Peloruside A Inhibits Growth of Human Lung and Breast Tumor Xenografts in an Athymic nu/nu Mouse Model

Colin J. Meyer¹, Melissa Krauth¹, Michael J. Wick², Jerry W. Shay³, Ginelle Gellert³, Jef K. De Brabander⁴, Peter T. Northcote⁵, and John H. Miller⁶

Abstract

Peloruside A (peloruside; Fig. 1), a marine sponge secondary metabolite originally isolated by West and colleagues (1) from Mycale henscheli collected in Pelorus Sound off the coast of New Zealand, is a potent microtubule-stabilizing agent (MSA; ref. 2) similar to paclitaxel, docetaxel, and ixabepilone (aza-epothilone B). Peloruside shows activity in the low nanomolar range against proliferation of cultured cancer cell lines (Table 1). Although standard chemotherapeutic agents such as paclitaxel (Taxol) and docetaxel (Taxotere) have been extremely effective in treating solid tumors of the lung, breast, and ovary, they have significant off-target toxic effects in addition to a low aqueous solubility, making it necessary to use a solubilizing agent such as Cremophor EL for paclitaxel and polysorbate 80 (Tween 80) for docetaxel for clinical use (3–6). Allergic and anaphylactic reactions to the vehicles used with the taxanes can cause patient discomfort and even death (6). The taxanes are also highly susceptible to development of multiple drug resistance (MDR) by overexpression of drug efflux pumps, in particular the P-glycoprotein (P-gp) pump (7, 8). Thus, new-generation MSAs that bind to the same site on β-tubulin as the taxanes (10), epothilone and discodermolide, have entered clinical trials with the epothilone B derivative, ixabepilone (Ixempra), reaching the market in 2007 as a therapeutic agent against metastatic breast cancer (11). Ixabepilone, however, similar to the taxanes, has significant side effects, including peripheral neuropathy, nausea, muscle pain, joint pain, and leucopenia, and has recently been withdrawn from the New Zealand market due to lack of interest. Discodermolide entered phase 1 clinical trials with Novartis in 2004 but was later discontinued in development due to pneumotoxicity. It was then picked up by Kosan Biosciences in conjunction with Amos Smith’s research laboratory at the University of Pennsylvania (Philadelphia, PA) where its binding domain is being characterized and its structure–activity relationships are being used to design
synthesize novel analogs with improved activity compared with the natural product (12).

Peloruside, another MSA under development as an anticancer agent, is particularly interesting because unlike the other new-generation MSAs discussed above, peloruside binds to a unique, non-taxoid site on β-tubulin that it shares with another marine sponge natural product, laulimalide (10, 13–15). In addition, peloruside and laulimalide, similar to the epothilones and discodermolide, retain their activity in cells that overexpress the P-gp efflux pump (13, 14), thus remaining active in cells that have acquired resistance to the taxanes by P-gp overexpression. Although peloruside inhibits proliferation of various cancer cell lines (Table 1; refs. 1, 14, 16–18), as well as activated T cells in a murine model of multiple sclerosis (19), in non-replicating cells such as bone marrow–derived macrophages and unstimulated T cells (19), peloruside shows limited to no cytotoxic activity in these non-mitotic cells. Although cancer-specific targeting has also been reported in which ras-transformed murine cancer cells (32D-ras) were more sensitive to peloruside compared with their parental cell line (32D), the mechanism of the cancer cell–selective action may not be antimitotic, as the generation times of the 2 cell lines were similar (20). Non-mitotic actions of microtubule-targeting agents have been recently reviewed (21, 22). A preclinical study using xenografts in mice was carried out with laulimalide that gave discouraging results because of significant toxicity and poor effectiveness in inhibiting tumor growth (23), although results were more encouraging in a second in vivo study on laulimalide (24).

The aim of the present study was to test peloruside for its effectiveness against tumor growth in vivo using a nude, immunocompromised mouse model and to determine how well the compound was tolerated relative to the taxane drugs, paclitaxel and docetaxel, and doxorubicin, another standard chemotherapeutic agent that causes DNA damage. Flank injections of cancer cells were used to establish xenografts of lung and breast tumor cells in an athymic nu/nu mouse model.

### Materials and Methods

#### Materials

Peloruside A was prepared from marine sponge extracts as previously described (1) and synthesized according to the procedure of Liao and colleagues (25). Purity of the natural product and the synthesized sample exceeded 98%. Paclitaxel, docetaxel, and doxorubicin were purchased from commercial sources.

#### Cell culture

**In vitro** cell culture was carried out in appropriate culture media supplemented with 10% fetal calf serum and 100 units/mL penicillin/streptomycin. Cells were grown at 37 °C in a humidified 5% CO2-air atmosphere. All cultured cells retained the characteristic phenotype as shown on the ATCC website or the NCI repository; however, no independent authentication was carried out to check the identification. In the present study, cells tested in cell culture but not in vivo included human metastatic breast cancer cells stably transfected with a luciferase transporter (MDA-MB-231/Luc) and human prostate cancer cells (PC-3), both obtained from ATCC. The luciferase transfection had no effect on the generation time of the MDA-MB-231 cells. All cells were obtained before 2005.

Three tumorigenic cancer cell lines were used to generate xenografts in mice. The non–small cell lung carcinoma (NSCLC) line NCI-H460 (H460) was obtained from the NCI Division of the

### Table 1. IC50 values (nmol/L) for peloruside A in different cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Tissue type</th>
<th>IC50, nmol/L</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human cancer cell lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-60</td>
<td>Promyelocytic leukemia</td>
<td>7</td>
<td>(16)</td>
</tr>
<tr>
<td>H441</td>
<td>Lung adenocarcinoma</td>
<td>6</td>
<td>(16)</td>
</tr>
<tr>
<td>IA9</td>
<td>Ovarian carcinoma</td>
<td>16</td>
<td>(14)</td>
</tr>
<tr>
<td>A2780</td>
<td>Ovarian carcinoma</td>
<td>66</td>
<td>(14)</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Breast cancer</td>
<td>4</td>
<td>(17)</td>
</tr>
<tr>
<td>MDA-MB-231/Luc</td>
<td>Metastatic breast cancer</td>
<td>50</td>
<td>Present study</td>
</tr>
<tr>
<td>SH-SY5Y</td>
<td>Neuroblastoma</td>
<td>15</td>
<td>(16)</td>
</tr>
<tr>
<td>PC-3</td>
<td>Prostate cancer</td>
<td>10</td>
<td>Present study</td>
</tr>
<tr>
<td>Mouse cancer cell lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P388</td>
<td>Leukemia</td>
<td>18</td>
<td>(1)</td>
</tr>
<tr>
<td>32D</td>
<td>Myeloid precursor</td>
<td>9</td>
<td>(16)</td>
</tr>
<tr>
<td>N2a</td>
<td>Neuroblastoma</td>
<td>76</td>
<td>(18)</td>
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<tr>
<td>Non-cancer cell lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse splenocytes</td>
<td>ConA-stimulated</td>
<td>83</td>
<td>(19)</td>
</tr>
<tr>
<td>Mouse BMM6 and unstimulated splenocytes</td>
<td>&gt;10 μmol/L</td>
<td>(19)</td>
<td></td>
</tr>
<tr>
<td>AUXB1</td>
<td>Chinese hamster ovary</td>
<td>17</td>
<td>(14)</td>
</tr>
<tr>
<td>LLC-PK1</td>
<td>Pig kidney</td>
<td>3.7</td>
<td>(16)</td>
</tr>
</tbody>
</table>

**NOTE:** Growth inhibition was calculated from an MTT cell proliferation assay after 3 to 4 days of culture in different concentrations of peloruside A. Seven-day IC50 values for peloruside in MDA-MB-231/Luc and PC-3 cells were estimated from Fig. 2 of the present study. Other values were taken from the literature. Abbreviation: BMM6, bone marrow macrophages.
Cancer Treatment and Diagnosis (DCTD) Tumor Repository (Frederick, MD). A second NSCLC line A549 was purchased from ATCC, and a P-gp-overexpressing MDR phenotype of OVCAR-8 ovarian carcinoma cells, designated NCI/ADR-RES, were obtained from the NCI DCTD Tumor Repository. No independent authentication of these tumorigenic cell lines was carried out. These cell lines were obtained before 2005.

Animals
Female athymic nu/nu mice between 5 and 6 weeks of age were obtained from Harlan, Inc. and maintained in pathogen-free conditions at the Institute for Drug Development (IDD) in San Antonio, TX or the University of Texas Southwestern Medical Center (UTSWMC) in Dallas, TX. All animal experiments were carried out following IACUC guidelines with ethical approval obtained from the appropriate institutional animal ethics committee.

Cell proliferation assay
In addition to direct cell counting with a Coulter Counter, an MTT colorimetric cell proliferation assay was used to monitor growth of cells in culture, as previously described (16).

In vivo xenograft studies
Three cell lines were used for mouse xenograft studies: 2 NSCLC cell lines H460 and A549 and 1 ovarian carcinoma cell line with an overexpressed P-gp phenotype NCI/ADR-RES. All cell lines were implanted subcutaneously by trocar into the right flank of female nude mice (nu/nu). Tumor dimensions were measured by a Vernier caliper. When the tumors had grown to approximately 58 mm³ in size, animals were paired by tumor size (day 1) into control and treatment groups (n = 7 animals per group). Peloruside and paclitaxel were administered as single agents via intraperitoneal (i.p.) injection once a day for 5 days (QD × 5) for H460 NSCLC cell xenografts. Other dosage schedules were also used for peloruside and paclitaxel in A549 and NCI/ADR-RES cells. Docetaxel was administered intravenously every other day for a total of 3 doses (Q2D × 3) for H460 and A549 cell xenografts. Weight loss and tumor growth were monitored periodically through the treatment schedule. The percent tumor growth inhibition (TGI) was calculated from the formula: TGI = [(DVc – DVe)/DVc] × 100 in which DVc is the difference between the final and the initial tumor volume of the non–drug-treated group and DVe is the change in tumor volume in the drug-treated group. Any animals that showed partial or complete tumor regression were excluded from the TGI calculation but were included in the statistical analysis calculation.

Statistical analysis
Statistical analyses were carried out using GraphPad Prism v 5.0 (GraphPad Software, Inc.). P ≤ 0.05 was accepted as significant. Given that multiple doses were compared, a one-way ANOVA with the Dunnett multiple comparison post hoc test was used.

Results
Peloruside effects on proliferation of cultured cancer cells in vitro
Peloruside is known to be effective in the low nanomolar range at inhibiting cell proliferation of a number of cancer and non-cancer cell lines (Table 1). To extend this range, growth of MDA-MB-231/Luc and PC-3 cells was monitored after treatment in culture with peloruside for up to 14 days (Fig. 2). Significant growth inhibition was observed at concentrations of 1 to 10 nmol/L in both cell lines, with nearly 100% inhibition at 10 nmol/L after 7-day exposure to peloruside. A 7-day IC₅₀ value was estimated for peloruside in both cell lines and added to the data of Table 1.

Peloruside, paclitaxel, and docetaxel effects on H460 xenografts in nu/nu mice
Using H460 NSCLC cell xenografts, peloruside was tested at 3 different doses for effects on tumor growth over a 12-day period. The inhibition of proliferation was compared with inhibition by the standard anticancer drugs paclitaxel and docetaxel at close to their maximum tolerated doses (MTD; Fig. 3A). Peloruside and paclitaxel were given i.p. and docetaxel was administered i.v. Control animals received i.p. vehicle consisting of 0.9% saline supplemented with 10% DMSO and 20% PEG-400. This is a standard formulation for lipophilic compounds. Because of time considerations and a shortage of peloruside stocks, it was not possible to experiment with different formulations. It was also important for comparison between drugs that the same vehicle was used for all the compounds in in vivo tests, as different formulations can affect the antitumor responses. Docetaxel was given i.v. as it is the recommended method by Sanofi-Aventis, using a stock solution in polysorbate 80 diluted in 13% w/w ethanol for i.v. injection (Sanofi product information). Tumor volume was measured by caliper every 4 days. Peloruside caused a dose-dependent decrease in tumor growth over the treatment period, with TGI values of 88% at 5 mg/kg and 99% at 10 mg/kg.
Peloruside A Prevents Tumor Growth

Figure 3. Tumor volume and body weight changes in H460 xenografts. Female nude mice (nu/nu) were injected with 5 × 10^6 H460 NSCLC cells s.c. by trocar using tumor fragments harvested from s.c. growing tumors in host nude mice. When tumors reached approximately 58 mm³ in size, about 7 days following implantation, animals were pair-matched by tumor size into one control group given vehicle (n = 7 mice) and 5 treatment groups (n = 7 mice/group). One treatment group, peloruside at 20 mg/kg, QD×5 is not presented in the graph because of high mortality (Table 2). Two combination treatment groups peloruside/paclitaxel and peloruside/docetaxel were also set up. Again, because of a high mortality in the peloruside/paclitaxel group (Table 2), only the peloruside/docetaxel group is graphed. The average weight of the control group was 21.7 g, and the range of the average weights for all the groups was 21.7 to 22.9 g. Drug treatments were begun on day one following pair matching. Single-agent (A) and combination treatment (B) effects on tumor volume (average mm³ ± SEM) are presented over a 12-day period. Body weight changes (C) are also graphed as the average percent change ± SEM. DTX, docetaxel; PLA, peloruside A; PTX, paclitaxel.

(P < 0.01, one-way ANOVA followed by a Dunnett post hoc test; Table 2). Any drug resulting in a TGI of ≥58% (the NCI standard criterion for antitumor activity) was considered as being a valid anticancer agent (26). One mouse showed a partial tumor regression of 53% at the 10 mg/kg peloruside dose. No tumor necrosis was seen in any of the mice, and no deaths occurred for the 5 and 10 mg/kg peloruside single-agent treatments. The 5 and 10 mg/kg peloruside treatments caused significantly greater TGI than that seen with either paclitaxel or docetaxel (Fig. 3 and Table 2). In the H460 xenograft model, the changes in tumor volume with docetaxel were not significantly different from the control. The difference in TGI between the 5 and 10 mg/kg peloruside treatments was not significant. There was a significant loss in body weight (Fig. 3C) ranging from 20% to 26% by 12 days for all treated animals except the docetaxel treatment group. Weight loss in the peloruside group was similar to that seen with paclitaxel.

Two combination treatments (QD × 5) were also tested in the H460 model, combining peloruside at 5 mg/kg i.p. with either paclitaxel (8 mg/kg i.p.) or docetaxel (6.3 mg/kg i.v.; Fig. 3B). The peloruside–paclitaxel combination led to the death of all animals on day 8 (Table 2). In the peloruside–docetaxel combination group, 2 animals underwent drug-related deaths. Of the 5 remaining individuals, the TGI was 99% (P < 0.0001). Weight loss in the peloruside–docetaxel combination was similar to that in the single-agent study.

Overall, peloruside showed an impressive dose-dependent single-agent antitumor activity in the H460 xenograft model. Combination therapy between peloruside and either paclitaxel or docetaxel was less encouraging due to significant mortality in both groups, 2 mice in the docetaxel group and all 7 mice in the paclitaxel group.

Peloruside, paclitaxel, and docetaxel effects on A549 xenografts in nu/nu mice

Because of the significant body weight loss in the 12-day treatment with H460 cells, a second xenograft study was carried out with A549 cells for a longer duration of 30 days. Different doses of peloruside and different schedules of administration were compared with paclitaxel and docetaxel (Fig. 4A). Peloruside was administered at 5 or 10 mg/kg i.p. QD × 5 or at 10 or 15 mg/kg Q2D × 3. Paclitaxel was administered at 16 mg/kg i.p. QD × 5 and docetaxel was administered at 13 mg/kg i.v. Q2D × 3. Peloruside, with TGI values ranging from 51% to 74%, again out-performed docetaxel and paclitaxel. Although the 10 mg/kg Q2D × 3 peloruside treatment had a TGI of only 51%, the decrease in tumor volume compared with control was significant (P < 0.01, one-way ANOVA with Dunnett post hoc test). The TGI values for paclitaxel (44%) and docetaxel (50%) were also significant (P < 0.05 and P < 0.01, respectively), although below the NCI criterion for antitumor activity. All treatments resulted in moderate to significant dose- and schedule-dependent weight loss that was regained after stopping administration of the drugs (Fig. 4B). The greatest weight loss (23.5%) was seen in the 10 mg/kg QD × 5 peloruside group; however, all weight lost was regained 2 weeks after dosing had finished, and positive weight gain was seen after this recovery.
Mild-to-severe tumor necrosis was observed in a number of the animals (Table 2), and although there were no deaths, there were no partial or complete tumor regressions either.

Peloruside, paclitaxel, and doxorubicin effects on NCI/ADR-RES xenografts in nu/nu mice

A third xenograft study was performed with a P-gp–overexpressing NCI/ADR-RES breast tumor model with treatment extended over 92 days (Fig. 5). Peloruside TGI values ranged from 19% to 73%, depending on the dose and schedule of delivery (Table 2). With the Q2D × 4 × 3 schedule, drug was given as 4 doses, one every other day for 3 cycles, with cycles beginning at days 1, 19, and 61; however, the last cycle was dosed on a Q4D × 3 schedule. The QD × 5 × 3 schedule involved daily injections for 5 days for a total of 3 cycles. Doxorubicin was administered at 2.5 mg/kg i.p., and 3 of the 7 animals in this group died during the treatments. Although TGI values for peloruside were more variable in this study, with only 2 of the 4 peloruside schedules giving TGI values above the NCI 58% cutoff for anticancer activity, treatment with peloruside was better tolerated compared with doxorubicin, thus allowing administration of multiple cycles. Peloruside at 10 mg/kg showed a greater maximum weight loss of 20% compared with doxorubicin at 10%; however, weight gain after cessation of dosing was less in the doxorubicin group than in the peloruside groups. Paclitaxel gave the best overall response in the NCI/ADR-RES xenograft model but at a 43% mortality (Table 2). Only one animal died in the peloruside treatments and that occurred at the highest dose schedule: 15 mg/kg i.p. Q2D × 4 × 3. It was unexpected that paclitaxel and doxorubicin would be as effective as they were, given that the NCI/ADR-RES cell line is reported to be resistant to these drugs which are known to be good Pgp substrates. It is possible that Pgp expression in the tumor cells was less than normal during the study.

Discussion

Properties of peloruside

Peloruside is effective against a wide variety of cancer cell types and non-cancer cells (Table 1). The original interest in peloruside as a potential lead compound for therapeutic development was stimulated by the discovery that it had a similar mode of action to paclitaxel and docetaxel, that of stabilization of the microtubule (2). It was later shown, similar to other drugs of its class, to also inhibit microtubule dynamics (17) and be active against paclitaxel-resistant cells (14).

The future of cancer therapy is likely to reside in therapies that target specific cancer gene products or oncogene networks (27, 28), but similar to standard chemotherapy, targeted therapies also run into problems of secondary off-target effects and resistance. Some of these problems stem from the genetic complexity and heterogeneity of individual cancers, redundancy in cancer networks, the lack of unique oncogene-specific drivers and signaling pathways, and the formation of resistant clones (27). The mapping of the cancer genome is an exciting development in anticancer research, and it is estimated that only about 5% of the cancer genome has been drugged. Paclitaxel and docetaxel as chemotherapeutic drugs, although directed at a target found in both cancer cells and normal cells, have been hugely successful in treating solid tumors (4) but have several drawbacks. These include dose-limiting toxicities (3–5) and problems with vehicle
reactivity (6). A major potential advantage of peloruside over the taxanes is that it would be effective in taxane-resistant tumors that have inherent or acquired drug resistance [mechanisms of resistance have been reviewed by Orr and colleagues (ref. 29) and Kavallaris (ref. 30)]. These mechanisms include P-gp overexpression, changes in β-tubulin isotype expression, and mutation of amino acids at the tubulin-binding site for the taxane drugs (30). Thus, peloruside might be able to expand on the options available in long-term taxane treatment, in particular as it is better tolerated in vivo than the taxanes [this study and Crume and colleagues (ref. 19)] and can be used in vivo in combination with the taxanes to give additive or synergistic responses (31). Synergistic interactions between peloruside and the taxane site drugs have been previously described in vitro in cultured cancer cell lines (32, 33).

Results from murine xenografts

Preclinical trials with peloruside in 3 mouse xenograft studies provided very strong in vivo support for further peloruside development as a potential chemotherapeutic agent to inhibit tumor growth and even, in some cases, cause tumor regression (Figs. 3–5 and Table 2). TGI values exceeded those of the taxanes in the H460 and A549 models, although in the NCI/ADR-RES model, paclitaxel displayed the highest TGI but at a high cost with 3 of 7 animals dying from drug-related causes. In this same NCI/ADR-RES model, peloruside was more effective than doxorubicin and better tolerated (3 deaths with doxorubicin; 1 at the highest dosing schedule with peloruside). As with the taxanes, peloruside...
treatment caused significant weight loss over the first 10 to 12 days, but this loss was regained in later treatment schedules, indicating a transient, but significant toxicity for all the MSAs tested. Recovery from doxanubicin treatment, however, was much reduced compared to peloruside and paclitaxel. The MTD for peloruside in a mouse was determined to be between 15 and 20 mg/kg, as mortality was 100% at 20 mg/kg after 8 days of treatment. A number of different dosing schedules were attempted, and with more trials and different schedules, even 20 mg/kg may be possible without significant mortality. Co-administration of peloruside with paclitaxel and docetaxel caused an unacceptable number of animal deaths in the H460 model. Peloruside at 5 mg/kg in combination with docetaxel at 6.3 mg/kg gave a TGI of 95%, a value greater than the single-agent values for peloruside of 88% and docetaxel of 19%, suggesting possible synergistic interactions between the 2 MSAs. Because different concentrations of peloruside and taxanes were not tested on tumor growth in vivo, a true synergy calculation was not able to be carried out (32, 33).

Comparing peloruside effects in xenograft models with cabazitaxel (9), durable tumor responses were seen in cabazitaxel in which no tumor growth was seen for 30 to 40 days after cessation of dosing compared with about 20 days for peloruside. In the cabazitaxel study, the highest nontoxic dose was based on a weight loss of no more than 20%, whereas some peloruside treatments reached a maximum of 23.5% weight loss.

Conclusions and Future Directions

On the basis of the overall antitumor activity of peloruside, an intensive single-agent and combination treatment in a panel of xenograft models would be a logical next step in the preclinical development of peloruside. A dose-finding study is needed to determine the MTD for peloruside and to try to minimize its toxicity that leads to high weight loss during and immediately after administration. It would also be important to begin a pharmacokinetic/pharmacodynamic study on peloruside in both human cell lines and mouse models of cancer, before moving into phase I clinical trials. Advancement of peloruside into clinical trials is currently restricted by limited access to the natural product (34, 35) and the lack of availability of a scaled-up synthesis to produce clinically relevant amounts of peloruside. Efforts are currently under way to address this problem of supply.

Disclosure of Potential Conflicts of Interest

J.W. Shay and J.K. De Brabander are consultant/advisory board members for Reata Pharmaceutical. P.T. Northcote has ownership interest in a U.S. patent on peloruside A. J.H. Miller has ownership interest in a U.S. patent on peloruside A. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: C.J. Meyer, M. Krauth, J.K. De Brabander, P.T. Northcote, J.H. Miller

Development of methodology: C.J. Meyer

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.J. Wick, J.W. Shay, G. Gellett, P.T. Northcote, J.H. Miller

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.J. Meyer, J.W. Shay, J.H. Miller

Writing, review, and/or revision of the manuscript: C.J. Meyer, M. Krauth, M.J. Wick, J.W. Shay, J.K. De Brabander, J.H. Miller

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.H. Miller

Study supervision: M.J. Wick

Other (synthesis design and execution of peloruside synthesis): J.K. de Brabander

Acknowledgments

The authors thank Dr. Deborah Ferguson of Reata Pharmaceuticals for critically reading the article.

Grant Support

This project was supported by funding from Reata Pharmaceuticals, Inc (C.J. Meyer, M. Krauth), Cancer Society of New Zealand (E11807; J.H. Miller), Wellington Medical Research Foundation (E1707; J.H. Miller, P.T. Northcote), Victoria University of Wellington (80624; J.H. Miller). J.K. De Brabander thanks Robert A. Welch Foundation for support (grant I-1422) and holds the Julie and Luis Beecherl, Jr., Chair in Medical Science.

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Received February 24, 2015; revised April 16, 2015; accepted May 28, 2015; published OnlineFirst June 8, 2015.

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1822 Mol Cancer Ther; 14(8) August 2015 Molecular Cancer Therapeutics
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Mol Cancer Ther 2015;14:1816-1823. Published OnlineFirst June 8, 2015.

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