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Original Article

Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315)

Frank Griesinger [a,*,1], Wilfried Eberhardt [b,1], Arnd Nusch [c], Marcel Reiser [d], Mark-Oliver Zahn [e], Christoph Maintz [f], Christiane Bernhardt [g], Christoph Losem [h], Albrecht Stenzinger [i], Lukas C. Heukamp [j,k], Reinhard Büttner [l], Norbert Marschner [m], Martina Jänicke [n], Annette Fleitz [n], Lisa Spring [n], Jörg Sahlmann [o], Aysun Karatas [p], Annette Hipper [p], Wilko Weichert [q], Monika Heilmann [r], Parvis Sadjadian [s], Wolfgang Gleiber [t], Christian Grah [u], Cornelius F. Waller [v], Martin Reck [w], Achim Rittmeyer [x], Petros Christopoulos [y], Martin Sebastian [z,1], Michael Thomas [y,1], the CRISP Registry Group [2]

[a] *Pius-Hospital Oldenburg, Universitätsklinik für Innere Medizin, Oldenburg, Germany*
[b] *Ruhrlandklinik, Westdeutsches Lungenzentrum am Universitätszentrum Essen, Germany*
[c] *Praxis für Hämatologie und internistische Onkologie, Ratingen, Germany*
[d] *PIOH – Praxis internistische Onkologie und Hämatologie, Köln, Germany*
[e] *MVZ Onkologische Kooperation Harz, Goslar, Germany*
[f] *Hämatologie-Onkologie, MVZ West GmbH Würselen, Germany*
[g] *Gemeinschaftspraxis für Hämatologie und Onkologie, Dortmund, Germany*
[h] *MVZ für Onkologie und Hämatologie im Rhein-Kreis, Neuss, Germany*
[i] *Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany*
[j] *Hämatopathologie Hamburg, Hamburg, Germany*
[k] *Lungen Netzwerk NOWEL.org, Oldenburg, Germany*
[l] *Institut für Pathologie des Universitätsklinikums Köln, Köln, Germany*
[m] *Praxis für interdisziplinäre Onkologie und Hämatologie, Freiburg, Germany*
[n] *Clinical Epidemiology and Health Economics, iOMEDICO, Freiburg, Germany*
[o] *Biostatistics, iOMEDICO, Freiburg, Germany*
[p] *AIO-Studien-gGmbH, Berlin, Germany*
[q] *Institut für Pathologie, Technische Universität München und German Cancer Consortium (DKTK), partner site Munich, München, Germany*
[r] *Lungenkrebszentrum, KRH Klinikum Siloah, Hannover, Germany*
[s] *Universitätsklinik für Hämatologie, Onkologie, Hämostaseologie und Palliativmedizin, Johannes Wesling Klinikum, Universitätsklinikum der Ruhr Universität Bochum, Minden, Germany*
[t] *Universitätsklinikum Frankfurt, Medizinische Klinik I, Schwerpunkt Pneumologie/Allergologie, Frankfurt, Germany*
[u] *MVZ Havelhöhe am Gemeinschaftskrankenhaus Havelhöhe, Berlin, Germany*
[v] *Medizinische Klinik I, Hämatologie, Onkologie und Stammzelltransplantation; Fakultät für Medizin, Universitätsklinikum Freiburg, Germany*
[w] *LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany*
[x] *Lungenfachklinik Immenhausen, Germany*
[y] *Onkologie der Thoraxtumore, Thoraxklinik Heidelberg gGmbH, German Center for Lung Research (DZL), Germany*
[z] *Medizinische Klinik II, Hämatologie/Onkologie, Universitätsklinikum Frankfurt, Germany*

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescence *in-situ* hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homologue; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic tyrosine receptor kinase 1; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1.

* Corresponding author at: Pius Hospital, Georgstr. 12, 26121 Oldenburg, Germany.
E-mail address: Frank.Griesinger@Pius-Hospital.de (F. Griesinger).

[1] These authors contributed equally.
[2] See Appendix A for collaborators names.

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ABSTRACT

Objectives: An increasing number of treatment-determining biomarkers has been identified in non-small cell lung cancer (NSCLC) and molecular testing is recommended to enable optimal individualized treatment. However, data on implementation of these recommendations in the "real-world" setting are scarce. This study presents comprehensive details on the frequency, methodology and results of biomarker testing of advanced NSCLC in Germany.

Patients and methods: This analysis included 3,717 patients with advanced NSCLC (2,921 non-squamous; 796 squamous), recruited into the CRISP registry at start of systemic therapy by 150 German sites between December 2015 and June 2019. Evaluated were the molecular biomarkers *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS*, *MET*, *TP53*, *RET*, *HER2*, as well as expression of PD-L1.

Results: In total, 90.5 % of the patients were tested for biomarkers. Testing rates were 92.2 % (non-squamous), 70.7 % (squamous) and increased from 83.2 % in 2015/16 to 94.2% in 2019. Overall testing rates for *EGFR*, *ALK*, *ROS1*, and *BRAF* were 72.5 %, 74.5 %, 66.1 %, and 53.0 %, respectively (non-squamous). Testing rates for PD-L1 expression were 64.5 % (non-squamous), and 58.5 % (squamous). The most common testing methods were immunohistochemistry (68.5 % non-squamous, 58.3 % squamous), and next-generation sequencing (38.7 % non-squamous, 14.4 % squamous). Reasons for not testing were insufficient tumor material or lack of guideline recommendations (squamous). No alteration was found in 37.8 % (non-squamous), and 57.9 % (squamous), respectively. Most common alterations in non-squamous tumors (all patients/all patients tested for the respective biomarker): *KRAS* (17.3 %/39.2 %), *TP53* (14.1 %/51.4 %), and *EGFR* (11.0 %/15.1 %); in squamous tumors: *TP53* (7.0 %/69.1 %), *MET* (1.5 %/11.1 %), and *EGFR* (1.1 %/4.4 %). Median PFS (non-squamous) was 8.7 months (95 % CI 7.4–10.4) with druggable *EGFR* mutation, and 8.0 months (95 % CI 3.9–9.2) with druggable *ALK* alterations.

Conclusion: Testing rates in Germany are high nationwide and acceptable in international comparison, but still leave out a significant portion of patients, who could potentially benefit. Thus, specific measures are needed to increase implementation.

1. Introduction

Lung cancer belongs to the three most frequently diagnosed cancers in Germany and accounts for 24 % and 16 % of the cancer-related deaths in men and women, respectively [1]. With 80 % of all lung cancer diagnoses, non-small cell lung cancer (NSCLC) is the most common histologic subtype, the majority of these being adenocarcinomas (46 % in women, 36 % in men) or squamous-cell carcinomas (15 % in women, 29 % in men) [2]. The course of disease in NSCLC is highly heterogeneous, with prognosis as well as therapeutic options depending on the molecular biology of the tumor. Several non-squamous tumors harbor mutations in oncogenic driver genes, allowing for a molecularly stratified, personalized treatment with approved targeted therapies. Such driver mutations are generally mutually exclusive of each other [3,4]. Therefore, biomarker testing is essential for determining the optimal treatment of patients with advanced NSCLC. Now and hereafter, the term "alteration" is used generically and can refer to a missense mutation, nonsense mutation, frameshift mutation, indel, duplication, gene fusion, deletion or amplification, depending on the molecular marker tested. In contrast to these molecular biomarkers, the biomarker PD-L1 is a protein expressed on either tumor or immune cells, the expression level is measured by determining the tumor proportion score (TPS).

According to international guidelines, all patients with advanced non-squamous NSCLC, regardless of their age, race or smoking status, plus all patients with advanced squamous NSCLC, who are non-smokers or younger than age 50, should be tested for, at a minimum, alterations in *EGFR*, *ALK*, *ROS1*, and *BRAF*; as well as for PD-L1 expression [3, reviewed in 5]. Additional recommended biomarker tests are alterations in the genes of *KRAS*, *HER2*, *MET*, *RET* and *NTRK* [3–6]. These recommendations are similar in Europe and Germany [7,8,4].

Several targeted therapies have been developed and licensed, which specifically inhibit the products of genes with common driver mutations. The presence of a corresponding so-called "druggable" alteration (in *EGFR*, *ALK*, *ROS1*, or *BRAF*) or a high expression of PD-L1 in tumor cells (TPS $\geq$ 50 %) has markedly changed the diagnostic and therapeutic algorithm for NSCLC [4,7]. If none of these alterations are detected, platinum-based doublet therapies were indicated until recently, resulting in approximately 80 % patients receiving chemotherapy [9]. With the approval of immune-checkpoint-inhibitor–chemotherapy combination therapies in 2018 and 2019, also for NSCLC with a PD-L1 expression of less than 50 %, the treatment algorithm changed.

Although this paradigm shift literally implies that virtually all patients with NSCLC must be tested prior to making any evidence-based treatment recommendations, so far, not much is known about molecular testing in real life scenarios. The CRISP clinical research platform was set up in order to collect representative data on molecular testing, treatment and outcome of unselected patients with advanced or metastatic NSCLC all over the country, in order to gain valuable insight into daily routine care in Germany. In the present analysis, we show our first results on the frequency, methodology and results of biomarker testing and highlight the areas for improvement.

2. Patients and methods

2.1. Study design

CRISP is an open, non-interventional, prospective, multi-center registry. The registry was reviewed by the responsible ethics committees and is registered at ClinicalTrials.gov (NCT02622581). For the present analysis, eligible patients were aged $\geq$18 years with confirmed NSCLC, stage IV or stage IIIB/C and ineligible for curative surgery and/or radiochemotherapy (here collectively referred to as "advanced" NSCLC). The patients must be able to understand and willing to sign written informed consent and to complete instruments for assessment of patient-reported-outcomes. A maximum of four weeks' time difference is allowed between start of first-line therapy and signed informed consent. Patients are followed until death or end of project. In order to collect data representative for routine systemic treatment in Germany, over 150 certified lung cancer centers, comprehensive cancer centers, hospitals and office-based oncology practices located all over Germany participate in CRISP. Study sites are encouraged to recruit patients consecutively.

Data on patients' demographic and tumor characteristics as well as biomarker testing and previous (non-palliative) treatments are documented at inclusion. During the follow-up period, data on additional molecular testing, all treatments, course of disease and outcome are updated at least every three months. Patients are treated according to their physician's choice based on the patients' individual needs and

schedules. The collected data is pseudonymized and transferred from patients' medical records to a secure web-based electronic case report form.

Regarding biomarker testing, every participating center/physician decides for themselves to which pathology lab the samples are sent, which test methods (e.g. NGS or standard sequencing) and which markers are requested. Each pathology lab follows their own methodology of testing and then reports the results back to the practice. The majority of pathologists in Germany running molecular diagnostics follow the strict quality assurance guidelines given by the German Accreditation Body (DAkkS, ISO17020) or participate in independent quality assurance measures (QUIP certificate). Within the CRISP registry, it is documented whether any biomarker test has been ordered or performed prior to inclusion, i.e. at start of first-line treatment. Currently *EGFR*, *ROS1*, PD-L1, *ALK*, *RET*, *BRAF*, *MET*, *KRAS*, *TP53*, and *HER2* are listed as biomarkers and can be directly documented as tested or not tested. Additional biomarkers can be specified as free text. Regarding testing results for PD-L1 expression, details on the TPS or on the Cologne Score (CS), are collected. The results were subsequently categorized for presentation.

2.2. Cohort definition

Patient enrolment into CRISP started on December 17, 2015. Patients with missing documentation on birth year, sex, tumor histology (squamous or non-squamous), molecular testing (yes/no), and missing start date of first-line therapy were excluded. First-line treatment was defined as any systemic palliative treatment, e.g. chemotherapy, or targeted therapy. For survival analysis, all patients starting first-line treatment until June 30, 2018 have been considered.

2.3. Statistical analysis

Descriptive statistical analyses were performed for the total population and by histology of the tumor (non-squamous vs. squamous). (Registry-) progression-free survival (PFS) was defined as the interval between start of first-line treatment and the date of progression or death. Patients without such an event were censored at last contact or at start of second-line treatment (whichever occurred first). PFS was estimated for all patients, who have been observed for at least one year (i.e. recruited until June 30, 2018) using the Kaplan-Meier method [10]. Of note, there are no specifications as to the timing, frequency or criteria of tumor assessment and thus PFS data should be considered as the best clinical approximation, but might not be identical to the PFS determined in clinical trials. All analyses were calculated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002–2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

3.1. Patient and tumor characteristics

Until data cut for this interim analysis on June 30, 2019, a total of 4,032 patients with advanced NSCLC had been recruited into the CRISP registry by 150 sites all over Germany (Fig. S1). The data on 3,717 patients were evaluable (see chapter 2.2), and of these, 2,921 (78.6 %) had a non-squamous and 796 (21.4 %) a squamous histology of the tumor. The patient and tumor characteristics of these patients are presented in Table 1. Median age at start of first-line treatment was 66 years for patients with non-squamous and 68 years for patients with squamous tumors. The proportion of male patients was markedly higher in squamous compared to non-squamous NSCLC (71.6 % vs. 57 %). The average body mass index was normal (25.6 ± 12.6 kg/m^2 for non-squamous and 25.4 ± 6.5 kg/m^2 for squamous NSCLC). Patients with squamous NSCLC more frequently reported a smoking history: 85.3 % vs. 78.0 % of the patients with non-squamous NSCLC. Looking at the histology in more detail, 91.9 % of the non-squamous tumors were classified as adenocarcinoma, 2.2 % as large cell carcinoma and 5.9 % had a different histology.

The patients were recruited by 150 active sites: 73 hospitals (49 %), and 77 practices/office-based oncologists (51 %), with more than half of the patients (60.8 %) being recruited by hospitals.

Table 1
Patient and tumor characteristics.

Characteristic at start of first-line treatment	Non-squamous NSCLC (n = 2,921)	Squamous NSCLC (n = 796)
Age in years, median (25–75 % quartile)	66.0 (59.0–73.0)	68.0 (60.0–74.0)
Sex		
Female	1,255 (43.0 %)	226 (28.4 %)
Male	1,666 (57.0 %)	570 (71.6 %)
Patients with any comorbidity [a]	2,436 (83.4 %)	725 (91.1 %)
Comorbidities according to the CCI [a,b]		
CCI = 0 [b]	1,710 (58.5 %)	340 (42.7 %)
CCI ≥1 [b]	1,210 (41.4 %)	456 (57.3 %)
Other comorbidities [c]	2,184 (74.8 %)	655 (82.3 %)
Diabetes without end organ damage	362 (12.4 %)	144 (18.1 %)
Arterial hypertension	1,295 (44.3 %)	389 (48.9 %)
Vasosclerosis	389 (13.3 %)	154 (19.3 %)
Performance Status		
ECOG 0	843 (28.9 %)	172 (21.6 %)
ECOG 1	1,302 (44.6 %)	407 (51.1 %)
ECOG ≥2	339 (11.6 %)	113 (14.2 %)
Unknown	398 (13.6 %)	94 (11.8 %)
Missing	39 (1.3 %)	10 (1.3 %)
Smoking status		
Current smoker	792 (27.1 %)	245 (30.8 %)
Former smoker (heavy)*	1,030 (35.3 %)	319 (40.1 %)
Former smoker (light)*	278 (9.5 %)	62 (7.8 %)
Former smoker (intensity unknown)	178 (6.1 %)	53 (6.7 %)
Never smoker	385 (13.2 %)	41 (5.2 %)
Unknown	257 (8.8 %)	74 (9.3 %)
Missing	1 (0.0 %)	2 (0.3 %)
Metastasis		
Yes	2,636 (90.2 %)	630 (79.1 %)
No	182 (6.2 %)	115 (14.4 %)
Not derivable (MX or missing)	103 (3.5 %)	51 (6.4 %)
Selected metastatic sites [a,c]		
Adrenal Gland	496 (17.0 %)	91 (11.4 %)
Bone	856 (29.3 %)	160 (20.1 %)
Brain	703 (24.1 %)	81 (10.2 %)
Liver	414 (14.2 %)	119 (14.9 %)
Lung (contralateral)	626 (21.4 %)	175 (22.0 %)

Data are number (%), unless indicated otherwise. **Abbreviations:** CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

[a] for all patients with values for this variable.

[b] Charlson Comorbidity Index (CCI) according to Quan [32].

[c] multiple answers possible.

* Definitions: Former smoker (heavy) quit smoking less than 15 years ago or quit smoking but had smoked more than 10 pack years. Former smoker (light) quit smoking more than 15 years before diagnosis or quit smoking and had smoked less than 10 pack years [11].

3.2. Testing rates and methodology of testing

A total of 92.2 % of the patients with non-squamous tumors and 70.7 % of the patients with squamous tumors had been tested for any

type of biomarker before start of first-line treatment. The overall testing rates for *EGFR*, *ALK*, *ROS1*, and *BRAF* in non-squamous NSCLC were 72.5 %, 74.5 %, 66.1 % and 53.0 %, respectively. Testing rates for PD-L1 expression were 64.5 % (non-squamous) and 58.5 % (squamous). The overall testing rates for all documented biomarkers (*EGFR*, *ROS1*, PD-L1, *ALK*, *BRAF*, *RET*, *MET*, *KRAS*, *TP53* and *HER2*) are listed in Table S1. The average testing rate for all patients increased over time, from 80.8 % in 2015/16, 86.1 % in 2017, 90.3 % in 2018, to 88.9 % in 2019 (data on file). Of note, the ongoing dynamics in biomarker testing have to be considered: in 2015, testing for activating *EGFR* mutations (exon 18–21), *ALK* rearrangements or aberrant expression of *ALK* protein, and for *ROS1* rearrangements had been included in the recommendations for the diagnostic work-up of patients with non-squamous NSCLC or with squamous NSCLC if they are never-smokers or light smokers (less than 10 pack years or stop of smoking more than 15 years ago) [11,12]. By now (in 2019), these recommendations have been expanded to include testing for the *BRAF* V600E mutation and the PD-L1 TPS as well as the additional biomarkers *KRAS*, *HER2*, *MET*, *RET* and *NTRK* [4–6].

Fig. 1 presents the frequency of biomarker testing before start of first-line treatment over time, showing that the testing rates of the "new" biomarkers *BRAF*, *KRAS*, *MET* and *TP53* are increasing steadily in non-squamous NSCLC (Fig. 1A). In 2019, the testing rate in patients with non-squamous NSCLC was 65.4 % for *EGFR* and 72.8 % for *ALK*; the testing rate for PD-L1 was 76.1 %. In patients with squamous NSCLC, the testing rates for *ROS1* and *BRAF* were 27.1 % and 27.7 % in 2019, respectively; while the testing rate for PD-L1 reached 77.4 % in 2019, drawing level with the testing rate for non-squamous tumors (Fig. 1B).

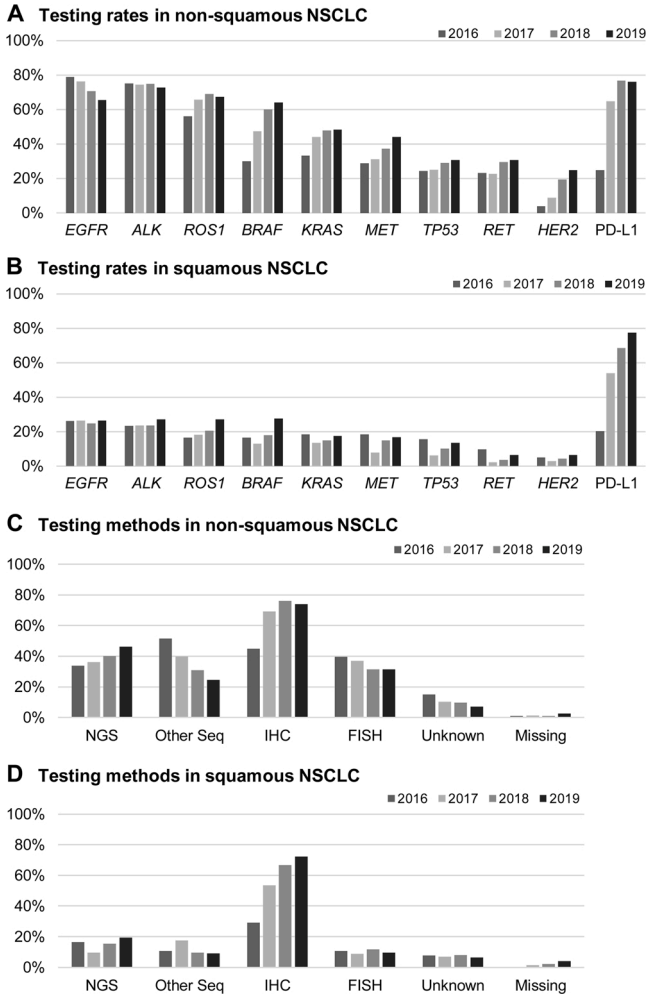

Fig. 1. Testing rates and testing methods.
Testing rates at start of first-line treatment for patients with **(A)** non-squamous and **(B)** squamous NSCLC. Testing methods used in patients with **(C)** non-squamous and **(D)** squamous NSCLC, multiple answers possible. Missing: testing was ordered/conducted, but no testing method or other details have been documented yet. **Abbreviations:** FISH, fluorescence *in-situ* hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; seq, sequencing.

With respect to the methodology of testing, immunohistochemistry (IHC) was the method applied most frequently, in 68.5 % of non-squamous and 58.3 % squamous tumors; followed by NGS, performed in 38.7 % of the non-squamous and 14.4 % squamous tumors (Fig. 1C and D). The combination of testing methods is shown in Table S2 for non-squamous and in Table S3 for squamous tumors.

Median turnaround time (interquartile range), defined as the time between testing order and testing result, was 13 calendar days (9.0–18.0) for NGS, 8 days (5.0–13.0) for other sequencing, 6 days for IHC (3.0–11.0), and 11 days (7.0–16.0) for FISH (data on file). Details on IHC testing for PD-L1 was documented for 1767 patients with non-squamous and 431 patients with squamous tumors, and revealed a similar usage of specific antibodies (data on file): Ventana SP263 (18.9 % non-squamous, 15.8 % squamous), DAKO 22-C3 (12.1 % non-squamous, 13.4 % squamous), DAKO 28-8 (7.0 % non-squamous, 7.9 % squamous), Ventana E1L3N (1.4 % both), other antibodies (2.4 % non-squamous, 2.6 % squamous), antibody not reported (55.2 % non-squamous, 55.0 % squamous).

3.3. Reasons for not testing

If no biomarker test had been ordered or performed, physicians were asked to document the respective reasons. In total, 462 of 3,717 patients (12.4 %) have not been tested for any biomarker; 229 (7.8 %) with non-squamous and 233 (29.3 %) with squamous tumors.

The reasons for not testing have been documented for 148 (5.1 %) patients with non-squamous and 206 (25.9 %) patients with squamous tumors. Looking more closely at this subgroup, the most frequently documented reasons for not testing (non-squamous/squamous NSCLC) were „no or not enough tumor material available" (27.0 %/9.2 %), "test not recommended for this group of patients" (14.2 %/57.3 %), or "other reasons" (47.9 %/22.8 %). Patients who had not been tested were more frequently male (n = 98 of 148 non-squamous [66.2 %]; n = 150 of 206 squamous [72.8 %]) or had a history of smoking (n = 129 of 148 non-squamous [87.2 %]; n = 171 of 206 squamous [83.0 %]) than patients who had been tested.

3.4. Testing results

The results of testing for molecular biomarkers for all 3,717 patients recruited are shown in Fig. 2A and B. Of note, these are real-world data of all patients receiving systemic first-line treatment for advanced NSCLC and thus percentages refer to all included patients, uniquely reflecting the daily routine. For non-squamous tumors, at least one molecular alteration was found in 42.9 % of the patients, while in 37.8 % of the patients, no molecular alteration could be detected (Fig. 2A). Molecular alterations in non-squamous tumors were most frequently found in *KRAS* (17.3 %), *TP53* (14.1 %), and *EGFR* (11.0 %); druggable molecular alterations were detected in *EGFR* (8.4 %), *ALK* (3.0 %), *ROS1* (0.6 %), and *BRAF* (0.8 %). Details on the testing results of these druggable biomarkers with corresponding approved targeted therapies are presented in Table 2. In squamous tumors, 29.3 % of the patients have not been tested, and no molecular alteration has been detected in 57.9 % (Fig. 2B); the by far most frequent molecular alteration was in *TP53* (7.0 % of all patients).

The percentages of patients tested for the respective biomarker with respect to all patients included in CRISP are shown in Fig. 2C and D. Of all patients with non-squamous tumors tested for the respective biomarker, 51.4 % had an alteration *TP53*, 39.2 % in *KRAS*, 15.1 % in *EGFR* and 9.3 % in *MET* (Fig. 2C). Percentages for the respective

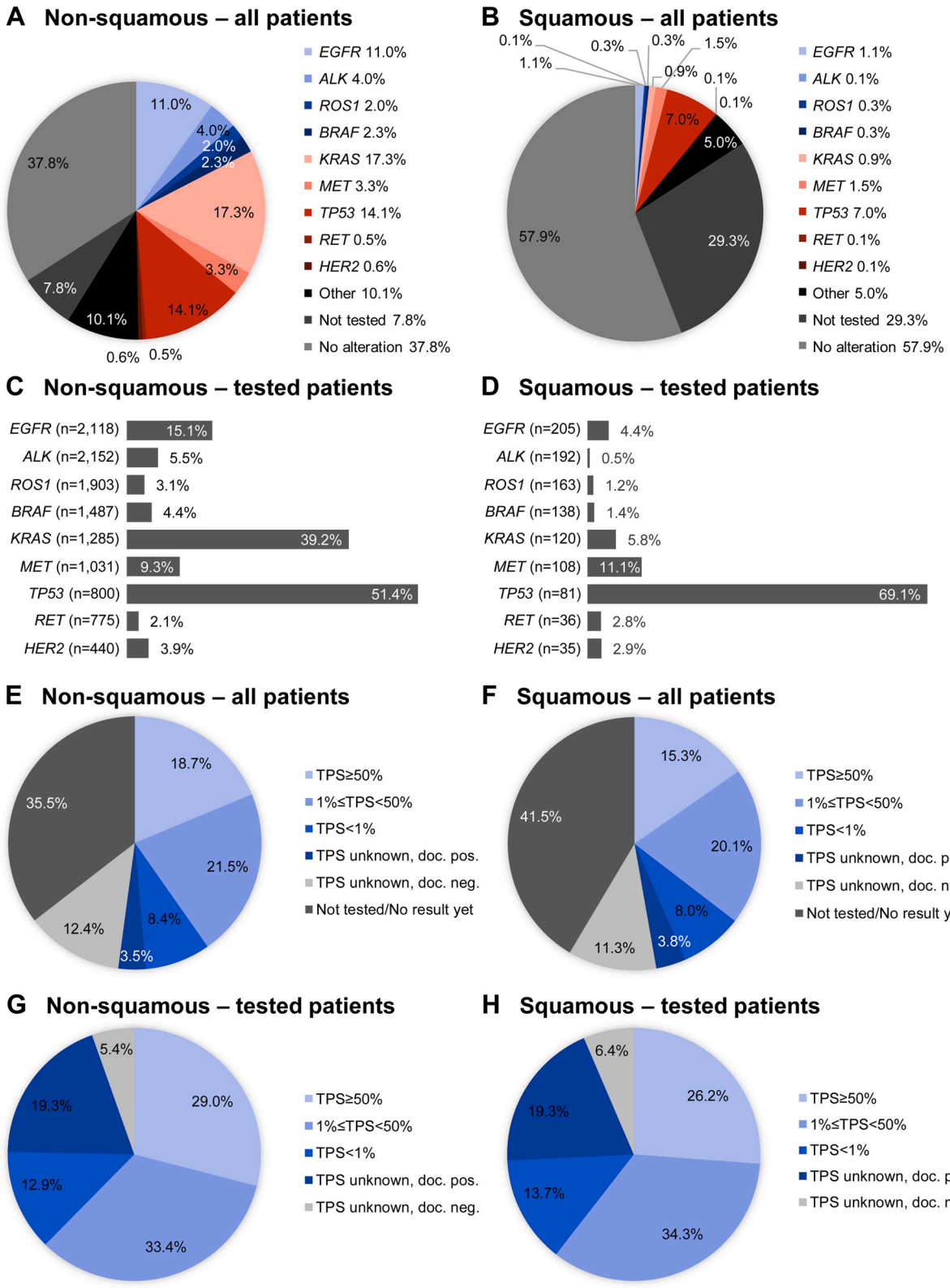

Fig. 2. Testing results for all recruited patients, as well as for tested patients.
Testing results for molecular alterations in **(A)** all recruited patients with non-squamous and **(B)** all recruited patients with squamous NSCLC. Cases with two mutations are depicted twice, see Table S4 and S5 on combinations of alterations. **(C)** Testing results for all patients, who had been tested for the respective biomarker with non-squamous and **(D)** squamous NSCLC. **(E)** Testing results for PD-L1 expression for all recruited patients with non-squamous and **(F)** squamous NSCLC. **(G)** PD-L1 testing results for all patients, who had been tested for PD-L1 expression with non-squamous and **(H)** squamous NSCLC. TPS ≥ 50 % (CS 5), 1 %≤TPS ≥ 50 % (CS 1–4), TPS < 1 % (CS 0). **Abbreviations**: doc., documented, neg., negative, pos., positive.

Table 2
Details on testing results.

Testing results at start of first-line treatment (% of all patients/% of tested patients)	Non-Squamous (n = 2,921)	Squamous (n = 796)
***EGFR* testing results available**	**2,118 (72.5 %/1.0 %)**	**205 (25.8 %/1.0 %)**
EGFR alteration [a]	320 (11.0 %/15.1 %)	9 (1.1 %/4.4 %)
Druggable [b]	245 (8.4 %/11.6 %)	8 (1.0 %/3.9 %)
Deletion 19	113 (3.9 %/5.3 %)	1 (0.1 %/0.5 %)
L858R	82 (2.8 %/3.9 %)	5 (0.6 %/2.4 %)
T790 M (Group II)	3 (0.1 %/1.4 %)	1 (0.1 %/0.5 %)
L858R + T790M	1 (0.0 %/0.0 %)	–
L858R + Group I	3 (0.1/%/0.1 %)	–
Group I	43 (1.5 %/2.0 %)	1 (0.1 %/0.5 %)
Non-druggable [c]	19 (0.7 %/0.9 %)	–
Unknown druggability [d]	56 (1.9 %/2.6 %)	1 (0.1 %/0.5 %)
***ROS1* testing results available**	**1,903 (65.1 %/1.0 %)**	**163 (20.5 %/1.0 %)**
ROS1 alteration [a]	59 (2.0 %/3.1 %)	2 (0.3 %/1.2 %)
Druggable [e]	17 (0.6 %/0.9 %)	–
Non-druggable [f]	8 (0.3 %/0.4 %)	–
Unknown druggability [g]	34 (1.2 %/1.8 %)	2 (0.3 %/1.2 %)
***ALK* testing results available**	**2,152 (73.7 %/1.0 %)**	**192 (24.1 %/1.0 %)**
ALK alteration [a]	118 (4.0 %/5.5 %)	1 (0.1 %/0.5 %)
Druggable [h]	89 (3.0 %/4.1 %)	–
Non-druggable [i]	14 (0.5 %/0.7 %)	1 (0.1 %/0.5 %)
Unknown druggability [d]	15 (0.5 %/0.7 %)	–
***BRAF* testing results available**	**1,487 (50.9 %/1.0 %)**	**138 (17.3 %/1.0 %)**
BRAF alteration [a]	65 (2.2 %/4.4 %)	2 (0.3 %/1.4 %)
Druggable (V600)	22 (0.8 %/1.5 %)	–
Non-druggable [j]	38 (1.3 %/2.6 %)	1 (0.1 %/0.7 %)
Unknown druggability [k]	5 (0.2 %/0.3 %)	1 (0.1 %/0.7 %)
PD-L1 testing result available	**1,885 (64.5 %/1.0 %)**	**466 (58.5 %/1.0 %)**
TPS ≥ 50 % (or CS 5)	547 (18.7 %/29.0 %)	122 (15.3 %/26.2 %)
TPS ≥1 % and <50 % (or CS 1–4)	629 (21.5 %/33.4 %)	160 (20.1 %/34.3 %)
TPS < 1 % (or CS 0)	244 (8.4 %/12.9 %)	64 (8.0 %/13.7 %)
TPS/CS unknown, documented as negative [l]	363 (12.4 %/19.3 %)	90 (11.3 %/19.3 %)
TPS/CS unknown, documented as positive [m]	102 (3.5 %/5.4 %)	30 (3.8 %/0.6 %)

Data are number (%), unless indicated otherwise.
Abbreviations: CS, PD-L1 Cologne score; FISH, fluorescence *in-situ* hybridization; IHC, immunohistochemistry; TPS, PD-L1 tumor proportion score.
[a] documented testing result "mutation/positive".
[b] documented testing result defined as deletion 19, L858R, T790 M, and/or group I.
[c] documented *EGFR* - testing result defined as group III.
[d] documented testing result "DNA/protein sequence unknown" or not specified.
[e] documented *ROS1* - testing result "translocation/FISH-positive".
[f] documented *ROS1* - testing result "mutation/FISH-negative".
[g] documented *ROS1* - testing result "no translocation/mutation/FISH-negative".
[h] documented ALK testing result "translocation/FISH-positive/IHC positive (+ to +++, unknown or not specified)".
[i] documented ALK - testing result "mutation/amplification".
[j] documented BRAF - testing result "alteration, other than V600".
[k] documented BRAF - testing result "DNA/protein sequence unknown" or not specified/FISH-positive/IHC positive.
[l] documented negative PD-L1 - testing result, but no documentation on TPS/CS.
[m] documented positive PD-L1 - testing result, but no documentation on TPS/CS.

druggable subgroups can be found in Table 2. Looking at the patients with squamous tumors tested for the respective biomarker, 69.1 % had an alteration in *TP53* and 11.1 % in *MET* (Fig. 2D).

Results for the PD-L1 expression are shown in Fig. 2E and F for all recruited patients and in Fig. 2G and H for those patients tested for PD-L1 expression. Patients with non-squamous/squamous tumors showed similarities: the TPS was ≥50 % for 18.7 %/15.3 %; 1–49 % in 21.5 %/20.1 %, and <1 % for 8.4 %/8.0 % of all patients (Fig. 2E and F). Calculating these percentages only for those patients who had been tested for PD-L1 expression (non-squamous/squamous), TPS was ≥ 50 % for 29.0 %/26.2 %, 1–49 % for 33.4 %/34.3 % and <1 % for 12.9 %/13.7 % of the patients (Fig. 2G and H).

Several patients presented with a combination of alterations (Tables S4 and S5). For example, of the 320 patients with non-squamous tumors and an alteration in *EGFR*, 62 also had an alteration in *TP53*, and 16 in *KRAS* (multiple answers possible, see Table S4 for all combinations).

The different methods for the detection of molecular alterations in *EGFR*, *ALK*, *ROS1* and *BRAF* are presented in the Tables S6 and S7. *EGFR* alterations in non-squamous NSCLC (n = 320), for example, were detected by NGS (n = 183), other sequencing (n = 129) or by an unknown (to the documenting site) method (n = 25). *ALK* alterations in non-squamous NSCLC were detected by NGS (n = 35), other sequencing (n = 13), immunohistochemistry (n = 49), FISH (n = 41), or by an unknown method (n = 7) (Table S6).

3.5. Progression-free survival

Median (Registry-) PFS for all patients with druggable *EGFR* or *ALK* alterations, as well as for all patients without druggable alterations or who had not been tested is shown in Fig. 3. The corresponding patient characteristics of these subgroups are listed in Table S8.

Median PFS for patients with a druggable *EGFR* alteration (exon 19, exon 21, group I and II) (n = 169) was 8.7 months (95 % CI 7.4–10.4) and 8.0 months (95 % CI 3.9–9.2) for patients with a druggable *ALK* alteration (n = 61). Median PFS for patients who had not been tested for molecular alterations, and for patients, for whom no druggable alteration (in *EGFR*, *ALK*, *ROS1*, or *BRAF*) was detected, was calculated for patients with non-squamous and squamous NSCLC, ranging from 3.9 to

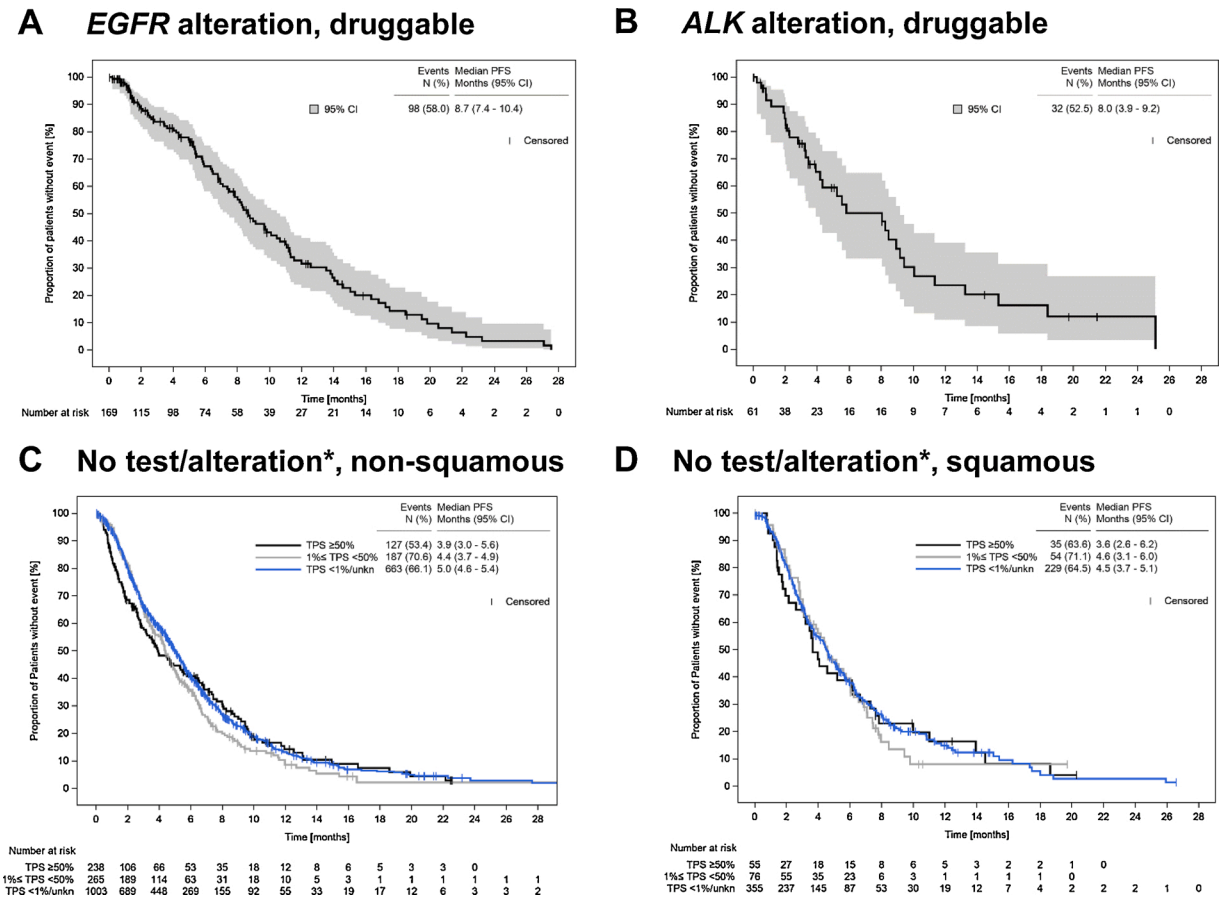

Fig. 3. Progression-free survival.
First-line PFS for patients with **(A)** any druggable alteration in *EGFR* (documented testing result defined as deletion 19, L858R, T790 M, and/or group I), **(B)** any druggable alteration in *ALK* (documented testing result defined as translocation/FISH-positive/IHC positive [+ to +++, unknown or not specified]). **(C-D)** First-line PFS for patients, who were not tested or for whom no druggable alteration (in *EGFR*, *ROS1*, *ALK*, or *BRAF*) could be detected; split up according to the PD-L1 TPS, **(C)** non-squamous tumors, **(D)** squamous tumors. All patients recruited up to and including June 30, 2018 were included into this outcome analysis. **Abbreviations:** CI, confidence interval; TPS, PD-L1 tumor proportion score; unkn., unknown. *no druggable alteration in *EGFR*, *ROS1*, *ALK*, or *BRAF*.

5.0 months for patients with non-squamous and 3.6–4.6 months for patients with squamous tumors, dependent on the amount of PD-L1 expression (Fig. 3C and D). PFS according to the different treatment regimens will be shown in future analyses, when the number of events are high enough to present informative results.

4. Discussion

This study on a large, representative, prospective cohort of patients with advanced NSCLC in routine care in Germany shows a high rate of biomarker testing, which increased over the last years. After approval of new agents, respective biomarker testing was quickly incorporated into routine clinical care. To our knowledge, this is the first study presenting comprehensive data on biomarker testing in a real-world setting, reflecting the treatment landscape of patients with advanced NSCLC in Germany.

Biomarker testing is strongly recommended in case of certain targeted therapies for patients with advanced NSCLC [4,6,13]. As such, biomarker testing has long since entered routine treatment, but not much is known about the implementation or the testing rate in this setting and variability of uptake into clinical practice has been denounced [5,14–16].

Looking at published testing rates of molecular markers, an increase in recent years could be observed: two retrospective analyses in the United States (US) between 2010 and 2015 reported molecular testing rates of 59–61 % [17,18]; a small online market survey in the US in 2015 (n = 157) reported a 87 % testing rate [19]. Gobbini and colleagues performed a prospective, multicenter observational study in Italy in 2014-15, and presented data on 1787 patients with a testing rate of 78 % [20]. An increasing overall testing rate over time could also be mirrored in our analysis, ranging from 80.8 % in 2015/16–88.9% in 2019.

Looking more closely at single biomarkers, a retrospective analysis collected in 2017 from a software providing decision support in the US reported a testing rate of 95 % for *EGFR* alterations [21]. In Europe, the retrospective PIvOTAL study (2011–2013, follow-up until 2016) presented testing rates of *EGFR* and *ALK* alterations of 65 % (Italy), 85 % (Spain), and 66 % (Germany) for NSCLC; however, the number of patients recruited for each country was very low with 174, 202, and 139 patients, respectively [22]. The aforementioned study by Gobbini et al. in Italy reported testing rates of 76 % for *EGFR*, 53 % for *ALK*, 27 % for *KRAS*, 16 % for *ROS1*, 14 % for *BRAF*, 5 % for *HER2*, and 4 % for *MET* [20]. The testing rates in our study (average of 2015–2019, see Table S1) were considerably higher.

With respect to the testing rates of PD-L1 expression, 65 % of the non-squamous and 59 % of the squamous tumors have been tested in our cohort. In the analysis based on data from the software providing decision support in the US, 57 % of the non-squamous and squamous tumors have been tested for PD-L1 expression [21]. A real-world study on PD-L1 testing in the US showed an increasing PD-L1 testing rate from 18 % in 2015 to 71 % in 2017 [23].

A total of 7.8 % (29.3 %) of the patients with non-squamous (squamous) tumors had not been tested in our study. Gobbini and colleagues

Table 3
Comparison of biomarker testing results.

Testing results	General literature [33,34,35,36]	Gobbini et al. [20]	Vanderlaan et al. [37]	Barlesi et al. [27].	CRISP	CRISP
Patients		N=1,787	N=1,009	N=17,664	N = 3,717	N = 3,717
Period		2014-2015	2004-2017	2012-2013	2015-2019	2015-2019
Study design		Prospective multicenter enrollment, observational real-world study	Retrospective analysis of specimens tested for predictive biomarkers at Beth Israel Deaconess Medical Center	Routine multicenter screening for 6 biomarkers	Prospective multicenter enrollment, observational real-world study	Prospective multicenter enrollment, observational real-world study
NSCLC		Advanced/recurrent NSCLC 15.7 % squamous	All stages NSCLC 3.8 % squamous	Advanced NSCLC 5 % squamous	Advanced non-squamous NSCLC	Advanced non-squamous NSCLC
Country		Italy	United States	France	Germany	Germany
		Percentage relative to patients tested for the respective biomarker	Percentage relative to all tested patients	Percentage relative to patients tested for the respective biomarker	Percentage relative to all patients	Percentage relative to patients tested for the respective biomarker
EGFR	15-30 %[1]	23.6 %	19.0 %	11 %	11.0 %	15.1 %
ALK	3.7 %	8.9 %	4.5 %	5 %	4.0 %	5.5 %
ROS1	1.2 %	3.9 %	0.7 %	–	2.0 %	3.1 %
BRAF	1.4 %	3.7 %	1.6 %	2 %	2.3 %	4.4 %
RET	1.2 %		0.4 %	–	0.5 %	2.1 %
KRAS	24-30 %	32 %	25.9 %	29 %	17.3 %	39.2 %
HER2	2 %	3.4 %	1.0 %	1 %	0.6 %	3.9 %
MET	3 %	14.7 %	1.2 %[2]	–	3.3 %	9.3 %
TP53		–	–	–	14.1 %	51.4 %

[1] in Western countries.
[2] (exon 14 mutation/amplification).

reported that 22.3 % of all patients did not receive any molecular test [20]. Further comparable numbers are scarce, as most studies exclusively present results on the tested patients.

When comparing our testing results with published studies, it is important to consider whether the results are given with reference to all patients with molecular testing vs. all patients (including those not tested at all). Because patients with a greater likelihood for a specific mutation are more often tested for this very same mutation, reported frequencies with reference to tested patients are susceptible to bias. This is the reason why we also reported the testing rates and results with reference to all patients. Our results compared to other published testing results are listed in Table 3, showing that the CRISP testing results are well in line with the general literature, underlining the representativeness of the CRISP registry (Table 3).

In our cohort, at least one molecular alteration was found in 42.9 % of all patients with non-squamous NSCLC, corresponding to 48.3 % of the patients with non-squamous tumors and any molecular testing (n = 1,252/2,587). This percentage of alterations relates well to the 42 % documented by Gobbini et al. [20]. Recently, Volckmar and colleagues published the results of NGS-based genetic profiling on a large number of patients in routine diagnostics in Heidelberg, Germany [24]. In their dataset, 27 % of the patients presented with alterations in *EGFR*, *BRAF*, *ALK* or *ROS1,* compared to 17.7 % of all patients with non-squamous NSCLC or 20.8 % of the patients tested for these specific alterations in our cohort (n = 517/2,482). This difference is probably due to the fact that all patients in the aforementioned study have been tested for all biomarkers with NGS, in contrast to the patients in the CRISP registry. Because of the differences in detection and scoring of PD-L1 expression, comparing the results of PD-L1 expression with other real-world studies is difficult. General literature reports 24–60 % of the patients with NSCLC expressing PD-L1 on the tumor cells [25]. A recent publication of the global EXPRESS study on 2,368 patients with PD-L1 data (using the PD-L1 IHC 22C3 pharmDx kit) reported 22 % patients with PD-L1 TPS ≥ 50 %, 52 % with PD-L1 TPS ≥ 1 % and 26 % with PD-L1 TPS < 1 % [26]; while the real-world study on PD-L1 expression in the US reported 10–33 % with TPS ≥ 50 % [23]. Our results are well in line: 29.0 %/26.2 % patients with non-squamous/squamous tumors had PD-L1 TPS ≥ 50 %, 62.4 % /60.5 % PD-L1 TPS ≥ 1 %, and 12.9 %/13.7 % PD-L1 TPS < 1 %.

The presence of a druggable alteration was associated with an improved median first-line PFS, not only in our results from Germany (median PFS for all patients with druggable *EGFR/ALK* alterations of 8.7/8.0 months vs. 5.0 months for patients without testing/alteration, non-squamous histology), but also in other European multicenter studies: Barlesi et al. (routine screening study in France) reported a median PFS of 10.0 months for patients with genetic alterations vs. 7.1 months [27]; Gobbini et al. (prospective observational study in Italy) reported a median PFS of 9.7 months for patients with *EGFR* or *ALK* alterations vs. 4.61 months for all patients in the study [20].

Despite guideline recommendations and general knowledge about the importance of biomarker testing, not every patient with advanced NSCLC is tested. Various reasons for this lack of universal testing have been listed: insufficient/inadequate tissue samples from biopsies, evaluation/selection of appropriate tests, long turnaround times, and reimbursement issues [5,14,18,28]. In our cohort, a lack of adequate tumor material accounted for a good portion of missing testing results, too. Both broader NGS-based assays able to evaluate all biomarkers in a single test and an optimization of tissue handling have been proposed to emend this situation [5]. Furthermore, liquid biopsies (e.g. for *EGFR* mutation testing) are entering clinical use, avoiding the need for percutaneous biopsy and thus presenting a feasible alternative for patients with an increased risk for biopsy [29].

The selection of appropriate tests is of major importance for PD-L1 expression: as mentioned before there is no standard approach, and subsequent treatment with e.g. pembrolizumab requires testing with different antibodies; there is an urgent need for harmonization of methodologies [30].

With respect to the turnaround times, the clinically acceptable turnaround time for biomarker testing results is 14 calendar days [6,14], this time-limit was kept in our cohort with 13 days for NGS, 8 days for other sequencing, 6 days for IHC, and 11 days for FISH. In contrast to other countries, reimbursement is not as big an issue for biomarkers in Germany; however, molecular testing is currently not reimbursed separately within the context of diagnosis of lung cancer in hospitals or specialized centers [31].

What can we say about the patients, who have not been tested? In our cohort, patients without biomarker testing more frequently had squamous tumor histology, were smokers, and male. These same characteristics have been shown to be associated with lack of testing in the PivOTAL study [22], showing that there still is a need for an information campaign among the treating physicians to test all patients with advanced NSCLC.

5. Limitations

The non-interventional design of this study is both a strength and a limitation; a strength, because it allows presentation of real-world data, and a limitation, because it precludes causal conclusions about differences between subgroups. Of note, these real-world data present testing rates and results for all patients with systemic therapy, and thus testing results may differ from results generated in studies including only patients with biomarker testing. Decisions about treatment are responsibility of the treating physicians and can depend on numerous factors. Furthermore, there are no strict specifications as to the timing, frequency or criteria of tumor assessment as in clinical trials (e.g. RECIST) and thus registry-PFS data should be considered as the best clinical approximation and might not be identical to the PFS determined in clinical trials. This study was designed for patients receiving systemic therapy; therefore, results may not be generalizable to the small group of patients not receiving any systemic treatment. Strengths of this project are the prospective data collection and the participation of both hospital and office-based oncologists all over Germany, recruiting a large, representative registry cohort.

6. Conclusion

The CRISP registry, with its comprehensive, prospective, nationwide data collection on biomarker screening and testing results can report representative numbers on NSCLC for Germany. The testing rates are increasing but there is still apt room for improvement. These data are valuable resources for all planned and newly accepted targeted therapies in NSCLC.

Declarations

All experiments comply with the current laws in Germany, where they were performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments.

CRediT authorship contribution statement

Frank Griesinger: Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Wilfried Eberhardt:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Arnd Nusch:** Investigation, Resources, Writing - review & editing. **Marcel Reiser:** Investigation, Resources, Writing - review & editing. **Mark-Oliver Zahn:** Investigation, Resources, Writing - review & editing. **Christoph Maintz:** Investigation, Resources, Writing - review & editing. **Christiane Bernhardt:** Investigation, Resources, Writing - review & editing. **Christoph Losem:** Investigation, Resources, Writing - review & editing. **Albrecht Stenzinger:** Resources, Writing - review & editing. **Lukas C. Heukamp:** Resources, Writing - review & editing. **Reinhard Büttner:** Resources, Writing - review & editing. **Norbert Marschner:** Writing - review & editing, Funding acquisition. **Martina Jänicke:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Supervision. **Annette Fleitz:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Visualization, Project administration. **Lisa Spring:** Conceptualization, Methodology, Formal analysis, Data curation, Project administration. **Jörg Sahlmann:** Software, Validation, Formal analysis, Data curation. **Aysun Karatas:** Funding acquisition. **Annette Hipper:** Funding acquisition, Project administration, Supervision, Writing - original draft. **Wilko Weichert:** Resources, Writing - review & editing. **Monika Heilmann:** Investigation, Resources, Writing - review & editing. **Parvis Sadjadian:** Investigation, Resources, Writing - review & editing. **Wolfgang Gleiber:** Investigation, Resources, Writing - review & editing. **Christian Grah:** Investigation, Resources, Writing - review & editing. **Cornelius F. Waller:** Investigation, Resources, Writing - review & editing. **Martin Reck:** Investigation, Resources, Writing - review & editing. **Achim Rittmeyer:** Investigation, Resources, Writing - review & editing. **Petros Christopoulos:** Investigation, Resources, Writing - review & editing. **Martin Sebastian:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **Michael Thomas:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition.

Declaration of Competing Interest

C. Bernhardt, A. Fleitz, W. Gleiber, C. Grah, M. Heilmann, M. Jänicke, C. Losem, C. Maintz, A. Nusch, P. Sadjadian, J. Sahlmann, L. Spring, C. Waller, M.-O. Zahn declare no conflict of interest concerning the topic of this publication. The institutions of C. Bernhardt, P. Christopoulos, W. Eberhardt, W. Gleiber, C. Grah, F. Griesinger, M. Groschek, M. Heilmann, C. Losem, C. Maintz, N. Marschner, A. Nusch, M. Reck, M. Reiser, A. Rittmeyer, P. Sadjadian, M. Sebastian, M. Thomas, C. Waller, and M.-O. Zahn received remuneration for the documentation of patient data. R. Büttner has received honoraria for lectures and advisory boards from AbbVie, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Illumina, Lilly, MSD, Novartis, Qiagen, Pfizer, and Roche; he is co-founder and scientific advisor for Targos Mol. Pathology Inc and has served as testifying advisor for MSD in GBA-assessment for pembrolizumab. P. Christopoulos has received grants and personal fees from Novartis, Roche, AstraZeneca and Takeda and personal fees from Pfizer, Chugai and Boehringer. W. Eberhardt has received research funding (to the institution) from Eli Lilly, AstraZeneca, and BMS; he has received honoraria for advisory boards and lectures from AstraZeneca, BMS, Merck/MSD, Roche, Pfizer, Novartis, Takeda, Boehringer Ingelheim, and Abbvie; honoraria for advisory boards from Bayer, Daichi Sankyo, and Janssen Cilag; honoraria for lectures from Baumgart Consult. F. Griesinger has received grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Bristol Myer Squibb, Celgene, MSD, Novartis, Pfizer, Roche, Takeda, and Lilly. M. Groschek has received grants from Roche, BMS, Novartis, Pfizer, Pierre Fabre, Celgene, Amgen, AstraZeneca, Sanofi, Medac, Octapharma, Gilead, TEVA, and Merck; honoraria from Roche, BMS, Novartis, Pfizer, Amgen, Merck, and Celgene; travel expenses from Roche, Celgene, Ipsen, Onkovis, Medac, and Gilead, and has attended advisory boards for Roche, BMS, Novartis, and Pfizer. L. Heukamp has received personal fees for an advisory role from Roche, NEO NewOncology, Pfizer, Bayer, BMS, and AstraZeneca. E. von der Heyde has received grants for non-interventional studies from Novartis, BMS, Boehringer Ingelheim, and Ipsen; and has attended advisory boards for BMS, Novartis, AstraZeneca. A. Hipper and A. Karatas have reported grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, MSD Sharp & Dohme, Lilly, Novartis, Pfizer, Roche, and Takeda to their employer AIO-Studien-gGmbH. N. Marschner has received travel expenses from Roche, Novartis, Celgene, TEVA and Amgen for attendance of advisory boards and honoraria from Böhringer Ingelheim for a lecture, N. Marschner is Chief executive officer and shareholder of iOMEDICO AG. M. Reck reports personal fees from Abbvie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Merck, MSD, Novartis, Pfizer, Roche, and Samsung. M. Reiser reports personal fees from Amgen, Abbvie, Novartis, Roche, and Celgene. A. Rittmeyer reports grants from Abbvie, AstraZeneca, BMS, Eli Lilly, MSD, Novartis, Pfizer, Boehringer Ingelheim, and Roche. M. Sebastian has

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Appendix A

Collaborators, CRISP Registry Group

Ababei, Juliana; Alt, Jürgen; Ammon, Andreas; Anhuf, Jürgen; Azeh, Ivo; Bauer, Stefan; Behringer, Dirk; Berger, Winfried; Bernhardt, Christiane; Bertram, Mathias; Boesche, Michael; Bohnet, Sabine; Bruch, Harald-Robert; Brückl, Wolfgang; Burkhard-Meier, Ulrike; Christopoulos, Petros; Däßler, Klaus-Ulrich; de Wit, Maike; Dechow, Tobias; Depenbusch, Reinhard; Dietze, Lutz; Dommach, Markus; Dörfel, Steffen; Eberhardt, Wilfried; Elender, Corinna; Elsel, Wolfgang; Emde, Till-Oliver; Faehling, Martin; Fietz, Thomas; Fischer, Jürgen R.; Flieger, Dimitri; Freidt, Anke; Freier, Werner; Frenzel, Christian; Fuchs, Florian; Fuchs, Roswitha; Gaska, Tobias; Gleiber, Wolfgang; Grah, Christian; Griesinger, Frank; Grohé, Christian; Groschek, Matthias; Güldenzoph, Björn; Günther, Andreas; Haas, Siegfried; Hackenthal, Matthias; Hagen, Volker; Hahn, Lars; Hannig, Carla Verena; Hansen, Richard; Harich, Hanns-Detlev; Heilmann, Monika; Heinrich, Kathrin; Hering-Schubert, Christiane; Heßling, Jörg; Hoffknecht, Petra; Hortig, Patricia; Hübner, Gerdt; Hummel, Horst-Dieter; Hutzschenreuter, Ulrich; Illmer, Thomas; Innig, Georg; Jaeschke, Bastian; Junghanß, Christian; Kaiser, Ulrich; Kamal, Haytham; Kambartel, Kato; Kern, Jens; Kimmich, Martin; Kingreen, Dorothea; Kirchen, Heinz; Klausmann, Martine; Klein, Ortwin; Kokowski, Konrad; Körber, Wolfgang; Kortsik, Cornelius; Koschel, Dirk; Krämer, Benoit; Krammer-Steiner, Beate; Laack, Eckart; Lamberti, Christof; Leistner, Rumo David; Losem, Christoph; Lück, Andreas; Maintz, Christoph; Martin, Kerstin; Medgenberg, Dirk; Metzenmacher, Martin; Meyer zum Büschenfelde, Christian; Meyn, Philipp; Moorahrend, Enno; Müller, Annette; Müller, Lothar; Neise, Michael; Nückel, Holger; Nusch, Arnd; Overbeck, Tobias; Pelz, Henning; Petersen, Volker; Peuser, Bettina; Plath, Margarete; Randerath, Winfried J.; Rauh, Jacqueline; Reck, Martin; Reichert, Dietmar; Reinmuth, Niels; Reiser, Marcel; Repp, Roland; Reschke, Daniel; Rittmeyer, Achim; Rodemer, Yolanda; Sackmann, Sandra; Sadjadian, Parvis; Sandner, Reiner; Sauer, Annette; Schäfer, Harald; Schaudt, Christoph; Schlag, Rudolf; Schmidt, Burkhard; Schmitz, Stephan; Schröder, Jan; Schroeder, Michael; Schulze, Mathias; Schumann, Christian; Schütte, Wolfgang; Schwaiblmair, Martin; Schwindt, Peter Florian; Sebastian, Martin; Seese, Bernd; Seipelt, Gernot; Sorgenfrei, Thomas; Steiff, Johannes; Steiniger, Heike; Trarbach, Tanja; Tufman, Amanda; Uhlig, Jens; Vehling-Kaiser, Ursula; von der Heyde, Eyck; von Verschuer, Ulla; Waller, Cornelius; Wehler, Thomas; Weißenborn, Georg; Weißinger, Florian; Wermke, Martin; Wesseler, Claas; Wiegand, Jörg; Wilhelm, Stefan; Wilke, Jochen; Zahn, Mark-Oliver; Zaiss, Matthias; Zeth, Matthias.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.10.012.

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Corrigendum

Corrigendum to "Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP registry (AIO-TRK-0315)" [Lung Cancer 152 (2021) 174–184]

Frank Griesinger[a,*,1], Wilfried Eberhardt[b,1], Arnd Nusch[c], Marcel Reiser[d], Mark-Oliver Zahn[e], Christoph Maintz[f], Christiane Bernhardt[g], Christoph Losem[h], Albrecht Stenzinger[i], Lukas C. Heukamp[j,k], Reinhard Büttner[l], Norbert Marschner[m], Martina Jänicke[n], Annette Fleitz[n], Lisa Spring[n], Jörg Sahlmann[o], Aysun Karatas[p], Annette Hipper[p], Wilko Weichert[q], Monika Heilmann[r], Parvis Sadjadian[s], Wolfgang Gleiber[t], Christian Grah[u], Cornelius F. Waller[v], Martin Reck[w], Achim Rittmeyer[x], Petros Christopoulos[y], Martin Sebastian[z,1], Michael Thomas[y,1], the CRISP Registry Group[2]

[a] *Pius-Hospital Oldenburg, Universitätsklinik für Innere Medizin, Oldenburg, Germany*
[b] *Department of Medical Oncology, University Hospital Essen, West German Cancer Center and Ruhrlandklinik, University Duisburg-Essen, Germany*
[c] *Praxis für Hämatologie und internistische Onkologie, Ratingen, Germany*
[d] *PIOH – Praxis internistische Onkologie und Hämatologie, Köln, Germany*
[e] *MVZ Onkologische Kooperation Harz, Goslar, Germany*
[f] *Hämatologie-Onkologie, MVZ West GmbH, Würselen, Germany*
[g] *Gemeinschaftspraxis für Hämatologie und Onkologie, Dortmund, Germany*
[h] *MVZ für Onkologie und Hämatologie im Rhein-Kreis, Neuss, Germany*
[i] *Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany*
[j] *Hämatopathologie Hamburg, Hamburg, Germany*
[k] *Lungen Netzwerk NOWEL.org, Oldenburg, Germany*
[l] *Institut für Pathologie des Universitätsklinikums Köln, Köln, Germany*
[m] *Praxis für interdisziplinäre Onkologie und Hämatologie, Freiburg, Germany*
[n] *Clinical Epidemiology and Health Economics, iOMEDICO, Freiburg, Germany*
[o] *Biostatistics, iOMEDICO, Freiburg, Germany*
[p] *AIO-Studien-gGmbH, Berlin, Germany*
[q] *Institut für Pathologie, Technische Universität München und German Cancer Consortium (DKTK), Partner site Munich, München, Germany*
[r] *Lungenkrebszentrum, KRH Klinikum Siloah, Hannover, Germany*
[s] *Universitätsklinik für Hämatologie, Onkologie, Hämostaseologie und Palliativmedizin, Johannes Wesling Klinikum, Universitätsklinikum der Ruhr Universität Bochum, Minden, Germany*
[t] *Universitätsklinikum Frankfurt, Medizinische Klinik I, Schwerpunkt Pneumologie/Allergologie, Frankfurt, Germany*
[u] *MVZ Havelhöhe am Gemeinschaftskrankenhaus Havelhöhe, Berlin, Germany*
[v] *Medizinische Klinik I, Hämatologie, Onkologie und Stammzelltransplantation, Fakultät für Medizin, Universitätsklinikum Freiburg, Germany*
[w] *LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany*
[x] *Lungenfachklinik Immenhausen, Germany*
[y] *Onkologie der Thoraxtumore, Thoraxklinik Heidelberg gGmbH, German Center for Lung Research, Germany*
[z] *Medizinische Klinik II, Hämatologie/Onkologie, Universitätsklinikum Frankfurt, Germany*

The authors regret that there was an error in affiliation (b). The correct affiliation is now listed above.

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* Corresponding author.
E-mail address: Frank.Griesinger@Pius-Hospital.de (F. Griesinger).
[1] These authors contributed equally.
[2] See Appendix A of original article for collaborators names.

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