



HAL
open science

Clinical impact of STK11 mutation in advanced-stage non-small cell lung cancer

Pietro Rosellini, Samuel Amintas, Charline Caumont, Remi Veillon, Sigolene Galland-Girodet, Alain Cuguilliere, Laurent Nguyen, Charlotte Domblides, Amandine Gouverneur, Jean-Philippe Merlio, et al.

► To cite this version:

Pietro Rosellini, Samuel Amintas, Charline Caumont, Remi Veillon, Sigolene Galland-Girodet, et al.. Clinical impact of STK11 mutation in advanced-stage non-small cell lung cancer. *European Journal of Cancer*, 2022, 172, pp.85-95. 10.1016/j.ejca.2022.05.026 . hal-03997235

HAL Id: hal-03997235

<https://hal.science/hal-03997235>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Clinical impact of *STK11* mutation in advanced-stage non-small-cell lung cancer

Pietro Rosellini, MD ¹, Samuel Amintas, PharmD ^{1,2}, Charline Caumont, MD ¹, Rémi Veillon, MD ¹, Sigolène Galland-Girodet, MD ³, Alain Cuguillière, MD ⁴, Laurent Nguyen, MD ⁵, Charlotte Domblides, MD, PhD ^{6,7}, Amandine Gouverneur, PharmD, PhD ^{1,2}, Jean-Philippe Merlio, MD, PhD ^{1,2}, Julien Bezin, PharmD, PhD ^{1,2}, and Pierre-Olivier Girodet, MD, PhD ^{1,2}

¹*CHU de Bordeaux, CIC1401, Service de Pharmacologie Médicale, Service de Biologie des tumeurs, Service des Maladies Respiratoires, F-33000 Pessac, France*

²*Univ. Bordeaux, Inserm CIC1401, Inserm CR1219, Inserm U1035, F-33000 Bordeaux, France*

³*Polyclinique Bordeaux Nord Aquitaine, F-33000 Bordeaux, France*

⁴*Bagatelle Hôpital d'instruction des Armées, F-33000 Villenave-d'Ornon, France*

⁵*Clinique Saint Augustin, F-33000 Bordeaux, France*

⁶*Department of Medical Oncology, Hôpital Saint-André, CHU Bordeaux-University of Bordeaux, F-33000 Bordeaux, France*

⁷*ImmunoConcEpt, CNRS UMR 5164, Bordeaux University, F-33000 Bordeaux, France.*

Corresponding author

Pr Pierre-Olivier Girodet

Center for Clinical Investigation - Pharmacology Department

Inserm CIC1401, U1045

Bordeaux University

Zone Nord, bât. 1A, BP36

146 rue Léo Saignat

F33000 Bordeaux, France

Phone: +33 557571560

Fax: +33 557574671

Email: pierre-olivier.girodet@u-bordeaux.fr

Abstract

Background: Mutations in *STK11/LKB1* gene present a negative impact on tumor immune microenvironment, especially with concomitant activating *KRAS* mutation. These recent data may explain a decreased response to immunotherapy treatment in *STK11* mutant non-small cell lung cancer (NSCLC).

Objective: The primary objective is to evaluate, in a real-life setting, overall survival (OS) in NSCLC patients according to the presence of *STK11* mutation. The secondary objective is to assess time to treatment failure (TTF) for the first line of chemotherapy or immunotherapy.

Methods: This observational multicentric study was conducted in Nouvelle-Aquitaine (France), for 24 months. Clinical, histopathological and imagery data were collected in each center while NGS analysis was performed in Bordeaux Hospital University. Patient's data were longitudinally followed from NSCLC diagnosis date to the occurrence of censoring events (therapeutic failure or death, as applicable) or until study end date.

Results: Median OS from the first drug administration was significantly longer for *STK11*^{wt} patients compared to *STK11*^{mut} patients (16.2 months [11 - nr] vs. 4.7 months [2.5 - 9.4]; Log-rank test $P < 0.001$). Presence of *STK11* mutation was significantly associated with shortened OS (RR = 2.26 [1.35 - 3.79], $P = 0.002$). First-line TTF was significantly shorter in *STK11*^{mut} population and the presence of the mutation was significantly associated with an increase in treatment failures (RR = 1.87 [1.21 - 2.89], $P = 0.005$). The type of treatment (chemotherapy, immunotherapy) does not influence the amplitude of reduced TTF in *STK11*^{mut} patients.

Conclusion: The presence of *STK11* mutation is associated to poor prognosis in NSCLC.

Key words: NSCLC; *STK11*; overall survival; TTF; Immunotherapy; *KRAS*

Word count: 2762

Abbreviations used

ALK: anaplastic lymphoma kinase

CCL9: chemokine (C-C motif) ligand 9

CTLA-4: cytotoxic T-lymphocyte-associated protein 4

ECOG PS: Eastern Cooperative Oncology Group Performance Scale

EGFR: epidermal growth factor receptor

ICI: immune checkpoint inhibitors

IL-23: interleukin 23

KRAS: kirsten ras proto-oncogene, GTPase

LKB1: liver kinase B1

NGS: Next Generation Sequencing

NK cells: natural killer cells

NSCLC: non–small-cell lung cancer

ORR: objective response rate

OS: overall survival

PCR: polymerase chain reaction

PD-1: programmed cell death protein 1

PD-L1: programmed cell death-ligand 1

ROS1: c-ros oncogene 1

STK11: serine/threonine kinase 11

TMB: tumor mutational burden

TKI: tyrosine kinase inhibitor

TP53: tumor protein p53

TTF: time to treatment failure

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide and is responsible for 1.76 million deaths per year [1]. In Non-Small Cell Lung Cancer (NSCLC), the identification of oncogenic driver alterations and the understanding of immune checkpoint protein's role lead to the development of targeted-drug therapies and immunotherapy, respectively. While these treatments has provided clinical benefits, the tumors inevitably develop drug resistance. For example, only about 20% of patients have a durable response to immune checkpoint inhibitors (ICI) as monotherapy in advanced or metastatic NSCLC [2,3]. Expression of *programmed death-ligand 1* (PD-L1) on the membrane of tumour is associated with an increased objective response rate (ORR) to PD-1/PD-L1 inhibitors [2–9], although this biomarker is neither sensitive nor specific [2,3,6,7,10–13]. A higher burden of non-synonymous somatic mutations (tumor mutation burden, TMB), is also correlated with increased likelihood of clinical benefit [8,14–16], but its detection is not currently used in routine clinical practice [17]. Thus, the mechanisms of resistance to immunotherapy in NSCLC remains largely unknown and no single biomarker is able to predict responders from non-responders [18].

Recent studies suggest that concomitant genomic alterations in *STK11* (Serine threonine kinase 11), *KRAS* (Kirsten ras proto-oncogene) and *TP53* (tumor protein p53) genes define NSCLC subgroups with distinct immune profiles and possibly different clinical responses to immunotherapy [19,20]. *STK11* gene is a tumour suppressor gene encoding the serine threonine kinase LKB1 (Liver kinase B1) that activate AMPK signalling pathway [21–23]. *STK11* mutations are found in many types of cancer such as NSCLC [24,25] and up to 30% of NSCLC patients present LKB1 inactivation [26]. *KRAS* gene is also a common pro-oncogenic factor in NSCLC, found in approximately 30% of tumors [27,28].

STK11 inactivation in mutated *KRAS* mouse pulmonary adenocarcinoma cell lines confers resistance to anti-PD1 and anti-CTLA4 monoclonal antibodies, decreases PD1 tumor expression and T-cell tumor infiltration [29]. In human pulmonary adenocarcinomas, concomitant *KRAS* and *STK11* mutations lead to a reduction in the T-cell-related transcriptional signature [30]. Indeed, *STK11^{mut}/KRAS^{mut}* lung tumors overproduce CCL9 and IL-23 cytokines inducing macrophages chemotactism and lower recruitment of T lymphocytes, NK cells and type 1 conventional dendritic cells (critical activator of antitumor

immune response) [31]. Such an immunosuppressive mechanism might explain a potential reduction of ICI treatment efficacy [31–33].

To date, few clinical studies have investigated the clinical consequences of *STK11* inactivating mutation in NSCLC, with divergent results [34–37]. In a recent review, the authors pointed out that further studies are needed to understand whether a single *STK11/LKB1* mutation, either associated with *KEAP1* and/or *KRAS* mutations, represents independent negative prognostic factors rather than predictive biomarker for treatment with ICI [38].

The main objective of this study is to evaluate, in real-life treatment situations, overall survival (OS) in NSCLC patients according to the presence of *STK11* mutation. The secondary objective is to assess, in the same study population, the time to treatment failure (TTF) for the first line of chemotherapy or immunotherapy treatment.

Methods

Study design

This observational study was conducted in several centers (Bordeaux University Hospital, Bagatelle Hospital, Bordeaux Nord Aquitaine and Saint Augustin clinics), located in Nouvelle-Aquitaine (France), for 24 months, from June 1st, 2018 to June 1st, 2020. Clinical and imagery data were collected in each center while genetic analysis was performed in a centralized laboratory (Department of Tumor Biology, Bordeaux University Hospital). Patient's data were longitudinally followed from NSCLC diagnosis date to the occurrence of censoring events (therapeutic failure or death, as applicable) or until study end date. Outcome measures were collected in an anonymised and protected database, located on Center for Clinical Investigation (CIC1401 Inserm, Bordeaux University Hospital), using Epi Info software (version 7.2.3.1, CDC, Atlanta, GA, USA). All investigations have been conducted according to the principles expressed in the Declaration of Helsinki. The research protocol was approved by the IRB/IEC of Bordeaux Hospital University (France) before the start of the study.

Participants

Subjects aged more than 18 years were eligible for enrolment if they had a histopathological diagnosis of NSCLC according to the WHO classification of tumours [39]. Main inclusion criteria were stage of locally advanced (not eligible for local treatment) or metastatic disease [40]. Patients received chemotherapy and/or immunotherapy as a first-line treatment. Main exclusion criterion was presence of a druggable genetic alteration (mutation or fusion) in *EGFR*, *ALK* or *ROS1* genes resulting in tyrosine kinase inhibitor (TKI) therapy. Details of inclusion/exclusion criteria and prohibited/authorised concomitant medications are provided in the online data supplement.

Gene mutation analysis

Somatic mutations within 15 genes of interest (*ALK*, *BRAF*, *EGFR*, *ERBB2*, *ERBB4*, *FGFR3*, *KIT*, *KRAS*, *MAP2K1*, *MET*, *NRAS*, *PDGFRA*, *PIK3CA*, *POLE*, *STK11*) were identified using targeted next-generation sequencing (NGS) between June 1st, 2018 and December 1st, 2019. The mutational status were determined by NGS, using a custom Ion Ampliseq panel (Thermo Fisher Scientific, Life Technologies, Les Ullis, France). Libraries were amplified by emulsion PCR (polymerase chain reaction), enriched using automatic system Ion Chef automaton

(Thermo Fisher Scientific) and then sequenced on 530 chips (ThermoFisher Scientific) using an Ion Torrent S5 sequencer (ThermoFisher Scientific) with a high average sequencing depth (greater than 300X). Torrent Suite™ version 5.0 software (ThermoFisher Scientific) was used to perform data analysis. Reads were mapped to the human hg19 reference genome. Data processing, alignment and mutation calling were performed using the Torrent Suite™. The Variant Caller detected point mutations with a variant frequency $\geq 2\%$ for Single Nucleotide Variation (SNV) and $\geq 5\%$ for short insertion/deletion (INDEL). VCF files generated by Variant Caller were annotated by the ANNOVAR [41].

Outcome Measures

The OS (primary endpoint) is defined as the time from the first administration of chemotherapy or immunotherapy to the patient's death, whatever its cause. The TTF (secondary endpoint) is defined as the interval from first-line treatment initiation to treatment failure related to death, disease progression, drug toxicity, addition of a new cancer therapy such as radiation therapy. A complete list of collected data is available in the online data supplement.

Statistical Analysis

Study endpoints were estimated based on the presence of *STK11* mutation, using Kaplan-Meier method and compared by Log-rank test. Prognostic factors were first determined using univariate Cox proportional risk models and then evaluated using time-dependent Cox models. Time-dependent variables are: First-line chemotherapy, first-line immunotherapy, second-line chemotherapy, second-line immunotherapy, period between first and second treatment and period following second-line treatment. For all models, a sensitivity analysis was performed, considering the chemo-immunotherapy combination in chemotherapy class and not in immunotherapy class, as in the main analysis. *Post hoc* analyses were carried out for all models with 4 variable categories: *STK11*^{wt}/*KRAS*^{wt} (Wild-type *STK11* and *KRAS* gene), *STK11*^{wt}/*KRAS*^{mut} (Wild-type *STK11* and Mutated *KRAS* gene), *STK11*^{mut}/*KRAS*^{wt} (Mutated *STK11* and Wild-type *KRAS* gene) and *STK11*^{mut}/*KRAS*^{mut} (Mutated *STK11* and *KRAS* gene). In each model and for each factor tested, the relative risk (RR), 95% confidence interval and the associated *P* value were presented. Imputation methods were not conducted for missing values, which are also presented. Qualitative variables were described in numbers and percentages. Quantitative variables were described in numbers, mean, standard deviation, median, range between 1st (q1) and 3rd (q3) quartiles. Comparisons between groups were

performed by means of two-sided independent t tests for variables with a parametric distribution, Chi-square or Fisher's exact test for comparison of proportions and the Mann-Whitney U test for comparison of nonparametric variables. The statistical analysis was performed using SAS software (SAS Institute, version 9.4, Cary, NC, USA).

Results

Study population

531 patients affected with NSCLC were identified in our NGS database. According to inclusion/non inclusion criteria, 159 patients were included in the study population for analysis (Figure 1).

Patients characteristics according to *STK11* mutational status are summarised in Table 1 and supplementary Table 1. In the studied population, patients, with advanced disease by definition, have higher ECOG score as compared to baseline population (score 2: 24.5% vs. 15.3%) and an increased frequency of metastases at diagnosis (81.8% vs. 51.1%). No significant differences were found for PD-L1 receptor exposure rate between the 2 populations.

Data of NGS analysis are shown in Supplementary Table 2. In the baseline population, 459 patients (86.4%) were *STK11*^{wt}, while 72 (13.6%) were *STK11*^{mut} (one patient had mutations in 2 exons). In the studied population, 111 patients (69.8 %) had at least one mutation and 48 patients (30.2 %) had no genetic mutation. In the study population, there was 122 (76.7%) *STK11*^{wt} and 37 (23.3%) *STK11*^{mut}. The median time of follow-up was 8.5 months (interval q1-q3: 3 – 13.6).

Median age at diagnosis of *STK11*^{mut} patients was 62.7 years (range q1-q3: 53.3 - 69.7), comparable to *STK11*^{wt} patients. ECOG score, proportion of metastatic patients at the time of diagnosis, and histological characteristics were not different between the two groups, despite the absence of squamous cell tumours in *STK11*^{mut} patients. PD-L1 receptor expression on cancer cells was higher in *STK11*^{wt} ($\geq 50\%$ in 37.7% vs. 21.6%), while the presence of *KRAS* mutation was statistically higher in *STK11*^{mut} (64.8% vs. 40.2%; $P = 0.008$).

In *STK11*^{mut} group, 31 patients (83.8%) received first-line chemotherapy and 6 (16.2%) immunotherapy. Among *STK11*^{wt} patients, 68% received chemotherapy, 26.2% immunotherapy and 5.8% a combination of chemotherapy and immunotherapy. Following first-line therapy failure, 17 patients (46%) *STK11*^{mut} and 62 (50.8%) *STK11*^{wt} received a second-line treatment. Patient characteristics, according to mutations in *STK11* and *KRAS* genes, are shown in Supplementary Table 3.

Overall survival

The median OS was 12.1 months (CI: 8.8 – 18, interval q1-q3: 3.34 – nr) in the studied population. Seventy-nine patients died (49.7%), among which 53 in *STK11*^{wt} group (43.4%) and 26 in *STK11*^{mut} group (70.3%) (Figure 2). Median OS was significantly shorter in *STK11*^{mut} (4.7 months, 95% CI: 2.5 - 9.4 vs 16.2 months, 95% CI: 11 - nr; $P < 0.001$) (Figure 2A). Similar results were obtained for co-mutations *STK11* and *KRAS* ($P = 0.0139$), (Figure 3A).

In Cox multivariate time-dependent model (Table 2), *STK11* gene mutation was significantly associated with a reduced OS (RR = 2.26 [1.35 - 3.79], $p = 0.002$). In *STK11*^{mut}, higher age at diagnosis of NSCLC was associated with a longer survival (RR = 0.93 [0.90 - 0.93], $P = 0.026$). *Post-hoc* analysis on the impact of double mutation *STK11* and *KRAS* showed comparable results, which is in favor of the predominant effect of *STK11* mutation on NSCLC prognosis (Supplementary Table 4).

Time to Treatment Failure

The median duration of first-line treatment was 3.2 months (q1-q3 interval: 1.4 - 8.2; mean: 5.3 months) in the studied population. In *STK11*^{wt} group, 98 therapeutic failures (80.3%) and 24 censures (19.7%) were observed, compared to 33 failures (89.2%) and 4 censures (10.8%) in *STK11*^{mut} group. Kaplan-Meier analysis showed that *STK11*^{wt} had a significantly longer TTF (median: 3.9 months; 95% CI: 3.1 - 5.9 vs. median: 2.2 months; 95% CI: 1.2 - 3.5; $P = 0.031$) (Figure 2B).

Multivariate analysis, adjusted to age at diagnosis, sex, smoking exposure, *KRAS* mutation, metastatic status at diagnosis, ECOG PS score at diagnosis and type of treatment, confirmed that *STK11* mutation was associated with an increased risk of first-line therapy failure (RR = 1.87 [1.21 - 2.89], $P = 0.005$), (Table 3). Although the number of patients receiving ICI was low, immunotherapy treatment or the combination of immuno-chemotherapy might be a protective factor against failure of first-line treatment in the studied population (RR = 0.37 [0.23 – 0.59], $P < 0.001$) and in *STK11*^{wt} group, conversely to *STK11*^{mut} group (Table 3).

Post-hoc analysis showed that reduced time to treatment failure is mainly dependent on *STK11* mutation rather than *STK11*-*KRAS* double mutation (Figure 3B and Supplementary Table 5).

Discussion

This study demonstrated that the presence of *STK11* mutation is associated to reduction in OS and TTF in advanced-stage NSCLC. This is, to our knowledge, the first study that evaluates the clinical impact of this gene mutation in a real-life cohort.

To date, the role of *STK11* mutation in NSCLC prognosis remains a matter of debate. In early-stage NSCLC, the reduction in STK11 protein expression has been described as an independent negative prognostic factor for survival [34,35]. By contrast, tumour specimens analysis from 221 surgically resected stage I and II NSCLC demonstrated no difference in survival between *STK11*^{mut} tumors (n=23; 10.4%) and *STK11*^{wt} tumors (n=198; 89.6%, $P = 0.17$) [36]. Similar pattern was found among 302 patients with advanced NSCLC treated with chemotherapy [37]. However, a retrospective study conducted on 2276 patients with NSCLC showed that *STK11* mutations were independently associated to poor prognosis whatever the type of treatment and regardless of the presence of *KRAS* mutations [42]. Moreover, preliminary results from the Keynote 042 trial reinforced the hypothesis that *STK11* mutation is a negative prognostic factor in NSCLC [43], which is consistent with the results obtained in our study on overall survival (primary outcome).

This observational study was not designed to compare the efficacy of chemotherapy and immunotherapy among patients with or without *STK11* mutation. Analysis of TTF (secondary outcome) provides useful information but should be interpreted with caution. First-line immunotherapy was a protective factor compared to first-line chemotherapy in the whole studied population. A similar trend was observed in *STK11*^{wt} group, although patients had higher level of PD-L1 expression. In *STK11*^{mut} group, TTF is reduced whatever the first-line of treatment administered. Thus, response to treatment is altered in *STK11*^{mut} patients either treated with chemotherapy or ICI, which is probably related to the consequences of STK11 mutation on NSCLC pathogenesis and prognostic rather than hypothetical mechanisms of resistance to drugs.

Although this study was conducted in real-life conditions, we paid a special attention to the representativeness of study participants. For example, no *STK11*^{mut} patient have been diagnosed with squamous cell histotype of NSCLC. It should be noted that the proportion of patients affected with squamous cell carcinoma is low, around 8%, in *STK11*^{mut} NSCLC ([37]), and that patients with an epidermoid histotype represented only 2.8% of subjects in our database. In *STK11*^{mut}, higher age at diagnosis was associated with a longer survival, as

younger patients were more likely to have aggressive diseases, rather than older patients. The proportion of *STK11*^{mut} patients in our cohort (23.3%) is consistent with those in the most recent studies on this topic [30,44]. However, we did not detect a significant correlation between the presence of *STK11* mutation, histotype ($P = 0.8$) and smoking exposure ($P = 0.2$), which was found by other authors [36,45–47]. Lastly, PD-L1 expression in the overall cohort was similar to previous study [18], although we report lower levels in *STK11*^{mut} patients.

In a *post-hoc* analysis, the effect of concomitant presence of *STK11* and *KRAS* mutations was assessed, mainly due to the abundant literature in this field of interest [19,20,44,48]. Briefly, the presence of *KRAS* mutation is not associated to a clinically important difference between groups. This finding strengthens the idea that the main results observed in our study are related to the presence of *STK11* mutation. Further studies are needed to determine if co-occurring genomic alterations in *STK11* and *KRAS* induce therapeutic vulnerabilities [38]. In addition, genomic position of *STK11* mutation, particularly the exon including the mutation, has been described as an independent prognostic factor in NSCLC [44]. Nonetheless, we paid particular attention to avoid multiple subgroups analysis. For example, the number of *STK11*^{mut} subjects was too low to compare OS and TTF among mutations subgroups (Supplementary Table 2). Although the NGS panel used for this study revealed the presence of mutations in the 15 genes described above, it remains possible that other mutations may have influenced our clinical endpoints, notably *KEAP1* and *TP53*, respectively involved in immunoresistance mechanisms and sensitivity to PD-1 blockade. Moreover, the impact of mutations of interest cannot be assessed among each chemotherapy and immunotherapy drug. Indeed, all *STK11*^{mut} patients who received first-line immunotherapy were treated with pembrolizumab, while nivolumab (n=4), pembrolizumab (n=2) and atezolizumab (n=6) were only administered as second-line therapy. Although this study is observational, all patients cases were discussed in a unique standardized multidisciplinary meeting and related therapeutic decisions were made according to international recommendations. Moreover, somatic mutations analysis were performed at the same Molecular Genetics Laboratory at in Bordeaux University Hospital.

Conclusion

The presence of STK11 mutation results in significant clinical impact in advanced-stage NSCLC. Despite its limitations, this real-life study confirms that STK11 mutation is a negative prognostic factor in NSCLC rather than a predictive marker of treatment response. Indeed, whatever the first line systemic therapy (chemotherapy or immunotherapy), STK11 mutation is also associated to reduced TTF. The study results suggest that additional prospective studies are needed to define the best treatment strategy for those patients at higher risk of morbidity and mortality. Further developments in immunotherapy and therapies targeting STK11 are research priorities to improve clinical outcomes for NSCLC patients.

Acknowledgments

We thank Mrs Ana-Jarne Munoz for her assistance in statistical analysis and Dr Sebastien Cossin for his assistance in hospital database management.

We thank Dr Alain Cuguillière (Robert Picque Hospital, Bordeaux, France), Dr Charlotte Domblides (Bordeaux University Hospital, Bordeaux, France) and Dr Laurent Nguyen (Saint Augustin clinic, Bordeaux, France) for their participation.

Funding: None

References

- [1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424. <https://doi.org/10.3322/caac.21492>.
- [2] Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–50. [https://doi.org/10.1016/S0140-6736\(15\)01281-7](https://doi.org/10.1016/S0140-6736(15)01281-7).
- [3] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:1627–39. <https://doi.org/10.1056/NEJMoa1507643>.
- [4] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:123–35. <https://doi.org/10.1056/NEJMoa1504627>.
- [5] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–65. [https://doi.org/10.1016/S0140-6736\(16\)32517-X](https://doi.org/10.1016/S0140-6736(16)32517-X).
- [6] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46. [https://doi.org/10.1016/S0140-6736\(16\)00587-0](https://doi.org/10.1016/S0140-6736(16)00587-0).
- [7] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–28. <https://doi.org/10.1056/NEJMoa1501824>.
- [8] Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2415–26. <https://doi.org/10.1056/NEJMoa1613493>.
- [9] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016;17:1497–508. [https://doi.org/10.1016/S1470-2045\(16\)30498-3](https://doi.org/10.1016/S1470-2045(16)30498-3).
- [10] Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer* 2016;16:275–87. <https://doi.org/10.1038/nrc.2016.36>.
- [11] Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014;515:568–71. <https://doi.org/10.1038/nature13954>.
- [12] Herbst RS, Soria J-C, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014;515:563–7. <https://doi.org/10.1038/nature14011>.
- [13] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;375:1823–33. <https://doi.org/10.1056/NEJMoa1606774>.
- [14] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348:124–8. <https://doi.org/10.1126/science.aaa1348>.
- [15] Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al.

- Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014;371:2189–99. <https://doi.org/10.1056/NEJMoa1406498>.
- [16] Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science* 2015;350:207–11. <https://doi.org/10.1126/science.aad0095>.
- [17] Wu Y, Xu J, Du C, Wu Y, Xia D, Lv W, et al. The Predictive Value of Tumor Mutation Burden on Efficacy of Immune Checkpoint Inhibitors in Cancers: A Systematic Review and Meta-Analysis. *Front Oncol* 2019;9:1161. <https://doi.org/10.3389/fonc.2019.01161>.
- [18] Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF, et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov* 2018;8:822–35. <https://doi.org/10.1158/2159-8290.CD-18-0099>.
- [19] Skoulidis F, Byers LA, Diao L, Papadimitrakopoulou VA, Tong P, Izzo J, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov* 2015;5:860–77. <https://doi.org/10.1158/2159-8290.CD-14-1236>.
- [20] Aredo JV, Padda SK, Kunder CA, Han SS, Neal JW, Shrager JB, et al. Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes. *Lung Cancer* 2019;133:144–50. <https://doi.org/10.1016/j.lungcan.2019.05.015>.
- [21] Nakada D, Saunders TL, Morrison SJ. Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. *Nature* 2010;468:653–8. <https://doi.org/10.1038/nature09571>.
- [22] Karuman P, Gozani O, Odze RD, Zhou XC, Zhu H, Shaw R, et al. The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death. *Mol Cell* 2001;7:1307–19. [https://doi.org/10.1016/s1097-2765\(01\)00258-1](https://doi.org/10.1016/s1097-2765(01)00258-1).
- [23] Spicer J, Ashworth A. LKB1 kinase: master and commander of metabolism and polarity. *Curr Biol* 2004;14:R383–385. <https://doi.org/10.1016/j.cub.2004.05.012>.
- [24] Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res* 2002;62:3659–62.
- [25] Contreras CM, Akbay EA, Gallardo TD, Haynie JM, Sharma S, Tagao O, et al. Lkb1 inactivation is sufficient to drive endometrial cancers that are aggressive yet highly responsive to mTOR inhibitor monotherapy. *Dis Model Mech* 2010;3:181–93. <https://doi.org/10.1242/dmm.004440>.
- [26] Matsumoto S, Iwakawa R, Takahashi K, Kohno T, Nakanishi Y, Matsuno Y, et al. Prevalence and specificity of LKB1 genetic alterations in lung cancers. *Oncogene* 2007;26:5911–8. <https://doi.org/10.1038/sj.onc.1210418>.
- [27] Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. *Nat Rev Cancer* 2003;3:459–65. <https://doi.org/10.1038/nrc1097>.
- [28] Rodenhuis S, van de Wetering ML, Mooi WJ, Evers SG, van Zandwijk N, Bos JL. Mutational activation of the K-ras oncogene. A possible pathogenetic factor in adenocarcinoma of the lung. *N Engl J Med* 1987;317:929–35. <https://doi.org/10.1056/NEJM198710083171504>.
- [29] Koyama S, Akbay EA, Li YY, Aref AR, Skoulidis F, Herter-Sprue GS, et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. *Cancer Res* 2016;76:999–1008. <https://doi.org/10.1158/0008-5472.CAN-15-1439>.
- [30] Schabath MB, Welsh EA, Fulp WJ, Chen L, Teer JK, Thompson ZJ, et al. Differential association of STK11 and TP53 with KRAS mutation-associated gene expression,

- proliferation and immune surveillance in lung adenocarcinoma. *Oncogene* 2016;35:3209–16. <https://doi.org/10.1038/onc.2015.375>.
- [31] Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. *Cell* 2018;172:1022-1037.e14. <https://doi.org/10.1016/j.cell.2018.01.004>.
- [32] Spranger S, Luke JJ, Bao R, Zha Y, Hernandez KM, Li Y, et al. Density of immunogenic antigens does not explain the presence or absence of the T-cell-inflamed tumor microenvironment in melanoma. *Proc Natl Acad Sci U S A* 2016;113:E7759–68. <https://doi.org/10.1073/pnas.1609376113>.
- [33] Sánchez-Paulete AR, Cueto FJ, Martínez-López M, Labiano S, Morales-Kastresana A, Rodríguez-Ruiz ME, et al. Cancer Immunotherapy with Immunomodulatory Anti-CD137 and Anti-PD-1 Monoclonal Antibodies Requires BATF3-Dependent Dendritic Cells. *Cancer Discov* 2016;6:71–9. <https://doi.org/10.1158/2159-8290.CD-15-0510>.
- [34] Liu S, Miao Y, Fan C, Liu Y, Yu J, Zhang Y, et al. Clinicopathologic correlations of liver kinase B1, E-cadherin, and N-cadherin expression in non-small cell lung cancer. *Appl Immunohistochem Mol Morphol* 2013;21:334–40. <https://doi.org/10.1097/PAI.0b013e31826b128b>.
- [35] Jiang L, Liang X, Liu M, Wang W, Ma J, Guo Q, et al. Reduced expression of liver kinase B1 and Beclin1 is associated with the poor survival of patients with non-small cell lung cancer. *Oncol Rep* 2014;32:1931–8. <https://doi.org/10.3892/or.2014.3432>.
- [36] Koivunen JP, Kim J, Lee J, Rogers AM, Park JO, Zhao X, et al. Mutations in the LKB1 tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. *Br J Cancer* 2008;99:245–52. <https://doi.org/10.1038/sj.bjc.6604469>.
- [37] Facchinetti F, Bluthgen MV, Tergemina-Clain G, Faivre L, Pignon J-P, Planchard D, et al. LKB1/STK11 mutations in non-small cell lung cancer patients: Descriptive analysis and prognostic value. *Lung Cancer* 2017;112:62–8. <https://doi.org/10.1016/j.lungcan.2017.08.002>.
- [38] Di Federico A, De Giglio A, Parisi C, Gelsomino F. STK11/LKB1 and KEAP1 mutations in non-small cell lung cancer: Prognostic rather than predictive? *Eur J Cancer* 2021;157:108–13. <https://doi.org/10.1016/j.ejca.2021.08.011>.
- [39] Travis W, Brambilla E, Burke A, Marx A, Nicholson A. WHO Classification of Tumours of the Lung, Pleura, Thymus and Herat. vol. 7. 4th ed. n.d.
- [40] Brierley J, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. Eighth ed. Oxford, UK ; Hoboken, NJ: John Wiley & Sons, Inc; 2017. n.d.
- [41] Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* 2010;38:e164. <https://doi.org/10.1093/nar/gkq603>.
- [42] Papillon-Cavanagh S, Doshi P, Dobrin R, Szustakowski J, Walsh AM. STK11 and KEAP1 mutations as prognostic biomarkers in an observational real-world lung adenocarcinoma cohort. *ESMO Open* 2020;5:e000706. <https://doi.org/10.1136/esmoopen-2020-000706>.
- [43] Cho BC, Lopes G, Kowalski DM, Kasahara K, Wu Y-L, Castro G, et al. Abstract CT084: Relationship between *STK11* and *KEAP1* mutational status and efficacy in KEYNOTE-042: pembrolizumab monotherapy versus platinum-based chemotherapy as first-line therapy for PD-L1-positive advanced NSCLC. *Tumor Biology, American Association for Cancer Research*; 2020, p. CT084–CT084. <https://doi.org/10.1158/1538-7445.AM2020-CT084>.
- [44] Pécuchet N, Laurent-Puig P, Mansuet-Lupo A, Legras A, Alifano M, Pallier K, et al. Different prognostic impact of STK11 mutations in non-squamous non-small-cell lung cancer. *Oncotarget* 2017;8:23831–40. <https://doi.org/10.18632/oncotarget.6379>.

- [45] Carretero J, Medina PP, Pio R, Montuenga LM, Sanchez-Cespedes M. Novel and natural knockout lung cancer cell lines for the LKB1/STK11 tumor suppressor gene. *Oncogene* 2004;23:4037–40. <https://doi.org/10.1038/sj.onc.1207502>.
- [46] Fang R, Zheng C, Sun Y, Han X, Gao B, Li C, et al. Integrative genomic analysis reveals a high frequency of LKB1 genetic alteration in Chinese lung adenocarcinomas. *J Thorac Oncol* 2014;9:254–8. <https://doi.org/10.1097/JTO.0000000000000056>.
- [47] Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008;455:1069–75. <https://doi.org/10.1038/nature07423>.
- [48] La Fleur L, Falk-Sörqvist E, Smeds P, Berglund A, Sundström M, Mattsson JS, et al. Mutation patterns in a population-based non-small cell lung cancer cohort and prognostic impact of concomitant mutations in KRAS and TP53 or STK11. *Lung Cancer* 2019;130:50–8. <https://doi.org/10.1016/j.lungcan.2019.01.003>.

Tables

Table 1

	Study population (n = 159)	<i>STK11</i> ^{mut} (n = 37)	<i>STK11</i> ^{wt} (n = 122)	<i>P</i> values
Age at diagnosis				
Median	62.9	62.7	63.5	
Interval q1 – q3	53.3 - 70.7	53.3 – 69.7	53.4 – 70.9	
Sex				0.69
Men	99 (62.3)	22 (59.5)	77 (63.1)	
Women	60 (37.7)	15 (40.5)	45 (36.9)	
Histology				0.57
Adenocarcinoma	130 (81.7)	30 (81.1)	100 (82)	
Epidermoid	3 (1.9)	0	3 (2.5)	
Other	26 (16.4)	7 (18.9)	19 (15.5)	
ECOG PS score				0.64
0	29 (18.3)	5 (13.5)	24 (19.7)	
1	83 (52.2)	20 (54.1)	63 (51.6)	
2	39 (24.5)	11 (29.7)	28 (23)	
3	8 (5)	1 (2.7)	7 (5.7)	
Metastasis at diagnosis				0.27
Yes	130 (81.8)	28 (75.7)	102 (83.6)	
No	29 (18.2)	9 (24.3)	20 (16.4)	
PDL1				0.14
< 1 %	56 (35.2)	17 (46)	39 (32)	
1 – 49 %	47 (29.6)	12 (32.4)	35 (28.7)	
≥ 50 %	54 (34)	8 (21.6)	46 (37.7)	
Missing	2 (1.2)	0	2 (1.6)	
<i>KRAS</i>				< 0.01
Muted	73 (45.9)	24 (64.8)	49 (40.2)	
wt	86 (54.1)	13 (35.2)	73 (59.8)	
Smoking status				0.22
Current smoker	80 (50.3)	18 (41.9)	62 (50.8)	
Ex-smoker	67 (42.1)	19 (55.8)	48 (39.4)	
Non-smoker	7 (4.4)	0	7 (5.7)	
Missing	5 (3.2)	0	5 (4.1)	
First-line treatment				0.11
Chemotherapy	114 (71.7)	31 (83.8)	83 (68)	
Immunotherapy	38 (23.9)	6 (16.2)	32 (26.2)	
Combined chemo-immunotherapy	7 (4.4)	0	7 (5.8)	
Second-line treatment				0.76
Yes	79 (49.7)	17 (46)	62 (50.8)	
Chemotherapy	21 (26.6)	5 (29.4)	16 (25.8)	
Immunotherapy	58 (73.4)	12 (70.6)	46 (74.2)	
No	80 (50.3)	20 (54)	60 (49.2)	
Dead	37 (46.3)	14 (70)	23 (38.4)	
Censored	43 (53.7)	6 (30)	37 (61.6)	
Death on 2 Jun 2020				< 0.01
Yes	79 (49.7)	26 (70.3)	53 (43.4)	
Censored	80 (50.3)	11 (29.7)	69 (56.6)	

Characteristics of the study population.

Data are presented as n (%), except age at diagnosis. ECOG PS, Eastern Cooperative Oncology Group Performance Scale; *KRAS*: Kirsten Rat Sarcoma virus; mut: Mutant; PDL1, Programmed cell death ligand 1; *STK11*, Serine/threonine kinase 11; wt: Wild-Type. *P* values were calculated with the use of a two-sided

independent t-test for variables with a parametric distribution and Fisher's exact test for comparison of proportions and the Mann-Whitney U test for comparison of nonparametric variables.

Table 2

	Study population (n = 154)		<i>STK11</i> ^{wt} (n = 117)		<i>STK11</i> ^{mut} (n = 37)	
	RR [95% IC]	<i>P</i> values	RR [95% IC]	<i>P</i> values	RR [95% IC]	<i>P</i> values
<i>STK11</i> ^{mut} vs. <i>STK11</i> ^{wt}	2.26 [1.35 – 3.79]	0.002	-	-	-	-
Ex-smoker vs. current smoker	0.59 [0.34 – 1.04]	0.067	0.41 [0.20 – 0.82]	0.012	1.29 [0.450 – 3.680]	0.639
Non-smoker vs. current smoker	0.39 [0.11 – 1.31]	0.127	0.20 [0.05 – 0.76]	0.019	-	-
Women vs. men	1.34 [0.81 – 2.20]	0.255	1.78 [0.93 – 3.39]	0.081	1.24 [0.492 – 3.100]	0.653
Age at diagnosis (per year)	1.01 [0.99 – 1.03]	0.501	1.03 [1.00 – 1.07]	0.035	0.93 [0.895 – 0.933]	0.026
<i>KRAS</i> ^{mut} vs. <i>KRAS</i> ^{wt}	1.06 [0.65 – 1.73]	0.815	0.88 [0.47 – 1.63]	0.675	2.46 [0.868 – 6.987]	0.090
Metastasis at diagnosis	3.48 [1.54 – 7.86]	0.003	4.16 [1.24 – 13.89]	0.021	3.15 [0.832 – 11.909]	0.091
ECOG PS 2-3 scores vs. ECOG PS 0-1 scores	4.73 [2.79 – 8.00]	< 0.001	4.53 [2.35 – 8.75]	< 0.001	5.82 [2.101 – 16.132]	< 0.001
First-line chemotherapy	2.10 [0.86 – 5.16]	0.106	1.80 [0.51 – 6.31]	0.361	3.03 [0.728 – 12.581]	0.128
First-line immunotherapy	0.82 [0.25 – 2.68]	0.738	0.54 [0.11 – 2.72]	0.452	1.93 [0.270 – 13.853]	0.511
Second-line chemotherapy	2.41 [0.52 – 11.25]	0.265	3.15 [0.43 – 23.33]	0.261	6.03 [0.372 – 97.574]	0.206
Second-line immunotherapy	6.47 [2.03 – 20.58]	0.002	5.07 [1.01 – 25.45]	0.048	13.96 [1.966 – 99.180]	0.008
Period between first and second treatment	8.36 [2.73 – 25.61]	< 0.001	7.27 [1.58 – 33.34]	0.011	26.68 [3.062 – 232.58]	0.003
Period following second-line treatment	23.33 [7.09 – 76.80]	< 0.001	25.80 [5.07 – 131.34]	< 0.001	116.26 [7.560 – 1787.6]	< 0.001

Time-dependent Cox analysis of the overall survival in the study population and according to *STK11* status.

ECOG PS, Eastern Cooperative Oncology Group Performance Scale; KRAS: Kirsten Rat Sarcoma virus; mut: Mutant; PDL1, Programmed cell death ligand 1; *STK11*, Serine/threonine kinase 11; wt: Wild-Type.

Prognostic factors were first determined using univariate Cox proportional risk models and then evaluated using time-dependent Cox models.

Table 3

	Study population (n = 154)		<i>STK11</i> ^{wt} (n = 117)		<i>STK11</i> ^{mut} (n = 37)	
	RR [95% IC]	<i>P</i> values	RR [95% IC]	<i>P</i> values	RR [95% IC]	<i>P</i> values
<i>STK11</i> ^{mut} vs. <i>STK11</i> ^{wt}	1.87 [1.21 - 2.89]	0.005	-	-	-	-
Ex-smoker vs. current smoker	0.96 [0.63 - 1.49]	0.870	0.75 [0.45 - 1.28]	0.292	1.46 [0.61 – 3.51]	0.402
Non-smoker vs. current smoker	1.29 [0.56 - 3.01]	0.549	1.15 [0.47 - 2.80]	0.760	-	-
Women vs. men	1.28 [0.85 - 1.92]	0.249	1.21 [0.71 - 2.05]	0.485	1.35 [0.59 – 3.11]	0.474
Age at diagnosis (per year)	1.00 [0.98 - 1.02]	0.723	1.00 [0.98 - 1.02]	0.723	1.00 [0.98 - 1.02]	0.723
<i>KRAS</i> ^{mut} vs. <i>KRAS</i> ^{wt}	0.95 [0.65 - 1.39]	0.790	1.00 [0.64 - 1.57]	0.990	1.22 [0.53 – 2.82]	0.641
Metastasis at diagnosis	3.11 [1.83 - 5.29]	< 0.001	2.72 [1.40 - 5.32]	0.003	4.19 [1.55 – 11.31]	0.005
ECOG PS 2-3 scores vs. ECOG PS 0-1 scores	2.54 [1.69 - 3.81]	< 0.001	2.13 [1.31 - 3.45]	0.002	4.11 [1.69 – 9.97]	0.002
First-line immunotherapy vs. first-line chemotherapy	0.37 [0.23 - 0.59]	< 0.001	0.35 [0.20 - 0.60]	< 0.001	0.46 [0.15 – 1.41]	0.174

Cox analysis of the time to treatment failure in the study population and according to *STK11* status.

ECOG PS, Eastern Cooperative Oncology Group Performance Scale; KRAS: Kirsten Rat Sarcoma virus; mut: Mutant; PDL1, Programmed cell death ligand 1; *STK11*, Serine/threonine kinase 11; wt: Wild-Type.

Prognostic factors were first determined using univariate Cox proportional risk models and then evaluated using Cox models.

Figures

Figure 1

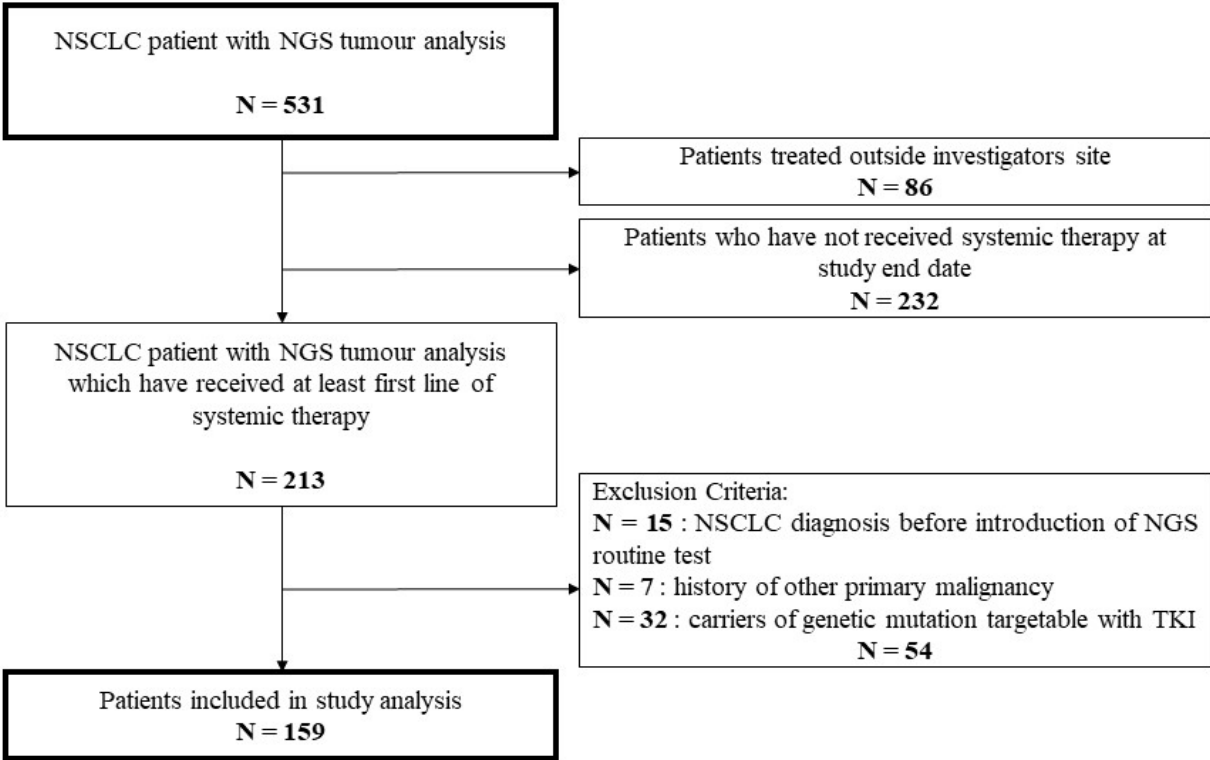
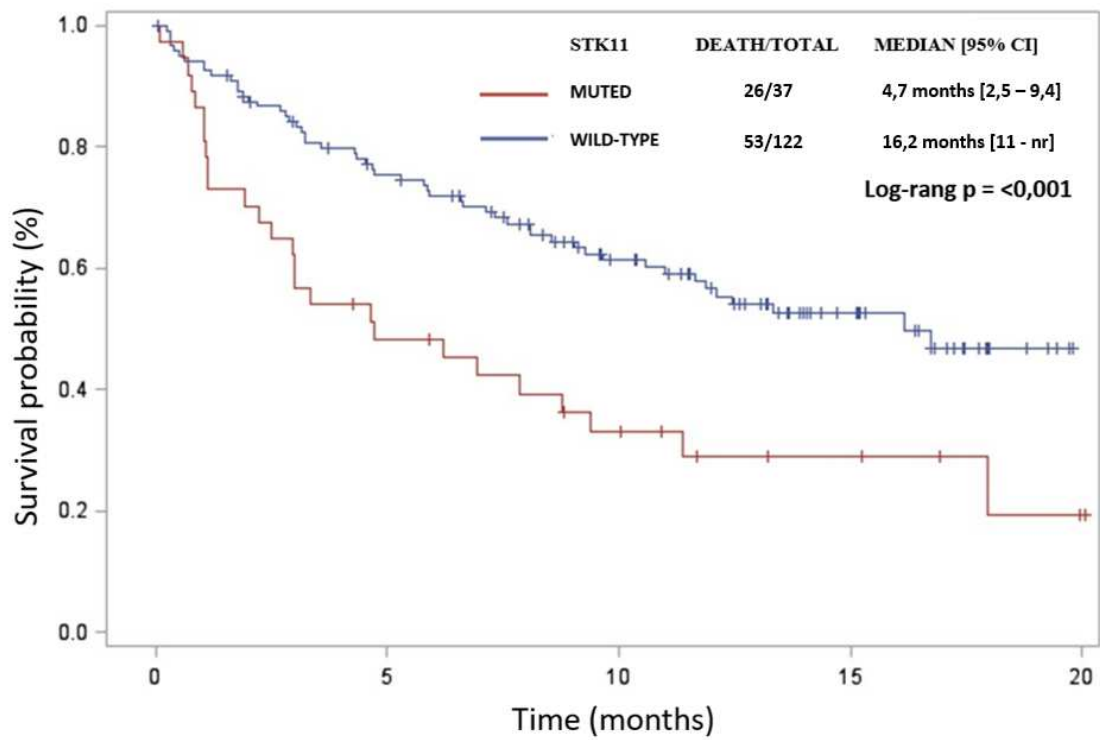


Figure 2

A



B

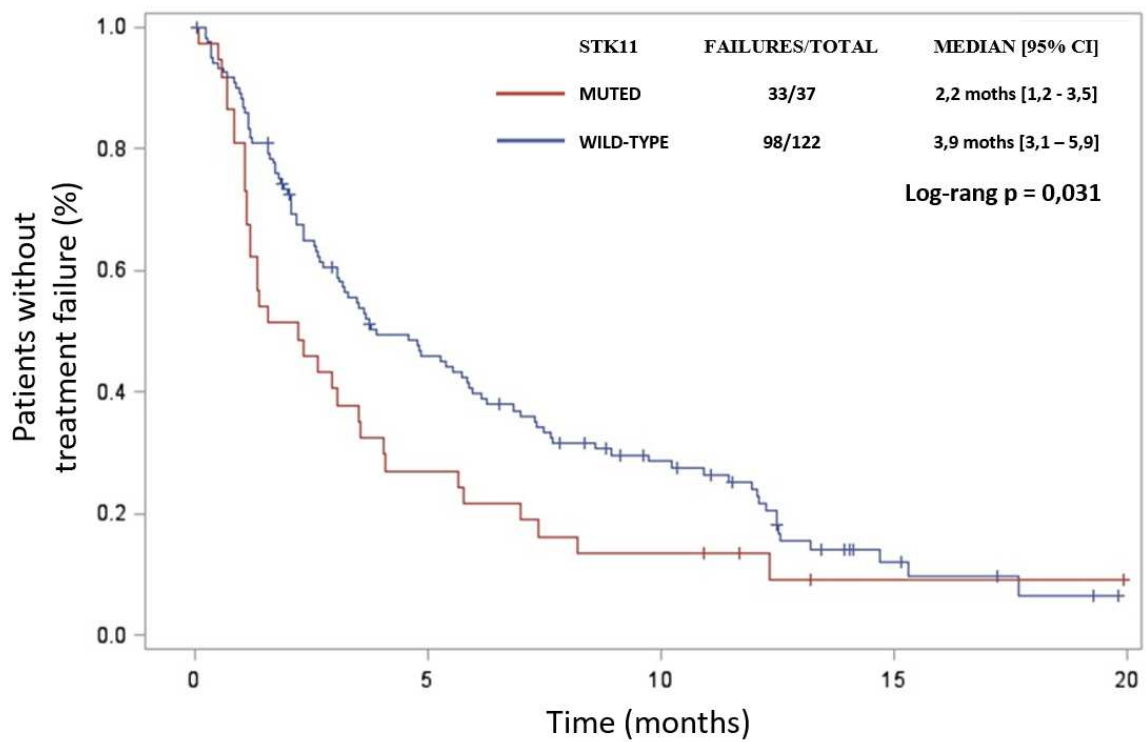
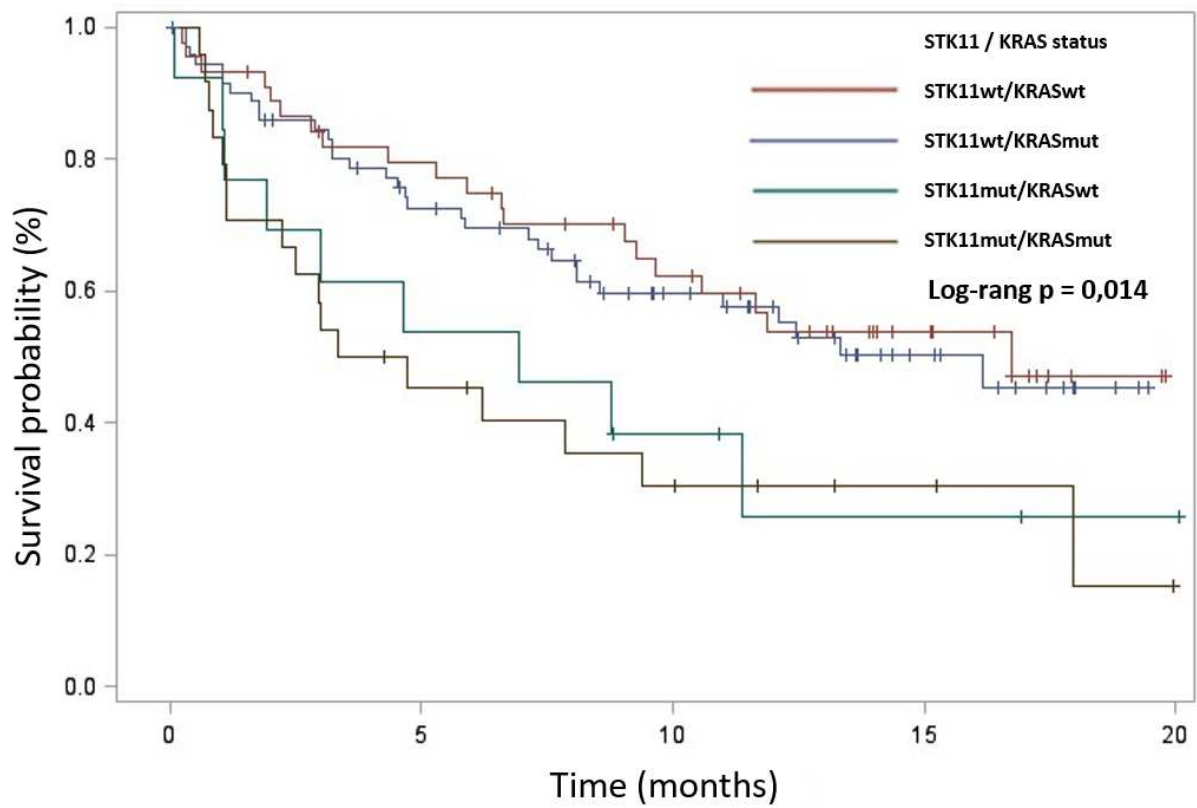


Figure 3

A



B

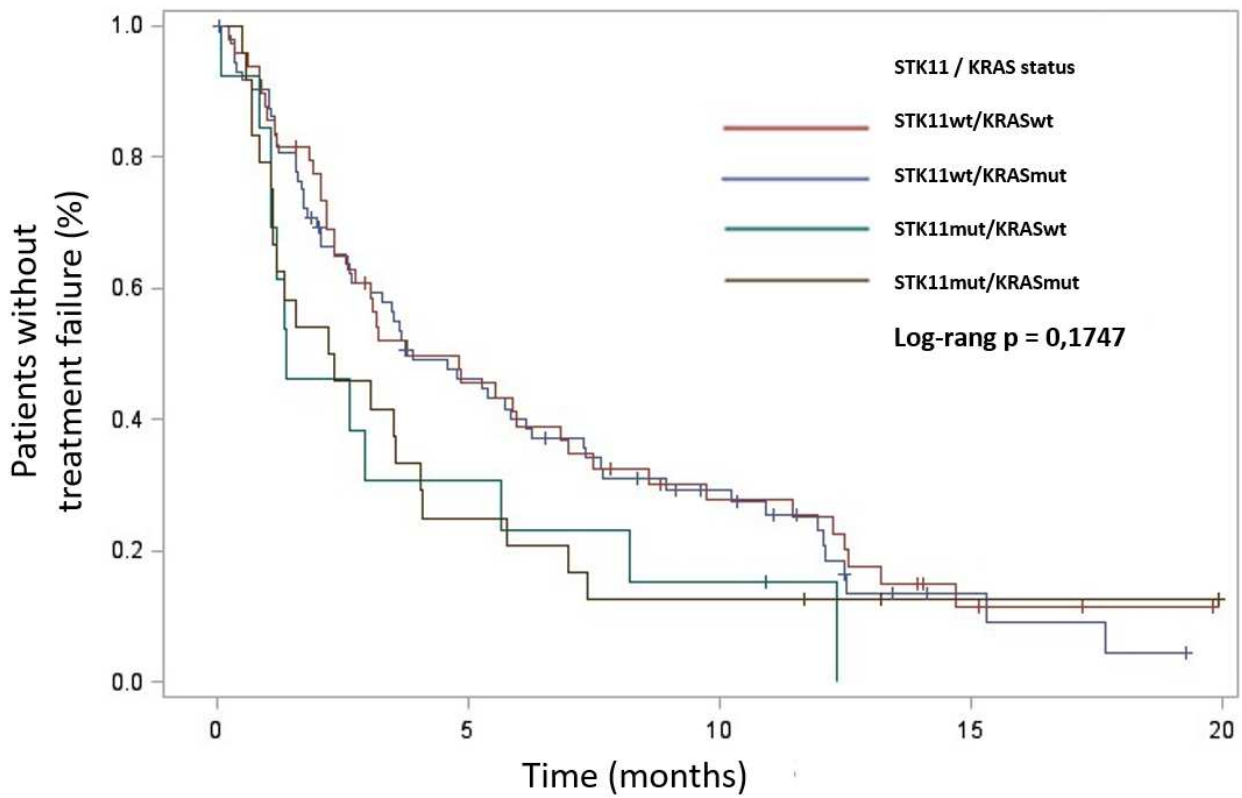


Figure legends

Figure 1

Flowchart describing recruitment of patients.

NGS, Next Generation Sequencing; NSCLC, non–small-cell lung cancer; TKI, tyrosine kinase inhibitor.

232 patients did not received systemic therapy for the following reasons: Early stage of NSCLC, patients treated with thoracic radiotherapy only and palliative care.

Figure 2

Kaplan-Meier analysis of the overall survival (A) and the time to treatment failure (B) according to *STK11* status.

Blue curve: *STK11*^{wt}. Red curve: *STK11*^{mut}.

CI, Confidence interval; STK11, Serine/threonine kinase 11.

P values were calculated using Log-rank test.

Figure 3

Kaplan-Meier analysis of the overall survival (A) and the time to treatment failure (B) according to *STK11* and *KRAS* status.

Red curve: *STK11*^{wt} / *KRAS*^{wt}. Blue curve: *STK11*^{wt} / *KRAS*^{mut}. Green curve: *STK11*^{mut} / *KRAS*^{wt}. Brown curve: *STK11*^{mut} / *KRAS*^{mut}.

KRAS: Kirsten Rat Sarcoma virus; mut: Mutant; STK11, Serine/threonine kinase 11; wt: Wild-Type.

P values were calculated using Log-rank test.