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New Evidence in Oncology is a publication for Canadian healthcare professionals in the field of oncology. Our journal provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice.

Our August 2010 issue presents coverage from two important international conferences: the 2010 ASCO Annual Meeting, held in Chicago, Illinois, from June 4–8, 2010; and the EHA Annual Congress, held in Barcelona, Spain, from June 10–13, 2010. The issue reports on important data from the PRIMA study investigating rituximab maintenance therapy in follicular lymphoma patients after response to front-line immunochemotherapy. New strategies and treatments for NHL and CLL are also discussed.

We would like to thank Dr. Silvy Lachance, Dr. David Macdonald, and Dr. Laurie H. Sehn for their Canadian perspectives; and Dr. Gilles Salles for his two investigator commentaries.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research. Slide presentations on various topics are available for download.
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- Oral green tea extract in patients with asymptomatic early stage chronic lymphocytic leukemia (Shanafelt TD, et al. ASCO 2010: Abstract 6522)

*Investigator Commentary*

An Interview with Dr. Gilles Salles on a Phase II Study of GA101 in Relapsed/Refractory NHL
Silvy Lachance, MD, FRCPC, CSPQ

Dr. Silvy Lachance is currently a hematologist, clinical researcher, and Director of the Stem Cell Transplant Program at the Maisonneuve-Rosement Hospital in Montreal, Quebec, and Professor of Medicine and Director of the Fellowship Program in Stem Cell Transplantation at the University of Montreal. In 1995, Dr. Lachance established the first Stem Cell Transplant Unit at the University Health Centre (CUSE) in Sherbrooke, Quebec. She joined the Hematology and Oncology Division of the Montreal General Hospital as a transplant physician in 1997 and became an Associate Professor of Medicine at McGill University in 2005, holding both positions until 2006. Dr. Lachance has served as chair of the Continuing Medical Education Committee of the Quebec Association of Hematologists and Oncologists, and is currently treasurer of the executive committee. She has also served as chair of the jury for the hematology specialty exam board of the Collège des Médecins du Québec (CMQ). Her research interests include stem cell transplant, graft-versus-host-disease, and lymphoproliferative disorders.

David Macdonald, MD, FRCPC

Dr. David Macdonald is a hematologist at the QEII Health Sciences Centre in Halifax, Nova Scotia, and Assistant Professor in the Division of Hematology at Dalhousie University’s Faculty of Medicine. Dr. Macdonald chairs the Hematology Cancer Site Team for Cancer Care Nova Scotia. His interests are in hematologic malignancies and, in particular, lymphoproliferative disorders. He has done a Clinical Trials Fellowship with the National Cancer Institute of Canada – Clinical Trials Groups and is actively engaged in clinical trials research. Dr. Macdonald has also completed a clinical fellowship in the lymphoma group at the British Columbia Cancer Agency in Vancouver, and he maintains a clinical research program in lymphoma.
Laurie H. Sehn, MD, MPH

Dr. Laurie H. Sehn is a Clinical Assistant Professor at the BC Cancer Agency and the University of British Columbia in Vancouver. She has been a medical oncologist and clinical investigator with the Lymphoma Tumour Group since 1998. Dr. Sehn has served on the Board of Directors of the Lymphoma Foundation Canada (LFC) since 2002 and is currently the Director of Research Fellowships for the LFC. Dr. Sehn’s research interests include all of the lymphoid cancers, with particular interest in the biology and treatment of large-cell lymphoma, the application of new imaging techniques such as PET scanning to lymphoma management, and innovative new approaches to treatment.

Investigator Commentaries

Gilles Salles, MD

Dr. Gilles Salles is a Professor in the Department of Hematology at the Centre Hospitalier Lyon-Sud, Lyon, France, and Head of the Research Unit Pathologie des Cellules Lymphoïdes at the University of Lyon. He served as Chairman of the Scientific Committee of GELA (Groupe d’Etude des Lymphomes de l’Adulte) until 2007 and is presently acting as vice-president of this group. He is also a member of several professional societies, including the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association. Professor Salles has been especially interested in the clinical and biological study of malignant lymphoma, and major focuses of his work include the description and validation of prognostic factors as well as clinical trials in indolent lymphomas. He has been involved as a coordinator or co-investigator in many clinical trials and studies within his field, and has published numerous articles in international peer-reviewed journals.
This issue of *New Evidence in Oncology* reports on findings from a number of key presentations given at two important medical conferences: the American Society of Clinical Oncology (ASCO) Annual Meeting, held in Chicago, Illinois, from June 4–8, 2010; and the European Hematology Association (EHA) Annual Congress, held in Barcelona, Spain, from June 10–13, 2010.

The ASCO Annual Meeting, attended by over 30,000 oncology professionals, is the leading scientific and educational forum for the presentation of the most current research in cancer treatment and care. The theme of the 2010 Annual Meeting was “Advancing Quality through Innovation.” The EHA Annual Congress, organized every June in a major European city, is the premier gathering of European hematologists. The Congress showcases the latest research in clinical, laboratory, and oncological hematology, as well as presents a major educational program for clinicians and hematologists-in-training.

In this report, *New Evidence* features a summary of data from the PRIMA study on the use of rituximab maintenance therapy in follicular lymphoma patients after response to front-line immunochemotherapy, followed by an interview with principal investigator Dr. Gilles Salles. New rituximab-chemotherapy combinations, improving patient outcomes and quality of life, and reducing toxicity in the treatment of NHL are also discussed. In CLL, studies identifying important prognostic markers and confirming FCR as the recommended first-line treatment in fit patients are examined. Other articles focus on promising new agents and chemotherapy combinations in NHL and CLL, such as GA101, navitoclax, and lenalidomide.
Rituximab Maintenance Therapy and New R-Chemo Combinations in the Treatment of Follicular Lymphoma

Lymphoid malignancies are among the cancers seen most frequently in Canada, of which follicular lymphoma (FL) is the most common subtype.\(^1\) Although FL is considered incurable, the development of treatment regimens that add rituximab to chemotherapy (R-chemo) has significantly improved progression-free survival (PFS), overall response (OR), and complete response (CR) rates in patients with this disease. R-chemo is now considered the standard treatment in FL.\(^2\) Based on the success of rituximab in FL, new R-chemo combinations and maintenance treatment with rituximab monotherapy (R-maintenance) are being examined in a number of ongoing clinical trials.

R-maintenance has demonstrated significant clinical benefit in patients relapsing after chemotherapy or R-chemo and in first-line patients after chemotherapy or rituximab monotherapy.\(^2\) Based on the positive results of these studies, R-maintenance is now being examined after induction treatment with R-chemo in the PRIMA study, a Groupe d’Étude des Lymphomes de l’Adulte (GELA)-sponsored intergroup phase III study. Studies are also examining the efficacy of R-maintenance versus observation post-autograft transplant. Based on the success of R-maintenance, many oncology settings in Canada and the U.S. have adopted this treatment strategy in FL.

The success of R-chemo in FL has led to the development of a number of new combination regimens in FL. Studies are examining the addition of rituximab to mitoxantrone, chlorambucil, and prednisolone (R-MCP); chlorambucil (R-chlorambucil); and lenalidomide (R-lenalidomide) in an effort to improve the efficacy and tolerability of treatment in FL.

Data from several of these studies were presented at ASCO 2010 and EHA 2010. This article reports on one study presented at both EHA and ASCO, three studies presented at EHA, and two studies presented at ASCO:

• The PRIMA study, presented at both EHA 2010 and ASCO 2010, demonstrated that two years of R-maintenance therapy after induction immunochemotherapy in previously untreated FL patients significantly improves PFS, with little additional toxicity.

• Results of a study presented at ASCO 2010 showed that peri-autograft rituximab in vivo purging and/or two-year R-maintenance post-autograft improves PFS in relapsed/resistant FL patients, compared to no rituximab.

• A phase III study presented at EHA 2010 demonstrated that R-MCP significantly improves response rates, PFS, and event-free survival (EFS) in patients with advanced FL, compared to MCP alone.

• Preliminary results of a phase II study presented at EHA 2010 showed that R-chlorambucil is a safe and promising new treatment regimen in untreated FL.

• A phase II study presented at ASCO 2010 showed that R-lenalidomide produces good OR and CR rates, and is well-tolerated in patients with untreated indolent B-cell NHL.

Rituximab maintenance in patients with follicular lymphoma after response to immunochemotherapy (PRIMA)

(Note: See the interview with Dr. Gilles Salles on page 31 for his commentary on this study.)

Background
The PRIMA study is a Groupe d’Étude des Lymphomes de L’Adulte (GELA)-sponsored intergroup phase III study investigating the efficacy of two years of rituximab maintenance treatment in patients with follicular lymphoma (FL) responding to first-line immunochemotherapy. Salles and colleagues presented results of the PRIMA study at ASCO 2010 and EHA 2010.1,2

Study design
• A total of 1,217 patients were enrolled in the study from 223 centers (25 countries) between December 2004 and April 2007.
• Patients received induction treatment with R-CHOP (75%), R-CVP (22%), or R-FCM (3%).
• Eligible patients responding to induction therapy (n = 1,018) were randomized (after stratification by regimen and response to induction) to:
  ◦ observation (n = 513);
  ◦ rituximab maintenance (R-maintenance) treatment with 375 mg/m² of rituximab every 8 weeks for 2 years (n = 505).
• The primary endpoint was progression-free survival (PFS) from randomization to rituximab maintenance or observation.
• Secondary endpoints included event-free survival (EFS), overall survival (OS), time to next anti-lymphoma treatment (TTNLT), time to next chemotherapy (TTNCT), response rates at the end of maintenance, safety and toxicity, and quality of life (QoL) using FACT-G and EORTC scales.
• Sample size was based on a 45% increase in median PFS, with a power of 80% to detect this difference.
• Interim analysis was planned after 258 events and a full analysis after 344 events.

Inclusion and exclusion criteria
• Patients included in the study were aged >18 years with previously untreated, histologically confirmed grades 1, 2, or 3a FL.
• Included patients had an Eastern Clinical Oncology Group (ECOG) performance status <2, with symptoms of FL indicating treatment.
• Patients were excluded if they had:
  ◦ transformed to high-grade lymphoma or grade 3b follicular lymphoma;
  ◦ regular corticosteroid use during the last four weeks (>20 mg/day prednisone);
  ◦ prior or concomitant malignancies;
  ◦ serious underlying medical conditions, poor renal, or poor hepatic function;
  ◦ HIV infection, active HBV, or HCV infection;
  ◦ sensitivity or allergy to murine products.
Key findings

- The primary endpoint of PFS was met at the planned interim analysis (intent to treat [ITT]: 513 observation, 505 rituximab maintenance).
- Median follow-up was 25 months from randomization (31 months from study entry).
- Median age of patients was 56 years (range 22–87 years), and 52% were male.
- Baseline characteristics and response to induction treatment were comparable across R-maintenance and observation groups.
- A significant improvement in PFS for R-maintenance was observed (two-year PFS 82%; 95% CI: 78–86 versus 66%; 95% CI: 61–70; p <0.0001). (Figure 1)

Figure 1. Progression-free survival after rituximab maintenance versus observation in FL patients

Figure 2. Progression-free survival in age, FLIPI score, induction chemotherapy, and response to induction subgroups after rituximab maintenance versus observation

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>Hazard ratio (HR)</th>
<th>N</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td></td>
<td>1018</td>
<td>0.49</td>
<td>0.38–0.64</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60</td>
<td></td>
<td>624</td>
<td>0.45</td>
<td>0.33–0.62</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td></td>
<td>394</td>
<td>0.59</td>
<td>0.39–0.90</td>
</tr>
<tr>
<td>FLIPI score</td>
<td>FLIPI ≤1</td>
<td></td>
<td>216</td>
<td>0.38</td>
<td>0.19–0.77</td>
</tr>
<tr>
<td></td>
<td>FLIPI = 2</td>
<td></td>
<td>370</td>
<td>0.39</td>
<td>0.25–0.61</td>
</tr>
<tr>
<td></td>
<td>FLIPI ≥3</td>
<td></td>
<td>431</td>
<td>0.61</td>
<td>0.43–0.87</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>R-CHOP</td>
<td></td>
<td>768</td>
<td>0.43</td>
<td>0.31–0.59</td>
</tr>
<tr>
<td></td>
<td>R-CVP</td>
<td></td>
<td>222</td>
<td>0.69</td>
<td>0.44–1.08</td>
</tr>
<tr>
<td></td>
<td>R-FCM</td>
<td></td>
<td>28</td>
<td>0.51</td>
<td>0.13–2.07</td>
</tr>
<tr>
<td>Response to induction</td>
<td>CR/CRu</td>
<td></td>
<td>721</td>
<td>0.52</td>
<td>0.38–0.70</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td></td>
<td>290</td>
<td>0.45</td>
<td>0.29–0.72</td>
</tr>
</tbody>
</table>

*Non-stratified analysis

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CI = confidence interval; CR = complete response; CRu = unconfirmed complete response; CVP = cyclophosphamide, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone; FLIPI = follicular lymphoma international prognostic index; PR = partial response; R = rituximab
• An independent response review committee confirmed the significant improvement in PFS in the R-maintenance arm (HR 0.53; 95% CI: 0.41–0.68).

• Benefits of R-maintenance were shown in all subgroups including age (<60 versus ≥60 years), follicular lymphoma international prognostic index (FLIPI) score, induction treatment, and response to induction treatment. (Figure 2)

• A significant improvement in TNLT for R-maintenance was observed (HR 0.61; p = 0.0003). (Figure 3)

• Improvements in response rates for R-maintenance were observed (Table 1); consistent improvements in other secondary endpoints were also found, including EFS and TNCT rates (data not shown).

• Adverse events (AEs) were reported in 35% (observation) and 52% (R-maintenance) of patients.

• The most common AEs were infections (22% observation, 37% R-maintenance).

• Grade 3/4 AEs were reported in 16% (observation) and 23% (R-maintenance) of patients (neutropenia <1% versus 4%; infections <1% versus 4% in observation and R-maintenance groups, respectively).

• At the time of analysis, few patients withdrew for toxicity-related reasons during maintenance (1 patient in the observation arm, 10 patients in the R-maintenance arm).

• Most deaths occurring throughout the study were related to lymphoma (12/18 observation, 10/13 R-maintenance).

Table 1. Response status after rituximab maintenance versus observation in FL patients

<table>
<thead>
<tr>
<th>Response</th>
<th>Rituximab maintenance (n = 389)*</th>
<th>Observation (n = 398)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease (SD)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>28 (7.2)</td>
<td>29 (7.3)</td>
</tr>
<tr>
<td>Complete response (CR/CRu)</td>
<td>260 (66.8)</td>
<td>190 (47.7)</td>
</tr>
<tr>
<td>Remaining in CR/CRu</td>
<td>209 (75)*</td>
<td>153 (56)</td>
</tr>
<tr>
<td>Converting from PR/SD to CR/CRu</td>
<td>49 (45)</td>
<td>37 (30)</td>
</tr>
</tbody>
</table>

*Sixteen (16) patients were not evaluated, and 22 patients had missing data.
†Two patients were not evaluated in the rituximab maintenance arm

Key conclusions

■ The PRIMA study demonstrates that two years of rituximab maintenance therapy after induction immunochemotherapy in previously untreated FL patients significantly improves PFS with little additional toxicity.

■ Further follow-up will allow evaluation of a possible effect on overall survival.

■ R-chemo followed by two years of rituximab maintenance represents a new standard of care for FL patients in need of treatment and constitutes a new platform to further develop more efficient and well-tolerated strategies.

Rituximab in relapsed/resistant FL patients as in vivo purging prior to high-dose therapy and to maintain remission following high-dose therapy

**Background**

At ASCO 2010, Pettengell and colleagues presented results of their study evaluating the effects of in vivo purging with rituximab and maintenance rituximab in patients with relapsed follicular lymphoma (FL) undergoing high-dose therapy with BEAM (carmustine, etoposide, cytosine arabinoside, melphalan) conditioning.1

**Study design**

- From October 1999 to April 2006, 280 of a planned 420 patients with relapsed FL were included in the study.
- Patients in first (n = 16), second (n = 222), or third remission (n = 41) who achieved either a complete response (CR; n = 83) or a very good partial response (PR; n = 196) to induction chemotherapy were included.
- Patients underwent a single randomization in a 2 x 2 design to rituximab purging 375 mg/m² weekly x 4 (n = 72) and/or maintenance rituximab 375 mg/m² every 3 months for 2 years (n = 69), or no rituximab (n = 70).
- The primary objective was to evaluate the effects of in vivo purging with rituximab and maintenance rituximab on time to disease progression.
- Secondary outcomes included response rates (RRs), overall survival (OS), and safety.

**Inclusion and exclusion criteria**

- Patients with the following characteristics were included in the study:
  - rituximab-naïve patients with relapsed follicular non-Hodgkin’s lymphoma (NHL);
  - limited bone marrow infiltration (<25% B-lymphocytes);
  - one to two prior chemotherapy regimens;
  - CD20 positive disease;
  - CR or good PR following re-induction of chemotherapy;
  - good performance status;
  - pathological material for review and polymerase chain reaction (PCR);
  - no histological transformation, previous transplant, or extensive prior radiotherapy.

**Key findings**

**Baseline characteristics and disposition**

- No differences in baseline characteristics were found between treatment groups.
- A total of 87 patients withdrew from the study:
  - fifty-seven (57) patients as a result of failure to mobilize;
  - five patients due to serious adverse events (SAEs);
  - nine patients due to lack of compliance;
  - four patients due to withdrawal of consent;
  - one patient due to withdrawal by physician;
  - nine patients for other reasons.

![Diagram of study design](image-url)

**Legend**

- BEAM = carmustine, etoposide, cytosine arabinoside, melphalan; NHL = non-Hodgkin’s lymphoma; PBPC = peripheral blood progenitor cell
Efficacy

- Progression-free survival (PFS) at 5 years was 54.1% versus 48% for in vivo rituximab purging versus none (log rank PFS; \( p > 0.20; \) HR 0.81, 95% CI: 0.58–1.13).
- PFS at 5 years was 59.4% versus 42.0% in patients receiving maintenance rituximab versus none (log rank PFS; \( p = 0.01; \) HR 0.65, 95% CI: 0.46–0.90).
- PFS in the intent-to-treat (ITT) population is presented in Figure 1.

Safety

- The success of salvage therapy is reflected in an overall survival (OS) at 5 years of 80.0% (95% CI: 0.54–1.45).
- OS in the ITT population is presented in Figure 2.

Figure 1. Effect of purging and maintenance rituximab on progression-free survival in patients with relapsed follicular lymphoma

![5-year progression-free survival](image)

Figure 2. Effect of purging and maintenance rituximab on overall survival in patients with relapsed follicular lymphoma

![5-year overall survival](image)

Table 1. Cause of death in 37 transplanted patients with relapsed follicular lymphoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cause of death n (deaths in remission)</th>
<th>NHL</th>
<th>Treatment complication</th>
<th>Second malignancy</th>
<th>Other (GvHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No purging or maintenance</td>
<td></td>
<td>4</td>
<td>0</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Purging/no maintenance</td>
<td></td>
<td>6</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2</td>
</tr>
<tr>
<td>Maintenance/no purging</td>
<td></td>
<td>5</td>
<td>(1)</td>
<td>–</td>
<td>(1)</td>
</tr>
<tr>
<td>Purging and maintenance</td>
<td></td>
<td>3</td>
<td>1 (1)</td>
<td>(3)</td>
<td>(1)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>18</td>
<td>6 (3.0%)</td>
<td>8 (3.9%)</td>
<td>7 (3.4%)</td>
</tr>
</tbody>
</table>

GvHD = graft-versus-host disease; NHL = non-Hodgkin’s lymphoma

Key conclusions

- This study shows that peri-autograft, rituximab in vivo purging, and two-year maintenance rituximab post-autograft gives a superior progression-free survival compared to no rituximab.
- To date, there appears to be no plateau on the survival curve with rituximab maintenance treatment.
- Engraftment and hematopoietic recovery were not compromised; maintenance rituximab appeared to be safe in this setting.

**Background**

At EHA 2010, Herold and colleagues reported the sixty-month (five-year) follow-up results of their phase III study examining the efficacy and safety of MCP (mitoxantrone, chlorambucil, prednisolone) versus MCP plus rituximab (R-MCP) in indolent non-Hodgkin’s lymphoma (NHL) and mantle cell lymphoma (MCL) patients.\(^1\)

**Study design**

- Previously untreated patients with advanced stage, symptomatic CD20-positive indolent NHL and MCL (n = 358) were included in the original study.
- Only patients with follicular lymphoma (n = 201) were included in this analysis.
- Patients were randomized to receive either:
  - MCP (n = 96): mitoxantrone (8 mg/m\(^2\) on days 3 and 4), chlorambucil (3 x 3 mg/m\(^2\) on days 3–7), and prednisolone (25 mg/m\(^2\) on days 3–7) every four weeks;
  - R-MCP (n = 105): MCP (as above) plus rituximab (375 mg/m\(^2\) on day 1), followed by interferon maintenance treatment (3 x 4.5 million IU per week) for patients achieving a complete response (CR) or partial response (PR).
- Study endpoints included overall response (OR) and CR rates, progression free survival (PFS), event-free survival (EFS), time to next treatment (TTNT), overall survival (OS), and toxicities.

**Key findings**

**Baseline characteristics and disposition**

- Median age of patients was 60 years (range 33–78 years) in the R-MCP group and 57 years (range 31–76 years) in the MCP group.
- In the R-MCP group, 50.5% (53/105) of patients were male; in the MCP group, 38% (36/96) of patients were male.
- Follicular lymphoma international prognostic index (FLIPI) subgroups included 14, 75, and 112 patients in low-, medium-, and high-risk groups, respectively.
- Baseline characteristics were comparable between groups.

**Efficacy**

- OR and CR rates were higher in the R-MCP group (OR: 92.4%; CR: 49.5%) than in the MCP group (OR: 75%; CR: 25%) \((p<0.001)\).
- PFS was 65% (median 86 months) in the R-MCP group versus 33% (median 35 months) in the MCP group \((p<0.0001)\). (Figure 1)
- In the FLIPI intermediate-risk subgroup (FLIPI 2), PFS was 70% (median PFS not reached) in the R-MCP group versus 36% (median 37 months) in the MCP group \((p=0.0017)\).
- In the FLIPI high-risk subgroup (FLIPI 3), PFS was 63% (median 86 months) in the R-MCP group versus 30% (median 29 months) in the MCP group \((p=0.0001)\).
• EFS was 62% (median 86 months) in the R-MCP group versus 30% (median 27 months) in the MCP group (p < 0.0001).
• In the FLIPI intermediate-risk subgroup (FLIPI 2), EFS was 69% (median EFS not reached) in the R-MCP group versus 33% (median 29 months) in the MCP group (p = 0.0001).
• OS was 86% (median not reached) in the R-MCP group versus 74% (median 108 months) in the MCP group (p = 0.028). (Figure 2)
• In the FLIPI intermediate-risk subgroup (FLIPI 2), OS was 93% (median OS not reached) in the R-MCP group versus 91% (median 89 months) in the MCP group (p = 0.21).


Bassi S, et al. EHA 2010: Abstract 0277

Rituximab and chlorambucil as front-line treatment for follicular lymphoma

Background
At EHA 2010, Bassi and colleagues presented results of their study examining the combination of rituximab and chlorambucil (R-chlorambucil) in untreated follicular lymphoma (FL) patients.1

Study design
• Since November 2001, 58 patients (28 male and 30 female) with FL received R-chlorambucil as first-line treatment.

Patients were given the following treatment protocol:
• Induction phase: four weekly infusions of rituximab at 375 mg/m² and six consecutive weeks of chlorambucil at 6 mg/m² daily;
• Restaging phase: 8–10 weeks from beginning of treatment, patients were restaged;
• Maintenance phase: if there was no progressive disease, patients were given four monthly infusions of rituximab and 14 days of chlorambucil each month for four consecutive months.

Key conclusions
• Rituximab plus MCP was significantly superior to MCP alone in all endpoints.
• Further research is needed to determine the best rituximab-chemotherapy combination in the treatment of follicular lymphoma.

Figure 1. Progression-free survival after treatment with MCP or R-MCP in follicular lymphoma patients (median follow-up 60 months)

Figure 2. Overall survival after treatment with MCP or R-MCP in follicular lymphoma patients (median follow-up 60 months)
**Key findings**

**Baseline characteristics and disposition**

- Median age at diagnosis was 56 years (range 29–79 years).
- Ann Arbor stage was advanced (stage III–IV) in 44 patients (76%), and 16 patients (27%) presented an extra-nodal localization; only 9 patients (15%) were symptomatic.
- Histological grading was available for 52 patients (grade 1 in 13 patients, grade 2 in 33 patients, and grade 3 in 6 patients).
- Follicular lymphoma international prognostic index (FLIPI) score was evaluable in 55 patients, and 31 patients (53%) were at low risk.

**Efficacy**

- After the induction phase, overall response (OR) rate was 98%, with 15 patients achieving a complete response (CR) and 42 a partial response (PR). (Table 1)
- After the consolidation phase, 46 patients achieved a CR and 11 achieved PRs; one patient remained in stable disease. (Table 1)
- With a median observation time of 32 months (range 7–103 months) from diagnosis, 43 patients (74%) have maintained their response; 40 patients (69%) are still in CR.
- Thirteen (13) patients (22%) relapsed, with a median time to next treatment of 21 months (range 6–66 months).
- Three patients died during treatment:
  - One patient died because of lymphoma at 42 months from diagnosis.
  - Two patients died due to other causes.

**Safety**

- All except one patient completed all planned treatments.
- The mean daily dose of chlorambucil received during the induction phase was 10 mg, while in the prolonged treatment was 8 mg.
- Chlorambucil dose was reduced in 25 patients (43%) mainly in the prolonged phase because of neutropenia; chlorambucil treatment was stopped in only one patient for persistent grade 3 neutropenia after the first consolidation cycle.
- One hepatitis B surface antigen (HBsAg)-positive patient did not conclude the treatment because of aspartate aminotransferase (AST)/alanine transaminase (ALT) elevation.
- No late toxicity has been observed.

---

**Table 1. Response rates after first-line treatment with rituximab and chlorambucil in 58 patients with follicular lymphoma**

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>42</td>
<td>72</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Overall response (OR) rate</td>
<td>57</td>
<td>98</td>
</tr>
<tr>
<td><strong>Maintenance phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Overall response (OR) rate</td>
<td>57</td>
<td>98</td>
</tr>
</tbody>
</table>

*Subsequently underwent high dose and peripheral blood stem cell (PBSC) re-infusion

---

**Key conclusions**

- Preliminary results showed rituximab plus chlorambucil to be a safe and feasible combination in untreated FL patients.
- In terms of efficacy, clinical results were similar to those obtained with more aggressive therapy, but with a lower toxicity and an easier management.
- Combination with rituximab and chlorambucil may be considered a valid first-line therapy, especially in FL patients not eligible for more aggressive chemotherapy regimens.

Background
Preclinical models have shown that lenalidomide in combination with rituximab in the treatment of indolent non-Hodgkin’s lymphoma (NHL) results in enhanced cell death relative to treatment with either agent alone.1,2 At ASCO 2010, Fowler and colleagues presented results of their phase II study evaluating the efficacy and safety of lenalidomide plus rituximab in patients with untreated, stage III/IV, indolent NHL.3

Study design
• The study is a phase II, open-label, single-arm trial designed to enroll 110 patients in three cohorts:
  ◦ fifty (50) follicular lymphoma (FL) patients;
  ◦ thirty (30) marginal zone lymphoma (MZL) patients;
  ◦ thirty (30) chronic lymphocytic lymphoma (CLL)/small lymphocytic lymphoma (SLL) patients.
• Patients (>18 years) with the following criteria were included:
  ◦ measurable (>1.5 cm) untreated indolent NHL (stage III or IV);
  ◦ European Clinical Oncology Group (ECOG) performance status <2;
  ◦ absolute neutrophil count (ANC) ≥1.5 x 10⁶/L and platelets ≥100 x 10⁹/L;
  ◦ adequate hepatic and renal function;
  ◦ no prior exposure to lenalidomide, no known hypersensitivity to thalidomide, and no HIV or active hepatitis infection.
• Patients received lenalidomide (20 mg/day) on days 1–21 and rituximab (375 mg/m²) on day 1 of each 28 day cycle for up to 6 cycles.
  ◦ SLL patients received lenalidomide in escalating doses: 10 mg/day in cycle 1, 15 mg/day in cycle 2, and 20 mg/day in cycle 3.
• Primary objective was to evaluate the overall response (OR) rate.
• Secondary objectives included complete response (CR) and partial response (PR) rates, progression-free survival (PFS), and toxicity.
• Response was assessed after 3 and 6 cycles using the International Workshop for Lymphoma Response Criteria methodology.

Key findings
Baseline characteristics and disposition
• At this time, 74 patients have been enrolled in the study, of which 48 have completed 6 cycles of treatment and are included in the analysis of toxicity and efficacy.
• To date, histologies include 13 MZL patients (27%), 5 SLL patients (10%), and 30 FL patients (63%).
• Median age of patients was 57 years (range 36–77 years); 54% of patients were male.
• Of the 30 patients for whom follicular lymphoma international prognostic index (FLIPI) scores were available, 87% were classified as either intermediate or high risk.

Efficacy
• OR rate of the intent-to-treat (ITT) population was 83%, with 69% of patients achieving a CR or unconfirmed CR (CRu). (Table 1).
• OR rate was highest in the FL patients (93%), compared with 80% in SLL patients and 62% in MZL patients. (Table 1)

Table 1. Response rates in 48 indolent NHL patients treated with lenalidomide plus rituximab

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>NE (n)</th>
<th>SD (n)</th>
<th>PR (n)</th>
<th>CR/CRu (n)</th>
<th>OR rate % (CR/CRu %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL 30</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>25</td>
<td>97 (86)</td>
<td>93 (83)</td>
</tr>
<tr>
<td>SLL 5</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>80 (40)</td>
<td>80 (40)</td>
</tr>
<tr>
<td>MZL 13</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>73 (55)</td>
<td>62 (46)</td>
</tr>
<tr>
<td>Total 48</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>33</td>
<td>89 (73)</td>
<td>83 (69)</td>
</tr>
</tbody>
</table>

*Patients were evaluable if they had at least one post-baseline assessment.
CR = complete response; CRu = unconfirmed complete response; FL = follicular lymphoma; ITT = intent to treat; MZL = marginal zone lymphoma; NE = not evaluable; NHL = non-Hodgkin’s lymphoma; OR = overall response; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma
Key conclusions

- The biologic combination of lenalidomide and rituximab in patients with untreated indolent B-cell NHL produces good overall and complete response rates.
- Toxicity profile of this combination regimen is mild, with manageable hematological adverse events.
- Further randomized trials using lenalidomide and rituximab are planned.

References:

Canadian perspective on the PRIMA study by Dr. Silvy Lachance, Dr. David Macdonald, and Dr. Laurie H. Sehn

Follicular lymphoma (FL) is an indolent disease characterized by responsiveness to treatment with a period of disease control, inexorably followed by disease progression and relapse. Despite recent advances in its treatment, FL remains incurable outside of stem cell transplant. Survival in patients with low-risk disease can be measured in decades, while survival in high-risk patients may be less than five years.

Treatment for FL is usually initiated when patients become symptomatic or when the disease impairs hematopoiesis, progresses rapidly, or is associated with bulky lymphadenopathy. Because there is no proven cure for FL, goals of treatment are to increase response and prolong the treatment-free interval in order to improve patient quality of life.

Maintenance treatment is one strategy that aims to prolong the treatment-free interval in FL. Characteristics of an appropriate maintenance treatment are ease of administration, low toxicity, and effectiveness. Rituximab meets all three characteristics and is therefore an ideal candidate for maintenance therapy in FL.

A previous European Organization for Research and Treatment of Cancer (EORTC) phase III randomized controlled trial by Van Oers, et al.1 showed a significant prolongation of progression-free survival (PFS) in patients with relapsed FL given rituximab maintenance (R-maintenance) versus observation. Several studies have also demonstrated a significant clinical benefit of R-maintenance in relapsed patients after chemotherapy or chemotherapy plus rituximab (R-chemo) and in first-line patients after chemotherapy or rituximab monotherapy.1-4 Given the standard use of R-chemo in first-line treatment for FL, a study examining the efficacy of R-maintenance after R-chemo is needed to confirm its utility in this setting.
The PRIMA study is a *Groupe d’Étude des Lymphomes de L’Adulțe* (GELA)-sponsored intergroup phase III study investigating the efficacy of R-maintenance in patients with FL responding to first-line immunochemotherapy. Patients with untreated FL were first treated with R-chemo; those showing a complete response (CR) or a partial response (PR) were randomized either to R-maintenance at 375 mg/m² every two months for two years or to observation alone.

Dr. Gilles Salles, Professor of Hematology at the Centre Hospitalier Lyon-Sud in Lyon, France, presented results of the PRIMA study at ASCO 2010 and EHA 2010.2,4 Results of the PRIMA study showed that after two years, R-maintenance significantly reduced the risk of disease progression by approximately 50%, compared to observation (82% versus 66%; p <0.0001). The benefits of R-maintenance were seen in low-, intermediate-, and high-risk follicular lymphoma international prognostic index (FLIPI) groups; in patients younger or older than 60 years; and in the three induction treatment groups (R-CHOP, R-CVP, and R-FCM). The PRIMA study confirms that R-maintenance following induction with R-chemo leads to a significant, clinically relevant prolongation of PFS, which is similar to results in the relapsed setting. Longer follow-up will be needed to determine the actual benefit of treatment on PFS and its impact on overall survival.

Adverse events (AEs) in the PRIMA study occurred more frequently with R-maintenance compared to observation (52% versus 35%), and an increase in infections was observed (37% versus 22%). Grade 3/4 toxicities were reported in 23% of patients in the R-maintenance arm, compared to 16% of patients in the observation arm. Despite an increase in overall AEs and infections, the majority of these events were low-grade and clinically manageable. Overall, safety results from the PRIMA study indicate that R-maintenance was generally well tolerated.

Based on data from the EORTC study, the use of R-maintenance has been extrapolated to the upfront setting in many oncology centers across Canada. Results from the PRIMA trial provide supportive evidence for this practice. In view of the clinical benefit and reasonable safety profile, the use of R-maintenance should be considered after first-line treatment to prolong remission in patients achieving a CR or PR to induction with R-chemo. However, R-maintenance is associated with an increased risk of neutropenia and infection despite its acceptable toxicity profile. Patients should therefore be made aware of the infectious risk and be monitored accordingly.

Several different dosing schedules for R-maintenance have been used in reported clinical trials. In the EORTC study, R-maintenance was given at 375 mg/m² every three months, based on pharmacokinetic data. The PRIMA study administered R-maintenance every two months, with the rationale that this schedule would sustain trough serum levels in a therapeutic range. To date, no trials have directly compared different dosing strategies; the optimal dosing schedule for R-maintenance therefore remains unclear.

Whether R-maintenance is a better strategy than rituximab re-treatment following first relapse will be addressed by an upcoming study under development by the Eastern Cooperative Oncology Group (ECOG). The optimal duration of R-maintenance is also unclear, but is being examined in several trials, including a German Study Group for Indolent Lymphomas (STIL) trial, which randomized FL patients to two or four years of R-maintenance treatment after first-line treatment with rituximab plus bendamustine.

Overall, the favourable results seen in the PRIMA trial support the standard practice of R-chemo followed by two years of R-maintenance for patients with previously untreated FL. Ongoing trials will further clarify the optimal dosing strategy and duration of maintenance therapy for patients with indolent lymphoma.


**Discussion on PRIMA at ASCO 2010 by Dr. Richard Fisher**

Following Dr. Salles’s ASCO presentation, Dr. Richard Fisher of the James P. Wilmot Cancer Center at the University of Rochester Medical Center in Rochester, New York, discussed the benefits of rituximab maintenance (R-maintenance) in follicular lymphoma (FL), based on the evidence to date. In his discussion, Dr. Fisher stated that the PRIMA study provides another piece of evidence to support the use of R-maintenance after rituximab plus chemotherapy (R-chemo) in the upfront setting. According to Salles,* et al., R-chemo followed by two years of R-maintenance should be viewed as a new standard of care for FL and the platform upon which new strategies are developed.

In relation to the optimal dosing schedule, Dr. Fisher argued that R-maintenance should be given every two months, since the goal of treatment ought to be to prevent relapse. Dr. Fisher concluded, “Five years after the beginning of rituximab induction and maintenance studies, the use of rituximab maintenance is currently indicated following all treatment programs in rituximab-sensitive patients.”
Improving Patient Outcomes and Quality of Life, and Reducing Toxicity in the Treatment of Aggressive NHL

Aggressive non-Hodgkin’s lymphoma (NHL) is a clinically and biologically heterogeneous group of neoplasms, the most common of which is diffuse large B-cell lymphoma (DLBCL). Non-DLBCL aggressive lymphomas include mantle cell lymphoma (MCL), HIV/AIDS-related NHL, Burkitt’s lymphoma (BL), and primary central nervous system lymphoma (PCNSL). Treatment goals in untreated aggressive NHL are oriented towards a disease cure. For patients with relapsed aggressive NHL, the goal is to achieve a complete response (CR) and extend the duration of remission, potentially increasing the chance of a cure.1 Aside from meeting treatment goals, ongoing research is also examining ways to reduce treatment toxicity and improve patient quality of life (QoL).

Over the past five years, the addition of rituximab to chemotherapy has improved clinical outcomes, resulting in new treatment standards in a number of NHL sub-types. Recent studies have established the standard of treatment for patients with newly diagnosed DLBCL as eight cycles of rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy (R-CHOP).1,2 However, some poor prognosis DLBCL patients relapse after standard treatment; researchers are investigating the use of rituximab maintenance therapy to improve outcomes in these patients.3

Reducing treatment cycles from 3 to 2 weeks (CHOP-21 versus CHOP-14) has improved clinical outcomes in both young and elderly patients with aggressive NHL.4,5 Studies examining the efficacy of CHOP-14 have given granulocyte colony-stimulating factor (GCSF) according to ASCO guidelines, which recommends GCSF as prophylaxis for patients with a ≥20% risk of febrile neutropenia and to support delivery of dose-dense regimens.6 The optimal dosage of GCSF required for dose-dense R-CHOP therapy has yet to be determined.

Although generally well tolerated, rituximab administration is associated with an increased risk of infusion-related reactions. Consequently, the standard administration rate, based on a slow initial rate of infusion followed by increments every 30 minutes, averages 6 hours for a first infusion and 4 hours for remaining infusions. This time- and labour-intensive process creates challenges both for the patient and for the busy oncology clinic. A recent study has shown a 90-minute schedule to be safe and well tolerated in NHL patients;7 studies are ongoing to confirm this finding.

Autologous stem cell transplantation (ASCT) is an effective treatment option in aggressive NHL, but associated morbidity and adverse events affecting quality of life (QoL) are drawbacks. Studies suggest that early moderate impairments largely return to pre-transplantation levels by day 100. In addition, 60% of patients report good to excellent QoL in years 1 to 4 after ASCT. However, QoL during post-ASCT treatment with rituximab and re-adaptation to normal life has not been examined.8

High-dose methotrexate (HDMTX) is considered the standard of care for newly diagnosed PCNSL and is used in combination with whole-brain radiotherapy (WBRT). However, treatment with WBRT is controversial, due to its association with delayed neurotoxicity. Ongoing research is needed to determine whether HDMTX is effective without the use of WBRT.9
Data from studies examining these treatment issues in aggressive NHL were presented at ASCO 2010 and EHA 2010. This article reports on five such studies, four from ASCO and one from EHA:

- Results of a study presented at ASCO 2010 suggested that rituximab maintenance prolongs disease-free survival but not overall survival (OS) in poor prognosis DLBCL and FL patients after chemotherapy induction with R-CHOP or R-EPOCH.
- A prospective study presented at EHA 2010 found that dose-dense therapy in the treatment of aggressive NHL remained well tolerated when granulocyte colony-stimulating factor (GCSF) was reduced from 10 to 5 vials per cycle.
- An exploratory non-random study presented at ASCO 2010 demonstrated that a rapid infusion protocol of rituximab beginning with the second cycle of treatment is well tolerated with no unexpected safety signals in NHL and CLL patients.
- A study presented at ASCO 2010 reported that rituximab maintenance after ASCT is effective and well tolerated in DLBCL patients who had been randomized to rituximab or observation post-ASCT in the GELA LNH98-3 trial.
- A final analysis from the first phase IV trial in PCNSL patients, presented at ASCO 2010, found no significant difference in OS when WBRT was omitted from the treatment protocol with HDMTX chemotherapy.

References:

Li YJ, et al. ASCO 2010: Abstract 8084

**Rituximab maintenance versus observation after R-CHOP or R-EPOCH chemotherapy in DLBCL and FL patients**

**Background**
At ASCO 2010, Li and colleagues presented data from their study investigating the efficacy and safety of rituximab maintenance therapy in poor prognosis diffuse large B-cell lymphoma (DLBCL) and stage III follicular lymphoma (FL) patients after R-CHOP or R-EPOCH chemotherapy treatment.

**Study design**
- Fifty (50) patients meeting the following criteria were included in the study:
  - untreated DLBCL (n=44) or stage III FL (n=6);
  - international prognostic index (IPI) 3–5 or bulky disease;
  - had achieved complete remission (CR) or unconfirmed complete remission (CRu) after 6–8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or R-EPOCH (rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone) with or without invasion field radiotherapy.
Patients were non-randomly assigned to two treatment arms for a period of two years or until relapse or death:
- rituximab (n = 21): 375 mg/m² at three month intervals;
- observation (n = 29).

Key findings
- Rituximab significantly prolonged two-year disease-free survival (DFS) compared with observation (93.3% versus 69.4%; p = 0.046). (Table 1, Figure 1)
- No significant difference in overall survival (OS) was seen between the rituximab and observation groups at the time of analysis (93.8% versus 87.7%; p = 0.519). (Table 1, Figure 2)
- Median DFS and OS were not reached in either treatment arm.
- The main adverse events (AEs) in the rituximab arm were grade 1/2 hematological toxicities; grade 3/4 AEs were rare (3.9%). (Table 2)

Table 1. Disease-free and overall survival in poor prognosis patients receiving rituximab maintenance therapy versus observation

<table>
<thead>
<tr>
<th></th>
<th>Total patients (n = 50)</th>
<th>DLBCL patients (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab (n = 21) (%)</td>
<td>Observation (n = 29) (%)</td>
</tr>
<tr>
<td></td>
<td>Rituximab (n = 17) (%)</td>
<td>Observation (n = 27) (%)</td>
</tr>
<tr>
<td>DFS at 1 year</td>
<td>93.3</td>
<td>74.8</td>
</tr>
<tr>
<td>DFS at 2 years</td>
<td>93.3</td>
<td>69.4</td>
</tr>
<tr>
<td>OS at 1 year</td>
<td>93.8</td>
<td>92.8</td>
</tr>
<tr>
<td>OS at 2 years</td>
<td>93.8</td>
<td>87.7</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; OS = overall survival

Table 2. Adverse events in 21 patients* receiving rituximab maintenance therapy

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Patients n (%)</th>
<th>Cycles n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>1/2</td>
<td>7 (33.3)</td>
<td>22 (21.4)</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>2 (9.5)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>1/2</td>
<td>8 (38.1)</td>
<td>15 (14.6)</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>1 (4.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1/2</td>
<td>2 (9.5)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1/2</td>
<td>6 (28.6)</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Transaminases</td>
<td>1/2</td>
<td>5 (23.8)</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>1 (4.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1/2</td>
<td>2 (9.5)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1/2</td>
<td>2 (9.5)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>1/2</td>
<td>3 (14.3)</td>
<td>8 (7.8)</td>
</tr>
</tbody>
</table>

*p Patients with poor prognosis who achieved complete remission or unconfirmed complete remission after 6–8 cycles of R-CHOP or R-EPOCH

Key conclusions
- Results suggest that rituximab maintenance for two years significantly prolongs DFS but not OS in untreated DLBCL and FL patients with poor prognosis.
- Toxicities seen with rituximab maintenance were few and mild.

Feasibility and safety of reducing the use of GCSF during dose-dense R-CHOP therapy

Background
At EHA 2010, Antognoli and colleagues presented data from their prospective study evaluating the feasibility of reducing the amount of granulocyte colony-stimulating factor (GCSF) given during dose-dense chemotherapy in the treatment of aggressive non-Hodgkin’s lymphoma (NHL). Evaluation of tolerance to therapy was assessed by monitoring hematological toxicity and infection.1

Study design
• Data was collected from June 2002 to July 2009.
• Analysis included 89 newly diagnosed non-Hodgkin’s lymphoma patients with the following histologies:
  - 87% of patients with diffuse large B-cell lymphoma (DLBCL);
  - 10% of patients with grade IIIb follicular lymphoma (FL);
  - 3% of patients with other lymphomas.
• Thirty-two percent (32%) of patients had a high-intermediate or high international prognostic index (IPI) score.
• Patients were treated with immunochemotherapy every 14 days: rituximab on day 1 and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) on day 2 followed by GCSF (lenograstim).
• In the first 10 patients, 7 vials of GCSF (range 5–11 vials) were used after each chemotherapy cycle.
• If treatment was well tolerated, administration of GCSF was prospectively reduced to 5 vials (range 7–11 vials).
• Tolerance to therapy was evaluated with complete blood counts at the beginning of each treatment cycle.
• Further reduction of GCSF vials (at least 3 per cycle) was acceptable if patients reached a leukocyte count over 20,000/mm3.

Key findings
• Of the 89 patients included in the study, 86 (96.6%) completed treatment.
• Median patient age was 62 years (range 26–75 years); 66% of patients were male.
• A median of 25 vials of GCSF (range 10–35 vials) was used for each patient, corresponding to 5 vials per cycle (range 0–10 vials).
• Therapy was delayed in 21% of patients due to severe adverse events (neutropenia, thrombocytopenia, infective episodes, and mucositis).
• Three (3) patients were switched to R-CHOP-21 due to poor tolerance of dose-dense chemotherapy.
• Hematological toxicity included grade 3/4 neutropenia (14 patients; 15%) and grade 3/4 thrombocytopenia (2 patients; 2%); other adverse events included febrile neutropenia (10 patients; 11%) and hospitalization (6 patients; 6.5%). (Table 1)
• Median leukocyte nadir was 3,525/mm3 (range 400–8,400 mm3), anemia nadir was 11 g/dL (range 5.8–5.5 g/dL), and thrombocytopenia nadir was 146,000/mm3 (range 43,000–328,000/mm3).
• In patients who completed the R-CHOP-14 scheduling, the complete remission rate was 87.2%, with an overall response (OR) rate of 96.5%.
• Overall survival (OS) was 84% after a median follow-up period of 25 months (range 4–90 months).

Key conclusions
- By modulating GCSF administration according to leukocyte count and reducing the number of GCSF vials from 10 to 5 per cycle, dose-dense therapy remained well tolerated.
- The rate of neutropenia and febrile episodes were comparable to those found in previous studies.
- The majority of patients completed R-CHOP-14 treatment, even when GCSF administration was reduced.

Rapid versus standard infusion rate for rituximab in a busy oncology practice

Background
At ASCO 2010, Paszkiewicz-Kozik and colleagues presented data from their exploratory, non-randomized study investigating the safety of rapid infusion with rituximab, as previously described by Sehn, et al.1,2

Study design
• Between January and December 2008, 125 patients with B-cell CD20-positive lymphoma were enrolled in the study.
• Within the study population, histologies included:
  - eighty patients with diffuse large B-cell lymphoma (DLBCL);
  - six patients with Burkitt’s lymphomas (BL);
  - twenty-two patients with follicular lymphoma (FL);
  - eleven patients with marginal zone lymphoma (MZL);
  - four patients with mantle-cell lymphoma (MCL);
  - two patients with chronic lymphocytic leukemia (CLL).
• Ongoing treatment regimens within the study group included:
  - R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; n = 82);
  - R-CVP (cyclophosphamide, vincristine, prednisone; n = 22);
  - BFM (Berlin–Frankfurt–Munster) regimen (n = 14);
  - rituximab monotherapy (n = 5);
  - rituximab maintenance therapy (n = 2).
• All patients received a first rituximab dose of 375 mg/m² using the standard infusion rate; patients then received rapid-rate or standard-rate infusions as per physician’s judgment.

Key findings
• Median number of rapid rituximab infusions was 5 (range 1–9 infusions); median infusion time was 111 minutes (range 90–180 minutes).
• During the first delivery (standard infusion), 8/123 patients (6.5%) experienced minor infusion reactions, including hypertension, tachycardia, rash, chills, sore throat, and fever; no reactions were noted on subsequent rapid infusions in these patients.
• During 528 subsequent rapid-rate infusions, 14 grade 1/2 reactions (2.7%) occurred in 11 patients, including hypertension, hypotension, anxiety with shortness of breath, or bradycardia.
• No infusion reactions occurred with subsequent standard-rate infusions (n = 123).
• Factors predicting occurrence of infusion reactions were not identified:
  - Standard infusion rate versus rapid infusion rate was not a predictor (hazard ratio [HR] 1.53; 95% CI: 0.68–3.45; p = 0.306).
  - Sex, age, histology, B symptoms, and bulky disease were not significant predictors.

Key conclusion
Results after one year of follow-up showed that administration of rituximab using a rapid infusion protocol beginning at the second cycle of treatment is as safe as using the standard protocol; rapid infusions may be routinely used in clinical practice.

Quality of life in DLBCL patients treated with rituximab versus observation after front-line autologous transplantation

**Background**

The Groupe d’Etudes des Lymphomes de l’Adulte (GELA) LNH98-3 study was a randomized, controlled trial comparing the induction regimens ACE (doxorubicin, cyclophosphamide, etoposide) and ACVBP (doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone) before high-dose therapy followed by autologous stem cell transplantation (ASCT) in patients with high-risk diffuse large B-cell lymphoma (DLBCL); a second randomization compared rituximab with observation post-ASCT.1

At ASCO 2010, Mounier and colleagues reported results of their study, which assessed quality of life (QoL) and fatigue in DLBCL patients who had been randomized to either rituximab or observation post-ASCT in the GELA LNH98-3 trial.2

**Study design**

- From October 1999 to November 2004, 330 patients responding to induction treatment in the GELA LNH98-3 trial received high-dose treatment followed by ASCT.
- Following response to ASCT, 269 patients were randomized to rituximab treatment (4 cycles) or observation only.
- Patients were given the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) at day 45 after ASCT and at each follow-up visit (100 days, 1 year, 2 years, and 3 years).
- Several covariates were examined including age, gender, treatment types, treatment-related toxicity, and a priori prognosis on QoL functional scales and symptom scales.
- Changes in mean QoL scores over time were analyzed with mixed models; analyses were done on an intention-to-treat (ITT) basis.
- The statistical method used required longitudinal follow-up with fixed time periods. Five post-treatment time periods were defined as 0–3, 4–8, 9–17, 18–29, and 30 months. For patients with more than one assessment available within a time period, the assessment was selected at random.

**Key findings**

- Of the 555 assessments collected, 64 were excluded (29 before the randomization, 5 after relapse, 30 as doublets); 491 assessments in 200 patients remained for analysis.
- Median patient age was 45 years (range 18–59 years); 68% were male.
- One hundred and seven (107) patients received rituximab maintenance, and 191 patients were in complete response/unconfirmed complete response (CR/Cru).
- Median follow-up was 52 months.
- Event-free survival (EFS) at four years was 81%.
- Improvements over time were observed in all scales except for nausea. (Figure 1)
- Age, gender, and previous treatment toxicities were not predictive of QoL scores.
- Frequencies of patients with clinically significant improvement (change in score >10) varied from 6% (constipation) to 56% (fatigue).

**Study design**

- **Second randomization:** 269 patients responding to ASCT randomized to rituximab treatment (4 cycles) or observation.
- **No HRQL assessments in 63 patients**
- **555 HRQL assessments in 200 patients**
- **Time since second randomization**
  - 0–3 months: 16
  - 4–8 months: 5
  - 9–17 months: 8
  - 18–29 months: 1
  - 30 months: 0
- **Analyzed**
  - 147
  - 95
  - 113
  - 86
  - 48
- **491 HRQL assessments analyzed in 200 patients**

*For patients with more than one available assessment within a time period, the assessment used for analysis was selected at random.

ASCT = autologous stem cell transplantation; HRQL = health-related quality of life
Key conclusions

- QoL data indicates that patients experience rapid recovery after ASCT in all subdomains.
- Differences in QoL improvement with time were not linked to rituximab maintenance.
- Results show that rituximab maintenance after ASCT is effective and well tolerated, and warrants further investigation.

Whole-brain radiotherapy in newly diagnosed primary central nervous system lymphoma: final results from G-PCNSL-SG-1 study

Background

At ASCO 2010, Thiel and colleagues presented results from the final analysis of the German Primary Central Nervous System Lymphoma Study Group (G-PCNSL-SG)-1 study, the first phase IV trial in primary central nervous system lymphoma (PCNSL) patients, designed to evaluate the efficacy of omitting whole-brain radiotherapy (WBRT) from first-line treatment with high-dose methotrexate (HDMTX) in newly diagnosed PCNSL.1

Study design

- G-PCNSL-SG-1 is a multicentre, phase IV randomized trial in newly diagnosed PCNSL patients.
- Immunocompetent patients with newly diagnosed PCNSL were randomized to either chemotherapy followed by WBRT (arms A1, B1) or chemotherapy alone (arms A2, B2).
- After randomization, all patients received six cycles of HDMTX (4 g/m2 on day 1, biweekly) from 1999–2007 and HDMTX plus ifosfamide (1.5 g/m2 on days 3–5, biweekly) from 2007–2009.
- Patients achieving a complete response (CR) received either consolidating WBRT (A1) or no further treatment (A2).
- Patients without CR received salvage WBRT (B1) or salvage chemotherapy using high-dose cytarabine (B2) (4 x 3 g/m2, given every 48 hours for 3 weeks).
- Primary objective was to examine the effect of WBRT omission from first-line treatment on overall survival (OS).
- A calculated sample size of 151 patients per group was needed to support the hypothesis that elimination of WBRT would be non-inferior to WBRT inclusion in the treatment of patients with PCNSL.
Key findings

- A total of 551 patients (median age 63 years) entered the study, and 537 received at least one course of HDMTX-based chemotherapy.
- Of those patients, 66 died on HDMTX, 60 dropped out, 411 entered the post-HDMTX phase, and 318 were treated per protocol (PP).
- Within the intent-to-treat (ITT) population (n = 411), two prognostic factors were found to be independent risk factors:
  - Median OS in patients age <60 years was significantly greater than in patients age ≥60 (38.4 vs. 14.2 months; p <0.005).
  - Patients with a Karnofsky performance score (KPS) of ≥70 had significantly longer OS than patients with a score of <70 (31.5 vs. 9.8 months; p<0.005).
- Within the PP population (n = 318) the following results were obtained:
  - Median OS in the chemotherapy plus WBRT arm (A1, B1; n = 154) was 32.4 months, as compared to 37.1 months in the chemotherapy alone arm (A2, B2; n = 164) (p = 0.70). (Figure 1)

Median progression-free survival (PFS) in the chemotherapy plus WBRT and chemotherapy alone arms was 18.3 months and 12 months, respectively (p = 0.13). (Figure 2)

Subgroup analyses demonstrated that PFS was significantly longer in the chemotherapy plus WBRT arm versus the chemotherapy alone arm both for patients with CR after HDMTX (36.3 vs. 21.5 months; p = 0.038) and for patients without CR (5.6 vs. 3.0 months; p = 0.003).

No significant differences in OS between treatment arms were observed in the subgroup analyses, either for patients with CR after HDMTX (38.8 vs. 39.4 months; p = 0.56) or for patients without CR (24.3 vs. 18.6 months; p = 0.1).

Late neurotoxicity was more frequently observed in both clinical evaluations (48.9% vs. 28%; p = 0.054) and neurological evaluations (72.8% vs. 41.7%; p = 0.04) in patients with CR treated with WBRT versus patients with CR not treated with WBRT. (Figure 3)
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Key conclusions

- No significant difference in overall survival was observed with WBRT omission in PCNSL patients treated with HDMTX chemotherapy.
- Progression-free survival prolongation in subgroup analyses confirms the role of WBRT for disease control.
- Late neurotoxicity was more frequent when patients received WBRT.
- Age and performance status are the most important risk factors for patients with PCNSL.


Canadian perspective by Dr. Silvy Lachance

The combination of rituximab plus chlorambucil (R-chlorambucil) is a promising new treatment regimen for patients with follicular lymphoma (FL) who are not candidates for standard chemotherapy. The study by Bassi, et al. examined the R-chlorambucil combination in 58 patients with untreated FL. Limitations of this study are its small sample size and observational cohort design, which did not include a control group.

The study also included patients as young as 29 years old (range 29–79 years; median 56 years). Chlorambucil is still widely used for the treatment of FL in older or unfit patients, but could impair or damage the stem cell pool in younger patients, increasing the risk of secondary cancers and myelodysplastic syndrome. Giving younger patients chlorambucil-based treatments as was done in this study is therefore unusual.

Before considering the use of R-chlorambucil in FL, we first need to determine whether this combination has an advantage over monotherapy with rituximab or chlorambucil. Although efficacy comparisons should not be made given the small sample size and the lack of a control group, the overall response (OR) rate of 98% compares favourably to other immunochemotherapy regimens used in the front-line treatment of FL. However, the median time to next treatment of 21 months is inferior to standard R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) treatment, which has proven to be 35 months with R-CVP versus 14 months with CVP (cyclophosphamide, vincristine, prednisone) (p <0.0001).1

The combination of R-chlorambucil was relatively well tolerated in this study. As expected, the chlorambucil dose was reduced in more than 40% of patients, and significant grade 3 and 4 neutropenia (22%) was observed. Data showing the incidence of infection would have been useful, but the authors did not provide this information.

The study by Bassi, et al. confirms the feasibility of combining rituximab with chlorambucil. This combination may become a first-line option in older or unfit patients with significant co-morbidities; however, R-chlorambucil should not be considered as a standard approach.

The Groupe d’Études des Lymphomes de l’Adulte (GELA) LNH98-3 study2 was a randomized, controlled trial comparing the induction regimens ACE (doxorubicin, cyclophosphamide, etoposide) and ACVB (doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone) before high-dose therapy and autologous stem cell transplantation (ASCT) in patients with high-risk diffuse large B-cell lymphoma (DLBCL). None of the patients in the study were exposed to rituximab as part of first-line treatment.
GELA LNH98-3 patients achieving a complete response (CR) underwent a second randomization, which compared maintenance rituximab to observation. At a median time of four years from the second randomization, a trend \((p = 0.1)\) towards increased event-free survival (EFS) for patients who received rituximab was observed. Given the significant impact of rituximab on disease control, the goal of this second randomization was to use rituximab in previously unexposed patients with DLBCL as maintenance therapy to improve disease-free survival (DFS) and to reduce the risk of post-ASCT relapse.

For patients responding to treatment and for those maintaining a CR after high-dose chemotherapy and ASCT, an improvement in quality of life (QoL) is expected over time. As expected, the study by Mounier, et al. demonstrated a marked increase in functioning until day +100, with the improvement in QoL reaching a plateau after one year. Although well tolerated, rituximab maintenance did not significantly improve EFS.

Pain scores and financial impact appeared to be lower in patients treated with rituximab versus observation. This finding is surprising, because patients on treatment often experience higher stress levels given their visits to the oncology clinic, disturbances in social and professional life, and financial burden. However, some patients on maintenance therapy may feel reassured by the possibility of reducing the risk of relapse and avoiding further treatment, which could partially explain the lower scores.

The majority of patients treated for B-cell non-Hodgkin's lymphoma (NHL) will receive rituximab as part of their first-line treatment. Outside mantle cell lymphoma (MCL), high-dose chemotherapy and ASCT are used as salvage therapy for resistant or recurrent B-cell lymphoma and not as part of first-line treatment. Rituximab is part of first-line immunochemotherapy, and its role as maintenance therapy in these patients is unknown. The disadvantage of maintenance rituximab is that maintaining patients on active treatment could potentially increase their risk of neutropenia, prolonged lymphopenia, and infection. Outside of a clinical study such as that of Mounier, et al., there is no indication for rituximab maintenance after high-dose chemotherapy and ASCT.

In Canada, the standard treatment for primary central nervous system lymphoma (PCNSL) is combination chemotherapy containing high-dose methotrexate, followed by whole brain radiotherapy (WBRT) in patients younger than 60 years. However, WBRT is known to be associated with significant neurotoxicity, particularly in older patients (>60 years). Despite significant improvements in the prognosis of PCNSL, with a median overall survival (OS) reaching three years, innovative approaches are needed to improve disease control, while reducing neurotoxicity.

The study by Thiel, et al. found no significant difference in OS between patients given WBRT and those not given WBRT; however, progression-free survival (PFS) was significantly improved with WBRT. These findings are not surprising, as the significant role played by WBRT in local disease control is well recognized. As expected, patients in CR after chemotherapy and WBRT demonstrated more late neurotoxicity when compared with those treated with chemotherapy alone.

Results of the Thiel, et al. study will help to better define patient groups more likely to benefit from WBRT. WBRT should be considered after combination therapy in younger patients (<60 years) with a good performance status (Karnofsky performance status [KPS] ≥70) and no significant co-morbidities; WBRT should be considered as salvage treatment in older or unfit patients. In all cases, the risks and benefits of adding WBRT to high-dose methotrexate-containing chemotherapy should be clearly explained to patients.

Dr. Salles: Maintenance therapy as a concept has been a long-standing treatment strategy in hematology. The first studies examining maintenance therapy in follicular lymphoma used interferon-alpha, which improved survival at the expense of tolerability. Rituximab is therefore an ideal candidate in these patients, due to its demonstrated efficacy and good safety profile when repeated infusions are given as a single agent over time.

Dr. Salles: In the PRIMA study, we gave one infusion of rituximab every two months for a period of two years. The RESORT study by the Eastern Cooperative Oncology Group (ECOG), comparing rituximab maintenance to re-treatment at relapse, used a three-month interval between rituximab infusions. A rituximab serum concentration of ≥25 μg/mL is thought to be necessary for maintaining anti-lymphoma activity; however, pharmacokinetic results of the RESORT study showed that only about 50% of patients had residual levels above this target. Giving one infusion every two months represents an ideal compromise: the majority of patients will have adequate residual levels of rituximab while balancing patient safety and burden.

Dr. Salles: Results of the PRIMA study demonstrated that rituximab maintenance reduces the risk of lymphoma recurrence by 50% compared to observation alone (HR 0.50; 95% CI: 0.39–0.64). Data showed that 82% of patients were free of disease at two years, compared to 66% in the observation arm, which is the best result we have seen to date in follicular lymphoma. Further, these PFS results may be amplified with longer follow-up time.
**New Evidence:** Were there patient groups that performed significantly better or worse with rituximab maintenance?

**Dr. Salles:** As part of the analyses initially planned in the study design, we did examine PFS in four major subgroups of patients. In the first subgroup analysis, we compared patients >60 years of age to those who were ≤60 years. As we would expect, patients >60 years had an increased risk of recurrence at two years. However, in both groups we saw a benefit of rituximab maintenance compared to observation alone, showing that this strategy is useful in patients of all ages.

In the second subgroup analysis, we compared patients with low-to-high follicular lymphoma international prognostic index (FLIPI) scores (FLIPI ≤1; FLIPI 2; FLIPI ≥3). Again, the benefit of rituximab maintenance was significant in all three FLIPI categories.

In the third subgroup analysis, we compared patients given R-CHOP, R-FCM, and R-CVP as induction treatment. In each regimen, eight cycles of rituximab were given with six cycles of CHOP or FCM, or eight cycles of CVP. The small sample sizes in the R-CVP (n = 222) and R-FCM (n = 28) arms meant that the study was not sufficiently powered to compare induction treatment groups. However, we noted that the benefit of rituximab maintenance appeared to be greatest in the R-CHOP group— a surprise finding, as we would expect the smallest improvement in PFS to be observed after the strongest induction regimen. This result suggests that the benefit of rituximab maintenance is greatest in patients given the strongest cytoreductive agent upfront.

Despite the higher PFS hazard ratios in the R-FCM and R-CVP groups, a trend in the benefit for rituximab maintenance was observed across all groups. In young patients with good performance status and a high FLIPI score, I would therefore choose a stronger induction treatment, such as R-CHOP, over less aggressive treatments such as R-CVP. In older patients or in those with a lower performance status, I might choose R-CVP in order to improve tolerability.

In the final subgroup analysis, we compared patients with a complete response (CR or CRu) to induction treatment to those with a partial response (PR). Rituximab maintenance was most beneficial in those with the best response to induction treatment, again solidifying the argument that the strongest regimen should be used upfront. Despite the variations across subgroups, all groups showed a benefit in PFS when given rituximab maintenance, compared to observation alone.

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**New Evidence:** Please comment on the results of the secondary endpoint analyses.

**Dr. Salles:** Secondary outcomes of the PRIMA study included event-free survival, time to next lymphoma treatment, time to next chemotherapy treatment, rates of conversion from PR to CR, and overall survival. Overall, secondary outcome results were in line with those of the primary outcome, PFS. The hazard ratio for the time to next chemotherapy treatment was 0.6 \((p = 0.001)\), which is of significant clinical benefit for the patient.

An important finding showed that the number of patients with CR at two years was higher in the rituximab maintenance arm, compared to the observation arm. The explanation for this result is two-fold. Of the patients who achieved an initial CR, the number who remained in remission was higher in the maintenance arm (75%) versus the observation arm (56%). More patients who had a PR after initial treatment converted to CR in the maintenance arm (45%), compared to the observation arm (30%). Therefore, rituximab maintenance also improved the quality of response over time.

The overall survival (OS) in both groups is currently around 97%, which is an excellent result. Given this favourable result, we did not observe a number of deaths sufficient to determine whether there is an OS advantage for rituximab maintenance. However, with a longer follow-up, we may be able to evaluate this question.
**New Evidence:** Were there any important safety signals observed with rituximab maintenance therapy?

**Dr. Salles:** Overall, an increased incidence of adverse events (AEs) was seen in the rituximab arm, which was mainly due to an increased rate of infections (grade 2 or higher). This is to be expected with rituximab, since we know from previous studies that the use of rituximab maintenance brings with it a two-fold increased risk of infection. However, rates of grade 3 or 4 neutropenia and infections were low, suggesting that the number of serious AEs directly related to rituximab was very low. Of the 500 patients included in the study, only 10 patients in the rituximab maintenance arm dropped out of the study for toxicity-related reasons (at the time of analysis), showing that maintenance rituximab was feasible and well tolerated.

**New Evidence:** What was the effect of rituximab maintenance on quality of life?

**Dr. Salles:** In the PRIMA study, we assessed quality of life (QoL) using the functional assessment of cancer therapy-general (FACT-G) and European Organization for Research and Treatment of Cancer (EORTC) scales. Assessment scores were similar across study arms, showing that the side effects observed with rituximab were well tolerated and did not result in a substantial reduction in QoL. These results also showed that the burden associated with the administration of one infusion of rituximab every two months has very little impact on QoL. Patients may also have felt some reassurance from knowing that they were continuing to receive treatment, which could have had an impact on the improved QoL in the rituximab arm.

**New Evidence:** Considering the cost in terms of safety and the benefit in terms of improved progression-free survival, is first-line maintenance therapy with rituximab justified?

**Dr. Salles:** The EORTC study by Van Oers, et al. has shown a benefit for rituximab maintenance in relapsing patients, with a hazard ratio of 0.69 ($p = 0.003$) in patients given R-CHOP. In the R-CHOP arm of the PRIMA study, we achieved a hazard ratio of 0.43, indicating that the magnitude of the effect of rituximab maintenance is greater when used first-line, versus in relapsed patients. Even though the EORTC and PRIMA studies were carried out in different settings and used slightly different dosing schedules, the large difference between the hazard ratios suggests that rituximab maintenance should be used first-line. Unfortunately, the PRIMA study does not show whether using rituximab again after a second relapse is beneficial. However, based on the strong efficacy results shown in first-line, I would re-treat with rituximab where there are late relapses that occur ≥3 years after starting first-line rituximab maintenance treatment.

I believe that the improvement in efficacy, balanced with the limited toxicity and a preserved QoL, will support the use of rituximab maintenance as a new standard of care in the treatment of follicular lymphoma. Based on these results, I would recommend using R-CHOP or R-CVP followed by rituximab maintenance in the majority of patients with follicular lymphoma. In general, I would use rituximab in any patients who respond to induction treatment, regardless of the quality of response or prognosis.

**New Evidence:** What are the next steps in the examination of rituximab as maintenance treatment in follicular lymphoma?

**Dr. Salles:** Given the large number of patients in the PRIMA study, an exploration of other clinical features of the disease, such as prognostic factors, biologic factors, and the results of PET scans, would be useful. A new German study will compare two years versus four years of maintenance treatment, which should be helpful in identifying the optimum duration of maintenance treatment. Also, new CD20 antibodies, such as GA101, or a combination of rituximab with immunomodulatory agents, such as lenalidomide, are now being examined as alternative treatments. However, we must not forget the importance of continually improving initial chemotherapy regimens.

To sum up: based on the results of studies to date, initial maintenance treatment with rituximab should be considered the standard of care in follicular lymphoma patients who respond to immunochemotherapy induction.

Recent developments in the treatment of chronic lymphocytic leukemia (CLL) have shifted the goal of treatment from symptom palliation to achievement of maximum disease control. The phase III CLL-8 randomized controlled clinical trial (RCT), conducted by the German CLL Study Group, demonstrated that adding the monoclonal antibody rituximab to FC (fludarabine, cyclophosphamide) chemotherapy (FR) in the first-line treatment of CLL resulted in significantly superior progression-free survival (PFS) and overall survival (OS). The CLL-8 trial was the first RCT showing a significant improvement in OS for one treatment over another in CLL.

Since the OS data from the CLL-8 study was presented at ASH 2009, FCR has become the recommended first-line treatment and standard of care for fit patients with CLL in many oncology centres in Canada and across the world. Further studies are being conducted to confirm FCR’s efficacy in clinical practice. Investigators are also examining the use of maintenance rituximab to lengthen the period until disease progression, a step towards achieving complete disease eradication. Other studies are determining the prognostic markers that identify CLL patients with superior responses to FC and FCR treatment.

Data from several of these studies were presented at ASCO 2010 and EHA 2010. This article reports on two studies from ASCO and three from EHA:

- One EHA 2010 effectiveness study demonstrated that maintenance rituximab increases remission time and improves PFS in CLL.
- Results of a historic comparison study at the M.D. Anderson Cancer Care Centre in the U.S. presented at ASCO 2010 showed that FCR significantly improves response rates and survival in advanced-stage CLL patients, compared to historic patients treated with FC.
- Further results from the CLL-8 study presented at EHA 2010 showed that 17p(del) and TP53 mutation are powerful and independent prognostic markers after first-line treatment with FC and FCR.
- Data from a 7.5-year follow-up to a study investigating the efficacy of first-line FC and FCR treatment presented at EHA 2010 confirmed that the addition of rituximab to the FC regimen improves PFS and OS.
- A study presented at ASCO 2010 investigating the cost-effectiveness of FCR in treatment-naive CLL patients found that the FCR regimen is cost-effective compared to FC.

Rituximab maintenance therapy in chronic lymphocytic leukemia

Background
Although combining the monoclonal antibody rituximab with fludarabine-containing chemotherapy regimens has significantly improved overall and disease-free survival in patients with chronic lymphocytic leukemia (CLL), relapses still occur in certain groups of patients. Whether or not CLL can be completely eradicated remains an open question. A key task at this stage of research is therefore to develop a strategy to lengthen the period until disease progression.

At EHA 2010, Zagoskina and colleagues presented results of their study examining the efficacy of rituximab maintenance therapy in CLL patients who had received induction chemotherapy or immuno-chemotherapy.

Study design
- A total of 193 CLL patients in remission were included in the study:
  - 110 patients (57%) were in complete remission (CR).
  - 83 patients (43%) were in partial remission (PR).
- Median age of patients was 59 years (range 38 to 74 years).
- Patients were treated with one of two regimens:
  - 107 patients received FCR (fludarabine: 25 mg/m² iv on days 2–4; cyclophosphamide: 300 mg/m² iv on days 2-4; rituximab: 375 mg/m² iv on day 1);
  - 86 patients received FC (fludarabine: 25 mg/m² iv on days 1–3; cyclophosphamide: 300 mg/m² iv on days 1–3).
- Patients were randomly assigned to one of two study arms:
  - observation (133 patients);
  - rituximab maintenance therapy (60 patients):
    - 4 weekly injections of rituximab (375 mg/m²) every 6 months for 2 years.

Key findings
- Relapses and deaths were significantly lower in patients in the rituximab arm who had received FCR, compared with patients in the observation arm (p = 0.001, p = 0.015, respectively).
- Patients in the rituximab arm treated with FC also showed fewer relapses and deaths, compared with patients in the observation arm (p = 0.0001, p = 0.002, respectively).
- A comparative analysis of progression-free survival (PFS) in patients who completed the two-year program revealed the following:
  - Median PFS in patients in the rituximab arm who had received FCR has not been achieved; median PFS was 42 months in the observation arm (p = 0.009).
  - Median PFS in patients in the rituximab arm who had received FC has not been achieved (p = 0.004); median PFS was 24 months in the observation arm (p = 0.001).
- Hematological toxicity did not exceed grade 1 during rituximab maintenance therapy.
- Infections were reported in 7% of patients in both study arms.

Key conclusions
- This study demonstrates the effectiveness of rituximab maintenance therapy in the treatment of CLL.
- Rituximab maintenance therapy increased remission times and improved long-term results of treatment.

**Background**
At ASCO 2010, Parikh and colleagues reported findings from a historic comparison of patients with Rai III/IV chronic lymphocytic leukemia (CLL) treated with front-line FC (fludarabine, cyclophosphamide) versus FCR (fludarabine, cyclophosphamide, rituximab) at the M.D. Anderson Cancer Center.1

**Study design**
- All patients with previously untreated CLL who met the National Cancer Institute – Working Group (NCI-WG) 1996 criteria for therapy and who had been treated with the M. D. Anderson front-line protocols using FC, with or without granulocyte colony-stimulating factor (GCSF), and FCR were included in the study.
- Treatment protocols were as follows:
  - FC: fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²) on days 1–3 ± GCSF 275 mg/m² daily, every 4 weeks for 6 courses;
  - FCR: fludarabine (25 mg/m²) and cyclophosphamide (250 mg/m²) on days 2–4; rituximab (375 mg/m² on day 1 for the first course and 500 mg/m² for courses 2–6), every 4 weeks for 6 courses.
- Approximately one-third of patients given FCR received antibiotic prophylaxis with sulfamethoxazole/trimethoprim for *pneumocystis jiroveci* pneumonia, and one-half of patients received valacyclovir for herpes simplex prophylaxis.
- Limitations of the study were two-fold:
  - Newer prognostic factors, such as immunoglobulin heavy chain gene mutation status, ZAP-70 and CD38 expression, and chromosomal abnormalities identified by fluorescent in situ hybridization (FISH), could not be incorporated in the multivariable model, since the study predated the routine use of these tests.
  - Flow cytometry results to assess minimal residual disease (MRD) were available only for the FCR group and not for the FC group.

**Key findings**
- Data were available for 93 patients treated with FC, of whom 38 patients (41%) had Rai III/IV CLL, and for 300 patients treated with FCR, of whom 102 patients (34%) had Rai III/IV CLL.
- Median age of the Rai III/IV CLL patients was 57 years (range 41–92 years) and 60 years (range 38–86 years) in FC and FCR patients, respectively; baseline characteristics are shown in Table 1.

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**Table 1. Baseline characteristics of previously untreated Rai stage III/IV CLL patients treated with FC or FCR**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FC (n = 38)</th>
<th>FCR (n = 102)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>57 (41–92)</td>
<td>60 (39–86)</td>
<td>0.56</td>
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<tr>
<td>Median Hgb, g/dL (range)</td>
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<td>Median PLT, k/µL (range)</td>
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<td>95 (8–406)</td>
<td>0.98</td>
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<tr>
<td>Median WBC, k/µL (range)</td>
<td>101 (2–278)</td>
<td>61 (2–619)</td>
<td>0.11</td>
</tr>
<tr>
<td>Median ALC, k/µL (range)</td>
<td>92 (9–259)</td>
<td>51 (8–558)</td>
<td>0.05</td>
</tr>
<tr>
<td>Median ß2M, mg/L (range)</td>
<td>4.4 (1.7–10.7)</td>
<td>4.5 (1.8–12.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Karyotype: FC (n = 29); FCR (n = 85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploid, n (%)</td>
<td>22 (76)</td>
<td>49 (58)</td>
<td>0.08</td>
</tr>
<tr>
<td>Del(11q), n (%)</td>
<td>0 (0)</td>
<td>4 (5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Trisomy 12, n (%)</td>
<td>2 (7)</td>
<td>7 (8)</td>
<td>0.81</td>
</tr>
<tr>
<td>Complex, n (%)</td>
<td>3 (10)</td>
<td>16 (19)</td>
<td>0.29</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>2 (7)</td>
<td>9 (11)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*ALC = absolute lymphocyte count; ß2M = beta-2 microglobulin; Hgb = hemoglobin; PLT = platelet count; WBC = white blood cell count*
• Rai III/IV CLL patients treated with FCR, compared to those treated with FC, showed a higher complete response (CR) rate (66% versus 29%, respectively; \( p = 0.001 \)) and overall response (OR) rate (92% versus 79%, respectively; \( p > 0.05 \)).

• Median PFS was 79 months in Rai III/IV CLL patients treated with FCR, compared to 36 months for those treated with FC. (Figure 1)

• Median OS was 120 months in Rai III/IV CLL patients treated with FCR, compared to 55 months for those treated with FC. (Figure 2)

• Results of a multivariate analysis of factors associated with PFS and OS are presented in Table 2.

• A higher incidence of grade 3/4 neutropenia and thrombocytopenia was observed with FCR compared to FC. (Table 3)

• No significant difference in infectious complications between the two treatments was seen. (Table 3)

Table 2. Multivariable analysis for PFS and OS in previously untreated Rai stage III/IV CLL patients

<table>
<thead>
<tr>
<th>Progression-free survival (PFS)</th>
<th>Variable</th>
<th>( p )-value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )-2M</td>
<td>0.001</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0.01</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Treatment with FCR</td>
<td>0.001</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival (OS)</th>
<th>Variable</th>
<th>( p )-value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>( \beta )-2M</td>
<td>0.001</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Treatment with FCR</td>
<td>0.002</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

\( \beta \)-2M = beta-2 microglobulin; \( p \) = hazard ratio

Table 3. Toxicity profile in previously untreated Rai stage III/IV CLL patients treated with FC or FCR

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FC (( n = 38 ))</th>
<th>FCR (( n = 102 ))</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of courses administered</td>
<td>151</td>
<td>512</td>
<td>–</td>
</tr>
<tr>
<td>Hematological toxicity by course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 neutropenia, %</td>
<td>17</td>
<td>22</td>
<td>0.21</td>
</tr>
<tr>
<td>Grade 4 neutropenia, %</td>
<td>24</td>
<td>27</td>
<td>0.44</td>
</tr>
<tr>
<td>Grade 3 thrombocytopenia, %</td>
<td>6</td>
<td>9</td>
<td>0.23</td>
</tr>
<tr>
<td>Grade 4 thrombocytopenia, %</td>
<td>4</td>
<td>6</td>
<td>0.32</td>
</tr>
<tr>
<td>Infectious complications by course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major infections (pneumonia and sepsis), %</td>
<td>8</td>
<td>7</td>
<td>0.70</td>
</tr>
<tr>
<td>Minor infections (urinary tract infection,</td>
<td>11</td>
<td>10</td>
<td>0.82</td>
</tr>
<tr>
<td>upper respiratory tract infection, herpes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simplex, herpes zoster), %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key conclusions

- In patients with previously untreated Rai III/IV CLL, FCR is associated with significantly improved response rates and survival, compared to historic patients treated with FC.

- All physically fit patients with previously untreated CLL who meet NCI-WG criteria for treatment should be treated with FCR, regardless of their Rai stage.

Impact of TP53 mutations on outcome: results from the CLL-8 trial

Background
Evidence has shown that TP53 mutations are associated with poor survival in chronic lymphocytic leukemia (CLL). However, data on the efficacy of chemoimmunotherapy in CLL patients with and without TP53 mutation are limited.

As part of the German CLL Study Group’s phase III CLL-8 study comparing FCR (fludarabine, cyclophosphamide, rituximab) to FC (fludarabine, cyclophosphamide) in previously untreated CLL patients, data on various prognostic markers were collected. Zenz and colleagues used this data in their study, which was designed to examine the impact of the TP53 mutation in CLL patients treated with FC or FCR. Results of the study were presented at EHA 2010.

Study design
- Analysis of TP53 mutation status by microarray-based re-sequencing assay (Amplichip p53 assay in development by Roche Molecular Systems) and confirmatory direct DNA sequencing were performed in a central reference laboratory.
- Samples were available for 628 patients (76.9%) at study entry; this cohort was representative of the full trial population in terms of other baseline prognostic factors and demographics.
- In addition, 94 follow-up samples of 89 patients at relapse were available.

Key findings
- Incidence of TP53 mutations was 11.9% (71/628; 41 in FC arm, 30 in FCR arm).
- Forty-two (42) of 51 patients (82.4%) with 17p deletion had TP53 mutation.
- Five percent (5%) of patients without 17p deletion (28/553) had TP53 mutation.
- Patients with TP53 mutation showed lower complete response (CR) and overall response (OR) rates as compared to the group without TP53 mutation. (Table 1)
- Lower response rates were observed for the TP53 mutation groups in both the FC and the FCR arms: CR was 3.2% and 11.1%, while OR was 51.6% and 74.1%, respectively. (Table 1)
- Median progression-free survival (PFS) was significantly shorter for patients with TP53 mutations (12.3 months versus 45 months; HR 4.4; p <0.001).
- Median PFS was longer for patients in the FCR group in the TP53 mutated subgroup (FC 12.1 versus FCR 15.4 months; HR 0.53; p = 0.019). (Figure 1)
- Patients with TP53 mutation showed a median OS of 39.4 months; median OS was not reached in all other patients (HR 6.0; p <0.001). (Table 2)
- Median OS was greater for patients in the FCR group in the TP53 mutated subgroup (FC 30.4 months versus FCR 52.4 months; p <0.001). (Table 2)
- Multivariate analysis was performed by Cox regression including age, stage, treatment arms, immunoglobulin heavy chain (IgHV) status, genomic aberrations, and TP53 mutation.
- Regarding PFS (n = 567), independent prognostic factors identified were:
  - 17p− (HR 3.6; p <0.001);
  - TP53 mutation (HR 2.2; p <0.001);
  - unmutated IgHV (HR 1.7; p <0.001);
  - age (HR 1.4; p <0.001);
  - FCR (HR 0.52; p <0.001).

Table 1. Response rates by TP53 mutation in CLL patients treated with FC or FCR

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Complete response (%)</th>
<th>Overall response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>6.9</td>
<td>62.1</td>
</tr>
<tr>
<td>No TP53 mutation</td>
<td>36.4</td>
<td>95.3</td>
</tr>
<tr>
<td>FC arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>3.2</td>
<td>51.6</td>
</tr>
<tr>
<td>No TP53 mutation</td>
<td>24.2</td>
<td>92.2</td>
</tr>
<tr>
<td>FCR arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>11.1</td>
<td>74.1</td>
</tr>
<tr>
<td>No TP53 mutation</td>
<td>47.8</td>
<td>98.2</td>
</tr>
</tbody>
</table>
Regarding OS (n = 580), independent prognostic factors identified were:
- 17p– (HR 3.5; p <0.001);
- TP53 mutation (HR 2.6; p <0.001);
- unmutated IgHV (HR 1.6; p = 0.035);
- FCR (HR 0.6; p = 0.019).

A total of 94 follow-up samples were collected on a median of 1,028 days after the initial sample (range 97–1,963 days).

Analysis of follow-up samples showed a 26.6% (25/94) incidence of TP53 mutation.

All 17 cases with TP53 mutation before treatment and with an available follow-up sample showed the same mutation.

Eight (8) follow-up samples showed a TP53 mutation that was not present initially (10.5%; 8/76 samples tested).

### Key conclusions

- **17p deletion and TP53 mutation (independent of 17p deletion) are powerful and independent prognostic markers after first-line FC and FCR treatment in CLL.**
- **TP53 mutations or 17p deletion account for 52% of FC/FCR refractory cases.**
- **TP53 mutations are associated with poor response, PFS, and OS in CLL.**
- **Analysis of TP53 mutations should be added to pre-treatment assessment of patients with CLL.**

### References:
Efficacy of FC and FCR regimens in the first-line treatment of patients with chronic lymphocytic leukemia: a 7.5 year follow-up

Background

At EHA 2010, Stadnik and colleagues presented data from a 7.5 year follow-up of their study examining the survival benefit produced by adding rituximab to the standard FC (fludarabine and cyclophosphamide) regimen (FCR) in treatment-naïve chronic lymphocytic leukemia (CLL) patients. In particular, the study investigated whether the presence of enlarged abdominal lymph nodes (EALN) and the absence of response after three cycles are associated with inferior survival.1

Study design

- Between 2002 and 2008, a total of 77 patients were consecutively included in the study, 43 in the FC arm and 34 in FCR arm; no strict exclusion criteria were used for recruitment.
- Assignment to FCR was based predominantly on the availability of rituximab in general practice; nearly all newer patients received FCR as part of their treatment.
- Treatment schedules were standard.
- Treatment was suspended or withdrawn in cases of severe toxicity; no dose reduction was done.
- Only 11 patients received fewer than 6 cycles (range 4–5 cycles).
- Response was defined according to National Cancer Institute (NCI) criteria.
- CD38 was measured by CytoFlow, with a 30% cut-off (available in 57 patients).
- VH genes were analyzed by cDNA sequencing with a 98% threshold (available in 32 patients).
- Lymph nodes were revealed by computerized tomography (CT) and ultrasound before therapy (available in 71 patients); ultrasound was also performed after 3 cycles and after completion of treatment.
- Lymph nodes >10 mm in diameter were considered abnormal, and nodes >100 mm in diameter were considered bulky.
- Early response (ER) was defined as partial response (PR) or complete response (CR) after 3 cycles of therapy; others were considered non-early responders (nER).

Key findings

- Treatment arms were well balanced with regard to sex (male-to-female ratio ~2:1) and age (median 59 years, range 43–78 years), but there was a tendency towards more advanced disease stage in the FC arm (21 versus 8 Binet C patients).
- Overall response (OR) and CR rates were numerically higher in the FCR arm than in the FC arm; no significant differences were found. (Table 1)
- After 7.5 years of follow-up, there were 36 events in the FC arm (84%) and 14 in the FCR arm (41%) ($p = 0.0002$).
- Twenty-four (24) deaths were registered in the FC arm (56%) and 5 in the FCR arm (15%) ($p = 0.0002$).
- Median progression-free survival (PFS) in the FCR arm was 35 months, compared to 21 months in the FC arm ($p = 0.006$). (Table 1)
- Median OS in the FCR arm was not reached; median OS was 42 months in the FC arm. (Table 1)
- Three-year overall survival (OS) in the FC arm was 54%, compared to 76% in the FCR arm ($p = 0.03$), based on analysis of 66 patients.
- Estimated four-year OS was 45% in the FC arm and 66% in the FCR arm ($p = 0.059$), based on analysis of 61 patients.
- After 7.5 years of follow-up, PFS and OS were significantly higher with FCR treatment ($p <0.05$). (Figures 1 and 2)

Table 1. Response to treatment in CLL patients treated with FC or FCR

<table>
<thead>
<tr>
<th>Response</th>
<th>FC (n = 43)</th>
<th>FCR (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>20 (46)</td>
<td>23 (67)</td>
<td>0.05</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>15 (35)</td>
<td>8 (24)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall response, n (%)</td>
<td>35 (81)</td>
<td>31 (91)</td>
<td>0.18</td>
</tr>
<tr>
<td>Stable disease/progression, n (%)</td>
<td>8 (19)</td>
<td>3 (9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>21</td>
<td>35</td>
<td>0.006</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>41</td>
<td>not reached</td>
<td>–</td>
</tr>
</tbody>
</table>

OS = overall survival; PFS = progression-free survival
Major prognostic factors
- CD38 status did not predict PFS and OS in the FCR arm.
- In the FC arm, patients with a high expression of CD38 had an inferior median PFS (19 months versus 32 months; \( p = 0.039 \)) and a tendency towards shorter median OS (40 months versus not reached; \( p = 0.06 \)).
- Median PFS was inferior in VH-unmutated cases in both the FC and FR arms (23 months versus 52 months; \( p = 0.05 \)); this group of patients also showed a tendency towards inferior OS (42 months versus not reached; \( p = 0.08 \)).
- Presence of EALN was associated with inferior PFS in both the FC and FCR arms; a trend to shorter OS in EALN-positive patients was observed (44 months versus not reached; \( p = 0.259 \)).
- Median PFS in patients with an ER was 30 months and 56 months (\( p = 0.064 \)) in the FC and FCR arms, respectively.

Key conclusions
- FCR regimen is recommended as a first-line CLL treatment in general clinical practice.
- Addition of rituximab to the FC regimen in first-line treatment improves OS and PFS.
- The three-year survival of patients treated with FCR is nearly two-fold higher compared to FC.
- The presence of EALN appears to be an independent adverse prognostic factor in CLL, associated with decreased PFS.
- Patients with response after three cycles of fludarabine-containing therapy have a favourable disease course.

Cost effectiveness of FCR in patients with previously untreated chronic lymphocytic leukemia

Background
At ASCO 2010, Hornberger and colleagues presented results of a cost-effectiveness analysis comparing FCR (fludarabine, cyclophosphamide, rituximab) and FC (fludarabine and cyclophosphamide) for the treatment of chronic lymphocytic leukemia (CLL). The analysis was conducted from a U.S. third-party payer perspective.1

Study design
- A decision-analytical model to project progression-free survival (PFS) and overall survival (OS) data over a time horizon of 15 years was developed.
- Costs calculated in 2009 U.S. dollars included chemotherapy drugs, administration, treatment of grade 3/4 adverse events, and salvage therapies after disease progression.
- Drug costs were based on the dose tables from the trial and were calculated using Medicare fee schedules.
- Utilities for stable and progressed disease were obtained from the literature.
- Main outcome measures were incremental cost-effectiveness ratio (ICER) for life-year and quality-adjusted life-year (QALY) gained.
- One-way and probabilistic sensitivity analyses (PSA) were conducted to assess the robustness of the results.

Key findings
- Using the area under the curve approach, FCR increased both PFS and OS by 1.9 years, and QALYs by 1.2 years, compared with FC.
- FCR incurred $28,000 higher costs for chemotherapy drugs and administration, and $3,500 for treatment of adverse events.
- Part (16%) of these increased costs for FCR was offset by higher treatment and administration costs for FC after progression due to early relapse.
- The net difference in costs between FCR and FC was $26,000, resulting in an ICER of $22,000.
- Results were sensitive to time horizon, cost of 100 mg vial of rituximab, and discount rate.
- The ICER exceeded $30,000 and $50,000 in 11% and 0.4% of probabilistic simulations, respectively.

Key conclusions
- The net difference in costs between FCR and FC compares well with the cost-effectiveness of oncology treatments in the United States.
- Among previously untreated patients with CLL, the chemotherapeutic regimen FCR is a cost-effective use of medical resources compared to FC.

The study presented by Parikh, et al. is a retrospective historical comparison, and the results need to be considered in that context. Non-standardized use of supportive care, such as granulocyte colony-stimulating factor (GCSF) or antimicrobial prophylaxis, could potentially have an impact on dose intensity differently in the two arms, resulting in unpredictable effects on treatment response. In addition, European Clinical Oncology Group (ECOG) performance status was not included in the baseline data presented. The possibility of patient selection bias therefore exists in this study. Furthermore, the subject numbers in the two arms, particularly in the standard FC arm (n = 38), are small.

Results of this non-randomized study suggest that FCR might be more effective than FC in patients with Rai III/IV CLL. Complete response (CR) rate, median progression-free survival (PFS), and median overall survival (OS) were superior in the cohort receiving FCR. Although more grade 3/4 neutropenia and thrombocytopenia occurred in the patients receiving FCR, these adverse events did not translate into a higher rate of major or minor infections. From the data presented, FCR appears to have been well tolerated.

Efficacy results for patients receiving FCR are explicitly stated in the study by Parikh: CR and overall response (OR) rates are 66% and 92%, respectively, and median PFS and OS are 79 months and 120 months, respectively. In the CLL-8 data updated by Hallek, et al. at ASH 2009, results for the Binet C subgroup were not stated as explicitly. However, taking the entire FCR arm in the Hallek study, which would overestimate the results for the Binet C subgroup, the results were not as impressive as in the study by Parikh: in CLL-8, CR and OR rates were 44% and 95%, respectively; median PFS was 58 months, with median OS not reached at median follow-up of 37 months. Rai III/IV patients from the study by Parikh appear to do substantially better on FCR than Binet C patients from the CLL-8 study.

An average of 5 cycles versus 4.5 cycles were administered to the FCR cohort in the Parikh and Hallek studies, respectively, suggesting better tolerance in the Parikh study. However, incidence rates of grade 3/4 hematologic toxicity cannot be compared between the two studies, because Parikh presents the incidence by treatment cycle and Hallek presents the incidence by patient.

The multivariate analysis in the Parikh study is limited by its absence of currently recognized important prognostic factors, such as immunoglobulin heavy chain gene mutation status, ZAP-70 and CD38 expression, and chromosomal abnormalities identified by fluorescent in situ hybridization (FISH). The independent predictive value of ß2M (HR 0.83 for PFS; 0.76 for OS) is confirmed in the randomized CLL-8 trial and others, and is readily available in most labs. ß2M is therefore a useful prognostic test to use in routine clinical practice. The alkaline phosphatase, while statistically significant, carried a hazard ratio of 0.99 and thus has low utility.

Interpreting the Parikh study and the CLL-8 study together, FCR appears to be highly effective and relatively safe in a carefully selected cohort of Rai III/IV patients. The CLL-8 data clearly shows that patients do not do well if the physician is unable to deliver more than three cycles of FCR (in Binet C patients, median PFS was 14 months if ≤3 cycles were delivered versus 44 months if ≥4 cycles were delivered). The dose intensity delivered in the Parikh study was higher, with corresponding superior results. Using this data, I would use FCR in more fit Rai III/IV patients. The cumulative illness rating scale (CIRS) might be a useful tool to determine fitness.

We are currently seeking provincial funding to use FCR as front-line treatment for symptomatic CLL. I intend to use FCR in all fit symptomatic patients requiring therapy. Judging fitness for treatment is subjective and includes patient preference. I am interested in the German CLL study group’s approach in its randomized CLL-10 study examining FCR versus bendamustine-R, as this study excludes unfit patients, as defined by a CIRS score >6.
The study by Zenz, et al. is a biological correlative study associated with the randomized CLL-8 clinical trial. Samples were available for TP53 mutational analysis on an impressive 77% of patients from the CLL-8 trial. This study is therefore well powered to evaluate the association of TP53 with treatment outcome.

In patients with TP53 mutation, FCR achieved better PFS (15.4 versus 12.1 months; HR 0.53; p = 0.019) and OS (52.4 versus 30.4 months; p <0.001) than FC. CR (11.1% versus 3.2%) and OR (74.1% versus 51.6%) rates were also better with FCR, although p-values were not reported. TP53 mutations were commonly associated with 17p deletion (82% of subjects with 17p deletion had TP53 mutation); however, in multivariate analysis, both TP53 mutation and 17p deletion maintained independent prognostic significance.

We routinely screen for β2M and perform FISH cytogenetics; however, I currently use FCR for front-line treatment of all fit symptomatic patients. If the current study had shown no benefit for FCR in patients with TP53 mutation, I might have considered screening for this marker and choosing not to give FCR in patients who test positive. However, the Zenz study reassures me that we have no reason to change our treatment approach in patients with TP53 mutation until treatments superior to FCR can be found.

The Zenz, et al. study confirms for TP53 mutations what we have seen in prior studies for 17p deletions. Both mutations can be absent at diagnosis and be acquired over the course of the illness, presenting at relapse. Our current treatment policies indicate screening for 17p deletion at diagnosis or prior to first therapy, but we have no policy related to screening at relapse in patients who were previously negative. I would therefore not be convinced by data from this study to screen for TP53 at relapse. Alemtuzumab or allogeneic stem cell transplant (ASCT) are available for selected patients who relapse after standard treatments. Both of these modalities have evidence supporting their use in patients with 17p deletions and may prove successful in patients with TP53 mutation.

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- 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,†

- Four-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 (all grades) reported in ≥10% of patients receiving SUTENT for treatment-naïve mRCC (n=375) 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. 26.1%), hypertension (23.7% vs. 1.1%), vomiting (24.0% vs. 10.0%), rash (22.7% vs. 7.3%), mucosal inflammation (20.0% vs. 1.1%) and hand-foot syndrome (20.3% vs. 0.6%).
  - The most common grade 3/4 adverse events (occurring in ≥10% of SUTENT patients) were hypertension (8.3% vs. 0.3%), fatigue (7.2% vs. 11.7%), thrombocytopenia (6.6% vs. 0%), neutropenia (6.7% vs. 2.5%) and hand-foot syndrome (5.1% vs. 0%).3

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

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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 the Prescribing Summary for complete information.

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**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.3

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1 Results of an interim analysis from a Phase III, randomized, multicentre, international trial. Patients were treated with either 50 mg SUTENT once daily in cycles of 4 weeks on/2 weeks off (n=375) or 9 MIU IFN-α 3 times per week, administered subcutaneously (n=375) until disease progression or study withdrawal. Primary endpoint was PFS and secondary endpoints included objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST), overall survival (OS) and safety.

3 Results of an interim analysis from a Phase III, randomized, multicentre, international trial. Patients were treated with either 50 mg SUTENT once daily in cycles of 4 weeks on/2 weeks off (n=375) or 9 MIU IFN-α 3 times per week, administered subcutaneously (n=375) until disease progression or study withdrawal. Primary endpoint was PFS and secondary endpoints included objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST), overall survival (OS) and safety.

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Indicated for first-line use in metastatic RCC.
New Developments in NHL Treatment with GA101, Navitoclax, Bendamustine, and Rituximab

The outcome of patients with non-Hodgkin’s lymphoma (NHL) has improved considerably in recent years; however, treatment failure as a result of drug resistance remains an ongoing problem. Advances in the understanding of the molecular pathogenesis of NHL have led to the development of new agents directed against specific molecular targets. A number of these targeted agents are being examined in preclinical and clinical trials in NHL.1

GA101 (RO5072759) is a fully humanized, glycoengineered, novel type II monoclonal antibody that binds with higher affinity to the CD20 type II epitope than classic type I antibodies such as rituximab.2,3 A phase I/II clinical trial by Salles, et al., showed GA101 to be well tolerated and to have promising efficacy in patients with relapsed/refractory CD20-positive lymphoid malignancies.3 Consequently, a phase II study is currently underway to examine the efficacy and safety of GA101 in heavily pre-treated indolent NHL patients.

Navitoclax (ABT-263) is a novel small molecule B-cell leukemia 2 (Bcl-2) family protein inhibitor, an orally bioavailable BH3 mimic that binds (Ki ≤1 nM) to Bcl-2, Bcl-xL, and Bcl-w with high affinity. Navitoclax also displays potent preclinical cytotoxicity (EC50 ≤1 μM) against human tumour cell lines (small cell lung carcinomas, and T and B lymphoid malignancies) that express Bcl-2. Navitoclax is being examined in a phase I/IIa study as a potential agent in relapsed/refractory lymphoid malignancies.4

Bendamustine, an alkylating agent with a purine-like benzimidazole ring, has shown promising activity as a single-agent and in combination with rituximab in indolent lymphomas. However, studies examining the efficacy of bendamustine in aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) are limited. The favourable safety profile and demonstrated efficacy of bendamustine when combined with rituximab make this regimen a promising option for the treatment of DLBCL. The combination of rituximab and bendamustine is currently being examined in a phase II study in DLBCL.5

Survival of patients with adult Burkitt’s lymphoma (BL), a cancer of the lymphatic system, has improved with the development of intensive multi-agent chemotherapy. However two-year survival rates remain under 65%; efforts to improve survival and decrease treatment-related toxicities are therefore needed. The safety of incorporating rituximab and liposomal doxorubicin into CODOX-M/IVAC in HIV patients with untreated Burkitt’s lymphoma is being examined in an ongoing study.6

Data from studies using these agents were presented at ASCO 2010 and EHA 2010. This article reports on three such studies from EHA and one from ASCO:

• A phase II study presented at EHA 2010 showed that single-agent GA101 was well tolerated in a group of heavily pre-treated indolent NHL patients, had good response rates, and was effective regardless of rituximab pre-treatment or refractoriness.

• Results of an ongoing phase I/IIa study presented at EHA 2010 indicated that navitoclax has promising activity in relapsed/refractory lymphoid malignancies and is well tolerated, with predictable thrombocytopenia that should be managed using an appropriate dosing regimen.
• Data from a phase II study presented at EHA 2010 demonstrated that the combination of rituximab plus bendamustine shows promising efficacy and is well tolerated in patients with relapsed/refractory DLBCL.

• A study presented at ASCO 2010 showed that incorporating rituximab and liposomal doxorubicin into CODOX-M/IVAC in HIV-positive or HIV-negative patients with Burkitt’s lymphoma appears to be safe.


Salles GA, et al. EHA 2010: Abstract 0558

GA101 in heavily pre-treated patients with relapsed/refractory indolent NHL

(Note: See the interview with Dr. Gilles Salles on page 69 for his commentary on this study.)

Background

At EHA 2010, Salles and colleagues presented results of the GAUGUIN study, a phase II non-randomized trial examining the efficacy of GA101 in heavily pre-treated patients with indolent non-Hodgkin’s lymphoma (NHL).1

Study design

• Forty (40) patients with relapsed/refractory indolent NHL were given GA101 in a low-dose (n = 18) or a high-dose (n = 22) cohort.

• GA101 was given on days 1, 8, 22, and then every 21 days for a total of 9 infusions over six months.

• GA101 was administered using the following dosing:
  ➥ 400 mg for all infusions in the low-dose cohort;
  ➥ 1600 mg on days 1 and 8, and 800 mg thereafter in the high-dose cohort.

• The first dose was 50% of subsequent doses; dose escalation was based on safety in a 3 + 3 design.

• Pre-medications included acetaminophen and antihistamines.

• Primary objective was to examine the efficacy and safety of the two GA101 doses.

• Secondary objectives were to examine:
  ➥ overall response (OR) rate;
  ➥ progression-free survival (PFS);
  ➥ event-free survival (EFS);
  ➥ pharmacokinetics;
  ➥ B-cell depletion and recovery;
  ➥ pharmacogenetic parameters (including FcγRIIa and IIIa).

• End of treatment response was evaluated four weeks after the last infusion (44 weeks after treatment start).

Study design

400 mg/20 patients

Low-dose GA101* (400 mg) x 8 cycles

G53

1600 mg

800 mg/20 patients

High-dose GA101* (1600/800 mg) x 8 cycles

*GA101 was given on days 1, 8, 22, and every 21 days thereafter (9 infusions)

NHL = Indolent NHL
**Key findings**

**Baseline characteristics and disposition**
- Patients were heavily pre-treated, with a median of four prior therapies.
- Most patients (60%) were rituximab refractory (patients not responding to or relapsing within six months after a previous rituximab-containing regimen).
- Median age of patients was 60.5 years (range 42–79 years), and 25/40 patients were male.
- There were no significant differences in demographics and baseline tumour burden between the two cohorts.
- The majority of patients (75%) completed all scheduled nine infusions.

**Safety**
- GA101 was well tolerated in both cohorts, with the most common adverse events (AEs) being infusion-related reactions, mostly grade 1/2. (Figure 1)
- Eleven (11) patients experienced at least one serious adverse event (SAE), with 5 SAEs related to GA101 (low-dose: 1 event; high-dose: 4 events).
- Treatment-related grade 3/4 hematological AEs included transient neutropenia (3 events in high-dose) and thrombocytopenia (1 event in high-dose).
- Four patients experienced at least one grade 3/4 infection (low-dose: 1 patient, high-dose: 3 patients).

**Pharmacokinetics**
- GA101 pharmacokinetics was similar to rituximab, characterized by two clearance components: one linear and one time-dependent saturable component consistent with target-mediated disposition.
- Overall, higher GA101 plasma concentrations were observed in the high-dose group, compared with the low-dose group. (Figure 2)

**Efficacy**
- A total of 38/40 patients were evaluable for end of treatment response.
- End of treatment response was 17% in the low-dose cohort and 55% in the high-dose cohort. (Table 1)
- Of 24 rituximab-refractory patients, six patients in the high-dose and one patient in the low-dose cohort responded. (Table 2)
- An additional refractory patient in the high-dose cohort with stable disease (SD) at end of treatment converted to partial response (PR) post-treatment. (Table 2)
- Responses occurred across all FcγRIIIA genotypes in both cohorts: of three responders in the low-dose group, two patients had the F/F genotype and one was unknown; of 12 responders in the high-dose group, five patients had the F/F genotype and seven had the F/V genotype.

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**Figure 1. Adverse events and infusion-related reactions after treatment with GA101 by dose cohort**
Figure 2. Pharmacokinetics of GA101 by dose cohort

<table>
<thead>
<tr>
<th>Time (day)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose (n = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose (n = 18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average GA101 (µg/mL)

Table 1. End of treatment response to GA101 by dose cohort

<table>
<thead>
<tr>
<th>Response</th>
<th>High-dose cohort (n = 22)</th>
<th>Low-dose cohort (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Stable disease, n</td>
<td>6*</td>
<td>6</td>
</tr>
<tr>
<td>Progressive disease, n</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>55</td>
<td>17</td>
</tr>
</tbody>
</table>

*One patient converted from SD to PR in the safety follow-up period (day 260)

Table 2. End of treatment response to GA101 in rituximab-refractory patients

<table>
<thead>
<tr>
<th>Response</th>
<th>Rituximab refractory (n = 24)</th>
<th>High-dose cohort (n = 11)</th>
<th>Low-dose cohort (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease, n</td>
<td>7*</td>
<td>3*</td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease, n</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>31.8</td>
<td>55</td>
<td>8</td>
</tr>
</tbody>
</table>

*One patient converted from SD to PR in the safety follow-up period (day 260)

Key conclusions

- In this group of heavily pre-treated indolent NHL patients, single-agent GA101 was well tolerated and showed a good response rate in the high-dose cohort.
- High efficacy was observed, regardless of rituximab pre-treatment or refractoriness.
- The superior response rates observed in the high-dose cohort, combined with pharmacokinetic data, indicate a dose-response relationship for GA101.
- These results, especially in rituximab-refractory patients, compare favourably with other naked or conjugated monoclonal antibodies currently investigated in NHL.
- GA101 represents a promising agent that can potentially improve the treatment of NHL.

Navitoclax (ABT-263) in relapsed/refractory lymphoid malignancies

Background
At EHA 2010, Wilson and colleagues presented results of their study assessing the safety, pharmacokinetics, and maximum tolerated dose (MTD) of navitoclax (ABT-263).1

Study design
• An ongoing phase I/IIa dose-escalating study using a modified Fibonacci 3 + 3 design is examining the safety, pharmacokinetics, and MTD of navitoclax in relapsed/refractory lymphoid malignancies.
• For cycle 1, navitoclax was administered on day –3 to assess pharmacokinetics and food effect.
• Beginning on day 1 of cycle 1, subjects were dosed non-fasting for 14 consecutive days on days 1–14 of a 21-day dosing cycle.
• In subsequent cycles, subjects received the drug on days 1–14, followed by 7 days off.
• Patients were enrolled in cohorts at successively higher dose levels, beginning at 10 mg. The dose was doubled for each subsequent cohort until one grade 3 toxicity was observed at the 160 mg dose level. Dose escalation continued to a dose level of 440 mg, and a maximum tolerable 14/21-day dose of 315 mg was declared.
• Patients have subsequently been enrolled at successively higher dose levels under a continuous 21/21-day dosing schedule, which follows a 150 mg lead-in dose for 7–14 days. Cohorts begin at a 200 mg dose level and have escalated to the current 425 mg cohort. A maximum tolerable 21/21-day dose of 325 mg was declared and determined as the recommended phase II schedule and dose.
• For the phase Ia portion, blood samples were collected during cycle 1 on day –3, day 1, and day 14 at 0 hours and at multiple post-dose time points. Additional samples were collected at 0 hours on day 14, cycles 2–6.
• Urine was collected 0–24 hours post-dosing on cycle 1, day –3.
• Platelet counts were extensively monitored throughout the study.
• Tumour responses were evaluated using the International Working Group (IWG) criteria and National Cancer Institute Working Group (NCI-WG) criteria for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) subjects.

MTD = maximum tolerated dose; PK pyruvate kinase

MTD = maximum tolerated dose; PK pyruvate kinase

\[ \text{MTD} = \text{maximum tolerated dose; PK pyruvate kinase} \]
Key findings

Baseline characteristics and disposition

• To date, 55 patients are enrolled in the study, all of whom have received at least one cycle of navitoclax:
  - 38 patients on 14/21-day dosing (highest level dosed: 440 mg; highest dose cleared: 315 mg);
  - 17 patients on 21/21-day continuous dosing (highest level dosed: 425 mg).
• Median age of patients was 59 years (range 20–81 years).
• Baseline histology was as follows:
  - six patients (11%) with diffuse large B-cell lymphoma (DLBCL);
  - four patients (7%) with mantle cell lymphoma (MCL);
  - sixteen patients (29%) with follicular center cell lymphoma (FL);
  - six patients (11%) with other indolent lymphomas;
  - twenty patients (36%) with CLL or SLL;
  - two patients (4%) with classical Hodgkin’s lymphoma;
  - one patient (2%) with peripheral NK/T-cell lymphoma.

Pharmacokinetics

• The pharmacokinetic profile of navitoclax on the 14/21-day schedule was linear and dose proportional from 10–440 mg, with a terminal half-life of approximately 17 hours.
• Peak concentration ($C_{\text{max}}$) occurred approximately nine hours post-dose.
• Inter-subject variability in area under the curve (AUC) was approximately 40%.
• Food increased navitoclax oral bioavailability by approximately 20% with the current lipid formulation, which does not appear to be clinically significant.

Safety

• Platelet nadirs were transient on the 14/21-day schedule and occurred on days 3–5.
• Common ($\geq 13\%$) treatment-related adverse events (AEs) are presented in Figure 1.
• Four patients on the 14/21-day schedule had dose-limiting toxicities (DLTs):
  - one patient at 160 mg had bronchitis;
  - two patients at 315 mg had elevated alanine transaminase (ALT) and grade 4 thrombocytopenia;
  - one patient at 440 mg had atrial fibrillation.
• Three patients on the 21/21-day schedule had DLTs:
  - one patient at 275 mg had grade 4 thrombocytopenia;
  - two patients at 425 mg had grade 3 ALT and grade 3 gastrointestinal (GI) bleed.
• Of 51 patients who discontinued therapy, 40 did so due to progressive disease, 6 due to AEs, and 5 withdrew consent.

Figure 1. Common ($\geq 13\%$) treatment-related adverse events in patients treated with navitoclax
Key conclusions

- Navitoclax has a linear pharmacokinetic profile and is well tolerated, with toxicity due to on-target effects and anti-tumour activity in patients with relapsed/refractory lymphoid malignancies.
- Thrombocytopenia was predictable and manageable.
- Lead-in dosing with 150 mg/day of navitoclax followed by continuous dosing minimizes platelet nadir and cycle variability.
- Based on the 21/21-day continuous dosing data, the maximum tolerated dose has been reached according to the modified Fibonacci 3 + 3 model.
- To mitigate platelet nadirs and stabilize cycle variability, the phase II recommended dosing regimen for navitoclax is 150 mg for a 7–14 day lead-in, followed by 325 mg/day continuous dosing.


Efficacy

- All 55 enrolled patients were evaluable for tumour response/efficacy:
  - one NK/T-cell lymphoma patient had a 75% reduction in cutaneous lesions;
  - two follicular lymphoma patients had an unconfirmed partial response (PR);
  - six CLL/SLL patients had confirmed PRs due to decreases in lymphadenopathy;
  - one CLL/SLL patient had an unconfirmed PR due to decreases in lymphadenopathy and circulating lymphocytes;
  - four additional CLL/SLL patients achieved ≥50% decrease in circulating lymphocytes.
- In patients with stable disease who showed a reduction in tumour size, responses ranged from 1% to 46%.
- Median progression-free survival (PFS) was 88 days (95% CI: 46–171 days).
- One patient treated with 80 mg navitoclax had a PR with 99% reduction after eight cycles; this patient had a radiographic response rate >30% and decreased circulating leukemia cells.
- One patient treated with 315 mg navitoclax had a PR with 75% reduction in cutaneous lesions after two cycles.


Bendamustine plus rituximab in relapsed/refractory diffuse large B-cell lymphoma

Background

At EHA 2010, Vacirca and colleagues presented initial results of their phase II clinical trial examining bendamustine plus rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).¹

Study design

- The study is an ongoing, open label, single-arm, Simon two-stage designed trial in patients with CD20-positive disease.
- Goal is to enroll up to 54 patients with DLBCL who have failed at least one prior therapy.
- Study treatment is given in six 28-day cycles as follows:
  - bendamustine at 120 mg/m² given on days 1 and 2;
  - rituximab at 375 mg/m² given on day 1.
- Primary objective is to measure the overall response (OR) rate of bendamustine plus rituximab.
- Secondary objectives are to measure:
  - duration of response;
  - time to progression;
  - progression-free survival (PFS);
  - safety profile.
- Safety is assessed weekly, and disease status is evaluated at the completion of every two cycles using the revised response criteria for malignant lymphoma.
- A two-stage Simon design was used to confirm interim response.

Inclusion/Exclusion criteria

- Patients included in the study have:
  - confirmed CD20-positive DLBCL;
  - at least one measurable lesion >1.5 cm;
Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; normal thyroid function with no major co-morbidities; left ventricular ejection fraction (LVEF) within normal range; relapsed/refractory (progression or non-response within the past 60 days) to at least one prior treatment.

Patients with prior bendamustine treatment or who are refractory to rituximab are excluded.

Key findings

- To date, the intent-to-treat (ITT) population includes 36 patients.
- Median age of patients is 74.5 years (range 54–90 years), with baseline ECOG status of 0 (15 patients, 42%), 1 (19 patients, 53%), and 2 (2 patients, 5%).
- In total, 76 cycles were administered to the modified ITT population (26 patients, median 3 cycles per patient).
  - two cycles were completed by 26 patients;
  - four cycles were completed by 12 patients;
  - six cycles were completed by 4 patients.
- Current efficacy data for 26 evaluable patients resulted in an OR rate of 58% (complete response [CR] 19%, partial response [PR] 39%). (Table 1)
- Responses by the revised international prognostic index (RIPI) score are presented in Table 2.
- Responses after treatment cycles 2, 4, and 6 are presented in Table 3.
- Treatment-related adverse events (AEs) included four grade 4 and twenty grade 3 hematologic events. (Table 4)
- Treatment was discontinued in 25 patients:
  - twelve patients with progressive disease;
  - five patients withdrew consent;
  - five patients based on investigator’s decision;
  - two patients due to disease-related death;
  - one patient with intercurrent illness.

Table 1. Response rates in relapsed/refractory DLBCL patients after treatment with rituximab plus bendamustine

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (OR)</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

RIPI = revised international prognostic index

Table 2. Best response by baseline RIPI score in relapsed/refractory DLBCL patients after treatment with rituximab plus bendamustine

<table>
<thead>
<tr>
<th>Baseline RIPI score</th>
<th>Response</th>
<th>RIPI 1</th>
<th>RIPI 2</th>
<th>RIPI 3</th>
<th>RIPI 4</th>
<th>RIPI 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Response rates by treatment cycle in relapsed/refractory DLBCL patients after treatment with rituximab plus bendamustine

<table>
<thead>
<tr>
<th>Cycle 2 (n = 26)</th>
<th>Cycle 4 (n = 12)</th>
<th>Cycle 6 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Patients (n)</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>13</td>
<td>50</td>
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<tr>
<td>Stable disease (SD)</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>
**Table 4. Grade 3/4 adverse events in relapsed/refractory DLBCL patients after treatment with rituximab plus bendamustine**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decreased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Leukocyte count decreased</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Key conclusions**

- Data suggests the combination of rituximab plus bendamustine is well tolerated and suited to an elderly, non-transplanted relapsed/refractory DLBCL population.
- Further data are required to fully evaluate response and utility of this regimen in patients with previous aggressive salvage therapies and stem cell transplants.


Gregory SA, et al. ASCO 2010: Abstract 8033

**Incorporation of rituximab and liposomal doxorubicin into CODOX-M/IVAC for HIV-negative and HIV-positive patients with untreated Burkitt’s lymphoma**

**Background**

At ASCO 2010, Gregory and colleagues presented results of their study examining the incorporation of rituximab and liposomal doxorubicin into CODOX-M/IVAC in HIV patients with untreated Burkitt’s lymphoma.1

**Study design**

- Results of the first stage (12 patients) of a Simon two-stage investigator-initiated trial (planned analysis) are reported.

- Low-risk patients were defined as:
  - normal lactose dehydrogenase (LDH);
  - stage I/II Burkitt’s lymphoma;
  - European Clinical Oncology Group (ECOG) <2;
  - no mass >10 cm.
- All other patients were high-risk.
- Low-risk patients received three cycles of doxorubicin and high-dose methotrexate (CODOX-M).

- High-risk patients received four alternating cycles of CODOX-M and ifosfamide, etoposide, and high-dose cytarabine (IVAC).

- Liposomal doxorubicin (40 mg/m²) was used in lieu of doxorubicin (day 1 CODOX-M).

- Rituximab (500 mg/m²) was added to days 0 and 8 of CODOX-M and to days 0 and 6 of IVAC; methotrexate was given at 3,000 mg/m² iv.

**Key findings**

- Eighteen patients have enrolled, of whom 12 were in the first stage of Burkitt’s lymphoma.
- The median age of patients was 43 years (range 23–70 years); 3/12 patients had HIV-positive disease, and 9/12 had high-risk disease.
- Eleven (11) patients were evaluable for response.
Key conclusions

- In preliminary analysis, the incorporation of rituximab and liposomal doxorubicin into CODOX-M/IVAC in Burkitt’s lymphoma appears to be safe.

- The prerequisite interim overall response rate was met, and accrual has continued to the second stage of the clinical trial.

- Based on the first stage of the trial, protocol recommendations for HIV-positive patients never on highly active antiretroviral therapy (HAART), or HAART within four weeks of study, are not to start HAART until completion of chemotherapy.

- An increase in enrollment to 36 patients is planned in order to yield adequate statistical power for the HIV-negative Burkitt’s lymphoma subgroup.

Emerging Strategies for the Use of New Agents in Chronic Lymphocytic Leukemia

An increased understanding of the various autocrine pathways governing B-cell survival and the tumour-cell microenvironment has led to the development of promising new agents in the treatment of chronic lymphocytic leukemia (CLL).\(^1\)\(^2\) Strategies for the use of new agents, both alone and in combination, are being explored in pre-clinical and early clinical trials.

GA101 is a humanized type II monoclonal antibody that induces cytotoxicity in B-CLL cells through apoptosis and antibody-dependent cytotoxicity (ADCC).\(^3\) Current phase I data demonstrate improved efficacy in vitro over rituximab,\(^4\) which will require substantiation in large scale clinical trials. While evidence from phase II and III trials may help transition GA101 use into the clinical setting, a better understanding of the mechanism of action of GA101 may aid in the development of tailored clinical immunomodulation strategies.\(^3\)

Immunomodulating agents, such as lenalidomide, have shown anti-tumour activity in clinical trials.\(^2\) Lenalidomide, a less toxic analogue of thalidomide, has demonstrated efficacy as both monotherapy and in combination with rituximab in relapsed/refractory CLL patients.\(^5\) However, adverse events (AEs) such as tumour flare and myelosuppression with these agents appear to be specific to their use in CLL. While overall AEs appear to be lower in CLL than in other B-cell malignancies, the optimal dose and scheduling of lenalidomide remains unknown.\(^6\)

The green tea extract epigallocatechin-3-gallate (EGCG) has been shown in vitro to contribute to B-cell apoptosis in CLL, possibly by modulating vascular endothelial growth factor (VEGF) receptor activation status.\(^1\) A phase I trial indicated that treatment with EGCG was well tolerated and may have clinical efficacy.\(^7\) EGCG may be useful as stabilizing therapy in B-CLL.

This article reports on five studies evaluating new treatment strategies in CLL. Two studies were presented at EHA 2010:

- An in vitro study showed that GA101 exerts higher anti-leukemic activity than rituximab in CLL blood samples.
- A second in vitro study suggested the major efficacy of GA101 when compared to rituximab is its induction of complement-dependent cytotoxicity (CDC) and direct cell death (DCD) in an additive manner.

Three studies were presented at ASCO 2010:

- A phase II study demonstrated that front-line monotherapy with lenalidomide is safe and efficacious in elderly CLL patients, with the quality of response improving over time.
- Early results of a second phase II study showed that combination therapy with lenalidomide and rituximab was well tolerated.
- A final phase II trial showed that the green tea extract EGCG appears to have modest clinical activity in asymptomatic CLL patients.

References:

**Background**

The efficacy of anti-CD20 monoclonal antibodies (mAbs) in B-cell lysis is a function of direct cell death (DCD), complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and synergy with chemotherapy. In vitro tests may help delineate the contribution of each pathway, allowing researchers to better define the mechanism of each treatment, with the possibility of tailoring clinical immunomodulation strategies.¹

At EHA 2010, Ysebaert and colleagues presented results from their study investigating the principle mechanism by which GA101, a new type II glycoengineered CD20 mAb currently in phase III clinical trials, exerts its activity in vitro against B-cell chronic lymphocytic leukemia (B-CLL) cells.²

**Study design**

- B-cell depletion, using either rituximab or GA101, was assessed by flow cytometric B-cell depletion assay using Ficoll-separated peripheral blood mononuclear cell (PBMC) fraction issued from untreated B-CLL patients (n = 17) and healthy donors (n = 16) in complement heat-inactivated medium.

- The same experiments were performed with sorted CD19-positive leukemic B-CLL cells (n = 3) to assess DCD in the absence of effector cells (no ADCC).

- PBMC and purified B-cells from CLL patients were cultured at 1 x 10⁷/mL for 7 days with 10 µg/mL of either rituximab or GA101.

- Pure ADCC was also assessed in the following manner:
  - B cells from 9 CLL patients were frozen before receiving FCR (fludarabine, cyclophosphamide, rituximab) for 6 cycles.
  - Peripheral blood lymphocytes were collected 6 to 12 months after FCR completion, activated or not by interleukin-2 (IL-2) for 3 days and used as effectors against autologous CLL cells (using a low E:T ratio of 0.4/1).
  - ADCC was measured using conventional 51-Chromium release assay with either rituximab or GA101.

- Depletion of B cells in cultures containing nurse-like cells (NLCs) was assessed in the following manner:
  - PBMC from four healthy donors were cultured in normal medium (RPMI) or conditioned medium (CM) (obtained from CLL patients after 15 days of co-culture with NLCs).
  - Depletion was measured as a percentage of CD19-positive lymphocytes by flow cytometry after seven days incubation with rituximab or GA101 at 10 µg/mL.
  - Statistical comparison was made by pairs, student t-test.

**Key findings**

- CD20 mAbs were more efficient in depleting B cells from total PBMC fractions than in inducing DCD of purified B-CLL cells (n = 3). (Figure 1)

- Rituximab and GA101 induced low rates of depletion in samples containing purified B-CLL cells, suggesting that these two antibodies displayed low intrinsic DCD against purified B-CLL cells. (Figure 1)

**Figure 1. Efficiency of rituximab and GA101 against total PBMC fractions versus purified B cells from CLL patients**

<table>
<thead>
<tr>
<th></th>
<th>PBMC</th>
<th>Purified B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
</tr>
<tr>
<td>GA101</td>
<td><img src="#" alt="Table" /></td>
<td><img src="#" alt="Table" /></td>
</tr>
</tbody>
</table>

*CLL = chronic lymphocytic leukemia; PBMC = peripheral blood mononuclear cell*
• A flow cytometric B-cell depletion assay in healthy and CLL donors suggested that rituximab and GA101 are equally effective in healthy donors; however, only GA101 induced B-cell depletion in PBMC fractions from CLL patients. (Figure 2)

• CLL cells had significantly lower CD20 density (mean 19,000 vs. 81,000 antibodies bound per cells in healthy B cells; $p <0.001$), indicating that GA101 efficiency is higher on B-CLL cells than on normal B cells.

• GA101 appeared to exert an increase in autologous ADCC compared to rituximab ($p = 0.05$). (Figure 3)

• In four consecutive normal donors, GA101 was able to deplete B cells, while rituximab-induced depletion was statistically diminished in CM NLC plus CLL. (Figure 4)

Figure 2. B-cell depletion from PBMC fractions with rituximab or GA101 in CLL patients and healthy donors

![Figure 2](image)

**CLL = chronic lymphocytic leukemia; PBMC = peripheral blood mononuclear cell**

Figure 3. Autologous antibody-dependent cellular cytotoxicity in CLL patients after 6 cycles of FCR

![Figure 3](image)

**CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; IL = interleukin**
Figure 4. B-cell depletion with rituximab or GA101 in CLL patients using a conditioned medium containing nurse-like cells

Key conclusions

- GA101 exerts higher anti-leukemic activity than rituximab in CLL samples.
- Results suggest that GA101 has higher autologous ADCC capacity after immunochemotherapy in the effector cells of CLL patients, compared to rituximab.
- In vitro tests carried out during the study suggest that GA101 overrides the protective effect of nurse-like cells, possibly due to enhanced CD16 binding and natural killer (NK) activation.

References:

Background

Understanding the mechanism of action of therapeutic monoclonal antibodies (mAbs) is fundamental to improving their efficacy in the treatment of B-cell chronic lymphocytic leukemia (B-CLL). Antibodies currently being investigated include anti-CD52 alemtuzumab, anti-CD20 rituximab, and more recently, third generation glycol-engineered anti-CD20 antibody GA101.1,2

At EHA 2010, Bologna and colleagues presented data from their study comparing the efficacy and mechanism of action of alemtuzumab, rituximab, and GA101 using whole blood assays from B-CLL patients.3

Study design

- B-CLL whole blood samples in citrate (0.1 M) were incubated for various times with alemtuzumab, rituximab, or GA101 and/or the blocking anti-CS antibody eculizumab.
- Death of CD19-positive B-CLL cells was measured by fluorescence-activated cell sorting (FACS) analysis.

Key findings

- Direct cell death (DCD), complement-dependent cytotoxicity (CDC), and phagocytosis induced by different mAbs were not significantly inhibited by citrate (0.1 M).
- Alemtuzumab efficiently lysed B-CLL targets; maximal lysis (62%) was reached at 1–4 hours with 10 µg/mL of the antibody.
- Rituximab induced more limited cell death (21%), with maximal lysis at 24 hours.
- Lysis by both alemtuzumab and rituximab was fully complement dependent, because it was inhibited by at least 90% in the presence of excess blocking by the anti-CS antibody eculizumab.

In vitro evaluation of alemtuzumab, rituximab, and GA101 in chronic lymphocytic leukemia

Bologna L, et al. EHA 2010: Abstract 0453

Background

Understanding the mechanism of action of therapeutic monoclonal antibodies (mAbs) is fundamental to improving their efficacy in the treatment of B-cell chronic lymphocytic leukemia (B-CLL). Antibodies currently being investigated include anti-CD52 alemtuzumab, anti-CD20 rituximab, and more recently, third generation glycol-engineered anti-CD20 antibody GA101.1,2

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- Rituximab induced more limited cell death (21%), with maximal lysis at 24 hours.
- Lysis by both alemtuzumab and rituximab was fully complement dependent, because it was inhibited by at least 90% in the presence of excess blocking by the anti-CS antibody eculizumab.
• GA101 killed B-CLL targets with more rapid kinetics than rituximab at both four hours (19.2% versus 7.9%) and at 24 hours (23.5% versus 21.4%).
• Lysis by both GA101 and rituximab correlated directly with CD20 expression levels (R2: 0.85 and 0.88, respectively).
• GA101 was required in concentrations at least 10 times higher than rituximab to induce equivalent complement activation; lysis of only 50%–65% of B-CLL cells was due to complement in whole blood.
• In addition to CDC, GA101 induced DCD of purified B-CLL or B lymphoma cell lines; this cell death involved the lysosomal pathway.
• Both rituximab and GA101 showed the same efficiency in phagocytosis assays, but phagocytosis was low in whole blood due to excess human immunoglobulins.

Key conclusions

■ The major activity of alemtuzumab and rituximab in the circulation is through complement-mediated toxicity.
■ GA101 induces both CDC and DCD in an additive manner, which may explain the major efficacy of GA101 with respect to rituximab against B-CLL samples in whole blood assays.

References:

Badoux X, et al. ASCO 2010: Abstract 6508

**Lenalidomide monotherapy in untreated elderly patients with chronic lymphocytic leukemia**

**Background**

Although the majority of patients with chronic lymphocytic leukemia (CLL) are over 70 years old, there is no established standard therapy for this population,1–4 and they are under-represented in clinical trials.5

At ASCO 2010, Badoux and colleagues presented results from a phase II study investigating the efficacy and safety of lenalidomide monotherapy in elderly patients with untreated CLL and/or small lymphocytic lymphoma (SLL).6

**Study design**

• Patients included in the study had the following characteristics:
  • untreated CLL/SLL with indications for therapy according to the 1996 National Cancer Institute Working Group (NCI-WG) criteria;
  • age ≥65 years;
  • European Clinical Oncology Group (ECOG) performance status 0–2;
  • creatinine <2 mg/dL;
  • bilirubin <2 mg/dL.
  • Each treatment cycle was 28 days in duration.
  • All patients were treated with lenalidomide orally at a dose of 5 mg/day for the first 56 days (2 cycles).
  • Dosing was titrated up to 25 mg/day, as tolerated, by 5 mg increments each subsequent cycle; treatment continued until progression.
  • Allopurinol was given at a dose of 300 mg from days 1–4.
  • Treatment schedule did not include mandated antibiotics, anti-viral, deep-vein thrombosis (DVT) or tumour flare prophylaxis.
  • Responses were assessed after 3 cycles and every 6 cycles thereafter.
  • Primary endpoints were progression-free survival (PFS), clinical response (2008 NCI-WG criteria), and incidence of grade 3/4 hematological toxicity.
  • Correlative studies, including analyses of lymphocyte subsets and serum immunoglobulin levels, were also conducted.
Key findings

Baseline characteristics and disposition
- Sixty (60) patients were enrolled in the study; all 60 received treatment and were evaluable for response and toxicity.
- Median age was 71 years (range 66–85 years), and 18 patients (30%) had Rai stage III or IV disease.
- Fourteen (14) patients (23%) had del(11q) and 6 patients (10%) had del(17p) by fluorescent in situ hybridization (FISH) analysis; 33 of 55 patients had unmutated IgVH genes.
- Of the 60 enrolled patients, 37 patients (62%) remain on lenalidomide.

Efficacy
- The overall response (OR) rate for all patients was 62%; OR was significant in patients aged ≥75 (35%; p <0.05).
- A complete response (CR) was achieved in 10% of patients, complete response with incomplete marrow recovery (CRi) in 5%, nodular partial response (nPR) in 5%, and a partial response (PR) in 42%. (Table 1)
- Two-year overall survival (OS) is estimated at 90%; two-year progression-free survival (PFS) is estimated at 60%. (Figure 1)
- At a median follow-up of 23 months, six patients had died and 24 had disease progression. (Figure 1)

Safety
- The most common grade 3/4 hematological toxicities were neutropenia (grade 3: 26% of cycles; grade 4: 12%), thrombocytopenia (grade 3: 13% of cycles; grade 4: <1%), and anemia (grade 3/4: <1%).
- Grade 3/4 infections occurred in 7% of patients.
- No grade 3/4 tumour lysis or tumour flare reactions were noted; 30 patients (50%) experienced grade 1/2 tumour flare.

Correlative studies
- There was a significant rise in median IgG levels after 15 cycles of therapy, compared to baseline (941 mg/dL vs. 724 mg/dL; p <0.001); median IgM levels also rose significantly over 21 cycles of therapy. (Figure 2)
- A significant normalization of peripheral blood (PB) lymphocytes with a rise in the total percentage of lymphocytes was noted. (Figure 3)

Table 1. Efficacy of lenalidomide as front-line monotherapy in elderly CLL patients

<table>
<thead>
<tr>
<th>Response category</th>
<th>NCI Response* (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Complete response (CR)†</td>
<td>6</td>
</tr>
<tr>
<td>CRi†</td>
<td>3</td>
</tr>
<tr>
<td>Nodular partial response (nPR)</td>
<td>3</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>25</td>
</tr>
<tr>
<td>Overall response (OR)</td>
<td>37</td>
</tr>
</tbody>
</table>

* 2008 NCI-WG criteria; † Four patients with flow cytometry–negative CR
CRi = complete response with incomplete marrow recovery; NCI = National Cancer Institute; NCI-WG = National Cancer Institute-Working Group

Figure 1. OS and PFS in elderly CLL patients receiving lenalidomide (median follow-up 23 months)
Figure 2. Changes in serum immunoglobulin levels in 37 elderly CLL patients after 21 cycles of lenalidomide therapy

Figure 3. Peripheral blood lymphocytes in 38 elderly CLL patients receiving lenalidomide

Key conclusions

- Monotherapy with front-line lenalidomide is safe and efficacious in elderly patients with untreated CLL; the quality of response improves with time.

- The most common lenalidomide-associated toxicity was neutropenia.

- Lenalidomide therapy resulted in a significant rise in serum immunoglobulin levels, as well as normalization of lymphocyte populations.

References:
Background
At ASCO 2010, James and colleagues presented early safety results from their ongoing multicentre, phase II study evaluating the efficacy and safety of combination therapy with lenalidomide and rituximab in treatment-naïve chronic lymphocytic leukemia (CLL) patients.1

Study design
- Patients with treatment-naïve CLL were eligible if they had normal kidney and liver function, no recent thromboembolic events, and a European Clinical Oncology Group (ECOG) performance status <2.
- Thirty-eight (38) enrolled patients were stratified by age into two study arms:
  - arm A: <65 years (n = 22);
  - arm B: ≥65 years (n = 16).
- Both arms received the following treatment schedule:
  - Lenalidomide was given at a starting dose of 2.5 mg for days 1–21 of each cycle.
  - Dose escalation of lenalidomide occurred on an individual basis on day 8 of cycle 1 and/or on day 1 of cycles 3–7 to a maximum dose of 10 mg if tolerated.
  - Rituximab was given during cycle 1 at a dose of 50 mg/m² on day 29, 325 mg/m² on day 31, and 375 mg/m² on day 33.

Key findings
Baseline characteristics and disposition
- Thirty-eight (38) patients were enrolled in the study; 30 were evaluable for safety and toxicity.
- Median age of all patients was 62 years (range 45–80 years); median age in treatment arm A was 56 years (range 45–64 years) and in arm B was 73 years (range 65–80 years).

Study design

<table>
<thead>
<tr>
<th>Rituximab 375 mg/m²*</th>
<th>Lenalidomide 10 mg</th>
<th>Lenalidomide 5 mg</th>
<th>Lenalidomide 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td>Day 1–7 8 15 22 29 31 33 35</td>
<td>Physical exam</td>
<td>Day 1 8 15 22 28</td>
</tr>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Physical exam</td>
<td>Cycle 2</td>
</tr>
<tr>
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</tbody>
</table>

*Split dose of rituximab in cycle 1 was given at 50 mg/m² on day 29, 325 mg/m² on day 31, and 375 mg/m² on day 33.
• Duration of disease was 3.7 years (range 5 months to 8.1 years) in arm A and 3.8 years (range 1 month to 10.25 years) in arm B.

• Eight (8) patients (36%) in arm A and 9 patients (56%) in arm B had Rai stage III/IV disease.

• Fifty percent (50%) of patients in arm A had an unmutated IgVH gene compared to 56% of patients in arm B.

• Incidence of cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) between arms A and B were del(17p) (14% vs. 0%), del (11q) (9% vs. 25%), and trisomy 12q (27% vs. 31%).

Safety

• The most common grade 3/4 adverse events (AEs) were neutropenia (60%), anemia (17%), and thrombocytopenia (13%); no cases of neutropenic fever, sepsis, or bleeding were observed. (Table 1)

• Cases of neutropenia responded well to growth factors and often recovered between cycles.

• Non-hematologic grade 3/4 AEs included infection (7%), rash (7%), and pulmonary embolus (7%). (Table 1)

• Protocol was amended to include aspirin (81 mg) as thromboprophylaxis after two episodes of pulmonary embolus were observed.

• The most frequent AEs (all grades) were tumour flare reactions (TFRs) (73%), fatigue (63%), and elevated transaminases (53%). (Table 1).

• TFRs were transient, occurred predominantly in the first 1–2 cycles, and most often were grade 1/2 in severity; one grade 3 event was reported in arm B. (Figure 1)

• Of the 38 enrolled patients, 7 patients discontinued treatment for reasons including ineligibility (1 patient), intolerance to rituximab (1 patient), Pneumocystis jirovecii pneumonia (1 patient), pulmonary embolism (1 patient), rash (1 patient), and thrombocytopenia (1 patient).

• For patients receiving >3 cycles of treatment, the median dose of lenalidomide in arm A (age <65 years) was 10 mg compared with 5 mg in arm B (age ≥65 years). (Figure 2)

• Patients in arm A tolerated a higher median dose (10 mg, 21 days/cycle) compared with arm B (5 mg, 21 days/cycle). (Figure 2)

<table>
<thead>
<tr>
<th>Table 1. Adverse events (≥15%) in CLL patients after combination treatment with lenalidomide and rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong>*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tumour flare reaction</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Infusion reactions</td>
</tr>
<tr>
<td>Elevated transaminases</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Thrombosis-embolism</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Pain (abdominal/back/chest)</td>
</tr>
</tbody>
</table>

*Maximum grade toxicity is reported for each patient during the 7 cycles of treatment.
Key conclusions

- Early results of this ongoing study suggest that immunotherapy with lenalidomide and rituximab is well tolerated.
- Tumour flare reaction, a frequent but low-grade AE, occurred rarely after the first 1–2 cycles.
- Neutropenia was the most frequently observed hematologic toxicity, but was not associated with discontinuation of treatment.
- Patients are still being enrolled to a total of 80 patients.

Oral green tea extract in patients with asymptomatic early stage chronic lymphocytic leukemia

Background
Green tea has long been touted as a health-promoting substance. In vitro testing and a phase I trial suggest the green tea extract epigallocatechin-3-gallate (EGCG) may have clinical efficacy for chronic lymphocytic leukemia (CLL) patients.1,2

At ASCO 2010, Shanafelt and colleagues presented data from their phase II trial evaluating the efficacy and safety of daily EGCG in patients with asymptomatic early stage CLL.3

Study design
• Previously untreated patients with asymptomatic, Rai stage 0-II CLL who did not meet National Cancer Institute (NCI) Working Group criteria for treatment and had a minimum absolute lymphocyte count (ALC) ≥10 x 10^9/L were eligible.
• Patients received Polyphenon E with a standardized dose of EGCG at 2,000 mg twice daily for up to 6 months.
• Response was classified using the NCI criteria and biological response.
• Biological response required patients to have a sustained ≥20% decline in ALC for at least two months and/or a ≥30% reduction in sum nodal products.
• Grade 2 adverse events (AEs) during cycle 1 attributed to study medication that did not respond to supportive care were considered dose-limiting toxicity (DLT).

Key findings
Baseline characteristics and disposition
• Forty-two (42) patients were enrolled in the study, including 6 patients from phase I treated at the phase II dose; 41/42 have completed active treatment.
• Median patient age was 60 years (range 41–78 years), 30 patients (71%) were male, and 29 patients (69%) had Rai stage I–II disease.
• Six (6) patients (18%) had unmutated IgVH, 27 patients (64%) had del(13q), 4 patients (10%) had trisomy 12, and one patient (2%) had del(11q) by fluorescence in situ hybridization (FISH) analysis.

Efficacy
• Median ALC at enrollment was 33 x 10^9/L (range 10–258 x 10^9/L).
• Patients received a median of 6 cycles (range 1–6 cycles) of treatment.

Table 1. Reduction of ALC and sum of nodal products in 42 patients with early stage CLL after treatment with Polyphenon E

<table>
<thead>
<tr>
<th>Best reduction in ALC</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 10% decline</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>At least 20% decline</td>
<td>22</td>
<td>52</td>
</tr>
<tr>
<td>At least 30% decline</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>At least 40% decline</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>At least 50% decline</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>At least 20% decline sustained for 2 months</td>
<td>13</td>
<td>31</td>
</tr>
</tbody>
</table>

Best reduction in nodes

| At least 50% reduction sum products | 20* | 69 |

Biological response or better

| Biological response or better | 29 | 69 |

*Patients with palpable adenopathy at enrollment (n = 29)

ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia

• One patient experienced a partial remission (PR) according to NCI Working Group criteria.
• Thirteen (13) patients (31%) experienced a sustained ≥20% reduction in ALC for at least two months, with a majority of patients experiencing a reduction in ALC during treatment. (Table 1)
• Of the 29 patients with palpable adenopathy at enrollment, 20 patients (69%) experienced at least a 50% reduction in the sum products of all nodal areas at some point during treatment. (Table 1)
• Analysis of response by prognostic factors and correlative studies on mechanism of action are ongoing.
### Safety

- Adverse events were generally mild with few patients experiencing grade 3 events, including transaminitis (2%), abdominal pain (2%), and fatigue (2%); no grade 4 events were reported. (Table 2)

- The most common grade 1/2 adverse events were nausea (60%), diarrhea (55%), transaminitis (45%), and abdominal pain (29%). (Table 2)

#### Table 2. Adverse events after treatment with Polyphenon E in patients with early stage CLL

<table>
<thead>
<tr>
<th>Adverse event*</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminitis</td>
<td>13 (31)</td>
<td>6 (14)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (21)</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (55)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12 (29)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (45)</td>
<td>4 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11 (26)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>13 (31)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (26)</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Classified according to Common Terminology Criteria for Adverse Events (CTCAE)

### Key conclusions

- Daily oral EGCG in the Polyphenon E preparation was well tolerated by CLL patients.

- EGCG appears to have a modest clinical activity with declines in ALC and/or lymphadenopathy observed in the majority of patients.

- EGCG-containing green tea extracts may have potential as disease-stabilizing agents in patients with early stage CLL.

### Canadian perspective by Dr. Laurie H. Sehn

The development of anti-CD20 monoclonal antibodies has revolutionized the management of lymphoid malignancies. Rituximab, a type I monoclonal antibody, has demonstrated improvements in overall survival (OS) when combined with chemotherapy in patients with non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL). GA101 (RO5072759), a novel type II monoclonal antibody, is a promising new therapeutic agent being examined in B-cell NHL and CLL.

GA101 binds with high affinity to a type II epitope on CD20 and is characterized by reduced complement-dependent cytotoxicity (CDC), which may minimize infusion reactions. Preclinical studies suggest that GA101 enhances antibody-dependent cellular cytotoxicity (ADCC) by 5–100 fold and results in superior direct cell death (DCD), compared to rituximab. GA101 has been shown to be significantly more potent and effective in depleting B cells, inducing dose-dependent anti-tumour activity and causing complete tumour regression, which has resulted in improved long-term survival in xenograft mouse models.1,2

The in vitro study by Ysebaert, et al. investigates the mechanisms by which GA101 and rituximab exert their activity against CLL cells. This study supports previous data showing that GA101 has improved ADCC capacity, compared with rituximab. However, the small number of samples used in this study makes it difficult to draw firm conclusions regarding its ability to induce DCD.

In a previously reported phase I clinical trial by Salles, \textit{et al.}, GA101 was well tolerated and exhibited promising efficacy in patients with relapsed/refractory CD20-positive lymphoid malignancies.\textsuperscript{2} Based on the success of phase I/II trials, Salles, \textit{et al.} performed a phase II study examining the safety and efficacy of two dosing schedules of GA101 in heavily pre-treated patients with indolent NHL. In this group of patients, GA101 was highly effective as a single agent, especially in the higher dose cohort. Response rates in rituximab-refractory patients were also encouraging.

An overview of safety results suggests that GA101 has a similar tolerability profile to rituximab, with no unexpected toxicities observed. Infusion-related reactions (IRRs) were the most commonly reported adverse events with GA101, but were relatively mild and reversible with supportive management. Similar to rituximab, IRRs with GA101 occurred most frequently with the first infusion and were less likely to occur in subsequent cycles.

In the phase I/II trials reported to date, GA101 has been administered according to the standard infusion schedule used for rituximab. However, the feasibility of a rapid infusion protocol for GA101, which would allow for more convenient delivery, is currently under investigation. Results from phase I and II studies are actively being examined to determine the best dosing strategy for GA101. Ongoing studies should further clarify the optimal administration and role of GA101 in B-cell NHL and CLL.

The study by Wilson, \textit{et al.} is a phase I/II study designed to examine the safety, optimal dose, and preliminary efficacy of navitoclax (ABT-263) in relapsed/refractory lymphoid malignancies. Navitoclax is a novel orally bioavailable small molecule that targets a subset of the Bcl-2 family of proteins. In this cohort of patients, navitoclax demonstrated a favourable safety profile, with thrombocytopenia being the primary dose-limiting toxicity. Hepatotoxicity was also observed, but appeared to be reversible with dose modification.

An initial look at efficacy suggests that navitoclax has promising activity in indolent lymphoma and CLL. The CLL cohort exhibited the highest response rate; however, it is too early to determine which patient subgroups may preferentially benefit from this agent. Based on results from this study and other early trials, an optimal dosing schedule for navitoclax has been suggested that should improve its safety profile. Future studies examining the optimized dosing schedule of navitoclax in combination with other agents will determine the utility of this compound in these patient populations.

Lenalidomide is an oral immunomodulatory agent commonly used in the management of multiple myeloma, which is being actively investigated in the treatment of other subtypes of lymphoma. Results of a previously reported trial in relapsed/refractory indolent lymphoma demonstrated impressive response rates and a favourable toxicity profile for single-agent lenalidomide.\textsuperscript{3}

The study by James, \textit{et al.} examines the safety of lenalidomide combined with rituximab in 33 patients with previously untreated CLL. In this study, hematological toxicities were observed, but were manageable and not associated with treatment discontinuation. Other toxicities, including tumour flare reactions, fatigue, and elevated transaminases, were generally mild and reversible. The majority of patients in the older age cohort (≥65 years) were unable to tolerate dose escalation of lenalidomide and therefore received a median dose of 5 mg, compared with a median dose of 10 mg in the younger patient cohort (<65 years). The combination of lenalidomide and rituximab is being investigated in ongoing studies, both in B-cell lymphoma and CLL. Preliminary results suggest that this combination is highly active and may ultimately offer an alternative approach to multi-agent chemotherapy.

New Evidence: Why might GA101 be a good treatment option for indolent NHL?

Dr. Salles: GA101 is a third-generation, humanized, glyco-engineered, anti-CD20, type II IgG1 antibody. Type II antibodies are characterized by a reduced complement-dependent cytotoxicity (CDC) and enhanced direct cell death (DCD), compared to type I antibodies. Modifications to the Fc portion of the antibody allow GA101 to bind with high affinity to the FcGammaRIIIA receptor, resulting in the induction of antibody-dependent cytotoxicity (ADCC). The design of GA101, as compared to type I antibodies, suggests that GA101 may be more efficacious than rituximab for the treatment of indolent lymphomas.

New Evidence: Please describe the design of the current phase II study.

Dr. Salles: We previously evaluated GA101 in a phase I study, which showed promising efficacy and tolerability for GA101 in chronic lymphocytic leukemia (CLL) and lymphoma patients. The primary objective of the current phase II study was to measure the efficacy and safety of GA101 in relapsed/refractory patients with indolent lymphomas. Secondary endpoints included progression-free survival (PFS), event-free survival (EFS), overall response (OR) rate, and pharmacokinetics.

Patients included in the study were randomized to receive either a low or a high dose of GA101. Patients in the low-dose group received 400 mg of GA101 for a total of nine cycles, while those in the high dose group received a loading dose of 1,600 mg for two cycles, followed by 800 mg for seven cycles. The majority of patients included in the study had follicular lymphoma (34/40) and were heavily pre-treated, with a median of four prior treatments. All but one patient had previously received rituximab, 24/40 patients were rituximab-refractory, and one quarter of the patients had received a prior transplant. Therefore, this study population was a group of patients who are typically difficult to treat.
**New Evidence:** Please discuss the safety results of the study.

**Dr. Salles:** In general, we did not observe many safety issues with GA101; the two most common side effects were infusion reactions and neutropenia. Grade 3/4 infusion reactions and neutropenia occurred much more frequently in the high-dose group (9% and 14%, respectively) than in the low-dose group (0% for both). Neutropenia appeared to occur more frequently at higher doses of the antibody, but this observation will need to be confirmed in future studies. Whether the higher incidence of neutropenia translated into the greater number of grade 3/4 infections seen in the high-dose group (5/22 patients) will also need to be evaluated, but the majority of these infections developed at a different time than neutropenia.

A number of serious adverse events (SAEs) occurred with GA101, the most common being infections such as herpes zoster, pneumococcus, and hemophilus. However, these infections are not uncommon in follicular lymphoma at this disease stage, and the majority of patients recovered. During the study, 75% of patients completed all doses of GA101, showing that the treatment was well tolerated.

Comparing the safety profile of GA101 with that of rituximab is difficult, as the doses that have been used are not comparable. However, the safety results seen in this study are similar to what we have seen using rituximab in patients with bulky disease. We noted that infusion reactions appeared to occur more frequently with GA101 compared to rituximab, even in the low-dose group, but the premedication did not include systematic use of steroids. We therefore need to fully evaluate the dose-effect relationship of GA101 to determine whether there are any important safety concerns. However, as a salvage treatment, GA101 showed no unexpected safety signals in this population of patients.

**New Evidence:** Please discuss the efficacy results of the study.

**Dr. Salles:** The OR rate was 55% in the high-dose group and 19% in the low-dose group, which is very promising for the first group. We also found that the majority of patients in the high-dose cohort had some tumor shrinkage; the effect was less impressive in the low-dose cohort, where tumor growth eventually progressed in some patients. These results suggest there may be a dose-effect relationship with GA101, which is very encouraging.

Two other important messages regarding the efficacy of GA101 stand out. If we look only at follicular lymphoma patients (n = 34), results follow the same trend as that of the general study population, with 50% and 21% of patients responding in the high- and low-dose groups, respectively. A good response rate was also seen in patients who were refractory to rituximab, with a 55% and 9% OR rate in the high- and low-dose cohorts, respectively. These response rates indicate that GA101 may be using a different mechanism of action than rituximab and could therefore be a good rescue treatment for patients who are rituximab-resistant. The strength of these results shows the power of this antibody as a potential new treatment option in indolent lymphoma patients.

**New Evidence:** What are the next steps in the development of GA101 for the treatment of indolent lymphomas?

**Dr. Salles:** Based on our results, we will continue to examine GA101 with doses ranging from 800–1000 mg per infusion. We will also continue to use a loading dose of 1,600 mg upfront, as this strategy may contribute to raising the circulating levels of GA101.

Several ongoing studies to examine GA101 in indolent lymphoma patients are currently underway. In North America and Europe, a phase III study is comparing the efficacy of chlorambucil monotherapy, GA101 plus chlorambucil, and rituximab plus chlorambucil as first-line treatment in CLL patients with co-morbidities. A study in rituximab-refractory patients is comparing combination therapy with bendamustine and GA101 to bendamustine monotherapy. These two important studies will help to assess the efficacy of GA101 in patients with indolent lymphomas.
SUTENT is indicated for the treatment of metastatic renal cell carcinoma of clear cell histology. Approval for MRCC is based on statistically significant progression-free survival in patients with good performance status (ECOG 0–1). There was a trend for overall survival advantage.

**Prescribing Summary**

**Patient Selection Criteria**

**INDICATIONS AND CLINICAL USE:** SUTENT (sunitinib malate) is indicated for the treatment of metastatic renal cell carcinoma (MRCC) of clear cell histology. Approval for MRCC is based on statistically significant progression-free survival in patients with good performance status (ECOG 0–1). There was a trend for overall survival advantage. Please refer to the Product Monograph for further information.

**CONTRAINDICATIONS:**
- Use of SUTENT is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- SUTENT is contraindicated in pregnant women.

**Special Populations:**

**Geriatrics (≥65 years of age):** Of the 450 patients with solid tumours reported from clinical studies of SUTENT, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

**Pregnant Women:** There are no adequate and well-controlled studies of SUTENT in pregnant women. Repeat-dose studies in animals have shown effects in reproductive organs. SUTENT should not be used during pregnancy in any woman not employing adequate contraception. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard of drug to the fetus. Women of childbearing potential should be advised against breastfeeding while taking SUTENT.

**Male Contraception:** Male patients should be surgically sterile or agree to use effective contraception during the period of therapy with SUTENT. SUTENT may cause embryonal and fetal developmental effects should the female partner of a male taking SUTENT become pregnant, as the drug may be present in the semen.

**Pediatrics:** The safety and efficacy of SUTENT in pediatric patients have not been established. However, physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for 3 months with sunitinib at doses that were approximately 0.4 times the recommended human dose (RHD) based on systemic exposure (AUC). The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment.

**Hepatic:** A single 50 mg dose of SUTENT was administered to patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment and to a control group of patients with normal hepatic function. The pharmacokinetic parameters evaluated demonstrated that dose adjustments might not be necessary for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. In addition, repeated administration of SUTENT was not studied in subjects with hepatic impairment.

**Renal:** SUTENT has not been studied in patients with renal impairment.

**MRCC Patient Population:**

**Treatment-Naïve MRCC:** A Phase 3 randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve MRCC. The primary endpoint was to compare PFS in patients receiving SUTENT versus patients receiving IFN-α.

Secondary endpoints included TTP, ORR, OS and safety. PFS was defined as the time from randomization to first documentation of objective tumour progression or death due to any cause, whichever occurred first. TTP was defined as the time from randomization to first documentation of objective tumour 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 Tumours (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. Three scheduled analyses were planned for this study: as the study met its primary endpoint of PFS at the time of the second interim analysis, the study protocol was amended to allow patients in the IFN-α group to cross over to receive sunitinib on documented disease progression, as agreed with the independent data and safety monitoring committee.

Interim Analysis: 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 MIU 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 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 ECOC performance status were comparable and balanced between the SUTENT and IFN-α groups. 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).

In the interim analysis, there was a statistically significant advantage for SUTENT over IFN-α in the primary endpoint of PFS, with the PFS for SUTENT more than double that of IFN-α (47.3 versus 22.0 weeks, respectively). Due to concerns that the overall study 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, 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. At the time of the interim 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. 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.

Table 1 summarizes the efficacy results of this Phase 3 study conducted in patients with treatment-naïve MRCC.

**Table 1. Treatment-Naïve MRCC Efficacy Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-Naïve MRCC</th>
<th>p-value (log-rank test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median, weeks)</td>
<td>47.3 (42.6, 50.7)</td>
<td>22.0 (16.4, 24.0)</td>
<td>&lt;0.000001a</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td>0.415 (0.320, 0.539)</td>
</tr>
<tr>
<td><strong>Time to tumour progression</strong></td>
<td>47.9 (45.9, 50.7)</td>
<td>22.3 (17.3, 31.3)</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>(median, weeks)</td>
<td></td>
<td></td>
<td>0.416 (0.318, 0.545)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td>38.7 (33.7, 43.8)</td>
<td>7.7 (5.2, 10.9)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>[% (95% CI)]</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

**CI=confidence interval, NA=not applicable**

* Assessed by blinded core radiology laboratory

**A comparison is considered statistically significant if the p-value is <0.0042 (0.05/Four stopping boundary)**

**Pearson Chi-square test**

* The results presented originate from the interim analysis with the exception of ORR that originates from the final data.
In the cytokine-refractory metastatic RCC (MRCC) trials, hypertension (all grades) was reported as an adverse event in 9% of treatment-naive patients on SUTENT and 1% of patients on IFN-α. Hypertension (≥200 mmHg systolic or ≥110 mmHg diastolic) occurred in 9/237 (4%) patients on placebo, 27% and 15% of patients on SUTENT and IFN-α, respectively. In the stratified analysis (OH vs. s1.5x LLN, ECOG performance status 0 vs. ≥1), and absence or presence of prior nephrectomy), the HR was 0.818 (95% CI: 0.669–0.999; p=0.049 by log-rank test, secondary analysis). The median OS for the IFN-α arm includes 25 patients who discontinued IFN-α treatment because of disease progression and crossed over to treatment with SUTENT. Following discontinuation from the study, 213 patients on the IFN-α arm received post-study cancer treatment, including 32% who received SUTENT; 182 patients on the SUTENT arm received post-study cancer treatment, including 11% who received SUTENT.

**Safety Information**

**WARNINGS AND PRECAUTIONS:**

- Patients receiving therapy with SUTENT should be monitored by a qualified physician experienced in the use of anti-cancer agents.
- Tumour Hemorrhage (see Hemorrhage section)
- Decreases in left ventricular ejection fraction (LVEF) (see Left Ventricular Dysfunction section)
- Hypertension (see Hypertension section)
- SUTENT has not been studied in patients with severe renal or severe hepatic impairment
- Myopathy and/or rhabdomyolysis (see ADVERSE REACTIONS, Post-Marketing Experience section)
- Cardiomyopathy, including fatal cases (see ADVERSE REACTIONS, Post-Marketing Experience section)
- Pulmonary embolism, including fatal cases (see ADVERSE REACTIONS, Post-Marketing Experience section)

**Carcinogenesis and Mutagenesis:** Carcinogenicity studies with sunitinib have not been completed. 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-naive study, three patients were discontinued due to treatment-related hypertension, including one with malignant hypertension.

In the GIST trial (Study A), hypertension (all grades) was reported as an adverse event in 51/257 (19%) patients on SUTENT and 7/102 (7%) patients on placebo. Severe hypertension (>200 mmHg systolic or >110 mmHg diastolic) occurred in 9/237 (4%) patients on SUTENT and no patients on placebo. SUTENT dosing was neither delayed nor reduced due to hypertension in any of the GIST patients in the GIST pivotal trial.

Treatment-related hypertension was reported in approximately 30% of patients receiving SUTENT for treatment-naive MRCC compared to 2% of patients receiving interferon-α (IFN-α). Severe hypertension (>200 mmHg systolic or >110 mmHg diastolic) occurred in 9% of treatment-naive 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 88/165 (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%) 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:** Cardiovascular events, including heart failure, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. Decreases in left ventricular ejection fraction (LVEF) of ≥20% and below are common in clinical trials of biologic (immunomodulatory) and non-biologic agents. In the double-blind treatment phase of GIST Study A, 22 patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below LLN. Nine (9) of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five (5) patients had documented LVEF recovery following intervention (dose reduction–1 patient; addition of antihypertensive or diuretic medications–4 patients). Six (6) patients went off study without documented recovery. Additionally, 3 patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF <40%; 2 of these patients died without receiving further study drug.

In the treatment-naive MRCC study, 27% and 15% of patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Two (<1%) patients who received SUTENT were diagnosed with congestive heart failure (CHF). One of the two patients with CHF discontinued the study.

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; Grade 2 and 6 were Grade 4). Six (6) of the treatment-naive MRCC patients had LVEF, including 3 Grade 3. Dose interruption occurred in 1 of these cases. In treatment-naive 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, all Grade 4.

**Other Cardiovascular Warnings:** There have been no cases of myocardial ischemia or myocardial infarction in patients with GIST exposed to either SUTENT or placebo. Two (2) patients with treatment-naive MRCC experienced treatment-related myocardial infarction (Grade 4), while 2 patients had Grade 3 myocardial ischemia. Two (2) patients with cytokine-refractory MRCC experienced Grade 3 myocardial ischemia, 1 patient had Grade 2 “cardiovascular toxicity” reported as an adverse event and 1 patient experienced a fatal myocardial infarction while on treatment.

**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. ACTH stimulation testing was conducted in over 400 patients across multiple clinical trials of SUTENT. In the GIST studies, 13 patients with normal baseline testing had abnormalities at post-baseline testing consisting of: peak cortisol levels post-stimulation less than normal (497 nmol/L, or 18 µg/dL), failure of stimulation to increase cortisol level by a normal amount (151 nmol/L, or 7 µg/dL), or failure of ACTH Gel test to detect doubling of cortisol level post-stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency. 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.

Thyroid dysfunction: Treatment-emergent acquired hypothyroidism was noted in 4% of GIST patients on SUTENT versus 1% on placebo. Although not prospectively studied in clinical trials, treatment-related hypothyroidism was reported as an adverse event in 15% of patients on SUTENT in the treatment-naïve MRCC study and two patients (0.6%) 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. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction, such as fatigue, should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

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: Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumour, urinary tract and brain hemorrhages. In the double-blind treatment phase of GIST pivotal trial (Study A), bleeding events occurred in 20% of patients (41/202) receiving SUTENT, compared to 11% (11/102) receiving placebo. In GIST Study A, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, 1 patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

In patients receiving SUTENT for treatment-naïve MRCC, 28% of patients had treatment-related bleeding events compared with 3% of patients receiving IFN-α. Eleven (2.1%) patients on SUTENT versus 1 patient (0.3%) 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 and 27/193 (14%) patients receiving IFN-α. 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 or GIST 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 hemoptysis 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. Treatment-related Grade 3 and 4 tumour hemorrhage occurred in 4/257 (approximately 2%) of GIST patients treated with SUTENT. One (1) patient with tumour hemorrhage had the SUTENT dose temporarily delayed. No patients discontinued treatment due to tumour hemorrhage. 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. One (1) case of febrile neutropenia (131) was reported in a patient receiving SUTENT on the GIST pivotal trial (Study A). 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: Grade 3 and 4 increases in serum lipase have been observed in 20 SUTENT patients (10%) versus 7 placebo patients (7%) with GIST. Grade 3 and 4 increases in amylase have been observed in 10 SUTENT patients (5%) versus 3 placebo patients (3%) with GIST. In patients with treatment-naïve MRCC, Grade 3 or 4 increases in amylase and lipase have been observed in 6% and 18% of SUTENT-treated patients and in 3% and 7% 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 GIST or 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 hypertension, 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 (restarting 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 may include dryness, thickness or cracking of the skin, blisters or occasional rash on the palms of the hands and soles of the feet. The above events were not cumulative, were typically reversible, generally did not result in treatment discontinuation and may include topical therapies for symptomatic relief.

ADVERSE REACTIONS:

Overview:

Two thousand, two hundred and eight (2208) patients with solid tumours, including 853 (39%) patients with GIST and 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 staring dose, on Schedule 4/2. One hundred two (102) patients received placebo in the randomized, double-blind, placebo-controlled clinical trial conducted in patients with GIST. Three hundred and sixty (360) patients received IFN-α in the randomized clinical trial conducted in patients with 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.

The most common treatment-related adverse reactions (≥20%) in patients with GIST or MRCC are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, hypertension, rash, hand-foot syndrome, skin discoloration, dry skin, hair colour changes, altered taste, and anorexia. The potentially serious adverse reactions of left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in WARNINGS AND PRECAUTIONS. Because clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ADVERSE REACTIONS in MRCC Patient Population:

Treatment-Naïve: The as-treated patient population for the interim safety analysis of the Phase 3 MRCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4–46.1) for SUTENT treatment and 4.1 months (range: 0.1–45.6) for IFN-α treatment. Dose reductions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 88 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 23% for IFN-α. Most treatment-related adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-related adverse events were reported in 69% and 38% of patients on SUTENT versus IFN-α, respectively. Common treatment-related adverse events of any grade for patients receiving SUTENT are fatigue, diarrhea, nausea, stomatitis, hypertension, hand-foot syndrome and ejection fraction decline. Table 2 compares the incidence of common (≥10%) treatment-related adverse events for patients receiving SUTENT versus those on IFN-α.
In the treatment-naive MRCC study, 75 (20%) versus 37 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 (14% 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 (15% on SUTENT, 7% on IFN-α) and hyperphosphatemia (6% on SUTENT, 6% on IFN-α). Other common Grade 3 laboratory abnormalities on SUTENT were hyponatremia (8%) and increased amylase (5%), and on IFN-α was hyperglycemia (6%). Hematologic laboratory abnormalities in the treatment-naive MRCC patient population are presented in Table 3.

Table 2. Treatment-Related Adverse Events Reported in at Least 10% of Patients with Treatment-Naive MRCC Who Received SUTENT or IFN-α

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SUTENT (n=375)</th>
<th>IFN-α (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>356 (95.5)</td>
<td>258 (68.8)</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>69 (18.4)</td>
<td>33 (8.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>70 (18.7)</td>
<td>40 (10.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>51 (13.6)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>40 (10.7)</td>
<td>12 (3.2)</td>
</tr>
</tbody>
</table>

Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>129 (34.4)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>37 (9.9)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Nervous system disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>175 (46.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>52 (14.1)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>67 (17.9)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>229 (61.1)</td>
<td>33 (8.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>195 (52.0)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>118 (31.5)</td>
<td>7 (1.9)</td>
</tr>
</tbody>
</table>

Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>115 (30.7)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Palmoplantar erythrodysesthesia syndrome</td>
<td>108 (30.0)</td>
<td>32 (8.5)</td>
</tr>
</tbody>
</table>

Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in extremity</td>
<td>66 (17.6)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>43 (11.5)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>206 (54.9)</td>
<td>43 (11.5)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>98 (26.1)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>76 (20.3)</td>
<td>28 (7.5)</td>
</tr>
</tbody>
</table>

Investigations

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction decreased</td>
<td>51 (13.6)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>46 (12.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

mx

The following terms have been combined: abdominal pain and abdominal pain upper.

**The following terms have been combined: rash, rash erythematous, exfoliative rash, rash follicular, rash macular, rash papular, rash pruritic, rash maculo-papular, rash psoriasiform and rash generalized.

Grade 4 hematology laboratory abnormalities in the Phase 3 MRCC study include neutropenia (2% on SUTENT, 1% on IFN-α) and anemia (2% on SUTENT, <1% on IFN-α). Grade 3 hematology laboratory abnormalities included neutropenia (15% on SUTENT, 8% on IFN-α), lymphopenia (16% on SUTENT, 24% on IFN-α), thrombocytopenia (8% on SUTENT, 1% on IFN-α), leukopenia (8% on SUTENT, 2% on IFN-α) and anemia (6% on SUTENT, 5% on IFN-α).

Table 3. Treatment-Emergent Laboratory Abnormalities Reported in at Least 10% of Treatment-Naive 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>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>211 (56)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>192 (51)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56)</td>
<td>69 (18)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>171 (46)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>75 (20)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>49 (13)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Renal/Metabolic

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>183 (49)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>173 (46)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (31)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Albumin</td>
<td>106 (28)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>65 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>61 (16)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Calcium increased</td>
<td>50 (13)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>49 (13)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Sodium increased</td>
<td>48 (13)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Hematology

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>289 (77)</td>
<td>65 (17)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>298 (79)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Platelets</td>
<td>255 (68)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>256 (68)</td>
<td>66 (18)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>293 (78)</td>
<td>29 (8)</td>
</tr>
</tbody>
</table>

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (1%), ALT (1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorus (<1%), potassium increased (<1%) and sodium decreased (<1%).

Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lipase (2%), creatinine (1%), neutrophils (1%), amylase (<1%), calcium decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

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 reductions 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 4. Treatment-related adverse events were observed 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-cause adverse events was similar to that of these treatment-related adverse events.

Table 4. Treatment-Related Adverse Events Reported in at Least 10% of Patients Treated with SUTENT in the Two Cytokine-Refractory MRCC Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE experienced by ≥10% patients</td>
<td>166 (98.2)</td>
<td>91 (53.9)</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUTENT</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>57 (33.7)</td>
<td>30 (15.8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24 (14.2)</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (14.2)</td>
<td>14 (8.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23 (13.6)</td>
<td>11 (6.5)</td>
</tr>
</tbody>
</table>
### Table 5. Abnormal Post-Baseline Laboratory Tests Occurring in at Least 10% of overall solid tumour patient population.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grade 1-4 (n%)</th>
<th>Grade 3/4 (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (hypoaalbuminemia)</td>
<td>47 (27.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>93 (55.0)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Amylase</td>
<td>47 (27.8)</td>
<td>8 (4.7)</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>97 (57.4)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Lipase</td>
<td>84 (49.7)</td>
<td>28 (16.6)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>20 (11.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Renal/Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (hypercalcemia)</td>
<td>19 (11.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Calcium (hypocalcemia)</td>
<td>72 (42.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>65 (38.5)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>100 (59.2)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Glucose (hyperglycemia)</td>
<td>30 (17.8)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Glucose (hypoglycemia)</td>
<td>34 (20.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>37 (21.9)</td>
<td>15 (8.9)</td>
</tr>
<tr>
<td>Potassium (hyperkalemia)</td>
<td>23 (13.6)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Sodium (hypernatremia)</td>
<td>22 (13.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Sodium (hyponatremia)</td>
<td>17 (10.1)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>83 (49.1)</td>
<td>25 (14.8)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<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 (56.6)</td>
<td>33 (19.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>99 (56.6)</td>
<td>5 (3.0)</td>
</tr>
</tbody>
</table>

Severity grading was consistent with Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

1 patient (0.6%) was missing.

Abbreviations: n=number of subjects; MRCC=metastatic renal cell carcinoma

### Other Adverse Reactions:

- **Musculoskeletal:** Rhabdomyolysis has been reported in some cases from non-pivotal clinical trials (see WARNINGS AND PRECAUTIONS and Post-marketing Experience sections).
- **Cardiovascular, Pulmonary Embolism, Pancreatic Function and Seizures:** See WARNINGS AND PRECAUTIONS section.

**Post-Marketing Experience:**

The following adverse reactions have been identified during post-marketing 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.

- **Blood and lymphatic system disorders:** Rare cases of thrombotic microangiopathy have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.
- **Cardiovascular:** Left ventricular failure, cardiac failure, cardiovascular ischemia-related events and rhythm disorder events have been reported in patients with pre-existing disease and/or cardiovascular risk factors, but a causal association with sunitinib could not be ruled out.
- **Endocrine disorders:** Rare cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see WARNINGS AND PRECAUTIONS, Thyroid Dysfunction section).
- **Hemorrhage:** Epistaxis is one of the most common hemorrhagic adverse events reported with sunitinib (see WARNINGS AND PRECAUTIONS, Hemorrhage section). Although most cases are mild and self-limited, serious cases have been reported through post-marketing experience.
- **Immune system disorders:** Hypersensitivity reactions, including angioedema, have been reported.
- **Infections and infestations:** Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported.
- **Rare cardiovascular, pulmonary embolism, pancreatic function and seizures:** 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).
- **Nervous system disorders:** Taste disturbance, including ageusia, has been reported.
- **Renal and urinary disorders:** Cases of renal impairment and/or failure, in some cases with fatal outcome, have been reported.
- **Musculoskeletal and connective tissue disorders:** 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).

Baseline ECG should be conducted prior to starting SUTENT, and ECGs should be performed periodically during therapy. SUTENT should generally not be prescribed to patients with...
abnormally long baseline QT/QTc intervals or AV block. If there are symptoms suggestive of arrhythmia or if the QT/QTc interval becomes markedly prolonged while the patient is on SUTENT, the drug should be discontinued.

**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 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; pioglitazone; 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 interval prolongation and/or torsade de points include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de points:

- 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)
- Quinolone antibiotics (e.g., moxifloxacin, gatifloxacin, ciprofloxacin)
- Antiarrhythmics (e.g., quinidine)
- Pentamidine
- Azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- Gastrointestinal drugs (e.g., domperidone, SM3 antagonists, such as granisetron, ondansetron, dolasetron)
- Beta-2-adrenoreceptor 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, digoxis, or HIV protease inhibitors (see WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation section). 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 section). 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 decreased SUTENT metabolism and decreased SUTENT plasma concentrations (see Drug-Drug Interactions section). Patients receiving SUTENT should not take St. John’s Wort concomitantly. To report any suspected adverse reactions associated with the use of health products, please visit the Canada Vigilance Program at www.healthcanada.gc.ca/medefect or call toll-free at 1-866-234-2345.

**Study References**


**SUPPLEMENTAL PRODUCT INFORMATION:**

Product Monograph available on request.

**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) Cmax and AUC0–∞, 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 section). 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 two cytokine-refractory 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 46% reduction in combined (sunitinib + active metabolite) Cmax and AUC0–∞, 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 section).

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-refractory 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 ECOG score.

**OVERDOSAGE:** 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. A few cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.
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