Supplementary Online Content

Joensuu H, Wardelmann E, Sihto H, et al. Effect of *KIT* and *PDGFRA* mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. *JAMA Oncol.* Published online March 23, 2017. doi:10.1001/jamaoncol.2016.5751.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. *KIT* and *PDGFRA* Mutation Type and Tumor Mitotic Count

Mutation type	**No. (%)**	**Tumor Mitotic Count* Median (IQR)**
KIT	268 (77.0)	7 (2-18)
Exon 11 deletion/insertion-deletion	148	8 (2-21)
Deletion involves codons 557 and/or 558	110	7 (3-21)
Deletion of codons 557 and 558 (557_558del)	30	17 (4-34)
Exon 11 duplication/insertion	21	6 (3-10)
Exon 11 substitution mutation	66	6 (2-12)
Exon 9 duplication mutation	25	7 (2-22)
Other	8**	4 (3-10)
PDGFRA	42 (17.5)	1 (0-4)
Exon 12	4	3 (1-4)
Exon 18	38	1 (0-4)
D842V	30	1 (0-3)
Wild-type for *KIT* and *PDGFRA*	22 (5.5)	8 (2-33)

Abbreviation: IQR = interquartile range; *PDGFRA*, platelet-derived growth factor receptor alpha gene.

*Counts per 50 high power fields of the microscope at central review of the tumor specimens. Central mitotic count was available for 332 (97.4%) out of the 341 patients.

**Includes 4 tumors with a *KIT* exon 13 mutation, 2 with a *KIT* exon 11 duplication/insertion mutation plus a substitution mutation, 1 with a *KIT* exon11 insertion mutation plus an insertion-deletion mutation, and 1 with a *KIT* exon 11 deletion mutation plus a *KIT* exon 11 insertion mutation.

eTable 2. Characteristics of the 149 Patients Who Had GIST With *KIT* Exon 11 Deletion or Deletion-Insertion (Indel) Mutation

Factor	**1 Year of Adjuvant Imatinib (n = 71) No. (%)**	**3 Years of Adjuvant Imatinib (n = 78) No. (%)**	***P***
Median (IQR) age at study entry, years	61 (49-68)	59 (50-69)	.82
Gender			
Male	37 (48.7)	39 (51.3)	
Female	34 (46.6)	39 (53.4)	.80
Median (IQR) tumor diameter, cm	10 (7-13)	9 (7-14)	.74
Tumor location			
Gastric	28 (38.9)	44 (61.1)	
Non-gastric	42 (55.3)	34 (44.7)	.05
Not available	1	0	
Tumor mitotic count*			
<6	28 (50.9)	27 (49.1)	
6-10	11 (40.7)	16 (59.3)	
>10	32 (48.5)	34 (51.5)	.68
Not available	0	1	
Tumor rupture before or at surgery			
No	57 (48.3)	61 (51.7)	
Yes	14 (45.2)	17 (54.8)	.76

Abbreviation: IQR = interquartile range.

*Counts per 50 high power fields of the microscope at central review of the tumor specimens.

eTable 3. Characteristics of the 121 Patients Who Had GIST With *KIT* Exon 11 Mutation Involving Codons 557 and/or 558

Factor	**1 Year of Adjuvant Imatinib (n = 57) No. (%)**	**3 Years of Adjuvant Imatinib (n = 64) No. (%)**	***P***
Median (IQR) age at study entry, years	58 (49-67)	59 (51-68)	.85
Gender			
Male	30 (47.6)	33 (52.4)	
Female	27 (46.6)	31 (53.4)	.91
Median (IQR) tumor diameter, cm	10 (7-13)	9 (7-13)	.79
Tumor location			
Gastric	27 (42.9)	36 (57.1)	
Non-gastric	29 (50.9)	28 (49.1)	.38
Not available	1	0	
Tumor mitotic count*			
<6	24 (48.0)	26 (52.0)	
6-10	9 (40.9)	13 (59.1)	
>10	24 (50.0)	24 (50.0)	.78
Not available	0	1	
Tumor rupture before or at surgery			
No	46 (47.4)	51 (52.6)	
Yes	11 (45.8)	13 (54.2)	.89

Abbreviation: IQR = interquartile range.

*Counts per 50 high power fields of the microscope at central review of the tumor specimens.

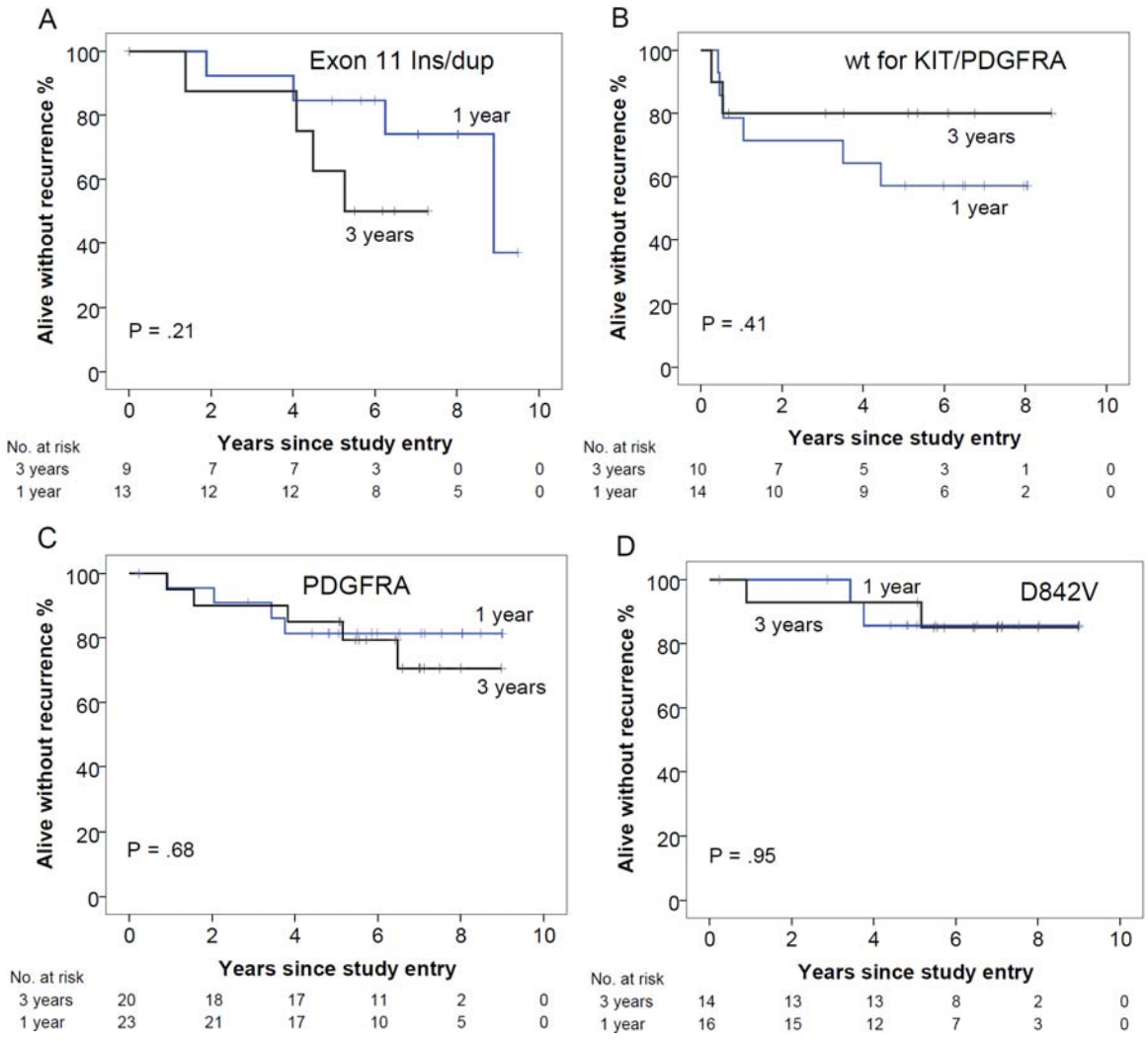
eTable 4. Characteristics of the 111 Patients Who Had GIST With *KIT* Exon 11 Deletion or Deletion-Insertion (Indel) Mutation Involving Codons 557 and/or 558

Factor	**1 Year of Adjuvant Imatinib (n = 53) No. (%)**	**3 Years of Adjuvant Imatinib (n = 58) No. (%)**	***P***
Median (IQR) age at study entry, years	58 (49-67)	60 (50-69)	.78
Gender			
Male	30 (50.0)	30 (50.0)	
Female	23 (45.1)	28 (54.9)	.61
Median (IQR) tumor diameter, cm	10 (7-13)	9 (7-13)	.74
Tumor location			
Gastric	24 (42.9)	32 (57.1)	
Non-gastric	28 (51.9)	26 (48.1)	.35
Not available	1	0	
Tumor mitotic count*			
<6	22 (52.2)	20 (47.6)	
6-10	8 (38.1)	13 (61.9)	
>10	23 (48.9)	24 (51.1)	.56
Not available	0	1	
Tumor rupture before or at surgery			
No	42 (47.7)	46 (52.3)	
Yes	11 (47.8)	12 (52.2)	.99

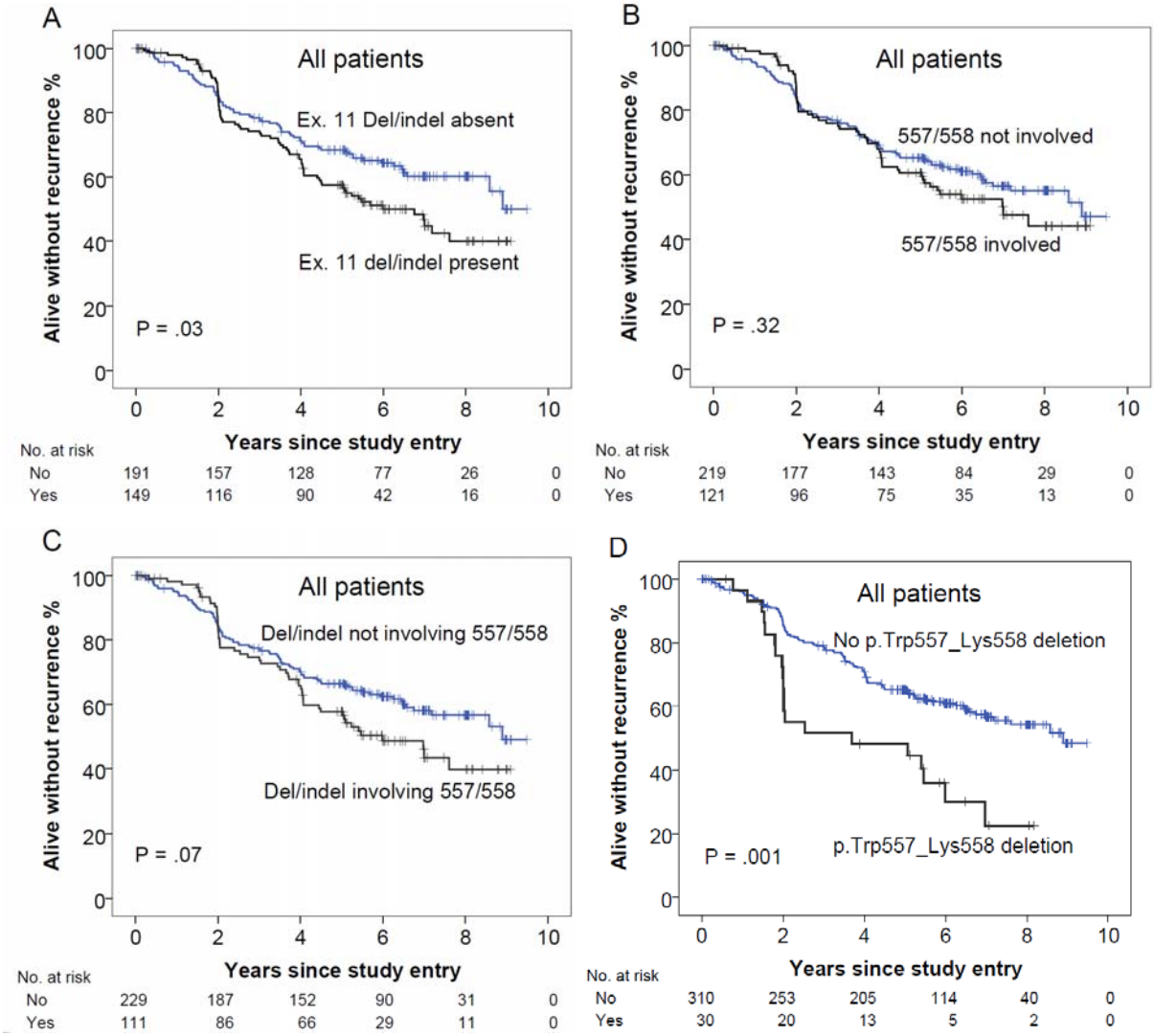
Abbreviation: IQR = interquartile range.

*Counts per 50 high power fields of the microscope at central review of the tumor specimens.

eFigure 1. Association of *KIT* Exon 11 Insertion/Duplication Mutations (A), Absence of *KIT* and *PDGFRA* Mutations (B), *PDGFRA* Mutations (C), and *PDGFRA* Exon 18 Substitution Mutation D842V (D) on Recurrence-Free Survival

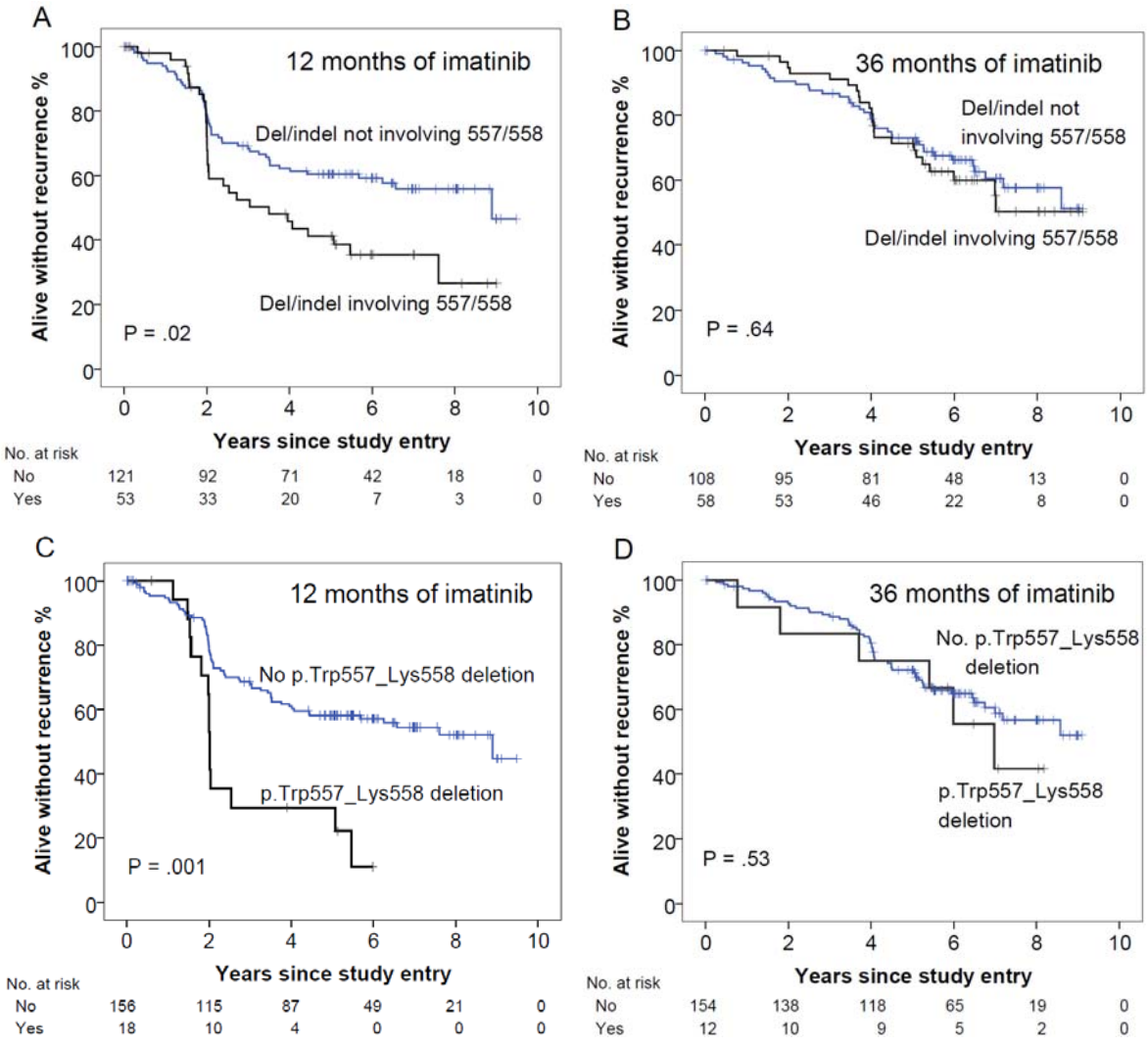


eFigure 2. Associations of *KIT* Exon 11 Deletion Mutations With Recurrence-Free Survival in the Study Cohort



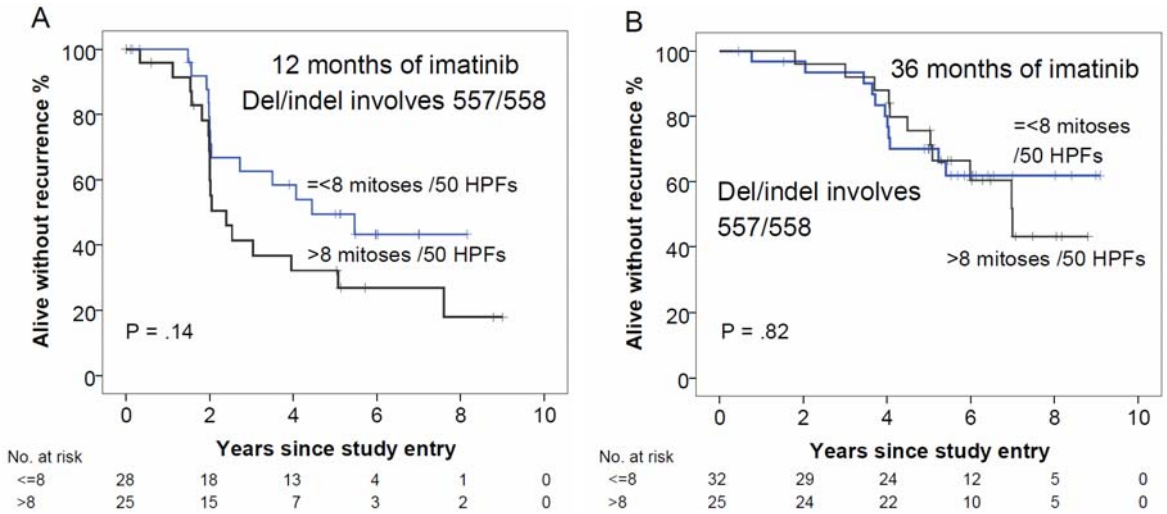
A, Presence of any deletion mutation or insertion-deletion (indel) mutation in *KIT* exon 11; B, presence of a mutation that involves *KIT* exon 11 codon 557 and/or codon 558 (a deletion/indel mutation or a substitution mutation); C, presence of a *KIT* exon 11 deletion mutation or indel mutation that involves codon 557 and/or codon 558; D, a deletion mutation of *KIT* exon 11 codons 577 and 558 only leading to p.Trp557_Lys588 deletion.

eFigure 3. Associations of *KIT* Exon 11 Deletion Mutations With Recurrence-Free Survival in the Random Allocation Groups



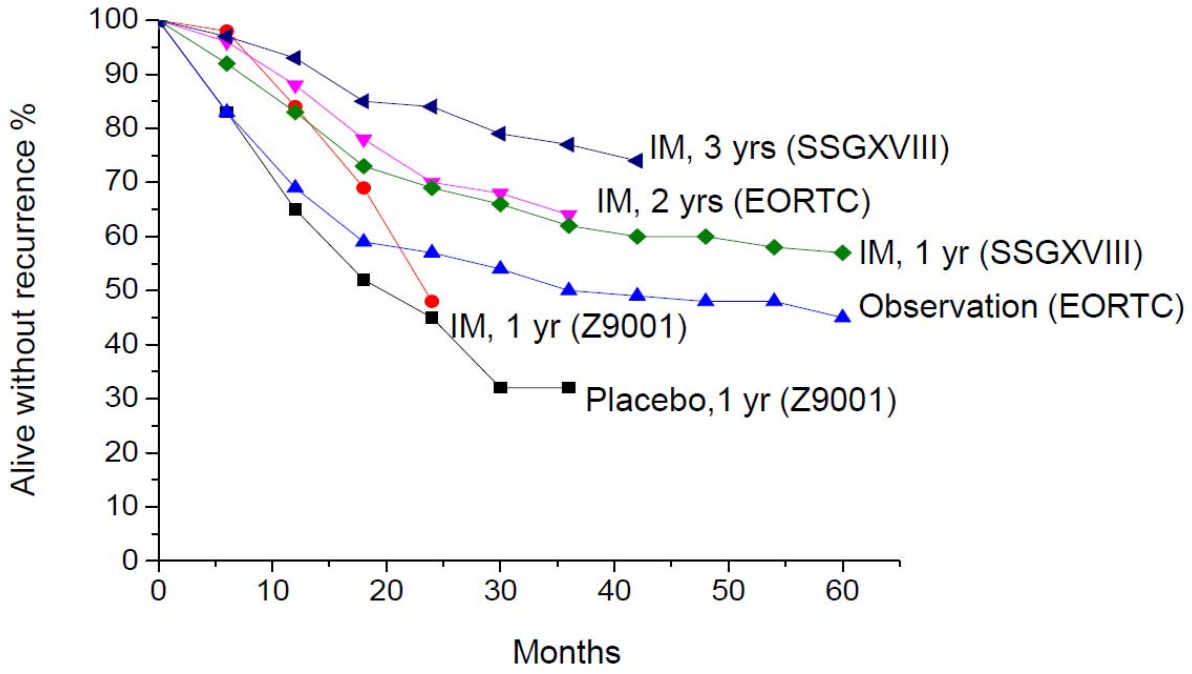
A, B: *KIT* exon 11 deletion mutations that do or do not involve codons 557/558 (a deletion/indel mutation or a substitution mutation): C, D: *KIT* exon 11 mutations leading to p.Trp557_Lys558del. Left panels: Patients assigned to 1 year of adjuvant imatinib; Right panels: Patients assigned to 3 years of adjuvant imatinib.

eFigure 4. Associations of GIST Mitotic Count With Recurrence-Free Survival in Patients With *KIT* Exon 11 Deletion Mutation That Involves Codons 557/558



A, Patients assigned to 1 year of adjuvant imatinib; B, Patients assigned to 3 years of adjuvant imatinib.

eFigure 5. Recurrence-Free Survival (RFS) of Patients With Localized GIST in Three Randomized Trials



The RFS curves are plotted either from the date of randomization (the placebo arm of the Z9001 trial, the observation arm of the EORTC trial) or from the date of stopping the planned duration of adjuvant imatinib (the rest of the curves). Regarding the ACOSOG Z9001 and the EORTC trials, the data were extracted from references 6 and 8. In the SSGXVIII trial the patients had high-risk GIST, and for the EORTC trial RFS of the high-risk subpopulation in the trial is presented. The RFS data of the high-risk group were not available from the ACOSOG Z9001 trial, and the plots shown correspond to patients who had GIST ≥10 cm in diameter. The slopes of the RFS curves tend to become the shallower the longer the duration of adjuvant imatinib. This comparison between the trials needs to be interpreted with caution due to differences in the study populations, and as GISTs that recur during adjuvant imatinib often have a high mitotic count[1] potentially leaving less aggressive tumors in the analysis.

[1]Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. *Cancer*. 2014;120(15):2325-2333.