Summary Table of Study Protocol

Title	Association Between Granulocyte Colony Stimulating Factor (G-CSF) use and Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) Among Elderly Patients With Breast (Stage I-III), lung (Stage I-III) or Prostate (Stage I-IV) Cancer
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EU Post Authorisation Study (PAS) Register No	*<<Insert Number>>*
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Marketing Authorisation Holder(s)	Amgen
Joint PASS	No

Research Question and Objectives	Is G-CSF use associated with an increased risk of Myelodysplastic Syndrome (MDS)/ Acute Myeloid Leukemia (AML) among elderly patients treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer? Primary objective: 1) Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, compare the risk of SEER-reported or Medicare-reported MDS/AML between those receiving G-CSF vs. not receiving G-CSF for each tumor type Secondary objective: 1) Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, describe the characteristics of patients overall, by tumor type, by use of G-CSF, and by occurrence of MDS/AML. 2) Calculate the pooled hazard ratio for MDS/AML following G-CSF use among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer.
Country of Study	US

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Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen
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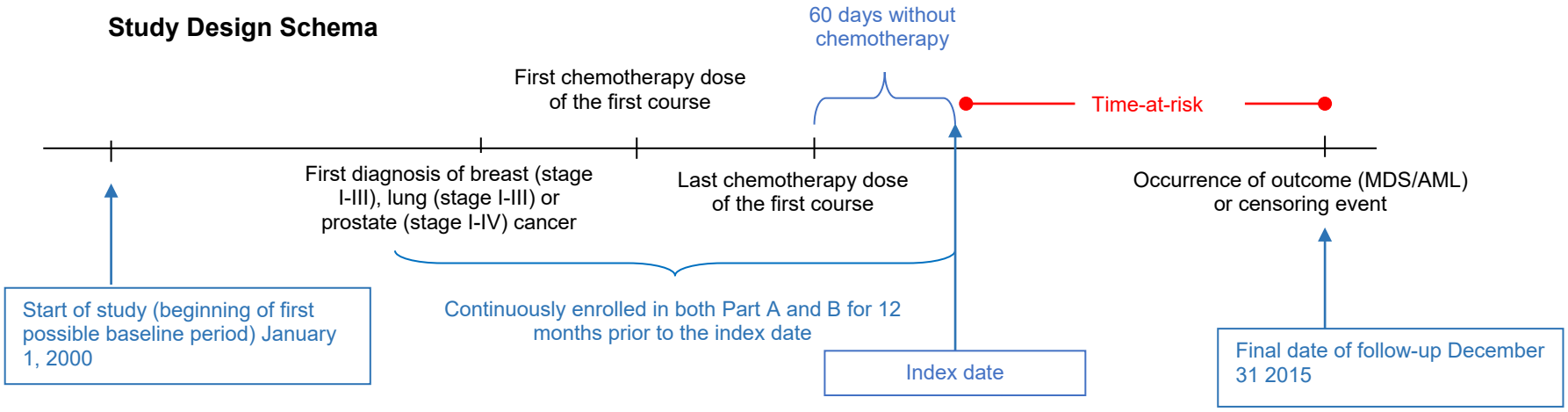
Study Design Schema



INCLUSION CRITERIA

- Chemotherapy following first diagnosis of breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer
- Index date (Sixtieth day without chemotherapy following last dose of first chemotherapy course) between Jan 1 2001 and Dec 31 2014

EXCLUSION CRITERIA

- Breast, lung, or prostate cancer not first primary cancer
- Cancer diagnosis made at autopsy or death certificate
- Unknown stage
- Death or SEER- or Medicare-reported MDS/AML anytime prior to index date
- ESRD prior to the index date
- Patient enrolled in HMO

EXPOSURES

At least 2 HCPCS/CPT codes for the same chemotherapeutic drug at least 7 days apart but within 12 months prior to the index date.

- alkylating drugs
- antimetabolites
- anthracyclines
- platinum drugs
- topoisomerase inhibitors
- taxanes
- other chemotherapy

At least 1 HCPCS code for G-CSF use (filgrastim or pegfilgrastim) within 12 months prior to the index date.

OUTCOMES

MDS or AML

- SEER-reported or Medicare-reported (two or more ICD-9-CM claims at least 1 month apart but within 12 months of each other OR at least one claim with death or hospice entry within 3 months with a blood count and bone marrow during a year prior to first claims)

Censoring events:

- Earliest of development of second cancer that is not MDS/AML, relapse chemotherapy (chemotherapy claims that occur ≥60 days after last chemotherapy dose), disenrollment, death or end of study period

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2. List of Abbreviations

Abbreviation	Description
AML	Acute myeloid leukemia
MDS	Myelodysplastic syndrome
SEER	Surveillance, epidemiology, and end results program
EU PAS	European Union Post-Authorisation Studies
ESRD	End-stage renal disease
HMO	Health maintenance organization
ICD-9-CM	International classification of diseases, ninth revision, clinical modification
AJCC	American joint committee on cancer
G-CSF	Granulocyte colony-stimulating factor
NOS	Not otherwise specified
IRR	Incidence risk/rate ratio
HR	Hazard ratio
CI	Confidence interval

3. Responsible Parties

4. Abstract

It has been well recognized that patients diagnosed with cancer have an increased risk for Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) following treatment.[1-7] Both radiation therapy and chemotherapy have been established as risk factors of secondary MDS and AML.[5,8-10] Patients receiving myelosuppressive chemotherapy with high risk of febrile neutropenia, commonly receive granulocyte colony stimulating factors (G-CSF) for febrile neutropenia prophylaxis.[11] Because G-CSF induces proliferation of myeloid progenitor cells, which are especially sensitive to myelosuppressive chemotherapy drugs, there is a biological plausibility for G-CSF to increase the risk of myeloid disorders such as MDS and AML[12,13] A systematic review of 25 randomized clinical trials (RCTs) that randomly assigned patients to receive G-CSF (n = 6,058) or no-G-CSF (n = 6,746) and had at least 2 years of follow-up observed that both risk of MDS/AML and intensity of chemotherapy was increased in patients receiving G-CSF support.[2] However, the authors were unable to differentiate between the causal effect of G-CSF and the causal effect of dose intensified chemotherapy as patients with G-CSF support are more likely to receive intense chemotherapy. Out of the previous two Surveillance, epidemiology, and end results program (SEER)-Medicare reports of patients receiving chemotherapy for breast cancer, one reported no association of G-CSF with risk of AML (Hazard Ratio [HR]: 1.14; 95% Confidence Interval [CI]: 0.67, 1.92)[10] and another reported an increased risk for MDS/AML following G-CSF use (HR: 2.14; 95% CI: 1.12, 4.08).[14] We propose a retrospective cohort study of breast, lung, and prostate cancer patients aged 66+ years selected including latest US SEER-Medicare data from January 1, 2001 to December 31, 2015 to evaluate the following objectives.

Objectives:

Primary objective:

1) Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, compare the risk of SEER-reported or Medicare-reported MDS/AML between those receiving G-CSF vs. not receiving G-CSF for each tumor type

Secondary objectives:

1) Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, describe the characteristics of patients overall, by tumor type, by use of G-CSF, and by occurrence of MDS/AML.
2) Calculate the pooled hazard ratio for MDS/AML following G-CSF use among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer.

Inclusion criteria:

Patients must satisfy the following criteria:

- Chemotherapy following first diagnosis of breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer
- Index date (Sixtieth day without chemotherapy following last dose of first chemotherapy course) between Jan 1, 2001 and Dec 31, 2014, leaving at least one year of potential follow-up for patients.
- Alive and at least 66 years of age at index date
- Continuous enrollment in both Part A and Part B Medicare for at least 12 months prior to the index date

Exclusion criteria:

Patients must not have any of the following criteria:

- Breast, lung, or prostate cancer is not their first primary cancer diagnosis
- Breast, lung, or prostate cancer diagnosis identified only at autopsy or on their death certificate
- Men with breast cancer diagnosis
- Unknown stage at first cancer diagnosis
- End-stage renal disease (ESRD) any time prior to the index date.
- Enrolled in Health maintenance organization (HMO) any time during the study period
- Diagnosed with MDS/AML or any other second primary cancer diagnosis any time prior to the index date.

Index date

Sixtieth day without chemotherapy following last dose of first chemotherapy course.

Follow-up

Baseline characteristics will be collected for patients 12 months prior to their index date. Follow-up time begins after (and including) the index date until the earliest of occurrence of the primary outcome (MDS/AML) or one of the following censoring events:

- Development of second cancer other than MDS/AML
- Relapse or second-line chemotherapy treatment (chemotherapy claims that occur at least 60 days after the last dose of first chemotherapy course)
- Disenrollment,
- Death
- End of study period.

Outcome

Outcome will be defined as SEER-reported or Medicare-reported MDS or AML diagnosis during the follow-up period.

A sensitivity analysis will be performed using outcome definition that is based on SEER-reported MDS or AML diagnosis during the follow-up.

Exposure

Patients will be considered exposed to G-CSF if there is at least one claim with a HCPCS code of G-CSF (filgrastim or pegfilgrastim) within one year prior to the index date.

Covariates

Chemotherapy:

At least two HCPCS or CPT codes for the same chemotherapeutic drugs within one year prior to the index date; Identified drugs will be categorized into following classes:

- alkylating drugs
- antimetabolites
- anthracyclines
- platinum drugs
- topoisomerase inhibitors

- taxanes
- other chemotherapy

Surgery:

Medicare inpatient claims will be used to identify cancer-related surgery.

Radiation therapy:

The primary source for information about radiation exposure is the SEER datafile PEDSF. Type of radiation therapy will be identified for specific tumor types (eg, Brachytherapy vs. External Beam radiotherapy for prostate cancer)

Other covariates:

- age at index date
- SEER registry
- year of index date
- American Joint Committee on Cancer (AJCC) stage
- race, eg, White, Black, Other, Unknown
- ethnicity (Hispanic, non-Hispanic, Unknown)
- hormone receptor status for breast cancer (ER-/PR-positive, ER-/PR-negative, unknown)
- histology of tumor
- lymph node status (positive, negative, unknown)
- tumor size
- Autoimmune diseases: Rheumatoid arthritis, Psoriasis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's Disease
- bone marrow transplantation
- modified Charlson comorbidity index within one year prior to the index date

Study Sample Size

A previous study on this topic using the SEER registry from 2001 to 2009 identified 56,251 eligible patients with 655 events.[1] In that study, the median follow-up time for patients with and without the event was 4.3 and 3.2 person-years, respectively. Based on this summary data, the overall 95% Poisson confidence interval estimate would be approximately 3.4 – 3.9 events per 1000 person-years. The precision for this study is expected to be greater because we will be able to include patients up to 2014.

Data Analysis

An attrition table will be created describing the numbers and type of patients excluded as each inclusion or exclusion criteria was applied to the database.

We will describe the counts and percentages for discrete quantities and means, standard deviations, medians and interquartile ranges for continuous quantities. The baseline patient characteristics will be described overall, by use of G-CSF, and by occurrence of MDS/AML. Baseline patient characteristics include demographics, covariates summarized in section 4, treatments (radiation, surgery), chemotherapy drugs and classes of chemotherapy drugs, and treatment with G-CSF (overall, by type, and number of doses). We will also describe the use of radiation during the follow-up period as counts and percentages and will include it as a time-varying confounder in the multivariable analyses.

The primary outcome for this study is the occurrence of MDS/AML. This outcome will be described using counts, percentages, rates per 1000 person-year follow-up time with appropriate 95% CIs, overall, and by key patient characteristics including treatment, G-CSF use, classes of chemotherapy drugs, and other covariates listed in *Other covariates* in section 4.

The unadjusted and adjusted incidence rate ratios (IRRs) and corresponding 95% CIs will be calculated for risk of MDS/AML comparing patients who received G-CSF vs. patients who received no G-CSF for each tumor type.

The time to event analysis will be used to calculate risk of MDS/AML comparing patients who received G-CSF vs. patients who received no G-CSF, for each tumor type. This time to event analysis will be summarized with Kaplan-Meier survival curves and their corresponding 95% survival bands.

Hazard ratios and 95% CIs will be estimated comparing patients who received G-CSF vs. patients who received no G-CSF, adjusting for radiation, chemotherapy, and other covariates:

- age at index date
- SEER registry
- year of index date
- AJCC stage
- race, eg, White, Black, Other, Unknown
- ethnicity (Hispanic, non-Hispanic, Unknown)

- hormone receptor status for breast cancer (ER-/PR-positive, ER-/PR-negative, unknown)
- histology of tumor
- lymph node status (positive, negative, unknown)
- tumor size
- Autoimmune diseases: Rheumatoid arthritis, Psoriasis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's Disease
- bone marrow transplantation
- modified Charlson comorbidity index within one year prior to the index date

Time-to-event models will be used, where time at risk will be calculated from the index date to the earliest of occurrence of MDS/AML or a censoring event. See inclusion/exclusion criteria in section 4 for further details on how events before the start of the follow-up time are handled. The proportional hazards assumption will be checked for each covariate graphically. A pooled hazard ratio will be calculated for MDS/AML following G-CSF use by pooling the Hazard Ratios calculated for the three tumor types. Primary analysis will be replicated in following subgroups of interest.

1. Patients receiving radiation therapy vs. no radiation therapy
2. Classes of chemotherapy drugs
3. Two separate study periods: 2001-2009 and 2010-2015

5. Amendments and Updates

Amendment #1: August 22nd, 2018

Superseding version: January 10th, 2019

6. Milestones

Milestone	Planned date*
Registration in the EU PAS register	*Approximately March 2019*
Start of data collection	*Approximately April 2019*
End of data collection	*Approximately May 2019*
Final data analysis	*Approximately September 2019*
Final report of study results	*Approximately March 2020*

These timelines are subject to change based on timely approval
EU PAS: European Union Post-Authorisation Studies

The study will be registered in the European Union Post-Authorisation Studies (EU PAS) electronic register. The study protocol will be uploaded as soon as possible after its finalization and prior to the start of data collection.

7. Rationale and Background

Cancer patients are at an increased risk of developing MDS or AML, but the reasons for this are unclear: treatment modality (surgery, chemotherapy, radiation), regimen, patient characteristics, and the characteristics disease itself are all possible contributing factors. Furthermore, prophylactic treatment with filgrastim or pegfilgrastim during treatment – used to treat neutropenia and boost white blood cell count during treatment – may also be associated with subsequent development of MDS/AML.

7.1 Diseases and Therapeutic Area

Both Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) are rare diseases that are common among patients older than 65 years. The age-adjusted incidence rate for MDS, in age groups <40, 40-49, 50-59, 60-69, 70-79, and 80+ years is reported to be 0.1, 0.7, 2.2, 8.6, 28.3, and 56.8 per 100,000 person-years, respectively. For AML, the SEER has reported an age-adjusted incidence rate per 100,000 person-years of 20.1 for 65+ years and 2.0 for those younger than 65 years.[15] MDS and AML developed after cancer treatment account for approximately 10-20% of cases of MDS/AML.[6] Patients who develop MDS/AML after cancer treatment typically have poorer survival than patients with *de novo* MDS/AML.[7] Therefore it is important to understand if G-CSF use is associated with an increased risk of MDS/AML among patients receiving chemotherapy for their cancer.

7.2 Rationale

During the PRAC assessment of RMP Versions 1 and 2 for Neulasta, (pegfilgrastim) in 2013/2014 the rapporteur recommended that the MAH should consider working in collaboration with an established cancer registry to collate and review adverse drug reactions relating to all the safety concerns in association with pegfilgrastim. Based on its review of EU and US alternative data sources, using criteria such as number of patients, accessibility, data collection period, collection and coding of chemotherapy and G-CSF treatments, and diagnosis of its events of interest (MDS and AML), the MAH has taken forward the US SEER-Medicare (Surveillance, Epidemiology, and End Results-Medicare) database.

It has been well recognized that patients diagnosed with cancer have an increased risk for MDS and AML following treatment.[1-7] Both radiation therapy and chemotherapy have been established as risk factors of secondary MDS and AML.[5,8-10] Patients receiving myelosuppressive chemotherapy, with high risk of febrile neutropenia, commonly receive

granulocyte colony stimulating factors (G-CSF) for febrile neutropenia prophylaxis.[11] Because G-CSF induces proliferation of myeloid progenitor cells, which are especially sensitive to myelosuppressive chemotherapy drugs, there is a biological plausibility for G-CSF to increase the risk of myeloid disorders such as MDS and AML.[12,13] A systematic review of 25 randomized clinical trials (RCTs) that randomly assigned patients to receive G-CSF (n = 6,058) or no-G-CSF (n = 6,746) and had at least 2 years of follow-up observed that both risk of MDS/AML and intensity of chemotherapy was increased in patients receiving G-CSF support.[2] However, the authors were unable to differentiate between the causal effect of G-CSF and the causal effect of dose intensified chemotherapy as patients with G-CSF support are more likely to receive intense chemotherapy. Out of the previous two SEER-Medicare reports of patients receiving chemotherapy for breast cancer, one reported no association of G-CSF with risk of AML (HR: 1.14; 95% CI: 0.67, 1.92)[10] and another reported an increased risk for MDS/AML following G-CSF use (HR: 2.14; 95% CI: 1.12, 4.08).[14] In a recent study by Calip, et al.[1] on breast cancer patients, found that MDS/AML risk was associated with anthracycline/cyclophosphamide-containing regimens (HR = 1.86, 95 % CI 1.33–2.61) and filgrastim (HR = 1.47, 95 % CI 1.05–2.06), but not pegfilgrastim (HR = 1.10, 95 % CI 0.73–1.66). The difference could be a result of difference in pharmacokinetics and the administration frequency of filgrastim (10-11 administrations in a cycle) and pegfilgrastim (one administration in a cycle) during the chemotherapy course.[16-18] The increased risk associated with filgrastim but not pegfilgrastim could also be a result of opportunity for frequent exposure eg, patients with congenital chronic neutropenia have an high risk of leukemic transformation because of their chronic exposure to G-CSF (which is used as a treatment for these patients).[13,19]

The study by Calip et al.[1] was based on breast cancer patients in the SEER-Medicare database from 2001 to 2009. Since then several years of additional data have been collected. In this study, we plan to include breast, lung, and prostate cancer patients from 2001 to 2013 and characterize the risk of AML/MDS for these patients. We selected breast, lung and prostate cancer because of the substantial sample size[20] and the high use of G-CSF in these patients[21]. Breast, lung, and prostate cancer are the three most common cancers and are estimated to account for 38% of total 1.7M new cancer cases in the United States (US) in 2018.[20] Similarly, in Europe, the 2018 estimates for new breast, lung, and prostate cancer cases are 523 000, 470 000, and 450 000, respectively.[22] Moreover, high use of G-CSF for primary prophylaxis in lung (47%) and

prostate (23%) cancer patients has been reported by a large retrospective study of patients initiating myelosuppressive chemotherapy in the Veterans Health Administration (VHA) database.[21] We propose a retrospective cohort study of breast, lung, and prostate cancer patients aged 66+ years selected including latest US SEER-Medicare data from January 1, 2001 to December 31, 2015. Two studies validated Medicare based algorithms against the SEER algorithms to identify MDS[23] and AML[24] and reported an increased specificity with use of Medicare based algorithm. Therefore, we will use the published definition (SEER-reported or Medicare-reported MDS/AML)[1] to evaluate the primary objective.

7.3 Statistical Inference (Estimation or Hypothesis)

We hypothesize that use of G-CSF in patients receiving chemotherapy is associated with modest increase in risk of MDS/AML after controlling for important covariates that can confound the association between G-CSF and MDS/AML. In this study, the null hypothesis is that use of G-CSF in patients receiving chemotherapy is not associated with increased risk of MDS/AML.

8. Research Question and Objectives

Is G-CSF use associated with an increased risk of MDS/AML among elderly patients treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer?

8.1 Primary objective

1) Among patients aged 66 years and older treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, compare the risk of SEER-reported or Medicare-reported MDS/AML between those receiving G-CSF vs. not receiving G-CSF for each tumor type

8.2 Secondary objectives

1) Among patients aged 66 years and older treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, describe the characteristics of patients overall, by tumor type, by use of G-CSF, and by occurrence of MDS/AML.
2) Calculate the pooled hazard ratio for MDS/AML following G-CSF use among patients aged 66 years and older treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer.

9. Research Methods

9.1 Study Design

This is a retrospective cohort study of breast, lung, and prostate cancer patients aged 66 years and older, selected from the US SEER-Medicare database from January 1, 2001 to December 31, 2014. Baseline characteristics, treatment, and chemotherapy drugs will be ascertained 12 months prior to index date (ie, Sixtieth day without chemotherapy following last dose of first chemotherapy course). Follow-up will accumulate after the index date. The "60 days without chemotherapy" window is designed to reduce the number of MDS/AML events captured that are not related to G-CSF use. Patients are followed until they develop MDS/AML or experience a censoring event, such as development of a second cancer, relapse, disenrollment, death, or end of the study period. The final date for follow-up is December 31, 2015. The primary endpoint is time from index date to diagnosis of MDS/AML. The main comparison is risk of MDS/AML among patients who received G-CSF vs. patients who received no G-CSF for each tumor type (breast, lung, and prostate cancer). The results will be replicated in following subgroups of interest:

1. Patients receiving radiation therapy vs. no radiation therapy
2. Classes of chemotherapy drugs
3. Two separate study periods: 2001-2009 and 2010-2015

9.2 Setting and Study Population

Patients are identified from the SEER-Medicare database. Medicare database provides claims for 93% of the patients diagnosed with cancer in SEER regions.[25] The SEER database contains comprehensive patient information, including stage, treatment modality, regimen, secondary cancers, hormone receptor status, Charlson score, demographics, and many other clinical and patient characteristics (see section 9.7 for details on SEER-Medicare database). We decided to include stage I-IV for prostate cancer because majority of patients diagnosed with prostate cancer that receive chemotherapy have stage IV diagnosis.

9.2.1 Study Period

Any patients diagnosed with stage I-III breast, lung, prostate cancer between January 1, 2001 and December 31, 2014 and who satisfy the inclusion and exclusion criteria will be included in the study. The index date will be the sixtieth day without chemotherapy following last dose of first chemotherapy course. Baseline characteristics,

treatment, and chemotherapy drugs will be ascertained 12 months prior to index date. Follow-up begins after the index date. The earliest start of the baseline period is January 1, 2000, and the last possible follow-up date is December 31, 2015.

9.2.2 Subject/Patient/Healthcare Professional Eligibility

9.2.2.1 Inclusion Criteria

Patients must satisfy the following criteria:

- Chemotherapy following first diagnosis of breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer
- Index date (Sixtieth day without chemotherapy following last dose of first chemotherapy course) between Jan 1, 2001 and Dec 31, 2014
- Alive and at least 66 years of age at index date
- Continuous enrollment in both Part A and Part B Medicare for at least 12 months prior to the index date

9.2.2.2 Exclusion Criteria

Patients must not have any of the following criteria:

- Breast, lung, or prostate cancer is not their first primary cancer diagnosis
- Breast, lung, or prostate breast cancer diagnosis identified only at autopsy or on their death certificate
- Men with breast cancer diagnosis
- Unknown stage at first cancer diagnosis
- End-stage renal disease (ESRD) any time prior to the index date.
- Enrolled in Health maintenance organization (HMO) any time during the study period
- Diagnosed with MDS/AML or any other second primary cancer diagnosis any time prior to the index date.

9.2.3 Baseline Period

Baseline characteristics will be collected for patients during 12 months prior to their index date.

9.2.4 Study Follow-up

Follow-up time begins after (and including) the index date until the earliest of occurrence of the primary outcome (MDS/AML) or one of the following censoring events:

- Development of second cancer other than MDS/AML
- Relapse or second-line chemotherapy treatment (chemotherapy claims that occur at least 60 days after the last dose of first chemotherapy course)
- Disenrollment,

- Death
- End of study period

9.3 Variables

9.3.1 Exposure Assessment

The type of cancer treatment (radiation, surgery, chemotherapy, G-CSF use) will be assessed during the 12-month baseline period prior to the index date (ie, sixtieth day without chemotherapy following the last dose of first chemotherapy). Radiation, however, will also be assessed in the follow-up period. The primary source for information about radiation exposure is the SEER datafile PEDSF. Type of radiation therapy will be identified for specific tumor types (eg, Brachytherapy vs. External Beam radiotherapy for prostate cancer). Medicare inpatient claims will be used to identify cancer-related surgery and the type of surgery. Patients will be considered exposed to G-CSF if there is at least one claim with a HCPCS code of G-CSF (filgrastim or pegfilgrastim) within one year prior to the index date. A single claim with a HCPCS code for G-CSF will be considered as one administration. More than one claims with a HCPCS code for G-CSF on a single day will be considered as one administration. Chemotherapy will be determined using a combination of ICD-9-CM, CPT, and HCPCS codes. For example, a patient is determined to have been treated with any of the following chemotherapy drug if they have at least two HCPCS or CPT codes for the same chemotherapeutic drugs within one year prior to the index date; Identified drugs will be categorized into following classes:

- alkylating drugs
- antimetabolites
- anthracyclines
- platinum drugs
- topoisomerase inhibitors
- taxanes
- other chemotherapy

9.3.2 Outcome Assessment

The primary outcome is the time to development of MDS/AML during the follow-up period. The diagnosis of MDS/AML will be assessed in two ways:

1) SEER-reported MDS/AML: First occurrence of the SEER-reported diagnosis of MDS or AML

2) SEER-reported MDS/AML or Medicare-reported MDS/AML: First occurrence of SEER-reported or Medicare-reported diagnosis of MDS/AML. Medicare algorithm ("2+BCBM") to identify MDS/AML is two or more ICD-9-CM claims of MDS/AML at least 1 month apart but within 12 months of each other OR at least one ICD-9-CM claim of MDS/AML with death or hospice entry within 3 months AND a blood count (BC) and bone marrow (BM) during a year prior to first claims.[23,24]

9.3.3 Covariate Assessment

Several other covariates are to be assessed, including:

- age at index date
- SEER registry
- year of index date
- AJCC stage
- race, eg, White, Black, Other, Unknown
- ethnicity (Hispanic, non-Hispanic, Unknown)
- hormone receptor status for breast cancer (ER-/PR-positive, ER-/PR-negative, unknown)
- histology of tumor
- lymph node status (positive, negative, unknown)
- tumor size
- Autoimmune diseases: Rheumatoid arthritis, Psoriasis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's Disease
- bone marrow transplantation
- modified Charlson comorbidity index within one year prior to the index date

Many of these are available in the SEER datafiles. Details of treatment with radiation, surgery, and chemotherapy as well as the calculation of the Charlson score will be assessed using Medicare claims.

9.3.4 Validity and Reliability

The completeness of case ascertainment of both MDS[23,26] and AML[24] in SEER has been a concern since 2001. MDS/AML as a primary malignancy has been captured in the SEER registry since 2001, and as a secondary malignancy since 2010.[26] In 2001, SEER guidelines stated that “a myeloid malignancy diagnosed after a previous myeloid malignancy would not be recorded as a subsequent primary”.[24] Since, ~30% of MDS cases progress to AML,[27] these cases will not be registered as AML from 2001-2009 leading to an underestimation of AML. In 2010, SEER guidelines allowed multiple myeloid primaries stating that "originally diagnosed in a chronic (less aggressive) phase and second diagnosis of a blast or acute phase more than 21 days after the chronic diagnosis."[24] This allowed for a narrower definition of second primary MDS/AML from 2010 onwards. Another concern regarding identification of MDS cases is that only 4% of the MDS cases from outpatient clinics are reported to cancer registries[28]. This leads to an underestimation of incidence MDS cases in SEER given that most MDS cases receive care in an outpatient setting.[23]

To resolve the concerns of case ascertainment associated with SEER-reported diagnosis alone, we have proposed to use an outcome definition for primary objective that requires the patient to have a MDS/AML identified by SEER-reported or Medicare-reported algorithms of MDS/AML. This algorithm was not validated but was used by Calip et al,[1] and is based on a validated MDS Medicare algorithm that has 78.05% sensitivity and 99.84% specificity[23] and a validated AML Medicare algorithm that has 89% sensitivity and 99.96% specificity when compared to SEER.[24] The Medicare algorithm (“2+BCBM”) to identify MDS/AML is two or more ICD-9-CM claims of MDS/AML at least 1 month apart but within 12 months of each other OR at least one ICD-9-CM claim of MDS/AML with death or hospice entry within 3 months AND a blood count (BC) and bone marrow (BM) during a year prior to first claim.[23,24]

Chemotherapy regimen will be ascertained using at least two HCPCS or CPT codes for the same chemotherapeutic drugs within 12 months prior to the index date, as used in a prior study.[1] In that same study, a sensitivity analysis was also performed comparing different claims algorithms for identifying MDS/AML and chemotherapy regimens and found no substantial difference in the results. A validation study has shown that chemotherapy claims in Medicare have good to excellent validity.[29] This study reported that, overall, chemotherapy algorithms in Medicare have a sensitivity of 93% with individual regimens having a sensitivity ranging between 81% and 91%.

Several other clinical and demographic covariates will be available from the SEER registry databases, including age, race, ethnicity, stage, hormone receptor status, stage, tumor size, histology, and radiation. Cancer-related surgery and type of surgery will be identified using inpatient Medicare claims.

9.4 Data Sources

The data sources will be the linked SEER registry and Medicare claims (see details on SEER-Medicare database in section 9.7). The SEER registry is a highly regarded, well-documented source of oncology data for the US, and contains many of the covariates related to outcomes, exposures, and other patient characteristics. Approximately 93% of patients diagnosed with cancer in the SEER reporting regions are linked to their Medicare files in this database.[25]

9.5 Study Size

A previous study on this topic using the SEER registry from 2001 to 2009 identified 56,251 eligible patients with 655 events, with a median follow-up time for patients with and without the event of 4.3 and 3.2 person-years, respectively. Precision in this study was high. For example, the overall 95% Poisson confidence interval estimate for the risk of MDS/AML was approximately 3.4 – 3.9 events per 1000 person-years. The precision for this current study is expected to be greater because we will be able to include patients up to 2014.

However, the number of MDS/AML events may be small for some subgroups. For example, in the Calip, et al. study, although the denominators were large, the number of events for various patient subgroups ranged from N = 14 to N = 565, with most subgroups experiencing > 30 events. Again, we expect the current study to have a high number of events due to greater ascertainment of MDS/AML in the registry and larger patient sample size.

9.5.1 Obtaining Data Files

Outcomes Insights, Inc., a study partner of the MAH, will be hosting the data files from the SEER-Medicare program, analyzing the data, and generating a report for the MAH. The MAH will neither perform the analysis nor have access to the raw SEER-Medicare data. Once a data request by Outcomes Insights. is approved, National Cancer Institute's (NCI) information technology contractor provides an invoice to Outcomes Insights the cost of creating requested data files. To ensure the security of the patient's information during transition of files, the SEER-Medicare data files are encrypted to a

thumb drive that is password-protected. These data files are compressed using the GZIP compression utility. IMS make the program available to unzip the files (see details on quality control and data security in section 9.7).

9.5.2 Linking Data Files

N/A

9.5.3 Review and Verification of Data Quality

Outcomes Insights team checks the integrity of the data and will report errors as the data are loaded.

9.6 Data Analysis

9.6.1 Planned Analyses

Several tumor-specific analyses are planned for this study. First, we will summarize the cohort selection algorithm with the size of the patient groups included and excluded. Second, descriptive analysis will be performed to describe patient characteristics, treatment (radiation, surgery) and classes of chemotherapy drugs, and chemotherapy drugs using appropriate descriptive statistics (eg, counts, percentages or means, medians, inter-quartile ranges). Third, crude (unadjusted) outcomes and follow-up time point and precision estimates will be calculated, and Kaplan-Meier survival curves will be used to summarize the time to event for several subgroups (tumor type, radiation, and chemotherapy drug classes). Fourth, multivariable analyses using time-to-event models will be performed to estimate the risk of MDS/AML and compare various subgroups of interest. In the multivariable analysis, radiation therapy following the index date will be treated as a time varying confounder. If sample size is appropriate, we will also evaluate the risk by type of G-CSF (filgrastim and pegfilgrastim) and dosage of G-CSF. A pooled hazard ratio will be calculated by combining the tumor-specific hazard ratios for breast, lung, and prostate cancer patients, if the heterogeneity of tumor-specific results is not substantial. And finally, the assumptions of the modeling and various sensitivity analyses, including competing risk analysis of the outcome and the censoring events will be conducted to investigate possible sources of bias.

9.6.1.1 Missing or Incomplete Data and Lost to Follow-up

Based on previous studies utilizing the same database, we expect a small amount of missing data (typically, about 0.1% of covariates have missing values, based on a previous study). Given that we do not expect a large degree of missing data, we do not plan to conduct any formal imputation. For variables other than staging (unknown

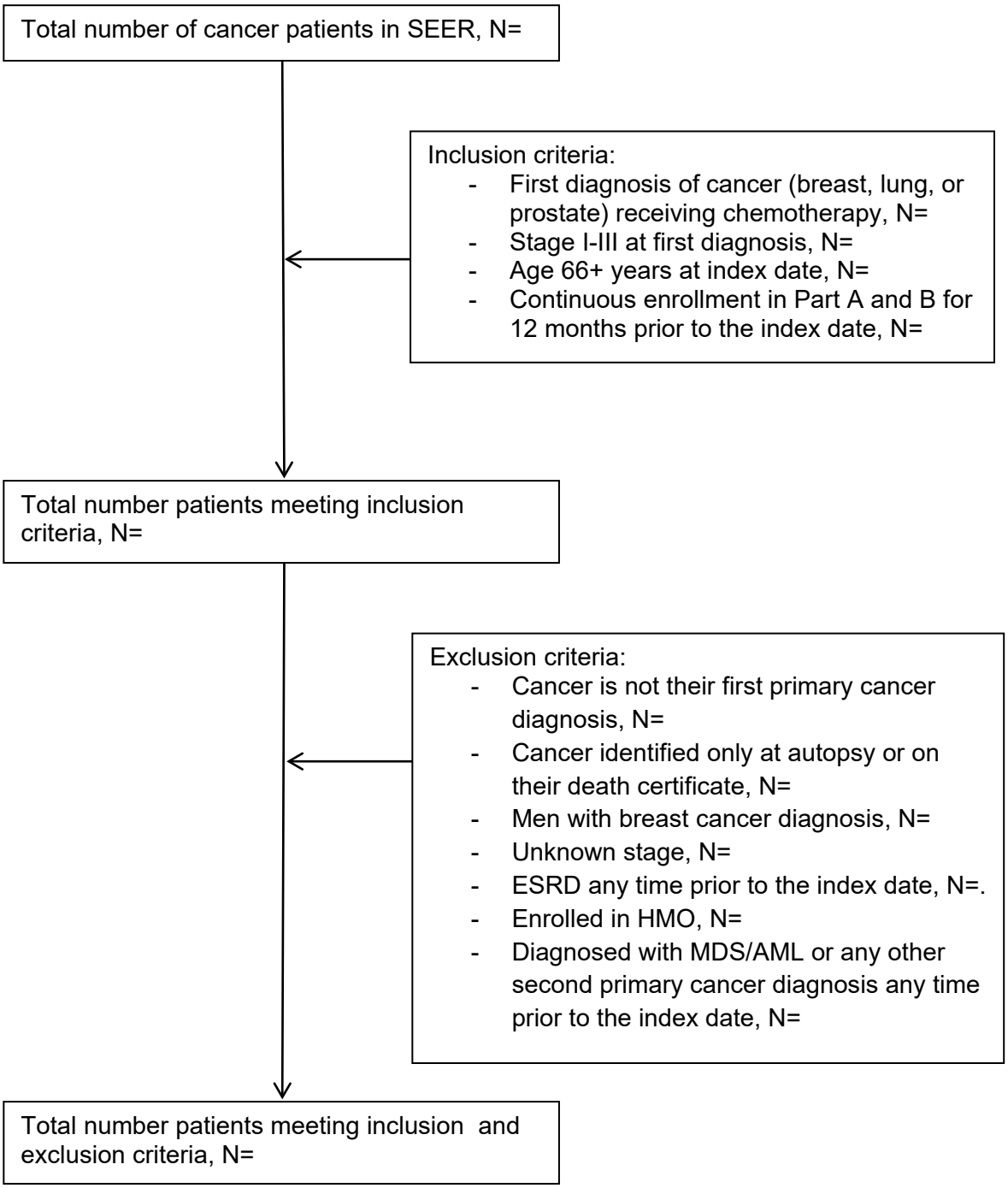
staging forms part of the exclusion criteria) we will include patients with missing data as a separate category (“Unknown” or “missing”) in the descriptive tables and unadjusted (crude) outcome tables where possible, but they will be excluded from multivariable modeling (complete case analysis).

9.6.1.2 Descriptive Analysis

9.6.1.2.1 Description of Study Enrollment

A study attrition table will be calculated for each tumor type, detailing the size of the sample as each inclusion/exclusion criteria are applied. A template for attrition table is presented for cancer patients in Figure 1 below.

Figure 1. Attrition Flow Chart



9.6.1.2.2 Description of Subject/Patient Characteristics

Analysis will be performed to describe patient characteristics, treatment modalities and regimens using appropriate descriptive statistics (eg, counts, percentages or means, medians, inter-quartile ranges). The descriptive statistics will be overall, by tumor type, by use of G-CSF, and by occurrence of MDS/AML. Several patient characteristics will be described, including the following:

- age at index date
- SEER registry
- year of index date
- American Joint Committee on Cancer (AJCC) stage
- race, eg, White, Black, Other, Unknown
- ethnicity (Hispanic, non-Hispanic, Unknown)
- hormone receptor status for breast cancer (ER-/PR-positive, ER-/PR-negative, unknown)
- histology of tumor
- lymph node status (positive, negative, unknown)
- tumor size
- Autoimmune diseases: Rheumatoid arthritis, Psoriasis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's Disease
- bone marrow transplantation
- modified Charlson comorbidity index within one year prior to the index date
- surgical procedure (mastectomy, breast-conserving surgery, surgery NOS)
- Chemotherapy drugs, duration, and class of chemotherapy drugs
- Radiation therapy overall and by type (eg, Brachytherapy vs. External Beam radiotherapy for prostate cancer) before and after the index date.
- G-CSF treatment, by type and dosage

9.6.1.3 Analysis of the Primary Endpoint

Unadjusted risk estimates of the outcomes

The primary outcomes for this study is the occurrence of MDS/AML identified as SEER-reported or Medicare-reported diagnosis (two or more ICD-9-CM claims at least 1 month apart but within 12 months of each other OR at least one claim with death or hospice entry within 3 months with a blood count and bone marrow during a year prior to first claims) of MDS/AML. These outcomes will be described using counts, percentages, rates per 1000 person-year follow-up time with appropriate 95% CIs, overall. The

outcomes will be presented comparing patients who received G-CSF vs. patients who received no G-CSF for each tumor type (breast, lung, and prostate):

A table describing the crude (unadjusted) outcomes will be generated with the number of events, the number at risk (overall denominator), point estimates of the incidence rate (IR) - proportion of patients that experienced the outcome over the total follow-up time, and corresponding 95% confidence intervals. The unadjusted incidence rate ratios (IRRs) and the corresponding 95% CIs will be calculated comparing the patients who received GCSF vs. those who did not receive GCSF.

The time to event (MDS/AML) comparing G-CSF use vs. no G-CSF use, will be summarized with Kaplan-Meier survival curves and the corresponding 95% survival bands. The rates of the competing/censoring events (death, second cancer) will also be described with unadjusted rates, counts, and percentages.

Multivariable modeling of the outcome

The risk of developing MDS/AML by use of G-CSF, adjusted for several patient characteristics, will be estimated using multivariable time-to-event models for each tumor type. The resulting adjusted hazard ratios (HRs) and corresponding 95% CIs will be estimated, after adjusting for several covariates, such as:

- age at index date
- SEER registry
- year of index date
- American Joint Committee on Cancer (AJCC) stage
- race, eg, White, Black, Other, Unknown
- ethnicity (Hispanic, non-Hispanic, Unknown)
- hormone receptor status for breast cancer (ER-/PR-positive, ER-/PR-negative, unknown)
- histology of tumor
- lymph node status (positive, negative, unknown)
- tumor size
- Autoimmune diseases: Rheumatoid arthritis, Psoriasis, Systemic Lupus Erythematosus, Ankylosing Spondylitis, Ulcerative Colitis, Crohn’s Disease
- bone marrow transplantation
- modified Charlson comorbidity index within one year prior to the index date
- surgical procedure (mastectomy, breast-conserving surgery, surgery NOS)

- Chemotherapy drugs, duration, and class of chemotherapy drugs
- Radiation therapy overall and by type (eg, Brachytherapy vs. External Beam radiotherapy for prostate cancer) before and after the index date.

Time-to-event models will be used, where time at risk will be calculated from the index date to the earliest of occurrence of MDS/AML or a censoring event. Radiation therapy will be treated as a time varying confounder. Additional analysis will be conducted to evaluate the association of type of G-CSF and dosage of G-CSF. See inclusion/exclusion criteria in section 4 for further details on how events before the start of the follow-up time are handled. The proportional hazards assumption will be checked for each covariate graphically. We will also present the adjusted incidence rate ratios (IRRs) and the corresponding 95% CIs will be calculated comparing the patients who received GCSF vs. those who did not receive GCSF.

A pooled hazard ratio will be calculated for MDS/AML following G-CSF use by pooling the Hazard Ratios calculated for the three tumor types if the heterogeneity of tumor-specific results is not substantial. Multivariable modeling will be subject to sufficient sample size (number of events) in the subgroups of interest.

9.6.1.3.1 Subgroup Analysis

We believe that radiation therapy and type of chemotherapy drugs could be effect modifiers for relationship between G-CSF use and MDS/AML. Therefore, primary analysis will be replicated in following subgroups of interest.

1. Patients receiving radiation therapy vs. no radiation therapy
2. Classes of chemotherapy drugs

The SEER policies regarding identification of multiple primaries changed in 2010 (see section 9.3.4 for details). These policy changes would likely impact the specificity of identifying MDS/AML. We will therefore conduct a subgroup analysis evaluating the primary objective in

1. Two separate study periods: 2001-2009 and 2010-2015

9.6.1.3.2 Sensitivity Analysis

A sensitivity analysis will be performed using outcome definition that is based on SEER-reported MDS or AML diagnosis during the follow-up.

9.7 Quality Control

Quality Control of SEER-Medicare database:

The SEER database provided by the NCI monitors its data quality. To maintain the quality of the data, there are contractual agreements with regional registries. Also, SEER's standards for data quality must be met before the data are transmitted from regional registries. SEER also provides ongoing education, training, and support for regional registrars, quality control (QC) of the data to prevent and correct errors, and scheduled monitoring and evaluation to identify areas needing improvement.[30] The Medicare database includes more than 55 million US citizens age 65 years and older and has substantially improved in quality over the years due to the concerted efforts by Centers for Medicare and Medicaid Services (CMS).[31,32]

The linkage of the SEER-Medicare data is a collaborative effort of the NCI, the SEER registries, and the CMS. The linkage of persons in the SEER data to their Medicare claims is performed by NCI and CMS and is not the responsibility of investigators seeking to use the data. To link SEER with Medicare data, the registries participating in the SEER program send individual identifiers for all persons in their files. These identifiers are matched with identifiers contained in Medicare's master enrollment file. Approximately, 93% of persons age 65 years and older in the SEER files are matched to the Medicare enrollment file.[25] The NCI has obtained a Certificate of Confidentiality that allows the NCI and its contractors who have access to the SEER-Medicare data to refuse disclosure of identifying information on research participants (eg, individual patients and individual providers) in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.[33]

Quality control of patient individual data protection:

The SEER-Medicare database does not include personal identifiers for patient and medical care providers. However, given the remote risk of patient re-identification, access to SEER-Medicare requires undergoing an approval process. This approval process by representatives of NCI and SEER ensures that the confidentiality of patients and providers is maintained. If the reviewing agencies have concerns about confidentiality arising from the project SEER-Medicare, data is not released regardless of whether an investigator has already been funded by another agency or organization to conduct an analysis. Moreover, SEER-Medicare database does not release regional identifiers including patient's Census tract and ZIP code, as well as the ZIP code for

physicians and hospitals. Once a data request by Outcomes Insights is approved, NCI's information technology contractor provides an invoice to Outcomes Insights to cover the cost of creating requested data files. To ensure the security of the patient's information during transition of files, the SEER-Medicare data files are encrypted to a thumb drive that is password-protected. These data files are compressed using the GZIP compression utility. NCI's information technology contractor makes the program available to unzip the files.[34]

Outcomes Insights will store all SEER-Medicare data related to this study on encrypted file systems. To protect the confidentiality of patients, no attempts will be made to identify individual patients, hospitals or physicians and in any publications and presentations of these data will not allow identification of patients, hospitals or physicians. The study data including analytical data files, program codes and logs, and aggregate results will be retained by Outcomes Insights, Inc. for 5 years after submission of the final results as per the data use agreement with the National Cancer Institute.

9.8 Limitations of the Research Methods

Although this study is based on high quality data and a relatively larger sample size than previous research, there are several limitations.

9.8.1 Internal Validity of Study Design

Cancer patients are at higher risk of developing MDS/AML than the rest of the population, and so it can be challenging to identify MDS/AML that is G-CSF related. The study design's delayed time at risk has been chosen to mitigate this issue; follow-up time starts 60 days after the last dose of chemotherapy. This will induce a survivor bias but likely remove patients who had latent/undiagnosed disease prior to treatment that is unrelated to G-CSF use.

Given the variety of treatment modalities and regimens, combined with the relative rarity of the outcome, there is not sufficient sample size to evaluate whether the risk of MDS/AML is greater for particular class or regimens of chemotherapy drugs.

9.8.1.1 Confounding

We believe there is a potential for confounding by indication, as patients with a baseline higher risk of MDS/AML may have been treated differently (ie, different intensity of chemotherapy, radiation, or use of G-CSF) compared to those at lower risk of MDS/AML. The baseline Charlson comorbidity score is included in the multivariable

model to help address this issue to some degree. We also plan to present the effect estimates stratified by classes of chemotherapy drugs and radiation therapy.

9.8.2 Analysis Limitations

Competing risks are another potential limitation for this study which will be addressed in the analysis using appropriate statistical methods (eg, Fine and Gray method) We will estimate the rates of the censoring events, alongside the outcome, to evaluate competing risks. Also, the exclusion of the patients during the 60 days without chemotherapy will create some survivor bias and a possibly healthier cohort of post-chemotherapy cancer patients.

This study includes elderly Medicare population who survived 60 days following last dose of chemotherapy in first course, we believe that results from the SEER-Medicare database can be applicable to similar younger patient population receiving G-CSF.

9.8.3 Limitations Due to Missing Data and/or Incomplete Data

Based on previous research in this area using these databases, we do not expect to have to address a large missing data issue.

10. Collection of Safety Information and Product Complaints

This study is analyzing secondary data from SEER-Medicare database and no safety data will be collected.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. Amgen reserves the right to terminate the study at any time.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

The intention of this study is to publish the results in a manuscript.

The results of the study will be reported in an observational research study report which will be registered in the EU PAS registry by the MAH. Patient identifiers will not be used in the publication of results.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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