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New Evidence in Oncology is a publication that 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. In addition, the investigator commentary sections provide information on key clinical studies from interviews with principal investigators. New Evidence also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our September 2011 issue presents coverage from the 2011 Annual Meeting of the American Society of Clinical Oncology (ASCO) held in Chicago, Illinois from June 3–7, 2011. The issue examines key studies in metastatic melanoma, hematology and ovarian cancer aimed at improving patient care, particularly in the era of personalized medicine. We would like to thank Dr. Silvy Lachance and Dr. Teresa Petrella for their Canadian perspectives.

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.
Contents

METASTATIC MELANOMA

New Treatment Strategies and Ongoing Clinical Research for Metastatic Melanoma

• An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases (Dummer R, et al. ASCO 2011: Abstract 8548)


• Vemurafenib: Phase III randomized, open-label, multicenter trial (BRIM-3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600E BRAF-mutated melanoma (Chapman PB, et al. ASCO 2011: Abstract LBA4)

• Molecular testing for BRAF V600 mutations in the BRIM-2 trial of the BRAF inhibitor vemurafenib in metastatic melanoma (Bloom KJ, et al. ASCO 2011: Abstract 10523)

• The burden of metastatic melanoma: treatment patterns, healthcare use, and costs (Reyes C, et al. ASCO 2011: Abstract 8565)

• Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma (Wolchok JD, et al. ASCO 2011: Abstract LB5)

• A phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma (Hodi FS, et al. ASCO 2011: Abstract 8511)

• Results from the first-in-human phase I study of the oral RAF inhibitor RAF265 administered daily to patients with advanced cutaneous melanoma (Sharfman WH, et al. ASCO 2011: Abstract 8508)

Canadian perspective by Dr. Teresa Petrella

HEMATOLOGY

Improving Patient Outcomes by Optimizing the Use of Rituximab in CLL and DLBCL

• A phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukemia: Results of the induction phase (Mauro FR, et al. ASCO 2011: Abstract 6629)

• R-CHOP14 versus R-CHOP21: Results of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma (Cunningham D. ASCO 2011: Abstract 8000)

• Maintenance with rituximab after autologous stem cell transplantation in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL): CORAL final analysis (Gisselbrecht C, et al. ASCO 2011: Abstract 8004)

• Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients with aggressive CD20+ B-cell lymphomas: Seven-year follow-up of the RICOVER-60 trial of the DSHNHL (Pfreundschuh M et al. ASCO 2011: Abstract 8029)

• Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate or high IPI grade diffuse aggressive NHL (Stiff P, et al. ASCO 2011: Abstract 8001)

Canadian perspective by Dr. Silvy Lachance
New Phase III Data on Bevacizumab for the Treatment of Newly Diagnosed, Advanced, and Recurrent Ovarian Cancer

• OCEANS: A randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer (Aghajanian C, et al. ASCO 2011: Abstract LBA5007)

• Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer (Kristensen G, et al. ASCO 2011: Abstract LBA5006)

• Independent radiologic review of GOG218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal or fallopian tube cancer (Burger RA, et al. ASCO 2011: Abstract 5023)

Contributors

Canadian Perspectives

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-Rosemont 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.

Teresa Petrella, BSc, MD, MSc, FRCPC

Teresa Petrella is a Medical Oncologist at the Odette Cancer Centre (OCC) in Toronto, Canada and an Assistant Professor at the University of Toronto. Dr. Petrella has a BSc in Molecular Biology from the University of Western Ontario and she completed her MD at Queen’s University. Her Internal Medicine and Medical Oncology training was at McMaster University. She subsequently completed a fellowship in Melanoma and Breast Cancer at the Toronto Sunnybrook Regional Cancer Centre along with a Masters degree in Health Research Methodology at McMaster University. She was the recipient of a CIHR/CAMO award for her research in vaccine therapy in combination with interferon for melanoma patients. Dr. Petrella joined the staff at OCC in 2002 and became the head of the Melanoma Site Group. She also chairs the Provincial Guidelines Melanoma Disease Site Group Program in Evidence Based Care the National Cancer Institute of Canada (NCIC) Melanoma Clinical Trials Group. Her research interests are in melanoma and breast cancer and she is currently the Principal Investigator for several multicentre trials investigating novel therapies in melanoma.
MELANOMA
Melanoma has historically been refractory to most standard systemic therapy. Metastatic melanoma has a poor prognosis, with the median survival for patients with stage IV disease ranging from eight to 18 months after diagnosis, depending on the substage.\(^1\) Two approved treatments, dacarbazine (DTIC) and interleukin-2 (IL-2), have not demonstrated an impact on overall survival (OS) in randomized trials.\(^2\)

However, new agents and treatment strategies are changing the landscape of the management of melanoma, aided by a greater understanding of the genetic abnormalities that catalyze the development and progression of the disease. The discovery of activating mutations in BRAF, for example, was followed by the discovery of other mutations, which allowed melanoma to be classified into a group of diseases. This also created the opportunity to develop therapies that target the activating molecules and their pathways.\(^3\)

New research is ongoing to explore novel agents and therapy combinations, identify additional prognostic biomarkers that may result in personalized therapy, and improve current treatment options.

At ASCO 2011, various studies were presented that highlighted the ongoing clinical advances in melanoma. This article reports on eight of these studies.

- An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases provides early efficacy signals and demonstrated that vemurafenib is well tolerated in symptomatic patients with melanoma metastatic to the brain.

- The BRIM-2 trial — a pivotal phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma — confirmed that vemurafenib is an active agent in patients with BRAF mutation-positive melanoma who have completed prior systemic therapy.

- BRIM-3 — a phase III randomized, open-label, multicentre trial comparing vemurafenib with DTIC in patients with V600E BRAF-mutated melanoma — showed that vemurafenib improves overall response rates (ORR), progression-free survival (PFS), and OS compared with DTIC in patients with previously untreated, V600E BRAF-mutated metastatic melanoma.

- Molecular testing with an investigational polymerase chain reaction (PCR) assay (the cobas 4800 BRAF V600 mutation test) has a higher sensitivity than Sanger sequencing and is robust, rapid and accurate. This test may have clinical utility in assessing the activity of vemurafenib for BRAF V600 mutations, as demonstrated in the BRIM-2 trial.

- A claims-based analysis assessed the burden of metastatic melanoma, including treatment patterns, healthcare use, and costs, and found that resource utilization and cost increased considerably after the development of metastases in patients with melanoma. Furthermore, targeted therapies are needed to improve outcomes and reduce the burden of disease.

- A phase III randomized study of ipilimumab plus DTIC versus DTIC alone as first-line treatment in patients with advanced melanoma demonstrated that combination therapy significantly improved OS. Furthermore, adverse events were similar to those seen in previous studies of ipilimumab alone.

- A phase I trial of ipilimumab plus bevacizumab in patients with advanced melanoma — the first combination study to investigate potential synergies of these agents — suggests that the combination can be safely administered.

- The first in-human phase I study of the oral RAF inhibitor RAF265 in advanced cutaneous melanoma defined the maximum tolerated dose (MTD) of this agent, and showed that clinical activity was observed at multiple dose cohorts in patients with BRAF mutant and wild type melanoma.

An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases

**Background**
Melanoma is a common cause of cerebral metastases, and indicates a poor prognosis. In phase I and II studies, vemurafenib has shown dramatic activity in metastatic melanoma harbouring V600-mutated BRAF. However, these studies excluded patients with active brain metastases and thus to date the activity of vemurafenib — an orally available inhibitor of oncogenic BRAF kinase — for brain metastases has remained unknown.

At ASCO 2011, Dummer and colleagues presented their early findings from an open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases.3

**Study design**
- The study was an open-label, single-arm trial of vemurafenib designed to evaluate the safety and efficacy of this agent in patients with metastatic melanoma and non-resectable brain metastases.
- Patients had BRAF V600 mutations (determined by the cobas 4800 BRAF V600 Mutation Test).
- Patients with an ECOG performance status of 0–2 had to have been pretreated with radiotherapy and/or chemotherapy and were on stable or decreasing doses of steroids, and had brain metastases-related symptoms.
- Vemurafenib was administered continuously at a dose of 960 mg twice daily, until progressive disease (PD) or toxicity.
- Staging by magnetic resonance imaging (MRI) brain and computed tomography (CT) of the thorax/abdomen was scheduled every four weeks in the first two months, and then every eight weeks thereafter.
- Overall survival (OS) was determined, as well as measurements of improvements in physical symptoms.
- Patients’ serum S100 levels were also determined.
- Adverse events (AEs), including serious adverse events (SAEs), were assessed.

**Key findings**
- Seven patients were enrolled in the study:
  - Median age was 47 years (range 24–50 years);
  - Median number of nine brain metastases in each patient (range: 3–18);
  - All patients had metastases at other organ sites;
  - Patients had an ECOG performance status of 0–2;
  - All patients were on dexamethasone.
- As of March 2011, patients have received treatment with vemurafenib for one to four months, with one patient on treatment for four months; one patient for three months; three patients for two months; and the remaining two patients for one month.
- Six patients reported 38 treatment-emergent AEs.
  - All AEs were grade 1 or 2.
  - There were no grade 3 or higher AEs reported.
- Of the 38 treatment-emergent AEs, 18 were reported by four patients as being possibly drug-related. (Table 1)
  - Four SAEs were reported by two patients, but were not treatment-related.

**Table 1. Adverse events in patients receiving vemurafenib (n = 7)**

<table>
<thead>
<tr>
<th>Total no. of AEs</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with AE</td>
<td>7</td>
</tr>
<tr>
<td>At least one AE</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Alanine aminotransferase increase</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>1</td>
</tr>
<tr>
<td>Masculo-papular rash</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
</tr>
</tbody>
</table>

_AE = adverse event_
Key conclusions

- To date, vemurafenib has been well tolerated in symptomatic patients with melanoma metastatic to the brain.
- This study provides early, strong results suggesting activity of vemurafenib in brain metastases.

References:


BRIM-2: An open-label, multicentre phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma

Background

Most agents tested in large phase II trials in patients with metastatic melanoma have response rates of 10–20%. Approximately 50% of melanomas harbour a V600E-activating mutation in the BRAF gene, which can now be targeted with investigational inhibitors. In a previous phase I study, treatment with vemurafenib led to a high incidence of tumour regressions in BRAF-mutant melanoma.1

At ASCO 2011, Ribas and colleagues presented results of the BRIM-2 study — a pivotal phase II trial of vemurafenib in previously treated patients with BRAF-mutant metastatic melanoma.2 The goal of the study was to confirm the best overall response rate (ORR) of vemurafenib in previously treated patients with BRAF V600-mutated melanomas.

Study design

- The trial was a single-arm, multicentre, open-label phase II trial in patients with stage IV disease who had received one or greater prior systemic therapy.
- Patients had brain metastases controlled for at least three months following local therapy.
• The primary endpoint was ORR as assessed by an independent review committee (IRC).

• Secondary endpoints were duration of response, progression-free survival (PFS), overall survival (OS), and safety.

• BRAF mutation status was determined using a PCR-based investigational, companion diagnostic assay (cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems).

• Patients received oral vemurafenib at a dose of 960 mg twice daily until progressive disease (PD), unacceptable toxicity, or death.

Key findings

• The trial included 132 patients with a median age of 51.5 years, who were enrolled between October 2009 and March 2010 for a median follow up of 10 months (range: 0.6–14.7 months).

  ◦ 54% of patients had an ECOG performance status of 1, and 61% had M1c stage disease; 49% of patients had elevated lactate dehydrogenase (LDH); and 49% had received more than one line of prior therapy (i.e., poor prognostic factors.)

• The ORR was 53% as assessed by independent review committee (IRC).

  ◦ 29% of patients had stable disease (SD).

  ◦ 14% of patients had PD. (Figure 1)

  ◦ There were no differences in response rates according to age, gender, performance status, disease stage, number of prior therapies or prior therapy with high-dose interleukin-2 (IL-2).

  ◦ There was a difference in response rates based on baseline LDH levels with higher response rates in patients with a normal LDH and a lower response rate in patients with a baseline LDH of greater than 1.5 times the upper limit of normal (ULN).

• The median duration of response was 6.8 months (95% CI: 5.6–not reached).

• The median PFS by intent-to-treat-analysis was 6.7 months (95% CI: 5.5–7.8 months) and the PFS at six months was 54%. (Figure 2)
• The median OS has not yet been reached after a median follow-up of 10 months. (Figure 3)
  - The OS at six months was 77% (95% CI: 70–85) and at 12 months was 58% (95% CI: 49–67).
• Adverse events (AEs) were generally reversible (with dose modification or interruption).
• The most common AEs (all grades) were arthralgia (seen in 59% of patients), rash (52%), and photosensitivity reaction (52%).
• The most common grade 3 AE was cutaneous squamous cell carcinoma (seen in 26% of patients), the majority of which were centrally reviewed as keratoacanthoma-type.
• 45% of patients required dose reductions, most commonly for rash, arthralgia, and liver function test abnormalities.
• 64% of patients had dose interruptions due to AEs.
• The median daily dose was 91% of the intended total dose.
• Only four patients discontinued therapy due to drug-related AEs.

**Figure 3. Overall survival**

![Graph showing overall survival](image)

**Key conclusions**

■ Based on positive results as assessed by the primary endpoint of ORR, the BRIM-2 trial confirms that vemurafenib is an active agent in patients with BRAF mutation-positive melanoma who have completed prior systemic therapy.

■ The trial met its primary endpoint, with an ORR of 53% and a 95% CI that excludes an ORR of 20%.

■ The toxicity profile of vemurafenib at 960 mg twice daily is manageable, with most AEs being reversible with dose modification or interruption.

■ The longer follow up of this study is complementary to the benefits in OS seen in the BRIM-3 trial: together, these trials provide evidence that vemurafenib is an effective agent for the treatment of patients with BRAF V600 mutation–positive melanoma.

**References:**
Background
About 50% of melanomas have an activating V600E BRAF mutation, which suggests that inhibition of the mutated BRAF kinase may be of clinical benefit. Previous phase I and II trials with vemurafenib have shown impressive response rates in V600E BRAF-mutated metastatic melanoma patients.1

At ASCO 2011, Chapman and colleagues presented the results of BRIM-3 — a phase III randomized, open-label, multicentre trial comparing vemurafenib with dacarbazine (DTIC) in previously untreated patients with V600E BRAF-mutated metastatic melanoma.2

Study design
• Patients with previously untreated, unresectable stage IIIC or stage IV melanoma (ECOG performance status 0 or 1, with no active CNS metastases) who tested positive for V600E BRAF mutation by the cobas 4800 BRAF V600 Mutation Test were randomized in a one-to-one ratio to oral vemurafenib (960 mg, twice daily) or intravenous DTIC (1,000 mg/m², three times weekly).
• Cross-over was not permitted and the trial was a non-blinded randomization.
• Co-primary endpoints were overall survival (OS) and progression-free survival (PFS) in the intent-to-treat (ITT) population.
• Secondary endpoints included objective response rates (ORR) and safety.

Key findings
• From January to December 2010, 675 patients were enrolled from 104 centres worldwide, and the cohorts were well-balanced.
  ◦ Approximately two-thirds of patients in both arms had stage M1c disease, and 42% of patients had elevated LDH levels.
• The data cut-off for this analysis was December 30, 2010.
• At the pre-planned interim analysis (50% of deaths needed for final analysis), the hazard ratios (HR) for OS and PFS were 0.37 (95% CI 0.26–0.55; p < 0.0001) and 0.26 (95% CI 0.20–0.33; p < 0.0001), respectively, both in favour of vemurafenib. (Figures 1 and 2)
At six months, the estimated OS was 84% for vemurafenib, versus 64% for DTIC.

- The median OS could not be analyzed at the time of this analysis.
- Improvements in OS were seen for all sub-groups examined.

- The median PFS was 5.3 months for vemurafenib, versus 1.6 months for DTIC, and was highly statistically significant in favour of vemurafenib.
- All pre-specified subsets of patients showed clear benefits in PFS.
- The ORR was 48.4% and 5.5% for vemurafenib and DTIC, respectively, among the 65% of patients evaluable for RR, to date.
- As a result of the promising data, independent data monitoring committee (IDMC) recommended that the DTIC cohort has been allowed to cross over to vemurafenib.
- At the time of analysis, 66% of vemurafenib patients and 25% of DTIC patients were still on treatment.
- The most common toxicities associated with vemurafenib that required dose modifications were: arthralgia, rash, photosensitivity, fatigue, and increased liver function tests (LFTs). (Table 1)
- Adverse events (AEs) of special interest were cutaneous squamous cell carcinoma (grade 3), keratoacanthoma, and skin papilloma (which are a function of vemurafenib and other drugs in this class).
- For all AEs, grade 3 toxicities were fairly uncommon for both study arms, as was discontinuation.

### Table 1. Selected adverse events (% of patients)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vemurafenib (n = 336)</th>
<th>Dacarbazine (n = 282)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Increase in LFTs</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>–</td>
</tr>
</tbody>
</table>

*LFT = liver function test; SCC = squamous cell carcinoma*
**Key conclusions**

- Vemurafenib is associated with statistically significantly improved OS and PFS compared to DTIC in patients with previously untreated, V600E BRAF-mutated metastatic melanoma.
- Vemurafenib was associated with a 63% decrease in the hazard ratio of death ($p < 0.001$) and a 74% decrease in the hazard of tumour progression ($p < 0.001$).
- The benefits of vemurafenib treatment were seen in all sub-groups, including poor prognosis patients.
- Vemurafenib had a manageable safety profile, with few drug-related discontinuations.
- This is the first single drug for melanoma to improve response rate, PFS and OS compared with standard chemotherapy.
- Vemurafenib is a promising new therapy and a foundation upon which to build future combination therapies.

**References:**


**Molecular testing for BRAF V600 mutations in the BRIM-2 trial of the BRAF inhibitor vemurafenib in metastatic melanoma**

**Background**

Early clinical trials have shown that vemurafenib has dramatic activity in patients with BRAF V600 mutation-positive metastatic melanoma. Preclinical and phase I clinical data show the drug has minimal activity in tumours lacking BRAF mutations, which creates the need for an accurate diagnostic test to identify appropriate patients for therapy.

At ASCO 2011, Bloom and colleagues presented on molecular testing for BRAF V600 mutations in the BRIM-2 trial, a phase II trial of vemurafenib in patients with BRAF V600 mutation-positive metastatic melanoma.

**Study design**

- To assess eligibility for BRIM-2, tumour samples were screened with an investigational PCR assay (cobas 4800 BRAF V600 Mutation Test) designed to detect the canonical V600E (1799T > A) mutation.
- 328 samples were tested, of which 327 samples gave valid results.
- BRAF mutations were detected in 184 samples (56.3%).
- 132 with BRAF-mutation positive melanoma were enrolled in the trial based on clinical eligibility criteria.
- Sanger sequencing was performed retrospectively on DNA samples from all enrolled patients.

**Key findings**

- 15 samples (11.4%) gave invalid Sanger results.
- Sanger methods detected a V600E mutation in 97 samples (73.5%), V600K mutation in nine samples (6.8%), and a wild-type result in 11 cases (8.3%). (Table 1)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Sanger</th>
<th>454 sequencing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>V600E (number of samples)</td>
<td>97</td>
<td>14</td>
</tr>
<tr>
<td>V600K (number of samples)</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Wild type (number of samples)</td>
<td>11</td>
<td>All†</td>
</tr>
</tbody>
</table>

* Of 15 samples (11.4%) that gave invalid Sanger results
† Median percentage of mutant alleles of 8%; ten of the 11 samples had a percentage <25%
• Samples were also subjected to deep sequencing with a quantitative picotiter plate pyrosequencing method to resolve differences between PCR and Sanger results.
• Using 454 sequencing of samples with invalid Sanger results revealed a V600E mutation in 14 cases, and a V600K mutation in one case.
• Of 11 samples with a wild type Sanger result, 454 sequencing detected a V600E mutation in all cases, with a median percentage of mutant alleles of 8%; 10 of the 11 samples had a percentage <25%.
• The presence of a V600K mutation was confirmed by 454 sequencing in all nine samples identified as having V600K mutations by Sanger.

Key conclusions

- Molecular testing for BRAF V600 mutations in the BRIM-2 trial showed that the investigational PCR test had a low failure rate.
- The PCR test was more sensitive in the detection of V600E mutations than Sanger sequencing, which may miss mutations in cases with a low percentage of mutant alleles.
- The PCR test detects V600K mutations.
- In all 132 cases, a codon 600 mutation was confirmed by Sanger and/or 454 sequencing.
- This multicentre clinical trial achieved robust, rapid and accurate molecular testing.


Reyes C, et al. ASCO 2011: Abstract 8565

The burden of metastatic melanoma: treatment patterns, healthcare use, and costs

Background
Frequently, the treatment of metastatic melanoma with currently available therapies provides limited clinical benefit, with infrequent durable responses and relatively low rates of survival. Few studies have examined healthcare utilization, costs, and treatment patterns of the disease.

At ASCO 2011, Reyes and colleagues presented their findings of a study on the burden of metastatic melanoma, including treatment patterns, healthcare utilization, and costs.1

Study design
- From January 1, 2007 to March 31, 2010, a claims-based analysis was conducted using data from a national commercial health insurer.
- Eligible patients were 18 years or older, and had two or more claims for metastatic disease (at least 30 days apart, and two or more claims for melanoma at least 30 days apart, or one or more claim for cancer-related treatment with a diagnosis of melanoma. Patients with a second primary cancer were excluded.
- Patients were continuously enrolled for six months prior to the index date (baseline) and more than three months post-index date (follow-up).
- The index date was the first metastatic melanoma diagnosis date.
- During the observation period, patients were examined from the index date to the end of the observation period (that being death, disenrollment, or end of the study period).
- First-line or second-line therapy began at the date of the first receipt of chemotherapy and ended at the earlier of either the start of subsequent-line therapy, start of best supportive care, or end of the observation period.
- Outcome measures included treatment patterns, total healthcare usage, average per-patient per-month costs, best supportive care (defined as hospice after the end of systemic therapy), and mortality.
Key findings

- The study enrolled 829 metastatic melanoma patients with a mean age of 58.8 years with a mean baseline comorbidity index of 3.42.
- A significantly higher percentage of patients received testing, imaging, and treatment during the follow-up compared with the six-month baseline period.
- Throughout the study period, 71% and 10% of patients had evidence of immunohistochemistry and molecular testing, respectively.
- 431 (52%) and 103 (12%) patients had evidence of starting first-line and second-line treatment, respectively.
- Temozolomide, interferon alfa 2b, and interleukin 2 were the most common systemic therapies.
- The rate of healthcare utilization (defined as events per person, per year) increased 1.5–5-fold from baseline to follow-up ($p<0.001$). (Table 1)
  - 0.28 versus 1.40 for inpatient, 19.11 versus 29.64 for office visits, 12.03 versus 26.87 for outpatient visits, and 0.96 versus 1.45 for emergency room (ER) visits.

Table 1. Rates of healthcare utilization

<table>
<thead>
<tr>
<th>Healthcare utilization</th>
<th>Rate (events/person/year)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Inpatient visits</td>
<td>0.28</td>
<td>1.40</td>
</tr>
<tr>
<td>Office visits</td>
<td>19.11</td>
<td>29.64</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>12.03</td>
<td>26.87</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.96</td>
<td>1.45</td>
</tr>
</tbody>
</table>

- The mean per-patient per-month healthcare costs increased five-fold from $1,855 at baseline to $9,495 during follow-up ($p<0.001$). (Figure 1)

Figure 1. Total per patient per month costs in baseline and follow-up periods

- All components of medical costs were significantly higher ($p<0.001$) during the follow-up period compared with the baseline period. (Figure 2)
- 21% of patients ($n=173$) had evidence of best supportive care (BSC) with a mean time to BSC of 261 days (Figure 3).
- 35% of patients died during the study period and among those who died, the mean survival time was 285 days.

Figure 2. Medical cost components per patient per month at baseline and follow-up periods
Key conclusions

- Resource utilization and cost increase considerably after the development of metastases in patients with melanoma.
- The low proportion of patients with first- or second-line treatment suggests frequent enrolment in clinical trials as an early or intervening treatment.
- More effective treatments, such as those targeting relevant biomarkers, are needed to improve outcomes and reduce the burden of metastatic melanoma.


Wolchok JD, et al. ASCO 2011: Abstract LBA5

Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma

Background

A phase III study of ipilimumab monotherapy in previously treated, unresectable or metastatic melanoma patients showed improved overall survival (OS). Additional background is provided by phase II data suggesting that the combination of ipilimumab with dacarbazine (DTIC) provided durable objective responses, as well as adverse events (AEs) consistent with other ipilimumab studies. Ongoing studies in the treatment of first-line metastatic melanoma include evaluation of combination of therapy with DTIC, a global standard of care, plus ipilimumab.

At ASCO 2011 Wolchok and colleagues presented the results of a phase III randomized study of ipilimumab plus DTIC versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma.

Study design

- The trial was a double-blind, phase III study of metastatic melanoma patients 18 years or older, with an ECOG performance status of 0–1, and no prior therapy for advanced disease.
- Patients with brain metastases or symptomatic autoimmune disease were excluded.
- During the induction phase, patients were randomized in a one-to-one ratio to ipilimumab (10 mg/kg) plus DTIC (850 mg/m²), or placebo plus DTIC (850 mg/m²) once every three weeks for four cycles, followed by DTIC every three weeks through week 24.
- During the maintenance phase, eligible patients received blinded ipilimumab or placebo every 12 weeks.
- The primary endpoint was originally progression-free survival (PFS); but it was changed to overall survival (OS) after it was learned that OS was the most accurate way to measure the efficacy of ipilimumab.
Key findings
- Of 502 patients from 24 countries, more than 50% of patients were poor prognosis with stage M1c disease (representing patients with visceral disease and/or elevated lactate dehydrogenase [LDH]) and 26% of patients had received adjuvant therapy.
- 37.2% of patients in the ipilimumab plus DTIC arm and 66.0% of patients in the DTIC alone arm received four induction doses.
- Approximately 20% of all patients received at least one dose of maintenance therapy.
- A significant improvement was seen in OS (hazard ratio [HR] = 0.72; \( p = 0.0009 \)) indicating a 28% reduction in the risk of death, and higher estimated one, two and three-year survival rates were seen with combination therapy.
- The median OS was 9.1 months for DTIC alone versus 11.2 months in the ipilimumab plus DTIC arm. (Figure 1)
- The combination therapy arm had a statistically significant improvement in PFS, with a hazard ratio of 0.76 (\( p = 0.006 \)), compared with DTIC alone. (Figure 2)
- Disease control rates did not differ between the two study groups.

Figure 1. Overall survival

Figure 2. Progression-free survival
• The duration of response was 19.3 months in the ipilimumab plus DTIC arm versus 8.1 months in the placebo plus DTIC arm, and the duration of response was sustained. (Figure 3)

• 56.3% of patients in the combination therapy arm (n = 247) and 27.5% of patients in the DTIC alone arm (n = 251) had grade 3/4 adverse events (AEs) including:
  ◦ Elevated alanine aminotransferase (ALT) (21.9% versus 0.8%)
  ◦ Elevated aspartate aminotransferase (AST) (18.2% versus 1.2%)
  ◦ Diarrhea (4% versus 0%)
  ◦ Rash (1.2% versus 0%)

• No intestinal perforations or hypophysitis were noted in either group.

• There were no drug-related deaths in the combination therapy arm, and one in the DTIC alone arm (which was due to gastrointestinal hemorrhage).

### Figure 3. Duration of response

![Figure 3. Duration of response](image)

Data shown for patients with a CR or PR

CR = complete response; DTIC = dacarbazine; PR = partial response

### Key conclusions

- Combination therapy with ipilimumab (at a dose of 10 mg/kg) plus DTIC significantly prolongs OS in the first-line treatment of metastatic melanoma versus DTIC alone.

- Ipilimumab, when combined with DTIC, provides durable responses.

- AEs were consistent with those noted in prior ipilimumab studies, and primarily affected the skin, gastrointestinal tract, liver and endocrine system.
  - The AEs were immune-based, and managed with established guidelines.
  - The rates of high-grade events differed from those seen in phase II trials, with a higher rate of transaminitis, and rates of diarrhea/colitis/gastrointestinal perforation were lower than expected.

- No drug-related deaths were noted with ipilimumab.

- This phase III randomized trial confirms that ipilimumab provides OS benefit in treatment-naïve metastatic melanoma patients.

### References:


A phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma

Background
In previous trials, it has been shown that cytotoxic T-lymphocyte (CTL)-associated antigen 4 (CTLA-4) blockade with ipilimumab — a targeted T cell antibody — demonstrated a survival advantage in advanced melanoma.1 Ipilimumab induces an immune-mediated tumour vasculopathy. In addition to its angiogenic effects, vascular endothelial growth factor (VEGF) is a potent immune suppressor of antigen presenting cells.

At ASCO 2011, Hodi and colleagues presented results of a phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma — the first combination study to investigate potential synergies of these two agents.2

Study design
• Eligible patients had stage III unresectable or stage IV disease, no bowel or central nervous system (CNS) metastases, an ECOG performance status of 0 or 1, adequate organ function and no autoimmune or bleeding problems, and had had more than four weeks since their last prior therapy.
• Patients received four courses of intravenous ipilimumab every three weeks and then every 12 weeks, and bevacizumab every three weeks.
• Patients with a good performance status could continue with up to a 40% increase in the sum of the longest tumour diameter, and no more than two new target lesions.
• Cohort 1 (five patients) comprised 10 mg/kg ipilimumab plus 7.5 mg/kg bevacizumab.
  ▶ Patients received induction therapy every three weeks for four cycles, and subsequently received maintenance bevacizumab every three weeks, with ipilimumab continuing every three months.
• If at least three or more patients did not experience dose-limiting toxicity (DLT) after the first 12 weeks, then cohort 2 could be enrolled at 10 mg/kg ipilimumab plus 15 mg/kg bevacizumab.
• An additional 12 patients could be treated at the maximum tolerated dose (MTD).

Key findings
• 22 patients were treated in this study.
• The median age was 57 years, and patients were predominantly female.
• Inflammatory adverse events (AEs) included giant cell arteritis (one patient), palpable purpura (one patient), hypophysitis (five patients), thyroiditis (three patients), grade 4 hepatitis (one patient), bilateral uveitis (two patients), and grade 2 colitis (one patient, although this was resolved).
• Positron emission tomography (PET) scans revealed early response activity and perfusion computed tomography (CT) demonstrated persistent decreased tumor blood flow.
• The best overall response rates (by RECIST criteria) showed six partial responses (27%), one complete response (5%), seven durable stable disease of at least six months (32%), and eight progressive disease (36%). (Figure 1)

Figure 1. Clinical efficacy of ipilimumab plus bevacizumab
• Response rates were also charted to show the clinical courses of patients on trial thus far.
  ◦ Several patients in cohort 1, for example, had prolonged stable disease before they experienced a partial response.
  ◦ One patient in the expanded cohort who experienced a complete response with stable disease for several months went into partial response, which then became a complete response after one year of therapy.
• The median follow up was 14 months, with a six-month PFS of 59% (95% CI: 36–76%), and a one-year OS of 72% (95% CI: 48–86%).
• Post-treatment biopsies in 14 patients revealed activated vessel endothelium with extensive T-cell trafficking not seen with ipilimumab alone, as well as non-productive central angiogenesis.
• Peripheral blood monitoring revealed marked increase in CD4/CCR7/CD45RO central memory cells in the majority of patients, not seen with ipilimumab alone.

Key conclusions

■ This is the first combination study to investigate potential synergies between ipilimumab and bevacizumab.
■ Results of this phase I trial suggest that ipilimumab plus bevacizumab can be safely administered, with management of noted toxicities. Effects on both tumour immunity and tumour vascular were observed.
■ The clinical activity of this combination and its correlatives suggest synergistic effects of ipilimumab and bevacizumab.
■ Ipilimumab plus bevacizumab combination therapy merits further exploration in a phase II trial for the treatment of advanced melanoma, and additional efforts to assess safety and efficacy are underway.

References:

Background
RAF265 is an oral small molecule multi-kinase inhibitor of mutant BRAF V600E and vascular endothelial growth factor receptor 2 (VEGFR2). It displays dose-dependent inhibition of tumour growth and regression in mutant BRAF V600E tumour xenografts, including primary human melanoma models.

At ASCO 2011, Sharfman and colleagues presented results from the first-in-human phase I study of the oral RAF inhibitor RAF265 administered daily to patients with advanced cutaneous melanoma.1

Study design
• The trial was designed as a dose escalation study to identify the maximum tolerated dose (MTD), safety, pharmacokinetic profile, progressive disease and anti-tumour activity of RAF265, and to develop a phase II dose expansion restricted to BRAF mutant melanoma patients.
• Various administration schedules of RAF265 were used: daily, weekly, and intermittent.
• Only the results for daily dosing in the arm 2 dose escalation schema were presented during this session, where patients were treated by a loading dose followed by continuous daily RAF265 oral solution at escalated dose levels (there were seven dose levels in this study).
• A Bayesian logistic regression model with overdose control guided the dose escalation.
• Patients who were 18 years of age or older, with histologically confirmed melanoma and measurable, locally advanced or metastatic disease, with a minimum four weeks having elapsed since any major surgery or prior investigational therapy were eligible for this study.


Results from the first-in-human phase I study of the oral RAF inhibitor RAF265 administered daily to patients with advanced cutaneous melanoma
**Key findings**

- 76 patients were enrolled with a median age of 60 years (range: 26–83 years).
- RAF265 was rapidly absorbed, with the maximal plasma concentration ($C_{\text{max}}$) observed at approximately three hours after drug administration (range: 1–8 hours).
- $C_{\text{max}}$, and area under the curve ($\text{AUC}_{0-\text{last}}$) increased proportionally with increasing dose.
- The mean elimination half-life ($t_{\frac{1}{2}}$) of RAF265 was 11 days. (Figure 1)

**Figure 1. Pharmacokinetic parameters**

![Pharmacokinetic parameters graph]

- Pre-clinical studies had indicated that 4,127 ng/mL was the effective concentration ($C_{\text{eff}}$), which fell between dose levels six and seven; however, the MTD was declared to be dose level six.
- Plasma angiogenesis markers showed decreases of soluble VEGFR2 (sVEGFR2) and increases in placental growth factor (PIGF) across dose levels.
- Statistically significant changes in angiogenesis marker levels were seen over time ($p <0.0001$) and across dose levels.
- There were limited grades 3 or 4 drug-related adverse events (AEs) at dose levels one to five. Adverse events at dose levels 6 and 7 are shown in Table 1.
- Seven dose-limiting toxicities (DLTs) were noted in six patients:
  - Pulmonary embolism (two patients), visual disturbances (one patient), hyperlipasemia (one patient), diarrhea (one patient) and ataxia (one patient).
  - Grade 3 thrombocytopenia (five patients) and 4 (two patients) occurred at 67 mg daily in the second cycle and was also considered dose limiting.
  - The MTD was declared at 48 mg once daily, at dose level six.
- 64 patients were evaluable for response:
  - The overall response rate (ORR) was 11% across all dose levels, and the median duration of response was approximately four months.
  - Patients with responses were seen across all the dose levels, and one complete response was seen at dose level seven.
  - Responses were seen in patients with both BRAF mutant tumours (n = 39, three partial responses), and BRAF wild-type tumours (n = 27, two PR and one CR).

**Table 1. Grade 3 or 4 adverse events**

<table>
<thead>
<tr>
<th>Toxities</th>
<th>Cohorts 1–5 ≤24 mg; n = 35 n (%)</th>
<th>Cohort 6 48 mg; n = 22 n (%)</th>
<th>Cohorts 7 and 7.1 67 mg; n = 19 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>–</td>
<td>–</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>–</td>
<td>2 (9.1)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>–</td>
<td>–</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>–</td>
<td>3 (13.6)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>–</td>
<td>–</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>–</td>
<td>2 (9.1)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>–</td>
<td>1 (4.5)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>–</td>
<td>1 (4.5)</td>
<td>–</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>–</td>
<td>–</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>–</td>
<td>1 (4.5)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>–</td>
<td>1 (4.5)</td>
<td>–</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>–</td>
<td>–</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>–</td>
<td>–</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>1 (5.0)</td>
<td>1 (4.5)</td>
<td>–</td>
</tr>
</tbody>
</table>
Key conclusions

- In this first in-human phase I study, the MTD of oral RAF265 on a continuous daily schedule was defined at 48 mg.
- The main dose-limiting toxicities were thrombocytopenia and visual AEs.
- Clinical activity was observed at multiple dose cohorts in patients with BRAF mutant and wild type melanoma.
- Statistically significant changes were observed in angiogenesis markers, PIGF and sVEGFR2, over time across all dose levels.
- Due to the long half-life of RAF265, an intermittent schedule is being explored to improve its therapeutic index.


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Canadian perspective by Dr. Teresa Petrella

Metastatic melanoma is a devastating disease with a very poor prognosis and historically, therapeutic options have been limited. However, new agents and treatment strategies are changing the landscape of the management of melanoma. Research is ongoing to explore these novel agents, identify therapeutic combinations, as well as uncover biomarkers that may further cause a paradigm shift toward personalized medicine. Personalized medicine is an emerging approach that may dramatically impact patient outcomes in the future.

When making treatment decisions for metastatic melanoma patients, a number of factors are considered that include, but are not limited to, molecular markers, tumour burden, rapidly versus slowly progressing disease, presence of brain metastases, performance status, and the ability to tolerate treatment.

For several decades, little progress has been made in the treatment of metastatic melanoma and standard therapies have had little impact on overall survival (OS). Vemurafenib and ipilimumab are promising new agents that have recently emerged. Both are regarded as major advances in this field offering patients superior outcomes when compared with standard therapy. Vemurafenib and ipilimumab are currently available in Canada through Early Access Programs pending approval by Health Canada.

The discovery of targeted therapies and tests for these targets has changed the landscape of cancer therapy and paved the way for personalized medicine. Vemurafenib is an example of a targeted therapy that inhibits the V600E-activating mutation in the BRAF gene and has demonstrated activity in metastatic melanoma patients harbouring this mutation. It is an oral agent which simplifies administration. It is also fast acting which makes it particularly useful in patients with extensive and rapidly progressing disease. Results are often observed within one to two weeks of treatment initiation. In addition, vemurafenib has a manageable toxicity profile. Squamous cell carcinoma is observed in approximately 23% of patients but if it is monitored well, caught early, and treated, it does not impact treatment or outcomes.

Both vemurafenib and ipilimumab have demonstrated an advantage with respect to OS—something that has never been seen with any other drug before in this therapeutic area. Ipilimumab has demonstrated durable responses of up to three years in the most recent trial and is also well tolerated. However 10% to 15% of patients can develop serious immune-related adverse effects (IRAEs) which require immunosuppressive therapy with steroids. These “serious potentially life-threatening complications” with ipilimumab require a committed multidisciplinary team to manage them. Currently, the challenge is how to better identify patients who are likely to respond as not to impose unnecessary toxicity.

Several studies assessing vemurafenib in the treatment of BRAF positive metastatic melanoma patients were presented at ASCO 2011. The study by Dummer, et al. demonstrated early efficacy signals for vemurafenib in an open-label pilot study of the agent in previously treated metastatic melanoma patients with brain metastases. These patients have a very poor prognosis usually measured in weeks and currently available therapy is inadequate. Brain metastases are commonly treated with either surgery followed by radiation or either whole-brain radiation or stereotactic radiation. The potential impact of these findings, once verified...
in larger studies with longer follow-up times, may revolutionize how these patients are treated. Vemurafenib has the potential to become the new standard of care for BRAF-positive patients with brain metastases.

Ribas, et al. presented the phase II BRIM-2 trial of vemurafenib in previously treated patients with BRAF-positive metastatic melanoma and Chapman, et al. reported on BRIM-3, a phase III randomized, open-label, multicentre trial comparing vemurafenib with dacarbazine (DTIC) in patients with BRAF-positive melanoma. Both trials allowed the enrollment of patients with high lactate dehydrogenase (LDH) and M1c disease—subgroups that have a poorer prognosis. Vemurafenib is the first drug to demonstrate improvement in response rates, progression-free survival (PFS), and OS over standard chemotherapy. The results are very impressive with rapidly observed responses and improvements in quality of life. In both of these studies, vemurafenib was well tolerated with photosensitivity, rash and arthralgias being common adverse events (AEs) that were manageable. Squamous cell carcinoma was not as prominent a problem as expected and the BRIM-3 trial showed its incidence to be only 12%, compared with 23% as seen in previous trials. Vemurafenib fills an unmet need for metastatic melanoma patients with BRAF mutations. It is very gratifying for physicians who, until recently have been unable to offer much hope to their patients. However despite these advances, unfortunately the majority of patients will die from their metastatic melanoma. Clinical trials, whenever appropriate should remain the mainstay of treatment in these patients.

Bloom, et al. evaluated the clinical utility and the reliability of the cobas 4800 BRAF V600 Mutation Test. Accurate molecular testing can be achieved with this test, which is a critical component of personalized medicine and this test will undergo approval simultaneously to vemurafenib. In Canada, funding and availability of the test will be governed provincially. It is likely that testing will be centralized as not all treatment centres have a molecular or melanoma pathologist. Strategies will need to be implemented to allow for efficient testing in order to avoid treatment delays. Ideally, it would be best if patients were tested for an array of molecular markers including BRAF, c-kit, NRAS, etc. before they became metastatic. However when the cobas test is approved it will likely be used for metastatic patients and hopefully also for high risk stage 3 patients. Given that the incidence of BRAF mutations can be 40–50%, fast and accurate testing for the mutation is necessary in order to initiate vemurafenib in a timely fashion, particularly in rapidly progressing disease.

The pharmacoeconomic analysis of the burden of metastatic melanoma by Reyes, et al. is an interesting study that is highly relevant in the current era of escalating drug costs. Studies such as this allow us to identify better ways to allocate available resources. It is difficult to tell how applicable the findings of this study would be to Canadian metastatic melanoma patients as some factors would likely be very different. In Ontario, the drug approval process includes the conduction of an economic analysis for each drug that is reviewed. In depth pharmacoeconomic analyses are becoming more important as cancer therapy costs escalate in Canada with the advent of targeted therapies.

Wolchok, et al. presented the results of a phase III randomized study of ipilimumab plus DTIC versus DTIC alone as first-line treatment in patients with unresectable advanced stage melanoma. This was a well-designed study with demonstrated OS improvement. The key finding of this study was the long duration of response. The three-year survival was 20.8% versus 12.2% in favour of ipilimumab plus DTIC and this is one of the few studies in metastatic melanoma to follow patients for this long. The risk for AEs is high with this treatment combination, which may be attributed to the agent that ipilimumab is paired with. Studies to identify safe and effective combinations with ipilimumab are ongoing as demonstrated by the phase I study of ipilimumab plus bevacizumab in patients with unresectable advanced stage melanoma by Hodi, et al. This is a novel approach that targets different mechanisms in melanoma. The first impression of this study is that ipilimumab plus bevacizumab is too toxic to be delivered safely, as 14 of 22 patients studied had inflammatory AEs. Despite this, studies like these are necessary to move science forward and phase I studies are the first step in identifying combinations that may be worthwhile and feasible to pursue. Multi-targeting is likely the way of the future; however, efforts need to focus on identifying agents that have scientific rationale and can be combined with the least amount of toxicity.

The study by Sharfman, et al. was a dose escalation study of a novel small molecule multi-kinase inhibitor, RAF265, in patients with advanced cutaneous melanoma. There were eight dose levels included in this study and 48 mg was selected as the maximum tolerate dose (MTD). Clinical activity was seen at multiple dose levels, though response rates were low. At present it is too early to predict the potential of this agent; however this is an interesting drug due to its multiple target potential.

Both vemurafenib and ipilimumab may revolutionize how metastatic melanoma patients are treated, with an agent such as vemurafenib having the potential to become the standard of care for BRAF-positive patients. As both of these agents may be approved in Canada in the near future, it will be important for oncologists, to understand and manage their AEs early. With the targeting of multiple pathways, a solid foundation is being laid for further research and treatment combinations that will optimize therapy, while taking into account the different onsets of efficacy or resistance mechanisms. Agents such as vemurafenib and ipilimumab are leading a new era for melanoma research with numerous opportunities that did not exist 10 years ago.
Improving Patient Outcomes by Optimizing the Use of Rituximab in CLL and DLBCL

The addition of rituximab to conventional chemotherapy regimens has improved outcomes in patients with chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL). One of the goals of continued research is to optimize the use of rituximab by identifying alternate chemotherapy partners, optimizing administration schedules, and incorporating stem cell transplantation into the treatment plan.

Data from studies examining these issues in CLL and aggressive non-Hodgkin lymphoma (NHL) were presented at ASCO 2011. This article reports on five such studies:

• A phase II study of rituximab plus chlorambucil that demonstrated the benefit, tolerability, and activity of this treatment regimen for elderly patients with CLL.

• A randomized trial of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)14 compared to standard therapy (R-CHOP21) in newly diagnosed DLBCL across all age groups demonstrated that there is no evidence that R-CHOP14 is superior to standard R-CHOP21 in improving overall survival (OS) or failure-free survival (FFS).

• The CORAL study demonstrated that there was no difference in outcomes for patients with relapsed DLBCL treated with R-ICE (rituximab, ifosfamide, carboplatinum, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatinum) prior to autologous stem cell transplantation (ASCT) nor was there a difference in post-ASCT maintenance with either rituximab or observation.

• The results of the seven-year follow-up of the RICOVER-60 trial, which compared six and eight cycles of CHOP therapy every two weeks with or without rituximab in elderly DLBCL patients, demonstrated that both six cycles of R-CHOP14 and eight cycles of R-CHOP14 resulted in a significantly better OS compared to six cycles of CHOP14.

• A prospective, randomized phase III trial demonstrated that patients with high-risk diffuse, aggressive NHL have a superior progression-free survival (PFS) if they undergo autotransplantation at the first response to induction therapy with CHOP with or without rituximab compared to receiving standard therapy (CHOP with or without rituximab).
A phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukemia: Results of the induction phase

Background
The addition of rituximab to fludarabine and cyclophosphamide (FCR) significantly improves outcomes of patients with chronic lymphocytic leukemia (CLL) in terms of progression-free survival (PFS) and overall survival (OS). However, significant toxicities such as myelotoxicity and immunosuppression limit the use of this regimen in some CLL patients, particularly the elderly and those with comorbidities.

The German CLL Study Group compared first-line therapy of fludarabine versus chlorambucil in a multicentre phase III study. Significant improvements for overall and complete response (OR, CR) were observed for fludarabine but there was no benefit in terms of PFS or OS. A single-arm study in previously untreated CLL patients demonstrated that the addition of rituximab to chlorambucil was effective and well tolerated. Based on the expected tolerability and potentially increased activity of this regimen, the combination of rituximab (R) with chlorambucil represents an attractive therapeutic option for elderly patients or for patients with comorbidities who cannot tolerate more intensive regimens.

This study was designed to determine whether R-chlorambucil is a feasible and beneficial first-line treatment for elderly patients with CLL and to define the role of maintenance with rituximab. At ASCO 2011, Mauro and colleagues reported on the tumour response and safety of R-chlorambucil induction therapy.

Key findings
- 97 patients were enrolled.
  - The median age was 70.0 years (range: 61–84 years) with 52.9% being older than 70 years;
  - 47.1% had one or more comorbidities;
  - 74.1% were Binet stage B or stage C;
  - 58% were IgVH unmutated, 22.9% showed adverse cytogenetic abnormalities (11q23-: 16.9%; 17p13-: 6.0%), and 1.2% had a p53 mutation.

Efficacy
- The OR rate was 81.2%, with computed tomography (CT)-confirmed CR observed in 16.5% of patients. (Figure 1)
- No evidence of residual disease by four-colour flow cytometry in both peripheral blood and bone marrow was detected in two of 14 CR patients.
Safety

- Serious AEs (SAEs; n = 20) were documented in 17 of 97 patients with five related to chlorambucil and three related to R-chlorambucil.
- The most common toxicities (all grades) were neutropenia (32% of patients; 9.1% of cycles) and thrombocytopenia (14.4% of patients; 3.3% of cycles).
  - Grade 3–4 neutropenia occurred in 19.6% of patients (4.9% of cycles).
  - Grade 3–4 infections occurred in 1% of patients (0.2% of cycles).
- Among patients who were older than 80 years, the median number of R-chlorambucil cycles administered was six.
- Planned treatment was completed by 75.2% of patients in the safety population (n = 97).
- Dose reduction of chlorambucil was required in 7.8% of cycles and this was a result of toxicity in 5.9% of cycles.

Maintenance phase

- Following the induction phase of the study, 66 patients were randomized to the maintenance phase (rituximab arm: n = 34; observation arm: n = 32).
- The maintenance phase is ongoing and as of May 2011, 31 patients remain on maintenance rituximab and 27 are in observation.

Key conclusions

- The induction phase of this study indicates R-chlorambucil is a well-tolerated first-line regimen with acceptable toxicity for elderly patients with CLL.
- R-chlorambucil is an active regimen associated with a high OR rate (81.2%), comparable with that previously reported.1

R-CHOP14 versus R-CHOP21: Results of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma

Background
The addition of rituximab to six to eight cycles (21 days per cycle) of standard therapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP21) has resulted in improved overall survival (OS) outcomes by 10–16% for patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL).1,2 Administering CHOP as a 14-day cycle (CHOP14) for six cycles was superior to standard CHOP21 for six cycles in patients older than 60 years, with a five-year OS improvement of 13%.3 The RICOVER 60 trial indicated that two additional cycles of rituximab-CHOP14 (R-CHOP14) for a total of eight cycles is not superior to six cycles of R-CHOP14 in patients older than 60 years.4 Cunningham and colleagues conducted a randomized trial to evaluate OS improvement of R-CHOP14 compared to standard therapy (R-CHOP21) in newly diagnosed DLBCL across all age groups.5 The final analysis of this study was presented at ASCO 2011.

Study design
• Newly diagnosed patients with CD20-positive DLBCL were randomized to receive either eight cycles of standard R-CHOP21 or six cycles of R-CHOP14 (plus granulocyte colony-stimulating factor [G-CSF]) with two additional cycles of single-agent rituximab.
• Patients were stratified by international prognostic index (IPI; 0–1, 2, 3, 4–5), age (60 years of age or younger versus older than 60 years) and by treatment centre.
• The primary outcome was overall survival (OS).
• Secondary outcomes were failure-free survival (FFS), toxicity, and response (complete response [CR] and unconfirmed CR [CRu]).

Key findings
• Between March 2005 and November 2008, 1,080 (540 in each arm) patients were recruited from 119 sites.
• Baseline patient characteristics were balanced between the two groups with a median age of 61 years in both arms.
• 52% of patients were older than 60 years, which reflects routine clinical practice.
• 81% of patients in the R-CHOP21 arm completed study therapy compared with 89% in the R-CHOP14 arm.
• G-CSF was not mandated for the R-CHOP21 arm but approximately half of the patients received it by the end of the trial. G-CSF was part of the R-CHOP14 protocol.
• Reported grade 3–4 toxicities in the R-CHOP21 and R-CHOP14 arms were neutropenia (77% and 37%, reflecting the use of G-CSF), thrombocytopenia (5% and 9%), as well as infection (25% and 19%, respectively), and there were no statistically significant differences in the non-hematological toxicities. (Table 1)

Table 1. Toxicity during treatment

<table>
<thead>
<tr>
<th>Grade ≥3 hematological toxicity</th>
<th>R-CHOP21 (%)</th>
<th>R-CHOP14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>77*</td>
<td>37</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>9*</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>11*</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ≥3 non-hematological toxicity</th>
<th>R-CHOP21 (%)</th>
<th>R-CHOP14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Cardiac</td>
<td>&lt;1</td>
<td>2.6</td>
</tr>
<tr>
<td>Neurobiological</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Other grade 5 toxicities</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

p <0.01 (considered significant due to multiple testing)
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
The CR/CRu rates were 63% and 58% for the R-CHOP21 and R-CHOP14 arms ($p = 0.15$) and the CR/CRu/PR rates were 88% and 90% ($p = 0.11$) for the two arms, respectively. (Figure 1)

With a median follow-up of 39 months, a total of 240 deaths were observed and 70% of the patients in each of the two groups are alive without progression. (Table 2)

There was no difference in the FFS rate between the R-CHOP21 and R-CHOP14 groups (hazard ratio [HR] = 0.99 [95% CI: 0.79–1.24] $p = 0.94$) and similar results were observed for OS (HR = 0.95 [95% CI: 0.74–1.23] $p = 0.70$). (Figures 2 and 3)

The two-year OS rates were 81% and 83% for the R-CHOP21 and R-CHOP14 groups, respectively. (Figure 3)

Most of the deaths occurred within the first 18 months of treatment and there were no significant differences in causes of death between the two groups.

Subgroup analyses based on prognostic variables were conducted and there were no differences in patient outcomes.

### Table 2. Follow up

<table>
<thead>
<tr>
<th>Events breakdown</th>
<th>R-CHOP21 n (%)</th>
<th>R-CHOP14 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive without progression</td>
<td>379 (70)</td>
<td>380 (70)</td>
</tr>
<tr>
<td>Alive with progression/relapse</td>
<td>38 (7)</td>
<td>43 (8)</td>
</tr>
<tr>
<td>Death without documented</td>
<td>32 (6)</td>
<td>30 (6)</td>
</tr>
<tr>
<td>progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression/relapse+death</td>
<td>91 (17)</td>
<td>87 (16)</td>
</tr>
</tbody>
</table>

CR = complete response; CRu = unconfirmed complete response; PD = progressive disease; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; SD = stable disease
Key conclusions

- There is no evidence that R-CHOP14 is superior to standard R-CHOP21 in terms of improving OS or FFS.
- Subgroup analyses did not identify any groups of patients who derive a greater benefit from R-CHOP14.
- A higher frequency of neutropenia was observed with R-CHOP21 treatment, which was the reason for primary prophylaxis with G-CSF in the R-CHOP14 treatment group.

References:


Maintenance with rituximab after autologous stem cell transplantation in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL): CORAL final analysis

Background
Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for chemosensitive relapsed diffuse large B-cell lymphoma (DLBCL). This finding is based on the Parma trial, which showed that the seven-year event-free survival (EFS) rate was 41% for the ASCT arm compared with 13% in the conventional arm. Prior to rituximab, various salvage regimens provided 50–68% response rates with adequate mobilization of hematopoietic peripheral stem cells for ASCT. No study has compared different salvage therapies and evaluated maintenance post ASCT. Furthermore, the outcome for relapsed patients treated with upfront rituximab is unknown and the role of rituximab following ASCT remains to be determined. These questions were addressed in the CORAL trial and the results were presented by Gisselbrecht and colleagues at ASCO 2011.

Study design
- Patients with relapsed or refractory CD20-positive DLBCL were randomized between R-ICE (rituximab, ifosfamide, carboplatinum, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatinum).
- Those who responded received ASCT following conditioning with BEAM (carmustine, etoposide, arabinoside, and melphalan) and were randomized to observation or maintenance with rituximab every two months for one year.
- The primary objective of the induction therapy portion of the study was to evaluate the overall response rate (ORR) adjusted for successful mobilization.
- For the maintenance therapy portion of the study, the primary objective was to evaluate the EFS two years after ASCT.
- The secondary objectives of this study were to evaluate:
  - Eligibility for transplantation;
  - Toxicities associated with R-ICE and R-DHAP prior to ASCT and then with rituximab after ASCT;
  - Time to progression or relapse;
  - Disease-free survival (DFS) for complete responders;
  - Overall survival (OS).
Key findings

Induction

- 481 patients were randomized in the induction part of the study from July 2003 to June 2008.
- The intent-to-treat (ITT) population consisted of 477 patients (243 treated with R-ICE and 234 with R-DHAP) and the median follow-up was 40 months.
- The median EFS for R-ICE was 6.51 months versus 7.49 months for R-DHAP, and the four-year EFS was 29% versus 33% for R-ICE and R-DHAP, respectively ($p = 0.2672$).
- The median OS for R-ICE was 34.53 months versus 58.97 months for R-DHAP, and the four-year OS was 48% versus 51% for R-ICE and R-DHAP, respectively ($p = 0.3380$).
- The mobilization adjusted response rate was 51.5% for R-ICE and 56.5% for R-DHAP, but there were fewer adverse events (AEs) for R-ICE.
- Prognostic factors that affected response and survival included relapse less than 12 months, secondary IPI greater than 1, and prior rituximab exposure.

Maintenance

- Following induction, 245 patients were randomized in the maintenance part of the study from October 2003 to October 2008.
- The median follow-up in the maintenance phase was 44 months.
- The ITT population consisted of 242 evaluable patients: 122 were randomized to receive rituximab and 120 were randomized to observation.
- The patient characteristics were generally similar between the two groups apart from the enrollment of more males than females in this study.
- Response rates were similar in the rituximab and observation groups, with 60% and 58% achieving complete response (CR) or unconfirmed complete response (CRu), and 39% and 38% of patients achieving a partial response (PR) in each of the two groups, respectively. (Table 1)
- There was no difference in the rituximab and observation arms with a three-year EFS of 54% for both groups ($p = 0.74$). (Figure 1)

Table 1. CORAL maintenance: response after induction before ASCT

<table>
<thead>
<tr>
<th>Response after induction treatment</th>
<th>Arm of second randomization</th>
<th>Rituximab n (%)</th>
<th>Observation n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>52 (43)</td>
<td>48 (40)</td>
<td></td>
</tr>
<tr>
<td>CRu</td>
<td>21 (17)</td>
<td>21 (18)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>47 (39)</td>
<td>45 (38)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2 (2)</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>122 (100)</td>
<td>120 (100)</td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; CRu = unconfirmed complete response; PR = partial response; SD = stable disease

- The progression-free survival (PFS) at three years was 54% for the rituximab group and 57% for the observation group ($p = 0.82$). (Figure 2)
• The three-year OS was also similar in both groups: 66% for the rituximab group and 69% for the observation group \( (p = 0.91) \). (Figure 3)

**Figure 3. CORAL maintenance: overall survival by treatment arm**

- PFS and OS were not affected by the type of induction treatment received or by the response achieved in the induction phase, which suggests that ASCT overcomes the poorer prognosis of patients who achieved only a PR prior to transplantation.
- In a univariate analysis of prognostic parameters:
  - Prior rituximab exposure significantly affected EFS \( (p = 0.0081) \);
  - Early relapse was also an adverse prognostic factor \( (p = 0.0439) \);
  - Secondary IPI of 2–3 significantly affected post-ASCT EFS \( (p = 0.0835) \) and OS \( (p < 0.0001) \).

**Key conclusions**

- **There was no difference between R-ICE and R-DHAP and between post-ASCT maintenance with rituximab or observation.**
- **Women did significantly better after ASCT with rituximab, which warrants validation in an external group of patients.**
- **Patients with early relapses to upfront rituximab-based chemotherapy have a poor prognosis.**

Background
Previous studies have demonstrated that elderly patients with diffuse large B-cell lymphoma (DLBCL) benefited from reducing the interval between cycles of therapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) from three weeks (CHOP21) to two weeks (CHOP14). Furthermore, the addition of rituximab to CHOP-21 (R-CHOP21) improved outcomes in elderly patients with DLBCL to a similar extent compared to CHOP21 without rituximab.1,2

At ASCO 2011, Pfreundschuh and colleagues presented the results of a seven-year follow-up of the RICOVER-60 trial, which compared six and eight cycles of CHOP therapy every two weeks with or without rituximab.3

Study design
• In the RICOVER-60 trial, elderly patients (age = 61–80 years) were randomized to one of four groups:
  ◦ Six cycles of CHOP14
  ◦ Eight cycles of CHOP14
  ◦ Six cycles of R-CHOP14
  ◦ Eight cycles of R-CHOP14
• Radiation therapy was planned to sites of initial bulk and/or areas of extranodal involvement.
• The primary endpoint was event-free survival (EFS).
• Secondary endpoints were progression-free survival (PFS) and overall survival (OS).

Key findings
• Between July 2000 and June 2005, 1,222 patients with CD20-positive DLBCL were recruited and were evaluable for this study.
  ◦ The median age was 68 years.
  ◦ The international prognostic index (IPI) was 1 for 30% of patients, 2 for 28%, 3 for 26%, and 4 or 5 for 16%.
• There were no differences between the four study groups with respect to long-term toxicity and the development of secondary neoplasms.
• The seven-year EFS and OS rates are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Seven-year EFS and OS for RICOVER-60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>7-year EFS</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>6xCHOP14 (n = 307)</td>
</tr>
<tr>
<td>8xCHOP14 (n = 305)</td>
</tr>
<tr>
<td>6xR-CHOP14 (n = 306)</td>
</tr>
<tr>
<td>8xR-CHOP14 (n = 306)</td>
</tr>
</tbody>
</table>

* median observation time of 82 months
CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

• In a multivariate analysis using six cycles of CHOP14 as the reference and adjusting for the stratification variables of elevated lactate dehydrogenase (LDH), stage 3 and 4 disease, Eastern Cooperative Oncology Group (ECOG) performance status >1, bulky disease, extranodal disease in more than one site, and age over 70 years, both six cycles of R-CHOP14 and eight cycles of R-CHOP14 significantly improved EFS, PFS, and OS:

**EFS**
- Six cycles of R-CHOP14: relative risk (RR) = 0.5, \( p < 0.001 \)
- Eight cycles of R-CHOP14: RR = 0.5, \( p < 0.001 \)

**PFS**
- Six cycles of R-CHOP14: RR = 0.5, \( p < 0.001 \)
- Eight cycles of R-CHOP14: RR = 0.5, \( p < 0.001 \)

**OS**
- Six cycles of R-CHOP14: RR = 0.6; \( p < 0.001 \)
- Eight cycles of R-CHOP14: RR = 0.7; \( p = 0.004 \)

• It was observed that six cycles of R-CHOP14 were slightly better than eight cycles of R-CHOP14 with respect to all endpoints and had a significantly better OS in patients with bulky disease (\( p = 0.005 \)).
Key conclusions

■ In contrast to the three-year follow-up of the RICOVER-60 trial, it was observed that not only six cycles of R-CHOP14, but also eight cycles of R-CHOP14 results in a significantly better OS compared to six cycles of CHOP14 after a median observation time of 82 months.

■ Due to its lower toxicity and shorter exposure to cyclophosphamide (10 weeks in six cycles of CHOP14; 15 weeks in eight cycles of CHOP14; 21 weeks plus one day in eight cycles of CHOP21), six cycles of CHOP14 in combination with eight cycles of rituximab is the preferred regimen for elderly patients with CD20+ DLBCL.

■ The significant superiority of six cycles of R-CHOP14 over eight cycles of R-CHOP21 in patients with bulky disease (and who received radiation to the involved areas) suggests that radiation to areas of bulky disease is more effective when given after six cycles of R-CHOP14 than after eight.

References:


Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for eight cycles to CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate or high IPI grade diffuse aggressive NHL

Background
High-dose therapy and autologous stem cell transplantation (ASCT) are considered the standard of care for relapsed chemosensitive, diffuse, intermediate, and high-grade non-Hodgkin lymphoma (NHL). A retrospective analysis of the GELA study (LNH-87) demonstrated that progression-free survival (PFS) and overall survival (OS) improved for patients with high-risk disease. Numerous subsequent prospective studies have been performed in high-risk groups comparing standard therapy to various approaches including multi-cycle dose-dense therapy starting at diagnosis, short-course standard induction therapy followed by high-dose therapy, and treating only responders after full-course induction chemotherapy. The addition of rituximab to induction regimens has improved outcomes for patients with diffuse aggressive NHL but those with high-risk disease still have only 50% long-term survival. Based on these data, the SWOG-led intergroup trial undertook a prospective, randomized phase III trial to compare six cycles of R-CHOP followed by ASCT compared with eight cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for patients with diffuse aggressive NHL in the high-intermediate and high international prognostic index (IPI) groups. The objectives of the study included comparing progression-free survival (PFS) rates and overall survival (OS) rates in patients treated with R-CHOP or CHOP alone for five cycles followed by R-CHOP for one cycle followed by ASCT, versus patients treated with three additional cycles of R-CHOP. The toxicity of both treatment approaches was also evaluated and a retrospective sub-analysis was conducted to evaluate the outcome after relapse for the two groups. The results of this study were presented by Stiff and colleagues at ASCO 2011.
Study design

- Eligible patients were induced with five cycles of CHOP or R-CHOP.
- Responders (patients in partial response [PR] or complete response [CR]) were then randomized between CHOP (with or without rituximab) for one cycle followed by autotransplant and CHOP (with or without rituximab for three cycles).
- The primary endpoints were toxicity and two-year PFS and OS.

Key findings

Patients and safety

- 397 patients (up to age 65) from 40 sites were registered in this study between September 1997 and December 2007.
  - Of 370 induction eligible patients, 253 were randomized after induction to standard (n = 128) or transplant (n = 125) therapies.
  - The characteristics of the patients randomized were similar to the characteristics of the patients who were initially induced on the study, and were identical between the two randomized groups.
- On the standard therapy arm, two patients did not receive CHOP with or without rituximab, one received only rituximab, and two had fatal toxicities.
- On the transplant arm, nine patients never received transplant and six had fatal toxicities (three of which were pulmonary toxicity).
- Grade 3/4 toxicities were higher for the transplant group and the leading toxicities in both groups were infection and gastrointestinal toxicity.

Efficacy

- The two-year PFS was 56% and 69% for the standard arm and the transplant arm, respectively (hazard ratio [HR] = 1.72 [95% confidence interval (CI): 1.18–2.51] p = 0.005), indicating a statistically significant benefit for transplant. (Figure 1)
- There was no difference in the OS for the two groups with the two-year estimate of 71% and 74% for the standard arm and the transplant arm, respectively (HR = 1.24 [95% CI: 0.81–1.91]) p = 0.16). (Figure 2)
- The post-relapse data indicate that the difference between PFS and OS was largely attributable to the patients who received a salvage transplant on the standard arm.
  - 46.8% of the 62 patients who relapsed were on the standard arm and 11 of these (18%) are in CR due to the autotransplant.
- There was no differential treatment effect of standard therapy versus transplant by histology (T-cell versus B-cell) for either PFS (p = 0.43) or OS (p = 0.53).

- For B-cell patients, there was no evidence of a differential treatment effect of rituximab in addition to CHOP induction therapy for PFS (p = 0.35) or OS (p = 0.29).
- Exploratory analyses revealed that there was a significant differential treatment effect between the high-intermediate and high IPI patients for both PFS (interaction p-value = 0.02) and OS (interaction p-value = 0.01).
  - For standard therapy versus transplant arms, the two-year PFS was 63% versus 66% for the high-intermediate IPI patients and 41% versus 75% for the high IPI patients. (Figure 3)
  - For standard therapy versus transplant arms, the two-year OS was 75% versus 70% for the high-intermediate IPI patients and 64% versus 82% for the high IPI patients. (Figure 4)
Figure 3. Outcome of all randomized patients based on IPI: progression-free survival

- **High-intermediate IPI patients only**
  - CHOP-R x1 + PBSCT: 81 patients, 32 relapsed or died, 2-year estimate 66%
  - CHOP-R x3: 84 patients, 38 relapsed or died, 2-year estimate 63%

- **High IPI patients only**
  - CHOP-R x1 + PBSCT: 44 patients, 13 relapsed or died, 2-year estimate 75%
  - CHOP-R x3: 48 patients, 20 relapsed or died, 2-year estimate 41%

95% CI = 95% confidence interval; HR = hazard ratio; IPI = international prognostic index; PBSCT = peripheral blood stem cell transplant; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Figure 4. Outcome of all randomized patients based on IPI: overall survival

- **High-intermediate IPI patients only**
  - CHOP-R x1 + PBSCT: 84 patients, 29 relapsed or died, 2-year estimate 70%
  - CHOP-R x3: 84 patients, 25 relapsed or died, 2-year estimate 75%

- **High IPI patients only**
  - CHOP-R x1 + PBSCT: 44 patients, 9 relapsed or died, 2-year estimate 82%
  - CHOP-R x3: 44 patients, 22 relapsed or died, 2-year estimate 64%

95% CI = 95% confidence interval; HR = hazard ratio; IPI = international prognostic index; PBSCT = peripheral blood stem cell transplant; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Key conclusions

- Patients with high-risk diffuse, aggressive NHL have a superior two-year PFS if they undergo autotransplantation at the first response to induction therapy with CHOP with or without rituximab compared to receiving standard therapy (CHOP with or without rituximab).

- A survival advantage has not yet been demonstrated, as 18% of the patients who relapsed on the standard therapy arm have had a long-term PFS after salvage autotransplantation.

- Histology (B-cell or T-cell) did not impact outcomes.

- Exploratory analyses revealed that for high-intermediate IPI and high IPI patients with diffuse aggressive NHL, early autotransplantation improves PFS for responders, with even greater advantages observed for patients with high IPI.

References:
In recent years, the addition of rituximab to fludarabine and cyclophosphamide (FCR) has significantly improved both progression-free and overall survival (PFS and OS) in patients with chronic lymphocytic leukemia (CLL). Despite the emergence of this new standard of care for the first-line treatment of CLL, many patients cannot tolerate FCR. For example, at our centre in Montreal, approximately 40% of newly diagnosed patients are unfit for treatment with FCR. In addition, although a minority of elderly patients with CLL may tolerate FCR, the vast majority require less aggressive treatment options due to the presence of comorbidities. For elderly patients or those with comorbidities, maintaining quality of life (QoL) is therefore crucial. Less aggressive treatments such as oral chlorambucil are often given in an outpatient setting to minimize toxicities in these patients. Despite the advantages of oral chlorambucil in elderly patients, its efficacy is limited. Other treatment options that minimize toxicities and improve efficacy are therefore needed.

Even though almost three quarters of patients with CLL are over 65 years, this population is typically under-represented in clinical trials. The study by Mauro, et al. examining the addition of rituximab to chlorambucil (R-chlorambucil) as first-line treatment of elderly patients with CLL is therefore important. When used alone, chlorambucil achieves an overall response (OR) rate of 35–55%. This study demonstrated an OR rate of 81% with R-chlorambucil, which indicates a significant contribution of rituximab to the efficacy of this regimen. Although a high response rate is important, this result will only become meaningful if associated with a significant delay in time to progression or time to second treatment.

In addition to promising efficacy results, the safety of R-chlorambucil appears acceptable, with 20 serious adverse events (SAEs) in 17 of 97 patients enrolled, with hematological toxicities being the most common. Considering the age of the study population, if the increased OR rate translates into prolonged time between treatments, the added toxicity appears worthwhile.

One puzzling point regarding the design of this study is that around 25% of patients had Binet stage A disease. As these patients are typically observed and are not actively treated, it would be interesting to know why the investigators included them in the study. In addition, because of the known increased risk of infection in this patient population, it would be helpful to know if anti-infectious prophylaxis was given.

Results of this study suggest that R-chlorambucil is an effective and relatively safe option in elderly patients. For older patients (>70 years) who cannot tolerate fludarabine-based regimens and for younger patients with significant comorbidities, R-chlorambucil is therefore a promising treatment option. Our centre, being a stem cell transplant centre, tends to focus on younger patients. However, for those patients unfit for transplant, I would consider using R-chlorambucil. The next step in examining the efficacy, safety, feasibility, and impact on QoL of R-chlorambucil in older patients with CLL is to perform a randomized study comparing upfront treatment with R-chlorambucil versus chlorambucil monotherapy.

After induction treatment, the study by Mauro, et al. randomized patients to receive rituximab maintenance or observation alone. There is no current role for rituximab maintenance in CLL and very few patients were included in each arm of this phase of the study. However, it will be interesting to see whether ongoing maintenance with rituximab prolongs the time to next treatment without adding to the toxicity of treatment.

In diffuse large B-cell lymphoma (DLBCL), the addition of rituximab to 6–8 cycles (21 days per cycle) of standard therapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP21) has resulted in improved OS outcomes. However, administering CHOP as a 14-day cycle (CHOP14) for six cycles may be superior to treatment with standard CHOP21. The study by Cunningham, et al. randomized patients with newly diagnosed DLBCL to R-CHOP14 or R-CHOP21. This was a well designed study, with the study population representing those patients seen in clinical practice. The median age of the study population was 61 years, and in both groups more than 50% of patients were older than 60 years. Given that hematological toxicities are frequent with R-CHOP treatment in older patients, the added use of granulocyte colony-stimulating factor (G-CSF) in the R-CHOP21 arm is not surprising to prevent treatment delays and infection. The mandatory use of G-CSF in the R-CHOP14 arm was associated with improved treatment delivery and contributed to the lower rates of neutropenia and infection.
At our centre in Montreal, R-CHOP21 is the standard first-line treatment for DLBCL across all age groups. Six to eight courses of treatment are typically given, according to mid-treatment response and assessment. However, despite R-CHOP21 being typically well tolerated in younger patients, it is associated with significant hematological toxicities and treatment delays in older patients. For patients with cardiac disease, the total dose of anthracyclines delivered in the study (8 x 50 mg/m² = 400 mg/m²) approached the maximum dosage allowed. R-CHOP14 for six cycles is therefore an interesting alternative to standard R-CHOP21 (with the added cost of mandatory G-CSF) but with the advantage of a short, dose-dense treatment.

The RICOVER-60 study presented by Pfreundschuh, et al. is a pivotal study by the German CLL Study Group (GCLLSG), comparing six versus eight bi-weekly treatments with CHOP14, with or without rituximab, in elderly patients with aggressive B-cell lymphomas. The patient population in this study is typical of that seen in clinical practice.

R-CHOP is now standard clinical practice in patients with aggressive lymphomas and should always be added to first-line treatment. When added to CHOP, rituximab is well tolerated and increases response rates, disease-free survival, and OS, compared with CHOP alone. In a dose-dense schedule, the addition of rituximab also reduces both anthracycline and cyclophosphamide exposure.

Results of this study demonstrated that six cycles of R-CHOP14 achieved slightly better outcomes than eight cycles of R-CHOP14 and significantly improved OS in patients with bulky disease. Given that eight cycles of R-CHOP14 was associated with increased treatment-related toxicities, it is likely that patients experienced more treatment delays and dose reductions than in those given six cycles of R-CHOP14. When R-CHOP is given in a dose-dense schedule every 14 days, there seems to be no added benefit of the last two cycles. Giving two additional cycles of R-CHOP14 may have also delayed further radiation treatment to bulky sites, and may have a dilatory effect on disease control. Based on the results of this study, it is clear that six cycles of R-CHOP14 is a promising alternative to eight cycles of R-CHOP21. While using six cycles of R-CHOP14 has the added cost of mandatory G-CSF, it provides a shorter, dose-dense treatment. In choosing between the two schedules of R-CHOP, patient preference, age, comorbidities, bulky presentation, and the need for post-chemotherapy radiation treatment are factors that should be considered.
OVARIAN
New Phase III Data on Bevacizumab for the Treatment of Newly Diagnosed, Advanced, and Recurrent Ovarian Cancer

Among ovarian cancers, surgery to remove as much of the tumour as possible is a mainstay of treatment but unfortunately, the majority of patients are diagnosed with advanced disease and require further treatment.

Bevacizumab, initially approved in 2004 in Canada for advanced colorectal cancer, became the first anti-angiogenic therapy made widely available for the treatment of several tumour types, including those of the ovaries. Since its approval for the treatment of ovarian cancer, bevacizumab is increasingly being recognized as a promising new therapy, through its targeted actions on vascular endothelial growth factor.

Several previous pivotal phase III randomized trials have demonstrated progression-free survival (PFS) benefit with bevacizumab in patients with previously untreated (including advanced) epithelial ovarian cancer (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC).1,2

At ASCO 2011, investigators presented data from studies examining the use of bevacizumab in newly diagnosed, advanced, as well as platinum-sensitive recurrent EOC, PPC, or FTC. These trials add further evidence to support the potential of bevacizumab to improve outcomes in a disease for which there have been few treatment advances in over a decade.

This article reports on three such studies:

- The OCEANS study — a randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent EOC, PPC, or FTC showed that bevacizumab halved the risk of progression in this setting.

- An interim analysis of overall survival (OS) in the Gynecologic Cancer Inter Group (GCIG) ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer showed that the addition of bevacizumab to standard chemotherapy demonstrated continued improvement in PFS, and a trend for improved OS, particularly for patients with more aggressive disease.

- Independent radiologic review of GOG218 — a phase III trial of bevacizumab in the primary treatment of advanced EOC, PPC, or FTC — confirmed a significant increase in PFS and suggests that response evaluation criteria in solid tumours (RECIST) can be applied objectively in primary ovarian cancers.

OCEANS: A randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer

Background
Results from the OCEANS trial build on findings from two previous phase III studies in newly diagnosed ovarian cancer, GOG 0218 and ICON7.1,2 Both of these studies showed that front-line bevacizumab in combination with standard chemotherapy, followed by continued use of bevacizumab alone, significantly increased progression-free survival (PFS) compared with chemotherapy alone.1,2

These new results of OCEANS (a double-blind, placebo-controlled phase III study of platinum-sensitive patients) — presented by Aghajanian and colleagues at ASCO 2011 — assessed the therapeutic impact of bevacizumab in combination with carboplatin (C) and gemcitabine (G), followed by single agent bevacizumab on progressive disease (PD). Results demonstrated that bevacizumab provided a statistically significant and clinically relevant benefit when added to chemotherapy in patients with recurrent, platinum-sensitive epithelial ovarian (EOC), primary peritoneal (PPC), and fallopian tube cancer (FTC).3

Study design
• The trial included women with recurrent, platinum-sensitive EOC, PPC, or FTC who had received no prior chemotherapy for recurrent ovarian cancer, and no prior bevacizumab.
• Patients had an ECOG performance status of 0–1 and no measurable disease.
• Patients were randomized in equal numbers (n = 242) to receive six to 10 cycles of standard chemotherapy (C and G) plus either bevacizumab 15 mg/kg every 3 weeks (Arm B), or a placebo (Arm A) concurrently, followed by maintenance treatment with single-agent bevacizumab (15 mg/kg) or placebo, respectively, until progressive disease (PD) or toxicity.
• The primary endpoint was investigator assessed PFS.
• Secondary endpoints were overall response rate (ORR), overall survival (OS), duration of response, and safety.
• PFS was also assessed an independent review committee.
• The final analysis of OS is not yet mature, and is planned when 353 events are observed.

Platinum-sensitive recurrent ovarian cancer*
• Measurable disease
• ECOG 0/1
• No prior chemo for recurrent ovarian cancer
• No prior BEV
• n = 484

Stratification variables:
• Platinum-free interval (6–12 vs. >12 months)
• Cytoreductive surgery for recurrent disease (yes vs. no)

AUC = area under the curve; BEV = bevacizumab; C = carboplatin; G = gemcitabine
*Epithelial ovarian, primary peritoneal, or fallopian tube cancer.
Key findings

• A total of 484 patients (242 per arm) were enrolled from April 2007 to January 2010.
• Patient characteristics were matched in study arms:
  - Approximately one-third of patients were aged 65 years and older.
  - Approximately 40% of patients had a platinum-free interval of six to 12 months, and 60% at more than 12 months.
• After a median follow up of 24 months, bevacizumab plus CG followed by single agent bevacizumab upon PD significantly increased PFS compared with CG alone (median 12.4 months versus median 8.4 months, HR = 0.484 (95% CI: 0.388–0.605), \( p <0.0001 \)). There was clear separation of the curves at approximately two months. (Figure 1)
• A subgroup analysis of PFS showed notable consistency among the subgroups: all demonstrated that bevacizumab plus chemotherapy improves PFS versus chemotherapy alone.
• Patients in the bevacizumab group had a statistically significant increase in ORR (78.5% versus 57.4%, \( p <0.0001 \)).
• The duration of responses was 10.4 months versus 7.4 months in the control arm (HR = 0.534 [95% CI: 0.408–0.698], \( p <0.0001 \), compared for descriptive purposes only).
• Although OS results are not yet mature, an interim analysis showed a trend favouring bevacizumab, with a median OS of 35.5 months, compared with 29.9 months for placebo (HR = 0.751 [95% CI: 0.537–1.052]; \( p = 0.094 \)). (Figure 2)
• The safety data was consistent with the known bevacizumab side effect profile. (Table 1)
  - Serious adverse events (SAEs) occurred in 25% of patients who received placebo, and in 35% of patients who received bevacizumab.
  - Grades 3 to 5 adverse events (AEs) of special interest occurred in 62% of patients who received placebo, and in 74% patients who received bevacizumab.
  - There was one study death in each arm.
  - For AEs of special interest hypertension and proteinuria were more common in the bevacizumab arm, and the rate of neutropenia and febrile neutropenia were the same in each arms.
  - There were no gastrointestinal perforations noted during the study period.

Figure 1. Primary analysis of progression-free survival

![Figure 1](image1.png)

Figure 2. Interim analysis of overall survival

![Figure 2](image2.png)

Table 1. Overview of adverse events

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>CG + placebo (n = 233)</th>
<th>CG + BEV (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Serious AE</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Grade 3–5 AE</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Grade 3–5 AE of special interest</td>
<td>62</td>
<td>74</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>&lt;1*</td>
<td>&lt;1†</td>
</tr>
</tbody>
</table>

*Acute myocardial infarction in one patient
†Intracranial hemorrhage in one patient

AE = adverse event; BEV = bevacizumab; C = carboplatin; G = gemcitabine
Key conclusions

- In this phase III trial, bevacizumab was shown to provide a statistically significant and clinically relevant benefit when added to chemotherapy in patients with recurrent, platinum sensitive EOC, PPC, and FTC, when compared with chemotherapy alone.
- Improvements were seen in PFS, ORR, and duration of response.
- Additional data are required to more fully evaluate OS.
- Safety data are consistent with those seen with trials of bevacizumab in that there were no GI perforations and no new safety signals arose as a result of this trial.
- This is the first trial of its kind that demonstrates a clinical benefit in these types of cancers after treatment with bevacizumab.
- Results suggest that this regimen should be considered a new option for patients with recurrent platinum-sensitive ovarian cancer, in which there are currently limited treatment options available.


Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer

Background

In 2006, the Gynecologic Cancer InterGroup (GCIG) ICON7 study — a multicenter, phase III randomized trial — was launched and designed to investigate the safety and efficacy of adding bevacizumab to standard chemotherapy in women with newly diagnosed ovarian cancer.

Results presented at the European Society for Medical Oncology (ESMO) 2010 meeting of bevacizumab combined with standard carboplatin (C) and paclitaxel (P) followed by continued single-agent bevacizumab demonstrated a benefit in progression-free survival (PFS) and suggested a trend for overall survival (OS) improvement, but results were immature (only 34% of the events required for final OS analysis). 1

At ASCO 2011, Kristensen and colleagues presented interim results of this trial. The analyses of mature PFS data suggest a PFS benefit from bevacizumab, and a trend toward OS. 2 Furthermore, a subgroup analysis of poor prognosis patients was performed in an exploratory manner.

The final analysis of OS will be performed when 715 deaths have occurred (with results expected in 2013).

Study design

- In the ICON7 study, eligible women with newly diagnosed or advanced epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC) were randomized in a one-to-one fashion to six cycles of thrice-weekly chemotherapy (carboplatin [C] area under the curve[AUC] 5 or 6 and paclitaxel [P] 175 mg/m²) alone, or the same chemotherapy given concurrently with bevacizumab (7.5 mg/kg) every three weeks, for a total duration of 12 months.

- Five or six cycles of this protocol were followed by continued thrice-weekly single-agent bevacizumab for 12 additional cycles, or until progression (whichever occurred first).

- Early disease was defined as International Federation of Gynecology and Obstetrics (FIGO) stage I or IIa (grade 3 or clear cell), capped ≤10%; advanced disease was defined as stage IIIb-IV.

- The primary endpoint of the trial was PFS; OS was the secondary endpoint.
Key findings

- From December 2006 to February 2009, 1,528 women were randomized from 263 centres in seven GCIG groups.
- Baseline characteristics were balanced between study arms: median age (57 years); most patients had serous histology (69%); high-risk early-stage disease (9%); high-risk/poor prognosis patients (30%).
- The mature PFS analysis had a median follow-up period of 19 months (cut-off November 2010).
- The gain in median PFS was 2.4 months, with the curves merging after two years.
- The median PFS in the bevacizumab arm was 19.8 months, versus 17.4 months in the control arm (HR = 0.87 [95% CI = 0.77–0.99], p = 0.039). (Figure 1)

Figure 1. Updated progression-free survival

- OS in the high-risk group (stage III with >1 cm after debulking, or stage IV with debulking) showed a clear difference in treatment effect:
  - 47% of patients in the control arm have died versus 34% in the bevacizumab group (HR = 0.64; 36% reduction in the risk of death);
  - The gain in median OS was approximately eight months (p = 0.002). (Figure 2)
- By risk group, there was a clear difference in OS effect in the high-risk group versus the other patient groups (where at present, no difference in OS has been seen) although the data are immature (median OS not yet reached, p = 0.64, HR = 1.07; final analyses expected in two years).

Figure 2. Overall survival in high-risk patients

Key conclusions

- The overall trend for improvement in OS from bevacizumab continued with a numerically larger benefit in poor prognosis patients.
- Interim survival data from this randomized phase III trial suggest that adding bevacizumab to standard C plus P chemotherapy for the treatment of newly diagnosed ovarian cancer may offer benefit over treatment with chemotherapy alone, particularly in patients with more aggressive disease.
- Bevacizumab combined with chemotherapy and continued alone (7.5 mg/kg for 12 months) versus chemotherapy demonstrated continued improvement in PFS, and a trend for improved OS continued in the total population.
- The treatment effect of adding bevacizumab to standard chemotherapy was greater in high-risk patients.
- Final OS results for this study are expected in 2013.

Independent radiologic review of GOG218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal or fallopian tube cancer

**Background**

The Gynecologic Oncology Group (GOG) 218 is a phase III, randomized, double-blind, placebo-controlled trial with three arms comparing placebo in combination with carboplatin and paclitaxel (CP) chemotherapy followed by placebo alone; bevacizumab in combination with carboplatin and paclitaxel chemotherapy followed by placebo alone; and bevacizumab in combination with carboplatin and paclitaxel chemotherapy followed by the maintenance with bevacizumab alone.

Data from this trial presented at ASCO 2010 suggested statistically significant improvements in progression-free survival (PFS) in previously untreated women with advanced epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC) who received a bevacizumab-based regimen, when compared with CP therapy alone. 1

At ASCO 2011, Burger and colleagues presented the results from an independent review of blinded radiologic and clinical data, to determine the reliability of response evaluation criteria in solid tumours (RECIST) in assessing progression in ovarian cancer and confirm these results. 2

**Study design**

- Scans were performed at regular intervals, as described in the study protocol.
- Radiographic images and clinical data were provided to the independent review committee (IRC).
- Data were reviewed in a blinded fashion, in accordance with a pre-specified charter following RECIST criteria.
- PFS was analyzed as an intent-to-treat analysis of all randomized subjects.
- The primary analysis of PFS as determined by the IRC was a stratified log-rank test comparing each experimental arm to the control arm.

**Key findings**

- 91% of patients participated in the IRC analysis.
  - Patients must have been on therapy for at least nine weeks and must have submitted baseline scans and at least one subsequent protocol-required set of scans to the IRC.
- For patients in the IRC analysis, 97.2% had all protocol-required scans submitted to the IRC.
- Subgroup analyses of PFS determined by the IRC were consistent with the primary PFS analysis by the IRC (Table 1) and with the previous investigator-assessed subgroup analysis.
- There was a high concordance between investigator-determined was observed for PD status (77%) and PD date (73%). (Tables 2 and 3)

<table>
<thead>
<tr>
<th>IRC-assessed PFS</th>
<th>Investigator-assessed PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I CP (n = 625)</td>
<td>Arm II CP + BEV (n = 625)†</td>
</tr>
<tr>
<td>Arm III CP + BEV (n = 623)†</td>
<td>Arm I CP (n = 625)</td>
</tr>
<tr>
<td>Arm III CP + BEV followed by BEV (n = 623)‡</td>
<td></td>
</tr>
<tr>
<td>Patients with events</td>
<td>203</td>
</tr>
<tr>
<td>Median, months§</td>
<td>13.1</td>
</tr>
<tr>
<td>Hazard ratio, stratified**</td>
<td>0.941</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.799–1.138</td>
</tr>
<tr>
<td>one-sided log-rank p value††</td>
<td>0.2663</td>
</tr>
</tbody>
</table>

*Censored for non-protocol therapy; †Censored for non-protocol therapy and CA-125 progression; ‡Events prior to cycle 7 from the concurrent CP + BEV and CP plus BEV followed by BEV arms were pooled for analysis; §Kaplan-Meier estimates; **Relative to Arm I (CP); ††Based on the total one-sided α, the final p-value boundary for statistical significance for each comparison was ≤0.0116

95% CI = 95%confidence interval; BEV = bevacizumab; CP = carboplatin plus paclitaxel; IRC = independent review committee; PFS = progression-free survival
Table 2. Investigator-versus IRC-determined progressive disease status concordance

<table>
<thead>
<tr>
<th>PD status assessed by the investigators, n (%)</th>
<th>Arm I CP (n = 625)</th>
<th>Arm II CP + BEV (n = 625)</th>
<th>Arm III CP + BEV followed by BEV (n = 623)</th>
<th>All patients (n = 1,873)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD status assessed by IRC, n (%)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>169 (27.0)</td>
<td>45 (7.2)</td>
<td>166 (26.6)</td>
<td>38 (6.1)</td>
</tr>
<tr>
<td>No</td>
<td>118 (18.9)</td>
<td>293 (46.9)</td>
<td>95 (15.2)</td>
<td>326 (52.2)</td>
</tr>
</tbody>
</table>

BEV = bevacizumab; CP = carboplatin plus paclitaxel; IRC = independent review committee; PD = progressive disease

Table 3. Investigator-versus IRC-determined progressive disease date concordance

<table>
<thead>
<tr>
<th>Arm I CP (n = 169)</th>
<th>Arm II CP + BEV (n = 166)</th>
<th>Arm III CP + BEV followed by BEV (n = 104)</th>
<th>All patients (n = 439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDDIRC = PDDINV</td>
<td>115 (68.0%)</td>
<td>119 (71.7%)</td>
<td>88 (84.6%)</td>
</tr>
<tr>
<td>Absolute value of difference between IRC and investigator-determined PD date</td>
<td>≤12 weeks</td>
<td>141 (83.4%)</td>
<td>147 (88.6%)</td>
</tr>
<tr>
<td>≥12 weeks</td>
<td>28 (16.6%)</td>
<td>19 (11.4%)</td>
<td>12 (11.5%)</td>
</tr>
</tbody>
</table>

BEV = bevacizumab; CP = carboplatin plus paclitaxel; IRC = independent review committee; PD = progressive disease; PDDINV = progressive disease date as determined by the investigator; PDDIRC = progressive disease date as determined by the independent review committee

Key conclusions

- The data from GOG218 represent the largest IRC analysis ever conducted in patients with ovarian cancer.
- Results from this study show that the IRC- and investigator-determined PFS analyses are highly consistent, with both confirming a significant increase in PFS for subjects treated with concurrent plus continued bevacizumab versus CP alone.
- The size of the IRC, high participation rate, and strong concordance observed between IRC- and investigator-determined data suggest that RECIST criteria can be applied objectively in primary ovarian cancers.

A New Era of Personalized Medicine
From ASCO 2011

INSIDE THIS ISSUE

MELANOMA: New Treatment Strategies and Ongoing Clinical Research for Metastatic Melanoma

HEMATOLOGY: Improving Patient Outcomes by Optimizing the Use of Rituximab in CLL and DLBCL

OVARIAN: New Phase III Data on Bevacizumab for the Treatment of Newly Diagnosed, Advanced, and Recurrent Ovarian Cancer

Canadian perspective on new agents for the treatment of metastatic melanoma by Dr. Teresa Petrella