CLINICAL CASE PRESENTATION

59-YEAR-OLD MALE WITH STAGE IV NON-SMALL CELL LUNG CANCER WITH AGGRESSIVE DISEASE*

Clinical Case Presentation By:
Tarek Mekhail, MD, MSc, FRCSI, FRCSEd
Associate Medical Director of Florida Hospital Cancer Institute and Director of Thoracic Cancer Program, Cancer Institute of Florida, Florida Hospital Medical Group

*Aggressive disease is defined by those patients who were primary platinum refractory (patients whose best response was progressive disease) or patients with rapidly progressing disease (time-to-progression within 9 or 12 weeks) after starting initial platinum-based treatment.1,2

INDICATION

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 6-7 and accompanying full Prescribing Information for CYRAMZA.
Dr. Mekhail Presents a Challenging Clinical Case of a Patient With Aggressive Disease*†

History of Present Illness
- 59-year-old white male previously in good health presented to his primary care physician with increasing shortness of breath and dry cough
- Chest X-ray showed right pleural effusion
- CT scan of the chest revealed right upper lobe peripheral lung mass and a moderate right pleural effusion with pleural nodularity
- CT scan of the abdomen shows multiple liver lesions and 2-cm right adrenal mass, all consistent with metastatic disease
- MRI scan of the brain was negative for metastasis. Tumor was PD-L1 negative by immunohistochemistry (TPS <1%)
- Patient was diagnosed with T2NXM1b, Stage IV adenocarcinoma of the lung

Past Medical History
- Well-controlled hypertension on ACE inhibitors
- Patient smoked half a pack a day from age 25 to 40. Quit 19 years ago

Social History
- Accountant
- Married with 3 children
- Oldest daughter will soon be married

Initial Treatment
- Patient was started on chemotherapy with pemetrexed and a platinum every 3 weeks with vitamin B12 and folic acid supplementation
- He developed progressive disease after 2 cycles of treatment with significant enlargement of the right lung mass. He also developed an increasing liver metastasis, increasing right adrenal nodule, and development of a new left adrenal nodule

Physical Exam/Review of Symptoms at Progression
- ECOG PS 1
- Patient was mildly fatigued
- He admitted to having right upper quadrant discomfort responding to analgesics
- Patient denied any hemoptysis

Response Assessment/Follow-Up Imaging
- A follow-up assessment identified an increase in the right lung mass from 3 to 7 cm, multiple liver lesions, right adrenal mass previously 2 cm, now 10 cm, 3-cm new left adrenal nodule.

Patient Attitude/Characteristics
- Patient very concerned about rapid progression of disease and would like to pursue further treatment that could help provide a response
- He is determined to slow his disease and try for as much time as possible with his family
- Patient still having relatively few symptoms from the cancer and would be able to consider further therapy

Treatment Plan
- A discussion with the patient regarding his options included immunotherapy as well as chemotherapy-based treatment. He elected to proceed with ramucirumab and docetaxel every 21 days

Why adding CYRAMZA may be appropriate
- Patient presents with aggressive disease*†
- ECOG PS 1
- Patient is hopeful for a response on additional therapy
- Patient has no prior history of hemoptysis, nor any tumor in proximity to major blood vessels

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This is a hypothetical patient case based on the author’s clinical experience with CYRAMZA in combination with docetaxel for mNSCLC.

† Aggressive disease is defined by those patients who were primary platinum refractory (patients whose best response was progressive disease) or patients with rapidly progressing disease (time-to-progression within 9 or 12 weeks) after starting initial platinum-based treatment. 1, 2

ACE=angiotensin-converting enzyme; ALK=anaplastic lymphoma kinase; CT=computerized tomography; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; mNSCLC=metastatic non-small cell lung cancer; MRI=magnetic resonance imaging; PD-L1=programmed death-ligand 1; P5=performance status; TPS=tumor proportion score; TTF-1=thyroid transcription factor 1.

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.
**ITT POPULATION (N=1253)**

<table>
<thead>
<tr>
<th></th>
<th>CYRAMZA + docetaxel</th>
<th>Placebo + docetaxel</th>
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<tbody>
<tr>
<td><strong>OS</strong></td>
<td>10.5 months† (9.5, 11.2)</td>
<td>9.1 months† (8.4, 10.0)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.86 (95% CI: 0.75, 0.98)</td>
<td>P=0.004</td>
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Hazard ratio 0.86 (95% CI: 0.75, 0.98); P=0.004

**REVEL Trial Design (N=1253)**

The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were required to have Eastern Cooperative Oncology Group performance status 0 or 1. Patients were randomized 1:1 to receive either CYRAMZA 10 mg/kg or placebo, respectively, with docetaxel 75 mg/m² every 21 days.

**SELECT IMPORTANT SAFETY INFORMATION**

- The labeling for CYRAMZA contains a Boxed Warning for: hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation.
- CYRAMZA contains additional Warnings and Precautions for: arterial thromboembolic events, which are sometimes fatal; hypertension; infusion-related reactions; clinical deterioration in patients with Child-Pugh B or C cirrhosis; reversible posterior leukoencephalopathy syndrome; proteinuria including nephrotic syndrome; thyroid dysfunction; and embryofetal toxicity. The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (95% vs 46%; 49% vs 40%), fatigue (95% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; 1% vs 1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs 1%), thrombocytopenia (13% vs 5%; 3% vs 1%), lactic acidosis (13% vs 5%; 0% vs 0%), and hypertension (11% vs 5%; 6% vs 2%). The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 6-7 and accompanying full Prescribing Information for CYRAMZA.

**CONSIDER CYRAMZA PLUS DOCETAXEL FOR PATIENTS WITH AGGRESSIVE DISEASE**

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**REVEL EXPLORATORY ANALYSES**: The REVEL trial was not powered for subgroup analyses, nor were any such analyses error-controlled. The primary platinum-refractory population (n=360/N=1253) was a pre-specified subgroup in the REVEL trial; however, the subgroup of patients with limited time on initial platinum-based therapy (≤8 or ≤12 weeks; n=200/N=1253 and n=448/N=1253, respectively) was not pre-specified. Each subgroup analysis presented was exploratory. Kaplan-Meier estimates and Cox regression analyses of OS and PFS were performed for all subgroups. The Cochran-Mantel-Haenszel test assessed differences in ORR between treatment groups. Safety analyses were performed on both subsets of patients from the safety population, defined as all patients who had received at least one dose of study drug.

**With Consistent Results in Patients With Aggressive Disease**

**Exploratory Subgroup Analysis: PATIENTS WITH REFRACTORY DISEASE (n=360)**

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<tr>
<td><strong>OS</strong></td>
<td>8.3 months† (6.6, 9.8)</td>
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<td>Hazard ratio</td>
<td>0.68 (95% CI: 0.68, 1.08)</td>
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Hazard ratio 0.68 (95% CI: 0.68, 1.08); P=0.10

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<td><strong>PFS</strong></td>
<td>4.0 months† (2.9, 4.4)</td>
<td>2.5 months† (1.6, 2.8)</td>
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Unstratified Hazard Ratio 0.68 (95% CI: 0.37, 0.93)

**ORR**

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Hazard ratio 0.86 (95% CI: 0.75, 0.98); P=0.004

The percentage of deaths at the time of analysis was 89% (558 patients) and 93% (583 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.

The percentage of events at the time of analysis was 88% (156 patients) and 92% (168 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.

Aggressive disease is defined by those patients who were primary platinum refractory (patients whose best response was progressive disease) or patients with rapidly progressing disease (time-to-progression within 9 or 12 weeks) after starting initial platinum-based treatment.

The percentage of deaths at the time of analysis in the CYRAMZA plus docetaxel arm was 75% (134 patients) and 77% (141 patients) in the placebo plus docetaxel arm.

The percentage of events at the time of analysis in the CYRAMZA plus docetaxel arm was 88% (156 patients) and 92% (168 patients) in the placebo plus docetaxel arm.

The REVEL trial was not powered for subgroup analyses, nor were any such analyses error-controlled. The primary platinum-refractory population (n=360/N=1253) was a pre-specified subgroup in the REVEL trial; however, the subgroup of patients with limited time on initial platinum-based therapy (≤8 or ≤12 weeks; n=200/N=1253 and n=448/N=1253, respectively) was not pre-specified. Each subgroup analysis presented was exploratory. Kaplan-Meier estimates and Cox regression analyses of OS and PFS were performed for all subgroups. The Cochran-Mantel-Haenszel test assessed differences in ORR between treatment groups. Safety analyses were performed on both subsets of patients from the safety population, defined as all patients who had received at least one dose of study drug.

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The labeling for CYRAMZA contains a Boxed Warning for: hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications. CYRAMZA contains additional Warnings and Precautions for: arterial thromboembolic events, which are sometimes fatal; hypertension; infusion-related reactions; clinical deterioration in patients with Child-Pugh B or C cirrhosis; reversible posterior leukoencephalopathy syndrome; proteinuria including nephrotic syndrome; thyroid dysfunction; and embryofetal toxicity. The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (95% vs 46%; 49% vs 40%), fatigue/asthenia (95% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; 1% vs 1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs 1%), thrombocytopenia (13% vs 5%; 3% vs 1%), lactic acidosis (13% vs 5%; 0% vs 0%), and hypertension (11% vs 5%; 6% vs 2%). The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.

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IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA if severe and/or tightness, chills, flushing, dyspnea, wheezing, hypotension, and hypertension. Monitor patients during the infusion for signs of symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations
• CYRAMZA is an angiogenic therapy that can increase the risk of gastrointestinal perforation. Discontinue CYRAMZA therapy in patients with impaired wound healing. withheld CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage
• CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticagulation or chronic therapy with NSAIDs or other antplatelet therapy other than one-time aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)
• Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension
• An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertension or cerebral ischemia occurred in clinical trials.

Infusion-Related Reactions (IRRs)
• Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypotension, and paresthesia. In severe cases, patients included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs of symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Clinical Deterioration in Child–Pugh B or C Cirrhosis
• Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatic encephalopathy, was reported in patients with Child–Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child–Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
• RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome
• Monitor proteinuria by urine dipstick and/or urinary protein concentration ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction
• Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity
• Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions
• The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (35% vs 46%; 49% vs 40%), fatigue/asthenia (35% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (35% vs 10%; 16% vs 10%), peripheral edema (19% vs 9%; 8% vs 5%), throat ulcer (13% vs 5%; 3% vs 1%), laceration increased (13% vs 5%; <1% vs <1%), hypotension (11% vs 5%; 4% vs 2%).
• The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in placebo plus docetaxel-treated patients.
• In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.

Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel–treated patients than in placebo plus docetaxel–treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related (0.5%) and hypotension (0.5%).
• For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel–treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions
• No pharmacokinetic interactions were observed between ramucirumab and docetaxel.

Use in Specific Populations
• Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug–associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.

• Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise breastfeeding women that breastfeeding is not recommended during treatment with CYRAMZA.

• Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.
Tarek M. Mekhail, MD, MSc, FRCSI, FRCSEd is currently the Associate Medical Director of Florida Hospital Cancer Institute and the director of the Thoracic Cancer Program at the Florida Hospital Cancer Institute. He is an associate professor at the University of Central Florida. Dr. Mekhail joined the Cancer Institute from the Cleveland Clinic where he was the director of the Lung Cancer Medical Oncology Program and The Hardis Chair of Oncology Research.

Dr. Mekhail completed his medical degree at Cairo University in 1984. He then completed his surgical training in the United Kingdom, where he earned fellowships of the Royal College of Surgeons of Edinburgh and the Royal College of Surgeons in Ireland. He completed his medical oncology fellowship at the Cleveland Clinic in Cleveland, Ohio.

Dr. Mekhail’s extensive experience and leadership in the field of lung cancer are assets to the US healthcare community, which can be attested by being voted one of the Best Doctors in America since 2007.

He has published more than 200 peer-reviewed articles, abstracts, and book chapters.