Original Article

The incidence of second primary malignancies after gastrointestinal stromal tumor before and after the introduction of imatinib mesylate

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Imatinib mesylate was FDA-approved in 2002 for the treatment of unresectable and metastatic GISTs and has become the standard of care. Its use has resulted in greatly increased survival rates for patients with GIST. The increased survival in patients with GIST raises concerns about long term effects of therapy, particularly the development of second primary malignancies (SPMs), which has been reported with imatinib treatment of chronic myeloid leukemia. In addition, the diagnosis of GIST itself may pose a risk for the development of SPMs. The purpose of this study was to examine the incidence of SPMs after GIST, particularly before (pre-imatinib era: 1992-2001) and after (imatinib era: 2002-2009), and factors related to the occurrence of SPMs. Data from the NCI's Surveillance Epidemiology and End Results (SEER) 1992-2009 program was utilized. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for these were calculated using SEER*Stat 8.0.1. Observed incidences were then compared between pre-imatinib and imatinib eras using Fisher's exact test. The relationship between the presence of SPMs and each of the variables was examined using logistic regression. There were significantly more patients in the imatinib era alive after follow-up (n=533, 63.99%) than in the pre-imatinib era (n=130, 22.41%, P<0.001). Overall, the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era (P=0.030). This difference was mainly accounted for by a higher incidence of colon adenocarcinoma in the imatinib era (P=0.023). Renal cell carcinoma also accounted for this difference. In contrast, the rate of melanoma of the skin was significantly lower in the imatinib era compared with the pre-imatinib era (P=0.030). In the pre-imatinib era for melanoma, the SIR was 17.64 (95% CI: 3.64-51.57). Patients with SPMs were significantly older at diagnosis (mean =64.18, SD =12.95) than patients without SPMs (mean =60.63, SD =15.27, P=0.024). Marital status was significantly related to the presence of SPMs (78.26% *vs*. 65.62%, P=0.0154) with those patients with SPMs more likely to be married compared to those without SPMs. This relationship is most likely due to increased survival. Of note, patients with SPMs had greater number of months of survival (mean =70.83, SD =51.54) than those without SPMs (mean =39.33, SD =37.30, P<0.0001). The findings in our study demonstrate that patients after GIST are at increased risk of developing SPMs and that this risk is increased following the introduction of imatinib in 2002. The increased incidence of SPMs in the era of imatinib could be explained by the increased survival of patients with metastatic GIST and therefore more time to develop SPMs, however, further studies are needed to investigate this mechanism.

Keywords: Gastrointestinal stromal tumor (GIST); imatinib mesylate; second primary malignancies

Submitted Jul 06, 2013. Accepted for publication Jul 23, 2013.

doi: 10.3978/j.issn.2218-676X.2013.07.04

View this article at: http://www.thetcr.org/article/view/1379/2960

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract with an annual frequency of 10 to 14.5 per one million of the population (1). GISTs express the cell-surface transmembrane receptor c-kit, a protein coded by the KIT proto-oncogene possessing tyrosine kinase activity. The numerous mutations of KIT seen in GIST result in constitutive activation of tyrosine kinase signaling, leading to uncontrolled cell proliferation and resistance to apoptosis (2-4). Tumors that lack KIT mutations have been found to express activating mutations in the related tyrosine kinase platelet derived growth factor receptor alpha (PDGFR) (5,6). Diagnosis of GIST has greatly increased following pathologic reclassification and the widespread adoption of c-kit immunoshistochemical staining (7,8). Prior to 2000, many GISTs were misdiagnosed as other smooth muscle tumors including sarcoma and leiomyosarcoma (3,7).

Imatinib mesylate, a tyrosine kinase inhibitor, competitively inhibits KIT, BCR-ABL, ARG, PDGFR, and PDGFR tyrosine kinases (9-12). Imatinib was FDA approved in 2002 for the treatment of unresectable and metastatic GISTs, and has since become the standard of care. Its use has resulted in greatly improved survival rates (13,14). Historically, treatment of GISTs had consisted of surgical resection of localized disease with an overall 5 year survival rate of approximately 50% (15-17). Patients with more advanced disease that could not be resected had a median survival less than 21 months. Responses to conventional chemotherapy and/or radiotherapy were poor (16,18-20).

Improved longevity in patients with GIST raises questions regarding the development of second malignancies in these patients. Not only may these patients have an increased risk due to the presence of a primary malignancy, but imatinib itself has been implicated in the development of second primary malignancies following increased survival (21). Studies have demonstrated a small risk of second cancers in patients receiving therapy with tyrosine kinase inhibitors for hematologic malignancies, mostly for CML (22). Additionally, patients with GIST have also been shown to be at risk for the development of SPMs regardless of treatment (23-25). The actual risk, particularly with regard to use of imatinib, is unknown.

The purpose of this study was to examine the incidence of SPMs after GIST, particularly before (pre-imatinib era: 1992-2001) and after (imatinib era: 2002-2009), and factors related to the occurrence of SPMs using a population-based approach.

Methods

Data collection

Data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) 1992-2009 program were utilized. Registries included were those from the SEERS 13 (San Francisco-Oakland, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterrey, Louisiana, Alaska, rural Georgia, and Detroit), representing approximately 13.4% of the U.S. population (26). All cases examined were confirmed to be malignant microscopically, not by death certificate or autopsy. Patients included were only those with active follow-up with primary endpoint data. Cases excluded were those in which the primary site of the tumor was unknown, and those in which GIST was considered localized as these patients would not have been considered as candidates for imatinib therapy during the time period studied [imatinib was only recently approved for adjunctive therapy for localized surgical resection (27,28)].

Diagnostic codes used for data from 1992-2000 were 8936 (GIST) from any site, and 8935 (sarcoma), 8890 (leiomyosarcoma), and 9560 (neurilemmoma) in the gastrointestinal tract (middle 1/3 of esophagus until the rectum). We included these soft tissue tumors of the gastrointestinal tract as these were likely originally misclassified cases of GIST (3,29). As the diagnostic accuracy of GIST improved after the widespread use of c-kit staining, only tumors classified as GIST were examined from 2001-2009. Variables examined in our analysis were sex, race, marital status, radiation, grade, vital status, age of diagnosis, months of survival, and person-time-years (time during which a subject is at risk of the study event).

Statistical analysis

The observed incidence of SPMs after GISTs was determined over time, as well as in each of the time periods, pre-imatinib and imatinib. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated using the estimated incidence in the age-adjusted general population in each of the time periods using SEER*Stat 8.0.1. Observed incidences were then compared between pre- and post-imatinib eras using Fisher's exact test.

The relationship between the presence of SPMs and each of the variables was examined using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Variables found to be significant or marginally significant ($P<0.10$) in each of the analyses were

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included in a logistic regression analysis that was then used to examine the odds of having an SPM or not. A similar analysis was undertaken to examine the relationship of era (pre- or post-imatinib) to each of the variables. Survival analysis was done using Kaplan-Meier method. Non-parametric measures were utilized due to the low incidence of SPMs. Statistical analysis system (SAS) was used for analysis. For all values, the significance level was set to P<0.05.

Results

Overall, the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era (P=0.030). This difference was mainly accounted for by a higher incidence of colon adenocarcinoma in the imatinib era (P=0.023). Renal cell carcinoma also accounted for this difference. In the imatinib era, the SIR of renal cell carcinoma was 4.57, which was significantly elevated compared with the expected age- and time- adjusted incidence for the general population (95% CI: 1.68-9.96). In contrast, the rate of melanoma of the skin was significantly lower in the imatinib era compared with the pre-imatinib era (P=0.030). In the pre-imatinib era for melanoma, the SIR was 17.64 (95% CI: 3.64-51.57) (*Table 1*).

Patients with SPMs were often older at diagnosis (mean =64.18, SD =12.95) than patients without SPMs (mean =60.63, SD =15.27, P=0.024) (*Figure 1*). Marital status was significantly related to the presence of SPMs (P=0.0154). There were more married patients with SPMs (78.26%) than without SPMs (65.62%).

There was no significant difference in person-time years. Patients with SPMs were at risk for 5 years (SD =5.32), while patients without were at risk for 2.93 years (SD =2.79). Sex (P=1.00), race (P=0.3631), grade (P=0.6862), radiation treatment (P=1.00) were not associated with the presence of SPMs (*Table 2*). In the multivariable logistic regression analysis, age was the most important factor related to someone's odds of developing an SPM or not in any time period. Patients who were older had a 3.7% greater odds per year (OR =1.037, CI: 1.002-1.073) of developing an SPM. Of note, patients with SPMs were more likely to be alive (62.5%) than those without SPMs (45.68%, P=0.0010) at the end of follow-up. In addition, they had greater number of months of survival (mean =70.83, SD =51.54) than those without SPMs (mean = 39.33, SD =37.30, P<0.0001) (*Figure 2*).

For validation of the pre-imatinib and imatinib era comparisons, other factors were compared between these cases. There were no differences between the pre-imatinib and imatinib eras with regard to age (P=0.0937), sex (P=0.9129), race (P=0.2163), marital status (P=1.00), grade (P=0.1506), or person time years (P=0.1346). There were more patients in the post-imatinib era alive (n=533, 63.99%) than in the pre-imatinib era (n=130, 22.41%) by the end of follow-up (P<0.0001). There were more people in the pre-imatinib era who received radiation for their tumors (n=36, 6.23%) than in the imatinib era (n=8, 0.96%) (*Table 3*).

Discussion

Our results demonstrate a higher incidence of certain SPMs after GIST compared with the general population, particularly melanoma and renal cancers (*Table 1*). This is consistent with previous studies which demonstrate the development of SPMs following increased survival after GIST (21,23). The higher incidence may also be related to increased medical surveillance following primary diagnosis, exposure to risk factors for GIST, or genetic predispositions of individuals to cancer. A small percentage of GISTs (less than 5%) may be associated with autosomal dominant germ line Kit or PDGFR mutations (30), which may predispose patients to develop tumor syndromes such as neurofibromatosis type 1, Carney triad, and familial GIST syndrome (31). There have been several reviews and case reports that demonstrate that GIST may occur synchronously with other tumors (23-25,31-35). These may be a result of a common exposure to carcinogenic agents resulting in the concurrent presence of malignancies. A study of 783 patients with GIST showed that approximately 20% develop other primary malignancies (23). The most common malignancies reported in patients with GIST include hematologic, prostate, breast, kidney, lung, female genital tract, and carcinoid tumors. Soft tissue and bone sarcomas, malignant melanoma, and seminoma have also been reported after GIST (24). Acute myelogenous leukemia has also been thought to be associated with GIST (36). Our findings of significantly higher rates of melanoma and genitourinary cancers, particularly renal cell carcinoma, after GIST are in line with these. Renal cancers occurred at a disproportionately higher rate than that for the general population after the introduction of imatinib, while melanoma occurred at lower rates after the introduction of imatinib.

While most melanomas involve persistent activation of MAPK pathways that involve signaling through serine/threonine kinase BRAF, various growth factor receptors including c-kit are likely overactivated in this cascade (37). A small percentage of melanomas demonstrate activating mutations of KIT, for which imatinib demonstrates significant efficacy (38,39). The observed decrease in incidence of

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Table 1 The incidence of SPMs after GIST in the pre-imatinib and imatinib eras

	1992-2001 pre-imatinib era						2002-2009 imatinib era						P value
	Observed	% O/total [336]	O/E	CI lower	CI upper	Excess risk	Observed	O/total [905]	O/E	CI lower	CI upper	Excess risk	(observed/ total)
All sites	13	1.146131805	2.037618	0.34	2.05	16.96	55	7.06940874	1.27	0.96	1.66	35.47	0.0303
Head and neck (tongue)	0	0	0	0	27.39	–2.94	1	0.128534704	1.07	0.03	5.97	0.2	1
Gastrointestinal tract (colon, stomach)	0	0.286532951	0	0	2.7	–29.78	12	1.542416452	1.31	0.68	2.28	8.44	0.0227
Respiratory system (lung)	1	0	1	0.03	5.59	0.05	9	1.156812339	1.35	0.62	2.56	6.97	0.1877
Melanoma of the skin	3	0.286532951	17.64#	3.64	51.57	58.65	0	0	0	0	2.72	–4.05	0.0295
Other non-epithelial skin	0	0	0	0	158.43	–0.51	2	0.257069409	11.76#	1.42	42.47	5.47	1
Soft tissue	1	0	35.29	0.89	196.6	21.46	0	0	0	0	16.01	–0.69	0.3103
Female breast	1	0.286532951	1.37	0.03	7.61	5.84	3	0.385604113	0.6	0.12	1.74	–6.07	1
Female genital system (uterine)	0	0	0	0	13.27	–6.06	3	0.385604113	1.55	0.32	4.53	3.18	0.5567
Ovary	0	0	0	0	46.89	–1.72	2	0.257069409	3.74	0.45	13.5	4.38	1
Male genital system (prostate)	4	0	3.05	0.83	7.82	26.02	8	1.028277635	0.96	0.41	1.89	–1.08	1
Urinary system (renal cell)	0	0	0	0	7.33	–10.98	8	1.028277635	2.26	0.98	4.45	13.34	0.0641
Urinary bladder	1	0	2.91	0.07	16.22	14.5	2	0.257069409	0.94	0.11	3.39	–0.39	1
Kidney and renal pelvis	0	0	0	0	23.97	–3.36	6	0.771208226	4.57#	1.68	9.96	14.03	0.1854
Eye and orbit	1	0	126.99#	3.22	707.52	21.64	0	0	0	0	71.19	–0.16	0.3097
Brain and other nervous system	0	0	0	0	61.69	–1.3	2	0.257069409	4.83	0.58	17.44	4.74	1
Endocrine system (thyroid)	0	0	0	0	63.35	–1.27	2	0.257069409	3.29	0.4	11.88	4.16	1
All lymphatic and hematopoietic diseases	1	0	3.89	0.1	21.68	16.41	3	0.385604113	0.84	0.17	2.44	–1.76	1
Kaposi sarcoma	0	0	0	0	477.21	–0.17	1	0.128534704	28.23	0.71	157.32	2.89	1

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melanoma in patients with GIST after the introduction of imatinib may speak to this shared mechanism by which GIST and melanoma evolve. The relationship between imatinib and renal cancers is less clear. There is a well-demonstrated role for vascular endothelial growth factor (VEGF) receptor tyrosine kinases in the pathogenesis of renal cell carcinoma (40).

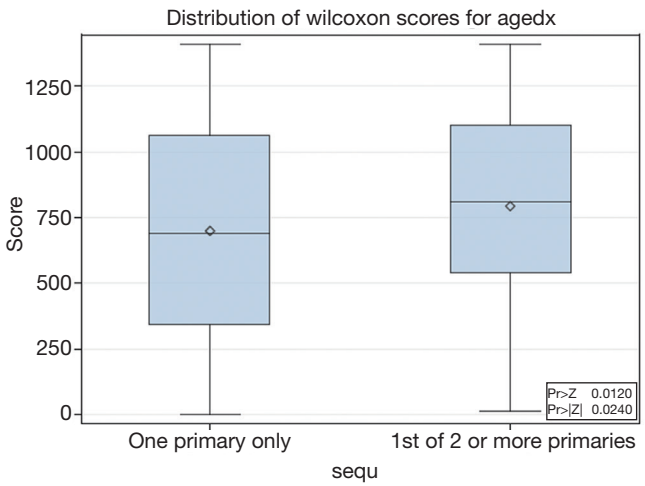

Figure 1 Patients with GIST diagnosed at an older age were significantly more likely to develop SPMs (P=0.024).

Tyrokine kinase inhibitors that target VEGF such as sunitinib have been successfully used in the treatment of renal cell carcinoma (41). Sunitinib is a distinct class of tyrosine kinase inhibitor with an entirely different mechanism than imatinib. It is unlikely to have affected a decrease in the incidence of renal cancers in GIST patients, but it remains unclear as to why the incidence would have risen. This is also the case for second primary gastrointestinal cancers (mostly colon adenocarcinomas), which occurred at a higher rate in GIST patients after the introduction of imatinib in our study. This, in addition to the higher rate of genitourinary cancers in patients with GIST, is consistent with findings in the literature (23,24). VEGF also plays a role in the pathogenesis of colon cancer, in addition to epidermal growth factor receptor (EGFR). Agents targeting VEGF and EGFR are utilized in colon cancer (42,43), which also have distinct targets from imatinib.

In our sub-analysis of the risk factors for SPMs after GIST, we found that older and married patients are more likely to develop SPMs. This is likely related to their increased survival and time available to develop SPMs. We found that patients who went on to develop SPMs had more months of survival and were more likely to be alive at the end of follow up. Several studies have shown that marriage is associated with increased survival (44-46). This finding, however, does

Table 2 Differences between patients with only one primary and those with second primary malignancies

Variable (n, % or mean, SD)		One primary only	At least 1 SPM	P value
Age		60.63 (15.27)	64.18 (12.95)	0.0240
Sex	Female	559 (42.70)	44 (42.31)	1.00
	Male	750 (57.30)	60 (57.69)	
Race	Black	218 (16.65)	13 (12.50)	0.3631
	White	879 (67.15)	71 (68.27)	
	Asian/Pacific Islander	207 (15.81)	19 (18.27)	
	American Indian/Alaskan	5 (0.38)	1 (0.96)	
Marital status	Married	754 (65.62)	72 (78.26)	0.0154
	Unmarried (single, widowed, divorced)	395 (34.38)	20 (21.74)	
Grade	Well-differentiated (grade I)	49 (12.73)	3 (9.68)	0.6892
	Moderately differentiated (grade II)	106 (27.53)	6 (19.35)	
	Poorly differentiated (grade III)	78 (20.26)	8 (25.81)	
	Undifferentiated/anaplastic (grade IV)	152 (39.48)	14 (45.16)	
Radiation	Yes	41 (3.14)	3 (2.88)	1.00
	No	1,266 (96.86)	101 (97.12)	
Vital status	Alive	598 (45.68)	65 (62.5)	0.0010
	Dead	711 (54.32)	39 (37.5)	
Survival (months)		39.33 (37.30)	104 (51.54)	<0.0001
Person time years at risk		2.93 (2.79)	5.11 (5.31)	0.3264

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not downplay the role of other factors such as imatinib in the increased incidence of SPMs. As our findings show, person-time-years was not significantly different between patients between the 2 eras (*Table 3*), implying that survival time was not the only risk factor for the development of SPMs.

The biggest limitation to our study is the assumption that imatinib was offered to patients who met the criteria for treatment after its FDA approval as SEER does not collect data on medication. To support this assumption, we demonstrated that there were no significant differences between the pre- and post-imatinib population with regard to age, sex, marital status, or grade (*Table 3*). There was however a significant difference with regard to the administration of radiation, a treatment modality that is recorded by SEER. As radiation was shown to be ineffective, it was used significantly less frequently in the era of imatinib. This further supports the ability of SEER data to detect patterns in treatment modalities. Another limitation was that GISTs were not able to be distinguished from other gastrointestinal smooth muscle tumors prior to widespread use of c-kit staining, and were often misclassified. We corrected for this by identifying and including sarcomas, leiomyosarcomas and neurilemomas as tumors for which early GISTs were likely mistaken (3,29). As in many epidemiologic survey studies, we must also be aware of the surveillance bias, which may have affected the incidence of SPMs in patients who already carried a primary diagnosis of cancer.

In summary, the findings in our study demonstrate that patients after GIST are at increased risk of developing SPMs and that this risk is increased following the introduction of imatinib in 2002, particularly those of the gastrointestinal and genitourinary tracts. While it is unknown why there is

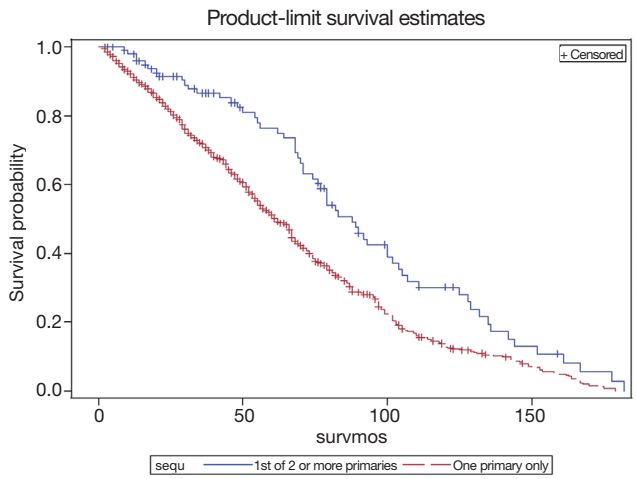

Figure 2 Patients with more than one primary were more likely to have survived longer than those patients who never developed SPMs (P<0.0001).

Table 3 Comparison of pre-imatinib and imatinib populations

Variable (n, % or mean, SD)		Pre-imatinib	Imatinib	P value
Age		61.65 (15.52)	60.37 (14.85)	0.0935
Sex	Female	249 (42.93)	354 (42.50)	0.9129
	Male	331 (57.07)	479 (57.50)	
Race	Black	84 (14.48)	147 (17.65)	0.2163
	White	407 (70.17)	543 (65.19)	
	Asian/Pacific Islander	86 (14.83)	140 (16.81)	
	American Indian/Alaskan	3 (0.52)	3 (0.36)	
Marital status	Married	352 (66.54)	474 (66.57)	0.5191
	Unmarried (single, widowed, divorced)	177 (33.46)	238 (33.43)	
Grade	Well-differentiated (grade I)	27 (10.67)	25 (15.34)	0.1506
	Moderately differentiated (grade II)	80 (31.62)	32 (19.63)	
	Poorly differentiated (grade III)	48 (18.97)	38 (23.31)	
	Undifferentiated/anaplastic (grade IV)	98 (38.74)	68 (41.72)	
Radiation	Yes	36 (6.23)	8 (0.96)	<0.0001
	No	542 (93.77)	825 (99.04)	
Vital status	Alive	130 (22.41)	533 (63.99)	<0.0001
	Dead	450 (77.59)	300 (36.01)	
Person time years at risk		3.25 (3.62)	2.73 (2.07)	0.1346

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an increased risk of these cancers, the increased incidence of SPM in the era of imatinib is likely explained by the increased survival of patients with metastatic GIST and therefore more time available to develop SPM. Nonetheless, clinicians following these patients should certainly be aware of the risk to allow for proper follow-up. Further studies are needed to investigate the mechanism.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2013.07.04). MX serves as an unpaid editorial board member of *Translational Cancer Research*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki. The study was reviewed and determined by the IRB to be exempt from formal committee review as it was research involving the collection of data from a source that was publicly available and did not contain unique patient identifiers. Informed consent was not obtained as it was a SEER database epidemiology study.

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Cite this article as: Phan K, Martires K, Kurlander DE, Gaddipati K, Xavier M. The incidence of second primary malignancies after gastrointestinal stromal tumor before and after the introduction of imatinib mesylate. Transl Cancer Res 2014;3(2):152-159. doi: 10.3978/j.issn.2218-676X.2013.07.04

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