crisis. Leu-

7. Savage, D. G., and Antman, K. H. Imatinib mesylate—a new oral

8. Cotter, F. E., Johnson, P., Hall, P., Pocock, C., al Mahdi, N., Cowell,
J. K., and Morgan, G. Antisense oligonucleotides suppress B-cell lym-
phoma growth in SCID-hu mouse model. Oncogene, 9: 3049–3055,
1994.


Subcellular and submitochondrial model of action of Bcl-2 like onco-

11. Miyashita, T., and Reed, J. C. Bcl-2 oncoprotein blocks chemother-
apic-induced apoptosis in a human leukemia cell line. Blood, 81:

12. Reed, J. C. Bcl-2 prevention of apoptosis as a mechanism of drug

13. Reed, J. C., Miyashita, T., Takayama, S., Wang, H. G., and Sato, T.,
Krajewski, S., Aime-Sempe, C., Bodrug, S., Kitada, S., and Hanada, M.
Bcl-2 family proteins: regulators of cell death involved in the patho-
genesis of cancer and resistance to therapy. J. Cell. Biochem., 60:

Versatility of BCR-ABL-expressing leukemic cells in circumventing

15. Cirinna, M., Trotta, R., Salomoni, P., Kosshev, V., Perrotti, D., and Calabretta, B. Bcl-2 expression restores the leukeno-
getic potential of a BCR-ABL mutant defective in transformation.

16. Raynaud, F. I., Orr, R. M., Goddard, P. M., Lacey, H. A., Lanca-
shire, H., Judson, I. R., Beck, T., Bryan, B., and Cotter, F. E. Pharma-
cokinetics of G3139, a phosphorothioate oligodeoxynucleotide anti-
sense of bcl-2, after intravenous administration or continuous subcuta-

17. Webb, A., Cunningham, D., Cotter, F., Clarke, P. A., di Stefano, F.,
Ross, P., Corbo, M., and Dziejmanowa, Z. BCL-2 antisense therapy in

Elts, A., Muller, M., Wolfik, K., Eichler, H. G., and Pehamberger, H.
bcl-2 antisense therapy chemosensitizes human melanoma in SCID

Hoeller, C., Lucas, T., Hoermann, M., Wolfik, K., and Pehamberger, H.
Hemosensitisation of malignant melanoma by BCL-2 antisense ther-

20. Lopes de Menezes, D. E., Hudon, N., McIntosh, N., and Mayer,
L. Molecular and pharmacokinetic properties associated with the
therapeutics of bcl-2 antisense oligonucleotide G3139 combined with
BCL-2 Antisense Oligonucleotide Genasense Is Active against Imatinib-resistant BCR-ABL-positive Cells

Tetsuzo Tauchi, Masahiko Sumi, Akihiro Nakajima, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/9/11/4267

Cited articles
This article cites 28 articles, 10 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/9/11/4267.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/9/11/4267.full.html#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.