# EXHIBIT 2011

# Fludarabine, Mitoxantrone, and Dexamethasone: An Effective New Regimen for Indolent Lymphoma

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***Purpose:*** **Although most patients with indolent lymphomas respond to initial therapy, virtually all experience relapse. Secondary therapy is often beneficial, but responses are rarely, if ever, durable. We conducted this phase II trial to evaluate the therapeutic efficacy and toxicity of fludarabine, mitoxantrone, and dexamethasone (FND) in patients with relapsed indolent lymphoma.**

***Patients and Methods:*** **Fifty-one patients with recurrent or refractory indolent lymphoma were treated with a regimen of fludarabine 25 mg/m$^2$/d intravenously (IV) on days 1 to 3, mitoxantrone 10 mg/m$^2$ IV on day 1, and dexamethasone 20 mg/d IV or orally on days 1 to 5. Treatment was repeated at 4-week intervals for a maximum of eight courses. Late in the course of this trial, trimethoprim-sulfamethoxazole (TMP-SMX) was incorporated for *Pneumocystis carinii* (PCP) prophylaxis.**

***Results:*** **Responses were complete (CR) in 24 patients (47%) and partial (PR) in 24 (47%). The median failure-free survival time was 21 months for CR patients and 9 months for PR patients. Notable activity of FND was seen even in the elderly, in those with high serum lactate dehydrogenase (LDH) or $\beta_2$-microglobulin levels, and in those with multiple prior treatment regimens. The predominant toxic effects were myelosuppression and infections; other toxic effects were modest. Infections occurred in 12% of courses. Almost half of the infections were proven or suspected opportunistic infections, including six cases of dermatomal herpes zoster and two cases of proven PCP pneumonia.**

***Conclusion:*** **The FND combination is highly active in patients with recurrent or relapsed indolent lymphoma and results in a high percentage of CRs. Because of the risk of opportunistic infections, we currently recommend prophylaxis with TMP-SMX and advise deletion of corticosteroids for patients who develop opportunistic infections.**

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ALTHOUGH INDOLENT lymphomas are often transiently controlled by standard chemotherapeutic regimens, they are ultimately progressive, fatal diseases.[1] New therapeutic agents, including the purine analog fludarabine phosphate and the anthracenedione mitoxantrone, have shown promise in recurrent low-grade lymphoma (LGL) when used as single agents. Response rates of 52% to 64% have been reported for fludarabine and 27% to 67% for mitoxantrone in recurrent LGL; most of the reported responses were partial.[2-7]

We previously conducted a phase I trial of fludarabine, mitoxantrone, and dexamethasone (FND) for the treatment of recurrent LGL.[8] While the primary objective of that study was to define the maximum-tolerated dose of the combination, clinical responses were seen at every dose level tested. The overall response rate was 71%, with 43% of patients having a complete response (CR) and 29% having a PR. The median duration of response was 18 months for patients who achieved a CR and 12 months for patients who achieved a PR.

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Based on the encouraging results from the phase I trial, we conducted this phase II trial to define more clearly the therapeutic efficacy and toxicity of the FND combination in patients with relapsed indolent lymphoma.

## PATIENTS AND METHODS

### *Patients*

Between January 1992 and December 1993, 55 adult patients with recurrent or refractory LGL (small lymphocytic, follicular small cleaved, or follicular mixed) or follicular large-cell lymphoma were enrolled onto the study. Patients were excluded if they had positive serology for the human immunodeficiency virus. Patients with prior mitoxantrone or fludarabine exposure were excluded, unless the exposure was more than 12 months previously and they had been responsive. Eligibility requirements included adequate marrow function (granulocyte count $> 1{,}500/\mu L$; and platelet count $> 100{,}000/\mu L$), liver function (bilirubin level $\leq 2.0$ mg/dL), renal function (creatinine concentration $\leq 1.4$ mg/dL), and cardiac function (ejection fraction $\geq 50\%$). Our institutional review board reviewed and approved the study, and signed informed consent was obtained from all participating patients.

The pretreatment staging evaluation included a serum chemistry profile, including lactate dehydrogenase (LDH) level, bone marrow biopsy, chest x-ray, and imaging of the abdomen with either computed tomography, ultrasound, or lymphangiogram. Most patients also had determinations of serum $\beta_2$-microglobulin level.

### *Treatment Schedule*

Patients received fludarabine 25 mg/m$^2$/d intravenously (IV) on days 1 to 3, mitoxantrone 10 mg/m$^2$ IV on day 1, and dexamethasone 20 mg/d IV or orally days 1 to 5. Antiemetics, most commonly ondansetron, were routinely given before chemotherapy. Treatment

was repeated at 4-week intervals for a maximum of eight courses. Patients with anticipated poor hematologic tolerance (poor prior chemotherapy tolerance, prior extensive radiotherapy, or age > 65 years) started at 20% lower doses of fludarabine and mitoxantrone. If a course of FND was complicated by mucosal bleeding, platelet count less than 20,000/$\mu$L, sepsis, granulocyte count less than 100/$\mu$L, or delayed blood count recovery greater than 35 days, fludarabine and mitoxantrone doses were reduced by 20% for subsequent courses. The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) was not mandated by protocol, but was permitted.

In September 1993, during the course of the trial, prophylaxis for *Pneumocystis carinii* pneumonia (PCP) was instituted, which consisted of trimethoprim-sulfamethoxazole (TMP-SMX), two double-strength tablets daily on Saturdays and Sundays. If PCP pneumonia occurred, subsequent FND cycles were given without dexamethasone.

### *Patient Monitoring During Therapy*

Monitoring of response included repetition of abnormal pretreatment examinations after the first two courses and after every subsequent three or four courses. Monitoring of cardiac status was performed after every two to three courses with cardiac scan or echocardiogram. For patients who had received prior anthracyclines, a potential cumulative cardiotoxic dose was estimated by assuming that a full cardiotoxic dose of mitoxantrone was 160 mg/m$^2$, and that of doxorubicin by bolus, 450 mg/m$^2$. (For doxorubicin by continuous infusion, the thresholds used were 675 mg/m$^2$ for 48-hour infusion and 800 mg/m$^2$ for 96-hour infusion). The following calculation was used: if the total doses of mitoxantrone and doxorubicin per square meter are "m" and "d" respectively, then m/160 + d/450 must be less than 1. If this potential cardiotoxic threshold was exceeded, or if cardiac symptoms occurred, discontinuation of mitoxantrone was advised.

### *Response Criteria and Data Analysis*

CR was defined as the disappearance of all clinical evidence of active tumor for a minimum of 8 weeks and absence of other symptoms. PR was defined as ≥ 50% decrease in the sum of the products of diameters of all measured lesions that persisted for at least 4 weeks. No lesions could increase in size and no new lesions could appear. Any response less than a PR was considered a treatment failure for this analysis. Monitoring of follicular lymphoma patients for molecular remission, ie, for the presence of circulating cells with *bcl*-2 gene rearrangement by the polymerase chain reaction,[9] was not performed in this trial. Survival and failure-free survival were measured from entry into the protocol until death or treatment failure (ie, relapse or toxic death), respectively.[10]

Data were tabulated to assess the utility of prognostic models that have been devised for previously untreated patients with aggressive lymphomas, including the international index[11] and a serologic model that incorporated serum LDH and $\beta_2$-microglobulin level.[12] Both of these models appear to be applicable to patients with previously untreated indolent lymphoma.[13,14] Likewise, information on prior therapy was correlated with response according to the analysis reported by Weisdorf et al.[15]

## RESULTS

### *Patients*

Of 55 patients enrolled, 51 could be evaluated for response. The four patients who could not be evaluated included three who refused any therapy after signing informed consent, and one who was ineligible by virtue of known refractoriness to mitoxantrone. The 51 patients in this report include five with mantle cell lymphoma, who, when entered, were categorized as having variants of small lymphocytic lymphoma (ie, disease considered to be low grade). Mantle cell lymphoma is often responsive to initial therapy, but, like indolent lymphomas, control is transient and there is no plateau of the failure-free survival curve. However, the median survival of patients with mantle cell lymphoma is shorter than with LGL, and many regard it as an intermediate-grade lymphoma.[16]

Pertinent patient features are listed in Table 1. The median age was 62 years. For all patients but one, abdominal imaging included computed tomography; the remaining patient had an ultrasound. Ten patients also had lymphangiography. Prior therapy included doxorubicin in all but four. Fourteen had received prior mitoxantrone (> 12 months previously). None had received purine analogs. The median number of prior regimens was two. The prior therapy was often intensive: 10 of those listed as having received one or two prior regimens had received front-line therapy with an alternating program of three chemotherapy combinations using 11 drugs.[17]

### *Response*

There were 24 CRs and 24 PRs, for an overall response rate of 94%. The median time to attainment of CR was after five courses (range, one to eight); all CR patients had achieved at least a PR after four courses (median, two). For those whose maximum response was a PR, the median time to PR was two courses (range, one to six). The median duration of CR was 21 months (range, 4 to 25+) (Fig 1). Twelve of 24 patients who had CRs remain in CR from 7 to 25 months. The median duration of PR was 9 months (range, 4 to 21+). Three patients who had PRs proceeded to have bone marrow transplantation (BMT) during PR at 3 to 5 months and are censored in Fig 1. Six patients have PRs ongoing from 7 to 21 months.

Among PR patients, nine developed progressive disease early (within 9 months): one within 1 month of discontinuation of FND, two while on FND, and six after early discontinuation of FND because of toxicity (see later) after a median of four courses. Six of these nine patients with early progression after FND did subsequently stabilize or respond to alternate therapy; three died of progressive lymphoma within 6 months, including one who had documented transformation to diffuse large-cell lymphoma.

Only three patients did not achieve at least a PR. Two of these patients had bulky disease and a high LDH level,

**Table 1. Patient Characteristics and Responses**

| Characteristic | No. of Patients | Number of Responses | | |
|---|---|---|---|---|
| | | CR | PR | < PR |
| All patients | 51 | 24 (47%) | 24 (47%) | 3 |
| Sex | | | | |
| Male | 26 | 11 | 13 | 2 |
| Female | 25 | 13 | 11 | 1 |
| Age, years | | | | |
| < 50 | 12 | 3 | 8 | 1 |
| 50-69 | 28 | 18 | 8 | 2 |
| ≥ 70 | 11 | 3 | 8 | — |
| Cell type | | | | |
| Small lymphocytic | 13 | 8 | 5 | — |
| Follicular small cleaved | 26 | 12 | 12 | 2 |
| Follicular mixed | 4 | 2 | 2 | — |
| Follicular large cell | 3 | 1 | 2 | — |
| Mantle cell | 5 | 1 | 3 | 1 |
| Prior chemotherapy regimens | | | | |
| 1 | 17 | 7 | 10 | — |
| 2 | 14 | 6 | 7 | 1 |
| 3 | 10 | 6 | 4 | — |
| ≥ 4 | 10 | 5 | 3 | 2 |
| Prior BMT | 2 | — | 1 | 1 |
| Prior abdominal/pelvic radiation | 10 | 6 | 3 | 1 |
| Response to primary therapy | | | | |
| CR ≥ 24 months | 21 | 9 | 11 | 1 |
| CR 12-23 months | 9 | 2 | 5 | 2 |
| PR ≥ 12 months | 13 | 9 | 4 | — |
| PR < 12 months | 6 | 4 | 2 | — |
| < PR | 2 | — | 2 | — |
| LDH | | | | |
| Normal | 41 | 20 | 20 | 1 |
| Elevated | 10 | 4 | 4 | 2 |
| $\beta_2$-microglobulin* (mg/L) | | | | |
| < 3 | 25 | 13 | 12 | — |
| ≥ 3.0 | 15 | 6 | 7 | 2 |
| $\beta_2$-microglobulin*/LDH | | | | |
| Both low | 23 | 12 | 11 | — |
| One elevated | 12 | 5 | 7 | — |
| Both elevated | 5 | 2 | 1 | 2 |
| International index score | | | | |
| 0, 1 Low | 3 | 2 | 1 | — |
| | 18 | 8 | 9 | 1 |
| 2 Low-intermediate | 26 | 14 | 11 | 1 |
| 3 High-intermediate | 4 | — | 3 | 1 |
| 4-5 High | 0 | — | — | — |

*$\beta_2$-microglobulin level not determined in 11 patients.

and they had disease progression after one cycle of FND. The third nonresponder had extensive prior therapy, including BMT, and had slow recovery of blood counts on FND, with disease progression after the third cycle before the blood counts recovered.

With a median follow-up duration of 20 months, the median survival and failure-free survival times from the time of entry onto the FND study were 34 and 14 months, respectively (Fig 2). The failure-free survival curve shows the continuing relapse pattern that is typical of indolent lymphoma.

Responses by disease features are listed in Table 1. There was notable activity of FND even in the elderly, in patients with a high LDH and/or high $\beta_2$-microglobulin level,[12,14] in those who had received multiple prior treatment regimens,[15] and in those who had had short durations of response to primary therapy. By the international index,[11,13] only four patients had high-intermediate risk, ie, three risk factors (and none had high risk); none of these four achieved a CR, but three did achieve a PR. Only five patients with mantle cell lymphoma were treated; four responded, but only one response was a CR. Our experience was limited with two predictably difficult subsets—those with prior refractoriness to primary therapy and those with prior BMT; we observed no CRs among four such patients, but there were three PRs.

### *Toxicity*

The 51 patients received a total of 257 courses of FND (median, six courses per patient). The predominant toxic effects were myelosuppression and infections. Other toxic effects were modest.

Of 182 courses assessable for hematologic toxicity, the median nadir granulocyte count was 1,100/$\mu$L and occurred at a median of day 15, and the median nadir platelet count was 133,000/$\mu$L and occurred at a median of day 14. The granulocyte count was less than 500/$\mu$L in 20% of courses, and the nadir occurred at 20 days or later in 26% of courses. The platelet count decreased to less than 100,000/$\mu$L in 31% of courses and to less than 50,000/$\mu$L in only 8% of courses; the platelet nadir occurred at 20 days or later in 14% of courses. Hematologic recovery to a granulocyte count of 1,000/$\mu$L and a platelet count of 100,000/$\mu$L was delayed beyond 35 days in 17 courses.

Fourteen patients began therapy at a reduced dose, per protocol, because of age or prior extensive therapy. Five with anticipated poor tolerance were actually able to tolerate full-dose therapy. Of 14 patients who started and stayed at reduced doses, five achieved a CR and another eight achieved a PR, so response was apparently not compromised by the lower starting dose.

Six patients required dose reductions because of myelosuppressive toxicity and nine patients had early discontinuation of therapy (after two to five courses) because of myelosuppression, which typically was first manifested as prolonged thrombocytopenia. Of these nine, five were over age 65, two had prior bone marrow transplantation, and one was age 62 and had received prior abdominal radiotherapy. Other reasons for early discontinuation of

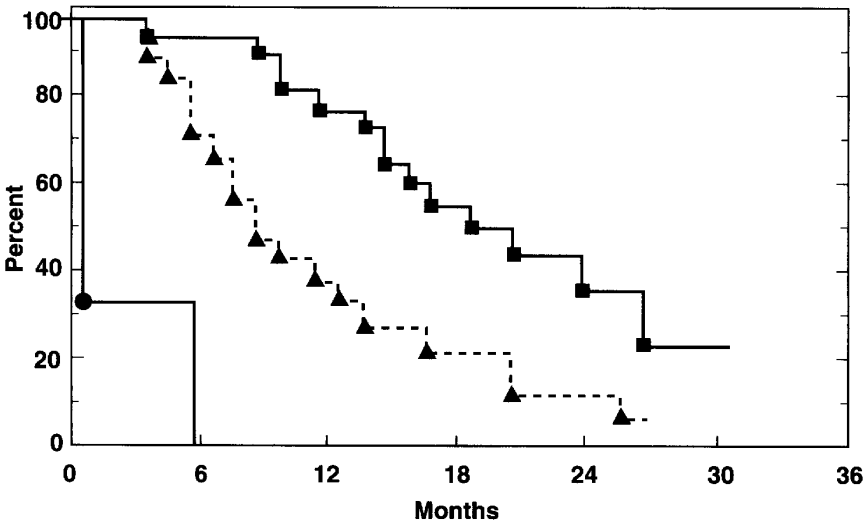


Fig 1. Failure-free survival by response: CR (■), PR (▲), and no response (●).

therapy included infectious complications in three, reduction of cardiac ejection fraction in three, attainment of a plateau PR status in four, and patient refusal by two.

Thirty infectious episodes occurred (12% of courses) among 22 patients. Five were minor and included urinary tract and upper respiratory tract infections. Twelve were more severe and were presumed to be bacterial infections, including 10 febrile episodes in the setting of neutropenia. There was one proven enterococcal bacteremia and one staphylococcal infection at the site of a subcutaneous venous access device. Thirteen infectious episodes were proven or suspected opportunistic infections. These included six cases of dermatomal herpes zoster, all of which remained localized and resolved; two cases of proven PCP and four other suspected PCP infections; and one case of *Mycobacterium avium-intracellulare* that was diagnosed in a patient 7 months after completion of FND and that was ultimately fatal. This was the only treatment-related death. One of the episodes of PCP occurred after the patient had completed therapy with FND. In September 1993, the protocol was amended to include prophylactic TMP-SMX, and no cases of PCP occurred thereafter.

Nonhematologic toxicity was modest. Eleven patients reported nausea, which was mild in all but one, and only

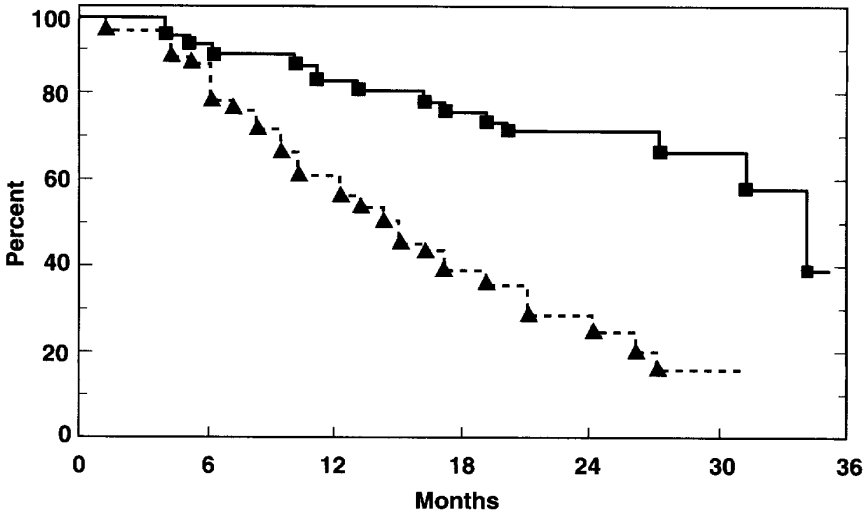


Fig 2. Survival (■) and failure-free survival (▲).

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