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

Welcome to the November 2017 issue of *Hot Spot*. In this issue, Dr. Blair Henry discusses a timely topic—Conscientious Objection in the era of MAiD: Standing to do or not do what exactly? Ms. Christina Crowe, Registered Psychotherapist, raises an interesting question—The chicken or the egg? Mental health and chronic illness. Mr. Michael Briganti, Drs. Susanna Cheng, Mark Pasetka and Alia Thawer describe in detail on Glucocorticoid-Induced Myopathy. Ms. Toby Rodin and Dr. Patrick Paladino update us on Continuing Medical Education. We have two inserts: the first one by Dr. Nadia Califaretti on Cyclin-dependent Kinase 4/6 Inhibitors in Hormone Receptor Positive HER2 Negative Advanced Breast Cancer: A review, and the second one by Dr. Parneet Cheema on Non-Small Cell Lung Cancer / 2017 Update (ASCO/ESMO/WCLC) – Practice Changing Studies Abound.

Hope you find our newsletter informative.

Conscientious objection in the era of MAiD: Standing to do or not do what exactly?

By Blair Henry, D. Bioethics, Senior Ethicist, Assistant Professor, Associate Member, School of Graduate Studies, University of Toronto

In a secular western society, legalization of any act does not in and of itself confer it with any special moral standing. As such, at a personal or particular level what might be considered legal could be viewed by some as immoral. Medical Assistance in dying (MAiD) provides an exacting illustration of this phenomenon.

In a law-abiding society, natural rights and freedoms should be bestowed on all citizens—no less so those who profess to undertake the work of healthcare. By example, Article 1 of the Universal Declaration of Human Rights, circa 1948 outlines "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act toward one another in a spirit of brotherhood. All human beings are born free and equal in dignity and rights."[1]

Having moral integrity means being faithful to deeply held religious or moral convictions. This willingness to live and act according to an internally consistent set of basic moral ideas is considered a desirable character trait. The argument holds that when individuals act contrary to these deeply held convictions, the link between principles and actions is severed. This self-betrayal could lead to loss of self-respect.[2]

Conscientious objection in healthcare involves the rejection of some action by a provider (an act which is considered safe, legal, and accepted by the larger community), primarily because the action would violate some deeply held moral or ethical value about right and wrong. This refers to the refusal by a healthcare professional (HCP) to execute an action or participate in a specific situation on the basis of conscience.[3]

Conscientious objection has not always reflected such a noble calling—Shakespeare would give the following voice to King Richard: "Conscience is

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but a word cowards use, devised at first to keep the strong in awe." (Richard III, V.iv.1.7)[4]

Fortunately, in modern times a more nuanced understanding has evolved. However, consensus on the formal standing on conscientious objection remains elusive. Mark Wicclar[5] categorized the following array of potential ethical positions:

The Incompatibility Thesis

This thesis assumes that conscience-based refusals to provide legal and professionally permitted goods and services within the scope of a practitioner's competence are incompatible with the practitioner's professional obligations.

The Conscience Absolutism View

According to conscience absolutism, in addition to not having an obligation to provide a good or service that violates a healthcare professional's conscience, the professional is not obligated directly or indirectly to participate in its provision or facilitate patient access to it.

The Compromise (or Moderate) View

Conventional compromise permits HCPs to refuse to provide a service or product that is against their conscience only if the following three conditions are satisfied:

- The HCP informs the patient if it is medically relevant to their medical condition
- The HCP refers the patient to another professional willing and able to provide the service
- The referral does not impose an unreasonable burden on the patient.

In its decision, the Supreme Court[6] stated that physicians have the right to refuse to assist a patient to die. Subsequently, the federal legislation implementing MAiD[7] provides that nothing compels medical practitioners to provide or assist in providing MAiD. Neither the court nor the federal legislation specifically addresses whether physicians who refuse to assist a patient in dying on moral or religious grounds might be required to refer the patient. However, what would constitute "assistance" was left out of the legislation.

To address this issue, the College of Physicians and Surgeons of Ontario (CPSO) referred to one of its existing policies on Professional Obligations and Human Rights, which outlined the following duties[8]:

- If a physician declines to provide assistance in dying for reasons of conscience or religion, they must do so in a manner that respects patient dignity.
- Physicians must not impede access to assistance in dying, even if it conflicts with their conscience or religious beliefs.
- The physician must communicate his/her objection to assistance in dying to the patient directly and with sensitivity.
- The physician must inform the patient that the objection is due to personal and not clinical reasons. In the course of communicating an objection, physicians must not express personal moral judgments.
- In order to uphold patient autonomy and facilitate the decision-making process, physicians must provide the patient with information about all options for care that may be available or appropriate to meet the patient's clinical needs, concerns and/or wishes.
- Physicians must not withhold information about the existence of any procedure or treatment because it conflicts with their conscience or religious beliefs.
- Where a physician declines to provide assistance in dying for reasons of conscience or religion, the physician must not abandon the patient. An effective referral must be provided. An effective referral means a referral made in good faith, to a non-objecting, available, and accessible physician or agency. The referral must be made in a timely manner to allow the patient to access assistance in dying.

Clearly the CPSO position falls into the "compromise" perspective for managing conscientious. However, division lines have been drawn and the "duty to refer", as it applies to MAiD, is already under legal challenge in Ontario.

To date, most MAiD policies identify the following acts as being considered forms of direct assistance and would be exempt under conscientious objection.

- supporting/educating healthcare professionals regarding the process of assisted dying
- counselling the patient about the option of assisted dying
- assessing the patient's eligibility for assisted dying
- procuring/preparing medications
- inserting an IV for the express purpose of assisted dying
- administering medications as part of the assisted dying protocol
- acting as the patient's primary nurse on the day that assisted dying is administered.

We need to remember that we are only 16 months into this new paradigm and our ability to accommodate and to be sensitive to the needs of all healthcare providers—while being patient centred—is being tested on both sides of this moral divide. In the interim, the creation of the MAiD Care Coordination Service (CCS) has enabled patients to directly self-refer—which has ensured somewhat better access for patients wanting to learn more and potentially seek this alternative at the end of life.

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The chicken or the egg? Mental health and chronic illness

By Christina Crowe, MACP, RP, (Cert) OACCPP, Registered Psychotherapist

Despite a growing body of research confirming a correlation between poor mental health and chronic physical illness, there is still a lack of screening, referral and resources to support Canadians suffering from both. People living with serious mental illnesses are at higher risk of experiencing a wide range of chronic physical conditions. And people living with chronic physical health conditions experience depression and anxiety at *twice the rate* of the general population. The groundbreaking Adverse Childhood Experiences (ACE) Study, one of the largest scientific research studies of its kind, with more than 17,000 participants, demonstrated childhood trauma increases the risk of physical and mental illness in adulthood. ACEs include abuse (emotional, physical, sexual), witnessing domestic violence, parental separation or divorce, or growing up in a household where members were mentally ill, substance abusers, or sent to prison. Over the course of a decade, the results demonstrated a strong, graded relationship between the level of traumatic stress in childhood and poor physical, mental and behavioral outcomes later in life, including susceptibility toward diseases like diabetes, COPD, cancer, cardiovascular disease, stroke and impaired immune function.[1] Yet, many patients continue to not be screened for childhood trauma and, further, when disease becomes evident, the mental illness portion remains untreated for many.

It seems intuitive that mental health and physical health are profoundly linked, but this has not yet translated to more comprehensive care for patients. Co-existing mental and physical conditions can diminish quality of life and lead to longer illness duration and inferior health outcomes.[2] The important interactions of our physiology, the experience of chronic illness, and social determinants of health (income, housing, and education) can mean a greater likelihood someone living with a mental illness or chronic physical condition will develop a co-existing condition.

People living with mental illnesses experience myriad physical symptoms from both illness and treatment, which can be a tricky problem, particularly in cancer care. Mental illnesses can alter hormonal balances and sleep cycles, while many psychiatric medications have side effects ranging from weight gain to irregular heart rhythms.[3] Mental illness influences the way people experience their physical conditions and can increase their vulnerability to continued poor physical health, as a result. Mental illness impacts social and cognitive functions and decreases energy levels, which can negatively impact the adoption of healthy behaviours cancer patients, in particular, are encouraged to implement.

Some chronic physical conditions can cause high blood sugar levels and disrupt the circulation of blood, which can impact brain function.[4] Mental and physical illnesses also share many symptoms, such as food cravings and decreased energy levels, which can increase food consumption, decrease physical activity and contribute to weight gain. People living with chronic physical conditions often experience emotional stress and chronic pain, which are both associated with the development of depression and anxiety. Experiences with disability can also cause distress and isolate people from social supports. There is some evidence the more symptomatic and chronic the physical condition, the more likely a person will also experience mental illness.[5] Thus, it is not surprising people with chronic physical conditions often self-report poor mental health.[6]

Trauma, mental illness and cancer

The 2010 Behavioral Risk Factor Surveillance System (BRFSS) survey showed approximately 62% of respondents reported being exposed to ACEs and about 1 in 10 respondents reported ever having been diagnosed with cancer. Component 1, which had the sexual abuse variables with the highest weights, was significantly associated with adulthood cancer. The authors concluded the association between ACEs and adulthood cancer may be attributable to disease progression through association of ACEs with risk factors for other chronic diseases.[7]

Adverse childhood experiences may be associated with an increased risk of lung cancer, particularly premature death from lung cancer. The increase in risk may only be partly explained by smoking, suggesting other possible mechanisms by which ACEs may contribute to the occurrence of lung cancer. For lung cancer identified through hospital or mortality records, persons with greater than or equal to six ACEs were roughly 13 years younger on average at presentation than those without ACEs.[8]

Recent research has found significantly higher rates of cancer among people with schizophrenia than expected.[9] People with schizophrenia have been found to have approximately twice the risk of developing gallbladder and bowel cancers, which may be linked to high-fat diets, a socioeconomically linked health component.[10]

Finally, people living with cancers face a higher risk of developing depression due, in part, to high levels of stress, emotional upset, and changes in body image.[11] A co-existing mental health problem can interfere with cancer treatment outcomes. For example, older women with breast cancer and a diagnosis of depression were significantly less likely to receive optimal treatment.[12]

What about 'stigma' and other barriers to access in Ontario?

The stigma associated with mental illness continues to be a barrier to the diagnosis and treatment of chronic physical conditions in people with mental illnesses. Stigma acts as a barrier in multiple ways:

- It directly prevents people from bringing their symptoms forward.
- Negative past experiences can prevent people from seeking health care out of fear of judgment.
- Stigma can lead to a misdiagnosis of physical symptoms as 'psychological'. This "diagnostic overshadowing" occurs frequently and can result in serious physical symptoms being either ignored or downplayed.[13]

Systemic barriers include:

- Short appointment times are often not sufficient to discuss mental or emotional health for people with complex chronic health needs.[14]
- Poverty determines housing; having a safe place to store ID, such as a valid OHIP card, becomes an issue for people in precarious housing, limiting access to healthcare in Ontario.

In summary, mental illness and chronic physical conditions share many symptoms, and their interaction is complex. Collaborative mental healthcare initiatives such as shared care approaches can link physicians and allied health with mental health specialists to provide support to clinicians treating patients with mental illnesses and chronic physical conditions. Knowing where to refer patients for collaborative and shared care is critical for better health outcomes. While the mental health system in Ontario is fractured, there are many providers available, from psychiatry, public regional programs and hospital psychotherapy providers, to community-based private psychotherapy. Advocacy to care for patients' whole body, not just from the neck down, is needed to work toward the best outcomes.

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Glucocorticoid-induced myopathy

By Michael Briganti, BSc, Alia Thawer, BScPharm, Mark Pasetka, PharmD, and Susanna Cheng, MD, Sunnybrook Odette Cancer Centre

Introduction

In the field of oncology, glucocorticoids such as prednisone and dexamethasone can be used to manage a multitude of ailments including lymphoma, multiple myeloma, chemotherapy-induced nausea and vomiting, as well as many others.[1] Although they can confer benefit, this class of medication can cause a variety of adverse effects.[2] With short-term use (days to weeks), some of the common adverse effects include hyperglycemia, hypertension, peptic ulcer disease, and insomnia.[2,3] As the duration of glucocorticoid therapy increases (weeks to months), patients are at a higher risk of experiencing ophthalmic, endocrinologic, skeletal, and dermatologic changes.[2,3] While the aforementioned adverse effects are more commonly noted, these medications have also been shown to induce myofibrillar damage resulting in progressive muscle weakness.[4-6] Even though the total incidence of myopathy is low (<1%), when glucocorticoids are used at a high enough dose and duration, the incidence of muscular disturbances can rise to 10 to 40 percent.[3-5] Therefore, it is crucial for healthcare providers to be able to recognize the signs of glucocorticoid-induced myopathy (GIM), in order to manage these patients effectively.

Pathophysiology

Skeletal muscle atrophy by glucocorticoids is a multi-mechanistic process that involves decreasing the rate of protein synthesis while also increasing the rate of protein catabolism.[6,7] Protein synthesis is decreased through the inhibition of amino acid transport into the muscle, limiting the stimulatory action of insulin-like growth factor 1 (IGF-1), and by down-regulating a transcription factor responsible for skeletal muscle development called myogenin.[7] The proposed mechanism of a glucocorticoid's catabolic effect is secondary to the activation of major cellular proteolytic systems.[7] These modifications to protein metabolism result in myofibrillar degradation, which causes decreased cross-sectional area of the muscle fibres resulting in muscle weakness. The main type of muscle fibres affected by GIM are the fast-twitch glycolytic fibres also known as the type IIB muscle fibres.[7,8] The mechanism of specificity for the fast-twitch muscle fibres is not known.[7]

Clinical presentation

In most cases of GIM, patients present with progressive weakening of the proximal muscles in the lower extremities such as the quadriceps.[9] The atrophy induced by glucocorticoids is usually insidious, painless, symmetrical and can affect activities of daily living (ADLs) such as the ability to climb stairs or stand up from a chair.[9] This type of myopathy can also occur in the acute form, which is characterized by rapid weakening of both the proximal and distal muscle groups.[6] The acute form of GIM is rare and generally occurs in an ICU setting when both large doses of glucocorticoids and the patient's acute illness contribute to muscle weakness and atrophy.[6]

Diagnosis, assessment, and management

The diagnosis of GIM is frequently determined by examining the timeline of glucocorticoid treatment initiation in relation to muscle weakness, as well as ruling out other causes of myopathy.[2,6] The diagnosis can be confirmed with improvement in strength within three to four weeks after dose reduction or discontinuation of the glucocorticoid.[5] The recovery time for patients varies and a complete recovery may take months. The levels of muscle enzymes including creatinine kinase, aldolase and lactate dehydrogenase (LDH) are usually in the normal range in patients with this type of myopathy.[6] Electromyography (EMG) results are also normal, as this test is mainly limited to the analysis of type I muscle fibres, which are not commonly affected in GIM.[11]

The dose and duration of glucocorticoid therapy that can induce myopathy is highly variable between patients.[4] In general, the higher the dose and duration is, the greater the likelihood to cause myopathy. Patient's taking a prednisone equivalent of 40-60 mg/day or more can experience clinically significant muscle weakness within two to four weeks while doses that are less than 10 mg/day are very unlikely to cause myopathy.[4,5,8] As the duration of therapy extends beyond one month, the risk of developing GIM continues to increase.[5] In a study with 60 glucocorticoid-treated patients with asthma, patients that took a prednisone equivalent of greater than 40 mg per day had significantly less hip flexor strength than control subjects not taking glucocorticoids, as well as patients taking less than 40 mg per day.[4] Other risk factors for GIM include patients who are male, inactive, have cancer, are older in age, or have a disease that affects the respiratory muscles.[8,9]

For patients that are experiencing GIM, a dose reduction or discontinuation of the glucocorticoid often results in improved muscle strength within three to four weeks.[5] Physical therapy is another method used to prevent and treat patients with myopathy secondary to glucocorticoids.[9] Exercise programs should be individualized based on the patient's medical status and usually includes both resistance and endurance training.[9] Although there is evidence that physical therapy is effective at attenuating this myopathy, more studies are required to determine which exercise protocols are most effective.[9,12] Investigational treatments for GIM include IGF-1, branched chain amino acids, creatinine, androgens, dehydroepiandrosterone (DHEA) and glutamine.[7,8] The majority of the evidence supporting these treatments derive from animal studies, thus additional evidence is required to elucidate the effectiveness of these agents.[7,8]

Discussion

There are still many aspects of GIM that have not been explored and a multitude of limitations on the current literature. There are no studies that compare the relative incidence of GIM between different glucocorticoid agents or if switching from one agent to another is beneficial. Most of the current literature is retrospective analysis and typically has several potential confounders. There is a lack strong evidence with regards to GIM treatment and the duration of time required for complete recovery. Future studies are required to expand our knowledge on this type of myopathy and to determine better methods of treating this condition when a dose reduction or discontinuation is not an option.

Glucocorticoid-induced myopathy may not occur in a high percentage of patients that take this class of medication. However, it is essential for healthcare professionals to be able to identify the risk factors, clinical presentation and treatment strategies in order to effectively manage these patients.

REFERENCES

Available upon request

Continuing Medical Education

By Toby Rodin, Odette Cancer Centre, and Patrick Paladino, PhD, elearning Manager, Oncology Education.com, elearning@oncologyeducation.com

Continuing Medical Education (CME) can update healthcare 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 activities in palliative medicine that are of interest to our readers. Please forward details of the CME activities to: **toby.rodin@sunnybrook.ca**

- **November 17, 2017.** Best of Oncology East Conference. Parkview Manor, Toronto, Ontario. **http://www.oncologyeducation.com/events/upcoming-events/best-of-oncology-east-2017/conference-home/**
- **November 17–18, 2017.** 1st ESTRO Physics Workshop Scottish Exhibition and Conference Centre, Exhibition Way, Glasgow, United Kingdom. **http://estro.org/congresses-meetings/articles/physicsws2017reg**
- **November 26–December 1, 2017.** Radiological Sciences of North America (RSNA) 103rd Scientific Assembly and Annual Meeting, McCormick Place, Chicago. **http://www.rsna.org/Annual-Meeting/**
- **November 30–December 1, 2017.** 5th GEC-ESTRO Workshop, "The Strength of Brachytherapy" Faculty of Medicine and Surgery" A. Gemelli Centro Congressi Europa (Conference Centre) Largo Francesco Vito no. 1, Rome, Italy. **http://estro.org/congresses-meetings/items/5th-gec-estro-workshop**
- **December 5–9, 2017.** San Antonio Breast Cancer Symposium, Henry B. Gonzalez Convention Center, San Antonio, Texas. **http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=115#.WW-RyvMclUI**
- **January 19, 2018.** Best of San Antonio Breast Cancer Symposium (SABCS). Toronto, Ontario. **https://www.oncologyeducation.com/events/upcoming-events/best-of-sabcs-toronto-2018/conference-home/**
- **January 26, 2018.** Best of Oncology West Conference. Toronto, Ontario. **https://www.oncologyeducation.com/events/upcoming-events/best-of-oncology-west-2018/**
- **February 15–17, 2018.** Multidisciplinary Head and Neck Cancers Symposium, Expanding Treatment Horizons, The Westin Kierland Resort and Spa, Scottsdale, Arizona. **http://headandnecksymposium.org/2018-Head-and-Neck-Symposium/Home/**
- **February 22–25, 2018.** 12th Annual Canadian Melanoma Conference. Banff, Alberta. **http://www.oncologyeducation.com/events/upcoming-events/12th-canadian-melanoma-conference/**
- **April 6, 2018.** Best of GU & GI Cancer Summit Canada. Toronto, Ontario. **https://www.oncologyeducation.com/events/upcoming-events/best-of-gu-gi-cancers-summit-2018/**

CME Programs

What I-O Really Means for Your NSCLC Patients. In this video, International guest speaker, Prof. Solange Peters, shares the stage with Dr. Sunil Verma to discuss the latest trends on I-O in NSCLC. Patient advocacy group, Lung Cancer Canada, also provides invaluable patient perspectives. **http://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/clcco-2017-what-i-o-really-means-for-your-nsclc-patients/**

This program meets the accreditation criteria as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada and has been accredited by the Office of Continuing Professional Development, Faculty of Medicine, McGill University for up to 1 Section 1 credits. Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at **www.ama-assn.org/go/internationalcme**. ***This program is accredited until March 2017.***

Learning Library in Pancreatic Cancer – Slide Deck. This slide deck offers a comprehensive overview in 4 key topics in pancreatic cancer including etiopathogenesis and diagnosis of pancreatic cancer; treating resectable disease; treating advanced disease; and supportive care/palliation of symptoms. The distinguished faculty includes Dr. Robert H. El-Maraghi, Dr. Daniel J. Renouf, Dr. Petr Kavan, and Dr. Steven Gallinger. Available in English and French.

English: https://www.oncologyeducation.com/information/gi-updates/slideshows/learning-library-on-pancreatic-cancer/

French: https://www.oncologyeducation.com/information/gi-updates/slideshows/biblioth%C3%A8que-sur-le-cancer-du-pancr%C3%A9as/

Canadian Immuno-Oncology Summit 2017 – Video Archive. These videos summarize presentations from this meeting, which focus on advances in immuno-oncology and the impact on Canadian clinical practice. Topics include toxicity management, side effects, and resistance; biomarker development and diagnosis in routine practice; clinically relevant application of I/O within the Canadian landscape; future avenues and developments in I/O treatment; and tumour-specific sessions including renal cell carcinoma, bladder cancer, hematologic malignancies, breast cancer, and lung cancer. Our faculty of speakers included influential North American medical oncologists across all tumour areas. **https://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/immuno-oncology-summit-2017/**

Madrid 2017 Key Clinical Trial Highlights and Roundtable Discussions – Video Archive. OncologyEducation was on-site at the 2017 Meeting in Madrid to share breaking clinical data highlights from key trials presented at the meeting. We also recorded roundtable discussion in breast, lung, GI, GU and skin cancers, featuring a panel of Canadian and International experts discussing pivotal trial data and the impact on Canadian clinical practice.

Clinical Trial Highlights: https://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/updates-from-madrid-2017-round-table-discussions/

Roundtable Discussions: https://www.oncologyeducation.com/events/oncologyeducation-events-video-archives/updates-from-madrid-2017-round-table-discussions/

Non-Small Cell Lung Cancer 2017 update (ASCO/ESMO/WCLC) Practice-changing studies abound

HOT SPOT

By Dr. Parneet K. Cheema, BSc, MD, MBiotech, FRCPC, Assistant Professor, Department of Medical Oncology, University of Toronto, Medical Oncologist, William Osler Health System

Early Stage Resected NSCLC

NSCLC–ADJUVANT trial[1]

- Adjuvant cisplatin-based chemotherapy is the standard of care for completely resected early-stage NSCLC and provides an OS of 5.4% across all stages.[2]
- In the RADIANT trial adjuvant erlotinib (EGFR TKI) +/- adjuvant chemotherapy in an unselect patient population did not result in improvements in overall survival (OS) or disease-free survival (DFS).[3]

Study design: ADJVUANT was a randomized phase III trial, conducted in China of patients with resected stage II-IIIA, EGFR positive (exon 19 deletion/exon 21 L858R), randomized to the EGFR TKI gefitinib 250 mg/day x 24 months versus cisplatin/vinorelbine x 4 cycles. The primary endpoint was DFS.

Results

- Baseline characteristics were well balanced, 64-65% had stage IIIA
  - No data were available on PET scans for staging prior to study entry
- **Gefitinib significantly improved DFS compared to chemotherapy**
  - **28.7 months vs 18 months; p=.005**
  - **3-year DFS: 34% vs 27%.**
- Outcomes were similar among all subgroups reported, including sex, smoking status, type of *EGFR* mutation, lymph node status (N1 vs. N2), and histology.

Impact on practice

This study shows an absolute improvement in three-year DFS of 7% with adjuvant gefitinib compared to the current standard of care chemotherapy. The criticisms of this study are that ~2/3 of patients had stage IIIA disease in which the absolute OS benefit of chemotherapy is the highest (HR:0.83). Thus, the study design should have included the option for chemotherapy in those eligible in the experimental arm. Also, 23% of patients refused chemotherapy opposed to only 5% in the gefitinib arm, and these patients were included in the intent-to-treat analysis. Finally, data on PET imaging prior to study entry were not presented. After three years, the DFS started to converge (after the study drug had been stopped), thus we need to question if we are simply delaying recurrence by providing an active therapy earlier, opposed to truly curing more patients. Thus, exposing patients to gefitinib for two years should be associated with an improvement in OS and we await these results prior to changing practice.

Unresectable Stage III

PACIFIC [4]

Sunnybrook Odette Cancer Centre Participation → Centre PI Dr. Parneet Cheema

- Median OS of patients with unresectable stage III NSCLC is 18 months with only 15% of patients alive at five years.[5]
- Standard of care for patients with a good performance status is platinum based chemotherapy, concurrent with radiotherapy (cCRT).[6]
- There have been no major advances in locally advanced NSCLC for several years with negative consolidative systemic therapy trials.[7]

Study design: PACIFIC was a randomized, phase 3, placebo controlled trial, evaluating durvalumab (anti-PDL1) as consolidation therapy for patients with unresectable stage III NSCLC who did not have disease progression after cCRT. Patients were treated within 1-42 days of completion of radiation with durvalumab 10 mg/kg q2 weeks x 1 year and were randomized after completion of cCRT. This was an unselect patient population according to PD-L1 status. Co-primary endpoints were PFS and OS.

Results

- Durvalumab resulted in significant improvement in PFS, overall response rates (ORR), time to death or distance metastases compared to placebo
  - **PFS: 16.8 months vs. 5.6 months; HR: 0.52; p<0.001**
- Benefit was seen in all pre-specified subgroups including non-smokers and was independent of PD-L1 positivity (positive defined as PD-L1 expression >25%)
  - ORR: 28.4% vs. 16%; p<0.001
  - Median time to death or metastases: 23.2 months vs. 14.6 months; HR:0.52 p<0.001
- Safety: Durvalumab was well tolerated with similar rates of grade 3/4 AE events to placebo (30% v*s* 26%). All cause pneumonitis (includes radiation and immune mediated pneumonitis) was slightly higher, 34% vs 25% (all grades)**.** Rate of discontinuation due to all-cause AEs was similar, 15% vs 10%.

Impact on practice

This is the first trial to show a clinically significant PFS advantage with consolidative systemic therapy following cCRT for unresectable stage III NSCLC, with durvalumab improving PFS by 11 months. Although we await the OS analysis, given that the PFS is ~17 months with durvalumab, and historical trials have demonstrated that the median survival in this patient population is only 18-24 months this PFS advantage is clinically significant. Also, durvalumab appeared to be safe. Anti-PD-L1 therapies have been associated with immune mediated pneumonitis, therefore there was concern about giving this class of drugs shortly after high dose radiation to the chest. Fortunately, the rates of pneumonitis were not considerably different. Data that we look forward to in addition to OS are results for patients that were PDL1 negative. This group was presented with patients that had PDL1 low expression (1-24 %), and thus results may differ for these patients once separated out.

Durvalumab is now a treatment option for patients with unresectable stage III NSCLC after completion of definitive cCRT with a platinum doublet and have not progressed. This indication has been filed with Health Canada.

Metastatic NSCLC

EGFR positive–FLAURA[8]

Sunnybrook Odette Cancer Centre Participation → Centre PI Dr. Parneet Cheema

- EGFR TKIs are standard of care first-line treatment for patients with tumours harbouring activating EGFR mutations.
- First generation EGFR TKI gefitinib improves median PFS (9 months) compared to standard chemotherapy (5-6 months) in patients with treatment naïve EGFR mutated NSCLC.[9]
- Second generation EGFR TKIs have demonstrated slightly longer PFS with 11 months with afatinib and 14.7 months with dacomitnib (not available in Canada).[10,11]
- Eventually resistance to 1st/2nd generation EGFR TKIs develops with 50-60% developing a T790M mutation in exon 20 of the EGFR tyrosine kinase domain.
- Osimertinib is a 3rd generation EGFR TKI that targets the sensitizing EGFR mutations (Del19 and L858R) in addition to the T790M mutation. Osimertinib has shown to improve median PFS (10.1 months) in patients with T790M positive NSCLC compared to platinum doublet (PFS 4.4 months).[12]
- Osimertinib has also shown to have CNS activity with CNS ORR of 54%-70% and responses seen with leptomenigeal disease.[13]

Study design: FLAURA is a randomized, phase 3, placebo controlled trial, comparing osimertinib to standard of care (gefinitib or erlotinib) for treatment naïve patients with advanced EGFR positive NSCLC. The primary endpoint was PFS.

Results

- Osimertinib significantly improved PFS
  - **Median PFS 18.9 months versus 10.2 months; HR 0.46; p<0.0001.**

    The PFS curves split early unlike previous 1st line EGFR TKI studies
- This benefit was seen in all subgroups, including smoking history, EGFR mutation, CNS metastases.
- There was no difference if the EGFR mutation was detected by tissue or with plasma ctDNA
- ORR: 80% versus 76%; HR 1.28: p=NS
- Less CNS progression was seen in patients with CNS metastases at study entry
  - Osimertinb 18.9% vs 42.7%, *although no brain imaging was required on the study*
- OS data are immature (25% maturity). Median OS not reached in either arms. HR:0.63; p=0.0068, this did not reach statistical significance
- Crossover data are not yet available
- Safety: 13% discontinued due to all cause in both arms. Rate of grade 3 any cause was numerically less than SOC 18% versus 28%.

Impact on treatment

Osimertinib significantly improved PFS compared to first generation EGFR TKIs. However, osimertinib also has activity following 1st/2nd generation EGFR TKIs and thus sequencing of EGFR TKIs is under debate. If patients were treated with a 1st/2nd generation EGFR TKI (gefitinib/erlotinib/afatinib) then receive osimertinib in 2nd line the cumulative PFS is 19-21 months (Figure 1). However, this applies to 50-60% of patients that are fortunate to develop the T790M mutation as their resistance mechanism to the 1st/2nd generation EGFR TKI. 40% of patients that are T790M negative, the cumulative sum for PFS is only 14-16 months as they would receive chemotherapy 2nd line. We have to also take into consideration the following when deciding if patients should be started with osimertinib or a 1st/2nd generation EGFR TKI followed by osimertinib if they are T790M positive:

1. QoL: 40% of patients that are T790M negative after a 1st/2nd generation EGFR TKI will get chemotherapy during that period, which has lower QoL compared to EGFR TKIs.
2. Morbidity with rebiopsing patients following progression on a 1st/2nd generation EGFR TKI.
3. Osimertinib has durable CNS activity, unlike 1st/2nd generation EGFR TKIs where it is limited. And, thus, important to consider for patients presenting with CNS metastases.
4. Finally, we have to remember that there is a significant drop off of NSCLC that never get to second line therapy and, thus, the cumulative PFS with the sequential approach only represents those patients well enough to get to second line therapy.

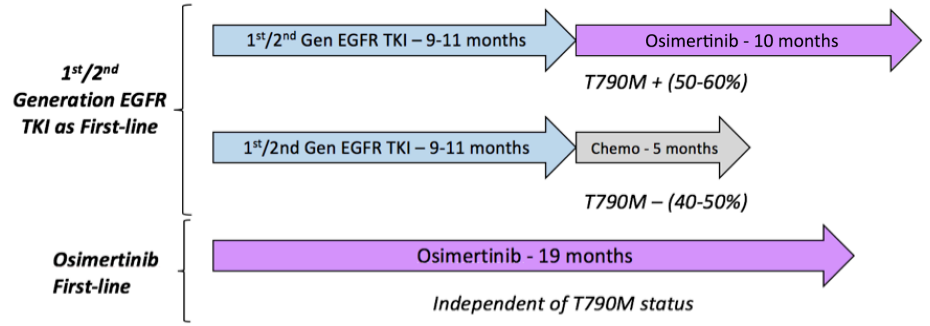

Figure 1: Progression-free survival with sequential EGFR TKIs versus upfront 3rd generation EGFR TKI with Osimertinib

ALK positive – ALEX[14,15]

Sunnybrook Odette Cancer Centre Participation → Centre PI Dr. Parneet Cheema

- The current standard of care for patients with newly diagnosed, advanced ALK+ NSCLC is the first generation ALK inhibitor (ALKi) crizotinib.[16]
- Alectinib a 2nd generation ALKi has efficacy in crizotinib resistant ALK+ NSCLC with a median PFS of 9.6 months and response of 52%.[17]
- J ALEX was presented in 2016, of alectinib versus crizotinib in ALKi naïve ALK+ NSCLC in a Japanese population at a dose of 300 mg po BID and resulted in significant improvement in PFS HR of 0.34, median not reached in alectinib arm, versus 10 months, as expected with crizotinib.[18]

Study design: ALEX, is a randomized, phase 3 trial of alectinib (dose of 600 mg po BID) to crizotinib in treatment naïve ALK+ NSCLC. This study was conducted internationally. The primary endpoint was PFS.

Results

- Aletinib significantly improved PFS compared to crizotinib
  - **PFS investigator (primary endpoint): Not reached vs 11.1 months; HR: 0.47, p<0.0001**
  - PFS independent review committee: 25.7 months vs 10.4 months ; HR: 0.50, P<0.0001
- ORR: 76% vs 83%; HR: 0.09
- Alectinib improved responses within the CNS, prevented progression in CNS and development of CNS metastases
  - Response in patients with measurable/non-measurable brain metastases 59% versus 26%
    Duration of response in measurable metastases: 17.3 vs 5.5 months
  - Progression in CNS at 12 months, HR 0.16; p<0.0001, 9.4% vs 41.4%
  - Subgroup of patients with CNS metastases at baseline (n=122)
    Delayed progression in brain 16% versus 58.3%; HR: 0.18, p<0.0001
  - Development of brain metastases in those that did not have CNS metastases at study entry
    4.6% versus 31.5%; HR: 0.14, p<0.0001
- OS immature: HR 0.76 , median OS not reached in either arm
- Safety: No significant differences. Rate of grade 3-5 was 41% with alectinib versus 50% with crizotinib.

Impact on treatment

Alectinib resulted in a 15-month improvement in PFS compared to crizotinib. However, OS data are immature and, thus, it can be debated that sequential approach of crizotinib then alectinib upon progression remains a treatment option. The factors that support alectinib as the preferred first-line therapy is that the PFS documented in two randomized trials with 1st line alectinib was 5-6 months larger than the sum of the PFS of the sequential approach of 19 months (PFS with crizotinib 10 months + PFS with alectinib 10 months). Understanding limitations of this sum being underestimated, as patients may be treated beyond progression, although balanced with the overestimation of benefit, as this assumes all patients move to second-line therapy. Also, brain metastases in ALK+ population contributes to significant cause of morbidity and mortality, and alectinib, in fact, led to a protective CNS effect and durable responses to patients with existing brain metastases. Thus, alectinib would be recommended as the preferred first-line treatment for advanced ALK+ NSCLC. Alectinib is currently approved by Health Canada for metastatic ALK+ NSCLC after failure of crizotinib and has been filed for the indication of first-line therapy in ALK+ NSCLC.

PD-L1 positive >50% - Keynote 024[19,20]

- Keynote 010, demonstrated that pembrolizumab had superior OS to docetaxel in patients with advanced NSCLC that had tumours expressing PD-L1 ≥ 1% that have failed platinum doublet.[21]
- PD-L1 expression in patients with advanced NSCLC correlates with improved responses to pembrolizumab.[22]

Study design: Keynote 024 was a randomized, phase 3 trial, of pembrolizumab 200 mg/kg fixed dose q3weekly compared to platinum/pemetrexed in treatment naïve patients with advanced EGFR/ALK wild-type NSCLC with high PD-L1 expression of ≥ 50%.

Results

- Pembrolizumab significantly improved Survival, PFS, and Response Rates with an improved safety profile
  - **Median OS: 30 months versus 14.2 months; HR: 0.63, p=0.002**
  - 55% of patients crossed over from chemotherapy to pembrolizumab
  - Two-year OS: 52% vs 35%
- PFS: 10.3 months versus 6.0 months; HR: 0.50; <0.001
- Crossover: 75% of patients in the chemotherapy arm received an anti-PD1/PDL1 either through crossover or off study
- Response: 46% vs 30%; p=0.0031
  - Patients treated with chemotherapy and receiving pembrolizumab second-line response was only 21%
  - Duration of response: Not reached versus 7.2 months
  - Safety: Grade 3-5: 31% versus 53%

Impact on practice

Pembrolizumab is now the standard of care first-line therapy for patients with EGFR/ALK wildtype metastatic NSCLC with tumours that have high PD-L1 expression (≥ 50%). This applies to both squamous and non-squamous NSCLC. A survival advantage of 16 months was seen with pembrolizumab despite 75% of patients receiving immune checkpoint inhibitors as second line. This study also highlights the importance of pathologists in the management of NSCLC and requesting PD-L1 status for NSCLC in a timely manner to allow oncologists to make biomarker driven treatment decisions. PD-L1 testing is now available in Canada and pembrolizumab is approved as first-line therapy for advanced NSCLC PD-L1 ≥ 50% and after failure of a platinum doublet in advanced NSCLC PD-L1 ≥ 1%.

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Cyclin-dependent Kinase 4/6 Inhibitors in Hormone Receptor Positive HER2 Negative Advanced Breast Cancer: A Review

HOT SPOT

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- CDK 4 and 6 are kinases which regulate the transition from G1 to S phase of the cell cycle.
- Estrogen binding to ER-alpha allows cyclin D to complex with CDK4/6 during G1, leading to inactivation of Rb, releasing E2F to drive expression of genes required for S-phase entry.
- Palbociclib, ribociclib and abemaciclib are highly selective, orally active inhibitors of CDK4 and CDK6, with the ability to trigger cell cycle arrest.
- Abemaciclib is structurally distinct, and more potent against D1/CDK4 than D3/CDK6.
- Palbociclib is approved with letrozole for patients who have not received prior systemic treatment for ABC, and with fulvestrant in disease progression after ET.
- Ribociclib has US FDA approval with an AI as initial endocrine-based therapy for HR+/HER2- ABC.
- Abemaciclib has FDA Breakthrough designation status as monotherapy after previous ET.

KEY PALBOCICLIB TRIALS

PALOMA-1/TRIO-18

- Randomized phase II study of letrozole +/- palbociclib in the first-line treatment of postmenopausal women with HR+/HER2- ABC.
- PALBO improved PFS to 20.2 mos vs LET alone at 10.2 mos (HR 0.488, one sided p <0.001).
- Trend towards improvement in OS in the PALBO arm (37.5 mos vs 33.3 mos, HR 0.837, p=0.280).

PALOMA-2

- Randomized double-blind placebo-controlled phase III trial designed to confirm PALOMA-1.
- PALBO/LET median PFS of 24.8 mos vs 14.5 mos in the placebo cohort (HR 0.58, p<0.001).
- OS data are immature.
- Neutropenia was the most common adverse event in the combination arm.
- Most common grade 3/4 AEs: neutropenia (PALBO vs placebo) in 66.4% vs 1.4%, leukopenia (24.8% vs 0%), anemia (5.4% vs 1.8%) and fatigue (1.8% vs 0.5%).
- Febrile neutropenia: 1.8% of patients on PALBO vs 0% on placebo.

PALOMA-3

- Randomized double-blind placebo-controlled phase III trial of PALBO and fulvestrant in previously treated HR+/HER2- ABC.
- PALBO/FULV resulted in median PFS of 9.5 mos vs 4.6 mos in placebo group (HR 0.46, p< 0.001).
- Most common grade 3/4 AEs (PALBO vs placebo): neutropenia (62.0% vs 0.6%), thrombocytopenia (2.3% vs 0%), and fatigue (2.0% vs 1.2%).

KEY RIBOCICLIB TRIALS

MONALEESA-2

- Randomized double-blind placebo-controlled phase III trial of ribociclib in combination with letrozole as first-line therapy; notable in that it met its primary endpoint early.
- At 26 mos F/U, treatment benefit was confirmed with median PFS 25.3 mos for RIBO/LET vs 16.0 mos for placebo/LET (HR 0.568, $p=9.63x10^{-8}$)
- Probability of remaining progression-free at 24 mos was 54.7% for patients receiving RIBO/LET vs 35.9% for those on placebo.
- At a median of 26 mos F/U of patients with measurable disease at baseline, ORR was 54.5% vs 38.8%, and clinical benefit rate was 80.2% vs 71.8%.
- For measurable disease, RIBO/LET had earlier and more durable tumour response, and higher proportion of patients with tumour reduction and greater % reduction in tumour size.
- OS data remains immature.
- Most common AEs in RIBO group: neutropenia (74.3%), nausea, infections (mainly urinary and upper respiratory tract infections), fatigue and diarrhea.
- Most common grade 3/4 AEs for RIBO: neutropenia (59.3%) and leukopenia (21%).
- No new cases of Grade 4 neutropenia were reported after cycle 9.
- Other grade 3/4 AEs for RIBO: increased AST (5.7%) and increased ALT (9.3%); liver enzyme levels returned to normal in all following RIBO discontinuation.
- Prolongation of QTcF > 480msec occurred in 3.3% of patients on RIBO within the first 4 weeks and was limited by proactive dose reduction/interruption.
- Most AEs in the RIBO group, irrespective of causality, were grade 1/2, thus allowing most patients to remain on treatment.
- Disease progression was most common reason for treatment discontinuation (39.8% vs 60.8%).
- No clinically meaningful or statistically significant differences in HRQoL were observed between treatment arms, suggesting that AEs did not significantly impact overall HRQoL.
- A clinically relevant reduction in pain from baseline (>5 points) was maintained up to and including cycle 15 in the RIBO/LET arm.

Table 1: Differences between CDK4/6 inhibitors

	Palbociclib	Ribociclib	Abemaciclib
Molecular wt (g/mol)	447.543	434.548	506.606
Molecular formula	$C_{24}H_{29}N_7O_2$	$C_{23}H_{30}N_8O$	$C_{27}H_{32}F_2N_8$
Half-life (hours)	26	36.2	17-38
Dosing	125mg daily (3/1 schedule)	600mg daily (3/1 schedule)	150/200mg twice daily (continuously)
Dose limiting toxicity	Neutropenia	Neutropenia	GI, Fatigue

Generously supported by an educational grant from Novartis

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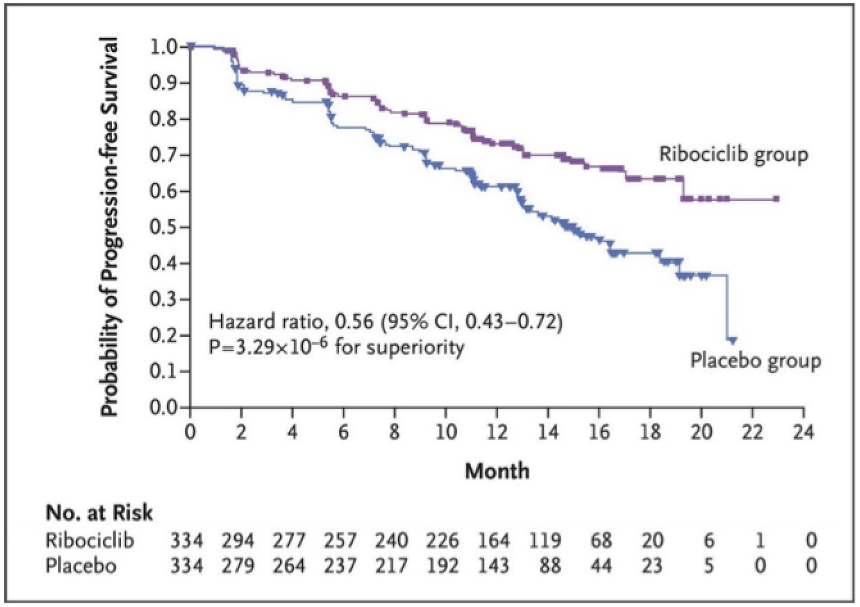

Figure 1: Kaplan-Meier Analysis of 15.3 Month PFS in MONALEESA-2

MONALEESA-3

- Phase III trial in men and postmenopausal women of FULV +/- RIBO in 1rst/2nd line mets.
- Includes patients with ABC, who may be treatment-naïve OR who have progressed after one line of ET (AI or antiestrogen).
- Includes patients with relapsed cancer > 12 mos from completion of (neo)adjuvant ET, with no treatment for advanced disease (first-line).
- Includes patients with relapsed cancer on/ within 12 mos from (neo)adjuvant ET with no treatment for advanced disease (first-line, early relapse).
- Includes patients with relapse more than 12 mos from completion of (neo)adjuvant ET, and then subsequent progression after one line of ET for metastatic disease (AI or antiestrogen).

MONALEESA-7

- Phase III study exploring ribociclib in combination with ET (tamoxifen or NSAI) in premenopausal women in the first line setting ABC; all receive goserelin.

KEY ABEMACICLIB TRIALS

MONARCH 1

- Phase II study of women with locally advanced/ MBC with progression on/after ET and max two lines of chemo for mets (one must contain taxane).
- Abemaciclib as monotherapy 200mg BID until disease progression.
- Objective response rate (ORR) was 19.7% and median PFS was 5.95 mos.
- Median OS was 22.32 mos.
- Most common AEs: diarrhea (all grades: 90%, grade 3/4: 19.0/0%), fatigue, nausea, decreased appetite, abdominal pain.
- Increased creatinine in 98.5% of patients, 0.8% were grade 3 and 0% were grade 4.

MONARCH 2

- Randomized double-blind placebo-controlled phase III trial of ABEMA 150mg BID with FULV.
- Patients had disease which had progressed on (neo)adjuvant ET or < 12 mos from the end of ET, or while receiving first-line ET for mets.
- ABEMA achieved median PFS 16.4 mos vs 9.3 mos for placebo arm (HR 0.553, p<0.001).
- Most frequent AEs of any grade (ABEMA vs placebo): diarrhea (86.4% vs 24.7%), neutropenia (46.0% vs 4.0%), nausea (45.1% vs 22.9%), fatigue (39.9% vs 26.9%) and abdominal pain (35.4% vs 15.7%).
- 25% more patients in the ABEMA arm experienced increase in serum creatinine c/w placebo.

MONARCH 3

- Randomized double-blind placebo-controlled phase III trial of adding ABEMA to NSAI (anas/let).
- Abemaciclib 150mg po twice daily, continuous schedule.
- 18-mos interim analysis was reported at ESMO in September 2017.

Table 2: Summary of Key CDK4/6 Inhibitor Trials: FIRST LINE SETTING

STUDY	POP'N	PHASE	CRITERIA	TREATMENT	PFS
PALOMA-1 N=165	PostMP HR+/ HER2-	II	First line ABC, de novo, no NSAI in (neo)adjuvant setting within 12mos	Letrozole/ palbociclib Letrozole	20.2mos 10.2mo
PALOMA-2 N=666	PostMP HR+/ HER-	III	As above	Letrozole/ palbociclib Letrozole/placebo	24.8mos 14.5mos
MONALEESA-2 N=668	PostMP HR+/ HER-	III	As above, history of cardiac dysfunction and QTcF >450msec excluded	Letrozole/ ribociclib Letrozole/placebo	25.3mos 16.0mos
MONALEESA-3 N=active	Men and postMP women HR+/ HER-	III	Subset will be as above, but also see Table 3 below	Fulvestrant/ ribociclib Fulvestrant/ placebo	Pending
MONALEESA-7 N=active	PreMP HR+/ HER-	III	As above, one line of chemo for MBC allowed	Tamoxifen/NSAI + Goserelin with Ribociclib/ Placebo	Pending
MONARCH 3 N=493	PostMP HR+/ HER-	III	As above	NSAI/ Abemaciclib 150mg BID NSAI/placebo	N/reach 14.7mos

- Med PFS not reached in the ABEMA arm vs 14.7 mos in the placebo arm (HR 0.543, p=000021)
- Most frequent AEs were (ABEMA vs placebo) diarrhea (81.3% vs 29.8%), neutropenia (41.3% vs 1.9%) and fatigue (40.1% vs 31.7%).
- Exploratory subgroup PFS analysis suggested patients with indicators of poor prognosis had substantial benefit from ABEMA, while in other patients (eg. long treatment-free interval or bone-only disease) single agent ET may be appropriate therapy.

NO CROSS-TRIAL COMPARISONS SHOULD BE MADE DUE TO DIFFERENCES IN PATIENT POPULATIONS BETWEEN STUDIES.

Pharmacology And Dosing Schedule

- PALBO initial dose is 125mg capsule OD, with food, for 21 days, followed by 7 days off.
- RIBO initial dose is 600mg OD (preferably in the morning) for 21days, followed by 7 days off; absorption is not affected by food.
- ABEMA initial dose is 150 or 200mg BID continuously.
- All undergo hepatic metabolism by CYP3A, thus concomitant use of strong CYP3A inhibitors (antibiotics, antifungals) or inducers (rifampin, anticonvulsants) should be avoided.
- QT prolonging agents eg antiarrhythmics and other agents eg haloperidol, methadone or IV ondansetron may result in QTc prolongation when co-administered with RIBO.

Toxicity and Safety Overview

- Neutropenia is rapidly reversible, with median duration 7-15 days.
- Febrile neutropenia is rare (eg. 1.5% in the MONALEESA-2 trial).
- Neutropenia reflects cytostatic (not apoptotic) effect on neutrophil precursors.
- Perform CBC/diff at baseline and Q2 weeks for the first 2 cycles and prior to each 28-day cycle.
- Dose re-escalations are not typically recommended following modification.
- Most non-heme AEs were grade 1/2, and grade 3/4 events are reversed by DR/DIs.
- Nausea/vomiting: use routine antiemetics, eg metoclopramide, prochlorperazine, or serotonin 5-HT3 antagonists prn (Caution: ribociclib and QTc).
- ABEMA-induced diarrhea has median time to onset 6 days, and resolves quickly with antidiarrheal agents or dose reduction.
- Especially for RIBO, perform liver enzymes at baseline, q2wks for the first 2 cycles, prior to each subsequent four cycles, and then as clinically indicated.
- For RIBO, baseline ECG should demonstrate QTcF < 450msec prior to initiating therapy, and QTcF should be monitored cycle 1 day 15, cycle 2 day 1, and then prn clinically.
- ABEMA is a competitive inhibitor of efflux transporters of creatinine, thus renal function should be monitored at baseline, cycle 1 day 15, then monthly.
- Creatinine increase on ABEMA does not affect glomerular function, but dose interruptions are typically considered for grade 3/4 toxicity.

Table 3: Review of Key CDK4/6 Inhibitor Trials: RELAPSE ON/WITHIN 12 MONTHS OF (NEO)ADJUVANT THERAPY, OR BEYOND FIRST-LINE

TRIAL	POP'N	PHASE	CRITERIA	TREATMENT	PFS
PALOMA-3 N=521	Pre and postMP women HR+/HER-	III	Progression during prior ET. Included progression during or within 12mos after adjuvant therapy. One prior line of chemo for ABC was allowed.	Fulvestrant/palbociclib Fulvestrant/placebo (preMP received goserelin)	9.5mos 4.6mos
MONALEESA-3 N=active	Men and postMP women HR+/HER-	III	As Table 2, + relapsed after (neo)adjuvant ET with no restriction, second-line ABC (progression after one line of ET for ABC). Prior chemo excluded.	Fulvestrant/ribociclib Fulvestrant/placebo	Pending
MONARCH 1 N=132	PostMP women HR+/HER-	II	Progression on/after endocrine therapy and maximum two lines of chemo.	Abemaciclib monotherapy 200mg BID continuously	5.95mos
MONARCH 2 N=669	Pre and postMP women HR+/HER-	III	Progression on (neo)adjuvant ET (<= 12mos), or while on first-line ET for ABC. No prior chemo.	Fulvestrant/abemaciclib 150mg BID Fulvestrant/placebo	16.4mos 9.3mos

Conclusion

- CDK4/6 inhibitors have been shown to be safe, well-tolerated oral agents.
- They represent a highly efficacious treatment strategy in combination with endocrine therapy (letrozole/anastrozole or fulvestrant) for HR+/HER2- ABC patients.
- MONALEESA-2 HRQoL data, using patient-reported outcomes, suggests the quality of time gained by delaying disease progression is preserved for RIBO/LET patients in the 1rst line.
- Ongoing phase III trials will strengthen their role in the treatment of the most common subset of advanced breast cancer.

References

Available upon request.