

# Impact of *KRAS* Mutation Status on Clinical Outcomes of First-Line Nivolumab-Ipilimumab Plus Chemotherapy in Advanced Non-Squamous NSCLC: Real-World Results from the INSIGHT-PL Study

**Authors:** K. Stencel<sup>1,2,3</sup>, T. Jankowski<sup>4</sup>, M. Bryl<sup>2,3</sup>, E. Kalinka<sup>1</sup>, M. Szwiec<sup>5,6</sup>, K. Bartnik-Delijewska<sup>7</sup>, K. Rogoziewicz<sup>8</sup>, B. Cybulska-Stopa<sup>9</sup>, Ł. Czarnecki<sup>10</sup>, M. Knetki-Wróblewska<sup>11</sup>, D. Kowalski<sup>3,11</sup>, M. Krzakowski<sup>11</sup>, M. Poznański<sup>12</sup>, A. Antczak<sup>12</sup>, J. Milanowski<sup>4</sup>, B. Budny<sup>2</sup>, D. Tworek<sup>13</sup>, K. Rzeszutek<sup>14</sup>, R. Ramlau<sup>15</sup>, A. Woźniak<sup>2</sup>, M. Osuch<sup>16</sup>, D. Polaczek<sup>13</sup>

<sup>1</sup>Polish Mother’s Memorial Hospital - Research Institute, Łódź, Poland, <sup>2</sup>Wielkopolska Center of Pulmonology and Thoracic Surgery of Eugenia and Janusz Zeyland, Poznań, Poland, <sup>3</sup>Polish Lung Cancer Study Group, <sup>4</sup>Department of Pneumology, Oncology and Allergology, Medical University of Lublin, Poland, <sup>5</sup>Clinical Oncology Department, University Hospital, Zielona Góra, Poland, <sup>6</sup>Department of Oncology and Radiotherapy, Collegium Medicum, University of Zielona Góra, Poland, <sup>7</sup>Lubusz Center for Pulmonology, <sup>8</sup>Department of Clinical Oncology, Lower Silesian Oncology, Pulmonology and Hematology Center, Wrocław, Poland, <sup>9</sup>Department of Clinical Oncology, Lower Silesian Oncology, Pulmonology and Hematology Center, Wrocław, Poland, <sup>10</sup>Department of Day and Outpatient Chemotherapy St. Raphael Specialist Hospital, Czerwona Góra, Poland, <sup>11</sup>Lung Cancer and Chest Tumours Department, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, <sup>12</sup>Department of General and Oncological Pulmonology, Medical University of Łódź, Poland, <sup>13</sup>Institute of Tuberculosis and Lung Diseases, Warsaw, Poland, <sup>14</sup>Voivodeship Complex of Healthcare Centers - Lung Disease Treatment and Rehabilitation Centre, Department of Pulmonology and Lung Cancer Chemotherapy, Łódź, Poland, <sup>15</sup>Department and Clinic of Oncology, Karol Marcinkowski Medical University in Poznań, <sup>16</sup>Bristol Myers Squibb, Warsaw, Poland

**Key message:** *KRAS* mutation status was not an independent predictor of treatment efficacy in patients with advanced non-squamous NSCLC treated with first-line nivolumab-ipilimumab plus chemotherapy, whereas PD-L1 expression remained associated with objective response.

## Introduction

*KRAS* mutations are the most common oncogenic alterations in advanced non-squamous non-small cell lung cancer (NSCLC), occurring in approximately 25-35% of cases, with *KRAS* G12C representing the most prevalent subtype.<sup>1,2</sup> Immune checkpoint blockade with nivolumab plus ipilimumab combined with two cycles of platinum-based chemotherapy is an established first-line treatment option for patients with advanced NSCLC without actionable driver alterations (EGFR, ALK, ROS1), providing durable survival benefits irrespective of PD-L1 expression.<sup>3</sup> Although *KRAS* mutations have been associated with distinct tumor biology and may influence the tumor immune microenvironment, their predictive value for outcomes with first-line chemo-immunotherapy remains controversial, with conflicting results reported across clinical trials and real-world studies.<sup>4,6</sup> Consequently, it remains unclear whether specific *KRAS* subtypes, including *KRAS* G12C, identify patients more or less likely to benefit from nivolumab-ipilimumab plus chemotherapy.

The aim of this study was to evaluate the association between *KRAS* mutation status and treatment outcomes in a nationwide real-world cohort of patients with advanced non-squamous NSCLC treated within the Polish National Drug Programme.

## Materials and methods

This retrospective, multicenter real-world study included consecutive patients with inoperable stage III-IV non-squamous NSCLC who initiated first-line nivolumab plus ipilimumab combined with platinum-based chemotherapy between January and December 2023 within the Polish National Drug Programme. Patients were classified according to *KRAS* mutation status as wild-type (WT), *KRAS* G12C, *KRAS* non-G12C, or *KRAS* not assessed (NA).

The primary outcomes were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR). Tumor response was assessed according to routine clinical practice. Survival outcomes were estimated using the Kaplan-Meier method, and multivariable logistic regression was performed to identify factors associated with objective response.

### Study overview

- **Study design:** Retrospective, multicenter, real-world study
- **Population:** 112 patients with stage III-IV non-squamous NSCLC
- **Treatment:** First-line nivolumab + ipilimumab + platinum-based chemotherapy
- ***KRAS* subgroups:** WT, G12C, non-G12C, NA
- **Endpoints:** ORR, DCR, PFS, OS, DoR
- **Statistics:** Kaplan-Meier analysis and multivariable logistic regression

## Results

Figure 1. Baseline characteristics of study population and *KRAS* mutation status

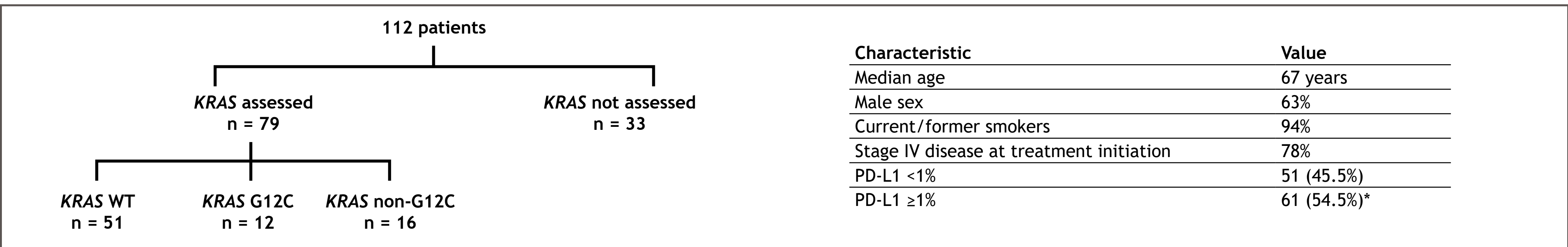


Figure 2. Best overall response according to *KRAS* mutation status. Distribution of best response categories by *KRAS* subgroup in patients with advanced nonsquamous NSCLC treated with first-line nivolumab-ipilimumab plus chemotherapy.

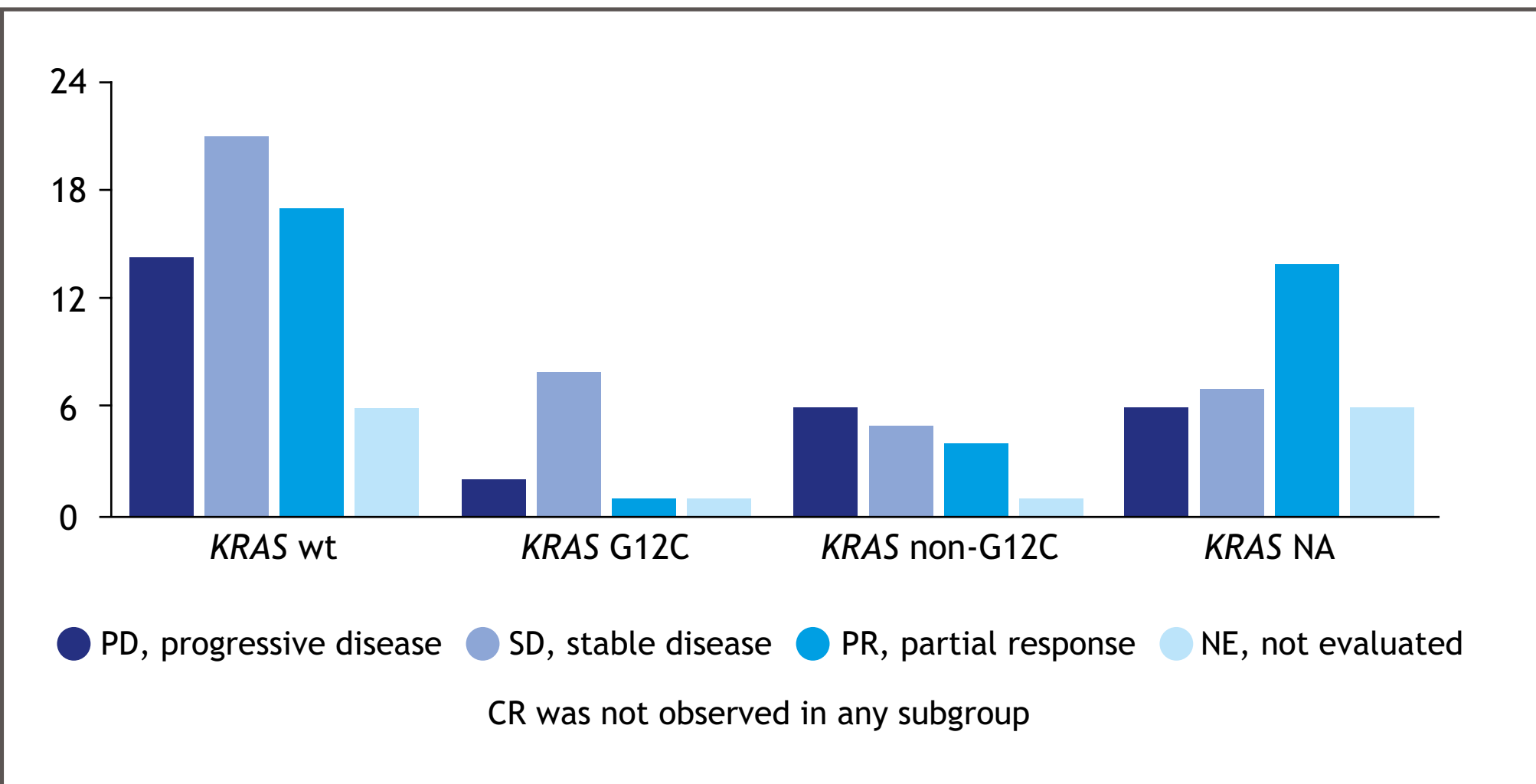


Figure 3. Progression-free survival according to *KRAS* mutation status. Median PFS was 6.3 months for patients with *KRAS* wild-type tumors, 7.7 months for *KRAS* G12C, 6.2 months for *KRAS* non-G12C, and 6.5 months for patients without available *KRAS* testing. No significant differences in PFS were observed between *KRAS* subgroups (log-rank  $p > 0.8$ ).

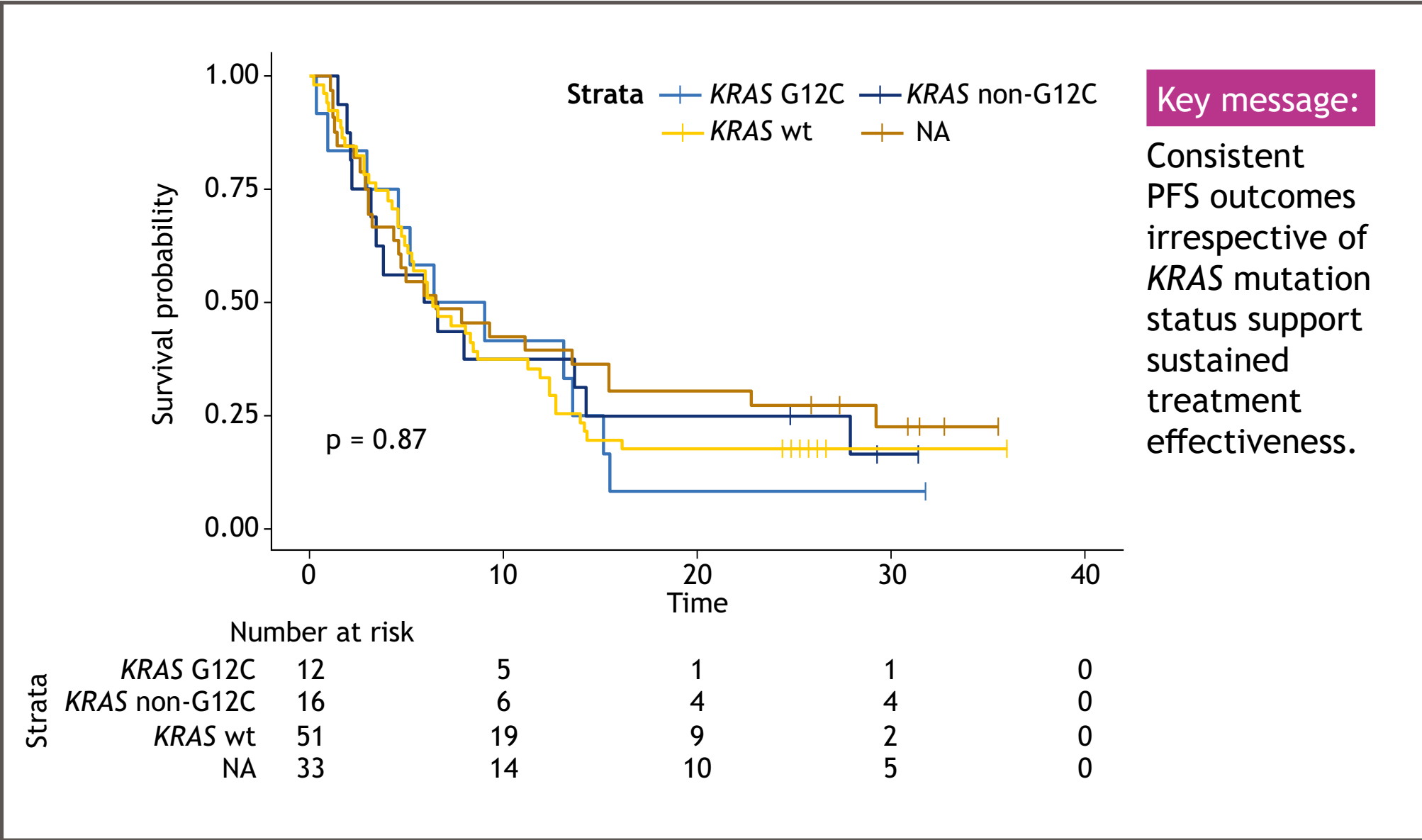


Figure 4. Overall survival according to *KRAS* mutation status. Median OS was 13.5 months in the *KRAS* wild-type group, 24.3 months in the *KRAS* G12C group, 15.5 months in the *KRAS* non-G12C group, and 13.5 months in patients without available *KRAS* testing. Overall survival did not differ significantly between *KRAS* subgroups (log-rank  $p = 0.959$ ).

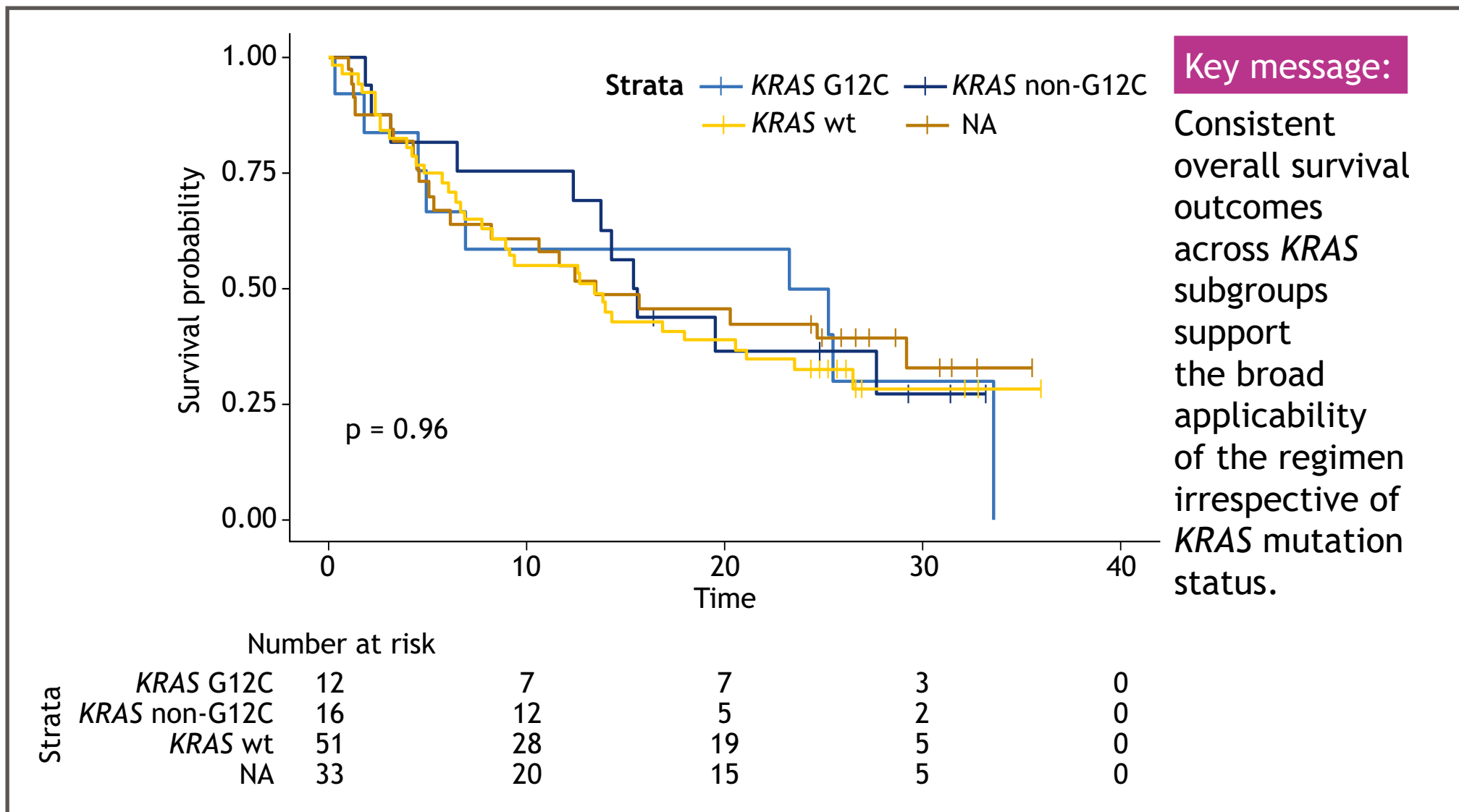
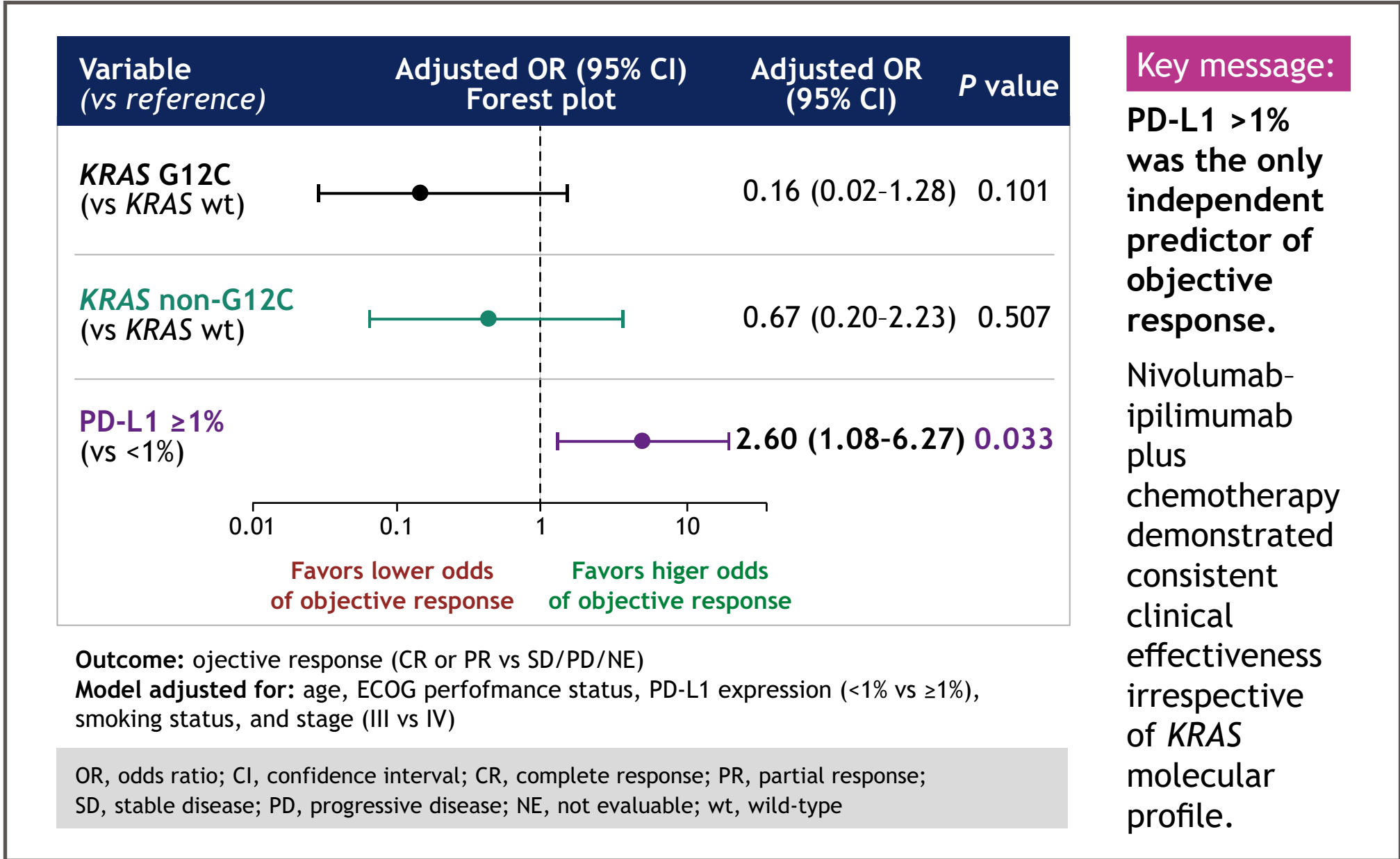


Figure 5. Independent Predictors of Objective Response. Multivariable logistic regression analysis



## Conclusions

- First-line nivolumab plus ipilimumab combined with platinum-based chemotherapy demonstrated consistent real-world effectiveness across *KRAS* molecular subgroups, with comparable PFS and OS outcomes, including in patients with *KRAS* G12C tumors.
- Although patients with *KRAS* G12C tumors had a numerically lower objective response rate, this was not reflected in PFS or OS, indicating that longer-term outcomes were maintained irrespective of *KRAS* mutation status.
- PD-L1 expression ≥1% was independently associated with a higher likelihood of objective response, supporting its role as a practical biomarker for informing treatment expectations.
- Overall, these nationwide real-world findings support the use of nivolumab plus ipilimumab and chemotherapy as an effective first-line treatment option across *KRAS* molecular profiles, with no evidence that treatment selection should be restricted by *KRAS* mutation status.

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