Impact of TP53 Mutations on Outcome in EGFR-Mutated Patients Treated with First-Line Tyrosine Kinase Inhibitors

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Abstract

Purpose: To analyze the impact of TP53 mutations on response to first-line tyrosine kinase inhibitors (TKI) in patients with EGFR-mutated non–small cell lung cancer (NSCLC).

Experimental Design: 136 EGFR-mutated NSCLC patients receiving first-line TKIs were analyzed. TP53 mutations were evaluated in 123 patients in relation to disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: TP53 mutations were observed in 37 (30.1%), 10 (27.0%), 6 (16.2%), 9 (24.3%), and 12 (32.4%) patients in exons 5, 6, 7, and 8, respectively. DCR was 70% in TP53-mutated patients compared with 88% in TP53-wild type (wt) patients [relative risk, RR, of disease progression: 3.17 (95% CI, 1.21–8.48), P = 0.019]. In particular, a 42% DCR was observed in patients with TP53 exon 8 mutation versus 87% in exon 8 wt patients [RR of disease progression 9.6 (2.71–36.63), P < 0.001]. Shorter median PFS and OS were observed in patients with TP53 exon 8 mutations compared with others (4.2 vs. 12.5, P = 0.058, and 16.2 vs. 32.3, P = 0.114, respectively); these differences became significant in the subgroup with EGFR exon 19 deletion (4.2 vs. 16.8, P < 0.001, and 7.6 vs. not reached, P = 0.006, respectively), HR 6.99 (95% CI, 2.34–20.87, P < 0.001) and HR 4.75 (95% CI, 1.38–16.29, P = 0.013), respectively.

Conclusions: TP53 mutations, especially exon 8 mutations, reduce responsiveness to TKIs and worsen prognosis in EGFR-mutated NSCLC patients, mainly those carrying exon 19 deletions. Clin Cancer Res; 23(9): 2195–202. ©2016 AACR.

Introduction

Patients with non–small-cell lung cancer (NSCLC) carrying specific sensitizing mutations at exons 18, 19, and 21 of the EGFR gene are usually sensitive to treatments with tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, or afatinib (1–3). However, not all patients respond equally to TKI treatments, despite the presence of an EGFR mutation, and approximately 20%–30% show primary resistance to TKIs (1, 4), inducing early progressive disease (PD) after the first month of treatment.

Although the mechanisms responsible for acquired resistance are well known (5), those responsible for primary resistance are not understood. Some studies have demonstrated that different EGFR mutations have different impacts on the outcome of TKI response (6–9). Moreover some primary resistance mechanisms have been hypothesized, such as BIM polymorphisms, MET amplification, PIK3CA mutations, and mutations of the PIK3CA/ART/mTOR pathway (10–12).

Mutations of the tumor suppressor TP53 gene occur in about 30%–40% of NSCLC patients and are highly correlated with smoking habits (13, 14). Exons 5 to 8 of the gene encoded for the DNA-binding domain and recognize a consensus sequence in the promoter of several genes involved in DNA repair, cell-cycle arrest, and apoptosis (15, 16). On the basis of the TP53 mutation classification performed by Poeta and colleagues (17), a recent study (18) has demonstrated that nondisruptive TP53 mutations are independent markers of shorter overall survival (OS) in patients with advanced NSCLC, regardless of EGFR and KRAS mutation status. However, no differences were observed in terms of response and progression-free survival (PFS) in patients treated with either erlotinib or chemotherapy.

There is preclinical evidence of a link between TP53 mutations and responsiveness to TKIs, in particular, gefitinib (19–21). Specifically, it has been shown that p53 is needed for gefitinib-induced apoptosis in NSCLC cell lines and leads to increased sensitivity to TKIs through the induction of FAS...
Canale et al.

Translational Relevance

EGFR-mutated patients are usually responsive to tyrosine kinase inhibitor (TKI) treatments. However, about 20%–30% of patients show primary resistance to TKIs, the underlying mechanisms of which are still unknown. In a case series of EGFR-mutated NSCLC patients treated with TKIs in a first-line setting, we found that patients with TP53 mutations showed a worse prognosis than TP53 wild-type patients. In particular, TP53 exon 8 mutations were associated with a significantly lower disease control rate (DCR) and shorter progression-free survival (PFS). These results were particularly significant in the subgroup of patients with EGFR exon 19 deletion, in which the presence of TP53 exon 8 mutation was associated with significantly lower DCR, and shorter PFS and overall survival. Once confirmed in an independent and larger case series, these results could have a decisive impact on the selection of EGFR-mutated NSCLC patients to be treated with first-line TKIs.

Materials and Methods

We retrospectively analyzed a total of 136 patients with advanced EGFR-mutated NSCLC treated with second- or further-line TKIs showing that TP53 mutations were more frequent in nonresponders than in responders, in line with our hypothesis of their potential role as resistance biomarkers to TKIs (22).

In this study, we aimed to assess the role of TP53 mutation in a cohort of EGFR-mutated advanced NSCLC patients that received TKI in first-line treatment. We analyzed and evaluated the status of TP53 gene and the different types of mutation, in relation to the different EGFR mutations and outcomes of patients in terms of overall response rate (ORR), disease control rate (DCR), duration of therapy, PFS, and OS.

Statistical analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables and as means ± SD or median and range, when appropriate, for continuous variables.

DCR was defined as the sum of complete response (CR), partial response (PR), and stable disease (SD), whereas ORR considered.

Duration of therapy was calculated from the date of initiation of first-line treatment to the last documented visit date during EGFR TKI monotherapy or time of disease progression.

The association between survival endpoints examined were PFS and OS. PFS was defined as the time from start of first-line treatment to disease progression or death, whichever occurred first. Patients who were alive and progression-free were censored at the date of the last follow-up update. OS was defined as the time from start of first-line treatment to death.

PFS and OS functions were estimated using the Kaplan–Meier method, and in the text were reported the median values and 95% CI in square brackets. The log-rank test was used to assess differences between molecularly defined groups. Cox proportional hazards regression models were used to evaluate the
association between type of mutation and survival endpoints. Results are reported as HR and 95% CI in square brackets. The proportional hazards assumption was evaluated by the Schoenfeld residuals.

A two-sided P < 0.05 was considered statistically significant. This was an exploratory study in which data were retrieved with a specific aim but not with a predefined key hypothesis. Any adjustment would have not resolved the problem of making valid statistical inferences as hypotheses would have been generated by the data.

All statistical analyses were performed using R version 3.2.3.

**Results**

**Patient characteristics**

Clinicopathologic characteristics of patients, type of *EGFR* mutation, TKIs received, and type of response to TKIs are reported in Table 1. The majority of patients were female (75.0%) and never smokers (59.0%). Almost all patients had a diagnosis of adenocarcinoma (98.5%). Six patients (4.4%) had an exon 18 point mutation (3 G719A, 2 G719S, 1 G719D), 74 patients (54.4%) showed an exon 19 deletion, and 56 (41.2%) had an exon 21 mutation (49 L858R and 7 L861Q). Among patients with exon 19 deletion, 2 had also an exon 20 T790M mutation. All patients received a TKI in the first-line treatment. In particular, 104 patients (76.5%) received gefitinib, 27 patients (19.8%) erlotinib, 24 patients (18.2%) afatinib, and 2 patients (1.5%) dacomitinib.

**Outcome of patients in relation to *EGFR* mutations**

ORR and DCR for TKIs in the entire case series were 56.0% and 91.9%, respectively. Table 1 summarizes the distribution of nonresponders, short-term responders, and long-term responders in relation to the different *EGFR* mutations. Among patients with exon 19 deletion, 52.7% were long-term responders compared with 31.2% and 41.7% of patients with exon 21 L858R mutation or those with the other *EGFR* mutations, respectively (P = 0.008).

Overall, median PFS was 11.6 months [7.9–14.6], (Fig. 1A). A significantly longer PFS was observed in patients with *EGFR* exon deletion, 52.7% were long-term responders compared with 31.2% and 41.7% of patients with exon 21 L858R mutation or those with the other *EGFR* mutations, respectively (P = 0.008).

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19 deletions with respect to patients with other types of mutation ($P = 0.026$; Fig. 1B). Median OS was 32.3 months [22.9–not reached (NR); Fig. 1C]. A significantly longer OS was observed in patients with exon 19 deletions with respect to patients with other types of mutation ($P = 0.004$; Fig. 1D).

At univariate survival analysis from Cox model, EGFR exon 19 deletion resulted a significant predictor of better PFS and OS [HR 0.64 [0.43–0.95], $P = 0.027$ and HR 0.47 [0.27–0.79], $P = 0.005$, respectively; results not shown]. Neither confounding nor modifying effect by age, gender, and smoking habits was observed.

**TP53 mutation**

Out of the 136 EGFR-mutated patients, 123 had biological material available for TP53 mutation analysis. Overall, 37 (30.1%) patients showed a TP53 mutation: 27.0% were on exon 5, 16.2% on exon 6, 24.3% on exon 7, and 32.4% on exon 8 (Table 1). Following a previous report’s differentiation of TP53 mutations into disruptive and nondisruptive (16), we found 13 disruptive and 24 nondisruptive mutations. Worthy of note is that all exon 6 mutations were disruptive, whereas all except one exon 8 mutations were nondisruptive (Supplementary Table S1).

Percentage of TP53 mutation was higher in males than in females, with no statistically significant difference ($P = 0.07$). The difference was statistically significant when considering exon 5 mutations only: 18.2% of mutation was observed in males, whereas 4.4% in females ($P = 0.02$). No statistically significant association was observed between any type of TP53 mutation and smoking habit and age (Supplementary Table S2). Finally, percentage of nondisruptive mutations was higher in males (33.3%) than in females (14.5%; Supplementary Table S2).

**TP53 status in relation to EGFR mutation**

No statistically significant association was observed among TP53 mutation (considering all types together) and different EGFR mutations (Supplementary Table S3). With regard to the distribution of TP53 gene mutations, a significant association was observed for TP53 exon 5 and exon 7 mutations with respect to EGFR mutations. In particular, TP53 exon 5 mutations were more frequently seen in patients with EGFR exon 21 L861Q mutation, whereas TP53 exon 7 mutations were more common in those with EGFR exon 19 deletion. Moreover, frequency of TP53 nondisruptive mutations was lower in EGFR exon 19-deleted patients than in other EGFR-mutated patients, although this difference was not statistically significant. Finally,
Table 3. Disease control rate (DCR) in relation to the different types of TP53 mutation.

<table>
<thead>
<tr>
<th>TP53 mutation</th>
<th>No (n = 22)</th>
<th>Yes (n = 100)</th>
<th>Unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mutations*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>10 (11.8)</td>
<td>75 (88.2)</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>11 (25.7)</td>
<td>26 (70.5)</td>
<td>3.17 [1.21-8.48]</td>
</tr>
<tr>
<td>Exon 5*</td>
<td>18 (61.3)</td>
<td>94 (84.0)</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>3 (30.0)</td>
<td>7 (70.0)</td>
<td>2.24 [0.45-8.92]</td>
</tr>
<tr>
<td>Exon 6*</td>
<td>20 (71.4)</td>
<td>96 (82.8)</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>1 (6.7)</td>
<td>5 (83.3)</td>
<td>0.96 [0.05-6.55]</td>
</tr>
<tr>
<td>Exon 7*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>21 (18.4)</td>
<td>93 (81.6)</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>1 (9.1)</td>
<td>9 (90.9)</td>
<td>-</td>
</tr>
<tr>
<td>Disruptive/nondisruptive*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt/diisruptive</td>
<td>14 (12.7)</td>
<td>96 (87.3)</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>7 (58.3)</td>
<td>5 (41.7)</td>
<td>9.6 [2.71-36.63]</td>
</tr>
<tr>
<td>Nondisruptive</td>
<td>8 (33.3)</td>
<td>16 (66.7)</td>
<td>3.27 [1.14-9.32]</td>
</tr>
</tbody>
</table>

*Sum does not add up to the total due to missing values.

all TP53 mutations found in patients with EGFR exon 21 L861Q mutation were nondisruptive (P = 0.02; Supplementary Table S3).

**TP53 mutation and response to TKIs**

The presence of TP53 mutation was significantly associated with a lower DCR in relation to TKI treatment (Table 3). In particular, patients with any of the TP53 mutations had a 3-fold risk of disease progression than TP53 wt patients (P = 0.019). Considering the different TP53 mutations, TP53 exon 8–mutated patients were associated with the worst response. In particular, 41.7% DCR was observed in TP53 exon 8–mutated patients with respect to 87.3% DCR in TP53 exon 8 wt patients (P < 0.001). RR of disease progression was almost 10-fold in exon 8–mutated patients than in wt patients, despite the poor precision of the estimated effect given by the limited number of patients carrying TP53 exon 8 mutation, P < 0.01; Table 3).

Nondisruptive TP53 mutation was also associated to a lower DCR. In particular, 86.7% DCR was observed in patients with TP53 wt or TP53-disruptive mutations, with respect to 67.2% DCR observed in patients with nondisruptive mutations. These latter patients had almost a 4-fold risk of disease progression than wt patients (Table 3). Interestingly, 92% of TP53 exon 8 mutations were nondisruptive.

Regarding the association between TP53 mutations and response to TKIs according to the type of EGFR mutation, interesting results were observed in the subgroup of patients with exon 19 deletion. Among 74 EGFR exon 19–deleted patients, 66 carried information on the TP53 mutational status. DCR was 98% in EGFR exon 19–deleted TP53 wt patients, whereas it was 70% in patients carrying a TP53 mutation (Supplementary Table S4).

No significant association was observed between TP53 mutations and response in patients with other types of EGFR mutation (data not shown).

The difference in ORR and DCR was even more marked considering TP53 exon 8 mutations (Supplementary Table S4).

Moreover, ORR and DCR were lower in EGFR exon 19–deleted patients with TP53 nondisruptive mutations (37.5% and 75%) than in patients with TP53-disruptive mutations or wt gene (70.7% and 93.1%, respectively; P = 0.079 and P = 0.151, respectively).

With regard to clinicopathologic characteristics of patients and response, no significant associations were observed between gender, age, or smoking habits and DCR or ORR. Moreover, no significant differences in terms of response were observed between patients treated with either gefitinib or erlotinib.

The frequency of TP53 exon 8 mutation was higher in nonresponders and responders of <3 months (58%) than in short- or long-term responders (4% and 5%, respectively, P = 0.004).

**TP53 mutation and survival**

No statistically significant difference was observed in terms of PFS and OS between TP53-mutated and wt patients. However, shorter PFS and OS were observed in patients with TP53 exon 8 mutations compared with all the other patients (Fig. 2A and B). No significant difference was observed in patients grouped by TP53 mutation type: TP53 exon 8 mutation versus TP53 nondisruptive mutations (other than exon 8) versus TP53 wt or TP53-disruptive mutations (Supplementary Fig. S1A and S1B).

In patients with EGFR exon 19 deletions, shorter, nonsignificant PFS and OS were observed in TP53-mutated patients with respect to TP53 wt patients (P = 0.081 and P = 0.317, respectively; Table 4). TP53 exon 8 mutations were significantly associated with shorter PFS and OS. In particular, patients with TP53 exon 8 mutations showed a median PFS and OS of 4.2 and 7.6 months, respectively, with respect to a median PFS of 16.8 months (P < 0.001) and a median OS not reached (P = 0.006) in the other patient groups (Fig. 2C and D). Cox regression model showed that TP53 exon 8 mutated patients had an almost 7-fold higher risk of disease progression or death than wt patients [HR 6.99 [2.34-20.87], P = 0.006] and death HR 4.75 [1.38-16.29], P = 0.013; Table 4]. The negative prognostic value of TP53 exon 8 mutation was not seen in patients with other EGFR mutations.

Finally, in EGFR exon 19–deleted patients, we observed that exon 8–mutated patients had a poorer prognosis than TP53 nondisruptive mutated (other than exon 8) patients and TP53 wt/TP53-disruptive–mutated patients. In particular, TP53 exon 8–disruptive–mutated patients had a higher risk of progression [HR 7.05 [2.35-21.17], P < 0.001] than TP53 wt patients. Whereas findings were not significant for patients with other nondisruptive TP53 mutations (Supplementary Fig. S1C). Similar results were found for OS (Supplementary Fig. S1D).

These data remained significant after adjusting for age, gender, and smoking habits.

No statistically significant difference in PFS and OS was observed in relation to TP53 mutations in patients treated with either gefitinib or erlotinib.

**Discussion**

In the current study, we analyzed the impact of TP53 mutations in relation to the outcome of advanced EGFR-mutated NSCLC patients treated with a TKI in the first-line setting. To the best of our knowledge, this was the first study to have analyzed the association between TP53 mutations and response to TKI, in a relatively large case series of EGFR-mutated patients. We found that TP53 mutation resulted as a primary resistance mechanism.
that significantly reduces response to TKI. In particular, TP53 exon 8 mutations were associated with a significantly lower DCR with respect to TP53 exon 8 wt. These data were even more significant for patients with EGFR exon 19 deletion, in which TP53 exon 8 mutations were associated with a significantly lower DCR and shorter PFS and OS. Conversely, the predictive role of TP53 mutation was not statistically significant in the subgroup of patients with other EGFR mutations.

TP53 mutations occur in about 50% of lung cancer patients and are more frequent in squamous cell lung carcinoma than in lung ADC (13), with mutation rates ranging from 25% to 40% in the latter (24–26). We observed a mutation percentage of 30% in our case series of EGFR-mutated ADC patients, in agreement with another study in which TP53 mutations analyzed separately in EGFR wt and EGFR mutated lung ADC patients showed mutation frequencies of 34.4% and 25.9%, respectively (18). The presence of a low number of smokers and high number of female among EGFR-mutated ADC patients contribute to a generally lower EGFR mutations and/or apoptosis (27). Disruption of p53’s normal function disrupts such cellular responses, leading to possible malignant cell transformation. Disruptive mutations lead to a complete, or almost complete, loss of p53 functions, whereas nondisruptive mutations can retain some of the p53 protein functional properties (17). Interestingly, there is some evidence that these maintained functional properties are associated with gain-of-function (GOF) activities (28–30).

A recent study has showed that nondisruptive TP53 mutations are associated with a worse prognosis in advanced NSCLC patients, in both EGFR wt and mutated patients (18). Moreover, a recent study has demonstrated that, in a small case series of EGFR-mutated patients treated with TKI, TP53 mutation was associated with a worse prognosis (31).

Table 4. Risk of PFS and OS in relation to TP53 exon 8 mutation in the subgroup of patients with EGFR exon 19 deletion

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>P</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mut</td>
<td>1.74 [0.92–3.29]</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>1.58 [0.64–3.87]</td>
<td>0.321</td>
</tr>
<tr>
<td>TP53 exon 8 mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>6.99 [2.34–20.87]</td>
<td>0.006</td>
</tr>
<tr>
<td>Mut</td>
<td>4.75 [1.38–16.29]</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Figure 2.

PFS (A) and OS (B) of patients with TP53 exon 8–mutated patients compared with TP53 exon 8 wt patients; PFS (C) and OS of TP53 exon 8–mutated patients compared with TP53 exon 8 wt patients in the subgroup of EGFR exon 19–deleted patients (D). NR, not reached.
Our case series included all EGFR-mutated patients treated with a TKI in the first-line setting. TP53 mutations were associated with a significantly lower DCR respect to wt patients, and the most significant result was that TP53 exon 8 mutation were associated with the worst prognosis. In particular, more than half TP53 exon 8–mutated patients showed PD within two months of start of therapy, with no CR recorded. Moreover, all TP53 exon 8 mutations except one were nondisruptive.

We observed that the predictive role of TP53 mutations was even more relevant in the subgroup of patients with exon 19 deletion, especially considering TP53 exon 8 mutation. In particular, patients with EGFR exon 19 deletion harboring a TP53 wt had an almost absolute (95%) DCR. On the other hand, patients with TP53 exon 8 mutation had a DCR of 25%. Interestingly, the impact of TP53 mutation was not statistically significant in patients with other types of EGFR mutations. We can hypothesize that, as exon 19–deleted patients are usually more responsive to TKIs (also confirmed by our results), the negative effect caused by the presence of TP53 mutations is more evident and significant in this subgroup than in those with other EGFR mutations. Of note, 2 patients with EGFR exon 19 deletion (TP53 wt) also had an EGFR exon 20 T790M mutation at baseline, and both showed a relatively short-term response to TKIs. This confirms that T790M, although rarely present at baseline, represents a marker of poor response to TKIs.

Results from some in vitro studies seem to endorse our hypothesis that TP53 is an important factor in determining TKI sensitivity. In particular, p53 wt has been found to be an important factor for gefitinib-induced apoptosis in NSCLC cell lines, whereas p53 mutant reduces gefitinib-induced apoptosis (19). The presence of p53-responsive elements on FAS promoter region (20) and the evidence that gefitinib treatment induces an upregulation of FAS on lung cancer cells (21) further suggest a link between TKI response and TP53 status. The correlation between TP53 mutation and TKI resistance has also been demonstrated in other in vitro tumor cell models, in particular in urothelial carcinoma (32, 33).

A recent study showed that GOF TP53 mutations are associated with a higher expression of EGFR, leading to hypothesizing a direct role of p53 protein on EGFR promoter (34) and corroborating our hypothesis of a direct connection between TP53 mutations and response to TKIs. Recent results presented at the 2015 ASCO Annual Meeting would also seem to confirm our observations (35, 36).

As our case series included all EGFR-mutated patients treated with TKI, we cannot exclude that TP53 mutations could have a role as prognostic, rather than predictive, factor. Nevertheless, a confirmation by an independent study of the very low response rate to TKIs in TP53 exon 8–mutated patients could clarify whether these patients can be referred to other treatment strategies. As conflicting data are present in the literature on the prognostic role of TP53 mutation in NSCLC (14, 18, 24), additional studies should be performed for clarification.

In conclusion, our results highlighted for the first time the involvement of TP53 mutation in determining primary resistance to TKI in EGFR-mutated NSCLC patients. TP53 exon 8 mutations seemed to identify a subgroup of EGFR-mutated patients with unlikely response to TKIs. These data are particularly relevant in patients with EGFR exon 19 deletion. Further studies are needed to clarify the reason why TP53 exon 8 mutations determined a poor prognosis in patients carrying EGFR exon 19 deletions. Once confirmed by an independent and larger case series, these results could have an important impact on the selection of EGFR-mutated NSCLC patients to be treated with TKI in the first-line setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

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Development of methodology: M. Canale, E. Chiadini, C. Dazzi, L. Capelli, A. Gamboni, V. Ladovini, P. Ulivi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Delmonte, C. Dazzi, M. Papi, C. Casanova, M. Marroti, A. Gamboni, L. Cinori
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Petracci, A. Delmonte, R. Chiari, L. Cinori, P. Ulivi
Writing, review, and/or revision of the manuscript: M. Canale, E. Petracci, A. Delmonte, C. Dazzi, C. Casanova, A. Gamboni, R. Chiari, C. Bennati, D. Calistri, P. Ulivi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Petracci, N. De Luigi, P. Ulivi
Study supervision: A. Delmonte, C. Dazzi, L. Cinori, D. Amadori

Acknowledgments

The authors wish to thank Cristiano Verna for editing the manuscript.

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Received April 19, 2016; revised September 30, 2016; accepted October 17, 2016; published OnlineFirst October 25, 2016.

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