KRAS mutations affect prognosis of non-small-cell lung cancer patients treated with first-line platinum containing chemotherapy

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ABSTRACT

KRAS mutations seem to indicate a poor outcome in Non-Small-Cell Lung Cancer (NSCLC) but such evidence is still debated. The aim of this planned ancillary study within the TAILOR trial was to assess the prognostic value of KRAS mutations in advanced NSCLC patients treated with platinum-based first-line chemotherapy. Patients (N = 540), enrolled in the study in 52 Italian hospitals, were centrally genotyped twice in two independent laboratories for EGFR and KRAS mutational status.

Of these, 247 patients were eligible and included in the present study. The primary endpoint was overall survival (OS) according to KRAS mutational status in patients harboring EGFR wild-type.

Sixty (24.3%) out of 247 patients harbored KRAS mutations. Median OS was 14.3 months and 10.6 months in wild-type and mutated KRAS patients, respectively (unadjusted Hazard Ratio [HR]=1.41, 95%Confidence Interval [CI]: 1.03-1.94 P = 0.032; adjusted HR=1.39, 95%CI: 1.00-1.94 P = 0.050). This study, with all consecutive patients genotyped, indicates that the presence of KRAS mutations has a mild negative impact on OS in advanced NSCLC patient treated with a first-line platinum-containing regimen. Trial Registration: clinicaltrials.gov identifier NCT00637910
INTRODUCTION

KRAS is a member of the ras gene family which encodes small G proteins with intrinsic GTPase activity. GTPase activity leads to protein inactivation and activates downstream effectors involved in multiple pathways including proliferation, differentiation and apoptosis. Point mutations occur in tumors resulting in the loss of intrinsic GTPase activity and consequently in the deregulation of cell proliferation signals [1].

KRAS is the most frequently mutated oncogene in Non-Small-Cell Lung Cancer (NSCLC) [2]. KRAS mutations are present in approximately 20% of lung adenocarcinomas, are more frequent in smokers, while infrequent in squamous cell tumors [3]. KRAS mutations in NSCLC are mainly missense in exon 2, codon 12 and 13, although other rare variants, such as codon 61, are also occasionally detected [4].

Although the ras gene was discovered almost thirty years ago, the role of KRAS mutations as prognostic and predictive markers in NSCLC cancer is still contentious [5, 6]. The available meta-analyses suggest that patients with wild-type KRAS have a better prognosis. On the other hand, the predictive role of KRAS mutations is uncertain caused by evidence mainly based on retrospective series with contradicting results likely due to patients selection bias, and therefore to the lack of proper planned randomized trials [7-11].

In addition, it seems that different types of KRAS mutations, according to the replaced bases, have a different role in carcinogenesis and drug response [12-15].

The aim of the study was to investigate, in terms of overall survival (OS) and progression free survival (PFS), the role of KRAS mutations in advanced EGFR wild-type NSCLC patients treated with first-line platinum-based chemotherapy.

RESULTS

Between October 12, 2007 and March 13, 2012 we collected and genotyped for KRAS and EGFR 540 patients in the TAILOR trial [16]. Of these, 213 patients were not eligible for the present study for various reasons: adjuvant therapy (N = 177), missing data (N = 24), early stages at the time of first-line treatment (N = 6), KRAS status not evaluable (N = 3) and early death (N = 3). Eighty patients with tumor harboring EGFR gene mutations were also excluded. Of the remaining 247 eligible patients, 187 (76.8%) had wild-type KRAS tumor, whereas 60 (24.3%) had a tumor with a mutated KRAS. Nine different types of KRAS mutations were identified and the three most common were G12C (43.3%), G12V (23.3%) and G12D (10.0%) as reported in Table 1. G13 mutation isoforms (G13C and G13D) were seen in 6.7% (N = 4) of all mutated cases.

The CONSORT diagram is illustrated in Figure 1 whereas the baseline characteristics of the patients included in the study according to KRAS mutational status are illustrated in Table 2.

KRAS mutational status was associated with tumor histology (P = 0.038) and smoking habit (P = 0.006). The mutated KRAS subgroup of patients had, as expected, a higher percentage of adenocarcinoma histology (85.0% compared to 65.8% for mutated and wild-type respectively) and a lower prevalence of never smoker patients (6.7% compared to 22.5% for mutated and wild-type respectively). All the other characteristics were well balanced between the two groups.

All patients received platinum-doublet chemotherapy in the first-line setting with higher percentage of wild-type KRAS tumor patients receiving gemcitabine (57.1%) as compared to mutated tumor patients (37.9%). The latter received pemetrexed in a higher (50.0%) percentage compared to wild-type (30.4%). Vinorelbine option was less frequent but homogenously administered (12.5% and 12.1% in wild-type and mutated tumor patients respectively).

One-hundred and thirty-five patients were randomized in the main clinical trial. In particular, 52.4% and 56.7% of wild-type and mutated patients respectively were further treated with docetaxel in second-line treatment. On the other hand, 47.6% of wild-type and 43.3% of mutated patients received erlotinib. Among the randomized patients a higher percentage of patients with KRAS mutant tumor did not reach the third-line treatment (76.7%) compared to wild-type (54.3%) (P = 0.028).

Survival outcomes

After a median follow-up of 52.5 months (95%Confidence Interval [CI] 42.0-64.7), 225 patients had progressed or died and 202 had died.

Median OS was 14.4 months (95%CI 10.9-19.4) for patients with wild-type KRAS tumor and 10.6 months (95%CI 8.4-12.9) for those with mutant tumor (Figure 2A). The survival of patients with tumor harboring mutated KRAS was significantly lower than in wild-type group (unadjusted Hazard Ratio [HR] = 1.41 95%CI: 1.03-1.94 P = 0.032; adjusted HR = 1.39, 95%CI: 1.00-1.94 P

### Table 1: Different type of KRAS mutations

| KRAS mutations | N   | %   |
|----------------|-----|-----|
| G12A           | 6   | 10.0|
| G12C           | 26  | 43.3|
| G12D           | 6   | 10.0|
| G12F           | 2   | 3.3 |
| G12R           | 1   | 1.7 |
| G12S           | 1   | 1.7 |
| G12V           | 14  | 23.3|
| G13C           | 2   | 3.3 |
| G13D           | 2   | 3.3 |

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Table 2: Patient’s characteristics

|                          | KRAS wt |        | KRAS mutated |        | P-value |
|--------------------------|---------|--------|--------------|--------|---------|
|                          | N  | %    | N  | %    |         |
| Patients                 |    |      |    |      |         |
| Age of diagnosis         | 187 | 75.7 | 60 | 24.3 | 0.257  |
| Sex                      |     |      |    |      |         |
| Male                     | 134 | 71.7 | 46 | 76.7 | 0.449  |
| Female                   | 53  | 28.3 | 14 | 23.3 |         |
| ECOG-PS                  |     |      |    |      |         |
| 0                        | 114 | 61.0 | 33 | 55.0 | 0.603† |
| 1                        | 64  | 34.2 | 25 | 41.7 |         |
| 2                        | 9   | 4.8  | 2  | 3.3  |         |
| Smoking                  |     |      |    |      |         |
| Never                    | 42  | 22.5 | 4  | 6.7  | 0.006‡ |
| Former smokers           | 88  | 47.1 | 30 | 50.0 |         |
| Smokers                  | 57  | 30.5 | 26 | 43.3 |         |
| Stage at diagnosis       |     |      |    |      |         |
| IIIA                     | 15  | 8.0  | 5  | 8.3  | 0.266‡ |
| IIIB                     | 24  | 12.8 | 4  | 6.7  |         |
| IIIB wet                 | 9   | 4.8  | 0  | 0.0  |         |
| IV                       | 139 | 74.3 | 51 | 85.0 |         |
| Grading                  |     |      |    |      |         |
| G1                       | 7   | 6.7  | 2  | 6.5  | 0.329† |
| G2                       | 34  | 32.4 | 6  | 19.4 |         |
| G3                       | 63  | 60.0 | 23 | 74.2 |         |
| Undifferentiated         | 1   | 1.0  | 0  | 0.0  |         |
| unknown                  | 82  | 29   |    |      |         |
| Histotype                |     |      |    |      |         |
| Adenocarcinoma           | 123 | 65.8 | 51 | 85.0 | 0.038  |
| Squamous                 | 49  | 26.2 | 5  | 8.3  |         |
| Bronchoalveolar          | 3   | 1.6  | 0  | 0    |         |
| Large cells              | 2   | 1.1  | 1  | 1.7  |         |
| Mixed                    | 6   | 3.2  | 3  | 5.0  |         |
| Other                    | 4   | 2.1  | 0  | 0    |         |
| Chemotherapy             |     |      |    |      |         |
| Carboplatin              | 44  | 24.3 | 16 | 26.7 | 0.715  |
| Cisplatin                | 137 | 75.7 | 44 | 73.3 |         |
| Chemotherapy             |     |      |    |      |         |
| Gemcitabine              | 105 | 57.1 | 22 | 37.9 | 0.019  |
| Vinorelbine              | 23  | 12.5 | 7  | 12.1 |         |
| Pemetrexed               | 56  | 30.4 | 29 | 50.0 |         |
| Chemotherapy             |     |      |    |      |         |
| No random                | 82  | 43.9 | 30 | 50.0 | 0.406† |
| Docetaxel*               | 55  | 52.4 | 17 | 56.7 | 0.679‡ |
| Erlotinib*               | 50  | 47.6 | 13 | 43.3 |         |
| Second-line              |     |      |    |      |         |
| None*                    | 57  | 54.3 | 23 | 76.7 | 0.028‡ |
| Pemetrexed**             | 18  | 37.5 | 3  | 42.9 | 0.905‡ |
| Gemcitabine**            | 11  | 22.9 | 2  | 28.6 |         |
| Vinorelbine**            | 13  | 27.1 | 1  | 14.3 |         |
| Docetaxel**              | 4   | 8.3  | 1  | 14.3 |         |
| Erlotinib**              | 2   | 4.2  | 0  | 0    |         |

# Chi-square for trend
† percentage calculated on randomized patients
‡ percentage calculated on patients who received third-line treatment
§ comparison between randomized and not randomized patients
¶ comparison among different treatments
‖ comparison between treatment performed and no treatment
Figure 1: Patient CONSORT diagram

Figure 2: Kaplan-Meier curves for survival. Curves for overall survival (A) and progression free survival (B) according to the KRAS status

Figure 3: Kaplan Meier curves for survival. Curves for overall survival A. and progression free survival B. according to the main different types of mutations (G12C, G12D, G12V)
The OS of patients expressing the three most common KRAS mutations, separately analyzed (G12C, G12D and G12V), was not different when compared to wild-type although all mutations had worsening trend (Figure 3A). The 4 patients harboring G13 KRAS mutations showed a median OS of 9.0 months.

ECOG-PS (HR = 1.79, 95%CI: 1.41-2.27 P < .001), sex (HR = 0.65, 95%CI: 0.47-0.89 P = 0.007) and tumor stage (HR = 1.18, 95%CI: 1.02-1.37 P = 0.024) were clinical factors significantly associated with OS. Risk estimate covariates are reported in Table 2.

Median PFS was 7.2 months (95%CI 6.3-8.8) for patients with wild-type KRAS tumor and 6.6 months (95%CI: 5.1-7.6) for those with mutant tumor (Figure 2B) (unadjusted HR = 1.24, 95%CI: 0.92-1.67 P = 0.164; adjusted HR = 1.32, 95%CI: 0.96-1.82 P = 0.092). As for OS, we could not find any statistical difference among patients with tumor harboring the three more common KRAS mutations, separately analyzed, and those with wild-type tumor (Figure 3B). Patients with G13 KRAS mutant tumor showed a median PFS of 3.9 months.

Tumor histology (HR = 0.70, 95%CI: 0.51-0.97 P = 0.033), ECOG-PS (HR = 1.53, 95%CI: 1.23-1.90 P < .001), and tumor stage (HR = 1.29, 95%CI: 1.11-1.48

Table 3: Prognostic evaluation of clinical and histopathological characteristics – Overall Survival

|                          | HR   | Lower 95% HR | Upper 95% HR | P-value |
|--------------------------|------|--------------|--------------|---------|
| Unadjusted               |      |              |              |         |
| Age at diagnosis         | 0.99 | 0.98         | 1.01         | 0.385   |
| ECOG-PS (2 vs 1 vs 0)    | 1.79 | 1.41         | 2.27         | <.001   |
| Histotype (squamous vs others) | 0.78 | 0.55         | 1.10         | 0.149   |
| Tumor stage (IV vs IIIB wet vs IIIB vs IIIA) | 1.18 | 1.02         | 1.37         | 0.024   |
| Tumor grade              | 1.28 | 0.94         | 1.73         | 0.113   |
| Smoking (smoking vs former and not smoking) | 1.31 | 0.92         | 1.88         | 0.135   |
| Sex (F vs M)             | 0.65 | 0.47         | 0.89         | 0.007   |
| Chemotherapy (cisplatin vs carboplatin) | 1.13 | 0.82         | 1.56         | 0.448   |
| Chemotherapy (gemcitabine vs vinorelbine) | 1.45 | 0.90         | 2.33         | 0.133   |
| Chemotherapy (pemetrexed vs vinorelbine) | 1.70 | 1.03         | 2.80         | 0.038   |
| KRAS (mut vs wt)         | 1.41 | 1.03         | 1.94         | 0.032   |
| KRAS (12C vs wt)         | 1.42 | 0.91         | 2.22         | 0.128   |
| KRAS (12D vs wt)         | 2.06 | 0.90         | 4.69         | 0.085   |
| KRAS (12V vs wt)         | 1.24 | 0.69         | 2.24         | 0.471   |
| Adjusted                 |      |              |              |         |
| KRAS (mut vs wt)         | 1.39 | 1.00         | 1.94         | 0.050   |
| ECOG-PS (2 vs 1 vs 0)    | 1.89 | 1.46         | 2.43         | <.001   |
| Tumor stage (IV vs IIIB wet vs IIIB vs IIIA) | 1.18 | 1.01         | 1.37         | 0.042   |
| Chemotherapy (gemcitabine vs vinorelbine) | 1.32 | 0.80         | 2.17         | 0.271   |
| Chemotherapy (pemetrexed vs vinorelbine) | 1.61 | 0.95         | 2.74         | 0.077   |
| Chemotherapy (cisplatin vs carboplatin) | 1.17 | 0.84         | 1.63         | 0.345   |

= 0.050). The OS of patients expressing the three most common KRAS mutations, separately analyzed (G12C, G12D and G12V), was not different when compared to wild-type although all mutations had worsening trend (Figure 3A). The 4 patients harboring G13 KRAS mutations showed a median OS of 9.0 months.
Risk estimate covariates are reported in Table 4.

**DISCUSSION**

In the last 20 years many studies, including meta-analyses, with more than 8,000 patients considered have been published analyzing the prognostic and predictive role of *KRAS* mutations in NSCLC. The majority of these results indicated *KRAS* as a negative prognostic and predictive marker [7-11, 17]. All these data were drawn from uncontrolled series and they included patients with different biological characteristics.

Our study confirms that a small negative prognostic effect of *KRAS* mutations can be observed in advanced NSCLC patients treated with a platinum-based doublet when EGFR mutant patients are excluded from the analysis. TAILOR results are superimposable to those found by Mascaux et al., the only meta-analysis performed on the role of *KRAS* in predicting efficacy of chemotherapy [10].

In addition, our epidemiological results are in line with literature: *KRAS* mutations are strongly correlated with smoking habit and adenocarcinoma histology and are
Interestingly enough, preliminary preclinical data obtained to confer different OS when compared to the wild-type.

KRAS elucidate any role for the three single most common actively on this issue [20, 21].

pronounced than in early stages and our group is working mutated tumors might have a DNA repair imbalance more effect such as DNA repair capability. Advanced other additional factor(s) could contribute to this prognosis of KRAS mutated patients is dependent on the role of the specific mutations in terms of response to treatment and tumor progression.

The concept that not all KRAS mutations behave in the same way and that they differently impact on tumor progression has been addressed [12, 14, 15]. This data together with the indications reported in our study may suggest that proper trials need to be planned to define the role of the specific mutations in terms of response to treatment and tumor progression.

In conclusion, although KRAS showed a prognostic effect in first-line platinum-based treatment in advanced NSCLC, this study leads us to conclude that it is not warranted to test KRAS in clinical practice, at least until a specific targeted therapy is available for this group of patients. However, the potential mechanism of resistance to platinum-based therapies of these tumors should be further explored.

MATERIALS AND METHODS

Study design

TAILOR was a not-for-profit multicentre, open label, randomized trial, funded by the Italian Regulatory Agency AIFA and conducted in 52 Italian hospitals, comparing erlotinib versus docetaxel in second-line NSCLC and details have been published elsewhere [16]. Within the TAILOR trial we planned an ancillary study to assess the prognostic value of KRAS mutations in advanced NSCLC patients treated with a first-line platinum containing regimens.

Briefly, tumor samples from registered patients were histologically centrally reclassified according with the 2004 WHO classification. Suitable samples were genotyped in parallel by investigators in two independent laboratories using two different techniques: EGFR by Sanger’s sequencing and restriction fragment length polymorphism whereas KRAS by Sanger sequencing and high-resolution melting analysis. Scorpion/ARMS technique was used for low-material samples. The Italian central authority and ethical review board at each participating Institution approved the protocol. The study complied with the declaration of Helsinki and was done in accordance with good clinical practice guidelines. Trial Registration: clinicaltrials.gov identifier NCT00637910.
Patients and eligibility criteria

Participating centers registered all consecutive patients with NSCLC before or during first-line platinum-based chemotherapy as well as patients recurred after a first-line adjuvant platinum-based chemotherapy. Only those with both EGFR and KRAS status centrally determined were included in the trial. All patients received platinum-based chemotherapy in combination with either vinorelbine, gemcitabine or pemetrexed according to the physician’s choice. Combinations with taxanes and with anti-EGFR agents were not allowed. Patients with EGFR mutations, early stages patients and patients receiving the adjuvant therapy were excluded from this analysis. All patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) between 0 and 2 and were at least 18 years of age. Exclusion criteria included any evidence of serious co-morbidities that the investigator judged as a contraindication to the participation in the study, pregnancy and breast feeding. Patients were considered former smokers if they smoked more than 100 cigarettes in their life and they stopped this habit for at least one year at the time of diagnosis as used in most of smoking-habits analyses [22, 23]. All patients who were eligible for participation provided written informed consent with all applicable governing regulations before undergoing any study procedure.

Statistical methods

The analysis was planned at the occurrence of 200 events, needed to detect a Hazard Ratio ≥1.60 (mutated KRAS vs. wild-type KRAS) assuming a KRAS mutation frequency of 25% with a statistical power of 80% and two-sided type I error of 5%.

The primary endpoint was OS defined as the time from the day of first-line treatment start to the date of death from any cause. The secondary endpoint was PFS defined as the time from the day of first-line treatment start up to the date of first progression or death from any cause, whichever came first. Patients who had not died or had disease progression at the date of study cutoff were censored at the last available information on status. Time-to-event data were described by the Kaplan-Meier curves. Cox proportional hazards models were used for univariate and multivariate analysis (adjusted for ECOG-PS, stage, type of first-line chemotherapy) to estimatereak and test demographic characteristics, clinical features, and biologic parameters for their associations with OS and PFS. We also evaluated OS and PFS according to the different subtypes of KRAS mutations.

Moreover we evaluated the association between the status of KRAS and clinical and histopathological characteristics by means of Chi-square test.

Results were expressed as HRs and their 95% confidence intervals and P values for two sided hypothesis test were reported.

All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC).

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CONFLICTS OF INTERESTS

The authors have declared no conflicts of interest.

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