HOT SPOT

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

Sunnybrook ODETTE CANCER CENTRE

Volume 15, Issue 2, May 2013

Editorial

By C. Danjoux, MD, FRCPC

The spring issue of *Hot Spot* has many interesting educational articles by our team of experts.

Are patients satisfied with their oncology care? How do we assess patient satisfaction? Dr. Camilla Zimmermann and colleagues describe a new scale for measuring patient satisfaction with oncology care.

Dr. Janet Ellis, a new contributor to *Hot Spot*, very eloquently reminds us of the need for better psychosocial oncology support in her article, *A call to action!* This call to action is but a first step towards achieving the vision that by 2015 every cancer patient will have access to psychosocial resources, standardized across the province and based on international best practice. In future issues Dr. Ellis will provide practical ideas on how to initiate or manage the psychosocial issues faced by our patients in the clinic.

Many of our patients have questions about nutrition and cancer. Breast cancer patients often ask if it is safe to consume soy foods? The OCC Clinical Nutritional Team has an excellent review of current studies on soy and breast cancer.

Health coverage for refugee claimants has become more complicated. Sally Bean's ethics perspective on the impact of recent changes to Interim Federal Health Program Funding on refugee claimants provides us with some practical solutions when caring for refugees.

To meet our continued educational needs Dr. Ewa Szumacher provides a list of CME conferences for *Hot Spot* readers.

This issue has two inserts. The one by Dr. Susanna Cheng is an overview of the results of new markers, and the reported results of new agents in recent studies in NSCLC.

Dr. Kathy Pritchard's insert on Hormone Receptor Positive Metastatic Breast Cancer in Postmenopausal Women summarizes the results of recent studies and provides a treatment algorithm guideline.

We hope that you enjoy the content of the spring *Hot Spot*.

The FAMCARE-P: A new scale for measuring patient satisfaction with oncology palliative care

By Breffni Hannon, MD, Christopher Lo, PhD, Camilla Zimmermann, MD, PhD

Patient satisfaction with care is a growing area of interest for health care providers, and is increasingly used as a marker of the quality of care provided by an institution.[1] Satisfaction with palliative care covers a broad range of domains including accessibility; coordination and personalization of care; symptom management; communication; emotional support; and support around decision making.[2] We have developed and validated a new measure for patient satisfaction with ambulatory oncology palliative care: the FAMCARE-Patient scale (FAMCARE-P).[3,4]

The FAMCARE-P was developed from a pre-existing measure of caregiver satisfaction, the FAMCARE scale. The FAMCARE is a 20-item self-report measure designed to measure informal caregiver satisfaction with oncology palliative care and is rated on a numerical rating scale from 1 (very dissatisfied) to 5 (very satisfied). It is usually completed one month after the death of the patient,[5,6] but has also been used prospectively.[7] We recognized that there were very few validated measures of patient satisfaction, and none that could be directly compared with caregiver scores. We therefore decided to modify the FAMCARE to generate a tool that could be used prospectively by patients.

To construct the FAMCARE-P, we rephrased items from the original FAMCARE scale to reflect patient rather

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than caregiver perspectives. We dropped three items that lacked association with other FAMCARE items, were not relevant to outpatient settings or were redundant based on other, similar items within the scale. This resulted in a 17-item scale. Next, we conducted an exploratory factor analysis to identify the underlying relationships between the variables measured by the scale. This revealed that, with the exception of one item, all other items cohered into a single dominant factor representing patient satisfaction. Interestingly, the dropped item was the only item on the scale assessing the outcome of an intervention (pain relief) rather than a process (e.g., information about how to manage pain). This non-coherent item was dropped, leaving a 16-item scale, which we named the FAMCARE-P16.[3]

We then performed a confirmatory factor analysis of the scale, designed to test whether the data fit a hypothesized measurement model.[4] We found that all the items cohered into a single factor (in other words, that the items were related to one another and that all measured satisfaction with care), but that the single factor structure was stronger for a reduced 13-item version of the scale (we termed this the FAMCARE-P13). To determine construct validity, we assessed correlations of the summated scores for the FAMCARE P13 and FAMCARE-P16 measures with the FAMCARE scale and with patient measures of performance status, symptom burden, satisfaction with communication, and quality of the relationship with healthcare providers. The correlations were all in the predicted directions. We also tested responsiveness to change for both versions and found that both the FAMCARE-P16 and the FAMCARE-P13 measures were responsive to change over time.[4]

Recently, we used the FAMCARE-P16 along with the caregiver FAMCARE measure in a cluster randomized controlled trial of early palliative care versus standard oncology care.[8] In paired analyses of our baseline data, comparing patient and caregiver satisfaction with care, we found that baseline levels of satisfaction were overall good, though patients were more satisfied than caregivers. Both groups were least satisfied with information regarding prognosis and pain management, and patients were more satisfied than caregivers with the following two items: "the way the family is included in treatment and care decisions" ($p<0.0001$ for paired differences); and "coordination of care" ($p=0.001$ for paired differences).[9] Following the palliative care team intervention, there was significant improvement in FAMCARE-P16 scores for patients in the early palliative care group compared to those in the usual care group ($p<0.01$).[8]

In conclusion, we have developed and validated a measure of patient satisfaction with care, the FAMCARE-P. Its responsiveness to change makes it useful for prospective studies and clinical trials evaluating satisfaction with palliative outpatient care in patients with advanced and progressive cancer. In addition, the FAMCARE-P may be used together with the FAMCARE scale for caregivers, allowing for direct comparison between patient and caregiver ratings.

Table 1. The 16-item FAMCARE-Patient scale (FAMCARE-P16)

1 = very dissatisfied, **2** = dissatisfied, **3** = undecided, **4** = satisfied, **5** = very satisfied.

How satisfied are you with:

1. Doctor's attention to your description of symptoms.
2. How thoroughly the doctor assesses your symptoms.
3. Information given about how to manage pain.
4. Information given about side effects.
5. Speed with which symptoms are treated.
6. Information given about your tests.
7. The way tests and treatments are performed.
8. The way tests and treatments are followed up by the doctor.
9. Information provided about your prognosis.
10. Answers from health professionals.
11. Referrals to specialists.
12. The availability of doctors to answer your questions.
13. The availability of nurses to answer your questions.
14. The way the family is included in treatment and care decisions.
15. Coordination of care.
16. The availability of the doctor to your family.

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References

1. World Health Organization. Quality Assurance in Health Care. WHO, Geneva, 1989.
2. Aspinal F, Addington-Hall J, Hughes R, Higginson IJ. (2003).Using satisfaction to measure quality of palliative care: A review of the literature. *J Adv Nursing 42*(4) 324-39.
3. Lo C, Burman D, Rodin G, Zimmermann C. (2009). Measuring patient satisfaction in oncology palliative care: psychometric properties of the FAMCARE-patient scale. *Qual Life Res*, 18, 747-752.
4. Lo C, Burman D, Hales S, Swami N, Rodin G, Zimmermann C. (2009). The FAMCARE-Patient scale: Measuring satisfaction with care of outpatients with advanced cancer. *European Journal of Cancer*, 45, 3182-3188.
5. Kristjanson LJ. (1986). Indicators of quality of palliative care from a family perspective. *Journal of Palliative Care*, 1, 8-17.
6. Kristjanson LJ (1993). Validity and reliability testing of the FAMCARE scale: Measuring family satisfaction with advanced cancer care. *Social Science and Medicine*, 36, 693-701.
7. Follwell M, Burman D, Le LW, Wakimoto K, Seccareccia D, Bryson J, Rodin G, Zimmermann C. (2009). Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. *J Clin Oncol, 27*(2), 206-213.
8. Zimmermann C, Swami N, Rodin G, Tannock I, Krzyzanowska MK, Leighl NB, Oza AM, Moore MJ, Rydall A, Donner A. (2012). Cluster-randomized trial of early palliative care for patients with metastatic cancer. *J Clin Oncol, 30*, suppl, abstr 9003.
9. Hannon B, Swami N, Krzyzanowska MK, Leighl N, Rodin G, Le LW, Zimmermann C. (2013). Satisfaction with oncology care among patients with advanced cancer and their caregivers. Qual Life Res. [Epub ahead of print].

A call to action!

By Janet Ellis, MD, FRCPC, Cancer Care Ontario Regional Clinical Lead for Psychosocial Oncology for Toronto Central-North

I am writing this perched on a stool in the Dominican Republic with the sound of the sea in the background. As a (relatively) newly appointed psychiatrist in the Odette Cancer Centre, my remit is to write an article for *Hot Spot* about psychosocial aspects of cancer. I usually try to find out who my audience is, so I sat down to read past issues of *Hot Spot* about two weeks ago. I skim-read through all 57 issues, with growing awe and amazement. Awe at such great writing and subject matter; amazement because in 2013 we are still unable to provide our patients the quality psychosocial-spiritual care described so eloquently since 1999. Not because of lack of expertise of our staff in our Patient Family Support Program, but because of lack of sufficient staff, space and programming.

I'll illustrate this with a couple of examples. There have been nine articles on talking to or supporting children or adolescents whose parents have cancer, 13 articles on the importance of spirituality in cancer and six articles on the stress and need for support by caregivers in cancer. When I arrived in September 2011, psychiatry still did not see caregivers, because, at that point, we had 0.35FTE psychiatrists for our 14, 000 new patients a year. We had no particular specialized support for our families facing cancer, tending to rely on Max and Beatrice Wolf Centre to follow those families who fell in their catchment area. With our increase in FTE in psychiatry, we widened referral criteria to include caregivers in acute distress related to the cancer. We have also started a parent group to provide support and education on how to cope as a family when a parent has advanced cancer. We have no formal outpatient spiritual care available, as yet. Because the staff has been used to working with little, each social worker, psychologist and psychiatrist is nimble and able. But the bottom line is that unless we have more staff and space, we cannot provide the programming or depth of care needed.

This is not a problem peculiar to the Odette Cancer Centre. Many cancer patients in Ontario, in fact, have far less access to specialized psychosocial oncology services where they receive their cancer treatment. Despite strong evidence that emotional distress in cancer patients is prevalent, associated with poor health outcomes, increased health care utilization, and is amenable to intervention, emotional support consistently remains the lowest-rated domain in the Ambulatory Oncology Patient Satisfaction Surveys (AOPSS) administered by NRC Picker across Ontario. Sunnybrook, for example, has fallen below the Ontario average in these domains, and I am not surprised. Not because of lack of expertise, but because of understaffing and lack of a strongly supported clinical and academic program to provide the emotional support.

Under-treatment of emotional distress in our cancer patients may partly result from under-detection of distress, but also from our lack of capacity to provide timely access to quality psychosocial specialized care. Our psychiatry and psychology wait time hovered between four and six weeks before increased staffing. As you can imagine, if a patient is overwhelmed with anxiety and depression at the beginning of chemotherapy or a five-week radiation therapy, waiting four to six weeks to be seen is unacceptable and falls far short of any national or international guideline for the provision of accessible, quality psychosocial care.

Without sufficient staffing and program support for our psychosocial oncology program (meaning psychiatry, psychology and social work), the OCC and other centres in the same position will not be able to provide gold standard, guideline-quality oncological care. Clearly all patients should have first-line nursing and patient education intervention. But psychosocial oncology should have the capacity to see at least 15% of our patients flowing through. For this, we need more staff and more space.

By no means do I mean this message to be complaining and negative, although I realize it runs the risk of being just that. I find it a privilege to be allowed access to people's experience in the cancer journey and believe it is possible to make a big difference. Yet, I feel the need to be aggressively clear. We know that there is significant distress in people with cancer, we know that less than half of these receive any extra help, we know that untreated distress affects treatment compliance and outcomes, and increases disability and family distress… and yet we know that distress can be helped… so, we need to act! All of us involved in cancer care need to advocate in our centres for excellent, evidence-based programming and well-funded, parallel psychosocial support throughout the cancer journey—from diagnosis, to navigating treatment, to survivorship or palliation, as well as bereavement support for family members and caregivers.

In my job contract, I was given a remit of program development in psychosocial oncology. I also have been given the role of Cancer Care Ontario Regional Clinical Lead for Psychosocial Oncology for Toronto Central-North. This is one of the first such (belated) specific psychosocial oncology lead roles and involves leading and advocating for the disciplines of psychiatry, psychology and social work that make up the specialized response to the whole domain of serious psychiatric, psychological, emotional and social distress in cancer. I have felt extremely well supported in these roles by the leadership of Patient Family Support, as well as the leadership of the Odette Cancer Centre working with our department of psychiatry and I am pleased to let you know that there are plans afoot to actively support these sentiments with actions of increased allocation of space and staff to better serve our patients and their families.

In accordance with the Ontario Cancer Plan III Goals and Toronto Central LHIN Strategic Priorities to *Improve Patient Outcomes* and to *Improve the Patient Experience*, Cancer Care Ontario is promoting the vision that by 2015 every cancer patient will have access to psychosocial resources, standardized across the province and based on international best practice. Please all take a minute to imagine how this will happen in your centre and why fully supported psychosocial programming seems to have taken a back seat for so long, despite compelling evidence and widespread knowledge of its importance.

I will do a "Tips on assessment and management of distress in your clinic" article for next issue, so stay tuned.

Soy and breast cancer

Submitted by Patient and Family Support Program, Clinical Nutrition Team

At the Odette Cancer Centre one of the most frequently asked questions of our clinical nutrition team by women who have been diagnosed with breast cancer is whether it is safe to consume soy foods. The following article from *The ASCO Post* written by Barrie R. Cassileth, PhD, and Ian Yarett gives an overview of the issue and provides guidelines regarding the use of soy. The article, along with references, can be found at **http://www.ascopost.com/issues/july-15-2012/soy-phytoestrogens-and-breast-cancer-an-enduring-dilemma.aspx**

Soy phytoestrogens and breast cancer: An enduring dilemma

The impact of soy consumption on breast cancer diagnosis and outcome remains of concern to clinicians and researchers. Although studied extensively in epidemiologic studies, as well as lab and animal research, no medical consensus on soy's effects has emerged. Many studies show that soy intake is associated with reduced incidence of breast cancer risk, but soy's phytoestrogen content continues to fuel concern that it may promote tumour growth, especially in estrogen-sensitive breast cancer.

This is a major issue of confusion for patients, who are exposed to conflicting media reports and marketed soy products with poorly supported health claims. Inconsistency in research findings, non-comparable study designs, and a dearth of clinical trials that assess the effect of soy on breast cancer outcome in humans have precluded the development of rigorous evidence-based guidelines to date. In this overview, we aim to summarize relevant findings and existing recommendations that may be useful to clinicians.

Estrogenic activity of soy isoflavones

Soy is a major source of isoflavones, particularly genistein and daidzein. These compounds are structurally similar to endogenous estrogen, and may act as selective estrogen receptor modulators with the ability to stimulate or inhibit depending on factors such as isoflavone concentration and the distribution of estrogen receptor types. Isoflavones also may modulate breast carcinogenesis via nonhormonal pathways.

Although many in vitro and preclinical results suggest that soy isoflavones have antiproliferative effects, other studies suggest that they can promote the growth of breast cancer cells. Much of this research used isolated genistein. However, data from at least one animal study in which soy isoflavones promoted tumour growth suggests that this effect is not seen when whole soy is consumed instead of isoflavones alone.

The effects of soy isoflavones in patients on tamoxifen therapy are similarly unclear; both synergistic and antagonistic interactions are reported. The exact nature and clinical implications of the estrogenic and antiestrogenic properties of isoflavones are not well understood.

Prevention

To reduce the risk of breast cancer, epidemiologic evidence generally describes an inverse relationship between soy consumption and breast cancer diagnoses, although the observed degree of protective benefit varies depending on the patients studied. While some reviews and meta-analyses suggest that soy intake reduces breast cancer risk only modestly if at all, other studies have found that consumption at higher levels, such as in Asian diets, may have a more distinct protective effect. Asians traditionally consume a much higher concentration of isoflavones than their Western counterparts—daily consumption in Japan ranges from 26 to 54 mg, compared to 0.5 to 3 mg in the United States.

Both dosage and timing of exposure to soy isoflavones appear relevant to their potential chemopreventive effect. Two recent meta-analyses found soy intake to be significantly associated with reduced risk of breast cancer in Asian, but not Western populations, which may be explained by both higher soy intake among Asians and their tendency to consume soy from an early age.

Several epidemiologic studies in fact suggest that diets rich in soy early in life and through puberty are associated with a decreased risk of breast cancer—and that introducing isoflavones into the diets of adult women may not have much impact on their cancer risk. This is generally consistent with animal studies, which suggest that soy intake is protective at specific stages of development, but not at other points.

Post diagnosis

Despite the inconsistent results of lab and animal studies and resulting concerns about whether soy might adversely affect breast cancer prognosis, there is a growing body of research in humans that supports soy consumption as safe. Three large epidemiologic studies published over the past few years, two in U.S. breast cancer survivors and one in Chinese survivors, found no adverse effects of soy consumption on outcome. Furthermore, they suggest that soy consumption at levels comparable to those among Asian populations does not detract from the benefits of tamoxifen therapy, and may even offer some protection against recurrence and cancer-related death. The largest of these studies, published in the *Journal of the American Medical Association* in 2009, followed 5,033 breast cancer survivors for a median of four years.

Based on these studies, the most recent guidelines from the American Cancer Society (ACS), released in April 2012, conclude that for breast cancer survivors, current evidence does not suggest that consuming soy foods is likely to have adverse effects on risk of recurrence or survival. It warns, however, that evidence "is more limited" with regard to isoflavone supplements.

The ACS position gained further support just one month after its release from an even larger study of 9,514 U.S. and Chinese breast cancer survivors, which found a significantly reduced risk of cancer recurrence in patients who consumed at least 10 mg of isoflavones (~3 g of soy protein) per day. The guideline does not mention a specific amount of soy that should be considered safe, unlike the previous ACS report on this topic in 2006, which specified a maximum of "three servings per day of soy foods.

Concluding thoughts

Despite some contradictory evidence in lab studies and animal models, a growing body of epidemiologic evidence suggests that soy food is safe to consume at moderate levels, and that clinicians need not advise against soy foods for breast cancer patients or survivors. Patients should avoid soy supplements, however, as these often provide very high doses of isoflavones and have not been well studied. More research and, ideally, human clinical trials are needed to elucidate the optimal dosage and timing of exposure for maximizing the anticancer effects of soy while minimizing the risk of harm.

Impact of recent changes to Interim Federal Health Program funding on refugee claimants: An ethics perspective*

By Sally Bean, JD, MA, Ethicist and Policy Advisor

Historically, the Interim Federal Health Program (IFHP) has provided refugee claimants' temporary expanded health care coverage, which included comprehensive health benefits including prescription and limited dental and vision coverage. Effective June 30, 2012, both the eligibility criteria and benefits covered for IFHP recipients changed significantly. Under the new legislation, depending on the category the individual belongs to, IFHP will pay for one of three different types of coverage: basic, expanded or public health and safety coverage (Table 1). Medavie Blue Cross, the company responsible for IFHP claims administration, requires providers to verify eligibility with Medavie before providing services.

All other treatment costs not covered by IFHP must be paid by the individual. For example, persons with basic IFHP coverage requiring medication for chronic disease management such as diabetes or chemotherapy would have to pay for their medication or IV chemo drugs out-of-pocket.

The IFHP coverage changes affect numerous stakeholders in different ways. Anticipated impacts to health care organizations include: 1) increased length of stay in acute care for persons with basic or public health and safety coverage who cannot afford medications or access alternative levels of care such as rehab or long-term care, 2) increased emergency department utilization and uncompensated care costs from persons with public health and safety coverage.

The IFHP cuts have created access to care barriers for some IFHP beneficiaries. By providing only public health and safety coverage to some beneficiaries, the IFHP cuts have increased the number of uninsured patients in Ontario. This increase to the uninsured patient population requires health care organizations and providers to consider their legal and ethical obligations to provide treatment for these patients. In emergency situations, health care professionals and organizations have obligations to patients without regard for their ability to pay. For example, Section 21 of Ontario's *Public Hospitals Act* obligates hospitals to admit a patient if "… by refusal of admission life would thereby be endangered …" Similarly, Section 18 of the Canadian Medical Association's Code of Ethics notes that a physician is to "provide whatever appropriate assistance … to any person with an urgent need for medical care." However, for less urgent or chronic conditions that may affect the patient's quality of life, the ethical obligations of individual clinicians and health care organizations are unclear.

Health care organizations are expected to be stewards of public resources to ensure that resources are used appropriately. Stewardship may be undermined if the number of patients requiring uncompensated services increases. From a stewardship perspective, health care organizations are placed in the difficult position to decide whether it is more cost-effective to deny non-urgent treatment or to provide it in order to prevent deterioration into a more costly emergency situation. Health care professionals experiencing increased requests for uncompensated treatment will need to determine the amount that is fair for them to provide without compensation given competing duties and obligations to insured patients.

In light of the recent legislative changes precipitating a change in health coverage for refugee claimants, health care providers and organizations will have to be familiar with appropriate procedures for managing their care; especially, if the refugee claimant has either basic or public health and safety coverage. From an ethics-based fairness perspective, it is important that decisions around access to care are made consistently. In order to promote a standardized approach, here is a suggested process for handling IFH cases:

1. Determine if a legal and ethical obligation to provide treatment exists. In your clinical judgment, is urgent care required? If yes, provide treatment based on medical need.
2. Which type of Interim Federal Health (IFH) coverage (i.e., expanded, basic or public health and safety) does the patient have? Health care providers can log on to the Medavie Blue Cross portal for additional information: **https://provider.medavie.bluecross.ca/**
3. Is the proposed treatment covered under the IFH recipient's type of coverage? Refer to benefit grids also contained in the Medavie Blue Cross portal.
4. If no, consider the following:
   - medical needs of patient, e.g., treatments impact on patient's overall health status. What impact would delaying or denying treatment have on patient?
   - impact on organization's ability to meet needs of Ontarians within its current context, i.e., what will be the resource burden?
   - patient's ability to offset organization's resource burden (i.e., ability to pay).

*Adapted from *Ethics Policy Brief Re: Changes to Interim Federal Health Program* issued by the University of Toronto, Joint Centre for Bioethics Uninsured Patient Task Force (UPTF) on Aug. 6, 2012. Sally Bean chairs the UPTF and was lead author on the brief.

Table 1: Types of IFHP coverage

Expanded:		**Basic:**		**Public health & safety:**	
Includes Basic coverage + Prescribed medications, limited dental & vision care, prosthetics & devices to assist mobility, home care and long-term care, psychological counselling and post-arrival health assessments	Includes: • Accepted refugees • Resettled refugees (gov. sponsored) • Victims of human trafficking	Includes: hospital services, services of a doctor or registered nurse, lab, diagnostic and ambulance services + Medications ONLY when required to prevent or treat a disease posing a public health or safety concern	Includes: • Refugee claimants from non-designated countries of origin (Non-DCO) • Resettled refugees (privately sponsored)	Includes care ONLY provided to diagnose, prevent or treat a disease posing a risk to public health or safety (i.e., notifiable diseases per the Public Health Agency of Canada, e.g., TB, HIV, Hepatitis B)	Includes: • Refugee claimants from Designated Countries of Origin (DCO) who apply after Dec. 15, 2012 • Rejected refugee claimants

Continuing Medical Education 2013

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**

- **May 2–3, 2013.** Target Insight VII: Rethinking Radiation Therapy for Metastatic Cancer, One King West,Toronto, Canada. **http://www.cepd.utoronto.ca/targetinsight/**
- **May 9, 2013.** 2nd Annual North Zone Palliative Care Conference "Sharing the Journey", Pomeroy Hotel & Conference Centre, Grande Prairie, Alberta. **http://gphospice.ca/events/2013-palliative-care-conference**
- **May 30–June 2, 2013.** 13th World Congress of the European Association for Palliative Care, Prague, Czech Republic. **http://www.eapc-2013.org/**
- **May 31–June 4, 2013.** 2013 ASCO Annual Meeting, McCormick Place, Chicago, Illinois. **http://chicago2013.asco.org/**
- **June 2–3, 2013.** BC Hospice Palliative Care Association Conference 2013, Sheraton Vancouver Airport Hotel, Richmond, BC, Canada. **http://www.bchpca.org/**
- **June 2–4, 2013.** Leading Practices—Transforming Care—Fifth National Palliative Care Congress, Houston, USA. **http://phdvacations.com/conference.php?conference_id=11045**
- **June 13–14, 2013.** Saskatchewan Hospice Palliative Care Association, "Out of the Shadows—Extending the Boundaries of Hospice Palliative Care" Delta Regina Hotel Regina, SK, Canada. **http://www.saskpalliativecare.org/events.html**
- **June 27–29, 2013.** The Annual MASCC/ISOO International Cancer Care Symposium, Berlin, Germany. **http://www.kenes.com/mascc**
- **August 9–10, 2013.** Best of ASCO Chicago, Fairmont Chicago, Chicago, Illinois. **http://boa.asco.org/**
- **August 16–17, 2013.** Best of ASCO Los Angeles Hyatt Regency Century Plaza, Los Angeles, California. **http://boa.asco.org/**
- **August 23–24, 2013.** Best of ASCO Boston, Boston Marriott Copley Place, Boston, Massachusetts. **http://boa.asco.org/**
- **September 3–6, 2013.** 12th Australian Palliative Care Conference, National Convention Centre, Canberra, ACT, Australia. **http://www.seatoskymeetings.com/bchpca/**
- **September 7–9, 2013.** 2013 Breast Cancer Symposium, San Francisco, California. **http://www.breastcasymposium.org**
- **September 17–20, 2013.** African Palliative Care Association—4th Triennial Conference, "Spanning Diseases, Crossing Boarders: 2013", Johannesburg, South Africa. **http://www.africanpalliativecare.org/conference2013/**
- **September 22–25, 2013.** ASTRO 55th Annual Meeting—2013, Georgia World Congress Center, Atlanta, Georgia, USA. **https://www.astro.org/Meetings-and-Events/2013-Annual-Meeting/Index.aspx**
- **October 3–6, 2013.** (IMFPC) International Multidisciplinary Forum on Palliative Care, Sofia, Bulgaria. **http://www.imfpc.org/**
- **October 11–13, 2013.** 10th Asia Pacific Hospice Conference 2013, Bangkok Convention Centre, Bangkok, Thailand. **http://aphc2013.com/**
- **October 28–29, 2013.** CANO 24th Annual Palliative Care Conference, Fantasyland Hotel, West Edmonton Mall, Edmonton, Alberta, Canada. **http://www.cano-acio.ca/events/2013/10/event154/?et_ID=collection_ID**
- **October 31–November 3, 2013.** 2013 Canadian Hospice Palliative Care Conference, Ottawa, Ontario, Canada. **http://conference.chpca.net/**
- **November 7–9, 2013.** Advanced Breast Cancer Second International Consensus Conference(ABC2), Centro de Congressos de Lisboa (Praça das Industrias), Lisbon, Portugal. **http://www.abc-lisbon.org/**
- **November 8–9, 2013.** 2013 Best of ASTRO, Hilton San Diego Bayfront, San Diego. **https://www.astro.org/Meetings-and-Events/2013-Best-of-ASTRO/Index.aspx**

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Targeted therapies in NSCLC

By Dr. Susanna Yee-Shan Cheng, BSc, MD, FRCPC

HOT SPOT

Introduction

Lung cancer patients today have more options of treatment than patients a decade ago. Much of the changes in management are due to the introduction of targeted therapies and personalized medicine for lung cancer patients. In fact, lung oncologists are leading the way in personalized cancer management. For decades, we treated all patients with NSCLC with chemotherapy, without any clinical or biological selection and with disappointing survival results. Today we can identify therapeutic targets for 20% of lung cancers and more are currently under investigations. More potential targets are being developed (Figure 1).

Therapeutic targets

1. EGFR (epidermal growth factor receptor) mutations

- Conformational change seen in the TK (tyrosine kinase) domain of mutated EGFR increases the activation of the domain and its affinity for ATP (and for EGFR TKIs) compared with wild type EGFR
- Small molecule tyrosine kinase inhibitors (TKIs) targeting the EGFR pathway have been shown to be effective therapies for NSCLC with activating mutations within the EGFR gene
- EGFR TKIs act as ATP analogues and compete for the tyrosine kinase catalytic site, interfering with receptor activation and resulting in decreased signalling to downstream survival and growth pathways

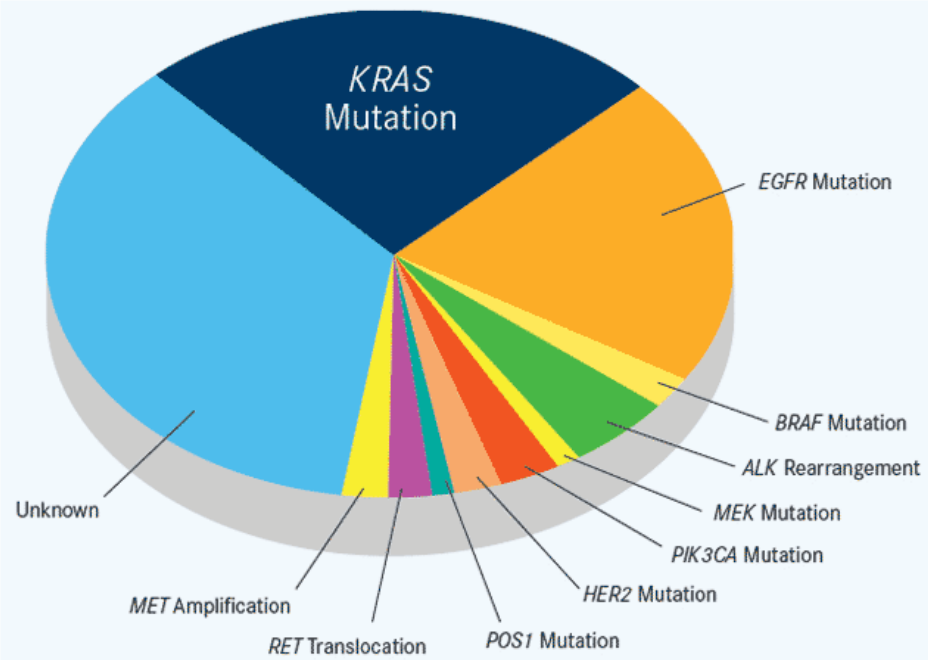


Figure 1.

2. EML4-ALK fusion oncogene

- EML4-ALK fusion oncogene arises from an inversion on the short arm of chromosome 2
- The resulting chimeric protein EML4-ALK contains an N terminus derived from EML4 and a C terminus containing the entire intracellular tyrosine kinase domain of ALK
- This chimeric protein has constitutive kinase activity
- EML4-ALK is highly oncogenic, activates the PI3K-AKT and MAPK-ERK pathways and induces lung tumours
- Crizotinib blocks the receptor for EML4-ALK

EGFR activating mutations and TKIs

Activating mutations

- **Exon 19** – base pair deletion—more common (62.2%)
- **Exon 21** – L858R point mutation—less common (37.8%)
- Rarer mutations exist, but are not routinely tested
- These mutations have prognostic and predictive significance
- **Prognostic** for longer progression-free survival and **predictive** of response to EGFR TKIs
- In multivariate analysis, association was found between poor PFS and male gender and the presence of L858R mutations

Clinical criteria associated with mutations

- Elderly
- Never a smoker (66.6%)—defined as having smoked fewer than 100 cigarettes in their life
- Female (69.7%)
- Asian (30%–40%)
- Adenocarcinoma (80.9%)
- Clinical characteristics alone are not sufficient to identify patients with *EGFR mutations*

Prevalence of mutations

- 10–12 % of all non-Asians harbour mutations
- 30–40% of Asians harbour mutations

Available agents and dosing

- First generation reversible EGFR TKIs—Gefitinib (Iressa) and Tarceva (Erlotinib)
- Irreversible second generation EGFR TKIs—Afatinib
  - Afatinib differs from first-generation EGFR TKIs both in its ability to bind HER2, and its irreversible binding to EGFR
- Recommended dosing:
  Gefitinib (Iressa): 250 mg po daily
  Erlotinib (Tarceva): 150 mg po daily
  Afatinib: 40 mg po daily

Response rates, toxicity and QOL

- First generation EGFR TKIs are associated with impressive *response rates* of approximately 60–70% in mutation-positive patients
- The median *progression-free survival* for patients with EGFR mutations on first-line EGFR TKIs is approximately 9–12 months
- There is evidence that EGFR TKIs crosses the blood-brain barrier and can improve brain mets
- The two most common adverse events are rash and diarrhea
- The incidence of rash varied from 37% to 78% in phase III clinical trials and appears to be dose-dependent, with up to 25% of patients experiencing severe reactions (grade 3 or greater)
- The incidence of diarrhea varies from 27% to 87%, with up to 25% of patients experiencing severe reactions (grade 3 or greater)
- Rare complications include transaminitis and interstitial pneumonitis

- The adverse events for afatinib reported through previous studies have been similar in type to those seen with other EGFR TKIs, although the frequency and severity appear to be greater
- Possible side effects of EGFR TKIs are:

acne	nail problems
dehydration	nausea
diarrhea	nosebleeds
dry skin	pain
itchiness	temporary hair loss
loss of appetite	trouble sleeping
mild skin rash	vomiting
mouth sores	weakness

Response to EGFR TKIs can be as quick as 10 days to see improvement

Laboratory testing

- protein expression determined by immunohistochemistry with mutation specific antibodies

Efficacy of EGFR TKIs

First line treatment

- Several trials support the use of EGFR TKIs in the first-line setting for EGFR mutation positive patients (Table 1)
- The **Iressa Pan-Asia Study (IPASS)** was the first randomized phase III study that confirmed the role of EGFR-TKI monotherapy as a first-line therapy for patients with a known EGFR mutation
- The objective response rate for EGFR mutation-positive patients treated with gefitinib (Iressa) was 71.2%, compared with 47.3% in patients treated with chemotherapy ($p < 0.001$)
- In the EGFR mutation-negative group, only around 1.1% of patients responded to gefitinib, compared with a response rate of 23.5% to chemotherapy ($p = 0.001$)
- Progression-free survival (PFS) was prolonged in the gefitinib group (hazard ratio [HR] 0.48; $p < 0.0001$). However, due to the significant portion of crossover to the TKI group, OS was similar
- This study also illustrated that it was detrimental to use TKIs as first-line therapy for *EGFR mutation-negative* patients who are suitable for chemotherapy
- Based on these results Iressa 250 mg po daily is approved for first-line treatment of EGFR mutation-positive patients with EAP approval
- Similar results support the first-line use of gefitinib 150 mg/100 mg po daily (EURTAC study) and afatinib 40 mg po daily (LUX Lung 3), but neither of these drugs is approved through EAP (Table 1)

Compilation of *EGFR* Mutational Status Studies

	Population	EGFR TKI	Response Rate, %		PFS, mo		HR
			EGFR TKI	Chemo	EGFR TKI	Chemo	
IPASS[a]	• Asian • Clinically enriched	Gefitinib	71.2	47.3	9.8	6.4	0.48
First-SIGNAL[b]	• Asian • Clinically enriched	Gefitinib	84.6	37.5	8.4	6.7	0.613
NEJ 002[c]	• Asian • EGFR+	Gefitinib	73.7	30.7	10.8	5.4	0.3
WJTOG3405[d]	• Asian • EGFR+	Gefitinib	62.1	32.2	9.2	6.3	0.489
OPTIMAL[e]	• Asian • EGFR+	Erlotinib	83	36	13.7	4.6	0.16
EURTAC[f]	• European • EGFR+	Erlotinib	54.5	10.5	9.7	5.2	0.37

a. Fukuoka M, et al. *J Clin Oncol*. 2011;29:2866-2874; b. Han JY, et al. *J Clin Oncol*. 2012;30:1122-1128; c. Maemondo M, et al. *N Engl J Med*. 2010;362:2380-2388; d. Mitsudomi T, et al. *Lancet Oncol*. 2010;11:121-128; e. Zhou C, et al. *Lancet Oncol*. 2011;12:735-742; f. Rosell R, et al. *Lancet Oncol*. 2012;13:239-246.

Table 1.

Combination EGFR TKI and chemotherapy

- No definite evidence that the combination of chemotherapy with EGFR TKIs is beneficial in EGFR mutation-positive patients
- Concurrent administration may not work for the reason of TKI-induced, G1-phase cell-cycle arrest. During the arrest, cell-cycle phase-dependent chemotherapeutic agents will not be effective
- Sequential therapies are possible options and are currently under investigation

Switch maintenance—Use of EGFR-TKI after chemotherapy

- The Sequential Tarceva in Unresectable NSCLC (SATURN) study investigated the use of maintenance erlotinib following the completion of first-line chemotherapy
- It demonstrated a significant improvement in progression-free survival for EGFR mutation-positive patients (44.6 versus 13 weeks, $p < 0.0001$)
- This would only be relevant for those EGFR mutation-positive patients who started on chemotherapy first

Benefit in EGFR wild type

Role as second line/maintenance and third line therapy in mutation-negative NSCLC

- In Canada, Erlotinib is currently approved for the second- and third-line treatment, regardless of mutational status, based on the significant overall survival results shown in the BR .21 study (two months OS benefit versus placebo)
- Therefore, no mutation testing is needed for second-line treatment with EGFR-TKIS

EGFR-TKI resistance

- Regardless of whether first- or second-generation EGFR TKIs are used, treatment is not curative and resistance invariably develops in about a year, as demonstrated clinically by disease progression
- Secondary mutations account for 50-60% of resistance to EGFR TKIs (erlotinib and gefitinib)
- Secondary mutations include: KRAS mutation and specific acquired EGFR mutations such as exon 20 (T790M)
- Resistance also seen with "bypass mechanisms": alteration in c-Met (amplification leading to activation of PI3K (downstream of EGFR), ERBB3 (over-expression) and epiregulin (autocrine loop activation), transformation to small cell lung cancer
- **Tumour flare/rebound progression** is a phenomenon often seen after stopping EGFR-TKIs upon tumour progression (incidence of 20–25%)
- Resuming the EGFR-TKI may often see improvement again
- Crucial that patients initiate second-line therapy relatively soon after discontinuation of EGFR-TKIs
- **Local therapy** in acquired resistance setting may extend survival
- Patients may have one to two sites of progression that may be amenable to local therapy (i.e., SBRT/radiation or surgical resection) while continuing on EGFR-TKIs subsequently
- **Afatinib** has been used as a single agent in patients with acquired resistance to erlotinib or gefitinib with modest success

- LUX-Lung 1, which randomized patients to placebo or afatinib following progression on a first-generation TKI. Patients treated with afatinib had a response rate of 7% and median PFS of 3.3 months compared to 1.1 months in the placebo group, with no statistically significant difference in overall survival
- Afatinib is currently available as fourth-line therapy for EGFR mutation-positive patients through special access program

EML4-ALK fusion oncogene

Fusion oncogene

- EML4-ALK translocations are mutually exclusive of EGFR and KRAS mutations
- Prognostic for longer PFS and predictive of response to crizotinib

Clinical criteria associated with this oncogene

- Younger patients (<50 yrs)
- Male gender
- Never smokers
- Signet ring cell adenocarcinoma
- TTF1 positive
- Clinical characteristics alone are, therefore, not sufficient to identify patients with *ALK*-positive disease

Prevalence of mutations

- Found in only 3–8% of all NSCLC

Available agent and dosing

- **Crizotinib (Xalkori)**—approved for EML4-ALK positive patients
- Recommended dosing: 250 mg po twice daily

Response rates, toxicity and QOL

- 70% response rate
- Median PFS 10 months
- The evidence suggests that crizotinib does NOT cross the blood-brain barrier
- With regard to **safety and tolerability**, common side effects include visual disturbance, nausea and vomiting, diarrhea and/or constipation, peripheral edema, dizziness, anorexia, dysgeusia, alanine transaminase (ALT) increase, and fatigue
- In most cases, side effects are mild and develop quickly, with only peripheral edema worsening over time
- Severe side effects are rare and include aspartate aminotransferase (AST) and ALT increases, pneumonitis, and neutropenia
- In most cases, visual disturbances develop within days of starting the drug and involve brief light trails, flashes, or image persistence occurring at the edges of the visual field, most often when there is a change in the ambient lighting. These visual changes seem to improve over time and appear to be fully reversible on cessation of dosing
- Recently, rapid-onset hypogonadism in male patients taking crizotinib has been noted, and serum testosterone levels should be routinely checked and replaced as appropriate.

Laboratory testing

- Molecular testing with either ALK FISH or ALK IHC with ALK specific antibodies

Efficacy of crizotonib

- Crizotonib was granted accelerated approval by FDA in 2011
- The approval was based on phase II single arm trial only in which 250 mg administered twice daily produced objective response rates greater than 50%, with response duration in the one-year range. By contrast, the standard chemotherapy regime for NSCLC typically produces responses of a few months at best in patients with advanced disease
- **Second line trial** (randomized phase III trial PROFILE 1007): crizotinib prolonged progression-free survival (PFS) by 7.7 months compared to 3.0 months among patients treated with single-agent chemotherapy, either pemetrexed or docetaxel (HR 0.49; 95% CI 0.37–0.64 ; $P < .0001$). The overall response rate was also significantly higher in patients treated with crizotinib at 65% versus 20%. ($P < .0001$)
- First-line trial is currently open comparing crizotinib to platinum/pemetrexed chemotherapy

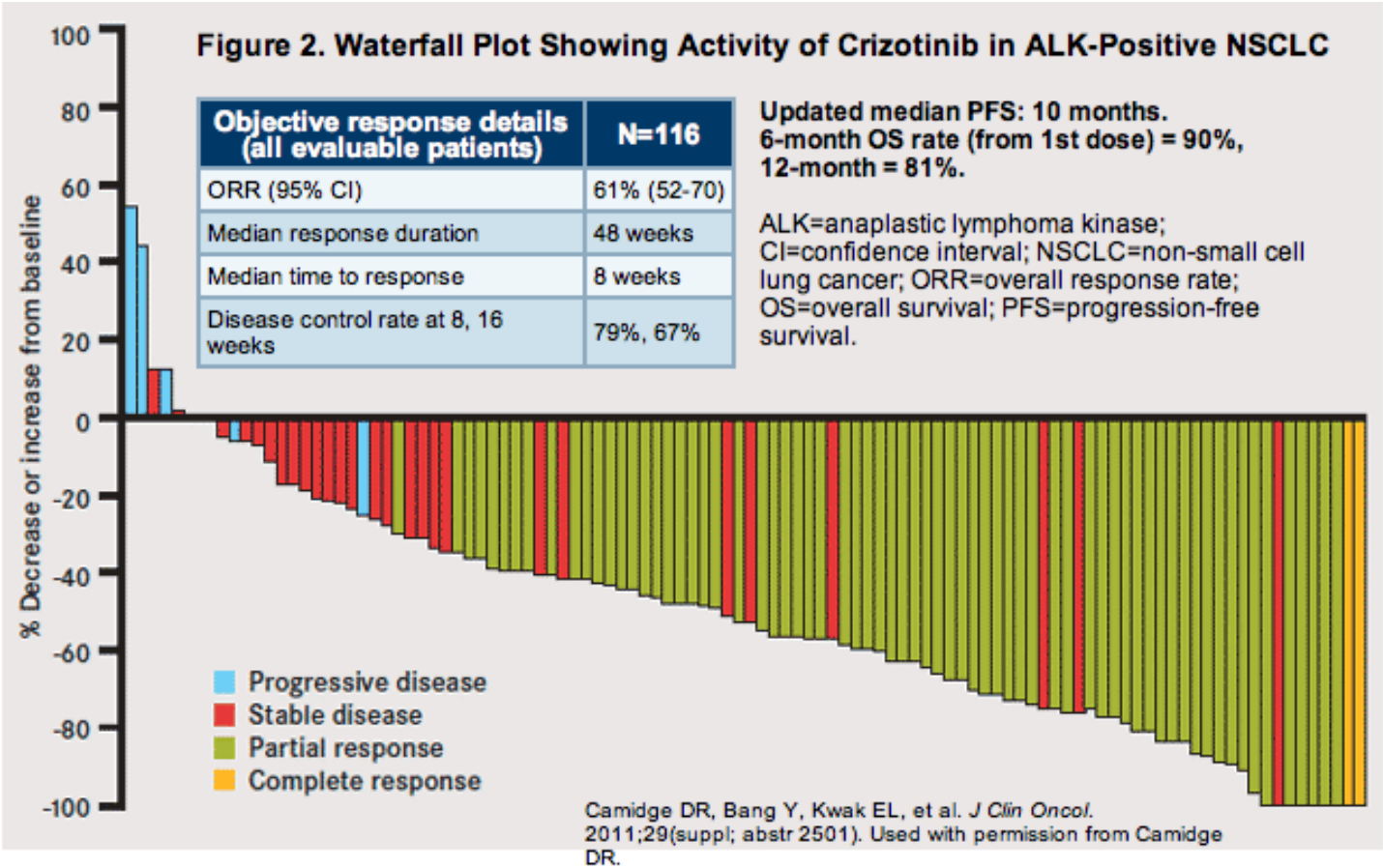


Figure 2.

Figure 3.

Resistance to crizotinib
- The most frequent mutations involve the gatekeeper residue (mutations of L1196M confer resistance via steric interference)
- Acquired resistance usually occurs within one year of starting crizotinib
- Frequency of this resistance mechanism is unknown
- Novel drugs are currently under investigation

Who to test
- Test all patients with non-squamous lung pathology
- On occasion, even mixed squamous pathology in patients who were never smokers should be tested (it is not common to have squamous pathology in never smokers—so perhaps mixed histologies are present)

Generously supported by an educational grant from Roche

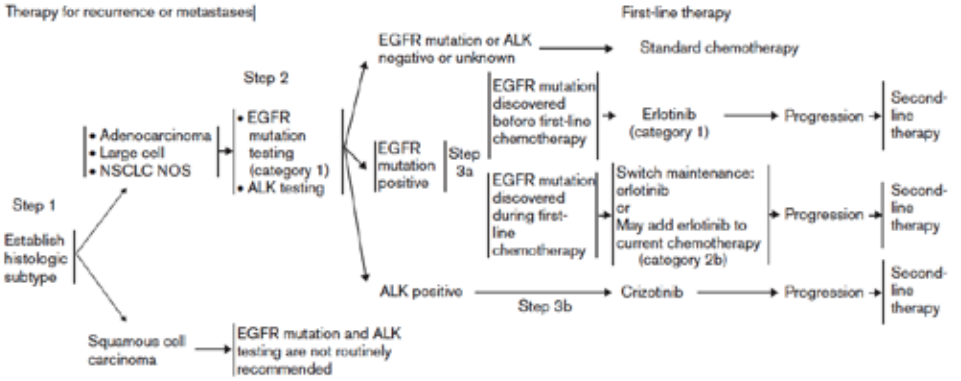
- EGFR mutations and EML4-ALK are mutually exclusive mutations
- EGFR mutations and KRAS mutations are usually mutually exclusive

Sufficient tissue?
- The processing and quality of tissue is crucial
- For cytology, specimens can be used for molecular testing when appropriately processed including generation of a cell block
- As few as 100 cells may be sufficient to detect EGFR mutations and as few as 50 cells to detect the presence of ALK gene rearrangements
- Tumour cellularity is important and is the most significant factor for test success regardless of whether a cytology or pathology specimen is used

How to test and when to test
- In Ontario, physicians are requesting testing of both EGFR mutations and EML4-ALK fusion gene through **www.egfr-canada.ca**
- There are two tests centres—Toronto and Hamilton
- Testing may take 2-3 weeks on average
- As lung cancer patients often do not have weeks of time to wait before initiating therapy, the earlier the testing is done, the better
- Ideally, testing should be done for all lung cancer pathology routinely at first diagnosis much like ER/PR/Her2neu is done routinely on all breast specimens

Conclusion
- Discovery of the EGFR mutation and EML4-ALK has changed the management of lung cancer
- The use of EGFR TKIs in unselected population is ill advised, especially in the first-line setting and in combination of chemotherapy
- Many more targeted agents are currently under investigation
- The future seems bright for lung cancer patients

Take-home message
1. All patients with non-squamous pathology should be tested for EGFR mutations and EML4-ALK fusion gene
2. All EGFR mutation-positive patients should be treated with a EGFR TKI as first-line therapy, followed by platinum doublet as second line and pemetrexed as third line, if suitable
3. Some indication to test patients who are never smokers with squamous pathology, as possibility that mixed histologies could exist
4. Treat with EGFR TKIs until proven progression and ready to start chemotherapy—given concerns for rebound growth once stopping EGFR TKIs
5. Molecular profiling of the tumour will likely dictate future clinical trials in lung cancer. Studies in unselected patient population will likely decline in number
6. Overcoming EGFR TKI resistance is a challenge. Several drugs are currently being investigated
7. Figure 4 below is NCCN practice guidelines—please note, currently Ontario government does not cover switch maintenance with erlotinib, nor the use of second-line erlotinib in those given first-line platinum doublet, as they will disallow coverage of third-line pemetrexed. Hopefully changes are in the works to conform to the NCCN guidelines in the future.



Therapy for recurrence or metastases. After the lung cancer histology is identified (step 1) as being nonsquamous, non-small-cell, epidermal growth factor receptor (*EGFR*, and *ALK* testing is recommended (step 2). Positivity for *ALK* mandates treatment with crizotinib (step 3B) as a first-line choice, positivity with the EGFR mutation mandates incorporation of erlotinib into the treatment protocol either as the first-line agent or as an adjacent agent (step 3A). Adapted and reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small-Cell Lung Cancer (V.2.2012). © 2012 National Comprehensive Cancer Network Inc. Available at: NCCN.org. Accessed [1 March 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Figure 4.

Hormone receptor positive metastatic breast cancer in postmenopausal women

HOT SPOT

By Kathy I. Pritchard, MD, FRCPC, FACP, Professor, Division of Medical Oncology, Department of Medicine, University of Toronto, Senior Scientist, Sunnybrook Research Institute

- 22,700 Canadian women will be diagnosed with breast cancer in 2013
- 70–75% of breast cancers are hormone receptor-positive (HR+)
- Aromatase inhibitors (AIs) have improved outcomes in postmenopausal women in both adjuvant and metastatic settings

Sequential endocrine therapy (ET)

- Aromatase inhibitors are important options in sequential endocrine therapy (ET) with:
  - Selective estrogen receptor modulators (SERMS)
  - Steroidal aromatase inhibitors (AIs)
  - Estrogen receptor downregulators (SERDs) such as fulvestrant

  remain current standard of care for postmenopausal women with HR+/human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC)
- Exemestane, fulvestrant, and the addition of mTOR inhibitors to ET have been assessed in phase III trials

Overview of clinical trial outcomes for HR+/HER2- ABC patients resistant to NSAI therapy

There are four Phase III trials involving 2,876 patients, including EFECT, SoFEA, CONFIRM and BOLERO-2, which assess the efficacy of various treatment options in this clinical setting, using PFS as the primary end-point.

- Standard dose fulvestrant (F250) and EXE are of comparable efficacy
- Adding an AI to F250 does not improve outcomes
- Doubling the dose of fulvestrant (F500) or adding everolimus to exemestane produces significant improvements in progression-free survival (PFS) compared with associated control treatments

CONFIRM Trial

Patients receiving F500 compared with those receiving F250 experienced:

- 20% reduction in the risk of progression (HR=0.80, 95% CI=0.68, 0.94)
- Incremental gain in median PFS of 1.0 month (6.5 months versus 5.5 months, p=0.006)
- No increase in toxicity

BOLERO-2 Trial

Patients receiving EXE+EVE compared to EXE+Placebo experienced:

- Reduction in the risk of progression of between 57% and 64% (locally and centrally assessed, HR=0.43, 95% CI=0.35, 0.54 and HR=0.36, 95% CI=0.27, 0.47)
- Net gain in median PFS of between 4.1 and 6.5 months (locally and centrally assessed, 6.9 months versus 2.8 months, p<0.001 and 10.6 months versus 4.1 months, p<0.001)
- At a median follow-up of 18 months, the overall survival (OS) data remained immature
- Higher rates of adverse events (AE) overall
  - Trial discontinuation due to toxicity (19% versus 4%)
  - Increased rates of serious AEs attributable to treatment (11% versus 1%)
  - Grade 3/4 stomatitis (8% versus 1%)
  - Infection (6% versus 2%) were the most common AEs associated with EVE+EXE

Treatment recommendations by patient group *(Figure 1)*

ET sensitive, indolent and low-burden disease

- Magnitude of clinical benefit supports the use of EVE+EXE
- May be of particular benefit in patients with bone-only disease
- Consideration should be given to patient age, functional status and co-morbidities
- Due to the increased risk of serious AEs with the addition of EVE to EXE, along with the potential for early onset of select AEs, careful proactive safety monitoring and toxicity management on EVE+EXE is strongly recommended

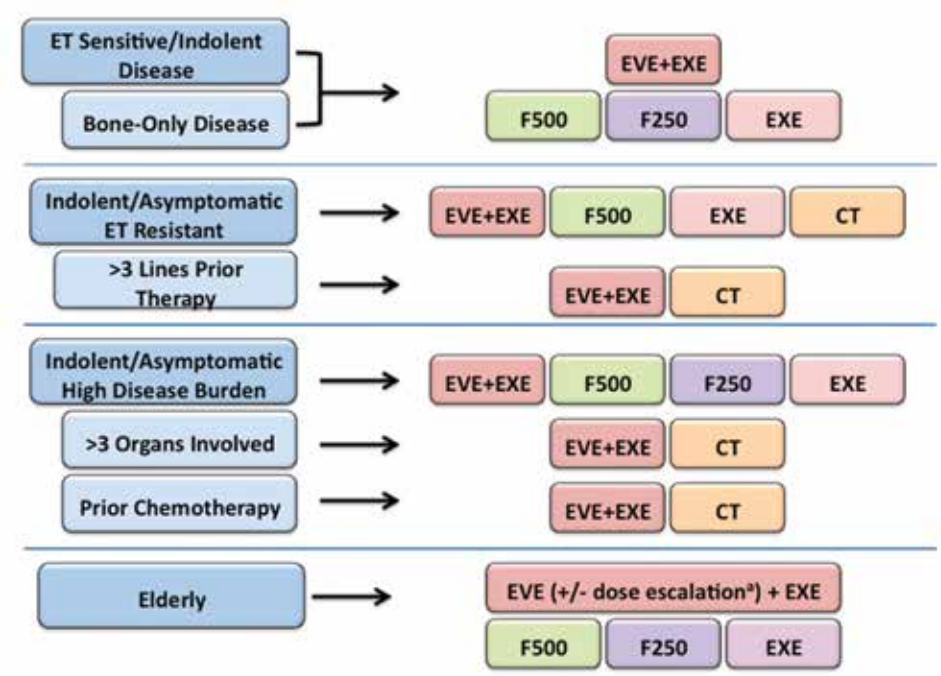


Figure 1: ET treatment guidelines for postmenopausal patients with HR+/HER2- ABC recurring or progressing on prior NSAI therapy[a]
Consideration should be given to a starting dose reduction of 5 mg daily, followed by potential dose escalation based on tolerance for patients older than 70 years, or for those with multiple comorbidities or frailties compromising overall health status.

ET resistant, indolent and low-burden disease

- More indolent progression and ET resistant disease can be treated with:
  - F500
  - EVE+EXE
  - Chemotherapy
  - EXE
- EXE+EVE is a good option with better tolerability and convenience relative to chemotherapy
- Chemotherapy remains the recommended treatment choice for patients with symptomatic visceral disease
- Patients for whom EVE+EXE is not well-tolerated, treatment with F500, EXE alone or chemotherapy should be considered

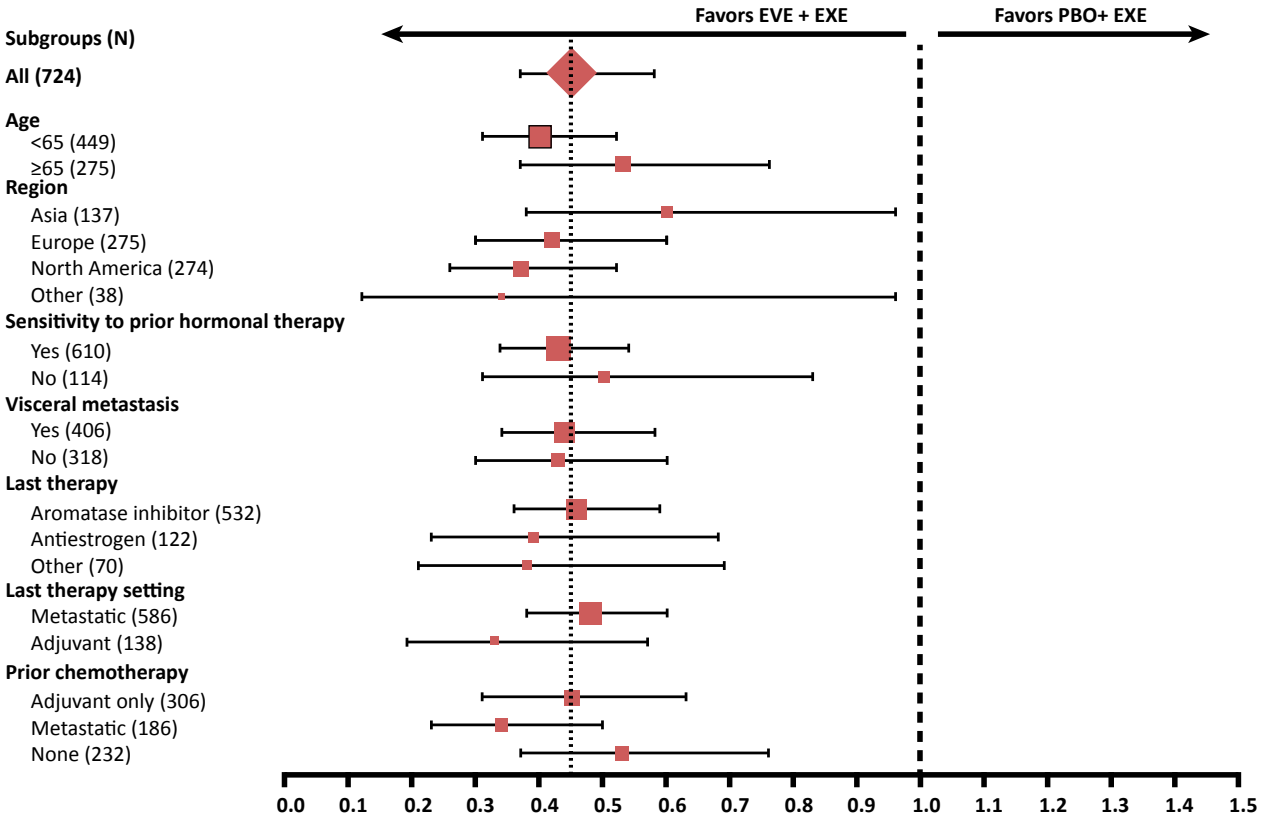
High-burden and indolent/asymptomatic disease

- Endocrine therapy is still the preferred option for HR+ ABC, even in the presence of visceral disease if it is asymptomatic or minimally symptomatic
- Chemotherapy is recommended for patients with rapidly progressive and symptomatic disease
- Patients with more indolent visceral disease or those who refuse chemotherapy may receive:
  - EXE
  - F500
  - EVE+EXE, along with a proactive safety management strategy

Elderly

- Elderly patients should be well-informed about the need for early toxicity reporting
- Thorough and proactive AE management
- Very elderly patients, or those with co-morbidities or compromised health status recommendation:
  - Dose escalation strategy of 5 mg and slowly increasing to a dose of 10 mg with demonstrated tolerance
  - In the event that an elderly patient is unable to tolerate EVE+EXE, the use of F500 or another ET regimen is encouraged

BOLERO-2 (18 month follow-up): PFS Subgroup Analyses



Baselga J, *et al. N Engl J Med.* 2012;366(6):520-9.

Figure 2: Forest plot of subgroup analysis in BOLERO-2

Conclusion

Sequential ET remains the goal of treatment for women with HR+/HER2-ABC who have recurred or progressed on prior NSAI therapy. Phase III trial results have demonstrated that:

- F250 and EXE are of comparable efficacy
- F500 and EVE+EXE produce statistically significant improvements in PFS compared to controls, with associated reductions in the risk of progression of 20% and 57% respectively

The rigor of evidence and the magnitude of clinical benefit support the use of EVE+EXE in most clinical cohorts (Figure 2). However, consideration should be given to:

- Patient's age
- Functional status
- Co-morbidities when selecting ET
- Use of a proactive EVE safety management strategy is encouraged

References available on request from the author.

NOVARTIS ONCOLOGY

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