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ANTIRESORPTIVE BONE THERAPY USE IN ADVANCED LUNG CANCER AND ASSOCIATED OUTCOMES

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THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Pharmacy
at the University of Kentucky

By

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Lexington, Kentucky

Director: Dr. Val R. Adams, Professor of Pharmacy Practice and Science

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2020

ABSTRACT OF THESIS

ANTIRESORPTIVE BONE THERAPY USE IN ADVANCED LUNG CANCER AND ASSOCIATED OUTCOMES

Background/Rationale: Studies have shown antiresorptive agents decrease skeletal related events in metastatic non-small cell lung cancer. However, two prevalence studies have found low utilization rates of antiresorptive therapy in advanced lung cancer. The first study reported a rate of 14.8% during the 1995-2009 time period, while the second study reported a 33% usage rate during the time frame of 2002-2011. We believe these low utilization rates are associated with the poor prognosis of these patients. The prognosis of advanced lung cancer has improved significantly since these trials were conducted, and the utilization of denosumab has not been evaluated. We hypothesize that intravenous antiresportive bone therapies are underutilized in patients with metastatic lung cancer.

Objectives: To characterize the utilization of antiresportive therapies in patients with metastatic lung cancer and to evaluate predictive factors in their initiation.

Methods: This study was a retrospective analysis of EHR data from the University of Kentucky Enterprise Data Warehouse (UKEDW) linked to Kentucky Cancer Registry (KCR) containing patients from 1/1/2013 to 1/31/2020. Patients diagnosed with metastatic lung cancer are included with "index date" being date of first systemic treatment. Key exclusion criteria included lack of systemic therapy provided at UK. Incidence of antiresorptive bone therapy initiation was measured. Descriptive statistics and multivariate logistic regressions were performed to assess factors predicting use and selection of agent.

Results: Over the study time period, only 16.3 % of patients who received their first systemic therapy at UK were initiated on an antiresorptive bone medication, with denosumab being the primary agent used (~65%). Logistic regression analysis shows that patients with bone metastasis present at diagnosis of stage IV NSCLC had 4.26 times the odds of receiving an antiresorptive bone medication (95% [CI: 2.146,8.442]) than those who did not have bone metastasis at diagnosis.

Conclusions: For metastatic non-small cell lung cancer patients receiving their first systemic therapy at the University of Kentucky, antiresorptive bone therapies are being underutilized with the primary predictor of use as bone metastasis at diagnosis.

KEYWORDS: Real World Evidence, Oncology, Non-Small Cell Lung, Bone Health

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03/19/2020

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DEDICATION

To my family and committee for their continuous support.

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CHAPTER 1. INTRODUCTION

With a current 5-year survival rate of around 20.5% overall and 5.8% for distant disease, lung cancer is the leading cause of cancer death and the second most commonly diagnosed cancer in the world [1, 2]. Although the prognosis of the disease seems grim, survival rates have shown a steady increase since the 1980s, with a concomitant decrease in incidence over the last 10 years by approximately 2.1%. Lung cancer is divided into two main subtypes: small cell and non-small cell [1]. Non-small cell lung cancer, abbreviated as NSCLC, can be further divided into adenocarcinoma, squamous cell carcinoma, or large cell (undifferentiated) carcinoma [3]. Regardless of the type of cancer detected, staging a patient is important in order to determine prognosis and the best treatment path to take. Furthermore, genetic screening is also an important factor in determining the presence of targetable mutations with therapy. While surgery is the most effective treatment modality in resectable cancer, patients with advanced non-operable disease with targetable mutations or programmed death ligand-1 (PD-L1) overexpression may benefit significantly from targeted or immunotherapies. These medications fall under the umbrella of precision medicine and have significantly increased the expected progression free survival and overall survival for metastatic NSCLC as compared to standard chemotherapy [4]. Additionally, the recent FDA approval of these agents for NSCLC has increased utilization, showing further promise in improving overall survival rates.

Evolution of Standard of Care for NSCLC

Over the past two decades, there have been several pivotal trials performed and therapies approved for NSCLC. Prior to the advent of targeted and immunotherapies, cytotoxic chemotherapy was the standard of care for advanced lung cancer. In 1994, a meta-analysis analyzing survival of advanced NSCLC patients receiving chemotherapy versus best supportive care showed that the median survival of 3.9 months for patients receiving best supportive care only increased to a median survival of 6.7 months with chemotherapy [5]. This indicates the extremely poor prognosis of advanced lung cancer patients, regardless of the administration of systemic chemotherapy. In 2002, Schiller et. al. published a study analyzing four chemotherapy regimens in 1155 eligible advanced

NSCLC patients in order to assess the combination of third generation chemotherapy agents with a platinum-based compound (platinum-doublet) on survival. Combinations of cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel were compared to cisplatin and paclitaxel. The study found a median overall survival of 7.9 months which did not differ significantly among any of the four groups [6].

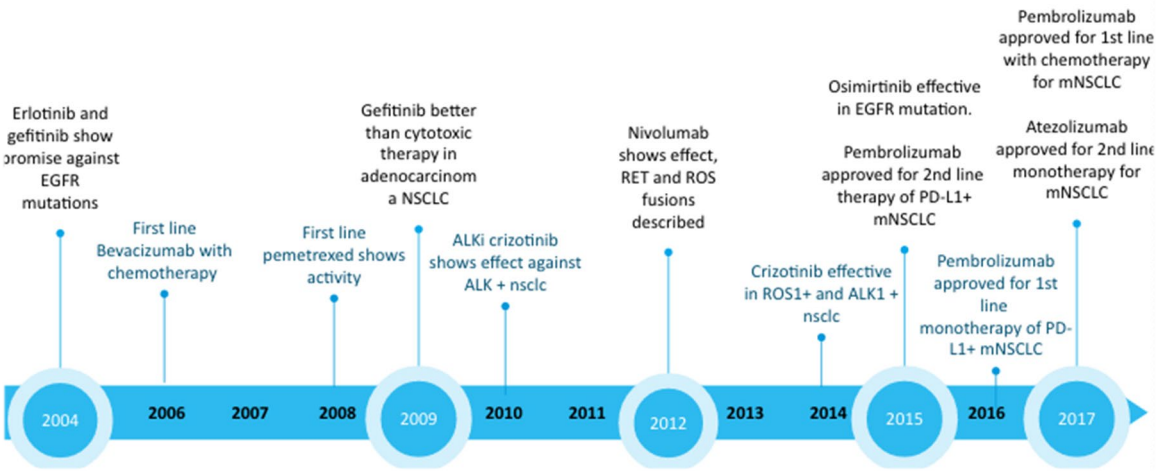
In 2004, tyrosine kinase inhibitors gefitinib and erlotinib showed positive results against first-generation epidermal growth factor receptor (EGFR) mutations, with gefitinib showing longer progression free and overall survival than chemotherapy in advanced lung (stage IIIB and IV) cancer patients in 2009 (PFS: 10.8 months versus 5.4 months; OS: 30.5 months versus 23.6 months) [7, 8]. Other therapies that targeted ALK, ROS1, and BRAF rearrangements soon followed, greatly increasing median progression free and overall survival in patients with targetable driver mutations (see figure 1.1 for timeline). The global phase III ALEX trial which began in August of 2014 aimed to compare tyrosine kinase ALK inhibitors alectanib versus standard of care crizotinib, in previously untreated ALK positive advanced NSCLC patients. While initial trial results showing superior efficacy and lower toxicity of alectanib to crizotinib were published in 2017, a recent trial update has reported median progression-free survival (PFS) for alectanib as 34.8 months versus 10.9 months with crizotinib. Furthermore, because the 5-year overall survival (OS) endpoint has not yet been reached, the update has reported that at 4 years, 62.5% of the patients in the alectanib group were still alive (52% with crizotinib). Compared to the aforementioned 5.2% overall 5-year survival rate, targeted therapies present an unprecedented survival advantage for patients with advanced NSCLC [9-12].

The final therapy class that has changed NSCLC standard of care includes immune checkpoint blockers (immunotherapy). In 2015, PD-1 inhibitor pembrolizumab, was shown to be better than docetaxel in second line metastatic NSCLC. One year later (2016), pembrolizumab was further approved for first line monotherapy of PDL positive metastatic NSCLC [7]. The KEYNOTE-189 trial showed an estimated 12-month survival rate of 69.2% [95% CI: 64.1, 73.8] in the pembrolizumab-combination group as compared to 49.4% in the placebo-combo group [95% CI:0.38,0.64] [13]. In 2017, pembrolizumab was further approved for first line treatment with chemotherapy in

metastatic NSCLC [4, 7]. In September 2018, the updated KEYNOTE-189 median OS was 22.0 months (95% CI : 19.5 to 25.2) in the pembrolizumab-combination group versus 10.7 months (CI: 8.7 to 13.6) in the placebo-combination group with a median PFS of 9.0 months (95% CI: 8.1 to 9.9) months and 4.9 (95% CI: 4.7 to 5.5) months, respectively [14].

In a disease that had a prognosis of about half a year *with* treatment just one decade ago to now having patients living more than a year with no progression, immunotherapy and targeted therapy have paved the way of hope for many advanced non-small cell lung cancer patients.

Figure 1.1 Timeline of Pivotal Trials and Drug Approvals for NSCLC Treatment [7]



Bone Metastases and Skeletal Related Events

The average age of diagnosis of non-small cell lung cancer is 70 years old with the majority of patients (57%) presenting with stage IV distant disease that has metastasized to a region outside of the lungs [1, 15]. The bones are one of the most common sites of metastasis (20-30%) and their involvement has been correlated with an increased incidence of skeletal related events or SREs [16, 17]. These may include hypercalcemia, bone fractures, spinal cord compression, or bone pain requiring local radiation. Normal bone is constantly being remodeled by two types of cells: osteoclasts and osteoblasts. While osteoblasts build and re-mineralize bone, osteoclasts absorb and break down bone. An imbalance of one of these processes can lead to either excessive buildup or breakdown of the bone, which can lead to the aforementioned skeletal related

complications. Bone metastases in cancer patients can be characterized as osteolytic, osteoblastic or mixed bone lesions. In NSCLC, bone metastases typically occur due to osteolytic lesions which manifest due to an imbalance of osteoclast resorption of the bone rather than tumor meditated bone destruction [18]. Bone metastases can cause a significant amount of pain and discomfort for the patient (commonly treated with opioid analgesics), further decreasing patient quality of life [19-21].

A Comparison of Antiresorptive Bone Therapies

Pamidronate

Pharmacology:

Pamidronate disodium is a bisphosphonate that inhibits resorption of the bone by binding to calcium phosphate (hydroxyapatite), seemingly blocking the mineral's dissolution. The agent has also been shown to inhibit excessive tumor induced osteoclastic activity in animal models without inhibiting bone formation and mineralization. The half-life elimination of pamidronate is 28 ± 7 hours whereas half-life in bone is estimated at 300 days [22]. Studies using pamidronate for osteolytic lesions in breast cancer and multiple myeloma dosed pamidronate disodium at 90 mg given every 3-4 weeks [23]. As pamidronate is renally eliminated, the medication becomes renally toxic when administered too quickly. In order to mitigate this adverse event, the 2007 American Society of Clinical Oncology clinical practice guideline recommends clinicians reduce initial pamidronate dose and administer infusion over a minimum of 2 hours (especially in patients with pre-existing renal impairment) [24].

Efficacy:

Pamidronate has been shown to be effective for bone metastases in breast and prostate cancers and multiple myeloma [22], and although not specifically approved for lung cancer, it is commonly used for other solid tumor patients as it was the first IV bisphosphonate approved. One retrospective analysis performed in 2009, did aim to characterize the tolerability of the bisphosphonate in the NSCLC population, however, the study had clear limitations including unbalanced study groups and a small population size. Nonetheless, pamidronate appeared to be well tolerated and safe but no clinical

conclusions could be made with regard to its efficacy compared to zoledronic acid in metastatic NSCLC [25].

Zoledronic Acid

Pharmacology:

Zoledronic acid (ZA) is an injectable bisphosphonate that inhibits osteoclast mediated bone resorption by specifically targeting the enzyme farnesyl pyrophosphate synthase. Zoledronic acid has a strong binding affinity to bone mineral with a high turnover rate. After IV infusion, ZA rapidly partitions to bone undergoing osteoclast resorption allowing the drug to target areas of bone metastases [26]. ZA reaches a maximum concentration in the body 24 hours after infusion, and its 146-hour half-life constitutes that it be administered once every 28 days. Furthermore, zoledronic acid has a less renally toxic profile than pamidronate, allowing for faster infusion time no shorter than 15 minutes. Hypocalcemia is a noted side effect, and calcium levels should be monitored with ZA administration. Cases of osteonecrosis of the jaw (ONJ) have been reported and can be mitigated by avoiding invasive dental procedures such as tooth extraction [26].

Efficacy:

Numerous randomized controlled studies have demonstrated zoledronic acid's effectiveness in delaying time to SREs in patients with metastatic NSCLC [27, 28]. One pivotal study by Rosen et al. looked at the long-term effects of 4 mg zoledronic acid administration over 21 months compared to placebo in NSCLC patients with bone metastases. This trial found a 31% reduced risk [HR 0.692, P=0.003] of developing an SRE as well as a longer median time to first SRE development (236 days 4mg, 155 days placebo) [29]. Patients in the zoledronic acid group also reported bone pain less frequently than the placebo group [29] with findings from studies by Van Moos and Henry et al. corroborating reductions in pain or opioid analgesic use secondary to bone-targeted agent administration [30]. A systematic review assessing the effects of bisphosphonates on bone pain and quality of life noted that a decrease in stable analgesic consumption was found in 58% - 75% of patients in four single arm studies [31]. Other studies have also demonstrated that the bisphosphonate may contain antitumor properties,

as it has been shown to act synergistically with chemo, targeted, and immunotherapies potentially increasing overall survival (OS) [32-35].

Denosumab

Pharmacology:

Denosumab is a human monoclonal antibody that binds to RANKL (receptor activator of NFκB ligand), a protein that is essential for the survival of osteoclasts. RANKL is responsible for activating the RANK receptor that is located on osteoclasts and their precursors [36]. By inhibiting the RANKL-RANK interaction, denosumab subsequently prevents the maturation and survival of osteoclasts, therefore reducing bone turnover [37].

Efficacy:

Six head-to-head randomized controlled trials have been performed comparing the efficacy of zoledronic acid and denosumab for the prevention of skeletal-related events in patients with solid tumors [38]. A systematic review published in 2012 comparing three of the identically designed phase III trials showed an increased time to first SRE and less total SREs in favor of denosumab. While zoledronic acid and denosumab appeared to be equivalent in overall survival and disease progression in this analysis overall, (HR= 0.98; 95% CI [0.91-1.06]), (HR=1.02, 95% CI [0.96-1.09]) [39], an exploratory sub-group analysis of one of these trials by Scagliotti et al. has shown a median overall survival benefit in favor of denosumab (9.5 months versus 8 months with ZA; HR =0.78, p = 0.01) in patients with NSCLC. This study also found a lower rate of serious adverse events in the denosumab group versus ZA group (66% versus 72.9%), with similar incidence of ONJ. Patients treated with denosumab had higher rates of hypocalcemia (8.6% versus 3.8%) [40].

A Comparison of Guidelines

Two major guidelines that comment on the use of these bone therapy agents include those from the National Comprehensive Cancer Network (NCCN) from the United States and those from the European Society of Medical Oncology (ESMO). Four points of comparison among the two guidelines include selection of bone therapy agent,

dosing, time of agent initiation, and optimal duration of therapy. (See Table 1.1 for summary of recommendations).

Bone Therapy Agent Selection:

Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend for the use of "orthopedic stabilization and palliative external beam radiation therapy" for bone metastases if there is a risk of fracture, and a 'consideration' for the use of bisphosphonate therapy (zoledronic acid or pamidronate) or denosumab in patients with metastatic NSCLC [41]. Details of therapy are left up to clinical judgement among the three agents, however the guideline does reference the aforementioned Scagliotti et al. study showing a survival benefit in favor of denosumab to ZA (9.5 months versus 8 months), and points out that the FDA has only approved "zoledronic acid and denosumab in patients with bone metastases with solid tumors" [40, 41]. To compare to the NCCN guidelines, the ESMO guidelines go into more detail of the different trials performed in each of the solid tumor states, and how the dosing and recommendations compare to each other. More specifically, the ESMO guidelines cite in detail the phase III trial that compared zoledronic acid to denosumab in 1776 non-breast/prostate solid tumor patients, stating that although the trial did not exclusively contain lung cancer patients, a large proportion (40%) had NSCLC, and showed an extended time to first SRE from 16.3 to 20.6 months, thus recommending therapy for patients with life expectancy >3 months and perceived high SRE risk. Similar to NCCN, the ESMO guidelines maintain the choice of antiresorptive bone therapy agent (zoledronic acid, denosumab, or pamidronate) open, while emphasizing that although ZA has not been proven superior to pamidronate per se (except for post-hoc analysis in breast), denosumab has shown greater efficacy to ZA in trials with pre-specified end-points [42].

Dosing:

NCCN NSCLC guidelines do not specify dosing of bisphosphonates or denosumab, leaving details of therapy up to clinical judgement [41]. With regard to dosing, ESMO cites the doses used in each of the bone-targeted therapy studies based on efficacy and regulatory approval. For all solid tumors, the guideline lists zoledronic acid 4 mg i.v. every 3-4 weeks and denosumab 120 mg subcutaneously every 4 weeks.

Pamidronate 90 mg i.v. every 3-4 weeks only received regulatory approval for breast cancer and multiple myeloma [42].

Time of Bone Therapy Initiation:

With regard to therapy initiation, NCCN NSCLC guidelines state that denosumab or intravenous bisphosphonates can be considered in patients with bone metastases [41]. ESMO guidelines make a more definitive recommendation on bone therapy initiation stating that bone-targeted therapy *should* be started at diagnosis of metastatic bone disease [42].

Optimal Duration of Therapy:

Both NCCN and ESMO guidelines state that optimal duration of antiresorptive bone therapy is unknown, although ESMO guidelines still recommend that therapy "should continue indefinitely and throughout the course of the disease" [41, 42].

With the numerous differences in recommendations between and within guidelines along with clear uncertainty with regard to optimal duration of therapy, patterns of antiresportive bone therapy use in real world practice is a necessary point of exploration.

Table 1.1: Summary of Guideline Recommendations Regarding Bone Therapy Use in NSCLC

Agent Selection	Dosing
NCCN & ESMO Leave choice between agents open but cite trials favoring denosumab over zoledronic acid	**NCCN:** Does not specify **ESMO:** zoledronic acid 4 mg i.v. every 3-4 weeks denosumab 120 mg s.c. every 4 weeks pamidronate 90 mg i.v. every 3-4
Time of Initiation	Optimal Duration
NCCN: 'consideration' for the use of bisphosphonate or denosumab in patients with bone metastases. **ESMO:** start at diagnosis of metastatic bone disease	**NCCN & ESMO**: optimal duration of therapy is unknown **ESMO:** but therapy "should continue indefinitely and throughout the course of the disease".

Literature Outlining Utilization of Antiresorptive Bone Therapies

There appear to be two studies that have assessed the prevalence and characteristics of metastatic lung cancer patients utilizing antiresorptive bone therapies. The first study looked at IV zoledronic acid or pamidronate administration prior to or after an SRE in breast, prostate, and lung cancers using data from two large US health systems from 1/1/1995 to 12/31/2009. The authors identified 332 patients with lung cancer and bone metastases and determined that only 14.8% of those patients received IV bisphosphonates [43]. The prevalence of denosumab use was not evaluated. The authors of this study also conducted a similar analysis of rates of skeletal related events in lung cancer patients from the same time frame and health system datasets. They found that 41.0% of NSCLC patients had an SRE at 6 months post diagnosis of bone metastases [20].

The second study utilized the Truven Health MarketScan® Commercial and Medicare databases from 2002-2011 [44]. This study was published in 2014 and the authors claim to be the first to characterize IV bone medication "practice patterns" in lung, prostate, and breast cancer patients with bone metastases using ICD-9 codes. This study identified 10,982 eligible lung cancer patients and found similar utilization results as the study above. Of the three solid tumor disease states examined, lung cancer patients received IVB's the least frequently (33% versus 59% for breast and 43% for prostate) and had the highest rate of IVB therapy treatment discontinuation at 12 months (83% lung versus 56% prostate and 45.8% breast). One limitation of this study included the fact that denosumab was dropped from analysis. It was FDA approved for the prevention of skeletal related events in November of 2010, and not enough claims were present to examine patterns of use among the three cancers [36, 44]. Another limitation was the non-differentiation of non-small cell lung cancer versus small cell lung cancer due to the nature of the claim's dataset.

Overall, both studies found an underutilization of bone medication use in metastatic lung cancer patients and there remains a large gap in knowledge of the true prevalence of bone health medication use in this population [43, 44]. The first study was performed during a time span that predated NCCN guideline recommendations of administering bone health medications for the NSCLC population, and both studies did not account for

the use of denosumab, which has shown superiority to zoledronic acid in three trials [41, 45, 46]. Furthermore, as both studies used date of bone metastasis diagnosis as the primary index, patients who received intravenous bone therapies without having a diagnosis of bone metastasis were not included in the final analysis, narrowing the view of real-life practice patterns. As these medications are currently in the guidelines, prescribing and administration patterns of intravenous bone therapies may have also changed and should be characterized, as actual rate of utilization in the NSCLC population is currently unknown.

Current information is also outdated as new targeted agents and immunotherapies have been approved since both prevalence studies were performed. Many of these therapies show an increased overall survival time in this population, so maintaining a good quality of life is essential in those additional months with a goal of delaying time to skeletal related event. Additionally, some targeted therapies have shown synergistic effects alongside bone-health medications with respect to tumor response and survival time, making the effect of their combinations an interesting point for exploration [47]. Finally, there is anecdotal evidence from University of Kentucky HealthCare (UKHC) that these medications are currently only being given to less than 20% of eligible non-small cell lung cancer patients. Contingent on the results, this may be a good area for a dissemination and implementation (D&I) protocol.

CHAPTER 2. METHODS

Overview

The primary aim of this study is to characterize the utilization of antiresportive therapies in patients with metastatic non-small cell lung cancer treated at University of Kentucky HealthCare. Furthermore, as the previously cited prevalence studies excluded denosumab in their analysis, a sub-aim of the study is to describe the overall utilization of these therapies broken down by agent (pamidronate, zoledronic acid, denosumab) and by year (1/1/2013 – 1/31/2020). Finally, as the NCCN guidelines for lung cancer do not specify the optimal dosage and frequency of these agents in lung cancer, a secondary aim is to describe trends in antiresorptive therapy usage (dose and frequency) for each agent and compare the selection of therapy based on age, gender, histology, and region of the country (urban versus rural). We hypothesize that antiresportive therapies are underutilized in patients with metastatic lung cancer.

Databases

The Kentucky Cancer Registry (KCR) as well as the University of Kentucky Enterprise Data Warehouse (UKEDW) were the two databases used to conduct this study. As established by legislation passed by the Kentucky General Assembly in 1990, KCR is the official population-based central cancer registry for the Commonwealth of Kentucky. Every healthcare facility in Kentucky is required to report any cancer case diagnosis or treatment to KCR through the use of the Cancer Patient Data Management System (CPDMS) established by the registry. As one of the registries constituting the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, one of the most ‘accurate and complete population-based cancer registries globally,’ the Kentucky Cancer Registry has received funding from the program to ensure the collection of quality data with enhanced and complete follow-up information. Furthermore, KCR is part of the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and submits annually to the North American Association of Central Cancer Registries (NAACCR) for objective evaluation of ‘completeness, accuracy, and timeliness’. Since 1999, KCR has received Gold status

from NAACCR, the highest level of certification, further supporting the rigor of the dataset [48].

The KCR data provided necessary histological, topographical, and demographic information that cannot be found in the UK database alone. [See Appendix 1 for KCR definitions]. Furthermore, the KCR data provided a more standardized, structured, and holistic collection of cancer diagnosis and treatment types and dates if a patient did not receive continuous care at one Kentucky facility (due to transfers or treatment at multiple sites). The initial population pulled from the KCR dataset was used as the source population and then linked to the UKEDW. UK HealthCare electronic health record (EHR) data provided detailed information regarding medication administration and laboratory test results during patient hospital and ambulatory care visits [49]. In order to conduct this study, access to identifiable private information was needed.

Data Collection

Stage IV non-small cell lung cancer cases from 1/01/2013 – 1/31/2020 were obtained from the Kentucky Cancer Registry and were linked to information from UK's Enterprise Data Warehouse. An honest broker from the UK Center for Clinical and Translational Science (CCTS) data collection team was supplied with patient identified cancer records, which were then linked to the electronic health records from the EDW by unique patient medical record number (MRN). Information linked from UKEDW included encounters containing antiresorptive bone medication administration, lab information, incidence of skeletal related events, etc. [See Appendix 2 for codes used in encounter identification] The final dataset provided to the investigators for analysis was de-identified.

Sample Selection

In order to determine incidence of antiresorptive bone therapy use in the UK stage IV NSCLC population, a source population needed to be defined. This population was denoted as the ‘denominator’ population and was limited to those deemed eligible to receive intravenous antiresorptive bone therapy. A proxy of eligibility included receiving systemic cancer therapy (chemotherapy or immunotherapy) at University of Kentucky

HealthCare (UKHC) Markey Cancer Center as an initial inclusion criterion. In order to capture different snapshots/scenarios of bone therapy use, further population stratification was performed by the three methods outlined below.

Population 1: Patient's first systemic treatment was received at UKHC.
Population 2: At least one systemic treatment was received at UKHC.
Population 3: Multiple systemic treatments were received at UKHC.

As Kentucky's only National Cancer Institute (NCI)-designated cancer center, the Markey Cancer Center has a large proportion of referrals for treatment, precision medicine, and clinical trials. Moreover, while many patients may present to Markey for initial surgical management or treatment, they may be referred out for more convenient management at partner facilities with closer proximity to the patient's home. As such, the methodology of source population stratification is intended to mimic different scenarios with regard to referral, and likelihood of being able to capture bone medication administration in a patient that may not have received continuous care at University of Kentucky.

As defined above, Population 1 is intended to mimic the most commonly expected scenario, whereby an intravenous antiresorptive bone medication is given close to first systemic treatment of a patient diagnosed with metastatic lung cancer in accordance with the guidelines cited above. Population 2 considers that UKHC is a referral center and attempts to capture a patient treated systemically at UKHC, regardless of whether it was the first instance, as this patient may have been diagnosed and treated elsewhere, then referred to UKHC for further management. Population 3 requires that patients received two or more systemic treatments at UKHC in order to increase the probability of capturing bone medication use due to increased facility contact points. See appendix 3 for visualizations of population scenarios.

Statistical Analysis

Descriptive Statistics

Descriptive statistics were performed to describe each patient population from the three populations outlined above as well as from the overall stage IV NSCLC population and the subgroup of those patients who did not receive systemic therapy. Variables of

interest included patient demographics, year of diagnosis, cancer histology, smoking status, geographic designation (rural versus urban), presence of metastases at diagnosis (bone, liver, or brain), and average days to first treatment (in general and systemic).

Utilization

Incidence of antiresorptive bone therapy use was determined for each population. This study was a retrospective analysis with an index date of first systemic therapy for each of the populations defined above. Incidence of bone therapy medication use was measured with initiation on same day as chemo/immune systemic therapy, within 1 month of treatment, and at interval points thereafter with affiliated percentiles and averages. Bone medication administration during an inpatient visit to UKHC with affiliated corrected serum calcium level of >12 mg/dL (Corrected Ca = serum calcium – serum albumin + 4) were noted, as antiresorptive bone agents can also be used to treat hypercalcemia of malignancy. After an incident case of antiresorptive bone medication use was identified, the associated patient was categorized as an intravenous antiresorptive bone therapy user. After incidence determination, subsequent patterns of bone medication use were analyzed with descriptive statics for most common medication, doses, and dosing frequencies.

Regression Analysis

Finally, a logistic regression was performed to determine factors predicting bone medication use. This was only done in population one as it is the most expected scenario of bone medication administration. Bone medication users were determined from the incident-case flag defined above. Variables of interest included patient demographics, year of diagnosis, cancer histology, smoking status, geographic designation (rural versus urban), and presence of metastases at diagnosis (bone, liver, or brain). Sub-group analysis for patients that presented with bone metastases at diagnosis was also performed. 95% confidence intervals were reported, and P values < 0.05 were considered to be statistically significant.

This study was reviewed and approved by the University of Kentucky Institutional Review Board. Data analysis was completed using SAS Version 9.4 and Microsoft SQL Server Management Studio v17.7.

CHAPTER 3. RESULTS

Characteristics of Study Population

Figure 3.1 depicts the study population obtained from the Kentucky Cancer Registry and subsequently linked to UK electronic health records. 1161 unique patients were diagnosed with stage IV NSCLC and were seen at UK at some point during the course of their treatment. Of those patients, 548 or 47% received at least one systemic treatment of chemotherapy or immunotherapy. 241 of those patients did not receive any systemic therapy at UK, leading them to be excluded from the three populations of interest shown in figure 3.2. Overall 307 patients received at least one systemic treatment at UK, and 295 of those patients received their first systemic treatment at UK. 104 patients received more than one systemic treatment at UK with the majority of this cohort (101 patients) also receiving their first systemic treatment at UK.

Figure 3.1 Final Study Population Derived from KCR and Linked to UK EHR Records

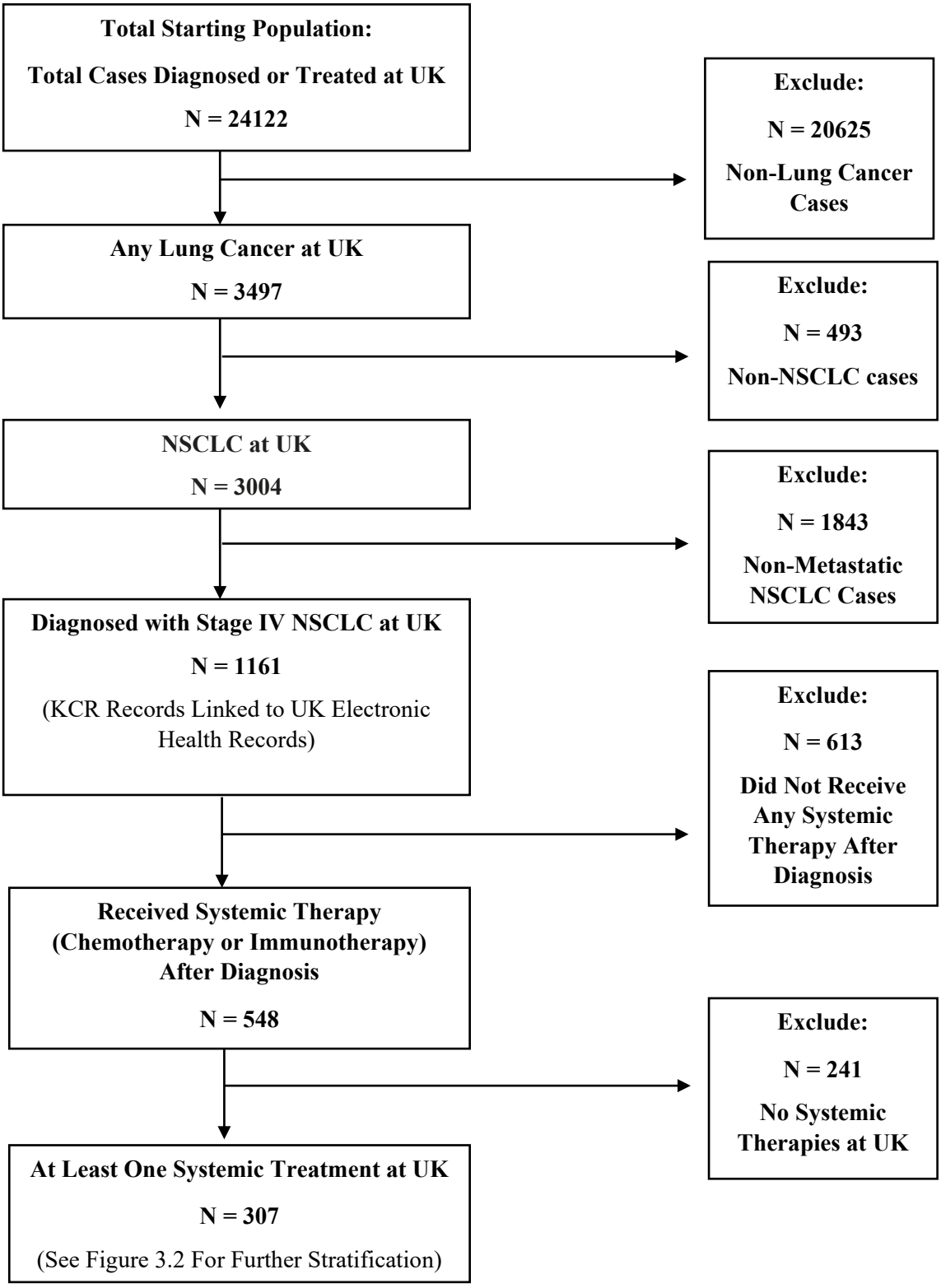
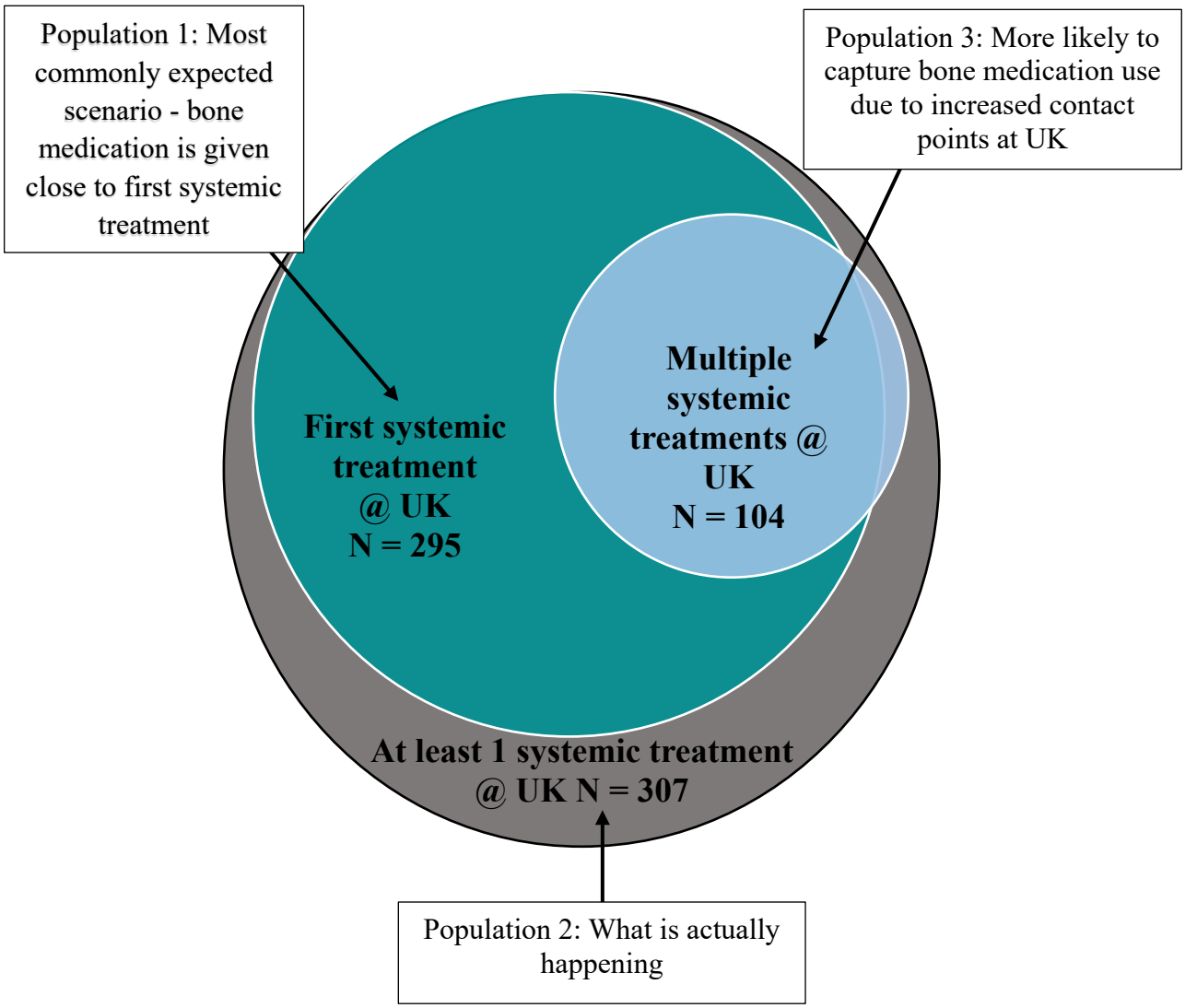


Figure 3.2 Final Study Population Further Broken Down into Three Population Scenarios



Descriptive Statistics

Table 3.1 provides descriptive statistics of the over-arching Stage IV NSCLC population, those who received any systemic therapy in the course of disease treatment, and those who did not receive systemic therapy. Breakdown of diagnosis by year appears to be proportioned consistently among years with the exception of 2019, likely due to incomplete case abstraction by the time the data were pulled as cases take time to be reported and recorded into the KCR dataset. Overall average age of diagnosis was 63.7 years. Patients who received systemic therapy appeared to have a slightly younger age distribution than those who did not receive systemic therapy (median = 62 versus 66).

There appears to be a slightly larger percentage of males diagnosed with stage IV NSCLC than females overall (56.6% versus 43.4%), and the predominant race of patients diagnosed is white (~93%) with a majority of patients classified as cigarette smokers (~87%). In the overarching population, the proportion of patients living in urban versus rural areas appears to be very similar, (51% versus 48%), however, it appears that patients who received systemic therapy were more likely to live in an area with urban designation (54% versus 44%). In all the stage IV cases diagnosed, the most common histology was adenocarcinoma (53.6%), with a higher proportion in those who received systemic therapy (60.8% versus 47.3%). Finally, patients who did not receive systemic therapy appear to have a higher percentage of bone and liver metastasis at diagnosis than those who received systemic treatment (37% vs. 33% bone and 19% vs 14% liver). Brain metastasis at diagnosis is slightly more prevalent in patients who received systemic therapy; however, the difference between groups appears minimal (41% vs 38%).

Similar to table 3.1, table 3.2 provides descriptive statistics of the three populations outlined in figure 3.2. Age, sex, race, and tobacco use appear to be similar across the three groups. Compared to the overall metastatic NSCLC population, patients who had any systemic therapy at UK appear to be diagnosed at a slightly earlier age (median 61 vs 64 years). Patients who had multiple systemic treatments at UK appear to live in an area with urban designation slightly more often than the larger encompassing population 1 and 2 (68% vs ~66%); however overall, more than half of patients receiving any systemic treatment at UK appear to live in an urban area. This is higher than the overall patient population where only about 51% of patients come from urban areas. The primary histology in all populations was adenocarcinoma (65-68%) and the majority of patients from each population were considered cigarette smokers or other tobacco users. Approximately 33-36% of patients presented with bone metastases and 17-19% with liver metastases at diagnosis. Presentation of brain metastases at diagnosis was significantly higher for populations 1 and 2 (~45%) as opposed to population 3 (~30%). The average time from diagnosis to first treatment for each population was ~12 days (median = 4 days), whereas the average time to first systemic treatment was significantly longer. Populations 1 and 2 had an average of about 60 days from diagnosis to first systemic treatment, whereas population 3 was shorter at approximately 50 days.

Table 3.1 Descriptive Statistics of the Over-arching Stage IV NSCLC Population by those Receiving Any versus No Systemic Therapy

Variable	Stage IV NSCLC N = 1161	Systemic Therapy N=548	No Systemic Therapy N = 613
Calendar Year Frequency (%)			
2013	181 (15.59%)	97 (17.70%)	84 (13.70%)
2014	197 (16.97%)	98 (17.88%)	99 (16.15%)
2015	192 (16.54%)	104 (18.98%)	88 (14.36%)
2016	174 (14.99%)	85 (15.51%)	89 (14.52%)
2017	215 (18.52%)	90 (16.42%)	125 (20.39%)
2018	159 (13.70%)	59 (10.77%)	100 (16.31%)
2019	43 (3.70%)	15 (2.74%)	28 (4.57%)
Age			
Mean (SD) Median (Q1, Q3) (Min, Max)	63.87 (10.23) 64 (57,71) (23,97)	61.44 (9.95) 62 (55, 69) (23, 87)	66.06 (9.99) 66 (58,73) (37,97)
Sex			
Male	657 (56.59%)	293 (53.47%)	364 (59.58%)
Female	504 (43.41%)	255 (46.53%)	249 (40.62%)
Race			
White	1086 (93.54%)	511 (93.25)	575 (93.80%)
Black	67 (5.77%)	32 (5.84%)	35 (5.71%)
Other	8 (99.31%)	5 (0.91%)	3 (0.48%)
Region			
Urban	593 (51.08%)	301 (54.93%)	292 (47.63%)
Rural	561 (48.32%)	245 (44.71%)	316 (51.55%)
Unknown	7 (0.60%)	2 (0.36%)	5 (0.82%)
Tobacco Use			
Cigarette smoker	1022 (88.18%)	480 (87.59%)	542 (88.71%)
Other tobacco user	17 (1.47%)	3 (0.55%)	14 (2.29%)
Never tobacco user	73 (6.30%)	41 (7.48%)	32 (5.24%)
Unknown	47 (4.06%)	24 (4.38%)	23 (3.76%)
Histology			
Adenocarcinoma	623 (53.66%)	333 (60.77%)	290 (47.31%)
Squamous Cell Carcinoma	251 (21.62%)	112 (20.44%)	139 (22.68%)
Other*	287 (24.72%)	103 (18.80%)	184 (30.02%)

Table 3.1 (continued)

Bone Mets at Diagnosis			
Yes	408 (35.14%)	180 (32.85)	228 (37.19%)
No	748 (64.43%)	368 (67.15%)	380 (61.99%)
Unknown	5 (0.43%)	-	5 (0.82%)
Liver Mets at Diagnosis			
Yes	193 (16.62%)	75 (13.69%)	118 (19.25%)
No	959 (82.60%)	470 (85.77%)	489 (79.77%)
Unknown	9 (0.78%)	3 (0.55%)	6 (0.98%)
Brain Mets at Diagnosis			
Yes	455 (39.19%)	223 (40.69%)	232 (37.85%)
No	698 (60.12%)	325 (59.31%)	373 (60.85%)
Unknown	8 (0.69%)	-	8 (1.31%)

(*Most commonly includes: not otherwise specified (NOS), large cell, neuroendocrine, and mixed histologies)
Means and standard deviations (in parentheses) are given for continuous variables, whereas frequencies and percentages (in parentheses) are given for categorical variables.

Table 3.2 Descriptive Statistics of Patients who Received Systemic Treatment by Population

Variable	**Population 1 N = 295**	**Population 2 N = 307**	**Population 3 N =104**
Age (years)			
Mean (SD) Median (Q1, Q3) (Min, Max)	60.86 (9.87) 61.00 (54,68) (36, 85)	60.84 (9.88) 61.00 (54,68) (36, 85)	59.61 (10.22) 60.00 (54, 67) (36, 85)
Sex			
Male	154 (52.20%)	162 (52.77%)	56 (53.85%)
Female	141 (47.80%)	145 (47.23%)	48 (46.15%)
Race			
White	269 (91.19%)	280 (91.21%)	95 (91.35%)
Black	23 (7.80%)	24 (7.82%)	7 (6.73%)
Other	3 (1.02%)	3 (0.98%)	2 (1.92%)
Region			
Urban	195 (66.10%)	201 (65.47%)	71 (68.27%)
Rural	98 (33.22%)	104 (33.88%)	33 (31.73%)
Unknown	2 (0.68%)	2 (0.65%)	-

Table 3.2 (continued)

Tobacco Use			
Cigarette smoker	259 (87.80%)	268 (87.30%)	86 (82.69%)
Other tobacco user	3 (1.02%)	3 (0.98%)	13 (12.5%)
Never tobacco user	24 (8.14%)	25 (8.14%)	4 (3.85%)
Unknown	9 (3.05%)	11 (3.58%)	1 (0.96%)
Histology			
Adenocarcinoma	193 (65.42%)	200 (65.15%)	71 (68.27%)
Squamous Cell Carcinoma	50 (16.95%)	50 (16.29%)	18 (17.31%)
Other*	52 (17.63%)	57 (18.57%)	15 (14.42%)
Days from Diagnosis to Treatment One			
Mean (SD) Median (Q1, Q3) (Min, Max)	11.98 (19.25) 4.00 (0,17) (0,148)	11.69 (18.96) 4 (0,16) (0,148)	12.42 (17.86) 4.00 (0,19) (0,78)
Days from Diagnosis to First Systemic Treatment			
Mean (SD) Median (Q1, Q3) (Min, Max)	60.82 (58.85) 50.00 (33,69) (3, 578)	60.23 (58.16) 50 (33,68) (3, 578)	54.30 (52.24) 41.00 (28.5, 61.5) (3, 397)
Bone Mets at Diagnosis			
Yes	100 (33.90%)	104 (33.88%)	37 (35.58%)
No	195 (66.10%)	203 (66.12%)	67 (64.42%)
Liver Mets at Diagnosis			
Yes	50 (16.95%)	52 (16.94%)	20 (19.23%)
No	243 (82.37%)	252 (82.08%)	84 (80.77%)
Unknown	2 (0.68%)	3 (0.98%)	-
Brain Mets at Diagnosis			
Yes	133 (45.08%)	137 (44.63%)	31 (29.81%)
No	162 (54.92%)	170 (55.37%)	73 (70.19%)

(*Most commonly includes: not otherwise specified (NOS), large cell, neuroendocrine, and mixed histologies)

Means and standard deviations (in parentheses) are given for continuous variables, whereas frequencies and percentages (in parentheses) are given for categorical variables.

Bone Therapy Utilization

Table 3.3 shows incidence of bone therapy initiation divided by population and agent. Of patients who received their first systemic therapy at UK, only 48 or 16.3 % were initiated on a bone therapy agent at UK in the course of their disease treatment. The most common agent used was denosumab (65%), with zoledronic acid and pamidronate constituting the other 35% in a nearly equal proportion. As population 1 and 2 are concentric, the distribution of bone therapy use for both populations was nearly identical, with population 2 containing only one more denosumab user than population 1. As such, population 2 was excluded from further descriptive analyses. Population 3, which consists of patients receiving multiple systemic therapies at UK, had a higher proportional; incidence of bone therapy initiation (22.12%) than the other two populations, with an even higher proportion of denosumab use (82%) as compared to zoledronic acid and pamidronate. Figure 3.3 shows that there is not a clear pattern in bone therapy initiation with regard to time. When looking at population 1, there appears to be no use in 2013, low initiation in 2014, initiation appears steady in 2015-2017, with a spike in initiation for 2018. Initiation in 2019 appears low likely due to the incomplete case abstraction to KCR as mentioned above. Population 3 shows a similar spike in bone therapy initiation in 2018 with nearly 43% of all bone therapy initiation occurring in that year.

Table 3.3 Overall Initiation of Antiresorptive Bone Therapy by Agent and Population

Agent	Denosumab	Zoledronic Acid	Pamidronate	All agents Frequency (% of total population)
Population 1 N= 295	31	8	9	48 (16.3%)
Population 2 N = 307	32	8	9	49 (15.96%)
Population 3 N =104	19	2	2	23 (22.12%)

Figure 3.3 Incidence of Antiresorptive Bone Therapy Initiation by Year for Populations 1 and 3

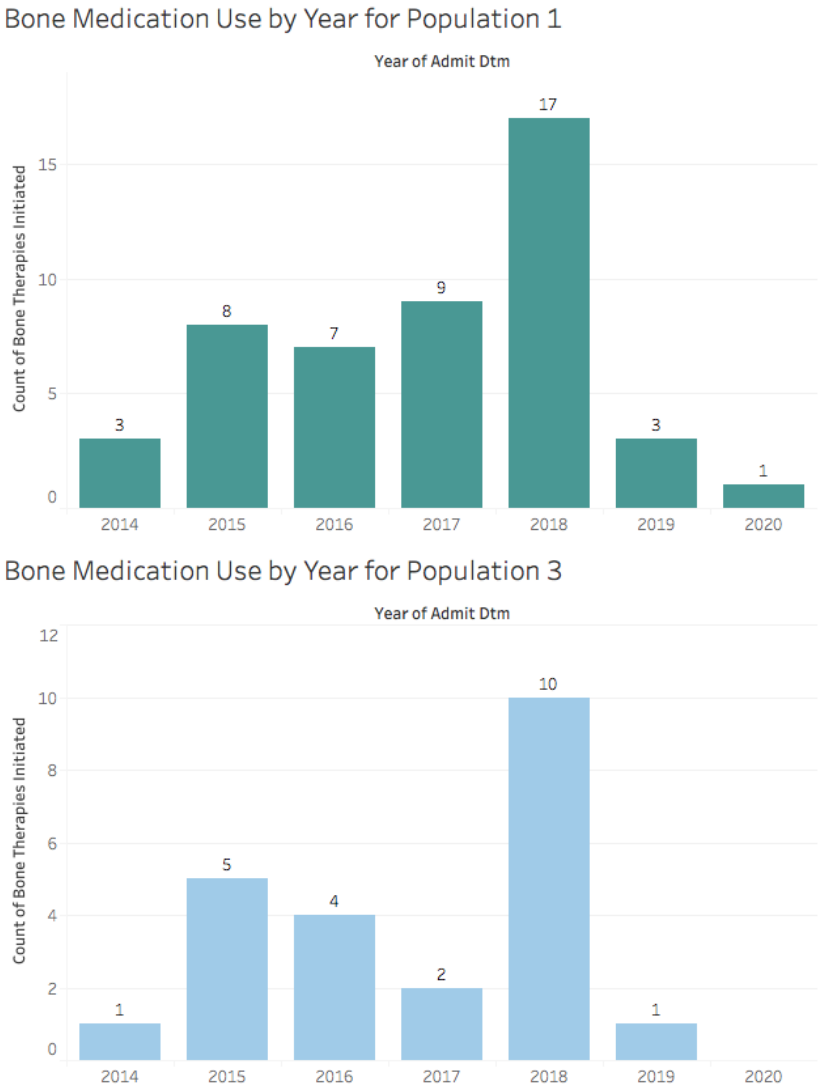


Table 3.4 shows the incidence of bone therapy initiation from time of first systemic treatment for populations 1 and 3 while table 3.5 shows the affiliated quantiles of days to bone therapy initiation since first systemic treatment. For population 1, a large proportion of patients were initiated on a bone therapy within 30 days of their first systemic treatment, with 25% of them beginning the therapy before or on the day of systemic therapy. Approximately 50% of population 1 patients began bone therapy within 2 months (60 days) of first systemic therapy, but nearly 25% of patients were not initiated on a bone therapy until after the 6-month post-first systemic therapy mark.

Comparatively, population 3 had a smaller proportion of patients initiated on bone therapies within 30 days of first systemic treatment, with only 10% of the population beginning both therapies on the same day. Approximately 50% of population 3 were started on a bone therapy within 85 days of first systemic therapy, with almost 30% still not having initiated bone therapy at 6 months post-first systemic.

Table 3.4 Incidence of Antiresorptive Bone Therapy Use from Time of First Systemic Treatment (Chemotherapy or Immunotherapy) for Populations 1 and 3

Population	Within 30 days from 1st systemic	Within 60 days from 1st systemic	Within 90 days from 1st systemic	Within 180 days from 1st systemic	More than 180 days from 1st systemic
Population 1 N = 48	18 (37.50%)	5 (10.42%)	7 (14.58%)	6 (12.5%)	12 (25%)
Population 3 N = 23	4 (17.39%)	4 (17.39%)	5 (21.74%)	3 (13.0%)	7 (30.4%)

Table 3.5 Quantiles and Affiliated Days of Bone Therapy Initiation for Populations 1 and 3

Level Quantile	Population 1 N = 48	Population 3 N = 23
	Days since first systemic therapy	
100% (Max)	1298	770
95%	696	696
90%	483	563
75% (Q3)	183	328
50% (Median)	61	85
25% (Q1)	0	43
10%	0	0
0% (Min)	-32	0

Table 3.6 shows all of the doses and frequencies of bone medication use for populations 1 and 3. The most common agent used in both groups was overwhelmingly subcutaneous denosumab, 120 mg given every 4 weeks. This dose and frequency constituted nearly half of all schedules. In population 1, one patient had a schedule of every 6 weeks, and another patient received a 60 mg dose at an unknown frequency. Zoledronic acid was typically administered as a 4 mg dose, with frequency unspecified. One patient received a dose of 3.3 mg which was likely due to renal adjustment. Pamidronate was given as either 60 mg or 90 mg infusions of varying lengths (2-24 hours). Population 3 showed a similar pattern with over half of patients receiving denosumab, 120 mg every 4 weeks.

Table 3.6 Common Doses and Frequencies of Bone Medication Use for Population 1 and 3

Population 1			
Common dose/route/frequency	No frequency provided	Every 30 days	Every 42 days
Denosumab			
60 mg	1		
120 mg	8	21	1
Zoledronic Acid			
3.3 mg	1		-
4 mg		7	-
Pamidronate			
30 mg		-	-
60 mg	2		-
90 mg	7 (1 hypercalcemia)		-
Population 3			
Common dose/route/frequency	No frequency provided	Every 30 days	Every 42 days
Denosumab			
120 mg	4	15	
Zoledronic Acid			
4 mg	2		
Pamidronate			
60 mg	1		
90 mg	1		

Regression Analysis

The following tables show a logistic regression performed in order to determine factors predicting the initiation of antiresorptive bone therapy agents for patients who received their first systemic therapy at UK (population 1). The dependent variable of interest was initiation of bone therapy during disease course treatment (yes/no). Mean-centered diagnosis age, sex, rural vs urban geographic designation, histology, bone, liver, and brain metastases were all parameters included in the model. Likelihood ratio, Score, and Wald's Chi-square tests indicate that at least one of the predictors' regression coefficient is not equal to zero in this model ($p < 0.05$) leading us to reject the null that all regression coefficients in the model are equal to zero. Tables 3.8 and 3.9 show the analysis of maximum likelihood estimates and odds ratio estimates respectively. The only significant predictors of bone medication initiation appear to be the presence of bone metastasis at diagnosis as well as having adenocarcinoma versus another type of non-squamous NSCLC histology. The odds of being initiated on a bone therapy are 4.256 times as large for a patient who has bone metastasis present at diagnosis than for a patient who does not present with bone metastasis at time of diagnosis [CI: 2.146,8.442]. Likewise, the odds of being initiated on a bone therapy are 3.5 times higher for those diagnosed with adenocarcinoma as opposed to another non-squamous histology [CI: 1.11, 11.11]. Sub-group analysis of patients with bone metastasis at diagnosis did not show any significant factors predicting bone therapy use other than histology mentioned above.

Table 3.7 Likelihood Ratio

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	31.4826	8	0.0001
Score	31.4143	8	0.0001
Wald	27.3034	8	0.0006

Table 3.8 Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-square	Pr > Chisq
Intercept	1	-2.0668	0.4288	23.2315	<0.0001
Diagnosis age	1	-0.0267	0.0172	2.4018	0.1212
Sex (male vs female)	1	-0.1931	0.3455	0.3124	0.5762
Rural vs Urban	1	0.2058	0.368	0.3127	0.576
Squamous cell vs Adenocarcinoma	1	0.00802	0.3851	0.0004	0.9834
Other Histology vs Adenocarcinoma	1	-0.6322	0.4072	2.4104	0.1205
Bonemets (1 vs 0)	1	0.7242	0.1747	17.1822	<0.0001
Brainmets	1	0.00958	0.3534	0.0007	0.9784
Livermets	1	0.2481	0.4351	0.3252	0.5685

Table 3.9 Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
Diagnosis age	0.974	0.941	1.007
Sex (male vs female)	0.824	0.419	1.623
Rural vs Urban	1.229	0.597	2.527
Squamous cell vs Adenocarcinoma	0.54	0.188	1.552
Other histology vs Adenocarcinoma	0.285	0.09	0.897
Bonemets (1 vs 0)	4.256	2.146	8.442
Brainmets	1.01	0.505	2.018
Livermets	1.282	0.546	3.007

CHAPTER 4. DISCUSSION

To our knowledge, this is the first study assessing the incidence of antiresorptive bone therapy utilization in EHR linked to cancer registry data since the approval of denosumab and several targeted and immunotherapies for metastatic NSCLC. This study is an important assessment of facility implementation of supportive care in the metastatic NSCLC population as the life expectancy of this population continues to increase.

To begin, the population breakdown from KCR aligns well with the national averages for lung cancer. 24,122 total cancer cases were diagnosed or treated at UKHC between 1/01/2013 – 1/31/2020. Of those cancer cases, 3497 or approximately 14.5% were lung cancer. This aligns with the national average where lung cancer comprises of approximately 13% of all cancer cases [1, 3, 15]. Of those cases, 3004 or ~86% were non-small cell lung cancer, again aligning with the national average of 85%. In this data set 39% of patients were stage IV. This is lower than the national average where 57% of cancer cases are diagnosed as metastatic but remains logical as UK is the largest referral cancer center in Kentucky. As UK contains many specialists and expert surgeons, numerous earlier stage lung cancer patients may be referred to UK for initial surgical resection, increasing the proportion of non-metastatic to metastatic cases. Our dataset correlation corresponding to the national average corroborates the accuracy and completeness of the KCR data set.

Most of the descriptive statistics performed on the data set align with national SEER averages and expectations. A few measurements that deviate from expectations include the percent of metastasis at diagnosis which appear to be higher than the national average for bone and brain metastasis and lower for liver. The higher averages may again be due to UK's nature as a referral center.

The population break down that was intended to capture different snapshots of bone therapy use resulted in a relatively concentric trichotomy of patients. Populations 1 and 2 were very similar in size, and population 3 was almost completely encompassed in both groups. This shows that for most patients who received any systemic therapy at UK, it

was the patient's first treatment, and for those who received multiple systemic therapies at UK, the patients likely received their first systemic treatment there as well. This indicates that patients are more likely to be systemically treated at UK initially, and then referred out rather than being referred in later in their course of treatment, which increases the chance of capturing bone therapy medication use if initiated close to or on the day of first systemic treatment.

The original population breakdown intended to separate patients who were deemed eligible to receive antiresorptive bone therapy by using the receipt of systemic therapy as a proxy. This is because if a metastatic NSCLC patient was deemed capable enough to receive chemotherapy or immunotherapy, then the patient should be able to tolerate an antiresorptive bone therapy as well. Two exceptions to this would be if a patient had a calcium level <8.5 mg/dL or severe renal impairment. With this in mind, most all of the patients in populations 1, 2, and 3 should have been initiated on an antiresorptive bone therapy agent at some point during their disease treatment course. Utilization, however, was found to be extremely low. The highest proportion of bone therapy initiation (~22%) was found in population 3, patients who received multiple systemic therapies at UK. This could be analogous to the fact that they received more than one systemic therapy which may point to good treatment response and clinician opinion of a better prognosis. Or, this may be simply due to a higher bone therapy capture rate due to increased contact points at UK. Regardless, the initiation rate is less than optimal.

In terms of bone therapy use by year, there is a spike in bone therapy initiation in 2018, the year that this project began. As this research project stemmed from anecdotal evidence of bone therapy underutilization from the hospital, word may have spread leading to an increase in prescribing. Of note, no bone therapy initiation was captured in 2013, which may correspond to the fact that a large proportion of patients received their first systemic therapy on average about 2 months after their diagnosis, and median administration of first bone therapy another 2-3 months after that. The lack of bone therapy use in this year may point to an extreme delay in bone therapy administration, or to a change in the EDW structure this early in the study period, leading to incomplete abstraction of bone therapy utilization in the years of 2013 – 2014.

The use of denosumab as the primary bone therapy agent is not surprising, due to the medication's cited efficacy over bisphosphonates and rapid administration time. Selection of bone therapy agent, if given in the outpatient setting, is highly dependent on patient insurance and prior authorization. If given inpatient, the less expensive/generic medication is more likely to be used.

The primary factor predicting bone therapy use was bone metastasis at diagnosis. This is not surprising, as the primary purpose of antiresorptive bone therapies is to decrease skeletal related events, which occur at a much higher rate in patients with bone metastasis. This however, should not limit the use of these agents to this patient population, as all metastatic lung cancer patients are at risk of developing bone metastasis and subsequently SRE's throughout the disease course. The results of this study indicate the need for further dissemination of information regarding skeletal related event morbidity in metastatic lung cancer patients, with the potential implementation of new order sets or clinical decision support systems to increase bone therapy utilization.

Study Strengths and Limitations

There are several strengths and limitations with the use of this KCR-EHR linked dataset. To begin, as the Kentucky Cancer Registry data collects information regarding all cancer cases around the state, we can be confident that we are catching most all lung cancer cases of any patient seen at University of Kentucky during any point of their cancer diagnosis or treatment – regardless if this was the patient's primary healthcare facility. Furthermore, the Kentucky Cancer Registry Data is not based on claims which would limit the population of interest to only those who are privately insured or have Medicare. (A stated limitation of the previous studies cited above). Also, the KCR dataset is structured with a set classification criterion for each variable, leading to a level of standardization amongst all patients. As long as a patient continues to seek care in Kentucky, KCR should capture the continuum of their care including treatment, surgery, biopsy, radiation, and survival information including death dates [48]. Not having survival information is another stated limitation of many claims data studies that must use database dropout as a proxy for death.

The KCR dataset does have its limitations with regard to details of therapy/surgery. For example, for patient X, treatment 1 may be classified as a 'non-definitive surgery'. This is highly non-specific and may be referring to the initial biopsy procedure performed for diagnostic purposes. If this were the case, the timeline of diagnosis to first treatment would be thrown off slightly. Also, the information in KCR is relatively limited to the care of the patient with regards to their cancer treatment. This means that if a patient was admitted to the hospital for a non-oncologic cause, the details of that admission may not be captured by the dataset. Due to these stated limitations, EHR data was used to fill in the gaps of some of the missing information. By using the structured KCR data as the initial means of data abstraction, the base population was narrowed down as was defined in figure 3.1 and linkage to EHR data became more structured. Unfortunately, as aforementioned, not all of the patients labeled as UK patients from the KCR side received all of their care at UK. To balance the need for a decent population size and the probability of capturing bone medication use, population stratification was necessary; however, this excluded a large proportion of patients that may have indeed received antiresorptive bone therapy at a different facility or without having received systemic therapy.

The strengths of the EHR data coincide with its detailed nature. Like KCR, data from the EDW is not based on claims, and supposedly captures all events in a patient's hospital or outpatient visit including medications, time of administration, associated labs, etc. The downside to the abundance of information, is that the data is often free text or unstructured leading to a lack of relative standardization among variable fields. The combination of KCR-EHR, however, creates a pseudo-structured dataset that helps mitigate field uncertainty.

Lessons Learned

Very important lessons were learned regarding the use of these linked datasets. First, an understanding of the flow of data into KCR is critical when determining validity of variable definitions, and areas of missing information. It is important to understand where the data comes from, how it gets categorized, the standards of data entry, and the need for use of clinical judgment to balance data and make conclusions. KCR is

structured to an extent, but EHR is not as standardized, so definitions need to be very specific and encompassing to ensure cases are captured appropriately.

Future Directions

Performing a bone therapy utilization analysis in a healthcare facility with EHR data is an extremely useful tool in comparing local practice to the national practice. Because other studies have looked at national claims data and found low utilization across the country, it is important to see how our facility compares. Furthermore, because of the availability of verified survival information from the KCR portion of the data, this data opens the door to do a survival analysis comparing groups who received bone medications and systemic therapy to those who did not.

Access to actual laboratory test results rather than just diagnosis codes indicating toxicities such as hypercalcemia of malignancy, or hypocalcemia or renal dysfunction leading to discontinuation of bone therapy medication use is valuable in creating a more detailed time to event analysis of bone therapy initiation and discontinuation. Furthermore, this study can be expanded to include other solid tumor states (breast and prostate) or the optimization of other quality of life improving therapies. After further exploration of secondary aims in this KCR-EHR dataset, an updated prevalence study in a claims database such as TRUVEN would provide useful insight into how practice has changed nationally and how we as a facility compare.

Conclusions

For metastatic non-small cell lung cancer patients receiving their first systemic therapy at the University of Kentucky, antiresorptive bone therapies are being underutilized with the primary predictor of use as bone metastasis at diagnosis. This gap in research findings and clinical practice presents an ideal opportunity for a dissemination and implementation (D&I) protocol to take effect at UKHealthCare. It is imperative to offer education regarding the evidence of providing intravenous antiresorptive bone therapy to eligible patients. This research can be disseminated through seminars and distribution of educational materials. Integration of this evidence could then take place through the implementation of an IV bone therapy stewardship program. Additionally,

the implementation of a departmental protocol aided by clinical decision support systems that streamline the evidence-based selection of bone therapy agent, appropriate dosing, and frequency can ensure a patient does not get omitted from supportive care therapy considerations.

APPENDICES

APPENDIX 1. KCR Definitions

Link to full KCR data dictionary: https://confluence.kcr.uky.edu/display/KAM

Select Categories	Code	Description
Lung topography	C340	Main bronchus Carina Hilum Bronchus intermedius
	C341	Upper lobe, lung Lingula Apex Pancoast tumor
	C342	Middle lobe, lung (Right lung only)
	C343	Lower lobe, lung Base
	C348	Overlapping lesion of lung
	C349	Lung, NOS Bronchus, NOS
Mets at Dx – Bone	0	None, no bone metastases
	1	Yes; distant bone metastases
	2	Not applicable
	3	Unknown whether bone is an involved metastatic site. Not documented in patient record
Summary Stage 1977	0	In-situ/non-invasive malignant tumor.
	1	Localized - tumor is confined to the organ of origin.
	2	Regional by direct extension - tumor has spread by direct extension to immediately adjacent tissues or organs.
	3	Regional to lymph nodes - tumor has spread into lymph nodes regional to the primary site of origin.
	4	Regional by both direct extension and regional lymph nodes.
	5	Regional, NOS - tumor is regionally spread, but the extent of regional spread cannot be determined, or is not specified.
	7	Distant metastasis - a tumor that has spread beyond the immediately adjacent tissues and has developed secondary or metastatic tumors or is systemic.
	9	Unknown/Unstageable

APPENDIX 2. UKEDW Data Definitions

Skeletal Related Event Definitions:

- pathological fracture
- radiotherapy to the bone (procedure of interest as proxy for SRE)
- surgery to bone (procedure of interest as proxy for SRE)
- spinal cord compression

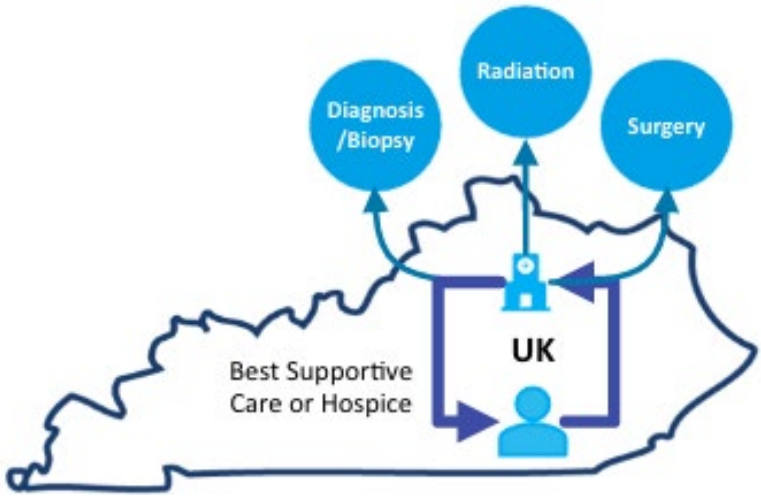
ICD-9 and HCPCs codes used from Table 4 of Measurement of skeletal related events in SEER-Medicare: a comparison of claims-based methods. [50]

IV Antiresorptive Bone Medications:

Drug Name	Common Brand Names	HCPCS Code	HCPCS code Dosage	Typical Dosing (varies frequently)
IV Zoledronic Acid	Zometa, Reclast	J3489	1 mg	Typical dose = 4 mg every 3-4 weeks
IV Pamidronate disodium	Aredia	J2430	30 mg	Typical dose varies
IV Denosumab	Xgeva, Prolia	J0897	1 mg	Typical dose = 120 mg every 4weeks

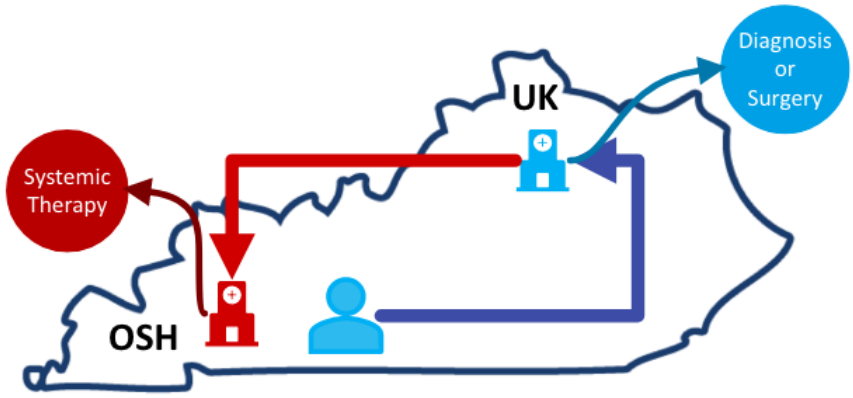
APPENDIX 3. Population Scenario Visualizations

Scenario 1: Patient did not receive any systemic therapy after diagnosis but did have a contact point at UK (this may have been for diagnosis, surgery, biopsy, or radiation) and patient may have opted for best supportive care or hospice.



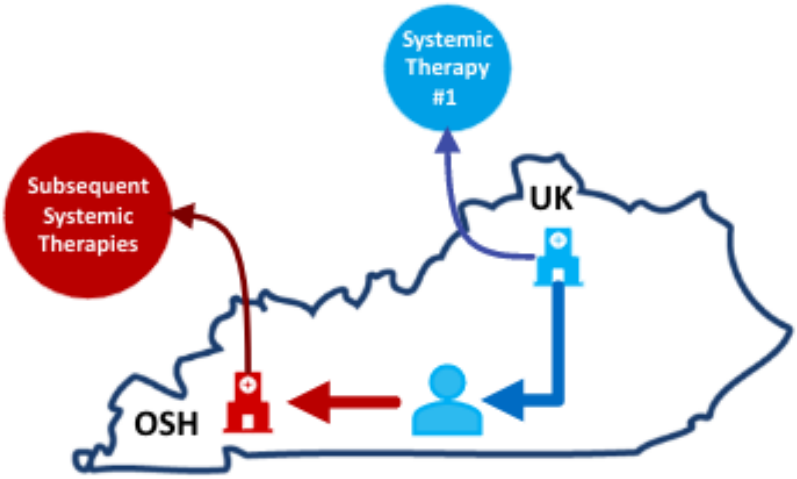
Scenario 2: Received Systemic Therapy (Chemotherapy or Immunotherapy) After Diagnosis

Scenario 2A: No systemic therapies at UK (may have been diagnosed of treated surgically at UK, but systemic treatment was received elsewhere)

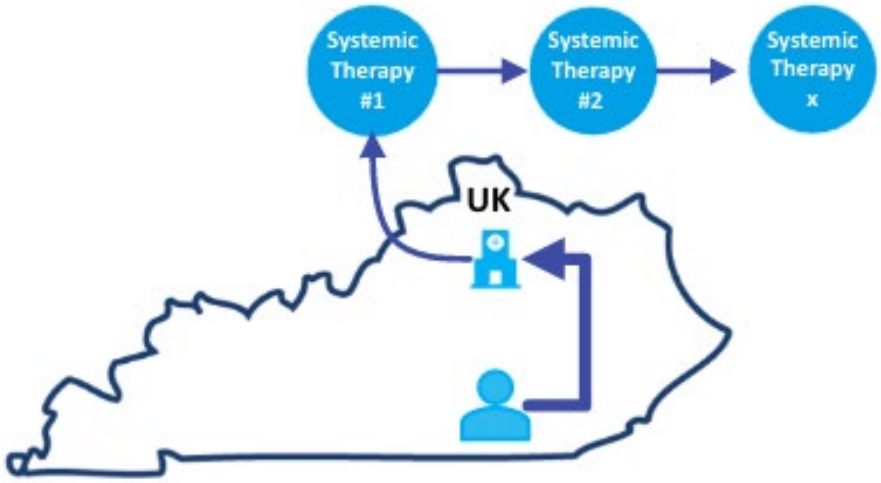


Scenario 2B: At least one systemic treatment at UK

Scenario 2B1: First systemic treatment at UK



Scenario 2B2: Multiple systemic treatments at UK (For most patients it was their first and subsequent treatments)



(Three patients were likely transferred to UK after receiving their first systemic treatment elsewhere)

OSH: Outside Hospital
UK: University of Kentucky

APPENDIX 4. Coding Definitions

Geographic Classification	Bealecode2013 description
Rural	• Urban population of 20,000 or more, not adjacent to a metro area • Urban population of 2,500 to 19,999, not adjacent to a metro area • Rural, not adjacent to a metro area • Counties in metro areas of fewer than 250,000 population' then RUC
Urban	• Urban population of 20,000 or more, adjacent to a metro area • Urban population of 2,500 to 19,999, adjacent to a metro area • Rural, adjacent to a metro area • Counties in metro areas of 250,000 to 1 million population • Counties in metro areas of 1 million population or more
Unknown	• Outside of state of reporting institution

Histology Classification	Histology Description
Adenocarcinoma	• Adenocarcinoma, nos • Papillary adenocarcinoma, nos • Mucinous adenocarcinoma • Adenosquamous carcinoma • Adenocar.w/neroendocr different • Adendocar w/mxd subtypes • Acinar cell cystadenocarcinoma • Invasive mucinous adenocarcinoma • Mucin-producing adenocarcinoma
Squamous Cell Carcinoma	• Squamous cell carcinoma, nos • Basaloid squamous cell ca
Other	• Large cell neuroendocrine ca • Non-sm cell carcinoma • Carcinoma, nos • Neoplasm, malignant • Neuroendocrine carcinoma, nos • Squam.cell carcin., keratin. Nos • Carcinoid tumor, nos

Histology Classification	Histology Description
Other (cont.)	• Giant cell carcinoma • Large cell carcinoma, nos • Papillary carcinoma, nos • Signet ring cell carcinoma • Spindle cell carcinoma • Acinar cell carcinoma • Atypical carcinoid tumor • Carcinoma, anaplastic, nos • Carcinoma, undiffer., nos • Carcinosarcoma, nos • Metaplastic carcinoma, nos • Pleomorphic carcinoma

Tobacco Use	Description
Cigarette smoker	• Cigarette smoker
Other tobacco user	• Mixed tobacco pro • Cigar/pipe smoker • Smokeless tobacco
Never tobacco user	• Never used
Unknown	• Unkn. /not recorded

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