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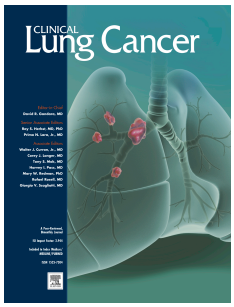

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KRAS-specific amino acid substitutions are associated with different responses to chemotherapy in advanced non-small cell lung cancer

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Abstract:

Background: Emerging data highlight different clinical behaviours according to *KRAS* amino acid substitutions (AASs) in non-small cell lung cancer (NSCLC) patients. We aimed to evaluate whether different *KRAS* AASs were associated with different responses to chemotherapy.

Methods: We retrospectively reviewed data from 1190 patients with *KRAS* mutations who underwent first-line platinum-based chemotherapy for stage IV NSCLC. The response to different chemotherapy regimens was evaluated using the RECIST criteria (v 1.1). Overall survival (OS) and time to progression (TTP) were secondary end points.

Results: Taxane was associated with the best response in the entire cohort (OR: 2.52 (95% CI: 1.82-3.48), p<0.001), especially in G12V patients (OR: 2.15 (95% CI: 1.05-4.41), p=0.036). Taxane was associated with improved TTP in the entire cohort (HR: 0.31 (95% CI: 0.26-0.38), p<0.001), especially in G13D patients (HR: 0.47 (95% CI: 0.22-1.01), p=0.054). Pemetrexed was associated with the worst TTP in the entire cohort, particularly in G12V patients, who had the worst response rates (HR: 0.55 (95% CI: 0.30-0.99), p=0.049). No impact on OS was observed according to different chemotherapy regimens and AASs.

Conclusion: *KRAS*-specific AAS appears to induce different responses to chemotherapy regimens after first-line platinum-based chemotherapy in advanced NSCLC.

Key words: chemotherapy, KRAS, amino acid substitution, non-small cell lung cancer

Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for nearly 80% of histological subtypes. The last decade has seen a dramatically increased understanding of molecular alterations in cancer, helping clinicians offer a more accurate prognosis for patients and adapt therapies. Lung cancer, especially NSCLC, has not been left behind. Indeed, for some years now, we have witnessed the progressive evolution of a histological classification of NSCLC towards a molecular classification [2, 3]. Especially in NSCLC adenocarcinomas, several oncogenic drivers have been discovered, and some have led to significant modifications in patients' management and prognosis. Hence, activating mutations of exons 18-21 of the *epidermal growth factor receptor* (*EGFR)* or *echinoderm microtubule-associated protein-like 4* (*EML4*) - *anaplastic lymphoma kinase* (*ALK*) translocation, conferring sensitivity to EGFR tyrosine kinase inhibitors (TKI) and ALK inhibitors, respectively, have been associated with significantly improved survival in metastatic NSCLC patients [4-6].

Meanwhile, the prognostic and predictive values of these two mutations appear to be clearly established [7, 8], which is not the case for others, especially for *V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue* (*KRAS*) mutations. Indeed, *KRAS* mutations are found in nearly 30-35% of lung adenocarcinomas and are more frequent in smoking patients; these mutations mainly occur on exon 2 codon 12/13, have been considered as a single entity for many years and have mainly been linked to poor prognosis in NSCLC [9]. However, recent data suggest that only a fleeting glimpse of *KRAS* mutations has thus far been explored [10]. Indeed, *in vitro* and *in vivo* studies suggest there is important heterogeneity among *KRAS* mutations, especially according to amino acid substitutions. Hence, previous studies have shown that according to amino acid substitution, different downstream signalling pathways appear to be

activated [11], leading to different clinical behaviours with a different prognosis [12, 13], different types of dissemination [14] or different responses to radiation therapy [15].

More interestingly, based on an *in vitro* study demonstrating different sensitivities to chemotherapies [16], previous authors have attempted to investigate the different profiles of chemosensitivity according to *KRAS* amino acid substitution. However, despite interesting results, the current literature is poor, contradictory and mostly based on small retrospective cohorts [17-20].

Consequently, we aimed to evaluate the response to different chemotherapy regimens according to *KRAS* amino acid substitution in a large cohort of metastatic NSCLC after first-line platinum-based chemotherapy.

Methods

This study was approved by the Ethics Committee of the French Society of Thoracic and Cardiovascular Surgeons (Approval Number: *2017-4-23-11-20-17-ReSt*).

We retrospectively reviewed data from patients suffering from NSCLC who underwent routine molecular testing for *KRAS* and *EGFR* between January 2007 and December 2015 at the molecular biology department of Strasbourg University Hospital (Strasbourg, France). Our study included stage IV NSCLC patients, according to the 7th TNM edition, with *KRAS* mutations who received platinum-based chemotherapy as a first-line treatment. Patients were excluded in cases of surgery, concurrent *EGFR* or *ALK* mutation, or the absence of documentation of response evaluation. Radiation therapy, as palliative treatment, was allowed during chemotherapy treatment.

Molecular analysis

Molecular analysis was performed at *KRAS* codons 12 and 13, as previously described [14]. Samples for molecular analysis were obtained from primary or metastatic tumour sites.

Covariate and data collection

Baseline patient characteristics were collected, including age at diagnosis, sex, histology, chemotherapy combination, *KRAS* amino acid substitutions, smoking history and response to treatment. Smoking status was characterized as never a smoker, <100 cigarettes in their lifetime, a former smoker, quit >1 year before diagnosis and a current smoker with an ongoing smoking habit or who quit <1 year before diagnosis. The Charlson comorbidity index (CCI) was calculated for each patient. We grouped patients into the following established categories according to their total score [21]: 0 (no comorbidity); 1–2 (average); 3–4 (moderate); and ≥5 (severe). Response to treatment was evaluated according to RECIST criteria (version

1.1) [22]. All baseline computed tomographic scans were reviewed by a dedicated radiologist who specialized in thoracic radiology during the multidisciplinary board.

Statistical analysis

Categorical data are presented as a number (percentage, %) and continuous data as the mean (standard deviation [SD]).

Associations between the RECIST response and clinicopathological characteristics, chemotherapy regimens and *KRAS* mutations were investigated with the use of the logistic regression model. According to RECIST criteria, complete and partial responses were pooled into the response group (RG); meanwhile, stable and progressive diseases were pooled into the non-response group (NRG).

The overall survival (OS) was defined as the time from the date of initiation of the first cycle of chemotherapy to the date of death from any cause. Patients still alive on the date of the last follow-up were censored. The time to progression (TTP) was defined as the time from the date of first treatment to the date of disease progression or death. Time-to-event variables were estimated using the Kaplan-Meier method and compared using a log-rank test.

A Cox proportional hazard model was used to estimate the crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) as well as to evaluate possible predictors of the OS and TTP. The follow-up duration was used as the time scale. Predictors of the OS and TTP associated with $P < 0.2$ on univariate analysis were included in the multivariable models. To limit the risk of α inflation, predictors identified in univariate analysis on the whole cohort were used in multivariate analysis for each subgroup analysis (i.e., pemetrexed, gemcitabine, taxane and bevacizumab groups). All tests were two-sided, and variables were considered significant for P-values <0.05. Statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

According to the selection criteria, 1190 *KRAS*-mutated patients with Stage IV NSCLC who received platinum-based chemotherapy as first-line treatment were included in the analyses.

The population demographics and clinical and pathologic characteristics of these patients are reported in Table 1.

Most patients were male (756 – 63.5%) and active smokers (896 – 75.3%), and the mean age at the time of treatment was 67.2 years (SD ± 10.4). Adenocarcinoma was the most represented histology (1134 – 95.3%). All patients were dead or had experienced a disease progression at the date of last follow-up.

Platinum-based chemotherapy was mostly associated with pemetrexed (476 – 40.0%), which was followed by vinorelbine (357 – 30%), taxane (238 – 20.0%) and gemcitabine (119 – 10.0%). In the taxane group, 119 (50.0%) patients were treated with bevacizumab.

Analyses of *KRAS* codon 12 mutations revealed 593 (49.8%) G12C, 240 (20.2%) G12V, 139 (11.7%) G12D, 73 (6.1%) G12A, 27 G12S (2.3%), 15 G12R (1.3%), 11 G12F (0.9%) and 1 G12L and G12N (0.1%). Because of their small proportion, G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions were included in “other G12” for further statistical analysis. Concerning codon 13, 48 (4.0%) KRAS G13C transversions and 38 (3.2%) G13D transitions were observed.

RECIST response analysis

Overall, at the end of follow-up period, a response to the treatments was observed in 345 (29.0%) patients.

The results of univariate and multivariate logistic regression analysis for the RECIST response are illustrated in Supplementary Table 1.

In univariate analysis, the age (OR 0.97; P< 0.001; 95% CI 0.96-0.99) and male sex (OR 0.49; P< 0.001; 95% CI 0.38-0.64) were found to be associated with the NRG. Chemotherapy regimens, including vinorelbine (OR 0.66; P= 0.01; 95% CI 0.47-0.91), were found to be associated with the NRG, while treatment with taxane (OR 2.52; P< 0.001; 95% CI 1.82-3.48) was associated with CR / PR. In the taxane group, bevacizumab administration (OR 2.91; P P< 0.001; 95% CI 1.72-4.92) was associated with the RG. The *KRAS* mutational status was not a significant predictor in univariate analysis of the whole cohort, while in patients treated with bevacizumab, only G12V mutations were associated with the RG (OR 3.37; P= 0.043; 95% CI 1.04-11.0).

In multivariate analysis, treatments with vinorelbine (OR 0.62; P= 0.01; 95% CI 0.44-0.87) and gemcitabine (OR 0.5; P= 0.01; 95% CI 0.30-0.83) were associated with NRG, while taxane regimen was associated with RG (OR 2.2; P< 0.001; 95% CI 1.56-3.10). *KRAS* mutational status was not a significant predictor in multivariate analysis of the whole cohort.

In the taxane group (Table 2), bevacizumab administration (OR 3.42; P< 0.001; 95% CI 1.87-6.27) was found to be independently associated with the RG at the multivariate analysis. According to different chemotherapy regimens, G12V mutations were associated with the NRG in the pemetrexed group (OR 0.55; P= 0.049; 95% CI 0.30-0.99), while they were found to be associated with the RG in both the taxane (OR 2.15; P= 0.036; 95% CI 1.05-4.41) and bevacizumab (OR 3.39; P= 0.047; 95% CI 1.02-11.3) groups.

Overall survival analysis

Overall, the 6- and 12-month survival rates were 87% and 5%, respectively (Supplementary Figure 1). The results of the Cox models for the OS are illustrated in Table 3.

In the univariate analysis, none of the variables of interest significantly influenced the OS. Of note, the *KRAS* mutational status was not a significant predictor of the OS on univariate analysis in the whole cohort or in patients treated with bevacizumab.

When analysed according to different chemotherapy regimens (i.e., pemetrexed, vinorelbine, taxane, gemcitabine or bevacizumab), the OS was not significantly influenced by KRAS amino acid substitutions (data not shown).

Time to progression analysis

Overall, the 3-, 6- and 9-month TTP rates were 69%, 6% and 1%, respectively (Supplementary Figure 2). The results of univariate and multivariable Cox models for TTP are illustrated in Supplementary Table 2.

In univariate analysis, the age (HR 1.02; P< 0.001; 95% CI 1.01-1.03) and male gender (HR 1.34; P < 0.001; 95% CI 1.19-1.51) were found to have a negative effect on the TTP, while not otherwise specified (NOS) histology improved the TTP (HR 0.65; P= 0.004; 95% CI 0.48-0.87). Chemotherapy regimens, including those with vinorelbine (HR 0.72; P< 0.001; 95% CI 0.62-0.82), gemcitabine (HR 0.79; P= 0.02; 95% CI 0.64-0.96) and taxane (HR 0.29; P< 0.001; 95% CI 0.25-0.35), were associated with a better TTP (Figure 1). In the taxane group, bevacizumab administration was associated with a better TTP (HR 0.84; P= 0.009; 95% CI 0.74 - 0.96) (Figure 2).

In multivariate analysis (Supplementary Table 2), treatments with vinorelbine (HR 0.76; P< 0.001; 95% CI 0.66-0.88) and taxane (HR 0.32; P< 0.001; 95% CI 0.26-0.38) were associated with a better TTP. *KRAS* mutational status was not a significant predictor in multivariate analysis of the whole cohort. However, G12D and G12V mutations tended to have a better TTP, albeit not significantly (HR 0.85; P=0.08; 95% CI 0.70 - 1.02 and HR 0.86; P= 0.07; 95% CI 0.74 - 1.01, respectively).

In the sub-group multivariate analysis (Table 3), only G13D mutations tended to have a better TTP when submitted to taxane, albeit not significantly (OR 0.47; P= 0.054; 95% CI 0.22 - 1.01). Finally, among patients treated with bevacizumab, all *KRAS* amino acid substitutions were associated with a worse TTP in multivariate analysis.

Discussion

In this large cohort study, we have shown that different types of *KRAS* amino acid substitutions may induce different responses to platinum-based chemotherapy regimens. Although *KRAS* mutations have been considered a unique entity for several decades, growing published evidence is highlighting the large heterogeneity of *KRAS* mutations, leading to different clinical and molecular behaviours. In particular, previous authors have attempted to investigate different responses to chemotherapy according to amino acid substitution. Garassino *et al*. [16], in an *in vitro* model using NSCLC cell lines, were the first to objectivise different response sensitivity patterns. Indeed, G12C expression was associated with a reduced response to cisplatin and increased sensitivity to Taxol and pemetrexed; at the same time, the G12D mutant was associated with resistance to Taxol and sorafenib. Finally, G12V had high sensitivity to cisplatin with more resistance to pemetrexed. These different responses to chemotherapy regimens might be at least partially explained on a molecular basis by the different downstream signalling pathways activated according to amino acid substitution. Hence, in an *in vitro* study, Ihle et al. reported that both *KRAS* G12C and G12V exhibited activated Ral signalling and decreased growth factor-dependent Akt activation, although the G12D mutation exhibited activated PI3K and MEK signalling [11]. Based on these results, few retrospective clinical studies have been conducted without providing unequivocal conclusions. Jänne *et al*. [18], in a retrospective study based on 83 patients, reported that patients with *KRAS* G12C and G12V had better OS, progression-free survival (PFS) and objective response rate (ORR) than did patients with other *KRAS* mutations when treated with selumetinib plus docetaxel. In line with these results, Cserepes *et al*. [19], in a retrospective study based on 167 patients harbouring *KRAS* mutations, showed a better response to cisplatin in G12V patients. Mellema *et al*. [17], in a larger multi-centre cohort study in the Netherlands on 464 patients, showed a higher ORR in G12V patients treated with taxanes. In contrast,

Metro *et al.* [20], in a retrospective cohort study based on 77 *KRAS* mutant patients, did not observe any difference according to amino acid substitution. However, all were relatively small cohort studies, limiting their level of evidence.

To the best of our knowledge, our study is thus far the largest published series on the impact of *KRAS* amino acid substitutions on the response to platinum-based chemotherapy regimens. In agreement with Garassino *et al.* [16], we have shown that G12V mutants were significantly more resistant to pemetrexed, with a lower ORR according to the RECIST criteria. Furthermore, pemetrexed was associated with a worse TTP than that of other chemotherapy regimens for all *KRAS* amino acid substitutions. Interestingly, in agreement with previous authors [16, 17], we have shown that taxane administration was related to an increased ORR in the whole cohort, especially in G12V patients, and a positive effect on TTP, especially in G13D patients, without impacting the OS. The explanation of this positive effect of taxane may rely on the interaction between microtubules and KRAS. Indeed, it has been previously noted that KRAS binds to microtubules with high affinity in a prenylation-dependent manner [23]. Hence, in cells treated with paclitaxel, cytoplasmic accumulation of KRAS was noted with reduced plasma membrane localization and redistribution into an endosomal compartment [24]. Beyond its anti-mitotic activity, taxane may disturb KRAS intra-cellular trafficking, explaining the anti-proliferative activity observed with taxane. Interestingly, as noted by previous authors [17, 25], patients in our cohort treated with taxane + bevacizumab had a higher ORR than did those treated with taxane alone, especially in G12V patients. This effect may rely on the up-regulation of vascular endothelial growth factor (VEGF) production in *KRAS*-mutated cancers, especially in codon 12 mutations [26-28]. However, although bevacizumab administration was related to a better ORR, it was related to a significantly worse TTP in each subgroup of *KRAS* amino acid substitution in multivariate analysis. One can speculate on several hypotheses after a primary response to explain these opposing effects. First,

bevacizumab, by blocking VEGF production, induces a hypoxic microenvironment, with angiogenic escape in a hypoxia-inducible factor (HIF)-dependent manner, leading to tumour proliferation. Second, a "rebound effect" may occur at the time of bevacizumab discontinuation. Third, bevacizumab may interfere with other intra-cellular molecular pathways, especially microRNAs (miRNAs) [29], and induce a totally opposite effect. Indeed, miRNAs are known to act as double-edged swords, playing the role of both oncogenes and tumour-suppressor genes depending on the stimulus. For example, miR29b has been shown in *KRAS* G12V mutant NSCLC cell lines to tip the balance between apoptotic sensitization and resistance depending on extrinsic stimulation [30]. However, these are only speculations, and further studies are necessary to elucidate these opposing effects of bevacizumab on *KRAS* mutants.

Nonetheless, these observations suggest a large heterogeneity of *KRAS* mutations. Hence, in the biology of *KRAS*-driven non-small cell lung cancer, *in vitro* studies have shown that two subgroups of *KRAS* mutated cells appear to exist. The first subgroup appears to depend on *KRAS* mutations for its survival, while the other does not [31]. Consequently, directly targeting *KRAS* in the "*KRAS*-independent" group does not appear to be relevant because it does not affect cancer cell survival *in vitro*. However, the complexities of *KRAS* mutations are not limited here. Indeed, previous authors have also shown that 3 major subgroups of *KRAS*-mutant NSCLC adenocarcinomas are defined by the co-existence of other genetic alterations, *STK11/LKB1*, *TP53* and *CDKN2A/B* [32]. These different genetic alterations appear to be predictive of the response to anti-PD1/PDL1 immunotherapy in *KRAS*-mutated NSCLC because the immune tumour micro-environment appears to differ according to these co-mutations [33, 34]. In line with these observations, *ALK* translocation and *KRAS* mutations have thus far been considered mutually exclusive. However, recent publications suggest a potentially higher rate of co-expression of these two molecular alterations than that expected

[35], which may have biological and clinical consequences, such as different responses to treatment regimens, requiring further explorations in larger studies than those published thus far.

Our study must be interpreted with caution based on a few limitations. First, it is a single-centre, retrospective cohort study. For this reason, we were not able to collect data such as performance status (PS), presence of brain metastases and use of carboplatin vs cisplatin, or time of use of radiation therapy, which may have partially biased our results. However, even though CCI cannot totally replace PS, it has been significantly associated in a recent work with survival after adjusting for PS in stage IIIB/IV NSCLC [36]. Otherwise, although cisplatin has been associated with a slightly increased ORR, the 1-y survival does not differ between these two chemotherapy regimens [37]. Because of the retrospective nature of our work, we did not have data from an *EGFR/KRAS/ALK* wild-type adenocarcinoma group for comparison. These data would be interesting in future studies to strengthen the results. Furthermore, except for G12C and G12V, the patient subgroups were relatively small. In particular, other G12 groups included various types of *KRAS* amino acid substitutions, preventing the exploration of all codon 12 biological effects. Moreover, because none of the patients was treated with platinum alone, the impact of different AASs on sensitivity to platinum was not evaluated. Hence, one can speculate that part of differences observed between chemotherapy regimens can be related to different sensitivity to platinum according to the AAS. Finally, because our centre is a 3rd referral centre, patients are addressed by various oncologists. Consequently, the number of courses of the chemotherapy regimen may have been different among patients and may have led to a possible bias.

In conclusion, this is the largest published series showing that *KRAS* amino acid substitutions may impact the response to chemotherapy. In particular, it appears that G12V patients are more resistant to pemetrexed. Otherwise, taxane appears to be an interesting therapeutic in

patients with *KRAS* mutations, especially G12V patients. Bevacizumab, although it is associated with a higher ORR, especially in G12V patients, appears to lead to a worse TTP. This opposite effect might require further investigations. Finally, as noted by previous authors, although ORR and TTP may differ according to the amino acid substitution and chemotherapy regimen, no impact on OS was noted [17, 19]. However, our study must be interpreted with caution based on its limitations. Prospective, multi-centre cohort studies are required to clearly elucidate the real impact of the heterogeneity of *KRAS* mutations. Nonetheless, these observations offer new hope to *KRAS*-mutant patients.

Clinical Practice Points

KRAS mutations, present in nearly 30-35% of lung adenocarcinomas and more frequent in smoking patients, have been considered as a single entity for many years and have been linked to poor prognosis in NSCLC. Current literature, mostly based on small retrospective cohorts, is poor and contradictory about the different profiles of chemo-sensitivity according to KRAS amino acid substitution.

Our study, performed on the largest published series to date, demonstrated that different types of KRAS amino acid substitutions may induce different responses to platinum-based chemotherapy regimens. In particular, we showed that G12V mutants were significantly more resistant to pemetrexed. Furthermore, pemetrexed was associated with a worse TTP than that of other chemotherapy regimens for all KRAS amino acid substitutions. Finally, we observed that taxane administration was related to increased therapy response outcomes in the whole cohort, especially in G12V and G13D patients.

In conclusion, our results suggest a large heterogeneity in profiles of chemo-sensitivity according to KRAS mutations. These observations offer new hope to KRAS-mutant patients and support the development of MEK inhibitors.

Conflicts of interests: None to declare

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Figure Legends:

Figure 1: Kaplan-Meier representation of time to progression according to chemotherapy regimen in the whole cohort.

Figure 2: Kaplan-Meier representation of time to progression according to bevacizumab use in the taxane group.

Supplementary Figure 1: Kaplan-Meier representation of survival in the whole cohort.

Supplementary Figure 2: Kaplan-Meier representation of time to progression in the whole cohort.

Table 1

Variable	N (%)	G12A	G12C	G12D	G12V	Other G12*	G13C	G13D	P
Age at diagnosis (n= 1090)									0.46
(years) (mean ± SD)	67.2 ± 10.4	67.1 ± 10.5	67.8 ± 10.3	66.7 ± 10.8	66.3 ± 10.6	66.8 ± 9.2	67.6 ± 10.1	65.7 ± 11.9	
Gender (n= 1090)									0.72
Female	434 (36.5%)	27 (37.0%)	196 (33.1%)	57 (41.0%)	103 (42.9%)	22 (39%)	13 (27%)	16 (42%)	
Male	756 (63.5%)	46 (63.0%)	397 (66.9%)	82 (59.0%)	137 (57.1%)	34 (61%)	35 (73%)	22 (58%)	
Smoking history (n= 1190)									0.37
Non-smoker	294 (24.7%)	15 (21.0%)	163 (27.5%)	29 (20.9%)	59 (24.6%)	15 (27%)	9 (19%)	4 (1.3%)	
Smoker	896 (75.3%)	58 (79.0%)	430 (72.5%)	110 (79.1%)	181 (75.4%)	41 (73%)	39 (81%)	37 (98.7)	
Histology (n= 1190)									0.45
Adenocarcinoma	1134 (95.3%)	69 (95%)	567 (95.6%)	132 (95.0%)	230 (95.8%)	56 (100%)	43 (90%)	34 (89%)	
NOS°	46 (3.9%)	4 (5%)	20 (3.4%)	6 (4.3%)	8 (3.3%)		4 (8%)	4 (11%)	
Squamous cell carcinoma	10 (0.8%)	0	6 (1.0%)	1 (0.7%)	2 (0.8%)		1 (2%)		
KRAS mutations (n= 1190)									
G12A	73 (6.1%)								
G12C	593 (49.8%)								
G12D	139 (11.7%)								
G12F	11 (0.9%)					11 (20%)			
G12L	1 (0.1%)					1 (2%)			
G12N	1 (0.1%)					1 (2%)			
G12R	15 (1.3%)					15 (27%)			
G12S	27 (2.3%)					27 (48%)			
G12V	240 (20.2%)								
G12Y	1 (0.1%)					1 (2%)			
G13C	48 (4.0%)								
G13D	38 (3.2%)								
G13V	3 (0.3%)								
Charlson Comorbidity Index (n= 1190)									0.21
0	136 (11.4%)	10 (14%)	85 (14.3%)	12 (8.6%)	23 (9.6%)	4 (7%)	2 (4%)		
1	341 (28.7%)	23 (32%)	155 (26.1%)	47 (33.8%)	80 (33.3%)	9 (16%)	20 (42%)	7 (18%)	
2	618 (51.9%)	34 (47%)	301 (50.8%)	71 (51.1%)	116 (48.3%)	40 (71%)	22 (46%)	31 (82%)	
3	95 (8.0%)	6 (8%)	52 (8.8%)	9 (6.5%)	21 (8.8%)	3 (5%)	4 (8%)		
Chemotherapy (n= 1190)									0.12
Platinum + Pemetrexed	476 (40.0%)	25 (34%)	260 (43.8%)	44 (31.7%)	87 (36.3%)	20 (36%)	25 (52%)	15 (39%)	
Platinum + Vinorelbine	357 (30.0%)	29 (40%)	176 (29.7%)	45 (32.4%)	53 (22.1%)	23 (41%)	13 (27%)	15 (39%)	
Platinum + Taxane	238 (20.0%)	10 (14%)	98 (16.5%)	35 (25.2%)	69 (28.7%)	10 (18%)	8 (17%)	8 (21%)	
Platinum + Gemcitabine	119 (10.0%)	9 (12%)	59 (9.9%)	15 (10.8%)	31 (12.9%)	3 (5%)	2 (4%)		
Bevacizumab (Platinum + Taxane only) (n= 238)									0.17
No	119 (50.0%)	6 (60%)	31 (32%)	22 (63%)	45 (65%)	7 (70%)	5 (63%)	5 (63%)	
Yes	119 (50.0%)	4 (40%)	67 (68%)	13 (37%)	24 (35%)	3 (30%)	3 (38%)	3 (38%)	

°NOS: not otherwise specified ; *Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions

Table 2: Multivariate^ sub-groups analyses of response to chemotherapy according to the RECIST criteria

	MULTIVARIATE ANALYSIS Pemetrexed Group (n=476)		MULTIVARIATE ANALYSIS Vinorelbine Group (n=357)		MULTIVARIATE ANALYSIS Gemcitabine Group (n=117)		MULTIVARIATE ANALYSIS Taxane Group (n=357)		MULTIVARIATE ANALYSIS Bevacizumab Group (n=119)	
Variable	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
KRAS mutations										
G12C	(reference)		(reference)		(reference)		(reference)		(reference)	
G12A	0.39(0.13-1.20)	0.10	1.2(0.47-3.09)	0.70	0.59(0.066-5.36)	0.64	0.63(0.13-2.91)	0.55	1.12(0.13-9.53)	0.92
G12D	0.9(0.44-1.85)	0.78	1.15(0.52-2.55)	0.74	1.65(0.43-6.33)	0.47	1.42(0.53-3.78)	0.48	1.57(0.39-6.31)	0.53
G12V	**0.55(0.30-0.99)**	**0.049**	0.81(0.36-1.82)	0.61	0.91(0.28-2.97)	0.88	**2.15(1.05-4.41)**	**0.036**	**3.39(1.02-11.3)**	**0.047**
Other G12	1.05(0.39-2.86)	0.92	1.4(0.51-3.84)	0.52	10.7(0.84-136.0)	0.07	0.4(0.073-2.16)	0.28	2.86(0.20-40.6)	0.44
G13C	1.17(0.48-2.85)	0.73	0.31(0.038-2.53)	0.27	1(.)	.	0.16(0.017-1.44)	0.11	0.36(0.032-4.02)	0.41
G13D	0.74(0.22-2.45)	0.62	1.25(0.33-4.75)	0.75	-	-	1.54(0.32-7.44)	0.59	1.02(0.087-12.1)	0.98
G13V	-	-	2.64(0.23-30.5)	0.44	-	-	0.99(0.95-1.03)	0.62	1.12(0.13-9.53)	0.92
Age at diagnosis (as continuous, years)										
	0.24(0.11-0.51)	**0.0002**	0.98(0.95-1.02)	0.31	0.99(0.93-1.05)	0.69			1 (.)	
Gender										
Female	(reference)		(reference)		(reference)		(reference)		(reference)	
Male	1.03(0.99-1.07)	0.18	0.81(0.39-1.70)	0.58	0.58(0.16-2.17)	0.42	0.9(0.43-1.85)	0.77	0.35 (0.08-	0.16

									1.51)	
Bevacizumab (Taxane group only ; n=238)										
No	-		-		-		(reference)			
Yes	-		-		-		**3.42(1.87-6.27)**	**<0.001**		-

CI: confidence interval °NOS: not otherwise specified; *Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions.

^To limit the risk of α inflation, predictors associated with P <0.2 identified in the univariate analysis of the whole cohort were used in the multivariate analysis for each subgroup analysis (i.e., pemetrexed, gemcitabine, taxane and bevacizumab groups). Bold values were used to highlight significant variables.

Table 3: Univariate analysis of overall survival (OS)

	UNIVARIATE ANALYSIS	
Variable	Hazard ratio (95% CI)	P
KRAS mutations		
G12C	(reference)	
G12A	1.02(0.80-1.30)	0.88
G12D	0.93(0.77-1.11)	0.42
G12V	0.96(0.83-1.12)	0.62
Other G12	0.98(0.75-1.29)	0.89
G13C	1.01(0.76-1.36)	0.92
G13D	0.95(0.69-1.32)	0.77
G13V	0.55(0.18-1.72)	0.31
Age at diagnosis (as continuous, years)		
	1(0.99-1.00)	0.74
Gender		
Female	(reference)	
Male	0.97(0.86-1.09)	0.61
CCI (as continuous)		
	1.00 (0.94-1.08)	0.92
Smoking history		
Non-smoker	(reference)	
Smoker	1.03(0.90-1.18)	0.64
Histology		
Adenocarcinoma	(reference)	
NOS	1.02(0.76-1.37)	0.89
Squamous cell carcinoma	0.91(0.49-1.69)	0.76
Chemotherapy		
Pemetrexed	(reference)	
Vinorelbine	0.98(0.86-1.13)	0.81
Taxane	1.03(0.88-1.20)	0.72
Gemcitabine	1.14(0.93-1.39)	0.20
Bevacizumab (Taxane group only)		
No	(reference)	
Yes	0.89(0.69-1.15)	0.38

NOS: not otherwise specified. Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions. CI: confidence interval

Table 4: Univariate and multivariate analyses on the time to progression (TTP)

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS Pemetrexed Group		MULTIVARIATE ANALYSIS Vinorelbine Group		MULTIVARIATE ANALYSIS Gemcitabine Group		MULTIVARIATE ANALYSIS Taxane Group		MULTIVARIATE ANALYSIS Bevacizumab Group	
	Odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P
Variable												
KRAS mutations												
G12C	(reference)		(reference)		(reference)		(reference)		(reference)		(reference)	
G12A	1.04(0.82-1.33)	0.74	1.16(0.77-1.75)	0.49	1.07(0.72-1.59)	0.74	0.73(0.35-1.50)	0.39	0.86(0.43-1.72)	0.66	**7.15(2.31-22.1)**	**<0.001**
G12D	0.96(0.80-1.16)	0.70	0.87(0.63-1.21)	0.42	0.94(0.67-1.31)	0.70	1.21(0.65-2.25)	0.54	0.8(0.48-1.31)	0.37	**5.63(2.62-12.1)**	**<0.0001**
G12V	0.9(0.77-1.05)	0.18	0.92(0.72-1.17)	0.50	0.82(0.60-1.12)	0.20	0.95(0.60-1.50)	0.82	0.96(0.68-1.35)	0.8	**3.43(2.03-5.82)**	**<0.0001**
Other G12	0.99(0.75-1.31)	0.97	1.18(0.74-1.87)	0.48	0.75(0.48-1.18)	0.21	0.86(0.27-2.80)	0.81	1.13(0.56-2.30)	0.73	**9.82(2.60-37.0)**	**<0.0001**
G13C	1.03(0.77-1.39)	0.83	1.09(0.72-1.64)	0.70	1.06(0.59-1.88)	0.85	2.38(0.56-10.1)	0.24	0.73(0.33-1.59)	0.42	**4.09(1.41-11.9)**	**0.01**
G13D	0.98(0.71-1.37)	0.92	1.1(0.60-1.99)	0.77	1.3(0.76-2.24)	0.34	-	-	0.47(0.22-1.01)	0.054	**4.53(1.37-15.0)**	**0.014**
G13V	0.64(0.20-1.98)	0.43	1.16(0.77-1.75)	0.49	0.54(0.17-1.70)	0.29	-	-	0.86(0.43-1.72)	0.66	**7.15(2.31-22.1)**	**<0.001**
Age at diagnosis												
(as continuous,	**1.02(1.01-1.03)**	**<0.001**	1.01(0.99-1.03)	0.48	0.98(0.96-1.01)	0.15	**1.06(1.01-1.11)**	**0.03**	1(0.97-1.03)	0.8	1(0.96-1.05)	0.88

years)												
Gender												
Female	(reference)		(reference)		(reference)		(reference)		(reference)		(reference)	
Male	**1.34(1.19-1.51)**	**<0.001**	0.84(0.59-1.19)	0.33	1.46(0.98-2.20)	0.07	**0.29(0.11-0.76)**	**0.012**	0.85(0.47-1.54)	0.6	1.17(0.56-2.44)	0.68
Smoking history												
Non-smoker	(reference)		-		-		-		-			
Smoker	0.99(0.87-1.13)	0.86	-		-		-		-			
Histology												
Adenocarcinoma	(reference)		(reference)		(reference)		(reference)		(reference)			
NOS	**0.65(0.48-0.87)**	**<0.001**	0.96(0.45-2.05)	0.92	0.53(0.22-1.26)	0.15	**5.95(1.50-23.6)**	**0.011**	1.02(0.37-2.81)	0.97		
Squamous cell carcinoma	1.12(0.60-2.09)	0.72	0.78(0.18-3.36)	0.74	-	-	**5.89(1.06-32.9)**	**0.043**	-	-		
Chemotherapy												
Pemetrexed	(reference)											
Vinorelbine	**0.72(0.62-0.82)**	**<0.001**	-		-		-		-			
Taxane	**0.29(0.25-0.35)**	**<0.001**	-		-		-		-			
Gemcitabine	**0.79(0.64-0.96)**	**0.02**	-		-		-		-			
Bevacizumab (Taxane group only)												
No	(reference)		-		-		-		(reference)			
Yes	**0.63(0.49-0.82)**	**<0.001**	-		-		-		0.79(0.57-1.10)	0.16		

NOS: not otherwise specified; Other substitutions G12 included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions. To limit the risk of α inflation, predictors identified in univariate analysis on the whole cohort were used in multivariate analysis for each subgroup analysis (i.e., pemetrexed, gemcitabine, taxane and bevacizumab groups). Bold values were used to highlight significant variables. CI: confidence interval

Figure 1

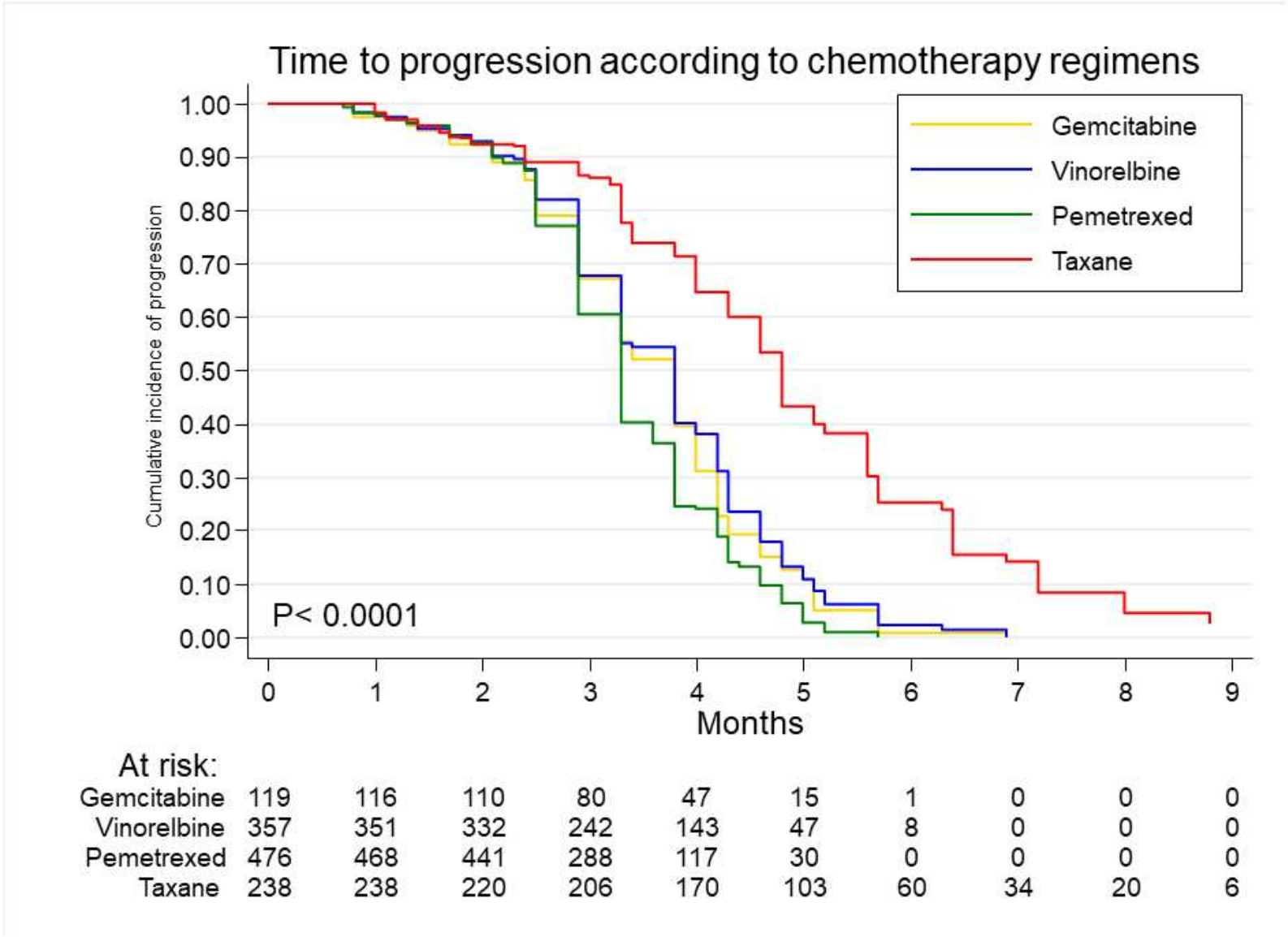
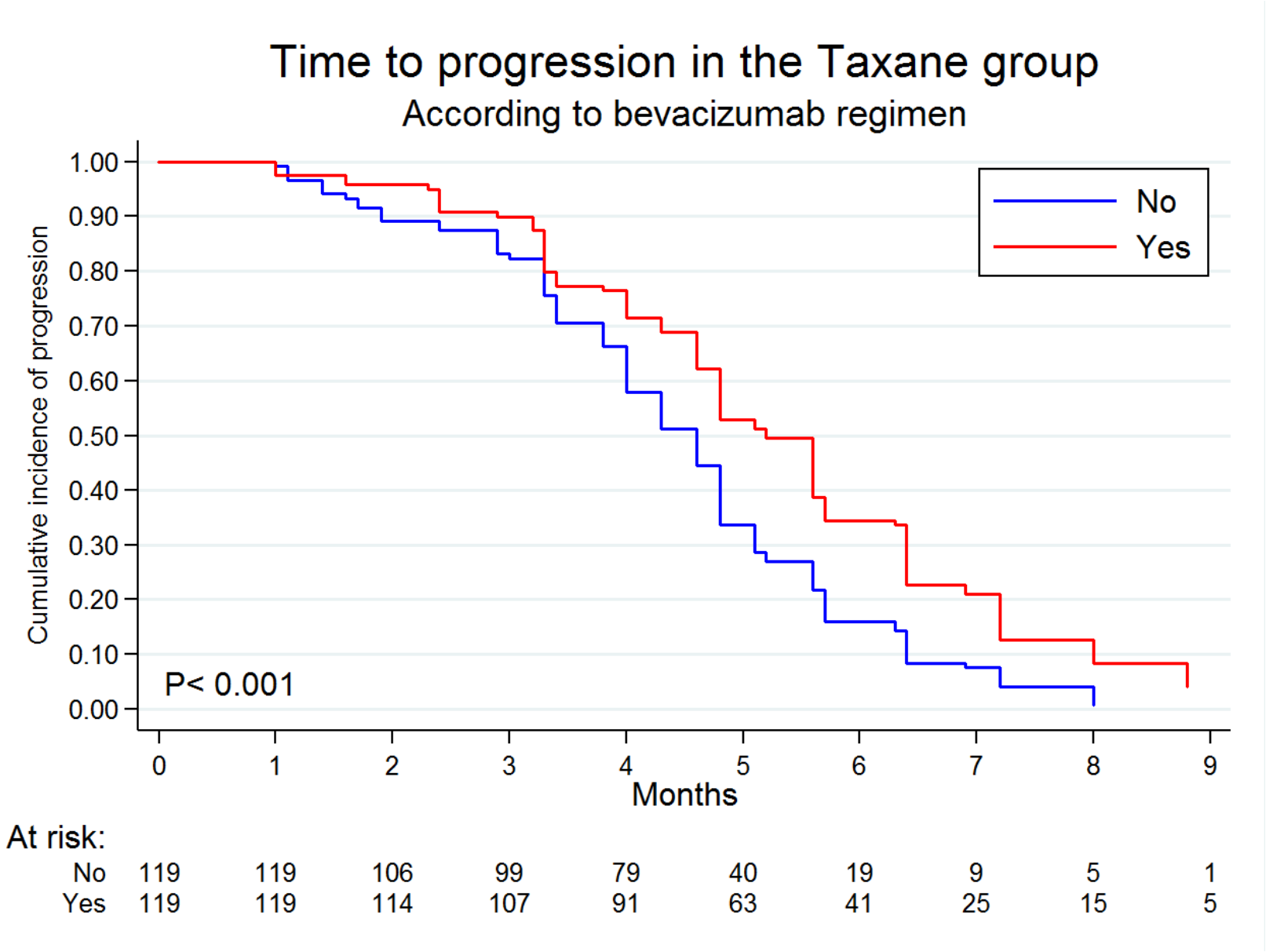
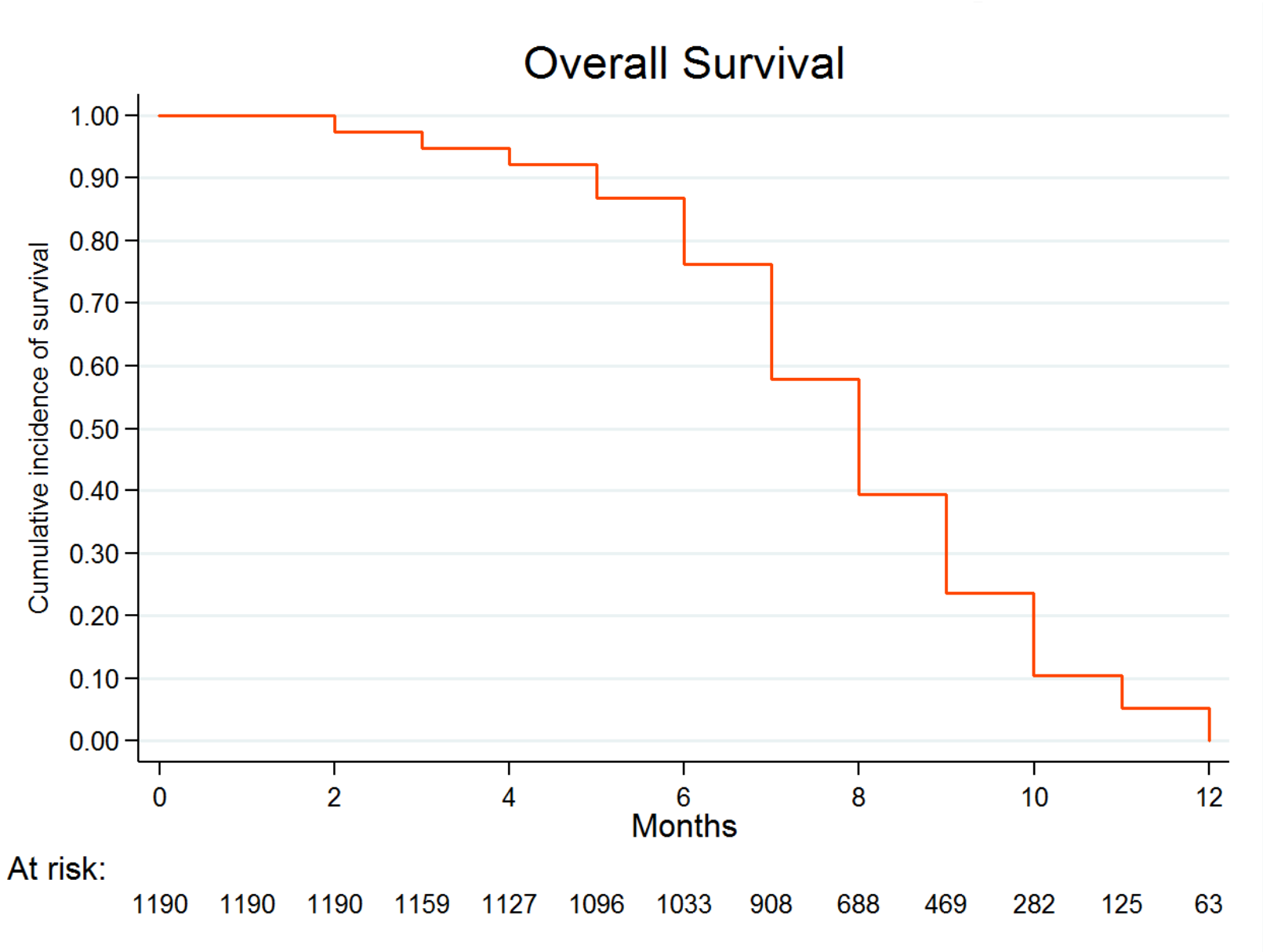

Time to progression according to chemotherapy regimens
Cumulative incidence of progression
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Gemcitabine
Vinorelbine
Pemetrexed
Taxane
P< 0.0001
0
1
2
3
4
5
6
7
8
9
Months
At risk:
Gemcitabine 119 116 110 80 47 15 1 0 0 0
Vinorelbine 357 351 332 242 143 47 8 0 0 0
Pemetrexed 476 468 441 288 117 30 0 0 0 0
Taxane 238 238 220 206 170 103 60 34 20 6

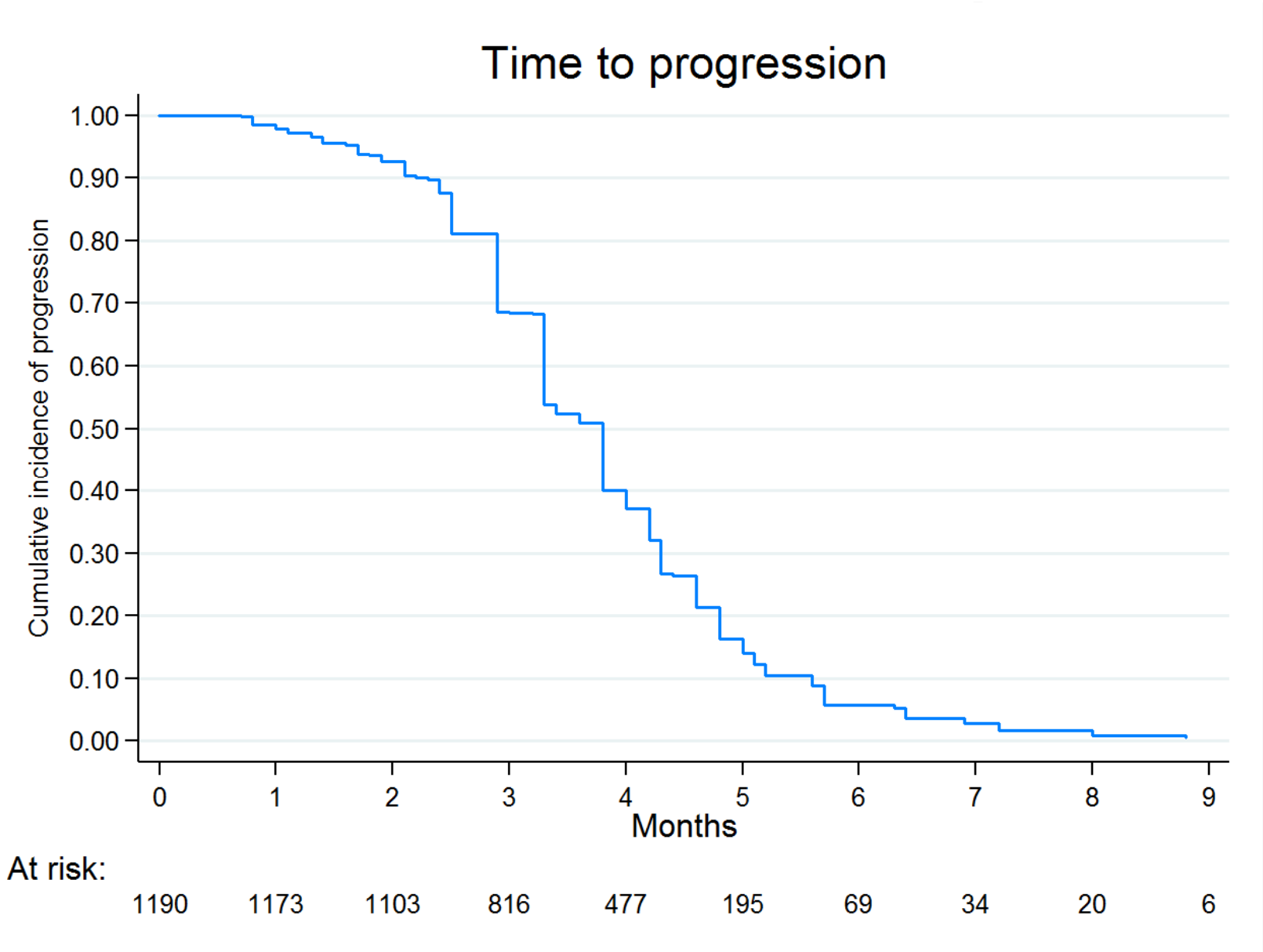
Figure 2



Supplementary Figure 1.



Supplementary Figure 2



Suplementary Table 1: Univariate and multivariate analyses of response to chemotherapy according to the RECIST criteria

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS (n= 1090)	
Variable	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
KRAS mutations				
G12C	(reference)		(reference)	
G12A	0.64(0.35-1.17)	0.15	0.68(0.37-1.25)	0.21
G12D	1.19(0.80-1.77)	0.39	1.1(0.73-1.66)	0.66
G12V	1.07(0.77-1.48)	0.70	0.88(0.62-1.24)	0.46
Other G12	1.08(0.60-1.97)	0.79	1.06(0.57-1.97)	0.86
G13C	0.92(0.48-1.79)	0.82	0.92(0.47-1.82)	0.82
G13D	1.15(0.57-2.33)	0.70	1(0.47-2.10)	0.99
G13V	1.24(0.11-13.8)	0.86	2.53(0.22-28.5)	0.45
Age at diagnosis (as continuous, years)				
	0.97(0.96-0.99)	**<0.001**	1(0.98-1.02)	0.84
Gender				
Female	(reference)		(reference)	
Male	**0.49(0.38-0.64)**	**<0.001**	**0.5(0.34-0.74)**	**<0.001**
Smoking history				
Non-smoker	(reference)			
Smoker	1.01(0.75-1.34)	0.97	-	
Histology				
Adenocarcinoma	(reference)			
NOS	0.66(0.33-1.35)	0.26	-	
Squamous cell carcinoma	1 (.)		-	
Chemotherapy				
Pemetrexed	(reference)		(reference)	
Vinorelbine	**0.66(0.47-0.91)**	**0.01**	**0.62(0.44-0.87)**	**0.01**
Taxane	**2.52(1.82-3.48)**	**<0.001**	**2.2(1.56-3.10)**	**<0.001**
Gemcitabine	0.66(0.40-1.08)	0.10	**0.5(0.30-0.83)**	**0.01**
Bevacizumab (Taxane group only ; n=238)				
No	(reference)			
Yes	**2.91(1.72-4.92)**	**<0.001**	-	

CI: confidence interval °NOS: not otherwise specified; *Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions.

^Predictors associated with P <0.2 identified in the univariate analysis were used in the multivariate analysis.

Supplementary Table 2: Univariate and multivariate analyses on the time to progression (TTP)

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS (n=1090)	
	Hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
Variable				
KRAS mutations				
G12C	(reference)			
G12A	1.04(0.82-1.33)	0.74	0.87(0.68 - 1.11)	0.25
G12D	0.96(0.80-1.16)	0.70	0.85(0.70 - 1.02)	0.08
G12V	0.9(0.77-1.05)	0.18	0.86(0.74 - 1.01)	0.07
Other G12	0.99(0.75-1.31)	0.97	0.85(0.64 - 1.12)	0.25
G13C	1.03(0.77-1.39)	0.83	0.86(0.64 - 1.16)	0.31
G13D	0.98(0.71-1.37)	0.92	0.98(0.70 - 1.37)	0.9
G13V	0.64(0.20-1.98)	0.43	0.44(0.14 - 1.39)	0.16
Age at diagnosis				
(as continuous, years)	**1.02(1.01-1.03)**	**<0.001**	1.01(1.00 - 1.02)	0.08
Gender				
Female	(reference)			
Male	**1.34(1.19-1.51)**	**<0.001**	1.03(0.84 - 1.27)	0.77
Smoking history				
Non-smoker	(reference)			
Smoker	0.99(0.87-1.13)	0.86		
Histology				
Adenocarcinoma	(reference)			
NOS	**0.65(0.48-0.87)**	**<0.001**	0.92(0.62 - 1.38)	0.7
Squamous cell carcinoma	1.12(0.60-2.09)	0.72	1.04(0.51- 2.12)	0.92
Chemotherapy				
Pemetrexed	(reference)			
Vinorelbine	**0.72(0.62-0.82)**	**<0.001**	**0.76(0.66 - 0.88)**	**<0.001**
Taxane	**0.29(0.25-0.35)**	**<0.001**	**0.31(0.26 - 0.38)**	**<0.001**
Gemcitabine	**0.79(0.64-0.96)**	**0.02**	0.89(0.72 - 1.11)	0.31
Bevacizumab (Taxane group only)				
No	(reference)			
Yes	**0.63(0.49-0.82)**	**<0.001**	-	

CI: confidence interval °NOS: not otherwise specified; *Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid substitutions. ^Predictors associated with P

<0.2 identified in the univariate analysis were used in the multivariate analysis. CI: confidence interval °NOS: not otherwise specified; *Other G12 substitutions included G12F, G12L, G12N, G12R, G12S, and G12Y KRAS amino acid