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Oblimersen Sodium

USAN; Prop INNM

Oncolytic
Antisense Oligonucleotide
BCL2 Expression Inhibitor

G-3139
NSC-683428
Genasense™

Heptadecasodium salt of antisense oligonucleotide from fragment 32-49nt (start codon region) of the BCL2 cDNA

P-Thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-thymidine heptadecasodium salt

CAS: 190977-41-4

EN: 230388

Abstract

Oblimersen sodium is an antisense oligonucleotide that targets human *bcl-2* mRNA. The protein product of the *bcl-2* gene is normally involved in regulating cell cycle processes. However, in cancer cells, the Bcl-2 protein is overexpressed, which increases metastatic potential, promotes chemotherapy resistance and prevents apoptosis. Oblimersen blocks the production of the Bcl-2 protein, thereby enhancing apoptosis in cancer cells. It also enhances the antitumor effects of a broad range of cytotoxic agents (taxanes, platinum agents, anthracyclines and antimetabolites) against various hematological malignancies, including lymphomas, leukemia and myeloma, as well as solid tumors, including breast, prostate, lung and colon cancers. In phase I/II clinical trials, administration of oblimersen as a continuous i.v. infusion or by s.c. injection is well tolerated and has moderate but clear antitumor activity. Oblimersen is highly protein bound, and is rapidly and widely distributed to highly perfused organs, particularly the lungs and bone marrow. Multiple treatment cycles of oblimersen are tolerable in most patients. Steady-state concentrations are linear with dose, and remain unchanged when administered in combination with cytotoxic agents. Oblimersen therefore represents a highly specific, targeted approach to treating a range of human cancers with increased efficacy and a reduced likelihood of side effects.

Introduction

Conventional treatments for human cancers include surgery, radiation and chemotherapy. These modalities act systemically and are therefore limited by their unfavorable side effect profiles. More recently, research efforts have begun focusing on novel approaches to treat cancer by specifically targeting cancer cells, while potentially leaving healthy cells intact. One such novel approach is antisense therapy (1). Antisense agents inhibit the expression of a target gene in a sequence-specific manner, and theoretically can be used to treat any disease that is caused by overexpressed genes. Antisense oligonucleotides directed against the *bcl-2* gene may have therapeutic potential against several different types of human cancers. The antisense oligonucleotide oblimersen sodium (G3139, Genasense™) is gaining recognition as a potential candidate for the treatment of several types of cancer, both as monotherapy and in combination with available chemotherapy regimens.

Oblimersen sodium is comprised of a phosphorothioate backbone linking 18 modified DNA bases and targets the first 6 codons of the human *bcl-2* mRNA sequence, thereby blocking the production of its target protein. Bcl-2 is a potent inhibitor of apoptosis that is overexpressed in many cancers. Overexpression of *bcl-2* is thought to be a fundamental cause of the inherent resistance of cancer cells to current anticancer treatments, such as chemotherapy, radiation and monoclonal antibodies. Furthermore, *bcl-2* overexpression is

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associated with poor response rates, decreased time to relapse and decreased survival in patients with a variety of tumors. By inhibiting the production of Bcl-2, oblimersen enhances apoptosis in tumor cells *in vitro* and *in vivo*. Moreover, evidence from preclinical and clinical studies demonstrates that oblimersen acts synergistically with many cytotoxic chemotherapy agents (*i.e.*, taxanes, platinum agents, anthracyclines and antimetabolites) against various hematological malignancies (*i.e.*, lymphoma, leukemia and myeloma) and solid tumors (*i.e.*, breast, prostate, lung and colon cancers) (1-3).

Oblimersen is currently being investigated in phase III trials for the treatment of malignant melanoma, multiple myeloma and chronic lymphocytic leukemia (CLL). Other clinical trials are ongoing in other tumor types, including prostate, breast, colorectal and small cell lung cancer (SCLC) and lymphomas.

Pharmacological Actions

Oblimersen is a potent inhibitor of *bcl-2* expression *in vitro* and *in vivo*, resulting in marked increases in apoptosis in several tumor types, including human prostate cancer LNCaP cells (4), human breast cancer MDA-MB-435/LCC6 cells (5), human melanoma 518A2 cells (6) and cells from patients with refractory multiple myeloma (7). However, the mechanism of action in human prostate cancer PC-3 cells appeared to be more complex. In these cells, oblimersen markedly reduced Bcl-2 protein expression and proliferation, but did not induce significant apoptosis (8).

Oblimersen enhances the cytotoxic effect of anticancer drugs against a variety of hematological malignancies and solid tumors. Preclinical studies demonstrated that oblimersen acts synergistically with doxorubicin and liposomal doxorubicin in a mouse xenograft model of human breast cancer (5), with dacarbazine in SCID mice bearing melanoma 5182 (6), with cisplatin in human nasopharyngeal carcinoma (9) and human gastric cancer xenograft models (10) in SCID mice, with bortezomib in multiple myeloma and non-Hodgkin's lymphoma (NHL) xenografts in SCID mice (11), with paclitaxel in the LNCaP xenograft model in nude mice (12), with rituximab in a human/SCID model of post-transplant lymphoproliferative disorder (13), with cyclophosphamide in SCID mice bearing human NHL (DoHH2) tumors (14) and with vinorelbine in a mouse model of human metastastic non-small cell lung cancer (NSCLC) (15). Oblimersen-containing combination therapies resulted in enhanced antitumor activity, durable tumor regressions, increased survival, and in some cases cure, of the tumor-bearing animals in the absence of increased toxicity. The effect appeared to be sequence-dependent, oblimersen pretreatment being most effective.

Experiments in athymic castrated male mice bearing human prostate cancer LNCaP xenografts showed that treatment with oblimersen (12.5 mg/kg/day i.p.) decreased tumor volume by up to 50% compared to precastration levels, which contrasts with a significant increase over 12 weeks in controls; this effect was correlated with changes in serum prostate-specific antigen (PSA) levels. These findings indicated that antisense Bcl-2 oligodeoxynucleotide therapy is able to delay the progression to androgen independence in prostate cancer (4).

Another study in nude mice bearing imatinib-resistant BCR-ABL-transformed TF-1 cells demonstrated the efficacy of oblimersen in increasing survival and reducing tumor volume, with complete tumor regression in 3 of 5 animals. Moreover, enhanced apoptosis was observed in cells from treated animals cultured with antileukemic agents including imatinib, daunorubicin and etoposide (16).

Triple combination of oblimersen, cisplatin and INX-6295, a c-*myc* antisense compound, proved to be more effective than single agents or double combinations in mice injected with human metastatic melanoma cell lines. A combination of oblimersen (0.2 mg/day i.v. x 4), cisplatin (3.3 mg/kg/day i.p. x 3) and INX-6295 (0.5 mg/day i.v. x 7) produced 85-98% tumor growth inhibition, as well as prolonging survival by 52-83%. Over half of the animals bearing NG melanoma had complete tumor regressions and 2 of 6 were cured on this combination (17).

Pharmacokinetics and Metabolism

The pharmacokinetic and metabolic profiles of oblimersen have been investigated in BALB/c mice (18). Following a single i.v. bolus dose or continuous s.c. dosing of [^{35}S]-labeled oblimersen, radioactivity was rapidly and widely distributed to highly perfused organs, particularly the lungs and bone marrow. The AUC was lower after i.v. than after s.c. administration. Radioactivity was slowly eliminated from the plasma, with a terminal half-life of 11 h following i.v. administration and of 22 h after s.c. administration. High plasma protein binding (> 85-98%) was seen. Biodistribution studies demonstrated high tissue/plasma ratios in major organs except the brain, with the highest ratios observed in the liver and kidney, followed by bone marrow and spleen. Oblimersen is metabolized to a variety of degradation products that are formed predominantly by the liver. Metabolism and elimination are more extensive with i.v. than with s.c. administration. Oblimersen is eliminated mainly in the urine and to a lesser extent in the feces.

Clinical Studies

Oblimersen is currently in phase III trials as monotherapy and in combination with other chemotherapeutic agents for refractory CLL, and as combination therapy for

the treatment of advanced malignant melanoma. It is also in clinical trials for refractory multiple myeloma, NHL, NSCLC, acute and chronic myeloid leukemia (CML), prostate, breast and colorectal cancer, and in children with solid tumors.

Oblimersen was studied as monotherapy in a phase I clinical trial in heavily pretreated patients with relapsed NHL (19, 20). Patients with follicular, small lymphocytic, diffuse large B-cell or mantle cell lymphomas expressing Bcl-2 received daily doses of oblimersen of 4.6-195.8 mg/m^2 by continuous s.c. infusion for 14 days. Although the dose of oblimersen was low in most patients, several major responses were observed; there was 1 complete response, 2 minor responses, 9 cases of stable disease and 9 cases of progressive disease. Computed tomography scans showed a reduction in tumor size in 2 patients. The number of circulating lymphoma cells was reduced in 2 patients, serum concentrations of lactate dehydrogenase were reduced in 4 patients, and in 2 of these patients symptoms improved. One patient with low-grade lymphoma who had progressive disease in nodes and bone marrow after 2 prior regimens achieved a complete response with oblimersen, which was maintained for over 3 years. Dose-limiting toxicity consisted of thrombocytopenia, hypotension, fever and asthenia, and the maximum tolerated dose was 147.2 mg/m^2/day.

Another phase I trial evaluated oblimersen in combination with doxorubicin in patients with advanced hepatocellular carcinoma (21). Oblimersen was administered as a continuous i.v. infusion for 8 days of a 21-day cycle, followed by a standard bolus injection of doxorubicin on day 5. Of the 10 patients evaluable for response, 2 had stable disease and 1 had a mixed response after 4-6 cycles. Dose-limiting toxicity was grade 4 myelosuppression, and grade 3 neutropenia was common, resulting in a change in schedule to every 28 days.

Sixteen patients with SCLC received oblimersen 5-7 mg/kg/day by continuous i.v. infusion for 8 days of a 21-day cycle in combination with carboplatin on day 6 and etoposide on days 6-8 (22). A partial response was obtained in 12 of 14 evaluable patients (86%) and 2 others had stable disease. The median time to disease progression was 5.9 months. Carboplatin and etoposide did not appear to affect the pharmacokinetics of oblimersen.

In 35 patients with advanced cancer, a phase I dose-escalation study was conducted using both 14- and 21-day i.v. infusions of oblimersen at doses of 0.6-6.9 mg/kg/day. No major antitumor responses were observed, but 13 (37%) patients had stable disease. Oblimersen was generally well tolerated in these patients, side effects including fatigue and reversible elevation in serum transaminases. Steady-state plasma levels increased linear to dose and were achieved at about 10 h, with a terminal half-life of approximately 2 h (23).

Another phase I study was conducted using a continuous i.v. infusion of oblimersen with escalating doses of fludarabine, cytarabine and filgrastrim (granulocyte colony-stimulating factor, or G-CSF) in patients with refractory/relapsed acute leukemia (24). Of 20 evaluable patients, 9 (45%) had a response, including 6 complete remissions. Adverse events included fever, nausea, emesis, electrolyte imbalance and fluid retention.

Escalating doses of oblimersen were assessed in a phase I study in patients with refractory/relapsed and chemotherapy-naïve mantle cell lymphoma (25). Oblimersen was administered at an initial dose of 3 mg/kg/day for 7 days of a 21-day cycle for up to 6 cycles or until disease progression. Patients who did not respond to initial treatment received 4 mg/kg/day for 7 days in subsequent cycles. A cohort of refractory/relapsed patients received an initial daily dose of 4 mg/kg oblimersen, which was escalated to 5 mg/kg/day in subsequent cycles. Of the 18 evaluable refractory/relapsed patients receiving the lowest dose of oblimersen, 1 had a complete response and 7 had stable disease. In patients who received escalated doses, 2 of 3 evaluable patients achieved a partial response. In the chemotherapy-naïve group, 5 disease stabilizations were obtained. Eight patients completed combination therapy with oblimersen and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). In this group, 2 patients had a complete response, 4 a partial response and 2 stable disease. The treatment was well tolerated and combination with R-CHOP did not appear to increase toxicity.

Oblimersen was studied in a phase I trial in combination with irinotecan in patients with metastatic colorectal cancer (26). Oblimersen 3-7 mg/kg/day was administered as a continuous i.v. infusion for 8 days with irinotecan (280-350 mg/m^2 i.v.) given on day 6 of a 21-day cycle. After 12 cycles, 1 patient who had previously been treated with irinotecan had persistent stable disease. In 3 of 9 irinotecan-naïve patients, a partial response was obtained in 1 after 2 cycles and 2 patients had stable disease after 6 and 8 cycles, respectively. The dose regimen of 5 mg/kg/day oblimersen and 280 mg/m^2 irinotecan was safe, while dose-limiting toxicity of grade 3-4 diarrhea, grade 3 nausea/vomiting, grade 4 neutropenia and febrile neutropenia was seen in half of the patients at the 5/350 dose level.

A phase I dose-finding study examined the efficacy of combined treatment with oblimersen and mitoxantrone in patients with metastatic hormone-refractory prostate cancer (27). Oblimersen was administered at doses of 0.6-5.0 mg/kg/day as a continuous i.v. infusion for 14 days of a 21-day cycle, with mitoxantrone 4-12 mg/m^2 given as an i.v. bolus on day 8. Two patients had a reduction in PSA of > 50%. One patient receiving oblimersen 1.2 mg/kg/day and the lowest dose of mitoxantrone had symptomatic improvement in bone pain. Five patients had stable disease and 1 of 7 with measurable disease had a partial response. The estimated median overall survival was 18.7 months. No dose-limiting toxicity was seen and, except for lymphopenia, toxicity was generally similar to that observed with mitoxantrone alone.

Results from other phase I clinical trials indicated that combinations of oblimersen and paclitaxel (28) or docetaxel (29) were well tolerated and associated with biological activity, and that a combination of oblimersen,

docetaxel and doxorubicin was also well tolerated and did not influence the pharmacokinetics of docetaxel or doxorubicin (30).

A phase I/II trial in patients with multiple myeloma refractory to vincristine, doxorubicin and dexamethasone (VAD) examined the effect of continuous i.v. infusion of oblimersen (7 mg/kg/day) for 7 days in combination with VAD on days 4-7. Of 5 patients treated at the time of reporting, 2 achieved a partial remission after 3 cycles and 1 had stable disease. The most frequently reported side effect was grade 2 fatigue (31).

Twelve patients with refractory SCLC entered a phase I/II trial using a 7-day continuous i.v. infusion of oblimersen at a fixed dose of 3 mg/kg/day, followed by paclitaxel 150 mg/m^2 on day 6 (32). No objective responses were observed, but 2 patients achieved stable disease, with 1 patient remaining stable on therapy for more than 30 weeks. The treatment regimen was well tolerated.

Another phase I/IIa trial investigated the combination of oblimersen and dacarbazine in 14 patients with advanced malignant melanoma (33). Oblimersen was administered i.v. or s.c. at daily doses of 0.6-6.5 mg/kg plus standard dacarbazine treatment. Six patients achieved antitumor responses: 1 complete, 2 partial and 3 minor responses. The estimated median survival of all patients exceeded 12 months. Lymphopenia was common, but no dose-limiting toxicity was observed.

Preliminary results of a phase I/II trial of oblimersen in patients with CLL were reported (34). Oblimersen was administered as a continuous i.v. infusion at a dose of 3 mg/kg/day for 5-7 days of a 21-day cycle in patients who had previously been treated with fludarabine. Of the 19 patients evaluable for response after at least 2 cycles of oblimersen, 2 achieved a partial response despite having failed a median of 3 prior treatment regimens, and 9 patients experienced disease stabilization. Circulating leukemia cells were reduced from baseline by > 25% in 7 of 11 patients (63%). Six of 17 patients (35%) showed a decrease in lymphadenopathy, and 5 of 15 patients (33%) a reduction in hepatomegaly or splenomegaly. Treatment was well tolerated.

Source

Genta, Inc. (US).

References

1. Biroccio, A., Leonetti, C., Zupi, G. *The future of antisense therapy: Combination with anticancer treatments.* Oncogene 2003, 22: 6579-88.

2. Reed, J.C. *Regulation of apoptosis by bcl-2 family proteins and its role in cancer and chemoresistance.* Curr Opin Oncol 1995, 7: 541-6.

3. Herbst, R.S., Frankel, S.R. *Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): A rational therapeutic to enhance apoptosis in therapy of lung cancer.* Clin Cancer Res 2004, 10: 4245S-8S.

4. Gleave, M., Tolcher, A., Miyake, H., Nelson, C., Brown, B., Beraldi, E., Goldie, J. *Progression to androgen independence is delayed by adjuvant treatment with antisense Bcl-2 oligodeoxynucleotides after castration in the LNCaP prostate tumor model.* Clin Cancer Res 1999, 5: 2891-8.

5. Lopes de Menezes, D.E., Hugon, N., McIntosh, N., Mayer, L.D. *Molecular and pharmacokinetic properties associated with the therapeutics of Bcl-2 antisense oligonucleotide G3139 combined with free and liposomal doxorubicin.* Clin Cancer Res 2000, 6: 2891-902.

6. Jansen, B., Schlagbauer-Wadl, H., Brown, B.D., Bryan, R.N., van Elsas, A., Müller, M., Wolff, K., Eichler, H.-G., Pehamberger, H. *Bcl-2 antisense therapy chemosensitizes human melanoma in SCID mice.* Nat Med 1998, 4: 232-4.

7. van de Donk, N.W., Kamphuis, M.M., van Dijk, M., Borst, H.P., Bloem, A.C., Lokhorst, H.M. *Chemosensitization of myeloma plasma cells by an antisense-mediated downregulation of Bcl-2 protein.* Leukemia 2003, 17: 211-9.

8. Lai, J.C., Benimetskaya, L., Santella, R.M., Wang, Q., Miller, P.S., Stein, C.A. *G3139 (oblimersen) may inhibit prostate cancer cell growth in a partially bis-CpG-dependent non-antisense manner.* Mol Cancer Ther 2003, 2: 1031-43.

9. Lacy, J., Loomis, R., Cheng, Y-C. *Bcl-2 antisense oligonucleotide (G3139, Genasense) chemosensitizes human nasopharyngeal carcinoma to cisplatin in vivo in a SCID xenotransplantation model*. Proc Am Assoc Cancer Res 2004, 45: Abst 2928.

10. Wacheck, V., Heere-Rees, E., Halaschek-Wiener, J., Lucas, T., Meyer, H., Eichler, H-G., Jansen, B. *Bcl-2 antisense oligonucleotides chemosensitize human gastric cancer in a SCID mouse xenotransplantation model.* J Mol Med 2001, 79: 587-93.

11. O'Connor, O., Srinivasan, S., Hernandez, F., Smith, E.A., Toner, L.E., Czuczman, M.S., Chanan-Khan, A.A. *Oblimersen (Bcl-2 antisense) enhances the antitumor activity of bortezomib (Bor) in multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) preclinical models.* Blood 2003, 102(11, Part 1): Abst 628.

12. Tolcher, A.W., Miyake, H., Gleave, M. *Downregulation of BCL-2 expression by the antisense oligonucleotide G3139 enhances paclitaxel chemosensitivity in the androgen-independent prostate cancer LNCaP xenograft model.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington DC) 1999, Abst 583.

13. Loomis, R., Carbone, R., Reiss, M., Lacy, J. *Bcl-2 antisense (G3139, Genasense) enhances the in vitro and in vivo response of Epstein-Barr virus-associated lymphoproliferative disease to rituximab.* Clin Cancer Res 2003, 9: 1931-9.

14. Klasa, R.J., Bally, M.B., Ng, R., Goldie, J.H., Gascoyne, R.D., Wong, F.M.P. *Eradication of human non-Hodgkin's lymphoma in SCID mice by BCL-2 antisense oligonucleotides combined with low-dose cyclophosphamide.* Clin Cancer Res 2000, 6: 2492-500.

15. Hu, Y., Masin, D., Tan, S., Ng, R., Yan, H., Bebb, G. *Establishment of an orthotopic xenograft model of human NSCLC to study the correlation of anti-metastasis and Bcl-2 expression.* Proc Am Assoc Cancer Res 2004, 45: Abst 4567.

16. Tauchi, T., Sumi, M., Nakajima, A., Sashida, G., Shimamoto, T., Ohyashiki, K. *BCL-2 antisense oligonucleotide Genasense is active against imatinib-resistant BCR-ABL-positive cells.* Clin Cancer Res 2003, 9: 4267-73.

17. Leonetti, C., Scarsell, M., Semple, S.S., Gillum, A.M., Natali, P.G., Zupi, G. *Combination of antisense therapy against bcl-2 and c-myc oncogenes with cisplatin shows a potent antitumor activity in melanoma lines.* Proc Am Assoc Cancer Res 2004, 45: Abst 555.

18. Raynaud, F.I., Orr, R.M., Goddard, P.M., Lacey, H.A., Lancashire, H., Judson, I.R., Beck, T., Bryan, B., Cotter, F.E. *Pharmacokinetics of G3139, a phosphorothioate oligonucleotide antisense to bcl-2, after intravenous administration or continuous subcutaneous infusion to mice.* J Pharmacol Exp Ther 1997, 281: 420-7.

19. Waters, J.S., Webb, A., Cunningham, D., Clarke, P.A., Raynaud, F., di Stefano, F., Cotter, F.E. *Phase I clinical and pharmacokinetic study of Bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma*. J Clin Oncol 2000, 18: 1812-23.

20. Webb, A., Cunningham, D., Cotter, F., Clarke, P.A., di Stefano, F., Ross, P., Corbo, M., Dziewanowska, Z. *BCL-2 antisense therapy in patients with non-Hodgkin lymphoma.* Lancet 1997, 349: 1137-41.

21. Knox, J.J., Chen, E., Feld, R, Oza, A.M., Nematollahi, M., Cheiken, R., Zwiebel, J., Moore, M. *A phase I study of oblimersen sodium (G3139) in combination with doxorubicin in advanced hepatocellular carcinoma. NCI protocol #5798.* Gastrointest Cancers Symp (Jan 22-24, San Francisco) 2004, Abst 148.

22. Rudin, C.M., Kozloff, M., Hoffman, P.C., Edelman, M.J., Karnauskas, R., Tomek, R., Szeto, L., Vokes, E.E. *Phase I study of G3139, a bcl-2 antisense oligonucleotide, combined with carboplatin and etoposide in patients with small-cell lung cancer.* J Clin Oncol 2004, 22: 1110-7.

23. Morris, M.J., Tong, W.P., Cordon-Cardo, C. et al. *Phase I trial of BCL-2 antisense oligonucleotide (G3139) administered by continuous intravenous infusion in patients with advanced cancer.* Clin Cancer Res 2002, 8: 679-83.

24. Marcucci, G., Byrd, J.C., Dai, G. et al. *Phase I and pharmacodynamic studies on G3139, a Bcl-2 antisense oligonucleotide, in combination with chemotherapy in refractory or relapsed acute leukemia*. Blood 2003, 101: 425-32.

25. Leonard, J.P., Hainsworth, J., Bernstein, S. et al. *Genasense (oblimersen sodium, G3139) is active and well-tolerated both alone and with R-CHOP in mantle cell lymphoma (MCL).* Blood 2003, 102(11, Part 1): Abst 490.

26. Ochoa, L., Kuhn, J., Salinas, R. et al. *A phase I, pharmacokinetic, and biologic correlative study of G3139 and irinotecan (CPT-11) in patients with metastatic colorectal cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 297.

27. Chi, K.N., Gleave, M.E., Klasa, R., Murray, N., Bryce, C., Lopes de Menezes, D.E., D'Aloisio, S., Tolcher, A.W. *A phase I dose-finding study of combined treatment with an antisense Bcl-2 oligonucleotide (Genasense) and mitoxantrone in patients with metastatic hormone-refractory prostate cancer.* Clin Cancer Res 2001, 7: 3920-7.

28. Morris, M.J., Tong, W.P., Cordon-Cordo, C., Drobnjak, M., Kelly, W.K., Slovin, S.F., Terry, K.L., DiPaola, R.S, Rosen, N., Scher, H.I. *A phase I trial of BCL2 antisense drug G3139 (Genta, Inc.) delivered by continuous intravenous infusion alone and in combination with weekly paclitaxel.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington DC) 1999, Abst 17.

29. Chen, H., Marshall, J., Trocky, N., Ling, Y., Baidas, S., Rizvi, N., Bhargava, P., Lippman, M., Yang, D., Hayes, D. *A phase I study of BCL-2 antisense G3139 (GENTA) and weekly docetaxel in patients with advanced breast cancer and other solid tumors.* Proc Am Soc Clin Oncol 2000, 19: Abst 692.

30. Esteva, F.J., Madden, T.L., Lammey, J., Symmans, W.F., Booser, D.J., Arun, B., Rivera, E., Brewster, A.M., Valero, V., Hortobagyi, G.N. *Phase I and pharmacokinetic (PK) study of oblimersen, a proapoptotic Bcl-2 targeting oligonucleotide, in combination with doxorubicin and docetaxel in metastatic and locally advanced breast cancer (BC).* Proc Am Soc Clin Oncol 2004, 23: Abst 3117.

31. van de Donk, N.W.C.J., Kamphuis, M.M.J., Frankel, S.R., Bloem, A.C., Lokhorst, H.M. *A phase I/II study of Bcl-2 antisense (G3139) combined with vincristine, adriamycin and dexamethasone (VAD) in patients with refractory multiple myeloma.* Blood 2002, 100(11, Part 1): Abst 3208.

32. Rudin, C.M., Otterson, G.A., Mauer, A.M., Villalona-Calero, M.A., Tomek, R., Prange, B., George, C.M., Szeto, L., Vokes, E.E. *A pilot trial of G3139, a bcl-2 antisense oligonucleotide, and paclitaxel in patients with chemorefractory small-cell lung cancer.* Ann Oncol 2002, 13: 539-45.

33. Jansen, B., Wacheck, V., Heere-Ress, E., Schlagbauer-Wadl, H., Hoeller, C., Lucas, T., Hoermann, M., Hollenstein, U., Wolff, K., Pehamberger, H. *Chemosensitisation of malignant melanoma by BCL2 antisense therapy.* Lancet 2000, 356: 1728-33.

34. Rai, K.R., O'Brien, S., Cunningham, C., Turkina, A.G., Ochoa, L., Frankel, S.R., Golenkov, A.K. *Genasense (Bcl-2 antisense) monotherapy in patients with relapsed or refractory chronic lymphocytic leukemia. Phase 1 and 2 results.* Blood 2002, 100(11, Part 1): Abst 1490.

Additional References

Hu, Q., Bally, M.B., Madden, T.D. *Subcellular trafficking of antisense oligoncleotides and down-regulation of bcl-2 gene expression in human melanoma cells using a fusogenic liposome delivery system.* Nucleic Acids Res 2002, 30(16): 3632-41.

Wasan, E.K., Waterhouse, D., Sivak, O., Bally, M.B., Klasa, R.J., Wasan, K.M. *Plasma protein binding, lipoprotein distribution and uptake of free and lipid-associated BCL-2 antisense oligodeoxynucleotides (G3139) in human melanoma cells*. Int J Pharm 2002, 241(1): 57-64.

O'Brien, S., Giles, F., Rai, K., Andreeff, M., Cunningham, C., Frankel, S., Keating, M. *Bcl-2 antisense (Genasense) as monotherapy for refractory chronic lymphocytic leukemia.* Blood 2001, 98: Abst 3213.