Cell Cycle/Apoptosis Molecule Expression Correlates with Imatinib Response in Patients with Advanced Gastrointestinal Stromal Tumors

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on behalf of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

Abstract

Purpose: Altered expression of cell cycle/apoptosis key regulators may promote tumor progression, reflect secondary genetic/epigenetic events, and impair the effectiveness of therapy. Their expression pattern might then identify gastrointestinal stromal tumor (GIST) patient subgroups with different response to imatinib and elucidate novel therapeutic targets.

Experimental Design: Immunohistochemical evaluation of expression of p53, p16, p21, CHK2, CCND1, BCL2, CDK4, and MDM2 was done on 353 histologically validated GIST patients enrolled into a European/Australasian phase III trial. *TP53* was screened for mutations in cases with presumptive nonfunctional protein; that is, high p53 and low expression of the two downstream molecules p21 and MDM2. Results were correlated with clinicopathologic data, KIT/PDGFRA mutation status, and imatinib dosage.

Results: Frequent impaired expression was found for BCL2 (78%), CHK2 (53%), p53 (50%), and p16 (47%). Stomach-originating GISTs showed significantly lower expression of p21, p16, and BCL2. KIT/PDGFRA wild-type GISTs had significant lower expression of CDK4. Eighty-eight percent of the high p53 expressers show low downstream target activation, indicating a nonfunctional p53 route. Of these high p53 expressers, 16.4% harbor a detectable *TP53* mutation. Multivariate analysis, including previously identified markers, showed an independent effect of p53 and p16 on progression-free survival (PFS). Patients with high level of CHK2 and p21 showed significantly better PFS upon a high-dose regimen.

Conclusions: Impaired p53, p16, BCL2, and CHK2 expression is common in advanced GISTs. Distinct patterns of expression correlate with tumor site, genotype, and PFS. Cell cycle/apoptosis maintenance is instrumental for optimal response to imatinib.
They are more frequent in advanced tumors (4). An orchestrated sequence of events has been suggested: KIT/PDGFRA mutation→14q deletion→22q deletion→1p deletion→8p gain→11p deletion→9p deletion→7q gain (4). Distinct chromosome imbalances are found more often in specific anatomic locations; that is, loss of 14q is more frequent in gastric GISTs and 1p and 15q losses are more frequent in small intestinal GISTs (5). Tumor genotype frequency is also distinct in different locations; that is, KIT exon 9 mutants originate mainly in small-intestine GISTs (6). Different gene expression profile and clinicopathologic features are correlated with specific genotype and anatomic location of GISTs (7, 8).

One possible target of the 9p deletion is CDKN2A gene (mapped to 9p21; refs. 9, 10). Its two transcripts, p16/INK4a and p14/ARF, play a major role in cell cycle and apoptosis control (Fig. 1A). Impairment of p16 in GISTs has been linked to adverse prognosis (9, 10).

Imatinib mesylate (Glivec/Gleevec, formerly STI571, Novartis Pharma AG) has been proven to target the KIT aberrant signaling inhibiting the proliferation and survival of GIST cells (Fig. 1A). Response of GIST to imatinib is defined as the absence of progression at the time of the first disease evaluation (2-3 months after starting therapy), whereas progression at this time point is considered as primary resistance. In patients who have experienced an initial stabilization, further progressions are considered as secondary resistance (11, 12). Primary resistance is found in tumors without detectable KIT/PDGFR mutatiions (wild-type GISTs) or harboring PDGFRA-D842V or KIT exon 9 mutations (13). KIT exon 9 mutants have been shown to benefit more from a higher-dose imatinib regimen (6). Secondary resistance is frequently caused by secondary KIT mutations (13). Given the advanced disease status in patients treated with imatinib, the co-occurrence of functional impairment of other genes is likely. Because the main targets of both constitutive KIT signaling in GIST and subsequently also of its inhibitors are apoptosis and survival, we investigated crucial key regulators of these processes: cell cycle regulators (CDK4, CCND1, p16, and p21) and apoptosis modulators (CHK2, p53, BCL2, and MDM2; Fig. 1A). As advanced GISTs harbor several cytogenetic changes, selective advantage is likely to result from alteration of cell cycle/apoptosis key regulators. Therefore, altered level of expression may indeed reflect occurrence of secondary genetic/epigenetic events and impairment of cell cycle/apoptosis mechanisms. We hypothesize maintenance of these mechanisms to be relevant for optimal response to imatinib. Accordingly, we explored if the level of expression of the studied molecules could be used as a prognostic tool in advanced GISTs treated with imatinib. Finally, identification of aberrant protein expression can lead to identification of additional therapeutic targets.

**Translational Relevance**

We investigated the cell cycle/apoptosis molecule expression in a large cohort of advanced gastrointestinal stromal tumor patients treated with imatinib. We identified frequent impaired level of expression and we showed that levels of p16 and p53 expression are independent prognostic markers for progression-free survival. Furthermore, we identified subsets of patients who may benefit from high-dose-regimen treatment. These results are useful for further understanding and for better clinical management of gastrointestinal stromal tumors.
Samples from patients enrolled in the prospective multicentric European Organization for Research and Treatment of Cancer phase III trial were used to construct tissue arrays. The expression of the above-mentioned molecules was assessed by immunohistochemistry and correlated with (a) clinicopathologic parameters at the start of therapy, (b) KIT/PDGFRA mutation status, and (c) ultimately progression-free survival (PFS) and overall survival (OS) upon treatment with high- and low-dosage imatinib.

**Materials and Methods**

**Patients.** Between February 2001 and February 2002, the European Organization for Research and Treatment of Cancer/SofTissue and Bone Sarcoma Group (EORTC/STBSG) in collaboration with the Italian Sarcoma Group and the Australasian Gastro-Intestinal Trials Group randomized patients with advanced GIST to receive imatinib at a daily dose of 400 mg versus 800 mg. Details on eligibility criteria, treatment, and follow-up are published (12). Both response and progression have been objectively assessed according to the RECIST criteria (14). The local institutional review board of each participating institution approved the study. Written informed consent was obtained from each patient.

**Tissue array construction and immunohistochemistry.** Paraffin-embedded samples from tumors removed surgically before the trial, hence imatinib-naïve, were available for translational research from 392 patients (41% of cases) enrolled in the trial. The majority of the specimens (>90%) were before radiotherapy or chemotherapy. Four tissue arrays were built. All cases were histologically and immunohistochemically validated (15). Multiple tissue cores (~4 per sample) with a diameter of 0.6 mm were taken using a tissue arrayer (Beecher Instruments) and arrayed on a recipient block using standard procedures (16). Immunohistochemistry was done according to standard procedures (for details, see Supplementary Table S1; ref. 17). As a negative control, sections were stained without adding the primary antibody. The slides were evaluated by three observers independently as previously described in detail (17). Intensity and percentage of positive neoplastic cells were evaluated. Mean of the sum of intensity and percentage of duplicate cores was used for the final analysis. The scores were then analyzed using the following cutoffs to identify high protein level of expression: BCL2 ≥3, p53 ≥3, p21 ≥2, p16 ≥2, MDM2 ≥3, CHEK2 ≥2, CDK4 ≥3, and CNND1 ≥2. Because p21 and MDM2 are downstream targets of p53, high levels of p53 (score >3) associated with low levels of MDM2 and/or p21 (score <2) are likely to reflect a nonfunctional/mutated p53 (18). Accordingly, levels of expression of MDM2 and p21 were correlated to a level of expression of p53 to identify nonfunctional protein. Data were collected through a homemade software.

**KIT/PDGFRA mutation analysis.** Genomic DNA was extracted from 10-μm sections of the same paraffin-embedded tumor blocks used for immunohistochemistry, using a macrodisssection technique to reduce contamination with nonneoplastic tissue. Exons 9, 11, 13, and 17 of the KIT gene were amplified and analyzed for mutations by denaturing high performance liquid chromatography prescreening followed by bidirectional sequencing, as previously described (6). PDGFRA exons 12 and 18 were further tested in specimens with no detectable KIT mutation. Correlations of mutation data with patient baseline characteristics and outcome are published (6).

**TP53 mutation screening.** PCR was done on TP53 exons 4 to 8 (primers are listed in Supplementary Table S2) in 10 μL reactions using 10 ng input DNA, 1× AmpliTaq Buffer II, 3 mmol/L MgCl2, 0.375 units AmpliTaq Gold DNA polymerase (Applied Biosystems), and 2 pmol M13 tailed primers. PCR was carried out at an initial denaturation step of 10 min at 95°C, followed by 40 cycles of 5 s at 95°C, 10 s at 60°C, and 10 s at 72°C, and a final elongation step of 10 min at 72°C.

PCR products were sequenced on an ABI 3700 DNA Analyzer, usingBig Dye Terminator Chemistry (Applied Biosystems). Sequences were analyzed with Mutation Surveyor TM DNA variant analysis software (version 2.61 Softgenetics, State College).

**Statistical analysis.** The results of the tissue array analysis were merged with the clinical database (cutoff date: December 2005; median follow-up: 42 mo). The statistical analysis included (a) correlation between the studied molecules, clinicopathologic parameters, and tumor mutation status was evaluated with ANOVA; (b) estimation of the univariate prognostic value of all factors was done using Cox univariate model, log-rank test, and Kaplan-Meier estimates; (c) building of Cox

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**Fig. 1 Continued.** B, advanced GISTs show heterogeneous pattern of expression with frequent impaired expression of p53, BCL2, p16, and CHK2 (black, high expression; white, low expression). Histograms recapitulating significant correlation of pattern of expression with location (C) and KIT/PDGFRA mutation status (D).
multivariate prognostic models for OS and PFS; for each end point, a first model based on markers only investigates whether the prognostic value of all markers are independent of each other; a second model, including all clinical and mutational parameters, investigates whether the marker expression levels add prognostic information to the model based on clinical and mutational data; (d) predictive factor analysis, aimed at finding out whether the marker expression levels may be used to define patient subpopulation(s) who may benefit from high-dose therapy (Cox multivariate model including the marker status, the allocated treatment, and an interaction term between these two factors). The evaluation of OS patients still alive and progression-free at the time of the analysis had been censored at the date of last follow-up. The Kaplan-Meier method was used to evaluate PFS and OS in the different groups of patients. Comparisons between groups have been performed using the log-rank test. The Cox regression model was used for the multivariate analysis. The cumulative incidence of response has been analyzed by the competing risk method, considering treatment discontinuation in the absence of response as a competing risk. Both univariate and multivariate analyses used logistic regression and Cox regression models. Factors found to be significant in the univariate analysis \((P = 0.05)\) were included in a step-down multivariate model. Prognostic factors used in this study are slightly different from those previously reported for the whole data set with a shorter follow-up, but not inconsistent \((6, 11, 12)\). Small-bowel primary localization dropped out of the multivariate model with the inclusion of KIT exon 9 mutation; high baseline granulocyte count is replaced by platelet count; low baseline hemoglobin, presence of lung lesions, and absence of liver lesions have dropped out of the model (the two last factors probably characterized the non-GIST patients, now excluded by the external review); baseline performance status has been added. These analyses were done using the SAS software, version 9.1.

Table 1. *TP53* mutations found in this study

<table>
<thead>
<tr>
<th>Location</th>
<th>Mutation name</th>
<th>Amino acid change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 4</td>
<td>C164T</td>
<td>T55I</td>
</tr>
<tr>
<td>Exon 4</td>
<td>C248T</td>
<td>A83V</td>
</tr>
<tr>
<td>Exon 4</td>
<td>C318G</td>
<td>S106R</td>
</tr>
<tr>
<td>Exon 4</td>
<td>11494delC</td>
<td></td>
</tr>
<tr>
<td>Intron 4</td>
<td>IVS376-1G&gt;A</td>
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<tr>
<td>Exon 5</td>
<td>G439A</td>
<td>V147I</td>
</tr>
<tr>
<td>Exon 5</td>
<td>C383T</td>
<td>P128L</td>
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<tr>
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<tr>
<td>Exon 6</td>
<td>C617G</td>
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<tr>
<td>Exon 7</td>
<td>C722G</td>
<td>S241C</td>
</tr>
<tr>
<td>Exon 7</td>
<td>G676A</td>
<td>G226S</td>
</tr>
<tr>
<td>Exon 7</td>
<td>C758T</td>
<td>T253I</td>
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</table>

NOTE: Data in bold are the cases for which immunostaining and sequencing results are shown in Fig. 2.

Fig. 2. *p53* immunostaining and relative mutation sequencing is shown for those cases in bold in Table 1 (magnification bar, 50 μm).
Results

Tumor features. For 2 of 392 patients, it was not possible to collect data due to the absence of representative cores. Three hundred fifty-three cases were histologically confirmed to be GIST. In 118 patients, the site of origin was clearly identifiable as stomach, whereas in 94 patients, the site of origin was the small bowel. The primary site of origin was not identifiable in cases with widespread intra-abdominal disease. High expression of BCL2, p16, CHK2, p53, CDK4, p21, MDM2, and CCND1 was found in 78%, 57%, 50% 47%, 31%, 27%, 13%, and 8% of the cases, respectively (Fig. 1B). Forty-one percent of cases revealed high p53 expression associated with either low p21 and/or low MDM2 expression. The results of mutation analysis for KIT/PDGFRA reported previously (6) include 302 cases from the present study: 198 (65%) harbored mutation in KIT exon 11, and 52 (17%) in exon 9; 36 (11.9%) cases were wild-type; and the remaining were harboring mutations in PDGFRA or in other KIT exons (6).

Correlation between studied molecules and tumor features. Significant correlation with site of origin was found for BCL2, p21, and p16 (Fig. 1C). Tumors of gastric origin show significantly higher proportion of BCL2, p21, and p16 low expressers when compared with tumors originating from the small intestine (Fig. 1C). A significantly higher proportion of CDK4 low expressers is found in wild-type GISTs (Fig. 1D). No correlation with mutation in KIT exon 11 or KIT exon 9 was found. Significant correlation was also found between CHK2 expression and number of mitosis per high power field and between each other's molecules.

TP53 mutation screening. Most of the cases (88%) with high p53 expression showed a low level of either MDM2 or p21. TP53 gene was screened and mutations were found in 13 cases (16.4%) out of 79 for which DNA was available (Fig. 2; Table 1).

Correlation with progression-free survival and overall survival. The univariate analysis showed a significantly worse PFS in patients with p16 low expression and with p53 high expression (Supplementary Fig. S1A-B; Supplementary Table S3). Accordingly, cases with presumptive nonfunctional p53 showed a worse PFS, too (Supplementary Fig. S1C; Supplementary Table S3). No marker had a statistically significant OS prognostic value. However, patients with presumptive nonfunctional p53 showed a marginally significant worse OS ($P = 0.062$; Supplementary Fig. S1D).

In the studied data set, other adverse independently significant prognostic factors of PFS were the presence of KIT exon 9 mutation, poor performance status, large diameter of the largest lesion, and high baseline platelet count.

Multivariate modeling, including already identified factors (6, 11), shows an independent effect on PFS of p16 and p53 (Table 2). This latter findings and the fact that these two molecules constitute alternative targets for tumor progression prompt us to explore the use of both markers to predict PFS (Fig. 3A). The use of both markers (either low p16 expression or high p53 expression versus high p16 and low p53) identifies a large subgroup of patients with a worse PFS ($P = 0.009$): 238 patients out of 333 for which the immunostain was informative (Fig. 3A). Furthermore, the use of both markers allow for identifying a large subgroup of patients with worse PFS even in the presence of KIT exon 11 mutation (Fig. 3B). Overall survival was not significantly affected by any marker level.

Predictive factor analysis. In terms of PFS, high-dose imatinib benefited only patients with a high level of CHK2 or p21; for both factors, the interaction test is statistically significant ($P = 0.03$; Supplementary Fig. S1A-B). A similar but nonsignificant interaction ($P = 0.08$) is observed for p53. For CCND1, high-dose therapy has a detrimental effect in patients with overexpression; the interaction test is significant for OS ($P = 0.03$; Supplementary Fig. S1C) and borderline for PFS ($P = 0.09$). It should be noted that a false discovery rate of 20% is associated to the predictive factors analysis.

The most important results of this study are summarized in Table 3.

![Fig. 3. A, Kaplan-Meier estimate for PFS in patients with either high p53 or low p16 versus the rest. B, Kaplan-Meier estimate for PFS in patients with high p53 or low p16 in patients with wild-type KIT or harboring mutation in exon 9 or 11.](image-url)

### Table 2. Independent markers from Cox multivariate analysis

<table>
<thead>
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<th>Variable</th>
<th>$P$</th>
<th>Hazard ratio</th>
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</thead>
<tbody>
<tr>
<td>Performance status</td>
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<td>1.36</td>
</tr>
<tr>
<td>Diameter</td>
<td>0.0093</td>
<td>1.002</td>
</tr>
<tr>
<td>KIT exon 9 mutation</td>
<td>&lt;0.0001</td>
<td>2.330</td>
</tr>
<tr>
<td>p16</td>
<td>0.0002</td>
<td>0.588</td>
</tr>
<tr>
<td>p53</td>
<td>0.0134</td>
<td>1.406</td>
</tr>
</tbody>
</table>
Discussion

We analyzed a large number of imatinib-naïve advanced GISTs from patients recruited for imatinib treatment in frame of a phase III clinical trial. Advanced GISTs showed a heterogeneous pattern of expression of the studied proteins that might reflect the acquisition of diverse secondary events during tumor progression.

Despite the heterogeneity, we could identify frequent altered expressions of cell cycle/apoptosis regulators, e.g., high expression of both BCL2 and p53 and low expression of CHK2 and p16. Observed distribution is mostly compliant with previous reports (10, 19, 20). However, we found a higher proportion of high expressers of p53 (20, 21). This is most likely due to inclusion of clinically advanced GISTs with overrepresentation of high-risk cases. BCL-2 overexpression might be responsible for selective advantage in survival of neoplastic cells given its anti-apoptotic function. As KIT activation by stem cell factor is known to lead to increased expression of BCL-2 (21), its frequent overexpression in GIST might result from the constitutional activation of KIT. Furthermore, its frequent overexpression might be targeted for additive or different therapy. Imatinib resistance in BCR-ABL–positive leukemic cells is reported to be reduced by targeting BCL-2 (22).

Intense nuclear p53 immunostain often occurs for increased half-life of a mutated protein. In our series, high p53 expression was frequent and prognostic for PFS. The mechanism driving the correlation with worse PFS is most likely due to a nonfunctional p53 protein, as suggested by the low level of the downstream molecules, p21 and MDM2 (18). Accordingly, TP53 impairment has been shown to induce imatinib resistance in BCR-ABL–positive leukemic cells (23). We found mutations in 16.4% of cases, selected on the basis of p53 protein expression. In agreement with our results, Ryu et al. showed TP53 mutations in 22% of the GISTs with high p53 protein expression (24). The low percentage of mutation in high p53 expressers might reflect its late occurrence in a subpopulation of cells, for which direct sequencing might not be able to identify it. We frequently observed low expression of p16 and CHK2. Down-regulation of these two tumor-suppressor genes might result in selective advantage of neoplastic cells. Loss of heterozygosity, inactivating mutations, and promoter hypermethylation may cause down-regulation of p16 in GIST (9, 25). The frequent low expression of CHK2 (gene mapping to 22q12.1) is concordant with the reported frequent deletion of 22q in GISTs (5).

Overexpression of MDM2, CDK4, and CCND1 is mainly due to genomic amplification (26, 27). High expression of these three oncogenes was infrequent in our study. Accordingly, amplification of the corresponding chromosomal regions (11q13, 12q14, and 12q14.3-q15, respectively, for CCND1, CDK4, and MDM2) is not a frequent event in GIST (5, 28).

We found a significantly higher proportion of BCL2, p16, and p21 low expressers in GISTs of gastric origin and a higher proportion of CDK4 low expressers in wild-type GISTs. Remarkably, we found GIST gastric location to be associated with low p16. The apparent contradictory association of an otherwise reported good prognostic marker, gastric origin, with a marker of worse prognosis, p16 low expression, underlines again the substantial difference of clinically advanced GIST. Furthermore, in this cohort, gastric origin is not an independent prognostic marker.

We did not find any significant correlation with other genotypes, which underscores the fact that the observed correlation are indeed due to the site of origin and not biased either by the relative enrichment of gastric GISTs for exon 11 KIT mutants or by relative enrichment of small-bowel GISTs for exon 9 KIT mutants. Evaluation of p53 and p16 show a significant and independent prognostic value on PFS. The immunohistochemical evaluation for these two molecules identifies a large group of patients with shorter PFS. These results reflect the importance of the maintenance of cell cycles/apoptosis regulation in GISTs for the optimal response to imatinib. In other words, if the levels of expression of proteins regulating proliferation and apoptosis are altered, the effect of the drug might be easily abolished and patients will experience disease progression. Notably, none of the evaluated molecules showed a significant correlation with OS. However, a trend toward shorter survival is shown in patients with nonfunctional p53.

Steinert et al. reported BCL2 expression to correlate with longer PFS on a cohort of 81 advanced GISTs treated with imatinib (29). We did not find any significant correlation with PFS. Furthermore, if BCL2 immunoscore is considered as a continuous variable (data not shown), it is significantly inversely correlated to PFS in univariate analysis; the higher the BCL2, the shorter the PFS. This discrepancy is most probably due to the small size of the sample used in the above-mentioned study (29).

Most likely, only a subgroup of patients benefits from a high-dosage regimen (12). Therefore, we investigated the

Table 3. Main findings of the study

<table>
<thead>
<tr>
<th>Overexpression in % of cases</th>
<th>Correlations with site/KIT mutation</th>
<th>Prognostic value after multivariate analysis</th>
<th>Predictive value</th>
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<tbody>
<tr>
<td>BCL2</td>
<td>78</td>
<td>Site</td>
<td>OS (PFS)</td>
</tr>
<tr>
<td>CCND1</td>
<td>8</td>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td>CDK4</td>
<td>31</td>
<td>KIT mutation</td>
<td>PFS</td>
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<td>CHK2</td>
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<td>MDM2</td>
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</tr>
<tr>
<td>p53</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Data inside parentheses are borderline significant values.
predictive value of the evaluated molecules. CHK2 and p21 showed a significant predictive value for PFS and CCND1 for OS. These results suggest that patients with a high level of CHK2 and p21 might benefit from high doses of imatinib. This is in agreement with the fact that high level of expression of these two molecules might reflect maintenance of the cell cycle/apoptosis process, and hence an effective response to imatinib can be achieved. Specifically, CHK2 can activate apoptosis of damaged cells and p21 acts as a downstream molecule of p53, promoting cell cycle arrest and apoptosis. Hence, the most likely scenario is that the high level of expression of CHK2 and p21 might be responsible for a better effect of a high dosage of imatinib.

In conclusion, we identified frequent impairment of cell cycle/apoptosis regulators in a large group of advanced treated GISTs; that is, p53, p16, CHK2, and BCL2. This underscores their importance in GIST tumor progression and unravel novel targets for alternative/additive therapy. A distinct pattern of expression correlates mainly with primary tumor location. Immunohistochemical assessment of apoptosis/cell cycle regulators might identify a subset of patients for high-dose treatment. Maintenance of cell cycles/apoptosis regulation in GISTS is important for optimal response to imatinib.

Disclosure of Potential Conflicts of Interest

J. Verweij, J.Y. Blay, commercial research grant, Novartis; M. Debiec-Rychter, J. Verweij, P.C.W. Hogendoorn, speaker’s honorarium, Novartis; J. Verweij, consultant, Novartis.

References

22. Kuroda J, Puthalakath H, Cragg MS, et al. Bim and Bad mediate imatinib-induced killing of Bcr/Abl+ leukemic cells, and resistance due to their loss is overcome by a BH3

Appendix

Investigators Who Contributed Clinical Data to the Study

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