

HOT SPOT

The Newsletter of the Rapid Response Radiotherapy Program
of the Odette Cancer Centre



Volume 16, Issue 3, August 2014

Editorial

By Dr. Edward Chow

Drs. Law, Yee and Tsao are to be congratulated on their recent promotion at University of Toronto. In this issue, our Sunnybrook Ethicist & Policy Advisor, Sally Bean, discusses “considering patient requests for second medical opinion.” Ms. Swami, and Drs. Hannon and Zimmermann from Princess Margaret Cancer Centre highlight the evidence and benefits in

early palliative care involvement. Dr. Stuart Bisland and his colleagues at Juravinski Hospital and Cancer Centre reported a retrospective review of pain management in patients with bony metastases secondary to prostate cancer. Dr. Ewa Szumacher provides us the list of CME events. Mr. Marko Popovic highlights the recent achievement of Rapid Response Radiotherapy Program

at the 2014 MASCC conference. We have four inserts by Drs. Jeannie Callum on myeloproliferative neoplasms, Parneet Cheema on non small cell lung cancer, Sunil Verma on management of anti-estrogen therapy resistant HER2-negative metastatic breast cancer, and Stephen Chia on survival in advanced hormone receptor positive breast cancer. We hope you find the newsletter useful.

Congratulations to our colleagues



Hot Spot congratulates Calvin H.L. Law, MD, MPH, FRCSC, on his promotion to Professor and Chair—The Hanna Family Research Chair in Surgical Oncology, Department of Surgery, Faculty of Medicine, University of Toronto. He is currently Chief—Odette Cancer Centre, Vice-President—Regional Cancer Services—Sunnybrook Health Sciences Centre, Regional Vice-President—Cancer Care Ontario, Adjunct Scientist—Institute of Clinical Evaluative Sciences.



Hot Spot congratulates Albert J.M. Yee, MD, MSc, FRCSC, on his promotion to Professor in the Division of Orthopaedic Surgery, Department of Surgery, Faculty of Medicine, University of Toronto. He is currently Co-Director in University of Toronto Department of Surgery Spine Program and Consultant in Surgical Oncology Odette Cancer Centre and Division of Orthopaedic Surgery, Holland MSK Program. He is the Orthopaedic Surgeon Coordinator in the Bone Metastases Clinic at Sunnybrook Odette Cancer Centre.



Hot Spot congratulates May Tsao, MD, FRCPC, on her promotion to the rank of Associate Professor in the Department of Radiation Oncology, University of Toronto.

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Considering patient requests for second medical opinions

By Sally Bean, JD, MA, Ethicist & Policy Advisor, Sunnybrook Health Sciences Centre

Envision the following illustrative case: a metastatic cancer patient's disease has not responded to treatment and has, unfortunately, progressed. The patient is experiencing significant symptoms and a reduced quality of life, but wishes to pursue further aggressive treatments that the most responsible physician believes will not provide any benefit to the patient. The patient and her family disagree with the physician's assessment and request a second medical opinion regarding additional therapeutic options. There is discussion among the interprofessional health care team whether the patient has a "right" to a second opinion. The team also considers any additional parameters that might exist such as whether the second opinion must be from a physician within the organization that possesses commensurate knowledge and expertise, or if it should be an independent, external second opinion.

The academic literature demonstrates that second medical opinions are sought for a variety of reasons based either on a recommendation by the physician or patient/family request. A few reasons a second opinion is suggested or sought include the following: to seek confirmation of an existing diagnosis, impaired trust between the patient and physician, to seek additional information regarding a proposed controversial or risky procedure, or the diagnosis is uncertain, etc.¹ In Canada, the number of second opinions routinely sought is unknown. Therefore, any associated resource implications that the second opinions might have regarding overall increased or decreased health resource utilization as a result are undetermined.

In rare circumstances in which a disagreement exists between the health care team and the patient or their substitute decision-maker, a second medical opinion is routinely identified in institutional end-of-life policies, as an important step in the conflict resolution process. Despite the routine use of second medical opinions pertaining to end-of-life disagreements, it is unclear if and when patients have a right to a second opinion and what, if any, reasonable limitations may apply.

The Canadian Medical Association's Code of Ethics states, "Respect your patient's reasonable request for a second opinion from a physician of the patient's choice."² Additionally, the Canadian Medical Protective Association notes, "Patients have the right to ask questions about their healthcare, and seek second opinions, if desired."³ The CMA's position seems to indicate that reasonable patient choice regarding the second opinion should be respected, while CMPA ostensibly states there is an unqualified right to a second opinion if requested by a patient. Nonetheless, physicians and health care institutions must determine what constitutes a reasonable request for a second opinion. For example, are requests for third or fourth opinions, or for an independent opinion external to the organization reasonable?

Two ethical issues that arise in second medical opinion decision-making include procedural fairness and autonomy. From a fairness perspective, it is problematic if decision-making around second medical opinions is made arbitrarily or differently within and across institutions.

Additionally, similar cases should be treated in a similar manner, which can be facilitated by an institutional policy or guideline on second medical opinions. In terms of autonomy, restrictive perspectives on second opinions may undermine the patient's ability to obtain care elsewhere or make an informed decision about their health care. Because Canadian patients are generally unable to self-refer, they need the facilitation of a specialist or family physician to obtain a second medical opinion. As a result, the patient is in a vulnerable position, which should be considered when evaluating the reasonableness of a request for a second medical opinion.

Absent clear, objective evidence that the patient's request for a second opinion is unreasonable, physicians should respect and assist the patient's request to the extent possible. Despite my recommendation to facilitate all reasonable requests for second opinions, more research on the utilization, impact and accommodation of second medical opinions in Canada is needed and should inform any subsequent policy development on the subject matter.

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Research

Early palliative care involvement: Evidence and benefits

By Nadia Swami, BSc, Breffni Hannon, MBChB, and Camilla Zimmermann, MD, PHD

Although it is often stated that patients with advanced cancer should be referred early to palliative care services, there has been scant literature supporting this practice. Early referral endorses the World Health Organization's definition of palliative care, which states that palliative care aims to improve "the quality of life of patients and their families... by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."¹ However, referral to palliative care tends to occur late in the disease process, or not at all.^{2,3} In order to better understand this discrepancy between policy and practice, we conducted a cluster randomized controlled trial (RCT) to assess the effects of early palliative care team involvement on various measures of quality of life and satisfaction with care in patients with advanced cancer.⁴

In preparation for this trial, we conducted a systematic review,⁵ which examined 22 RCTs published between 1984 and 2007. Interventions included not only palliative care teams, but also coordination, nursing, or counselling services. Only four of 13 studies assessing quality of life showed significant results. However, most studies were underpowered and the majority was conducted late in the cancer trajectory, making recruitment and retention of participants challenging. None of the studies specifically examined the impact of an early palliative care intervention on outpatients with advanced cancer.⁵

Two additional RCTs were subsequently published examining early palliative care interventions in patients with advanced cancer. Bakitas et al. conducted a study involving 322 participants with advanced cancer and an estimated prognosis of one year. Participants were randomized to either routine care or to a palliative care problem-solving telephone intervention provided by advanced practice nurses.⁶ Temel et al. randomized 151 patients with advanced non small cell lung cancer to an early palliative care team intervention or to usual oncology care

alone.⁷ Both studies showed improved quality of life and mood in the early palliative care groups compared with usual care. We also conducted a phase II trial, which demonstrated the efficacy of our palliative care clinic in improving symptom control and satisfaction with care at one week and one month after the first clinic visit.⁸

We proceeded to conduct a Canadian Cancer Society-funded cluster RCT of early palliative care in patients with advanced cancer attending the Princess Margaret Cancer Centre (PM); the results were recently published in *The Lancet*.⁴ In this trial, patients attending 24 medical oncology clinics from five different tumour sites (lung, gastrointestinal, genitourinary, breast, and gynecological) were randomized to consultation and monthly follow-up by a multidisciplinary palliative care team, or to standard oncology care. Patients were eligible if they were ≥ 18 years of age and had advanced cancer (stage III or IV), an Eastern Cooperative Oncology Group performance status of 0-2, and an estimated prognosis of six to 24 months (the latter two were determined by each patient's primary oncologist). Of 461 consenting patients, 228 were randomized to the early palliative care intervention and 233 to the control group. The intervention included an initial consultation in the outpatient palliative care clinic with a palliative care physician and nurse, monthly assessments in the clinic, follow-up phone calls from a palliative care nurse after each clinic visit, and access to the on-call palliative care team 24 hours a day, as needed. In addition, patients had access to the acute palliative care unit at the PM, and were referred to community-based services such as home care or home visiting palliative care physicians, as necessary. Patients completed measures on quality of life (two measures), symptom control, satisfaction with care, and problems with medical interactions at baseline and once monthly for four months. At three months there was significant improvement in one of the two quality-of-life measures, as

well as with satisfaction with care, in the intervention group compared to the control group. At four months, compared to standard care, early referral to palliative care significantly improved quality of life (both measures), patient satisfaction with care, and symptom severity.⁴

The results of our cluster RCT build on the previous work of Temel (2010) and Bakitas (2009), and show promising findings in favour of early specialized palliative care involvement for patients with a wide range of advanced solid tumour malignancies. Our study also demonstrates that early referral to palliative care improves not only the quality of life of patients with advanced cancer, but also their satisfaction with care.⁴ The evidence base in favour of early palliative care is now quite robust and supports timely, integrated involvement of palliative care services for patients with advanced cancer.

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Research

A retrospective review of pain management in patients with bony metastases secondary to prostate cancer

By Stuart Bisland, MD, PhD, Nisha Goel, BSc, Greg Pond, PhD, and Marissa Slaven, MD

Prostate cancer is the most common cancer amongst Canadian men accounting for 27% of all cancers in Canada with an average of 470 newly diagnosed cases per week.¹ Up to 70% of patients with prostate cancer will eventually develop metastases to bone (M1b), with metastases localized predominantly to lower spine (74%), ribs (70%), pelvis (60%) and thigh (44%).² As many as 90% of patients with prostate cancer and bone metastasis live with intractable cancer-induced bone pain (CIBP).^{3,4} The precise etiology of CIBP remains ill-defined,^{5,6} and response to treatment varies considerably from one patient to the next. Opioids remain the mainstay of treatment and must be carefully monitored in patients with chronic pain who often receive treatments over many months to years. Other adjuvant treatment strategies exist that can potentially limit the need for opioids. Non-steroidal anti-inflammatories (NSAIDs), bisphosphonates, neuroleptics and radiotherapy are among the most commonly prescribed adjuvant therapies.^{7,8} Hormone therapy is also an important strategy for treating prostate cancer and potentially limiting the progression of metastases and related CIBP.⁹ All available treatments have variable efficacy along with side effects that can limit their extended use and tolerability.

This study was, therefore, conducted as a retrospective chart review to evaluate

the treatment of pain in patients with CIBP. The primary goal was to improve understanding of how opioids and adjuvant treatments are currently being used in a real world setting.

Methodology

The Pain and Symptom Management Clinic (PSMC) is an outpatient interdisciplinary palliative care clinic based at the local regional cancer centre in Hamilton, Ontario. A total of 50 patients with known M1b prostate cancer who attended PSMC from 2006 to 2012 were randomly selected for chart review. Data were collected for each patient visit to the PSMC over a six-month period.

The Kaplan-Meier method was used to estimate the time to event outcomes of time to first pain recurrence and time to first change in morphine equivalent dose. Pain recurrence was defined as a 2-point increase in ESAS pain score on consecutive visits where ESAS was completed. An increase in morphine equivalent dose was defined as any change in dose from visit to visit. Logistic regression analysis was used to investigate factors prognostic for opioid use at any time. A repeated measures analysis using generalized estimating equations (GEEs) was performed to investigate if the ESAS score was related to opioid use or change in morphine equivalent dose across time points. A backwards stepwise selection was used to create a multi-variable

model. Given the small number of patients, removal criteria were defined as a p-value > 0.15. Statistical significance was defined at $\alpha = 0.05$ level of significance, and all tests and confidence intervals were two-sided.

Results

Mean age at study entry was 73 years with a median (interquartile range [IQR]) prostate serum antigen (PSA) level of 42 (8–146). Almost half (46%) of patients had a Gleason score of ≥ 9 . Hydromorphone was the most commonly prescribed opioid (58% of patients) along with the long-acting Hydromorphone (39%). Additionally, 49% of patients were prescribed morphine-based opioids. Approximately 48% of patients also were prescribed oxycodone with (20.8%) or without (27.1%) acetaminophen. Only four patients were prescribed fentanyl patch. Median morphine milligram equivalent dose for 46 patients was 65.3 mg, while two patients were not prescribed opioids because of allergies. Additional adjuvant analgesics included non-steroidal anti-inflammatories (8%) and neuroleptics (20%), and steroids (83%).

Median (95% CI) time to pain recurrence documented on ESAS was 5.8 months. Median time to increased opioid dose was 2.5 months from the time they started attending the PSMC.

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2014 MASCC/ISOO International Symposium on Supportive Care in Cancer

By Marko Popovic, BHSc(C), Research Coordinator

In late June 2014, 24 trainees from the Rapid Response Radiotherapy Program took part in the 2014 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) International Symposium on Supportive Care in Cancer held in Miami, FL. Fifty-three abstracts from our program were submitted to the conference. In total, we delivered 43 poster presentations, which represented about 10% of the poster presentations internationally. Our students presented 10 oral presentations and five e-poster discussions. Furthermore, two of our students were awarded “Young Investigator of the Year” awards—a prestigious honour recognizing the excellence of investigators under the age of 40. Congratulations to Young Investigator award winners Erin Wong and Karrie Wong on their magnificent successes at the symposium.



Erin Wong

MASCC’s 2014 conference brought together some of the world’s most preeminent thinkers in supportive care in cancer. The vast majority of conference attendees were physicians, pharmacists, nurses and other professionals with considerable experience in this field. Nevertheless, our team of mostly undergraduate and medical school students was able to demonstrate the



Karrie Wong

profound impact of involving students in clinical research, both in terms of the quality of the research, and in its impression on the professional lives of students. Thriving student collaboration in the research process is impossible without the support of a dedicated team of mentors in our program. Congratulations to all involved in the vast success of the RRRP at MASCC 2014.

A retrospective review of pain management in patients with bony metastases secondary to prostate cancer

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Most (65%) patients either had no change or one increase in baseline opioid dose over the six-month period, while only 6% required five or more increases in opioid dose. Neither ESAS scores, PSA nor Gleason scores were prognostic for dose of opioids, the time to first recurrence in pain, or increase in opioid dose.

Conclusion

Although patients with CIBP are at high risk of suffering from intractable pain, this need not be the case. In our patient population, pain scores did not increase for almost the entire study period and most patients required few increases in their opioid dose. Multi-modal treatment strategies were employed in the current study including, adequately dosed opioids, NSAIDs, bisphosphonates, chemotherapy, radiotherapy, and steroids for patients receiving care from a specialized multidisciplinary team.

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Continuing Medical Education 2014

By Ewa Szumacher, MD, FRCP(C)

Continuing Medical Education (CME) can update health care professionals on the latest advances for modifications to their clinical practice. At the request of the CME organizers, Hot Spot will list the national and international CME activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: Ewa.Szumacher@sunnybrook.ca

- **August 2–5, 2014.** The Australian and New Zealand Society of Palliative Medicine Gold Coast Australia, Australia. <http://aphn.org/australian-and-new-zealand-society-of-palliative-medicine-anzspm-conference-2014/>
- **August 25–28, 2014.** CARO 2014 ASM Outcomes, St. John's, Newfoundland, Canada. <http://www.caro-acro.ca/>
- **September 2–5, 2014.** The Australian and New Zealand Society of Palliative Medicine Gold Coast Australia, Gold Coast, QLD, Australia. <https://www.etches.com/ehome/65181>
- **September 4–6, 2014.** Breast Cancer Symposium, San Francisco, California, USA. <http://breastcasym.org/>
- **September 5–6, 2014.** 18th Annual Interdisciplinary Conference on Supportive Care, Hospice, and Palliative Medicine, Houston, Texas, USA. <http://www.mdanderson.org/education-and-research/education-and-training/schools-and-programs/cme-conference-management/conferences/cme/conference-management-18th-annual-interdisciplinary-conference-on-supportive-care-hospice-and-palliative-medicine.html>
- **September 7–11, 2014.** 18th International Conference on Cancer Nursing, Panama City, Panama. http://www.isncc.org/?page=18th_ICCN
- **September 9–12, 2014.** 20th International Congress on Palliative Care, Montreal, Canada. www.palliativecare.ca/
- **September 14–17, 2014.** ASTRO—56TH Annual Meeting: Targeting Cancer: Technology & Biology, San Francisco, California, USA. www.astro.org/Meetings-and-Events/2014-Annual-Meeting/Index.aspx
- **September 15–18, 2014.** HPCA (Hospice Palliative Care Assoc of South Africa), South Africa. delshe@hPCA.co.za
- **October 15, 2014.** Palliative Care 2020. Toward integration of palliative care in an age-friendly EU, Brussels, Belgium. <http://www.palliativecare2020.eu/>
- **October 17, 2014.** 3rd Annual Sunnybrook Education Conference, Toronto, Canada. <http://sunnybrook.ca/education/>
- **October 17–18, 2014.** Best of ASTRO, Miami, Florida, USA. <https://www.astro.org/Meetings-and-Events/2014-Best-of-ASTRO/Index.aspx>
- **October 22–25, 2014.** 46th Congress of the International Society of Paediatric Oncology, Toronto, Canada. <http://siop.kenes.com/>
- **November 13–16, 2014.** 6th European Multidisciplinary Meeting on Urological Cancers, Lisbon, Portugal. <http://www.esmo.org/Conferences/EMUC-2014-Urological-Cancer>
- **November 19–21, 2014.** 2nd Congress on Paediatric Palliative Care: A Global Gathering, Rome, Italy. <http://www.maruzza.org/congress-2014/>
- **December 9–13, 2014.** San Antonio Breast Cancer Symposium, San Antonio, Texas, USA. <http://breastcasym.org/>
- **December 12–14, 2014.** 4th International Gastrointestinal Cancer Conference, Istanbul, Turkey. <http://igicc2014.org/>
- **January 15–17, 2015.** Gastrointestinal Cancers Symposium, San Francisco, California, USA. <http://gicasymp.org/>
- **February 5–8, 2015.** GOG Semi-Annual Meeting, San Diego, California, USA. <http://www.gog.org/meetinginformation.html>
- **February 13–15, 2015.** 22nd International Conference of Indian Association of Palliative Care, Hyderabad, India. <http://iapcon2015hyd.com/>
- **February 26–28, 2015.** 2015 Gastrointestinal Cancers Symposium, Orlando, Florida, USA. <http://gucasymp.org/>
- **May 8–10, 2015.** EAPEC, 14th World Congress of the EAPC, Copenhagen, Denmark. eapc2015@interplan.de

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Scan the QR code with your smartphone to read past issues of Hot Spot

By Jeannie Callum, MD, FRCPC, Associate Scientist, Sunnybrook Health Sciences Centre

Late-breaking abstract: Ruxolitinib in the treatment of polycythemia vera (PV) resistant to or intolerant to hydroxyurea¹

The RESPONSE trial is a randomized, open-label, phase 3 trial in PV comparing ruxolitinib (Jakavi) with single-agent best available therapy (BAT), as selected by the investigator (Figure 1). BAT most frequently included hydroxyurea (59%), interferon (IFN) (12%), and observation (15%). The primary endpoint was the composite of: the absence of the need for phlebotomy from week 8 to 32, and the reduction in spleen volume at week 32.^{1,2}

A key secondary endpoint was the percentage of patients who achieved complete hematologic remission (CHR) at week 32. CHR was defined as hematocrit control, platelet count $\leq 400 \times 10^9/L$, and WBC count $\leq 10 \times 10^9/L$.

In the ruxolitinib group, 21% of patients achieved the primary endpoint versus 1% of patients in the BAT group (OR=28.64, 95% CI: 4.50-1206; $p < 0.0001$) (Figure 2). CHR was achieved in 23.6% of patients receiving ruxolitinib versus 8.9% of patients receiving BAT (OR=3.35, 95% CI: 1.43-8.35; $p = 0.0028$).

Ruxolitinib was generally well tolerated. The most frequently reported non-hematologic adverse events (AEs) were headache, diarrhea and fatigue (Table 1). Other AEs of interest included infections and disease progression (Table 2). The main hematologic AEs were low hemoglobin and thrombocytopenia (Table 3). Spleen volume was reduced in the majority of patients on ruxolitinib (Figure 3). Symptom improvement, as measured by the MPN-SAF (Myeloproliferative Neoplasm Symptom Assessment Form) score was remarkably superior with ruxolitinib, as compared to BAT. Thromboembolic events occurred in one of 110

patients on ruxolitinib, as compared to six of 111 on BAT. Only 15.5% of ruxolitinib treated patients discontinued therapy for progression/intolerance.

The starting dose of ruxolitinib was 10 mg BID, titratable from 5 mg OD up to 25 mg BID.² At week 32, two-thirds of patients in the ruxolitinib arm were receiving 10 mg or 15 mg BID. Most dose adjustments occurred within the first eight weeks of treatment, whereby 37% of patients had dose increases and 9% of patients had dose reductions.

Myeloproliferative Neoplasms—Clinical 1 CALR mutations

Guglielmelli et al. reported on the prognostic value of CALR (calreticulin) mutations in the presence of other mutations in patients with primary myelofibrosis (PMF). In this study, the most frequent mutations were JAK2V617F (56.2%), CALR (24.8%) and ASXL1 (19.3%). Approximately one-quarter (26.6%) of patients had high molecular risk (HMR) mutations while 6.5% of patients had no identified mutations.³

Patients with CALR mutations showed significantly better overall survival (OS) across all International Prognostic Scoring System (IPSS) risk categories, with a median OS of 20.2 years (HR 0.46, 95% CI 0.27-0.78; $p = 0.003$) compared with patients with no mutations (median 8.2 years). CALR mutations were an independent prognostic factor (HR 0.14, 95% CI 0.27-0.86; $p < 0.0001$) in both IPSS low- and intermediate-1-risk patients. The difference in OS was borderline for higher risk patients. The presence of CALR was an independent prognostic factor in patients with HMR and low molecular risk (LMR) mutations. OS in patients with no mutations was reduced versus patients with LMR and was similar to OS in patients with HMR mutations.³

Rumi et al. investigated the impact of the founding driver mutations JAK2, MPL and CALR on OS and transformation to AML in patients with PMF. The frequency of the mutations were 64.7%, 4% and 22.4% respectively while the remainder were triple-negative.⁴

CALR patients were significantly younger, with lower leukocyte counts, higher platelet counts, and lower IPSS and dynamic IPSS (DIPSS) risk levels. Mutation status had a major impact on transformation to

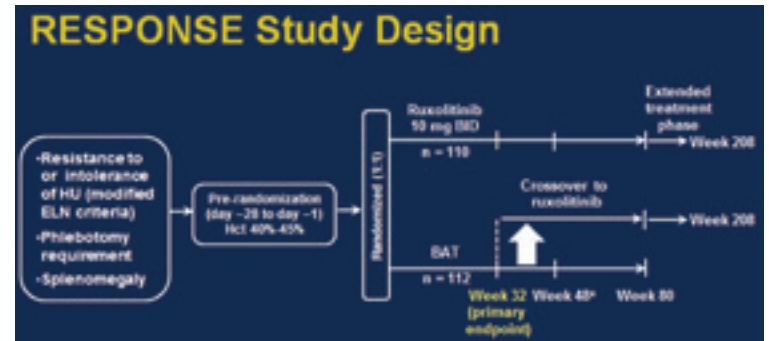


Figure 1. Reproduced with permission

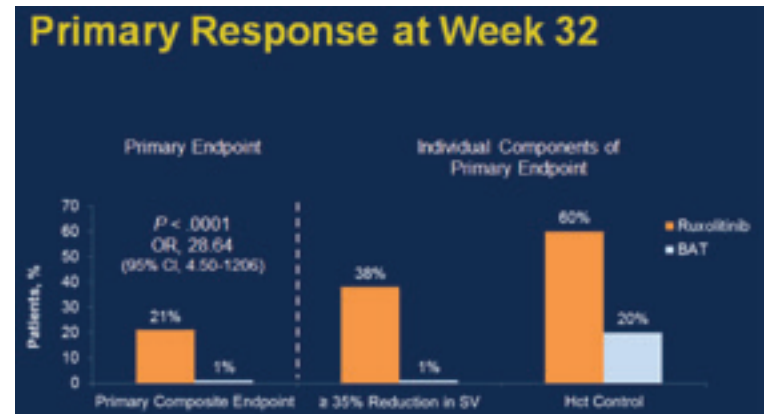


Figure 2. Reproduced with permission

Patients, %	Ruxolitinib (n = 110)		BAT (n = 111)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Headache	16.4	0.9	18.9	0.9
Diarrhea	14.5	0	7.2	0.9
Fatigue	14.5	0	15.3	2.7
Pruritus	13.6	0.9	22.5	3.6
Dizziness	11.8	0	9.9	0
Muscle spasms	11.8	0.9	4.5	0
Dyspnea	10.0	2.7	1.8	0
Abdominal pain	9.1	0.9	11.7	0
Asthenia	7.3	1.8	10.8	0

Events occurring in at least 10% of patients in either treatment group.

Table 1: Nonhematologic adverse events up to week 32 (regardless of causality). Reproduced with permission

This educational work is sponsored by Novartis Canada

Patients, n (%)	Ruxolitinib (n = 110)	BAT (n = 111)
Infections		
All infections	46 (41.8)	41 (36.9)
Grade 3 or 4	4 (3.6)	3 (2.7)
Herpes zoster	7 (6.4)	0
Grade 3 or 4	0	0
Progression to MF and AML^a		
MF	2 (1.8)	1 (0.9)
AML	1 (0.9)	0
Non-melanoma skin cancers^b		
All NMSC	4 (3.6)	2 (1.8)
Grade 3 or 4	3 (1.8)	1 (0.9)

^a After week 32, there was 1 transformation to MF in the ruxolitinib arm and 2 in the BAT arm (after crossover); there was 1 transformation to AML in the BAT arm (after crossover).
^b A higher rate of NMSC was reported in the ruxolitinib arm (4.7 vs 2.7 pts/100-PY); no patients discontinued treatment for NMSC.
^c A higher proportion of patients in the ruxolitinib arm had a prior history of NMSC or pre-cancerous skin condition compared to the BAT arm (10.9% vs 6.3%), including all 4 ruxolitinib patients and 1 of the 2 BAT patients.
^d Patients randomized to ruxolitinib had a longer prior exposure to HUJ (162.9 vs 145.6 weeks).

Table 2: Other adverse events of interest up to week 32. Reproduced with permission

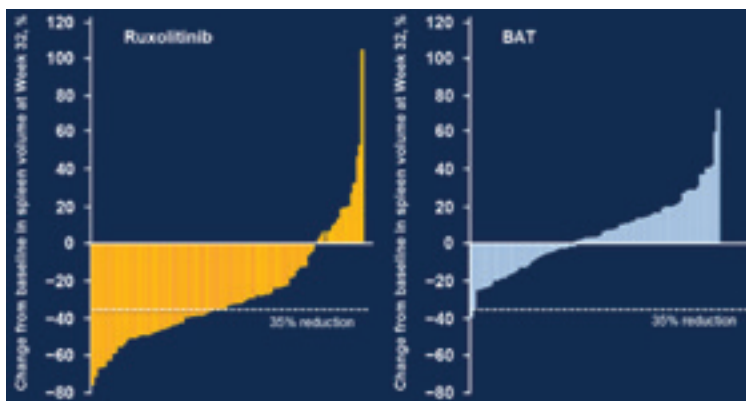


Figure 3: Percentage change in spleen volume at week 32. Reproduced with permission



Table 3: Hemoglobin and platelet levels. Reproduced with permission

AML and OS. Triple-negative patients had the highest cumulative incidence of transformation to AML whereas CALR+ patients had the lowest 10-year cumulative incidence of AML (31.9% versus 9.5%, respectively, $p=0.028$). Univariate analysis also showed that CALR+ patients had longer OS than those with JAK2 or MPL mutations or patients who were triple negative.⁴

Verger et al. looked at the effect of IFN alpha (IFNa) on hematologic and molecular outcomes in patients with essential thrombocythemia (ET). This study looked at 14 patients who had ET, were treated with IFNa, who were JAK2 or MPL negative, CALR+, and had sequential DNA samples. Median IFNa treatment was 26.5 months. All these patients achieved a CHR. The median CALR allele burden was 43% prior to treatment and 19% in the last available sample ($p=0.018$).⁵

Treatment duration heavily influenced changes in allele burden. In four patients with long treatment duration (median 60 months), CALR burden fell by more than 90% while there was no change in allele burden in seven patients who received only short-duration treatment (median 18 months).⁵

Open-label trial of ruxolitinib in PMF, post-polycythemia vera myelofibrosis (PPV-MF), or post-ET myelofibrosis (PET-MF)

The JUMP study is an open-label, multicentre, expanded-access study in patients with myelofibrosis, designed to assess the safety and efficacy of ruxolitinib. Patients with intermediate-1, intermediate-2 or high-risk disease with splenomegaly were enrolled.⁶

The most common hematologic Grade ≥ 3 AEs were anemia (32.5%) and thrombocytopenia (10.8%). A total of 14.6% of patients discontinued therapy due to AEs, most frequently anemia (1.9%) and thrombocytopenia (1.4%). The most frequent non-hematologic grade ≥ 3 AEs were pneumonia (3.7%), dyspnea (1.7%), diarrhea (1.5%) and pyrexia (1.5%).⁶

Favourable effects on palpable spleen length from baseline were seen. The estimated probabilities of progression-free survival (PFS), leukemia-free survival (LFS), and OS at 48 weeks were 0.88 (95% CI, 0.84-0.91), 0.91 (95% CI, 0.88-0.94), and 0.92 (95% CI, 0.89-0.94), respectively.⁶

Phase I/II open-label study of JAK1/2 inhibitor momelotinib in PMF, PPV-MF or PET-MF

This study examined if dose escalation above the previously studied 300 mg OD dosage provided incremental benefit. Dosage was escalated to 200 mg or 250 mg BID in 61 patients. Seventeen patients discontinued

treatment due to adverse events. The most common \geq Grade 3 AEs were thrombocytopenia (28%), pneumonia (12%), fatigue (12%), elevated lipase (8%), and anemia (7%). Sixty-six per cent of patients showed a spleen response. Since momelotinib 200 mg BID offered no therapeutic benefit versus 300 mg OD, the latter dose was selected for phase III studies.⁷

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Early stage NSCLC

RADIANT

Background:

- Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), improves overall survival (OS) of patients with advanced NSCLC after failure of ≥ 1 chemotherapy regimen and in the maintenance setting post induction with a platinum doublet.^{1,2}
- The RADIANT trial was designed to evaluate the efficacy of adjuvant erlotinib in patients with resected stage IB to IIIA NSCLC. The primary endpoint was disease-free survival (DFS). Exploratory analysis of earlier studies found that high EGFR high protein expression by IHC or gene amplification detected by FISH predicted improved outcomes to erlotinib and, thus, enrolment into RADIANT was limited to these patients.³
- After enrolment began in September 2006, scientific and clinical data revealed that patients who harbour EGFR Del19 or L858R mutations (EGFR M+) confer sensitivity to EGFR TKIs and derive the greatest clinical benefit.⁴ Erlotinib significantly improved progression free survival (PFS) compared with first-line chemotherapy in patients with advanced EGFR M+ NSCLC.⁵
- The secondary endpoints of RADIANT were then later amended to DFS and OS in patients with EGFR M+ NSCLC.
- Limited data of EGFR TKIs in resected EGFR M+ NSCLC patients exist (BR19, included 15 patients with EGFR M+ treated with adjuvant gefitinib, also an EGFR TKI).⁶

New data:

- RADIANT was a randomized phase III trial of two years of erlotinib versus placebo in completely resected stage IB-III A NSCLC.⁷ Adjuvant chemotherapy was at discretion of the treating physician.
- The primary endpoint of DFS in the intent to treat population (n=973) was not improved with the addition of erlotinib, nor was OS.
- In the subset of patients with EGFR M+ (n=161) there was a non-significant 18-month improvement in DFS at two years with erlotinib (46.4 mos versus 28.5 mos, HR: 0.61, p=NS).⁸ There was no significant difference in DFS at four years and OS is still maturing. Baseline characteristics of patients in this subgroup analysis had major differences with more stage IIIA patients and patients with larger tumours in the placebo arm.

Implications for practice:

There is no clinical benefit to adjuvant erlotinib after resection of stage IB-III A NSCLC. Although the results of adjuvant therapy with erlotinib in the subset of EGFR M+ NSCLC patients are suggestive, there remains uncertainty on the clinical benefit and it cannot be recommended until confirmatory randomized controlled trials are conducted.

Advanced NSCLC—Squamous cell carcinoma

SQUIRE

Background:

- Squamous cell carcinoma subtype of NSCLC (sq-NSCLC) accounts for 25%–30% of NSCLC. Cisplatin/gemcitabine is currently standard first-line therapy for these patients with advanced NSCLC. Advances in NSCLC with targeted therapies have been limited to adenocarcinoma subtype (adeno-NSCLC).
- The FLEX trial reported a statistically significant improvement in OS with addition of cetuximab, a monoclonal antibody to EGFR, to platinum doublet in both advanced adeno-NSCLC and sq-NSCLC. The uptake of cetuximab was limited by

- its modest improvement in OS of 1.2 mos (11.3 mos versus 10.1 mos, HR: 0.87, with a 5% improvement at 1 year) and its supportive study BMS099 showed no significant improvement in OS.^{9,10}
- Subgroup analysis of FLEX revealed that sq-NSCLC patients and those patients who had an EGFR H-score of >200 derived the greatest benefit from cetuximab.
- Nectinumab is a humanized monoclonal antibody to EGFR.
- INSPIRE was a randomized phase III trial of nectinumab with cisplatin/pemetrexed versus cisplatin/pemetrexed alone in advanced non-squamous NSCLC, enrolment in this study was halted due to increased risk of thromboembolic events (TE) and sudden death.¹¹

New data:

- SQUIRE is a phase III trial of gemcitabine/cisplatin +/- nectinumab, as first-line treatment of patients with advanced sq-NSCLC.¹² Patients received up to six cycles of cisplatin/gemcitabine +/- nectinumab and in those patients in the nectinumab arm were continued on maintenance therapy until disease progression or unacceptable toxicity.
- This was the largest first-line clinical trial in patients with sq-NSCLC. 1,093 patients were enrolled and included patients with an ECOG 2.
- Primary endpoint of OS was improved with the addition of nectinumab to cisplatin/gemcitabine (median OS of 11.5 mos versus 9.9 mos, HR:0.84, p=0.012 and a 5% improvement at 1 year).
- Progression free survival (PFS), although significant was marginally improved (5.7 mos versus 5.5 mos, HR: 0.85, p=0.02), with no difference in overall response rates (ORR).
- No biomarker was found. EGFR H-score was not predictive of improved outcomes.
- The rate of grade ≥ 3 arterial and venous TE was 8.9% versus 4.6% in the nectinumab and control arms, respectively and the rate of fatal TE was low and no different between the study arms. Toxicity profile was as expected for an anti-EGFR antibody, with less infusion reactions than reported with cetuximab.

Implications for practice:

Nectinumab is a new targeted treatment for sq-NSCLC. However, the improvement of OS when added to standard chemotherapy is modest (1.6 month absolute difference), which questions its clinical significance. The results are comparable to FLEX with cetuximab, although nectinumab may have increased uptake, as the clinical benefit is in the sq-NSCLC population where there are limited therapeutic options. In Canada, the use of nectinumab will also depend on its cost effectiveness.

Advanced NSCLC—Second line therapy

REVEL

Background:

- Three agents are approved as second line therapy following platinum doublet, docetaxel, pemetrexed and erlotinib with median OS of 7–8 months.^{1,13–15}
- Bevacizumab, a vascular endothelial growth factor receptor (VEGFR), improves survival when given with carboplatin/paclitaxel, as first-line treatment of advanced non squamous NSCLC.¹⁶
- Ramucirumab is a VEGFR-2 monoclonal antibody.

New data:

- REVEL is a phase III trial of docetaxel +/- ramucirumab for second line therapy in advanced NSCLC.¹⁷ Patients were treated until disease progression or unacceptable toxicity. All histologies were eligible.
- Addition of ramucirumab to docetaxel lengthened survival with a median OS of 10.5 mos versus 9.1 mos, HR 0.86, p=.02, and improved PFS (HR: 0.76, p<0.0001). OS and PFS advantage were seen irrespective of histologies.
- Ramucirumab in addition to docetaxel significantly increased ORR (23% vs. 14%; p<0.001).
- There were no safety concerns seen; safety profile as expected for an anti-VEGFR agent.



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Implications for practice:

Although this study met its primary endpoint, the addition of ramucirumab to docetaxel had a modest improvement in survival. The observed > 20% response rate is almost double than expected with current approved second line therapies. Quality of life will strengthen these data and will be presented at a later meeting.

Advanced NSCLC—EGFR mutation positive

Pooled survival data with Afatinib

Background:

- Presence of EGFR activating mutations (M+) defines a distinct subtype of NSCLC, sensitive to EGFR TKIs. Exon 19 deletion (Del19) and missense mutation in exon 21 (L858R) account for 90% of EGFR activating mutations.¹⁸
- Standard of care for advanced EGFR M+ NSCLC patients is a first line EGFR TKI. Multiple randomized controlled trials have reported improved PFS and OS with upfront EGFR TKI with gefitinib or erlotinib in EGFR M+ patients compared to standard chemotherapy.^{5,19-22} However, among these trials, no difference in OS has been reported, most likely due to the high proportion of crossover from chemotherapy to EGFR TKIs after study completion (65%–95% crossover rates). The median OS reported in these trials ranges from 18.6 to 39 months, which is much longer than historical controls of chemotherapy trials (median OS of 8–10 months).^{23,24}
- LUX-Lung 3 and LUX-Lung 6 were two randomized controlled trials comparing second generation EGFR TKI afatinib to either cisplatin/pemetrexed or cisplatin/gemcitabine. Similar to first generation EGFR TKI trials, afatinib reported improvement in PFS and ORR compared to chemotherapy, but no improvement in OS.^{25,26}
- The preliminary analysis of OS in both studies included patients with rare EGFR activating mutations including exon 20 insertions and T790M mutations that are associated with resistance to EGFR TKIs.²⁷

New data:

- A pooled analysis of LUX-Lung 3 and LUX-Lung 6 for OS was conducted and included only those patients with either Del19 and L858R EGFR mutations.²⁸

- Patients treated with afatinib had a significant improvement in OS compared to chemotherapy (median OS of 27.3 mos versus 24.3 mos, HR: 0.81, p=.037).
- The survival advantage was driven mainly by patients with Del19 mutation with an 11-month improvement in median OS with afatinib (31.7 mos versus 20.7 mos, HR 0.59, p=0.0001). There was no difference in OS in patients with L858R mutation.
- Rate of crossover was comparable in both LUX-Lung 3 and 6 compared to first generation EGFR TKI trials.

Implication for practice:

- This pooled analysis is the first study to show an improvement in OS in patients with advanced EGFR M+ NSCLC treated with an upfront EGFR TKI, which provides ongoing support that standard of care for these patients is a first-line EGFR TKI.
- The median OS seen in this pooled analysis was comparable to first generation EGFR TKI trials and an OS benefit may have been detected due to the large number of patients. The individual trials of both LUX-Lung 3 and LUX-Lung-6 the median OS of patients with common mutations was not statistically improved with afatinib although there was a trend in favour of afatinib similar to first generation EGFR TKI trials.
- As there is no direct comparison of afatinib to first generation EGFR TKIs, one EGFR TKI cannot be recommended over another, although afatinib may be the treatment of choice in those patients with Del19, although this needs to be balanced with the toxicity profile. More insight on this will be obtained from LUX-Lung 7, a head-to-head trial of gefitinib to afatinib, which has recently completed enrolment.

New therapies—Immune checkpoint blockade

KEYNOTE-001

Background:

- Programmed death-1 (PD-1) is an immune checkpoint receptor expressed by activated T-cells, which downregulates T-cell activation upon interaction with its ligands PD-L1 and PD-L2. Tumour expression

Table 1: Efficacy of pembrolizumab according to line of therapy and PD-L1 status

	Treatment Naïve PD-L1 Positive NSCLC		Previously Treated PD-L1 Positive NSCLC		Previously Treated PD-L1 Negative NSCLC	
	RECIST	irRC	RECIST	irRC	RECIST	irRC
Best ORR	n=42	n=45	n=159	n=177	n=35	N=40
ORR	26%	47%	23%	19%	9%	13%
DCR	64%	78%	42%	51%	31%	53%
PFS	n=42	n=45	n=177	n=177	n=40	n=40
Median, mos	6.75	9.25	2.75	4.0	2.5	4.0

ORR, overall response rate; DCR, disease control rate; PFS, progression free survival; PD-L1, program death 1 ligand 1; NSCLC, non small cell lung cancer; irRC, immune response criteria.

of PD-L1 can engage PD-1 of activated T-cells suppressing the immune response and protecting the tumour from T-cell attack.

- Data were presented from phase I trials of two anti PD-1 antibodies pembrolizumab and nivolumab in treatment-naïve and previously treated patients with advanced NSCLC. Also, phase I data with the anti-PD-L1 antibodies MEDI3746 and MPDL3280A in previously treated advanced NSCLC were presented.
- KEYNOTE-001 is an ongoing phase 1 multi-cohort study of two doses of pembrolizumab as monotherapy in patients with advanced NSCLC. This study was selected for further discussion.^{29,30}

New data:

- PD-L1 positivity was defined as $\geq 1\%$ of tumour cells expressing PD-L1 detected by immunohistochemical staining. The rate of PD-L1 positivity in this trial was 62% of previously treated patients, and 78% of treatment-naïve patients, of which 78% were non-squamous histology and 87% were former or current smokers.
- ORR, disease control rate (DCR) and PFS with pembrolizumab according to line of therapy and PD-L1 staining are presented in Table 1.
- Responses by RECIST or immune response criteria (irRC) to pembrolizumab correlated with PD-L1 expression.

- Responses in treatment-naïve patients were durable with a median time on therapy of 218 days. 100% (11/11) of patients who responded by RECIST criteria and 90% (19/21) of patients who responded by irRC are ongoing.
- In the treatment-naïve cohort, 80% of patients experienced a drug-related adverse event (AE), usually grade 1-2 in severity. Most common AEs were fatigue (22%), pruritus (13%), hypothyroidism (9%), dermatitis acneiform (7%), diarrhea (7%) and dyspnea (7%). One case of grade 3 pneumonitis led to discontinuation of drug. In previously treated patients the AE profile was similar, although 4 of 217 patients (1.8%) experienced grade 3–4 pneumonitis.

Implications for practice:

Pembrolizumab is well tolerated and has antitumor activity in the first-line setting in patients with advanced NSCLC who express PD-L1 and in previously treated patients. The phase 1 data with anti-PD-1/PD-L1 antibodies are encouraging and support these drugs as a potential new class of therapy for the treatment of advanced NSCLC. Confirmatory trials with anti-PD-1 and anti-PD-L1 inhibitors are underway, including trials in combination with targeted therapies, CTLA-4 inhibitors and in earlier stage NSCLC.

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Clinical significance of overall survival and progression-free survival in advanced hormone receptor positive breast cancer

HOT SPOT

By Stephen Chia, MD, FRCP(C), Medical Oncologist, Associate Professor of Medicine, Chair – British Columbia Breast Tumour Group, British Columbia Cancer Agency, University of British Columbia

Advanced hormone receptor positive breast cancer

- Hormone receptor (ER and/or PR) positive breast cancer is the most prevalent subtype in both early and advanced stage breast cancer.
- Though improvements in survival of metastatic breast cancer (MBC) have been demonstrated over time, and are likely related to the use of newer systemic agents, the gains have been relatively modest.¹
- More recently it has been the HER-2 positive subtype that has made further significant improvements in overall survival based on clinical trials of pertuzumab and TDM1 as first- and predominantly second-line therapy respectively in HER2+ MBC.^{2,3}

Mechanisms of endocrine resistance

- Proposed mechanisms of endocrine resistance include activation of cross-talk pathways (e.g., EGFR, HER-2, IGFR, Src) and/or activation of downstream

- pathways (PI3K-Akt-mTOR; MAPK-MEK; and cell cycle activation).⁴
- The most frequently altered genomic aberration in ER+ (luminal) breast cancers are mutations in the phosphatidylinositol 3-kinase (PIK3CA) gene, with an observed frequency of 45% in luminal A breast cancers and 29% in luminal B breast cancers.⁵
- Preclinical studies have also demonstrated an interaction between the mTOR pathway and ER signalling, resulting in ligand-independent receptor activation.⁶

BOLERO-2: Primary endpoint—Progression-free survival

- BOLERO-2 is a large, randomized, phase III trial comparing exemestane + placebo to exemestane plus everolimus (an mTOR inhibitor) in 724 post-menopausal women with hormone receptor positive advanced breast cancer previously treated with a non-steroidal aromatase inhibitor (NSAI).⁷
- Stratification was based on ‘sensitivity’ to prior hormonal therapy (84% of the population) and presence of visceral disease (56% of the population).
- The minority of patients (16%-21% per arm) had received the NSAI in the adjuvant setting.
- The primary efficacy endpoint of BOLERO-2 was progression-free survival (PFS) by local assessment.

- With a median follow-up of 18 months (final analysis for PFS), there was a clear statistical and clinically significant improvement in PFS in favour of everolimus and exemestane (7.8 months) versus placebo and exemestane (3.2 months) with a hazard ratio of 0.45 (95% CI: 0.38–0.54) p<0.0001.
- The control arm in BOLERO-2 replicated the efficacy of the exemestane arms in the EFECT⁷ and SoFEA⁸

- studies in terms of PFS, demonstrating consistency in the limited efficacy of exemestane alone following prior NSAI exposure (Table 1).
- There was a greater rate of serious adverse events (as defined in the protocol) in the everolimus and exemestane arm (23%) compared to the placebo and exemestane arm (12%).
- Despite the greater rate of grade 3 and 4 toxicities, the time to definitive

Table 1: Primary and secondary efficacy endpoints of hormonal clinical trials in ER+ MBC following prior exposure to NSAI. * Meta-analysis of EFECT and SoFEA efficacy data. E: exemestane

Trial	Median PFS	p value	Median OS	p value
EFECT ⁷				
exemestane (E)	3.7 months	p=0.653	22.6 months ^{12*}	p=0.72
fulvestrant	3.7 months		21.9 months	
SoFEA ⁸				
exemestane (E)	3.4 months	p=0.56	22.6 months ^{12*}	p=0.72
fulvestrant	4.8 months		21.9 months	
BOLERO-2 ⁶				
placebo + E	3.2 months	p<0.0001	26.55 months ¹⁰	p=0.14
everolimus + E	7.8 months		30.98 months	



This educational work is sponsored by Novartis Canada

deterioration of QOL (as measured by the EORTC QLQ C30 GHS) was longer in the everolimus + exemestane arm versus the placebo + exemestane arm (8.3 months versus 5.8 months, $p=0.0084$).⁹

BOLERO-2: Secondary endpoint—Overall survival

- Overall survival (OS) was a predefined secondary efficacy endpoint of the BOLERO-2 study.
- The protocol assumptions were that the expected median OS in the placebo + exemestane arm was 24 months. The addition of everolimus to exemestane was calculated to improve the OS to 32.4 months (an eight-month absolute improvement in OS)—which corresponds to a HR of 0.74.
- With a median follow-up of 39 months now, the final OS analysis was recently presented at the EBCC-9 meeting.¹⁰
- The overall survival difference in BOLERO-2 was not statistically significant. The median OS in the everolimus + exemestane arm was 30.98 months compared to 26.55 months in the placebo + exemestane arm [HR 0.89; 95% CI 0.73–1.10; $p=0.14$] (Table 1).
- This numerical difference in median OS between the two arms of 4.4 months is potentially in keeping with a maintenance of benefit seen in the median PFS difference gained with everolimus and exemestane over placebo and exemestane.
- There was demonstration of a longer median time from randomization to either first chemotherapy or death in the everolimus and exemestane arm (11.86

months; 95% CI 10.45–13.08) versus placebo and exemestane (5.98 months; 95% CI 5.09–7.39).

- No new safety signals were seen with longer follow-up on the study. The rate of reported grade 3/4 adverse events was 55% in the everolimus arm and 29% in the placebo arm.

Conclusions

- The improvement in PFS for the combination of everolimus and exemestane (median PFS of 7.8 months; hazard ratio of 0.45 (95% CI: 0.38–0.54) $p<0.0001$), as demonstrated in BOLERO-2, is both clinically and statistically significant.
- This has led to the combination of everolimus and exemestane as a standard of care option in Canada in ER+ post-menopausal MBC with prior exposure to NSAI.
- Though a statistical difference in OS was not demonstrated in the final efficacy analysis of BOLERO-2, as this was a secondary endpoint, perhaps it was not only underpowered to detect a statistical difference, but also somewhat unrealistic to expect the magnitude of difference powered for in the statistical plan of BOLERO-2.
- Accounting for and addressing post-progression survival is important in attempting to correlate PFS and OS.¹¹
- In clinical trials that have demonstrated a PFS benefit, lack of a statistical significance in OS may not simply imply lack of improvement in OS, especially when there are associated long median post-progression survivals.¹¹
- While the ability to demonstrate improvements in overall survival in large phase III clinical trials in MBC have

been challenging and limited, it should remain a gold standard goal.

- However, attention to powering the studies appropriately and adequately for OS as a primary endpoint (or co-endpoint) is pivotal.
- Quality maintained improvements in PFS of significant clinical magnitudes are an important clinical efficacy endpoint if we hope to continue to improve the quality and quantity of life for women battling MBC.

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Management of anti-estrogen therapy resistant HER2-negative metastatic breast cancer

HOT SPOT

Drs. Adriana Matutino, MD, Clinical Oncology Fellow at Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo-SP, Brazil and Sunil Verma, MD, MED, FRCPC, Sunnybrook Health Sciences Centre

Introduction

Recent population-based studies have confirmed an improvement in survival rates for women with metastatic breast cancer (MBC), mostly due to the availability of more effective drugs.^{1,2} Hormone receptor (HR)-positive breast cancer is the most frequent subtype of breast cancer, comprising about 60%–70% of all breast cancer cases. Oophorectomy was first shown to cause regression of unresectable breast cancer in 1896³ and, since then, therapies aiming at estrogen deprivation have become standard of care for hormone receptor-positive (HR+) MBC.⁴ Even though some patients with HR+ MBC have a sustained clinical benefit from anti-estrogen treatment, most patients will progress after one year of first-line anti-estrogen therapy. Therefore, studies were designed to identify new strategies in patients considered as having hormone resistant disease.⁵ In recent clinical trials, the definition of hormone-resistant MBC is variable,^{6,7} with the 2nd International Consensus Conference for Advanced Breast Cancer (ABC2), defining it progression of disease during the first two years of adjuvant endocrine therapy or *de novo* progression on first-line endocrine therapy for advanced disease. Here, we present a

review on the current treatment options to manage HR+ MBC patients and some of the future strategies designed to overcome anti-estrogen treatment resistance.

Current endocrine treatment approach for HR+ HER2-negative metastatic breast cancer

Estrogen deprivation therapy is one of the most important mechanisms to treat hormone-sensitive breast cancer in the metastatic setting.⁸ Endocrine treatment of breast cancer is based on strategies that decrease estrogen production, block signaling through the estrogen receptor (ER), or antagonize and degrade ER itself.⁵ Endocrine therapy may be suitable for HR+ MBC patients who have none to mild to moderate symptoms related to the disease, who present mainly with bone as a single site of metastatic disease or who have limited visceral metastases and those who have prolonged DFI, and do not need rapid response to improve symptoms. Patients with rapidly progressive visceral disease or with a risk or evidence of end-organ dysfunction or significant disease-related symptoms should be given chemotherapy. The choice of endocrine agent should be based on menopausal status, comorbidities, agents received in the adjuvant setting and the drug safety profile.⁸⁻¹⁰

Anti-estrogen treatment for patients who have progressed on prior endocrine treatment

For patients with disease progression following endocrine therapy, ongoing anti-estrogen treatment is a reasonable option, provided they are not symptomatic

and their disease continues to be slowly progressive and they have had a reasonable response to first-line endocrine therapy or prolonged DFI with adjuvant endocrine therapy. Patients who have rapidly progressive metastatic disease should be treated with chemotherapy. No definitive recommendation can be given for a specific endocrine treatment cascade, and the best option after progression is currently unknown.⁸ For premenopausal women who progress following first-line treatment, menopause should be induced and then the treatment approach for postmenopausal women is generally considered.⁸ For postmenopausal women, there is a lack of clinical trials to address the optimal sequence of therapy from the first- to the second-line setting. A choice between the available agents should be individualized based on prior treatment received.⁸

• *Aromatase inhibitors (AI)* — No differences in efficacy between the different AIs were seen in the second-line setting. In a randomized, multicentre and multinational open-label phase IIIb/IV study, 713 patients with disease progression on a prior antiestrogen treatment were enrolled and randomly assigned to treatment with either letrozole or anastrozole.¹¹ Letrozole was significantly superior to anastrozole in the overall response rate (19.1% versus 12.3%, $P=0.013$), although there were no significant differences between the treatment arms in the rate of clinical benefit, time to treatment failure or overall survival.¹¹ The administration of

exemestane in the second-line setting after progression on a non-steroidal AI (anastrozole or letrozole) was evaluated in a 2011 systematic review of nine studies, with clinical benefit for exemestane after any non-steroidal AI failure or before treatment ranging from 12% to 55%, and the time to progression ranging from 3.7 to 5.2 months. Only one study reported a median overall survival with exemestane at 15.2 months.¹²

- *Fulvestrant* — Fulvestrant results in similar overall response rates and overall survival compared with an AI.¹³ However, these studies utilized a lower dose of fulvestrant (250 mg monthly) than what is now known to be the most effective dose (500 mg monthly). Whether use of a higher dose of fulvestrant results in an improvement in clinical outcomes compared with AI therapy is not known.¹³ In addition, the combination of fulvestrant (250 mg monthly) plus anastrozole appears not to provide additional advantage over fulvestrant (250 mg monthly) or an AI alone, as a second-line treatment¹⁴.
- *Tamoxifen* — There are limited data to inform the benefit of tamoxifen in the second-line setting. In a combined analysis of two randomized trials evaluating a sequence strategy (i.e., tamoxifen followed by anastrozole or vice versa), 137 women crossed over to tamoxifen. Second-line treatment with tamoxifen resulted in a 10% overall response rate (ORR) and a clinical benefit rate (ORR plus stable disease for ≥ 6 months) of 49%.¹⁵



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Third- or later line therapy

For women who progress after two lines of endocrine therapy, treatment must be individualized based on their prior treatment response, tumour burden, and preferences for treatment. In general, patients who have progressed after multiple lines of endocrine therapy should receive chemotherapy. However, for patients who are asymptomatic with slowly progressive disease, continuation of endocrine therapy is reasonable.

Endocrine plus molecular targeted therapy as a strategy to overcome hormone resistance

Currently available

Mammalian target of rapamycin [mTOR] inhibitor

An emerging mechanism of endocrine resistance is aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) signaling pathway. Growing evidence supports a close interaction between the mTOR pathway and ER signaling. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which leads to ligand-independent receptor activation.⁷

- **Exemestane plus everolimus** — The benefit of everolimus plus the steroidal AI, exemestane, was shown in the Breast Cancer Trials of Oral Everolimus (BOLERO-2) trial, which enrolled 724 women who had progressed on non-steroidal aromatase inhibitors.⁷ Patients were randomly assigned treatment with exemestane (25 mg daily) plus placebo or exemestane plus everolimus (10 mg daily). The combination of exemestane and everolimus resulted in improved outcomes with an improvement in PFS (median, 7.8 versus 3.2 months;

HR 0.45, $p < 0.001$; higher ORR (9.5 versus 0.4%) and improved quality of life.⁷ Recent data from the 2014 EBCC meeting show a numerical improvement in OS, but this was not statistically significant (median OS, 30.9m versus 26.5m, $p = 0.14$).¹⁶ Serious side effects (grade 3/4) associated with everolimus are stomatitis (8%), dyspnea (4%), non-infectious pneumonitis (3%), elevated liver enzymes (3%) and hyperglycemia (5%).⁷

Agents being studied

Inhibitor of class I histone deacetylases (HDAC)

Entinostat is an oral selective inhibitor of HDAC, which is a protein required for the control of gene expression. It exerts an antiproliferative effect and promotes apoptosis in breast cancer cell lines and has been evaluated as a second- or later-line treatment targeting resistance to hormonal therapies in estrogen receptor–positive breast cancer.

- **Exemestane plus entinostat** — A randomized, placebo-controlled, phase II study evaluated 130 patients who had previously progressed on AI therapy randomly assigned to treatment with entinostat (5 mg daily) combined with exemestane (25 mg daily) versus exemestane alone. The combination of the two drugs improved median PFS to 4.3 months versus 2.3 months (HR 0.73; 95% CI, 0.50 to 1.07; one-sided $P < .055$). Median overall survival was an exploratory end point and improved to 28.1 months with both drugs versus 19.8 months with EP (HR, 0.59; 95% CI, 0.36 to 0.97; $P < .036$). Fatigue and neutropenia were the most frequent grade 3/4 toxicities. Treatment discontinuation because of adverse events was higher in the combination group versus the exemestane alone group (11% versus 2%).¹⁷

Inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6)

- **Palbociclib plus letrozole** — Palbociclib (formerly known as PD 0332991) is a highly selective, orally administered inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). In preclinical studies, it was shown to selectively inhibit the proliferation of ER-positive breast cancer cell lines.¹⁸ The first results of a phase II, randomized trial of letrozole with or without palbociclib as first-line therapy were reported at the 2012 San Antonio Breast Cancer Symposium abstract.¹⁹ In this trial, 165 patients with advanced ER-positive, HER2-negative breast cancer were randomly assigned treatment with letrozole (2.5mg daily) with or without palbociclib (125mg daily on days 1 to 21) on a four-week cycle. Treatment with letrozole plus palbociclib resulted in: a significant increase in the median PFS compared with letrozole alone (26 versus 7.5 months, HR 0.32, 95% CI 0.19-0.56, $p < 0.001$) and median duration of response (nine versus five months); a higher ORR (34 versus 26%); higher rate of serious (grade 3/4) neutropenia (14 versus 0%), although there were no reports of neutropenic fever. Two phase III trials are now underway. The Paloma-2 trial is testing the combination of palbociclib plus letrozole as initial treatment for advanced or metastatic breast cancer²⁰; the Paloma-3 trial is testing palbociclib in combination with fulvestrant in patients who progressed on endocrine therapy.²¹

Steroid receptor coactivators (SRC) inhibitors

The SRC 1, 2, and 3 are widely implicated in nuclear receptors-mediated diseases, especially in cancers, with the majority of studies focused on their roles in breast cancer. They are a family

of membrane-associated non-receptor tyrosine kinases, which are involved in multiple signaling pathways regulating normal cell growth, angiogenesis, steroid receptor activation, and cell survival.^{22,23} In HR+ breast cancer cell lines, SRC activity increases in response to estrogen stimulation, suggesting that SRC may facilitate estrogen receptor-activated proliferative signaling.²⁴ In addition, constitutive activation of SRC-dependent signaling pathways can lead to estrogen-independent growth.²⁴ Preclinical studies combining SRC inhibitors with antiestrogens have shown synergistic antitumor activity.^{25,26} In a phase II trial, limited single-agent activity was observed with dasatinib twice daily in patients with advanced HR+ breast cancer, but the trial was not exclusive for HR+ HER2 negative, with most women expressing HER2 also.²⁷ Trials of dasatinib combined with endocrine therapy in patients with HR+ MBC are underway using a better tolerated once-daily schedule of dasatinib.^{28,29}

Discussion

It is important to recognize the natural history and emergence of endocrine resistance when selecting appropriate therapy for HR+ Her 2 negative MBC. Patients with endocrine-responsive disease may continue to derive benefit from sequential anti-estrogen treatment strategies. Increased study and adoption of agents that target and overcome endocrine resistance may allow patients to delay the need for systemic chemotherapy. Selection of appropriate therapy depends on evaluation of clinical evidence and a complete understanding and discussion of treatment-related toxicity along with patient preference.

REFERENCES

References available upon request