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

Volume 17, Issue 4, November 2015

Editorial
Dr. Cyril Danjoux, Sunnybrook Odette Cancer Centre, University of Toronto

The shorter, colder November days are ideal for a good read. We hope that you find the following articles in this issue of Hot Spot intellectually challenging and academically satisfying. Dr. Mary Vachon has been a contributor to Hot Spot since its inception. She informed us that she is stepping down as one of our valued contributors. We thank her for all her help with the RRRP and Hot Spot over the years. Her dedication and commitment was an inspiration for us. Her last article entitled Reflections on Empathic Distress Fatigue and Compassion summarizes her decade-long experience with stages of burnout caused by caregivers being overworked and having to cope with demanding clients. She leaves us with an encouraging message about new coping strategies to overcome empathic distress and strengthen resilience based on neural plasticity research.

Earlier this year a unanimous Supreme Court decision placed a one-year moratorium on professional regulatory bodies to implement policies for Physician Aid-in-Dying. In her timely article on Professional Obligations & Conscientious Objection in Physician Aid-in-Dying (PAD), Sally Bean, JD, MA, provides an analysis of how the colleges are addressing the difficult task of accommodating individual health care providers and health care institutions that may wish to conscientiously object to the provision of PAD while still enabling eligible patients to have reasonable access to Physiciain Aid-in-Dying.

Screening for post-traumatic stress disorder in cancer patients by Christina Crowe, HBSc., MA, Counselling Psychology, reviews the recent changes in classification of post-traumatic stress disorder. As research improves our knowledge of cancer, as a traumatic event, we may continue to better define screening, diagnosis and treatment measures to help patients cope with their symptoms.

General Practice from Delivery Room to Hospice: The Role of the GP in End of Life Care by Leila Gaind, Teri Crockford CNS, Marissa Slaven, MD, Palliative Care, McMaster University, addresses the impact of increased demand for hospice palliative care due to demographic changes, on specialized palliative care workers, and offers a possible model to involve family physicians in end-of-life care.

You may find the list of CME and upcoming meetings helpful in planning your academic education.

The insert by Dr. Parneet Cheema offers an update on non small cell lung cancer from the World Conference on Lung Cancer 2015. A second insert by Drs. Xiao Zhu and Yooj Ko is titled Latest advances in colorectal cancer: An update on new therapies for refractory CRC and Regorafenib toxicity management.

Enjoy the November issue of Hot Spot.

In this issue of Hot Spot:

Editorial
Reflections on empathic distress fatigue and compassion
Professional obligations and conscientious objection in physician assisted dying
Screening for post-traumatic stress disorder in cancer patients
General practice from delivery room to hospice: The role of the GP in end-of-life care
Continuing Medical Education 2015

Inserts
World Conference on Lung Cancer 2015—Non-small cell lung cancer update
Latest advances in colorectal cancer: An update on new therapies for refractory CRC and regorafenib toxicity management
Reflections on empathic distress fatigue and compassion
By Dr. Mary Vachon, PhD, RN

Having been a contributor to Hot Spot since its inception, this will be my last column. I remain deeply committed to the field, but since my practice no longer involves as many palliative clients it seems time to “pass the baton”.

My involvement in palliative care dates from studying the stress of the staff at the Royal Victoria Hospital as the palliative care unit opened. Previously, my colleagues and I had studied the stress of the staff at Princess Margaret Hospital in the early 1970s. I felt blessed to be involved at the beginning of a new field. By my retirement patient and family care would be excellent. “Only” 50 years into my practice I have no thoughts of retiring. My hope is that the fact that I am not seeing as many palliative care clients reflects excellent palliative care. Sometimes what I hear convinces me that is true. At other times, I have to wonder. A young woman, whose husband died after a very short time in a palliative care unit, said “There has to be a better way than palliative care”. I said, “Palliative care was supposed to be the better way.” She spoke of the micro aggressions of a nurse who, when the wife complained about her husband not receiving his pain medication on time, turned to the husband, who had only recently regained cognitive functioning, and said, “You don’t need your wife to speak for you. You can speak for yourself.” Personally, I experienced the overt anger of a surgeon who, when I complained that my husband’s phone call requesting an MRI that the emergency room physician said needed to be ordered was not returned, made it very clear that any complaints about his secretary were reflections of his competence and were not to be tolerated. Thankfully, palliative care friends and his family doctor were prepared to be compassionate and helpful.

The above anecdotes illustrate various stages of burnout and what has been called compassion fatigue. Our work in the 1970s found that caregivers complained of being overworked and experiencing demanding consumers. Caregivers, such as those above, would report the same. Part of the issue is related to the difference between empathy and compassion. “Empathy makes it possible to resonate with others’ positive and negative feelings. In empathy one feels with someone, but one does not confuse oneself with the other; that is, one still knows that the emotion one resonates with is the emotion of another. If this self–other distinction is not present, we speak of emotion contagion” (Singer & Klimecki, 2014, R875). Klimecki and Singer (2012) have suggested a change in terminology to empathic distress fatigue rather than compassion fatigue. Gilbert and Choden (2014) note that empathy and compassion are not the same and empathy is not always compassionate. Empathy is a very important attribute of compassion, but empathy can be used in all kinds of non-compassionate ways. The intention to transform suffering is one of the features that distinguish compassion from empathy (Halifax, 2013).

Klimecki et al. (2013) investigated the neural plasticity underlying the augmentation of empathy and compassion. Using videos portraying human suffering, empathy training, but not memory training (control group) increased “negative affect and brain activations in anterior insula and anterior midcingulate cortex brain regions previously associated with empathy for pain. In contrast, subsequent compassion training could reverse the increase in negative affect and augment self-reports of positive affect. In addition, compassion training increased activations in a non-overlapping brain network spanning ventral striatum, pregenual anterior cingulate cortex and medial orbitofrontal cortex.” Training caregivers in compassion may reflect a new coping strategy to overcome empathic distress and strengthen resilience. Important work in this field is also being done by Roshi Joan Halifax (Halifax, 2013). Crucial to compassion is self-compassion. As we learn to practice self-compassion may we become even more compassionate with our patients and their families.

REFERENCES
Professional obligations and conscientious objection in physician assisted dying

By Sally Bean, Ethicist & Policy Advisor, Sunnybrook Health Sciences Centre, University of Toronto Joint Centre for Bioethics, Adjunct Lecturer, Dalla Lana School of Public Health, Adjunct Lecturer, Institute of Health Policy Management & Evaluation, Associate Member, School of Graduate Studies

The right to freedom of conscience and religion is protected by the Canadian Charter of Rights and Freedoms. However, the right is subject to reasonable limitations. In the health care context, when physicians choose to limit the health services they provide due to reasons of conscience or religion, this practice limitation is commonly referred to as “Conscientious Objection” (CO).¹

In early 2015, a unanimous Supreme Court of Canada (SCC) ruled in Carter v. Canada (Attorney General) 2015 SCC 5 that the federal Criminal Code legislation that prohibited Physician Assisted Dying (PAD) violated Sec. 7 Charter rights to life, liberty and security of the individuals that brought the Charter challenge and other persons similarly situation.² The SCC placed a one-year moratorium on implementation of the ruling to allow for a regulatory response.² As a result of the Carter decision, health care providers, institutions, and policy makers are considering what implementation of PAD should look like in practice. One key consideration is how to accommodate individual health care providers and health care institutions that may wish to conscientiously object to the provision of PAD while still enabling eligible patients to have reasonable access to PAD. Given the importance of the role of the physician in PAD, addressing CO is particularly pressing for physicians. In Carter, the SCC made brief mention of physician CO and noted that nothing in their ruling compels physicians to provide PAD. Moreover, the SCC noted that a decision on physician CO fell to physicians’ colleges, Parliament, and the provincial legislatures.³

In 2014, the American Thoracic Society (ATS) issued a policy statement pertaining to CO in intensive care medicine.³ In the ATS statement, the authors well summarized four ethically relevant reasons to accommodate CO and four ethical reasons not to accommodate CO. The four noted reasons to accommodate CO included to: 1) protect the clinicians’ moral integrity, 2) respect clinicians’ autonomy, 3) improve the quality of medical care, and 4) identify needed changes in professional norms and practices.³ Conversely, the four reasons not to accommodate CO pertained to: 1) honour core professional commitments, 2) protect vulnerable patients, 3) prevent excessive hardship on other clinicians or the institution, and 4) avoid invidious discrimination.³ Ultimately, the ATS recommended that in order to foster a consistent approach, institutional policies to address CO should be established versus an ad hoc approach and, where possible, individuals with a potential CO should provide advance disclosure so proactive measures may be taken.³

In Ontario, the College of Physicians and Surgeons of Ontario (CPSO) requires that physicians who wish to conscientiously object for reasons of conscience or religion, do so in a manner that respects patient dignity, ensures access to care, and protects patient safety.³ In the PAD context, “ensuring access to care” requires that physicians must provide information about all clinically relevant options and cannot withhold information because it is inconsistent with personal conscience or beliefs.³ If the physician is unwilling to provide the service for reasons of conscience or religion, an “effective referral” must be provided.³ In an associated Frequently Asked Questions to the CPSO policy, it clarifies that an effective referral entails referral to another health care provider that does not CO to the service sought and must be available and accessible to the patient.³ Some health care providers have expressed concern that being required to provide an effective referral makes them complicit with an act that violates their conscience or religion, while others contend that an effective referral is a reasonable balance between patients and health care provider interests.

While accommodating CO in the PAD context is a contentious matter, it requires a delicate balancing of the rights and interests of both the patient and health care provider. To the extent possible, proactive measures to identify and address potential CO to PAD should be identified in advance and may require development of additional infrastructure, such as a secure registry managed by the CPSO. Additionally, policy makers must be mindful not to polarize the discussion of CO by positioning the rights and interests of physicians and patients against one another: everyone loses if this occurs.

REFERENCES
Screening for post-traumatic stress disorder in cancer patients

By Christina Crowe, HBSc, MA, Counselling Psychology

Introduction

Post-traumatic stress disorder (PTSD) is a mental health disorder more commonly associated with current military personal and veterans. However, PTSD has an incidence of about 9–10% in the general population, also affecting first responders such as police, firefighters and paramedics, victims of trauma, such as violent attacks or vehicle accidents, sexual assault (rape) or war. The diagnosis of a life-threatening illness was formerly included as a potential trauma in the Diagnostic and Statistical Manual III (DSM-III) and IV under PTSD/anxiety disorders. However, a PTSD diagnostic criterion is an area of great controversy. In the most recent DSM-V, PTSD due to a medical condition or chronic illness has been excluded. Nevertheless, emotional distress, post-traumatic symptoms (PTS) and PTSD in cancer care are still relatively new fields of research, largely found within the psycho-oncology subspecialty, and this article summarizes what clinicians can do to screen for patients who are suffering and potentially improve outcomes for patients.

Screening

Research supports the notion that a cancer diagnosis is, in fact, traumatic. However, not all patients will develop confirmed PTSD or symptoms of PTSD. In an exploration of patients with advanced cancer who develop PTSD, 66.7% report that their cancer diagnosis was the traumatic trigger event for them, despite other traumas, such as the death of a loved one. In Canadian cancer clinics, the Edmonton Symptom Assessment System (ESAS) provides initial support for screening for emotional distress in cancer patients. The ESAS asks a patient to self-assess how they feel on a scale of 0 to 10, scoring symptoms such as feelings of depression, anxiety, appetite, sense of wellbeing and drowsiness. Other standardized and validated screening tools commonly used with cancer patients include the Beck Depression Inventory (BDI), the Canadian Problem Checklist (CPC), and the Posttraumatic Stress Disorders Check List – Civilian (PCL-C). The PCL-C has been validated for use in screening adult cancer patients.

Diagnosis

The development and understanding of PTSD as a psychiatric disorder has undergone significant change from the DSM-I to the DSM-V. By the DSM-V, it has moved from being classified as an anxiety disorder to a new category of “Trauma and Stress-Related Disorders.” In the DSM-V, diagnosis of PTSD requires exposure to an event that involved or held the threat of death, violence or serious injury. “Exposure” can happen directly to the patient, be witnessed by the patient, be happening to someone close to the patient, or if the patient is repeatedly exposed to graphic details of the traumatic event. The event must also be tied to symptoms of reliving the distressing experience of the event, upsetting dreams, flashbacks and ongoing emotional distress. For more than one month, the patient experiences avoidance, dissociation, loss of interest in past activities, detachment, numbness and self-destructive behaviours, feeling constantly on guard or alert to danger, startles easily, trouble sleeping or concentrating. Overall, this patient is experiencing significant distress and it’s interfering with his/her ability to go about normal daily tasks.

Considerations

In cancer patients some of the most common symptoms of PTSD presentation include flashbacks or re-experiencing a traumatic moment, avoidance, helplessness/hopelessness and intrusive symptoms. While most cancer patients, in general, will not exhibit all criteria, many patients will experience some or most of these aspects in their cancer journey, which the literature demonstrates may impact the course of their disease and treatment. The cancer experience is fraught with many potentially traumatic moments, including patients knowing that without treatment, they will die, and they may also die as a result of their treatment. As the research with this unique population continues to build, the characteristics specific to cancer will continue to inform screening, diagnosis and treatment.

When to refer

Many cancer centre programs already recognize the importance of psychosocial support for patients. Research suggests there are also socioeconomic risks associated with cancer patients developing PTSD symptoms. One study shows women with PTSD (and a history of mood and anxiety disorders) were four times more likely to be unable to work due to the emotional distress, compared to patients without PTSD. Given the many touch points a cancer patient has during the course of diagnosis and treatment, there is a shared responsibility to screen for emotional distress, including PTSD. In Ontario, patients have access to public psychiatric care from a psychiatrist or from a family physician specializing in trauma psychotherapy. Patients also have access to some public and more private psychotherapy, through hospitals, regional community programs, religious chaplains, and private registered psychotherapists and social workers.

As the research continues to grow in the area of trauma and the cancer experience, evidence for the treatments with the most reliable outcomes will also grow. Currently, cognitive behaviour therapy (CBT) with use of grounding techniques, eye movement desensitization and reprocessing (EDMR), and psychotherapy are all treatments with various levels of evidence for PTSD in cancer patients.

REFERENCES

Across Canada, hospice palliative care services are facing increasing pressures due to the rapidly aging population and a high prevalence of chronic life-limiting illnesses (Canadian Hospice Palliative Care Association, 2013).

As it stands, there are not enough specialized palliative care workers to satisfy the needs of this demographic, and there has been a push for other health care providers to step in and assume a greater responsibility for end-of-life care (Canadian Hospice Palliative Care Association, 2013).

This pressure has been felt by organizations such as the Quality Hospice Palliative Care Coalition of Ontario and the Canadian Hospice Palliative Care Association, and has led to the development of innovative and integrated models of palliative care (Canadian Hospice Palliative Care Association, 2013).

Though these models differ in some regards, most share the common goal of developing a collaboration between family physicians and inter-professional palliative care teams, which generally include a palliative care nurse, a palliative medicine physician, a bereavement counselor, a psychosocial-spiritual advisor, and a case manager (Marshall, 2008). Through the inclusion of family physicians, palliative care services can become more generalized and, thus, available to a greater population (Canadian Hospice Palliative Care Association, 2013). However, despite the general consensus that changes must be made, no universal model of care exists yet in Canada.

According to Hospice Palliative Care Ontario, the ultimate goal of palliative care is to “provide comfort and dignity for the person living with the illness,” (Hospice Palliative Care Ontario, 2014). The scope of palliative care is not limited to the relief of physical pain and symptoms, and also encompasses a patient’s psychological, spiritual, emotional, and cultural needs. Currently, only 16–30% of Canadians have access to hospice palliative care services despite a growing demand, which means that many individuals lack the appropriate services and support during the final stages of their illness (Quality Hospice Palliative Care Coalition of Ontario, 2011). While “palliative care” refers to a philosophy of care, a residential hospice is a setting that provides end-of-life care to the terminally ill. The care provided at residential hospices is administered with the intention of relieving pain and suffering, and ameliorating the quality of life for patients dealing with advanced illnesses.

The Dr. Bob Kemp Hospice is located in Hamilton, Ontario. Since its initial opening nearly 30 years ago, the Dr. Bob Kemp Hospice has grown to include hospice volunteers, a day program, and, in 2007, opened a residential hospice holding 10 beds and has served hundreds of patients. The Dr. Bob Kemp Hospice residential program supports family physicians as the primary palliative caregivers. The hospice employs two palliative care specialists as medical directors, who assume a part-time role, attending interdisciplinary team meetings on a weekly basis to review the patients and ensure that a high quality of care is being delivered. While the directors are available for consultation and guidance, the patient’s family physician assumes the primary responsibility of administering care, which may involve writing orders, seeing the patient, and completing and signing the death certificate. Working alongside the palliative care team, the family physician is provided invaluable support regarding symptom management, medication dosage, and communication between patients and their families. Through this collaborative model, the family physicians are exposed to the fundamental aspects of palliative care, thus increasing their knowledge base and skill set, which may lead to long-term benefits for the community (Weckmann, 2008).

In order to better understand the experience of family physicians in administering palliative care at the residential hospice so as to inform any improvements or changes in the current model of care, we surveyed any physicians who had had a patient admitted to the Dr. Bob Kemp Hospice residential program during the six-month time period of January 2014–June 2014. The surveys were initially sent out via fax, during the first two weeks of July 2014. Physicians were given an option to respond by fax, phone or e-mail, or to indicate that they did not wish to participate. A follow-up phone call was made if the survey had not been returned after 10 business days.

In total, 76 physicians were contacted. Out of this group, 32 physicians responded, yielding a response rate of 42%. Of these physicians 15% had been in practice for five years or less and 85% had been in practice for more than 10 years. Physicians were asked to rate how comfortable they felt generally providing end-of-life care, on a scale of 1 to 5 with 1 being very uncomfortable and 5 being very comfortable. Both the mean and the median level of comfort were 4 and the range was 1–5. Physicians were then asked to rate their comfort level caring for patients in the residential hospice on the same scale. The mean and median again were both 4 but the range was 3 to 5. The majority of physicians (59%) felt equal levels of comfort caring for their patients in the hospice or out of the hospice. However, it is interesting to note that for physicians who rated their comfort level providing end-of-life care as less than 4 (8/32 or 25%), the majority of these (7/8) reported that their comfort levels providing end-of-life care was higher in the residential hospice setting than at home.

Family physicians were also asked their overall level of satisfaction with care at the hospice on a scale of 1–5. The mean rating was 4.8; the median was 5 and the range was 3–5. Finally, family physicians were asked in the survey if they had visited their patient while they were in hospice and 81% reported having done so.

One confounding variable that may have affected the study was the fact that the surveys were sent out during the summer months of July and August, a time when many physicians are on vacation and, therefore, out of the office. A second issue may be those physicians with positive experiences may be more inclined to provide feedback than those with negative experiences.

**Conclusions**

There are many benefits that come from involving family physicians in end-of-life care. For one, this model offers a sustainable solution for communities by increasing the knowledge and skill level of primary physicians. Furthermore, in the report, “The Way Forward” the Canadian Hospice Palliative Care Association identifies building capacity as one of the pillars of successful, sustainable palliative care solutions (Canadian Palliative Care Association, 2013). By building capacity in the community, primary caregivers such as family physicians become equipped with the tools to provide palliative care, which helps to reduce the number of avoidable and costly hospital admissions (Canadian Hospice Palliative Care Association, 2013).

A residential hospice model where General Practitioners act as most responsible physicians for patients with the support of an interdisciplinary palliative care team is not only sustainable, but also well accepted by family physicians and has the potential to enhance physicians’ comfort level providing end-of-life care for patients.

References available on request
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


**CME courses**

- Navigating Later Lines of Treatment for Advanced Colorectal Cancer: Optimizing Targeted Therapies to Improve Outcomes. This case-based course presents systemic therapy options available for metastatic colorectal cancer beyond the first-line setting, as well as the current utility of predictive biomarkers in the disease. This activity is an Accredited Group Learning Activity (Section 1), as defined by the Maintenance of Certification program of The Royal College of Physicians and Surgeons of Canada, for 1.0 MOC. This activity was approved by the Canadian Society of Internal Medicine. Register and visit the CME portal for more information. [www.oncologyeducation.com](http://www.oncologyeducation.com)
- New course available! Optimizing Outcomes in Advanced Prostate Cancer. This course will provide an update in prostate cancer, as it pertains to disease heterogeneity and mechanisms of androgen receptor resistance, sequencing of drugs in metastatic castrate-resistant prostate cancer, and will also discuss recent guidelines and current management practices. Register and visit our CME portal for more information. [www.oncologyeducation.com](http://www.oncologyeducation.com)
- March 9–12, 2016. 2016 AAHPM & HPNA Annual Assembly. The premier educational event for hospice and palliative care providers, Chicago, IL
- October 7–11, 2016. ESMO Copenhagen, Denmark. [www.esmo.org/Conferences/ESMO-2016-Congress](http://www.esmo.org/Conferences/ESMO-2016-Congress)
World Conference on Lung Cancer 2015
Non-small cell lung cancer update

Dr. Parneet K. Cheema, BSc, MD, MBiotech, FRCP, Department of Medical Oncology, Sunnybrook Odette Cancer Centre

Early stage

Background

- Adjuvant cisplatin-based chemotherapy for completely resected early stage NSCLC provides an OS benefit of 5.4%.1
- Bevacizumab in addition to carboplatin/paclitaxel as first-line therapy in advanced NSCLC improved PFS and OS (E4599), whereas its addition to cisplatin/gemcitabine had no significant benefit (AVAiL).2,3

New data

- Randomized Phase III Trial of Adjuvant Chemotherapy with or without Bevacizumab in Resected Non-Small Cell Lung Cancer (NSCLC): Results of E1505
- Study design: Randomized, phase III trial, resected stage IB (≥4 cm) to IIIA NSCLC, all histologies (squamous NSCLC eligible as safety concerns with resected disease expected to be low), platinum doublet (with vinorelbine, pemetrexed, gemcitabine, or docetaxel) x 4 cycles +/- bevacizumab 15 mg/kg IV q 3 weekly x 1 yr. Primary endpoint: OS.
- Results: N=1501 enrolled, after 41 months of follow-up, independent DSMC advised to release results due to futility. Chemotherapy was prespecified and, thus, well balanced, 25% of patients received cisplatin/vinorelbine, 20% cisplatin/gemcitabine. 1/3 of patients were squamous cell carcinoma.
- OS: HR: 0.99, p=0.93 and DFS: HR: 0.98, p=0.75
- Safety: Significant increased neutropenia, hypertension and grade 3-5 adverse events with bevacizumab. No unexpected adverse events.
- Conclusion: The addition of bevacizumab to adjuvant chemotherapy did not improve survival. Data according to platinum doublet is not yet available.

Impact on practice

- Negative trial. As bevacizumab is rarely used in Canada for advanced stage NSCLC mainly due to the negative results of the AVAiL trial, this trial will have little impact on clinical practice.

Locally advanced NSCLC

Background

- 30% of patients present with stage III disease of which half are elderly patients (≥70)
- The benefit of concurrent chemo/radiation (CRT) in elderly population remains unclear.

New data (Canadian content)

- CRT versus Radiotherapy Alone in Elderly Patients with Stage III NSCLC: A Systematic Review.
- Study design: Systematic review. Four reports of three studies (n=407 elderly patients).
- Results: OS in elderly patients was superior in those treated with CRT compared to RT alone (HR 0.66, p=0.0009). PFS was also improved with CRT (HR 0.67, p=0.001).
- Safety: Treatment-related death: 5% CRT, 4% RT. Increased hematologic toxicity (neutropenia and thrombocytopenia) with CRT. Rate of febrile neutropenia with CRT was low (2.5%).

Impact on practice

- This provides support to consider CRT for fit elderly patients. Determining what chemotherapy to give patients would also need to be considered. Carboplatin-based chemotherapy concurrent with RT has shown to improve survival compared to RT alone, including randomized data in elderly patients and may be a consideration if a patient cannot tolerate cisplatin.4,5

Advanced NSCLC

Advanced NSCLC – ImmunoOncology

Background

- Phase II and III trials targeting the PD1/PD-L1 pathway in advanced NSCLC improved survival over standard chemotherapy, however responses were low.6,8
- Cytotoxic chemotherapy has an immune-modulatory effect.9 Thus, combining PD1/PD-L1 with cytotoxic chemotherapy could increase immune response by increasing number of antigens presented to T-cells and changing tumour microenvironment.
- Combination of the anti-PD1 nivolumab with ipilimumab, an anti-CTLA4 antibody (dual immune checkpoint inhibition) has activity across multiple tumour types including phase III data in advanced melanoma and has a manageable safety profile.9
- Initial data of nivolumab/ipilimumab combination in metastatic NSCLC at doses used in melanoma yields high adverse events and moderate responses, thus the dosing and scheduling needed to be optimized.10

New data – Atezolizumab

- Atezolizumab and Chemotherapy Phase 1b: Atezolizumab (MPDL3280A) Combined with Platinum-based Chemotherapy in NSCLC: A Phase 1b Safety and Efficacy Update
- Study design: Phase 1b, treatment naïve, 3 cohorts: atezolizumab 15 mg/kg IV q 3 weeks + carboplatin/paclitaxel or carboplatin/pemetrexed or carboplatin/nab-paclitaxel x 4–6 cycles. All histologies, not limited to PD-L1 positive patients. Primary endpoint: safety. Enrollment not yet complete.
- Results: ORR:
  - All cohorts (n=41): 63%
  - Carboplatin/paclitaxel cohort (n=8): 50%
  - Carboplatin/pemetrexed cohort (n=17): 77%
  - Carboplatin/nab paclitaxel (n=16): 56%
- Characteristics of responses: durable, complete responses were noted and no unconventional immune related responses were reported.
Impact on practice

Provocative data, confirmatory trials required to change practice. Phase III trials of atezolizumab with various combinations of chemotherapy are currently underway, as is a phase III trial (CheckMate 227) of nivolumab versus nivolumab/ipilimumab versus standard platinum doublet in first-line setting.

Advanced NSCLC – EGFR positive

First-line 3rd generation EGFR TKI

- EGFR TKIs are recommended first-line therapy for advanced EGFR mutated NSCLC.
- AZD9291 is an oral irreversible EGFR TKI that is selective for EGFR sensitizing mutations (Del19 and L858R) in addition to the resistance mutation T790M.

New data

- AZD9291 in Treatment-Naïve EGFRm Advanced NSCLC: AURA First-Line Cohort.
- Study design: Phase 1, treatment-naïve cohort, AZD9291 80 mg or 160 mg po OD, EGFR mutated (included mutations other than Del19 and L858R).
- Results: N=160, ORR 67%, 83% and DCR 93%, 100% for 80 mg and 160 mg respectively. Maximum duration of response and PFS were 18 and 19.2 months respectively (medians not yet mature).
- Toxicity: Most common were rash, diarrhea. Any grade 3 AE 17%. 5% of drug-related AE led to discontinuation. ILD rate was low. Hyperglycemia 5%.
- Conclusion: AZD9291 has encouraging activity in treatment-naïve advanced NSCLC patients and is well tolerated with low rates of hyperglycemia, which is more commonly seen with another third generation EGFR TKI rociletinib.

Impact on practice

The phase III trial FLAURA (NCT02296125) is comparing AZD9291 80 mg po OD versus standard of care EGFR TKI in treatment-naïve patients with advanced EGFR mutated NSCLC. Sites within Canada, including Sunnybrook Odette Cancer Centre, are currently enrolling patients. At this meeting, preclinical data were also presented showing high brain-to-plasma drug concentrations of AZD9291 compared to gefitinib. Patients with asymptomatic untreated brain metastases are included in FLAURA.

Uncommon EGFR mutations

- Standard first-line therapy for advanced NSCLC harbouring the common activating EGFR mutations (Del19, L858R) is an EGFR TKI where PFS range from 9 to 13 months. Less is known about the management of patients harbouring the 10% of EGFR mutations that are uncommon.
- Pivotal phase II/III trials (Lux Lung 2/3/6) with afatinib in treatment-naïve population included patients with uncommon mutations. Post hoc analysis found that uncommon mutations G719X in exon 18, S768I and L861Q in exon 21 appeared to be sensitive to afatinib. Exon 18 mutations PFS 13.6 months and OS of 26.4 months. De novo T790M and exon 20 insertions did not derive benefit from afatinib.11
- Multiple retrospective analyses of local or national databases were presented to gain insight into management of these mutations.

New data (combination of retrospective database studies)

Brazilian National Cancer Institute Database
- Domingues P. Clinical Outcomes in Patients with NSCLC, Harboring Rare EGFR Mutations

Results:
- Clinical characteristics: Comparable to wild type EGFR patients, with an equal distribution of sex and a majority being smokers
- Median OS (treated with an EGFR TKI): p=0.001
  - Common mutations: 62.9 mos.
  - Uncommon mutations: 17.2 mos.
  - EGFR WT: 25 mos.
- Time to treatment failure (treated with an EGFR TKI): p=0.001
  - Common mutations: 13.9 mos.
  - Uncommon mutations: 3.4 mos.
  - EGFR WT: 3.9 mos.
- Individual mutations had variability in OS, and TTF
- Conclusion: All EGFR mutations are not created equal. Clinical characteristics and outcomes of uncommon mutations differ from common mutations.

Single Japanese Centre Database, Kinki-chuo Chest Medical Center, Osaka
- Kanazu, M. EGFR TKI Treatment Response in Advanced NSCLC with Uncommon Mutations
- Results: ORR/PFS to 1st generation EGFR (erlotinib or gefitinib):
  - Exon 21 L861Q; ORR 33% (6 pts), PFS 7.6 mos.
  - Exon 18 G719X; ORR 12.5%, PFS 1.8 mos.
  - G719A: PFS 8.2 mos.
  - G719S: PFS 1.7 mos.
  - G719C: PFS 1.1 mos.
- Conclusion: Uncommon mutations are less responsive to first generation EGFR TKIs compared to common mutations. Although, patients with exon 21 L861Q or exon 18 G719A may derive benefit from first generation EGFR TKIs.

Czech National Lung Cancer Registry
- Pasek M. Rare and Common EGFR Mutations in Patients with Advanced NSCLC Treated with EGFR TKI: A Registry-Based Study.
• Results:
  • Clinical characteristics: Uncommon mutations more frequently found in smokers
  • ORR/PFS/OS with gefitinib
    - Exon 18 G719X (n=21): ORR 18%, OS 10.9 mos., PFS 8.6 mos.
    - Exon 20 (n=7): ORR 14%, OS 8.6 mos., PFS 2.6 mos.
• Conclusion: Similar to previous reports, exon 18 mutations are less responsive to first-generation EGFR TKIs compared to common mutations, and exon 20 show resistance to EGFR TKIs.

Japanese databases (Aichi Cancer Centre & COSMIC), >16,000 patients
• EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Sensitivity to Afatinib or Neratinib but Not to Other EGFR-TKIs.
• Results:
  • Frequency of exon 18 mutations: 3% of all mutations in EGFR mutations. Most common: G709X, G719X, and Del118.
  • Pre clinical data: IC90 ratio of EGFR TKIs were studied and compared to IC90 for common mutation Del 19. The IC90 were the lowest for second-generation EGFR TKI with afatinib or neratinib compared to first-generation TKIs (erlotinib and gefitinib) and third-generation (AZD9291 and CO1686).
• Conclusion: This data was consistent with retrospective data that exon 18 mutations are less responsive to first-generation EGFR TKIs. Afatinib may be the best therapeutic option for exon 18 mutations based on Lux Lung 2/3/6 pooled prospective data and supported by this in vitro data.

Impact on practice
Indiscriminate use of EGFR TKIs when an EGFR mutation is found should not be standard practice. First-generation EGFR TKIs appear to be less effective in exon 18 G719X and both first generation and second generation are not effective for exon 20 insertions. A practical approach to first-line systemic therapy with currently available retrospective and prospective data could be as follows: exon 20 mutations clinical trial or chemotherapy, de novo T790M mutation third-generation EGFR TKI (AZD9291 or rociletinib) ideally through a clinical trial or chemotherapy, exon 21 L861Q and exon 18 G719X would favour afatinib based on prospective and preclinical data with close monitoring to detect early progression (in the scenario of G719C/S possibly having resistance to EGFR TKIs).

Beyond progression of an EGFR TKI (based on T790M status)

Background
• Invariably patients with EGFR mutated NSCLC treated with an EGFR TKI develop resistance; 60% of which develop the acquired EGFR resistance mutation T790M.
• IMPRESS study was a phase III study of continuation of gefitinib in combination with chemotherapy versus chemotherapy alone in patients with acquired resistance to gefitinib. Previously reported there was no impact on PFS, ORR or DCR with continuing gefitinib. Subgroup analysis by T790M status was presented.
• Rociletinib is an orally available small molecule that inhibits common EGFR mutations (Del 19, L858R) and T790M. ORR in patients harbouring the T790M mutation is 59%. Early reports have noted responses in patients with T790M negative tumours, further data on these patients was presented.

New data – IMPRESS

Results:
• T790M+ (40%): PFS 4.6 mos. with gefitinib (n=81) vs. 5.3 mos. (n=61) with placebo, HR: 0.97, p=0.88.
• T790M- (54%): PFS 6.7 mos. with gefitinib (n=46) vs. 5.4 mos. (n=59) with placebo, HR: 0.67, p=0.07.
• OS not mature. However, continuation of gefitinib in T790M+ patients appeared harmful, HR 2.16; p=0.017, although OS trended in favour of gefitinib in T790M negative patients HR was 0.83, p=0.66 with only 21% maturity.

Impact on practice
Continuation of EGFR TKI upon progression with chemotherapy may have a role in T790M- patients, although OS data are still immature and prospective analysis will be required to change practice.

New data – TIGER X
• Rociletinib in NSCLC Patients with Negative Central Testing for T790M in TIGER-X.
• Study design: Phase II/II study of T790M+ and - patients. Phase II component required central testing for T790M. Key endpoints ORR and safety.

Results:
• T790M- by central testing (n=37): ORR 35%, DCR 65%.
• T790M- by central testing, T790M+ local testing (n=28): ORR 36%, DCR 64%.
• T790M- by central testing, T790M- local testing or not available (n=9): ORR: 33%, DCR 67%.
• Hypothesis on why T790M- patients responded to rociletinib:
  • Tumour heterogeneity: may explain discordant results
  • Testing method: COBAS testing, THERASCREEN detection were concordant. Thus different testing method would not have picked up missed T790M mutations.

Results:
• Study design: 261/265 patients had plasma samples at baseline for T790M analysis, ctDNA analysis by BEAMing.
• Results:
  • T790M+ (40%): PFS 4.6 mos. with gefitinib (n=81) vs. 5.3 mos. (n=61) with placebo, HR: 0.97, p=0.88.
  • T790M- (54%): PFS 6.7 mos. with gefitinib (n=46) vs. 5.4 mos. (n=59) with placebo, HR: 0.67, p=0.07.
  • OS not mature. However, continuation of gefitinib in T790M+ patients appeared harmful, HR 2.16; p=0.017, although OS trended in favour of gefitinib in T790M negative patients HR was 0.83, p=0.66 with only 21% maturity.

Implications for practice
Current data suggest that both T790M+ and - patients derive benefit from rociletinib. 35% responses in pretreated NSCLC that are T790M- is impressive compared to currently available second-line options. Interestingly, AZD9291 another third-generation EGFR TKI that targets T790M also reported responses in 21% of T790M-patients. Further exploration of these findings is needed. Further exploration of these findings is needed. Further exploration of these findings is needed. Further exploration of these findings is needed.

Practical Implementation of Biomarker Testing (Canadian content)

Background
• IASCL guidelines recommend EGFR and ALK testing for patients with a diagnosis of advanced non-squamous NSCLC and results should guide treatment decisions. Testing at an earlier stage is also encouraged to allow for rapid initiation of systemic therapy upon disease recurrence.
• A recent international survey of medical oncologists found that in North America 24% of patients with advanced NSCLC do not have EGFR testing.
• One major barrier for biomarker testing and implementing personalized medicine
for advanced NSCLC patients is oncologists having to wait for biomarker results while running the risk of patients clinically deteriorating without therapy.

- Reflex testing for EGFR/ALK has been adopted by a few centres to expedite biomarker results for the treating medical oncologist. The definition of reflex testing is pathologists requesting EGFR and ALK at time of diagnosis of non-squamous NSCLC irrespective of clinical stage. This is opposed to the practice of routine testing where the medical oncologist requests EGFR/ALK at time of first visit with a patient with a diagnosis of advanced NSCLC.

**New Data**

- Impact of Reflex EGFR/ALK Testing on Time-To-Treatment and Integration of Personalized Medicine in Advanced NSCLC Patients
- Study design: Retrospective, centre analysis of Sunnybrook Health Sciences Centre. Compared data from time periods pre and post implementation of reflex testing.

- Results: With the implementation of reflex testing, there was a significant improvement in time to optimal first-line therapy according to biomarker status, 36 days versus 24 days, p=0.036. Reflex testing impacted quality of testing with significantly fewer tests requested being unsuccessful due to insufficient tissue, inappropriate tissue or tissue not sent from holding lab to the testing lab. Number of unsuccessful tests for EGFR 14% versus 4%, p=0.039, and for ALK 17% versus 3%, p=0.037. During the time period of reflex testing there was a significant increase in EGFR and ALK testing across all stages and in patients with advanced stage disease and there was a significant increase in biomarkers available to medical oncologists at patient’s first consultation.

- Conclusion: Reflex testing for EGFR/ALK by pathologists at time of diagnosis of non-squamous NSCLC irrespective of a patient’s clinical stage appeared to improve quality outcomes, including faster time to optimal systemic therapy and less unsuccessful test requests.

**Implications for practice**

Centres may consider implementing reflex testing as a mechanism to reduce barriers encountered with implementing personalized medicine in advanced NSCLC. Ideally this could be coordinated at a national level.

**Advanced NSCLC – Brain metastases**

**Background**

A third of patients with advanced NSCLC will, at some point, develop CNS metastases.

The central nervous system (CNS) is a frequent site of progression in ALK+ NSCLC patients treated with crizotinib.

**New data – ALK positive**

Pooled Analysis of CNS Response to Alectinib in Two Studies of Pre-Treated ALK+ NSCLC

Study design: Pooled analysis of two phase II trials (NCT01871805 and NCT01801111), single-arm, multicentre studies enrolled ALK+ NSCLC patients previously treated with crizotinib. Alectinib 600 mg po BID. Secondary endpoints CNS ORR and CNS duration of response (DOR)

- Results: N=225
  - Measurable disease at baseline (n=50): ORR 64%, CR 22%, DCR 90%. Median disease control was 10.8 mos.
  - Measurable or non-measurable CNS metastases at baseline (n=136):
    - ORR 47%, CR 37%, DCR 85% and median disease control 11.1 mos.
    - Prior radiation (n=95): ORR 36%, DCR 86%

- No prior radiation (n=41): ORR 59%, DCR 83%

- CNS site of progression:
  - No CNS metastases at baseline: 8%
  - Overall: 17%

- Safety: There was no difference between pooled population with or without brain metastases.

- Conclusion: Alectinib has CNS activity in ALK+ NSCLC patients that was independent of previous radiation. Duration of CNS response seemed to be similar to that of systemic response. Phase III trial ALEX (NCT02075840), a study of alectinib versus crizotinib as first-line therapy for advanced ALK+ NSCLC, will provide further information on CNS efficacy, as CNS endpoints have been incorporated.

**New data – Immunotherapy**

A Phase II Trial of Pembrolizumab for Untreated Brain Metastases from Non-Small Cell Lung Cancer.

- Study design: Phase II trial, advanced NSCLC or melanoma with at least one untreated brain metastases, treated with pembrolizumab 10 mg/kg q2weeks IV. If progressive disease patients could have RT or surgery and continue pembrolizumab.

- Results: N=18 advanced NSCLC patients; ORR in CNS was 33%, equivalent to systemic ORR of 33%. All patients with a systemic response had a CNS response, except one patient who transiently responded then progressed. Ongoing durable responses.

- Safety: Neurologic adverse events regardless if study drug-related or not were all grade 1.

- Conclusion: Small study, but suggests that pembrolizumab has durable activity on CNS metastases and may be correlated with systemic response.

**Impact on treatment**

Currently radiation is the primary therapy for a majority of patients with CNS disease, with surgery reserved for select cases, both of which can cause toxicity and delay systemic treatment. With advanced NSCLC patients living longer and the evolving landscape of new systemic therapies that show promising CNS activity, this justifies a multidisciplinary approach to the management of brain metastases.

**REFERENCES**

13. Mok TS. ESMO 2014 Congress. Abstract LBA2_PR.
Latest advances in colorectal cancer: An update on new therapies for refractory CRC and Regorafenib toxicity management

Dr. Xiao Zhu, University of Alberta and Dr Yooj Ko, University of Toronto

Biomarkers for Regorafenib

Background

• Regorafenib is a tyrosine kinase inhibitor that targets multiple receptors including VEGFR-1, 2, and 3, as well as PDGFR and RAF.
• It is approved for use in patients with refractory advanced colorectal cancer, after progression on multiple standard therapies including Fluoropyrimidine, Oxaliplatin, Irinotecan, Bevacizumab, and in KRAS wild type, an EGFR inhibitor.
• Two phase III trials, CORRECT and CONCUR, demonstrated the superiority of Regorafenib in the refractory setting, as compared to placebo in both Western and Asian patients, with an improvement in overall survival (OS) of approximately 1.5 to 2.5 months.

New data

• Tabernero et al published the results of the biomarker sub-study in August 2015.
• 503 of the 760 patients in CORRECT were included for mutational analysis, and tumours were tested for common mutations including KRAS, PIK3CA, and BRAF.
• Using BEAMing technology that detects mutations in plasma DNA, 69% of patients were found to have KRAS mutations, 17% had PIK3CA mutations, and 3% had BRAF mutations.
• Mutations in either KRAS and PIK3CA were not predictive of benefit from Regorafenib, with both wild type (wt) and mutant (mt) patients achieving similar gains in progression-free survival (HR for KRAS wt = 0.52, KRAS mt = 0.51; PIK3CA wt =0.50, PIK3CA mt = 0.54).
• BRAF mutations were not analyzable due to the small number of mutations in the study.
• Baseline circulating DNA concentration was also examined, and patients with both low (< median) and high (> median) baseline circulating DNA benefited equally from Regorafenib (HR for low DNA concentration = 0.53, high DNA concentration = 0.52).
• However, baseline circulating DNA concentration was prognostic of survival in patients who received placebo, with patients in the low concentration group having better OS (HR 0.31).
• Separately, 611 patients also had protein analysis performed, where concentrations of 15 proteins associated with angiogenesis or colorectal cancer pathogenesis were quantitated. Soluble TIE-1 was the only protein associated with differing HR in benefit from Regorafenib on survival on univariate analysis; however, this effect was not significant on multivariate analysis.

Implications for practice

• Despite pre-planned biomarker sub-study, no mutations or proteins were identified as predicative of benefit from Regorafenib in these refractory patients.
• Although this lends reassurance that this agent is likely to provide benefit across a broad range of patient subgroups, further research is clearly needed to elucidate the optimal patient population for this targeted agent.

Regorafenib toxicity management

Background

• Although Regorafenib improved overall survival compared to placebo, as demonstrated in CORRECT and CONCUR, it is associated with a number of clinically significant toxicities.

<table>
<thead>
<tr>
<th></th>
<th>CORRECT study</th>
<th>RECURSE study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Regorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>505</td>
<td>255</td>
</tr>
<tr>
<td></td>
<td>534</td>
<td>266</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>61 (54–67)</td>
<td>61 (54–68)</td>
</tr>
<tr>
<td></td>
<td>63 (27–82)</td>
<td>63 (27–82)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td>55%</td>
</tr>
<tr>
<td>1</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>45%</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>Yes</td>
<td>54%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>No. prior therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>18% (2 prior)</td>
<td>17% (2 prior)</td>
</tr>
<tr>
<td>3</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>≥4</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td>Time from diagnosis to metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18 months</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>≥ 18 months</td>
<td>82%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>79%</td>
<td>79%</td>
</tr>
</tbody>
</table>
**Biomarkers for Regorafenib**

**Background**
- Regorafenib is a tyrosine kinase inhibitor that targets multiple receptors including VEGFR-1, 2, and 3, as well as PDGFR and RAF.
- It is approved for use in patients with refractory advanced colorectal cancer, after progression on multiple standard therapies including Fluoropyrimidine, Oxaliplatin, Irinotecan, Bevacizumab, and in KRAS wild type, an EGFR inhibitor.
- Two phase III trials, CORRECT and CONCUR, demonstrated the superiority of Regorafenib in the refractory setting, as compared to placebo in both Western and Asian patients, with an improvement in overall survival (OS) of approximately 1.5 to 2.5 months.

**New data**
- Tabernero et al published the results of the biomarker sub-study in August 2015.
- 503 of the 760 patients in CORRECT were included for mutational analysis, and tumours were tested for common mutations including KRAS, PIK3CA, and BRAF.
- Using BEAMing technology that detects mutations in plasma DNA, 69% of patients were found to have KRAS mutations, 17% had PIK3CA mutations, and 3% had BRAF mutations.
- Mutations in either KRAS and PIK3CA were not predictive of benefit from Regorafenib, with both wild type (wt) and mutant (mt) patients achieving similar gains in progression-free survival (HR for KRAS wt = 0.52, KRAS mt = 0.51; PIK3CA wt =0.50, PIK3CA mt = 0.54).
- BRAF mutations were not analyzable due to the small number of mutations in the study.
- Baseline circulating DNA concentration was also examined, and patients with both low (< median) and high (> median) baseline circulating DNA benefited equally from Regorafenib (HR for low DNA concentration = 0.53, high DNA concentration = 0.52).
- However, baseline circulating DNA concentration was prognostic of survival in patients who received placebo, with patients in the low concentration group having better OS (HR 0.31).
- Separately, 611 patients also had protein analysis performed, where concentrations of 15 proteins associated with angiogenesis or colorectal cancer pathogenesis were quantitated. Soluble TIE-1 was the only protein associated with differing HR in benefit from Regorafenib on survival on univariate analysis; however, this effect was not significant on multivariate analysis.

**Implications for practice**
- Despite pre-planned biomarker sub-study, no mutations or proteins were identified as predicative of benefit from Regorafenib in these refractory patients.
- Although this lends reassurance that this agent is likely to provide benefit across a broad range of patient subgroups, further research is clearly needed to elucidate the optimal patient population for this targeted agent.

---

**Regorafenib toxicity management**

**Background**
- Although Regorafenib improved overall survival compared to placebo, as demonstrated in CORRECT and CONCUR, it is associated with a number of clinically significant toxicities.

---

**Table: CORRECT and RECORECE study**

<table>
<thead>
<tr>
<th></th>
<th>CORRECT study</th>
<th>RECORECE study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Regorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>505</td>
<td>255</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td>61 (54–67)</td>
<td>61 (54–68)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>1</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>KRAS mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41%</td>
<td>37%</td>
</tr>
<tr>
<td>Yes</td>
<td>54%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>No. prior therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>≥4</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Time from diagnosis to metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18 months</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>≥ 18 months</td>
<td>82%</td>
<td>81%</td>
</tr>
</tbody>
</table>
In CORRECT, Regorafenib was associated with higher incidence of both all-grade (93% versus 61%) and grade 3–4 (54% versus 15%) toxicity, with the most common being fatigue, hand-foot skin reaction (HFSR), and diarrhea. Similar results were seen in CONCUR, where higher all-grade (97% vs 45%) and grade 3–4 (53% vs 14%) toxicity was seen with Regorafenib. The most common toxicities included HFSR, hyperbilirubinemia, and increased transaminases. Despite more frequent toxicity with Regorafenib, quality of life was not significantly different between treatment groups in either trial.

New data

**In a previous phase II randomized trial, TAS-102 was shown to improve overall survival compared to placebo (9.0 versus 6.6 months, HR 0.56) in patients refractory to or intolerant of standard therapies.**

**New data**

- Mayer et al. conducted a phase III trial (RECOURSE) comparing TAS-102 to placebo in patients with refractory advanced colorectal cancer, the results of which were published in May.
- This double-blind study randomly assigned 800 patients in a 2:1 ratio to receive TAS-102 or placebo.
- The primary end point of overall survival favored TAS-102 with median OS being 7.1 months for those who received TAS-102, as compared to 5.3 months for placebo (HR 0.68).
- Approximately half of the patients were KRAS mutant. Patients benefited equally regardless of KRAS mutation status.
- The most common toxicities included leukopenia (77%; 21% grade 3–4), anemia (77%; 18% grade 3–4), and neutropenia (67%; 38% grade 3–4). There was one treatment-related death due to sepsis.
- Although a formal quality-of-life analysis was not performed, patients treated with TAS-102 maintained their performance status for longer compared to patients receiving placebo (time to deterioration to ECOG ≥2 of 5.7 vs 4.0 months).

**Implications for practice**

- Judicious use of Regorafenib requires proper patient education and vigilant monitoring of toxicity, especially within the first few cycles during which toxicity is most likely to develop.
- Although many toxicities are not unique to Regorafenib, some are infrequently encountered with other therapies (e.g., HFSR). Preventive measures and timely treatment of new-onset toxicity are essential in mitigating significant complications and maintaining the quality of life of patients.

**New agent in Refractory setting: TAS-102**

**Background**

- TAS-102 is an orally administered combination of a thymidine-based nucleic acid analogue, Trifluridine, and a thymidine phosphorylase inhibitor, Tipiracil hydrochloride.
- Trifluridine is the active cytotoxic component of TAS-102 and its triphosphate form is incorporated into DNA resulting in antitumor effects. Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase and, when combined with Trifluridine in TAS-102, prevents rapid degradation of Trifluridine, allowing for higher plasma levels of the active component.

**Table**

<table>
<thead>
<tr>
<th></th>
<th>CORRECT study</th>
<th>RECOURSE study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td>mOS months</td>
<td>6.4 (3.6–11.8)</td>
<td>5.0 (2.8–10.4)</td>
</tr>
<tr>
<td>mPFS months</td>
<td>1.9 (1.6–3.9)</td>
<td>1.7 (1.4–1.9)</td>
</tr>
<tr>
<td>Response rate</td>
<td>41%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- **New agent in Refractory setting: TAS-102**
- **Background**
- **Implications for practice**

References available on request
Despite more frequent toxicity with both all-grade (93% versus 61%) and grade 3-4 (54% versus 15%) toxicity, with the most common being fatigue, hand-foot skin reaction (HFSR), and diarrhea.

Similar results were seen in CONCUR, where higher all-grade (97% vs 45%) and grade 3-4 (53% vs 14%) toxicity was seen with Regorafenib. The most common toxicities included HFSR, hyperbilirubinemia, and increased transaminases.

Although most frequent toxicity with Regorafenib, quality of life was not significantly different between treatment groups in either trial.

New data

- Since the initial publication of CORRECT in 2013, multiple clinical summaries on toxicity management regarding Regorafenib have been published (De Wit, 2013; Sastre, 2014; Grothey, 2014). Key common toxicities are briefly highlighted here.
- Fatigue: patients should be counselled on the high likelihood of developing fatigue, and appropriate workload reduction and exercise, as tolerated, are recommended.
- HFSR: manifests as painful hyperkeratotic lesions most commonly developing at pressure spots, including finger tips, palms, toes, and sole of the feet. It occurs early in the course of treatment, usually within 2–4 weeks. Prevention with avoidance of friction and pressure, and the use of moisturizers containing keratolytic such as urea or salicylic acid are recommended. Treatment for existing HFSR includes steroid cream and analgesia.
- Diarrhea: similar to diarrhea associated with many other anticancer therapies. Loperamide may be effective in the treatment of grade 1–2 Regorafenib-induced diarrhea. Careful attention to fluid intake should be taught to patients.
- Liver toxicity: although many patients who develop elevations in liver enzymes are asymptomatic, Regorafenib can lead to life-threatening liver dysfunction. In CORRECT, liver failure was seen 1.6% of patients treated with Regorafenib, compared to 0.4% in those receiving placebo. Transaminases and bilirubin should be checked every two weeks at a minimum during the first two cycles, and treatment should be discontinued if transaminases rise to >20 times upper limit of normal (ULN), or if they rise to >3 times ULN with concomitant bilirubin elevation to >2 times ULN.

In a previous phase II randomized trial, TAS-102 was shown to improve overall survival compared to placebo (9.0 versus 6.6 months, HR 0.56) in patients refractory to or intolerant of standard therapies.

New data

- Mayer et al. conducted a phase III trial (RECOURSE) comparing TAS-102 to placebo in patients with refractory advanced colorectal cancer, the results of which were published in May.
- This double-blind study randomly assigned 800 patients in a 2:1 ratio to receive TAS-102 or placebo.
- The primary end point of overall survival favored TAS-102 with median OS being 7.1 months for those who received TAS-102, as compared to 5.3 months for placebo (HR 0.68).
- Approximately half of the patients were KRAS mutant. Patients benefited equally regardless of KRAS mutation status.
- The most common toxicities included leukopenia (77%; 21% grade 3–4), anemia (77%; 18% grade 3–4), and neutropenia (67%; 38% grade 3–4). There was one treatment-related death due to sepsis.
- Although a formal quality-of-life analysis was not performed, patients treated with TAS-102 maintained their performance status for longer compared to patients receiving placebo (time to deterioration to ECOG ≥2 of 5.7 vs 4.0 months).

Implications for practice

- Judicious use of Regorafenib requires proper patient education and vigilant monitoring of toxicity, especially within the first few cycles during which toxicity is most likely to develop.
- Although many toxicities are not unique to Regorafenib, some are infrequently encountered with other therapies (e.g., HFSR). Preventive measures and timely treatment of new-onset toxicity are essential in mitigating significant complications and maintaining the quality of life of patients.

New agent in Refractory setting: TAS-102

Background

- TAS-102 is an orally administered combination of a thymidine-based nucleic acid analogue, Trifluridine, and a thymidine phosphorylase inhibitor, Tipiracil hydrochloride.
- Trifluridine is the active cytotoxic component of TAS-102 and its triphosphate form is incorporated into DNA resulting in antitumor effects. Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase and, when combined with Trifluridine in TAS-102, prevents rapid degradation of Trifluridine, allowing for higher plasma levels of the active component.

References available on request