Expanding the Horizons

Communiqué from ICML 2008

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Princess Margaret Hospital Phase II Consortium: An Alliance of Integrity and Innovation
New Evidence in Oncology is a publication for Canadian healthcare professionals. We provide oncology specialists with timely scientific data from research presented at international and Canadian oncology conferences. The journal features a Canadian perspective, in which key opinion leaders comment on how recent developments could shape Canadian clinical practice.

Our July 2008 issue presents coverage of the 10th International Conference on Malignant Lymphoma (ICML), held in Lugano, Switzerland, from June 4–7, 2008. The issue includes an overview of therapies for chronic lymphocytic leukemia, a look at strategies for non-Hodgkin’s lymphoma treatment, and a preview of GA101, a new monoclonal antibody in early development. We would like to thank Dr. Laurie Sehn for her article on monitoring follicular lymphoma patients on rituximab maintenance therapy.

We are also pleased to include a profile of the Princess Margaret Hospital Phase II Consortium, which is conducting many important clinical trials in Canada.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and reports on other recent oncology research. Slide presentations on various topics are available for download.
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The 10th International Conference on Malignant Lymphoma (ICML), the principal international forum devoted to basic and clinical research into lymphoid neoplasms, took place in Lugano, Switzerland, from June 4–7, 2008. Since the first meeting in 1981, ICML has attracted many scientists to Lugano, and 3,000 physicians from all over the world, including hematologists, clinical oncologists, pathologists, and leading researchers involved in the study and treatment of lymphoid neoplasms, participated this year. ICML 2008 dealt with results and perspectives of basic as well as clinical research. Highlights of some key presentations are reported in this issue of *New Evidence in Oncology*. 
Non-Hodgkin’s Lymphoma Update

This year, the International Conference on Malignant Lymphoma (ICML) celebrated its 10th anniversary. It has been a transitional year for ICML, one in which participants at the conference reflected on the progress made in the treatment of lymphoma, particularly through the development of monoclonal antibodies such as rituximab. Rituximab was the world’s first licensed monoclonal antibody therapy for non-Hodgkin’s lymphoma (NHL). It is currently used in patients with aggressive and indolent forms of lymphoma.

A great deal of major data has now been presented on rituximab — its use in first-line, second-line, and maintenance treatment. The question that now arises is: Where do we go from here? How do we incorporate the findings into clinical practice? How do we make treatment decisions? This section on non-Hodgkin’s lymphoma (NHL) highlights some of the discussions and presentations that took place at ICML.

Diffuse Large B-cell Lymphoma

Meenakshi Kashyap

Elderly patients with poor-prognosis diffuse large B-cell lymphoma show improved outcome after dose-dense rituximab

Background
At the 2007 Annual Meeting of the American Society of Hematology (ASH), Pfreundschuh and colleagues presented the first interim analysis from a phase II trial conducted to investigate if dose-dense rituximab administration, in conjunction with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy, could result in an earlier plateau of serum rituximab levels and further improve outcomes in elderly patients with poor-prognosis diffuse large B-cell lymphoma (DLBCL). At ICML 2008, Pfreundschuh and colleagues presented data on the second analysis of this trial.

Study design
• Elderly patients aged 61–80 years (n = 125) with aggressive CD20+ B-cell lymphoma received six cycles of biweekly CHOP-14 combined with twelve infusions of rituximab (375 mg/m²) on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99.
• Radiotherapy was planned to sites of initial bulk and/or extranodal involvement.
• Patients (n = 306) treated within the RICOVER-60 trial with six cycles of CHOP-14 and eight infusions of rituximab served as control.
• The primary endpoint was event-free survival.

Key findings
• Of the 125 patients, 124 were evaluable for response.
• Dose-dense rituximab resulted in plateau trough serum levels of rituximab as early as day 1 of the first chemotherapy cycle. Higher rituximab levels were maintained throughout the treatment as compared with eight biweekly applications in the control population. (Figure 1)
• Because three therapy-associated deaths were observed among the first twenty patients treated, prophylaxis with acyclovir for cytomegalovirus (CMV) and cotrimoxazole for Pneumocystis carinii became mandatory for the patients who continued to receive therapy.
• Despite a less favorable study population, DENSE-R-CHOP-14 resulted in a somewhat higher complete remission rate (82% versus 78%) in all patients.
• Event-free survival and progression-free survival were not different compared with the eight biweekly applications of rituximab in the control group. However, a subgroup analysis of patients according to IPI risk group showed that DENSE-R-CHOP-14 resulted in a higher complete response rate (82% versus 68%) of patients with poor-prognosis disease (IPI 3–5). This advantage translated into a better two-year event-free survival rate (68% versus 58%) of these patients. (Figures 2 and 3)
Study design

CD20+ DLBCL
Stages I–IV
61 to 80 years

Six cycles

Twelve doses of rituximab

Weeks

Figure 1: Trough serum levels
**Figure 2: Event-free survival**

![Graph](image)

* with censoring at 24 months

IPI = International Prognostic Index; R = rituximab

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**Figure 3: Progression-free survival**

![Graph](image)

IPI = International Prognostic Index; R = rituximab
Key conclusions

■ Densification of rituximab in combination with six cycles of CHOP-14 achieves earlier and higher rituximab serum levels, and higher complete response and event-free survival rates in elderly patients with poor-prognosis DLBCL.

■ The increased toxicity (grade 3/4 infections) can be controlled by specific prophylaxis. (Figure 4)

■ These observations from a phase II trial need to be further confirmed in a randomized study.

Figure 4: Effect of prophylaxis on grade 3/4 infections

References:
Background
Positron emission tomography (PET) using the glucose analogue F-18-fluorodeoxyglucose (FDG) is now widely used for staging and treatment monitoring in patients with Hodgkin’s disease (HD) and non-Hodgkin's lymphoma (NHL). Lymphomas are highly sensitive to chemotherapy or radiotherapy, and with the current treatment options, substantial long-term cure rates of 50% are expected for aggressive NHL. At the end of treatment, lymphoma patients often present with a residual mass. Numerous studies have shown the effectiveness of PET in the detection of residual disease at the end of therapy. PET and PET in combination with computed tomography (PET/CT) after a few cycles of chemotherapy is now recognized as an important prognostic factor in aggressive lymphoma.1

Limited-stage diffuse large B-cell lymphoma (DLBCL) is defined as Ann Arbor Stage I–II, no B symptoms, non-bulky (<10 cm) tumour that is encompassable within a radiation field. Primary management of DLBCL typically entails the combined modality approach of abbreviated chemotherapy and involved-field radiotherapy (IFRT).

Beginning in 2005, the BC Cancer Agency recommended that all patients with limited-stage DLBCL undergo PET scanning following three cycles of standard, every three weeks R-CHOP. The goal was to identify chemo-sensitive patients, regardless of the clinical risk factors, who could be treated with chemotherapy alone.

At ICML 2008, Sehn and colleagues presented data on the outcome of patients with a limited-stage DLBCL treated according to the BCCA PET-based algorithm. 2

Study design
• The study was a retrospective analysis of the initial 65 prospective patients identified in the BC Cancer Lymphoid Database who met the following criteria:
  • Age ≥16 years
  • Newly diagnosed, biopsy-proven DLBCL
  • Limited-stage disease (Stage I-II, <10 cm, no B symptoms, radiation encompassable)

Limited-stage diffuse large B-cell lymphoma patients with a negative PET scan following three cycles of R-CHOP can be effectively treated with abbreviated chemoimmunotherapy alone

IFRT = involved field radiation therapy
The objective of the analysis was to assess the outcome of patients with a limited-stage DLBCL treated according to the PET-based algorithm.

FDG-PET / CT scans were performed between days 14 and 21, following three cycles of standard, every three weeks R-CHOP.

All scans were performed at a single centre.

Initial staging PET / CT scans were not performed.

Results were reviewed according to the NHL International Harmonization Project guidelines.$^3$

Key findings

PET status after three cycles of R-CHOP was as follows:
- Forty-eight patients (74%) were PET negative.
  - 46 patients received one additional cycle of R-CHOP.
  - One patient received IFRT due to chemo-toxicity.
  - One patient died from toxicity prior to receiving further therapy.
- Seventeen patients (26%) were PET positive, with median survival of 2.7 months (range 1.3–7); all 17 patients received IFRT (~3500 cGy in 20 fractions).
  - Three patients with positive PET relapsed (2 with DLBCL and 1 with FL) were “out of field.”
  - Two patients have since died from lymphoma after palliative chemotherapy, and one patient with FL is alive and well after additional IFRT.

One patient with negative PET relapsed in the site of the original disease (stage-modified IPI 3); this patient is alive with disease following IFRT and salvage chemotherapy.

Seventeen patients (26%) were PET positive, with median survival of 2.7 months (range 1.3–7); all 17 patients received IFRT (~3500 cGy in 20 fractions).

- Three patients with positive PET relapsed (2 with DLBCL and 1 with FL) were “out of field.”
- Two patients have since died from lymphoma after palliative chemotherapy, and one patient with FL is alive and well after additional IFRT.

The two-year estimated progression-free survival (PFS) is 93% overall.

- Estimated two-year PFS is 97% for PET-negative and 83% for PET-positive patients, $p = 0.04$. (Figure 1)
- The two-year overall survival is 97% for PET-negative and 76% for PET-positive patients, $p = 0.12$. (Figure 2)
Key conclusions

- PET scanning may be an effective assessment tool to identify chemo-sensitive patients with limited-stage DLBCL who can avoid radiation.

- Patients with a negative PET after three cycles of R-CHOP can be appropriately treated with abbreviated chemoimmunotherapy alone.

- Using this treatment algorithm will aid in avoiding the long-term toxicity of radiation.

- Longer follow-up is required to assess overall outcome in both negative and positive PET patients.

- This approach needs to be tested in the context of a prospective, randomized, controlled trial.


Canadian perspective by Dr. Lemieux

The study presented by Pfreundschuh and colleagues was interesting because, although enough mature data exists about rituximab chemoimmunotherapy regimens in DLBCL, we still have no real data on the pharmacokinetics of rituximab or on the ideal schedule and dosage for rituximab administration. For example, in the GELA trial rituximab was administered on day 1 of each of the eight CHOP cycles. By contrast, the U.S. Intergroup’s study (E4494) administered four rituximab infusions with six chemotherapy cycles and five rituximab infusions with eight cycles.

Pfreundschuh and colleagues investigated the effect of administering four extra rituximab infusions during the first two cycles of the R-CHOP-14 regimen in the treatment of DLBCL. The infection rate was high at the beginning of the study, but the investigators were able to control infections with antibiotics after that. When compared with a historic cohort of patients treated with standard R-CHOP-14, the results of the Pfreundschuh study seem to indicate that patients with a high IPI do better with the dense regimen. These results show that it’s possible to safely escalate (with antibiotic prophylaxis) the total dose of rituximab. These findings will need to be evaluated in the context of a randomized clinical trial and are, for now, just hypothesis generating.

PET scanning has gained a lot of interest in the past few years. Clinicians can use a PET scan in a number of ways: to stage, to identify patients with less favorable disease, and to evaluate response to therapy. Even though PET scans are done on a regular basis in a number of places in Canada, we are still trying to find the best way to incorporate scanning into our day-to-day practice. Many questions need to be answered before PET scanning can be considered a standard of care, the most important being the issue of standardization.

The BCCA strategy presented by Laurie Sehn is very helpful. Their question is simple: Can PET scans after three cycles of R-CHOP identify chemo-sensitive patients with limited-stage DLBCL? If so, this approach could be used to avoid radiotherapy treatment in these patients. As expected, in the Sehn study the group of patients who had PET negative scans after three cycles of chemotherapy plus rituximab seemed to do a bit better. Adopting this tactic may help to improve survival. But again, since follow-up has not been long enough, these results need to be confirmed in randomized trials.
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FRAGMIN. The only low molecular weight heparin indicated to treat Cancer-Associated Thrombosis (CAT) in Canada.¹

Venous thromboembolism (VTE) is a frequent medical complication in patients with cancer, occurring in 4 to 20% of cases.²

FRAGMIN Achieved A Statistically-Significant 52% Relative-Risk Reduction In Recurrent VTE vs. Oral Anticoagulant Therapy³,*,†

No Significant Difference In The Incidence Of Bleeding Between FRAGMIN and Oral Anticoagulant Therapy (OAC) Was Demonstrated.¹,³,†

<table>
<thead>
<tr>
<th></th>
<th>FRAGMIN n=336</th>
<th>OAC n=336</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Bleeding</td>
<td>8%</td>
<td>15%</td>
<td>n/a</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6%</td>
<td>4%</td>
<td>0.27</td>
</tr>
<tr>
<td>All Bleeding</td>
<td>14%</td>
<td>19%</td>
<td>0.09</td>
</tr>
</tbody>
</table>


- Evidence-based FRAGMIN dosing: 200 IU/kg sc once daily (maximum 18,000 IU daily) for the first month, followed by a maintenance dose of ~150 IU/kg sc once daily for 2–6 months sc.³
- INR or APTT monitoring is not required.¹,⁴
- FRAGMIN is eligible for reimbursement under many provincial formularies.⁴

Adverse Events: Clinically-significant adverse reactions with FRAGMIN and other LMWHs include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions. In clinical trials with hospitalized patients with severely-restricted mobility, the incidence of thrombocytopenia was 0.54% at days 14 and 21. Injection-site hematomas are a common side effect with FRAGMIN, occurring at a frequency of <5% with lower (prophylaxis) doses and <10% with higher (treatment) doses. FRAGMIN should be used with care in patients with hepatic insufficiency, renal insufficiency or a history of gastrointestinal ulceration. Please consult Prescribing Information for complete dosing instructions, warnings and precautions and adverse events.

FRAGMIN should not be administered intra-muscularly. FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Contraindications: FRAGMIN should not be used in patients who have: hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) or to other low-molecular-weight heparins and/or heparin; history of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an in vitro platelet-aggregation test in the presence of FRAGMIN is positive; septic endocarditis (endocarditis lenta, subacute endocarditis); uncontrollable active bleeding; major blood-clotting disorders; acute gastrudodenal ulcer; cerebral hemorrhage; severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy; other conditions or diseases involving an increased risk of hemorrhage; injuries to and operations on the central nervous system, eyes and ears; or spinal epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding.

Platelet counts should be determined prior to the start of treatment with FRAGMIN and subsequently, twice weekly for the duration of treatment. Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia, or platelet defects. Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered in patients at higher risk of bleeding and receiving FRAGMIN, such as the elderly, patients with renal impairment or the extremes of body weight, during pregnancy, or for children.

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Rituximab added to front-line CHOP significantly improves time to treatment failure and response duration in all FLIPI risk groups of patients with advanced-stage follicular lymphoma

Follicular Lymphoma

Meenakshi Kashyap

Background

Hiddemann and colleagues\(^1\) have conclusively demonstrated that the addition of rituximab to front-line therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) results in a significantly better outcome for patients with symptomatic, advanced-stage follicular lymphoma compared with those receiving CHOP alone. R-CHOP was found to be superior to CHOP for all tested response parameters, including time to treatment failure \( (p < 0.001) \), remission rate \( (p < 0.011) \), response duration \( (p < 0.001) \), time to next chemotherapy \( (p < 0.001) \), and overall survival \( (p < 0.016) \). These beneficial effects were seen in all analyzed subgroups, including patients younger than 60 years and patients 60 years and older, as well as patients with low- or high-risk profiles according to the International Prognostic Index (IPI).

The Follicular Lymphoma International Prognostic Index (FLIPI) was developed to overcome some of the limitations of IPI. FLIPI is an extremely simple and reproducible prognostic index that defines three risk groups with different overall survival rates.\(^2\) However, FLIPI was based on protocols that did not include rituximab. Buske and colleagues\(^3\) recently demonstrated that FLIPI can be used to distinguish high-risk, intermediate-risk and low-risk advanced-stage follicular lymphoma patients with respect to time to treatment failure in patients who are treated with front-line rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

At ICML 2008, Hoster and colleagues presented the results of their investigation into whether the benefit of rituximab added to front-line chemotherapy could be seen in all FLIPI risk groups.\(^4\)

Study design

- Data from patients with Ann Arbor Stage III or IV follicular lymphoma who were recruited in the GLSG Trial between May 2000 and August 2003 were used for the analysis. This trial randomly compared efficacy and safety of first-line CHOP to R-CHOP.\(^2\)
- The study retrospectively evaluated FLIPI on prospectively documented data and compared overall response rate (ORR), time to treatment failure (TTF) and response duration (RD) between the two treatment arms stratified according to the three FLIPI risk groups: low-risk, intermediate-risk, and high-risk groups.
- All patients were in need of therapy at the time of inclusion.
- First-line treatment consisted of induction therapy with CHOP +/- rituximab and post-remission therapy in the case of complete or partial response (CR or PR).
- Post-remission therapy was either high-dose radiochemotherapy followed by autologous stem cell transplantation (ASCT) (only in patients younger than 60 years) or interferon maintenance therapy.
- The application of ASCT was stratified according to the primary induction regimen.
- Treatment failure was defined as either stable disease to induction or progression or death from any cause.
- Response duration was defined for patients with CR or PR after induction.
- Kaplan-Meier estimates were calculated for TTF and RD.
- Treatment arms were compared by means of the log-rank test.
Key findings

- Of 566 evaluable patients, 70 (12%) patients were classified as low-risk (LR), 241 (43%) as intermediate-risk (IR), and 255 (45%) as high-risk (HR) according to FLIPI.
- Overall response rates for R-CHOP versus CHOP were 97% versus 87% ($p = 0.16$) in the LR group, 97% versus 92% ($p = 0.08$) in the IR group, and 96% versus 91% ($p = 0.13$) in the HR group. (Table 1)
- Prolongation of TTF already seen in the complete cohort was not different in the FLIPI risk groups.
- With a median follow-up of 4.3 years, the five-year TTF was 83% versus 43% (median not reached versus 3.9 years, $p = 0.0019$) in the LR group, 74% versus 38% (median not reached versus 3.4 years, $p < 0.0001$) in the IR group, and 50% versus 20% (median 5.0 versus 2.3 years, $p < 0.0001$) in the HR group. (Table 2)
- The five-year response duration was 86% versus 50% (median not reached versus 3.8 years, $p = 0.0093$) in the LR group, 76% versus 39% (median not reached versus 3.4 years, $p < 0.0001$) in the IR group, and 52% versus 22% (median 5.0 versus 2.3 years, $p < 0.0001$) in the HR group. (Table 3)
- The percentage of responding patients younger than 60 years receiving ASCT was 36% and did not significantly differ between treatment arms (35% after CHOP and 37% after R-CHOP) or FLIPI risk groups (38% of LR, 32% of IR and 42% of HR patients).

### Table 1: Rates of patients with complete or partial remission

<table>
<thead>
<tr>
<th>FLIPI LR</th>
<th>R-CHOP</th>
<th>CHOP</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>evaluable</td>
<td>39</td>
<td>31</td>
<td>70</td>
</tr>
<tr>
<td>CR or PR</td>
<td>38</td>
<td>27</td>
<td>65</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>97</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>FLIPI IR</td>
<td>evaluable</td>
<td>113</td>
<td>119</td>
</tr>
<tr>
<td>CR or PR</td>
<td>110</td>
<td>109</td>
<td>219</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>97</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>FLIPI HR</td>
<td>evaluable</td>
<td>126</td>
<td>125</td>
</tr>
<tr>
<td>CR or PR</td>
<td>121</td>
<td>114</td>
<td>235</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>96</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>ALL</td>
<td>evaluable</td>
<td>278</td>
<td>275</td>
</tr>
<tr>
<td>CR or PR</td>
<td>269</td>
<td>250</td>
<td>519</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>94</td>
<td>89</td>
<td>92</td>
</tr>
</tbody>
</table>

CR = complete remission; FLIPI = Follicular Lymphoma International Index; HR = high risk; IR = intermediate risk; LR = low risk; ORR = overall response rate; PR = partial response rate
**Table 2: Five-year time to treatment failure with median follow-up of 4.3 years**

<table>
<thead>
<tr>
<th>FLIPI risk group</th>
<th>R-CHOP</th>
<th>CHOP</th>
<th>Hazard ratio and p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF Median</td>
<td>TTF Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (LR)</td>
<td>83% not reached</td>
<td>43% 3.9 years</td>
<td>HR 0.248 (95% CI, 0.096–0.642) p = 0.0019</td>
</tr>
<tr>
<td>Intermediate risk (IR)</td>
<td>74% not reached</td>
<td>38% 3.4 years</td>
<td>HR 0.0306 (95% CI, 0.194–0.484) p &lt;0.0001</td>
</tr>
<tr>
<td>High risk (HR)</td>
<td>50% 5.0 years</td>
<td>20% 2.3 years</td>
<td>HR 0.458 (95% CI, 0.324–0.646) p &lt;0.0001</td>
</tr>
</tbody>
</table>

**FLIPI = Follicular Lymphoma Prognostic Index; TTF = time to treatment failure**

**Table 3: Five-year response duration**

<table>
<thead>
<tr>
<th>FLIPI risk group</th>
<th>R-CHOP</th>
<th>CHOP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD Median</td>
<td>RD Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (LR)</td>
<td>86% not reached</td>
<td>50% 3.8 years</td>
<td>0.0093</td>
</tr>
<tr>
<td>Intermediate risk (IR)</td>
<td>76% not reached</td>
<td>39% 3.4 years</td>
<td>0.0001</td>
</tr>
<tr>
<td>High risk (HR)</td>
<td>52% 5.0 years</td>
<td>22% 2.3 years</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**FLIPI = Follicular Lymphoma Prognostic Index; RD = response duration**

**Key conclusions**

- Overall response rates were similarly high after R-CHOP in all FLIPI risk groups.
- The benefit of rituximab in terms of prolonged time to treatment failure and prolonged response duration was clearly observed in all FLIPI risk groups.
- Use of combined immunochemotherapy in patients with advanced-stage follicular lymphoma is justifiable regardless of their risk profile.
- Further follow-up is needed to evaluate the effect on overall survival.

**References:**
4. Hoster E, Unterhalt M, Buske C, et al. The addition of rituximab to frontline CHOP significantly improves time to treatment failure and response duration in all FLIPI risk groups of patients with advanced-stage follicular lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group. Program and abstracts of the 10th International Conference on Lymphoma; June 4–7, 2008; Lugano, Switzerland; Abstract 330.
**Background**

The combination of mitoxantrone, chlorambucil, and prednisolone (MCP) is effective and well tolerated in patients with indolent non-Hodgkin’s lymphoma. Herold and colleagues conducted an open-label phase III trial to investigate the efficacy and toxicity of the standard MCP chemotherapeutic regimen versus the combination of rituximab and MCP (R-MCP), both followed by interferon maintenance, in patients with previously untreated advanced follicular lymphoma. In their study, the investigators observed a significant improvement in complete and overall response rate (CR and ORR), event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) with R-MCP at a median follow up of 47 months. At ICML 2008, Herold and colleagues presented the 51-month follow-up data from their phase III trial.

**Study design**

- Previously untreated patients with advanced-stage, symptomatic CD 20-positive indolent non-Hodgkin’s lymphoma and mantle cell lymphoma (n = 358) were included in the study.
- Baseline characteristics did not differ between the two arms with regard to FLIPI, ECOG performance status (PS), and stage.
- Results reported are those of the follicular lymphoma patients (grade 1 and 2), who represented the majority of patients and for whom the sample size was calculated; this was not a subgroup analysis.
- Patients were randomized to receive either MCP chemotherapy (n = 105) (mitoxantrone: 8 mg/m², days 3 and 4; chlorambucil: 3 x 3 mg/m², days 3 through 7; prednisolone: 25 mg/m², days 3 through 7; every 4 weeks) or MCP plus rituximab (n = 96) (375 mg/m², day 1).
- Study endpoints included response rate, especially complete response, time to progression, event-free survival, and overall survival.

**Key findings**

- Data for the median follow-up of 51 months showed no significant differences in toxicities. (Table 1)
- Overall response rate was 92.4% for R-MCP versus 75% for MCP (p = 0.0009), with a complete response rate of 49.5% for R-MCP versus 25% for MCP (p = 0.0004).
- Progression-free survival was significantly higher in the R-MCP arm compared with the MCP arm (68% versus 36%, median not reached versus 29 months, p <0.0001). (Figure 1)
- Overall survival at 50 months increased in the R-MCP arm compared with the MCP arm (86% versus 74%, median not reached in either arm, p = 0.0205). (Figure 2)
Table 1: Toxicity (NCIC–CTC)

<table>
<thead>
<tr>
<th>Condition</th>
<th>R-MCP (n = 105)</th>
<th>MCP (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells, CTC grade 3/4</td>
<td>72%</td>
<td>58%</td>
</tr>
<tr>
<td>Platelets, CTC grade 2–4</td>
<td>23%</td>
<td>27%</td>
</tr>
<tr>
<td>Infection, CTC grade 3/4</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

\[p = 0.0556\]

CTC = common toxicity criteria; NCIC = National Cancer Institute of Canada

Figure 1: Progression-free survival in follicular lymphoma patients, median follow-up 51 months

NR = not reached; PFS = progression-free survival

Figure 2: Overall survival in follicular lymphoma patients, median follow-up 51 months

NR = not reached; OS = overall survival
Key conclusions

- Rituximab plus MCP is significantly superior to MCP alone with regard to the primary endpoint (response rate) and produces an impressively high rate of complete remission.

- R-MCP significantly prolongs progression-free survival and overall survival in follicular lymphoma patients, as shown by the relatively mature data from the median follow-up of 51 months.

References:

Canadian perspective by Dr. Lemieux

The study by Hoster and colleagues is very interesting, because it shows that R-CHOP appears to work for all patients regardless of their FLIPI status. R-CVP, not R-CHOP, is the standard of care for follicular lymphoma in a number of places in Canada. Because there have been no studies showing R-CHOP to be superior to R-CVP, these findings will not change clinical practice in Canada. Nonetheless, the results of this study are worth noting.

The follow-up data of the East German Study Group are good, but again R-MCP is not the standard of care in Canada. So this study is not really relevant to Canadian clinical practice either. With further follow-up, R-MCP continues to show positive results, demonstrating that the addition of rituximab to chemotherapy has an impact on TTP and survival. These results are in line with three other studies on first-line rituximab chemoimmunotherapy in follicular lymphoma (see Table 1).

Now, what’s the best R-chemotherapy? We don’t know; but R-CVP, which is used in a number of places in Canada, seems to be a valid option.

Where do we go from here? We are still waiting for the results on a number of important studies. Two of those studies are the Prima study (NCT00140582) and the University College London Hospitals’ study (NCT0011293). Rituximab maintenance therapy has gained a lot of interest in Canada because a number of studies have shown a significant effect on PFS; others have shown an effect on survival (van Oers, et al. Blood 2006; Forstpointner, et al. Blood 2006). The real impact of maintenance treatment after chemoimmunotherapy is still not known. The Prima study will most likely answer this question once and for all. The University College London Hospitals’ study will address another important question. Is “watch and wait” still an option, or can we have an impact on our patients’ survival by treating earlier with rituximab?

A lot of questions still need to be answered: What about radioimmunotherapy? High dose therapy? Questions such as these need to be answered in the context of a randomized trial. So, there’s still a lot of work to be done, but the future of treatment for follicular lymphoma seems bright.

Table 1: Phase III studies : R-Chemo versus Chemo

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Median follow-up (months)</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>Median TTP, TTF or EFS</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiddemann, et al. Blood 2005;106: 3725–3732.</td>
<td>CHOP (205) R-CHOP (223)</td>
<td>18</td>
<td>90 96</td>
<td>17 20</td>
<td>61 28 TTF; p &lt;0.001</td>
<td>90 95 2-yr OS; p = 0.016</td>
</tr>
<tr>
<td>Herold, et al. ICML 2008: Abstract 329.</td>
<td>MCP (96) R-MCP (105)</td>
<td>47</td>
<td>75 92</td>
<td>25 50</td>
<td>36 68 50 mo. PFS; p &lt;0.0001</td>
<td>74 86 p = 0.0205</td>
</tr>
<tr>
<td>Salles, et al. ASH 2007: Abstract 792.</td>
<td>CHVP-IFN (156) R-CHVP-IFN (175)</td>
<td>60</td>
<td>72 81</td>
<td>59 75</td>
<td>37 53 5-yr EFS; p = 0.0004</td>
<td>79 84 p = not significant</td>
</tr>
</tbody>
</table>

CR = complete response; EFS = event-free survival; ORR = overall response rate; OS = overall survival; TTF = time to treatment failure; TTP = time to progression
Mantle Cell Lymphoma

Meenakshi Kashyap

European Mantle Cell Lymphoma Network: An update on current first-line trials

Background

Mantle cell lymphoma (MCL) accounts for up to 6% of all cases of non-Hodgkin’s lymphoma.\(^1\) It is characterized by a moderately aggressive clinical course and poor prognosis. MCL has the worst five-year overall survival of any non-Hodgkin’s lymphoma.\(^2\) Conventional chemotherapy achieves only short-term remission despite high initial response rates of 70%–80%. The addition of rituximab to standard chemotherapy regimens has been shown to be superior to chemotherapy alone with respect to remission induction, progression-free survival, and overall survival.\(^3\)

At ICML 2008, the European MCL Network presented results of its investigation on the impact of various combined immunochemotherapy regimens.\(^4\) Additionally, the role of rituximab maintenance was evaluated in elderly patients. In younger patients, based on the excellent results of the Hyper-CVAD regimen by Khouri and colleagues,\(^5\) dose-intensified regimens with implementation of high-dose cytarabine were investigated.

Study design

- Elderly MCL patients were initially randomized between eight cycles of R-CHOP (standard arm) and six cycles of R-FC (experimental arm).
- Patients who achieved either partial or complete response (PR or CR) subsequently received either interferon maintenance (standard arm) or a single rituximab dose every two months (experimental arm).
- In the younger MCL patients, the standard arm (R-CHOP induction followed by myeloablative consolidation: 12 Gray TBI, 2 x 60 mg/kg cyclophosphamide) was compared to the implementation of high-dose cytarabine into induction (R-CHOP / R-DHAP) and consolidation (10 Gray TBI, 4 x 1.5 g/m\(^2\) Ara-C, 140 mg/m\(^2\) melphalan).

Study design: patients >60 years

- 4 x R-CHOP
- 3 x R-FC
- PR, CR
- 4 x R-CHOP
- 3 x R-FC
- PR, CR
- IFN-α maintenance (3 x 3 M IU/week) or Peg IFN (1 mg/kg week)
- Rituximab maintenance (all 2 months)

Study design: patients <60 years

- 3 x R-CHOP
- 3 x R-CHOP
- PR, CR
- 3 x R-DHAP
- alternating stem cell mobilization after course 6
- DexaBEAM (stem cell mobilization)
- PR, CR
- Cyclo 120 mg/kg + TBI 12 Gray
- Melphalan 140 mg/m\(^2\)
- PBSCT
- PR, CR
- TBI 10 Gray
- Ara-C 4 x 1.5 g/m\(^2\)
- Melphalan 140 mg/m\(^2\)
- PBSCT

CR = complete response; PR = partial response; TBI = total body irradiation
**Key findings**

- Both studies recruited a total of more than 700 patients.
- The median age of the elderly MCL patients was 70 years with 64% of patients displaying a high intermediate- to high-risk IPI.
- In the elderly MCL patients, induction was well tolerated with mainly hematological toxicity (grade 3/4 leukocytopenia, 61% in the R-CHOP arm versus 70% in the R-FC arm; and thrombocytopenia, 17% versus 38%). (Table 1)
- Febrile neutropenia rates were 19% and 9% for the R-CHOP and R-FC regimens respectively.
- Despite a poor risk profile, combined immunochemotherapy achieved an 84% response rate (51% complete response [CR] or unconfirmed complete response [CRu]) confirming previous study results. (Table 2)
- Although the impact of maintenance is not yet evaluable, both time to treatment failure (TTF) and overall survival (OS) are encouraging with 78% and 83% at 12 months, respectively. (Figure 1)
- Patients on maintenance, especially the CR patients, showed a favorable clinical course with only 4 relapses in 38 patients (11%) observed to date.

<table>
<thead>
<tr>
<th>Table 1: Toxicity of induction in patients &gt;60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Response rate in patients &gt;60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documented therapy</strong></td>
</tr>
<tr>
<td>R-CHOP</td>
</tr>
<tr>
<td>R-FC</td>
</tr>
<tr>
<td><strong>Documented response</strong></td>
</tr>
<tr>
<td><strong>Abort without staging</strong></td>
</tr>
<tr>
<td><strong>Complete response (CR)</strong></td>
</tr>
<tr>
<td><strong>Unconfirmed complete response (CRu)</strong></td>
</tr>
<tr>
<td><strong>Partial response (PR)</strong></td>
</tr>
<tr>
<td><strong>Stable disease (SD)</strong></td>
</tr>
<tr>
<td><strong>Progressive disease (PD)</strong></td>
</tr>
<tr>
<td><strong>Expired (EX)</strong></td>
</tr>
</tbody>
</table>

CR + CRu: 51%  
CR + CRu + PR: 84%
• In the younger MCL patients, toxicity was mainly hematological with grade 3/4 leukocytopenia (55% in the R-CHOP arm versus 76% in the R-CHOP / R-DHAP arm); and thrombocytopenia (14% versus 78%). (Table 3)
• Febrile neutropenia rates were 11% and 18% respectively.
• Combined immunochemotherapy achieved an impressive 91% response rate (56% CR/CRu) after induction. (Table 4)
• After high-dose consolidation, CR/CRu rate increased to 83%.
• Both TTF and OS were remarkable (83% and 90% at 12 months, respectively). (Figure 2)

Figure 1: Time to treatment failure in patients >60 years

Figure 2: Time to treatment failure in patients <60 years
Table 3: Toxicity of induction in patients <60 years

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Frequency</th>
<th>%</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R-CHOP (n = 97)</td>
<td></td>
<td>R-CHOP/R-DHAP (n = 104)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R-CHOP/R-DHAP</td>
<td></td>
<td>R-CHOP/R-DHAP</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1 or 2</td>
<td>46</td>
<td>48</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>10</td>
<td>10</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>1 or 2</td>
<td>30</td>
<td>31</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>53</td>
<td>55</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>1 or 2</td>
<td>10</td>
<td>12</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>59</td>
<td>69</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>Platelets</td>
<td>1 or 2</td>
<td>21</td>
<td>22</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>13</td>
<td>14</td>
<td>80</td>
<td>78</td>
</tr>
</tbody>
</table>

Table 4: Response rate in patients <60 years

<table>
<thead>
<tr>
<th>Documented therapy</th>
<th>216</th>
<th>62%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>R-CHOP/R-DHAP</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Documented response</td>
<td>189</td>
<td>55%</td>
</tr>
<tr>
<td>Abort without staging</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>59</td>
<td>31%</td>
</tr>
<tr>
<td>Unconfirmed complete response (CRu)</td>
<td>40</td>
<td>21%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>73</td>
<td>39%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>8</td>
<td>4%</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>9</td>
<td>5%</td>
</tr>
<tr>
<td>Expired (EX)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Key conclusions

- Combined immunochemotherapy results showed impressive response rates in two prospective international trials.
- Further recruitment and follow-up will determine the role of rituximab maintenance and high-dose cytarabine in this distinct subtype of malignant lymphoma.

Autologous stem cell transplantation and rituximab for mantle cell lymphoma

Background
The role of stem cell transplantation (SCT) in the treatment of mantle cell lymphoma has not been clearly delineated. Khouri and colleagues of the M.D. Anderson Cancer Center in Houston, Texas, employed an aggressive approach by treating mantle cell lymphoma patients with Hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone) and high-dose methotrexate/cytarabine (M/A), followed by autologous stem cell transplantation (ASCT). This regimen seems to offer an improved outcome with estimated five-year event-free survival (EFS) and overall survival (OS) rates of 54% and 72% after a follow-up period of 48 months.\(^1\)

In an effort to further improve these results, Capote and colleagues combined in vivo purging with rituximab, post-transplant consolidation with Hyper-CVAD-M/A, and immunotherapy post-ASCT with rituximab.\(^2\) Data from the Capote study were presented at ICML 2008.

Study design
- Between February 2000 and June 2006, 44 adult patients (33 male, 11 female) aged <70 years with previously untreated (n = 40) or relapsed (n = 4) mantle cell lymphoma were enrolled in the study.
- Patients with ECOG performance status >3, HIV-positive status, HVC serology, or severe organ dysfunction were excluded.
- The regimen consisted of five phases:
  - Four courses of chemotherapy with Hyper-CVAD-methotrexate/AraC
  - In vivo purging of B-cells with 375 mg/m\(^2\) rituximab administered weekly for four weeks
  - Mobilization of progenitor cells and leukapheresis
  - High-dose chemotherapy with ICT-CY or BEAM
  - Immunotherapy post-autologous stem cell transplantation (ASCT) with 375 mg/m\(^2\) rituximab administered weekly for four weeks

Key findings
- Following induction chemotherapy, an overall response rate (ORR) of 97% was seen in evaluable patients.
- Twenty-six patients (59.1%) received ASCT.
- An ORR of 100% and complete response (CR) of 55% were observed in patients who received consolidative ASCT.
- Therapy was well tolerated, with a 9.1% (n = 4) treatment-related mortality (including mortality in ASCT patients).
- Five-year event-free survival (EFS) and overall survival (OS) for all patients were 34.6% and 62.0% respectively.
- Five-year EFS and OS (with a 36.9 month median follow-up) for patients who underwent transplantation were 42.7% and 70.34% respectively. (Figure 1)
Figure 1: Five-year event-free survival and overall survival

Key conclusions

- The therapeutic scheme evaluated in this study of chemotherapy, in vivo purging with rituximab, ASCT, and rituximab immunotherapy post-ASCT is safe and feasible.
- The treatment regimen produces durable remissions and may offer new therapeutic opportunities for the treatment of patients with mantle cell lymphoma.

References:

Canadian perspective by Dr. Lemieux

Mantle cell lymphoma (MCL) is still an incurable disease, but survival data are improving. The key questions remain: What is the best strategy for the treatment of this disease? How will new drugs affect outcome?

In this regard, the European Mantle Cell Lymphoma Network study is very important. The authors were able to conduct an international randomized study with more than 700 patients, which is really remarkable since this disease is very rare.

Data coming out of this study have the potential to change clinical practice. We may have answers to important questions such as:
- Will chemotherapy before a bone marrow transplant make a difference? Will it improve survival?
- What is the best chemotherapy: R-CHOP or R-FC?
- Will rituximab maintenance therapy change outcome?

While waiting for further results, the best treatment for MCL is still debatable. As part of that discussion, the presentation by Capote was noteworthy. Autologous bone marrow transplantation has shown good results in a number of phase II studies. In the only phase III study available, the European MCL Network demonstrated that early consolidation with myeloablative radiochemotherapy significantly improves PFS as compared to IFN maintenance. (Dreyling, Blood 2005)

Hyper-CVAD is one of the protocols used for treating MCL. This protocol, developed at the M.D. Anderson Cancer Center, has shown good results in the past. The findings presented by Capote indicate that using a transplantation strategy with rituximab as an in vivo purging agent will further improve results.

In conclusion, no data presented at ICML will likely change clinical practice for MCL at this time. We will have to wait to see the results of the European MCL Network trial, and hope that new drugs will soon be available to develop a different therapeutic strategy.
Follicular Lymphoma: Monitoring Patients on Rituximab Maintenance Therapy

Laurie Sehn, MD, MPH
Medical Oncologist at the BC Cancer Agency, Clinical Assistant Professor at the University of British Columbia

**Introduction**

Follicular lymphoma (FL) is the most common subtype of lymphoma in North America, with median survivals of 8–10 years historically reported. Recent advances in FL treatment have markedly improved outcome: median survival is now approaching two decades. The addition of the chimeric anti-CD20 monoclonal antibody rituximab to chemotherapy has been shown to significantly improve progression-free survival and overall survival in patients who are previously untreated and in those with relapsed and refractory disease. Randomized clinical trials have also demonstrated a significant benefit for rituximab maintenance therapy in both of these clinical settings following response to induction therapy. (Table 1) Patients have been shown to benefit from rituximab maintenance therapy regardless of whether they had been treated with chemotherapy alone, rituximab monotherapy, or rituximab chemoimmunotherapy.

**Table 1: Randomized rituximab maintenance therapy trials in follicular lymphoma**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Induction therapy</th>
<th>Maintenance rituximab efficacy and safety results</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hochster (ASH 2005)⁹</td>
<td>Untreated</td>
<td>CVP</td>
<td>Significant improvement in median PFS (61 months vs. 15 months, ( p &lt; 0.001 )) and four-year OS (91% vs. 71%, ( p = 0.03 )) in the maintenance arm as compared with the observation arm</td>
<td>No information</td>
</tr>
<tr>
<td>Ghielmini (Blood 2004)¹⁰</td>
<td>Untreated/relapsed</td>
<td>Rituximab</td>
<td>Significant improvement in EFS (23 months vs. 12 months, ( p = 0.02 )) in the maintenance arm as compared with the observation arm</td>
<td>10% vs. 3% grade 3/4 non-hematologic, and 18% vs. 17% grade 3/4 hematologic toxicities in the maintenance arm as compared to the observation arm</td>
</tr>
<tr>
<td>Hainsworth (JCO 2005)¹¹</td>
<td>Relapsed</td>
<td>Rituximab</td>
<td>Significant improvement in PFS (31.3 months vs. 7.4 months, ( p = 0.007 )) in the maintenance vs. re-treatment arms</td>
<td>No treatment-related hospitalization or discontinuation of therapy due to toxicity in either arm</td>
</tr>
<tr>
<td>Forstpointner (Blood 2006)⁶</td>
<td>Relapsed</td>
<td>FCM vs. R-FCM</td>
<td>Significant improvement in response duration (median not reached vs. 26 months, ( p = 0.035 )) in the maintenance arm as compared with the observation arm</td>
<td>No significant differences in hematologic and non-hematologic toxicities between the maintenance and observation arms</td>
</tr>
<tr>
<td>Van Oers (Blood 2006)¹²</td>
<td>Relapsed</td>
<td>CHOP vs. R-CHOP</td>
<td>Significant improvement in PFS (51.5 months vs. 14.9 months, ( p &lt; 0.001 )) and three-year OS (85% vs. 77%, ( p = 0.011 )) in the maintenance arm as compared with the observation arm</td>
<td>10.8% vs. 5.4% grade 3/4 neutropenia (NS: ( p = 0.07 )), and 9% vs. 2.4% grade 3/4 infection (( p = 0.009 )) in the maintenance arm as compared with the observation arm</td>
</tr>
</tbody>
</table>

EFS = event-free survival; OS = overall survival; PFS = progression-free survival
Monitoring patients during and after rituximab maintenance therapy

During rituximab maintenance therapy, patients should be monitored for the following:

- **Infusion and hypersensitivity reactions**
  The British Columbia Cancer Agency (BCCA) approach to treating advanced-stage, symptomatic follicular lymphoma involves eight cycles of R-CVP followed by maintenance rituximab therapy for two years in patients responding to induction therapy. To address the logistical challenge of delivering this drug, BCCA developed a rapid infusion schedule for rituximab administration.13 (Table 2) This schedule has been found to be well tolerated, with no observed grade 3 or 4 infusion reactions. Asthenia, pyrexia, influenza-like illness, pain, and hypertension can occur during the IV infusion.14

While it is recommended that the first dose of rituximab be given according to the administration schedule outlined in the product monograph, patients can receive all subsequent doses (including all maintenance doses) according to the abbreviated administration schedule. As a precautionary measure, patients should be under constant visual observation for the first dose of maintenance rituximab — during all dose increases and for 30 minutes after infusion is completed. For all subsequent maintenance doses, constant visual observation is not required.15

- **Fatal cytokine release syndrome and rare severe mucocutaneous reactions**
  Rarely seen in patients with FL, fatal cytokine release syndrome usually occurs within 1–2 hours of initiating the first rituximab infusion.15 For severe reactions, infusion should be stopped immediately and patients evaluated for tumour lysis syndrome and pulmonary infiltration. Infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.15
  Reactions similar to Stevens-Johnson syndrome have been anecdotally reported.15 Rituximab should be discontinued in patients who exhibit mucocutaneous reactions.15

- **Hypogammaglobulinemia**
  Long-term rituximab maintenance therapy may lead to prolonged B-cell depletion and hypogammaglobulinemia.10,12 Gammaglobulin levels may remain low during rituximab maintenance therapy. However, the degree of hypogammaglobulinemia is generally mild and of little clinical consequence. Empiric infusion of gammaglobulin is not indicated, and therefore routine monitoring of gammaglobulin levels in asymptomatic patients is unnecessary. In patients with recurring infections or serious infections not responding to therapy, gammaglobulin levels should be measured and gammaglobulin infusion considered if levels are significantly depressed.

### Table 2: BCCA approach to treating follicular lymphoma

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>BCCA approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited stage disease</td>
<td>Involved field radiation (IFRT)</td>
</tr>
<tr>
<td>Advanced stage, asymptomatic</td>
<td>Close follow-up under continued observation</td>
</tr>
<tr>
<td>Advanced stage, symptomatic</td>
<td>R-CVP x 8 cycles, followed by maintenance rituximab (375 mg/m²) every 3 months x 8 doses over 2 years in patients responding to induction</td>
</tr>
<tr>
<td></td>
<td>All doses of rituximab after first dose given by rapid infusion (90 min) 20% over 30 min 80% over 60 min</td>
</tr>
</tbody>
</table>

- **Infections**
  No increase in infections was seen in the maintenance arm compared with the observation arm in the SAKK trial.10 However, the EORTC 20981 trial reported a higher rate of infection in the maintenance arm.12 Grade 3/4 infections occurred in 3% of patients on observation and 9% of those receiving maintenance treatment (p = 0.009). Grade 3/4 infections reported in ≥1% of patients in the maintenance arm were pneumonia (2%), respiratory tract infection (2%), febrile infection (1%), and herpes zoster (1%). There was no cumulative toxicity in terms of infections reported over the two-year maintenance period.14
  Patients should be monitored every three months at the time of infusion for evidence of progressive disease and signs of infection.15

- **Cytopenias**
  In the EORTC 20981 trial, neutropenia was more commonly seen in the maintenance arm. The incidence of grade 3/4 neutropenia was 5% in patients on observation and 11% in patients receiving maintenance (p = 0.07).12 Complete blood count and differential should be evaluated before and after each treatment for possible development of neutropenia.15 If neutropenia is observed, rituximab should be held until count recovery is noted. Empiric treatment with granulocyte-colony stimulating factor is unnecessary in asymptomatic patients.

- **Vaccinations**
  The safety of immunization with any vaccine following therapy with rituximab, particularly live viral vaccines, has not been studied. The ability to generate an immune response during chemoimmunotherapy may be limited.14 All patients should be advised to update vaccines prior to treatment initiation if possible. Immunization with live vaccines may be detrimental. Patients are recommended to receive the influenza vaccine annually.16 (Table 3)
Viral re-activation

New, re-activated, or exacerbated viral infections with rituximab maintenance therapy have been identified in clinical studies or post-marketing reports. The majority of patients with viral infections were profoundly immune-suppressed.

All lymphoma patients should be tested for both Hepatitis B surface Ag and Hepatitis B core Ab. Patients who test positive in either test should be treated with lamivudine (100 mg/day orally) for the entire duration of rituximab maintenance and for six months afterwards. These patients should also be monitored with frequent tests (at least every two months) for liver function and hepatitis B virus DNA. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist who has experience managing hepatitis. Halting rituximab maintenance should be considered.

Following completion of maintenance rituximab, patients can be monitored expectantly every four months with a routine physical examination, and lab and radiological investigations as clinically indicated.

Information concerning long-term toxicity is scarce. But in the five randomized trials, rituximab maintenance therapy was generally well tolerated and associated with minimal toxicity. The ongoing PRIMA, SAKK 35/03, RESORT, and a number of other prospective, randomized trials have been designed to further investigate safety and efficacy of rituximab maintenance therapy. These trials will also provide valuable data on the optimal duration of maintenance therapy in FL patients. The trials are summarized in Table 4.

Summary

Recent advances in the management of follicular lymphoma have resulted in a substantial improvement in outcome. The addition of rituximab to induction chemotherapy followed by its use as maintenance therapy has allowed more patients to achieve sustained durable remissions and has demonstrated clinical benefit in both previously untreated and relapsed and refractory patients.

The use of rituximab maintenance therapy for up to two years following induction therapy has been carefully evaluated in clinical trials and is generally well tolerated and associated with minimal risk. However, consideration for potential acute and delayed toxicities is necessary to ensure that safety is optimized. Ongoing clinical trials will assess the utility and feasibility of maintenance rituximab in additional clinical settings and for longer durations.

Table 3: Immunizations for patients with lymphoma, Hodgkin’s lymphoma, myeloma and leukemia

<table>
<thead>
<tr>
<th>Type of immunization</th>
<th>When should it be given?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine</td>
<td>Every year, in the autumn</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>At the time of diagnosis of the lymphoma-type illness and then once again 5 years later</td>
</tr>
<tr>
<td>Tetanus/diphtheria</td>
<td>Every 10 years</td>
</tr>
<tr>
<td>Meningococcal types A and C vaccine and Hemophilus influenza type b vaccine</td>
<td>Once only, if the spleen is to be or was removed or treated with radiation</td>
</tr>
<tr>
<td>Polio vaccine</td>
<td>Oral polio vaccine should never be taken by patients with lymphoma-type illness. It has been replaced by inactivated polio vaccine, which is safe for patients with lymphoma-type illness</td>
</tr>
<tr>
<td>Measles</td>
<td>Never (exception: see hematopoietic stem cell transplant guidelines, link below)</td>
</tr>
<tr>
<td>Mumps</td>
<td>Never (exception: see hematopoietic stem cell transplant guidelines, link below)</td>
</tr>
<tr>
<td>Rubella</td>
<td>Never (exception: see hematopoietic stem cell transplant guidelines, link below)</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Never (exception: see hematopoietic stem cell transplant guidelines, link below)</td>
</tr>
</tbody>
</table>

For travel to urban areas of developing countries: Less than 4 weeks no immunization; Greater than 4 weeks: Hepatitis A vaccine, Inactivated typhoid injectable vaccine, Hepatitis B vaccine

http://www.bccdc.org/content.php?item=193
Table 4: Ongoing clinical trials of rituximab maintenance therapy in follicular lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Description</th>
<th>Clinical Trials ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMA17</td>
<td>Untreated</td>
<td>Induction: 8 x rituximab combined with 8 cycles of CVP or 6 cycles of CHOP in 21-day cycles or 6 cycles of FCM in 28-day cycles or 6 cycles of MCP in 28-day cycles. Maintenance: Patients either receive rituximab 375 mg/m² every 8 weeks for 24 months (12 injections) or no treatment.</td>
<td>NCT00140582</td>
</tr>
<tr>
<td>SWS-SAKK18</td>
<td>Untreated</td>
<td>Induction: Weekly rituximab, weeks 1–4. Maintenance: Patients achieving partial or complete response randomized to 1 of 2 maintenance treatment arms. Arm I: Patients receive rituximab every 2 months for 4 treatments. Arm II: Patients receive rituximab every 2 months for up to 5 years in the absence of disease progression or unacceptable toxicity.</td>
<td>NCT00227695</td>
</tr>
<tr>
<td>ECOG (RESORT)19</td>
<td>Untreated</td>
<td>Induction: Weekly rituximab, weeks 1–4. Maintenance: Patients with a partial or complete response to induction rituximab randomized to 1 of 2 treatment arms. Arm I (re-treatment rituximab): Patients receive rituximab once a week for 4 weeks after disease progression. Arm II (scheduled rituximab): Patients receive a single dose of rituximab every 13 weeks until disease progression.</td>
<td>NCT00075946</td>
</tr>
<tr>
<td>Intergrupo Italiano Linfomi20</td>
<td>Untreated/relapsed</td>
<td>Induction: 4 courses of R-FND (R 375 mg/m², fludarabine 25 mg/m², mitoxantrone 10 mg/m², dexamethasone 10 mg) followed by consolidation with 4 weekly rituximab infusions. Maintenance: Patients with a complete response or partial response randomized between rituximab maintenance (375 mg/m² every 2 months for 4 doses) or observation.</td>
<td>ML17638</td>
</tr>
<tr>
<td>UK Watch and Wait21</td>
<td>Untreated</td>
<td>Patients randomized to 1 of 3 treatment arms. Arm I: Patients undergo observation only until disease progression. Arm II: Patients receive rituximab once a week for 4 weeks. Arm III: Patients receive induction rituximab as in Arm II. Patients then receive maintenance rituximab once on day 1 of weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100.</td>
<td>NCT00112931</td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia Overview

Evolving Strategies in Rituximab Chemoimmununtherapy for First-line and Relapsed Chronic Lymphocytic Leukemia

Meenakshi Kashyap

The anti-CD20 monoclonal antibody rituximab has totally transformed the manner in which chronic lymphocytic leukemia (CLL), a disease traditionally perceived to be incurable, can now be treated. Rituximab acts synergistically with several cytotoxic agents. The addition of rituximab to effective frontline regimens has changed treatment goals from symptom palliation to attaining maximal disease control, prolonging survival and possibly curing the disease.

Rituximab in relapsed and previously untreated CLL

The R-F regimen
Byrd and colleagues conducted the randomized CALGB 9712 phase II study to determine the efficacy, safety, and optimal administration schedule for rituximab with fludarabine in previously untreated CLL patients. Patients were randomized to receive

- six monthly courses of fludarabine concurrently with rituximab, followed two months later by four weekly doses of rituximab for consolidation therapy,

or

- sequential fludarabine alone, followed two months later by rituximab consolidation therapy.

A total of 104 patients were randomized to the concurrent (n = 51) and sequential (n = 53) regimens. An overall response (OR) rate of 90% and significantly higher complete response (CR) rate of 47% were observed in the concurrent group as compared with the 77% OR and 28% CR rates in the sequential group. (Figure 1) In a subsequent retrospective multivariate analyses, Byrd and colleagues compared the treatment outcome for patients treated in the CALGB 9712 and CALGB 9011 trials. Their results indicated statistically significant higher progression-free survival (PFS) and overall survival (OS) in patients who received fludarabine and rituximab as compared with patients who received fludarabine alone.

The R-FC regimen
Wierda and colleagues evaluated the fludarabine, cyclophosphamide, and rituximab (R-FC) regimen in 177 previously treated CLL patients to see if CR for previously treated patients could be improved. CR was achieved in 25% of 177 patients, and nodular partial remission (nPR) and partial remission (PR) were achieved in 16% and 32% of patients, respectively. The overall response rate was 73%. (Figure 2) Thirty-two percent of the 37 complete responders tested achieved molecular remission in bone marrow. The R-FC regimen induced the highest CR rate reported in a clinical trial of previously treated patients with CLL.

At the M.D. Anderson Cancer Centre, Keating and colleagues initiated a phase II trial to determine if CR rates in previously untreated CLL patients could be increased to 50% or more. The single-arm study of R-FC as initial therapy was conducted in 224 patients with progressive or advanced CLL. Patients enrolled in a previous regimen that utilized FC served as historical controls. The CR rate, proportion of patients with less than 1% CD5 and CD19 cells in their bone marrow, time to treatment failure, time to progres-
sion, and survival were significantly better with R-FC than with FC. CR was achieved in 70% and OR was achieved in 95% of R-FC-treated patients. A CR of 67% (138/207) was observed in the bone marrow of patients whose bone marrow was evaluated for residual disease. These patients had less than 1% CD5- and CD19- coexpressing cells. This was the highest response rate reported for any regimen in previously untreated patients with CLL. The time to treatment failure analysis showed that 69% of patients treated with the R-FC regimen were projected to be failure-free at four years.

In an update to this study, Tam and colleagues4 reported an OR rate of 95%, with CR in 72%, nPR in 10%, PR due to cytopenia in 7%, and PR due to residual disease in 5% of patients treated with the R-FC regimen. (Figure 1) The six-year overall survival and failure-free survival were 77% and 51% respectively. Among patients with a partial response or better, median time to progression was 80 months, with a six-year projected PFS of 60%.

In light of positive phase II data, the R-FC induction regimen is now being assessed in large, randomized phase III trials in both first-line and relapsed settings. The first interim analysis performed for the R-FC regimen in the CLL-8 trial met its primary endpoint of >35% improvement in PFS. The trial has now been stopped and secondary endpoints are being evaluated.7

The R-FC-lite regimen
In the Keating study4, grade 3/4 neutropenia was seen in 52% of 927 evaluable treatment courses. Tarhini and colleagues8 investigated reduced doses of fludarabine and cyclophosphamide in combination with an increased dose of rituximab in 50 patients to see if neutropenia rates could be decreased without compromising efficacy. An OR rate of 100% was observed in 42 evaluable patients regardless of the Rai stage, age, or chromosomal abnormalities. CR and PR/nPR rates were 86% and 14% respectively. (Figure 1) Of the 35 patients in complete response, no CD5/CD19 positive cells were detected in 94% of the patients. No minimal residual disease (MRD) was seen in 78% of the 36 patients in CR. This study demonstrated that it is possible to reduce toxicity by decreasing the concentrations of fludarabine and cyclophosphamide and still maintain efficacy by increasing the concentration of rituximab.

The R-FCM regimen
Bosch and colleagues9 have previously demonstrated that the FCM regimen is active in patients with relapsed CLL. To further improve response, Hillmen and colleagues10 compared the R-FCM regimen to FCM in a randomized, phase II trial of 52 patients with relapsed CLL. Each arm had 26 patients. Adding rituximab to FCM resulted in a higher CR rate (43% CR + CRI [complete remission with incomplete marrow recovery] for R-FCM and 13% CR + CRI for FCM). (Figure 2) Five patients in the R-FCM arm compared to two in the FCM arm achieved MRD negativity. The results of this study suggest that adding rituximab to FCM appears to be more effective for the treatment of relapsed CLL than using FCM alone.

Faderl and colleagues11 investigated the combination of mitoxantrone with R-FC (R-FCM) in untreated, symptomatic CLL patients (n = 31). The R-FCM regimen was compared with the R-FC historical controls. Response rates at completion of therapy were an OR of 97% with a CR of 80%, nPR of 10%, and a PR of 7%. (Figure 1) Of 23 patients with CR, 65% patients were found to have <1% CD19+/CD5 cells by flow cytometry analysis. MRD negativity, assessed by polymerase chain reaction, was observed in 59% of the 17 patients with CR. CR plus nPR rates in R-FCM versus R-FC were 80+10 and 85+7 respectively. While R-FCM was found to be active in front-line CLL, the addition of mitoxantrone to R-FC did not provide any additional benefit.

The R-PC regimen
Purine analogs and alkylators are important agents for treating chronic lymphocytic leukemia. Of the purine analogs active in CLL, pentostatin appears to be the least myelosuppressive. Weiss and colleagues12 previously reported pentostatin and cyclophosphamide (PC) to be active and well tolerated in patients with relapsed or refractory CLL. Subsequently, Lamanna and colleagues13 added rituximab to PC for the treatment of 46 patients with either previously treated CLL (n = 32) or other low-grade B-cell neoplasms (n = 14). For CLL patients, there were 24 responses (75%), including 25% CRs. (Figure 2) Seventy-five percent of fludarabine-refractory patients responded to this regimen.

Building on the prior results with pentostatin in CLL, Kay and colleagues14 initiated a trial of combined pentostatin, cyclophosphamide, and rituximab in 63 symptomatic, previously untreated patients. A CR of 41%, nPR of 22%, PR of 28%, and an OR of 91% were observed in patients treated with this regimen. (Figure 1) Many patients with a CR also lacked evidence of MRD by two-colour flow cytometry. The R-PC regimen was found to be equally effective in young as well as older (>70 years) patients and in patients with del(11q22.3) versus other favourable prognostic factors.

The R-CFA regimen
Serum β2-microglobulin greater than or equal to 4 mg/L has been previously identified by Keating and colleagues15 to be a prognostic factor for lower CR rates and shorter PFS following first-line chemotherapy in patients with CLL. R-FC in combination with alemtuzumab, a humanized monoclonal antibody that targets CD52, (R-CFA) has previously been demonstrated by Wierda and colleagues16 to be active in relapsed or refractory disease with CR, PR, and OR rates of 24%, 38%, and 65%
respectively. (Figure 2) Wierda and colleagues also evaluated the activity of this regimen in high-risk CLL patients with a National Cancer Institute (NCI) indication for front-line therapy.\textsuperscript{16}

The objective of this second study was to evaluate the ability of R-CFA to increase the proportion of patients with <5% CD5/CD19+ cells in bone marrow to 66% following three courses of treatment, without significantly increasing the incidence of pneumonia or sepsis, compared with a historic group of patients treated with the R-FC regimen. The R-CFA regimen was administered to 40 high-risk CLL patients. Twenty-six patients were evaluable for response. An objective response rate of 96% was seen in the R-CFA regimen. (Figure 1) CR was higher for patients in the R-CFA cohort (69%) as compared with R-FC (60%). Mutation status, ZAP70 expression, and CD38 expression did not correlate with CR or OR.

### Figure 1: First-line rituximab chemoimmunotherapy in CLL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Concurrent</th>
<th>Sequential</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-F</td>
<td>F – 25 mg/m² d 1-5, c 1-6</td>
<td>F – 25 mg/m² d 1-5, c 1-6</td>
<td>51</td>
<td>47%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>R – 375 mg/m² d 1,4, c 1, d 1, c 2-6</td>
<td>R – 375 mg/m² weekly x 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 months observation then</td>
<td>2 months observation then</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CFA</td>
<td>R – 375 mg/m² weekly x 4</td>
<td>R – 375 mg/m² weekly x 4</td>
<td>53</td>
<td>28%</td>
<td>77%</td>
</tr>
</tbody>
</table>

- Byrd 2003

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-F</td>
<td>300</td>
<td>72%</td>
<td>95%</td>
</tr>
</tbody>
</table>
|         | Tam 2008

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-F</td>
<td>31</td>
<td>80%</td>
<td>97%</td>
</tr>
</tbody>
</table>
|         | Faderi 2007

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-P</td>
<td>63</td>
<td>41%</td>
<td>91%</td>
</tr>
</tbody>
</table>
|         | Kay 2007

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CFA</td>
<td>40</td>
<td>69%</td>
<td>96%</td>
</tr>
</tbody>
</table>
|         | Wierda 2007

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR (%)</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-FClite</td>
<td>50</td>
<td>86%</td>
<td>100%</td>
</tr>
</tbody>
</table>
|         | Tahrini 2007

- a = alemtuzumab; C = cyclophosphamide; c = cycle; d = day; CR = complete response; F = fludarabine; M = mitoxantrone; OR = overall response; P = pentostatin; Q3M = every 3 months; R = rituximab
Figure 2: Second-line rituximab chemoimmunotherapy in CLL

Achievement of durable complete response is a new goal of clinical research in CLL. Rituximab maintenance therapy has been demonstrated to provide a clear clinical benefit after induction with chemoimmunotherapy with rituximab, chemotherapy alone, or rituximab monotherapy in previously untreated, and relapsed and refractory follicular lymphoma. There is some evidence to show that rituximab maintenance therapy in CLL could provide a similar benefit. A number of studies are exploring the role of maintenance rituximab in achieving MRD-negative CRs.

R-F induction followed by rituximab maintenance

Rituximab in sequential combination with fludarabine has resulted in higher remission rates and longer response duration in patients with CLL. Based on their recent experience in indolent non-Hodgkin’s lymphomas, Del Poeta and colleagues looked at whether consolidation and maintenance therapy with rituximab could prolong the response duration in patients with CLL. Their phase II trial in 75 symptomatic, untreated patients with CLL was based on a consolidation and maintenance therapy with rituximab for patients in CR or PR who were positive for MRD, as determined by flow cytometry.

Patients received six monthly cycles of fludarabine followed by four weekly doses of rituximab. Twenty-eight patients who were positive for MRD were then consolidated with four monthly cycles of rituximab (375 mg/m²) followed by 12 monthly low doses of rituximab (150 mg/m²).

The addition of a consolidation and maintenance therapy with rituximab prolonged response duration significantly in patients with MRD-positive CLL. Based on NCI criteria, 81% achieved a CR, 13% had a PR, and 5% had either no response or disease progression. (Figure 3) MRD-positive patients in CR or PR who received consolidation therapy (n = 28) had a significantly longer response duration (87% versus 32% at 5 years) compared with a subset of patients who did not receive consolidation therapy (n = 18).
All patients experienced a long PFS from the end of induction treatment (73% at 5 years). Within the subset of ZAP-70-positive patients, MRD-positive, consolidated patients had a significantly longer response duration (69% versus 0% at 2.6 years) compared with MRD-positive, unconsolidated patients.

**First induction with R-FC subsequent to second induction with R-F followed by maintenance with rituximab**

Egle and colleagues designed a study which incorporated a two-part induction strategy with rituximab maintenance therapy in previously untreated CLL patients. The study was a phase II trial with 40 patients. During induction therapy, R-FC was administered for three cycles as per the Keating protocol followed by R-F for three cycles as per the Byrd protocol. Maintenance therapy with rituximab was administered every three months for two years. Patients were followed up for three years, with staging visits every six months inside the study schedule after the end of maintenance. A CR and CR tox (inability to score as a CR because of persisting cytopenia) rate of 83% following R-FC as first induction therapy was observed at week 12. A CR and CR tox rate of 94% following R-F as second induction therapy was observed at week 24. CR and CR tox rate at first-stage maintenance therapy was 100%. At weeks 12 and 24, 42% and 59% of patients respectively were negative for MRD. Induction therapy with R-FC and R-F at the first stage of rituximab maintenance therapy demonstrated an almost 100% complete response rate. (Figure 3)

**R-FCM induction followed by maintenance with rituximab**

Bosch and colleagues in a prospective clinical trial treated 69 chemotherapy-naïve patients with R-FCM as induction therapy followed by maintenance with rituximab. Thirty-eight patients were evaluable for response to the first part of the treatment (R-FCM induction therapy). An OR of 92%, CR of 77%, nPR of 7%, and PR of 8% were observed in 38 evaluable patients. Of the 77% CRs, 36% patients were MRD-negative and 41% patients were MRD-positive. Two out of four PR cases were MRD-negative. Data on prolongation of response duration with rituximab maintenance are awaited. (Figure 3)

**Figure 3: Rituximab maintenance therapy in CLL**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance (up to two years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R – 25 mg/m² d 1–3, c 1–6</td>
<td>R – 375 mg/m² QM</td>
</tr>
<tr>
<td>C – 200 mg/m² d 1–3, c 1–6</td>
<td></td>
</tr>
<tr>
<td>M – 6 mg/m² d 1, c 1–6</td>
<td></td>
</tr>
<tr>
<td>R – 375 mg/m² d 1, c 1</td>
<td>n = 69</td>
</tr>
<tr>
<td>R – 500 mg/m² d 1, c 2–6</td>
<td>CR 77% OR 92% Bosch 2007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RF/R C</th>
<th>RF/C M/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>F – 25 mg/m² d 1–5 QM x 6; followed by R – 375 mg/m² QW x 4; followed by (n = 28) R – 375 mg/m² QW x 4 R – 150 mg/m² QM x 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>F – 25 mg/m² d 2–4, c 1; d 1–3, c 2–3</td>
<td>n = 75</td>
</tr>
<tr>
<td>C – 250 mg/m² d 2–4, c 1; d 1–3, c 2–3</td>
<td>CR 81% OR 94% Del Poeta 2008</td>
</tr>
<tr>
<td>M – 6 mg/m² d 1, c 1</td>
<td></td>
</tr>
<tr>
<td>R – 375 mg/m² d 1, c 2–3</td>
<td></td>
</tr>
<tr>
<td>R – 500 mg/m² d 1, c 2–3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First Induction</th>
<th>Second Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>F – 25 mg/m² d 1–3, c 1</td>
<td>F – 25 mg/m² d 1–3, c 1</td>
</tr>
<tr>
<td>C – 250 mg/m² d 1–3, c 1</td>
<td>R – 375 mg/m² d 1–3, c 1</td>
</tr>
<tr>
<td>M – 6 mg/m² d 1, c 1</td>
<td>2 months observation then</td>
</tr>
<tr>
<td>R – 375 mg/m² weekly</td>
<td>R – 375 mg/m² weekly x 4</td>
</tr>
<tr>
<td>n = 40</td>
<td>CR 65% OR 83% Egle 2007</td>
</tr>
<tr>
<td>CR 43% OR 94%</td>
<td></td>
</tr>
<tr>
<td>CR 50% OR 100%</td>
<td></td>
</tr>
</tbody>
</table>

A = alemtuzumab; C = cyclophosphamide; c = cycle; d = day; CR = complete response; F = fludarabine; M = mitoxantrone; OR = overall response; P = pentostatin; QM = monthly; Q3M = every 3 months; QW = weekly; R = rituximab
The future of rituximab-based therapies

In addition to the above-mentioned combinations, novel rituximab-based combinations such as R-chlorambucil, R-bendamustine, R-OF-A, and R-FC-lumiliximab are also being explored. (Table 1). Data from the phase III CLL-8 and REACH trials are also eagerly awaited.

Data from these trials have the potential to transform the manner in which patients with CLL will be managed and treated in the future.

Table 1: Novel rituximab chemoimmunotherapy regimens under investigation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patient criteria</th>
<th>Phase</th>
<th>clinicaltrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-OF-A</td>
<td>Relapsed/refractory CLL</td>
<td>Phase I/II</td>
<td>NCT00472849</td>
</tr>
<tr>
<td>R-Chlorambucil2</td>
<td>Previously untreated CLL</td>
<td>Phase II</td>
<td>NCT00532129</td>
</tr>
<tr>
<td>R-Bendamustine2</td>
<td>Previously untreated (Binet stage C or Binet B) or relapsed CLL</td>
<td>Non-randomized, open-label, phase II</td>
<td>NCT00274989</td>
</tr>
<tr>
<td>R-FC-Lumiliximab2</td>
<td>Relapsed CLL</td>
<td>Phase II/III</td>
<td>NCT00391066</td>
</tr>
</tbody>
</table>

Phase III R-FC Induction Therapy Trials in Chronic Lymphocytic Leukemia

Meenakshi Kashyap

Background
Phase II trials of rituximab in combination with fludarabine and cyclophosphamide (R-FC) have clearly demonstrated an improved response in relapsed (Figures 1, 2) as well as first-line (Figures 3, 4) chronic lymphocytic leukemia (CLL).\textsuperscript{1,2} National Comprehensive Cancer Network (NCCN) practice guidelines currently recommend the R-FC regimen as one of the treatment regimens for first-line and second-line therapy.\textsuperscript{3} A recent multivariate analysis by Tam and colleagues indicates that R-FC therapy is the strongest independent determinant of survival in previously untreated patients with CLL receiving fludarabine-based therapy.\textsuperscript{2} (Figure 5)

Figure 1: Second-line R-FC — high response rates in patients with relapsed and refractory CLL\textsuperscript{1}
Figure 2: Second-line R-FC — median survival over 3 years in patients with relapsed and refractory CLL

![Graph showing the median survival over 3 years in patients with relapsed and refractory CLL. Median OS: 42 months. Median TTP: 28 months.]

- **Outcome**
  - **n**
  - **Patients at t = 0 (n)**
  - **Died** 80 177
  - **Relapsed** 60 129

OS = overall response; t = time; TTP = time to progression

Figure 3: First-line R-FC — a high proportion of complete responses in chemotherapy-naïve patients

![Bar chart showing the ORR of 95% (n = 300). 22 patients had PR/nodular PR, and 72 patients had CR.]

- **CR** = complete response; **ORR** = overall response rate; **PR** = partial response
Figure 4: First-line R-FC — improved overall survival following complete response in chemotherapy-naïve patients²

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>217</td>
<td>p = 0.12</td>
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<tr>
<td>nPR</td>
<td>33</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>PR-i</td>
<td>21</td>
<td>p = 0.16</td>
</tr>
<tr>
<td>PR-d</td>
<td>16</td>
<td>p = 0.10</td>
</tr>
<tr>
<td>Fail</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; nPR = nodular PR; PR-i = met all criteria for CR except for incomplete recovery of blood counts; PR-d = residual disease in blood, nodes, spleen, marrow or other sites

Figure 5: F±P versus F±M/C versus R-FC — improved survival with R-FC in chemotherapy-naïve patients²

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>FC/M</td>
<td>140</td>
<td>p = 0.37</td>
</tr>
<tr>
<td>R-FC</td>
<td>300</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; nPR = nodular PR; PR-i = met all criteria for CR except for incomplete recovery of blood counts; PR-d = residual disease in blood, nodes, spleen, marrow or other sites
Promising data from phase II R-FC trials have led to the investigation of this regimen in the large, randomized phase III CLL-8 and REACH trials for first-line and relapsed CLL respectively.

The CLL-8 trial
- The CLL-8 trial, conducted by the German CLL Study Group (GCLLSG), is an open-label, multicentre, two-arm, randomized, phase III trial of R-FC versus FC in previously untreated patients with CLL.4 (Figure 6)

- The primary objective of this trial is to assess progression-free survival (PFS).

- Secondary outcomes include event-free survival (EFS), overall survival (OS), disease-free survival (DFS), duration of remission, time to new CLL or death, rates of molecular, complete and partial remission, response rates and survival times in biological subgroups, rates of treatment-related adverse effects, pharmacoeconomic impact, and quality of life.

- The first interim analysis performed for the CLL-8 trial met its primary endpoint of >35% improvement in PFS with rituximab.

- The trial has now been stopped and all secondary endpoints are being analyzed.5

**Figure 6: The CLL-8 trial — R-FC versus FC in previously untreated patients with CLL4**

- Untreated B-CLL
- Binet B requiring treatment or Binet C
- ECOG PS 0–1
- n = 817

Rituximab
Cycle 1: 375 mg/m²
Cycles 2–6: 500 mg/m²

Fludarabine
25 mg/m² iv, days 1–3

Cyclophosphamide
250 mg/m² iv, days 1–3

CR = complete response; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PR = partial response; PS = performance status; Q4W = every 4 weeks; SD = stable disease
## The REACH Trial

- The REACH trial is a randomized, phase III study of rituximab combined with FC. It is being conducted in rituximab-naïve patients with CLL who are in their first relapse and are sensitive to fludarabine (remission of ≥6 months) if previously treated with a fludarabine-containing regimen (Figure 7). This regimen is being compared to the FC regimen.6
- The primary objective of this trial is to assess PFS.
- Secondary outcomes include EFS, DFS, response duration, response rate, overall survival, and proportion of patients with molecular remission.

### Figure 7: The REACH trial — R-FC versus FC in patients with relapsed CLL6,7

- **CLL**
- **Binet B or C**
- **Relapsed disease, excluding fludarabine refractory**
- **ECOG PS 0–1**
- **n = 551**

**Rituximab**
- Cycle 1: 375 mg/m²
- Cycles 2–6: 500 mg/m²

**Fludarabine**
- 25 mg/m² iv, days 1–3

**Cyclophosphamide**
- 250 mg/m² iv, days 1–3

**Randomize**
- R-FC Q4W X 3
- CR, PR
- R-FC Q4W X 3

**Restage**
- R-FC Q4W X 3
- SD, PD off study

**Summary**

- The R-FC regimen has had a major impact on CLL therapy.
- The promising responses seen with this regimen have shifted the primary goal of treatment from symptom relief to extending remission and, possibly, even survival.

### Canadian perspective by Dr. Kuruvilla

Most of the published studies that have evaluated rituximab chemoimmunotherapy in CLL have been either single-centre or retrospective studies. British Columbia and Quebec are the only provinces in Canada that currently fund rituximab for the treatment for CLL. In the other provinces (and with my practice in Ontario), treating physicians are eagerly awaiting prospective data on progression-free and overall survival along with pharmacoeconomic data from major randomized trials such as the CLL-8 and REACH trials. Major data from the CLL-8 trial is expected at ASH 2008. Positive data from these trials will aid in the wider adoption of the R-FC regimen in first-line and relapsed CLL.

References:
A NEW FIRST-LINE STANDARD FOR THE MANAGEMENT OF MRCC¹,²

**PrSUTENT®:** AN ORAL MULTITARGETED RECEPTOR TYROSINE KINASE INHIBITOR³

Sunitinib (SUTENT) is the first-line standard of care for mRCC patients with good or intermediate prognosis.¹

**More than doubled median PFS**
- 47.3 weeks with SUTENT vs. 22.0 weeks with IFN-α (95% CI: 42.6, 50.7 and 16.4, 24.0, respectively [p<0.000001])³,†

**4-fold higher objective-response rate**
- 27.5% with SUTENT vs. 5.3% with IFN-α (95% CI: (23.0, 32.3) and (3.3, 8.1) respectively, [p<0.0001])³,†

**Manageable adverse-event profile³**
- The most common adverse events reported in ≥10% of patients receiving SUTENT for treatment-naïve mRCC (n=375) (all grades vs. IFN-α [n=360]) were fatigue (50.9% vs. 51.1%), diarrhea (53.1% vs. 12.5%), nausea (44.3% vs. 33.3%), dysgeusia (42.1% vs. 13.6%), dyspepsia (25.6% vs. 3.1%), stomatitis (25.1% vs. 1.7%), anorexia (25.6% vs. 26.0%), hypertension (24.0% vs. 10.0%), vomiting (22.7% vs. 7.3%), mucosal inflammation (20.0% vs. 1.1%) and hand-foot syndrome (20.3% vs. 0.6%).

- The median progression-free survival estimates were 48.3 versus 31.3 weeks for SUTENT and IFN-α arms, respectively.³

**DEMONSTRATED SIGNIFICANTLY LONGER PROGRESSION-FREE SURVIVAL VS. IFN-α³,†**

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**Important safety information³**
- Treatment-related tumour hemorrhage has been observed in patients receiving SUTENT.
- Decreases in left ventricular ejection fraction have been reported. Baseline and periodic evaluations of LVEF should be considered.
- Patients should be monitored for hypertension and treated as appropriate. Those with uncontrolled hypertension should not be treated with SUTENT.
- SUTENT has not been studied in patients with severe renal or hepatic impairment.
- Rare cases of myopathy and/or rhabdomyolysis have been reported.
- Contraindicated in pregnant women and patients with hypersensitivity to sunitinib malate or other components of SUTENT.

Please refer to Prescribing Summary for complete information.
The CD20 antigen is a B-lymphocyte surface protein that plays a role in the development and differentiation of B-cells into plasma cells. It is expressed on normal and malignant pre-B- and mature B-lymphocytes, but is absent in hematopoietic stem cells, activated B-lymphocytes (plasma cells), and normal tissues.

The CD20 antigen is an ideal target for anti-CD20 monoclonal antibodies (MABs) because it does not shed, modulate, or internalize.\(^1\)

Anti-CD20 MABs can cause lysis of B-lymphocytes by multiple mechanisms\(^2\) such as:

- activating the complement cascade and immune effector cells — antibody-dependent cell-mediated cytotoxicity (ADCC)
- complement-dependent cytotoxicity (CDC)
- directly inducing apoptosis

Different CD20 MABs operate various effector mechanisms in vivo, depending on whether they are type I or type II antibodies.\(^3\) These distinct types of anti-CD20 antibodies have been identified on the basis of their ability to eradicate lymphoma xenografts generated by intravenous injection of tumour cells into the tail veins of CB-17 severe compromised immune deficiency (SCID) and CB-17 SCID Beige mice.

Type I MABs, such as rituximab — the first chimeric anti-CD MAB — and the murine 1F5, have been found to utilize CDC lysis to clear lymphoma cells in vivo, while type II MABs, such as the murine B1, do not. Both types of MABs, however, are equally effective in ADCC.\(^4\) In vitro assays by Cragg and Glennie suggest that the main difference between B1 and rituximab (and 1F5) lies in the ability of the type II MAB to induce high levels of apoptosis.

Most investigators believe that increasing ADCC in patients with non-Hodgkin’s lymphoma (NHL) has the most potential for improved clinical activity.\(^2\) The fact that response to rituximab is dependent on specific FcyRIIIa polymorphisms supports this theory. These FcyRIIIa polymorphisms result in different binding affinities of the FcyRIIIa receptors for the Fc region of IgG on macrophages and Natural Killer (NK) cells, which in turn alter the level of ADCC mediated by these cells.\(^5\)

Several new anti-CD20 MABs are therefore being generated to have genetically altered sequences to enable them to bind with greater affinity to the FcyRIIIa receptor on ADCC effector cells. Researchers are also investigating engineering strategies to humanize MABs for improving pharmacokinetics, efficacy, and safety of anti-CD20 MABs.

Umana and colleagues previously presented data on GA101, the first humanized, new-generation, glycoengineered, type II, anti-CD20 antibody.\(^6\)

GA101 mechanism of action differs from type I MABs, such as rituximab, ocrelizumab and ofatumumab, in the following ways: (Table 1)\(^2\)

- increased direct cell death due to type II epitope recognition and elbow-hinge modification
- increased ADCC via increased affinity to the ADCC receptor FcyRIIIa
- lower CDC activity as compared with rituximab
At ICML 2008, Umana and colleagues presented updated results from in vitro and in vivo studies of GA101.7

**Key findings**

- GA101 brought about increased direct cell death in both a panel of NHL cell lines and in ex vivo samples from patients with a variety of B-cell malignancies.
- In B-cell depletion assays with whole blood from healthy donors and from B-cell leukemic patients, an assay combining ADCC-, CDC- and apoptosis-mediated mechanisms of action, GA101 was significantly more potent and efficacious than other CD20 antibodies, including rituximab and non-glycoengineered GA101. (Figure 1)
- Higher antibody concentration of GA101 was needed to deplete B-cells in B-cell patient blood.
- In the SU-DHL-4 xenograft model, treatment with a 30 mg/kg weekly dose of GA101 resulted in superior efficacy in terms of tumour growth inhibition and complete tumour remission as compared with rituximab. (Figure 2)
- Tumours that progressed under first-line rituximab treatment responded to second-line treatment with GA101. (Figure 3)
- Treatment with GA101 increased the median and overall survival in the orthotopic-disseminated Z138 MCL model as compared with rituximab.
- In the hCD20 transgenic mice, GA101 demonstrated superior B-cell depletion. The increased B-cell depletion extended into the peripheral lymphoid compartments and to the range of B-cell subsets targeted.
- Analogous findings were observed in Cynomolgus monkeys, where the efficacy of GA101 in depleting B-cells in lymphoid tissues was compared with that of rituximab.

<table>
<thead>
<tr>
<th>Antibody name</th>
<th>Type</th>
<th>ADCC</th>
<th>CDC</th>
<th>Direct effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Chimeric IgG1</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ocrelizumab</td>
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<td>+++</td>
<td>+/-</td>
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<tr>
<td>PRO131921</td>
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<td>Ofatumumab</td>
<td>Human IgG1</td>
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<td>++++</td>
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</tr>
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<td>AME-133</td>
<td>Humanized IgG1</td>
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<td>GA-101</td>
<td>Humanized IgG1</td>
<td>++++</td>
<td>–</td>
<td>+++</td>
</tr>
</tbody>
</table>

ADCC = antibody-dependent cell-mediated cytotoxicity; CDC = complement-dependent cytotoxicity

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**Table 1: Characteristics of anti-CD20 antibodies in vitro**

---

At ICML 2008, Umana and colleagues presented updated results from in vitro and in vivo studies of GA101.7

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- Analogous findings were observed in Cynomolgus monkeys, where the efficacy of GA101 in depleting B-cells in lymphoid tissues was compared with that of rituximab.
Figure 1: GA101 is superior to rituximab in whole blood assays

B-cell depletion — whole blood assay (24h) in healthy volunteer (FcyRIIIa genotype: F/F)

B-cell depletion — whole blood assay (24h) in B-CLL patient blood

Figure 2: Superior efficacy and complete tumour remission in aggressive subcutaneous SU-DHL-4 diffuse large B-cell xenograft model

Vehicle
Rituximab (1 mg/kg) QW x 3, i.v.
Rituximab (10 mg/kg) QW x 3, i.v.
Rituximab (30 mg/kg) QW x 3, i.v.
GA101 (1 mg/kg) QW x 3, i.v.
GA101 (10 mg/kg) QW x 3, i.v.
GA101 (30 mg/kg) QW x 3, i.v.

QW = weekly
Key conclusions

- GA101 is a fully humanized monoclonal antibody that recognizes a CD20 type II epitope.
- GA101 exhibits superior ADCC, direct cell-death induction, and reduced CDC.
- Treatment with GA101 results in superior B-cell depletion in whole blood assay.
- GA101 treatment demonstrates superior efficacy in various NHL xenograft models, including diffuse large B-cell, mantle cell, and follicular lymphomas.
- In vivo efficacy studies in Cynomolgus monkeys and huCD20 transgenic mice confirm the in vitro findings.
- GA101 is currently being assessed in phase I/II trials (NCT00517530).

References:
Profile

The Princess Margaret Hospital Phase II Consortium: An Alliance of Integrity and Innovation

Debra Locking

In 2001, when the call came from the National Cancer Institute (NCI) for organizations that had the capabilities and facilities to conduct phase II clinical trials of NCI-sponsored therapeutic agents, the team at Princess Margaret Hospital (PMH) was only too ready to respond. After submitting an extensive proposal, PMH was awarded the prestigious contract — the first group outside of the United States ever to attain the honour. However, this milestone achievement was only the beginning. No one could have envisioned how successful the newly founded Princess Margaret Hospital Phase II Consortium would become.

The NCI is the U.S. federal government’s principal agency for conducting and supporting cancer research. The Princess Margaret Hospital Phase II Consortium is a new entity devoted to advancing the development of the latest NCI anticancer therapies.

The primary purpose of the Consortium, as its name implies, is to conduct phase II clinical trials, including the design of protocols that investigate promising new and combination therapies. At its inception the goal was to conduct between four and ten trials annually. Currently, the PMH Consortium takes pride in the fact that more than 1200 patients have been enrolled in approximately sixty trials. High priority is placed on pivotal drug development trials that require rapid initiation, completion, and data reporting. At present, approximately 30 molecules are being evaluated in phase II trials.

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The Princess Margaret Hospital Phase II Consortium, directed by Dr. Amit Oza, began as an alliance of only three centres: Princess Margaret Hospital, with Dr. Malcolm Moore, Dr. Amit Oza, and Dr. Lillian Siu sharing the role of Principal Investigator; the Juravinski Cancer Centre in Hamilton, under the direction of Dr. Hal Hirte; and the London Regional Cancer Centre, with Dr. Eric Winquist. It is a testament to its success that this initial three-group consortium has flourished to include fifteen centres, including two in the United States.

The close working relationship between the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) and the PMH Consortium is complex, but highly successful. The NCIC CTG conducts phase I, II, and III trials. The two organizations take care not to be in direct competition, but Dr. Oza admits, “We try to be fairly collaborative, but there is a certain level of healthy competition.”

It is important to all members of the PMH Consortium that they have complete flexibility in designing the clinical trials, which are then approved by the NCI. Clearly this has proved to be a successful formula for all parties involved, since a renewal submission was presented in 2006 and rapidly approved.

The PMH Phase II Consortium is part of the Drug Development Program at Princess Margaret Hospital. In fact, the Drug Development Program (DDP) is the umbrella organization under which the PMH Consortium operates. Dr. Oza describes the two organizations as being “an interacting matrix, completely intertwined.”

### Princess Margaret Hospital Phase II Consortium 2008

<table>
<thead>
<tr>
<th>Centre</th>
<th>Principal Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Princess Margaret Hospital, Toronto</td>
<td>Dr. Malcolm Moore</td>
</tr>
<tr>
<td></td>
<td>Dr. Amit Oza</td>
</tr>
<tr>
<td></td>
<td>Dr. Lillian Siu</td>
</tr>
<tr>
<td>Juravinski Cancer Centre, Hamilton</td>
<td>Dr. Hal Hirte</td>
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<td>London Regional Cancer Centre, London</td>
<td>Dr. Eric Winquist</td>
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<td>Ottawa Regional Cancer Centre, Ottawa</td>
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<td>Sunnybrook Health Sciences Centre, Toronto</td>
<td>Dr. Kathleen Pritchard</td>
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<tr>
<td>Cancer Centre of Southeastern Ontario, Kingston</td>
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<td>Centre hospitalier de l’Université de Montréal, Montréal</td>
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<td>Roswell Park Cancer Institute, Buffalo, New York</td>
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<tr>
<td>Fox Chase Cancer Center, Philadelphia, Pennsylvania</td>
<td>Dr. Gary R. Hudes</td>
</tr>
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The PMH Drug Development Program conducts the high-quality phase I and II clinical studies that have made Princess Margaret Hospital a world leader in innovative research.

Currently, the PMH Drug Development Program is the largest early phase trials program in Canada. Emphasis is placed on correlative and translational studies to complement phase II trials. This important translational research enables a better understanding of the mechanisms of action of anti-cancer therapies and drug resistance, molecular factors predicting response and resistance, and tumour microvasculature and angiogenesis.

Clinical trials conducted by the Princess Margaret Hospital Phase II Consortium are primarily focused on ten priority disease sites: colorectal, pancreas, renal, bladder, prostate, small and non-small cell lung, ovary, cervix, and head and neck.

The objective of translational research is to rapidly translate scientific findings into therapies that provide tangible patient benefit.

Clinical trial accrual by disease site

The Princess Margaret Hospital Phase II Consortium has achieved many notable successes

The ambitious goals that the leaders of the PMH Consortium had envisioned have been realized in many tangible ways. The group’s success is evident not only by the growth of the program, but by the number of research fellows that have been trained and gone on to hold senior positions internationally. The peer-reviewed program has produced myriad reports and presentations, including a notable collection of published articles. In fact, five PMH Consortium abstracts were accepted by ASCO this year alone — a significant achievement in the highly competitive scientific milieu.

Despite the rapid growth of the program, Dr. Amit Oza stresses that the organization is founded on a solid basis of clinical excellence and rigorous ethical standards. The PMH Phase II Consortium collaborated with the Ontario Cancer Research Ethics Board to develop a centralized Research Ethics Board which oversees many of the activities conducted by the group. In addition, Drs. Moore, Oza, and Siu ensure that all the Principal Investigators are well qualified and accredited with the National Cancer Institute. Every trial conducted by the Consortium is monitored according to the Good Clinical Practice guidelines mandated by Health Canada and the Food and Drug Administration.

“Conducting every trial to the highest standard of quality is a primary goal.”
**The vital role of the community oncologist**

The Peel Regional Cancer Center in Mississauga, the newest member of the Phase II Consortium, has been instrumental in enabling community oncologists to enroll patients in clinical trials. In cooperation with the Community Oncologists of Metropolitan Toronto (COMET), the affiliated centres are committed to designing appropriate trials and streamlining the enrolment process. One exciting innovation is the development of a website that will allow community oncologists to refer patients directly to the PMH clinical trials program. Although treating patients with rare tumour types may not be realistic in a community setting, the groups are exploring ways to provide the greatest benefit to the patient.

For all members of the PMH Phase II Consortium team, primary emphasis is placed on creating a supportive environment for patients involved in clinical trials. In a culturally-diverse environment such as Toronto, the PMH team strives to ensure that cultural or language barriers never stand in the way of a patient participating in a trial. Most importantly, all patients are afforded the opportunity to learn about the vital role they play in the advancement of scientific understanding.

As the Princess Margaret Hospital Phase II Consortium progresses into its eighth year, its reputation as an international centre of excellence remains secure. In the words of Dr. Amit Oza, “We constantly strive to develop the molecules that will make a real difference. That is our objective.”

“Whether you’re discussing the intent of a trial or explaining standard treatment, clear and honest communication is the most important thing you can give a patient. It is vital that a patient is never misled.” —Dr. Amit Oza

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**Malcolm J. Moore, MD, FRCPC**

Dr. Moore is Director of the Drug Development Program and Chief of Division of Medical Oncology at Princess Margaret Hospital. He is a Professor of Medicine and Pharmacology in the Department of Medical Oncology and Hematology at PMH and the University of Toronto, and a Senior Scientist in the Division of Experimental Therapeutics at the Ontario Cancer Institute. Dr. Moore’s primary research interest is the development of innovative cancer therapies, including a number of agents now indicated to treat hormone refractory prostate cancer, pancreatic, and urothelial cancer.

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**Lillian Siu, MD, FRCPC**

Dr. Siu is a staff physician in the Department of Medical Oncology and Hematology at Princess Margaret Hospital and an Associate Professor at the University of Toronto. Dr. Siu is Director and Principal Investigator of the PMH Phase I Consortium. Dr. Siu has been the principal investigator for many phase I, II, and III trials supported by the NCI, NCIC, and the pharmaceutical industry. Dr. Siu’s extensive research extends to the design of novel dose-escalation schemes for phase I trials, and the development of relevant biological endpoints for new classes of anti-tumour compounds.

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**Amit M. Oza, MD, FRCPC**

Dr. Oza is a senior staff physician in the Department of Medical Oncology and Hematology at the Princess Margaret Hospital and Professor in the Department of Medicine at the University of Toronto. He is also a scientist with the Ontario Cancer Institute and Co-Chair of the Gynecology Site Group for NCIC CTG. Dr. Oza has been the principal investigator and co-investigator in phase I, II, and III trials for gynecological cancer and advanced colorectal malignancies. His research interests are focused on the development and validation of novel therapeutic strategies for cancer, including molecular targeted therapies.
INDICATIONS AND CLINICAL USE

FRAGMIN® (dalteparin sodium injection) is indicated for:

- Thromboprophylaxis in conjunction with surgery.
- Treatment of acute deep venous thrombosis.
- Unstable coronary artery disease (UCAD), i.e., unstable angina and non-Q-wave myocardial infarction.
- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency.
- Extended treatment of symptomatic venous thromboembolism to prevent recurrence of venous thromboembolism in patients with cancer.
- Reduction of deep vein thrombosis (DVT) in hospitalized patients with severely restricted mobility during acute illness. Decreased mortality due to thromboembolic events and complications has not been demonstrated.

CONTRAINDICATIONS

FRAGMIN should not be used in patients who have the following:

- Hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) (see WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Pregnant Women), or to other low molecular weight heparins and/or heparin.
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an in vitro platelet-aggregation test in the presence of FRAGMIN is positive.
- Septic endocarditis (endocarditis lenta, subacute endocarditis).
- Uncontrollable active bleeding.
- Major blood-clotting disorders.
- Acute gastroduodenal ulcer.
- Cerebral hemorrhage.
- Severe uncontrolled hypertension.
- Diabetic or hemorrhagic retinopathy.
- Other conditions or diseases involving an increased risk of hemorrhage.
- Injuries to and operations on the central nervous system, eyes and ears.
- Spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding.

SPECIAL POPULATIONS

Pregnant Women:

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal “Gasing Syndrome” in neonates. Cases of Gasing Syndrome have been reported in neonates when benzyl alcohol has been administered in amounts of 99-404 mg/kg/day. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

Teratogenic Effects: As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

Nursing Women:

It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

Pediatrics:

The safety and effectiveness of FRAGMIN in children have not been established.
Geriatrics:
Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

Patients with Extreme Body Weight:
Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.

Safety Information

WARNINGS AND PRECAUTIONS

Special Warnings and Precautions
The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal “Gasing Syndrome” in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see Special Populations, Pregnant Women).

General

FRAGMIN should NOT be administered intra-muscularly.
FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Cardiovascular

Use in Patients with Prosthetic Heart Valves: Cases of prosthetic valve thrombosis have been reported in these patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see WARNINGS AND PRECAUTIONS, Patient Selection Criteria, SPECIAL POPULATION, Pregnant Women).

Use in Unstable Coronary Artery Disease: When thrombolytic treatment is considered appropriate in patients with unstable angina and non-Q-wave myocardial infarction, concomitant use of an anticoagulant such as FRAGMIN may increase the risk of bleeding.

Gastrointestinal

FRAGMIN should be used with caution in patients with a history of gastrointestinal ulceration.

Hematologic

Hemorrhage: Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin use. As with other anticoagulants, FRAGMIN should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Platelets/Thrombocytopenia: Platelet counts should be determined prior to the start of treatment with FRAGMIN and, subsequently, twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. Its incidence is unknown at present.

Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During FRAGMIN administration, special caution is necessary in rapidly-developing thrombocytopenia and severe thrombocytopenia (<100 000/µL). A positive or unknown result obtained from in vitro tests for antiplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparinoids would contraindicate FRAGMIN.

Hepatic

FRAGMIN should be used with caution in patients with hepatic insufficiency, as these patients may have potentially higher risk of hemorrhage.

Peri-Operative Considerations

Spinal/Epidural Hematomas:
When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see CONTRAINDICATIONS and ADVERSE REACTIONS).

When a higher dose (5000 IU s.c.) of FRAGMIN is administered for thromboprophylaxis in conjunction with surgery, no spinal/epidural invasion should be performed for at least 12 hours following the last dose of FRAGMIN and the next dose should be held until at least 12 hours after the anaesthetic procedure. Alternatively, when a lower dose (2500 IU s.c.) of FRAGMIN is administered, the dose can be initiated 1 - 2 hours prior to surgery. FRAGMIN injection
should be given after spinal/epidural anaesthesia and only if the anaesthesiologist considers the spinal/epidural puncture as uncomplicated. Indwelling catheters should not be removed or manipulated for at least 10 - 12 hours following the last dose of FRAGMIN.

Use in Knee Surgery: The risk of bleeding in knee surgery patients receiving low molecular weight heparins may be greater than in other orthopedic surgical procedures. It should be noted that hemarthrosis is a serious complication of knee surgery. The frequency of bleeding events observed with FRAGMIN in orthopedic surgery patients is derived from clinical trials in hip replacement surgery patients. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin in this patient population.

Selection of General Surgery Patients: Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, and age 60 years or above.

Renal
FRAGMIN should be used with caution in patients with renal insufficiency.

Patients with impaired renal function should be carefully monitored because the half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population. Dose reduction should be considered in patients with severe renal impairment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Clinically significant adverse reactions observed with use of FRAGMIN and other low molecular weight heparins include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions.

Post-Marketing Adverse Reactions
In post-marketing experience, the following undesirable effects have been reported:

Bleeding: Intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hemorrhage have been reported occasionally leading to fatality

Blood and Lymphatic System: thrombocytopenia, thrombocytethmia

Skin and Subcutaneous Tissue Disorders: skin necrosis, alopecia

Immune System Disorders: immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications), anaphylactic reactions

Injury, Poisoning and Procedural Complications: spinal or epidural hematoma

DRUG INTERACTIONS

Drug-Drug Interactions
FRAGMIN should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatories and thrombolytic agents because of increased risk of bleeding. Acetylsalicylic acid (ASA), unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarctions.

Drug-Food Interactions
Interactions with food have not been established.

Drug-herb Interactions
Interactions with herbs have not been established.

Drug-lab tests Interactions
Interactions with lab tests have not been established.

Drug-lifestyle Interactions
Interactions with lifestyle have not been established.

To report an adverse event, please contact: your physician, pharmacist or Pfizer Medical Information: 1-800-463-6001.

DOSAGE AND ADMINISTRATION

Dosing
Thromboprophylaxis in Conjunction with Surgery
The dose of FRAGMIN required for adequate prophylaxis without substantially increasing bleeding risk varies depending on patient risk factors.

General surgery with associated risk of thromboembolic complications: 2500 IU s.c. administered 1 - 2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5-7 days or longer.

General surgery associated with other risk factors: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative, 2500 IU s.c. is given 1-2 hours before the operation, with 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

Elective hip surgery: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative 2500 IU s.c. is given 1-2 hours before the operation and 2500 IU s.c. 4-8 hours after surgery, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.
The pre-operative dose may be omitted and an initial dose of 2500 IU s.c. administered 4-8 hours after the operation, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer. Omission of the pre-operative dose may reduce risk of peri-operative bleeding, however increased risk of venous thromboembolic events is possible. This option is based on the results of the North American Fragmin Trial (NAFT), which excluded patients at high risk of bleeding, i.e., documented cerebral or gastrointestinal bleeding within 3 months prior to surgery, defective hemostasis, e.g., thrombocytopenia (<100 x 10^9/L), ongoing anticoagulant treatment.

_Treatment of Acute Deep Vein Thrombosis_

The following dosage is recommended: 200 IU/kg body weight given s.c. once daily. The expected plasma anti-Xa levels during subcutaneous treatment would be <0.3 IU anti-Xa/mL before injection and <1.7 IU anti-Xa/mL 3 - 4 hours after injection. In order to individualize the dose, a functional anti-Xa assay should be performed 3 - 4 hours post-injection. The single daily dose should not exceed 18 000 IU. The following weight intervals are recommended to be adapted to the single-dose prefilled syringes as in the table below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46-56</td>
<td>10 000</td>
</tr>
<tr>
<td>57-68</td>
<td>12 500</td>
</tr>
<tr>
<td>69-82</td>
<td>15 000</td>
</tr>
<tr>
<td>83 and above</td>
<td>18 000</td>
</tr>
</tbody>
</table>

For patients with increased risk of bleeding, a dose of 100 IU/kg body weight given s.c. twice daily or 100 IU/kg body weight administered over a period of 12 hours as continuous i.v. infusion, can be used. The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.0 IU anti-Xa/mL 3 - 4 hours after injection.

Normally concomitant treatment with vitamin-K antagonists is started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin complex factors (FII, FVII, FIX, FX) have decreased to a therapeutically level, in general for approximately 5 days.

_Extended Treatment of Symptomatic Venous Thromboembolism (VTE) to Prevent Recurrence of VTE in Patients with Cancer_

**Month 1:** 200 IU/kg body weight given s.c. once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

**Months 2-6:** Approximately 150 IU/kg given s.c. once daily using the table shown below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤56</td>
<td>7 500</td>
</tr>
<tr>
<td>57-68</td>
<td>10 000</td>
</tr>
<tr>
<td>69-82</td>
<td>12 500</td>
</tr>
<tr>
<td>83-98</td>
<td>15 000</td>
</tr>
<tr>
<td>≥99</td>
<td>18 000</td>
</tr>
</tbody>
</table>

_Dose reductions for chemotherapy-induced thrombocytopenia:_ In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm³, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm³. For platelet counts between 50,000 and 100,000/mm³, FRAGMIN should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustment using the pre-filled syringes), depending on the patient’s weight (table below). Once the platelet count recovers to ≥100,000/mm³, FRAGMIN should be re-instituted at full dose.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Scheduled Dose (IU)</th>
<th>Reduced Dose (IU)</th>
<th>Mean Dose Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤56</td>
<td>7 500</td>
<td>5 000</td>
<td>33</td>
</tr>
<tr>
<td>57-68</td>
<td>10 000</td>
<td>7 500</td>
<td>25</td>
</tr>
<tr>
<td>69-82</td>
<td>12 500</td>
<td>10 000</td>
<td>20</td>
</tr>
<tr>
<td>83-98</td>
<td>15 000</td>
<td>12 500</td>
<td>17</td>
</tr>
<tr>
<td>≥99</td>
<td>18 000</td>
<td>15 000</td>
<td>17</td>
</tr>
</tbody>
</table>

_Unstable Coronary Artery Disease (Unstable Angina and Non-Q-Wave Myocardial Infarction)_

120 IU/kg body weight given s.c. twice daily with a maximum dose of 10 000 IU/12 hours. The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.6 IU anti-Xa/mL 3 - 4 hours after injection. These levels were obtained from another patient population. Treatment should be continued for up to 6 days. Concomitant therapy with ASA is recommended.

_Deep Vein Thrombosis in Hospitalized Patients with Severely-Restricted Mobility_

In hospitalized patients with severely-restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

_Use in Patients with Renal Impairment_

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Administration of low molecular weight heparins to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance <30 mL/min), which may lead to an increased risk of bleeding. This effect has not yet been determined for FRAGMIN. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

_Anticoagulation for Hemodialysis and Hemofiltration_

**Chronic renal failure, patients with no other known bleeding risk:** Hemodialysis and hemofiltration for a maximum of 4 hours: dose as below, or only i.v. bolus injection of 5000 IU. Hemodialysis and hemofiltration for more than 4 hours: i.v. bolus injection of 30 - 40 IU/kg body weight followed by i.v. infusion of 10 - 15 IU/kg body weight per hour. This dose normally produces plasma levels lying within the range of 0.5 - 1.0 IU anti-Xa/mL.

**Acute renal failure, patients with high bleeding risk:** i.v. bolus injection of 5 - 10 IU/kg body weight, followed by i.v. infusion of 4 - 5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2 - 0.4 IU anti-Xa/mL.
Dilution
FRAGMIN solution for injection may be mixed with isotonic sodium chloride or isotonic glucose infusion solutions in glass infusion bottles and plastic containers. Post-dilution concentration: 20 IU/mL.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.

1 mL 10 000 IU
Isotonic NaCl Infusion (9 mg/mL) 500 mL
or
Isotonic Glucose Infusion (50 mg/mL) 500 mL.
The infusion rate is 10 mL/hour. The solution should be used within 24 hours.

Study References


SUPPLEMENTAL PRODUCT INFORMATION

Overdosage
Accidental overdosage following administration of FRAGMIN may lead to hemorrhagic complications. FRAGMIN should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of FRAGMIN is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulphate. The dose of protamine to be given should be 1 mg protamine per 100 anti-Xa IU of FRAGMIN administered. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-Xa activity is never completely neutralized (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available. Refer to the protamine sulphate Product Monograph for further directions for use.

Product Monograph available on request.

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Kirkland, Quebec
H9J 2M5
SUTENT, indicated for the treatment of metastatic renal cell carcinoma of clear cell histology, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

**Prescribing Summary**

**INDICATIONS AND CLINICAL USE:** SUTENT (sunitinib malate) is indicated for the treatment of metastatic renal cell carcinoma of clear cell histology.

**WARNINGS AND PRECAUTIONS**

- **Hepatic Impairment:** SUTENT has not been studied in patients with hepatic impairment.
- **Renal Impairment:** SUTENT has not been studied in patients with renal impairment.
- **Anti-Tumour Agent**

**SIDE EFFECTS:**

- **Infusion Reaction:** Patients treated with SUTENT may experience a range of infusion reactions including hypotension, flushing, dyspnea, and rash.
- **Hypertension:** SUTENT has been associated with hypertension.
- **Embryonal and Fetal Developmental Effects:** SUTENT can cause embryonal and fetal developmental effects in animals. Women of childbearing potential should take effective contraception while taking SUTENT.

**PRODUCT INFORMATION**

- **SUTENT** is contraindicated in pregnant women.

**NOC/c**

MRCC Patient Population

**Treatment-Naive MRCC:** A Phase 3 randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naive MRCC. The primary objective was to compare PFS in patients receiving SUTENT versus patients receiving IFN-α. Secondary objectives included TTP, ORR, OS, and safety. PFS was defined as the time from randomization to first documentation of objective tumor progression or death due to any cause, whichever occurred first. TTP was defined as the time from randomization to first documentation of objective tumor progression. ORR was defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST), relative to the total population of randomized patients. OS was defined as the time from randomization to date of death due to any cause. Safety was reported as type, incidence, severity, timing, seriousness, and relatedness of adverse events and laboratory abnormalities.

Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MU three times a week. During the first cycle, patients randomized to the IFN-α arm received increasing doses from 3 MU per dose for one week, 6 MU per dose for the second week, and 9 MU per dose thereafter. Tumour assessment was performed every 28th day of each cycle for the first 4 cycles and every 12 weeks thereafter. After the first cycle, 65 of 375 patients on the IFN-α arm were assessed as having disease progression or died, compared to 39 of 375 patients on the SUTENT arm. Patients were treated until disease progression or withdrawal from the study for another reason.

The ITT population for this interim analysis included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. There were 15 patients randomized to the IFN-α arm who withdrew consent prior to starting the treatment; therefore, the AT population included 375 randomized to SUTENT and 360 randomized to IFN-α. Histological evaluation demonstrated that 90% of the enrolled MRCC patients in both treatment arms had clear cell histology. Baseline age, gender, race, and ECOG performance status were comparable and balanced between the SUTENT and IFN-α groups. Demographics and patient characteristics are shown in Table 9. The most common site of metastases present at screening was the lung (78% versus 80%, respectively), followed by the lymph nodes (58% versus 53%, respectively), and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% versus 77%, respectively).

A planned interim analysis showed a statistically significant advantage for SUTENT over IFN-α in the primary endpoint of PFS, with PFS for SUTENT more than double that of IFN-α (47.3 versus 22.0 weeks, respectively). Due to concerns that the overall survival results may have been influenced by results for patients randomized to the IFN-α arm who were assessed as experiencing disease progression or death prior to reaching the 9 MU dose (see previous page), an additional analysis was performed in which patients who had disease progression or died during Cycle 1 were not included. Results of this analysis also demonstrated a statistically significant difference in PFS between the two treatment groups (HR=0.343, 95% CI: 0.24-0.48, p<0.0001). The median PFS estimates were 48.3 versus 31.3 weeks for SUTENT and IFN-α arms, respectively.

The secondary endpoint of ORR was more than 4 times higher for SUTENT than IFN-α (27.5% versus 5.3%, respectively). Data were not mature enough to determine the overall survival benefit; at the time of this analysis, 374 of 750 patients enrolled (50%) continued on study, 248/375 (66%) on the SUTENT arm and 126/375 (34%) on the IFN-α arm. Efficacy results are summarized in Table 10 and the Kaplan-Meier curve for PFS is shown in Figure 2. The results were similar in the supportive analyses and they were robust when controlling for demographic (age, gender, race and performance status) and known risk factors.
Carcinogenesis and Mutagenesis: Carcinogenicity studies with sunitinib have not been performed. Sunitinib has been tested for genotoxicity in a series of in vitro assays (bacterial mutation, human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test and did not cause genetic damage.

Cardiovascular
Hypertension: Blood pressure was monitored on a routine basis in the clinical studies. In the treatment-naïve study, one patient was discontinued due to treatment-related grade 4 hypertension.

Treatment-related hypertension was reported in approximately 24% of patients receiving SUTENT for treatment-naïve MRCC compared to 1% of patients receiving interferon-alfa (IFN-α). Severe hypertension (>200 mmHg systolic or >110 mmHg diastolic) occurred in 5% of treatment-naïve patients on SUTENT and 1% of patients on IFN-α. In the cytokine-refractory metastatic RCC (MRCC) trials, hypertension (all grades) was reported as an adverse event in 47/169 (28%) patients on SUTENT. Hypertension (>150 mmHg systolic or >100 mmHg diastolic) occurred at least once during the study for 86/165 (52%) patients on SUTENT; severe hypertension (>200 mmHg systolic or >110 mmHg diastolic) occurred in 10/165 (6%) patients on SUTENT. SUTENT dosing was delayed or reduced due to hypertension in 8/165 (4.9%) cytokine-refractory MRCC patients.

Patients should be monitored for hypertension and treated as appropriate with standard antihypertensive therapy. Temporary suspension of SUTENT is recommended in patients with severe hypertension. Treatment may be resumed once hypertension is controlled. Patients with hypertension that is not controlled by medications should not be treated with SUTENT.

Left Ventricular Dysfunction: Decreases in left ventricular ejection fraction (LVEF) of ≥20% and below the lower limit of normal (LLN) occurred in approximately 4% of SUTENT-treated cytokine-refractory MRCC patients and 2% of placebo-treated patients.

In the treatment-naïve MRCC study, 21% and 12% of patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. One (<1%) patient who received SUTENT was diagnosed with congestive heart failure (CHF).

In cytokine-refractory MRCC Studies 1 and 2, a total of 24 patients (14%) had treatment-emergent LVEF values below the LLN. Five (5) of 24 patients on SUTENT with LVEF changes recovered without intervention. Five (5) patients had documented LVEF recovery following intervention (dose reduction- 3 patients, addition of antihypertensive or diuretic medications- 2 patients). Eight (8) patients went off study without documented recovery and 6 patients are ongoing on study without recovery.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug.

These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

In the presence of clinical manifestations of CHF, discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and/or >20% below baseline.

QT Interval Prolongation: There is clinical evidence that SUTENT prolongs QT interval, PR interval, and decreases the heart rate. Patients with Qtc interval prolongation, atrioventricular (AV) block, and those taking concomitant drugs with dysrhythmic potential were excluded from the pivotal trials, therefore there is no information regarding safety of SUTENT therapy in this group. Because excessive prolongation of the PR interval can result in AV block, caution should be used if SUTENT is prescribed to patients in combination with other drugs that also cause PR interval prolongation, such as beta-blockers, calcium channel blockers, digitalis, or HIV protease inhibitors.

Pre-clinical data (in vitro and in vivo) demonstrate SUTENT causes QT interval prolongation.

Particular care should be exercised when administering SUTENT to patients who are at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug, or who are taking concomitant drugs with potential to cause QTc interval prolongation (see DRUG INTERACTIONS section). Bradycardia and AV block are recognized risk factors for torsade de pointes. For this reason, because SUTENT causes Qtc prolongation in association with prolongation of the PR and RR intervals, this raises particular concern with respect to proarrhythmic potential. QT interval prolongation may lead to an increased risk of torsade de pointes.

Torsade de pointes has been observed in <0.1% of SUTENT-exposed patients. SUTENT therapy should be discontinued if symptoms suggestive of arrhythmia occur.

Venous Thromboembolic Events/ Pulmonary Embolism: Seven (2%) patients receiving SUTENT for treatment-naïve MRCC and 4 (2%) patients on the 2 cytokine-refractory MRCC studies had venous thromboembolic events reported. Six (6) of these patients had pulmonary embolism, 1 was Grade 3 and 5 were Grade 4. Five (5) patients had DVT, 1 each with Grade 1 and 4, and 3 with Grade 3. Dose interruption occurred in 1 of these cases. In treatment-naïve MRCC patients receiving IFN-α, 6 (2%) venous thromboembolic events occurred; 1 patient (<1%) experienced a Grade 3 DVT and 5 patients (1%) had pulmonary embolism, 1 Grade 1 and 4 with Grade 4.

Other Cardiovascular Warnings: Two (2) patients with treatment-naïve MRCC experienced myocardial infarction (1 Grade 2 and 1 Grade 3), while 1 patient had Grade 3 myocardial ischemia. Two (2) patients with cytokine-refractory MRCC experienced Grade 3 myocardial ischemia, 1 had Grade 2 "cardiovascular toxicity" reported as an adverse event and 1 patient experienced a fatal myocardial infarction while on treatment.

Drug-Drug Interactions: Sunitinib is metabolized primarily by CYP3A4. Potential interactions may occur with drugs that are inhibitors or inducers of this enzyme system (see DRUG INTERACTIONS).

Endocrine and Metabolism
Adrenal Function Effects: Adrenal toxicity was noted in pre-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 1.1 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT or MRI scanning performed on 336 patients treated with SUTENT demonstrated no evidence of adrenal gland hemorrhage or necrosis. ACHT stimulation testing was conducted in over 400 patients across multiple clinical trials of SUTENT. In the cytokine-refractory MRCC studies, 28 patients with normal baseline testing had abnormalities at post-baseline testing and 3 patients had a treatment-emergent adverse event of adrenal insufficiency, which were not considered by the investigator to be related to SUTENT.

Patients treated with SUTENT should be monitored for adrenal insufficiency when they experience stress such as surgery, trauma, or severe infection.

Hypothyroidism: Although not prospectively studied in clinical trials, hypothyroidism was reported as an adverse event in 2% of patients on SUTENT in the treatment-naïve MRCC study and one patient (<1%) in the IFN-α arm, and in 4% of patients across the two cytokine-refractory MRCC studies. Additionally, TSH elevations were reported in 2% of cytokine-refractory MRCC patients. Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism.

Patients with symptoms suggestive of hypothyroidism, such as fatigue, should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Gastrointestinal
Gastrointestinal Perforation: Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, (likely linked to tumour necrosis) have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Hemorrhage: In patients receiving SUTENT for treatment-naïve MRCC, 28% of patients had bleeding events compared with 7% of patients receiving IFN-α. Seven (1.9%) patients on SUTENT versus 0% of patients on IFN-α experienced Grade 3 or greater treatment-related bleeding events.

Bleeding events occurred in 50/169 (26%) patients receiving SUTENT for cytokine-refractory MRCC. Most events in cytokine-refractory MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). Two (2) cytokine-refractory MRCC study patients with pulmonary metastases experienced hemoptysis considered to be related to SUTENT administration.

Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC patients included rectal, gingival, upper GI, genital and wound bleeding.

Treatment-related tumour hemorrhage has been observed in patients receiving SUTENT. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening hemorrhage or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT in a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC.

Routine assessment of this event should include serial complete blood counts (CBCs) and physical examination.

Hematologic Events: Decreased absolute neutrophil counts of Grade 3 and 4 severity were reported in 13.1% and 0.9% patients, respectively. Decreased platelet counts of grade 3 and 4 severity were reported in 4% and 0.5% of patients respectively. The
above events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT. Supportive care for hematologic events may include colony stimulating factors. **Hepatic/Biliary/Pancreatic** In patients with treatment-naïve MRCC, Grade 3 or 4 increases in amylase and lipase have been observed in 5% and 16% of SUTENT-treated patients and in 3% and 6% of patients receiving IFN-α. In the cytokine-refractory MRCC studies, grade 3 or 4 increases in amylase and lipase have been observed in 4.8% and 16.9% of SUTENT-treated patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects receiving SUTENT for MRCC. Pancreatitis was observed in 2 solid tumour patients (0.4%). Hepatic failure was observed in <1% of solid tumour patients treated with SUTENT. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued and be provided with appropriate medical care. **Neurologic** Seizures: SUTENT has not been studied in patients with known brain metastases. In clinical studies of SUTENT, seizures have been observed in <1% of subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypotension, headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Discontinuation of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician, although the evidence to support this recommendation (restoring treatment) is extremely limited. **Skin and Tissues**: Skin discoloration, possibly due to the active substance colour (yellow) is a common treatment-related adverse event occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUTENT. Other possible dermatologic effects (including events associated with the underlying disease) leading to discontinuation of SUTENT versus those on IFN-α. The most common Grade 3 chemistry abnormalities observed on both SUTENT and IFN-α in the randomized clinical trial in patients with treatment-naïve MRCC. Most adverse events are reversible and do not need to result in discontinuation. If necessary, these events can be managed through dose adjustments or interruptions. **ADVERSE REACTIONS** **Overview**: Two thousand, two hundred and eight (2208) patients with solid tumours, including 927 (42%) patients with MRCC, have been treated with SUTENT (sunitinib malate) in 25 completed and ongoing clinical trials. Most of these patients received SUTENT (sunitinib malate) once daily as a 50-mg oral capsule, as a starting dose, on Schedule 4/2. Three hundred and sixty (360) patients received IFN-α in the treatment-naïve MRCC. Most adverse events are reversible and do not need to result in discontinuation. If necessary, these events can be managed through dose adjustments or interruptions. **Table 1: Treatment-Related Adverse Events Reported in at least 10% of Patients with Treatment-Naïve MRCC Who Received SUTENT or IFN-α**

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades</strong></td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>357 (92.5)</td>
<td>206 (54.9)</td>
</tr>
<tr>
<td></td>
<td>329 (91.4)</td>
<td>113 (31.4)</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (1.2)</td>
<td>25 (6.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51 (13.6)</td>
<td>25 (6.9)</td>
</tr>
<tr>
<td></td>
<td>5 (1.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>9 (2.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Table 2: Treatment-Emergent Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve MRCC Patients Who Received SUTENT or IFN-α**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades</strong></td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>AST</td>
<td>195 (52)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>171 (46)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>196 (52)</td>
<td>60 (16)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>156 (42)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>118 (31)</td>
<td>19 (5)</td>
</tr>
<tr>
<td></td>
<td>15 (1.4)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td></td>
<td>9 (2.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**In the treatment-naïve MRCC study, 20 (17%) versus 14 patients (10%) experienced treatment-emergent Grade 4 chemistry laboratory abnormalities on SUTENT versus IFN-α, respectively. The most common Grade 4 chemistry abnormalities were hyperuricemia (12% on SUTENT, 8% on IFN-α) and increased lipase (3% on SUTENT, 1% on IFN-α). The most common Grade 3 chemistry abnormalities observed on both arms were increased lipase (13% on SUTENT, 5% on IFN-α) and hypophosphatemia (4% on SUTENT, 6% on IFN-α). Other common Grade 3 laboratory abnormalities on SUTENT were hyponatraemia (5%) and increased amylase (4%), and on IFN-α was hyperglycaemia (6%). Hematologic laboratory abnormalities are presented in Table 2.**
### Renal/Metabolic

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>246 (66)</td>
<td>175 (49)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>155 (41)</td>
<td>112 (31)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>152 (41)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>134 (36)</td>
<td>115 (32)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>132 (35)</td>
<td>133 (37)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>73 (19)</td>
<td>54 (15)</td>
</tr>
<tr>
<td>Albumin</td>
<td>68 (18)</td>
<td>67 (19)</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>58 (15)</td>
<td>49 (14)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>51 (14)</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>42 (11)</td>
<td>54 (15)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>40 (11)</td>
<td>35 (10)</td>
</tr>
</tbody>
</table>

**Hematology**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>271 (72)</td>
<td>166 (46)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>266 (71)</td>
<td>232 (64)</td>
</tr>
<tr>
<td>Platelets</td>
<td>244 (65)</td>
<td>77 (21)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>223 (59)</td>
<td>227 (63)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>292 (78)</td>
<td>202 (56)</td>
</tr>
</tbody>
</table>

### Cytokine-Refractory MRCC

The data described below reflect exposure to SUTENT in 169 patients with cytokine-refractory MRCC enrolled in Studies 1 and 2. The median duration of treatment was 5.5 months (range: 23 days to 11.2 months) for Study 1 and 7.9 months (range: 6 days to 1.3 years) for Study 2. Dose interruptions occurred in 48 patients (45%) on Study 1 and 45 patients (71%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. Permanent discontinuation from the study due to treatment-related adverse events occurred in 7 patients (8%) on Study 1 and 6 patients (10%) on Study 2. Treatment-related adverse events are presented by maximum severity grade for at least 10% of the MRCC patient population in Table 3. Treatment-related adverse events were experienced by nearly all of the patients with MRCC. Fatigue, gastrointestinal disorders, such as nausea, diarrhea, stomatitis, dyspepsia, vomiting and constipation, dysgeusia; skin discoloration; anorexia and rash were the most common treatment-related adverse events (experienced by at least 20% of the patients). The relative frequency of the most common all-causality adverse events occurred in 7 patients (8%) on Study 1 and 6 patients (10%) on Study 2. Dose interruptions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. Permanent discontinuation from the study due to treatment-related adverse events occurred in 7 patients (8%) on Study 1 and 6 patients (10%) on Study 2. Treatment-related adverse events are presented by maximum severity grade for at least 10% of the MRCC patient population in Table 3.

#### Laboratory Test

<table>
<thead>
<tr>
<th>Total Bilirubin</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (11.8)</td>
<td>105 (62.1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Gastrointestinal

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>125 (74.0)</td>
<td>12 (7.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>99 (58.6)</td>
<td>33 (19.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>99 (58.6)</td>
<td>25 (14.8)</td>
</tr>
</tbody>
</table>

### Hematology

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>47 (27.8)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47 (27.8)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>65 (38.5)</td>
<td>31 (20.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>68 (40.2)</td>
<td>9 (5.3)</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorder

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in extremity</td>
<td>21 (12.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>105 (62.1%)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Dysestesia</td>
<td>71 (42.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (14.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>17 (10.1)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>40 (23.7)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>122 (72.2)</td>
<td>12 (7.1)</td>
</tr>
</tbody>
</table>

### Cardiovascular

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>47 (27.8)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

### Pulmonary Embolism

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
</tbody>
</table>

### Pancreatic Function

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
</tbody>
</table>

### Seizures

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
</tbody>
</table>

### Hypothyroidism

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
</tbody>
</table>

### Other Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1-4, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>116 (68.6)</td>
<td>22 (13.0)</td>
</tr>
</tbody>
</table>

### Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably
estimate their frequency or establish a causal relationship to drug exposure. Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. Rare cases of myopathy and/or rhabdomyolysis, some with acute renal failure, have been reported. Most of these patients had pre-existing risk factors and/or were receiving concomitant medications known to be associated with these adverse reactions. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice. (See WARNINGS AND PRECAUTIONS section)

DRUG INTERACTIONS

Overview: Sunitinib is metabolized primarily by CYP3A4. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme system.

Drug-Drug Interactions

CYP3A4 Inhibitors: Co-administration of SUTENT (sunitinib malate) with inhibitors of the CYP3A4 family may increase SUTENT concentrations. Concomitant administration of SUTENT with CYP3A4 inhibitors should be avoided. These include, but are not limited to: non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil); antifungals (e.g., ketoconazole, fluconazole, itraconazole, voriconazole); macrolide antibiotics (e.g., erythromycin, clarithromycin, telithromycin); fluoroquinolone antibiotics (e.g., ciprofloxacin, norfloxacin); and some HIV antivirals (e.g., ritonavir, indinavir).

CYP3A4 Inducers: Co-administration of SUTENT with inducers of the CYP3A4 family may decrease SUTENT concentrations. Concomitant administration of SUTENT with CYP3A4 inducers should be avoided. CYP3A4 inducers include but are not limited to: barbiturates (e.g., phenobarbital); anticonvulsants (e.g., carbamazepine, phenytoin); rifampin; glucocorticoids; pimozide; and some HIV antivirals (e.g., efavirenz, nevirapine).

Drugs Which Prolong the QT/QTc Interval: The concomitant use of SUTENT with another QT/QTc-prolonging drug is discouraged. However, if it is necessary, particular care should be used. Drugs that have been associated with QT/QTc prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/herbal compositions, other drugs, and foods known or thought to cause QT/QTc prolongation should be avoided.

- Antiarrhythmics (Class IA, e.g., quinidine, procainamide, disopyramide; Class III, e.g., amiodarone, sotalol, ibutilide, Class IC, e.g., flecainide, propafenone)
- Antipsychotics (e.g., thioridazine, chlorpromazine, pimozide, haloperidol, droperidol)
- Antidepressants (e.g., amitriptyline, imipramine, maprotiline, fluoxetine, venlafaxine)
- Opioids (e.g., methadone)
- Macrolide antibiotics (e.g., erythromycin, clarithromycin, telithromycin)
- Quinoline antibiotics (e.g., moxifloxacin, gatifloxacin, ciprofloxacin)
- Antimalariais (e.g., quinine)
- Pentamidine
- Azoic antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- Gastrointestinal drugs (e.g., domperidone, 5HT3 antagonists, such as granisetron, ondansetron, dolasetron)
- Beta-2-adrenoceptor agonists (e.g., salmeterol, formoterol)
- Tacrolimus

Drugs Which Prolong the PR Interval: Caution should be used if SUTENT is prescribed to patients in combination with other drugs that also cause PR interval prolongation, such as beta blockers, calcium channel blockers, digitals, or HIV protease inhibitors (See WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation). The above list of potentially interacting drugs is not comprehensive. Current scientific literature should be consulted for more information.

Drug-Food Interactions: Grapefruit juice has CYP3A4 inhibitory activity. Therefore, ingestion of grapefruit juice while on SUTENT therapy may lead to decreased SUTENT metabolism and increased SUTENT plasma concentrations (see Drug-Drug Interactions). Concomitant administration of SUTENT with grapefruit juice should be avoided.

Drug-Herb Interactions: St. John’s Wort is a potent CYP3A4 inducer. Co-administration with SUTENT may lead to increased SUTENT metabolism and decreased SUTENT plasma concentrations (see Drug-Drug Interactions). Patients receiving SUTENT should not take St. John’s Wort concomitantly. To report an adverse event, please contact: your physician, pharmacist or Pfizer Medical Information: 1-800-463-8001.

Administration

DOSAGE AND ADMINISTRATION: The recommended dose of SUTENT (sunitinib malate) is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. SUTENT may be taken with or without food.

Dose Modification: Daily doses should not exceed 50 mg nor be decreased below 25 mg. Dose modification of 12.5 mg is recommended based on individual safety and tolerability.

CYP3A4 Inhibitors: Concurrent administration of sunitinib malate with the CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in combined (sunitinib + active metabolite) C\textsubscript{max} and AUC\textsubscript{0-∞} values, respectively, after a single dose of sunitinib malate in healthy volunteers. Doses of SUTENT may need to be reduced to a minimum of 25 mg daily, and clinical response and tolerability should be carefully monitored, in patients receiving a potent CYP3A4 inhibitor such as ketoconazole (see DRUG INTERACTIONS). Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential should be considered. NOTE: This recommendation is based on pharmacokinetic data from healthy volunteers. In clinical trials conducted to date, the safety and efficacy of SUTENT with concomitant use of CYP3A4 inhibitors has not been established. In the 2 cytokine-redirectory MRCC studies, 14 of the 169 patients used a potent CYP3A4 inhibitor concomitantly with SUTENT with no modification of the starting dose of SUTENT.

CYP3A4 Inducers: Concurrent administration of sunitinib malate with the potent CYP3A4 inducer, rifampin, resulted in a more than 23% and 45% reduction in Terminal half-life of (sunitinib + active metabolite) C\textsubscript{max} and AUC\textsubscript{0-∞} values, respectively, after a single dose of SUTENT in healthy volunteers. The dose of SUTENT may need to be increased (maximum 50 mg), and clinical response and tolerability should be carefully monitored, in patients receiving SUTENT with a potent CYP3A4 inducer, such as rifampin (see DRUG INTERACTIONS). Selection of an alternate concomitant medication with no or minimal enzyme induction potential should be considered. NOTE: This recommendation is based on pharmacokinetic data from healthy volunteers. In clinical trials conducted to date, the safety and efficacy of SUTENT with concomitant use of CYP3A4 inducers has not been established. In the two cytokine-redirectory MRCC studies, 33 of the 169 patients received a potent CYP3A4 inducer concomitantly with SUTENT with no modification of the starting dose of SUTENT.

Special Populations: No dose adjustment is required on the basis of patient age, body weight, creatine clearance, race, gender or ECQG score.

OVERDOSAGE: No overdose of SUTENT (sunitinib malate) was reported in completed clinical studies. Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage.

References:

SUPPLEMENTAL PRODUCT INFORMATION

Product Monograph available on request.

Patients receiving therapy with SUTENT should be monitored by a qualified physician experienced in the use of anti-cancer agents.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid pregnancy. Patients who presented with cardiac events, pulmonary embolism or cerebrovascular events within the previous 12 months were excluded from clinical studies. It is unknown whether patients with these concomitant conditions may be at higher risk of developing drug-related left ventricular dysfunction. These patients should be carefully monitored for clinical signs and symptoms of congestive heart failure while receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

In the presence of clinical manifestations of congestive heart failure, discontinuation of SUTENT is recommended.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsade de pointes, which has been seen in <0.1% of patients.

Hemorrhagic events including tumour-related hemorrhage have occurred. Perform serial complete blood counts (CBCs) and physical examinations.

Hypothyroidism may occur. Monitor thyroid function in patients with signs and symptoms of hypothyroidism and treat per standard medical practice.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection.

CBCs and serum chemistries should be performed at the beginning of each treatment cycle.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common grade 3/4 lab abnormalities occurring in ≥8% of patients receiving SUTENT (vs. IFNα) included hyperuricemia (12% vs. 8%) and lipase (13% vs. 5%). Grade 3 hematology lab abnormalities included neutropenia (11% vs. 7%), lymphopenia (12% vs. 22%), and thrombocytopenia (8% vs. 0%).

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