HOT SPOT

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

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

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Editorial

By Dr. Edward Chow

Happy New Year. Welcome to the first issue of *Hot Spot* in 2012. On behalf of the Editorial Board, we wish all of our readers a prosperous and healthy year. In this issue, Dr. Sally Bean writes on who gets access to care: ethical obligations and the uninsured patients. Dr. Jeff Myers discusses when to refer to palliative care: distinguishing between the field of palliative care and palliative care-related clinical competencies. Dr. Albert Yee highlights the ongoing phase I clinical research on photodynamic therapy for vertebral metastases. Dr. Ewa Szumacher reminds us of the upcoming medical conferences. Ms. Angie Giotis talks about management of hand-foot syndrome. We have two inserts: one by Dr. Hans Chung on stereotactic body radiotherapy for liver metastases and the other by Dr. Susanna Cheng on angiogenesis as a target in treating non-small cell lung cancer. We hope our newsletter continues to be a useful resource to all of you and we're happy to hear your comments, too.

Congratulations to Dr. Carlo DeAngelis

We congratulate Dr. Carlo DeAngelis, PharmD, Clinical Pharmacy Coordinator–Oncology in the Department of Pharmacy at Sunnybrook Odette Cancer Centre, upon being appointed as a Pharmacy Clinician Scientist–Oncology at Leslie Dan Faculty of Pharmacy at the University of Toronto. This is a joint position with the university and is a first for the pharmacy profession in Canada.

Who gets access to care? Ethical obligations and the uninsured patient

By Sally Bean, JD, MA, Bioethicist & Policy Advisor, Sunnybrook Health Sciences Centre and the University of Toronto, Joint Centre for Bioethics

Envision the following hypothetical case: a 45-year-old male arrives at the emergency room and is diagnosed with a tear in his bowel caused by previously undetected colon cancer. Urgent surgery is provided to fix the tear and a follow-up course of chemotherapy is the recommended treatment. The patient has lived in Canada for 20 years without legal status and has worked as a labourer since his arrival. He does not have the financial ability to pay for his recommended cancer therapy, but will most certainly die soon if treatment is not provided. The patient does not have any family in his country of origin and cannot access oncology treatment there. Unfortunately, this is not an unusual scenario. Health care providers are

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In this issue of Hot Spot:

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frequently faced with decisions regarding whether an uninsured patient, a person currently without provincial health insurance coverage, will be given access to non-urgent (i.e., chronic) health care. In deciding whether to provide care, decision-makers must consider multiple competing factors. I will focus on the legal and ethical landscape health care providers must navigate when making decisions whether to treat uninsured patients.

The legal foundation for our current health care system, the Canada Health Act, RSC 1985, c. C-6, states, "the primary objective of Canadian health care policy is to protect, promote and restore the physical and mental well-being of *residents of Canada* and to facilitate reasonable access to health services without financial or other barriers." By basing health insurance eligibility on a person's residency status, there will be persons who do not meet residency requirements and are, therefore, currently ineligible for health insurance. Each province establishes its residency requirements for provincial health insurance eligibility. In Ontario, for example, OHIP coverage is currently based on a legal residency standard, which has two components: 1. Person resides in Ontario for 1 of 10 different qualifying conditions, AND 2. Person meets physical presence requirements, i.e., 90-day wait period and resides in Ontario for 153 days in a 12-month period.[1] There are two broad categories of uninsured patients who do not currently meet residency standards, out-of-country and resident uninsured. An out-of-country patient includes a tourist on vacation who falls ill, while an uninsured resident could be an eligible person awaiting the 90-day OHIP wait period or persons living here without legal status.

Based on the Canadian Medical Association's Code of Ethics (s. 18, 2004) and the Public Hospitals Act, RSO 1990, c P. 40 (s. 21), it is clear that ethically and legally, physicians and public hospitals are required to provide emergency care to uninsured persons. However, since there is no legal requirement to provide non-urgent care, treatments for chronic conditions that over time could even become life-threatening are typically not provided unless the uninsured patient has the ability to pay for medical care. Inability to pay can lead to devastating consequences for the patient who is unable to access health care. However, providing care to uninsured patients may have negative consequences for Ontarians seeking access to medical care by prolonging wait times. Additionally, if there is a pre-existing therapeutic relationship, physicians and health care institutions may feel obligated to provide pro bono non-urgent care to uninsured patients without the ability to pay. Finally, health care providers and institutions must also weigh potential liability implications such as an uninsured patient obtaining care in Ontario and returning to their home country to sue in a foreign legal jurisdiction.

Considering uninsured patients seeking non-urgent care from an ethics perspective entails weighing of competing duties and obligations to the uninsured patient, insured patients seeking access to care and the broader public health care system, and applying a fair and open process in making a decision. A health care provider must first use their professional clinical judgment to ascertain whether urgent or non-urgent care is required. If it is the former, they are legally and ethically bound to provide care irrespective of a patient's ability to pay. However, if it is the latter, then difficult decisions regarding whether to provide care must be made. Increasingly, some health care organizations have institutional protocols governing if and under what circumstances non-urgent uninsured patients can receive access to care. Institutional policy ideally promotes fair and consistent treatment of uninsured patients and alleviates the burden of health care professionals having to decide either without guidance or on a case-by-case basis. On one hand, deciding solely on a patient's ability to pay for services will further disadvantage many already vulnerable persons and adds a new element into the therapeutic relationship, i.e., the ability to pay for health services. However, on the other hand, decision-making based only on a patient's medical need could encourage system abuse and threaten ongoing sustainability of our health care system. Treatment decisions around whether uninsured patients will receive access to non-urgent care is a complex issue without an easy solution, but having an appreciation of the legal and ethical obligations is a solid starting point to address the issue.

*This article is adapted from a blog series written by Sally Bean on the topic of Uninsured Patients that appeared in Sunnybrook's The Grey Zone blog in 2011 (**http://yoursay.sunnybrook.ca/**).*

Reference

1. MOHLTC OHIP Eligibility Fact Sheet. 2009, April; Regulation 522 of Ontario's Health Insurance Act.

When to refer to palliative care: Distinguishing between the field of palliative care and palliative care-related clinical competencies

By Jeff Myers, MD, CCFP, MSEd, Head—Palliative Care Consult Team, Co-Program Head—Patient and Family Support Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre

As the term "palliative care" is used with increasing comfort, as part of the patient-care lexicon, advocacy efforts are being aimed towards "earlier palliative care referral". Our institution's Palliative Care Consult Team (PCCT) members are more frequently being asked, "When is a palliative care consult appropriate?" From my perspective, the answer to this question is not straightforward, as a description such as "the provision of end-of-life care" is an inadequate representation of the breadth of knowledge and skills of palliative care clinicians.

What is meant by "palliative care-related clinical competencies"?

It has been proposed that clinical palliative care be categorized into three distinct levels. Skills and competencies considered to be at the primary level are those relevant to any clinical practice, regardless of both profession and level of expertise. In theory, these skills would be attained and maintained by every health care professional. Secondary palliative care then refers to specialist clinicians and organizations providing specialty care, which is often in the form of palliative care consultation. Finally, tertiary palliative care refers to the palliative care practised at academic centres where the specialist knowledge about complex clinical issues is also researched, translated, exchanged and taught.

Leaders in the field of palliative care are currently endeavouring to clearly define and describe primary level palliative care-related competencies for various clinical contexts. Irrespective of context, however, among these would be competencies such as basic symptom management, communication skills and effective goals of care discussions.

When should a particular patient be referred for a palliative care consultation?

For the Sunnybrook PCCT, we strongly endorse a shared model of care delivery and advocate for our involvement in the care of patients for whom palliative care-related clinical issues reach a level of complexity beyond the "primary" category. Admittedly, this generates an additional layer of difficulty when attempting to clearly label clinical issues as being "palliative care-related". This is best explained through the example of "pain management", as the necessary skill set differs substantially based on the clinical context. For a man with prostate cancer and pain secondary to bone metastases, primary level palliative care-related competencies would include initiating routine and/or breakthrough opioids, addition of a neuropathic agent, if indicated, and maintaining an iterative discussion addressing the implications of metastatic disease. Following implementation and evaluation of the plan, if pain persists or worsens, we would encourage a referral for palliative care consultation. The ideal intent would be for ongoing shared care as "secondary" level competencies for this scenario are most likely required. If the main concern for the patient is not bony pain but, in fact, pain related to a separate etiology (e.g., migraines, chronic low back pain, fibromyalgia, osteoarthritis), despite having a life-limiting illness, in the setting of an otherwise stable patient the chronic pain issue would not be viewed as appropriate for palliative care consultation. Chronic pain management is a different specialty unto itself and although a certain amount of overlap exists, it is critical to acknowledge there are key differences between the two.

As a team, we sincerely hope to have our knowledge and skills accessed and utilized to the extent we are involved in more than care at the end of a patient's life. A different way to provide guidance around when to seek the input of a palliative care clinician, perhaps the two best dividing lines for our involvement in any symptom (e.g., complex or refractory pain, breathlessness, fatigue, nausea, distress, family dynamics, etc.) are first, whether the symptom is directly related to the underlying life-limiting illness and second, from the perspective of their underlying illness whether a patient is stable or there is overall progression towards the end-of-life phase. In the setting of an essentially stable patient, the palliative care team would generally not get involved with symptoms not directly related to the underlying life-limiting illness. However, if a specific symptom directly attributable to the illness has not responded to basic interventions, a palliative care consultation would be highly appropriate, even if the patient were otherwise stable from their underlying illness. Admittedly, this may leave one with the sense of a fairly substantial "grey zone". This is the precise reason why the PCCT encourages and is open to a dialogue about specific patients, as it is only through these kinds of conversations we will all gain a better understanding as to when a palliative care clinician could and should provide input.

Photodynamic therapy (PDT) for vertebral metastases: A prospective phase I clinical trial

By Dr. Albert Yee, MD, MSc, FRCS(C), Spine Surgeon, Sunnybrook Health Sciences Centre, University of Toronto

Background

An estimated 10 per cent of primary breast, prostate, lungs, thyroid and renal cell tumours metastasize to the spine. These lesions are extremely painful and significantly affect the quality of life of advanced stage cancer patients. The majority of these tumours are detected before surgical intervention is required and most patients receive radiation therapy for their spine lesions for symptomatic relief. However, complete pain control, duration of pain control along with a high recurrence rate of lesions and soft tissue complications makes radiation a less than an ideal treatment. In addition, pre-operative radiation therapy is a significant negative prognosticator for surgical outcomes. To improve the treatment options for patients with advanced cancer with spinal lesions we investigated a new minimally invasive therapy, known as photodynamic therapy (PDT) that targets metastatic spine lesions directly and has limited side effects.

Patient selection

This project aims to complement existing treatment for vertebral metastases. Patients eligible for the study include individuals with vertebral disease where vertebroplasty/kyphoplasty and minimally invasive surgical techniques are an option to help in restoring spinal stability.

Specifically, this trial does not impact available treatment that is a current clinical standard. Patients may have either failed radiation therapy, or radiation therapy/radiosurgery may be a component of planned treatment. We are interested in patients who may be eligible for spinal surgery/vertebroplasty/kyphoplasty (where PDT will be applied as a single treatment adjunct at the time of surgery).

The procedure

PDT involves the use of a photo-activated chemotherapeutic agent given intravenously that, when stimulated by non-thermal wavelength-specific light, allows for selective ablation of tumour tissue. We intend to demonstrate that PDT is a minimally invasive method with low morbidity and mortality by which spinal tumours can be ablated and later stabilized through vertebral osteoplasty, optimizing quality of life and providing effective treatment. One of the challenges of PDT is the ability to deliver light to the target location. Vertebral osteoplasty (i.e., vertebroplasty, kyphoplasty) is used clinically for the treatment of painful osteoporotic compression fractures of the spine and spinal metastases. This MIS surgical technique allows for direct injection of bone cement into the vertebral body to augment the vertebra's mechanical strength, which subsequently affords the surgeon access to the vertebral body with limited exposure. The technique can be readily adapted to allow intra-vertebral placement of small-diameter optical fibres coupled to a laser source for direct illumination of metastatic lesions for vertebral PDT. As vertebral osteoplasty is directed towards mechanically stabilizing diseased vertebra with less consideration in ablating local tumour tissue, our approach is attractive in that applying vertebral PDT at the time of osteoplasty will treat local tumour tissue biologically and may additionally improve upon the success and longevity of vertebral osteoplasty.

As this trial is the first application of PDT for vertebral metastases with the goal of evaluating safety and efficacy, the first six patients recruited will receive light only, without the drug. This will provide the team with additional light transmission and attenuation data in human diseased bone. Thanks to the collaboration of investigators from the Bone Metastasis Clinic and the Rapid Response Radiotherapy Program (RRRP), Odette Cancer Centre at Sunnybrook Health Sciences Centre, we have screened several patients for eligibility. To date, we have enrolled one patient and have successfully applied the laser portion of the PDT treatment as an adjunct to vertebral osteoplasty. Please refer eligible patients to the bone metastases clinic at Sunnybrook Odette Cancer Centre.

Inclusion Criteria:	**Exclusion Criteria:**
• Osteoplasty will be directed to a targeted vertebral level • No neurologic compromise • Symptomatic with axial pain from vertebral metastatic involvement and are at risk for pathologic fracture and eligible for vertebral osteoplasty (i.e., percutaneous vertebroplasty, kyphoplasty) • Symptomatic pathologic fracture without spinal canal compromise or neurologic deficit that are eligible for vertebral osteoplasty • Age between 20 and 85 with established metastatic vertebral bony disease in the spine • Radiographic progression and/or pain symptoms of a documented vertebral metastasis despite non-surgical therapies	• Progressive neurological compromise • Purely osteoblastic vertebral metastatic disease • Active central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, requirement for corticosteroids and/or progressive growth. CNS metastases must be stable for > 2 weeks prior to screening) • Inability to avoid sun exposure for 5 days post-PDT therapy (per Verteporfin precautions) • Cognitive impairment and/or language barriers to study participation • Severe hepatic impairment (Child's C) with active hepatitis or hepatic disease • Anticipated life expectancy of less than twelve weeks • Nursing mothers, pregnant, currently breastfeeding or trying to get pregnant • Asymptomatic for vertebral metastatic disease • Hyperphotosensitivity conditions, including porphyria • Hypersensitivity to Verteporfin or any other ingredients of Visudyne

Management of hand-foot syndrome

By Angie Giotis, BScPhm, ACPR

Hand–foot syndrome (HFS), also called palmar–plantar erythrodysesthesia (PPE), is a dermatologic toxic reaction associated with certain conventional chemotherapeutic agents (e.g., 5-fluorouracil, capecitabine, cytarabine, docetaxel, doxorubicin, pegylated liposomal doxorubicin). More recently, hand-foot skin reaction (HFSR) has been described with multi-targeted tyrosine kinase inhibitors (MKI) (e.g., sunitinib, sorafinib). The mechanism of HFS and HFSR is still unknown and may vary depending on the agent. It may be related to increased metabolism of the agents via keratinocytes, drug accumulation in the skin through excretion by sweat glands, may be cytokine-mediated, or may be an indirect effect of inhibition of proangiogenic pathways. The damage caused to deep capillaries in the soles of the feet and palms of the hands leads to a COX inflammatory-type reaction.[1]

Incidence of HFS with conventional chemotherapy ranges from 6% to 68% with a typical onset after one to 21 days of treatment, and up to several months with continuous low-dose therapies. The incidence of HFSR with MKI therapy has been reported to be between 9% and 62% and typically develops within the first one to three months after initiation of therapy. With classic HFS initial symptoms are dysesthesia and tingling in the palms, fingers and soles of the feet with erythema, which may progress to burning pain with dryness, cracking, desquamation, ulceration, edema and rash. The palms of the hands are more frequently affected than the soles of the feet, and HFS can uncommonly affect other parts of the body. Although HFSR initially presents like HFS, it is not diffuse but, instead, lesions are localized to areas of trauma or friction such as joints, tips of fingers, toes, and heels. Lesions may progress to blisters or hyperkeratotic callus-like plaques and can display a surrounding erythematous halo.[1] HFS has been observed to be more common in black patients than in white patients. Blistering and ulceration are often preceded by hyperpigmentation and thickening of the skin and it has been proposed that a different grading system be used to account for these characteristics.[2]

Without prompt management, HFS can progress to an extremely painful and debilitating condition potentially leading to infection and worsened quality of life. With more patients being prescribed oral agents for home use, it is important that patients understand the importance of adhering to treatment and prevention strategies, and informing their doctor or health care team immediately when symptoms of HFS appear.

Prevention measures include minimizing stresses on the skin such as friction or heat, and wearing comfortable, loose-fitting clothes, shoes and gloves. Moisturizing the affected area by applying emollients or soaking in cool to lukewarm water and then applying petroleum jelly may help. Elevating the hands and feet can help reduce edema. Any cuts or scrapes require prompt attention to prevent infection. Liquid bandages have been used in patients experiencing fissures caused by dry skin associated with EGFR inhibitors and may also help mend broken skin in patients experiencing HFS.

There is anecdotal evidence for local treatments such as topical anesthetics, steroids and keratolytic agents like urea. A recent study in metastatic breast cancer patients showed pyridoxine was effective for the prevention of HFS associated with capecitabine compared to historical controls. However, randomized clinical studies have shown no benefit and it cannot be recommended for routine preventative use.[3] The COX-2 inhibitor celecoxib, has been studied for the prevention of HFS with inconclusive results. However, a recent study comparing oxaliplatin/capecitabine ± celecoxib to capecitabine ± celecoxib 200 mg/m^2 twice daily for 14 days of a three-week cycle, showed significant reduction in both Grade 1 and 2 HFS (grade 1: 29% vs. 52% P = 0.025, grade 2: 11.76% vs. 30% P = 0.024).[4]

Once established, the most effective management of HFS is treatment interruption, dose reduction or discontinuation. Patient education is a critical component in managing HFS and HFSR and should include preventative strategies and early detection to allow for optimal management.

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2. Saif M. Capecitabine and hand-foot syndrome. Expert Opin. Drug Saf. 2011;10(2):159–169.
3. Yoshimoto N, et al. Impact of prophylactic pyridoxine on occurrence of hand-foot syndrome in patients receiving capecitabine for advanced or metastatic breast cancer. Breast Cancer. 2010;17:298–302.
4. Zhang RX, et al. The effect of COX-2 inhibitor on capecitabine-induced hand-foot syndrome in patients with stage II/III colorectal cancer: A phase II randomized prospective study. J Cancer Res Clin Oncol. 2011;137(6):953–957.

Continuing Medical Education 2012–2013

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**

- **February 4–6, 2012**
  The 6th World Congress World Institute of Pain
  http://www2.kenes.com/wip/Pages/Home.aspx?gclid=CMKpusXf2awCFQd_5Qod8HDbrg
- **February 23–25, 2012**
  Palliative Medicine and Supportive Oncology 2012– The 15th Annual Symposium
  http://www.clevelandclinicmeded.com/live/courses/2012/pm12/overview.htm
- **March 14–16, 2012**
  The 9th Palliative Care Congress
  http://www.pccongress.org.uk/
- **April 29–May 1, 2012**
  Annual Hospice Palliative Care Ontario Conference
  http://hpcconference.on.ca/
- **June 1–5, 2012**
  2012 ASCO Annual Meeting
  http://www.eurolink-tours.co.uk/Oncology_congress/2012-asco-annual-meeting-1-860.html
- **June 4–6, 2012**
  International Death, Grief and Bereavement Conference: Hospice and Palliative Care
  http://www.uwlax.edu/conted/dgb/
- **June 7–9, 2012**
  8th Annual Advanced Learning in Palliative Medicine Conference
  http://www.ubccpd.ca/Events/CPD_Conferences/8th_Annual_Advanced_Learning_in_Palliative_Medicine_Conference.htm
- **June 10–12, 2012**
  International Conference on Opioids (ICOO)
  http://www.pnpco.com/13098.pdf
- **August 27–30, 2012**
  World Cancer Congress
  http://www.worldcancercongress.org/
- **October 9–12, 2012**
  19th International Congress on Palliative Care
  http://www.palliativecare.ca/en/
- **October 28–31, 2012**
  ASTRO's 54th Annual Meeting
  http://www.astro.org/Meetings/AnnualMeetings/index.aspx
- **November 22–25, 2012**
  The 2nd International Multidisciplinary Forum on Palliative Care
  http://www.imfpc.org/

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Stereotactic body radiotherapy for liver metastases

HOT SPOT

Hans T. Chung, MD, FRCPC, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto

Surgical resection remains the standard of care for liver metastases. For unresectable lesions, stereotactic body radiotherapy (SBRT) is rapidly emerging as an attractive option. As compared to radiofrequency ablation, another form of nonsurgical local treatment, SBRT is completely non-invasive. Unlike conventional radiotherapy, the objectives of SBRT are to escalate the dose to the target lesion and, thus, improve local control while limiting dose to nearby critical structures and, thus, reduce complications. The fundamental prerequisites for optimal delivery of SBRT are precise localization of the target lesion; account for tumour motion due to respiration; generate a treatment plan to deliver highly conformal radiation to the target volume with a sharp dose gradient to maximize liver sparing; and image-guidance at the time of radiation delivery.

SBRT has been applied to metastatic disease in the brain, spinal cord, bone, liver and lung. SBRT is generally limited to patients with oligometastases, which is defined as one to five metastatic deposits in the entire body.

Intent of SBRT is for either:

1. debulking of dominant lesions prior to systemic treatment
2. consolidative treatment of large lesions that are not responsive to systemic treatment, and
3. definitive treatment for oligometastases.

Background

- Recently, two pivotal prospective studies reported the safety and efficacy of SBRT for liver metastases
- In the Princess Margaret Hospital study, 70 patients were enrolled in a phase 1 study to evaluate the safety and efficacy of a six-fraction regimen. The radiation dose was individualized based on the volume of irradiated liver, and corresponding risk of radiation-induced liver disease (Lee et al., 2009)
  - Acute toxicities: Only six patients had grade 3 toxicities (elevation of liver enzymes, gastritis, nausea). Among grade 2 toxicities, 12 (18%) patients had elevation of liver enzymes, 5 (7%) had gastritis, 12 (18%) had lethargy, 4 (6%) had nausea, 3 (4%) had liver pain
  - No dose-limiting toxicities or radiation-induced liver disease was observed
  - Late toxicities: one grade 4 duodenal bleed; one grade 5 malignant small bowel obstruction due to tumour progression and invasion into duodenum; one grade 4 small bowel obstruction through an abdominal hernia; two grade 2 non-traumatic rib fractures
  - Local control at one year was 71%.
- In a multi-institutional phase I/II study from the USA, 47 patients received 60 Gy in three fractions. Based on surgical literature, the protocol specified that at least 700 cc of normal liver should receive less than 15 Gy (Rusthoven et al., 2009)
  - No radiation-induced liver disease, grade 4–5 toxicities or bleeding/thrombotic complications observed with subsequent bevacizumab. One patient had grade 3 soft tissue toxicity with skin breakdown in the anterior abdomen. Grade ≥ 3 toxicity was 2%
  - Local control was 95% and 92% at 1y and 2y, respectively. In subset analyses, lesions with maximum diameter of 3 cm or less had a 2y local control rate of 100%, compared to 77% for lesions greater than 3 cm
- Acute side effects may include fatigue, nausea, vomiting, heartburn, loss of appetite and chest wall pain
- Potential late complications include radiation-induced liver disease, stomach or duodenal ulcer, elevated liver function tests, bowel obstruction, gastrointestinal bleeds, rib fracture and biliary sclerosis. The risk of any of the above grade ≥3 late complications is less than 5%.

Eligibility

Patients potentially eligible for SBRT for liver metastases at the Odette Cancer Centre include the following:

- one to three liver metastases from any solid tumour except a germ cell tumour or lymphoma
- inoperable or medically unsuitable for resection

Generously supported by an unrestricted educational grant from Roche.

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Stereotactic body radiotherapy for liver metastases

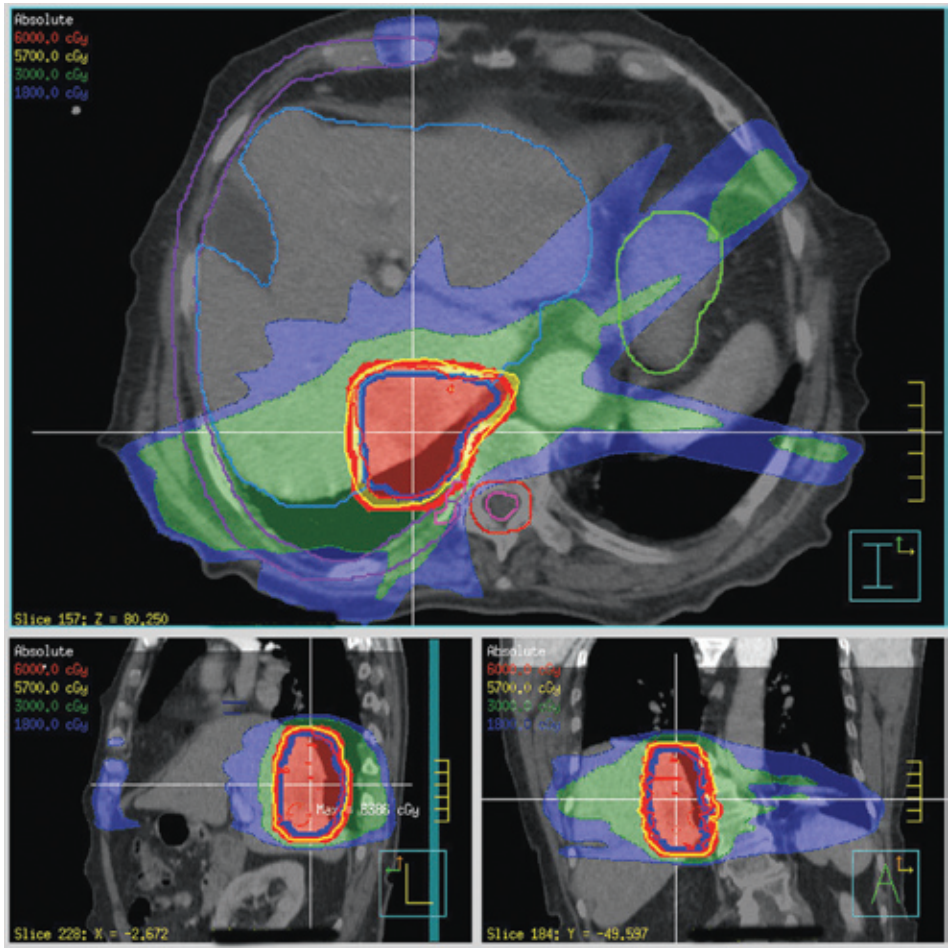

Figure 1.

- maximum tumour diameter ≤ 6 cm
- ≥ 800 mL uninvolved liver, Child's A liver score
- KPS ≥ 60%, life expectancy ≥ 3 months
- no chemo two weeks before to four weeks after SBRT.

Patient set-up

- Different techniques to address tumour motion have been described, but they can be broadly divided into motion-restrictive and motion-compensating approaches. The former includes techniques that limit respiratory motion, such as abdominal compression devices or breath holding. The latter includes techniques that account for respiratory motion, such as respiratory gating or real-time tumour tracking.
- Patients undergo a planning 4D-CT scan with contrast, which is often fused with the diagnostic scans to facilitate tumour delineation. A 4D-CT allows us to evaluate liver and target motion with respiration.

Target definition and dosimetry

- Target volumes and organs at risk (i.e., kidneys, liver, spinal cord, chest wall, stomach, heart) are contoured by the radiation oncologists.
- A radiation plan is then generated using pre-established dose-constraints to organs at risk (see Figure 1). No consensus prescription dose has been made, but the majority of studies have used 30 Gy to 60 Gy in at least two fractions.

Positional verification on treatment day

- On the day of treatment, the patient is immobilized in the same manner as the planning CT scan. An on-board x-ray volumetric imaging system (i.e., cone-beam CT scan) scans the patient. These scans are compared with the planning CT scan to check for positional differences. Any differences are corrected before starting treatment.

For clinic referral, please call 416-480-4205 for Dr. Hans Chung or Dr. William Chu.

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Angiogenesis as a target in treating non-small cell lung cancer (NSCLC)

Susanna Cheng, MD, FRCPC, Medical Oncology, Sunnybrook Odette Cancer Centre, University of Toronto

HOT SPOT

- Lung cancer is the leading cause of cancer deaths in both women and men worldwide
- NSCLC accounts for approximately 85% of all lung cancer cases
- significant advancements have been made in the treatment of NSCLC over the last decade, but prognosis for advanced stage disease remains poor with median survival ranging between 10 and 13 months with first line treatment
- with an increased understanding of tumour biology and discovery of novel agents that target specific pathways such as angiogenesis, there is an opportunity to further improve the outcomes of patients with advanced NSCLC

Angiogenesis and cancer

- Angiogenesis is a pathological adaptation of a normal biologic process by tumour cells to gain survival advantage
- by altering the dynamic balance between proangiogenic and antiangiogenic factors, solid tumours attain the capacity to grow beyond a size that otherwise would be unsustainable with normal vasculature
- VEGF induces the proliferation, migration, and survival of vascular endothelial cells and stimulates the recruitment of bone marrow-derived endothelial progenitor cells to the new vessels
- there is a multitude of physiologic pro-angiogeneic factors including fibroblast growth factors (FGF), epidermal growth factors (EGF), matrix metalloproteinases (MMP), placental growth factor (PGF) and platelet-derived growth factor (PDGF)
- the most important proangiogenic factor is the vascular endothelial growth factor (VEGF), which drives the rate limiting step in both physiologic and pathologic new vessel formation
- VEGF has five isoforms - VEGF A, -B, -C, -D and -E
- VEGF has generally been used to refer to the VEGF A isoform
- the biologic action of VEGF is mediated through its interaction with surface VEGF receptors of which there are three members: VEGFR 1, -2 and -3

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VEGF and NSCLC

- VEGF expression has been observed in all forms of NSCLC, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma
- studies have shown that the degree of tumour-associated angiogenesis correlates with disease progression and serves as a marker of unfavourable survival outcome
- a recent study suggests a correlation between VEGF and nicotine, a carcinogen linked to lung cancer

Bevacizumab (Avastin) and NSCLC

- Anti-angiogenesis therapy is one of the most active areas of clinical investigation in NSCLC
- only intervention in the first-line treatment of advanced NSCLC that has led to a major improvement in survival outcomes (two months) in the last five years
- Avastin is a full humanized monoclonal antibody that binds VEGF-A
- Avastin results in a more mature vasculature that is thought to facilitate the delivery of chemotherapeutic agents by decreasing microvascular permeability and decreasing intra-tumoural pressure, which may explain why bevacizumab acts synergistically with cytotoxic or other targeted agents (Figure 1)

Bevacizumab in combination with chemotherapy

- **ECOG phase III study (E4599)** of carboplatin and paclitaxel (CP) with or without bevacizumab (15 mg/kg) was a pivotal study enrolling 878 patients with recurrent and advanced (stage IIIB and IV) NSCLC (Figure 1)
- patients were randomized to receive chemotherapy alone (n=444) or chemotherapy plus bevacizumab (n=434)
- patients without progressive disease (PD) after induction therapy in the CP+bev arm continued to receive bevacizumab until PD or unacceptable toxicity
- median overall survival (OS) of 12.3 months, 10.3 months in favour of bevacizumab (HR 0.79; 95% CI, 0.67 to 0.92; p=0.003)
- median progression-free survival (PFS) of 6.2 versus 4.5 months (HR=0.66; 95% CI, 0.57 to 0.77; p<0.001)
- response rate of 35% versus 15% (p<0.001) in favour of the bevacizumab containing arm

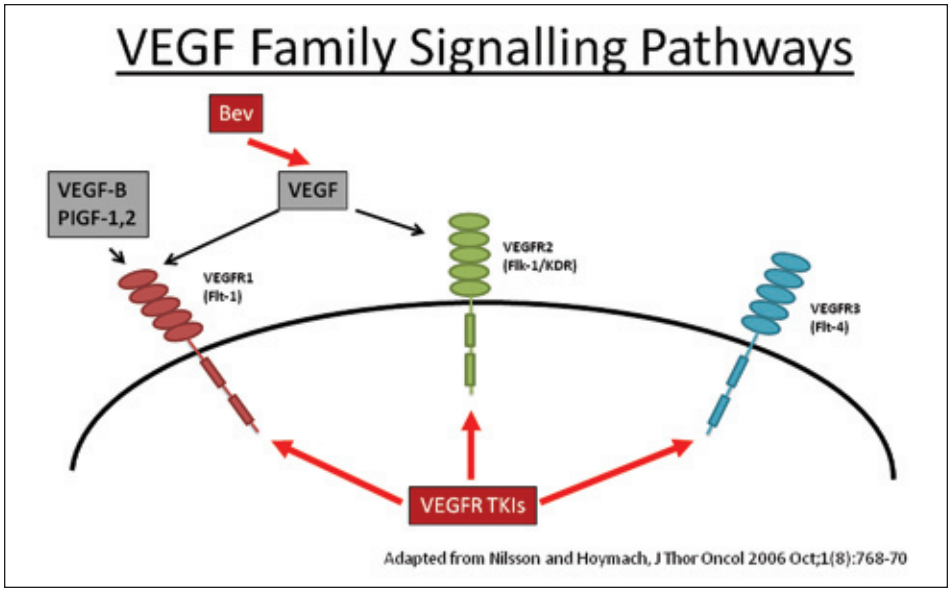

Figure 1.

- incidence of adverse events such as bleeding, hypertension, proteinuria, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash and headache were significantly higher among the patients treated with bevacizumab ($p < 0.05$)
- 15 of the 17 treatment-related deaths were recorded in the bevacizumab arm
- despite the deaths, the survival benefit in the overall patient population clearly outweighed the added toxicity risk, which led to the approval of this regimen by the FDA and Health Canada in 2006 and European Medicines Agency (EMA) in 2007 (Figures 2 and 3)
- **AVAil (Avastin in lung cancer) trial** was a three-arm phase III randomized trial conducted in Europe that evaluated two different doses of bevacizumab (7.5 mg/kg and 15 mg/kg) in combination with a different chemotherapy cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2
- a total of 1,043 patients were randomized to placebo (347), low-dose bevacizumab (n = 345) and high-dose bevacizumab (n = 351)
- PFS was 6.1, 6.5 and 6.7 months respectively in favour of the Avastin arms
- RR was 20%, 30% and 34%, again in favour of Avastin arms
- however, there was no OS benefit
- the reason for the failure of the AVAil to demonstrate a survival advantage has been ascribed to different factors including the use of a potentially more effective cisplatin combination chemotherapy regimen, the use of a three-arm trial design that was underpowered to detect a modest survival advantage and the lack of maintenance Avastin arm (Figure 4)
- Avastin has been studied with other chemotherapy combinations
- multiple phase II trials have established the safety and improved efficacy of bevacizumab when combined with other platinum doublets (carboplatin + docetaxel, carboplatin + pemetrexed)
- none have shown significant OS benefits, only PFS benefits

Targeting VEGF and EGFR

One treatment strategy being investigated is simultaneously targeting both VEGF and the epidermal growth factor receptor (EGFR).

- EGFR is an important stimulator of both tumour growth and angiogenesis in many cancer types, including NSCLC
- BETA Lung evaluated the anti-EGFR drug erlotinib (Tarceva®) with or without bevacizumab, as second-line therapy in NSCLC patients who had received no prior anti-VEGF or anti-EGFR therapy
- although patients who received the bevacizumab/erlotinib combination did not live longer compared with patients who got erlotinib alone, PFS time was doubled
- in a second phase III trial, called ATLAS, patients who were treated with bevacizumab and erlotinib following chemotherapy lived about a month longer (PFS) without their disease getting worse than patients who got bevacizumab alone. Overall survival time was not significantly improved

Promising results were reported from a phase II study that combined chemotherapy

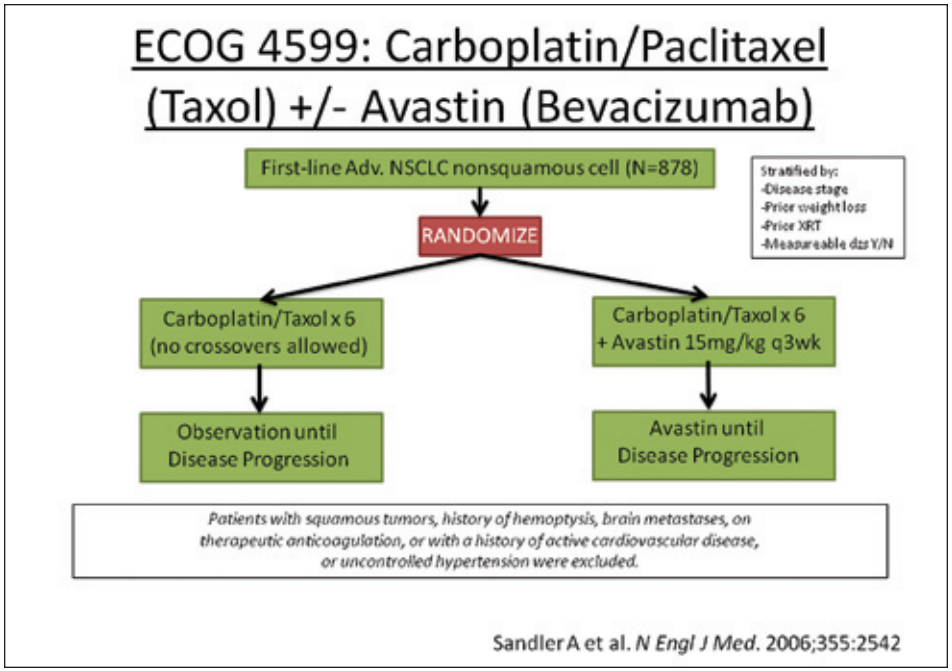

Figure 2.

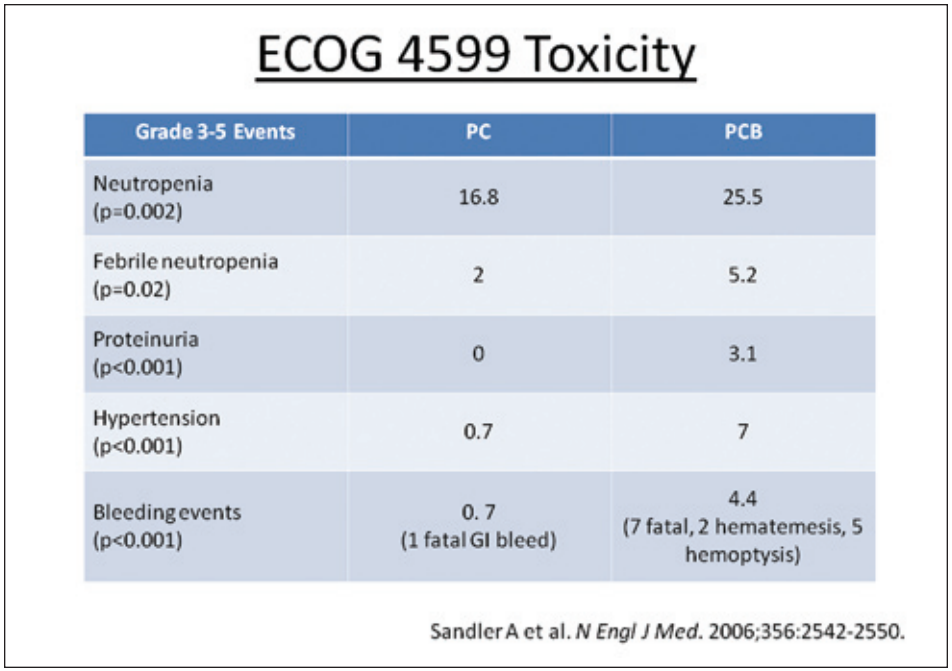

Figure 3.

with both bevacizumab and the anti-EGFR antibody agent cetuximab (Erbitux®).

- 54% of patients had at least partial tumour shrinkage, PFS and OS times were about seven months and 14 months, respectively
- a phase III trial using this treatment approach is forthcoming

New agents in development

A number of new antiangiogenic agents are in development for NSCLC. Please see Table 1 (page 4).

Safety issues of antiangiogenesis therapy in NSCLC

- Avastin is contraindicated in:
  - patients with squamous histology
  - untreated brain metastases
  - presence of hemoptysis
- VEGF inhibition may be associated with hypertension, impaired wound healing and, infrequently, gastrointestinal perforations, fistula formation, thromboembolic complications, and reversible posterior leukoencephalopathy
- Antiangiogenic therapies are rarely used in combination with radiation because of the danger of tracheoesophageal fistulas when these agents are combined with chest radiation
- Side effects from sunitinib or sorafenib therapy may include diarrhea, fatigue, nausea, stomatitis, hypertension, and mucosal inflammation
  - have also been associated with a number of dermatological toxicities, including hand-foot skin reaction and rash (primarily sorafenib), hair depigmentation (sunitinib), and subungual splinter hemorrhages (both agents)
  - Sunitinib has been associated with both pulmonary and cerebral hemorrhage
  - Sunitinib requires the monitoring for the development of hypothyroidism, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation

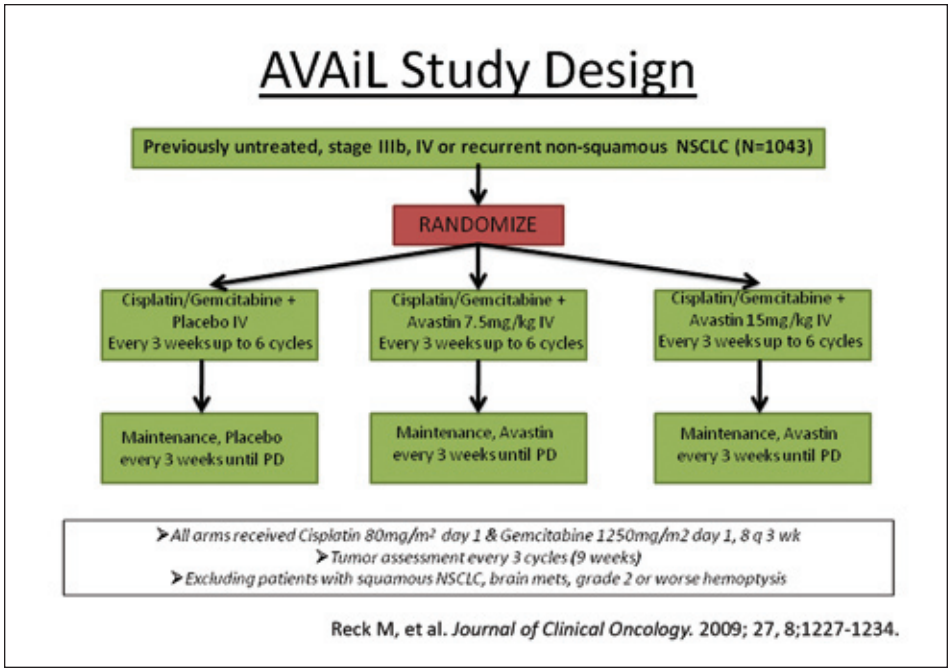

Figure 4.

Potential biomarkers for anti-VEGF therapy in NSCLC

- numerous studies have suggested **the development of hypertension** could be a marker of clinical response to BV therapy
- ECOG 4,599 trial included an analysis of the clinical course of patients who developed hypertension (defined as BP >150/100 at baseline or at the end of cycle 1 or an increase of >20 mmHg in diastolic BP between these two time points) during treatment
- the median OS among patients in the BV/chemotherapy arm who developed high blood pressure was 15.9 months (95% CI, 13.4 to 20.3 months) compared with 11.5 months for patients who did not have hypertension (95% CI, 10.4 to 13.4 months)
- ECOG 4,599 trial also analyzed the **expression of several single nucleotide polymorphisms (SNPs)** as marker of response to BV therapy
- results indicated that specific germ line polymorphisms were associated with improved response rates in the BV treatment arm
- patients with these polymorphisms had a 44% response rate to BV therapy versus 16% among patients without these specific SNPs

The role of Avastin in clinical practice

- greater than 70% of patients would **be ineligible** for frontline therapy with a bevacizumab-containing regimen based on the presence of one or more exclusion criteria employed in the E4599 trial
- the exclusion criteria were: poor performance status, brain metastasis, therapeutic anticoagulation, squamous histology, hemoptysis

The future

- patient selection is important for the optimal use of these agents
- it is highly desirable that predictive markers of response and/or toxicity be established to assist in the optimal selection of patients
- the presence of significant squamous differentiation on histologic evaluation remains the only established marker that predicts for increased risk of bleeding complications
- use of anti-VEGF as second- or third-line therapy or in the adjuvant setting remains to be determined
- to date, trials with most antiangiogenesis agents continue to show mixed results with modest benefits only

References

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2. Korpanty G, Smyth E, Carney DN. Update on anti-angiogenic therapy in non-small cell lung cancer: Are we making progress? J Thorac Dis. 2011;3:19–29. doi:10.3978/j.issn. 2072-1439.2010.11.11

Table 1. Anti- Angiogenic Drugs Under Investigation in NSCLC				
Name of drug	**Mechanism of action**	**Studies**	**Population**	**Results**
Motesanib	an oral angiogenesis inhibitor by targeting VEGFR -1, -2, and -3	MONET1 a randomized, placebo-controlled phase III trial of Motesanib for advanced NSCLC randomized to receive Carboplatin/ Paclitaxel plus either Motesanib (125 mg once daily; Arm A) or placebo (Arm B)	untreated patients with non-squamous NSCLC	Median PFS was 5.6 mos vs. 5.4 mos in favour of the motesanib arm (P=0.0006). Overall RR were 40% and 26% for the two arms, respectively (P<0.0001)
Ramucirumab	antibody against VEGFR-2	a phase II study	Pretreated patients	10 of 15 lung cancer patients (67%) saw tumour shrinkage
		a phase III trial is enrolling—patients will be randomly assigned to treatment with the chemotherapy drug Docetaxel, either with or without Ramucirumab		pending
BIBF 1120	an investigational triple angiokinase inhibitor that targets FGRF, PDGFR and VEGFR	phase III trials LUME lung 1—second line Docetaxel +/- BIBF1120 LUME lung 2—second line Pemetrexed +/- BIBF1120)	for NSCLC for patients who have relapsed or progressed on front line therapy	pending
Aflibercept	VEGF Trap is a soluble recombinant fusion molecule combining portions of the extracellular domains of human VEGF receptors-1 and -2 fused to the Fc segment of human immunoglobulin IgG1	VITAL phase III studies with Docetaxel in a multinational randomized study	failed one platinum-based line of therapy	pending
		phase II study in combination with Cisplatin and Pemetrexed		pending
VEGF Receptor Tyrosine Kinases Inhibitors: targeting the receptor tyrosine kinase activity of the VEGF receptor				
Sorafenib (oral agent)	targets threonine kinases c-Raf and b-Raf, the VEGFRs 1, 2 and 3, PDGRF, the proto-oncogene RET and c-KIT	phase II studies—Sorafenib 400 mg po bid • most frequent grade 3 treatment-related adverse events were hand-foot syndrome and hypertension • study in first line treatment	previously treated with not more than two regimens	produced no objective responses • 59% SD, median PFS was 2.7 mos and median OS was 6.7 mos failed to show any benefit and was closed prematurely
		phase II trial of Erlotinib +/- Sorafenib	previously treated with up to two prior chemotherapeutic regimens	showed improvement in PFS , even in squamous histology subset
		trials with Sorafenib with Carbo and Paclitaxel	first line treatment	suggested negative results due to interaction of Sorafenib with the pharmacokinetics of chemotherapeutic regimen
		NEXUS trial—Sorafenib + Cisplatin + Gemcitabine		Pending
Sunitinib (oral agent)	oral agent that inhibits VEGFR, PDGFR, c-KIT and RET	phase II studies	second or third line therapy	PFS 3 months OS 9 months
Vandetanib (Zactima)	multi-targeted TKI with potent activity against VEGFR-2, VEGFR-3, EGFR and RET	ZEST trial—Vandetanib vs. Erlotinib	salvage therapy in NSCLC who have progressed on frontline chemotherapy	no difference in RR or PFS or OS
		ZODIAC study—Vandetanib (100mg) combined with Docetaxel vs. Docetaxel alone		ORR was 17% vs. 10% p<0.001 but no difference in OS
		ZEPHYR—comparing Vandetanib to BSC in those who have progressed on chemo and EGFR inhibitors	pending	
Vascular Disrupting Agents				
Vadimezan DMXAA (5,6 dimethylxanthenone-4-acetic acid)	• selectively target newly formed tumour-associated blood vessels • shown to promote apoptosis of tumour blood vessel endothelial cells, resulting in the breakdown of tumour vasculature and hemorrhagic tumour necrosis	ATTRACT-1 phase II trial		failed to show benefit interim analysis resulting in early termination of the trial and discontinuation of the clinical development program in NSCLC