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Citation for published version (APA):

Mellema, W. W., Masen-Poos, L., Smit, E. F., Hendriks, L. E. L., Aerts, J. G., Termeer, A., Goosens, M. J., Smit, H. J. M., van den Heuvel, M. M., van der Wekken, A. J., Herder, G. J. M., Krouwels, F. H., Stigt, J. A., van den Borne, B. E. E. M., Haitjema, T. J., Staal-Van den Brekel, A. J., van Heemst, R. C., Pouw, E., & Dingemans, A-M. C. (2015). Comparison of clinical outcome after first-line platinum-based chemotherapy in different types of KRAS mutated advanced non-small-cell lung cancer. *Lung Cancer*, 90(2), 249-254. <https://doi.org/10.1016/j.lungcan.2015.09.012>

Document status and date:

Published: 01/11/2015

DOI:

[10.1016/j.lungcan.2015.09.012](https://doi.org/10.1016/j.lungcan.2015.09.012)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Comparison of clinical outcome after first-line platinum-based chemotherapy in different types of *KRAS* mutated advanced non-small-cell lung cancer

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ARTICLE INFO

Article history:

Received 7 April 2015

Received in revised form 22 August 2015

Accepted 13 September 2015

Keywords:

Non-small cell lung cancer

KRAS mutation

Chemotherapy

Outcome

Type of *KRAS* mutation

ABSTRACT

Objectives: As suggested by in-vitro data, we hypothesize that subtypes of *KRAS* mutated non-small cell lung cancer (NSCLC) respond differently to chemotherapy regimens.

Methods: Patients with advanced NSCLC and known *KRAS* mutation, treated with first-line platinum-based chemotherapy, were retrieved from hospital databases. Primary objective: to investigate overall response rate (ORR), progression free survival (PFS) and overall survival (OS) between different types of platinum-based chemotherapy per type of *KRAS* mutation.

Results: 464 patients from 17 hospitals, treated between 2000 and 2013, were included. The majority of patients had stage IV disease (93%), had a history of smoking (98%) and known with an adenocarcinoma (91%). Most common types of *KRAS* mutation were G12C (46%), G12V (20%) and G12D (10%). Platinum was combined with pemetrexed ($n = 334$), taxanes ($n = 68$) or gemcitabine ($n = 62$). Patients treated with taxanes had a significant improved ORR (50%) compared to pemetrexed (21%) or gemcitabine (25%; $p < 0.01$). Patients treated with bevacizumab in addition to taxanes ($n = 38$) had the highest ORR (62%). The PFS was significantly improved in patients treated with taxanes compared to pemetrexed (HR = 0.72, $p = 0.02$), but not OS (HR = 0.87, $p = 0.41$). In patients with G12V, significantly improved ORR ($p < 0.01$) was observed for taxanes, but not PFS or OS. Patients with G12C or G12D mutation had comparable ORR, PFS and OS in all treatment groups.

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Conclusion: *KRAS* mutated NSCLC patients treated with taxane-based chemotherapy had best ORR. Response to chemotherapy regimens was different in types of *KRAS* mutation. Especially patients with G12V had better response to taxane treatment.

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1. Introduction

Personalized medicine has a major role in optimizing treatment and outcome of advanced cancers. Therapy focused on molecular characteristics has taken a substantial part in new treatment strategies for non-small cell lung cancer (NSCLC). Successful treatments have been developed for advanced NSCLC patients with an *EGFR* mutation or *ALK* translocation [1,2]. In non-squamous NSCLC, routine testing for these mutations is recommended as per guidelines when patients are no candidates for treatment with curative intent [3]. In the Netherlands, *KRAS* mutation is part of routine testing as a selection tool for *EGFR* mutation testing since both mutations are almost always mutually exclusive [4]. *KRAS* mutation is observed in 20–30% of NSCLC patients, predominantly in patients with adenocarcinoma [5]. Its presence has an infamous reputation of quick progression and poor response to chemotherapy [6]. However, the current understanding is that *KRAS* mutated NSCLC patients have a similar response and survival compared to patients with *KRAS* wild type (wt) tumors [7–10]. Until now, no effective targeted therapy has been established and standard platinum-based doublet chemotherapy remains the recommended treatment option in this large group of patients.

Alternatively, optimizing treatment for NSCLC patients with a *KRAS* mutation might also be accomplished by selecting the best chemotherapy for these patients. A *KRAS* mutation occurs predominantly in codon 12, 13 or 61. Most common types of *KRAS* mutation are G12C, G12V, and G12D (<http://www.mycancergenome.org>). In-vitro data generated by Garassino et al. suggested differential sensitivity to chemotherapeutic agents across NSCLC cell lines harboring a G12C, G12V or G12D *KRAS* mutation [11]. They concluded that the G12C mutation was most sensitive to pemetrexed and paclitaxel, G12D was resistant to paclitaxel therapy and G12V was slightly less sensitive for pemetrexed. Exposure to gemcitabine resulted in a similar response in the 3 types of mutation. The aim of this multicenter, retrospective study was to investigate differences in overall response rate (ORR), progression free survival (PFS) and overall survival (OS) between subtypes of *KRAS* mutation in NSCLC patients treated with first-line commonly available platinum doublets.

2. Methods

2.1. Study subjects

We retrospectively selected all consecutive NSCLC patients with known *KRAS* mutation, treated with first-line platinum-based chemotherapy for metastatic disease and response evaluated by CT scan using RESIST criteria. Palliative radiotherapy during chemotherapy treatment was allowed. Exclusion criteria were: unknown mutational status; (concurrent) *EGFR* or *ALK* mutation; no documentation of response evaluation; adjuvant chemotherapy or chemoradiotherapy.

Patients were derived from databases from 17 hospitals in the Netherlands. All patients had access to the same standard of care treatment. Both regional and academic hospitals participated in this study. The following data were retrieved from the medical records: age, sex, smoking history, World Health Organization Per-

formance Status (PS), histology, type of *KRAS* mutation, stage of disease, site of metastasis, chemotherapy combination, number of courses, response to treatment, type of second line treatment, number of lines of chemotherapy, date of diagnosis, date of start treatment, date of progression and date of death or date of last contact. The ethics committee of the VU University Medical Center Amsterdam approved this study.

2.2. *KRAS* mutational screening

From formalin-fixed paraffin-embedded tissue, tumor was macrodissected and DNA was extracted. Two methods were used for *KRAS* mutation analysis. In 16/17 hospitals, mutation analysis was performed using high resolution melting followed by polymerase chain reaction and sequencing of the *KRAS* exons 2 and 3. At one site mutation analysis was performed by Sanger sequencing only.

2.3. Statistical analysis

The primary objective was to evaluate differences in ORR, PFS and OS between different types of platinum-based chemotherapy per type of *KRAS* mutation. PFS was defined as time from start of first-line chemotherapy till objective disease progression or death; OS was defined as the time from start of treatment till death. The relation between categorical parameters was tested using Pearson's χ^2 -test or Fishers exact test for testing small cell sample sizes ($n \leq 5$). Kaplan–Meier curve was used to estimate the distribution of survival. Log-rank test was used to test difference in survival between subgroups. To estimate the hazard ratio (HR), cox regression analysis was used. The following variables were considered in a multivariate analysis: age, gender, performance score, histology, smoking history and stage of disease. *P*-Values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

In total, data from 464 *KRAS* mutated patients with advanced NSCLC who received palliative platinum-based chemotherapy as first-line treatment were subtracted from databases of 17 hospitals. Patients were treated between 2000 and 2013, most patients (78%) between 2010 and 2013. Sixty patients in the present study were also part of a previously published study [10].

The patient characteristics are listed in Table 1. The mean age was 61 years ($SD \pm 9$), a majority of patients had stage IV disease (93%), 98% of the patients had a history of smoking and 2% of patients had squamous cell carcinoma. Cisplatin ($n=261$) or carboplatin ($n=203$) was combined with pemetrexed ($n=334$), taxane ($n=68$) or gemcitabine ($n=62$). In the taxane group, 38 patients received treatment with carboplatin/paclitaxel/bevacizumab (CPB). Codon 12 mutations were detected in 89% of the patients. G12C (46%) was the most common *KRAS* mutation followed by G12V (20%) and G12D (11%). Other codon 12 mutations were present in 12% of the patients. In 1 patient a double mutation was found: G12R+G12S.

Table 1
Patient characteristics.

	n (%)
Mean age (±SD)	61 (9)
Gender	
M	229 (49%)
F	235 (51%)
Smoking history	
Current	220 (47%)
Former	195 (42%)
Never	6 (1%)
Missing	43 (9%)
Performance status	
0	139 (34%)
1	220 (54%)
≥2	48 (12%)
Histology	
Adeno	424 (91%)
Large cell	32 (7%)
Squamous cell	8 (2%)
Stage	
IIIb	33 (7%)
IV	431 (93%)
Platinum	
Cisplatin	261 (56%)
Carboplatin	203 (44%)
Chemotherapy	
Platinum/pemetrexed	334 (71%)
Platinum/gemcitabine	62 (14%)
Platinum/taxan	68 (15%)
With bevacizumab	38 (8%)
Without bevacizumab	30 (7%)
Type of KRAS mutation	
G12C	209 (46%)
G12V	93 (20%)
G12D	49 (11%)
G12A	32 (7%)
G13C	21 (5%)
G12S	12 (3%)
G13D	12 (3%)
Q61H	10 (2%)
G12F	6 (1%)
G12R	5 (1%)
G13V	3 (0%)
Q61L	2 (0%)
Q61P	1 (0%)
G12L	1 (0%)
G13R	1 (0%)
G13R G12S	1 (0%)
Unknown	5 (3%)

3.2. Outcome of general study group

The ORR in the general study group was 26%. Patients treated with taxanes had a significant higher ORR compared to the other platinum combinations (Table 2). In particular, patients treated with CPB had a ORR of 62%. Fig. 1 demonstrates PFS and OS in the general study group. Patients treated with taxanes had a significantly improved PFS compared to pemetrexed (multivariate HR=0.72 (95% CI. 0.54–0.96); $p=0.02$), but not OS (multivariate HR=0.87 (95% CI. 0.63–1.20); $p=0.41$). Performance score was the only significant prognostic factor and was considered in the multivariate analysis. No difference was found between patients receiving taxanes only and in addition with bevacizumab in PFS or OS ($p=0.86$ and $p=0.75$, respectively). The presence of patients with squamous cell carcinoma had no influence on outcome. The one-year survival rate was significantly improved for patients treated with taxanes (41%), compared to pemetrexed (25%) or gemcitabine (32%; $p=0.03$).

Fig. 1. Outcome in whole study group. Black line: pemetrexed; grey line: gemcitabine; dotted line: taxanes. A. Progression free survival in months. B. Overall survival in months.

3.3. Outcome of most common types of mutation

In Tables 2 and 3 results of the 3 most frequent types of KRAS mutation is listed. Patients with G12V mutation had a significantly improved ORR, when treated with taxanes compared to pemetrexed or gemcitabine. For patients with G12V mutation relevant differences were seen in median PFS and OS rates in favor of taxanes, but this was not significant. However, in patients with a G12C or G12D mutation, ORR, PFS and OS were comparable between all treatment groups. Figs. 2 and 3 illustrate PFS and OS respectively per type of mutation.

To study predictive or prognostic relevance of one of the KRAS mutation subtypes, survival plots were made irrespectively of treatment. No significant differences were found in median PFS between the most common types of KRAS mutation: 4.9 (95% CI, 4.1–5.7) months, 4.8 (95% CI, 3.0–6.6) months and 4.3 (95% CI, 3.2–5.4) months for G12C, G12V and G12D, respectively ($p=0.45$). Also, no significant differences were found in median OS between the types of mutation: 10.4 (95% CI, 7.8–13.1) months, 8.0 (95% CI, 6.4–9.5) months and 8.3 (95% CI, 7.0–9.5) months, respectively ($p=0.46$). Median OS was comparable between codon 12, codon 13 and codon 61 ($p=0.40$).

4. Discussion

Platinum-based chemotherapy containing a taxane showed the best ORR in this cohort of KRAS mutated advanced NSCLC patients, especially when bevacizumab was added. Taxanes showed significant improved PFS compared to pemetrexed. Patients with a G12V mutation favor treatment with taxanes in terms of response and showed non-significant but clinically relevant changes in survival. In patients with G12C or G12D KRAS mutation all platinum combinations had a similar outcome.

To our knowledge, this is the largest series reporting on therapeutic outcome to first-line platinum-based treatment in KRAS mutated NSCLC patients and first to report preference

Table 2
Outcome in whole study group and most common types of *KRAS* mutation.

Chemotherapy regimen (N)	ORR	Median PFS in months (95% CI)	Median OS in months (95% CI)
Whole group			
PEM (334)	21%	4.3 (3.8–4.8)	8.2 (7.0–9.4)
GEM (62)	25%	4.0 (2.7–5.3)	8.3 (4.2–12.3)
TAX (68)	50%	5.8 (4.4–7.3)	14.0 (9.0–19.0)
	$p < 0.01$	Log-rank test $p = 0.05$	Log-rank test $p = 0.26$
G12C			
PEM (145)	23% (16–30)	4.5 (3.7–5.3)	9.9 (7.2–12.7)
GEM (32)	32% (15–50)	3.9 (1.3–6.6)	10.0 (4.9–15.1)
TAX (31)	40% (21–59)	5.4 (3.6–7.1)	12.3 (8.2–16.4)
	$p = 0.12$	Log-rank test $p = 0.42$	Log-rank test $p = 0.50$
G12V			
PEM (67)	17% (8–27)	4.2 (2.5–5.9)	7.0 (4.7–9.3)
GEM (11)	18% (9–45)	3.0 (1.8–4.1)	5.6 (0.0–19.7)
TAX (12)	67% (35–98)	6.9 (0.0–13.9)	19.4 (15.3–23.6)
	$p < 0.01$	Log-rank test $p = 0.09$	Log-rank test $p = 0.20$
G12D			
PEM (37)	16% (2–29)	4.1 (2.7–5.4)	7.5 (4.5–10.4)
GEM (6)	17% (26–60)	5.0 (3.4–6.7)	8.3 (6.0–10.6)
TAX (6)	50% (7–107)	5.8 (1.4–10.3)	8.5 (0.9–16.0)
	$p = 0.16$	Log-rank test $p = 0.58$	Log-rank test $p = 0.89$

Abbreviations: PEM: pemetrexed; GEM: gemcitabine; TAX: taxane; PFS: progression free survival; OS: overall survival; CI: confidence interval.

Table 3
Univariate regression analysis of progression free survival and overall survival.

Chemotherapy regimen (N)	Median PFS in months (95% CI)			Median OS in months (95% CI)		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Whole group						
PEM (334)	1.00	–		1.00	–	
GEM (62)	1.07	0.81–1.42	0.62	0.90	0.66–1.22	0.48
TAX (68)	0.73	0.55–0.96	0.03	0.78	0.58–1.06	0.11
G12C						
PEM (145)	1.00	–		1.00	–	
GEM (32)	0.84	0.56–1.35	0.39	0.72	0.45–1.15	0.17
TAX (31)	0.88	0.59–1.31	0.54	0.94	0.60–1.47	0.78
G12V						
PEM (67)	1.00	–		1.00	–	
GEM (11)	1.58	0.82–3.03	0.17	0.92	0.45–1.9	0.82
TAX (12)	0.64	0.35–1.18	0.15	0.54	0.28–1.07	0.08
G12D						
PEM (37)	1.00	–		1.00	–	
GEM (6)	0.94	0.39–2.27	0.90	1.22	0.46–3.21	0.69
TAX (6)	0.61	0.24–1.57	0.31	0.88	0.33–2.30	0.79

Abbreviations: PEM: pemetrexed; GEM: gemcitabine; TAX: taxane; PFS: progression free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval.

for chemotherapy. Previously it has been described that NSCLC patients with a *KRAS* mutation may have a significantly lower ORR to treatment with either pemetrexed or gemcitabine compared to *KRAS* wt patients [12]. In the same study it was found that the presence of a *KRAS* mutation is both a poor predictive and prognostic biomarker. However, this study comprised a small group of *KRAS* mutated NSCLC ($n = 39$) only. Other studies in patients with advanced NSCLC report no difference in clinical outcome after chemotherapeutic treatment by *KRAS* mutational status [8–10]. In a preclinical study, Garassino et al. demonstrated differences in response to chemotherapeutic regimens per type of *KRAS* mutation in lung cancer cell lines. Pemetrexed was most effective in G12C, but less in G12D or G12V [11]. Gemcitabine had a similar response in all 3 types and paclitaxel showed best response in G12C and G12V but less in G12D. In our retrospective analysis we could not confirm the sensitivity of the types of *KRAS* mutation to the respective regimens. However, we did find differences in sensitivity between types of *KRAS* mutation that support the hypothesis that drug sensitivity may differ depending on the type of *KRAS* mutation.

To our knowledge, *KRAS* mutation has not been linked previously to taxane sensitivity. Increased sensitivity to taxane in NSCLC patients with a *KRAS* mutation may be explained by the role in mitosis of downstream effectors of *KRAS* [13]. Taxanes stabilizes microtubules during mitosis, resulting in apoptosis of the dividing cell. It has been described that activated ERK, downstream of *KRAS*, has an important role in regulation of the stabilization of microtubules [14]. It has also been reported that apoptosis induced by paclitaxel is dependent on activation of the MAP kinases [15]. One may hypothesize that continuous activation of the MAPK pathway due to a *KRAS* mutation may therefore lead to sensitivity to taxane. The addition of bevacizumab to taxane resulted in highest response rate in our group of patients. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF), a pro-angiogenic factor that may play a role in tumor progression and metastasis [16,17]. Bevacizumab induces inhibition of new tumor vasculature, regression of existing tumor microvasculature and normalization of remaining tumor vasculature [18]. Increased VEGF expression has been observed in *KRAS* mutated NSCLC [19,20]. This may influence the response to VEGF targeted

Fig. 2. Comparison of progression free survival (PFS) of chemotherapy regimens per most common types of *KRAS* mutation. Black line: pemetrexed; grey line: gemcitabine; dotted line: taxanes. A. PFS in months of patients with G12C; B. PFS in months of patients with G12V; C. PFS in months of patients with G12D.

Fig. 3. Comparison of overall survival (OS) of chemotherapy regimens per most common types of *KRAS* mutation. Black line: pemetrexed; grey line: gemcitabine; dotted line: taxanes. A. OS in months of patients with G12C; B. OS in months of patients with G12V; C. OS in months of patients with G12D.

therapy. Although our observations are not substantiated by pre-clinical evidence, it is hypothesis generating, and can easily be studied in prospective clinical trials.

There is a great demand for effective treatment strategies in *KRAS* mutant cancer. Despite numerous attempts, direct inhibition of mutated RAS protein has not been successful and is believed to be undruggable. The first success in targeting downstream effectors of *KRAS* in NSCLC is reported by Janne et al. In a randomized, placebo-controlled phase II trial, NSCLC patients with advanced disease harboring a *KRAS* mutation and failed first-line treatment were randomized between selumetinib and docetaxel or docetaxel

and placebo. Median OS comparable in the selumetinib group and placebo group (9.4 months versus 5.2 months, $p = 0.21$). However, PFS and ORR were significantly improved [23]. A phase III study is now enrolling patients. Encouraging data is published on a shut-down of *KRAS*-G12C variant by selective and irreversible binding of a designed small molecule [24]. Other types of *KRAS* mutation or *KRAS* wt could not be shut down by the compound. This could be an important step toward targeted treatment of *KRAS* mutated cancer. Further development of the compound for clinical testing is in progress.

Our study has some limitations. First, this study has heterogeneity in treatment regimens and treatment decisions, because of many participating hospitals. Also, response was not centrally reviewed, which may produce a bias in the estimation of response. Because of its retrospective nature and selection, this patient study group may not be representative. Firm conclusions cannot be drawn based on our data, among others because of the small sample size in subgroups. However, we provide some evidence and give rationale that *KRAS* genotyping could be considered for selecting patients for treatment with platinum combined with taxanes.

Ihle et al. suggested that there is a difference in behavior of different types of *KRAS* mutation, due to activation of different downstream growth signaling pathways [22]. In this preclinical study, using mutant *KRAS*-transfected NSCLC cell lines, it was found that G12C mutation had a downstream stimulation of RAF and RAL, but G12D stimulation of RAF and AKT. Further research is needed on the biology and signaling of different types of *KRAS* mutation, to improve understanding of the differential effect of chemotherapy on distinct *KRAS* mutations and develop more effective (targeted) treatments.

In conclusion, taxane-based chemotherapy showed significantly improved ORR and prolonged PFS compared to other platinum-containing regimens in the whole study group. Response to first-line platinum-based chemotherapy was dissimilar in different types of *KRAS* mutated NSCLC patients. Especially G12V had better response to taxane treatment. More understanding on tumor biology of *KRAS* mutated NSCLC and its subtypes is urgently needed. Further, we encourage study of taxane-based chemotherapy in advanced NSCLC patients with a *KRAS* mutation in randomized control trials.

Financial support and conflict of interest

All authors state they have no financial supports or conflict of interest.

Acknowledgements

We thank the following contributors for providing data: Willemijn Engelsman-Theelen, Mark de Mol, Anneke Horstman, Jeroen Hiltermann, Clemens Prinsen, Nils't Hart.

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