Drugs of the Future 2008, 33(4): 323-327

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.04.1189133

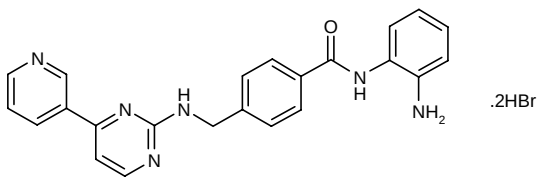
MGCD-0103

Histone Deacetylase Inhibitor
Apoptosis Inducer
Oncolytic

MG-0103

N-(2-Aminophenyl)-4-[4-(3-pyridyl)pyrimidin-2-ylaminomethyl]benzamide dihydrobromide

InChI=1/C23H20N6O/c24-19-5-1-2-6-21(19)28-22(30)17-9-7-16(8-10-17)14-27-23-26-13-11-20(29-23)18-4-3-12-25-15-18/h1-13,15H,14,24H2,(H,28,30)(H,26,27,29)



$C_{23}H_{22}Br_2N_6O$
Mol wt: 558.2686

CAS: 944537-89-7

CAS: 726169-73-9 (free base)

EN: 342540

Abstract

MGCD-0103 is an orally active isoform-selective histone deacetylase (HDAC) inhibitor under development by MethylGene in cooperation with Pharmion. Histone acetylation represents an attractive target in cancer therapy since abnormal acetylation is a frequent feature of human cancer and can result in dysregulation of cell cycle control and aberrant gene expression. In preclinical studies, MGCD-0103 demonstrated inhibitory activity against a variety of human cancer cell lines and in murine models of cancer. Early *in vivo* studies have shown inhibition of HDAC at clinically achievable doses (45 mg/m^2) with tolerable toxicity. Phase I-II trials in lymphoma, leukemia, myelodysplastic syndromes (MDS) and solid tumors are under way.

Synthesis*

MGCD-0103 can be prepared as follows. Reaction of 4-(aminomethyl)benzoic acid methyl ester hydrochloride (I) with pyrazole-1-carboxamidine hydrochloride (II) affords guanidine (III). 3-Acetylpyridine (IV) is then heated with dimethylformamide dimethyl acetal to furnish the enaminone (V), which is cyclized with guanidine (III), giving the pyridyl pyrimidine (VI). After saponification of the methyl ester (VI) by means of LiOH, the resulting carboxylic acid (VII) is coupled with *o*-phenylenediamine (VIII) to provide the title compound (1). Scheme 1.

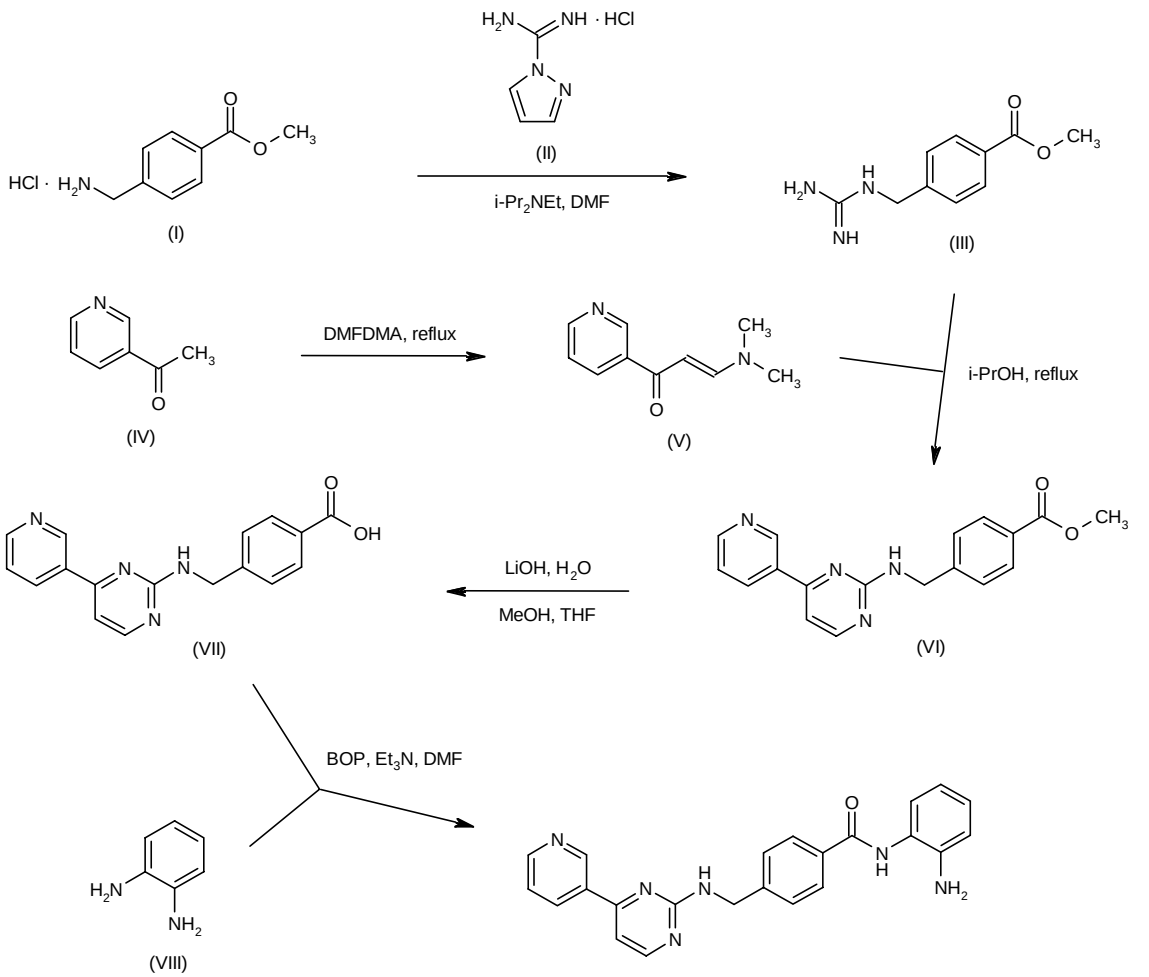
Background

Tumorigenesis is thought to arise through a complex interaction of the dysregulation of various proteins controlling critical cell processes. These include disruption of the cell cycle, survival and apoptosis pathways, and cell differentiation. Protein function can be disturbed by chromosomal mutation or translocation, resulting in the production of structurally abnormal proteins, or by altered expression of a normal gene. Methylation of specific DNA sequences, notably repeated CpG dinucleotide islands, results in gene silencing. This silencing is mediated by recruitment of histone deacetylases (HDACs), which remove the steric hindrance of acetyl groups attached to specific lysine residues in histone complexes. The result is a tighter chromatin structure (2). Conversely, histone acetylation is associated with an open chromatin structure and gene expression. Hypermethylation and histone deacetylation are frequently seen in human cancers, resulting in gene silencing (3). Treatment with HDAC inhibitors has been shown to increase the expression of several cell cycle-active genes, including *p21$^{WAF/CIP}$*, an inhibitor of cyclin-dependent kinase (CDK). Furthermore, HDAC inhibitors have been shown to induce antiproliferative effects and induce differentiation, cell cycle arrest and apoptosis.

Such diverse actions would be difficult to explain entirely by alterations in histone acetylation status. Indeed, in addition to modification of gene expression mediated through altered acetylation of DNA-associated

J. Kell. Consultant Haematologist, University Hospital of Wales, Cardiff CF14 4XW, UK. Correspondence: Jonathan.Kell@cardiffandvale.wales.nhs.uk. *Synthesis prepared by N. Serradell. Prous Science, Provenza 388, 08025 Barcelona, Spain.

Scheme 1: Synthesis of MGCD-0103



histones, several HDACs have been shown to co-precipitate with other nonhistone proteins (4, 5), in particular with the chaperone proteins heat shock protein (HSP) 70 and HSP90. HSP70 associates with hydrophobic regions of proteins, protecting them from aggregation and aiding folding (4), while HSP90 protects proteins from polyubiquitination, which would lead to increased destruction of client proteins, including BCR-ABL and cRAF, in the proteosome (5).

Four principal classes of HDAC inhibitors have been developed thus far: hydroxamic acid derivatives, short-chain fatty acids, cyclic peptides and phenylenediamines (6). The prototypic group of drugs is derived from hydroxamic acid and includes suberoylanilide hydroxamic acid (SAHA, vorinostat, Zolinza®; Merck & Co.), now licensed by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (CTLC) (7) and in phase II/III trials for mesothelioma (8), trichostatin A, a naturally occurring fungal antibiotic (9), and belinostat (PXD-101), which has demonstrated activity in preclinical models of prostatic carcinoma (10). Valproic acid is a short-chain fatty acid that has been used in the treatment of epilepsy for many years and is now in clinical trials in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) (www.clinicaltrials.gov). Romidepsin (Gloucester Pharmaceuticals) is a depsipeptide in phase II trials for CTCL, myeloma and solid tumors (11; www.clinicaltrials.gov). MS-275 (now SNDX-275; Syndax) is a benzamide derivative in early-phase trials in chronic myelomonocytic leukemia (CMML), MDS and AML, solid tumors and lymphoma (www.clinicaltrials.gov).

Acetylation of HSP90 appears to be dependent on the class II HDAC HDAC6, which is inhibited by hydroxamic acid derivatives, but not by benzamide derivatives. On the other hand, HSP70 appears to be dependent on HDAC1 and HDAC2 and thus is potentially targeted by these newer agents. Whether this selectivity is of clinical benefit remains unclear and awaits the results of randomized phase III trials.

MGCD-0103 (MG-0103) is an orally active phenylenediamine HDAC inhibitor currently being assessed in numerous phase I-II trials as single-agent therapy and in combination with azacitidine, gemcitabine or docetaxel in hematological malignancies and solid tumors. The agent has received orphan drug designation from the FDA and the EMEA for the treatment of Hodgkin's lymphoma and AML (12).

Preclinical Pharmacology

MGCD-0103 is an isotype-selective HDAC inhibitor targeting HDAC isozymes 1, 2, 3 and 11, with IC_{50} values in the 0.1-2.0 μM range. It has little activity against HDAC isozymes 4-10 (IC_{50} > 20 μM) (13). The activity of MGCD-0103 has been tested in several cell lines using an MTT assay, showing activity against A549 lung cancer cells, HCT 116 colon cancer cells, MDA-MB-231 breast cancer cells and T24 bladder cancer cells. The IC_{50} was in the 0.2-1.0 μM range for each tumor compared to values of 0.5-5 μM for either SNDX-275 or vorinostat (14).

In human HCT 116 colon cancer cells, MGCD-0103 at 1 μM induced a greater degree of apoptosis than SNDX-275, a structurally related HDAC inhibitor, at similar concentrations. MGCD-0103 increased apoptosis by 120% relative to control compared to a 50% increase for SNDX-275. These changes correlated with increased histone acetylation, cell cycle arrest and induction of *p21*$^{WAF/CIP}$ (14). In human leukemia RPMI 8226 cells, the expression of interleukin-6 (IL-6) was induced 8-fold compared with control after 24-h exposure to 1 μM MGCD-0103 (15). Inhibition of histone acetylation was also seen in white blood cells (WBCs) from healthy human volunteers after *in vitro* incubation with MGCD-0103 and in WBCs of mice treated with 60 or 90 mg/kg (16). Similar oral doses in HCT 116-xenografted mice induced a 3-fold greater increase in histone acetylation and a 1.4-fold increase in *p21* expression (13). Tumor growth in murine xenograft models of A549 lung cancer was inhibited by 15-30 mg/kg/day MGCD-0103 i.p. Similarly, 70-80 mg/kg/day p.o. resulted in 47-81% growth inhibition of DU 145 prostate cancer xenografts. A-431 epidermoid carcinoma xenografts were similarly inhibited (14).

HDAC inhibition with MGCD-0103 appears to be synergistic with conventional chemotherapy. Using A549 lung cancer xenografts, the nucleoside analogue gemcitabine 80 mg/kg resulted in 45% growth inhibition, whereas co-administration of 30 mg/kg MGCD-0103 resulted in 76% growth inhibition. Similar results were seen in PANC-1 pancreatic carcinoma xenografts. The time lag to the development of tumors was increased from 24 days with gemcitabine to 36 days with the combination (17). To date, no significant toxicity has been reported in preclinical models.

Pharmacokinetics and Metabolism

MGCD-0103 is orally active but shows low bioavailability, ranging from 42% in rats to under 5% in dogs, with a half-life of 35-80 min (13). After a single oral dose of 90 mg/kg in mice, plasma concentrations were 2.3, 0.21 and 0.015 μM after 2, 8 and 24 h, respectively (16). The half-life was 9 h, with an AUC of 1300 ng.h/ml among patients with advanced leukemia administered a dose of 60 mg/m^2, with a C_{max} of 169 ng/ml at 80 mg/m^2 (18). In patients with solid tumors treated with 36 mg/m^2, on day 1 the C_{max} was 80.6 ng/ml, the AUC was 453 ng.h/ml and the $t_{1/2}$ was 11.3 h, with respective values on day 12 of 126 ng/ml, 611 ng.h/ml and 7.1 h (19). These data were confirmed in 19 patients with leukemia or MDS (20). The $t_{1/2}$ ranged from 7 to 11 h, with a t_{max} of 0.5-1.0 h. The C_{max} was 124 ng/ml at 40 mg/m^2 and was proportional to the dose (21).

Clinical Studies

MGCD-0103 has been studied in dose-escalating phase I trials in patients with advanced and aggressive solid malignancies, including lung, colorectal and renal tumors and NHL, administered either daily, twice or thrice weekly (19, 22-25). On the thrice-weekly schedule, histone acetylation increased in a dose-dependent manner, correlating with HDAC inhibition. Approximately 40% of patients showed at least 20% inhibition of HDAC activity, while 60% had at least a 50% increase in histone acetylation. Three patients with renal cell cancer and 1 with colorectal cancer had stable disease (22, 25).

In patients with high-risk MDS or AML treated with increasing oral doses of MGCD-0103 twice (40-83 mg/m^2) (21) or thrice (20-80 mg/m^2) (18) weekly, 3 patients (14%) achieved complete remission on the thrice-weekly schedule at 60 and 80 mg/m^2 (18). Histone acetylation was increased 1.5-3.5-fold in responders. A similar study continues to recruit older patients with untreated high-risk MDS or AML, or younger adults with relapsed or refractory AML (26).

Several ongoing trials are assessing MGCD-0103 alone or in combination with conventional chemotherapy (azacitidine, gemcitabine, docetaxel) in patients with leukemia, MDS, relapsed or refractory Hodgkin's lymphoma and NHL and solid tumors (27-35).

The MGCD0103-005 trial combines azacitidine with MGCD-0103 in patients with high-risk MDS and AML (32). Data presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO) reported responses in 7 patients with leukemia treated in this trial. Six of these responding patients were treated with 90 or 100 mg/m^2 MGCD-0103 thrice weekly. Of the 7 responding patients, 3 achieved CR, 3 achieved CRp (CR with incomplete recovery of platelets) and 1 patient achieved a partial response (PR). Toxicity was mild and limited to anorexia, nausea (in 2 patients at 135 mg/m^2) and vomiting (1 patient of 8 in the 90 mg/m^2 cohort) (36). Similar results were reported at another meeting later in the year (37).

Interim results were also reported last year from the ongoing phase II MGCD0103-010 trial in patients with relapsed/refractory Hodgkin's lymphoma (29). Patients were treated with MGCD-0103 starting at 110 mg 3 times weekly every 4 weeks, with dose reductions in case of

toxicity. An objective response rate of 40% (2 CR and 6 PR) was obtained in 20 evaluable patients. The most frequent adverse events were nausea, fatigue, vomiting, diarrhea, anorexia, pneumonia, abdominal pain and weight loss, which were mostly manageable with dose modification. Inhibition of HDAC in peripheral blood mononuclear cells (PBMCs) of most patients was observed. A decrease in serum thymus- and activation-regulated chemokine (TARC) levels appeared to be predictive of response to therapy (38, 39).

An open-label, multicenter phase II trial (MGCD0103-008) is evaluating MGCD-0103 (110 mg 3 times weekly every 4 weeks, with dose escalation or reduction depending on toxicity) in patients with relapsed or refractory follicular and diffuse large B-cell lymphoma (30). In an interim analysis of 25 evaluable patients, 1 with follicular lymphoma had a CR and PR was obtained in 2 patients with diffuse large B-cell lymphoma and 1 with follicular lymphoma. Hematological toxicity was minimal and other common adverse events included nausea, fatigue, diarrhea, anorexia, vomiting and weight loss. As in other studies, most patients showed inhibition of HDAC activity in PBMCs (40).

Conclusions

MGCD-0103 is an orally active HDAC inhibitor that has been shown to increase histone acetylation at clinically achievable submicromolar concentrations, with preferential activity on HDAC1, 2, 3 and 11. The precise mechanism of inhibition remains uncertain, but there is potential for combining this modality with existing chemotherapy. The drug has shown promise in early trials in resistant and refractory cancer and appears to exert preferential effects on tumor cells compared to normal tissue. It appears to be better tolerated than vorinostat, which is less specific in its action but was recently licensed for CTCL. Vorinostat represents the first agent in this drug class to be licensed for cancer therapy.

The principal toxicities recorded to date are mainly limited to mild gastrointestinal problems, such as anorexia, nausea and vomiting. Such a favorable toxicity profile promises that MGCD-0103 will lend itself to combination therapy with existing chemotherapy schedules. Preclinical data support its combination with gemcitabine, with potentiation of apoptosis in PANC-1 pancreatic cell lines. Such observations raise the question of the mechanism of sensitization to chemotherapy and how to schedule these drugs to best exploit their interaction. Studies are presently recruiting to combine MGCD-0103 with gemcitabine in solid tumors (35) and with azacitidine in MDS and AML (32). The effects on MDS with monosomy 7, a subset of MDS with poor outcome, will be awaited with particular excitement, as this disease has recently been shown to be potentially more responsive to azacitidine than other subtypes of MDS (36). Other phase II trials include combination with docetaxel (60 or 75 mg/m^2) in solid malignancies, including breast and non-small cell lung carcinoma (34). The results of these trials can be expected in the next 18-24 months.

Several other HDAC inhibitors, including belinostat and romidepsin, are at a similar stage of clinical development for MDS and solid malignancies. On the basis of early data, these drugs appear to have similar efficacy and spectrum of action, but there are no comparative data. Given the early promising data for MGCD-0103 and other selective HDAC inhibitors, we may find ourselves on the verge of a new dawn for epigenetic therapies in human cancer.

Sources

MethylGene, Inc. (CA); developed in collaboration with Pharmion Corp. (US).

References

1. Delorme, D., Zhou, Z. (MethylGene, Inc.). *Inhibitors of histone deacetylase*. EP 1590340, JP 2006514998, US 2004142953, US 6897220, WO 2004069823.

2. Peterson, C.L., Laniel, M.A., Peterson, C.L., Laniel, M.A. *Histones and histone modifications*. Curr Biol 2004, 14(14): R546-51.

3. Fraga, M.F., Ballestar, E., Villar-Garea, A. et al. *Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer*. Nat Genet 2005, 37(4): 391-400.

4. Johnson, C.A., White, D.A., Lavender, J.S., O'Neill, L.P. *Human class I histone deacetylase complexes show enhanced catalytic activity in the presence of ATP and co-immunoprecipitate with the ATP-dependent chaperone protein Hsp70*. J Biol Chem 2002, 277(11): 9590-7.

5. Bali, P., Pranpat, M., Bradner, J. et al. *Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90*. J Biol Chem 2005, 280(29): 26729-34.

6. Yoshida, M., Matsuyama, A., Komatsu, Y. et al. *From discovery to the coming generation of histone deacetylase inhibitors*. Curr Med Chem 2003, 10(22): 2351-8.

7. *Merck & Co.'s Zolinza approved by FDA for CTCL*. Merck & Co., Inc. Press Release, October 8, 2006.

8. *Suberoylanilide hydroxamic acid (SAHA) versus placebo in advanced malignant pleural mesothelioma (NCT00128102)*. ClinicalTrials.gov Web site, February 25, 2008.

9. Tsuji, N., Kobayashi, M., Nagashima, K. et al. *A new antifungal antibiotic, trichostatin*. J Antibiot 1976, 29(1): 1-6.

10. Qian, X., Ara, G., Mills, E., LaRochelle, W.J., Lichenstein, H.S., Jeffers, M. *Activity of the histone deacetylase inhibitor belinostat (PXD101) in preclinical models of prostate cancer*. Int J Cancer 2008, 122(6): 1400-10.

11. *Gloucester Pharmaceuticals reports clinically significant responses in pivotal trial of romidepsin for cutaneous T-cell lymphoma at the 2007 American Society of Hematology (ASH) Annual Meeting*. Gloucester Pharmaceuticals, Inc. Press Release, December 10, 2007.

12. *MethylGene and Pharmion announce U.S. orphan drug designation granted by the FDA for MGCD0103 for the treatment of acute myelogenous leukemia (AML)*. MethylGene, Inc. Press Release, February 14, 2008.

13. Vaisburg, A. *Discovery and development of MGCD-0103 - An orally active HDAC inhibitor in human clinical trials*. Drugs Fut 2006, 31(Suppl. A): Abst L57.

14. Li, Z., Zhou, N., Fournel, M. et al. *Antitumor activities of MGCD0103, a novel isotype-selective histone deacteylase inhibitor*. Eur J Cancer - Suppl 2004, 2(8): Abst 83.

15. Maroun, C., Liu, J., Kalita, A. et al. *Induction of interleukin-6 expression by the histone deacetylase inhibitor, MGCD0103, in leukemia patients in vivo correlates with clinical efficacy*. Proc Am Assoc Cancer Res (AACR) 2007, 48: Abst 1831.

16. Bonfils, C., Kalita, A., Liu, J., Besterman, J.M., Li, Z. *Development of whole cell HDAC enzyme assay to analyze inhibitory activity of MGCD0103 in vitro and in vivo*. Proc Am Assoc Cancer Res (AACR) 2005, 46: Abst 606.

17. Nguyen, H., Gravel, S., MacLeod, R. *Synergistic antitumor activity of the isotype-selective histone deacetylase inhibitor MGCD0103 in combination with gemcitabine*. 17th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 14-18, Philadelphia) 2005, Abst C220.

18. Garcia-Manero, G., Minden, M., Estrov, Z. et al. *Clinical activity and safety of the histone deacetylase inhibitor MGCD0103: Results of a phase I study in patients with leukemia or myelodysplastic syndromes (MDS)*. J Clin Oncol 2006, 24(18, Suppl.): Abst 6500.

19. Siu, L.L., Carducci, M., Pearce, L. et al. *Phase I study of isotype-selective histone deacetylase (HDAC) inhibitor MGCD0103 given as three-times weekly oral dose in patients (pts) with advanced solid tumors*. 17th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 14-18, Philadelphia) 2005, Abst C77.

20. Garcia-Manero, G., Minden, M., Estrov, Z. et al. *A phase I study of the histone deacetylase inhibitor MGCD0103 (MG-0103) given as a three-times weekly oral dose in patients with leukemia or myelodysplastic syndromes (MDS)*. Blood 2005, 106(11): Abst 4639.

21. Lancet, J.E., Nichols, G., Assouline, S. et al. *A phase 1 study of MGCD0103 given as a twice weekly oral dose in patients with advanced leukemias or myelodysplastic syndromes (MDS)*. Blood 2006, 108(11): Abst 1971.5.

22. Carducci, M., Siu, L.L., Sullivan, R. et al. *Phase I study of isotype-selective histone deacetylase (HDAC) inhibitor MGCD0103 given as three-times weekly oral dose in patients (pts) with advanced solid tumors*. J Clin Oncol 2006, 24(18, Suppl.): Abst 3007.

23. Kalita, A., Maroun, C., Bonfils, C. et al. *Pharmacodynamic effect of MGCD0103, an oral isotype-selective histone deacetylase (HDAC) inhibitor, on HDAC enzyme inhibition and histone acetylation induction in phase I clinical trials in patients (pts) with advanced solid tumors or non-Hodgkin's lymphoma (NHL)*. 41st Annu Meet Am Soc Clin Oncol (ASCO) (May 13-17, Orlando) 2005, Abst 9631.

24. Gelmon, K., Tolcher, A., Carducci, M. et al. *Phase I trials of the oral histone deacetylase (HDAC) inhibitor MGCD0103 given either daily or 3x weekly for 14 days every 3 weeks in patients (pts) with advanced solid tumors*. 41st Annu Meet Am Soc Clin Oncol (ASCO) (May 13-17, Orlando) 2005, Abst 3147.

25. Siu, L.L., Carducci, M., Chen, E.X. et al. *Phase I study of an oral isotype-selective histone deacetylase (HDAC) inhibitor in patients (pts) with advanced solid tumors*. Eur J Cancer - Suppl 2006, 4(12): Abst 300.

26. *MGCD0103 in elderly patients with previously untreated AML/high risk MDS or adults with relapsed/refractory disease (NCT00374296)*. ClinicalTrials.gov Web site, February 27, 2008.

27. *A phase I study of MGCD0103 given three-times weekly in patients with leukemia or myelodysplastic syndromes (NCT00324129)*. ClinicalTrials.gov Web site, February 27, 2008.

28. *A phase I study of MGCD0103 given twice weekly in patients with leukemia or myelodysplastic syndromes (NCT00324194)*. ClinicalTrials.gov Web site, February 27, 2008.

29. *Study of MGCD0103 (MG-0103) in patients with relapsed or refractory Hodgkin's lymphoma (NCT00358982)*. ClinicalTrials.gov Web site, February 27, 2008.

30. *Study of MGCD0103 given three times weekly in patients with relapsed and refractory lymphoma (NCT00359086)*. ClinicalTrials.gov Web site, February 27, 2008.

31. *A phase II study of MGCD0103 (MG-0103) in patients with refractory chronic lymphocytic leukemia (NCT00431873)*. ClinicalTrials.gov Web site, February 27, 2008.

32. *A phase I/II study of MGCD0103 with azacitidine in patients with high-risk MDS or acute myelogenous leukemia (NCT00324220)*. ClinicalTrials.gov Web site, February 27, 2008.

33. *MGCD0103 administered in combination with azacitidine (Vidaza®) to subjects with relapsed or refractory Hodgkin's or non-Hodgkin's lymphoma (NCT00543582)*. ClinicalTrials.gov Web site, February 27, 2008.

34. *Study to evaluate combination treatment of MGCD0103 and docetaxel (Taxotere®) for subjects with advanced cancer tumors (NCT00511576)*. ClinicalTrials.gov Web site, February 27, 2008.

35. *A phase I/II study of MGCD0103 (MG-0103) in combination with gemcitabine (NCT00372437)*. ClinicalTrials.gov Web site, February 27, 2008.

36. Garcia-Manero, G., Yang, A.S., Klimek, V. et al. *Phase I/II study of a novel oral isotype-selective histone deacetylase (HDAC) inhibitor MGCD0103 in combination with azacitidine in patients (pts) with high-risk myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML)*. J Clin Oncol 2007, 25(18, Suppl.): Abst 7062.

37. Garcia-Manero, G., Yang, A.S., Klimek, V. et al. *Phase I/II study of MGCD0103, an oral isotype-selective histone deacetylase (HDAC) inhibitor, in combination with 5-azacitidine in higher-risk myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML)*. Blood [49th Annu Meet Am Soc Hematol (Dec 8-11, Atlanta) 2007] 2007, 110(11): Abst 444.

38. Younes, A., Pro, B., Fanale, M. et al. *Isotype-selective HDAC inhibitor MGCD0103 decreases serum TARC concentrations and produces clinical responses in heavily pretreated patients with relapsed classical Hodgkin lymphoma (HL)*. Blood [49th Annu Meet Am Soc Hematol (Dec 8-11, Atlanta) 2007] 2007, 110(11): Abst 2566.

39. Younes, A., Pro, B., Fanale, M. et al. *A phase II study of MGCD0103, a novel oral isotype-selective histone deacetylase inhibitor, in patients with relapsed or refractory Hodgkin lymphoma*. Haematologica [7th Int Symp Hodgkin Lymphoma (Nov 3-7, Cologne) 2007] 2007, 92(Suppl. 5): Abst C014.

40. Younes, A., Wedgwood, A., McLaughlin, P. et al. *Treatment of relapsed or refractory lymphoma with the oral isotype-selective histone deacetylase inhibitor MGCD0103: Interim results from a phase II study*. Blood [49th Annu Meet Am Soc Hematol (Dec 8-11, Atlanta) 2007] 2007, 110(11): Abst 2571.