Efficacy of DMP 840: A Novel Bis-Naphthalimide Cytotoxic Agent with Human Solid Tumor Xenograft Selectivity


ABSTRACT

DMP 840, a novel bis-naphthalimide, was evaluated for antitumor efficacy in several tumor models in mice. As measured by a tumor growth inhibition assay, i.e., administration of DMP 840 to athymic nude mice at doses at or below the maximum tolerated dose resulted in curative activity against four human solid tumor xenografts, MX-1 mammary carcinoma, CX-1 and DLD-2 colon adenocarcinomas, and LX-1 lung carcinoma, producing full or incomplete regressions and/or percent tumor growth inhibition of ≥96%. The efficacy of DMP 840 in the mice was dose dependent. The activity of DMP 840 against the human tumors surpassed that demonstrated by several clinically used and investigational anticancer agents. In long-term growth delay studies, DMP 840 induced full regressions in 20 of 20 mice bearing MX-1 tumors, and tumors in one-half of these mice remained regressed for over 5 months. In addition, DMP 840 was curative against exponentially growing DLD-2 tumors staged at 500 mg and MX-1 tumors staged at 1000 mg. The bis-naphthalimide was equally efficacious when administered i.v. or i.p., but was slightly less active after oral dosing. Against both the MX-1 mammary carcinoma and the DLD-2 colon adenocarcinoma, some measure of schedule dependence was observed; the optimum schedule was daily for 9 days. Against L1210 and P388 murine leukemias, DMP 840 demonstrated little or no activity and was inactive against B16 murine melanoma. Overall, these results suggest that DMP 840 may be a human solid tumor selective cytotoxic agent.

INTRODUCTION

DMP 840 (NSC D640430; (R,R)-2,2’-[1,2-ethanediylbis[iminoo-(1-methyl-2,1-ethanediyl)]bis[5-nitro-1H-henbenz][1,3,4]dione(dimethanesulfonate)] is a novel bis-naphthalimide currently undergoing Phase 1 anticancer clinical trials. DMP 840 (Fig. 1) evolved from a protein kinase C inhibitor screen in which bis-naphthalenesulfonamides were identified as a class of active compounds. XB596, a bis-naphthalimide with cytotoxic activity, was discovered as a result of an analogue program in the bis-naphthalenedione series. XB596 ([4,3-(3-nitronaphthalene-1,8-dicarboximido)propylamino]-1-(3-nitronaphthalene-1,8-dicarboximido)butane hydromethanesulfonate) demonstrated broad-spectrum, antiproliferative activity in vitro and good activity against selected human solid tumor xenografts in nude mice (1). XB596 was shown to bind potently and with guanine-cytosine sequence selectivity to DNA and to demonstrate potent antiproliferative activity in vitro against a variety of cell lines derived from different murine and human tumor types (1). DMP 840 was identified by an extensive analogue program in a bis-naphthalimide series in which human solid tumor efficacy and solubility were optimized (2–4), while DNA binding properties were retained.5 Recent studies have shown that DMP 840 was efficacious against xenografts of human colon carcinomas and childhood rhabdomyosarcomas (5). This paper describes the activity of DMP 840 against selected murine tumors and human carcinomas xenografted in athymic nude mice and demonstrates that DMP 840 is possibly a human solid tumor selective tumoricidal agent.

MATERIALS AND METHODS

Animals. Athymic nude mice bearing the nu/nu gene were utilized for all human tumor xenografts. Mice were obtained from Charles River Laboratories (Wilmington, MA; outbred, CD-1 background) or Taconic Laboratory Animals and Service (Germantown, NY; outbred, Swiss background) or were bred at Glenolden Laboratory (outbred, Swiss background). Female mice, 6–10 weeks old, weighing 20–25 g were used for most experiments. In a few experiments male mice within the same weight range were employed. Transplantable murine tumors were maintained in the mouse of origin and transferred to the appropriate F1 hybrid for chemotherapy studies (DBA/2 and BALB/c × DBA/2 F1, for P388 and L1210 murine leukemias and C57BL and C57BL/6 × C3H F1, for B16 murine melanoma). Female mice weighing 18–22 g were used (Charles River Laboratories, Wilmington, MA). All studies were conducted in accordance with the guidelines of the NIH “Guide for the Care and Use of Animals” and after protocol review by the Institutional Animal Care and Use Committee). In keeping with the policy of this Committee for the humane treatment of tumor-bearing animals, mice were euthanized when tumors reached ≥10% of their total body weight.

Tumors and Cell Lines. The MX-1 human breast carcinoma xenograft, the LX-1 human lung carcinoma xenograft, and the CX-1 human colon adenocarcinoma xenograft were utilized for many years in the NCI screening panel of experimental tumors and as a result have been well characterized (6). The DLD-2 human colon adenocarcinoma xenograft was established by Dexter et al. (7). All human tumor lines were passaged as s.c. implants in nude mice. The P388 and L1210 murine leukemia lines and B16 murine melanoma line were obtained from the NCI® Tumor Repository (Frederick, MD) and maintained by serial passage in the appropriate mouse strain.

Drugs. DMP 840 was synthesized by chemists at The DuPont Merck Pharmaceutical Co. 20(S)-Camptothecin was a gift from the Sabinsa Corp (Edison, NJ). Mitoxantrone was kindly provided by the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, and taxol was provided by the Bristol-Myers Squibb Company (Princeton, NJ). All other agents (5-fluorouracil, cisplatin, cyclophosphamide, doxorubicin, methotrexate, and vincristine) were purchased from Sigma Chemical Co. (St. Louis, MO). All agents except taxol were formulated as solutions or suspension in 0.25% methylcellulose containing 2% (v/v) polyoxyethylene sorbitan monooleate for administration to tumor-bearing nude mice. Taxol was formulated in 5% ethanol/Cremophor (Cremophor EL; Sigma) in 0.9% saline. DMP 840 and other agents were prepared on the first treatment day, stored in the dark at 4°C and then used throughout the duration of the various treatment regimens. The injection volume for the various routes of administration was 0.2 ml.

Assessment of Activity in Murine Tumor Models. The methods used for chemotherapy studies against the murine L1210 and P388 leukemias and


The abbreviations used are: NCI, National Cancer Institute; MTD, maximum tolerated dose; TGI, tumor growth inhibition.

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2 Special acknowledgments are due to Dr. W. Fraser, Dr. K. B. Avis, and the late Dr. R. F. Landesman for the generous gifts of the MX-1, L1210, P388, and C57BL/6 murine tumor lines.

B16 melanoma have been described in detail elsewhere (8). Briefly, 1 × 10^6 L1210 cells, 1 × 10^6 P88 cells, or a 5% B16 tumor brei were implanted i.p. in the appropriate strain of mice on day 0. Test mice were randomized into treatment groups of six animals each for antileukemia studies or 10 animals/group for antimelanoma studies. The desired dosage of DMP 840 or the vehicle was injected i.p. or i.v. once daily for 5–9 consecutive days, beginning 1 day after implantation. Mice were generally held for 30 days (60 days for B16 experiments), and activity was calculated according to mean survival times as

\[
\% \text{T/C} = \frac{\text{Mean survival time of treated mice}}{\text{Mean survival time of control mice}} \times 100
\]

in which T/C is treated versus control. The NCI criteria for activity were utilized: a % T/C of ≥120 in P388 experiments; and ≥125 in L1210 and B16 experiments (6).

**Assessment of Activity in Human Tumor Models.** Athymic nude mice were inoculated s.c. in the inguinal area with 0.2-ml aliquots of a 25% (w/v) tumor mince prepared in sterile 0.9% saline (9). DLD-2, CX-1, MX-1, or LX-1 tumors were excised after propagation in passage mice and then minced. Pulpable tumors appeared within 7–14 days and weighed 50–100 mg as estimated by caliper measurement, as described below. Prior to chemotherapy, mice were pair-matched by tumor weights into groups of 8–10 animals each, and compounds or vehicle were administered parenterally or p.o. following predetermined treatment schedules. Dose levels used in these studies generally ranged from the predetermined MTD for DMP 840 and various reference drugs to several serial 2-fold dilutions. The MTD for each compound was determined in preliminary studies using conventional mice and defined as that dose which produced no greater than 10% mortality in the treated animals.

For tumor growth inhibition studies, mice were weighed and euthanized 15–19 days after the initiation of chemotherapy (28 days in the case of CX-1). At that time tumors were excised and weighed. Net tumor weights (final actual weight minus the estimated start weight at the beginning of chemotherapy) were determined and utilized to calculate the TGI expressed as a percentage:

\[
\% \text{TGI} = 1 - \frac{\text{Mean net tumor weight, treated group}}{\text{Mean net tumor weight, control group}} \times 100
\]

For tumor growth delay studies, mice were held until tumors ranged from the predetermined MTD for DMP 840 and various reference drugs to several serial 2-fold dilutions. The MTD for each compound was determined in preliminary studies using conventional mice and defined as that dose which produced no greater than 10% mortality in the treated animals.

Tumor weights, at the beginning of chemotherapy and at weekly intervals thereafter until termination of the experiment, were estimated using two dimensional caliper measurements and the formula for an ellipsoid:

\[
\text{Tumor wt} = \frac{L \times W^2}{2}
\]

where L is the major axis and W is the width of the tumor (9). Moderate activity and significant activity were defined as TGI of 58–89% and ≥90%, respectively (6). Tumor growth inhibition data were analyzed for statistical significance using the pooled variance t test. Regressions were classified as full regression indicating complete disappearance of a tumor, or incomplete regression indicating tumor shrinkage from the initial starting mass. Mice with regressions were excluded from TGI determinations.

For tumor growth delay studies, test and control mice were held until tumors progressed to ≥10% of their total body weight at which time they were euthanized. Tumor weights were estimated at weekly intervals, using caliper measurements as described above, until the study was terminated (usually day 180) or mice had to be euthanized because of tumor burden. Because of the curative activity of DMP 840, most growth delay studies were actually used to assess the extent and duration of compound-induced regressions.

### RESULTS

**Activity against Human Tumors.** Initial efficacy studies of DMP 840 against human tumor xenografts were conducted using i.v. administration of the compound, a 9-day treatment schedule, and decreasing doses of DMP 840 starting near the MTD. Using a tumor growth inhibition assay to assess efficacy and starting with tumors estimated at 50–100 mg, DMP 840 demonstrated curative activity against all four human tumor xenografts tested (Table 1). The compound exhibited curative activity at doses ranging from 2.5 to 10 mg/kg against the MX-1 and DLD-2 carcinomas but was curative only at the 10-mg/kg dose against the CX-1 and LX-1 carcinomas. The activity of the compound was dose dependent. Doses of DMP 840 below 2 mg/kg produced, at best, marginal to modest activity or were inactive, depending on the tumor type tested.

The activity of DMP 840, averaged from several experiments, against the four human tumor xenografts discussed above, was compared to that of several clinically used and investigational anticancer agents with diverse mechanisms of action (Table 2). The administration of DMP 840 at or near the MTD resulted in several full or incomplete regressions and TGI of ≥96%. In many experiments against the MX-1, DLD-2, and CX-1 carcinomas, all tumors treated with a dose of DMP 840 at or near the MTD regressed, only the more...
resistant LX-1 lung carcinoma failed to exhibit 100% regressions in at least one experiment. The broad-spectrum, high-level activity of DMP 840 was superior to that of most of the other antitumor agents tested. Only the newer agents, camptothecin and taxol, and the established cyclophosphamide and vincristine produced efficacy comparable to that of DMP 840 in tested models; these agents all exhibited curative activity against the more responsive mammary carcinoma MX-1 tumor model.

Since DMP 840 caused regressions in all the evaluated xenografts at the termination of short-term growth inhibition studies, it was of interest to determine how long these regressions were maintained. A series of studies using a tumor delay assay was conducted in the MX-1 mammary carcinoma model. The effect of DMP 840 on the growth delay of 50–100 mg MX-1 tumors is shown in Fig. 2. A significant finding was that the tumor growth inhibition assay underestimated the activity of DMP 840. At the time when mice were euthanized on day 15–19 for tumor growth inhibition determinations (Tables 1 and 2),

### Table 2: Comparative activity of DMP 840 and selected antitumor agents against human tumor xenografts

<table>
<thead>
<tr>
<th>Anticancer agent</th>
<th>Treatment regimen</th>
<th>DLD-2 (colon)</th>
<th>CX-1 (colon)</th>
<th>MX-1 (breast)</th>
<th>LX-1 (lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMP 840</td>
<td>10–12 mg/kg, i.v.</td>
<td>99 (1 FR, 6 IR)</td>
<td>98 (7 IR)</td>
<td>&gt;96 (2 FR, 4 IR)</td>
<td>96 (1 IR)</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>12–20 mg/kg, i.v.</td>
<td>33 nt-inactive</td>
<td>40 nt-inactive</td>
<td>61 nt-inactive</td>
<td>2</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2–4 mg/kg, i.v.</td>
<td>29 nt-inactive</td>
<td>60 nt-inactive</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Taxol</td>
<td>24/36 mg/kg, i.m./i.v.</td>
<td>nt (all FRs)</td>
<td>90 (1 FR, 2 IR)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.5 mg/kg, i.v./i.p., q1d × 9</td>
<td>45 nt-inactive</td>
<td>50 nt-inactive</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1 mg/kg, i.v.</td>
<td>30 nt-inactive</td>
<td>47 nt-inactive</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>0.5 mg/kg, i.v.</td>
<td>nt</td>
<td>55 nt-inactive</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>20(S)-Camptothecin</td>
<td>1–4 mg/kg, i.m., q2d-term.</td>
<td>nt</td>
<td>99 (1 IR) (all IRs)</td>
<td>nt</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50–100 mg/kg, i.v., q3p., q1d × 9</td>
<td>56 nt-inactive</td>
<td>99 (7 IR)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Captaxatrone</td>
<td>2 mg/kg, i.v.</td>
<td>44 nt-inactive</td>
<td>80 nt-inactive</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

*a Treatment schedules used: q1d × 9, once daily (days 1–9); q2d × 5, once daily on alternate days (days 1, 3, 5, 7, and 9); q2d term, once daily on alternate days until study terminated; q4d × 3, once daily every 4 days (days 1, 5, and 9).

*b nt/inactive, not tested in this study but inactive according to historical data from NCI (6); nt, not tested.

The growth delay assay demonstrated that tumors were still regressing. By day 26, 20 of 20 tumors in both the 10- and 5-mg/kg dose groups had completely regressed, as had 16 of 20 tumors in the 2.5-mg/kg group. Between days 33 and 100, many tumors recurred, most notably in mice in the 5- and 2.5-mg/kg treatment groups; but although these tumors eventually regrew until euthanization was required, the antitumor activity of DMP 840 was nevertheless evident by the marked tumor growth delay demonstrated by these tumors. After 100 days, there was little tumor recurrence. At 150 days, tumors in all 10 mice (50%) remaining on study from the original 20 mice in the 10-mg/kg treatment group were still completely regressed, thus demonstrating the exceptional curative activity of DMP 840 and the durability of the regressions it produced.

To assess the activity of DMP 840 under more stringent conditions, exponentially growing MX-1 mammary carcinomas were staged at 1 g prior to challenge of mice with 5- and 10-mg/kg doses of DMP 840. All tumors regressed following the course of a 9-day treatment (Fig. 3). Five months after DMP 840 treatment was stopped, 50% of the mice had regressed tumor burdens, although two mice in the high dose group (10 mg/kg) died from unknown causes without tumor progression. DLD-2 colon adenocarcinoma, staged at 500 mg, also was susceptible to the curative activity of DMP 840; more than 70% of the mice treated with a 10-mg/kg dose of DMP 840 were free of tumors 6 months after the final treatment.

Studies to determine if the efficacy of DMP 840 was dependent upon the route of administration were performed using 50–100 mg MX-1 mammary and DLD-2 colon tumors in nude mice (Table 3). In the MX-1 tumor model, DMP 840 was equally efficacious when given i.v. or i.p. but was somewhat less active when administered p.o. DMP 840 was more toxic when injected i.p.; the MTD for the i.p. route was 6.2 mg/kg compared to 12.5 mg/kg for i.v. administration. Further studies comparing the efficacy of DMP 840 administered i.v. and p.o. were conducted using the xenografted DLD-2 adenocarcinoma and the results confirmed the finding that greater efficacy was demonstrated with i.v. administration (Table 3). On the basis of these comparative studies, the i.v. route was selected as the preferred route of administration for DMP 840 and was used for all subsequent studies.

Having established that the i.v. route was an effective route of DMP 840 administration, the effect of different treatment schedules on the efficacy of i.v. administered DMP 840 were examined. Typical results from several studies of various treatment schedules are presented in Table 4 and indicate that there was schedule dependence, the degree of which varied with the xenograft used. Against the DLD-2 colon

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*Unpublished data.*

**Fig. 2. Tumor growth delay study of DMP 840 against MX-1 human mammary carcinoma.** At the time when mice were euthanized on day 15–19 for tumor growth inhibition determinations, Table 2 and indicate that there was schedule dependence, the degree of which varied with the xenograft used. Against the DLD-2 colon

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*Unpublished data.*

**Fig. 2. Tumor growth delay study of DMP 840 against MX-1 human mammary carcinoma.** At the time when mice were euthanized on day 15–19 for tumor growth inhibition determinations, Table 2 and indicate that there was schedule dependence, the degree of which varied with the xenograft used. Against the DLD-2 colon

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*Unpublished data.*
carcinoma DMP 840 was extremely efficacious regardless of the schedule used or the total amount of compound administered. When the treatment dose in each treatment schedule was reduced 4-fold from the high dose, at or near the MTD for that schedule, the curative activity of DMP 840 was retained, with the exception of the daily for 5 days schedule. The 2.5- and 10-mg/kg doses of DMP 840, administered on a daily for 9 days schedule, consistently produced a higher percentage of regressions than were demonstrated with the other schedules and their doses. Against the MX-1 mammary carcinoma, the schedule dependence of DMP 840 was more obvious. Of the various schedules evaluated against both xenografts, the daily for 9 days schedule appeared to be optimum since it was curative even at the lower 2.5-mg/kg dose. Consequently, the daily for 9 days schedule was selected as the preferred schedule.

A study was conducted to ascertain if resistance developed following DMP 840 treatment in vivo. Nude mice with actively growing MX-1 or DLD-2 tumors, which had initially been inhibited following treatment with DMP 840, were rechallenged with the original treatment regimens of DMP 840 (Table 5). Rechallenge with DMP 840 (5 and 10 mg/kg) resulted in growth inhibition as well as tumor regression. The efficacy of DMP 840 was also dose dependent in animals that were rechallenged with DMP 840. Retreatment of mice with 10 mg/kg DMP 840 produced tumor reregression in 2 of 4 rechallenged MX-1 mammary tumors and 6 of 6 rechallenged DLD-2 colon tumors.

The 6 rechallenged DLD-2 tumors remained regressed throughout the course of the 180-day study whereas rechallenged MX-1 tumors all regrew within 60 days of rechallenge. Only 1 of the 5 DLD-2 tumors rechallenged with the 5-mg/kg dose regrew before the study ended whereas all the rechallenged MX-1 tumors progressed within 30 days of rechallenge. Retreatment of mice with the 2.5-mg/kg dose resulted in negligible activity.

**Efficacy against Murine Tumors.** In a study of the activity of DMP 840 against murine leukemias, this bis-naphthalimide demonstrated little or no activity against the P388 tumor line (Table 6). Moderate activity was observed only when both the compound and the tumor cells were administered i.p. (% T/C = 153), but no activity was exhibited when i.v. injections of DMP 840 were utilized. DMP 840 was slightly more active against the L1210 leukemia, with marginal efficacy (% T/C < 150) demonstrated after either i.v. or i.p. treatment. Against the i.p. B16 melanoma, DMP 840 was inactive regardless of whether it was administered i.v. or i.p., DMP 840, administered i.p. or i.v. at its MTD was also inactive against s.c. implanted B16 melanoma.

**DISCUSSION**

DMP 840 is one of the most active compounds in a new class of anticancer agents, the bis-naphthalimides, a series that demonstrated potent *in vitro* activity against tumor cell lines (1). There is evidence that DNA is the molecular target for DMP 840 (4). Although DMP 840 intercalates into DNA, the mechanism of tumoricidal activity of DMP 840 has not yet been fully defined. The compound is cytotoxic against quiescent as well as proliferating tumor cells, and doxorubicin resistant as well as the more sensitive parental cell lines (3). *In vivo*, DMP 840 has shown only marginal to modest activity against the murine leukemias and no activity against B16 murine melanoma. Lo Russo et

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**Table 3 Antitumor activity of DMP 840 against MX-1 and DLD-2 human tumor xenografts using various treatment routes**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Treatment route</th>
<th>Optimum dose (mg/kg/day)</th>
<th>No. of regressions</th>
<th>TGI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX-1 (mammary)</td>
<td>i.v.</td>
<td>10.0</td>
<td>9/9</td>
<td></td>
</tr>
<tr>
<td>i.p.</td>
<td>6.2</td>
<td>7/7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.o.</td>
<td>20.0</td>
<td>3/9</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>DLD-2 (colon)</td>
<td>i.v.</td>
<td>10.0</td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>p.o.</td>
<td>20.0</td>
<td>8/8</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 4 Antitumor activity of DMP 840 against DLD-2 and MX-1 human tumor xenografts using various treatment schedules**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Treatment schedule</th>
<th>Dose (mg/kg/injection)</th>
<th>No. of regressions</th>
<th>Total no. of mice</th>
<th>TGI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLD-2</td>
<td>q.d.* (day 1)</td>
<td>40.0</td>
<td>4/10</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.0</td>
<td>1/10</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b.i.d. (day 1)</td>
<td>20.0</td>
<td>3/10</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0</td>
<td>2/10</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d. (days 1, 5, 9)</td>
<td>40.0</td>
<td>3/10</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.0</td>
<td>3/10</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b.i.d. (days 1, 5, 9)</td>
<td>20.0</td>
<td>5/10</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0</td>
<td>1/10</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d. (days 1–5)</td>
<td>10.0</td>
<td>8/9</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>2/9</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>MX-1</td>
<td>q.d. (day 1)</td>
<td>40.0</td>
<td>4/10</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d. (days 1–5)</td>
<td>10.0</td>
<td>8/9</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d. (days 1–9)</td>
<td>10.0</td>
<td>9/9</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>9/9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*q.d., once daily; b.i.d., twice daily.*

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*Unpublished observations.*
by assessing complete and partial tumor regressions present 30 days after the final treatment cycle. Tumors doubled in size after the initial treatment cycle, were rechallenged with the same regimen that was originally administered. The efficacy of each treatment cycle was followed on day 1. Efficacy was based on the mean survival time of treated versus control mice (% T/C); the NCI criteria for activity, % T/C < 120 (P388) and % T/C > 125 (L1210 and B16) were utilized (6).

al. (10) have reported that DMP 840 exhibited modest to moderate activity against selected murine solid tumors. Thus, DMP 840 has demonstrated little or no activity against several murine tumor models, hematopoietic neoplasms and solid tumor types, used for many years to select anticancer agents for clinical evaluation. However, the efficacy of DMP 840 against human solid tumor xenografts, as reported herein, has been exceptional.

Against the human MX-1 mammary carcinoma and the DLD-2 colon adenocarcinoma, DMP 840 demonstrated curative activity and a relatively wide therapeutic window, with curative doses ranging from 2.5 to 12.5 mg/kg. However, it is the activity of DMP 840 against these resistant tumors (12-16); however, in many cases their activity is not equivalent to the dose-dependent activity of DMP 840. The excellent activity of DMP 840 against human tumor xenografts has been substantiated by Houghton et al. (5) who found that this compound produced regressions in 5 of 6 rhabdomyosarcomas and significant tumor growth inhibitory activity against 4 of 7 colon adenocarcinomas.

DMP 840 was efficacious against both early (50–100 mg) and late-staged (500–1000 mg) tumors. Efficacy was route dependent in that greater efficacy was demonstrated with parenteral administration than with oral treatment; however, DMP 840 exhibited curative activity regardless of whether it was injected i.v. or i.p. DMP 840 was quite efficacious when administered following several different treatment schedules but was most efficacious when injected i.v. for 9 consecutive days. Preliminary results suggest that resistance to DMP 840 does not readily develop following an initial course of treatment and tumors treated with one cycle of DMP 840 may remain responsive to further cycles.

L1210 and P388 murine leukemias, long employed as primary screen in the NCI preclinical drug development program, have been criticized as selecting only antilymphoma and antileukemic agents but not solid tumor active compounds (11, 17). Consequently, several alternative solid tumor models, both murine and human, have been proposed and are now utilized in anticancer discovery programs to uncover solid tumor-selective agents (11). The human tumor xenograft in nude or immunodeficient mice is one such model that has shown promise in predicting clinical success (18). Several newer anticancer agents, such as taxol (19), camptothecin analogues (13), the anthracyrrozoles (20), the diarylsulfonyleureas and gemcitabine (17), and the cyclopropylpyrroloindole analogues (14) have all demonstrated some measure of activity against human tumor xenografts. Many of these agents are currently being evaluated clinically and along with DMP 840 will help assess the predictability of xenograft models for clinical success. DMP 840 is now undergoing Phase I studies in the clinic based on its broad-spectrum, curative activity against early- and late-staged human tumor xenografts.

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Efficacy of DMP 840 against experimental tumors.


Efficacy of DMP 840: A Novel Bis-Naphthalimide Cytotoxic Agent with Human Solid Tumor Xenograft Selectivity


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