

TREATMENT AND OUTCOME OF A REAL-WORLD COHORT OF PATIENTS WITH ADVANCED, NON-SQUAMOUS NSCLC AND KRAS MUTATIONS WITH A SPECIAL FOCUS ON KRAS G12C

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BACKGROUND

Lung cancer is the most common cancer worldwide, and non-small cell lung cancer (NSCLC) accounts for 85% of the cases. Mutations in the KRAS gene belong to the most frequent oncogenic driver mutations. Details on the current treatment and outcome of patients with advanced NSCLC and mutations in the KRAS gene in routine care are scarce and KRAS mutations have been long perceived as “undruggable”. Considering recent developments regarding specific small molecule inhibitors of the KRAS mutation subtype G12C, we analyzed patient characteristics, treatment reality and outcome in a representative advanced NSCLC (stage IIIB/C, IV) cohort in Germany with KRAS G12C and non-G12C mutations.

METHODS

CRISP is a non-interventional, prospective, multi-center, national clinical research platform collecting representative data on molecular testing, treatment and outcome of patients with metastatic NSCLC in Germany. Patients with advanced, non-squamous (nsq) NSCLC and KRAS mutations were identified within the 3717 evaluable patients recruited by 73 sites (cancer centers, hospitals and office-based oncology practices) into the registry CRISP from December 2015 to June 2019 in Germany. Details on patients' characteristics, treatment and outcome were analyzed in the subgroups of KRAS G12C and non-G12C mutated patients.

RESULTS

Patient and tumour characteristics

Until data cut on June 30, 2019, 4032 patients with advanced NSCLC were recruited into the CRISP registry, of which 3717 were evaluable. Of these, 1434 had been tested for KRAS mutations and 511 test results had been positive. Patients with unknown mutations (n=63) and patients with squamous NSCLC (n=7) were excluded from the analysis, resulting in 441 patients with advanced, non-squamous NSCLC with known KRAS mutation. KRAS G12C was present in 171 (5.9% of nsq / 4.6% of all) cases and non-KRAS G12C in 270 (9.2% of nsq / 7.3% of all) cases. The distribution of KRAS mutation subtypes is shown in **Figure 1**. Age and sex distribution were similar in patients with KRAS G12C

and non-G12C mutations, with 45.0% and 46.3% female patients (**Table 1**). Median age at the start of 1st-line treatment of patients with KRAS G12C (non-G12C) mutations was 64 years, respectively. ECOG performance status was 0 in 36.8% of G12C mutated patients and in 34.8% of non-G12C mutated patients. The proportion of current/former smokers was in the G12C group 93.0% and in the non-G12C group 84.1%; and most frequent metastatic sites were bones (35.7% / 27.0%), contralateral lung (29.2% / 24.4%), and brain (27.5% / 24.4%) (**Table 1**).

Treatment of patients with KRAS mutations

In palliative 1st-line treatment, 48.5% patients with G12C mutation received a checkpoint inhibitor (CPI), either as single agent or combined with chemotherapy, while patients with other KRAS mutations received a CPI in 40.7% of cases (**Figure 2**). A total of 38.6% (G12C) and 47.4% (non-G12C) received platinum-combination therapies. So far, second-line treatments have been documented for 48 pts (G12C) and 60 (63.8%) patients with G12C and 60 (63.8%) with non-G12C mutations received a checkpoint-inhibitor (**Figure 3**). Since many patients had not completed 1st-line treatment at the time of analysis, patients with early disease progressions might be slightly overrepresented in the current 2nd-line treatments, which should be considered when interpreting the data.

Clinical outcome of patients with KRAS mutations

Survival was similar for patients with KRAS G12C and non-G12C mutations: median PFS was 4.4 months (95% CI 3.2-6.4) vs. 4.8 months (95% CI 4.3-5.7) (**Figure 4**); median OS was 10.1 months (95% CI 7.0-12.3) vs. 9.4 months (95% CI 7.1-10.8) (**Figure 5**).

CONCLUSION

Here we present comprehensive real-world data from the prospective, representative registry CRISP in Germany on the treatment and outcome of 441 patients with advanced NSCLC and KRAS mutations, with a special focus on the G12C mutation subtype. These data shed light on the patients' characteristics and current treatment and may well serve as important historical control for clinical studies on the treatment and outcome of this patient subgroup.

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Table 1

Characteristic at start of first-line treatment	KRAS G12C mutation n=171	KRAS non-G12C mutation n=270
Age in years, median (25-75% quartile)	64.0 (57.0-71.0)	64.0 (58.0-72.0)
≥ 65 years	84 (49.1%)	132 (48.9%)
Sex		
Female	77 (45.0%)	125 (46.3%)
Male	94 (55.0%)	145 (53.7%)
Charlson Comorbidity Index (CCI)		
CCI=0	96 (56.1%)	166 (61.5%)
CCI≥1	75 (43.9%)	104 (38.6%)
Performance Status		
ECOG 0	63 (36.8%)	94 (34.8%)
ECOG ≥ 1	91 (53.2%)	140 (51.8%)
Unknown	15 (8.8%)	34 (12.6%)
Missing	2 (1.2%)	2 (0.7%)
Smoking status		
Current smoker	65 (38.0%)	84 (31.1%)
Former smoker	94 (55.0%)	143 (53.0%)
Never smoker	4 (2.3%)	17 (6.3%)
Unknown	8 (4.7%)	26 (9.6%)
Missing	0 (0.0%)	0 (0.0%)
Metastasis		
Yes	162 (94.7%)	244 (90.4%)
No	8 (4.7%)	17 (6.3%)
Not derivable (MX or missing)	1 (0.6%)	9 (3.3%)
Selected metastatic sites		
Bones	61 (35.7%)	73 (27.0%)
Brain	47 (27.5%)	66 (24.4%)
Liver	26 (15.2%)	20 (7.4%)
Lung (contralateral)	50 (29.2%)	67 (24.8%)
Adrenal gland	30 (17.5%)	55 (20.4%)

Table 1 Selected patients and tumor characteristics

Figure 1

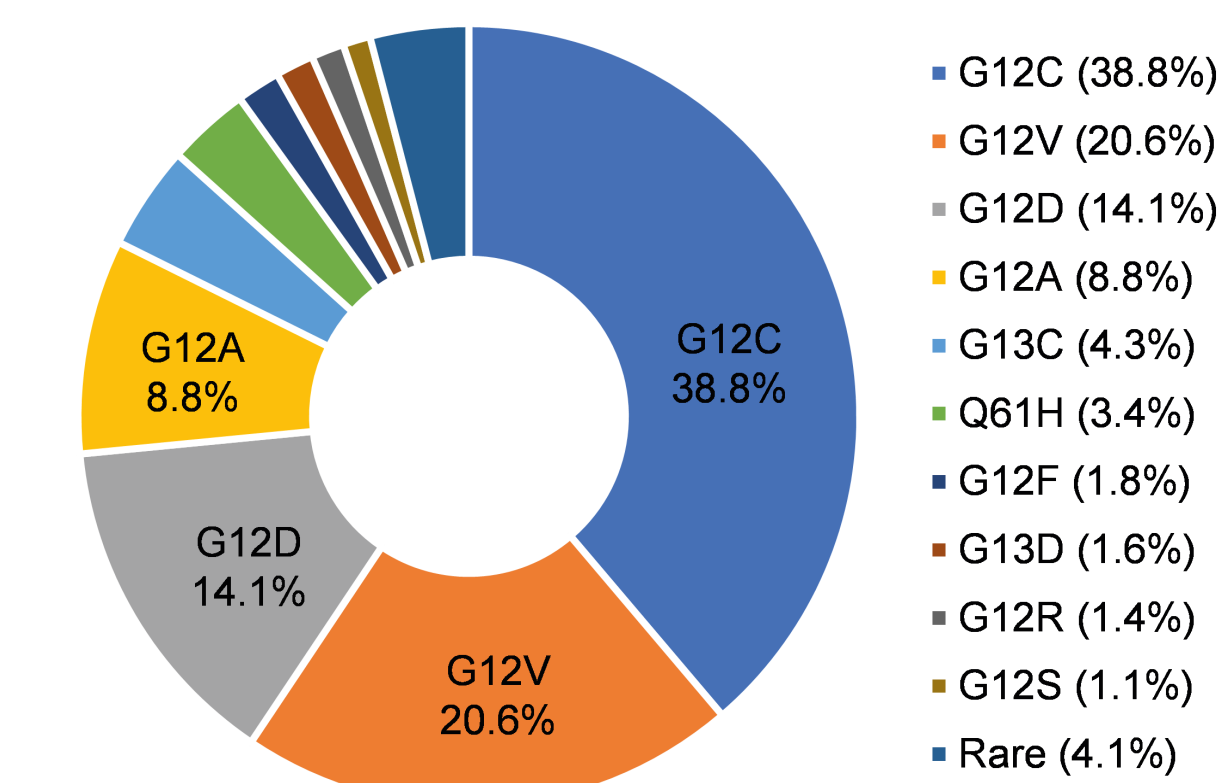


Figure 1: Subtypes of KRAS mutations.

Figure 2

1st-line treatment strategy

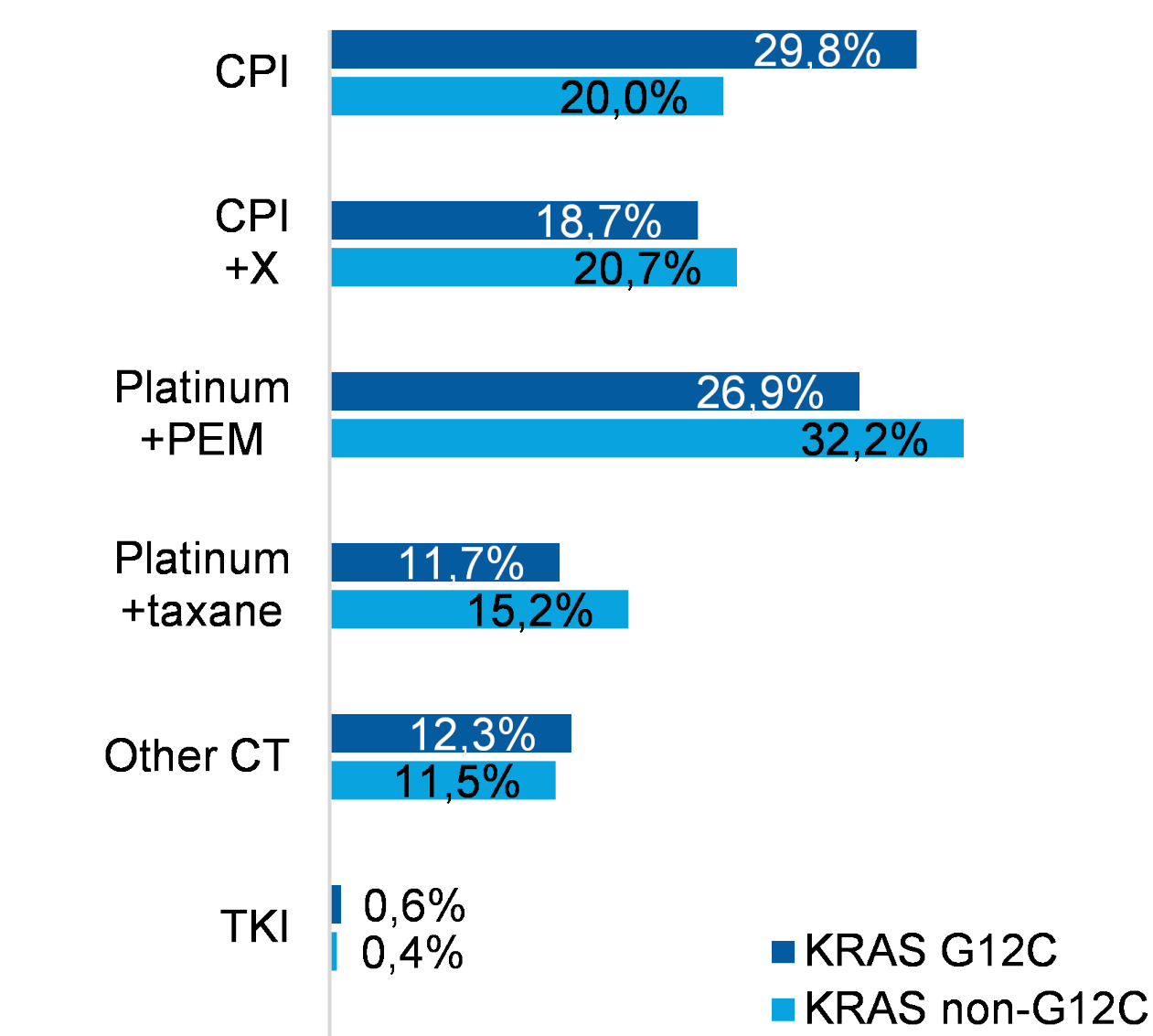


Figure 2: Top first-line treatment regimen for patients with KRAS G12C or non-G12C mutations.

Abbreviations: CPI, checkpoint inhibitor; CT, chemotherapy; TKI, tyrosine kinase inhibitor; PEM, pemetrexed; X, any chemotherapy

Figure 3

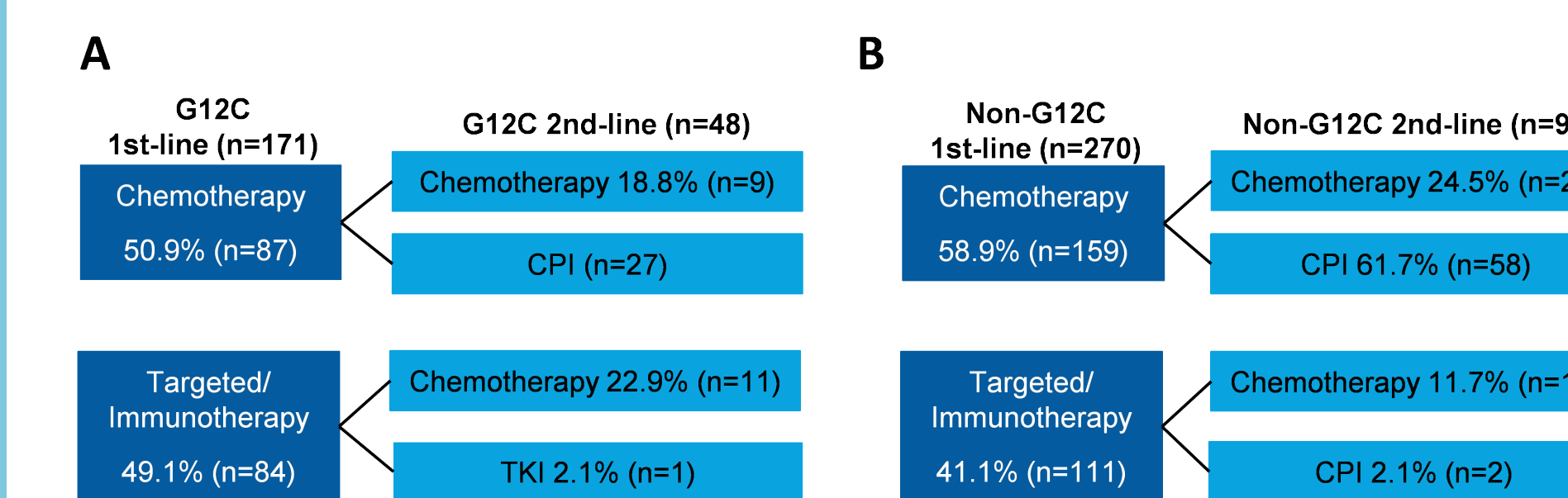


Figure 3: Treatment regimen in patients with KRAS G12C (non-G12C) mutation who already started second-line treatment.

Abbreviations: CPI, checkpoint inhibitor; CT, chemotherapy; TKI, tyrosine kinase inhibitor

Figure 4

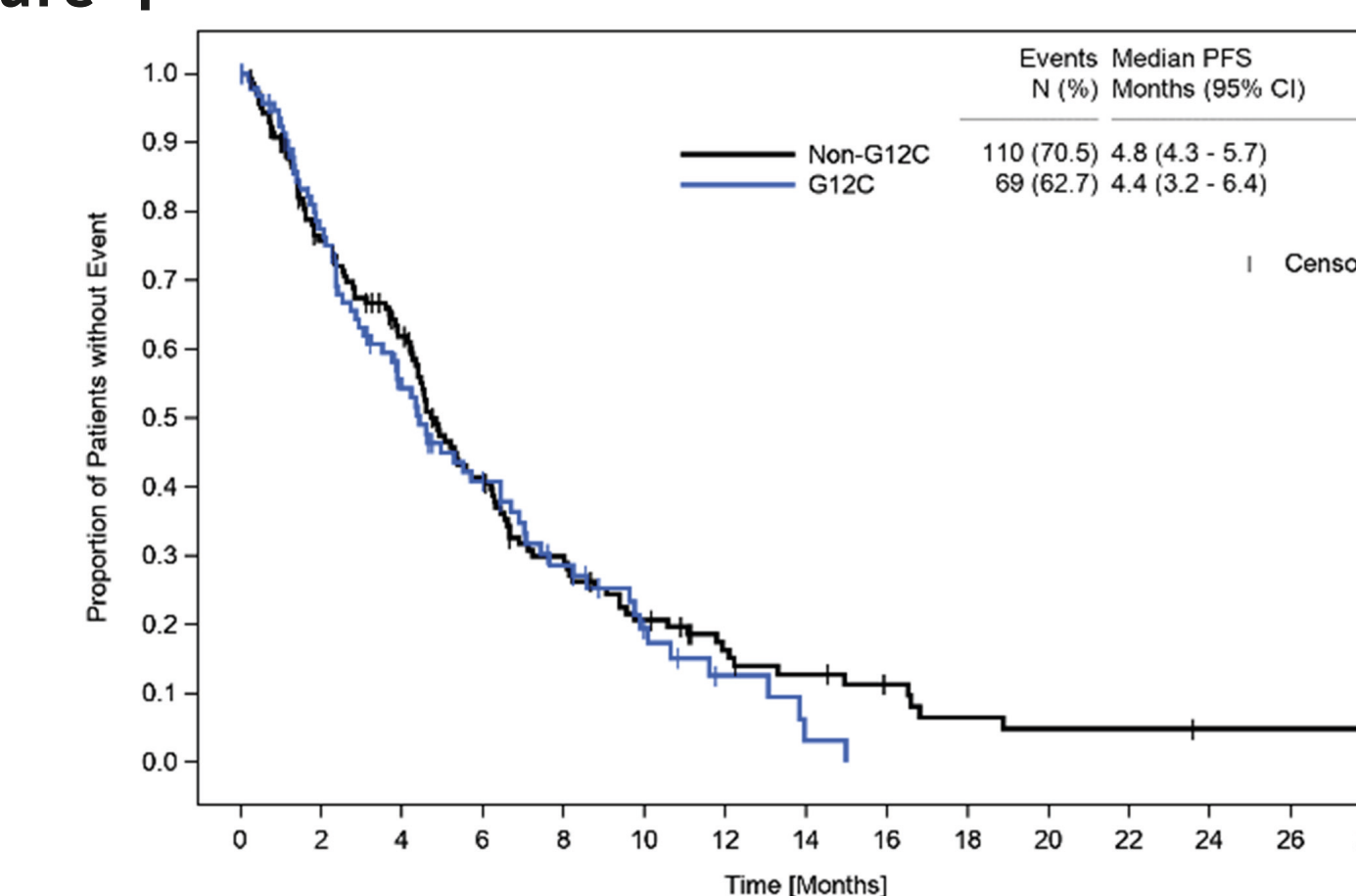


Figure 4: First-line PFS in patients with advanced NSCLC and KRAS mutations

Abbreviations: NSCLC, non-small cell lung cancer; PFS, progression-free survival

Figure 5

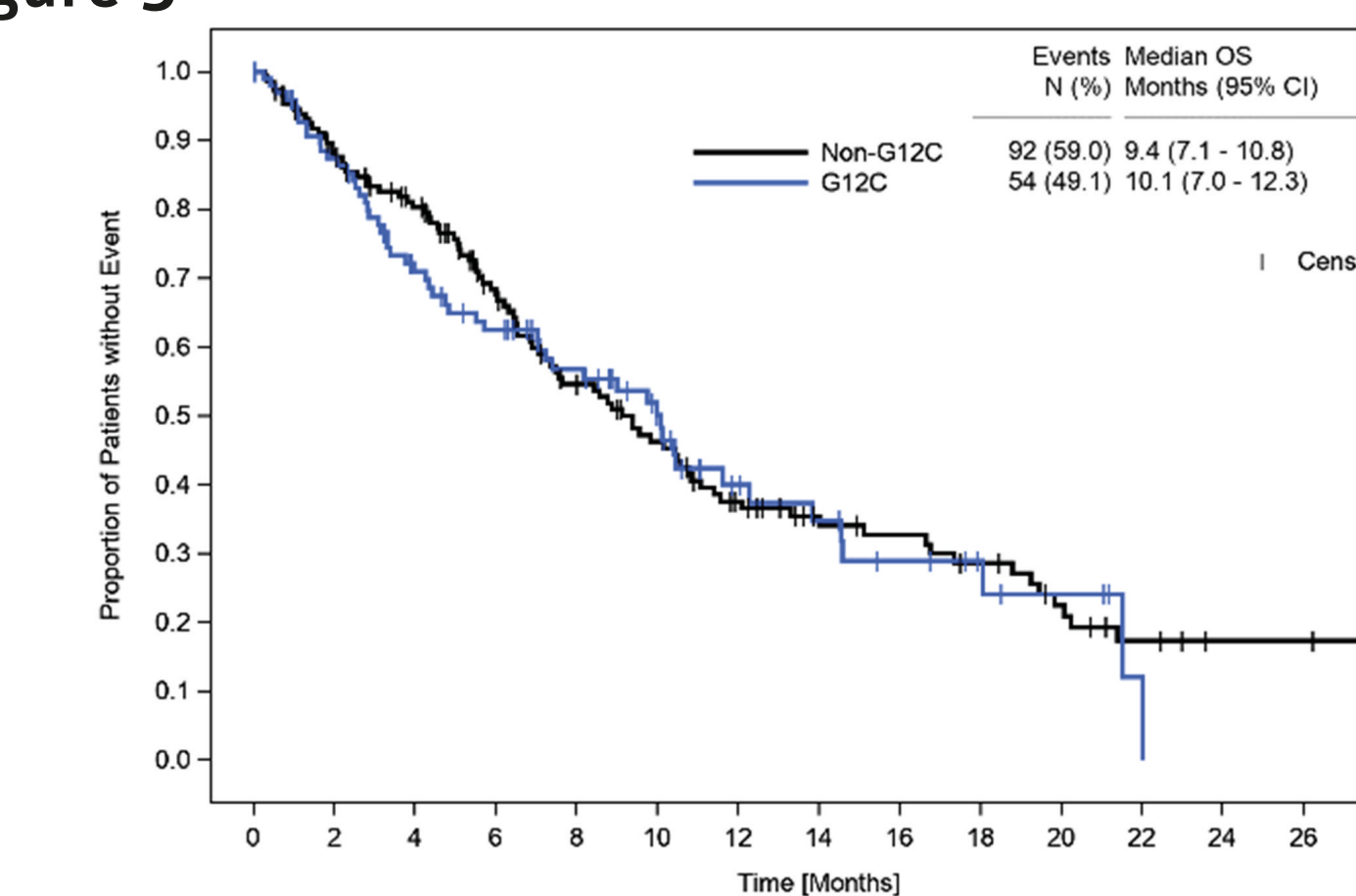


Figure 5: First-line OS in patients with advanced NSCLC and KRAS mutations

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival