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Second Primary Malignancy (SPM) Analyses in a Disease Registry Study

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ABSTRACT

In hematology clinical trials, monitoring for SPMs plays an important role in the assessment of safety for new agents in drug development. The correlation of exposure to the experimental drug to the development of an SPM has become an important analysis in the reporting of clinical trials. This presentation reports the SPM analyses performed in a US registry trial in which study physicians chose the treatment regimen administered to patients with newly diagnosed multiple myeloma. SPMs were monitored carefully, and a specific SPM case report form was filled out at each study visit. SPMs were categorized as hematologic, solid tumor, or non-melanoma skin cancers. Patients are followed for at least 5 years. Analyses included incidence, incidence rates (SPMs per person-years), time-to-event, and risk factor assessments. We used the first SPM event start date to calculate drug exposure. For the specified drug exposure without SPM, we used the minimum of discontinue, death or data cutoff dates to the drug start date. For the No Therapy group, we used the minimum of SPM start date, discontinue, death or data cutoff dates to the informed consent date. Patient outcomes are also reported.

INTRODUCTION

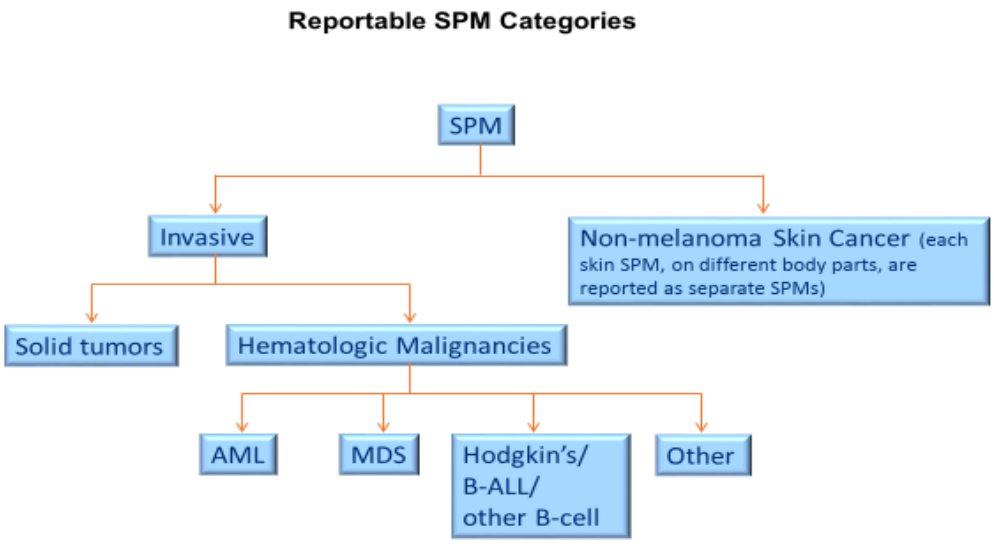
Improvements in cancer treatments, supportive care, and early detection have resulted in an increasing number of cancer survivors. It has been reported that the current 5-year survival rate for all cancer patients combined is approximately 66% (Wood 2012). The improvements in the survival of cancer patients has revealed a new clinical challenge; the development of the life-threatening problem of second primary malignancies (SPMs) (Wood 2012, Donin 2016, Thomas 2012). Data from the National Cancer Institute Epidemiology and End Results (NCI SEER) database shows that 18% of reported incident cancers are SPMs, making SPMs the third most common cancer diagnosis (Curtis 2006). In addition, cancer survivors, compared with the general population, have a 14% increased risk of developing a malignancy. These data show that patients who have had one cancer are at risk for the development of another cancer for as long as they survive. The occurrence of SPMs may be due to the effects of the treatment of the first cancer, the influence of genetic susceptibility of the patient, environmental exposures, behavioral factors (particularly tobacco and excessive alcohol use), as well as factors related to the first cancer (Wood 2012, Thomas 2012). The growing number of patients with subsequent malignancies developing after the diagnosis of a first cancer requires that data regarding the occurrence of SPMs in clinical trials be carefully collected and analyzed in an attempt to identify high-risk groups and interventional clinical strategies. Moreover, currently there is no biological marker available that identifies which SPMs are related to primary cancer treatments. Therefore, one must rely on statistical methods to indicate which treatments and which patients are at high-risk for the development of SPMs.

SPM ANALYSES

An SPM is a new primary malignancy that occurs after the diagnosis of a previous primary malignancy. The following are not SPMs and need to be excluded before the diagnosis of a previous malignancy; progressive disease, the development of metastases, or relapse of the previous malignancy. In addition, one must ensure that the reported tumor is actually a cancer. For example, the terms “neoplasm” or “neoplasia” can refer to either a benign tumor or a cancer. Therefore, it is important to obtain a copy of the pathology report for documentation. Risk management plans require SPMs to be reported as serious adverse events (SAEs) and the surveillance of patients for the development of SPMs continues beyond

study treatment discontinuation by a patient. For example, the National Institutes of Health (NIH) require patients who have been exposed to a chimeric antigen receptor (CAR)-T-cell treatment (adoptive immunotherapy) during a clinical trial to be followed for 15 years for the occurrence of SPMs. In addition, the occurrence of an SPM is considered as an important medical event even if it does not meet other serious criteria. Second primary malignancies are to continue to be reported as important medical events throughout study participation, including during the long-term observation phase.

Once an SPM is diagnosed, it is categorized as either an Invasive SPM (malignancies that are systemic diseases such as hematologic malignancies or solid tumor cancers that are metastatic or at risk to develop metastases) or a non-melanoma skin cancer (cancers that rarely metastasize and are easily cured by local excision). Progressive malignant melanomas frequently metastasize and are classified as solid tumor cancers (an invasive SPM).



The reconciliation of SPM data between the safety database maintained by Global Drug Safety (GDS) and the clinical database maintained by Database Operations (DBO) is a key process. This reconciliation is performed to ensure that events in the safety database and those in the clinical database are consistent. It also ensures that all SPMs diagnosed during a study are reported in both the safety and clinical databases and that the SPM verbatim terms are mapped to similar preferred terms in both databases, preventing double counting in the statistical output.

The exposure and duration of exposure to a specific treatment are important variables to analyze as risk factors for the development of SPMs. Patients exposed to the treatment prior to the detection of an SPM are those who are included in the group as “exposed to the treatment”. Patients that did not receive the treatment prior to the diagnosis of the SPM are included in the “control” group as not exposed patients.

DIAGRAM 1: Diagram 1 below shows the possibilities for when a SPM could occur in relation to exposure to a selected agent. SPMs that occur after exposure to an agent may be related to the effects of the agent.

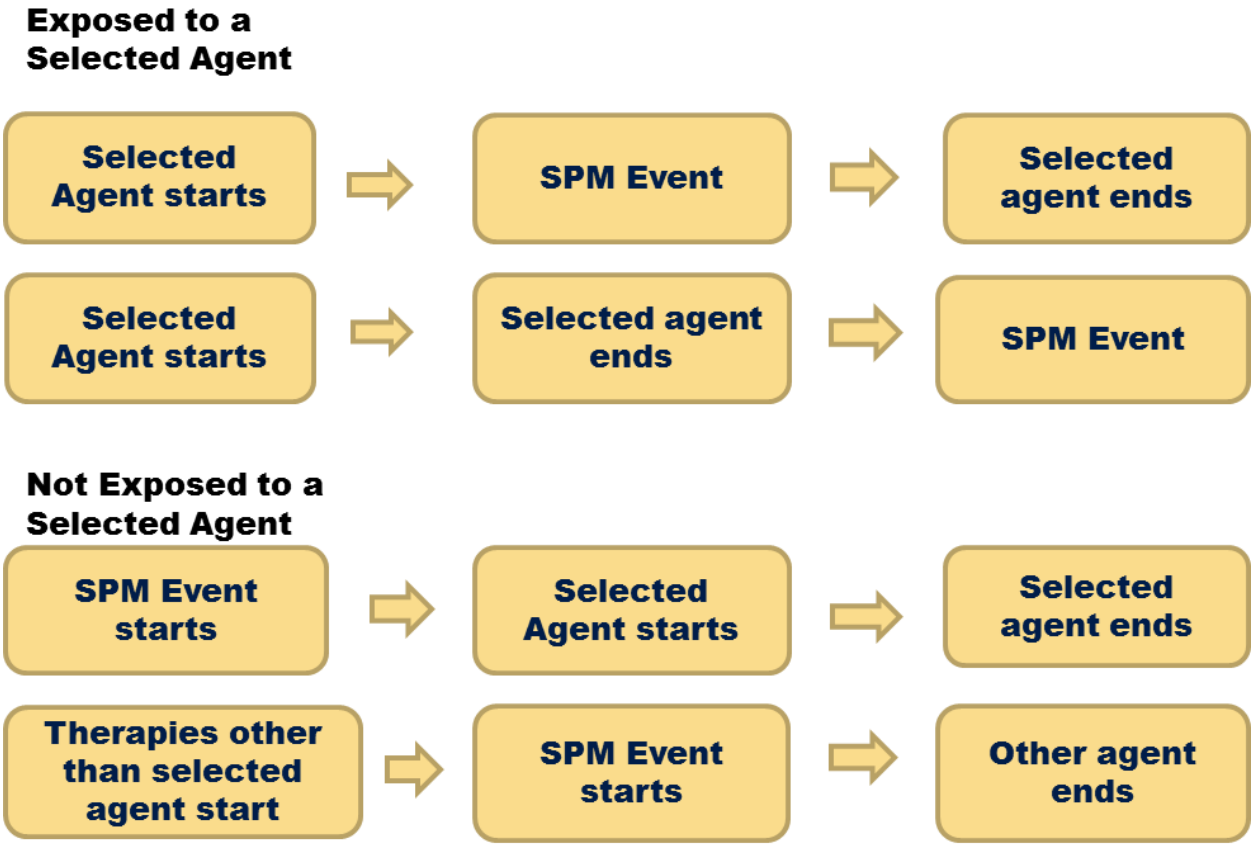


Diagram 1. SPM Exposed or Not Exposed in Selected Agent Exposure Definition.

The start date for an SPM (date of detection of the SPM) should not be missing. If it is missing, or partially missing, the start date will have to be imputed. If a stop date exists, it generally means that the SPM was a local solid malignant tumor that could be treated with surgery with or without radiation therapy.

In randomized studies with large numbers of patients with adequate follow-up and complete and accurate data collection, commonly performed analyses include the raw incidence frequencies of patients who develop an SPM and the exposure adjusted incidence rate of patients who develop an SPM (the number of SPM patients per patient-years of follow-up). The comparison of the results of these analyses between exposed and not exposed groups represent the initial exploration as to whether or not a specific therapy is associated with the occurrence of SPMs. The incidence rate can correct for differences in follow-up time between the exposed and not-exposed groups. This is important as the raw incidence of SPMs will increase over time in a population with increased follow-up time.

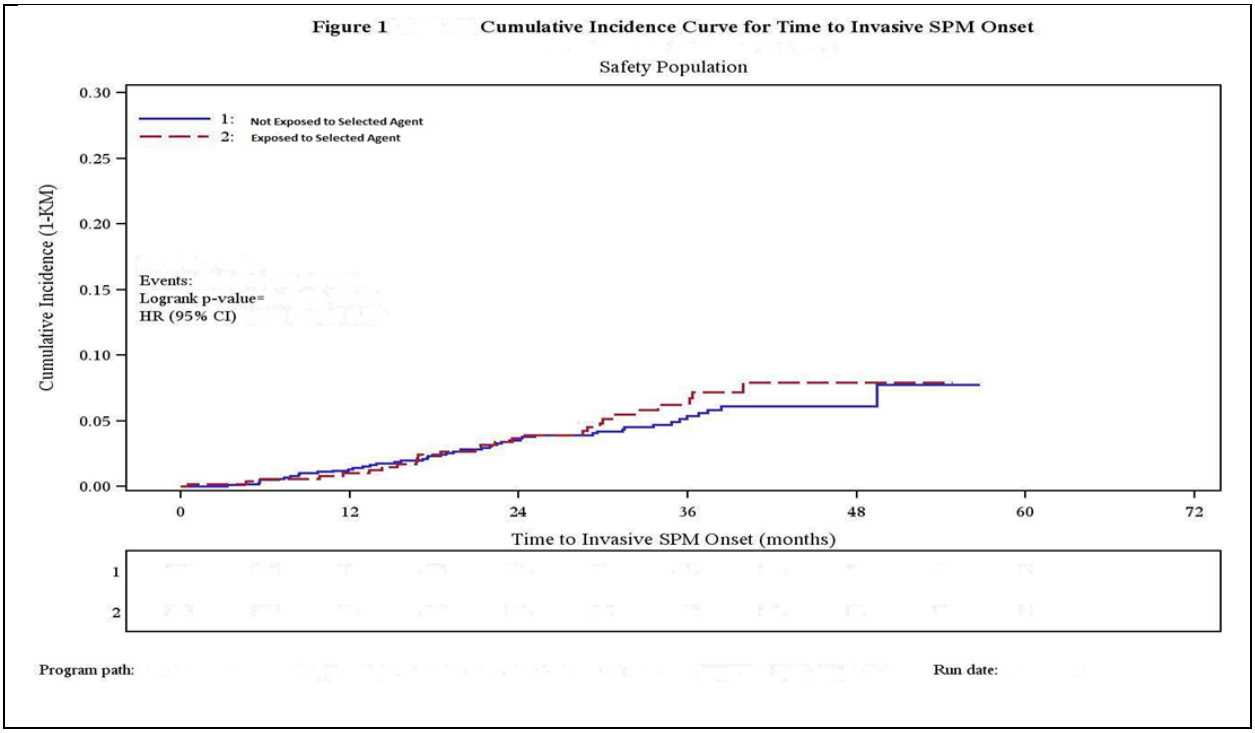
A significant separation in the Kaplan-Meier (KM) curves of the cumulative incidence of patients with SPMs over time in favor of the not-exposed compared with the exposed group indicates a treatment exposure related association to the occurrence of SPMs. We defined the time to event for the exposed group as the time from the start of exposure till SPM and in the absence of an event, we used the time to censoring defined as the time from the start of exposure to the minimum of the death, discontinuation and the data cut-of date. The time to event for the non-exposed group was defined similarly starting from the initiation of any therapy at diagnosis or the enrollment date in the event the Multiple Myeloma remains

untreated.

The events included in the SPM-free survival curve are the occurrence of an SPM and death. Comparisons of the SPM-free survival curves and the KM overall survival curves of the exposed and not-exposed treatment groups may be utilized to determine if a treatment provides clinical benefit even if the treatment is associated with the occurrence of SPMs.

Risk factor analyses were also performed. Univariate analysis of baseline factors identified variables that could be risk factors for the occurrence of SPMs. These variables were then included in a multivariate analysis. The multivariate analyses identify variables which continue to be predictive in the presence of other factors in the model.

OUTPUT 1: Output 1 is an example of a KM curve of the cumulative incidence of SPMs occurring in patients after exposure to a selected agent versus those SPMs that occurred in patients not exposed to the selected agent.



Output 1. KM Curve of Cumulative Incidence of SPMs for Patients Exposed to Selected Agents vs. Not Exposed to Selected Agents.

OUTPUT 2: Output 2 shows a table of univariate analyses of baseline variables that could possibly be risk factors for the development of SPMs. Factors with a P-value < 0.X in these analyses are selected to be included in the multivariate model (Output 3).

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Table 3
Cox Regression for Time to Invasive SPM- Univariate Analysis of Selected Risk Factors
Safety Population

Risk Factors	Label	DF	Estimate	Std.Err.	Chi-Square	P-value	Hazard Ratio (95% CI)
Treatment Groups	group 1 vs. group 2	x	x	x	x	x	x(x, x)
Baseline Creatinine Clearance	<60 vs >=60 ml/min	x	x	x	x	x	x(x, x)
Baseline Hemoglobin	<=10 vs >10 g/dL	x	x	x	x	x	x(x, x)
Prior History of Invasive Malignancy	Yes vs No	x	x	x	x	x	x(x, x)
Baseline ECOG	>=2 vs 0 or 1	x	x	x	x	x	x(x, x)
Sex	Male vs Female	x	x	x	x	x	x(x, x)
Age Group	>75 vs <=75	x	x	x	x	x	x(x, x)
Ethnicity	Hispanic Latino vs Non-Hispanic Latino	x	x	x	x	x	x(x, x)
Baseline Stage	III vs I/II	x	x	x	x	x	x(x, x)
Baseline Body Mass Index	>=25 vs <25 kg/m2	x	x	x	x	x	x(x, x)

* This is just an example. More factors in a real study analysis.

Output 2. Risk Factors – Univariate Analysis for Selected Agents

OUTPUT 3: Output 3 demonstrates multivariate analyses utilized to identify possible risk factors related to the development of SPMs in study patients.

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Table 4
Cox Regression for Time to Invasive SPM- Multivariate Analysis of Selected Risk Factors
-Comparisons of Selected Group 1 vs Group 2
Cox Model Starting with Selected Groups and Important Risk Factors (p<0.x* from univariate analysis)
Safety Population

Independent Variables Selected [1]	Label	Chi-Square	P-value	Hazard Ratio (95% CI)
Selected Groups	Group 1 vs. Group 2	x	x	x(x, x)
Baseline Creatinine Clearance	<60 vs >=60 ml/min	x	x	x(x, x)
Baseline Body Mass Index	>=25 vs <25 kg/m2	x	x	x(x, x)

* The Important Risk Factors was selected from univariate analysis with p-value condition.

Output 3. Risk Factors – Multivariate Analysis for Selected Agents and Selected Factors

CONCLUSION

In conclusion, it is important to accurately and completely collect SPM data in this era in which effective treatments for various cancers are being developed. Unfortunately, cancer survivors are at risk to develop subsequent cancers. Determining whether a treatment is associated with an increased occurrence of SPMs can support risk-benefit analyses for the treatment. Finding the risk factors associated with SPMs can signal the need for strategies to mitigate the risk of SPM in patients with these risk factors at diagnosis.

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