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Recurrence-free Survival and Safety of Imatinib in Patients With Gastrointestinal Stromal Tumour (GIST) in Greece

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Abstract. *Aim: The purpose of the Imadje study was to confirm the efficacy and safety of imatinib, following resection of kit-positive gastrointestinal stromal tumour (GIST), in the adjuvant setting in the Greek population. Patients and Methods: A total of 34 adult patients already receiving imatinib were enrolled. Recurrence-free (RFS) and overall survival, as well as time to treatment failure and safety were assessed. Results: Overall survival could not be estimated in the present study, as no death occurred. Overall, 91.2% of patients were recurrence-free at 36 months, while the median time to treatment failure was 35 months. No new or unexpected safety findings were observed. Mutation analysis in 14 patients showed that the most frequent mutations were located in KIT exon 11 (64.3%) and exon 9 (28.6%). Univariate analysis showed that only surgical resection with a margin classification of R0 was associated with better RFS. Conclusion: Adjuvant treatment with imatinib for 3 years in patients with intermediate to high risk of recurrence was proven to prolong RFS, while being well-tolerated and not exhibiting a negative impact on patient compliance with therapy.*

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Gastrointestinal stromal tumour (GIST) is the most common (80%) mesenchymal tumour of the gastrointestinal tract (1, 2). At present, GISTs are considered to originate from stem cells that differentiate toward interstitial cells of Cajal phenotype expressing tyrosine kinase receptor KIT or platelet-derived growth factor receptor alpha (PDGFRα) (1). GISTs are positive for the CD117 antigen, an epitope of the KIT receptor tyrosine kinase, in almost all cases (3). KIT is a 145-kDa transmembrane glycoprotein with tyrosine kinase activity that serves as a receptor for stem cell factor. GISTs can occur throughout the entire gastrointestinal tract and may also have extragastrointestinal involvement (2).

GISTs are most commonly found in the stomach (60%), small intestine, jejunum and ileum (30%), duodenum (5%), rectum (2-3%), colon (1-2%), and oesophagus (<1%). A small percentage of tumours arise from the omentum, mesentery, and peritoneum (4).

The most frequent symptoms of GIST include gastrointestinal bleeding, abdominal pain, and palpable masses, while some with small GISTs are asymptomatic (1). There is a slight prevalence in males, while the median patient age is around 60-65 years, with a wide range. The estimated unadjusted incidence of GISTs is around 1/100,000 per year (5).

The standard treatment of localized GIST is the complete surgical excision of the lesion, without dissection of clinically negative lymph nodes. The risk of relapse can be substantial which can be determined with certain risk classifications. The development of imatinib changed the available treatments and the outcome of patients with GISTs dramatically (1). Imatinib has become a standard first-line drug for the treatment of GIST and is predominantly recommended for patients with unresectable, recurrent, or metastatic GIST (5).

Imatinib is a small-molecule protein tyrosine kinase inhibitor. It inhibits the activity of several tyrosine kinases, including KIT, the receptor for the stem cell factor encoded by the *KIT* proto-oncogene, and PDGFRα and PDGFRβ. Imatinib has been approved as an adjuvant therapy in patients with KIT-positive GIST who have undergone surgical resection and are at significant risk of relapse (6).

Large randomized phase III controlled-trials have demonstrated that 400 mg of imatinib daily for 1 year prolonged the recurrence-free (RFS) in patients with localized GISTs with a diameter of ≥3 cm and a macroscopically complete resection (7, 8), while one of these trials that compared 1- with 3-year adjuvant treatment with imatinib favoured longer treatment regarding RFS and overall survival (OS) (8). However, adjuvant therapy should not be considered when the risk of relapse is low, while a shared decision-making process is required when this risk is intermediate (9). The benefit of adjuvant imatinib may vary according to the type of *KIT*/*PDGFRA* mutation, being greater in patients with *KIT* exon 11 deletion mutations (10).

The purpose of the Imadje study conducted in Greece was to assess the RFS and to confirm the safety of imatinib-use in typical practice in patients with GIST in the adjuvant setting. In parallel, the mutational status and compliance were correlated with the data, where this was available.

Patients and Methods

This observational study was performed on a multicentre, regionally dispersed basis across Greece. The sites were located in large urban centers to ensure the representative nature of the institutions involved. Eligible patients were those that were either already receiving imatinib in the adjuvant setting according to the Summary of Product Characteristics for no more than 6 months before inclusion in the study. Patients that had already received imatinib in an adjuvant setting for at least 1 but no more than 3 years and who had interrupted adjuvant treatment during in the previous 6 months prior to enrolment were also eligible for participation. From the latter group, patients were included only if the physician considered that it was necessary to recommence adjuvant treatment with imatinib according to the results of the Scandinavian Sarcoma Group and Sarcoma Group of the AIO multicentre (SSGXVIII/AIO) recommendations (8). Eligible patients were not to have been treated with any investigational agent within 4 weeks prior to baseline. Overall, 34 out of the 35 screened patients were enrolled in the study from nine sites.

Patients were treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types, and provided a signed informed consent prior to any study activities. The maximum planned follow-up period for each study participant was 36 months. Patients were also followed up for 28 days after the last administration of imatinib for possible serious adverse events (AEs) *via* scheduled visits and telephone communications. Institutional Review Board approval was obtained for each participating site prior to patient enrolment.

Statistical analysis. For the estimation of sample size, a 1-year RFS rate of 83% was used; namely H_o: p=83% and H_a: p=98% where p was the proportion of patients without recurrence, H_o was the null hypothesis and H_a the alternative hypothesis. According to one-sample analysis and with power of 0.8, the estimated required sample size was 33 patients. By calculating a 20% drop out rate, the final sample size was 39.6.

Continuous variables are presented with mean, standard deviation, median, minimum and maximum values. Quantitative variables are presented with absolute and relative frequencies.

RFS was defined as the time from enrolment to the first documented recurrence or death due to any cause. If a patient did not have any documented recurrence or did not die, RFS was censored at the time of the last follow-up.

Kaplan-Meier estimates and 95% confidence interval (CI) of the RFS rate at each time point are graphically presented. Additionally, an estimate of the median RFS time and hazard ratio is provided, as well as the mean and standard deviation (SD). Multiple linear regression analysis with the stepwise method was conducted in order to find independent factors associated with time until recurrence or relapse.

Time to treatment failure (TTF) was defined as the time from enrolment to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death, whichever occurred first. Kaplan-Meier estimates and 95% CI of the TTF rate at each timepoint are graphically presented. Additionally, an estimate for the median TTF time is provided. TTF was also described with the mean, standard deviation and hazard ratio.

Overall survival (OS) was defined as the time from study enrolment to time of death due to any cause. If a patient did not die, OS was censored at the time of the last follow-up. Kaplan-Meier estimates and 95% CI of the OS rate at each timepoint were graphically presented. Additionally, estimates for the mean (SD) and median OS time are provided.

Patient compliance with treatment was assessed according to the ratio of the number of tablets actually taken to the number prescribed.

The significance of prognostic factors (including age, gender, mutational status, tumour size, mitotic count, study drug dosage, *etc*.) was evaluated with univariate Cox regression analysis and afterwards with multivariate Cox regression analysis (final model). The backward selection procedure with removal criterion p>0.20 based on a likelihood ratio test was performed to identify significant variables.

Results

Half of the 34 enrolled patients did not complete the study as three patients (8.9%) withdrew early due to disease progression and 14 patients (41.2%) withdrew from the study for other reasons. The most frequently reported reason for early withdrawal in these 14 patients was loss to follow-up (five out

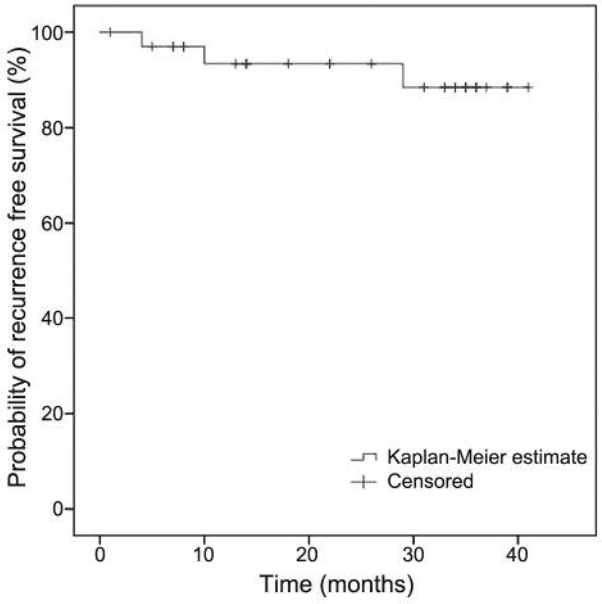

Figure 1. *Kaplan-Meier estimates of recurrence-free survival during the study.*

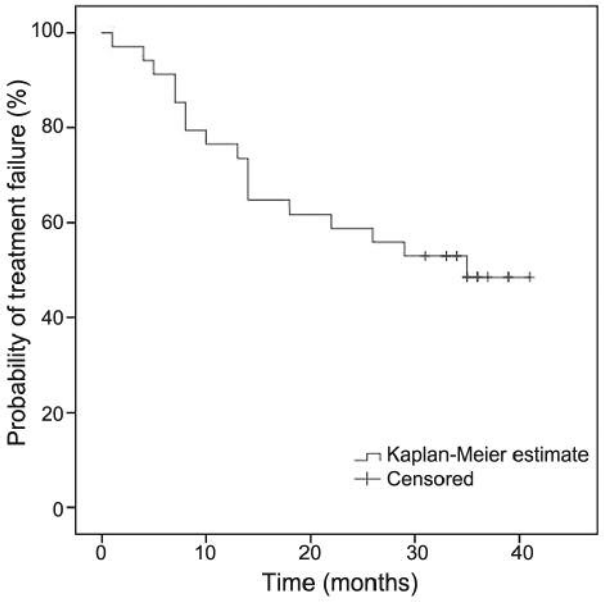

Figure 2. *Kaplan-Meier estimates of time to treatment failure during the study.*

of 14 patients, 35.7%), followed by withdrawal of consent (four out of 14 patients, 28.6%), whereas three patients (21.4%) withdrew due to an AE. The mean and median duration of observation was 23.56 and 31 months, respectively.

Among the 34 study patients, an approximately equal distribution was observed for both genders, with a slight predominance of males (52.9% males *vs*. 47.1% females). The mean (±SD) age was 61.91±14.87 years. The vast majority of the study population (79.4%) had an initial Eastern Cooperative Oncology Group performance status of 0, indicating that the patients were fully active. The median time from the diagnosis of the primary disease was 2 months. Most patients (88.2%) were diagnosed with primary disease within 6 months prior to study entry. Median tumour size was 7.65 cm and the median value of mitoses per 50 optic fields was 6.0. All patients had previously undergone resection, the vast majority of whom with R0 margins, but none of the patients had received any other antineoplastic therapy in the past. The tumour was most frequently located in the stomach (50%) and/or small intestine (23.5%). More rarely tumor was located the jejunum (8.8%) and the duodenum, ileum, liver, abdomen, kidney, and omentum (2.9% each). According to the Armed Forces Institute of Pathology (AFIP) criteria, most patients presented with a high risk of recurrence (73.6%), while 23.5% of the study population had an intermediate and 2.9% had an unspecified risk.

Efficacy. OS could not be estimated as no death occurred during the study. The median RFS was not reached. However, the mean RFS was 38.17 months (95% CI=35.02-41.32 months, with 91.2% of patients being recurrence-free at 36 months.

Kaplan-Meier estimates of RFS are graphically presented in Figure 1. The patients who were alive without recurrence were censored on the date of the last follow-up.

Univariate analysis showed that only surgical resection with R0 margin classification was associated with better RFS (p=0.133, R^2=0.140).

The median TTF was 35 months for the overall study population, while it was not reached in responders (without disease progression, N=30). The mean TTF of the responders was 28.58 months (95% CI=23.37-33.78 months) and of the overall study population was 27.32 months. Kaplan-Meier estimates of TTF are graphically presented in Figure 2.

Compliance and mutational analysis. Compliance with imatinib therapy was not assessed for all patients due to a lack of recorded data. According to the available data, more than 85% of the patients with relevant recorded information (data availability ranged from 48-57% at months 3 through 30 and was 23.5% at month 36) throughout the study period had 100% compliance with imatinib therapy.

Mutation analysis was performed for 14 patients (41.2% of the study population) in total throughout the study duration. The most frequent mutation recorded in the study population was located in *KIT* exon 11 (nine patients; 64.3% of the tested patients), followed by exon 9 (four patients; 28.6% of the tested patients). Other *KIT* mutations found in the study population were in exons 13 (one patient; 7.1% of

Table I. *Summary of safety information for patients who experienced at least one adverse event**.

		Patients (N=28), n (%)*	Adverse events (N=170), n (%)*
Seriousness	Non-serious	23 (82.1)	137 (80.6)
	Serious	14 (50)	32 (18.8)
	Not available	1 (3.6)	1 (0.6)
Relation to treatment	Not related	22 (78.6)	61 (35.9)
	Related	23 (82.1)	104 (61.2)
	Not available	1 (3.6)	5 (2.9)
Grade of severity#	I (Mild)	22 (78.6)	118 (69.4)
	II (Moderate)	17 (60.7)	28 (16.5)
	III (Severe)	8 (28.6)	10 (5.9)
	IV (Life-threatening)	1 (3.6)	2 (1.2)
	V (Death)	0 (0)	0 (0)
	Not determined†	1 (3.6)	1 (0.6)
	Not available	1 (3.6)	11 (6.5)
Outcome	Recovered	14 (50)	39 (22.9)
	Recovered with sequelae	0 (0)	0 (0)
	Recovering	8 (28.6)	21 (12.4)
	Death	0 (0)	0 (0)
	Unknown‡	4 (14.3)	11 (6.5)
	Not available	16 (57.1)	99 (58.2)
Action taken	No action	21 (75)	105 (61.8)
	Dose adjustment/ temporary discontinuation	8 (28.6)	12 (7.1)
	Permanent discontinuation	5 (17.9)	8 (4.7)
	Treatment given	18 (64.3)	33 (19.4)
	Non-drug therapy given	1 (3.6)	1 (0.6)
	Hospitalization	4 (14.3)	4 (2.4)
	Other	2 (7.1)	2 (1.2)
	Initiation of new treatment	1 (50)	1 (50)
	Scheduled surgery	1 (50)	1 (50)
	Not available	1 (3.6)	11 (2.9%)

*Data may overlap. †Not determined as recorded by the investigator. ‡'Unknown' was an option in the Case Report Form. #According to the National Cancer Institute Common Toxicity Criteria (19).

Table II. *Summary of the overall recorded serious adverse drug reactions to imatinib.*

Preferred term	Number of patients, (%) (N=34*)
Eyelid oedema	3 (8.8)
Anaemia	2 (5.9)
Cholecystitis	1 (2.9)
Conjunctivitis	1 (2.9)
Gastrointestinal haemorrhage	1 (2.9)
Melena	1 (2.9)
Orbital oedema	1 (2.9)
Rash	1 (2.9)
Pruritic rash	1 (2.9)

*Total number.

the tested patients) and 17 (one patient; 7.1%), while *PDGFRA* mutations were found in exons 12 (one patient; 7.1%) and 18 (one patient; 7.1% of patients). It is worth noting that one patient presented four *KIT* mutations (in exons 9, 11, 13 and 17) combined with two *PDGFRA* mutations (in exons 12 and 18), while one more patient had two concurrent *KIT* mutations (in exons 9 and 11).

Modification of dosage. At baseline, all patients were receiving 400 mg of imatinib. Modification of dosage was recorded in four patients throughout the study: in three imatinib dosage was initially increased due to disease progression but afterwards led to treatment discontinuation, whereas in one patient, the dosage was reduced and finally discontinued due to an AE. There were 11 patients (32.4%) who had at least one dose interruption, either temporary or permanent. The occurrence of an AE was the most frequent reason for imatinib dose interruption.

Safety. The mean number (±SD) of AEs per patient was 6.07±4.65. Over the duration of this study, an AE occurred in 82.4% of the enrolled patients, whereas 41.2% experienced a serious AE; adverse drug reactions (ADRs) and serious ADRs occurred in 67.6% and 17.6% of the study patients, respectively. There were no deaths during the study.

As was previously mentioned, the most common aetiology for imatinib interruption (temporary or permanent) was the occurrence of AEs followed by disease progression. There were overall eight patients in whom study treatment was temporarily interrupted and five in whom it was permanently discontinued (23.5% and 14.7% of patients, respectively) due to AEs. The most common AEs that led to the temporary interruption of imatinib affected the gastrointestinal tract followed by skin/subcutaneous tissue disorders. Rash or pruritic rash which was causally related to imatinib was the most frequently recorded event for permanent discontinuation of study treatment (three patients, 9.1% of patients). Altogether, 170 AEs were recorded in the course of the study in 28 patients (Table I). In the majority of the patients, the AEs were non-serious and mild or moderate.

Patients who had to permanently discontinue imatinib were all with high-risk disease (AFIP criteria), mainly over 70 years of age with tumour localization in the stomach. Severe or life-threatening AEs were more commonly recorded in the those aged over 70 years. The most frequently recorded AEs were anaemia (47.1% of patients), diarrhoea (26.5% of patients) and eyelid oedema (17.6% of patients), while the most frequently recorded SAEs were eyelid oedema and anaemia (each affecting 8.8% of patients), followed by pyrexia (5.9% of patients).

Throughout the study, 13 serious ADRs were recorded (Table II). The most frequently recorded non-serious ADRs

to imatinib were anaemia (29.4% of patients), diarrhoea (26.5% of patients) and eyelid oedema (11.8% of patients), whereas the most frequently reported serious ADRs were eyelid oedema (8.8% of patients) and anaemia (5.9%).

Discussion

OS could not be estimated in the present study, as no death occurred during the study period. 91% of the study population was recurrence-free at 36 months, which is in accordance with previous studies that showed that adjuvant therapy with imatinib (1 or 3 years) prolonged RFS (7, 8). Specifically, 3 years of adjuvant imatinib compared to 1-year imatinib treatment was shown to improve the 5-year RFS of patients with GIST having a high estimated risk for recurrence after surgery, with 65.6% and 47.9% of the patients, respectively, being alive without recurrence (8). It is worth highlighting that apart from patients with a high risk of recurrence (73.6%), the study population also included those with an intermediate risk. The analysis of the data provided real-world evidence that adjuvant therapy with imatinib for 3 years also has a beneficial impact on the 3-year RFS in patients with intermediate-risk of recurrence, which complements the proven benefit on patients with a high risk of relapse (11). Moreover, AEs in these patients did not interfere with the beneficial effect of the treatment on both OS and RFS, providing therefore further evidence in favour of potentially choosing this adjuvant treatment also for patients with an intermediate risk of relapse.

The most frequently observed mutation in this study was located in *KIT* exon 11, which agrees with the findings of previous studies (8, 10). The analysis of the association of well-established prognostic factors (age, gender, tumour location, size, mitotic count, mutational status, type of resection) with the recurrence of the disease in the study population revealed that only microscopically radical resection (R0) of the tumour favoured RFS. A previous study had demonstrated that the R1 resection had a negative impact on disease-free survival, apart from other established prognostic factors (12), while a recent study clearly demonstrated the impact that certain mutations have on disease progression (10). Furthermore, patients with certain mutations have been found to benefit the most from the longer duration of adjuvant imatinib treatment (10). However, no significant association was observed between mutational status and disease progression in the present study, which might be at least partly attributed to the fact that the mutational status was recorded in less than a half of the study population. In addition, tumour rupture was not recorded in the present study and therefore its impact on disease progression could not be evaluated. The small sample size may similarly have accounted for the fact that other well-established prognostic factors did not show a significant association with disease progression.

At 36 months, 41.2% of patients (14 out of the 34) did not complete the study or discontinued imatinib for reasons other than GIST recurrence, whereas in the study of Joensuu *et al*. the percentage in the 36-month therapy group was lower (25.8%) (8). This discrepancy can be partially attributed to the restrictions of the observational design of this study; more than one-third of the patients that did not complete the study were considered lost to follow-up. AEs that led to permanent treatment discontinuation occurred in 14.7% of patients in this study, which in turn was comparable to that of other studies (7, 8, 13). Only three patients (8.9%) experienced a recurrence of their disease during the study period that can be clearly recognized as treatment failure.

More than 80% of the patients with relevant recorded information throughout the study period were 100% compliant with imatinib therapy. Previous studies have shown that adherence to imatinib therapy by patients with GIST in both the adjuvant and metastatic settings can be difficult to achieve, not only because of undesired AEs but also as a result of the requirement for long-term continuous daily self-administration. In the adjuvant setting, adherence to imatinib therapy may be even more laborious, as patients receiving adjuvant imatinib often do not experience disease symptoms after tumour removal (8, 14). The improved compliance with imatinib therapy demonstrated in the present study may be due to a lack of recorded data, as adherence to treatment was not assessed for all patients. However, in a retrospective study by Tsang *et al*., overall compliance of patients receiving imatinib for GIST and chronic myeloid leukaemia was also high (75%) (15). Furthermore, the greatest level of compliance among patients with GIST (77%) was found in those initially treated with 300 or 400 mg/day imatinib (14, 15). Therapy of all patients in the present study was also initiated with the latter imatinib dose of 400 mg/day, a factor that probably played a role in the compliance rates noted above.

Treatment with imatinib in the adjuvant setting appeared to be overall well-tolerated by patients with GIST in Greece. The overall safety profile was similar to those of previous studies on imatinib (7, 8, 13, 16-18). Nevertheless, the incidence of AEs was lower in this study compared to other published data (7, 8, 13, 16). These variations might be attributed to patient selection criteria as well as the overall study design and were anticipated due to the real-life setting of this study. Other than eligibility for treatment with imatinib as per the label and the duration of treatment with imatinib, no other restrictions were set regarding patient selection. Furthermore, no new safety or unexpected findings were observed. From other published data, Joensuu *et al*. evaluated the safety of a 3-year treatment with imatinib in the adjuvant setting in high-risk patients with resectable GIST (8). In their study, almost every

patient had an AE, while the incidence of severe or life-threatening AEs was slightly higher compared to that of the present study, probably due to the inclusion of high-risk patients only. In the study of Italiano *et al*., drug-related AEs were mainly mild and moderate and were medically manageable (13), findings that are also in agreement with those of the present study.

Conclusion

Overall, this study concluded that imatinib was well tolerated, with a manageable AE profile in the adjuvant setting, with no new or unexpected AEs reported. Adjuvant treatment with imatinib for 3 years was proven to prolong RFS, regardless of the mutational status and risk of relapse, while prolonged treatment with imatinib did not show any negative impact on patient compliance with therapy.

In conclusion, the present study contributed real-world evidence data that are in overall alignment with the published data on imatinib treatment for the same condition and may conclusively be projected to the global pool of patients with resectable GIST in the adjuvant setting.

Data Availability

The raw data used to support the findings of this study are available from the corresponding Author upon request.

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Conflicts of Interest

Dr Boukovinas has received research grants and honoraria, including participation in Advisory Boards, from Roche, MSD, Bristol-Myers Squibb, Pfizer, Novartis, Merck, AstraZeneca, LEO Pharma, Servier, Sanofi, Ipsen, Genesis Pharma, Regeneron, Boehringer Ingelheim, and Lilly. Dr Kotsakis has received research grants and honoraria for participation in Advisory Boards from MSD, Roche, BMS, AstraZeneca and Amgen. Dr Kosmidis; Honoraria received for Investigator Meeting from Novartis, MSD. V. Sidiropoulou and O. Kousidou are employees of Novartis Oncology (Hellas).

Dr Aravantinos, Dr Michalaki, Dr Christodoulou, Dr Papandreou and Dr Avgerinos do not have any conflicts of interest.

Authors' Contributions

Dr Boukovinas contributed to study design, protocol writing, patient recruitment, and article review. Dr Kotsakis, Dr Androulakis, Dr Aravantinos, Dr Michalaki, Dr Christodoulou, Dr Avgerinos, and Dr Papandreou contributed to patient recruitment, and article review. Dr Kousidou, Dr Sidiropoulou and Dr Kosmidis contributed to article review.

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